Industrial Catalytic Processes for Fine and Specialty Chemicals

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Edited by

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Notations

Abbreviations

BCR	bubble column reactor
CFD	computational fluid dynamics
COFs	covalent organic frame works
CSTR	continuous stirred tank reactor
CVD	chemical vapor deposition
DP	deposition precipitation
GL	gas-liquid
GLS	gas-liquid-solid
HTs	hydrotalcites
LS	liquid-solid
MOFs	metal organic frameworks
O/W	oil in water
PAMAM	polyamidoamine
PVD	physical vapor deposition
SMSI	strong metal support interaction
STR	stirred tank reactor
TOF	turn over frequency
TON	turn over number
TS-1	titanium silicalite-1
W/O	water in oil
ZIF	zeolitic imidazole framework

Notations

a	distance
a	phase fraction
a_B	interfacial area, m^2/m^3
a_p	surface area of the particle, m^2/m^3
A	reactant A or its concentration/pre-exponential factor/Arrhenius constant
A_E	external surface area of a catalyst

B	reactant B or its concentration/breakage rate
b	momentum exchange coefficient from fluid to solid/probability of breakage of bubble
C	concentration
c	compaction modulus
C_A	concentration of A, kmol/m^3
C_B	concentration of B, kmol/m^3
C_D	drag coefficient
C_{eq}	concentration of the solute in the equilibrium saturated solution
C^*	equilibrium interfacial concentration (kmol/m^3)
D	concentration of species D/coalescence rate/reactor diameter and impeller diameter, m/diffusion constant/dispersion
d_1,d_2	maximum and minimum diameter of the sphere with liquid film
D_A	diffusivity
d_B, d_b	bubble diameter, m
D_e	effective diffusion coefficient/dispersion coefficient
D_i	diffusivity of ith component, m^2/s
D_{eq}	equilibrium dispersion
D_o	initial dispersion
d_p	particle diameter, m
d_p	pore diameter
d_o	diameter of orifice in an orifice plate (m)
d_B/d_b	bubble diameter (m)
d_T	tank/tube diameter (m)
E	turbulence dissipation rate/porosity
E	enhancement factor
E_1, E_2	Ergun constants
E_{ads}	activation energy for adsorption
E_{diff}	potential energy barrier for diffusion
E-factor	waste/kg product/environmental factor
E_o	Eötvös number
F	momentum exchange force, kg/m^2 s^2
Fl	flow number
G	elasticity modulus
g	acceleration due to gravity, m/s^2/collision dissipation of energy
g_{ij}	radial distribution function
G_v	change in bubble characteristics due to mass transfer per unit volume per unit time
H	height of tank (m), Henry's constant [(kmol/m^3)$_L$/(kmol/m^3)$_G$]
h	Planck's constant/heat transfer coefficient
Ha	Hatta number

H_A	Henry's constant (kmol/m^{3}Pa)
j	gas flux, kmol/m^{2}s
k	reaction rate constant, subscript indicating a reaction, turbulent kinetic energy, m^2/s^2
K	equilibrium constant, subscript indicating species/reaction
K^*	thermodynamic equilibrium constant
k, k_1	reaction rate constant, units as per the order of reaction
K_A, K_B and K_E	adsorption constant
k_{ads}	rate constant of adsorption
K_B	Boltzman constant
k_B	Boltzmann's number
k_{des}	rate constant of desorption
k_g	mass transfer coefficient, m/s
k_i	breakup efficiency
K_{Ai}	adsorption equilibrium constant of species i
K_L	mass transfer coefficient, s^{-1}
k_L, k_l	mass transfer coefficient, m/s
K_m	Michaelis constant
k_{mn}	reaction rate constant
k_{ov}	overall reaction rate constant, m^3/kmol/s
K_{ov}	overall mass transfer coefficient (1/s)
k_{ov}, k_{mn}	overall rate constant, (m^3/kmol)$^{m+n-1}$(m^3/kg)s^{-1}
k_r^2	rate coefficient for diffusion
k_s	sintering rate constant
k_s	mass transfer coefficient from liquid to solid phase (m/s)
K_{sp}	solubility product
k_T	diffusion coefficient of kinetic energy flux
L	bubble length characteristics
l	pore length
l	frequency of collision
L	ligand
l_k	Kolmogorov length scale
m	viscosity/reaction order
m_{AB}	reduced mass of the colliding molecules
m_i	Henry's constant of species i [(kmol/m^3)$_L$/(kmol/m^3)$_G$]
m_k	internal coordinate such as bubble diameter or length, m
m_s	solid shear viscosity
n	reaction order/turbulent viscosity/frequency of decomposition/number of reactants
N	impeller speed/rate of internal diffusion/Avogadro's number
N_j	minimum suspension velocity

Nu	Nusselt number
N_A	Avogadro number
n_e	number of eddies per unit volume
n_i	number of bubbles per unit volume
p	reaction order/pressure, Pa
P	product P or its concentration/probability factor or steric factor/power
P_c	probability of collision
P_{H_2}	partial pressures hydrogen
P_O	saturation vapor pressure/power number
P_s	effective solid pressure
Pr	Prandtl number
Q	product Q or its concentration/flow rate, m^3/s/molar concentrations of the species in solution/impeller discharge flow
q^*	relative diffusivity factor
Q_{a0}	internal heat of adsorption
q_{ie}	collision rate of bubbles with turbulent eddies
r	rate of reaction, subscript indicating specific reaction/product/radius of the particle, m
R	radius (m)/rate of reaction/universal gas constant
R_A	reaction rate constant for formation/consumption of A
Re	Reynolds number
Re_b	Reynolds number for bubble
Re_p	particle Reynolds number
s	factor for impeller/surface tension
S	source terms/degree of supersaturation
S_0	initial sticking probability
Sc_t	turbulent Schmidt number
S_{ie}	collision cross-sectional area
Sh	Sherwood number
Sc	Schmidt number
S_q	sticking coefficient
S_t	total surface area
T	local granular temperature tank diameter, m and temperature, K/temperature
t_d	time for diffusion
t_k	turbulent time scale
t_O	induction period
$\boldsymbol{U}$, U, u_G, u_L	superficial velocity, m/s
u_{pt}	particle terminal velocity (m/s)
V, V'	bubble volume, m^3

V_m	volume of adsorbate as monolayer
V_p	velocity of particle, m/s/geometric pellet volume
w	weight of the catalyst per unit reactor volume, kg/m^3/collision efficiency
w	weights
$\boldsymbol{X}$	position vector of dispersed phase
Z	collision frequency

Greek Letters in Notation

α	hold up
ξ_s	solid bulk viscosity
β	resolve later
ΔE	activation energy (kJ/Kmol)
$\Delta \Gamma$	Gibbs free energy
$\Delta \Gamma \nu$	Gibbs free energy change for nucleation
$\Delta \Gamma_\sigma$	interfacial energy
$\Delta \Gamma_\varpi$	free energy change
$\Delta H°$	heat of reaction, (kJ/kmol),
$\Delta S°$	standard change of enthalpy (at reference temperature) (kJ/kmol K)
$\Delta H°_A$	isoelectric heat of adsorption
D_o	initial dispersion
ϕ	bubble number density/Thiele modulus
η, η_c	catalyst effectiveness factor
λ	mean free path
θ	degree of surface coverage
μ	viscosity (Pa s)
ν	vibrational frequency/RPM/kinematic viscosity (Pa s m^3/kg)
σ_c	Constriction factor
τ	tortuosity factor
φ	Thiele modulus
φ_m	mass ratio of gas to liquid
φ^P	porosity of the pellet
Γ'	rate of diffusion
δ	film thickness (m)
ρ	density (kg/m^3)
n	hold up/energy (turbulent energy) dissipated per unit volume
σ	surface tension (N/m)

Subscripts

A	of component A
B	of component B

c	capillary/catalyst
C	continuous phase
col	collision
D	dispersed phase
E	of component E
g, G	gas phase
i	*i*th phase or species
j	*j*th tank or cell
js	just suspension
jsg	just suspension in presence of gas
k	*k*th phase
kin	kinetic
l, L	liquid phase
m	of component m
P	polymerization
p	particle
s	solid phase, solid surface/empirical factor for impeller
S	Suspension
t	turbulent
VG	volumetric flow rate in presence of gas

Preface

Fine and specialty chemicals are essential for everything we do in our daily lives. These chemicals cater to several key applications required for maintaining and enhancing our quality of life, and will become increasingly important. The fine and specialty chemicals sector is facing many challenges today for variety of reasons, such as fragmented capacity, relatively low capital and technology intensity, faster erosion of margins due to commoditization of products, the rising costs of raw materials and energy, and stricter environmental regulations. These challenges also offer new opportunities to innovate and create a competitive edge. Catalysis and catalytic processes are the keys for developing globally competitive and environmentally benign methods of converting natural resources into fine and speciality chemicals. Replacement of the stoichiometric reactions by the catalytic reactions, development and implementation of new catalyst systems and technologies to make the processes environmentally friendly, energy efficiency and being globally competitive are the needs of the hour.

With this background, we have started a large and ambitious program entitled Indus Magic (an acronym for innovate, develop and up-scale modular, agile, intensified and continuous processes; see www.indusmagic.org for more information). CSIR-National Chemical Laboratory (NCL), which is a premier research laboratory in the area of chemical and allied sciences in India, is the nodal laboratory for executing the Indus Magic program. CSIR-NCL interacts closely with the chemical industry in India and abroad and develops knowledge bases and intellectual property to address relevant problems of this industry. As part of the Indus Magic program, we work closely with the fine and specialty chemicals sector to identify industry needs. The industrial catalysis and catalytic processes was identified as one of the key needs and was incorporated as one of the major sub-programs of Indus Magic. We organized a workshop on industrial catalysis and catalytic processes as part of this work (see http://induscap.ncl.res.in for more information). The workshop brought together several experts on industrial catalysis from research institutes, academia, and industry. This book essentially originated from the Indus Cap workshop.

Catalysts (homogeneous or heterogeneous) reduce the activation energy barrier for transformations and facilitate better control on selectivity. Therefore, the development and

selection of the right catalyst can make a substantial impact on process viability and economics. Besides the right catalyst, it is also essential to develop an appropriate reactor type and process intensification strategies for effective translation of laboratory processes to practice. Harnessing the full potential of catalysis and catalytic processes for sustainably making fine and specialty chemicals requires coordinated efforts—especially through the dissemination of knowledge on the fundamentals and practices of industrial catalysis and catalytic processes. This book attempts to do this by focusing on fundamentals and applications of industrial catalysis and catalytic processes employed in the manufacturing of fine and specialty chemicals. It also highlights opportunities in existing technologies, as well as with industrial practices and real life case studies. An attempt is made to provide an appropriate blend of academic, research, and industrial-based information that is required for translating ideas into practice.

This book deals with specific aspects of catalysis and catalytic processes. Emphasis is given to key aspects, including catalyst synthesis and characterization, selection of reaction media, catalyst deactivation and regeneration, and catalytic reaction engineering. Application of catalysis to specific areas relevant to fine and specialty chemicals sectors are discussed. The material in this book has been arranged in two parts: fundamentals (Chapters 2–7), and applications (Chapters 8–16). An attempt is made to provide a holistic overview of catalysis, catalytic processes, and their implementation in manufacturing of fine and specialty chemicals. Chapter 1 provides an overview and introduction to catalysis and catalytic processes. Aspects covered in Part one (fundamentals) and Part two (applications) are briefly outlined here.

Part one of the book presents fundamentals of catalysis and reaction engineering. Key aspects of homogeneous and heterogeneous catalysis are discussed. The emphasis is on presenting the important, basic principles to industrial chemists and engineers. The basic principles are illustrated with the help of some of the industrially important reactions, such as hydrogenation, carbonylation, and hydroformylation. Aspects of kinetic modeling and of catalytic reactions are also discussed and illustrated with examples. The subject of selecting and designing reaction media is also included in this part (Chapter 6). The discussion includes catalysis in unusual reaction media, such as ionic liquids and supercritical fluids, as well as their applications to catalytic transformations. Important topics of catalyst synthesis and characterization, as well as catalyst deactivation and regeneration, are discussed in separate chapters (Chapters 4 and 5 respectively). Key aspects of catalytic reactions and reactor engineering are presented in Chapter 7.

Part two of the book brings out various applications of catalysis and catalytic processes in practice. Emphasis is on illustrating applications in manufacturing of API, perfumery, pesticides, and other fine and specialty chemicals. Chapters 8 and 9 provide broad discussions on the application of catalysis and catalytic processes to the fine and specialty chemicals sector. These include various important reactions, such as hydrogenation, oxidation, various coupling reactions, asymmetric hydrogenation, and rearrangement reactions. Use of ion exchange resins as

catalysts for manufacturing fine and specialty chemicals is discussed in Chapter 10. Various aspects, like reactor configurations, selection of resins, process integration, process separations, and the environmental impact of using resins as catalysts, are included. The next five chapters (Chapters 11–15) present catalysis in specific sectors, such as API manufacturing, perfumery, chemicals from renewable resources, carbonylations, hydroformylations and synthesis of carbamates. These chapters provide a brief account on historical developments of catalysis in respective applications, challenges and success stories, as well as its current status. Chapter 16 briefly discusses aspects of scale-up, illustrated by the examples of scaling up butylation and organotin compounds. The discussion in the part two is organized in such a manner so as to be useful to practicing chemists and engineers, as well as researchers working in these areas.

The last chapter (Chapter 17) summarizes the current status and outlines some thoughts on the path forward. We hope that this book will stimulate further work on this very important subject matter, from both industrial and scientific points of view.

Because the development of catalysis and catalytic process is a multi-disciplinary area, there is no single book that can cater to the needs of practicing chemical technologists, process development chemists, and research students working in this field. Here, we have attempted to provide information ranging from the selection of suitable catalysts, to the development of catalytic processes. This will be useful and relevant for applications to variety of chemistries used in fine and speciality chemicals sector. For beginners, this book will provide an overview of reaction engineering, industrial catalysis, catalysts synthesis, characterization, and the applications used in the industrial processes for fine and speciality chemicals. We hope that this book will be useful to anyone interested in industrial catalysis and catalytic processes; in particular to practicing engineers, process chemists, R&D managers, and chemistry and chemical engineering students working in catalysis area. All those involved in catalysis and catalytic process development can also use this book as a reference.

We would like to acknowledge many people who have made this book possible. First of all, we would like to thank all the contributors to this book. We are grateful to many of our students, associates, colleagues and collaborators with whom we worked on different research and industrial projects. We would also like to acknowledge financial support from CSIR for the Indus Magic (CSC123) project that allowed us to undertake our work on catalytic processes, and to develop this book. Many of our colleagues and students have contributed to this book in different ways. We also wish to thank the editorial team at Elsevier for their patience and understanding during the long process of developing this book.

Vivek V. Ranade and Sunil S. Joshi
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CHAPTER 1

Catalysis and Catalytic Processes

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1.1 Introduction

Chemical and allied industries manufacture products that are essential for creating and sustaining modern societies. The chemical (and biological) transformations necessary to make these essential products often involve the use of catalysts. The catalyst (which can be either homogeneous or heterogeneous) provides a reduced activation energy barrier to transformations and facilitates better control on selectivity. The development and selection of the right catalyst, therefore, can make a substantial impact on process viability and economics. Besides the right catalyst, it is essential to develop the right reactor type and process intensification strategies for effective translation of the laboratory process to practice.

With strict environmental regulations, rising raw material prices, depleting feedstocks, and a call for green chemistry as driving forces, the chemical industry faces a larger challenge with both opportunities and risks. Catalysis is of paramount importance in the chemical industry due to its direct involvement in the production of 80% of industrially important chemicals. Catalysts are involved in more than $10 trillion in goods and services of the global gross domestic product (GDP) annually. It is estimated that the global demand on catalysts is more than $30 billion, and a very robust growth is projected in the future. There is an urgent need to develop cost-effective and environmentally benign methods of converting natural resources into fine and specialty chemicals using highly efficient catalysts and employing cleaner methodologies. The advancements in catalysis and applications to the chemical industry are very significant and are responsible for cleaner processes. Replacement of the stoichiometric reactions by catalytic reactions and application of new catalyst systems and technologies to make the processes environmentally friendly, energy efficient, and globally competitive are current needs.

A catalyst is a substance that provides an alternative route of reaction where the activation energy is lowered. Catalysts don't affect the chemical equilibrium associated with a reaction; they merely change the rates of reactions. Catalysts are classified in a variety of different ways. The commonly used classification by reaction engineers is based on number of phases, such as

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- homogenous catalysis (catalyst and substrate in same phase) or
- heterogeneous catalysis (solid catalyst and substrate is a gas and/or liquid)

Basic concepts of catalysis are briefly introduced in the following section.

It is important to combine the understanding of catalysis with key reaction engineering expertise to translate the potential of a catalyst in the form of a practically implemented catalytic process or plant. Any catalytic reactor has to carry out several functions like bringing reactants into intimate contact with the active sites on a catalyst (to allow chemical reactions to occur), providing an appropriate environment (temperature and concentration fields) for adequate time, and allowing for removal of products. A reactor engineer has to ensure that the evolved reactor hardware and operating protocol satisfy various process demands without compromising safety, the environment, and economics. Naturally, successful reactor engineering requires bringing together better chemistry [thermodynamics, catalysis (replace reagent-based processes), improved solvents (supercritical media, ionic liquids), improved atom efficiency, waste prevention — leave no waste to treat] and better engineering (fluid dynamics, mixing and heat and mass transfer, new ways of process intensification, computational models, and real-time process monitoring and control). Some of these aspects are briefly discussed in Section 1.3. Organization of this book is outlined in the last section of the chapter.

1.2 Catalysts and Catalytic Reactions

The word *catalyst* was first used in 1835. Over the years, it has been established that a catalyst influences kinetics of a process without undergoing any change itself. A catalyst does not alter the thermodynamics of a reaction. In simple words, a catalyst alters the route without altering the destination (see Fig. 1.1). Here the route is the metaphor for activation energy — minimum energy input for a chemical system to undergo a chemical reaction and the transition state of a chemical reaction.

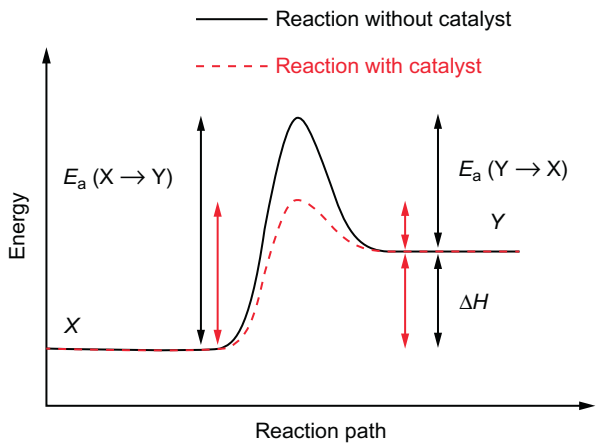


Fig. 1.1
A catalyst allows reaction to proceed through an alternative path.

The terms that are often used in the context of catalytic activity are turnover number (TON), to define the productivity of a catalyst, and turnover frequency (TOF), to define the catalyst activity or TON per unit time.

The TOF is defined in terms of active catalytic centers, such as

$$\text{TOF} = \frac{\text{volumetric rate of reaction}}{\text{number of centers/volume}} = \frac{\text{moles}}{\text{volume} \cdot \text{time}} \frac{\text{volume}}{\text{moles}} = \text{time}^{-1}$$

TOF may be in a range of 10^{-2} to 10^{2} for industrial applications.

The TON is defined as a measure of capacity of the catalyst for accelerating the reaction such as

$$\text{TON} = \text{TOF} \times \text{Lifetime of a catalyst}$$

Typically TON is in the range of 10^{6} to 10^{7} for industrial applications.

The role of a catalyst becomes even more important when multiple reactions are thermodynamically feasible. In such cases, an appropriate catalyst manipulates the reaction rates in such a way that selectivity toward a desired product increases. Several factors and parameters influence the overall performance of a catalyst. The selection of a catalyst for an industrial process therefore depends on the role it is supposed to play. The effect of a catalyst on kinetics of the reaction needs to be understood in detail to get an insight about the surface chemistry involved that would help in the design of a specific catalysis. It is therefore important to understand the elementary steps through which a catalyst influences overall performance.

Homogeneous catalysts typically form a complex with one of the reactants, which eventually transforms it into the product after interacting with other reactants. The process is essentially similar to homogeneous reactions in the absence of a catalyst and is often controlled by mixing reactants and a catalyst species on a molecular level. In contrast to this, in a heterogeneous catalyst, several additional steps are involved along with reaction occurring on the catalyst surface, such as

- external diffusion toward a catalyst pellet
- internal diffusion toward a catalyst surface
- molecular adsorption on a catalyst surface
- surface reaction
- desorption from a catalyst surface
- internal diffusion away from the catalyst surface
- external diffusion away from the catalyst pellet

These steps need to be understood to select an appropriate reactor and operating strategy. This procedure will be discussed later in this book.

Heterogeneous catalysis allows easy separation and reuse of a catalyst. An example of heterogeneous catalysis is Haber's process, where iron powder is used as a catalyst to enable the

conversion of nitrogen and hydrogen gas to ammonia. A heterogeneous catalyst has "active sites," which are the centers of reaction. Once adsorbed (either physically or chemically), the substrate undergoes a reaction, and the product is desorbed subsequently, rendering the surface of the catalyst free for further activity. Homogeneous catalysis has the inherent disadvantage of lack of ease of separation of product and catalyst after the reaction. Esterification of acetic acid with methanol to give methyl acetate in the presence of an H^+ ion is a very common example of homogeneous catalysis. Significant work is also being actively pursued to develop a "heterogenized" homogeneous catalyst that uses solids as supports for anchoring of the homogeneous catalysts. This would make it technically heterogeneous, but it would retain the characteristic reactivity pattern of a homogeneous catalyst. One example of such heterogenized homogeneous catalyst is silica-supported sulfuric acid.

Besides the classical catalysts mentioned earlier, several other catalytic processes have been developed, which include biocatalysis (using enzymes), photocatalysis (acceleration of photoreaction using a catalyst), and electrocatalysis (acceleration of electrochemical (half) reactions). Enzymes are being increasingly used as catalysts for a variety of chemical transformations, including conversion of organic wastes to useful chemicals. Significant efforts are being made to develop the next generation of electrocatalysts for fuel cell applications or for converting carbon dioxide into a variety of useful chemicals. Without getting into the details of catalysts and catalytic processes, it will be useful to discuss the key properties of a catalyst here.

1.2.1 Characteristics of Catalysts

Catalytic substances have a tendency to form complexes. A large number of substances that have been observed to show catalytic properties are from the VIII Group and IB Group of the periodic table (which have unpaired *d* electrons). Another interesting property of catalytic materials is the small energy differences between valence shells, which lead to a number of oxidation states.

The characteristics of a catalyst may be defined by *activity*, *selectivity*, *stability*, and *accessibility*. All four terms refer to the favorability of a catalyst to form a product. Activity is generally found to increase with temperature. All the other three are trade-offs with activity and depend on a specific reaction. Ideally a catalyst should undergo the same catalytic cycle multiple times without a reduction in its ability to influence the reaction. The number of times a catalyst converts a substrate to product is measured in terms of TON.

Selectivity of the catalyst is characterized in following different ways:

- *Chemo selectivity* is when a catalyst favors reaction with one substrate in a reaction mixture over another. For example, an oxidizing agent may favor the oxidation of an aldehyde group over a hydroxyl group present on the same moiety.
- *Regioselectivity* is when a catalyst favors the synthesis of a product based on the position it acquires in the substrate. For example, a formyl group can be attached to either the primary,

terminal carbon atom or the secondary, internal carbon atom, leading, respectively, to the linear and the branched product in hydroformylation.
- *Diastereoselectivity* is a phenomena wherein a catalyst may direct a substrate selectively favoring formation of one stereomer over another if a substrate has stereogenic centers.
- *Enantioselectivity* refers to the catalyst favoring synthesis of one enantiomer of product over another, even when the substrate itself is achiral.

Morphology and material strength are important characteristics for heterogeneous catalysts. They are manufactured in a variety of morphology like pellets, trilobes, and extrudates. The overall pressure drop and effectiveness of the catalyst depends on size and shape of the heterogeneous catalyst. Resistance to crushing, attrition, and abrasion are also important characteristics that need to be understood in case of solid or solid supported catalysts.

Thermal characteristics and the range of temperature for which the activity would be the highest without compromising on the selectivity is an important factor in the selection of a catalyst for the desired process.

The catalyst characteristics need to be appropriately accounted for (including activation as well as deactivation of catalyst) while designing a suitable reactor for carrying out catalytic reactions in practice. Before discussing some aspects of practical reaction and reactor engineering, key aspects of homogeneous and heterogeneous catalysts are briefly discussed in the following sections.

1.2.2 Homogeneous Catalysts

Many industrial processes have been developed using homogeneous catalysts. It is being employed in oxidation, carbonylation, hydroformylation, oligomerization, polymerization, hydrocyanation, and synthesis of fine chemicals, among other processes (Hagen [23]). Some other homogenously catalyzed reactions include ester hydrolysis, Diels-Alder reaction, Cannizzaro reaction, and enzymatic processes.

As mentioned earlier, catalytic processes that occur in the same phase as the reaction medium are termed homogeneous catalytic processes. The applicability of a homogeneous reaction mixture has been known for several centuries, such as for fermentation process. Charles Bernard Desormes and Nicolas Clement were arguably the first researchers to make an attempt to postulate a rational theory for catalysis or the intermediate compound theory [1] to explain the homogeneous catalytic effect of nitrogen oxides for the manufacture of sulfuric acid using the lead chamber process. These catalysts may be metal complexes or common reagents such as mineral acids, and they can be uniformly distributed in the bulk reaction mixture. Because in a homogenous catalyst system each molecule of the catalyst is distributed in the reaction mixture, it would mean more active sites are available to interact with the substrate. Hence, these reactions proceed at milder conditions and lower catalyst concentration. Another advantage of homogeneous catalysts is the ease of understanding the catalytic chemistry because the mechanism of the reaction is only dependent on the kinetics and not on the diffusion rates.

Homogeneous catalysts used in industrial chemistry are generally from organometallic compounds (compounds with a metal-carbon bond). The central metal atom is bound to organic and inorganic ligands. The catalyst environment can be easily modified to alter the catalytic properties by manipulating ligands. Transition metals play a major role in the development of these organometallic complexes. This is because of the availability of *d*-orbitals of transition metals, which allow ligands to bond in such a way that they are available for further reaction. Rhodium phosphine-based metal complexes such as $[RhCl(PPh_3)_3]$ have been found to be an effective catalyst for the hydrogenation of olefins. On account of the stability of transition metal complexes, the process temperatures are generally limited to 200°C, and this becomes a limitation of homogeneous catalysis. Because the catalyst is completely dispersed in the reaction media, these systems face difficulties in separation or recovery of catalysts.

Significant efforts have been and are being spent on deciphering mechanisms of homogeneous catalysis to facilitate further development of new catalyst systems. Tolman [2] proposed a mechanism with which a reaction is catalyzed by homogenous organometallic complexes, which was referred to as the 16 or 18 electron rule (see Fig. 1.2). It postulates the role of the oxidation state and coordination number of the metal center of the transition metal complex. The organometallic complexes referred to are the transition metal complexes with CO, N_2, CN^-, RNC, PR_3, π-aryl, π-allyl, $-SiR_3$, and π-acyl ligands, which have high ligand field strength and covalent bonding. The two major postulates of the rule are as follows [2]:

- Diamagnetic organometallic complexes of transition metals exist in any measurable quantity only if the valence shell of central metal contains 16 or 18 electrons.
- The intermediates that are formed during the course of the reaction should also contain 16 or 18 valence shell electrons.

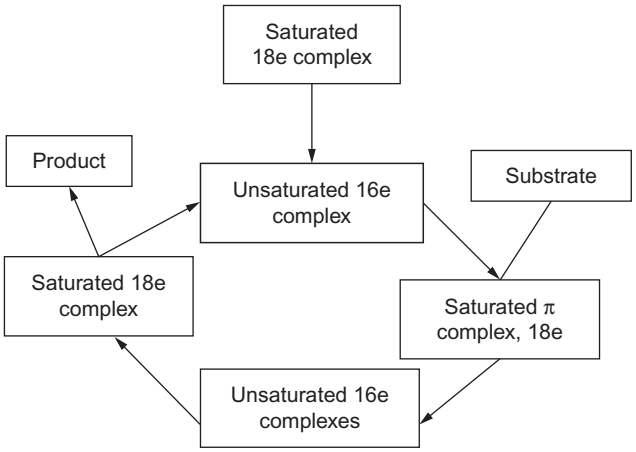


Fig. 1.2
Cycle explaining the 16/18 electron rule.

To understand the catalytic cycle in homogeneous catalysis, a stoichiometric reaction with well-defined transition metal complexes can be used to elucidate the steps involved. Labeled compounds can also be used to validate the postulated reaction mechanism by employing spectroscopic identification techniques. Various in situ spectroscopy techniques such as infrared spectroscopy (IR), nuclear magnetic resonance (NMR), electron spin resonance (ESR), and Raman are very helpful in developing a better understanding of homogeneous catalysis. It has been observed that Infrared spectroscopy has been very useful in studying carbonyl complexes.

1.2.3 Heterogeneous Catalysts

The use of heterogeneous catalysts in the chemical industry began in the early 1800s with Faraday being among the pioneers of heterogeneous catalysis and discovering the use of platinum for oxidation. These systems were in use during the Second World War for reactions such as dehydrogenation of methyl cyclohexane to form toluene in the presence of Pt-Al_2O_3 or in alkane isomerization using Cr_2O_3-Al_2O_3. After the war, with diversification in chemicals synthesized and advancement of technology, heterogeneous catalysts were used for the hydrocracking of high-boiling petroleum using Ni-aluminosilicate to form fuels. This revolutionized the automobile industry. Another application of solid catalysts was in the synthesis of polyethylene from ethylene by polymerization in the presence of Ziegler-Natta ($TiCl_4$-$Al(C_2H_5)_3$) catalysts. Heterogeneous catalysts are used for innumerable reactions such as oxidation, nitration, coupling, condensation, and hydrogenation.

Heterogeneous catalysis facilitates a large number of chemical reactions. The use of heterogeneous catalysts in fine chemicals is gaining importance because of the following reasons [3]:

- Because the catalyst is not in the same phase as the reacting molecules, it allows for a higher possibility of catalyst recovery and recyclability. Chemical bonds are formed with the catalyst either through physisorption or chemisorption during the reaction and broken thereafter to regenerate the catalyst, albeit with loss of activity in some cases [4].
- Solid acid catalysts are easier to handle in comparison with conventional mineral acids such as H_2SO_4 and hydrofluoric acid (HF). They reduce capital cost and also ensure material safety because they have less corrosivity.
- Heterogeneous catalysts for bulk chemicals have been used since the beginning of chemical industries, hence the processes and their roles in the mechanism of the organic synthesis are well understood in most cases. Therefore they can be downscaled for their applications in fine chemicals to some extent.
- Myriad catalysts with acidic or basic properties exist or have been designed to synthesize particular species, which ensures product maximization. Mixed metal oxide, clays, zeolites, silica, alumina, zirconia, and heteropolyacids are a few classes of catalysts

used predominantly. They can be modified to a large extent through impregnation of homogeneous catalysts or metals and structural changes.
- Microporous and mesoporous structures or sieves and honeycomb-like structures allow heterogeneous catalysts to be highly shape and stereo selective. These designs give enzyme-like efficiency to the catalyst.

A new stage of development in heterogeneous catalysts came with the objective of using renewable feedstocks and environmentally benign processes and techniques for downstream waste reduction. Catalysts that have high efficiency and better surface properties are being developed for process intensification [5].

A catalyst facilitates reaction through the formation of complexes with reacting species. The product formed doesn't have the tendency to bond with the catalyst, which implies the catalyst surface is regenerated. However, this is only partially correct. The surface and structure of the catalyst are modified with each reaction. For instance, in the case of a pure metal catalyst, surface roughness and crystallinity change, whereas in the case of metal oxides there is a change in the ratio of metal and oxygen. Commercial catalysts are generally available in various physical forms such as powder, pellets, granules, and extrudates. Pore size plays a major role in structure and therefore in catalytic performance (conversion, selectivity, yield, TOF, and TON). Porous catalysts offer a large surface area, the ability to support varied chemical functionalities, and the ability to form different networks according to the applications. Broadly catalysts are classified into three kinds of porous materials:

- Microporous: Pore diameter is less than 2 nm. A typical example of a microporous catalyst is zeolite. It has a crystalline and well-defined structure. It has a silicon, aluminum, and oxygen framework, and water or another cation may be present in the pores. Activated carbon is also microporous adsorbent and has varying origins, thermal resistance, and porosity, depending on the method of synthesis.
- Mesoporous: Pore diameter is between 2 and 50 nm. Mesoporous solids are synthesized through a templating approach, wherein surfactants are used for directing the structure. Subsequently, the surfactant is removed, and a mesoporous system is obtained that replicates the surfactant assembly [6].
- Macroporous: Pore diameter is greater than 50 nm. Macroporous material can be synthesized by a sol-gel method such as porous silica, alumina, and zirconia gels. In the case of zirconia gels, a metal salt precursor is used for the epoxide mediated sol-gel method followed by phase separation. Morphology of the catalyst would be governed by temperature and amount of solvents or reactants used [7].

Activity is the rate at which a reaction proceeds in presence of a catalyst. The activity of the heterogeneous catalyst depends on the reaction conditions of temperature, pressure, and catalyst loading with respect to reactants and on reactor conditions such as flow rate and surface area of reactor. Another characteristic of a catalyst is selectivity, which is the extent

to which a catalyst promotes synthesis of the desired product over all the possible products, including those with lower free energy. (Note: in a reaction without the selective catalyst, only products with lowest free energy would have been formed.) Selectivity is dependent on time, temperature, and other reaction parameters.

Among the most commonly used metals for heterogeneous catalysts are transition metals like platinum, rhodium, nickel, ruthenium, palladium, cobalt, magnesium, vanadium, and iron, among others [8].

Another important aspect of the catalyst is possible catalyst deactivation. The most typical causes of deactivation of heterogeneous catalyst are the following:

- Aging/thermal degradation: deactivation resulting from changes in structure.
- Sintering: an increase in the average size of the crystallites due to coalescence of small particles on continued usage of catalyst.
- Fouling/coking: deposition of high-molecular-weight "carbon-hydrogen" compounds or primary carbons on the catalyst surface.
- Poisoning: inhibitory substances bind strongly to the active catalytic sites on the surface.

Catalytically active complex in homogeneous catalysis may similarly be deactivated due to structural changes in the active complex as well as poisoning because of binding with inhibitory substances. The reasons for possible deactivation need to be understood to develop appropriate regeneration strategies.

To prevent deactivation, "promoters" may be added such as in the case of ammonia synthesis, where aluminum oxide is added along with iron to prevent fusion of the particles.

Catalyst characterization plays an important role in understanding and improving overall performance of catalytic processes. A substrate may be either physically adsorbed (physisorption) or chemically adsorbed (chemisorption) on the surface of a heterogeneous catalyst. The difference between the two phenomena needs to be explicitly understood. Although there are no bonds formed in physisorption, only weak van der Waals forces are responsible for keeping the substrate on the catalyst surface. In chemisorption, there is electron transfer and formation of strong bonds between catalyst and substrate. This renders chemisorption to be a more selective process and leads to the formation of a single layer on the surface unlike in physisorption, where multiple layers may be formed with each adsorbed molecule of the first layer acting as a site for the next [9]. The commonly available techniques of characterization of catalysts with most researchers are TEM (transmission electron microscopy), XRD (X-ray diffraction), and EXAFS (extended X-ray absorption fine structure). More details of characterization are discussed later in the book. With the characterization and properties of the catalyst known, specific catalysts may be designed for the required process. It is important to remember that test conditions are not the same as the reaction conditions, thus there might be some variation in the properties of the catalysts. Besides this,

several other factors related to reaction and reactor engineering need to be taken into account while translating the catalytic process into practice. These aspects are briefly outlined in the following section (and are discussed later in Chapter 7).

1.3 Reaction and Reactor Engineering

Reaction and reactor engineering involves establishing a relationship between reactor hardware and operating protocols with various performance issues as listed in Table 1.1.

Table 1.1 Reaction and reactor engineering

Reactor Performance		Hardware and Operating Protocol
Conversion and selectivity Product quality Catalyst activity and life Stability and operability Safety Environmental impact	⟺	Reactor configuration: size and shape, feed and exit nozzles Mode of operation: batch, semibatch, continuous Start-up and shutdown protocols Operating conditions: flow rate, pressure, temperature, flow regimen, RTD Reactor internals: baffles, heat transfer coils, distributors

A process engineer is faced with a host of questions while establishing a relationship between reactor hardware, operating protocol, and reactor performance. In this section, some of these questions and the relevant tasks of a reactor engineer are discussed briefly. The major questions being faced by a reactor engineer can be grouped into three classes:

- What chemical transformations are expected to occur?
- How fast will these changes occur?
- What is the best way to carry out these transformations?

The first question is in the realm of thermodynamics and chemistry. Knowledge of chemistry and reaction mechanism is helpful to identify various possible chemical reactions. Thermodynamics provides models and tools to estimate free energies and the heat of formations of chemical compounds from which the energetics of all the possible chemical reactions can be examined. These tools help a reactor engineer to identify thermodynamically more favorable operating conditions. More information on these topics can be found in chemical engineering thermodynamics textbooks [10,11]. The second question of estimating how fast the thermodynamically possible chemical transformations will occur involves a knowledge of chemistry, reaction kinetics, and various transport processes like mixing, heat, and mass transfer. Analysis of the transport processes and their interaction with chemical reactions can be quite difficult and is intimately connected to the underlying fluid dynamics. Such a combined analysis of chemical and physical processes constitutes the core of chemical reaction engineering.

The first step in any reaction engineering analysis is formulating a mathematical framework to describe the rate (and mechanism) by which one chemical species is converted into another in the absence of any transport limitations (chemical kinetics). The rate is the mass, in moles of a species, transformed per unit time, whereas the mechanism is the sequence of individual chemical events, whose overall result produces the observed transformation. Although the knowledge of mechanism is not necessary for reaction engineering, it is of great value in generalizing and systematizing the reaction kinetics. The knowledge of rate of transformation, however, is essential for any reaction engineering activity. The rate of transforming one chemical species into another cannot be predicted with accuracy. It is a specific quantity that must be determined from experimental measurements.

Measuring the rate of chemical reactions in the laboratory is itself a specialized branch of science and engineering. The rate is formally defined as the change in moles of a component per unit time and per unit volume of reaction mixture. It is important that this rate be an intrinsic property of a given chemical system and not a function of any physical process such as mixing or heat and mass transfer. Thus, the rate must be a local or point value referring to a differential volume of reaction mixture around that point. It is, therefore, essential to separate the effects of physical processes from the measured experimental data to extract the information about the intrinsic reaction kinetics. It is a difficult task. More information about chemical kinetics and laboratory reactors used for obtaining intrinsic kinetics can be found in textbooks like Smith [12], Levenspiel [13], and Doraiswamy and Sharma [14]. Assuming that such intrinsic rate data is available, chemical kineticists have developed a number of valuable generalizations for formulating rate expressions, including those for catalytic reactions. Various textbooks cover aspects of chemical kinetics in detail [12,13,15].

Once the intrinsic kinetics is available, the production rate and composition of the products can be related, in principle, to the reactor volume, reactor configuration, and mode of operation. This is the central task of a reaction and reactor engineering activity. The first step of reactor engineering is to select a suitable reactor type. In catalytic reactors, multiple phases are almost always involved (see examples cited in Refs. [14,16–19]). Several types of reactors are used for such catalytic and multiphase applications. Broadly, these reactors may be classified based on presence of phases, such as

- gas-liquid reactors: stirred reactors, bubble column reactors, packed columns, and loop reactors;
- gas-liquid-solids reactors: stirred slurry reactors, three-phase fluidized bed reactors (bubble column slurry reactors), packed bubble column reactors, trickle bed reactors, and loop reactors; or
- gas-solid reactors: fluidized bed reactors, fixed bed reactors, and moving bed reactors.

Existence of multiple phases opens up a variety of choices in bringing these phases together to react. Krishna and Sie [20] have discussed a three-level approach for reactor design and selection:

- Strategy level I: catalyst design strategy
  - gas-solid systems: catalyst particle size, shape, porous structure, and distribution of active material
  - gas-liquid systems: choice of gas-dispersed or liquid-dispersed systems, ratio between liquid-phase bulk volume and liquid-phase diffusion layer volume
- Strategy level II: injection and dispersion strategies
  - reactant and energy injection: batch, continuous, pulsed, staged
  - state of mixedness of concentrations and temperature
  - separation of product or energy in situ
  - contacting flow pattern: co-, counter-, or cross-current
- Strategy level III: choice of hydrodynamic flow regimen
  - packed bed, bubbly flow, churn-turbulent regimen, dense-phase, or dilute-phase riser transport

Besides these considerations for selecting an appropriate reactor and mode of operation, several other factors need to be considered while designing a catalytic reactor. Some of the key issues are the following:

- Understanding gas-liquid and liquid-solid transport processes: mass and heat transfer across multiple phases play a crucial role in determining the performance of multiphase catalytic reactors. Ramchandran and Chaudhari [18] have elucidated these points very well in their classic book on three-phase catalytic reactors, and interested readers should consult the original book.
- Understanding intraparticle transport processes: mass and heat transfer effects are important even on a catalyst particle scale. Most of the catalysts are porous, and therefore species and heat transport within the pores of catalyst particles control concentration and temperature profiles within the catalyst particle (and therefore conversion and selectivity). There are several ways by which effective Thiele modulus is defined to account for different shapes of catalyst pellets and different reaction orders. Interested readers may consult Levenspiel [21].
- Compensating inhibition/deactivation of catalyst: various possible reasons for catalyst deactivation were mentioned earlier. Catalyst activity may be reduced due to deposition of inhibitors on active sites. Inhibitors may be consumed in reactions unlike catalysts. The most commonly used strategies with which one may compensate for reduced activity of catalyst are by reducing flow rate or increasing temperature to maintain conversion at the design level.
- Manipulate selectivity of desired product: several strategies for enhancing selectivity of desired products have been proposed by the classical chemical reaction engineering (CRE) approach. These include manipulation of operating temperature or temperature profile across the reactor according to difference in activation energies of competing reactions (use high temperature if activation energy of reaction producing desired product is higher than

reactions producing by-products). Several possible ways of enhancing selectivity by manipulating pore sizes of catalyst are discussed by Worstell [22] and may be followed.

For translating this understanding into practice, more often than not, key obstacles are lack of knowledge on how flow-patterns and contacting influence process performance and how these change with the reactor scale. It is impossible to provide detailed quantitative treatment to issues discussed earlier in this chapter. More detailed treatment of reaction and reactor engineering is provided in Chapter 7.

1.4 Organization of This Book

The book is aimed at providing a comprehensive methodology and state-of-the-art tools for industrial catalysis. The intended audience of the book is chemical engineers, process development chemists, and technologists working in chemical industries and industrial research laboratories as well as research students working in the area of industrial catalysis and catalytic processes. This book will be an important source for researchers and scientists working in the chemical industry involved in developing improved catalysts and catalytic processes.

This introductory chapter introduces readers to the interesting, challenging, and important field of catalysis and catalytic processes. Part I covers fundamentals of catalysis and catalytic reaction engineering. Part II covers important industrial applications of catalysis and catalytic processes. The epilog recaptures the key points and the lessons learned from our experience of applying the material discussed in this book for addressing practical process engineering problems. The potential benefits of catalytic processes and the probable pitfalls are reemphasized. Some comments on future trends in catalysis and catalytic processes are included.

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CHAPTER 2

Fundamentals of Homogeneous Catalysis

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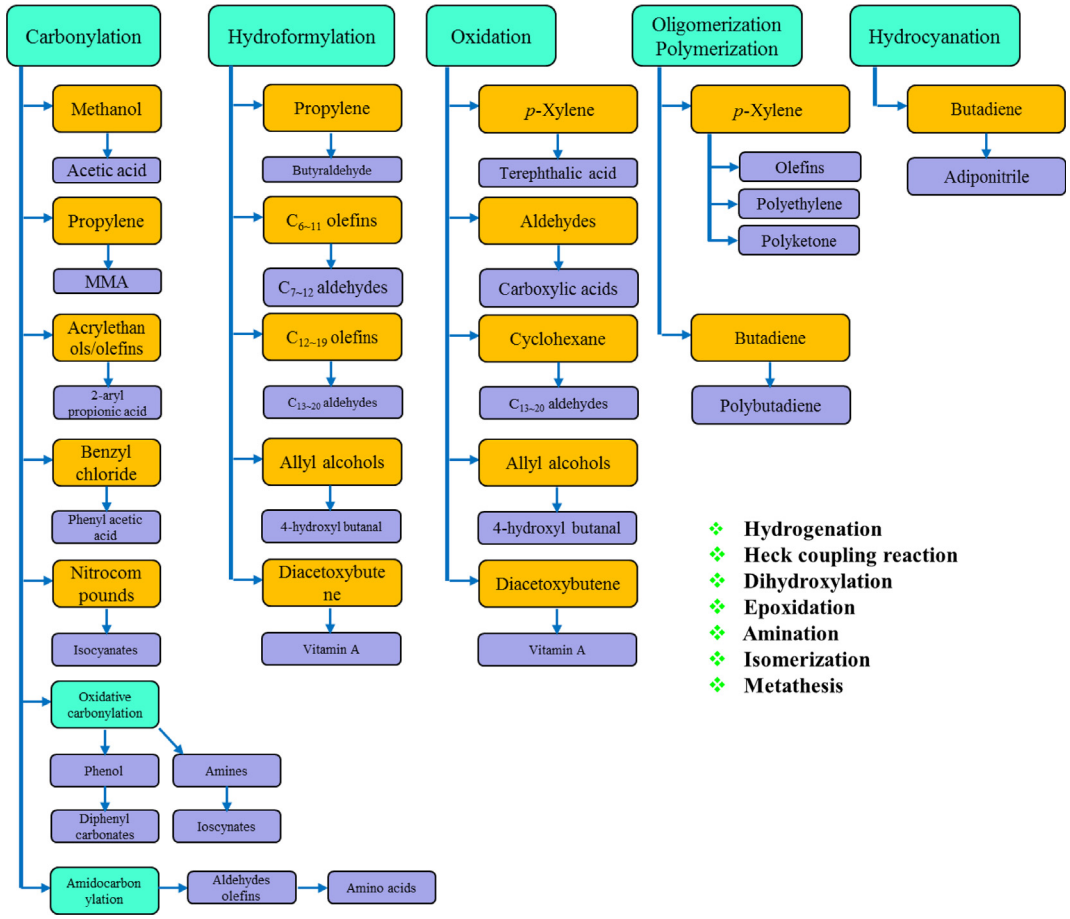
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2.1 Introduction

Catalysis has made a significant impact on the growth of the chemical and petroleum industries to fulfill economic, political, and environmental demands. Initial success in the development of petroleum refinery and petrochemicals was rapidly followed by applications in pollution control processes. Today, more than 60% of chemical products and 90% of chemical processes are based on catalysis. The resources, performance, and cost of catalysts determine the commercial viability of most chemical processes, and hence, the demand for continuous development and discoveries of catalysts and catalytic processes is also growing. Catalysts are generally classified as either "heterogeneous" or "homogeneous," depending on the form in which they are employed in the process. For practical reasons, heterogeneous catalysts have been more widely used in industry despite several fundamental shortcomings. Homogeneous catalysts, on the other hand, have some unique features by which they are able to activate several abundantly available and cheaper feedstocks such as CO, H_2, olefins, and alcohols at milder conditions leading to discoveries of processes involving hydroformylation, carbonylation, metathesis, oxidation, epoxidation, C-C coupling, oligomerization, and polymerization. A summary of homogeneous catalytic reactions in practice is presented in Table 2.1. Homogeneous catalysis using soluble metal complexes or metal salts as catalysts are known for synthesis of chemical products with different functional groups with high activity and selectivity at milder reaction conditions. Thus, homogeneous catalysis has contributed its own share to the development of the chemical industry. The advances in coordination chemistry have facilitated the fundamental understanding of the mechanism of these reactions on a molecular level [1,2]. Homogeneous catalysts are unique due to their high activity and selectivity in asymmetric catalysis for chiral molecules and emerging applications in carbonylation, hydroformylation, and epoxidation reactions for commodity as well as specialty products [3–6]. In this chapter, recent advances in fundamentals of homogeneous catalysis are reviewed with a focus on basic concepts and examples to illustrate recent advances in catalysis, reaction pathways, kinetics modeling, and reaction engineering aspects, which will be valuable to understanding the overall performance of a catalyst and process.

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Table 2.1 Example of homogeneous catalysis in practice



2.2 Distinguishing Features of Homogeneous Catalysts

The homogeneous catalysts employed in practice cover the following types: soluble nonmetallic acids and bases, metal salts, organometallic complexes with monodentate or bidentate ligands, nonaqueous ionic liquids (NAILs), metal clusters, and enzymes. These are molecularly dispersed in the same phase (liquid) as the reactants and have less interfacial barriers compared to heterogeneous catalysts. Some specific advantages are (a) feasibility at milder operating conditions facilitating wider applicability to reactants, including some thermally sensitive and nonvolatile reactants involved in specialty products; (b) higher activity and selectivity as a result of low temperature and ease of access to catalytic sites; (c) can be tailored to give high regio- and stereoselectivity useful in synthesis of optically active products;

(d) unequivocally characterized and can be synthesized in a well-defined and reproducible way; (e) heat and mass transfer resistances can be easily eliminated, leading to better control of temperature at catalytic sites due to higher heat capacity and efficient heat transfer in the liquid phase unlike heterogeneous catalysis in which hot spot formation is a major problem; (f) the ability to activate substrates such as hydrogen, carbon monoxide (CO), oxygen, and olefins at milder operating conditions; and (g) better understanding of the nature of active species, catalytic reaction pathways, and reaction mechanism. Despite these attractive features, applications of homogeneous catalysts have been limited due to (a) difficulties in industrial-scale separation of the products from the catalyst and its effective reuse for economic viability; (b) most promising reactions employ expensive catalysts consisting of noble metal complexes, the recovery, recycle, and reuse processes for which are also highly expensive; and (c) sensitivity of the catalysts to trace impurities and thermal stability, leading to catalyst deactivation and posing difficulties in handling. The past 2–3 decades have witnessed a large number of discoveries using homogeneous catalysis, but only a few of these have transformed to industrial scale. Therefore, it is not surprising that most of the successful homogeneous catalytic processes are those in which the products are volatile and separable by distillation without affecting the catalyst. In other cases, energy intensive separation steps are involved that play a crucial role in process economics and viability. To overcome the problems associated with separation of catalysts and reuse, extensive research efforts have been made on "heterogenizing" the homogeneous catalysts leading to development of several new concepts. These catalysts combine the advantages of homogeneous catalysts such as well-defined molecular species and mild conditions with ease of separation of heterogeneous catalysts (solid or liquid). This approach will expand the use of homogeneous catalysts to wider applications, including those for fine chemicals, pharmaceuticals, and specialty products. However, compared to the large number of innovative chemical transformations and catalysts discovered on a laboratory scale, a very small fraction has been used in industry due to difficulties in recycling, product separation, sensitivity of catalysts to trace impurities, and possible catalyst deactivation.

2.3 Basic Concepts in Homogeneous Catalysis

It is generally understood that a catalyst "accelerates" a chemical reaction, and the fundamental understanding of the role of catalysis depends on the elementary interactions among the reactants and catalyst precursors or the active species formed during the reactions. In most homogeneous catalysts, co-catalysts, ligands, and promoters are involved which also participate in stoichiometric interactions in such a way that the catalyst/co-catalyst/promoters are regenerated during a catalytic cycle while transforming the reactants to the products. Let us consider a reaction of components A and B to give products P and Q in the presence of a catalyst C:

$$A + B \rightleftarrows P + Q \tag{2.1}$$

Thermodynamic considerations tell us that the difference in the free energy of the reactants and the products $\triangle G$ should be negative for the reaction to be feasible [7,8]. Similarly, if the reaction equilibrium constant, $K_e (= \exp(-\triangle G/RT) \gg 1$, the equilibrium of reaction (2.1) lies essentially to the right side, and forward reaction is favorable. The presence of a catalyst does not change the reaction equilibrium but accelerates the rate at which equilibrium is attained. The catalyst alters the reaction pathway in such a way that the free energy of activation is reduced significantly compared to the uncatalyzed reaction, whereas the overall change in the free energy of the reaction equals that of an uncatalyzed reaction. This is shown schematically in Fig. 2.1. The role of catalysts and reaction pathways would also depend on the type of catalyst used, which can be illustrated for homogeneous transition metal complex catalysts. Some key concepts and examples are discussed next.

2.3.1 Elementary Steps in Homogeneous Catalysis

Homogeneous transition metal complex catalysts generally involve a metal and a ligand with or without a promoter. Some examples are $RhCl(PPh_3)_3$, Wilkinson catalyst for hydrogenation of olefins; $HRh(CO)(PPh_3)_3$, for hydroformylation of olefins; $[Rh(CO)_2I_2]^-$/HI, for carbonylation of methanol; $Co(OAc)_2/Co(OAc)_2$/HBr, for oxidation of *p*-xylene; Pd(pyca)(PPh_3)(OTs)/TsOH/LiCl, for carbonylation of aryl alcohols/olefins; and *Rh*(1)*R*, *RDIPAMP*, for asymmetric hydrogenation of olefins (L-dopa). The elementary steps in a catalytic cycle can be broadly described as: (a) conversion of a catalyst precursor complex to an active form either by ligand dissociation or interaction with a co-catalyst or promoter, (b) activation of reactant A by the active complex, (c) activation of reactant B by the product of step b, and (d) intramolecular reaction in coordination sphere followed by reductive elimination to form a product and regenerate the catalyst in original active form. The feasibility of these steps would depend on some concepts established in coordination chemistry of transition metals, thermodynamics, and kinetics of elementary steps. Some distinguishing features of transition metals relevant to catalysis are: (a) transition metal elements distinguish

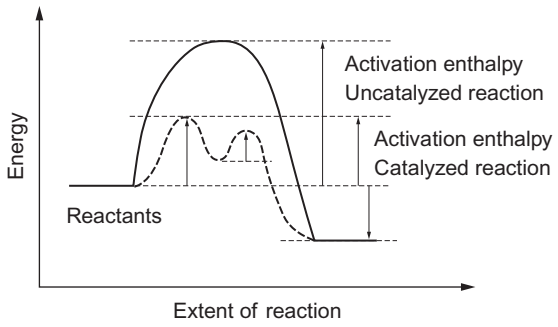


Fig. 2.1
Potential energy diagram for a catalytic reaction.

from the main group elements in which their *d*-shells are only partially filled with electrons, which facilitates coordination with ligands and activation of reactants through formation of σ or π bonds; (b) the accessibility of different oxidation states and coordination numbers; (c) the ability to stabilize a variety of unstable intermediates such as metal hydrides, carbonyls, and metal alkyls in relatively stable but kinetically reactive forms; (d) the ability to promote rearrangements via ligand migration (reactions within the coordination sphere); (e) the ability to assemble and orient several reaction components within the coordination sphere (template effect); and (f) the ability to accommodate both participative and nonparticipative ligands. Generally, the overall reaction is driven by the slowest step in the catalytic cycle, referred to as a rate-determining step. The basic concepts of homogeneous transition metal complex catalysis are described with examples in several monographs and reviews [2,9–11]. Some important elementary steps and catalytic cycles for a few important examples are summarized here.

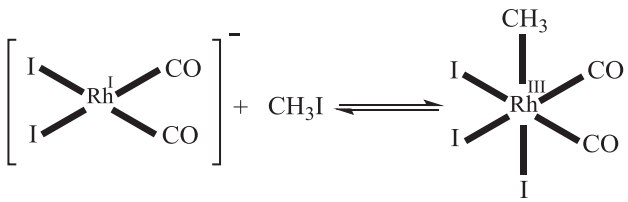
2.3.1.1 Oxidative addition

A common reaction involved in activation of substrates by homogeneous metal complex catalysts is the "oxidative addition" in which the formal oxidation state and coordination number of the metal changes by one or two. These reactions are well understood on a molecular level [12,35] and form the basis of catalytic cycles in many well-known homogeneous catalytic reactions involving hydrogenation, carbonylation, and hydroformylation. The reaction can be described as:

$$\left[\mathrm{M}^{n}(\mathrm{L})_{m}\right] + \mathrm{X}-\mathrm{Y} \rightarrow \left[\mathrm{M}^{(n+2)}\mathrm{XY}(\mathrm{L})_{m}\right] \tag{2.2}$$

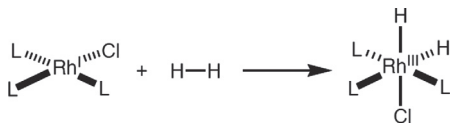
It is necessary that the metal complex is a coordinatively unsaturated and in lower oxidation state. On oxidative addition of $\mathrm{X}-\mathrm{Y}$ (reactant) to $[\mathrm{M}_n(\mathrm{L})_m]$, a 16-electron coordinatively unsaturated complex, the oxidation state of the metal increases by 2, leading to a coordinatively saturated 18-electron complex. Examples relevant to homogeneous catalysis are found in activation of hydrogen and alkyl halides:

Activation of methyl iodide (methanol carbonylation)



(2.3)

Activation of H_2 (hydrogenation of olefins)

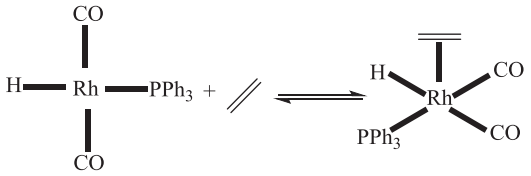


(2.4)

2.3.1.2 Coordination

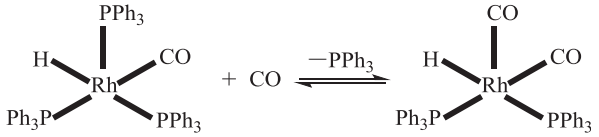
Activation of substrates through coordination involves interaction of the substrate XY with catalyst complex such that integrity of the molecule XY is maintained. Although the distribution of electrons over the XY bonds may be radically altered, X and Y remain formally bonded to each other and XY coordinates in its entirety and not X or Y individually. Typical examples are activation of olefins, acetylenes, and CO. This process is analogous to the "nondissociative adsorption" in heterogeneous catalysis. Examples of activation by coordination are:

Activation of olefins (hydroformylation)



(2.5)

Activation of CO (hydroformylation)

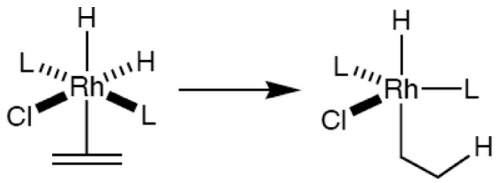


(2.6)

2.3.1.3 Insertion

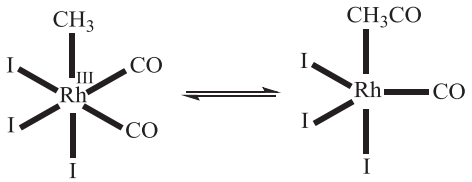
The reaction of coordinated substrates within the coordination sphere is referred as an "Insertion" reaction. Insertion occurs with vacation of a coordination site, and the ligands involved are mutually *cis*. Insertion from an 18-electron complex gives a coordinatively unsaturated 16-electron species. Typical examples are found in insertion of olefin in the M—H bond and insertion of CO in the M—C bond in olefin hydrogenation and carbonylation reactions, respectively, as shown next:

Insertion of olefin in M—H bond



(2.7)

Insertion of CO in M—C bond

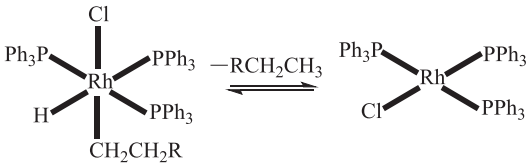


(2.8)

2.3.1.4 *Reductive elimination*

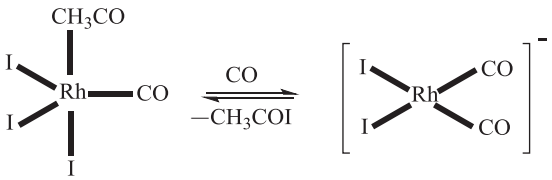
The reductive elimination reaction is the reverse of "oxidative addition," in which the oxidation state and coordination number of the complex may reduce by one or two. This is an important step in regeneration of the active catalytic species and completion of a catalytic cycle through one turnover. Examples of reductive elimination in olefin hydrogenation, methanol carbonylation, and hydroformylation are shown here:

Olefin hydrogenation



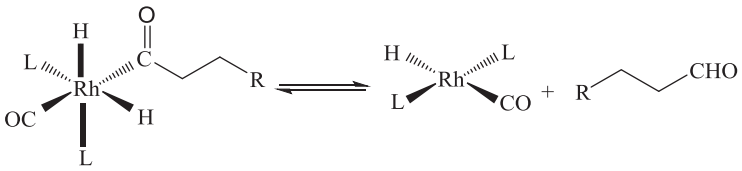
(2.9)

Methanol carbonylation



(2.10)

Hydroformylation



(2.11)

2.4 Catalytic Cycle

One of the requirements in catalysis is that the catalyst must be regenerated during the reaction so that it is not consumed stoichiometrically. The catalytic cycle consists of a number of elementary reactions as described earlier following the rules of organometallic chemistry. These reactions follow the 16/18 rule proposed by Tollman [11], which states, "Dimagnetic organometallic complexes of transition metals may exist in a significant concentration at moderate temperatures only if the metal's valence shell contains 16 or 18 electrons. A significant concentration is one that may be detected spectroscopically or kinetically in a gas, liquid or solid state. Organometallic reactions including catalytic ones proceed by elementary steps involving only intermediates with 16 or 18 valence electrons." Although the catalytic cycles for various reactions are consistent with basic elementary steps discussed earlier and the 16/18 electron rule, they differ depending on the nature of substrates and requirement of promoters to facilitate the overall catalytic reaction. The following examples illustrate how the basic reactions have been used not only to explain the mechanism of the catalytic reactions but also to discover some of the processes.

2.4.1 Hydrogenation of Olefins Using the Wilkinson Catalyst

Hydrogenation of terminal olefins using the Wilkinson catalyst [13] is an elegant example of application of the 16/18 electron rule to explain the catalytic cycle and mechanism of homogeneous catalysis. The catalytic cycle proposed is shown in Fig. 2.2. In the proposed mechanism, two possibilities of coordination of either hydrogen or olefin by the coordinatively unsaturated 16-electron precursor $RhCl(PPh_3)_3$ have been considered. In one of the loops (steps 1–6), the following steps are involved: (a) "oxidative addition" of hydrogen to a square planar 16-electron complex $RhCl(PPh_3)_3$ to give an 18-electron dihydride species, $H_2RhCl(PPh_3)_3$; (b) in steps 2 and 3, Lewis base dissociation of ligand $L(PPh_3)$ follows coordination by olefin to form $H_2RhCl(PPh_3)_2$ and $H_2RhCl(PPh_3)_2(CH_2{=}CHR)$, respectively; (c) in step 4 "insertion" of olefin between the M—H bond occurs to give an unstable 16-electron hydrido-alkyl species, $(RCH_2CH_2)RhHCl(PPh_3)_2$; and (d) in step 5, coordination of $L(PPh_3)$ gives an 18-electron hydrido-alkyl species, $(RCH_2CH_2)RhHCl(PPh_3)_3$, which on "reductive elimination" gives alkane, (RCH_2CH_3) product and regenerates the catalyst $RhCl(PPh_3)_3$ as a 16-electron species. Thus, this catalytic cycle is consistent with the elementary steps as well as the 16/18 electron rule. It is important to note here that depending on the olefin type and relative stability of the intermediate species and ligands used, different rate behavior and modification of the catalyst cycle are expected. For example, ethylene is known to form a stable complex with $RhCl(PPh_3)_3$ [13], and hence it is not readily hydrogenated with $RhCl(PPh_3)_3$, unlike olefins such as cyclohexene or 1-hexene. Similarly, in the presence of excess PPh_3, the ligand dissociation step is suppressed, and hence rate inhibition is observed.

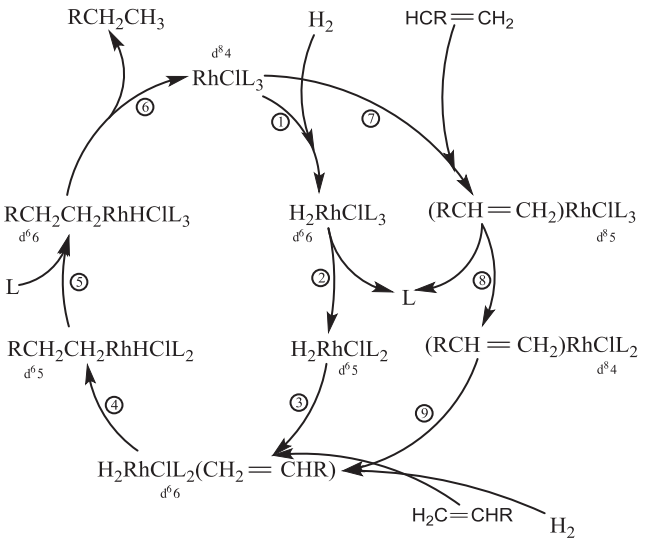


Fig. 2.2
Hydrogenation of terminal olefins by $RhCl(PPh_3)_3$ [11,13].

2.4.2 Hydroformylation of Propylene Using Co and Rh Complex Catalysts

Hydroformylation of olefins to aldehydes is a key step in the manufacture of Oxo alcohols and is one of the largest-scale homogeneous catalytic processes in industry for the production of C4–C40 alcohols with widely expanding applications in pharmaceuticals and fine chemicals. Two types of catalysts are used in industry consisting of high-pressure Co and low-pressure Rh complexes. The applications of hydroformylation, catalysts, and processes are reviewed extensively in several monographs and reviews [14,15,15a]. Here the catalytic cycle of the two main types of catalysts and the basic principles of homogeneous catalysis will be illustrated.

(a) *Co catalyzed hydroformylation*: In one of the earliest process for hydroformylation of olefins using unmodified Co catalysts, typically Co salts or Co carbonyl complex ($Co_2(CO)_8$) are used as precursors along with H_2 and CO, and irrespective of the type of precursor used, an intermediate species, $HCo(CO)_4$ is formed as an active precursor. The catalytic cycle proposed [15b] as shown in Fig. 2.3. In this mechanism, an 18-electron species, $HCo(CO)_4$ loses CO ligand by a Lewis base dissociation to give a 4-coordinate, 16-electron species, $HCo(CO)_3$, which is believed to be the active species in hydroformylation of olefins.

$$HCo(CO)_4 \rightleftharpoons HCo(CO)_3 + CO \tag{2.12}$$

The next step in the catalytic cycle involves coordination of an olefin to form an 18-electron hydrido-olefin complex, which undergoes a rapid hydride migration to give a 16-electron Co (I) alkyl species, $[(CO)_3CoCH_2CH_2R]$. The next steps involve

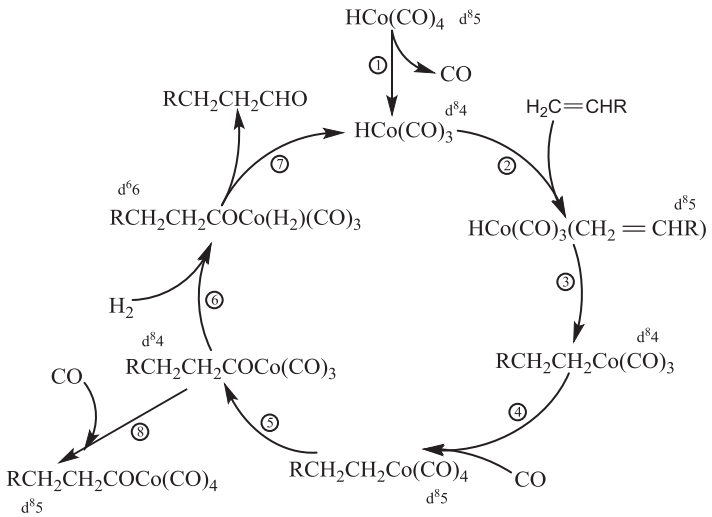


Fig. 2.3
Hydroformylation of olefins by $HCo(CO)_4$ [11].

coordination of CO to form an 18-electron alkyl complex, followed by *insertion* of CO to form a 16-electron acyl species, $(CO)_3Co(CO)CH_2CH_2R$. Further *oxidative addition* of hydrogen to give an 18-electron acyl Co dihydride species, followed by *reductive elimination* gives, aldehyde product, RCH_2CH_2CHO regenerating the active species, $HCo(CO)_3$. The distinguishing feature of the Co catalyzed hydroformylation is that the active species is formed outside the catalytic cycle and that the active species is in equilibrium with CO under reaction conditions. This is the reason the rate of hydroformylation is inhibited with increasing CO pressure, as it reduces the active species concentration.

(b) *Rh catalyzed hydroformylation*: Hydroformylation of olefins with Rh complex catalyst is considered a major breakthrough in homogeneous catalysis, as it requires lower temperatures and pressures compared to the Co catalysts and gives the desired high regioselectivity of the aldehyde products. Technological details of the catalysts and processes are available elsewhere [15a]. The catalytic cycle for the Wilkinson hydroformylation catalyst, $HRh(CO)_2(PPh_3)_2$, is briefly discussed here in the context of basic principles involved. Two types of catalytic cycles have been proposed (see Fig. 2.4) for hydroformylation of olefins [16], which mainly differ in the sequence of ligand dissociation and olefin coordination steps. In one case, the first step is initiated

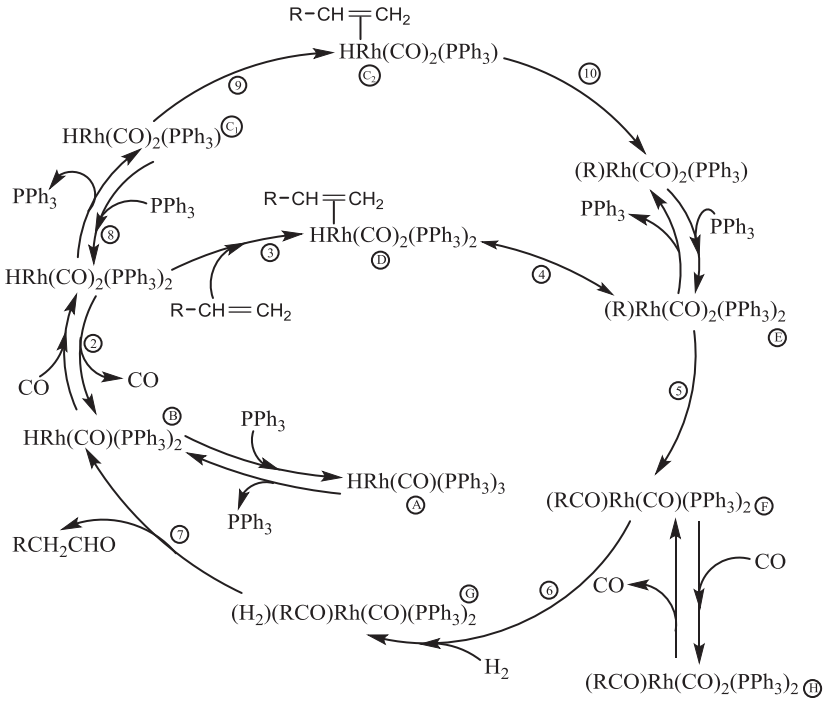


Fig. 2.4
Catalytic cycle for hydroformylation of olefin with the $HRh(CO)_2(PPh_3)_2$ catalyst.

by dissociation of a ligand PPh_3 from $HRh(CO)_2(PPh_3)_2$ to form a 4-coordinate 16-electron species, $HRh(CO)_2PPh_3$. This follows coordination of olefin, hydride migration, and coordination of PPh_3 ligand similar to that in a Co catalyzed cycle to give an 18-electron species, $(RCH_2CH_2)Rh(CO)_2(PPh_3)_2$. In the next steps, alkyl migration follows oxidative addition of hydrogen and reductive elimination to produce aldehyde simultaneously regenerating $HRh(CO)_2(PPh_3)_2$. In the alternative associative cycle (see Fig. 2.4), olefin coordination occurs directly to the 18-electron penta-coordinate Rh species, $HRh(CO)_2(PPh_3)_2$, without a prior dissociation of either CO or PPh_3 ligand. However, the dissociative mechanism is more consistent with experimental results as well as the 16/18 electron rule.

2.4.3 Carbonylation of Methanol to Acetic Acid

Carbonylation of methanol is yet another large-volume process using homogeneous catalysts for which there is no viable heterogeneous catalytic alternative to date. The details of catalytic processes, reaction mechanism, and industrial processes are addressed in several reviews [14,15,15a,17]. The catalytic cycle [17] for methanol carbonylation is shown in Fig. 2.6. The overall reaction is given as:

$$CH_3OH + CO \rightarrow CH_3COOH \tag{2.13}$$

Carbonylation occurs only in the presence of a catalyst consisting of Rh and iodide. Both Rh and iodide are essential components for the reaction. The catalytic cycle in Fig. 2.5 shows two loops, one to form an active substrate methyl iodide, CH_3I, by a stoichiometric reaction between methanol and hydro-iodic acid and the second the carbonylation of methyl iodide through several steps to produce acetic acid regenerating Rh species and hydro-iodic acid, HI. In the actual process, precursors such as $RhCl_3 \cdot 3H_2O$ and HI are introduced in the reactor along with CO. The reaction of $RhCl_3$ with CO in the presence of HI produces an active Rh species, $[Rh(CO)_2I_2]^-$, which is shown to be an active species in carbonylation of methanol. It is important to note that both the Rh catalyst and the co-catalyst/promoter HI are regenerated during the catalytic cycle. For the main catalytic cycle, the steps involving *oxidative addition* of CH_3I to $[Rh(CO)_2I_2]^-$, follows CO insertion to the acyl complex, 3a, CO coordination, and reductive elimination to produce CH_3COI and active catalyst, 1a. CH_3COI then reacts rapidly with H_2O to produce acetic acid and HI. In effect, except methanol and CO, none of the catalyst components are consumed, making the overall reaction catalytic.

The preceding examples illustrate how the basic principles of homogeneous catalysis are able to explain the reaction mechanism and catalytic cycles as well as design catalyst systems consisting of single or multiple components. It is important to note that there are exceptions

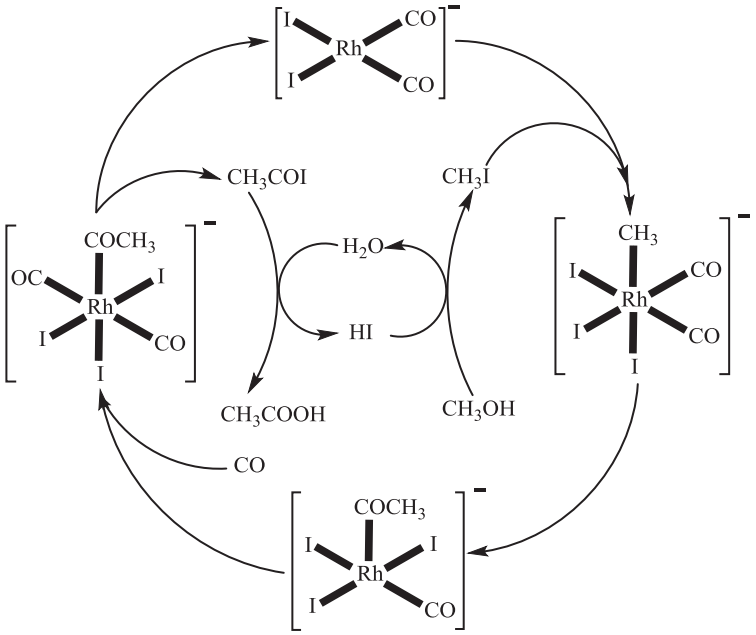


Fig. 2.5
Catalytic cycle for carbonylation of methanol [17].

to these general rules depending on the reactivity of different substrates and catalytic complexes and the stability of the intermediate species formed. The catalytic cycles form a sound basis for the development of molecular-level rate models to represent the kinetics of the homogeneous catalytic reactions.

2.5 Catalyst Performance

The performance of a catalyst is determined in many ways. For fundamental understanding of the catalyst performance, usually initial rate of reaction, turnover number (TON), and turnover frequency (TOF) terms are useful. These are defined as:

$$\text{Initial rate} = \frac{\text{Amount of substrate consumed}}{\text{Volume} \times \text{Time}} \text{ in units of kmol}/\left(\text{m}^3.\text{Sec}\right) \text{or equivalent units.} \tag{2.14}$$

The initial rate is determined at lower conversions ($<10\%$) of the substrate such that it can represent the reaction conditions specified at the beginning of the reaction in a batch reactor or inlet of a continuous reactor. In a continuous reactor, it is preferable to conduct experiments

such that the per pass conversion is less than 10%, which is referred to as differential conditions. In a batch reactor, the initial rate can be determined from concentration–time profiles but only considering less than a 10% conversion.

$$\text{TON} = \frac{\text{Amount of substrate reacted}}{\text{Amount of catalyst}},\ (\text{mole/mole}) \tag{2.15}$$

TON is a measure of the number of catalytic cycles that the reaction has gone through. It can be determined for any level of conversion and gives information related to the cost of the catalyst for a particular transformation and whether the reaction is catalytic or not.

$$\text{TOF} = \frac{\text{Amount of substrate reacted}}{\text{Amount of catalyst} \times \text{time}}, \left(\frac{\text{mole}}{\text{mole time}}\right) \text{or} \frac{1}{\text{time}} \tag{2.16}$$

TOF is a measure of intrinsic catalytic activity and is determined at low conversion levels (<10%). It requires a precise knowledge of the catalytic species on a molecular level, which is often possible in homogeneous catalysis. Even in the case wherein a catalyst precursor is well characterized as a molecular species, in reality, it is distributed as a different species through which the catalytic cycle operates. TOF calculations based on catalyst precursor are formally correct if they are involved in the rate-determining step. However, for practical purposes, TOF calculations based on precursor concentration give useful information for industrial applications. With a knowledge of rate-determining steps and characterization of a true catalytically active species in the catalytic cycle, more precise TOF calculations are possible.

For industrial process development, it is equally important to determine if the substrate is completely convertible, defined as conversion:

$$\text{Conversion}\,(\%) = \frac{\text{Amount of substrate reacted}}{\text{Amount of substrate charged}} \times 100 \tag{2.17}$$

The information of initial rate and TOF based on the substrate conversion is useful when only single reactions are involved. For multistep reactions involving parallel and consecutive steps with more than one product, it is important to determine selectivity of a product in addition to TOF. The various types of selectivity definitions used in catalysts are:

Chemoselectivity: The selective conversion of one functional group in the presence of other dissimilar but reactive groups are referred as *Chemoselectivity*:

$$\text{Chemoselectivity}\,(\%) = \frac{\text{Amount of aproduct formed (moles)}}{\text{Amount of substrate reacted(moles)} \times \text{Stoichiometric coefficient}} \times 100 \tag{2.18}$$

Regioselectivity: The selective conversion of a functional group to a desired regio-isomer is defined as regioselectivity.

$$\text{Regioselectivity } (\%) = \frac{\text{Amount of a product fornmed, moles}}{\text{Total amount of products formed, moles}} \times 100 \tag{2.19}$$

Stereoselectivity: In asymmetric catalysis, wherein, the product of interest is an optically active isomer, in addition to chemo and regioselectivities, stereoselectivity is important. Stereoselectivity is defined as "enantiomeric excess" (ee) defined as the selective conversion of a substrate to one stereo-isomer in preference to another.

$$\text{ee} = \frac{R - S}{R + S} \tag{2.20}$$

Where, R and S represent the molar amounts of two or more optical isomers.

2.6 Catalyst Deactivation

Deactivation of a catalyst affects the catalytic activity as well as selectivity of the products leading to poor performance of the catalysts [1,18–20]. Catalyst deactivation severely impacts the economics of catalyst utilization, separation of products, and overall process viability. Although the subject of catalyst deactivation has been treated with much detail in heterogeneous catalysis, it has not received as much attention as it deserves in academic studies in homogeneous catalysis. At the same time, an important aspect of commercial successes of homogeneous catalytic processes has been the discoveries on avoidance of catalyst deactivation as much as the development of active/selective catalysts. The homogeneous catalyst systems can be a single-component metal complex either with or without a promoter. In many cases, excess of free ligand is used as a promoter to enhance rate or selectivity or to stabilize the catalyst. In other cases, the catalyst system requires one or more promoters, which all have catalytic roles. Thus, in homogeneous catalysis, it is required to maintain the concentrations of the main catalytic complex as well as the promoters constant during several catalytic turnovers. Any changes in the concentrations of metal complexes or promoters during the course of reactions can lead to deactivation of the catalyst, lowering the process performance.

One should differentiate between deactivation and inhibition because both these phenomena are common in homogeneous catalysis. In "inhibition" the active catalyst is usually converted by reaction with a reactant/product or excess ligand/promoter by an equilibrium reaction reducing the effective concentration of active catalyst. However, if appropriate concentrations are maintained, a steady state catalyst activity is achieved. In deactivation, an irreversible change in catalytic species occurs that cannot be reversed during the course of reaction and requires external treatment to regenerate the catalyst or recover the expensive metal value. The deactivation of homogeneous catalysis can be described by following categories:

(a) decomposition of active metal salt or complex to inactive form by reaction with impurities, co-products, or even the reaction products, for example, deactivation of Rh complex catalyst for hydroformylation of olefins due to formation of a dimeric phosphide-bridged clusters [18,19]; (b) precipitation of metals by decomposition under certain conditions to inactive metal, for example, precipitation of soluble Pd catalyst to Pd metal in Wacker process for oxidation of ethylene at lower concentrations of reoxidants such as $CuCl_2$ and oxygen and decomposition of Co carbonyl complex to metallic Co under hydroformylation conditions at lower pressures of CO; (c) decomposition of ligand or promoters to inactive products induced by reaction with solvents, reactants, side products; and (d) thermal decomposition of active catalytic complex to inactive forms and instability of the catalysts at higher temperatures caused by uncontrollable exothermic reactions. In homogeneous catalysis, in general, any decrease in the concentration of a species in catalytic cycle can lead to inhibition or deactivation, which strongly depends on a sequence of equilibrium reactions. Hence, maintaining the reaction conditions, such as pressure, temperature, ratio of gaseous reactants, and so on plays a key role in avoiding catalyst deactivation. For a more detailed account of deactivation of homogeneous catalysts, refer to recent papers [1,19].

2.7 Kinetics and Mechanism

A knowledge of catalytic reaction kinetics is an important aspect of understanding the reaction mechanism, catalytic cycles, and rate dependency on operating reaction variables, as well as to develop rate equations that form a scientific basis for the design of reactors. Indeed, kinetics is one of the most powerful tools to validate reaction mechanisms, in combination with isolation and characterization of catalytic intermediates, the nature of active catalytic species, and computational techniques such as density functional theory (DFT). Unlike heterogeneous catalysis, where the nature of active catalytic species is not easy to determine on a molecular level despite significant advances in the spectroscopic technique, the mechanism of homogeneous catalytic reactions is often better defined in terms of molecular species and consistent with the rules of organometallic chemistry (described in Section 2.2). In this section, some basic considerations to kinetic modeling of homogeneous catalytic reactions will be addressed along with examples of industrially relevant reactions and catalyst systems.

2.7.1 Classification of Catalysts and Reactions

As a general approach to kinetic modeling, it is first necessary to classify the catalysts and reactions involved, so that a theoretical basis as well as experimental planning of kinetic study leads to reliable results. The homogeneous catalysts known to date consist of either a single molecule (metal salt or a metal complex) or a mixture of catalyst, co-catalyst, and promoters. Generally reactions involve gas and liquid reactants, with reaction taking place in the liquid phase, wherein the catalyst components are present in solution state.

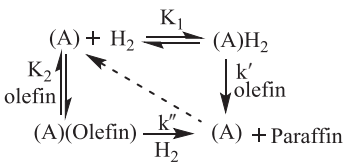
Many practical examples of homogeneous catalysis involve multiphase catalytic reactions in which reactants/products may be present in the gas phase or an immiscible liquid phase affecting the effective concentrations of these at the catalytic sites and the rate behavior. In general, the catalytic systems can be categorized as [21]:

1. reactions (single or multistep) with a single component catalyst; for example, hydrogenation [$RhCl(PPh_3)_3$], hydroformylation [$HRh(CO)_2(PPh_3)_2$], and oligomerization of olefins (Ni complex catalyst)
2. reactions involving multicomponent catalyst systems; for example, methanol carbonylation [Rh-methyl iodide catalyst], Wacker process for oxidation of ethylene to acetaldehyde [$PdCl_2/CuCl_2$], carbonylation of styrene and aryl alcohols using Pd complex catalyst [Pd Complex, TsOH, and LiCl]
3. complex multiphase catalysis involving catalyst in one phase, while gas and liquid reactants/products are in other immiscible gas or liquid phases; for example, biphasic catalytic hydroformylation

Kinetic modeling of homogeneous catalytic reactions has been extensively studied [22]. Despite significant advances in mechanistic studies, several rate models are empirical and lack interpretations based on the well-established mechanisms and catalytic cycles. This is primarily due to complexity in derivation of rate equations and limited experimental rate data. A few selected case studies are discussed here, mainly considering model examples and recent developments in novel catalytic systems.

2.7.2 Hydrogenation Reactions

Hydrogenation of olefins is an excellent example for which the molecular-level approach is well established. For the catalytic cycle shown in Fig. 2.2, the following simplified scheme was considered [13] for hydrogenation of cyclohexene using $RhCl(PPh_3)_3$ catalyst:



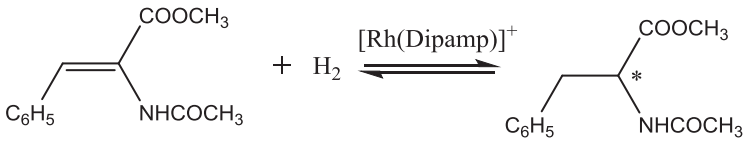
(2.21)

It is assumed that the precursor A, $RhCl(PPh_3)_3$, forms equilibrium species rapidly with both olefin and hydrogen, and the steps involving reactions of these intermediates with hydrogen or olefins, respectively, are rate determining. The following rate equation was derived for rate of reaction:

$$r = \frac{kK_{H_2 2}C_{H_2}C_{ol}C_{Rh}}{1 + K_{H_2}C_{H_2} + K_{ol}C_{ol}} \tag{2.22}$$

This rate equation represented experimental rate data on hydrogenation of cyclohexene [13] and allyl alcohol [23]. This rate form is analogous to that known in heterogeneous catalysis using Langmuir–Hinshelwood models assuming a single-site adsorption–reaction mechanism. Similar experimental and modeling studies on hydrogenation of cyclohexene, maleic acid, ally alcohol, and acrylamide using homogeneous $RuCl_2(PPh_3)_3$ catalyst [23a,24] have also been reported.

Asymmetric hydrogenation of methyl-(*Z*)-α-acetamidocinnamate, a key step in synthesis of the chiral drug L-dopa (for Parkinson's disease), has been investigated by [24a], wherein detailed mechanisms were considered to derive rate equations and determine kinetic parameters.



(2.23)

They considered the following catalytic cycle for hydrogenation using $[Rh(DIPAMP)]^+$ catalyzed hydrogenation. Their kinetic studies showed that the predominant stereo-isomer, (*S*)-*N*-acetylphenylalanine methyl ester, was formed from the minor and less-stable catalytic species, $[Rh(DIPAMP)(mac)]^+$, by virtue of its much higher reactivity toward H_2. They observed a decrease in enantioselectivity with H_2 pressure, which is explained considering different rate-determining steps at lower and higher H_2 pressures. The proposed rate equations for the two cases are [24a]:

Case 1: Oxidative addition of H_2 as a rate-determining step for both stereo-isomers

$$r_{R-prod} = \frac{k_2^{maj} K_1^{maj} [H_2][Rh]_{tot}}{K_1^{maj} + K_1^{min}} \tag{2.24}$$

$$r_{S-prod} = \frac{k_2^{min} K_1^{min} [H_2][Rh]_{tot}}{K_1^{maj} + K_1^{min}} \tag{2.25}$$

Case 2: Oxidative addition of H_2 for R-isomer and a steady state equation for S-isomer

$$r_{R-prod} = k_2^{maj} [H_2][Rh] \tag{2.26}$$

$$r_{S-prod} = \frac{k_2^{min} k_1^{min} [H_2][Rh]}{K_1^{maj} \left(k_{-1}^{min} + k_2^{min} [H_2]\right)} \tag{2.27}$$

The nonlinear effects in enantioselectivity of asymmetric hydrogenation of olefins are observed due to association of chiral ligands inside or outside the catalytic cycle [25].

2.7.3 Carbonylation Reactions

The ability of transition metal complexes to coordinate with CO and facilitate intramolecular reactions such as "insertion" between M—H and M—C bonds has allowed important discoveries in the development of catalytic carbonylation processes. Besides major successes such as carbonylation of methanol to acetic acid using Rh or Ir complex catalysts, carbonylation of a variety of organic substrates are known for expanding their applications in clean, atom-efficient synthesis as well as new innovative processes for industrially important products [26]. Carbonylation reactions involve multicomponent catalyst systems, and hence the kinetic modeling of such reactions is highly complex. Some important studies are discussed here.

The catalytic cycle for carbonylation of methanol shown in Fig. 2.5 suggests that the overall rate of carbonylation may be dependent on methanol, hydro-iodic acid (HI as a promoter), Rh concentrations, and CO pressure depending on the rate-determining step. However, for a wide range of conditions of practical interest, the carbonylation rate was found to be zero order with methanol concentration and CO pressure and varied linearly with only Rh and HI concentrations [26a,27]. This observation is consistent with the oxidative addition of methyl iodide to $[Rh(CO)_2I_2]^-$ as a rate-determining step and *in situ* IR spectroscopic characterization of $[Rh(CO)_2I_2]^-$ [17]. In a further study, Dake et al. [28] reported that the rate of carbonylation is dependent on methanol concentration and CO pressure under certain conditions and interpreted the results as a possible shift in the rate-determining step. This suggests that extrapolation of the kinetics should be done with care for such catalytic reactions.

Carbonylation of olefins, dienes, and acetylenes has been investigated for synthesis of carboxylic acid derivatives [26], among which carbonylation of aryl olefins and alcohols has led to innovative processes for anti-inflammatory drugs such as ibuprofen and naproxen. Seayad et al. [28a] studied kinetics of carbonylation of styrene using a homogeneous $Pd(OAc)_2$/PPh_3/*p*-toluenesulfonic acid (TsOH) catalyst system. The carbonylation rate was found to be first order with Pd and zero order with styrene up to a certain concentration with a remarkable promoting effect by water. The rate increases with CO pressure below 3.4 MPa, but at higher *P*CO (>3.4 MPa), it was found to be independent of CO partial pressure. The following empirical form of rate equation was proposed.

$$R_A = \frac{k_1 P_{CO}(1 + K_B B)^2 CD}{(1 + k_{CO} P_{CO})(1 + k_D D)^2} \tag{2.28}$$

In a recent report, Li and Chaudhari [28b] investigated kinetics of hydroxycarbonylation of styrene using Pd(pyca)(PPh_3)(OTs)/PPh_3/TsOH/LiCl catalyst in a stirred batch reactor. The effects of catalyst, styrene, and water concentrations and the partial pressure of CO on the rate of hydroxycarbonylation as well as the concentration–time profiles have been investigated over a temperature range of 368–388 K.

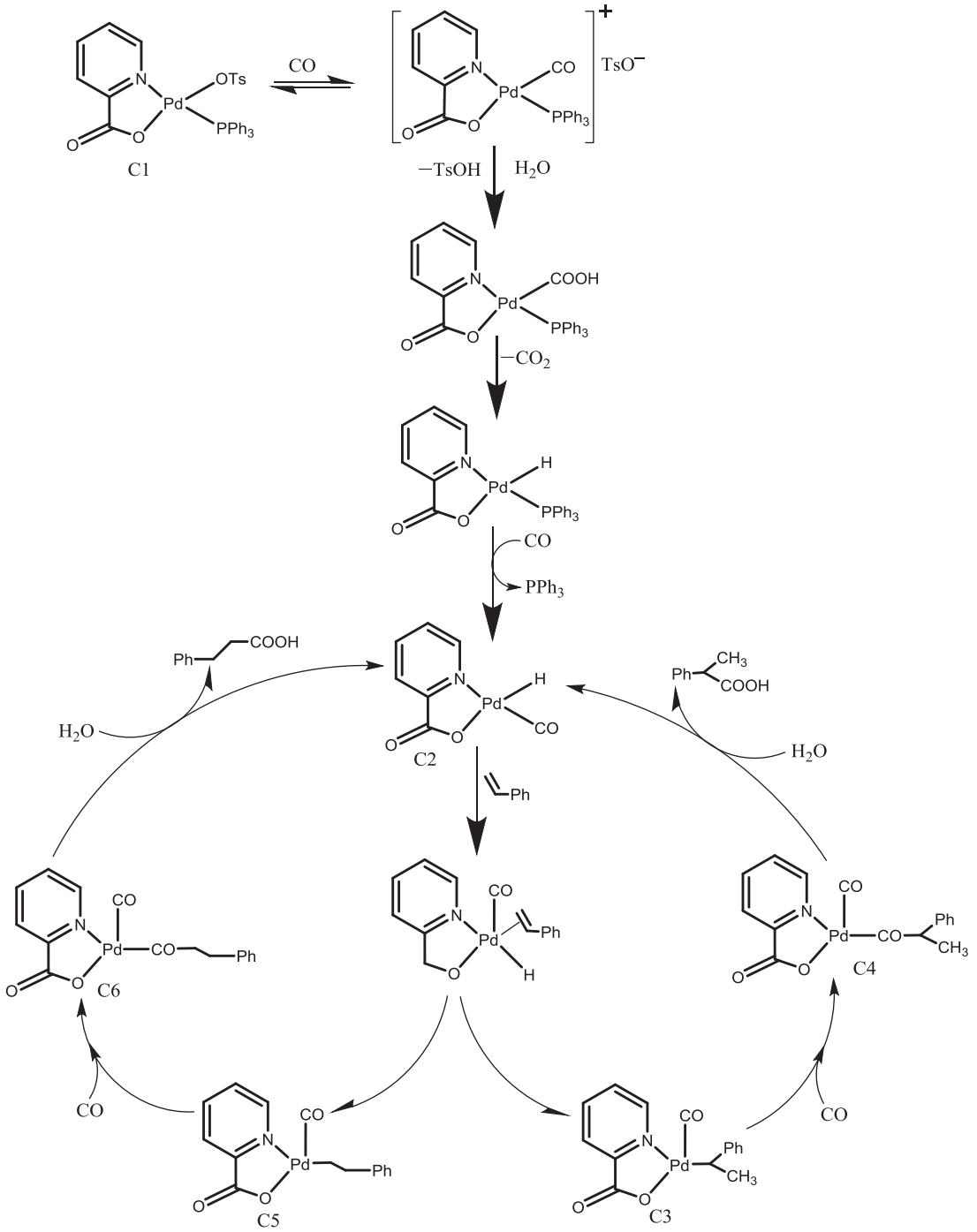


Fig. 2.6
Catalytic cycle for carbonylation of styrene.

A unique observation was the CO pressure dependent induction period, which was leading to lower rates of carbonylation at the start of the reaction. A molecular-level description of the reaction mechanism (see catalytic cycle in Fig. 2.6) has been proposed to explain the observed trends. The results were found to be consistent with a mechanism based on a Pd-hydride complex as an active intermediate species. The proposed mechanism also captured the experimentally observed trends of induction period. The approach of microkinetic modeling used here does not require the assumption of a rate-determining step and provides a good description of the complex trends observed with respect to reaction parameters over a wide range of conditions.

2.7.4 Hydroformylation Reactions

Hydroformylation reactions using Co and Rh complex catalysts have been widely studied to understand the role of ligands, solvents, and catalyst precursors on catalytic activity and regioselectivity but with limited efforts in developing rate equations. In an early study, the rates of hydroformylation of propylene and cyclohexene were studied by Natta et al. [29] using a Co complex catalyst. The reaction was found to be first order with olefin, catalysts, and hydrogen, but showed inhibition of rate with CO. These trends are consistent with the catalytic cycle shown in Fig. 2.6, but only empirical rate laws were proposed. A detailed kinetics of hydroformylation of 1, hexane, allyl alcohol, and vinyl acetate was investigated by Deshpande using a low-pressure Rh complex catalyst [30–32]. They proposed the following rate equation to represent rate data for these substrates:

$$r = \frac{k[\mathrm{H_2}]^m[\mathrm{CO}][\mathrm{Rh}][\mathrm{OL}]}{(1+K_1[\mathrm{OL}])^n(1+K_2[\mathrm{CO}])^p} \tag{2.29}$$

The rate of hydroformylation showed a strong inhibition with CO and a mild inhibition with olefins. The CO inhibition is consistent with the formation of inactive dicarbonyl species, as observed by *in situ* spectroscopic studies [16], but olefin inhibition does not have similar evidence from mechanistic studies. More recent studies [33,34] derived a rate equation for Rh catalyzed hydroformylation based on a simplified mechanism based on the catalytic cycle in Fig. 2.4:

$$\begin{aligned}
&\mathrm{HRh(CO)L_2} + \mathrm{CO} \overset{K_1}{\rightleftharpoons} \mathrm{HRh(CO)_2L_2} \\
&\mathrm{HRh(CO)_2L_2} + \mathrm{HCR{=}CH_2} \overset{K_2}{\rightleftharpoons} \mathrm{Rh(CO)L_2(COCH_2CH_2R)} \\
&\mathrm{Rh(CO)L_2(COCH_2CH_2R)} + \mathrm{H_2} \xrightarrow{k} \mathrm{HRh(CO)L_2} + \mathrm{RCH_2CH_2CHO} \\
&\mathrm{Rh(CO)L_2(COCH_2CH_2R)} + \mathrm{CO} \overset{K_3}{\rightleftharpoons} \mathrm{Rh(CO)_2L_2(COCH_2CH_2R)} \\
&\mathrm{Rh(CO)_2L_2(COCH_2CH_2R)} + \mathrm{CO} \overset{K_4}{\rightleftharpoons} \mathrm{Rh(CO)_3L(COCH_2CH_2R)}
\end{aligned} \tag{2.30}$$

Rate equation (Eq. (2.7)) derived for oxidative addition of H_2 to the acyl Rh species as a rate-determining step represented experimental rate data for 1-decene and styrene satisfactorily:

$$r = \frac{kK_1K_2[H_2][CO][Rh][\text{ Olefin}]}{1 + K_2[CO] + K_1K_2[CO][\text{ Olefin}] + K_1K_2K_3[CO]^2[\text{ Olefin}] + K_1K_2K_3K_4[CO]^3[\text{ Olefin}]} \tag{2.31}$$

A summary of kinetic models for Rh catalyzed hydroformylation is presented elsewhere [34a].

2.8 Scale-Up and Practical Considerations

Most academic studies on homogeneous catalysis have been performed on scales in which a few mg of catalysts were used with limited attention to practical aspects of reactor design and scale-up. Most of the industrial processes fall into the category of gas–liquid reactions using soluble catalysts, and hence the general concepts of mass transfer with reaction developed for gas absorption with reaction are applicable (see details in Chapter 7). However, one distinguishing feature is that gas removal processes are very rapid, occurring mainly at the gas–liquid interface, and hence reactors are used with maximum gas–liquid interfacial area. In contrast, homogeneous catalytic reactions essentially occur in the bulk liquid phase with or without some gas-to-liquid mass transfer limitations. Unfortunately, the design and scale-up of these processes have not received adequate attention of researchers in academic schools beyond kinetic studies. A careful consideration of the complex reaction mechanism, mass transfer limitation, and catalyst deactivation and how these processes will change on scale-up needs to be given.

2.9 Conclusions and Future Trends

In this chapter, a brief summary of the fundamentals of homogeneous catalytic reactions is presented with the goal to introduce the important basic principles to industrial chemists and engineers. General principles and elementary reactions involved in activation of common substrates that consist of major chemical feedstock such as olefins, CO, H_2, alcohols, and O_2 by metal complexes are discussed with examples relevant to industrial catalytic processes. Further, the concept of the catalytic cycle and the role of principle catalysts and co-catalysts/promoters has been discussed with examples such as hydrogenation, hydroformylation, and carbonylation reactions. The kinetic modeling of homogeneous catalytic reactions is discussed considering both empirical and mechanistic models with examples of experimental validation. Most of the models investigated so far consider one of the steps as rate controlling; however, rigorous methodologies for analysis of kinetics with multiple rate-determining

steps and discrimination of rate models needs to be done. Kinetics can provide an additional tool to validate reaction mechanisms and catalytic cycles in addition to *in situ* characterization of catalytic intermediates by spectroscopic methods [37] and computational studies [36,38,39]. The industrial homogeneous catalytic processes often involve gas–liquid reactions with complex reactions, which requires careful analysis of the role of mass transfer, mixing, and related reaction engineering issues to enable better understanding of the reactor design and scale-up. This chapter can provide a starting point of introduction for industrial as well as academic researchers to analyze newly emerging homogeneous catalytic processes.

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CHAPTER 3

Heterogeneous Catalysis

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3.1 Introduction

Catalysis plays a key role in the production of chemicals and fuels. Traditionally, catalytic processes are classified into homogeneous and heterogeneous. In homogeneous catalysis, catalyst and reactants are in the same phase, while in heterogeneous catalysis they are in different phases. Heterogeneous catalysis is associated with the engineering advantages of the ease of catalyst separation from reactants and products, and the regeneration of the solid catalyst. A majority of catalysts used in heterogeneous catalytic processes is in the form of solids. Research on heterogeneous catalysis began in the early 1800s. Faraday was the pioneer in this area of research who had investigated platinum-facilitated oxidation reactions. Thereafter, several other catalytic processes were developed for chemicals, pharmaceuticals, materials, polymers, energy, etc. All these catalytic reactions played an inevitable part in the industrial revolution. Catalysis has been applied extensively to abate pollutants in automobile exhaust gases and in several chemical reactions. Desirability of catalytic processes requires high catalytic activity and selectivity, which can be achieved by controlling the design of catalyst materials with adequate structure and active sites. Determination of active sites and the mechanism involved in chemical reactions are of significance in heterogeneous catalysis.

In the early 20th century, Fritz Haber successfully synthesized ammonia by reacting molecular nitrogen and hydrogen at high pressure using an osmium catalyst. It was the starting point of the industrial revolution of heterogeneous catalysis. Following up on Haber's work, BASF scientists Carl Bosch and Alwin Mittasch conducted several catalytic reactions using a variety of catalysts and came up with a cheap and active Fe compound as a commercial catalyst. The same process was used for making raw explosive materials at the time of World War I for Germany. After the war, the technology for synthesizing methanol through catalytic hydrogenation of carbon monoxide was developed. It was one of the appropriate ways for converting carbon monoxide into chemicals and fuels. The same technology was adopted by Germany during World War II for supplying synthetic fuels to war machines. In the same decade, refinery catalysts for alkylation, cracking, and dehydrogenation were also developed, which was a major breakthrough in the petroleum industry. Also during that time, the

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Fischer-Tropsch process for conversion of syngas to hydrocarbons by the use of Co/Fe catalysts compensated petroleum shortage. Later, hydrotreating catalyst technology was developed for sulfur, nitrogen, and metal-free fuels. The 1960s to the 1990s were considered a major industrial revolution period in developing several heterogeneous catalysts including shape-selective catalysts for petrochemicals, fine chemicals, specialty chemicals, plastics, clothing, and building material industries [1]. Hydroxylation of phenol was developed up to the industrial scale by Enichem using a titanium silicalite-1 (TS-1) catalyst [2]. Rhodia industrialized a process (10,000 tons per year) for the production of vanillin, a flavor ingredient, starting from phenol using heterogeneous catalysts. The synthesis entails four catalytic steps: hydroxylation of phenol with H_2O_2, gas-phase *ortho*-methylation with methanol, hydroxymethylation, and oxidation of benzyl alcohol using TS-1, lanthanide phosphate, zeolite, and supported noble metal catalysts, respectively [3]. They also developed a zeolite-catalyzed fixed bed technology for acylation of anisole-forming *para*-acetylanisole, which is superior in terms of *para*-selectivity, cost-efficiency, and environmental factor (E-factor) to the traditional process. As a follow up, they applied the same principle for developing acetyl veratrole [4]. Enichem reported an eco-friendly process for converting cyclohexanone to cyclohexanone oxime using a TS-1 catalyst in the presence of ammonia and hydrogen peroxide. The subsequent Beckmann rearrangement step to produce caprolactam was carried out using a solid acid catalyst [5]. IMI reported the industrial application of heterogeneous catalysis in Heck reactions. They used Pd/C catalyst for the coupling between *para*-bromoanisole and octyl acrylate to generate octyl-*p*-methoxycinnamate [6]. Transition metal oxides (eg, rhenium, molybdenum, or tungsten oxide) supported on high surface area alumina or silica were used for the olefin metathesis. The other important catalytic processes in fine chemicals were the highly regioselective ibuprofen synthesis (3500 tons per year; Hoechst Celanese Corp., currently BASF; Pd-based catalyst), the Hoffmann-La Roche and BASF process for hydroformylation of diacetoxy butenes to 2-methyl-4-acetoxy butanol (an intermediate for Vitamin A, >600 tons per year), Heck coupling of 3-bromopyridine and but-1-ene-3, 4-diol followed by asymmetric hydrogenation to pyridine diol (intermediate for drugs in treatment of allergic conditions of eyes, nose, and skin), the Mallinckrodt process for nitrobenzene to *p*-nitrophenol, oxidation of *p*-cresol to *p*-hydroxybenzaldehyde (intermediate for antibiotics like Amoxicillin, Cephalosporin), and hydrogenation of butynediol to *cis*-butenediol (intermediate for Vitamin B_6), etc. [7].

In the early stages, catalysis technology development was used during political turmoil, and later it was used for economic development, survival, and environmental protection. At present, heterogeneous catalysis covers almost 80% of global market shares. The demand for heterogeneous catalysts is growing annually. In 2010, it was at about US $14 billion. The expected estimation for 2015 is around US $20 billion (Fig. 3.1) [8]. Table 3.1 presents some important industrial catalytic processes developed in the last century [9,10]. Of late, heterogeneous catalysts are being exploited in the conversion of renewable resources into fuels

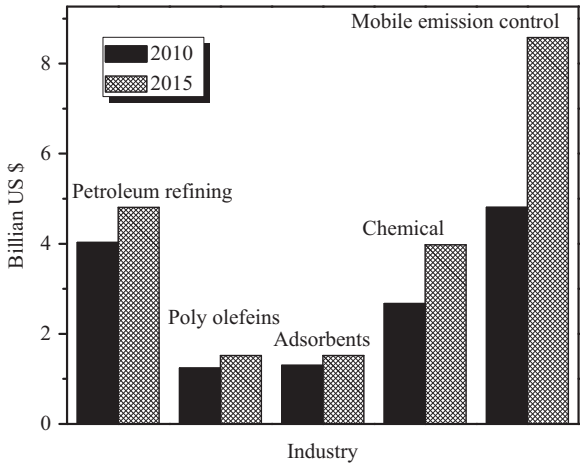


Fig. 3.1
Demand of heterogeneous catalysis in various sectors. *Data taken from Ref. [8].*

Table 3.1 Some commercial catalytic processes using solid catalysts [9,10]

Catalytic process	Commercial catalyst	Discoverer (year)	Area of application
Sulfuric acid (contact process)	Pt, V_2O_5	Winkler (1875), Knietsch (1888; BASF)	Chemical manufacturing, processing of metals, fertilizers, explosives, and drugs
Nitric acid by NH_3 oxidation	Pt/Rh nets	Ostwald (1906)	Chemicals, explosives, fertilizers, dyes, metal purification, and perfumes
Ammonia synthesis from N_2 and H_2	$Fe/Al_2O_3/K_2O$	Mittasch, Haber, Bosch (1908) Production (BASF, 1913)	Chemicals, fertilizers, gunpowder, and explosives
Methanol synthesis from CO and H_2	Cu/ZnO, ZnO/Cr_2O_3	Mittasch (1923)	Bulk chemicals and fuels
Hydrocarbons by CO hydrogenation	Fe, Co, Ni	Fischer, Tropsch (1925)	Automotive fuels and solvents
Cracking of hydrocarbons	Al_2O_3/SiO_2	Houdry (1937)	Fuels and detergents
Alkylation of alkenes with isobutane	$AlCl_3$	Ipatief, Pines (1932)	High-octane fuels
Naphtha reforming/ dehydrogenation/ isomerization	Pt/Al_2O_3	Vladimir, Haensel	High-octane fuels
Hydrogenation of coal to hydrocarbons	Fe, Mo, Sn	Bergius (1913), Pier (1927)	Fuels
Oxidation of benzene, naphthalene	V_2O_5	Weiss, Downs (1920)	Chemicals
Ethylene polymeriziton (low pressure)	Ti compounds, $TiCl_3/Al(R)_3$	Zeigler, Natta (1954)	Polymers and bulk chemicals

and chemicals. Understanding, at the molecular level, the way surfaces catalyze chemical transformations is a challenge in this area. This chapter focuses on the fundamental aspects of reaction kinetics and deactivation-regeneration processes of heterogeneous catalysts.

3.2 Catalytic Steps in Heterogeneous Catalysis

Heterogeneous catalysis is a surface phenomenon. The surface area of the catalyst should be large, and the surface must be accessible to reactants. Heterogeneously catalyzed reactions proceed through chemical and physical reaction steps (Fig. 3.2). The elementary steps involved in heterogeneous catalytic reaction are as follows: (1) external diffusion of reactants from bulk phase to catalyst surface followed by its internal diffusion to approach active sites, (2) adsorption of reactants on active sites, (3) surface reaction, and (4) desorption of products from the active sites followed by their diffusion out of the catalyst. All these steps are important in determining the overall rate of the catalytic reaction. Variation in the rate of any of these steps leads to change in the overall rate of the reaction. The following section provides some details on these reaction steps.

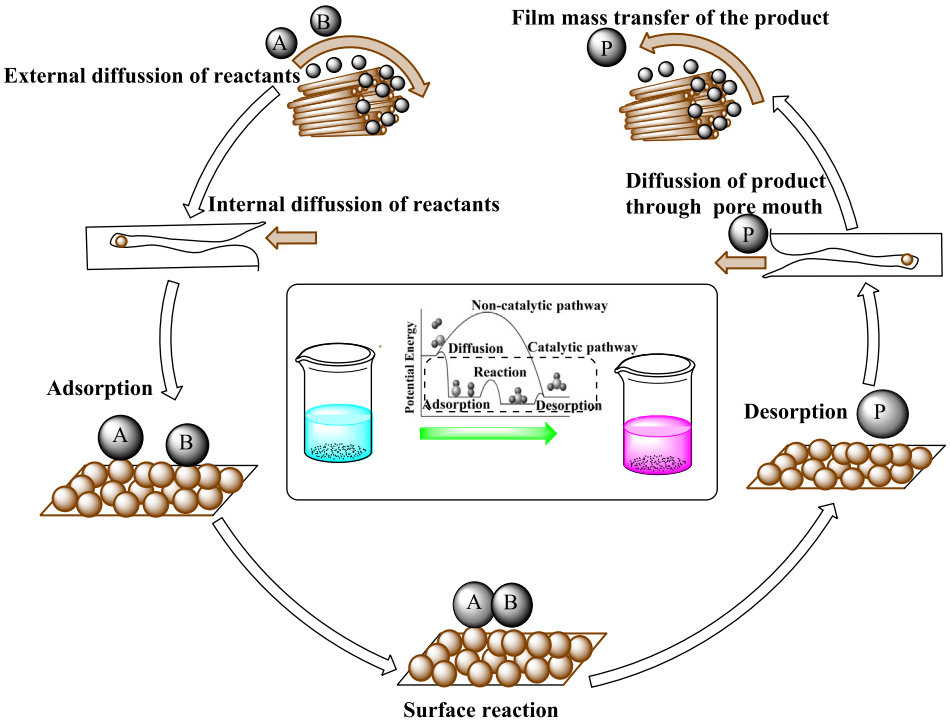


Fig. 3.2
Reaction steps involved in heterogeneous catalysis.

3.2.1 Diffusion

Diffusion is a voluntary intermixing or motion of atoms or molecules promoted by thermal energy. In heterogeneous catalysis, diffusion is an imperative step for determining the reaction rate. It is exhibited in two kinds of motion: external diffusion and internal diffusion. Diffusion of reactants from the bulk phase to the external surface of the catalysts is called external diffusion (or film diffusion), whereas diffusion occurring through the external surface to the active sites in the internal surface is called internal diffusion or intraparticle diffusion or pore diffusion. Intraparticle diffusion and chemical transformation steps occur concurrently. Chemical reaction within the porous catalyst depends on the pore dimension and degree of intraparticle diffusion constraint. It is important to understand the concentration sketch inside the pore for calculating the reaction rate in the inner part of the catalyst pore. Thiele put forward a mathematical model for quantitative estimation of intraparticle diffusion effect on the chemical reaction rate. The equation for Thiele modulus (ϕ) is

$$\phi = \lambda l = l\sqrt{\frac{4k_r''}{d_P D_A}} \tag{3.1}$$

where λ is the mean free path, l is pore length, k_r'' is the rate coefficient for diffusion, d_p is the pore diameter, and D_A is diffusivity. Pore diffusion can significantly vary the rate of catalytic reaction. It is related to the effectiveness factor η, which is the ratio of integral mean of real reaction rate at local concentrations to the ideal reaction rate at external surface concentration and accordingly,

$$\eta = \frac{\int_{z=0}^{l} k_r'' C_A(z)dz}{k_r'' C_{As} l} = \frac{1}{l}\int_0^l \frac{\cosh(\lambda(l-z))}{\cosh(\lambda l)}dz = \frac{\tanh(\lambda l)}{\lambda l} = \frac{\tanh(\phi)}{\phi} \tag{3.2}$$

But the Thiele modulus is appropriate only for first-order reactions with porous catalyst slabs having straight cylindrical or irregular pores. In order to calculate the effectiveness factor, η, for different reaction orders a modified equation (Eq. (3.3)) is used.

$$\phi = \frac{V_P}{A_E}\sqrt{\frac{n+1}{2}\cdot\frac{4k_r''}{d_P D_A}} \tag{3.3}$$

Here, V_P is the geometric pellet volume and A_E is the external surface area of the catalyst and n is the order of reaction. This equation is valid only for $n > 0$ and for explaining nonidealized pore shapes.

The ability of reactants to approach each other on the catalyst surface increases with an increase in the rates of external and internal diffusion processes. It depends mainly on temperature, pressure, solvent used in the reaction, and particle size of the catalyst. Rate of diffusion (Γ) is related to temperature (T) as follows:

$$\Gamma = \nu e^{\frac{-E_{\text{diff}}}{K_B T}} \tag{3.4}$$

where E_{diff} is the potential energy barrier for diffusion, ν is vibrational frequency, and K_B is Boltzmann constant. The mobility of atoms or molecules increases with temperature, which in turn enhances the overall reaction rate. In high-temperature catalytic processes, external diffusion has no significant role in the overall rate as there is no external mass transfer resistance. But diffusion in the catalyst pores controls the reaction. At high temperatures, pressure difference is developed across the pores, with associated coerce flow of particles through the pores. Fick's law is adopted to describe the diffusion occurring inside the catalyst pellet. Rate of internal diffusion (N) is defined as

$$N = -D_e\left(\frac{\partial C}{\partial z}\right) \tag{3.5}$$

where C is the number of moles of component per unit pore volume, z is the diffusion coordinate, and D_e is the effective diffusion coefficient. Diffusion coefficient (diffusivity) depends on the porous medium, temperature, and the nature and concentration of diffusants.

Depending on the pore dimension of the solid catalyst and the mean free path of the reactant molecule, diffusion occurs mainly in three ways. When the pore diameter (d_P) is larger than the mean free path (λ) of the diffusant, diffusion occurs in the same manner as observed outside the pore (bulk or molecular diffusion). When $d_P \approx \lambda$, the diffusing molecule collides more with the pore walls than with other molecules, which is known as Knudsen diffusion. It is normally not observed in liquids. When reactant size is close to the pore diameter, as in microporous zeolites, the reactant is diffused in the pores while keeping continued contact with the pore walls; such diffusion is known as configurational diffusion, or intracrystalline diffusion. Diffusion occurring in microporous materials is governed by the reactants' interaction with the pore walls. The intraparticle effective diffusivity is proportional to $T^{3/2}$ in the case of molecular diffusion, and $T^{1/2}$ in the case of Knudsen diffusion [11]. In mesoporous materials, Knudsen diffusion is more important; however, surface diffusion and capillary effect also have a role.

In the case of the catalyst pellet with the pores of nonuniform shape and pores interconnected to each other with different cross sectional area, it is difficult to describe the diffusion in each pathway separately. Determination of effective diffusion coefficient, which describes diffusion, i.e., the

average proceeding at any position in the pellet, is the common way to illustrate diffusion in such cases. The effective diffusivity (D_e) for bulk or Knudsen diffusion is defined as:

$$D_e = \frac{D_{AB}\phi_P\sigma_c}{\tau} \tag{3.6}$$

where τ is tortuosity, which is the ratio of actual distance traveled by a molecule between two points to the shortest distance between those points, ϕ_p is the porosity of the pellet, and σ_c is the constriction factor, which addresses the differences in cross sectional area of the pores, and is defined as a function of the ratio of the maximum to the minimum area of the pores.

Specific problems of diffusion in porous solids have been described in several books and reviews because of their considerable practical importance in the petroleum and chemical process industries. Transport occurs through fine porous materials principally by diffusion, and they control the overall reaction rate of a chemical process. The pore structure of a catalyst has a significant influence on the diffusion of a substrate over the surface. Under similar conditions, diffusion in an arbitrary pore network is generally found to be slower than in a set of straight cylindrical capillaries. The random orientations result in augmentation in the diffusion path length, and decrease in the concentration gradient. All such effects derived from pore orientation, connectivity, size variation, etc., can be explained by using the tortuosity factor, where it is assumed that the effect of pore geometry and structure is the same for all pore sizes and diffusion mechanisms. Commonly, it is represented by Eq. (3.7),

$$D = \varepsilon_p D_p/\tau \tag{3.7}$$

where D is the diffusion constant, ε_p is porosity, D_p is the diffusivity for straight cylindrical pores of the same diameter, and all the other effects are handled by the factor τ, the tortuosity factor. This equation allows the simple calculation of diffusivities of different sorbates by utilizing the information of any one of the sorbates. However, these assumptions are unsatisfactory in broad or bimodal pore distributions. In such cases, it is essential to consider the variation in pore diffusivity with pore diameter rather than taking a single average value. Generally, tortuosity is inversely related to porosity. In some reports tortuosity is defined as the ratio of actual pore length to the distance in the direction of flux [12].

Some diffusion processes are controlled by the equilibration of molecules on the surface in a void of zeolites, and the potential of a molecule to cross over the barrier (such barriers are known as the diffusion barrier). The surface sites are separated by an energy barrier of distance *a,* and diffusion is considered as the leaping of adsorbate from one site to another over the hurdles; a is referred to as the hopping length [13]. The narration of distance (a) traveled with time (t_d) for diffusion is given as

$$a^2 = 4Dt_d \tag{3.8}$$

From Eq. (3.8), the diffusion constant (D) is expressed as

$$D = \frac{1}{4t_d}a^2 \tag{3.9}$$

3.2.2 Adsorption

Adsorption of reactants on the active surface of a catalyst is the most important step in heterogeneous catalytic reactions. The active site provides chemically suitable, partially uncoordinated, sites for adsorption of reactant molecules. Adsorption can occur directly or indirectly on the surface. In direct adsorption, the reactant molecule (adsorbate) directly forms a bond with the active site. But, in indirect adsorption, the molecules initially form a precursor state of adsorption and are free to flow through the surface, and later stick on a particular active site. Several aspects, such as nature and surface area of the adsorbent, nature of the adsorbed gas, temperature, and pressure of the gas, control the extent of adsorption on surfaces [14].

Molecules adsorbed on the surface in their condensed phase stick for a certain period of time and then return to the gas phase. The duration of stay of the adsorbate molecule on the adsorbent surface is influenced by the nature of the adsorbate, adsorbent, capillary forces, surface heterogeneity, and number of gas molecules run over the surface as well as their kinetic energy. The gas molecules strike the surface elastically or inelastically. In an elastic collision, the gas molecule sees no change in its energy and reflects back into the gas phase without altering the system; whereas in an inelastic collision, the gas molecule may lose or gain energy in the process of adsorption. Molecules interact with the surface either through physical adsorption via van der Waal forces (dispersion forces, short-range repulsive forces, electrostatic forces, or polar molecule adsorption) or chemical adsorption via chemical hybridization of the atoms of the adsorbate, where the activation energy conquers and electrons are transferred between the surface and adsorbed molecule. There exists a weak force of attraction between adsorbate and adsorbent in physical adsorption with heat of adsorption in the range 20–40 kJ mol^{-1} and the molecule retains its electronic structure (although there can be a chance of structural distortion). Chemical adsorption involves relatively strong and selective adsorption of adsorbate on the adsorbent surface with heat of adsorption ranging between 40 and 400 kJ mol^{-1}. It results in the formation of a monolayer as all the adsorbed atoms or molecules create a strong bond with the surface. On the other hand, in physisorption, multilayer adsorption of atoms or molecules occurs. The deciding factors to distinguish physisorption with chemisorption are the magnitude of heat adsorption, the heat of adsorption variation with coverage, reversibility, extent of adsorption, pressure dependence, rate of adsorption, and rate of desorption.

3.2.2.1 Heat of adsorption

Heat of adsorption is an important property used to distinguish the type of adsorption and for the determination of degree of surface heterogeneity. When a molecule is adsorbed on a catalyst surface, usually heat energy is liberated. This loss in energy is mostly associated with structural changes of the reactant molecule in the adsorbed state with respect to the free (gaseous) state. The value of heat of adsorption depends on the strength of a bond formed during adsorption and degree of surface coverage (θ). Isosteric heat of adsorption (ΔH°_{A}) is calculated using the Clausius-Clapeyron equation, which is written as

$$\triangle H^{\circ}_{A} = R\left\{\left[\frac{\partial \ln P}{\partial\left(\frac{1}{T}\right)}\right]\right\}_{\theta} \tag{3.10}$$

where R is the universal gas constant, θ is the fraction of adsorbed sites at a pressure, P and temperature, T. A plot of $\ln P$ versus $1/T$ yields a straight line with a slope of $\Delta H^{\circ}_{A}/R$.

3.2.2.2 Concept of precursor-mediated adsorption

Taylor and Langmuir [15] suggested that adsorption is mediated by a precursor state. It is then transformed into a chemisorbed state. This kind of adsorption is frequently found in several solid catalyzed systems. The precursor state is mainly of two types: intrinsic precursor state and extrinsic precursor state. The former corresponds to adsorption on a clean surface, and the latter represents on the surface already containing some adsorbed species. The molecule incident on the catalyst surface transforms into a precursor state. It will then be free to move over the surface and find an empty site with higher sticking probability of adsorbed molecule over the surface. Kisliuk first proposed the kinetic model of precursor-mediated adsorption [16]. In following up on this model, several modifications were established by various groups. According to the Kisliuk model, nondissociative molecular adsorption occurs on a limited number of identical sites. When a reactant approaches the clean surface, either the probability of adsorption or the probability of migration to the nearest sites will be possible. But for the molecule adsorbed on the occupied sites there is only the probability of migration or desorption. According to King and Wells [17], the trapping coefficient, α, is used to express the probability of the precursor state formation. The initial sticking probability, S_o, is decided by α and the competition between adsorption and desorption from the precursor state. The ratio between the sticking coefficient and the initial sticking probability is given by the expression:

$$\frac{S_\theta}{S_o} = \left[1 + K\left(\frac{1}{\theta_{req}} - 1\right)\right]^{-1} \tag{3.11}$$

This equation is applicable for explaining both dissociative and nondissociative adsorptions [17,18].

3.2.2.3 Adsorption isotherms

Adsorption isotherms represent the mass of adsorbate adsorbed on unit mass of adsorbent at constant temperature for pressures from zero to saturated vapor pressure of the adsorbate. Determination of adsorption isotherms is a preliminary step in determining the pore textures. An adsorption isotherm is attained by measuring the amount of gas adsorbed across a wide range of relative pressures at a constant temperature. Desorption isotherms are formed by measuring the gas removed as the pressure of adsorbate is lowered. The term θ is used to demonstrate the fractional coverage of a surface with a particular adsorbed atom or molecule, and is defined as the ratio of the volume of adsorbate per volume required for monolayer coverage (V/V_m). Adsorption isotherms are the most suitable way for explaining the adsorption phenomenon and are used for determining the surface area and pore properties of the materials. There are several mathematical models for describing the adsorption process through adsorption isotherms. A few important models are discussed in the following sections.

3.2.2.3.1 Freundlich adsorption isotherm

In 1909, Freundlich derived a relationship between the extent of gas adsorption per unit mass and the corresponding pressure under isothermal conditions, known as Freundlich adsorption isotherm. It is expressed as follows:

$$\theta = KP^{1/n} \tag{3.12}$$

where θ is the mass of adsorbate per unit adsorbent and P is pressure; K and n are constants which depend on the nature of adsorbent and adsorbate gas at a given temperature. A graphical representation of Freundlich adsorption isotherm is shown in Fig. 3.3. This model illustrates the nonideal and reversible adsorption and no restriction on monolayer formation. They are also applicable to multilayer adsorption with nonuniform distribution of adsorption over

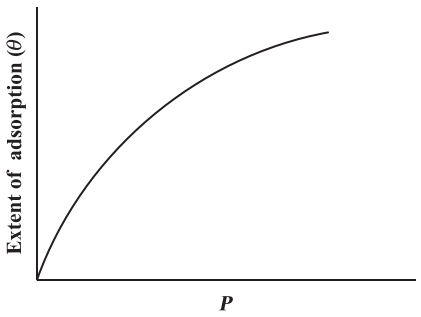


Fig. 3.3
Freundlich adsorption isotherm.

the surface. It is appropriate to use this for heterogeneous systems, especially for organic compounds and highly reactive species on activated carbon and molecular sieves. It is useful only for the adsorption at lower pressure. The value of θ increases with an increase in P, but when $n > 1$ it does not increase suddenly. The plot of $\log(\theta)$ versus $\log P$ shows a straight line with a slope of $1/n$ and intercept of $\log K$. The slope gives an idea of surface heterogeneity and adsorption intensity. In chemisorption, normally, this value is less than unity, and in cooperative adsorption it is greater than unity. When $1/n$ value is close to zero, the surface becomes more heterogeneous [19,20].

3.2.2.3.2 Langmuir adsorption isotherm

Irvin Langmuir put forward a more precise theory of adsorption for the monolayer adsorption on uniform surfaces [9,18]. The model was derived considering the following assumptions: (1) adsorption occurs only at a single layer of specific localized sites (chemical adsorption), (2) interactions between the adsorbed molecules and their transport over the surface can be ignored, and (3) all the adsorbed sites are energetically identical and equivalent; enthalpy of adsorption is independent of coverage. The equilibrium reaction for monolayer adsorption can be represented as

$$A + S \leftrightarrow A - S \tag{3.13}$$

$A - S$ represents the adsorbed molecule (A), and S is the surface site. The overall reaction rate considering both adsorption and desorption is given as follows:

$$r = k_{\text{ads}} P_{\text{A}}(1 - \theta_{\text{A}}) - k_{\text{des}}\theta_{\text{A}} \tag{3.14}$$

where r is the overall reaction rate; θ_{A} and $(1 - \theta_{\text{A}})$ are fractions of surface covered and uncovered, respectively, by a molecule A; k_{ads} and k_{des} correspond to rate constants of adsorption and desorption, respectively; and P_{A} is the pressure of adsorbed gas. When reaction is at equilibrium, the value of r becomes zero and the extent of adsorption and desorption become equal. Accordingly,

$$P_{\text{A}}\frac{k_{\text{ads}}}{k_{\text{des}}} = \frac{\theta_{\text{A}}}{1 - \theta_{\text{A}}} \tag{3.15}$$

On rearranging Eq. (3.15), the equilibrium fractional coverage (θ_{A}) is expressed as:

$$\theta_{\text{A}} = \frac{KP_{\text{A}}}{1 + KP_{\text{A}}} \tag{3.16}$$

where $K = k_{\text{ads}}/k_{\text{des}}$. A plot of P_{A} versus θ_{A} (Fig. 3.4) allows determination of the equilibrium saturation point for the adsorption of molecules on surface sites. Langmuir adsorption is

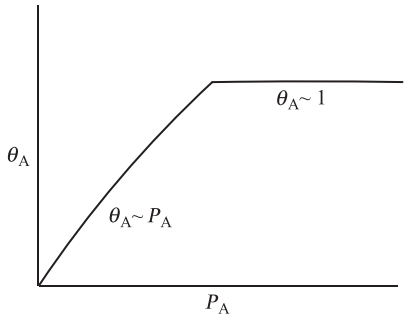


Fig.3.4
Langmuir adsorption isotherm.

also applicable to bimolecular systems with dissociative and nondissociative modes of adsorption. In the case of bimolecular dissociative adsorption,

$$A_2 + 2S \leftrightarrow 2A - S \tag{3.17}$$

at equilibrium condition, the equation for adsorption can be written as

$$(KP_{A_2})^{1/2}(1-\theta_A) = \theta_A \tag{3.18}$$

or

$$\theta_A = \frac{(KP_{A_2})^{1/2}}{1+(KP_{A_2})^{1/2}} \tag{3.19}$$

For nondissociative adsorption of A and B, the fractional coverage of A and B (θ_A and θ_B, respectively) over the surface sites can be expressed by the following empirical relationships:

$$\theta_A = \frac{K_A P_A}{1+K_A P_A + K_B P_B} \tag{3.20}$$

$$\theta_B = \frac{K_B P_B}{1+K_A P_A + K_B P_B} \tag{3.21}$$

Here, $K_A = k_{ads(A)}/k_{des(A)}$ and $K_B = k_{ads(B)}/k_{des(B)}$.

3.2.2.3.3 Multilayer physisorption isotherms

The Brunauer-Emmett-Teller (BET) model is the most accepted model for calculating monolayer coverage of adsorbate. The basic assumptions of the BET model are the following: (1) the heat of adsorption of the first layer is constant and lateral interactions are ignored, (2) the rate of adsorption of any layer is equal to the rate of desorption of the next layer lying above it, and (3) the heat of adsorption of the second, and all other, layers is equal to the heat of the liquefaction of gas. For infinite number of layers, the adsorption is defined by Eq. (3.22),

$$\frac{1}{V\left[\left(\frac{P_o}{P}\right)-1\right]}=\frac{1}{V_mC}+\frac{C-1}{V_mC}\left(\frac{P}{P_o}\right) \tag{3.22}$$

where V is the volume of gas adsorbed at a pressure P, V_m is the volume of adsorbate as monolayer, P_o is the saturation vapor pressure of adsorbate, P/P_o is the relative vapor pressure, and C is the BET constant related to heat of adsorption and liquefaction. This equation is in linear form with an intercept $1/V_mC$ and slope of $(C-1)/V_mC$. Substituting the value of V_m, total surface area (S_t) of a material can be determined using the following equation [21],

$$S_t=\frac{V_mN\sigma}{V} \tag{3.23}$$

where N is the Avogadro number, σ is the cross sectional area of the adsorbed molecule, and V is the molar volume of adsorbate gas. For a nitrogen molecule, the generally accepted value of σ is 0.162 nm^2. Specific surface area is then determined from the total surface area per unit molar weight of adsorbed species.

3.2.2.3.4 Temkin isotherm

Temkin developed a model for explaining the variation of heat of adsorption in the CO chemisorption processes on the crystal planes of Pt. By ignoring the extremely low and large values of concentrations, the model assumes that the heat of adsorption (a function of temperature) of all molecules in the layer would decrease linearly rather than logarithmically with the coverage. This model presumes a linear variation of the heat of adsorption with the coverage for all molecules in a layer. Accordingly,

$$K=K_oe^{\frac{Q_{a_o}(1-\alpha\theta)}{RT}} \tag{3.24}$$

where Q_{a_o} is the initial heat of adsorption, θ is the surface coverage, and α is a constant. It is assumed that the surface is uniform, and single-site adsorption takes place. But it is known from Eqs. (3.15) and (3.16) that

$$KP=\frac{\theta}{1-\theta} \tag{3.25}$$

Substituting the value of KP in Eq. (3.24), it takes the form

$$K_oPe^{\frac{Q_{a_o}(1-\alpha\theta)}{RT}}=\frac{\theta}{1-\theta} \tag{3.26}$$

Taking logarithm and rearranging the previous equation:

$$\ln P = -\ln\left(K_o e^{\frac{Q_{a_o}}{RT}}\right) + \frac{\alpha Q_{a_o}\theta}{RT} + \ln\frac{\theta}{1-\theta} \tag{3.27}$$

$$\ln\left(K'_o P\right) = \frac{\alpha Q_{a_o}\theta}{RT} + \ln\frac{\theta}{1-\theta}\left[\text{where}\, K'_o = K_o e^{\frac{Q_{a_o}}{RT}}\right] \tag{3.28}$$

The value of K'_o is independent of the coverage, θ, and the last term of Eq. (3.28) does not change as much with the coverage. For chemisorptions, αQ_{a_o} is high so that ln P principally depends on $\frac{\alpha Q_{a_o}\theta}{RT}$. Hence, a linear relationship between θ and ln P is is established.

$$\theta = \frac{RT}{\alpha Q_{a_o}} \ln\left(K'_o P\right) = A \ln\left(K'_o P\right) \tag{3.29}$$

This is the Temkin equation for uniform surface sites. For nonuniform surface sites, the equation can be written as

$$\theta = \frac{RT}{\alpha Q_{a_o}} \ln\left(\frac{1 + K'_o P}{1 + K'_o P e^{\frac{-\alpha Q_{a_o}}{RT}}}\right) \tag{3.30}$$

At lower values of $K'_o P e^{\frac{-\alpha Q_{a_o}}{RT}}$ ie, $K'_o P e^{\frac{-\alpha Q_{a_o}}{RT}} << 1$ and in the case of dissociative adsorption, the equation obtained is similar to Eq. (3.29) [22,23].

3.2.2.4 Types of adsorption isotherms

According to IUPAC recommendations, experimentally observed adsorption isotherms are classified mainly into six types, I–VI (Fig. 3.5). The shape of isotherm depends on the porous structure of a solid. Type I isotherm is characteristic of a microporous material; for

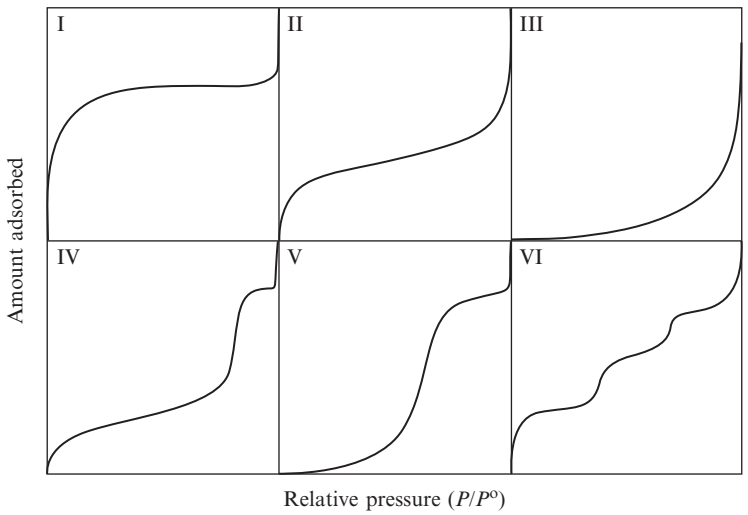


Fig. 3.5
Different types of adsorption isotherms.

example, active carbon, zeolite, and zeolite-like crystalline solids. It is described by the Langmuir equation. In such materials, the adsorbate-pore wall interaction is much higher causing the adsorption to occur even at very low relative pressures. They are characterized by a horizontal plateau. The asymptotic value of the mass adsorbed approaches and maintains a steady state even for very high gas pressures. High pressure is usually required for complete filling of pores with the adsorbate. But in the case of microporous materials, this happens in the low relative pressures region itself, without any capillary condensation. In other words, these isotherms show micropore filling, but no multilayer adsorption. Chemisorption often shows type I isotherm. The BET method cannot be applied to measure the surface area of the microporous materials [21]. Type II isotherms are often found for adsorptions in mesoporous materials and in disperse, nonporous, or macroporous materials, where the monolayer adsorption occurs at low relative pressures followed by a multilayer adsorption at high relative pressures. Type III and type V are observed where there is a small adsorbate-absorbent interaction and the heat of adsorption is less than the heat of liquefaction. This results in the preferential adsorption of the incoming molecule on another adsorbed molecule rather than on a vacant site, which restricts the monolayer formation. Type III isotherm is generally shown by nonporous or macroporous solids with characteristic weak gas-solid interaction, and type V is depicted by mesoporous or microporous solids and may be instigated through the adsorption of either polar or nonpolar molecules. Porous adsorbents with pores in the range of 1.5–100 nm (generally mesopores) exhibit type IV isotherm. They describe mono- and multilayer adsorption with capillary condensation. The lower pressure region of the graph is similar to type II, which explains the formation of the monolayer followed by the multilayer. The hysteresis of adsorption-desorption isotherms gives an idea about their pore shape. Type VI isotherms are usually exhibited by uniform ultramicroporous solid surfaces and involve the stepwise formation of monomolecular adsorption layers, and each step attributes to the adsorption on one set of active sites; and step height indicates monolayer capacity. They are usually observed in the case of well-crystallized zeolite X or silicates.

The isotherms of several solid systems display hysteresis, which are normally observed in the case of adsorptions in porous material with capillary condensation. Hysteresis is typically ascribed to diverse pore properties, which include different pore sizes and pore body (eg, ink bottle-shaped pores). Experimentally, four kinds of hysteresis loops are commonly observed (Fig. 3.6) [24]. The H1 loop indicates narrow distribution of uniform cylindrical-like

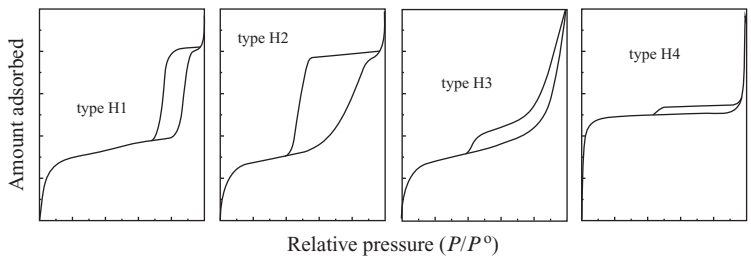


Fig. 3.6
Common hysteresis loops observed in type IV adsorption isotherms.

pores, or agglomerates, of compacts of approximately uniform spheres. In H2 type hysteresis, determination of pore size and shape is more complicated, where network effects have more importance. In comparison with H1 and H2 hysteresis loops, there is no confinement in adsorption at high P/P^{o} observed in the case of the H3 loop. It is given by an assembly of flexible platelike particles or slit-shaped pores. Type H3 hysteresis also contains a steep region associated with a closure of the hysteresis loop, due to the tensile strength effect. Complex materials containing both micropores and mesopores are exhibited in the H4 type hysteresis loop [25].

3.2.2.5 Kinetics of adsorption

A molecule approaches the surface of an adsorbent and ultimately gets entrapped in a potential known as the sticking potential. The rate of adsorption (r_{ads}) is the most appropriate way to explain this fact. It can be expressed in terms of partial pressure of a molecule in the gas phase over the surface,

$$r_{ads} = k' P^{x} \tag{3.31}$$

where x is the kinetic order, k' is the rate constant, and P is the partial pressure. Substituting the value of k' from the Arrhenius equation, the above is expressed as

$$r_{ads} = A e^{-E_{ads}/RT} p^{x} \tag{3.32}$$

where E_{ads} is the activation energy for adsorption and A is the pre-exponential factor. As per the kinetic theory of gases, the rate of interaction or collision between gaseous molecules and unit surface sites in a unit time (R_{col}) is proportional to the mean molecular velocity and concentration of molecules,

$$\text{Flux or } R_{col} = \frac{P}{(2\pi m K_B T)^{1/2}} \tag{3.33}$$

where K_B is the Boltzmann constant, P is the pressure of the system in Nm^{-2}, m is the mass of the molecule in kg, and T is the temperature in Kelvin. Considering a simple case, the rate of adsorption is proportional to the molecular flux (or rate of collision) and the actual efficiency of sticking them on the surface, which is called the sticking probability (S).

$$r_{ads} = S R_{col} \tag{3.34}$$

$$r_{ads} = \frac{SP}{(2\pi m K_B T)^{1/2}} \tag{3.35}$$

The sticking probability varies with the adsorbate, trapping probability, number of occupied and bare sites, surface heterogeneity, steric factor, and activation energy. In an approach of simple activated adsorption, the sticking probability is defined as

$$S = \sigma f(\theta) e^{-E_{ads}/RT} \tag{3.36}$$

where σ is the steric factor, $f(\theta)$ is a function of existing surface coverage of adsorbed species, and E_{ads} is the activation energy of adsorption. It is assumed that S is directly proportional to the amount of empty surface sites. This assumption is most appropriate for the nondissociative adsorption of a molecule. Then, $f(\theta)$ is proportional to $(1-\theta)$. Accordingly, Eq. (3.35) takes the form:

$$r_{ads} = \frac{\sigma f(\theta) e^{-E_{ads}/RT} P}{(2\pi m K_B T)^{1/2}} \tag{3.37}$$

Activation energy for adsorption and steric factors may be significantly influenced by the surface coverage. Then, $E_{ads} = E_{ads}(\theta)$ and $\sigma = \sigma(\theta)$. Usually activation energy increases with an increase in the coverage. Considering these factors, the equation for r_{ads} can be rewritten as

$$r_{ads} = \frac{\sigma(\theta) f(\theta) e^{-E_{ads}(\theta)/RT} P}{(2\pi m K_B T)^{1/2}} \tag{3.38}$$

3.2.3 Surface Reactivity: Concept, Kinetics, and Mechanism

Heterogeneous catalytic reactions are usually carried out over the surface of a solid catalyst. The catalyst surface has free vacancies, which provides active sites for adsorbing the reactant molecules [9,26]. When reactants come in contact with active surface sites, the molecule or atoms (nondissociated or dissociated) stick over the surface due to the chemical force of attraction and heat of interaction between the reactant molecules and the active catalyst surface. The adsorbed molecules may react with each other leading to formation of new product molecules, and then the formed product departs away from the surface and makes available the vacant sites for adsorption by fresh reactant molecules. The mechanism of the surface reaction in a heterogeneous catalytic process is mainly explained by two well-known approaches: the Langmuir-Hinshelwood mechanism and the Eley-Rideal mechanism. The pathways and kinetics of such mechanisms are discussed here.

3.2.3.1 Langmuir-Hinshelwood mechanism

The Langmuir-Hinshelwood (LH) mechanism is explained on the basis of the following assumptions: The reactants, either monomolecular or bimolecular, adsorb on the active sites of a catalyst surface (S) in a nondissociative approach, and then the surface reaction occurs between two adjacent chemisorbed molecules to form product P, which is desorbed out from the surface (Fig. 3.7). This mechanism has been applied for many reactions including commercial processes; eg, (1) oxidation of CO into CO_2 in presence of a Pt catalyst, (2) CO hydrogenation to methanol on a ZnO catalyst, (3) hydrogenation of ethylene on a Cu catalyst, (4) Pt- or Au-catalyzed reduction of N_2O, and (5) ethylene oxidation to acetaldehyde using Pd catalysts [10]. There are two kinds of kinetic considerations in heterogeneous catalysis, effective, or macrokinetics, and intrinsic, or microkinetics. Macrokinetics considers the

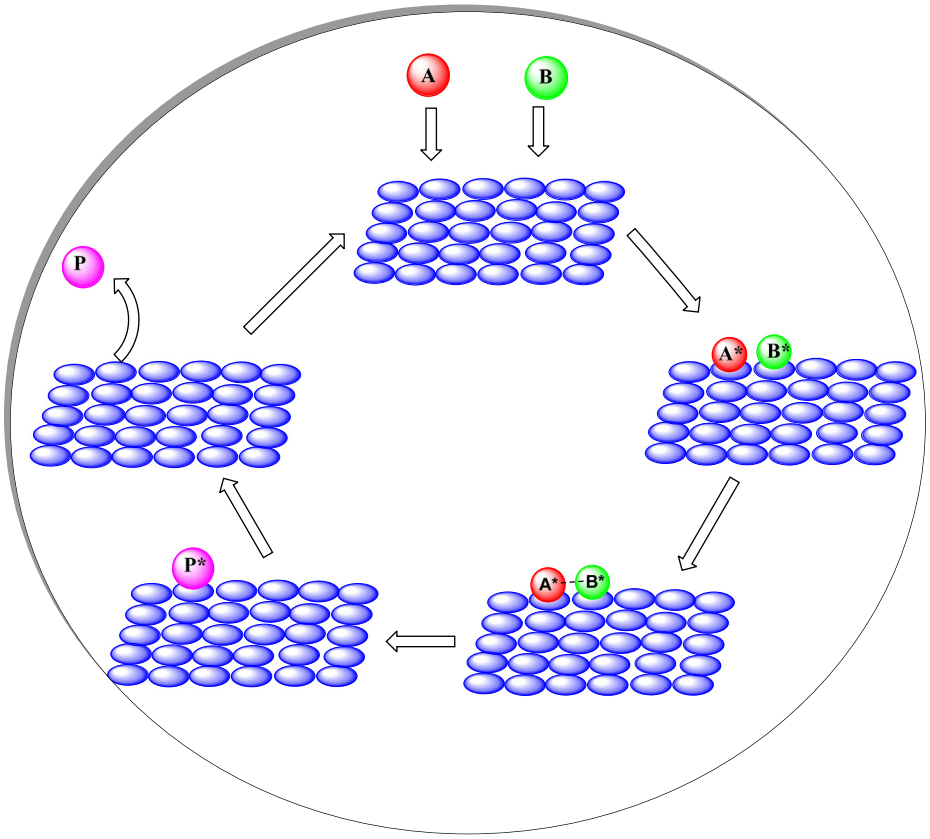


Fig. 3.7
Schematic representation of Langmuir-Hinshelwood mechanism.

kinetics of overall reaction, whereas microkinetics refers to the kinetics of individual chemical transformation steps (adsorption, surface reaction, and desorption). Unimolecular surface reactions follow the given reaction steps shown here:

$$A_{(gas)} + S \underset{k_{-A}}{\overset{k_{+A}}{\rightleftharpoons}} A\text{-}S$$

$$A\text{-}S \underset{k_{-R}}{\overset{k_{R}}{\rightleftharpoons}} P\text{-}S$$

$$P\text{-}S \underset{k_{-D}}{\overset{k_{D}}{\rightleftharpoons}} P_{(gas)} + S$$

The rate of the reaction can be expressed either by a rate-determining step approximation or by a steady state approximation.

3.2.3.1.1 Rate-determining step approximation

The rate-determining step controls the overall reaction rate. Any of the three steps described earlier (adsorption of a reactant, surface reaction, and desorption of product) can possibly act as the rate-determining step. Consider the case where the surface reaction is the rate-determining step and the adsorption of reactant (A) and desorption of product (P) are quasi-equilibrated steps. The rate of reaction (r) is proportional to the surface coverage of A.

$$r = k_R \theta_A \tag{3.39}$$

The kinetic expression of this reaction can be derived by considering equilibrium. It is assumed that the surface coverage of the product (θ_P) is small, which is suitable especially with a small conversion of A and a lower reaction rate.

$$k_{+A} P_A (1 - \theta_A) = k_{-A} \theta_A \tag{3.40}$$

The fraction of surface coverage of adsorbent A is expressed as

$$\theta_A = \frac{K_A P_A}{1 + K_A P_A} (K_A = k + A/k - A) \tag{3.41}$$

From Eqs. (3.39)–(3.41), rate of the reaction can be written as

$$r = \frac{k_R K_A P_A}{1 + K_A P_A} \tag{3.42}$$

The order of this reaction varies according to the pressure of adsorbate, or the rate constant of adsorption. If the term $K_A P_A$ is small, then it is a first-order kinetics in A, and its higher value leads to a zero-order kinetics in A.

If the adsorption of reactant A on the surface is the rate-determining step and the other two steps (product formation and desorption) are relatively fast and quasi-equilibrium, then the rate is proportional to the empty sites available on the surface.

$$r = k_{+A} P_A \theta_E \tag{3.43}$$

This fractional coverage of vacant sites, $\theta_{E,}$ is not possible to determine directly. The solid catalyst contains a specific amount of energetic hubs, which are considered as the active sites of the catalyst. They may contain adsorbed species θ_A, θ_P and vacant sites θ_E. Thus, the total surface concentration is the sum of all three parameters and the normalized form of the equation is expressed as

$$\theta_E + \theta_A + \theta_P = 1 \tag{3.44}$$

The concentration of adsorbed species on the surface sites (θ_A and θ_P) is measured in the range of zero-surface coverage to full-surface coverage (which is assumed to be one). From the

reaction equilibrium steps, we obtain $\theta_A = \frac{\theta_P}{K_R}$ and $\theta_P = \frac{P_P \theta_E}{K_D}$. Substituting these values in Eq. (3.44), eliminating θ_A and θ_P and solving for θ_E, the expression changes to

$$\theta_E = \frac{1}{1 + \left[(1 + K_R)P_p/(K_R K_D)\right]} \left(K_R = \frac{k_{+R}}{k_{-R}}; K_D = \frac{k_{+D}}{k_{-D}}\right) \tag{3.45}$$

Substituting for θ_E from Eq. (3.45) into 3.43 yields a form of the rate expression, which contains either constants or measurable concentrations:

$$r = \frac{k_{+A} P_A}{1 + K_R' P_p} \left(K_R' = \frac{1 + K_R}{K_R K_D}\right) \tag{3.46}$$

At lower conversions, the rate is dependent on P_A due to low P_p value and is a first order in A. At higher values of P_p, $r = \frac{k_{+A} P_A}{K_R' P_p}$. It is a first order in A and hindered by P_P. This may be caused by the close approach of equilibrium through fast adsorption of A, and large coverage of surface by A and P.

When desorption of the product is the rate-determining step, the overall reaction rate is controlled by the third sequential step; and the rate is described by Eq. (3.47).

$$r = k_{+D} \theta_P \tag{3.47}$$

The value of θ_P is obtained by substituting the values of θ_A and θ_E in Eq. (3.44) and the rate equation becomes

$$r = \frac{k_{+D} K_A K_R P_A}{1 + (K_A + K_A K_R) P_A} \tag{3.48}$$

This equation is quite similar to the case where surface reaction is the rate-determining step. In each of the three cases, the rate of reaction is derived based on the rate-determining step approximation. But this method has limitations as rate determination is largely related to reaction conditions such as reactant concentration, temperature, etc. Hence, this method is applicable only to a few cases.

3.2.3.1.2 Steady state approximation

The rate expression derived using steady state approximation is an inclusive form, covering a diverse range of conditions. According to this approximation, for a closed batch or transient system, the change in concentration with respect to time is approximately zero. As per the general definition of rate, the overall reaction rate is written as [26]

$$r = \frac{-dC_A}{dt} = \frac{dC_P}{dt} = k_D \theta_P \tag{3.49}$$

Applying steady state approximation to the degrees of creation and vanishing empty sites on the catalytically active surface,

$$\frac{d\theta_E}{dt} \approx -k_{+A}P_A(1-\theta_A-\theta_P)+k_{-A}\theta_A+k_D\theta_P-k_{-D}P_P\theta_P=0 \tag{3.50}$$

Similarly, applying this approximation to the rates of change of θ_A and θ_B with respect to time,

$$\frac{d\theta_A}{dt} \approx k_{+A}P_A(1-\theta_A-\theta_P)-k_{-A}\theta_A-k_R\theta_A=0 \tag{3.51}$$

$$\frac{d\theta_P}{dt} \approx k_R\theta_A-k_D\theta_P=0 \tag{3.52}$$

Combining Eqs. (3.49), (3.51) and (3.52),

$$r=\frac{k_R\dfrac{k_{+A}}{k_{-A}}P_A}{\left(1+\dfrac{k_R}{k_{-A}}\right)+\left(1+\dfrac{k_R}{k_D}\right)\dfrac{k_{+A}}{k_{-A}}P_A} \tag{3.53}$$

If the adsorption and desorption rates are much higher than the rate of surface reaction (ie, k_{+A}, k_{-A} and $k_D >> k_r$), then, the previous equation can be approximated as

$$r=k_R\frac{\dfrac{k_{+A}}{k_{-A}}P_A}{1+\dfrac{k_{+A}}{k_{-A}}P_A} \tag{3.54}$$

ie,

$$r=\frac{k_RK_AP_A}{1+K_AP_A} \tag{3.55}$$

At low partial pressure of A, the rate is a first order in A and, in high partial pressure, it becomes a zero order as $K_AP_A >> 1$. But

$$K_A=K_{A,\infty}e^{\left[\frac{(-\triangle H_{ads})}{RT}\right]} \tag{3.56}$$

where $(-\triangle H_{ads})$ is the heat of adsorption of a molecule, A, on the active catalyst surface. The negative sign indicates the exothermic nature of adsorption. For low temperatures, the fractional coverage of A is close to unity, and the rate is a zero order.

$$r \approx k_R = k_{R,\infty}e^{\left[\frac{-E_a}{RT}\right]} \tag{3.57}$$

When the temperature is low, activation energy, E_a, is relatively large and the rate is found to be low. At high temperatures, the reaction becomes first order and the rate is expressed as

$$r \approx k_RK_AP_A = k_{R,\infty}K_{A,\infty}e^{\left[\frac{E_a-(-\triangle H_{ads})}{RT}\right]}P_A \tag{3.58}$$

In bimolecular surface reactions, the surface-adsorbed reactants, A and B, are regarded as the rate- determining step [22].

$$A_{(gas)} + S \underset{k_{-A}}{\overset{k_{+A}}{\rightleftharpoons}} A\text{-}S$$

$$B_{(gas)} + S \underset{k_{-B}}{\overset{k_{+B}}{\rightleftharpoons}} B\text{-}S$$

$$A\text{-}S + B\text{-}S \underset{k_{-R}}{\overset{k_{+R}}{\rightleftharpoons}} P\text{-}S \quad \text{(rate determining step)}$$

$$P\text{-}S \underset{k_{-D}}{\overset{k_{+D}}{\rightleftharpoons}} P_{(gas)} + S$$

At a lower conversion, the values P_P and θ_P are low, K_{-R} is negligible, and then follows the irreversible rate law. Thus the rate of a reaction is written as

$$r = k_{+R}\theta_A\theta_B \tag{3.59}$$

Substituting the values θ_A and θ_B derived from Langmuir isotherms, the rate is expressed as

$$r = \frac{(k_{+R}K_AK_BP_AP_B)}{(1 + K_AP_A + K_BP_B)^2} \tag{3.60}$$

The rate increases initially with P_A. But a high P_A value results in a decrease in the rate of formation of the product due to a high surface of coverage of A with no regard for the other reactant species B. From Eq. (3.59), it is known that rate is proportional to θ_A and θ_B, where the lower value of θ_B decreases the reaction rate.

If bimolecular reactions occur through dissociative adsorption followed by the surface reaction of atomic species,

$$A_2 + 2S \rightarrow 2A - S$$

Then, fractional coverage θ_A is given as

$$\theta_A = \frac{\sqrt{K_{A_2}P_{A_2}}}{1 + \sqrt{K_{A_2}P_{A_2}}} \tag{3.61}$$

and the irreversible rate expression can be written as

$$r = k_{+R}\theta_A = \frac{k_{+R}\sqrt{K_{A_2}P_{A_2}})}{\left(1 + \sqrt{K_{A_2}P_{A_2}}\right)^2} \tag{3.62}$$

In another prospect, the catalyst exhibits two different types of active sites, which may undergo competitive adsorption where one reactant adsorbs on one set of adsorbent sites, and the second reactant on the other site. Hydrogenation or dehydrogenation relating to hydrocarbon and organic molecules are the reactions that occur through this scheme [27,28]. In such cases, the rate of irreversible reaction is expressed as

$$r = \frac{C_1 C_2 k_R K_A K_B P_A P_B}{(1 + K_A P_A)(1 + K_B P_B + K_P P_P)} \tag{3.63}$$

where C_1 and C_2 represent concentrations of the two surface sites. NO decomposition to N_2 and O_2 with manganese oxide catalysts [29] and benzene hydrogenation using Fe catalysts [30] are examples of catalytic reactions that follow the Langmuir-Hinshelwood mechanism.

3.2.3.2 Eley-Rideal mechanism

This mechanism is observed for bimolecular surface reactions, in which only one of the reactant molecules is adsorbed on the active catalytic surface. The reactant molecule in the gas phase undergoes a chemical reaction with the surface-adsorbed reactant through direct collisions with them. The mechanistic steps are depicted in Fig. 3.8. Oxidation of ethylene to ethylene oxide is a well-known example which follows the Eley-Rideal mechanism. In this reaction, originally adsorbed oxygen reacts with ethylene in the gas phase to form ethylene oxide. However, sometimes the dissociative adsorption of oxygen takes place, which leads to

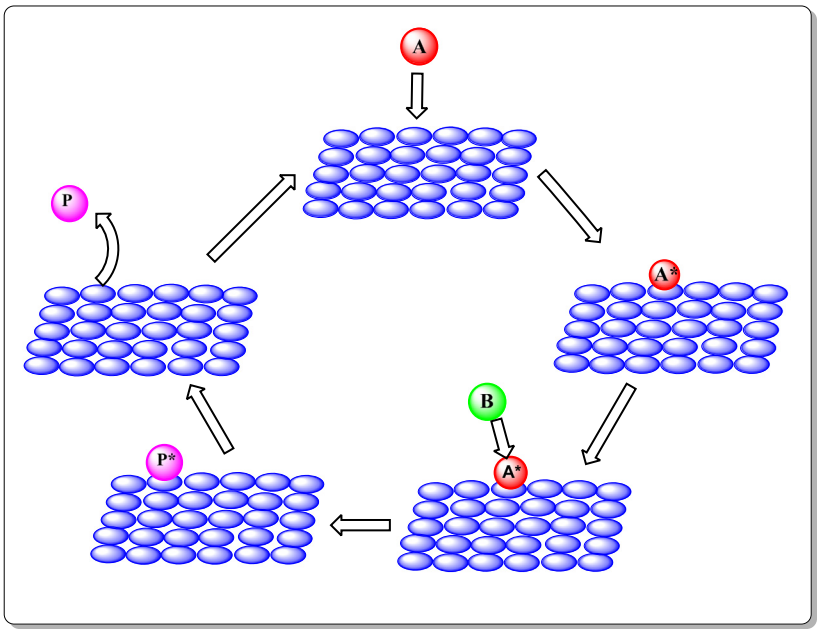


Fig. 3.8
Schematic representation of Eley-Rideal mechanism.

formation of unwanted products. Oxidation of ammonia with Pt catalysts and selective hydrogenation of acetylene to ethylene on Ni or Fe catalysts are other important examples explained by this mechanism. In this mechanism, the first step, that is, the process of adsorption of A on the surface active sites, is reversible and occurs in equilibrium. In the second irreversible step, the chemical reaction of the gas phase molecule with the surface-adsorbed A is considered the rate-determining step.

$$A_{(\text{gas})} + S \leftrightarrow A - S$$
$$A - S + B_{(\text{gas})} \xrightarrow{K_R} P - S(\text{rate} - \text{determining step})$$
$$P - S \leftrightarrow P$$

The rate of a reaction is directly proportional to $\theta_A P_B$, ie,

$$r = k_R \theta_A P_B \tag{3.64}$$

Substituting the value of θ_A, the rate equation becomes

$$r = \frac{k_R K_A P_A P_B}{1 + K_A P_A} \tag{3.65}$$

This is the general expression for the rate of reaction, which occurs through the Eley-Rideal mechanism and is known as Eley-Rideal kinetics. At lower values of P_A and at constant P_B, $K_A P_A$ is negligible, so the rate can be first order in A and B. In other words, $r = k_R K_A P_A P_B$. At high P_A values, $r = k_R P_B$, which is a zero order in A and a first order in B. Even at a constant P_A, it is a first order in B.

3.2.4 Desorption

Desorption is a phenomenon contradictory to adsorption, which occurs as a final catalytic step in heterogeneous-catalyzed reactions. It involves the removal of surface-adsorbed species and makes the surface ready for further adsorption by new reactant molecules. The reactants, or products in their adsorbed state in thermal equilibrium, are locked in a characteristic potential limit. Induction of electronic or thermal energy is necessary to overcome the potential barrier and to facilitate the desorption process. This elementary process is always endothermic in nature and found to be a slow process occurring in several catalytic reactions carried out under high-pressure conditions [31]. At low temperatures, adsorbed species are normally retained on the surface. When the temperature is increased, the adsorbed molecule may decompose and undergo the surface reaction between the molecules or atomic species; further, it will desorb from the surface and return back to the gaseous phase. The rate of desorption is directly related to the surface concentration of adsorbate. Temperature plays a key role in the rate of desorption. In general, rate of desorption is defined as

$$r_{\text{des}} = k_{\text{des}} N = k_{\text{des}} C(1 - \theta_E) \tag{3.66}$$

where k_{des} is the rate constant for desorption and N is the concentration of surface-adsorbed species, which can be expressed as $N = C(1 - \theta_E)$. Taking into consideration the Arrhenius equation, the rate constant for desorption is given by:

$$k_{des} = Ae^{\frac{-E_{des}}{RT}} \tag{3.67}$$

Hence, the rate of desorption is expressed as

$$r_{des} = \upsilon N e^{\frac{-E_{des}}{RT}} \tag{3.68}$$

where E_{des} is the activation energy for desorption, which is equivalent to enthalpy of adsorption; and A is the pre-exponential factor, which is also known as the frequency factor (υ) for overcoming the potential barrier of desorption. The surface residence time of adsorption is closely interconnected with desorption, and it is defined as the average residing time of a molecule on a surface in particular reaction conditions [32]. The average residence time of the molecule prior to desorption is described by the formulae:

$$\tau = 1/k_{des} \tag{3.69}$$

or

$$\tau = \tau_0 e^{\frac{-\Delta H_{ads}}{RT}} (\text{where } \tau_0 = 1/A \text{ or } 1/\upsilon) \tag{3.70}$$

3.3 Definitions

Activity, selectivity, and stability are the most frequently used terms to describe the efficiency of a catalyst. *Activity* is the speed at which reactants are converted into products. It is generally defined by the term *rate,* which is defined as moles of product formed or reactant converted per unit time and unit weight of catalyst (mol Kg^{-1} h^{-1} or mol L^{-1} h^{-1}). The rate of a reaction depends on reaction temperature and is expressed by the Arrhenius equation as follows:

$$k = Ae^{-E_a/RT} \tag{3.71}$$

where k is rate constant, E_a is the activation energy of a reaction, A is the pre-exponential factor, R is the gas constant, and T is the reaction temperature in Kelvin units. The conversion of a reaction indicates the overall catalytic activity and is expressed as the amount of reactant converted per amount of reactant fed. Turnover number/turnover frequency (TON/TOF) is generally used to express the specific activity of a catalyst. TON is used for determination of the longevity of a catalyst, whereas TOF is the actual quantification of specific activity of a particular catalyst for a particular reaction under explicit reaction conditions per unit time. It is defined as

$$\text{TOF} = \frac{\text{Moles of reactant converted or product formed}}{\text{Moles of active sites of catalyst} \times \text{time}} \tag{3.72}$$

In fact, it is not always easy to calculate TON/TOF accurately in heterogeneous-catalyzed reactions because the estimation of the number of active sites is not a trivial task. Hence, it is of importance to understand the active sites playing the key role in a particular reaction for calculating TOF.

Selectivity is an important criterion in industrial catalysis. Selectivity of a catalyst is its ability to direct reaction toward formation of desired products. In general, selectivity is described as the number of moles of the specific product formed in comparison to the total number of moles of the reactant converted. Chemical, thermal, and mechanical *stability* of a catalyst is important in deciding the life of a heterogeneous catalyst. A number of factors including decomposition, coking, poisoning, and sintering lead to the deactivation of catalysts. Catalyst deactivation is followed by measuring the activity and selectivity as a function of time. Long catalyst life is an important criterion in catalyst designing.

3.4 Types of Solid Catalysts

Heterogeneous catalysts can be classified in several ways according to their structure, internal architecture, chemical properties, and area of application. They are mainly divided into two categories: porous and nonporous materials. Porous materials are the major constituents of solid industrial catalysts. Their structural and textural properties are more impressive than the nonporous analogs. Introduction of porous catalysts, especially zeolites, has spread vital energy into industrial and academic research because of their advantages like catalyst stability, selectivity, longer lifetime, and product quality as well as their nontoxic and noncorrosive nature. Based on pore size, porous materials are further divided into three types: microporous (pore diameter < 2 nm), mesoporous (pore diameter in the range 2–50 nm), and macroporous (pore diameter > 50 nm). Porous and nonporous materials can also be subdivided into bulk and supported catalysts.

3.4.1 Bulk Catalysts

Bulk catalysts include a large variety of solids, which are widely applicable in industrial processes. Metal oxides, multicomponent oxides, zeolites, clays, hydrotalcites, metal organic frameworks (MOFs), covalent organic frameworks (COFs), ordered mesoporous materials, hierarchical zeolites, carbon, carbides, nitrides, etc., fall under the class of bulk catalysts.

3.4.1.1 Zeolites and mesoporous silica

Zeolites are an important class of microporous materials. Usually, their pore size ranges from 0.2–1 nm. Chemically, zeolites are crystalline microporous aluminosilicates with a three-dimensional network composed of SiO_4^{4-} and AlO_4^{5-} tetrahedra. The extra charge on alumina tetrahedra is compensated by alkali or alkaline earth metal cations. These cations are easily exchangeable with H^+ ions forming Brønsted acid sites. Tetrahedral units of silica

and alumina are arranged together through the sharing of an oxygen atom to form subunits, which polymerize to form sheetlike polyhedra and three-dimensional tertiary building blocks. The systematic arrangement of these three-dimensional building units result in materials with different porosity, and a caged zeolite of three-dimensional lattice structures [33–35]. The formation steps of zeolites from their parent units are described in Fig. 3.9 [36]. Table 3.2 presents some zeolites and their classification.

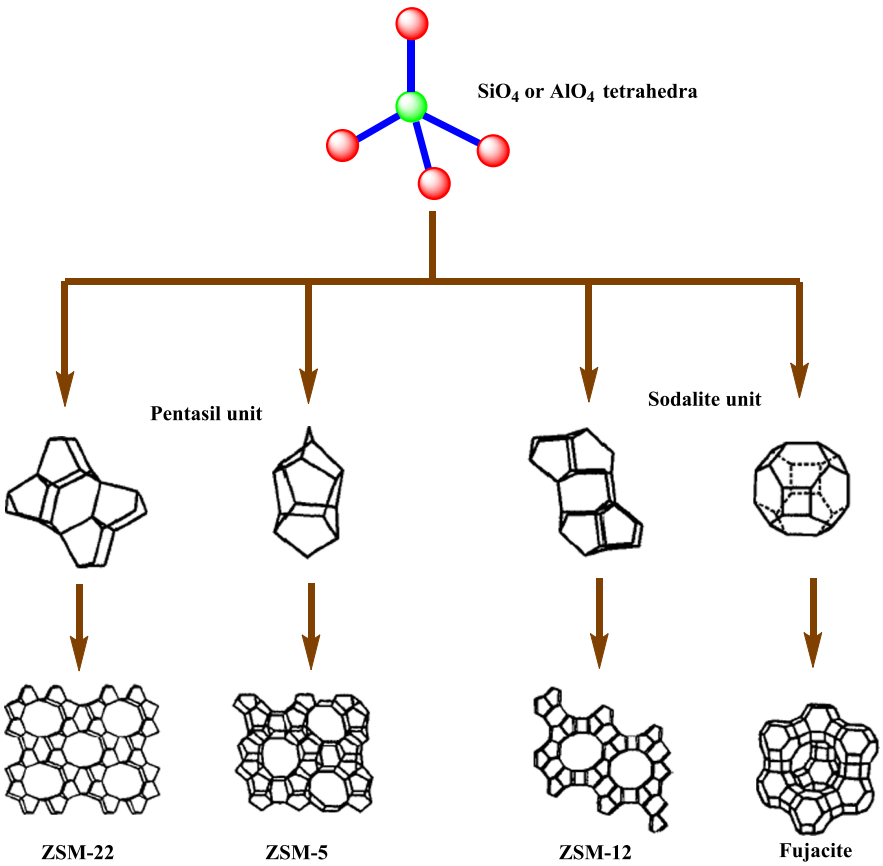


Fig. 3.9
Formation of zeolites from their parent units [36].

Table 3.2 Zeolites classification in accordance with their pore diameter

Class	Pore size (nm)	Examples
Small pore	0.30–0.45	Zeolite A
Medium pore	0.45–0.60	ZSM-5, ZSM-23, ZSM-11
Large pore	0.60–0.80	Zeolite-X, Zeolite-Y, Zeolite-β
Extra-large pore	0.80–1.0	UTD-1

Shape-selective catalysis is nothing but the catalytic reactions that depend on the structure and size of the catalyst and size of the reactant and product molecules. The shape selectivity usually increases with decreasing pore size. Large pore zeolites exhibit little or no selectivity. A small size porous network of zeolites are accessible only to reactants and products which can penetrate through the pore aperture. Shape selectivity can occur in three different ways. In the first case, only reactants with suitable size and shape interact with the active sites inside the porous network, and the remaining reactants are blocked from entering the pores. For example, the cracking of a *n*-heptane over H-ZSM-5 occurs at a faster rate than their branched isomers (2-methylhexane, 3-methylhexane, and 2,3-dimethylpentane). In the second case, the product of a particular size and shape can only come out through the pore channel. Methylation of toluene into xylene on ZSM-5 is a well-known example, where the desired product, *para*-xylene, is formed with 90% selectivity. *Ortho*- and *meta*-xylenes of large size isomerize inside the zeolite cavity, forming a thinner *para*-xylene, which quickly diffuses out from the pores. In the third case, shape selectivity is related to the chemical intermediate formed during the reaction. According to this, only those intermediates whose geometry fit into the zeolite pore channels can be formed during the catalytic process. Transition state selectivity and product selectivity is quite difficult to sort out. A schematic representation, with an example, of shape-selective catalysis is depicted in Fig. 3.10 [10].

The unique properties of zeolites such as acidity, shape selectivity and high thermal stability, structural versatility, and ion-exchangeability empower them to be valuable technical catalysts in the field of petrochemistry, fine chemicals, and chemical intermediates. Various postsynthetic methods, which include ion-exchange and chemical vapor deposition (CVD), are used for fine tuning of pore properties and altering the pore size of zeolites [37]. Transition metals (Ti, Cr, V, etc) incorporated in zeolites (in place of silica) improved their redox properties and are widely applied for selective oxidations, hydroxylation, and ammoxidation reactions [38]. Tetrahedral framework aluminum atoms are the main source of active sites in zeolite-catalyzed reactions. Zeolites are used for both acid- and base-catalyzed reactions. This active site formation occurs due to the charge imbalance between Si and Al in the framework. For instance, zeolite-based catalysis covers about 40% of the global industrial catalytic process. However, it has limitations in the catalytic reaction of bulky molecules, as the zeolite inhibits facile mass transfer of those molecules to and from the active sites. Diffusion controls the molecular transport and separation process in micro-mesoporous materials. At the end of the 1980s, microporous crystalline materials with uniformly large micropores, greater than 1 nm, were introduced [39]. But they have limitations from a practical point of view due to low thermal and hydrothermal stability compared to the silica-based molecular sieves. Aluminophosphates are a known example in this category. Its framework appears to be neutral and does not exhibit any catalytic activity. Metal incorporation on it generates moderate acidic and redox sites and acts as single-site heterogeneous catalysts [40].

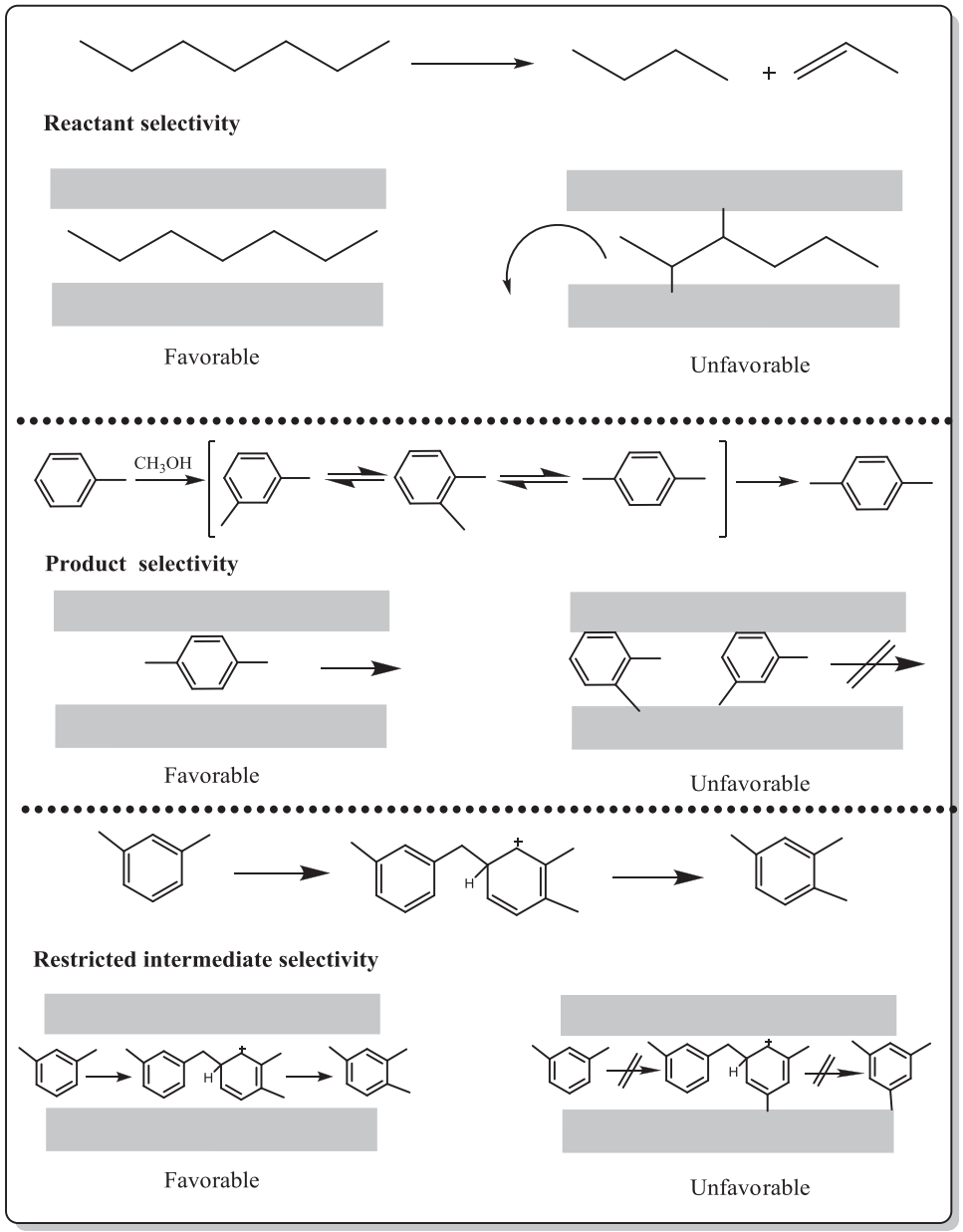


Fig. 3.10
Shape selective catalysis in zeolites [10].

The last few decades has witnessed the development of ordered mesoporous silica and aluminosilicate materials such as M41S, which were first introduced by Mobil [41]. However, despite their large pores, these mesoporous materials with amorphous framework are low in acidity and hydrothermal stability, limiting them in terms of commercial utility. More specifically, in the last decade, the development of mesoporous materials with zeolitic features has received a lot of attention. These combined zeolitic/mesoporous materials are expected to be exemplary, since they present enhanced ease of diffusion and accessibility for larger molecules while maintaining their enormous stability, catalytic activity, and selectivity as zeolites. Several synthetic strategies were reported to produce zeolite materials of better pore accessibility. Conventionally, a template-assisted method was used for this modification. Mesoporosity could be induced in zeolite materials even without any template. Templating methods can be mainly classified into three classes: solid templating, supramolecular templating, and indirect templating. The nontemplating methods are categorized into two classes: controlled crystallization and demetallation. In the latter, preferential extraction of at least one of the constituent metallic elements of the zeolite framework, and in the former, controlled crystallization is performed to achieve engineered materials. Ordered mesoporus materials are one of the alternatives to solve limitations of zeolites [41–48]. SBA-*n* ($n = 11,12,15,16$, etc., Santa Barbara Amorphous) is another important material in this category, which was reported in 1998, prepared by using nonionic surfactants [49]. Pore wall thickness of these series is larger due to the absence of electrostatic effects in the synthesis medium, which in turn increases their thermal and hydrothermal stability compared to the M41S class.

3.4.1.2 MOFs and COFs

MOFs and COFs are the other important class of highly porous, crystalline, solid materials. MOF is fabricated by three-dimensional networks of metal ions coordinated to multidentate organic molecules, also known as porous coordination polymers [50]. MOFs have possible application in heterogeneous catalysis due to their unique scope and advantages in tuning adsorption properties, altering the surface sites over the framework, uniform pore size distribution, high dispersion of components, high surface area, etc. [51,52]. Their diversity in the framework type is one of the significant advantages in comparison to zeolites and aluminophosphates. Their high surface area makes them attractive supports for metals, metal oxides, etc. MOFs are used as acid catalysts, base catalysts, catalysts for a C–C bond-forming reaction, and polymerization reactions. Nevertheless, the disadvantages, like low thermal and chemical stability and high sensitivity toward moisture, are hindering their use as commercially feasible catalysts. Zeolitic imidazole frameworks (ZIFs) are a subclass of MOFs, which exhibit advantages of both zeolites and MOFs such as excellent chemical and thermal stability, crystallinity, microporosity, and high surface area. They are comprised of tetrahedrally coordinated transition metal ions (Fe, Co, Cu, Zn) linked to organic imidazolate ions where the metal-imidazole-metal angle is nearly the same as a Si–O–Si bond angle in zeolites [53]. It is a very good material for CO_2 capture and utilization. COFs are an

emerging class of synthetic porous crystalline materials. Their tailorable structure and textural properties in combination with their high porosity increase the possibilities of novel application in heterogeneous catalysis which comprise as support for metal catalysts [54].

3.4.1.3 Oxides

Metal oxides with highly electronegative oxygen form a stable chemical bond with supported elements. It is widely accepted that tuning the structure, morphology, composition, surface properties, and crystallographic phases for particular chemical reactions of oxide catalysts is a fascinating area of research. Alumina, silica, first row transition metal oxides, and ceria are oxides that are widely employed as catalysts, or catalyst supports, because of their ease of availability and unique properties.

Alumina is an amphoteric oxide, and in general, it has been used as an acid catalyst. Aluminum oxide exists in many forms: α, χ, η, δ, κ, θ, γ, and ρ. Their formation depends on the precursor selection and heat treatment of aluminum hydroxide or aluminum oxyhydroxide. α−Alumina is the most thermodynamically stable form compared to other crystalline phases. Their structure occurs in closed packed layers of oxo-anions with Al^{3+} distributed between tetrahedral and octahedral locations, and the difference in distribution results in different phase formations. η- and γ-alumina are commonly used, which have been regarded as defect spinal lattice structures. The irregular arrangement of tetrahedral interstices forms the tetragonal distortion in the spinal structure. They are structurally different, where tetragonal character is lesser and density of stacking faults in the oxygen sublattice is higher for η-alumina compared to γ-alumina. In addition to their structural properties, textural properties also differ to a great extent. The structure and type of alumina decide its surface chemistry and catalytic activity (Fig. 3.11) [55].

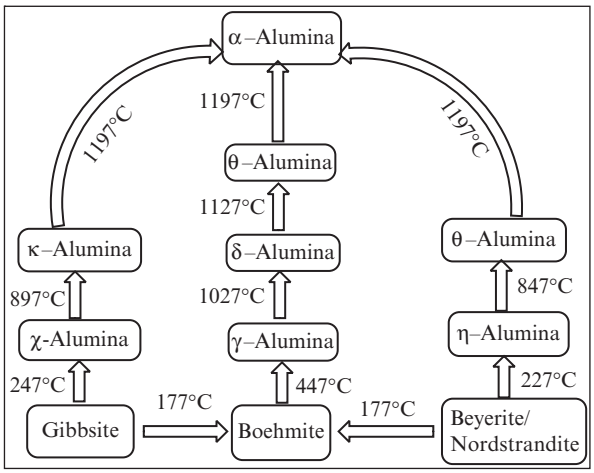


Fig. 3.11
Different forms of alumina [40,55].

Silica is normally employed in the form of amorphous silica, which is a weak Brønsted acid. Its structure is made up of SiO_4 tetrahedron units, where O is bridged between 2 Si atoms. Altering the textural properties by changing preparation conditions was reported [56]. Generally, silica is well known in catalysis as support and catalyst. Alkaline earth metal oxide is another class of simple oxides, used in organic reactions, renewable energy generation, and CO_2 utilization. MgO was extensively used as a catalyst in this sector. The strength, density, and nature of surface basic sites control the reaction. It is prepared by the calcination of $Mg(OH)_2$, where the O^{2-} ion formed is situated in the corners and edges of the crystalline surface. Coordinatively unsaturated Mg^{2+} ions form weak Lewis acid sites. More commonly, it is used for base-catalyzed reactions [57].

Transition metal oxides are commercially valuable due to their versatile application. In fact, they are widely used as catalysts in various chemical reactions, which include selective oxidation, selective dehydrogenation, hydrogenation, alkylation, carbonylation, aldol condensation, amination, ammoxidation, and hydrogen production. Their variable oxidation state makes them suitable for selective oxidation and reduction reactions. In addition to this, they act as good photocatalysts for various reactions including solar water splitting. Transition metal oxides appear in many crystallographic forms, and they are normally stable even at high temperatures and pressures. In the majority of transition metal oxides, the oxygen anion is present in the form of close-packed layers, whereas the metal cations are present in the holes surrounded by the anions. The columbic nature of the ionic lattice creates a strong electric field normal to the surface. The presence of surface acidity and basicity as well as cationic/anionic vacancies are one of the key attractions of transition metal oxides in catalysis [58]. TiO_2 is the one important class of oxide materials which occurs mainly in anatase and rutile crystallographic phases. The structures of rutile and anatase phases can be described in terms of chains of TiO_6 octahedra. The crystalline structure of rutile and anatase TiO_2 is tetragonal [59]. The tetragonal anatase structure contains 12 atoms per unit cell, whereas the rutile structure contains 6 atoms per unit cell. Anatase forms a metastable phase with high surface area and then transforms slowly into the thermodynamically stable rutile phase (at 623°C). TiO_2 is a wide band gap semiconductor, which has been extensively investigated in solar energy application and in photocatalysis. Other transition metal oxides, like Fe_2O_3, Cr_2O_3, and V_2O_5, are also used as catalysts in reactions like oxidative dehydrogenation and selective oxidation of alkenes [60–62].

Cerium oxide and zirconium oxide form an important class of metal oxide catalysts. They are bifunctional catalysts and contain both acid and base sites, which make them attractive in catalytic conversion of CO_2 to value- added chemicals, and in bifunctional heterogeneous catalytic reactions [63]. The high oxygen mobility and redox property of CeO_2 make them an attractive catalyst for selective oxidation, reduction, and oxidative dehydrogenation reactions. It is formed in a calcium fluorite like structure, in which metal atoms occupy a cubic close-packed arrangement, and oxygen ions are situated in tetrahedral holes [64].

Zirconia is formed mainly in tetragonal and monoclinic crystallographic phases. The tetragonal phase is a metastable phase with high surface area. Its monoclinic form is thermodynamically stable.

Multicomponent oxides and mixed metal oxides are used more widely as catalysts in academia and industry than simple oxides. Mixed metal oxides are oxides which contain two or more metal cations in a defined stoichiometry. Catalytic activity of such materials is always better than the physical mixing of individual oxides. It is quite difficult to say the exact active site on these catalysts because of their chemical and structural complexity. The arrangement of one metal ion depends on the nature and chemical environment of the other, which ultimately has an influence on the catalytic activity [65].

3.4.1.4 Layered compounds

Layered compounds are an interesting class of catalysts which have been widely used in industry. They can be categorized into three classes: (1) neutral layered compounds, (2) compounds containing negatively charged layers with compensating cations in the interlayer space, and (3) compounds containing positively charged layers with compensating anions in the interlayer space. Brucite and other hydroxides, phosphates, and chalcogenides are examples of neutrally layered compounds. The second class is widely found in nature; for example, montmorillonite, hectorite, beidellite, etc. Layered double hydroxides (eg, hydrotalcites) are the example of the third class [66]. The cations or anions present on the interlayer space of layered materials undergo ion-exchange. Swelling properties, high surface area, and ion-exchange properties of such materials make them attractive compounds for various applications. The cationic clays are generally synthesized from the minerals having negatively charged aluminosilicate layers with compensating interlayer cations. The clay mineral contains generally two types of sheets comprised of $Si(O,OH)_4$ tetrahedron and $M(O,OH)_6$ octahedron ($M = Al^{3+}$, Mg^{2+}, Fe^{3+}, or Fe^{2+}) as fundamental building units. Material composition and particle size may affect their adsorption properties, cation exchange capacities, and catalytic activity. Clays may exhibit both Brønsted and Lewis acid sites. The Brønsted acidic site is from the external OH groups, and the Lewis acid site in smectite is generated by substitution of 3 coordinated Al^{3+} ions for Si^{4+} in tetrahedral sheets [67]. Further, the hydrophilic-hydrophobic properties of these materials can be altered by suitable selection of exchangeable cations. Clay minerals find several applications in the field of catalysis especially in petroleum refineries [68]. Pillared clays are an advanced modification of clay material. They are large pore, strongly acidic, and thermally stable compounds. They are recognized as important catalysts for cracking, acid-catalyzed reactions, alkylation of aromatics, and bulk and fine chemical synthesis [69].

Hydrotalcites (HTs; anionic clay) are layered double hydroxides of general formula $[M^{2+}_{(1-x)}M^{3+}_{x}(OH)_2]^{x+}(A^{n-}_{x/n})\cdot yH_2O$. They have applications in base-catalyzed organic reactions and in medicine [70,71]. Their structure resembles brucite, in which a part of bivalent

metal ions is isomorphically substituted with trivalent metal ions, resulting in the formation of a positive charge on the layers. The extra positive charge is balanced by anions such as CO_3^{2-}, NO_3^-, F^-, and Cl^- present in the interlayers. Water of crystallization is generally observed in the hydrotalcite galleries. It can be used as an additive in polymers, and as a precursor for magnetic materials. The main advantage of HT catalysts is their controllable acid-base properties to a certain level. HTs are decomposed to yield mixed oxides with strong Lewis base groups [72].

3.4.1.5 Carbon

Carbon is widely used for solid catalytic reactions, either directly as a catalyst or as a catalyst support. It is present in a large number of forms, which include diamond to fullerene and graphite to carbon nanotubes. Carbon with high surface area and good thermal stability, like activated carbon, is preferable as a catalyst in several reactions. Activated carbon is a crude form of graphite with a large surface area and porous structure. They are used in the industry for several applications such as zinc-oxygen depolarization in dry cell, chlorination of hydrocyanic acid to cyanogen chloride and ultimately to cyanuric chloride, oxidation reactions, destruction of phosgene, etc. Moreover, it is used largely as a support for metal catalysts and for applications in the pharmaceutical and chemicals industry [73]. The adsorption properties of activated carbon are controlled not only by its porous structure, but also by its chemical composition and surface functionality. Oxygen surface groups highly influence the surface characteristics of carbon. The presence of such groups may generate the acid-base adsorption sites. Like oxygen, the surface functionality present on carbon materials depends on their origin and pretreatment. Two concurrent processes occur during carbon-catalyzed reactions. The first is the adsorption of substrate on the active carbon surface by dispersion forces or ion-exchange via oxygen, and the second is the atomic oxygen development on the graphene interlayer spacing on all sp^2 carbon atoms. The gas phase oxidation reaction by using these materials is restricted due to their affinity to irreversible oxidation. The carbon catalyst is used for NO removal [74]. Recent studies focused on nano varieties of carbon as a catalyst and a catalyst support. They are attractive due to their advantages such as high purity, homogeneity, and ordered pore texture. The carbon nanomaterials show good catalytic activity in heavy crude oil cracking reactions [75].

3.4.1.6 Carbides and nitrides

Transition metal carbides and nitrides are formed by incorporation of carbon and nitrogen atoms into the interstitial spaces between the metal atoms. These materials display the physical properties of ceramics and electronic properties metals. Molybdenum- and tungsten-derived carbides were largely used as a bulk catalyst. They find use in hydrogenation, hydrazine decomposition, methane reforming, hydrodesulfurization, ammonia synthesis isomerization, cracking, and Fischer-Tropsch synthesis [40,76].

3.4.2 Supported Catalysts

Catalyst supports can be inert or active in the reaction. They can also act as a stabilizer to prevent agglomeration of the active phase. The efficiency of supported catalysts is ruled by the structural and textural properties of the active phase. Choice of the support is made based on several criteria such as chemical nature, particle size, morphology, surface area, pore properties, hydrophobic-hydrophilic nature, and metal-support interaction. Proper designing of supported catalysts is highly important for generation of additional active sites, increasing mechanical resistance of the catalyst composite, metal particle size stabilization, metal dispersion, etc. Alumina, silica, mesoporus silica, amorphous SiO_2-Al_2O_3, ternary oxides, zeolites, TiO_2, ZrO_2, CeO_2, MgO, etc., are some of the commonly used supports. Zeolite-type materials, ordered mesoporous materials, clays, activated carbon and other carbon varieties, MOFs and COFs are also used as supports. Supported metal oxides, surface-modified oxides, supported metal catalysts, supported sulfide catalysts, and hybrid catalysts are the different varieties of supported catalysts. Some important catalytic processes with supported catalyst systems are presented in Table 3.3 [10,77,78].

Table 3.3 Supported metal and metal oxide catalysts in chemical transformations [10,77,78]

Catalyst	Reaction condition	Reaction(s)
Ni/MgO	–	Pre-reforming and primary steam reforming
Fe/Cr_2O_3	350–450°C	Water gas shift reaction
Cu/ZnO	140–260°C	
Ni/Al_2O_3	500–700°C, 20–40 bar	CO methanation
Ru/MgO	80–180°C, 0.8 bar	CO_2 methanation
0.5% Ru/SiO_2	229–293°C, 1 bar	
5% Rh/TiO_2	100–165°C	
Ni/Al_2O_3	750–950°C, 30–35 bar	Steam reforming of methane
Cu–Mo/HZSM-5	240°C, 20 bar	CO_2 conversion to DME
Cu-ZrO_2/HZSM-5	250°C, 50 bar	
Pd/ZnO/MWCNT	250°C, 30 bar	CO_2 hydrogenation to methanol
Au/Fe_2O_3,	250°C, 50 bar	
Au/ZnO		
Au/TiO_2		
$Cu/ZnO/ZrO_2$	220°C, 80 bar	
$Cu/ZnO/Al_2O_3$	170°C, 50 bar	
Ni/α-Al_2O_3	–	Secondary steam reforming (methane to CO, CO_2 and H_2)
Pt/TiO_2	500°C	Dehydrogenation of cyclohexane to benzene
Pt/Al_2O_3		
Pt/MgO		
Pt/TiO_2		
ZnO/Cr_2O_3	250–400°C, 200–300 bar	Methanol synthesis from CO
$CuO/ZnO/Cr_2O_3$	230–280°C, 60 bar	

Continued

Table 3.3 Supported metal and metal oxide catalysts in chemical transformations—cont'd

Catalyst	Reaction condition	Reaction(s)
Co or Ni/Al_2O_3	100–200°C, 200–400 bar	Nitriles to ammines
Cr_2O_3/Al_2O_3	500–600°C, 1 bar	Butane to butadiene
Ag/support	200–250°C, 10–22 bar	Ethylene oxidation
V_2O_5/support	400–450°C, 1–2 bar	Benzene or butene to maleic anhydride
V_2O_5/TiO_2	400–450°C, 1.2 bar	*o*-Xylene or naphthalene to phthalic anhydride
$CuCl_2/Al_2O_3$	200–240°C, 2–5 bar	Oxy chlorination of ethylene
Al_2O_3/SiO_2	300°C, 40–60 bar	Ethyl benzene from benzene and ethylene
Cr_2O_3/MoO_3 Cr_2O_3/SiO_2	50–150°C, 20–80 bar	Polymerization of ethylene
Ni/SiO_2-Al_2O_3 $MoO_3/CoO/Al_2O_3$	320–420°C, 100–200 bar	Hydrocracking of vacuum distillate to produce gasoline
Pt/Al_2O_3	400–500°C, 20–40 bar	Isomerization of light gasoline and m-xylene to o/*p*-xylene
$Pt/Al_2O_3/SiO_2$	400–500°C, 20–40 bar	
Pt/Al_2O_3	470–530°C,13–40 bar H_2	Catalytic reforming of naphtha (high-octane gasoline, aromatics, and LPG)
$NiS/WS_2/Al_2O_3$ $CoS/MoS_2/Al_2O_3$	300–450°C, 100 bar H_2	Hydrodesulfurization of crude oil fractions
$MnOx/Al_2O_3$, V_2O_5activated carbon	100°C	Benzyl alcohol oxidation
Pd/γ-Al_2O_3	88°C	
Pd/SiO_2-Al_2O_3	80°C	
1.3 wt% Au/TiO_2	25°C, O_2:CO (1:1)	Preferential oxidation of CO
1 wt% Au/Ti-SBA-15	50°C, O_2:CO(4.3:1)	
5 wt%$Au/MgO/Al_2O_3$	40°C, O_2:CO(0.5:1)	

Supported metal oxide catalysts consist of at least one active metal oxide component dispersed on the surface of a support. The surface properties, like acidity and basicity of oxides, can be tuned by deposition of promoters. Such catalysts are known as surface-modified catalysts. The metal oxide on the support may exist in a separate crystalline or amorphous phase retaining its characteristic properties or forming a compound with a new composition with an altered property [79]. Rhenium oxide, copper oxide, chromium oxide, molybdenum oxide, tungsten oxide, and vanadium oxide are the commonly used active surface oxides [80]. Supported metal oxides are potential catalysts in petroleum refineries, renewable energy, olefin metatheses, and other important chemical syntheses [81,82].

Supported metal catalysts are used in hydrogen production, hydrogenation, oxidation, reforming reactions, vehicle emission control, and fine chemical synthesis. They are generally made up of small metal crystallites dispersed on high surface area supports. Metal particle

size influences reactivity. Supports help in preventing metal sintering [83]. The higher the surface area of the metal, the higher would be the catalytic activity. The concept of strong metal support interaction (SMSI) was first discussed elaborately in 1978 for CO hydrogenation with TiO_2-supported group VIII noble metal catalyst. CO and H_2 chemisorptions of TiO_2-supported group VIII noble metals decreased by increasing their reduction temperature from 200°C to 500°C. But the metal was well dispersed without sintering. Even the chemisorptions were suppressed at higher reduction temperature for catalysts, giving better catalytic efficiency for CO hydrogenation. This was due to strong metal support interactions [84]. Initially, this decrease in chemisorption was correlated with the electronic perturbation of metal atoms, which was generated by their interaction with Ti cations of the surface. But this was limited for explaining the metals of large crystallite size, because surface metals cannot interact effectively with larger atomic distance Ti ions. After several investigations in this area, it was concluded that when TiO_2 undergoes reduction, they are partially reduced into TiO_x species, which is migrated and distributed over the metal surface. The reduced Ti^{3+} forms a strong interaction with the metal atom, which facilitates the catalytic reduction of CO. Metal support interaction is mainly influenced by energetic, geometric, and electronic properties. Depending on their strength, they can be categorized into weak, medium, and strong metal-supported interactions. For materials with high resistance to reduction such as Al_2O_3, SiO_2, MgO, and carbon, weak or no supported metal interaction is observed, although some exception at higher reduction temperatures may be noted. Metals of nanoparticle size on zeolite present medium metal support interaction [85]. Strong metal-supported interaction is normally observed for highly reducible oxides like TiO_2, MnO, Ta_2O_5, etc. Local anion deficiency is one important requirement, which usually makes better contact between metal and reduced supports. TiO_2-supported Pt, Pd, Ir, Os, Ru, and Rh are the known examples for SMSI effect [86].

Supported metal catalysts—for example, supported Co, Cu, Ni, Pd, Pt, Re, Rh, Ru, and Ag—are widely used in hydrogenation reactions. Almost all the hydrogenation catalysts contain fine metal dispersion over the support. Pd and Pt catalysts are usually employed for reduction of nitro compounds. For chloro-substituted amine production, Pt is more preferable to Pd due to the higher dehydrochlorination ability of Pt. Pd/C was found to be effective catalysts for the hydrogenation of cyclohexanone to cyclohexanol. Pd supported on metal oxides is effective for CO hydrogenation. The product distribution varies with varying the metal oxide support. La_2O_3, MgO, and ZnO supports show better affinity toward methanol formation, while TiO_2 and ZrO_2-supported Pd form a higher amount of methane. Pd on more acidic supports (Al_2O_3) yields higher selectivity to dimethyl ether.

The degree of dispersion is a highly important factor for deciding catalytic efficiency. For example, Ni supported on SiO_2 exhibits hydrogenolysis of ethane at a faster rate compared to Ni/Al_2O_3 and Ni/SiO_2-Al_2O_3. This is due to the difference in metal dispersion and metal deactivation. Ni is more highly dispersed on SiO_2 than on Al_2O_3. Acid centers of alumina

are responsible for a large amount of coke formation, which finally deactivates the catalyst [86]. The electronic properties of supported materials also influence catalytic activity. For example, in the dehydrogenation of cyclohexane to benzene, benzene selectivity decreases with *n*-character of the semiconductor. Among several semiconductor oxide supports (TiO_2, Al_2O_3, MgO, SiO_2), Pt on TiO_2 gives the highest benzene selectivity (76%) while Pt/SiO_2 shows the least (23%). It is noted that strong *n*-type semiconductor oxide supports (eg, Pt/ZnO) are not effective for this transformation [87]. The influence of electronic interactions of the support and active phases can be explained considering Cu is supported on semiconductor oxides for CO hydrogenation reactions. The electron density flows from Cu to *p*-type semiconductor oxide support and enables better catalytic efficiency compared to the Cu/*n*-type and insulator oxide analogs [88]. The oxidation state of metal influences the chemisorption and product selectivity behaviors. For example, Rh in a zero-valent state supported on SiO_2 results in dissociative chemisorption of CO, leading to a hydrocarbon product. On the contrary, Rh^+ on ZnO or La_2O_3 facilitates associative chemisorption and yields alcohol. When both zero and univalent oxidation state Rh species are present, a mixture of hydrocarbon and alcohol products are obtained.

The particle size of surface metal species plays a key role in catalytic activity and selectivity. Supported Au nanoparticles are interesting material for oxidation catalysis. Their catalytic efficiencies depend largely on the preparation method. The catalytic nature of Au nanoparticles can be tuned by the choice of support. For example, metal oxide-supported Au (except SiO_2 and Al_2O_3) shows higher activity in CO oxidation than in Au powder. Supported Au catalysts were effective for partial oxidation reaction [89]. For improving the catalytic efficiency, multimetal-supported catalysts have also been explored. Metal-support interaction is one of the parameters affecting the catalytic activity by controlling the physical and chemical properties of the multimetallic system. Stabilization of a desired morphology also controls the catalyst activity.

Carbon is an attractive catalyst support for fine and specialty chemicals because of its excellent properties like a large specific surface area, high porosity, outstanding electron conductivity, and moderate chemical inertness. Among several carbon materials, activated carbon and carbon black are the preferred choice as a support due to their large availability and low cost. They are mostly used as supports to the noble metal catalysts [90]. Surface chemical properties are the important factors that influence the carbon-supported catalyst preparation and their activity. When the carbon surface contains a certain number of heteroatoms in the form of functional groups, they contribute to the surface acidity/basicity and hydrophilicity. Surface oxygen plays a key role in the dispersion of metal [91]. The presence of heteroatoms can bring some kind of active phase-support interaction, although these happen to a lesser extent in other supported catalysts like oxides. Relative inertness is an important parameter when carbon is used as a support in selective hydrogenation reactions. Low reactivity, or inertness, of the carbon surface will be useful for better mutual interaction between the metals, and the metals and promoters in the preparation of bimetallic catalysts,

and the metal promoted by metal oxide catalysts, respectively. These kinds of material are highly applicable in the hydrogenation of carbon oxides into methanol and methane. The preparation method of the supports and their treatment can also influence their catalytic performance. Activated carbon is the right choice as a support for the precious metals, while considering stability in the weak acid and alkaline conditions. For example, Pd/C is used for maleic acid hydrogenation in the presence of water instead of Ni catalysts. A carbon-supported precious metal catalyst is also applicable in specialty chemical manufacturing including dyestuff, organic pigment, cosmetics, and the food industry. Although activated carbon supports are highly advantageous, they are complicated in the reproduction because they are made from natural materials [92]. Table 3.4 lists the application of carbon-supported noble metal catalysts in some fine chemical synthesis [9,92,93].

Table 3.4 Carbon-supported metal-catalyzed reactions in fine chemicals synthesis [9,92,93]

Reaction	Catalyst	Reaction conditions/remarks
Hydrogenation of biphenyl to phenyl cyclohexane	5% Pt/C	100°C, H_2(500 psig), methanol (solvent), yield of phenyl cyclohexane = 66%
	5% Pd/C	100°C, H_2(500 psig), methanol (solvent), yield of phenyl cyclohexane = 89%
	5% Rh/C	25–125°C, H_2(500 psig), various solvents used, yield of phenyl cyclohexane = 45–78%
Diphenyl ether to cyclohexane ether	5% Pt/C, 5% Pd/C, 5% Rh/C	H_2(68 bar), ethanol (solvent)
Nitro benzene to aniline	Pd/C	50°C, H_2(3–5 bar)
Hydrogenation of *p*-chloro substituted aromatic nitro compounds	Pd/C	75°C, H_2(3 bar), most solvents
	Pt/C	75°C, H_2(10 bar), low polar solvents, *p*-chloroaniline is the product
Hydrogenation of 2,4,5-trichloro nitrobenzene	Ir-Fe-Cu/C, Ir-Fe/C, Pt-S/C	90°C, H_2(10 bar), toluene (solvent)
Nitro benzene to 1,2-diphenyl hydrazine	Pd/C	50°C, H_2(50 psig), low polarity solvent, base
Nitrobenzene to 4-amino phenol	Pt/C	150°C, H_2(15–45 psig), H_2SO_4
Disproportionation of rosin	Pd/C	200–240°C
Cyclohexane to benzene	Pd/C	200–500°C
Hydrogenation of alkenes to alkanes	Pd/C	20°C, H_2(15 psig), various solvents
Hydrogenation of nitril of *p*-cyanobenzoic acid to *trans*-tranexamic acid	Pd/C	100°C, H_2(50 bar), NaOH
9,10-Hydroxymethyltrypticine to octadecahydro-9,10-bis (hydroxymethyl trypticine)	Pd/C or Ru/C	150°C, H_2(4000 psig), ethanol (solvent)

Continued

Table 3.4 Carbon-supported metal-catalyzed reactions in fine chemicals synthesis—cont'd

Reaction	Catalyst	Reaction conditions/remarks
Benzanthracene to 5,6 dihydrobenzanthracene	10% Pd/C	25°C, H_2(20 psig), ethyl acetate; yield of dihydrobenzanthracene = 97%
Benzanthracene to 8,9,10, 11-tetrahydrobenzanthracene	Pt/C	25°C, 20 psig, ethyl acetate; yield of 8,9,10,11-tetra hydrobenzanthracene = 95%
Benzoic acid to cyclohexane carboxylic acid	Pd/C	170°C, 1–1.7 MPa, yield cyclohexane carboxylic acid = 100%
Nitric oxide to hydroxylamine	Pt/C	5°C, 1 bar, NO: H_2 = 1:3
Cyclohexane to benzene	Pt/C	200–500°C
1,4-Butynediol to 1,4-butanediol	Ru-Pd (4:1)/C	60–180°C, H_2(1–50 bar)
Cyclohexanol to cyclohexanone	Co/C or Ni/C	200°C, Flow rate = 1×10^{-2} h^{-1}
Reductive alkylation of halonitro compound	5%RhS_x/C	180°C, H_2(1300 psig), acetone (alkylating agent)
Reductive alkylation of nitroaromatics	Pt/C or Pd/C	<50°C, H_2(15 bar)
Amine-coupled aromatic alkylation with ketone	Pt/S/C	25°C, H_2(20–34 bar)
N-Ethyl-*N*-butulamine (ENBA) from *n*-butyraldehyde and mono-ethylamine	5%Pt/C	80°C, H_2(24 bar), yield of ENBA = 94.6%

3.4.2.1 Immobilized or grafted catalysts

Immobilized or grafted catalysts are prepared by immobilization of the catalytic structure on the support either by adsorption, encapsulation, or covalent bonding. These immobilized/grafted/tethered catalysts possess the advantageous features of both homogeneous and heterogeneous catalysts. This is one way to heterogenize homogeneous catalysts for their easy separation and repeated use in reactions [94,95]. In some cases, immobilization enhances catalytic activity. For example, an aminocatalyst supported on mesoporous silica exhibits enhanced activity for Henry addition of nitromethane to aldehyde [96]. Silanol groups of the support participate in the reaction-facilitating adsorption of aldehyde through formation of H-bonds [97]. Leaching of the active site during the reaction is often an issue with immobilized catalysts.

Organic-inorganic hybrid catalysts obtained by anchoring different organic groups on an inorganic matrix, usually oxides, are used as heterogeneous catalysts for various reactions. Conventionally, they are prepared by simple adsorption or impregnation methods. Generally, silica or silica-alumina is used as an inorganic matrix due to its versatile properties. The covalent grafting of organic molecules on the silica surface allows for the heterogenization of acidic, redox, and chiral function organocatalysts. The tethering of multiple functional

groups while maintaining the cooperative effect for higher catalytic efficiency compared to those of homogeneous catalysts were studied [98–100]. Alkylamine and alkyl aminopyridine immobilized on acidic silica-alumina act as a bifunctional catalyst for Michael addition reactions, where lower aluminum content is preferable for better catalytic activity [101]. Organometallics immobilized on silica (titanium organometallic complexes anchored to silica, immobilized Ni and Pd complexes) showed remarkable application in olefin polymerization and hydrogenation reactions [102,103]. Periodic mesoporous organic silica is an interesting support for generating ordered inorganic-organic hybrid materials. These ordered hybrid materials have research interest in organic chemistry. A Rh-based catalyst tethered to a polyamidoamine (PAMAM) dendronized silica gel shows good activity in a hydroformylation reaction [104]. Dendrimer-encapsulated metal nanoparticle was also investigated extensively [105]. Immobilized ionic liquids are another important class of heterogenized catalysts that got much attention in recent times. Numerous reactions such as hydroformylation, metathesis, carbonylation, hydrogenation, hydroamination, C–C coupling, and enantioselective reactions have been catalyzed using these materials [106].

3.4.3 Key Issues in Catalyst Process Scale-Up

The important steps involved in a catalytic process include: (1) catalyst development, (2) performance and quality testing of a catalyst, (3) designing of an appropriate mechanically stable form of the catalyst, and (4) kinetic designing and suitable reactor selection. The compilation of information regarding the market requirement of the products, the cost of the particular catalyst, and availability of their raw materials in the near future is the primary step. Comprehensive investigation in the laboratory and pilot scale is the important stage in process of industrialization, which involves the experimental design of a better quality, stable, and economically profitable catalyst through optimizing procedures via changing catalyst precursor and synthesis conditions. Quality-performance checking and assessment to determine if the scheme is technically and economically feasible for further stages is carried out in pilot stages. The properties such as catalyst lifetime, mechanical and thermal stability, and poison resistance need special care at the pilot-stage of catalyst production. Adoption of simple methods like precipitation and impregnation is highly impressive to attain a relatively fast and successful scale-up process. Commercial accessibility of the material, benign reactants and solvents, high quality and yield of the products and E-factor (waste/kg of the product) are the prime factors that need to be focused on in the scaling up of a process. Improvement of processes for low off-gases and wastewater, including those for fine chemicals, are important. Reproduction of catalysts in small-scale preparation, milligrams to gram, is a strong means in scaling up of the catalyst to minimize the pilot-level investments. Reaction kinetics is important for the scale-up of catalytic processes. Selection of the appropriate reactor, minimization of transport limitations, isothermal operation, and the prechecking of catalyst stability are the important criteria that need careful experimental attention in reaction kinetics

[107]. In fine and specialty chemical production, with the intricate reaction pathways, the selectivity is the key issue to make the process an economically viable one. Selectivity is directed by chemical means, which is possible to selection of reaction pathway, solvent, catalyst, and operating conditions. However, it also depends on the engineering aspects.

3.5 Solid Catalysts in Industrial Processes

Solid catalysts are the major representatives in industrial chemical research. The triumph of industrial catalysis in national development is based mainly on heterogeneous catalysis technology. In 2013, the heterogeneous (solid) catalyst sector governed the catalyst market with a global demand exceeding 4900 KT due to their advantages in separation, recyclability, etc. It was around 80% of the global market share. The solid catalyst technology is spread over various sectors, such as chemical manufacturing, petroleum refining, pharmaceuticals, polymer synthesis, renewable fuel and transportation fuel production, and several others. Chemical manufacturing is the major consumer of the catalyst. It demands 1800 KT; that is, about 40% of the total demand. It is expected to grow rapidly in coming years, especially in Asia Pacific and Latin America. Environmental catalysis, petroleum refineries, and the polymer industry are the other major consumers of catalysts [108]. The new approaches in catalyst designing and application always make a great impact on the global catalyst market. Table 3.5 presents an overview of major industrial processes using solid catalysts [109].

3.6 Catalyst Preparation Methodologies

Catalyst preparation and activation are major challenges in real-life catalyst research. Each and every factor in catalyst manufacture, like preparation methodology, separation, drying, calcination, shaping, and crush strength strongly influences the catalytic activity, selectivity, and stability. In early years, only the pragmatic aspects were taken into consideration for catalyst preparation. This scenario has changed from exploring the fact behind enchantment to scientific designing, using solid-state, analytical, thermodynamic, and kinetic principles. Catalyst design with specific active surface sites is the central challenge in solid catalyzed reactions. Catalytic properties of the synthesized material are related to every synthesis step involved with the quality of the raw material. The unit operation for catalyst development is pivotal to the chemical industry due to the high influence of the mode of preparation in catalytic activity, selectivity, stability, and regeneration. Drying, calcination, composition, synthesis temperature, stirring speed, aging, amount of precipitant, etc., are some important factors which have an effect on catalytic efficiency. The method of selection purely depends on the requirement of characteristic properties for a particular application. Although there are several scientific advances in catalyst preparation, the practicability is more applicable than theory in an industrial point of view. At present, several methods are in use for catalyst preparation. Here, these are categorized into conventional and advanced methods.

