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Iridium Catalysis

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Editor
Prof. Pher G. Andersson
Uppsala University
Department of Biochemistry and Organic Chemistry
Box 576, BMC
S-751 23 Uppsala
Sweden
pher.andersson@biorg.uu.se

ISSN 1436-6002 e-ISSN 1616-8534
ISBN 978-3-642-15333-4 e-ISBN 978-3-642-15334-1
DOI 10.1007/978-3-642-15334-1
Springer Heidelberg Dordrecht London New York

Cover design: KünkelLopka GmbH

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Volume Editor

Prof. Pher G. Andersson

Uppsala University
Department of Biochemistry
and Organic Chemistry
Box 576, BMC
S-751 23 Uppsala
Sweden
pher.andersson@biorg.uu.se

Editorial Board

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Leibniz-Institut für Katalyse e.V.
an der Universität Rostock
Albert-Einstein-Str. 29a
18059 Rostock, Germany
matthias.beller@catalysis.de

Prof. John M. Brown

Chemistry Research Laboratory
Oxford University
Mansfield Rd.,
Oxford OX1 3TA, UK
john.brown@chem.ox.ac.uk

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Campus de Beaulieu
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35042 Rennes Cedex, France
pierre.dixneuf@univ-rennes1.fr

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Kaiser-Wilhelm-Platz 1
45470 Mülheim an der Ruhr, Germany
fuerstner@mpi-muelheim.mpg.de

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Department of Chemistry
Colorado State University
Fort Collins, Colorado 80523-1872, USA
hegedus@lamar.colostate.edu

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Organisch-Chemisches Institut
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69120 Heidelberg, Germany
ph@uni-hd.de

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Department of Applied Chemistry
Graduate School of Science and Engineering
Tokyo Institute of Technology
2-12-1 Ookayama, Meguro-ku,
Tokyo 152-8550, Japan
tikariya@apc.titech.ac.jp

Prof. Luis A. Oro

Instituto Universitario de Catálisis Homogénea
Department of Inorganic Chemistry
I.C.M.A. - Faculty of Science
University of Zaragoza-CSIC
Zaragoza-50009, Spain
oro@unizar.es

Prof. Manfred Reetz

Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1
45470 Mülheim an der Ruhr, Germany
reetz@mpi-muelheim.mpg.de

Prof. Qi-Lin Zhou

State Key Laboratory of Elemento-organic Chemistry
Nankai University
Weijin Rd. 94, Tianjin 300071 PR China
qlzhou@nankai.edu.cn

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The series *Topics in Organometallic Chemistry* presents critical overviews of research results in organometallic chemistry. As our understanding of organometallic structures, properties and mechanisms grows, new paths are opened for the design of organometallic compounds and reactions tailored to the needs of such diverse areas as organic synthesis, medical research, biology and materials science. Thus the scope of coverage includes a broad range of topics of pure and applied organometallic chemistry, where new breakthroughs are being made that are of significance to a larger scientific audience.

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In references *Topics in Organometallic Chemistry* is abbreviated Top Organomet Chem and is cited as a journal.

Preface

The use of iridium in catalysts for organic reactions is a rapidly evolving field that covers a wide range of chemical reactivity. With this in mind, it has been a pleasure to edit this volume on Iridium Catalysis, which aims to present the reader with a comprehensive resource that covers the field and focuses on recent advances in the area. All chapters have been written by leading chemists in the corresponding area and I am extremely thankful to them for their contributions and efficient collaboration in this project: Robert H Crabtree, Carmen Claver, Montserrat Dieguez, Oscar Pamies, Andreas Pfaltz, David H. Woodmansee, Jonathan M.J. Williams, Ourida Saidi, Michael J. Krische, John F. Bower, Alan S. Goldman, Jongwook Choi, John F. Hartwig, Mark J. Pouy, Luis A. Oro, and Daniel Carmona. I am also grateful for all help received from SPRINGER, especially from Jutta Lindenborn.

I hope that this book will be useful to researchers, teachers, and students involved in organic synthesis and that it might also attract new people to the interesting field of catalysis.

Uppsala, Sweden
2010

Pher G. Andersson

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Top Organomet Chem (2011) 34:1–10
DOI: 10.1007/978-3-642-15334-1_1

Introduction and History

Robert H. Crabtree

Abstract Iridium had shown no special advantage in heterogeneous catalysis and this situation seemed to carry over into the early work in homogeneous catalysis. In particular, the failure of $IrCl(PPh_3)_3$, the Ir analog of Wilkinson's catalyst, to give catalytic hydrogenation strongly influenced thinking at the time. The developments that changed the situation were Shrock and Osborn's work on $[(cod)RhL_2]^+$ complexes that showed how lowering the L:M ratio from 3 to 2 gave improved catalysts, followed by our own finding that $[(cod)IrL_2]^+$ and especially $[(cod)IrLL']^+$ complexes are even more highly active, particularly for highly substituted alkenes. This performance is absent in the classical coordinating solvents then standard in the field but only appears in weakly coordinating solvents like dichloromethane. A special property of the Ir complexes is a pronounced directing effect caused by catalyst binding to substrate functionality, leading to very high diastereoselectivity of the reduction. Asymmetric hydrogenations consistently gave lower *ee* values for iridium over rhodium, however, so academic work still strongly emphasized Rh. The exceedingly rapid rates of hydrogenation with Ir attracted industrial attention, because rate is such an important factor in that case, and Novartis' catalytic asymmetric route to the pesticide (S)-Metolachlor employs iridium, even though the ee value is only ca 80%. Leading applications of these and other Ir catalysts up to about 1,990 are also discussed. Work by Pfaltz, Burgess, and Andersson showed how efficient asymmetric Ir catalysts could be made by judicious choice of ligand. Alkane dehydrogenation by reverse hydrogenation also proved possible with Ir catalysts.

Keywords CH activation · Hydrogenation · Isotope exchange

R.H. Crabtree
Department of Chemistry, Yale University, 225 Prospect Street, PO Box 208107, New Haven, CT 06520 8107, USA
e-mail: robert.crabtree@yale.edu

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1 Introduction

The catalysis field began in the nineteenth century with work on heterogeneous platinum group metals from such contributors as Berzelius, Faraday, Döbereiner, Mitscherlich, Davy, Sabatier, and Ostwald [1, 2]. Iridium never held a very high place in the field, however, because it showed no special advantages. Rylander expresses this point well in his classic 1967 work on heterogeneous catalysis [3].

> Iridium. . .makes a fair catalyst and its lack of use stems partly from neglect and partly from the fact that some platinum metal has usually proved more suitable whenever a comparison was made.

The position for heterogeneous Ir is little changed today, as shown by the entries in the Encyclopedia of Reagents for Organic Synthesis [4]. Heterogeneous Pd, Pt, Ru, and Rh catalysts are all discussed in detail but Ir and Os are omitted.

This background influenced the first work in homogeneous catalysis, where Pd, Pt, Ru, and Rh all gained early favor over Ir and Os. Neglect again played a role – investigators tend to follow up lines previously shown to be successful – but an important factor was the failure of $IrCl(PPh_3)_3$, the Ir analog of Wilkinson's catalyst, to give catalytic hydrogenation.

2 Vaska's Complex

The work of Lauri Vaska [5] at Clarkson College in the 1960s deserves special attention. His investigations on $IrCl(CO)(PPh_3)_2$, now known as Vaska's complex, were the first to give iridium a major and distinctive role for organometallic chemists in contributing to the understanding of oxidative addition, a fundamental reaction step in homogeneous catalysis. This work was particularly impressive since it was carried out at a small college with undergraduate coworkers. He showed that a variety of molecules A–B were able to react with $IrCl(CO)(PPh_3)_2$ to give $Ir(A)(B)Cl(CO)(PPh_3)_2$, the oxidative addition product. By monitoring the CO stretching frequencies of the adducts, he was able to establish the oxidative character of the reaction and rank different A–B molecules in terms of their relative oxidizing tendency. The stability of the adducts did not bode well for their intermediacy in catalysis, however, and indeed Vaska's complex never showed any more than a modest degree of catalytic activity. Iridium was therefore considered to be interesting only in giving isolable analogs of species thought to be important in catalysis by rhodium complexes.