Table 3.5 Industrial processes based on heterogeneous catalysts [109]

Process step	Chemical reactions	Catalyst	Operating conditions	Reactor type/ reaction type	Licensors/catalyst suppliers
Acetoxylation	Ethylene + acetic acid → vinyl acetate	Pd/activated carbon or SiO_2, or Al_2O_3 with promoters (Cd, Pt, Rh, & Au)	140–180°C & 5–12 bar 150–200°C, 8–10 bar	Fixed bed multitubular reactor Fluidized bed/vapor phase	Bayer, Hoecht, B.P. Chemicals (London)
	Butadiene + acetic acid → 1,4-diacetoxy-2-butene → 1,4 butane diol → tetrahydrofuran	1. Pd/activated charcoal promoted by tellurium 2. Cation exchange resin	1. 70°C, 70 bar 2. 60°C, 50 bar	Fixed bed reactor/ liquid phase	Mitsubishi-Kasei corporation
	Propylene + acetic acid → allyl acetate → allyl alcohol	1. Pd/activated charcoal 2. Acidic ion exchange resin	1.150–250°C, 5–10 bar 2. 60–80°C	Fixed bed reactor/ vapor phase	Showa Denka, Daicel Chemical Industries, Hoecht, and Bayer
Alkylation	Benzene + ethylene → ethyl benzene	BF_3-Al_2O_3	100–150°C, 25–35 bar	Multitubular reactor with shell side cooling/ vapor phase	UOP LLC
		USY zeolite extrudates	≈270°C, 38 bar	Two dual bed reactors operated in series/liquid phase	Lummus-UOP
		ZSM-5 zeolite extrudates	400–450°C, 15–30 bar	Multibed adiabatic reactor/vapor phase	Mobil-Badger
		MCM-22 extrudates	Not available	Multibed adiabatic reactor/liquid phase	EB-MAX, Mobil/Raytheon
		Packaged zeolite	Not available	Two-phase process	CDTech/ABB Lummus Global and Chemical Research
	Benzene + propylene → cumene	65–70% H_3PO_4/SiO_2	200–260°C, 30–40 bar	Four adiabatic bed reactors/vapor phase	SPA, UOP LLC
		Beta zeolite	Not available	Fixed bed/liquid phase	Q-MAX, UOP LLC
		MCM-22	Not available	Not available/liquid phase	Raytheon E&C/Mobil
	Phenol + methanol → cresol + xylenol	MgO promoted with other oxides (Mn, Cu, Ti, U, and Cr)	420–460°C	Multitubular heat transfer reactor/vapor phase	General Electric, Croda Synthetic Chemicals, and Nippon Cressol
	Phenol + isobutylene → *p-tert*-butyl phenol	Zeolites, activated clays, ion exchange resins	90–100°C; 120°C	Two adiabatic reactors in series/vapor phase	Bayer, Dow Chemical, Grace Davisson, Rhom & Hass, and United Catalysts
	Toluene → xylene	Noble metal/Al_2O_3 or Zeolite	Not available	Fixed bed reactor/ vapor phase	Toray, UOP
		ZSM-5	400–470°C, 20–35 bar H_2 pressure	–	Mobil/Raytheon

Continued

Table 3.5 Industrial processes based on heterogeneous catalysts—cont'd

Process step	Chemical reactions	Catalyst	Operating conditions	Reactor type/ reaction type	Licensors/catalyst suppliers
Ammonolysis	Phenol + NH_3 → aniline	Alumina-silica and co-catalyst of Ce, V, or Ti	425°C, 200 bar	–	Scientific Design
	meta-Cresol + NH_3 → *meta*-toluene	TiO_2-SiO_2 pellets	–	Fixed bed reactor/gas phase	Mitsui Petrochemical
Ammoxidation	Propylene + NH_3 + 1.5O_2 → acrylonitrile	Bi_2O_3/MoO_3 with Fe	400–500°C, 0.5–2 bar	Fluidized bed reactor, tubular fixed bed reactor	BP Chemicals (formerly Sohio)-catalyst suppliers, Ugine Kuhlmann (fixed bed process), Snamprogetti (fixed bed process)
	Xylene ammoxidation	$V_2OAl_2O_3$, V_2O_5/ Cr_2O_5/Al_2O_3	300–450°C	Fixed bed multitubular vapor phase reactors, fluidized bed	Showa Denko(*m*- and *p*-xylenes), Japan Catalytic Chemical Industry, BASF (*o*-xylene), Mitsubishi-Badger now Raytheon E&C (*m*-xylene)
Carbonylations	CO + chlorine → phosgene	Activated carbon, granules	223°C	Multitubular reactor	Caloric GmbH, Haldor Topsoe
Dehydration of alcohols	1-Phenyl ethanol → styrene	TiO_2/Al_2O and TiO_2/ silica	180–300°C, 1–2 bar	Fixed bed adiabatic reactor/vapor phase	ARCO, Shell, Nizhnekamsk (CIS)
Dehydrochlorination	C_{10}–C_{13} chloride → linear olefins	Silica-alumina and pd-on-alumina	200–350°C	Liquid phase	Grace Davison, PQ Corp., Johnson Matthey
Dehydrogenation	Ethyl benzene → styrene	Iron oxide and potassium carbonate mixture with one or more promoters (Cr_2O_3, Ce_2O_3, MoO_3, CaO, MgO, and V_2O_5	530-760°C	Adiabatic reactors, isothermal reactors	ABB Lummus Global, UOP LLC, Fina/Raytheon, Lungi, BASF, Dow/ Engelhard
	Catadiene → catofin	Chromia-alumina cylindrical pellet	558–650°C, 0.1–0.25 atm	Different type of reactors	ABB Lummus Global
	C_2–C_4 olefin dehydrogenation	0.3 wt% Pt/Al_2O_3 with Zn and Cu promoters	600–630°C, slightly above atm pressure	Four radial fixed bed reactors with interchange heaters between reactors	UOP LLC
	C_2–C_4 olefin dehydrogenation-(steam active reforming)	0.2–0.6 wt% Pt on zinc aluminate	600°C, 3.5 atm	–	Phillips Petroleum
	C_{10}–C_{14} alkanes → olefins	Pt on basic alumina with promoter	400–600°C, 3 bar	Adiabatic fixed bed reactor	UOP LLC (Pacol-Olex™)
	Isopentane → isoprene	Fe_2O_3-K_2CO_3-Cr_2O_3, Sr-Ni-phosphate	600°C	–	Shell

Epoxidation	Ethyl benzene hydroperoxide + propylene → propylene oxide	Compounds of V, W, Mo, or Ti on silica	–	–	Shell, Arco, and Nizhnekamsk
Hydration	$C_2H_4 + H_2O \rightarrow C_2H_5OH$	Liquid phosphoric acid adsorbed in the pores of a kieselguhr or silica support	250–300°C; 60–70 bar	Adiabatic fixed bed reactor	Union carbide, Hulls, Shell, BP (Possible licensors)
	Acrylonitrile + H_2O → acrylamide	Raney Cu or Cu chromite	80–120°C	Slurry reactor	Mitsubishi-Kasel, Cyanamid, Mitsui Toatsu, Dow
Hydrochlorination	$CH_3OH + HCl \rightarrow CH_3Cl$	γ-Al_2O_3 supported $CuCl_2$ or $ZnCl_2$ and silica-alumina	300–380°C; 3–6 bar	Adiabatic fixed bed reactor	United Catalysts, Alcoa, Engelhard, Akzo Nobel
Hydrogenation	Aniline → cyclohexylamine and dicyclohexylamine	Cobalt (46%) on SiO_2 with basic promoters such as Mn or Ca oxide	230°C; 40–60 bar	Fixed bed and slurry reactors	Engelhard, United Catalysts, Synetix, Celanese (suppliers)
	Benzene → cyclohexane	Ni on Al_2O_3, Pt on Al_2O_3, sponge or raney Ni	150°C or less	A series of 3 to 4 adiabatic fixed bed reactors in series, operated with cooling between the beds (vapor phase or mixed phase) and nonadiabatic multitubular reactor (liquid phase and mixed phase)	United Catalysts, Celanese, Engelhard, Johnson Matthey, Activated Metals and Chemicals, Grace Davison, Precious Metal Corp, Synetix, UOP LLC (suppliers); ABB Lummus Global, UOPLLC, and CDTECH (licensors)
	Benzoic acid → cyclohexane carboxylic acid	Pd on carbon	170°C; 90–200 psig hydrogen pressure	Three continuous stirred reactors connected in series and equipped with cooling oil	Engelhard, Johnson Matthey, and Precious Metal Corp. (suppliers)
	Naphthalene → tetralin → decalin	Nickel sulfide or Ni-Mo catalysts	400°C; 20–60 atm pressure	Fixed bed reactor (liquid phase)	Engelhard, Grace Davison, Activated Metals and Chemicals Inc.
	Phenol → cyclohexanone	Pd (0.2–0.5%) on zeolite or alumina (for gas phase process), Pd on carbon (liquid phase process)	140–170° and slightly above atmospheric pressure; 175°C and 13 atm. (using Pd/C)	Fixed bed reactor (in gas phase and in liquid phase)	Acreom/Procatalyse, BASF, Engelhard, Hulls, ICI Katacolsynetix, Johnson Matthey, Precious Metals Corp., United Catalysts (suppliers)

Continued

Table 3.5 Industrial processes based on heterogeneous catalysts—cont'd

Process step	Chemical reactions	Catalyst	Operating conditions	Reactor type/ reaction type	Licensors/catalyst suppliers
	Phenol → cyclohexanol	Ni on silica or alumina	120–200°C and 20 atm	Fixed bed reactor	Criterion, Engelhard, United Catalysts, Synetix, Celanese, Acreon
	Furan → tetrahydrofuran	Ni-based catalysts, Pd/C catalysts	100–150°C; 20 bar	–	–
	Hydrogenation of aliphatic unsaturates	Pd/Al_2O_3, Ni/Al_2O_3, Pt/Al_2O_3, Ni-W, raney Ni	–	Adiabatic reactors with intermediate cooling or nonadiabatic multitubular reactor	CDTECH, UOP LLC (KLP process), UOP LLC, and Hulls (licensors); Engelhard, United Catalysts, Johnson Matthey, Activated Metals, Grace Davison, Precious Metal Corp., Criterion, BASF, Synetix, UOP LLC (suppliers)
	Adiponitrile → hexamethyldiamine	Zr-promoted Ni or Co on Kieselguhr (high-pressure process); raney or sponge Ni (low-pressure process)	200–300 bar and 90–150°C (high pressure process); 60–100°C and 20–50 atm pressure.(low pressure process)	Adiabatic fixed bed reactor (high-pressure process); slurry reactor (low- pressure process)	Engelhard, United Catalysts, Synetix, Celanese, Acreon (suppliers)
	Nitrobenzene → aniline	52–65% Ni on kieselguhr or silica-alumina	300–475°C and 1–5 bar	Fixed bed multitubular reactor (gas phase)	Engelhard, United Catalysts, Celanese (suppliers)
		0.2–0.5% Pd/Al_2O_3	275–400°C and 1–5 bar pressure	Fixed bed multitubular reactor (gas phase)	Engelhard, Johnson Matthey, Precious Metal Corp., United Catalysts
		30% Cu on silica, 30% Cu on 66% ZnO, Cu-Mn-Fe oxides on pumice	200–300°C, and 1–10 bar pressure	Multitubular reactor (gas phase)	Engelhard, United Catalysts, Celanese (suppliers)
		Cu 15% promoted with 0.3% Cr, Ba, and Zn	250°C and 1–5 bar	Fluidized bed reactor	Engelhard, United Catalysts (suppliers)
	Furfural → furfuryl alcohol	Copper chromite	1–2 bar, 100–140°C	Fixed bed reactor (vapor phase)	United Catalysts, Engelhard (suppliers)
	Benzaldehyde → benzyl alcohol	$Pt/Al_2O_3/LiO$	70–120°C, 10–40 bar	Slurry or trickle bed reactor	Engelhard, Johnson Matthey, and Precious Metals Corp.
	Acetone diacetone → methyl isobutyl ketone	Acidic ion-exchange resins impregnated with Pd, 0.1–0.5% Pd/ zirconium phosphate, Nb/Pd/Ion exchange	130–140°C and 30 bar	Trickle phase multitubular reactor	RWA-DEA, Veba-Chemie, Tokiuyama Soda, Sumitamo Chemical, Hulls AG, Edeleanu
	Maleic acid or maleic ester → 1,4-butane diol and tetrahydro furan	Acidic ion-exchange resin	–	Fixed bed adiabatic reactor	Davy Technology

Hydrogenolysis	Toluene → benzene	Cr_2O_3, Al_2O_3, Mo_2O_3/Al_2O_3,CoO/Al_2O_3	550–650°C; 35–70 bar	Two fixed bed reactor in series with cold hydrogen	United Catalysts, Engelhard
Isomerization	*meta*-xylene → *ortho*-xylene and *para*-xylene	Pt/ZSM5 (low crystal size), Pt on zeolite, Pt on silica or alumina or silica-alumina	400–480°C, 4.5–29 bar	Fixed bed reactor	Mobil
	Ethyl benzene → xylene	0.5 wt% Pt on silica or alumina or silica-alumina	425–480°C, 11–20 bar, H_2/CH=4–6:1		Engelhard, Arco, IFP
		Pt on Al_2O_3	400°C, 12.5 bar		UOP LLC
	Ethyl benzene → benzene	Pt on zeolite, acidic ZSM-5 partially exchanged with Pt	427–460°C, 15–18 bar H_2/CH = 1.5–2		UOP LLC
		Pt on ZSM5	400–480°C, 4.5–29 bar H_2: CH = 1:1 to 5:1		Mobil
Oxidation (inorganic)	$SO_2 \rightarrow SO_3 \rightarrow H_2SO_4$	6–9% V_2O_5 and alkali metal sulfates (2–4 ratio V to alkali metal)	–	Adiabatic fixed bed reactors with intermediate cooling between the beds	Haldor Topsoe, United Catalysts (suppliers) Enviro-chem systems (process licensors)
	Ammonia → [1]nitric oxide → [2]nitrogen dioxide → [3]nitric acid	Pt/Rh wire and Pt/Rh/Pd	1. 800–940°C, 3–6 bar, or 7–12 bar 2. 50°C, 3–6 bar, or 7–12 bar	–	Engelhard, Johnson Matthey, Degusa
Oxidation (organic)	Ethylene to ethylene oxide	Silver oxide	220–300°C and pressures of 10–20 bar	Multitubular heat transfer reactor	CRI-Shell, Scientific Design, Nippon Shokubai, and Union Carbide (licensors)
	Propene to acrolein	Bismuth molybdate (improved by the Fe and Ni and Co or K)	300–400°C and 1.5–2.5 bar pressure	Multitubular reactor with heat transfer liquid	BP/Amoco, Knapsack, Mitsubishi Petrochemical, Nippon Shokubai, Sumitomo, Uhde GmbH
	Propene → acrolein → acrolyc acid	Mo-V/SiO_2, $Mo_{100}V_{10}$ Al_3Cu_{10}/Al sponge, $Mo_{17.7}V_3$ $As_{1.43}/SiO_2$, $Mo_{12}V_2$ $W_{0.5}/SiO_2$, $Mo_{12}V_3Cu_{2.5}Fe_{1.25}$ $Mn_{0.1}$ $Mg_{0.1}$ $P_{0.1}$, $Mo_{12}V_{4.8}$ $W_{2.4}Cu_{2.2}Sr_{0.5}/Al_2O_3$, $Mo_{12}V_3$ Cu_3 Zn_1/SiO_2, $Mo_{100}V_{20}$ Cu_2	200–400°C	Multitubular fixed bed reactor	TOSOH, Rikagaku Res. Labs., Toagosei Chem. Industry, Nipon Kayaku, Celanese, BASF, Nippon Shokubai, Sohio, Sumitomo Chemical, Mitsubishi Petrochemical

Continued

Table 3.5 Industrial processes based on heterogeneous catalysts—cont'd

Process step	Chemical reactions	Catalyst	Operating conditions	Reactor type/ reaction type	Licensors/catalyst suppliers
	Benzene → maleic anhydride	V_2O_5 and MoO_3 on α-Al_2O_3	350–450°C and 2–5 bar O_2 pressure	Multitubular heat transfer reactors with 13,000–22,000 one-in od tubes of 13–16 ft length	Engelhard (suppliers), Alusuisse Italia (LonzaS.p. A), Scientific Design
	Butane → maleic anhydride	Vanadium phosphorous oxides [$(VO)_2P_2O_7$]	400–480°C and 2–3 bar	Multitubular heat transfer reactors	Scientific Design, ABB Lummus Global/LonzaS. p.A., B.P. Chemicals, Huntsman, Mitsubishi, Sisas (licensors), Engelhard (supplier)
	o-Xylene or naphthalene → phthalic anhydride	$V_2O_5/K_2SO_4/SiO_2$, V_2O_5/TiO_2 and they are with various promoters (Nb, K, Cs, Rb, P)	325–425°C	Multitubular heat transfer reactors	Lonza, S.p.A., LurgiOl Gas Chemie
	Methanol to formaldehyde	Silver catalyst, Mo-Fe oxide (ratio of 1.5–2) with promoters V_2O_5, CuO, Cr_2O_3, CoO, and P_2O_5	680–720°C (Silver catalyst) 280–400°C (Fe-Mo catalyst)	Adiabatic reactor (silver catalyst); nonadiabatic multitubular reactor (iron molybdate system)	ABB Lummus Global, Partec Resources (silver catalyst); HaldorTopose, Petron (Fe/Mo catalyst) [licensors]
	Isobutylene or *tert*-butyl alcohol to methacrolein to methacrylic acid	First stage-Mo/Bi/Fe/ a/P/b (a = one or more of Co, Ni, Mn, Mg, Sb, W and b = one or more K, Cs, Tl), Mo-W-Te Second stage	300–420°C and 1–3 bar (first stage) 270–350°C (second stage)	Two packed bed adiabatic reactors in series	Ashai glass, Japan Methacrylic Monomer Co.
Oxychlorination	Ethylene → 1,2-dichloro ethane → vinyl chloride	$CuCl_2$ on Al_2O_3 or other supports	220–240°C	Fixed bed reactor; fluidised bed reactor	Abermale, Rhodia, PPG, Mitsui toatsu, Geon, ToyaSoda, Solutia, Shell, Akzonobel
Catalytic reforming	(1) Dehydrogenation of cyclo hexane to aromatics; (2) Dehydroisomerization alkyl cyclopentanes to aromatics; (3) Isomerization of paraffins; (4) Dehydrocyclization of parffins to aromatics; (5) Hydro cracking	Pt/Al_2O_3, $Pt\text{-}Re/Al_2O_3$, $Pt\text{-}Ir/Al_2O_3$, $Pt\text{-}Sn/Al_2O_3$	275–375 psig (semi-regenerative units); 50–75 psig (cyclic and continuously regenerated units	Fixed bed reactors (semi-regenerative units); swing reactor with necessary valving and manifolding (cyclic unit); moving bed reactor (continuous regenerated unit)	Acreon, Criterion, Indian Petrochem, Inst. Mexicano Petrol, Kataleuna, UOP LLC, Procatalyse (suppliers); Exxon Research and Engineering, Howe baker, IFP, UOP LLC (licensors)

Hydro treating	Hydrodesulfurization; hydrodeoxygenation; hydrodenitrogenation; hydrogenation of aromatics; hydrogenation of olefins; hydrodemetallization	Alumina-supported catalysts (eg, CoO/MoO_3/Al_2O_3; NiO/MoO_3/Al_2O_3)	–	Multiple beds in a single reactor shell with the provision of introducing cold hydrogen quench between the beds, radial reactors, downflow reactors/liquid phase and vapor phase	Acreon, Akzo Nobel, BASF, Catalysis & Chemical, Chevron Res.& Tech., Criterion, Grace Davison, Haldor Topsoe, Inst. Mexicanopetro,Katalenna, Orient, Procatalyse, United Catalysts (suppliers) Akzo Nobel, CD Tech, Chevron Res.& Tech., Criterion/ABB Lummus Global, Exxon res. & engr., Haldor Topsoe, IFP, Kellog Brown & Root, UOP LLC (licensors)
Hydrocracking		Zeolite, Pt, or Pd supported on Zeolite or Al_2O_3; Ni-Mo, Ni-W, Pt-Pd supported on Al_2O_3, or SiO_2-Al_2O_3, or zeolites	Operation conditions vary according the feed & reactor designing Characteristic ranges are 1500–2500 psig, 316–371°C with contact time of 1.5 h	Catalyst shape-1/6 and 1/8 in extrudates as cylinders or shaped cylinders or pore Multiple bed reactors with interstage cooling, operated as a trickle bed with concurrent flow of h_2 and liquid flow	Acreon, Akzo Nobel, Catalyst & Chemicals, Chevron Research & Tech., Haldor Topsoe, Kataleuna, Orient, Procatalyse, UOP LLC, Zeolyst (suppliers) ABB Lummus Global, Chevron Research & Tech., IFP, Kellog Brown & Root, Shell Global Solutions, VebaOel Tech., UOP LLC (licensors)
Isomerization	Isomerization of light hydrocarbons	Pt or chloride Pt/Al_2O_3, Pt/zeolite (0.3 wt% Pt typical) exist in the form of extrudates, spheres, cylinders	The reaction is carried out at the vapor phase; 120–260°C and 18–28 atm pressure	Two adiabatic reactors in series with intermediate cooling	Acreon, Akzo Nobel, Engelhard, Procatalyse, United Catalysts, Zeolyst (suppliers) ABB Lummus Global, CD-Tech/Lyondell, Engelhard, IFP/HRF, Kellog Brown & Root, Phillips Petroleum, UOP LLC (Licensors)
Oligomerization	C_3-C_4Olefien to low molecular weight polymer	ZSM-5 zeolites	–	Fluidized bed system with reactor and regenerator	Raytheon engineers and constructors/Mobil

Continued

Table 3.5 Industrial processes based on heterogeneous catalysts—cont'd

Process step	Chemical reactions	Catalyst	Operating conditions	Reactor type/ reaction type	Licensors/catalyst suppliers
Fluid catalytic cracking	High-boiling, high-molecular weight hydrocarbon fractions of petroleum crude oils → more valuable gasoline, olefinic gases, and other products	Rare earth exchanged zeolite (REY); ultrastable Y zeolite (USY); rare earth exchanged ultrastable hydrogen Y zeolite	–	Transfer line reactor with specially designed catalyst separator vessel, stripper, and regenerator designed for highly efficient combustion	Akzo Nobel; Engelhard; Grace Davison; Inst. Mexicanodepetro.; Interact (FCC additives), PQ Corp. (zeolites) [suppliers] ABB Lummus Global, Engelhard, Exxon Research & Engineering, Kellog Brown & Root, Shell international, Stone & Webster/IFP, UOP LLC (licensors)
Oxygenates	Isobutylene + methanol → methyl *tert*-butyl ether	Acidic ion-exchange resins	10–20 bar; 60–90°C (various reports); exothermic reaction is favored	Two adiabatic fixed bed reactors in series with intermediate cooling/liquids with some units mixed phase	Bayer AG, Dow Chemical, Mitsubishi Kasei, Rohm and Hass (suppliers); Acro chemical, CDTECH, IFP, NesteOy. Engineering, Phillips Petroleum, Snaam-Progetti, SpA, Sumitomo Chem, UOP/ Hulls, UOP LLC (licensors)
Methane steam reforming	$CH_4 + H_2O \leftrightarrow CO + H_2$	Ni supported on refractory alumina or ceramics	800–1000°C; 8–35 bar	–	BASF, Dycat International, Haldor Topsoe, Synetix, United Catalysts (suppliers) ABB Lummus Global, Davy Process Tech., Foster Wheeler, Haldor Topsoe, Jacobs Engineering, Kellog Brown & Root, Technip, Selas, Krupp-Uhde, Synetix (licensors)
High temperature shift conversion	$CO + H_2O \rightarrow H_2 + CO_2$ (exothermic process)	Iron oxide-chromium oxide, CuO promoted Fe_2O_3-Cr_2O_3	350–400°C	Fixed bed adiabatic process	BASF, Dycat International, Haldor Topsoe, Synetix, United Catalysts, (suppliers); Kellog Brown & Root, Haldor Topsoe (licensors)

Low temperature shift conversion		Copper oxide-ZnO, alumina incorporated copper oxide-ZnO in place of some ZnO (Cr_2O_3, MnO, or other metal oxide promoters also used)	200–250°C	Fixed bed adiabatic process	Haldor Topsoe, Synetix, United Catalysts (suppliers) Kellog Brown & Root, Haldor Topsoe (licensors)
Naphtha steam reforming	$C_nH_m + nH_2O \rightarrow nCO + (m/2 + n)H_2$	Catalyst is same as used in methane steam reforming	450–500°C	–	BASF, Dycat International, Haldor Topsoe, Synetix, United Catalysts (suppliers); Kellog Brown & Root, Haldor Topsoe (licensors)
Methanol synthesis	$CO + H_2 \rightarrow CH_3OH$	CuO-ZnO-Al_2O_3 6×4 mm or 6×3 mm in the form of tablets	50–100 bar and 200–270°C	Quench converter, adiabatic reactors with intermediate cooling, multitubular isothermal reactors, tube-cooled convertor	Haldor Topsoe, Synetix, United Catalysts (suppliers) Acid-Ammine technologies, Haldor Topsoe, Kellog Brown & Root, Kvaerner Process Tech., Linde AG, Lurgi, Synetix (licensors)
Methanation	Carbon oxides → Methane	Nickel on Al_2O_3 or other refractory carriers (20–34 wt% of Ni)	250–325°C	Adiabatic reactor (feed gas usually contains 0.2–0.5 mol% CO and 0.01–0.2 vol% of CO_2	Haldor Topsoe, Synetix, United Catalysts, (suppliers); Haldor Topsoe, Kellog Brown & Root, Lee Consulting, Linde AG, Synetix, Uhde GmbH (licensors)
Ammonia convertor	$N_2 + H_2 \rightarrow NH_3$	Fe_3O_4 in the form of granules with several promoters (Al_2O3, K_2O, CaO, and MgO)	350–550°C and 100–300 bar	Quench converters, indirect cooling converters (gas phase reaction)	Haldor Topsoe, Engelhard, Synetix, United Catalysts (suppliers); Haldor Topsoe, Kellog Brown & Root, Lee Consulting, Linde AG, Synetix, Uhde GmbH (licensors)

3.6.1 Conventional Methods

3.6.1.1 Precipitation and coprecipitation

In this method, solid catalyst is prepared from the liquid solution or colloidal solution of the corresponding salt. Nitrate, oxalate, sulfate, or chloride salts of active material are normally used for precipitation. The solid phase formation occurs through nucleation followed by crystal growth. This route mainly involves supersaturation, nucleation, and growth. The supersaturation process is related to concentration, temperature, p^H of the solution, and acid or base addition. If the supersaturation exceeds the limit, it results in the formation of amorphous precipitate. Nitrate and sulfate precursor salts and hydroxide, or carbonates of Na, K and ammonium precipitants are widely used in the industry for preparing the catalyst through the precipitation method. The final product formed during the precipitation procedure is considered as the precursor of a final catalyst. The precipitation method is normally employed for preparing simple and multicomponent oxides and supported catalysts. Coprecipitation is an advancement of the precipitation method for solid catalyst generation, where multicomponents are present. It involves the simultaneous precipitation of two different components from the same solution containing a mixture of salts. They are allowing the homogeneous distribution of active sites in both of the components, which helps the formation of a solid solution. Special attention to be made during coprecipitation is to avoid independent precipitation; p^H should be kept constant throughout the reaction. The fundamental difference between these methods is that precipitation gives high-purity materials and coprecipitation gives stoichiometric mixtures with well-defined phases [110–112].

3.6.1.2 Fusion and alloy leaching

The fusion method is used for the synthesis of metallic alloys by melting oxides, or elements of a particular composition and phase, using metallurgical principles. The combination of oxides and elements in atomic dispersion can also be prepared by this approach. The catalyst prepared by this method is useful especially for structure-sensitive reactions. Holding time and mechanical mixing of the melt affects the extent of chemical conversion. Most of the oxides are thermodynamically unstable in their liquid state. In such cases, there is a chance of equilibration between the gaseous oxygen present in the furnace and liquid oxide, which is directed for the thermochemical reduction of high formal oxidation states, oxidation of liquid oxides, and modification of the chemical structure and composition of the oxide. Cooling is an important process for controlling the chemical structure formation and composition in the fused catalyst preparation method. This method is an expensive and large energy-consuming process. Pd-Zr metallic glass, Pt-Rh grid, K, Al, Mg, and calcium-promoted Fe_3O_4, V_2O_5-$K_2S_2O_7$ are the widely used catalysts prepared by this method. This process is energy intensive and uneconomic compared to the normal precipitation method. A skeletal metal

catalyst is prepared by the fusion followed by metal leaching. For example, in the Ni-Al alloy, Al leaching out by NaOH is known to produce Raney Ni or sponge Ni. At present, skeletal catalysts, especially Ni and Cu, are used widely for commercial hydrogenation, ammonolysis, and reductive alkylation [113,114]

3.6.1.3 Sol-gel process

The sol-gel process is the polycondensation of the liquid form of precursor salts. It is a two-step process. In the first step, a liquid suspension of the solid is formed by hydrolysis and partial condensation of a precursor. In the second step, the solution is condensed further into a gel consisting of three-dimensional continuous networks. The resulting material is a solid-encapsulated solvent. It is known as aquasol (or aquagel) and alcosol (or alcogel) when water and alcohol, respectively, are used as a solvent. These encapsulated liquids can be dried out from the gel either by evaporation or by supercritical extraction. The solid product attained from the former route is referred to as xerogel, and the latter is known as aerogel. Multicomponent materials may be prepared with a controlled stoichiometry by mixing sols of different compounds. Solution chemistry, aging, drying, and calcination/sintering are the important parameters to control the catalytic property of material prepared by this method. The sol-gel method can be used for preparation of tailored materials like dispersed metals, oxidic catalysts, chemically modified supports, and unsupported catalysts. Versatility of this method permits fine-tuning of various properties of the materials such as texture, composition, homogeneity, and structural properties of solids [115,116].

3.6.1.4 Flame hydrolysis method

The gaseous mixture of precursor, hydrogen, and oxygen runs continuously in a flame reactor, which results in the hydrolysis of the precursor; generally the volatile compounds with water vapor form the corresponding product. Metal oxides are normally synthesized with this method from their corresponding chlorides. This method is frequently used in industry for fumed silica manufacture. High purity of the chemical, well-formed particles, and extremely small loss during drying and ignition are the unique advantages of this method [117].

3.6.1.5 Hydrothermal method

The hydrothermal method involves the aging, or ripening, of precipitate, gels, and flocculates relatively at low temperatures (100-300°C) in an aqueous medium, or mother liquor. Such thermal treatment is responsible for the structural and textural modifications, nucleation, and crystal growth. These operations are controlled by changing p^H, temperature, pressure, time, and concentration. Zeolite is one important class with a wide industrial application prepared by this method, where the amorphous gel undergoes crystallization around the

templates, resulting in the formation of uniform porous crystalline solids. Hydrothermal treatments are more often carried out in a liquid medium, although they consist of a dry gelation (steam stabilization) method for BEA and Y-zeolites. The conventional hydrothermal methods, and their modifications, are used for synthesizing a large kind of solid catalytic material with varying structure and morphology [45,118,119].

3.6.1.6 Impregnation, ion-exchange, and deposition-precipitation

Impregnation, ion-exchange, and deposition-precipitation (DP) methods are used generally for making surface- modified or supported catalysts. In impregnation, a certain volume of precursor solution with active components is made in contact with the support materials for a definite period of time, and then the entrapped liquid is dried out followed by calcination, resulting in the formation of supported catalysts. On the basis of the volume of the solution, these can be classified into wet impregnation, or incipient wet impregnation and dry impregnation. In the first case, the support is immersed in an excess solution of active precursor for a specified time and then the solid is recovered and dried. The second method is more precise in nature, where an active precursor solution, with the same, or slightly higher, volume of the pore volume of the support, is added to the support for incorporation followed by drying. The chemical environment and concentration of the active phase over the surface of a support depends on the condition adopted in the preparation steps [120,121].

The ion-exchange method is the advanced technique of impregnation, where the ions of the precursor are exchanged for ions already present on the surface of a support during the impregnation step. The ion-exchange process is usually carried out until it reaches the equilibrium. The exchanged ion forms an electrostatic interaction with the support surface. However, the kinetics of exchange occurs very fast, and this will direct an uneven distribution of the precursor inside the pores. This method is generally used for creating Brønsted acid sites in zeolite material by replacing the NH_4^+ ion for a Na^+ ion followed by calcination. This method can also be followed for generation of bifunctional sites on the surface of materials (eg, clays and functional oxides) [122,123].

DP was developed to prevail over the limitations of the impregnation method. The slow precipitation of the active catalyst precursor occurs with a simultaneous interaction with the support surface. Once nucleation occurs, the precipitate is deposited exclusively on the support. The variations in the concentration of precipitating agent, pH, and valence state of the metal precursor and reducing agent are the important factors controlling the active catalyst formation. In order to avoid sudden precipitation, solution concentration of the precursor solution ought to be maintained between solubility and supersolubility regions. This method is often used for preparation of the supported noble metals and nonnoble metal catalysts [124].

3.6.1.7 Grafting

Grafting is the method generally used for making the hybrid catalysts. This involves the chemical reaction between the functional groups and the surface of support.

3.6.2 Advanced Methods

Advanced methods are primarily aimed at controlling the size and morphology in nano/micro-structured catalysts. Some of these methods are briefly discussed here.

3.6.2.1 Chemical and physical vapor deposition

CVD leads to the formation of a nonvolatile solid structure, particle, or film by the reaction of precursors in the vapor phase in the hot-wall reactor under the conditions suitable for nucleation of particles in the vapor phase. CVD is a feasible choice for the preparation and surface modification of a variety of versatile nano-structured catalysts. This method is well established for carbon nanotubes synthesis. Moreover, it shows significant advantages over the conventional wet chemical methods for preparation of supported catalysts [125]. Atmospheric CVD, low-pressure CVD, metal organic CVD, plasma-assisted CVD, laser-assisted CVD, and photo CVD are different approaches for accomplishing catalyst production through CVD. Physical vapor deposition (PVD) is mainly achieved by thermal evaporation, by resistive heating, or electron beam heating, laser ablation, and a nonthermal process and sputtering. In this method, the gasified material condenses on the substrate to form a needed layer without any chemical reaction occurring in the entire process.

3.6.2.2 Ultrasound methods

High-intensity ultrasound is exploited as a facile tool for the synthesis of nano-structured catalysts without applying high temperatures, high pressure, and long reaction times. The sonochemical method is an important approach and is specifically used for the production or modification of nanomaterials through ultrasonic irradiation. The physical or chemical effects of the ultrasound generate unique hot spots. This localized heating zone attains high temperature-high pressure chemistry (5000°C and ~1800 bar pressure) and permits the benchtop synthesis. This excellent facility is utilized for the production of a variety of nano-structured and amorphous metals, alloys, carbides, metal oxides, semiconductors, and zeolite catalysts [126,127]. Volatile and nonvolatile precursors can be used for making catalysts through sonochemical methods. In volatile precursors (usually dissolved in nonvolatile solution), free metal atoms are generated by bond breaking due to the hot spot formed by the conduction of ultrasound. Then, these atoms are brought into the liquid portion and nucleate to form nanoparticles. Diverse structured nanomaterials can be prepared by appropriate selection of templates or stabilizers. Nonvolatile precursors dissolved in a volatile solution experience the sonolysis of the solvent vapor to form radicals or other

high-energy species, which act as a strong reductant. The catalyst prepared by the sonochemical approach shows high activity in refinery and hydrogenation reactions [128].

3.6.2.3 Microemulsion method

The microemulsion method is useful for the synthesis of metal nanoparticles with a narrow size distribution and control on the composition in the case of bimetallic particles. Microemulsion is the system that contains water, oil, and surfactant, where the dispersed phase contains monodispersed droplets in the size range of 5–100 nm [129]. Micelle and reverse micelle are the two varieties of microemulsion. They are also known as oil in water (o/w) and water in oil (w/o) microemulsion where, in the former case, the internal structure contains small oil droplets in a continuous water phase, and in the latter, small water droplets are in a continuous oil phase. The reverse micelle method is commonly employed for the synthesis of nanocatalytic materials, which include metal nanoparticles, metal oxides, bimetallic nanoparticles, and other important materials. Size of water droplets, surfactant concentration, and the nature of the precipitation agent are some important factors which can manipulate the properties of nanoparticles prepared by microemulsion methods. They can be synthesized either by mixing microemulsions containing the metal precursor and the precipitating agent or reducing agent, or through the direct addition of the precipitating agent into the microemulsion containing the metal precursor. In the former case, the reactants are efficiently mixed through intermicellar exchange during the collision between micelles. Nucleation and particle growth is related to the size and shape of the nanodroplets and the type of the surfactant and stabilizer. In the direct addition method, the mechanism is based on interlamellar nucleation, growth, and particle aggregation [130,131].

3.6.2.4 Mechanochemical synthesis

The blending of active material or its precursor with promoters and structural additives by a mechano-chemical mixing is the straightforward approach for preparing catalysts. Mixing, milling, and squeezing are the possible ways for this approach. This method can be used in the alteration of structural and textural properties of catalysts. However, in some cases, the synergic effect between the active material and support is relatively lower in the case of catalysts prepared by this method than by other preparation methods [132].

3.7 Catalyst Characterization Techniques

Deep insight into the fundamental aspects of heterogeneous catalysts can be derived from catalyst characterization studies using spectroscopy, microscopy, diffraction, adsorption-desorption, etc. Once a material is prepared, its life chart, which includes its structure, morphology, chemical composition, stability, and reactivity, needs to be established. In solid materials, the surface may change with the chemical environment to which they are exposed. So it is imperative to determine the nature, number, and different type of surface active sites and

properties of surface planes. This knowledge helps in designing modified catalysts with superior properties. Characterization of catalysts is also important for catalyst marketing, reactor design, modeling, and quality control in catalyst manufacturing [9,133–135]. Some important techniques used to characterize heterogeneous catalysts and the information derived from those studies is listed in Table 3.6.

Table 3.6 Characterization techniques for solid catalyst and information derived

Characterization techniques	Types of phenomenon	Type of source	Information derived
X-ray diffraction	Diffraction	X-ray	Phase determination, quantitative phase analysis, calculation of lattice parameters, crystallite size and strain, structure refinement of unknown faces
Extended X-ray absorption fine structure (EXAFS)	Absorption	X-ray	Structure and coordination of surface atoms
Gas adsorption method (physical)	Adsorption-desorption	Probe gas molecule (NH_3, CO_2, etc.)	Specific surface area, pore volume, average pore diameter, pore size distribution, micro/mesopore area, micro/mesopore volume, pore geometry
Gas adsorption method (chemical)	Adsorption-desorption	Probe gas molecule (H_2, CO, etc.)	Particle size measurement, metal dispersion, metal surface area
Temperature-programmed desorption (TPD)	Adsorption-desorption	NH_3, CO_2, isopropylamine	Determination and quantification of acidic/basic sites, strength of acid/base sites
Temperature-programmed reduction and temperature-programmed oxidation (TPR and TPO)	Adsorption-desorption	H_2,CO (for TPR) O_2, N_2O (for TPO)	Ease of reduction or oxidation, degree of interaction of reductant or oxidant with different active sites on the catalyst, extent of reduction; redox properties of a catalyst
Thermogravimetry	Weight loss with temperature	Temperature	Chemical state of the species, thermal stability and moisture content, hydrophobic nature, determination of decomposition temperature so that it is possible to find out the suitable calcination temperature of the material, study of reaction kinetics and pyrolysis kinetics
XPS, UPS	Photoelectron spectroscopy	Photon	Surface structure, valence state, elemental composition
Auger electron spectroscopy (AES)		Electron	Atomic composition on the surface, special distribution of elements
UV-visible	Electronic transition/ absorption/reflectance	UV-visible light	Electronic structure of molecules, coordination of metal cations, band gap of solids, presence and type of defects, particle size

Continued

Table 3.6 Characterization techniques for solid catalyst and information derived—cont'd

Characterization techniques	Types of phenomenon	Type of source	Information derived
IR/FT-IR	Molecular vibration/ transmittance/ absorption	Infrared light	Nature, structure, and amount of residual impurities; type and quantification of acid/ base sites with probe molecules
Raman spectroscopy	Molecular rotation and molecular vibration/ absorption	Infrared light	Nature of molecular species, determination of the structure of noncrystalline surface phases, identifies the surface species formed during catalyst preparation and pretreatment, detects and quantifies defect sites
Solid-state MAS NMR	Nuclear spin flip	Radio frequency	Bulk and surface structural elucidation, local coordination, surface acidity/basicity, investigation of porosity, adsorption, and transport process
EPR/ESR	Electron spin flip	Microwave	Nature and structure of paramagnetic species, oxidation state, transient paramagnetic reaction intermediates
TEM (HRTEM, HRSTEM, EFTEM)	Microscopic imaging	Electron beam	Morphology, elemental composition, crystallinity, phase determination, nanoporosity, and topological parameters

3.8 Catalyst Deactivation and Regeneration

Catalyst life is always a major concern in the industry due to large expenses incurred in catalyst replacement and process shutdown-cum-restart operations. The decay time of a catalyst depends on operation conditions, material type, reactor design, feed, and other factors. In some cases, lack of control on operation leads to fast deactivation of the catalyst. For example, in steam reforming of naphtha, uncontrolled operation causes the formation of a large amount of carbon, poisoning the inner and outer surface of the catalyst pellets, which ultimately lead to rapid deactivation of the catalyst. The concept of demise is a universal truth for any system or material. Hence, catalyst deactivation is unavoidable. Extension of decay, enhancement of reaction rate, and regeneration/reactivation of the catalyst are the probable solutions to overcome this problem. In order to develop the deactivation-defiant catalyst and the reactivation process, it is important to understand the physical and chemical causes of catalyst deactivation. Different origins are associated with deactivation which include: (1) poisoning of the catalyst, (2) fouling, coking, and carbon deposition, (3) thermal degradation or sintering, (4) gas/ vapor-solid and solid-state reactions, and (5) mechanical failure of the catalyst. In these, (1) and (4) are chemical in nature and (2) and (5) are physical in nature (Fig. 3.12).

Poisoning occurs through strong chemical adsorption of a species (reactant/product/impurity in the feed) on the active sites, obstructing them from participating in the reaction. In addition

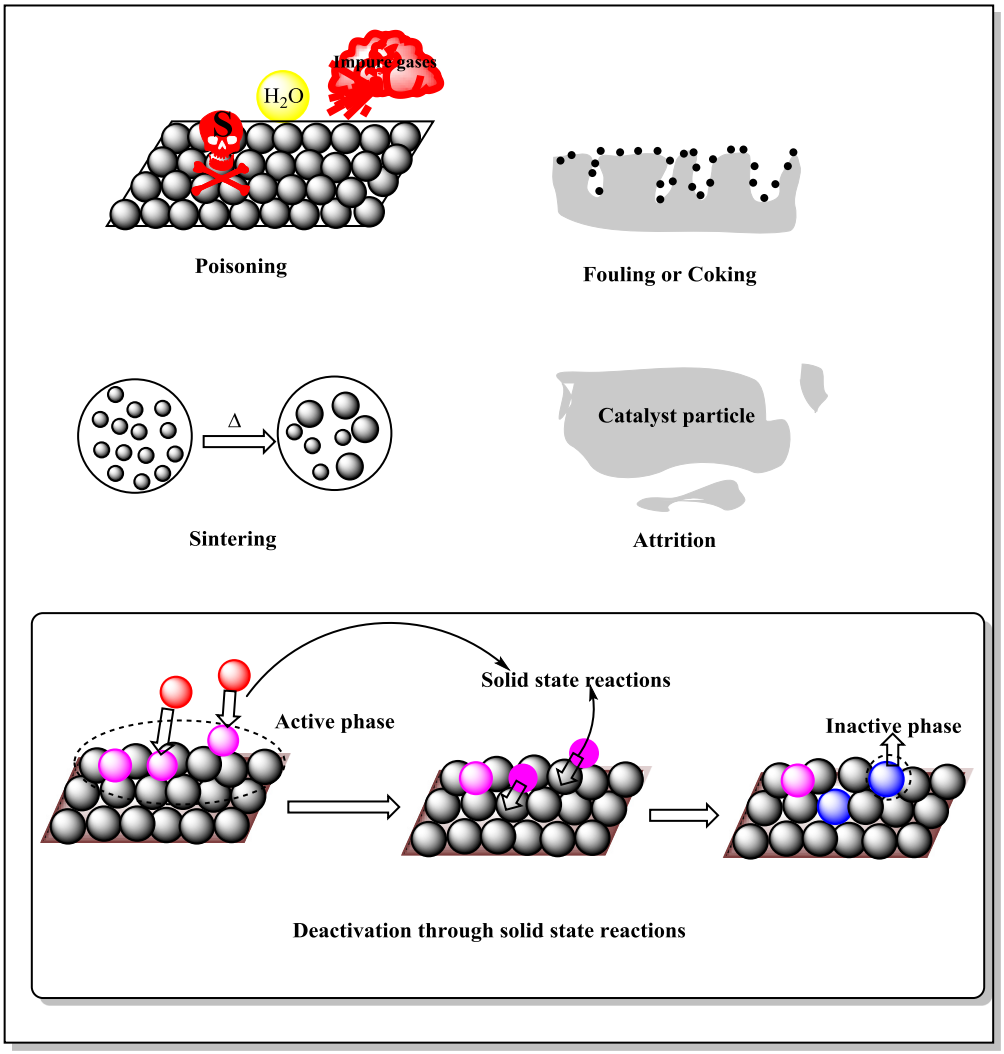


Fig. 3.12
Means of catalyst deactivation.

to the physical blockage of adsorption sites, adsorbate may lead to alteration of geometry or electronic structure of the active site. Alternatively, the surface of the catalyst may be reconstructed by the strongly adsorbed poison. Contaminants like organic bases (amines, for example) and ammonia deactivate the acid catalyst in petroleum refinery, and a sulfur or arsenic compound acts as poison in metal hydrogenation reactions. The degree of efficacy of a poison on the catalyst surface for a particular reaction depends on the equilibrium constant and the activity of product formation [136]. Common chemical species that lead to catalyst poisoning are as follows: (1) group VA and group VIA elements such as N, P, As, Sb, O, S, Se, and Te (interact through s and p orbitals with metal), (2) heavy metals and ions of Pb, Hg,

Bi, Sn, Zn, Cd, Cu, and Fe, (3) molecules which adsorb through multiple bonds (CO, NO, and HCN), (4) ammonia, water, and organic bases, and (5) various oxides of O, S, and carbon. Based on the strength of chemical adsorption of the poison on the catalyst surface, the deactivation of a catalyst by a poisoning mechanism can be categorized as selective or nonselective, and reversible or nonreversible. Regeneration of a poisoned catalyst is almost impossible in most cases. Hence, prevention of contact with poisons is a better option. Employing a pretreatment step by purifying the feed is recommended. In the case of metal contaminants, decaying effect can be restrained by selective poisoning of unwanted metals. Controlling the reaction conditions, which lower the strength of adsorption of poisons, can also prevent catalyst poisoning.

Fouling is another cause of catalyst deactivation. It is the mechanical deposition of contaminants (usually carbonaceous material from the fluid phase) on the catalyst surface which results in the physical blocking of the pores and/or active sites of a solid catalyst. The decay of a catalyst happening through such physical constraints is known as fouling or coking. The carbonaceous materials are mainly carbon and coke, where carbon is obtained by the disproportionation of CO, and coke is obtained by the decomposition or condensation of hydrocarbons. The degree of coke formation may vary according to catalyst composition, reactants composition, and operating conditions. In addition, catalyst fouling can also be caused by other contagions like fly ash in selective catalytic reduction, and zinc deposits from motor oil in emission control. Coke deposition and consequent deactivation of a catalyst can be prevented to a certain level by controlling the catalyst composition and reaction conditions. Usually, in catalytic reforming, carbon deposition is limited by induction of high hydrogen partial pressure. To minimize the amount of carbon deposition, the catalyst can be modified with additives or promoters, in which they act as a rate enhancer of gasification of adsorbed carbons and eventually reduce the carbon content and extend the life of a catalyst. Other means of avoiding coke formation are through sulfur passivation of metal surfaces, decreasing metal dispersion, lowering the acidity of oxide or sulfide, the use of shape-selective molecular sieves, and employment of supports with large pores.

High temperatures during operation may lead to thermal degradation of the catalyst. Solid-state reactions between different components in the catalyst and sintering are the possible causes of such degradation. Due to the thermal effect, the catalyst loses its surface area either through loss of metal area via metal particle migration and agglomeration or through loss of the support area through crystallization, structural modification, and structural collapse of the pores. The thermal effect also results in the chemical transformation of the catalytic to the noncatalytic phase. The former is generally referred to as sintering and normally occurs at high temperatures, above 500°C, and is enhanced by the presence of water molecules. Sintering is most often observed in the case of supported metal catalysts, although it can occur in principle for both supported and unsupported catalysts. Temperature, atmosphere, type of metals and their dispersion on the support, support selection, presence of promoter, and pore size are the important factors which control the sintering and redispersion rate. Most

of the sintering processes are irreversible in nature. They can be prevented by opting reaction conditions and tuning the catalyst properties. The rate of metal sintering can be diminished by opting the reaction temperature lower than that of the melting temperature of the active metal. A similar approach is also valid for retarding the recrystallization of metal oxides. In addition to temperature, the amount of water vapor also interferes in crystallization and structural modification of oxide carriers. In order to prevent such sintering processes, it is important to minimize the water level on the surface of supported catalysts. The inclusion of a thermal stabilizer is another way to avoid sintering (eg, addition of high-melting noble metal to base metal Ni).

Deactivation through solid-state reactions is the advanced form of sintering and is closely related to poisoning at high temperatures. It involves the reaction of the vapor phase with the catalyst surface, solid-support or solid-promoter reactions, and it transforms from one crystalline phase to another. They are considered a chemical route for deactivation, and exist in both supported metals and metal oxides. The gas/vapor interaction with a metal catalyst results in the formation of volatile compounds, which are the inactive phase of the catalyst. The formation of the inactive $Rh_2Al_2O_4$ phase in an automotive convertor using Pd-Rh/Al_2O_3 catalysts is an example of solid transformation occurring in metal catalysts. They primarily involve the vaporization of Rh metal into the Rh_2O_3, which further undergoes the solid-state reaction with alumina to form a corresponding catalytically inactive crystalline phase. Stepwise conversion of γ-Al_2O_3 into the δ-Al_2O_3 by thermal treatment, where the surface area changes from 150 to less than 50, and transformation of the anatase to rutile phase at high temperatures are examples of solid transformations present in metal oxide catalysts.

Mechanical failure through attrition or crumbling of agglomerate is an imperative problem in industrial catalytic processes. The mechanical failure of a catalyst occurs by way of crushing of the catalyst granules or pellet owing to the load or packing, attrition, size diminution, or fracture of the catalyst granules or pellet, particularly in slurry and fluidized bed and erosion of catalyst particle or coatings at high velocity. They may arise due to mechanical, thermal, or chemical stress. Mechanical stress is normally found in fluidized or slurry beds, where the fracture or erosion of a catalyst form occurs due to collision between catalyst particles with each other or with the reactor walls and formation of shear force resulted by cavitations at high velocities. Thermal stress arises due to difference in the thermal expansion coefficients at the interface between the two unlike materials, which are mainly caused by sudden changes of temperature (either in heating or cooling). Chemical stress is a kind of stress which occurs within the catalyst particle due to variation of phase density distribution via chemical reaction. For example, overloading of carbon or other impurities on the inside of the pores or surface of a catalyst generates stress over the primary particles, which results in abrasion and agglomeration of particles. The method of catalyst preparation and pretreating conditions influence the attrition resistance of the catalyst. Normally, higher strength materials have higher resistance. This is the reason for lowering the attrition rate of γ-Al_2O_3 prepared by the sol-gel method compared to normal γ-Al_2O_3. The implementation of more

sophisticated preparation methods, pretreatment, and shaping methods can control the catalyst deactivation through attrition. The proverb "Prevention is better than a cure" is exactly applicable in treating catalyst decay in commercial catalytic processes. The catalyst deactivation can be prevented generally by either modifying the catalyst or modifying the process (Fig. 3.13).

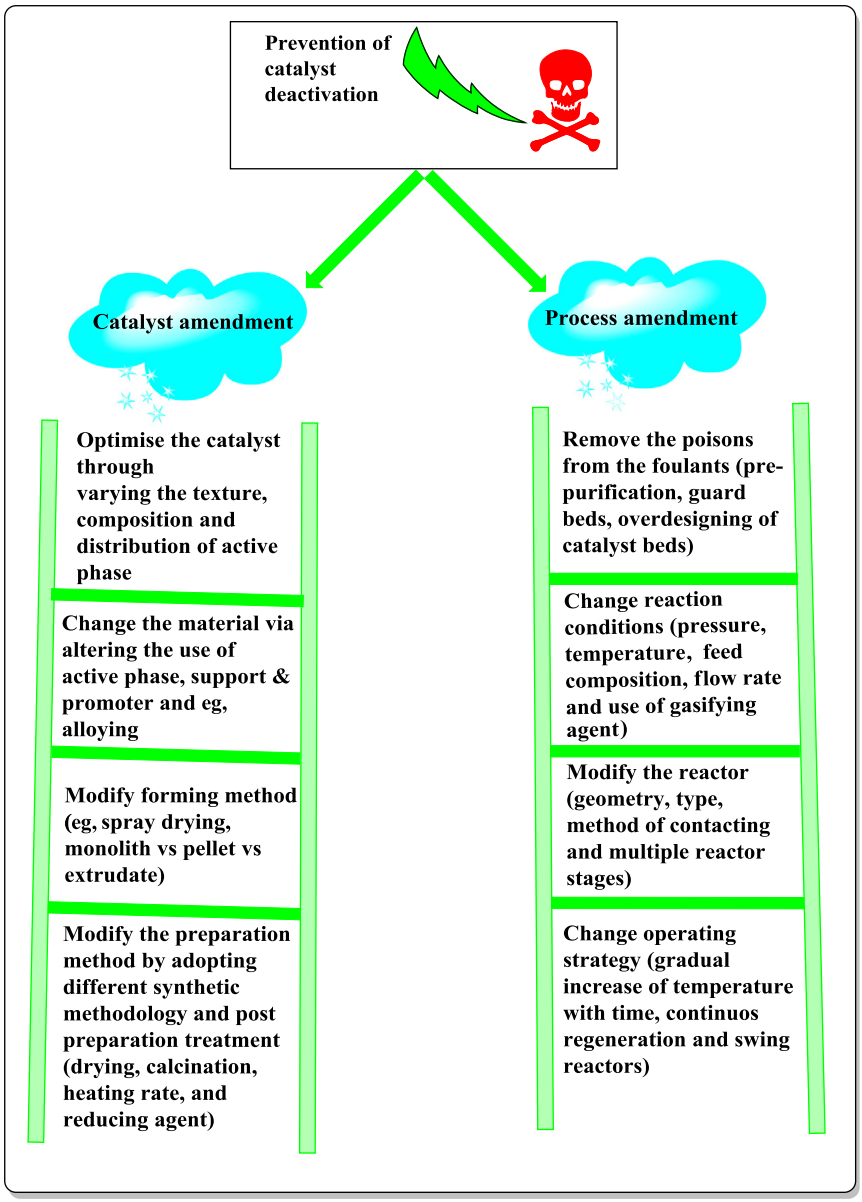


Fig. 3.13
Possible approaches for preventing catalyst deactivation [137].

In spite of several efforts to prevent deactivation, activity loss through deactivation of a catalyst is inevitable in most of the cases. In such situations, it is important to restore catalytic activity through regeneration processes for further reuse. The reactivation or regeneration ability of catalysts is decided on the type of deactivation. Carbon or coke formation is reversible, and the catalyst can be reactivated generally by gasification with hydrogen, water, or oxygen. At the same time, sintering is an irreversible process and reactivation in this case is quite complex. Redispersion of selected noble metal is possible only at specified conditions. Chemical washings, mechanical treatment, thermal treatments, and oxidation or reduction are some important ways to remove the poisons from the catalyst surface [137]. Continuous regeneration of a catalyst is economically feasible only for the case of a catalyst system which undergoes deactivation at a faster rate.

Regeneration of the catalyst deactivated by coke or carbon is carried out, normally, by the gasification process; and the rate of gasification depends on the type of gas used and the reactivity and structure of the carbonaceous species [138–142]. Oxygen is more often used for gasification. However, it suffers from the drawback of exothermicity. Overheating occurs due to its exothermic nature, which ultimately creates an option for sintering. In such cases, for the control over temperature, a mixture of oxygen and inert gas or oxygen and steam are used for the gasification of carbonaceous material. The removal of sulfur poison from the catalyst surface by gasification process did not take place. Gasification of sulfur with oxygen or steam at high temperatures in a reforming or hydrogenation reaction leads to sulfate, but then it reduces back to NiS on contact with hydrogen. Also, high temperature leads to sintering. Regeneration of a deactivated catalyst by sintering is brought about through the redispersion of the metal or the metal oxide phase by treatment with oxygen, chlorine, nitric oxide, and hydrogen. The redispersion of the agglomerated Pt phase supported on alumina carried by treatment with oxygen and chlorine at high temperatures is an example for such regeneration. Similar processes are also applicable to other alumina-supported noble metal catalysts. But these process conditions may not be applicable for Pt on other supports or other supported metals.

3.9 Fine and Specialist Chemicals: Focus Needs on Catalyst Selection

Chemical industries are mainly categorized into three sectors. They are fine chemicals, specialty chemicals, and commodity/bulk chemicals. There is no precise definition to differentiate these sectors on their inherent properties, but they can be defined concisely on the basis of their existing viewpoint. Bulk chemicals are the set of chemicals which are produced in large scale and longer duration with less economic design. Specialty chemicals signify their application and capability to enhance the customer product performance. Fine chemicals are the chemicals known for their purity and chemical specificity. In contrast to bulk chemicals, fine and specialty chemicals have a low worldwide production capacity, high

value-added chemicals, high-purity, specificity, and high-cost chemicals. Fine chemicals are complex and multifunctional molecules with high purity and low thermal stability. They are mostly carried out in liquid phase, and their production involves multistep processes by using multipurpose equipment. Conventionally, homogeneous catalysts; simple inorganic or organic compounds like mineral acids, para-toluene sulphonic acid, and methane sulphonic acid; or transition metal salts as well as the stoichiometric quantity of inorganic oxidants, metal hydrides, and organometallic complexes are employed for fine and specialty chemical production. Although they are cheap, they have their own problem in separation, purification, and waste management. Heterogeneous catalysis is more advantageous than homogeneous and enzyme catalysis. In the past century, heterogeneous catalysis is not imperative in the fine chemical industry although it is an inevitable part of the petrochemical and refining industries. At present, heterogeneous catalysis is the alternative stepping stone to achieve the greener, sustainable, and low-salt technology in fine chemical production. Solid acid catalysts, solid base catalysts, supported metal catalysts, tethered metal complex catalysts, and immobilized catalysts are commonly used in the production of fine and specialty chemicals through the aromatic electrophilic substitution reactions, rearrangement reactions, cyclization reactions, stereo-/regio-/chemoselective syntheses via hydrogenation, oxidation, and C-C bond-forming reactions. A large number of highly selective heterogeneous catalytic processes can be found in the literature, where these ideologies can be appropriate for fine chemical production. However, there are several factors that have to be met to accomplish these processes into commercially viable and economically profitable ones. They include: (1) catalyst performance, (2) substrate specificity, (3) commercial availability of the catalyst, and (4) catalyst deactivation [5,143].

Structure, chemical composition, surface area per unit weight, and particle size of the catalyst are important parameters that need to be focused on in the selection of a catalyst for fine and specialty chemicals. The properties of the surface of a catalyst majorly control the kinetics of the chemical reaction. The catalytic active surface should be sufficiently high, have stability under thermal pretreatment, and in reaction conditions should be satisfactory; preferred structure and chemical composition should be stable. Some catalytic reactions occur only in the presence of a specific surface structure. Careful tuning in the structure and chemical composition of the catalyst is obligatory in fine chemical production. The size of a catalyst is an important parameter to achieve a good rate of production. Various ranges of sizes of the catalyst particles can be used, but the activity depends on which type of reactor the catalyst will be operated in. The majority of reactions engaged in the fine and specialty chemicals are in the liquid phase process and dissolved gaseous-liquid reactions. A hydrogenation reaction with a gaseous hydrogen is an example of a dissolved gaseous-liquid reaction, where the gaseous hydrogen first dissolves in liquid and then moves to the surface of a catalyst. In general, 10 to 100 μm particle size is generally used for the commercial production of fine chemicals. With catalyst particle sizes below 3 μm, different issues are faced in different reactors [5].

The slurry phase reactor is one of the commonly employed reactors in the fine chemical industry. In such cases, heavy catalyst particles are beneficial because of the ease of separation of the catalyst from the reaction products by settling or decanting the liquid. The minimum size ideal for the slurry phase reactor is 3 μm. But in fact, this size is not sufficient to achieve the higher surface area needed, in order to obtain an economically feasible rate of production. These limitations can be overcome by employing porous catalyst particles. The porous catalysts exhibit larger surface area irrespective of particle size. But they are limited mainly for two reasons: (1) a low rate of transport in narrow pores and (2) difficulty in maintaining the mechanical strength of the catalyst to avoid the deactivation process like attrition. To avoid the large pressure drop, the size of the catalyst particle used in fixed bed reactors should be a bit high compared to that in the slurry phase reactors. The selectivity of the product is a highly important criterion in fine chemical production. The length of the pores is an important factor in desired product selectivity, where the longer length pores may cause a further reaction of desired products into unwanted products. The other important parameter is the transport properties of the catalyst. The speed of transport of the reactant to the catalyst surface, the speed of the product away from the catalyst surface, and the heat transport process play a crucial role in achieving the desired product. The mechanical strength of the catalyst is the most important, once the marketable applications are looked into. The selection of suitable porous catalysts can avoid the pressure drop and separation problems while maintaining the sufficient surface area. The porous catalysts with particle sizes of 3–100 μm are particularly significant for the selective catalytic reactions [5]. Metallic catalysts are the most attractive category among solid catalysts for the fine chemical production. Several parameters of such catalysts influence their catalytic performance, which include type of metal and support and metal loading. Metal dispersion of 10 to 60%, 20–200 A° of metal crystallite size, position and oxidation state of metals on the support, high surface area (100–1500 m^2/g), pore structure, and acid-base properties of the support are the factors that should be taken into consideration while designing heterogeneous catalyst systems for fine chemicals [144].

3.10 Summary

Most of the industrial chemical processes are catalyzed by solid (heterogeneous) catalysts. Heterogeneous catalysts are more easily recoverable (after the reaction) and reusable (in subsequent recycling experiments) than homogeneous catalysts. However, the heterogeneous nature of active sites is one of the major issues affecting the catalytic activity and selectivity in certain reactions. A detailed knowledge of the active sites generated during reactions through in situ characterization studies provides fundamental insight of the catalyst and catalytic process and at the same time can enable designing of a superior active and selective catalyst. This chapter provides an overview of heterogeneous catalysis, various reaction steps involved in catalytic process, methods of catalyst preparation and characterization, and finally catalyst deactivation and possible solutions to prevent deactivation or extend the life of the catalyst.

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CHAPTER 4

Catalyst Synthesis and Characterization

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4.1 Introduction

4.2 Bulk Catalysts

Catalysts are broadly classified as either bulk or supported. Bulk catalysts are solids which are largely homogeneous in phase and composition at the spatial level. This is unlike supported catalysts where the catalyst contains a distinct active phase and a "support" or "carrier" component. The primary role of the latter is to provide a substrate with a high surface area for dispersion of the active phase, provide microstructure, mechanical, and thermal resistance to the catalyst. Bulk catalysts encompass a wide variety of materials. The Ullman's Encyclopedia [1] carries a comprehensive compilation of these materials. These include binary oxides such as alumina, silica and magnesia to transition metal oxides such as chromia, zirconia or titania. Complex multi component oxides such as aluminosilicates, heteropolyanions, multicomponent mixed metal oxides such as bismuth molybdates and their promoted versions. Skeletal metals or metal alloys such as metal gauzes and sponge or skeletal metals like Raney™ nickel. These also include Fused catalysts, carbons, ion exchange resins, molecularly imprinted catalysts, MOF's and metal salts.

A gray area in this classification is metal and metal oxide catalysts with high loading of the active phase, comprising up to 80 wt% of the catalyst. Technically, these materials include a support, but in a minority concentration. These are classified by Perego et al. as mixed-agglomerated catalysts [2].

The majority of bulk catalysts are prepared from base metals because of their lower costs. Some exceptions are gauze catalysts like Rh, Pt, Pd, and their alloys, which are precious metals.

The primary requirements of a good commercial catalyst are high selectivity and productivity with a reasonable service life. A variety of materials are tailored to accomplish these criteria. Bulk catalysts are used when the material which effectively catalyzes a particular class of reactions has a relatively low TOF (turn over frequency), such as base metals and their oxides. The low TOF is compensated for by a larger content of the active phase in the catalyst.

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Typical applications are selective oxidation or ammoxidation, acid or base catalyzed reactions such as dehydration, esterification, alkylation, isomerization, and *trans*-alkylation. Gauzes and alloys, which include noble metals, are used in the form of a pad of fine nonporous wires or fine powders in applications where it is necessary to minimize resistance to intra-particle diffusion.

Between noble metals and base metals, cost is an important differentiator. Precious metal catalysts are significantly more active than base metals but they are expensive and not selective for all types of reactions. Susceptibility to poisoning by impurities such as compounds of sulfur, arsenic, mercury, and nitrogen, often found in feedstock, is another factor. The lower cost of base metals affords the use of part of the catalyst as a sacrificial material for reacting with these impurities and trapping them, thereby protecting the portion of the catalyst bed which is located at its downstream.

Bulk mixed oxide catalysts are complex materials and exhibit diversity by way of properties such as variable oxidation states and coordination number, polymorphism, redox behavior, acidity, basicity, defects, and involvement of lattice oxygen in reactions. Their preparation requires good control of process parameters and raw materials.

4.2.1 Overview of Types

Bulk catalysts are used in a plethora of applications. Aluminas are useful in applications such as the dehydration of alcohols and in the hydrolysis of COS. They, along with silica and magnesia, are widely used as supports/carriers. The transition metal oxides such as CoO and MoO_3, $CoMoO_4$, multicomponent bismuth molybdates, Mo-V-Nb-Te, and heteropolyacids are used predominantly as catalysts for selective oxidation and ammoxidation to produce chemicals like acrolein, acrylic acid, and acrylonitrile, amongst others. Copper chromite catalysts are used for hydrogenation and hydrogenolysis applications. Bulk Ni-Mo-Co catalysts "NEBULA™" are offered for hydrotreating applications as competition to the conventional alumina supported Co-Mo and Ni-Mo catalysts. Titania finds use in photocatalysis of pollutants and VOC's. Metal gauzes like Pt, Rh, and their alloys are used in the production of nitric acid and also for the selective reduction of NO_x. Platinum gauze was used for commercial production of sulfuric acid but it has been replaced by vanadium pentoxide-based fused catalysts. Skeletal metal catalysts such as sponge nickel are used for hydrogenation reactions to prepare specialty chemicals and APIs. Zeolites which are classified as multicomponent oxides are useful in cracking, isomerization, transalkylation, and shape selective catalysis reactions in the refining and petrochemical industry. Heteropoly acids are used for acid catalyzed reactions such as alkylation, dehydration, dehydroxylation, esterification, isomerization, and so on. Ion exchange resins are used for etherification, hydration, alkylation, and esterification reactions. MOFs are used for H_2 storage.

4.2.2 Methods of Preparation

The method of preparation of bulk catalysts varies with the type of catalyst. Simple or mixed oxides, and even mixed agglomerated oxide catalysts and heteropoly acids, are prepared largely by precipitation. The sol-gel technique is sometimes used. Zeolites are prepared by hydrothermal synthesis. Sponge metals and alloy catalysts are prepared by melt alloying (fusion) and quenching. Resins, such as IERs, are prepared by cross linked polymerization.

4.2.2.1 Precipitation

Precipitation has been the mainstay in the preparation of bulk catalysts because of its ease of practice and also that it is accomplished with relatively simple and inexpensive equipment. The typical steps constitute selection of precursor salts, preparation of a solution of the desired concentration of the solute, precipitation and aging at desired conditions of pH, temperature, and pressure. This is followed by a series of steps which may be common to other methods of preparation as well, such as washing, drying, comminution, shaping, and thermal treatment such as calcinations and activation.

Parameters which are important in precipitation are listed below. A combination of these parameters needs to be adopted to achieve the desired properties of the final product precipitate:

- Precursor salts: The anions present in the precursor salts influence the property of the precipitate. Srikanth et al. [3] have reported the formation of single and mixed phases along with differences in size and shape of the precursor particle used for preparing ZnO by homogeneous precipitation of different salts of zinc with urea. The relative ease with which anions of the metal salts can be removed from the precipitate by washing varies. This results in some of them remaining behind in the final product in the form of residual impurities. For example, nitrates tend to decompose during calcination and, hence, do not leave a residue, whereas sulfates tend to leave residual sulfate in the final product.
- Concentration of precursor (solute) and slurry concentration: These two parameters determine the degree of saturation of the solution, and along with other parameters, affect the relative extent of nucleation and particle growth, thereby influencing properties such as particle size and morphology which are important physical parameters. An example where a slurry concentration influences the peptization index and type number of pseudoboehmite is cited by Block and Scherzer [4]. The peptization index is an important property in the forming of pseudoboehmite into different geometric shapes.
- Temperature of precipitation: Temperature affects the relative extent of nucleation and particle growth and, hence, the microstructure of the precipitate. Salim et al. [5] have shown how a combination of temperature of precipitation and post-precipitation aging at the same temperature increases BET surface area, mesoporosity, and the nickel metal area while inhibiting the reduction of nickel.

- pH of precipitation: It influences the kind of chemical species formed, interaction with support, and also physical properties such as surface area, porosity, particle size, and shape. Babu and Murthy [6] have used TPR, IR, and TGA studies to show the effect of pH on the transition of nickel species from basic carbonate to nickel silicate with increasing pH of precipitation.
- The post-synthesis aging conditions of the precipitate can influence particle size, its distribution, and microstructure through mechanisms such as Ostwald ripening, and also metal dispersion. Bailey et al. [7] found that aging a precipitate of nickel—silica catalyst results in an increase in surface area of nickel and also the BET surface area of the reduced catalyst. They attribute this to dissolution of silica during the aging step to form nickel silicate.
- The effect of the combination of pH and temperature on the formation of different precursors of alumina is evident from the results of Van Straten and De Bruyn [8]. Details are provided in the section on alumina in this chapter.

Precipitation is a process by which a solute, which, in dissolved form, is separated as a solid phase from the solution. It is a process similar to crystallization except that its rate is generally much faster. It is comprised of three steps: super saturation; nucleation; and crystal growth.

Nucleation results in the formation of nuclei which grow into primary particles, which in turn grow further into secondary particles by a process of aggregation. Nucleation is dominated by the extent of super saturation of the solute, whereas aggregation is controlled by other factors such as shear rate, surface charge, and growth rate of crystals.

For a solute to separate as a solid phase from its solution into a solvent, its concentration must first exceed its saturation solubility. This is expressed by the equation

$$\log Q > \log K_{sp} \tag{4.1}$$

where Q is the product of molar concentrations of the species in solution raised to their respective coefficients and K_{sp} is the solubility product.

The degree of super saturation is expressed by the equation:

$$S = \frac{(C/C_{eq})}{C_{eq}} \tag{4.2}$$

Where S is the degree of super saturation, C is the concentration of solute in the supersaturated solution, and C_{eq} is the concentration of the solute in the equilibrium saturated solution. The degree of super saturation in precipitation is four to six orders of magnitude higher than in the case of crystallization. This results in the formation of much smaller crystals relative to crystallization.

Some methods by which super saturation can be achieved are listed below:

(i) Increasing concentration of the solute by way of evaporation of the solvent or by decreasing the temperature and therein solubility of the solute. This amounts to decreasing log K_{sp} in Eq. (4.1) above to meet the criterion. These are the predominant methods utilized in crystallization. Cooling the solution to increase super saturation is used when the solute is highly soluble and the equilibrium saturation concentration of the solute exceeds 0.2 g/g solvent. For substances which are soluble, where the equilibrium saturation concentration of the solute, C^*, is less than 0.2 g/g solvent, either cooling, or evaporation, or flash evaporation are used. For substances with a small change in equilibrium saturation concentration with temperature, $dC^*/dT < 0.005$ g/g solvent/°C, evaporation of solvent is used [9].

(ii) Changing the pH by addition of a suitable reagent "precipitant" to decrease solubility is the predominant method used in precipitation. In this case log Q, in Eq. (4.1) is altered to achieve the criterion for precipitation. This method is used for slightly soluble substances, where the equilibrium saturation concentration of the solute is less than 0.01 g/g solvent. The principle of common ion effect may also be used to induce this change and shift the equilibrium in favor of formation of a precipitate.

(iii) In catalysis, the physicochemical properties of the solid phase play an important role, hence, in actual commercial practice, concentration of the solute, temperature and pH are manipulated to achieve this end in precipitation.

Catalysis being a surface phenomenon, the control of the microstructure of catalytic materials is important. Catalysts range from amorphous materials like aluminas and silicas to highly crystalline materials like zeolites, which have very uniform pore size and are used in shape-selective catalysis applications. The degree of super saturation can be used to modulate the type/nature of the precipitate formed. Depending on the extent of super saturation of the solute, precipitates turn out either amorphous or crystalline in nature. Growth of precipitates and crystals takes place by aggregation. Whether the precipitate is crystalline or amorphous is dictated by whether aggregation occurs in an oriented manner or in a disordered manner, in effect it depends on the relative rates of orientation and aggregation during the growth phase. Orientation is favored by the low extent of super saturation, where the molecules get sufficient time to relax and arrange within the crystal lattice, while disordered aggregation which results in the formation of polycrystalline material is favored by a higher extent of super saturation, while a very high extent of super saturation results in the formation of amorphous material. In the latter two cases, the rate of addition of molecules to the growing solid particle is faster than the time required for relaxation.

Uniformity of composition, morphology, and microstructure of the precipitate are important for materials to function effectively as catalysts. The shape of the precipitate also assumes importance for flow characteristics of solids in processes such as continuous tableting, where

the feed should easily flow to the die. Achieving a precipitate which is homogeneous in terms of characteristics such as particle size distribution and shape requires maintaining the same level of super saturation of the solute throughout the precipitation. This is challenging even in co-precipitation because of mass and heat transport limitations which result in local super saturation. One way of overcoming this is to resort to homogeneous precipitation by mixing reagents such as HMTA (hexamethylene tetramine) or urea with the reactants. These compounds undergo rapid hydrolysis at a given temperature resulting in a sharp and sudden change in pH. This has been demonstrated by Candal et al. [10] where single-sized spherical amorphous particles of $Cu(OH)_2$ are produced using this technique. In this technique, a single burst of nucleation occurs followed by particle growth.

In multicomponent precipitation, differences in the solubility product K_{sp} of the solutes can result in heterogeneity. This can be overcome to an extent by precipitation from solutions which are at high levels of super saturation or by resorting to continuous precipitation.

Conducting the precipitation reaction in a confined space is another way of improving homogeneity, chemical purity, mono-dispersity of size and controlled shape, high degree of crystallinity, defect-free. This method is used for synthesizing nanoparticles using soft matrices such as microemulsions, or polymer solutions, or liquid crystals, semi-rigid matrices such as Langmuir Blodget films of gels or polymers, and hard matrices such as zeolites, layered frameworks, and mesoporous materials. This is reviewed by Trindade [11].

Strategies for controlling size, shape, uniformity of composition, dispersion, structure, and surface characteristics while precipitating metallic particles in liquid media are reviewed by Goia et al. [12]. They have reviewed the pros and cons of three different methods, (i) phase breakdown where metal is divided into fine particles when it is either in the molten or the solid state. This is accomplished by atomizing the liquid or grinding the solid; (ii) phase transformation, where finely divided metal precursors are converted into fine metallic particles through processes such as pyrolysis; and (iii) phase build-up where chemical precipitation or chemical vapor deposition are used. Parameters in precipitation, which are important for achieving the properties described above, are explained with examples. The use of redox potential and surfactants/dispersants and seeding for controlling particle size; factors such as the degree of super saturation, rate of nucleation, use of complexing agents and reductants, templates, seeds, and capping agents which have been demonstrated to control particle shape are reviewed. The hydrophilic and hydrophobic character of solvents in controlling surface properties of metallic particles is covered. The effect of standard redox potential of individual metals on the composition of the particles of their mixtures is also addressed.

Precipitation may be carried out either as a batch or continuous operation. In batch precipitation, depending on the chemical precursors used and the requirement of pH range of precipitation, either a precipitating reagent is added to a solution of a solute which is to be precipitated, or vice versa. In either of these situations, the reaction environment

undergoes a continuous, significant change in parameters such as concentration of the solute, pH, temperature (if it is not controlled), concentration of solids in the resultant slurry, and concentration of by-product solutes. These changes may result in heterogeneity in the characteristics of the precipitate which manifests as broad particle size distribution, difference in shape, and possibly even the chemical species formed in certain cases. Homogeneity can be further increased by precipitation in a confined space (as cited in the preceding section) but this could add to costs, which can adversely affect commercial feasibility in the manufacture of low cost bulk materials.

Continuous precipitation, on the other hand, affords much better uniformity of the environment of precipitation. Parameters such as solute concentration, pH, and temperature can be maintained within a narrow range by using proper process control loops. Continuous precipitation requires robust process control and automation which adds to the cost of hardware.

4.2.2.1.1 Nucleation

In the nucleation step, molecules or ions form clusters. This process is reversible until a critical cluster size is achieved, at which point stable nuclei start to form. Further growth decreases the Gibbs free energy of nucleation, making the process thermodynamically feasible. The Gibbs free energy change for nucleation ΔG_n is expressed as:

$$\Delta G_n = \Delta G_v + \Delta G_s \tag{4.3}$$

Where ΔG_v is the free energy change due to cluster formation, a negative quantity and ΔG_s is the interfacial energy formed due to the new surface through cluster formation. When the cluster size exceeds a critical radius, ΔG_n becomes a negative quantity with increasing radius of the cluster [13].

Nucleation is termed homogeneous when there is no contribution by external factors such as seeds or rough surfaces of the walls of the container. When such factors, including dust, initiate nucleation, it is called heterogeneous nucleation.

The next step in precipitation is crystal growth. This depends on concentration, pH, temperature of the medium, and aging [2]. Growth of precipitates occurs by two mechanisms, growth and aggregation [14].

The extent of super saturation can be used to control the particle size of the precipitate. The rate of nucleation is a power (law) function of the extent of super saturation [15], while crystal growth is a linear/direct function of the extent of super saturation [16,17], thus by restricting the extent of super saturation of the solute to a certain level after nucleation, particle growth can be favored at the expense of nucleation. Frank et al. [18] have shown how this can be manipulated in the disposal of phosphoric acid from effluent streams by growing large crystals of calcium hypophosphate which are easily filterable.

On the other hand, small crystal size is preferred in catalysis to minimize resistance to internal diffusion. Achieving a high degree of super saturation is critical to this end. The lower the solubility of the product, the higher the extent of super saturation. Typical salts which have sparing solubility in aqueous media are hydroxides, carbonates, phosphates, sulfates and sulfides, arsenates, halogenated salts of I and F, cyanides, and acetates [19]. Of these, the hydroxides and carbonates are preferred intermediates because of added advantages such as not leaving behind a residue in the catalyst, ease of thermal decomposition, and minimal hazardous emissions during their decomposition [2].

Genck [20] has shown how ultrasonics can be used to create microbubbles or cavities, which when collapsed, can induce nucleation in the metastable concentration zone to initiate nucleation without seeding. This can decrease induction time. The duration of ultra-sonication can be manipulated from burst to continuous, thereby regulating nucleation, thus controlling crystal size distribution. Sonawane et al. [21] have shown the use of ultra-sonication for enhancing the rate of nucleation while inhibiting the rate of crystal growth for the continuous production of calcium carbonate with a controlled morphology such as narrow particle size distribution and smaller particle size. Ultra-sonication improves micro-mixing in the reaction medium.

4.2.2.1.2 Polymorphism: Ostwald's law of stages

Crystalline materials can exist as isomorphs or polymorphs. The former crystallize in near identical forms and are chemically similar, whereas the latter are chemically identical but have different crystalline forms. During precipitation or crystallization, the polymorph with the highest super saturation forms first. According to the Ostwald rule of stages, this polymorph is invariably less stable from a thermodynamic perspective. Its conversion to a more stable thermodynamic form can be a slow process. Formation of a given polymorph can at times be affected by mixing [22].

4.2.2.2 Sol-gel

The sol-gel technique is adopted when there is a requirement for a high degree of control over the textural properties of the material and also the dispersion of components is required at near molecular scale. Materials of high purity can be produced due to the use of precursors with very low impurity concentrations. This technique is widely used in preparing ceramics and thin films.

Sol-gel chemistry encompasses hydrolysis of metal salts to form sols, condensation reactions of the hydrolyzed molecules in the sol, followed by gelation to form a macro-molecule which is then aged. The gel is dried and calcined to obtain the final product.

Sols are suspensions of solid particles in a liquid phase. Their equivalent of particles suspended in a gas phase medium is called aerosol. Liquid particles which are suspended in a gaseous

medium are called fog and smoke if these particles are solids. The size of these suspended solid particles ranges between 1 and 1000 nm. They present properties such as Brownian movement. Sols are classified as particulate or polymeric depending on whether the suspended particles they contain are dense oxide particles or branched macromolecules. The latter do not contain dense particles of a size greater than 1 nm [23]. Silica sols tend to form polymeric sols except under extreme conditions such as high pH and excess water. In contrast, other oxides tend to form particulate sols. The ability to form polymeric networks rests with the number of bonds which a monomer can form. This is referred to as *functionality "f."* Polyfunctional polymers with $f > 2$ either form dense spheroidal particles or fractal polymeric structures, depending on the solubility of the particles in the solvent medium. The former are Euclidean objects where their mass changes as the cube of the radius whereas in the case of fractal particles, the mass changes at radius raised to the mass fractal dimension of the particle. As a result the density of a fractal particle decreases as its size increases.

Precursors which are used in sol-gel process are either inorganic salts of metals or organic compounds such as alkoxy compounds. Metal alkoxides readily react with water and hydrolyze to form a hydroxylated metal moiety with the liberation of an alcohol.

$$M(OR)_4 + H_2O \longrightarrow (OH) - M(OR)_3 + ROH \tag{4.4}$$

Where M = metal or Si and R = alkyl.

The degree of hydrolysis depends on the quantity of water and catalyst used, thus hydrolysis can be either partial or complete. In the latter case, all the —(OR) are replaced with —(OH). Inorganic salts undergo hydrolysis in a similar manner.

The hydroxylated alkoxides, also called monomer units, react further via a condensation reaction to form polymeric compounds with M—OH—M or M—O—M bonds through reactions called olation or oxolation, respectively.

A gel is a molecule which has reached macroscopic dimensions to a point where it extends throughout the solution. It is characterized by a continuity of both the solid [gel] phase as well as the liquid [sol] phase which it encompasses. And both phases exist in colloidal dimensions. Gels can form as polymeric networks or through the agglomeration of particles or by entanglement of chains. Bonds that hold gels together may be irreversible, as in the case of polymeric gels or reversible, as in the case of particulate gels [24].

Aging of the gel constitutes continuation of the formation of monomer particles or polymeric segments within this sol phase. These attach themselves to the existing gel network or particles. Dissolution and reprecipitation of oligomers can be likened to the process of Ostwald ripening which takes place during aging of precipitates. A process called syneresis, which comprises shrinkage of the gel phase and the resultant expulsion of liquid phase from the pores occur during aging of some gels.

The sol-gel chemistry of silicates differs from that of nonsilicates mainly in the former being less reactive. This section is focused on silicas and aluminas because they are amongst the most widely used materials as carriers and catalysts. Other systems are covered briefly.

4.2.2.2.1 Hydrolysis of nonsilicate inorganic precursors

The salts of metals get solvated in aqueous medium to form metal-aquo ions with the general formula $[MO_NH_{2N-h}]^{(z-h)+}$, where N is the coordination number and h the molar ratio of hydrolysis. The solvation results in the coordinated water molecule becoming acidic. The degree of hydrolysis depends on the acidity of the coordinated water and the degree of charge transfer. When $h=0$, an aquo-ion results which is represented by the general formula $[MO_NH_{2N}]^{z+}$, Similarly, when $h=2N$ an oxy-ion, $[MO_N]^{(2N-z)-}$, results. When $0<h<2N$, for $h=N$ a hydroxo complex, $[MOH_N]^{(N-z)-}$ results, while for $h>N$ a oxo-hydroxo complex, $[MO_x(OH)_{N-x}]^{(N+x-z)-}$, results, and when $h<N$ a hydroxyo-aquo ion, $[M(OH)_x(OH_2)_{N-x}]^{(z-x)+}$, results [24]. The ease of hydrolysis depends on three factors (i) an increase in charge density on the metal, (ii) the number of metal ions bridged by hydroxo or oxo ligands, (iii) and the number of H atoms contained in the ligand. Hydrolysis becomes difficult as the number of hydroxo ligands coordinating to the metal increase [23]. Parameters which are important for complex formation are the charge z, coordination number N, electronegativity $\chi^0_{M,}$ and pH of the medium, in addition to ligand field stabilization.

Kepert et al. [25] have shown qualitatively how the combination of the charge on the molecule and the pH of the medium influence the formation of various hydrolysis complexes such as aquo, hydroxo, oxo complexes, and their combinations (Fig. 4.1). A partial charge model developed by Livage et al. [24,26] provides quantitative explanation of this relationship.

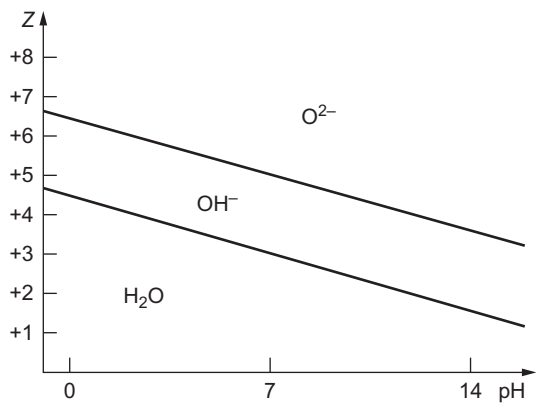


Fig. 4.1
Charge versus pH for hydrolyzed species in solution [25].

4.2.2.2.2 Condensation of nonsilicate inorganic precursors

Condensation reactions which follow hydrolysis proceed by one of two mechanisms depending on the coordination state of the metal:

Nucleophilic substitution,

$$M1 - OX + M2 - OY^{-} \rightarrow M1 - OX - M2 + OY \tag{4.5}$$

Or by nucleophilic addition,

$$M1 - OX + M2 - OY^{-} \rightarrow M1 - OX - M2 - OY \tag{4.6}$$

Oxo-ligands which are present in oxy-ions, $[MO_N]^{(2N-z)-}$, which predominate in the high pH/high charge combination undergoing the addition reaction when at least one of the reactants is coordinatively unsaturated. In the absence of coordinative unsaturation, they need to be activated by the addition of acid or a reducing agent. Aquo-ligands which are present in aquo-ions, in the low pH—low charge domain do not undergo condensation. They need to be activated by the addition of a base or oxidizing agent. Hydroxo-ions, which exist in the intermediate pH—intermediate charge combination, readily condense as soon as at least one hydroxyl ion is present in the coordination sphere [23].

Olation is a condensation reaction in which an hydroxyl bridge forms between metal centers. Linear, branched, or ring structures are possible. The kinetics of olation depends on the lability of the aquo ligand, size, and electronegativity and electronic configuration of the metal center. Smaller charge and larger size favors olation [23].

Oxolation is another type of condensation reaction in which an oxo bridge is formed between metal centers. Depending on whether the metal center is coordinatively saturated or unsaturated, condensation proceeds either by nucleophilic addition or by nucleophilic substitution. Oxolation is a two-step process with the first step catalyzed by bases and the second by acids, hence, this reaction takes place over a wider range of pH than oxolation, but its kinetics are slower and minimal at the iso electric point [23].

Condensation of neutral precursors is affected by the partial charge on the H_2O ligand, resulting in the formation of hydroxides, oxyhydroxides, and finally, fully condensed oxides [27]. Polyanions, which are also called polyacids, result from oxolation reactions at higher pH.

Gellation: The formation of gel or precipitate is dependent upon various factors such as the kinetics of condensation and process parameters such as temperature, speed of mixing, and pH gradients [28]. Livage et al. [24] have shown that between Cr^{3+} and Fe^{3+}, the latter form precipitates while the former forms gels at 25 °C, which is attributed to faster kinetics of condensation in the latter.

The role of anions: Anions present themselves as counter ions present in inorganic salts. They compete with aquo ligands for coordination or complexation with the metal center, which

affects hydrolysis and condensation reactions [29]. This, in turn, affects particle morphology and stability [29]. Electronegativity of the counter ion is an important parameter which affects complexation.

Metal alkoxide precursors: These are, in general, more reactive than their inorganic counterparts and require strict control of reaction conditions. They can form oligomers which affect their reactivity. Alcoxolation is an additional condensation reaction in metal alkoxides which results in the formation of M—O—M bonds in addition to oxolation. Both acid and base catalysts influence the final product. Acid catalysts produce less branched polymers compared to base catalysts. Oxo-alkoxides are analogs of polyacids which are observed as condensation products of inorganic precursors. The relative rates of hydrolysis, oxolation, alcoxolation (specific to alkoxide precursors), and olation govern the structure of products formed from alkoxide precursors. This is similar to what happens in inorganic salt precursors where counter ions from the salts affect these reactions [23].

4.2.2.3 Pyrogenic oxides

Kerner [30] has provided a very concise and illustrative review of pyrogenic oxides. Oxides such as SiO_2, Al_2O_3, TiO_2, and ZrO_2 which are commonly used as catalyst supports are also produced by the flame hydrolysis method. In this process a mixture of metal precursors such as metal chlorides, chlorosilanes, and organic siloxanes are vaporized, mixed with hydrogen and oxygen and combusted in a burner. The water formed from the combustion of hydrogen hydrolyses the metal precursors and the high temperature facilitates the further conversion of the hydrolysis products to the oxides. The by-products HCl or alcohols which form depending on the precursor which is used, are recovered. The mechanism of formation of primary particles consists of nucleation followed by growth resulting from subsequent deposition. Further growth to form aggregated structures takes place by coagulation and coalescence. The size of aggregated particles can be controlled by adjusting the residence time in the flame hydrolysis section. Parameters such as flame temperature, oxygen: hydrogen ratio, precursor concentration, and the residence time are used to control the properties of the product.

When compared to oxides formed from the precipitation route, pyrogenic oxides are characterized by high purity, much smaller particle size, spherical shape, and little to nil internal surface area. Therefore, the specific surface area is highly dependent on the particle size. Pyrogenic silicas are X-ray amorphous, whereas the corresponding aluminas are crystalline. The temperature and residence time in the flame hydrolysis section affect the form of the oxide (eg, the aluminas may consist of the γ or the δ forms), while in the case of titania, the anatase phase which is dominant at lower temperatures, tends to transform to the rutile phase at higher temperatures. Similarly, ZrO_2 converts from monoclinic form to tetragonal at higher temperatures.

Pyrogenic oxides present interesting properties. Silicas are predominantly hydrophilic. The aluminas tend to be weakly alkaline in water and present Lewis acid sites upon total dehydroxylation. Titanias may present both acidic and basic behavior depending on the coordination of the hydroxyl groups to the Ti. Zirconia shows a higher degree of basicity than titania.

Pyrogenic oxides can be formed into shaped catalyst particles by any of the conventional methods such as spray drying, extrusion, or tableting. The silica is used in catalysts for VAM. The alumina is used as a wash coat in three-way catalysts. VOC treatment and water treatment are other major applications.

4.2.2.4 Hydrothermal synthesis

Zeolites-based materials are microporous and/or mesoporous crystalline materials, widely used as catalysts and adsorbents in refinery and petrochemical processes, and the manufacturing of specialty and fine chemicals [31]. These materials are known for their acidic, basic, and redox properties. These materials have replaced many catalysts for various applications rendering the advantage of not generating effluent and minimizing undesired products. With the increasing environmental concerns, these materials with different pore structures, acidic, basic, and redox properties make them attractive catalysts/adsorbent for a wide array of applications. Below are the applications of different zeolites, metallosilicates, and Silico-Aluminophosphates based materials in refinery, petrochemical processes, specialty and fine chemicals [32]. Applications of zeolites in refining, petrochemical, specialty and fine chemicals is given in Table 4.1 below.

Table 4.1 Applications of zeolites in refining, petrochemical and specialty and fine chemicals

Process/Application	Feed	Product/Goal	Zeolite/SAPO—Used in Catalyst Formulation
Applications in refinery processes			
Cracking (FCC/FCC additive)	Vacuum distillates and residues	Gasoline/light olefins	H-Y, USY, ZSM-5
Selectoforming	Light gasoline	Increase octane number	Erionite
Hydrocracking	Gas oils, lube oils	Gasoline/middle distillates	H-Y, Al_2O_3/H-Y
Dewaxing	Middle distillates and lubricants	Improve cold flow properties	ZSM-5 and Mordenite
Isodewaxing	Lube oils	Improve cold flow properties	SAPO-11
Hydroisomerization	n-C_4,	i-C_4 olefins	Mordenite
	Light gasoline n-C_5/C_6	i-C_5/C_6	Mordenite
Isomerization	n-C_4 olefins	i-C_4 olefins	Ferrierite
	n-C_5/C_6 olefins	i-C_5/C_6 olefins	Ferrierite, ZSM-5
Oligomerization	C_3 olefins	Diesel	ZSM-5

Continued

Table 4.1 Applications of zeolites in refining, petrochemical and specialty and fine chemicals—cont'd

Process/Application	Feed	Product/Goal	Zeolite/SAPO—Used in Catalyst Formulation
Applications in petrochemical processes			
Aromatization	C_6/C_7	Benzene toluene	L-type
	C_3/C_4	Benzene toluene xylenes	ZSM-5
Aromatics treatment (alternative to clay treatment)	Reformate, aromatics extracts/streams containing olefins	Reduce olefins content (reduce bromine index)	MCM-22
Xylene isomerization	C_8 aromatics	p-Xylene	Mordenite, ZSM-5
Toluene disproportionation	Toluene	Xylene and benzene	Mordenite
Selective toluene disproportionation	Toluene	p-Xylene	ZSM-5
Transalkylation	Toluene and Trimethylbenzene	Xylenes	Mordenite
	Benzene and Diisopropylbenzene	Cumene	Mordenite
	Benzene and Diethylbenzene	Ethyl benzene	Mordenite
Alkylation	Benzene and ethylene/ethanol	Ethyl benzene	ZSM-5/Beta
	Benzene and propylene	Cumene	Beta/Mordenite/MCM-22
	Benzene and long chain olefins	Linear alkyl benzenes	Mordenite
Selective alkylation	Ethyl benzene and ethylene/ethanol	p-diethyl benzene	ZSM-5
Methanol to olefins	Methanol	C_2, C_3, other olefins (C_3 major)	ZSM-5
	Methanol	C_2 and C_3 olefins	SAPO-34
Methanol to DME	Methanol	DME	SAPO-34
Applications in specialty and fine chemicals			
Cracking of MTBE	MTBE	i-C_4 olefin	ZSM-5/alumina
Oxidation	Phenol	Hydroquinone and catachol	Ti silicalite
	Propylene	Propylene oxide	Ti silicalite
	Allyl chloride	Epichlorohydrin	Ti silicalite
Ammoxidation	Cyclohexanone and ammonia	Cylohexanone oxime	Ti silicalite
Hydration	Cyclohexene	Cylohexanol	ZSM-5
Amination with ammonia	Methanol and ammonia	Methyl-, dimethyl amines	CHA
	Ethylene oxide and ammonia	Ethanol amine	
	Acetaldehyde and ammonia	Methyl pyridines	ZSM-5

Table 4.1 Applications of zeolites in refining, petrochemical and specialty and fine chemicals—cont'd

Process/Application	Feed	Product/Goal	Zeolite/SAPO—Used in Catalyst Formulation
	Formaldehyde, acetaldehyde and ammonia	Pyridine and methyl pyridines	ZSM-5
	Isobutene and ammonia	Tert-butylamine	ZSM-5
Isomerization	Chlorotoluene	m-Chloro toluene	ZSM-5/Beta
	o-Dichlorobenzene and p-dichlorobenzene	m-Dichloro benzene	ZSM-5/Beta
Acetylation	Anisole and acetic anhydride	p-Methoxy acetophenone	Beta
	Veratrole	Dimethoxy acetophenone	H-Y
Beckmann rearrangement	Cyclohexanone oxime	epsilon-Caprolactum	ZSM-5

Adapted from Refs. [32,33]

The synthesis of zeolites is reviewed by many authors [34–38].

These literature reports capture, in general, all the relevant factors which influence the zeolite synthesis. The scope for this chapter section is limited to synthesis of zeolites on a commercial scale. The important factors which influence the synthesis of zeolite structure are the type of reactants/precursor source, molar gel composition, seeding, pH of the reactant gel composition, aging time and temperature, hydrothermal crystallization time and temperature, filtration, washing, drying, and calcination [39–41].

The type of precursor source of Al and Si in the zeolite synthesis is important as it affects the quality and cost of the zeolite. Common Si precursor sources are precipitated silica, sodium silicate, and silica sol, whereas the Al sources are corresponding sulfate/nitrate/chloride salts and sodium aluminate. In addition, the type of templates, such as organic amines, quaternary ammonium halides and hydroxides strongly influence the crystallization and quality of the zeolite. In addition to the Si and Al precursor sources, the molar gel composition affects the crystallization kinetics, phase purity, crystallinity, and other properties of the zeolite [42,43]. Prior to scaling up detailed study is always undertaken to understand the effect of each raw material, its quantity and purity on the zeolite product quality. In addition, the effect of mixing/agitation time is studied to know the effect on crystallite size and crystallinity. Seeding is mainly done to avoid formation of competing phases during the hydrothermal crystallization and minimizing the hydrothermal crystallization time [44,45]. Zeolite synthesis is critical to pH of the molar gel composition. The pH of the molar gel composition determines the kinetics of crystallization [46]. The aging time affects the crystallite size. In general, the higher the aging time, the smaller the crystallite size. With a higher hydrothermal crystallization temperature, the synthesis time is minimum [47]. The

post synthetic processing, such as filtration, washing, ion exchange, drying, and calcination also affect the product quality. Filtration is done to separate the zeolite from the mother gel. The filtrate is washed thoroughly to ensure removal of excess alkali, silica, and alumina from the zeolite. Drying and calcination is done to remove the template, if any, associated with the zeolite. The ion exchange is done with mineral acids and/or ammonium salts to exchange the alkali associated with zeolite at exchange sites in the framework with suitable cations or to convert it to proton or ammonium form. The zeolites are formed in different shapes and sizes, such as microspheres, by spray drying, the spheres by granulation/spherodizing, the extrudates and other suitable shape with or without using binders. Methods of forming are covered in other sections of this chapter. The hydrothermal synthesis of zeolites on commercial scale poses environment, safety and health issues. Hence, the choice of raw materials to be used becomes important. The typical effluent from a zeolite synthesis stream contains silica, alumina, organic templates, and ammoniacal nitrogen and other salts. The drying calcination exhaust streams contain NO_x, CO_x. It is always a challenge for zeolite manufactures to treat the effluent/exhaust streams by suitable methods to comply with the regulatory norms.

Shape selective Catalysis: Pore mouth regulation of zeolites: ZSM-5 is widely used as an industrial catalyst for the alkylation, isomerization, and cracking of hydrocarbons. ZSM-5 which is modified by silylation is useful as a shape selective catalyst for selectively producing the 1,4 dialkyl benzene isomer. Das etal. [48] assigned to IPCL [now Reliance Industries Limited] shows a catalyst which can produce 1,4 diethylbenzene with per pass isomer selectivity exceeding 99 mol%. Similar behavior can be realized by modifying the ZSM-5 with phosphorus, antimony, boron, or magnesium [49]. Pre-coking a ZSM-5 catalyst which is modified by P, B, Sb or Mg for improving the selectivity of 1,4 dialkyl benzene isomers is shown in Ref. [50].

4.2.2.5 Fused catalysts

Fused catalysts are distinguished from other catalysts by virtue of their passing through the stages of melting and solidification during their preparation. These catalysts can be prepared with a high degree of dispersibility. The methods cited in literature for the preparation of fused catalysts are pyrometallurgical techniques, heating in crucibles made from refractory oxides such as alumina, magnesia, zirconia, and alloys such as ferrotungsten, pure tungsten, or carborandum. Use of protective layers in the crucible is prescribed to prevent contamination from the material composition of the crucible. A radiating arc electric furnace, oxyhydrogen blow torch, or water-cooled electrodes are used for melting the oxide [51].

The hardware required for the preparation of fused catalysts is cost-intensive and the process is energy-intensive because the reactants have to be melted. Induction furnaces are more energy efficient than traditional pyrometallurgical methods where applicable. The preparation of fused catalysts does not involve the calcination step, which is necessary in other methods of catalyst preparation, such as precipitation, impregnation, or sol-gel. Further, while fusion is carried out on the timescale of minutes, calcination usually involves a prolonged treatment

on the timescale of hours. This offsets some of the overall cost of energy required for preparation of fused catalysts. The exothermic heat of reaction is also used to minimize the cost of energy. An example is the "EXO-MELT" process developed by the Oak Ridge National Lab USA for preparing nickel aluminides [52].

Knowledge of thermodynamics and phase diagrams is necessary for the preparation of fused catalysts. Thermo-calc™ AB Software of Sweden provides thermodynamic and mobility databases along with their software, which includes stable and meta-stable heterogeneous phase equilibria and thermochemical data. Databases of phase diagrams are available from International alloy phase diagram database of ASM (American Society for metals). The phase diagram describes the existence of different liquid and solid phases with different compositions as a function of temperature. Alloys constitute intermetallic compounds which may be of variable or fixed composition. These may be formed through eutectic, peritectic, eutectoid, or peritectoid type of reactions or as solid solutions during cooling of a melt of a mixture of the individual metals. Eutectics are solid alloys of a unique composition whose melting point is the minimum over the entire composition range of these metals. They solidify from the liquid phase mixture of the individual metals at the eutectic point. Peritectic reaction is one in which a solid phase reacts with the molten liquid phase with which it is in contact to form a new solid phase. Eutectoid reaction is a three-phase reaction where a solid transforms into two other solid phases simultaneously when it is cooled. A peritectoid reaction is a three-phase reaction where two solid phases transform to form a third phase when cooled.

In the preparation of fused metallic alloy catalysts there is intimate mixing at the atomic level at the melt stage. This is analogous to methods such as sol-gel or flame hydrolysis, the difference being that the reactants pass through a molten stage in the former. This difference in the physical phase of the reactants during processing results in topochemical changes in the case of sol-gel whereas there is the possibility of isotropic chemical reactivity in the catalyst preparation by fusion, provided the phase segregation is prevented by super-cooling [53]. When metal oxides change in oxidation state due to decomposition at high temperatures of fusion [54], and control of their kinetics [55], is again used to form solids which are thermodynamically metastable and, hence, are either catalytically active or act as precursors for preparation of catalysts with unique properties, making them useful for oxidation reactions.

Fused Vanadium oxide catalysts are used for the oxidation of ortho-dialkylbenzenes to their corresponding anhydrides. The ones used for oxidation of sulphur dioxide to sulphur trioxide are classified as SLP (supported liquid phase) catalysts. The oxide(s) are supported on an inert carrier. This oxide phase exists in a homogeneous molten state at reaction conditions. The preparation of similar catalysts is covered by Vrbaski [56].

The preparation of fused catalysts passes through the stages of melting, controlled solidification, and post treatment which may also involve activation to bring the catalyst to its active form. Scholgl has described these steps in detail in Ref. [53]. A summary of the same is reproduced below. During the formation of the melt, Scholgl has highlighted the

importance of parameters such as kinetics, hold time, efficiency of mechanical mixing, and homogeneity of temperature in the melt in order to achieve homogeneity of composition of the melt. The effect of valence of the metal in the oxide form, purity, and its form in preparing alloys and mixed oxides is covered. The nature of the gas phase over the melt also affects the phase of the final product. The formation of oxide by reaction with oxygen from the environment or the formation of a scale on the surface which retards mixing is also highlighted. Concentration gradients arising due to differences in chemical potential, mechanical mixing, and electric fields, depending on the hardware used, are cited.

In the step of cooling the melt, the kinetics of crystallization, uniformity of temperature across the bulk of the melt, the rate of cooling, and annealing affect the composition of the final alloy. Slow cooling rates result in the thermodynamic equilibrium composition of the resultant alloy. Cooling at very high rates of the order of 10^4 K/s, which is also called super cooling or melt quenching, is recommended when the objective is to form amorphous, glassy phases which may be metastable in composition. In this situation, restructuring during cooling is minimal and near atomic level dispersion in the melt is maintained in the solid phase. These materials can be transformed into nanocrystalline materials which may themselves be metastable in composition and also be active as catalysts. The free energy, stored in these metastable glassy phases as a result of preventing crystallization during solidification, is used for this transformation. However the activity of such materials with metastable components is generally temporary and dies down with the conversion of the solid to a stable phase, unless the metastable state is regenerated *in situ* during use of the catalyst. Metastability is desirable as with fused iron oxide catalysts which are used for manufacturing ammonia. It may be undesirable in intermetallics. Rapid cooling also effects formation of smaller crystallites. Schlogl [53] has drawn attention to how the rate of cooling coupled with annealing can be used to alter the texture of materials from metastable glassy amorphous states, which are homogeneous in composition, to states of crystalline solids pure in composition or those interspersed with varying degree of metastable phases. The fused iron oxide catalyst used for manufacturing ammonia is cited as an example where metastability results due to phase segregation arising from ex-solution of oxides which are used as structural promoters. The formation of such crystallographic states is unique to melt alloying and cannot be prepared by the route of precipitation followed by calcinations. Preparation by fusion provides a means to control heterogeneity over the micro-meso-macro dimensional levels by adjusting the rates of cooling and subsequent annealing.

4.2.3 Skeletal Catalysts

Raney™ or sponge, or skeletal nickel (also referred to as nickel aluminide), and sponge cobalt catalysts are used extensively for hydrogenation reactions such as reductive alkylation, hydrogenolysis, dehalogenation, and desulfurization applications in organic reactions [57].

Copper catalysts and noble metals like platinum, ruthenium, and palladium are also produced in sponge form. Promoters such as lanthanides and transition metals are incorporated to modify the activity for certain applications. An advantage of these catalysts is that they are prepared and available in reduced active form by the supplier. The end user need not invest in hardware for reactivation of these catalysts.

The method of preparation consists of the following steps:

- Typically a mixture of two metals, one which is active for the target reaction and the second, a sacrificial metal, is treated to form an alloy. This is accomplished by pyrometallurgical techniques or by mechanical alloying. In the former technique the mixture of the metals to be alloyed is heated to a melt by using equipment such as an induction furnace and in the latter technique, it is subjected to intense mechanical forces to form an alloy. The composition of the initial mixture is important in realizing the desired composition of the alloy. Devred et al. [58] have shown this effect along with argon gas atomization of the melt. Proper melting of the mixture and through mixing of the melt is important to realize an alloy which is homogeneous in composition at the macro level. Heterogeneity may still occur at the grain level. Dopants or promoters such as Mo, La are added to improve selectivity or durability of the catalyst [59].
- The alloy formed in the previous step by melting/fusion is cooled to form a cast. The rate of cooling is an important parameter which influences the final composition of the alloy if formation of multiple phases is possible, as per the phase diagram. Fouilloux [60] has reviewed the effect of cooling and annealing on the composition of the alloy, which is reported in the literature for Raney nickel catalyst. Rapid melt quenching followed by treatment with hydrogen is reported to increase activity significantly [61].
- Alloying is followed by comminution of the alloy to desired particle size. This is done by using equipment such as jaw crushers or hammer mills to break the alloy to a smaller size. The smaller particles are then ground in high energy ball mills to the desired particle size. Particle sizes are in the 20–100 μm range. Fine grades can have as high as >70% fraction with particle size lower than 40 μm. Devred et al. [58] have compared atomization with an inert medium such as argon gas as an alternative to casting and sizing by grinding. This technique results in microspheroidal morphology which is rich in the $NiAl_3$ phase. It is reported to result in higher catalytic activity.
- The sacrificial metal is leached away chemically to leave behind a spongy structure of the active metal. The sponge metal thus formed is generally in active form. The composition of the alloy is also reported to influence the extent of leaching [59] Leaching conditions are important as they affect the extent of removal of the sacrificial metal from the alloy and also its deposition as oxide in the pores of the sponge catalyst. This, in turn, affects the microstructure, mechanical strength, and final activity of metal sponge [60].
- The sponge metal is pyrophoric in nature and it is stored in a medium such as water or alkalized water. Aging of the sponge due to oxidation resulting from dissolved oxygen in

the storage medium is an important aspect. Passivation by controlled oxidation and surface coating is reported in the literature by Birkenstock [62].

- In use, these catalysts may deactivate due to different reasons depending on the application. Abrasion in liquid phase catalytic reactions is a major cause of deactivation. This renders the separation of the catalyst from the product difficult. Other causes are loss of activity due to formation of carbonaceous deposits on the surface, loss of microstructure/surface area and in some cases where oxidizing agents are used, oxidation of the metal [59].
- In summary, the final activity of sponge catalysts is a cumulative function of aspects such as the composition of the alloy formed, the extent of leaching of the sacrificial metal, the type of residue of the sacrificial metal which is left behind in the sponge catalyst, and aging during its storage.

4.2.4 Pyrometallurgical Methods

The preparation of sponge metal catalysts starts with the alloying of two metals. One of these is a metal which is catalytically active for the end application, while the other metal is a sacrificial material which is leached away from the alloy to create porosity in the bulk framework of the active metal. Sponge catalysts are prepared by pyrometallurgical methods where a mixture of metals is melted by the application of heat. The use of an induction furnace is a more energy efficient technique where induction effects are used as a means to generate heat for melting and, hence, alloying of the metals. ORNL has developed the Exo-Melt process where the Ni and Al metals are loaded in a particular manner to harness the exothermicity of the reaction. This decreases energy consumption to a half or a third of conventional alloying [52]. The melt is then quenched either by dropping it into a cooling medium, such as water, or allowed to cool naturally in air. Key considerations are energy costs, minimizing oxidation of the metals during the process of alloying, and phase segregation during the cooling step.

4.2.5 Melt Quenching

Nickel aluminides are also prepared by the process of melt quenching. This consists of rapid cooling of the melt, cooling rates of the order of magnitude of 10^6 K/s. This is reported to influence the microstructure, improve phase homogeneity, produce metastable crystalline phases, or nano-crystalline alloy phases, or amorphous and noncrystalline glassy phases [63]. Fan et al. [64] have studied this aspect in Ni-Al alloys. They report larger residue of the Ni_2Al_3 phase in the skeletal catalyst after leaching which stabilizes the skeleton, results in lower surface area, higher porosity, larger mean crystallite size, and higher activity for liquid phase hydrogenation of certain organic compounds [65].

Variants wherein melt quenching is followed by treatment with hydrogen at elevated temperature are reported to enhance performance [61]. This step is carried out immediately prior to leaching out the Al from the alloy. The authors report improved activity for the hydrogenation of cyclohexanone. They attribute the improved performance to formation of

certain alloy phases from which the Al component can be easily leached, resulting in higher specific surface area of the catalysts.

4.2.6 Mechanical Alloying

Alternate methods of preparation such as mechanical alloying are also reported [66]. While conventional methods use high temperatures to melt and alloy the metals, mechanical alloying is carried out at ambient temperature. This process consists of ball milling mixtures of powder of the metals to be alloyed. The milling is carried out in an inert environment such as argon gas. The alloy thus formed is passivated by introducing air in a controlled manner at intermittent stages during the milling step and also prior to removal of the alloy powder from the ball mill. This further process is similar to that practiced for conventional sponge nickel catalysts, that is, digestion in an aqueous solution of KOH to leach away one of the metals, such as Al in the case of nickel aluminides. This is followed by a second step of passivation to render the dry catalyst safe for characterization. The samples are reactivated in hydrogen at 773 K for 3 h prior to testing their activity. The authors report higher activity of catalysts prepared by mechanical alloying for the hydrogenation of benzene to cyclohexane.

4.2.7 Reduction and Passivation/Stabilization

Some of the major bulk metal catalysts such as those used in the steam prereforming of hydrocarbons to manufacture syngas, or for the water gas shift reaction to produce hydrogen, or methanation catalysts, or the bulk nickel catalysts used for hydrogenation of aromatics are active only when the active phase is present in the metallic state. They are prepared as oxides or mixed oxides and need to be reduced to the metallic state in order to render them active.

Reduction can be brought about either by heating the catalyst to elevated temperatures in an atmosphere of a reducing gas such as hydrogen, a mixture of CO and $H_{2,}$ or through wet chemical reduction such as treatment with a solution of hydrazine or sodium borohydride. The former is practiced widely for large scale industrial production of catalysts which are fairly resistant to sintering at elevated temperatures. When the catalytic material is not tolerant to elevated temperatures, such as nanocatalysts, the wet chemical reduction technique is used.

Ease of reactivation of the reduced and stabilized catalyst in the commercial reactor where it is used for the end application is also an important consideration because user plants may be limited by hardware necessary to achieve the conditions conducive to reactivation. Other advantages of the ease of re-reduction or reactivation are energy savings and minimizing nonproductive time which is required to reactivate the catalyst.

Reduction of the oxide form of the catalyst to metallic state renders it pyrophoric and, hence, requires stabilization or passivation to render it safe for handling. The preferred method of reduction is to treat the catalyst to dry hydrogen at elevated temperature. Hydrogen can form explosive mixtures with air and adequate care must be taken to ensure that the medium of

reduction is free of oxygen (concentration <50 ppm). Generally a mixture of hydrogen in an inert gas such as nitrogen is passed over the catalyst at fairly high space velocities, ranging up to a few thousand h^{-1} to dissipate the heat generated due to chemical reduction and also to carry away the moisture formed due to the reaction. The temperature and concentration of hydrogen are increased in a very controlled manner. The reduction is an exothermic process. Therefore, it has to be carried out in a very controlled manner to prevent local high temperature (hot spots) in the catalyst bed. Hot spots can lead to loss of surface area of the reduced metal due to sintering. Sintering is aggravated by temperature and also the presence of moisture. Moisture is formed during reduction. This needs to be removed continuously from the reduction medium by using in-line dryers. For single phase solids, sintering by surface diffusion becomes important when the temperature is 0.2–0.3 times the melting point, also called the Huttig temperature [67]. At a temperature which is ~0.5 times the melting point, also called the Tammann temperature, volume diffusion becomes important [68]. Both processes result in a loss of surface area of the active metal, which in turn results in loss of activity or stability of the catalyst. Exposure of the catalysts to high temperatures can also result in the formation of undesirable compounds such as the aluminates of metals.

Reduced metal catalysts tend to be pyrophoric and need to be stabilized or passivated. The process of stabilization consists of forming a film of an easily decomposable compound such as a film of oxide on the surface of the active metal. This step is exothermic and it is carried out in a controlled method by exposing the reduced catalyst to a medium containing oxygen at temperatures close to ambient. The rate of stabilization is controlled by limiting the concentration of oxygen in the medium. Like reduction, this is also a slow step and it is time-intensive and the same general considerations which are applicable to reduction are applicable to passivation. Williams [69] assigned to Imperial Chemical Industries, shows that the use of CO_2 in combination with O_2 for passivation of reduced catalysts renders the catalyst not only much safer to handle, but also facilitates reactivation of the catalyst with hydrogen in the commercial reactor at much lower temperatures than when the catalyst is passivated with oxygen alone. Reduced and passivated catalysts must be stored and handled with care because of the danger of pyrophoricity in the event the passive oxide film dislodges.

4.3 Catalyst Supports

Catalysis is a surface phenomenon. Catalyst supports, which are also called as carriers, form an integral part of the catalyst formulation, having myriad functions. Amongst them are:

- dispersing the active phase to increase its surface area, thereby increasing activity of the catalyst.
- anchoring the active phase to retain its dispersion for longer durations under operating conditions, thereby increasing the stability of the catalyst.

- lend acidity to the catalyst, as in bifunctional catalysts, such as those used in the reforming of naphtha to aromatics, where a chlorided alumina carrier is used to support the active metals such as platinum and rhenium [70].
- some carrier materials are useful as carriers and also as catalysts. Carriers made from materials such as γ-Al_2O_3 are catalytically active for acid catalyzed reactions besides their function as carriers.
- purity of the carrier is very important in applications such as catalytic epoxidation of ethylene to ethylene oxide [71].
- lend proper microstructure to the catalyst particle to enable high accessibility of the surface to the catalyst to reactants and facilitate ease of diffusion of reactants and products, which affect both activity and selectivity.
- manage pressure drop across the reactor.
- provide adequate mechanical strength to withstand mechanical stresses imparted during operation at severe conditions such as high pressure, pressure fluctuations, and also stresses during handling.
- resistance to thermal stress is also imparted by carriers to allow the catalyst to withstand operation at elevated temperatures including hydrothermal conditions.
- catalyst bed supports are refractory materials which are largely chemically inert to the application. They serve to hold the catalyst bed in position within the reactor vessel. In some applications, these materials also serve to trap chemical and particulate impurities in the feed, thereby protecting the active catalyst bed which is located downstream.
- inert support materials can also serve as diluents or as a heat sink in reactions which are highly exothermic.

Common materials used as carriers are silicas, diatomaceous earth, various forms of alumina, titania, zeolites, magnesia, LDO's hydrotalcites, cordierite, activated carbons, alkaline earth aluminates, SiC, and alundum.

Binders are different from carriers. Binders are materials which are used to lend shape to catalyst particles. These are used as additives in relatively small concentrations when the components of a catalyst formulation lack the inherent ability to bind into a formed mass of the desired shape with adequate mechanical strength. Some materials such as psuedoboehmite can be peptized to induce self-binding. Peptization is a process which leads to partial, local gelation of the material, thereby inducing plasticity which is important for binding and extrudability.

4.3.1 Aluminas

Aluminas are used extensively as supports, binders, as catalysts for the dehydration of alcohols or the hydrolysis of carbonyl sulfide, and also as desiccants to remove moisture from feed streams. They are amphoteric in nature. The properties of alumina powders such as microstructure, morphology, acidity, and the ratio of amorphous to crystalline form (at the

oxide hydroxide stage) can be varied over a significantly wide range by changing the method of their preparation. Aluminas are prepared either by controlled precipitation using aqueous solutions of inorganic salts of aluminum, and an alkali such as caustic soda lye or by sol-gel routes forming alkoxides of aluminum, followed by their hydrolysis. Aluminas can also be prepared by flame hydrolysis. These three methods of preparation leave distinctive characteristics in the end product. Aluminas prepared by the precipitation route have high porosity, but relatively higher impurities such as silica, soda, and iron oxide. Aluminas which are prepared by the alkoxide route tend to be highly pure and have good binder properties. Aluminas prepared by flame hydrolysis have a very small particle size and very little porosity.

Different forms such as pseudoboehmite, bayerite, nordstrandite, or Gibbsite form depending on the process parameters used during precipitation, such as pH and temperature. These are either oxide-hydroxides or trihydroxides of aluminum. Of these, Gibbsite is produced economically as an intermediate in the Bayer process. The effect of temperature and pOH of precipitation on the form of alumina produced is evident from the results of Van Straten et al. [8] which are reproduced in Fig. 4.2 below. Lower temperature and pH of precipitation favor the formation of pseudoboehmite, whereas higher temperatures and higher pH favor the formation of Gibbsite. The sequential formation of polymorphs viz. amorphous → pseudoboehmite → bayerite → Gibbsite by Ostwald's law of stages is also shown in this work.

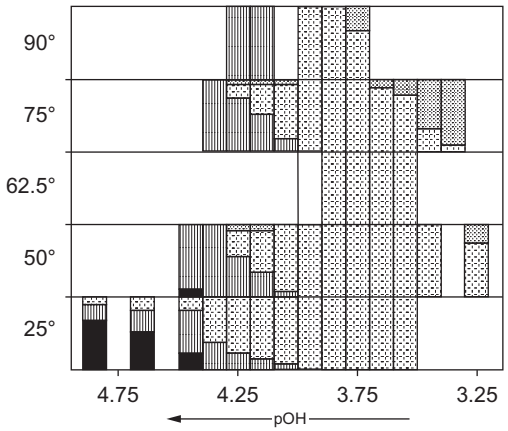


Fig. 4.2
Histogram of alumina phases as a function of temperature and pOH. *Adapted from Van Straten and De Bruyn [8].*

Pseudoboehmite aluminas with widely varying properties such as crystallite size, particle size, shape/morphology, microstructure, gel content, resistance to attack by acids, resistance to sintering due to exposure to high temperature, and friability index can be prepared by varying

the preparation conditions. Dispersibility (extent of solubility in nitric acid solution) and nitric acid gelation (the rate of gelation upon contact with a solution of nitric acid) are important considerations in the use of these materials as carriers or binders and these properties too can also be varied by adjusting the parameters of preparation. Grades of dispersible booehmite which can be used to prepare colloidal sols are available, such as Disperal and Dispal alumina grades offered by SASOL. Alumina is also available in colloidal hydrosol form, which is useful for the preparation of spheroidal particles using the oil drop method. Catalogs of Pural and Catapal Alumina offered by SASOL [72] and Catalogs of Versal aluminas offered by UOP [73] present the entire range of properties offered by these suppliers for alkoxide and precipitated route aluminas, respectively. These catalogs are available on the Internet. These properties affect secondary characteristics such as bulk or packing density, microstructure (BET surface area, pore volume and pore size distribution), and mechanical properties of the formed catalyst particles.

Zamorategui et al. [74] have shown the effect of drying on textural properties. Their work shows that spray drying results in a higher surface area of the γ-Al_2O_3 produced subsequently from freeze drying and oven drying in the case of pseudoboehmite prepared by homogeneous precipitation.

Upon calcinations at elevated temperature, these materials transform into different crystallographic forms (polymorphs). A general schematic from the reference "Oxides and hydroxides of aluminum," [75] (Fig. 4.3).

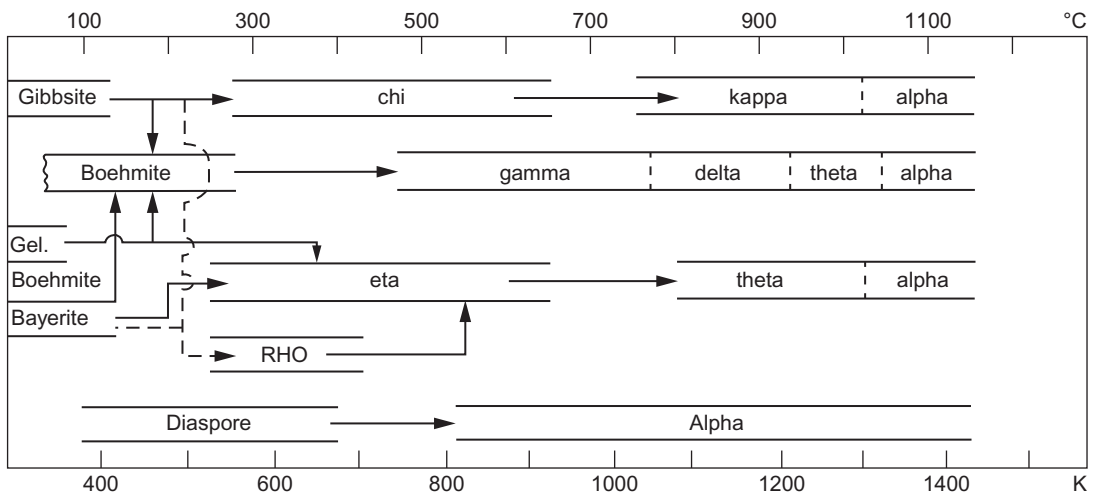


Fig. 4.3
Thermal transitions of aluminas. *Reproduced from Wefers and Chanakya [75].*

Knowledge of the form of precursor and the conditions under which these transitions take place is important to prevent the formation of undesired forms of alumina during calcination, and also to achieve the desired properties of the final product. Al^{27} MAS-NMR studies show that the ratio of tetrahedrally to octahedrally coordinated Al ions increases with calcination for the transition $\gamma \rightarrow \delta \rightarrow \theta$. The number of strong acid sites also decreases significantly in this order [76]. In addition to the form of the alumina, physical properties such as specific surface area and pore volume can also be varied during calcination.

Gamma alumina is widely used as a catalyst for the dehydration of alcohols, and also as a carrier in reactions where acidity is important. Eta alumina which forms from bayerite is used in the preparation of carrier in reactions where strong acidity is not desired [77].

α-Al_2O_3 (corundum) is used in the preparation of catalysts for the epoxidation of ethylene to ethylene oxide [71]. It can be prepared with a range of BET surface areas depending on the precursor used. Corundum of medium—low surface area ($\sim$50 m^2/g) is prepared by the topotactic decomposition of diaspore or by the high temperature calcination of gibbsite, whereas a very low surface area (1–3 m^2/g) is produced by sintering alumina powders at high temperatures around 1100–1300 K. The corundum retains the memory of the lamellar structure of the precursors while the lamellae increase in thickness [76].

4.3.2 Silicas

The use of silica as a support for catalysts or as a binder for catalysts is well known. The surface chemistry of silica and a wide array of silica with different physical properties makes these materials suitable for various applications. Different types of silica are used either as support/carrier, as catalyst in combination with other oxides/active metals, and as binder for catalysts. These materials also find applications in coatings/paints as a matting agent, anti-blocking agent in polymer films, an adsorbent for drying applications, an abrasive agent in dentifrice applications, a filler in rubber, tires, and paper industries. Classification of silica depends on the preparation method adopted and difference in physicochemical properties. They are classified in following categories; silica sols, silica gels, precipitated silicas, and fumed silicas [78,79].

The types of silica of interest are silica sols, silica gels, precipitated silicas, and fumed/pyrogenic silicas. The suitability of these materials depends on the properties and advantages they offer in a particular application. Typical properties of different types of silicas are given in Table 4.2 below.

Table 4.2 Properties of different types of silicas

			Precipitated Silica	Silica Gel	Pyrogenic Silica
CAS-Nr			112926-00-8	112926-00-8	112945-52-5
Specific surface area	ISO 5794-1, Annex D	m^2/g	50–800	20–1000	50–400
Average primary particle size	TEM	nm	2–20	n.a.	7–40
Mean particle size[a]	–	µm	3–3000	0.1–5000	n.a
Pore volume	IUPAC, App. 2, Pt. 1		Macroporous	Micro- and mesoporous	n.a
Loss on drying	ISO 787-9	%	3–6	ca. 3	0.5–2
Loss on ignition	ISO 3362-11	%	3–12	5–6	0.5–2.5
pH-value	ISO 787-9		6–8	4–8	3–5
DBP-number	ASTM D2414	g/100 g	50–350	n.a	100–350
Tapped density	ISO 787-11	g/1	90–450	n.a	50–150
SiO_2 content[b]	–	%	98–99	>99.5	>99.9
Al_2O_3[b]	–	%		<0.05	<0.05
TiO_2[b]	–	%			<0.03
Fe_2O_3[b]	–	%	<0.03		<0.003
Na_2O_3[b]	–	%	<1	<0.1	
HCl[b]	–	%	n.a.		<0.025
SO_3 (sulfate)	–	%	<0.8		n.a

N.a. = not available; a = various methods; b = based on ignited substance.
Reproduced from Ref. [80]

Silica sols, silica gels, and precipitated silicas with a wide array of physicochemical properties are prepared by different methods. The preparation process essentially involves the following steps in common:

- Formation of silicic acid monomers
- Polymerization of silicic acid to form primary silica particles
- Growth of primary silica particles
- Agglomeration of primary particles to form precipitate

Fig. 4.4 illustrates the preparation of fumed silica powders, silica sols, gels, and precipitated silica powders [79,81].

The basic building block is silicic acid, which is obtained by reacting an alkali silicate with an acid. During the precipitation, primary particles are formed, which subsequently lead to formation of silica sol. The silica sol or colloidal silica particles are precursors for silica gels and precipitated silica powders. The process conditions determine the size of colloidal particles/agglomerates and ultimately the physicochemical parameters. The formation of silica

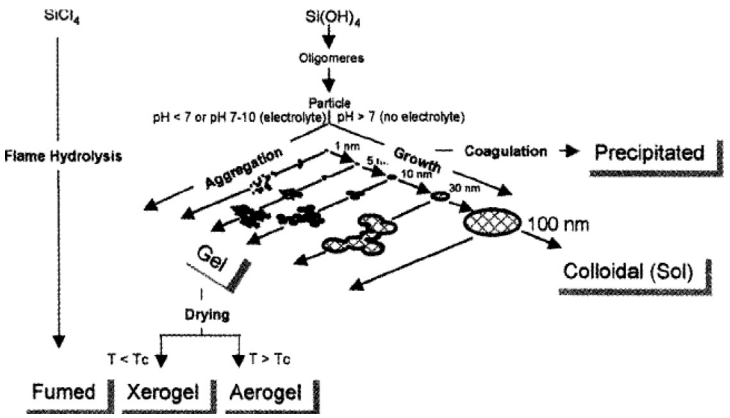


Fig. 4.4
Brief preparation of pyrogenic silica, precipitated silica, and colloidal silica sols.
Reproduced from Ref. [79].

sol from silicic acid, the growth of silica sols, and polymerization are all in general affected by pH and the electrolyte/salt content in solution. The growth of the silica sol occurs at a pH above 7 and essentially in the absence of salts. Polymerization/aggregation of silica sols occur in both acidic and alkaline media. In an alkaline medium, the polymerization occurs essentially in the presence of salts/electrolytes. The colloidal particles form gels by aggregation. The properties of the final silica gels depend on the process conditions (ie, solid concentration, temperature, size of silica sol, and pH of gelation). By optimizing these precipitation parameters, precipitated silicas with different physicohemical properties are obtained.

4.3.2.1 Types of silica

4.3.2.1.1 Colloidal silica

These types of silicas are of interest due to their applicability in several commercial applications. Polymeric, spheroidal silica particles suspended in the liquid phase with a diameter in nanometer range are typically referred as "Colloidal Silicas." They are amorphous, nonporous in nature, and often suspended in an aqueous medium. The stability of the liquid phase is rendered by the addition of small concentrations of salts containing NH^{4+}, Na^{+},or any other suitable cation. A colloidal solution of silica is a stable dispersion of particles. The diameter of the silica particles ranges from 1 to 100 nm. When the particles are small, they remain in the colloidal form and do not settle. Particles significantly smaller than 5 nm are difficult to stabilize at high concentration, while particles much greater than 150 nm are subject to gravitational sedimentation. Colloidal silica varies from other types of silica. They are

available in liquid form differing in size, content, and surface area. It is possible to prepare stable suspensions with concentrations of particles exceeding 50 wt% solids. Preparation of colloidal silica is carried out in multiple steps. An alkali silicate solution of a particular concentration is brought into contact with acidic resins to exchange the alkali. The resulting silica nuclei are allowed to grow to a particular size. The resulting colloidal solution is stabilized by pH adjustment [82]. The neutralization is carried in solids with a concentration range of 10–15 wt%. Uniform particle size and growth of the primary particles is important to obtain monodipsersed silica sol. The stabilization of sol is done by pH adjustment and concentrated by evaporation to increase the solids concentration. Sols with more solids content can be obtained with larger particles. The stability of the sol depends on the particle size, solvent composition, solids content, and the presence of stabilizers. The stability of silica sol decreases with increasing silica concentration, increasing salt concentration, increasing content of polyvalent cations, and increasing temperature. The surface of most of the colloidal silica grades is anionic. The surface is covered with silanol groups and the particles are stabilized by cationic species such as sodium or ammonium. In an alternate method of syntheses, alkoxysilanes are hydrolyzed to obtain colloidal particles of high purity. Fig. 4.5 illustrates the typical manufacturing process for colloidal silicas/silica sols (Ion Exchange method) [80].

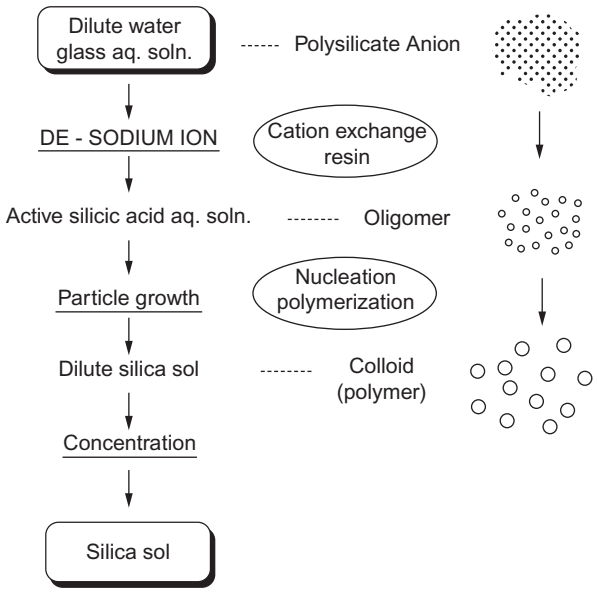


Fig. 4.5
The typical manufacturing process for colloidal silicas/silica sols (Ion Exchange method).
Reproduced from Ref. [80].

The typical properties of silica sols is shown in Table 4.3 below [83].

Table 4.3 Typical properties of silica sols

Stabilizer	Ultimate Particle Size (nm)	Solids (wt%)	pH	Relative Density	Viscosity (mPa s)
Acidic medium	11–14	20	2.0–4.0	NA	5–25
NH_4^+	7	12	7.5–7.8	1.07	<100
	14	17	9.5–10.0	1.10	<250
	14	12	5.0–5.5	1.07	<100
	17	17	9.5–10.0	1.10	<100
	30	20	5.0–5.5	1.12	<100
K^+	17	18	8.6–9.0	1.11	<150
	30	28	7.5–7.8	1.18	<200
	30	30	10.0–10.3	1.19	<150
Na^+	7	14	10.0–10.5	1.08	<100
	8	15	9.5–10.0	1.09	<100
	14	17	9.5–10.0	1.10	<100

Reproduced from Ref. [83].

4.3.2.1.2 Silica gel

Silica gels are polymerized silica particles. The surface is covered with silanol groups, which are hydrophilic in nature. The properties of silica gel depend on the extent of agglomeration and the size of the primary particle. The pore volume, pore size distribution, surface area, and surface chemistry are tailored by optimizing the synthesis parameters. Silica gels are well known for their adsorption properties and, hence, employed in many industrial processes. Silica gel due to its high surface area and particle size are used in catalyst formulations for applications in catalytic cracking [84,83]. Fig. 4.6 illustrates the formation of silica sols and subsequently, the silica gels [85].

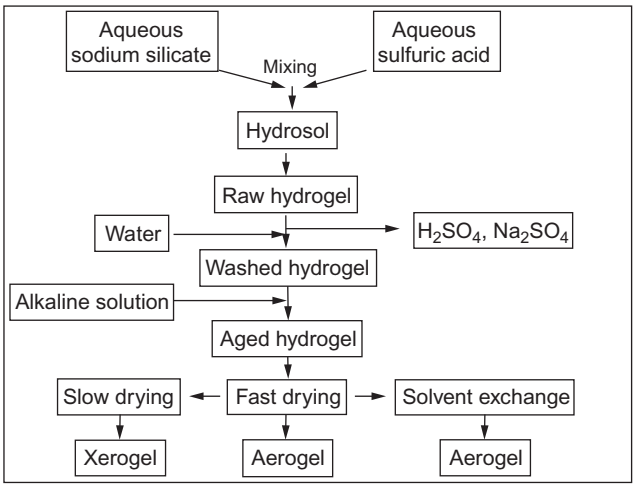


Fig. 4.6
Formation of silica sols and subsequently, the silica gels. *Reproduced from Ref. [85].*

4.3.2.1.3 Fumed silica

Fumed silicas, or pyrogenic silicas are prepared by reacting chlorosilanes in a hydrogen-oxygen flame at elevated temperatures. The product formed is steam treated to remove HCl associated with the solids. Pyrogenic silicas are fine, light weight agglomerated nanomaterials. The primary particle size is in the range of 5–30 nm. The properties of pyrogenic silica can be fine-tuned to get the desired properties by varying the flame temperature and composition. Pyrogenic silica with specific surface areas in the range 50–400 m^2/g is available in the market for various applications. These materials are employed in preparation of catalyst as support [86–88].

Fig. 4.7 illustrates the preparation of pyrogenic silica [79].

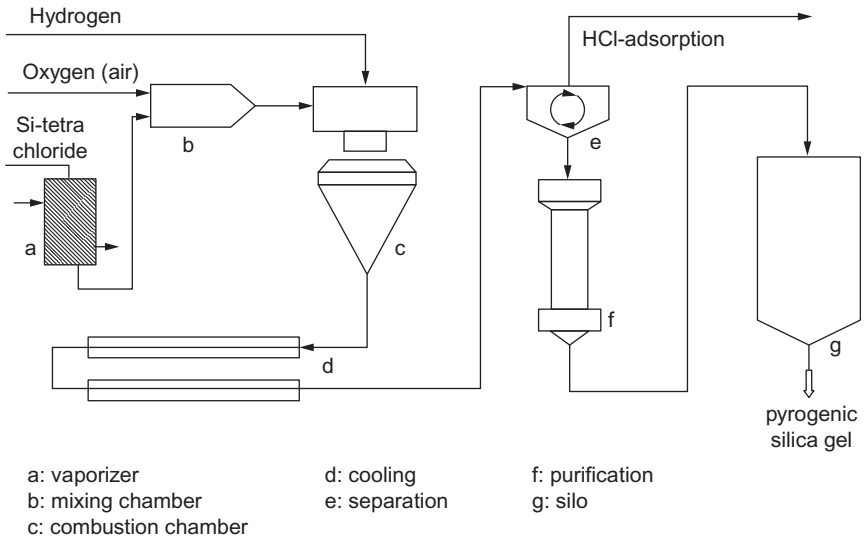


Fig. 4.7
Preparation of pyrogenic silica. *Reproduced from Ref. [79].*

Pyrogenic silica is promising in the preparation of suitable catalysts due to its high chemical purity, well defined spherical primary particles, nonporous nature, and low loss of drying/ignition.

4.3.2.1.4 Precipitated silicas

Precipitated silicas are prepared by reacting sodium silicate with an acid. Typical acids used for precipitating sodium silicate are sulfuric acid, hydrochloric acid, carbon dioxide, or a combination of carbon dioxide with mineral acids. Properties of the precipitated silica can be fine-tuned by using suitable precipitation conditions, such as precipitation time, the addition rate, the concentration of reactants, their temperature, and the pH of gellation [89]. In general, sodium silicate and acid solutions are introduced simultaneously into a stirred vessel containing water. Primary particles are formed during the precipitation, which subsequently

get coagulated into aggregates. The aggregates extend during the course of the precipitation into a three-dimensional network, which determines the properties of the final precipiated silica [90,91].

4.3.2.1.5 Silica as catalyst and catalyst support

In catalysis the use of precipitated silicas, silica gels and pyrogenic silica is limited to catalyst supports. But the use of modified silicas or their mixed oxides is well known in catalysis due to their interesting properties. This is evident from literature reports [92–94]. The silica–alumina matrix is employed in preparation of FCC and FCC additives on commercial scale. Due to homogeneous distribution of silica throughout the alumina matrix SiO_2–Al_2O_3 these additives possess higher acidity as compared to Al_2O_3-coated SiO_2 and SiO_2-coated Al_2O_3 supports [95,96].

Cu, Ni and Co supported on SiO_2 are used in the preparation of vide array of applications. Cu supported on silica is well known hydrogenation catalyst for preparing amines. Phosphoric acid supported on silica is used in the alkylation of aromatic hydrocarbons [97], hydration of olefins, direct conversion of triglycerides to olefins and paraffins [98].

Silane modified silica gels are widely used in heterogeneous and phase transfer catalysis. The silicas treated with aminosilanes are used as support to anchor active elements. The anchoring of Ru on an aminopropylsilane modified silica is use as a catalyst for hydrogenation and isomerization [99].

The SiO_2 carrier or its mixed oxide supports are available in different properties, size, and shapes. Acidic/basic or any other active metal/metal oxides are loaded on the suitable supports for making catalyst with desired properties [100].

There are literature reports which discuss the preparation of silica and silica supports with different properties such as, pore size distribution, and surface area. These include silica with mesoporous to macroporous range [101,102].

A catalyst consisting of bismuth phosphomolybdate supported on silica is disclosed in Ref. [103]. The catalyst precursors in solution are added to an aqueous solution of an aqueous colloidal silica sol containing 30 wt% silica. A catalyst consisting vanadium oxide, a chromium oxide, and a boron oxide as catalyst components, and silica as a carrier is prepared by spray-drying a silica sol containing vanadium, chromium, and boron compounds [104]. In general in both the above cases, the silica provides strength, attrition resistance, and it acts to disperse the catalyst particles.

Silica-supported cobalt catalysts for Fischer–Tropsch synthesis are prepared by uniform dispersion of the Co particles over the support in presence of silica gel [105–107].

In the preparation of catalysts, the addition of SiO_2 increases the surface area of the alumina support and introduces acid sites required for some reactions [108,109]. SiO_2 is also known to reduce metal support interaction facilitating formation of the more actives [110,111].

Pyrogenic silicas are employed for immobilization of enzymes in enzyme catalysis to increase the accessibility of substrates to the enzymes' active sites. They help to overcome low catalytic activity due to mass transfer limitations [112]. Different silica supports are used for heterogenizing the homogeneous catalysts for various applications.

4.4 Catalyst Forming

Catalysis being a surface phenomenon, the kinetics of catalytic reactions proceed most effectively when resistances to mass and heat transfer are minimal. This suggests that smaller catalyst particles and high porosity are better. This is indeed practiced in the case of slurry reactors where particle sizes are typically ~20 μm (d_{50}), and in fluid bed reactors where the d_{50} (median particle size) is typically 50–70 μm. In these cases, it is mass and heat transfer resistances which attain importance.

However, other considerations make it necessary to manufacture catalysts in different shapes and sizes. Fixed bed reactors are easier to design and operate and cheaper to build. In this case, keeping pressure drop across the catalyst bed at a manageable level is important to minimize the cost of feeding reactants, and also the cost of hardware. This is achieved by increasing the size of the catalyst particle and sacrificing activity due to diffusional limitations.

The reaction conditions are dictated by thermochemistry and catalysts need to be designed to operate under these conditions. These conditions can at times be very severe, ranging to a few hundred bar pressure (as in ammonia synthesis or hydrotreating applications) or temperatures up to 950 °C (as in reforming in the steel industry to reduce iron ore to metallic iron). In such situations, resistance to mechanical and thermal stresses becomes important at the expense of porosity within the catalyst particle.

Yet other considerations arise from process requirements, such as operation at very high space velocities, ranging from a few thousand to a few hundred thousand h^{-1}, as in the case of automobile exhaust after treatment, where monolithic catalysts are used. In such cases, pressure drop and attrition due to erosion become important considerations. Operating temperatures are high, which makes the reaction heat and mass transfer limited. In these cases, the catalyst must have very good resistance to thermal stresses and also good heat transfer properties. In this case, the active phase is wash coated on a monolith in the form of a thin film.

Rapid deactivation of the catalyst as in FCC (fluidized catalytic cracking) or managing exothermicity (as in the ammoxidation of propylene to acrylonitrile) necessitates the use of fluid bed reactors where the catalyst has to be in microspheroidal form to facilitate continuous regeneration and heat management, respectively.

When the active cycle length of the catalyst is small, such as a few hours, it has to be continuously circulated between a reaction zone and a regeneration zone using moving bed

reactors. In these circumstances, motility becomes important. A spherical shape and good resistance to attrition/abrasion become important features of the catalyst.

The size of catalyst particles typically varies from as low as ~20 μ diameter in slurry and fluid bed catalytic applications, to a few centimeters in a fixed bed reactor application. Their shapes vary from the nearly perfect spherical to plain, or ribbed extrusions, trilobes, triaxes, plain or ribbed cylinders, hollow cylinders, plain rings, rings with holes, and monoliths. In the selective reduction of NO_x from off gas of large power plants, structured catalysts such as rotating monoliths measuring up to 20 m in diameter are used [113]. In some cases, as in BASF's CAMOL™ technology [114], for catalytically assisted steam cracking of naphtha, catalysts are coated directly on the surface of reactor tubes. This is also seen in fuel exhaust emission control catalysts. Schuth and Hesse [115] have reviewed different methods of forming in detail and the following sections draw upon information provided therein.

4.4.1 Common Elements in Catalyst Forming

Some elements which may be common to different methods of forming are listed below:

Comminution: This is the step of decreasing the particle size of the raw material. This is carried out by equipment such as a ball mill, hammer mill, or jet attritors. Achieving proper particle size and its range is important in forming.
Peptizing agents: These are reagents which are added to move the pH of the paste slightly away from the point of zero charge (ZPC). This involves some amount of dissolution, hydrolysis, condensation, and gelation which results in imparting the proper rheology to the paste during kneading.
Binders: Common binders are silica sol, aluminas, and clays. These function by virtue of their morphology and a good description of this is provided in the book chapter Schuth and Hesse [115].
Viscosity modifiers: Plasticizers are additives which are organic compounds, some of which are water soluble, lending a degree of pseudoplasticity to the blend during the kneading step. This facilitates smooth extrusion or eases the process.
Lubricants: Their role is predominantly to decrease friction between the kneaded paste and the wall of the barrel of the extruder. Some common compounds are glycerine, lower glycols, and mineral oils.
Porosity aids: These are organic compounds or natural products which burn out at the temperature of calcinations of the product and leave void spaces within the catalyst particle. Compounds like saw dust or celluloses, starches, and others are commonly used.
Drying and calcinations: For a liquid-filled catalyst particle, drying takes place in three stages: initial preheating where heat is transferred from the heating medium to the surface of the catalyst particle and the rate of drying increases before it reaches a plateau. The constant rate period follows, where the rate of drying remains constant because it is sustained by the capillary flow of liquid from the interior of the catalyst particle. And lastly,

the falling rate period where the quantity of liquid in the interior of the catalyst particle is insufficient to sustain the rate of drying. Vapor can also form in the interior of the catalyst particle during this stage. Shrinkage of the catalyst particle takes place during drying. Diffusional gradients and capillary forces formed during drying exert mechanical stress within the catalyst particles [116]. These gradients and stresses grow with the increasing dimension of the catalyst particle. Hence, the importance of control in the drying step increases with the size of the catalyst particle. Microspheroidal catalysts, which are as small as 40–200 μ in diameter, are dried almost instantaneously during their preparation by spray drying. In spite of their small size fractures, rupture and disintegration of these particles is still observed. In some cases, especially in supported metal catalysts, redistribution, or segregation of the active phase occurs within the particle during drying and calcination. The optimum temperature of calcinations is important because decomposition of precursors of the active component, as well as phase changes, occur during this step. It is important to achieve the correct crystallographic phase.

Diverse equipments are used for the drying and calcinations of catalysts. Microspheriodal catalysts are spray dried. When sphericity is not an important consideration, Spin flash dryers or calciners (SFD/C) are used for producing materials in powder form. These are continuous processes and yield high productivity. Other continuous methods are band dryers, rotary calciners, and tunnel kilns. Box dryers have a low productivity and are used when the residence time of calcinations is large, or in the case of formed catalysts which may undergo attrition in moving beds. Air is the medium of choice, unless there is a specific need for an inert medium. Heating is done using electrical heaters or by burning fuel, as in the case of direct fired heaters where hot flue gas is used as a heating medium. Where the catalyst composition is reactive to components in flue gas, indirect heating is resorted to by using the flue gas to heat a medium such as air, and the hot air is fed to the catalyst.

Common problems faced in operation are the plugging of the spray nozzle of spray dryers or die plates of extruders.

4.4.2 Microspheroidal Catalysts

Catalysts which are of microspheroidal morphology are used in slurry reactor and fluidized bed reactor applications. The typical particle size, d_{50} depends on the application and ranges from about 20 to ~70 μ. Quality of fluidization and retention of the catalyst within the reaction zone are important in fluidized bed operation. Properties of the catalyst such as bulk density, sphericity of the catalyst particle, particle size distribution, and resistance to attrition become important in this situation. These materials are prepared by the spray drying operation. In spray drying, a slurry of the components is first prepared. The solid content of this slurry can vary from 5 to 50 wt% depending on the application. The formation of a stable slurry which can be pumped is important to achieve a final product which is homogeneous on the macroscale. To achieve this, the slurry should have proper rheological properties such as

flow, density, and viscosity and also stability, that is, reasonably good suspension of the solid particles therein during the spray-drying step. The unit operations used are comminution, wherein either solids are ground into fine powders down to few micron in size by dry mechanical methods such as ball milling or jet milling, or by wet mechanical methods such as Pearl™ mill or Netsch™ mill. The slurry is maintained in an agitated condition to render it homogeneous. In certain cases it is necessary to cool the slurry to enhance the duration of its stability. The slurry is then fed to a spray drying chamber which consists of a cylindrical vessel with a conical base. This chamber is maintained at a slight vacuum ~10–15 mm water column. The aspect ratio (*L*/*D*) of the spray drying chamber is decided by the type of device used for atomization of the slurry. The aspect ratio is smaller in the case of rotary atomizers. Feeding of the slurry is done by atomizing it by using either a single or multiple fluid pressure nozzle (hydraulic nozzle), where a high pressure positive displacement pump is used in to create the pressure required for spraying. In the case of two fluid nozzles, the motive force for atomizing the slurry is pneumatic, such as compressed air at high pressure. In rotary disc atomizers, centrifugal force is used for atomization.

The design of the pressure nozzle is critical because it determines the size and distribution of the droplets of slurry in the spray drying chamber. Orifice size and swirl chambers decide the combination of flow rate and spray angle. Droplet size is cited by Sauter mean diameter. Droplet size is a function of the viscosity and surface tension of the slurry to be spray dried. This needs to be correlated with the actual particle size of the product through trials. Internal components of the nozzle are specially designed. The construction material of the spray nozzle is also critical, especially when the slurry has abrasive constituents in it. Silicon carbide is used in such cases. Erosion of the nozzle has an adverse effect on properties of the spray dried product. A good description is given in Product bulletins of Delavan Spray technologies. Hot air is fed into the spray drying chamber either co-current or counter-current to the slurry feed. Proper distribution of hot air is important to this operation. Proper spraying of the slurry into discrete droplets and the proper rate of drying ensures that the product is produced in the form of discrete particles with a nearly perfect spherical shape. Formation of deformed particles, hollow particles, broken particles, or particles with satellites affects the quality of fluidization. These result from a number of factors, satellites form an inter-particle collision of droplets of slurry prior to adequate drying, deformed particles due to collision with the wall of the spray drying chamber prior to formation of a firm shell, dimpled particle due to non-rotation of the particles, and bulged particles due to pressure exerted by vapor formed inside the particle due to nonoptimal rate of drying. Optical microscopy and Scanning Electron Microscopy are useful techniques in determining the morphology of spray dried particles. The dried product is separated in a cyclone which is located downstream of the spray drying chamber. A filter bag is located further downstream to minimize emission of particulate matter in to the environment. The product is finally calcined to suit the application. Important properties of the final product are residual moisture content (percent loss on ignition), bulk density, resistance to attrition, and morphology.

4.4.3 Spherodizing/Nodulizing

The packing of particles in fixed beds is most effective when the particles are spherical in shape. Furthermore, spheres have the advantage of ease of motility when compared to other shapes. Hence from the perspective of minimizing channeling of the reactant fluid through a fixed bed of catalyst, or when there is a need to have a moving bed reactor, as in the case of processes where the catalyst deactivates relatively rapidly and needs to be continuously regenerated, as in Universal Oil Product's CCR™ (Continuous catalytic reforming of naphtha) process or their OLEFLEX™ process for the dehydrogenation of lower paraffins. A spherical form also eases the manufacturing process of a catalyst by facilitating use of continuous mode of unit operations because of better motility.

Catalyst particles can be shaped as spheres by at least two techniques. Spheroidization and the oil drop technique are used, besides spray drying, which is used for manufacturing microspheroidal catalysts such as those used in FCC of vacuum gas oil, or fluid bed oxidation such as the ammoxidation of propylene to produce acrylonitrile. Spheroidizing consists of shaping a precursor which is a powder into spherical particles using equipment called a pan spheroidizer or pan nodulizer. The spheroidizer consists of a pan or a drum which is placed at a suitable angle and rotated using a motor. The speed of rotation and the angle of placement of the pan can be adjusted. In the case of a pan, it is maintained at an angle of about 50° relative to the floor. It is rotated at a critical speed which depends on the diameter of the pan and the tilt angle of the pan to facilitate discharge of formed spheres from the pan [113]. The solid powder which is to be spherodized is first milled to reduce its particle size. Sieving is also employed to achieve a certain range of particle size. A liquid medium usually consisting of other components, a chemical which serves as a binder is sprayed on to the powder which is placed in the rotating pan. The powder is bound to initially form fine particles which then grow into larger spherical particles by virtue of consecutive coating or layering of the powder in the pan. Additional powder or slurry is added to the pan depending on the size of the final product. A good description of the physical processes which take place during spherodizing is given in Ref. [117]. These are described as wetting and nucleation, followed by consolidation and coalescence, and finally, attrition and disintegration into smaller particles. Irrespective of whether densification takes place by coalescence or layering, it must take place in a coherent manner to produce a good quality product. Inter-particle and particle-wall collisions contribute to the process of densification. Spheroidizing is a technique which forms reasonably spherical particles which are less dense compared to other methods of forming such as extrusion or tableting. It is a low cost method of forming. Spherodization produces a product with a wide range of sizes (diameter), hence, it needs to be classified. Equipment used for classification are Vibrosieves (vibrating sieves) which has a set of sieves and is vibrated electro-mechanically. Huba and Malkin in a US patent which is assigned to Diamond Shamrock Corporation [118] describe a method of spheroidizing alumina based catalysts wherein

controlled release of the binder is shown to result in better sphericity and crush strength. Chemicals which minimize shrinkage of the spheres during drying are also cited. Vladislav [119] cites the use of alumina seed bodies in the solution which is sprayed during nodulization.

4.4.4 Oil Drop Technique

Hoekstra [120] describes a method to prepare spheroidal alumina. Better sphericity is achieved compared to spherodizing. This consists of preparing an alumina chlorohydrosol. This sol is then admixed with a weak base having a strong buffering action and an increased rate of hydrolysis at an elevated temperature. The rapid hydrolysis at the elevated temperature brings about almost instantaneous gelling of the alumina hydrosol into spheres (hydrogels). The mixture is dropped in the form of discrete droplets (prilled) into a medium in which these droplets are insoluble, such as nujol or liquid paraffin which have a relatively high boiling point. The path length of the heated organic medium and its density at the temperature of hydrolysis of the weak base are important criteria. Correct choice of these parameters ensures that the droplets of the sol which are prilled get sufficient residence time to set into sufficiently hard spheres which do not stick to each other. The hydrogels are aged in the organic medium and, subsequently in a basic medium. This is followed by washing, drying, and calcinations to realize the final alumina spheres. The composition of the sol, concentration of the aging medium, and process parameters during aging can be adjusted to achieve alumina spheres with bulk density varying over the range 0.24–0.73 John Hayes, US patent 3,346,336 [121] is a variant of US 2,620,314 [120] where expensive gelling agent is substituted with alkali hydroxides. Silica spheres can be obtained using a similar process, but silica sol is much less stable and needs to be prilled soon after preparation of the sol.

4.4.5 Extrusion

Extrusions are a common shape in which many catalysts are formed. Extrusions are solid shapes whose length dimension is significantly larger than its diameter. The typical aspect ratio, L/D, is ~3–6. Important consideration is given to balancing between the triad of good packing of the catalyst extrusions in the reactor to avoid channeling of the reactant, minimizing associated pressure drop across the catalyst bed, and minimizing intra-particle diffusion resistances. To achieve this, the important properties of the extrusions are their length, diameter, aspect ratio (L/D) and its range and to minimize the degree to which the extrusions are bent along the linear axis. Pressure drop and the geometric (external or exposed) surface area are dependent on the exact shape of the extrusions. For a given diameter and length, these vary with minor modifications such as plain solid smooth extrusions, hollow extrusions, ribbed extrusions such as tri-axial, quadralobes, stars, or extrusions with partitions such as wagon wheels or in the extreme case, honeycomb monoliths. Besides size and shape, other important properties are bulk density, specific surface area, porosity and pore size distribution,

mechanical properties such as crush strength (resistance to mechanical load), and attrition or resistance to abrasion (resistance to erosion due to flow of reactant or rubbing during handling). Extrusion results in higher compaction within the particle than in the case of spherodizing, but less than in the case of tableting. The process of extrusion is suited for mass production at a relatively low cost. The control of shape (degree of linearity) and size (length) is not as uniform as in tableting.

The process of extrusion starts with the selection of a grade of raw material which will result in the target microstructure and properties of the final extruded product. Important properties of the raw material are purity, specific surface area, porosity and pore size distribution, particle size (d_{50}), and dispersibility (the extent of solubility of the material in an acid solution of defined strength). The raw material, such as pseudoboehmite in the case of alumina extrusions, is subjected to comminution in the dry state using equipment such as ball mills or Jet mills. This step breaks down the material to the target particle size. This is followed by kneading. In this step the powder is preferably peptized by adding a reagent which partially solubilizes and/or gels the raw material, for example the action of dilute nitric acid or dilute acetic acid as in the case of pseudoboehmite is added and the mixture is thoroughly mixed using high speed mixers/blenders or by the application of weight, such as heavy mechanical rollers. Commercial equipment such as Eirich mixers, Mix mullers, Plough shear mixers, and Planetary mixers are available for this application. In the case of raw materials which peptize relatively rapidly, equipment called a Mixtruder is used which carries out both the steps of mixing-peptization and extrusion in the same equipment. In this case, the screw of the extruder is designed to facilitate both blending and extrusion. A fair description of the physical changes which are observed during the step of peptization is provided in Ref. [122]. From a chemical perspective, the acid solution can be expected to locally dissolve the pseudoboehmite into Al^{3+} ions followed by its hydrolysis, condensation, and gelation. These steps induce lubricity or plasticity as well as binding of the individual particles of alumina and covert the dry powder into a pasty mass which extrudes smoothly. Basically, the powder which is to be extruded is converted to a state with the correct rheology for extrusion. Pseudoplastic is the preferred rheology of extrudable pastes because this renders them flowable by the shear created by the movement of the screw of the extruder and the paste assumes a stable shape as soon as the shear is removed/terminated at the end of the die plate of the extruder [115]. Rheology modifiers such as poly vinyl alcohol, poly vinyl pyrrolidone, or ammonium alginate are included in certain cases to facilitate extrusion [115]. With the correct concentration of moisture, degree of peptization, and the extent of blending, the mixture invariably assumes the form of small granules with a certain degree of plasticity which renders it suitable for extrusion. In actual commercial operation, proper consistency of the mix to be extruded is invariably judged by operator "feel" which comes with experience. The step of kneading is preferably carried out in a controlled environment where there is reasonable control over temperature and humidity. Extrusion is conducted with Auger screw extruders which

may be mounted either horizontally or vertically. These consist of a screw which rotates in a metallic barrel which has a provision for cooling by circulating cooling water. It is fitted with a die plate at one end. The die has multiple apertures of a size designed to account for shrinkage of the extrusions during the drying step. Heat is generated during the mixing step and also during the extrusion step. Care has to be taken to maintain the moisture content of the mix until it is extruded. The barrel of the extruder has a provision for circulating coolant to prevent the mix from drying out and jamming the die plate. Sizing of the longitudinal dimension of the extrusions is done by a blade which rotates at a speed synchronized with the movement of the screw of the extruder to facilitate sizing of the extrusions. The extrusions may or may not be aged at ambient condition or special environmental conditions prior to drying and calcinations at elevated temperature. This type of aging can lend "green" strength to the extrudates which contribute to the microstructure and mechanical properties of the final product. Common problems encountered in the product are rough surfaces, unevenly cut ends, chipping and, deformed "banana" shaped extrusions.

4.4.6 Tableting or Ringing

Tableting, which is also called ringing, is a method of forming or shaping catalyst particles through the process of compaction. The material to be tableted is subjected to a degree of mechanical stress where plastic deformation sets in. A graphical relation between ductility, melting point, elastic modulus, and Mohs hardness is used as a rule of thumb to estimate whether a given material is tablet-able or not [123]. Tableting results in highly regular shapes with high mechanical strength, which is at the expense of porosity. This is explained by the Heckel equation, which shows that the relationship between porosity and the pressure applied during tableting is exponential and much of the porosity is lost in the region of lower pressure [115]. This necessitates the use of pore formers if porosity is important for the end application. The raw materials consist of a powder which is comminuted to a fine powder. Achieving proper particle size is important to achieve good adhesion. Other important properties are moisture content and the density of the powder. In general, unit operations such as wet compaction [kneading, drying, crushing] or dry compaction (briquetting and crushing) are essential for proper densification of the raw material to render it suitable for tableting. Sometimes this has to be carried out repeatedly. Typical unit operations are as follows: the powder of the main ingredient is densified through granulation in a device such as Roll Compactor. Optionally, it is mixed with the binder or pilling aid component such as talc, graphite, PVA, mineral oil, or even inorganic materials such as silicates, aluminates, some hydroxides, and oxides. This is followed by screening to remove oversized and undersized particles. The granules are then dried to the desired level, which is monitored by loss on drying or loss on ignition at a specified temperature. A lubricant such as graphite, stearic acid, or PVA may be added in a second step to the above mix in a dry milling operation. In the next step, the mix is blended and sent to a tableting machine for tableting. Tableting is accomplished with the application of hydraulic pressure. Continuous tableting is carried out

by machines which have a turn-table housing the dies, which rotates continuously at a fixed RPM. The powder to be tableted is continuously fed to these dies by a feeder. A scrapper cum tail over device is positioned to remove excess powder from the top of the die. A set of top and bottom punches which are operated in a synchronized manner by motorized rotating cam rollers facilitate pre-compression and main compression which gives the final shape to the tablet. The same set of punches also facilitate ejection of the formed tablet from the die. Catalysts can be tableted in different shapes such as tablets (height < diameter) cylinders (height > diameter), cylinders with holes, cylinders with ribs on the external surface, or a combination of holes and ribs.

During tableting there is high compaction which can result in a decrease in porosity. This method is resorted to in applications where the catalyst has to operate under severe conditions where it is subjected to significant thermal and or mechanical stress. Mechanical properties become important in these situations.

The tools used in tableting are made from special hardened alloy materials. Adequate finish of the tools is very important to get tablets of good physical appearance and quality as well as to minimize breakage of tools during tableting.

Common problems in tableting and their likely causes are nicely described in the Ref. [124]. This is reproduced verbatim below.

- *Tablet weight variation occurs due to variation in punch working lengths, for which there are a variety of causes such as mechanical wear and tear and also adhesion of residue of granules to be tableted.*
- *Picking which* refers to adherence of the compressed granule on to the punch face. This also occurs due to mechanical wear and tear or insufficient lubricant or non-optimal moisture content in the raw material.
- *Sticking* is defined as general granule adherence to the punch-tip surface. In addition to the causes responsible for picking, inappropriate tablet profile may impact tablet hardness and density and cause sticking.
- *In capping,* there is laminar separation of the body of the tablet or cup. A common cause is entrapment of air in the body of the tablet.
- *Poor tablet definition (embossing):* This problem is attributed to poor embossing design (ie, too small or too shallow), worn punch faces due to abrasive formulation, or excessive polishing.
- *Tablet hardness/breakage issues are due to* uneven punch lengths across a set, incorrect binding agents in the formulation, or capping due to air entrapment.

4.4.7 Structured Catalysts

Cybulski and Mouljin [113] have provided an overview of structured catalysts. They differentiate structured catalysts from conventional fixed bed catalysts on the basis of

randomness of packing which exists in the latter case. Structured catalysts are used for overcoming problems such as mal-distribution of flow of the reaction medium, pressure drop, and fouling due to dust which are encountered in conventional fixed bed reactors. They cite three types of structured reactors viz. monoliths, membrane catalysts, and arranged catalysts. Between them, the monoliths exhibit very limited radial mixing which is restricted to the channels, the membrane reactors exhibit some degree of mass transfer between the channels and the arranged catalysts exhibit intense radial mixing. In effect, there is zero mixing across the reactor in case of monoliths, intense radial mixing across the reactor in the case of arranged catalysts, and limited radial mixing in the case of membrane reactors.

Incorporated monolithic catalysts are those in which the active component is uniformly incorporated into the basic structure of the monolith and it qualifies for consideration as a bulk catalyst. The supported catalyst version is the wash-coated monolithic catalyst which is extensively used in abatement of pollution arising from on-road and off-road vehicles and for Selective Catalytic Reduction of NO_x from stationary applications such as off-gas from power plants. Membrane reactors are useful in applications which are limited by thermodynamic equilibrium such as alkane dehydrogenation, where diffusion of the product, hydrogen, to outside the reaction zone favors the forward reaction. Classes include catalytic membranes which are themselves active for the reaction and also facilitate selective diffusion of reaction components across the membrane. An example is provided for the steam reforming of methane in Ref. [125]. Alternatively, a combination of an active catalyst which is located in a ceramic membrane reactor, which by itself is not catalytically active, can also be used. An example of the latter is provided in Ref. [126] which reports a membrane reactor housing a catalyst which is active for the dehydrogenation of C_2–C_6 paraffin where benefits are a higher product yields. Part of the co-product hydrogen permeates from the reaction zone to an adjacent combustion zone, where it generates heat to supplement the endothermic dehydrogenation reaction. The reaction equilibrium is also driven in a forward direction leading to an increase in product yields. Membrane reactors are also useful for increasing selectivity by regulating concentrations of co-reactants or products in reaction mixtures. An example is the oxidative dehydrogenation of ethane (ODHE). Studies with a MIEC (dense mixed ionic-electronic conductor) membrane of composition $Ba_{0.5}Sr_{0.5}Co_{0.8}Fe_{0.2}O_{3-\delta}$ for the ODHE is reported by Serra et al. [127]. The membrane was prepared by wet milling followed by pelletizing. The membrane allows the diffusion of oxygen from the outer surface through vacancies in the membrane material and makes this oxygen available on the inner surface of the membrane. This results in the significant depression of total combustion reactions and hence, enhanced ethylene selectivity. Eltron Research and Development have developed a catalytic membrane reactor for the oxidative coupling of methane to ethylene (www.eltronrsearch.com) [128]. They report that an oxygen transport membrane coated with a complex metal oxide catalyst converts a mixture of methane and ethane through oxidative dehydrogenation, utilizing anionic oxygen species from the surface of the membrane to provide a much higher conversion of methane with attendant higher selectivity to ethylene.

4.5 Catalyst Scale-Up

In going from laboratory to commercial scale, the scale-up factors may range significantly high from 10 to 10,000 depending on whether the product is a specialty or a commodity chemical. This large change in scale requires change in the size and type of equipment used. This calls for validation of the new equipment. The following aspects are commonly encountered during scale-up:

- Sampling of raw materials, intermediates, and products should be done in a manner that represents the bulk of the sample. Any change in the source of raw material or equipment should be validated. Standard protocols should be followed uniformly from laboratory to pilot to commercial stage.
- Temperature ramp rate and cooling rates in processes, such as crystallization by hydrothermal synthesis, can be very different at the commercial scale when compared to small laboratory reactors. In the latter case, the reaction mass can be heated or cooled at significantly faster rates. This affects the time-temperature history and hence the overall kinetic rate of reaction. The batch time needs to be optimized. It can also affect product phase and purity if the product has a low window of tolerance for this process parameter. If the product is a high value specialty material which is sensitive to variations in process conditions, or if the rejected product is difficult to dispose of, it is always prudent to scale up in stages.
- Achieving good heat and mass transfer in the process: spatial homogeneity in process parameters such as temperature, pH and concentration/composition of reactants, and intermediates in large reactors becomes an important consideration during scale-up of batch processes. These can be addressed through proper mixing at the micro, meso, and macro levels. Proper design of the reactor and agitators is important to this end. Reactors are equipped with vertical baffles to promote mixing. They prevent effects such as solid body rotation in chemical reactors and to direct fluid flow in heat exchangers. The number of baffles and their orientation relative to the wall of the vessel and the direction of rotation of the agitator blade are important to achieve the desired result. Baffles are typically installed at a certain distance from the wall of the vessel to prevent formation of dead zones and to enhance mixing by turbulence when the agitator speed is sufficiently high. The type of agitator is selected as appropriate to the fluid properties of the reaction mixture and the desired orientation of mixing. Rushton turbine and spiral turbines promote radial mixing while propeller blades and pitched blades provide axial mixing. Anchor type agitators with scrappers are used for viscous liquids [129] has reviewed this aspect. Multiple axial blades are used in large vessels where the L/D is >1. Maintaining the correct distance between the axial blades is important. The rate of addition of feed components and the spatial point of addition of the feed in relation to the vessel geometry and the agitator are important. CFD (computational fluid dynamics) based modeling is a useful

tool in understanding aspects of spatial distribution of heat and mass within the reactor [130]. If particle size of the end product is important, one needs to be mindful of possibility of attrition due to strong agitation.

- Modeling and simulation software such as ASPEN or SYMIX are valuable in scaling-up. This software provide modules for modeling solids, polymers, distillation, basic engineering, economic evaluation, energy efficiency, batch and dynamic simulation, and the database of thermophysical property data.
- Adopting continuous precipitation for a larger scale of production is also a good option. This may result in achieving better process control over the parameters used for precipitation because the size of the precipitation vessel is much smaller and contents can be routed to a hold tank. An example is provided in Ref. [131]. This ensures that the entire reaction mass experiences more uniform exposure to reaction conditions.
- Good control of process parameters is essential. Automation is very helpful in this regard. This is achieved by using PID process control loop based instrumentation. PID controllers need to be properly tuned to realize accuracy and precision. They also need to be calibrated at appropriate intervals to prevent errors due to drift in stability. PLC (programmable logic controllers) or DCS (distributed control systems) are used to facilitate automation through remote setting and control of parameters. Data acquisition through SCADA captures time trends of process parameters and stores them on storage media. This makes trouble-shooting easy.
- Washing and separation are important steps in precipitation to remove unwanted impurities from the product and to recover the product. Equipment which is generally used during laboratory development is a glass or Buchner funnel with a filter paper. Repeated slurry in a solvent, followed by filtration is frequently resorted to in the laboratory. This method is not only unwieldy but also time-consuming in commercial operation. As the batch size increases, it becomes necessary to move to other equipment which is capable of handling the volume conveniently. These are filter presses, basket centrifuges, or agitated Nutsche filters. This change makes it necessary to undertake further experimentation to optimize the quantity of wash water and the duration required to achieve the desired specifications of the product in this step. In the case of filter presses with a vertical orientation of the filter plates, one needs to be mindful of potential segregation of the product due to effects of gravity. Representative sampling can pose challenges in this situation.
- Uniformity during thermal treatments, such as drying and calcination is important. As the batch size increases, significant variation in the local value of temperature within the spatial geometry of the dryer or calciner is possible. Good design is essential to minimize this variation. This involves use of a convective flow within the calciner by using a fan or a blower, properly orienting the heating elements, and effectively insulating the furnace to minimize heat loss. During scale-up, it is good practice to sample the product from various locations within the furnace at the validation stage to rule out the possibility of

heterogeneity in properties. Rotary calcination equipment or fluid bed calcination provide better contact between the catalyst sample and the heating medium and, hence, more uniformity when compared to a box or tray dryer/calciner.

- Different types of dryers and calciners are used industrially. Box dryers and calciners are used during laboratory development. These are time and labor-intensive. In commercial operation, the type of dryer or calciner is selected keeping both the heat treatment schedule required for a product and the productivity in mind. SFD/C or Rotary calciners are continuous processes which are convenient and productive. Convenience has to be balanced with cost and technical requirements. The application of continuous calcination may sometimes be limited by the need for the considerably long duration of calcination for certain products which makes it impractical or expensive to use rotary equipment for calcination.
- For drying and calcination operations, the source of heat could be electrical, hot flue gas from direct fired heaters where the catalyst comes in contact with the flue gas, or indirect fired heaters where the hot flue gas is used to indirectly heat a medium such as air, which is then used for heating the catalyst. Consideration for selection is mainly cost of the fuel, thermal efficiency of the equipment, and tolerance of the product to the heating medium. The medium of calcination can affect the properties of the end product if the product is sensitive to components therein. Examples are the potential for poisoning of the active phase from sulfur which may be present in the flue gas of direct fired heaters, or the presence of CO_2 which can form unwanted carbonates with salts/precursors of the catalyst. The presence of moisture in the heating medium has the potential to promote sintering of the active phase, especially during reduction of catalysts in a stream of hydrogen.
- Cost is an important consideration in commercialization. Where possible, affordable commercial grade bulk raw materials should be chosen at the R&D stage unless product quality necessitates an expensive grade.
- At the commercial scale of production, the investment cost of hardware can become significant. In order to keep this as low as possible, the corrosive nature of raw materials should be taken into consideration at the R&D stage.
- Matching equipment size to batch size during the development and piloting stages is important to avoid complications such as short-circuiting or by-passing of fluid/wash water during washing. Productivity: elaborate process versus simple process
- Effluent disposal is an important consideration. Some chemicals like mercury cannot be let out in the environment. There are very tight restrictions on the release of many metals, especially Cr and Ni in effluent streams. These aspects need to be taken into consideration at the R&D stage to ensure that the project does not get killed at the scale-up stage.
- Water management/water and environment conservation are important considerations. Sustainability norms require less water usage and a move towards zero discharge of effluents. Developing processes which require minimum input of water to the process,

reuse of waste water through recycle, and its recovery using methods such as reverse osmosis become important considerations. In this context, it is desirable to avoid working with low slurry concentration during precipitation if it is technically possible to achieve the desired properties of the product by manipulating other process parameters.

- Risk mitigation studies at the R&D stage help to ensure smooth scale-up. This consists of dedicated experiments to map the operating space/envelope and also to understand critical steps in the process which have low tolerance to deviation of process parameters.

4.6 Catalyst Characterization

Characterization of catalysts is very important for establishing structure-performance relationships which increase our understanding of how a given catalyst functions, and opens up avenues for developing improved versions and for designing new catalysts.

Most industrial catalysts are used in large quantities, ranging from close to a metric ton to a few hundred metric tons per reactor charge. In many cases, they are produced in smaller batches which are then mixed to prepare one commercial charge. The preparation may pass through a number of product intermediates before arriving at the final product. Parameters which are important to the performance of industrial catalysts range across such properties as the presence of impurities, chemical entities, microstructure, size, form, and thermal and mechanical integrity during operation. It is important to achieve these properties consistently across batches. In order to facilitate this, definite properties or characteristics are identified and defined for precursors and product intermediates at every stage. These properties are monitored rigorously throughout the process of manufacture. Hence, the characterization of industrial catalysts encompasses intermediates formed during their manufacture and is not restricted to the end product alone. Characterization of the end product catalyst is a sort of "finger printing" of its physicochemical characteristics which minimizes the risk of its nonperformance.

During their service life, commercial catalysts experience environments, some of which are difficult to simulate in the laboratory. The cycle length and lifetime of catalysts can range over a few years in service. Hence, testing each batch of catalyst for its life cycle is very tedious and time-consuming, and, hence, impractical. If correlations can be drawn between physicochemical characteristics of catalysts and their performance, it makes it possible to certify commercial catalyst samples for their performance through limited testing, which includes performance testing. Hence, qualifying catalysts through their characterization involves considerable empiricism or semi-empiricism and relies heavily on past experience.

Broadly, metals catalyze hydrogenation, dehydrogenation, hydrogenolysis, and oxidations and their structure is much simpler than that of oxides. Oxides on the other hand, present diverse structures, non-stoichiometry and polymorphism. They catalyze (amm)oxidation, desulfurization, isomerizations, alkylations, and cracking reactions. Operando techniques are

providing avenues to monitor changes in the catalyst as they catalyze reactions and this is enabling the determination of structure-performance relationships.

Dispersion of the active phase is of paramount importance in all heterogeneous catalysts and especially in supported metal catalysts. In the case of bulk catalysts, aspects such as phase composition, structure, polymorphism, non-stoichiometry, acidity, and steric hindrance become important. Properties such as lattice oxygen, metal-oxygen bond strength, host structure, redox, multifunctionality of active sites, site isolation, and phase cooperation, which are propounded by Grasselli [132], are understood as important parameters for the activity of bulk catalysts.

New concepts are evolving regarding the structure activity relationship of bulk oxide catalysts. Concepts such as length of the metal oxygen bond, site isolation, bifunctional sites, contact synergy, and remote control were proposed over the years to explain the reactivity of bulk oxide catalysts. Recently, Wachs et al. [133] have reviewed these concepts in light of studies with advanced characterization techniques and proposed a new perspective to the functioning of bulk oxide catalysts. The use of tools such as low energy ion scattering (LEIS), energy resolved XPS (ER-XPS), high resolution TEM (HR-TEM), methanol IR-spectroscopic chemisorptions, and methanol temperature programmed reaction (TPSR) are highlighted. These studies show that the outermost surface of bulk oxide catalysts is different from the bulk, unlike what was thought earlier. Furthermore, this outermost surface is responsible for activity of the catalyst, hence the authors suggest that earlier concepts should be used cautiously [133].

4.6.1 Physico-chemical Properties

4.6.1.1 Catalyst microstructure

The microstructure of catalysts comprises properties such as specific surface area, pore volume, pore size distribution, and pore shape. Catalysis being a surface phenomenon, surface area is an important property. In the preparation of bulk catalysts, the conditions of preparation, such as precipitation, are adjusted to achieve this end. Microstructure of solids is commonly determined by the physisorption of adsorbates such as nitrogen. Alternate adsorbates such as argon, Krypton, water, or alcohols are also used but less frequently. Typically the physisorption of the probe gas at temperatures close to those of its condensation is used in these experiments. These adsorbates present six basic types of adsorption isotherms depending on the nature of the solid. The shape of the adsorption-desorption isotherm gives an idea about the type of porosity, pore shape, the strength of adsorbate-adsorbent interactions, and the nature of physical processes such as formation of a monolayer of adsorbate, multilayers, or capillary condensation and complete filling of the pores with liquid. Determination of surface area and pore size distribution is carried out using a number of methods which are themselves based on a number of assumptions. Identifying the type of isotherm is the starting point because it helps select the analytical model best suited for the sample at hand.

4.6.1.2 Specific surface area

A number of different methods are used for determining specific surface area of solids from physisorption data. Key differences between these methods are as follows. The BET (Brauner–Emmett–Taylor) equation, [134], Langmuir or Dubinin–Kaganer method require an estimate of the volume of gas equivalent to monolayer coverage. The methods of Harkins-Jura, *t*-plot or α_s-plot are used to determine specific surface area using empirical equations [135]. It is important to use the appropriate method depending on the characteristics of the sample. Nitrogen is commonly used as an adsorbate and it is suitable for most solids with surface areas >0.5 m^2/g. Krypton, which has a low vapor pressure at liquid nitrogen temperature, is used as the adsorbate for determining the specific surface area of samples which are very low, 0.05–0.5 m^2/g. In the case of solids with ultramicropores with diameter <0.7 nm, Argon is used as the adsorbate because it can fill these pores at a much higher relative pressure than nitrogen. Nitrogen does not give accurate values for zeolites. Argon is needed as the adsorbate for accurately determining pore size of zeolites samples [136]. The reason is attributed to the interaction of the quadrapole moment of nitrogen with the surface groups such as hydroxyls or charge compensating cations on the surface of zeolites [137]. It is important to use the correct region of the isotherm to determine surface area. This region is different for different models and equations. For example, the BET equation which is used for determining surface area of mesoporous materials (Type IV isotherm) uses a region between 0.05 and 0.33, while the Dubinin–Kaganer equation, which is used for determining the specific surface area of micropores uses relative pressures below 0.01. The Harkins-Jura method gives results comparable to the BET equation in relative pressure range 0.01–0.13. In the case of *t*-plots, a wide region of relative pressure between 0.08 and 0.75 is considered appropriate. It uses the BET surface area as a primary standard and the presence of micropores or slit shaped pores or capillary condensation of adsorbate in mesopores requires specific treatment with the t-plot method. The α_s-plot is a modified *t*-plot which needs adsorption on a nonporous reference material in addition to the sample, and requires interpolation. It is used for Type III or Type V isotherms, which cannot be handled by any other method, and also for Type II adsorption isotherm without an indication of onset of monolayer formation. All modern instruments used for this purpose have software with appropriate models which is provided with the instrument.

4.6.1.3 Porosity

The catalyst particle has to be porous in order to achieve high surface areas. Furthermore, for the internal surface to be easily accessible to reactant molecules, the pores should be sized larger than the kinetic diameter of the reactant molecule. Ease of diffusion of products from the interior of the catalyst particle to the bulk is also important from the perspective of product selectivity. The Lennard-Jones collision diameter or the Chung diameter are also used as alternatives to the kinetic diameter "Transport of gases and vapors in glassy and rubbery polymers," [138]. Transition between molecular, Knudsen and surface diffusion depends

not only on the pore size of the catalyst, but also on the process conditions. Hence, the figures reproduced below should be taken as a very general guideline. Transition of mechanism of diffusion as a function of pore diameter is shown in Fig. 4.8 [139].

In the adsorption of an adsorbate on to the surface of an adsorbent, a monolayer of adsorbate molecules is first formed. This is followed by formation of multilayers. The thickness of these layers can be determined either theoretically or empirically, using equations of

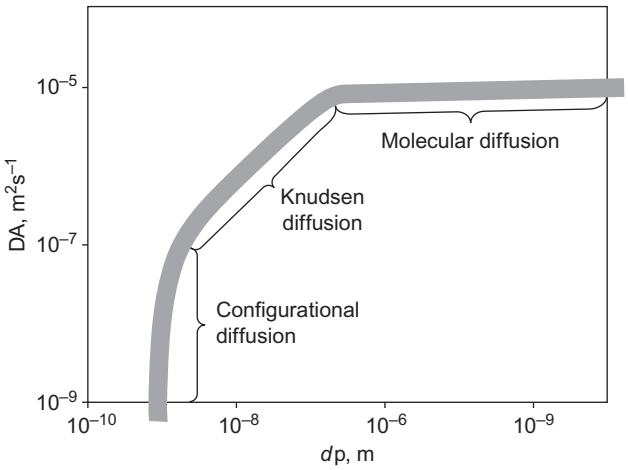


Fig. 4.8
Relationship between mechanism of diffusion and pore diameter. *Reproduced from Ref. [139].*

Harkins-Jura or Halsey or graphically from *t*-curves from data generated through experimentation by Cranston-Inkley or de Boer. It is used for analyzing pore size distributions as well as calculating specific surface area by the *t*-plot method. The *t*-curve is not universally applicable to all materials and it is applied at >0.4 relative pressure.

4.6.1.4 Pore size and shape

Pore size is classified by IUPAC nomenclature as Micropores: pore diameter <2 nm; Mesopores: pore diameter between 2 and 50 nm and Macropores: pore diameter >50 nm. The Kelvin equation, which relates pore radius to relative pressure during the process of capillary condensation in the adsorption of gases at temperature close to the point of their liquefaction temperature, forms the basis for determining pore size and pore size distributions. It applies well to the mesopore region of the adsorption isotherm, where pore filling occurs by capillary condensation. It applies to pores of size >4 nm up to 95 nm. Average pore size is calculated as 4 times the pore volume divided by specific surface area.

The pore volume is determined from the volume of gas adsorbed at saturation vapor pressure. The Dubinin–Radushkevich equation is used for determining the pore volume of microporous materials.

Pore shape and pore size distribution: Pores can be of various shapes such as cylindrical, ink-bottle, slit, wedge, etc. These can be identified from the shape of the hysteresis loop of the adsorption isotherm. At least five differently shaped hysteresis loops, called type A–E, have been identified in the type IV adsorption isotherm. These are attributed to different shapes of pores. These hysteresis curves have been reclassified into four types H1–H4 by IUPAC.

Pore shape is an important character of a catalyst or adsorbent because it can limit accessibility and or diffusibility of reactants and products. It is also important to choose the appropriate model for determining pore size distribution based on this consideration. Common methods which are used to determine pore size distributions are BJH (Barret-Joyner-Halenda), Cranston-Inkley, DFT (density function theory) method, and the Horvath-Kawazoe method for micropores. In these models, pore filling by physical adsorption on the pore walls in addition to capillary condensation, which was suggested by Wheeler, is considered. This aspect was neglected in the Kelvin equation. Generally, the desorption leg of the isotherm is used for determining pore size distributions for reasons attributed to better realization of thermodynamic equilibrium. Ink-bottle pores are an exception to this. The BJH method assumes that pores are cylindrical, but it applies to slit-shaped pores as well. The desorption branch of the isotherm is used for reasons cited earlier. This method computes pores downward of radius 30 nm. It ignores larger pores, but the contribution from these is generally small and does not affect the pore size distribution. The Cranston-Inkley method assumes cylindrical pores closed at one end. It is reported to be more accurate than the BJH method. The model-less method and MP (micropore analysis method) methods are used in combination for determining pore size distributions which cover the entire range from micropores to macropores. The former uses certain criteria which need to be fulfilled to validate the correctness of results. This model does not assume pore shape and uses hydraulic radii, excepting for thinning corrections. In summary, it is important to identify the pore shape and basic character of the sample from the adsorption isotherm and apply the most appropriate model.

The upper end of the mesoporous region and macropores in solid materials, with pore diameter between 3 nm and 150 μm, are characterized by Mercury Porosimetry. In this case, the intrusion of mercury at high pressure is used to determine surface area, pore size, and pore size distribution. Mercury being a nonwetting liquid, it is necessary to apply pressure ranging from 2 bar to up to 4000 bar to counter resistance due to surface tension of the liquid. It is a quick and simple method with the following limitations: formation of amalgam with some metals such as Au, can be destructive and crush formed catalyst particles, the contact angle used in the Washburn equation, which is used to determine pore size, can change between intrusion and extrusion of mercury and the this equation assumes cylindrical pores or slits [140].

4.6.1.5 Elemental/composition analysis

The composition and relevant chemical properties of catalysts are determined at different stages during their preparation by using various techniques. It is important to establish correlation of the chemical properties with performance prior to scale-up. These correlations

serve to fingerprint catalyst formulations. Composition is determined by methods such as wet chemical, atomic absorption spectroscopy (AAS), energy dispersive analysis of X-rays (EDAX) or X-Ray fluorescence (ED-XRF/WD-XRF) and inductively coupled plasma analysis (ICP). Infra-red spectroscopy, UV-VIS and flame photometry are also useful to this end. ICP and XRF are commonly used techniques for chemical analysis in industry. ICP is the method of choice for determining components present in small concentrations in the catalyst. XRF is helpful for quick screening of elements present in the catalyst. Elemental analysis requires use of standards for calibration of the analyzers. In addition to chemical analysis other techniques are used to study the chemical properties of catalysts. These techniques includes, temperature programmed studies (TPD, TPR, TPO, OSC), UV-DRS, XPS, XRD, solid state NMR and Raman spectroscopy which are covered in subsequent sections.

4.6.2 Mechanical Properties

Formed catalysts go through significant handling during their manufacture and as well as during charging into the reactor. These operations subject the catalyst to mechanical stress. The typical service life of most industrial catalysts can range from a year upwards to even 5–10 years. During this period, the catalyst is subjected to operating conditions which can be severe, such as high pressures 50–150 bar g and/or temperatures 800–950 °C, or subject to inter-particle or particle-wall collisions as in fluidized or moving beds. The catalyst is also subjected to intermittent regenerations where it encounters conditions which are significantly different from those of regular operation. It is also subjected to inadvertent conditions due to process trips and upsets. An industrial catalyst should be able to survive these conditions during its service life. Some important mechanical properties of catalysts are crush strength and resistance to attrition. A boiling water standard test also finds mention in Clariant Corporate news (Clariant introduces ShiftMax®120 HCF: New HTS catalyst with essentially no hexavalent chromium, source: newsroom.clariant.com). Catalysts are formed into suitable size and shape to provide optimal voidage to balance between pressure drop and intra-particle resistances to heat and mass transfer, and also to facilitate removal of heat from the bed in the case of exothermic reactions. Loss of crush strength and loss of attrition are distinguished by the resultant particle size. In the crushing of catalyst particles, their size decreases predominantly from 0.2 to 0.8 of the original particle size, where as in the case of attrition, the particle size decreases predominantly to 0.1–10 μm [141]. These smaller particles cause problems ranging from increased pressure drop across the catalyst bed to fouling of downstream equipment. In case of supported noble metal catalyst or catalysts, where the active phase is high value and recoverable, this results in monetary loss.

4.6.2.1 Crush strength

Formed industrial catalysts are prepared by a series of processes which result in increasing particle size through aggregation and agglomeration, all the way from nanometer to micrometers. Further forming is done by physical compaction to form catalysts ranging in

particle size up to a millimeter or centimeter sizes. This latter step is done with or without the inclusion of binders [141]. The crush strength of these catalysts is attributed to material properties and microstructure. Wu et al. [142] have cited literature related to the theoretical aspects. They have cited the works of Knudsen, who attributed crush strength to porosity and the size of primary particles, Rumpf, Pietsch and Johnson et al. whose works attribute crush strength to binding with material bridges or binding without material bridges, interfacial forces, capillary pressure, adhesive and cohesive forces, and interlocking which hold together the macroscopic structure.

Specifications of mechanical properties of commercial catalysts tend to be based largely on empirical relations or analogy from similar applications, or on prior experience. These can be tuned by analyzing the residual mechanical strength of spent catalysts, but this is not only time-consuming but involves the risk of failure. Empiricism is resorted to because of the diverse and complex conditions which catalyst particles encounter during the actual operation in commercial reactors. These involve thermal, mechanical, and chemical stress as also fatigue, from normal operation and upsets, which are difficult to simulate in the laboratory. The disadvantage of this approach is that high crush strength requires a higher degree of compaction during forming and this is achieved at the cost of porosity and surface area. This, in turn, affects the effectiveness of performance of the catalyst. A scientific basis is therefore highly desirable. This calls for simulation of reaction conditions during measurement of mechanical properties.

Existing methods for determination of crush strength report the results as average value and standard deviation. Wu and Li [142] have shown that a Weibull distribution based on the failure of catalyst particles at a specific load can be used to predict the probability of catalyst particle failure due to mechanical load and it is a more useful method than reporting the mean and standard deviation of crush strength of a sample. They reason that the critical threshold of failure of catalyst particles which can lead to problems during commercial operation is low, say 5–10%. Hence, the percentage of catalyst particles with low strength matters more than the value of the average strength of the sample. Thus, dispersion of the values of catalyst particle strength is more important than the average value. They have cited references which show that the Weibull distribution represents catalyst strength data the best. The reason they cite is that the cause of brittle fracture in catalyst particles stems from inherent flaws such as defects, dislocations, and discontinuities due to heterogeneity in the case of composite materials—the weakest link theory. They have further shown that the Weibull statistical distribution can be used to predict the probability of failure.

Catalysts are produced in a variety of shapes in order to achieve a balance between minimal pressure drop across the catalyst bed and minimal resistance to heat and mass transfer within the catalyst particle. The catalyst particles must retain their geometric shape and size throughout their service life. Deterioration results in the formation of smaller particles or fines which increase pressure drop across the catalyst bed and affect operation. The resistance

of catalyst particles to form smaller particles and especially powder upon application of a compressive load is called its crush strength. Ad-hoc homemade methods for determining crush strength can serve the purpose of qualifying catalysts. However, it is always recommended that a standard method such as ASTM method is used because this eliminates or minimizes variations inherent in in-house methods and makes universal comparisons between catalyst samples easier. In this test, the sample is subjected to a compressive force and the force at which the particle breaks is captured/identified. Most modern instruments are based on load cells and they are designed to identify this point automatically. These instruments can be hooked up to a computer for the purpose of statistical analysis, such as determining the minimum and maximum values and calculating average and standard deviation. The test is called single pellet or bulk crush strength, depending on whether a single particle is subjected to compressive force at a time or whether a multitude of particles are simultaneously subjected to it.

ASTM method 4179-11: Single pellet crush strength of formed catalysts and catalyst carriers. This method is applicable to catalysts which have a regular shape which is within a narrow finite range along all three dimensions. The difference in any given dimension is due to limits of tolerance of the method by which these catalyst particles are made. Tablets, pellets, rings, and spheres are included in the scope of testing. In these shapes the length, breadth, height, or diameter are fairly constant to a low degree of tolerance. Differences in dimensions between particles of a given shape and size cannot be distinguished visually. The crush strength is reported as the average load in kg or Newton at which the particle breaks.

ASTM method 6175: Standard method for radial crush strength of extruded catalyst and catalyst carrier particles. Extrusions are cylindrical particles where the ratio of length to diameter of the particle is significantly larger than in the case of cylindrical tablets, pellets, or rings. Furthermore, there is significant difference between the lengths of different particles of the same lot. The extrusions are not perfectly straight and a degree of curvature is common. These features introduce difficulties in achieving good repeatability in the single particle crush test method. The crush strength in this case is normalized for the difference in length between individual particles and it is reported as the average crush strength per millimeter, for example, kgf/mm or Newton/mm at which the extrudate breaks. This test is primarily for catalyst extrudates with a diameter ranging from 1/16″ to 1/8″ and an extrudate length to diameter ratio ≥ 1.

ASTM method D7084-04: Standard method for determination of bulk crush strength of catalysts and catalyst carriers. In this test, a reasonable number of catalyst particles are weighed and subjected simultaneously to a series of premeditated compressive loads in a staged manner. The particles are removed and sieved at every stage and the weight of the intact particles and the fines is recorded. The data is then plotted to determine the load at which the fines equal 0.5 wt% of the sample taken. The load at this point is reported as the bulk crush strength of the sample. This test is limited to catalyst particles which are in the range of 1/32″–3/16″ diameter. It is very

useful for determining crush strength of catalysts of any shape, including irregularly shaped catalyst particles and extrusions, which tend to have a degree of curvature during their forming. This test is a closer simulation to the analogous phenomenon which may take place in actual commercial reactor operation, than the single pellet test.

Pretreatment of the sample such as drying under specified set of conditions is important in these tests.

Li et al. [143] have attempted to correlate bulk crush strength with the single pellet method. They have shown that catalyst particles which are oxides fail due to brittle fracture in both the methods. They have also shown that the fragments formed in the bulk crush strength shows two additional morphologies when compared to the single particle test and these correspond to fractures on two sides and local peeling, respectively. Data treatment for both methods is different and both follow a Weibull distribution. The single particle method provides a means to predict the probability of strength failure at a given force.

Instruments which are used for determining crush strength of catalysts are supplied by VINCI Technologies and McMesin.

4.6.2.2 Loss on attrition

Attrition of catalysts results in the formation of fine particles which can increase pressure drop across the bed, or foul, or plug equipment which is located downstream of the reactor. In some cases such fines may be pyrophoric and cause risk of explosion or fire. Loss of valuable metals is also a consideration. Attrition is caused by friction or abrasion resulting from inter-particle collisions or collisions of catalyst particles with the walls of containers as during handling or with piping, as in continuous catalytic recirculation, or due to the flow of fluids past their surfaces as is predominant in the case of fluid bed reactors or slurry reactors.

Standard tests which are used for determining resistance to attrition depend on the size of the catalyst particle. Tablets, pellets, rings, extrusions, and irregular granules are subjected to a tumble test. The container used in tumble tests may be cylindrical in shape or drum shaped with or without baffles. In these tests, a weighed amount of sample of the catalyst is subjected to tumbling by rotating the container at a fixed RPM for a set duration of time. The weight percent fines formed after the test is determined and reported as percent loss on attrition [LOA (wt%)]. When the catalyst is in the form of microspheres or very small granules, as are used in fluidized catalyst beds or slurry reactors, a sample is subjected to attrition by the flow of a fluid, such as air at high velocity. This is known as the Jet attrition test.

ASTM D4058-96(2011)e1 is used for catalyst particles of a variety of shapes ranging from 1/16″ to ¾″. It was developed with samples which had losses on attrition <7 wt%.

ASTM D5757-11 is a Standard test method for determination of attrition and abrasion of powdered catalysts by air jets. This method is developed for spherical or irregularly shaped catalyst particles of size 10–180 μm, and skeletal densities 2.4–3.0 g/cm^3, which are insoluble in water. The catalyst bed is fluidized with a jet of air at a predetermined pressure for a specific time duration. Particles which attrite to a size <20 μm are reported as fines.

Pretreatment of the sample such as drying under specified set of conditions is important in these tests.

4.6.3 Density

Commercial catalytic reactors are vessels made of stainless steel or special alloy steel, depending on their service conditions. Their design capacity is cited in terms of their working volume. It is important to charge the reactor with adequate volume of catalyst and to ensure that the catalyst charge is packed properly in the reactor. This is necessary to minimize channeling of the reactant fluids and to ensure that the design space time is met. Hence, it is necessary to know the packing volume of the catalyst.

In some cases where it is necessary to maintain a low pressure drop across the catalyst bed, radial flow reactors are used. The catalyst bed is held within a basket with perforations inside the main reactor vessel. In other cases where the catalyst deactivates relatively fast, it is necessary to move the catalyst between a reaction and a regeneration zone using a moving bed reactor. Movement of the catalyst may be done using mechanical devices such as scallops. In the case of highly exothermic reactions or reactions which deactivate very fast, it may become necessary to use a fluidized bed reactor to facilitate dissipation of heat and to move the catalyst rapidly between a reaction and regeneration zone. In all these cases, the weight of the catalyst also assumes importance to ensure that it is within the design criteria of the hardware. In slurry reactors, adequate settling of the catalyst is important for its recovery for recycle. In all of the above cases it is important to know the weight of the catalyst in addition to its volume. This is required to ensure that the weight is within the design limits of the hardware and also for proper operation such as proper fluidization in fluid bed reactors or settling in slurry reactors. The packing density becomes handy in such cases.

The different types of particle densities are described below. Many authors use some of these terms interchangeably which can cause confusion.

4.6.3.1 Absolute density

Absolute density, which is also known as the true, or apparent, or skeletal density, is the ratio of mass of the material to the volume of the material, in which volume excludes the contribution from pores and voids. This parameter is determined by a technique called pycometry. Helium is used as the probe because it can penetrate both pores and voids.

Use of skeletal density finds mention in fluid bed applications of catalysts as in FCC in the calculation of particle densities from pore volume [144].

4.6.3.2 Envelope density

Envelope density, also called particle density or apparent density, is the ratio of mass of a material to the volume of the material. This volume includes the pores within the material, but excludes the voids between particles. This parameter is relevant in calculating the Thiele modulus for mass based rates [141]. This parameter is measured using dry free flowing powders which envelope the catalyst particles and fill the voids but do not enter the pores.

4.6.3.3 Packing density

Packing density, which is also known as bulk density, is the ratio of the mass of the material to its volume, where volume includes pores as well as void spaces between particles of the material. It is also known as apparent bulk density (ABD), or compacted or tapped bulk density (CBD) depending on whether the volume is compacted by tapping or vibration or not. Its importance is addressed in detail at the beginning of this section. While determining bulk density in the laboratory it is important to account for adsorbed moisture present in the catalyst. Drying of the sample is necessary. The measuring vessel which is used to determine the volume should have a diameter which is large enough to minimize the effects of bed voidage which otherwise results from poor packing. Tapped BD is determined by mechanically tapping the vessel containing the catalyst particles for a fixed number of times. This is best done using automated instruments. The method used for determining CBD depends on the size of the catalyst particle. It is recommended that ASTM methods are used because these issues are addressed therein.

ASTM D4164-13 is used for determining mechanically tapped density of formed particles which do not break upon tapping. Extrusions, spheres, or formed pellets of size 0.8–4.8 mm nominal diameter qualify for this method. When the nominal diameter exceeds 4.8 mm ASTM D4699-03(2013) is recommended for the measurement. This method involves vibratory packing. For fine catalyst particles and powders with diameter <0.8 mm, ASTM D4781-03 (2013) is recommended. This method uses mechanical tapping.

4.6.4 LOI

Loss on ignition is another important property. Catalysts may contain adsorbed moisture or volatile organic compounds or anions such as nitrates, chlorides, or carbonates which desorb or decompose upon heating. LOI is an important property for accurately determining the metal content of catalysts for reasons of quality assurance, as well as cost and pricing. Supported noble metals catalysts are expensive. The metals account for the major cost of these catalysts. These metals are recovered from the spent catalyst. It is necessary to know

the exact concentrations corrected for LOI. In general the sample is heated at a target temperature and cooled in a desiccator for such duration that there is no more significant loss in weight. UOP275-98, UOP-412-87 and UOP-954-11 methods are used for determining LOI by treating samples in air at 900 °C, 500 °C and at a temperature which is based on volatility of components in the catalyst, respectively. These methods are applicable to both fresh and spent catalysts, formed as well as powders. The loss in weight includes all volatile and combustible components present in the catalyst.

4.6.5 Particle Size

The particle size of catalysts which is also called loosely as grain size, is an important parameter because it is used to minimize pressure drop across the catalyst bed at the cost of decreased activity due to increased intra-particle diffusional effects. Exceptions are perhaps microspheroidal catalysts.

Depending on the shape and size of the catalyst particle, its size can be determined by any of the following techniques: Physical measurement using precision instruments such as Vernier Callipers, Sieve analysis, Laser diffraction, Light scattering, Sedigraphy, or Electron microscopy.

In the case of large particles of a regular shape, such as spheres, cylinders, tablets, rings, or extrudates whose dimensions are of the order of >1 mm, tools such as Vernier callipers or a micrometer screw gage are used to determine the dimensions. Measurements are made on a significant number of particles, such as 50 or 100, depending on the level of accuracy and the result is reported as average dimension along with standard deviation. This is a tedious labor-intensive method.

Sieve analysis is another technique which is relatively less labor-intensive. A set of sieves conforming to ASTM or BIS standards is mounted onto a electro-mechanical sieve shaker for a set duration and the fractions collected in sieves of different sizes are collected and weighed to provide the distribution. This is a simple technique. In sieve analysis it is important to ensure that the openings are not blocked by catalyst particles either initially or during measurement. This can affect the results. Periodic cleaning even during measurement may be necessary for obtaining accurate results. Also, all material adhering to the surface of the sieve has to be recovered. Sieves, especially of the finer mesh, are delicate and prone to damage such as deformation or tear, which can again affect the results. This operation can generate fine dust and care has to be taken to avoid exposure. Like the manual measurement, sieve analysis also requires a significant quantity of catalyst usually at least upwards of 500 g. It is amenable to irregularly shaped particles. Thirty four sieves with mesh size ranging from No. 635 (20 μm) to No. 3 (5.6 mm), and then further twenty one sieves in sizes from ¼″ (6.3 mm) up to 4″ (100 mm) are available. For particles of size <20 μm, it becomes inevitable to depend on sophisticated techniques such as sedigraphy or lazer diffraction.

In the case of catalysts which are microspheroidal, or irregular granules, or in the form of fine powders with the largest dimension <20 μm, rate of sedimentation (measurement range 0.1–300 μm) or lazer diffraction (measurement range 0.01–3500 μm) techniques are used for their measurement. Zetasizers are used for determining particle size in the nanometer range from 0.3 nm to 5 μm by dynamic light scattering. These instruments can be used to determine zeta potential measurements on particles of size 3.8 nm to 100 μm using electrophoretic light scattering, and also determine molecular weights from 9800 Da to 20 MDa by static light scattering. Some advantages of these techniques are their speed of measurement, which is in a matter of seconds to a few minutes, and the quantity of sample required is very small, of the order of a few milligrams. These techniques also do not generate dust. Most industrial catalysts form agglomerates during their preparation rather than exist as single crystals. Sampling is critical and has to be representative of the population. The results are typically reported as a log plot of cumulative percentage versus particle size. Typically, values at d_{10}, d_{50} and d_{90}, which correspond to the average particle size at 10, 50 and 90 V% of the sample are reported. The particle size distribution is rarely gaussian. Hence the graphical plot of particle size should be examined to get a better understanding. Both sedigraphy and lazer diffraction techniques require that the sample be suspended in the measurement medium. Selection of the medium consists of considering solubility of the catalyst in it as well as the relative buoyancy of the catalyst particles in this medium. The latter is a critical parameter in sedigraphy because this technique depends on the difference in rates of settling with particle size in a stagnant medium of fluid. Suspension is achieved by subjecting the sample to ultrasonication. Disintegration of the particle may take place during this operation. In the case of lazer diffraction, it is possible to carry out the measurement on dry samples by dispersing them with a jet of compressed air. However, the range of measurement is reduced to 0.1–3500 μm. It is also possible to measure without subjecting the sample to ultrasonication. Comparison of particle size before and after ultrasonication can be used to determine whether the catalyst particles are sensitive to mechanical stress. Measurement of particle size distribution by sedigraphy and lazer particle size does not always agree, although both techniques rely on optical phenomena. Interpretation of size requires assuming that the catalyst particles approximate certain regular shapes. These techniques also cannot distinguish between single crystals or agglomerates. This is a limitation in these techniques which can be overcome by using techniques such as particle size analysis using dynamic image analysis, or optical or electron microscopy as complementary techniques.

4.6.6 X-Ray Diffractometry

This technique is used for determining crystal structure of solids by utilizing the behavior of diffraction of an incident beam of X-rays by the crystal planes of the lattice. It can be used to characterize crystalline solids which have a crystallite size greater than about 30 Å using the

Braggs equation $n\lambda = 2d \text{ Sin } (\theta)$. It is a very useful technique in the preparation and characterization of catalysts including bulk catalysts. Some important uses in catalysis are:

- Identification of crystalline phases. Powder diffraction file databases which are available in the software supplied with modern machines allow for finger printing the diffractogram of the sample with that of a reference diffractogram which is stored in the database library. A near exact match of all the peaks in the reference diffractogram with that of the sample is desirable. Some exceptions are small peaks lost in noise or due to strong preferred orientation or due to anisotropic disorder [145].
- Determining the quantity of crystalline phases in a mixture by using internal or external standards. The integrated area under the peak is used for this purpose.
- Extent of crystallinity. This is useful in the hydrothermal synthesis of crystalline materials such as zeolites. X-ray diffraction can be used to study the rate of crystallization and also the degree of crystallization which acts as a guideline for determining the point of termination of the crystallization step. This is usually done by using a reference sample as a standard. Reitveld analysis is used for quantifying crystalline compounds in a mixture.
- The crystallite size is an important parameter in catalysis. It reflects on the extent of dispersion of the active phase and also the fraction of specific crystal planes which are exposed to the reactant. The apparent crystallite size is determined from line broadening of the XRD lines. It is important to take into account the line broadening due to instrumental effects and also due to imperfections in the crystal structure that cause strain and distort the lattice. The former is determined using a standard sample or through calculations. The Scherrer equation $\beta = k \times \lambda / (L_{\text{vol}} \times \text{Cos}(\theta))$, where the crystallite size is related to the volume averaged column height (L_{vol}) depending on the shape of the crystallite, and other parameters which are largely unknown. Hence, it is recommended to use column heights as a basis rather than apparent crystallite size. Other precautions are to ensure that the sample is dry and finely ground.
- Determination of unit cell parameters. An example where this is useful is in determining the extent of dealumination of Y zeolite which is used as a catalyst in FCC of heavy hydrocarbons such as vacuum gas oil.

4.6.7 Thermal Analysis

Thermal analysis techniques used in catalysis encompass thermogravimetry (TG), differential thermal analysis (DTA), and differential scanning calorimetry (DSC). Evolved gas analysis is used as an accessory in these techniques to derive information about the identity of volatile species formed due to the thermal changes. Generally a mass spectrometer is used for this.

In TG, a small quantity generally ~0.1–0.5 g is loaded onto a pan of a microbalance and a stream of gas is made to flow past the sample at a constant rate. The type of gas used varies with the purpose of the study, such as air is used for oxidation, air or inert gas such as nitrogen

for thermal decomposition, a mixture of hydrogen in nitrogen for reduction, or mixture of gaseous hydrocarbon in inert gas for studying coke deposition. This is possible provided the instrument is configured for this service. The sample is heated at a desired constant rate, typically 10 °C/min and the change in mass of the sample as a function of temperature is recorded. The first derivative of this weight change enables identification of the exact temperature at which the change manifests. An optimum ramp rate is critical to obtain good resolution and a realistic representation of the temperature at which the change takes place. This technique can be used for applications such as identification of compounds from the DSC-TG signature, determining the purity of a sample, loss of volatile residue upon drying or ignition, determining reaction rate, or activation energy or heat of reaction. Usually there is a loss in weight, but in the case of reduced or spent catalysts which contain metals, a weight gain is observed due to oxidation of the metal to its corresponding oxide.

This technique is usually coupled with DTA or DSC. In DTA, a sample and a reference material are heated at a constant ramp rate with a common heater. The reference material is selected such that it does not undergo significant changes in weight or phase in the range of temperature of the study. The difference in temperature between the sample and the reference is recorded as a signal in addition to the change in weight as a function of temperature. In DSC the sample and the reference are heated by individual heaters in such a manner that the difference in temperature between them is negligible. The current needed to maintain isothermality between the sample and the reference is recorded as a signal. DTA or DSC is used to obtain information about the temperatures of phase transitions and the corresponding heats/enthalpies.

4.6.8 Pulse Chemisorption: Metal Dispersion

Metal dispersion is the extent to which an active phase is distributed over a support material. It is a measure of the fraction of the surface of the active phase in the catalyst which is accessible to reactant molecules for reaction. Metal dispersion is especially important for structure insensitive reactions where the activity is solely determined by the number of active centers which are accessible to the reactant. Pulse chemisorption is a convenient cost-effective technique where a probe molecule is used to determine dispersion. The measurement may be done by either a dynamic flow method at atmospheric pressure or a static/volumetric method under vacuum. Both these methods use reactor sections which are made of glass or quartz for reasons of their low interaction or reactivity with the probe molecules. This is necessary to avoid contribution from the surface of metal reactors. The surface of the catalyst is cleaned either by purging with an inert carrier gas, or by applying vacuum at elevated temperatures. Different probe molecules are reported in literature. Oxygen is commonly used for catalysts containing platinum or palladium or copper or molybdenum or nickel. Hydrogen and oxygen are used for catalysts containing platinum, CO is used for palladium and platinum. N_2O is used for catalysts containing copper.

In the dynamic method, a U tube reactor is used to hold the catalyst. A carrier gas flows through the reactor and the probe gas is pulsed into the carrier gas until the surface of the catalyst is saturated. The fraction of the probe gas which exits the reactor without chemisorption is measured using an analytical device such as a TCD or FID detector, depending on the type of probe gas. Metal dispersion is determined from the quantity of gas chemisorbed by using the stoichiometry of chemisorption between the adsorbent and absorbate. When a TCD is used as detector, the carrier gas is selected so as to provide maximum sensitivity with respect to probe gas. Determination of the dispersion of monometallic platinum on γ-Al_2O_3 by the chemisorption and titration of hydrogen and oxygen has been reported by Benson and Boudart [146]. In the static method there is a provision to distinguish between weakly and strongly chemisorbed fractions of the probe gas by intermediate degassing. Sufficient time is provided to ensure equilibrium between the gas phase and adsorbed probe molecules.

The use of chemisorption for determining metal dispersion has complications. In the case of bimetallic or multimetallic catalysts, the chemisorption may become an activated process. This is attributed to the formation of bimetallic clusters of metals. An example is the determination of the dispersion of platinum tin catalysts which are supported on γ-Al_2O_3 [147], where the chemisorption measurement is carried out at 150 °C. The method allows the determination of unalloyed Pt, and also Pt which is alloyed to Sn. The dispersion is correlated with activity for the dehydrogenation of n-decane. While determining the dispersion of metals using the hydrogen-oxygen titration, the chemisorption sites may get progressively deactivated due to the strong adsorption of water which is a product of the reaction. In the case of alumina supported metals the alumina is reported to act as a scavenger [146]. Different probe molecules have been used for determining the dispersion of metals in catalysts. In the chemisorption of CO on Pt, the CO can chemisorb either through a linear or a branched configuration which adds to the difficulty [148]. Different methods have been proposed for determining the dispersion of Mo. Reddy et al. [149] have measured the dispersion of Mo using static chemisorption at −77 °C, whereas Vissers et al. [150] have studied the dynamic chemisorption of oxygen of on Mo/carbon supports at 333 K. R.A. van Santen et al. [151] have used the same method for determining the dispersion of Ni supported on zeolites. It is recommended to follow a method where the dispersion determined by any given method is correlated with activity of the catalyst. Pulse chemisorption is also used to calculate the average size of the metal cluster. The method is an indirect one and it is based on assumptions. Hence, it is best complemented with results from direct techniques such as TEM (transmission electron microscopy) and HR-TEM.

4.6.9 Temperature Programmed Studies

In temperature programmed studies, the desorption or reaction of probe molecules with components of the catalyst is assessed as a function of temperature. These studies provide valuable information about the catalyst. Some techniques which are commonly used are: Temperature programmed desorption of ammonia for measuring acidity, temperature

programmed reduction to determine the ease and degree of reduction, spillover effects or metal-support interaction in supported metal catalysts, temperature programmed oxidation to determine the kind of polymeric deposits on spent catalysts, and oxygen storage capacity of oxides which is important in catalysts used for the oxidation of pollutants.

The typical equipment consists of a quartz flow through reactor with a furnace designed for minimum temperature lag and accurate ramping of the temperature. A detector such as a TCD (thermal conductivity detector) is used. A mass spectrometer may also be used for expanding the capability. The hardware and material of construction are selected such that they are chemically compatible with the probe gas used. Plumbing is heated to minimize condensation/adsorption of the probe gas. Since the temperature is continuously ramped, the dead volume from the reactor to the detector is kept at a minimum to minimize the lag in time at which the process actually takes place and the time of its detection by the detector. Cold traps are used to condense moisture (in situations where this forms) and prevent its contribution to the signal from the detector. Modern instruments are equipped with good process control software with a provision for automatic sequencing of events. Data acquisition software with facility for peak de-convolution, calculation of peak areas of individual peaks, and their reduction to the final derived values, such as acidity expressed as mmol NH_3/g catalyst or percentage dispersion, is desirable. A high degree of automation is necessary for achieving good repeatability and reproducibility of measurement because some of these processes are vulnerable to a degree of variability due to slow adsorption or desorption of the probe gas.

Temperature programmed reduction: In this technique the basic objectives are to determine the peak temperature (T_{max}) at which the sample undergoes reduction and also measure the quantity of hydrogen consumed in the process. The sample is typically heated at a rate of 5–10 °C/min in a mixture of 5–10 vol% hydrogen in nitrogen or argon. Moisture which is formed as a product of reaction is collected in a cold trap and the change in concentration of hydrogen is determined continuously by the detector. The TPR pattern is plotted as a change in concentration of hydrogen with temperature of the sample. This plot provides information about the temperature of peak reduction of the sample and whether the reduction takes place as a single or multiple events. The detector signal is reduced by software to determine the area under individual peaks which can be used to determine the amount of hydrogen consumed by the event represented by that peak. Quantitation requires calibration of the detector signal with a standard calibration gas mixture.

TPR provides information about the temperature of peak reduction of the sample. When compared with reference samples, this information can be used to determine the relative ease of reduction of the sample which manifests as lower temperature of reduction; this may also be due to spillover effect [152]; extent of reduction of a fresh sample in oxide form, or the extent of reduction in reduced, and stabilized catalysts are determined from the peak area. The T_{max} in TPR has been used to qualitatively identify formation of different chemical species in nickel silica catalysts [153]. It is also used for identifying metal-support interactions

which push the T_{max} of the reduction event to higher temperatures. TPR is a bulk technique hence it is inappropriate to use it to determine metal dispersion. This technique is useful in industry as a quality assurance tool to fingerprint catalyst products. Samples subjected to TPR can be pyrophoric at the end of the study and they should be passivated prior to exposure to atmosphere and disposed-off in a safe manner.

Temperature programmed desorption: In this technique, the surface of a sample which is cleaned by thermal treatment or by applying vacuum is first saturated with an adsorbate. Physisorbed or weakly adsorbed component is removed by flushing with flow of an inert carrier gas or by providing thermal energy. The sample is then heated at a constant rate and the peak temperature of desorption of the adsorbate is determined. The temperature of desorption reflects on the strength of adsorption of the adsorbate on the surface of the catalyst. The higher the temperature of desorption, the stronger the adsorption. Sharp peaks indicate homogeneity of surface energy whereas broad diffused peaks or multiple peaks indicate heterogeneity of surface energy in the catalyst.

The TPD of ammonia is widely used for reporting acidity of catalysts. The peak temperature of desorption T_{max} is used qualitatively to describe the relative strength of adsorption/acid strength and the area under the curve as a measure of the amount of acidity which is expressed in mmol NH_3/g catalyst. However, Bartholomew and Farrauto [154] do not recommend it because it lacks specificity, gives inconsistent results, and inaccurate measures of adsorption strength. ASTM D4824-03 is a standard method where the adsorption or chemisorption of ammonia or pyridine on catalysts is used for measuring the acidity.

Temperature programmed oxidation: TPO is frequently used for determining the amount of carbonaceous species on spent catalysts. A mixture of 1–5 vol% O_2 balance Helium is flowed over the sample which is heated at a constant rate. The products of combustion such as CO and CO_2 are measured using a TCD detector. The use of a mass spectrometer enables identification between the two. When the amount of carbonaceous deposits is low, it is difficult to detect these gases using a TCD. In this situation, these gases are converted to methane using a methanation catalyst and the measurement is done using a FID detector. Lower temperatures of combustion are interpreted as reactive "soft coke" which has a higher H/C. Marafi et al. [155] have reviewed the work of Matsushita and Hauser where they have studied the TPO of spent hydroprocessing catalysts and categorized the coke in "soft" and "hard.". Solubility in organic solvents such as toluene and THF are also used to distinguish between these forms of coke. The presence of metals, such as Pt in the vicinity of the carbonaceous deposits, is also reported to facilitate combustion at lower temperatures due to a catalytic effect or the spillover of oxygen. Gjervan et al. [156] have shown this through their TPO studies of spent catalytic reforming catalysts.

Besselmann et al. [157] have used a combination of TPR, reaction with toluene and subsequent TPO to correlate redox properties with various vanadia species.

4.6.10 Microscopy: Optical, SEM, EDAX, TEM, SAED

Microscopy is a visual technique and encompasses optical microscopy and electron microscopy.

Optical microscopy, which is also known as Light microscopy, is limited to a resolution of 200 nm with magnifications up to 1000×. It is useful in examination of gross surface morphology such as the shapes and sizes of catalyst particles such as spray dried catalysts of typical diameter 20–200 μm. It is also useful for examining the surface of coatings for imperfections such as creep or cracks which develop during heat treatment or from aging. Looking up metal clusters of the size of a few nm in diameter requires the use of techniques with much higher resolution viz. Electron microscopy. Scanning electron microscopy has a resolution down to 1–3 nm. The resolution depends on the whether the instrument has a tungsten filament or a field emission gun. In this technique, the sample is scanned with a beam of electrons and the resultant emissions such as secondary electrons are used to form an image to determine topology of the sample. Back scattered electrons are used for elemental mapping to determine distribution of elements in a sample. Catalysts containing refractory oxides as supports have poor electrical conductivity and tend to accumulate charged particles on their surface during SEM measurement resulting in a phenomenon called "charging" which manifests as bright areas in the SEM micrograph with loss of detail. This is overcome by the deposition of elements like gold or platinum, which are good conductors of electricity, on the surface of catalysts by a technique called plasma sputtering.

When combined with EDAX (energy dispersive analysis of X-rays), the elemental composition of the selected area can be determined. In this technique, X-rays emitted as a result of scanning the surface of the sample with a beam of electrons is used to identify elements and also quantify them. This technique is used for profiling elemental concentration across the cross section of catalyst particles. This technique is useful for ascertaining uniform distribution of the active phase along the cross section of formed catalyst particles. Dongara et al. [158] have used this technique in the development of a catalyst composites for the dehydrogenation of paraffins. In certain cases it is beneficial to distribute the active phase selectively across the cross section of formed catalyst particles (eg, Egg-shell, egg-white, or egg-yolk distribution of the active phase). The egg-white distribution assumes importance when the reaction is limited by film diffusion as in the case of highly exothermic reactions or in the case of sequential reactions where the desired product is an intermediate. Negiz et al. [159] show a layered catalyst for selective hydrogenation of MAPD and Propadiene in C_3 streams to propylene. Riley and Vora [160] show a catalyst comprising a dense inert core and a catalytically active outer layer to facilitate continuous feeding of fresh catalyst with continuous withdrawal of spent catalyst from the reactor for the dehydrogenation of hydrocarbons. The egg-yolk distribution has been reported to be advantageous for the Short contact time

catalytic partial oxidation of methane using Rh/Al_2O_3 catalysts, where significantly higher conversion and selectivity to H_2 has been reported over a wide range of WHSV [161].

Elemental mapping using EDAX is useful to check for homogeneous distribution of the active phase over the spatial geometry of the catalyst particle. It is useful in the case of bulk catalysts which are prepared by compounding. In compounding, a number of different components are thoroughly mixed and formed into a desired shape. EDAX is a bulk technique and must not be confused with XPS (X-ray photoelectron spectroscopy) which is a surface technique.

TEM can go down to resolution of 0.1–0.2 nm, which is in the range of atomic resolution. This is by virtue of the small wavelength of electrons. Electrons are transmitted through the sample and analyzed using a variety of imaging techniques, such as bright field, dark field, phase contrast, and selected area diffraction to derive information ranging from shape and size to grain boundaries and dislocations, and also crystal symmetry. TEM is useful for detecting small metal clusters which are 2–3 nm in size. Scattering by crystalline matrices and phase contrast effects from the matrix makes detection difficult. Sehested [162] has used DFT and ETEM to study the influence of surface morphology of Nickel crystallites. These studies indicate that "step" sites are important for activity of steam pre-reforming catalysts. Different forms of carbon different formed on steam pre-reforming catalyst have been characterized using TEM.

SAED (selected area electron diffraction) can be used to identify the crystal structure of a specific part of the sample which is actually being observed.

4.6.11 Solid State MAS-NMR

In magic angle spinning—nuclear magnetic resonance technique a solid sample is spun in a magnetic field to average out the effects of various nuclear spin interactions such as dipolar effect, chemicals shift effect, anisotropic effect, and quadrupolar effect which are orientation dependent. This provides data which is useful in determining the chemical shift anisotropy of the nuclei. This technique is useful in the synthesis of catalysts to confirm whether the desired structure of the metal moiety or environment around it is formed, as in mixed oxides. An example is the location of Al in zeolites and the environment of Al atoms in zeolites [163]. It is used to track changes in the environment of metal atoms in the catalyst after use to get a better understanding of cause of its deactivation. Miro et al. [164] have used ^{27}Al-MAS NMR and ^{129}ZXe-MAS NMR to explain the deactivation of H-Mordenite during SCR of NO_x. This technique is also used for determining changes in the structure of metal moiety when reactants, intermediates and products are adsorbed on the surface of solid catalysts [165].

4.6.12 Diffuse Reflectance Spectroscopy

The Infra-red, Visible, and Ultra Violet spectra cover transitions ranging from molecular rotation, molecular vibration to electronic transitions, mainly the latter two transitions. Wavenumbers covered are from 250 to 50,000 cm^{-1}. Diffuse reflectance spectra in IR is known as DRIFTS and in the UV-VIS range it is known as DRS. When a sample is irradiated with light, then depending on the nature of the sample, some of that light is transmitted, some reflected, some absorbed, some scattered and some of it causes luminescence. In DRS technique light, the diffused form of reflection which arises from multiple reflections, refraction, and diffraction is used to draw information about the sample. In the study of bulk catalysts, the DRS techniques are used to derive information about the local coordination and structure, and band gap energy. Jentoft [166] has covered the technique and also cited the advantage of DRS over transmission spectroscopy at higher wavenumbers and for gathering spectra of surface species, using sulfated zirconia as an example. Ross-Medgaarden and Wachs [167] have reviewed published literature and also used UV-Vis DRS to determine the local structure of bulk and surface tungsten oxides on alumina, zirconia, and silica. The local structure is related to the ligand to metal charge transfer (LMCT) bands transitions in the UV, Vis and near-IR regions. They have used the edge energy of the LCMT to determine the number of covalent bridging tungsten-oxygen-tungsten bonds in bulk mixed oxide tungstates and polyoxotungstates. They have used Raman spectroscopy as a complementary technique along with DRS to determine local molecular structures of surface tungsten species on oxide supports.