Just as the H_2 oxidative addition product of Vaska's complex is relatively stable, the same holds for the iridium analog of Wilkinson's catalyst. The reason for the lack of high catalytic activity of $IrCl(PPh_3)_3$ is that once the required oxidative addition of H_2 has taken place, the product, $IrH_2Cl(PPh_3)_3$, is stable and does not dissociate a phosphine to provide a site for binding of substrate alkene. The essence of catalysis is the involvement of unstable catalytic intermediates. For example, $RhH_2Cl(PPh_3)_3$, the analogous intermediate from Wilkinson's catalyst, is unstable in that it does easily lose a PPh_3 ligand – the one trans to the high trans effect hydride – and thus liberates a coordination site at which the substrate alkene can bind. The resulting alkene dihydride complex, $RhH_2Cl(alkene)(PPh_3)_2$, now has both substrates bound, both alkene and hydrogen, and can thus proceed directly to product by alkene insertion into the Rh–H bond to give an alkyl hydride that can reductively eliminate the alkene product. The reason for the difference between Rh and Ir is probably the systematic increase in M–L bond strengths on going from the second row of the transition metals to the third. In line with this idea, moving to a Wilkinson type complex of a smaller and more tightly bound phosphine, PEt_3, is enough to halt the catalysis even for Rh because $RhH_2Cl(PEt_3)_3$ is a stable species.

3 Schrock and Osborn Catalysts

The situation changed when Schrock and Osborn [6, 7] at Harvard developed catalysts in which the ligand to metal ratio was 2:1 and not 3:1, thus avoiding the need for phosphine dissociation. At the same time, they also removed the chloride ligand from the inner sphere and replaced it by an outer sphere "noncoordinating" anion, often BF_4. Building on Chatt's work [8] showing that 1,5-cyclooctadiene (cod) is a reliable ligand for Rh(I), they synthesized $[(cod)Rh(PPh_3)_2]BF_4$. Under hydrogen, the cod is removed by hydrogenation to cyclooctane and the solvated $[(solv)_2Rh(PPh_3)_2]^+$ cation is formed. This is an active hydrogenation catalyst, but the key point is that the system is no longer limited to PPh_3 as in the Wilkinson case. Instead, a wide variety of phosphines, L, or chelating phosphines, L–L, can give catalytically active species $[(cod)Rh(L)_2]BF_4$ or $[(cod)Rh(L\text{-}L)]BF_4$. This led to the possibility of using asymmetric ligands like Kagan's chelating *diop* that allow asymmetric hydrogenation of prochiral alkenes to give homochiral products with high ee.

While the Schrock and Osborn catalysts worked well in the Rh series, the analogous iridium compounds, also studied by them, did not show any special advantages. The reason proved to be that instead of forming analogs of the $[(\mathrm{solv})_2\mathrm{Rh}(\mathrm{PPh}_3)_2]^+$ cation, the iridium species $[(\mathrm{cod})\mathrm{Ir}(\mathrm{L})_2]\mathrm{BF}_4$ reacted differently with hydrogen. The product was the relatively stable $[(\mathrm{solv})_2\mathrm{IrH}_2(\mathrm{PPh}_3)_2]^+$ cation. This gave a modest catalytic rate but, as in the case of heterogeneous Ir catalysts, no special properties were apparent that would make them the focus of an investigation. The reason the Ir compounds behave differently is again the rise in M–L bond strengths on going from Rh to Ir. This allows the H_2 oxidative addition product to form for Ir but not for Rh. The two M–H bonds formed in the oxidative addition have to "pay for" breaking the H–H bond of H_2 if the oxidative addition is to be thermodynamically allowed.

4 Distinctive Reactivity for Ir in Hydrogenation Catalysis

The next step came in the laboratory of Hugh Felkin, a very distinguished physical organic chemist, working at the CNRS Natural Products Institute at Gif-sur-Yvette near Paris. Felkin is perhaps best known for his formulation of the Felkin–Anh rule for predicting the diastereoselectivity of nucleophilic attack in organic carbonyl compounds [9]. He had become interested in the organic applications of transition metals and had hired a series of postdoctoral coworkers from the UK to look into the area. On this basis, I was working as an *Attaché de Recherche* with a *3ème cycle* doctoral thesis student from Oxford, George Morris. The plan was to look at the $[(\mathrm{cod})\mathrm{Ir}(\mathrm{L})_2]\mathrm{BF}_4$ series with the idea of isolating stable intermediates analogous to the ones that were presumed to be important in the Schrock–Osborn hydrogenation catalysts.

One of the fixed assumptions in homogeneous hydrogenation catalysis at that time was that reducing, coordinating solvents like MeOH or EtOH were preferred and oxidizing solvents like dichloromethane were best avoided. This came from the work on the Wilkinson catalyst, showing that the alcohols acted well but the catalyst deactivated in chlorinated solvents such as dichloromethane. The Schrock–Osborn hydrogenation work confirmed the role of coordinating solvents with the finding that the catalyst precursor forms solvated $[(\mathrm{solv})_2\mathrm{Rh}(\mathrm{PPh}_3)_2]^+$ cations under hydrogen. For Rh, catalytic activity was maintained, however, because the solvent ligands being labile, alkene substrates are able to gain access to the metal, a step that is followed by oxidative addition of H_2. The resulting alkene dihydride intermediate undergoes insertion and reductive elimination just as in the Wilkinson cycle.

Working from the principle that a catalyst should be maximally unstable without actually decomposing, I had tried "noncoordinating" solvents like dichloromethane for the $[(\mathrm{cod})\mathrm{Rh}(\mathrm{L})_2]\mathrm{BF}_4$ case and seen that a high catalytic rate was achievable in certain cases. When George Morris began work on the Ir series, he included noncoordinating solvents and found high activity for dichloromethane. The solvent effect in this case was extremely high: dichloromethane not only gave much faster catalysts than the traditional solvents but now even highly substituted alkenes – poor ligands and therefore poor substrates for classical catalysts – were reactive. None of these effects were seen with the Rh series, so iridium was special. A factor that may well explain the inertness of dichloromethane in these cases is the cationic charge on the metal, making them more resistant to deactivation by oxidizing solvents.

During a discussion with G Pannetier (Université Paris VI) in Paris, he mentioned that he thought he had seen evidence for mixed pyridine–phosphine derivatives of the type $[(\mathrm{cod})\mathrm{Rh}(\mathrm{PPh}_3)(\mathrm{C}_5\mathrm{H}_5\mathrm{N})]\mathrm{BF}_4$ in the Rh series. On returning to Gif, I confirmed this result by isolating the compound and mentioned it to Morris, who tried to obtain the iridium complex. Our initial idea was that a 1:1 phosphine to metal catalyst might be even more active than the 2:1 species.

The PPh_3 derivative showed very promising activity, but Morris tried a few other phosphines as well and identified tricyclohexylphosphine as the best of these. In fact, the new PCy_3 catalyst was spectacularly active, particularly for highly substituted alkenes for which classical catalysts gave zero rate. Indeed, the lower the catalyst concentration, the higher the apparent rate, presumably due to mass transfer limitations for dissolution of the hydrogen. Our first attempt to publish these results in *J. Am. Chem. Soc.* failed because the referees were not impressed. We therefore published then in *J. Organometal Chem.*; but at the time, the results attracted little attention [10]. This was a period when organic chemists were already familiar with organolithium reagents, but transition metals had not yet been fully integrated into their thinking. In addition, we had used substrates like hexene, cyclohexene, 2-methyl-2-butene, and 2,3-dimethyl-2-butene that were regarded as unrepresentative of complex organic molecules.

By 1980, I was already at Yale and met Bill Suggs at Bell Labs, where he was working on catalysis from the organic perspective. With characteristic generosity, he suggested we collaborate on trying to use $[(\mathrm{cod})\mathrm{Ir}(\mathrm{PCy}_3)(\mathrm{C}_5\mathrm{H}_5\mathrm{N})]\mathrm{BF}_4$ for hydrogenation of substrates that were more complex than simple hydrocarbons. This proved successful, was published in *Tet Lett*, and did begin to interest organic chemists [11]. This experience made me think that it would be good to try the catalyst for more complex substrates.

I consulted Sam Danishevsky's wife, Sarah, who was then working in the Yale Department on synthetic problems. She suggested that a good problem would be to look for directing effects of preexisting functionality on the diastereoselectivity of hydrogen addition. My graduate student, Mark Davis, took up the problem and found evidence for very high selectivity in unsaturated cyclic alcohols. An OH group on one face of the substrate molecule was able to bind to the metal in such a way that the two hydrogen atoms could only add to that same face of the ring that contained the OH group. These papers [12, 13], published in *Organometallics* and *J. Org. Chem.*, together with parallel work from Stork and Kahne [14] at Columbia, were the trigger that attracted the interest of a much broader organic community. No doubt Stork's eminence in the field played a major role in acceptance of the work. From that point onward, development of the iridium catalyst and its many analogs passed into the hands of organic chemists. In the first such example, Arthur Schultz at RPI published a synthesis of (+)-Pumiliotoxin C in 1985–1987 that employed $[(cod)Ir(PCy_3)(C_5H_5N)]BF_4$ for carbonyl-directed hydrogenation of a trisubstituted C=C bond [15].

5 Further Developments in Hydrogenation

The Ir catalysts are also active for a number of other reactions. In a purely mechanistic study from 1985, we looked at H/D exchange between deuterium and a number of organic substrates [16]. We found that initial binding of the catalyst to a ligating group such as a quinoline nitrogen allowed the catalyst to cyclometalate at a specific adjacent site, followed by rapid deuteration at that site. This was much later adapted for selective tritiation by pharmaceutical chemists, who needed to be able to follow the metabolic fate of drugs by radioisotope labeling. Traditional syntheses had incorporated tritium at an early stage, resulting in tedious syntheses and production of radioactive waste on a significant scale. In the catalytic variant, the tritium is introduced in one step, making the iridium catalyst a standard in the field. In mechanistic work with Odile Eisenstein, the noted computational organometallic chemist from Montpellier (France), the reason for the rapid isotope exchange was traced to the presence of an unusually flat potential energy surface that in turn results from compensatory changes in M–L bond energies through the cycle [17].

Asymmetric hydrogenation with analogous catalysts proved possible. Pfaltz introduced cationic iridium complexes with chiral mixed P,N-donor ligands as catalysts for asymmetric hydrogenation. A phosphino–oxazoline (PHOX) was found to be best when combined with the large, weakly coordinating anion tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (BArF); the anion helps avoid deactivation and reduces moisture sensitivity. Hydrogenation of trisubstituted stilbenes were carried out with high levels of enantioselectivity. Under optimized conditions, turnover numbers were $>5{,}000$ [18–20]. Burgess and coworkers have had success with asymmetric carbene oxazoline ligands [21]. An unusual sulfinylimine phosphine ligand, applied to challenging trisubstituted stilbene substrates by Ellman, gives ee’s of up to 94% [22]. Andersson has shown advantages from chiral bidentate phosphine thiazoles in asymmetric hydrogenation of aryl alkenes and aryl alkene esters, substrates that can be difficult to hydrogenate with classical catalysts [23].

In a commercially important example, a related iridium catalyst equipped with a ferrocenyl bis phosphine ligand of Togni’s proved active for the key asymmetric hydrogenation in the production of an important agrochemical, the herbicide (S)-metolachlor, having the trade name Dual Magnum®. The key step in the process is the asymmetric hydrogenation of an imine intermediate with an iridium ferrocenyl diphosphine catalyst. The isolated imine can be hydrogenated at a hydrogen pressure of 80 bar and 50°C with a substrate-to-catalyst ratio of $>10^6$. Complete conversion is reached within 4 h with an enantioselectivity of 79% with an initial turnover frequency (TOF) exceeding $1.8 \times 10^6\ h^{-1}$ [24].

6 Mechanism

Mechanistic aspects of the iridium catalysts have attracted attention. For catalytic reactions where Ir does show special properties, we need to ask what mechanistic factors are at work that differentiate the two metals. An important difference between Rh and Ir is the much easier accessibility of the M(V) state for Ir. For example, $IrH_5(PPh_3)_2$ is a stable species while no Rh analog has ever been reported. The mechanism invoked for Rh(I) hydrogenation catalysts involves cycling between Rh(I) and Rh(III) oxidation states. An attractive possibility for the Ir catalyst is an Ir(III) Ir(V) cycle, although this is still subject to debate. Hall, Burgess, and their coworkers report computational data that favors this III–V cycle for diene hydrogenation by a closely related Ir catalyst, for example [25].

In all the applications described above, the iridium catalyst showed special properties not so far obtainable with any other metal. We now move on to reactions in which iridium is active but where other metals have also been shown to be suitable.

7 Alkane Activation

A point of particular interest to me even at Gif but particularly on my move to Yale in 1977 was whether such an active hydrogenation catalyst as we had in hand could be induced to reverse direction to provide catalytic alkane dehydrogenation to alkene or arene. This would constitute a CH activation. Granted, the reaction would be endoergic, but I felt it might be possible to capture or remove the hydrogen in some way to drive the reaction. The importance of CH activation was impressed on me right from my doctoral work with Joseph Chatt, who held that CH activation would be the next big field in transition metal chemistry after nitrogen fixation.

This approach seemed feasible because Alexander Shilov, working at the Chernogolovka Institute of Chemical Physics, had already shown catalytic deuteriation and chlorination of alkanes by Pt complexes. My discussions with colleagues in the late 1970s suggested that this result was discredited by the majority of workers in the West – as I felt, unjustly so. It was thought that colloidal Pt metal, a well-known heterogeneous catalyst for alkane conversions, might be the true active species. Personally, I felt that the selectivity for reaction at the terminal methyl of the alkane substrates seen by Shilov was much more consistent with homogeneous than heterogeneous catalysis. Pt-catalyzed reactions of alkanes are now fully confirmed and widely studied and the field is called “Shilov chemistry” [26].

My initial plan involved dehydrogenation of cyclic alkanes to give stable arenes, particularly of cyclopentane to give cyclopentadienyl derivatives. My own experimental efforts with Pt were unavailing, but Jennifer Quirk, a graduate student of mine working on Ir, took an interest in the project and found a small yield of Cp complex from $[IrH_2(acetone)_2(PPh_3)_2]BF_4$ in dichloromethane. This was too small a yield to publish and so she looked for hydrogen acceptors that could drive the reaction. After trying more than 70 alkenes, she obtained success with $tBuCH{=}CH_2$. The yield was now high enough to publish. This time, *J. Am. Chem. Soc.* accepted the manuscript, which was published in 1979 [27]. George Whitesides was clearly a referee on the manuscript because he contacted me before proceeding with his report to warn me, in an entirely kindly way, that such results were often misconceived and later might have to be retracted with consequent damage to my career. I admitted that there was a risk but wanted to go ahead anyway. At a Gordon Conference several years later, he mentioned in his talk that he had been doubtful about our results, but with the accumulation of later results, most notably from Bob Bergman at UC Berkeley [28], he was happy to state that he now believed the work was correct. Bergman, being a highly respected figure in the field, did the most to convince colleagues of the reality of homogeneous CH activation. His work, being stoichiometric, does not directly enter into this discussion of catalysis, but it was undoubtedly very influential. The groups of Bill Jones at Rochester and Bill Graham at Edmonton also published very similar findings during the same period [29, 30]. These key contributions demonstrated stoichiometric oxidative addition of alkane CH bonds to highly reactive Ir or Rh intermediates generated by photolysis of a stable precursor.

Hugh Felkin was also working in the area and, by 1982, developed the first truly catalytic systems for alkane conversion to alkenes, using $tBuCH{=}CH_2$ to drive the process [31–33]. A variety of catalysts proved useful including $[IrH_5(PPh_3)_2]$. An important point that emerged was the strong kinetic selectivity for the formation of the 1-alkene from n-alkane, implying that the same selectivity for initial attack at the terminal methyl group applied here as Shilov had seen earlier. This outcome is entirely opposed to the selectivity seen for electrophilic and radical attack, which occurs preferentially at the 2° positions or 3° for branched alkanes. Once again, this provided evidence for the absence of any classical organic reaction pathways in this chemistry. Our own later catalyst $[Ir(O_2CCF_3)H_2(PPh_3)_2]$ shows similar behavior and dates from 1987 [34].

Alan Goldman developed much improved catalysts and also obtained detailed mechanistic information in the 1990s [35, 36]. An unexpected variant developed by Saito, by our own group and most extensively by Goldman, was acceptorless dehydrogenation. It turned out that the reaction could be driven by reflux because the hydrogen was continuously pumped out of the solvent by the reflux action [37–39].