4.6.13 XPS

X-ray photo electron spectroscopy distinguishes itself from most other techniques in that, it enables monitoring the outermost atomic layers of the surface of the catalyst as opposed to the bulk, 2–10 nm from the surface. In this technique, the sample is bombarded with an X-ray photoelectron beam and the kinetic energy of the resultant photoelectron which is emitted, or that of the photon or electron emitted due to relaxation, is used to determine binding energy and identify elements therefrom. Interference due to energy levels of different elements coinciding presents some difficulty. It enables determination change in dispersion of metals on the surface of carriers, segregation and surface enrichment and change in oxidation state when the catalyst is subjected to different treatments such as oxidation, reduction, or reaction. XPS can also be used to detect presence of poisons such as different states of sulfur (such as sulfide or sulfate) or heavy metals on spent/poisoned catalysts [168]. Binding energy shifts provide information about the local environment of the element such as its oxidation state. Guse et al. [169] have used it for studying changes in the surface composition of Co/Mn oxide catalysts for Fischer-Tropsch synthesis upon calcination, reduction, and during its use for the hydrogenation of CO.

4.6.14 Operando Spectroscopy

This technique enables simultaneous monitoring of the reaction on the surface of the catalyst and changes that the catalyst undergoes as it is catalyzing the reaction. Multiple spectroscopic methods such as UV-VIS, NMR, Laser Raman, FTIR, XRD, EXAFS, mass spectrometry, gas chromatography coupled with optical microscopy are available in operando mode. Coupling spectroscopy with microscopy provides spatial resolution. This is a step change from erstwhile spectroscopic techniques where the catalyst was characterized at conditions under high vacuum which were far removed from the actual reaction conditions. Since changes in the catalyst are identified as the reaction progresses, this technique improves the possibility of understanding structure-performance relationships. Special *in situ* catalytic reaction cells are used. While these cells can be operated at conditions of high temperature and pressure, these conditions are not always suited for obtaining good spectral data which is a limitation.

4.7 Summary

Bulk catalysts are those catalysts where a carrier is either not used or it is used as a minor component. They exhibit diverse properties and their preparation requires good control over quality of precursor raw materials and process parameters.

Industrial bulk catalysts are prepared mainly by precipitation. Properties of the precipitate are achieved by controlling the relative rates of nucleation and crystal growth. This is done by judicious selection of process parameters such as precursor salts, solute and slurry concentration, temperature and pH of precipitation and post synthesis aging, drying, and calcination. The sol-gel route is used for preparing materials with very high homogeneity of composition. Flame hydrolysis is used to prepare pyrogenic oxides which are nonporous. Surface area is governed by particle size. Advantages are in achieving spherical shape and control over the X-ray crystalline phase. Fusion or melt quenching are used to prepare fused metal alloy catalysts. Formation of metastable phases by super cooling can impart catalytic activity to the material. Skeletal alloys are prepared by pyrometallurgical techniques, followed by leaching away one of the metal components to leave behind a spongy structure of the other metal. The alloy can be prepared by pyrometallurgical or mechanical alloying techniques, and also by melt quenching. Reduction and stabilization of supported metal catalysts is a time-consuming process, especially when the concentration of the metal phase is high. This activity is perceived as unproductive by the end use customer. Pre-reduced and stabilized catalysts helps end user plants to easily reactivate these catalysts at much milder conditions than those required for the reduction from the oxide form and thereby save on cost of expensive hardware and also unproductive time which is otherwise required for reduction of the catalyst.

Catalyst supports serve to improve dispersion of the active phase and lend properties which enhance the service life of the catalyst. Alumina, silica, and zeolites are the major support materials which are used in industrial catalysts. Alumina can be prepared in different forms depending on the precursors and the preparation conditions used. It finds diverse applications such as catalytic, carrier/support for supported metal or metal oxide catalysts, a binder in forming of catalysts, and as desiccant or feed purification agent. Silica is used primarily as a carrier and a binder in catalyst forming applications.

Catalysts need to be formed in to various shapes to overcome pressure drop limitations in fixed bed reactors, for motility in moving bed and fluid bed reactors to facilitate ease of regeneration or for efficient heat and mass transfer. Various unit operations are needed in forming. These range across comminution, mixing and mulling, kneading, extrusion, spray drying, prilling, spherodizing, and tableting. Specialized equipment is used for these operations. Structured catalysts such as monoliths, membrane reactors, and arranged catalysts are used to overcome the issues of maldistribution of flow, high pressure drop fouling due to dust, and better heat and mass transfer. These three classes provide the option of controlling the degree of radial mixing across the channels of the monolith or the cross section of the reactor. Membrane reactors are used to overcome thermodynamic equilibrium limitation of reversible reactions, to generate heat from the by-products of reactions as a supplement for endothermic reactions, and also to control concentration of co-reactants in order to improve product selectivity.

Catalyst scale-up is multidisciplinary. Premium quality of product, cost effectiveness, high productivity, meeting statutory regulations such as liquid effluent and gaseous emissions quality, and sustainability form the crux of a good catalytic process. Scale-up involves addressing limitations in heat and mass transfer, ensuring efficiency of mixing. It involves the judicious selection of hardware at the development stage which can be translated to commercial production. Selection of raw materials which are cost effective, environmentally friendly and easy to dispose is important. Conservation of utilities and water are also important aspects.

The characterization of catalysts is important for the design of new catalysts and improvement of existing ones. A good part of characterization, especially the physical properties is empirical to semi-empirical and relies on past experience. Operando spectroscopy is changing this to an extent by becoming an enabler for determining structure-performance relations. Characterization serves to fingerprint industrial catalysts during their production and minimize the risk of their not performing. Characterization encompasses the mapping of morphology, microstructure, tolerance to mechanical and thermal stress, and the chemical nature of the catalyst.

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CHAPTER 5

Catalyst Deactivation and Regeneration

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5.1 Introduction

Catalysis plays a vital role in the manufacture of fuels, industrial chemicals, fine chemicals and specialty chemicals. Whether the reactant is derived from a fossil fuel like petroleum or from renewable biomass, the role of catalysis is imperative to make the desired process economical and environmentally friendly. Moreover, catalysis is expected to play a significant role in achieving sustainable energy and clean environmental goals. A catalyst should not only be highly active and selective for a particular process, but it should also sustain the process for very long duration (preferably for years, as in the case of ammonia process). But, in reality, it is not easy to accomplish these two aims, high activity and long catalyst life, simultaneously. Though some catalysts show high initial activity, their life is very short due to the rapid loss of activity, that is, deactivation, as is the case with fluid catalytic cracking (FCC) catalysts. Hence, every catalyst has a finite life, which could be seconds, days, or years. In fact, catalytic reactions and deactivation reactions occur in parallel time scale. Hence, one of the most important goals of any catalyst development program is to find catalysts that are active for long periods, without needing frequent regeneration. Though it is possible in principle to regenerate and reuse a deactivated catalyst, it does not make economic sense as an ongoing process has to be halted for regeneration of the catalyst, which affects productivity. A good diagnostic of deactivation process helps to prolong the active life of a catalyst.

Catalyst deactivation may happen due to various reasons like coke/carbon formation, sintering, poisoning, or phase change as a result of solid-state transformations. In the case of acid- or base-catalyzed reactions, the deactivation mostly occurs as a result of coking, whereas in the case of supported metal catalysts, the deactivation may mostly be attributed to the formation of coke or is due to the combined effect of coking and sintering of the metal. Some catalysts lose their activity due to the chemical transformation of the catalyst that occurs during the reaction, which causes loss of active species on the catalyst surface (formation of volatile

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compounds). Thus deactivation mechanisms differ from catalyst to catalyst, while they also depend on process conditions.

There were many reviews and books that addressed deactivation phenomena in depth [1–11], while there were also proceedings from dedicated symposia [12–18]. The purpose of this chapter is to describe causes of catalyst deactivation and how to overcome it. Since it is difficult to accommodate various issues concerning deactivation of catalysts in a single chapter, we will attempt to address deactivation in general with particular emphasis on a few classes of catalysts.

5.2 Reasons for Catalyst Deactivation

All the catalysts deactivate, though at different rates, depending on the deactivation process. Deactivation mostly happens because of unwanted (or side) reactions, parallel reactions, poisoning of active catalytic sites by any of the contaminants present in the feed, or simply because of the blockage of surface or pores by the coke (carbonaceous material) formed during the reaction through the cracking or condensation of reactants and/or products. Sometimes the product formed can decompose on prolonging the reaction time and strongly adsorb on the catalyst surface. Similarly, a catalyst may be covered with dust or plugged with fly ash as is the case with catalysts used for the treatment of flue gas from a coal-based thermal power plant. Thermal degradation of the catalyst may occur when a reaction produces a lot of heat due to the high exothermicity of the process or when the reaction itself is conducted at high temperatures. This degradation can be in the form of sintering of active metal phase leading to reduction in metal surface area or loss of surface area of the support. In the case of metal oxide catalysts, their surface area may reduce due to sintering at high temperatures leading to deterioration in activity. The support may also undergo a phase change leading to change of its interaction with the active species. A metal catalyst may also react with various impurities present in the feed, such as chlorine, sulfur, and oxygen, thus leading to change in the phase or formation of a new phase. Table 5.1 lists various important industrial catalysts, their typical life, and cause of their deactivation.

There are various reasons for catalyst deactivation, which may broadly be categorized as

(i) Fouling, coking, and carbon deposition
(ii) Thermal degradation and sintering of the catalyst
(iii) Poisoning of active sites
(iv) Loss of active catalyst phase due to evaporation
(v) Attrition

Usually, causes of deactivation are chemical, thermal, or mechanical. The processes (i) and (v) are mechanical in nature, (ii) and (iii) are chemical in nature, while (iii) is due to thermal effect.

Table 5.1 Typical lives and causes for the deactivation of some industrial catalysts

Catalyst	Reaction	Operating Conditions	Typical Life (years)	Reasons for Deactivation
Fused iron oxide with promoters	$N_2 + H_2 \Leftrightarrow NH_3$	450–470°C; 200–300 atm	10–15	Sintering of metal
Vanadium and potassium sulfate on SiO_2	$2SO_2 + O_2 \Rightarrow 2SO_3$	420–600°C; 1 atm	5–10	Formation of inactive compounds; catalyst disintegration
Pt-Rh gauze	$NH_3 + \frac{5}{2}O_2 \Rightarrow 2NO + 3H_2O$	800–900°C; 1–10 atm	0.1–0.5	Loss of surface texture; loss of Pt
Supported nickel	$CO + H_2 \Leftrightarrow CH_4 + H_2O$	250–350°C; ~30 atm	5–10	Poisoning by S, As
Cu + Zn on Al_2O_3	$CO + 2H_2 \Leftrightarrow CH_3OH + H_2O$	225–300°C; 50–100 atm	2–5	Sintering, poisoning by S, Cl, and carbonyl
Co-Mo-sulfides	Desulfurization of petroleum oils	250–400°C; 20–50 atm	1–10	Coking, metal deposition, pore blockage
Nickel on α-Al_2O_3 or $CaAl_2O_4$	$CH_4 + H_2O \Leftrightarrow CO + 3H_2$	700–850°C; 20–30 atm	1–3	Sintering, carbon deposition, S-poisoning
Fe_3O_4 on Cr_2O_3	$CO + H_2O \Leftrightarrow CO_2 + H_2$	350–450°C; 20–30 atm	1–3	Slow sintering and pellet disintegration
Cu + Zn on Al_2O_3	$CO + H_2O \Leftrightarrow CO_2 + H_2$	180–250°C; 10–30 atm	1–3	Poisoning by S and sintering of Cu
Supported fe-molybdate	$CH_3OH \rightarrow HCHO + H_2O$	280–300°C; ~1 atm	~1	Formation of inactive compounds, disintegration
Pt + promoter on Al_2O_3	Alkanes and naphthalene to aromatics (naphtha reforming)	480–520°C; 5–20 atm	<0.1–1	Coking, S-poisoning, metal sintering
Zeolites; SiO_2/Al_2O_3	Cracking of heavy petroleum oils into lighter materials	500–560°C; ~1–2 atm	$\sim 10^{-8}$	Rapid coking, deposition of metals and N-compounds
Ag on α-Al_2O_3 with alkali	$2C_2H_4 + O_2 \Rightarrow 2C_2H_4O$	200–270°C; 10–20 atm	1–3	Poisoning by S and Cl; slow sintering

5.3 Fouling, Coking, or Carbon Deposition

Fouling of a catalyst may occur due to physical deposition of an unwanted species on the catalyst surface that blocks the active sites. A catalyst may have short life because of fouling, when a carbonaceous material or a chemical compound such as metal oxide is deposited on the catalytic site. In the case of catalytic processes that involve organic moieties, particularly hydrocarbons that can rapidly undergo dehydration, carbon-rich formations can grow on the surface of the catalyst, which is referred to as coke. In most cases, deposition of carbonaceous material on the catalytic sites is a major reason for its nonavailability for further participation in the reaction, thus leading to its deactivation. Sometimes carbon deposition in large quantities can lead to disintegration of the catalyst, as in the case of catalysts used for steam-reforming reaction to produce synthesis gas (syngas). The terms *coke* and *carbon* are coined arbitrarily. As a convention, carbon is considered to be formed by CO disproportionation, while coke is formed through condensation or decomposition of hydrocarbon reactants/products. The carbonaceous material deposited may be a polymer or an oligomer that has high carbon content (C/H >0.5) or a material consisting of mostly carbon which could be amorphous or even crystalline graphite, depending on the conditions of reaction including the duration of the reaction. Though coke- or carbon-forming processes involve chemisorption, they can be categorized as mechanical as a result of the physical damage they cause to the formulated catalysts. There were a number of books and reviews that dealt with deactivation due to carbon and coke formation [10,19–23]. The carbon deposits can deactivate the active sites in one or more than one of the following ways:

(i) Chemisorbs strongly as monolayer or in multiple layers covering the active site (metal, metal oxide, acid, or base site)
(ii) Physically covers the active site making it inaccessible to the reactant
(iii) Plugs the pores (meso or micro) of the catalyst, thus blocking the access of active sites to the reactant
(iv) Damages or changes the physical texture of the catalyst as a result of growth of carbonaceous material

The major effects of fouling during the reaction are

(i) drop in activity, necessitating the increase of reactor temperature continuously in order to compensate for the loss in activity, and
(ii) gradual increase in pressure drop across the bed (from inlet to outlet) as a result of blocked flow paths.

Loss of catalytic activity and physical destruction of the catalyst by carbon deposits can occur rapidly (within hours or days) under unfavorable conditions; understanding and control of these effects is very important [22]. As mentioned earlier, coke is produced by decomposition or condensation of hydrocarbons on metal. In the case of reactions that have CO as one of the reactants or produced as one of the products (steam reforming (SR), dry reforming, water gas

shift reaction), carbon can be a product of CO disproportionation ($2CO \rightarrow C + CO_2$). The actual forms of coke may vary from high molecular weight hydrocarbons such as condensed polyaromatics to carbons such as graphite, depending on the conditions under which the coke is formed and aged. Coke formation on oxide surfaces is quite complex, as it can be seen as a kind of condensation-polymerization on the surfaces resulting in the generation of CH_x like species where x may vary in the range of 0.5–1. Hence, the coke formation mechanism that initially begins with the formation of olefins but ultimately ends as carbon-rich aromatic compound may involve (i) olefin polymerization, (ii) cyclization of olefin, and (iii) formation of substituted benzenes or polynuclear aromatics. All these pathways proceed via carbonium ion intermediates, which are catalyzed by Brønsted acid sites.

The type of coke formed depends on the constituents of the reaction mixture, reaction operating conditions, and composition of the catalyst. In general, coke is of two types, soluble coke ($C/H = 0.5–1$) which can easily be removed by dissolving in a solvent, and insoluble coke ($C/H > 1$) which is not soluble in any organic solvent. In the case of coke formed during fixed bed reactions, both the types of coke can be removed by burning it in dilute streams of oxygen at higher temperatures. The concentration of O_2 is controlled to control the heat generated during combustion of coke to CO_2. In a petroleum refinery, during various secondary refining processes coke formation varies from process to process. During reforming, hydrodesulfurization (HDS), isomerization, etc., coke is formed to a lesser extent, when compared to FCC. Hence, in the later case, the catalyst is continuously regenerated and recirculated. In the case of porous catalysts, the loss in catalytic activity is more rapid in the beginning of the reaction, as loss in porosity is much more rapid compared to drop in surface area. For catalysts with long life, after an initial rapid drop in activity, the activity may come down asymptotically with time on stream of the reaction (Fig. 5.1).

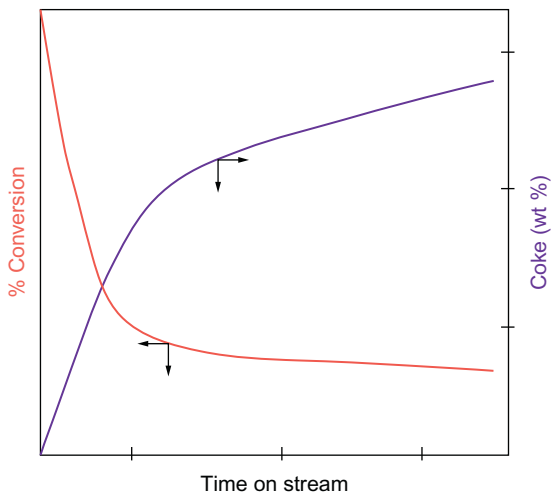


Fig. 5.1
Relationship between loss of catalytic activity and coke deposited with time on stream.

Dehydrogenation of hydrocarbon is the first step during coke formation; hence increasing H_2 pressure can lead to reduced coking. However, if partial pressure of feed or temperature is increased, coke formation is favored.

Carbon or coke formed on supported metal catalysts has been reviewed in depth by many authors [10,19–22]. Carbon can either adsorb physically or chemisorb strongly blocking the reactants from the metal sites. Mechanism of carbon deposition and coke formation on metal catalysts in the presence of CO and hydrocarbons is shown in Figs. 5.2 and 5.3. Carbon monoxide is normally dissociated on a metal site to form C_α, this in turn can react to form a polymeric carbon film C_β. These reactive carbons (C_α and C_β) are converted to graphitic carbon, which is less reactive [22]. Usually, some carbons formed at low temperatures do not affect activity immediately, whereas carbons formed at high temperature (>650°C), particularly graphitic carbons, deactivate the metal catalysts by encapsulating them.

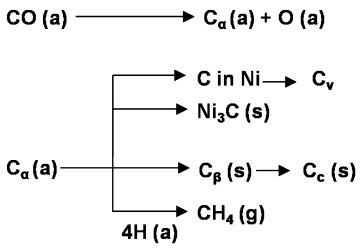


Fig. 5.2
Carbon formation, transformation, and gasification on metal catalyst [22].

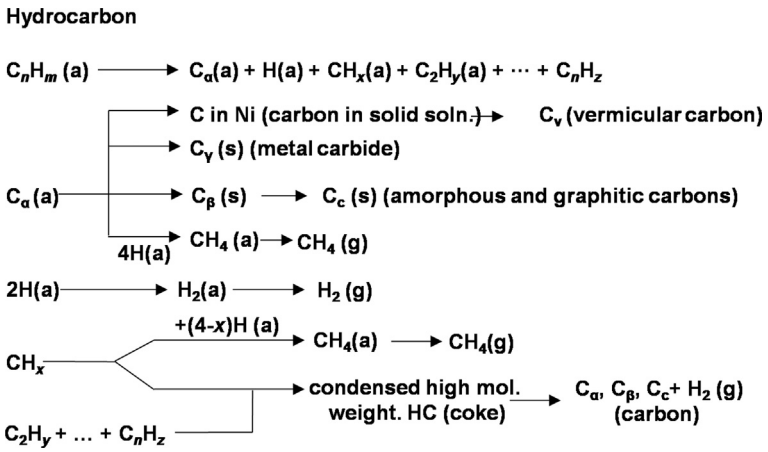


Fig. 5.3
Formation and transformation of coke on metal surface [22].

A description on the deactivation of metal catalysts will further become clear upon the discussion of coke formation by SR of hydrocarbon and dry reforming of methane (DRM).

Moreover, the catalyst systems used for these reactions would be of great help to understand the deactivation by coke formation.

5.3.1 Deactivation of Catalysts During Syngas Generation

Synthesis gas generation is an important catalytic process as it is used for the production of important industrial chemicals like methanol and ammonia, in addition to hydrogen generation. Syngas is also important for the production of diesel range liquid fuels via gas to liquid (GTL) process and for the synthesis of dimethyl ether (DME). Usually, industrial hydrogen is produced through SR of natural gas, while the product syngas obtained from dry (CO_2) reforming is more suitable for GTL and DME production, as it has low H_2/CO ratio. Deactivation due to sintering and coke formation is a serious problem in SR as well as in dry reforming. We now address the major causes of catalyst deactivation in the case of SR and dry reforming.

5.3.1.1 Coke formation during steam-reforming reaction

Steam reforming of methane (SRM) is an endothermic reaction; hence it is operated at high temperatures of 700–900°C. In this reaction Rostrup-Nielsen [24] observed three kinds of carbon species: (i) whiskerlike carbon formed on the catalyst surfaces at greater than 450°C [25–27]; (ii) encapsulated hydrocarbons formed by polymerization at less than 500°C [28–30], and (iii) pyrolytic carbon formed by cracking of hydrocarbons at above 600°C [30,31]. The CO dissociation leads to the formation of adsorbed atomic carbon (C_α), amorphous carbon (C_β), vermicular carbon (C_v), bulk Ni carbide (C_γ), and crystalline graphitic carbon (C_c) (Fig. 5.2) [22]. The formation of different species depends on the operating conditions and the type of catalyst. Table 5.2 provides information on carbons formed at different temperatures, their structure type, and their reaction temperature with hydrogen [22]. During SRM, carbon is initially formed in the form of fibers or whiskers, with small metal particles (mostly Ni) sitting on top of the whisker. This leads to the breakdown of the catalyst and carbon is deposited on the active sites leading to the blockage of the reformer tube. This coke deposition also leads to nonuniform distribution of flow along the reformer tube, which may cause increased localized heating of the hot tubes. Xu and Froment [32,33] proposed a reaction scheme of SR reaction as shown in Fig. 5.4.

Table 5.2 Different forms of carbons formed by decomposition of CO on Ni catalysts [22]

Designation of Carbon	Temperature of Formation (°C)	Structure Type	Reaction Temperature With H_2 (°C)
C_α	200–400	Atomic carbon on the surface	200
C_β	250–500	Polymeric amorphous films or filaments	400
C_v	300–1000	Vermicular filaments, fibers, whiskers	400–600
C_γ	150–250	Nickel carbide	275
C_c	500–550	Crystalline graphite	550–850

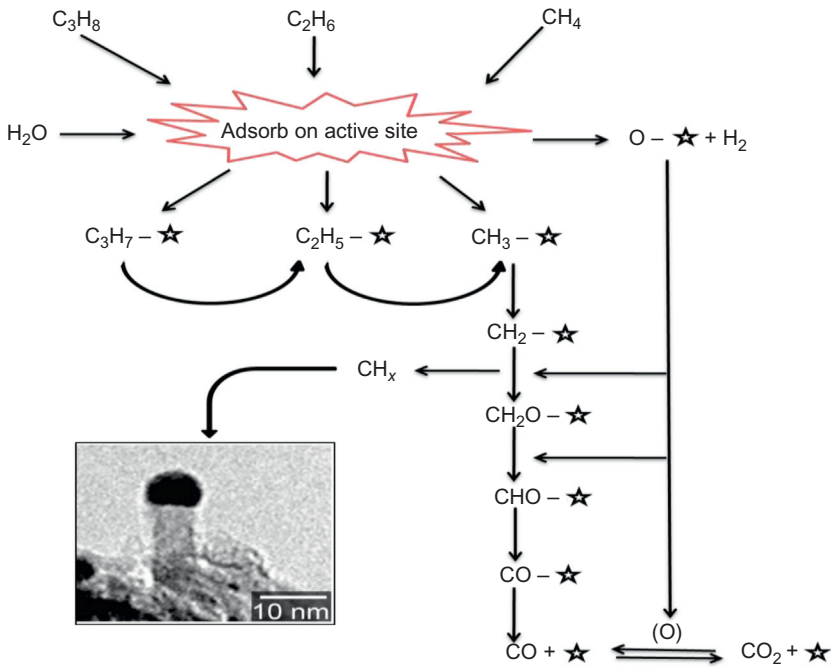


Fig. 5.4
Reaction scheme of steam reforming of natural gas for synthesis gas production.
(*: surface active site)

In the SR reaction, two reactions are mostly responsible for the formation of carbon.

(i) CH_4 decomposition (methane decomposition, MD)

$$CH_4(g) \Leftrightarrow C(s) + H_2(g) \qquad \Delta H^{o}_{298\,K} = +75\,kJ\,mol^{-1} \tag{5.1}$$

(ii) Boudouard reaction (BR)

$$2CO(g) \Leftrightarrow C(s) + CO_2(g) \qquad \Delta H^{o}_{298\,K} = -171\,kJ\,mol^{-1} \tag{5.2}$$

The kinetics of the reaction, experimental conditions and design of the reformer are important factors to be taken into consideration to understand the coke formation. During SR, carbon-consuming reactions ($C + CO_2 \rightarrow 2CO$ and $C + H_2O \rightarrow CO + H_2$) are usually balanced by the carbon-forming reactions. The thermodynamic equilibrium constant (K) of MD, BR, and equilibrium carbon at various steam to carbon (S/C) ratios are shown in Fig. 5.5A and B as a function of temperature at 1 atm pressure.

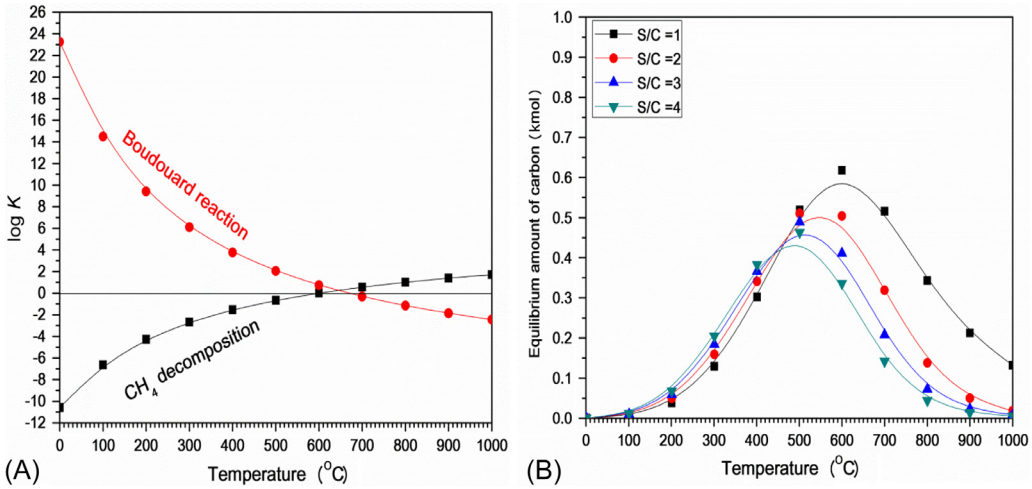


Fig. 5.5

(A) Thermodynamic equilibrium constant (K) for MD and BR against the reaction temperature. (B) Equilibrium carbon formed at various S/C ratios, different temperatures, and at 1 atm pressure. (Plots were generated based on Gibbs free energy minimization principle using HSC Chemistry 5.1 software.)

Fig. 5.5A shows that equilibrium constant (K) of MD increases with the temperature with a simultaneous fall in CO disproportionation reaction. The carbon atoms formed during the described reactions dissolve within the metal particle, migrate through the particle to nucleate into whiskers or filaments. The filament carbon specially grows at a specific site on the nickel surface [34]. These carbon whiskers have high mechanical strength and, hence, become the basis for destruction of the catalyst particles. Fig. 5.5B shows the carbon formed at equilibrium in the SRM at various temperatures. An increase in steam to carbon ratio decreases the amount of carbon formed on the surface of the catalyst.

Under SR conditions, nickel carbide is not a stable phase. Hence, after an induction period (t_O), carbon nucleates in the form of whiskers and grows at a constant rate (Fig. 5.6) [35].

$$\frac{dCw}{dt} = k_c(t - t_O) \tag{5.3}$$

The structure or morphology of the carbon and degree of graphitization depends on the kind of metal and its particle size, the hydrocarbon reactant, and the reaction temperature. In the case of MD, carbon formation rate increases with induction period (t_O) while addition of promoters to the nickel catalyst helps to delay the dissociation of CH_4 and carbon nucleation. Carbon nucleation is directly correlated with the size of the Ni crystallites, with smaller Ni crystallites giving less carbon. Bengaard et al. [36] demonstrated this aspect by carrying out TGA experiments with two Ni catalysts having different metal dispersion, but with the same activity. On the other hand, carbon formation rate is much lower on noble metal catalysts

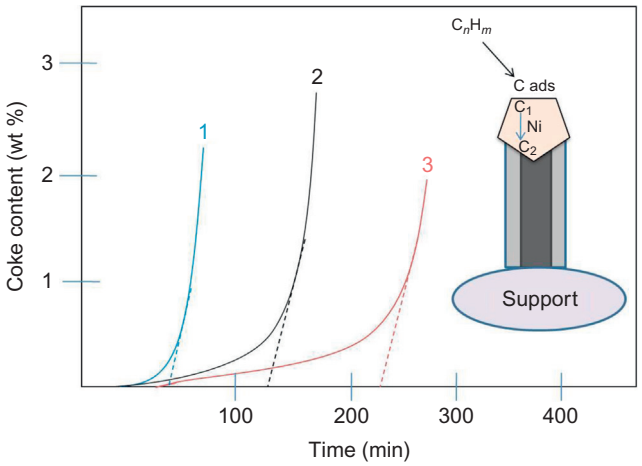


Fig. 5.6
Mechanism of whisker carbon growth [35].

compared to Ni catalysts, as the dissolution of carbon in the former is quite low. Rostrup-Nielsen [37] observed only a few layers of carbon on the surface of the Ru by HRTEM analysis of used SRM catalysts.

A small amount of dopant, particularly alloy-forming dopant, reduces carbide formation on the nickel surfaces. Trimm [38] has studied the effect of tin on SRM reaction as it reduces coke significantly. When about 0.5% Sn is added, it influences the rate of the SR reaction. Nichele et al. [39] proved that Ni/ZrO_2 catalyst is highly active for ethanol SR, but the presence of Lewis acid sites on ZrO_2 support attributed to coordinately unsaturated Zr^{4+} ions led to the coke formation. The addition of CaO to the support reduced the Lewis acidity, while it improved the resistance to coking. HRTEM studies show multiwalled carbon nanotubes (33–37 nm in diameter) on Ni/ZrO_2, while they are completely absent on CaO-impregnated ZrO_2 as depicted in Fig. 5.7.

Recently, Zhou et al. [40] showed that less coke is formed on bimetallic Ni-Pt catalysts supported on Al_2O_3 during SR of various fuels such as methane, kerosene, and ethanol compared to the Ni/Al_2O_3 catalyst. In the case of SR of heavier hydrocarbons ($>C_6$), carbon deposited on the catalyst surface is enhanced on supply of aromatics. Tubular reformers cannot tolerate the formation of whisker carbon in SR reaction. By keeping steady-state activity of carbon less than one, it is possible to extend the induction period (t_O) of carbon growth to infinity [35]. This induction period depends on the kinetic balance between the surface reaction of the hydrocarbon with oxygen species and the dissociation of hydrocarbon into adsorbed carbon atoms which can dissolve in the nickel crystals. Moraes et al. [41] showed Ni/CeO_2-nanocube with small amounts of Pt as more active with good catalyst stability during SR of ethanol. Addition of Pt promotes the hydrogenation active carbon species on

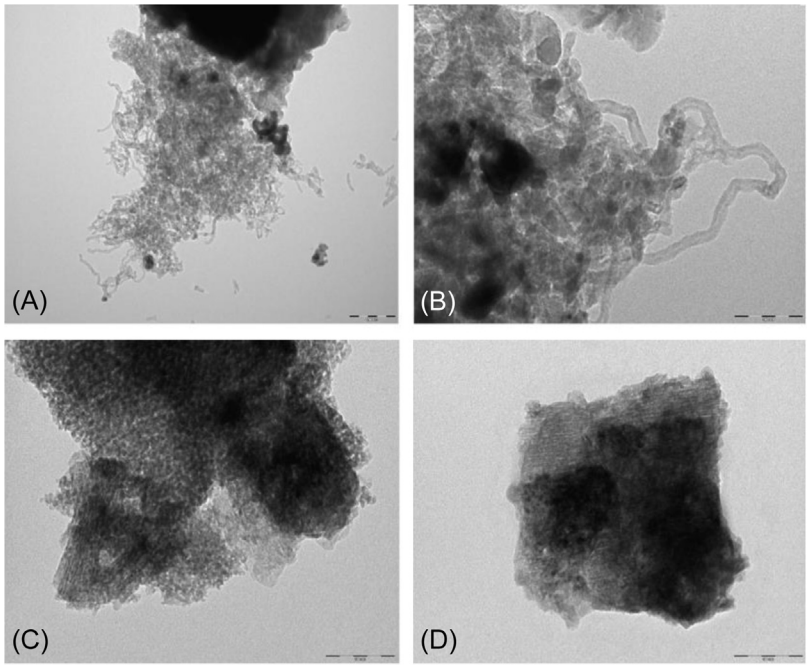


Fig. 5.7
TEM of spent catalysts Ni/ZrO_2 (A and B) and CaO-doped Ni/ZrO_2 (C and D) [39].

the surface at a higher rate than carbon diffused in the bulk nickel. These findings show an alternative way for minimization of carbon buildup on Ni-based catalysts during SR reaction.

Nature of the support and the metal-support interface plays an important role, as shown by Cassinelli et al. [42]. They correlated the highest specific reaction rate and $TOFs_{CH_4}$ of La-containing Pd catalysts in SRM to the electronic interaction between Pd- and La-modified alumina with the formation of $Pd^0[Pd^{\delta+}O_xLa]$-like species that promotes the CH_4 activation and carbon oxidation. Based on the deactivation results, a kinetic scheme has been proposed by Vicente et al. [43] for the SR of ethanol. They explained the formation of the different types of coke and their relationship with reaction conditions. The coke deposited at 300°C is amorphous and blocks metallic sites, whereas the coke formed at high temperatures is filamentous, increased with reaction temperature, but has low effect on catalyst deactivation as it does not block active metal sites.

5.3.1.2 Coke formation during dry (CO_2) reforming reaction

DRM is slightly more endothermic than SR reaction; hence it requires high temperatures to get equilibrium conversion that gives syngas with $H_2/CO = 1$.

$$CH_4 + CO_2 \Leftrightarrow 2CO + 2H_2 \qquad \left(\Delta H^{o}_{298\,K} = +247\,\text{kJ mol}^{-1}\right) \tag{5.4}$$

Dry reforming is invariably accompanied by deactivation, as a result of carbon deposition. The most widely used catalysts for DRM are Ni based, and most of these catalysts undergo severe deactivation due to carbon deposition.

In order to design catalysts that deactivate minimally, it is necessary to understand the elementary steps involved in the activation and conversion of CH_4 and CO_2. From a thermodynamic point of view, DRM reaction requires high temperatures (>800°C) to attain equilibrium conversion and H_2/CO ratio close to 1. But the simultaneous occurrence of reverse water gas shift reaction causes decrease in H_2/CO ratio to <1.

$$CO_2 + H_2 \Leftrightarrow CO + H_2O \qquad \left(\Delta H^{o}_{298K} = +41.2\,\mathrm{kJ\,mol^{-1}}\right) \tag{5.5}$$

At the operating reaction temperature and partial pressure some side reactions also occur along with dry reforming reaction, with some of them leading to coking of catalysts. Important among them are MD (Eq. 5.6) and BR (Eq. 5.7).

$$CH_4(g) \Leftrightarrow C(s) + H_2(g) \qquad \left(\Delta H^{o}_{298K} = +75\,\mathrm{kJ\,mol^{-1}}\right) \tag{5.6}$$

$$2CO(g) \Leftrightarrow C(s) + CO_2(g) \qquad \left(\Delta H^{o}_{298K} = -171\,\mathrm{kJ\,mol^{-1}}\right) \tag{5.7}$$

Fig. 5.8 shows that DRM reaction proceeds above 660°C while carbon formation as a result of BR and MD starts below this temperature. Because the BR is dominant up to 700°C, the major carbon formation occurs in the 550–700°C temperature range [44,45]. At higher temperatures (700°C), carbon formation is dominant due to mostly MD.

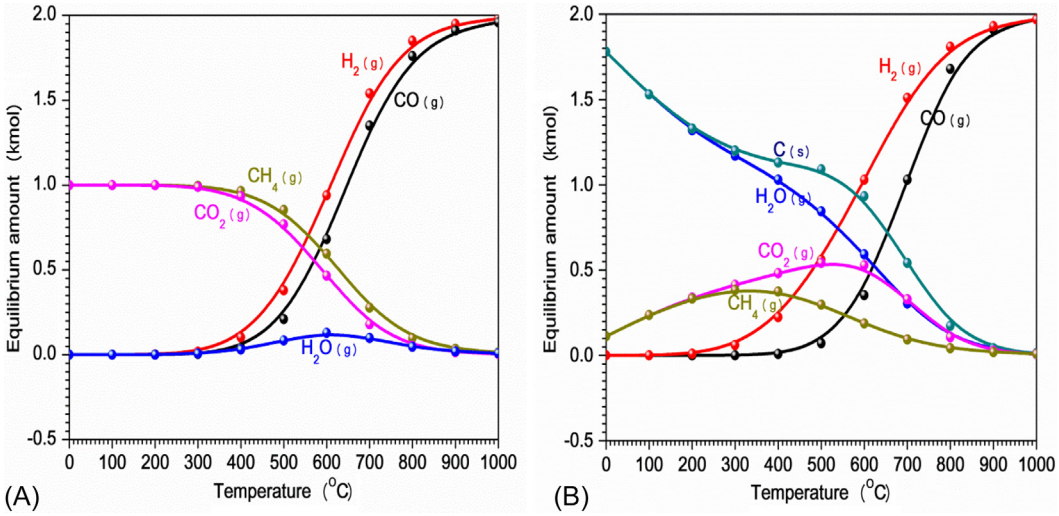


Fig. 5.8

Thermodynamic equilibrium plots of DRM at 1 atm, 0–1000°C and at inlet feed ratio of $CO_2/CH_4 = 1$. (A) Assuming no carbon formation, (B) along with carbon formation. (Plotted based on Gibbs free energy minimization using HSC Chemistry 5.1 software.)

Carbon formed over the catalyst during DRM differs in morphology [46], depending on the concentration of the active metal on the surface [47], location of the active metal [48], type of the support or promoters used [49], nature of the active metal [50], reaction temperature [51], and the duration of the reaction [52]. There are five distinct carbons that form during DRM reaction due to MD and BRs. These are

1. polymeric films and filamentous carbon (amorphous);
2. atomic carbon (dispersed, surface carbide);
3. vermicular whiskers/fibers/filaments (polymeric, amorphous);
4. graphitic platelets and films (crystalline); and
5. nickel carbide (bulk).

Out of the various kinds of carbons formed, amorphous carbon which is called C_α carbon is more reactive. This carbon is bound to metallic centers through first coordination [53]. The polymeric carbon composed of carbon-carbon chains is less reactive compared to amorphous carbon. These carbons can be oxidized in mild conditions and hence do not block active metal sites on the catalyst surface [54]. Hence, these carbons are called soft carbons. In the case of graphitic carbon, it consists of polynuclear aromatics like six-membered ring compounds, which are less reactive and require high temperatures for oxidation [53]. As a result, these carbons are called hard-type carbons, and they block the active sites leading to severe deactivation of catalysts. In some cases, active carbons are transformed to less active or inactive carbons with increasing reaction temperature and reaction time [55].

When DRM and propane was carried out using two different catalysts, Ni/SiO_2 and Ni/Mg(Al)O, higher coke formation was observed with propane [56]. Dehydrogenation of C_3 carbons was observed on the catalyst surface, which is a good coke precursor. However, less coke was observed on Ni/Mg(Al)O catalysts compared to Ni/SiO_2. Nagaoka et al. [57] studied dry reforming reaction over Ru supported on Al_2O_3, SiO_2, MgO, and TiO_2. No catalyst deactivation was observed, even after carbon formation, as the active carbon formed on the catalyst did not block the catalytic Ru metal sites.

Filamentous whisker carbon and encapsulating carbon were observed over $6Ni/Al_2O_3$ and $3Co_3Ni/Al_2O_3$ catalysts by Hyuk son et al., leading to rapid deactivation of the catalysts. On the other hand, Mg-promoted MgCoNi/c-Al_2O_3 catalyst exhibited high catalytic activity ($XCH_4 > 95\%$ for 200 h) along with good coke resistance during DRM. Addition of Mg and Co accelerates the decomposition/dissociation of CH_4 and CO_2 [58]. These results are explained by carbon XPS spectra of spent catalysts (Fig. 5.9). On 6Ni spent catalyst, the peak observed at 284.7 eV is attributed to graphitic carbon while the peak at 281.8 eV is assigned to the metal carbide. No coke formation occurred in the case of MgCoNi/c-Al_2O_3 catalyst.

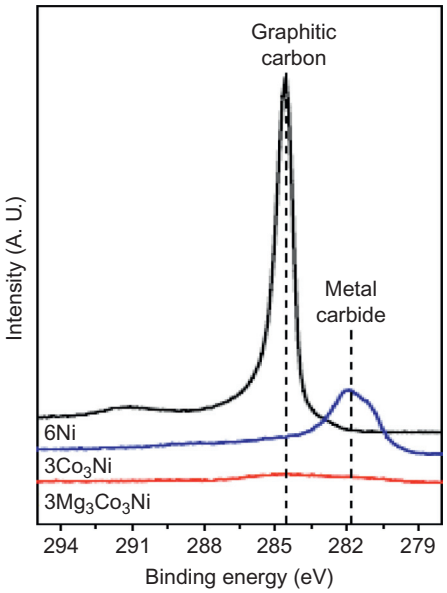


Fig. 5.9
C1s XPS spectra of various spent Ni catalysts.

Koo et al. [59] reported that the addition of the Ce to the $Ni/MgAl_2O_4$ showed excellent coke resistance in both steam and carbon dioxide reforming of methane. They identified the graphitic carbon formed over $10Ni/MgAl_2O_4$ catalyst, when no Ce is added. This illustrates that Ce induced the adsorption and dissociation of H_2O and CO_2 due to its Ce^{4+}/Ce^{3+} redox couple, which supplies active oxygen to remove deposited coke as soon as it is formed. As discussed earlier, the presence of noble metals inhibited the carbon formation, hence neither carbon nanotubes nor nanofibers are observed on noble metal catalysts during dry reforming reaction [60]. Aparicio et al. [61] reported a mechanism of carbon oxidation through participation of surface hydroxyl groups present in Rh/Al_2O_3 catalyst. Carbon oxidation, in addition to the number of interfacial sites, also depends on the diffusion of the hydroxyls from the support to Rh and/or the migration of carbonaceous species from Rh to the hydroxyls on the support. This migration/diffusion helps to keep Rh catalysts free of carbon deposition during DRM [61]. When chloride and nitrate precursors were used for Ru in Ni-Ru bimetallic catalysts supported on SiO_2, significantly higher dispersion was observed with nitrate precursor [62]. Chlorides are expected to block the active sites at the Ni-Ru interface, thus lowering the activity [62,63]. In the case of Rh in 2.5%Rh–2.5%Ni/SiO_2 catalyst, use of nitrogen precursor produced only 5.6 wt% carbon against 36.5 wt% carbon, when chloride precursor was used [64]. Use of nitrate precursor helped in the formation of Ni-Ru or Ni-Rh bimetallic clusters which led to the increased activity as a result of higher

metal dispersion, offering greater resistance to the coke deposition [47]. Koubaissy et al. studied carbon formation on Ni/CeZr and Ni-Rh/CeZr catalyst surfaces. They observed carbon nanotubes on monometallic Ni catalyst and amorphous carbon formation on Ni-Rh bimetallic. This shows that a difference in the morphology of the carbon formed can influence the deactivation [65].

5.3.2 Coke Formation During Heavy Hydrocarbon Conversions

The coke formed during conversion of heavy hydrocarbons in a petroleum refinery process is highly complex to understand. For example, coke deposited during HDS of heavy hydrocarbon residua has been classified into three types [66]:

(i) Type I deposits: These are reversibly adsorbed normal aromatics deposited at low temperatures.
(ii) Type II deposits: Asphaltenes reversibly adsorbed in the initial stages of reaction.
(iii) Type III deposits: These originate due to condensation of large aromatics that crystallize at high temperatures on prolonged reaction time. Severe deactivation occurs due to this hard coke, which requires to be oxidized at high temperatures [66].

5.3.3 Deactivation Due to Deposition of Species Other Than Carbon

During heavy feedstock processing in a petroleum refinery, deactivation due to metal deposition is a major problem. Usually, heavy crudes contain metals like V and Ni in the form of organometallics. If they are not removed before hydrotreating/HDS, the catalysts used in these processes may deactivate due to their deposition on the catalyst surface. It is presumed that the metal complexes break down at higher H_2 pressures, paving the way for metals to react with H_2S thus forming sulfur deposits. These deposits can cover the active site surface or block flow paths in the reactor leading to large pressure drop across the reactor. In the case of FCC catalysts, V can react with acid sites of the zeolite, slowly leading to the destruction of its structure. The Ni present in the feed can also lead to excessive dehydrogenation thus paving the way for coke formation. Investigation of the V and Ni metal concentration profiles in FCC catalyst particles showed homogeneous distribution of V throughout the catalyst particle, while Ni is mostly present at the periphery.

Material of construction of the reactor tube is also very important, as metals can leach out from its walls during the catalytic process. These are mostly iron oxides or chromium oxide, which may deposit on the top layers of the catalyst bed close to the inlet of the reactor. These deposits can cause large pressure drops, if not removed.

5.4 Thermal Degradation and Sintering of the Catalysts

Thermal degradation of the catalysts at reaction temperatures is a serious problem, particularly in the case of supported metal catalysts. Thermal damage of the catalysts can be classified into three categories:

(i) shrinkage of metal surface area due to growth of metal crystallites, which is called sintering of metals;
(ii) loss of surface area of the support due to increase in crystallite/particle size of the support, which may be accompanied by a loss of porosity, and
(iii) change of catalytic phase from active to a nonactive catalytic phase.

5.4.1 Sintering and Redispersion of Metals in Supported Metal Catalysts

Sintering of metals is a physical phenomenon which is thermally activated. Usually sintering is defined as the loss of active surface area via structural modification of the metal crystallites in the catalyst or loss of support surface area due to growth of its crystallite size. The effect of sintering on catalytic activity was reviewed by many authors, particularly with regard to supported metals [67–75]. Sintering occurs in both supported metal catalysts as well as in unsupported catalysts. Many parameters including temperature, type of metal and its melting point, atmosphere under which catalyst is treated, porosity and surface area of the support, presence of promoters/impurities, etc., influence sintering of the metals.

Loss of active metal surface area happens via agglomeration and coalescence of small metal crystallites into larger ones, that leads to lower surface to volume ratio. In the case of structure-sensitive reactions, activity undergoes change with increasing metal crystallite size due to the sintering. The impact of sintering could be very large or moderate. Various types of mechanisms were proposed for sintering of the metals: (i) migration of crystallites, (ii) migration of atoms, (iii) spreading and splitting, and (iv) vapor transport. In the case of crystallite migration, when crystallites are very small, the whole crystal migrates to form thermodynamically stable large crystal. This is more feasible when metal-support interactions are weak and dispersion of metal is not that good. Similar to crystals, atoms can also migrate and coalesce to form crystallites.

Fig. 5.10 depicts crystallite and atomic migration [1]. In the former case, the whole crystallite migrates over the surface of the support and forms large crystallite followed by its collision and coalescence with other crystals. In the case of atomic migration, metal atoms are detached from crystallites and migrate; during this process they are captured by bigger crystals. The latter are more dominant when metal dispersion is very high. Though it is difficult to say which mechanism is operating for a catalyst under particular conditions, it is possible that all mechanisms may be operational simultaneously. Sintering is dominant when the metals are of

low melting point, as the sintering through vapor transport can occur at high temperatures. This path is dominant in the case of supported Pt group metals particularly in oxidizing conditions, as the oxides formed are of low melting point compared to the corresponding metals.

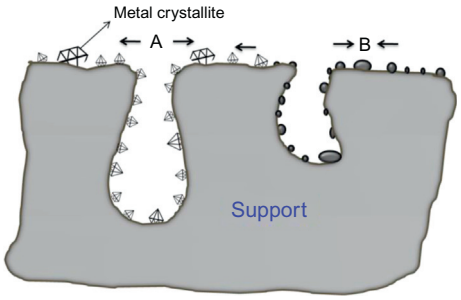


Fig. 5.10
Conceptual model of metal crystallite (A) and atom (B) migration [1].

In case of metal sintering, metal atoms exposed on the surface decrease, causing decrease in the reaction rate. Hence, reactions on metal surfaces have been categorized into surface-sensitive and surface-insensitive reactions. This classification is based on the influence of dispersion on the turnover frequency (TOF). The TOF (number of molecules converted per exposed metal atom per second) is varied in the case of surface-sensitive reactions. Specific surface sites participate in the surface-sensitive reactions, whose concentration in turn depends on the dispersion. When the dispersion is decreased, the number of corner and edge sites also become reduced affecting the TOF. Hydrogenolysis of ethane on a supported Pt catalyst is a good example of structure-sensitive reaction. In the case of structure-insensitive reactions, specific activity is independent of changes in metal crystallite size, that is, sintering has no effect on TOF. Examples of structure-insensitive reactions include CO hydrogenation on supported cobalt, nickel, iron, and ruthenium catalysts [1]. Sintering of metals is proposed to occur in the following ways [76]:

(i) Ostwald ripening, in which migration of metal atoms is accounted as the main reason for the sintering;
(ii) migration of entire crystallites or coalescence is considered to happen, and
(iii) interfacial thermodynamic model, which considers the spreading and splitting of crystallites.

These different mechanisms operate for different metals under different reaction conditions.

Sintering processes are generally accelerated by steam, as it takes place at higher temperature. Because larger crystallites are more stable—for example, metal-metal bond energies are often stronger than metal-support interaction (bond strength 5–15 kJ/mol)—thus smaller

crystallites diminish in size while the size of the larger ones increase. These mechanisms of metal crystallite growth may occur simultaneously and may be coupled with each other through a complex physicochemical process including (1) dissociation and emission of metal atoms, (2) adsorption and trapping of metal atoms, (3) diffusion of metal atoms, metal-containing molecules, and/or metal crystallites across support surfaces, (4) spreading of metal or metal oxide particles, (5) support surface wetting by metal or metal oxide particles, (6) nucleation of metal particles, (7) coalescence, or bridging between, two metal particles, (8) capture of atoms or molecules by metal particles, (9) liquid formation, (10) metal volatilization through volatile compound formation, (11) splitting of crystallites in O_2 atmosphere due to formation of oxides of different specific volume, and (12) metal atom vaporization [1].

Crystallite growth due to sintering of supported metals is a complex and chemical phenomenon, making it difficult to understand its mechanistic aspects. The sintering process mainly depends on the temperature, atmosphere, metal type, metal dispersion, presence of promoters or impurities, surface area of the support, texture, and porosity. Activation energies of sintering depend on the nature of the metal, support, and the gas atmosphere. Metals are known to sinter rapidly in an oxygen and steam environment and relatively slowly in hydrogen. However, it depends on the metal to support interaction and may be related to changes in the surface structure due to adsorbed species such as H, O, or OH in H_2, O_2 or steam-containing atmospheres, respectively. There were several reports [74] that under oxidizing conditions, sintering is higher when compared to reducing conditions at high temperatures as shown in Fig. 5.11. In the case of noble metals, stability in the presence of air decreases in the order Rh > Pt > Ir > Ru. Formation of volatile RuO_4 is attributed to the relative instability of Ru in supported metal catalysts.

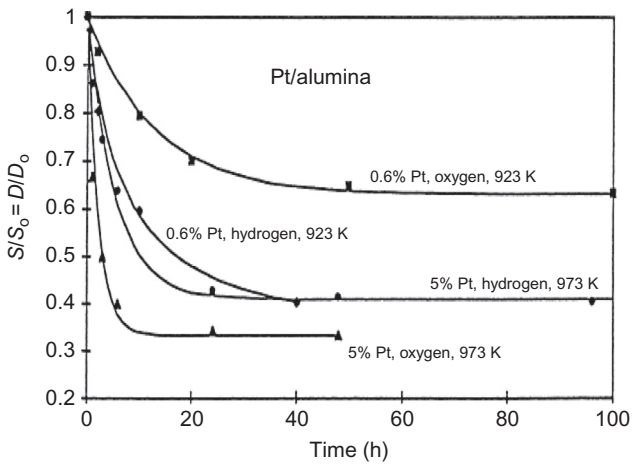


Fig. 5.11

Effect of H_2 and O_2 atmospheres and metal loading on sintering rates of Pt/Al_2O_3 catalysts [74].

The effect of temperature and atmosphere can be seen from Fig. 5.11, as the surface area is reduced almost exponentially in the initial stages of heating, while it slows down later almost becoming linear with time on stream. These data may be consistent with a shift from crystalline migration at low temperatures to atomic migration at high temperatures [77]. As stated earlier, rate of sintering has an exponential relationship with temperature. Activation energy of sintering, E_{act}, varies in the 30–150 kJ/mol range. It decreases with increasing metal loading. It changes with the atmosphere and increases in the order: NO, O_2, H_2, N_2. It was experimentally shown that at temperatures $\geq$650°C, rate of metal surface area loss (based on H_2 chemisorption) as a result of sintering of Ni/SiO_2 in H_2 atmosphere is high. As may be seen from the plot (Fig. 5.12) of normalized dispersion (percentage of metal exposed at any given time divided by the initial percentage exposed) versus time, there is about 70% loss of metal surface area within 50 h of heating at 750°C [77]. It was also reported that stability of metal oxide species changes in different gas atmospheres, if there is strong metal to support interaction. For example, NiO supported on SiO_2 is relatively stable in air compared to H_2 [74].

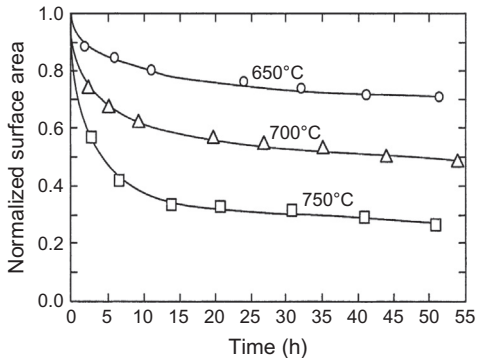


Fig. 5.12

Data of normalized Ni surface area (based on H_2 chemisorption) vs. time during sintering of 13.5% Ni/SiO_2 in H_2 at 650°C, 700°C, and 750°C [77].

Sintering rates are much higher for noble metals in O_2 than in H_2. Similarly, sintering is high for noble and base metals in H_2 relative to N_2 [67,68,72–75]. Thermal stability of a given metal decreases with different supports in the order $Al_2O_3 > SiO_2 >$ carbon. In a reducing atmosphere (H_2), stability of the metal crystallite decreases with decreasing melting point of the metal, which is in the order Ru > Ir > Rh > Pt > Pd > Ni > Cu > Ag. But this order may change if there is metal to support interaction. In oxygen atmosphere, the sintering of Pt group metals follows a different order: Rh > Pt > Ir > Ru, which is related to the vapor pressure of their corresponding oxides. At higher vapor pressures the sintering is rapid. In a reductive atmosphere, sintering takes place through metal species, while metal oxide species participate in an oxidizing atmosphere. Other factors like shape, size of the crystallite [78], roughness of the support [79], and impurities present either in support or metal influence the sintering process. Impurities such as carbon, O_2, Ca, or Ba may decrease the metal atom

mobility. But other impurities like Pb, Bi, Cl, F, or S can enhance the sintering process of the metal and also the catalyst surface. Surface defects and porous nature of the support can hinder the sintering process by affecting the migration of metal particles. Rare earth oxides like CeO_2 and La_2O_3 can hold the noble metal atoms better due to localized chemical interaction between the support and metal as in the case of automotive exhaust converter catalysts [80–82].

The rate of sintering of the metals can be shown to follow a simple power law expression [1].

$$\frac{d(D/D_o)}{dt} = -k_s(D/D_o)^n \tag{5.8}$$

where k_s is the sintering rate constant, D and D_o are dispersion at time t and initial dispersion, respectively, while n is the sintering order which is in the range of 3–15 for typical catalyst systems. This general power law expression is not valid for the sintering process as this expression implies zero value at t_∞. But, in general, the rate of sintering slows down and a finite value of dispersion (D_{eq}) is observed after a particular time. Hence, a generalized power law expression was proposed:

$$\frac{d(D/D_o)}{dt} = -k_s\left(D/D_o - D_{eq}/D_o\right)^m \tag{5.9}$$

The term $-D_{eq}/D_o$ accounts for the observed asymptotic approach of the typical dispersion versus time curve to a limiting dispersion D_{eq} at infinite time (see Fig. 5.11) while n varies from 1 to 2. For example, rate constant for Ni on alumina ($k_s = 0.083$) is less than Pt on alumina ($k_s = 0.76$) at 650°C under H_2 atmosphere [83,84]. Hence, rate of sintering is lower in the case of nickel/alumina catalyst, because of the lower heat of vaporization of Ni. Also, these results are attributed to strong metal to support interaction between Ni and alumina.

SR reaction is highly endothermic and hence limited by heat transfer. Generally, nickel-based catalyst is used for this reaction. At high reaction temperatures, Ni crystals rapidly sinter above Tamman temperature (863 K for Ni) and the catalytic activity varies with nickel surface area. To prevent Ni sintering, metal to support interaction plays an important role. It was reported that modified vermiculite-supported Ni catalysts showed good thermal stability in simultaneous oxidative conversion and CO_2 reforming of methane to produce syngas [84].

5.4.2 Sintering and Thermal Degradation of Support

In addition to metal sintering, loss of surface area of the support due to sintering also contributes significantly to the rapid deactivation of the catalysts. When the support sinters, the supported metal particles come closer to form larger crystallites. Moreover, as a result of sintering of the support, the nature of the surface changes, leading to a change in the metal to support interaction. It is also possible that during sintering of the support, small metal particles are trapped inside the pores of the support thus affecting their accessibility to the reactants.

Sintering of catalyst has been dealt with by Baker et al. and Trimm [67,85]. Supports can sinter through one or a combination of the following processes: (i) surface diffusion, (ii) solid-state diffusion, (iii) evaporation/condensation of volatile atoms/molecules, (iv) diffusion of grain boundaries, and (v) phase transformation.

Silica and γ-Al_2O_3, being stable oxides are stable in oxidizing conditions, whereas carbon is stable only in reducing conditions. Thermal properties of a support material may get affected if it has impurities, as the impurities may occupy the defect sites or may form new phases. In addition, supports can also undergo thermal change/damage making them less effective as supports. For example, metal may react with the support to form a structured inactive compound as is the case with Ni on Al_2O_3, which forms spinel on heating at high temperatures. Presence of alkali metals may accelerate sintering, while calcium, barium, nickel, and lanthanum form thermally stable structured oxides such as spinels or perovskites.
Steam accelerates sintering of support by generation of mobile surface hydroxides [$Si(OH)_2$], which are volatized at higher temperatures to form larger particles. This type of surface hydroxides are formed during SRM [68]. It is also possible that a phase change of the support occurs on heating; for example, γ-Al_2O_3 to α-Al_2O_3. It is also reported that presence of chlorine promotes sintering and grain growth in MgO, TiO_2 during high-temperature calcination as shown in Fig. 5.13 [86]. On the other hand, sulfuric acid treatment of hydrated alumina (gibbsite) followed by two-step calcination, results in a very stable transitional alumina with needle-like particle morphology [85].

Highly dispersed metals on the support can also accelerate sintering of support, as nickel accelerates the loss of Al_2O_3 surface area in Ni/Al_2O_3 catalysts. Last but not least, reaction of support with reactants should be avoided. For example, Al_2O_3 is not used as a support in selective catalytic reduction (SCR) catalysts as it reacts with SO_3 present in the exhaust gas.

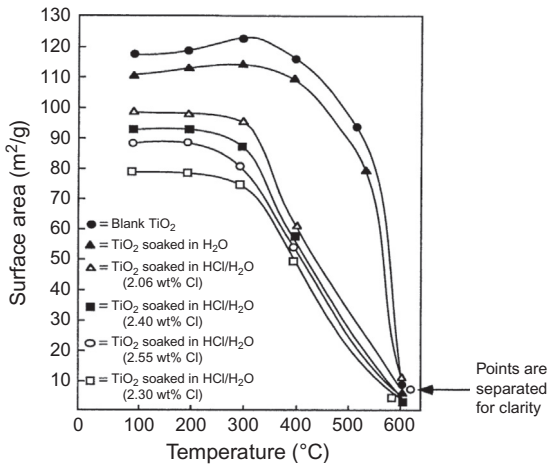


Fig. 5.13

BET surface area of titania as a function of thermal treatment and chlorine content of fresh samples (before pretreatment). Samples were treated at different temperatures for 2 h [86].

5.4.3 Effect of Metal and Support Sintering on Catalytic Activity

Effect of sintering on catalytic activity was reviewed by Baker et al. and Bartholomew et al. [14,67]. If the reaction is structure sensitive, specific activity can either increase or decrease with increasing crystallite size due to sintering. Hence, for a structure-sensitive reaction, the impact on activity either is very high or moderate. On the other hand, for a structure-insensitive reaction, sintering may show no change in specific activity (per unit surface area). In case of structure-insensitive reaction, the decrease in mass-based activity is proportional to the decrease in metal surface area. Hydrogenolysis of ethane and SR of ethane are structure sensitive, while hydrogenation of CO on supported cobalt, nickel, iron, and ruthenium catalysts is structure insensitive [1].

5.4.4 Poisoning

Poisoning is the loss of catalyst activity when strong chemisorption of impurity occurs on the active sites. These impurities may be present in the feed stream. However, sometimes the product or byproduct formed also acts as a poison. Poisoning by impurity depends on its adsorption strength relative to the reactant competing for the same catalytic sites. The higher the strength of adsorption, the stronger the poisoning effect.

Catalytic poisons are very specific; a poison for one reaction need not be a poison for another reaction. For example, CO is a poison for Pt anode catalysts of PEMFC (polymer electrolyte membrane fuel cell), while it is a fuel for SOFC (solid oxide fuel cell) anodes, where the Ni catalysts at very high temperatures are used. Similarly CO is poison in ammonia synthesis (for reduced iron catalyst), while it is a reactant in Fischer Tropsch synthesis, where iron oxide is a catalyst. Catalytic poisons may be classified based on their selectivity for active sites, the kind of reactions poisoned by them and their chemical nature. Table 5.3 provides information on how various types of catalysts are poisoned.

Table 5.3 Typical poisons for different types of catalysts

Catalyst	Active Species	Reaction	Poison	Mode of Poisoning
Zeolites	Acid	Cracking	Basic molecules Heavy metals; V, Ni	Neutralization of acidity Destruction of zeolite, coking
Transition metals	Metal	Hydrogenation/ dehydrogenation	S, P, As, Hg, Pb	Chemisorption
Nickel	Metal	Steam reforming	H_2S, As	Chemisorption
Silver	Metal	Ethylene oxidation	Acetylene	Fouling by coke
Vanadium oxide	Oxide	Oxidation	As	Mixed oxide phase
Co-Mo-Al_2O_3	Sulfide	HDS	Asphaltenes, N-compounds	Metal deposits, fouling

A poison may simply block the active site by geometric effect or change the adsorption property of other species by electronic effect. For example, adsorption of a basic compound onto an acid catalyst (isomerization catalyst) affects its performance. Similarly, oxygen is a poison in the hydrogenation of ethylene on nickel catalysts. The catalytic performance is changed when the chemical nature of the active sites is changed due to formation of a new compound. Many catalysts are deactivated by poisonous compounds like alkali metals, heavy metals, arsenic, phosphorous, iron, sulfur, and chlorides which exist in the form of submicrometer-size particles. These poisons penetrate the catalyst by capillary condensation of poison in the pores or by the diffusion of the gaseous poisons. Nickel and platinum catalysts are highly sensitive to sulfur poisoning; hence in commercial processes, particularly in petroleum and chemical processes, sulfur levels are brought down to less than 0.5 ppm.

According to the type of interaction with metals and their chemical origin, poisons are classified into four groups as given in Table 5.4.

Table 5.4 Common poisons classified according to their chemical structure [1]

Chemical Type	Examples	Type of Interaction With Metals
Groups VA and VIA	N, P, As, Sb, O, S, Se, Te	Through s- and p-orbitals, shielded structures are less toxic
Groups VIIA	F, Cl, Br, I	Through s- and p-orbitals, formation of volatile halides
Toxic heavy metals and ions	As, Pb, Hg, Bi, Sn, Zn, Cd, Cu, Fe	Occupy d-orbitals, may also form alloys
Molecules which adsorb with multiple bonds	CO, NO, HCN, benzene, acetylene, other unsaturated hydrocarbons	Chemisorption through multiple bonds and back bonding

The effect of poisoning depends on the concentration of poison in the feed stream which is an important parameter during practical operation. The interaction of catalytic metal with Group VA–VIIIA elements depends on the number of electron pairs available for bonding and the degree of shielding of the sulfur ion by the ligands [1,87]. Hence, the order of decreasing toxicity for poisoning of a metal by different sulfur species is H_2S, SO_2, SO_4^{2-}; that is, in the order of increased shielding by oxygen. Increasing atomic or molecular size and electronegativity enhance the toxicity for poisoning of a given metal, whereas the effect of toxicity will be lower for poisoning of a given metal, if the poison can be gasified by O_2, H_2O, or H_2, if they are present in the reactant stream [88].

5.4.4.1 Types of poisoning

In principle, poisoning can be classified into three types: (i) selective, (ii) nonselective, and (iii) antiselective poisoning. This classification is based on the relationship between loss in catalytic activity and the concentration of the poison in the feed or the relative surface coverage by the poison (Fig. 5.14).

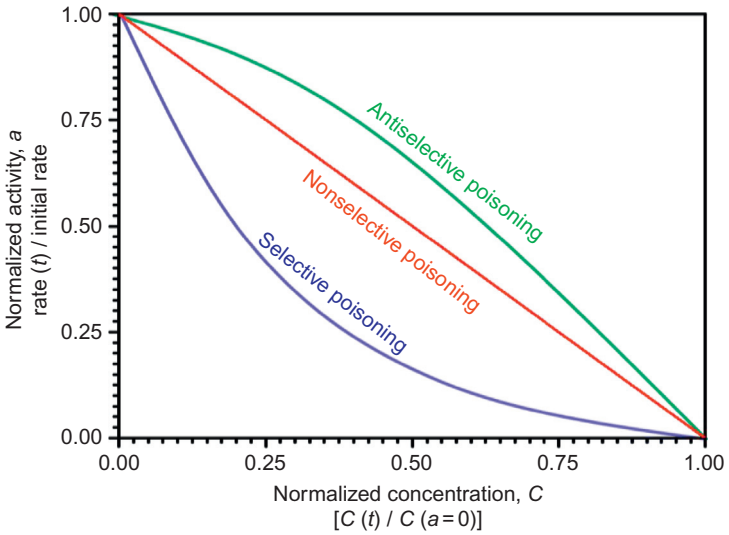


Fig. 5.14
Effect of poisoning in terms of normalized activity vs. normalized poison concentration. *Courtesy: Kluwer Academic Publishers.*

5.4.4.1.1 Selective poisoning

Selective poisoning occurs when the catalytic activity drops rapidly in the initial stages of the reaction along with increasing surface coverage by the poison, while the deactivation rate tempers down at higher coverage by poison. This shows that the poison is adsorbed preferably on more active sites (eg, CO poisoning at low temperature on Pt surface) [89]. This type of poisoning occurs when the catalyst has active centers of different strength or they may be heterogeneously distributed. For example, in the case of metal catalysts, the small number of metal atoms present at the corners and edges of crystallites are more active and contribute more to the overall catalytic activity than the other surface atoms. Hence, these metal atoms are poisoned in the beginning of poisoning process causing a rapid drop in initial catalytic activity even at low surface coverages by the poison. In the case of acid catalysts like silica-alumina and zeolites, as they generally possess sites with a heterogeneous distribution of acid strength, poisoning by basic components can lead to selective poisoning. Selective poisoning can also occur when the reaction takes place in a shell or particle envelope or when diffusion effects are predominant.

5.4.4.1.2 Nonselective poisoning

Nonselective poisoning occurs when the fall in catalytic activity is directly proportional to the amount of poison on the catalyst. This type of poisoning occurs when all the catalytic sites are equal in strength; for example, poisoning of Pt by As in the hydrogenation of cyclopropane [90]. This usually happens in the case of facile reactions such as hydrogenation

of cyclopropane over highly active hydrogenation catalysts like Pt. Moreover, the chemisorption of As is strong; hence it may not discriminate between strong and weak adsorption sites.

5.4.4.1.3 Antiselective poisoning

In "antiselective" poisoning, initially lesser active sites are blocked. As a result, initial loss in catalytic activity is less pronounced, and the loss becomes more pronounced with increasing surface coverage by the poison. Poisoning by Pb during CO oxidation is a good example [91]. Antiselective poisoning may also happen when the reaction takes place over multiple sites and a critical number of sites need to be blocked before the concentration of the multiple active centers decreases rapidly. There may be situations in metal catalysis when the poison preferentially adsorbs on the less active crystal planes leaving the more active ones unaffected. Another situation that can lead to antiselective poisoning is when the poison influences the activity of the metal catalytic site electronically by filling the partially empty bands, and a critical amount of filling is necessary before the activity is substantially reduced.

5.5 Loss of Catalytic Phase Due to Evaporation

A catalytic metal may directly evaporate, though it is uncommon as most of the metals vaporize at temperatures higher than 1273 K. But catalytic phases can be lost through reaction with one of the reactants, like forming corresponding oxides which have lower melting points. For example, loss of Ni as Ni-carbonyl has been reported in reactions involving Ni catalysts and CO as reactant under reducing conditions. In case of oxidation of NH_3 to NO using Rh-Pt gauze as the catalyst, loss of Pt occurs due to its loss in the form of platinum oxide. On the other hand, addition of Rh reduces the Pt loss and also it promotes surface restructuring. Similarly, during the aromatization of small alkanes to yield aromatics, loss of Zn was observed when the reaction was carried out over Zno-ZSM-5. Various classes of compounds that have high probability of volatility are listed in Table 5.5.

Table 5.5 Examples of volatile compounds formed by combining with one of the reactants

Gaseous Environment	Likely Compound	Example of Compound	Temperature of Formation (K)
CO, NO	Carbonyls, nitrosyl carbonyls	$Ni(CO)_4$, $Fe(CO)_5$	0–573
Oxygen	Oxides	RuO_3	298
		PbO	>1123
H_2S	Sulfides	MOS_2	>823
Cl, F, and B	Halides	$PtCl_4$, PtF_6, and $PdBr_2$	–

However, there is paucity of information on the formation of the compounds in Table 5.5. Bartholomew found evidence for around 50% Ru loss while testing of Pd-Ru as automobile exhaust catalyst for 100 h [92]. This loss was attributed to the formation of Ru-oxide, which led to loss of NO reduction activity of the catalyst. Similarly, it was reported that Ni/Al_2O_3 catalyst deactivated during methanation of CO at high partial pressure (>20 kPa), though the temperature (~673 K) was not that high, mostly due to the loss on Ni in the form of $Ni(CO)_4$. Agnelli et al. carried out kinetic modeling of the formation and migration of $Ni(CO)_4$ [93]. They have reported that initial sharp crystallite size distribution evolved during several hours of sintering at low reaction temperatures (500 K) to a bimodal system consisting of small spherical crystallites having large faceted crystals with (111) planes. The sintering process was modeled on the lines of Ostwald ripening involving mass transport of mobile subcarbonyl intermediates. Based on their investigations, they have proposed two solutions for controlling the loss of Ni: (i) increasing reaction temperature and decreasing CO partial pressure to reduce the $Ni(CO)_4$ formation, and (ii) change of catalyst composition in such a way to alloy Ni with Cu or addition of alkali metal to temper the carbonyl migration.

In case of Ru supported on NaY and Al_2O_3 catalysts, for carrying out hydrogenation of CO to methane, Goodwin and coworker studied the effect of atmosphere, support and metal particle size on the loss of Ru due to carbonyl formation [94,95]. They have observed significant loss of Ru in both the systems. Titania-supported Ru did not show significant loss of Ru, but the loss was further reduced if the catalyst contains large metal crystallites (>3 nm). The lower rate of Ru loss for the catalysts containing larger crystallites may be attributed to lower surface energy (higher average coordination number of surface atoms) of larger crystallites. Thus a generalized mechanism of deactivation due to the formation and evaporation of volatile metal compounds may be depicted as in Fig. 5.15.

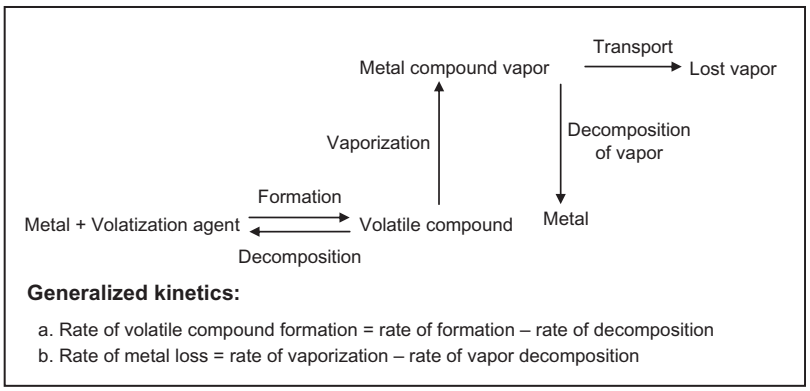


Fig. 5.15
Generalized volatilization mechanism of deactivation involving metal catalysts.

5.6 Attrition and Mechanical Failure

A catalytic process, in addition to chemical reasons, may be affected by mechanical issues. The mechanical failures can be caused due to (i) crushing of catalyst pellets, granules, or even monoliths as a result of heavy load on their top, (ii) breakup of catalyst pellets followed by its attrition, (iii) erosion of catalyst particles or monolith coating in automotive catalysts at high exhaust flows. In the case of moving or fluidized beds, erosion can become a serious problem. It is known that tolerance to high attrition is an essential feature of FCC catalysts, as the catalyst granules are continuously recirculated between the reactor and regenerator a few hundred times in a day. As a rule of thumb, there should not be more than 1 wt% loss of the catalyst per day due to attrition. Similarly, attrition can be a severe problem in slurry bubble column reactors used for the FT synthesis. Fines generated due to attrition can also impart color to the product, as could be the case during hydrogenation of vegetable oils. Attrition can be easily observed using an electron microscope by inspecting the catalyst particles for its rounding or smoothing off. Attrition rate can be measured by methods such as ultrasonic and jet cup test systems (see Chapter 2 in Ref. [96]).

Loss of wash-coated material on a monolith catalyst may occur by erosion, during their application as catalysts for SCR of NOx due to very high flow of flue gas and fly ash. Erosion of wash coat also can be observed either by using optical or electron microscope, and its extent can be estimated by loss in weight of the monolith. Catalyst pellets may be crushed due to heavy load present on their top. One of the reasons for a large pressure drop could be attributed to the plugging of flow paths by powder that came out of the catalyst, in addition to the blockage by the carbon formed. During mechanical failure of the catalysts, initially the catalyst tablet is fractured into smaller particle agglomerates which further breaks into much smaller particles or powder due to erosion/abrasion.

Erosion may be caused by mechanical stresses, fracture may be due to thermal, mechanical, and/or chemical stresses. During SR and steam cracking, catalysts are affected by mechanical failure as a consequence of growth of carbonaceous material inside the pellets. Ring tablets of iron molybdate used in the oxidation of methanol to formaldehyde are known to undergo mechanical failure (breakup) due to the formation of iron and molybdenum oxide phases. In the case of FCC, during attrition the more valuable zeolite component, which is responsible for acid activity, may preferentially be lost due to attrition. On the other hand, if the fluidized particles are too hard, they may damage the internal walls of the reactor due to abrasion.

5.7 Prevention of Catalyst Deactivation

As discussed in Section 5.1, catalysts are required to be nondeactivating to continue the process till the industry desires or at least they should not deactivate in a short time span. Though in principle it is possible to regenerate the deactivated catalysts by removing the coke or poison by

washing with a solvent and/or by burning in oxygen, it is not possible to shut down the operations frequently as it affects productivity. Sometimes, it is not possible to get back the entire activity, which may affect the catalyst performance after some regenerations. Hence, it is always the aim of any catalyst development to lengthen the good activity period as much as possible without any regeneration. This will be possible, only if reasons of deactivation can be diagnosed. Some typical reasons for deactivation and solutions for the deactivation are given in Table 5.6.

Table 5.6 Methods of prevention of catalyst deactivation

Basic Mechanism	Cause	How to Minimize
Poisoning	Blockage of sites by strong adsorption of impurity	Purification of feed; adding guard chamber; additives to be added to selectively adsorb poison; varying reaction conditions; change in mass transfer regime to minimize loss of activity
Fouling by coke or carbon	Free radical reactions in gas phase	Prevent formation of free radicals, minimize free space; lower temperature; use of free radical traps, flush with gasifying agents (eg, H_2, H_2O)
	Free radical reactions at reactor walls	Coat reactor with inert material
	Formation and growth on metal surfaces	Avoid coke precursors (eg, alkenes, aromatics); addition of gasifying agents (eg, H_2, H_2O), promote catalyst with additives to increase rate of gasification or to change ensemble size; passivate metal surfaces with sulfur; control the dispersion
	Formation and growth on metal oxides, sulfides	Decrease acidity of oxide or sulfide; avoid coke precursors in feed; use shape-selective zeolites; operate at lower temperature
	Formation of gas phase coke, vermicular carbons and liquid or solid coke in high quantities; hot spots in pellet or bed	Minimize formation of free radicals or coke precursors as described; use of gasifying agents; incorporate catalyst additives, which lowers solubility of carbon in metal or change ensemble size; use supports with large pores Use wash coat on monoliths or small pellets; use slurry or fluidized bed reactor, use gas as diluents
Sintering	Metal particle or subparticle migration	Lower reaction temperature; use thermal stabilizers; avoid water and other substances that facilitate metal migration
	Crystallization and/or structural modification or collapse of structure	Lower the reaction temperature; use support stabilizers; avoid water and other substances like Cl_2 that facilitate migration of species originating from the support

Poisoning is a major reason for deactivation of supported metal catalysts such as Pt-Al_2O_3 used in the naphtha reforming process of a petroleum refinery. Usually, the presence of sulfur compounds in the naphtha feed can affect the catalyst performance; hence it is removed to below 1 ppm before it is sent for processing in the reformer. Similarly, in the case of SR, water gas shift reaction and methanation of CO reactions, a promoted ZnO is used as guard bed to remove even traces of sulfur. Additives that selectively passivate or react with the poisons are

used with FCC catalysts. Nickel present in the FCC feed is passivated with Sb- or Bi-containing additives, while vanadium is neutralized by Sn-containing additives.

Carbon formation or coking is a major problem with most of the high-temperature catalytic processes. Though it is not possible to completely avoid coking, it can be minimized by decreasing the coke precursors such as presence of olefins in the reactant stream and high boiling aromatics. Coke deposition is also reported to be reduced by using bimetallic catalysts or metal promoters like Re and Ir to Pt catalysts. Metal promoters are also known to reduce the sintering of metals like Pt. In addition, coke formation is also reduced on small ensembles of metal particles. Presence of chloride ions on the support in case of naphtha reforming catalysts is known to decrease sintering of Pt. Because moisture in the reactant stream can wash out the chloride ions from the support and enhance the sintering of the support, it has to be completely removed from the input stream. But, in the case of reforming catalysts, a small concentration of water (20–40 ppm) is deliberately kept to maintain the desired Brønsted acidity of the catalysts.

5.8 Regeneration of the Deactivated Catalysts

In an industrial catalytic process, if the performance of a catalyst falls below minimum required level, it is difficult to sustain the process due to economic reasons. Hence, the process is halted and the catalyst is either regenerated or discarded, if it is not possible to regenerate. If the cost of the catalyst is lower than regeneration cost, then a fresh catalyst is loaded. The decision to discard or regenerate the catalyst will depend on the value of the catalyst, feasibility of recovering valuable components like noble metals, facilities for external regeneration of the catalyst, the time required to regenerate and reload the catalyst, and the effect of plant shutdown time on downstream or upstream processes. At the end of the day, it is the economic feasibility that counts. When the catalyst deactivates quite rapidly as in the case of FCC, moving fluidized bed or swing reactor systems are used, so that catalyst is continuously regenerated. The deactivated catalysts may be regenerated in many ways as shown in Table 5.7.

Table 5.7 Regeneration procedures for some representative deactivated catalysts

Cause of Deactivation	Regeneration Procedure
Poisoning	Sulfur-poisoned noble metal catalysts can be treated in H_2 at suitable temperature. Alternately, sulfur can be oxidized carefully. For base metals, oxidation may not be recommended as metal sulfates may be formed.
Fouling	Catalyst fouled due to coke can be regenerated by burning in carefully controlled O_2 atmosphere and appropriate temperature. This process should be carried out carefully to avoid high local temperatures that will damage the catalyst.
	Metal deposits on the surface layers of the bed may be skimmed off or the top few layers of the catalyst bed may be replaced.
Sintering	Sintered noble metals, as in the case of reforming catalysts, may be regenerated by oxy-chlorination procedure.

As given in Table 5.7, if metals are inadvertently poisoned by sulfur or nitrogen compounds, the catalysts may be regenerated by flushing in H_2 at a suitable temperature. In case of heavy coke formation, passing a suitable gas through the catalyst bed may remove most of the carbonaceous material. If the traces of coke are still remaining or coke could not be removed by flushing with solvent, it may be burned off carefully in controlled dilute oxygen flow. This controlled regeneration in dilute oxygen is preferred to avoid temperature excursions that may permanently damage the catalyst. However, it should be noted that regeneration is possible, only if the deactivation is caused by reversible causes such as poisoning, coking, and sintering (only sometimes it is reversible). Redispersion of Pt in sintered Pt/Al_2O_3 reforming catalyst can be accomplished by injecting chlorine compounds along with the N_2-O_2 gas mixture used for burning off the coke. The added chlorine reacts with the surface Pt oxide to form Pt-Cl-O complex that is well distributed on the surface of the support, which can form finely dispersed Pt metal particles on reduction.

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CHAPTER 6

Selection of Reaction Media

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6.1 Introduction

Solvents are compounds that are generally liquid at room temperature and atmospheric pressure; they are able to dissolve other substances without chemically changing them. The liquid mixture formed on dissolving a substance (*solute*) in a solvent is termed a *solution*. The molecules of the solution components interact with one another. Solutions are obtained by mixing liquid, solid, or gaseous components with liquids, the liquid always being termed the solvent. When two liquid components are combined, it is arbitrary which of the two components is considered to be the solvent and which the solute; the liquid component present in excess is usually termed the solvent. The production of chemicals is known for its high consumption of raw materials, especially solvents [1]. The amounts of waste produced can range from 25 to over 100 kg of waste per kg of product [2]. Compared to other industries, solvent recycling is not a common practice. While recycling is seen as viable from those outside the industry, less than 50% of solvent is reused and recycled [1]. Solvents are the source of about 40% of the anthropogenic volatile organic contents (VOCs) entering the atmosphere. Removal of residual solvent from products is usually achieved by evaporation or distillation and most popular solvents are, therefore, highly volatile. Spillage and evaporation inevitably leads to atmospheric pollution, a major environmental issue of global proportions. Moreover, worker exposure to VOCs is a serious health issue. Many chlorinated hydrocarbon solvents have already been banned or are likely to be in the near future. Unfortunately, many of these solvents are regularly used because of their desirable properties and are, therefore, widely popular for performing organic reactions. Another class of solvents which presents environmental problems comprises the polar aprotic solvents, such as dimethylformamide and dimethyl sulfoxide, that are the solvents of choice for many nucleophilic substitutions, for example. They are high boiling and not easily removed by distillation. They are also water miscible which enables their separation by washing with water. Unfortunately, this inevitably leads to contaminated aqueous effluent.

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These major concerns over VOCs and other emissions are motivating chemists to recycle solvents, reduce solvent use, or switch to solvents with better environmental profiles. A strong evolutionary path is being developed for replacement of conventional solvents which are environmentally suitable. Currently, solvent replacement is driven by regulations implemented to protect our environment and health. And one of the most important topics in this area is to find a suitable material that can act as an alternative solvent to the conventional one.

In the context of green chemistry, several issues influence the choice of solvent. It should be relatively nontoxic and relatively nonhazardous; for example, not inflammable or corrosive. One of the 12 principles of green chemistry is prevention: It is better to prevent waste than to treat or clean up waste after it is formed. In the past decade, many innovative solvent systems have been developed, such as supercritical fluids (SCFs), ionic liquids, water, and polyethylene glycol. Water is often described as Nature's solvent. It is already used quite widely on an industrial scale, particularly in emulsion polymerization processes and hydrodistillations. SCFs have fascinated chemists and over the last 30 years this interest has been accelerated. The most useful SCFs to green chemists are water and carbon dioxide, which are renewable and nonflammable. Under these conditions, their properties are significantly altered and unusual chemistry can result. Ionic liquids have many properties that have led to their use as reaction media and in materials processing. They have no (or exceedingly low) vapor pressure, so volatile organic reaction products can be separated easily by distillation or under vacuum. They are thermally stable and can be used over a wide temperature range compared with conventional solvents, and their properties can be readily adjusted by varying the anion and cation. Although these solvents are very successful, new solvents are still needed because a universal green solvent does not yet exist. Especially, with recent emphasis on the sustainability and eco-compatibility of the green solvents, bio-based solvents have been recognized as a next generation of alternative solvents to the conventional petroleum-based ones. Because bio-based solvents are normally derived from agricultural crops, such as corns, soybeans, citrus fruit skins or tree barks, some of their most significant advantages are that they have low toxicity, high biodegradability, lower VOCs are released, and less pollution is generated during the manufacture of the product than for a petroleum-based product. In addition, the product or the process developed by using bio-based solvents sometimes has many other advantages, such as reduced disposal costs, improved worker safety, and the ability to market "green consumerism." All these properties have effectively motivated chemists to work on this topic. And until now, many bio-based chemicals have been proposed as green solvents including glycerol, D-limonene, 2-methyltetrahydrofuran, gluconic acid aqueous solution, aqueous solutions of carbohydrates, ethyl lactate, γ-valerolactone (GVL), and others. A part of these bio-based solvents has also attracted some interest from industries. However, at this moment, diversity and versatility of bio-based solvents are far from abundant. This strictly restricts the applications of bio-based solvents. There is no doubt that bio-based solvents will play an important role in the near future.

6.1.1 Classification of Solvents

Classification of solvents can be done by one of four basic methods: by solvent power (solubility properties/parameters), evaporation rate/boiling point, chemical structure, and hazard classification. Further, they can be classified on the basis of physical hazard (eg, flash point), labeling classification, toxicity, etc. At a practical level, solvents can be classified according to intermolecular forces between solvent molecules: polar (dipole-dipole) and hydrogen bonding.

6.1.2 Solvent Properties

A good industrial solvent generally requires the following basic properties:

1. Clear and colorless
2. Volatile without leaving a residue
3. Good long-term resistance to chemicals
4. Neutral reaction
5. Slight or pleasant smell
6. Anhydrous
7. Constant physical properties according to the manufacturers' specification
8. Low toxicity
9. Biologically degradable
10. As inexpensive as possible

6.1.3 Available Tools for the Solvent Selection

Solvents are some of the most important classes of chemicals throughout society and the chemical industry. Solvents are used in a wide variety of processing steps and also for chemical transformations in many industrial sectors. For thousands of years solvents have been regularly used in separations and extraction procedures as well as cleaning solutions. When selecting a solvent for one of these widely varied applications, one needs to choose based on the properties required for a particular application. These can be the following mentioned properties.

6.1.3.1 Solubility

The solubility of solute (substance) in the solvent mainly depends on the following factors.

6.1.3.1.1 Intermolecular forces

A substance is generally readily soluble in a solvent if the forces of attraction in the pure substance are of the same order of magnitude as the forces of attraction in the pure solvent. A substance is generally insoluble in a solvent if the forces of attraction between its molecules are significantly higher or lower than in the pure solvent. In this case more energy is

required to overcome the forces of attraction in the pure components than is released on formation of the solution. This is the explanation of the rule of thumb "Like dissolves like." The intermolecular forces of attraction differ: They are strongest in crystalline solids, weaker in amorphous solids and liquids, and weakest in gases [3].

6.1.3.1.2 Ionic (Coulomb) forces

Forces of attraction between ions of opposite charge are termed ionic or Coulomb forces. Coulomb forces are responsible for the stability of ionic crystals (eg, NaCl). When such a compound is dissolved in a polar solvent, dissociation and simultaneous salvation of the ions occur.

6.1.3.1.3 Dipole-dipole forces

Dipole-dipole forces are forces of attraction between molecules with a finite, permanent overall dipole moment. The distance between the dipoles depends largely on the position of the poles in the molecule [4].

6.1.3.1.4 Dispersion (London-van der Waals) forces

Dispersion forces are formed by mutual induction of atomic dipoles due to the electromagnetic field between the nucleus and electrons of the atom [5].

6.1.3.1.5 Hydrogen bonds

Substance possessing hydroxyl or amino groups shows the hydrogen bonding (eg, water, alcohols, acids, glycols, and amines). These molecules act as hydrogen donors and thus form a bond with hydrogen acceptors (eg, esters and ketones). Water, alcohols, and amines act both as hydrogen donors and acceptors. Very weak hydrogen bonds also exist in halogens and sulfur. Hydrogen bonds are highly dependent on the mutual orientation of the molecules and thus on the temperature [6,7].

The strengths of hydrogen bonds in solvents have been divided into three classes [8].

1. Solvents with weak hydrogen bonding (hydrocarbons, chlorinated hydrocarbons, nitro compounds, nitriles)
2. Solvents with moderately strong hydrogen bonding (ketones, esters, ethers, aniline)
3. Solvents with strong hydrogen bonding (alcohols, carboxylic acids, pyridine, water, glycols, amines)

Solvents that undergo hydrogen bonding may act as proton donors or acceptors [9].

1. Proton donors (eg, trichloromethane).
2. Proton acceptors (eg, ketones, esters, ethers, aromatic hydrocarbons).
3. Combined proton donors and acceptors (eg, alcohols, carboxylic acids, primary and secondary amines, water).

4. No hydrogen bonding (eg, aliphatic hydrocarbons). No hydrogen bonds exist in solvent mixtures comprising solely proton acceptors; hydrogen bonds are only formed in the presence of a proton donor and result in an increase in miscibility [9,10].

6.1.3.1.6 Thermodynamic principles

Forces of attraction act between the molecules of the pure components and between the different molecules in the solution. If the forces of attraction in the solution are greater than those in the pure components, dissolution is accompanied by a decrease in the internal energy of the system. The process is exothermic and heat is released. If, however, the forces of attraction between the molecules of the pure components are greater than those in the solution, the internal energy of the system is increased with absorption of heat. Most dissolution processes are endothermic and are thus promoted by a temperature increase: The solubility has a positive temperature coefficient. Exothermic dissolution processes have a negative temperature coefficient (ie, the solubility decreases with rising temperature).

6.1.3.2 Dipole moment, polarity, and polarizability

Solvents are often subdivided according to their polarity, that is, polar and nonpolar solvents in order to describe their suitable properties. The term *polarity* includes various parameters such as dipole moment, polarizability, hydrogen bonding, entropy, and enthalpy. Highly symmetrical molecules (eg, tetrachloromethane and benzene) accordingly have no dipole moment; other aromatic hydrocarbons and dioxane exhibit very small dipole moment. Less symmetrical molecules with strong bond dipoles have dipole moments between 1.6 and 1.9 D (alcohols, esters, and glycol ethers); glycols and ketones have higher values (2.3–2.9 D). The solvents with the largest dipole moments (3.7–5.0 D) are ethylene carbonate, nitropropane, dimethylformamide, and dimethyl sulfoxide. The dissolution behavior of a solvent cannot be predicted solely on the basis of its dipole moment. For example, dioxane ($\mu = 0.4$ D) is a very good solvent and has a comparable solvency to dimethyl sulfoxide ($\mu = 4.0$ D). Dipole-dipole and induction forces in solvents or solutions decrease with increasing molecular mass of the solvent [11]. Since this effect is not reflected in the dipole moment of the solvent, a polarizability parameter is used to describe the dipole-dipole interaction forces [12]. This parameter can be calculated from the ionization potential, polarizability, and dipole moment [13]. The greater the polarizability, the stronger are the dipoles induced by an external electromagnetic field; the magnitude of the polarizability and strength of the dispersion forces are thus related to one another [13–15].

However, just as one needs to select from these properties in order to meet certain performance criteria, green chemistry would suggest that reduced hazard is equally a performance criterion that needs to be met in the selection of a solvent. Some of the types of hazard that are common with a wide range of widely used solvents include the following:

- Inherent toxicity
- Flammability

- Explosivity
- Stratospheric ozone depletion
- Atmospheric ozone production
- Global warming potential

Just as one needs to optimize the classical physicochemical property balance to select the proper solvent for a specified application, one also needs to optimize the selection or design of a new solvent or solvent system to meet the criteria of hazard reduction.

6.1.3.3 Computation-based solvent selection

Over the last few decades, the computer-aided molecular design (CAMD) method has been widely used for solvent screening and design [16–21]. The CAMD studies are mainly focused on solvents for separation processes, most importantly for extraction, distillation and crystallization. Marquardt and coworkers developed a hybrid-based model and data-driven framework for the screening of promising solvents to optimize reaction rates [22]. The framework consists of two sequences such as identification of model to predict solvent effects on reaction rate constants from experimental data and computer-aided screening exploring a databank of solvents. The results obtained from framework were in good agreement with experimental data. Wang and Achenie presented a hybrid global optimization approach for solving solvent design problems modeled by mixed integer nonlinear programming [23,24]. Gebreslassie and Diwekar proposed a novel CAMD methodology for the design of optimal solvents based on an efficient ant colony optimization algorithm [25]. Abildskov et al. described a computer-aided solvent-screening methodology for biocatalytic systems composed of enzyme, essential water, and substrates/products dissolved in a solvent medium, without cells [26]. The methodology was computationally simple, using group contribution methods for calculating constrained properties related to chemical reaction equilibrium, substrate and product solubility, water solubility, boiling points, toxicity, and others. Cheng and Wang introduced a computer-aided process/solvent design to find a feasible biocompatible solvent for an extractive fermentation and separation process [27].

6.1.3.4 Catalyst solvent interaction

The catalytic activity and selectivity were found to be strongly affected by solvent properties such as dipole moment and dielectric constant. Solvent-catalyst interaction also influences the rate of reaction and affects the yield of the product [28–31]. Nowadays specific interactions between substrates, catalysts, and solvents are investigated by means of NMR and other techniques to better understand the molecular basis of catalysis.

6.1.4 The Need for Alternative Solvents

Using the principles of green chemistry, researchers in industry and academia are developing new solvents or solvent systems which reduce the intrinsic hazards associated with traditional solvents. In some cases new substances are being designed and developed to be used as solvents while in other cases some of the best-known and characterized substances in the world are finding new applications as solvents. Of course, using no solvent at all in certain circumstances can be the ultimate solution to minimizing solvent-associated hazards. Some of the leading areas of work in alternative green solvents include the following:

- Aqueous solvents
- Supercritical or dense-phase fluids
- Ionic liquids
- Solventless conditions
- Fluorous solvents
- Renewable solvents

6.2 Traditional Solvents

Traditional solvents are classified as hydrocarbons, chlorinated solvents, and oxygenated solvents (see Table 6.1). The hydrocarbon solvents are generally derived from the petroleum fraction. Prior to the 1920s, benzene was frequently used as an industrial solvent, especially for

Table 6.1 Classification of solvents

Solvent	Polar Forces	Hydrogen Bonding
Oxygenated solvents with OH functionality (eg, methanol, ethanol, propanol, butanol, etc.)	Moderate/high	Donors
Other oxygenated solvents (eg, methyl ethyl ketone, acetone, diacetone alcohol, isophorone, methyl isobutyl ketone, acetate esters, glycol ethers, glycol ether esters, etc.)	High	Strong acceptor
Aliphatic hydrocarbons (eg, cyclohexane, *n*-hexane, etc.)	None	None
Aromatic hydrocarbons (eg, benzene, toluene, xylene, etc.)	Low	Weak acceptor
Chlorinated solvents (eg, carbon tetrachloride, chloroform, methylene chloride, vinyl chloride, trichloroethene, etc.)	High	Strong acceptor

degreasing metal. As its toxicity became obvious, benzene was supplanted by other solvents, especially toluene (methyl benzene), which has similar physical properties but is not as carcinogenic. Benzene, kerosene, xylene, and/or other petroleum derivatives are used as an industrial solvent for cleaning or dissolving water-insoluble substances such as greases and oils.

The physical and chemical properties of chlorinated solvents are well understood and documented extensively in the literature. Chlorinated hydrocarbons have a better solvency than corresponding nonchlorinated compounds for resins, polymers, rubber, waxes, asphalt, and bitumen. Chlorinated hydrocarbons are miscible with other organic solvents, but are insoluble in water. They have a sweetish odor. Increasing the number of chlorine substituents reduces the combustibility and improves the solvency, but also increases the toxicity. All chlorinated hydrocarbons may decompose under the action of light, air, heat, and water. Decomposition can be reduced but not completely prevented by adding stabilizers. On account of their health hazard, some chlorinated hydrocarbons may no longer be used as conventional solvents, for example, tetrachloromethane, tetrachloroethane, and pentachloroethane. Dichloromethane, trichloroethylene, perchloroethylene, and 1,1,1-trichloroethane are increasingly being replaced for reasons of industrial hygiene and environmental protection, particularly of water.

6.3 Water as Reaction Media

6.3.1 Introduction

Organic synthesis in water is a rapidly growing area of research since it holds great promise for the future in terms of the cheap and environmentally friendly production of chemicals [32–36]. Water is the most common molecule on the planet and therefore the cheapest solvent we can use, so it may seem somewhat surprising to nonchemists that it is not more widely used. Beyond using no added solvent in a reaction or process, water is probably the greenest alternative we have. To understand when and why water is an ideal solvent for some processes and when it would be detrimental, we must first consider its general properties as a solvent. Water is highly polar solvent and has a high dielectric constant, contains extensive hydrogen bonding, and is a good Lewis base. This means that nearly all ionic compounds dissolve well in water by efficient solvation of the ions, and therefore any ion in water becomes associated with several water molecules. Although water is an excellent solvent for many inorganic species, it is also able to dissolve some organic molecules efficiently, for example, sugars, proteins, and low-molecular-weight acids.

Because of its extensive hydrogen bonding, the boiling point, melting point, and critical points of water are much higher than those of acetone, ethanol, and other organic solvents. There are many reasons why water is a desirable solvent. It is nonflammable so from the safety

point of view it is a good solvent. In reaction and process it has several advantages in that it has low cost. Due to density of 1 g $cm^{-3,}$ water provides a sufficient difference from organic substances for easy biphasic separation. It is polar so that it is easy to separate from apolar solvents. It has very high dielectric constant and it favors ionic reactions. It has high solubility for many gases. From an environmental point of view, it is renewable, widely available in suitable quality, and odorless and colorless so that contamination can be easily recognized.

However, there are also disadvantages when using water as a solvent, such as the low solubility of several organic compounds and the moisture-sensitive nature of many catalysts and reagents, which can lead to their deactivation. The high heat capacity of water is disadvantageous as it means that aqueous phases are difficult to heat or cool rapidly, and distilling water is energy intensive. Also, although water and organic phases usually separate well, most organic compounds possess a small degree of solubility in water and this can lead to difficulties in purifying the aqueous phase after use. Therefore, care must be taken not to release contaminated water into the environment.

6.3.2 Biphasic Systems

Using water as a reaction solvent can be an effective method of separating homogeneous catalysts from a reaction mixture and allowing them to be recycled and reused to give higher turnover numbers and reduce waste [37,38]. The low solubility of organic compounds in the aqueous phase can be overcome by using surfactants or phase transfer reagents. In the ideal process the organic substrate will be water soluble and the product insoluble, so separation will be easy. In addition to forming biphasic systems with many VOC solvents, alternative solvents such as fluorous media and supercritical carbon dioxide ($scCO_2$) can also be used and afford interesting biphasic systems. In aqueous-organic biphasic catalysis, catalysts are used that will preferentially dissolve in the aqueous phase so that they can be recycled. The catalyst typically consists of a ligand and suitable metal salt. The ligands can be designed so that the resulting catalytic metal complex is hydrophilic, or at least water soluble (see Fig. 6.1).

In all aqueous-organic systems, it is important to note that water is a potent nucleophile. Sulfonated phosphines are perhaps the most widely used ligands in this field because they are soluble over a wide pH range, very poorly soluble in nonpolar organic solvents, exhibit good stability, and are easily prepared [39]. Also, phosphine ligands are common components in many transition metal-catalyzed reactions. Other classes of ligands, including amines, *N*-heterocyclic carbenes, tris(pyrazolyl)borates, and porphyrins, have been rendered water soluble by adding suitable hydrophilic groups. Essentially, the presence of any group that can form strong hydrogen bonds is often sufficient to impart water solubility. Hydrophilic groups that have been used include hydroxyl, sugar, amine, acid, and polyethylene glycol.

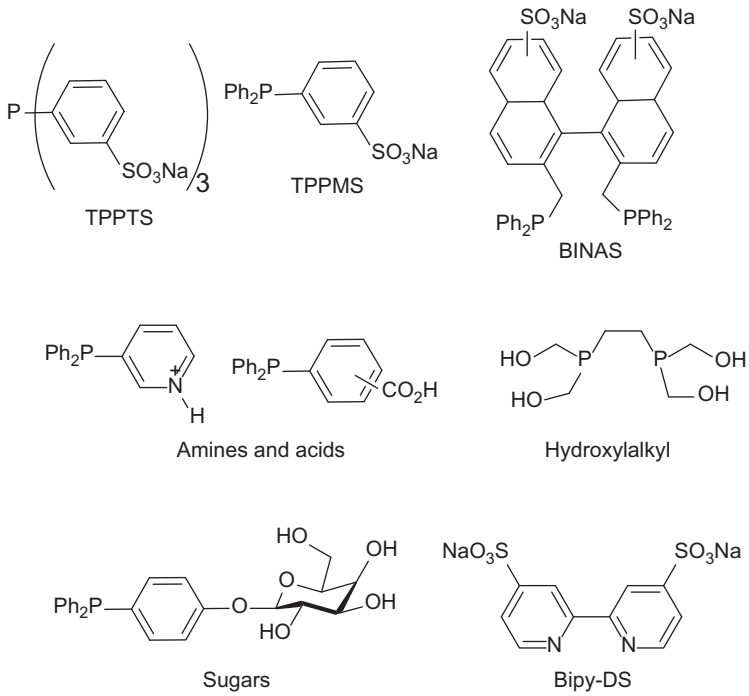
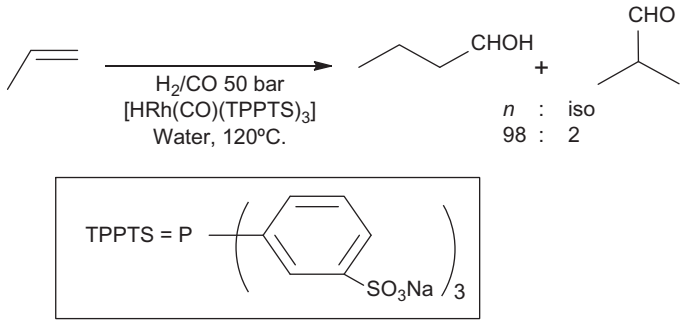


Fig. 6.1
Water-soluble sulfonated phosphine and nitrogen-containing ligands.

6.3.2.1 Hydroformylation

The synthesis of aldehydes via hydroformylation of alkenes is an industrially important process and is used to produce a million tonnes of aldehydes a year [39]. Most of these require organic solvents. However, in 1975 a water-soluble rhodium phosphine complex was discovered that could also perform this reaction and ultimately, this led to industrial process by Ruhrchemie-Rhone-Poulenc. Initially, the continuous hydroformylation of propene was performed on a scale of 120,000 tonnes per year but is now at a level of 800,000 tonnes per year [37–39]. The process uses only gaseous substrates: propene, hydrogen, and carbon monoxide. These dissolve in the aqueous phase but the product forms a separate organic phase that can be separated easily and is virtually free from rhodium contamination. The process achieves high yields and selectivity under relatively mild conditions (Scheme 6.1) [37].

This process replaced toxic solvents and works under mild reaction conditions that lead to significant energy conservation. High selectivity toward desired linear aldehyde isomer was achieved and very low loss of precious metal catalyst. Since the development of this process, other types of hydrophilic phosphines have been employed for the reaction on a laboratory scale, and these give higher activities and sometime better *n*:iso ratios. However, they are generally more complex structures and more expensive than TPPTS and therefore the original

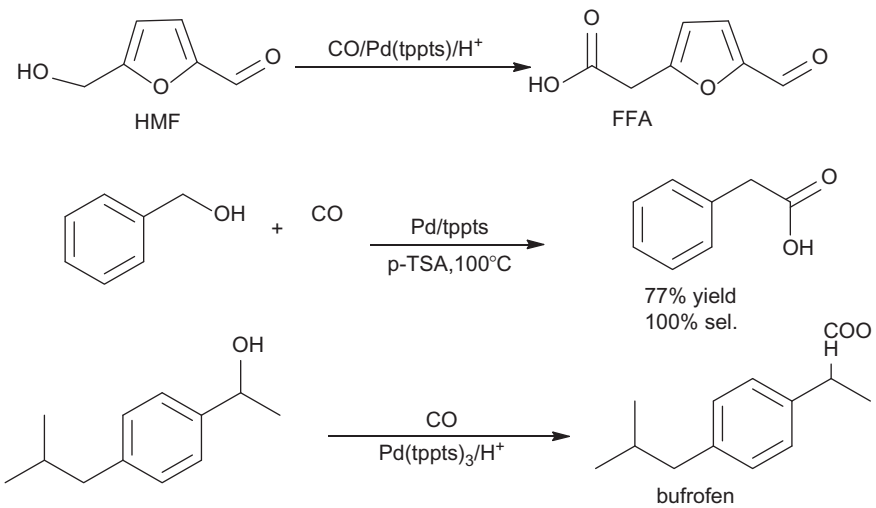


Scheme 6.1
Hydroformylation of propene to *n*-butanal.

ligand is still used. Pioneering studies of aqueous biphasic catalysis with water-soluble organometallic complexes were performed by Joo and coworkers, in hydrogenation [40] and Kuntz, in hydroformylation [41].

6.3.2.2 *Carbonylation*

Sheldon and coworkers showed palladium-catalyzed carbonylations in water. The $Pd(TPPTS)_3$ complex was shown to catalyze the carbonylation of hydroxymethyl furfural in the presence of a Brønsted acid cocatalyst. They subsequently showed that the same system catalyzed the carbonylation of benzyl alcohol to phenylacetic acid in quantitative selectivity [42]. The same methodology was also applied to the synthesis of ibuprofen by aqueous biphasic carbonylation of 1-(4-isobutylphenyl)ethanol (Scheme 6.2) [43]. The reaction is proposed to involve the



Scheme 6.2
Alcohol carbonylation in an aqueous biphasic system.

formation of an intermediate carbenium ion which reacts with the Pd(0) complex to afford an alkylpalladium(II) species [44].

The aqueous-organic biphasic catalytic system involving a water-soluble catalyst can be a great advantage in terms of catalyst and product separation and at the same time easy recycling of homogeneous catalyst. Application of water-soluble palladium catalysts for oxidative carbonylation of aniline to *N*,*N*-diphenyl urea has been reported [45]. The water-soluble palladium catalysts prepared from sulfonated *N*-containing ligands were found to be highly stable under reaction conditions and easily recyclable due to insoluble urea product in the reaction medium.

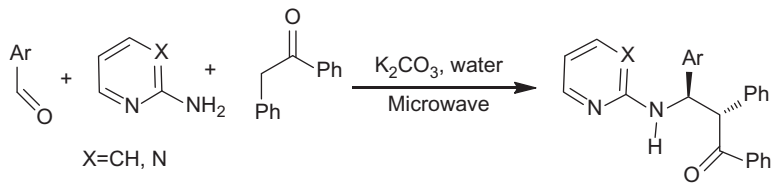
6.3.3 Organic Synthesis

6.3.3.1 Suzuki-Miyaura reactions

The ligand-free Suzuki-Miyaura reactions using stilbene-4,4′-bis[(1-azo)-3,4-dihydroxybenzene]-2,2′-disulfonic acid diammonium salt as a promoter in water have been reported. The desired carbon-carbon bond formation works under mild conditions with high efficiency and good functional group tolerance [46]. Highly efficient heterogeneous palladium catalyst has been prepared for the Suzuki-Miyaura cross-coupling reaction in water via a simple procedure [47]. The polystyrene-supported palladium catalyst can be recycled up to 10 times without significant loss of activity.

6.3.3.2 Michael reactions

In the 1970s, Hajos and Parrish [48] and Wiechert and coworkers [49] independently reported that the Michael addition of 2-methylcyclopentane-1,3-dione to vinyl ketone in water gives the corresponding conjugated addition product without the use of a base catalyst. Similar enhancement of reactivity was found in the Michael addition of 2-methyl-cyclohexane-1,3-dione to vinyl ketone, which finally led to optically pure Wieland-Miescher ketone [50]. The reaction, however, proceeds under more drastic conditions. Microwave-assisted Mannich reaction for highly stereoselective synthesis of β-aminoketones has been studied by controlling the steric hindrance of the substituents using potassium carbonate as a catalyst and water as the reaction medium (Scheme 6.3) [51].



Scheme 6.3
The synthesis of β-aminoketones.

6.3.3.3 Aldol reaction

The aldol reaction of various cyclic ketones with aryl aldehydes has been developed using primary-tertiary diamine-Brønsted acid as a catalyst in the presence of water [52].

6.3.3.4 Amination reactions

The palladium-catalyzed allylic aminations of allylic alcohols have been described in the presence of pure water [53].

6.3.3.5 Cycloaddition reactions

The 1,3-dipolar cycloaddition reactions of several hydrophobic nitrones have been investigated in both homogeneous organic solutions and aqueous suspensions [54]. Reactions in water suspensions exhibited great rate accelerations over homogeneous solutions. Small changes were also observed to the stereoselectivity of the reactions.

6.3.3.6 Diels-Alder reactions

Breslow and coworkers have performed some of the most outstanding work in this field. They found that the rates of reaction and selectivity in the Diels-Alder reactions are improved in an aqueous system [55]. Additionally, the presence of salts or β-cyclodextrins can enhance the hydrophobic effect, which causes organic molecules to cluster together in aqueous solution, and further accelerates the Diels-Alder reaction.

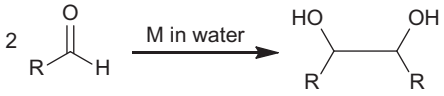
6.3.3.7 Mannich reactions

The one-pot three-component Mannich reaction involving aldehydes, aromatic amines, and cycloalkanones has been studied using boric acid and glycerol in water to obtain major syn diastereoselectivity [56]. These reactions, which proceed very slowly in organic solvents, become quite faster in water.

6.3.3.8 Metal-mediated and catalyzed reactions

The development of metal-mediated carbon-carbon bond formation reactions in water (and air) have opened new avenues in chemistry and fundamentally changed "organometallic reactions." Extensive studies showed that various metal-mediated C—C bond formations, including "Grignard-type" reactions, can be carried out well in aqueous media, and sometimes these reactions are even more effective than those in organic solvents in terms of both product yields and chemo- (as well as stereo-) selectivities [57]. The pinacol coupling of carbonyl compounds to give 1,2-diols has been carried out in aqueous media. Clerici and Porta extensively studied the aqueous pinacol coupling reactions mediated by Ti(III) (Scheme 6.4) [58].

The Sonogashira coupling of various aryl halides with terminal acetylenes has been developed in the presence of an amphiphilic, polystyrene-poly-(ethylene glycol), resin-supported, palladium-phosphine complex in water under copper-free conditions to offer the corresponding



M = Zn-Cu, Mg, Mn, Zn, In, Sm, Al, Ga, Cd

Scheme 6.4
Pinacol coupling in water.

biarylacetylene derivatives in high yields [59]. The Suzuki cross-coupling reaction in water in the presence of a chitosan-*g*-(methoxyl triethylene glycol)- or (methoxy polyethylene glycol)-supported palladium(0) catalyst has been described without additional phase transfer reagents [60].

6.3.3.9 Microwave-assisted reactions

The use of microwave irradiation as a heating source in combination with water as a solvent was reviewed [61]. For example, in challenging transition metal-catalyzed coupling reactions, time can be reduced from hours or days to minutes, and if the reaction is performed in a sealed vessel there is often no need to apply an inert atmosphere. Reactions studied to date utilizing both water and microwave heating include carbon-carbon couplings (Suzuki, Heck, Sonogashira, etc.), carbonylations, hydrogenations, heterocycle synthesis, Mannich-type reactions, nucleophilic substitutions, ring openings of epoxides, and many more particularly noteworthy are phosphine-free with low palladium loading. The Leadbeater group have extensively studied microwave effects in various carbon-carbon coupling reactions [62]. In addition to organic reactions, acid-catalyzed hydrolysis of cellulose has been performed in a rapid and controlled manner using a microwave reactor [63]. The aqueous phase microwave-assisted reactions will play an important role in the rapid development of biorefinery-based materials and chemicals.

6.4 SCFs as Reaction Media

6.4.1 Introduction

SCFs have long fascinated chemists and over the last 30 years this interest has accelerated. SCF technology has rapidly grown as an alternative to some of the conventional methods of extraction, separation, reaction, fractionation, materials processing, particle formation processes, and analysis [64–73]. There is even a journal dedicated to the subject, the *Journal of Supercritical Fluids*. These fluids have many interesting and unusual properties that make them useful media for separations and spectroscopic studies as well as for reactions and synthesis. SCFs may be defined as the state of a compound, mixture, or element above its critical pressure (P_c) and critical temperature (T_c), but below the pressure required to condense it into a solid. In this region, the SCF exists in an intermediate phase between liquid and gas phases [74–76]. Carbon dioxide (CO_2), water, ethane, ethene, propane, xenon, ammonia, nitrous oxide, and

fluoroform are some of the significant compounds useful as SCFs. CO_2 is the most common candidate for use as an SCF due to its low toxicity, flammability and cost, ready availability, stability, and environmental acceptability. Some substances have readily accessible critical points; for example, T_c for carbon dioxide is 304 K (31°C) and P_c is 74 atm, whereas other substances need more extreme conditions. Hence, the amount of energy required to generate $scCO_2$ is relatively small. For example, T_c for water is 647 K (374°C) and P_c is 218 atm. The most useful SCFs to green chemists are water and carbon dioxide, which are renewable and nonflammable.

Both batch and continuous-flow reactors have been used for reactions in SCF. Batch reactors can be readily equipped with a suitable window to assess homogeneity of the reaction mixture and are widely used in academic research. These windows can also be used for spectroscopic analysis such as FT-IR. One of the main differences between SCFs and conventional solvents is their compressibility. Conventional solvents require very large pressure changes to vary their density, whereas the density of an SCF changes significantly on increasing pressure. Solubility in an SCF is related to density; therefore, this medium has the added benefit of being tuneable, and hence the solubility of species can be directly controlled. Purification or reaction quenching can thus be achieved by reducing solvent density and precipitating the product. Varying the density can also affect the selectivity and outcome of some chemical reactions.

6.4.2 Supercritical Carbon Dioxide

In many cases, carbon dioxide is seen as the most practicable supercritical solvent. It is inexpensive and can be obtained as a byproduct of fermentation and combustion. As compared with other alternatives, it is nontoxic, nonflammable, relatively inert, and not a VOC. Carbon dioxide also provides many chemical advantages, for example, it cannot be oxidized and therefore oxidation reactions using air or oxygen as the oxidant have been intensively investigated. Also, it is inert to free radical chemistry, in contrast to many conventional solvents. This has led to much research into polymerizations initiated by free radicals [77]. These advantages enhance its green credentials by reducing waste [78]. There are also a number of practical advantages associated with the use of $scCO_2$ as a solvent. Product isolation to total dryness is achieved by simple evaporation and could prove useful in the final steps of pharmaceutical syntheses where even trace amounts of solvent residues are considered problematic. Given the critical point of carbon dioxide, most processes reported to date have been conducted in a pressure range of 100–200 bar. The potential danger of such conditions should never be ignored, and safety precautions should be taken for all experiments.

Advantages of $scCO_2$ as a solvent:

- No liquid waste/solvent effluent
- Nonflammable

- Nontoxic to the environment/personnel
- Available cheaply and in 499.9% pure form
- Low viscosity
- Gas miscibility
- Simple product isolation by evaporation to 100% dryness
- High diffusion rates offer potential for increased reaction rates
- Density can be varied to control reagent/product solubility, "tunable" solvent
- Relatively inert and nonoxidizable

6.4.2.1 Chemical examples

A large and continually expanding list of reactions has been performed in $scCO_2$ [79–83]. Many of these reactions include aldol reactions, carbonylations, cyclizations, epoxidations, esterifications, carbon-carbon cross-coupling reactions, hydrogenations, hydroformylations and polymerizations, etc. (Scheme 6.5). By far the most extensively studied of these are hydrogenations and hydroformylations because of the high solubility of reagent gases in $scCO_2$ compared to conventional organic solvents. Many reactors are equipped with high-pressure windows to view the ongoing reactions.

6.4.2.2 Hydrogenation and hydroformylation

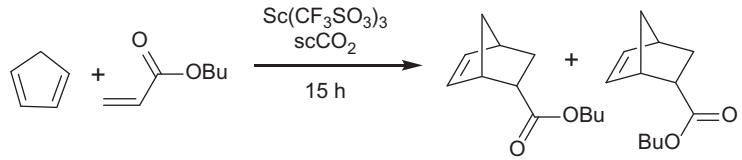
The use of $scCO_2$ as a solvent for catalytic hydrogenation was pioneered by Poliakoff and has been commercialized by Thomas Swan and Co. for the manufacture of trimethyl cyclohexanone by Pd-catalyzed hydrogenation of isophorone (Scheme 6.6) [84].

The miscibility of $scCO_2$ with hydrogen results in high diffusion rates and provides the basis for achieving much higher reaction rates than in conventional solvents. The high reaction rates allow for the use of exceptionally small flow reactors. Chemoselectivities with multifunctional compounds could be adjusted by minor variations in reaction parameters. Similarly, $scCO_2$ has been used for olefin hydroformylation using an immobilized rhodium catalyst [85].

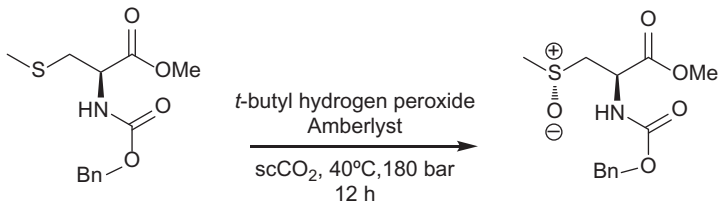
6.4.2.3 Oxidations

Just as with water, $scCO_2$ is also an ideal inert solvent for performing catalytic aerobic oxidations; it is nonflammable and completely miscible with oxygen. Recently, much interest has also been focused on catalytic oxidations with hydrogen peroxide, generated in situ by Pd-catalyzed reaction of hydrogen with oxygen, in $scCO_2$-water mixtures [86]. The system was used effectively for the direct epoxidation of propylene to propylene oxide over a Pd/TS-1 catalyst [87]. These reactions probably involve the intermediate formation of peroxycarbonic acid by reaction of H_2O_2 with CO_2 (Scheme 6.7).

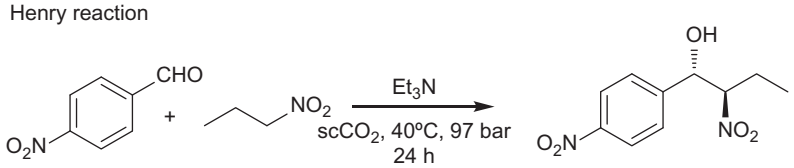
Diels-Alder reaction



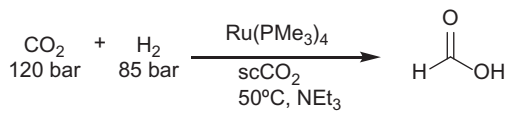
Diastereoselective sulfur oxidation



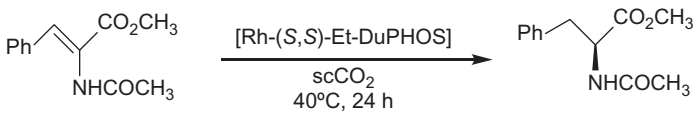
Henry reaction



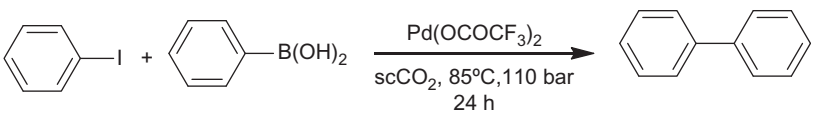
Hydrogenation of carbon dioxide



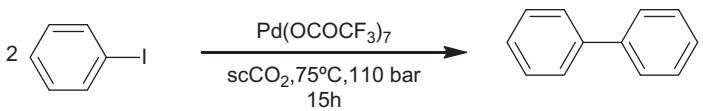
Asymmetric hydrogenation



Suzuki cross-coupling reaction

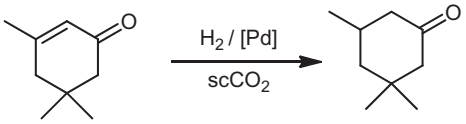


Homocoupling

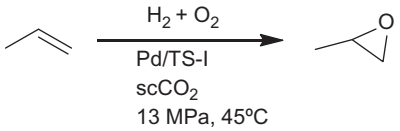


Scheme 6.5

Some organic reactions studied in $scCO_2$ medium.



Scheme 6.6
Hydrogenation of isophorone in $scCO_2$.



Scheme 6.7
Epoxidation of propylene in $scCO_2$.

6.4.2.4 *Biocatalysis in $scCO_2$*

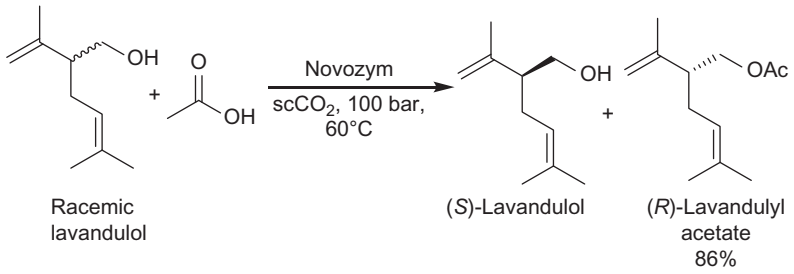
A wide range of biocatalytic reactions have been performed in $scCO_2$ as reaction media [88,89]. These reactions are hydrolysis reactions, esterifications, carboxylations, and polymerizations, etc. Carbon dioxide is potentially reactive, so that in these studies, one must be aware that it can form carbamates within the enzyme structure, or can react with water to form carbonic acid. Enzymes are generally more stable in $scCO_2$ than in water. *Candida antarctica* lipase (Novozym 435)–catalyzed resolution of 1-phenylethanol was successfully performed at temperatures exceeding 100°C using $scCO_2$ [90]. Matsuda et al. found that the enantioselectivity of alcohol acylations catalyzed by Novozym 435 in $scCO_2$ could be controlled by adjusting the pressure and temperature [91].

Enzyme-catalyzed oxidations with O_2 have also been successfully performed in $scCO_2$, for example, using cholesterol oxidase [92] and polyphenol oxidase [93]. The use of $scCO_2$ as a solvent for biotransformations clearly has considerable potential, and we expect that it will find more applications in the future.

Pressure and temperature can also significantly affect the activity and selectivity of enzymes in $scCO_2$. Biocatalysis in $scCO_2$ could be particularly important in the transformation of biofeedstocks. For example, the supported lipase enzyme (Novozym 435) can be used for the quantitative esterification of lavandulol using the naturally sourced acyl donor, acetic acid (Scheme 6.8). In this and many biocatalytic studies, to prevent catalyst degradation, the reaction temperatures must be kept below a threshold level.

6.4.2.5 *Materials synthesis and modification in $scCO_2$*

The application of $scCO_2$ to the synthesis and modification of well-defined polymers and nanomaterials has enormous potential and as such has been extensively investigated [94]. Materials can also be impregnated with or reacted in the presence of CO_2-philic metal



Scheme 6.8
Biocatalytic esterification of biosourced chemicals.

complexes that can be subsequently reduced or thermally decomposed to give metal nanoparticles. For example, an organometallic silver complex has been used to give a silver-PMMA composite material [95]. The synthesis of silver nanostructures has been reported using $scCO_2$ in the presence of polyvinylpyrrolidone and ethylene glycol [96]. Using SCF processes such as these, polymers and inorganic materials have been formed into films, fibers, and spherical particles. For example, mesoporous silicate films and mesoporous silica hollow spheres have both been recently prepared using $scCO_2$-based technologies [97,98].

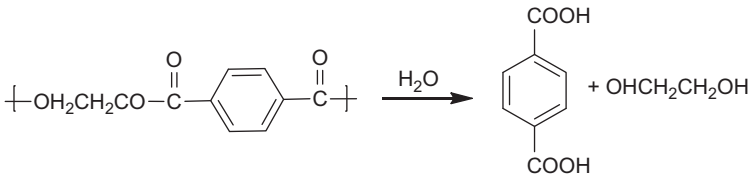
6.4.3 Supercritical Water and Near-Critical Water as Reaction Media

When water is heated to high temperatures between 100°C and 374°C (its critical temperature) in a sealed vessel or under pressure, its properties approach those of supercritical water (SCW) and its hydrogen bond network breaks down [99–101]. In this temperature range, water can be called high temperature, superheated, or near critical (NCW). It has a lower viscosity, polarity, density, and surface tension than water at room temperature. However, diffusivity and specific heat capacity increase. In general, many organic compounds and inorganic salts are more soluble in NCW. NCW has a polarity similar to acetone and at higher temperatures becomes completely miscible with toluene. The solvent properties of NCW are similar to those of a polar organic solvent such as acetone. As K_w (the ion product of water) increases with temperature, $[H_3O^+]$ and $[OH^-]$ concentrations are high compared to room temperature, and this leads to many of the interesting properties of NCW and SCW. The NCW is less corrosive than SCW and requires lower temperatures and pressures. Therefore, as a form of water, NCW has been used as an alternative to organic solvents in extractions, recrystallizations, chromatography, and decontamination and waste treatment. A wide and increasing range of synthetic reactions have been performed in NCW (around 275°C, 60 bar) and SCW (around 400°C, 200 bar) [102,99]. Many fields such as food and paper and pulp industries use NCW. Recently research in this area has increased, especially in extractions and microwave-assisted syntheses. Above the critical point of water, gases are highly miscible so that SCW has advantage over NCW and is used for oxidation reactions.

Extensive research has been conducted using this unusual solvent [99,100]. For example, *p*-isopropenylphenol can be prepared through the decomposition of bisphenol in the absence of a catalyst [103]. Separation and isolation of *p*-isopropenylphenol could be achieved due to the organic-aqueous nature of the reaction by cooling the reaction mixture to room temperature, at which point the product precipitates. Maximized yields of the desired product were obtained by performing the reaction at 350°C for 20 min.

6.4.3.1 Chemical examples

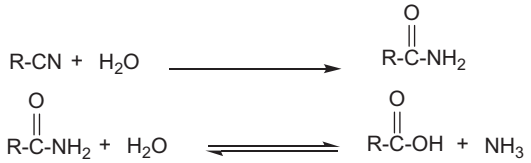
Hydrolysis reactions have been extensively reported in NCW for polymeric materials as well as for low-molecular-weight molecules. Mandoki [104] reported a process for depolymerizing condensation polymers using NCW without addition of bases or acids. More particularly, polyethylene terephthalate, polybutene terephthalate, nylon 6, and nylon 66 were hydrolytically depolymerized (Scheme 6.9).



Scheme 6.9
Hydrolysis of polyethylene terephthalate.

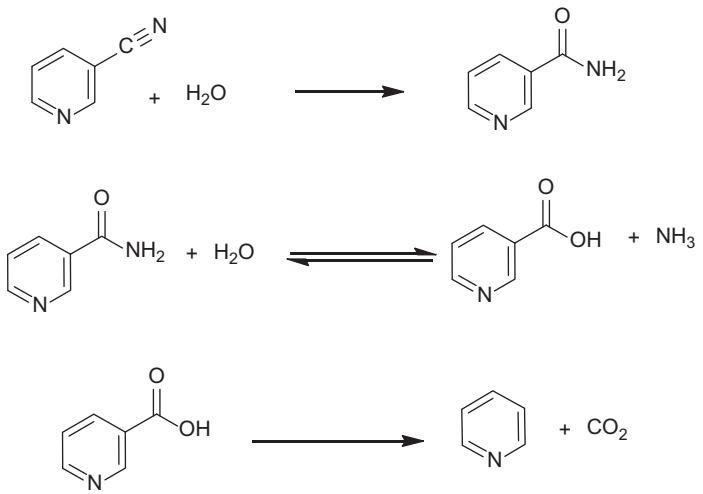
Siskin et al. [105] showed the hydrolysis of polyacrylonitrile to low-molecular-weight oligomeric materials, with the generation of ammonia instead of the toxic hydrogen cyanide formed by conventional thermolysis processes. Holliday et al. [106] reported that triglyceride-based vegetable oils can be hydrolyzed into their fatty acids constituents. The authors studied NCW and SCW. Although the conversion yields are comparable in both media, NCW induces significantly less degradation of the fatty acid products. Minowa et al. [107] have shown that the hydrolysis of cellulose to glucose in NCW can be achieved in the absence of catalyst.

Alkyl and aryl nitriles can also be hydrolyzed when submitted to NCW conditions. The hydrolysis proceeds by multistep sequence as shown in Scheme 6.10. Katritzky et al. [108] have reported that benzonitrile is converted to benzamide and benzoic acid at 250°C over a period of 5 days, and they conclude that the amide and the acid were in equilibrium. Under these conditions some decarboxylation can also occur. An et al. [109] have reported the product distribution for the hydrolysis of benzonitrile as a function of time and temperature. Iyer and Klein [110] reported the reaction of benzonitrile in NCW at 330°C at a variety of pressures, yielding as products butyramide, butyric acid, and ammonia (Scheme 6.10).



Scheme 6.10
Reactions of nitriles in NCW.

Katritzky et al. [108] reported the hydrolysis of 3-cyanopyridine in NCW at 200°C and 250°C. In addition to the corresponding amide and carboxylic acid products, decarboxylation to pyridine was also observed (Scheme 6.11).



Scheme 6.11
Hydrolysis of 3-cyanopyridine.

Despite the fact that an aqueous environment may not seem to be an appropriate medium for the dehydration of alcohols, such transformation can proceed surprisingly well in NCW. For instance, Kuhlmann et al. [111] reported that cyclohexanol undergoes complete dehydration at 250–300°C and that the acid-catalyzed conversion is enhanced by the addition of traces of acid.

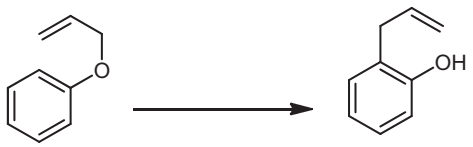
Xu and coworkers [112–115] studied mechanistic aspects regarding the dehydration of *tert*-butanol. In NCW at 250°C, *tert*-butanol reacts rapidly to form an equilibrium mixture of *tert*-butanol and isobutene. The rate of reaction can be enhanced by the addition of trace amounts of sulfuric acid.

Kuhlmann et al. has reported [116] rearrangement of pinacol to pinacolone in NCW (Scheme 6.12). The rearrangement took place in 60 min at 275°C with negligible alkene formation. In contrast to the use of NCW, classical methods required boiling 25% sulfuric acid for 3 h to promote the rearrangement.



Scheme 6.12
Pinacol rearrangement to form pinacolone.

An et al. [117] first reported Claisen rearrangement of allyl phenyl ether in NCW (Scheme 6.13). At 200°C and 240°C for a period of 10 min, the conversion to 2-allylphenol increased significantly, 10% and 84%, respectively. At higher temperatures (245°C and 250°C) and longer reaction time (60 min), an array of products appeared. These products included phenol, 2-(2-hydroxyprop-1-yl)-phenol, and 2-methyl-2,3-dihydrobenzofuran.



Scheme 6.13
Claisen rearrangement of the allyl phenyl ether to the 2-allylphenol.

6.4.3.2 Limitations and safety of NCW

Although NCW provides a number of benefits over traditional chemical processes, there are limitations. Many reactions produce water as a byproduct, such as the Friedel-Crafts reactions, and may be equilibrium limited in an NCW system due to the extreme amount of water present. It may be possible to use a temperature between the solubility of the reactants and products so that the products fall out of solution as they are formed, which would help drive the reaction to completion.

The processing conditions for an NCW operation are also different from most traditional syntheses, resulting in the need for more robust equipment. This equipment needs to be capable of resisting corrosion (due to water dissociation) and temperatures and pressures up to 350°C and 10 MPa. Safety is always a major concern in high-pressure systems because of the enormous energy storage.

6.4.4 CO_2-Expanded Solvent Media

Gas-expanded liquids (GXLs) consist of large amounts of a pressurized compressible gas such as CO_2 dissolved in an organic solvent. The GXLs have the combined properties of a compressed gas and a traditional solvent, resulting in solvent properties that can be adjusted through variations in the pressure [118–120]. The advantages of carbon dioxide-expanded liquids (CXLs) are that they have higher oxygen miscibility (up to two orders of magnitude)

compared to organic solvents [121], adequate solubility of transition metal catalysts, enhanced turnover frequencies, comparable or better product selectivities than in neat organic solvent or $scCO_2$, and facile catalyst separation. Compared to $scCO_2$ (hundreds of bars), CLXs have environmental and economical advantages as they substantially (up to ~80%) replace organic solvents with dense-phase CO_2 and milder process pressure (tens of bars). These advantages were recently demonstrated for the homogeneously catalyzed oxidation of cyclohexene by iron porphyrin complexes in CO_2-expanded acetonitrile [121,122].

CO_2-expanded methanol is explored for the extraction of neutral lipids and free fatty acids from microalgae [123]. The extractions were carried out under moderate temperature and pressure to reduce the eventual larger scale capital and processing costs. The use of these methods for the extraction of lipids from microalgae could present an advantage to the use of conventional solvents because they require little to no flammable, highly volatile, or chlorinated organic solvents. CXLs are demonstrated as an attractive media for heterogeneously catalyzed oxidations of cyclohexene [124]. The results showed that CXLs significantly reduce the use of conventional organic solvents as reaction media and also enhance catalyst stability against leaching. Xie et al. reported the hydrogenation of nitriles to form the corresponding primary amines in CO_2-expanded THF and ethanol [125]. Duggan and Roberts showed aggregation and precipitation of gold nanoparticle clusters in CO_2-expanded dimethyl sulfoxide [126]. The addition of CO_2 to the solvent mixture results in subtle changes in solvation of the nanoparticle ligands such that nanoparticle stabilization can be drastically affected.

6.5 Ionic Liquids as a Reaction Media

6.5.1 Introduction

Solvents are often used in bulk quantity, bear a huge cost, and are ranked highly among the damaging chemicals. Moreover, due to the volatile nature of some chemicals, solvents are difficult to contain. Therefore, various cleaner technologies need to be introduced that are environment benign and placed as of significant importance both in academia and in industry. In order to develop a sustainable chemistry based on clean technology, the best solvent would be no solvent at all. Considerable efforts have been made to design reactions that proceed under solvent-free conditions using modern techniques. One of the major focus areas is using ionic liquid as solvent.

In general, an ionic liquid consists of salt where one or both of the ions are large and the cation has a low degree of symmetry. These factors are responsible for reducing the lattice energy of the crystalline form of the salt, hence lowering the melting point. Several other terms such as room-temperature ionic liquids, nonaqueous ionic liquids, molten salts, and fused salts are used as nomenclature for ionic liquids. In general, ionic liquid is in a liquid state below 100°C. The first ionic liquid synthesized in the year 1914 was ethyl ammonium nitrate [$C_2H_5NH_3$]

[NO_3] with melting point 12°C [127]. But due to its explosive nature this ionic liquid did not attract further application-based research. Moreover, it did not attract to develop much interest until the discovery of binary ionic liquids (mixture of aluminum[III] chloride and 1,3-dialkylimidazolium chlorides) [128]. Ionic liquids are widely used as "green" solvents: extragents, electrolytes, sensors, liquid crystals, and so on due to their multifarious properties. First, due to its inherent low volatility (negligible vapor pressure) they do not evaporate to environment. Second, some of the ionic liquids are immiscible with organic solvents and provide a polar alternative with nonaqueous nature for two-phase systems. Third, they are good solvents for a whole range of inorganic and organic materials. The fourth significant difference is that this ionic liquid occurs at temperature as low as 90°C, whereas conventional catalytic reaction requires much higher temperatures, typically 300–1000°C. Most importantly, ionic liquids can be recycled several times to offer comparable performance in chemical transformations.

As a designer solvent, the properties of ionic liquids can be adjusted to suit the requirement of a particular process. By simple changes in the ionic structure, properties such as melting point, viscosity, density, and hydrophobicity can be varied. Solubility of ionic liquid in water also depends on the alkyl chain length. For example, 1-alkyl-3-methylimidazolium tetrafluoroborate salts [129] are miscible with water at 25°C where the alkyl chain length is less than 6. But above six carbon atoms, they form a separate phase when mixed with water. The ionic liquid 1-(*n*-butyl)-3-methylimidazolium hexafluorophosphate $[BMIM]^+PF_6^-$ even forms triphasic mixtures with water and alkanes. This behavior is highly beneficial during the product separation and solvent extraction processes. Many classes of chemical reactions such as the Diels-Alder reaction, Friedel-Crafts reactions, and biocatalysis can be performed using ionic liquids as solvent.

Although acidic ionic liquids are excellent catalysts and solvents in many processes, its uses are restricted due to several disadvantages like moisture sensitivity character and difficulty of separation of products containing heteroatoms from the ionic liquid, while leaving the ionic liquid intact. The chemistry in ionic liquids and its robustness depends on a user-friendly process. Therefore, water-stable ionic liquids have become increasingly important. Various ionic liquids have been found to be hydrophobic but can dissolve many organic molecules with the exception of alkanes and alkylated aromatic compounds (toluene). Ionic liquid such as [bmim][PF_6]([bmim]$^+$=1-butyl-3-methylimidazolium) forms triphasic mixture with alkane and water [130]. For clean synthesis this multiphasic behavior has important implications and is analogous to the use of fluorous phases in some chemical processes [131]. The products and byproducts of the reaction mixture can be separated from the ionic liquid by solvent extraction with either water or an organic solvent when transition metal catalyzed exclusively dissolved in ionic liquids is used in the reactions process. The process is very important when a precious metal catalyst or a catalyst with expensive ligands is used, ensuring that both the ionic liquid and catalysts will be recycled and reused. Moreover, some

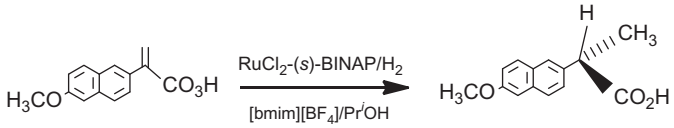
volatile products can be separated from the ionic liquid and catalyst by simple distillation as the ionic liquid has effectively no vapor pressure and therefore cannot be lost.

No special condition is required while carrying reactions in neutral ionic liquid. There is often no need to exclude water or carry out reaction under an inert atmosphere. This ability of ionic liquids makes reactions extremely straightforward and allows for easy separation of the product.

6.5.2 Reactions in Neutral Ionic Liquids

6.5.2.1 Hydrogenation reaction

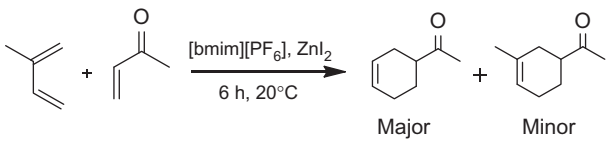
Various hydrogenation reactions have been extensively studied using neutral ionic liquid as solvent. The importance of using ionic liquid is that homogeneous transition metal catalysts can be used and the products of the reaction can be easily separated from the ionic liquid and catalyst [132]. Various hydrogenation reactions, including hydrogenation of cyclohexane and complete hydrogenation of benzene rings, have been extensively studied [134]. Recently developed asymmetric hydrogenation reactions for the synthesis of (*S*)-Naproxen in the ionic liquid [bmim][BF_4] are shown here in Scheme 6.14 [135].



Scheme 6.14
Asymmetric hydrogenation reaction using [bmim][BF_4] ionic liquid.

6.5.2.2 Diels-Alder reactions

Neutral ionic liquids also act as excellent solvents for the Diels-Alder reaction, showing significant improvement in rate of reaction over molecular solvents including water which was normally considered to enhance the rate of reaction [136]. With addition of a mild Lewis acid such as Zn(II) iodide, the selectivity can be improved from 4:1 to 20:1 (Scheme 6.15) [137]. The ionic liquid and catalyst can be recycled and reused after solvent extraction or direct distillation of the product from the ionic liquid.



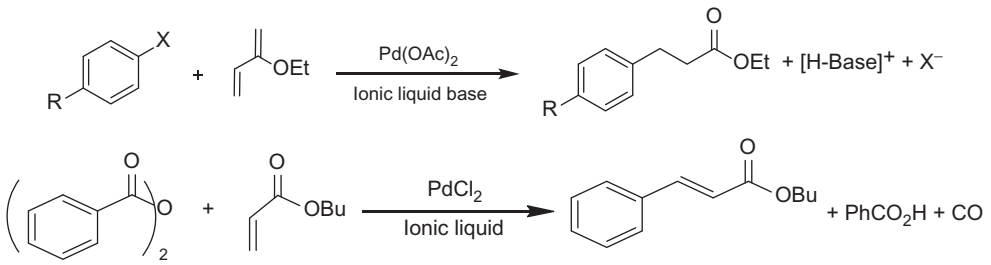
Scheme 6.15
The zinc(II) iodide-catalyzed reaction of isoprene with but-3-en-2-one in the ionic liquid [bmim][PF_6].

Chloroaluminate(III) ionic liquid can be used in this reaction, but the moisture sensitivity of these systems is the greatest disadvantage [138].

6.5.2.3 Heck reactions

Many palladium complexes dissolve in ionic liquids and are very useful for the palladium-catalyzed coupling of aryl halides with alkanes (Heck reaction). The products and byproducts of this reaction can be extracted with either water or alkanes solvents [139]. Therefore the expensive catalyst can be easily recycled as it remains in the ionic phase. This is the greatest advantage over the conventional Heck reaction where the catalyst is usually lost at the end of the reaction and noxious dipolar solvents are used in reactions.

In the Heck reaction, aromatic anhydrides are used as a source of the aryl group (Scheme 6.16). The advantage of using anhydride as the source is that the byproduct benzoic acid generated can be converted back to anhydride and the halide containing waste is not formed.



Scheme 6.16
The Heck reactions of aryl halides and anhydrides in ionic liquids.

6.5.2.4 Nucleophilic displacement reaction

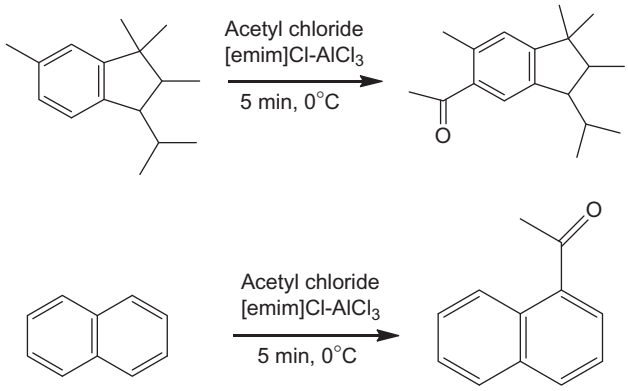
Nucleophilic displacement reaction is one of the most common reactions in organic synthesis.

Earlier reactions were carried out in dipolar aprotic solvents such as DMF and DMSO. The disadvantages of using these solvents are difficult to separate from the product. The advantage of using the ionic liquid process is that the products of the reaction can be extracted into an organic solvent such as toluene, leaving the ionic liquid behind. The best example of nucleophilic displacement reaction using ionic liquid is the alkylation on the nitrogen and oxygen atom of indole and 2-naphthol when treated with a haloalkane and base (usually NaOH or KOH) in [bmim][PF_6] [140]. The reaction rates are similar to those carried out in dipolar aprotic solvent.

6.5.3 Reactions in Acidic Ionic Liquids

6.5.3.1 Friedel-Crafts reaction

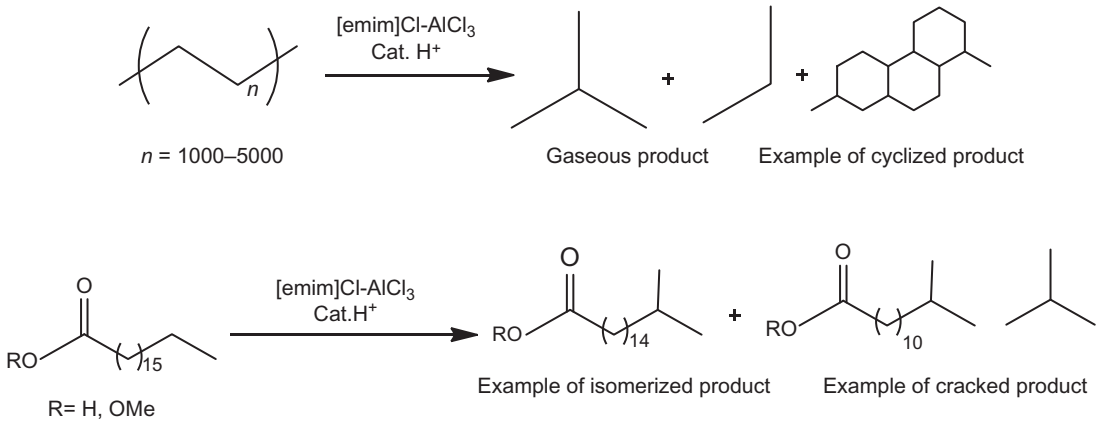
The Friedel-Crafts reaction prompted by Lewis acid has been found to work efficiently in chloroaluminate(III) ionic liquids [141]. Various commercially available fragrance molecules have been synthesized by Friedel-Crafts acylation reactions in these ionic liquids. Traseolide (5-acetyl-1,1,2,6-tetramethyl-3-isopropylindane) and Tonalid(6-acetyl-1,1,2,4,4,7-hexamethyltetralin) have been made high yield in the ionic liquid [emim]Cl-$AlCl_3$ (Scheme 6.17). In the acylation of naphthalene, the ionic liquid gives the highest known selectivity for the 1 position [142].



Scheme 6.17
The acylation of 1,1,2,6-tetramethyl-3-isopropylindane (upper) and naphthalene (lower) in [emim]Cl-$AlCl_3$.

6.5.3.2 Cracking and isomerization reaction

This reaction occurs readily in acidic chloroalluminate(III) ionic liquids. A good example of this is the reaction of polyethylene, which is converted to a mixture of gaseous alkane (C_nH_{2n} where $n = 3$–5) and cyclic alkanes with a hydrogen to carbon ratio of less than 2 [143]. Product distribution obtained from this reaction depends on the reaction temperature and differs from other polyethylene recycling reaction in that aromatics and alkenes are not formed in significant concentration [143]. The other significant difference is that this ionic liquid reaction occurs at a temperature as low as 90°C whereas conventional catalytic reactions occur at a higher temperature about 300–1000°C [144]. Fatty acids such as stearic acid or methyl stearate follow a similar kind of reaction which undergo isomerization, cracking, and dimerization reactions. This has been used to convert solid steric acid into the more valuable liquids, isostearic acids (Scheme 6.18) [145]. The isomerization and dimerization of oleic acid and methyl oleate has also been found to occur in chloroaluminate(III) ionic liquids [146].

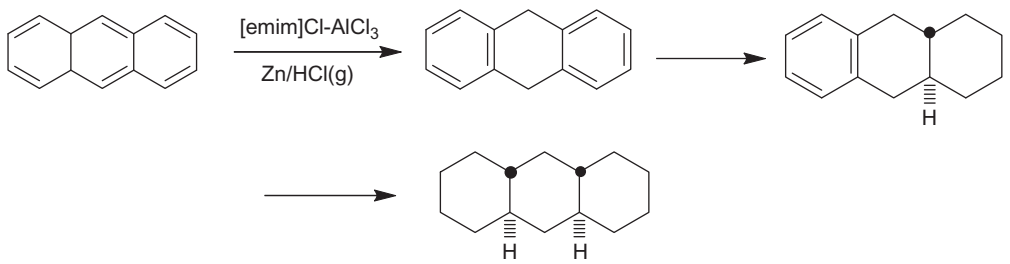


Scheme 6.18

Isomerization and cracking reactions of alkanes and alkyl chains in chloroaluminate(III) ionic liquids [143,145,146].

6.5.3.3 Hydrogenation reaction

A highly colored paramagnetic solution is formed when polycyclic aromatic hydrocarbons dissolve in chloroaluminate(III) ionic liquids when reducing agent like electropositive metal and a proton source results in the selective hydrogenation of the aromatic compound. This hydrogenation occurs at ambient temperature and pressures, whereas catalytic hydrogenation reaction requires high pressure and high temperature and also an expensive platinum oxide catalyst. For example, pyrene and anthracene can be reduced to perhydropyrene and perhydroanthracene at ambient temperature and pressure; only the thermodynamically most stable isomer of the product obtained (Scheme 6.19) [147]. Moreover, if the reduction in ionic liquid is carefully monitored, a number of useful intermediate products can be isolated.



Scheme 6.19

The sequence in the reduction of anthracene to perhydroanthracene.

Ionic liquids have multifarious properties. One of the main areas of ionic liquid applications today is catalyst. The variety of reactions where ionic liquids are used as solvent includes

oxidation and reduction, polymerization, cross-coupling, and hydroformylation. Due to their high cost and rather specific physical properties (high viscosity and low diffusion coefficient), however, the practical use of ionic liquid is somewhat limited.

6.6 Renewable Solvents as a Reaction Media

6.6.1 Introduction

Renewable feedstocks are found best sources for the solvents and can be used as alternatives for current VOCs. These solvents can be used as is without any need for modification of equipment or procedure. Naturally occurring feedstock such as cellulose and starch possess the large number of oxygen atoms so that most renewable solvents have oxygen-containing functional groups, alcohols, esters, and ethers being the most common. However, many currently employed solvents also contain these groups. The most extensively used group of VOC solvents that cannot be biosourced are chlorinated hydrocarbons such as methylene chloride, etc. Hydrocarbons including aromatics could potentially be biosourced through transformations of cellulose and lignocelluloses using the biorefinery. The various biosourced platform chemicals or building blocks that can be produced either biologically or chemically from natural feedstocks are shown in Fig. 6.2. These platform chemical bearing many acid and alcohol functionalized molecules. Significant development is ongoing to yield new bioderived polyesters in the field of polymer chemistry using esterification reactions.

Another approach to biomass-derived chemical production is production of syngas from biomass gasification and Fischer-Tropsch technology for the production of methanol or hydrocarbons [148]. The variety of feedstocks such as waste materials, forest products, energy crops, and aquatic biomass are used for production of platform chemicals or fuels from biomass [149]. Extensive research is ongoing in the area of cellulose conversion, and cellulose-derived chemicals and fuels have a promising future. In the last decade, due to the increase in the cost of crude oil, bioderived fuel production, bioethanol, and biodiesel have therefore gained attention significantly. These liquids can also be used as solvents in chemistry. The glycerol produced during biodiesel production can be used directly as a solvent or converted into diols, esters, ethers, and a variety of other chemicals [150].

In terms of a life-cycle analysis, the biosourced solvents are nominally green but they are not perfect. They are still VOCs and have associated risks including flammability, atmospheric pollution, and user exposure. Also, as is regularly highlighted in media coverage of biofuels, biosourced chemicals may not be carbon neutral because significant amount of energy and fertilizers are used in their production. Therefore, it would be advisable to consider social, economic, and environmental advantages and disadvantages during complete environmental economic analysis. Additionally, in most cases, as can be seen from their molecular structure (see Fig. 6.3), biosolvents are not inert when compared to conventional solvents such as

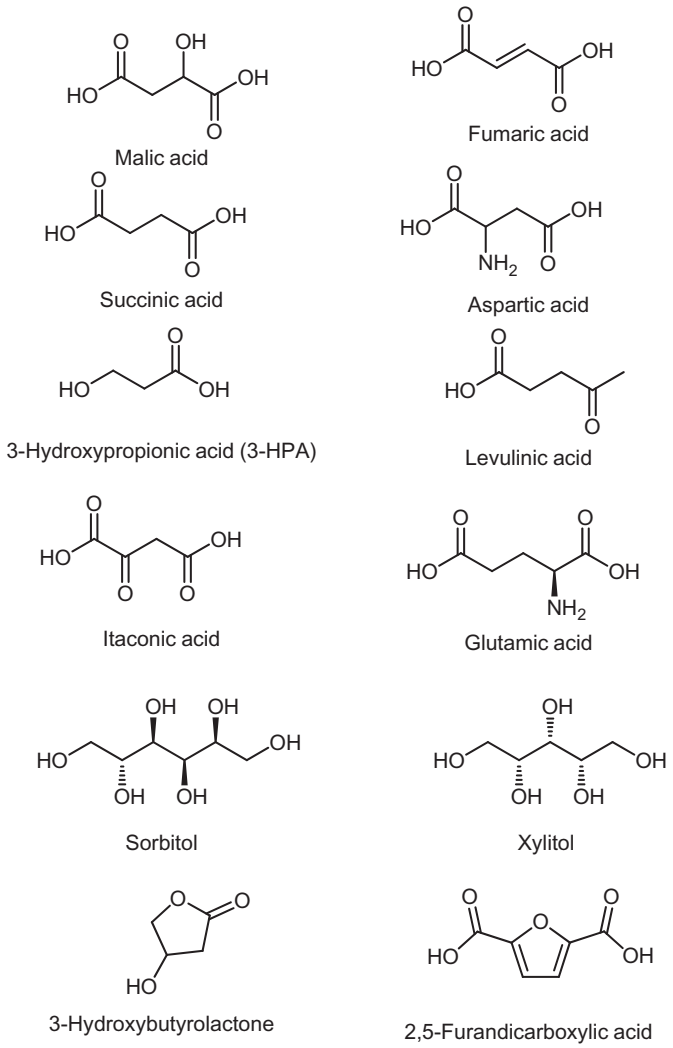


Fig. 6.2
Biosourced platform chemicals.

methylene chloride and toluene. For example, alcohols can undergo oxidation, substitution, and dehydration reactions. Due to corrosive nature biosourced acetic acid has limitations as a green solvent.

6.6.2 Chemical Examples

6.6.2.1 Alcohols including glycerol

Ethanol and methanol are common solvents of choice used in various laboratories worldwide. However, their use has declined for reactions and separations recently. Petroleum-sourced alternatives such as halogenated and aromatic solvents are being preferred over these alcohols.

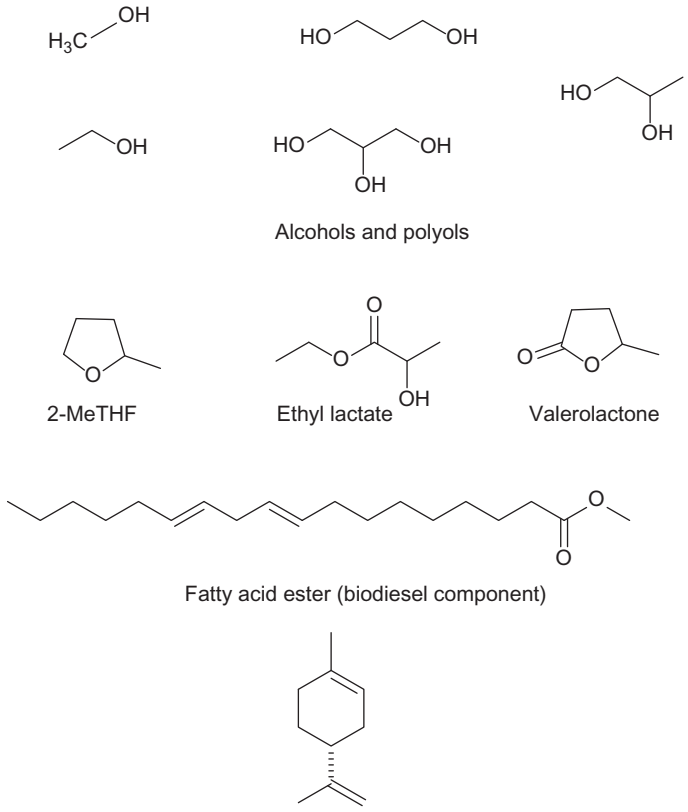


Fig. 6.3
Some solvents available from renewable feedstocks.

Methanol and ethanol both are volatile, possess low flash points, and large explosion ranges. This implies that there are significant hazards associated with their use especially when compared to many other alternative solvents including glycerol. Ethanol is generally produced through fermentation of starch crops but routes from cellulose, which can come from waste materials, are gaining momentum. Methanol can be produced from syngas that can be obtained through biomass gasification. Ethanol is commonly used as a solvent for substances intended for human use such as in scents, flavors, coloring agents, cosmetics, and medicines. It is widely used in food industry and in the extraction of natural products. Ethanol is also used in thermometers. The physical properties of ethanol stem primarily from the presence of its hydroxyl group and the shortness of its carbon chain. The hydroxyl group is able to participate in hydrogen bonding, rendering ethanol more viscous and less volatile than other less polar organic compounds of similar molecular weight. It is a versatile solvent as it is miscible with water and with many organic solvents including acetone, diethyl ether, glycerol, and toluene. It is also miscible with low-molecular-weight aliphatic hydrocarbons such as pentane and hexane. Its miscibility with water contrasts with that of long chain alcohols (five or

more carbon atoms) whose water miscibility decreases sharply as the number of carbons increases. The polar nature of the hydroxyl group renders many ionic compounds soluble in it including sodium and potassium hydroxides, ammonium chloride, and bromide, etc. Since the ethanol molecule has a nonpolar end, it also dissolves nonpolar substances including many essential oils and numerous flavoring agents, coloring agents, and medicinal compounds.

Methanol is very similar to ethanol in physicochemical properties but it is toxic. This low toxicity profile of ethanol therefore makes it a preferred solvent for most applications, for example, medicinal agents. Synthetic procedures, however, need a solvent having ease of removal from the reaction mixture and the greater volatility of methanol makes it the solvent of choice. As ethanol and methanol are common laboratory solvents, their application in extraction and reaction chemistry is not discussed at length here. Details on many procedures using these solvents can be found in standard chemistry textbooks and some primary literature.

The present era interest in ethanol lies in the success of some new and exciting procedures reported recently which make use of acid catalysis in aqueous ethanol for the esterification of platform molecules [151,152]. This reaction also highlights the reactivity of alcohols as ethanol is one of the substrates in the reaction. It is likely that ethanol and water will continue to play a prominent role as solvents in new transformation chemistry being developed.

Glycerol, a byproduct of biodiesel production and other processes, is nontoxic and has promising physical and chemical properties as an alternative solvent [153,154]. It has a very high boiling point and negligible vapor pressure. Glycerol can dissolve many organic and inorganic compounds. It is poorly miscible with water, some ethers, and hydrocarbons. Therefore, instead of distilling products from this reaction, medium simple extractions using other solvents such as ether and ethyl acetate for the product separation are also possible. It is noteworthy that glycerol can be converted to methanol, ethanol, 1-propanol, and propanediols through hydrogenolysis reactions and therefore is a potential feedstock for generation of other solvents [155]. High conversions and selectivities have been obtained for a range of catalytic and stoichiometric reactions performed in glycerol including nucleophilic substitutions and stoichiometric reductions ($NaBH_4$) as well as catalytic reductions (H_2 with Pd-C), Heck and Suzuki couplings, and enzymatic transesterification reactions [156]. Although in most of the cases glycerol could not be described as an optimum alternative solvent, these studies indicate the potential that it holds for future investigations. In fact there are some promising outcomes for glycerol as a reaction medium. For yeast-catalyzed reductions of prochiral β-keto esters and ketones, excellent yields and selectivities have been reported with glycerol [157]. Isolated yields and enantioselectivities in this case are acceptable when compared to the reaction in water and even found to be superior to the results obtained with ionic liquids or fluorous media. The only setback in these studies is that a significantly longer reaction time was needed to obtain the same conversions in glycerol as in water. Glycerol carbonate can be prepared from glycerol via a number of routes including

its reaction with dimethyl carbonate catalyzed by lipase enzymes [158]. This compound has potential as a biosolvent for coatings, cosmetics, pharmaceuticals, and as a lubricant. However, as it is relatively a new material in the chemical industry limited data is currently available about it.

6.6.2.2 Esters

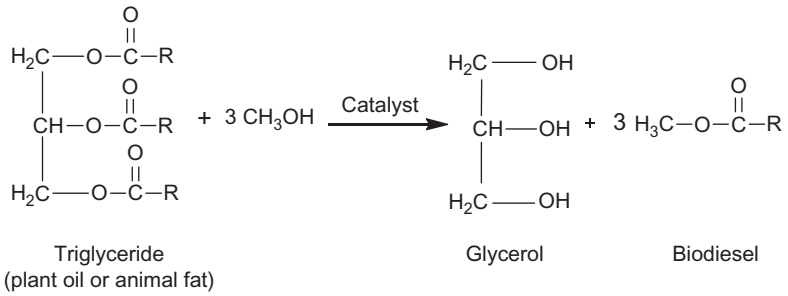
The various esters such as ethyl lactate, 2-ethylhexyl lactate, and fatty acid esters are green solvents and used in industries for various purposes: for example, 2-ethylhexyl lactate used in the degreaser, agrochemical formulation, fatty acid esters used as biodegradable oil for green inks. Ethyl lactate is widely used as biodegradable cleaning fluid due to its excellent solvent properties. It has also found industrial applications in specialty coatings and inks. Isoamyl lactate is used as an environmentally friendly solvent and household cleaner. Ethyl lactate has a boiling point of 154°C and melting point of 26°C. It has the potential to replace many toxic halogenated solvents. Due to the presence of both ester and alcohol functional groups, ethyl lactate has been explored very little in synthetic chemistry. It is successfully used to prepare magnetic tapes in combination with THF by replacing the methyl ethyl ketone (butan-2-one) and toluene [159].

GVL is another biorenewable ester with potential uses as a solvent [160]. It has a low melting point (31°C), high boiling point (207°C), and is miscible with water and biodegradable. Interestingly, the vapor pressure of GVL is very low, even at high temperatures, only 3.5 kPa at 80°C. It does not form an azeotrope with water and therefore water can be removed by distillation, as can volatile organic components because of GVL's low volatility and high boiling point. Its high boiling point may also be advantageous in some reaction chemistry by allowing increased rates of reaction. It is stable in air (does not form peroxide) and it does not hydrolyze in water.

6.6.2.2.1 Biodiesel

Plant oils or animal fats including rapeseed, soybean, and even waste vegetable oil are potential sources for biodiesel. The mustard, flax, sunflower, canola (rape), and even algae crops have are showed promising use in biodiesel production. These sources consist of monoalkyl esters, mainly methyl esters of long chain fatty acids which are obtained through transesterification of the triglycerides with an alcohol, which is usually methanol (Scheme 6.20).

Biodiesel has several advantages in that it has lower toxicity than toluene and methylene chloride and has low vapor pressure and high flash point [161]. It has excellent compatibility with other organic solvents. It has excellent environmental benefits such as it can be easily bioresourced from various feedstocks, is readily biodegradable, is a low volatile organic compound, and nonozone-depleting compound.



Scheme 6.20
Synthesis of biodiesel.

Methyl soyate (the biodiesel derived from soybean oil and methanol) is finding industrial applications including cleaning and degreasing technologies. In industry, solvents are generally needed to dissolve a material and then are often evaporated to restore the original material. So, the two important parameters, solvent power and evaporation rate, are important to choose a better solvent. The solvent power is measured by kauri-butanol value (KBV), which is a measure of the solubility of kauri gum in the solvent. A high KBV indicates a high solvent/dissolving power. Methyl soyate has a KBV of 58, indicating that it is a strong solvent [161]. Unsaturated fatty acid esters have larger KBVs than saturated fatty esters. The length of the carbon chain of the fatty acid has a significant effect on the solvent power of the biodiesel: the longer the chain, the weaker the solvent power.

An extensive work on the use of soybean oil biodiesel as a renewable alternative to organic solvents has been done [162]. Biodiesel can be used as a solvent in free radical-initiated polymerization reactions (see Fig. 6.4) [163].

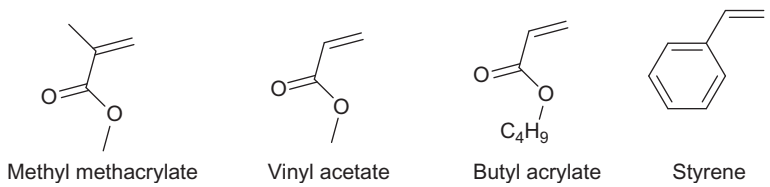


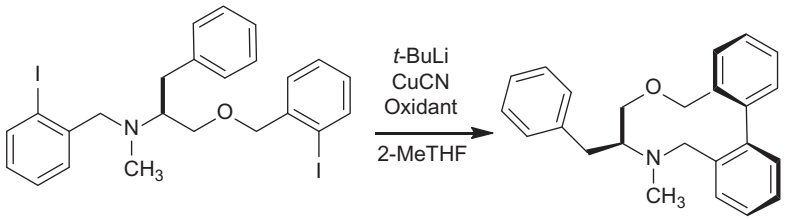
Fig. 6.4
Monomers polymerized in biodiesel.

6.6.2.3 2-Methyltetrahydrofuran (2-MeTHF)

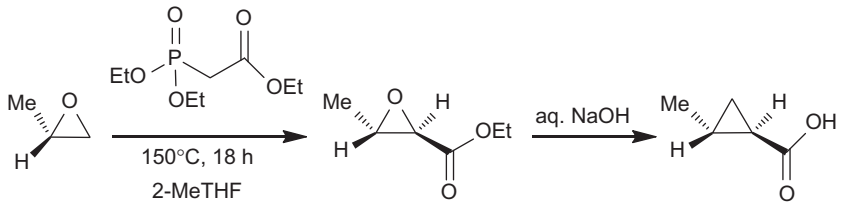
2-MeTHF can be obtained by hydrogenation of 2-furaldehyde, the 2-2-furaldehyde produced using agricultural waste such as corncobs and bagasse [164]. The 2-MeTHF has similar properties to conventional THF. However, the difficulty associated with THF is that it is miscible with water. This complicates the process in many of these reactions, and separation of

organic and aqueous phases becomes difficult. In contrast, 2-MeTHF provides clean organic-water phase separations and therefore has the potential to reduce waste streams through streamlining some separation processes. It has a higher boiling point than THF and therefore higher reaction temperatures can be used, which reduces overall reaction times. It has a low heat of vaporization, which means less solvent is lost during reaction reflux and this saves energy during distillation and recovery. Unfortunately, like most ethereal solvents, 2-MeTHF forms peroxides when exposed to air if no stabilizer is present.

Another alternative to typical ethereal solvents such as diethyl ether, THF, DME, and dioxane is cyclopentyl methyl ether (CPME) [165]. The CPME has the advantage that rate of peroxide formation is very slow, and therefore CPME is green in terms of risk avoidance and other criteria. The various classical and modern synthetic procedures have been reported in CPME as solvent [140]. The various organometallic reactions such as Grignard, Reformatskii, lithiations, hydride reductions, and metal-catalyzed couplings are reported by using 2-MeTHF, as an alternative for THF. The biaryl in an excellent yield was isolated in 2-MeTHF as solvent [166] (Scheme 6.21). In this reaction, 2-MeTHF gave superior diastereoselectivities compared with other solvents including THF. 2-MeTHF has also been used as an alternative to dichloromethane in biphasic reactions including amidations, alkylations, and nucleophilic substitutions [167]. The 2-MeTHF is used as solvent in many pharmaceutical process development labs [168,169]. For example, Horner-Wadsworth-Emmons reaction can be performed in 2-MeTHF using commercially available (*S*)-propylene oxide and triethylphosphonoacetate (Scheme 6.22). The yield was found to be strongly influenced by the solvent used, and 2-MeTHF was found to be the superior solvent.



Scheme 6.21
Copper-mediated synthesis of medium-sized biaryl containing rings in 2-MeTHF.



Scheme 6.22
Synthesis of (*R*,*R*)-2-methylcyclopropanecarboxylic acid with enhanced yields using 2-MeTHF.

6.6.2.4 Terpenes and plant oils

The two most commonly used solvents such as turpentine and D-limonene can be isolated from the essential oils and oleoresins of plants such as conifers. They are both immiscible with water. Due to similar molecular weights and structures to substituted cyclohexanes and toluene, D-limonene have solvent properties intermediate between these two VOCs. Turpentine is a liquid obtained from the distillation of tree resin. It consists mainly of the monoterpenes α-pinene and β-pinene. As a solvent, it is used to thin oil-based paints and for producing varnishes. D-Limonene is the main component of oil extracted from citrus fruit rinds and is therefore a byproduct of the fruit juice industry. In particular, D-limonene is finding wide use in the manufacture of household and personal cleaning products, partly because of its pleasant aroma. It is also finding uses as an oil-rig cleaning agent, in paints, fragrance additives, cooling fluids, and other specialty products. D-Limonene is being considered as an alternative for methyl ethyl ketone, acetone, toluene, xylene, and many chlorinated solvents. The reactivity of the C═C double bonds must be taken into account during the application of this solvent in synthetic chemistry.

Limonene has been found an alternative to hexane which was used in rice bran oil extraction processes [170,171]. The yield and quality of crude rice bran oil obtained from the limonene extraction were almost comparable to those obtained using hexane. The solvent was recyclable in such a process. As shown in Fig. 6.5, three types of polymerization reaction have been reported by using D-limonene as reaction media. There are several advantages for limonene as solvent. It has low toxicity compared with the toluene and methylene chloride. It can be bioresourced from various feedstocks and is biodegradable.

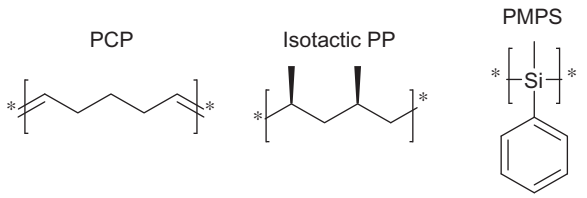


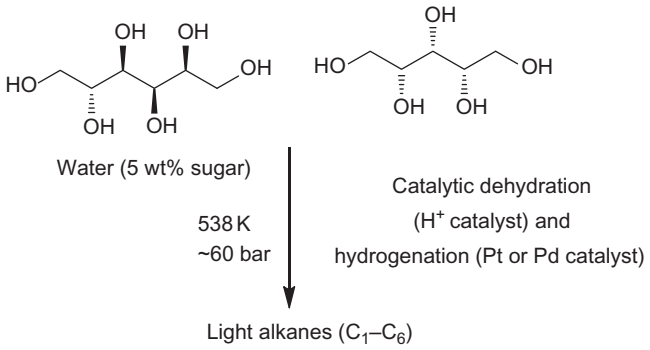
Fig. 6.5
Polymers prepared in D-limonene: poly(cyclopentene) (PCP), isotactic polypropylene (PP), and poly(methylphenylsilane) (PMPS).

Norbornene, 1,5-cyclooctadiene, cyclohexane, and cyclopentene were polymerized by ring-opening metathesis polymerization using Grubb's second-generation catalyst in presence of limonene as solvent [172]. D-Limonene and α-pinene have been used as renewable solvents and chain transfer agents in polymerization of α-olefins [173].

Polymethylphenylsilane has also been prepared in D-limonene via a standard Wurtz-type synthesis and by using this solvent, and significant effect on the molecular weight was achieved [174]. In summary, use of D-limonene has yielded interesting results in polymer chemistry.

6.6.2.5 Renewable alkanes

Synthesis of liquid hydrocarbons from biomass feedstocks is the current era of research [175–177]. Dumesic and coworkers reported that stream of alkanes could be synthesized by aqueous phase reforming of sorbitol over a bifunctional catalyst. The sugar is sequentially dehydrated using a solid acid and hydrogenated catalyst using a precious metal catalyst such as platinum or palladium (Scheme 6.23) [177].



Scheme 6.23
Dehydration and hydrogenation of the platform chemicals sorbitol and xylitol.

Long chain alkanes were produced with varying the chain length in this study, and selectivity over chain length was found to vary with pH and/or the amount of solid acid added. The hydrocarbons could also be used as solvents. However, they are flammable and hazardous and not perfect green solvents.

6.7 Summary and Outlook of Future

The nonconventional reaction media holds much more promise than traditional solvents for the development of a sustainable chemical manufacturing industry using the various homogeneous, heterogeneous, and enzymatic catalytic methodologies. Water found as cheap, abundantly available, nontoxic, and nonflammable solvent and the use of aqueous biphasic catalysis provides an ideal basis for recovery and recycling of the catalyst. Water is also the ideal solvent for many enzyme-catalyzed processes. $scCO_2$ also has many potential benefits in the context of sustainability. Like water, it is cheap, abundantly available, nontoxic, and nonflammable. It is also an extremely suitable solvent for homogeneous, heterogeneous, and biocatalytic processes, and it can be easily separated from the catalyst and product by simply releasing pressure. In $scCO_2$ media reaction rates are very high, owing to its intermediate properties, between a gas and a liquid. The ionic liquid, or polyethylene glycol, also hold promise as reaction media for a variety of catalytic processes integrated with product separation and catalyst recycling. Ionic liquids are potentially attractive alternatives for performing

conversions which are not feasible in water or $scCO_2$. The disadvantages of ionic liquid are high price and/or limited availability coupled with issues of biodegradability and/or aquatic toxicity. There is enormous work going on to develop methods for the production of a range of commodity chemicals from biomass. Chemists are investigating ways to catalytically deoxygenate platform chemicals and glycerol, and this may lead to further biosourced molecules with suitable solvent properties. Additionally, many researchers are studying the catalytic conversion of cellulose directly into alcohols and alkanes. Therefore, the future looks bright for biosourced solvents. However, many of these solvents are still VOCs and therefore a long way from being perfect green solvents. Many are highly flammable and some are toxic. On the other hand, some are biodegradable. In the immediate future, the solvents discussed in this chapter can be used as slot-in replacements for petrochemically sourced VOC solvents. However, significant research is needed to assess the applicability of these solvents in chemical processes. One-pot syntheses via catalytic cascade processes, involving chemo- and biocatalysis, and based on water and carbon dioxide as basic raw materials and reaction media, would seem to provide the ideal basis for a sustainable chemical industry.

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CHAPTER 7

Catalytic Reaction Engineering

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7.1 Introduction

Catalysts and catalytic reactions lie at the heart of the chemical process industry. Many of the chemical (and biological) transformations necessary to make fine and specialty chemicals involve the use of catalysts. Several such examples are discussed in Part II of this book. Analysis of how these transformations occur is termed chemical reaction engineering (CRE), which has evolved into one of the major and distinguishing disciplines in chemical engineering. It influences a variety of aspects, including techno-economic feasibility of the process of interest. In catalytic reactions, a homogeneous or heterogeneous catalyst provides a reduced activation energy barrier for the transformation and facilitates better control on selectivity. The development and selection of the right catalyst therefore can make a substantial impact on process viability and economics. Besides the right catalyst, it is essential to develop the right reactor type and process intensification strategies for effective translation of laboratory process to practice. Reaction engineering deals with these aspects and therefore plays a crucial role in chemical and allied process industries. In this chapter, the application of CRE to catalytic reactions is discussed.

The key aspects of reaction and reactor engineering are briefly discussed in Chapter 1. It may be useful to recapitulate some of those points here; the reader may also refer to the discussion in Chapter 1. A thorough understanding of thermodynamics and the chemistry of the reacting system under consideration is an essential prerequisite for carrying out reaction engineering analysis. Basic thermodynamic analysis will help identify favorable operating conditions and strategies to achieve the desired performance. The theories and modeling tools required to carry out these functions are fairly well developed and do not involve any consideration of actual reactor hardware and underlying fluid dynamics. An understanding of chemistry allows one to represent the overall transformations into key (consistent with thermodynamics) chemical reactions. Reaction engineering analysis can then focus on how fast these chemical reactions will occur. The effective rate of chemical reactions often depends on intrinsic reaction kinetics and various transport processes like mixing, heat and mass transfer. Analysis of the transport processes and their interaction with chemical reactions

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can be quite complex and is intimately connected to the underlying fluid dynamics. Such a combined analysis of chemical and physical processes constitutes the core of CRE.

CRE analysis therefore inherently encompasses a wide range of scales, from the atomic scale on which elementary reactions take place, to the reactor scale (or even in some cases to global scale/life cycle analysis). These interactions are shown schematically in Fig. 7.1. Reaction engineering is no longer limited to the defined brackets of relating the kinetics of the reaction to the reactor performance. This has been transformed into integration of knowledge from various streams of disciplines with advanced experimental techniques and modeling tools for relating molecular scale phenomena to plant scale operations [14,64].

Multiscales are inherent in any reacting system and analysis of various scales involved in the overall reaction process includes a wider range of objectives, such as design of the catalyst, modification of the surface properties to tune the reaction in a desired way, prediction of intermediate and bulk properties, rate analysis, reduction in empirical information, development of theoretical background, finding out reaction networks and mechanisms, optimal reactor design and development of control strategies. Terms like microscale, mesoscale, and macroscale are generally used in a relative manner. In the larger view shown in Fig. 7.1, the microscale processes refer to molecular scale processes and the macroscale processes refer to plant scale or even larger scale, up to the entire planet. The major role of CRE lies between these extremes, shown inside a rectangle of *black dotted lines*. These scales are further divided into microscale (reaction kinetics), mesoscale (particle/bubble level processes), and macroscale (reactor). The scope of this chapter is restricted to these scales (from reaction kinetics to reactor scale analysis).

The reaction kinetics or the rate of transforming one chemical species into another must be determined from experimental measurements. Measuring the rate of chemical reactions in the laboratory is in itself a specialized branch of science and engineering. It is important that this rate is an intrinsic property of a given chemical system and is not a function of any physical process such as mixing or heat and mass transfer. It is therefore essential to separate the effects of physical processes from the measured experimental data to extract information about the intrinsic reaction kinetics. Assuming that such intrinsic rate data is available, chemical kineticists have developed a number of valuable generalizations for formulating rate expressions, including those for catalytic reactions. Various textbooks cover aspects of chemical kinetics in detail [30,65,99]. Some aspects of this are briefly discussed in this chapter.

Once the intrinsic kinetics is available, the production rate and composition of the products can be in principle related to the reactor volume, reactor configuration and mode of operation by solving mass, momentum and energy balances over the reactor. This is the central task of a reaction engineering activity. Here it is important to first select the appropriate type of reactor for carrying out the desired transformations. A wide variety of reactor types have been developed and used. Different reactor types and key aspects of their hydrodynamic and transport characteristics (mixing, heat and mass transfer) are briefly discussed in this chapter. Some

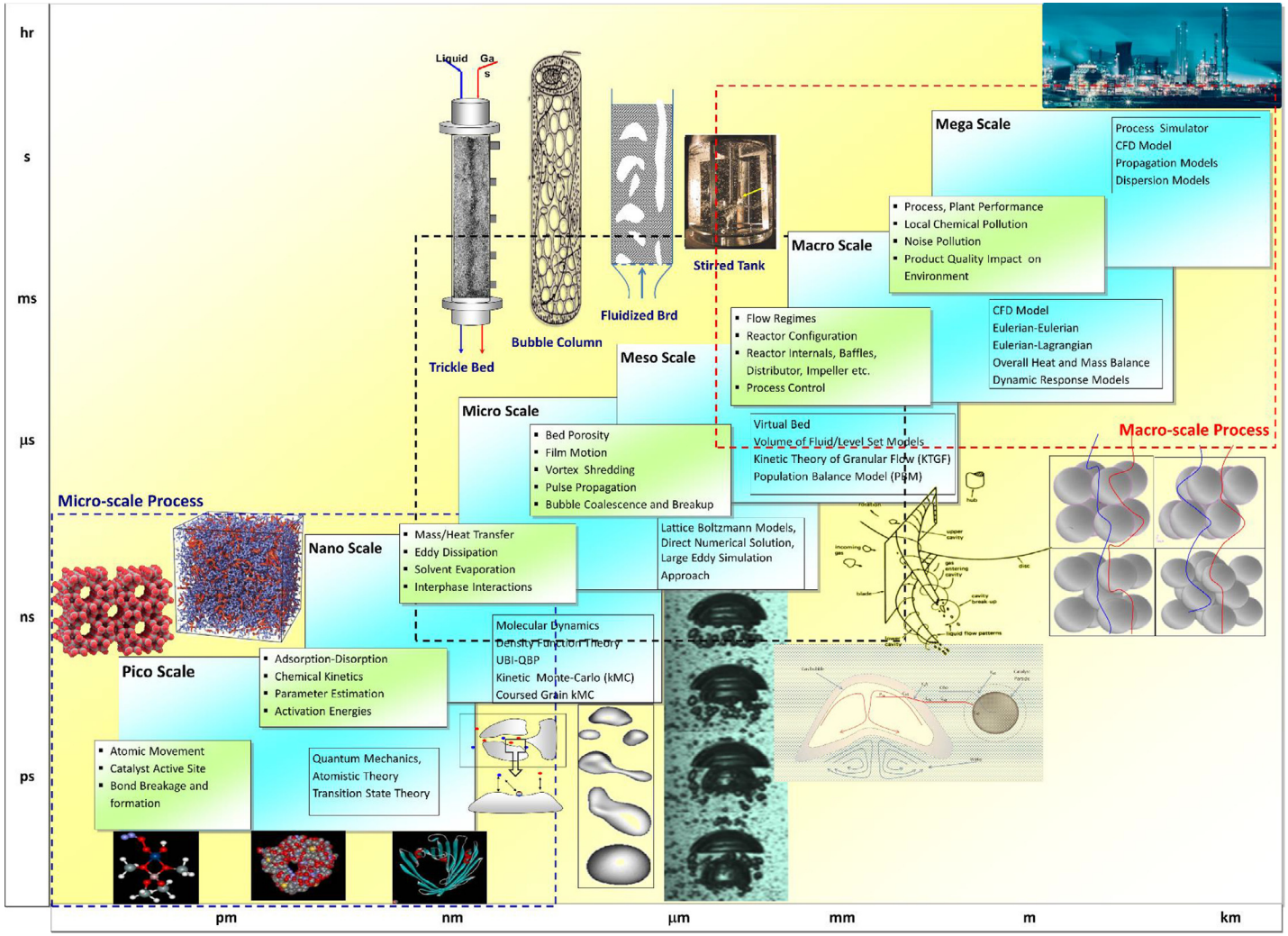


Fig. 7.1
Schematic of scales involved in reaction-reactor chemical engineering.

comments on state-of-the-art computational fluid dynamics (CFD)-based modeling of these reactors are included. Aspects of scale-up are also briefly commented upon. The material provided in this chapter, along with the cited references, is expected to provide a useful introduction and starting point of systematic reaction engineering analysis of catalytic reactions.

Reactions may be catalyzed either by homogeneous catalysts or heterogeneous catalysts, as discussed in Chapters 1–3. Key aspects are briefly summarized here before other engineering aspects are discussed. As mentioned earlier, a catalyst is a substance which provides an alternative route of reaction which has lower activation energy and thereby enhances the rate of reaction. In homogeneously catalyzed systems, the catalyst and the substrate are in the same phase. In heterogeneously catalyzed systems, the catalyst is typically solid and the reactants are in gas or liquid phases. Key characteristics of these catalytic systems are briefly summarized in Table 7.1. A homogeneous catalyst typically forms a complex with one of the reactants, which eventually transforms it into the product after interacting with other reactants. The process is essentially similar to homogeneous reactions in the absence of a catalyst and is often controlled by the mixing of reactants and catalyst species on a molecular level. In contrast to this, in a heterogeneous catalyst, several additional steps such as transport from bulk to surface of the catalyst pellet, diffusion inside the pellet and adsorption are involved, along with the reaction occurring on the catalyst surface. These steps need to be understood in order to select the appropriate reactor and operating strategy. This will be discussed later in this chapter. In the following section, key concepts of reaction kinetics applied to catalytic reactions are discussed.

Table 7.1 Key characteristics of homogeneous and heterogeneous catalytic systems

	Homogeneous Catalysis	Heterogeneous Catalysis
Catalyst form	Soluble in liquids (transition metal complexes with ligand)	Metals supported on solids or metal oxides
Operating conditions	Generally milder operating conditions (ie, low pressure and temperature)	Relatively higher pressure and temperature
Mass transfer	Higher; rates usually controlled by agitation	Lower; diffusion may be one of the rate-controlling steps
Heat transfer	Higher heat transfer rates	Poor heat transfer rates; overheating may lead to sintering and deactivation
Catalyst separation/addition	Separation is difficult; because catalyst is soluble, addition of catalyst is easy	Separation is relatively easy; catalyst addition/removal is difficult
Active sites and mechanisms	Active sites can be well defined; understanding the reaction mechanism is relatively straightforward	Active sites are nonuniformly distributed over a solid surface; mechanisms are not well understood

7.2 Kinetics of Catalytic Reactions

Reaction kinetics essentially deals with the quantification of rates at which chemical reactions progress. This essentially involves formulating a mathematical framework to describe the rate (and mechanism) by which one chemical species is converted into another in the absence of any transport limitations (chemical kinetics). The rate is the mass, in moles of a species, transformed per unit time, while the mechanism is the sequence of individual chemical events, whose overall result produces the observed transformation. Though knowledge of the mechanism is not essential, it is of great value in generalizing and systematizing the reaction kinetics. The rate of transforming one chemical species into another cannot be predicted with accuracy. It is a specific quantity which must be determined from experimental measurements in spite of recent advances in computational chemistry and molecular modeling.

Measuring the rate of chemical reactions in the laboratory is itself a specialized branch of science and engineering. The rate is formally defined as the change in moles of a component per unit time and per unit volume of reaction mixture. It is important that this rate is an intrinsic property of a given chemical system and is not a function of any physical process, such as mixing or heat and mass transfer. Thus the rate must be a local or point value referring to a differential volume of reaction mixture around that point. It is therefore essential to separate the effects of physical processes from the measured experimental data to extract information about the intrinsic reaction kinetics. It is a difficult task and requires special efforts to achieve this in practice, especially for catalytic reactions involving multiple phases. More information about chemical kinetics and about laboratory reactors used for obtaining intrinsic kinetics can be found in textbooks like Smith [99], Doraiswamy and Sharma [20], and Levenspiel [65]. Assuming that such intrinsic rate data is available, chemical kineticists have developed a number of valuable generalizations for formulating rate expressions, including those for catalytic reactions. Various textbooks cover aspects of chemical kinetics in detail [30,65,99].

For catalytic systems, multiple phases are invariably present and therefore it is important to understand the influence of the presence of multiple phases while expressing inherent reaction kinetics. In this section, basic mathematical models used to represent reaction kinetics are briefly discussed. A discussion on the interaction of transport processes with chemical reactions is also included. The information discussed here will provide a basis for further discussion on reactor selection as well as analyzing reactor scale processes, which are discussed in subsequent sections.

7.2.1 Reaction Rate Expressions

Basic chemical kinetics models for homogeneous reactions are either based on collision theory (which is based on kinetic theory of gases) or transition state theory [25,26]. The rate expressions obtained from these models may be simplified and usually expressed as (for homogeneous reactions between species A and B)

$$\text{Rate} = Ae^{-\frac{\Delta E}{RT}} C_A^m C_B^n \tag{7.1}$$

where A is the frequency factor, R is the universal gas constant, T is a temperature in Kelvin and ΔE is the activation energy. m and n are the order of reaction with respect to species A and B, respectively.

For reactions catalyzed by a homogeneous catalyst, the catalyst is soluble in liquid phase reactants and gas phase reactants are dissolved in liquid phase in order for a reaction to occur. The reactions of interest usually occur in liquid phase, quite similar to the usual homogeneous reactions. Therefore most of the reactions are expressed as

$$A_{(G)} + bB_{(L)} \rightarrow P_{(L)} \tag{7.2}$$

Rate of consumption of A can be expressed in the following form:

$$R_A \left[\frac{\text{moles of A}}{\text{volume of liquid} \times \text{time}}\right] = -k_{mn} C_A^m C_B^n \tag{7.3}$$

where k_{mn} is the effective rate constant and C_A and C_B are concentrations of reactants A and B in reacting phase. The overall order of reaction is $m + n$. The rate constant, k_{mn}, is the reaction rate constant and is a function of temperature and the catalyst concentration. For the constant catalyst concentration, the chemical reaction rate constant is dependent on the temperature in the form of Arrhenius rate equation as

$$k_{mn} = Ae^{-\frac{\Delta E}{RT}} \tag{7.4}$$

where A is called the Arrhenius preexponential factor or a frequency factor and ΔE is the energy of activation.

In heterogeneously catalyzed reactions, the catalytic reaction rates are often expressed in terms of the catalyst quantity used for the reaction in three different forms, as follows:

$$R_A = \frac{\text{moles of A consumed}}{\text{weight of catalyst} \times \text{time}} \tag{7.5}$$

$$R_A = \frac{\text{moles of A consumed}}{\text{surface area of catalyst} \times \text{time}} \tag{7.6}$$

$$R_A = \frac{\text{moles of A consumed}}{\text{moles or volume of catalyst} \times \text{time}} \tag{7.7}$$

As discussed in Chapters 3 and 4, homogeneous and heterogeneous reactions take various paths leading to the final product. Reaction rate expressions are often expressed in terms of concentration of the reacting species and catalyst loading. Depending upon the extent of information available on the reaction mechanism, the rate expression can also be represented in

terms of intermediate complexes of the species as discussed in Chapter 2 for homogeneous reactions and in Chapter 3 for heterogeneous reactions.

It should be noted that reaction kinetics involves quantification of molecular scale phenomena. For catalytic systems, besides molecular reactions among species, several other physical processes such as interphase mass and heat transfer as well as interaction of reacting and catalytic species need to be taken into consideration. It should be noted that homogeneous reactions go through formation of several intermediate complexes. For heterogeneous reaction systems, several steps of adsorption and desorption of species on the catalytic surface as well as external mass transfer need to be considered while formulating effective reaction rates. Some of these aspects are already discussed in Chapter 3.

Here a generic case of a gas-liquid-solid reaction is briefly discussed. A gaseous reactant A is dissolved in liquid phase reactant B. The following steps may be envisaged:

- transfer of A from gas phase to liquid phase: $C_{AG} \rightarrow C_{Al}$
- adsorption of species A on solid surface, that is, $C_{Al} \rightarrow C_{As}$
- adsorption of species B on solid surface, that is, $C_{Bl} \rightarrow C_{Bs}$
- reaction between adsorbed species A and B: $C_{As}+C_{Bs} \rightarrow C_{Es}$
- desorption of product E to the bulk of the liquid, that is, $C_{Es} \rightarrow C_{El}$

These various steps are schematically shown in Fig. 7.2 (single and two-site reactions are shown in this figure). For each of the elementary steps as defined in terms of adsorption, reaction and desorption, the overall rate of reaction can be expressed in terms of the overall rate constant, total active site for adsorption and the adsorption constants for species i (K_i). After rearranging and eliminating unknown surface concentration, one can get rate expression in the following general form:

$$R_A = \frac{(\text{kinetic factor})\,(\text{driving force})}{(\text{adsorption factor})^n} \tag{7.8}$$

where n is the number of reactants.

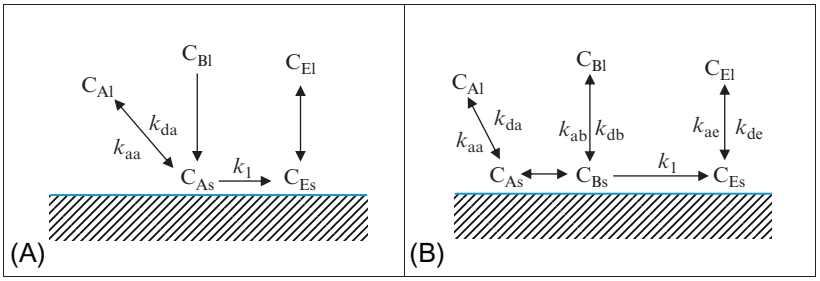


Fig. 7.2
Gas-liquid-solid reaction. (A) Single-site adsorption and reaction. (B) Dual-site adsorption and reaction.

For the reaction scheme described in Fig. 7.2, one can arrive at the following rate expression:

$$R_A = \frac{k_{ov} C_A C_B}{1 + K_A C_A + K_B C_B + K_E C_E} \tag{7.9}$$

where

$$k_{ov} = k_1 K_A S_T \tag{7.10}$$

where k_1 is a reaction rate constant expressed in m^3/kmol/s and adsorption equilibrium constant $K_A = k_{aa}/k_{da}$. k_{ai} and k_{di} are adsorption and desorption constants for ith species. S_T is the concentration of the active site available for the adsorption process and expressed as kmol/kg.

The adsorption equilibrium rate constant can be related with temperature with the following thermodynamic relation:

$$K_A = \exp\left(\frac{\Delta S^o}{R} - \frac{\Delta H^o}{RT}\right) \tag{7.11}$$

For dual-site adsorption mechanisms, the reaction rate takes the following form:

$$R_A = \frac{k_{ov} C_A C_B}{(1 + K_A C_A + K_B C_B + K_E C_E)^2} \tag{7.12}$$

where

$$k_{ov} = k_1 K_A S_T \tag{7.13}$$

Here, k_1 is expressed in terms of a second-order reaction rate constant with its units as m^3/kmol/s. The previous type of rate expressions are called Langmuir-Hinshelwood/Hougen-Watson (LHHW) type rate expressions. These rate expressions include detailed information about the mechanisms involved in the reactions, adsorption-desorption processes, and inhibition phenomena. For further information, readers may refer to Hougen and Watson [39], Yang and Hougen [116] and Barnard and Mitchell [6] for various classes of reactions. Nonlinear complex forms of LHHW type reaction rate expressions are difficult to use in engineering model equations. Therefore, alternatively, intrinsic rate expressions can also be expressed in terms of overall rate constant and the reaction order in the form of power law kinetics as follows:

$$R_A = k_{ov} C_A^m C_B^n \tag{7.14}$$

where k_{ov} is the overall rate constant with a unit of $(m^3/kmol)^{m+n-1}(m^3/kg)s^{-1}$. The power law rate expression is easier to use and easiest for fitting the experimental data over the limited range of concentration. However, this rate expression does not include any mechanistic aspect

of adsorption-reaction-desorption steps and it may therefore fail if used for extrapolation beyond the range of data on which it is based. It may be noted that the effective reaction order may change because of large variation in concentration and temperature during the course of the reaction. LHHW type of models, which account for adsorption-reaction constants (k_{ov} and K_{eq}) along with their variation with temperature, are better suited for such cases than the power law modeling approach.

7.2.2 Interaction of Reactions With Transport Processes

As mentioned earlier, catalytic reactions involve various transport processes besides reactions on a molecular scale (please also refer to Chapters 2 and 3 for more detailed discussion). Some aspects of reactions with homogeneous and heterogeneous catalysts are outlined in Table 7.1. Some aspects of interactions of chemical reactions with various transport processes are discussed for different types of reactions in the following.

7.2.2.1 Gas-liquid reactions

Gas-liquid reactions are one of the important classes of homogeneously catalyzed reactions encountered in the manufacturing of a variety of chemicals. Gas-liquid reactions proceed through the following steps:

- mass transfer from the gas phase to the gas-liquid interface
- mass transfer from the gas-liquid interface to the bulk liquid
- reaction in the bulk of the liquid in presence of a catalyst

Gas-liquid reaction processes can be represented in terms of different physical models: film theory by Whitman [113], penetration theory by Higbie [38], surface renewal theory of Danckwerts [18], and multicomponent diffusion theory by Taylor and Krishna [55]. Film theory is applicable as long as diffusion coefficients of reacting species are not very different. It is widely used and accepted for analyzing effective rates of gas-liquid reactions (see for example various cases discussed by Doraiswamy and Sharma [20]).

Film theory provides a simplified framework for analyzing complex processes occurring in gas-liquid reactions. It assumes that the mass transfer resistance is located across a thin film adjacent to the interface between different phases. Through a comparison of relative rates of transport processes and reactions, an effective rate expression may be derived. Assuming pseudo-steady state, film theory allows the following representation of a gas-liquid reacting system:

$$D_i \frac{d^2 C_i}{dx^2} = R_i \tag{7.15}$$

where D_i is the diffusivity of the ith species with C_i concentration, R_i is the rate of reaction for ith species, and x is the distance from the interface. Suitable boundary conditions need

to be defined across the film for solving the previous equation. From the film theory perspective, the mass transfer coefficient is represented as

$$-D_i \left.\frac{dC_i}{dx}\right|_{x=0} = \frac{D_i}{\delta}(C_{Ai} - C_{AL}) = k_L(C_{Ai} - C_{AL}) \tag{7.16}$$

where δ is the film thickness and k_L is the mass transfer coefficient expressed in m/s.

The overall mass transfer process is comprised of the transport of reactants from bulk gas to the gas-liquid interface and from the gas-liquid interface to the bulk of the liquid (shown schematically in Fig. 7.3).

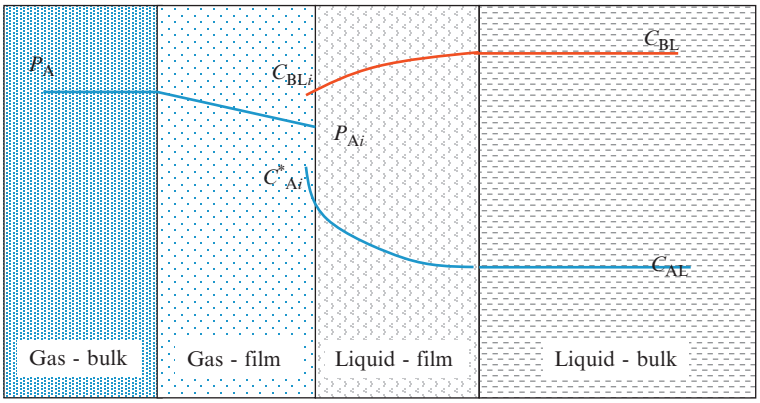


Fig. 7.3
Gas-liquid reaction (concentration profiles near gas-liquid interface).

The overall mass transfer coefficient may be related to the mass transfer coefficient of individual phases as

$$\frac{1}{k_L a_B} = \frac{1}{H_A k_G a_B} + \frac{1}{k_L a_B} \tag{7.17}$$

where $k_L a_B$ is the overall mass transfer coefficient, s^{-1}; H_A the Henry's constant; $k_G a_B$ the gas-side mass transfer coefficient, s^{-1}; $k_L a_B$ the liquid-side mass transfer coefficient, s^{-1}; a_B the gas-liquid interfacial area, m^2/m^3.

Based on the relative rates of transport processes and reactions, different regimes have been defined: slow reactions, fast reactions, and instantaneous reactions. These regimes are best defined using the dimensionless numbers representing relative rates of transport processes and chemical reactions. The following two dimensionless numbers, Hatta number (Ha) and relative diffusivity factor (q^*), are used:

$$Ha = \frac{\left[\frac{2}{m+1} D_A k_{mn} \left(C^*_A\right)^{m-1} C^n_{Bl}\right]^{1/2}}{k_L} \text{ and } q* = \frac{C_B D_B}{\nu C^*_A D_A} \tag{7.18}$$

Typical concentration profiles for slow reactions [$Ha < 0.2$] are shown in Fig. 7.4. If the mass transfer rate is much higher than the chemical reaction rate, the concentration profile of a reacting gas within the bulk liquid will be flat. For cases where rates of chemical reactions are faster than the rate of mass transfer, reactions also occur within the liquid-side film, as shown in Fig. 7.5. In such cases, the rate of the absorption of gases is enhanced because of the reaction taking place in the film. This is quantified by defining the enhancement factor (E) as

$$E = \frac{\text{Gas flux in presence of reaction}}{\text{Gas flux in pure mass transfer}} = \frac{j_A}{k_L\left(C_A^* - C_{AL}\right)} \tag{7.19}$$

Film theory-based simple models can be conveniently formulated and solved to obtain the following expression for the enhancement factor, E [111]:

$$E = \frac{Ha}{\tanh(Ha)}\left[1 - \frac{C_{AL}}{C_A^*}\frac{1}{\cosh(Ha)}\right] \sim \frac{Ha}{\tanh(Ha)} \quad \text{for low } C_{AL} \tag{7.20}$$

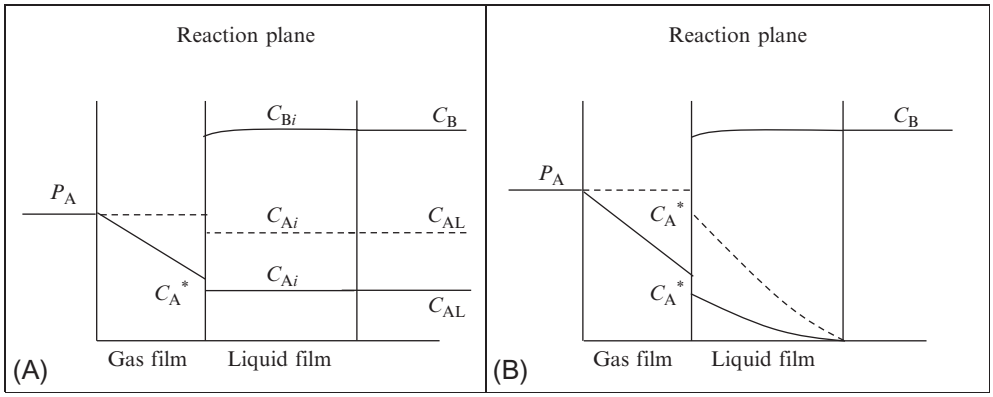


Fig. 7.4

Gas-liquid reactions: slow reactions. (A) Slow reaction: kinetically controlled. (B) Pseudo-first order mass transfer controlled reaction with respect to the gas phase.

It can be seen from the previous expression that the enhancement factor is always greater than 1. If the reaction rates are so fast that reaction occurs instantaneously, then effective reaction rates are no longer a function of reaction kinetics. In such a case, gas and liquid phase reactants do no coexist and reaction occurs in a plane lying within a liquid film (see Fig. 7.5B).

For instantaneous (relative to the mass transfer rate) reactions, the enhancement factor can be obtained as [65]

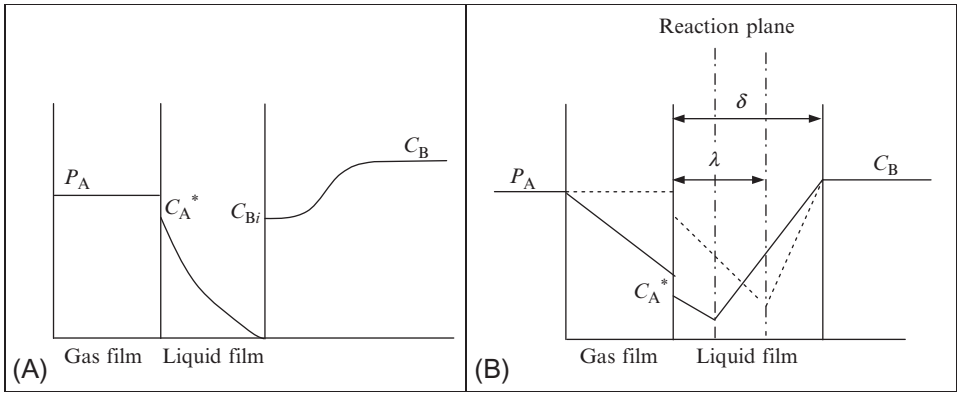


Fig. 7.5

Gas-liquid reactions: fast and instantaneous reactions. (A) Diffusion-controlled $(m-n)$th order reaction. (B) Instantaneous reaction occuring in the liquid film.

$$E = 1 + \frac{De_B C_B}{\nu De_A C_A} = 1 + q* \tag{7.21}$$

Thus for instantaneous reactions, the enhancement factor is solely a function of relative diffusivities. Overall gas-liquid reaction rates can be deduced from the diffusivity of reactants, mass transfer coefficient and reaction kinetics and are given in Table 7.2.

Table 7.2 Gas-liquid reaction rate analysis [73]

Regime	Conditions	Rate Equations
Slow reaction: kinetically controlled	$k_L a_B C_A^* \gg R_A$ and $Ha \ll 1$	$R_A = -k_{mn} C_A^m C_B^n$
Slow reaction: mass transfer controlled	$k_L a_B C_A^* \ll R_A$ and $Ha \ll 1$	$R_A = -k_{mn} C_A^*$
Pseudo mth order reaction	$1 < Ha < q^*$	$R_A = \frac{Ha}{\tanh(Ha)}$
Fast (m,n)th order reaction	$Ha \sim q^*$	Numerical solution for R_A
Instantaneous reaction	$Ha \gg q^*$	$E = 1 + q^*$

The expressions listed in Table 7.2 are shown pictographically in Fig. 7.6.

For fast reactions (with a large Hatta number), the enhancement factor equals the Hatta number. For instantaneous reactions, the diffusivity factor q^* limits the extent of enhancement.

Though this section primarily focused on gas-liquid systems, the discussion is directly applicable for homogeneously catalyzed liquid-liquid reactions. Such reactions are therefore not discussed separately. Instead, a generic discussion of gas-liquid-solid reactions is included in the following section. It should be noted that the discussion is equally applicable to liquid-liquid-solid or can be extended to gas-liquid-liquid-solid reactions.

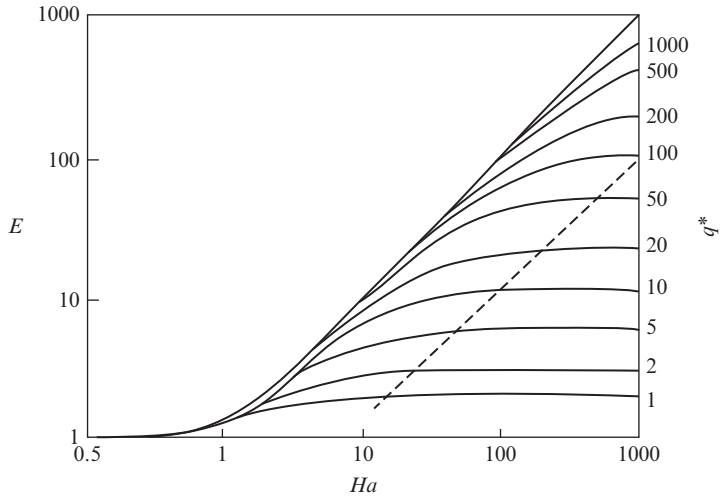


Fig. 7.6

Relationship between enhancement factor (E) and Hatta number (Ha) for (1, 1) order reaction. *From P.L. Mills, P.A. Ramachandran, R.V. Chaudhari, Multiphase reaction engineering for fine chemicals and pharmaceuticals, Rev. Chem. Eng. 8 (1–2) (1992) 1–176; A. Gianetto, P.L. Silveston, Multiphase chemical reactors: theory, design, scale-up, Hemisphere, New York, 1986.*

7.2.2.2 Gas-liquid-solid reactions

The presence of an additional solid phase adds one more transport resistance to reactants apart from the gas-liquid phases. Overall, the gas-liquid-solid multiphase mass transport and reaction system is schematically shown in Fig. 7.7. Mass transfer across each phase is defined in terms of gas-liquid mass transfer, liquid-solid mass transfer and diffusion inside the catalyst particle if the catalyst is porous. Commercially, both porous as well as nonporous

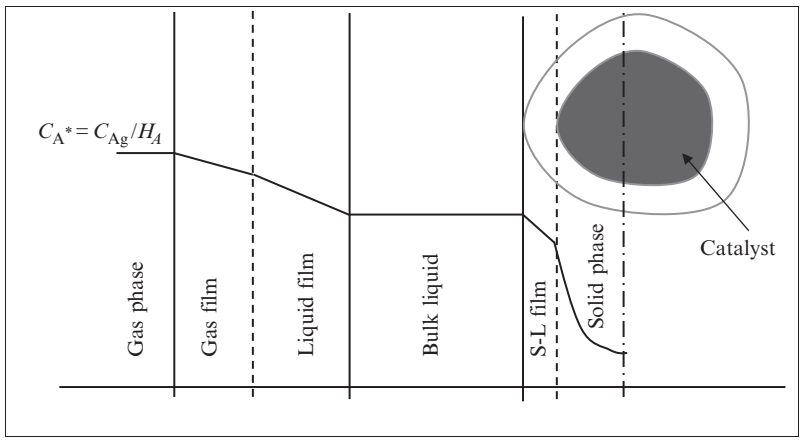


Fig. 7.7

Gas-liquid-solid reaction.

catalysts are used for carrying out reactions. For nonporous catalysts, reactions occur on the surface of the catalyst and mass transfer from liquid to the solid phase needs to be accounted in gas-liquid transport resistance, as described in the previous section.

Mass transfer to a solid catalyst surface can be accounted in the form of a mass transfer coefficient as follows:

$$R_A = k_s a_P \left(C^*_{AL} - C_{As}\right) \tag{7.22}$$

where k_s is the mass transfer coefficient from liquid phase to solid phase, m/s; a_P the external surface area of the catalyst particle per unit volume of the reactor.

Therefore, the overall mass transfer rate equation takes the following form:

$$R_A = \underbrace{\left[\frac{1}{k_L a_B} + \frac{1}{k_s a_P}\right]^{-1}}_{\frac{1}{k_{ov}}} C^*_A \tag{7.23}$$

The overall mass transfer coefficient is considered while deriving effective rate expression. The inherent reaction kinetics is represented either by power law or Langmuir-Hinshelwood type rate expression. For nonporous catalysts and first-order reactions with excess of liquid phase concentrations C_{BL}, the rate expression takes the following form:

$$R_A = w k_1 C_{As} \tag{7.24}$$

Eliminating the unknown catalyst surface concentration of C_{As}, the effective reaction rate expression takes the following form:

$$R_A = \left[\frac{1}{k_L a_B} + \frac{1}{k_s a_P} + \frac{1}{b k_1}\right]^{-1} C^*_A \tag{7.25}$$

In the case of a porous catalyst, in addition to gas-liquid and liquid-solid mass transfer resistance, intraparticle diffusional resistance exists inside the porous catalyst. The equation to relate the intraparticle diffusion with the reaction rate for first-order reaction kinetics with excess of B concentration is as follows:

$$\frac{De_A}{r^2}\frac{d}{dr}\left(r^2 \frac{dC_A}{dr}\right) = \rho_P k_1 C_A \tag{7.26}$$

where De_A is an effective diffusivity of the reactant A in the porous catalyst in m^2/s and r is the radius of the catalyst. Using appropriate boundary conditions (zero concentration gradient at the center of the particle and C_{As} as the concentration at the surface of the particle), one obtains

$$\frac{C_A}{C_{As}} = \frac{1}{(r/R)} \frac{\sinh(3\phi r/R)}{\sinh 3\phi} \tag{7.27}$$

where ϕ is the Thiele modulus, which is defined as

$$\phi = \frac{R}{3}\left(\frac{\rho_P k_1}{De_A}\right)^{1/2} \tag{7.28}$$

The overall rate of reaction can be written as

$$R_A = \frac{3bDe_A}{\rho_P R}\left(\frac{dC_A}{dr}\right)_{r=R} \tag{7.29}$$

It is often necessary to use numerical methods to solve nonlinear intraparticle diffusion-reaction equations. It is therefore convenient to define the catalyst effectiveness factor (η_c):

$$\eta_c = \frac{\text{Actual rate of reaction } (R_A)}{\text{Rate of reaction in absence of diffusional resistances}} \tag{7.30}$$

Therefore, the overall rate of reaction for first-order kinetics becomes

$$R_A = \eta_c b k_1 C_{As} \tag{7.31}$$

Eliminating unknown surface concentration C_{As}, an expression similar to the nonporous catalyst can be formulated as

$$R_A = \left[\frac{1}{k_L a_B} + \frac{1}{k_s a_P} + \frac{1}{\eta_c b k_1}\right]^{-1} C_A^* \tag{7.32}$$

The catalyst effectiveness factor (η_c) for first-order reaction kinetics can be derived as [88]

$$\eta_c = \frac{1}{\phi}\left(\coth 3\phi - \frac{1}{3\phi}\right) \tag{7.33}$$

The previous expression is derived by assuming an isothermal operation. However, for highly exothermic reactions, the catalyst particle may not remain in an isothermal condition. In such situations, the rise in temperature inside the catalyst particle leads to higher reaction rates than rates at the surface, and therefore the catalyst effectiveness factor can increase more than unity. Catalyst effectiveness factors in such cases may be estimated by simultaneously solving mass and energy balances. Interested readers may refer to Doraiswamy and Sharma [20] and Ramachandran and Chaudhari [85] for more detailed treatment of this topic.

The analysis discussed so far has been related to local processes: local reaction rates as functions of local concentrations, temperature as well as local rates of various transport processes. It is essential to develop reactor scale models using such local level submodels. The reactor scale models may be classified into two types: reaction engineering models

(with simplified representation of underlying fluid dynamics of reactors) and reactor engineering models (with greater emphasis on interaction of reactions with underlying fluid dynamics). These two types of models are discussed in the following sections.

7.3 Reaction Engineering Models

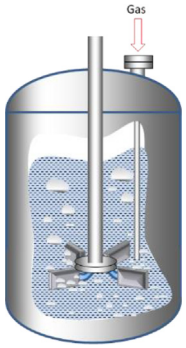
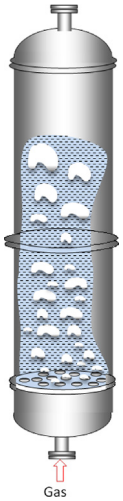
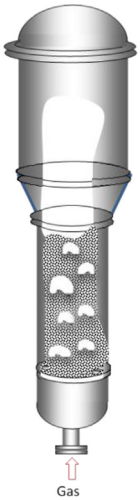
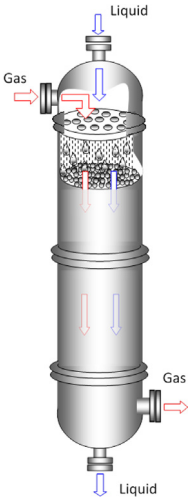
The purpose of reaction engineering models is to relate reactor design, operating protocol, and reactor performance. It encompasses everything related to the engineering of chemical transformations. Chemical transformations or reactions can occur only if the reactant molecules are brought into molecular contact (mixed) under an appropriate environment (temperature and concentration fields, catalysts) for an adequate time. A process vessel, which provides such necessary conditions to favor the desired reaction and allows for removal of products, is a reactor. It is important to ensure that optimal conditions (such as temperature, concentration, and pressure) are provided in this specially designed reactor volume. Usually some mechanical means (such as pumping or stirring or gravity-driven flow) are used to realize desired conditions. In practice, spatial and temporal variations in concentrations of chemical species and temperature within the reactor lead to suboptimal utilization of the reactants or their conversion to the desired product. Thus the capability of a reactor design in effecting a certain process depends largely on its ability to realize the best possible contacting pattern, provide adequate residence and contact time, and, hence, realize the maximum potential of the activity that is "locked in" in the catalyst. This idea has been discussed using the concept of reactor efficiency by Ramachandran and Chaudhari [85]. Reactor efficiency is defined as the ratio of the total amount of desired product produced to the amount of desired product produced if all of the catalyst was exposed to the reactant concentrations at the reactor inlet. Reactor efficiency is one of the measures which reflects the effect of the flow pattern of the phases involved. The first step in reaction engineering therefore is selection of an appropriate contacting pattern and type of reactor. This is briefly discussed in the following.

7.3.1 Selection of Reactor

There are several types of reactors used for such catalytic and multiphase applications. The broad reactor types classified based on the presence of phases and three-level approach for reactor selection and design as proposed by Krishna and Sie [56] are discussed in Chapter 1. Various other factors which need to be considered while designing a catalytic reactor were also briefly mentioned. The most commonly used reactors and their key attributes are summarized in Table 7.3. The contacting pattern, key attributes of mixing and transport processes and overall strategy proposed by Krishna and Sie [56] need to be used to evolve appropriate flow pattern/contacting pattern. The goal is to decide on a flow pattern that optimally utilizes the catalyst. In other words the catalyst has a certain intrinsic activity, and the contacting pattern should try and realize that activity in all parts of the reactor. A case of a gas-liquid-solid reactor is briefly discussed here to illustrate.