8 Conclusion

Iridium is now a well-accepted choice for homogeneous catalysis, thanks to the historical developments discussed. Shrock and Osborn's work on $[(cod)RhL_2]^+$ complexes that showed how lowering the L:M ratio from 3 to 2 gave excellent catalysts. We found that $[(\mathrm{cod})\mathrm{IrL}_2]^+$ and especially $[(\mathrm{cod})\mathrm{IrLL}']^+$ complexes become very highly active, even for highly substituted alkenes, but only in weakly coordinating solvents such as dichloromethane. The Ir complexes show a pronounced directing effect of existing functionality on the diastereoselectivity of the reduction. The exceedingly rapid rates of hydrogenation with Ir attracted industrial attention, and Novartis' catalytic asymmetric route to the pesticide (S)-Metolachlor employs iridium, even though the ee value is only ca 80%. Work by Pfaltz, Burgess, and Andersson showed how efficient asymmetric Ir catalysts could be made by a judicious choice of ligand. Alkane activation by reverse hydrogenation also proved possible with Ir catalysts.

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Top Organomet Chem (2011) 34:11–29
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Iridium-Catalyzed Hydrogenation Using Phosphorus Ligands

Montserrat Diéguez, Oscar Pàmies, and Carmen Claver

Abstract Due to the requirement of obtaining enantiomerically pure products through environmentally friendly technologies, the development of new methods in asymmetric catalysis is becoming an important approach to asymmetric synthesis. Asymmetric hydrogenation is one of the most applied catalytic reactions for the preparation of enantiomerically pure products. Iridium complexes containing phosphorus ligands have been less applied as catalysts in hydrogenation reaction than their corresponding rhodium complexes. On the other hand, most of the iridium complexes used as catalyst in hydrogenation reaction contain phosphorus–nitrogen ligands. However, iridium complexes containing a great variety of mono- and bidentate phosphorus ligands (phosphines, phosphinites, phosphites, phosphoramidites, and the combination of these functionalities) have been applied in hydrogenation reaction with different grades of success. In the early days, diphosphines were the most widely used phosphorus ligands. However, they are generally difficult to synthesize and prone to oxidation. In recent years, chiral phosphites, phosphinites, phosphonites, and phosphoroamidites have emerged as new types of ligands, which present several advantages and high catalytic activity and selectivity. Homogeneous and heterogeneous systems have been studied, allowing the recycling of catalysts. Slight modifications in the electronic and steric properties of the ligands influence the catalytic results, which indicates the potentiality of modular ligands. Imines, including unfunctionalized N–H imines and cyclic imines as quinolines and other substrates, have been transformed in the corresponding chiral amines with ee higher than 95% in many cases. Binol-derived phosphoroamidite constitute one of the most successful ligands in these asymmetric reaction achieving, in some cases, practically total enantioselectivity.

Keywords Asymmetric catalysis · Asymmetric hydrogenation · Imine · Iridium catalysts · Phosphorus ligands

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M. Diéguez, O. Pàmies, and C. Claver (✉)
Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo s/n, Tarragona 43007, Spain
e-mail: montserrat.dieguez@urv.cat; oscar.pamies@urv.cat; carmen.claver@urv.cat

Contents

1 Introduction

Hydrogenation catalyzed by transition metals is one of the most efficient methods for reduction of C=C, C=O, and C=N double bonds [1, 2]. Among the different transition metals used, iridium plays an important role in the organic transformations through hydrogenation [3]. To achieve the highest levels of reactivity and selectivity in catalytic hydrogenation, a careful selection and design of the ligand is perhaps the most crucial step. Particular effort has been developed in the last years in the synthesis of phosphorus ligands due to the effectiveness of these ligands in homogenous catalysis. Their diversity (phosphines, phospholes, phosphetanes, phosphinites, phosphonites, phosphites, phosphoramidites, etc.) together with the possibilities of variation of electronic and steric properties make these ligands extremely attractive for catalysis, providing, in many cases, successful results. Chelate phosphorus chiral ligands are considered to be the best ligands for transition metals. In the early days, diphosphines were the most widely used phosphorus ligands. However, they are generally difficult to synthesize and prone to oxidation. In recent years, chiral diphosphites, diphosphinites, diphosphonites, and phosphoroamidites have emerged as new types of ligands, which present several advantages and high catalytic activity and selectivity in metal catalyzed reactions. These ligands, however, are more prone to hydrolysis than phosphines. Their modular nature enables their steric and electronic properties to be finely tuned. For example, binaphthol and its derivatives are a class of chiral diols that are useful for synthesizing these ligands and varying their properties. Interestingly, each catalytic process requires a particular type of ligand. There is no universal type of ligand that can be considered to be more efficient than the others because efficiency also depends on the nature of the substrate [4].

Due to the requirement of obtaining enantiomerically pure products through environmentally friendly technologies, the development of new methods in asymmetric catalysis is becoming an important approach to asymmetric synthesis. Asymmetric hydrogenation is one of the most applied catalytic reactions for the preparation of enantiomerically pure products. Many chiral phosphorus ligands have been developed to be applied in this important reaction [5–7].

Iridium complexes containing phosphorus ligands have been less applied as catalysts in hydrogenation reaction than the corresponding rhodium complexes containing phosphorus ligands. On the other hand, most of the iridium complexes used as catalyst in hydrogenation reaction contain phosphorus–nitrogen ligands. However, iridium complexes containing a great variety of phosphorus ligands (phosphines, phosphinites, phosphites, phosphoramidites) have been applied in hydrogenation reaction with different grades of success. Due to the effectiveness of the iridium catalysts in C=N hydrogenation, the iridium complexes are mainly used as catalysts in imines and related substrates. Although the asymmetric hydrogenation of imines presents important drawbacks (the coordination of substrate, which can take place through both the nitrogen donor atom and the double bond, the *E*/*Z* isomeric mixture of imine substrates, and the poisoning effect of the resultant amines on the catalysts), recent progress in the field of asymmetric hydrogenation of imines allow high activities and enantioselectivities [8].

In general, two different kinds of iridium precursors are used. Isolated cationic $[Ir(COD)_2]A$ complexes and the "in situ" precursors formed from the neutral dimer $[Ir(\mu\text{-}Cl)(COD)]_2$ by addition of the corresponding phosphorus ligand.

This chapter collects the most relevant cases of iridium complexes applied in hydrogenation reaction classified according to the nature of the phosphorus ligand.

2 Application of Bidentate Phosphorus Ligands

2.1 Bidentate Diphosphines

Iridium complexes containing diphosphines have been mainly used as catalysts in the asymmetric hydrogenation of imines for the preparation of chiral amines. Optically active amines are useful intermediates in the synthesis of biologically active compounds. Therefore, the development of efficient methods for their preparation is synthetically important. The first reports concern the use of iridium with the well-known diphosphines DIOP [9, 10], BINAP [10], and BDPP [10, 11] (Fig. 1) as ligands in the hydrogenation of acyclic and cyclic imines. Excellent enantioselectivities (ee's up to 90% at $T = 0°C$, $P_{H2} = 40$ bar) were obtained in the hydrogenation of *N*-[(2*Z*)-1-methoxypropan-2-ylidene]-2,6-dimethylaniline, which is used as a model herbicide precursor [12, 13], with the $[Ir(BDPP)(OCOCF_3)_3]$ catalyst system. The use of a mixture of THF/CH_2Cl_2 (3/1) was found to be crucial, although in some cases, the use of pure THF provided faster hydrogenation rates. The authors also observed that increasing the hydrogen pressure increases the catalytic activity without changing the enantiomeric excess. For substrates 2,3,3-trimethyl-3H-indole and *N*-[(1*E*)-1-phenylethylidene]aniline, moderate enantioselectivities were obtained. Interestingly, for the latter substrate Ir-BINAP catalytic

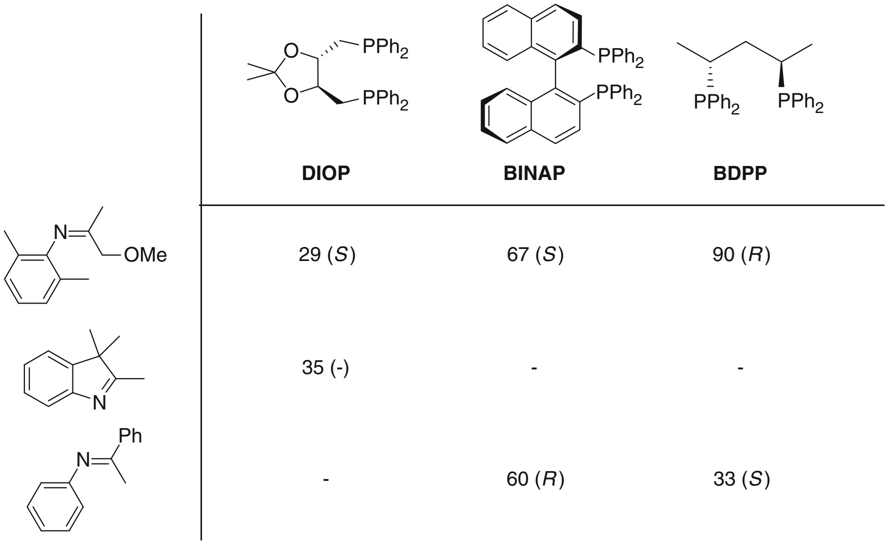
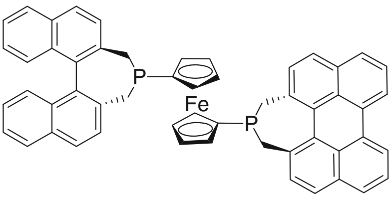


Fig. 1 DIOP, BINAP, and BDPP diphosphine ligands. Summary of the best results obtained in the Ir-catalyzed hydrogenation of several imines

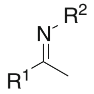
system provides higher enantioselectivities than Ir-BDPP. Later, Claver and coworkers found that using [Ir(COD)((*S*,*S*)-BDPP)]PF_6 (COD = 1,5-cyclooctadiene), at 5 bar of hydrogen and 40°C lead to complete conversion of *N*-(α-methyl-p-methoxybenzylidene)-benzylamine. The best enantioselectivity was obtained in the case of the corresponding immobilized catalyst in montmorillonite K-10 (MK-10) providing ee's up to 59% [11].

Diphosphine ferrocene derivatives as the axially chiral (*R*,*R*)-f-binaphane or (*S*,*S*)-f-binaphane (**1**) ligands (Fig. 2) were successfully used in the iridium-catalyzed hydrogenation of different imines using the dinuclear [Ir(μ-Cl)(COD)]$_2$ as iridium source. In the case of acyclic arylimines, the Ir/(*R*,*R*)-f-binaphane (**1a**) catalyst achieve high enantioselectivities (up to 99%). The addition of iodine as additive was required in the hydrogenation of these substrates [14]. The corresponding (*S*,*S*)-f-binaphane was the only ligand, among a number of electron-rich chiral phosphines evaluated, providing high enantioselectivity in the Ir-catalyzed hydrogenation of unfunctionalized N–H imines. The use of a solvent mixture of MeOH/CH_2Cl_2 (2:1) leads to complete conversion and enantioselectivity up to 95% [15]. The authors proposed a mechanism were the Ir^{III}-catalyzed hydrogenation of imines in the presence of I_2 as the additive is possible (Scheme 1). The oxidative addition of I_2 to the Ir^{I} precursor **A** generates the Ir^{III} complex **B**. The heterolytic cleavage of H_2 can occur in the presence of an amine to form the Ir^{III}–H species **C**. An imine substrate can coordinate with **C** in a η^1 or η^2 fashion. Migratory insertion of the η^2-imine into the Ir^{III}–H bond forms an Ir^{III}–amide complex. The heterolytic cleavage of H_2 by the Ir^{III}–amide intermediate gives an amine and regenerates the Ir^{III}–H species **C** [16].

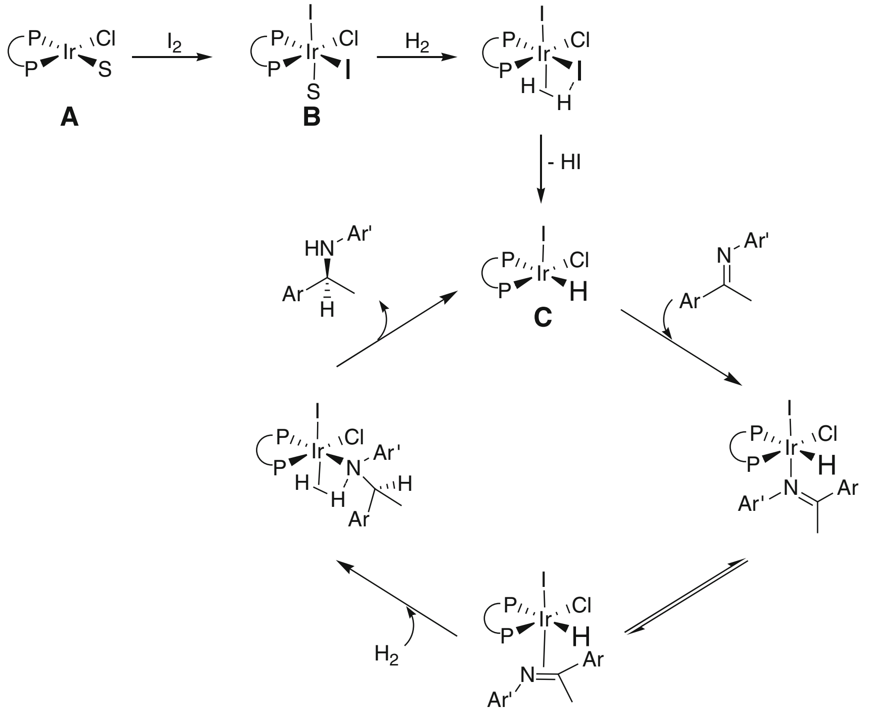
Fig. 2 f-Binaphane ligands **1**. Summary of the best results obtained in the Ir-catalyzed hydrogenation of *N*-arylimines using **1a**



1a (***R*,*R***)
1b (***S*,*S***)



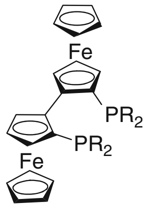
R^1	R^2	%ee
Ph	Ph	84
Ph	2,6-Me_2-C_6H_3	>99
4-OMe-C_6H_4	2,6-Me_2-C_6H_3	98
4-CF_3-C_6H_4	2,6-Me_2-C_6H_3	99



Scheme 1 Proposed mechanism for the Ir-f-binaphane-catalyzed hydrogenation of imines. S = substrate or solvent

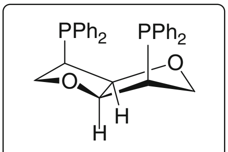
Other 2, 2′-disubstitued biferrocene derivatives (ligands **2**, Fig. 3) also tested using the dinuclear [Ir(μ-Cl)(COD)]$_2$ as the iridium source provided total conversion in arylimine hydrogenation, although with poor-to-moderate enantioselectivity (20–33% ee) [17]. The low enantioselectivies are assumed to be related to the conformational flexibility of this type of bifep ligands.

Cationic iridium complexes with 3,6-bis(diphenylphosphino)hexahydrofuro [3,2-b]furan (**3**) as ligand (Fig. 4) [18], catalyzed asymmetric hydrogenation of several acyclic imines under atmospheric hydrogen pressure, providing chiral amines in quantitative yields and enantioselectivities from 80 to 94%. Contrary to the above-mentioned Ir-diphosphine catalysts, the Ir-**3** complexes formed efficient catalysts under atmospheric hydrogen pressure, whereas at higher pressures, the catalytic activity of the system was drastically reduced. Neutral [Ir(μ-Cl)(COD)]$_2$-**3** systems were inactive, suggesting that cationic, unsaturated intermediates are preferred with the Ir-**3** catalyst. This was further supported from the pronounced effect that different solvents had on the catalyst's activity. Coordinating solvents such as THF and methanol effectively deactivated the catalyst, whereas in 1,2-dichloroethane, quantitative yields of the secondary amine were obtained.

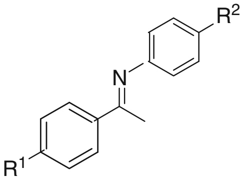


2a R= Ph
2b R= 3,5-Me$_2$-C$_6$H$_3$
2c R= 3,5-Me$_2$-4-OMe-C$_6$H$_2$

Fig. 3 Biferrocene diphosphine ligands **2**



3



R^1	R^2	%ee
H	H	84
OMe	H	80
Cl	H	81
H	OMe	94

Fig. 4 Diphosphine ligand **3**. Summary of the best results obtained in the Ir-catalyzed hydrogenation of *N*-arylimines

Moreover, Dimeric and trimeric Ir(III) polyhydride complexes (Fig. 5) were formed from the reaction of [Ir(**3**)(COD)]PF_6 with molecular hydrogen at atmospheric pressure and were found to inhibit catalytic activity.