Reactions which are performed in three-phase catalytic systems can be generically described by a gas phase reactant (designated as A), which dissolves in the liquid and then reacts on the solid catalyst surface with a reactant B which is in the liquid phase. For simplicity, we assume that reactant B is practically nonvolatile and, hence, it may not enter the gas phase. The product formed is typically in the liquid phase (which, in slurry systems, completely wets the catalyst). A typical example of such a reaction system can be the hydrogenation of unsaturated hydrocarbons, with hydrogen being in the gas phase [83,102,109].
The catalyst, which may be native metal or metal impregnated on a porous support like carbon or alumina, is suspended in liquid so that, after dissolving in the liquid film, the gas meets the reactant molecules from the liquid phase on the catalyst surface (outer surface in the case of a native metal catalyst and by diffusion through the pores of the catalyst in the

Table 7.3 Commonly used catalytic reactors and their key attributes

Aspect	Slurry Stirred Reactor	Slurry Bubble Column Reactor	Three-Phase Fluidized Reactor	Trickle Bed Reactor
Schematic				
Operation	May not handle very high catalyst loading	Countercurrent operation preferred	Gives operational flexibility for a wide range of processes	Suitable for systems requiring large catalyst loading
Solid loading	Less effective	Less effective	Good operating characteristics	Excellent
Solid holdup	0.01–0.1	0.01–0.3	0.2–0.6	0.4–0.6
Particle size/ separation	Small particles, needs catalyst separation	Needs catalyst separation	Particle attrition and agglomeration, yet popular choice	Quite flexible
Attrition	High	Fair	Fair	Low

Continued

Table 7.3 Commonly used catalytic reactors and their key attributes—cont'd

Aspect	Slurry Stirred Reactor	Slurry Bubble Column Reactor	Three-Phase Fluidized Reactor	Trickle Bed Reactor
Heat transfer	Excellent	Excellent	Good	Poor
Mass transfer	Excellent	Very good	Very good	Good
Dispersed phase holdup	0.01–0.1 (gas)	0.05–0.5 (gas)	0.1–0.5 (gas)	0.02–0.2 (liquid)
Degree of backmixing	Very high	Medium	Medium	Low
Viscous/ foaming liquid	Handles well	Handles very well	Handles very well	Not equipped to handle
Pressure	Low	Medium	Medium	High pressure
Mixing	Well mixed	Mixed system	Well mixed	Plug flow with poor mixing
Energy input	High	Low	Moderate	Moderate

case where the catalyst is metal impregnated onto porous support). Subsequent to reaction, the products are released into the liquid phase (see Eq. 7.2).

For carrying out such a reaction, all three phases (gas, liquid, and solid) need to be present in the reactor. When the stoichiometric requirement of the reaction demands a lot of liquid and less gas, the reactor configuration to be chosen is the slurry bubble column or the three-phase stirred tank. Sometimes the external mass transfer limitations around catalyst particles are limiting (discussed in greater detail later), in which case the choice is clearly the stirred tank wherein the mechanical stirring action is practically independent of the bubble-motion induced agitation and can be independently set by using an appropriate impeller/motor. In case the stoichiometric requirement is for a higher fraction of gas and less liquid, the reactor system is the three-phase fluidized bed. The latter supports large gas-to-liquid ratios and also larger particle sizes (500 μm to a few millimeters), while the former reactors usually employ finer particles (1–200 μm range).

Ideally, purely from a reactor efficiency point of view, the three-phase reactor would preferred to be a countercurrent one (shown schematically in Fig. 7.8A) in which gas and liquid (with species A and B, respectively) enter from opposite directions, and where there is a higher concentration of A (near gas inlet) one would have a depleted liquid stream (lower concentration of B), and vice versa at the other end. The catalyst particles would be suspended in the slurry phase, and with this countercurrent trick, one would ensure a relatively uniform rate on the catalyst particles no matter what their locations in the vessel. The ideal contacting flow pattern involves the countercurrent movement of gas and liquid (slurry) phases in a plug flow manner.

However, from a hydrodynamic point of view, this is very difficult to run. The primary reasons for this difficulty come from the fact that countercurrent systems always have flooding limitations,

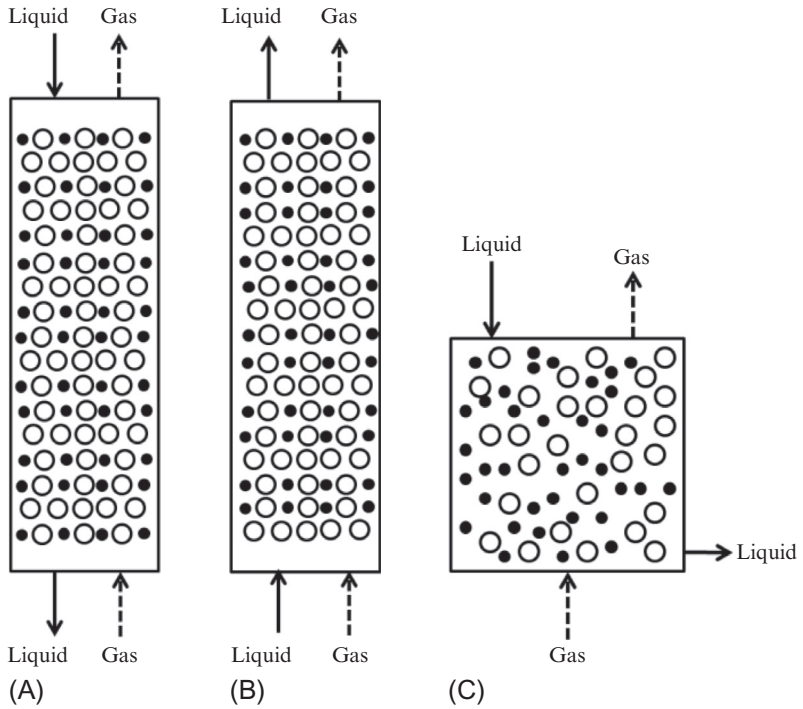


Fig. 7.8

Possible ideal contacting patterns in three-phase slurry reactors. (A) Countercurrent (gas and liquid in plug flow). (B) Cocurrent (gas and liquid in plug flow). (C) Mixed (gas and liquid in mixed flow).

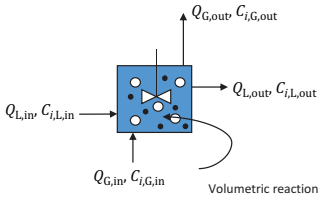
and the window of flow rates for stable operation is relatively small. Thus the typical choice for stable operation of slurry reactors is a cocurrent system (Fig. 7.8B), in which the gas and liquid are arranged to flow concurrently and the catalyst particles are suspended in slurry. The target is to have both gas and liquid in plug flow. Cocurrent flow mode leads to a somewhat less favored concentration distribution of reactants in the vessel: at the inlet plane, both gas and liquid species are at their respective highest concentrations, which progressively deplete as one moves toward the exit. As a result, the outlet zone of the reactor cannot be utilized effectively. However, in the interest of feasible and stable operation from a hydrodynamic standpoint, the cocurrent contacting pattern is usually the pattern of choice. Both the three-phase fluidized bed and the slurry bubble column reactor adhere to this contacting philosophy. However, there may be situations when either the stoichiometric requirement of relative species concentrations, the requirement of maintaining a certain gas-to-liquid flow ratio, or certain transport limitations or requirements of heat addition or removal may supersede the requirements of plug flow pattern. Hence the only feasible way (as well as ensuring stable operation) is to contact the phases to have a mixed flow of gas and liquid, which is achieved in a three-phase stirred tank. Fig. 7.8C shows such a contacting pattern.

7.3.2 Reactor Scale Models

Based on the understanding of contacting patterns, a hierarchy of models with varying degrees of complexity can be developed for catalytic reactors. Depending on the level of fluid flow information, these models are classified as idealized (mixed and plug) flow models, nonideal (axial dispersion and mixing cell) flow models and advanced CFD-based models. CFD models are mainly used for designing and optimizing the configuration of the reactor and are discussed in Section 7.4. In this section, the lower order models used mainly for reactor sizing and identifying desired operating conditions are briefly discussed.

Quantitative evaluation of the contacting patterns and reactor mixing is performed with the help of tracer studies, and elaborate methodology for this is available in open literature (see Refs. [23,37,71,98,122]). In idealized flow models, the fluid is assumed to be completely mixed (mixed flow reactor: MFR) or to move in the plug flow mode (plug flow reactor: PFR). PFR and MFR are two limiting cases of mixing that are considered for reactor analysis. These approaches are extensively used and discussed in almost all of the reaction engineering textbooks [28,30,65].

In the mixed flow model, the concentration of all reactants and products is considered to be uniform, representing complete mixing inside the reactor. The following balance equations are solved to find conversion of reactants at the reactor outlet (steady state):

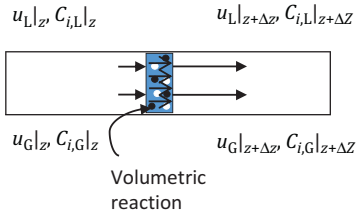


$$\left.\begin{aligned}
&\text{Gas phase}: \left(Q_G C_{i,G}\right)_{in} - \left(Q_G C_{i,G}\right)_{out} = -\left(k_L a\right)_i \left(\frac{\left(C_{i,G}\right)_{out}}{m_i} - \left(C_{i,L}\right)_{out} \right) \\
&\text{Liquid phase}: \left(Q_L C_{i,L}\right)_{in} - \left(Q_L C_{i,L}\right)_{out} = +\left(k_L a\right)_i \left(\frac{\left(C_{i,G}\right)_{out}}{m_i} - \left(C_{i,L}\right)_{out} \right) \pm R_i
\end{aligned}\right\} i = A, B \tag{7.34}$$

where m_i is Henry's constant for component i $[(\text{kmol/m}^3)_l/(\text{kmol/m}^3)_g]$. k_L and a are interphase mass transfer coefficient and interfacial area per unit volume, respectively.

In Eq. (7.34), the left-hand side indicates molar rates of reactant species (i = A, B) entering and leaving the reactor and the right-hand side indicates the rate at which gaseous reactants (i = A, B) are dissolved in the liquid phase. The governing equation for the liquid phase is written in the form of balance of reactant species (A, B) in liquid phase entering and leaving the reactor. The source of these species is due to mass transfer from gas to liquid phase and consumption of the reactants (or generation of products) is due to the reaction taking place in the liquid phase.

In the plug flow model, the fluid is assumed to move like a plug with no mixing in the direction of flow. The following equations can then be formulated:



$$\left.\begin{aligned}\text{Gas phase}: \alpha_G u_G \frac{dC_{i,G}}{dz} &= -(k_L a)_i \alpha_G \left(\frac{C_{i,G}}{m_i} - C_{i,L}\right)\\ \text{Liquid phase}: \alpha_L u_L \frac{dC_{i,L}}{dz} &= (k_L a)_i \alpha_L \left(\frac{C_{i,G}}{m_i} - C_{i,L}\right) \pm \alpha_L R_L\end{aligned}\right\} i = A, B \tag{7.35}$$

Eq. (7.35) is solved to find changes in the concentration of reactants and products in gas and liquid phases along the length of the reactor.

The idealized flow approximations of fluid being completely mixed or flowing like a plug are rarely realized in practice. More often than not there exist concentration gradients in the reactors (deviation from the mixed flow assumption) or there exist some degree of mixing in the direction of the flow (deviation from the plug flow assumption). In order to account for such nonidealities in flow behavior, an axial dispersion model or a tanks-in-series (mixing cell) model is used. In the axial dispersion model, the axial dispersion (mixing) of gas and liquid phases is accounted for through the dispersion terms De_{AG} and De_{AL}, respectively. The mass balance for gaseous reactant A across the reactors takes the following form:

$$De_{AG}\left(\frac{d^2C_{AG}}{dz^2}\right) - u_G\left(\frac{dC_{AG}}{dz}\right) - k_L a_B \rho (C_{AG} - C_{AL}) = 0 \tag{7.36}$$

$$De_{AL}\left(\frac{d^2C_{AL}}{dz^2}\right) - u_L\left(\frac{dC_{AL}}{dz}\right) + k_L a_B \rho (C_{AG} - C_{AL}) = k_s a_P (C_{AL} - C_{As}) = \eta_c b k_{mn} C_{As}^m C_{Bs}^n \tag{7.37}$$

Similarly, mass balance for the liquid phase component B can be written as

$$De_{BL}\left(\frac{d^2C_{BL}}{dz^2}\right) - u_L\left(\frac{dC_{BL}}{dz}\right) = k_s a_P (C_{BL} - C_{Bs}) = \eta_c k_{mn} C_{As}^m C_{Bs}^n \tag{7.38}$$

In order to solve the previous equations, suitable boundary conditions need to be defined, such as

At $z = 0$

$$De_{AG}\left(\frac{dC_{AG}}{dz}\right) = u_G(C_{AG} - C_{AGi}), \quad De_{AL}\left(\frac{dC_{AL}}{dz}\right) = u_L(C_{AL} - C_{ALi}) \tag{7.39}$$

and

$$De_{\mathrm{BL}}\left(\frac{dC_{\mathrm{BL}}}{dz}\right)=u_{\mathrm{L}}(C_{\mathrm{BL}}-C_{\mathrm{BL}i}) \tag{7.40}$$

At the exit of the reactor, that is, $z = L$

$$\frac{dC_{\mathrm{AG}}}{dz}=\frac{dC_{\mathrm{AL}}}{dz}=\frac{dC_{\mathrm{BL}}}{dz}=0 \tag{7.41}$$

For porous and spherical catalyst particles, separate equations for reaction-diffusion must be written in spherical coordinate form as

$$\frac{De_{\mathrm{A}}}{r^2}\frac{d}{dr}\left(r^2\frac{dC_{\mathrm{A}}}{dr}\right)=\rho_{\mathrm{P}}k_{mn}C_{\mathrm{A}}^{m}C_{\mathrm{B}}^{n} \tag{7.42}$$

$$\frac{De_{\mathrm{B}}}{r^2}\frac{d}{dr}\left(r^2\frac{dC_{\mathrm{B}}}{dr}\right)=\rho_{\mathrm{P}}k_{mn}C_{\mathrm{A}}^{m}C_{\mathrm{B}}^{n} \tag{7.43}$$

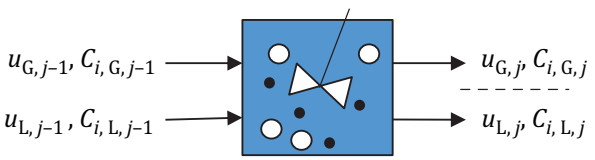
The boundary condition at the catalyst surface connects the particle surface diffusing flux with the mass transfer from the bulk of liquid to the surface of the catalyst as

$$D_{\mathrm{em,A}}\left(\frac{dC_{\mathrm{A}}}{dz}\right)=k_{\mathrm{As}}(C_{\mathrm{AL}}-C_{\mathrm{As}}) \tag{7.44}$$

$$D_{\mathrm{em,B}}\left(\frac{dC_{\mathrm{B}}}{dz}\right)=k_{\mathrm{Bs}}(C_{\mathrm{BL}}-C_{\mathrm{Bs}}) \tag{7.45}$$

where D_{em} is the molecular diffusivity of the components. The previous set of particle equations (Eqs. 7.42–7.45) can be solved independently for different reactant surface concentrations C_{ALs} and C_{BLs} and the relationship between the catalyst effectiveness factor (η_{c}) can be developed. The solution to the axial dispersion model can then be obtained using numerical methods.

Though the axial dispersion model accounts for the deviation from ideal plug flow behavior, it can also mathematically describe systems approaching complete backmixing. The tanks-in-



series or mixing cell models are also used to account for the gas and liquid backmixing in three-phase reactors. In these models, a reactor is divided into N parts (tanks) along the length of the reactor and the liquid phase in each part (tank) is considered to be fully backmixed. The

dispersed phase can be considered to be either in plug flow or fully backmixed. The degree of backmixing is characterized by the number of tanks; for example, $N = 1$ represents the limiting case of complete backmixing and $N = \infty$ ($\sim$10 in practice) represents the limiting case of a plug flow behavior. A uniform distribution of catalyst particles is usually assumed. The governing equations of the mixed flow model are extended for each tank to formulate governing equations for gas and liquid species as (for the jth tank)

For jth cell (steady state: gas phase in plug flow and liquid phase in mixed mode),

$$\int_0^{1/N} \chi_i \varphi_i \left(C'_{i,\mathrm{G},j} - C'_{i,\mathrm{L},j}\right) d\xi = \left(C'_{i,\mathrm{G},j} - C'_{i,\mathrm{G},j-1}\right) + \frac{\chi_i}{N}\left(C'_{i,\mathrm{L},j} - C'_{i,\mathrm{S},j-1}\right)$$

$$C''_{i,\mathrm{L},j} = C''_{i,\mathrm{L},j-1} + \lambda_i R''_i$$

$$C'_{i,\mathrm{G},j} = \frac{C_{i,\mathrm{G},j}}{C_{i,\mathrm{G},0}}, C'_{i,\mathrm{L},j} = \frac{m_i C_{i,\mathrm{L},j}}{C_{i,\mathrm{G},0}}, C''_{i,\mathrm{L},j} = \frac{C_{i,\mathrm{L},j}}{C_{i,\mathrm{L},0}}$$

$$\chi_i = \frac{Lk_\mathrm{L}a}{u_\mathrm{G} m_i}, \varphi_i = \frac{u_\mathrm{G} m_i}{u_\mathrm{L}}, \chi_{\mathrm{S},i} = \frac{Lk_\mathrm{s}a_\mathrm{p}}{u_\mathrm{L}}, \lambda_i = \frac{L}{u_\mathrm{L}} \tag{7.46}$$

Please note that these equations are written by assuming plug flow of the gas phase in each mixing cell. Several researchers have used the mixing cell model to simulate three-phase reactors [84]. Chaudhari et al. [123] have discussed the formulation of a mixing cell model and have used it to simulate a slurry bubble column reactor for reductive alkylation of *para*-phenylenediamine.

In many fine and specialty chemical industries the semibatch mode is used, where gas is fed continuously while the liquid phase on the other hand is fed once at the start of the reaction. There is thus no net inflow or outflow of liquid in the reactor to the reactor. The fed gas either gets completely consumed in the reaction (operation as a dead-end reactor which has no outflow of gas) or it gets partly consumed in the reactor and unconverted gas flows out of the reactor (which may or may not be recycled). Often, stirred tank reactors or slurry bubble column reactors are operated in a semicontinuous manner. Design of the semicontinuous reactors involves calculation of the batch time required for completion of the reaction for the desired conversion. The reaction engineering models presented earlier can be extended to represent a semibatch or semicontinuous mode of operation of catalytic reactors in a straightforward manner.

7.3.3 Estimation of Parameters Appearing in Reactor Scale Models

The reaction engineering models discussed in an earlier subsection include several parameters representing various transport processes, such as mass transfer coefficients (gas-liquid (liquid side) k_L, gas-liquid (gas side) k_G and liquid-solid k_s), interfacial area per unit volume a,

dispersion coefficient and so on. In order to solve the reaction engineering models, it is essential to have a reliable and accurate estimation of these parameters. Thermodynamic parameters such as Henry's law constant (m_i) can be estimated in a simpler manner because their estimation does not depend on the flow or on any time-dependent phenomenon. Mass transfer coefficients may be evaluated in well-defined geometries with known flow fields using classical theories like film theory, penetration theory, surface renewal theory or boundary layer theory. However, accurate prediction of mass transfer coefficients, and indeed other similar transport coefficients, is frequently not possible. Estimations often rely on empirical correlations based on dimensionless numbers. However, such correlations are reactor and process specific, and therefore quite limited in their applicability. An extensive selection of such empirical correlations is presented by Cussler [17]. Readers may be referred to several other excellent reviews (and references cited therein) which present various correlations for estimating parameters appearing in reaction engineering models (Ref. [11] for three-phase slurry reactors; Ref. [88] for trickle bed reactors; Ref. [81] for stirred reactors; Ref. [53] for three-phase fluidized reactors; Ref. [20] for variety of other reactors and so on).

In summary, there are many known techniques to estimate the transport parameters but most of them are application or equipment specific. It is many times required to understand the underlying fluid dynamics of a specific reactor in more detail for reliable design and scale-up. The models which account for detailed multiphase fluid dynamics of reactors and use them for reactor design and optimization are called reactor engineering models. These are briefly discussed in the following section.

7.4 Reactor Engineering Models

While the lower order models described in Section 7.3 are useful for quick prediction of the overall performance of a reactor, these models rely on simplified flow approximations and often fail to account for change in the local fluid dynamics or transport processes during the presence of internal hardware or changes in flow regimes. Moreover, these models are also based on empirical knowledge of various transport processes/parameters (as discussed in Section 7.3.3). Some of these limitations may be avoided by using more advanced reactor models which solve momentum equations along with the mass and energy balances. It will be useful to understand the existence of multiple length and time scales existing in multiphase catalytic reactors while formulating objectives and governing equations for such advanced reactor models.

It will be useful to refer to Fig. 7.1 while discussing multiple scales. The following processes occur in a multiphase catalytic reactor, spanning the largest scale (macroscale/reactor scale) to the smallest scale (molecular scale):

- distribution/segregation of reacting phases
- phase deformation, elongation, contraction and interaction

- interphase mass transfer
- convection, recirculation by mean velocity
- turbulent dispersion by large eddies
- reduction in segregation length scale
- laminar stretching of small eddies/molecular diffusion and chemical reaction

Unless the reactions are very fast, the last two points related to microscales in the previous list are usually not rate limiting and therefore need not be considered. Mesoscale processes involve processes occurring on a single bubble or a group of bubbles and solid particles. Phase segregation, breakage or coalescence of bubbles, liquid maldistribution, uneven solid distribution and dead zones can affect the overall performance of a reactor to a large extent, especially with the scale of the reactor. Uncertainties associated with mesoscale processes are considered one of the major reasons for the uncertainty involved in scale-up. Macroscale processes control overall phase mixing as well as mesoscale processes. The interaction of these processes in a typical multiphase catalytic stirred tank reactor is illustrated in Fig. 7.9.

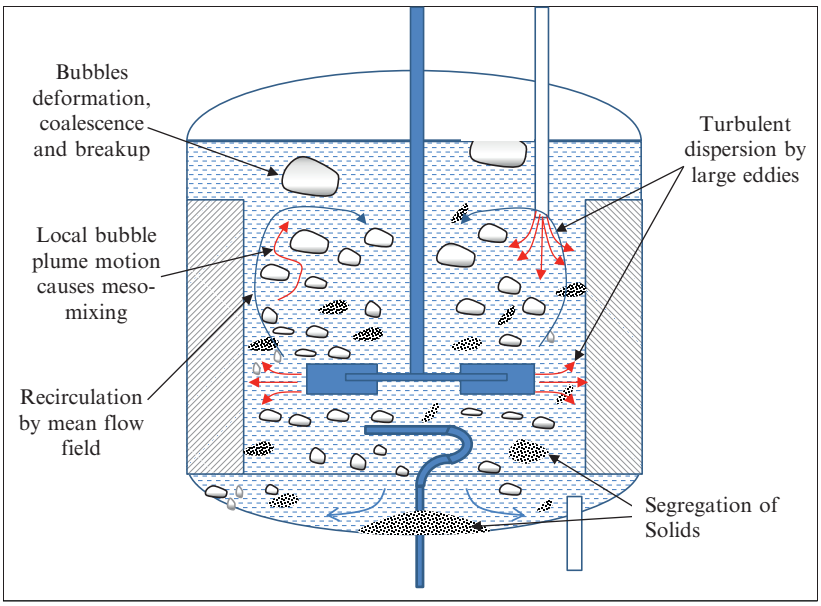


Fig. 7.9
Typical macroscale phenomenon in three-phase stirred reactor.

CFD-based models offer the possibility of a quantitative understanding of these processes occurring on multiple scales. Ranade [86] and Jakobsen [41] have presented a detailed discussion on various aspects of developing and using CFD models for chemical reactor engineering applications. The overall approach of reactor engineering models is schematically shown in Fig. 7.10. Different approaches for modeling turbulent flows, multiphase flows and reacting flows have been discussed in detail. Not only governing

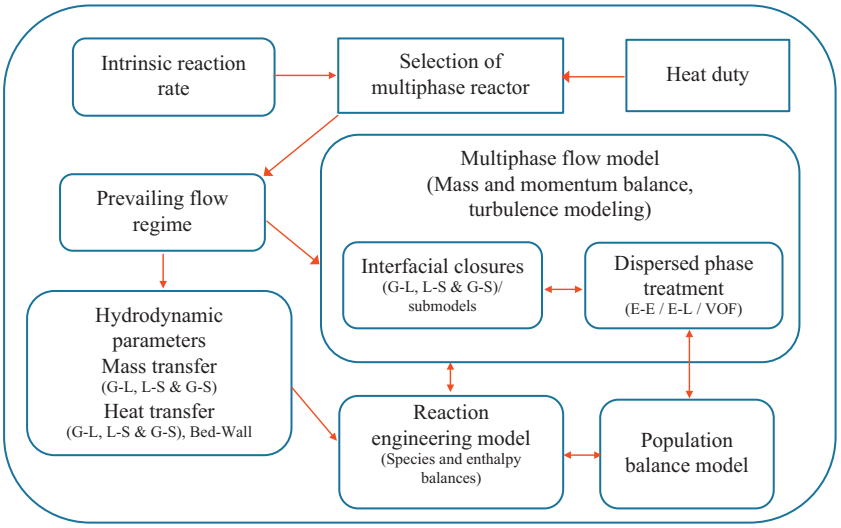


Fig. 7.10
Schematic of multiphase reactor modeling approach.

equations for these different modeling approaches but also corresponding numerical methods required for the solution of these model equations were discussed. For the sake of brevity, we have not repeated these here. Interested reader may refer to the book by Ranade [86]. Here we have included key aspects of four specific reactors to illustrate the application of such reactor engineering models.

7.4.1 Stirred Tank Reactors

Stirred tank or agitated reactors are comprised of one or more impellers with external or internal heating or cooling jacket/coil. These reactors are some of the most commonly used in the chemical process industry due to their excellent operational flexibility. Stirred tanks are employed in wide numbers of applications, including mixing, blending, solid dissolution and polymer processing, besides carrying out several single phase and multiphase reactions. Mixing and transport rates can be easily manipulated by selecting the appropriate hardware configuration, such as height-to-diameter ratio, use of baffle and agitation speed. The standard configuration of stirred reactors is used with a cylindrical tank with the dish end at the top and bottom with one or more impellers centrally located. Gas can be either self-induced or sparged. These reactors can also be operated in batch, semibatch or continuous mode of operation with gas, liquid and solid phases. Excellent handbooks, textbooks and reviews on various aspects of stirred tanks are available [45,79,81,107]. In catalytic reactions, various phases need to be contacted efficiently for reaction to occur. In this section, some aspects of multiphase stirred reactors are discussed.

Fluid dynamics of stirred tanks are controlled by the following factors:

- vessel configuration (size, shape)
- number, type and location of impellers, baffles, spargers and other internals
- operating parameters (impeller speed, physical properties of system under consideration)

Usually, cylindrical vessels are used. Impellers and baffles determine the prevailing flow pattern in a given stirred vessel. Impellers may be classified as radial flow, axial flow or mixed flow. These classifications are based on the generated flow pattern. Commercial stirred tank reactors are often employed with more than one impeller; these impellers can be of the same shape and size or a combination of them, depending upon the applications and flow pattern they produce. For example, two pitched blade turbines produce axial dominated flow with one single loop, while a radial turbine produces multiple flow loops, as shown in Fig. 7.11. In some situations, it may be beneficial to operate an axial flow impeller in an upflow mode instead of downflow. Radial flow impellers generate shear dominating flow, which is suitable for better mixing and dispersion of dispersed phases.

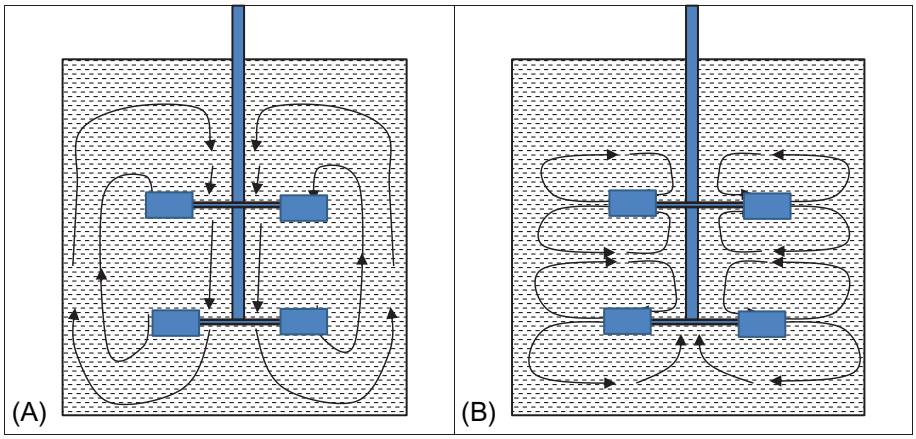


Fig. 7.11
Flow pattern produced by two turbines due to their interaction. (A) Flow pattern due to axial impeller. (B) Flow pattern due to radial impeller.

Apart from the mixing and circulation of fluids, in catalytic reactors, impellers need to realize adequate solid suspension and gas-liquid as well as solid-liquid mass transfer rates. Impellers producing axial flow with high pumping capacities perform better for solid suspension. Solid suspension is characterized in terms of on-bottom motion, complete off-bottom suspension and uniform suspension. The complete off-bottom suspension of particles is defined as the condition when no particle resides on the vessel bottom for more than a second. The minimum impeller speed required to achieve this condition is called N_{JS}. The quality of solid suspension can also be measured in terms of the shape and height of a cloud of suspended

solid particles. Gas-liquid mass transfer mainly depends on interfacial area (inversely proportional to bubble size). Realized interfacial area is inversely related to the energy dissipation rate. Therefore radial impellers which have better power dissipation capabilities are preferred for gas-liquid dispersion applications. Some applications of stirred tank reactors for catalytic reactions are listed in Table 7.4.

Table 7.4 Some applications of multiphase stirred tank reactors

Process	Catalyst	Reactor Type	Pressure (atm)	Temperature (°C)
Benzoic acid from toluene and air	–	CSTR, GL	9–12	125–175
m-Chloroaniline by hydrogenation of nitrochlorobenzene	Sulfited Pt/C	STR, GLS	5–12	50–80
Cyclododecene by hydrogenation of 1,5,9-cyclododecatriene	Pd/γ-alumina	STR, GLS	10	40–80
Sorbitol from glucose	Raney nickel	STR, GLS		
Chloroanilines from nitrobenzene	Sulfided Pt/C Ni/SiO_2			
2-Methylcyclohexanol from *o*-cresol				
Caprolactam from cyclohexylamine	Polyphosphoric acid	STR	1	80–100
Ethylene from propylene chlorohydrins from Cl_2, H_2O	–	CSTR, GL	3–10	30–40
Isooctane (2,2,4-trimethylpentane (TMPA) from isooctenes	Pd/γ-alumina			
Cumene hydroperoxide from cumene and air	Metal porphyrins	STR, LS	2–15	95–120
o-Methylbenzoic acid from xylene and air	–	CSTR, GL	14	160

Three-phase stirred reactor performance can be analyzed with different hydrodynamic parameters, such as (1) power input, (2) minimal speed of agitation for solid suspension, (3) minimal speed of agitation for complete dispersion of gas, (4) gas holdup (or recirculation), (5) mixing time, (6) bubble size, (7) heat and mass transfer characteristics and so on. The number of variables in terms of hardware configurations (impeller type and its dimension,

reactor dimension and distance between them, etc.) and operating parameters (gas flow rate, impeller speed, particle size distribution, properties of gas and liquid, etc.) make the design, analysis and scale-up of stirred tank reactors difficult. Two important parameters in impeller design are power number (Po or N_P) and flow number of pumping number (Fl or N_Q), which are given as

$$Po = \frac{P}{\rho N^3 D^5} = f\left(\frac{ND^2}{\nu}, \frac{N^2 D}{g}, \frac{D}{T}, \frac{H}{T}, \text{etc.}\right) \tag{7.47}$$

$$Fl = \frac{Q}{ND^3} \tag{7.48}$$

where P is power dissipation by impeller and Q is impeller discharge flow. These numbers are used to estimate power dissipation and internal circulatory flow, which are needed for estimating prevailing flow regimes and other relevant parameters. Various hydrodynamic regimes are observed in stirred tank reactors for different impeller speeds, gas flow rates and solid loadings [89,90]. A priori knowledge of prevailing flow regimes in stirred tank reactors is essential for the selection of design parameters and scale-up. Three prominent flow regimes can be identified in stirred tank reactors [77]:

- *Flooding*: observed at lower impeller speed or higher gas flow rate; this is typically a gas-dominated regime and is not a desirable operating regime for most cases
- *Complete dispersion*: observed at intermediate impeller speed and gas flow, where gas bubbles get dispersed throughout the reactor
- *Gas recirculation*: with further increase in the speed of the impeller, the flow is dominated by liquid

These flow regimes are schematically shown in Fig. 7.12. Similar flow regime characteristics exist for gas-liquid-solid stirred tank reactors.

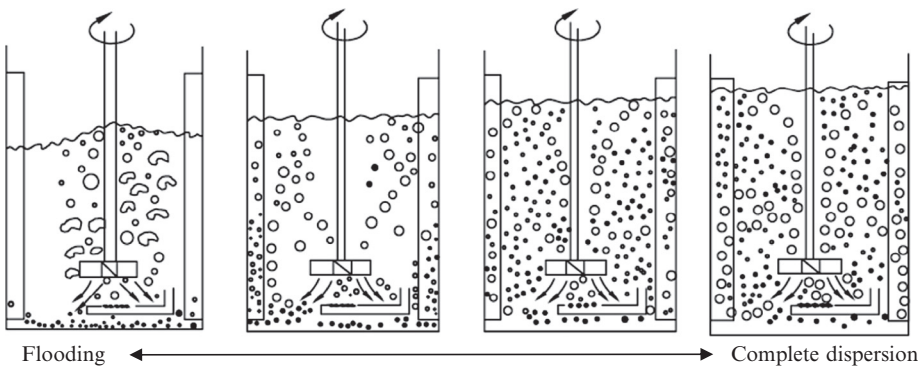


Fig. 7.12
Flow regimes in three-phase stirred tank reactors.

It should be noted that the presence of gas hinders solid suspension, and often higher impeller speeds are required to maintain the quality of the solid suspension in the presence of gas. Several correlations have been proposed for estimating key design parameters of multiphase stirred reactors (see Refs. [29], [81] and references cited therein). For catalytic reactors, the critical impeller speed necessary to ensure suspension of solids may be estimated using the correlation proposed by Zwietering [121] and its variants [3,49,76] as

$$N_{\mathrm{JS}} = \frac{s d_{\mathrm{p}}^{0.2} v^{0.1} (g\Delta\rho)^{0.45} \phi_{\mathrm{m}}^{0.13}}{\rho_{\mathrm{l}}^{0.45} D^{0.85}} \tag{7.49}$$

where s is an empirical factor for the impeller and ϕ_{m} is the mass ratio of gas to liquid $\times$ 100. More power input is required for solid suspension in the presence of gas; hence $N_{\mathrm{JSg}} > N_{\mathrm{JS}}$. Many of the correlations proposed in published literature are applicable only to the impellers, baffles and vessel sizes considered in the published studies and therefore are quite specific. For example, the influence of gas flow rate on critical impeller speed for the Rushton turbine (RT) is estimated as [12] (Bujalski, 1986)

$$N_{\mathrm{JSg}} = N_{\mathrm{JS}} + 0.94 Q_{\mathrm{G}} \tag{7.50}$$

Besides suspension, the interphase mass transport rate needs to be estimated for using stirred tanks as catalytic reactors. The overall gas-liquid mass transfer in the stirred tank can be estimated using the correlations of the following type:

$$\langle k_{\mathrm{L}} a \rangle = C_{k_{\mathrm{L}}a} \left(\frac{P_{\mathrm{G}}}{V} \right)^{a} v_{\mathrm{g}}^{b} \tag{7.51}$$

where P_{G} is power consumption in the presence of gas. For air-water systems, van't Riet [110] has suggested $C_{k_{\mathrm{L}}a} = 0.026$, $a = 0.4$ and $b = 0.5$. Further, Kiełbus-Rąpała and Karcz [52] have given the values for these constants for various types of impellers in single and double impeller arrangements.

The presence of solids in stirred tanks shows a twofold trend; that is, at lower solid concentration, the volumetric mass transfer coefficient increases with solid loading up to solid concentration 2.5, and then it decreases with an increase in solid loading [52]. The following correlation is suggested as a function of solid loading:

$$\langle k_{\mathrm{L}} a \rangle = C_{k_{\mathrm{L}}a} \left(\frac{P_{\mathrm{G}}}{V} \right)^{a} v_{\mathrm{G}}^{b} \left(\frac{1}{1 + m_1 \alpha_{\mathrm{s}}^2 + m_2 \alpha_{\mathrm{s}}} \right) \tag{7.52}$$

For a RT, the values of the constants are $a = 0.031$, $b = 0.43$, $C_{k_{\mathrm{L}}a} = 0.515$, $m_1 = -186$ and $m_2 = 12$. More information may be found in van't Riet [110], Chapman et al. [12], Joshi et al. [45], Bartos and Satterfield [7], Oguz et al. [78], and Yawalkar et al. [118].

Liquid-solid mass transfer may be estimated as [40,57,69]

$$Sh = \frac{k_s d_p}{D} = 2 + a\left(\frac{\varepsilon^{1/3} d_p^{4/3}}{\nu}\right)^b Sc^{1/3} \tag{7.53}$$

where $(\varepsilon^{1/3} d_p^{4/3}/v)$ is termed as a turbulent Reynolds number. For stirred tank reactors, $a = 0.13$ and $b = 3/4$. Additional details may be found in the review by Beenackers and van Swaaij [124].

CFD-based models can prove to be very useful while designing and scaling up large, industrial scale, multiphase catalytic stirred tank reactors. Ranade [86] has discussed computational modeling of multiphase flows in stirred tanks in detail, along with examples. More recently, Sardeshpande and Ranade [94] and Khopkar and Ranade [51] discussed the application of CFD models for two- and three-phase stirred tank reactors containing solid particles. These works and the references cited therein may be referred to for developing detailed CFD models for multiphase stirred reactors.

7.4.2 Slurry Bubble Column Reactors

Bubble column reactors are extensively used in carrying out gas-liquid and gas-liquid-solid reactions in a variety of important industrial reactions, including hydrogenation, oxidation, hydroformylation, chlorination, bioreactions and so on. Some applications of bubble column reactors in fine and specialty chemicals are given in Table 7.5. These reactors provide good mixing and heat transfer characteristics. Gas is sparged from the bottom of the reactor in the form of a bubble. Radially nonuniform distribution of gas bubbles (gas volume fraction) leads to buoyancy driven internal circulation within the bubble column. Bubble sizes depend on physical-chemical properties, sparger design and superficial gas velocity. The mean and turbulent flow generated by gas bubbles is used to keep catalyst particles in a suspended condition.

Table 7.5 Applications of bubble column reactors

Process	Catalyst	Reactor Type	Pressure (atm)	Temperature (°C)
Oxidation of ethylene to acetaldehyde	-	BCR	9–12	125–175
Oxidation of acetaldehyde to acetic acid	Sulfited Pt/C	BCR-GLS	5–12	50–80
Synthesis of methanol from syngas conversion	Copper	BCR-GLS	50–150	275–350
Hydrolysis of phosgene		BCR-GLS		
Ozonization of wastewater				

Continued

Table 7.5 Applications of bubble column reactors—cont'd

Process	Catalyst	Reactor Type	Pressure (atm)	Temperature (°C)
Fischer–Tropsch (FT) process for synthetic fuels	Fe, cobalt catalyst	BCL-GLS		
Partial oxidation of ethylene to acetaldehyde	Pd-Cl_2 on charcoal	BCR		
Oxidation of acetaldehyde to acetic acid		BCR		
Oxidation of *p*-xylene to dimethyl terephthalate	Cobalt naphthenate and acetic acid	BCR	4–10	150–180
Hydrolysis of phosgene		BCR		
Ozonization of water		BCR		

Various configurations of bubble columns have evolved based on the requirements of efficient contacting bubbles, redistribution of bubbles, suspension and circulation of solids and so on. Some of these variants are shown schematically in Fig. 7.13. Bubble column reactors are commonly used with internal cooling or heating coils for effective heat management. Multistage or sectionalized bubble column reactors are used in cases where axial backmixing needs to be controlled. Packed

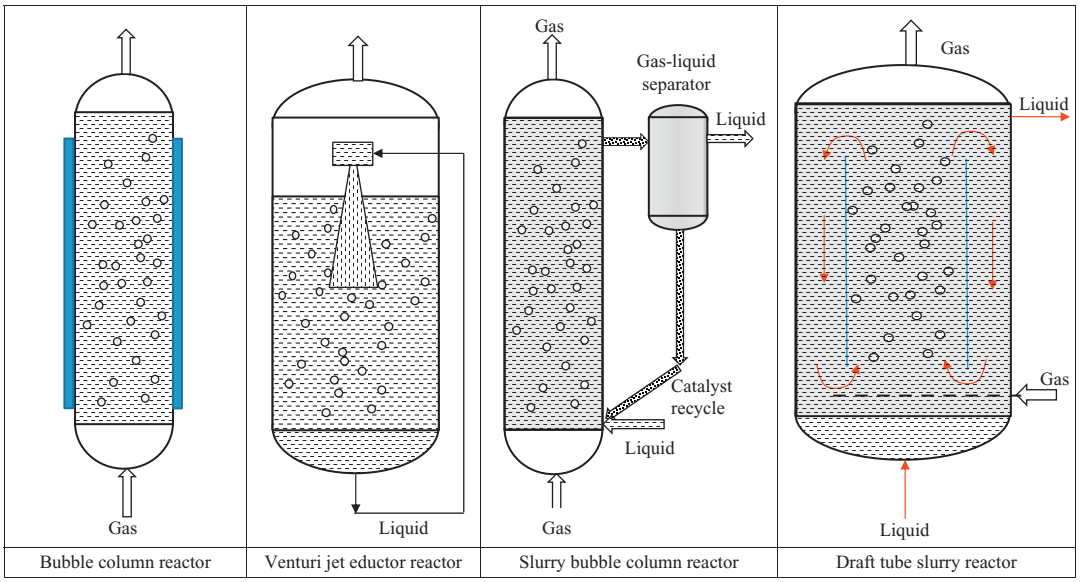


Fig. 7.13
Configurations of gas-liquid and gas-liquid-solid slurry bubble column reactors.

bubble column reactors are also used in practice. Bubble column reactors are usually operated in a continuous mode. There are also several variants of bubble columns, such as external or internal loop reactors and jet loop reactors (with gas eductors). Jet loop reactors are typically downflow bubble column reactors and offer excellent gas-liquid performance.

Bubble columns offer several advantages, such as simple operation without any moving parts; excellent mixing, heat and mass transfer rates; low catalyst attrition rates; and the ability to accommodate a wide range of residence time requirements. Some of the disadvantages of bubble columns are backmixing in liquid phase (may result in lower conversion and unfavorable selectivity) and limitations on catalyst size and loading.

Despite their simple operation, bubble column reactors exhibit some of the most complex hydrodynamics due to spatiotemporal variations in interactions among gas, liquid and solid phases. Two major flow regimes exist in bubble column reactors: the homogeneous regime and the heterogeneous regime. The homogeneous flow regime is observed at relatively lower gas velocities (typically for a superficial gas velocity of less than 0.05 m/s). In this flow regime, bubbles are relatively smaller in size and are uniform (usually 0.5 to 2–3 mm). Liquid recirculation in the reactor is also relatively quiescent and the rate of bubble coalescence and breakup is also lower in this flow regime. The heterogeneous flow regime, also called churn-turbulent flow regime, is observed at higher superficial gas velocities with a large variation in bubble-size distribution. With the increase in gas flow, nonhomogeneity in bubble size, shape and unsteadiness increases. This flow regime is characterized by a meandering/swirling bubble plume with larger liquid circulating zones along the height of the column [8,46]. Bubble plume oscillations are axially asymmetric. Typical flow regimes and a schematic of churn-turbulent flow are shown in Fig. 7.14.

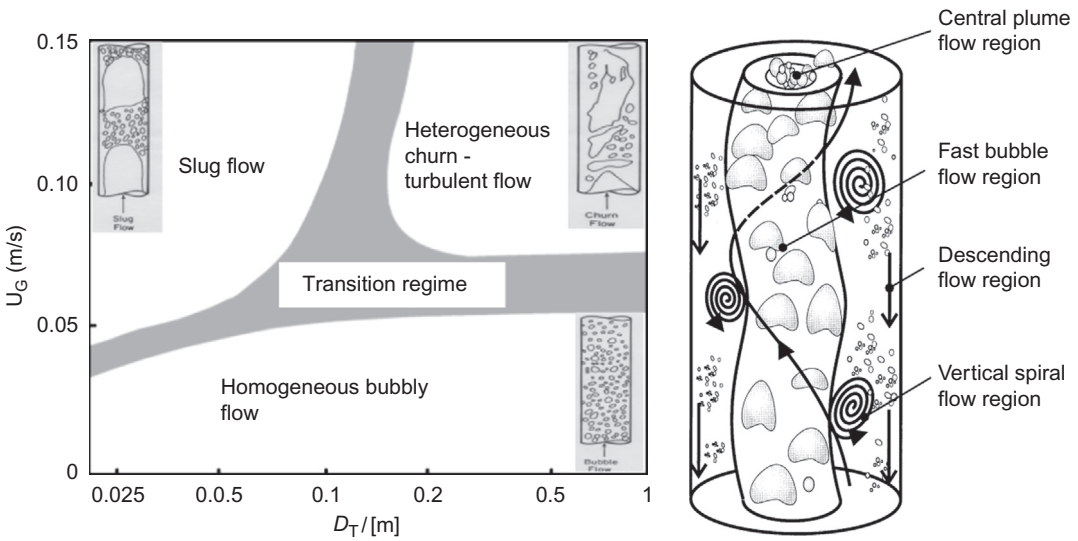


Fig. 7.14
Flow regimes and schematic of churn-turbulent flow in bubble column reactor.

Slug flow regime is observed in smaller reactor diameters, where slugs are formed at higher gas flow rates because of wall restriction. This omits the disadvantage of liquid backmixing of the bubble column to some extent, and higher rates of heat and mass transfer can be achieved. Reactor diameter has a major role in slug flow characteristics. The smaller the diameter, the more sustainable the slug. Miniaturization of the reactor diameter has several advantages in terms of generating bubbles/slugs of definite sizes and shapes. This enables much better control of backmixing and heat and mass transfer rates. These miniaturized bubble column (or tubular gas-liquid) reactors are also finding applications in carrying out reactions relevant to fine and specialty chemicals.

Key parameters of interest for designing bubble column reactors can be estimated using various correlations published in open literature. Bubbles generated through orifices differ in size and shape depending on the properties of the gas, liquid and solid phases and the type of orifice. The following correlations may be used for prediction of the mean bubble size:

$$d_b^* = \left[\frac{6 d_o \sigma_L}{g(\rho_L - \rho_G)}\right]^{1/3} \tag{7.54}$$

$$\frac{d_B}{d_T} = 26\left(\frac{g d_T^2 \rho_L}{\sigma_L}\right)^{-0.5}\left(\frac{g d_T^3 \rho_L^2}{\mu_L^2}\right)^{-0.12}\left(\frac{u_g}{\sqrt{g d_T}}\right)^{-0.12} \tag{7.55}$$

Wilkinson's [125] correlation for calculating bubble size is given as

$$d_B = 3 g^{-0.44} \sigma^{0.34} \mu_L^{0.22} \rho_L^{-0.45} \rho_G^{-0.11} u_G^{-0.02} \tag{7.56}$$

Polydispersity of bubbles is inherent in bubble column reactors with lower variation in bubbly flow and a wide range of distribution in a heterogeneous regime.

For situations where empirical correlations may not provide adequate confidence, it is essential to develop detailed CFD-based models. The reader may refer to books by Ranade [86] and Jakobsen [41] as well as some of the excellent reviews [48,54,87,100]. Relatively less information is available on CFD modeling of slurry (gas-liquid-solid) bubble column reactors as compared with gas-liquid bubble column reactors [35,59,108,112,120]. Most of these simulations have used constant bubble sizes. Guillen et al. [35] have suggested the use of two bubble-size models for better prediction of results for churn-turbulent flows. These works and references cited therein may be referred to for developing detailed CFD models for multiphase bubble column reactors.

7.4.3 Trickle/Packed Bed Reactors

Trickle bed reactors are gas-liquid-solid contacting devices used for carrying out various catalytic reactions such as hydrogenation, oxidation, hydrocracking, hydrotreating, chlorination and so on. Key advantages of trickle bed reactors are simplicity in operations (no moving parts, can handle large pressure), ability to handle large quantities of a solid catalyst with minimal attrition, lower backmixing compared to other three-phase reactors such as slurry bubble column or stirred tank reactors and so on. These reactors are therefore suitable for slower reactions. A wider range of particle sizes and shapes can easily be accommodated in trickle bed reactors. However, heat transfer rates are poorer; therefore highly exothermic reactions may lead to local hot spots. Use of a smaller catalyst particle size may lead to a higher pressure drop. If trickle bed reactors are operated under partially wetting conditions, catalyst utilization may not be complete. Typical applications of catalytic reactions carried out in trickle bed reactors are listed in Table 7.6.

Table 7.6 Some applications of trickle bed reactors

Reaction Type	Process	Catalyst	Pressure (MPa)	Temperature (K)
Oxidation reactions	Ethanol oxidation	Pd/Al	2	343–373
	Wet oxidation of phenol	Pt/Al_2O_3	3–10	100–200
	Oxidation of formic acid/ oxidation of organic matter in wastewater treatment/ oxidation of phenol	Co/SiO_2-AlO_2, CuO	0.1–1.5	300–403
Hydrogenation reactions	Hydrogenation of adipic acid to 1,6-hexanediol	Pd, Pt, Ni, Cu	3–10	323–423
	Selective hydrogenation of acetylene to separate compound from C4 fraction in presence of butadiene	Au/Al, Pd/Al_2O_2	0.1–2.5	313–523
	Hydrogenation of crotonaldehyde and α-methyl styrene to cumene	0.05% Pd on Al_2O_3	0.1– 5	373–773
	Hydrogenation of 2-butyne-1,4-diol	Ni	10–30	350–450
	Hydrogenation of caprolactone and adipic acid	Cu	15–25	450–550

Continued

Table 7.6 Some applications of trickle bed reactors—cont'd

Reaction Type	Process	Catalyst	Pressure (MPa)	Temperature (K)
	Hydrogenation of aniline to cyclohexylaniline	Pd/Al_2O_3	3–20	298–313
	Hydrogenation of glucose to sorbitol	Ru/C	8	373–393
	Maleic anhydride	Raney nickel, Pt/C	1–5	200–400
	Acid esters to alcohols			
	Hydrogenation of coal liquefaction extracts	$Ni\text{-}Mo/Al_2O_3$	7	593–623
Esterification	Esterification of acetone and butanol	Strong acidic ion-exchange resin		
F–T synthesis	Fischer-Tropsch reaction	Co/TiO_2	10–50	450–650

In trickle bed reactors, gas and liquid phase reactants flow in a downward direction over a bed of solid catalyst particles (see Table 7.3). Proper distribution of fluid phases in the catalyst bed often controls the reactor performance and heat transfer efficiency. The gas and liquid phases are fed to the reactor bed via an appropriate distributor. Liquid distributors are generally in the form of multiple nozzles with openings at various radial positions with a central inlet. Other types like bubble cap distributors, sieve plate distributors, or a layer of fines are also used at the top of the column for achieving uniform distribution. In some large trickle bed reactors, redistribution of reactant phases is necessary to avoid hot spot formation inside the reactors. Controlling bed temperature is one of the major concerns in trickle bed reactors. It can be performed by intermediate quenching using external jackets or internal cooling coils. In some cases the gas and/or liquid streams are recycled to increase effective fluid velocity to control temperature and also manipulate desired conversion levels. Unconverted reactants and products formed are taken out from the bottom of the reactors. The bottom portion therefore consists of a gas-liquid separator. For large volume processing, multiple reactors may be operated in series or parallel. For some fine and specialty chemical manufacturing, trickle bed reactors are also operated in a semibatch mode (liquid as a batch with a complete recycle).

Whenever the requirement of catalyst loading is not high or the mechanical strength of the catalyst is not very good, nonrandom (or structured) packing may be used. These structured packings require a lower pressure drop to operate. The structured packings of different varieties include coated structured packing or monolith channels (structured beds). Other operating features and the possibility of using intermediate quenching and redistribution are also applicable to these reactors. Some monolith reactors comprise just a single monolith so that liquid maldistribution along the length of the bed can be avoided. However, liquid

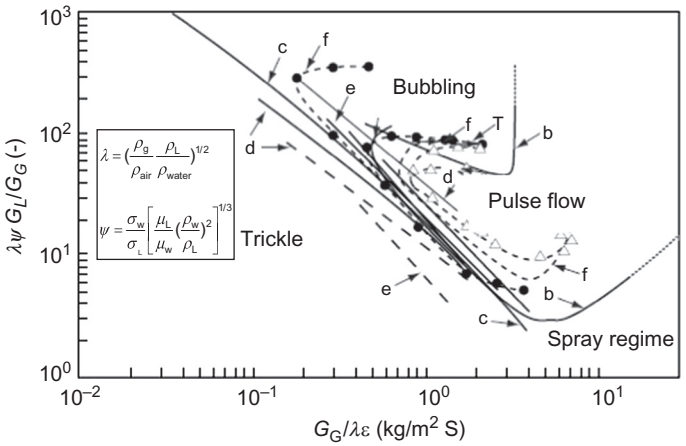
distribution at the inlet becomes very critical in this case. Liquid distribution, wetting of the channel surface, and the possibility of the surface drying out because of vaporization caused by energy liberated due to chemical reactions are some of the important concerns in monolithic reactors.

In conventional trickle bed reactors, a catalyst supported on inert material is used to provide adequate mechanical strength to the pellets. Some catalysts are in the form of an eggshell, where the outer layer is impregnated with an active catalytic material on a core region made up of inert support. These types of catalysts are useful when high temperature gradients exist inside the catalyst particle when reactions are highly exothermic. Various catalyst shapes like spherical, cylindrical, extrudates and trilobes are used in practice. In some cases, particle shapes such as cylindrical tubes, Raschig rings and wire gauge, pall rings, and filaments, which give lower pressure drop (at the cost of lower catalyst loading), are used. The catalyst bed is usually supported on a sieve plate (with wire mesh).

Four distinct flow regimes are observed in trickle bed reactors:

- *Trickle flow regime*: This flow regime is observed at low gas and liquid flow rates, where gas-liquid interaction is smaller. Liquid flows in the form of a film/rivulet over the catalyst. This is considered a low interaction flow regime compared to other flow regimes in trickle bed reactors. Low pressure drop, low gas-liquid throughputs, less catalyst attrition, and suitability for foaming liquids are some of the advantages of trickle flow operation. Depending on reaction type, particle wetting can be advantageous or disadvantageous. In the trickle flow regime, heat and mass transfer rates are poor compared to other flow regimes in trickle bed reactors.
- *Pulse flow regime*: This flow regime is observed at moderate gas and liquid flow rates. Interaction among the phases increases and the liquid phase occupies the entire flow cross section. This process leads to formation of alternate gas-liquid enriched zones. For nonfoaming liquid, gas-liquid bands are quite distinct and the liquid-rich band contains small gas bubbles in its tail. In the case of a foaming liquid, liquid-rich bands contain large gas bubbles and the gas volume fraction in liquid-rich bands is significant. Most industrial trickle bed reactors are operated close to the boundary of the trickle to pulse flow regime [21,126], taking advantage of both operating regimes (trickle as well as pulse). The pulse flow regime has advantages in terms of wetting and effective utilization of the catalyst bed and high heat and mass transfer rates, and is therefore increasingly used in practice.
- *Bubble flow regime*: At a low gas flow rate and moderate/high liquid flow rates, the liquid phase occupies the entire portion of the bed and becomes a continuous phase while the gas phase is flowing in the form of bubbles in the downward direction. This way, intimate interaction among the phases is possible at the expense of a higher pressure drop. Higher liquid holdup leads to backmixing, which may not be suitable for

some of the reactions. Complete wetting of bed and high heat and mass transfer rates are some of the advantages and may be suitable for cases with the liquid phase as a limiting component or for highly exothermic reactions. This flow regime occurs typically at V_G <0.75 kg/m^2 s and V_L <12 kg/m^2 s. The most generalized form of the flow regime map in the form of dimensionless numbers is shown in Fig. 7.15.



a - Gianetto *et al.* (1970)
b - Sato *et al.* (1973)
c - Charpentier et Favier (1975)
d - Chou *et al.* (1977)
e - Specchia et Baldi (1977)
f - Sai et Vaema (1988)

Fig. 7.15
Flow regime map [96].

- *Spray flow regime*: This flow regime is observed at low liquid and high gas flow rates. The liquid phase becomes dispersed droplets and the gas phase is a continuous phase. This flow regime typically occurs at V_G >1.25 kg/m^2 s and V_L <12 kg/m^2 s. The typical gas phase Reynolds number is 100, beyond which spray flow is observed. Due to higher gas flow rates, gas recycling is required. Low liquid holdup, high gas-liquid mass transfer rates and low foaming ability are typical characteristics of this flow regime.

Various key parameters required for design and scale-up of trickle bed reactors may be obtained from a book by Ranade et al. [88] and references cited therein. Numerous studies on porosity distribution in randomly packed beds are available [19,68,101,127]; Stephenson and Stewart, 1986). These experimental and computational studies have shown that the bed porosity is higher near the vicinity of the reactor wall and it fluctuates significantly in the near wall region (about four to five particle diameters in width). Mueller [70] has proposed a correlation for radial variation of axially averaged porosity as a function of column diameter, particle diameter and average porosity.

Wetting efficiency directly affects the performance of the trickle bed reactors due to inefficient contacting of reactants and catalysts. Therefore it is desired to operate the bed near a completely wetting condition. In some situations, partial wetting may promote gas-liquid mass transfer and hence an increase in the reactant performance. General guidelines for operating trickle bed reactors with wetting efficiency of 0.7–0.9 and performance is lower for both upper range >0.6 and a complete wetting condition. The following correlations may be used for calculating wetting efficiency as a function of the gas and liquid phase Reynolds number. Wetting efficiency in trickle bed reactors varies 30–100%, with liquid phase Reynolds number (Re_L) changes from 3 to 100. Al-dahhan and Dudukovic [1] have proposed a correlation of wetting efficiency (η_{CE}) for trickle bed reactors operated under pressure (0.31–3 MPa) as

$$\eta_{CE} = 1.104 Re_L^{0.33} \left[\frac{1 + [\Delta P/Z]/\rho_L g}{Ga_L} \right]^{1/9} \tag{7.57}$$

The following correlation proposed by Burghardt et al. [10] may be used for calculating wetting efficiency as a function of the gas and liquid phase Reynolds number:

$$\eta_{CE} = 3.38 Re_L^{0.22} Re_G^{-0.83} \left(d_p \sqrt{\frac{g\rho_L^2}{\mu_L^2}} \right)^{-0.512} \tag{7.58}$$

A few other correlations reported by Ring and Missen [92] and El-Hisnawi et al. [24] may be useful for calculating wetting efficiency in trickle bed reactors.

Gas-liquid mass transfer is another important parameter required for design of the trickle bed reactor. Gas-liquid mass transfer is a function of gas and liquid velocities and particle diameter given by Sato et al. [96] as

$$k_L a = 6.185 \times 10^{-3} d_p^{-0.5} u_L^{0.8} u_G^{0.8} \tag{7.59}$$

The following correlation proposed by Fukushima and Kusaka [31] may be useful in a more generalized form, including fluid properties and trickle and pulse flow regimes.

In the trickle flow regime,

$$\frac{k_L a_B d_p^2}{D(1-\varepsilon_l/\varepsilon_B)} = 2 \left(\frac{S_p}{d_p^2} \right)^{0.2} Re_L^{0.73} Re_G^{0.2} \left(\frac{\mu_L}{\rho_L D} \right)^{0.5} \left(\frac{d_p}{d_T} \right)^{0.2} \tag{7.60}$$

In the pulse flow regime,

$$\frac{k_L a_B d_p^2}{D(1-\varepsilon_l/\varepsilon_B)} = 0.11 Re_L Re_G^{0.4} \left(\frac{\mu_L}{\rho_L D} \right)^{0.5} \left(\frac{d_p}{d_T} \right)^{-0.3} \tag{7.61}$$

A few other correlations may be considered for calculating the gas-liquid mass transfer coefficient from studies of Goto and Smith [33], Turek and Lange [106], and Wild et al. [114].

Liquid-solid mass transfer is represented in terms of Sherwood number as a function of Reynolds number and Schmidt number in a similar manner as that of stirred tank and bubble column reactors.

$$\eta_{CE} Sh = a(Re)^b Sc^{1/3} \tag{7.62}$$

where, a and b are constants, with different numbers proposed by various studies [15, 50, 61, 97, 103]. For example, Chou et al. [15] have proposed $a = 0.72$ and $b = 0.54$ for the trickle flow regime, with additional terms $(Re_G)^{0.16}$ and $a = 0.43$ and $b = 0.22$ for the pulse flow regime. Similarly, Tan and Smith [103] have proposed $a = 4.25$ and $b = 0.48$.

The *gas-solid mass transfer* coefficient can be calculated using the correlation proposed by Dwivedi and Upadhyay [22]:

$$k_{GS} = 0.4548 \left(\frac{H_A u_G}{\varepsilon_B}\right) (Re_G)^{-0.4069} \left(Sc_G^{-0.667}\right) \tag{7.63}$$

Boelhouwer et al. [9] measured heat transfer rates in a 0.11-diameter column filled with 6-mm glass beads for an air-water system and suggested values of $a = 0.111$ and $b = 0.8$ for trickle as well as pulse flow regimes.

$$Nu = a(Re)^b Pr^{1/3} \tag{7.64}$$

Bed to wall heat transfer can be considered from the following correlation proposed by Muroyama et al. [74]:

$$Nu = 0.012 Re_l^{1.7} Pr_l^{0.33} \quad \text{for trickle flow regime} \tag{7.65}$$

$$Nu = 0.092 \left(\frac{Re_l}{\varepsilon \beta_l}\right)^{0.8} Pr_l^{0.33} \quad \text{for pulse flow regime} \tag{7.66}$$

More details on heat transfer in trickle bed reactors can be found in Crine [16], Ranade et al. [88] and Taulamet et al. [104].

When it is critical to estimate spatial variation of liquid distribution, concentrations, and temperatures within a trickle bed reactor under consideration, it is best to use CFD-based models. Several approaches, such as percolation theory [16], network model [105], Eulerian-Eulerian with the multifluid models [4,34,43,119] and lattice Boltzmann-type models [68], have been practiced to simulate gas-liquid flow in trickle bed reactors. For more details on these approaches and illustrations of applications of detailed CFD models for simulating the performance of trickle bed reactors, readers may be referred to the works of Ranade [86] and Ranade et al. [88].

7.4.4 Fluidized Bed Reactors

Fluidized bed reactors are another class of multiphase catalytic reactors which have unique advantages in terms of heat and mass rates and mixing. In two- or three-phase fluidization systems, gas and liquid phases are used as carrier fluids, with internal or external separation of the solid catalyst for recycling. Fluidized bed reactors are employed in a wide variety of industries, including petroleum, fine and specialty industries, fuel and mineral processing, waste treatment and complexities. The hydrodynamics of fluidized bed reactors is quite complex. Besides fluid properties (density, viscosity, etc.), solid phase properties such as density, size and shape, cohesion/adhesiveness and restitution coefficient play a significant role in fluidization behavior. Several variants of fluidized bed reactors with different fluidization regimes (risers, downers, circulating fluidized beds, spouted beds and so on) have evolved over the years [58,86].

Fluidized reactors offer several advantages, such as rapid mixing of phases (uniformity in product quality), excellent rates of heat and mass transfer and relatively simple operations. Solid catalysts may be recycled using internal or external separators (with or without regeneration). This offers an opportunity to use a rapidly deactivating catalyst. Some disadvantages are higher catalyst attrition, erosion of reactor internals and significant backmixing. Some of the applications of catalytic fluidized bed reactors are listed in Table 7.7.

Table 7.7 Gas-liquid and gas-liquid-solid fluidized bed reactor applications

Process	Catalyst	Reactor Type	Pressure (atm)	Temperature (°C)
Vinyl chloride from ethylene and Cl_2	–	G-S fluidized bed	2–10	450–550
Maleic anhydride	V_2O_5	G-S fluidized bed	2–10	300–450
Ethylene oxide from ethylene and air	Ag	G-S fluidized bed	1	270–290
Acrolein from formaldehyde and acetaldehyde	MnO, silica gel	G-S fluidized bed	1	280–320
Acrylonitrile from air, propylene, and ammonia	Bi phosphomolybdate	G-S fluidized bed	1	400
Phthalic anhydride		G-S fluidized bed		
Vinyl acetate		G-S fluidized bed		
Chloromethane		G-S fluidized bed		
Calcination/roasting of ores		G-S fluidized bed		
o-Cresol and 2,6-xylenol		G-S fluidized bed		

Continued

Table 7.7 Gas-liquid and gas-liquid-solid fluidized bed reactor applications—cont'd

Process	Catalyst	Reactor Type	Pressure (atm)	Temperature (°C)
Enzyme production	Gel-entrapped *Sphingomonas*	Three-phase fluidized bed		
Extractive fermentation of lactic acid	Immobilized *Rhizopus oryzae*	Three-phase fluidized bed		
Ethanol fermentation on immobilized fluidized bed		Three-phase fluidized bed		
Hydrogen peroxide		Three-phase fluidized bed		
Crystalline silicon		G-S fluidized bed		

In designing a fluidized bed system, particle size plays a major role because it is one of the major factors in fluidization characteristics apart from gas velocity. Geldart [32] has shown four different categories of fluidization based on the mean particle (see Fig. 7.16). This classification provides a simple way to recognize different fluidization regimes: type A, aeratable fluidization (medium size, medium density particles which are easier to fluidize); type B, sandlike fluidization (heavier particles which are difficult to fluidize); type C, cohesive fluidization (typical powderlike solid particle fluidization); and type D, spoutable fluidization (large density and larger particles).

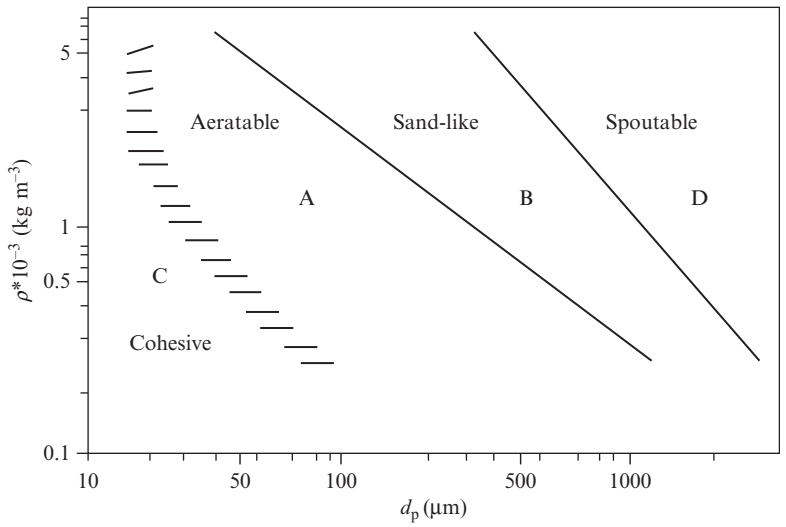


Fig. 7.16

Geldart classification of particles for fluidization. *Group A*: Particles of 30–100 μm, density ~1500 kg/m^3, easily fluidizable. *Group B*: Particles of 100–800 μm, density between 1500 and 4000 kg/m^3, sandlike material, rigorous fluidization nature. *Group C*: Fine-size particles (~20 μm) with dominance of intraparticle or cohesive forces (eg, flour, cement, etc.) *Group D*: Large-diameter particles ~1–4 mm, dense and spoutable (eg, peanuts, coffee beans, coal, etc.).

Fluidization may be broadly classified into two regimes: homogeneous fluidization and heterogeneous fluidization. In homogeneous or particulate fluidization, particles are fluidized uniformly without any distinct voids. In heterogeneous or bubbling fluidization, gas bubbles devoid of solids are distinctly observable. These voids behave like bubbles in gas-liquid flows. They exchange gas with the surrounding homogeneous medium with change in size and shape while rising in the medium. Harrison et al. [36] suggested that if the size of gas voids (bubbles) within the fluidized bed is greater than 10 times that of the particle diameter, fluidization is called bubbling fluidization. Overall flow regimes in fluidized bed reactors are shown schematically in Fig. 7.17.

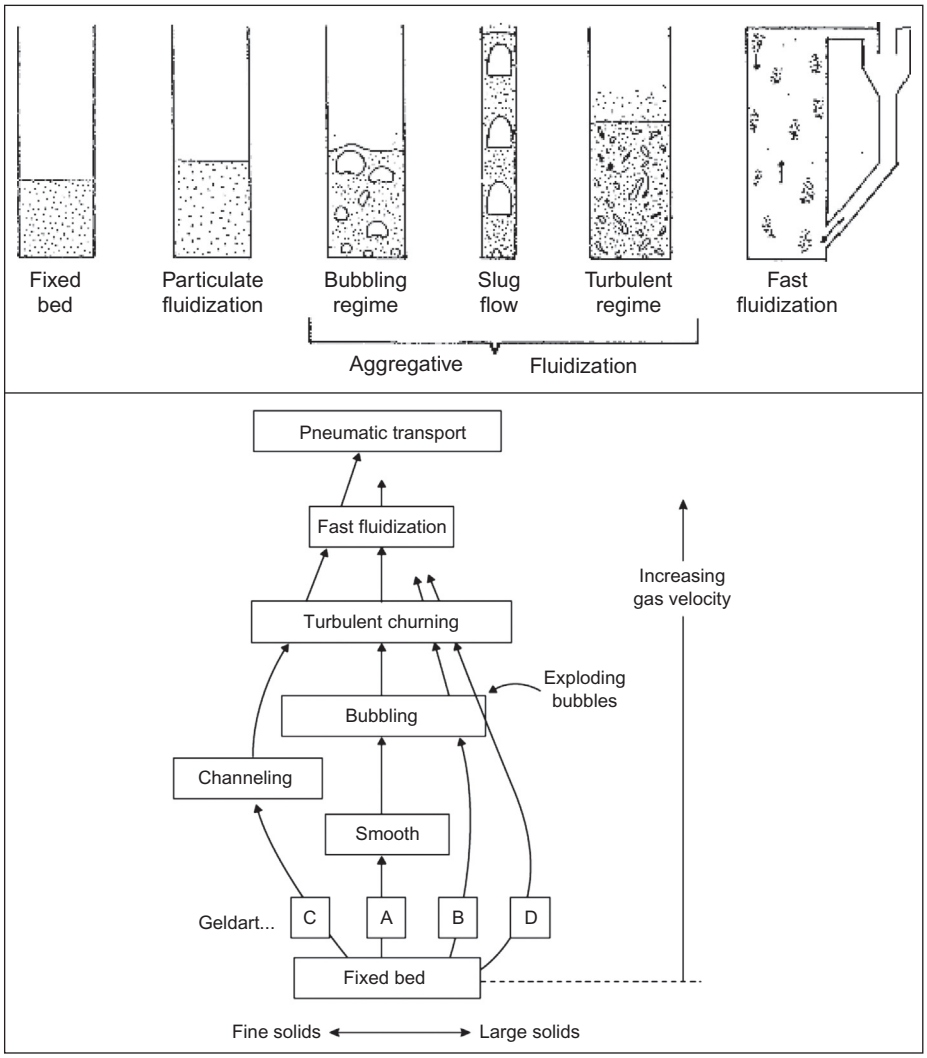


Fig. 7.17
Various flow regimes of fluidized bed reactors.

A fixed bed regime is observed when gas velocity is below the minimum velocity required for fluidization. Onset of fluidization occurs when gas velocity exceeds minimum fluidization velocity. In particulate fluidization, the bed expands smoothly with substantial particle movement and the bed surface is well defined. Particulate fluidization is observed only for Geldart-A type particles, and this is also a very common phenomenon for liquid-solid fluidization. A bubbling fluidization regime is observed at much higher velocities than homogeneous fluidization, in which distinguishable gas bubbles grow from the distributor, may coalesce with other bubbles and eventually burst at the surface of the bed. These bubbles intensify the mixing of solids and gases and bubble sizes tend to increase further with a rise in fluidization velocity. A slugging regime is observed when bubble diameter increases up to the reactor diameter (this typically occurs with small diameter reactors). In a turbulent regime, bubbles grow and start breaking up with expansion of the bed. Under these conditions, the top surface of the bed is no longer distinguishable. Bubble breakup results in many small voids with a cluster of solids. In fast fluidization or pneumatic fluidization, particles are transported out of the bed and need to recycle back into the reactor. No distinct bed surface is observed.

Each flow regime offers distinct features and advantages. Three-phase fluidized bed reactors differ from slurry bubble column reactors mainly in the volume fraction of solids. Solid volume fraction handled in three-phase fluidized beds is much higher (10–50%) compared to slurry bubble columns (less than 5%). Occasionally, three-phase fluidized bed reactors are also operated in a counterflow manner in which liquid is fed from the top and withdrawn from the bottom of the reactor. This mode of operation is used when particle density is lower than liquid phase, especially for polymeric particles. Particles are fluidized by downward flowing liquids and rising gas bubbles help in churning the bed, which helps in effective contacting of phases.

Extensive studies are available on fluidized bed reactor hydrodynamics and reaction engineering models. Earlier, Davidson's approach of modeling a bubbling fluidized bed reactor was the key contribution in accounting for bubble scale related transport phenomena. In this approach, three phases are considered for modeling purposes: emulsion phase (uniform solid concentration in the gas phase), cloud region (solids around bubbles and in the wake region) and the bubble phase. This design approach is adequately supported by correlations developed through extensive experimental data for various design parameters, such as volume fraction of the phases, bubble sizes, bubble velocity, heat and mass transfer among the phases [66,67,73,117,128]. Some of these correlations are summarized in the following:

The *gas-liquid mass transfer coefficient* for a three-phase fluidized bed reactor can be calculated using the following correlation proposed by Nguyen-Tien et al. [75]:

$$k_L a = 0.39\left(1 - \frac{\phi_s}{0.58}\right) u_L^{0.87}, \quad \phi_s < \left(0.58 - 0.7 u_G^{0.15}\right) \tag{7.67}$$

For a high-interaction regime and in the bubble disengagement zone, gas-liquid mass transfer can be calculated from the correlations suggested by Lee et al. [63]:

For the bubble disengagement zone,

$$k_L a = 2.36 \times 10^{-5} u_G^{0.686} u_L^{0.469} d_p^{0.788} \sigma_L^{-1.532} \mu_L^{-0.548} \tag{7.68}$$

For bubble coalescing or slug flow regime,

$$k_L a = 1.10 \times 10^{-6} u_G^{0.940} u_L^{0.381} d_p^{0.790} \sigma_L^{-2.273} \mu_L^{-0.671} \tag{7.69}$$

Similar to stirred reactors, *liquid-solid mass transfer* can be calculated from the correlation which is a function of the turbulent dissipation rate and the Schmidt number proposed by Arters and Fan [2]:

$$Sh = \frac{k_s d_p}{D} = 2 + 0.695 \left(\frac{\varepsilon^{1/3} d_p^{4/3}}{\nu}\right)^{0.6} Sc^{1/3} \tag{7.70}$$

Heat transfer from particle to fluid in the fluidized bed reactor is given in a correlation proposed by Richardson et al. [91]:

$$Nu' = Re^{0.62} Pr^{0.33} \frac{\varepsilon_s^{0.38}}{1 - \varepsilon_s} \tag{7.71}$$

This liquid-solid heat transfer coefficient is further utilized to calculate the heat transfer coefficient for a three-phase fluidized bed reactor using the following correlation:

$$h = h' \varepsilon_G^{0.45} \left(\frac{0.396}{u_G^{0.45}} + \frac{0.6768}{u_p}\right) \tag{7.72}$$

where u_G is the gas superficial velocity and u_p is the particle terminal velocity in liquid at ambient pressure.

Similarly, the heat transfer coefficient for liquid-solid systems and gas-liquid-solid fluidized bed reactors in terms of a modified Nusselt number and Reynolds number is given by Kang et al. [47]:

For a liquid-solid system,

$$\overline{Nu} = 0.053\ \overline{Re}^{0.8} Pr^{0.6} \tag{7.73}$$

For a gas-liquid-solid system,

$$\overline{Nu} = 0.036 \overline{Re}^{0.81} Pr^{0.65} \tag{7.74}$$

where the modified Nusselt number and Reynolds number are defined as

$$\overline{Nu} = \frac{h d_p (1-\varepsilon_s)}{k \varepsilon_s} \text{ and } \overline{Re} = \frac{d_p \rho_L u_L}{\mu_L \varepsilon_s} \tag{7.75}$$

Key aspects of fluidized bed reactor design are extensively covered in monographs by Kunii and Levenspiel [60], *Handbook of Fluidization* by Yang [115], and *Gas-Solid-Liquid Fluidization* by Fan [27].

In the absence of correlations or empirical information, CFD or discrete element based models can be used to gain insight into fluid dynamics of catalytic fluidized bed reactors. Ranade [86] discusses several approaches and models for simulating fluidized bed reactors. This book may be referred to for more details on CFD modeling. In recent years, several case studies have been published based on applications of CFD models for simulating reacting fluidized bed systems. For example, Chen et al. [13] simulated a fluidized bed polymerization reactor (CFD model with population balance models for capturing particle size distribution and kinetic theory of granular flow [KTGF] models). Simulated results of Chen et al. [13] adequately capture key observations of the considered polymerization reactor.

For simulating gas-liquid-solid fluidized bed reactors, the liquid phase needs to be considered a continuous phase and gas and solid phases are considered dispersed phases. Because three-phase fluidized bed reactors use relatively larger size particles ranging from 200 to 2000 μm and high solid loading (10–50%) compared to three-phase slurry reactors, detailed solid-fluid and solid-solid interactions need to be considered in the CFD model. Similar to gas-solid fluidized bed reactors, KTGF models need to be coupled with multifluid CFD models. Relatively few studies are available on CFD modeling of three-phase fluidized bed reactors ([5]; [44]; [42,80]). These may be referred to for more information on the modeling of three-phase fluidized bed reactors.

It is often necessary to use reaction and reactor engineering models in an iterative fashion. Reaction engineering with idealized models is useful for understanding the upper and lower bounds on performance and for identifying important issues which control the performance. Studies using idealized models are also helpful in determining desired performance targets for transport processes like mixing, mass and heat transfer. Engineering creativity, experience and accumulated empirical information is generally used to evolve preliminary reactor configurations. Reactor simulation models are then developed to evaluate these different reactor configurations. In a conventional methodology, the reactor engineer has to rely on experimental and semiempirical tools to obtain knowledge of fluid dynamics, which is essential to address many crucial design issues. Several references for this purpose have been cited in this section. Wherever such available information is not adequate, experiments on pilot scale reactors are designed and carried out. The usefulness of pilot scale studies depends on how well these pilot reactors mimic the fluid dynamics and mixing in proposed

large-scale reactors. Recent advances in computational flow modeling and computational resources allow one to develop detailed CFD models to establish the relationship between reactor hardware and reactor performance. Key references for this purpose are also cited in this section. The aspects of reaction and reactor engineering discussed in this chapter may be used to understand and to enhance performance of industrial catalytic reactors.

7.5 Summary and Conclusions

In this chapter we have provided an overview of reaction and reactor engineering aspects of catalytic processes. The role of microscale, mesoscale and macroscale processes was highlighted. After establishing the intrinsic kinetics of reactions occurring on microscales, approaches for quantifying the interaction of transport processes and chemical reactions on mesoscale were discussed. The discussion and cited references provide adequate information on quantifying mesoscale processes for gas-liquid (or liquid-liquid) and gas-liquid-solid reactions.

The mesoscale understanding needs to be incorporated in the reactor scale models. Some aspects of reactor selection are discussed and additional references are cited, which may be referred to for further information. The role of contacting pattern was also discussed. Basic governing equations for different degrees of backmixing (ideal PFR, plug flow reaction with dispersion, mixed reactors (single or in series)) are presented. Such macroscopic models involve several parameters representing underlying fluid dynamics and transport processes of these catalytic reactors. Key aspects of fluid dynamics and transport processes for four major reactor types are then discussed: stirred reactors, bubble column reactors, trickle bed reactors and fluidized bed reactors. In recent years, advances in CFD have realized an ability to simulate complex fluid dynamics and transport processes of these reactors rather accurately. Relevant references for the same are cited. It is expected that CFD models will be increasingly used for reactor engineering applications.

We have made an attempt to provide a systematic approach to understanding various elements of hydrodynamics, interphase and intraparticle mass transfer, fluid phase mixing and reaction kinetics relevant to multiphase catalytic reactors. The discussion on key reactor engineering issues and various modeling approaches will help in selecting appropriate models and their combinations. It is essential to emphasize that it is extremely important to correctly identify and define the reactor engineering objectives, analyze various key issues relevant to achieving the defined objectives, and formulate an appropriate modeling approach and tools which are consistent with the set objectives. A diagnostic analysis of the significance of various factors that may be contributing to specific process performance is helpful to simplify the models and select appropriate models for design purposes. We hope that the discussion in this chapter will help the reactor engineer make an appropriate selection of modeling approach and models.

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CHAPTER 8

Catalysis for Fine and Specialty Chemicals

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8.1 Introduction

8.1.1 Catalyst and Catalytic Processes

Catalysis and catalysts play an important role in producing chemicals that have wide applications resulting in the enhancement of quality of our live. Catalytic innovation is the key in developing new technology and can lead to higher productivity, industrial safety, a clean environment, and energy savings. Thus, the development of catalytic processes is of the utmost importance for better economics, better utilization of raw materials and energy so as to reduce the environmental impact and hence, sustainability.

The application of the catalytic process in chemistry antecedes the etymology of the word catalyst. Enzymes for the fermentation and production of alcohol have been known for centuries and so has the process of fat hydrolysis and the production of diethyl ether. Berzelius recognized the phenomena by correlating observations such as the enhanced conversion of starch to sugar by acids, hastening of combustion of gases with platinum, the oxidation of alcohol to acetic acid, and called it catalysis in 1835. In 1908, the synthesis of ammonia from nitrogen and hydrogen using osmium as a catalyst was discovered by Haber. Sabatier received a Nobel Prize in 1912 for the hydrogenation of ethylene and CO over Ni and Co catalysts. In 1938 Bergius converted coal to liquid fuel by high-pressure hydrogenation in the presence of an iron catalyst. Considerable work was done in catalysis between the 1800s and early 1900s, but the Second World War elicited extensive progress in the field of catalysis. The development of Fischer Tropsch synthesis in Germany, which involved production of hydrocarbons and oxygenated compounds from CO and hydrogen over alkalized iron catalyst, is one such example. Eventually the significance of this process lead to the development of industrial catalysts which improved production rates of bulk chemicals, such as nitric acids, methanol, and polymers like ethylene.

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8.1.2 The Role of Catalysts for Fine and Specialty Chemicals

Fine and specialty chemicals have been around for more than 100 years and the term "specialty chemicals" has been used interchangeably with "performance chemicals." They are synthesized with the aim of either being used as is or in the form of additives with some chemicals. Adhesives, surfactants, and lubricants are a few examples of specialty chemicals. William Henry Perkin was probably the first one to synthesize a commercially viable process for making a specialty chemical, mauve dye. Since then, companies engaged in the synthesis of specialty chemicals have been growing [134].

These organic chemicals are generally manufactured in batches and are used either directly for consumer products such as agrochemicals, or for synthesis of other commodities, such as the use of plasticizers in the polymer industry, or the synthesis of pharmaceutical products. From the early 1950s until the 1980s, the growth of chemical industry has led to the establishment of some really specific synthesis methods for specialty chemicals and they have not been changed much, as have those in the pharmaceuticals, electronics, and food industries.

8.1.2.1 The changing role of catalyst in the present scenario

Today, industries are aiming for a "less is more" approach in the synthesis of industrial chemicals. In this regard, catalysts can enhance the reaction, reduce the quantity of input, and decrease the load on effluent treatment if they can be recovered readily, as is the case with heterogeneous catalysts. There is an increasing impetus on making the chemical processes more environmentally benign and assigning a higher economic value to cleaner process rather than to a process with higher yields. With this aim, the shift towards "Green Chemistry" is an encouraging one. It means industries are looking for a reduction in waste generation at the source level itself, rather than posttreatment to reduce the environmental impact.

Most of the fine and specialty chemical synthesis is governed by stoichiometric processes. The volume of production is lower compared to the bulk chemical process which leads to the assumption that there is no need to adapt new and improved methods. Case in point, catalysis was developed in the 19th century to improve the manufacture of bulk chemicals from petroleum sources and hence it was never really considered for fine and specialty chemicals until recently. Another factor is that since the manufacture of fine and specialty chemicals is a time-dependent process, it means the manufacturer does not want to invest in an environmentally superior process when an economically superior process is readily available.

R.A. Sheldon introduced the term E factor in order to assess the environmental impact of the manufacturing processes. E factor is defined as the mass ratio of waste to the desired product. The atom economy concept is an extremely useful tool for evaluation of the amounts of waste that will be generated by alternative processes and can help to select the best route for manufacturing.

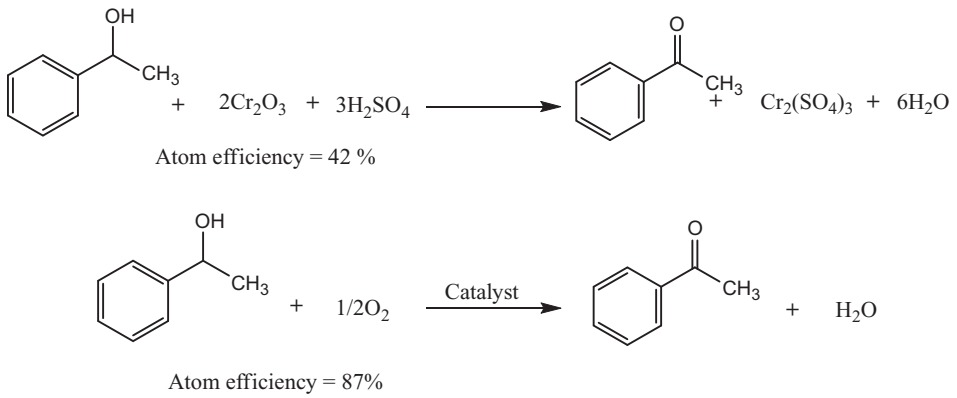
8.1.2.1.1 Terms to define "Greenness"

The measure of cleanness of a process is its E factor, atom efficiency, and environment quotient. Each of these terms needs to be comprehended fully by the reader to understand the difference between a green process and a conventional process.

8.1.2.1.2 Atom efficiency [135]

The atom utilization or atom selectivity is defined as the ratio of the molecular weight of the desired product to the sum of the molecular weights of all materials produced in the process, according to the stoichiometric equation (100% yield). This gives a more comprehensive idea of the waste generated in a process.

In the fine and specialty chemical industry, most of the waste generated is due to the stoichiometric reagent used in the process along with a multistep synthesis route. The first step to be taken to improve the process is to replace the use of stoichiometric reagents by catalyst. A comparison of oxidation of alcohol to ketone using catalyst and using stoichiometric reagents may help in elucidating the concept of atom efficiency further [136] (Scheme 8.1).



Scheme 8.1
Comparison of atom efficiency for catalytic and stoichiometric oxidation reaction.

8.1.2.1.3 E factor

The by-products produced per kg of product are known as E factor and also includes the solvents and any other supporting reagents used in the process. It is a more comprehensible concept as it does not directly account for a 100% yield. Water is the only exception that is it is not considered during the calculation of E factor because it would lead to extremely high E factor values if calculated for aqueous streams, although all the inorganic and organic solvents coming out as a part of the aqueous stream are accounted for.

Another way to explain E factor is the ratio of the amount of raw material minus the product produced to the product. This way it becomes much easier to find the E factor. Ideally, of course it should be zero. The E factor increases significantly as we move from bulk to fine chemicals, especially pharmaceuticals because of the multiple-step process and stoichiometric reagents used [136]. It has been observed that the waste generated by the fine and specialty chemical industry per kg of the product produced is significantly high compared to the bulk chemical industry (Table 8.1).

Table 8.1 E factor of different chemical industries [136]

Industry	Tonnage	kg Waste/kg Product
Oil refining	10^6–10^8	<0.1
Bulk chemicals	10^4–10^6	<1 to 5
Fine chemicals	10^2–10^4	5 to >50
Pharmaceuticals	10–10^3	25 to >100

8.1.2.1.4 Environmental quotient

Only considering the waste generated is not the most suitable method, and there is also a need to analyze the effect of the waste generated. This is where the term environmental quotient (EQ) of the process comes into play. The EQ is obtained by multiplying the E factor by an arbitrarily assigned unfriendliness quotient, Q. The Q value is predefined.

This is important because one cannot directly equate two different types of waste streams only on the basis of amount or nature. For example, 1 kg of calcium carbonate and 1 kg of chromium salts cannot be given the same EQs. Similarly, 1 kg of calcium carbonate and 10,000 kg of calcium carbonate also cannot be given the same EQ. The EQ value will depend on several other factors, such as recyclability and reusability of waste.

8.1.2.2 The role of catalysis in waste minimization

Since the advancement of industrial chemistry began, much of the focus has been on bulk chemical manufacture and so with the advent of greener principles for synthesis, the burden of waste reduction has been laid on that sector only, completely ignoring the fine and specialty chemical industry. This is possibly because the volumes of production are relatively low, implying that the waste generated would also be low, but here the comparison of toxic waste generated must not be made with that of the bulk chemicals, but with that of the scale of production of the fine chemicals (kg waste/kg product). The need for waste minimization through application of green chemistry in the field of fine and specialty chemicals has been found to be both necessary and viable. There have been many differences between the kind of

waste generated in bulk chemical manufacture and specialty/fine chemical manufacture. The primary differences are [137]:

- The general complexity in structure and overall thermal stability of the fine and specialty chemicals necessitates the use of moderate reaction conditions and reaction media. The multistep nature of the synthesis yields large quantities of undesirable materials in the overall synthesis.
- The process for fine and specialty chemicals is generally carried out in batches rather than using a continuous process, as in the case of bulk chemicals. Their E factors are of the order of 5–50 kg waste per kg product, compared with values of $<$1–5 kg for bulk chemicals, and $\sim$0.1 for refinery operations. This means that fine and specialty chemicals in general are "dirtier."
- There is a need for specific and highly selective reactants to carry out a certain reaction for the synthesis of fine and specialty chemicals. Consider oxidation, where in a bulk chemical synthesis air/oxygen might be suitable for carrying out the oxidation, and for a fine and specialty chemical, hydrogen peroxide might be used although it would be more expensive.

The role of catalyst in waste reduction can most conveniently be explained by the example of the classical Friedel-Crafts (FC) acylation of anisole which was done by stoichiometric reagents, but zeolite was found to be a commercially viable catalyst for this reaction. Compared to alkylation, an acetylation reaction needs more than stoichiometric amounts of an acylating agent such as aluminum chloride or boron fluoride. Zeolite was suggested to replace stoichiometric reagents and was successful in the case of more reactive aromatic species such as anisole [136]. Zeolite has since been used for acetylation of other aromatic moieties.

While looking at any process, one needs to consider not only the yield of the desired product, but also the amount of undesired waste generated. Here comes the role of catalytic processes. There are a lot of catalysts suitable for the synthesis of fine and specialty chemicals which increase the selectivity of the required compound, and in turn, help minimize waste. Green chemistry will help take us a step further in this direction. Principally, it implores a chemist to choose a process that is not just high in the yield of one, but low in the yield of anything else, and it puts an economic value on eliminating waste at the source level itself [136]. Here, waste is any and everything generated in the reaction apart from the desired product.

The development of catalytic processes instead of stoichiometric processes is the need of the hour. Improvement in catalysis will help in intensifying a process and open up a lot of doors to newer synthesis processes with higher selectivity, such as those found in stereoselective catalysts used for the synthesis of certain platform chemicals. Catalysts in specialty chemicals, especially heterogeneous catalysts, will increase productivity due to the ease of separation and economic viability as the catalyst, in most cases, can be reused number of times.

The process of change might be slow but we can see that there has been some increase in the role of heterogeneous catalysts.

Catalysis has been descried briefly in Chapter 1, while homogeneous catalysis, heterogeneous catalysis, catalyst characterization, and deactivation have been covered in the first section of this book in more detail. This chapter provides a broad discussion on the application of catalysis and catalytic processes to the fine and specialty chemicals sector, which includes various important reactions employing homogeneous as well heterogeneous catalysts, and covers such reactions as hydrogenation, oxidation, various coupling reactions, asymmetric hydrogenation, and rearrangement reactions, and so on.

8.2 Homogeneous Catalysts

The fundamentals of catalysis and reaction engineering have been presented in Part 1 of this book. The basic principles of homogeneous catalysis are also presented in Chapter 2 of this book. In this chapter, we attempt to cover the industrially relevant homogeneous catalytic processes for synthesis of fine and specialty chemicals. The fine and specialty chemical industry is extremely diverse, encompassing pharmaceuticals, dyestuffs, food additives, agrochemicals, polymer additives, flavors and fragrances, various chemical intermediates, etc. Carbonylation, hydroformylation, coupling reactions (including Heck, Suzuki, and Grignard reactions), asymmetric catalysis (epoxidation and hydrogenation), and oxidation reaction, which are commonly practiced in fine and specialty chemical industry, have been covered in some detail to elucidate the utility.

8.2.1 Carbonylation Reaction

Carbonylation reaction is the inclusion of a C=O species in a substrate. There has been a considerable interest in the use of carbon monoxide industrially as a renewable feedstock. CO can be synthesized from burning elemental carbon in a limited supply of oxygen, reduction of carbon dioxide at high temperature, dehydration of formic acid, and the preparation of synthesis gas or it may be obtained from chemical sources, such as phosgene. The inclusion of a CO group is an industrially significant catalytic process. High atom economy and formation of more than one C–C bond is possible through carbonylation.

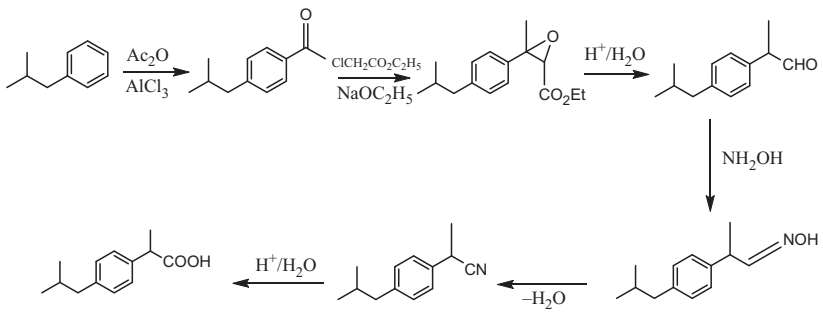
One of the best examples for industrial applications of carbonylation was developed by Monsanto—rhodium catalyzed process for production of acetic acid from methanol and carbon monoxide [1]. The active catalyst in the process is $[RhI_2(CO)_2]^-$, and this is one of the few processes where kinetics has been very well established. The process involves mild reaction conditions of 30–40 bars pressure and 150–200°C temperature. The material of construction for the plant is generally special alloy stainless steel due to the corrosiveness of iodide. Products obtained from carbonylation include esters, lactones, carboxylic

acid, isocyanates, urea, carbamates, and heterocycles. As far as the central atoms for catalyst are concerned, group VIII element, rhodium, palladium, cobalt, and nickel are suitable choices for carbonylation of organic halides [2]. Metal catalyzed carbonylation of benzyl halides to give phenyl carboxylic acid has been studied. One application of the process is in the synthesis of phenyl acetic acid used in perfumery and pesticides. Biphasic catalyst systems have also been developed for the purpose. The carbonylation of benzyl chloride was carried out in 5–10 mol% of $Co(CO)_6$ catalyst and benzyl trialkylammonium surfactant in a biphasic medium employing diphenyl ether and aqueous 40% NaOH as solvent.

Carbonylation using palladium as catalyst has been studied and found to improve the yield, as in the case of carbonylation of 5-hydroxymethyl furfural in water-soluble palladium catalysts. In general, palladium is a better catalyst than nickel [3]. Carbonylation can be explained through a lot of examples and processes. Chapter 14 presents recent advances in the development of new catalysts for carbonylation reactions. The synthesis of intermediates, which are vital in the fine and specialty chemical industry, have been given below to further illustrate specific catalysts for carbonylation.

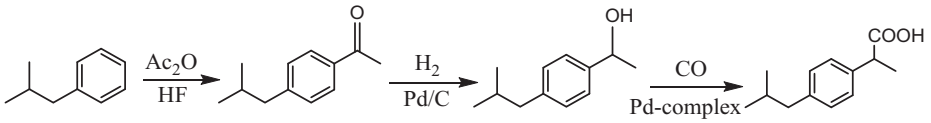
8.2.1.1 Synthesis of ibuprofen

Ibuprofen is a widely used drug in the treatment of rheumatoid arthritis, acute gout, and osteoarthritis. Conventionally, it is produced by the classical Boots route (Scheme 8.2).



Scheme 8.2
Boots process for synthesis of ibuprofen [4].

The main drawback of this process is the use of stoichiometric reagents and multistep synthesis. Many variations of this process are in use; however, overall efficiency of these processes is very low. A major breakthrough in the ibuprofen technology came with the development of a catalytic three-step process developed by Hoechst A.G. in collaboration with Celanese Corp. in 1992. Reactions involved in the process are given in Scheme 8.3.



Scheme 8.3
Catalytic process for ibuprofen [5].

The advantages of the BHC process (Boots-Hoechst-Celanese process) are a catalytic three-step process with close to 100% atom utilization. Overall efficiency of the process is 80% and it is an eco-friendly process with the use of Pd in catalytic amounts [5,6]. Carbonylation of 1-(4′-isobutylphenyl) ethanol or IBPE in the presence of a palladium catalyst complex system is the key step in the manufacture of ibuprofen by this new route. The reaction can be carried out using $PdCl_2(PPh_3)_2$ as catalyst at 130°C with a pressure of 162 bar. The process selectivity is around 95%. This process has been commercially used to produce ibuprofen although it is not free of drawbacks, such as a product-catalyst separation problem, harsh operating conditions, and low catalyst selectivity.

Another homogeneous catalyst system that has been developed for a single step synthesis of ibuprofen by carbonylation of IBPE is ($PdCl_2(PPh_3)_2$ or Pd(pyca)). The Pd(pyca) complex was shown to have a selectivity of ~99% for ibuprofen [7,8]. With the proper choice of ligands and promoters, high selectivity to ibuprofen is obtained at lower pressures such as 50–60 bar with very high activity. This has been discussed in more detail in Chapter 14 of this book. Biphasic catalysis, as well as heterogenization of homogeneous catalysts has helped to overcome the catalyst-product separation problems.

8.2.1.2 Synthesis of carbamates [9]

Carbonylation of aromatic nitro compounds is an important area of study because it can be used to synthesize urea, isocyanates, and carbamates, etc., which are intermediates in the fine and specialty chemicals industry. Carbamates are esters of carbamic acid with the formula is shown in Fig. 8.1.

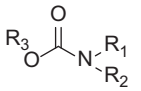
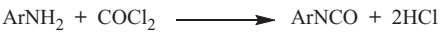


Fig. 8.1
Structure of carbamates.

Carbamates can be employed in various industries such as polymers for the synthesis of polyurethane, which is used in foams, elastomers, and solids; in agriculture for the synthesis of pesticides such as carbofuran (Furadan), carbaryl (Sevin), fenoxycarb, ethienocarb, and fenobucarb; and in preservatives and cosmetics. Carbamates have immense applications in pharmaceuticals related to Alzheimer's Disease such as rivastigmine and neostigmine, which are

cholinesterase inhibitors; in anxiolytic and muscle relaxant drugs such as meprobamate, felbamate, and tybamate; and for HIV treatment, such as darunavir, which is a protease inhibitor.

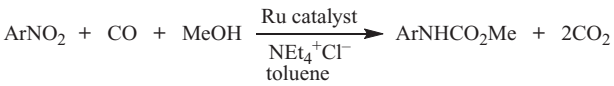
The conventional synthesis of carbamates involved phosgenation of amine, or reaction of amine with phosgene, followed by the formation of carbamic ester. The reaction is shown in Scheme 8.4.



Scheme 8.4
Conventional synthesis of carbamates.

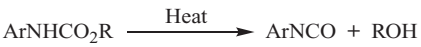
Here the amine, phosgene, and alkoxy substituted alkyl groups are reacted in the presence of a water-immiscible solvent in the same reaction vessel at the same time, in the presence of an acid-binding agent to yield the desired product [10]. The issues with this synthesis route are excess phosgene used, which generates a large amount of a highly toxic and corrosive effluent.

An alternate and cleaner route for carbamates involves the use of ruthenium, rhodium, and iron as transition metal catalysts with carbon monoxide as ligand in the carbonylation of nitro aromatics to form carbamates (Scheme 8.5).



Scheme 8.5
Carbamate with ruthenium catalyst.

Carbamates are important insecticides and can be transformed to isocyanates by thermal cracking (Scheme 8.6).



Scheme 8.6
Carbamates to isocyanates.

Hence, the importance of this reaction also lies in the fact that it can be used for making isocyanates, which would otherwise be obtained by a reaction of corresponding amines with phosgene.

Reductive carbonylation of nitrobenzene with ruthenium carbonyl complexes particularly, $Ru_3(CO)_{12}$ and $Ru(CO)_3(PPh_3)_2$ in the presence of toluene-methanol, at 170°C and 60 bar pressure of carbon monoxide, was performed and tetraethyl ammonium chloride was used as cocatalyst. The reaction was highly selective towards $PhNHCO_2Me$. Substituted aromatic nitro compounds were also used as substrates with $Ru_3(CO)_{12}$ as catalyst because it was more

active than $Ru(CO)_3(PPh_3)_2$. Although 100% conversion was obtained using ethanol, the selectivity for carbamate was low, whereas in the presence of methanol, full conversion was slower, but selectivity was higher. Another factor which influenced the synthesis was carbon monoxide pressure, which increased the yield to 50 bar, but beyond had an adverse effect on the rate. Activity and selectivity were both positively influenced with the increase in temperature, 170°C being the most suitable with high selectivity and activity. Higher temperatures gave diminutive yields and the range of operation was narrow.

The use of heterogeneous catalysts such as copper-based catalysts with halide promoters has also been found to be effective for a heterogeneous gas-solid oxidative carbonylation. This process typically involves the reacting of primary amine (such as aniline in gas phase), a compound with at least one hydroxyl group, carbon monoxide, and molecular oxygen in the same reaction vessel, in the presence of a catalyst, which is in solid state. The catalyst may be a heterogenized using a support. In this process, the gaseous compounds exiting are CO, CO_2, and O_2 which can be easily separated. The remaining compounds—amine, alcohol, water, and carbamate, are in liquid phase. Alcohol can be removed by evaporation. Amine and crystallized carbamate would remain along with water. Typically, amine is insoluble in water and can be separated followed by filtration to isolate carbamates [11]. Alkoxycarbonylation of amines to carbamates has been discussed in more detail in Chapter 15 of this book.

8.2.1.3 Synthesis of N,N-diphenyl urea (symmetrical urea)

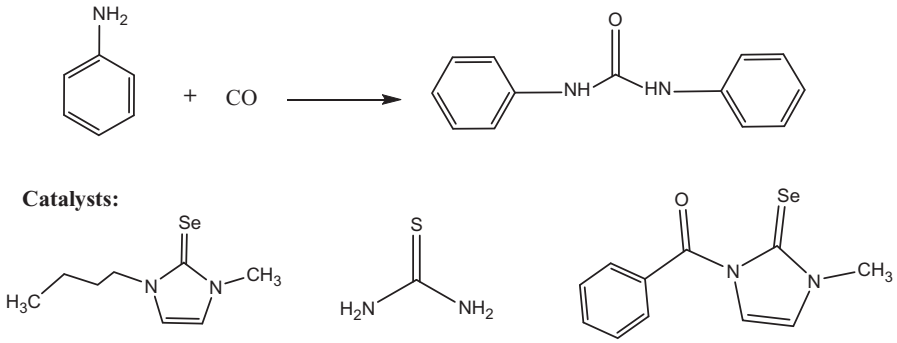
Urea has been an important derivative of carbonyl compounds. The applications are in agro chemistry, pharmaceuticals, dyes and intermediates, polymer chemistry for plasticizers or stabilizers, and as antioxidants in gasoline, among others. The common routes for synthesis of symmetrical urea include reaction of amines with compounds like isocyanates, formamides, or carbamates; or reaction of amines with CO in the presence of transition metal catalysts like Pd, Ru, Rh, etc. with the goal of reducing the environmental impact, newer processes using CO_2 as carbonylation agent are also being looked at [12].

N,*N*′-Diphenylurea has applications in the synthesis of sulfa drugs, isocyanates, and other chemicals. Phosgenation was followed earlier but as in the case of carbamate synthesis, the process led to the generation of toxic and corrosive effluent, as well as it was expensive and, hence, could not be carried out on a large scale. An industrially accepted route for the synthesis involves urea and aniline along with water as a solvent, and hydrochloric acid as a catalyst. A 40% yield of *N*,*N*′-diphenylurea is obtained. The waste stream includes aniline, waste water, and HCl as gas [13].

As stated in the previous case study, reductive carbonylation has been studied using rhodium, ruthenium, and palladium. Another catalyst for consideration for oxidative carbonylation of amines or reductive carbonylation of nitro compounds is selenium-based catalysts; especially for the synthesis of symmetric urea. These catalysts have a marked advantage in

terms of their ease of availability and ability to act as phase transfer catalysts, but the downside of employing these catalysts is the noisome selenium containing intermediates.

Oxidative carbonylation of aniline with carbon monoxide and air in [BMIM]BF_4 (ionic liquid) was catalyzed by 1,3-dialkylimidazole-2-selenone at 90°C for 6 hours. The yield of *N*,*N*-diphenylurea was 94% (Scheme 8.7).



Scheme 8.7
Carbonylation of aniline [14].

The noxious odor of H_2Se could be avoided in the catalysis because of the unavailability of selenium to directly synthesize such derivatives. The mechanism for such synthesis is still not completely understood [14].

Carbonylation reactions are practiced mostly in bulk chemical manufacture, hence, the process chemistries have been well established, thus, there has been a need for bringing in more novel routes with improved efficiencies for synthesis of fine chemicals. These newer methods for carbonylation will reduce the involvement of toxic chemicals, such as phosgene or HCN in the process. Carbonylation of olefins, amines, and phenols/alcohols are becoming a major area of interest for homogeneous catalysts in developing novel catalytic systems for synthesis of fine chemicals, especially pharmaceuticals. Ruthenium, platinum, and palladium play a special part in this chemistry because of the ability to facilitate reaction at milder conditions and maximum efficiency [15].

One of the major issues with such a homogeneous catalyst system is catalyst-product separation, owing to the scarce solubility of the substituted urea products even in highly polar solvents. A robust and active catalyst system employing the conventional transition metal precursors has been devised for oxidative carbonylation of amines in a water-organic solvent biphasic system [16]. The complexes are rendered water-soluble by making their complexes with water-soluble N-ligands, which can be separated from the product easily and

recycled several times. The synthesis of highly dispersed Pd nanoparticles stabilized by immobilizing them on an amine functionalized zeolite support; and its application for the oxidative carbonylation of amines is also reported [17]. The catalyst provides highly active, recyclable heterogeneous catalysts for the oxidative carbonylation of amines for the selective synthesis of disubstituted ureas. However, the major challenges are in developing feasible catalyst-product separation protocols and making the recycle of catalysts an economically feasible technology.

8.2.2 Hydroformylation Reaction

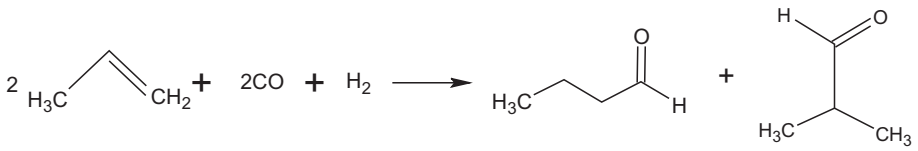
Hydroformylation is the addition of CO and H_2 or synthesis gas to an olefin in the presence of a catalyst for formation of an aldehyde. The reaction leads to a mixture of products, both branched and linear aldehydes, which is attributed to a possible isomerization of the double bond during the reaction. Thus the ratio of regioselective products needs to be considered. The chirality of the product is dependent on the substituent groups present on the α,α-disubstituted olefins. Hydroformylation was discovered in 1938 by Otto Roelen and he called it "oxo process." It is still one of the most important industrial synthesis processes and represents one of the largest homogeneously catalytic reactions in the chemical industry.

Rhodium and cobalt are the primarily used catalysts in this synthesis and a typical structure is $[HM(CO)_xL_y]$, where L can be further CO or an organic ligand. In terms of activity, the catalysts can be listed as:

$$Rh \gg Co > Ir,\ Ru > Os > Pt > Pd \gg Fe > Ni$$

Cobalt has distinct advantages as a catalyst such as (1) resistance towards poisons, (2) low price compared to rhodium, and (3) does not require a complete recycle. However, an issue observed with the use of cobalt is the deposition of Co which causes reactor fouling and blockage of valves. Where cobalt is more resilient towards catalytic poisons, rhodium is effective in catalysis of olefins with less than 10 carbons in the chain. Those Rh complexes may be sufficiently more reactive than Co, and up to 1000 times more effective. The optimization of the process is ultimately dependent on the activity, selectivity (chemo and stereo), and stability of the catalyst system.

Hydroformylation is a well-established commercial process for the manufacture of aldehydes which have applications in plasticizers, detergents, dyes, the food industry, etc. The reaction holds an important position in industrial homogeneous catalysis both in terms of scale and value. This reaction has attracted attention for the synthesis of fine chemicals and pharmaceuticals because of the possibility of developing cleaner routes. The most important olefin starting material is propene, which is mainly converted to 1-butanol and 2-ethylhexanol via the initial product butyraldehyde (Scheme 8.8).



Scheme 8.8
Hydroformylation of propene.

Prior to the introduction of rhodium catalysts for hydroformylation, dicobalt octacarbonyl was used which was modified with phosphines to increase the yield of linear aldehydes. Rhodium catalysts such as $[HRh(CO)(PPh_3)_3]$ can operate at 100°C and 10–25 bar and give a high ratio of linear to branched product. The active catalyst precursor for cobalt catalysts is $[HCo(CO)_4]$; similarly for rhodium catalyst it is $[HRh(CO)(PPh_3)_3]$. Mechanism of hydroformylation of propene with $[HRh(CO)(PPh_3)_3]$ is shown in Fig. 8.2.

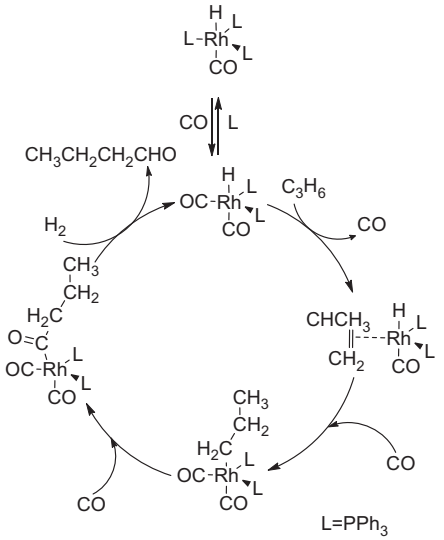


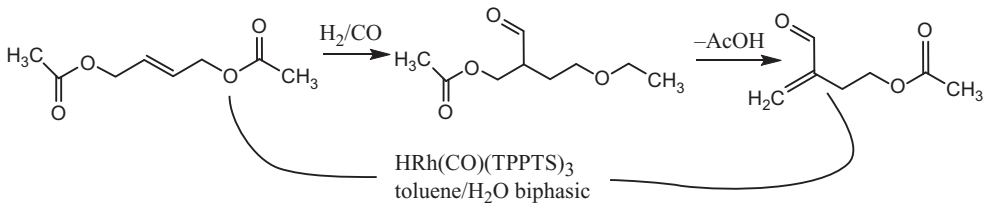
Fig. 8.2
Hydroformylation of propene with $[HRh(CO)(PPh_3)_3]$ [18].

To elucidate the process of hydroformylation in fine chemical industry, a few examples are discussed in the following subsections.

8.2.2.1 Synthesis of 2-methyl-4-acetoxy butenal (intermediate for vitamin A)

The intermediate to the synthesis of vitamin A, 2-methyl-4-acetoxy butenal (MAB), was synthesized by hydroformylation of 1,4-diacetoxy-2-butene (DAB). This route was developed as a replacement to the phosgenation route. The hydroformylation takes place in 162 bar pressure at 75°C and the yield 2-formyl, 1-4-diacetoxybutene (DAFB) of was 77% [19].

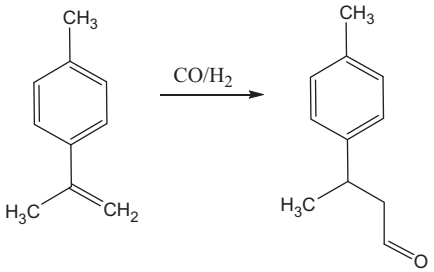
Recovery and reuse of rhodium catalyst posed a problem in this process along with the difficulty in the separation of pure product. Recently, it was proved that through a one-step synthesis using a water-soluble Rh complex catalyst (prepared from $[Rh(COD)Cl]_2$ and 3,3′,3″-Phosphanetriyltris(benzenesulfonic acid) trisodium salt (TPPTS) ligand) in a biphasic system, 99.9% conversion of DAB with nearly 100% selectivity for 2-formyl-4-acetoxybutene (FAB) was achieved via tandem hydroformylation-deacetoxylation reaction [20] (Scheme 8.9).



Scheme 8.9
One-step synthesis of FAB [21].

8.2.2.2 Synthesis of limonenal

Catalytic hydroformylation helps in synthesis of a large number of aldehydes useful for perfumery. Starting material may be different types of terpenes. This conversion of naturally occurring raw materials to aldehydes has been studied in some detail. Commercial synthesis for compounds such as limonenal or spirambrene were established by Celanese by hydroformylation of limonene (Scheme 8.10), and by Givaudan and Vigon by hydroformylation of 2-carene, respectively. Limonene aldehyde can be mixed with a large number of compounds and act as perfumes/perfuming agents in cosmetics, creams, lotions, odorizers, and toilet soap. spirambrene has a woody, spicy odor and is a component of perfumes [22].



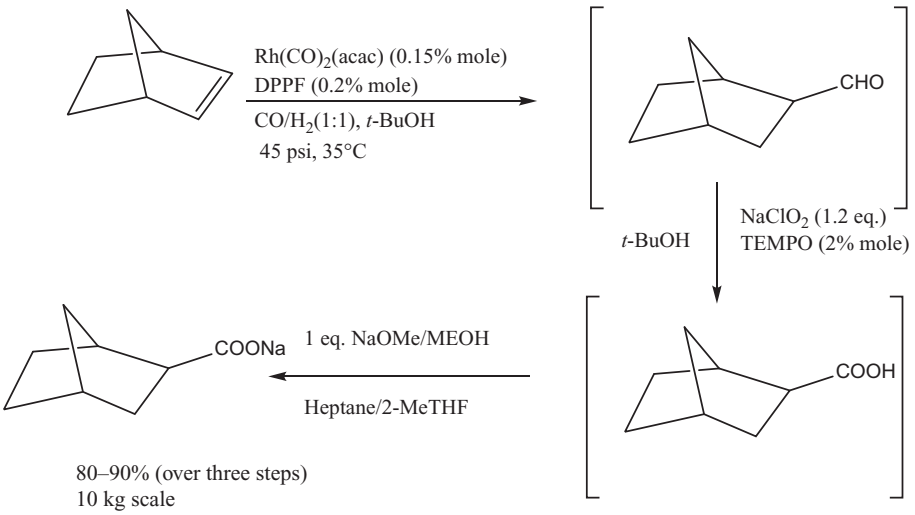
Scheme 8.10
Limonene hydroformylation.

Limonene hydroformylation was studied in the presence of triphenyl phosphine or PPh_3 as auxiliary ligands and pyridinium *p*-toluenesulfonate or PPTS, as an acid cocatalyst [23]. According to the Celanese process, the synthesis of the desired product could be carried out in a stainless steel autoclave. Limonene, PPh_3 and rhodium catalyst like $RhCl(CO)[P(C_6H_5)_3]_2$ were mixed together and the autoclave was flushed with syn gas. Rhodium compound was used in quantities based on that of the hydrocarbon—preferably 15–400 ppm. Further addition

of a mixture of equal volume H_2 and CO was added to the reactor to bring the pressure to 200 bar. The reaction was performed in the range of 100–150°C and the maximum observed pressure during the process was 270 bar. The work-up of the process involved separation of aldehyde by distillation under nitrogen pressure. A reported theoretical yield of the aldehyde was 83% with a product purity of 98% [24].

Hydroformylation is one of the most important applications of homogeneous catalyst. With the development of newer catalytic methodologies, including a newer class of ligands has led to expansion in the scope of the reaction. Ligands such as organophosphites are less sensitive towards oxidations and act as strong acceptors leading to higher rate of reaction.

Apart from the two examples given above, the role of hydroformylation is significant for pharmaceuticals such as in synthesis of pharmaceutical building block A. This was developed by Pfizer and the production was on 8 kg scale using Rh/DPPF, 2.4 bar syn gas at 35°C. Overall yield of A was 80% (Scheme 8.11).



Scheme 8.11
Pharmaceutical building block A with Rh/DPPF [25].

The major issues with the homogeneous catalysis are stability of the catalyst complex and catalyst-product separation, and are barriers that need to be overcome to develop an economically feasible process. This can be done by using biphasic catalysts, heterogenizing homogeneous catalysts, and supporting homogeneous complex catalysts on ionic liquid film.

8.2.3 Coupling Reactions

Coupling reactions involve formation of a C–C bond and are simple and straightforward. Industrially, coupling reactions form a part of a large number of multistep synthesis processes. These reactions are highly selective and give good yields because they involve specific

reactions between carbon centered anions with polar compounds such as esters and ketone, and metal halides. There are two types of couplings:

1. Cross coupling: This involves two different species forming a C–C bond such as bromobenzene and vinyl chloride to give styrene.
2. Homo coupling: This involves formation of C–C bond between two identical partners such as conversion of iodobenzene to biphenyl.

The ligand and the catalyst of choice play an important part in the reactivity and selectivity of the product. With the advent of transition metal catalysts such as palladium, nickel, and cobalt, the rates of coupling reactions have increased manifold. There has been a lot of focus on palladium as a catalyst for coupling reaction because it gives a very high activity allowing for higher conversion at moderate conditions compared to other metal counterparts [26].

A critical area of study in these processes is the inhibition and deactivation of catalyst but if that can be dealt with, then these reactions provide several advantages, such as total cost reduction. An example of such deactivation is the cyanation of haloarenes in presence of $Pd(PPh_3)_4$ as a catalyst. Due to formation of a polycyano palladium complex such as $[Pd(CN)_4]^{-2}$ and the consequent removal of phosphine ligand, the catalyst is deactivated. Reactive intermediates present in the reaction may inhibit or deactivate the catalyst hence the mechanism needs to allow a counter ion to safeguard the activity of the palladium catalyst [27]. Coupling reactions are susceptible to the presence of water or oxygen. However, using the water-soluble sulfonated phosphines, made by the reaction of triphenyl phosphine with sulfuric acid coupling, can be carried out in aqueous solutions. Oxygen in the air causes more disruptions to the coupling reactions [28]. This is because of the reaction progressing via unsaturated metal complexes without 18 valence electrons. These ligands have empty coordination sites which are very labile towards oxygen. For instance, nickel and palladium form a zero valent complex which reacts with the carbon halogen bond to form a metal halogen and a metal carbon bond.

Coupling reactions involving varied species have been in purview. Homogeneous catalysts involving metals Na, Pd, Cu, Fe, and Ni have been used. Wurtz reaction (R-X and R-X species), Ullmann reaction (aryl halide), Heck reaction (alkene with aryl halide), Negishi coupling (R-Zn-X and R-X species), Grignard reaction (aryl/vinyl magnesium halide and aldehyde/ketone coupling), and Suzuki reaction ($R\text{-}B(OR)_2$ and R-X) are common coupling reactions that have been studied. Similar to the Wacker type synthesis where a water or hydroxide ion would react with olefin-palladium complex to form carbon-oxygen bond, it was designed to generate carbon nucleophiles which would give C–C bonds. In 1965, a reaction of π-allylpalladium chloride and malonate (or acetoacetate) to give allylmalonate (or allylacetoacetate) was reported, followed by coupling reaction of aryl halide and olefinic compounds being developed by Heck and Mizoroki [29]. Further development in the use of organometallics for these reactions has given milder, broader, and better catalytic systems. Palladium is one of the most commonly used transition metals in such synthesis due to its ability

to perform coupling at low temperature, for substrates with low reactivity, and also has a high turnover number making it economical compared to nonprecious metals such as copper, nickel, and iron. With regards to the issue of removal of transition metals in Active Pharmaceutical Ingredient (API), some efficient catalyst scavengers need to be developed. Apart from the central atom, the ligand plays an important role in determining the rate and selectivity (regio and chemo) of a reaction. The mechanism in Fig. 8.3 illustrates that the reaction starts with formation of a π-allylpalladium complex with oxidative addition of Pd(0) to an allylic compound. A divalent Pd source may be used and eventually reduced in situ with the addition of the alkene, the nucleophile, or the phosphine ligand. If two different ligands are used, the allyl fragment becomes "asymmetric." The sp^3 and sp^2 character of the carbon atoms depends on the proximity of the carbon atom to the ligand. Allyl group is an anion in the complex but palladium is more electrophilic than the allyl group, hence, it undergoes a nucleophilic attack. Pd(0) leaves eventually taking the electrons with it and the product is obtained while the catalyst can be recycled.

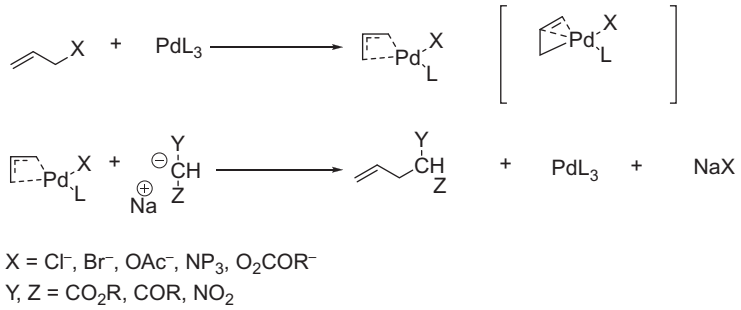


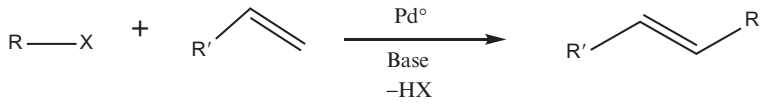
Fig. 8.3
Reaction mechanism for coupling [1].

Some reactions discussed here are commonly employed in the synthesis of fine chemicals such as Heck coupling, Suzuki coupling, and Grignard coupling and have been explained with the help of specific case studies. Application of various coupling reactions in API industry has been elucidated in Chapter 12 in more detail.

8.2.3.1 Heck coupling reaction

In 1968, Richard F. Heck reported that in situ generated RPdX (R = Me or Ph, X = halide) can be added to olefins at room temperature. Formation of styrene proceeds through addition of phenylpalladiumchloride to ethylene followed by elimination of palladium. Interestingly, in the beginning Pd(II) was used for the alkylation of olefins but this was not a catalytic process since Pd was oxidized to Pd(0). However, Heck suggested the use of $CuCl_2$ to re-oxidize palladium to make the process catalytic with respect to palladium (Scheme 8.12).

A Heck coupling reaction involves bond formation between aryl halides and alkenes in the presence of a base. Palladium is a versatile and efficient catalyst system for the purpose, and this



Scheme 8.12
Palladium catalyzed Heck coupling for olefins and alkyl halides.

reaction of aryl/vinyl halide olefins is an important process in C–C bond forming processes in synthetic organic chemistry (Fig. 8.4). Sources such as aryl triflates, diazonium salts, sulfonyl halides, aroyl halides, and aromatic sulfinic acid sodium have been utilized. There has been a much needed improvement in catalytic systems also. In the reaction with unactivated aryl chlorides, harsh conditions are required hence, there is a need to develop better catalyst systems.

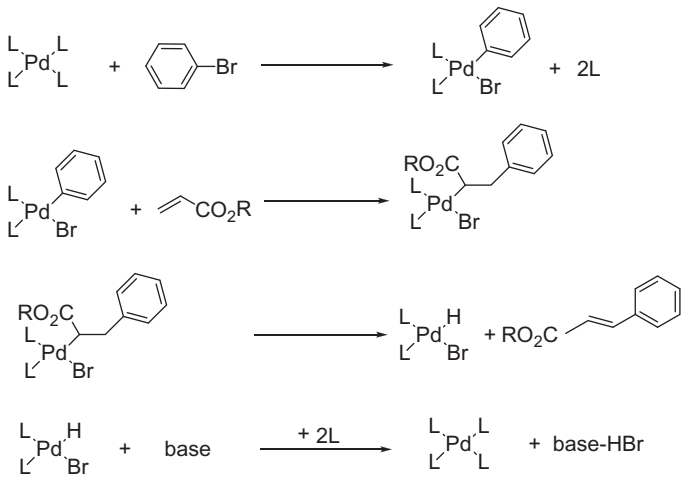


Fig. 8.4
Mechanism of Heck coupling [1].

The selectivity and reactivity of the substrate with the metal center is dependent on the ligand associated. Screening of phosphines, phosphites, and phosphorous amidites for different reactions gave varying results. Bulky groups tend to propagate faster catalysis. Kinetics of each ligand, each anion, concentrations, etc., play an important role in determining the rate, hence, no generalizations can be made regarding any catalyst system.

The application of this reaction is in, but not limited to, pharmaceutical and agrochemical industry. Products such as prosulfuron (herbicide), naproxen (antiinflammatory drug), eletriptan (asthma drug), and taxol (drug against cancer) have been synthesized with Heck type coupling [26]. Prosulfuron and naproxen discussed below can be used to highlight further aspects of this process.

8.2.3.1.1 Synthesis of prosulfuron

A sulfonyl urea herbicide, prosulfuron is manufactured industrially in large amounts every year (Fig. 8.5). Heck reaction is one of the primary steps involved in the synthesis of prosulfuron via reaction of 2-sulfonatobenzenediazonium on 3,3,3-trifluoropropene.

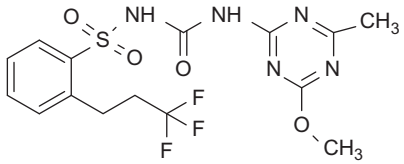
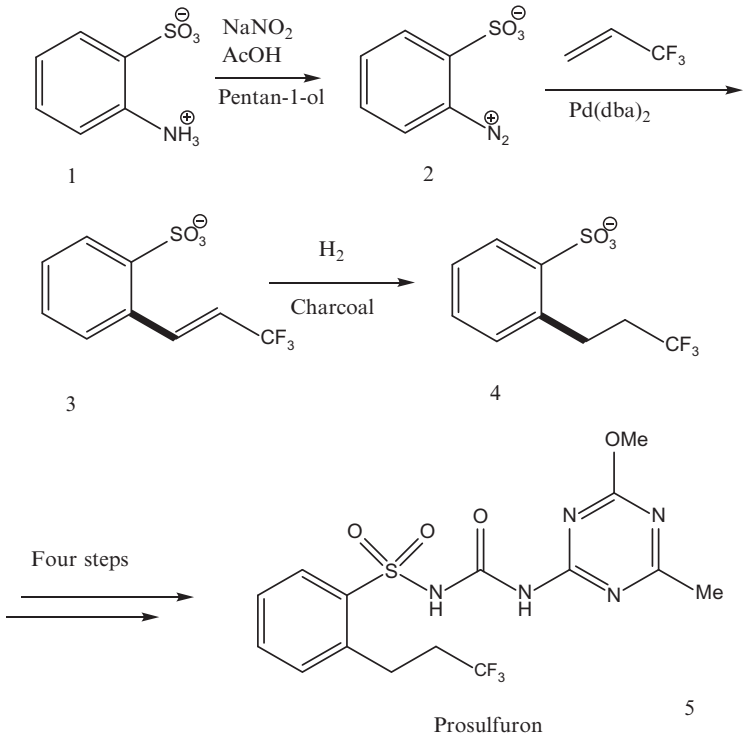


Fig. 8.5
Structure of prosulfuron.

It is a colorless, odorless crystalline compound. Although photolytically stable this compound is prone to rapid hydrolysis. It is a Class III toxic substance by both the EPA and WHO standards. It works by inhibiting the synthesis of branched amino acids such as valine, luecine, and isoleucine, thus stopping cell division and plant growth. It is a highly selective herbicide and after application it kills weeds in three weeks.

Starting with 2-aminobenzenesulfonic acid (1) and ending with sodium 2-(3,3,3-trifluoropropyl)-benzenesulfonate (4), a process involving diazotization followed by Heck-Matsuda coupling and hydrogenation was developed by Syngenta (formerly Ciba-Geigy). The coupling reaction was performed in the presence of a homogeneous palladium catalyst which was in situ converted to a heterogeneous catalyst for hydrogenation [31]. The catalyst used in the process could be completely separated from the reaction mixture by filtration and recycled after the hydrogenation step. This makes the process more efficient because the catalyst can be completely utilized (Scheme 8.13).

Palladium was selected as the catalyst of choice. $Pd(dba)_2$ (where dba = *trans*, *trans*-dibenzylidene acetone) was generated in situ from dibenzylideneacetone and palladium chloride in a stainless steel vessel at 60°C. Dibenzylideneacetone (molar ratio diazonium salt to dibenzylideneacetone 1:0.04) and sodium acetate (molar ratio diazonium salt to sodium acetate 1:0.1) were mixed in pentanol and a solution of $PdCl_2$ was added to it. After cooling the mixture was added to suspended diazonium salt. For the formation of (3), 3,3,3-trifluoropropene (molar ratio diazonium salt to 3,3,3-trifluoropropene 1:1.01) was introduced during 5 hours by stirring until no diazonium salt could be detected. Further hydrogenation was performed. The process gave a yield of 93% finally and an average yield of 98% in every step. The turnover number was low due to high palladium loading but the entire palladium could be recovered by filtration because of the addition of charcoal over the hydrogenation step [31].



Scheme 8.13
Synthesis of prosulfuron starting with 2-aminobenzenesulfonic acid [30].

In order to make the process cost effective, pentan-1-ol was selected as solvent because it was compatible for all three steps [30]. The use of alcohol was also found effective in reducing the diazonium salts [32]. It is imperative that the reaction temperature for coupling be kept below the decomposition temperature of the diazonium ion (ie, between −20°C and +40°C). The ideal temperature for hydrogenation is 200°C and 40 bar pressure.

8.2.3.1.2 Synthesis of naproxen

Naproxen is an antiinflammatory drug used for conditions such rheumatoid arthritis and postoperative pain (Fig. 8.6). The process is designed to selectively synthesize the (*S*) (+)-enantiomer because the (*R*)-isomer is a liver toxin. The world's largest producer of this drug is Albemarle.

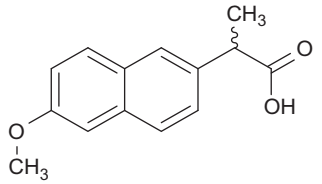
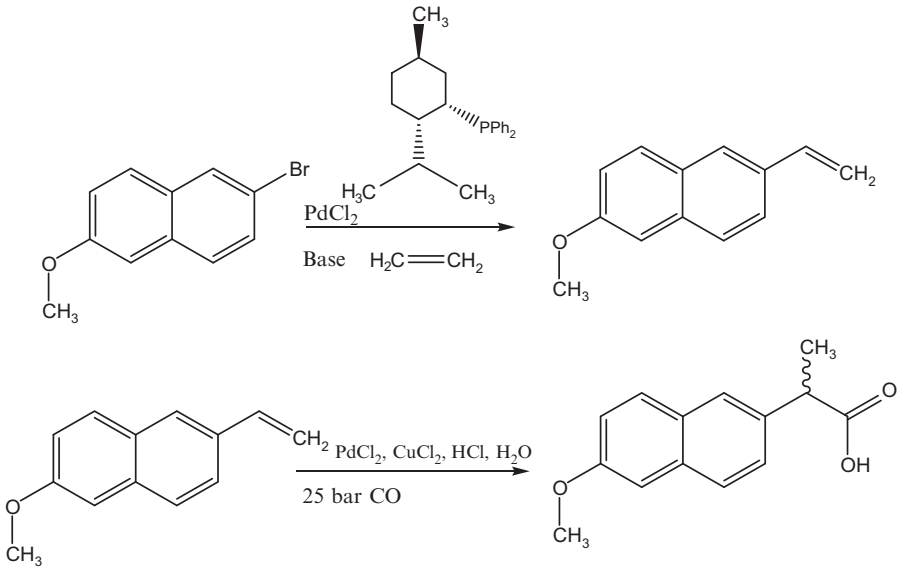


Fig. 8.6
Structure of naproxen.

It is a two-step synthesis—first, the Heck coupling reaction and second, a palladium catalyzed hydroxycarbonylation. Palladium chloride is used in the process as a metal source and the neomenthyl diphenyl phosphine (NMDP) ligand is used to reach a substrate to catalyst ratio of 2000–3000 (Scheme 8.14).



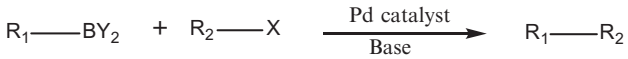
Scheme 8.14
Two-step synthesis of naproxen with palladium as a catalyst.

This is an established process which involves synthesis of 6-bromo-2-naphthol from 1,6-dibromo-2-naphthol by treatment with sulfur dioxide in presence of a base and then formation of a 6-bromo-2-methoxynaphthalene from 6-bromo-2-naphthol, before the former undergoes vinylation with ethylene. Palladium catalyzed vinylation was performed on 6-bromo-2-methoxynaphthalene before the final carboxylation step to obtain naproxen. $Pd(OAc)_2$ was used as the catalyst (0.049 mmol catalyst for 49.8 mmol 6-bromo-2-methoxynaphthalene) and was loaded along with the substrate and NMDP in a Hastelloy autoclave. Vinylation was performed using ethylene in methanol as a solvent. Vinylation progressed at a temperature range of 80–85°C with a pressure of 400–1000 psi from ethylene and the conversion took place in a duration of 5 hours [33]. Work-up of the process involved cooling the reaction mixture and subsequently releasing the ethylene pressure. The product mixture was filtered and the precipitate was washed with dichloro methane (DCM) (Scheme 8.14).

Heck coupling plays a major role in the fine chemicals synthesis, especially in the production of stereoselective drugs and agrochemicals. Rilpivirine for AIDS treatment, eletriptan, an antimigraine drug, and varenicline for aid in smoking cessation have been developed using Heck coupling reactions [34].

8.2.3.2 Suzuki-Miyaura coupling reaction

Suzuki coupling is defined as a process for formation of the C–C bond between an organic halide and organoboron compound. Principally, the organic halide acts as an electrophile and the organometallic compound acts as a nucleophile. The Suzuki-Miyaura reaction was reported in 1979 and has since become an important method for aryl-aryl bond formation. The advantages of the process are its mild reaction conditions, ease of availability of boronic acids, and the ability to synthesize highly functionalized molecules. The reaction may be sensitive to oxygen and degassing needs to be done prior to the reaction to avoid de-boronation. This reaction may proceed in water because the phenyl boronic acid is soluble in water. Suzuki coupling is employed in making rigid chain polymers with high thermal stability and maybe used in conducting polymers or high performance engineering materials [3]. It is catalyzed by palladium for large-scale synthesis of drugs and intermediates (Scheme 8.15).



Scheme 8.15
Suzuki coupling with palladium catalyst.

The reaction starts with Pd(0) catalyst, followed by formation of a substrate-ligand complex. After the formation of aryl-aryl bond, palladium catalyst is regenerated (Fig. 8.7).

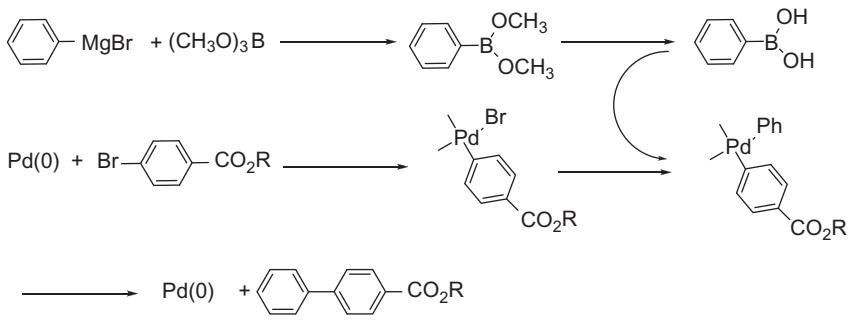


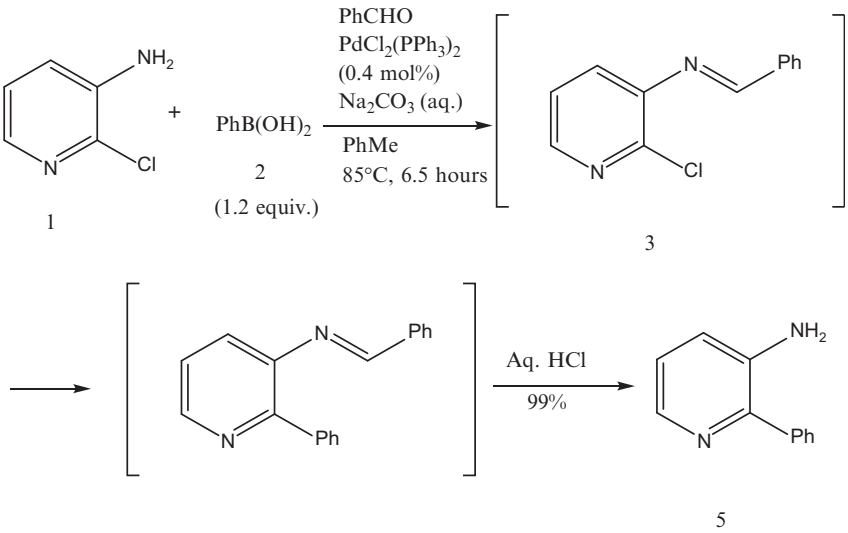
Fig. 8.7
Mechanism of Suzuki coupling [1].

Other catalysts used in the coupling reaction are based on nickel. Ni(0) has been employed successfully for coupling reactions of less reactive aryl chlorides. Ni catalysts have many advantages over Pd such as more reactivity and economic viability. They have been found to be complementary in their effect to the Pd analogs. The robustness to reaction conditions and ease of separation from the product also make Ni an attractive choice for catalysis in Suzuki reactions, however it also has some disadvantages. Ni has been found to be particularly effective for aryl chlorides with no side products getting generated. Ni(0) complex, $Ni(PPh_3)_4$,

is difficult to handle as it is air sensitive and highly toxic and needs to be prepared in situ from $NiCl_2$(dppf) or $NiCl_2(PPh_3)_2$. Therefore, as is the case with Heck coupling, bulky phosphorus ligands with a large variety of structures, especially bulky phosphites, lead to extremely high turnover numbers as has been illustrated from the examples from pharmaceuticals.

8.2.3.2.1 Synthesis of 3-amino-2-phenylpyridine [35]

3-Amino-2-phenylpyridine (5) is an important pharmacophore present in potent, nonpeptidic NK1 receptor antagonists, and was developed at Pfizer (Scheme 8.16).

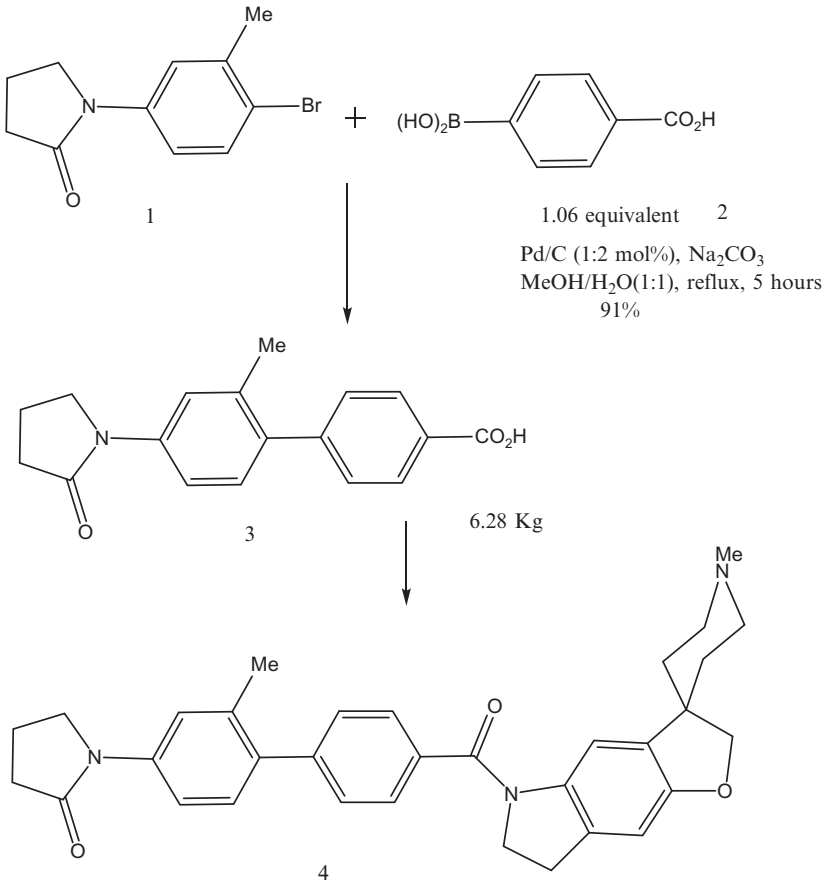


Scheme 8.16
3-Amino-2-phenylpyridine by Suzuki coupling [29].

The Suzuki coupling was performed to introduce a phenyl group. The amine group needed to be protected as an imine before the coupling. This was done by heating the substrate with benzaldehyde to reflux in toluene. Here, a one-pot synthesis was followed and amine, benzaldehyde, and phenylboronic acid (2) were premixed in toluene at room temperature for 10 minutes, followed by treatment with $PdCl_2$-$(PPh_3)_2$ and aqueous Na_2CO_3. The catalyst was suitable for the given reaction conditions and the coupling was performed at 85°C for 6.5 hours. The formed imine was converted to amine by treatment with HCl. The desired product from coupling was obtained in a quantitative yield as oil that crystallized upon standing.

8.2.3.2.2 Pharma intermediate for treatment of depression

Another application of the Suzuki reaction is preparation of multikilogram scale pharma intermediate (4) given in Scheme 8.17.

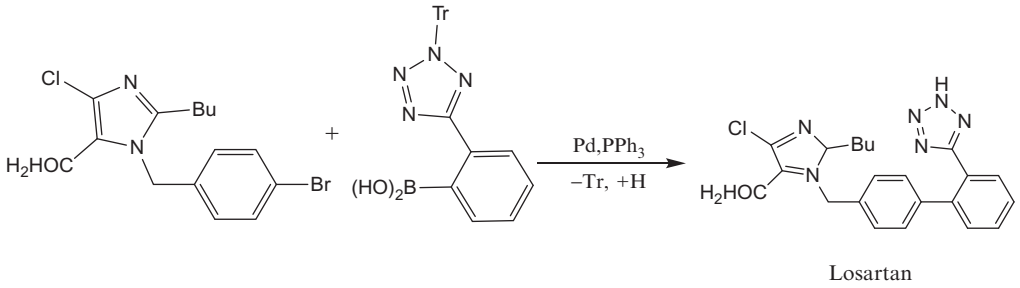


Scheme 8.17
Pharma intermediate [29].

It has been developed by SmithKline Beecham Pharmaceuticals and is used in the treatment of depression. Earlier it was prepared via the coupling of aryl bromide (1) and boronic acid (2) using typical conditions with $Pd(PPh_3)_4$ as catalyst. The disadvantages of the process were the unfavorable economics of catalyst, sensitivity to air, and difficulty in catalyst-product separation [36]. A heterogeneous catalyst (Pd on charcoal) was chosen for countering the above problems.

8.2.3.2.3 Synthesis of sartan type drugs

Suzuki coupling is used in the synthesis of the "sartan" type of drugs, which have been known to be used for blood pressure regulation. The reaction was carried out in THF in the presence of water and potassium carbonate as the base. Here, the bulky trityl group was used as a protecting group and could be removed after the reaction using an acid. A proposed mechanism for the purpose was the reaction of arylboronic acid with hydroxide ions to give $ArB(OH)_3$, which is more reactive toward electrophilic attack compared to the aryl boronic acid itself (Scheme 8.18).



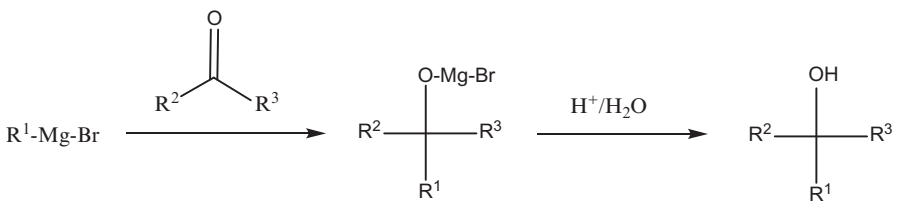
Losartan

Scheme 8.18
Synthesis of losartan [37].

Suzuki reaction plays a vital role in pharmaceutical and agrochemical industry such as in the synthesis of antifungal agent called anidulafungin, a drug called febuxostat for treatment of gout and hyperuricemia, and in the synthesis of garenoxacin, a quinoline antibiotic [34].

8.2.3.3 Grignard coupling reaction

Grignard reagents or organomagnesium reagents are used in the Kumada-Corriu reaction which is commonly catalyzed by Ni or Pd-based catalysts. They have a limited scope in fine chemicals and pharmaceutical industry and are used only in large-scale synthesis of simple substrates because of high reactivity of the reagent. Iron, cobalt, and manganese have been found to be effective catalysts for this synthesis too. The addition of an alkyl, aryl, or vinyl magnesium halide with an aldehydes or a ketone group leads to formation of C–C bond and is called Grignard reaction. Grignard reagents can be conveniently obtained from the halides of RBr or RCl with Mg and Li metals. They are synthesized by reaction of alkyl, aryl, or vinyl halide with magnesium metal in an ethereal solvent. Such carbon centered anions (RMgBr or RLiCl) may react with polar compounds such as esters, ketones, and metal chlorides which are specific and give high yield. However, these Grignard reagents tend to not react with alkyl or aryl halide (except allyl or benzylic halides), which works in favor of preventing homo-coupling between the alkyl or aryl halides. The rate and selectivity of the process was fairly low before the introduction of transition metals as catalysts (Scheme 8.19).



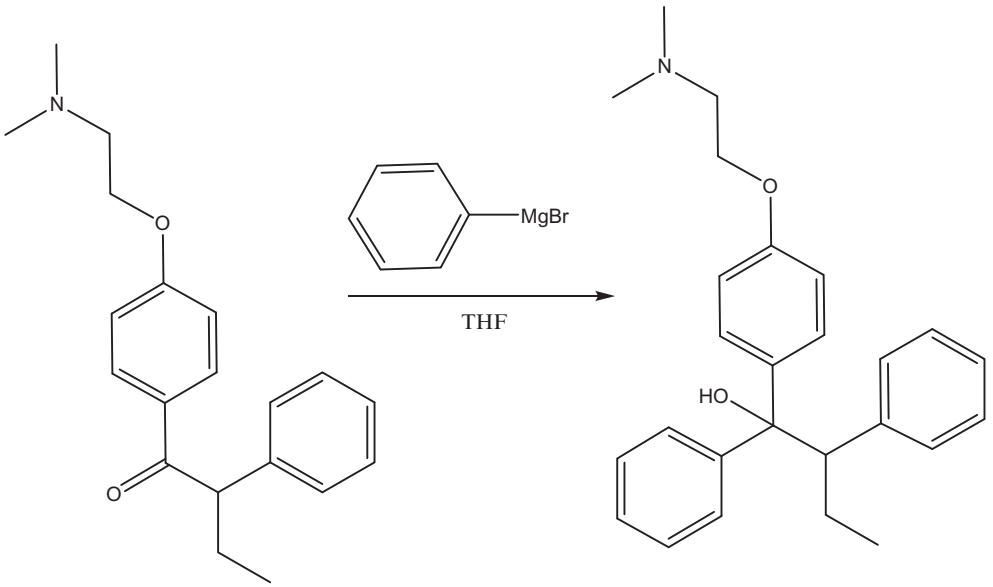
Scheme 8.19
Model Grignard coupling reaction.

A limitation of the reaction is the inability of the reagent to tolerate any water in the reaction mixture. This can be avoided by carrying out the reaction in organic solvents such as tetrahydrofuran or diethyl ether.

The examples discussed in this section—tamoxifen and adapalene, find applications in pharmaceuticals. Similarly, other organic synthesis through Grignard coupling also find application in fine chemicals, which include C–C bond formation.

8.2.3.3.1 Synthesis of tamoxifen

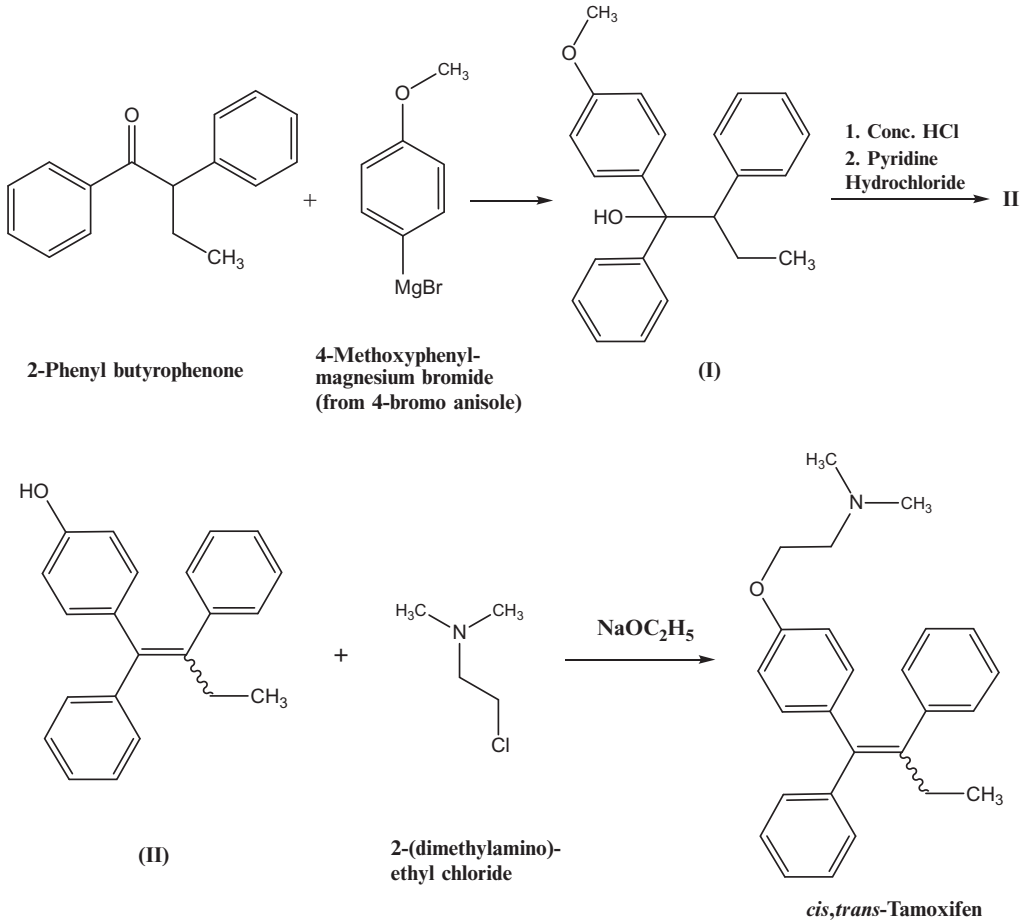
An example of the Grignard reaction is a key step in the (nonstereospecific) industrial production of tamoxifen [38] which is used as a drug in the treatment of breast cancer (Scheme 8.20).



Scheme 8.20
Structure of tamoxifen.

Tamoxifen acts as an antiestrogen in breast tissue, thus blocking the activity of endogenous estrogen. Although there are some known side effects such as hot flashes in the users of this drug and the body eventually becoming resistant to the effectiveness of the drug, it has been used for the treatment for some time now [39].

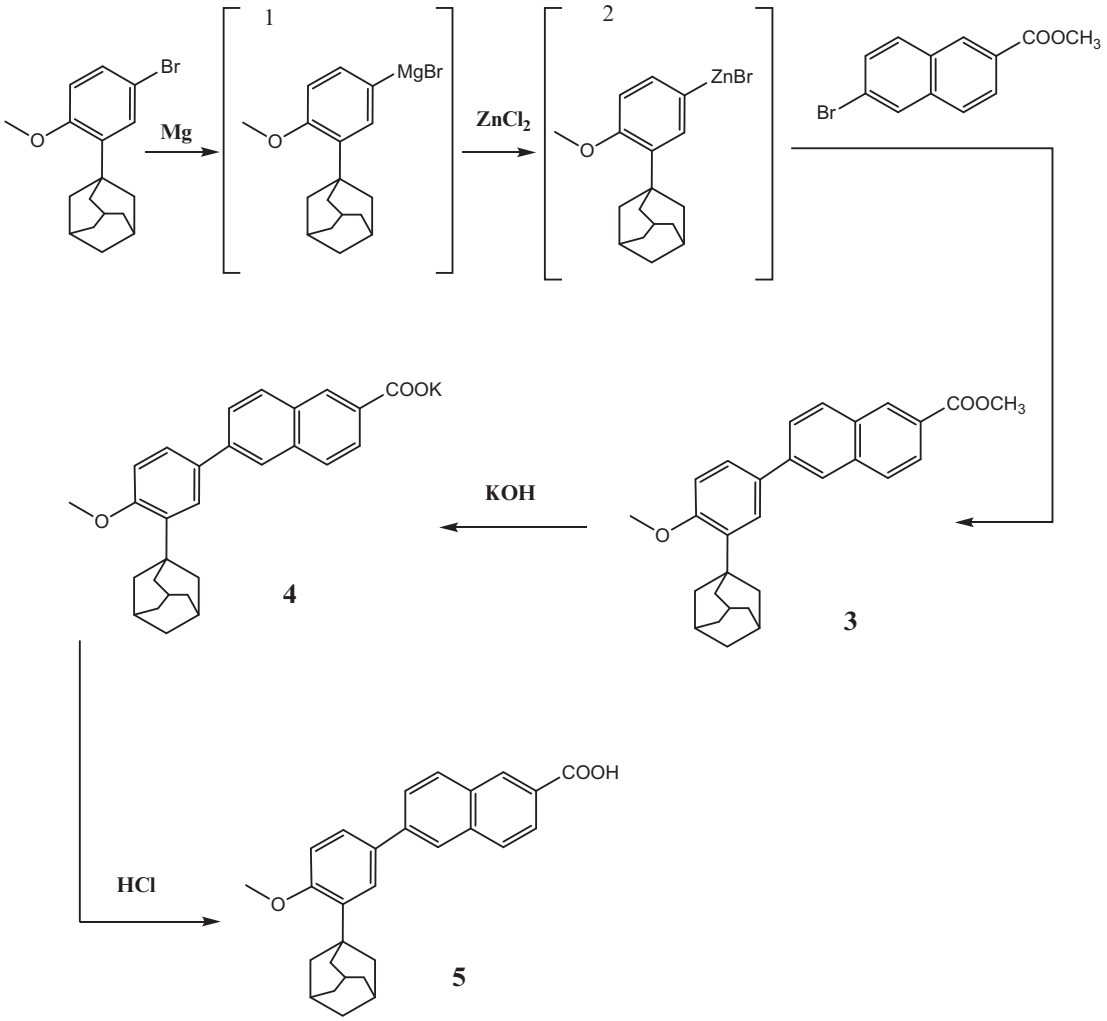
The first step of the reaction proceeds through Grignard coupling, and 2-phenyl butyrophenone reacts with a Grignard reagent to produce a tertiary alcohol. Further reaction involves addition of acid followed by the addition of 2-(dimethylamino) ethyl chloride, then treating with a base to produce *cis*, *trans* isomers of tamoxifen (Scheme 8.21).



Scheme 8.21
Tamoxifen synthesis by Grignard coupling [40].

8.2.3.3.2 Synthesis of adapalene

Adapalene is a synthetic retinoid for treatment of dermatological disorders such as acne, psoriasis, and photo-aging. It is synthesized by a $ZnCl_2$-mediated coupling of Grignard reagent and aryl bromide. A gradual process is carried out to convert aryl magnesium bromide compounds to aryl zinc halide. Grignard reagent is added slowly to a mixture of $ZnCl_2$ (5 mol%), $PdCl_2(PPh_3)_2$ (2 mol%), and aryl bromide. The conversion of organomagnesium compound to organo zinc halide was initiated at 20–25°C, but the temperature rapidly rises and the stirring is allowed to continue for one more hour [41]. The yield of the product is found to be 86% and the work-up involves washing the product with EDTA disodium salt to reduce the residual concentration of Zn/Mg [42] (Scheme 8.22).



Scheme 8.22
Synthesis of adapalene [41].

The cross-coupling chemistry was initially centered on carbon to carbon bond formation, but has recently made progress in the synthesis of carbon to heteroatom bonds. This section elucidates that the ligand and transition metals are the key elements in these procedures and effect the rate and selectivity for a formation of the desirable substrate.

8.2.4 Asymmetric Catalysis

Asymmetric catalysis is a method to accelerate the organic synthesis while controlling the stereoselectivity of the product yielding the required chiral compounds. Since chirality is vital in bioactive molecules, demand for chiral compounds is growing rapidly, particularly in the pharmaceutical industry and in agrochemicals, the food and fragrance industry. Traditional

methods of forming enantiomerically enriched compounds included either purification of naturally occurring chiral compounds or by resolving racemic mixture of enantiomers. However, problems of excess amounts of precursors and low yields pushed the growth of catalysis in asymmetric synthesis. The use of rhodium complexes with chiral phosphine ligands for catalyzing the enantioselective addition of H_2 to one of the faces of a prochiral olefinic substrate to generate a chiral C–H center with high enantioselectivity was performed in 1970s by William Knowles and his colleagues at Monsanto. This was considered a major breakthrough in asymmetric catalysis [43]. L-DOPA was a result of the commercialization of this process. Knowles even shared the Nobel Prize in 2001 with Noyori and Sharpless for their contribution to asymmetric catalytic hydrogenation and oxidation, respectively.
The importance of asymmetric catalytic processes lies in providing an atom efficient and cleaner route for synthesis of desirable enantiomers in the least number of steps.

An important concept to discuss here is enantiomeric excess (ee). It is the measure of purity for chiral compounds. It indicates the excess of one enantiomer to the other in a sample. A racemic mixture will have an ee of 0% while a pure enantiomer will have an ee of 100%. While molecules with chiral centers rotate plane polarized light by a certain angle (specific rotation), the enantiomeric molecules rotate the plane in the opposite direction with equal magnitude, thus the optical purity or ee of a substance can be measured [44]. This specific rotation is a physical property which is fixed for a molecule.

The optical purity of a mixture of enantiomers is given by:

$$\%\,\text{optical purity of sample} = \frac{100 * (\text{specific rotation of sample})}{(\text{specific rotation of a pure enantiomer})}$$

Fig. 8.8 represents the mechanism by which an enantioselective catalyst operates. The metal atom allows both substrates to form coordinate bonds with it and then at the required proximity,

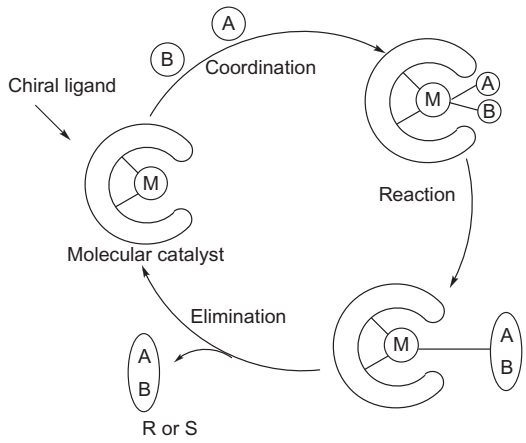


Fig. 8.8
Mechanism of asymmetric catalysis [45].

the substrates react to form a product followed by breaking of the coordinate bond and regeneration of the catalyst.

In the selection of the catalyst, it is important to choose a chiral metal center and coordinating ligand should be close to the metal center to impart the chirality to the reactant and ensure a higher selectivity. Among the different metal centers possible, it is preferable to have a tetrahedral or octahedral geometry rather than a square planar because it is difficult to impart chirality to such geometry. But designing this catalytic system is not easy since many of the metals used in organometallic chemistry form a very labile complex or do not support the ligands necessary for providing high selectivity during the synthesis. For example, Cr and Co can be used in complexes with CO ligand in high oxidation states such as +6. But CO ligand in this complex is very labile and quickly gets separated during catalysis and the chirality is not regenerated. Similarly, Ni is a tetrahedral metal center and forms a chiral complex with four different ligands, but the complex does not stay inert in reaction. Pd complexes have been explored for homogeneous catalysis but they do not prove to be very efficient because they do not follow the 18 electron rule and breakdown into smaller complexes with +3 or +2 oxidation states. Thus the selection of the ligand and metal is a complicated process. This underscores the achievement of Noyori, Sharpless, and Knowles in asymmetric catalysis.

Asymmetric synthesis is difficult to achieve because the enantiomers have identical enthalpies and entropies which implies that unless directed externally, there will be a formation of a racemic mixture. Here asymmetric induction plays an important role [46]. In asymmetric induction, a chiral feature, maybe the substrate, catalyst or environmental factor, is introduced to the reaction to promote the desired product over the other enantiomer through interactions at the transition state. This reduces the activation energy needed for the desired enantiomer. These interactions are represented in Fig. 8.9. The two diastereoisomers are of different transition energies hence, the one

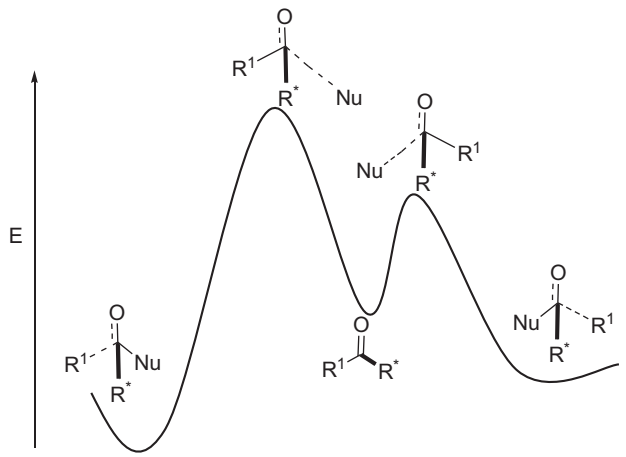
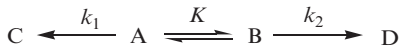


Fig. 8.9
Asymmetric synthesis based on difference in transition states.

with the lower energy is formed in a larger amount. This process can be intramolecular when a chiral starting material is used and a specific enantiomer of a specific diastereoisomer is needed. Thus, the chiral metal catalyst plays an important role in the accurate discrimination among enantiotropic groups in achiral molecules, and it can accelerate the formation of desired stereoselective molecule. It is also possible to design a chiral metal catalyst which can differentiate between diastereomeric transition states with accuracy of 10 kJ/mol.

To explain the asymmetric induction further, aldol reaction can be considered. Here, this asymmetric induction occurs intra-molecularly because of the chiral nature of substrate. Since the aldol reaction is already diastereoselective, an enantiopure aldehyde will generate a diastereomerically and enantiomerically pure product.

In asymmetric catalysis, a rule that applies to such systems where different substrates in equilibrium with each may lead to formation of different products, is called the Curtin-Hammett principle (eg, Scheme 8.23).



Scheme 8.23
Substrates in equilibrium in asymmetric synthesis.

This reaction equation implies that A and B, which are interconverting at a rate K can form two products C or D which is an irreversible step. However, depending on k_1 and k_2, the yield of C and D will vary [47]. If K is higher than both k_1 and k_2 then C:D will not be the same as A:B and will be determined by the relative energy in the transition states for each of these products. It has been assumed that the reactant A and B are at the same energy levels but actually they have some difference in energy level. For Curtin-Hammett principle to be used, this difference should be low. Thus the product quantity would depend not only on k_1 and k_2, and the difference of energy level for C and D, but also on the difference in A and B. This phenomena has been represented in Fig. 8.10.

Thus, highly selective catalysts are vital to improve ee of the desired compound in a process, particularly from the point of view of generating therapeutics with complex structures and specific applications. It is of utmost importance to use asymmetric metal complexes as catalysts for various applications [48]. However, unless the process is viable, reliable, and economical, it cannot be used commercially.

In asymmetric synthesis, coordination complexes are used as catalysts. The chirality of the complex is derived from the chirality of the ligand. Here, ligand permutation is related to flexibility in the generation of the enantiomer. The biggest advantage of this catalytic system is the effectiveness even at low concentrations, which also renders the system suitable to industrial scale processes. One complex that has been found to be effective is a metallocene based structure. It is a pseudotetrahedral complex also referred to as the “piano stool” complex

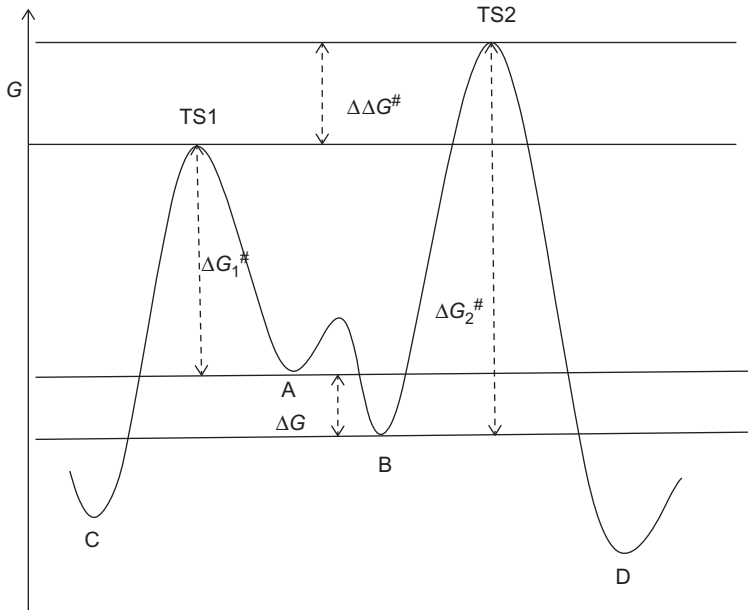


Fig. 8.10
G is the Gibbs free energy for each moiety in the reaction.

where the metal has three ligands bonded to it and one metallocene or arene group such as phosphine. Phosphine ligands have a similar structure and have been used in asymmetric hydrogenation, which is one of the most widely researched catalytic processes and can give highly selective enantiomers. A range of chiral, bidentate, and phosphine ligands with C_2 symmetry have been developed. Some examples of these ligands are shown in Fig. 8.11.

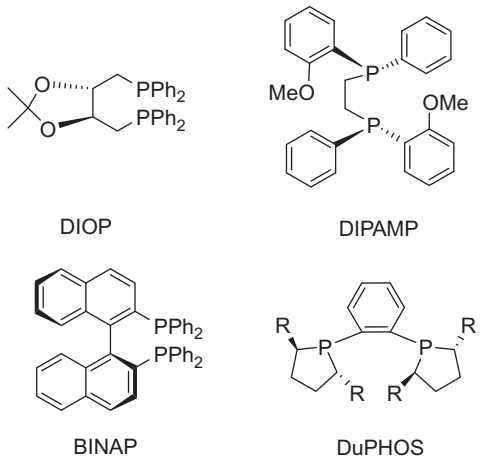
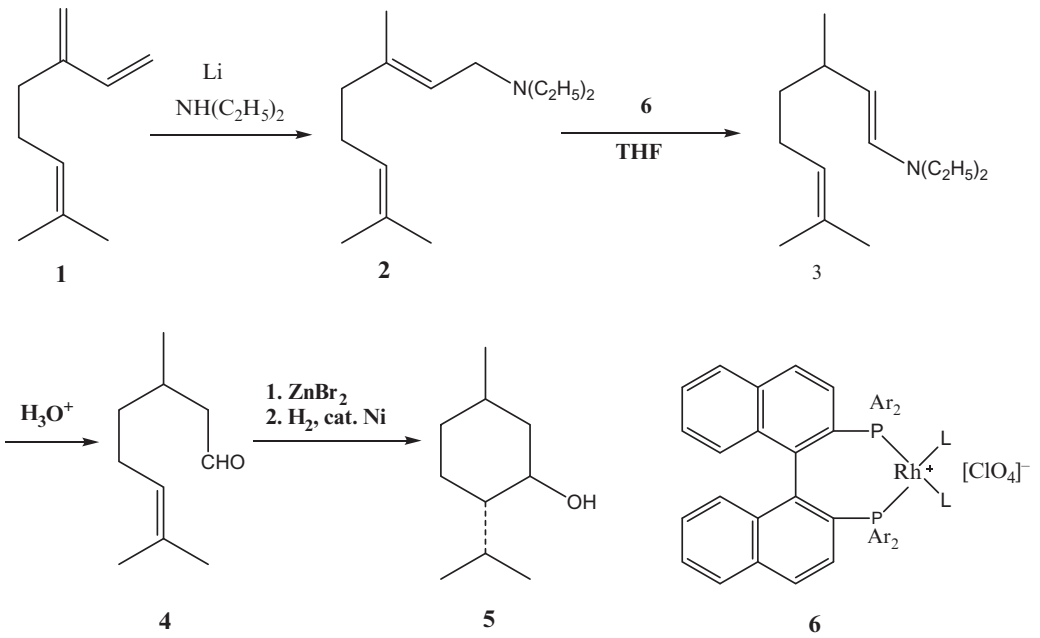


Fig. 8.11
Chiral bidentate catalysts for asymmetric synthesis [49].

For the isomerization of allylic amines to optically active enamines, catalytic Rh(I) complexes with a BINAP or (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) ligand has been found effective. Synthesis of (−)-menthol (5) from myrcene (1) is an example of an industrial application of asymmetric catalysis. (*S*)-BINAP-Rh^+ (6) is used as the catalyst and the reaction proceeds through isomerization of geranyldiethylamine (2) to (*R*)-citronellal (*E*)-enamine (3). The citronella (4) has an optical purity of 96–99%. This process is used at Takasago International Corporation, Japan with the approximate turnover number of 8000 mol/mol Rh catalyst. The Rh catalyst can be recycled to result in an overall efficiency of chiral multiplication of 400,000 mol product/mol Rh catalyst [50] (Scheme 8.24).



Scheme 8.24
Industrial application of asymmetric catalysis for (−)-menthol [3].

Before the Nobel Prize-winning discovery of the role of organometallic catalysts in asymmetric synthesis, versatile catalysts such as dioxirane and proline were used. Dioxirane was particularly useful for asymmetric epoxidation before the use of tartrate based catalysts was discovered. Fig. 8.12 shows the generation of the catalyst dioxirane from potassium peroxymonosulfate and a ketone. This could be applied to epoxidation of olefins without any functional groups. The ketone is regenerated after epoxidation. The chirality of the ketone determines the asymmetry of the epoxide formed [52].

Proline based catalysts were found to be useful for aldol condensation in the 1970s. Fig. 8.13 represents the mechanism for this condensation leading to synthesis of a progesterone

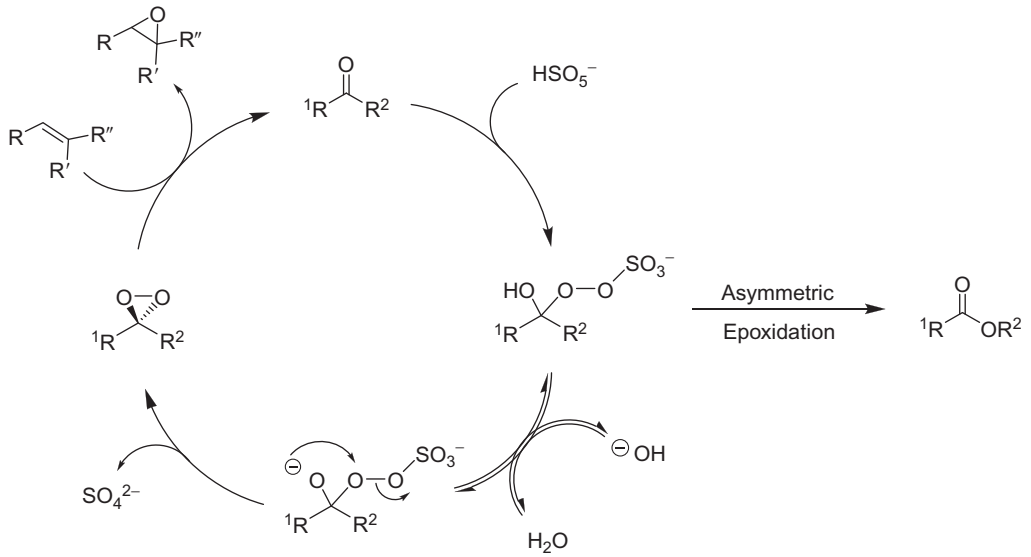
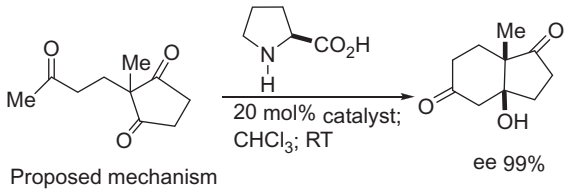


Fig. 8.12
Mechanism of epoxidation and generation of dioxirane.



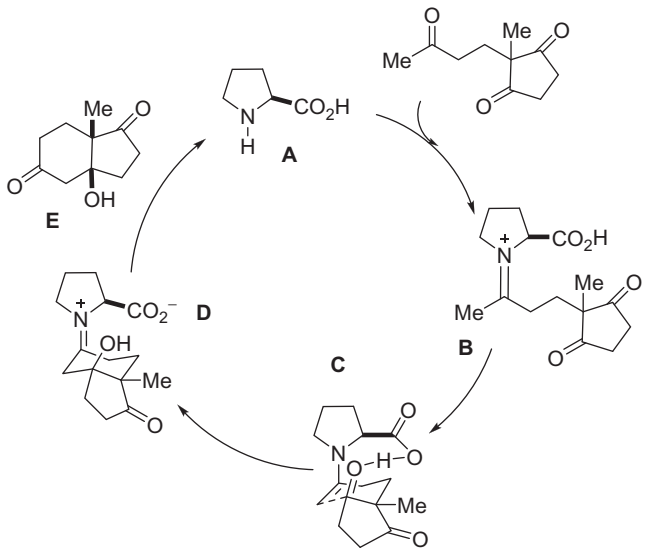
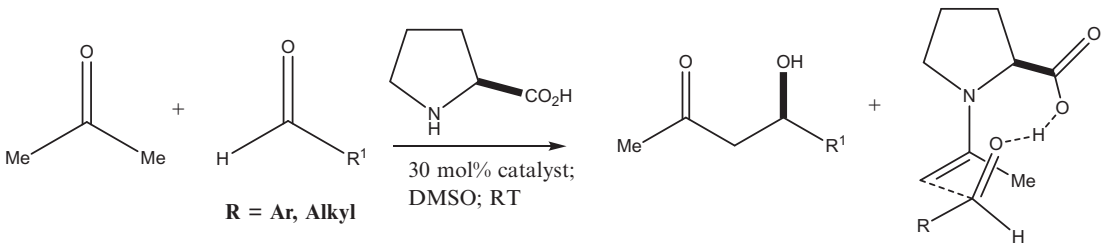


Fig. 8.13
Mechanism of proline catalyzed asymmetric synthesis of a progesterone intermediate [48].

intermediate. An asymmetric enolate cannot be generated selectively, but the significance of this discovery was understood only once the intermolecular reaction with this secondary amine was elucidated in 2000 [53]. Since then proline and other related catalysts have become significant in such asymmetric reactions [48]. The first step in the catalytic reaction is formation of carbinolamine followed by iminium structure (B). The next step is the formation of an enamine through an oxazolidinone, then a C–C bond formation by nucleophilic addition of enamine to carbonyl group (C). Finally, the product (E) is separated through the hydrolysis of iminium (D) group and the catalyst (A) is regenerated. The differentiation in stereomer occurs during the step C [54] (Scheme 8.25).



Scheme 8.25
Intermolecular aldol condensation using proline based catalyst system [48].

Similar to the examples discussed above, there are many specific catalysts designed for asymmetric catalysis. In any asymmetric catalysis, the chiral efficiency ultimately relies on the chirality of the catalyst and the overall reaction conditions. A high turn over number (TON) and turn over frequency (TOF) is required to make the synthesis viable and economically feasible. The enantioselectivity should be at least more than 50% to justify the application of a particular catalyst and the metal center must have a nonplanar geometry to allow variation in chirality through variation in bonded ligands [45]. Common reactions where asymmetric catalysis has been used are epoxidation of olefins, hydrogenation, isomerization, condensation, etc. A few examples have been discussed below to exemplify the nature and role of asymmetric catalysis in the fine and specialty chemical industry.

8.2.4.1 Asymmetric hydrogenation for synthesis of L-DOPA and metolachlor

Rhodium has been a popular choice for homogeneous asymmetric hydrogenation and the substrates generally involve a coordinating group close to the olefin. Chemicals have been produced on an industrial scale with these catalysts. However, with the use of iridium as catalyst, the scope of target compounds was expanded [55] and they can be easily prepared and handled. They do not require a polar coordinating group near the C=C bond. For arylolefins, high enantioselectivities and ee as high as 95% with turnover numbers of 5000 have been achieved [56]. There is a scope of improving the catalyst stability because iridium

catalysts have a tendency to trimerize. Iron has been found to bring about asymmetric hydrogenation but the overall rate and selectivity is lower than that with precious metals [57]. Phosphine ligands with a C_2 symmetry have been used because they result in the best enantioselectivity.

Asymmetric hydrogenation is used in the fine chemical industry for agrochemicals and pharmaceuticals. This can be illustrated by considering two vital chemicals—L-DOPA and metolachlor. The synthesis of both these fine chemicals involves a step of asymmetric hydrogenation.

8.2.4.1.1 Synthesis of L-DOPA

L-DOPA is a drug developed for the treatment of Parkinson's disease (Fig. 8.14). It is produced in large quantities on an industrial scale and the process chemistry is already well established. Hydrogenation of cinnamic acid derivative was developed by Knowels at Monsanto. Here, rhodium complexes as catalysts are applied for hydrogenation of α-dehydroamino acid derivatives with asymmetric diphosphine as the ligand, which induces the enantioselectivity. On application of bis(diphenylphosphino) derivatives as ligands, only minor variations are observed [1].

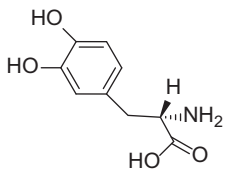
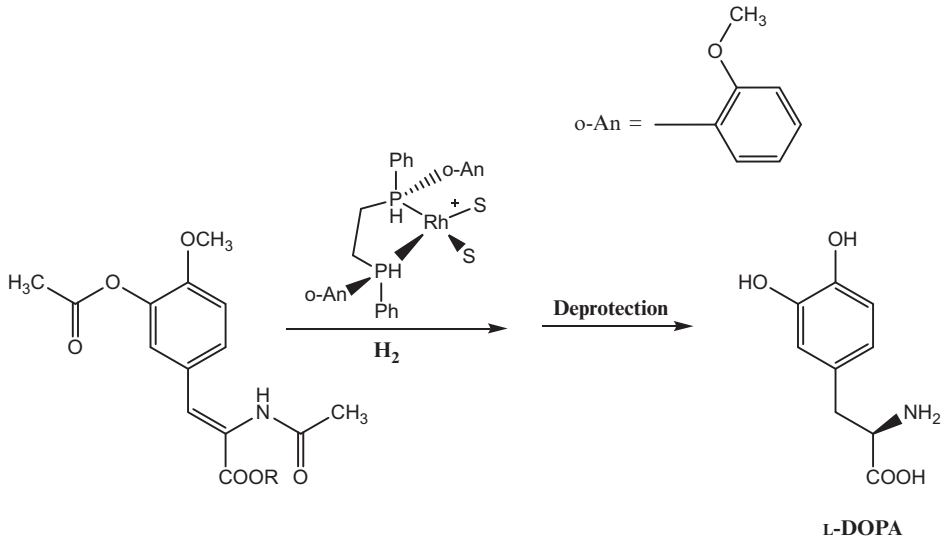


Fig. 8.14
Structure of L-DOPA.

Scheme 8.26 explains the reaction scheme for synthesis of L-DOPA [58]. The first step in this synthesis is an Erlenmeyer azlactone synthesis in which 3-alkoxy-4-hydroxybenzaldehyde is condensed with acetylglycine in the presence of sodium acetate. 2-Methyl-4-(3′-alkoxy-4′-acetoxybenzal)-5-oxazolone is obtained as product from this step and is subjected to mild hydrolysis to obtain α-acetamido-4-hydroxy-3-alkoxy-cinnamic acid acetate. This hydrolysis ensures the ease of formation of the L-enantiomorph as a major product in the subsequent process. The above mentioned cinnamic acid derivative then undergoes asymmetric hydrogenation to form *N*-acetyl-3-(4-hydroxy-3-alkoxy phenyl)-alanine acetate which is present in two enantiomorphs with an 86/14 L/D mixture and 72% optical purity. L-enantiomorph can be crystallized and separated from the reaction mass. The recovered L-enantiomorph is then subjected to hydrolysis to remove the acetyl and alkyl group resulting in L-DOPA.



Scheme 8.26
Two-step synthesis of L-DOPA [1, 2].

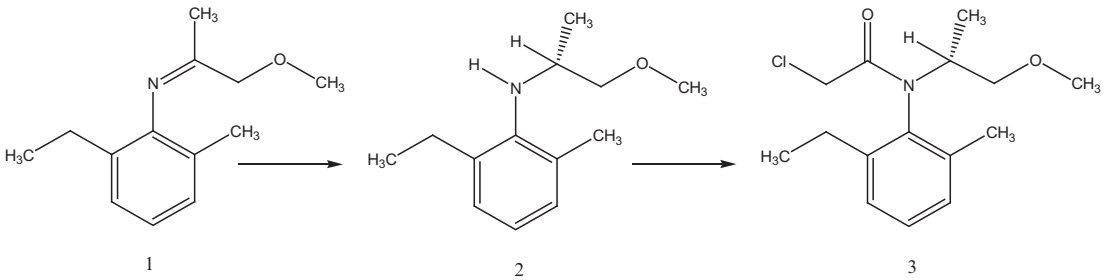
Apart from L-DOPA, naproxen, ibuprofen, ketoprofen, and flurbiprofen are also drugs of interest which involve asymmetric hydrogenation [1].

8.2.4.1.2 Synthesis of metolachlor

Amines have been found to play a significant role in the pharmaceutical and agrochemical industries and are responsible for development of a number of new asymmetric catalytic processes. However, there have been fewer efficient catalytic systems developed for imines. Asymmetric catalytic hydrogenation of imines has been found to have application in the synthesis of the herbicide metolachlor [59]. It is an N-chloroacetylated, N-alkoxyalkylated ortho-disubstituted aniline. Metolachlor has four possible stereoisomers and was earlier marketed as a mixture of all the products. It was eventually established in 1982 that the herbicidal activity of metolachlor is from the 1-(*S*)-diastereomers. A new process had to be developed to synthesize enantiomerically enriched precursor of metolachlor [60].

A catalyst system was developed for the industrial scale hydrogenation of imines—the homogeneous iridium-xylophos system. This process can be specifically used for synthesis of herbicides such as metolachlor or (*S*)-2-chloro *N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl) acetamido [61]. Scheme 8.27 depicts hydrogenation proceeded by contacting compound (1) with imine under hydrogen pressure of 80 bar at 50°C, leading to formation of (2). On reaction of chloroacetyl chloride and (2) in a nonpolar solvent such as toluene, (3) was obtained. This step was carried out at 0–5°C. At catalyst to substrate ratio of as high as 500,000, the resulting amine was found to have a conversion of 99% and ee of 76%. The process does not involve generation of any corrosive acids hence, there is no need

to use specialized equipment, as opposed to the conventional art in which an additive was required in the presence of acetic acid to bring about similar conversion. The xylophos ligand has been found to be highly effective in hydrogenation of imines. (3) is marketed as (*S*)-metolachlor [62].



1 2 3

Scheme 8.27
Synthesis of metolachlor.

8.2.4.2 Epoxidation reaction

Epoxidation is one of the commercially important applications of enantioselective homogeneous catalysts. Epoxides are generally intermediates for further reactions and lead to formation of mixture of enantiomers, generally when alkenes are prochiral. Some important kinds of epoxidations mentioned are:

- The Katsuki-Sharpless epoxidation of allylic alcohols,
- The Jacobsen asymmetric epoxidation of alkenes,
- The Sharpless asymmetric hydroxylation of alkenes with osmium tetroxide, and
- The Jacobsen enantioselective ring-opening of symmetric epoxides (eg, cyclohexene oxide).

On stereospecific olefin epoxidation, two distinctive chiral centers are created simultaneously. This process was developed by Sharpless and coworkers [65].

The Sharpless epoxidation reaction is applied for the synthesis of 2,3-epoxyalcohols from primary and secondary allylic alcohols [63]. The chirality of the resulting product is decided by the nature of the chiral tartrate diester employed in the reaction and enantioselectivity is achieved by the titanium based catalyst system, generally formed from titanium tetra(isopropoxide) and diethyl tartrate [64]. *tert*-Butyl hydroperoxide is a well-known source of oxygen atoms and is a selective and relatively stable reagent which makes it easy to handle. By Sharpless epoxidation, epoxides can be easily converted to diols, aminoalcohols, or ethers

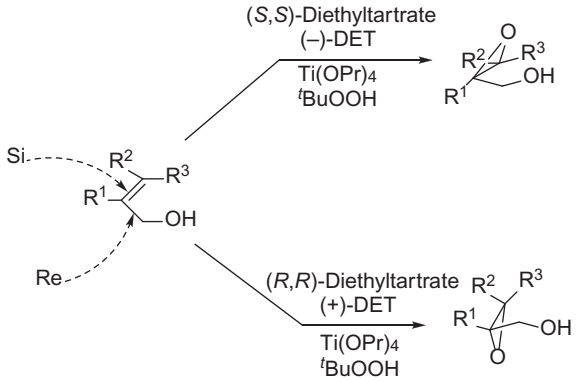
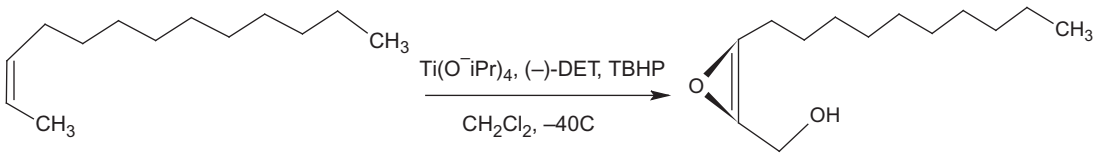


Fig. 8.15
Mechanism of Sharpless epoxidation.

(Fig. 8.15). The products have high enantiomeric purities and can be used for preparation of a large number of intermediates for fine chemicals such as for methymycin, erythromycin, leukotriene C1, and (+)-disparlure [66].

Amongst the many applications of asymmetric epoxidation in agrochemicals, one is in the synthesis of the intermediate for the pheromone for gypsy moth, (+)-disparlure which was a chiral epoxide and was commercially manufactured in 1981 (Scheme 8.28). It was synthesized to reduce the ever-increasing population of the gypsy moth. It works on the principle of mating disruption—the pheromone is sprayed at multiple points, hence the male of the species is distracted by the multiple "false" target points, thus reducing the actual mating. This has been found to be an effective method. It is specific to a particular species and thus does not harm the other creatures that might be vital to the cycle as natural predators or pollinators. It was first used in North Eastern United States and eventually spread to the rest of the continent.

Asymmetric epoxidation was performed using D-(−)-diethyl tartrate. The operating temperature was −20°C in a Teflon-lined reactor in an inert atmosphere of nitrogen. The yield



Scheme 8.28
Epoxidation for synthesis of (+)-disparlure [67].

was 80% and the enantiomeric purity was 90–95%. Water was found to deactivate the catalyst, hence the use of molecular sieves was proposed. The work-up was simplified because of crystallinity of enantiomer [67]. Epoxy alcohol was then oxidized to the aldehyde, followed by Wittig reaction. The double bond was then hydrogenated to obtain (+)-disparlure. There was an increase in the scale of production and reduction in the cost of the chemical, once asymmetric catalysis route was adopted.

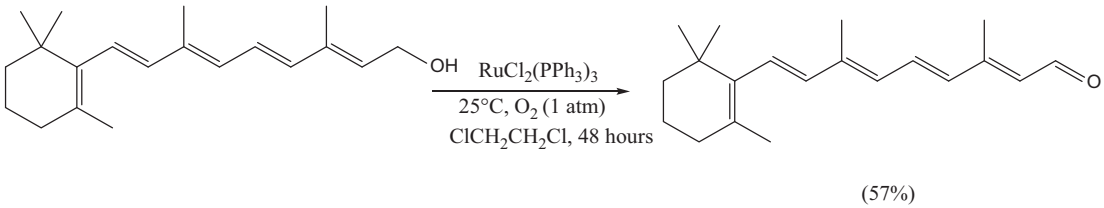
8.2.5 Oxidation Reaction

Both homogeneous and heterogeneous catalysts are used in oxidation catalysis. Platinum or iron are typical catalysts for this process. For the oxidation of organic compounds, homogeneous catalysts such as carboxylates of cobalt, iron, and manganese are used. The reaction proceeds through a radical chain reaction where the organic radicals produced combine with oxygen to give hydroperoxide intermediates. Generally, the selectivity is determined by bond energy such as when oxygen replaces benzylic C–H bonds much faster than aromatic C–H bonds [68].

Oxygen is the most abundant and cheapest source of oxygen atoms, especially when air can directly be used as an oxidant. Amongst commodity chemicals manufactured through oxidation ethylene oxide, styrene, adipic acid, phenol, and acetaldehyde are used in synthesis of certain specialty chemicals. Phenol is synthesized through oxidation of cumene to convert it into a hydroperoxide which is then decomposed into acetone and phenol. A common process for the use of homogeneous catalyst in oxidation is in the synthesis of terephthalic acid. It is a radical catalyzed oxidation with O_2 and cobalt salt initiators. The separation of the product can be easily done by filtration and the liquid containing the catalyst can be removed. The commercial value of terephthalic acid lies in the production of polyesters with aliphatic diols as a comonomer [1]. Although manufacturing of bulk chemicals through oxidation is well established, and newer and cleaner routes of production have been accepted, mostly homogeneous catalysts and stoichiometric amount of chemicals are used in oxidation for synthesis of fine chemicals. Thermal instability of fine chemicals also implies that they be produced in liquid phase and in moderate conditions of temperature and pressure. The reactor systems of choice are batch or semibatch processes, while continuous and fluidized bed reactors are used for bulk chemicals [69].

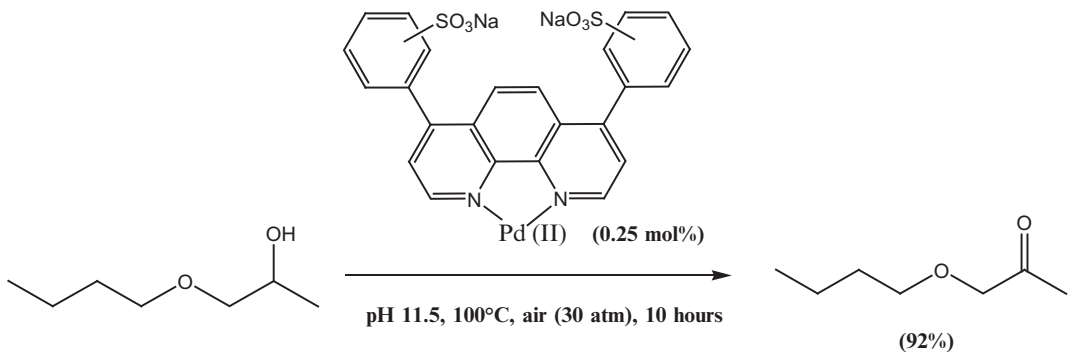
Metal catalyzed oxidations are of two kinds—those involving peroxometal and those with oxometal species as the active oxidizing agent. The oxidation state of the metal undergoes a two-electron change in the case of oxometal, unlike in peroxometal. A stoichiometric oxidation takes place in the oxidized state of the catalyst in the absence of hydrogen peroxide. Peroxometals include catalysts with a d(0) configuration such as Mo(VI), W(VI), Ti(IV), Re(VII) which are relatively weak, whereas oxometals include Cr(VI), Mn(V),

Os(VIII), Ru(VI) and Ru(VIII), that are strong oxidants in their highest oxidation states [70]. An example of such a conversion is oxidation of retinol under mild conditions with $RuCl_2(PPh_3)_3$ under mild conditions (Scheme 8.29).



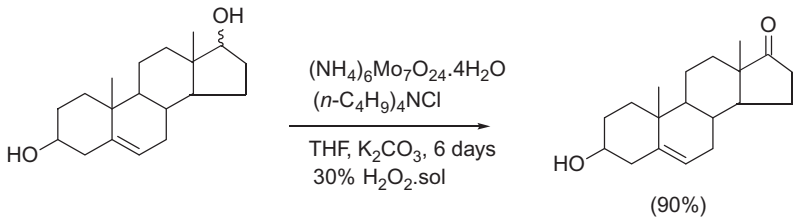
Scheme 8.29
Oxidation of retinol with ruthenium catalyst [70].

Trinuclear ruthenium carboxylates such as $Ru_3O(O_2CR)6Ln$ (LDH_2O, PPh_3) are effective for aerobic oxidation of lower aliphatic alcohols. For benzylic and allylic alcohols, another modified system that was suggested was the $RuCl(OAc)(PPh_3)_3$/hydroquinone/ $Co(salophen)(PPh_3)$ system. A common catalyst for oxidation of primary aliphatic, benzylic, and allylic alcohols to their corresponding aldehydes was $RuCl_2(PPh_3)_3$, hydroquinone and oxygen, in $PhCF_3$ as solvent. $Pd(OAc)_2$ in combination with $NaHCO_3$ as base and dimethyl sulfoxide (DMSO) as solvent have been reported as catalysts but the problem with palladium-based systems is that they have lower activity and high catalyst to substrate ratio. But Sheldon et al. reported the use of water-soluble palladium(II) bathophenanthroline for aerobic oxidation of alcohols. This catalyst system proved to be stable and recyclable (Scheme 8.30).



Scheme 8.30
Palladium(II) bathophenanthroline for aerobic oxidation of alcohols [71].

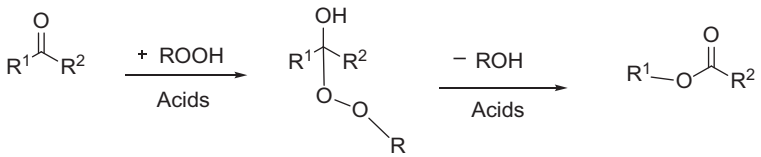
As peroxo complexes along with H_2O_2, molybdenum and tungsten are effective. Mo and W containing heteropolyanions are effective for alcohol oxidations. In fact, such systems allow for the oxidation of more hindered species selectively (Scheme 8.31).



Scheme 8.31
Oxidation of hindered species with Mo and W heteropolyanions as catalyst [71].

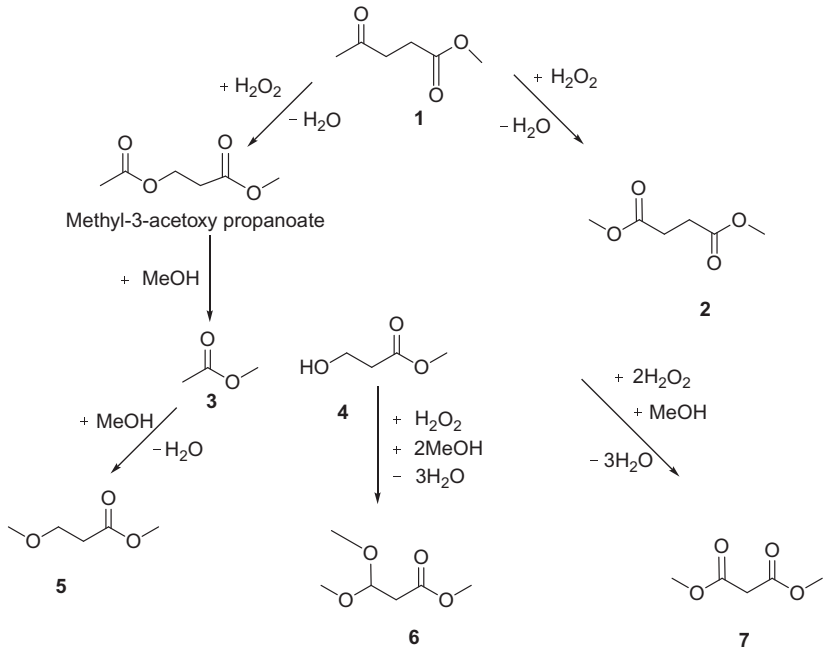
Thermo catalytic routes for oxidation can be an alternative to the biological route with more relaxed temperature and *p*H control, and it might even be less energy intensive. One such example is succinic acid which is an important building block chemical from biomass. The applications lie in synthesis of succinates by esterification with monoalcohols which are used in making plasticizers, lubricants, and chemical intermediates [72]. Levulinic acid (LA) is another important derivative from lignocellulosic sources. The derivatives from LA can also be used to synthesize succinic acid or its esters. Manganese, ruthenium, and vanadium are common catalysts for the purpose. Methyl levulinate can be converted to dimethyl succinate using Bronsted and Lewis acid catalysts under mild conditions.

The process takes place in two steps: (1) addition of peroxide to the C=O group leading to formation of a Criegee intermediate, and (2) migration of the alkyl group adjacent to the carbonyl to allow insertion of an oxygen atom into the C–C bond. The catalytic sites interact with the carbonyl group, the peroxide and/or the Criegee intermediate to facilitate the addition or the migration step and influence the final product distribution. Solvent polarity and the metal cation of the triflate salt in Lewis acid catalysts is a strongly influencing factor for the reaction (Scheme 8.32).



Scheme 8.32
Acid-catalyzed oxidation of ketone for formation of Criegee intermediate using peroxide [72].

Use of strong Brønsted acids ensured a selectivity of 60% for dimethyl succinate. To underscore the role of solvent polarity, it was reported that a shift from methanol to hexane led to a decrease in the selectivity from 60% to 14% (Scheme 8.33).



Scheme 8.33
Products obtained from acid-catalyzed oxidation of methyl levulinate with hydrogen peroxide in methanol [72].

This entire section gave an overview of the importance of homogeneous catalysts in fine and specialty chemical industry. Historically, these catalysts were developed for bulk chemical synthesis since the large scale of production could counter the expenditure of development, use, and recovery of these catalysts. Their share, specifically of organometallic compounds, grew because high selectivity towards desired products could be achieved and the environmentally benign characteristics made them safe and easy to use [1]. The formation of this coordination complex allows highly reactive moieties to be stabilized so that a controlled reaction can take place. The metal center increases probability of reaction between substrates by formation of coordination bond of the substrates on the same metal center. Ligands in these catalysts play the role of controlling the selectivity (chemoselectivity and stereoselectivity).

However, there are a few limiting factors to homogeneous catalysts [21] such as:

- Separation of products is a practical challenge because without recycling, the process becomes unviable for certain metal complex catalysts.
- Novel synthetic routes suffer from lower selectivity and yield.
- The synthesis of complexes can be a challenge due to lower thermal stability, making procedures like distillation for product separation redundant. Catalyst immobilization plays

an important role with regards to thermally unstable catalysts and in cases where product and reaction mixture remain homogeneous after the completion of reaction. However, this method can be employed only in cases where supported catalysts give the same activity as homogeneous catalysts and are economically manufactured.

- Catalytic activity is highly dependent on the reactor design and equipment selection. Hence a complete understanding of the reaction kinetics and role of catalyst is important in deriving maximum efficiency from the system.
- Homogeneous catalyst developed from academic research criteria are focused on selectivity rather than high activity and recyclability, which is a primary demand of a commercial process.
- Development of ligands for the specific catalyst on a large scale is a hindrance for the process and so is the compatibility of the catalyst with all steps in a multistep process [73].

Instability of organometallic catalysts, as mentioned above is a reason why these catalysts get deactivated. Ligands and the metal center, both have a role to play in the stability:

- The trend observed in the periodic table regarding stability of a particular organometallic compound indicates that in groups 1, 2, and 13–15, the stability decreases as one moves downwards towards the heavier elements. For example, methylpotassium is less stable compared to methyllithium. This is due to decreasing bond strength. However, such a trend is not true in d-block elements (groups 3–12) where the stability increases as one moves downwards.
- Lithium, sodium, and aluminum (groups 1, 2, 13) are more sensitive to air and water but metals from groups 14 and 15 do not react as violently. $Al_2(CH_3)_6$ is likely to undergo immediate reaction to liberate methane which burns to flames in the presence of air, but tetramethylsilicon would remain unaffected under the same conditions.
- The number or characteristics of a ligand bound to the metal center would affect the properties of the catalyst tremendously. Carbon-based complexes have a large variety of binding and catalyst structures which depend on the hybridization state of the bonding metal atom.

Despite the problems, homogeneous catalysts have proven to be useful in a myriad of reactions such as enantioselective synthesis, oxidation, carbonylation, and hydroformylation, among others. They have been effective in such catalysis because the metal center allows a variety of molecules with any functional group to form a coordinate with it. Novel catalysts need to be developed to counter the issues discussed above.

8.3 Heterogeneous Catalysts

The fundamentals of catalysis and reaction engineering have been presented in Part 1 of this book. The catalysis and catalytic processes has been discussed in Chapter 1, while the basic principles of homogeneous catalysis discussed in Chapter 2, heterogeneous catalysis in Chapter 3, and catalytic reaction engineering in Chapter 7. In this chapter, we have attempted to

cover the industrially relevant heterogeneous catalytic processes for synthesis of fine and specialty chemicals.

The design of a novel catalyst and development of new catalytic applications is a multidisciplinary activity and requires understanding about chemistry, chemical engineering, and material science. Thus, the design, development, and preparation of a new catalytic process require detailed knowledge of catalyst properties, materials, and the science of catalyst preparation. Most of the heterogeneous catalysts consist of an active material (metal crystallite), a promoter, and a carrier or support. The surfaces of these metal crystallites contain sites (atoms or collections of atoms) which are responsible for catalyzing various transformations/reactions. Sometimes, promoters are also added in small quantities to improve the catalytic activity. Active metal or metal oxides are dispersed in the pores of the "support" in the form of nanoparticles. Catalyst supports are porous, have high surface area, and significant pore volume to increase the thermal stability of the catalyst and provide better metal dispersion.

Generally, heterogeneous catalysis involves gaseous reactants being passed over a solid surface. As explained before, the heterogeneous catalytic reactions involve physisorption, followed by chemical reaction, and then desorption of the product to regenerate the free catalyst surface. Transition metals or metal oxides such as, Fe, Co, Ni, Cu, Ru, Rh, Pd, Ir, Pt, Au, etc., are employed as active metal catalysts because they have the ability to catalyze chemical transformations due to their unique property of changing oxidation states by donating or accepting electrons. This results in making or breaking of bonds on the surface, enabling the catalytic activity. Among the most popular reactions through this process are: hydrogenation, oxidation, and dehydrogenation. Metal oxides such as zeolite, silica, and alumina can also be used in heterogeneous acidic or basic reactions [74,75]. The acidity of the catalyst may be increased by impregnating with compounds such as phosphoric or sulfuric acid. Phosphoric acid coated silica is used in acid-catalyzed transformations such as esterification, condensation, hydration, etc.

8.3.1 Metal Oxides: Zeolites, Hydrotalcites, Titanium Silicates

In the synthesis of fine and specialty chemicals, most commonly used catalysts include alumina or aluminum oxide (alumina), silica, and zeolites. Hydrotalcite and titanium silicates are relatively new in their role in the commercial/industrial scale synthesis of fine chemicals, but have great potential for developing such applications.

8.3.1.1 Zeolites

Aluminosilicates are acidic catalysts made from SiO_2 and Al_2O_3. They have SiO_4^{4-} ions that have a tetrahedral structure (Fig. 8.16). In this structure, some Si atoms are replaced with Al atoms. The structure of zeolite is like a cage with cavities and multiple channels. These allow

only a particular size of molecules to enter and presently 130 different framework structures are known. Hydrogen ions are associated with the aluminum atoms and provide acidity to the catalyst.

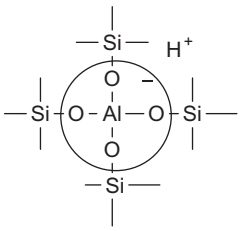


Fig. 8.16
Structure of aluminosilicates.

Zeolites have become an exciting group of catalysts for the present researchers. Zeolites have a microporous structure which means they have a lot of vacant spaces in the three-dimensional (3D) structure giving room for cations such as sodium and calcium, and molecules of water. These positive ions are rather loosely held and can readily be exchanged for others in a contact solution. One of the common applications of zeolites is as molecular sieves which allow only straight chain molecules to seep through and have been used in petroleum refining. ZSM-5 is another commonly used zeolite. It is prepared from sodium aluminate (a solution of aluminum oxide in aqueous sodium hydroxide) and a colloidal solution of silica, sodium hydroxide, sulfuric acid, and tetrapropylammonium bromide [76]. Due to the unique characteristics of zeolites, they are currently being used and developed to a large extent for catalysis in fine and specialty chemicals.

8.3.1.2 Hydrotalcite

Hydrotalcite is so named due to its similarity in appearance with talc and its high water content. It has multiple layers and the structure depends on the stacking pattern. For example, it may have a 3-layered rhombohedral structure or a 2-layer hexagonal structure. This is dependent on the conditions maintained during synthesis of the catalyst. Chemical composition of hydrotalcite can be varied through changing the ratio of compounds of Mg and Al added but a general formula can be represented as $[Mg_{3-x}Al(OH)_{8-2x}]_2[(CO_3)(H_2O)_{4-x}]$ [77]. The cations can be monovalent, divalent (Mg^{2+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, or Ca^{2+}) or trivalent (Al^{3+}, Cr^{3+}, Mn^{3+}, Fe^{3+}, Co^{3+}, Sc^{3+}, or La^{3+}) and the anions can be anion (CO_3^{2-}, SO_4^{2-}, or NO^{3-}, halide ions, silicate anion ($SiO(OH)_3^-$). The cations, M(II) and M(III) can coordinate up to six times with OH^- ions and form an octahedral structure which form joint layers. These layers can be bonded through ionic or van der Waals forces. In these layers the structure can be stacked with insertion of anionic and water molecules (Fig. 8.17).

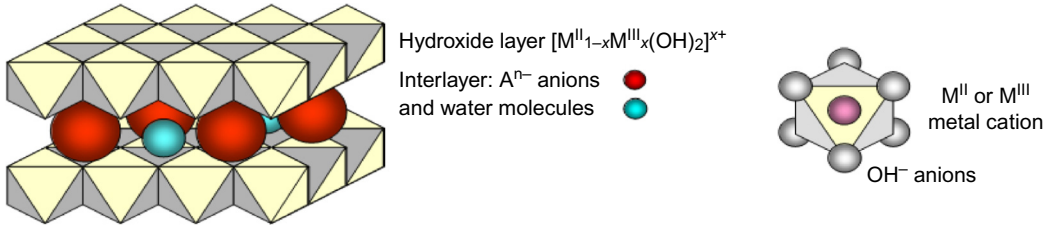


Fig. 8.17
Structure of layered double hydroxide.

The synthesis of hydrotalcite goes through multiple stages. First stage involves, an aqueous solution of Mg and Al mixing under vigorous stirring with heating. The product formed after the hydrothermal reaction is allowed to age for a duration of 18–20 hours after which it is filtered and washed. This washed residue is impure and contains sodium, carbonate or hydroxide anions, depending on starting material. It has to be washed with hot distilled water. Calcination and ratio of Mg/Al compounds added plays a major role in determining the activity of the catalyst so formed [78] (Fig. 8.18).

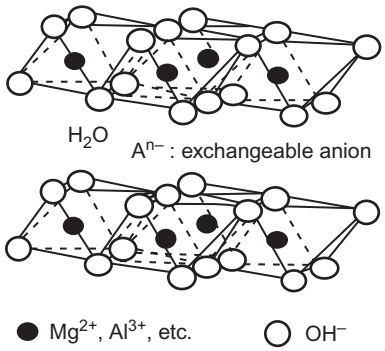


Fig. 8.18
Structure of hydrotalcite [79].

Hydrotalcite can be used as redox catalysts, acid/base catalysts, and even as catalyst supports. The tunability of hydrotalcite for promoting either an acid or base catalyzed reaction due to its bi-functionality gives it a wider scope of application in fine and specialty chemical industry. Copper or a heavy metal can be used to modify the hydrotalcite structure for oxidation or reduction reactions. They can be used for preparation of catalysts for synthesis of H_2 and in use of biofuel refining, such as for pyrolysis oil from biomass. Hydrotalcite has proven effective for oxidation of aromatic compounds at benzylic positions, such as diphenylmethane, fluorine, and xanthene for formation of ketones [79]. They have been proved to be capable of replacing conventional base catalysts such as NaOH and KOH. Other advantages include ease of separation, recycling possibilities, and decreased corrosion of material.

8.3.1.3 Titanium silicate (TS)

Titanium silicate is a zeolite type composite material with tetrahedral TiO_4 and SiO_4 forming a mordenite framework inverted structure. Thus, TS has a 3D system which consists of zeolitic micro pores and has a large number of active sites. It can be specifically designed and modified for industrial oxidation, hydroxylation, and ammoxidation type processes.
The activity of the catalyst can be attributed only to the isolated titanium active sites because sites with nonisolated titanium (TiO_2) do not show any selectivity or activity for oxidation reactions with H_2O_2 [80]. In the presence of H_2O_2 this catalyst can be utilized for hydroxylation of organic compounds [81].

The formation of several different sodium and potassium titanium silicates takes place when amorphous titanium silicate precursors are treated hydrothermally in alkaline media [82]. TS has been used for diphenols and propylene oxide in industrial production. The use of this system for fine chemicals has not been fully explored but it has been proven effective for synthesis of paracetamol and caprolactam. TS has high coordination ability due to Ti(IV) sites and stereoselectivity due to high distribution on the hydrophobic silica structure which makes it a useful catalyst for the synthesis various of chemicals [80].

What follows is a discussion of commonly practiced reactions in the fine chemical industry through heterogeneous catalysts such as; FC reaction, Fries rearrangement, ammoxidation, hydroxylation, condensation, and Diels-Alder reactions.

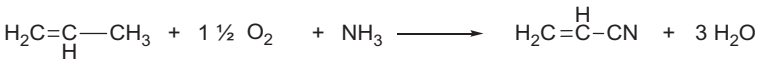
8.3.2 Ammoxidation Reaction

Ammoxidation is the process of conversion of a methyl group to a nitrile in the presence of a heterogeneous catalyst. It can be performed in the vapor phase with a partial insertion to selectively insert nitrogen from gaseous ammonia into an activated methyl group, which may be bonded to olefin, aromatic, and N-heteroaromatic compounds. These products qualify as intermediates for fine chemicals such as dyestuffs, pharmaceuticals, etc. A few important commercial catalysts that can be used for this process are discussed in the following subsections.

8.3.2.1 Bimetallic bismuth molybdate and bismuth phosphomolybdate [18]

One of the earliest breakthroughs in ammoxidation reactions for industrial scale production was in the use of Bi_2O_3/MoO_3 catalysts for conversion of propene to acrylonitrile. This process was named the SOHIO process after the discovery at Standard Oil of Ohio and was performed at 450°C and 1–2 bar in a fixed bed tubular reactor. Propene is reacted with ammonia and atmospheric oxygen through the reaction given in Scheme 8.34.

Here, the catalyst can oxygenate propene, activate ammonia for reaction, and then be regenerated by the atmospheric oxygen. While the exact mechanism is not known, it is



Scheme 8.34
Propene ammoxidation.

proposed that the propene group forms a complex with the molybdenum center which is followed by abstraction of hydrogen from the alkane. Then the ammonia is activated at the surface of Mo center and the oxidation of allyl group takes place. The ammonia leads to formation of iminomolybdenum groups which convert the activated methyl group in propene to nitrile. The formation of the allyl-Mo complex and hydrogen abstraction are the rate determining steps.

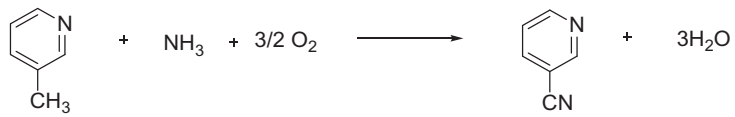
The selectivity for acrylonitrile through this process is more than 70% and side products include HCN, carbon dioxide, acetaldehyde, and acetonitrile. Applications of acrylonitrile are in the production of fibers.

The SOHIO process was developed for ammoxidation in 1957 and holds the largest share in synthesis of acrylonitrile industrially.

8.3.2.2 Supported vanadium oxide

Vanadium catalysts have been found to be effective in the oxidation/ammoxidation type reactions. These catalysts can transfer oxygen easily from bulk to the surface where reactant molecules can get oxidized. Among different vanadium catalysts, combination of V_6O_{13} and V_2O_5 has been found effective for ammoxidation of 3-picoline to the corresponding nitrile. Vanadium, molybdenum, and antimony oxides have also been explored for the reaction with the use of alumina and silica supports.

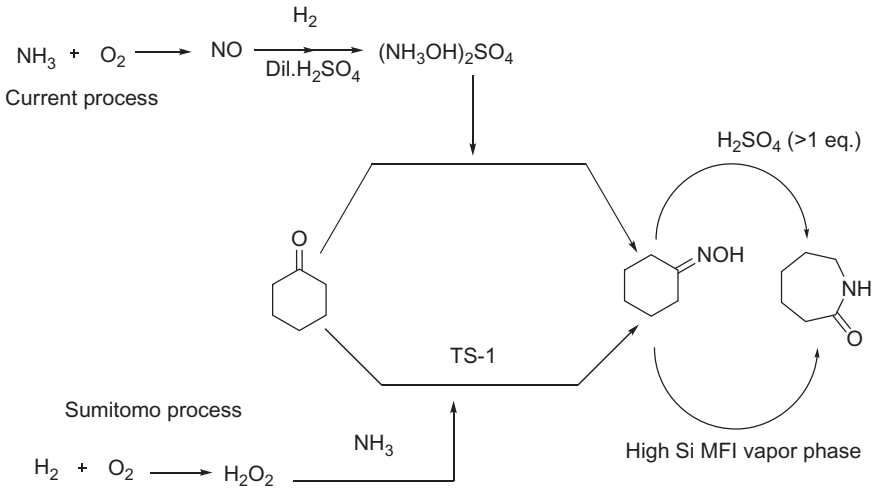
For the conversion of *n*-butane to maleic anhydride supported vanadium phosphates (VPO) were employed [83]. Here, the ratio of vanadium to phosphate i.e. the support and the amount of loading, play a role in enhancing the catalytic reaction. In the conversion of 2,6-dichlorotoluene (DCT) to 2,6-dichlorobenzonitrile (DCBN) VPO catalysts were evaluated. A better conversion of DCT was achieved with VPO supported (36% loading) on phosphated zirconia because of high acidity from the support. VPO/SiO_2, VPO/γ alumina and VPO/TiO_2 (anatase) showed high conversion efficiency compared to the use of only bulk VPO catalysts [84] (Scheme 8.35).



Scheme 8.35
Ammoxidation of 3-picoline to corresponding nitrile with vanadium catalysts [83].

8.3.2.3 Titanium silicate

An example of TS catalyzed Ammoxidation is shown in Scheme 8.36. This is an industrially important chemical with a 60,000 TPA production capacity plant. The product is obtained at 80–90°C under positive pressure and the excess ammonia is removed with solvent. This method of production of caprolactam ensures a cleaner process compared to the conventional one because synthesis of ammonium sulfate can be avoided [85].



Scheme 8.36
TS catalyzed ammoxidation.

Among other catalysts systems discussed for ammoxidation are antimony-iron oxide (Sb/Fe_3O_4) catalysts for ammoxidation of allyl alcohol to form acrylonitrile with a yield of 83–84% [86].

Ammoxidation finds applications in the pharma industry for the synthesis of vitamin B intermediates or the polymer industry for acrylonitrile synthesis. Hence, to promote efficiency and catalytic recycle, conventionally used homogeneous catalysts are increasingly being displaced by supported catalysts. They not only ensure catalyst recovery, but also promote the reaction through higher acidity.

8.3.3 Fries Rearrangement

Fries rearrangement of aromatic alcohols serves as a valuable step for synthesis of specialty chemicals such as dyes, pharmaceuticals, and agrochemicals. Hydrofluoric acid, aluminum chloride, titanium chloride, and tin chloride have been the known catalysts for Fries rearrangement. However, they are highly corrosive and toxic chemicals and they cannot be regenerated or recycled after the catalytic process.

The first step of the reaction is the formation of coordinates between Lewis acid such as $AlCl_3$ and the carbonyl oxygen from acyl group, which is more electron rich than the phenolic oxygen atom. Due to polarization of the bond between the acyl residue and the phenolic oxygen atom, the aluminum chloride shifts to phenolic oxygen (rearrangement) in the second step. In the third step, the generated acylium carbocation reacts in a classical electrophilic aromatic substitution with the aromatic ring (Fig. 8.19).