An iridium(I) complex with the 1,2-bis(*tert*-butylmethylphosphino)ethane (**4**) and tetrakis(3,5-bis(trifluoromethyl)phenyl)borate as the counter anion catalyzes the hydrogenation of several acyclic aromatic *N*-arylimines under atmospheric hydrogen pressure at room temperature, giving the desired chiral amines with high-to-excellent enantioselectivities (up to 99% , Fig. 6) [19]. The authors also tested (*S*)-BINAP (Fig. 1) and (*R*)-Ph-PHOX (PHOX = 2-[2-(diphenylphosphino) phenyl]-4,5-dihydrooxazole) ligands with lower enantioselectivities [19]. Both steric and electronic properties of the ligand and the combination with the BArF anion are in the base of the efficacy of this catalytic system. On the other hand, attempted hydrogenations of *N*-(2,2,2-trifluoro-1-phenylethylidene)aniline and *N*-(1,2,2-trimethyl-propylidene)aniline under the same conditions resulted in

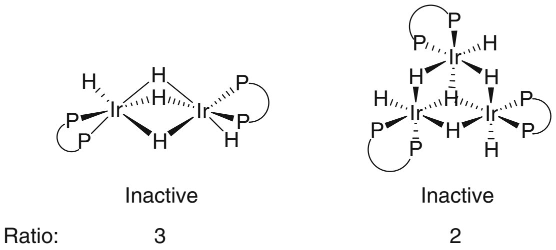
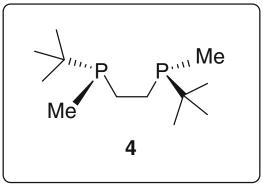


Fig. 5 Dimeric and trimeric hydride complexes obtained from the reaction of [Ir(COD)**3**]PF_6 with H_2



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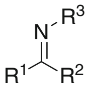


R^1	R^2	R^3	%ee
Ph	Me	Ph	86
4-MeO-C_6H_4	Me	Ph	69
4-F-C_6H_4	Me	Ph	84
Ph	Me	4-MeO-C_6H_4	84
Ph	Me	4-Cl-C_6H_4	83
Ph	Me	4-CF_3-C_6H_4	99

Fig. 6 Diphosphine ligand **4**. Summary of the best results obtained in the Ir-catalyzed hydrogenation of *N*-arylimines

complete recovery of the starting materials. In an effort to rationalize the steriochemical outcome of the reaction, the authors assumed that the reaction proceeds through a four-membered transition state; namely, the C=N function interacts with the Ir–H bond trans to the Ir–P bond. Two transition states, **A** and **B** (Fig. 7), are possible, in which **A** is more preferable than **B** because there is a large steric repulsion between the N-aryl group (Ar') and the *tert*-butyl group on the phosphorus atom in **B**. It is generally known that unsymmetric imines exist mostly as *anti* isomers, and hence, the reaction via transition state **A** eventually leads to secondary amines with the **R** configuration [19].

Recently, several diphosphines (ligands **5**–**8**, Fig. 8) were used for the metal-catalyzed asymmetric hydrogenation of exocyclic enamines [20]. The best results were obtained for the MeO-BiPhep (**5**) ligand using the catalytic system $[Ir(\mu\text{-}Cl)(COD)]_2$/**5**/$I_2$ with up to 96% enantioselectivity at 50°C and 20 bar of pressure (Fig. 9). This system had previously been applied with excellent results, full conversion, and ees up to 96% at 50 bars, for the hydrogenation of quinolines [21]. Later on, the scope of this Ir/**5** system has been extended to the hydrogenation of 2-benzylquinolines and 2-functionalized and 2,3-disubstituted quinolines, achieving ees up to 96% [22]. Substituted 1,2,3,4-tetrahydroquinolines are an

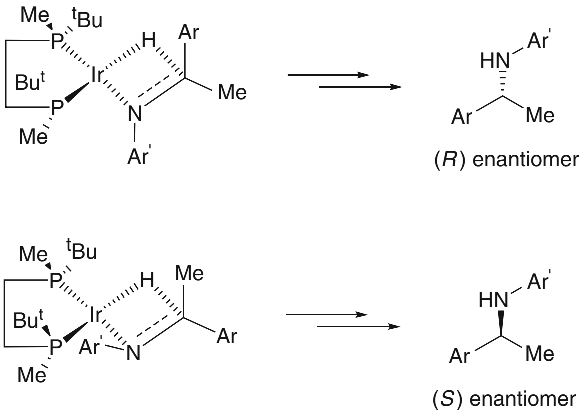
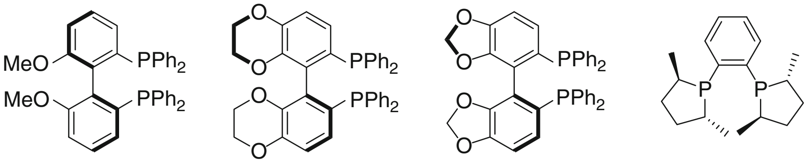
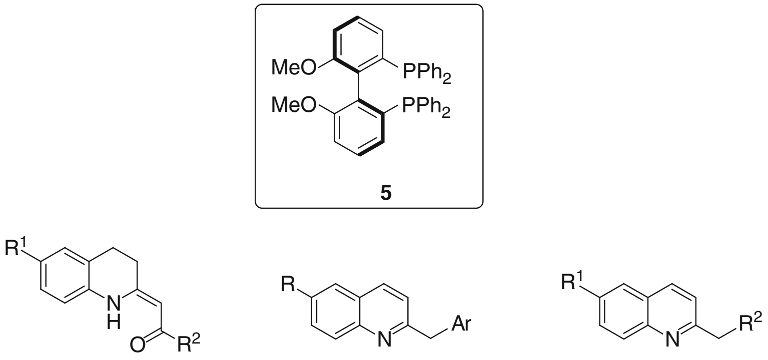


Fig. 7 Possible transition states leading to secondary amines



5 **6** **7** **8**

Fig. 8 Diphosphine ligands **5**–**8** applied in the Ir-catalyzed asymmetric hydrogenation of exocyclic enamines



R^1/R^2	%ee
H/Ph	96
H/Me	94
H/n-C_3H_7	85
Me/Ph	90
F/Ph	96

R/Ar	%ee
H/C_6H_5	94
H/2-MeC_6H_4	95
H/1-$C_{10}H_7$	95
Me/C_6H_5	95
F/C_6H_5	96

R^1/R^2	%ee
H/COPh	96
H/COMe	90
H/(n-Pr)	95
Me/COPh	94
F/COPh	96

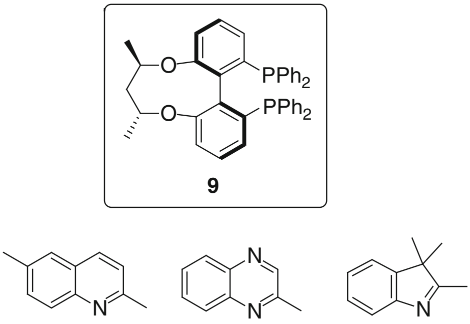
Fig. 9 Summary of the best results obtained in the Ir-catalyzed hydrogenation of quinolines using ligand **5**

important class of biologically active compounds [23]. Mechanistic studies revealed that the hydrogenation mechanism of quinoline could involve a 1,4-hydride addition, isomerization, and 1,2-hydride addition, and the catalytic active species may be a Ir(III) complex with chloride and iodide [24].

Chan and coworkers developed a new diphosphine **9**, related to MeO-BiPhep **5** (Fig. 10) [21]. [Ir(μ-Cl)(COD)]$_2$/**9**/I$_2$ catalytic system provided similar enantioselectivities than [Ir(μ-Cl)(COD)]$_2$/**5**/I$_2$ in the Ir-catalyzed hydrogenation of quinolines but higher enantioselectivitites in the reduction of 2-methyl-quinoxaline and 2,3,3-trimethylindolenine (Fig. 10).