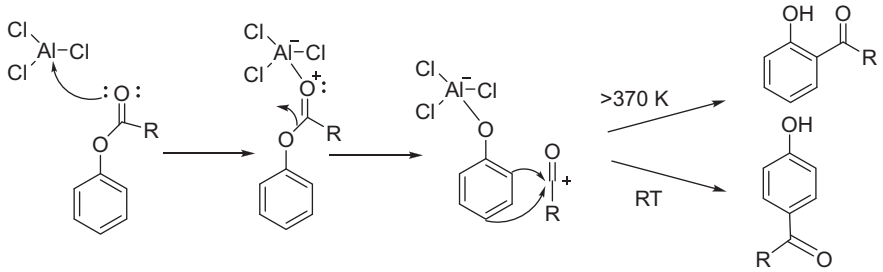


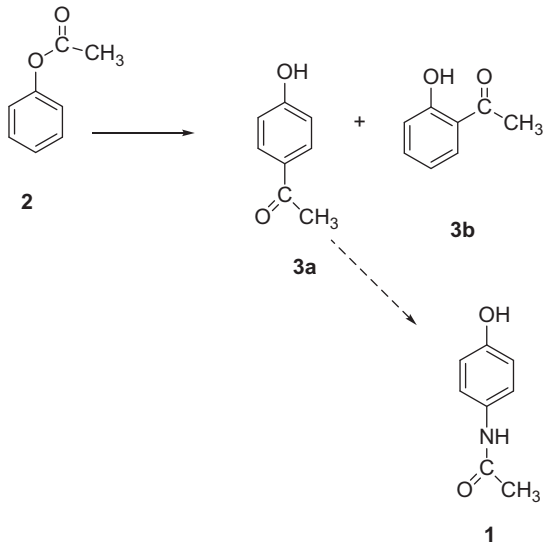
Fig. 8.19
Mechanism for Fries rearrangement through carbocation intermediate.

Finally, the abstracted proton after rearrangement comes out as HCl where the Cl^- comes from $AlCl_3$. The substitution reaction in this case is dependent on temperature. A higher temperature favors ortho product whereas low temperature favors para product which depends on thermodynamic versus kinetic reaction control. The ortho product can form a more stable bidentate complex with the aluminum ion. Nonpolar solvents favor formation of ortho product and increasing polarity increases the ratio of the para product [87].

8.3.3.1 Synthesis of paracetamol

Paracetamol, a common analgesic is made from Fries rearrangement of phenyl acetate (2) in *p*-hydroxyacetophenone (3a).

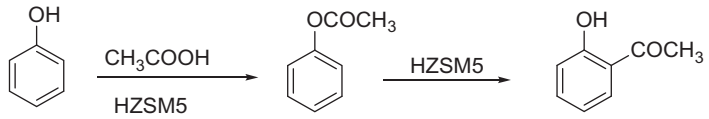
A proposed catalyst for the reaction is methane sulfonic acid or MSA which is a biodegradable and easy-to-handle liquid. It has very similar chemical performances (yield, conversion, and selectivity) combined with a lower impact on the environment [88]. MSA used in catalytic quantities (maximum 28.6%) gave ortho product between 160°C and 190°C and conversion in this case was 20–30%. A 100% conversion and high selectivity for para product was obtained when molar ratio of MSA to phenyl acetate was eight compared to four for the same reaction using HF. Separation of the product was possible through extraction with water. Then the product was separated from the aqueous phase by extraction in organic solvent (Scheme 8.37).



Scheme 8.37
Synthesis of paracetamol by MSA [88].

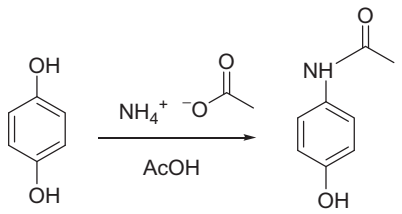
Although the catalyst is environment-friendly, the use in high quantities renders the process uneconomical. Thus, the use of heterogeneous catalysts which are reusable, such as zeolites and sulfonic resin nafion or Amberlyst are being explored in the Fries rearrangement of phenyl acetate. Thermal stability and limited specific areas in this system evidence the need for a greater size pore system. Mesostructured SBA 15 was modified with arenesulfonic acid and was found to be an active catalyst for Fries rearrangement of phenyl acetate in the liquid phase. They are better catalysts than other homogeneous and heterogeneous acid catalysts. The catalyst is found to be stable and there is no loss of sulfur during the reaction. The reaction was performed in a Teflon-lined stainless steel autoclave to safeguard from the corrosion of reactants and catalyst. The rearrangement of phenyl acetate was performed at 100–170°C in an initial pressure of nitrogen of 4 bar which would increase the boiling point of reactants and maintain the liquid phase at reaction temperature [89].

Synthesis of *o*- and *p*-hydroxyacetophenones has been reported through a one-pot, two-step process using acid zeolites. The process involved esterification of phenol with acetic acid and the generated phenylacetate subsequently underwent the Fries rearrangement to give *o*- and *p*-hydroxyacetophenones. The reaction, when performed in gas phase with acetic acid as acylating agent and zeolite catalysts, led to formation of phenylacetate followed by formation of *o*-hydroxyacetophenone. This was formed in a selective yield of 40% and the molar ratio of *o*-hydroxyacetophenone/phenylacetate was the highest with ZSM-5 catalyst amongst gamma, beta, and ZSM-5 type zeolites [90] (Scheme 8.38).



Scheme 8.38
Role of zeolite in synthesis of *o*-hydroxyacetophenone [90].

Hydroquinone and ammonium acetate (amidating agent) have been used for direct synthesis of paracetamol (acetaminophenone). The reaction gave paracetamol in high yield and selectivity (>95%) when performed in acetic acid at elevated temperatures. This process has not yet been performed on a large scale and potential depends on the possibility of solvent recycle and by-products [91] (Scheme 8.39).



Scheme 8.39
Synthesis of acetaminophen from hydroquinone using ammonium acetate [91].

It is possible to modify these catalysts to obtain better yield and commercially demonstrable route.

8.3.4 Diels-Alder Reaction

Diels-Alder reaction is an addition of a conjugated diene with a substituted alkene (dienophile) for the formation of substituted cyclohexene system. The name is in honor of Otto Paul Hermann Diels and Kurt Alder who first described this process in 1928 and were awarded the Nobel Prize in Chemistry in 1950 [92]. It is a stereoselective and regioselective reaction and is a common method for formation of six-membered systems. If this reaction is performed using other systems like carbonyls and imines, it leads to formation of heterocycles and the process can be termed as hetero-Diels-Alder reaction. Diels-Alder can be reversible, too, and is termed as retro Diels-Alder reaction [93]. Among common catalysts used for these reactions are Lewis acids, such as zinc chloride, boron trifluoride, tin tetrachloride, and aluminum chloride which tend to form homogeneous complexes in the reaction with the dienophile. This makes it more electrophilic towards the diene which increases the reaction rate and improves region and stereoselectivity [94]. Among heterogeneous catalysts, Sc(III)-zeolite was found effective for synthesis of piperidine derivatives through imino

Diels-Alder reaction [95]. Silica gels can also be modified with above mentioned Lewis acids and act as promoters as well as supports for the reaction.

8.3.4.1 Mechanism of the Diels-Alder reaction

The cycloaddition reaction of a diene and a dienophile involves the four π-electrons of the diene and two π-electrons of the dienophile. Here the formation of the product is favored because of formation of energetically more stable σ-bonds. In alkynyl dienophile, another dienophile can be included if the product is not too sterically hindered. Thus Diels-Alder is a simple and effective method for formation of unsaturated six-membered rings (Fig. 8.20).

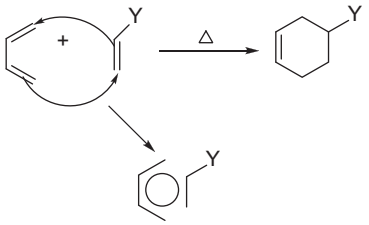


Fig. 8.20
Mechanism of Diels-Alder reaction.

If the orbitals are of similar energy, there is an overlap between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile. The electron withdrawing group of dienophile facilitates this process and substituents such as CHO, COR, COOR, CN, C=C, Ph, or halogen promote the reaction further. Basically, the dienophile should be as electron rich as possible (Fig. 8.21).

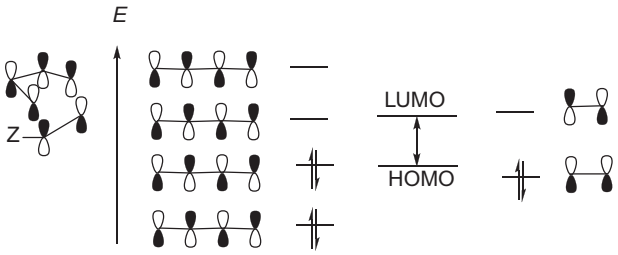


Fig. 8.21
Overlap of the molecular orbitals.

As mentioned before, the products in this reaction can be stereoisomers. This would depend on whether the dienophile lies under or away from the diene in the transition state. The endo product is usually the major product (due to kinetic control) (Fig. 8.22).

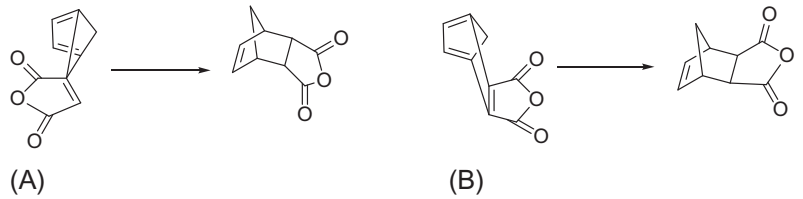


Fig. 8.22
(A) Diene and dienophile aligned directly over each other gives the endo product (dienophile under or in = endo). (B) Diene and dienophile staggered with respect to each other gives the exoproduct (dienophile exposed or out = exo).

Traditionally used Lewis acids are extremely sensitive to water which means they are required in high catalytic loading. Large catalytic loading is also required because the Lewis acids tend to bond with the oxygen of the dienophile, thus slowing down the kinetics of the process [96]. Transition metal-based Lewis acid catalysts have few marked advantages over other catalyst systems such as:

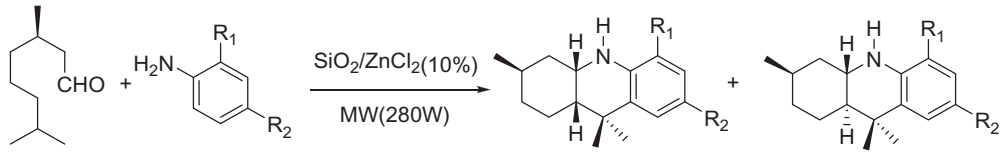
- ability to improve the rate of reaction by up to a 100 times with a reasonable amount of loading
- oxygen reduces catalytic activity, hence, it should be resilient to that effect
- it should be selective towards the desired product and have a fixed geometry to allow formation of desired enantiomer and stereomer
- it should have the ability to bind with a functional group such as the dienophile oxygen
- the catalyst should allow olefins to freely react without having any binding influence on it.

8.3.4.2 Synthesis of acridines

DA reactions may be classified as Carbo-DA (CDA) reactions or hetero-DA reactions (HDA), which would then be classified as oxa-DA reaction (HDA of carbonyl compounds) and imino (aza)-DA reaction (HDA of imines). The imines mentioned here may react as either dienophiles or azadienes [97]. For the preparation of quinolines, cycloaddition reaction of *N*-arylamines (Schiff's base) with nucleophilic olefins is a common method. This is catalyzed by Lewis acid catalysts. For various tetrahydroquinolines and quinolines, acid-catalyzed cycloaddition between the C–C–N–C azadiene moieties of *N*-aryl imines and dienophiles has become a conventional route. The imino DA reaction allows better control over the formation of stereoisomers and the creation of an additional ring. An important intermediate in fine chemical was octahydroacridine or OHA which could be synthesized using a broad range of Lewis and Brønsted acid catalysts such as like $TiCl_4$, BF_3OEt_2, $EtAlCl_2$, $FeCl_3$, Et_2AlCl, and CF_3COOH. Silica can be employed effectively as a support in this case to heterogenize the catalyst and promote recyclability.

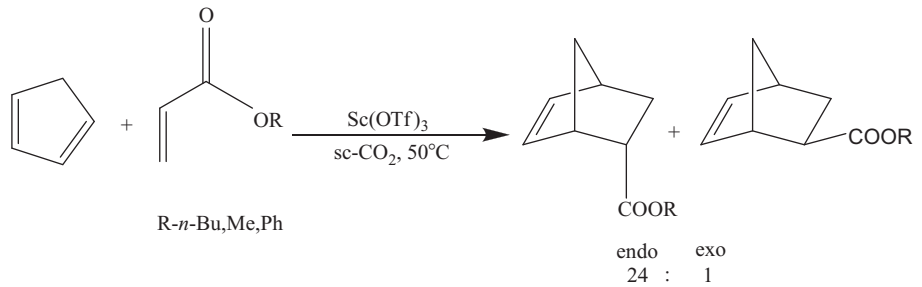
Different procedures have been suggested for the synthesis of OHA skeleton including the acid-catalyzed isophorone-aniline condensation, Beckmann rearrangement of oxime sulfonate,

catalytic hydrogenation of acridine, and amino-Claisen rearrangement of geranyl aniline. However, an efficient method suggested for green synthesis of OHA was a simple one-pot hetero-Diels-Alder reaction starting from (+)-citronellal and *N*-arylamines in the presence of a solid supported catalyst ($SiO_2/ZnCl_2$), under MW irradiation and without any solvent [98]. This process was found to be the most atom-economical, giving the OHAs in high yields and, with 100% of stereoselectivity (some cases) (Scheme 8.40).



Scheme 8.40
OHAs using solid supported catalyst ($SiO_2/ZnCl_2$) [98].

Green chemistry plays a significant role in improving the catalytic processes such as Diels-Alder reactions. For instance, the role of supercritical carbon dioxide as an environmentally benign solvent for reaction between *n*-butyl acrylate and cyclopentadiene was investigated wherein Lewis acid catalyst scandium tris(trifluoromethanesulfonate) was used due to its solubility in sc-CO_2 [99] (Scheme 8.41).



Scheme 8.41
Supercritical carbon dioxide as solvent for Diels-Alder reaction [99].

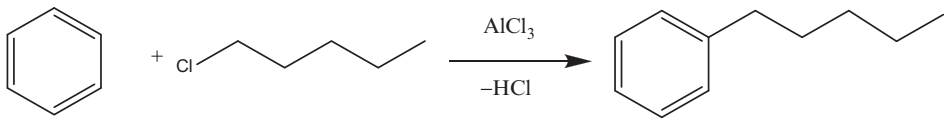
The solvent pressure could be modified to obtain maximum selectivity of the endo derivative. This process was found to be less hazardous, reduce energy consumption, ensure ease of separation, and minimize waste. Amongst some applications of acridine derivatives are synthesis of orange dye. OHA is specifically used for synthesis of citronella, which is an essential oil.

8.3.5 Friedel-Crafts Reaction

Origins of FC reaction occurred in 1887 when Charles Friedel and James Mason Crafts isolated arylbenzene by the treatment of amyl chloride with $AlCl_3$ in benzene [100]. This was one of the first descriptions of the use of Lewis acid for organic reactions [100]. Favorable catalysts for

FC alkylation are generally Lewis acids and include BF_3, $BeCl_2$, $TiCl_4$, $SbCl_5$, or $SnCl_4$. Apart from these, strong Brønsted-acids such as sulfuric acid and superacids such as $HF{\cdot}SbF_5$ and $HSO_3F{\cdot}SbF_5$ have also been found to be affective in FC alkylation.

In reactions that use aluminum chloride as catalysts there is a formation of complex between the product and the catalyst which is the primary reason why catalysts are needed in more than stoichiometric amount. After the reaction and subsequent hydrolysis, the catalyst is lost which leads to the environmental consequences of its disposal. Thus, there are obvious disadvantages of using such catalysts and there is a need to shift to environmentally benign and economical processes which use metal or acid catalysts in less than stoichiometric quantity. The homogeneous and inefficient catalysts can be replaced with heterogeneous catalysts in FC reactions. Amongst the alkylating agents, researchers are trying to substitute alkyl chlorides with less toxic agents like alcohols because water would be the only by-product of such reactions. In this regard, the application of activated double bonds and styrene-like compounds would give no side product at all (Scheme 8.42).



Scheme 8.42
Friedel-Craft alkylation with $AlCl_3$.

8.3.5.1 Heterogeneous catalytic systems for acylation, allylation and benzylation type reactions

8.3.5.1.1 Zeolites in FC acylation reactions

The zeolite could be modified to promote the reaction through varied Si/Al ratio and the model reaction was the acylation of anisole by acetic anhydride and acetyl chloride. The reaction was carried out at 70°C under batch conditions using the substrate anisole as solvent. Lanthanum was used to modify zeolites and proved to be an active agent in the acylation. The Si/Al content along with the rare earth metal concentration had a role to play in the catalyst behavior. With the increasing hydrophobicity of the de-aluminated catalyst, there was an increase in the yield observed. When the catalytic activity of zeolite Beta (NaY) was compared to the de-aluminated HY-zeolites, about the same yield of acylated product was found. However, when the much higher content of acid sites per gram in zeolite Beta is taken into account, the de-aluminated Y-zeolites were found to be more active per acid site [101] (Fig. 8.23).

8.3.5.1.2 Allylation reaction

$Mo(CO)_6$ and $W(CO)_6$ have been used as catalysts for the allylation and cinnamylation of electron-rich arenes. Methyl eugenol is an ingredient in spices and essential oils and has been synthesized through reaction of allyl carbonate and 1,2-dimethoxy benzene in a single step

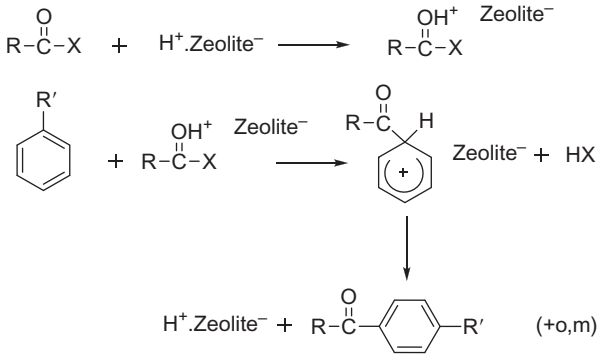
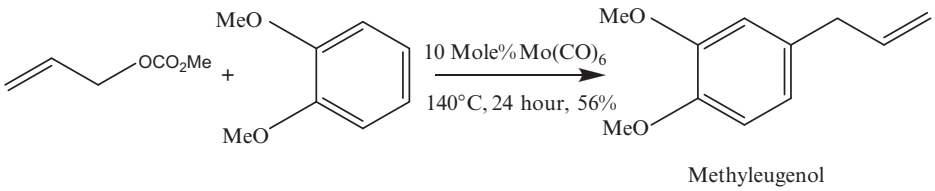


Fig. 8.23
Mechanism of zeolite-catalyzed acylation of aromatics [101].

process. Similarly, another process developed for this chemical used diruthenium complex as catalyst. However, a problem with both these catalysts was deactivation on exposure to moisture and air. Thus there has been some work conducted on replacing this catalyst system (Scheme 8.43).



Scheme 8.43
Friedel-Craft allylation/cyclization reaction yielding methyl eugenol.

8.3.5.1.3 Benzylation of toluene/benzene by benzyl chloride

FC reaction of toluene/benzene with benzyl chlorides leads to formation of diphenylmethane and is an important reaction in the chemical industry. It is used in synthesis of dyes, soaps, detergents, creams and lotions, and perfumes. It is an intermediate for benzophenone which is used for organic synthesis such as for floral odors in perfumery, as a fixative in the polymer industry and as a UV sensitizer for photo polymerization. Some catalyst systems have been identified to replace the conventional process of homogeneous catalysis, which are wasteful in terms of catalysts used (stoichiometric amounts) and polluting (due to toxic reagents and by product streams). These have been discussed in the following subsections.

8.3.5.1.3.1 Modified hydrotalcite [102] Lewis acids for the reaction have been reported in the literature but, basic catalysts for benzylation have not been studied in detail. The anionic clay, hydrotalcite, is a highly basic heterogeneous catalyst which was successfully

employed for FC benzylation. It was calcined between 200°C and 800°C and showed good activity for toluene benzylation. The benzylation activity increased with an escalation in calcination temperature. Here, chlorides and oxides of iron form the active sites on the catalyst surface. Modifications on the anionic clay, such as with In2O3 or gallium, show very high activity despite of the presence of moisture and air. Fe-Mg hydrotalcite was used to study a model reaction of toluene benzylation between 80°C and 110°C with ratio of benzyl chloride to aromatic substrate being 1:13 and catalyst loading being 0.1 g/mL benzyl chloride. The reaction proceeds with structural collapse of hydrotalcite and subsequent formation of metal chlorides and oxides which is why the activation temperature had a great role to play in the reaction. The product synthesized was only monosubstituted and did not have any side reactions.

8.3.5.1.3.2 Supported zirconia catalysts [103] Another system for effective catalysis is the use of microwave radiation in the presence of unsupported antimony salt and supported antimony salt on zirconia. The benzylation of benzene and related compounds was performed with benzyl chloride and afforded diphenylmethane in high yields. Here it is important to note that the zirconia catalyst in itself has no effect on the reaction, but provides the site for support to the active catalyst which improves the redox potential and increases the surface acidity. The catalyst pore size and temperature of reaction played an important role in the reaction. Sulfated zirconia has been known to be a useful catalyst for reactions requiring high acidity, but low temperature of operation. Doped zirconia is likely to have better acidity and stability, hence, Sb and Bi oxide were used to form mixed oxides with zirconia. The role of microwave here was to reduce reaction time by affecting the kinetics and ensure better work-up with reduction in toxic reagents. Ratio of benzene to benzyl chloride was 2:1 with 20 mg catalyst for every 1 mmol of benzyl chloride. A higher ratio of reactants would give higher selectivity, but on an industrial scale this is the most achievable value. The product was extracted with ether. Optimum temperature for the reaction was 80°C and increase in weight of catalyst increased the product formation. Amongst other advantages of the catalyst was the fact that it could be reused several times after washing was the most important, although there was a reduction in activity after each run. In comparison to unsupported antimony chloride catalyst for benzylation, 5% Sb-zirconia was a better system due to higher surface area for active sites of the catalyst.

8.3.6 Hydroxylation Reaction

Introduction of a hydroxyl group (–OH) in an organic compound is referred to as hydroxylation. These reactions may be facilitated with enzymes or catalysts, such as inorganic salts or ligands. An application of this reaction is to convert hydrophobic substances to hydrophilic and allow dissolution in water. In pharmaceuticals, this method allows the activation and deactivation of certain drugs. The added oxygen is derived from

hydroxylating agents such as atmospheric oxygen, hydrogen peroxide, and nitrogen oxide, among others.

The products obtained from hydroxylation are hydroxytoluene isomers, naphthalene isomers, methyl hydroxyl anthracene isomers, etc. They have many industrial applications such as—phenolic resins from cresol and dihydroxy benzene, lubricants, additives for oil, solvents, antioxidants, dyestuff, pharma intermediates, disinfectants, etc. The substrates for the process include toluene, xylene, dimethyl and diethyl naphthalene, and other alkylated aromatic compounds or their isomers. Chloro substituted (chlorotoluene, chloroethyl benzene, chloromethyl naphthalene), nitro substituted (nitrobiphenyl, nitrotoluene), amino substituted, and sulfonic substituted aromatics can also be used as substrates for hydroxylation [104].

Catechol obtained from hydroxylation of phenol with TS1 as catalyst can be converted to an intermediate for vanillin by addition of a single methyl group. The number of steps in this process has been considerably reduced leading to lower waste [105].

8.3.6.1 Catalysts and hydroxylating agents

Hydrogen peroxide is used as an oxidant in many cases for batch processes [106]. But there have been reports of use of N_2O as oxidant for benzene to phenol with ZSM-5 as catalyst [107]. Hydrogen and oxygen with palladium supported on TS1 [108], and molecular oxygen with poly (metal) salt of dihydroxyanthraquinone dissolved in water as catalyst [109] have been used for the same process.

Many catalysts have been studied for this process and found usable. For benzene to phenol conversion, iron [110], mono-vanadium(V) ammonium salt (and other derivatives) with substituted heteropolyamines [111], and mesoporous molecular sieves with copper loading have been used as catalyst at atmospheric pressure of oxygen [112].

The above mentioned processes are not commercial because of either low catalytic activity, and low conversion and selectivity, along with a high temperature requirement in certain cases. During hydroxylation it is preferred if the amount of moisture does not exceed 7.5% because higher water reduces the product formation [104].

8.3.6.2 Aluminum silicates for hydroxylation [104]

Phenol was hydroxylated to synthesize dihydroxybenzene in the presence of 30% by wt. hydrogen peroxide with crystalline aluminosilicate as catalyst. The process involved mixing of phenol and catalyst with a slow addition of H_2O_2 over a duration of 1.5 hours with slow heating (max. temperature 54°C). This temperature was maintained for almost 4 hours and then the product was cooled and filtered. The dihydroxybenzene in total product was 6.8 wt% and the selectivity to ortho to para isomers was about 2:1. The ideal conditions proposed for such reaction was a temperature range of 40–150°C and a ratio of phenol or aromatic compound in

the range of 1.1–1. The catalyst should contain 10–80% faujasite or modernite with 1–15% by weight a rare earth metal.

8.3.6.3 Platinum catalyzed hydroxylation

A process using platinum as catalyst was proposed by Shilov for fast and enantioselective hydroxylation of aromatic compounds. $PtCl_4$ or Pt(IV) was used as an aqueous mixture of $PtCl_2$ and $PtCl_4$ compounds [113]. Such a process was the first example of hydroxylation of methane with complete selectivity. The reaction mechanism is given in Fig. 8.24 (Scheme 8.44).

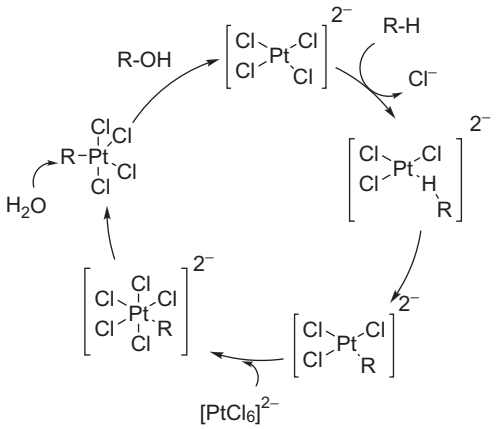


Fig. 8.24
Proposed mechanism for Shilov electrophilic process [114].

$$CH_4 + PtCl_6^{2-} + H_2O \xrightarrow[H_2O,\ 120^\circ C]{PtCl_4^{2-}} CH_3OH + PtCl_4^{-} + 2HCl$$

Scheme 8.44
Hydroxylation of methane.

An improvement in the process included the use of a divalent ligand (bidiazine ligand family) along with $PtCl_2$ to prevent any over oxidation of methane following the same mechanism. Here the SO_3 group is the oxidant [115] (Scheme 8.45).

$$CH_4 + 2H_2SO_4 \xrightarrow[100^\circ C]{(bpym)PtCl_2} CH_3OSO_3H + 2H_2O + SO_2$$

Scheme 8.45
Bidiazine ligand for methane sulfonation.

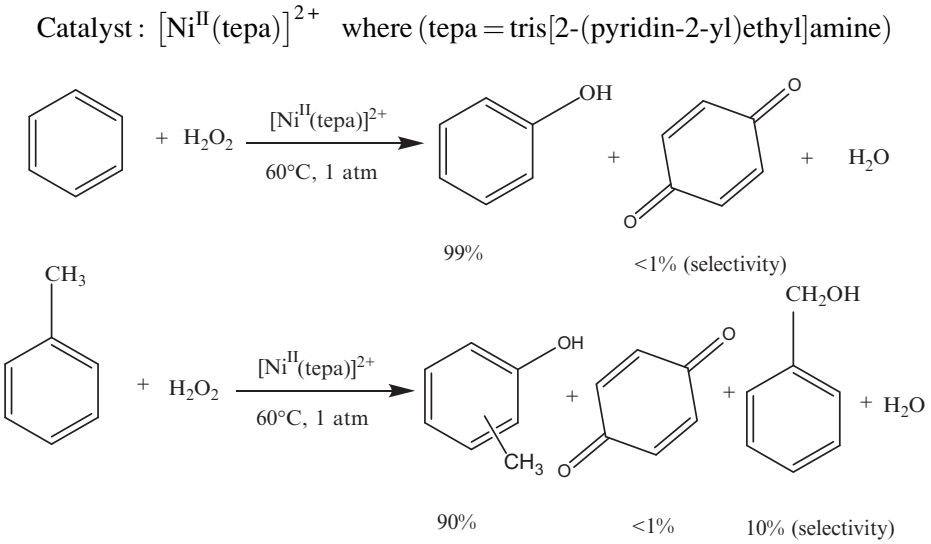
8.3.6.4 Vanadium phthalocyanine [116]

Hydrocarbon was reacted with H_2O_2 in a molar ratio of 1:0.05 or 1:10. A polar solvent such as acetonitrile was needed for this reaction and was in the ratio of 1:3 to 1:20 with respect to hydrogen peroxide depending on the substrate. The catalyst chosen was vanadium phthalocyanine or a derivative of it and the temperature was 25–100°C with a continuous or batch mode of operation. The product was separated by fractional distillation.

As an example of the reaction, anisole was taken in a flask with H_2O_2 (50% aq. solution) and polar solvent while the catalyst was added with vigorous stirring. A temperature of 65°C was maintained for 8 hours followed by filtration through a Buckner funnel and silica column to remove catalyst. Guaiacol and 4-methoxyphenol were formed with a yield of 17.5% yield and anisole conversion was of 18%. The advantage of the process was the recyclability of the catalyst. The advantages of the process lie in the use of environmentally benign reagents under mild conditions.

8.3.6.5 Nickel complex [117]

In a recent development, hydroxylation of benzene to form phenol was performed using a Ni(II) complex at 60°C. The yield reported was as high as 21% and quinone or diphenol were not observed in the process. The turnover number for the process was 749 which has been highest reported so far. With toluene as a substrate, the selectivity for cresol was 90% with the same mechanism (Scheme 8.46).



Scheme 8.46
Hydroxylation of aromatic compounds.

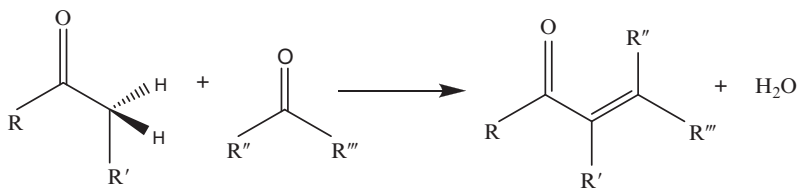
As discussed above, there are a lot of applications for the products synthesized by hydroxylation of aromatic compounds. The catalysts have evolved over time for this process as shown in this section. While conversions are low, a high selectivity for desired product along with the use of a recyclable catalyst makes the process viable to be taken up on industrial scale. An example of success of this process is the huge scale of production of catechol and hydroquinone in continuous mode which was started by EniChem in 1986 in Italy. Temperature, solvent polarity, and hydrogen peroxide concentration and conversion are major factors that decide the selectivity and purity of the product [118].

8.3.7 Aldol and Knoevenagel Condensation Reaction

The combination of two molecules/moieties with the loss of a smaller molecule to form a larger molecule catalyzed in presence of an acid or base moiety is called a condensation reaction. Molecules lost are generally water, acetic acid, or hydrochloride. The combination can be of functional groups within the same molecule and be termed as intramolecular condensation or maybe between two functional groups of different species called intermolecular condensation. Amongst the different types of condensation reactions, Aldol condensation and Knoevenagel condensations are important from the perspective of heterogeneous catalysis for fine chemical synthesis.

8.3.7.1 Aldol condensation reaction

Aldol condensation involves reaction of an enol with a carbonyl group, which leads to the formation of β-hydroxyaldehyde or β-hydroxyketone and elimination of water molecule. The product formed is a conjugated enone (Scheme 8.47).



Scheme 8.47
Aldol condensation reaction.

This reaction proceeds with formation of C–C bond followed by dehydration or elimination. The dehydration can progress with a strong base or an acid and the mechanism is represented in Fig. 8.25.

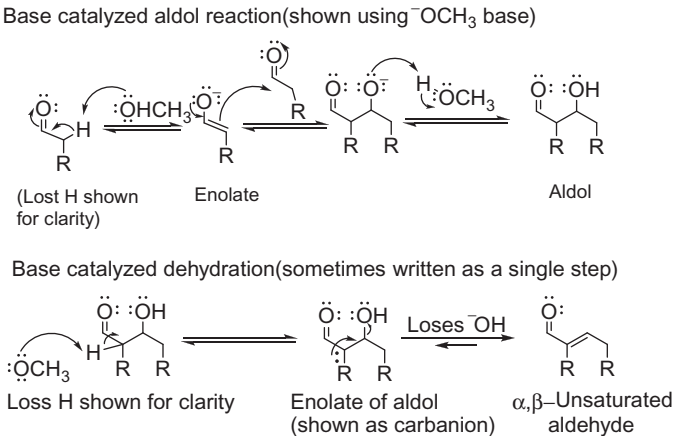
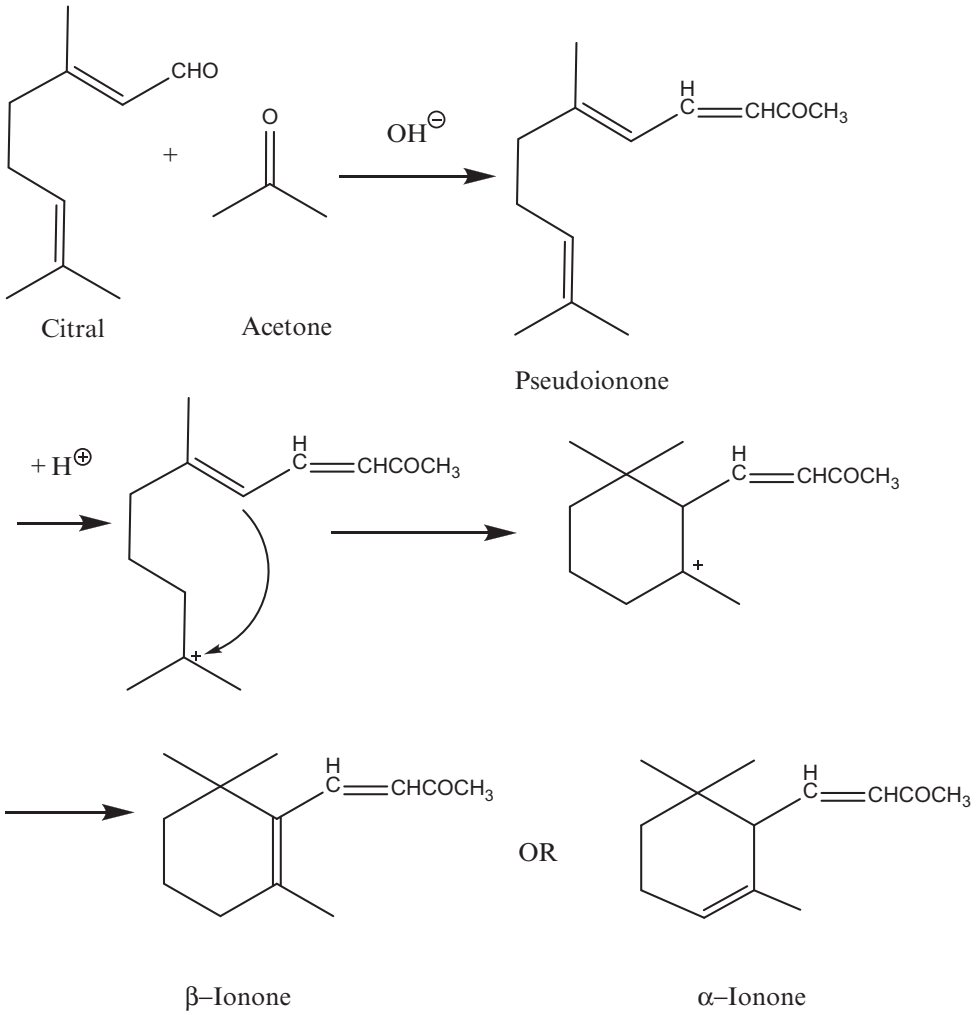


Fig. 8.25
Base catalyzed mechanism of aldol condensation [119].

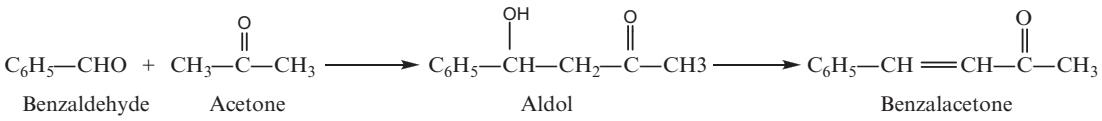
Application of aldol condensation is to increase chain length and obtain high molecular weight aldehydes used in solvents, perfumes, flavoring agents, pharmaceuticals, dyestuff, and polymers. Heterogeneous catalysts applied for this process include hydrotalcite (major catalyst), vanadium phosphate [120], mixed oxides [121], and supported ionic liquids derived from choline.

Hydrotalcites have been discussed in Section 8.3.1.2 of this chapter. They have a large surface area and act as basic catalysts for aldol condensation. The structure of hydrotalcite was modified with the addition of mixed oxides and replacing certain cations to increase the activity for synthesis of pseudoionones through condensation of ketones and citral [122]. This reaction followed by cyclization consequentially gave α and β ionones which have applications in perfumeries. β ionone is also an intermediate in vitamin A synthesis. The aldol condensation was performed in a stainless steel reactor with hydrotalcite at 398 K for 4 hours under the autogenous pressure. The conversion of citral was 98% with the pseudoionones selectivity of 68% proving heterogeneous catalysts to be more efficient than homogeneous (Scheme 8.48).

It was illustrated [123] that for aldol condensation of acetone with benzaldehyde, hydrotalcite acted as a basic catalyst when the reaction was performed at low temperatures. No activity was detected on a carbonated or pure form of hydrotalcite and on the decarbonated (calcined at 723 K) hydrotalcite. But once the catalyst was rehydrated at room temperature after calcination at 723 K, the activity soared to a maximum, suggesting that the hydroxide ions were the reason for catalysis. The yield of product was more than 85 mol% (Scheme 8.49).

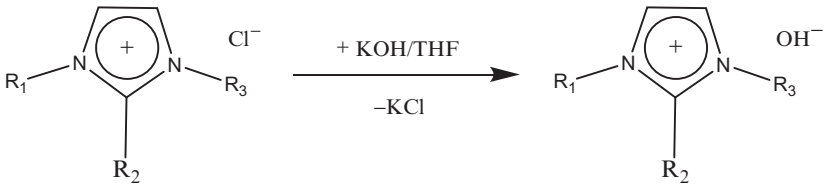


Scheme 8.48
Citral and acetone condensation reaction mechanism [122].

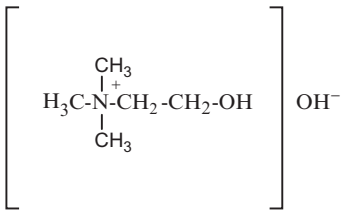


Scheme 8.49
Aldol condensation of acetone with benzaldehyde [123].

For Aldol condensation, apart from the metal hydroxide structures described above, ionic liquids can be used. To make the catalyst recyclable and effective, it can be supported on a metal oxide and used as a basic catalyst. Impregnation of choline (CH) on MgO support was done to form CHMgO [124]. Here CH is derived by action of potassium hydroxide on an ionic liquid with imidazolium cation (Scheme 8.50).



Basic ionic liquid from imidazolium catalyst



Choline hydroxide molecule

Scheme 8.50
Formation of basic choline catalyst [124].

Jasminaldehyde, used in perfumery, was synthesized using both CH and CHMgO for Aldol condensation of benzaldehyde and heptanal. A high conversion was achieved and the selectivity was as high as 84% (Fig. 8.26).

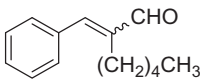
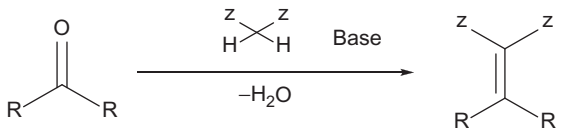


Fig. 8.26
Structure of jasminaldehyde.

A possible by-product can be formed through cyclization of heptanal but it can be avoided through slow addition of heptanal with respect to benzaldehyde.

8.3.7.2 Knoevenagel reaction

Knoevenagel condensation involves nucleophilic reaction between a carbonyl functionalized molecule and active hydrogen compound. Similar to aldol condensation the combination step is followed by a dehydration/elimination step and the formation of a conjugated product. The catalyst should be weakly basic [125] (Scheme 8.51).



Scheme 8.51
Knoevenagel condensation.

The z group should be electron withdrawing to ensure a labile hydrogen ion that can undergo nucleophilic reaction even in the presence of a mild base.

Knoevenagel condensation is a useful process for fine chemicals because of the possibility of generating alkenes from carbonyl containing molecules in the presence of base catalysts. Application of such a process is found in pharmaceuticals, such as in the synthesis of antimalarial drugs and benzothiazines which show anticancerous properties [126], disperse dyes, α,β-unsaturated alkenes, etc.

The most important step in the industrial scale production of the antimalarial drug is the Knoevenagel condensation [127]. This compound along with artemether inhibits the growth of parasites in red blood cells, thus helping counter malaria (Fig. 8.27).

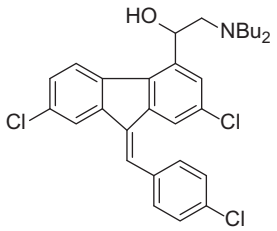
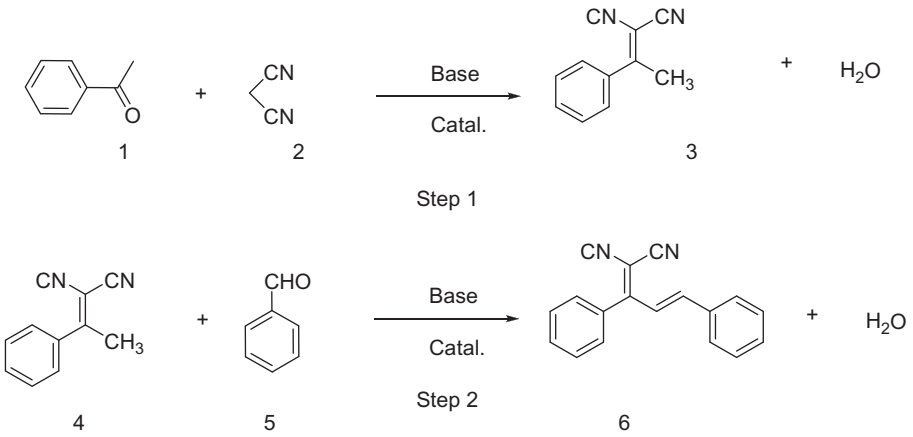


Fig. 8.27
Structure of lumefantrine.

Malonitrile contains a reactive methylene group which is condensed with a carbonyl group for synthesis of dicyanomethylene group. These molecules are intermediates for methylene dyes which are used in textiles, dye laser, optical applications, and photopolymerization. The product, 1,1-dicyanomethylenebutadiene is used as a disperse dye and has nonlinear optical properties. The reaction scheme in Scheme 8.52 shows that the process includes two steps, Knoevenagel condensation of malonitrile and acetophenone, followed by condensation with benzaldehyde. To combine both the steps in a single reactor, basic heterogeneous catalysts such as zeolites, hydrotalcite, and aluminophosphate oxynitrides (ALPON) have been suggested [128]. ALPON was found to show high activity and selectivity for the entire process. It possesses better basic sites than alkaline exchanged γ zeolites but poorer than magnesium oxide or hydrotalcite; however, for this synthesis this is the most appropriate catalyst [129].

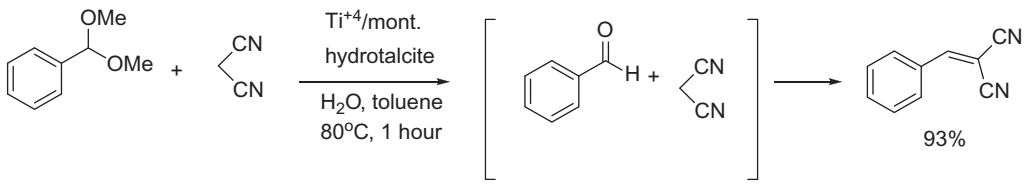


Scheme 8.52
ALPON catalyzed synthesis of 1,1-dicyanomethylenebutadiene [128].

The reaction using ALPON was performed by reaction of malonitrile with acetophenone at a temperature of 100°C to yield *R*-methylbenzylidenemalononitrile with a 100% selectivity and 90% yield. Then benzaldehyde was added to the reactor and the temperature was increased to 150°C. This was maintained for 6 hours. The substrate was completely converted and the yield of 1,1-dicyanomethylenebutadiene was 92%.

Another important derivative obtained through Knoevenagel condensation is benzylidene malonitrile. This can be modified to form alpha alkyl or alkenyl derivatives which are resistant to deterioration on exposure to radiation such as UV to stabilize organic materials [130]. Apart from this, benzylidene malonitrile finds applications in insecticides, fungicides, and pharmaceuticals as cytotoxic agents against tumors [131].

The synthesis of this molecule is undertaken in a one-pot process from benzaldehyde dimethyl acetal and malonitrile. Two catalysts are used here (1) titanium(IV) exchanged montmorillonite (Ti^{+4}-mont.) to perform hydrolysis of the acetal group following which (2) Knoevenagel condensation takes place in the presence of hydrotalcite (Scheme 8.53).



Scheme 8.53
Benzylidene malonitrile by Knoevenagel condensation.

Ti^{+4}-mont. is a Brønsted acid which catalyzes acetal hydrolysis and the obtained benzaldehyde can react with methylene active compound. The water generated from the dehydration step of condensation makes the deprotection of dimethyl acetal faster and promotes the reaction. It was observed that without hydrotalcite, only benzaldehyde was obtained, but without Ti^{+4}-mont., no reaction occurred. This catalyst system gave a higher yield than the homogeneous catalysts such as *p*-toluenesulfonic acid and piperidine. The catalyst could be recovered and reused up to five times with good catalytic activity.

Condensation reactions are vital in nature and formation of biological compounds such as proteins, which are nothing but amino acids bound through peptide linkages, are formed through a simple condensation process and in other biochemical transformations. While only two types of carbonyl condensation reactions are discussed in this section, this process can be performed between large varieties of molecules to form myriad of products. The carbonyl condensation processes have the scope of synthesizing long-chain molecules through forging new C–C bonds.

8.4 Summary and Conclusions

This chapter presented existing, as well as novel processes for employing homogeneous in addition to heterogeneous catalysts in fine and specialty chemicals. From the 1800s when Faraday used platinum for oxidation, to the present methods of using transition metal complexes or mesoporous metal oxide catalysis, the catalysis has come a long way. Zeolite, hydrotalcite, and titanium silicate have found large-scale applications in the synthesis of fine and specialty chemicals through acid-base catalyzed reactions. Similarly, nickel, platinum, and vanadium have been employed for various chemical transformations.

It is evident that heterogeneous catalysts are employed in a multitude of reactions with high efficiency. Obvious reasons for the success of these catalysts are the ease of catalyst recovery, recyclability, ease of handling, high specificity towards desirable products, and variable structure which allows changes in the acidity or basicity of the structure.

Homogeneous catalysts allow a better space time yield compared to typical heterogeneous catalysts and reduces the cost of product generated per unit mass of catalyst. High selectivity offered by homogeneous catalysts also ensures reduction in waste, less downstream processing, and the effective use of feed stocks. For example, though metallocene catalysts are effective for polymerization, these have not replaced the Ziegler-Natta catalyst because the cost of catalyst per unit of product is significantly lower [1].

The shift towards renewable feed stocks and cleaner processes is pushing development towards processes generating minimal waste and requiring the least downstream processing. In this chapter, the role catalysis can play towards realizing goals of green chemistry is elucidated. Heterogeneous catalysts have a major role to play in achieving those goals because

of the ease of separation of catalysts. Enzymes are increasingly playing a significant role in the synthesis of fine and specialty chemicals (though these were not discussed in this chapter). A combination of enzymes supported on heterogeneous catalysts has also been explored.

Recent advances in process intensification and with the inherent effectiveness of continuous processing, there is an increasing trend towards developing continuous catalytic processes for fine and specialty chemicals. Separation processes like distillation and solvent extractions are amongst the most common continuous processes used in fine and specialty chemicals. However, continuous reactors are increasingly being used. Either multiple continuous stirred tank reactors or tubular continuous reactors are being used. More and more processes in fine and specialty chemicals manufacturing are being converted from batch (or semibatch) mode to continuous mode (see eg, conversion of batch process to continuous process is metformin hydrochloride production [132]). These are green methods for engineering and innovation, and are much needed in today's chemical industry [133].

In this chapter, we discussed the role of catalysts and their evolution over time for synthesis of various fine and specialty chemicals. While there are many aspects to be considered in a synthesis apart from the catalyst used such as reactor design and environment for the reaction, the scope of the chapter was limited to discussion about catalysts and their role in such synthesis. We hope that the information presented in this chapter along with the other complementary chapters in this book will stimulate further development of continuous and catalytic processes for manufacturing fine and specialty chemicals.

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CHAPTER 9

Ion Exchange Resin Catalyzed Reactions—An Overview

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9.1 Introduction

Catalysis, in a conventional sense, refers to accelerating rate of reaction using a substrate, known as catalyst, that reduces the activation energy level for the reaction to occur by providing a platform for reactants to react (adsorb + react, in heterogeneous catalysis); without the catalyst in itself, getting consumed in the whole process and without altering chemical equilibria/thermodynamics of the reaction. Chemical synthesis is an important area in all fields and is greatly facilitated by catalysis. It has been estimated that post-1980, more than 80% of the industrial processes in fine chemicals, the petrochemical industry, and the biochemical/pharmaceutical industry are using catalysis [1,2]. A large number of substances can be used as catalysts and classification can be very difficult at times for the combination of their properties eg, organic/inorganic; acids/bases; metals/organo-metallic; living (enzymes)/nonliving, and so on. It is evident that choice of catalyst for any reaction system is not simple. Homogeneous catalysis refers to the catalyst in the same phase (soluble), while heterogeneous catalysis refers to the catalyst in a different phase, typically the solid phase. Catalysis continuously strives to approach the most suitable form and activity of materials as the best possible option for carrying out chemical synthesis and therefore, catalyst activity, selectivity, life, recovery and recycle are the most predominant issues in this area. The techno-economic viability of the process is dependent on the parameters listed above and apart from that lower byproduct formation, minimizing the environmental impact have significant roles in further dictating overall sustainability of the process. In this regard, a newer area of green process or green chemistry essentially indicates direct or indirect involvement of newer catalytic systems that are more environmentally friendly.

The conventional route uses homogeneous catalysis mainly in the form of acids or bases. Even today, homogeneous catalysis is believed to be dominating the catalysis in industrial practice for a variety of reasons. Though the processes are well established, they suffer a major drawback with respect to ease of separation of the catalyst and therefore, recovery and

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reuse of the catalyst is a major concern apart from corrosion and pollution considerations. Essentially, to alleviate concerns pertaining to soluble catalysts, applications of solid catalysts have been developed. Hundreds of solid acids and base catalysts have been developed/researched in last 50 years [3], especially for their effectiveness (vis-a-vis soluble catalysts), activity, selectivity, separation, economics, and process operations such as liquid and vapor phase reactions. The modern day instrumentation and characterization facilities have also helped in evolving newer materials and understanding surface behavior for these solid catalysts. The important features, materials and advantages and disadvantages of different forms of catalysis are summarized in Table 9.1. The main disadvantages in using acid homogeneous catalyst are corrosion and difficulty in the separation of catalyst. In this regard, it is obvious that materials that provide similar acidic/basic properties useful for carrying out reactions with ease of separation would, in principle, clearly substitute the existing homogeneous catalysts. To impart acidic or basic properties to any solid material for use as a catalyst, usually the solid material can itself be acidic or basic in nature, such as ion exchange resins or an appropriate solid base can be used to immobilize the active catalyst component that can even be a biological species such as an enzyme. In such supported materials, the bonding with the active species can be very different ranging from covalent bonding to noncovalent bonding and the interactions of catalyst species are predominantly due to the ionic nature and electrostatic interactions for chemical materials. It is also important to note that the performance of such catalysts strongly depends on the nature of immobilizing species, the density of the immobilization, the number of active sites, and on the nature of the material on which immobilization takes place. The method of immobilization is important in this respect as it affects the majority of the factors mentioned as above. The nature of immobilization and procedures are significantly different in biological catalysts that deal largely with the biologically active microorganisms. Though, a number of heterogeneous catalysts such as acid clays, zeolites, solid acid catalysts-supported heteropoly acids, ion exchange resins, etc., can be used, the exact comparison in terms of activity, reaction performance, regeneration/deactivation, and cost is not always possible for the same reaction due to lack of experimental data and literature. Further, generalization in this regard is again difficult as one catalyst may have better activity than others for a specific reaction only. For example, synthesis of dimethyl ether by dehydration reaction of methanol can be carried out using solid acid catalysts such as γ-alumina, zeolites, and ion exchange resins. Comparison of different types of homogeneous and heterogeneous catalysts for the rarely reported synthesis of polyoxymethylene dimethyl ethers has been recently given by Wang et al. [4] in which sulfuric acid, *p*-toluenesulfonic acid, Y-zeolite, ZSM-5, different types of ion exchange resins (eg, Amberlyst 15) were screened for their catalytic activity and selectivity. Interestingly, the study here found the ion exchange resin catalyst to be most effective both in terms of conversion and selectivity. In fact, for reactions such as etherification of phenols/naphthols with isobutylene/isoamylene, resin catalysts can allow the reaction to occur, but the homogeneous catalysts have limitations or fail [5]. In one analysis, it was reported that out of total industrial processes that employ solid acid-base catalysts, close to 45% processes employ zeolites, followed by ∼30% oxides as catalysts.

Industrial processes that employ ion exchange resins as catalyst comprise nearly 10–15% of the total [3]. In this regard, it is still a developing stage for ion exchange resins as catalysts. In view of the lack of theoretical guidelines in selection, it is recommended that the necessary information may be best obtained through experimentation and the proper choice of catalyst is critical for techno-economic feasibility of the process.

Table 9.1 Comparison of catalysts

		Heterogeneous Catalyst	
	Homogeneous (Soluble)	**Ion Exchange Resin**	**Other Solid catalyst (Acids/Bases)**
Examples	Sulfuric acid, hydrochloric acid, *p*-toluene sulfonic acid, acetic acid	Cation resins Anion resins	γ-Alumina, immobilized catalyst precursor on materials such as silica, clays, zeolites, metal oxides, heteropolyacids, heteropolyacid supported on carbon, supported titanates
Thermal stability	Allows high temperature	Limited Cation resin up to 120°C Anion resin up to 60°C	Limited to high
Chemical stability	Good	Limited to good	Limited to good
Separation	Difficult	Easy	Easy
Corrosiveness	Corrosion problems	No/less corrosion problems	No/less corrosion problems
Design	Simple/easy	Simple/easy	Simple/easy
Safety	Relatively unsafe handling	Can be safely handled	Can be safely handled
New development	Limited	Many new developments	Many new developments
Reaction/selectivity	Limited	• Permits reactions not possible with aqueous acid/base • At times, selectivity can be high, not possible with aq. acid/bases • Many times reduces/eliminates side reactions	• Permits reactions not possible with aqueous acid/base • At times, selectivity can be high, not possible with aq. acid/bases • Many times reduces/eliminates side reactions
Cost/life	Lower cost (low initial cost)	Lower cost-long life (high initial cost)	Lower cost-long life (high initial cost)
Use	Once used	Repeated use	Repeated use
Waste disposal	Waste disposal problems	Less/no problems	Less/no problems

9.2 Ion Exchange Resins as Catalyst

Ion exchange catalysts have acidic or basic groups that can facilitate acid/base catalyzed reactions by providing acidic or basic sites in a solid heterogeneous medium resulting in easy separation of the catalyst apart from other benefits. The commercial ion exchange resins are functional polymers and are classified as strong acid resin, weak acid resin, strong base resins, and weak base resins—the nature and attributes of these functional groups are well discussed in many literature reports [6,7]. Fig. 9.1 schematically shows the internal pore distribution in the resin bead for a typical non-isoporous resin. It contains a fraction of macropores that are main channels for the faster diffusion of reacting species and colonies of micropores that house a major portion of ion exchange sites responsible for high capacity in terms of mmol/g of resin. The resin can be entirely macroporous as one limiting case, and then consequently have a relatively low surface area and capacity compared to entirely microporous resin as in another limiting case that can have large capacity, but lowered rates. Most resins belong to intermediate cases containing both macropores and micropores and its distribution is crucial to the functioning and effectiveness of the resin for any specific reaction. Fig. 9.2 shows resin functionality associated with different types of resins. From a practical point of view, strongly acidic cation and strong base anion resins are mostly useful as catalysts while all types of resins are useful for different kinds of separation or purification applications. The strong acid resins have a mainly sulfonic acid group and perform in the same way as that of homogeneous sulfuric acid catalyst through the dissociation of acid; H^+ species. The weak acid resins have carboxylic acid that is weakly dissociating and again resembles weak acid in its action. The strong acid resins are commonly used in reactions like esterifications and in alkylations. The strong base resins can have a hydroxyl group similar to homogeneous bases and weak base resins have amine functionality with nitrogen having a lone pair of electrons acting as a free base group. Here again, too, strong base resins behave in a similar manner to that of a soluble strong base like NaOH and use of these has been reported for reactions like ester hydrolysis or in condensation reaction. Some important industrial processes that employ ion exchange resins as catalyst include the production of solvents such as methyl tert-butyl ether (MTBE), production of alcohols such as sec- and tert-butanol, isopropanol, production of esters such as methyl acetate, sec-butyl acetate, isopropyl esters, manufacture of ketones such as methyl isobutyl ketone (MIBK), and alkyl phenols, etc.

It is difficult to exactly define the acidity or basicity strength of ion exchange resin catalyst similar to their counterpart-strong/weak acid or base in solutions and catalytic activity is most commonly correlated with acid strength. It is a more complex issue for the solid catalysts in general and ion exchange resins, in particular, due to issues pertaining to availability and ability to provide ions. For ion exchange resins, capacity is given commonly in terms of the number of exchange sites per unit weight of dry resin (mmol/g). However, for a particular reaction, it is possible that not all sites are available for catalysis due to various reasons and

defining/comparing activity of resin catalyst can be misleading. Similar to a homogeneous acid/base catalyst, pK_a or pK_b values for solid ion exchange resins can also be used to grade resins as strong/medium/weak acidity/basicity, but are rather incomplete definitions [8,9]. The Hammett acidity function for homogeneous acids relates to pK_a values and is easier to understand or use for defining acidity scale. Here, stronger Hammett numbers relate to stronger acid character. However, these are not commonly used with ion exchange resin catalysts due to the difficulties in measurements and issues pertaining to complexities of solid catalysts.

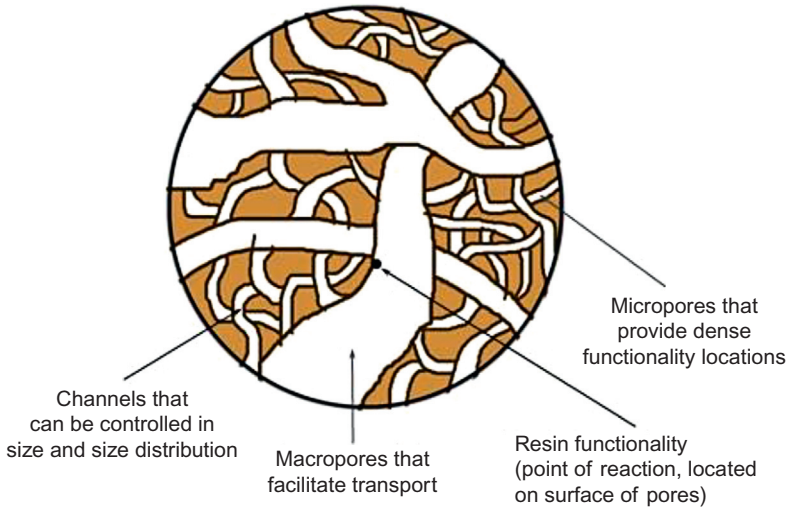


Fig. 9.1
Schematic representation of porous resin bead.

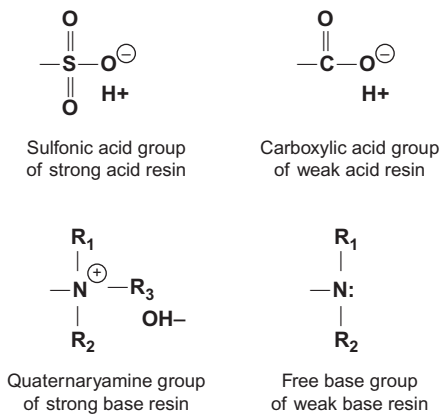


Fig. 9.2
Functionality in ion exchange resins.

A number of commercial resins such as Amberlyst ion exchange catalysts for alkylation, condensation, esterification, etherification, hydration, and hydrogenation reactions; Dowex resins; Nafion, Indion catalyst-grade resins [10–12]; have been available and many of them claim to offer high catalytic activity, long life, low pressure drop in fixed bed reactor operations, good stability, and operability under aqueous/nonaqueous conditions. The scan of various ion exchange resin catalysts reveals more common use of resins such as Dowex 50, Amberlyst 15, Nafion H, Amberlite IR-120, Indion 130, Amberlyst 35, apart from specific class of Dowex, Diaion, Lewatit, Nafion, etc. An excellent specific review of literature on cation resins as catalyst in 1990s is given by Chakrabarti and Sharma [13] with a listing of many cation resin catalyzed reaction studies and resins employed. Broader reviews try to provide information on reactions and industrial processes employing solid acid-base catalysts, including ion exchange resins by Tanabe and Holderich [3]; progress on catalytic technology in Japan [14]; catalytic processes developed in Europe in 1980s [15] and commercialized catalytic technologies in the United States [16]. An interesting aspect of ion exchange resins as catalyst is that because of their ionic nature, catalyst modification is also possible by replacing the ion with another suitable ionic species or metal ions, etc., although typically strong sulfonic acid resins in H^+ form are used to resemble homogeneous strong acids. It is also possible to combine or sequentially carry out more than one reaction step in a controlled manner. For example, preparation of 5-hydroxymethylfurfural from sucrose has been reported in a sequence of four steps: hydrolysis, dehydration, glucose/fructose isomerization, and dehydration using cation and anion exchange resins [17].

9.2.1 Differentiating Ion Exchange Resin Catalyst from Homogeneous Catalyst

It has been observed many a times that reaction rates are faster with a homogeneous catalyst like sulfuric acid as compared to a heterogeneous catalyst like ion exchange resin. Also, that homogeneous catalysts can be well mixed in the reaction medium as against slurry type of mixing or fixed bed/fluidized bed operation with ion exchange resins. Thus, it is the "soluble catalyst" versus "insoluble catalyst" that makes the difference. The resins as catalyst behave differently than corresponding homogeneous acids in spite of having similar acidity/activity due to their basic difference in terms of the physical form and the number and format of acidic sites made available for the reaction to take place. This difference also highlights the importance of the physical size of resins in commercial operations and reactor configuration. As a consequence, differences have been observed in terms of rates, selectivity, effectiveness, catalyst separation, side product formations, reactor operation, product separation, pollution issues and therefore overall productivity, and cost effectiveness. Also, it is possible to have "tailor-made" ion exchange resin catalysts for any specific reaction, practically impossible with homogeneous catalysts.

Commercially, the ion exchange resins are available as spherical resin beads and are highly porous. The porous nature of the resin is highly important in its capacity as catalyst and it directly affects the rate of overall catalytic process. In general, the overall rates are determined by the individual rates of diffusion in the pores of the resin particle and rate of chemical reaction. The theoretical aspects of catalysis are still not very clear and hence there is difficulty in describing the mechanism in many reactions. However, diffusion and reaction dictate the process and most of the ion exchange catalysis revolves around solving these issues for better conversion, selectivity, and high rates.

It is quite convenient to modify the rates of the ion exchange process through material modification to facilitate diffusion of the reacting species. Apart from this, ion exchange resin selectivity is also affected due to pore size and size distribution, mainly through steric hindrance and accessibility to the ionic sites. In this respect, the resin catalyst can be classified on the basis of its pore structure as (Table 9.2):

Microporous (pore size less than 2 nm)
Macroporous (pore size above 50 nm)
Mesoporous (pore size in the range of 2–50 nm)
Isoporous (uniform or same pore size)

Typically, the micropores provide a high surface area that is required for the reaction, whereas, macroporous resins have a comparatively much smaller surface area. The resins are characterized therefore in terms of contribution of micropores/macropores and surface area. Usually a combination of macropore and micropore is preferred to obtain benefits of both higher rates of diffusion through the macropore and high surface area and density of catalytic sites in micropores. In such situations, both swelling and mass transfer phenomena are important from the point of view of modeling the reaction and catalyst performance; there could be differences in swelling due to solvent type and high microporous area, not necessarily implying high catalytic activity [18]. Van de Steene et al. [19] have observed the strong effect of resin swelling on resin sites accessibility and catalytic activity in transesterification of ethyl acetate with methanol to ethanol using gel and macroporous resins; gel resins outperforming macroporous resins. Nunan et al. [20] have suggested change in the efficiency of catalytic sites through swelling of resin by polar solvents with reference to Nafion H ion exchange resin catalyst. Panneman and Beenackers [21] have studied MTBE synthesis using various macroporous strong acid resins and indicated strong differences in catalytic activity in these resins. They also reported lack of data on intraparticle diffusivities in ion exchange resins. For ion exchange resins, the degree of crosslinking controls the pore size and, therefore the rates of diffusion, and this is an important parameter in the selection of resin of the same polymeric backbone.

Table 9.2 Differences in gel and macroporous resins as catalyst

Gel Resins as Catalyst	Macroporous Resins as Catalyst
Resembles mostly rigid transparent beads	Opaque beads
Resembles homogeneous structure	Resembles heterogeneous structure
Usually DVB content is low (poor catalyst, if high crosslinking)	High DVB content is possible
Swelling is important—solvent effect	Swelling is not important; effective in both swelling and nonswelling solvents
Can collapse, if dry—no catalyst activity	No such limitation
Microporous	Micropore areas embedded in macroporous bead
High surface area	Relatively low surface area
Poor resistance to attrition	Excellent resistance to various types of attrition
Poor resistance towards oxidants	Less sensitive to oxidants
Limited application in catalysis due to limitations of swelling, kinetics, mass transfer, etc.	Wide applications in catalysis, high rates
	Allows ion exchange catalysis in aqueous, nonaqueous, nonpolar solvents, and such reactants

The polymeric backbone and functionality are the two important parameters for the ion exchange resin catalysts. In recent years, the use of styrene-divinylbenzene resins is more common (divinylbenzene (DVB) is the crosslinking agent). However, the resin backbone can be of any other polymer such as phenol-formaldehyde, polyacrylic, and so on. Specialized and expensive forms, such as perfluorinated sulfonic acid ion exchange resins, are also available that are considered superacids and have terminal $–CF_2CF_2SO_3H$ group. The perfluorinated polymers exhibit high acidity, better thermal and chemical stability and the high acid strength is comparable to the strength of 100% sulfuric acid [22–24]. The degree of crosslinking can be anywhere from 2% to 20%, however most commercial resins have a degree of crosslinking, typically between 8% and 12%. The lesser degree of crosslinking naturally favors a loose framework of the resin matrix, providing gel-type properties or swelling properties. The swelling behavior again impacts the ion exchange catalyst performance and can be advantageous in certain cases. Swelling of the resins for modified resins in the solvent has been studied in detail and very high increments upon decreasing the crosslinking percentage (up to 0.5% DVB) were reported [25]. However, it is essential to understand here that such gel-type resins require a suitable medium/solvent for swelling to take place or else their catalytic activity would be drastically limited or even negligible in the absence of swelling. Casas et al. [26] have reported high selectivity for symmetrical linear ethers on microporous resins for the dehydration reaction of 1-octanol, 1-hexanol, and 1-pentanol, and have suggested swelling as a key factor for higher selectivity. The impact of swelling can be limited or even completely eliminated by increasing degree of crosslinking as in the case of macroporous resins. Thus, macroporous resins can be suitable with both, swelling or nonswelling solvents. The importance of solid polymeric backbone and functionality can be easily understood from the fact that many times, reactions or selectivity can be so different with these resins, it is practically not possible that with using homogeneous

acids/bases—something that can be attributed to the combination of both physical and chemical effects is possible only with such resins/catalysts. Many times, selectivity in resin catalyzed reactions cannot be explained on the basis of resin pore structure and molecular sizes alone. The reasons for such marked differences and selectivity are still not very clear. An interesting viewpoint with respect to selectivity of ion exchange resin catalyst is that it is said to lie halfway between nonselective soluble catalysts and extremely selective enzyme catalysts [13]. Though exact prediction of this type is difficult, it is nonetheless the driving force for developing newer resins with very high selectivity approaching the highest limits.

The most important aspect of catalysis-active catalyst precursor is attached to the polymeric backbone. In ion exchange catalysts, it is the ionic group or functional group providing acidic/basic sites that is attached to the polymeric backbone as described above, depending on the type of resin. The commercial resins are thermally and chemically stable for the ranges specified and also have mechanical stability along with good life for the catalyst. The acid resins can be employed up to 120°C while the base resins have comparatively lower thermal stability and can be used only up to 50–60°C for all practical purposes without significant loss in activity. Cation exchange resins tend to lose capacity due to degradation in the form of desulfonation and loss of activity if exposed to higher temperatures for prolonged periods. Nafion resins can withstand higher temperatures, up to 200°C. Though newer materials are being researched that can withstand high temperatures, the limit to maximum operating temperature can be a major disadvantage for the use of ion exchange resins as catalyst at present.

9.3 Heat Transfer, Mass Transfer, and Reaction Rates in Resin Catalysts

As is the case with heterogeneous catalytic process, the following steps occur for the catalytic reaction:

1. Bulk diffusion of reacting species to catalyst surface
2. Film diffusion-film surrounding the ion exchange catalyst bead
3. Pore diffusion of the reacting species to the ionic catalytic sites
4. Adsorption and reaction on the surface of ion exchange resin catalyst
5. Pore diffusion of the reaction products, followed by film diffusion and bulk diffusion

The reactant species have to migrate to reacting sites on the resin (catalytic sites) for reaction to occur. Thus, diffusion of the reactants is one major difference between the catalysis using soluble catalyst and catalysis using ion exchange resin catalysts. In fact, there has been substantial evidence suggesting similar chemical reaction kinetics and reaction mechanism in both. In ion exchange separations where the role of resin is to exchange ions to effect separation; ion exchange being instantaneous, the overall rate is invariably controlled by pore diffusion of the diffusing species. However, for ion exchange resin catalysts, since the

chemical reaction rates are similar to homogeneous reaction and definite, a proper accounting of different rates is inevitable. Though ideally one is required to incorporate all the steps contributing to overall rate, a simplified mechanism often helps, and assuming that film diffusion has negligible contribution, the following different scenario can possibly exist:

1. Chemical reaction much slower than the pore diffusion
2. Pore diffusion much slower than the chemical reaction
3. Both pore diffusion and chemical reaction rates are comparable

In the first limiting case, the overall rate is controlled by the chemical reaction, while in the second case, it is the pore diffusion which is controlling. In the third case where both the mechanisms have significant or recognizable contribution, the overall rate must consider contribution of both the reaction as well as diffusion and a simplified form of rate controlling model does not apply. In practice, the overall rate is affected by both pore diffusion and chemical reaction. This aspect is further complicated by the fact that the two rates differ in terms of their temperature dependence. The increase in the rate of diffusion with the increase in temperature is believed to be less as compared to the rate of chemical reaction. These differences could be location-specific and reaction-specific, and therefore difficult to generalize. Such understanding, however, is very important in process configurations like reactive distillation. It is also possible to manipulate the rates through selection of smaller particle size. As a limiting case, catalyst in fine powder form will have a chemical reaction dominating the overall rate, moving into reaction rate controlled zone [27]. The use of fine particle size, however, will create problems handling of the catalyst, in separation of the catalyst and may clog the reactor. These aspects, however, require careful considerations from a specific reaction point of view.

Rehfinger and Hoffmann [28] have examined macropore diffusion in the MTBE synthesis using methanol and isobutylene and have suggested it as a typical example of intraparticle diffusion controlling. They also proposed application of the Shell-Core model for describing the process since the rate of reaction is considered to be very high. Sawarkar et al. [29] have also proposed shrinking the core mechanism for alkylation of phenylacetonitrile with alkyl halide in the presence of aqueous sodium hydroxide and strong base resins in OH^- form (Dowex SBR and Dowex MSA-1). A comparison of microporous and macroporous resins indicated pore diffusion controlled mechanism. Such tri-phase catalysis can be complex, requiring alternate contact of organic and aqueous phases with resin sites. It was also suggested that lower diffusion rates may be expected in view of tri-phase catalysis requiring coexistence of two liquid phases in the pores of the catalyst. Panneman and Beenackers [30] have studied liquid phase hydration of cyclohexene catalyzed by strong acid ion exchange resin Amberlite XE 307 (macroporous) using solvent mixtures of water and sulfone and indicated difficulty in finding a suitable co-solvent for miscibility in two liquid phases and consequently, a significant effect on reaction rates/activity of resin. Recently, Silva and Rodrigues [2] have

studied the mechanism of mass transfer in ion exchange resin catalyzed reaction and have suggested that mass transfer is mainly macropore diffusion controlled and resistance in the gel microspheres is negligible for bidisperse pore structure catalyst.

One more important aspect from a reaction point of view is the environment for the reaction. The effect of solvent, mentioned earlier in connection with swelling of the resin, is more critical from a reaction point of view. There can be completely aqueous environment, mix of aqueous and organic solvent (eg, water-acetone mixture) or complete organic (nonaqueous) environment. The rates are drastically altered by the nature of environment for a variety of chemical reactions [22]. While it can be expected that in a complete aqueous environment the reaction progress would be similar to that in dissolved homogeneous catalysts, it would be difficult to predict reaction mechanism and progress in mixed solvent scenario. Thus, apart from resin type and parameters discussed above, the proper choice of reaction conditions in terms of solvent/environment is also very important in ion exchange catalysis.

Based on the above discussion, one can mathematically model the ion exchange resin catalyzed reactions using different forms and more commonly using the concept from a homogeneous model, pseudo-homogeneous model or complex heterogeneous model, involving different assumptions. Pseudo-homogeneous model, as the name suggests, assumes a reaction mechanism similar to that in a homogeneous catalyst, while the difference between the two catalysts is mostly attributed to the sorption on resin phase. A more suitable approach is believed to consider ion exchange resin-based catalysis in the form of adsorption-reaction, and using the Langmuir-Hinshelwood or Rideal-Eley mechanism. The L-H model assumes adsorption of all the reactants that are rate determining and reaction, while the Rideal-Eley mechanism assumes reaction between one reactant in fluid phase with those adsorbed. These models have been used extensively to explain various ion exchange resin catalyzed reactions and for a wide range of concentrations [2,19,20,27,31–46].

Though the information on ion exchange resin as catalyst and resin catalyzed reactions has been widely discussed in the literature, the present day understanding of the fundamental issues pertaining to the catalytic activity and characteristics of resin are still far from clear. This is evident from the fact that compared to zeolites and other solid catalysts, applications of ion exchange resin catalysts are limited for industrial applications. Also, the majority of the studies can be seen as an attempt to explore various types of resins for specific reaction and an effort to correlate the results with resin type/acidity/basicity or pore structure, etc., rather than providing understanding that would help in a priori selection of the resin for any reaction type. Also, due to the difficulty in preparation of ion exchange resins that is science and art both, most of the research work employs commercial resins for the studies and therefore lacks development in terms of resins modification. The mathematical modeling of the reaction and reactors also lack generality in terms of application. It is required that models be developed to incorporate fundamental understanding of reaction and materials chemistry,

reaction kinetics, and transport issues. These limitations have to be overcome in the future to clearly bring out essential features of ion exchange resin catalyst that are required for specific reactions so as to facilitate an increased number of applications in the real world.

9.4 Ion Exchange Resin Catalyzed Chemical Reactions

The concept of ion exchange resins as a functional polymer having acidic or basic character that represents solid acid or base has been widely exploited in various types of reactions such as esterification, hydrolysis, condensation, dehydration, carbonylation, and hydrogenation, etc. Different types of resins are available as commercial catalysts that differ in polymer matrix, functional groups and subsequently, in final reaction behavior dictating catalyst activity and selectivity. For some reactions, the presence of water/aqueous environment is useful, while for organic reactions, even water of resin may have to be completely removed by using anhydrous alcohol. Sometimes, there are issues such as the presence of impurities, activity loss due to temperature effects, drying of gel resins for prolonged periods, or OH form of resins primarily due to reaction of atmospheric carbon dioxide and therefore, such resins require proper care/handling or pretreatment. Thus, the basic issues pertaining to ion exchange catalysis include:

A. Nature and type of resin
B. Porous nature/polymeric backbone and suitability for the reaction under consideration
C. Overall productivity for the reaction-activity and selectivity
D. Catalyst reuse and number of cycles/life
E. Cost of the catalyst/resin
F. Reactor type/reactor operation/ease of operation

Although there have been established materials and methods for ion exchanger solids such as ion exchanged zeolites that are used for catalysis, the present discussion is largely restricted to polymeric ion exchange resins that can be used as solid catalysts.

Chemical reactions using ion exchange catalysis mainly involve the types given in Table 9.3.

Table 9.3 Examples of ion exchange resin catalyzed reactions

Cation Resin Catalyzed Reactions	Anion Resin Catalyzed Reactions
Esterification	Esterification
Hydrolysis	Hydrolysis
Condensation	Condensation
Dehydration	Hydration
Hydrogenation	Dehalogenation
Cyclization	Cyclization
Carbonylation	Acylation
Amidation	

There have been numerous reports and reviews well in place which enlist most of the work on the above reactions [3,13,23,47,48]. More recently, Barbaro and Liguori [49] have reviewed specifically ion exchange resin/resin supported catalysts. Some reactions can be catalyzed by both types of resins-acid or base resin catalysts, making the choice of resin not as straightforward as in conventional ion exchange resin catalysis. A complete state-of-the art review is beyond the scope of the presentation here. Hence, only important and the most relevant aspects are discussed that identify and evaluate the essence of the processes involving ion exchange resins as catalyst.

9.4.1 Esterification Reactions

Esterification (direct or transesterification) is an important class of reactions in the preparation of perfumery, flavors, pharmaceuticals, plasticizers, solvents, and intermediates. It is probably one of the most researched areas in ion exchange resin catalysis.

The esterification reaction for the preparation of methyl acetate using acetic acid and methanol is given below. The reaction can be liquid phase reaction using homogeneous (eg, sulfuric acid) or heterogeneous catalysts (eg, cation exchange resins).

$$CH_3COOH + CH_3OH \leftrightarrow CH_3COOCH_3 + H_2O$$

Alcohols can react reversibly with many acids to form esters and these processes are known as esterification reactions used widely in industry for a variety of products. The reactions are typically acid catalyzed with sulfuric acid as homogeneous catalyst. The application of solid acidic and super-acidic catalysts can prove to be very effective from the viewpoint of activity, selectivity, reusability, ester contamination, waste/effluent problems, and economy in the manufacture of esters [48,50]. The ion exchange resins that can be used as a heterogeneous catalyst mainly include strong acid resins such as Amberlyst 15 [13,51–56]. Phalak et al. [55] reported comparison of three different ion exchange resin catalysts for esterification reaction of methanol and acetic acid—Amberlyst 15, Dowex 50W (macroporous), and Amberlite IR-120 (gel type) and have found significant differences with different resin catalysts, not just in gel and macroporous resins, but also in macroporous catalysts. Giménez et al. [34] have studied vapor phase esterification reaction of acetic acid and ethanol and have also reported differences among the macroporous resins that were attributed to differences in structural characteristics. Influence of resin catalysts (Purolite CT 269, Amberlyst 46 and 48) on side reactions of the esterification of *n*-butanol with acetic acid has been discussed [57]. Comparison of reaction behavior for two different ion exchange resins for the esterification reaction of acetic acid and isobutanol was given by Izci and Bodur [36]. Van de Steene et al. [19] have reported ion exchange resin (gel and macroporous) catalyzed transesterification of ethyl acetate with methanol to ethanol and have suggested resin swelling dictating accessibility to active sites and hence,

catalytic activity to explain the differences in rates in these resins. The rates of reaction depend on the type of acid, alcohol, and type of catalyst employed. For homogeneous catalyst, batch, or continuous operations can be employed, finally requiring acid to be neutralized, while in the case of ion exchange resins as catalyst, fixed bed column operations are commonly employed with substantial ease of operation and separation of the reaction species. For esterification reactions, if the reaction is accompanied by side reactions, there could be distinct advantage to using a heterogeneous catalyst such as ion exchange resin to suppress undesirable side reactions [51,52].

A very large number of reactions have been studied using ion exchange resin catalysts such as Amberlyst 15, Nafion H, Indion 130, and so on. Nafion-based materials were generally considered superior to other resin catalysts in view of high acidity [48]. However, in view of solvents often being polar, higher activity can still be observed with both types of resin catalysts for reactive substrates. In cases where reactants have low activity, it may be possible to enhance conversion levels through the use of ion exchange resin catalysts having high acidity such as Nafion resin.

Another important application in today's context is biodiesel production which is typically carried out using homogeneous catalysts and has great potential for using solid acid catalysts. Transesterification of vegetable oils involves reaction of triglyceride with alcohol in the presence of acid or base catalyst (homogeneous or heterogeneous). Ion exchange resins—basic and acidic have been used as catalysts for the synthesis of biodiesel from soybean oil and methanol. A strongly basic macroporous resin is considered to be a most suitable active catalyst and it was possible to reach 100% selectivity to methyl esters. Some laboratory synthesized resins were also reported to be effective in this regard [58]. The use of commercial ion exchange resins was also reported in transesterification of triolein for biodiesel production from triolein where Amberlyst 15 was found to be highly effective [59]. Shibasaki-Kitakawa et al. [60] have reported use of different ion exchange resin catalysts—both anion and cation exchange resins and have found better activity with anion exchange resins. Co et al. [61] reported continuous packed column reactor studies on transesterification of coconut oil using anion exchange resin and found strong mass transfer/pore diffusion effect. Esterification of fatty acids has been reported by Jeřábek et al. [62] in an attempt to understand differences in gel and macroporous resin catalysts. With reference to biodiesel production, another aspect has been studied for the acetylation of glycerol that is formed in the process, using different ion exchange resin catalysts [63]. The esterification of glycerol with acetic acid is expected to result into products that can be used as bio-fuels or as raw materials for the production of biodegradable polyesters. Various solid acid catalysts including ion exchange resins for biodiesel production have been reviewed by Sharma and co-workers [64].

Reactive distillation has increasingly gained importance in esterification and hydrolysis reactions where ion exchange catalyst is used for carrying out the reaction and distillation to separate

the product and drive the reaction in the forward direction. Production of esters by reactive distillation using surface-sulfonated resin catalysts has been recommended by Blagov et al. [57]. The synthesis of methyl acetate as discussed above is a classic example for reactive distillation [45,65,66]. Kinetically controlled reactive distillation requires knowledge of chemical kinetics that is usually lacking for different resins. Experimental data needs to be obtained by decoupling the reaction and adsorption processes. For reactive distillation at boiling temperatures of liquid, there is significant effect of pressure on reaction and product composition.

9.4.2 Etherification Reactions

A well-known and industrially practiced reaction includes reaction of methanol and isobutylene to give product MTBE, a solvent and extensively used in fuels. The catalyst system can be a strongly acidic ion exchange resin having sulfonic acid groups, preferably styrene-DVB matrix and a number of research publications have reported on various aspects of resin catalysis such as resin type, acidity, reaction kinetics and mass transfer, reactant ratio, effect of temperature, and so on [28,33,67,68]. It has been found that macroporous sulfonic acid ion exchange resins as catalysts are most suitable for MTBE synthesis. While the conventional processes face problems due to equilibrium conversion and can have conversion up to 90–95%, the newer development in terms of reactive distillation can allow isobutylene conversions up to 99% due to efficient removal of MTBE product immediately after its forming and thus driving the reaction to near complete conversion. MTBE production process has been reported for liquid phase reaction involving macroporous cation exchange resin catalysts such as Amberlyst 15, Dowex M32, etc. and that differences in process performance in terms of conversion, kinetics, and mass transfer are evident from these studies, eg, some ion exchange resin catalysts giving higher conversion, and so on [21]. A pseudo-homogeneous model was considered using first-order reversible reaction kinetics in isobutene and MTBE; the mechanism believed to incorporate protonation of olefin by methanol solvated protons followed by reaction of carbonium ion with methanol. Parra et al. [67] have reported liquid phase synthesis of MTBE using 12 different styrene-DVB resin catalysts and have suggested acidity of the resin (acidic capacity) to be the most important factor and less influence of other parameters such as surface area and porosity of resin. The terminology, however, had less clarity due to the attempt in correlating greater density of sulfonic groups to catalytic activity, though logical, difficult to quantify in clear terms.

Similar to MTBE, ethanol and isobutylene can be reacted to give ethyl tert-butyl ether (ETBE). It was reported that acidity of resins is an important factor in these reactions and differences in the reaction rates with different resins were attributed to this factor. The reaction of methanol and ethanol with mixed olefin streams using Amberlyst 15 as catalyst has been discussed by Zhang et al. [69], along with a listing of different ethers and iso-olefins. The industrial streams that normally contain substantial amounts of other inert species can retard the

etherification reactions, and such effects need to be considered for industrial applications while utilizing individual reaction data from research. The effectiveness of different gel and macroporous ion exchange resin catalysts for liquid phase etherification of two alcohols—ethanol and tert-butyl alcohol for ETBE synthesis—has also been reported [70]. The side reactions and formation of other byproducts in resin catalyzed ETBE synthesis have been studied by Badia et al. [71] and have found dimerization of isobutene as the most relevant side reaction. Dimerization of isobutene in the presence of seven different ion exchange resin catalysts was reported by Honkela et al. [72].

Synthesis of tert-amyl methyl ether (TAME) using different ion exchange bead catalysts and also fibrous ion exchange catalyst (SMOPEX-101) was reported by Pääkkönen and Krause [43]. It was indicated that the kinetics here followed a single-site mechanism for isomerization and a dual-site mechanism for the etherification reaction. Effect of hydrogen ion exchange capacity on the activity of resin in TAME synthesis was also reported by [73], indicating possible strong influence of diffusion resistance on the reaction rate.

Chakrabarti and Sharma [52] have successfully used Amberlyst 15 catalyst for etherification of α-methylstyrene. Recently, the influence of resin catalysts, *p*-toluenesulfonic acid and zeolites was discussed for the etherification of glycerol and ethylene glycol by isobutylene [38]. The authors have found that initial rates of etherification are in good agreement with the catalyst acidity for both the catalyst groups, and also that solvent polarity effect was crucial. Simultaneous hydration and etherification of isoamylene using Amberlyst 15 and Amberlyst 35 has been reported by [37]. Etherification of 1-octanol with ethanol in synthesis of ethyl octyl ether has been reported using 22 cation exchange resins as catalyst in an attempt to understand influence of resin morphology [74].

The etherification of olefins with alcohols represents one of the largest volume applications in the area of ion exchange resin catalysis [48].

9.4.3 Some Other Important Reactions Using Ion Exchange Catalyst

9.4.3.1 Hydrolysis

Hydrolysis represents a class of chemical reactions where substrate modification (addition) takes place due to water. Hydrolysis reactions are typically acid or base catalyzed, again the conventional process utilizes homogeneous acid/base for the reaction. Some hydrolysis reactions can be catalyzed by both types of resins—acid or base resin catalysts. The common hydrolysis reactions include: hydrolysis of esters to yield alcohols and carboxylic acid, hydrolysis of amides resulting in ammonia or amine, etc. The reactions are reversible and are characterized by very slow reaction rates in the absence of catalyst. Even with an ion exchange catalyst, the rates are altered considerably by the degree of crosslinking/porosity of the resin.

An important example in hydrolysis is an ion exchanged catalyzed reaction, such as hydrolysis of methyl acetate or ethyl acetate to products as methanol and acetic acid; and ethanol and acetic acid, respectively. Hydrolysis of methyl acetate (MeOAc) to acetic acid and methanol is important as methyl acetate is produced in large quantities as a byproduct during the synthesis of polyvinyl alcohol and pure terephthalic acid.

9.4.3.2 Carbonylation reactions

Carbonylation reactions that involve modification of organic/inorganic substrate with carbon monoxide form a very important class of organic reactions for which a variety of catalysts are commonly employed. It is a well-established industrial process for the production of carboxylic acids, aldehydes, esters, etc. (eg, converting methanol to acetic acid, acetylene to acrylic acid).

One important example of ion exchange catalysis in this class is carbonylation of formaldehyde to glycolic acid which after further esterification to methyl glycolate, followed by catalytic hydrogenation, yields ethylene glycol. The conventional route to ethylene glycol involves partial oxidation of ethylene to ethylene oxide, followed by hydration to ethylene glycol. While a number of synthesis routes have been explored for this reaction, such as high pressure reaction via glycolate involving sulfuric acid as a homogeneous catalyst, the application of solid acid catalyst here eliminates the requirement of high temperature/pressures and corrosion problems, apart from environmental pollution issues. Application of strong acid resin with complete formaldehyde conversion and increased yield above 80% has been reported [75]. The effect of solvent has been very significant in these reactions and selectivity is drastically affected with the use of different solvents and in the presence of water.

9.4.3.3 Hydrogenation reactions

The addition of hydrogen to C=C or C=O bond is an excellent tool for a variety of industrial reactions in pharmaceuticals, agrochemicals, fine chemicals, and so on. Ion exchange resins have to compete with many other established homogeneous and heterogeneous catalysts, such as transition metal catalysts.

9.4.3.4 Dehydration reactions

Dehydration of 1,4-butanediol to tetrahydrofuran (THF) using strong acid cation exchange resin has been reported by Vaidya et al. [46]. This reaction is an important step in the manufacture of THF, in the processes starting from acetylene and maleic anhydride and the dehydration step can be accomplished using a variety of homogeneous and heterogeneous catalysts such as mineral acids, alumina, silica gel, and ion exchange resins. There was significant effect of solvent, as discussed earlier and the lower activity with polar solvents like water and ethanol was attributed to competitive adsorption of –OH of these solvents with –OH groups of 1,4-butanediol.

In an attempt to upgrade the quality of diesel through the addition of linear ethers containing more than nine carbons, liquid phase dehydration of different alcohols such as 1-octanol, 1-hexanol, and 1-pentanol to corresponding ethers was reported using various macroporous and gel-type ion exchange resin catalysts from types of Amberlyst, Dowex, and Nafion NR50. The results indicated yields of linear symmetrical ethers depend on the resin structure [26]. The process can be of relevance to the petroleum refinery for obtaining reformulated diesel fuels having better characteristics. While some other heterogeneous catalysts (eg, alumina based catalysts) have been reported for such reactions, application of ion exchange resins as catalyst can be highly useful in terms of efficiency and selectivity in dehydration reactions.

9.4.3.5 Alkylation reactions

The alkylation reactions involve modification due to the addition of alkyl group in place of hydrogen species. There have been numerous reports on alkylation of aromatics using olefins, alcohols, alkyl esters, and alkyl halides. One important example in this class is alkylation of phenol [76] carried out in entirely anhydrous conditions using ion exchange resins as catalyst (eg, Amberlyst 15). Chandra and Sharma [77] reported alkylation of phenol with MTBE and other tert-butyl ethers using Amberlyst 15, Indion 130, Bayer K-2661 macroporous resins, and Nafion NR50 in an attempt to directly employ MTBE rather than isobutylene from MTBE decomposition. Alkylated phenols and derivatives find use as antioxidants, herbicides, and insecticides, etc., and are widely used commercially. Alkylation using isobutylene is also commonly used for reactive separations for variety of organic chemicals and is separately discussed later.

Conventional Friedel-Crafts alkylation reactions in homogeneous acid catalysis mostly result in the formation of complex reaction mixtures. The requirement of stronger acidity here with respect to many low reactive components, ion exchange resins with high acidity such as Nafion-H, are shown to be quite useful in many alkylation reactions and reactions of alkylation of benzene with ethylene/propylene; ethylbenzene with ethylene; alcohols with benzene; alkylation of aromatic hydrocarbons with alkyl halides, etc., have been reported [23]. Botella et al. [78] reported alkylation of isobutene with 2-butene using Nafion/silica composites and have compared the performance with other solid acid catalysts such as zeolite H-beta and sulfated zirconia. Sun et al. [79] have reported benzylation of benzene and *p*-xylene with *p*-methylbenzyl alcohol using Nafion resin/silica composite. Their comparison with commercial Amberlyst 15 resin catalyst and *p*-toluenesulfonic acid in this reaction showed that the later low acidity catalysts have no activity compared to strong acidity Nafion resins.

Although, increasing the acidity/activity assumes particular importance in alkylation reactions, these ion exchange resin catalysts have to compete with other solid acid catalysts such as zeolites for many applications. A comparison of various catalysts such as low

acidity resins with that high acidity resins along with structural differences in the catalysts, surface area/activity, and effect of composites/functionalization can be highly useful in this regard.

9.5 Ion Exchange Catalysis: Operation and Reactor Design

The catalytic reactions can be carried out in batch or a continuous manner. Continuous reactions have an advantage of producing large quantities of products in shorter periods of time. The normal operation in the batch process involves feeding the reactants in a batch reactor, such as acid and alcohol in esterification, followed by acid/base catalyst addition, such as HCl or sulfuric acid, bringing the reaction mass to the desired reaction conditions with stirring, removing one of the products to drive the reaction to completion (eg, water in the case of esterification), and finally isolation of the product. A detailed review on multiphase catalytic reactors has been presented by Ramachandran and Chaudhari [80] and Mills and Chaudhari [81]. In the case of resins as catalyst, the batch operation is in the form of slurry reactor and specific parameters such as catalyst loading, stirring to keep catalyst uniformly suspended in the reactor, heat and mass transfer, etc., are to be monitored. After the reaction, the catalyst can be easily separated from the reaction mass by filtration and can be reused. The batch to continuous change is not simple and requires specific considerations from the point of view of reaction and reactor—chemical engineering considerations from the point of view of reaction rate, mass transfer, and heat transfer being most important (Figs. 9.3 and 9.4). For continuous processes, typically a fixed bed reactor operation is employed where the ion exchange resin is packed in the form of catalyst bed and reactants are fed in a specific manner. The particle size of the resin is important here from the point of view of pressure drop across the reactor as smaller the size, the higher the pressure drop. Apart from pressure drop, specific design considerations may also be required for handling such smaller sizes of catalyst such as design and arrangement of catalyst support, avoiding catalyst carryover, etc. The commercial ion exchange resins are available in spherical bead forms with specific size/size range. Generally, a bead size of 0.4–1.1 mm is preferred, however smaller sizes up to 1 mm and larger size of about 2 mm are also possible [13]. Leveneur et al. [27] have attempted to correlate kinetics and internal mass transfer in ion exchange catalyst for the synthesis of peroxycarboxylic acids and have confirmed kinetic control for small resin sizes and pore diffusion influences above sizes higher than 300 μm. The particle size distribution was also incorporated in the model to account for the combined effects of reaction kinetics and pore diffusion.

The control of particle size has been an important concern in manufacturing of these resins. The conventional suspension polymerization often gives resin product with wide particle size and size distribution. Because many application of ion exchange resin catalysts require a specific particle size, broader Gaussian distribution of sizes leads to further screening of the

catalyst for suitable particle size, consequently often leading to wastage of resin, as sizes below or above the desired range have to be discarded, affecting overall productivity and economics of the process. Finding a solution to utilization of such waste is one issue in the production technologies of ion exchange resins and has been discussed later in this chapter. There are, however, some technologies that offer pearl polymerization process with narrow particle size distribution (eg, Dowex Monosphere) thereby lowering waste, increasing yield of desired resin product, and thus improving economics of the process.

The fixed bed reactor design can be multitubular to facilitate heat removal. Some other reactor types such as plate column, bubble column, expanded bed reactor, and loop reactor, etc., have also been discussed in the literature and some of them have been employed for commercial production using ion exchange resin catalysts. Weaver et al. [24] reported batch reactor and fixed bed reactor studies on alkylation reactions using fluorocarbonsulfonic acid polymer catalysts. Rehfinger and Hoffmann [68] have reported liquid phase reaction of isobutene and methanol using Amberlyst 15 catalyst in continuous stirred tank reactor (CSTR). There are a number of catalytic processes that are used industrially, for example, continuous esterification process is used industrially to make methyl acetate from acetic acid and methanol and ethyl acetate from acetic acid and ethanol; fixed bed reactor operation/reactive distillation for manufacture of MTBE [82]. Zhang et al. [69] reported fixed bed ion exchange resin packed reactor for etherification reaction involving mixed olefins and alcohol. Linnekoski et al. [41] reported etherification studies using CSTR for Amberlyst 16 resin catalyst. Lietti et al. [40] reported gas phase alcohol coupling reaction (vapor phase dehydration) for preparation of ethers in fixed bed reactors using Amberlyst 35 resin as catalyst. Similar vapor phase alcohol dehydration studies have been reported using continuous flow reactor using Nafion H catalyst [20]. Shibasaki-Kitakawa et al. [60] have employed an expanded bed reactor packed with anion exchange resin for continuous transesterification reaction in biodiesel production. Lei et al. [39] have studied kinetics of liquid phase catalytic dehydration using macroporous acid resins for synthesis of dimethyl ether from methanol using a fixed bed microreactor and examining different reactor combinations, such as fixed bed reactor followed by catalytic distillation column, fixed bed reactor followed by distillation columns in series, and catalytic distillation column followed by ordinary distillation column.

Bisphenol A can be produced from acetone and phenol using ion exchange resin catalyst and high acetone conversion can be achieved by employing phenol as solvent. The byproduct of the reaction, water, reduces the activity of the resin and hence, needs to be removed continuously for stable reactor operation. Such industrial reactions also need the strategy of simultaneous reaction and separation, and the separation step can be devised in different forms. The simulated moving bed reactor has been reported in such cases to prevent catalyst deactivation [83].

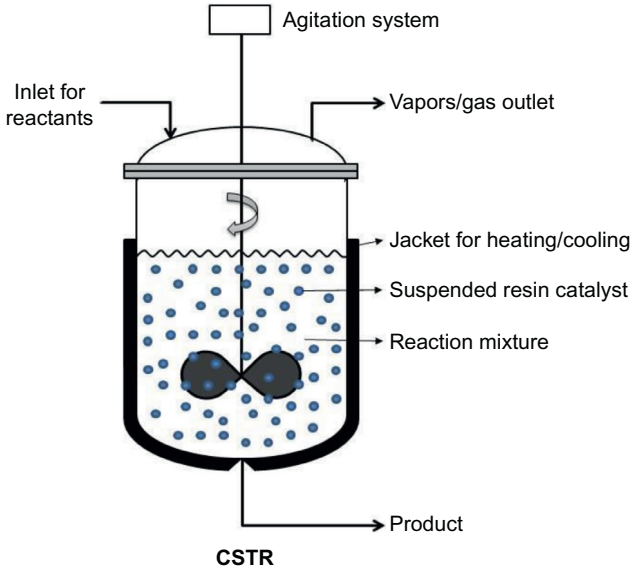


Fig. 9.3
Continuous stirred tank reactor.

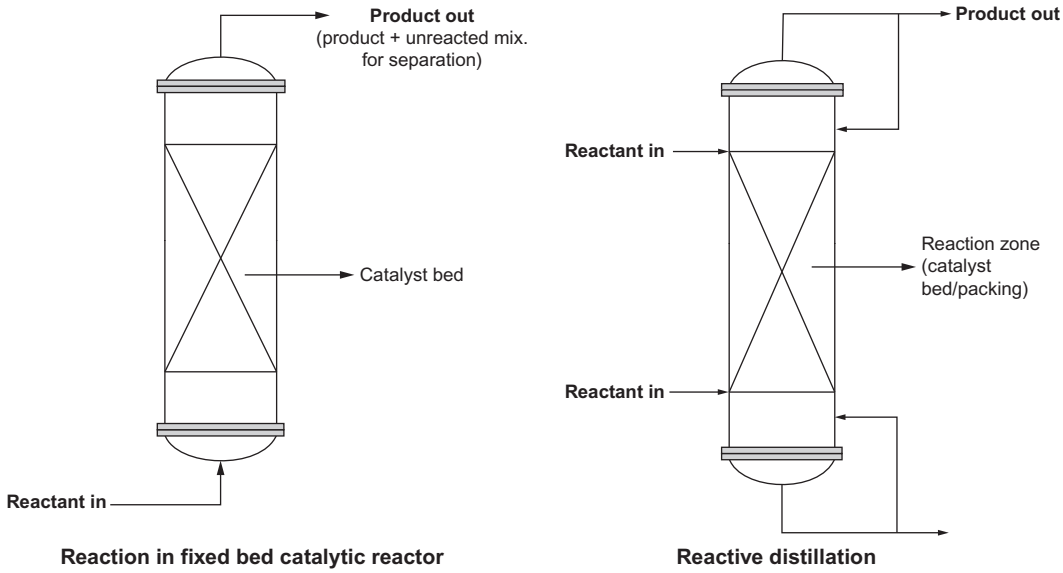


Fig. 9.4
Fixed bed reactor operation schematic: conventional and reactive distillation.

There are some specific reactions that can be carried out using supercritical conditions. For example, hydration of propylene in the manufacture of isopropanol and sec-butanol production by hydration of butenes may be carried out using fixed bed operation using an ion exchange catalyst under supercritical conditions.

The understanding of reactors for ion exchange catalysis largely relies on the standard methodology based on batch reactor, fixed bed reactor, and such and/or modified forms of gas-liquid-solid reactors. In this regard, a substantial knowledge base is still required, especially on the following issues:

1. Newer reactor types/geometry, design, and operation
2. Performance optimization on the basis of reaction type
3. Process control and automation
4. Process integration/intensification including reaction-reaction and bifunctional catalysis; multiple reactions; reaction-separation, etc.
5. Scale-up of reactor and uncertainty
6. Mathematical modeling and predicting reactor performance; reactor hardware/software
7. Economics

Thus, the choice of reactor operation largely depends on experimental/pilot plant data and prior experience with reference to the abovementioned aspects for any reaction.

9.6 Ion Exchange Catalysis for Process Separations

Ion exchange catalysis has also been used to effect process separations, especially in the event of difficult separations, such as separation of close boiling mixtures. Here, the difference in the reactivity of one of the components in the mixture is exploited to effect separation. Alternatively, both components can react to yield products that can be easily separated. For example, in the separation of *m*-cresol and *p*-cresol, both the compounds have close boiling points and can be separated using ion exchange resin catalyzed alkylation reaction. The concept of reactive separation of this nature has been reported and discussed for many years for both homogeneous and heterogeneous catalysts [84]. Chaudhuri et al. [85] have reported this separation using Amberlyst 15 as ion exchange catalyst and have also compared relative rates for alpha methylstyrene using homogeneous catalyst, indicating no difference in the relative rates for homogeneous and heterogeneous catalysts. Similar separation studies were also reported for separation of 2,6-xylenol and *p*-cresol for different alkylating agents.

Separation of phenol and *o*-chlorophenol by etherification reaction with isobutylene catalyzed by Amberlyst 15 was reported by Ghosh and Sharma [86]. The difference in the reactivity of ethanol and isopropanol was exploited using alkylation (isobutylene) reaction for the Amberlyst 15 catalyst to effect their separation [87]. Isobutylene reacts with ethanol in the presence of Amberlyst 15 to give ETBE, while it reacts with isopropanol and gives isopropyl

tert-butyl ether. The differences in the rates here were attributed to differences in acidity of the two alcohols. A similar strategy was used for separation of the mixture of isopropanol and tert-butanol where only isopropanol was found to react with isobutylene in presence of Amberlyst 15, while no reaction with tert-butanol was observed under the experimental conditions. Ion exchange resins have also been considered for reaction-separation. The application of strong acid resin was reported for the preparation of barium chloride from barite [88]. The conventional process of $BaCl_2$ manufacture involves reaction of BaS or barium carbonate and hydrochloric acid, number of steps, and has problems due to effluents such as toxic hydrogen sulfide gas (if sulfide is used) and corrosion. The concept of employing ion exchange resins has two steps in a specified manner to yield barium chloride product. In the first step, resin in Na^+ form is allowed to react with dilute BaS stream, so that resin is converted in Ba^{2+} form, and the second step involves elution of barium chloride product using sodium chloride solution. However, not many examples of this kind are reported in the literature.

The above discussion clearly highlights application of reactive separation methodology using ion exchange catalysis for variety of mixtures and especially for close boiling mixtures.

9.7 Ion Exchange Catalysis in Wastewater Treatment

Ion exchange separations, as an independent technology, has been well established in separations such as water treatment, wastewater treatment, process separations such as acid separations, food processing, the pharmaceutical, and chemical industries, in general. The important aspects pertaining to ion exchange separations and catalysis have been well reported in the literature [6–9,88–91]. Bhandari et al. [8,9,91] have discussed removal of different types of acids using ion exchange resins by describing the sorption process mechanism in weak base resins; acid removal from wastewaters being an important problem in chemical and petrochemical industries. Recently, Ranade and Bhandari [7] have elaborated ion exchange processes for wastewater treatment in detail by outlining acid streams in different processes.

Esterification reactions can also be important from the point of view of wastewater treatment. For example, for the treatment of wastewaters containing acetic acid, esterification reaction using methanol can be used to convert acetic acid to methyl acetate for easy recovery and separation. However, such reactive separation can be considered only for appreciable concentrations of acetic acid and techno-economic viability of these reactive separations need careful attention prior to its application. Xu and Chuang [92] suggested catalytic distillation as an attractive way to remove acetic acid from wastewaters. It was also suggested that such methodology can provide up to 80% energy savings apart from avoiding corrosion problems of conventional distillation and the strategy was presented using Amberlyst 15 resin catalyst for esterification of acetic acid with methanol. Esterification of acetic acid from waste streams with C_6 and C_7 alcohols has been suggested to be advantageous and reactive distillation

appears to be suitable option for treatment of wastewaters using esterification of acetic acid with suitable alcohol to yield value added products [90].

Perchlorate removal from wastewaters is an important problem where ion exchange resin can be employed. Kim and Choi [93] have suggested integration of ion exchange and catalytic decomposition by using Pd-supported ion exchange resins as bifunctional material for both adsorption and catalysis. The driving force in adopting such a strategy is that if only resin is used for sorption and removal of perchlorate, though higher capacity can be expected, disposal/regeneration can be very difficult/costly. This difficulty can be taken care of, if the resin after sorption can be made to undergo decomposition of sorbed perchlorate through the use of catalytic Pd on the bifunctional resin, and carrying out catalysis using hydrogen.

9.8 Ion Exchange Catalysis and Process Integration

9.8.1 Reactive Distillation

Reactive distillation is a process integration for combining reaction and separation steps in one single piece of equipment. Consequently, it is expected to offer many advantages over conventional methodology of separate and distinct reaction and separation operations, mainly through lowered capital and operating costs. However, it is not easy to synchronize reaction and separation rates and currently, major applications in this area pertain to reactions having high rates, coupled with similarity in reaction and separation temperatures. Though a very large number of publications in this area have been seen for almost over two decades, the number of practical applications has been limited. The publications mainly relate to experimental work on various types of reactions, mainly esterification or etherification, design of reactive distillation, control and computer simulation, and such theoretical studies. The design and optimization of the reactive distillation processes is complex because of the inherent coupling of phase equilibria, transport processes (multicomponent mass transfer/heat transfer), and reaction kinetics issues apart from catalyst selection and type; making controlling of the process extremely difficult [94–96]. The progress on reactive distillation has been recently reviewed by Lutze and Gorak [97]. Overall, it is still a challenging task to design and optimize reactive distillation by combining reaction and separation. Below, we briefly give an overview of recent developments in this area in the context of some important examples.

The reactive distillation operation, especially those using ion exchange resin catalysts, has gained tremendous attention in recent years in esterification reactions, preparation of ethers such as MTBE, and so on. One very important and socially relevant example in this is lactic acid manufacture, which is a an important chemical in food, pharmaceutical, and chemical industries; but most importantly, polymers of lactic acid provide alternatives in the form of biodegradable polymers most relevant from environment protection point of view. Recovery of lactic acid (produced chemically or through fermentation route) is generally

difficult and a number of conventional to novel separation processes have been researched in this regard. The high-purity product can be obtained through esterification with methanol or ethanol and the ester is recovered by distillation, hydrolyzed with water, evaporated and the alcohol recycled [98]. Mo et al. [99] have studied reactive distillation for liquid phase hydrolysis of methyl lactate using cation exchange resin in an attempt to conceptually design reactive distillation column using esterification-hydrolysis method for lactic acid recovery.

González and Fair [35] have reported preparation of tert-amyl alcohol in reactive distillation column using macroporous strong acid resin Amberlyst 15. All the issues such as reaction kinetics, equilibria, and mass transfer were evaluated for this hydration reaction. Recently, Li et al. [100] have discussed synthesis and design of reactive distillation columns by giving examples such as MTBE from isobutylene and methanol, and strong acid resin catalyst or homogeneous catalyst such as sulfuric acid, and have felt that feed splitting is also an important variable in process intensification for combining reaction and separation. Synthesis of dimethyl ether using catalytic distillation has been reported by Lei et al. [39]; by reactive distillation in dividing wall column [101]. Kamath et al. [102] have attempted a comparison of reactive distillation with process alternatives and have suggested that though reactive distillation can be superior in giving maximum selectivity, the conventional processes can be competitive in terms of the cost. Recently, the concept of hybrid reactive distillation column has been proposed that includes both reactive and nonreactive sections, providing multiple feasible configurations for the desired selectivity [103].

9.9 Regeneration/Reactivation and Life of Ion Exchange Catalysts

Ion exchange, in general, a cyclic process requiring regeneration of the resin after the exhaustion cycle is over. However, ion exchange resin catalysts do not get consumed and hence, these resin catalysts can be used for hundreds of cycles without regeneration, if properly used (however, some lowering of catalyst activity due to exchange of other ions may require regeneration). Thus, compared to the conventional homogeneous process, the cost or usage of the catalyst is spread over a wider span in terms of time extending up to the life of resin which is very long, making true cost of catalyst significantly lower than the homogeneous catalyst.

However, catalyst can get deactivated due to loss of capacity or ionic sites. The deactivation can be temporary (due to exchange with other ions, temporary pore blocking, or neutralization) or permanent (loss of active functionality, permanent pore blockage, or resin disintegration, etc.). This may happen due to thermal desulfonation of cation exchange sites or due to chemical deactivation of the catalytic sites. Reaction of polymers of styrene with oxidizing agents such as peroxides can deactivate resin and reduce capacity. Similarly, neutralization of acidic sites due to base, if present in the feed stream, also reduces the acid resin capacity. Further,

fouling of ion exchange resins is common due to contaminants. Parra et al. [67] have studied the deactivating effect of ammonium and Fe(III) on different ion exchange resin catalysts in etherification reaction and have felt that ammonium could be responsible for steric hindrance due to formation of H-bonding with sulfonic groups. Regeneration of deactivated catalyst or recovery of the lost capacity can be sometimes possible if cause of deactivation is known and if it can be repaired through treatment such as acid/alkali or solvent treatment. Organic foulants from resin catalysts can be removed by washing of the resin with the appropriate solvent. However, if the polymer matrix is damaged, recovering the capacity and therefore, regeneration step may not be possible. Therefore, deactivation and regeneration of the catalyst is important in reactions catalyzed by ion exchange resins and mainly depends on the type of reaction for which resin is used as catalyst.

9.10 Ion Exchange Catalysis: Challenges Ahead

9.10.1 New Materials/Methods/Designs

Newer ion exchange resins are being explored for high thermal stability so that the catalyst can withstand higher temperatures of reaction without degradation. The nafion resins that can presently withstand up to 200°C, are expensive compared to the conventional ion exchange resin catalysts. Thus, newer developments are needed for low cost resins with high thermal stability. Apart from thermal stability, chemical stability is also important for the ion exchange resin catalysts. Conventional resins fail in strong oxidizing environment (eg, presence of hydrogen peroxide). The popularity of nafion resin catalysts appears to be mainly due to higher acidity under different conditions as compared to conventional resins and both chemical and thermal stability. However, nafion resins that are perfluorinated ion exchange polymers have limited activity in nonpolar solvents or for vapor phase reactions. To overcome these limitations, research on materials such as nanocomposites of nafion resin has been suggested [22]. The concept here envisages entrapment of nafion resin particles within porous silica backbone to retain very high acidity/activity of nafion resin.

Ion exchange resin catalysts can be modified in terms of the functionality. If the catalyst can be bifunctional, it can be used for multiple steps of the reaction. Thus, providing multifunctional character to the resin, to the extent desired with respect to reaction steps, could be advantages for ion exchange catalysis. This also could be part of developing tailor-made resins as not much information is available on the application of bifunctional resin catalysts. Talwalkar and Mahajani [104] have reported one-step synthesis of MIBK from acetone using metal doped ion exchange catalyst—a commercial bifunctional ion exchange resin catalyst. Some newer developments in the form of replacing part of the hydrogen ions by other species can also be explored. Bernhard et al. [105] had suggested replacing part of hydrogen ions of ion exchange resin with polyvalent ions/inorganic ions, such as Mg or barium

ions. Performance benefits for such exchanges for various reactions, however, have not been established so far. Ion exchange resin catalyst modified with metal-porphyrin for oxidation of epinephrine has been proposed recently with elucidation of role of metal such as Mn in catalysis [106]. Recently, Kim and Choi [93] have attempted generating Pd clusters within ClO_4^- selective strongly basic anion exchange resin for perchlorate removal from wastewaters. However, employing such methodology, at present, certainly appears to be cost-intensive compared to conventional ion exchange treatment.

The above discussion pertaining to newer resins highlights modifications in stability (thermal and chemical), functionality and acidity of the resin to increase catalytic performance of the resin. Newer resins also can have further improvements in terms of pore size and size distribution, so as to drastically increase reaction rates for desirable reactions. The development in this regard will also therefore affect selectivity of the resin. Though a lot of information is available on the pore structure characterization and modification, it is still difficult to identify and characterize different reactions using different matrices under similar conditions and this requires enormous efforts. It would be certainly helpful, therefore, to evolve theoretical guidelines in this regard, such that performance of the resin can be predicted a priori for any reaction type and set of reactants/solvents.

Newer forms of ion exchange resin catalyst can also be part of development in future. Pääkkönen and Krause [43] have reported use of novel ion exchange fiber catalyst, SMOPEX-101, for etherification reactions and have found that this catalyst is superior to Amberlyst 35 resin catalyst in the synthesis of ethers bulkier than TAME, that was attributed to its open structure and as a consequence, negligible mass transfer resistance. The fibrous resin catalyst was prepared by grafting polyethylene fiber with styrene and sulfonating the grafted fiber with chlorosulfonic acid that gives sulfonic acid group for catalytic activity on the polymer backbone.

A concept of magnetic ion exchange resins, though attempted in wastewater treatment for the removal of pollutants, has not been given attention in ion exchange resin-based catalysis. In fact, this could form an attractive proposition for metal doped resins or bifunctional resins, where the magnetic property of the resin can be exploited for reaction catalysis, especially those pertaining to metal catalyzed reactions. These resins, as well, can be explored for selective removal of deactivating species, thereby improving reaction performance and resin activity.

Use of ion exchange materials in the other forms such as ion exchange membranes can also be possible development in terms of resin-based catalysis. Chemical and physical modifications of such materials can also be interesting from catalysis point of view. The application of a fibrous ion exchanger as carrier of the catalyst—Fe-EDTA immobilized on the functional groups, for hydrogen sulfide removal has been reported recently [107] where fibrous form is expected to facilitate gas-liquid mass transfer.

Newer developments also need to drastically reduce the cost of specialized ion exchange resin catalysts that have better catalytic properties like nafion. In this regard, newer development like coating perfluorosulfonic acid on suitable inert support has been discussed in the literature [24].

Development with respect to avoiding deactivation of resin catalysts, regeneration/reactivation or easy and environmentally friendly disposal of spent resins need to be explored in detail. Incineration of harmful, spent resins can be potentially damaging to the environment and this can be avoided, if spent resins can be catalytically regenerated [93]. However, use of such catalytically loaded resins (eg, Pd-loaded resins) can have high material costs. Spent resins for development of newer useful materials could be one attractive alternative in this regard, though cost of preparing these materials could be high/prohibitive, especially if chemical or thermal modification/treatment is extensive. Development of spherical activated carbons from spent ion exchange resins is one alternative discussed in the literature. Activated carbons are probably the most widely used adsorbents worldwide for a variety of applications, ranging from color removal to removal of specific chemicals/metals/pollutants, and so on. The commercial activated carbons are available in various forms, such as powder, granules, spherical, fibers (including nano-fibers), etc., to suit specific applications. The cost variation in these is also large, ranging from very cheap material to highly expensive advanced materials. The nature of activated carbon and its application depends on its surface area, pore size/pore size distribution, and surface properties. The nature of carbons is strongly dependent on the origin/source apart from the activation methodology or surface modification. Our recent work in this respect [108] showed that activated carbons with a surface area as high as 1000 m^2/g could be developed using acid resins which could be further modified using thermal or chemical treatments (Fig. 9.5).

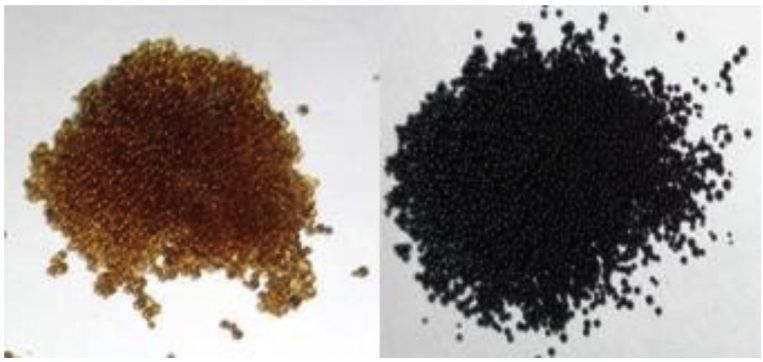


Fig. 9.5
Converting strong acid resin T-42 into spherical activated carbon.

The development of spherical activated carbons, especially using polymeric resin waste, can be an attractive option that can be highly useful for various applications in process separations and in wastewater treatment, apart from utilizing existing waste. It is important to evaluate different physical/chemical modifications that will further enhance utility of such materials.

There could be other aspects of ion exchange resins in terms of application and process engineering. The use of ion exchange catalysis and reactive distillation is expected to be increasing and therefore, process optimization on both reaction and design become important. Different reactor combinations can be explored in this regard and ion exchange resin in the form of packing offers very attractive option in process engineering. Resin itself can be molded in the form of desired packing or it can be coated on a suitable commercial packing. Many novel combinations are possible in this regard.

9.11 Summary

Ion exchange resins as catalyst can provide a large number of advantages in terms of reaction process and reactor operations with significant benefits in terms of better reaction control, reduced side reactions and side products, mild operating conditions, and ease of operation apart from minimizing corrosion problems associated with homogeneous catalysis. However, compared to homogeneous catalysis and also with other commercial solid acid catalysts, there is still a lot of scope to develop and improvise ion exchange resin-based catalysis, both in terms of resin catalyst and operation. Process integration such as reactive distillation can also contribute significantly to future development.

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CHAPTER 10

Hydrogenation for Fine Chemical Synthesis: Status and Future Perspectives

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10.1 Introduction

Due to various environmental concerns, the chemical industry is in the process of severe structural changes. Great numbers of companies are focusing their research and development (R&D) and production on certain key competencies. In comparison to the petroleum refineries and the bulk chemical industry, the area of fine chemical synthesis is expected to grow more rapidly because fine chemicals are essential feed stocks for pharmaceuticals, agrochemicals, and lifestyle products. There are no globally accepted definitions of bulk, fine, and specialty chemicals, nor are these classifications based on any inherent properties. A substance that is correctly termed a bulk chemical might well have been known as a fine chemical at an earlier stage. A working interpretation of fine chemical is one with a price of more than \$10 kg^{-1} and a volume of less than 10,000 tons per annum on a global scale. Also, fine chemicals are characterized by a relatively complex molecular structure and often contain chiral centers. Generally, the synthesis of fine chemicals results in large amounts of by-products (5 to more than 100 kg per kg of product) [1,2]. Considering the economic as well as environmental point of view, this amount of waste needs to be reduced. Hence, the so-called green chemistry is of particular importance in the area of fine chemical synthesis. One of the solutions to the problems of fine chemical synthesis is the use of novel catalytic reactions in place of more strenuous methods of classic organic synthesis. The use of catalytic methods often results in the reduction of reaction steps for the synthesis of the desired product. Consequently, a meaningful waste reduction (as well as cost reduction) is quite possible. However, in order to be of interest for realistic applications, some particular points must be considered for fine chemical synthesis such as:

- Costs of ligands and catalyst metals (productivity of the catalyst).
- Space-time yield of the process (activity of the catalyst).

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- Recycling of the catalyst and contamination of the product with ligands and metals.

As previously stated, in the fine chemicals industry, many chemical conversions require stoichiometric amounts of reagents and thus, generate large amounts of waste. R&D is therefore driven by the need to decrease waste, use less toxic reagents and solvents, improve energy efficiency, and recycle the catalysts so as to achieve more sustainable processes [3–6].

10.1.1 Catalytic Hydrogenations

The continuous modernization in hydrogenation technology is proof of its immense importance in the manufacture of specialty and fine chemicals. New advancements in equipment, process intensification, and catalysis represent major areas that have undergone extensive advances. Improvements in chiral catalysis methods to support and fix homogeneous catalysts, high-throughput screening, spectroscopic and electrochemical online process monitoring, supercritical processing, and sonochemical activation methods illustrate the scope and breadth of the evolving technology applied to hydrogenation processes.

Catalytic hydrogenations in the fine chemicals industry are commonly carried out with heterogeneous catalysts. Homogeneous catalysts are generally applied for highly selective transformations such as enantioselective reductions. For both heterogeneous and homogeneous catalysts, hydrogenation with molecular hydrogen is an atom economic transformation and the cleanest possible method. Alternatively, hydrogen donors, such as isopropanol or formic acid can be applied in transfer hydrogenation reactions. In the field of catalytic hydrogenation reactions, several important discoveries have been reported in the last 150 years. Sabatier and coworker [7,8] investigated the application of highly dispersed metals, such as nickel, in the hydrogenation of organic species. The selective semihydrogenation of C≡C-bonds in the presence of Pb-doped palladium on calcium carbonate catalysts invented by Lindlar was an important breakthrough in the field of catalytic hydrogenation reactions [9–11]. During the last decade, asymmetric hydrogenations, spearheaded by Knowles [12] and Noyori [13], were milestones in the field of hydrogenation. Catalytic hydrogenations can be carried out in a variety of ways, such as in the liquid or gas phase and in batch-wise, or in continuous mode. In the continuous processes, normally fixed-bed reactors or fluidized-bed reactors are used. The proper choice of a reactor system depends on various aspects, such as the selection of catalyst, reaction parameters, heat formation, space-time-yield, residence time, hydrogen pressure, mass-transport phenomena, temperature, solvent, and finally, the economics of the process.

10.2 Hydrogenation Under Ex Situ Conditions

In the hydrogenation processes under ex situ conditions, the hydrogenating agent (such as hydrogen gas) is added from an external source. There are several types of ex situ hydrogenation reactions that are employed to produce compounds that are regularly used in various fields (Fig. 10.1).

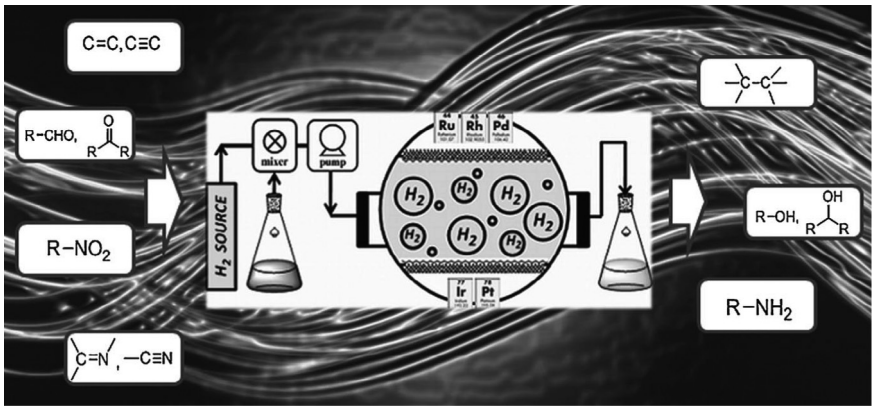


Fig. 10.1
Ex situ hydrogenation (continuous flow method). *Reproduced with permission from M. Irfan, T.N. Glasnov, C.O. Kappe, ChemSusChem 4 (2011) 300.*

Heterogeneous catalytic hydrogenations under ex situ conditions are normally highly selective and easy to work up, the catalyst can often be recovered and recycled, and the processes are atom efficient. It is therefore no surprise that somewhere between 10% and 20% of the reactions used to produce chemicals today are catalytic hydrogenations under ex situ conditions [14,15]. Despite the importance of the technique, and mainly because of its multidisciplinary nature, chemists and engineers have a hard time finding solutions to this highly specialized subject.

Generally, the metals which are applied in heterogeneous catalysis are organized in a face-centered cubic tightly packed crystal structure in which each atom has a maximum of 12 nearest neighbors. The metal atoms at the surface are the only ones presenting vacancies where the reactants can bind. For this reason, a catalyst is made in such a way that the metal particles are highly dispersed on a porous support with high surface area and it shows higher activity. For example, palladium supported on carbon has higher activity than palladium supported on graphite.

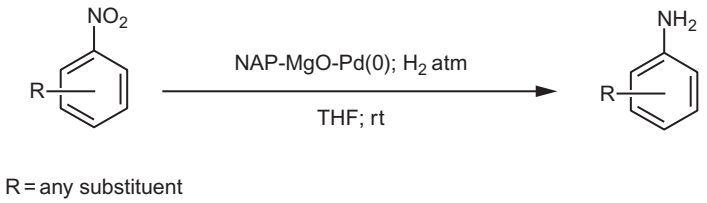
The adsorption of substrate on the catalyst surface takes place in two stages: physisorption characterized by weak forces (van der Waals) and chemisorption that involves the formation of chemical bonds. Chemisorption can be associative, meaning that the adsorbate maintains its chemical structure intact (eg, in the case of alkenes adsorbed onto platinum on carbon), or dissociative, when by binding to the metal, the structure of the adsorbate is disintegrated (as in the case of hydrogen adsorbed onto platinum on carbon).

10.2.1 Hydrogenation of Nitro Compounds

A variety of reagents have been reported for the reduction of nitro compounds to the corresponding amines [16]. Among them, the typical and still adopted method is the reduction with iron and hydrochloric or acetic acid under homogeneous conditions [17]. Other metals

such as zinc or tin in the presence of hydrochloric acid have also been reported [18]. However, these processes present difficulties in product isolation after the reaction [19]. In order to avoid these drawbacks of the traditional processes, a number of heterogeneous catalysts have been reported in recent years [20]. These catalysts offer several advantages over their homogeneous counterparts with consideration of recovery, recycling, as well as reduction of undesired toxic wastes. Baralt and Holy [21] reported the reduction of nitrobenzene to aniline by applying polymer-anchored anthranilic acid-palladium complexes under high pressures of 500–800 psi at a temperature of 70–100°C. Palladium supported on charcoal catalyzes the reduction of nitro compounds using triethylammonium formate as the hydrogen source at reflux temperature [22]. Unfortunately, high temperatures, pressures, and longer reaction times are necessary for these methods of reduction.

Lakshmi Kantam et al. [23] reported the reduction of a variety of aromatic and aliphatic nitro compounds to the corresponding amines at ambient temperatures in good to excellent yields by using ligand-free nanocrystalline magnesium oxide-stabilized palladium(0) catalyst with molecular hydrogen as the reductant (Scheme 10.1).

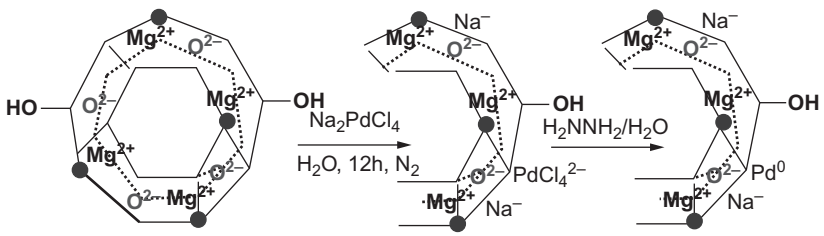


Scheme 10.1

Reduction of nitroarenes. *Reproduced with permission from M. Lakshmi Kantam, R. Chakravarti, U. Pal, B. Sreedhar, S. Bhargava, Adv. Synth. Catal. 350 (2008) 822–827.*

10.2.2 Preparation of Nanocrystalline MgO Stabilized Palladium Catalyst

NAP-Mg-PdCl$_4$: NAP-MgO (brunauer–emmett–teller (BET) 600 m^2 g^{-1}, 1 g) was treated with Na_2PdCl_4 (294 mg, 1 mmol) dissolved in 100 mL decarbonated water with stirring for 12 h under a nitrogen atmosphere to afford the brown colored NAP-Mg-PdCl$_4$. Then the catalyst was filtered, and washed with deionized water, acetone, and dried (Scheme 10.2).



Scheme 10.2

Preparation of nanocrystalline MgO-stabilized palladium catalyst. *Reproduced with permission from M. Lakshmi Kantam, R. Chakravarti, U. Pal, B. Sreedhar, S. Bhargava, Adv. Synth. Catal. 350 (2008) 822–827.*

NAP-Mg-Pd(0): NAP-Mg-$PdCl_4$ (1 g) was reduced with hydrazine hydrate (1 g, 20 mmol) in 20 mL dry ethanol for 3 h under a nitrogen atmosphere to get the black-colored, air-stable NAP-Mg-Pd(0) (Pd 0.99 mmol g^{-1}).

To identify the best catalytic system for the reduction of nitro compounds; various supported palladium catalysts were screened using nitrobenzene as a model substrate and the results are presented in Table 10.1.

Table 10.1 Comparative study on different supported palladium catalysts for the reduction of nitrobenzene[a]

Enter	Catalyst	Time (h)	Conversion (%)[b]
1	Pd-MgO	2.0	98
2	PdMgLaO	2.0	70
3	Pd-C	2.0	15
4	Pd-SiO_2	2.0	6

[a]Reaction conditions: nitrobenzene (1 mmol), catalyst (0.015 g), dry THF (4 mL), room temperature, under H_2 atmosphere.
[b]Determined by GC.
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Among the different catalysts screened, [NAP-Mg-Pd(0)] exhibited higher conversion than the other (Table 10.1, entry 1). The greater reactivity of [NAP-Mg-Pd(0)] can be explained by the structural features of the nanocrystalline magnesium oxide as support. NAP-MgO hasathree-dimensional polyhedral structure, showing the presence of high surface concentrationsof edge/corner and various exposed crystal planes (such as 002, 001,111), whichlead to inherently high surface ionic charges per unit area. The NAP-MgO has (i) Mg^{2+} sites of the Lewis acid type, (ii) O_2 sites of the Lewis base type, (iii) lattice bound hydroxy groups, (iv) isolated hydroxyl groups, and (v) anionic and cationic vacancies [24].

Screening of various solvent systems using [NAP-Mg-Pd(0)] catalyst showed that tetrahydrofuran (THF) is the most suitable solvent for this reaction (Table 10.2). Among the solvents, toluene and dimethyl formamide (DMF) gave the reaction product in moderate yields.

Table 10.2 Effect of various solvents for the reduction of nitrobenzene using [NAP-Mg-Pd(0)][a]

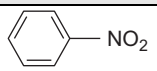
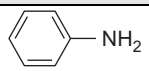
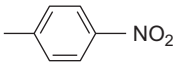
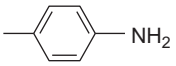
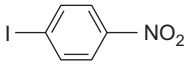
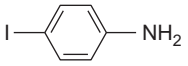
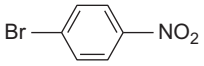
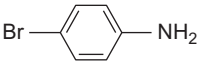
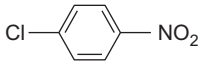
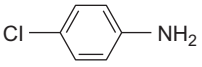
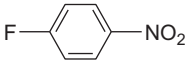
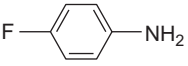
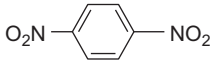
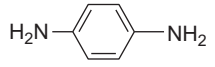
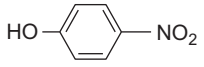
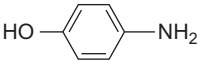
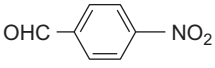
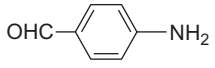
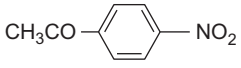
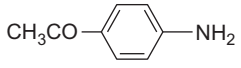
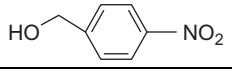
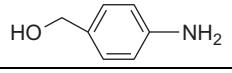
Enter	Solvent	Time (h)	Conversion (%)[b]
1	THF	2.0	98
2	Toluene	2.0	85
3	DMF	2.0	60
4	Methanol	2.0	–
5	Isopropyl alcohol	2.0	–

[a]Reaction conditions: nitrobenzene (1 mmol), NAP-Mg-Pd(0) (0.015 g), solvent (4 mL), room temperature, under H_2 atmosphere.
[b]Determined by GC.
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Interestingly, the reaction did not proceed at all in methanol or isopropyl alcohol to give the desired product, but resulted in the formation of some unidentified product.

It was found that the reaction works selectively and efficiently with a wide range of nitro-substituted aromatic compounds under atmospheric pressure and at room temperature (Table 10.3). During the reduction of 4-nitrohalobenzenes, such as 4-nitroiodobenzene and 4-nitrobromobenzene, trace amounts of the dehalogenated products were formed, although for

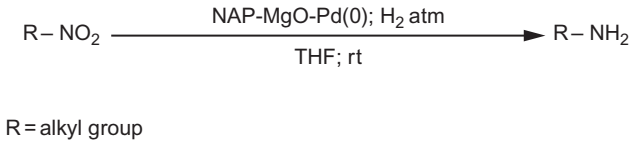
Table 10.3 Reduction of various nitroarenes using [NAP-Mg-Pd(0)][a]

Entry	Substrate	Product[b]	Time (h)	Yield (%)[c]
1			2.0	98, 98[d], 74[e]
2			3.5	90
3			2.5	98
4			2.5	93
5			2.0	98
6			2.0	98
7			1.0	98
8			1.5	98
9			3.0	98
10			2.0	95
11			3.0	93

[a]Reaction conditions: aromatic nitro compound (1 mmol), NAP-Mg-Pd(0) (0. 015 g, 1.48 mol%), dry THF (4 mL), room temperature, under H_2 atmosphere.
[b]All the products were characterized by comparison of their ^{1}H NMR spectra with those of the authentic samples.
[c]NMR yields based on the nitroaromatics.
[d]Yield after fifth cycle.
[e]Yield after tenth cycle.
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4-nitrochlorobenzene and 4-nitrofluorobenzene, no dehalogenated products were detected. Even in the presence of electron-donating groups (Table 10.3, entries 2 and 8), the reaction proceeds under room temperature and atmospheric pressure to afford the product in almost quantitative yields.

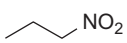
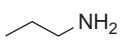
To widen the scope of the catalyst, several aliphatic nitro compounds were then subjected to reduction to their corresponding amines under the same reaction conditions (Scheme 10.3). These substrates also afforded the products in moderate to good yields (Table 10.4) although they required much longer reaction times than those of the aromatic nitro compounds.



Scheme 10.3

Reduction of aliphatic nitro compounds. *Reproduced with permission from M. Lakshmi Kantam, R. Chakravarti, U. Pal, B. Sreedhar, S. Bhargava, Adv. Synth. Catal. 350 (2008) 822–827.*

Table 10.4 Reduction of various aliphatic nitro compounds under H_2 atmosphere using [NAP-Mg-Pd(0)][a]

Entry	Substrate	Product[b]	Time (h)	Yield (%)[c]
1	—NO_2	—NH_2	4.5	92
2			6.5	88
3			6.5	88
4			4.5	92

[a]Reaction conditions: aliphatic nitro compound (1 mmol), NAP-MgO-Pd(0) (0.015 g, 1.48 mol%), dry THF (4 mL), room temperature, under H_2 atmosphere.
[b]All the products were characterized by comparison of their ^{1}H NMR spectra with those of the authentic samples.
[c]NMR yields based on the nitroaliphatic compound.
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Importantly, the catalyst was recovered by simple filtration after the reaction. The filtrate was analyzed for leaching of palladium metal using atomic absorption spectroscopy (AAS) and it was observed that there was no leaching of palladium metal during the course of the reaction. NAP-Mg-Pd(0) catalyst was recovered and reused without further activation up to ten cycles (Table 10.3, entry 1). A slight decrease in the activity of the catalyst was found in the course of the recycling experiments. The small amount of decrease in the activity of the catalyst may be attributed to decrease in the surface area of the catalyst by the hydration of the catalyst due to water formation during the reaction.

A new development in hydrogenation using electrodeposited porous metals and alloys is being developed which leads to recyclable, stable catalysts [25] with a high surface area of controllable surface morphology. These materials, which are prepared by electrodeposition in the presence of H_2 evolution, have an open honeycomb morphology, favoring mass flow to the surface for catalysis in aqueous solution. They have been tested using hydrogenation of 4-nitrophenol as a model reaction. For example, copper has been doped with noble metals such as Pd and Au, to create porous CuPd [25b] and CuAu [25c] respectively, with catalytic activity tuned by varying the amount of noble metal that is added to the porous Cu scaffold. The CuAu alloy deposited with the formation of mixed oxide species that were shown to be crucial to the catalytic behavior, leading to excellent activity for the reduction of 4-nitrophenol. A significant increase in the rate of 4-nitrophenol hydrogenation was attributed to the presence of both cationic Cu and cationic Au on the surface (see Fig. 10.2). Very low gold loadings were required (below 2%), which indicated that this type of material with controlled porosity could be further developed to industrially stable, porous materials using a minimal amount of costly precious metals. Further work on such similar surfaces should lead to a broader range of hydrogenation catalysts, which are more stable than supported nanoparticles in industrially relevant conditions.

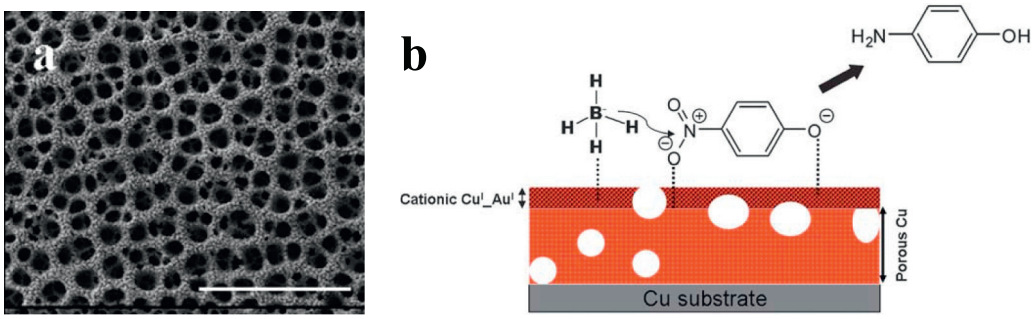


Fig. 10.2

Porous surfaces of Cu/Au created by electrodeposition (A) (scale bar is 500 μm) and illustration of the reaction adsorbed 4-nitrophenol and $NaBH_4$ at a cationic Cu-Au surface (B).
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10.3 Asymmetric Synthesis

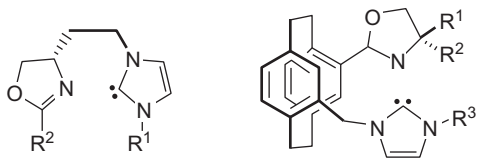
For obtaining enantiomerically enriched compounds, the asymmetric hydrogenation of unsaturated compounds such as ketones and imines represents one of the most valuable methodologies [26]. Asymmetric hydrogenation of carbonyl compounds have been reported by Mikami et al. and Tu and coworkers [27] using ruthenium catalysts with excellent yields and enantiomeric excess. These methods use dihydrogen and miniscule amounts of chiral transition metal complexes and are recognized as cost-effective and operationally simple.

In sharp contrast, the asymmetric hydrogenation of arenes/heteroarenes is a rarely explored, although it provides economical and forthright access to the corresponding chiral saturated and partially saturated molecules bearing cyclic frames. This may be attributed to the following reasons: the high stability of these compounds and some heteroaromatic substances containing sulfur and nitrogen atoms may poison the chiral catalysts.

Asymmetric hydrogenation can basically be classified into two categories; homogeneous and heterogeneous hydrogenation.

Asymmetric hydrogenation catalyzed by homogenous *N*,*P*-iridium catalysts have a cationic iridium as the central metal, an *N*,*P*-ligand, a 1,5-cyclooctadiene ligand, and a BARF {tetrakis(3,5-bis(trifluoromethyl) phenyl)borate} as counter ion. Generally, a six-member ring is formed from the *N*,*P*-ligand and the iridium center. The *P*-center is most frequently a phosphine, but phosphites and phosphinites have also been prepared and tested. All the early *N*,*P*-ligands featured oxazoline or structurally similar five-membered rings such as imidazoline as the *N*-ligating fragment. These catalysts were primarily used for the asymmetric hydrogenation of unfunctionalized alkenes [28].

Chiral *N*-heterocyclic carbene ligands are frequently used in the asymmetric hydrogenation reactions [29]. Two complexes containing chelating *N*-heterocyclic carbene and *N*-centers (Fig. 10.3) have been tested in the catalytic enantioselective hydrogenation of unfunctionalized alkenes. Iridium complexes from these ligands were among the first carbene complexes invented to catalyze an asymmetric hydrogenation with high enantioselectivities (>98%) [30]; The second *C*,*N*-ligand (Fig. 10.3) have chiral centers and planar chirality [31]; the iridium complex of this ligand produced a relatively unreactive catalyst for hydrogenation of unfunctionalized alkenes, and the enantioselectivities obtained were poor (<38% ee for all of several substrates).



$R^1 = 2,6\text{-}^{i}Pr_2C_6H_3$ $R^1 = R^2 = Me$

$R^2 = 1\text{-Ad}$ $R^3 = \text{mesityl}$

Fig. 10.3

N-heterocyclic carbene ligands applied to catalytic asymmetric hydrogenation of unfunctionalized alkenes. *Reproduced with permission from M.T. Powell, D.-R. Hou, M.C. Perry, X. Cui, K. Burgess, J. Am. Chem. Soc. 123 (2001) 8788; C. Bolm, T. Focken, G. Raabe, Tetrahedron: Asymmetry 14 (2003) 1733.*

Immense progress has been made on the enantioselective hydrogenations with homogeneous ruthenium complexes containing chiral phosphine ligands. By applying

ruthenium binaphthyl diphosphine complex bearing axial chirality [BINAP], efficient asymmetric hydrogenations have been performed from a variety of prochiral olefin substrates such as diketene, α,β-unsaturated carboxylic acids, enamides carbonates, and allyl alcohols [32]. The reaction provides a practical method for asymmetric synthesis of the biological antiinflammatory compounds, naproxen, and isoquinoline alkaloid family such as (*R*)-laudanosine (Fig. 10.4).

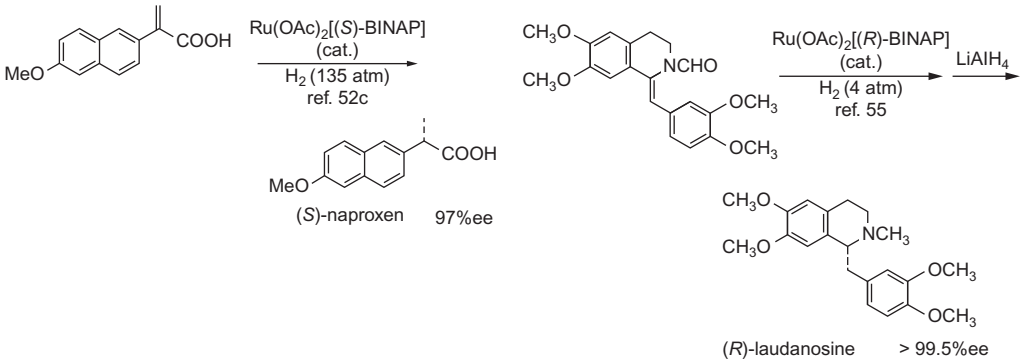
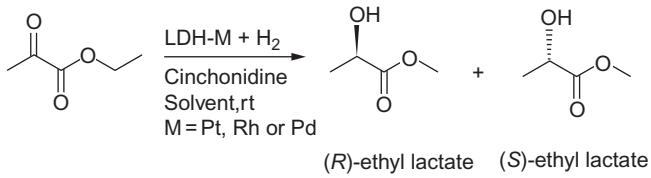


Fig. 10.4

Application of asymmetric hydrogenations with homogeneous ruthenium complexes. *Reproduced with permission from T. Naota, H. Takaya, S.-I. Murahashi, Chem. Rev. 98 (1998) 2599.*

Ruthenium complexes containing similar optically active diphosphine ligands such as H_8-BINAP, 2,2′-dimethyl-6,6′-bis(diphenylphosphino)biphenyl (BIPHEMP), and bis-steroidal phosphine also afford practically high enantioselectivities for the catalytic hydrogenation reactions [33].

Enantioselective hydrogenation under heterogeneous conditions is technically straightforward. For industrial processes, heterogeneous catalysts are favored because they can be efficiently separated and reused. In the year 1956, Akahori et al. [34] reported the asymmetric hydrogenation of azalactones catalyzed by silk-fibroin-supported palladium (Scheme 10.4). Later, the asymmetric hydrogenation of prochiral ketones using a Raney nickel or platinum catalyst that was modified by chiral auxiliaries such as tartaric acid or cinchona alkaloids was reported by the same group.



Scheme 10.4

Asymmetric hydrogenation of ethyl pyruvate. *Reproduced with permission from M. Lakshmi Kantam, K. Vijaya Kumar, B. Sreedhar, Synth. Commun. 37 (2007) 959–964.*

10.3.1 Asymmetric Hydrogenation of α-Ketoesters

Asymmetric hydrogenation of α-ketoesters was reported two decades ago by Orito et al. [35], in which cinchona alkaloid-modified platinum was used for enantioselective hydrogenation of ethyl pyruvate to ethyl lactate. Later, different research groups investigated this reaction [36–40]. The highest enantiomeric excess (ee 95–97%) was obtained using the supported Pt/cinchonidine systems [36,40]. As far as the properties of the supported platinum catalysts are concerned, proper platinum dispersion, the type of support material, and pore size distribution are very important. Suitable supports such as alumina, silica, and zeolites have been studied. Collier et al. [41] have investigated the enantioselective hydrogenation of ethyl pyruvate by solvent-stabilized nanoparticles of Pt and Pd prepared by metal vapor synthesis. Enantioselective hydrogenation of ethyl pyruvate was reported by supported Rh nanoclusters stabilized by polyvinylpyrrolidene with cinchonidine as chiral modifier [42]. The utilization of other transition metals, such as Ru, Rh, Pd, and Ir, to replace Pt, resulted in lower enantioselectivity [41–43]. Layered double hydroxides (LDHs), a new class of basic mixed hydroxides have recently received much attention in view of their potential usefulness as materials, anion exchangers, and more importantly, as catalysts [44]. Lakshmi Kantam et al. [45] reported the catalytic performance of supported LDH-Rh, Pt, and Pd nanoparticles in the enantioselective hydrogenation of ethyl pyruvate using cinchona alkaloid as chiral modifier (Scheme 10.4).

10.3.2 General Procedure for the Preparation of LDH (Mg-Al-Cl) Support

The preparation of LDH (Mg-Al-Cl) was based on the literature procedure [46]. A mixture of $MgCl_2{\cdot}6H_2O$ (30.49 g, 0.15 mol) and $AlCl_3{\cdot}6H_2O$ (12.07 g, 0.05 mol) was dissolved in 200 mL of decarbonated and deionized water. To this aqueous solution, 100 mL of sodium hydroxide (2 M) solution at 25°C was slowly added, and an additional amount of 2 M NaOH solution was added to maintain a pH of 10 under nitrogen flow. The resultant suspension was stirred overnight at 70°C. The solid product was isolated by filtration, washed thoroughly with deionized water, and dried overnight at 80°C.

10.3.3 General Procedure for the Preparation of LDH-Pt and LDH-Pd Catalysts

LDH-Pt and LDH-Pd catalysts were prepared by the ion exchange method. K_2PtCl_6 (0.200 g, 0.4115 mmol) and Na_2PdCl_4 (0.200 g, 0.8223 mmol) were dissolved separately in 50 mL of deionized water. To these aqueous solutions, 1 g of LDH (Mg-Al-Cl) was added and stirred overnight at room temperature under a nitrogen atmosphere. The solid catalyst was filtered and washed thoroughly with 500 mL of deionized water, dried at 80°C overnight, and finally reduced with hydrogen. The platinum content in the LDH-Pt catalyst was 0.6 wt.%, and the Pd content in the LDH-Pd catalyst was 0.5 wt.% as determined by AAS.

10.3.4 General Procedure for the Asymmetric Hydrogenation of Ethyl Pyruvate

The hydrogenation reactions were performed in a 100 mL stainless steel autoclave at room temperature. To 1 g (8.6 mmol) of redistilled ethyl pyruvate in 15 mL of solvent, 6 mg (0.02 mmol) of the chiral modifier, cinchonidine, and 50 mg of the catalyst were added, and the reaction mixture was flushed with hydrogen gas several times before the autoclave was pressurized with hydrogen gas up to 70 bar. The stirring was continued at 1000 rpm and the progress of the reaction was monitored every hour by high-performance liquid chromatography (HPLC).

Table 10.5 clearly indicates that among the solvents investigated, THF is the best solvent with ee values 72, 70, and 68 for LDH-Pt, LDH-Rh, and LDH-Pd, respectively. A similar effect was observed in the hydrogenation of ethyl pyruvate using finely dispersed oxide-supported rhodium nanoclusters with cinchonidine [42]. With LDH-Rh catalyst and cinchonidine modifier in acetic acid as solvent, complete conversion of ethyl pyruvate to ethyl lactate with 80% ee is observed, but the main drawback with this system is leaching of the metal from the support. All the catalysts are recyclable, and consistent activity is observed for three cycles.

Table 10.5 Effect of solvent on the enantioselective hydrogenation of ethyl pyruvate to ethyl lactate

Catalyst	Solvent	Time (h)	Conversion (%)	ee (%)
LDH-Pt	THF	6	100	72
	Methanol	6	100	65
	Toluene	6	100	57
LDH-Rh	THF	6	100	70
	Methanol	6	100	60
	Toluene	6	100	55
LDH-Pd	THF	6	100	68
	Methanol	6	100	50
	Toluene	6	100	45

Reaction conditions: substrate (8.6 mmol), catalyst (50 mg), solvent (15 mL), room temperature, H_2 pressure (70 bar). Enantiomeric excesses based on HPLC yields.

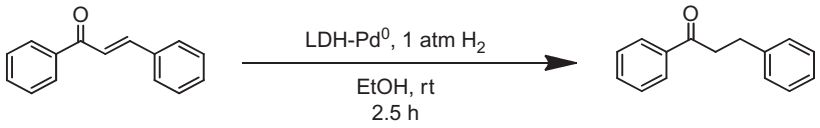
Reproduced with permission from M. Lakshmi Kantam, K. Vijaya Kumar, B. Sreedhar, Synth. Commun. 37 (2007) 959–964.

During the enantioselective hydrogenation of ethyl pyruvate to ethyl lactate catalyzed by LDH-Rh, LDH-Pt, and LDH-Pd, cinchonidine not only functions as a chiral modifier that modifies ethyl pyruvate into (*R*)-ethyl lactate, but also accelerates the reaction rate. Initially the ees increase with an increase in cinchonidine, but on further increase, there is a decrease of enantioselectivity. The decrease in ee when the concentration of cinchonidine is high is due to the side reaction of cinchonidine during the conversion of ethyl pyruvate to ethyl lactate. Also some cinchonidine was getting hydrogenated, resulting in the decrease in enantioselectivity [47].

10.4 Selective Hydrogenation

10.4.1 Chemoselective Hydrogenation of the Olefinic Bonds by Using Pd-Based Catalysts

Chemoselective hydrogenation of olefinic double bonds is an indispensable tool for the synthesis of natural products, pharmaceuticals, and functional materials [48–50]. The most promising method for performing these transformations is by employing transition metals particularly palladium under catalytic conditions using molecular hydrogen. Many of these processes were realized using Pd/C in combination with various additives like pyridines, amines, ammonium acetate, ammonia, and diphenylsulfide that results in the selective reduction of olefinic bond in the presence of aromatic halogens [51,52], aromatic carbonyls [53,54], epoxides [55], benzyl [53,54,56,57], benzyl esters [51], and *N*-carbobenzyl protective groups [51]. Selective hydrogenations of substituted γ-amino α,β-unsaturated esters were accomplished without affecting the benzyl ester or benzyl ether functionality using Pd/C in EtOAc in absence of additives [58]. Notably, Felpin and Fouquet [59] have reported the selective hydrogenation of olefins by in situ generated Pd^0/C catalyst from $Pd(OAc)_2$ and charcoal in methanol. A chemoselective hydrogenation method was demonstrated by Hirota et al. [60] using finely dispersed palladium catalyst in silk-fibroin. Ihm et al. [61] showed the potential application of Pd (II) complexes supported on a modified macroporous polymer bead for the hydrogenation of olefins. Similarly, Zecca et al. [62] used the ion-exchange resins-supported palladium catalyst for the same reaction. Dendrimer-encapsulated palladium nanoparticles were also explored for the chemoselective hydrogenation of olefins with modest success [63]. All these reports reveal the important requirement for an improved catalytic system for the chemoselective hydrogenation of olefin in the presence of various sensitive functional groups. Lakshmi Kantam et al. [64] reported a LDH supported palladium nanoparticles (LDH-Pd^0) catalyst for the hydrogenation reaction of (E)-chalcone using ethanol as a solvent at room temperature under one atmosphere hydrogen pressure (Scheme 10.5).



Scheme 10.5

Chemoselective hydrogenation of (E)-chalcone over LDH-Pd^0 catalyst. *Reproduced with permission from M. Lakshmi Kantam, T. Parsharamulu, S.V. Manorama, J. Mol. Catal. A Chem. 365 (2012) 115–119.*

The reaction proceeded with complete chemoselectivity and only the olefinic bond was reduced. Various reaction parameters were examined for hydrogenation of (E)-chalcone using LDH-Pd^0 as a catalyst and molecular hydrogen as the reducing agent at room temperature. The reusability of LDH-Pd^0 catalyst showed consistent activity and selectivity up to five cycles. After each cycle,

LDH-Pd^0 was recovered by simple filtration, washed, air-dried, and used directly for the next cycle without further purification. The Pd metal content of the fresh and used catalyst was found to be 9.48% and 9.32%, respectively, as measured by inductively coupled plasma (ICP) atomic emission spectroscopy (AES), which suggested that leaching was minimal.

The transmission electron microscopy (TEM) images of the catalyst before and after the catalytic reaction are shown in Fig. 10.5A and B, respectively. The Pd nanoparticles, seen as dark particles, are dispersed on the LDH support.

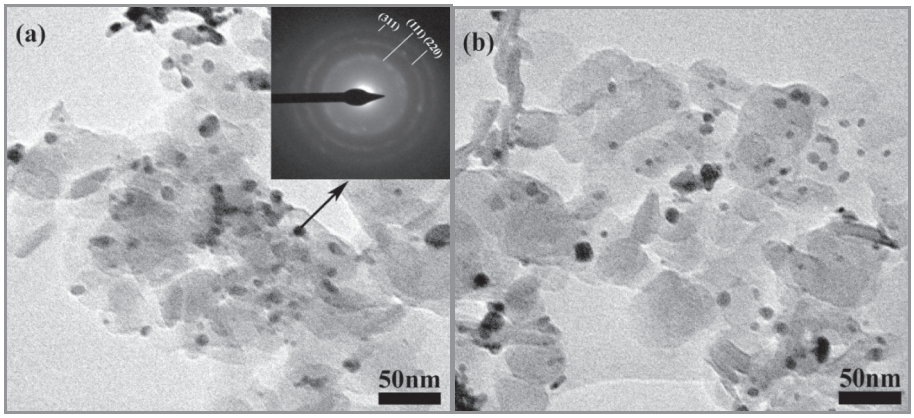


Fig. 10.5
TEM images of the LDH-Pd0: (A) fresh catalyst, inset shows the corresponding SAED pattern of Pd nanoparticle and (B) used catalyst. *Reproduced with permission from M. Lakshmi Kantam, T. Parsharamulu, S.V. Manorama, J. Mol. Catal. A Chem. 365 (2012) 115–119.*

Lakshmi Kantam et al. also reported the selective hydrogenation of chalcone using palladium impregnated magnesium lanthanum (Pd/Mg-La) mixed oxide as a heterogeneous catalyst and molecular hydrogen as the reducing agent at room temperature [65]. The results are depicted in Table 10.6. The reduced product was obtained in excellent yield and selectivity.

Table 10.6 Screening of reaction parameters for the hydrogenation of chalcone[a]

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	Pd/MgLa	Ethanol	2.5	97
2	Pd/MgLa	Ethyl acetate	4.0	97
3	Pd/MgLa	Methanol	4.0	97
4	Pd/MgLa	Toluene	4.0	97
5	Pd(II)Mg/La	Ethanol	6	98
6	Pd/MgLa	Ethanol	10	97
7	Pd/C	Ethanol	2.5	63[c]

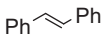
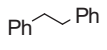
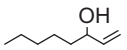
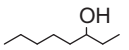
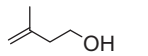
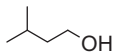
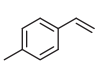
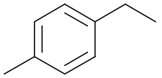
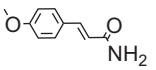
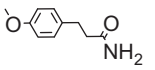
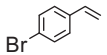
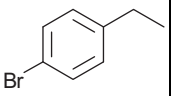
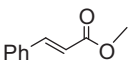
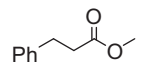
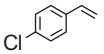
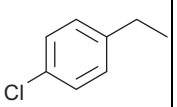
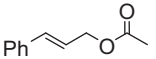
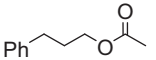
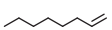
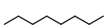
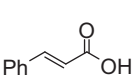
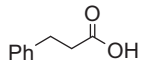
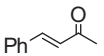
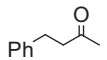
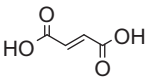
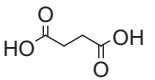
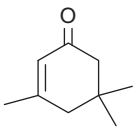
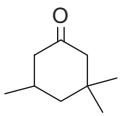
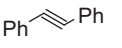
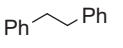
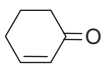
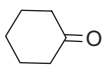
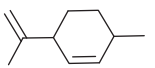
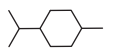
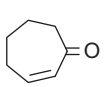
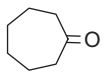
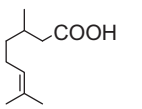
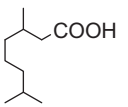
[a]Reaction conditions: *trans*-chalcone (2 mmol), 15 mg of Pd/MgLa mixed oxide catalyst (0.677 mmol% of palladium), solvent (10 mL), stirring under one atmosphere of hydrogen pressure at room temperature.
[b]Isolated yields.
[c]Commercial 5% Pd/C catalyst was used.
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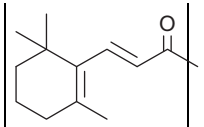
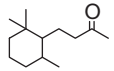
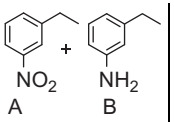
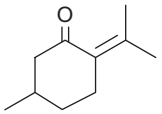
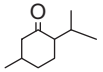
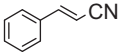
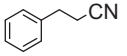
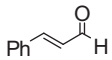
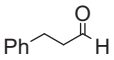
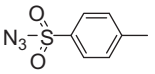
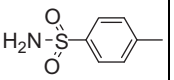
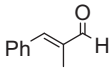
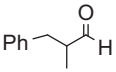
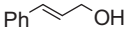
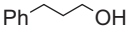
As can be seen in Table 10.6, longer reaction time was needed for the full conversion of the starting material using ethyl acetate, methanol, or toluene as solvents (Table 10.6, entries 2–4) while ethanol gave excellent yield and selectivity with reduced time (Table 10.6, entry 1). The activity of Pd(II)/MgLa mixed oxide catalyst in the hydrogenation reaction of chalcone was less compared to the Pd/MgLa mixed oxide and a longer reaction time was needed for completion of the reaction. However, complete chemoselectivity was also observed in the case of Pd(II)/MgLa mixed oxide catalyst (Table 10.6, entry 5). It is remarkable to note that the carbonyl group of the chalcone was not affected and not a trace amount of any by-product was formed, even when the reaction was continued for 10 h (Table 10.6, entry 6). In the comparative study, commercially available 5% Pd/C (same equivalents of Pd as in Pd/MgLa mixed oxide) showed poor selectivities and yields under the similar experimental conditions (Table 10.8, entry 7). After the completion of the reaction, the Pd/MgLa catalyst was removed quantitatively by simple centrifugation and the filtrate was concentrated under reduced pressure.

Performing the reaction of different unsaturated compounds under the optimized reaction conditions led to high selectivity with yields ranging from 80% to 98% (Table 10.7, entries 1–28). In the case of aromatic or aliphatic unfunctionalized substrates, the catalyst exhibits high activity (Table 10.7, entries 1–3 and 6). Thus trans-stilbene, styrene, 4-methylstyrene and 1-octene were successfully converted to their corresponding alkanes with 94–96% isolated yield. Remarkable chemoselectivity was observed in the hydrogenation of aromatic halides such as 4-chlorostyrene or 4-bromostyrene (Table 10.7, entries 4 and 5). In these cases, only the olefinic double bonds were reduced and the formation of dehalogenated products was not observed. Importantly, a wide range of functional groups, such as aldehydic, ketonic, alcoholic, carboxylic, amide, and ester moieties remain intact in the selective hydrogenation of olefinic double bonds under the reaction conditions (Table 10.7, entries 7–28).

In the hydrogenation of cyclic and aromatic α,β-unsaturated ketones, the olefinic bond was selectively hydrogenated without reducing the carbonyl moiety (Table 10.7, entries 7–12). Significantly, sterically more hindered tri-substituted olefinic ketones such as isophorone (Table 10.7, entry 8), ionone (Table 10.7, entry 11), and pulegone (Table 10.7, entry 12) afforded the reduced products with high yields and selectivity. Remarkably, in the hydrogenation of α,β-unsaturated aldehydes, such as cinnamaldehyde and α-methyl cinnamaldehyde high yields of the desired products were obtained and no partial reduction of the carbonyl functionality occurred to produce the alcoholic by-product (Table 10.7, entries 13 and 14). The aromatic as well as aliphatic alkenols with terminal double bonds such as oct-1-en-3-ol and 3-methylbut-3-en-1-ol were hydrogenated to their corresponding saturated alcohols in good yields (Table 10.7, entries 15–17). Moreover, a wide range of functional groups, carboxylic, amide and ester moieties remain intact in the chemoselective hydrogenation of olefinic double bonds under the reaction conditions (Table 10.7, entries 18–22 and 25). Thus, maleic acid (Table 10.7, entry 21) was hydrogenated without any further hydrogenation of

Table 10.7 Selective hydrogenation of different unsaturated compounds[a]

Entry	Substrate	Product	Time (h)	Yield (%)	Entry	Substrate	Product	Time (h)	Yield (%)
1			1	96	16			1	94
2			0.5	94	17			1	94
3			0.5	94	18			2	96
4			2	98	19			2	96
5			2	98	20			2	96
6			1	94	21			7	96
7			2	96	22			2	96
8			2	98	23			2	96
9			1	94	24			2	94
10			1	94	25			2	98

11			2	98	26			2	A = 0 B = 0
12			2	98	27			2	98
13			2	96	28			0.5	96
14			2	96					
15			2	96					

[a]Reaction conditions: substrate (2 mmol), 15 mg Pd/MgLa mixed oxide catalyst (0.67 mmol% of Pd), ethanol (10 mL), stirring under one atmosphere hydrogen pressure at room temperature.

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the carboxylic group. The reduction of diphenylacetylene produces dibenzyl as the sole product with 96% yield (entry 23).

In Table 10.8, the results from the investigation of recycling of the catalyst are presented. The Pd/Mg-La mixed oxide catalyst shows consistent activity and selectivity up to five cycles with four different substrates. After each cycle, Pd/MgLa mixed oxide catalyst was recovered by simple centrifugation, washed, air dried, and used directly for the next cycle without further purification. The Pd metal content of the fresh catalyst is 9.62%, and in the case of the used catalyst, it was found to be 9.58% measured by AAS suggested that there was no leaching of Pd.

Table 10.8 Recyclability test of the catalyst with different substrates[a]

Substrate	Yield[b]				
	Fresh	Run 1	Run 2	Run 3	Run 4
trans-Chalcone	97	97	97	97	–
Diphenylacetylene	96	96	96	96	–
Cinnamaldehyde	96	96	96	96	96
trans-Stilbene	96	96	96	96	–

[a]Reaction conditions: substrate (2 mmol), 15 mg of Pd/MgLa mixed oxide catalyst (0.677 mmol% of palladium), ethanol (10 mL), stirring under one atmosphere of hydrogen pressure at room temperature.
[b]Isolated yield.
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10.5 In Situ Hydrogenation

The reduction of multiple bonds using hydrogen gas and a metal catalyst is a reaction common to all organic chemists. Far less established is the possibility of achieving reduction with the aid of an organic molecule as the hydrogen donor in the presence of a catalyst, a process known as catalytic transfer hydrogenation. In 1952, Braude et al. [66] made the proposal that catalytic hydrogen transfer from an organic donor molecule to a variety of organic acceptors might be possible under mild conditions. This process is but one of several possible hydrogen transfer reactions which were classified by Braude and Linstead [67] as catalytic transfer hydrogenation.

This reaction type can be realized in principle by thermal means, homogeneous catalysis, heterogeneous catalysis, photochemical means, or with biological processes. However, few systematic studies were directed toward the catalytic transfer hydrogenation. Knowledge of

the principal reaction, however, goes back to the turn of the century, when Knoevenagei and Bergdolt [68] first observed that dimethyl 1,4-dihydroterephthaIate is disproportionate readily in the presence of palladium black to dimethyl terephthalate and (mostly *cis*) hexahydroterephthalate. Several years later, Wieland [69] observed the same reaction with dihydronaphthalene.

Diverse transfer hydrogenation systems have been reported in the literature, but most of them use costly metals (Ir/Rh complexes) [70] or poorly active and very unstable complexes (Fe complexes) [71]. Notwithstanding a recent report by Morris on highly effective iron-based transfer hydrogenation catalysts [72], ruthenium complexes prevail to date as the best compromise between price and reactivity [73]. Amongst the numerous ruthenium complexes reported [74] for transfer hydrogenation, one of the first very active catalysts was the complex $[Ru_2(CO)_4(\mu\text{-}H)(C_4Ph_4COHOCC_4Ph_4)]$ (Fig. 10.6, number 1), synthesized in 1984 by Shvo. This complex is also known as Shvo's catalyst [75]. Many applications have been reported with 1 (Fig. 10.6) in hydrogen transfer reactions [76]. In 2007, Frost synthesized an interesting variation, 3 (Fig. 10.6, number 3) , of $[Ru(Cl)\text{-}(PPh_3)_2(indenyl)]$ 2 (Fig. 10.6, number 2), [77] first reported by Oro [77]. Complex 3 is remarkably active in transfer hydrogenation in formic acid. Casey has reported a novel complex (4) (Fig. 10.6, number 4) bearing an O-trimethyl silyl ether (OTMS)-substituted indenyl ligand, showing activity in transfer hydrogenation reactions [78].

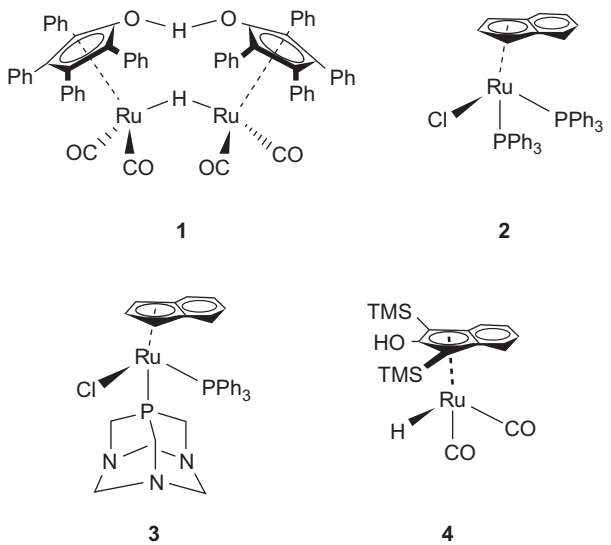
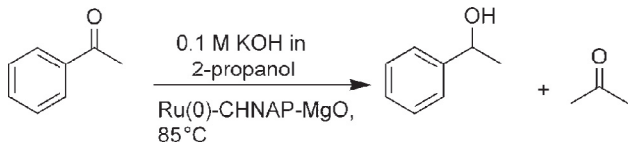


Fig. 10.6

Ruthenium complexes for transfer hydrogenation. *Reproduced with permission from S. Manzini, C.A.U. Blanco, S.P. Nolan, Adv. Synth. Catal. 354 (2012) 3036.*

However, the application of such catalysts is limited, partially due to the issues of separation and recycling of the catalysts. To overcome such difficulties, immobilization of homogeneous catalysts on insoluble supports has received extensive interest in recent years, as it facilitates the separation, recovery, and reuse of catalysts [79]. However, there are only a few reports on the effective transfer hydrogenation using immobilized catalysts [80,81].

Lakshmi Kantam et al. [82] reported the "gasless" approach for carrying out the hydrogenation of carbonyl functional groups by using 2-propanol, as the source of H_2 and ruthenium nanoparticles stabilized on nanocrystalline magnesium oxide with ionic liquids as the catalyst (Scheme 10.6).



Scheme 10.6

Transfer hydrogenations of acetophenone with 2- propanol over Ru(0)-CHNAP-MgO catalyst. *Reproduced with permission from M. Lakshmi Kantam, R. Sudarshan Reddy, U. Pal, B. Sreedhar, S. Bhargava, Adv. Synth. Catal. 350 (2008) 2231–2235.*

10.5.1 Preparation of the Catalyst

The catalysts were prepared by treating magnesium oxide crystals with choline hydroxide (CH) [82] in dry THF. NAP-MgO (1.0 g) and CH (0.5 mL) were taken in a 50-mL round-bottomed flask containing 25 mL of dry THF and stirred under a nitrogen atmosphere for 4 h. The CHNAP-MgO was then filtered and washed several times with acetone and dried under vacuum. CHNAP-MgO (1.0 g) was stirred with $RuCl_3$ (0.415 g) in 75 mL of freshly prepared deionized water at 25°C for 24 h under a nitrogen atmosphere. The solid was filtered, washed with deionized water, and acetone, and dried overnight at 110°C to obtain Ru-(III)-CHNAP-MgO. The final Ru(0)-CHNAP-MgO catalyst was obtained after hydrogenation of the solid at 280°C for 4 h. The prepared Ru(0)-CHNAP-MgO catalyst was gray in color and from the elemental analysis, the Ru content was determined to be 1.64 mmol g^{-1} (Ru content: 16.6 wt.%).

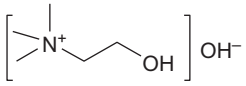
10.5.2 General Procedure for the Transfer Hydrogenation of Carbonyl Compounds With Ru(0)-CHNAP-MgO Catalyst

A reaction mixture containing 1 mmol of the substrate, 5 mL of 2-propanol and KOH in 2-propanol (0.1 mol), was placed in a two-neck, round-bottomed flask equipped with a septum port, reflux condenser, and a guard tube. To this mixture were added 50 mg of freshly vacuum-dried catalyst Ru(0)-CHNAP-MgO. The transfer hydrogenation reaction was carried under reflux at 85°C. ^{1}H NMR, MS and IR analyses confirmed the identity of the products.

The reusability of the catalyst was tested after washing the used catalyst with 2-propanol followed by drying at 100°C.

As can be seen from Table 10.9, catalysts Ru(0)-CHCP-MgO, Ru(0)-CHCM-MgO and the ruthenium catalyst without CH, Ru(0)-NAPMgO afforded 81%, 65%, and 64% yields after 6 h (Table 10.9, entries 2, 3, and 9). The best result was obtained with the catalyst Ru(0)-CHNAP-MgO (95%). NAP-MgO is purely ionic and has a three-dimensional polyhedral structure which, having the presence of high surface concentrations of edge/corner and various exposed crystal planes (such as 0 02, 0 01, and 1 1 1), leads to inherently high surface reactivity per unit area. The NAP-MgO has (i) Mg^{2+} sites of the Lewis acid type, (ii) O_2 sites of the Lewis base type, (iii) lattice bound hydroxy groups, (iv) isolated hydroxyl groups, and (v) anionic and cationic vacancies. The commercial-MgO (BET-SA = 25 m^2 g^{-1}) samples are generally large cubic crystals, on the other hand conventionally prepared-MgO (BET-SA = 252 m^2 g^{-1}) samples are thin hexagonal platelets about 150 nm long and 10 nm thick having large exposed areas of the (1 0 0) crystal face. Thus, NAPMgO did indeed display the highest activity compared to CP-Mg O and CM-MgO [24].

Table 10.9 Transfer hydrogenation of acetophenone with different catalysts at 85°C[a]



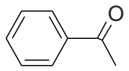
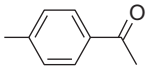
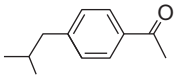
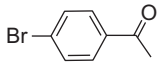
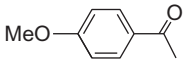
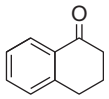
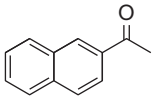
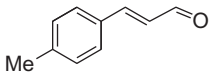
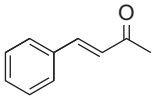
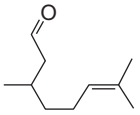
Choline hydroxide (CH)

Entry	Catalyst	Time (h)	Yield (%)[b]
1	Ru(0)-CHNAP-MgO	6	95
2	Ru(0)-CHCP-MgO	6	81
3	Ru(0)-CHCM-MgO	6	65
4	Ru(III)-CHNAP-MgO	6	30
5	$RuCl_3$	6	0
6	CHNAP-MgO	12	0
7	NAP-MgO	6	0
8	CH	12	0
9	Ru(0)-MAP-MgO	6	64

[a]Reaction conditions: substrate (1 mmol), 2-propanol (5 mL), KOH in 2-propanol (0.1 mol), catalyst (8.2 mol%), refluxed at 85°C.
[b]Isolated yields.
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The active catalyst Ru(0)-CHNAP-MgO, was tested for the selective transfer hydrogenation of various carbonyl compounds with 10 mol% KOH in 2-propanol and in all cases the reaction was completed within 6–10 h with high yields (Table 10.10). The efficiency and stability of the newly established catalytic system was examined in detail with acetophenone as the substrate. The reduction proceeds to completion giving excellent isolated yields through five successive cycles (Table 10.10, entry 1). The selective reduction of

Table 10.10 Transfer hydrogenation of various carbonyl compounds with 2-propanol over Ru(0)-CHNAP-MgO catalyst[a]

Entry	Substrate	Time (h)	Yield (%)[b]
1		6	95, 91[c]
2		6	93
3		6	94
4		6	95
5		6	94
6		10	89
7		10	92
8		10	93
9		10	90
10		10	84

[a]Reaction conditions: substrate (1 mmol), 2-propanol (5 mL), KOH in 2-propanol (0.1 mol%) catalyst (0.05 g), refluxed at 85°C.
[b]Isolated yields.
[c]Fifth cycle.
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4-methyl-cinnamaldehyde, 4-phenylbut-3-en-2-one and citronellal (Table 10.10, entries 8–10) afforded the corresponding alcohols in excellent yields, albeit with longer reaction times. It is important to note that the high yields were obtained in the reduction of 4-isobutylacetophenone and 6-methoxy-2-acetophenone (Table 10.10, entries 3 and 5) and the

corresponding alcohols are intermediates for the synthesis of ibuprofen and naproxen, respectively. The average turnover number for our catalytic system is 11. Ru(0)-CHNAP-MgO catalyst was recovered and reused for four cycles under the same reaction conditions.

10.6 Simple Hydrogenation in the Area of Energy Sector

10.6.1 γ-Valerolactone Properties and Its Products as Fuel

γ-Valerolactone (GVL) is a 5-carbon (valero-) cyclic ester with five atoms (four carbons and one oxygen) in the ring (γ-lactone). GVL is a colorless liquid stable at normal conditions and has a sweet, herbaceous odor, which makes it suitable for the production of perfumes and food additives [83]. The properties of GVL (Table 10.11) make it both stable and reactive enough to produce a variety of compounds, including butene, valeric acid, and 5-nonanone [84], and allows GVL to be used as a solvent derived from biomass. GVL is liquid at normal conditions and has a high boiling point. It does not decompose or degrade with time, even in the presence of water or oxygen, is stable at moderate temperatures, and does not form peroxides in air [83]. GVL has low toxicity (LD50 oral-rat = 8800 mg kg^{-1}), and the main risk is flammability; however, the low volatility of GVL makes the flammability risk at normal conditions low. Other useful thermodynamic data for several reactions involving GVL have been predicted by Dixon et al. [85].

Table 10.11 Main properties of GVL

Property	Value
CAS-No	108-29-2
Formula	$C_5H_8O_2$
MW (g/mol)	100.112
Refractive index (n20/D)	1.432
Density (gm/L)	1.05
Flash point (°C)	96
Melting point (°C)	−31
Boiling point (°C)	207–208
Solubility in water (%)	100
ΔH_{vap}(KJ/mol)	54.8
$\Delta_c H^{\circ}_{liquid}$(KJ/mol)	−2649.6

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GVL can be used directly as a liquid fuel or as an additive to current petroleum fuels similar to ethanol. Mixtures of 90 vol% conventional gasoline with 10 vol% GVL, or 10 vol% ethanol were compared by Horvath et al. [83], and they observed that the mixture with GVL had a lower vapor pressure, which improved the combustion at similar octane numbers. GVL has not been tested as a pure fuel, but it has similar combustion energy to ethanol (29.7 MJ kg^{-1}) and a higher energy density. A major issue with using GVL as a pure fuel is its high water

solubility; however, water can be distilled from the GVL as there are no azeotropes, in contrast to the case of ethanol.

10.6.2 Levulinic Acid Hydrogenation to Produce GVL

Homogeneous catalyst systems using formic acid as a reducing agent are reported for the synthesis of GVL from levulinic acid (LA) [86,87]. Hydrogenation of LA was also reported over several bi-metallic catalysts on different supports (eg, carbon, Al_2O_3, TiO_2, and ZrO_2) at higher temperatures (180–250°C) and pressures [88,89].

Lakshmi Kantam et al. [90] reported that hydroxyapatite as a novel support for Ru in the hydrogenation of LA to GVL at low temperatures and pressures with an excellent rate c. 15.0 mol h^1 $(mol_{Ru})^1$ of GVL using H_2O as solvent.

10.6.3 Preparation of Catalysts

The hydroxyapatite was prepared according to published procedures [91,92]. In a typical experiment, a solution of calcium nitrate tretrahydrate (32.6×10^{-2} mol) in 200 mL water was brought to pH 11–12 with concentrated (25%) ammonia solution and thereafter diluted to 500 mL. A solution of diammonium hydrogenphosphate (31.8×10^{-2} mol) in 300 mL water was brought to a pH of 11–12 with concentrated (25%) ammonia solution and thereafter diluted to 600 mL. Under vigorous stirring, the phosphate solution was added drop wise to the solution of the calcium salt over a period of c. 2 h to produce a milky white precipitate, which was then stirred and boiled for 30 min. After filtration, the precipitate was washed thoroughly and dried at 100°C overnight and then calcined at 500°C for 3 h. The calcined hydroxyapatite is hereafter denoted as hydroxy apatite (HAP). The metal catalysts (Ru, Ni, Pt, Pd) supported on HAP are prepared by impregnation method.

10.6.4 Hydrogenation of LA

Hydrogenation of LA was carried out in a 100 mL mechanically stirred Parr autoclave equipped with a photoionization detector (PID) controller 4848. In a typical experiment, about 2.0 g (17.3 mmol) of LA and 38.0 g of water were added with ~0.1 g of ex situ reduced catalyst sample.

The reaction was performed at a H_2 pressure of ~0.5 MPa, reaction temperature in the range 50–70°C, and the stirring speed of 1000 rpm. The samples were by GC and GC-MS. The carbon mass balance is 98% in all the measurements unless otherwise mentioned.

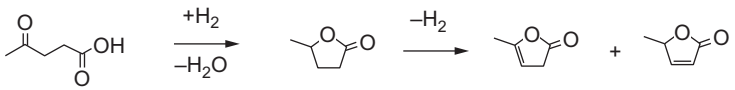
The activity data over M/HAP (M = Ru, Pd, Pt, and Ni) catalysts in the hydrogenation of LA to GVL is reported in Table 10.12.

Table 10.12 Hydrogenation of LA to GVL over metals supported on hydroxyapatite[a]

S. No	Reduced Catalyst	Conversion (%)	Selectivity		
			GVL[b]	α-AL[c]	β-AL[d]
1	HAP	2	99	–	–
2	5 wt.% Ru-HAP	99	99	–	–
3	5 wt.% Pd-HAP	26	90	4	5.6
4	5 wt.% Pt/HAP	42	88	8	4.0
5	5 wt.% Ni/HAP	18	65	22	12
6	5 wt.% Ru-HAP[e]	20	99	–	–

[a]H_2 pressure: 0.5 MPa, 5% of LA (2.0 g ~ 17.24 mmol), ~0.100 g of catalyst, water (38 mL) at a reaction temperature of 70°C.
[b]GVL, γ-valerolactone.
[c]AL, α-Angelica lactone.
[d]AL, β-Angelica lactone.
[e]Unreduced Ru/HAP catalyst.
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Prior to the reaction, the catalyst samples were reduced using 5% H_2/Ar at 450°C for 3 h and immediately transferred to autoclave with subsequent addition of the reaction mixture. In the comparative analysis, Ru/HAP catalyst demonstrated superior activity and selectivity over the other metal catalysts which showed significant amounts of by-products i.e. α- and/or β-Angelica lactones. The unreduced Ru/HAP exhibited 20% conversion with 99% selectivity towards GVL, thus suggesting surface metallic Ru species to be responsible for the high hydrogenation activity. Formation of α-, β-angelica lactones (Scheme 10.7) may be explained by dehydrogenation of GVL.



Scheme 10.7
Hydrogenation of LA to GVL over Ru/HAP catalyst using ethanol and water as solvents. *Reproduced with permission from M. Sudhakar, M. Lakshmi Kantam, V. Swarna Jaya, R. Kishore, K.V. Ramanujachary, A. Venugopal, Catal. Commun. 50 (2014) 101–104.*

The Ni/HAP sample showed unusually high amount of α-Angelica lactone (~22%). Hydrogenation of LA is carried out using ethanol and/or H_2O as solvents and the data is reported in Table 10.13.

These results show that at 70°C using EtOH and EtOH + H_2O (1:1) as solvents, conversion of LA is fairly good (92%) with 72–86% selectivity to GVL and about 14–28% of ethyl levulinate. Formation of ethyl levulinate is expected by transesterification of LA with ethanol

Table 10.13 Hydrogenation of LA to GVL over Ru/HAP using ethanol and water as solvents[a]

Entry	Catalyst	Solvent	T (°C)	Conversion (%)	Selectivity	
					GVL	EL
1	Ru/HAP	Ethanol	70	92	76	22
2	Ru/HAP	Ethanol + H_2O	70	92	82	14
3	Ru/HAP	H_2O	70	99	99	Nil
4	Ru/HAP	H_2O	60	99	99	–
5	Ru/HAP	H_2O	50	99	99	–
6	Ru/HAP	Toluene	70	30	92 & 8% AL[b]	–

[a]Conditions: 5% of LA (2.0 g, 17.24 mmol), 5 wt.% Ru/HAP (0.100 g),water (38 L), H_2 (0.5 MPa); GVL, γ-valerolactone; EL, ethyl levulinate.
[b]AL, α-Angelica lactone; reaction time: 4 h.

(Table 10.13, entries 1 and 2). A reason for choosing ethanol as a solvent was to explore the nature of Ru/HAP catalyst towards reforming of aqueous ethanol anticipating that in situ H_2 can be generated and the external H_2 may be avoided for the hydrogenation of LA. Unfortunately, we found ethyl levulinate as a by-product and no activity due to reforming of ethanol is found when ethanol was used as a solvent.

The hydrogenation of LA was further tested at different time intervals (1–4) under optimized reaction conditions over Ru/HAP and the data is reported in Table 10.14. It shows that a steady increase in the rate of GVL formation is observed from 1 h to a reaction time of 4 h.

Table 10.14 Reaction time vs. rate of GVL formation over Ru/HAP catalyst

Time (h)	% Conversion	% Selectivity (GVL)	r_{GVL} [mol h^{-1} $(mol_{Ru})^{-1}$]
1	5.5	99.5	3.03
2	32.6	99.5	9.88
3	69.4	99.0	13.96
4	99.0	99.0	14.98

Conditions: 5% of LA (2.0 g, 17.24 mmol), 5 wt.% Ru/HAP (0.100 g), water (38 mL), H_2 (0.5 Pa), GVL, γ-valerolactone; reaction time: 1–4 h.
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The activity data on recyclability studies over Ru/HAP catalyst is reported in Fig. 10.7. The Ru/HAP displayed good recyclability with a slight decrease in LA conversion, which is possibly due to loss of catalyst during recovery with each subsequent cycle.

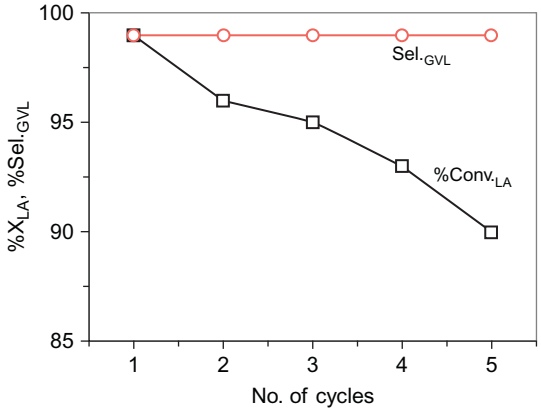


Fig. 10.7

Recyclability studies over 5 wt.%Ru/HAP during the hydrogenation of levulinic acid. *Reproduced with permission from M. Sudhakar, M. Lakshmi Kantam, V. Swarna Jaya, R. Kishore, K.V. Ramanujachary, A. Venugopal, Catal. Commun. 50 (2014) 101–104.*

10.7 Kinetics of Hydrogenation

Chemical kinetics is of increasing significance in catalysis, acting as a bridge between the theory and practice of catalytic processes. Today, chemical kinetics provides a theoretical basis, experimental techniques, and calculative methods, which allow the development of accurate and dependable models for qualitative and quantitative depiction of catalytic processes [93–101].

Certain specific features of hydrogenation reactions are very important in kinetic studies:

- The diversity of catalytic systems, and hence, the possible diversity of intermediates and mechanisms, giving rise to different kinetic behaviors.
- The complex nature of these reactions, giving rise to multistep mechanisms. The complexity of reactions, leading in various directions.
- The variety of adsorbed forms of hydrogen under different conditions, with possible penetration into the subsurface layer of the catalyst, complicating the kinetics.
- The existence of temperature maximum of hydrogenation rate (near 200°C at atmospheric pressure.

The kinetic data and their interpretation in the case of liquid phase hydrogenation may be complicated by the following effects:

1. The three-phase nature of the system means that hydrodynamic factors and the transport to the boundary must be taken into account [103–105].

2. Numerous influences of the liquid reactants and solvent, due to solvation of the reactive system, catalyst and active complexes, to ionic and dipole interactions, and to the change in reactivity in concentrated solutions [106–108].
3. Increased likelihood of inhibition by mass and heat transfer, and by dissolution of the components.
4. The possibility of transition from one stationary or quasi-stationary regime to another, in particular, because of abrupt changes in the concentration ratios of components in closed systems, which may give rise to drastic changes in kinetic relationships [109,110].

The Langmuir-Hinshelwood mechanism [111] assumes that the species to be hydrogenated and hydrogen react in the adsorbed state in the ideal layer [93,98], given that the slow step is the surface interaction. The general kinetic equation follows:

$$r = k\frac{P_1^{n_1}P_2^{n_2}}{\left(L + k_1P_1 + k_2P_{H_2}^m + k_3P_2^n\right)} \tag{10.1}$$

where P_1, P_{H_2}, and P_2 are the partial pressures of the original substance, hydrogen and the product respectively; r is the reaction rate, the remaining symbols denote constants. For this mechanism, it is usual that $n_1 = 1$, and $L = 0$ or 1. For low coverages $z = 0$, and the above equation becomes

$$r = kP_1^{n_1}P_{H_2}^{n_2} \tag{10.2}$$

For atomic and molecular adsorption of hydrogen, the index m has values of 0.5 and 1, respectively, and $1 = 2$ corresponds to the interaction of two particles in the surface layer.

In a real surface layer [93,98,110], the reaction rate may be given by an equation similar to (10.1), but with different meanings of the constants. Eq. (10.1) may also be valid for other slow steps, perhaps with minor amendments [98].

The Eley-Rideal mechanism [111] assumes that one of the components enters the reaction from a chemisorbed state, and the other comes from a state of physical adsorption or directly from the gas phase (collision mechanism).This mechanism can also be represented by Eq. (10.1), although some constants in the denominator will vanish.

10.8 Summary

- The reduction of a wide range of organic nitro compounds to the corresponding amines in good to excellent yields has been achieved using a recyclable heterogeneous catalyst, [NAP-Mg-Pd(0)]. This method is mild, exceedingly efficient, and highly selective.
- A wide range of functional groups is well tolerated under the reaction conditions. The method utilizes easy handling procedures, and the separation of the products from the reaction system can be achieved by simple filtration followed by solvent removal.

- LDH-supported nano noble metal heterogeneous catalysts are synthesized by ion exchange of K_2PtCl_6, Na_2PdCl_4 and impregnation of $RhCl_3{\cdot}3H_2O$ followed by reduction with H_2. The LDH-Rh, Pt, and Pd catalysts are tested in the enantioselective hydrogenation of ethyl pyruvate to ethyl lactate with very good yields and enantiomeric excesses (ees) of up to 72% were obtained with Pt. The catalyst was recovered and reused for several cycles with consistent activity.
- Transfer hydrogenation of various carbonyl compounds was achieved in excellent yields by ruthenium nanoparticles stabilized on the nanocrystalline magnesium oxide by the incorporation of CH, a basic ionic liquid. The procedure is simple, efficient, and the catalyst can be recycled five times.
- Palladium/magnesium-lanthanum mixed oxide catalyst is found to be an efficient heterogeneous catalyst for the chemoselective hydrogenation of olefinic double bonds in the presence of various functional groups. The catalyst was recovered by centrifugation and reused for several cycles with consistent activity and selectivity.
- The Ru supported on hydroxyapatite catalyst showed significantly high activity and selectivity in the hydrogenation of LA at low pressure and temperature. TPD of NH_3 and CO_2 studies indicated that acid-base sites on Ru/HAP seem to influence the hydrogenation of LA. In the comparative analysis, the rate of GVL is found to be in the order Ru>Pt>Pd>Ni. The Ru/HAP was stable up to four recycles and displayed good to excellent yields [c. 15.0 mol h^{-1} $(mol_{Ru})^{-1}$] of γ-valerolactone, a fuel additive that can be synthesized from bio-mass derived LA. Further, thorough characterization studies are needed on the surface properties of $Ru/Ca_5(PO_4)_3(OH)$.
- This chapter presents an overview of hydrogenation processes carried out under ex situ and in situ conditions. It starts with a general description of fine chemicals and the importance of hydrogenation reactions for fine chemical synthesis. A discussion about asymmetric hydrogenation of organic compounds has also been carried out. Various methods adopted for the synthesis of different catalysts and their applications for hydrogenation reactions has been discussed in detail.
- The work presented in this chapter stimulates a new dimension in the area of catalysis and the area is wide open for the synthesis of fine and specialty chemicals.

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CHAPTER 11

Heterogeneous Catalysis for Perfumery Chemicals

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11.1 Introduction

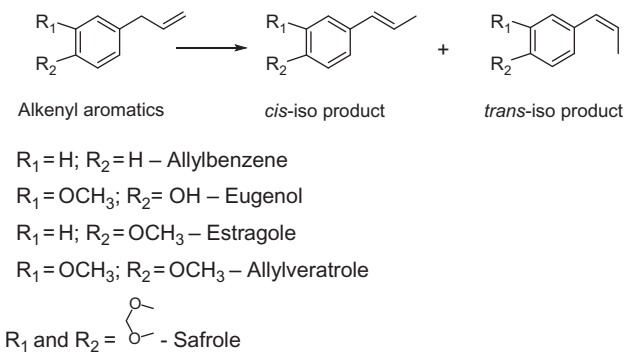
The use of perfumery chemicals goes back thousands of years. The word perfume comes from Latin words *per=through, fume=smoke* ("through smoke"). This implies burning aromatics (plants) for fragrance. Perfumery chemicals can be synthetic and natural. The majority of the natural fragrant chemicals are extracted from plants or are of animal origin. The extracts of plants, derived as essential oils, have a wide combination of aromatics that provide diverse fragrant and flavor properties. Essential oils include odorous volatile substances that evaporate when exposed to air, rendering the odor to oils. Essential oils contribute around 17% to the fragrance and flavor industries, with the majority of it as flavors in the food industry (50–60%). In the perfumery industry, the usage of essential oils is around ~20%. The annual turnover of these fragrant molecules is more than US$ 6 billion and it is met mainly by more than 100 essential oils [1]. The specific molecules can be isolated from a natural extract (essential oil) to obtain a specific fragrance. During the 20th century, the use of perfumery and cosmetic products became common and this enhanced the consumption and production of perfumery chemicals. As the demand for fragrance/flavors is huge and growing with the advent of urbanization in recent decades, which consequently purports that the natural extracts alone are insufficient to cater to the day-to-day requirements. This opened up a new avenue for the production of diverse fragrant molecules synthetically that resembled the smell from natural sources. In parallel, the growth in organic chemistry that conjoined in many sectors helped in the production of synthetic fragrant molecules, and efforts were made to make them more economical than the natural products.

The first synthetic perfumery note used was of jasmine [2]. It is estimated now that less than 5% of perfumery molecules are derived from natural sources. In addition, to meet the high demand of original and new fragrances, the industry strives to develop new molecules and/or formulations periodically. To be more competitive, 16–18% of the annual turnover is being invested in the research and development to realize new and fresh notes [3]. With the surge in

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the application of catalysis and catalytic materials for the synthesis of fine and specialty chemicals in the early half of the last century, synthetic substituents of natural perfumery molecules began to be realized and produced thorough catalytic routes. Although both homogeneous and heterogeneous catalysts are used for the production of fragrant molecules, the former is deployed more in the perfumery industry as in many other fine and specialty chemical industry sectors. However, it is also known that this catalysis poses separation difficulties and disposal problems. In the era of atom economy, E-factor, and green chemistry principles, the design and use of active heterogeneous catalysts is viable and practical, besides economical. In this chapter, the synthetic production of some perfumery molecules through various commonly practiced organic transformations will be discussed. In the discussion, emphasis will be made on the double bond isomerization of alkenyl aromatic compounds, a reaction chemistry that was carried out in our laboratory for more than a decade, where the product molecules have high fragrant value.

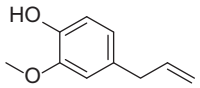
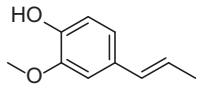
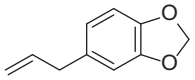
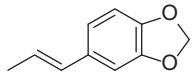
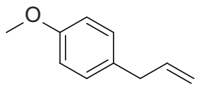
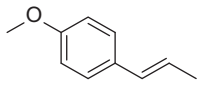
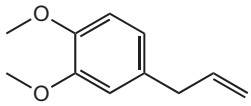
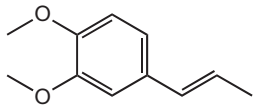
Isomerization is among several simple organic transformations for the production of perfumery chemicals. In this class, isomerization of alkenyl aromatic compounds to the corresponding thermodynamically stable isomers is an important reaction that produces a range of perfumery molecules. The double bond in the alkenyl group gets migrated to a position conjugated with the benzene (Scheme 11.1) and renders a mixture of both *cis* and *trans* isomers, with both having similar perfumery notes in large number of cases and hence, are dispensable to separate. The alkenyl aromatics of interest that can be isomerized to molecules with perfumery notes are eugenol, estragole, safrole, and allylveratrole. The iso-compounds of all these molecules have potential commercial value. A detailed discussion on these reactions and a brief outlook and discussions on the other classes of reactions (condensation, hydrogenation, and selective oxidation) for the synthesis of perfumery molecules are discussed.



Scheme 11.1
Isomerization of alkenyl aromatics.

Among the isomerized products of alkenyl aromatics, isoeugenol has wider applications in perfumery and flavoring for formulating insect attractants, UV absorbers, and biocides (Table 11.1). Isoeugenol (odor description: clove, spicy, sweet, woody) is also used in medicine (local antiseptic and analgesics) and for the production of vanillin and ferulic acid. Isosafrole is used as a major raw material in flavor industry to produce piperonal, ethyl vanillin, and vanillin with dense flavor. In addition, it is also used in pepticide and in the medicinal industry. Isomerization of estragole to *trans*-anethole has high industrial demand as intermediates for the synthesis of various perfumery chemicals [4,5]. *Trans*-anethole also finds application in the alcoholic beverage industry, food industry, and in the formulation of oral sanitation products. It is one of the precursors for the synthesis of anisic aldehyde, a synthetic intermediate for fragrance and flavor industries.

Table 11.1 Perfumery molecules through isomerization of alkenyl aromatics and their importance

Reactant	Product	Importance[a]
 Eugenol	 Isoeugenol	Flavoring agent, for vanillin production
 Safrole	 Isosafrole	Raw material for the production of piperonal, vanillin, isoeugenol, ethyl vanillin, etc. Raw material in medicinal and pesticide industry
 Estragole	 Anethole	Flavoring ingredient in toothpastes and mouthwashes
 4-Allyl veratrole	 4-Propenyl veratrole	Flavoring ingredient in food, pharmaceuticals

[a]In the context of products and nature of the reaction.

Isomerization reaction can be extended to terpenes, another important class of natural sources for flavor and fragrance. When it comes to the fragrance industry, any discussion must include reactions involving terpene. Molecules with a woody-amber odor are frequently used in the fragrance industry and are relatively expensive to produce [6]. Terpenes can also undergo condensation, hydrogenation, oxidation, hydroformylation, and cyclization to produce fine chemicals that are of perfumery interest [7]. Among many, isomerization of terpenes, such as longifolene and α-pinene, are important in the perfumery sector. The isomerization of

α-pinene (an inexpensive major constituent (ca. 85%) of turpentine oils) to camphene has high commercial value, as the product is an essential intermediate in the synthesis of isoborneol, isobornyl acetate, and camphor, which are extensively used in the fragrance industry [8]. The oxygenated derivative of isolongifolene, an isomerized product of longifolene, has been widely used in the perfumery and pharmaceutical industries because of its woody and floral notes [9].

Condensation reactions that lead to the formation of C–C (or C–X where X = N, S or O) bonds is very important for the synthesis of fine chemicals and in particular, for perfumery chemicals synthesis. Both solid acids and bases as heterogeneous catalysts are used for C–C bond forming reactions through various condensation protocols. Among them, aldol condensation is one of the important C–C bond forming reactions that produces a wide range of chemicals with various perfumery notes. Aldol condensation of acetone with citral gives pseudoionones, which are the acyclic precursor for α- and β-ionones [10]. These ionones have great industrial potential and are extensively used in fragrances and pharmaceuticals. Jasminaldehyde which has a violet scent, also known as α-amylcinnamaldehyde, with a fragrance note of jasmine can be synthesized by cross aldol condensation of heptanal and benzaldehyde [11]. Hydroformylation is another en route for C–C bond formation reaction and employed for the synthesis of several perfumery molecules that possess aldehyde functionality, such as aldehydes of limonene, isopulegol, isopulegyl acetate, and pinenes [7,12]. The importance of this reaction is that both linear and branch molecules of perfumery interest can be made [13]. Hydrogenation is an important reaction in the synthesis of perfumery chemicals, in particular after the advent of selective (region and stereo) hydrogenation of olefinic (C═C) and carbonyl (C═O) compounds [14].

In this chapter, the application and importance of heterogeneous catalysis in perfumery chemistry is discussed, focusing on isomerization, condensation, hydrogenation, and selective oxidation reactions. More emphasis is given to the isomerization of alkenyl aromatics and to their corresponding iso-products using hydrotalcites, and their modified forms (*vide infra*) as solid base catalysts. The advantage of using hydrotalcites as heterogeneous catalyst and the science behind its activity for isomerization of alkenyl aromatics is also discussed.

11.2 IP and Industrial Outlook

Fragrance and flavors, one of the high value-low tonnage sectors in fine and specialty chemicals, is one of the industries that touches human lives in different forms, immaterial of economic status, from toiletry items costing less than a dollar a product to high-end perfumes costing several hundreds of dollars for few ml. With a market value estimated around US$ 30 billion for this industry segment, it is expected to influence the economy of both producing and consuming nations. The industries are largely categorized on the basis of classes of chemicals they are involved with and mostly they protect the industry knowledge of both synthesis that uses catalytic materials and the formulation through intellectual property rights. Among the continents, Europe represents the largest worldwide market for fragrances and

perfumes, with global estimated sales volume of US$ 22 billion in 2011. The Global Industry Analysts Inc. estimated the global fragrances and perfumes market to cross US$ 33 billion by 2015. The large middle-income class populations in two highly populated nations and developing economies like China and India are poised to provide a huge growth opportunity and would be an add-on driving force.

A search using Thomson Innovation on the IP analysis of flavors and fragrances using catalytic materials support these market trends. If one were to see the top assignees (Fig. 11.1) in this segment, Procter & Gamble tops in the list with around 250 unique inventions in this domain. This is followed by BASF, International Flavors and Fragrances, and Kao Corporation.

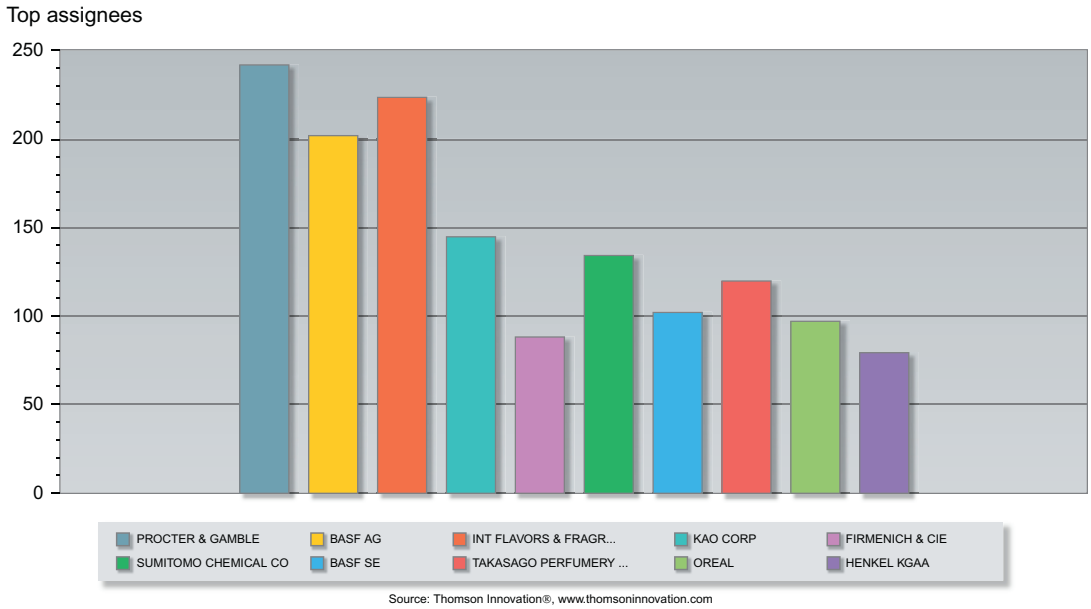


Fig. 11.1

IP portfolio of top assignees on catalytic approaches for fragrance and perfumery chemicals (Thomson Innovation: Title and Abstract = (cataly*) AND Title, Abstract and Claims = (fragran* or perfum*)—accessed on January 20, 2015).

If one were to see the top publishing countries (Fig. 11.2), Japan leads the list closely followed the United States and by European Patents. As stated earlier, the developing economies such as China and India are also catching up on this domain with a reasonable share on the inventions and a closer to lead countries such as Germany in the previous century. It is worth mentioning here that the Council of Scientific and Industrial Research (CSIR), India, the parent organization of the authors/editors of this chapter/book and one of the world's largest publicly funded organization, has been one of the top publishing assignees in this domain in the Asia-Pacific region, suggesting the importance placed on this field of research by CSIR.

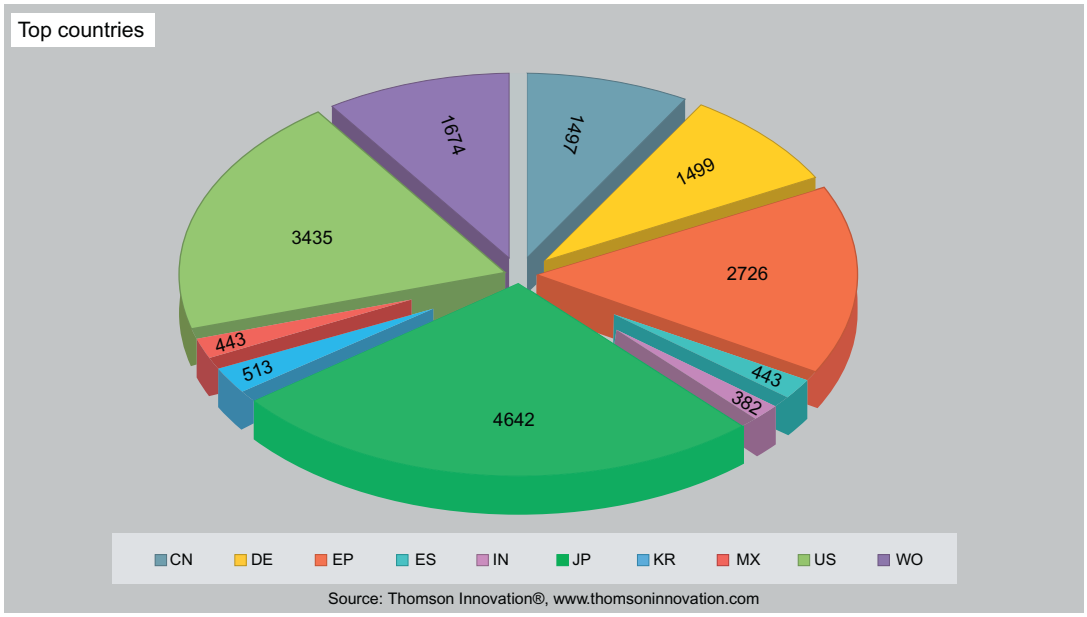


Fig. 11.2

IP portfolio of top publishing countries on catalytic approaches for fragrance and perfumery chemicals (Thomson Innovation: Title and Abstract = (cataly*) AND Title, Abstract and Claims = (fragran* or perfum*)—accessed on January 20, 2015).

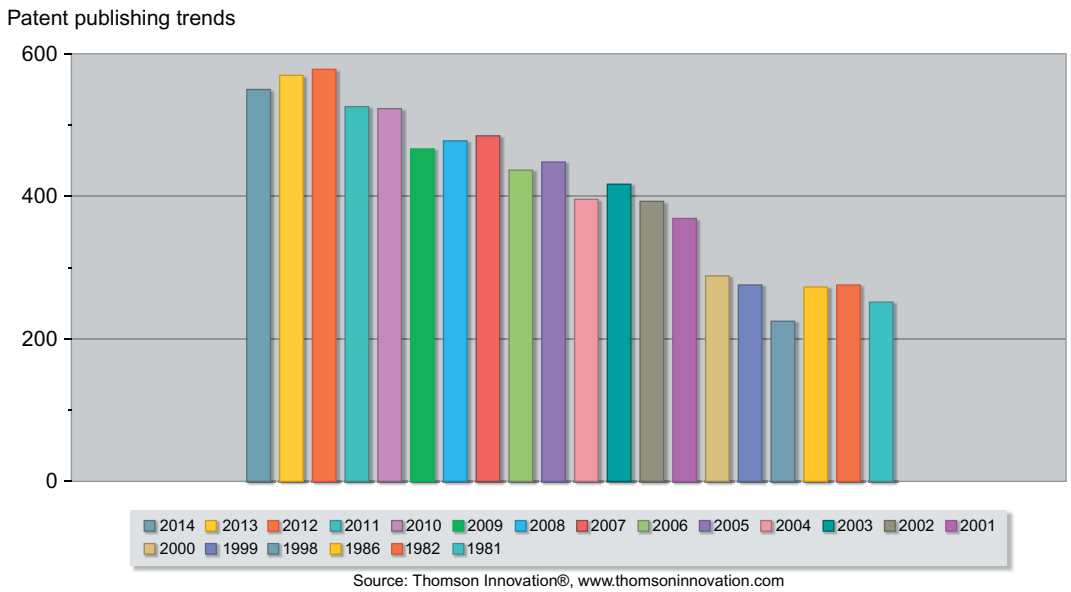


Fig. 11.3

IP portfolio of the yearly publishing trend on catalytic approaches for fragrance and perfumery chemicals (Thomson Innovation: Title and Abstract = (cataly*) AND Title, Abstract and Claims = (fragran* or perfum*)—accessed on January 20, 2015).

Further, if one were to assess the time period of the inventions (Fig. 11.3), it is clear that maximum inventions were protected in recent years, suggesting the current importance of this field, both in terms of scientific competition and economic influence. More than 500 unique inventions per year were filed in the last five years (more than 2.2% per annum considering the overall contributions in this filed since 1700) fervently augments the active IP contribution in this field. Some of the examples disclosed in these patents related to specific kinds of reactions are discussed in Section 11.4 of this chapter.

Although the fragrance industry is very much closely guarded, a 2013 study reported in Perfumer and Flavorist by Global Industry Analysts, says the industry is expected to reach about US$ 45.6 billion in 2018, (ie, roughly three years from now). This growth is expected mainly for two reasons, namely underpenetrated emerging markets and innovative products. Givaudan, a Swiss company, is reported to be the largest company in the world producing fragrance ingredients and flavors with a market share of ~25%. This was closely followed by International Flavors and Fragrances (sale value over US$ 3 billion) which also has a major patent portfolio. Recent market research reports the current Indian perfume market had revenues of around US$ 227 million in 2012, and is expected to increase to half a billion dollars by the end of 2017, although another report pegs at US$ 1.5 billion in the next couple of years considering the under-tapped market potential of burgeoning growth of people of middle-income class who now no longer consider perfumery products a luxury. Of this market, flavors and fragrances share is around 50% while the rest is aroma chemicals and essential oils. Many small and medium enterprises have been involved in the synthesis of various aroma chemicals and precursors, both for captive consumption and for export.

11.3 Approach—Homogeneous, Heterogeneous, and Bio-Catalytic Routes

Fragrant molecules can be synthesized by chemocatalysis and bio-catalysis routes. In the former, both homogeneous and heterogeneous catalyzed reactions are practiced. Usually, natural fragrance molecules will be of a single enantiomer and the catalyst needs to be stereoselective for the production of compounds with the specific configuration that gives the right fragrance [15]. Homogeneous catalysis usually includes mineral acids, alkali, metal complexes, metal ions, organometallic complexes, and to some extent, organic molecules for bio/organo catalysis [16]. The most common are mineral acids and alkali/alkaline earth compounds that leave huge waste and are environmentally unfriendly. During the first phase of the perfumery industry, acids and alkalis were predominantly used for catalyzing reactions. This was mostly due to the low cost, ease of availability, and most importantly, not much concern about the waste produced and its associated disposal problems. Although in general, homogeneous catalysts are more active and selective, owing to the homogeneity of the active site, they have several demerits. The separation of the catalyst from products is difficult

and hence, purification becomes tough, energy intensive, and expensive. Homogeneous catalysts, such as metal complexes, or organometallic complexes [16], are also used for reactions under discussion such as isomerization, condensation, and redox reactions. Isomerization of alkenyl aromatics can be done over homogeneous alkali in alcoholic media at very high temperature. These catalysts are often used in stoichiometric or superstoichiometric quantities and thus, produce waste streams and pose handling problems [17–19]. Homogeneous metal complexes like $ZnBr_2$ and $ZnCl_2$ are reported for α-pinene oxide isomerization [20]. Despite homogeneous catalysts being selective, they are in many cases inefficient if a specific isomer or enantiomer that exhibits a particular perfumery note is needed, where bio-catalysis plays an important role. However, they are very expensive and difficult to synthesize.

In the current scenario of significant environmental concern, industries are more focused to develop heterogeneous catalytic routes for their known advantages, such as ease of separation, reusability, relatively inexpensive, and easy to handle, besides many other advantages over their homogeneous/bio-catalysis counterpart. Heterogeneous catalysts are widely used in the refining, petrochemical industry, and pharmaceutical industries [21]. Even though it is less active and selective than homogeneous/bio catalyst, it is economical because of easy separation from products and being largely reusable. The main advantages of solid catalysts over conventionally used homogeneous catalysts are: environmentally benign, non-corrosive, and easily separable from the product mixture, and through proper design, can render high activity, selectivity, and longer life. High regio- and chemo-selectivity can be introduced in these heterogeneous catalysts through shape selectivity in porous solids, and through functionalization (acid, base, redox, chiral moiety, etc.) thereby allowing multi-step/cascade reactions. Such approaches render the synthesis of perfumery molecules with specific structure and/or stereochemistry. The application of heterogeneous catalysts for the synthesis of fine and specialty chemicals is receiving increased attention in recent years, as it provides inexpensive, safe, clean, and more environmentally sustainable processes that are easily adaptable in industries. Details on the use of heterogeneous catalysts for the synthesis of perfumery molecules are discussed in the following sections.

Bio-catalysis is another important branch of catalysis for the synthesis of compounds with cosmetic notes [22]. Bio-catalysts include enzymes, bacteria, cyanobacteria, yeast, microalgae, and animal cell. With the right entity, one can selectively produce molecules of perfumery interest at high kinetic rates. If a facile enzymatic catalysis method is available, this method is more preferred for being cost effective than chemical catalysis that generally operates under mild reaction conditions. The key component is identifying, designing, and validating the applicability of the enzyme for a given reaction and once found appropriate, methods are available for it to be produced in large quantity and deployed as bio-catalysts [23]. Furthermore, bio-catalysis is often carried out in water as a reaction media, which is greener and thus avoids the use of organic reagents/solvents. If the perfumery molecule is insoluble in water, biphasic systems are often used in those cases [15].

In bio-catalysis, lipases are the most studied enzymes for the synthesis of a particular enantiomer of perfumery molecules from a broad range of substrates [24]. Reports are available regarding the use of lipase as a bio-catalyst for perfumery chemicals in non-aqueous solvents, also. Ionic-liquids and supercritical fluids are also used as non-aqueous solvents for esterification and transesterification [24]. Lipases are also used for the hydrolysis of medium-chain length fatty acid [25], acetylation of alcohol, [26] and esterification of fatty acid to produce cosmetic esters [27–29]. Cutinase, one of the most common enzymes, is used for the synthesis of hexyl octanate in very high yield without forming any side product [30]. Several commonly available fragrant and flavor compounds of the terpene family can undergo biotransformation using bio-catalysts [15]. Another advantage in bio-catalysis is that one can immobilize the enzyme (for example, lipase) onto a solid support and thus, make it more efficient like solid catalysts (Fig. 11.4).

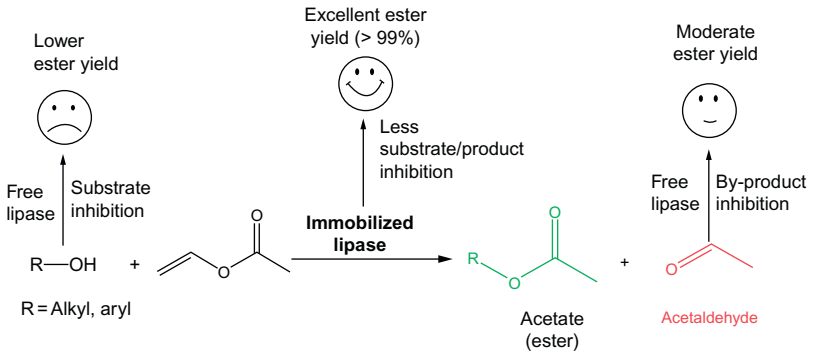


Fig. 11.4

Positive effect of immobilization of lipase on solid support for the synthesis of acetate. The alcohol and acetaldehyde are the deactivating agents for the transesterification reaction; however, immobilization helps to lessen this deactivation effect [24].

Enantioselective biotransformation to produce δ-lactone is reported using enzymes. The importance of bio-catalysis in these transformations is that different enantiomers of δ-lactone possess different odor and hence, enantioselective synthesis is required and enzymes are efficient for these reactions [31]. Bacteria and enzyme catalyzed oxidation of isoeugenol to vanillin (4-hydroxy-3-methoxybenzaldehyde), one of the most important flavors widely used in the food industry, in moderate to good yields is reported recently [32,33]. In the past few years, the use and studies of bio-catalytic production of fine chemicals, in particular for specific odorants is increasing [34].

11.4 Heterogeneous Catalysis—Reaction Classification

11.4.1 Isomerization

Isomerization is one of the important transformations for the production of molecules of perfumery interest. This includes largely olefin and terpene isomerization that produces

molecules of significant perfumery interest. A US patent dated back in the 1940s claims that α-pinene can be isomerised to camphene over pyrophyllite, a mineral found in rock. The authors reported that at a reaction temperature of 155°C, α-pinene can be converted to camphene and the product can be separated by distillation [35]. Isomerization of longifolene to isolongifolene is reported over nano crystalline solid super acid catalysts. Nano crystalline sulphated zirconia catalysts with superior acidity is claimed to be very active with high selectivity that shows high atom economy, low E-factor and promise as green catalyst for this transformation [36].

β-isophorone, another important molecule in perfumery industry, can be produced from its alpha isomer through isomerization. Metal catalyst (Fe, Co, Cr, Mn, Ni, Al, Ti) with acetyl acetonate gave a yield of 85% of β-isophorone [37]. *Cis-trans* isomerization of *cis*-anethole to *trans*-anethole was reported over rhodium salts in alcoholic medium wherein authors claimed that halides, organic and inorganic rhodium salts catalyzed this reaction at high temperature (up to 200°C) under reflexing/high pressure (up to 100 bar) conditions [38]. Double bond isomerization of alkenyl aromatics is one of the important reactions to obtain molecules of diverse perfumery notes. In this reaction, alkenyl alkoxy benzenes with a non-conjugated double bond with benzene ring undergo double bond isomerization to produce alkenyl alkoxy benzenes with conjugated double bonds. A detailed discussion on this reaction over solid base catalysts is summarized below.

11.4.1.1 Isomerization of alkenyl aromatics

Isomerization of alkenyl aromatics is generally carried out using alkali and alkaline-earth derived catalysts, as they are often catalyzed by bases [39]. Precious metals such as ruthenium and osmium catalysts are also used for this reaction [40]. In view of the environmental footprint and cost, use of heterogeneous catalysts for enabling this reaction would be advantageous. The mechanism of this base-catalyzed reaction involves abstraction of hydrogen of the active methylene group of allylic chain to form a secondary carbanion. The secondary carbanion would further undergo resonance stabilization to primary carbanion to form its propenyl counterpart, iso products. Conventionally, these reactions were catalyzed by alkali such as KOH in alcoholic solutions (more often in higher alcohols) at high temperatures. These bases are generally used in stoichiometric or superstoichiometric quantities to that of the compound being isomerized, resulting in large quantities of caustic waste streams and posing handling problems.

Cerveny et al. studied isomerization of eugenol over alcoholic alkali solution and reported that the conversion decreased with a reduction in the concentration of alkali [41]. A quantitative yield using KOH or KOtBu as catalyst was obtained in the presence of Aliquat336, a phase transfer agent under solvent-free condition [18,42]. Kameda and Yoneda have reported homogeneous isomerization of estragole and eugenol over $[RhH_2(Ph_2N_3)(PPh_3)_2]$ in dimethyl sulfoxide (DMSO) under hydrogen atmosphere (1 atm) at 30°C. They found that the isomerization rate under hydrogen atmosphere was faster than under nitrogen, and proposed

that the active species was formed through the reaction of dihydrido-rhodium complex with hydrogen [43]. Microwave assisted isomerization reactions of eugenol, safrole, and estragole were also reported using both conventional bases, such as, KOH and KOtBu in alcohols, as well as over KF/Al_2O_3 [17,19]. Eugenol isomerization under microwave irradiation (MWI) using alcohols as solvents at different KOH concentrations is reported [17]. The MWI enhanced the yield and decreased the reaction time. Thach and Strauss have reported 73% conversion at 200°C in 15 min for eugenol and 81% at 230°C for estragole under MWI with 0.2 M NaOH [19].

However, these homogeneous processes involve a multi-step synthesis using stoichiometric or superstoichiometric reagents that often result in a mixture of products. This leads to problems related to environmental damage, corrosion, recycling, and separation. Replacement of conventional alkali-based catalysts by solid base catalysts is widely accepted due to easier process handling, effluent control, and easy separation for a cleaner environment [21,44,45]. Radhakrishna et al. carried out isomerization of eugenol and safrole over KF on neutral Al_2O_3 in ethylene glycol and obtained 78% yield at 200°C for eugenol and 76% yield at 150°C [46,47]. Conversion improved when they used dry media without any solvent [46]. Sokolskii and Trukhachova studied isomerization of eugenol over palladium on Al_2O_3 under liquid phase and concluded that the activity depended on the sequence of addition of reagents [48]. Modified zeolites, when used for eugenol isomerization showed a conversion around 70–90% in helium and hydrogen, along with other products depending on the reaction atmosphere and metal ion used [49].

Alkali metals supported on various Al_2O_3, synthesized by impregnation at higher temperatures were studied for isomerization of safrole. Nearly 100% conversion was achieved in 1 h at room temperature under nitrogen. However, this catalyst had disadvantages, such as hazardous handling and environmental unfriendliness. Expensive metal complexes, such as $(PPh_3)RhCl_2$ were also used as catalyst for this reaction [49]. Cp_2TiCl_2 when used as catalyst for this transformation under Grignard conditions ($BrCH_2CH_2Br/Mg/THF$) resulted in 80% conversion in 2 h under nitrogen at room temperature [50]. Qian et al. have used the same catalyst, in the presence of Mg alone and reported a higher conversion (92% with *cis*:*trans* ratio of 5:95) and proposed a highly unstable Cp_2Ti species (formed upon reduction of Cp_2TiCl_2 by Mg) as the active catalyst for the isomerization reaction [51].

Recently, Spence et al. performed isomerization of alkenyl aromatics over K_2CO_3/Al_2O_3 catalyst and reported a conversion of 20% for eugenol and 26% for estragole [52]. Casilda et al. conducted isomerization of eugenol over alkali-modified mesoporous NbMCM-41, wherein incorporation of alkali metals showed isomerization activity for eugenol. Rubidium loaded NbMCM-41 gave a maximum of 90% conversion under ultrasound and the activity showed a correlation with basicity [53]. Crochet et al. reported 99% yield of anethole from estragole within 15 min under MWI using Ru-complexes as homogeneous catalysts with highly *trans* selective products [54,55]. Although these catalysts show good conversion for iso products of

alkenyl aromatics, the catalysts are either expensive or not eco-friendly. In the last decade, an increase in the development and use of solid base catalysts for base catalyzed reactions has been witnessed and among them, hydrotalcite-like compounds are one of the potential solid base catalytic materials. They are economically viable and environmentally friendly and with their inherent and tunable basicity make them as efficient solid base catalysts for many base catalyzed reactions, including isomerization reactions [56]. An extensive discussion on the isomerization of alkenyl aromatics over these materials is discussed below.

Hydrotalcite-like (HT-like) materials, otherwise referred to in literature as layered double hydroxides (LDHs), find versatile applications as catalysts, catalyst supports, ion-exchangers/adsorbents, composite materials, drug carriers, and functional materials [57]. HT-like materials are a family of natural and synthetic anionic clay materials with general molecular formula $[M(II)_{1-x}M(III)_x(OH)_2][A^{n-}]\cdot mH_2O$, where M(II) and M(III) are divalent and trivalent cations, A^{n-} is the interlayer anion and "x" can generally have values between 0.2 and 0.33. With their different and interesting set of properties, they are efficient catalysts for a wide range of organic reactions, in particular for base-catalyzed reactions [56,58,59]. With a good knowledge of structure-activity relation for these materials, the number and strength of basic sites in them can be tuned precisely to cater to a specific reaction [59]. The schematic structural representation of these compounds is given in Fig. 11.5.

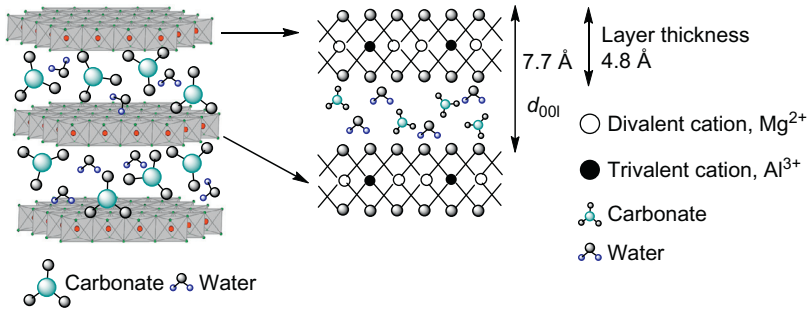


Fig. 11.5
Schematic structural presentation of hydrotalcite-like compounds.

The basic hydrotalcite was studied extensively for isomerization of alkenyl aromatics such as eugenol, estragole, allylveratrole, and safrole to their corresponding iso-compounds that are of perfumery interest. In accordance with the published literature, Mg and Ni containing hydrotalcites (HTs) with Al as trivalent cation and carbonate in the layers possess maximum basicity. Hydrotalcite-like (HT-like) compounds in their as-synthesized form possess Brønsted basic sites and on calcination get converted to mixed oxides which have Lewis basicity. Those calcined materials upon rehydration (treatment with water) regain the layered HT structure (popularly called memory effect) with enhanced Brønsted basicity that is reported to be active for isomerization reaction [60–62].

MgAl HTs with varying Mg/Al ratio gave good isomerization activity with increasing Mg/Al atomic ratio [63]. In the case of NiAl HTs with different Ni/Al atomic ratios, NiAl4 (Ni/Al atomic ratio = 4.0) gave the maximum activity with 82% conversion of eugenol to isoeugenol. Among various hydrotalcites screened with M(II)/Al atomic ratio of 3.0 and 4.0, with different bivalent metal ions (where M(II) = Mg, Ni, Co, Cu and Zn), Mg and Ni offered maximum activity for the isomerization of alkenyl aromatics. The activity increases with M(II)/Al atomic ratio up to 4, and decreases thereafter. This was due to variation in the basicity of the materials calculated using phenol adsorption studies (Fig. 11.6) and a reasonable correlation was deduced between the basicity and the isomerization activity.

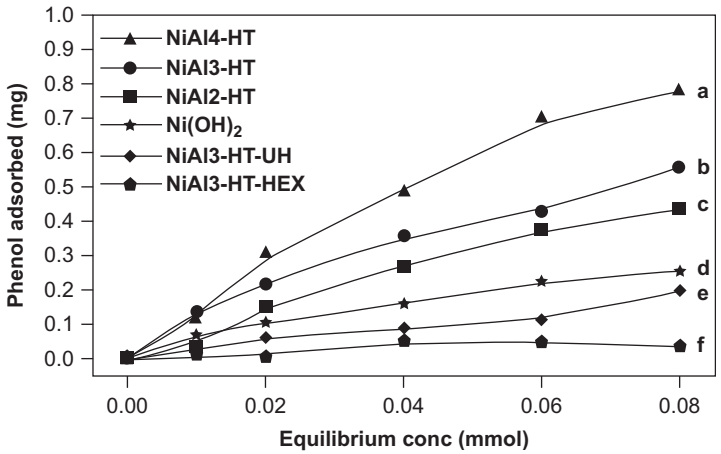


Fig. 11.6

Phenol adsorption studies of some of the samples synthesized; UH- sample synthesized by urea hydrolysis; HEX-sample synthesized by hexamine hydrolysis [61].

For isomerization of eugenol and estragole, the maximum activity was witnessed for hydrotalcite with Mg/Al atomic ratio 4 (MgAl4-HT) and for safrole MgAl6-HT at 200°C [62,64]. In the case of MgAl6-HT, safrole conversion of 98% with 10:90 *cis*:*trans* ratio was achieved [65]. Nearly stoichiometric conversion (>98%) of eugenol to isoeugenol was realized for NiAl3-HT in 24 h and 99% for estragole over MgAl4-HT in 6 h [61,64]. These results prove that an optimum concentration of Ni and Mg in the lattice is necessary to achieve high yield of the products, which also varied with the nature of the substrate. The reaction condition optimization showed polar solvents with high boiling points (namely DMF (dimethyl formamide), DMSO (dimethyl sulfoxide), DMA (dimethyl acetamide)) favored the reaction [62] and the activity increased with an increase in temperature up to 200°C. Further rise in temperature causes decomposition of products and reactants.

Only hydrotalcites prepared through co-precipitation under low supersaturation are active for the isomerization of alkenyl aromatics. The co-precipitated MgAl and NiAl hydrotalcite were compared with other synthesis methods, like sequential precipitation, reversal addition,

instantaneous addition, ultrasonication, hexamine hydrolysis, urea hydrolysis, and hydrothermal treatments. Among them, co-precipitated samples showed higher activity than all other samples for isomerization of eugenol and estragole [62,64]. Samples synthesized by co-precipitation offered maximum surface area while very poor activity was noted for samples synthesized through urea or hexamine hydrolysis [61].

From all the studies, it was understood that Ni and Mg containing hydrotalcite are active for these reactions and synergic effect for Ni and Mg in the same HT was then tested, in order to know whether activity of one metal will promote the other. In another study, Co, Zn, Cu, Mn and Fe were introduced into the layers to assess such synergism with inactive metals. It was found that only Ni, along with Mg in the layer, is active for isomerization of alkenyl aromatics [64]. The activity increased with an increase in Ni content in MgAl-HT for eugenol isomerization, while it dropped for estragole isomerization [62,64]. The studies with different trivalent cations like Al, Fe, Cr, along with Mg as divalent cation in hydrotalcite, showed that MgAl HTs are the most active followed by MgFe-HT and MgCr-HT [62,65].

Table 11.2 Isomerization of allylbenzene over modified MgAl3-HT [59]

Catalyst[a]	Conversion (%)	Product distribution (%)	
		Cis	*Trans*
MgAl3-HT	59	10	90
K(5%)MgAl3-HT	75	12	88
Rb(5%)MgAl3-HT	96	10	90
Cs(5%)MgAl3-HT	96	13	87
Pd(5%)MgAl3-HT	50	12	88
Pd(0.5%)MgAl3-HT	49	12	88
Ag(5%)MgAl3-HT	0	0	100
MgAl3-C-HT	0	0	100
MgAl3-R-HT	51	11	89

[a]Substrate: allylbenzene(0.5 g); solvent: DMF(20 ml); catalyst weight: 250 mg; reaction temperature/time: 160°C/6 h. MgAl3-C-HT: HT calcined at 450°C (mixed metal oxides); MgAl3-R-HT: Rehydrated hydrotalcite (interlayer have hydroxyl anions).

These studies show that not one kind of hydrotalcite is efficient in isomerizing all alkenyl aromatics; however, it is clear that Ni and Mg HTs are active for these reactions and changes in composition/metal ions of hydrotalcite lattice strongly influenced the isomerization activity. Alkali metal ions impregnation over MgAl3-HT promoted the catalytic activity, probably due to an increase in the basicity of catalysts, while precious metal impregnation retarded or did not influence the activity (Table 11.2).

The reaction over $Mg(OH)_2$, $Al(OH)_3$, $Ni(OH)_2$ and calcined HT confirmed the necessity of hydrotalcite layers and Brønsted basic sites for these reactions. To deduce the mechanism of this reaction, a simple molecule of alkenyl aromatics, allylbenzene, was selected and its isomerization to *trans*-β-methyl styrene was studied [60]. Reasonable correlation existed

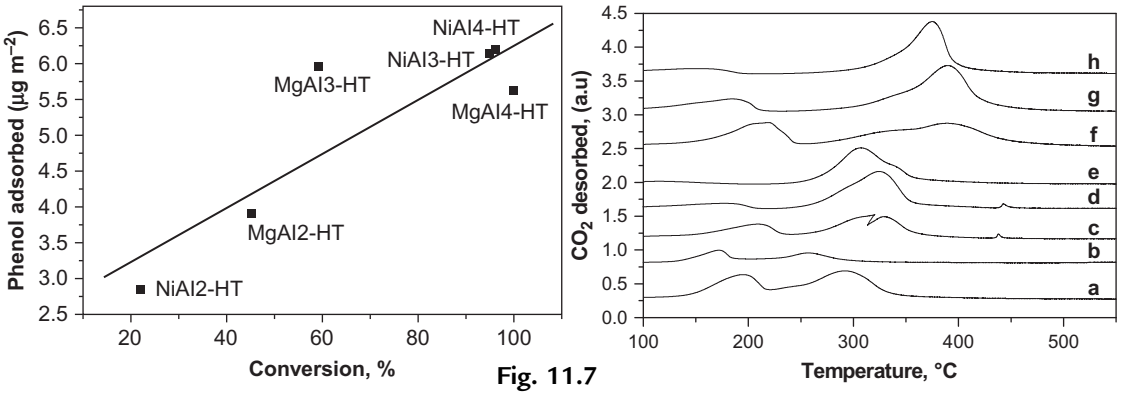


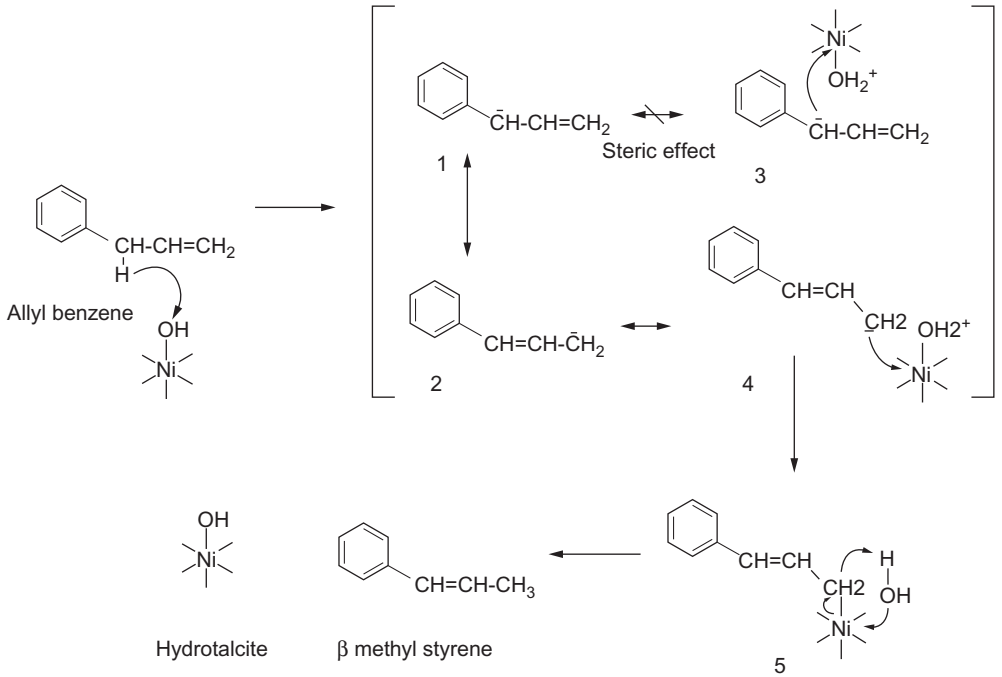
Fig. 11.7

Correlation between phenol adsorption and isomerization activity (above) and Temperature programmed desorption of: (a) CoAl2-HT; (b) ZnAl2-HT; (c) NiAl2-HT; (d) NiAl3-HT; (e) NiAl4-HT; (f) MgAl2-HT; (g) MgAl3-HT; and (h) MgAl4-HT (below) [60].

Table 11.3 Concentration of basic sites as computed from CO_2 TPD measurements for various catalysts [60]

Catalyst	CO_2 desorbed				
	110–150°C (μ mol/g)	170–210°C (μ mol/g)	250–330°C (μ mol/g)	380–440°C (μ mol/g)	560–590°C (μ mol/g)
MgAl2-HT	0	1570	0	3019	0
MgAl3-HT	0	1192	0	4309	0
MgAl4-HT	702	0	0	4222	0
NiAl2-HT	0	728	2010	12	0
NiAl3-HT	0	685	2798	30	0
NiAl4-HT	417	0	3216	0	0
CoAl3-HT	0	980	1704	0	0
ZnAl3-HT	0	791	935	0	0

between the allylbenzene isomerization activity with the amount of phenol adsorbed and concentration of basic sites derived from CO_2-TPD as given in Fig. 11.7 and Table 11.3. As discussed before, an abstraction of hydrogen of active methylene group of allylic chain of alkenyl aromatics by Brønsted basic site of hydrotalcite is driving the reaction (Scheme 11.2). This forms a secondary carbanion and the structural hydroxyl groups attached to M^{2+} are likely to be involved in this abstraction. The secondary carbanion would further undergo resonance stabilization to stable primary carbanion. The further attack on the protonated hydroxyl groups of catalyst occurs at the *trans* position, which is thermodynamically and sterically favored, leading to predominant formation of *trans*-isomer. Delaminated LDHs in formamide were also screened for isomerization of allylbenzene, which showed very poor conversion (5%). This further suggests that the layered structure with surface hydroxyl groups as Brønsted basic centers and/or the co-presence of interlayer anion are essential in offering surface basic sites for driving this reaction.



Scheme 11.2
Mechanistic pathway for the isomerization of alkenyl aromatics (allylbenzene as model molecule) [59].

When the isomerization reaction was conducted under conventional thermal heating, it required a relatively high temperature and longer reaction time and further, the catalysts were also not recyclable. In order to overcome these challenges, the reaction was conducted under MWI. Under optimized conditions, MgAl4-HT showed 99% conversion of estragole to anethole with 86% *trans* selectivity. A good correlation was observed between the activity of the catalysts and the basicity derived using Hammett measurements. High boiling-high polar solvents like DMF, DMSO, and DMA gave high conversion ($95 \pm 3\%$) in shorter time (1 h), while high boiling-low polar, low boiling-high polar, and low boiling-low polar solvents such as acetonitrile, THF (tetrahyrofuran) showed poor activity. MgAl4-HT catalyst was recyclable for up to six cycles without significant activity loss.

Isomerization of different alkenyl aromatics over MgAl4-HT showed substantial variation in the activity, irrespective of the nature of heating. The conversions of allylbenzene, estragole and allylveratrole to the desired product were more favorable, whereas for safrole and eugenol, the conversion was lesser. Theoretical calculations were done to corroborate the experimental data. It was found that with change in the substitution on the aromatic ring, the pK_a values of methylene proton (–CH_2–) of the allyl group, whose abstraction by the basic sites is the crucial step for this double bond migration, also varied. This variation in pK_a showed

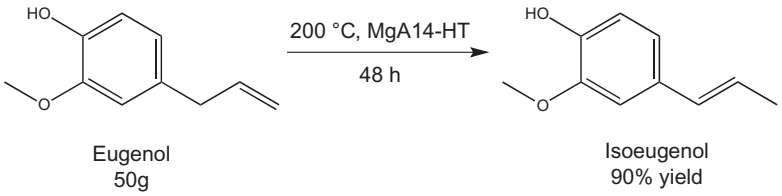
a direct correlation with conversion. Further, the energetics calculation validated that the *trans* products are more favorable than *cis* products, which corroborated well with the experimental results. In summary, reaction under microwave offered both energy and environmental benefits by using a lesser volume of solvent, shorter reaction time, and at lower reaction temperature with efficient recyclability of catalysts [66].

Scale-up study was undertaken in the perspective of industrial relevance for eugenol. For these studies, MgAl4-HT was selected, after gaining knowledge that MgAl4-HT is an equally active catalyst similar to NiAl4-HT, besides being economical and environmentally friendly. Around 90% conversion of eugenol was obtained (for 50 g scale) in 48 h (Scheme 11.3); this was low as compared to lab scale (0.5 g) suggesting engineering aspects have to be considered while scaling.

The kinetics investigation on MgAl4-HT on isomerization of eugenol was carried out as a function of the amount of the catalyst, substrate, stirring speed, and temperature. The rate of formation of isoeugenol was first order at lower amount of catalyst. The rate constant for the formation of isoeugenol was 6.4×10^{-3} min^{-1}. The formation of isoeugenol was linear with consumption of eugenol with higher *trans* selectivity. In order to check the mass transfer resistance or whether the reaction was diffusion free, stirring speed variation was done. The reaction proceeded very slowly without stirring and initial rate increased with increasing stirring speed. The low rates at lower stirring speed (up to 700 rpm) were attributed to the possible mass transfer resistance at the liquid-solid interface, due to lower kinetic energy on the substrate which restricts the substrate to pass through the interfacial boundary layer (external mass transfer). When the stirring speed increased to 800 rpm, increase in the rate occurs, showing lowering of mass transfer resistance at the interface. Further increase in stirring speed to 1000 rpm had no significant effect on the initial rate; the reaction proceeded through the kinetic regime, confirming negligible mass transfer resistance.

Increase in the catalyst amount increased the total available active sites and thus increased the rate of reaction. No significant change in the initial rate for isomerization was observed over 250 mg catalyst (substrate to catalyst wt. ratio 2) and approached saturation. Variation of substrate amount showed that with an increase in the substrate, a drop in initial rate occurred, suggesting substrate inhibition kinetics. The available active catalytic sites were incapable of catalyzing a higher amount of substrate within the specific reaction time. This may due to the adsorption of a higher amount of eugenol molecules on the catalyst surface (catalyst weight was fixed) which would block the active site initially.

The dependence of temperature on the rate of eugenol isomerization revealed two activation energy regions at low and higher temperatures. Up to 180°C, the temperature had a direct effect on the reaction to overcome the external diffusion limitations of the substrate and with a further increase in temperature, the reaction goes through a kinetically-controlled regime.



Scheme 11.3
Isomerization of eugenol to isoeugenol over MgAl4-HT.

The structure-property-activity of isomerization of eugenol and alkenyl aromatics of perfumery interest was studied over different catalysts. To understand such strong influence on the nature of cation on HT-like lattice on the isomerization activity, incorporation of inactive Cu^{2+} in the NiAl binary HT was done; conversion of eugenol significantly decreased wherein substitution of 25 at% of Ni^{2+} by Cu^{2+} completely annihilated the isomerization activity (Table 11.4) [67].

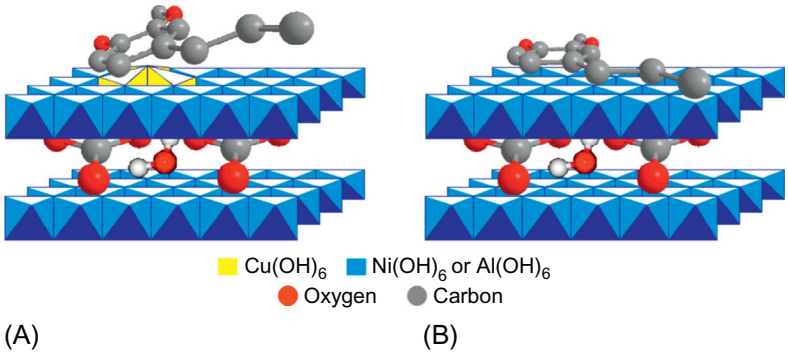
Table 11.4 Isomerization of eugenol over NiCuAl ternary hydrotalcites [60]

Catalyst[a]	Conversion (%)	Product distribution (%)	
		Cis	*Trans*
NiAl3-HT	77	16	84
NiCuAl9802-HT	42	27	73
NiCuAl9505-HT	47	21	79
NiCuAl9010-HT	24	34	66
NiCuAl7525-HT	0	0	0
NiCuAl5050-HT	5	0	100
CuAl3-HT	2	0	100

[a]Substrate: eugenol (500 mg); solvent: DMF (20 ml); catalyst weight: 250 mg; reaction temp/time: 200°C/6 h; NiAl*x*-HT where *x* stands for Ni/Al atomic ratio or NiCuAl*yz*-HT, where "*yz*" stands for the nominal Ni:Cu atomic ratio for ternary systems.

Phenol adsorption and TPR measurements concluded that the variation in the strengths of the hydroxyl groups associated with Ni^{2+} and Cu^{2+} was one of the main reasons for the significant variation in the activity. Phenol adsorption measurements revealed that CuAl-HT possessed less concentration of basic sites and NiAl3-HT had maximum basic sites among the samples studied. Besides the basicity of the samples, the structural orientation of hydroxyl groups is also critical. A multi-centered catalytic site model (Scheme 11.4) was proposed wherein Ni^{2+} clusters along with structural hydroxyls in appropriate configuration participate in the double bond shifting through coordinative adsorption, which was further confirmed through in situ DRIFTS [67].

The structure-surface-activity studies were further probed through *operando* DRIFTS measurements for select samples (NiAl3-HT which is active and NiCuAl9010-HT which is less active). Studies were done to clarify the reasons behind thereof, such as: (i) with the addition of Cu^{2+} the activity dropped significantly for NiAl-HT; (ii) at lower temperature the



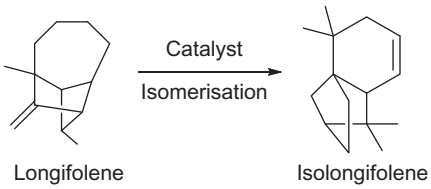
Scheme 11.4

Schematic representation of eugenol interaction with wells of hydroxyls in NiCuAl-HT (A) and NiAl-HT (B). Hydroxyl groups are not indicated for the sake of simplicity, and that they correspond to the corners of the octahedral [66].

reaction did not occur, (iii) heated/calcined catalysts were inactive, and (iv) catalysts were not effectively recyclable. In situ studies revealed that the mode of adsorption of eugenol over Ni and Cu containing NiAl-HT lattice were different and concluded that this difference could be the reason for the significant variation in the activity. The studies further proved that a minimum temperature is required for eugenol to adsorb on the catalyst surface. In addition, the adsorbed eugenol that could not be easily desorbed during the reaction is attributed to the deactivation of the catalysts during recycles [68]. To conclude, a minimum temperature is required, along with optimal presence of Brønsted basic sites to drive the isomerization reaction under optimized reaction conditions.

11.4.1.2 Isomerization of terpenes

Isomerization of longifolene to isolongifolene is one of the simple reactions representative of terpene compounds. This isomerization can be carried out in liquid phase acid or base catalysis. In liquid phase, longifolene isomerized slowly in a mixture of sulphuric-acetic acid at 80°C for 14 days [69]. Studies were also reported over liquid acids such as $BF_3{\cdot}OEt_2$ [70,71], bromoacetic acid [72], and camphene carboxylic acid [73]. However, the current interest is to use environmentally friendly heterogeneous catalyst for bulk perfumery chemical synthesis. Isomerization of longifolene to isolongifolene (Scheme 11.5) can be carried out over solid acid catalysts.

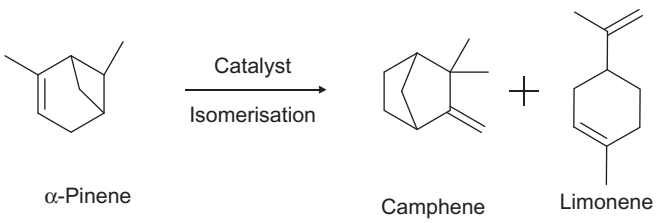


Scheme 11.5

Isomerization of longifolene to isolongifolene.

Nano-crystalline sulphated zirconia was reported as an efficient solid acid catalyst for this reaction. Brønsted acidity within the pores of sulphated zirconia helps in this reaction. This leads to maximum activity in a long reaction run and yielded >90% conversion and ~100% selectivity for iso-longifolene [74]. Further rearrangement of isolongifolene to 7-isopropyl-1, 1-dimethyltetralin was observed with variation in Brønsted to Lewis acid ratio of sulphated zirconia. The tetralin and its derivatives are used in cosmetics and laundry detergents, and also in fragrance industries [75]. In the case of nano-crystalline sulphated zirconia, with an increase in the Brønsted to Lewis acid sites ratio, the tetralin formation increased; in other words, the formation of rearranged products of isolongifolene can be controlled by tuning Brønsted to Lewis acid ratio [75]. In another study, alumina grafted on silica was used for isomerization of longifolene. The textural properties and acidity of the catalyst played an important role as observed in the case of sulphated zirconia. A conversion of 97% and 95% selectivity was achieved with pore-engineered alumina on silica [76].

Supported heteropoly acids are also reported to be active catalyst for isomerization of longifolene. Silica-supported $H_3PW_{12}O_{40}$ (PW) was explored under solvent-free conditions that showed high activity. The catalyst showed higher turnover frequency of around 6000 (catalyst loading 0.15–5 wt%). These materials can also be used for other terpene isomerization reactions, for example, α-pinene to camphene. Using the same catalyst supported on silica, a turnover frequency as high as 5750 was observed for α-pinene, confirms the efficiency of catalyst [77]. Isomerization of α-pinene can give two types of products depending on the distribution of acidic sites. The Lewis acidic sites can produce tricyclic products (camphene, β-pinene, tricyclene, etc.) and Brønsted sites will give mono cyclic products (limonene, terpinene, terpinolene, *p*-cymene) [78]. The pore architecture and acidity of the catalyst can influence the selectivity of final products [7]. Camphene and limonene are the main products of isomerization of α-pinene (Scheme 11.6). Limonene is used to synthesise oxygenated compounds of perfumery interest.

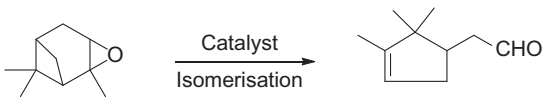


Scheme 11.6
Isomerization of α-pinene to camphene and limonene.

Isomerization reactions are usually carried out using TiO_2 as solid acid catalyst in industry [79]. TiO_2 is a weak acid and hence, the reaction rates are low. In a perspective to find a better and more active catalyst, several solid acids were tried for the isomerization. Zeolites are frequently

studied acid catalysts for these reactions. Natural minerals with zeolite character show activity for these reactions [20]. Dealuminated mordenite and faujasite zeolites also show good activity for these reactions. It is observed that low selectivity for desired products in the case of faujasite over mordenite is due to their larger pores [80]. Natural zeolite-clinoptilolite was also used for these reactions and the selectivity decreases with an increase in the reaction rates. Zeolite are studied extensively because the water present within the pores helps in the generation of protons that drive the reaction [78]. With tunable pore architecture and acidity of zeolites, one can improve the selectivity of desired products (camphene or limonene). A few other catalysts are also used for isomerization of α-pinene, such as silica supported rare earth metal oxide catalyst, clays, etc. [81].

Isomerization of epoxides of terpenes to their corresponding aldehydes or alcohols is also useful for the production of fragrance molecules. The isomerization of α-pinene oxide to campholenic aldehyde (Scheme 11.7) over acid catalyst is one such reaction where formation of number of side products is likely, which increases markedly with a rise in the temperature (≥100°C) [82]. Homogeneous $ZnBr_2$ and $ZnCl_2$ showed good activity for α-pinene oxide isomerization, but are not environmentally friendly due to toxicity, corrosiveness, and the presence of heavy metal zinc, which can cause water pollution [83]. Zeolites (US-Y) with large pores (pores ~12 Å) showed good activity and selectivity when the reaction was conducted at lower temperature. A selectivity of 75% was observed when the reaction was performed at 0°C over commercial zeolite and the conversion increased upon dealumination. 100% conversion observed with 70–75% selectivity to campholenic aldehyde under optimized reaction conditions. An increase in the conversion with dealumination suggests that the Brønsted acidity associated with aluminium is not the main active center for this isomerization [82].



Scheme 11.7
Isomerization of α-pinene oxide to campholenic aldehyde.

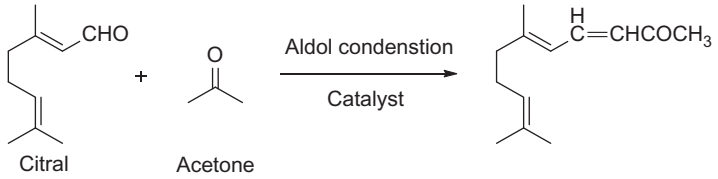
Other than isomerization, condensation reactions are also extensively used for the synthesis of fragrant molecules. Some of these reactions involving simple chemistry are discussed in the following section.

11.4.2 C–C(X) Bond Forming Reactions

11.4.2.1 Aldol condensation of citral and acetone

Aldol condensation of acetone with citral gives pseudoionones (Scheme 11.8), which can be synthesized through acid or base catalysis route. The acid catalysts route is less active, whereas base like MgO and hydrotalcite are active. Climent et al. explored both acid and base

catalysts for this reaction and confirmed that the formation of pseudoionones is more favorable via base route [84]. Among the base catalysts studied, mixed oxides (Mg-Al oxides) derived from hydrotalcites showed higher reaction rates than MgO at 60°C. The activity of MgAl mixed oxides increased upon activation (rehydration), in other words through memory effect over calcined hydrotalcite.



Scheme 11.8
Aldol condensation of citral with acetone.

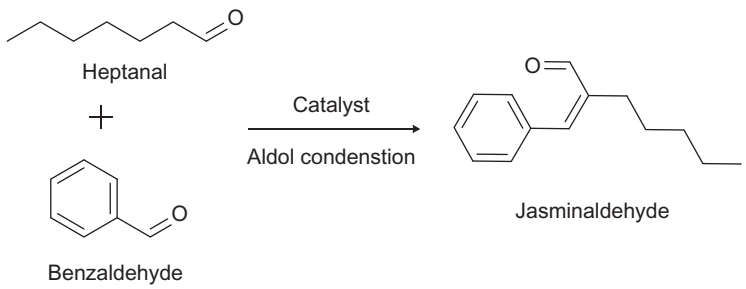
It is known that the addition of water onto oxides obtained through calcination of hydrotalcite rehydrates and structurally revert to hydrotalcite with concomitant generation of Brønsted basic sites [85]. These Brønsted basic sites are responsible for high reaction rates and activity. In another study, hydrotalcite synthesized under different conditions at different temperatures were screened for aldol condensation of citral and acetone. It was found that with aging conditions, the structural properties and the activity varied. The hydrotalcite with well-dispersed layers and high surface area show higher activity [10]. The MgO and hydrotalcite as base catalyst, both with and without modification, are explored for these reactions [86–88]. The alkali doped MgO for these reactions showed that all alkali ions bigger than Li in ionic radii blocks the pores and kills the activity. Even in case of Li, only up to specific amount of Li (0.5 wt%) on MgO facilitates reaction while at higher concentration of Li, the activity decreased. It is likely that at a higher concentration of alkali, particle agglomeration occurs along with pore blocking that annihilates the activity [89]. Alkali doped (Li, Na, K) rehydrated hydrotalcite were also used in citral aldol condensation reactions. With doping of alkali, the activity of catalysts increased with strength and number of basic sites [90].

Amberlyst 35 W, silica-supported heteropolyacid (HPA) and silica-supported triflic acid (TFA) are also used as acid catalysts for condensation of citral and acetone. Usually, acid sites are not good for these reactions as mentioned earlier. The acid catalysts yields are low for this reaction. Around 20–40% of condensed product was obtained with acidic ion-exchange resins and sulphated TiO_2/MCM-41 [91,92]. This is significantly lesser than its homogeneous counterpart, sulphuric acid.

11.4.2.2 Aldol condensation of heptanal and benzaldehyde

Aldol condensation of heptanal and benzaldehyde gives jasminaldehyde; this reaction is catalyzed in a facile manner using base catalyst at a high reaction rate while acid catalyst give slower rates. The formation of self-condensed product of heptanal (Scheme 11.9) as a major

side product ((*E*)-2-*n*-pentyl-2-*n*-nonenal) is one of the disadvantages during this reaction. For this reason, during acid and base catalysis, the mole ratio of benzaldehyde to heptanal has to be kept high, to keep the concentration of heptanal low at any given point of reaction. However, high concentration of benzaldehyde in the reaction mixture may also cause separation problems of unreacted benzaldehyde. The concentration of heptanal can also be kept low by stepwise addition of heptanal over a longer reaction run. The heptanal self-condensation can also be lowered by introduction of methanol to reaction mixture. The heptanal reacts with methanol to form its hemiacetal derivative [11].



Scheme 11.9
Aldol condensation of heptanal and benzaldehyde.

Among base catalyst, hydrotalcite is found to be more active for aldol condensation of heptanal and benzaldehyde. The activated hydrotalcite with Mg/Al atomic ratio 3.5 was reported to give a maximum heptanal conversion of 98% with 86% selectivity for jasminaldehyde. These catalysts are reusable without much loss in their activity even under solvent free conditions. The reaction rate and order of reaction was calculated using kinetic studies [93]. It was also found that reconstructed hydrotalcite (with Mg/Al atomic ratio 3.5) is more active and selective than as-synthesized and activated hydrotalcites for solvent-free aldol condensation of heptanal and benzaldehyde [94]. Magnesium organo silicates (MOS; synthetic talc) was reported to be active for jasminaldehyde synthesis through aldol condensation with amine functionalities. The amine/diamine functionalities were introduced into the interlayer of MOS and these catalysts gave highest conversion of heptanal (99%) with 82% selectivity of jasminaldehyde [95]. Modified chitosan is found to be an active base catalyst for this reaction. Under solvent-free conditions, modified chitosan gave a maximum conversion of >99% and 88% selectivity to jasminaldehyde and recyclable up to six cycles [96].

Kinetics studies showed that the reaction is first order for the formation of jasminaldehyde. The studies proved that a particular amount of heptanal is required for selective formation of jasminaldehyde, wherein heptanal-benzaldehyde ratio of 1:4 gave the maximum rate. Formation of jasminaldehyde follows Langmuir-Hinshelwood rate model with R^2 value of 0.95 [97]. Silica-immobilized piperazine as organocatalyst is found to be active for solvent-free aldol condensation of heptanal with benzaldehyde. The catalyst showed high selectivity for jasminaldehyde and activity maintained with cycles [98].

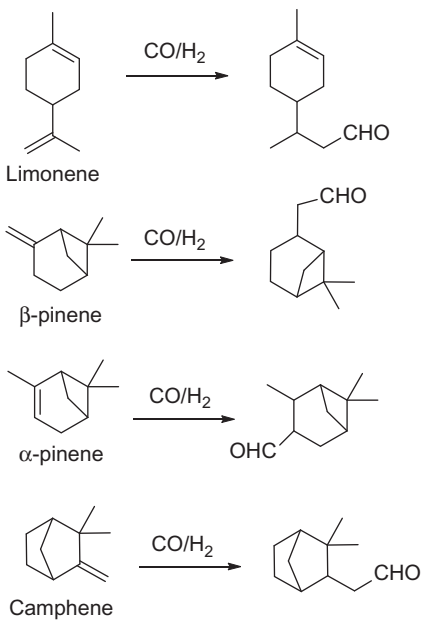
Thermally stable and large surface area hydrotalcite supported on hexagonal mesoporous silica (CHT/HMS) is also active for this reaction as solid base. With 20% (w/w), CHT/HMS gave 86% selectivity towards jasminaldehyde with less by-product formation. The bi-functional character of CHT/HMS with weak acidic sites and base sites help in selective formation of jasminaldehyde. Benzaldehyde gets activated over weak acid sites by protonation of carbonyl groups and basic sites drive the attack of heptanal with these activated carbonyl groups of benzaldehyde [99]. Among bifunctional catalysts for this reaction, amino grafted Zr-terephthalate metal-organic framework is found to be active. A Lewis acid site from Zr and basicity of amino groups in the cage of MOF accelerates the cross aldol condensation, thereby improving the selectivity [100]. NaOH-cationic micellar systems are found to be active and selective bifunctional catalyst for these reactions which gave 99% heptanal conversion with 90% selectivity towards jasminaldehyde. These NaOH-micellar catalysts are reusable without consumption of NaOH and the surfactant concentration and reaction temperature influence the selectivity of jasminaldehyde [101].

Usually acid catalysts are found to be less selective than base catalysts for jasminaldehyde synthesis. Mesoporous MCM-41 aluminosilicates was reported to be an active acid catalyst for selective formation of jasminaldehyde by cross-aldol condensation of heptanal and benzaldehyde. The reaction was conducted in methanol as it helps in the acetalization of heptanal with methanol, thereby minimizing its self-condensation. Mesoporous silica-alumina with its meso pore size is found to be more active than large pore zeolite. The pore architecture and acidic sites make it a good catalyst for selective formation of jasminaldehyde. The high activity of Al-MCM was due to its ability for acetalization of aldehyde and further slow hydrolysis of acetal, thereby preventing the self-condensation of heptanal. Followed by these steps, the cross aldol condensation occurs over acidic sites to form jasminaldehyde. This makes Al-MCM-41 a good catalyst for selective formation of jasminaldehyde at high reaction rates [11].

Similar to Al-MCM, mesoporous Al-KIT-6 was also reported to be good catalyst for selective formation of jasminaldehyde even with low benzaldehyde to heptanal mole ratio [102]. Solvent-free jasminaldehyde synthesis through aldol condensation was also reported over double metal cyanide and sulfonic acid functionalized silica. Propyl sulfonic acid functionalized silica gel gave both cross and self-condensed products. In case of Fe-Zn double metal cyanide, 93% conversion of heptanal with 77% selectivity towards jasminaldehyde was observed. The presence of coordinately unsaturated Zn^{2+} in the structural framework of Fe-Zn double metal cyanide helps in the activity for condensation [103]. In the case of zeolite, microporosity assists preferential formation of self-condensed products thereby leading to lesser selectivity for jasminaldehyde. However, on the contrary in the case of amorphous aluminophosphate (ALPO), the weak acidic and basic character makes it better catalyst for selective formation of jasminaldehyde with high activity. The weak acidic site will activate benzaldehyde by protonation of carbonyl group and basic sites helps to generate enolate of heptanal and thus enabling the reaction occurs through acid-base bifunctionality [104,105].

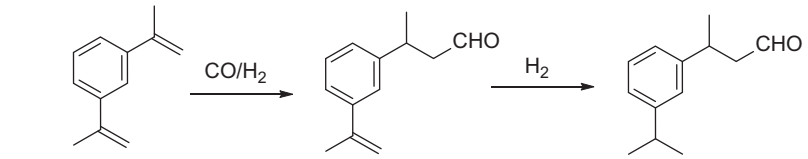
11.4.2.3 Hydroformylation

Aldehydes are a major class of molecules with perfumery notes. Thus, hydroformylation of terpenes to produce aldehyde are of great importance in perfumery chemicals (Scheme 11.10). Limonene and β-pinene can be easily hydroformylated among terpenes. Hydroformylation of limonene, β-pinene and camphene are studied extensively in comparison to β-citronellene, linalool and nerolidol [106]. Major work on the hydroformylation of terpenes have used rhodium derived homogeneous catalysts [107,108]. Vieira et al. have carried out rhodium-catalysed hydroformylation of terpenes (β-citronellene, linalool and nerolidol) in a water-toluene biphasic system. The Rh catalyst was active with excellent yields and resulted in a mixture of products with pleasant odor [106]. Cobalt complex along with Rh is also used for hydroformylation of pinenes of perfumery interest. In a study, low conversion of 3-formyl pinane was obtained by using Rh and Co complex as hydroformylation catalysts [109]. Platinum(II)/$SnCl_2$/phosphine catalysts were studied for hydroformylation of β-pinene, limonene, and camphene, and obtained linear aldehydes with high stereoselectivities. In the case of β-pinene high yield of *trans*-10-formylpinane was obtained, while limonene and camphene gave a mixture of products [110]. High activity of terpene hydroformylation was also observed over dirhodium complex with better selectivity under low temperature and pressure [109].



Scheme 11.10
Hydroformylation of some terpenes.

BASF has been doing extensive work on hydroformylation of terpenes, such as β-isophorone [111,112] suggesting the importance of this reaction in the fragrance industry. β-isophorone can be hydroformylated to corresponding aldehyde, which is an intermediate for α-damascone, an important fragrant compound. As demonstrated earlier, Rh complex can efficiently catalyze hydroformylation of β–isophorone [111]. Fragrant molecule Florhydral® (3-isopropylphenyl)butyraldehyde) can be synthesized by hydroformylation of *m*-diisopropenylbenzene over Rh complex (Scheme 11.11) and with further hydrogenation. Excellent results were obtained when Rh catalyst used in water-toluene biphasic systems; however, the major drawback of this reaction is the formation of dialdehyde, hydroformylation of both olefinic parts [113].

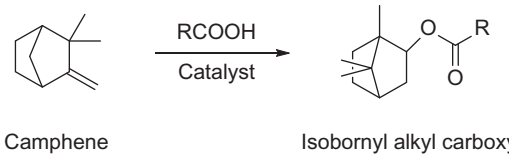


Scheme 11.11
Hydroformylation of *m*-diisopropenylbenzene.

In Chapter 14 of this book (Carbonylations and Hydroformylations), Kelkar discusses some of the fragrance chemicals produced through hydroformylation reaction.

11.4.2.4 C–X bond formation

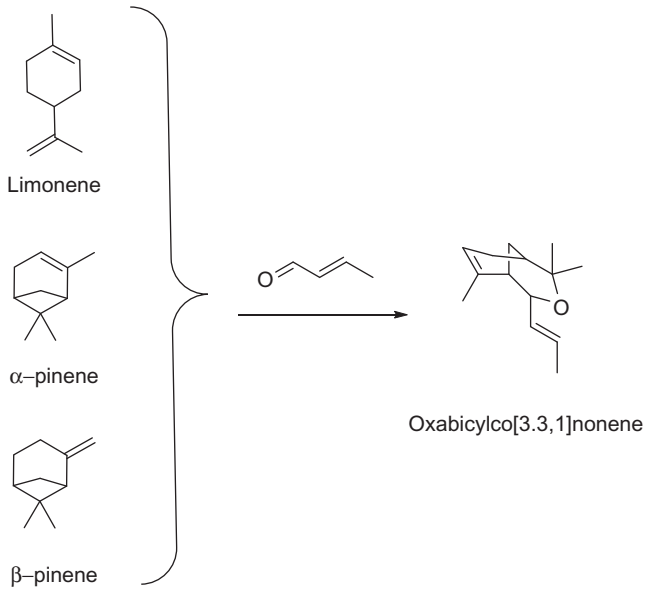
Synthesis of esters, ethers and lactones which find application in the fragrance industry is largely formed through this reaction. Compared to other reactions, heterogeneous catalyzed synthesis of such compounds are scarce in literature. Esterification of camphene (Scheme 11.12) with acids gives isobornyl carboxylates which possess a strong characteristic fragrance and are used in soap formulations, cosmetic perfumes, and pharmaceutical products [8,114].



Scheme 11.12
Esterification of camphene.

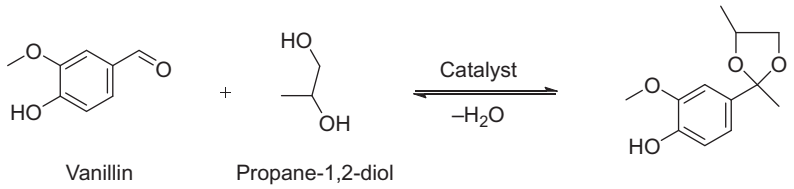
Solid acid catalysts like zeolites, functionalized silica materials, and sulfonated poly styrene resins have been used for acetoxylation of camphene [115–117]. Silica supported HPA ($H_3PW_{12}O_{40}$) was used successfully for the esterification of camphene using C2, C4 and C6 short-chain carboxylic acids in liquid phase with 90% conversion and 100% selectivity [118].

Utilization of mono-terpenes as a precursor for the fragrance chemicals is one of the important fields of research due to their ease of availability. Limonene, a by-product of the orange juice industry, and α and β-pinene, constituents of turpentine oils, are among many of the most widely studied monoterpene hydrocarbons. Acid catalyzed cycloaddition of crotonaldehyde to these terpenes (Scheme 11.13) leads to some fragrant oxobicyclo [3.3.1]nonene [119]. Acidic cesium salt $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ as solid acid catalyst in dichloroethane yielded ~95% conversion with >95% selectivity of the desired bicyclic product.



Scheme 11.13
Cycloaddition of crotonaldehyde to terpenes.

Acetals are a group of chemicals which find direct applications as fragrances, in cosmetics, food and beverage additives, although acetylation process are normally deployed to protect carbonyl groups [120,121]. Vanillin based acetals (Scheme 11.14) are used to imitate vanilla flavors in foods and beverages [122]. Multiple heterogeneous acid catalysts based on zeolites like USY, Beta 1, Beta 4, ZSM-5, ITQ-2 and mordenite were screened for this

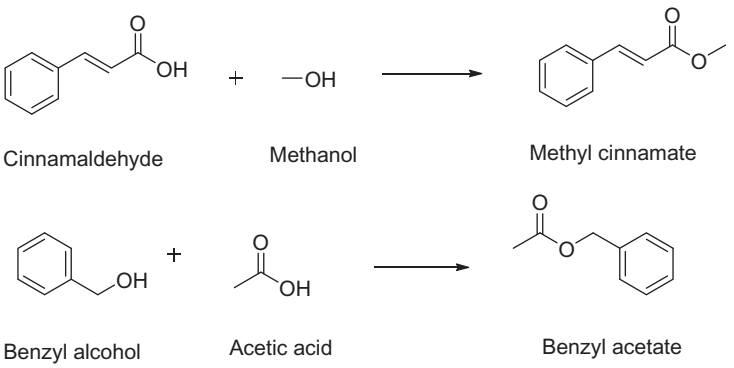


Vanillin Propane-1,2-diol

Scheme 11.14
Acetylation of vanillin.

reaction and obtained a >85% yield of acetal [123]. Palladium catalyzed acetylation of terpenes are well known homogeneously catalyzed reactions and the resulting esters find application in the perfume and flavor industries. However, research is further needed to find suitable heterogeneous catalyst for this reaction [124,125].

Esters give pleasant aromas and can be synthesized in the laboratory by esterification of corresponding acids with alcohols (Scheme 11.15). Cinnamic acid on esterification with methanol gives methyl cinnamate, which possesses a strawberry smell. Esterification of benzyl alcohol with acetic acid gives benzyl acetate, one of the primary constituents of many essential oils and a common fragrant molecule. Many studies are reported on benzyl acetate synthesis through esterification, although it is worth discussing here the reaction driven by solid acid catalysts. Acidic zeolites are reported to be good catalysts for these reactions wherein the selectivity depends on the pore architecture [126]. In another study, silicotungstic acid/zirconia supported SBA-15 is used as solid acid catalyst for these reactions. In this study, the activity increased with the acidity of the catalyst and an excellent selectivity of benzyl acetate (96%) was obtained over an optimized catalyst (15 wt% silicotungstic acid/zirconia on SBA-15) [127]. Sulphate, borate, and phosphate modified alumina, silica and zirconia are also studied for these reactions [128].



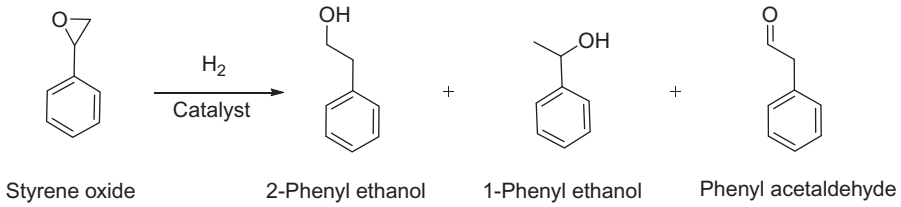
Scheme 11.15
Esterification of aromatic compounds.

11.4.3 Hydrogenation

In general, a fragrance chemical always has multiple functionalities like alcohol, aldehyde, esters, and unsaturated carbons, etc., and thus the reactions involving hydrogenation need to be highly selective for the production of diverse fragrance chemicals. Different methodologies like bio-hydrogenation (reduction), asymmetric hydrogenation, or metal catalyzed selective hydrogenation are used depending on the nature of the reactant.

2-Phenyl ethanol (2-PEA) with rose petal odor finds application in perfumes, deodorants, soaps, detergents, and some cosmetics [121,129,130]. Industrially, 2-PEA was produced by Friedel-Crafts reaction of benzene using homogeneous catalysts and Grignard reaction of

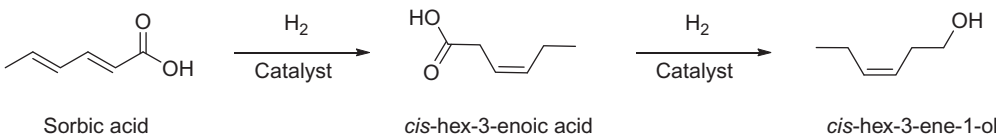
chlorobenzene with ethylene oxide—both reactions involve corrosive chemicals and are expensive. A new process from styrene via styrene oxide involves the hydrogenation of styrene (Scheme 11.16) oxide over heterogeneous catalyst and is identified as the most environmentally friendly route for the production of 2-PEA [131].



Scheme 11.16
Hydrogenation of styrene oxide.

Raney Nickel was identified as the potential heterogeneous catalyst however requires alkali promoter; Yadav and Chandalia reported for the first time a base-free reduction of styrene derived styrene oxide over Pd/C catalyst with 90.2% yield of 2-PEA form styrene [132]. Several attempts were made by the researchers to improve the yield of 2-PEA using different palladium supported catalysts such as Pd/AC, Pd/γ-Al_2O_3, Pd/MgO, Ru/C, Pt/C, Cu/SiO_2ZrO_2 and Pd/Chitosan [133–136]. Among them, basic supports like Pd/MgO and Pd/Chitosan gave high conversion with very high selectivity however with small amounts of by-products such as 1-phenly ethanol, phenyl-acetaldehyde or ethyl benzene. Recently, Yadav et al. reported the polyurea supported Pd-Cu catalyst in supercritical CO_2 with 100% conversion and 100% selectivity [137], and Pd supported heterogeneous catalysts with $\geq$99.9% 2-PEA selectivity were also patented for the production of the same [138].

cis-Hex-3-ene-1-ol, often referred to as leaf alcohol that has an odor of fruits and vegetables, is an intensively used fragrance chemical obtained from sorbic acid [139]. Initial studies used methyl sorbate for the production of *cis*-Hex-3-en-1-ol through methyl-*trans*-hex-2-enoate or *trans*-hex-2-enoic acid [140,141]. Due to cheaper availability of sorbic acid compared to its methyl ester selective reduction of sorbic acid to *cis*-hex-3-ene-1-ol through *cis*-hex-3-enoic acid (Scheme 11.17) was studied and few metal complexes found successful in homogeneous two-phase hydrogenation [142]. Leitmannova and Cerveny reported the first successful heterogeneous catalytic hydrogenation of sorbic acid to *cis*-hex-3-enoic acid using [pentamethylcyclopentadienyl Ru(sorbic acid)]CF_3SO_3 complex immobilized over silica with 2 wt% Ru loading at 85°C and 5 Mpa hydrogen pressure [143].

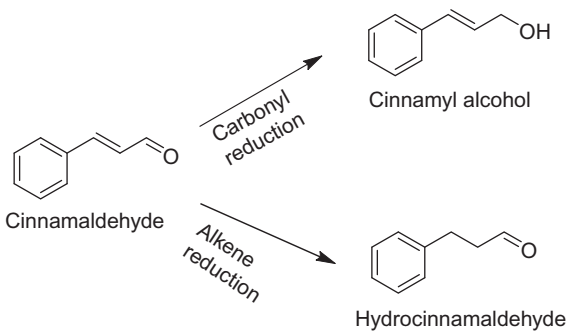


Scheme 11.17
Selective hydrogenation of sorbic acid.

Though this was found to be successful for the separation of the catalyst from the product mixture, the catalyst could not be reused due to leaching. Heterogeneous selective and reusable catalyst for the production of *cis*-hex-3-en-1-ol/*cis*-hex-3-enoic acid from sorbic acid is an open challenge.

Chemo-selective catalytic hydrogenation of α,β-unsaturated aldehydes into the corresponding unsaturated alcohols by hydrogenation at the C═O bond is highly desirable from an industrial point of view. Though this is one of the older subjects of research with high selectivity that has already been achieved, research is still being pursued on this particular reaction due to its industrial importance, and is a model reaction to find catalyst structure, selectivity, and for mechanistic understanding [144].

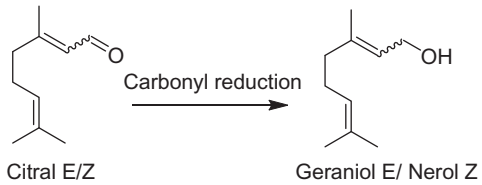
Cinnamyl alcohol, a component in flower compositions, is a valuable chemical for perfumery industry and a starting material for the production of cinnamyl esters [145].



Scheme 11.18
Hydrogenation of cinnamaldehyde.

Hydrocinnamaldehyde is the thermodynamically favored product and thus the selective reduction to cinnamyl alcohol (Scheme 11.18) has always been an interest of researchers. Pt, Ru, Co, Cu, Au and bimetallic catalysts are reported on the selective hydrogenation of cinnamaldehyde [146–151]. Obtaining high selectivity with high conversion under ambient conditions using a reusable heterogeneous catalyst is the problem to be resolved in the production of hydrocinnamaldehyde.

Citral (3,7-dimethyl-2,6-octadienal) is one of the main components in lemongrass oil. It has three hydrogenation sites: a carbonyl group, a C═C bond conjugated with the carbonyl group, and an isolated C═C bond. Citral exists as *cis*- and *trans*-isomers and selective partial hydrogenation of citral leads to important fragrance chemical namely, geranial and nerol (Scheme 11.19)



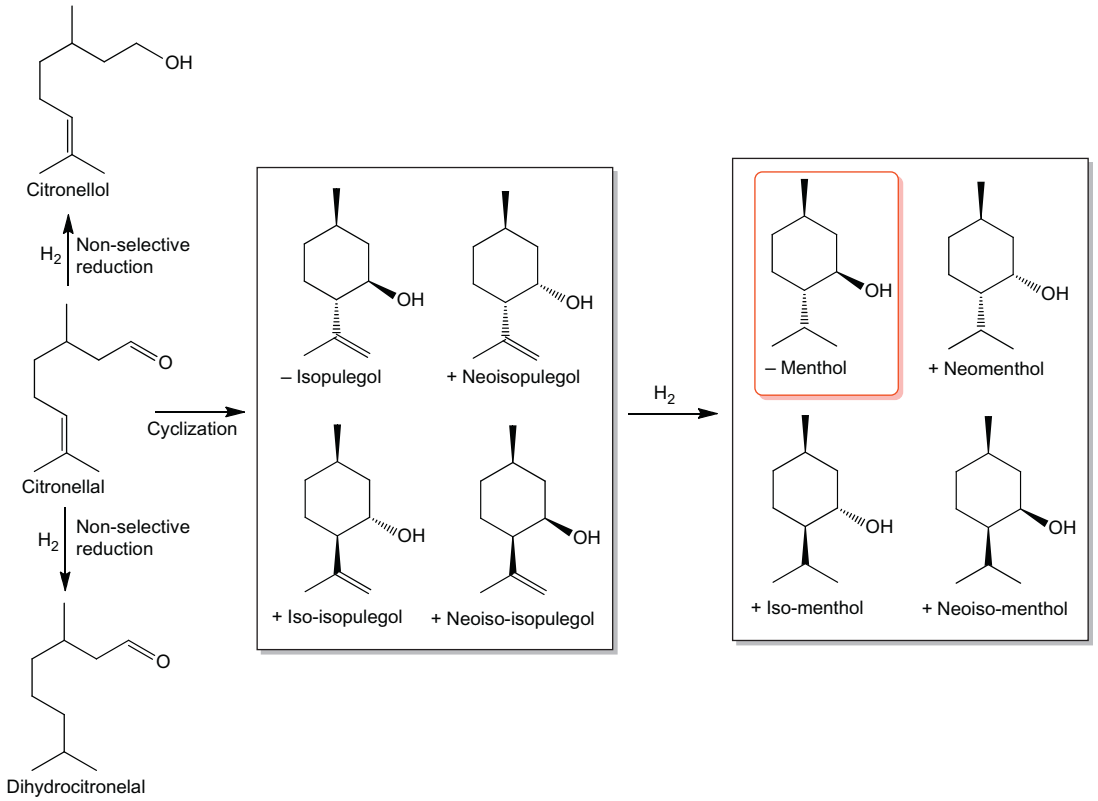
Scheme 11.19
Partial hydrogenation of citral.

It is yet another example for selective reduction of α,β-unsaturated aldehydes and ruthenium supported on charcoal/carbon promoted by iron was found to be successful for this reduction [152]. Complete hydrogenation of citral leads to menthol and much research work has also been published on the synthesis of menthol from citral [153,154].

More than 70% of edible oils in the world belong to vegetable oils and hydrogenation of these has been used since the first half of the twentieth century to expand the application of vegetable oils in the food industry [155]. Hydrogenated vegetable oils provide distinctive flavor, crispness, creaminess, plasticity, and oxidative stability to common foods. However, formation of *trans*-unsaturated fatty acids (TFA) and completely saturated fatty acids have adverse side reactions during the process, and TFA intake in the human diet has been linked to unhealthy shifts in serum lipid profiles and coronary heart disease [156]. Noble metals supported catalysts were screened for their activity and selectivity for this hydrogenation reaction and Pd was found to be efficient [157–160]. Mass transfer limitations associated with this reaction were overcome by the high surface area supports and recently Pd supported structured silica catalysts showed higher activity with *cis* unsaturated fatty acid [161]. A recent review shows that novel hydrogenation process can produce *trans*-fatty acids below the level of 8% [155].

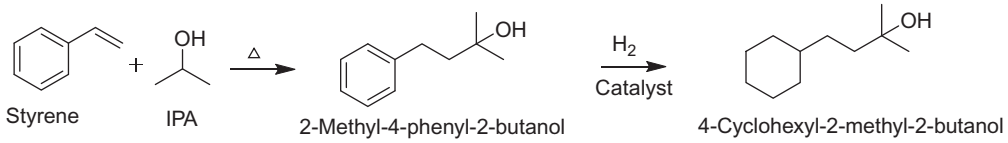
(−)-Menthol is an important compound in the pharmaceutical, flavor, and fragrance industries because of its organoleptic properties and owing to its intense flavor. Commercially, it was produced by Takasago process from myrcene, using multiple steps and homogeneous catalysts [162]. Recently, routes for synthesis of menthol from citronellal (or citral) using heterogeneous catalysts that on cyclization produced enantiomers of isopulegol which on hydrogenation gave menthol [163,164].

Multiple heterogeneous catalysts were reported in the production of (+/−) menthol from both citral and citronellal (Scheme 11.20) using supported Ni, Rh, Pd and Ir containing catalysts [154,163–165]. Recently researchers are interested in selective production of (−) menthol rather than the racemic mixture. Milone et al. reported >85% menthol yield from (+) citronellal [166] while Pt-loaded H-β zeolite and nickel supported sulphated zirconia catalysts gave selective (−) menthol from racemic (+/−) citronellal [167,168].



Scheme 11.20
Hydrogenation pathways for citronellal to (−) menthol.

4-Cylcohexyl-2-methyl-2-butanol, commonly known as coranol, is a fragrance with a lily-of-the-valley odor [169]. This was produced by high temperature reaction of styrene with isopropanol (IPA) followed by ring hydrogenation (Scheme 11.21). Ru/SiO_2 catalyst with very low Ru loading of 0.34 wt% was patented for this important ring hydrogenation reaction [170].

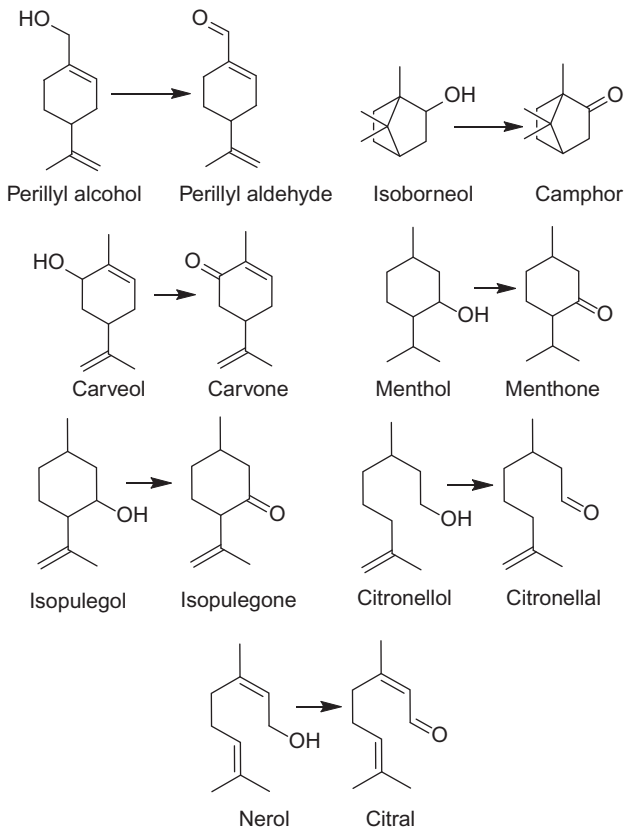


Scheme 11.21
Process for the production of 4-cylcohexyl-2-methyl-2-butanol.

Though hydrogenation reactions are achieved relatively easily rather than the oxidation reactions, one-pot conversion involving multiple reactions for menthol production needs further research.

11.4.4 Selective Oxidation

Oxidation reactions are always a challenging area of research due to the difficulties associated with product selectivity and thus, an economically acceptable yield. Several tailored catalysts are reported depending on the needs of the oxidation reaction. Terpenic compounds are an important biomass-based renewable feedstock that find enormous application in the flavor and fragrance industries [114]. For example, terpenic alcohols on oxidation give valuable fragrance aldehydes and ketones (Scheme 11.22).

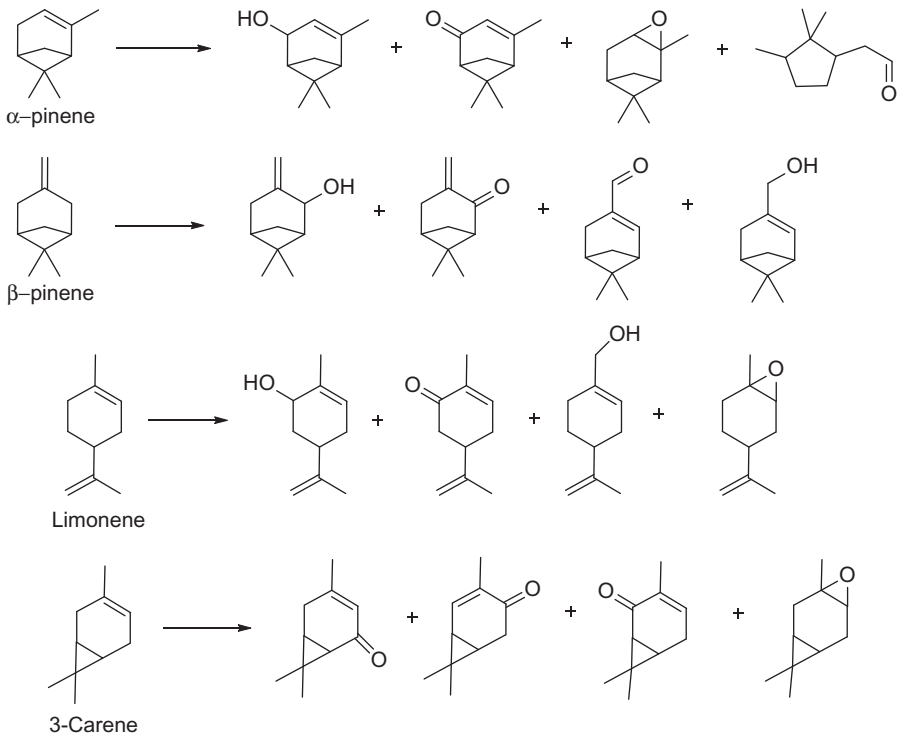


Scheme 11.22
Oxidation of terpenic alcohols.

Every product is associated with specific aroma properties like perillyl aldehyde used as food additive for flavoring and in perfumery to add spiciness; camphor has a strong aromatic odor; menthone and isopulegone have aromatic odors used in perfumery. Heterogeneous catalysts under environmentally benign conditions are reported in literature with variable degrees of conversion levels for these reactions [171,172]. Non-activated mono-terpenic alcohols such as menthol, isopulegol, and citronellol mostly yielded lesser conversion than their

activated counterparts like carveol, and nerol and thus, further research is necessary to achieve improved conversions.

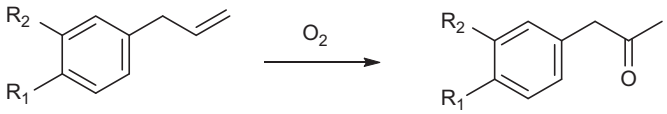
Selective alkene oxidation is the first step in the commercialization of biomass derived terpenes for them to be used in the fragrance industry and this reaction generally renders diverse intermediate chemicals (Scheme 11.23), as this reaction often leads to multiple oxidation products due to epoxidation or alkenyl oxidation [173,174].



Scheme 11.23
Different products obtained during the oxidation of important terpenes.

Homogeneous catalysts, in general, yield high conversion selectively to a product while heterogeneous catalyzed oxidation often result in lesser conversion with multiple products [174,175]. Palladium is reported to be an efficient catalyst for oxidative acetylation of terpenes and homogeneous palladium acetate/benzoquinone yielded 100% conversion of mono terpene with 96% total oxidation product selectivity [125,176,177]. Au and Pd supported on TiO_2 are also recently reported for the allylic oxidation of α-pinene [178]. Recently, Goncalves and Gusevskaya have achieved 90–95% conversion of limonene with higher than 90% chemo-selective products using $Pd(OAc)_2$/benzoquinone/$M(OAc)_2$ (M = Cu, Co or Mn) as homogeneous catalyst [179]. Selective epoxidation of terpenic olefin is also

reported earlier with 100% conversion and 90% epoxide selectivity using metal acetyl-acetonates as catalysts [180]. To surmise, finding a selective heterogeneous catalyst of such selective oxidation reaction always remains a challenge for researchers.

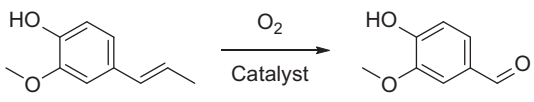


Compound	R_1	R_2
Eugenol	OH	OCH_3
Methyleugenol	OCH_3	OCH_3
Estragole	OCH_3	H
Safrole	-O-CH_2-O-	

Scheme 11.24
Oxidation allylbenzene compounds.

The functionalization of naturally occurring olefins other than terpenes can provide oxygenated compounds with different properties. Biomass derived allylbenzene compounds such as eugenol, methyleugenol, safrole, and estragole are important feedstock (whose isomerization is discussed earlier in this chapter) on oxidation yield aromatic methyl ketones that finds application in many fragrances (Scheme 11.24). Dimerization and oxidative cleavage are important drawbacks of this reaction [180]. Recently, Parreira et al. used palladium chloride as catalyst in the absence of any co-catalyst and achieved >95% conversion with >90% ketone selectivity.

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is found in nature and extracted from different natural resources and the annual world demand for vanillin is 12,000 tons; however, only 1800 tons are produced from natural sources [181].



Isoeugenol Vanillin

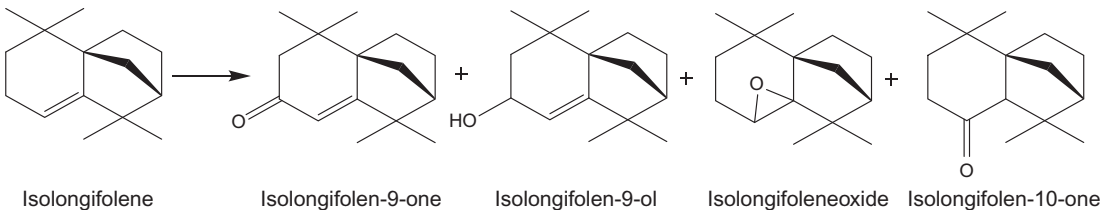
Scheme 11.25
Oxidative cleavage of isoeugenol to vanillin.

Isoeugenol (2-methoxy-4-(prop-1-en-1-yl)phenol) obtained by the isomerization of naturally available eugenol can be oxidized to vanillin (Scheme 11.25) by biochemical or chemical conversions [182,183]. Homogeneous catalysts like salen complexes, iodobenzene diacetate and H_2O_2 in the presence of the *n*-Bu_4NVO_3/pyrazine-2-carboxylic acid catalytic combination are found to be efficient for this reaction [184–186]. Adilina et al. have recently reported

the cobalt porphyrin intercalated into lithium taeniolite clay as a heterogeneous catalyst for this reaction using molecular oxygen as oxidant and obtained 72% yield of vanillin [187].

Benzaldehyde and substituted benzaldehydes are important intermediates for the synthesis of several fragrant chemicals and several reviews are published on the selective oxidation of benzyl alcohol to benzaldehyde [188,189]. Several homogeneous, as well as heterogeneous catalysts are reported, which are mostly IP protected, for the synthesis of substituted benzaldehydes [190–193]. Obtaining decent yields of the desired aldehydes without affecting the substituted groups (for example, *p*-cymene oxidation to *p*-isopropyl benzaldehyde, popularly known as cuminaldehyde) has always has been a daunting task that is currently practiced in industries with sub-optimal yields and thus, provides potential opportunities for heterogeneous catalysts to overcome.

Isolongifolene, another biomass-based compound can be obtained by the isomerization of longifolene and, the oxygenated derivatives of this occupy a vintage place in the modern perfume industry because of their extremely rich woody and floral odor. The reported processes for this reaction uses traditional oxidants like permanganates, dichromates, and peroxo compounds in stoichiometric amounts and obtained a mixture of oxygenated products (Scheme 11.26) [194–197].



Scheme 11.26
Oxygenated products of isolongifolene.

Cobalt-containing MCM-41 is reported to be efficient for the heterogeneous catalyzed oxidation of isolongifolene using molecular oxygen as oxidant [198]. The final mixture contained 90 wt% oxygenated products with 90% selectivity towards isolongifolen-9-one.

11.5 Opportunities and Future Directions

It is clear that the fragrance and flavor industry, whether for India or for the world, will be growing significantly in the next few years and the expected market capital in these years is likely to reach US$ 45 billion. Knowing that the price of most of the natural essential oils has increased phenomenally in the last two decades owing to their scarce availability, it is pertinent that researchers have to isolate the molecules of interest (and in most of the cases known except for indigenous resources) and try to synthesize them. Such an approach needs a strong research and development requirement, which unfortunately has not been creditably

given. Further, most of the synthetic approaches involve harsh and environmentally non-conducive conditions for the synthesis of these molecules. This provides ample avenues to test benign solid heterogeneous catalysts for many diverse classes of reactions, leading to perfumery molecules of industrial importance, some of which were discussed in this chapter. New solid materials are being synthesized with custom-designed properties such as tunable redox ability, optimized metal dispersion, site isolation, efficient control of acidity and basicity, endeavoring to realize the catalytic transformation with high turnovers, specificity, and long-term stability. If some of these materials (other than those which are conventionally used in hydrogenation reactions using supported metal catalysts) are tested and proved to be efficient for a given transformation, this will augment support of using heterogeneous catalysts for the synthesis of perfumery chemicals. One of the examples demonstrated in this chapter, namely isomerization of allylic aromatics, is a step in this direction. While writing this chapter, an industry from a southern region of India has been approached for the synthesis of iso-eugenol from eugenol using the LDH based heterogeneous catalyst discussed in Section 11.4.1. Chemoselective oxidation or hydrogenation to produce desired perfumery chemicals is always a challenge and thus provides an opportunity to design and develop suitable heterogeneous catalysts that have the potential to overcome. Most of the reactions in this segment are employed using conventional oxidants (which are environmentally unfriendly) or unselective catalysts and thus, being produced in sub-optimized yields in industries. Furthermore, policy-level changes should be made conducive for this industry to sustain, in particular for India backed by standardized norms. Enantioselective synthesis of fragrant molecules is gaining significant attention with an endeavor to realize new notes. Theoretical studies, in recent years, are assisting in the design of such new fragrant molecules. One of the recent examples was where molecular modelling helped in the design of an organocatalyst (enol activation catalysts) for the enantioselective synthesis of unique Cashmeron odorants that have floral-fruity musky with a conifer-type odor, through novel asymmetric Brønsted acid catalyzed Michael addition of unactivated α-substituted ketones [199]. It is also interesting to note that the largely produced perfumery molecule, vanillin, has also been used not only for its intended purpose but as a platform molecule to synthesize various value added bio-based products, a new area emerging advocating diversification and utilization of renewable, here lignin [200]. The key role that can be played by the heterogeneous catalysis for the synthesis of perfumery chemicals is highly promising (like it was done in the 1970s onwards for the refining of petroleum to make fuels and petrochemicals). However, focused and dedicated research and development is necessary in collaboration with the industry to realize this endeavor.

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CHAPTER 12

Use of Catalysis for API Manufacturing

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12.1 Introduction

The pharmaceutical industry spends billions of dollars to discover new drug molecules that have efficacy, safety, quality, and affordability. Many of the reactions are carried out in the synthesis of these molecules by making use of catalysts. Catalysts plays a major role in making the product affordable by reducing the cost of the process and pollution (greener and environmentally friendly technologies). Catalysts have an impact on both fundamental science and the emerging technologies in the fine chemicals, as well in the active pharmaceutical ingredients (APIs). These benefits continuously accelerate the interest in the catalyst and its application in catalytic reactions.

Advances in catalysis have had a tremendous impact on the pharmaceutical, as well as fine chemical process development. Catalysis enables the synthesis of new highly complex small-molecule in fewer steps, especially enantiomerically pure chiral molecules, with increased atom economy, and often high selectivity and yield. New processes are developed using catalysts, even for the generic APIs to economize the cost and to file new processes to overcome patent infringement.

Along with the most widely used catalyst for various types of synthetic reactions, many different types of catalyst are reported for their use in the API manufacturing.

There may be challenges in the use of catalyst, catalytic systems, their recovery, cost, availability, and toxicity, but still the benefits they offer to the pharmaceutical industry for large and moderate to small volume products is quite substantial.

Several reports are available for the development of alternate catalysts derived from abundant, nontoxic metals and simple ligand systems. Catalyst from new base metals platforms are also of interest because they may enable new chemistry not previously observed with the use of traditional precious metal catalysts.

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12.2 Regulatory Requirement

In the past few years, global regulators of the pharmaceutical industry have raised several concerns about the safety and quality of the drugs that are marketed and manufactured by using catalyst. The question of contamination of catalyst in APIs becomes critical and important. This catalyst contamination may be toxic, may lead to degradation of API or formation of new impurities, or act as a poison for the patient.

One may use the US FDA emphasized guidelines for Quality by Design (QbD), traceability and risk-based manufacturing to avoid contamination due to catalyst carryover. Quality risk management principles are applied to arrive at the allowable limits of the catalyst in the API that is used to manufacture the dosage form of the drug.

12.2.1 Inorganic Impurities (ICH Q 3A; 3.2)

The ICH Q3A Guideline classifies impurities as organic, inorganic, and residual solvents. However, inorganic impurities are not appropriately addressed. New guidelines are being written for metal contamination [1–6]. The following information is provided in the ICH Q3A:

> *Inorganic impurities are normally detected and quantified using Pharmacopoeial or other appropriate procedures. Carryover of catalysts to the new drug substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in the new drug substance specification should be discussed.*
>
> *Acceptance criteria should be based on Pharmacopoeial standards or known safety data.*

EMEA "Guideline on the Specifications limits for residues of metal catalyst or metal reagents," applicable since September 1, 2008 also refers to the metal catalyst and reagents. In this guideline the metal residues are considered to be from catalyst, reagents used, and wear and tear of the surfaces of equipment used for manufacturing of the drug.

The objective of this EMEA guideline is to recommend maximum acceptable concentration limits of metal residues arising from the use of metal catalysts or metal reagents in the synthesis of drug substances and excipients, considering the safety of the patient.

Thus, the analytical method used for detecting and quantifying the content of catalyst is important. During process development if catalyst is used, it becomes very important to include steps to avoid carryover of catalyst contamination. If catalyst has been used in any of the critical reactions to synthesize API, its final specification should include the content of catalyst and meet the permissible limits. If the safety limits for the content of catalyst are not accessible in any of the available or reported references, then the manufacturer has to establish the toxicity data of the API before setting safety limits for acceptance criteria. This has to be done by carrying out the prescribed standards for toxicity and safety.

The ICH Q3 guideline classifies metal residues into three categories based on their individual level of safety concerns and sets concentration limits. The limits are based on the maximal daily dose (MDD), duration of treatment, and administration route of the drug product as well as the permitted daily exposure (PDE) of the metal residue. Metal residues can either be present in the original form of the metal or as a form of the metallic element altered by downstream chemical processing.

The guideline also includes recommendations on testing strategies, analytical procedures, and reporting levels in pharmaceutical substances or drug products.

The three classes according to current ICH Q 3A guideline are:

Class 1 metals: Metals of significant safety concern. This group includes metals that are known or suspected human carcinogens, or possible causative agents of other significant toxicity.
Class 2 metals: Metals of low safety concern. This group includes metals with lower toxic potential to man. They are generally well tolerated up to exposures that are typically encountered with administration of medicinal products. They may be trace metals required for nutritional purposes or they are often present in food, or readily available nutritional supplements.
Class 3 metals: Metals of minimal safety concern. This group includes metals with no significant toxicity. Their safety profile is well established. They are generally well tolerated up to doses that are well beyond doses typically encountered with the administration of medicinal products. Typically they are ubiquitous in the environment or the plant and animal kingdoms.

The widely used metal for the catalysts are currently included in this guideline ICH Q3D and are listed in Table 12.1. This table includes their Class, Permitted Daily Exposures (PDEs) for elemental impurities in (mg/day), Limits for Individual Metal Catalysts and Metal Reagents

Table 12.1 Permitted daily dose exposures (PDEs) for elemental impurities

Element	Class	Oral PDE (g/day)	Parenteral PDE (g/day)	Inhalation (µg/day)
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	100	10	1
Tl	2B	8	100	1
Au	2B	100	100	1
Pd	2B	100	10	1

Continued

Table 12.1 Permitted daily dose exposures (PDEs) for elemental impurities—cont'd

Element	Class	Oral PDE (g/day)	Parenteral PDE (g/day)	Inhalation (µg/day)
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	1500	60
Cr	3	11000	1100	3

Notes: PDA reported in the Table 12.1 (g/day) have been established on the basis of safety data described in the monographs in Appendix 3 of ICH Q3D guideline and new drug products. The PDE in the monographs are not rounded. For practical purposes the PDEs in the Table 12.1 have been rounded to 1 or 2 significant figures. PDEs less than 10 have 1 significant figure and are rounded to the nearest unit. PDEs greater than 10 are rounded to 1 or 2 significant figures are as appropriate. The principles applied to rounding in the Table 12.1 may be applied to PDEs derived for other routes of administration. The classification has been reported as described in the ICH Q3D Section 4.

Refer to this guideline for Exposure Limit, Concentration limit for different routes of administration and Analytical Procedures and Rational for setting limit for PDE.

Global Regulators and the FDA is charged with protecting the public health by regulating and ensuring the safety, effectiveness, and security of human and veterinary drugs and has put in certain controls on the content limit of the catalyst in the APIs.

Even ICH Q 3A has been revised and harmonized to ensure that new requirements have the necessary input from the regional regulatory authorities to help protect patient safety, and also to help avoid differing approaches and standards among the pharmacopoeias and the regulators.

New ICH Q3 D Guideline for Elemental Impurities

The long-awaited "Guideline for Elemental Impurities — Q3D — step 2b version dated 25 July 2013" was published on ICH website on August 5, 2013 and the ICH Steering Committee moved this Guideline to stage 4 in September 2014 (became official).

There are three components of this guideline:

- The evaluation of the toxicity data for potential elemental impurities,
- The establishment of a PDE for each element of toxicological concern,
- The development of controls designed to limit the inclusion of elemental impurities in drug products to levels at or below the PDE.

Developing a strategy to limit elemental impurities in the drug product is consistent with risk management processes identified in ICH Q9 (Available on the ICH website). The process is described in this guideline as a four steps process to assess and control elemental impurities in the drug product: identify, analyze, evaluate, and control.

Many other articles have been published on the subject, however Regulatory Authority depends on the ICH Guideline and thus it is most essential to follow ICH Q3D/Q3A for the control of metallic catalyst content in the final API.

Elemental Classification as per ICH Q3D

The elemental impurities included in ICH Q3D have been placed into categories as depicted below:

Class 1 elemental impurities: The elemental impurities As, Cd, Hg, and Pb, are significantly toxic across all routes of administration. Typically they have limited or no use in the manufacture of pharmaceuticals but can be present as impurities in commonly used materials (eg, mined excipients) and cannot be readily removed from the material. Because of their unique nature, these four elemental impurities require consideration during the risk assessment across all potential sources of elemental impurities.

"*Class 2 elemental impurities*: These are toxic to a greater or lesser extent based on route of administration. In addition, some of the elements present in this category are infrequently observed as impurities in materials used to produce drug products and as such, unless intentionally added, have a low probability of inclusion in the drug product and do not present a significant risk. Class 2 elemental impurities are further categorized to establish when they should be considered in the risk assessment and when their contribution can be judged to be negligible.

Class 2A: The following elemental impurities require assessment across all potential sources and routes of administration: V, Mo, Se, and Co due to their higher relative natural abundance (US Geological Survey, 2005).

Class 2B: The following elemental impurities require assessment across potential elemental impurity sources only if they are intentionally added to the processes used to generate the material under evaluation: Au, Tl, Pd, Pt, Ir, Os, Rh, Ag, and Ru.

Class 3 elemental impurities: Are impurities with relatively low toxicity (high PDEs) by the oral route administration, but require consideration in the risk assessment for other routes of administration (eg, inhalation and parenteral routes). For oral routes of administration, unless these elements are intentionally added as part of the process generating the material, they do not need to be considered during the risk assessment. For parenteral and inhalation products, the potential for inclusion of these elemental

impurities should be evaluated during the risk assessment. The elemental impurities in this class include: Sb, Ba, Li, Cr, Cu, Sn, and Ni.
Class 4 elemental impurities: Are elemental impurities that have been evaluated but for which a PDE has not been established due to their low inherent toxicity and/or regional regulations. If these elemental impurities are present or included in the drug product, they are addressed following the practices defined by other guidelines and regional regulation. The elements in this class include: Al, B, Fe, Zn, K, Ca, Na, Mn, Mg, and W."
(Note: This text is as per the ICH Q3D draft guideline that was published for public comments).

The risk due to used catalyst carryover as contaminant in the API may be mitigated by a number of control majors. These include, but are not limited to:

- Identification of the steps in the manufacturing process that result in the reduction of elemental impurities through specific or nonspecific purification steps;
- Implementation of in-process or upstream controls, designed to limit the concentration of the elemental impurity in the drug product;
- Establishment of specifications for materials manufactured using catalyst to limit the level of elemental impurity contributions to the APIs. This control may be used when materials are either manufactured in-house or procured from validated vendor;
- Establishment of specification limits for the drug substance APIs;
- Establishment of specification limits for the drug product;

Reliance on the compliance with compendial standards for materials used in drug product processes.

The Table 12.2 included in the ICH 3QD, reproduced below for control of elemental impurities in the Drug Product (Finished dosage), may be used [2].

Table 12.2 Elemental impurities in the drug dosage

Sr. No.	Elemental impurity	Included elemental impurities	Include in risk assessment
1	Class 1	As, Pb, Cd, Hg	Yes
2	Class 2 A	V, Mo, Se, and Co	Yes
3	Class 2B	Ag, Au, Tl, Pd, Pt, Ir, Os, Rh, and Ru	Yes only if intentionally added
4	Class 3	Sb, Ba, Li, Cr, Cu, Sn,	Dependent upon route of administration–see Class 3 description
5	Class 4	B, Fe, Zn, K, Ca, Na, Mn, Mg, W, Al	No

Analytical Procedure for Catalyst Detection and Quantification

- The determination of elemental impurities should be conducted using appropriate procedures suitable for their intended purposes. Unless otherwise justified, the test should be specific for each elemental impurity identified for control during the product risk assessment. Pharmacopoeial procedures or suitable validated alternative procedures for determining levels of elemental impurities should be used.

12.3 Significance of Catalysis in API

12.3.1 General

APIs are complex chemicals and their synthetic manufacturing process generally involves a number of reaction steps. Some of the drug molecules, peptides, and biotech products (large molecules) are also manufactured using enzymatic or metallic catalyst. Many of the fine chemicals, which are manufactured using catalysts, become starting materials for the synthesis of APIs. Almost all the catalytic reactions that are practiced in fine chemical synthesis are practiced in API synthesis to manufacture either the critical starting materials or the intermediates for active ingredients or APIs themselves. So basically, the principle applied to catalytic reactions in the API industry does not differ from those for fine chemical manufacturing. The only difference is the application of the strict regulatory control for the carryover residues of the catalyst in the APIs as described in the Section 12.2 of the chapter.

12.3.2 Atom Economy

Atom economy or efficiency is one of most important parameters from a sustainable development point of view and, hence, the Green Chemistry, it is of utmost importance to develop a process generating no or minimum waste. Atom efficiency allows reactions to be advantageous and economical as well environmentally friendly [8,9].

It is important to study the reaction kinetics when catalysts are used. The principles of using computational tools for studying chemical kinetics and catalysis are described in a book titled "Chemical Kinetics and Catalysis" [7].

Atom Economy Synthesis of Ibuprofen (BHC)

One of the best examples of the green chemistry application is the manufacturing of **Ibuprofen** by the Boots-Hoechst-Celanese (BHC) route.

An improved process patent was filed for three steps to manufacture Ibuprofen from isobutyl benzene. As one can see, this is an atom efficient synthesis where no wastes are generated. This improved synthesis won "Presidential Green Chemistry Challenge Greener Synthetic Pathway Award" in 1997 [10].

In the first step, isobutyl benzene is acylated using acetic anhydride with hydrofluoric acid as catalyst (homogeneous), the 4-isobutylacetophenone was then hydrogenated using Raney Nickel (heterogeneous) catalyst to alcohol and finally carbonylated using palladium (heterogeneous) (Table 12.3).

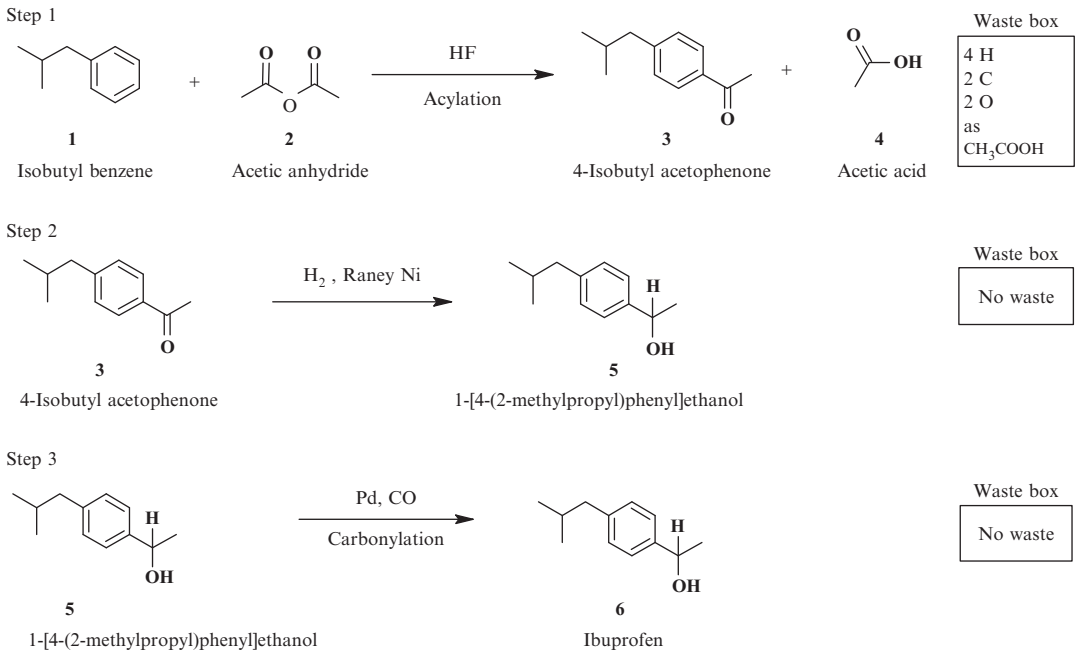


Table 12.3 Atom economy in the green synthesis of Ibuprofen

Reagent		Used in Ibuprofen		Unused in Ibuprofen	
Formula	**Molecular weight**	**Formula**	**Molecular weight**	**Formula**	**Molecular weight**
$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
$C_4H_6O_3$	102	C_2H_3O	43	C_2H_3O	59
H_2	2	H_2	2		0
CO	28	CO	0		0
Total		Ibuprofen		Waste product	
$C_{15}H_{22}O_4$	266	$C_{13}H_{18}O_2$	206	$C_2H_4O_2$	60

This indicates the atom economy of the process and the benefits of the use of catalyst Ni for reduction of ketone to alcohol and Pd for carbonylation.

12.3.3 Catalytic Reactions in API

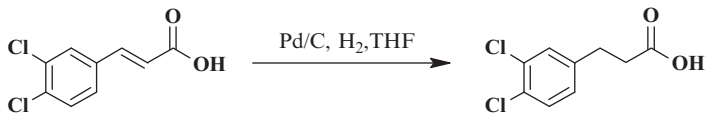
A large number of chemical transformations are carried out to synthesize various intermediates employed in API manufactured. A few reactions such as hydrogenation, carbonylation, carboxylation, hydroformylation, various coupling reactions, and protection, de-protection

reactions, etc., are briefly discussed here to indicate the usefulness in manufacture of fine and specialty chemicals. The examples discussed here are mainly from API and the intermediates used in the manufacturing.

12.3.3.1 Hydrogenation

Carbon-carbon multiple bonds

A complication in the hydrogenation of alkenes can be double bond migration and *cis-trans* isomerization. The ability of metal catalysts to promote these reactions is generally in the order: Pd > Ni > Rh > Ru > Pr = Ir. Platinum catalysts are therefore useful when double bond migration is to be avoided [11].

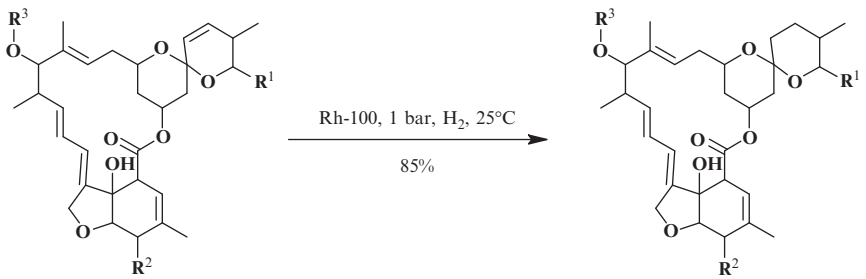


7 **8**

>99% yield

Avermectin to Ivermectin

Homogeneous Rh and Ir catalysts can be particularly useful for selective alkene hydrogenations. For example, in the manufacture of the pharmaceutical **Ivermectin** [12].



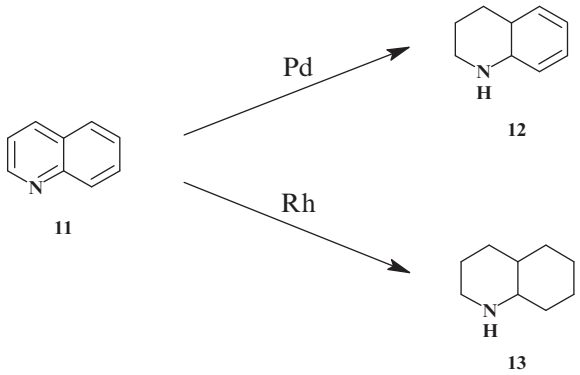
9
Avermectin

10
Ivermectin

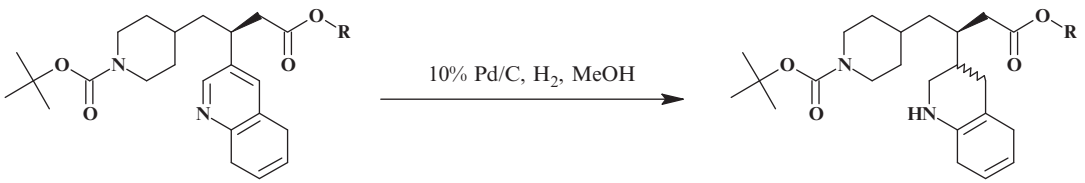
Aromatic ring compounds

a. Carbocycles
   The catalytic hydrogenation of substituted benzenes is used to produce substituted cyclohexanes. The activity of catalysts for the hydrogenation of aromatic rings are in the order Rh > Ru > Pt > Ni > Pd.
b. Heterocycles
   Heterocycles are easier to hydrogenate than carbocycles. Heterocyclic compounds such as pyridines, quinolones, isoquinolines, pyrroles, indoles, acridines, and carbazoles can be hydrogenated over Pd, Pt, Rh, and Ru catalysts. Acidic solvents such as acetic acid and aqueous HCl are often used to facilitate hydrogenation, as the pyridinium salt is more easily reduced than is the free base.

Generally, Pd is the preferred catalyst for selective hydrogenation of nitrogen containing heterocyclic rings in the presence of carbocyclic rings (Schemes 12.1 and 12.2) [13].



Scheme 12.1

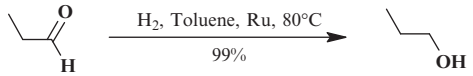


Scheme 12.2

Carbonyl compounds

a. Aldehydes

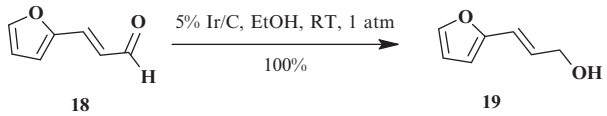
Saturated aliphatic aldehydes can be hydrogenated over Pt, Ru, Sponge Nickel™ or Ir catalysts to the corresponding primary alcohols at 5–150°C and 1–30 bar hydrogen pressure. Pd tends to be an ineffective catalyst for aliphatic aldehydes, but is the metal of choice for aromatic aldehydes. Ru is the catalytic metal of choice for the hydrogenation of aliphatic aldehydes [14].



16 Propanal — 17 Propan-1-ol

The selective reduction of unsaturated aldehyde such as crotonadehyde and cinnamaldehyde, the carbonyl reduction of (hydrogenation) is generally less facile than

olefin hydrogenation, thus making selective reduction of the unsaturated aldehydes to the unsaturated alcohol quite difficult. Pt/C is used commercially to produce cinnamyl alcohol from cinnamaldehyde. Os and Ir catalysts have also been shown to be highly selective for the formation of a-b unsaturated alcohols [15].

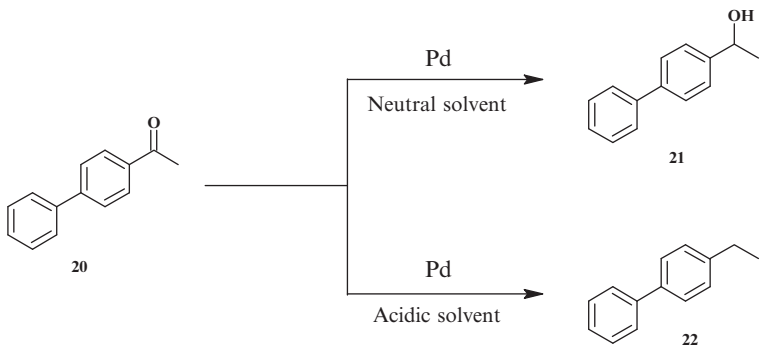


18 19

b. Ketones

Ketone hydrogenation is similar to that of aldehyde hydrogenation, but is usually less facile due to increased steric hindrance and lower electrophilicity at the carbonyl group. Saturated aliphatic ketones can be hydrogenated over Pt, Ru, or Ir to the corresponding secondary alcohol at 5–150°C and 1–30 bar hydrogen pressure.

Aromatic ketones are best hydrogenated over Pd catalysts and can be hydrogenated to the corresponding alcohol or alkyl aromatic (by hydrogenolysis). Acidic condition, elevated temperature, and polar solvent favor hydrogenolysis [16].

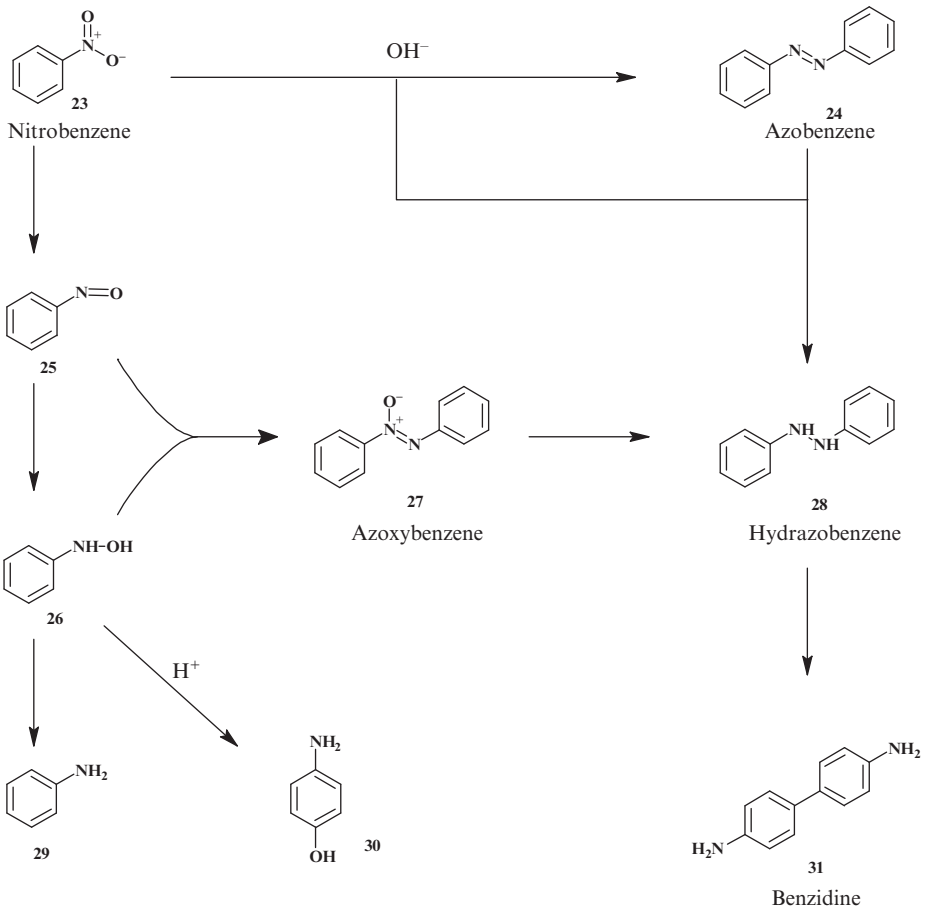


20 21 22

Nitro and Nitroso compounds

Aromatic nitro compounds are hydrogenated to the corresponding amine over Pd, Pt, and Sponge Metal^{TM} catalysts. An aromatic nitro group is generally the most easily hydrogenated of all functional groups and proceeds under very mild conditions. Nitro functions are reduced so readily that hydrogen mass transfer effects and resistances may influence the overall reaction rate.

Reaction pathway for the hydrogenation of the nitro compound [17,18].



Halonitroaromatics

Selective hydrogenation of halonitroaromatics to the corresponding haloaminoaromatics is most commonly carried out with Pt catalysts. Palladium catalysts generally cause high levels of dehalogenation [19].

Reductive alkylation

Reductive alkylation involves the reaction of a primary or secondary amine with an aldehyde or ketone to form a secondary or tertiary amine, respectively. Formation of the imine intermediate is favored by acidic conditions. The imine intermediate is seldom isolate. [20]

Reductive aminations

The reaction is essentially the same as a reductive alkylation except that the "amine" feedstock employed is ammonia. The catalyst of choice is similar to that above. Co and Ni are most selective for primary amines with Pd and Pt tending to give a considerable proportion of

secondary amine. Excess ammonia is employed to suppress hydrogenation of the carbonyl to the corresponding alcohol [20].

Imines

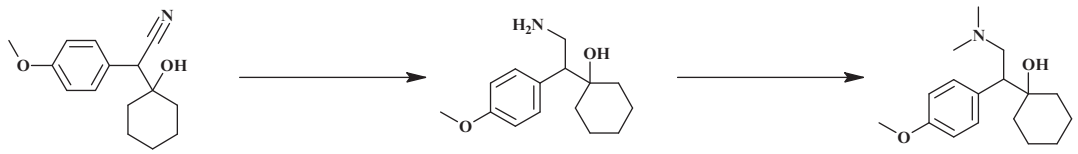
Reductive alkylations/aminations involve the condensation of a carbonyl compound with an amine to form an imine or aminol intermediate, which undergoes hydrogenation to the amine [20].

Nitriles

The catalytic hydrogenation of nitriles is widely used for the preparation of primary amines. Many different metallic catalysts have been employed for this duty, but amongst the most effective are Ni, Co, Pd, Rh, and Pt.

Unwanted secondary or tertiary amines can be formed via the reaction of the desired product with the intermediate imine, and control of the reaction conditions is critical to achieve high selectivity [20].

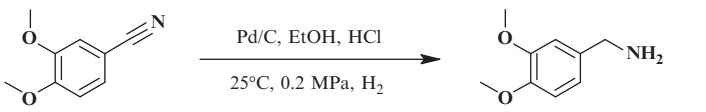
An example of a commercial application of this chemistry is the hydrogenation and alkylation to produce the antidepressant Venlafaxine. Both Ni and Pd have been used on large scale for this conversion.



32 **33** **34**

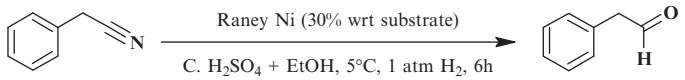
Venlafaxine

For aromatic nitriles in ammonia or acidic media, Pd and Pt are preferred for the production of primary amines. In neutral solvent, Pt and Rh are preferred for the formation of secondary amines, and Pd for the production of tertiary amines.



35 **36** .HCl

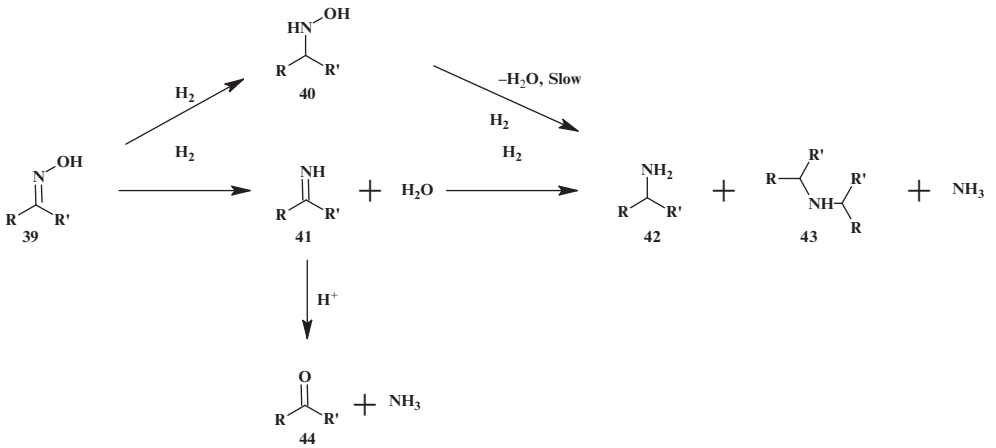
In acidic, aqueous media, nitriles can undergo reductive hydrolysis of the imine intermediate to yield aldehydes and/or alcohols in average yield. Ni or Pd are the catalysts of choice for this reaction, which can be affected at RT and 1 bar H_2 pressure.



37 **38**

Oximes

Hydrogenation of oximes to amines usually proceeds through the corresponding imines as intermediates, which can give rise to secondary amines, or via hydrolysis to carbonyl compounds or alcohols [20].



Of the Platinum Group Metals, Rh is the preferred catalytic metal for the formation of primary amines, usually producing less secondary amine product than Pd.

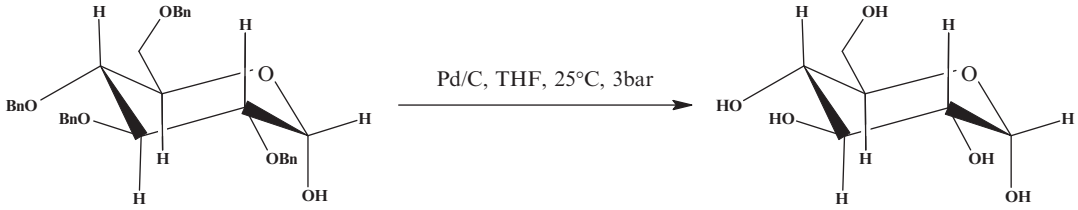
Hydrogenolysis

A. Deprotection reactions

In the manufacture of pharmaceuticals and fine chemicals, there is often a requirement for a protection strategy to minimize possible side reactions during a synthesis. Small, easily removed protection, available for a range of functional groups, is highly desired. One such easily removed protection is derived from the facile catalytic hydrogenolysis of benzylic groups. The classic functional groups requiring protection are alcohols, acids, and amines [21].

a. *O*-Debenzylation

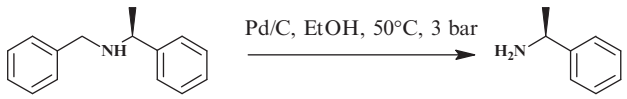
Typical reaction conditions for an *O*-debenzylation are 20 to 30°C and 25 to 50 psi H_2pressure. The classical Pd/C catalyst used for this reaction is Pearlman's catalyst (a 20% palladium hydroxide on carbon catalyst), but in most cases it is possible to use a catalyst with a much lower Pd content as a range of more active and selective catalysts with reduced metal loadings have been developed. Solvent choice is critical, and commonly employed solvents are THF, ethanol, ethyl acetate, and acetic acid. Reaction rates are often fastest in THF. Catalyst design effects are important for catalyst performance. Catalysts with eggshell metal distributions which are unreduced, typically perform better than uniform metal distribution and/or reduced catalysts.



45 46

Debenzylation of 2, 3, 4, 6-*tetra*-*O*-benzyl-D-glucopyranose

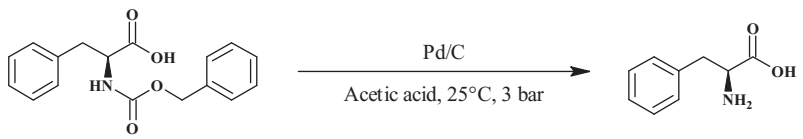
b. *N*-Debenzylation
N-Debenzylations are usually more difficult to perform than *O*-debenzylations. Typical reaction conditions for an *N*-debenzylation are 50 to 60°C and 25 to 50 psi H_2 pressure [20].



47 48

Debenzylation of *N*-benzyl *n*-methylbenzyl amine.

c. Removal of carbobenzyloxy protecting group
Typical reaction condition for the removal of carbobenzyloxy (Cbz) protecting groups are 25 to 35°C and 25 to 50 psi H_2 pressure. It is not possible to accurately follow the course of reaction by hydrogen uptake, as for the removal of a Cbz protecting group, 1 mole of carbon dioxide is generated for each mole of hydrogen consumed. Solvent choice is again critical with considerations similar to that for an *N*-debenzylation. The presence of acid in the reaction solution helps to prevent catalyst inhibition through the protonation of the amine product. Commonly employed solvents are methanol, ethanol, ethyl acetate, acetic acid, and alcohol/acid solvent mixtures. Both unreduced and reduced metal and eggshell metal distribution catalysts perform well [20].

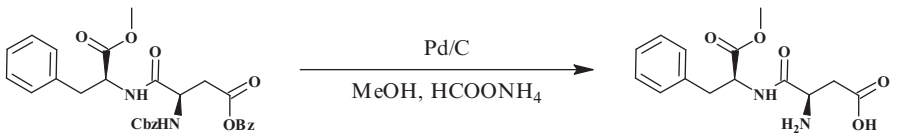


49 50

Deprotection of *N*-benzyloxycarbonyl-L-phenylalanine

d. Deprotection reactions via transfer hydrogenation [20]
The use of a hydrogen donor rather than gas phase hydrogen has many processing advantages including: no pressure equipment requirement; no need for H_2 storage,

delivery systems or gas measurement; the use of standard vessels and equipment; and potential chemo selectivity advantages (eg, deprotection in the presence of an aryl chloride). A different and often beneficial reaction selectivity can be observed during catalytic hydrogenation using a hydrogen transfer agent instead of hydrogen gas.



51 52

B. Hydrodehalogenations

Hydrogenolytic cleavage of carbon-halogen bonds is normally carried out with either Pd or Ni catalysts under relatively mild reaction conditions (5–100°C, 1–10 bar H_2 pressure).

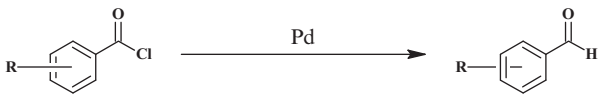
$$RX + H_2 \rightarrow RH + HX$$

$$X = F, Cl, Br, I$$

Pd is the most active and preferred catalytic metal. Large catalyst loadings are required with Ni catalysts because of the poisoning properties of the released halide ion.

C. Rosenmund reduction

The Pd catalyzed hydrogenolysis of acyl chlorides to the corresponding aldehyde is referred to as the Rosenmund reduction. It is a standard method for the conversion of carboxylic acids to aldehydes [20].



53 54

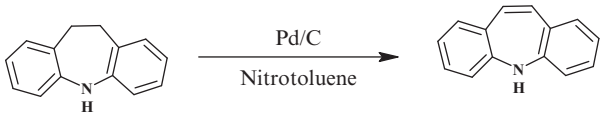
Transfer hydrogenations

When hydrogen gas and/or hydrogenation plant is not readily available, then a hydrogenation may be achieved using a chemical hydrogen donor. In effect, the catalyst dehydrogenates the donor molecule to generate hydrogen to carry out the hydrogenation. The donor molecule and catalyst should be selected with care so that the rate of hydrogen release is comparable to the rate of hydrogenation of the feedstock. Typical donor molecules include cyclohexene, formates, phosphinates, propan-2-ol, and indolene [22].

12.3.3.2 Dehydrogenation

Catalytic thermal dehydrogenation is an endothermic process, and hence, high operating temperatures (up to 350°C) and high catalyst loadings (3–10% with respect to feedstock) are often necessary. At such high temperatures, most PGM complexes decompose, so homogeneously-catalyzed dehydrogenations in the liquid phase are usually not feasible [20].

A particular dehydrogenation of industrial importance is the formation of imino stilbene from iminodibenzyl:



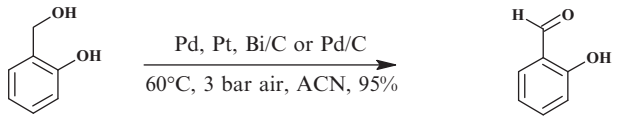
55 56

The product is an intermediate in the preparation of Carbamazepine — a treatment for epilepsy.

Oxidative dehydrogenation

An alternative way of improving the thermodynamics of dehydrogenation processes is to use oxygen as the hydrogen acceptor, so yielding water is a by-product. This technique has been successfully employed in the oxidation (or oxidative dehydrogenation) of alcohols to yield carbonyl compounds and/or carboxylic acids [20].

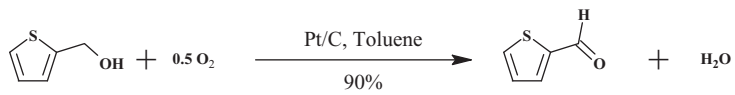
If the substrate is an aromatic alcohol, then the most active catalyst is often Pd or Pt or a combination of these metals (eg, 4%Pd, 1%Pt, and 3% Bi/C Type 430).



57 58

2-hydroxybenzaldehyde

In contrast to hydrogenation systems, sulfur-containing moieties do not appear to poison PGM catalysts under oxidation conditions. For example, 2-thienylmethanol can be readily oxidized to the corresponding aldehyde in >90% yield with a Pt/C catalyst in toluene. Furthermore, the catalyst can be reused several times.



59 60

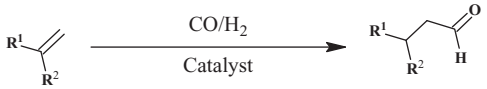
12.3.3.3 Carbonylation

The general descriptor "carbonylation" covers a wide variety of reactions in which carbon monoxide adds a carbonyl based functional group to organic molecules.

Hydroformylation

Rhodium-catalyzed hydroformylation is an industrial process of fundamental importance. Based on purely steric factors, gem-substituted olefins with both aryl and alkyl groups usually have a tendency to give the linear hydroformylation product. They also display lower reaction

rates than mono substituted olefins. The use of bidentatediphosphate or diphosphine ligands in combination with simple rhodium precursors, such as [Rh (acac)$(CO)_2$] can give very high linear selectivity [23,24].



61 62

Pd-catalyzed (Heck) carbonylation

Since the initial publications on this series of reactions by Richard Heck in 1974 [25], many other researchers have contributed to improving the scope of the reaction through extending the range of suitable substrates and moderating the conditions required. Reactions are now effective for the conversion of many aryl, heteroaryl, benzylic and vinyl halides, and sulfonates [26].

Alkoxycarbonylation

Alkoxycarbonylation uses water or alcohols as nucleophiles to form carboxylic acids or esters. The limited interaction of alcohol/alkoxide with the palladium catalyst makes this the most robust of this group of reactions and this is reflected in a significant number of industrial applications [27]. Catalysts with aryl-substituted phosphine ligands (both monodentate, eg, PPh3, and bidentate, eg, dppp, dppf) are effective for reacting a wide variety of aryl and heteroaryliodide, bromide, and triflate derivatives.

Aminocarbonylation

Aminocarbonylation uses ammonia or amines to formamides and can be carried out using similar conditions in the alkoxycarbonylation, although excess amine acts as an inhibitor of the reaction. One means to overcome this limitation is to use transamination of the phenyl ester formed by alkoxycarbonylation with phenoxide [28].

Reductive carbonylation

Conditions for the reductive carbonylation forming aldehydes initially described by Heck involved the use of syngas (1:1 H_2/CO) at high pressure, ca. 100 atmospheres. The reaction proceeds best with monodentate phosphine ligands, and recently much lower pressure reactions (ca. 5 bar) for aryl iodides, bromides, and triflates were shown to be possible using the bulky alkyl-substituted ligand diadamantyl-*n*-butylphosphine [29].

Pd-catalyzed carbonylation of alkenes and alkynes

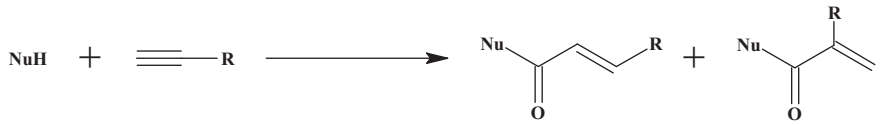
a. Alkenes
   The reaction of carbon monoxide with alkenes shows remarkable changes in selectivity based on the properties of the ligands bound to Pd, and in particular, the bite angle for bisphosphines. With 1,2-bis(di-*t*-butylphosphinomethyl)-benzene alkoxycarbonylation of

ethene using methanol yields methyl propanoate, a useful precursor in the preparation of methyl methacrylate [30]. This process has been developed to commercial scale by Lucite International with a 120,000 m.t./year plant operating in Singapore in 2009.

$$CH_2=CH_2+CO+CH_3OH \rightarrow CH_3CH_2CO_2CH_3$$

b. Alkynes

Carbonylation of alkynes provides a versatile route to a variety of unsaturated carbonyl derivatives depending on the nucleophilic reagent. For example, reaction with amines yield acryl amides and with thiols, yields unsaturated thioesters, and, as for alkenes, high regioselectivity can be obtained for terminal alkynes.



63 64 65 66

12.3.3.4 Decarbonylation

Both Pd and Rh catalysts have been used to decarbonylate aldehydes (to produce alkanes) and acyl chlorides (to produce chloroalkanes or chloroarenes).

$$RCOX \rightarrow RX+CO \ (X=H,Cl)$$

There are also reports of the effective decarbonylation of carboxylic anhydrides, ketones, and ketenes. Dihydrocinnamaldehyde can be decarbonylated with Rh(Rh-40[$RhCl(CO)(PPh_3)_2$] or Rh-100 [$RhCl(PPh_3)_3$]) to for methylbenzene in 96% yield [31].

12.3.3.5 Hydrosilylation

Hydrosilylation (often referred to as hydrosilation) is the addition of an H–Si bond across a carbon═carbon double bond.



67 68 69

The reaction finds practical application in the "curing" or hardening of silicone polymers effected by the cross coupling of different silicone fragments.

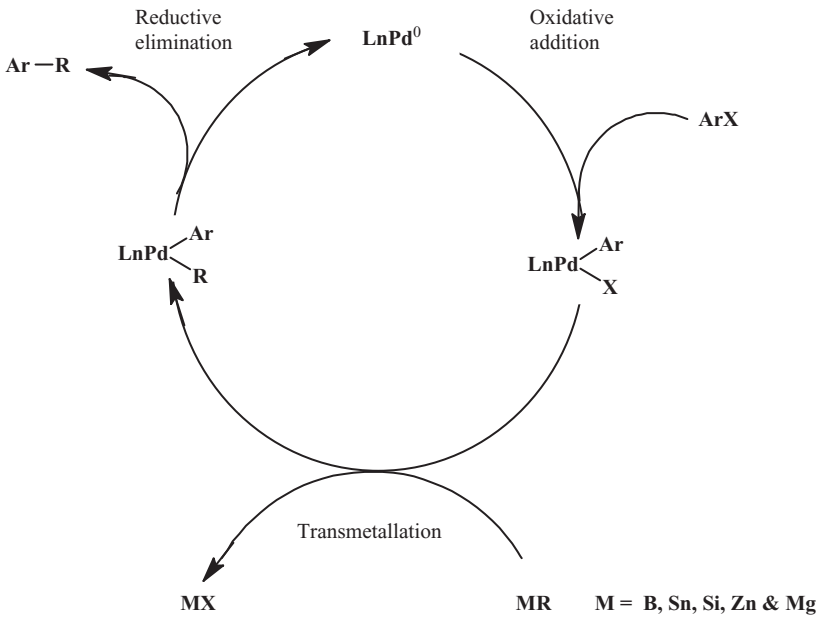


70 71 72

Platinum compounds are extremely active catalysts for this reaction [32].

12.3.3.6 Cross-coupling reactions

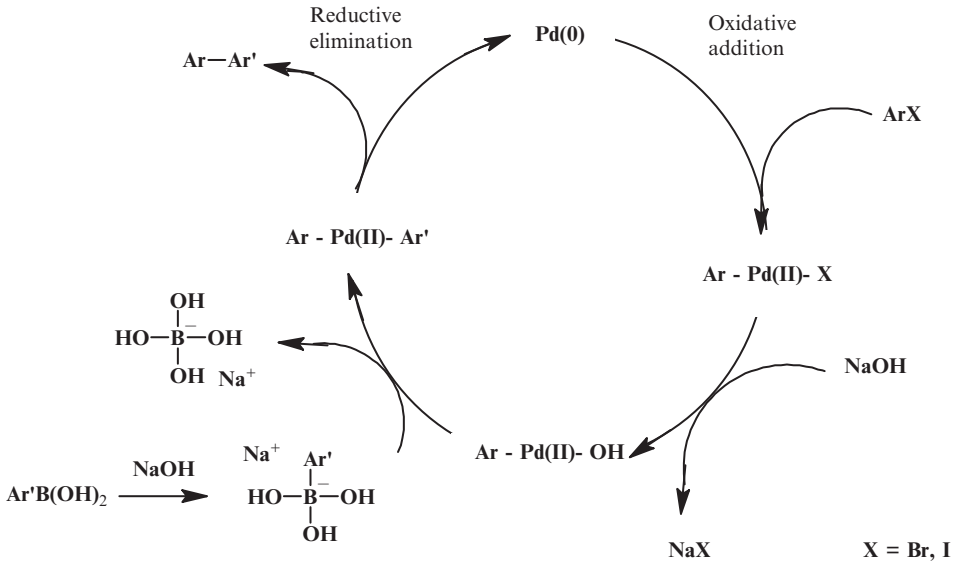
A transition metal complex, typically a Pd complex, mediated substitution of an aryl, vinyl or alkyl halide, or pseudohalide by a nucleophile is generally referred to as a cross-coupling reaction and typically it follows the oxidative addition, transmetalation, and reductive elimination steps. Although C–C bond forming reactions have been known since the development of Grignard reagents, recent advances by Negishi, Suzuki, and Kumada/Tameo have greatly increased the scope and industrial applicability of cross-coupling reactions [33].



Suzuki coupling

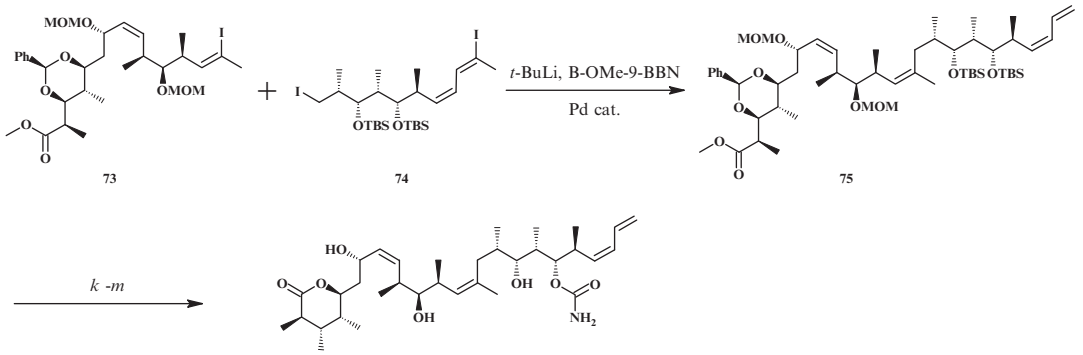
In the last two decades, the development of new and highly active catalysts by various academic and industrial groups has dramatically increased the scope and commercial viability of organic synthesis via Pd catalyzed carbon-carbon coupling. Powerful coupling methodologies, such as Heck, Suzuki, Sonogashira, Negishi, Tsuji-Trost, and Buchwald-Hartwig coupling, enable synthetic organic chemists to accelerate total syntheses of APIs via carbon-carbon coupling. [34,35,36] Among the various name reactions in C–C coupling, Suzuki coupling has become the most practiced reaction in industry as evidenced by a recent literature search [37–41].

As shown in the scheme below, the choices of the ligand, metal, base, and solvent are important in determining the oxidative addition, transmetalation, and reductive elimination steps.

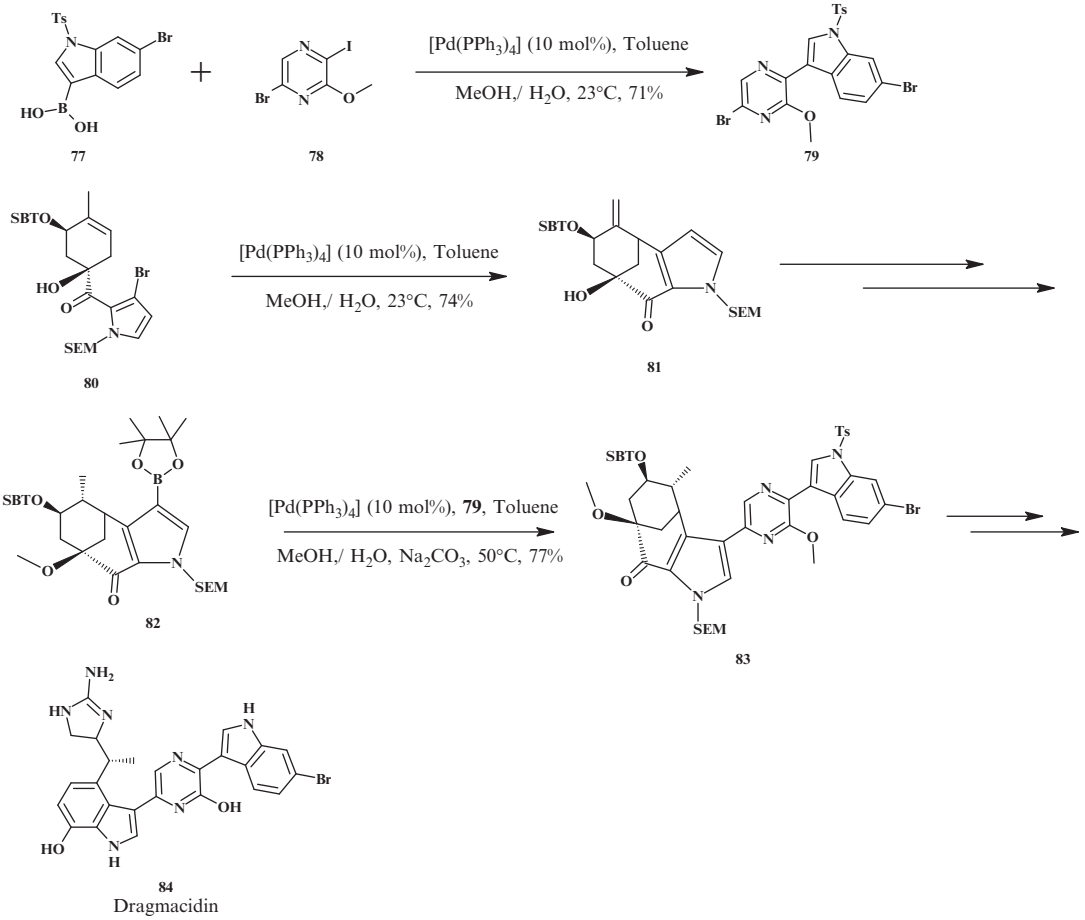


Application in pharmaceutical industry

1. Synthesis of (+)-dicodermolide antifungal, immunosuppressive and cytotoxic [38].



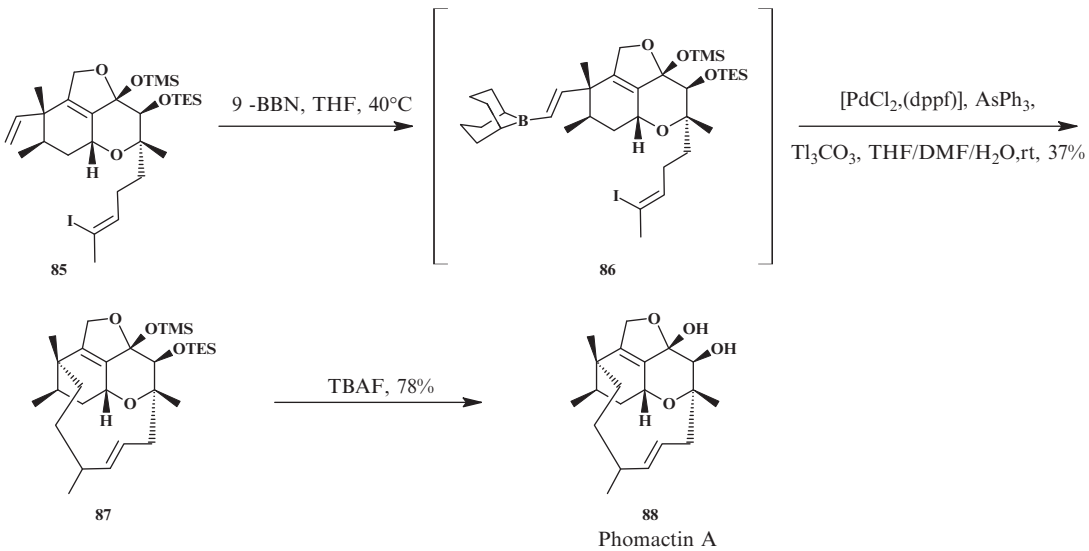
2. Synthesis of bis-indole alkaloid Dragmacidin D [39].



77 78 79 80 81 82 83 84

Dragmacidin

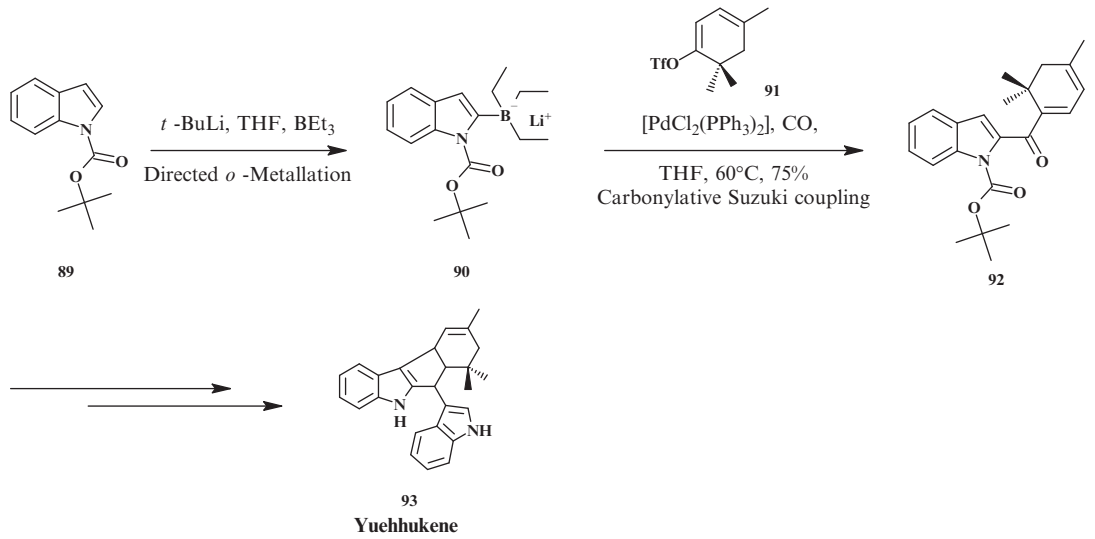
3. Synthesis of diterpene (+)-phomactin A is a biologically active marine natural product [40].



85 86 87 88

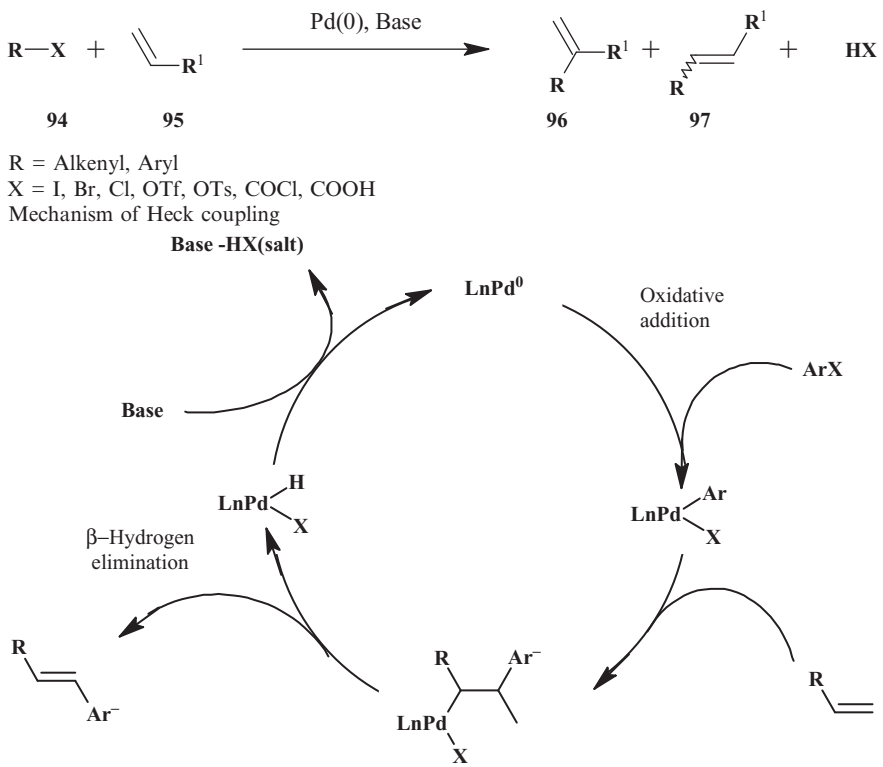
Phomactin A

4. Synthesis of yuehhukene [41].



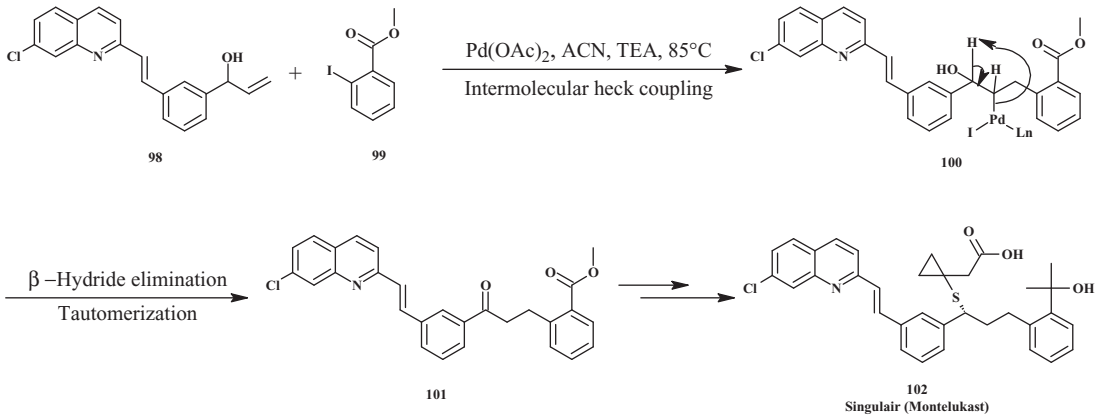
Heck coupling

A Japanese scientist, Mizoroki (1971) and an American scientist, Heck (1972) independently developed a protocolto couple, an aryl or alkenyl halide or pseudohalide with an olefin in the presence of a Pd based catalyst [73,74].



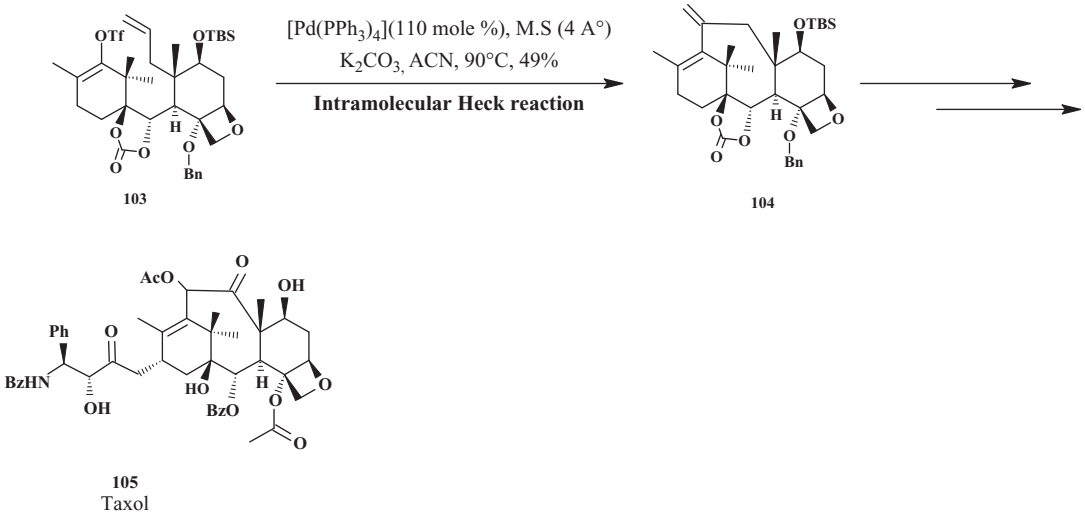
The application of this chemistry includes the synthesis of hydrocarbons, conducting polymers, light emitting electrodes, dyes, and enantioselective synthesis of natural products.

- Application in the pharmaceutical industry
  1. Synthesis of Singulair,® Merck's treatment for asthma and allergies using $Pd(OAc)_2$ [42,43].



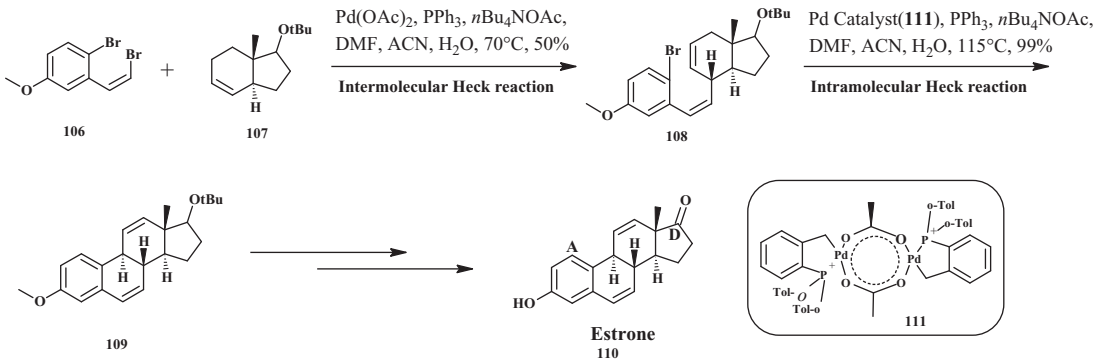
Synthesis of Singulair (montelukast)

  2. Synthesis of paclitaxel (Taxol®) treatment for breast cancer, lung cancer, and ovarian cancer using [Pd(PPh3)4] [44].

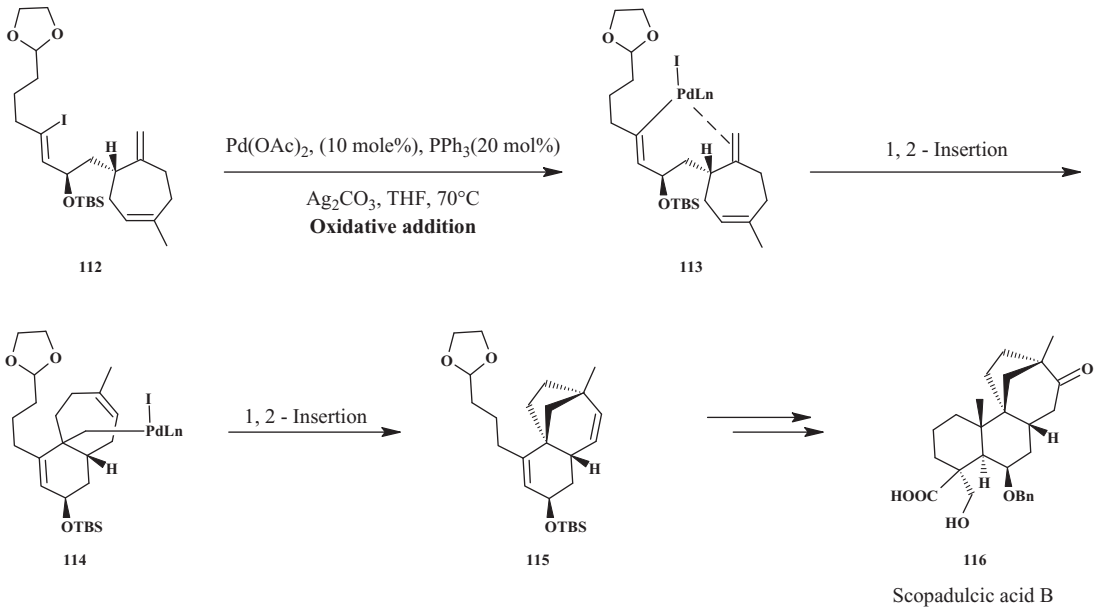


Synthesis of taxol

3. Synthesis of estrone [Pd] [45].

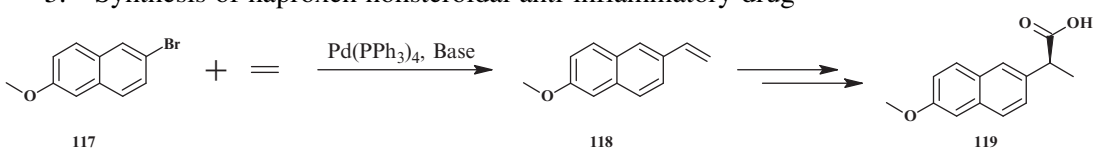


4. Synthesis of scopadulic acid [$Pd(OAc)_2$] [46].



Synthesis of sopadulic acid

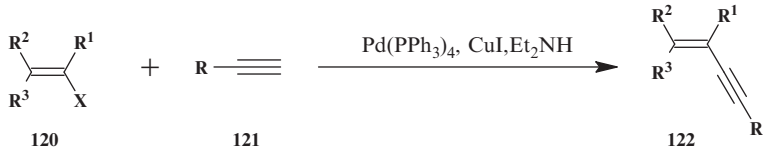
5. Synthesis of naproxen nonsteroidal anti-inflammatory drug



Sonogashira coupling

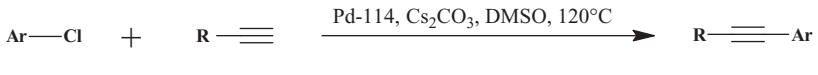
The classical Sonogashira reaction involves the coupling of terminal alkynes with aryl or vinyl halides (mostly iodides) in the presence of a palladium catalyst with a copper (I) cocatalyst, and

an amine base [47,48]. Typically, the reaction requires anhydrous and anaerobic conditions, but newer procedures have been developed where these restrictions may not be important [49]. The basic mechanism is very similar to the standard coupling, where Cu is responsible for activating the alkyne. Homocoupling of the alkyne can be a major problem in Sonogashira coupling.



120 121 122

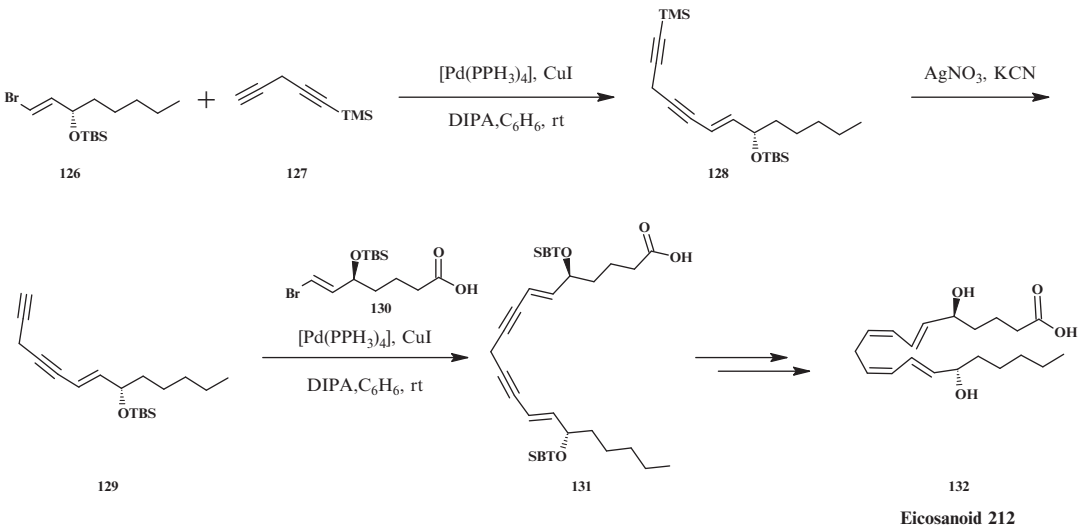
Cu-free Sonogashira reactions have been demonstrated successfully by using (Cy3P) 2PdCl2, Pd-114 [50]. Inorganic bases instead of organic amines can also be used.



123 124 125

Application in organic synthesis

1. Synthesis of eicosanoid 212 [50].



126 127 128 129 130 131 132

Eicosanoid 212

Cross-coupling with organometallic reagents

The use of aryl-, alkenyl-, or alkyl-metal complexes as coupling partners containing metals or metalloids such as magnesium, zinc, tin, or silicon has been getting a lot of interest recently, although the chemistry had been discovered several decades ago. Generally, the use of various organometallic reagents as coupling partners is highly dependent on the nature of the substrate and reaction conditions [51,52].

$$R-X+R^1MY_n \xrightarrow{\text{Pd catalyst}} R-R^1+MXY_n$$

$$R-R^1 = \text{aryl, alkenyl, alkyl}$$

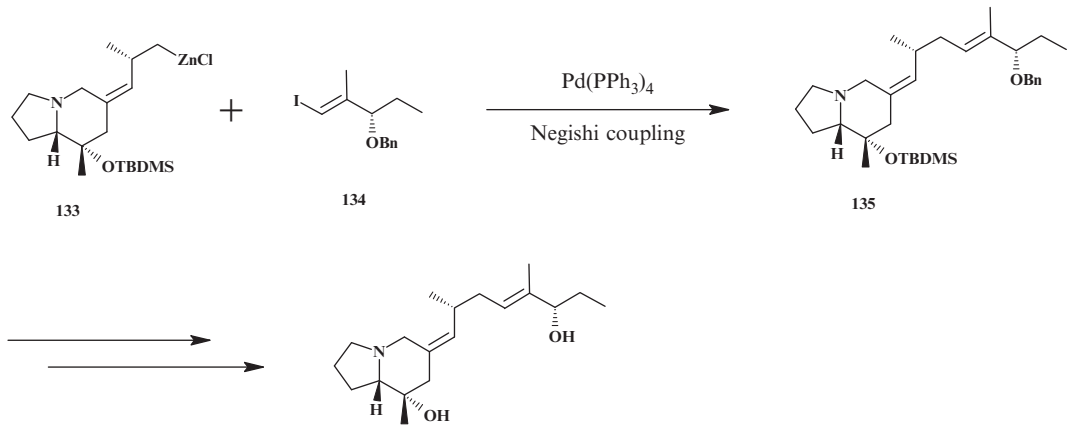
M = Mg: Kumada
M = Zn, Zr: Negishi
M = Sn: Stille
M = Si*: Hiyama
*Si = is a metalloid

A. Kumada coupling
Kumada followed by Corriu, Hayashi, and Tamao were able to use Grignard reagents as the Nucleophilic coupling partners in cross-coupling chemistry. Although the earlier work includes the use of Ni- based homogeneous catalysts, Kumada coupling has continually developed using palladium catalysts. Often, Pd- based Catalysts are performed over nickel base catalyst due to their lower toxicity, and higher activity and selectivity, although Ni complements Pd in several cases [52,53].

B. Negishi coupling
The Pd-catalyzed cross coupling of organozinc reagents with various aryl halides and pseudohalides has been pioneered by Negishi, hence this reaction is known today as Negishi Coupling. Most organozinc reagents can be prepared either in advance or in situ by the reaction of organomagnesium, organolithium, or organoaluminium compounds with a zinc halide. Although less reactive than their organomagnesium counterparts, organozinc reagents present the advantage of having a wide range of functional group tolerances (eg, inertness to ketones, esters, amines, nitriles, nitro compounds, etc.) [54,5].

Application in the pharmaceutical industry

1. Synthesis of pumiliotoxin A [55].



133 134 135

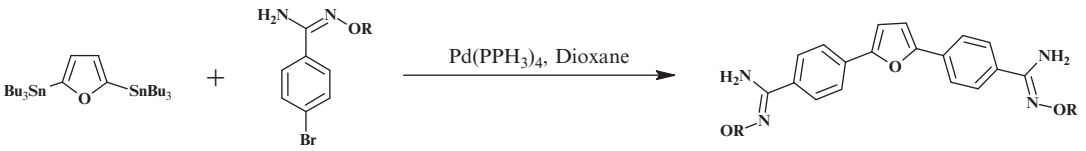
136
Pumiliotoxin A

C. Stille coupling

The Kosugi-Migita-Stille reaction is a very versatile Pd-catalyzed transformation, which allows the formation of C–C bonds from a variety of organohalides or pseudohalides with organostannanes. Despite their toxicity, organostannanes are still widely used due to their stability, compatibility with various functional groups, as well as versatility to form products from a diverse combination of organohalides and organostannanes.

$$R-X+R^1SnR_3 \xrightarrow{\text{Pd catalyst}} R-R^1+XSnR_2$$

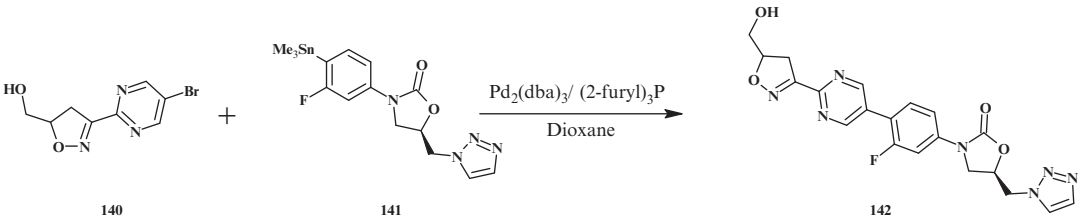
When organostannanes are used as the nucleophilic coupling partners, Pd is the metal of choice. Triphenylphosphine is typically the ligand of choice. For instance, Pd (Ph3P) $_4$, Pd-101 was used to synthesize the prodrug furamidine, which was used against Pneumocystitis carinii pneumonia and human African trypansomiasis [56].



137 138 139

Synthesis of furamidine

Less electron-rich ligands such as tri-2-furylphosphine, $(2\text{-furyl})_3P$, and $AsPh_3$ seem to accelerate the transmetallation step, which is believed to be the rate determining step. $Pd_2(dba)_3$ in combination with$(2\text{-furyl})_3P$ was used by AstraZeneca in the synthesis of antibacterial oxazolidinone derivatives [57].

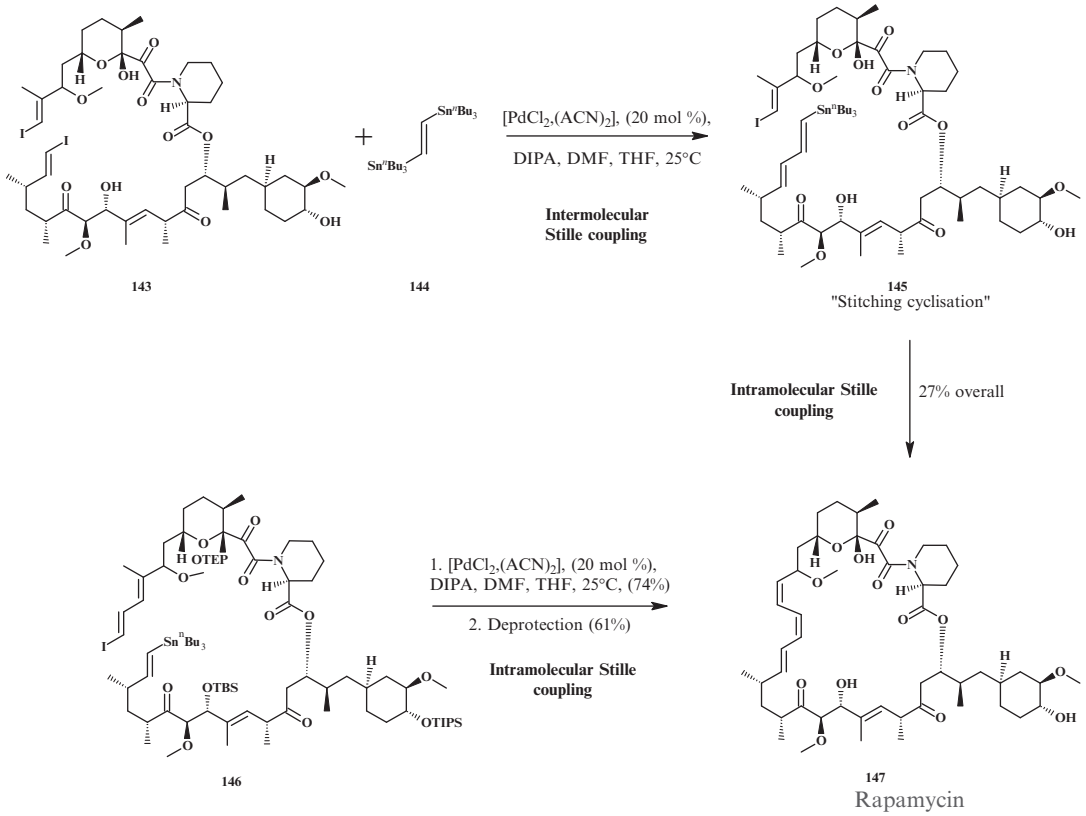


140 141 142

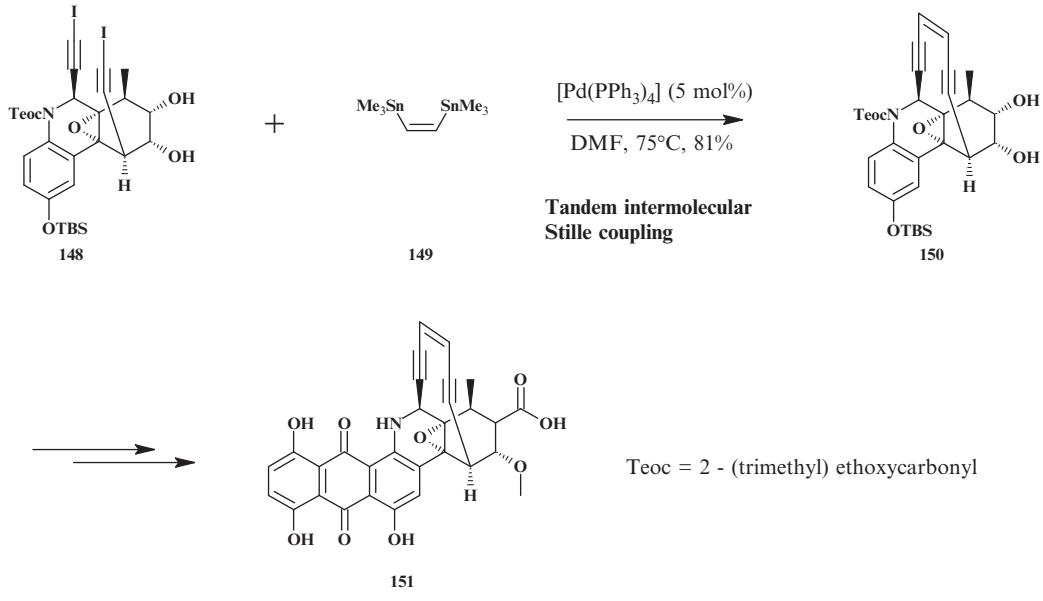
Synthesis of an antibacterial agent

Other pharmaceutical application

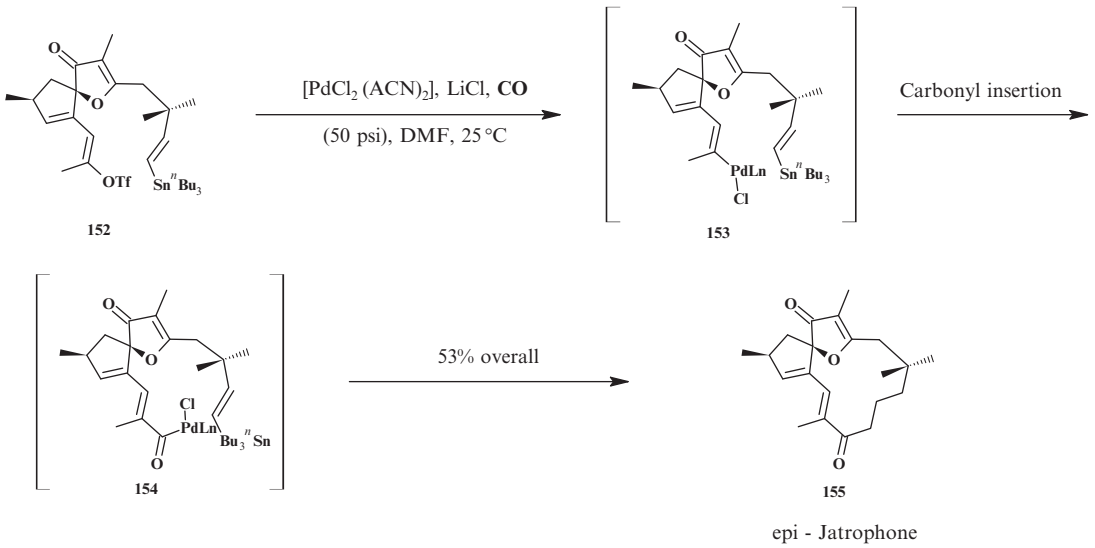
1. Synthesis of rapamycin/sirolimus (prevent rejection in organ transplantation) [58].



2. Synthesis of dynamycin (Prevent bacterial, viral and Fungai infections) [59].



3. Synthesis of jatrophone antileukemic [60].



D. Hiyama/Hiyama — Denmark coupling
The use of organosilicon compounds as coupling partners has been very attractive due to their wide availability, diversity, stability, and low toxicity, as well as high tolerance to various reaction conditions. Due to their lower activity, organosilicon reagents have to be activated to their corresponding hypervalent Si (V) species in order to be able to participate in the transmetalation step. Usually, stoichiometric amounts of fluoride-based additives are used. Generally, Hiyama coupling is performed using unsophisticated Pd-based catalysts. For instance, Hiyama reported the coupling of vinyl, ethynyl, and allylsilanes with organohalides (aryl, vinyl, allyl) to take place in the presence of a simple Pd-catalyst, [(−allyl)PdCl]2, Pd-110 [61].

12.4 Process Optimization in API Manufacturing

Scale-up experiments are carried out to ensure a seamless transfer from laboratory-scale to a commercially viable process.

Generally, the process that is scaled up, optimized, and validated for transfer to the commercial manufacturing is also termed an Authorized process. Thus, Authorized process or technology is a thoroughly researched, developed, and validated document for manufacturing, along with authorized amendments (Fig. 12.1).

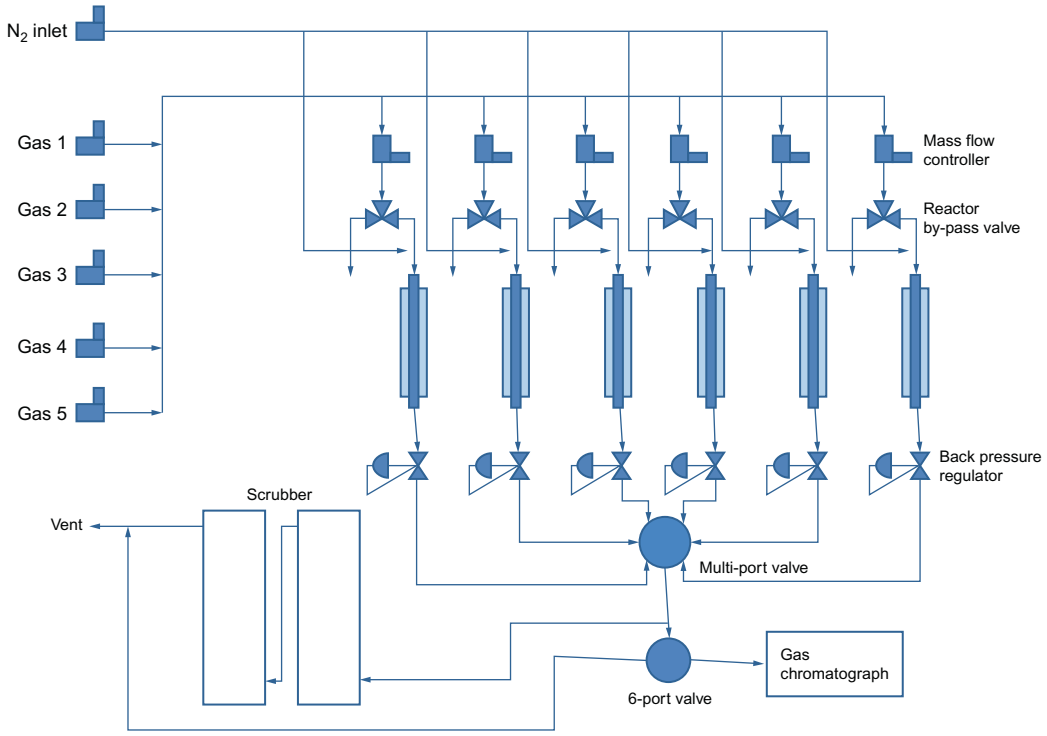


Fig. 12.1
Catalyst screening set-up.

Selection of Catalyst

Developing catalyst and selection of right catalyst is many a times a hit-or-miss process [62–72]. A few basic principles may be applied like,

- Type of reaction (Oxidation, Reduction, Amination, etc.)
- Structure of the molecule (Activity, Conjugation, *cis*, *trans*, etc.)
- Which site is to be selected for catalysis
- Solvent that is allowed for the reaction.

For hydrogenation reaction the selection of catalyst will depend on the following basic requirements

- The catalyst must chemisorb H_2 (metals Co, Rh, Ir, Ni, Pd and Pt are suitable)
- The chemisorptions is too strong for Sc, Ti, V, and Cr and Mn groups and as a result these metals are not effective catalyst.
- Fe, Ru, and Os chemisorb most gases firmly, and barely chemisorb N_2.
- Chemisorb strengths, for Co and Ni, are weaker than those of the Fe group. Absorption for CO_2 and H_2 are very weak.

- Rh, Pd, Ir, and Pt barely chemisorb H_2, but not CO_2.
- Cu, Ag, barely chemisorb CO and ethylene.
- These relative chemisobtion strengths enable us to make some simple predictions regarding their suitability as catalysts for specific reactions.
- Silver is a good adsorber and Tungstone adsorbs very strongly.

This design may be used more effectively for catalyst screening and catalysis.

12.4.1 Factors that Influence the Process Optimizations

The World Health Organization (WHO) defines process validation as "the documented act of providing that any procedure, process, equipment, material, activity or system which actually leads to expected results."

Process validation is the collection and evaluation of data from the process design stage throughout production, which establishes scientific evidence that the process is capable of consistently delivering quality products.

- As per the US FDA, any aspect of operation, including significant change to the premises, equipment or process, which may affect the quality of the product directly or indirectly shall be qualified and validated.
- Process knowledge management and training as per SOPs.
- MSDS of all chemicals to be handled should be available to all as and when required.
- A process design can eliminate or reduce hazards from chemical reactions.
- Engineering Control Measures include process cooling, addition rate, ventilating systems, agitation patterns, instrumentation, and process controls. When scaling up a process, it is important to assess the adequacy of existing control measures.
- During scale-up, it is essential to assess adequacy of existing control measures.
- Raw materials and inventory control.
- Proper distribution of duly signed and authorized documents. Obsolete documents should be dealt with and kept separately.
- Cycle time reduction to increase the productivity.
- Batch size optimization to fully utilize the reactor capacity.
- Optimum usage of utilities like ice, chilled water, brine, steam, water, and electricity.
- Minimize breakdowns and process deviations.
- Well-timed commercialization.
- Cost reduction via import substitution.
- Operational excellence by in-house expertise and state of the art technology, which includes statistical design of experiments (DoE), time and motion study, and reaction calorimetry.
- Conducting process safety audits. Process safety is strongly influenced by the design and scale of a reactor.

- Minimizing work and rework. Reduce the number of process deviations and out of specification batches by proper control of parameters through properly designed systems.
- Quality should be at the core of all activities. CGMP guidelines shall be strictly followed.
- Cleanliness and hygiene must be maintained all times.
- Approved contingency plan shall be ready.
- Product distribution records shall be maintained.
- Calibration of all process controlling devices shall be done at suitable intervals of time and documented.

Volume Time Output (VTO)

VTO of a chemical process represents the cost of occupancy of a reactor for a particular process or API synthesis. High VTO indicates that a particular synthetic step is costly in terms of "Reactors Hours" used for proposed output. VTO for a particular process is calculated by total volume of all reactors (M^3) that are occupied times $\times$ the hours per batch divided by the output for the batch of API or intermediate measured in kilogram.

$$\text{VTO} = \frac{\text{Volume Nominal of all reactors}(M^3) \times \text{times per batch}(\text{hours})}{\text{Output per step}\{\text{kg}\}}$$

Raw conversion cost of an API synthesis is calculated from the VTO, given the operating cost and usable capacity of a particular reactor. Often times, for a large volume of APIs, it is economical to build a dedicated production plant rather than to use space in a general pilot plant or manufacturing plants.

The development of a process for API needs to be challenged right from literature survey to final dispensing by taking into consideration continuous improvement. Critical Parameters that need to be considered during process development:

1. Equipment to be used for
   a. Exploratory or investigational work
   b. Screening of the catalyst
   c. Kinetics data investigation
2. Selection of Appropriate Catalytic System
   a. Catalyst (regulatory requirement should be reviewed)
   b. Solvent
   c. Acids
   d. Basis
   e. Modifiers. Promoters or retarders

3. Determination of the influence of
    a. Pressure
    b. Temperature
    c. Mixing or agitation
    d. Concentration

12.4.2 Development of Catalytic Process in the Laboratory

12.4.2.1 Hydrogenation reaction using catalyst

Normally hydrogenation is carried out in a laboratory glass assembly or stainless steel small reactor from 1 g scale to 100 gm.

- Substrate is dissolved in a suitable solvent, nitrogen is purged, and water quantity is adjusted.
- Catalyst is charged. Flask containing substrate is fitted to the HYDROGEN assembly.
- Vacuum is applied and system is evacuated by nitrogen and then by hydrogen.
- Hydrogen is filled in assembly till Eudiometer is full and water is measured.
- Reaction mixture is cooled if required and stirred magnetically.
- Consumption of hydrogen is recorded.
- Simultaneously, two flasks can be used to study the performance of catalyst, kinetics or carrying out usage testing of catalyst.
- In process control and monitoring is carried out using Thin Layer Chromatography and instruments like FTIR, HPLC, NMR, or by specific optical rotation in case of chiral molecules.

12.4.2.2 Pilot plant model of hydrogenation

One to five kilogram scale batch size hydrogenation can be carried out in Pilot Plant model of reactors.

Reactor design is very a important aspect in heterogeneous catalytic hydrogenation. This model should be such that has good mass transfer capability (good stirring and mixing) and has a good gas purging system. Normally it is observed that Hydrogenation reaction gives better results with a reactor with baffles. It is simply attributed to the fact that mass transfer problem is minimized, and collision rate is increased because of turbulent mixing (Fig. 12.2).

12.4.2.3 Technology transfer report [TTR] needs to be generated at the end of this exercise

- When at least three batches with consistent results are performed in the manner described in the manufacturing guide and as per the desired BMR, a scale-up data is generated.
- Any Unusual Incident if occurred is noted and investigated for Corrective and Preventive Action (CAPA)



Fig. 12.2
Scale-up hydrogenation reactor at ASolution Pharmaceuticals Pvt. Ltd.

- Any process deviation, if observed, is documented and an action plan is prepared so as to avoid its reoccurrence. Its impact on Quality, and yield is investigated.
- Consistency of Yield, conversion to product, and impurity profile is assessed and reported.
- Catalyst recovery study is also studied.
- Solvent recovery and solid waste generated are actually measured.
- Man and material motion study is recorded.
- Handling of raw materials and safety data is generated.
- Quality consistency of 3 batches carried out is assessed as per predetermined specifications.
- Material is sent for toxicity data and/or clinical trials if need be.
- If all the above data is within acceptable limits, then process economics and costing is carried out in order to convert or translate technology into commercial production.
- The above TTR is of utmost importance while designing a commercial plant.
- Suggestions in writing can be accepted from people who have been actually involved in all operations.
- Statistical data is prepared.
- Reprocessing/reworking if required is developed and, and written procedure is updated.
- All attempts are made to increase efficiency of the process.

Above are general considerations for making a technology transfer report.

12.5 Most Frequently Employed Catalysts and Examples in the API Industry

The list of the frequently used catalysts in API industry is quite big. Though the scope of this chapter is not to include phase transfer catalysts (PTC), it should be remembered that it is used in the manufacture of a number of important and critical intermediates for APIs and final drug substance. The most important point is the selection of the catalyst and its isolation from the final product and the analytical method to monitor the content in the API.
A number of books have been published on PTC and many presentations as well as articles have been written and are available on the Internet. Enzymatic catalysts are also used for many API manufacturing processes, which is also not covered in this chapter, as it is again, a major subject. [75,76]

Palladium, Platinum and Rhodium are the most common precious metals used in the catalytic process [78]. Carbon is used most widely as a support and it is chemically inert, has good porosity, and easy to burn to recover precious metals. Nickel is the most widely used metal from the base metal group and also has a good recovery value. Precious metal catalysts generally are effective at milder conditions while nickel catalyst generally needs higher temperatures and pressure conditions. It is sometime possible to replace precious metals by nickel for cost benefits at optimized operating parameters (Table 12.4).

12.5.1 Major Catalysts Used

The choice of catalyst depends on its availability and its cost is a major consideration. For academic purposes, one can use costly catalysts irrespective of the cost of the product. From a commercial point of view, a ratio of cost of product to cost of catalyst is very important. Its

Table 12.4 List of the major catalysts

Catalyst	Ratio%
Copper chromium oxide (copper chromite)	10–20
Palladium, platinum, or rhodium on support	10
Platinum oxide	1–2
Raney nickel	10–20
Cobalt	10–20
Ruthenium dioxide	1–2
Ruthenium on support	10–25

Notes:

1. The ratio of catalyst to substrate is based on the weight of catalyst and not on the percentage of catalyst to substrate.
2. It is often convenient to measure the volume of wet Raney Nickel; when the catalyst is settled 1.0 cc is equivalent to 1.5 g.
3. Normally it may be sufficient to use 10% ratio, however if catalyst is standing for more than 6 months, it may be necessary to use more ratio.
4. Dry stable nickel catalysts are also available with which 15–20% weight ratios of catalyst to substrate should be satisfactory.
5. Cobalt could be used in the same manner as nickel as wet dry catalyst.

handling, storage, efficiency as catalyst, recovery problems, and concentration in the finished product, etc., are some of the important factors.

The list of the frequently used catalyst in API industry is quite big. Though the scope of this chapter is not to include phase transfer catalysts (PTC), it should be remembered that it is used in the manufacture of number of important and critical intermediates for APIs and final drug substance. The most important point is the selection of the catalyst and its isolation from the final product and the analytical method to monitor the content in the API. A number of books have been published on PTC and many presentations as well as articles have been written and available on the Internet [1].

Enzymatic catalysts are also used for many API manufacturing, which is also not covered in this chapter, as it is again a major subject.

Palladium, Platinum and Rhodium are the most common precious metals used in the catalytic process. Carbon is used most widely as a support and it is chemically inert, and it has good porosity and easy to burn to recover precious metals.

Nickel is most widely used metal from base metal group and also has a good recovery value.

Precious metal catalysts generally are effective at milder conditions while Nickel catalyst generally needs higher temperature and pressure conditions. It is sometime possible to replace precious metals by Nickel for cost benefits at optimized operating parameters.

The preceding table gives a rough idea about the usage of catalysts.

Melting them together in certain proportions makes alloy of the metal and aluminum. The aluminum is dissolved using sodium hydroxide. The remaining metal from the allowed "domain" become particles with high a surface area and is charged with hydrogen.

It is extremely flammable in air and must be handled with water. It is commercially available, but best if prepared just before use.

12.5.1.1 Nickel

Other forms are nickel on Kieselguhr and form Urushibara, this can be used in acid solution (Hoax) and can give better results than noble metal catalysts (better discrimination and better yield) [75–77].

12.5.1.2 Platinium

Platinum is used as dioxide powder or on metal support, and is commercially available as active at 70–80°C/60–70 atm^{-1}. It does not get poisoned easily (has high resistant to poisoning). It is good for the reduction of aromatic rings, however it does not discriminate. It can reduce –COOH, but only at high pressure of around 500–950 atm. It is used to reduce aldehydes, ketones, and even sugars. One should not use platinum black because it is highly variable. Adam's catalyst, ie, PtO_2 (it has storage shelf life stability) and platinum on support are the most common forms of platinum and are commercially available. It may be used for wide variety of reductions, including

hydrogenation and hydrogenolysis, depending on the conditions, which are mostly milder than other catalyst. However it can be easily poisoned by amines and sulfur.

12.5.1.3 Ruthenium

Cost is a Major Consideration

Ruthenium is used as dioxide or metal on support and is commercially available. This is generally active around 70–80°C at 60–70 atm. It has high resistance to poisoning (does not get poisoned easily). It is good for reduction of aromatic bonds, but it not discriminates (not selective). It reduces COOH, but only at high pressure of around 500 to 950 atm. It is possible to reduce aldehydes, ketones, and even sugars.

Catalyst Inhibitors or Poisons

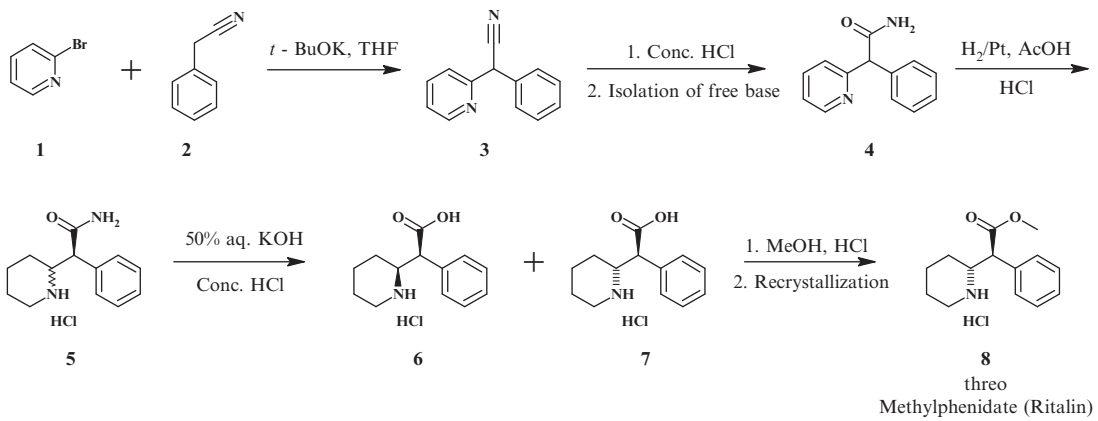
Metals and metal salts are used as catalyst inhibitors or poisons. Magnesium, nickel, cobalt have no effect on $PdCl_2$ reductions. Platinum reduction may be inhibited by aluminum (Al), cobalt (Co), and bismuth (Bi). Visaversa, Pt reductions increased by Fe, Cu, Zn, Ag, Pb. Raney Nickle is completely inhibited by mercuric chloride, but 50% inhibited by $AgSO_4$.

12.5.2 Frequently Used Catalyst

12.5.2.1 Platinum

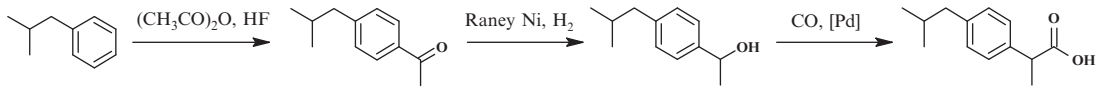
Synthesis of methylphenidate (Ritalin) analogues [78].

Deutsch et al. improved upon the existing synthetic pathway of (threo-methylphenidate) [79].



12.5.2.2 Raney nickel

As discussed, an improved synthesis by BHC required only three steps. This improved synthesis won the presidential Green chemistry challenge greener synthetic pathway award in 1997 [82]. After a similar acetylation, hydrogenation with Raney Nickel gave the alcohol (11), which underwent palladium-catalyzed carbonylation [80,83].

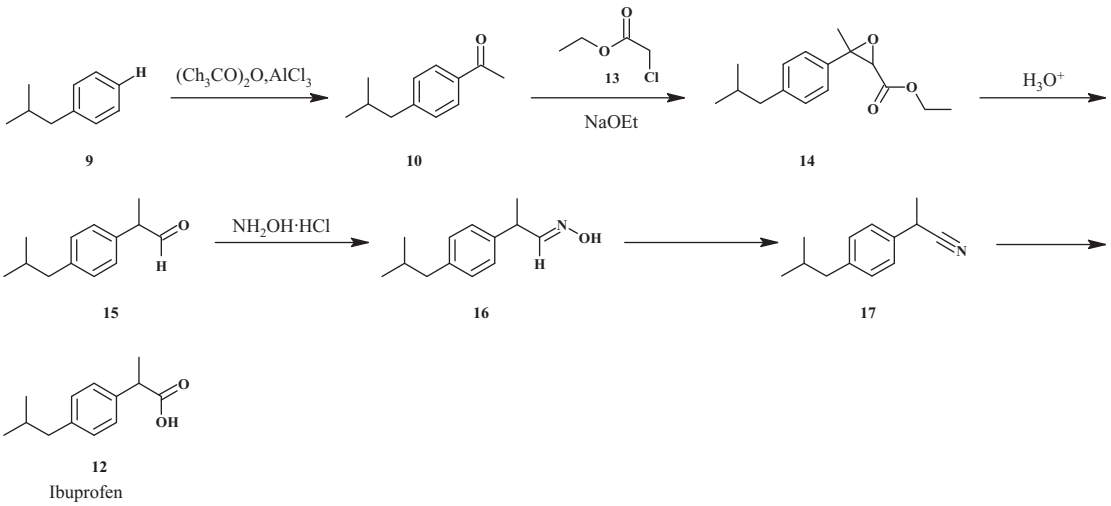


9 **10** **11** **12**
Ibuprofen

An electrochemical carboxylation of a *para*-isobutylbenzyl chloride to Ibuprofen is promoted under supercritical carbon dioxide [84].

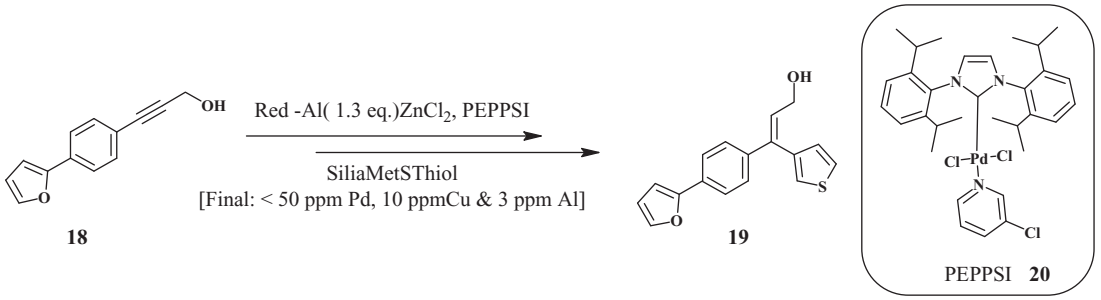
12.5.2.3 Aluminum chloride

The synthesis of this compound is a popular case study in green chemistry. The original Boots synthesis of Ibuprofen consisted of six steps, and started with the Friedel-Crafts acetylation of isobutyl benzene (9). Reaction with ethyl chloroacetate (13) (Darzens reaction) gave the α,β-epoxyester (14), which was hydrolyzed and decarboxylated to the aldehyde (15). Reaction with hydroxylamine gave the oxime (16), which was converted to the nitrile (17), and then hydrolyzed to the desired acid (12) [80,81].



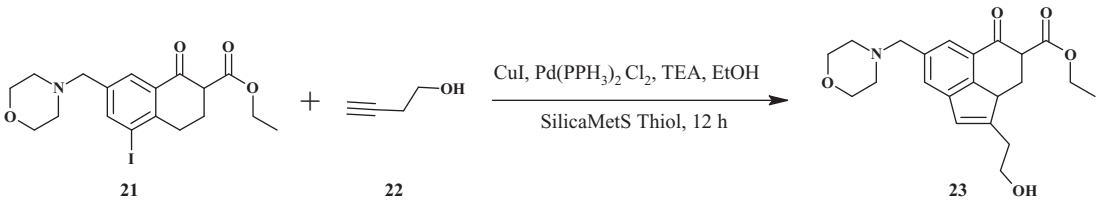
12.5.2.4 Red AL

In 2009, J&J, in collaboration with Solvias published a paper in which they developed a mild Sonogashira reaction using various metal catalysts [85].



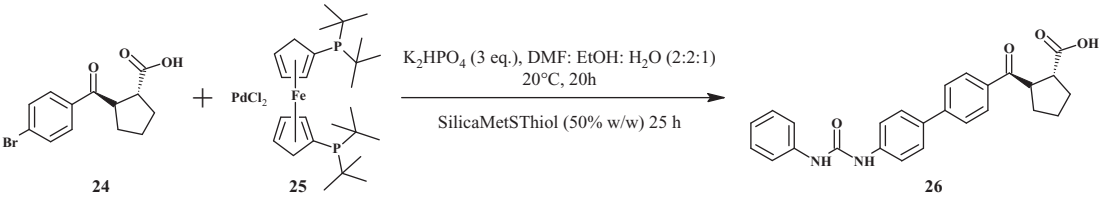
18 19 PEPPSI 20

In 2006, Pfizer published a paper in which they removed palladium and copper impurities in a 20 kg pilot plant scale. They made two subsequent treatments using SilicaMetSThiol (20% + 7% w/w) at room temperature for 12 h. After scavenging using SilicaMetSThiol, the desired product was obtained with a yield of 76% and contained only 17 ppm Pd and 1 ppm Cu. An alternative method was also tried using 80% w/w of Deloxan THP (Degussa AG) overnight followed by Basification with Na_2CO_3 [86].



21 22 23

In 2010, Abbott Laboratories published a paper in which they removed palladium and iron impurities using SilicaMetSThiol (50% w/w relative to 1) Thus, palladium and iron levels were respectively 6 ppm. Take a look at Abbott's publication for more details [87].

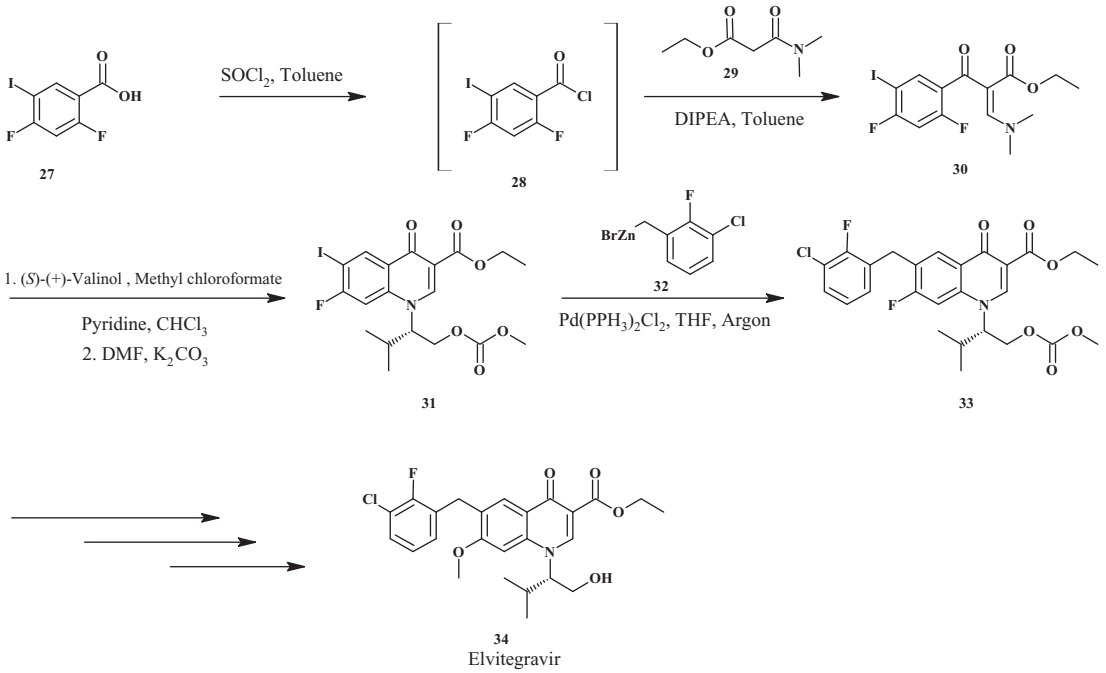


24 (*R*, *R*)- trans 4 25 26

Crude : 400 ppm Pd, 165 ppm Fe
Final : 6 ppm Pd, 66 ppm Fe

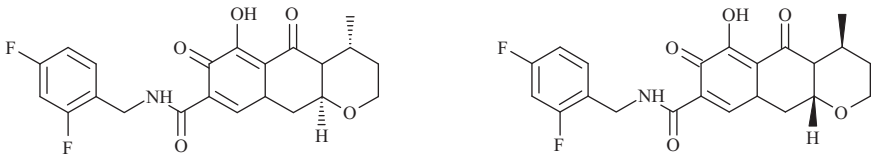
Zinc

US 7176220 patent discloses elvitegravir, solvate, stereoisomer, tautomer, pharmaceutically acceptable salt thereof or pharmaceutical composition containing them and their method of treatment. The chemistry involved in the above patent is depicted below in the Scheme [88].

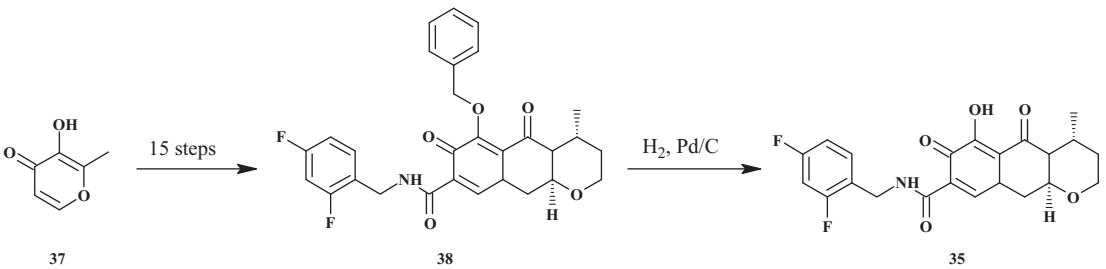


12.5.2.5 Palladium

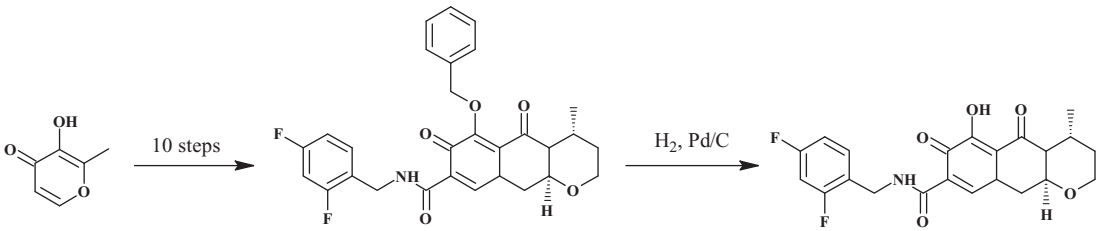
Compound (35) and (36), which are useful as anti-HIV drugs and shows by formulae [89].



Reaction scheme for synthesis of these compounds [89–97].



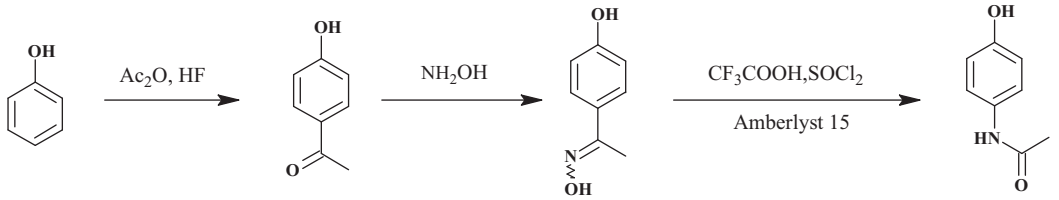
Furthermore, the following reaction scheme describe an improved method of synthesizing the compound [90–97].



37 38 35

12.5.2.6 Amberlyst 15

An alternative industrial synthesis development by Hoechst-Celanese involves direct acylation of phenol (39) with acetic anhydride catalyzed by HF, Conversion of the ketone (40) to a ketoxime (41) with hydroxylamine, followed by the acid-catalyzed Beckmann rearrangement to give the amide (42) [98,99].

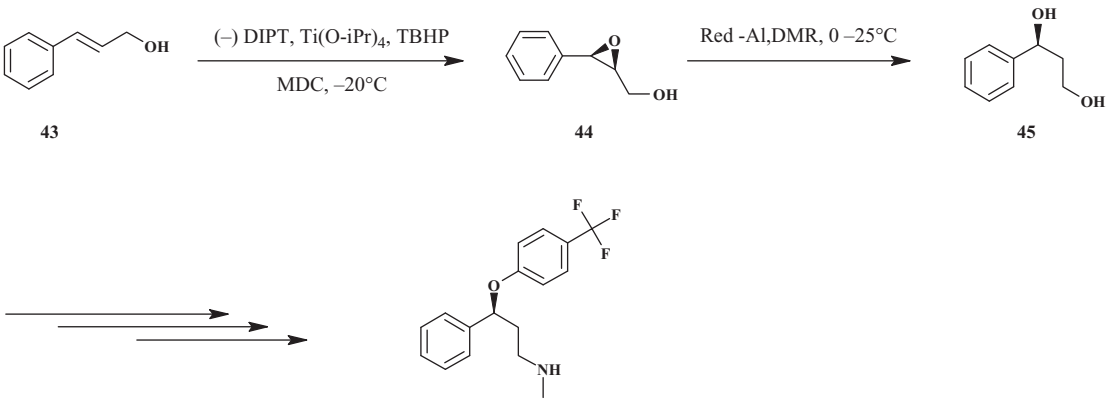


39 40 41 42

Paracetamol

12.5.2.7 Red Al

The 1-phenyl-1,3-propanediols (45) are prepared from cinnamyl epoxy alcohols (44) by Red-Al reduction. The chiral cinnamyl epoxy alcohols are made by asymmetric epoxidation of cinnamyl alcohols (43) [100,101].



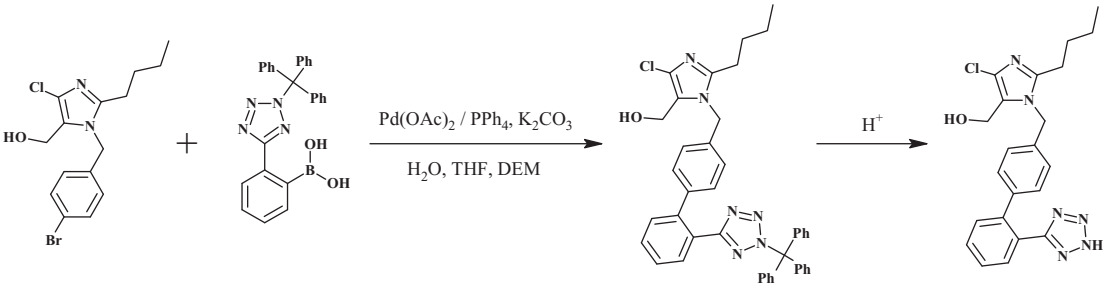
43 44 45

46

(*S*)-(+)fluoxetine hydrochloride

12.5.2.8 Palladium acetate

Efficient synthesis of Losartan (50) (a nonpeptide angiotensin II receptor antagonist) [102].

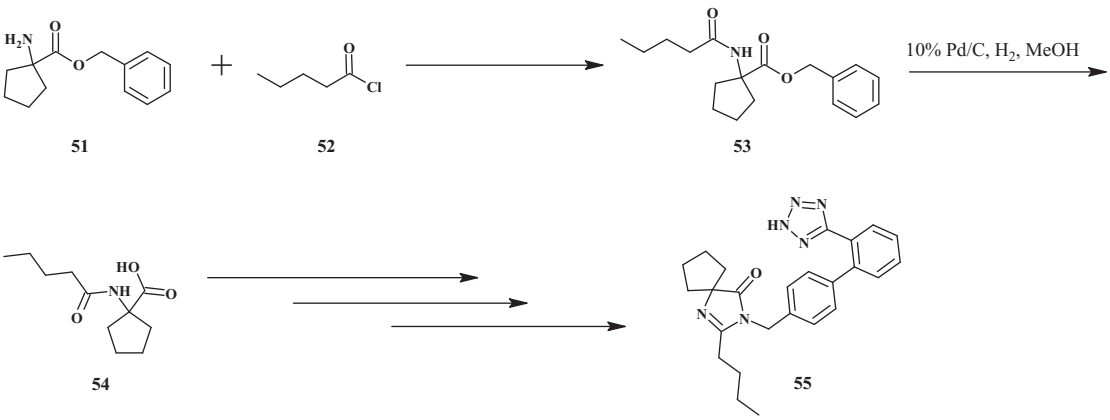


47 48 49 50

Losartan

12.5.2.9 Palladium

Synthesis of debezylated intermediate of Irbesartan (55) using Pd/C [103].



51 52 53 54 55

Irbesartan

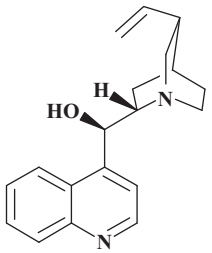
12.5.3 Heterogeneous Catalytic Reaction Details

Catalysts generally react with one or more reactants to form intermediates that subsequently give the final reaction product, and in the process, regenerating the catalyst.

Besides the regularly used transition metal catalyst like Pd supported on solid surface like activated carbon, there are three main areas of heterogeneous catalysis that the research has focused on in the API synthesis.

- Catalyst supported on modified metal surfaces with chiral molecules.
- Attempted Immobilized catalysts (covalent bonding).
- Synthetic organic ligands and metal sources to build chiral metal organic framework (MOFs).

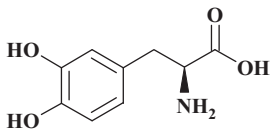
1. Important success in chiral modification of metal surface has come from the use of Cinchona alkaloids, though numerous other classes of natural products have been evaluated. These alkaloids have been shown to enhance the rate of substrate hydrogenation by 10–100 times, such that less than one molecule of cinchona alkaloid (56) is needed for every reactive site on the metal. In fact, the presence of excess of the chiral modifier can cause a decrease in the enantioselectivity of the reaction. [104]



56
Cinchonidine (one of the cinchona alkaloids)

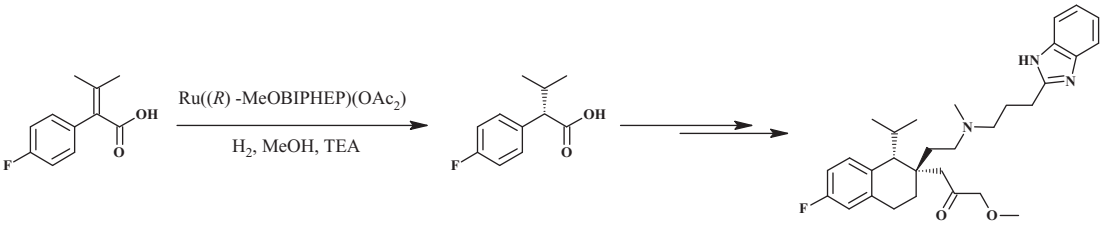
2. Covalent bonding of the catalyst to a polymer or other support is the most common use of the immobilized catalysts. Immobilization of the catalyst may also be achieved by adsorption onto a surface, ion exchange, or even physical encapsulation. Potential for the proximity of the support may change the behavior of the catalyst by lowering the enantioselectivity of the reaction. This may be avoided by binding the catalyst to the support by a long linker. Proximity of the support has been shown even to enhance the performance of the catalyst.
3. Construction of the skeleton of MOFs that incorporates chiral reaction sites from a number of different components, potentially including chiral and achiral organic ligands, structural metal ions, catalytically active metal ions, and/or preassembled catalystically active organometalic cores [105].

A synthetic method practiced on an industrial scale for one of the APIs, L-Dopa (57) by using asymmetric hydrogenation is:



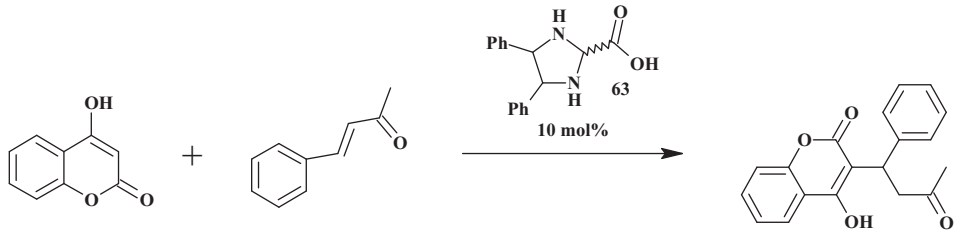
57
L-3,4-dihydroxyphenylalanine (L -DOPA)

Synthesis of Mibefradil (60) was improved by replacing resolution with asymmetric hydrogenation, reducing the number of steps and increasing the yield of key intermediate from 70 to 80% [106].



58 **59** Key intermediate **60** Mibefradil

Another example of asymmetric synthesis of the drug Warfarin (64) in a Michael addition of 4-hydroxycoumarin (61) and benzylidineacetone (62) [107].



61 **62** **64** Warfarin

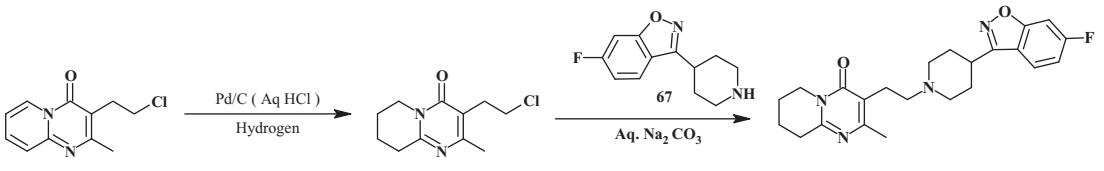
12.5.3.1 Synthesis of Warfarin

Various catalysts have been employed during the synthesis of APIs. Among them, the use of Nobel Metal catalysts has received more attention, due to their versatility in various types of organic transformations. Since Nobel Metal catalysts like platinum, palladium, and rhodium are all very expensive, their recycling and thereby, reuse becomes very important to bring down the impact of catalyst cost in the overall cost of the API.

A few of the examples of APIs, where catalysts for hydrogenation have been used in one or more steps of their synthetic scheme are depicted below.

12.5.3.2 Risperidone

Risperidone (68) is an anti-psychotic drug used for the treatment of bipolar disorders. In its synthetic scheme, an intermediate, having a pyridopyrimidine ring (65), is reduced to its tetrahydro derivative (66), before it is converted to Risperidone (68). This reduction is achieved by catalytic hydrogenation using Pd/C. Recycling the catalyst used plays an important role in keeping the cost of manufacture under control. This is efficiently done by RPG Life Sciences, which carried out the hydrogenation in dilute hydrochloric acid under pressure [108]. By this method, the catalyst could be recycled several times.

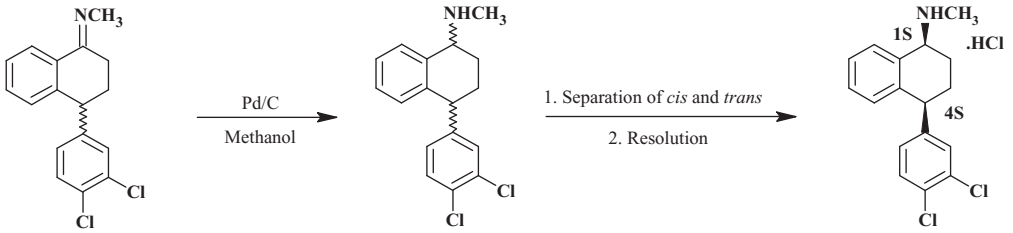


65 66 68

Risperidone

12.5.3.3 Sertraline

Sertraline hydrochloride (71) is an antidepressant drug that achieved blockbuster status generating more than $5 billion in sales before its patent expiry. In the synthetic scheme shown below, a Schiff's base (69) is reduced to the amine (70), which is a mixture of 4-isomers. This reduction is achieved by Pd/C in an alcoholic solvent, preferably methanol [109]. The hydrochloride salt of intermediate (70) is then subjected crystallization to separate *cis* and *trans* isomers, followed by classical resolution of the *cis* isomer to obtain (1*S*, 4*S*) Sertraline (71).



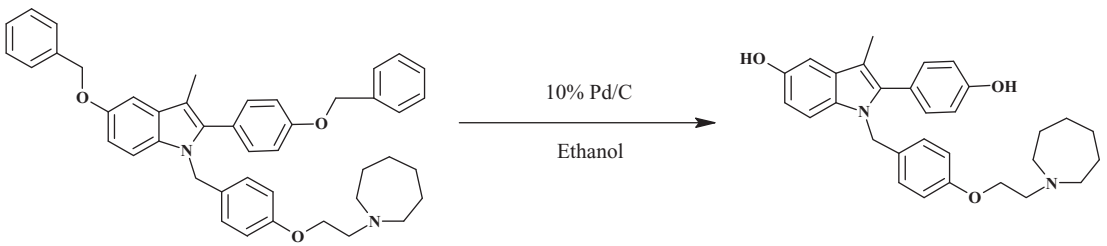
69 70 71

Sertraline HCl

12.5.3.4 Bazedoxifene acetate

Bazedoxifene (73) is a drug developed by Wyeth (now Pfizer).

Bazedoxifene, marketed by Pfizer as the acetate salt, is used for the treatment of postmenopausal osteoporosis. In the synthesis of Bazedoxifene, the benzyl protecting groups, as shown in the intermediate (72), are removed by catalytic hydrogenation using Pd/C to obtain the final drug [110].

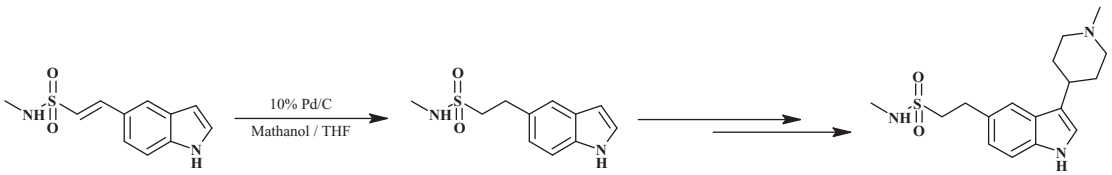


72 73

Bazedoxifene

12.5.3.5 Naratriptan

Naratriptan (76) is an anti-migraine drug invented by GSK. The double bond in the side chain of the indole intermediate (74) is reduced by Pd/C in methanol/THF to obtain the intermediate (75), which is then converted to Naratriptan (76) [111].



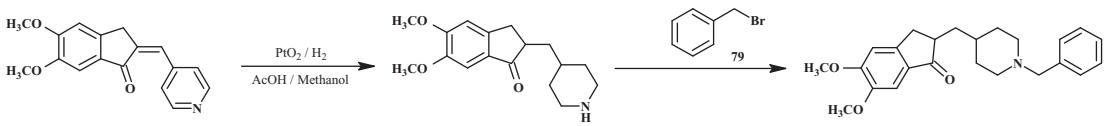
74 75 76 Naratriptan

12.5.4 Platinum Metal Catalyst

Among the Nobel Metals, platinum is more expensive than palladium and is used either as a free metal or its oxide, with carbon as a carrier. Because of its prohibitive cost, unless it is recovered and reused, the cost of the API would remain very high.

12.5.4.1 Donepezil

Donepezil (80), an anti-Alzheimer's drug, marketed as its hydrochloric acid salt, was discovered by Eisai, whose synthesis involves use of platinum oxide as a precious metal catalyst for the hydrogenation step [112]. The intermediate (77) is catalytically hydrogenated using hydrogen and platinum oxide as catalyst. The double bond and the pyridine ring in intermediate (77) are both simultaneously reduced to the piperidine derivative as shown in intermediate (78). Donepezil (80) is then obtained by treating the intermediate (78) with benzyl bromide (79) in the presence of a base.



77 78 80 Donepezil

OH

12.5.5 Nickel Catalyst

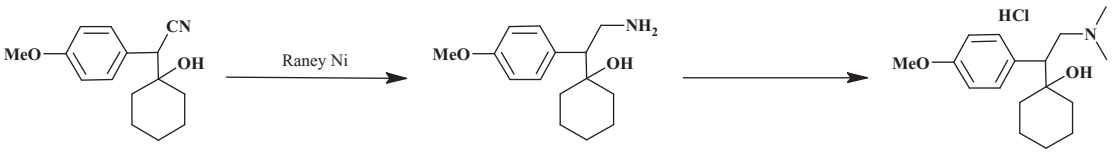
Finely divided Nickel Aluminum alloy, best known as Raney Ni is a well-known catalyst for hydrogenation. It is much cheaper than the Nobel Metal catalyst like palladium or platinum and hence, one need not bother about recovery and recycling of the catalyst. **However it is also**

pyrophoric like the Nobel Metal catalysts and one needs to exercise caution while handling as well as destroying the spent (used) catalyst.

It has a variety of applications in the chemical industry in general, and the pharmaceutical industry in particular. Chemical transformation, such as the reduction of a ketone to alcohol, reduction of a nitrile (cyano) group to alkyl amino group, reduction of a nitro group to an amino group, and dehalogenation, etc., can all be done very efficiently without formation of any impurities. Let us look at some of its applications in the pharmaceutical industry for the synthesis of drugs.

12.5.5.1 Venlafaxine

It was once a blockbuster drug marketed as *Effexor* by Pfizer (originally developed by Wyeth). It is an antidepressant drug. Its synthesis involves reduction of the cyano group in intermediate (81) to primary amino group as shown in intermediate (82), which is then treated with formaldehyde and formic acid to obtain Venlafaxine (83) as an HCl salt [113].

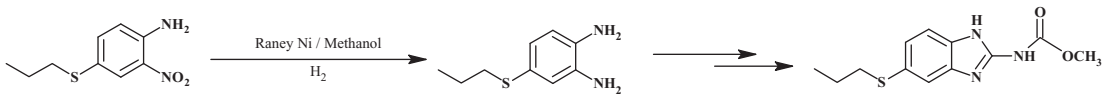


81 82 83

Venlafaxine

12.5.5.2 Albendazole

It is very old drug and is still used for both human as well as animal healthcare, but more as a veterinary drug. It is a broad spectrum anthelmintic originally invented by Smith Kline Laboratories. Synthesis involves preparation of a 1, 2 diaminointermediate (85), which is prepared from a nitro precursor (84) by catalytic hydrogenation using Raney Ni in THF as solvent [114]. The intermediate (85) is then cyclized and converted to Albendazole (86).



84 85 86

Albendazole

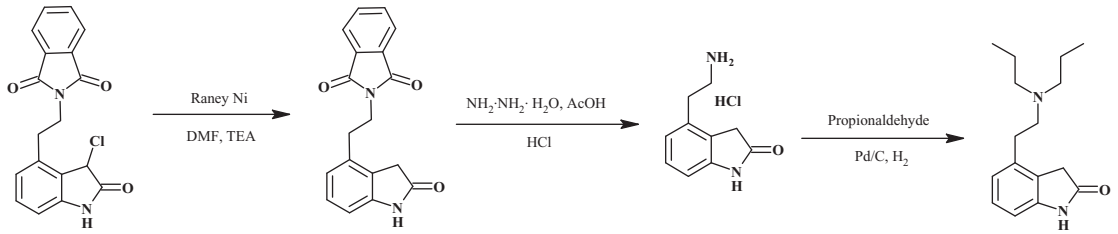
12.5.5.3 Raney Ni

Raney Ni is also used for the purpose of dehalogenation. In the synthesis of Ropinirole (90), the chlorine attached to the oxindole ring is removed by treatment with Raney Ni. Ropinirole

is an anti-Parkinson's drug, invented by GSK. In an elegant synthetic route designed by scientists at USV Limited, an Indian company, the chlorooxindole (87) is dehalogenated by Raney Ni in the presence of triethylamine in dimethylformamide as solvent to get dehalogenated derivative (88) and is then treated with hydrazine hydrate to remove the phthalimido group to obtain the aminoethyloxindole (89) [115].

Later, the amino group is di-*n*-propylated using *n*-propionaldeyde in the presence of palladium catalyst. Here the intermediate (89) undergoes reductive alkylation in the presence of *n*-propionaldehyde to obtain Ropinirole (90), which is then converted to its HCl salt.

Thus in the synthesis of Ropinirole, Both Raney Ni and Pd/C are used as catalysts. In the original process patented by GSK, expensive palladium catalyst was used even for the dehalogenation step, and later this was replaced by the cheaper catalyst Raney Ni, by USV Limited scientists, giving tremendous cost benefits. Competitive costing, besides international quality, is one of the important criteria for cornering major generic market share once the patent expires.



12.5.6 Enantioselective Synthesis

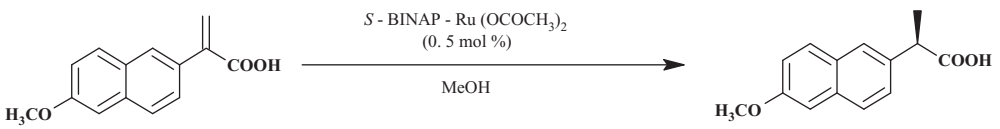
It is also called chiral synthesis or asymmetric synthesis in which only one enantiomer of chiral molecule is formed. Enantioselective synthesis is a key process in modern chemistry and is particularly important in the field of pharmaceuticals, as the different enantiomers or stereoisomers of a molecule have often different biological activity. Sometimes the unwanted enantiomer may turn out to be toxic, as was the case in one of the old drugs, Thalidomide, where pregnant women taking the drug as the racemate resulted in their newborns having physical deformities. This event, actually, was the beginning of the importance of chirality in the pharmaceutical industry.

12.5.6.1 Enantioselective catalysis

Enantioselective catalysis (or known traditionally as asymmetric catalysis) refers to the use of chiral coordination complexes as catalysts. The catalysts are typically rendered chiral by

use of chiralligands. Most enantioselective catalysts are effective at low concentrations, rendering them well suited for industrial scale synthesis, as even exotic and expensive catalysts can be used affordably. Perhaps the most versatile of enantioselective synthesis is asymmetric hydrogenation, which is able to reduce a variety of functional groups. The design of new chiral catalysts is dominated by development of new ligands. A ligand is an ion or a molecule (functional group) that binds to a central metal atom to form a coordination complex.

William S. Knowles and R. Noyori pioneered metal catalyzed enantioselective synthesis. The discovery of BINAP — Ru (II) complex catalysts was a major advance in stereo-selective organic synthesis. The scope of application of these catalysts is far reaching. These chiral Ru complexes serve as catalyst precursors for the highly enantioselective hydrogenation of a range of α, β and β, γ — unsaturated carboxylic acids, as shown below in the synthesis of *S*-Naproxen, where the naphthyl acrylic acid intermediate (91) is asymmetrically reduced to form the anti-inflammatory drug, ***S*-Naproxen** (92) [89].