2.2 *Bidentate Diphosphinite, Phosphite–Phosphinite, Diphosphite and Phosphine–Phosphoroamidite Ligands*

Furanoside diphosphinite ligands **10** and **11** (Fig. 11) were applied in the Ir-catalyzed asymmetric hydrogenation of several dehydroaminoacid derivatives [25]. The best enantioselectivities (ee's up to 78%) were obtained in the reduction of methyl *N*-acetamidoacrylate with ligand **10**. These results using the Ir/**10–11** catalysts precursor show that enantiomeric excesses are strongly dependent on the absolute configuration of the C-3 stereocenter of the carbohydrate backbone. The best enantioselectivity were therefore obtained with ligand **10** with an



9

$[Ir(\mu\text{-}Cl)(COD)]_2$ / **9** / I_2	92 (*S*)	65 (*R*)	55 (*R*)
$[Ir(\mu\text{-}Cl)(COD)]_2$ / **5** / I_2	90 (*S*)	80 (*R*)	72 (*R*)

Fig. 10 Diphosphine ligand **9**. Comparison of the best results obtained in the Ir-catalyzed hydrogenation of several substrate types using ligands **5** and **9**

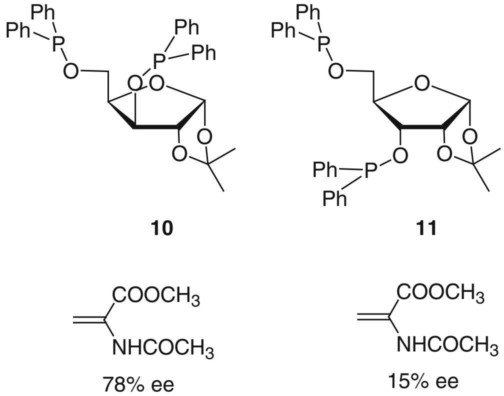


Fig. 11 Summary of the best results obtained in the Ir-catalyzed hydrogenation using furanoside diphosphinite ligands **10** and **11**

S configuration of C-3 of the carbohydrate backbone. Interestingly, in the case of using Rh/**10**–**11** catalysts systems, the best enantioselectivity were obtained with ligand **11**.

Later, furanoside diphosphinite ligands **12**, but with C$_2$-symmetry, provided enantioselectivities up to 70% in the asymmetric hydrogenation of several *N*-arylimines (Fig. 12) [26]. The electronic effect of the ligand on enantioselectivity is considerable. Results were best when electron-donating groups are present on the phenyl rings (ligand **12b**). On the other hand, the use of additives was detrimental to both conversion and enantioselectivity.

The furanoside phosphite–phosphinite ligand **13**, related to the previously diphosphinite ligands **12**, was also applied to the asymmetric hydrogenation of *N*-arylimines, increasing the enantioselectivities up to 76% (Fig. 13) [26]. Precursors based on cationic [Ir(cod)$_2$]BF$_4$ provided better yields and enantioselectivities than

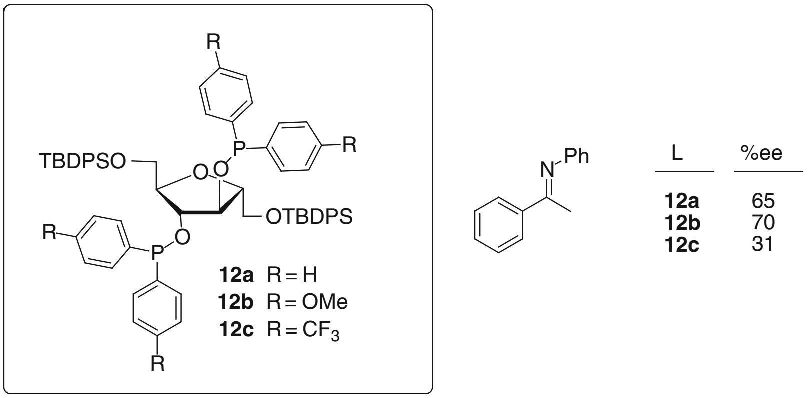


Fig. 12 Summary of the best results obtained in the Ir-catalyzed hydrogenation using furanoside C_2-diphosphinite ligands **12**

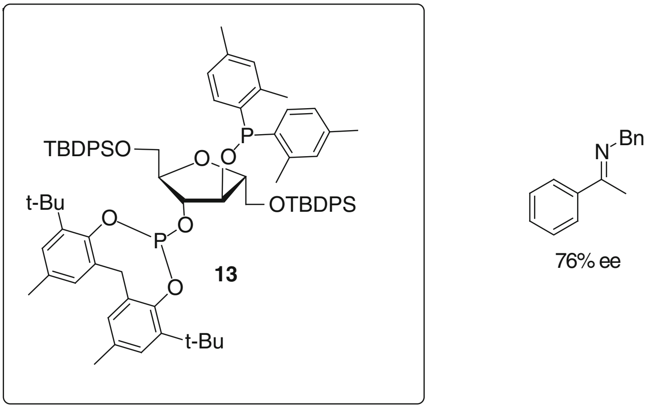
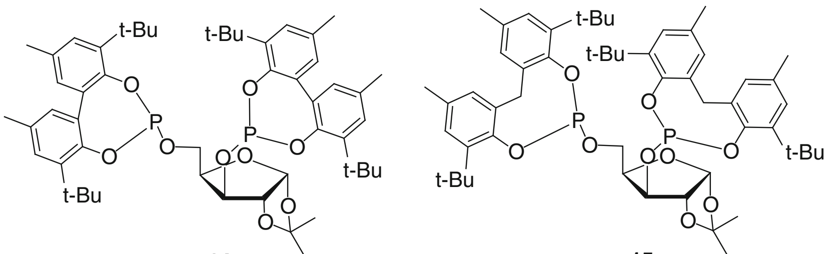


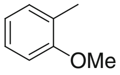
Fig. 13 Summary of the best results obtained in the Ir-catalyzed hydrogenation using furanoside phosphite–phosphinite ligand **13**

the neutral ones formed from the dimer $[Ir(\mu\text{-}Cl)(COD)]_2$. The use of benzylamine and phthalimide was beneficial in terms of enantioselectivity.

One of the challenges in hydrogenation is the reduction of substituted aromatic substrates. This transformation cannot be performed using molecular catalysts. Ru-nanoparticles have shown to be catalytically active [27]. In this aspect, iridium nanoparticles ($[Ir(THF)_x(\mathbf{L})_y(BF_4)_z]$, **L**= diphosphite ligands) stabilized with furanoside diphosphite ligands **14** and **15** (Fig. 14) have recently been applied in the asymmetric hydrogenation of *ortho*-methylanisole and *meta*-methylanisole with high *cis*-selectivity (up to 100%) but low enantioselectivity [28]. Although both diphosphite ligands stabilized iridium nanoparticles with spherical shape and a narrow size distribution, nanoparticles stabilized with ligand **14** were found to be slightly smaller than those bearing ligand **15**. This fact correlates with the higher

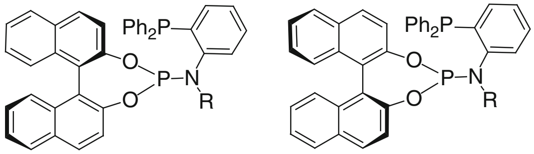


14 **15**



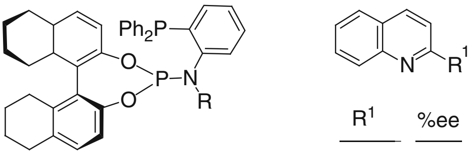
100% *cis*-selective
<5% ee

Fig. 14 Summary of the best results obtained in the Ir-catalyzed hydrogenation using nanoparticles stabilized with furanoside diphosphite ligands **14** and **15**



16a R = (S)-1-(1-naphthyl)-ethyl
16b R = Ph

17a R = (S)-1-(1-naphthyl)-ethyl
17b R = (S)-1-phenyl-ethyl



18 R = (S)-1-phenyl-ethyl

R^1	%ee
Me	96
Bu	97
Ph	95

Fig. 15 Phosphine–phosphoroamidite ligands **16**–**18**. Summary of the best results obtained in the Ir-catalyzed hydrogenation quinolines using ligand **18**

activity obtained with Ir-nanoparticles stabilized with ligand **14** than the ones with ligand **15** and is due to its concomitant higher surface area. It should be pointed out that rhodium and ruthenium nanoparticles provide higher reaction rates than the iridium ones.