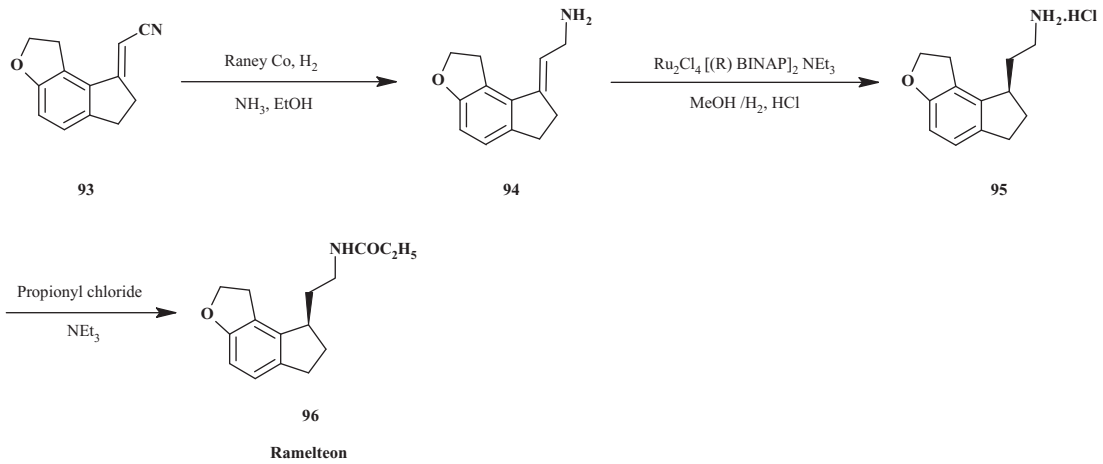
91 **92**

***S* - Naproxen**
92 % yield and 97% ee

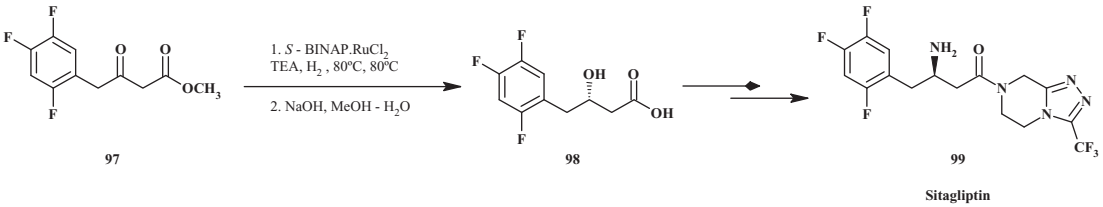
Another example of the use of Ruthenium BINAP complex for enantioselective hydrogenation [116] has been demonstrated in the asymmetric synthesis of *S*-ramelteon. This drug has been approved by the US FDA for the treatment of insomnia and is marketed by Takeda Pharmaceuticals as **Rozerem**, approved for long-time use. The synthesis is shown below.

In the above synthetic method, asymmetric hydrogenation is carried out by using Ru-BINAP complex to give a chiral intermediate (95) which when treated with propionylchloride gives *S*-Ramelteon (96) [117].

In the above synthesis, use of **Raney Co** as a hydrogenation catalyst has been demonstrated for the reduction of a nitrile to an alkyl amine function. Raney Co is reported to be superior to Raney Ni, especially in the case of hydrogenation of oximes or nitriles. The unsaturated nitrile intermediate (93) is hydrogenated in the presence of Raney Co to give an unsaturated amino intermediate (94), which undergoes asymmetric hydrogenation, as described above to give the chiral intermediate (95), which when acylated with propionyl chloride, gives **Ramelteon** (96).



Use of Ru-BINAP complex has been reported in the synthesis of one of the blockbuster drug, Sitagliptin, which is marketed by Merck as *Januvia*. Sitagliptin is a dipeptidyl peptidase inhibitor-IV (DDP-IV) inhibitor used for the treatment of diabetes. In the synthetic scheme, the trifluoroacetoacetate derivative (97) is hydrogenated with Ru-BINAP catalyst at a pressure of 90 pounds to give the chiralhydroxy derivative (98), **which** is converted through a series of steps to Sitagliptin (99) [118].



12.6 API Case Studies

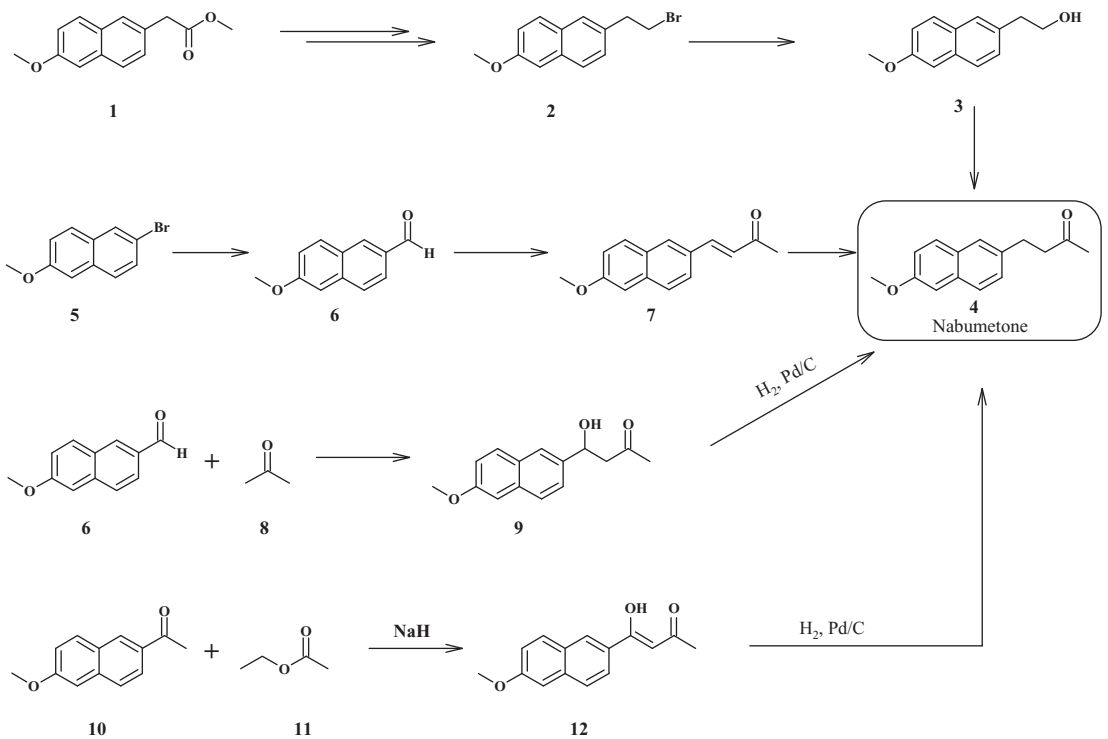
Considering that catalyst has shown the path to minimize the waste generation, its use in API manufacturing is expected to grow. It creates overall efficiency of the synthetic process and Green Chemistry or Green technology. A few examples where catalyst is used for synthesis of APIs employing modern chemistry are presented here. The examples quoted are very important to understand the phases in technology development, and may be useful as a guideline for development of various catalytic chemistries.

12.6.1 Synthesis of Nabumetone

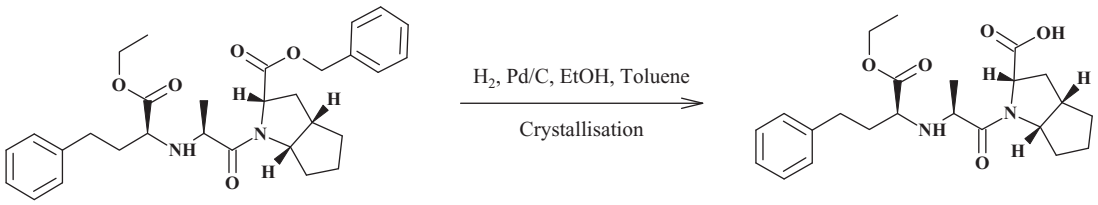
Several methods have been reported for the manufacture of Nabumetone, an anti-inflammatory drug. [119–126] Two methods are practiced on a commercial scale. One of the routes uses 6-methoxynaphthaldehyde as a starting material, whereas the other uses 2-methoxy-6-acetylnaphthlene. At one of the companies, the second route of synthesis was used, wherein ethyl acetate is reacted with 2-methoxyacetylnaphthalene in the presence of sodium hydride to

yield 4-(6-methoxy-2-naphthyl)-4-hydroxy-butene-2-one. The company was successful in using sodium methoxide instead of sodium hydride to get the same intermediate. This intermediate was then reduced using 5% Pd/C under mild pressure (2–3 kg/cm^2). In order to avoid impurity formation due to partial reduction or over-reduction, the most important parameters were the temperature, solvent, the pH, and time of reaction. The company was able to master this to get fairly pure product, which could meet the Pharmacopoeia monograph specification in single crystallization, including Pd content. The most important part was the recycle of the catalyst for more than 30 to 35 cycles by simply adding just 1% additional catalyst. In this case, the company was able to use right filter cartridge during catalyst filtration to avoid carryover of the Pd metal content to meet the regulatory specifications of less than 5 ppm Pd. In fact, the internal specifications were less than 1 ppm of Pd. After using the catalyst for 30–35 cycles, the reactivity of the catalyst did reduce, however, it was still active, and its use could be continued for another 10 to 15 cycles, but with longer time of reaction. The catalyst then was sent for recovery and reactivation, with almost 85 to 90% recovery.

This case study demonstrates that though the catalyst is expensive, with proper DoE, one may be able to reduce the cost of catalyst, make reaction efficient and economical with minimum waste generation. Thus, the type and catalyst with its particle size and surface area, temperature of reaction, solvent of reaction, time of reaction, pH of reaction, type of stirrer, and pressure, etc., are the important parameters which should be standardized during process development to get consistent quality and economy. The scheme is represented below.



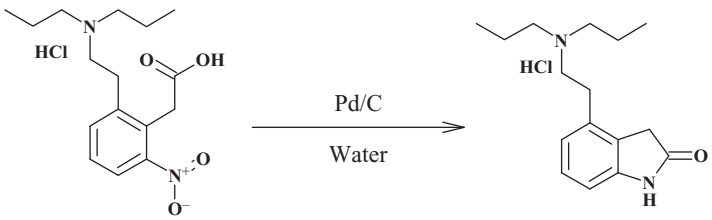
12.6.2 Synthesis of Ramipril



13 14

Ramipril Benzyl ester (13) is debenzylated with hydrogen in alcohol in the presence of Pd/C at 1.5 to 1.8 kg/cm^2 hydrogen pressure below 15°C to give Ramipril (14) [127–134]. In this case, also we found that with the right parameters, the catalyst could be recycled, though not for as many cycles as in the case of Nabumetone. The catalyst could be recovered and activated for recycling. The reaction yield was almost stoichiometric and impurity formation was almost below detectable limits. The catalyst content was also below acceptance limit (Pharmacopoeia monograph specification). The enantiomeric purity was retained.

12.6.3 Synthesis of Ropinirole

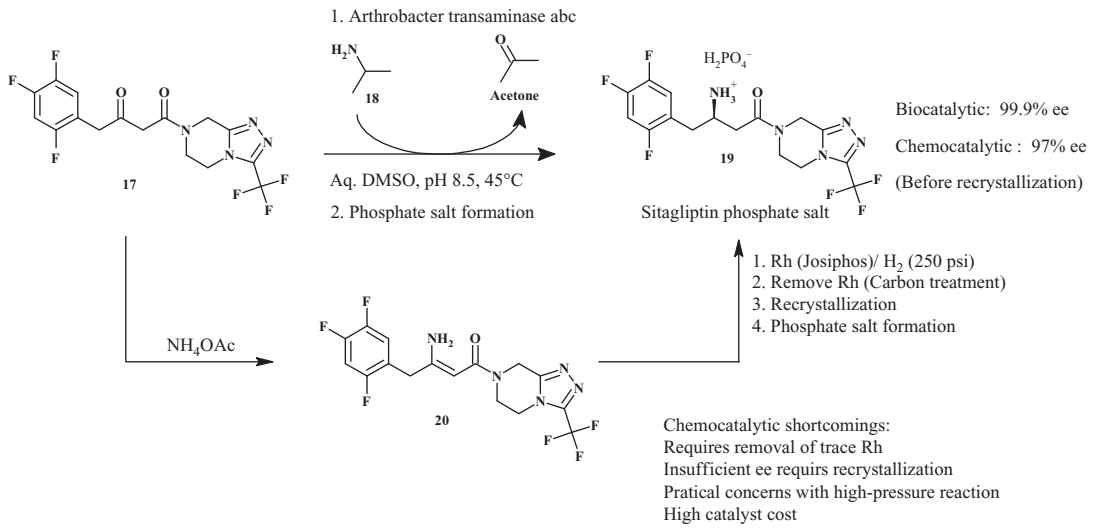


15 16

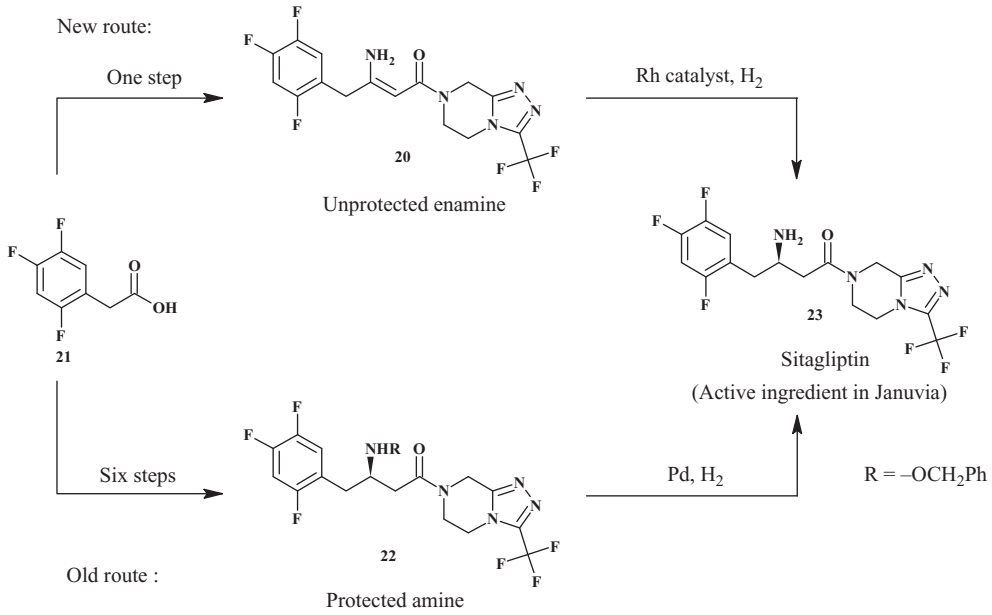
Reductive cyclization of 2-nitro-6-(2-di-*n*-propylamineoethyl)phenylacetic acid hydrochloride (15) in water with hydrogen gas in the presence of palladium over activated carbon to form Ropinirole. HCl (16) [135–147]. After removal of catalyst (Pd/C), the Ropinirole base is then extracted in solvent from basic pH, leaving behind most of the impurities (inorganic as well as organic) formed in the process. The catalyst selection and process parameter development in the laboratory are very important for getting the right quality and cost reduction.

12.6.4 Synthesis of Sitagliptin

One of the most prominent uses of biocatalysis in process chemistry today is in the synthesis of Januvia®, a DPP-4 inhibitor developed by Merck for the management of type II diabetes. The traditional process synthetic route involved a late-stage enamine formation, followed by rhodium-catalyzed asymmetric hydrogenation to afford the API sitagliptin. This process suffered from a number of limitations, including the need to run the reaction under a high-pressure hydrogen environment, the high cost of a transition-metal catalyst, the difficult process of carbon treatment to remove trace amounts of catalyst, and insufficient stereoselectivity, requiring a subsequent recrystallization step before final salt formation [148,149].



Codexis, a small biotech company, engineered a transaminase enzyme from the bacteria Arthrobacter through 11 rounds of directed evolution for Merck. The engineered transaminase contained 27 individual point mutations and displayed activity four orders of magnitude greater than the parent enzyme. Additionally, the enzyme was engineered to handle high substrate concentrations (100 g/L) and to tolerate the organic solvents, reagents and byproducts of the transamination reaction. This biocatalytic route successfully avoided the limitations of the chemocatalyzed hydrogenation route: the requirements to run the reaction under high pressure, to remove excess catalyst by carbon treatment, and to recrystallize the product due to insufficient enantioselectivity, were obviated by the use of a biocatalyst. Merck and Codexis were awarded the Presidential Green Chemistry Challenge Award in 2010 for the development of this biocatalytic route toward Januvia® [135–147].

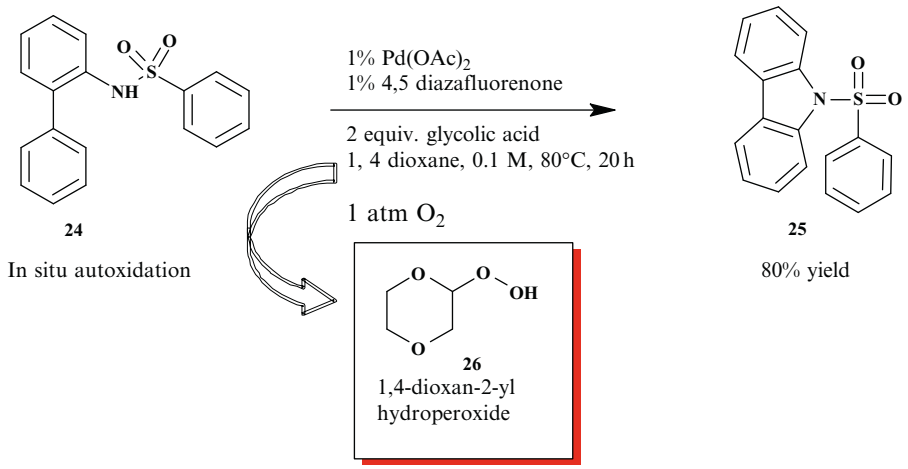


Merck process chemists redesigned and significantly shortened the original synthesis of type II diabetes drug candidate sitagliptin (Januvia) to include an unprecedented efficient hydrogenation of an unprotected enamine. The Merck scientists working on the revised synthesis discovered that the amino group could be efficiently introduced by an unprotected hydrogenation using a rhodium catalyst with a ferrocenyl phosphineligand named Josiphos [151]. The new synthesis involved first coupling of trifuorophenyl acetic acid (21) and triazole building blocks to form diketoamidesd (17), which in turn is converted to the enamine (20), this sequence is carried out without isolating intermediates. The enamine is hydrogenated, sitagliptin (19) is isolated and recrystallized as the phophonic acid salt, and the rhodium Josiphos catalyst is recovered. The revised synthesis increases the overall yield by nearly 50% and reduces the amount of waste by more than 80%. A comprehensive tale of green chemistry for Sitagliptin process intensification and industrial asymmetric catalysis has been described by Dr. Aman A. Desai [150].

The novel enamine hydrogenation is reported to be one of the most efficient means to prepare β-amino acid derivatives [151]. Green chemistry principles may be applied to drug discovery and development program. Emerging techniques for performing greener drug discovery chemistry are addressed together with cutting-edge topics like biologics discovery in a book titled "Green Strategies for Drug Discovery" [152].

12.6.5 Palladium-Catalyzed Aaerobic Oxidative C–H Amination

Synthesis of 2-unsubstituted and 2-substituted *N*-aryl benzimidazoles has been reported by Rapolu Kiran Kumara and Tharmalingam Punniyamurthy [153]. Palladium catalyzed aryl C–H Amination with O_2 via in situ formation of peroxide-based oxidant(s) from dioxane.



$(DAF)Pd(OAc)_2$ (DAF = 4,5-diazafluorenone) catalyzes aerobic intramolecular aryl C–H amination with *N*-benzenesulfonyl-2-aminobiphenyl (24) in dioxane to afford the corresponding carbazole (25) product. Mechanistic studies show that the reaction involves in situ generation of peroxide species from 1,4-dioxane and O_2, and the reaction further benefits from the presence of glycolic acid, an oxidative decomposition product of dioxane. An induction period observed for the formation of the carbazole product correlates with the formation of 1,4-dioxan-2-hydroperoxide via autoxidation of 1,4-dioxane, and the in situ-generated peroxide is proposed to serve as the reactive oxidant in the reaction.

12.6.6 Heterogenization of Pd-NHC Complexes

Heterogenization of Pd-NHC complexes onto a silica support and their application in the Suzuki-Miyaura coupling under batch and continuous flow conditions has been reported in the literature [154]. These silica-immobilized materials were successfully applied as catalysts in the Suzuki-Miyaura coupling of aryl chlorides and bromides under mild conditions. The materials exhibited improved stability when the catalytic reaction was done under anhydrous conditions and could be recycled up to five times without significant loss of activity. When the reaction was conducted in a continuous flow micro reactor, these catalysts showed good activity during at least 2 h on stream.

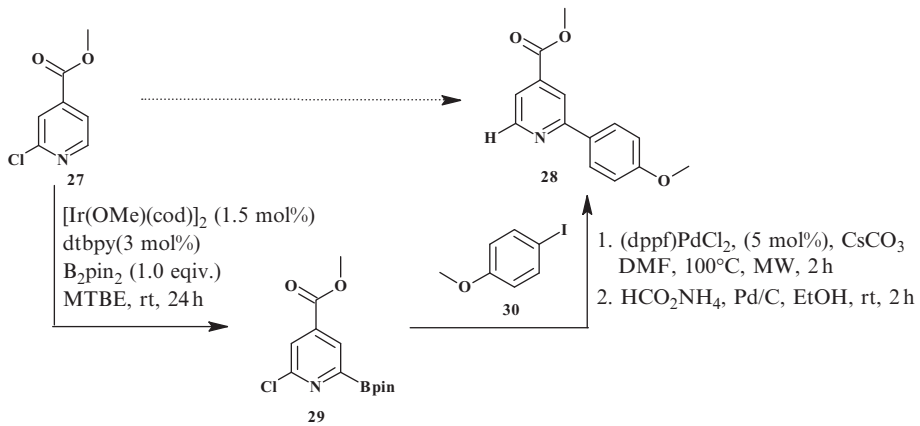
12.6.7 Fischer-Tropsch Synthesis

Fischer-Tropsch synthesis on a ruthenium catalyst in two-phase systems: an excellent opportunity for the control of reaction rate and selectivity. [155] The activity and selectivity of Fischer–Tropsch synthesis over hydrophobic Ru/C catalysts were efficiently controlled in the reaction medium consisting of organic and aqueous phases. A higher reaction rate was observed in two-phase systems compared to Fischer–Tropsch synthesis in the organic phase; however, catalyst localization in the organic phase leads to higher and tunable selectivity to long-chain hydrocarbons.

12.6.8 Doping with Cheaper Catalyst

There is a search for cheaper catalysts with high activity and stability in Ce-M-O systems (M = Fe, Co, Ni) [156]. Doping with cheaper transition metal ions could reduce the application price, however, usually doping degrades the catalytic activity. The preparation of Ce-M-O solid solutions (M = transition metal) with the aim to achieve cheaper catalysts with high activity and stability has been reported. Systematic sample characterizations indicate that the existence of more transition metal hydroxides is beneficial for the formation of Ce-M-O solid solutions and that the formation reaction involves a complicated process (eg, nucleation, dehydration, Ostwald attachment, doping in ceria lattice, and oriented growth). When tested as the catalysts for CO oxidation, the solid solutions of M = Fe maintained excellent catalytic performance, much higher than ever reported, even when Fe doping levels reach 15%. No sign of deactivation was detected for M = Fe after 100 h reaction, which compares to the apparent decrease in catalytic activity for M = Co or Ni. By studying the doping effect on structure, reducibility, oxygen storage capacity, and catalytic performance, it is demonstrated that Fe doping led to lattice crystal shrinking, lattice distortion, and restrained grain growth of CeO_2, yielding a synergistic effect in promoting oxygen storage capacity and catalytic activity. The results reported herein may provide some direction for exploring advanced catalysts at lower prices.

12.6.9 Iridium-Catalyzed C–H Borylation of Pyridines

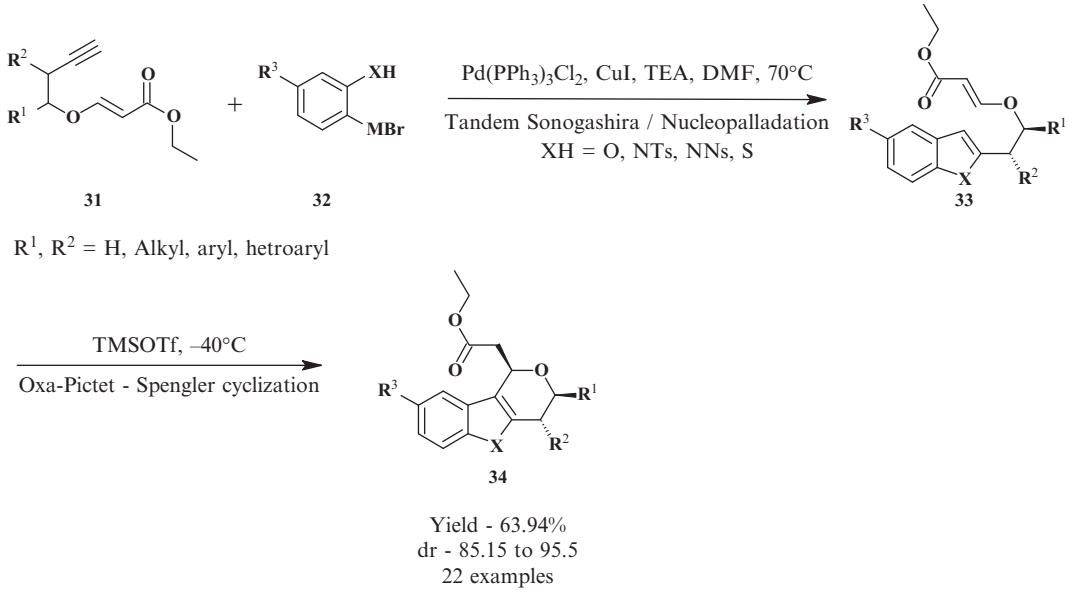


The iridium-catalyzed C–H borylation is a valuable and attractive method for the preparation of aryl and heteroarylboronates [157]. However, application of this methodology for the preparation of pyridyl and related azinylboronates can be challenged by low reactivity and the propensity for rapid protodeborylation, particularly for a boronate ester *ortho* to the azinyl nitrogen. Competition experiments have revealed that the low reactivity is due to inhibition of the active catalyst through coordination of the azinyl nitrogen lone pair at the vacant site on the iridium. This effect can be overcome through the incorporation of a substituent

at C-2. Moreover, when this is sufficiently electron-withdrawing, protodeborylation is appropriately slowed to permit isolation and purification of the C-6 boronate ester. Following functionalization, reduction of the directing C-2 substituent provides the product arising from formal *ortho* borylation of an unhindered pyridine ring.

12.6.10 Stereoselectivity

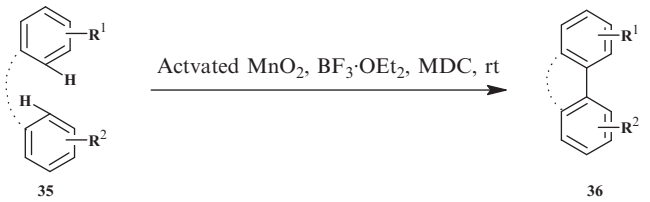
Stereoselective synthesis of C-fused pyranoindoles, pyranobenzofurans and pyranobenzothiophene scaffolds using oxa-Pictet-Spengler type reaction of vinylogous carbonates [158].



C-fused pyranoheterocycles can be readily assembled using an intramolecular Oxa-Pictet–Spengler type reaction of vinylogous carbonates (31) in a highly stereoselective manner. Required indole and benzofuran rings tethered to vinylogous carbonates are prepared by a tandem Sonogashira coupling-nucleopalladation reaction. The entire process can also be carried out in a "one-pot" manner starting from homopropargyl alcohol. The C-fused pyranoindoles could be converted to spirooxindoles as well as to ring expanded products under oxidative conditions.

12.6.11 Oxidative Biaryl Coupling

An economical and environmentally friendly oxidative biaryl coupling promoted by activated MnO_2 [159].



An activated manganese dioxide (MnO_2)-$BF_3 \cdot OEt_2$ oxidation system was developed to efficiently mediate the intramolecular as well as intermolecular biaryl coupling. The oxidative coupling proceeds smoothly at ambient temperature to deliver the corresponding five- to eight-membered tricyclic products in good to excellent yields. The employment of the combination of MnO_2 and $BF_3 \cdot OEt_2$ is attractive on the basis of economic and environmental issues.

12.6.12 Effects of CO_2 Pressure and pH on the Suzuki Coupling of Basic Nitrogen Containing Substrate

The Suzuki coupling reaction of basic nitrogen containing substrates (2-bromo- and 2-chloro-4-aminopyridine, and 2-bromo and 2-chloropyridine) with phenylboronic acid using Pd $(TPP)_2Cl_2/K_3PO_4$ in acetonitrile-water biphasic solvent systems under a CO_2 or a N_2 atmosphere is discussed. It was observed that 2-halo-4-aminopyridine produced quantitative yields of coupled products under a CO_2 atmosphere while the yields for the 2-halopyridines were poor. In contrast, the yields of coupled products for the 2-halopyridines substrates were quantitative under a N_2 atmosphere, while only poor yields were realized for the 2-halo-4-aminopyridines under the same conditions. Evidence is presented which suggests that the presence of CO_2 alters the pH of the aqueous phase of the reaction system and the accompanying efficiency of the coupling process. Using a series of buffers to adjust the pH of the aqueous phase, the pH dependence associated with the efficiency of the coupling process is illustrated [160].

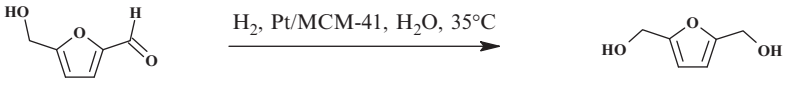
12.6.13 Glycosylation

Glycosylation with *N*-acetyl glycosamine donors using catalytic iron (III) triflate: from microwave batch chemistry to a scalable continuous-flow process [161].

Efficient and highly selective glycosylation reactions of peracetylated β-D-*N*-acetyl gluco- and galactosamine have been reported using catalytic iron (III) triflate under microwave conditions or in a continuous flow process. Simple β-glycosides and β-(1 → 6), β-(1 → 2) and β-(1 → 3) linked disaccharides bearing various protecting groups were obtained in high yields.

12.6.14 Hydrogenation of 5-Hydroxymethylfurfural

Selective hydrogenation of 5-hydroxymethylfurfural to 2,5-bis-(hydroxymethyl)furan using Pt/MCM-41 in an aqueous medium: a simple approach [162].



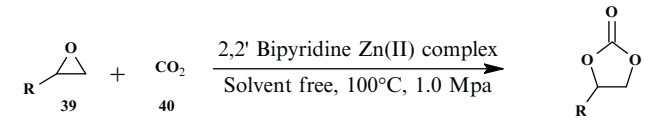
37
5-Hydroxymethylfurfural (HMF)

38
2,5-Bis-(hydroxymethyl) furan (BHMF)

The hydrogenation of HMF (37) has been conducted in a neutral aqueous medium. Without any additive, HMF (37) was hydrogenated to 2,5-bis-(hydroxymethyl)furan (38) (BHMF) with complete conversion and selectivity (98.9%) using Pt/MCM-41 as catalyst. A very low temperature of 35°C and 0.8 MPa of hydrogen pressure were used to accomplish the highest selectivity of BHMF within a reaction time of 2 h. Different reaction parameters such as reaction time, hydrogen pressure, and the amount of water was optimized to achieve the highest catalytic activity. In particular, the presence or absence of water and the amount of water played an important role to determine the conversion and product distribution of the reaction. For instance, in the absence of water or a large excess of water, the selectivity of BHMF was decreased. In addition, instead of water, the influence of three different groups of organic solvent was also explored to obtain BHMF under the studied reaction conditions. It has been observed that the studied organic solvents strongly influenced the catalytic performance, such as solvents with a negative δ value, which followed a clear trend with the substrate conversion, whereas no impact was observed for solvents with a positive δ value. Catalyst recycling experiments revealed that the catalyst could be recycled several times without any significant loss of catalytic activity.

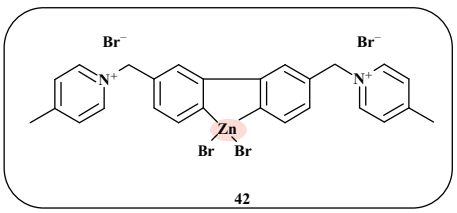
12.6.15 Cyclic Carbonates

New bi-functional zinc catalysts based on robust and easy-to-handle N-chelating ligands for the synthesis of cyclic carbonates from epoxides and CO_2 under mild conditions has been reported [163].



39 40 41

R = Me, *n*-Bu, CH_2Cl, Ph



42

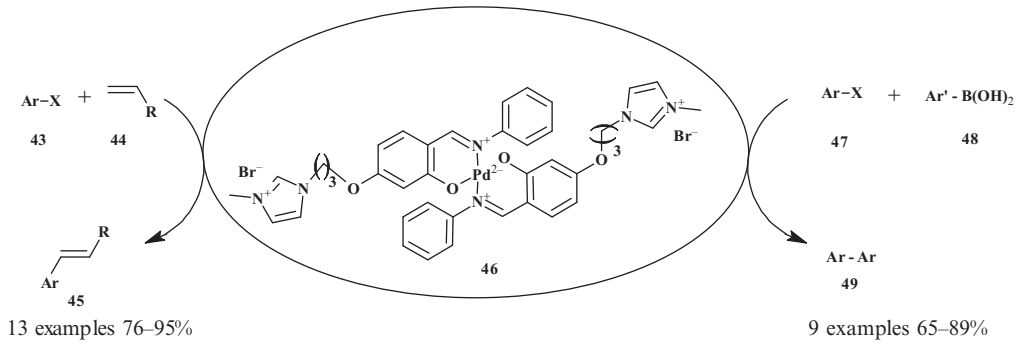
A series of novel zinc complexes were prepared by covalent linkage of various imidazolium-based ionic liquid moieties with the 2,2′-bipyridine ligand on the two sides of the 4,4′-position. The zinc (II) complexes (42) containing the rigid N-chelating ligand proved to be stable, highly efficient, and easy-to-handle catalysts towards the synthesis of cyclic carbonate (41) from epoxide (39) and CO_2 (40) without the use of any co-catalyst or organic solvent. The catalysts can be easily recovered and reused without significant loss of activity and selectivity by control of the solvent. The kinetic study uncovered that the reaction was first-order with respect to the epoxide. Moreover, a plausible reaction mechanism was proposed, in which the zinc center could promote ring opening of the epoxide for the synergetic effect with the anion X^- in ILs.

12.6.16 Photo Catalytic Suzuki Cross-Coupling Reaction

An efficient photo catalytic Suzuki cross-coupling reactions on Au-Pd alloy nanoparticles under visible light irradiation is of great interst. [164] It is reported that highly efficient photo catalysts comprising supported nanoparticles (NPs) of gold (Au) and palladium (Pd) alloys, which utilize visible light to catalyze the Suzuki cross-coupling reactions at ambient temperature. The alloy NPs strongly absorbs visible light, energizing the conduction electrons of NPs, which produce highly energetic electrons at the surface sites. The surface of the energized NPs activates the substrates and these particles exhibit good activity on a range of typical Suzuki reaction combinations. The photocatalytic efficiencies strongly depend on the Au:Pd ratio of the alloy NPs, irradiation light intensity and wavelength. The results show that the alloy nanoparticles efficiently couple thermal and photonic energy sources to drive Suzuki reactions. Results of the density functional theory (DFT) calculations indicate that transfer of the light-excited electrons from the nanoparticle surface to the reactant molecules adsorbed on the nanoparticle surface activates the reactants. The knowledge acquired in this study may inspire further studies of new efficient photo catalysts and a wide range of organic syntheses driven by sunlight.

12.6.17 Imidazolium Ionic Liquid-Tagged Palladium Complex

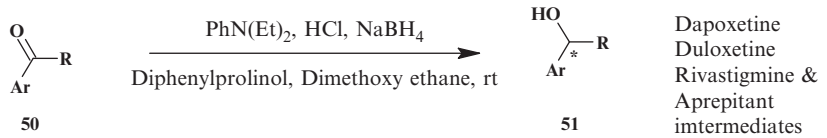
Imidazolium ionic liquid-tagged palladium complex has been reported as an efficient catalyst for the Heck and Suzuki reactions in aqueous media. [165]



An air stable, water soluble, and efficient ionic liquid-tagged Schiff base palladium complex (46) was prepared. The synthesized complex was well characterized by NMR, mass spectrometry, FT-IR, UV-visible spectroscopy, and powder X-ray diffraction. The complex was used as a catalyst for the Suzuki and Heck cross-coupling reactions in water. Good to excellent yields were achieved using a modest amount of the catalyst. In addition, the catalyst can be easily reused and recycled for six steps without much loss in activity, exhibiting an example of sustainable and green methodology. Imidazolium ionic liquid-tagged palladium complex is used as efficient catalyst for the Heck and Suzuki reactions in aqueous media [166].

12.6.18 Corey–Itsuno Reduction of Ketones

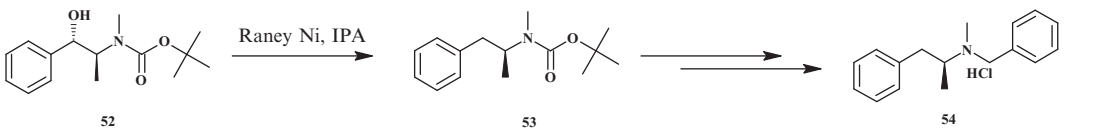
Corey–Itsuno reduction of ketones has been reported as a safe and inexpensive process for synthesis of some of the important API Intermediates [167].



A number of drugs such as dapoxetine, fluoxetine, Atomoxetine, Revastigmine, Duloxetine, and Aprepitant involve asymmetric reduction of benzylicketone as a key step to introduce chirality into the drug molecule. The preparation of (*N*,*N*-diethylaniline borane) DEANB from (*N*,*N*-diethylaniline) and NaBH4 and its in situ use in an asymmetric reduction of prochiralketones, using (*S*)-α,α-diphenylprolinol catalyst to produce some API intermediates on a large scale has been reported.

12.6.19 Benzphetamine Hydrochloride

An efficient, and scalable process has been reported for benzphetamine hydrochloride [168].

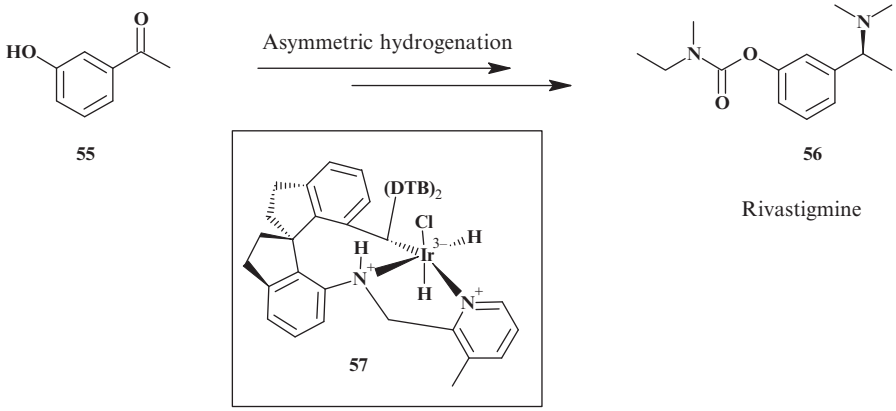


N - Boc -pseudoephedrine N - Boc -Methamphetamine Benzphetamine hydrochloride

The process to yield high purity benzphetamine (54) under mild conditions has been reported. Accordingly, deoxygenation of ephedrine/pseudoephedrine HCl (52) with an excess of Raney Ni in isopropanol was attempted in an autoclave at 50–55°C (pressure observed up to 2–3 kg); to our satisfaction, the reaction proceeded to completion within 2–3 h and cleanly afforded the desired product (methamphetamine) (53) after filtration of the catalyst.

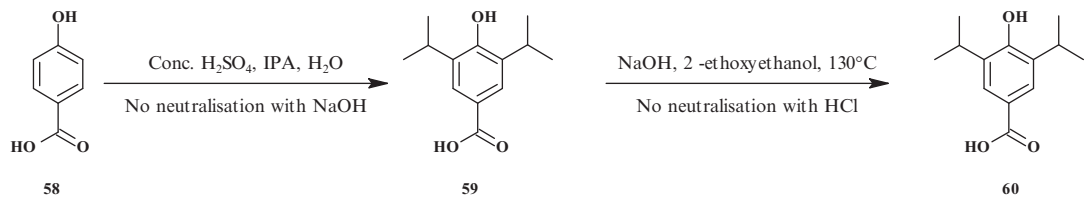
12.6.20 Synthesis of Rivastigmine

Industrial scale-up of enantioselective hydrogenation for the asymmetric synthesis of Rivastigmine [169].



Two efficient processes for the synthesis of Rivastigmine (56), one of the most potent drugs for the treatment of mild-to-moderate dementia of the type presenting in Alzheimer's disease, has been developed. One of the processes used for the asymmetric hydrogenation the highly efficient chiral spiro catalyst, Ir-SpiroPAP(57). The first route has been scaled up to manufacture intermediate (*S*)-3-(1-dimethylaminoethyl) phenol on a commercial scale. This has been found suitable for the manufacture of Rivastigmine in API demand.

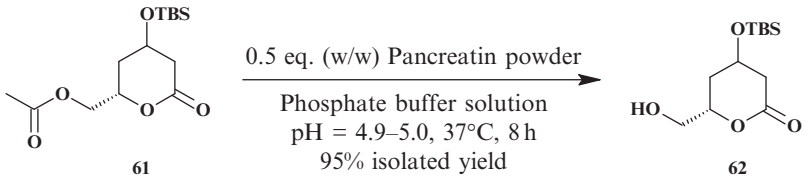
12.6.21 Synthesis of Propofol



Isopropanol was used as the propylating agent instead of direct propylene gas; in this method, propylene is generated in situ using IPA and strong acid (H_2SO_4) or Aluminosilicate catalyst. A commercially viable manufacturing process for propofol (60) is to avoid acid–base neutralization events during isolation of intermediate, 2,6-di-isopropylbenzoic acid (59) and crude propofol. This thus simplifies the synthesis on industrial scale to a considerable extent. Syntheses of five impurities/related substances (USP and EP) are also described in this reference [170].

12.6.22 Chemoselective Pancreatin Powder-Catalyzed Deacetylation

An application of chemoselective pancreatin powder-catalyzed deacetylation reaction in the synthesis of key statin side chain intermediate (4*R*, 6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydropyran-2-one has been reported [171].



61 62

However, the quest for increased efficiency has drawn the development of these drugs towards structural refinement of natural compounds with structural modifications that finally resulted in the fully synthetically built derivatives. Moreover, reactions with anhydrous $HBF_4 \cdot OEt_2$ guanidinium nitrate/NaOMe couple a catalytic amount of acetyl chloride in methanol scandium trifluoromethanesulfonate catalyst, dibutyltin oxide, *p*-toluenesulfonic acid, hydrazine hydrate in THF, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in complete decomposition and no alcohol (62) was detected in the crude reaction mixture, although acetate (61) was completely consumed.

12.6.23 Synthesis of Valsartan

Valsartan is large volume product now on the market. The original patented process has been modified to fall in the green chemistry concept with Scale-up of Key Suzuki–Miyaura Coupling over Silia*Cat* DPP-Pd catalyst. [172]

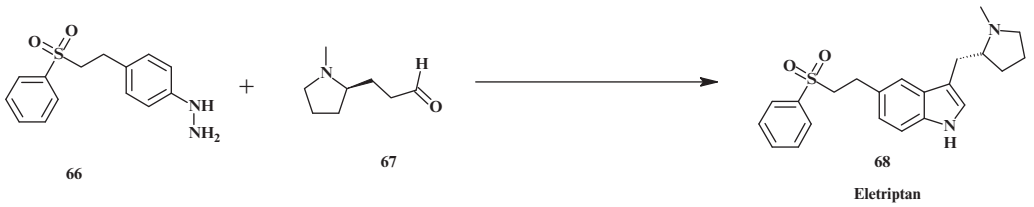


63 64 65

The study of the scale-up of the heterogeneous Suzuki-Miyaura coupling reaction in batch conditions between 2-chlorobenzonitrile (63) and 4-tolylboronic acid (64), a key step in *valsartan* synthesis, to produce 4′-methyl-2-biphenylcarbonitrile (65) over the Silia*Cat* DPP-Pd catalyst in ethanol under reflux allows us to identify the optimal reaction conditions.
In general, the heterogeneous reaction over a solid-bound catalyst is greener because no catalyst-product separation step is required at the end of the reaction, beyond simple filtration, while in many homogeneous syntheses of drugs, the pharmaceutical industry produces between 25 and 200 kg or more of waste for every kilogram of API manufactured, with 75–80% of the waste produced being solvent (liquid) and 20–25% hazardous solid.

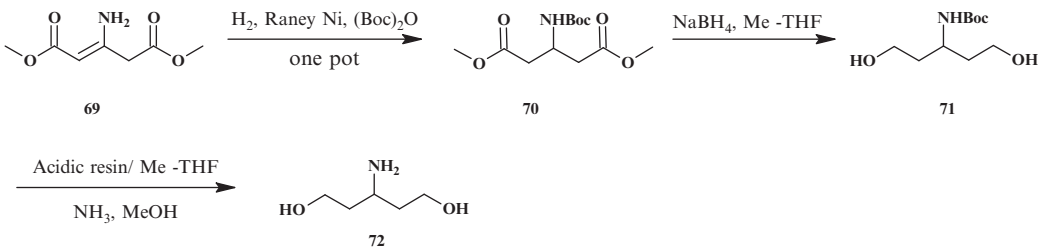
12.6.24 Synthesis of Elitriptan

Synthesis of elitriptan [173] by using Fisher Indole reaction approach has been reported in the literature.



Eletriptan (68) belongs to the class of drugs known as Triptans. The catalyst used was removed by filtration through a filter aid, and the solvent was distilled at reduced pressure to give the free base as clear oil. The development of a second-generation process for the synthesis of Eletriptan via a Fischer indole cyclization is reported that offers several potential advantages over the current route of manufacture including cost, throughput, and safety.

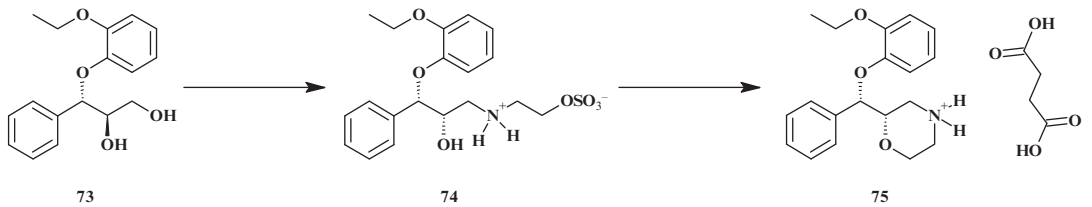
12.6.25 Scalable Non-Aqueous Process to Prepare Water Soluble 3-Amino-pentan-1,5-diol



The development of a nonaqueous process for the synthesis of 3-amino-pentan-1,5-diol (72) is reported. Beginning with dimethyl acetone-1,3-dicarboxylate (69), a telescoped sequence of reductive amination, Boc protection, sodium borohydride reduction, and acidic resin-mediated deprotection generates the title compound. The key to this efficient process is the telescoped deprotection, purification and nonaqueous isolation of the 3-amino-pentan-1,5-diol. The process involves four optimized chemical reactions using two solvents in 89% overall yield and 97–98% purity [174].

12.6.26 Synthesis of (S,S)-Reboxetine Succinate

Commercial synthesis of (*S*,*S*)-reboxetine succinate has been described in an open literature and considered as the *cheapest commercial chemistry for manufacture* [175].



73 74 75

(*S, S*) - Reboxetine succinate

The development of a synthetic process for (*S*,*S*)-reboxetine succinate (75), a candidate for the treatment of fibromyalgia, is disclosed from initial scale-up to deliver material for registrational stability testing through to commercial route evaluation and subsequent nomination. This entails evaluation of several alternative routes to result in what would have been a commercially attractive process for launch of the compound.

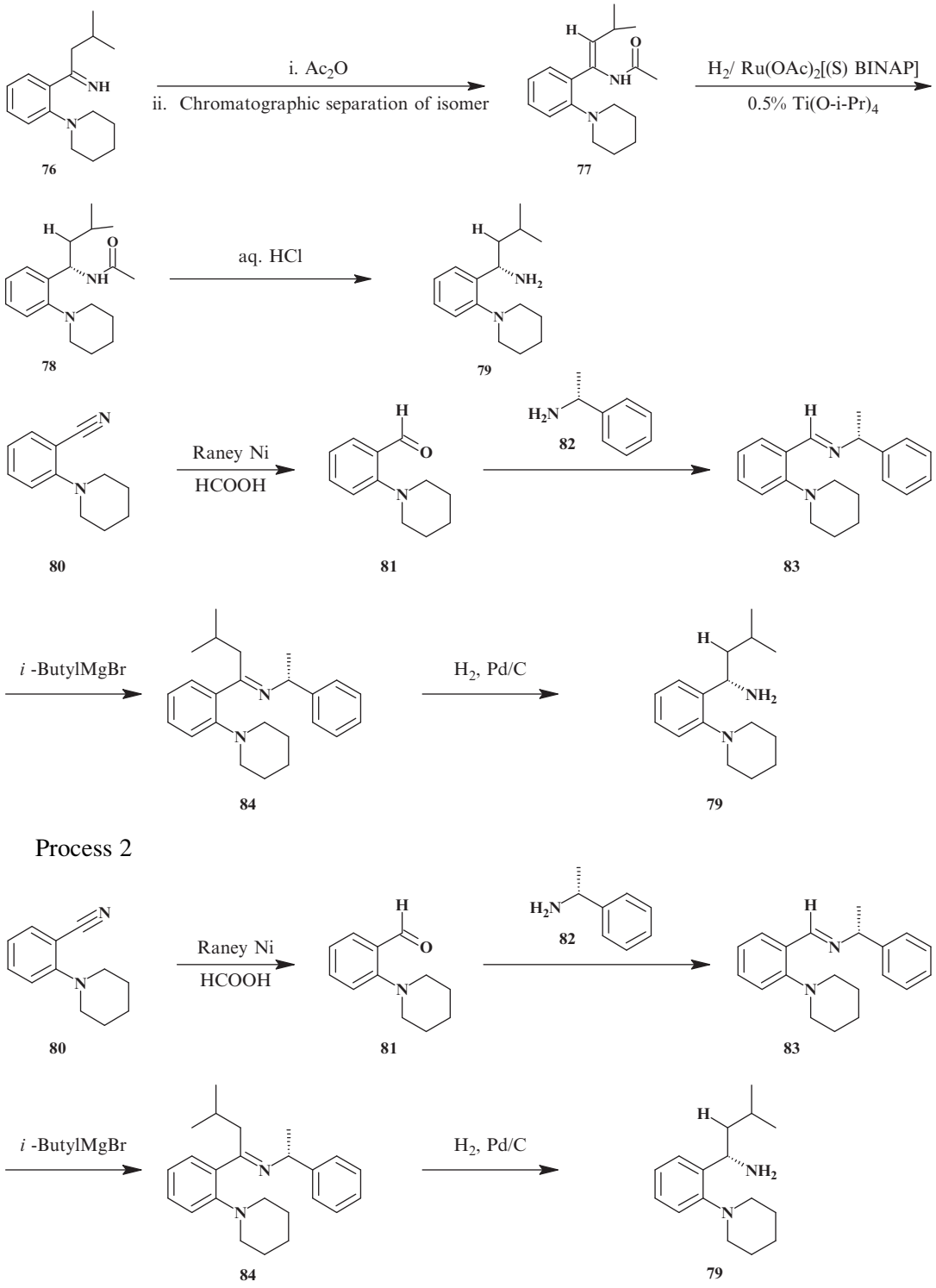
12.6.27 Correlated Bifunctionality in Heterogeneous Catalysts

Selective tethering of cinchonidine (Cd) next to supported Pt nanoparticles has been described as an effective catalyst system [176]. A strategy has been devised to add molecular functionality to heterogeneous catalysts in a spatially correlated fashion. The idea was tested for a specific system where enantioselectivity was added to a Pt/SiO_2 catalyst by tethering Cd selectively to silica sites adjacent to the metal nanoparticles. The reported methodology relies on the selective strong adsorption of the cinchona alkaloid on the platinum surface, the same interaction responsible for the chiral modification; the catalyst was first exposed to a Cd molecule to which a propyltriethoxysilane moiety was added, the excess was then washed away with a pure solvent, and the click chemistry used to link the chiral modifier to the surface of the silica support was finally triggered via thermal activation. The resulting samples were thoroughly characterized by using several titration and spectroscopic techniques, and their catalytic performance for the hydrogenation of ethyl pyruvate was contrasted with that seen for similar catalysts where Cd tethering is done in a random fashion. Superior performance has been reported with the correlated-tethering samples, mainly in terms of activity but also with respect to enantioselectivity. Correlated-tethering samples show performance comparable to that obtained by adding the cinchona in the solution under similar conditions. The effects of the location within the molecular structure of Cd where tethering is performed, the Cd:Pt molar ratio, and the solvent used have been evaluated.

12.6.28 Synthesis of Repaglinide

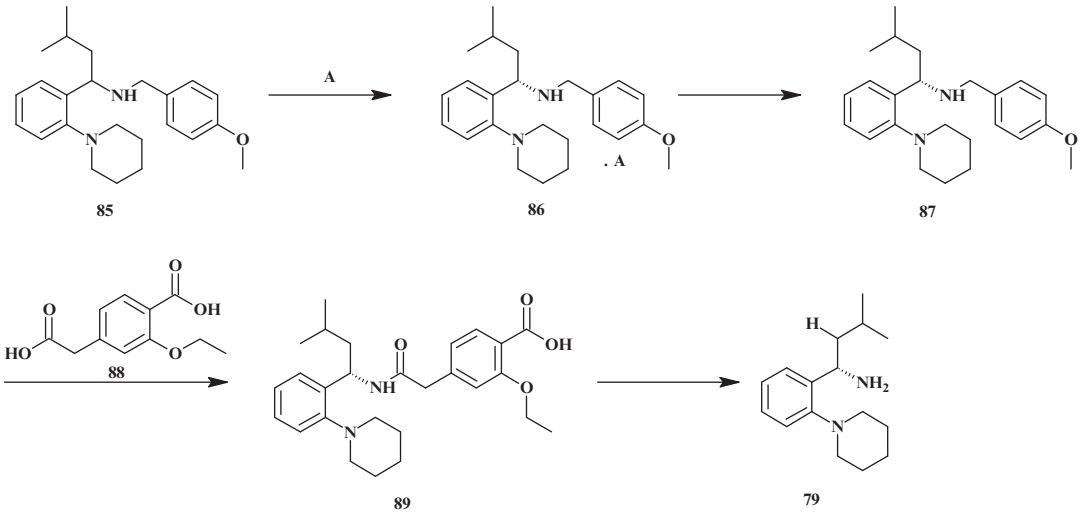
Three processes have been reported in the open literature for the synthesis of Repaglinide and are described below briefly. [177,178]

Process 1



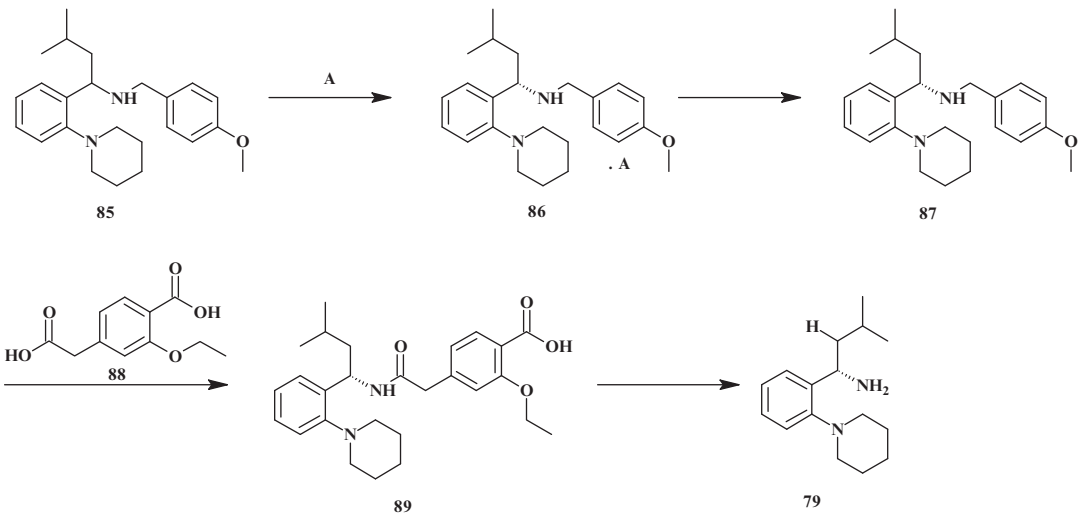
Process 2

Process 3

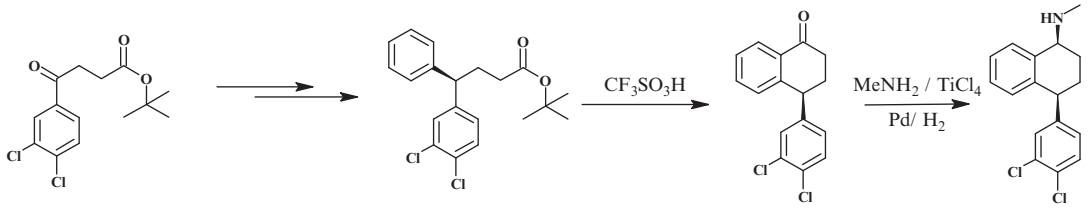


12.6.29 Synthesis of Duloxetine HCl

A novel process has been reported for preparation of duloxetine HCl. Process for racemization of undesired isomer (*R*)-(−)-*N*,*N*-dimethyl-3-(l-naphthalenyloxy)-3-(2-thienyl) propanamine (91) with KHMDS as base to obtain racemic compound (*RS*)-*N*,*N*-dimethyl-3 (1-naphthyloxy)-3-(2-thienyl)propanamine free bases (92) as shown in the scheme [179].



12.6.30 Synthesis of Sertraline [180]



93 94 95 96 Sertraline

Synthesis of (+)-Sertraline

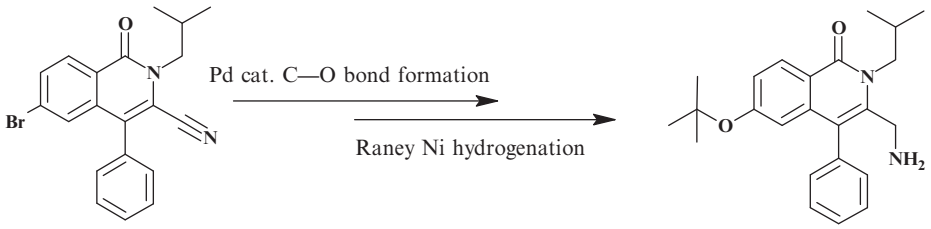
One of the synthesis described starts from 3,4-dichlorobenzophenone which is subjected to Wittig olefination to give 1,1-diaryl olefin (87% yield). Asymmetric dihydroxylation of olefin yields chiral diol (78% yield). Selective oxidation of the primary alcohol with IBX in DMSO gives aldehyde (85% yield). This Aldehyde by Wittig olefination gives the α,β-unsaturated ester (90% yield).

Hydrogenolysis of ester (10% Pd/C, H_2 (20 psi), MeOH) at the benzylic position leads to the formation of saturated ester (62% yield). Ester on subsequent hydrolysis and cyclization under acidic conditions gives tetralone (68% yield and 88% ee).

Finally, reductive amination ($TiCl_4$, excess $MeNH_2$, $Pd/CaCO_3$, H_2 (50 psi)) of yields sertraline (35% yield and 88% ee). For additional information refer 12.5.4.3.

12.6.31 Isoquinolone Derivative as a Potent DPP-4 Inhibitor

Development of large scale synthesis using palladium-catalyzed cross-coupling reactions for an Isoquinolone derivative as a potent DPP-4 inhibitor has been reported [181]. The insertion of an oxygen atom at the 6-poition of isoquinolone was achieved by cross-coupling reaction using 6-bromoisoquinolone and sodium tertbutoxide (*t*-BuONa) in the presence of Pd(OAc)2 and rac-BINAP as a catalyst to afford 6-tertbutoxyisoquinolone in good yield. Dipeptideyl peptibase-4 (DPP-4) inhibitors have been used as a new class of antidiabetic drugs.

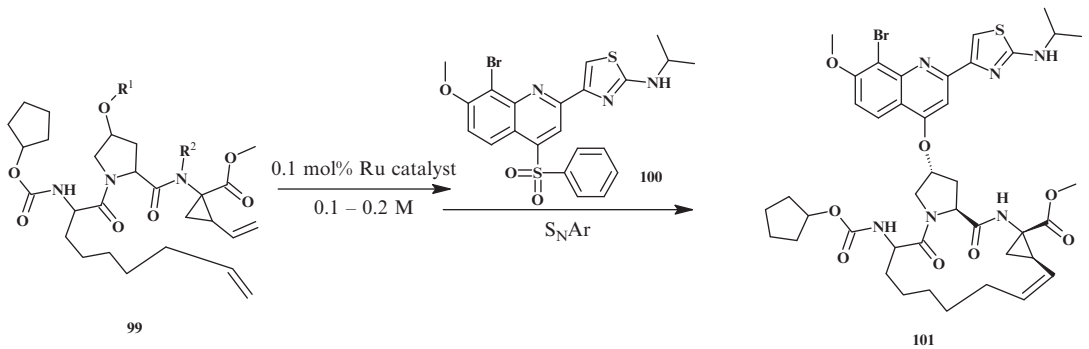


97 98

An efficient large-scale synthesis of a novel DPP-4 inhibitor **1**, an isoquinolone derivative bearing an aminomethyl group at the 3-position and carbamoylmethoxy group at the 6-position, is described. An effective and convenient synthetic method utilizing a key intermediate possessing a cyano group at the 3-position, and a halogen atom at the 6-position has been reported. The key reaction, the insertion of an oxygen atom at the 6-position of isoquinolone was achieved by a cross-coupling reaction using 6-bromoisoquinolone and sodium *tert*-butoxide (*t*-BuONa) in the presence of $Pd(OAc)_2$ and rac-BINAP as a catalyst to afford 6-*tert*-butoxyisoquinolone in good yield. The cyano group at the 3-position was hydrogenated in the presence of Raney Nickel to give the aminomethyl moiety of compound **1**. The synthetic route has been successfully applied to multikilogram-scale preparations with good yield and high quality.

12.6.32 Macrocyclic Hepatitis C Virus Protease Inhibitor BI 201302

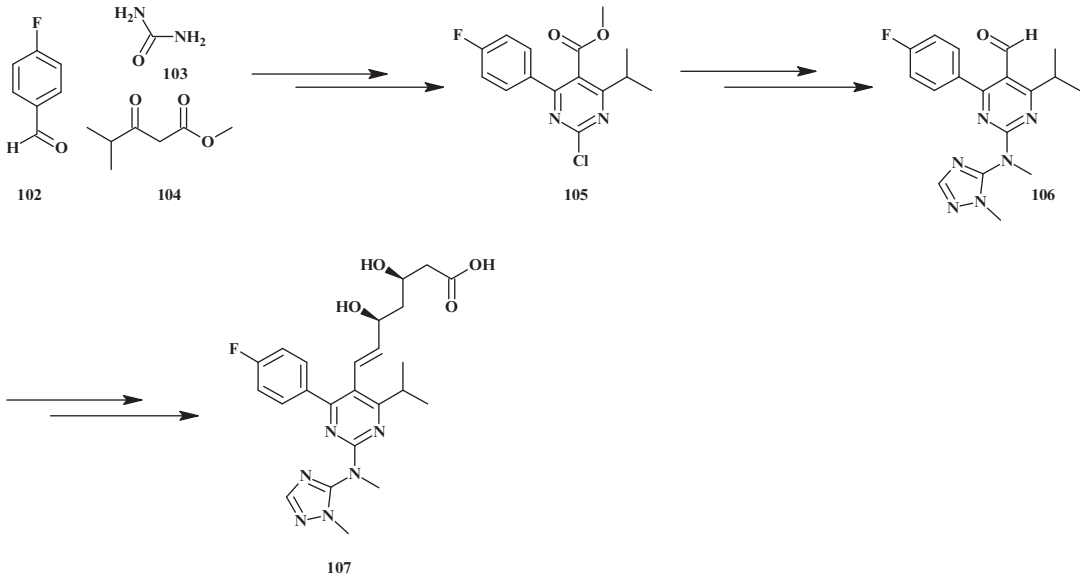
A highly convergent and efficient synthesis of a macrocyclic hepatitis C virus (HCV) protease inhibitor BI 201302 has been reported [181]. Recently, two anti-HCV drugs were approved by the FDA to treat HCV-infected patients. The high ruthenium (Ru) catalyst loading (3–5 mol%) for RCM reaction was impractical due to not only its high cost, but also the extreme difficulty of removing high levels of residual Ru metal from the final API.



A highly convergent large-scale synthesis of a 15-membered macrocyclic HCV protease inhibitor BI 201302 was achieved, in which the key features are the practical macrocyclization by Ru-catalyzed ring-closing metathesis (0.1 mol% Grela catalyst, 0.1–0.2 M concentration) and the efficient sulfone-mediated SNAr reaction.

12.6.33 Next-Generation Statin

Development of a scalable process for the synthesis of a next-generation statin has been reported. [182]

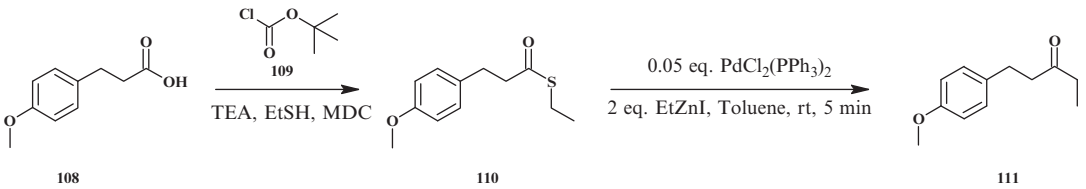


Purification sequence via an intermediate crystalline form is highlighted as a method of controlling the final API quality. The protocol involved the use of a metal catalyst (copper, in particular) together with an oxygen-based oxidant. The calcium salt was selected as the final salt form for oral solid dosage development, and this selection was further supported by the prevalence of other marketed statin drugs as calcium salts (eg, Atorvastatin and Rosuvastatin).

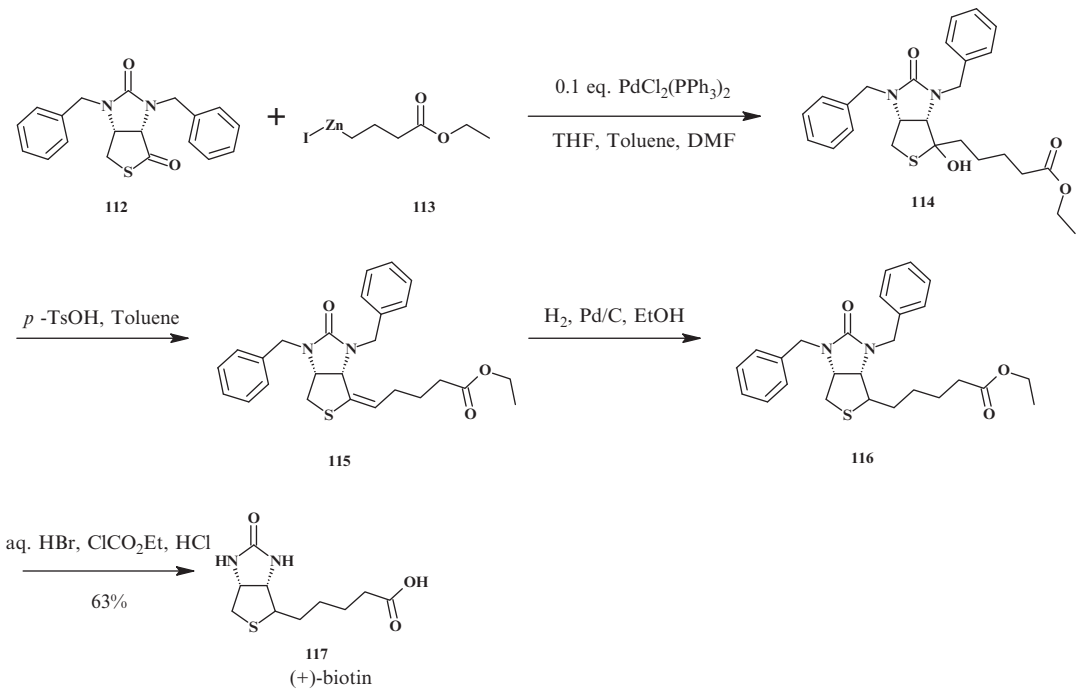
This manuscript details the process research and development of a convergent and safe approach to a multikilo scale. Specific highlights of the process development efforts will be described, including the development of a dehydrogenation method for dihydropyrimidines and a thermochemically safe synthesis of a 1,2,4-aminotriazole fragment. A key feature of the synthesis is the use and optimization of a modified Julia–Kocienski olefination reaction. Unprecedented dependence of the product olefin geometry on reaction temperature has been reported, where an E:Z ratio as high as 200:1 can be obtained. Initial insights into the mechanistic rationale for this observation are also provided. Finally, a purity improvement sequence via an intermediate crystalline form is highlighted as a method of controlling the final API quality.

12.6.34 Synthesis of Biotin

The advantage of the method reported in this reference is that the reaction stops at the ketone and does not proceed to a tertiary alcohol. In addition, the protocol is compatible with functional groups such as ketones, acetates, sulfides, aromatic bromides, chlorides, and aldehydes.



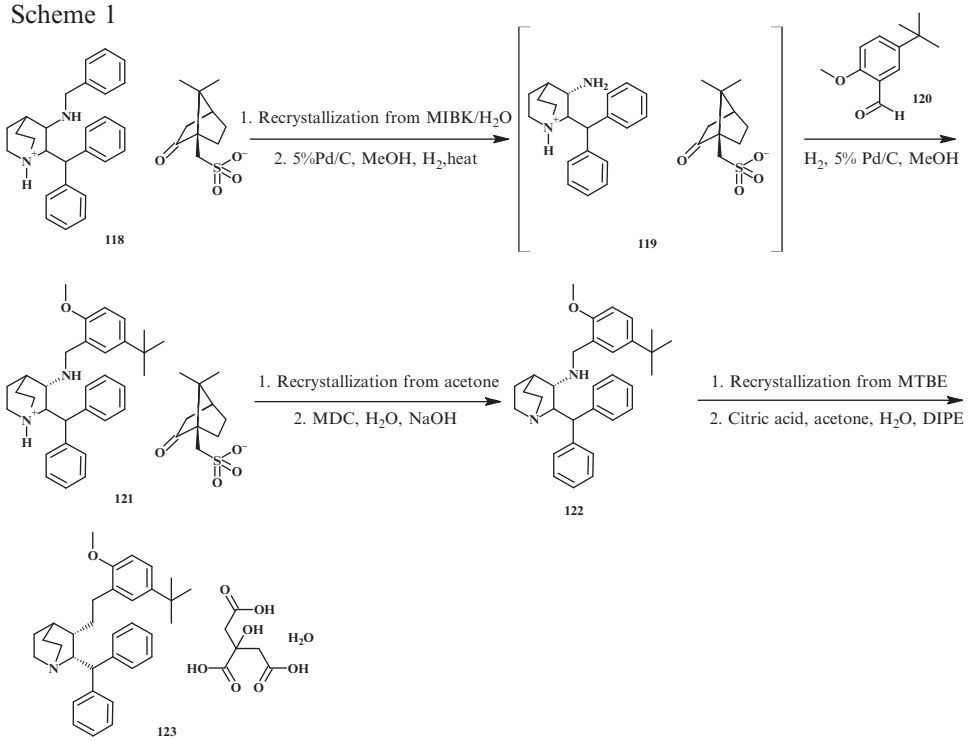
The reaction (interrupted) has been used in the synthesis of biotin [183].



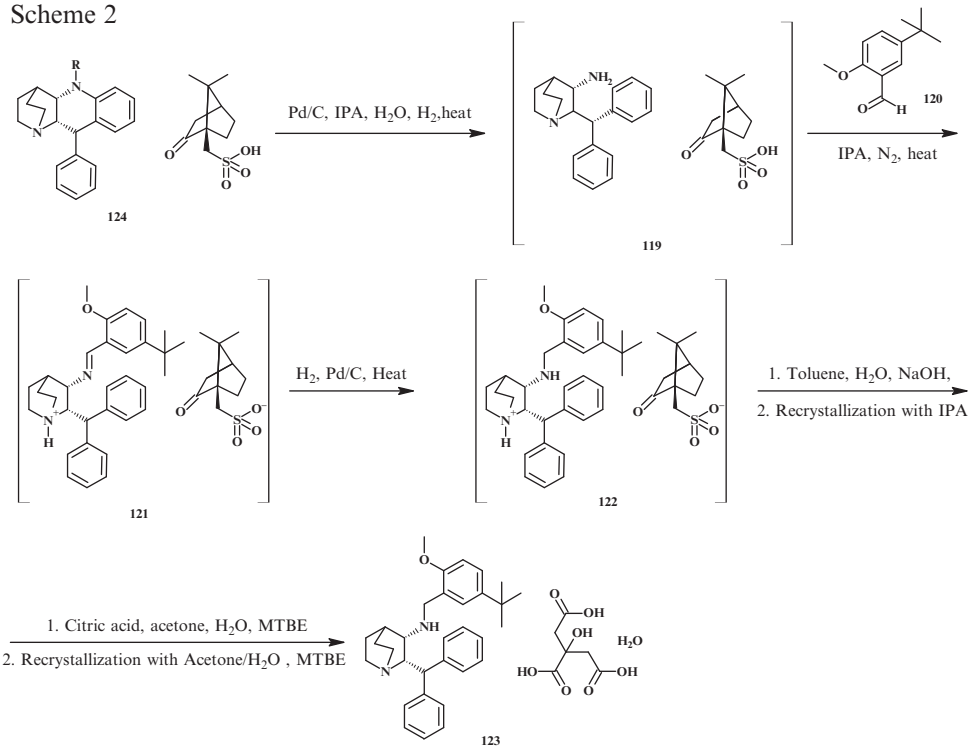
This reaction was preceded by the conceptually related Fukuyama reduction.

12.6.35 Synthesis of Maropitant Citrate Monohydrate [184]

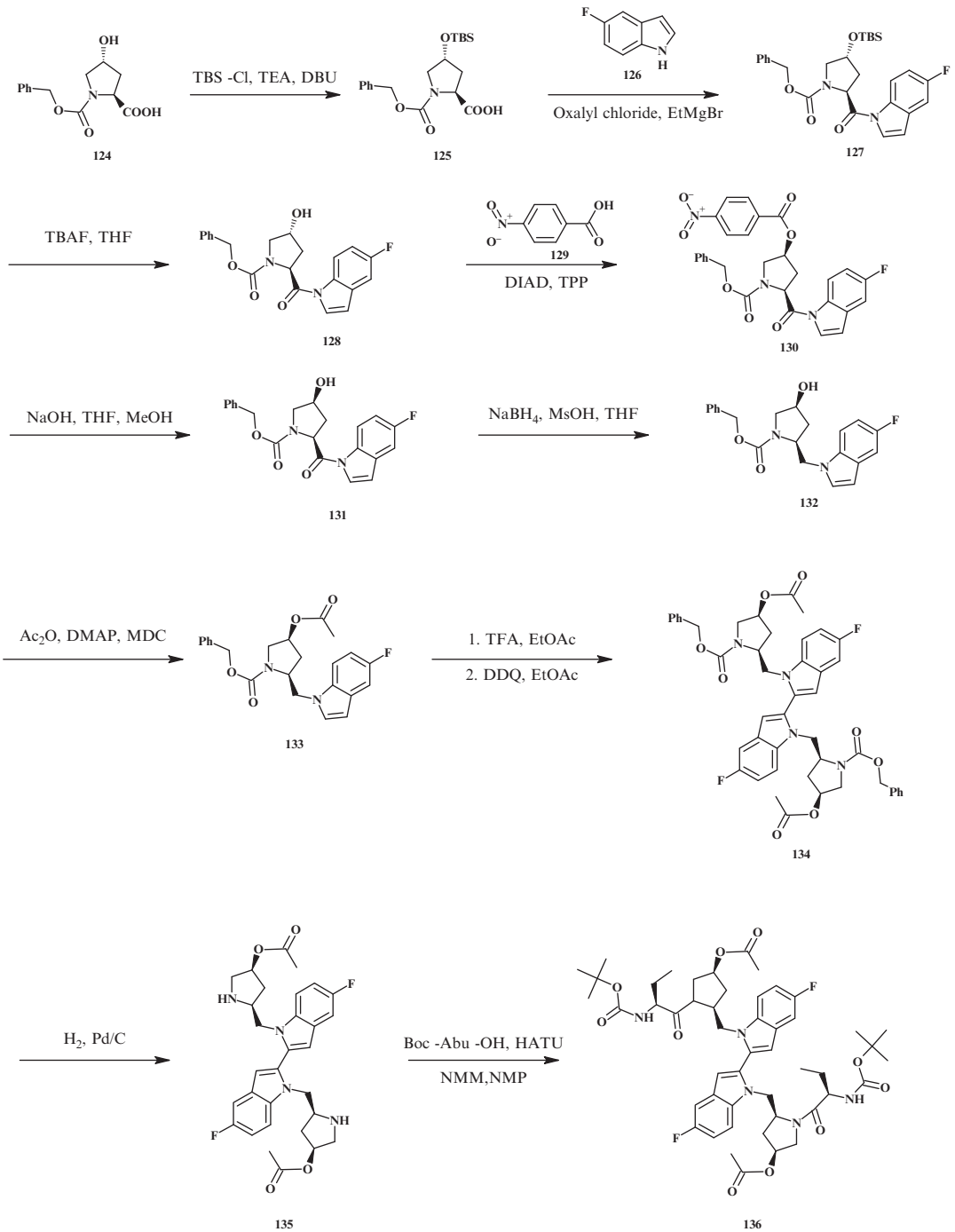
Scheme 1



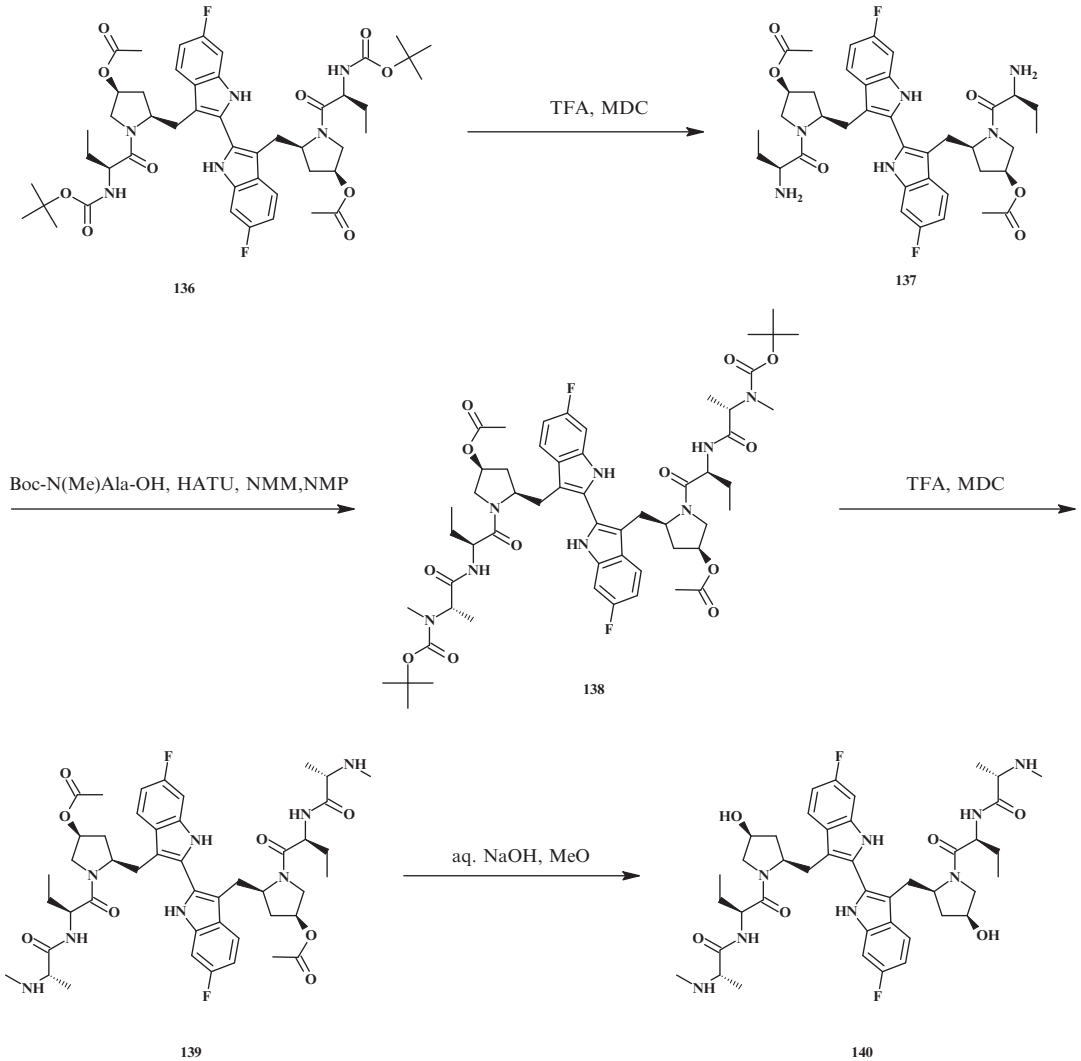
Scheme 2



12.6.36 Synthesis of Birinipitant [185]



Scheme continue.....

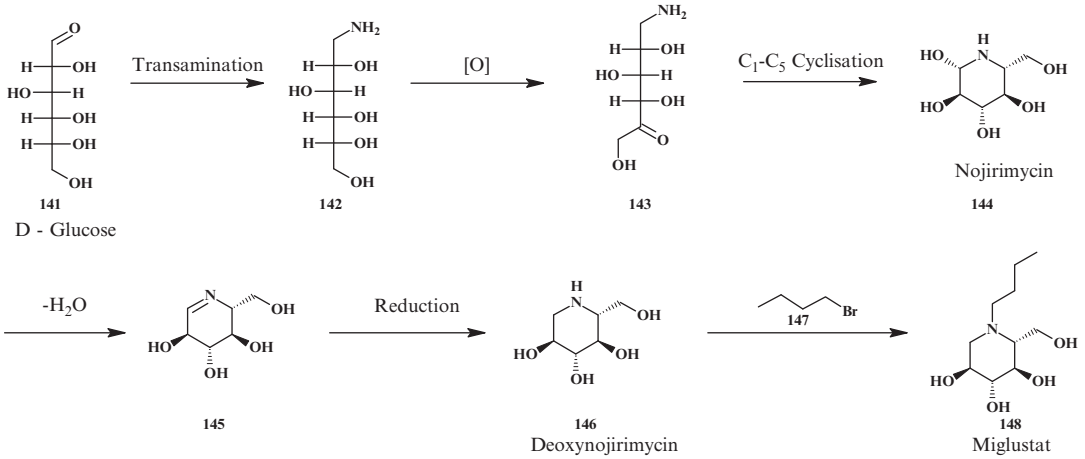


136 137 138 139 140

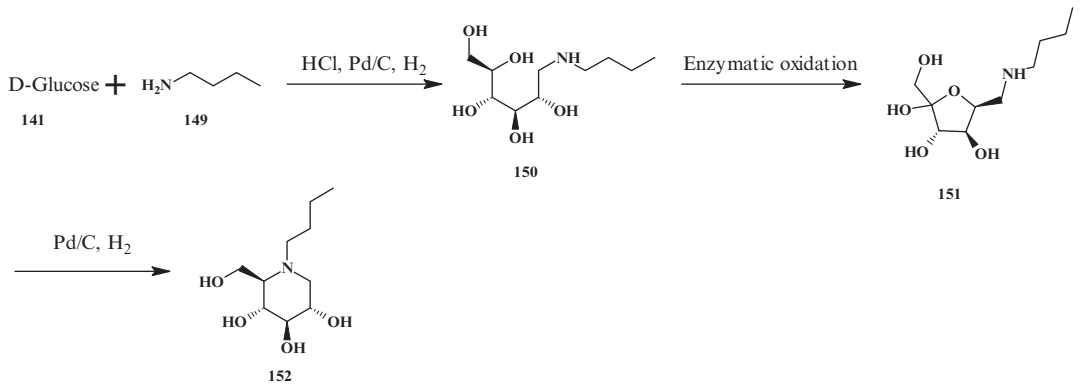
12.6.37 Synthesis of Miglustat

Miglustat is a synthetic derivative of a family of polyhydroxylated alkaloids or an amino sugar extracted from plants and microorganisms. Its synthesis starts from D-glucose sugar in plants. The sugar is then aminated and oxidized to amino fructose sugar, which then can form a cyclic aminohemiacetal called nojirimycin. Then the dehydration and reduction takes place successively before the formation of deoxynojirimycin, which is a precursor of miglustat. Since it is a synthetic derivative drug, alkylation of deoxynojirimycin can be synthesized in the laboratory with 1-butyl halide as described in the scheme [186].

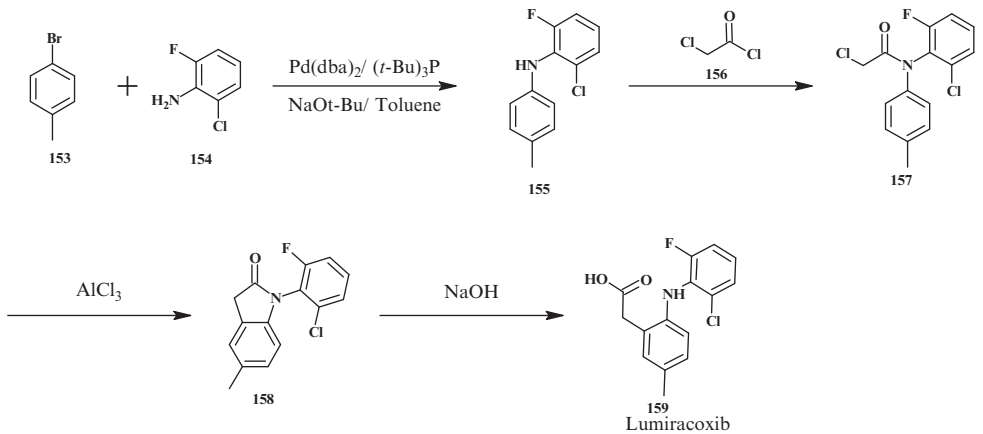
Scheme 1



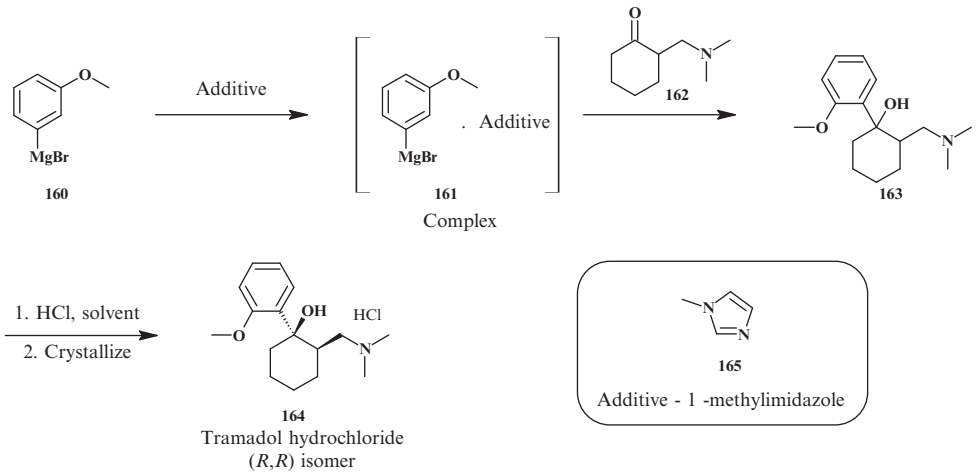
Scheme 2



12.6.38 Synthesis of Lumiracoxib [187]



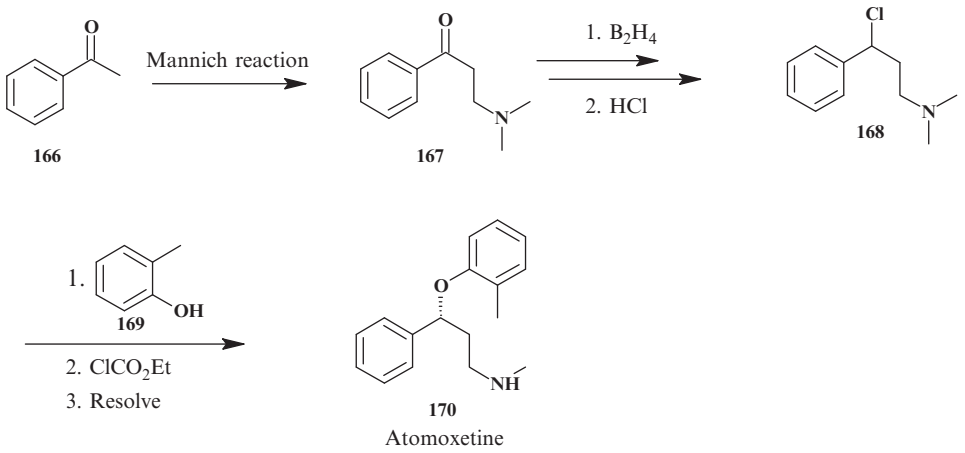
12.6.39 Synthesis of Tramadol



It is reported that 24 g of magnesium turnings under 425 mL of dry THF was added 177 g of *meta*-bromoanisole at such a rate as to keep the reaction at reflux. After the addition, reflux was continued for one hour. At a temperature of 60°C, 77 g of 1-methylimidazole (165) was added. A precipitate formed. The mixture was stirred until all of the precipitate dissolved. The temperature was allowed to fall to 28°C, and then the solution of Mannich base (162) in toluene was added over 15 min, while a temperature rise to 60°C was observed. During 2 h, the reaction mixture was stirred and allowed to cool to room temperature. The mixture was cooled to 15°C and 420 mL of 4 M ammonium chloride in water was slowly added, keeping the temperature under 30°C. To the mixture was added 350 mL of water. The mixture was cooled while 215 mL of concentrated hydrochloric acid was added, giving a pH of 1.0. The top, organic layer was separated and discarded. The aqueous layer was washed with 150 mL toluene and the toluene discarded. The aqueous mixture was cooled in an ice bath and taken to pH 9.5 with 355 mL of concentrated ammonium hydroxide. The mixture was extracted with 140 mL of toluene. The two-phase mixture was filtered before separation to remove insolubles. The aqueous layer was extracted with a second 140 mL of toluene, and the toluene extracts were combined. Small amounts of toluene were added for transfer. Approximately 90 mL of toluene was distilled out to remove water. The toluene solution was assayed to show there is 106 g of a mixture of *trans*/*cis* isomers of (163) there, in a 90.3/9.7 ratio (HPLC). A simple assay of the solution is to remove the solvent from a few milliliters of the sample by rotary evaporation followed by drying in high vacuum. The solution can be used such as in Example 8 type experiments, or concentrated further. An additional extraction of the original aqueous layer with toluene gave 5.4 g more of the desired product (164) [188].

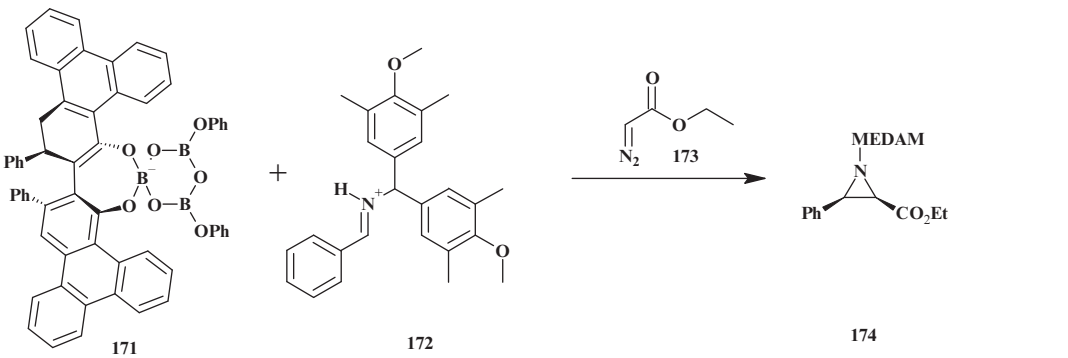
12.6.40 Synthesis of Atomoxetine

Atomoxetine (brand name: Strattera) is a norepinephrine reuptake inhibitor approved for the treatment of attention-deficit hyperactivity disorder (ADHD). First step is a Mannich reaction between acetophenone (166), paraformaldehyde and dimethylamine [189].



12.6.41 Iso-VAPOL Ligand Synthesis

The iso-VAPOL ligand synthesis, solid-state structure and its evaluation as a BOROX catalyst has been reported. The iso-VAPOL ligand is just as effective as VAPOL in the catalytic asymmetric synthesis of aziridines at one-tenth the cost. [190]



The new vaulted biarylligandiso-VAPOL is an isomer of VAPOL but has the chiral pocket of VANOL. The synthesis of iso-VAPOL involves a cycloaddition/electrocyclization cascade (CAEC) similar to one that is used for VAPOL, except that the starting material for iso-VAPOL is less than one-tenth the cost. The solid-state structure of iso-VAPOL was determined as

well as that of VANOL since it had not been previously reported. The structures of iso-VAPOL and VANOL are compared to the known solid-state structure of VAPOL and it is found that all three ligands have the cisoid conformations in the solid-state; the dihedral angle between the two aryl groups is less than 90°. In addition, all three ligands pack in the solid-state with no inter-molecular hydrogen bonds. This is the opposite of what has been reported for BINOL where all known structures exist with transoid conformations where the dihedral angle is >90°, and where the BINOL units pack with hydrogen bonds between neighboring BINOL units. Spectroscopic evidence including ^{1}H and ^{11}B NMR spectra are presented which indicate that the iso-VAPOL ligand will form BOROX catalysts with $B(OPh)_3$ in much the same way as VAPOL catalysts which have previously reported and characterized both by spectroscopy and X-ray crystallography. Support for the BOROX catalysts can also be taken from the fact that iso-VAPOL BOROX catalysts give essentially the same asymmetric inductions as the VAPOL BOROX catalyst over a range of substrates

12.7 Summary

Catalysis has provided an opportunity for reaction efficiency improvement in processes, better enatiomeric selectivity, improved economics, environmental protection, and reduction in waste generation. Multiple choices are available for the selection of catalyst for performance enhancement through fast catalyst screening.

Recent trends in cross-coupling are becoming quite obvious and have been discussed in open literature, [191–200] and covers a number of topics like selecting prominent ligand types, Pd-phosphine pre-catalyst, and Pd N-heterocyclic carbene complexes, etc.

Continuous flow reactors are also reported to be used for catalysis reactions, which includes scale-up and large-scale applications for the synthesis of APIS. Generally, the fine chemical and API industry have smaller volume and employ batch manufacturing processes. Numbers of products are manufactured in the same facility on a campaign basis using the same equipment. Continuous catalytic reactors have been made possible with the advent of flow chemistry development and a few examples are also reported for large-scale manufacturing. For example, most of the large volume APIs, like Paracetamol, Ibuprofen, Sulphamethoxazole, Metformin, and Gebapentine, etc., are manufactured in batch mode, while a few among these, like Ibuprofen, is manufactured in continuous mode. There are a few more popular arylpropionic acids, which may be manufactured by using similar chemistry and catalysis like, Naproxen (Syntex), Ketoprofen (Wyeth-Ayerst), Indoprofen (Farmitalia), Fenoprofen (Lilly), Carprofen (Hoffmann-LaRoche), and Flurbiprofen (Upjohn), etc. Microreactor technology has also shown a way for handling highly exothermic hazardous reactions and the safe use of high pressure, high temperature continuous reactors. There is an urgent need to develop continuous catalytic processes for important large volume drug molecules like HIV drugs.

S. Petrovic and et al., have reported that different types of catalysts are used in the pharmaceutical industry including PTC, Enzyme, Catalyst supported on Ion exchange resins, Bio-catalysis, and Asymmetric synthesis using homogeneous chiral Ruthenium-phosphine catalyst, etc. There is ample scope to extend the use of such catalysts to other API molecules and is expected to grow in the future [201–203].

New challenges in the catalysis include design of catalyst for specific reactions. Complex catalyst structure design may be preferred rather than molecular catalyst. It is possible that the design of catalyst is based on devices used for processes. Attempts are also made for designing adoptive systems and alternatives to fossil feedstock using catalyst by design. The future areas for research could be Nanostructures heterogeneous catalysts, Molecular catalysts systems, predictive catalysis, and new catalytic converters. All these may be applied in the complex drug synthesis or mimicking the process followed by nature [191–194].

It is very essential to develop a process which is not only technically feasible, but also economically as well, the economy challenges of technology development can only be met through integrated efforts in catalysis science and chemical engineering.

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CHAPTER 13

Catalysis for Renewable Chemicals

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13.1 Introduction

Sustainability as a policy concept has its origin in the Brundtland Report of 1987 [1]. The document was concerned with the tension between the aspirations of mankind towards a better life on the one hand and the limitations imposed by nature on the other hand. However, Kuhlman and Farrington [2] in their review article have redefined sustainability as a concern for the well-being of future generations and in particular, irreplaceable natural resources as opposed to the gratification of present needs, which we call well-being. According to them, these two do not need to be in opposition but should complement one another. Thus it goes without saying that renewable resources are pillars of sustainability. Since energy is the backbone for any technology development, efforts towards sustainable development in the earlier days were more focused towards harvesting energy from nonpetroleum resources viz. wind, solar, geothermal, and hydel, though in the strictest sense they would not fall under the purview of renewable as the source is not regenerated in a specific time interval, these therefore are more appropriately coined as alternative sources of energy. The term renewable received significance after it was joined with fuels. Renewable fuels thus are fuels which are replenishable. It is not always evident when a resource can be considered renewable. Kuhlman and Farrington proposed that a resource is nonrenewable if it cannot be recovered or replenished with today's technology within practicable costs and time. In early 1800, petroleum emerged as a major resource for the chemical industry. Environmental awareness leading to legislation of the Clean Air Act by the US EPA, coupled with rising prices of crude oil, and excessive agriculture output, were the main drivers to revisit the idea of exploiting biomass as a renewable resource. Corn became the predominant feedstock for biochemical production because of its abundance and ease of transformation.

A major food vs. fuel controversy arose in 2008, primarily as corn was the main feedstock for bioethanol and edible oils such as soya, rapeseed, canola, and corn were being used for biodiesel. Cellulose being the largest resource of carbohydrate sugars, the focus naturally shifted from simple carbohydrate feedstock to the more complex form of lignocellulosic feedstock. This gave birth to exploration of second generation feedstock for renewable

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chemicals. This shift brought forth numerous challenges. Second generation feedstock being quite complex in nature, getting sugars out for fermentation proved equally challenging and cost-intensive. As a consequence, many of the industrial players and researchers shifted their focus from fuels to renewable chemicals which were a better value proposition in terms of pricing and volumes traded.

13.2 Feedstock

Feedstock perhaps has been one of the challenges to commercializing large biorenewable projects. The nature of feedstock has undergone considerable change in its composition since the early days of renewable chemicals and fuels. In the early days, renewable feedstocks were majorly exploited by fermentation. As a result, the earliest feedstocks were those that were easiest to ferment. Molasses, a by-product of sugar industry, was the first to be explored, followed by starch containing feedstocks viz. tubers and grain, and finally now it is the lignocellulosic feedstock such as wood and agri-waste. As the carbohydrate feedstocks transitioned from molasses to lignocellulosic material, oil-bearing feedstocks, too, followed a similar movement from simple to processed edible oil-bearing seeds such as rapeseed and soya, to corn gradually encompassing nonedible oil seeds (like castor, jatropha), industrial by-products (acid oil, deodorizer distillate), and unconventional exploratory feedstocks, such as algae.

13.2.1 Feedstock Pretreatment

The transition of feedstock emphasized the need for a pretreatment process to make the raw material molecule available for process reaction.

Molasses C typical composition consists of 40–50% sugars (sucrose, glucose, and fructose), 8–12% inorganic matter, and 8–12% water. The rest of the composition is made up of mostly organic substances generated during sugar processing. These include caramelized sugars, melanoidins, humins, and other complex coloring matter. Thus, the use of molasses as a feedstock for processes other than established yeast fermentation without any cleaning, would definitely involve process challenges. Hence, efforts are necessary to clean molasses for removal of unwanted impurities, especially if it has to be processed using a heterogeneous catalysis process. Starch-based feedstocks are much cleaner and easier to handle as the feed is composed of a single sugar type, predominantly glucose and its oligomers (chain length max 3–4 units). The use of starch-bearing material is facilitated by suitable hydrolysis processes wherein starch is hydrolyzed to release free glucose. Various enzymes are commercially available for starch hydrolysis [3]. Lignocellulosic materials are an intimate mixture of cellulose, hemicellulose, and lignin that are difficult to separate and to process (Fig. 13.1).

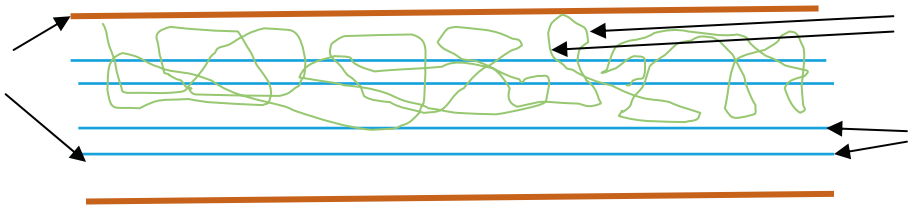


Fig. 13.1
Schematic structure of cellulose.

Its utilization involves two major approaches. First, wherein a fractionation process separates these three components, and each of the components is then processed in a different manner to yield a different product, whereas in the second approach, the entire biomass is converted either into a complex liquid or gasified into a mixture of simple gaseous products which are reconstituted using special catalysts to yield value added chemicals.

As mentioned earlier in the text, these three components have diverse chemical properties. Cellulose is a polymer composed of glucoside units connected via b-1,4-glycosidic linkages; as compared to hemicellulose, it is more stable and difficult to hydrolyze by chemicals or enzymes. Hemicellulose on the other hand is more easily hydrolyzed than celluloses and is composed of pentose such as xylose and arabinose. Both cellulose and hemicellulose are potentially a very important, largely untapped renewable source of chemicals (Fig. 13.2).

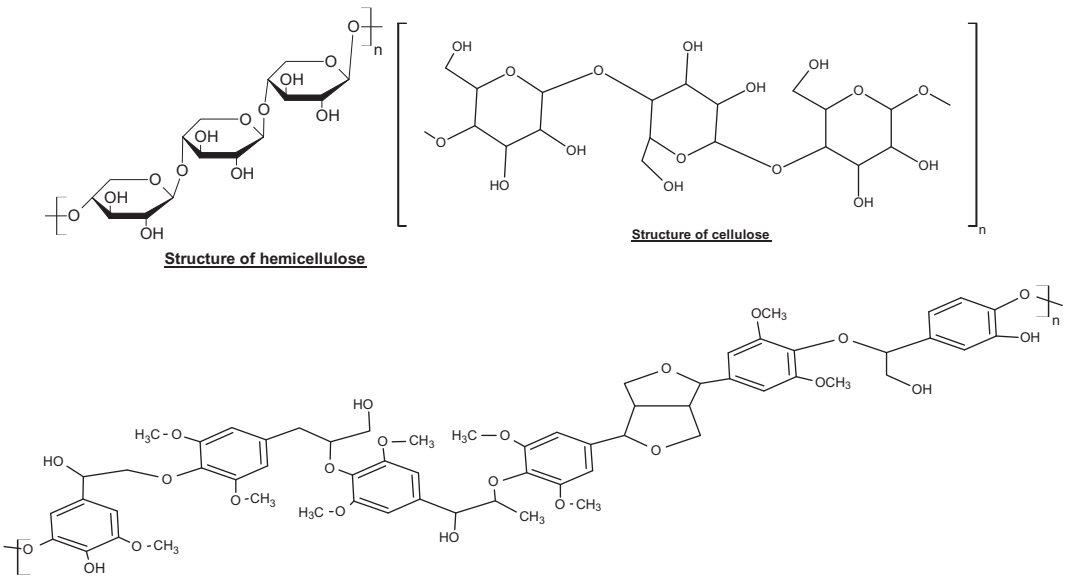


Fig. 13.2
Components of lignocellulose.

Lignin has a very complex polymeric structure based on interconnected aromatic derivatives and by nature, is recalcitrant to hydrolysis. Arrival of lignocellulose feedstocks generated a whole new activity of feedstock pretreatment [4]. Various pretreatment methods have been reported in literature, wherein these components are separated from each other, taking advantage of the difference in their chemical properties. We shall not discuss them here as it falls outside of this book's purview (Fig. 13.3).

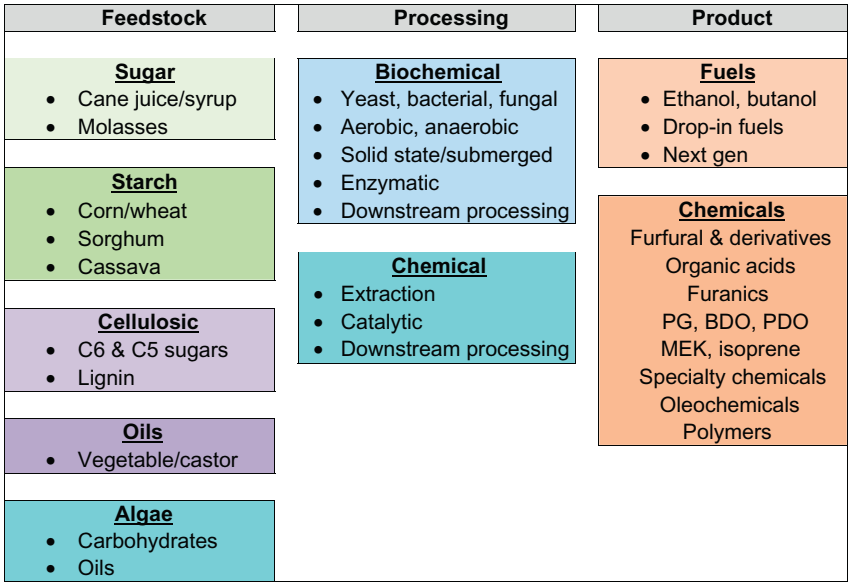


Fig. 13.3
Typical bio-refinery model.

In fact, biomass processing has become analogous to petroleum refinery and has graduated from a biofuel producing unit to a bio-refinery complex, wherein numerous products are afforded from a single biomass source. For this bio-refinery model to be successful, new processes will need to be developed for the bio-refinery to parallel the chemical refinery in terms of process cost, efficiency, and environmental impact.

13.3 Selection of Biochemicals

Most of the biochemicals that are being pursued over the last decade find their origin in the report [5] jointly prepared by Pacific Northwest National Laboratory (PNNL) and the National Renewable Energy Laboratory in 2004. The main objective of this study report was to identify the top 10 opportunities for the production of value added chemicals from biomass that would economically and technically support the production of fuels and power in an integrated bio-refinery, and identify the common challenges and barriers of associated production technologies.

To begin, a group of over 300 possible building block chemicals was assembled from a variety of resources, including previous DOE and National Laboratory reports and industry and academic studies. The initial screening criteria included the cost of feedstock, estimated processing costs, current market volumes and prices, and relevance to current or future bio-refinery operations. These 300 chemicals were subjected to bio-refinery fit criteria table as mentioned in Table 13.1.

Table 13.1 Selection matrix for biochemical selection

	Direct Product Replacement	Novel Products	Building Block Intermediates
Characteristic	Competes directly against existing products and chemicals derived from petroleum	Possesses new and improved properties for replacement of existing functionality or new applications	Provide basis of a diverse portfolio of products from a single intermediate
Examples	Acrylic acid obtained either from propylene or lactic acid	Polylactic acid (glucose via lactic acid is the sole viable source	Succinic, levulinic, glutamic acids glycerol, syngas
Upside	Markets already exist. Easy to understand cost structures and growth potential. Substantially low market risk	Novel products with unique properties hence, cost issues less important. No competitive petrochemical routes. Differentiation usually based on desired performance. New market opportunities. Most effective use of properties inherent in biomass	Product swing strategies can be employed to reduce market risks. Market potential is expanded. Capital investments can be spread across wider number of unit operations. Incorporates advantages of both replacement and novel products
Downside	Strictly competing on cost. Competing against depreciated capital	Market not clearly defined. Capital risk is high. Time for commercialization may be long	Identifying where to focus R&D

Almost 50 potential building block candidates resulted from this initial screening. Continuing to use the strategic fit criteria (direct replacement, novel properties, and potential utility as a building block intermediate) shown in Table 13.1, the 50 potential candidates were fitted using a carbon number classification framework of one to six carbon compounds as shown in Table 13.2.

From this table going forward, a final list of 12 building block chemicals from sugar were short-listed as shown in Table 13.3.

All though most of the chemicals explored in this study were for identification of potential building blocks, there exists many other biochemicals not included in this scope of study. These are generally molecules having high value applications in the domain of pharma, foods, and

Table 13.2 Rationale for biochemical selection

C No.	Name	Projected or Known Use	Selected for Top 30	Rationale
1	Formic acid	Reagent	N	Very limited use as BB, use mostly for adding C1
1	Methanol	BB	N	Super commodity. Can be obtained from syngas
1	Carbon monoxide (+H_2 gives syngas)	BB	Y	
1	Carbon dioxide	Reagent	N	Thermodynamic barrier
2	Acetaldehyde	Intermediate	N	Very limited use as BB
2	Acetic acid & anhydride	Reagent and intermediates	N	Limited use as BB, large commodity scale today from syngas. Adds C2
2	Ethanol	Fuel	N	Major use envisioned as fuel. Limited BB. Likely to be a super commodity.
2	Glycine	Reagent	N	Very limited BB. Few uses envisioned
2	Oxalic acid	Reagent	N	
2	Ethylene glycol	BB& product	N	
2	Ethylene oxide	BB& reagent	N	
3	Alanine	Intermediate	N	
3	Glycerol	BB	Y	
3	3-Hydroxypropionic acid	BB	Y	
3	Lactic acid	BB	Y	
3	Malonic acid	BB& reagent	Y	
3	Serine	BB	Y	
3	Propionic acid	BB & reagent	Y	
3	Acetone	Intermediate	N	Super commodity. Obtained as by-product from cumene to phenol synthesis
4	Acetoin	Intermediate	Y	
4	Aspartic acid	BB	Y	
4	Butanol	BB	N	Large commodity chemical, not a good BB, but large intermediates market. No competitive advantage from biomass
4	Fumaric acid	BB	Y	
4	3-Hydroxybutryolactone	BB	Y	
4	Malic acid	BB	Y	
4	Succinic acid	BB	Y	
4	Threonine	BB	Y	
5	Arabinitol	BB	Y	
5	Furfural	BB	Y	

Table 13.2 Rationale for biochemical selection—cont'd

C No.	Name	Projected or Known Use	Selected for Top 30	Rationale
5	Glutamic acid	BB	Y	
5	Glutaric acid	BB	N	Very limited market. Intermediate set of derivatives
5	Itaconic acid	BB	Y	
5	Levulinic acid	BB	Y	
5	Proline	BB	N	Limited market. Intermediate set of derivatives
5	Xylitol	BB	Y	
5	Xylonic acid	BB	Y	
6	Aconitic acid	BB	Y	
6	Adipic acid	Intermediate	N	Super commodity. Examined previously by DOE/industry with little success
6	Ascorbic acid	BB	N	Limited market. Intermediate set of derivatives. Subject of successful NIST ATP work
6	Citric acid	BB	Y	
6	Fructose	BB	N	Other routes to derivatives would be easier than from fructose
6	2,3 Furan dicarboxylic acid	BB	Y	
6	Glucaric acid	BB	Y	
6	Gluconic acid	BB	Y	
6	Kojic and comeric acid	BB	N	Very limited market. Intermediate set of derivatives
6	Lysine	BB	Y	
6	Sorbitol	BB	Y	

BB, building block.

cosmetics. The markets for these biochemicals adhere to a typical cost: consumption relationship as depicted in the Fig. 13.4.

13.4 Biocatalysis

Biocatalysis is the use of nature's catalysts viz. enzymes, to perform chemical transformations of organic compounds. These transformations involve enzymatic or fermentative conversions. Enzyme-based processes operate at lower temperatures; produce less toxic waste, and

Table 13.3 Final list of selected biochemical building blocks

Building Blocks
1, 4-Diacids (succinic, fumaric malic)
2,5-Furan dicarboxylic acid
3-Hydroxypropionic acid
Aspartic acid
Glucaric acid
Glutamic acid
Itaconic acid
Levulinic acid
3-Hydroxybutyrolactone
Glycerol
Sorbitol
Xylitol/arabitol

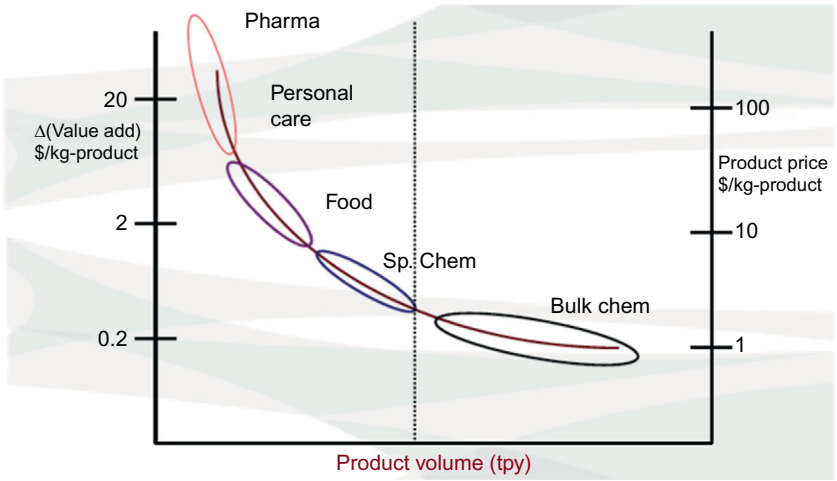


Fig. 13.4
Cost and consumption based classification of biochemicals.

fewer emissions than conventional chemical processes. Precise chemical selectivity allows enzymes to use less purified raw materials. These characteristics can be exploited to increase the energy efficiency and improve the environmental profile of chemical reactions used in manufacturing. As a result, biocatalysis has a great potential for wide range of industrial applications. Enzymes that have been more or less isolated, or enzymes still residing inside living cells both are employed for biocatalysis.

13.4.1 Advantages of Biocatalysis

The most important advantage of enzymes lies in their ability to selectively catalyze reactions forming the specific desired product. This ability is a combined result of three major types of selectivity displayed by enzymes.

(a) *Chemoselectivity*: Since the purpose of an enzyme is to act on a single type of functional group, other sensitive functionalities, which would normally react to a certain extent under chemical catalysis, would not be affected by the enzyme. Furthermore, the enzymes act under mild conditions, thereby minimizing undesired side-reactions such as isomerization, racemization rearrangement, and decomposition which often plague traditional methodology. Thus biocatalytic reactions tend to be "cleaner." As a result, laborious purification of product(s) from impurities emerging through side-reactions can largely be omitted.
(b) *Regioselectivity and diastereoselectivity*: Due to their complex three-dimensional structure, enzymes that may distinguish between functional groups, though chemically similar, are situated in different regions of the substrate molecule, thereby promoting highly stereo-specific and regio-specific conversions.
(c) *Enantioselectivity*: Since almost all enzymes are made from L-amino acids, enzymes are chiral catalysts. As a consequence, any type of chirality present in the substrate molecule is "recognized" upon the formation of the enzyme-substrate complex. Thus a prochiral substrate may be transformed into an optically active product and both enantiomers of a racemic substrate may react at different rates. Thus, pharmaceutical chemists have a great interest in the use of biocatalysts, especially in racemic synthetic steps.

Another important advantage of biocatalysts is that they are completely biodegradable in the environment and hence, are environmentally friendly.

13.4.2 Classification of Enzymes

According to the International Union of Biochemistry and Molecular Biology (IUBMB), the enzymes are classified into six main classes [6] as follows:

(a) *Oxidoreductases*: They catalyze oxidation and reduction reactions that occur within the cell involving oxygenation, or overall removal or addition of hydrogen atom equivalents. These types of enzymes are widely used in industrial reactions. They require cofactors such as nicotinamide adenine dinucleotides (NAD) and flavines (FAD) in the reactions. Examples of such classes of enzymes include dehydrogenases, oxidases, oxygenases, and peroxidases.
(b) *Transferases*: They catalyze the transfer of functional groups (eg, amino, methyl, hydroxymethyl, glycosyl, acyl, alkyl, phosphate, and sulfate groups) by means of a nucleophilic substitution reaction. The industrial applications of transferases include the use of various glycosyltransferases for the synthesis of oligosaccharides. Examples of this class include methyltransferases, aminotransferases, kinases, and phosphorylases.
(c) *Hydrolases*: They catalyze the addition of water to a substrate (hydrolysis). Hydrolytic enzymes are more commonly used in organic synthesis to produce intermediates for

pharmaceuticals and pesticides. Examples of this class include phosphatases, amidases, proteases, esterases, and lipases.

(d) *Lyases*: These enzymes are responsible for catalyzing addition and elimination reactions. Lyases are enzymes cleaving C–C, C–O, C–N, C–S, and other bonds by elimination, leaving double bonds or rings, or conversely adding groups to double bonds. Lyases are found in cellular processes in organic synthesis, the citric acid cycle, and in the production of cyanohydrins. Examples of this class of enzymes include decarboxylases, aldolases, and synthases.

(e) *Ligases*: They catalyze the formation of bonds between two molecules or they join two molecules. These enzymes catalyze reactions that involve the creation of chemical bonds with nucleotide triphosphates. They are important in certain cellular processes, such as connecting nucleotides in DNA replication. Examples of this class of enzymes include synthetases and carboxylases

(f) *Isomerases*: These types of enzymes catalyze the rearrangement of atoms within a molecule such as racemization and epimerization. The successful isomerase-based process involves the use of glucose isomerase for the production of high-fructose corn syrup, which is used as an alternative sweetener to sucrose in the food and beverage industry. Examples of this class include racemases and mutases.

13.4.3 Michaelis-Menten kinetics

As with standard chemical reactions, biocatalytic reactions also have characteristic kinetics and reaction rates based on the reaction equation. Enzyme catalyzed reactions are best expressed by Eq. (13.1) also known as Michaelis-Menten kinetics

$$v = \frac{V_{\max} S}{K_m + S} \tag{13.1}$$

where $V_{\max}$ is the maximum rate of reaction and K_m, the Michaelis constant gives a sense of the affinity of the enzyme for the substrate. Note that when $[S] \gg K_m$ (small K_m = high affinity), the reaction kinetics are first-order with respect to the enzyme concentration, and equal to the max rate $V_{\max}$. When $[S] \ll K_m$ (large K_m = low affinity), the kinetics are first order with respect to substrate concentration.

To determine the parameters of interest, one can graphically represent the data. Rearranging the Eq. (13.1) as

$$\frac{1}{v} = \frac{V_{\max}}{K_m} \times \frac{1}{S} + \frac{1}{V_{\max}}$$

A plot of $1/v$ versus $1/S$ will give a Lineweaver-Burke plot, where the slope is $K_m/V_{\max}$ and the y-intercept is $1/V_{\max}$. Note that the reaction rates should be *initial* rates, determined when the substrate is in excess and essentially constant.

For design purposes, one will need to know the kinetic parameters to size a reactor and set the process cycle time. However, for the initial selection process, one can choose an enzyme based on conversion, yield and selectivity and determine the kinetic characteristics after selection of best enzyme for the process.

$$\text{Conversion} = X = \frac{Si - Sf}{Si} \times 100\%$$

$$\text{Yield} = \frac{Pf - Pi}{Si} \times 100 \text{ for each product}$$

If the products are chiral, one can estimate *ES* (elantioselectivity) as

$$ES(R) = \frac{R - S}{R + S} \times 100\%$$

While the kinetics is important for an efficient process, these can often be optimized by adjusting the reaction conditions (eg, pH, temperature, cosolvents, etc.). One can use basic engineering knowledge for optimization to get the fastest reaction. It is much more difficult to control the selectivity, and is more likely to require a *biological* optimization rather than standard physicochemical-based *engineering* optimization. Mostly in chiral reactions, one would like an enzyme to deliver the highest *ES* material possible, while also achieving "good" conversions in the initial phase. The goal of process development is to then make that good conversion better.

13.4.4 Types of Biocatalysis

13.4.4.1 Bio-Transformations and Fermentations

(a) *Bio-transformations*: Specific modification of a precursor to a defined product with structural similarity using one of the abovementioned transformations is called a bio-transformation or bioconversion. Such transformations demand use of highly specific pure enzymes. For industrial purposes, the desired enzymes are isolated from microbial strains and their growth is optimized to obtain a sufficient quantity of enzymes. The enzymes may be produced extracellular (ie, secreted in the medium) or intracellular. The enzymes are then separated by downstream processing and further purified to desired purity levels. Commonly used techniques for enzyme purification include ultra high speed centrifugation, electrophoresis, and chromatography (gel permeation, affinity, or ion-exchange). These purification techniques are cost-intensive and purified enzymes are highly expensive. The cost contribution in process can be significantly reduced by using the enzymes which are immobilized and thus offer convenience in the recycle. Immobilization also imparts stability to the enzymes.

(b) *Fermentations*: Many biological conversions involve longer pathways, comprising many reaction steps. Such types of conversions are generally termed as fermentations. The fermentation technology is generally based on metabolic pathways of a living

microbial cell (either a wild type or an engineered type). These cells are cultured in a fermentation vessel under controlled optimum conditions of temperature, pH, and dissolved oxygen to enhance the growth of selected microbes while preventing contamination by undesired microorganisms. During fermentation, the cells grow and synthesize new enzymes and cofactors, which in turn are utilized for desired enzymatic conversion. Many times fermentations involve coupling of cofactors for few enzymatic steps, requiring additional enzymatic reactions along with specific cofactors. Parales et al. [7] have reported successful deployment of multienzyme systems on laboratory scale. As a result of many sequential and parallel enzymatic reactions occurring in fermentative conversions, the product of metabolic activity usually bears no structural resemblance to the compounds supplied to the microorganism.

13.4.4.2 Isolated Enzymes and Whole-Cell

Isolated, as well as whole-cell enzymes are currently used as biocatalysts. The whole-cell enzyme catalyst is used when bio-transformation reactions require multiple enzymes, or when it gets difficult to isolate the enzyme from the cell. To obtain the desired product, the whole-cell based biocatalyst system utilizes an entire microorganism. The advantages of whole cell system include selective synthesis using cheap and abundantly available raw materials (like corn starches) and they catalyze multistep reactions. The enzymes are more stable in the long run as compared to free enzymes, as the enzymes in whole cells are protected from the external environment. The activity of an enzyme will depend on how much enzyme is present. The *specific activity* is defined as the amount of material converted per unit time per mass of enzyme, for example:

$$\text{Specific Activity} = \frac{\text{Moles of substrate}}{\text{mg of protein} \times \text{min}}$$

While screening a free enzyme system, one can fix the catalyst amount and compare specific activity among the different samples for selecting the best enzyme. On the other hand, the whole cell screen gives varying amounts of cells. In order to then compare specific activity, one must normalize based on cell mass. We can define a whole cell based specific activity as follows:

$$\text{Specific Activity} = \frac{\text{Moles of substrate}}{\text{mg of cells} \times \text{min}}$$

Two novel industrial processes that utilize whole-cell biocatalysts are

(a) Production of L-lactic acid, used as a food additive and an important feedstock for the production of other chemicals such as polylactic acid, acetaldehyde, polypropylene glycol, acrylic acid, and pentadione [8].

(b) 1,3-Propanediol (PDO) is an intermediate widely used in the synthesis of polyesters and polyurethanes [9]. However, the whole cell system has certain drawbacks and many a times in vitro single-enzyme or multienzyme systems may achieve higher volume-specific productivity than in vivo cell systems, because living cells will require additional activities related to membrane transport, synthesis of macromolecules, and regulation mechanisms not required for the actual conversion [10]. In addition to higher productivity, isolated enzymes have numerous benefits like simpler product purification and the use of simple reaction apparatus [11].

13.4.5 Biocatalyst Immobilization

Most of the processes catalyzed by enzymes for technical and economical reasons, necessitate reuse, or continuous use, and stabilization of the biocatalyst for a longer duration. Enzymes are in aggregates with other entities, or as attached (or immobilized) to inert solid support. These can also catalyze reactions in a similar manner as individual molecules in solutions. In fact, immobilization of enzymes improves the operational stability as a result of increased enzyme loading and reduces the effluent treatment costs as compared to free enzymes. Immobilized enzymes are more resistant than living cells to extreme conditions of temperature, pH, organic solvent, and substrate and product concentrations. The term immobilized enzymes refers to enzymes physically confined or localized in a defined region of space with retention of their catalytic activities, which can be repeatedly and continuously used [12]. The solid support can be organic or inorganic material. Typical examples of solid supports used for immobilizing enzymes include cellulose, silica, glass, ceramics, proteins, carbon, metallic oxides, and various membranes. The method of immobilization and its support material depends on the type of desired application. Hence, from an industry point of view, cost-effectiveness and easier means are essential properties of immobilization techniques.

The long-term reuse of immobilized enzymes in industry also needs the preparation of stable derivatives having accurate functional properties for a given reaction [13]. Enzymes can be immobilized in various ways, depending on the enzyme to be immobilized and its desired application. Some of these include

(a) *Covalent binding*: It is a conventional method of immobilization, which can be achieved by directly attaching the enzyme to the material through covalent linkage [14]. The isolated enzymes are usually attached through amino, ether, thio-ether, or carboxyl groups to a solid support (eg, porous glass, cellulose, ceramics, metallic oxides). This is a widely used technique for stable nature of bonds formed between enzymes and matrix and the enzyme is not released into the solution on use.
(b) *Adsorption*: Ion exchangers are commonly used in industry to adsorb enzymes as adsorption due to ion-exchange offers operational stability to enzyme. Typical examples

include cation and anion exchange resins such as diethylaminoethyl cellulose carboxymethylcellulose (CM-cellulose), etc.

(c) *Entrapment in polymeric gels*: The technique is based on the occlusion of an enzyme within a polymeric network, which retains the enzymes but allows the substrate and products to pass through. Enzymes are trapped in gel volume by changing temperature or adding a gel-inducing chemical. Enzymes are covalently or noncovalently bonded to the gel, which in most cases is made up of calcium alginate. The technique is fast and cheap hence, offering certain advantages, but has limitations for mass transfer.

(d) *Intermolecular cross-linking*: The technique involves cross-linking of enzymes with bi-functional reagents such as glutaraldehyde, dimethyl adipimidate, and aliphatic diamines.

(e) *Encapsulation*: In this technique, enzymes are enveloped in devices (such as hollow fibers, cloth fibers, microcapsules, film semipermeable membrane), which allows low molecular weight substrates and products to pass through the membrane [15]. The method imparts availability of large surface area between polymeric material and the enzyme however many a times there is a partial loss of enzyme activity during encapsulation [16].

13.4.6 Use of Immobilized Enzymes for Biodiesel Production

Biodiesel has gained importance in the recent past for its ability to replace fossil fuels, which are likely to run out within a century. Especially, the environmental issues concerned with the exhaust gases emission by the usage of fossil fuels also encourage the usage of biodiesel, which has proved to be far more eco-friendly than fossil fuels. Biodiesel fuel does not produce sulfur oxide, halogens, carbon monoxide, and minimizes the soot particulate [17].

Biodiesel fuel (fatty acid methyl esters, FAME) produced by transesterification of triglycerides has attracted considerable attention as a renewable, biodegradable, and nontoxic fuel [18]. Recently, lipase-catalyzed transesterification has become more attractive for biodiesel production since the glycerol can be removed easily and the purification of FAME is simple [19]. Biodiesel can be produced from vegetable oils, animal fats, microalgal oils, and waste products of vegetable oil refinery or animal rendering and used frying oils.

Immobilized enzymes could be employed in the biodiesel production with the aim of reducing the production cost by reusing the enzyme [20]. Literature about the biodiesel production by immobilized enzymes shows that most of the researchers have used lipases from different sources for biodiesel production. Different immobilization supports like ceramics, kaolinites, silica, and zeolites have been used for lipase immobilization [21]. Costs of chemical biodiesel production have still been lower than those of the enzymatic processes, however if the pollution of the natural environment is also taken into consideration, these costs are comparable [22].

13.4.7 Nonaqueous Biocatalysis

Enzymes are highly specific catalysts and function in natural aqueous solvents. But the majority of the bio-transformation reactions in industrial synthesis often involve organic molecules insoluble in water. The reaction conditions generally necessary for chemical synthesis, such as high temperatures or pressures, organic solvents, etc., are mostly unfavorable for enzymes. While the enzymes can work in organic solvents, their activity considerably slows down as compared to that in water [23]. Protein engineering and directed evolution have aided in the development of enzymes that show improved activity in organic solvents [24]. The nonaqueous biocatalysis finds applications in synthesis of pharmaceutical precursors and drugs like pure enantiomers, single isomers, chiral molecules, biopolymers, etc. Because of high heat of vaporization and high boiling point, water is the least desired solvent of choice for organic reactions [25].

Recent developments have succeeded in producing highly active biocatalysts for use in organic reactions by developing simple, scalable, and low cost techniques. Some recent techniques include physical, chemical approaches to site-directed mutagenesis, lyophilization (freezedrying), and molecular techniques, and also by using ionic liquids as solvents in biocatalytic reactions [26].

13.4.8 Design Strategy

For both purified enzymes and whole-cells based processes, the following basic guidelines can be followed for designing a biocatalytic process:

(a) selecting a catalyst, either enzyme or whole cells
(b) establishing a baseline process
(c) process optimization
(d) determine optimal process configuration for targeted delivery

The number of catalysts to be screened with whole cells based process will typically be larger than for a purified enzyme due to lack of information available about whole cell system versus an enzyme which is more or less well defined. Initial screening process for a whole cell biocatalysis may also include medium optimization, substrate inhibition and catabolite repression studies.

Once the initial candidate enzyme/cells are identified initial kinetic data is collected to achieve conversion within a certain amount of time. For a free enzyme process, one can always add more catalyst while whole cell processes typically run at the maximum achievable cell density.

To identify product inhibition challenges reactions must be carried out in the presence of end products and then study its impact on reaction kinetics and equilibrium. Similarly, substrate-product mass balance will indicate whether by-products exist. While establishing

a baseline process, it is not necessary to fully characterize the by-products or determine inhibition constants. It is standard practice to optimize the pH and temperature, for purified enzyme systems and for whole cell growth or conversion. Optimization of a medium is carried out for whole cells based process for both and growth and conversion stage. In the case of enzyme catalyzed reactions, optimization of a buffer is carried out as different salts (ions) affect enzymes to different extent.

At the end of process optimization, one should have identified each design challenge and also established operating range and operational limits. Since the space time depends on a starting substrate concentration, one only need to know the total mass to determine the volume (or flow rate for a fixed volume) needed for conversion. If it's not a continuous process, one will need to calculate the number of runs (for batch or fed-batch reactors) necessary to achieve target mass. For a plug flow reactor (PFR), the time is a space time, in which concentration varies as a function of position (distance) in the reactor. For a batch reactor (BR), concentration varies as a function of actual time. The flow rate for BR and PFR is a volumetric flow rate. For a Continuous Stirred Tank Reactor (CSTR), the flow rate is usually defined as a mass or molar flow rate, and if this is set, the reactor volume is what needs to be determined.

One can also use the specific activity to do an algebraic determination of required conversion time. This is analogous to a reaction velocity and is sufficient if the rate doesn't change appreciably with substrate concentration (ie, large km). Given a certain enzyme or cell concentration, one can calculate activity per unit volume, and then determine the time needed to achieve a desired conversion based on the production target. The total batch cycle time should include growth time (for a whole cell process), conversion time, and vessel prep/ turnaround time.

13.4.9 Key Issues in Scale-Up

In principle, the design and analysis of biocatalytic system can be done by combining knowledge of the kinetics of biological reactions with material and energy balances. However, in practice, the degree of complexity of these systems increases due to time varying properties of biological catalyst which may show complex kinetic patterns. Also, depending on the nature of biocatalysts, the fermentation broth may exhibit complex flow patterns and deviation from ideality depending on the viscosity of fermentation broth. In case of high viscosity fermentations, imperfect mixing could occur at large scale, resulting in broad residence time distribution and may have a significant effect on the extent of any microbial or enzymatic reaction. Most biological reactions are multiphase systems where biocatalyst may be present as a solid phase, for example, as an immobilized enzyme or as an individual cell. In case of aerobic fermentations, gas is sparged into a bioreactor to supply oxygen and remove carbon dioxide. To achieve the desired degree of conversion of reactants to products, or to supply sufficient nutrients for optimal cell growth, interphase heat and mass transfer must occur to a sufficient

extent and at an optimal rate. The transport of O_2, CO_2, and other sparingly soluble gases is one of the major challenges in scale up of bioreactors.

13.4.10 Role of Genetic Engineering in Biocatalysis

Most of the enzymes required for specific conversions may not be produced on a commercial scale. However, recent advances in biotechnology techniques have enabled the development of many biocatalytic tools which are used in industrial applications. Biotechnology enables scientists to maximize the effectiveness and efficiency of enzymes and microbes, or to custom-tailor the specificity of enzymes, improve catalytic properties, or broaden the conditions under which enzymes can function so that they are more compatible with existing industrial processes. With the help of bioinformatics tools and libraries' researchers, companies are beginning to design and create novel microbial systems that perform multistep processes to metabolize renewable sugars into chemical building blocks, monomers, polymers, and acids. Genetic engineering is one such tool that enables industrial biotechnology researchers to improve nature's enzymes or develop diverse microbial systems from bacteria, yeasts, and fungi to marine microorganisms that produce desired concoctions of enzymes at scales enabling their use in industrial applications. Scientists search for enzyme-producing microorganisms in the natural environment (bioprospecting) and then use genomic, proteomic, and bioinformatics tools to identify genes that express enzymes with specific biocatalytic activities. Once identified, the enzymes are characterized for their ability to function in specific industrial processes. Useful enzymes are further improved, employing biotechnology techniques, such as rational design, gene shuffling, or directed evolution techniques [27]. Manufacturing capabilities are imparted to these microbes by introduction of genes from other organisms that are expensive or too difficult to cultivate in industrial quantities.

Once these enzymes are discovered and improved, they can be produced in commercial quantities using either naturally occurring or genetically modified organisms (GMOs). Currently, it is common for genetically engineered microbes (eg, bacteria or yeast improved through gene shuffling) to carry out the fermentation. Fermentation and reproduction of the organism are normally done in contained stainless steel fermentation tanks or systems, similar to those that produce human therapeutic proteins or bulk yeast for the brewing industry.

Several industrial compounds such as amino acids for animal feed, biodegradable plastics, or textiles fibers are now routinely produced using GMOs. The reconstruction of DNA strands from their chemical base elements according to computer-aided designs for metabolic platforms has given rise to the term "synthetic biology." This has allowed biotechnologists to create artificial metabolic pathways consisting of a series of previously unknown enzymatic activities leading to the synthesis of metabolic intermediates that are not observed in nature. The metabolic engineering field involves construction of microbes that can be used as biocatalysts for the cost-effective production of fuels, chemicals, and pharmaceuticals.

Basic elements of metabolic engineering aims at metabolic pathway design, construction, and optimization. These elements encompass a lot more disciplines than genetic engineering and molecular biology and include components from chemical reaction engineering, biochemistry, graph theory, and optimization [28]. From all hydrolysis products generated from cellulosic biomass, or directly available carbohydrates, like sucrose, glucose, and fructose, there are metabolic routes that will allow their conversion into central intermediates, such as pyruvate or acetyl-CoA, and then further into other products. Microorganisms that are able to form a desired product from glucose are usually not naturally able to convert all other biomass hydrolysate components like xylose and other pentose sugars into the product. Therefore, for all available hydrolysate components, conversion pathways are engineered into recombinant microorganisms to achieve high yields on biomass. One of the challenges associated with utilization of biomass-derived sugars, particularly those produced by chemical hydrolysis, is the formation of degradation products that may be inhibitory during fermentation.

Generally, microbial cells are less productive when consuming crude mixtures of hydrolyzed monosaccharides rather than glucose. The main pathway for glucose conversion is the glycolysis. Fig. 13.5 shows how it merges with pathways for conversion of second most important biomass monomer xylose.

13.4.11 Success Stories: Large-Scale Bio-Based Renewable Products at Commercial/Near Commercial Stage

13.4.11.1 1, 3-Propane diol (PDO)

The main use of 1,3-PDO is as monomer for production of large volume polymers like poly (trimethylene) terephthalate (PTT) and polyester. Other applications include polyurethane manufacturing, laminats, cosmetics, adhesives, paints, automobile linings, etc.

It has traditionally been produced via petrochemical routes at a scale much smaller than for 1,2-PDO, but recently 1,3-PDO production by fermentation of glucose and glycerol has been developed. Glycerol fermentation to 1,3-PDO is performed by many natural organisms. The pathway involves merely two steps, and requires anaerobic conditions (Fig. 13.6).

Firstly, coenzyme B12-dependent glycerol dehydratase is used to obtain 3-hydroxypropionaldehyde, which is then reduced to 1,3-PDO by an NADH-dependent oxidoreductase. This pathway is used by microorganisms like *Citrobacter* sp., *Clostridium* sp., and *Klebsiella* sp. [29].

In fed-batch fermentations on 1- and 200-L scale the *Clostridium butyricum* AKR102a strain reached 94 g/L 1,3-PDO with an overall productivity of 3.3 g/L/h [30]. The yield was 0.52 g/g, because the requirement for NADH implies that part of glycerol is oxidized to

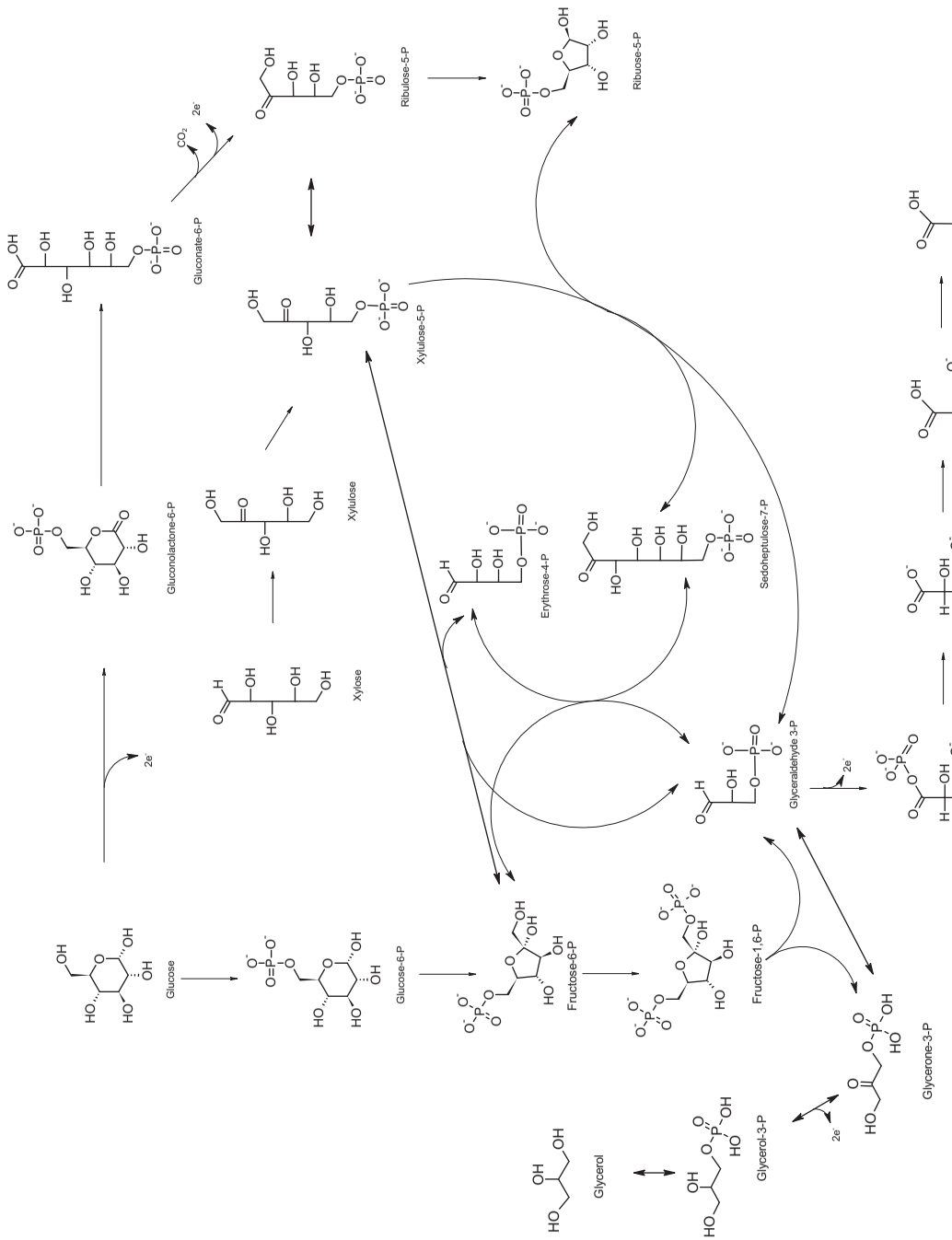


Fig. 13.5
Metabolic pathway for important biomass monomers glucose and xylose to pyruvate.

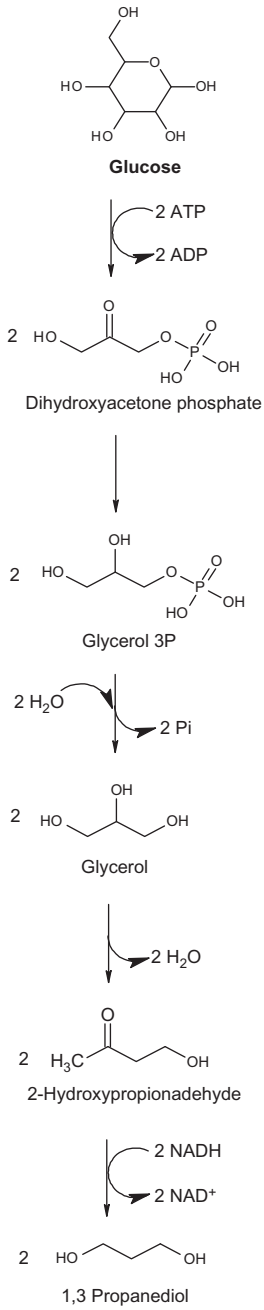


Fig. 13.6
Pathway for production of 1,3-propanediol from glycerol and glucose.

side products such as carboxylic acids and CO_2. Using a metabolically engineered *C. acetobutylicum* strain, 0.54 g/g has been achieved.

The other pathway is starting from monosaccharide or polysaccharide substrates, producing 1,3-PDO from glucose, corn hydrolysate, or sugarcane molasses. No known natural organism has been reported to ferment sugars directly to 1,3-PDO. The attempts using sugars as substrate have been made with genetically engineered microorganisms [31] carrying genes for the conversion of sugar to glycerol and then to 1,3-PDO. For this, the glycolysis is performed up to dihydroxyacetone phosphate which is then reduced and dephosphorylated to glycerol (Fig. 13.6). Such a pathway has been introduced in *Escherichia coli*. However, *E. coli* lacks coenzyme B12, which is required by glycerol dehydratase. Therefore, the pathway to synthesize coenzyme B12 was introduced in *E. coli*, including a reactivation enzyme.

In a DuPont patent, the highest reported 1,3-PDO concentration is upto 141 g/L, with a yield of 0.44 g/g of glucose [32]. A higher yield, 0.51 g/g, was achieved in a fermentation that led to 135 g/L 1,3-PDO and a productivity of 3.5 g/L/h.

The fermentative production of 1,3-PDO is performed at 45,000 t/a scale by a joint venture of DuPont and Tate & Lyle in Loudon, Tennessee, United States and recently announced their intention to increase capacity by 35%. The joint venture, has successfully commercialized the production of 1,3-PDO from renewable resources under the trade names Susterra® and Zemea®. Susterra® PDO is targeted at industrial application while Zemea® is aimed at the personal care sector. Susterra® PDO is copolymerized with terephthalic acid to produce PTT sold by DuPont under the trade name Sorona® which has been targeted at clothing, carpet and automotive textile markets. The French company Metabolic Explorer has announced the construction of a bio-based 1,3-PDO plant in South East Asia with an initial capacity of 8000 tons and is expected to have a final capacity of 50,000 tons.

13.4.11.2 Isobutanol

The fields of application of isobutanol (2-methyl-1-propanol) closely resemble its isomer, 1-butanol. Isobutanol is a building block chemical which can be used in solvents, rubber, and transportation fuels. The overall estimated market for Isobutanol as a chemical and solvent is about $15 billion. When mixed with gasoline, isobutanol provides more energy than ethanol. It is also less corrosive and can be easily transported through existing pipelines.

Many microorganisms are currently being studied for Isobutanol production like *Saccharomyces cerevisiae*, *Corynebacterium glutamicum*, *B. subtilis*, and *Clostridium cellulyticum* [33–36].

However, because of *S. cerevisiae's* robustness and ability to deal with industrial substrates, it is being employed for large-scale production. The metabolic pathway generally used is a modification of the pathway to L-valine (Fig. 13.7).

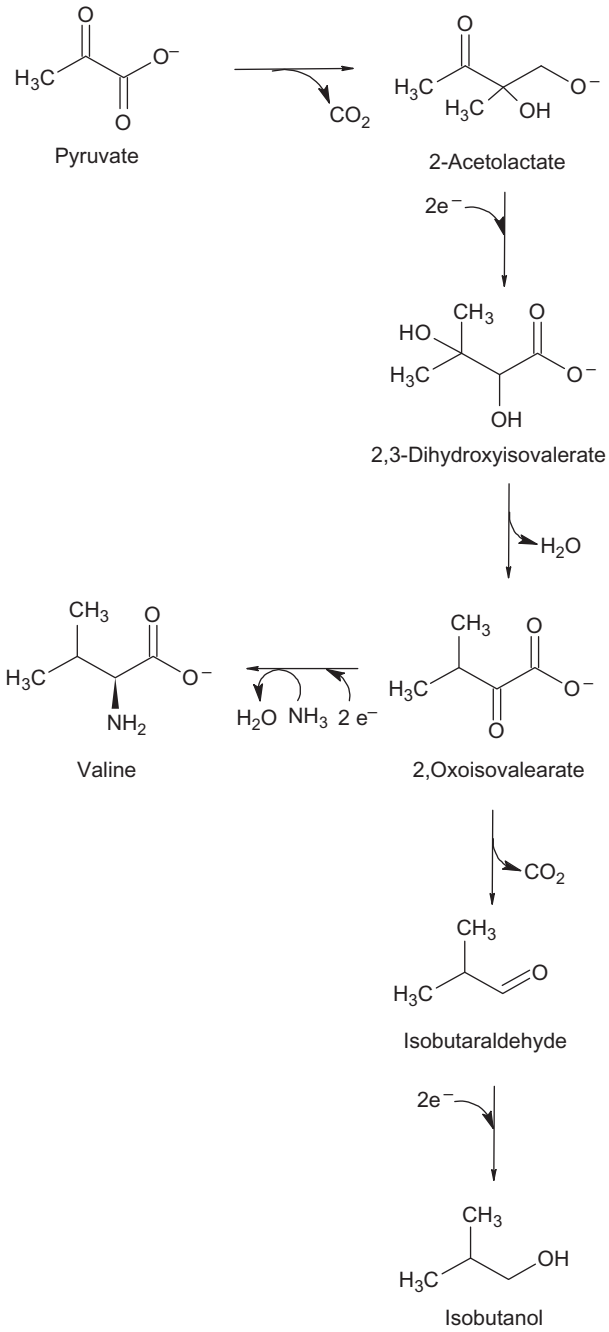


Fig. 13.7
Pathway for the production of Isobutanol.

After conversion of carbohydrates to pyruvate, two molecules of pyruvate are coupled to acetolactate by acetolactate synthase, releasing CO_2. Using NADPH, this is reduced to 2,3-dihydroxyisovalerate, which is then dehydrated to 2-oxoisovalerate. A subsequent decarboxylation yields isobutyraldehyde, which is reduced to isobutanol, using NADPH. Thus, a maximum of 1 mol isobutanol per mole of glucose (0.41 g/g) can be achieved if competing reactions are blocked. By choosing suitable enzymes, the pathway's dependency on NADPH was removed and the maximum yield was achieved, using anaerobic conditions. The highest published isobutanol concentrations are about 22 g/L, achieved at yield on glucose of about 0.35 g/g and with a productivity of about 0.2 g/L/h [37]. The toxicity of isobutanol to *E. coli* limits the production. Using in situ stripping with gas at nontoxic isobutanol concentrations, a productivity of 0.69 g/L/h was maintained during 72 h [38].

Isobutanol production from biomass using recombinant microorganisms is approaching large-scale commercialization. In the United States, Gevo has retrofitted a corn ethanol plant in Luverne for the production of Isobutanol and has successfully produced 50,000 gallon of renewable Isobutanol. Gevo plans to expand the capacity to 18 mmgpy of isobutanol. The key aspects of the technology [39] are the use of genetically modified *S. cerevisiae* to produce isobutanol and simultaneous removal of isobutanol from fermented broth, termed as GEVO Integrated Fermentation Technology (GIFT) process [40].

Another company, Butamax, which is a joint venture of BP and DuPont, is committed to commercializing biobutanol as a transportation fuel using patented technology [41]. For demonstrating the technology, an advanced facility was built in Hull, UK, specifically to execute testing for commercial plant design, technology risk mitigation, and ongoing technology improvement. In 2013, Butamax announced commencing of a retrofit of an ethanol plant in Lamberton, Minnesota for the production of biobutanol. The cutting-edge separation technology package includes a novel corn oil removal system and is an integral part of a full retrofit to biobutanol production.

13.4.11.3 1,4-Butanediol

1,4-Butanediol (BDO) is produced via petrochemistry at a scale of about 1.3 million t/a. It is used as an industrial solvent and can be converted into polyesters, polyurethanes, γ-butyrolactone, and spandex fibers. Owing to its structure and reaction activities, it is widely used as a platform chemical for synthesis of polymers, specialty chemicals, and chemical intermediates. Like many commodity chemicals of interest, 1,4 BDO is not a compound produced naturally in any known organism.

Major bio-based routes which are currently under development include direct conversion of sugars to 1,4 BDO, and hydrogenation of bio succinic acid to 1,4 BDO. Direct conversion of sugar to 1,4 BDO has been successfully achieved by a US-based biotechnology company, Genomatica, which has developed technology and manufacturing process to make bio BDO.

Genomatica researchers have developed a fermentation route to 1,4 BDO using genetically engineered *E. coli*. The metabolic route selected branches off from the citrate (TCA) cycle at 2-oxoglutarate (Fig. 13.8).

This is decarboxylated by 2-oxoglutarate decarboxylase to succinate semialdehyde, which is then reduced by 4-hydroxybutyrate dehydrogenase. The next reduction of the carboxylic acid group is done after CoA activation by 4-hydroxybutyryl-CoA reductase. In the final step, 4-hydroxybutyraldehyde is reduced using an alcohol dehydrogenase [42]. This led to production of 18 g/L BDO from glucose in 120 h. One of the important factors that impacts the process viability to produce bio BDO from sugars is the product tolerance of the selected biocatalyst. Genomatica researchers used evolutionary engineering methods to increase the tolerance of *E. coli* to 1,4 BDO to more than 100 g/L, thus overcoming a potential major hurdle to commercialization. Upon engineering the final three enzymes of the pathway, 115 g/L BDO was achieved with a productivity of 3.3 g/L/h [43].

13.4.11.4 Succinic acid

Succinate, which is mostly derived from petrochemicals, is currently used as a surfactant, an ion chelator, and as an additive in the pharmaceutical and food industries. However, its use in specialty chemicals is relatively small at 15,000–30,000 t/year worldwide [44]. The current focus of bio-based succinate production is targeting a much larger commodity chemical market ~300,000 t/year [45]. It is estimated that around $10 billion market of bulk chemicals could be produced from succinate as an intermediary feedstock. Succinic acid occurs in most organisms as intermediate of the citrate cycle (Fig. 13.9).

It can be excreted as a major fermentation end-product by microorganisms like *Actinobacillus succinogenes*, *Anaerobiospirillum succiniciproducens*, *Mannheimia succiniciproducens*, and some recombinant *E. coli*, and *C. glutamicum* strains [46]. Much research has been done on maximizing the product yield and anaerobic conversion of sugars. When using only glucose as electron donor, and supplementing additional carbon using CO_2 or carbonate salt, the achievable yield on glucose would be 1.12 g/g. The theoretical yield of ~1.1 g/g has been achieved using pre-grown engineered *E. coli*. After an aerobic cultivation stage, anaerobic production occurred up to 99 g/L succinic acid with a productivity of 1.3 g/L/h [47]. The highest reported succinic acid concentration is 146 g/L, using fed-batch production of *C. glutamicum*. A yield of 0.92 g/g was achieved and the productivity was 3.2 g/L/h [48].

Commercial fermentative production of succinic acid has been announced by several companies, using different microorganisms. Bioamber, along with Mitsui and Co., is currently building the world's largest succinic acid plant in Sarnia, Canada with a nameplate capacity of 30,000 tons/annum. A yeast-based catalyst has been jointly developed by Bioamber and Cargill for the production of succinic acid. Other leading companies involved in the commercialization of bio succinic acid include Myriant, BASF with Purac, and DSM with Roquette.

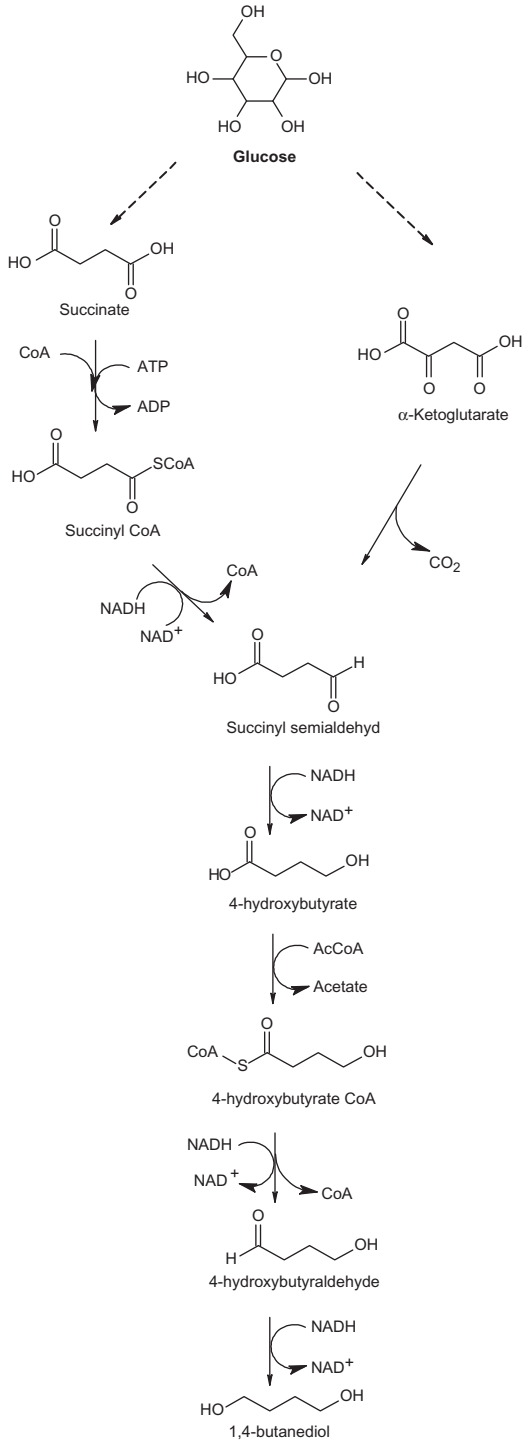


Fig. 13.8
Glucose metabolism pathways of 1,4 BDO production.

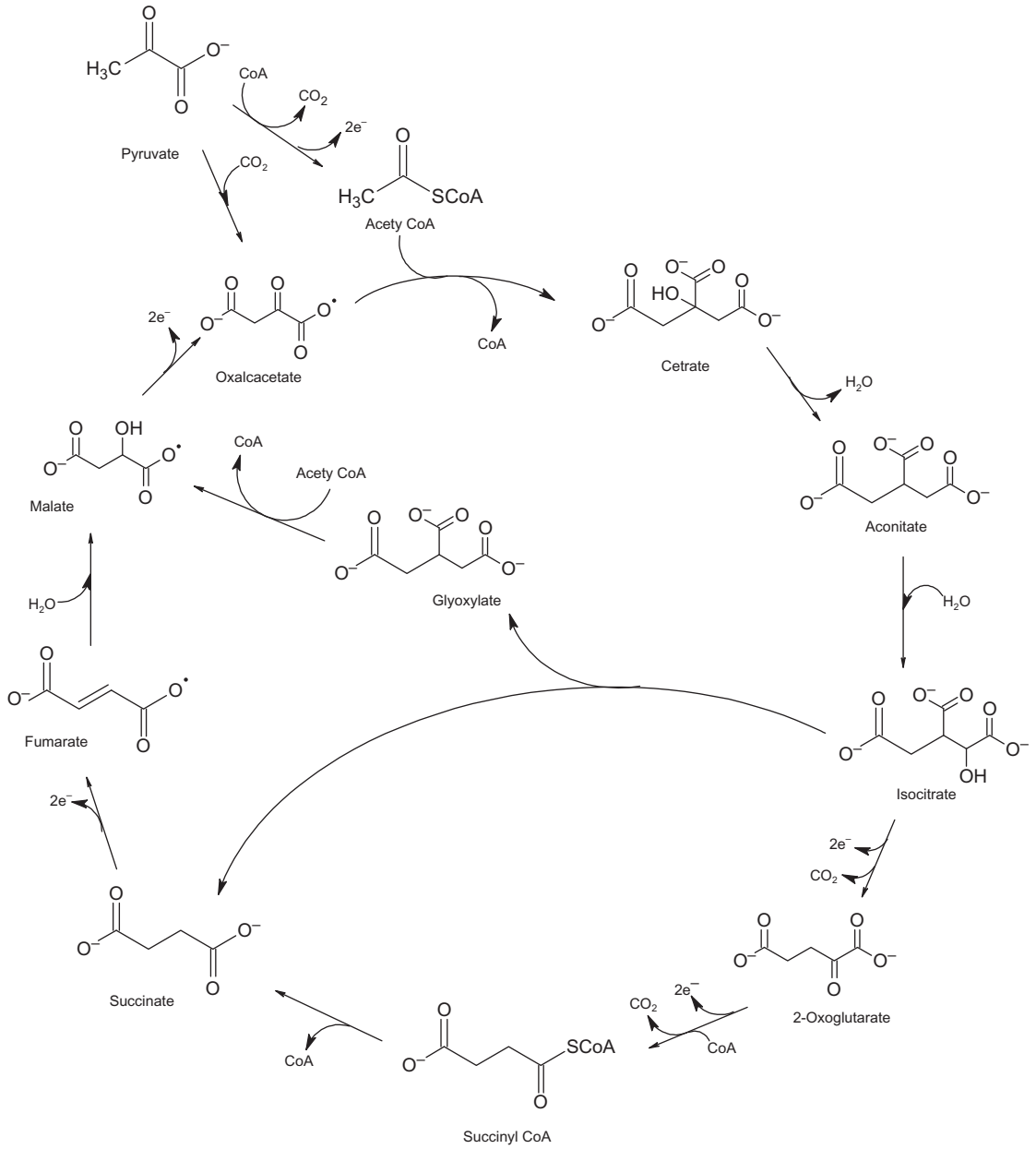


Fig. 13.9

Citric acid cycle showing succinic acid and other intermediates.

13.4.11.5 Butadiene

1,3-Butadiene is predominantly used as a monomer for synthetic rubbers, but also for some plastics. It is used as an intermediate in the production of some important chemicals. Global demand was forecast at over 20 billion pounds in 2011, or more than $20 billion per year. Major applications of butadiene include styrene butadiene rubber, paper coatings, gloves, wetsuits and foams, and nitrile butadiene rubber, etc.

Recent fluctuations in crude oil prices, coupled with demand variations due to regulatory scenario have pushed the chemical industry toward identifying bio-based routes for production of butadiene. Several global chemical companies have declared partnerships with biotechnology companies for development of bio butadiene.

Global Bioenergies in Europe is developing processes to convert renewable resources into hydrocarbons like butadiene, isobutene, and propylene. The processes developed by Global Bioenergies are based on the design of artificial metabolic pathways composed of several enzymes that catalyze previously undescribed reactions not observed in nature. Several modified enzymes that catalyze a specific reaction of the artificial metabolic pathway have been integrated into a bacterium which has been shown to be able to convert sugar into butadiene and other light olefins. Global bioenergies invention is based on the design of a novel biocatalyst for the synthesis of volatile diene compounds, like butadiene, by conversion of light alkenols using an enzyme catalyzing a dehydration reaction [49]. *E. coli* bacteria are engineered to produce these precursors from glucose and subsequently engineered to convert the butenol isomers into butadiene.

The biotechnology company, Genomatica, has been working on an extensive program in butadiene, with Versalis and Braskem as the initial partners. The objective is to develop commercial processes for the production of butadiene from a range of renewable feedstocks, for licensing to and use by the global chemical industry. Genomatica utilizes *in silico* stoichiometric models of *E. coli* metabolism that identify metabolic pathways for biosynthetic production of butadiene [50]. Separate strain design strategies have been described with incorporation of different heterologous reaction capabilities into *E. coli* or other microorganisms leading to butadiene producing metabolic pathways from acetyl CoA, glutaconyl-CoA, glutaryl CoA, 3-amino butyryl CoA, 4-hydroxy butyryl-CoA, erythrose-4-phosphate, or malonyl-CoA plus acetyl-CoA.

The maximum theoretical butadiene yield from glucose is 1.09 mol/mol (0.33 g/g). The pathway presented in Fig. 13.10 achieves a yield of 1 mol of butadiene per mol of glucose utilized.

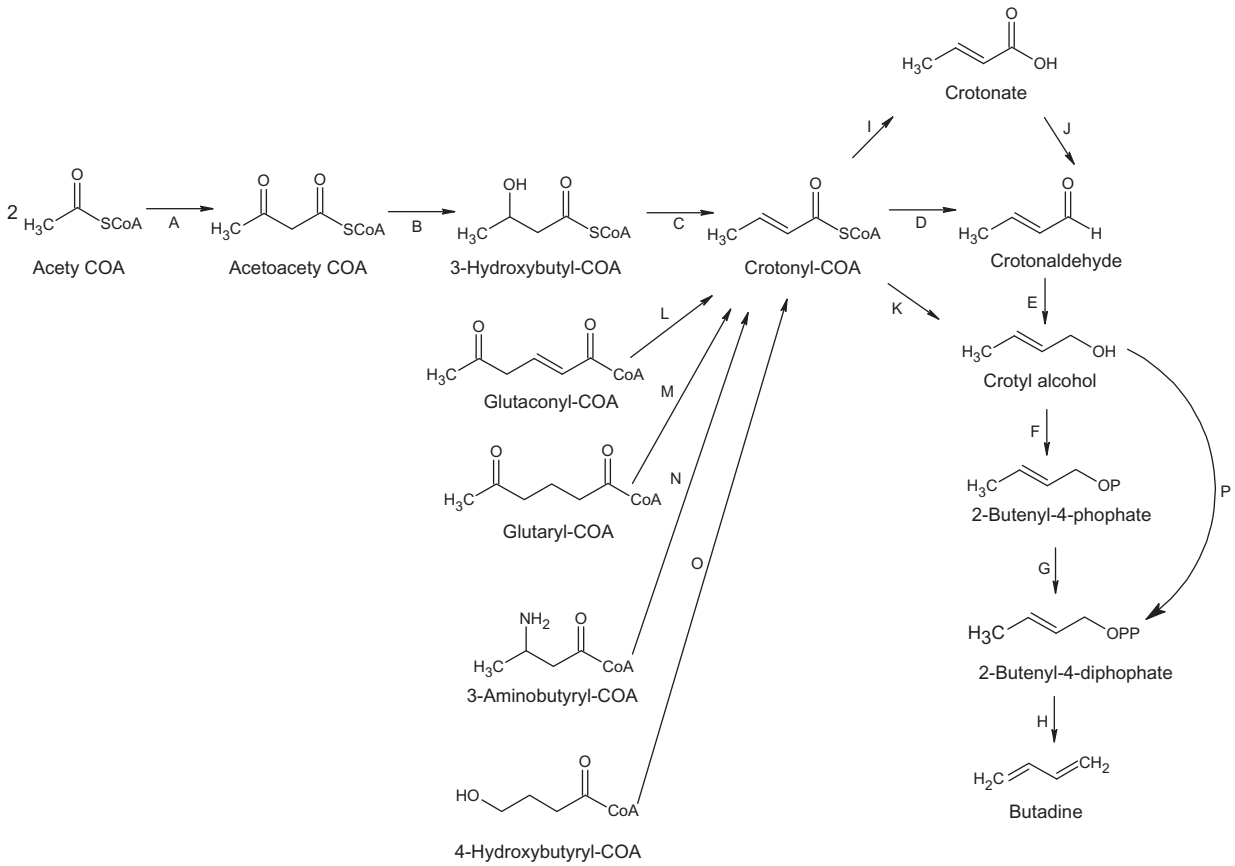


Fig. 13.10

Pathways for production of butadiene from acetyl CoA, glutaconyl-CoA, glutaryl CoA, 3-amino butyryl CoA, 4-hydroxy butyryl-CoA.

13.4.12 Recent Advances in Commercialization of Renewable Chemicals and Associated Challenges

Several renewable chemical technologies are being developed across the globe using a biochemical or chemocatalytic route and are at different stages of development and commercialization. Some of the recent technologies which have crossed the initial valley of death and have traversed pilot and demonstration stages have been discussed in this section, along with common major challenges in commercialization of renewable chemicals.

Genomatica's commercial-scale bioprocess for the production of 1,4 BDO directly from carbohydrates has enabled production of thousands of tons of 1,4 BDO since 2012. Based on Genomatica's process, Novamont is building a plant in Adria, Italy, with a production capacity of approximately 40 million pounds per year and will use biomass sugars as the renewable feedstock (Fig. 13.11).



Fig. 13.11
Novamont's bio-BDO plant (in left) and Myriant's bio-refinery for succinic acid at Lake providence, LA (in right).

Genomatica focused on an integrated biotechnology platform that made this faster and less expensive than traditional bioprocess development and scale-up. The key differentiator of this platform included an emphasis on modeling and techno-economic analysis from the very start and using this information to guide decisions on development of organism, fermentation, and downstream process design. Genomatica's computational platform, allowed identification of which enzymes to be added or deleted from *E. coli* to increase 1,4 BDO and eliminate the formation of undesirable products such as acetate, pyruvate, and, ethanol. The process involved an iterative approach based on models to guide experiments and interpret data, followed by using the experimental results to improve the model and provide further experimental guidance. Through this unique strategy, increase in 1,4 BDO production over 20,000-fold was achieved in

just 18 months. Combining this integrated approach with commercial expertise enabled bio-based 1,4 BDO comparable to oil based BDO at $50 a barrel.

Another important factor that impacts the overall process viability in fermentation process is product tolerance. The economic models indicated that cost-advantaged commercial production of 1,4 BDO will require a host organism (*E. coli*) to produce and tolerate BDO concentrations of 100 g/L (10% BDO in water) or higher. Since *E. coli* naturally can tolerate only 5–6% BDO concentrations, Genomatica scientists leveraged adaptive evolution technology that allows organisms to gradually acclimatize and adapt to different environments over a period of months. In order to carry this out effectively, Genomatica developed proprietary machines that automate the ability to maintain organisms in changing conditions (eg, increasing BDO concentrations) over extended periods. Using these machines, the tolerance of *E. coli* was increased to BDO concentrations above 10%, thus overcoming a potential major hurdle to commercialization. It is important to note that the bio-based BDO process is able to switch between glucose and sucrose, depending on relative prices and availability. Genomatica scientist engineered *E. coli* to use both glucose and sucrose equally well, which can allow chemical manufacturers to control their costs more effectively. Different feedstocks are also preferred in different geographies, based on local growing conditions and markets. For example, while glucose from corn may be favored in the United States, low-cost sugarcane-derived sucrose will be the preferred feedstock for 1,4 BDO production in Brazil, and sucrose from sugar beets is available and would be preferred in the UK and other parts of Europe. Such feedstock flexibility should facilitate wide adoption of new bio-BDO manufacturing processes.

Another renewable chemical which is near commercialization is bio-based succinic acid. Myriant Technologies is utilizing a fermentation based technology platform to produce succinic acid. Myriant has scaled up the process and is producing ton-sized samples for testing by customers for different applications. Myriant is building a 30 million lbs/year Succinic Acid plant in Lake Providence, Louisiana (Fig. 13.11). The key reasons behind Myriant's success have been; assembling critical partners at different stages of development, including funding partners for R&D and commercialization; partners for scale up and engineering on an integrated platform; validation of process economics at every stage of development; and securing market approval for the product and supply agreements before putting the commercial scale plant.

Both 1,4 BDO and succinic acid technologies have gone through systematic processes for scale up involving laboratory optimization, pilot plant trials, and demonstration scale plants for generating commercial samples prior to commercialization. The key reasons for successful scale up have been integrated, robust, validated process and products, validated raw materials, trained and experienced production team, dedicated and detailed project management, formal risk analysis and mitigations, thorough commissioning and start-up, and on site R&D support.

In general, common challenges faced during commercialization of renewable chemicals technologies, especially fermentation-based technologies, include contamination minimization and management at large scale; raw material and water quality management including recycle streams; maintaining specifications of product and by-products with increase in scale; achieving process robustness and control; and minimization of effluent treatment costs. It is important to study the environmental impact of renewable chemicals technologies and products to validate assumptions of GHG reductions and energy savings. Regulatory approval procedures related to effluent chemicals and use of GMOs need to be studied in detail as the rules and permissible limits are different for different geographies. Regulatory framework for the protection of intellectual property in different countries needs to be considered to safeguard large investments associated with development of new technologies.

Commercialization of renewable chemicals is always riskier due to availability of low cost counterparts produced from the petrochemical route. In the absence of regulatory support, market penetration is difficult for renewable chemicals. Since no green premium is available from the consumer for renewable products, this makes it necessary to match cost of renewable chemicals with petrochemicals.

13.5 Chemo Catalysis

Despite the fact that heterogeneous catalysis has been a key enabling technology in the chemical and petroleum industries, the use of heterogeneous catalysts in existing bio-refineries (eg, corn wet mills and wood processing plants) is quite limited, primarily due to the major issue relating mass transfer. However, these catalysts are being explored to convert individual components from fractionated biomass to different value added chemicals. However, the nature of these components poses a major challenge to heterogeneous catalyst applications.

If we look to the history of catalyst development, the catalysts were primarily developed to cater to the needs of the petroleum industry. The feed molecules of these petroleum industries were small and quite simple hydrocarbons. The primary focus of the catalysts developed was to excite the stable hydrocarbon bonds in these hydrocarbons to instill chemical reactivity. On the other hand, due to the higher level of functionality present in biomass based feedstocks, unwanted side-reactions are plenty, so naturally heterogeneous catalyst technologies developed for the petrochemical industry are typically inadequate for selectively converting biomass to chemicals and fuels. Further complicating the conversion of biomass is the requirement that the reactions will typically need to be accomplished in the condensed phase, where the solvent is commonly water, rather than the gas phase used for petrochemicals. The catalytic conversion of biomass-derived materials in the aqueous phase introduces a broad array of new questions ranging from those concerning fundamental mechanisms to process applications.

- How do molecules with a high level of functionality adsorb on metal or metal oxide surfaces?
- How can specific C–C or C–O bonds be converted in the presence of multiple reactive functional groups?
- What role will water play in the reactions?
- How must catalytic structures be modified for biomass?
- How can hydrothermal stability be built into the catalysts?
- Can the reaction systems be coupled with separations?

The answers to these questions will be an important bridge to solving the product-specific catalysis technology challenges for biomass utilization. For these reasons new catalyst technology approaches will be needed for converting biomass to useful products.

13.6 Adsorption of Carbohydrates on Metals/Metal Oxides

Whereas the adsorption of alkenes on metals and metal oxides has been extensively examined, understanding of the adsorption behavior of carbohydrates and their derivatives, which have multiple functional groups through which adsorption can occur, is quite limited. The challenge associated with understanding adsorption behavior of these multifunctional group molecules becomes even more complex when trying to characterize adsorption under reaction conditions, as the reaction is commonly performed in the condensed phase. Additionally, carbohydrates and their derivatives have stereo isomers that can have very different adsorption behavior. As an example, when the adsorption of a range of sugars in the aqueous phase onto hydrous zirconium oxide and iron oxide was examined using a Langmuir monolayer adsorption isotherm approach [51], the experimentally determined Langmuir equilibrium constant and maximum amount of the sugar required to form a monolayer on the surface were found to be strongly dependent on the stereoisomer used. Particularly, the stereochemistry of the three neighboring hydroxyl groups on the C(2), C(3), C(4) carbon atoms strongly impacted the resulting adsorption behavior. These differences were significantly more pronounced for the interaction of the sugars with hydrous zirconium oxide than with hydrous iron oxide. It was speculated that the difference between the two hydrous metal oxides could be attributed to the ionic radii of the metal ions.

This differential adsorption phenomenon will also be exhibited by reaction products if they have significant amount of functionality. Several studies with glycerol, ethylene glycol, and propylene glycol, which are the hydrogenolysis products of sugars, indicate that all readily adsorb on Ru, but when present together, glycerol and ethylene glycol are preferentially adsorbed relative to propylene glycol [52,53].

These constraints imposed by bio-renewable conversions have led to significant interest in using biocatalysts. While important progress continues to be made with biocatalysts, significant

technical challenges around catalyst robustness for large-scale application still remain. If bio-renewables are to become a significant source of fuels and industrial chemicals, both chemical catalyst and biocatalyst technologies will need to be developed.

13.7 Selective Bond Cleavage

Bio-renewable feedstocks will typically consist of multiple functional groups, with the most common for carbohydrate-based feedstocks being hydroxyl groups. As these feedstocks generally contain excess oxygen for fuel or chemical applications, there is a need to develop conversion technology that will selectively remove oxygen. Reactions of particular interest to accomplish oxygen removal are dehydration and decarbonylation/decarboxylation, although when the goal is to produce fuels, oxygen removal can also be achieved during condensation or ketonization reactions [54–59]. In the dehydration of polyhydroxylated compounds, the goal is to control C–O cleavage without concomitant C–C cleavage. A reaction that clearly demonstrates these competing challenges is the hydrogenolysis of sorbitol, xylitol, or glycerol. This reaction is thought to be initiated by dehydrogenation of the sugar alcohol to either an aldehyde or ketone, so a kinetic mechanism for the system must address the relative reactivity at the different carbon positions, as well as the adsorption behavior of the reactant. The range of reaction considerations in the hydrogenolysis reaction nicely represents the types of issues that are present in the catalytic conversion of many carbohydrate-derived species and can be used to develop insight into the ability to selectively break C–C and C–O at specific locations. The catalyst system most frequently used for the reaction is Ru/carbon in a highly basic solution. In this reaction sequence, the dehydrogenation/hydrogenation reactions are metal catalyzed and the dehydration/retrol-aldol reactions by solution hydroxyls [60] (Fig. 13.12).

13.8 Aqueous Phase Considerations

Carbohydrates and their multifunctional derivatives commonly have limited or no volatility and as such, their conversion systems are likely to use the condensed phase. As the deconstruction of starch or cellulose to monosaccharides is performed in water, subsequent condensed phase processing will likely be in the aqueous phase. Heterogeneous catalysts have received relatively little attention with respect to how the presence of condensed water at the catalyst/solution interface can influence the kinetics and mechanisms of the resulting reactions. Neurock and coworkers [61] have studied the effect of aqueous phase on the thermodynamics and kinetics for many of the elementary reaction steps including adsorption, diffusion, desorption, and surface reactions. They observed that reaction steps that involve charge transfer were most strongly impacted. They also studied the effects of water solvation, and observed that the solution could play an important role in the reaction mechanism through direct participation in the catalytic pathways.

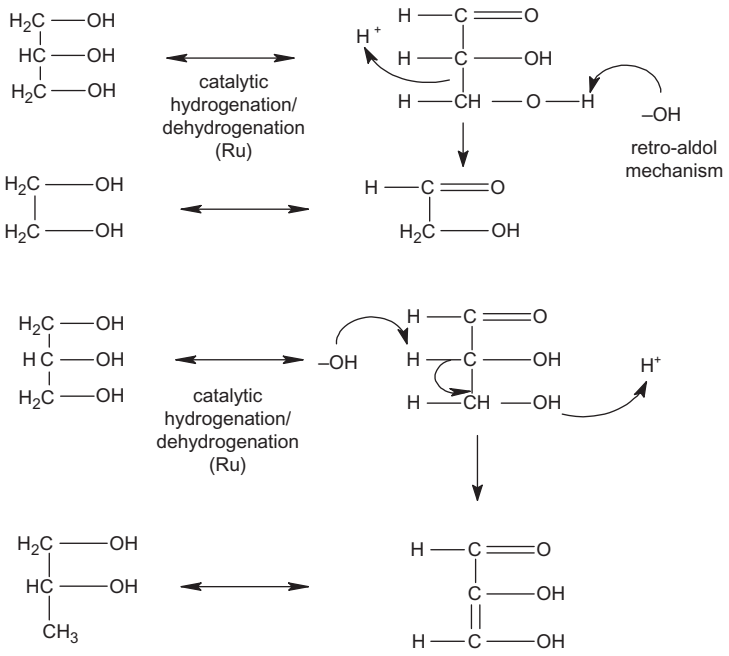


Fig. 13.12
Retro-aldol and dehydration reactions in hydrogenolysis of glycerol.

13.9 Catalyst Design for Biomass Conversion

Given that bio-renewable-derived molecules will commonly need to be converted in the condensed phase, designing catalysts for converting these molecules will not only need to consider the chemistry at the active site, but also the reaction sphere around the active site. Enzymes have evolved to create these active domains in which the active site itself can consist of multiple amino acid moieties and the amino acids surrounding the active site can modify the reaction sphere around the active site. Taking this cue from nature, heterogeneous catalysts in which both the active sites and reaction spheres are carefully controlled may prove to be particularly effective in the active and selective conversion of bio-renewables. Diaz et al. examined the use of acid-functionalized mesoporous silica to control the reaction environment in the catalytic esterification of glycerol with fatty acids to produce monoglycerides. Although glycerol esterification with fatty acids can lead to formation of mono-, di-, or triglycerides, only the chemical properties of the monoglycerides are suitable as an emulsifying agent and so there is a need to minimize the formation of di- and triglycerides. In constructing their catalysts, they used three attributes within the mesopores to control the catalytic performance of the material. First, propylsulfonic acid groups were tethered to the interior of the pore. This functionalization was performed on mesoporous materials, which all had narrow pore distributions but with different average pore diameters. The use of the strong acid

group, in conjunction with tuning the pore diameter, led to a MCM-41-SO_3H catalyst having high activity and selectivity for glycerol esterification to monoglycerides. The good catalytic performance of propylsulfonic acid-functionalized mesoporous silica catalyst was attributed to a combination of strong acidic sites located inside the mesopores (see Fig. 13.13), as well as the narrow pore size distribution that diminished the formation of secondary di- and triglyceride products.

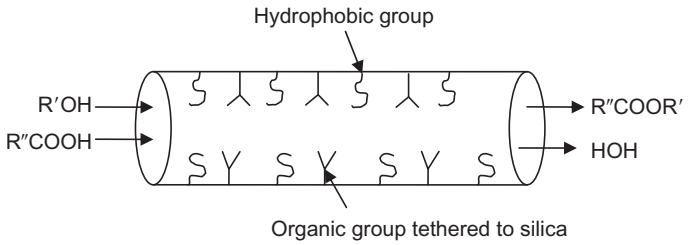


Fig. 13.13
Schematic diagram of MCM pore structure.

The catalytic activity of the propylsulfonic acid functionalized mesoporous silica catalyst was compared to that of *p*-toluenesulfonic acid, which had high activity but poor selectivity to the desired monosaccahrides [62].

13.10 Hydrothermally Stable Catalytic Materials

The presence of a condensed phase in a reaction system creates a new challenge involving finding catalysts that possess adequate stability. The challenge can be magnified when the reaction is being performed in the aqueous phase. Hydrothermal stability has been a longstanding issue for heterogeneous catalysts, which has received a great deal of attention. However, much of the work on creating hydrothermally stable solid catalysts has focused on recalcitrance to water vapor and not condensed water. Aqueous-phase catalytic conversions of bio-renewables will necessitate solid catalysts that can maintain their stability to temperatures as high as 230°C. An interesting class of materials that has been examined for use in the conversion of bio-renewable molecules is sulfonated carbons. Using glucose carbonization, followed by sulfonation with concentrated sulfuric acid, sulfonated carbons were produced (Fig. 13.14).

Depending on the carbonization conditions, carbon-based materials with an acid content of up to 1.34 mmol/g were reported [63]. It was speculated that the carbonized glucose formed polycyclic aromatic sheets with the sulfonic acid groups bound to the edges of the sheets [64]. This type of catalyst material displayed good stability in condensed phase reactions. The sulfonated carbon materials were found to have good activity for fatty acid esterification with methanol and were stable to repeated batch reaction testing at temperatures of 80–180°C. The stability of sulfonated carbons in aqueous media was tested satisfactorily using the

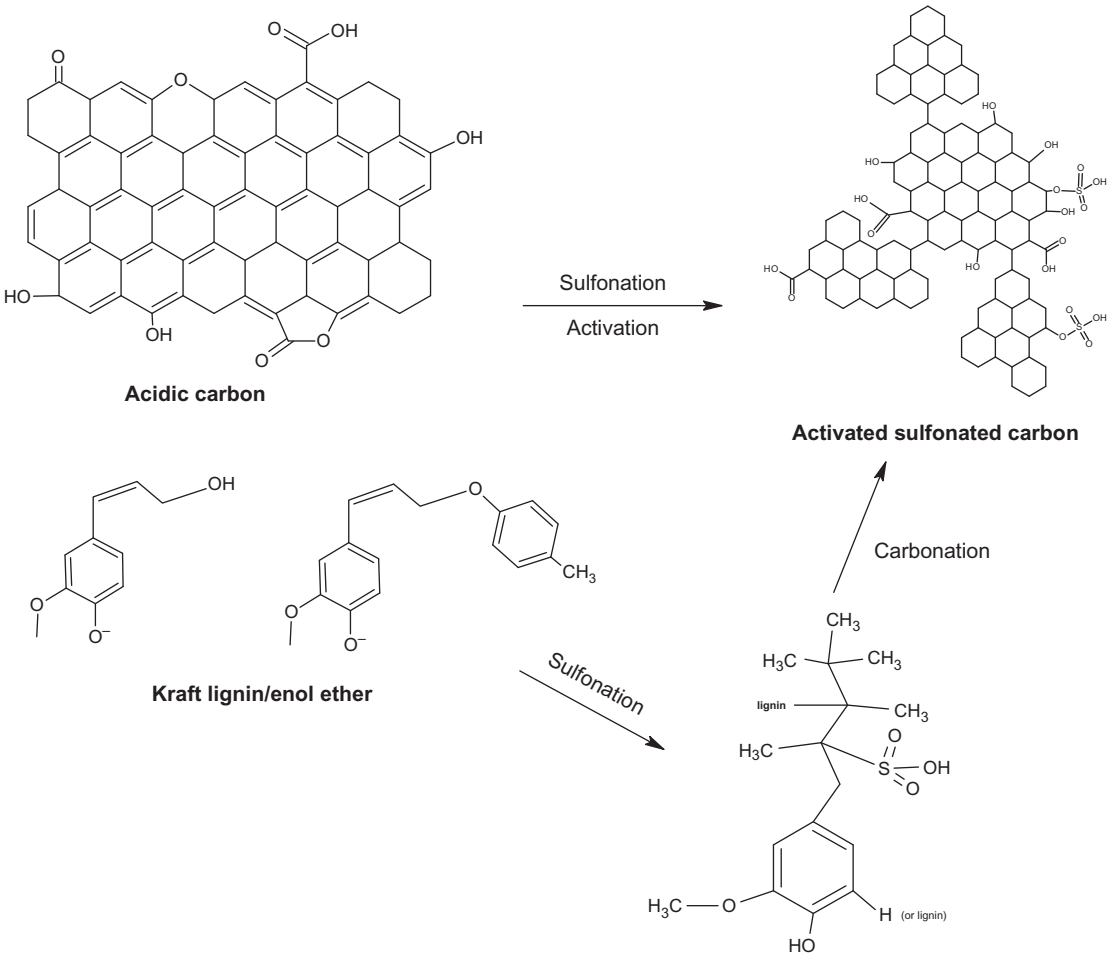


Fig. 13.14
Scheme for preparing sulfonated carbon catalysts.

cellulose hydrolysis reaction at 150°C [65]. However, these materials did not provide means for controlling the pore size distribution of the catalysts. Therefore, several approaches have been taken to create mesoporous sulfonated carbons with narrow pore size distribution wherein sugar or a similar carbon precursor is impregnated on a catalyst with well defined pore structure [66]. While these sulfonated carbon materials appear to have promising hydrothermal stability properties, key characterization validating the long-term stability of the materials has not been reported. Reproducible activity through 3–5 batch reaction cycles, although important, is inadequate to determine whether the sulfonic acid groups are slowly being lost. Also, acid catalyzed bio-renewable reactions can require that the catalysts be stable in the aqueous phase at temperatures as high as 230°C, so the sulfonated carbon materials need to be tested at these high temperatures.

13.11 Application of Heterogeneous Catalyst in Renewable Chemistry

13.11.1 Catalytic Hydrogenation Reactions

13.11.1.1 Hydrogenation of glucose and derivatives

Catalytic hydrogenation of sugars has been one of the most exploited industrial processes. Glucose obtained from starch or sucrose hydrolysis is hydrogenated to sorbitol (c. 800,000 t/year), a commodity product used in the food, pharmaceutical, and chemical industries, as well as an additive in many end-products. The main by-product of the reaction is gluconic acid formed by the Cannizaro reaction and mannitol formed by sorbitol epimerization (Fig. 13.15).

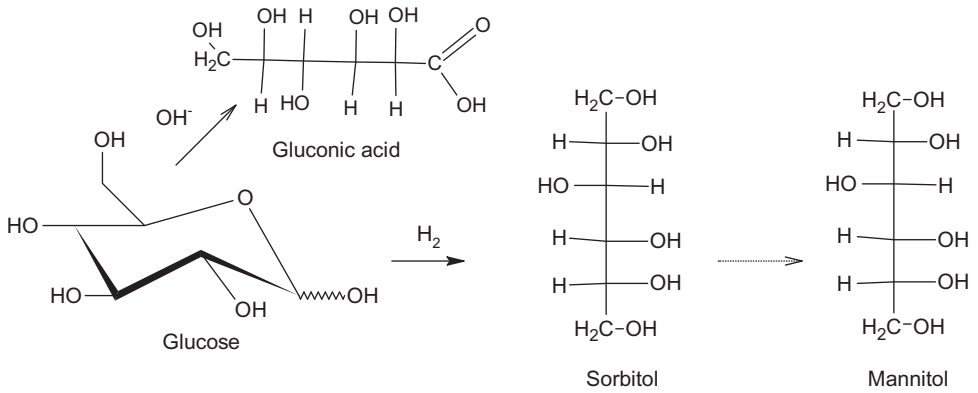


Fig. 13.15
Reduction of glucose.

Most of the industrial production is still conducted batch-wise on Raney Nickel catalysts promoted with electropositive metal atoms such as molybdenum and chromium [67] but because of the risk of nickel or metallic promoter leaching, they tend to be replaced by supported ruthenium catalysts, which are also more active. Glucose hydrogenation using Ru-Pt/C bimetallic catalysts is more selective to sorbitol due to low rate of epimerization, cracking, and polymerization. Platinum alloying also extends the catalyst stability because it prevents any oxidation of ruthenium [68,69].

13.11.1.2 Reduction of pentose sugars

Xylose is similarly reduced on a variety of metal catalysts based on nickel to xylitol. Xylose was hydrogenated into xylitol, a polyol widely employed as food, cosmetic, and pharmaceutical additives (Fig. 13.16).

Hydrogenation reactions were mainly achieved industrially in the presence of Raney Nickel catalysts affording up to 98% yield, but the catalysts suffered from deactivation due to the leaching of promoters, surface restructuring, and poisoning by strongly adsorbed organic

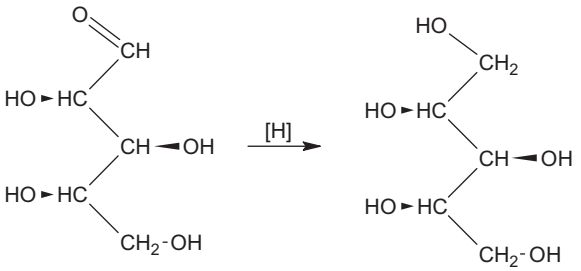


Fig. 13.16
Reduction of xylose.

molecules. A continuous ultrasound irradiation was able to decrease catalyst deactivation. Ru/C catalysts have a higher activity than Raney Nickel and are less prone to deactivation. Xylitol yields higher than 98% were reported on Ru/SiO_2 and Ru/ZrO_2 catalysts [70].

13.11.2 Oxidation Reactions

Oxidation reactions are widely used for upgrading carbohydrates to a variety of high added-value chemicals used in detergents or pharmaceuticals (vitamin C). Although enzymatic and microbial oxidation reactions are widely used for that purpose, homogeneous catalysis is also widely used. Thus, oxidation with hypochlorite mediated by TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) has been generalized to a large number of carbohydrates [71]. Sucrose is one such example which can be oxidized in this manner to yield more than 80% tricarboxysucrose [72] (Fig. 13.17).

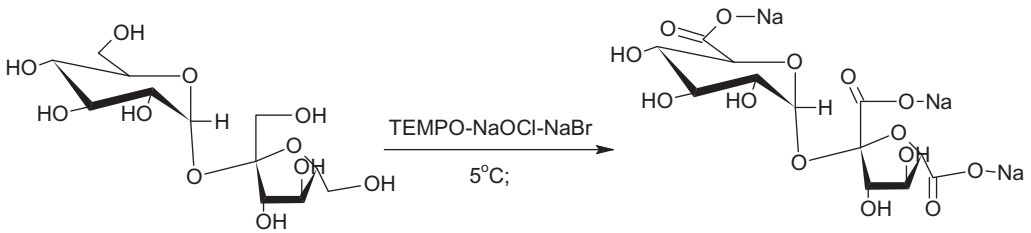


Fig. 13.17
Selective oxidation of sucrose.

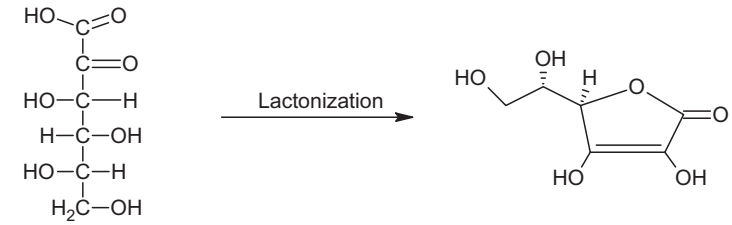
The catalytic system can be improved by adding co-catalysts such as laccase enzyme, which makes it possible to replace the nongreen hypochlorite agent with oxygen. The catalytic system can also be immobilized to afford better catalyst recovery [73]. The catalytic system $RuCl_2(PPh_3)_3$/TEMPO can also be used to replace hypochlorite by oxygen [74]. Oxidation reactions with H_2O_2 mediated by metal phthalocyanine catalysts are also proven to be very efficient to oxidize various carbohydrates, including the oxidation of insoluble substrates such

as native starch [75]. Carbohydrate oxidation reactions with oxygen catalyzed by supported metals underwent a considerable development in the 1990s following pioneering works in the early 1970s [76]. The oxidation of carbohydrates on metal catalysts has been reviewed by Besson and Gallezot [77]. Glucose oxidation to gluconic acid, a biodegradable chelating agent and an intermediate in the food and pharmaceutical industries, was achieved with air oxidation in presence of palladium catalysts.

Unpromoted palladium catalysts, although active in glucose oxidation, the rate of reaction is low because of the overoxidation of Pd-surface and the selectivity is also not attractive owing to side oxidation reactions. The use of Pd-Bi/C catalysts enhances the rate of glucose oxidation to gluconate by almost 20 times with almost 100% selectivity. Bismuth acts as a co-catalyst protecting palladium from overoxidation because of its stronger affinity for oxygen [79]. These results are almost comparable with the enzymatic glucose oxidation.

Glucose can also be oxidized in the presence of gold catalysts [80–82] with oxygen at basic pH, however, the activity is strongly dependent on particle size and the selectivity is much lower than that for Pd-Bi catalysts [79]. Gluconate can also be oxidized with oxygen on Pt-catalysts into glucarate or 2-keto-D-gluconate, the latter being a valuable intermediate.

At basic pH, the yield to 2-ketogluconate is limited by the formation of degradation products [83]. However, at lower pH, the reaction proceeded to almost completion with 98% selectivity [84]. In a similar manner, oxidation of lactose yields almost quantitative yields of 2-ketolactobionate at pH 7 [85]. The oxidation of L-sorbose to 2-keto-L-gulonic acid, an important intermediate in the synthesis of vitamin C, has been extensively studied by Baiker and coworkers [86–88] (Fig. 13.18).



2-Keto-L-gluconic acid (side product)

Fig. 13.18
Lactonization of 2-ketogluconic acid to ascorbic acid.

The Pt/Al_2O_3 catalyst, promoted or not with bismuth, gives a poor yield. However, adsorbing hexamethylenetetramine (HMTA) on the surface of Pt/C catalyst (HMTA/Pts mol/mol = 0.1) increases the selectivity from 51% to 95% at 30% conversion. Selectivity also improves (66% at 50% conversion) upon addition of trace amounts of tributylphosphine, but the improvement is lower as compared with amines. Fructose is oxidized to 2,5-furanedicarboxylic

acid with a bifunctional acidic and redox catalyst consisting of cobalt acetylacetonate encapsulated in sol-gel silica [89] (Fig. 13.19).

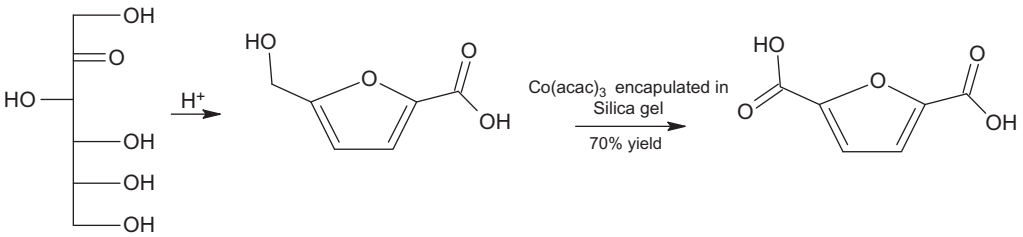


Fig. 13.19
Synthesis of FDCA.

13.11.2.1 *Oxidation of hemicellulose*

Oxidation of hemicellulose yields a mixture of dibasic acids. H. Lin and coworkers have studied the oxidation presence of zirconium dioxide and have reported 42% molar yields. This approach is quite interesting as it minimizes dehydration reactions of xylose which are known to form furfural [90] (Fig. 13.20).

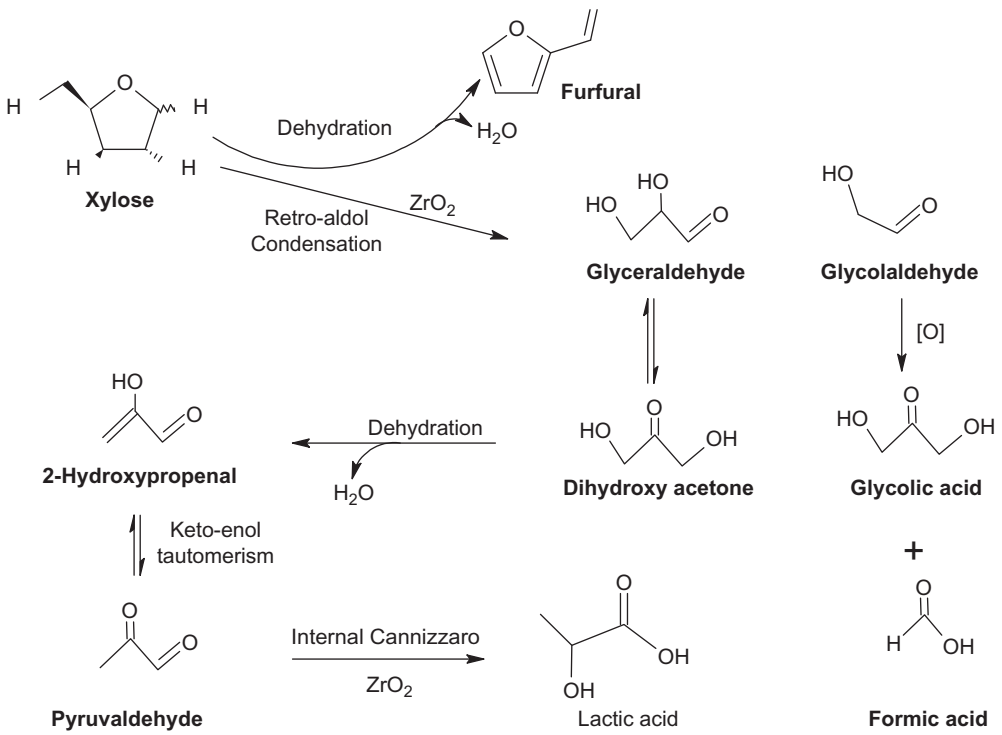


Fig. 13.20
Various oxidation products from xylose.

13.11.2.2 Oxidation of lignosulfonates

Chemicals such as vanillin can be obtained by catalytic oxidation of lignosulfonate [91] (Fig. 13.21).

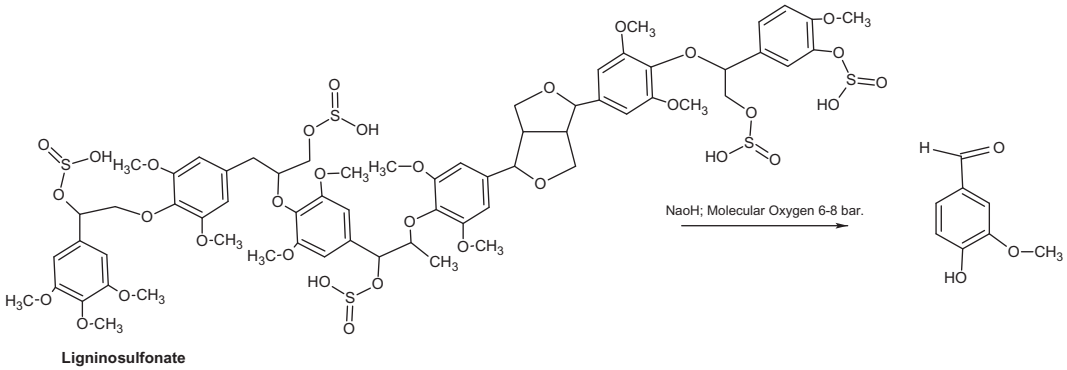


Fig. 13.21
Oxidation of lignin to vanillin.

13.12 Oxidative Decarboxylation

There is great interest in converting C6 carbohydrates available in large supply from cellulose, starch, or sucrose into C5 and C4 polyols that are not very present in biomass, and find many applications in food and nonfood products. Thus, glucose can be converted to arabitol by an oxidative decarboxylation of glucose to arabinonic acid followed by hydrogenation to arabitol on Ru catalysts in BR [92] (Fig. 13.22).

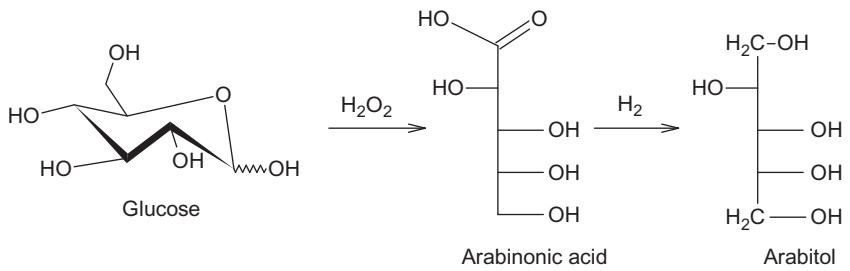


Fig. 13.22
Oxidative decarboxylation of glucose.

13.13 Dehydroxylation of Carbohydrates

Deoxyhexitols consisting of C6 diols, triols, and tetrols are well suited to replace polyols derived from petrochemistry for applications in polyester and polyurethane manufacture (Fig. 13.23).

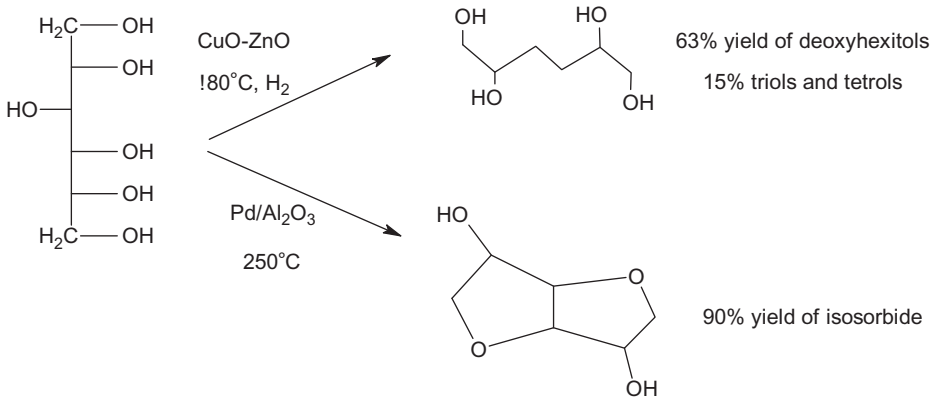


Fig. 13.23
Synthesis of isosorbide.

Sorbitol as a model molecule was treated with copper-based catalysts (33% CuO-65% ZnO) in the temperature range of 180–240°C under H_2-pressure to yield more than 60–70% deoxyhexitols [93]. In contrast, operating in the presence of palladium catalysts at 250°C under 80 bar of hydrogen pressure, cyclodehydration reactions of sorbitol and mannitol occurred with formation of cyclic ethers: isosorbide, 2,5-anhydromannitol, 2,5-anhydroiditol, and 1,4-anhydrosorbitol [94]. Up to 50% and 90% yield of isosorbide is obtained from sorbitol and mannitol, respectively. The mixtures of polyols so obtained can be effectively employed to synthesize alkyd resins and make decorative paints with a performance comparable to the commercial products. Recently, Huber et al. [95] demonstrated production of alkanes from aqueous sorbitol using Pt/Pd supported SiO_2-Al_2O_3 catalyst. The hydrogen required for hydrogenation reaction was produced by Aqueous-phase reforming (APR) of aqueous sorbitol in the same reactor. The APD/H of aqueous sorbitol however resulted formation of C5–C6 hydrocarbons.

13.14 Catalysts for Starch Modification

Due to its large availability and low cost, native starch has been used for a long time in the preparation of different end-products. To obtain specific properties, native starch has to be chemically or enzymatically modified. As native starch is an insoluble, partially crystallized solid polymer, chemical modifications are difficult to achieve with heterogeneous catalysts and therefore require the use of soluble catalysts. To meet specific hydrophilic properties, native starch has been either modified by oxidation [96,75,97] or by grafting hydrocarbon chains [96,98] (Fig. 13.24).

Hydrophilic starch obtained by partial oxidation is widely used in the paper and textile industries and can be potentially applied in a variety of applications (eg, for the preparation of paints, cosmetics, and superabsorbents). The oxidation occurs at the C6 primary hydroxyl

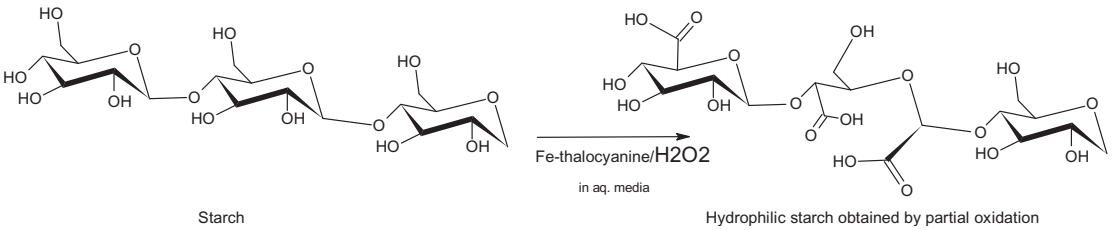


Fig. 13.24
Starch modification.

group or at the vicinal diols on C2 and C3 involving a cleavage of the C2–C3 bond to give carbonyl and carboxyl functions. Several transition metal catalysts based on Fe, Cu, or W salts (0.01–0.1 mol%) have been proposed to activate H_2O_2, which is a well-suited oxidant from an environmental and economical point of view. However, the concentration of metal ions was quite high and heavy metals were retained by the carboxyl functions of oxidized starch, which has good complex forming properties. Efficient catalytic methods for native starch oxidation with H_2O_2 in the presence of iron tetrasulfophthalocyanine (FePcS) are reported in literature [75]. Starches from different origin (potatoes, rice, wheat, corn) can be oxidized by H_2O_2 following two operational modes. Oxidation in aqueous suspension in the presence of iron phthalocyanine gives both carboxylic and carbonyl groups, while the oxidation of native starch by incipient wetness method provides 1.5 carboxyl and 5.6 carbonyl functions per 100 AGU. This process is applied successfully to the oxidized starches of different physical and chemical properties (amylose/amylopectin ratio, granule size, temperature of gelatinization) obtained from different crops (potato, wheat, rice, corn). This catalytic system is very flexible, because by simple modifications of the reaction conditions, it is possible to prepare oxidized starches with the desired level of carboxyl and carbonyl functions that are suitable for different applications. To prepare more hydrophobic starches for specific applications, partial substitution of starch with acetate, hydroxypropyl, alkylsiliconate, or fatty-acid ester groups are described in the literature. Octadienyl ethers of starch can be prepared by grafting octadienyl chains by butadiene telomerization catalyzed by hydrosoluble palladium catalytic systems [96,98].

13.15 Dehydration of Sugars to Furan Derivatives

The catalytic processes to obtain furan derivatives from carbohydrates and the catalytic routes from furan intermediates to chemicals and polymers have been reviewed by Hu et al. [99]. Various catalysts, such as dealuminated mordenite (Si/Al = 11) for converting hexose sugars to Hydroxy methyl furfural (HMF) are reviewed by these authors. Amongst various solvents studied Dimethyl sulfoxide (DMSO) is best suited because it prevents the formation of levulinic and humic acids (Fig. 13.25).

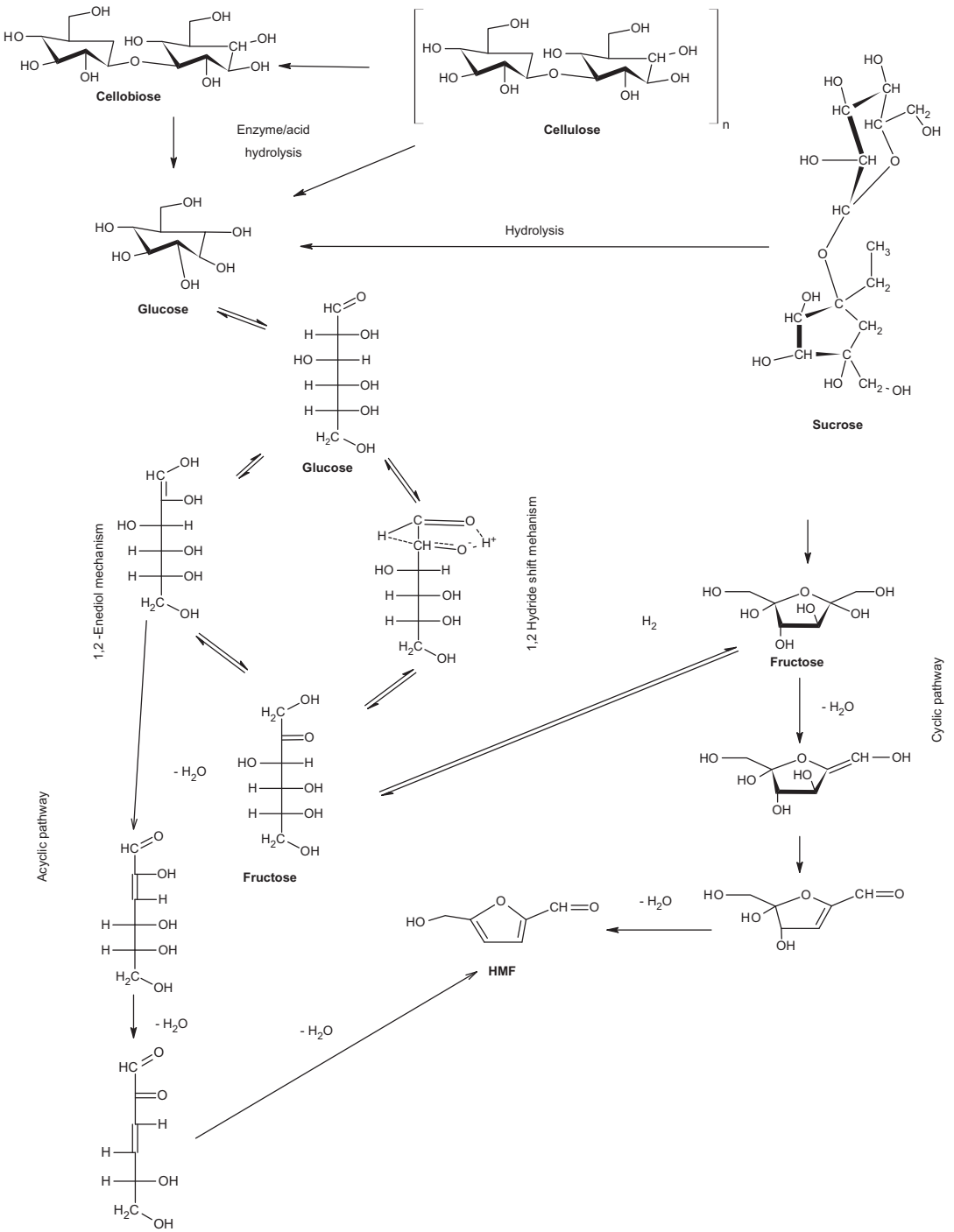
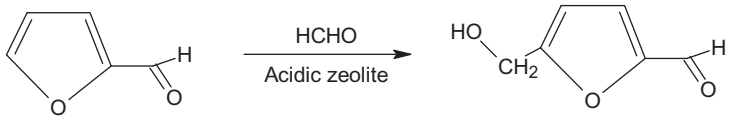


Fig. 13.25
Mechanistic routes for glucose dehydration. *From Ref [99].*

The fructose route to HMF has not been industrially developed; HMF is actually synthesized by hydroxymethylation of furfural with formaldehyde which is obtained industrially (by dehydration of pentoses and hemicelluloses.



In a similar manner, dehydration of C5 sugars in presence of acids gives furfural (Fig. 13.26).

The hydrogenation of HMF in the presence of metal catalysts (Raney nickel, supported platinum metals, copper chromite) leads to quantitative amounts of 2,5-bishydroxymethylfuran used in the manufacture of polyurethanes, or 2,5-bishydroxymethyltetrahydrofuran which can be used in the preparation of polyesters [100] (Fig. 13.27).

Vapor phase hydrogenation of furfural can be advantageously carried out on copper catalysts supported on activated carbon [101] (Fig. 13.28).

Liquid phase hydrogenation at 80°C in ethanol on Raney Nickel modified by heteropolyacid salts resulted in a 98% yield to furfuryl alcohol [102]. Oxidation of HMF by air on platinum catalysts yields selectively 5-formyl-2-furancarboxylic acid, which is further oxidized to 2,5-furandicarboxylic acid a potential substitute of terephtalic acid [103] (Fig. 13.29).

HMF to 2,5-furandicarboxyaldehyde is achieved at 90°C with air as oxidizing agent in the presence of V_2O_5/TiO_2 catalysts with a selectivity up to 95% at 90% conversion [104], assigned to Agrichimie [105].

As sugars are unable to undergo aldol condensation reaction, a reaction important for synthesis of long chain compounds, furanic molecules obtained as a result of sugar dehydration are looked upon as potential candidates for synthesizing higher chain compounds [106] (Figs. 13.30 and 13.31).

13.16 Catalytic Conversion of Triglycerides

Catalytic hydrogenation of vegetable oils or triglycerides extracted from the seeds of various plants using metal catalysts have been known for a long time, and are the subject of continuous improvements in terms of activity, catalytic conversion of triglycerides to surfactants and emulsifiers, such as fatty alcohol sulfates, fatty acid esters, alkylglucosides, and ethoxylated FAME are recent developments in the domain of oleochemistry (Fig. 13.32).

Fatty acid ester of glycerol are efficient surfactants obtained either by transesterification of triglycerides with glycerol (glycerolysis) or by esterification of fatty acids with glycerol.

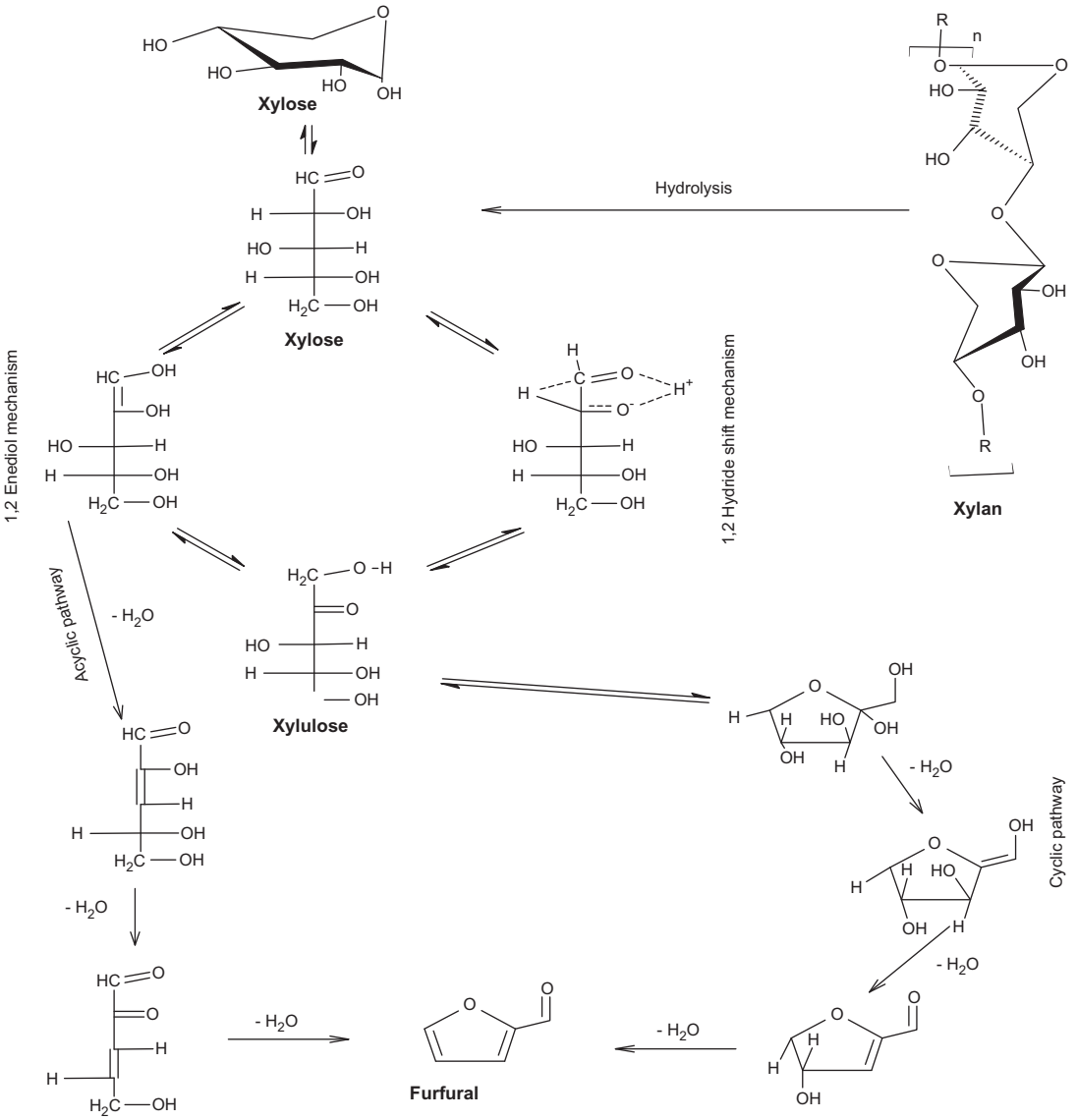


Fig. 13.26
Mechanistic routes for xylose dehydration. *From Ref [99].*

The challenge in both cases is to obtain selectively glycerol monoesters that are non-ionic surfactants with a good hydrophilic/hydrophobic balance employed in food, cosmetics, and pharmaceuticals. Glycerolysis reactions have been conducted on basic oxides to replace liquid bases. Blancquart et al. [107] have employed various basic oxides (ZnO, MgO, CeO_2, La_2O_3) to catalyze methyl stearate glycerolysis. The selectivity to monoglyceride is rather

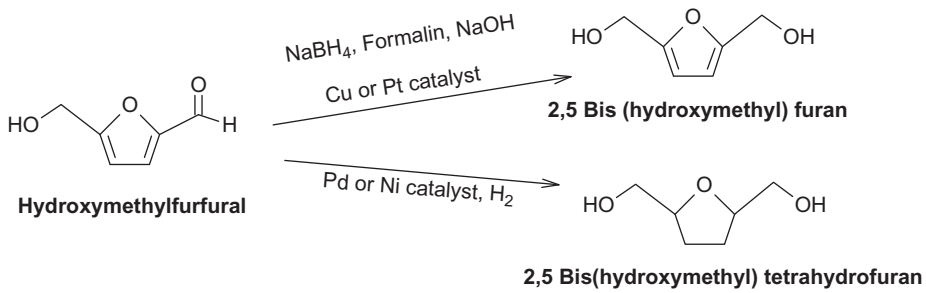


Fig. 13.27
Reduction of HMF.

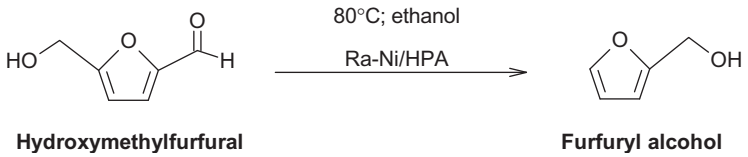


Fig. 13.28
Conversion of HMF to furfuryl alcohol.

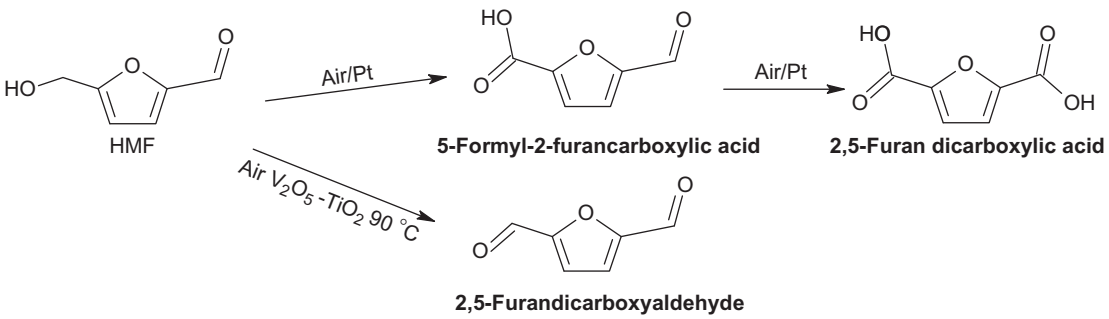


Fig. 13.29
Oxidation reactions of HMF.

similar to that obtained with homogeneous catalysts and the nature of the oxide had little effect. Doping MgO with lithium increased the basicity and conversion, but did not change selectivity. Glycerolysis of rapeseed oil on MgO catalysts gave a 63% yield to monoglyceride [108]. The preparation of glycerol monoester by esterification of fatty acid with glycerol was achieved with acidic solids to substitute sulfuric acid [109–115]. Fatty acid esters of sugars are also very important biodegradable and biocompatible surfactants that are prepared either by transesterification of methyl ester with sugar on basic catalysts, or by esterification of fatty acids with sugar on acidic catalysts. Liquid acids and bases have been replaced by enzymatic catalysis with lipase, giving a higher yield to monoester [116,117], but solid catalysts have not been used extensively so far.

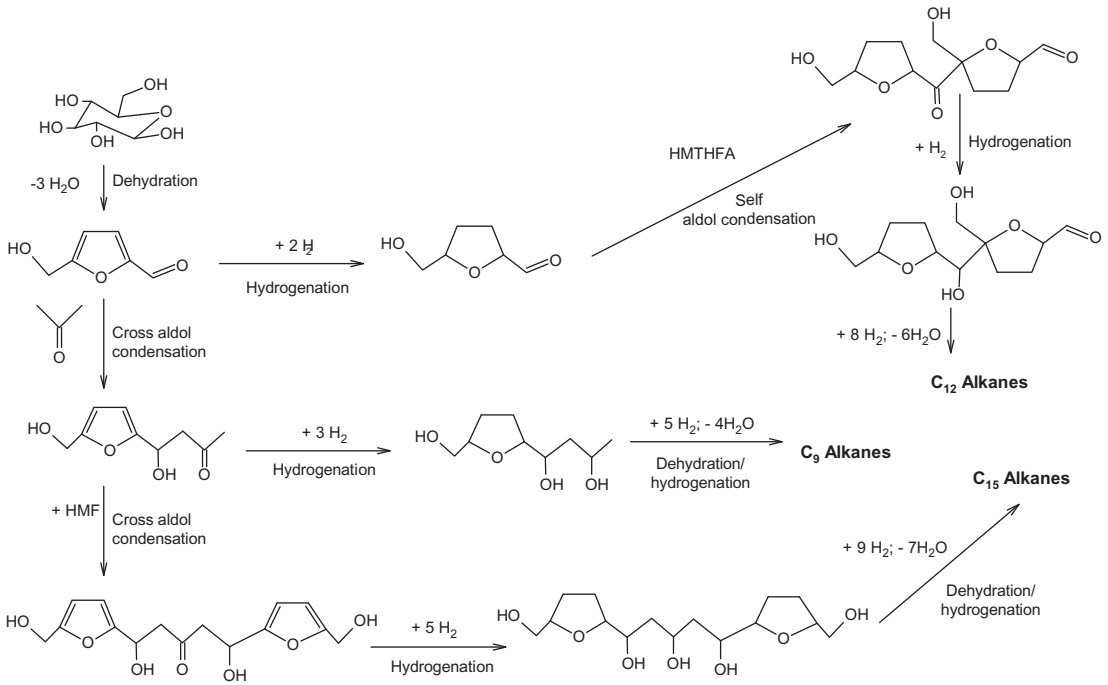


Fig. 13.30
Dehydration followed by Aldol condensation of C6 sugars.

Alkylglucosides are a class of valuable commercial surfactants particularly for cosmetics applications because of their biocompatibility. They are obtained by acetalization of carbohydrates with fatty alcohols in the presence of acid catalysts (Fig. 13.33).

Glucose acetalization gives a mixture of products with glucofuranoside or glucopyranoside rings. Zeolites and MCM-41 have been used as acidic catalysts to achieve the acetalization of glucose with alcohols of different chain lengths [118,119]. It was shown that shape selectivity effects decrease the amount of oligomers formed and that activity and selectivity can be controlled with the Si/Al ratio. In the glucosidation of *n*-butanol at 393 K, the furanoside/pyranoside ratio increased from 2.5 to 6 as the pore diameter of MCM-41 decreased from 5.3 to 2.5 nm, because of the lower diffusivity of the more bulky pyranoside ring in small pores. The kinetics and selectivity of glycosylation between glucose and n-butanol has been investigated in details over various dealuminated H-Y zeolites by Chapat et al. [120].

Fatty alcohols are obtained by hydrogenation of fatty acids or fatty acid esters in the presence of metal catalysts. The selective reduction of unsaturated esters to unsaturated alcohols is particularly difficult to achieve. The selective hydrogenation of methyl oleate to the corresponding unsaturated alcohol was achieved with Ru-Sn-B/Al_2O_3 catalysts prepared by reduction with $NaBH_4$ of Ru and Sn salts co-impregnated on alumina [121] (Fig. 13.34).

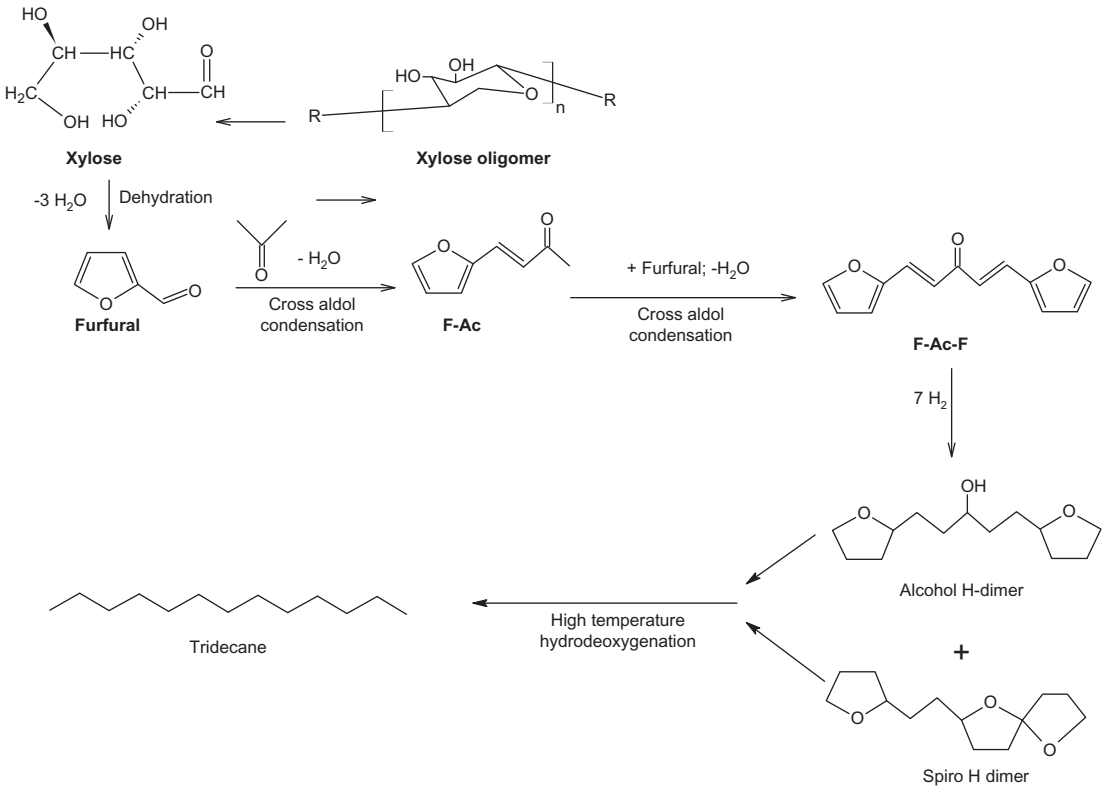


Fig. 13.31
Dehydration followed by Aldol condensation of C5 sugars.

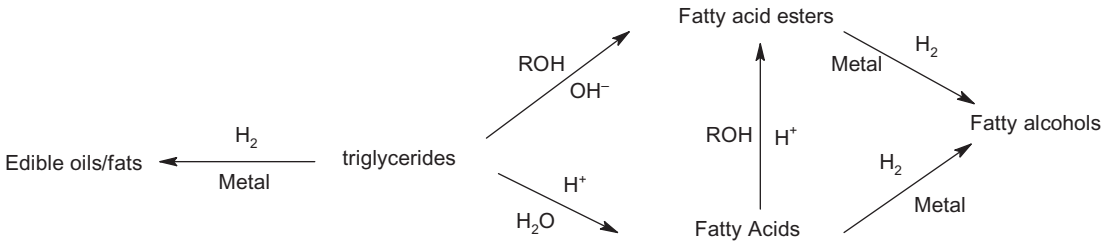


Fig. 13.32
Catalytic reactions of triglycerides.

13.17 Catalytic Conversion of Triglycerides to Lubricants

Because almost 50% of lubricants leak and spread out into the environment, there is a need for biodegradable lubricants produced from renewable sources. Fatty acid esters could be suitable lubricants, but their resistance to oxidation and tribological properties need to be improved. This can be achieved by epoxidation of the fatty acids followed by alcoholysis of the epoxide.

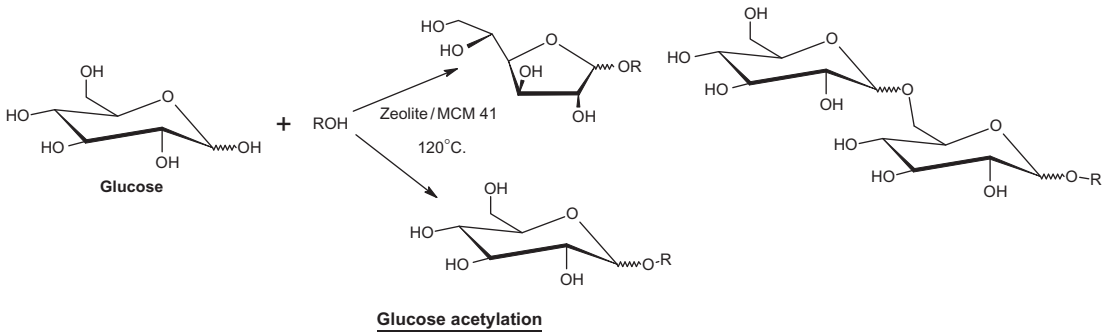


Fig. 13.33
Preparation of renewable surfactants.

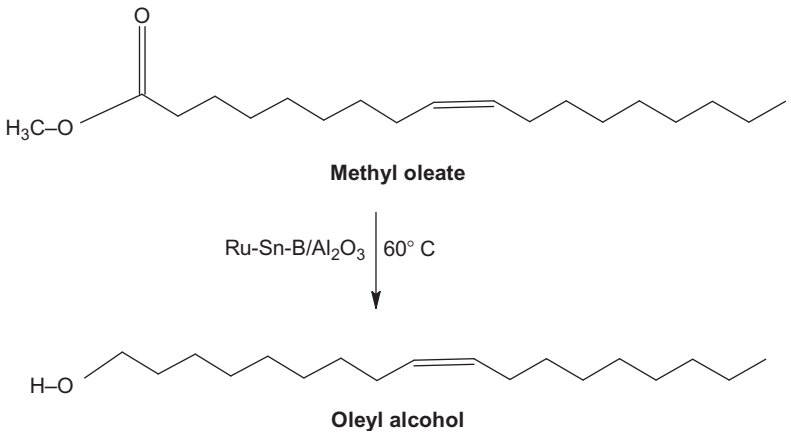


Fig. 13.34
Synthesis of fatty alcohols.

The epoxidation of FAME is traditionally conducted in strong acidic media (eg, with peracetic acid in sulfuric acid solutions). It has been shown that these reactions can be conducted by a environmentally benign route in the presence of acidic solids. Thus, the epoxidation of a mixture of FAME from sunflower oil were epoxided by tertbutylhydroperoxide (TBHP) at 363 K in the presence of Ti-MCM-41 catalysts, yielding 98% conversion with 85% selectivity to mono-epoxy compounds [122] (Fig. 13.35).

Ti/SiO2 (aerosil) catalysts showed comparable activity and selectivity indicating that the presence of ordered mesoporous framework is not necessary. In the same way, Rios et al. [123] used different Ti-MCM-41materials with pore diameters ranging from 1.9 to 4.1 nm, and amorphous Ti/SiO2 catalysts with different Ti-dispersion to perform methyl oleate epoxidation with TBHP at 70°C. Selectivities higher than 95% were obtained, whatever the structure of the supporting material, provided the titanium is well dispersed. It was shown that no leaching

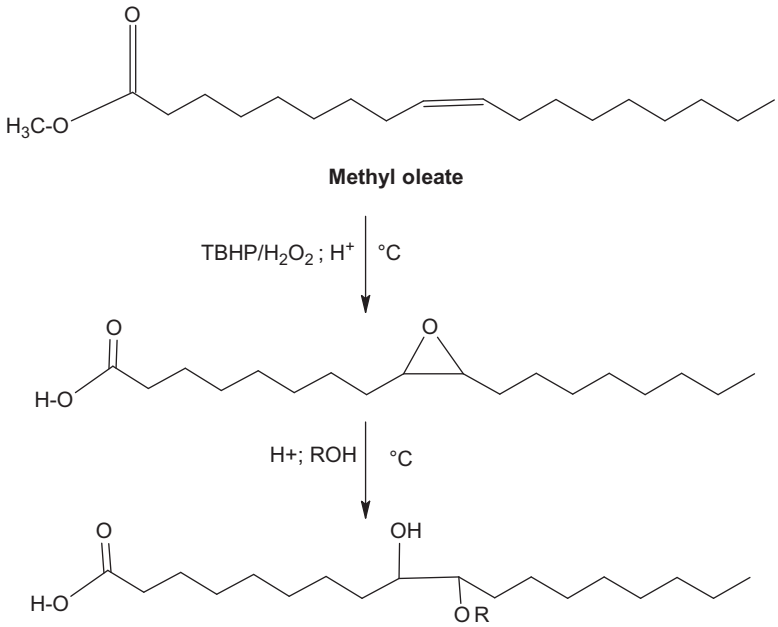


Fig. 13.35
Epoxidation of fatty alcohols.

occurs and that catalysts can be recycled. The alcoholysis with different alcohols of epoxidized FAME was studied on acidic resins of various structure and acid strength [124]. The addition of methanol on epoxidized methyl oleate at 60°C in the presence of Nafion entrapped in silica (SAC13) or Amberlyst 15, a sulfonated styrenedivinylbenzene copolymer, resulted in complete conversion with selectivity higher than 98%, but the reaction rate was higher on the more acidic SAC13 catalyst than on Amberlyst 15. On the other hand, a too strong acidity was detrimental to selectivity in the case of branched alcohols such as neopentanol.

13.18 Catalytic Conversion of Triglycerides to Polymers

Catalytic reactions involving C–C bonds are widely used for the conversion of unsaturated fatty compounds to prepare useful monomers for polymer synthesis. Heterogeneous catalysis has played a modest role so far in the production of monomers for polymer manufacture. Interestingly, dimerization of fatty acids by montmorillonite clays at 250°C results in diacids that can be hydrogenated to diols. These diacids and diols can be employed to produce polyesters, polyethers, polyamides, and polyurethanes. Homogeneous catalysis has been widely used to prepare monomers. Catalytic C–C coupling reactions of unsaturated fatty compounds have been reviewed by Biermann and Metzger [125]. Hydroformylation reaction of soybean and linseed oils catalyzed by rhodium complexes gave polyaldehydes in quantitative yield [126]. Metathesis reactions involving unsaturated fatty compounds to prepare

v-unsaturated fatty acid esters were applied by Warwel et al. [127]. Thus, the ethenolysis of methyl oleate catalyzed by ruthenium carbenes developed by Grubb yields 1-decene and methyl-9-decenoate, which can be very useful to prepare monomers for polyolefins, polyesters, polyethers and polyamides (Fig. 13.36).

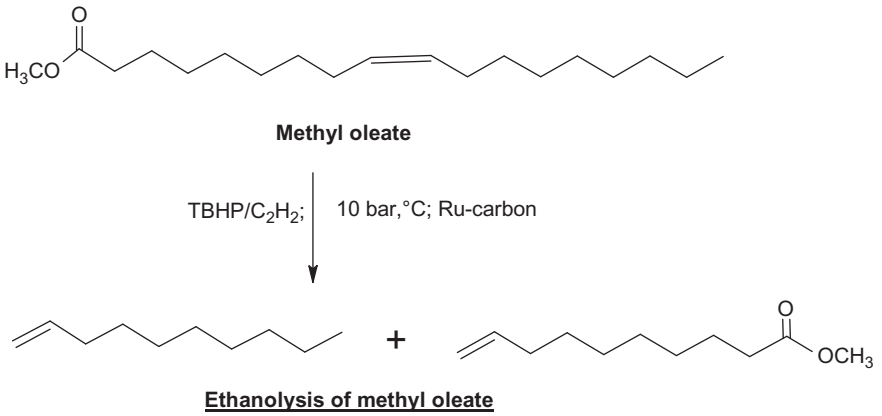


Fig. 13.36
Application of fatty acid esters in polymers.

13.19 Catalytic Conversion of Glycerol

13.19.1 Oxidation of Glycerol to C3 Oxygenates

The selective oxidation of glycerol leads to various valuable oxygenates. Most of these compounds are currently prepared by enzymatic reactions and have a small market because of their high price. Besson and Gallezot [77] have shown that they can be obtained by oxidation with air of aqueous solutions of glycerol in the presence of carbon-supported platinum and palladium catalysts (Fig. 13.37).

The selectivity can be tuned by promotion of the noble metals with bismuth or by operating under controlled pH. Garcia et al. [78] found that the oxidation of glycerol at basic pH on palladium and platinum catalysts yielded 70% glycerate. Using bismuth-promoted platinum under similar reaction conditions, the oxidation leads to dihydroxyacetone with a 25% yield. Fordham et al. [128] found that glyceric acid oxidation on 5% Pt-1.9% Bi/C catalyst yielded 74% hydroxypyruvic at 80% conversion at acidic pH (3–4), but on the same catalyst under basic condition (pH 10–11), a 83% yield to tartronate was obtained at 85% conversion. Abbadi and van Bekkum [84] obtained a 93% selectivity to hydroxypyruvic acid at 95% conversion of glyceric acid on 5% Bi-5% Pt/C catalyst without pH regulation. Fordham et al. [128] have studied the preparation of mesoxalic acid by oxidation of sodium tartronate on PtBi/C catalyst at 60°C without pH control; the maximum yield was 65% at 80% conversion.

Fig. 13.37
Various chemicals from glycerol.

A total conversion of tartronic acid was obtained at 80°C giving 50% yield of mesoxalic acid with no other products, because all by-products were totally oxidized into CO_2. More recently, the oxidation of glycerol was conducted in the presence of gold catalysts in basic medium [129,130].

Glycerol was oxidized with oxygen at 60°C with a selectivity of 100% at 56% conversion on 1 wt.% Au/activated carbon. Graphite supported catalysts gave comparable results. The selectivity of glycerol oxidation on gold catalysts loaded various supports were shown to depend critically upon the size of gold particles [131].

13.20 Conversion of Glycerol to Polyglycerols and Derivatives

Polyglycerols obtained by dehydration of glycerol are employed as surfactants, lubricants, cosmetics, and food additives, etc. Their esterification with fatty acids leads also to valuable emulsifiers or metal working fluids. There are three challenges in the etherification of glycerol, viz.: (i) replace liquid bases by solid catalysts to achieve a greener and more efficient process; (ii) control the chain length to obtain a suitable hydrophilic lipophilic balance in PGEs; (iii) avoid the formation of acrolein by internal dehydration. The etherification of glycerol by dehydration in the presence of liquid bases leads to a mixture of dimers, trimers, and cyclic or branched oligomers. Zeolites have been used to take advantage of shape selectivity effect to minimize oligomer formation [132,133]. The selectivity to monoglycerol was improved over Cs-ZSM-5 catalyst, but the activity was too low [134]. A fair compromise between activity and selectivity was obtained by Clacens et al. [135] using cesium impregnated mesoporous MCM-41.

13.21 Hydrogenolysis of Glycerol to 1,2- and 1,3-PDO

Glycerol can be selectively dehydroxylated either to 1,2-PDO, a chemical that can advantageously replace ethylene glycol as antifreezing agent or to 1,3-PDO, which copolymerized with terephtalic acid, give polyesters with unique mechanical properties. 1,3-PDO is currently produced by catalytic routes from ethylene oxide (Shell route) or acrolein (Degussa-DuPont route). The microbial production of 1,3-PDO is under development by DuPont-Genencor to produce 1,3-PDO from glucose [136]. Chaminand et al. [137] studied the hydrogenolysis of aqueous solutions of glycerol at 180 8C under 80 bar H2-pressure in the presence of supported metal catalysts in an attempt to produce selectively 1,2- and 1,3-PDO. Different catalysts (Cu, Pd, Rh), supports (ZnO, C, Al_2O_3), solvents (H_2O, sulfolane, dioxane), and additives (H_2WO_4) were tested to improve reaction rate and selectivity. The best selectivity (100%) to 1,2-PDO was obtained by hydrogenolysis of water solution of glycerol in the presence of CuO/ZnO catalysts. To control the selectivity toward 1,3-PDO, the reaction was conducted with rhodium catalysts with tungstic acid added to the reaction

medium. The best selectivity to 1,3-PDO (1,3-PDO/1,2-PDO = 2) was obtained by operating in sulfolane. The presence of iron dissolved in the reaction medium was also beneficial for the selectivity to 1,3-PDO. A mechanism was proposed to account for the effect of the different reaction parameters (Fig. 13.38).

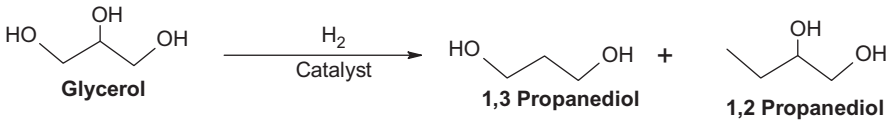


Fig. 13.38
Reduction of glycerol.

13.22 Catalytic Conversion of Terpenes

Heterogeneous catalysis is increasingly used for the conversion of terpenes and derivatives in the place of homogeneous processes. The three main starting materials employed in terpene chemistry are α- and β-pinene, which are extracted from turpentine oil, a coproduct of paper pulp industry, and limonene extracted from citrus oil. They are used for the synthesis of flavors and fragrances (F&F), although these compounds are often more easily obtained by catalytic routes from hydrocarbons (Fig. 13.39).

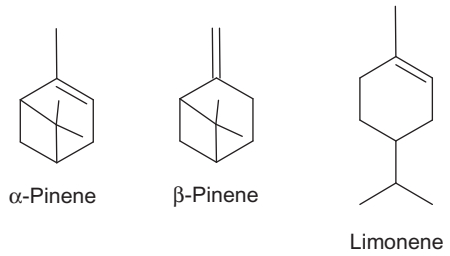


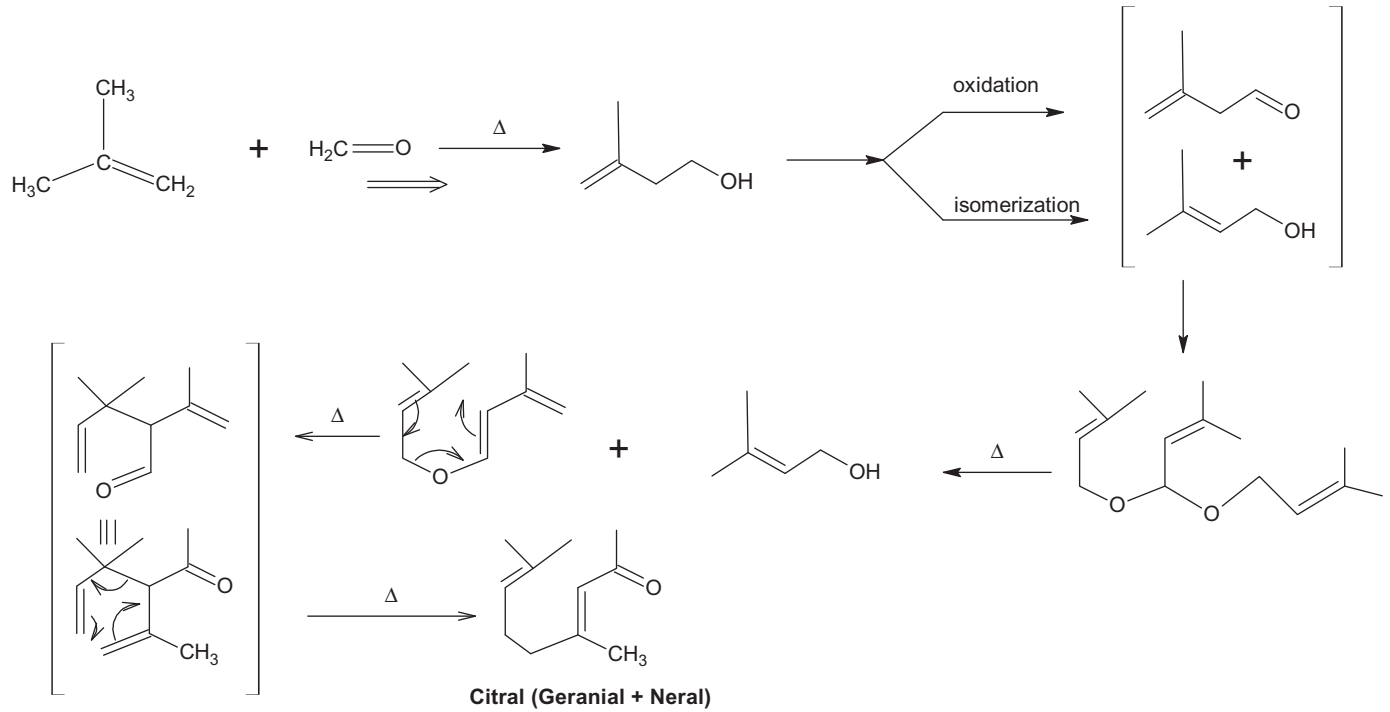
Fig. 13.39
Three main terpene base molecules.

Thus, citral synthesis requires five steps from α-pinene whereas it is obtained with a 95% yield in the BASF process starting from formaldehyde and isobutene [138] (Fig. 13.40).

p-Cymene, a precursor of p-cresol and various F&F, was obtained by dehydrogenation of α-pinene at 300°C in a continuous fixed-bed flow reactor in the presence of 0.5 wt.% Pd/SiO_2 [9].

Under similar conditions, but starting from limonene, p-cymene was obtained with a 97% yield and the catalytic activity was stable for 500 h on stream [139] (Fig. 13.41).

More interestingly, p-cymene was produced under similar reaction conditions with nearly 100% yield from a mixture of di-pentene (Sylvapine DP-378), showing that raw materials need not be purified and still be converted in one step to desired product [138]. The conversion



Citral (Geranial + Neral)

Fig. 13.40
BASF process of citral manufacture from isobutene.

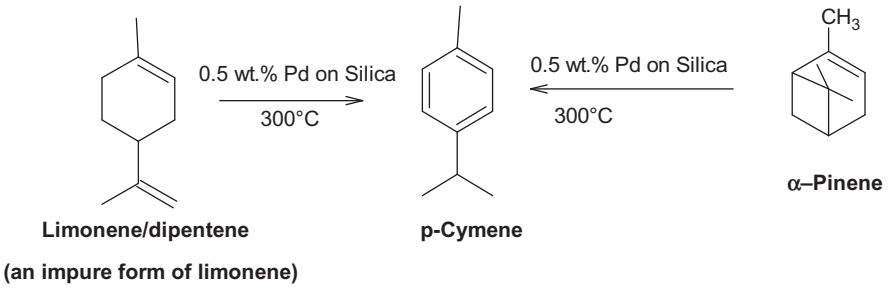


Fig. 13.41
Synthesis of p-cymene.

of α-pinene oxide to campholenic aldehyde, an important intermediate in the synthesis of sandalwood-like fragrances, is traditionally carried out in the presence of $ZnCl_2$ or $ZnBr_2$ salts (Fig. 13.42).

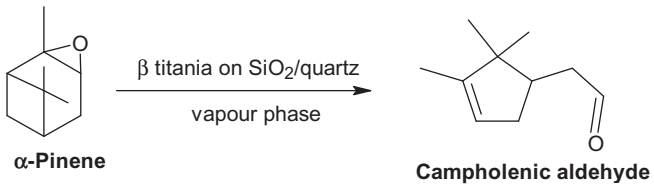


Fig. 13.42
Synthesis of campholenic aldehyde.

Alternative routes have been described using solid catalysts with Lewis acid sites, giving high yield of campholenic aldehydes [140–143].The liquid phase alkoxylation of limonene with C1–C4 alcohols to 1-methyl-4-[a-alkoxy-isopropyl]-1-cyclohexene was carried out both in batch and continuous fixed-bed reactor at 60°C on various acidic catalysts [144] (Fig. 13.43).

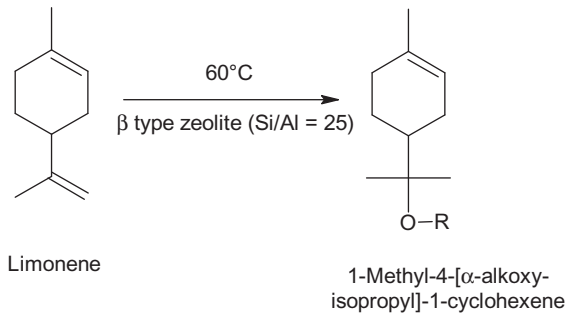


Fig. 13.43
Alkoxylation of limonene.

The best yields were obtained in BR (85%) or continuous reactor (81%) using a beta type zeolite with $SiO_2/Al_2O_3 = 25$.

Solid basic catalysts can advantageously be used to replace soluble catalysts in the conversion of terpene derivatives (Fig. 13.44).

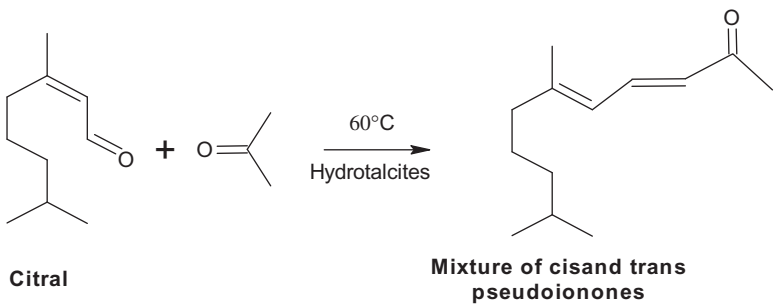


Fig. 13.44
Coupling of citral with acetone.

Thus, the aldol condensation of acetone with citral was achieved in the presence of rehydrated hydrotalcite with a 96% yield to a mixture of cis- and trans-pseudoionone by operating in liquid phase at 60°C [145]. Heterogeneous catalysts are also widely used for selective hydrogenation of terpenes derivatives, eg, to convert aldehydes to the corresponding alcohols (cinnamaldehyde to cinnamyl alcohol, citral to geraniol and nerol, etc.) however, most of the terpenes derivatives used in F&F are not synthesized from natural terpenes. There are also interesting examples of terpene conversion catalyzed by organometallic complexes. Thus, Byrne et al. [146] have shown that (*R*)-limonene oxide can be copolymerized with CO_2 (also a renewable feedstock!) in the presence of β diiminate zinc acetate to yield high molecular weight (10 kg/mol) polycarbonate (Fig. 13.45).

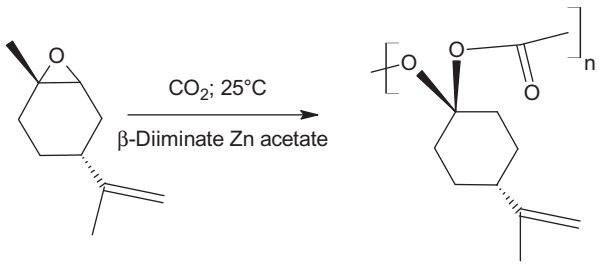


Fig. 13.45
Co polymerization of limonene oxide.

13.23 Cascade Catalysis

It involves enzymatic catalysis, homogeneous catalysis and heterogeneous catalysis in a specific sequence without recovery of intermediate products. The combination of enzymatic and chemical steps can give better yields. Thus, Frost [147] has shown that direct enzymatic

conversion of glucose to catechol is limited to 5% yield because of the poisoning of the strain by the aromatic molecule. Instead, a 43% yield to catechol was obtained by combining enzymatic and decarboxylation steps. Various examples of one-pot reactions combining enzymatic and chemo-catalytic steps were given by Bruggink et al. [148,149].

One of the most representative examples consists of a four-step conversion of glucoside to aminodeoxysugar without intermediate product recovery as described below (Fig. 13.46).

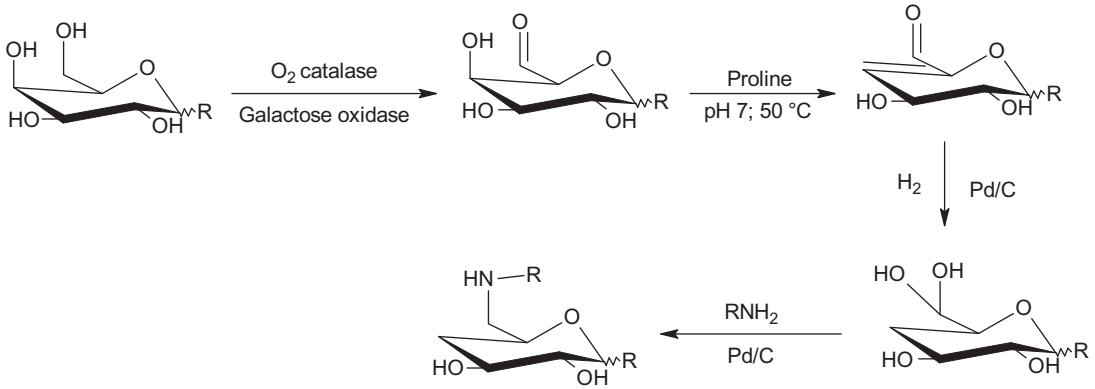


Fig. 13.46
Application of cascade catalysis in synthesis of aminodeoxysugars.

13.24 Summary and Future Trends

Only few examples were selected in this paper from a very active field of basic research covering multidisciplinary topics published in a great diversity of journals. The R&D on biomass derived products is also rapidly expanding. Chemical companies have started extensive R&D efforts on developing bio-based chemicals. According to the report "Vision for Energy and Biobased Products in the United States," [150] the share of target chemicals that are biobased could reach 25% by 2030. To meet the challenge a large integrated research effort in chemistry, biochemistry, and genetics, as well as in chemical and biochemical engineering, will be required. In view of the diversity and complexity of the raw materials employed as feedstocks in bioproduct synthesis, the processes leading to end-products are necessarily different from present processes starting from fossil fuels. Although the cost of many platform molecules issued from biomass are comparable to those of many current chemical intermediates, their processing costs is much higher. New flow sheets have to be developed to decrease the cost and to increase the quality of end-products, because even if they may prefer bio-based products, consumers do not want to pay more and have lower quality products. Flow sheets of organic synthesis from hydrocarbons have been improved for more than a century; it may require some time to reduce the processing costs of biomass derivatives to

make competitive bio-products. Catalysis has a major role to play at converting biomass into useful products. Presently, a comparatively limited number of researchers in academia are active in this field. In view of the importance of environmental and economic challenges to meet, the workforce should be strengthened to develop this exciting field of research. Importantly, lifecycle analysis studies should be conducted in parallel to validate the benefits of new processes in terms of ecology and economy.

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CHAPTER 14

Carbonylations and Hydroformylations for Fine Chemicals

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14.1 Introduction

The development of environmentally benign and clean synthetic methodologies is one of the most important goals of current research in chemistry. Conventional technologies for pharmaceuticals and fine chemicals are mostly chemistry intensive, with a focus on products with desired purity and productivity. These synthetic routes also have the drawbacks of generating significant quantities of waste, with inorganic salts as by-products, and of using corrosive and toxic reagents. However, because of strict environmental regulations and increasing competition, the emphasis of the work is on the development of environmentally cleaner and atom-efficient synthetic routes. Catalysis has made a significant impact in the development of innovative processes, new competitive technologies and environmental compatibility. Homogeneously catalyzed carbonylation and hydroformylation reactions are particularly attractive in this context. They have the potential to provide clean, atom-efficient routes for the synthesis of molecules, with carboxylic acid, aldehyde and amide functional groups to replace stoichiometric, multistep routes using toxic and hazardous reagents [1,2].

Rhodium (Rh) catalyzed hydroformylation of olefins and carbonylation of methanol showcase successful utilization of processes catalyzed by homogeneous metal complexes. Both processes have been in operation for almost five decades and have gone through several changes since their inception, and new plants based on improved technologies have come up over the years. The separation of expensive Rh complex catalysts from the reaction products has presented a challenge, and strict control of the reaction conditions is necessary to avoid loss of rhodium during recycling. Thus both processes are viable at a very high scale of operation and for volatile products that can be separated by distillation. This is probably the reason for the utilization of expensive rhodium catalyst for commodity chemicals where plant capacity is high and sufficient to absorb the high cost of the process control equipment necessary to keep rhodium catalysts in active form during recycling.

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Extensive research efforts on the synthesis of novel organometallic complexes with a focus on ligand design have opened up new opportunities for the application of homogeneous catalysts for the synthesis of a wide range of specialty organic products useful in pharmaceuticals and fine chemicals as well as bulk commodity products [3,4]. Significant advancements in organometallic chemistry and in situ characterization techniques have led to a better understanding of the catalytic intermediates involved in the reaction, and to enabling control of catalytic activity and selectivity. Also, significant research efforts are being devoted to the development of new approaches for catalyst-product separation, such as immobilization of soluble catalysts, biphasic catalyst systems, membrane separation, and so on. [5].

In this chapter, some important recent examples of potential applications of hydroformylation and carbonylation reactions in industry are presented. Work carried out on the development of new strategies for the separation of catalysts in carbonylation reactions is presented in the subsequent section.

14.2 Hydroformylation

Hydroformylation of olefins represents one of the largest commercial processes based on homogeneous catalysis for the manufacture of a wide range of aldehydes ~10 million tonnes per annum (TPA). Aldehydes are valuable end products and intermediates in the synthesis of bulk chemicals like alcohols, esters, and amines, with end applications in plasticizers and detergents. The first plant based on cobalt (Co) catalyst started in the 1940s and the process has undergone several changes, with processes differing mainly with the type of catalyst (Co and Rh complexes) used [6]. The low-pressure hydroformylation process based on Rh/phosphine ligands is the dominant process; almost 70% of the capacity based on ethylene, propylene and butene uses this process and is operated mostly by Dow Chemicals, BASF, and Mitsubishi [2].

Ruhrchemie developed the concept of aqueous biphasic hydroformylation using a water-soluble tris(3-sulfophenyl)phosphine trisodium salt (TPPTS) ligand [2]. The process was commercialized in 1984 in Germany. A major advantage of the process is easy catalyst/product separation by keeping the catalyst in the water phase (Rh loss in parts per billion (ppb) quantity) and avoiding thermal stress. However, the process is suitable only for water-soluble lower olefins to get acceptable rates.

Major issues in all the hydroformylation processes are regioselectivity (*n*:*iso* ratio of aldehyde products), operating pressures, carbon monoxide (CO) inhibition, recycling and recovery of expensive catalysts and complex multiphase (gas-liquid) reaction engineering [7]. According to the analysis of Wiese and Obst [8], for a hydroformylation plant of 400,000 TPA capacity, loss of 1 parts per million (ppm) Rh/kg product amounts to a loss of several million euros.

This highlights the crucial role of efficient recycling and recovery of the Rh catalyst and necessary process controls.

A major focus of the work on hydroformylation has been on the development of improved ligands with high stability and a high *n*:*iso* ratio of aldehydes. The price and stability of the ligand significantly affects the overall cost of the process [2]. Union Carbide developed bisphosphinite-type ligands (Fig. 14.1), which have high activity (30 times higher compared to triphenylphosphine) and stability and give products with a high *n*:*iso* aldehyde ratio compared to triphenylphosphine as a ligand [9–11]. Several plants have come using this technology, and the exceptional stability of the catalyst can be seen from the fact that catalyst replacement was not required for 11 years for the first plant built in the United States in 1995 [12]. Thus for producing 2-ethylhexanol a bisphosphinite-based catalyst is preferred, while when isobutyraldehyde is desired, a catalyst based on triphenylphosphine is preferred [12].

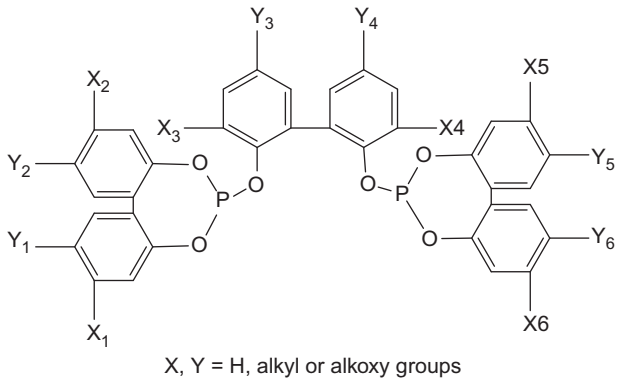
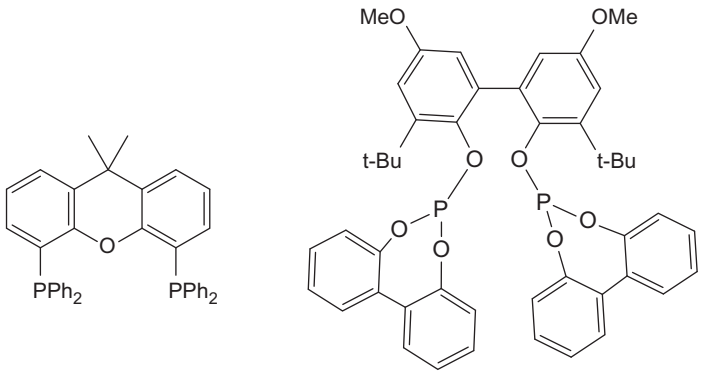


Fig. 14.1
General structure of bisphosphinite-type ligands.

Hydroformylation is a mature technology; however, its industrial applications are known mainly for unsubstituted olefins as substrates (C_2-C_{18}), and it is viewed as a process for the commodity chemical industry. Possible reasons for this are risks associated with the use of CO/H_2 gases under high pressure and recycling/recovery costs associated with the use of costly Rh-based catalysts. A major advantage of hydroformylation is perfect atom economy, and ligands developed within the past 20 years offer excellent regioselectivity, chemoselectivity and functional group tolerance [6,13]. For example, xantphos and biphephos ligands (Fig. 14.2) lead to high selectivity for linear aldehydes from terminal alkenes and are available commercially. Significant research is being carried out on the synthesis and evaluation of different types of ligands to tune the regioselectivity and new applications for synthesis of complex, nonvolatile organic products [2,14,15].



Xantphos **Biphephos**

Fig. 14.2
Structure of xantphos and biphephos ligands.

The promising applications based on hydroformylation of substituted olefins for synthesis of complex organic products have not been fully exploited. In the following section, recent examples of the utilization of hydroformylation reactions for the synthesis of fine and specialty chemicals are presented.

14.2.1 Hydroformylation of 1,4-Diacetoxy-2-Butene for the Synthesis of Vitamin A Intermediate

Hydroformylation of 1,4 diacetoxy-2-butene (DAB, **1**) is an interesting example for the synthesis of 2-methyl-4-acetoxy butenal (MAB, **3**), a key intermediate in the synthesis of Vitamin A (Fig. 14.3). BASF [16] and Hoffmann-La Roche [17] have developed commercial processes for the synthesis of Vitamin A, with hydroformylation of 1,4 diacetoxy-2-butene (DAB, **1**) as one of the important steps (Fig. 14.3). The process developed at BASF involves isomerization of DAB to 1,2-diacetoxy-3-butene (Fig. 14.3, **1a**). Hydroformylation of 1,2-diacetoxy-3-butene (**1a**) gives the branched aldehyde (Fig. 14.3, **2a**), which on elimination of acetic acid gives MAB (**3**) as the product. The Wittig reaction of MAB leads to Vitamin A acetate (**4**) as the product. The process developed by Hoffmann-La Roche starts with hydroformylation of 1,4-diacetoxy-2-butene (**1**) to give aldehyde **1b** (1,4-diacetoxy-2-formyl butane, DAFB) as the product (Fig. 14.3). Deacetoxylation of **1b** to **2b** (2-formyl-4-acetoxy-1-butene, FAB) followed by isomerization of **2b** gives MAB (**3**) as the product. Aldehyde MAB obtained as the product is thermally sensitive and its separation from the homogeneous Rh complex catalyst is a challenge. As per the patent [16], the yield of aldehyde was about 77% and recovery and reuse of the expensive Rh catalyst was a critical step.

In order to overcome the catalyst/product separation problem, the reaction has been investigated in a biphasic medium by using an Rh-TPPTS catalyst [18] and by using a tethered Rh

complex catalyst [19]. The hydroformylation of DAB using an $[Rh(COD)Cl]_2$/TPPTS complex catalyst in a two-phase system (toluene and water) was studied in a batch reactor at 348 K and 6.8 MPa syngas pressure. Under biphasic reaction conditions, 2-formyl-4-acetoxy-1-butene (FAB, **2b**) was formed as the only product by deacetoxylation of DAFB (**1b**). The biphasic catalyst was active and highly stable for the synthesis of FAB (**2b**) as a product as seen from the recycling results; however, inert conditions were required during catalyst/product separation to avoid oxidation of TPPTS used as a ligand. A tethered catalyst was prepared by using the Wilkinson complex $[Rh(CO)Cl(PPh_3)_2]$, phosphotungstic acid and neutral alumina as support [19]. The tethered catalyst was air stable and complete conversion of DAB with 75% selectivity to FAB was observed. The catalyst was active and selective even after six recycling experiments.

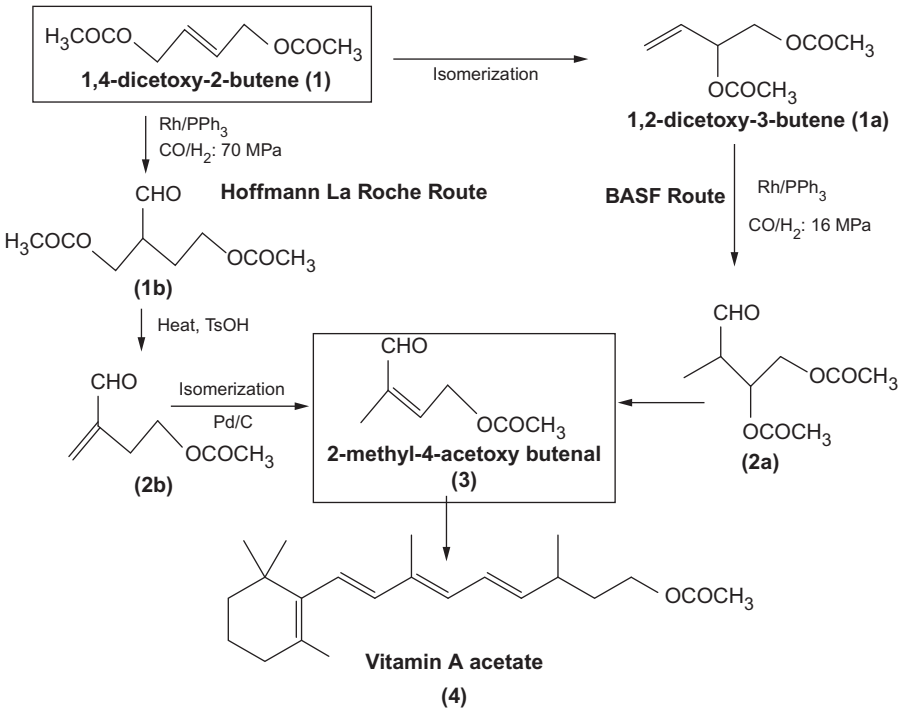


Fig. 14.3
Synthesis of vitamin A acetate with hydroformylation as key step.

14.2.2 Synthesis of (S)-Allysine Ethylene Acetal

(*S*)-Allysine ethylene acetal is an intermediate in the manufacture of angiotensin-I converting enzyme (ACE) and neutral endopeptidase (NEP) inhibitors, which are under clinical trial (Fig. 14.4). Dr. Reddy's Laboratories and Chirotech Technology Ltd. have developed a noninfringing process for the synthesis of (*S*)-allysine ethylene acetal [20]. A five-step process has been developed for the production of (*S*)-allysine ethylene acetal using a combination

of two catalytic technologies, namely rhodium-catalyzed tandem isomerization/hydroformylation and bioresolution.

Starting from crotonaldehyde, the synthesis involves acetal formation with ethylene glycol (**5**) followed by linear selective isomerization/hydroformylation to yield predominantly glutaraldehyde monoethylene acetal (**6**). After an aqueous extraction to remove and recover the transition metal catalyst, a Strecker reaction followed by hydrolysis and benzoylation afforded the appropriate N-substituted racemic amino acid (**8**). Bioresolution of this racemate using a thermophilic L-acylase from archaeon *Thermoccocus litoralis* enabled separation of the linear product from the corresponding branched isomers and provided (*S*)-allysine ethylene acetal (**9**) with >99% ee and >99% purity. Various phosphite-based ligands were screened for the hydroformylation step with $Rh(CO)_2(acac)$ catalyst, and biphephos was found to be the suitable ligand on the basis of product yield, catalyst/product separation and overall process economics. Tandem isomerization/hydroformylation was carried out using an Rh/biphephos catalyst system (Rh:L ratio: 1:1.2) at 353 K using an S:C ratio of 4000 and 0.3 MPa syngas pressure. The desired linear aldehyde (glutaraldehyde monoethylene acetal, **6**) was obtained with high selectivity and an *n*:*iso* ratio of 15:1. Based on this process, (*S*)-allysine ethylene acetal has been produced on a several hundred kg scale [20].

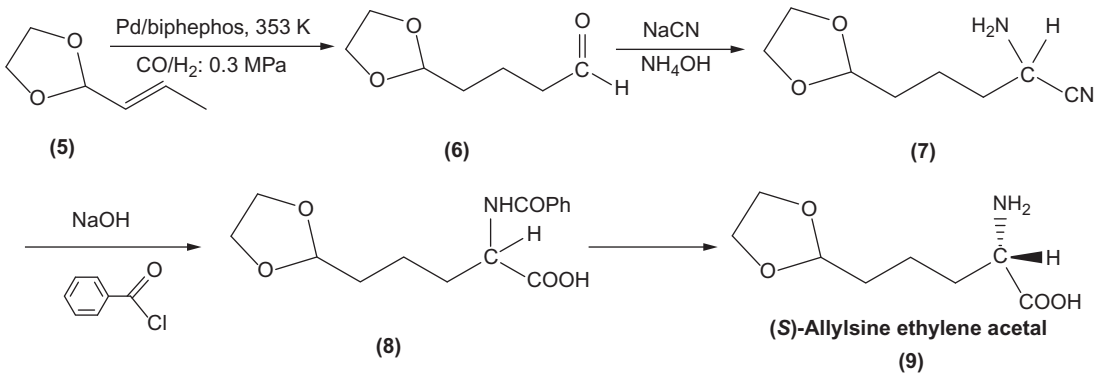


Fig. 14.4
Synthesis of (*S*)-allysine ethylene acetal with Rh-biphephos catalyzed asymmetric hydroformylation as important step.

14.2.3 Hydroformylation of Norbornylene to Exo-Aldehyde

Racemic exo-norbornyl-2-carboxylic acid is used as a building block for a variety of pharmacologically active molecules. Gu et al. [21] at Pfizer worldwide research and development have developed a three-step protocol for kilogram-scale synthesis of (±)2-exo-norbornyl carboxylic acid starting from norbornylene, with low-pressure hydroformylation as the crucial step (Fig. 14.5). Various ligands available were screened for the hydroformylation step and dppf (1,1′-bis (diphenylphosphino)ferrocene) was found to be a suitable ligand, with high activity and desired selectivity [21]. Hydroformylation of norbornylene (8.0 kg) with

0.15 mol% $Rh(CO)_2(acac)$ with dppf (0.3 MPa H_2/CO, 308 K, *t*-BuOH) gave the exo-aldehyde exclusively. Oxidation with $NaClO_2$ and TEMPO (2 mol%) was performed directly on the *t*-BuOH solution from the hydroformylation reaction to give 2-exo-norbornyl carboxylic acid, which was isolated as the sodium salt, in 80% overall yield. This process is considered a new benchmark for low-pressure hydroformylation of cyclic, bridged olefins [21].

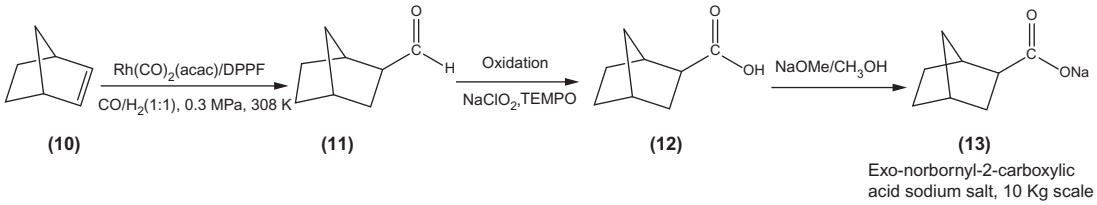


Fig. 14.5
Synthesis of exo-norbornyl-2-carboxylic acid.

14.2.4 Hydroformylation in Fragrances

Aldehydes are extensively utilized in the perfumery industry; hence hydroformylation finds several applications in the fragrance industry [22] (see Fig. 14.6). Various fragrance chemicals produced using a hydroformylation reaction include 2-methylundecanal (**14**) and 2-methyldecanal (**15**) involving hydroformylation of 1-decene [13], Vertral (**16**) produced by hydroformylation of exo-dicyclopentadiene with Rh_2(2-Et-hexanoate)$_4$ [23], Florhydral

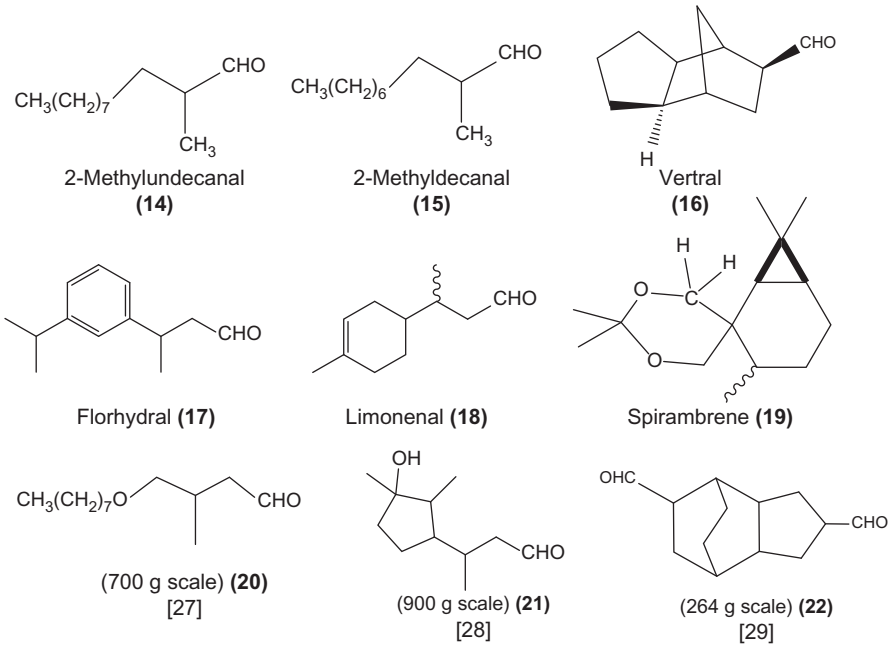


Fig. 14.6
Fragrance chemicals based on hydroformylation.

(**17**), Limonene aldehyde (**18**) practiced by Celanese [24] and Spirambrene (**19**) manufactured by Givaudan and Vigon by hydroformylation of 2-carene [25,26]. There are recent patents on the synthesis of fragrance chamicals prepared on >100 g scale based on hydroformylation (**20** [27], **21** [28], **22** [29]) (Fig. 14.6). Although they are not prepared commercially, the scale of operation (>100 g) indicates potential interest in commercialization in the future [13]. Details on fragrance chemicals are covered in depth in Chapter 11.

14.2.5 Hydroformylation of N-Allyl Phthalimide

Amino aldehydes are important bifunctional synthetic intermediates used in pharmaceutical, fragrance, agrochemical and other fine chemical applications. High purity of the product is desired for further applications. Hydroformylation of *N*-allyl phthalimide (**23**) (phthalimide as the protecting group for the amine group) is an important step in the synthesis of amino aldehydes with high selectivity. Dow Global Technologies Inc. has carried out hydroformylation of *N*-allyl phthalimide (**23**) on a 200-g scale using an $Rh(CO)_2(acac)$/biphephos catalyst system [30] (Fig. 14.7). The reaction was carried out at 353 K with

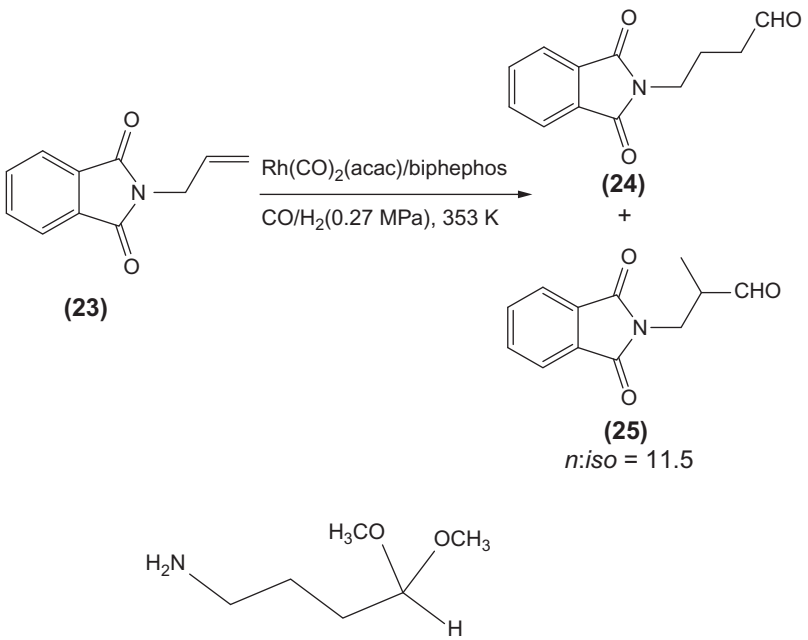


Fig. 14.7
Hydroformylation of *N*-allyl phthalimide.

0.27 MPa of syngas, and the desired linear aldehyde (**24**) was obtained in 11.5:1 linear/branched ratio with the Rh-biphephos catalyst. Acetal protection of the aldehyde and cleavage of the phthalimide gave the protected amino aldehyde (**26**), with high purity (~98%) useful as a pharmaceutical intermediate.

14.2.6 Racemic Naproxen by Rhodium-Catalyzed Hydroformylation Route

Synthesis of DL-naproxen [2-(6-methoxynaphthyl) propanoic acid] is conventionally performed by multistep stoichiometric organic synthesis (Syntex process) using toxic/corrosive reagents, which poses serious environmental issues. Brown reported a catalytic route based on hydroformylation using sugar-derived phosphines [31]. In the late 1980s, Parrinello and Stille [32] reported the first asymmetric hydroformylation synthesis of (*S*)-naproxen using a Pt-bisphosphine catalyst.

Rajurkar et al. [33] have investigated the synthesis of DL-naproxen (**30**; Fig. 14.8) by an environmentally benign, catalytic two-step hydroformylation-oxidation route. The regioselective hydroformylation of 6-methoxy-2-vinylnaphthalene (**27**) was carried out using an $Rh(CO)_2(acac)$/dppe (2-bis(diphenylphosphino)ethane) catalyst at 373 K and CO/H_2 pressure of 5.51 MPa to obtain 95% conversion of 2-methoxy-6-vinylnaphthalene (**27**) with 95.2% selectivity for 2-(6-methoxynaphthalene-2-yl)propanal (**28**; Fig. 14.8). The regioselectivity of the reaction was strongly dependent on the ligand used and best results were obtained with the use of an $Rh(CO)_2(acac)$/(dppe) catalyst system. The hydroformylation product (2-(6-methoxynaphthalene-2-yl)propanal) (**28**) was oxidized to DL-naproxen (**30**) in 80% yield using aqueous H_2O_2 and catalytic Na_2WO_4.

Significant work has been carried out in both academic and industrial labs, which led to efficient asymmetric hydroformylation catalysts with high enantioselectivity and regioselectivity for vinyl arene hydroformylation. However, further work is necessary to make the asymmetric hydroformylation route economically attractive and to compete with the efficient process economics of the resolution used in the manufacture of (*S*)-naproxen [34].

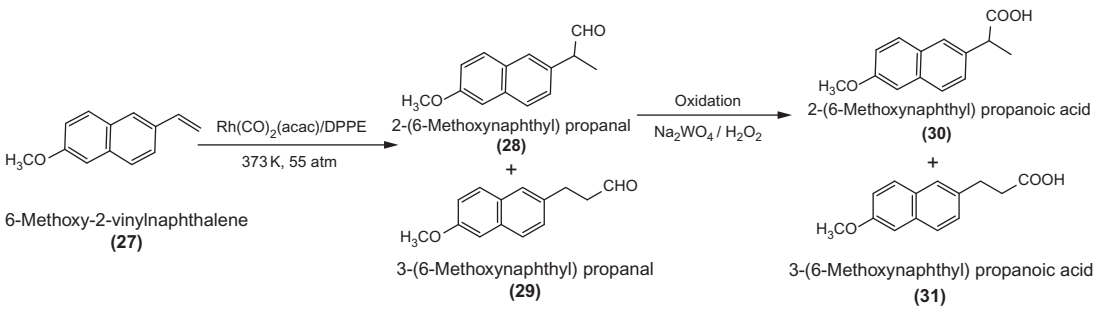


Fig. 14.8
Catalytic synthesis of racemic naproxen [33].

14.2.7 Hydroaminomethylation for the Synthesis of Amines

Aryl substituted amine derivatives and heterocyclic amine derivatives have wide-ranging applications, particularly for pharmaceuticals. In an important development, Botteghi et al. [35] and Rische and Eilbracht [36] demonstrated the importance of hydroaminomethylation in the synthesis of pharmaceutically active diaryl propylamines. Hydroaminomethylation involves hydroformylation and reductive alkylation (conventionally carried out in separate steps with different catalysts) in one pot using the same catalyst with high regioselectivity, eliminating the need for product separation between the steps, resulting in high overall yield (Fig. 14.9). Hydroaminomethylation has been extensively investigated to prepare a wide range of pharmacologically important amines with end applications as drugs; some important examples are presented in Fig. 14.10.

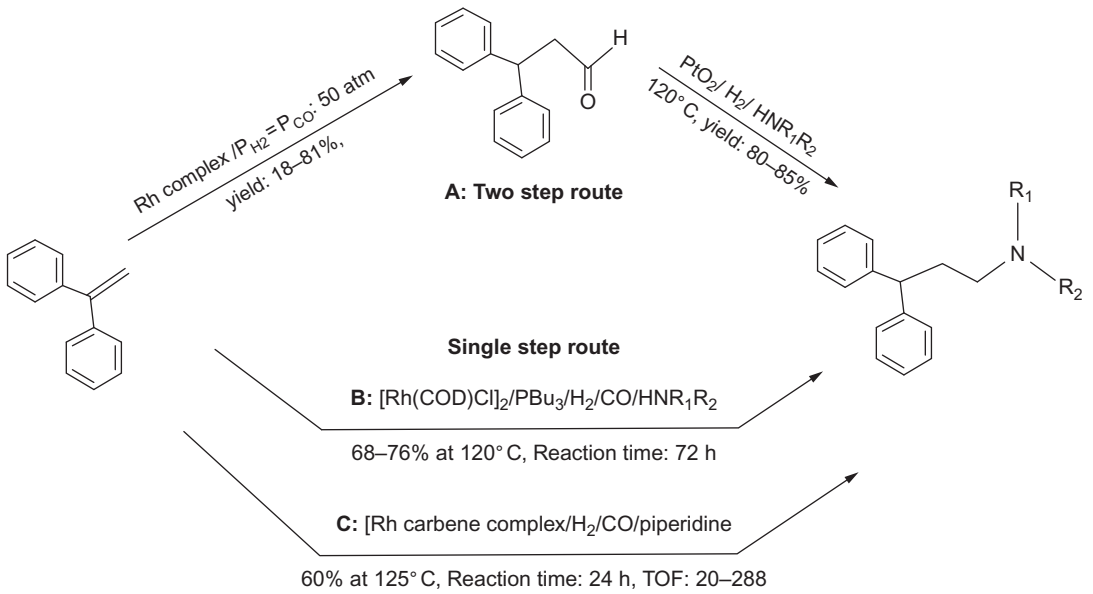


Fig. 14.9

Synthesis of diaryl propylamines using a conventional two-step ((A) Botteghi et al. [35]) and single-step hydroaminomethylation route ((B) Rische and Eilbracht [36] and (C) Ahmed et al. [37]).

Beller and coworkers [37] have carried out pioneering work on the synthesis of a variety of pheniramines, exemplified by compound fenpiprane (**32**), and other derivatives by hydroamination of 1,1-diphenyl ethylene with various amines, using an Rh-carbene complex as a catalyst [37]. A significant improvement in catalytic activity (TOF up to 288 h^{-1}), yields between 85–95% and high substrate conversions (up to 99%) were observed at 398 K, CO/H_2 pressure of 6.0 MPa (1.0 MPa CO and 5.0 MPa H_2). Heterocyclic allylic amines undergo hydroaminomethylation to form pharmaceutically active diamines, such as etymemazine (**33**)

[38], while hydroaminomethylation of 1-arylallyl alcohols with specific amines leads to the synthesis of ibutilide (**34**) and fexofenadine (**35**) [15,39]. Vieira and Alper [40] have developed a strategy for intramolecular hydroaminomethylation of aryl olefins for the synthesis of the 2-benzazepine moiety (**36**) (Fig. 14.10), which constitutes a core structure for a number of pharmacologically important compounds with end applications as drugs. The Rh catalyst developed [40] does not require a phosphine ligand and tolerates a wide range of amines. Important amines like ± Coniine (**37**) [41], 2-benzazepines (**36**) [40], 1,2,3,4-tetrahydroisoquinolines (**38**) [42] and MDL28726 (**39**) [43] have been prepared by intramolecular hydroamination reaction (Fig. 14.10). Work carried out so far has established hydroaminomethylation as an important method for the synthesis of a wide range of amines; however, further efforts are necessary to exploit the reaction on a commercial scale.

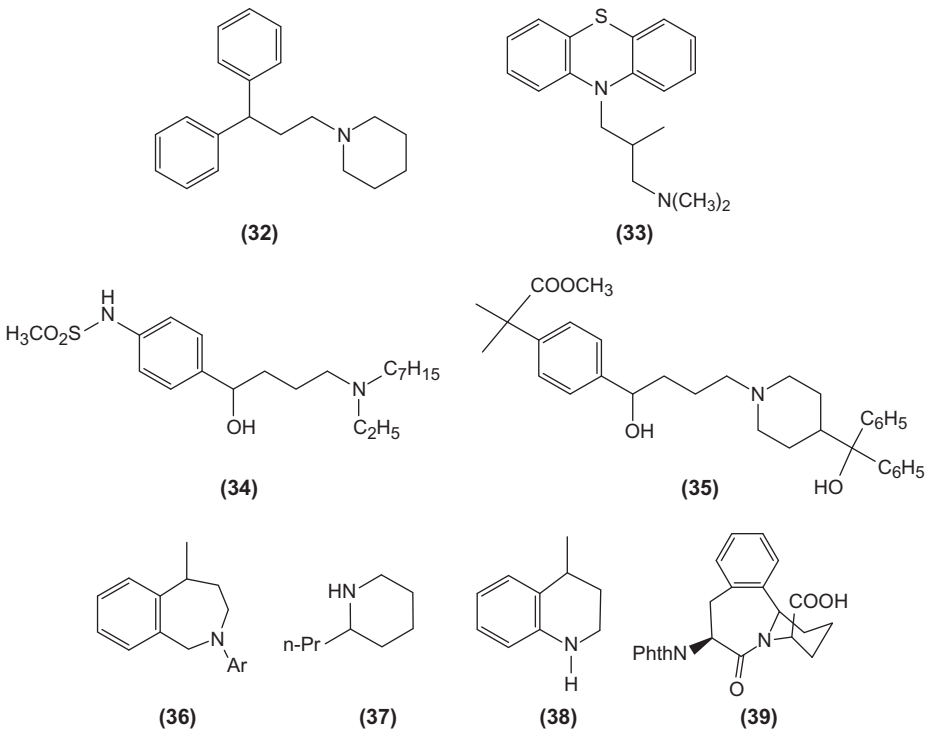


Fig. 14.10
Important amines synthesized using a hydroaminomethylation reaction.

14.3 Carbonylation

Carbonylation reactions are atom efficient and utilize a cheaper feedstock such as CO for the synthesis of a variety of products like aldehydes, carboxylic acids, carbonates and amide derivatives [4,44,45]. Carbonylation of methanol to acetic acid (>10 million TPA) represents one

of the most successful applications of homogeneous catalysis and has been the most preferred route over the past five decades. Development of a low-pressure (453 K and 3–4 MPa) and highly selective Rh complex catalyst with iodide promoters was considered a major breakthrough in carbonylation chemistry. This process was the preferred route for 25 years. Subsequently, British Petroleum came up with an improved methanol carbonylation process using an iridium (Ir) complex catalyst system in 1995 [46]. Details of the methanol carbonylation are described in excellent reviews [46–48]. In 1983 Eastman Chemicals developed an Rh catalyst-based process for the synthesis of acetic anhydride by carbonylation of methyl acetate [49].

Thus initial commercial processes were based on expensive Rh and Ir catalysts and mainly for commodity chemicals. Unlike in a hydroformylation reaction, other transition metals are active for a carbonylation reaction, and a significant amount of work has been carried out using other metals like cobalt and palladium (Pd) in particular [45,50]. The manufacture of ibuprofen, one of the important antiinflammatory drugs, based on the Hoechst-Celanese process involving carbonylation as one of the important steps was the path-breaking technology in pharmaceutical chemistry [51].

This has led to significant activity in Pd-catalyzed carbonylation reactions. Pd-catalyzed carbonylation [1] has emerged as an attractive tool for the fine chemical industry because CO is an inexpensive reagent and the resulting carboxylic acid derivatives represent versatile products. By changing the nucleophile in this reaction, an enormous variety of carbonyl compounds is accessible (Fig 14.11). A significant amount of work is being carried out on the development of improved catalysts/processes with applications in specialty chemicals. A brief account of important processes developed in the recent past is presented in the following. The details presented are based on recent publications/patents.

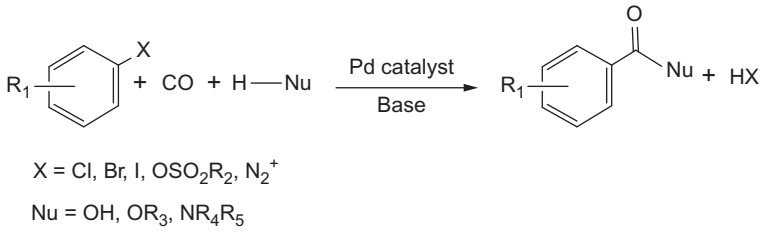


Fig. 14.11
General reaction for Pd-catalyzed carbonylation aryl-X compounds with various nucleophiles.

14.3.1 Synthesis of Ibuprofen by Carbonylation Route

The Hoechst-Celanese process for the synthesis of ibuprofen represents one of the best examples of an application of catalysis in developing a clean, atom-efficient process replacing the stoichiometric route [51]. This is the first example of a three-step catalytic process for the manufacture of a drug replacing the conventional reagent-based process involving six steps. The process won the prestigious Kirk Patrick award for collaborative process development

and has been operating with a capacity of 3500 TPA at Celanese in the United States since 1983 [52]. In this process [53], carbonylation of 1-(4-isobutylphenyl)ethanol (IBPE, **40**) is carried out using a $PdCl_2(PPh_3)_2$ catalyst with aq. HCl/methyl ethyl ketone in a biphasic system to obtain ibuprofen (**42**) with high selectivity. However, high CO pressure (16–35 MPa) is necessary to achieve the desired high regioselectivity.

Seayad and coworkers observed high selectivity to ibuprofen (99%), with very high TOF (800–1200 h^{-1}) at significantly lower pressure of 5.4 MPa with $Pd(PPh_3)_2Cl_2$ [54,55] or Pd(Pyca)(PPh_3)(OTs) (Pyca = pyridine-2-carboxylato) [56] as catalyst precursors with LiCl and TsOH (TsOH = *p*-toluenesulfonic acid) as promoters (Fig. 14.12). The Pd complex/LiCl/TsOH catalysts developed were found to be efficient for carbonylation of various alcohol or olefin substrates, giving high TOF values and selectivity to corresponding carboxylic acids [54–56]. Seayad [57] has carried out detailed kinetic investigations using a $Pd(PPh_3)_2Cl_2$/LiCl/TsOH catalyst system. A three-step reaction pathway involving the formation of an active palladium(0) species; the formation of an active carbonylation substrate, 1-(4-isobutylphenyl) ethyl chloride; and the main carbonylation catalytic cycle have been proposed [57]. The effect of various reaction conditions on the average rate of reaction was investigated in a temperature range of 378–398 K and the average rate of carbonylation was found to have first-order dependence with concentration of water, 0.8 with CO, 0.7 with IBPE, and 0.43 with respect to catalyst concentration. An empirical semibatch reactor model was derived and the reaction rate parameters were evaluated based upon a simplified scheme. The rate model was found to satisfactorily predict the concentration versus time profiles at all temperatures.

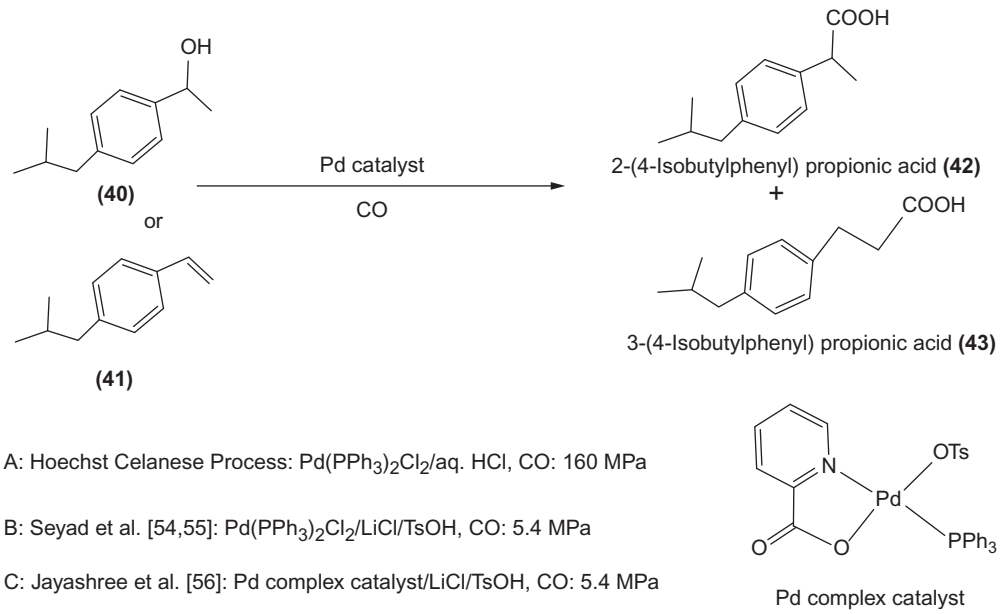


Fig. 14.12
Synthesis of ibuprofen using Pd complex catalysts.

Significant work is being carried out on the development of immobilized catalysts for ibuprofen synthesis; the details are presented in Section 14.4.

14.3.2 Synthesis of GP IIb/IIIa Receptor Antagonist SB-214857-A (Lotrafiban)

Atkins et al. [58] from Glaxo-Smith Kline Pharmaceuticals have developed a novel and efficient five-step route for the synthesis of the GP IIb/IIIa receptor antagonist SB-214857-A (Lotrafiban) (**46**) on a 40 kg scale involving aminocarbonylation as one of the steps. SB-214857-A is a potent nonpeptidic glycoprotein IIb/IIIa antagonist and consequently inhibits platelet aggregation. Carbonylation of iodo derivative (**44**) to corresponding amide (**45**) was carried out at 373 K using $Pd(PPh_3)_2Cl_2$ loading of 1.8 mol% and a CO pressure of 0.1 MPa to obtain 79% yield (64.7 kg isolated yield) of the amide (**45**) (Fig. 14.13). One of the advantages of this route is the low pressure, high yield aminocarbonylation reaction using a simple and commercially available $Pd(PPh_3)_2Cl_2$ catalyst.

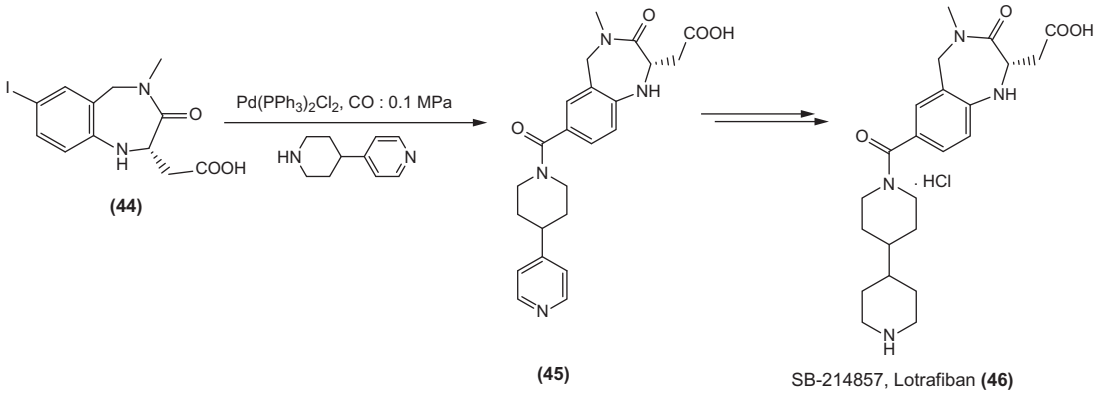


Fig. 14.13
$Pd(PPh_3)_2Cl_2$ catalyzed aminocarbonylation for the synthesis of SB-214857A [59].

14.3.3 Synthesis of Monoamine Oxidase-B Inhibitor Lazabemide

Hoffmann-La Roche has developed a single-step process for the synthesis of Monoamine Oxidase-B inhibitor lazabemide (*N*-(2-aminoethyl)-5-chloro-pyridine-2-carboxamide) (**47**), which has potential application as an antiparkinson agent [60]. This development is considered significant for the success of metal-complex catalysis in the pharmaceutical industry. Thus the original eight-step synthesis route was shortened with the help of a Pd-catalyzed process involving aminocarbonylation of commercially available 2,5-dichloropyridine [61]. Aminocarbonylation provides a much improved single-step route for the synthesis of

lazabemide with high activity and selectivity (Fig. 14.14) [61]. The process is developed on a multiton scale using a $Pd(PPh_3)_2Cl_2$ catalyst at 403 K, using toluene as a solvent. The activity of the catalyst is good and a turnover number of 3000 with high TOF ($100\ h^{-1}$) is reported, with 65% yield of lazabemide (**47**) as the product [60–62]. The catalyst is removed at the end of the reaction by extraction with aqueous NaCN.

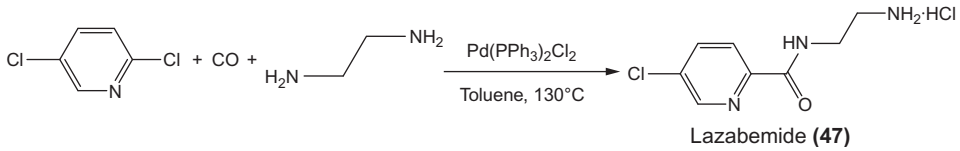


Fig. 14.14
Synthesis of lazabemide involving carbonylation of 2,5-dichloropyridine.

14.3.4 Synthesis of Aromatic Aldehydes by Carbonylation of Halide Derivatives

Beller and coworkers [63] in collaboration with Degussa have developed a palladium-catalyzed process for the synthesis of aromatic and heteroaromatic aldehydes from the corresponding bromides with very high catalyst productivity. Aromatic aldehydes are used as intermediates in a number of transformations and heteroaromatic aldehydes are useful intermediates for the synthesis of a number of biologically active molecules [63].

Various bidentate ligands were screened with $Pd(OAc)_2$ and remarkably di-1-adamantyl-*n*-butylphosphane (cataCXium A) showed very high activity. Carbonylation of aromatic and heteroaromatic bromides is carried out at 373–393 K using a Pd/cataCXium-A catalyst system (Pd loading 0.25 mol% and Pd:L ratio of 1:3) and 0.5 MPa synthesis gas pressure with toluene as a solvent (Fig. 14.15). Tetramethylethylenediamine (TMEDA, 0.75 equiv.) was used as a base to neutralize acid formed during the reaction. The main advantage of the process is that synthesis gas can be used as an environmentally benign formylation source at low pressure (0.5 MPa) and low Pd loading (0.25 mol%), and in most cases greater than 90% yield of aldehyde product is obtained. The high air stability of the cataCXium-A ligand enables the operations to be carried out in the air without decreasing the catalyst activity. Direct carbonylation of bromo derivatives is a significant improvement over conventional processes and has reduced the formation of waste products significantly. The process is being used for the synthesis of various aromatic aldehydes commercially on >100 kg scale. This is the first example of the industrial application of reductive carbonylation of aryl halides for the synthesis of aldehydes [63].

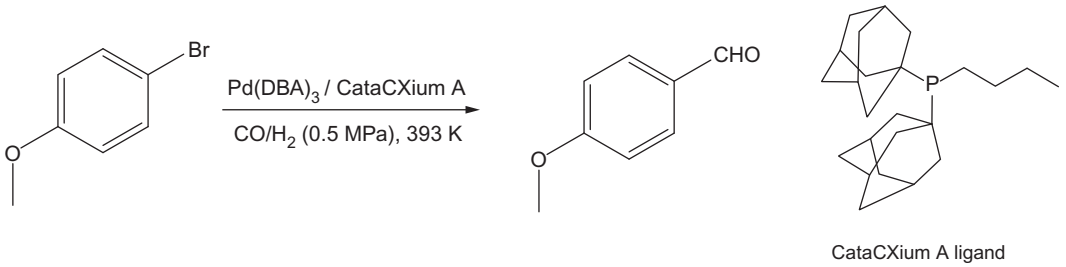
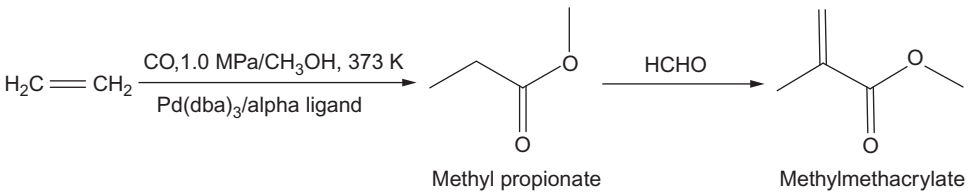


Fig. 14.15
Carbonylation of aromatic bromides with Pd/CataCXium A.

14.3.5 Lucite Process for the Synthesis of Methylmethacrylate

Methylmethacrylate (MMA) is an important chemical intermediate in the synthesis of various acrylic polymers. Lucite (formerly Ineos Acrylics) and Kvaerner have developed a new technology (Alpha process) to produce MMA from ethylene in three steps: two separate catalytic reactions and a complex series of distillations in the final product separation stage [64]. In the first stage, ethylene, CO and methanol are reacted in the liquid phase at very mild conditions (1.0 MPa and 373 K) using a palladium-based phosphine ligand catalyst ($Pd_2(dba)_3$/1,2-bis(di-*tert*-butylphosphinomethyl)benzene) to produce methyl propionate (MeP), with 99.8% selectivity (Fig. 14.16) [65]. Various bidentate phosphine ligands were screened and good activity with exceptionally high selectivity to methyl propionate (>99.8%) was obtained with 1,2-bis(di-*tert*-butylphosphinomethyl)benzene as the ligand. The MeP is then used in the second step to react with formaldehyde in the gaseous phase over a fixed bed heterogeneous catalyst in the presence of methanol to produce MMA and water. Pure MMA is separated using six distillation steps.

The process is environmentally safer compared to the conventional acetone cyanohydrin (ACH) process route. According to Lucite, the manufacturing cost of the Lucite process (Alpha process) is almost 40–50% lower than the conventional cyanohydrin process. The process has been operating at a 120,000 TPA plant in Singapore since 2008 [64].



Alpha ligand = 1,2-bis(di-*tert*-butylphosphinomethyl)benzene

Fig. 14.16
Lucite process for the synthesis of methylmethacrylate.

14.3.6 Novomer Process for Acrylic Acid

Acrylic acid is a bulk chemical produced from propylene and is dependent on the petrochemical feedstock. Novomer is working on the development of a novel process for the synthesis of acrylic acid by carbonylation of ethylene oxide, which is expected to be abundantly available from shale gas [66] (Fig. 14.17).

The process involves carbonylation of ethylene oxide using a proprietary catalyst based on cobalt, developed in collaboration with professor Geoffrey Coates, Cornell University [67] (Fig. 14.17). The catalyst is highly active and selective, giving 99% selectivity to propiolactone at 313–363 K and CO pressure of 4.0–6.0 MPa. In the first stage of the process, carbonylation of shale gas-based ethylene oxide is carried out to form propiolactone. Propiolactone is converted into acrylic acid in the second stage using established technology developed by Celanese in the 1980s. Novomer will be testing the process using a continuous plant with a capacity of 5 kg acrylic acid per day [66]. The process is expected to be safer, to reduce the carbon footprint and to result in significant cost saving.

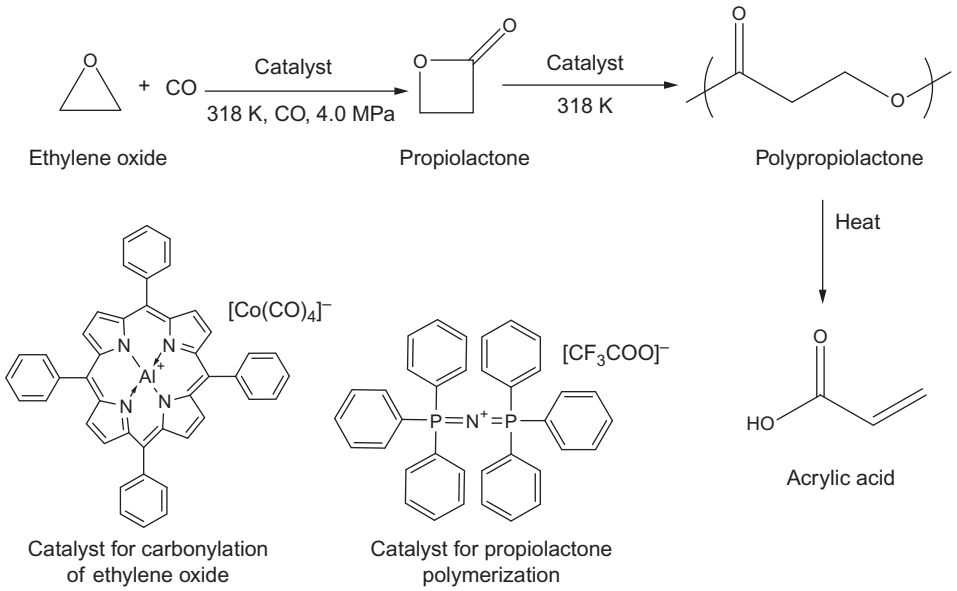


Fig. 14.17
Novomer process for the synthesis of acrylic acid [68].

14.4 Catalyst/Product Separation

Carbonylation (hydroformylation and carbonylation) reactions are important because they provide clean and atom-efficient processes for chemicals. However, as presented in earlier sections, most of the successful processes are for bulk chemicals and use homogeneous transition metal-based catalysts.

Recycling/recovery of catalysts is essential in these processes, considering the high cost of catalysts and ligands necessary for achieving the desired results. Difficulties in separating the catalyst from the product and recycling have limited the applications of carbonylation reactions on the industrial scale. The issue of catalyst/product separation is even more critical in fine chemicals and pharmaceutical products that are thermally sensitive and high boiling compounds. Also, most homogeneous catalysts are thermally sensitive and decomposition of the expensive catalyst will add to the cost of the process.

During the last few decades, the focus of the work has been on the development of new strategies for heterogenizing homogeneous catalysts to combine the advantages of homogeneous and heterogeneous catalysis [69]. The strategies used for the immobilization of catalysts include immobilizing the homogeneous catalyst in one solvent (water-soluble, fluorous biphasic or ionic liquid biphasic) and reactants and products in another solvent, supporting organometallic complexes by various techniques like anchored or tethered, polymer-bound, supported liquid-phase, dendrimer-supported catalysts [70,71] and ossified catalysts [72]. The use of solvent engineering using supercritical fluids [73,74] and gas-expanded liquids [75] has also been studied in order to achieve facile separation of the catalysts from the reaction mixture. In the following section brief details of various strategies used for catalyst/product separation in carbonylation reactions are presented.

14.4.1 Biphasic Catalysis

In this approach the catalyst is immobilized in one solution phase, while the reactants and products are predominantly present in another liquid phase [5].

14.4.1.1 Aqueous biphasic systems

Successful commercialization of the aqueous biphasic hydroformylation of propylene has led to significant work in this area [76]. The Rh complex is made water soluble with a TPPTS ligand and Rh leaching in this process is negligible (ppb level). Because most of the organic compounds have very low solubility in water, the catalyst and products are separated by mere phase separation, leaving the catalyst in the aqueous phase. However, because of the very low solubility of long-chain alkenes in water, the rates of reaction are too low for commercialization of this process for higher olefins and other water-insoluble reactants [5]. Carbonylation of olefins and alcohol derivatives has been investigated using a Pd-TPPTS catalyst system and the catalyst was found to be active and stable until 373 K; however, at 393 K, Pd decomposition to metal was observed [77]. The use of additives like lithium chloride (LiCl) or polyvinyl alcohol was found to restore activity at higher temperatures. Jayasree et al. [78] observed high activity and high selectivity to ibuprofen using a Pd complex containing pyridine carboxylate and TPPTS as ligands; however, a CO atmosphere was necessary for catalytic recycling at 388 K.

Various strategies have been tried to overcome the problem of solubility of reactants in the aqueous phase. Chaudhari et al. [79] developed the concept of interfacial catalysis to enhance the activity of an aqueous biphasic catalytic hydroformylation reaction with an Rh-TPPTS catalyst system several folds with the use of a small amount of PPh_3 ligand in the organic phase. In another approach PPh_3 was derivatized with a polyethylene glycol chain to make it water soluble [80]. Under reaction conditions, the polyether side chains undergo a phase transition and the complex becomes more soluble in the organic phase, giving high activity. Upon cooling, the phase transition is reversed and the catalyst returns to the aqueous phase, resulting in easy catalyst/product separation.

14.4.1.2 Fluorous biphasic system

The use of a fluorous biphasic system is based on the immiscibility of fluorinated compounds with organic solvents, which is due to the polar C—F bond [81]. The miscibility of fluorous and organic solvents is temperature dependent. At room temperature the two phases are well separated, but at higher temperatures the system becomes homogeneous. This allows one to combine a homogeneous reaction at higher temperatures with catalyst/product separations at lower temperatures.

Horvath and Rabai [82] demonstrated hydroformylation with a toluene/perfluoromethylcyclohexane solvent and $Rh(CO)_2(acac)$-$P(C_2H_4C_6F_{13})_3$ catalyst system. A significant amount of work has been carried out on fluorous biphasic hydroformylation since. A major advantage of this system is that the catalyst remains completely in the fluorous phase and the reactant/products are separated in the organic phase. However, special ligands containing fluorine are required for good solubility of the catalyst in a fluorous solvent [83–85]. The requirement of fluorous solvents and special ligands containing fluorine are cost centers; hence, no commercial applications have been reported so far.

14.4.1.3 Ionic liquid biphasic systems

Ionic liquids have been used as a solvent for carbonylation reactions, and more specifically for hydroformylation reactions, and excellent review articles have appeared [86]. Ionic liquids have very low vapor pressure and good thermal stability. It is possible to tune their solubility and acidity/coordination properties by varying the nature of the anions and cations systematically [87]. Ionic liquids are good solvents for a wide range of both organic and inorganic materials. At the same time they are insoluble in many organic solvents and provide a nonaqueous polar alternative to water in two-phase systems.

Significant progress in recent years has allowed biphasic ionic liquid hydroformylation catalysts to be engineered by careful choice of ionic liquid and through rational ligand designs to provide very effective catalyst immobilization and acquire optimized catalytic performance. Ionic liquids generally exhibit rather low syngas solubility, which makes biphasic hydroformylation systems prone to mass transfer limitations. Also, the solubility

of olefins is higher in ionic liquids compared to that in water; however, it is significantly lower compared to organic solvents. Thus in most cases, activity with an ionic liquid biphasic system was found to be low and the cost of ionic liquid to be very high; hence, their use as a solvent may be expensive [88].

14.4.2 Heterogenization of Homogeneous Catalysts

Heterogeneous catalysts prepared by supporting homogeneous metal complex catalysts on supports have the inherent advantages of homogeneous catalysts like high activity and selectivity coupled with the separation advantage of heterogeneous catalysts. The combination of properties is especially valuable when transition metal catalysts are applied in fine chemical synthesis. In many cases, especially if the product is designed for medical, cosmetics, food processing and similar applications, strict limits for the content of catalyst residues (especially transition metals) in products must be obeyed. Also, the possibility of catalyst reuse is very important because transition metal organometallic catalysts are usually quite expensive. Various techniques have been developed for the synthesis of new hybrid heterogenized homogeneous catalysts. Moreover, the advances in spectroscopic techniques (infrared, Raman, solid-state nuclear magnetic resonance, X-ray photoelectron spectroscopy) allow detailed characterization of organometallic compounds on solid surfaces. Various strategies used in the carbonylation reactions are presented in the following.

14.4.2.1 Supported ionic liquid-phase catalyst (SILC)

Based on the early work of Arhancet et al. [89] on the supported aqueous-phase catalyst systems, Menhert et al. [90] developed a technique for the immobilization of ionic liquid phase onto solid supports for a hydroformylation reaction. In a supported ionic liquid-phase catalyst (SILC) system, the surface of the solid support (eg, silica) is modified with a monolayer of ionic liquid (IL) fragments. IL film is immobilized on this high surface area porous solid and the homogeneous catalyst is dissolved in the IL layer. The resulting catalyst is a solid, with the active species being solubilized in the IL phase and behaving as a homogeneous catalyst [90]. Typically, there is no direct interaction between the surface of the support and the homogeneous catalyst (Fig. 14.18). The SILC for a hydroformylation reaction consists of an Rh precursor with a ligand modified with ionic moieties for good solubility in ionic liquid. The details are given in review articles [91,92].

The main advantage of SILC is that the amount of ionic liquid used is very small compared to IL biphasic reactions. Also, because of the dispersion of IL containing a dissolved catalyst on porous support, the substrate can readily diffuse to the catalyst, which works as a homogeneous catalyst. Thus SILC combines the most attractive features of homogeneous catalysis like high activity and selectivity with benefits of heterogeneous catalysts such as large

interfacial reaction areas and ease of product separation. SILC has been investigated for hydroformylation reaction [92] in detail and also for methanol carbonylation to acetic acid [93].

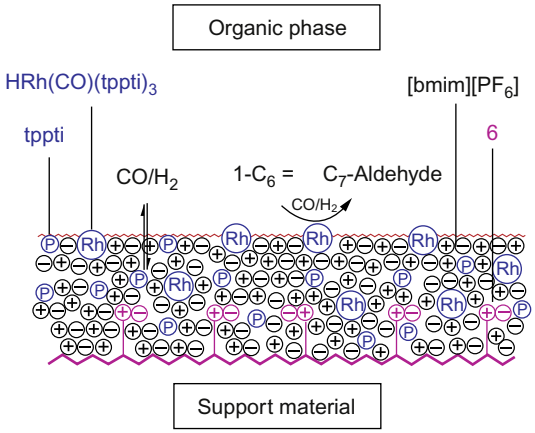


Fig. 14.18
Schematic for a supported ionic liquid-phase catalyst (SILC) [90].

Hydroformylation of olefins has been investigated in the liquid phase (higher olefins $> C_5$ olefins) as well as in a fixed bed reactor (lower olefins, C_4 and lower olefins) using SILCs [92]. However, leaching of Rh was found in the liquid phase at high aldehyde concentrations and aldehyde concentration less than 50 wt% was necessary to minimize leaching of the ionic liquid and catalyst in the liquid phase [92]. Also, the activity observed with SILC in the liquid phase was significantly lower than in the homogeneous system [91].

An important development in the use of SILCs has been gas-phase hydroformylation of lower olefins (propylene and butane) at 373 K in a fixed bed reactor using an Rh-sulfoxantphos based SILC. Thermal pretreatment of the silica gel support was found to improve stability of the SILC significantly [92]. The catalyst gave consistent performance for 200 h on a stream with >97% selectivity to butanal. A slight drop in activity observed was due to the accumulation of aldehyde condensation products in the catalyst, which were removed by applying a vacuum to the catalyst. Initial activity was restored and consistent performance was observed for more than 700 h on stram [92]. In a more recent study, Haumann et al. [94] successfully carried out isomerization/hydroformylation of a highly diluted, technical C4 feed containing 1.5% 1-butene, 28.5% 2-butenes, and 70% of inert *n*-butane at 373 K with an Rh-biphephos SILC system. The catalyst showed 81% conversion of butenes with 92% selectivity to *n*-pentanal for 500 h even at low concentrations.

Riisager and coworkers have investigated vapor-phase carbonylation of methanol in a fixed bed reactor with an SILC prepared from $[Rh(CO)_2I_2]^-$ [93,95]. Gas-phase carbonylation of a mixture of methanol and methyl iodide (75:25 wt%) was carried out at 2.0 MPa pressure and 453 K. At low gas space velocity, complete conversion of methanol was obtained

with 75% selectivity to methyl acetate and 25% selectivity to acetic acid. According to Riisager et al. [93], the process design of the fixed bed SILC requires a smaller reactor size than the current technology in order to obtain the same productivity, which makes the SILC carbonylation concept potentially interesting for technical applications.

The advantages of SILCs over homogeneous catalysts make their future application attractive. The development is very recent and significant work needs to be done to address issues like catalyst leaching, life of the catalyst and so on.

14.4.2.2 Tethered catalyst for carbonylation reactions

Carbonylation catalysts have been heterogenized by a technique called "tethering" using various heteropoly acids as tethering agents based on the procedure reported by Augustine et al. [96]. A schematic of the tethered Rh complex catalyst for a hydroformylation reaction is presented in Fig. 14.19 [19]. There are few reports on the hydroformylation of styrene and higher olefins using tethered Rh complex catalysts [97] and carbonylation of olefins and alcohols using tethered Pd complex catalysts [98]. Chansarkar et al. [19] have investigated the hydroformylation of DAB using tethered Wilkinson complex catalysts in detail. The catalysts were prepared using various supports and heteropoly acids and characterized in detail. Based on the detailed characterization, a possible structure of the tethered catalyst was proposed with the loss of one PPh_3 from the hydroformylation catalyst ($HRh(CO)(PPh_3)_3$) (Fig. 14.19). The kinetics of the reaction was investigated in detail in a temperature range of 333–353 K and the catalyst was found to be stable for six recycling experiments [19].

Sarkar et al. [98] have prepared a tethered catalyst using a [Pd(pyca)(PPh_3)(OTs)] complex, with solid matrices having an ordered framework and high surface area as zeolite NaY (surface area 700 $m^2\ g^{-1}$) and phosphotungstic acid [$H_3PW_{12}O_{40}$, xH_2O] as the molecular tether to form a highly stable catalyst. The catalyst was characterized in detail by various spectroscopic techniques. Carbonylation of substituted olefins and alcohols was performed at 388 K and 5.4 MPa CO pressure using this tethered catalyst without the addition of any free acid (protic/aprotic) promoter, with highly promising results. Thus 95% conversion of IBPE with 98% selectivity to ibuprofen was observed in 13 h.

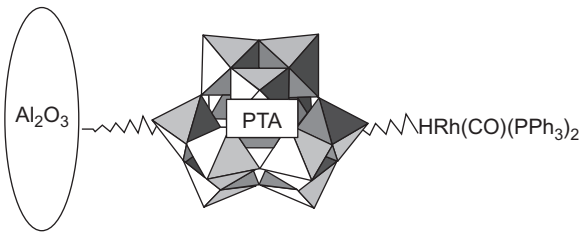


Fig. 14.19
Schematic representation of a tethered Rh catalyst for a hydroformylation reaction [19].

14.4.2.3 Anchored catalysts for carbonylation reactions

Anchoring of homogeneous catalysts to the inorganic support gives advantages of both homogeneous catalysis and heterogeneous catalysis. Anchored catalysts have been prepared by modifying the support with APTS (3-aminopropyl trimethoxysilane) as the anchoring agent [99] and by using phosphane modified silica [100]. The metal complex is bound to the "N" or "P" of the anchoring agent, giving a heterogenous catalyst. Anchored catalysts have been investigated in detail for hydroformylation [100,101] and carbonylation [99,102] reactions, giving good activity and selectivity.

Nowotny et al. [100] have prepared phosphane-modified support by grafting $Ph_2P(CH_2)_2SiCl_3$ on both amorphous silica gel and on Mobil Composition of Matter No. 41 (MCM-41). The anchored catalyst prepared with MCM-41 as a support was found to be a good catalyst for styrene hydroformylation (complete conversion with >99% selectivity to aldehydes at 333 K and 6 MPa syngas pressure) and was stable for four recycling experiments. Mukhopadhyay et al. [101] have prepared an anchored catalyst using APTS as an anchoring agent and MCM-41 as a support. The catalyst was found active for various olefins and gave >99% conversion with 95% selectivity to aldehydes for styrene hydroformylation at 373 K and 4 MPa syngas pressure. The catalyst was stable for six recycling experiments, showing high stability.

Palladium-catalyzed synthesis of ibuprofen (Hoechst-Celanese process) has been investigated in detail; however, limited reports are available on heterogeneous catalysts for this reaction [102,103]. Mukhopadhyay et al. [102] have developed an anchored Pd complex catalyst using MCM-41 as a support and APTS as an anchoring agent for the carbonylation reaction (Fig. 14.20). Carbonylation of various olefins and alcohols was carried out at 388 K and

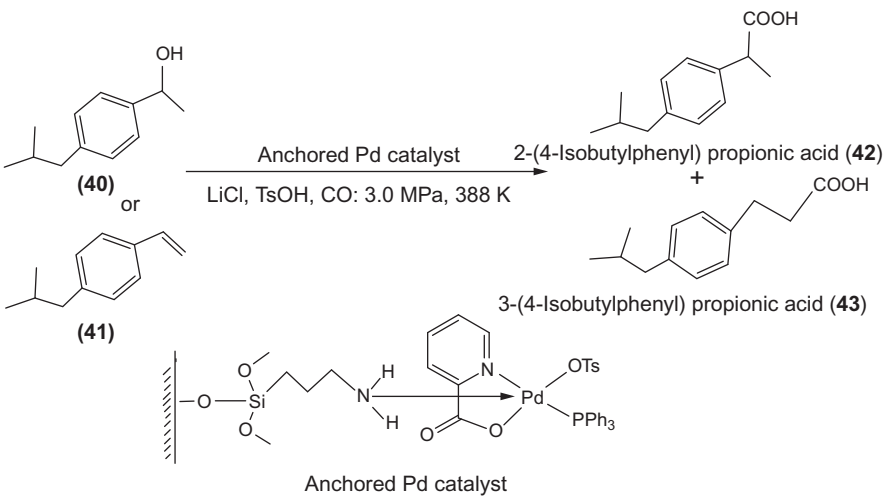


Fig. 14.20
Synthesis of ibuprofen using anchored Pd complex catalyst [102].

3.0 MPa pressure. The catalyst was found to be highly active and selective for carbonylation of IBPE, and 95% conversion with 97.5% selectivity to ibuprofen (**42**) was obtained in 12 h [102]. The catalyst was recycled three times without a drop in performance for styrene hydroformylation, showing good stability.

14.4.2.4 Ossified catalyst for carbonylation reactions

Ossification provides one more approach for immobilization of metal complexes, generating highly selective, stable and recyclable heterogeneous catalysts for carbonylation and other reactions [104].

Metal complexes with sulfonated ligands (sodium salt) are water soluble in nature. However, salts with divalent metals like Ca, Sr, and Ba are essentially water insoluble. This property is used in the preparation of ossified catalysts. The schematic of the catalyst preparation is presented in Fig. 14.21 [72]. Sarkar and Chaudhari [72] prepared an ossified palladium catalyst from [Pd(TPPTS)(OTs)] by precipitation with barium nitrate. The characterization of the catalyst showed that the key features of their homogeneous metal complex analogs are retained on immobilization [72]. The catalyst was used for carbonylation of olefins and alcohols to corresponding carboxylic derivatives and was found to be active and selective. Thus 93% conversion of IBPE with 99.8% selectivity to ibuprofen was observed in carbonylation of IBPE at 388 K, 5.4 MPa pressure in 11 h. The catalyst was recycled four times without a drop in activity [72].

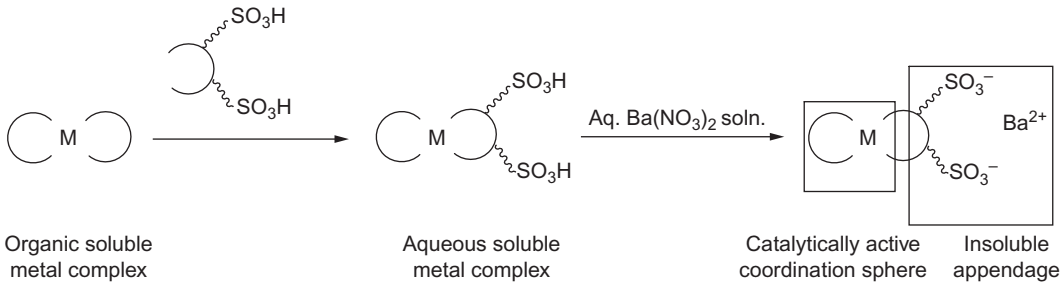


Fig. 14.21
Synthesis of ossified catalyst [72].

Pagar et al. [105] have prepared an ossified catalyst by exchanging $HRh(CO)(TPPTS)_3$ with $Ba(NO_3)_2$. However, the activity of the catalyst was found to be low for a hydroformylation reaction; hence, a supported ossified catalyst was prepared by precipitating an Rh complex with barium nitrate impregnated on carbon. The supported ossified Rh catalyst was found to be highly active for hydroformylation of 1-decene, and 95% conversion of 1-decene with 89.5% selectivity to aldehydes was obtained at 373 K and 4.14 MPa syngas pressure. Recycling studies showed that the catalyst was stable for five recycling experiments, retaining high

activity with negligible leaching of Rh (0.6%). Various heterogenized homogeneous catalysts used for hydroformylation of higher olefins have been compared for their activity (Fig. 14.22) and the supported ossified catalyst was found to give a better performance. Ossification is a recent concept and detailed investigations are necessary before further applications are to be considered.

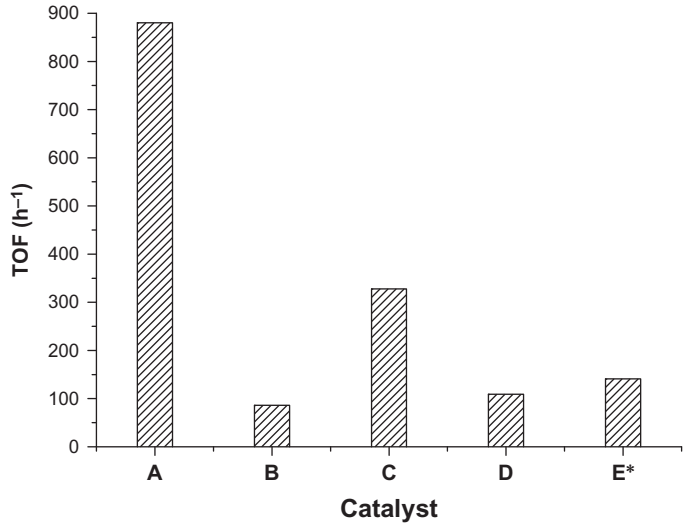


Fig. 14.22

Hydroformylation of 1-decene using ossified Rh catalyst A: Comparison with other heterogeneous catalysts. **Reaction conditions**: Temperature: 373 K, $pCO + H_2$: 4 MPa: A—Ossified Rh catalyst supported on carbon [105]; B—Ossified Rh catalyst [105]; C—Tethered Rh catalyst using phosphotungstic acid as tethering agent and zeolite Y as support [101]; D—Anchored Rh catalyst using APTS as anchoring agent and MCM-41 as support [101]; E*—Encapsulated Rh catalyst in zeolite Y, hydroformylation of 1-octene was investigated [101]; *—1-octene was used as reactant.

14.5 Conclusions and Challenges for Future Commercialization

Because of the cheaper and abundantly available CO/H_2 feedstock and the possibility of developing cleaner catalytic routes, carbonylation reactions have attracted significant interest for applications in fine chemicals, pharmaceuticals and specialty products.
A significant amount of work is being carried out on the development of improved catalysts, new and atom-efficient routes and novel strategies for catalyst/product separation for these reactions, as outlined in this chapter. However, at the present stage very few commercial technologies have been developed compared to the number of publications showing novel synthesis. Some of the challenges envisaged for future applications include the following:

- Hydroformylation and carbonylation involve multiphase reactions; hence, better understanding of reaction kinetics and reactor engineering aspects is necessary.
- Most of the processes are based on costly rhodium, iridium and palladium catalysts. There is a need to design catalysts with high activity and selectivity and to develop catalysts using cheaper metals like ruthenium, iron, and so on.
- The ligand is an integral part of an active catalyst and also one of the cost centers in the process. There is a need to identify ligands that are out of patent for future developments.
- A major challenge in the practical application of carbonylation reactions has been the separation of products from the catalysts and economic utilization of the catalysts through recycling and recovery of the expensive metals. Conventional methodologies like distillation may not be useful for the synthesis of complex organic molecules due to limitations of thermal stability.
- New concepts for catalyst product separation like biphasic catalysis and heterogenization of homogeneous catalysts by various techniques have been developed on a conceptual basis. However, further work needs to be carried out to establish long-term stability of these catalysts.

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CHAPTER 15

Alkoxycarbonylation for Fine Chemicals: Carbamates

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15.1 Introduction

Carbamates are esters of carbamic acid, that is, NH_2COOH, which is theoretically the simplest amino acid on molecular basis. The acid itself, however, is too unstable and its existence is realized only as its salts or esters, ie, carbamates. The "urethane" or ethyl carbamate was the first carbamate synthesized by Wohler [1], in as long back as 1845, from urea and ethyl alcohol. It is noteworthy that urethane was introduced as a hypnotic by Dr. Oswald Schmiedeberg in 1885. Carbamate moiety has been a subject of immense interest, and detailed studies have been carried out by researchers worldwide with regard to the reactions involving carbamates. Adams et al. [2] have covered in great detail the more basic aspects of carbamates including their nomenclature, physicochemical properties, synthesis, and reactions.

Carbamates display the properties of carboxylic acid esters as well as amides. The chemical reactions of carbamates include those of esters, amides, and enols. The most abundantly known carbamate is the ethyl carbamate or urethane, which has been used as a precursor to isocynates in the synthesis of polyurethanes (PUs).

The applications of carbamates span a wide range, from the synthesis of commodity chemicals like PUs, herbicides, and pesticides [3] to several fine and specialty chemicals like drug intermediates in the pharmaceutical industry. In terms of volume of production on a global scale, PU foam is the largest application of the carbamate moiety. This chapter covers in brief the general applications of carbamates, their synthesis on laboratory as well as industrial scales, and also a section on the studies of methoxycarbonylation of amines for carbamate synthesis carried out by the authors.

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15.2 Applications of Carbamates in Industry

Carbamates are an important class of compounds and find wide applications in pharmaceutical, agricultural, and polymer industry. Some of the important products are reported here. All the products listed are not being produced commercially today as products with better efficacy are available in the market, but still have been presented to illustrate the wide utility of this reaction.

Carbamates are well-known cholinesterase inhibitors, a few popular examples of which are rivastigmine, neostigmine, and physostigmine. Acetylcholine is a neurotransmitter released at the muscle-nerve joints. The cholinesterases are enzymes which break down the acetylcholine, causing the muscles to relax. The carbamate cholinesterase inhibitors are known to inhibit the enzyme. Rivastigmine, which is (*S*)-3-[1-(dimethylamino)ethyl]phenyl *N*-ethyl-*N*-methyl carbamate, inhibits both acetylcholinesterase as well as butyrylcholinesterase. It is effective in the treatment of dementias associated with Parkinson's and Alzheimer's diseases. Neostigmine is used to treat Myesthania Gravis, a condition resulting in fluctuating muscle weakness and fatigue; while physostigmine is used for the treatment of anticholinergic poisoning.

Meprobamate, 2-methyl-2-propyl-1,3-propandiol dicarbamate, is used as an anxiolytic agent. However, it is a controlled drug in the United States owing to its potential to cause physical and psychological dependence; and in the European Union, its use is suspended as it is found to cause significant side effects. Carisoprodol, which is chemically (*RS*)-2-{[(aminocarbonyl)oxy]methyl}-2-methylpentyl isopropyl carbamate, is a modification of Meprobamate, and it is useful as a skeletal muscle relaxant, for relief from the pain and discomfort caused by muscle spasms. This drug, though under scrutiny for its potential to cause dependence, is still available in the US and European markets.

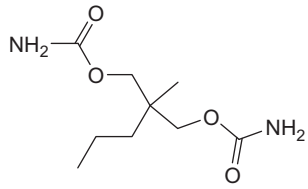
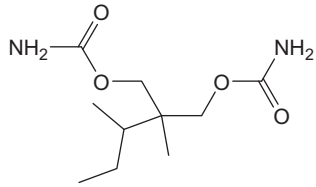
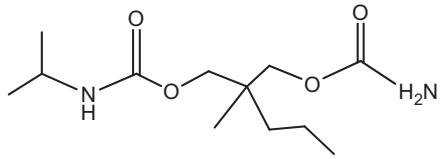
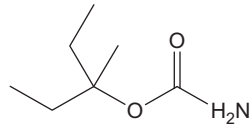
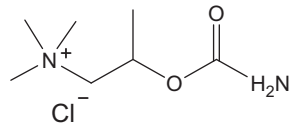
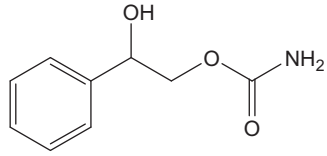
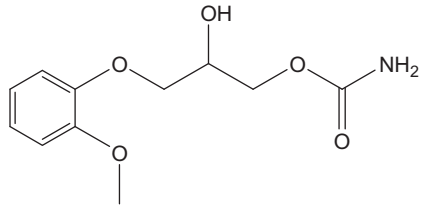
Lecanu et al. [4] have reported dimethyl-carbamic acid 2,3-bis-dimethylcarbamoyloxy-6-(4-ethyl-piperazine-1-carbonyl)-phenyl ester as a new drug specifically designed to achieve a multitargeted neuroprotective approach for the treatment of Alzheimer's disease. The authors report that the drug inhibits acetylcholine esterase activity both in vivo and in vitro.

A few other examples of carbamates in the drug industry are listed in Table 15.1.

The benzimidazole 2-carbamic acid esters have shown to possess antihelminthic activity (Fig. 15.1).

These carbamates possess the ability to bind selectively and more preferentially to helminthic tubulin compared to mammalian tubulin, and hence they display the antimitotic activity. It was the discovery of the anthelminthic activity of thiabendazole in 1961 that triggered the introduction of a series of the benzene ring substituted benzimidazole-2-carbamates bearing anthelminthic activity. However, owing to their potential to cause hepatotoxicity, they are

Table 15.1 Carbamates in pharmaceutical industry

S. No.	Drug	Brand Name	Structure	Therapeutic Category
1	Meprobamate	Miltown, Equanil, Meprospan		Anxiolytic
2	Mebutamate	Capla, Dormate		Anxiolytic/ antihypertensive
3	Carisoprodol	Soma, Sanoma, Carisoma		Muscle relaxant
4	Emylcamate			Anxiolytic/ muscle relaxant
5	Bethanechol chloride	Duvoid, Myotonachol, Urecholine, Urocarb		Cholinergic agent
6	Styramate			Muscle relaxant, anticonvulsant
7	Methocarbamol	Robaxin		Muscle relaxant

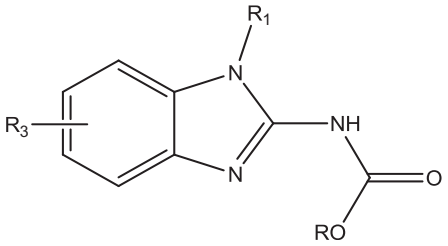


Fig. 15.1
General structure of benzimidazole-2-carbamates. R = alkyl/cycloalkyl; R_1 = alkyl/aryl/acyl; R_3 = alkyl, aryl, amino, halo, or heterocyclic substituent.

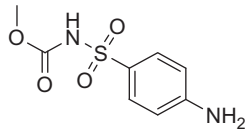
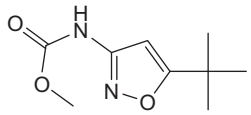
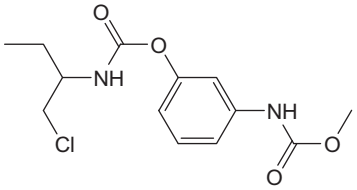
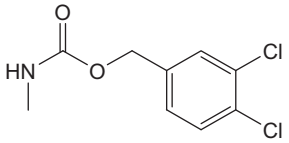
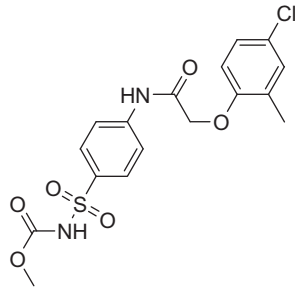
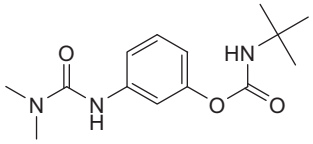
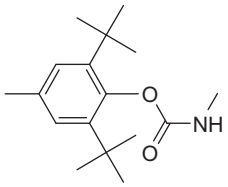
restricted presently to veterinary use. A few examples of the albendazole carbamates which exhibit anthelminthic activity include albendazole, mebendazole, fenbendazole, oxfendazole, etibendazole, etc.

Carbamates on thermal degradation yield isocyanates. Industrially, aliphatic and aromatic isocyanates represent very important intermediates. Especially in the polymer industry, polyisocyanates such as 2,4-toluene diisocyanate (TDI) or methylene 4,4′-diphenyl diisocyanate (MDI) are the starting materials for the synthesis of many PUs [5]. PU foams find their application in furniture and interiors, construction, electronic markets and home appliances, the packaging industry, and as coatings and sealants. According to the market report released by Transparency Market Research titled "Polyols (Polyether and Polyester) and Polyurethanes (Rigid foam, Flexible foam, CASE) Market For Furniture, Construction, Electronics and Appliances, Automotive, Footwear and Packaging—Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2012–2018," the polyol demand was over 7.5 million tons in 2012 and is expected to cross 10.4 million tons by 2018, growing at a CAGR of 5.5% from 2012 to 2018. According to the report, the PU demand in 2012 was worth US $43.2 billion and is expected to reach US $66.4 billion by 2018, growing at a CAGR of 7.4% from 2012 to 2018 [6].

Carbamates are used as insecticides, acaricides, nematicides, and fungicides. Carbamate insecticides are widely used in agricultural and domestic plant protection. They act as cholinesterase inhibitors, affecting nerve impulse transmission. Carbaryl was the first member of the family of carbamate insecticides used after its introduction in 1956.

Carbamates are relatively less toxic compared to their organophosphorous counterparts because the carbamylation of the cholinesterases which they cause is unstable, and their regeneration is rapid. Also, carbamates do not cause delayed neuropathy. Toxicity of carbamates is a measure of cholinesterase inhibition. Various carbamates have different lethal doses of exposure for study animals. The acute dermal toxicity is generally low or moderate, with the exception of Aldicarb (Table 15.2).

Table 15.2 Carbamates in agricultural industry

S. No.	Brand Name	Chemical Name	Structure	CAS No.
		Carbamate Herbicides		
1	Asulam	Methyl-*N*-[(4-aminophenyl) sulfonyl]carbamate		3337-71-1
2	Carboxazole	Methyl 5-*tert*-butyl-1,2-oxazol-3-ylcarbamate		55808-13-4
3	Chlorprocarb	3-[(Methoxycarbonyl)amino] phenyl *N*-[1-(chloromethyl) propyl]carbamate		23121-99-5
4	Dichlormate	3,4-Dichlorobenzyl methyl-*N*-methylcarbamate		1966-58-1
5	Fenasulam	Methyl 4-[2-(4-chloro-*o*-tolyloxy)acetamido] phenylsulfonylcarbamate		78357-48-9
6	Karbutilate	3-[[(Dimethylamino) carbonyl]amino]phenyl *N*-(1, 1-dimethylethyl)carbamate		4849-32-5
7	Terbucarb	2,6-Bis(1,1-dimethylethyl)-4-methylphenyl *N*-methylcarbamate		1918-11-2

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Table 15.2 Carbamates in agricultural industry—cont'd

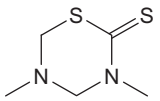
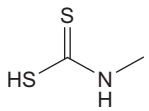
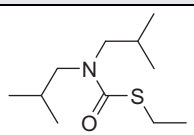
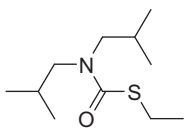
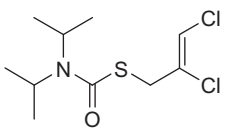
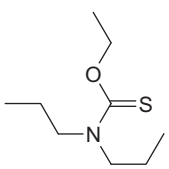
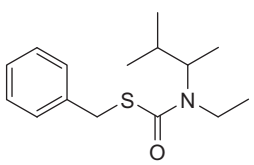
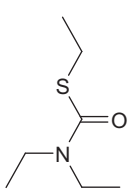
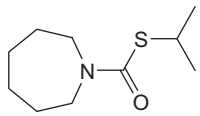
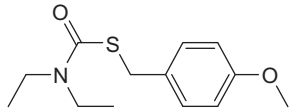
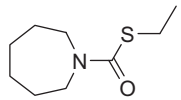
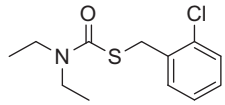
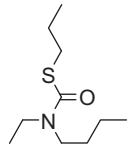
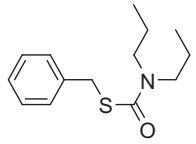
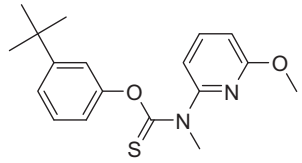
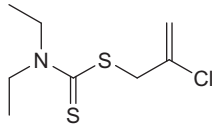
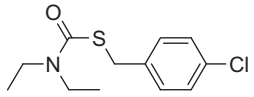
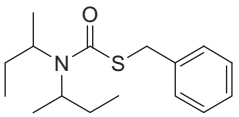
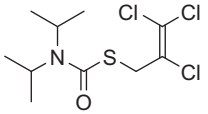
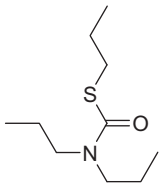
S. No.	Brand Name	Chemical Name	Structure	CAS No.
Dithiocarbamate Herbicides				
1	Dazomet	Tetrahydro-3,5-dimethyl-2H-1,3,5-thiadiazine-2-thione		533-74-4
2	Metam	*N*-methylcarbamodithioic acid		144-54-7
Thiocarbamate Herbicides				
1	Butylate			2008-41-5
2	Cycloate	*S*-ethyl diisobutyl (thiocarbamate)		1134-23-2
3	Di-allate	*S*-(*EZ*)-2,3-dichloroallyl diisopropyl(thiocarbamate)		2303-16-4
4	EPTC	Ethyl *N*,*N*-di-*n*-propylthiocarbamate		759-94-4
5	Esprocarb	*S*-benzyl (*RS*)-1,2-dimethylpropyl(ethyl) thiocarbamate		85785-20-2
6	Ethiolate	*S*-ethyl diethyl (thiocarbamate)		2941-55-1

Table 15.2 Carbamates in agricultural industry—cont'd

S. No.	Brand Name	Chemical Name	Structure	CAS No.
7	Isopolinate	*S*-isopropyl azepane-1-carbothioate		3134-70-1
8	Methiobencarb	*S*-4-methoxybenzyl diethyl(thiocarbamate)		18357-78-3
9	Molinate	*S*-ethyl azepane-1-carbothioate		2212-67-1
10	Orbencarb	*S*-2-chlorobenzyl diethyl (thiocarbamate)		34622-58-7
11	Pebulate	*S*-propyl butyl(ethyl) thiocarbamate		2008-41-5
12	Prosulfocarb	*S*-benzyl dipropyl (thiocarbamate)		52888-80-9
13	Pyributicarb	*O*-3-*tert*-butylphenyl 6-methoxy-2-pyridyl(methyl) thiocarbamate		88678-67-5
14	Sulfallate	2-Chloroallyl diethyl (dithiocarbamate)		95-06-7
15	Thiobencarb	*S*-4-chlorobenzyl diethyl (thiocarbamate)		28249-77-6

Continued

Table 15.2 Carbamates in agricultural industry—cont'd

S. No.	Brand Name	Chemical Name	Structure	CAS No.
16	Tiocarbazil	*S*-benzyl di-*sec*-butyl (thiocarbamate)		36756-79-3
17	Tri-allate	*S*-2,3,3-trichloroallyl *N*,*N*-diisopropylcarbamothioate		2303-17-5
18	Vernolate	*S*-propyl dipropyl (thiocarbamate)		1929-77-7

Carbamates have also gained considerable importance in the preparation of small molecule libraries [7]. Carbamates have played a key role in understanding of DNA structures [8]. "Rubisco" is the most abundant enzyme used in biological systems bearing a carbamate functionality and plays an important part in fixation of CO_2 by photosynthesis, which probably is the most important biochemical reaction of an ecosystem [9].

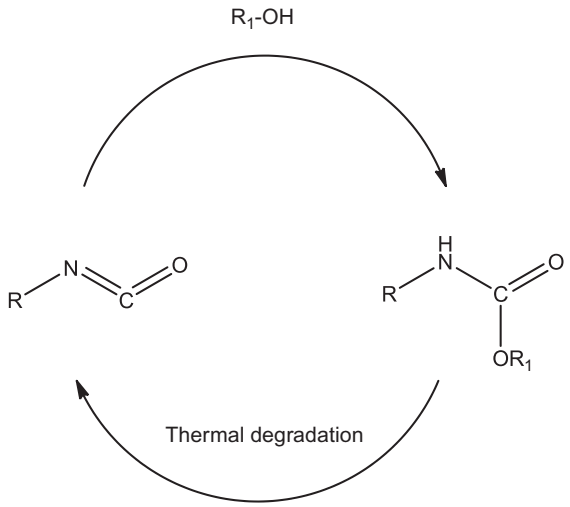
15.3 Synthesis of Carbamates

Among a plethora of methods for carbamate synthesis, amine phosgenation is the major technology employed for commercial production of carbamates. Several attempts have been made to synthesize carbamates with nonphosgene routes, many of which are reagent based while others are catalytic, eco-friendly alternatives.

15.3.1 Reagent-Based Methodologies

15.3.1.1 Nonphosgene, reagent-based methods for carbamate synthesis

Isocyanates are facile sources of carbamates and vice versa. Compounds containing hydrogen atoms attached to oxygen react with isocyanates. All types of alcohols—primary, secondary, tertiary, and polyhydric—react to give carbamates [10,11] (Scheme 15.1), the only exception being triphenylcarbinol, which gives no reaction [12].

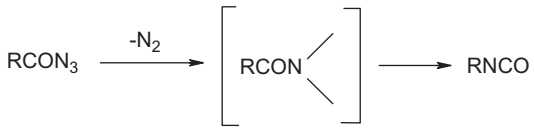


Scheme 15.1
General scheme for the synthesis of carbamates from isocyanate and alcohol.

Phenols, including polyhydric phenols, react, especially in the presence of aluminum chloride [13]. Therefore, all the methods for the preparation of isocyanates are useful for the synthesis of the carbamates of choice, by the consequent reactions with appropriate alcohols. The various reagent-based, nonphosgene, classical methods of synthesis of isocyanates (and consequently carbamates) are described here.

15.3.1.2 Curtius rearrangement of acid azide

The method other than the phosgene reaction, which has been used most, is the Curtius rearrangement of an acid azide in a neutral solvent [14]. The thermal decomposition of acid azides yields isocyanates, which further give the corresponding amine, urea, or carbamate depending on the nucleophilic medium used, ie, water, amine, or alcohol, respectively [15]. Although there are several methods available in literature, the acyl azides are generally prepared by the reaction of the active carboxylic acid derivatives like acid chlorides or anhydrides with sodium azide (Scheme 15.2).



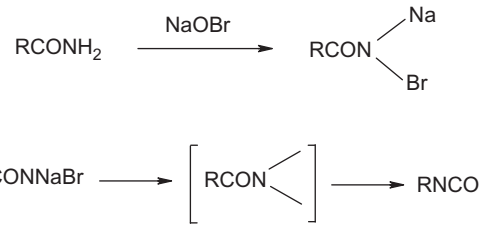
Scheme 15.2
Synthesis of isocyanates by Curtius rearrangement of acid azides.

Curtius used the method for the preparation of substituted ethylene diisocyanates. However, he prepared the diazide by treating substituted succinic hydrazides with nitrous acid. Yields

from the reaction are usually good, as in the case of undecyl isocyanate, which was obtained in 81–86% yield. Several variants of the Curtius rearrangement method have been reported, either multistep or single-stage (one-pot) syntheses.

15.3.1.3 Hofmann rearrangement of amides

This method is useful only for those isocyanates which do not react readily with water, since an aqueous medium is required. The reaction of bromine with an amide results in an *N*-bromoamide intermediate, which in presence of an aqueous hydroxide results in an *N*-bromoamide anion, which later undergoes a rearrangement to yield the isocyanate. The isocyanate on nucleophilic addition of an alcohol gives the corresponding carbamate (Scheme 15.3).

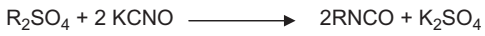


Scheme 15.3
Synthesis of isocyanates by Hofmann rearrangement.

The Hofmann rearrangement reaction has been reported with the use of several oxidants and bases.

15.3.1.4 Double decomposition reactions

The reaction between organic halides or sulfates and salts of cyanic acid was one of the first methods used for the preparation of isocyanates. Wurtz, in 1849, prepared alkyl isocyanates by this method (Scheme 15.4).

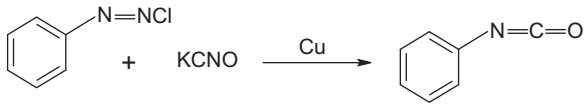


Scheme 15.4
Synthesis of isocyanate by double decomposition.

The reaction between the alkyl sulfate and potassium cyanate (Scheme 15.4) was conventionally the best method for the synthesis of methyl or ethyl isocyanate. In addition, acyl isocyanates may also be prepared in this manner.

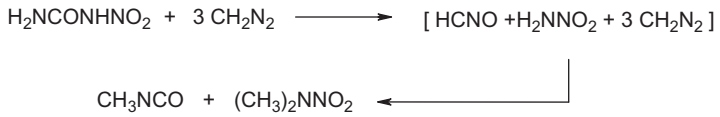
15.3.1.4.1 Other miscellaneous methods

Diazonium chlorides react with potassium cyanate in the presence of copper to give isocyanates (Scheme 15.5).



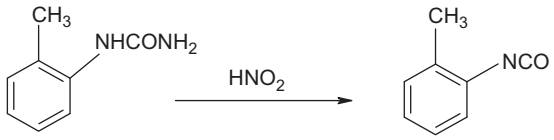
Scheme 15.5
Synthesis of isocyanates from diazonium chlorides.

Degner and von Pechmann reported that the reaction between diazomethane and nitrourea produced methyl isocyanate (Scheme 15.6).



Scheme 15.6
Synthesis of isocyanate from nitrourea.

o-Tolylurea in the presence of nitrous acid is converted to the isocyanate (Scheme 15.7).



Scheme 15.7
Synthesis of isocyanate from monosubstituted urea.

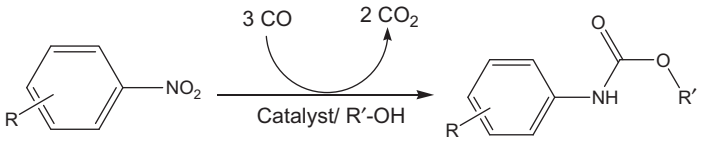
The routes mentioned for carbamate synthesis either deal with handling of potentially hazardous chemicals or require acids and bases in stoichiometric amounts, which produces inorganic salts that end up with aqueous effluent. Several efforts have been made for the preparation of carbamates using nontoxic or less toxic reagents and for the development of novel environmentally friendly methodologies.

15.3.2 Eco-Friendly Synthesis Methods

In the past few decades, several catalytic, mild, and eco-friendly routes have been explored for the synthesis of carbamates, involving the use of mild and less hazardous chemicals; for example, substrates like nitroaromatics, amines, or substituted ureas and carbonylating agents like carbon monoxide and dioxide or dimethyl carbonate (DMC).

15.3.2.1 Carbonylation of nitroaromatics to carbamates

For several years, the catalytic carbonylation of nitroaromatics has been extensively studied as an alternative for the phosgene-based production of isocyanates. The reaction, if carried out in alcohol media, leads to the formation of carbamates (Scheme 15.8).



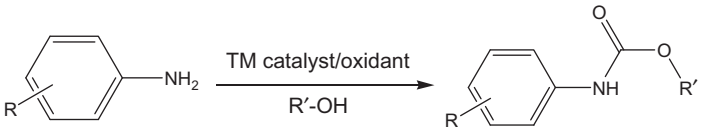
Scheme 15.8
General scheme for catalytic carbonylation of nitroaromatics to carbamates.

The advantages of carbonylation of nitroaromatics were foreseen long ago and have attracted attention for several decades [16], especially for the preparation of aromatic isocyanates, since the isocyanates find direct application in PU industry as active precursors. Buckeley and Ray [17] reported the carbon monoxide-mediated reduction of nitrogen-oxygen aromatic bonds, and were successful in converting nitrobenzene to azobenzene, nevertheless under extremely harsh conditions (250°C, 3000 bar), forming carbon dioxide. This discovery initiated the research on various reduction processes of the nitroso aromatic linkage assisted by transition metal complexes using CO. Later on, in 1967, Hardy and Bennet [18] reported catalytic carbonylation of nitro compounds with transition metal catalysts including rhodium, palladium, or other metal salts in the presence of a Lewis acid promoter. Since then, several homogeneous, heterogeneous, and heterogenized metal complex catalysts in conjunction with several ligands have been explored for the nitroaromatic carbonylation. Polynuclear precursors like carbonyl clusters of rhodium or ruthenium constituted notably active catalysts for carbonylation, especially when used with co-catalysts like tetraethylammonium chloride [19]. The presence of a co-catalyst was essential for the catalysis to proceed efficiently and specifically; for instance, diamine ligand was required with a palladium catalyst.

15.3.2.2 Oxidative carbonylation of amines to carbamates in alcohol medium

The oxidative carbonylation of amines offers an immensely attractive route for the synthesis of substituted ureas and carbamates, owing to the cheap and abundantly available raw materials used in this route. Most importantly, this route employs carbon monoxide, which is much less toxic than phosgene. Additionally, despite the toxic nature of carbon monoxide, it is widely employed in industry for fine chemical synthesis. Another advantage is the ease with which CO can be activated using transition metal catalysts—a basis for vastly studied and exploited carbonylation chemistry.

A schematic presentation of this reaction is given in Scheme 15.9.



Scheme 15.9
General scheme for catalytic oxycarbonylation of amines to carbamates.

Oxidative carbonylation of aromatic amines to carbamate is reported to be effectively carried out using a variety of noble metal catalysts such as Pd, Pt, Rh, Ir, Ru, etc., in presence of promoters or re-oxidants such as iodide compounds or *p*-benzoquinone, etc., under high pressures of $CO:O_2$ gas mixture and high temperature. The selectivity and conversion of the carbonylation reaction is dependent on the type of catalyst used, concentration of amine, $CO:O_2$ ratio, and temperature. Typical reaction temperatures range between 353 and 493 K, whereas pressure usually lies between 3 and 10 MPa. Se, Te, and Co catalysts have also been used for carbonylation of aliphatic and alicyclic amines, but these catalysts show very low activity toward the carbonylation of aromatic compounds [20]. Alper and Hartstock [21] described a homogeneous $PdCl_2$-$CuCl_2$ catalyst for the carbonylation reaction at room temperature and atmospheric pressure. Wan et al. [22] have shown that the polymer-supported bimetallic catalyst PVP-$PdCl_2$-$MnCl_2$ exhibits high activity and selectivity for the oxidative carbonylation of amines under atmospheric pressure in presence of base. Shi and Deng [23] have reported a gold complex [$(Au(PPh_3)$ Cl] as an active catalyst for oxidative carbonylation reaction for the first time. These researchers have also developed a relatively simple catalyst system consisting of $PdCl_2$ and sulfated zirconia for the efficient synthesis of carbamates [24]. Shi et al. [25] have reported an efficient catalyst system, Pd complex-ionic liquid, for the carbonylation of amines and shown the reusability of catalyst with slight loss in catalytic activity.

15.3.2.3 Carbon dioxide-mediated carboxylation of amine to carbamate

The CO_2-based carbonylation chemistry holds the potential of being industrially the most attractive, due to the nontoxic nature and the abundant availability of carbon dioxide as the carbonylating agent. However, the major challenge associated with this route remains the activation of CO_2. The utilization of carbon dioxide in the synthesis of carbamates can represent an attractive alternate route to conventional phosgene or isocyanate-based routes (Scheme 15.10).

$$R\text{-}NH_2 + CO_2 + R'\text{-}X \xrightarrow{\text{Catalyst}} RNHCOOR' + HX$$

Scheme 15.10
Carboxylation of amine with carbon dioxide.

Chisholm and Extine [26] in 1977 showed that transition metal complexes of *N*,*N*-dimethyl amide $M(Me_2N)n$ add onto CO_2 giving metal-carbamato derivatives. Later Tsuda et al. [27] reported the catalytic conversion of amines and carbon dioxide to carbamates. Kojima et al. [28] found that aluminum porphyrin is able to activate CO_2 and the catalytic system thus generated yields carbamate from amine and epoxide under ambient condition with TON of ~35. Ruthenium-catalyzed carboxylation of secondary amines and terminal alkynes has been reported to give enol carbamates in good yields with high regio- and stereoselectivity [29]. Higher yields of carbamates were realized when alkyl halides and a suitable "host-guest"

type of additives such as macrocyclic poly-ethers or onium salts or strong organic bases with the ability to delocalize their charge were employed as additives [30]. However, the disadvantage of this methodology was that it requires stoichiometric amount of alkyl halide and produces an equal amount of halide salts as a waste.

15.3.2.4 Carboxylation of amine to carbamate using organic carbonate

The alcoxycarbonylation of amines, which may also be termed as the aminolysis of organic carbonates, is a facile and attractive synthetic route to carbamates (Scheme 15.11).

$$RR'NH + R''OCOOR'' \xrightarrow{\text{Catalyst}} RR'NHCOOR'' + R''OH$$

Scheme 15.11
Carboxylation of amine with organic carbonate (where R,R′ = H, alkyl or aryl; R″ = alkyl or aryl group).

Alcoxycarbonylation is one of the most attractive nonphosgene methods for the synthesis of carbamates. In the following Section (15.5), the methoxycarbonylation by organic carbonates is taken up in greater detail, with prior art on the subject, chemistry of the reaction, and some studies performed in our group on the lead oxide-catalyzed methoxycarbonylation of aniline by DMC for the synthesis of methyl-*N*-phenyl carbamate as a case study.

15.4 Carbamate Synthesis by Methoxycarbonylation of Carbonates

The major reasons for this route being under intense investigation for the last three decades are as follows:

1. *Nonphosgene*: This transformation requires an amine and an organic carbonate as substrates, which are much safer to handle as compared to those used in the conventional phosgene-based technology. Also, the process produces only an alcohol as a coproduct.
2. *Easy availability of the carbonate*: The industrial production of DMC by oxidative carbonylation of methanol has been achieved by Enichem [31] and Ube [32]. Due to this, organic carbonates like DMC are cheaply and abundantly available. Besides, the organic carbonates of high boiling alcohols [33] or phenols [34] can be obtained conveniently by transesterification of DMC or diethyl carbonate. Thus, nonphosgene routes to carbonic acid diesters like DMC and aromatic diesters like diphenyl carbonate (DPC) are also available.
3. *Eco-friendly*: The conventional phosgenation route to carbamates generates large amounts of salts, which are generated when the hydrochloric acid formed in the process is neutralized with an alkali. Also, the process is highly exothermic, and requires elaborate cooling apparatus, which adds to the capital expenditure. The methoxycarbonylation does not generate any acidic or alkaline byproduct. Also, the reaction is only slightly exothermic.

4. *Atom economy*: Phosgene-based carbamate synthesis results in low chemoselectivity, and hydrolyzable chlorinated byproducts are formed. Methoxycarbonylation can be tailored using appropriate catalyst in conjunction with optimal reaction conditions and parameters to get a high selectivity to carbamates. The alcohol coproducts generated in the alcoxycarbonylation reaction can also be reused for the synthesis of the organic carbonate, thereby improving the atom economy of the process [35].
5. *Economical*: Unlike the other routes for amine carbonylation, this route does not require the expensive transition metal catalysts, but much more economical catalysts like salts or compounds of zinc, lead, and tin. Also, no promoter or co-catalysts are required, thus eliminating the possibility of generation of salts or undesirable byproducts.

15.5 Catalysis of Alcoxycarbonylation Reaction

The literature on carboxylation of amine to carbamate using organic carbonate is summarized in Table 15.3. Most of the reported literature shows that this reaction has been carried out preferably with the organic carbonate as a substrate as well as solvent. The catalysts with moderate to good activity reported for methoxycarbonylation include strong bases [47] such as alkali metal alkoxides, or Pb, Zn, Co, Sn, Al, Mn, and Ti organometallic complexes and compounds.

Table 15.3 Literature on carboxylation of amine using organic carbonate

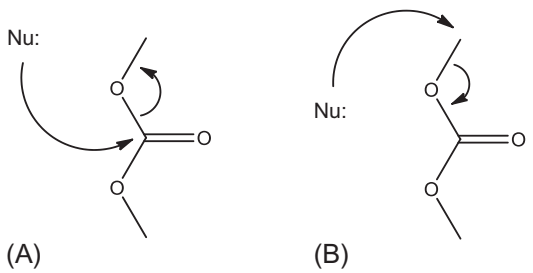
S. No.	Substrate	Carbonate	Catalyst	Time (h)	Temp (°C)	Amine (conv, %)	Carbamate (yield, %)	Ref.
1	C_6H_5-NH_2	DMC	$Zn(OAc)_2.H_2O$	1	160	98	97	[36]
2	*m*-Cl-C_6H_4-NH_2	DEC	NaH	1.5	25	–	70	[37]
3	C_6H_{13}-NH_2	DMC	$Pb(NO_3)_2$	2	25	–	93	[38]
4	C_3H_7-NH_2	DMC	$Pb(NO_3)_2$	2	120	99	99	[39]
5	C_6H_5-NH_2	DMC	γ-Al_2O_3	48	100	98	93	[40]
6	*p*-Cl-C_6H_4-NH_2	DMC	γ-Al_2O_3	48	90	100	95	[41]
7	$C_{10}H_{21}$-NH_2	DMC	$scCO_2$	17	90	100	85	[36]
8	$C_{10}H_{21}$-NH_2	DEC	$scCO_2$	20	130	96	83	[42]
9	*n*-C_4H_9-NH_2	DMC	$Yb(OTf)_3$	8	130	80	65	[37]
10	C_6H_5-NH_2	DMC	$Yb(OTf)_3$	8	80	–	93	[40]
11	*p*-NO_2-C_6H_4-NH_2	DMC	$Yb(OTf)_3$	8	80	–	96	[39]
12	C_6H_5-CH_2-NH_2	DEC	MCM-41-TBD	24	125	99	98	[38]
13	C_6H_{11}-NH_2	DEC	MCM-41-TBD	24	125	92	90	[41]
14	C_6H_{11}-NH_2	DMC	BMImCl	1	170	100	83	[43]
15	C_6H_5-CH_2-N(CH_3)H	DMC	BMImCl	1	170	100	99	[42]
16	H_2N-$(CH_2)_6$-NH_2	DMC	$Sc(OTf)_3$	40	20	100	80 (dicarbamate)	[44]
17	C_6H_5-NH_2	DMC	ZrO_2/SiO_2	7	170	89	53	[45]
18	1,5-Naphthalene diamine	DMC	Anhydrous $Zn(OAc)_2$	3	170	100	95	[46]

Lewis acids, such as $AlCl_3$, $SnCl_2$, $ZnCl_2$, $Zn(OAc)_2$ and $FeCl_3$ as well as precious metal complexes like those of rhodium and ruthenium have also proved to be effective catalysts [48].

The organophosphorus acids like diphenyl phosphinic acid $Ph_2P(O)OH$, diphenyl phosphate $(PhO)_2P(O)OH$, dibutyl phosphate $(BuO)_2P(O)OH$, and *n*-butyl phosphate $(BuO)P(O)(OH)_2$ have also been reported to exhibit good catalytic activity toward the alcoxycarbonylation of aromatic amines with DMC as well as DPC, with very high selectivity to the corresponding carbamates [49]. The role of the P-acid catalysts resembles greatly the carbamoylphosphate synthetase in living systems with regard to generation of carbamate anion. Aresta et al. [3], in another report, have extended this investigation to aromatic diamines focusing the attention on 4,4′-methylendianiline and 2,4-diaminotoluene (TDA), as the corresponding dicarbamates are suitable precursors to MDI and TDI, respectively. Interestingly, the reaction conditions can be tailored in this case to generate either the mono- or dicarbamates selectively [50].

Synthesis of carbamate from dialkyl carbonate and amines in the presence of γ-Al_2O_3 [41], MCM-41-TBD [38], and Yb(OTf) [40] has also been reported. SiMa and coworkers have demonstrated alkoxy carbonylation of primary and secondary amines by DMC using ionic liquids (eg, salts of substituted imidazolium). The ionic liquids function both as catalyst as well as solvents, and they also facilitate catalyst-product separation. Tundo et al. have also reported CO_2-promoted carboxylation of aliphatic amines to carbamate in excellent yield under supercritical conditions (90 bar CO_2; 130°C). Extensive screening study on microporous and mesoporous zeolites and metal oxide catalysts has been reported for synthesis of methyl-*N*-phenyl carbamate from DMC and aniline.

Ono and Tundo have done pioneering work for synthesis of several important organic intermediates using DMC as a benign building block. Ono et al. have explained the mechanism in which DMC imparts two different reactions, methoxycarbonylation and methylation. According to the authors, of the two available sites on DMC for nucleophilic attack, the carbonyl carbon of the DMC molecule is attacked at temperatures lower than 90°C, while the methyl carbon is attacked at higher temperatures of more than 160°C. This leads to methoxycarbonylation and methylation reactions, respectively (Scheme 15.12).



Scheme 15.12

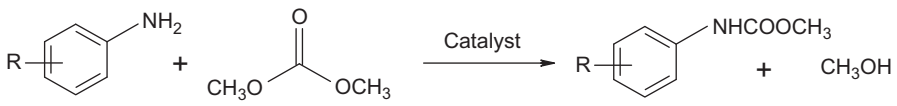
Nucleophilic substitution on DMC in (A) methoxycarbonylation and (B) methylation (where Nu: is the nucleophile).

15.6 Chemoselectivity in Alcoxycarbonylation Reaction

Alcoxycarbonylation of amines has been reported with several acidic, basic catalysts, and aromatic carbonates like DPC or aliphatic carbonates like DMCs have most frequently been employed as the carbonates. Owing to its easy availability, DMC has been used as the carbonate in several reports for investigation of activities of various catalysts. DMC is generally used as a carboxylating or methylating agent, and the chemoselectivity can be tuned using appropriate reaction conditions and catalysts.

15.7 Methoxycarbonylation of Aniline as a Model Substrate

With regard to the utility of catalytic methoxycarbonylation of amines for the environmentally benign synthesis of carbamates, the lead-catalyzed reaction does not offer the best option considering the toxicity of lead; nonetheless, the excellent catalytic activity of the metal salts for this reaction attracts academic attention. The aim of the work presented, therefore, was to investigate the catalytic activity of lead compounds toward methoxycarbonylation of amines **1** with dimethylcarbonate **2**, for the selective synthesis of a carbamate **3** (Scheme 15.13). For this purpose, the catalytic activity of lead compounds was first of all compared, and then further investigations were carried out using the selected lead catalyst, with aniline as the model substrate and DMC as the methoxycarbonylation agent as well as the solvent. The reactivity of different amines toward methoxycarbonylation using the model catalyst also was investigated, and the carbamates products formed in the reaction were isolated and characterized by conventional spectroscopic methods.



1 2 3

Scheme 15.13
General scheme for the catalytic synthesis of carbamates.

Using the red lead (Pb_3O_4) catalyst, a standard concentration-time (C-T) profile for aniline methoxycarbonylation of aniline in DMC solvent was obtained using analysis of reaction samples drawn at various time intervals. The liquid samples of the reactions were analyzed by GC and HPLC for the quantification of aniline and methyl *N*-phenyl carbamate (MPC), respectively, based on standard calibration curves. It was found that MPC was formed in all the reactions with high selectivity and the C-T profile drawn showed excellent agreement between aniline consumption and MPC yield, as observed from Fig. 15.2.

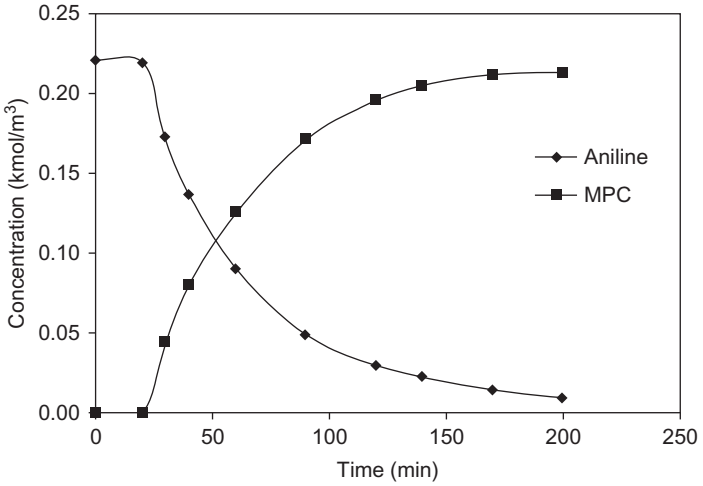


Fig. 15.2
Concentration-time profile for Pb_3O_4-catalyzed methoxycarbonylation of aniline in DMC. *Reaction conditions*: Aniline 0.222 kmol/m^3, Pb_3O_4 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, temperature 433 K, agitation 10 Hz, time 200 min.

15.7.1 Catalysis of the Reaction

The Pb_3O_4-catalyzed methoxycarbonylation of aniline in DMC medium highlighted a few intriguing aspects, in view of which a mechanistic investigation of the reaction was apparently interesting. The reaction exhibited an induction period of approximately 20 min in the reaction, under the experimental conditions investigated. A similar induction period has been reported by Fu et al. [36] in the lead nitrate-catalyzed methoxycarbonylation of aniline with DMC. The authors have studied the effect of catalyst pretreatment on the induction, wherein the catalyst has been pretreated with methanol and DMC, which resulted in the elimination of induction period. This essentially shows that the lead catalyst is first modified with DMC, which is then attacked by the nucleophilic amine, resulting in the elimination of carbamate.

Some key observations during the course of the study were as follows:

- The induction period was found to be inversely proportional to the catalyst concentration. The effect was studied in the range of 1.2–4.8 kg/m^3 concentration of Pb_3O_4. However, the decrease was not linear.
- At aniline concentration variations in the range of 0.11–0.429 kmol/m^3, no pronounced effect of aniline concentration variation was observed on the induction period.
- The induction period decreased with increasing temperature, within the study range of 423–443 K. This indicated probable formation of active metal complex or species, being formed more efficiently at higher temperatures, thereby causing the induction period to decrease.

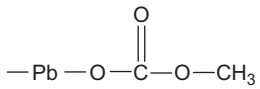
- No notable adverse effect of MPC and methanol formed in the reaction was observed in the range of theoretical yields on charge basis (ie, assuming quantitative conversion of aniline to MPC with 100% chemoselectivity). However, it is reported in the literature that the alcohol generated in the reaction adversely affects the reaction rates in the methoxycarbonylation of amines for the synthesis of carbamates [3]. Therefore, higher concentration of methanol was studied. It was found that, at the concentrations higher than 10% w/w, there was drastic adverse effect on the reaction rate, and there was no apparent conversion of aniline at 60% methanol (% w/w).

  Red lead showed good recyclability for methoxycarbonylation of aniline. Under optimized conditions, it showed good reusability up to at least three recycles in terms of aniline conversion and selectivity to MPC. Fu et al. [36] have proposed in the PbO-catalyzed aniline methoxycarbonylation, that the catalyst sites are modified during the course of this reaction, and this actually causes an elimination of induction period on recycle.

15.7.2 Reaction Mechanism

For the metal-catalyzed synthesis of alkyl carbamates, starting from an amine and an organic carbonate, two plausible mechanistic approaches can be envisaged:

1. activation of the organic carbonate with the metal catalyst, followed by the nucleophilic attack of amine on the carbocation of the carbonate-lead adduct or
2. the activation of amine with lead catalyst, followed by the nucleophilic attack of this adduct on the carbocation of organic carbonate

Fu and Ono [36] have proposed a mechanism for the methoxycarbonylation in the PbO-catalyzed methoxycarbonylation of aniline, wherein the activation of DMC with lead to form a  type of species is shown, which eventually is attacked by the basic amine to form carbamate. The form of lead that initiates the catalytic cycle is described as the surface Pb-OH groups, which are modified by DMC. The latter is a versatile moiety, which has two carbon centers at which the amine nucleophile may react: the *carbonyl* group and the *methyl* group. When a nucleophile attacks at carbonyl carbon of DMC, the cleavage of acyl-oxygen bond results in a methoxycarbonylation product, whereas a methylation product is obtained when the nucleophile attacks at the methyl carbon of DMC, by the alkyl-oxygen bond cleavage (refer to Scheme 15.12).

Distaso and Quaranta [51] have carried out the IR studies for finding out the mode of coordination, according to which, the coordination via the carbonyl oxygen is evident. Though the carboxylation reaction of amines with CO_2 cannot be compared to that with organic carbonates in terms of mechanism, we find some analogy in the sequence of steps in the two reactions. According to Srivastava et al. [52], in the zeolite-catalyzed carboxylation

of aniline, the CO_2 first binds with the metal, followed by the oxidative addition of amine to the metal to yield carbamate. Baba et al. have proposed a similar mechanism for Zn-catalyzed methoxycarbonylation of amines [17]. Based on this approach, a mechanism for Pb_3O_4-catalyzed methoxycarbonylation of aniline has been proposed. The schematic representation of the proposed mechanism is shown in Fig. 15.3.

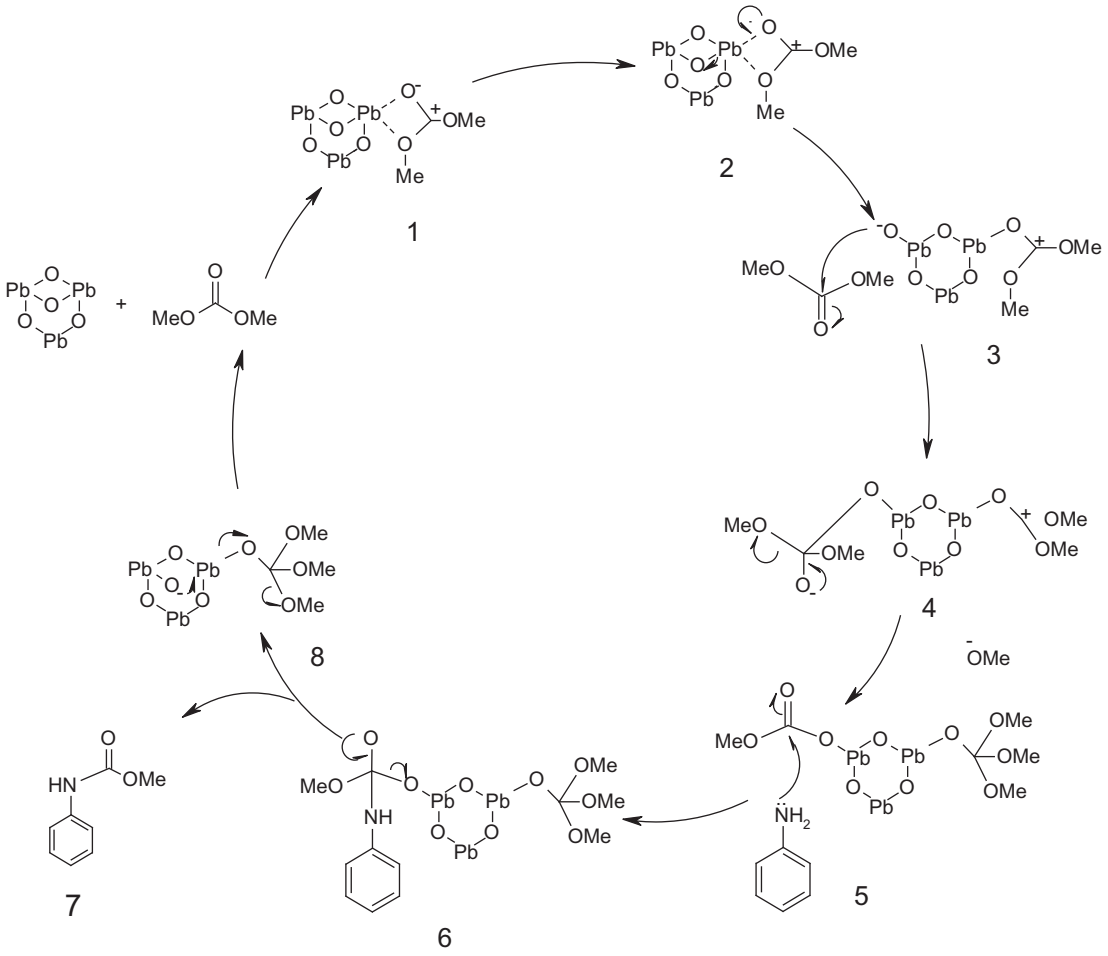


Fig. 15.3
Plausible mechanism (I) for Pb_3O_4-catalyzed methoxycarbonylation of aniline.

According to another approach, the activation of amine takes place first by coordination with the metal, followed by the attack of this adduct onto DMC. Xiao et al. [46] have done IR investigations on the DMC-mediated, zinc acetate-catalyzed methoxycarbonylation of 1,5-naphthalenediamine (NDA). According to this study, the pretreatment effect of DMC on zinc acetate in the temperature range of 403–453 K showed no modification of the latter, as evident from the unchanged IR patterns of the catalysts, whereas the pretreatment study for

zinc acetate catalyst with NDA showed disappearance of the characteristic values and appearance of new bands at 3116 and 901/cm, and also a shift in the ν_a and ν_s of COO^- group, indicating formation of a complex of the amine with zinc, at temperatures beyond 403°K. This study showed that two molecules of NDA could coordinate with one molecule of zinc acetate. The authors have concluded from the study that the activation of amine first takes place with the catalyst, which then acts as the suitable nucleophilic agent, and attacks DMC, to yield the carbamate. A similar mechanism could be proposed for the Pb_3O_4-catalyzed methoxycarbonylation of aniline with DMC, which is shown in Fig. 15.4.

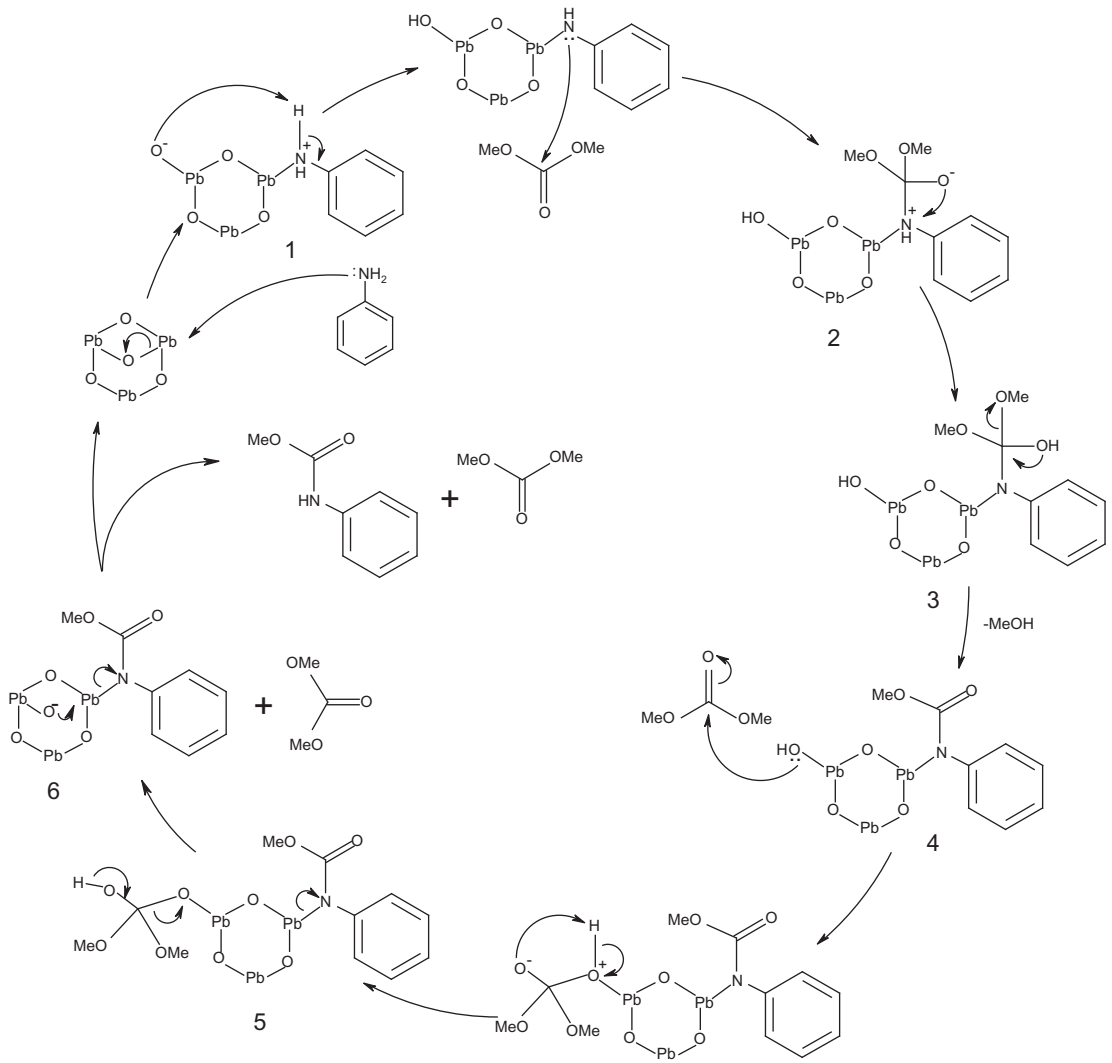


Fig. 15.4
Plausible mechanism (II) for Pb_3O_4-catalyzed methoxycarbonylation of aniline considering modification of the catalyst by aniline as the initiation of catalytic cycle.

To find out the behavior of the catalyst and sequence of steps in the mechanism, a few reactions on the pretreatment effect were carried out. In this study, the catalyst Pb_3O_4 was pretreated with DMC and aniline independently at different temperatures, and these catalysts were then tested for the model aniline methoxycarbonylation reaction, to check if the induction period disappeared. It was observed that, at ambient temperature, there was no activation of either aniline or DMC with Pb_3O_4. Experiments performed at temperatures beyond 423 K with DMC showed that the color of catalyst changed, and also the induction period disappeared when the solid catalyst recovered from this DMC pretreatment experiment was used.

IR spectra were recorded for fresh and pretreated Pb_3O_4 catalysts as well as for the catalyst recovered from a typical aniline methoxycarbonylation experiment. The Pb-O stretching frequency in the cyclic structure of Pb_3O_4 was observed at 531/cm. This frequency, in the case of PbO, is 465 and 505 [53]. From the IR spectrum of the DMC pretreated catalyst, it was evident that there is modification in the structure of the catalyst. A similar IR spectrum of aniline pretreated catalyst showed no difference from that of unused Pb_3O_4, which is in complete agreement with the experimental evidence, where the aniline pretreated catalyst does not eliminate the induction period. The elimination of induction period due to DMC pretreatment is obviously due to the formation of an active catalyst complex. The modified Pb complex is speculated to have the structure as shown in Fig. 15.5B. The coordination of DMC through the carbonyl oxygen is obvious from the disappearance of $\nu_{(C=O)}$ at 1780/cm. The C-O stretching frequency in the DMC-Pb complex probably shifts to 1321/cm. The red shift is much higher compared to the coordination of DMC with other catalysts like $Sc(OTf)_3$ or other such reported metal catalysts. The higher shift can be assigned to the high electronegativity of Pb compared to Sc [54].

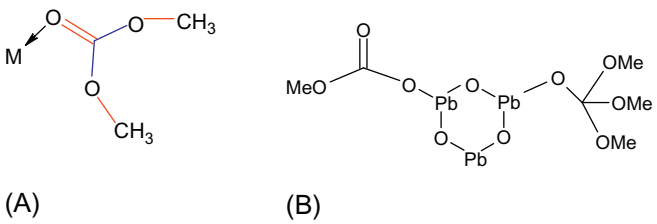


Fig. 15.5

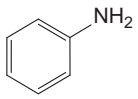
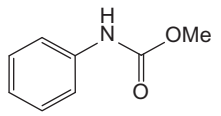
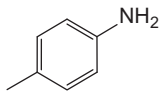
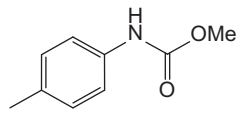
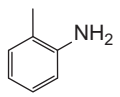
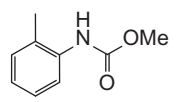
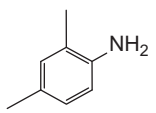
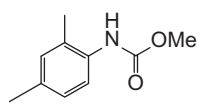
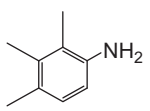
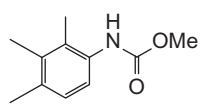
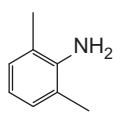
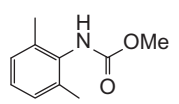
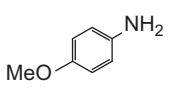
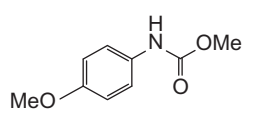
(A) Shifts in IR frequencies due to coordination of DMC with metal and (B) possible adduct formed due to pretreatment of Pb_3O_4 with DMC.

The observations are consistent with those of $Sc(OTf)_3$-catalyzed methoxycarbonylation of amines, wherein Distaso and Quaranta [44] have demonstrated that the pretreatment of the scandium triflate catalyst with DMC causes a coordination of DMC via the carbonyl oxygen to metal (Sc). Similarly, in the present study, the shift to red ($\Delta\nu_{(C=O)} < 0$) allows us to exclude coordination modes A or B in Fig. 15.5.

15.7.3 Screening of Amine Substrates

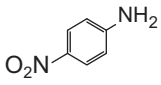
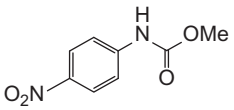
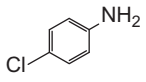
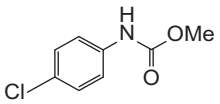
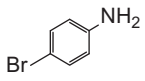
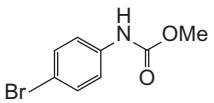
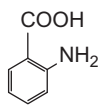
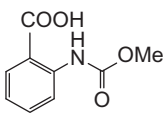
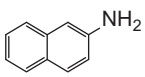
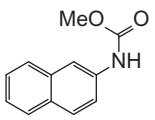
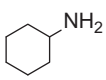
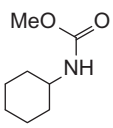
Various amines were screened for the Pb_3O_4-catalyzed methoxycarbonylation by DMC. It was found that aliphatic amines gave excellent yields of the carbamates, while the yields varied vastly in case of aromatic amines. The carbamates were identified by GC-MS analyses, and also by IR, NMR, and elemental analyses. The carbamates were isolated from reaction mixtures by column chromatography or solvent extraction. The results obtained in the amine screening study are presented in Table 15.4.

Table 15.4 Screening of amines for Pb_3O_4-catalyzed methoxycarbonylation using DMC

S. No.	Amine	pK_a	Carbamate	Amine Conversion (%)	Carbamate Yield (%)
1		4.64		95.7	91.84
2		5.07		95.05	92.41
3		4.38		88.70	83.08
4		–		97.05	91.81
5		–		95.81	92.33
6		–		95.28	93.28
7		5.29		86.98	84.37

Continued

Table 15.4 Screening of amines for Pb_3O_4-catalyzed methoxycarbonylation using DMC—cont'd

S. No.	Amine	pK_a	Carbamate	Amine Conversion (%)	Carbamate Yield (%)
8		0.98		35.11	34.23
9		3.81		83.22	79.85
10		3.91		81.8	80.17
11		2.04		2.5	0
12		3.92		84.4	80.65
13		9.82		86.44	–

Notes: (a) There was no or very low conversion of the amine and (b) many peaks observed on GC, indicating formation of several byproducts.
Reaction conditions: Amine 0.222 kmol/m^3, Pb_3O_4 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, temperature 433 K, 10 Hz, reaction time 120 min.

In the substrate screening experiments, it was found that the aromatic amines having better basicity were better substrates. Analogously, the amine conversions and carbamate yields increased with increasing pK_a values of the amine substrates. For example, in Table 15.4, it can be observed that, 4-toluidine (entry 2, pK_a 5.07) is a better substrate than 4-nitroaniline (entry 8, pK_a 0.98) or anthranilic acid (entry 11, pK_a 2.04). This is in agreement with the proposed reaction mechanism, where the efficiency of the nucleophilic attack of the amine on the DMC carbocation depends on the neucleophilicity of the NH_2 group. Moderately or strongly activating substituents on the aromatic ring are expected to give better amine conversions

(entries 2–7) and product yields, while deactivating substituents on the ring should make the amines (entries 8–11) comparatively less active substrates. This is exactly what is observed from Table 15.4.

15.8 Summary

This chapter introduces readers to the interesting area of catalysis having application in carbamate synthesis. It presents the basic chemistry in carbamate synthesis while summarizing important aspects of catalyst development by a model case study.

Alkoxy carbonylation is an important nonphosgene route for carbamate synthesis. This transformation requires an amine and an organic carbonate as substrates, which are easily available in the market, and are much safer to handle as compared to those used in the conventional phosgene-based technology. Various carbamates can be synthesized by this method, which find wide applications in pharmaceutical, agricultural, and polymer chemicals.

A detailed investigation on lead oxide-catalyzed methoxycarbonylation of aniline to methyl-*N*-phenyl carbamate using DMC has been also reported. The lead oxide was found to be an excellent catalyst for selective carbamates synthesis, and an attempt to understand the chemistry of its catalysis for methoxycarbonylation has been made. The catalyst system has been applied to several substituted aromatic amines resulting in corresponding carbamates, demonstrating the usefulness. From an industrial manufacture perspective, lead is admittedly not the most suitable candidate as catalyst of choice; nevertheless, we sincerely hope that this exploration in understanding the catalysis and chemistry of reaction will add value to future development of safer, eco-friendly, and effective catalysts for this promising reaction.

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CHAPTER 16

Challenges in Scale-Up of Specialty Chemicals—A Development Chemist's Perspective

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16.1 Introduction

Specialty chemicals are functional or performance chemicals used in specific applications. They could be either a single entity or formulations to enhance performance. Specialty chemicals form a major growth area in the emerging countries, typically China, India, and other Asian nations. Defined very loosely on the basis of the price/volume basis, the chemical value chain, distinguishing niche, fine and specialty, and commodity chemicals, is shown in Fig. 16.1.

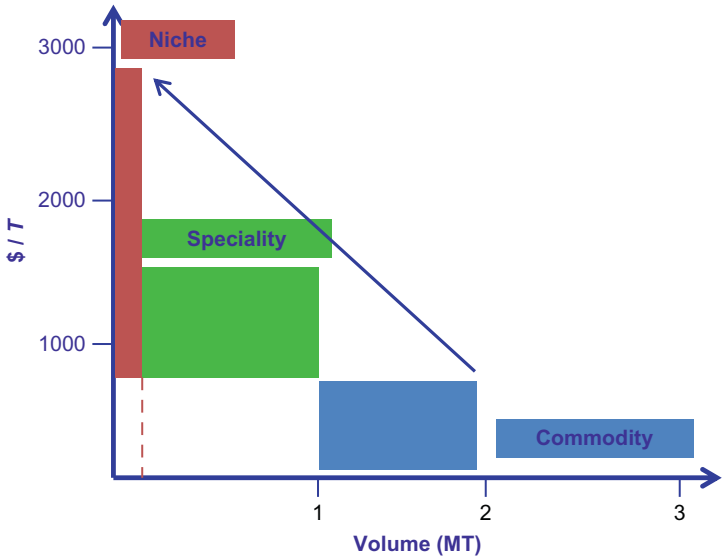


Fig. 16.1
The chemical value chain.

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The chemical value chain can also be distinguished as shown in Table 16.1.

Table 16.1 The chemical value chain—broadly categorized

Commodity (Basic)	Speciality	Niche (Knowledge)
Petrochemicals	Adhesives	Agrochemicals
Fertilizers	Catalysts	Pharmaceuticals
Inorganic chemicals	Coatings	Biotechnology
Alkalies-chloralkalies	Pharma additives	
Aromatics	Plastic additives	
Thermoplastics/sets	Lubricants	
Industrial chemicals	Emulsifiers	

Global forecasts indicate specialty chemicals will grow at 5.2 CAGR (compound annual growth rate) during 2013–18, with the major growth evident in emerging markets in Asia [1].

This chapter records some of the challenges faced during the author's fruitful and challenging career as a process development chemist. For the sake of simplicity, it is constructed in the form of some case studies based on process development projects undertaken. Information considered proprietary or confidential in nature is not presented by the author, except as referred to in the published literature.

16.2 Scale-Up of Specialty Chemicals: A Chemist's Perspective

The development of a chemical process from laboratory to commercial scale is fraught with many pitfalls. A 1 kg laboratory optimized process magnified to 1000 kg commercial scale will be accompanied by a similar scale of errors if not noticed or rectified at the laboratory scale. Therein lie the skills of a development chemist, which is highlighted in a small-/medium-scale chemical plant where chemical engineering inputs may not be available or vice versa. There is a perpetual risk of missing/ignoring many unit operations during the laboratory scale optimization that have to be factored in when the process is scaled up commercially. Some operations viz. filtration may be easily performed in a laboratory but could limit productivity on a commercial scale if not appropriately attended to at the laboratory scale.

Some points mentioned here may appear mundane or taken for granted due to long exposure/experience, but ignoring them at the time of process optimization has led to delays or abandonment of the project altogether. Some classical examples follow.

In gas-liquid reactions conducted in the laboratory the development chemist uses a glass tube for sparging—it is possible that a sparger is not present on the reactor in the plant.

The crude product may need high vacuum for purification by distillation, and the plant is equipped with pump offering ~30 mm, but the process needs <1 mm vacuum.

The laboratory process is optimized using sophisticated analytical instruments such as GC, GC-MS, which may not be available at the plant, making all the laboratory efforts for developing the process an exercise in futility.

The processes to make speciality or niche chemicals are generally proprietary in nature, and the manufacturer is cautious about its porosity or loss of process secrecy. In view of this, they may opt to undertake many operations that may not be in their sphere of competency. For example, in one of the projects undertaken, to guard the proprietary nature of the process, the catalyst was developed in-house. All was well during the laboratory stage of process optimization until the next stage. Pilot trials of development arrived, and the process of catalyst preparation also had to be scaled up. It was realized then that the catalyst activation using hydrogen gas resulted in an uncontrollable exotherm, which had to be aborted, fortunately without any loss or damage. The exotherm that occurred at the 100 g scale of the catalyst preparation was not observed in the lab scale preparation of a 5–10 g scale. Of course, the process was successfully commissioned once this observation was rectified by the use of a mixture of nitrogen and hydrogen during the catalyst activation. A catalyst manufacturing firm would have anticipated this and taken correct process operation steps in the lab scale development itself.

A fatal error a development chemist may make is the use of pure or lab-grade reagents as raw materials during the laboratory scale process optimization. It is recommended to use the raw materials that are to be used for the commercial scale of operation even in the laboratory during process optimization. This not only helps in selecting the raw material for commercial scale operations but also to fix the specifications of the raw materials to be used.

Another major issue that needs adequate attention is educating the plant and production team use and handling instructions for the raw material that will be used. MSDS (Material safety data sheet), toxicity data, material handling, and storage information are as important as the process document itself.

There are several gaps a chemist and a chemical engineer each face in the domain of the other. To have a seamless transfer of process technology from laboratory to pilot to plant, they need to work in tandem, sharing their expertise and skill when required. A chemist may not be aware of the issues of reaction kinetics and transport phenomenon, and a chemical engineer may not have information on the reaction mechanism of the process. This is possible in gas-liquid catalytic reactions such as hydrogenation, where the nitro to amino reaction proceeds via several intermediate formations, some very hazardous. The engineer may be qualified to suggest a reactor design for such reactions, such as an impeller type and a heat

transfer design for dissipating the reaction heat effectively to ensure safe and reproducible process operations.

The net result of an optimized process is to have

- robustness
- simplicity of operation
- minimized operational hazards
- efficient online, in-process checks—GC/IR/TLC/titrimetry—tests that will be done rapidly but with a fair amount of reproducibility

Raw materials: finalizing the specifications and test methods between user and producer will make the process of development more seamless. Conducting a "performance test" of the raw material is an ideal step in the process development, more so when an additional supplier is being shortlisted. Scale of this "performance test" can be decided by the team leader in consultation with other partners in the process development, such as R&D, operations, and sourcing team.

Sustainability and efficiency should be the buzzwords for this activity. This not only leads to process efficiency but also reduces effluents—an idea whose time had come at least 20 years ago, especially in the Indian "small-scale" manufacturing sector. It failed to notice this important cog in the wheel, making many processes inefficient, in cost as well as quality. This is one area where the development chemist is found lacking and should be in constant dialog with the engineering and effluent management team. There are case studies in abundance that demonstrate how recovering and recycling of some ingredients from the effluent not only have made processes commercially viable but also have led to improved quality of the product, giving an edge over competitive products.

A critical aspect to highlight the overlapping of an efficient process and green/environmental considerations is reproduced in Table 16.2 [2].

Table 16.2 Process and green chemistry have similar goals

Goal	Considerations	
	Process	Environmental
Minimum synthesis steps	Efficiency	Less energy and waste
Avoid hazardous reagents	Safety, scalability	Safety, less pollutants
Ease of isolations	Scalability, throughput	Less waste
Avoid severe conditions	Scability, robustness, cost	Less energy
Achieve high selectivity	Purity, efficiency	Less waste

In the speciality chemical segment, given the nature and volume of production, most processes are batch types, and the reactor engineering is a prominent tool of exploitation. This enables the manufacturer to make many "campaign-based" products within the same reactor configuration.

16.3 Case Studies

16.3.1 Butylation and Products of Butylation

Several butylated products are used in the chemical industry. The most extensive among them are alkyl phenols, illustrated in Tables 16.3 and 16.4.

Table 16.3 Alkyl phenols extensively used industrially

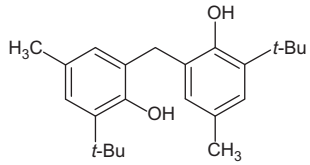
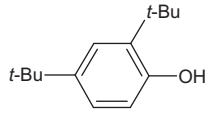
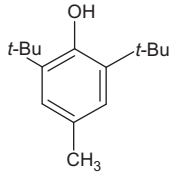
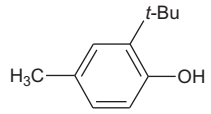
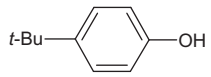
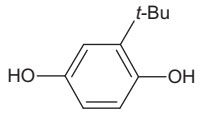
Name	CAS Nr	Structure
2,2′-Methylenebis-(6-tertiary butyl-4-methylphenol)	119-47-1	
2,4-Di-tertiary butylphenol	96-76-4	
Butylated hydroxytoluene	128-37-0	
2-Tertiary butyl-4-methylphenol	2409-55-4	
p-Tertiary butylphenol	98-54-4	
t-Butylhydroquinone	1948-33-0	

Table 16.4 Erstwhile Ciba Specialty Chemicals "Irga" brand of antioxidants [3]

Brand	CAS Nr	Substance Name	Application
Irganox 1010	6683-19-8	Pentaerythritol tetrakis 3-(3,5-di-*tert*-butyl-4-hydroxy phenyl) propionate	Nondiscoloring stabilizer for plastics, synthetic fibers, adhesives, etc.
Irganox 1076	2082-79-3	Octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate	Prevents thermo-oxidative degradation
Irganox 1330	1709-70-2	3,3′,3″,5,5′,5″-Hexa-*tert*-butyl-α,α′,α″-(mesitylene-2,4,6-triyl)tri-*p*-cresol	Primary antioxidant; resistant to leaching
Irgafos 168	31570-04-4	Tris(2,4-ditert-butylphenyl) phosphite	Secondary antioxidant; prevents process induced degradation

Industrially, butylation reactions involve gas-liquid types, and the nature of the Indian chemical industry scale of manufacturing (large, medium, or small) dictates the source of 1-butylene. The source of isobutene is a major contributor to making the process technology economic and workable. Isobutylene in its pure form could be an ideal source (Fig. 16.2).

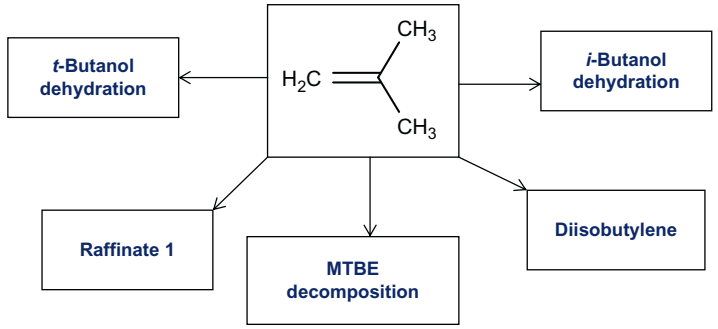


Fig. 16.2
Isobutene sources—a schematic illustration.

Alternative routes to *i*-butylene:

- alcohol dehydration (*iso*-/*tert*-butanol) [4,5]
- MTBE (methyl tertiary butyl ether) cracking
- raffinate
- diisobutylene cracking

1-Butene from butyl alcohol dehydration is a high-temperature catalytic reaction source of butanol, and whether it is *iso* or tertiary will decide the conditions of dehydration.

The *t*-butanol dehydration can be effected by VP (vapour pressure), catalytic processes. Table 16.5 gives results of such a process.

$T = 160°C$, Cat.: Si/Al, Fixed Bed

Table 16.5 Butanol dehydration at a glance

Conditions	Results
Feed gas (l/h)	132
Space velo (l/h)	400
% conversion of *t*-BA	91
Yield of *i*-butene (%)	89
Selectivity (%)	97

Likewise, isobutene can be produced by dehydration of isobutanol under the following conditions (Table 16.6) [6]:

Conditions: 300°C, GHSV (gas hourly space velocity) = 221 StdL kg cat.$^{-1}$ h^{-1}

Table 16.6 Product composition of butanol dehydration

Compound	Composition (mol%)
i-Butanol	13.4
Water	43.0
Isobutene	40.5
(*c*+*t*)-2-Butene	1.6
Others[a]	1.6

[a]1-Butene; diisobutyl ether; isobutane.

MTBE cracking: MTBE is yet another source for *i*-butene. Cracking MTBE can generate pure *i*-butene. Methanol as a co-product can be recycled. The process of cracking MTBE is endothermic and is acid catalyzed at temperatures ~250°C and low pressure to enable isobutene recovery. To avoid dehydration reaction as a parallel activity, the MTBE stream is mixed with water/steam. Per pass conversion of MTBE can be >99% with matching selectivity.

The Raffinate-1 (normally referred to as C4R1) obtained from naphtha cracking and after extraction of butadiene is another source for *i*-butene, although the concentration in the stream is barely 50%. This stream after reacting with phenols gives an exit gas that can also be isomerized to *i*-butene, but more about this later in the chapter (Table 16.7).

Table 16.7 A typical raffinate-1 composition

Component	Wt%
C_2/C_3 hydrocarbons	1 max
Total butanes	5–20
n-Butene	15–20
Isobutene	35–50
(*cis*+*trans*) butenes	20–27
1,3-Butadiene	0.5 max

Diisobutylene cracking [7]: diisobutylene cracking is another option of preparing isobutene for butylation.

Clearly, based on the preceding information, the challenge for medium-scale chemical industries in the butylation business in India was: buy or make *i*-butene. If made internally, then the appropriate route or source needed selection. From the development chemist's point of view, the option was to propose a "swing" strategy that would consider the technocommercial conditions prevailing at any given time:

- raw material availability
- scalability of the process
- productivity
- unit cost of butylation

Among the aforementioned routes, dehydration of isobutanol may be preferred and buying the raffinate containing ~50% *i*-butene for reasons mentioned earlier.

After the butylation reaction, the exit raffinate stream typically has the composition shown in Table 16.8.

Several references exist in the literature (both published and patented) where *n*-butene has been isomerized to *i*-butene by the vapor phase catalytic process [8].

At Quality Industries, this development project was able to isomerize the *n*-butene to levels that encouraged exploring the scaling up of the process. Table 16.8 demonstrates the results obtained from skeletal isomerization of *n*-butene from the exit stream of raffinate.

Table 16.8 Composition of the C_4 stream before and after isomerization

Components	Wt%	
	Exit Stream	Isomerized
C_2/C_3 hydrocarbons	1 max	
Total butanes	25–28	
n-Butene	~40	18–35
i-Butene	2–5	22–28
(*cis* + *trans*) butene	20–27	
1,3-Butadiene	< 1%	

This stream was then used to butylate the *p*-cresol to make di-*tert*-buty *p*-cresol (BHT), a commonly used antioxidant in industrial applications.

The transformation occurred at high temperatures ranging from 350 to 500°C at GHSV of ~2. The catalyst life was dependent on the impurities in the exit gas stream, typically carryover nonvolatile organics viz. unreacted *p*-cresol, BHT, or intermediates, leading to coking and

blocking of active sites in the catalyst. Regeneration of the catalyst could be repeatedly done using elevated temperatures converting the coke to CO_2.

The success of the entire process was dependent on engineering and required high-pressure compressors and condensers to first purify the exit gas stream and compressing the isomerized gas for storage.

The challenges from a development chemist's perspective were many:

1. Catalyst preparation—because it was proprietary. The annual requirement would be not attractive enough for collaborating with a catalyst manufacturer. This would mean making it in-house; an added advantage of this action would be maintaining the confidentiality of the process. On the other hand, many issues could crop up, and the manufacturer would not have the competency to troubleshoot given that their expertise is in "Specialities." It would also mean that a separate infrastructural and operational setup would be required for the catalyst preparation.
2. Gas analysis—online in the early 1990s when the Indian chemical SMEs were not exposed to automation required for such unit operations.
3. The exit gas stream required purification to eliminate residual impurities, which poisoned the catalyst. This entailed separation columns and low-temperature condensation.

The other challenge in this chemistry encountered were the following.

Catalyst selection for butylation [9]: heterogeneous/homogeneous catalysts. Several catalysts exist in the literature. A solid Brønsted acid catalyst was best suited to achieve the optimum—improved per pass conversion. For productivity and selectivity, for example, some catalysts gave high mono butyl selectivity.
Butylation process: selection of the process—batch or continuous—was another challenge. In the continuous process, selection of reactor type—trickle bed or bubble column type reactor—was for optimum gas-liquid-catalyst contact. This will enhance throughput, improve quality, and reduce capex.

16.3.2 Organotin Chemistry

Organotin compounds are widely used industrially [10,11] as:

- PVC (polyvinyl chloride) stabilizers
- catalysts for industrial production of many chemicals
- biocides in antifouling paints, wood preservation, etc.
- agrochemicals

PVC stabilizers are the largest application area for organotin compounds. Whereas the US organotin stabilizers are in practically all rigid PVC applications, in Europe it finds application

more in rigid, transparent applications where PVC processing conditions are more severe. Two types of tin stabilizers are used: tin carboxylate and tin mercaptide. Table 16.9 gives a short use pattern of organotin stabilizers in the EU [12,13].

Table 16.9 Tin as PVC stabilizer

Application	Tin Stabilizer (%)	Total Tin Stab. Tons
Rigid calendered films	83.3	10,000
Rigid sheets and profile	12.5	1500
Rigid others	4.2	500
Total		12,000

Currently, the triorganotin compounds are under scrutiny for their toxicological and environmental concerns worldwide. However, the mono- and diorganotin have no such issues. In view of this, preparing the mono- or diorganotins selectively can be a challenging task for a chemist.

Organotin compounds are known to catalyze many reactions and are widely used in the chemical industry [14–16].

Generally, the organotins are prepared by via the Grignard or trialkyl aluminum route using $SnCl_4$ as the building block.

$$3SnCl_4 + 4(C_4H_9)_3Al \rightarrow 3(C_4H_9)_4Sn + 4AlCl_3$$

$$SnCl_4 + 4CH_3MgCl \rightarrow (CH_3)_4Sn + 4MgCl_2$$

The tetraorganotin is then used to make other organotins via the redistribution reaction to make mono-, di-, and triorganotins as shown below:

$$3R_4Sn + SnCl_4 \rightarrow 4R_3SnCl$$

$$R_4Sn + SnCl_4 \rightarrow 2R_2SnCl_2$$

$$R_4Sn + 3SnCl_4 \rightarrow 4RSnCl_3$$

These moieties are then used to build other organotins, for example, PVC stabilizers. Of particular interest and relevance to this work is the preparation of methyltin stabilizers.

Although the Grignard route gives clean precursors for the building block, industrially there are always issues of safety and hazards associated with Grignard reactions. To overcome this at Baerlocher India Research and Development Centre Pvt Ltd, part of Baerlocher GmbH, one of the world's largest manufacturers of PVC stabilizers, a development project was undertaken to make methyltin by the direct reaction of MeCl and Sn [17,18]:

$$2MeCl + Sn \rightarrow Me_2SnCl_2$$

The dimethyltin dichloride thus formed can be disproportionated using $SnCl_4$ to produce a mixture of mono- and dimethyltin chloride and then converted to the PVC stabilizer, mercaptide, or carboxylates type.

Many parameters were needed to be addressed:

- Raw materials: Tin—solid melting >220°C; methyl chloride—liquified gas.
- Reactor design—CSTR (continuous flow stirred-tank reactor) or tubular? CSTR—load of stirring tin (molten mass).
- Use of solvent? What type? Reaction conditions: gas-solid or gas-molten reaction? High pressure/Temp. homogenizing—efficient contact of the raw materials for effective reaction.
- Catalyst—Hetero or homogeneous type? Reusable—method to isiolate

Considering all the preceding points, the process that was optimized in the laboratory used

- a pressure reactor with an efficient stirrer
- dimethyltin dichloride as a solvent for efficient contact between molten tin and methyl chloride
- catalysts—tin tetrachloride-amine/phosphine complex; DMSO (dimethylsulfoxide)
- analysis of the products an important requirement in view of identifying and quantifying trimethyltin formation (Table 16.10)

Table 16.10 Experimental results

Cat. Complex						Product Distribution % by GC		
Amine/Phosphine		$SnCl_4$	Tin (g)	*T* (°C)	*t* (h)	$MeSnCl_3$	Me_2SnCl_2	Me_3SnCl
Triethylamine	33.5	86.5	200	185	2.8	4.3	92.3	0.3
Tripropylamine	54.9	100.1	225	185	3.0	3.2	96.8	BDL
Trioctylamine	36.0	26.6	60	185	4.5	11.3	85.6	0.4
Tributylphosphine	67.5	87.1	200	185	2.5	5.6	92.6	0.2
Trioctylphosphine	75.9	53.4	122	185	9.7	3.0	97.6	0.1
Triphenylphosphine	89.2	86.8	200	185	4.0	11.6	87.5	0.2

Amine/phosphine complex with $SnCl_4$ MeCl Press: 8 bar, Tin.

The amine/phosphine-$SnCl_4$ complex was not actually a catalyst but a reagent. Furthermore, the hazardous nature of the complex and the quantity used per batch was not an ideal situation from a productivity and chemistry point of view. Nevertheless, the experiments achieved two goals of production:

- Dimethyltin dichloride by direct reaction of methyl chloride and tin was demonstrated.
- High purity dimethyltiin dichloride and <0.5% trimethyltin chloride were shown.

Further optimization of the process was undertaken whereby the DMSO-DMTDC complex showed catalytic activity in producing dimethyltin dichloride. To have an efficient contact between methyl chloride and molten tin, dimethyltin dichloride was used as a reaction medium.

Table 16.11 Experimental results

Tin (g)	DMSO	DMTDC	T (°C)	t (h)	Product Distribution % by GC		
					$MeSnCl_3$	Me_2SnCl_2	Me_3SnCl
300	15	150	200	180	0.8	98.9	0.3
200	10	200	200	180	1.5	98.1	0.6

Table 16.11 clearly established the efficacy of using the DMSO-DMTDC complex as a means of reacting tin directly to produce dimethyltin dichloride.

The project team was still facing challenges for recycle of:

- catalyst
- solvent

This was solved through operations such as distillation.

Based on these results, the process was validated and optimized up to a pilot scale of 100 kg tin per batch.

From a development chemist point of view a new challenge would be to

- Optimize the process in a trickle bed/continuous mode, which will ensure reduced capital expenditure, lower manufacturing cost (power requirement to stir molten tin), and eliminate unit operation of distillation of dimethyltin dichloride.
- Extend this chemistry of direct reaction to higher organotins viz. butyltin and octyltin, which are the other commonly used organotins.

16.3.3 Ozone as a Source to Produce Value-Added Chemicals

Ozone is a very reactive gas with strong oxidizing property. It used for potable water purification, as a disinfectant in sewage treatment, and for bleaching natural fibers. It has also found application in transforming chemicals for value addition, commercially [19]. Production of value-added products, by the now famous Criegee mechanism [20], is well established (Fig. 16.3).

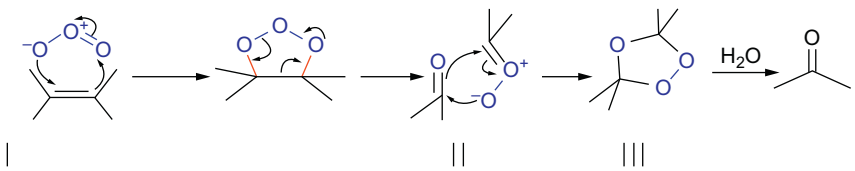


Fig. 16.3
Criegee mechanism.

As a result of its dipolar structure, the ozone molecule may lead to 1–3 dipolar cyclo addition on unsaturated bonds, with the formation of primary ozonide (I) corresponding to the reaction. In a protonic solvent such as water, this primary ozonide decomposes into a carbonyl compound (aldehyde or ketone) and a zwitterion (II) that quickly leads to a hydroxy-hydroperoxide (III) stage that, in turn, decomposes into a carbonyl compound and hydrogen peroxide.

Several industrial research groups are using ozone to study novel oxidation reactions [21,22] (DSM; Lonza). These groups have clearly established that ozone can be advantageously applied for the clean oxidation of different unsaturated starting materials. They have also established that oxidation of unsaturated starting materials using ozone results in lower waste treatment costs and may be a cleaner alternative to many obnoxious and effluent generating oxidizing agents.

That is not to say that this technique is risk free; quite the opposite is true. The intermediate—ozonoide—is highly unstable and may degrade autocatalytically (Figs. 16.4 and 16.5).

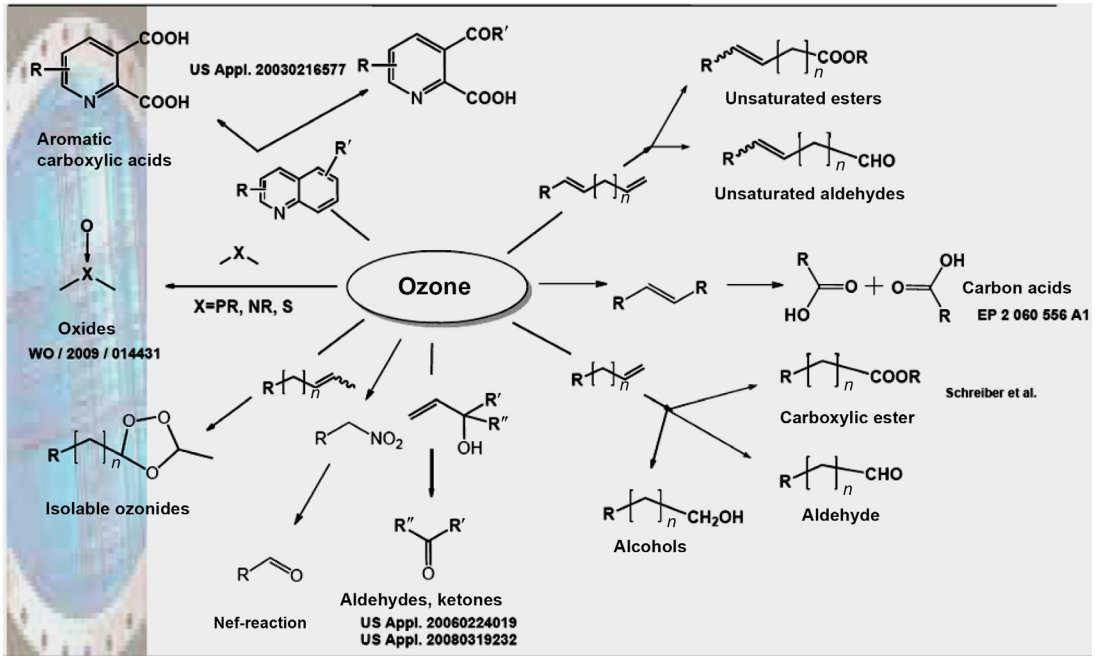


Fig. 16.4
Lonza's ozonolysis map.

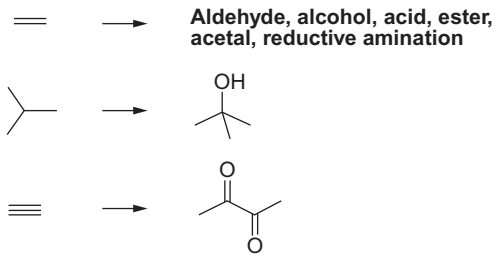


Fig. 16.5
DSM has been involved in commercializing ozone oxidation products typically.

They also claim to have developed a novel oxidation method using a catalyst and ozone wherein the toluene derivatives are oxidized in near quantitative yield to produce the corresponding aldehydes.

Ozone can be considered the cleanest oxidizing agent for unsaturated compounds. It eliminates use of noxious oxidizing agents viz. chromic acid, nitric acid, or permanganese salts required in stoichiometric amounts for oxidation. It also offers operational flexibility in swinging between continuous and discontinuous downstream processing. The nature of ozone generation is such that scale-up can be done seamlessly by just increasing the batteries of the ozone-generating unit from gram to kilogram scale.

The other commercial process is the oleic acid ozonolysis to produce azelaic and pelargonic acids. Both these products are value added and find application in speciality lubricants.

Ozone is generated electrically by applying a high-voltage alternating current across two electrodes between which the oxygen feed gas is made to flow. The electrical discharge causes dissociation of the oxygen molecules into two oxygen atoms, which react with the oxygen to form ozone.

Table 16.12 gives a design basis for generating ozone at 50 kg/h.

Table 16.12 Design basis for generating ozone [23]

Design basis: 50 kg/h		
Feed gas	**Air**	**Oxygen**
Ozone conc. Cooling water T (°C)	1.5 wt% (20 g/M^3) 18°C	6 wt% 18°C
Consumption data per kg ozone		
Energy Cooling water	17.7 kWh 2.6 M^3	11.6 kWh 1.5 M^3 2.7 kg

Challenges facing ozonolysis: needless to say, ozonolysis is fraught with several hazards, chemical as well as toxic.

- The nature of the intermediate ozonoide formed across an unsaturation is highly unstable, and the downstream processing of this intermediate to the final product has to be done carefully. It is necessary to perform a detailed risk analysis of the process under development.
- The ozonoide formation and its chemistry and handling should be studied in detail, given the unstable nature of this intermediate.
- The contact metals need to be chosen with proper care and understanding of the chemistry. Ozone, being highly reactive, has compatibility issues with many metals. Mention must be made here of Lonza's pioneering work of applying the microreactor technology concept for ozonolysis reactions, higher throughput in comparison to the convention reactor technology in use for ozonolysis.
- In a power-starved country like India, the cost of generating ozone at ~50 kg/h could be prohibitive, making the technology unviable.

16.4 Closing Remarks/Conclusion

The three case studies have tried to highlight some of the difficulties faced by a development chemist. However, there are many more practical difficulties and challenges that may have been faced, especially when developing processes for small- and medium-size chemical manufacturers, and therein were challenges that needed to be overcome, some of a technical nature and some very rudimentary. In summary, some tips to successfully overcome them are mentioned below:

- Use a commonsense approach
- Simplify the process
- Strive for robustness
- Mimic plant conditions
- Forge chemist/engineer partnerships
- Use DoE prudently to optimize

Acknowledgments

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CHAPTER 17

Epilogue

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The role of catalysis and catalytic processes is well established and well recognized in chemical and allied industries. This is particularly so for the refinery, petrochemicals, and bulk chemicals industries. The use and role of catalysis and catalytic processes in the fine and specialty chemicals sector is somewhat different than the industries mentioned earlier because of the relatively smaller manufacturing plants and other special requirements of this sector. The fine and specialty chemicals sector is facing several challenges. Considering the rising costs of raw materials, energy, and space, as well as stricter regulations regarding safety and the environment, it is essential for the fine and specialty chemicals sector to implement various process intensification (PI) strategies. PI may be broadly defined as the ability to obtain better results in terms of purity, selectivity, and yield of the desired product by manipulating rates of relevant reactions and transport processes to enhance process performance (more throughput, better quality, less energy consumption, less waste, safer, etc.). Catalysts and catalytic processes play a very crucial role in realizing this PI and therefore performance enhancement. Recent years have seen a substantially enhanced interest in developing and implementing catalytic processes for the fine and specialty chemicals sector.

In this book, we have tried to provide an overview of fundamentals (Part I) as well as applications (Part II) of catalysis and catalytic processes to the fine and specialty chemicals industry. The key concepts in homogeneous and heterogeneous catalysis are discussed. The selection of reaction media also influences catalytic activity and therefore performance. Synthesis and characterization as well as deactivation and regeneration of heterogeneous catalysts are discussed. This discussion will be useful to identify promising catalysts for carrying out desired chemical transformations. A fundamental basis for understanding catalysis and using this understanding to realize desired performance are discussed. After establishing the catalyst and process conditions, a necessary basis on reaction engineering and design of catalytic reactors is discussed in detail. The second part of the book essentially discusses specific reactions and examples of catalytic processes relevant to the fine and specialty chemicals sector. Catalysis and catalytic processes of hydrogenation, oxidation, carbonylation,

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and hydroformylation reactions are discussed. Specific examples of catalytic processes for perfumery chemicals as well as the active pharmaceutical ingredients (API) industry are discussed. Use of catalysis for deriving fine and specialty chemicals from renewable resources are also discussed. Some aspects of scale-up, particularly from the chemist's perspective, are touched on. The selection of examples used in this book may appear somewhat biased because many of these are drawn from our own as well as various contributors' own research and consulting experiences. An attempt is, however, made to evolve general guidelines, which may be useful for solving real-life problems.

At this juncture, it will be useful to recapitulate the key points and the lessons learned from our experience of applying the material discussed in this book for addressing industrially relevant issues. Based on our experience, it is extremely important to correctly:

- recognize and quantify thermodynamic constraints,
- identify the expected role of the catalyst considering these constraints and possible reactions, and
- identify required characteristics of the "ideal" catalyst.

It is also important to broadly understand and quantify process economics to clearly define performance and cost targets for catalysts. It may be useful to remember to practice the so-called Occam's razor, which may be stated as, "It is futile to do with more, what can be done with less." There are many instances where simple, conventional catalysts may provide an elegant and adequate solution. For example, conventional catalysts like copper, cobalt, iron, and manganese can be employed for oxidation reaction instead of more expensive and sophisticated catalyst systems comprising silver, platinum, or palladium.

It is, however, important to emphasize here the maxim that says, "One should always try to make things as simple as possible (following the Occam's razor) but not simpler." It may be necessary to match the complexity of the desired chemistry with complexity of the catalyst system. One should have an expertise and skill to select an appropriate family of catalysts, promoters, inhibitors, and so on to achieve the desired objectives. More often than not projects of developing catalytic processes to achieve set targets are likely to overrun the budget (of time and other resources) due to inadequate attention paid to these initial steps of the overall project. Inadequate attention to these steps may even lead to a failure to achieve the set objectives. We hope that some of the examples discussed in this book are useful to emphasize this.

It is beneficial and more efficient to describe and analyze overall chemical transformations into several elementary steps. It is always easier to identify requirements of such elementary transformation steps and define requirements of "ideal" catalysts for these. It should be noted that many of these elementary steps may not even require a catalyst. The critical analysis of requirements of "ideal" catalysts for these steps and identifying the performance controlling

step are often crucial factors in determining the success of the project. Apart from identifying requirements of an "ideal" catalyst, it is essential to account for the possible influence of reaction media, the possible impact of catalyst deactivation/regeneration, catalyst recovery and cycle, as well as reactor configuration. The catalyst characterization often plays a key role in understanding possible reasons of catalyst deactivation and in providing clues for regeneration strategies. Some practical aspects of manufacturing the catalyst required for the commercial plant are also important and may influence the shortlisting of a catalyst family for the desired transformations.

It will not be possible to include here comments on different reactions discussed in this book. As an illustration of key points, some comments on two important reactions commonly employed for production of fine and specialty chemicals (hydrogenation and oxidation) are included here.

- Reactions between hydrogen and organic compounds require very high reaction temperatures (more than 400°C) in the absence of a metal catalyst. Several metals catalyze such hydrogenations and bring down the required reaction temperatures and pressures. Hydrogen forms a hydride with the metal on the catalytic surface. This hydride is then transferred to the substrate.
- Noble metals such as Pt, Pd, Ru, and Rh, as well as nonnoble metals such as Raney Ni and iron, are the commonly used metal catalysts. Selection of the catalyst depends on a variety of factors such as cost and availability of the catalyst, operating pressure, temperature, and needed equipment for carrying out reactions (including material of construction). Though noble metal catalysts appear to be costly, usually their activity, selectivity, and recyclability often make them the catalysts of choice.
- Most of the hydrogenation reactions are highly exothermic and usually carried out in the presence of a solvent. The choice of a solvent depends on factors such as cost, heat capacity, and boiling point of a solvent and its possible interaction with the catalytic cycle. Despite the issues related to safety, methanol is one of the most widely used solvents for hydrogenation.
- Catalytic hydrogenation reactions are multiphase, and it is therefore extremely important to understand the interaction of various transport processes (mass and heat transfer) and the reaction kinetics to avoid unpleasant surprises during scale-up.
- Recent developments such as use of iron nanoparticles in a polymer matrix allow hydrogenations with iron without issues such as rusting [1].
- In the case of homogeneous catalysts for hydrogenation, appropriate selection and design of ligands offer better control on the selectivity. It is also possible to design the chiral ligands with which selectivity toward a specific enantiomer can be obtained [2].
- A large number of oxidations in fine and specialty chemicals are carried out in the presence of stoichiometric reactants such as chromium (IV) reagents, periodate, or permanganate. Significant work is needed on developing catalytic processes of oxidations using air or

oxygen. This is quite challenging because of the presence of organic compounds with multiple functional groups [3].
- While using homogeneous catalysts, the ligand's susceptibility to degradation in strong oxidizing conditions needs to be understood, and appropriate ligands need to be developed. For example, Ruthenium catalyst with TEMPO or (2,2′,6,6′-tetramethylpiperidin-1-yl)oxyl has been found to be a highly selective catalyst for aerobic oxidation of alcohols to primary or secondary aldehydes and ketones [4].
- Graphene has great potential as a support for an oxidation catalyst such as platinum, palladium, and vanadium. The high surface area of graphene support improves the metal dispersion as well as leads to better chemical and mechanical stability [5].
- Many oxidation reactions with air or oxygen are carried out using a boiling reactor to realize adequate management of heat liberated during oxidation. Selection of a solvent as well as the design of the boiling reactor are crucial in successful realization of such oxidation processes.

It is important to reemphasize the key desired attributes of any catalytic process, more particularly for the fine and specialty sector, which is notorious for generating more waste per kg of useful product. These are as follows:

- Atom efficient processes: atom efficiency is a ratio of mass of atoms in the desired product and mass of atoms in the reactants. This is beyond the usual concepts of selectivity or yield and takes into account overall atom economy. Estimation of atom efficiency is now routinely used for selecting the best process route. It should be remembered that the actual amount of waste produced in the process should be estimated considering possible losses in recycling solvents and catalysts.
- Inherently safer processes: many of the fine and specialty chemicals are manufactured in batch or semibatch processes. Due importance should be given to the order of charging the various reactants and their compatibility. Appropriate selection of a solvent having the appropriate boiling point, which may help to control the reaction temperature automatically, is important. It is often desirable to use continuous processes, which lead to compact reactors and significantly smaller inventory and therefore inherently safer processes.
- Inherently cleaner processes: replacement of stoichiometric reagents by catalytic reaction for the synthesis is the best way to make the processes cleaner. One of the reasons why the fine and specialty chemical industry produces more waste per kg of the product is because it involves multistep synthesis. Recent advances in continuous flow processing may be harnessed to integrate such multistep synthesis for better performance as well as inherently cleaner processes.
- Low footprint: recent advances in PI and continuous processing need to be used to realize compact manufacturing plants having low spatial and environmental footprints.

- Less demanding on energy and other utilities: the fine and specialty chemical industry is under tremendous pressure to reduce its energy requirement. The best strategy will be to integrate expertise in catalysis, process chemistry, reaction engineering, and PI to develop an intensified continuous plant. The continuous plant will not just be safer but will also be less demanding on the energy requirement and thereby will reduce the utilities.

Thus, catalysts are essential for realizing a "sustainable" fine and specialty chemicals sector. The word *sustainable* is used here in the most general sense including economic, environmental, and social sustainability.

The use of renewable resources for manufacturing a wide range of fine and specialty chemicals will play crucial role in realizing such sustainability. In the early days, many fine and specialty chemicals like dyes and solvents were produced from trees, agricultural crops, and animals. However, after World War II, most of these were displaced by petroleum derivatives. Presently, around 90% of organic chemicals are derived from petroleum. Due to rising raw material prices, increased pollution, and carbon footprints, there has been a growing interest in shifting back to renewable biomass resources to reduce dependence on at least some of the fossil fuel-derived chemicals. Renewable biomass resources can make an important contribution toward a sustainable industrial society. Cellulose and hemicellulose have shown possible routes to a variety of aliphatic compounds, including sugars, alcohols, aldehydes, and acids, for example, ethanol, butanol, lactic acid 1, 3-propanediol, xylitol, 5-methylfurfural, HMF (Hydroxy methyl furfural), levulinic acid, succinic acid, and formic acid, and some of them are already being produced on a commercial scale [6–9].

Catalysis will also play a key role in activating and using carbon dioxide for manufacturing useful chemicals. Several efforts are being made in this direction. For example, efforts are being taken to convert anthropogenic carbon dioxide to various important chemicals such as formic acid and its esters, formamides, methanol, dimethylcarbonate, alkylenecarbonates, carbamicacidesters, lactones, carboxylic acids, and polycarbonates by catalytic transformation [10–12].

We believe that further research and efforts on developing better catalytic processes are required in the following areas:

- Application of homogeneous catalysis in fine and specialty chemicals: use of homogeneous catalyst for synthesis of fine and speciality chemicals is still very limited, mainly because of a number of issues such as difficulties in catalyst recycle, high cost of transition metal, nonavailability of complex ligand, expensive ligand, and so on. Efforts should be made to address these issues to make the processes economically feasible.
- Catalyst-product separation technologies: major challenges for the future are in developing industrially feasible catalyst-product separation technologies as well as the

development of immobilized metal complex catalysts retaining high activity, selectivity, and stability.

- Mixed metal catalyst systems: bimetallic catalyst systems, mixed metal oxides or mixed oxides obtained by thermal decomposition of layered double hydroxide (LDH) have very interesting properties such as high thermal stability, high surface area, good homogeneity, and good metal dispersion. In the synthesis of hydrotalcite like compounds there is a wide range of variables, which give the possibility of producing tailor-made materials: different M^{2+} ions like Mg, Fe, Co, Ni, Cu, Zn, and their mixtures; different M^{3+} ions like Al, Cr, Fe, and their mixtures; different charge balancing anions; amount of interlayer water; and crystal morphology. It is possible to manipulate the acidity or basicity by proper selection of M^{2+} and M^{3+} ions. Such compounds have great potential and can be utilized to develop a clean and recyclable catalyst system.
- Biomass conversion to fine and specialty chemicals: to have a sustainable development, there is an urgent need to develop facile strategies for biomass conversion to valuable chemicals and fuels. Approaches need to be developed for synergistic coupling of catalytic, hydrolytic, and thermochemical methods of biomass conversion into a fully integrated biorefinery. The efforts are also required to develop strategies for the production of platform chemicals, such as levulinic acid and γ-valerolactone by using new efficient catalyst systems.
- Carbon dioxide utilization: various chemistries and catalyst systems are being developed to activate carbon dioxide to convert into industrially useful products. Efforts are also required for development of efficient catalysts for carbon dioxide capture and utilization to make it commercially feasible.
- Intensified and continuous processes/process equipment: significant advances have been made in developing intensified and continuous processes as well as process equipment for fine and specialty chemicals (see eg [13,14]). Such advances need to be harnessed widely to make a significant impact on conservation of valuable raw materials and utilities, significant reduction in spatial and environmental footprints, and enhanced safety.

The list is merely suggestive. The complexity of various chemistries may greatly expand the list on which further research is required. Another area that deserves mention here is computational modeling for rational design of catalysts. With the advances in density functional theory, it is possible to describe reactions at catalyst surfaces with high accuracy. Theoretical methods can be used to describe surface chemical reactions and understand the variations in the performance of different catalysts. Efforts should be made to exploit the computational tools to design an efficient tailor-made new catalyst system for use in the fine and speciality chemical industry. We have not included this important aspect in this book. However, in the coming years, it will be imperative to harness power of computational models for developing and optimizing catalyst systems (main catalyst, promoter, ligands, etc.). Several efforts in that direction are being made (see eg [15–18]).

Adequate attention to key issues mentioned in this book and creative use of catalysis will make significant contributions toward more effective and cleaner manufacturing of fine and specialty chemicals. This will eventually help to realize the goal of sustainably enhancing quality of life. New advances in catalysis and chemical engineering may be assimilated using the concepts and examples discussed in this book. We hope that this book will stimulate applications of catalysis and catalytic process in the fine and specialty chemicals industry.

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