A set of novel phosphine–phosphoroamidite ligands **16**–**18** (Fig. 15) possessing two elements of chirality have been prepared through a modular synthetic approach and successfully applied in the Ir-catalyzed asymmetric hydrogenation of

2-substituted quinolines. Particularly remarkable are the enantiomeric excesses up to 97% achieved in the iridium-catalyzed hydrogenation of 2-substituted quinolines, where (11b*S*)-*N*-[2-(diphenylphosphino)phenyl]-*N*-[(*S*)-1-(naphthalen-1-yl) ethyl]-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-d:1′,2′-f] [1,3,2]dioxaphosphepin-4-amine **18** proved to be the most selective ligand. Substantially lower enantioselectivities were obtained with the mismatched diastereomer **17b** and with the *N*-phenyl-substituted ligand **16b**, missing a second element of chirality [29].

3 Application of Monodentate Phosphorus Ligands

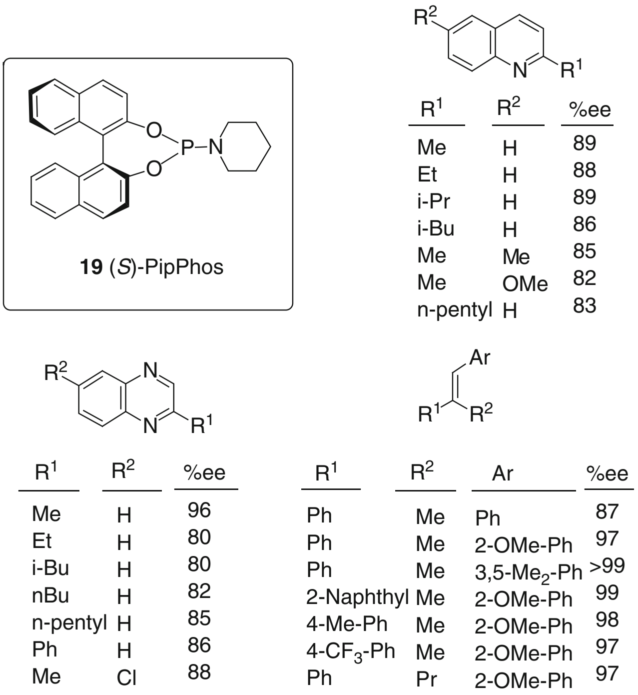
3.1 Monodentate Phosphite, Phosphoroamidite, and Phosphorothioite Ligands

Bidentate chiral ligands were considered superior over monodentate ones in metal-catalyzed asymmetric hydrogenation for more than 30 years [1, 2, 5–7] as chelation was believed to be necessary to impart the rigidity to the metal complex for an efficient transfer of chirality. Recently, chiral monodentate phosphines, phosphonites, phosphoramidites, and phosphites were reported to lead to excellent results in the asymmetric hydrogenation of α- and β-dehydroamino acids, itaconic acid derivatives, and enamides [30–33]. Monodentate phosphite and phosphoramidite ligands have the advantage of being readily accessible, highly diverse, air stable, and inexpensive compared to most bidentate ligands [31, 34, 35]. In addition, they are amenable to parallel synthesis [36–38].

Binol-derived phosphoroamidite PipPhos (**19**) has been successfully used as a ligand for the Ir-catalyzed asymmetric hydrogenation of 2- and 2,6-substituted quinolines [39], 2- and 2,6-substituted quinoxalines [40], and *N*-aryl imines [41] (Fig. 16).

In the hydrogenation of quinolines, the presence of tri-*ortho*-tolylphosphine and/or chloride salts as additives was highly adventitious, increasing the enantioselectivities up to 89%. NMR studies indicated that no mixed complexes are formed upon addition of tri-*ortho*-tolylphosphine [39]. Moreover, in order to examine the stability of the catalyst during the reaction, the enantioselectivity was monitored over time. An increase of the enantioselectivity over 24 h was observed. The low ee at the beginning of the reaction may be explained by the slow formation of the catalytically active species during the first hour (10% of conversion). This is also confirmed by the induction time that is observed in the hydrogenation. So, prestirring the iridium complex in the presence of the ligand under the reaction conditions during 1 h is necessary to achieve the highest levels of enantioselectivity.

In the hydrogenation of 2- and 2,6-substituted quinoxalines, the presence of piperidine hydrochloride as additive full conversions and enantioselectivities of up to 96% were obtained [40]. These results represent the highest selectivity reached for this class of heterocyclic compounds reported as yet [22, 42, 43].



19 (*S*)-PipPhos

R^1	R^2	%ee
Me	H	89
Et	H	88
i-Pr	H	89
i-Bu	H	86
Me	Me	85
Me	OMe	82
n-pentyl	H	83

R^1	R^2	%ee
Me	H	96
Et	H	80
i-Bu	H	80
nBu	H	82
n-pentyl	H	85
Ph	H	86
Me	Cl	88

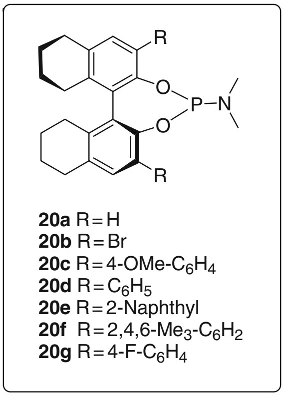
R^1	R^2	Ar	%ee
Ph	Me	Ph	87
Ph	Me	2-OMe-Ph	97
Ph	Me	3,5-Me_2-Ph	>99
2-Naphthyl	Me	2-OMe-Ph	99
4-Me-Ph	Me	2-OMe-Ph	98
4-CF_3-Ph	Me	2-OMe-Ph	97
Ph	Pr	2-OMe-Ph	97

Fig. 16 Summary of the best results obtained in the Ir-catalyzed hydrogenation of quinolines, quinoxalines, and *N*-aryl imines using binol-derived phosphoroamidite PipPhos **19** ligand

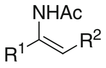
Ir-PipPhos catalysts lead also to very high enantioselectivity in the asymmetric reduction of several *N*-aryl acetophenone imines [41]. The reaction is strongly solvent dependent: in protic solvents such as methanol, no reaction was observed. Excellent conversions and high enantioselectivities were obtained in toluene and dichloromethane. It was also observed that pressures above 5 bar caused a slight decrease in enantioselectivity and shorter reaction times. An interesting anion effect was observed using different iridium precursors, with cationic $[Ir(COD)_2]BArF$ giving the best results. High reaction rates were observed with $[Ir(COD)_2]PF_6$ (full conversion in 30 min); however, the enantioselectivity remained at 65%. No conversion was observed using neutral $[Ir(\mu\text{-}Cl)(COD)]_2$ as catalyst precursor at room temperature and 5 bar; however, at 50 bar and 60°C, the reaction goes to completion, yielding the product amine with 61% ee. In addition, it was also observed that the presence of electrodonating substituents in the 2-, 3- and 5-position of the aryl ring enhances enantioselectivities up to >99%. If the substituent is 2-methoxy, the resultant secondary amines are easily oxidatively deprotected using trichloroisocyanuric acid to give the primary amines in good yield with full retention of enantioselectivity.

In situ-generated iridium complexes containing bulky 3,3′-substituted H8-phosphoroamidites **20** as ligands catalyzed the asymmetric hydrogenation of nonfunctionalized enamines in high yield and good-to-excellent selectivities (Fig. 17). Enantioselectivities are positively affected by addition of noncoordinating salts (i.e., $NaClO_4$, $NaBF_4$, etc.). The authors also found an important effect of the substituents of the biaryl group on the catalytic performance. Therefore, activities and enantioselectivities were best using ligand **20c** [44]. These results represent the highest selectivity reached in the Ir-catalyzed hydrogenation of enamides reported as yet. So far, only two studies on this topic have been reported [45, 46], and the best enantioselectivity obtained was up to 60% [46].

The spiro-phosphoroamidite ligand **21** (Fig. 18) was successfully applied in the enantioselective hydrogenation of cyclic *N*,*N*-dialkyl enamines for the synthesis of optically active cyclic tertiary amines, including those having a six-membered ring or a fused ring (ee's up to 94%) [47]. The author used this asymmetric hydrogenation reaction to synthesize the isoquinoline alkaloid crispine A [48], which was isolated from *Carduus crispus* (welted thistle) and has a significant cytotoxic activity [49, 50]. The asymmetric hydrogenation of enamine **22** performed under optimized conditions using the catalyst Ir/**21** produced crispine A in 97% yield with 90% ee (Scheme 2).

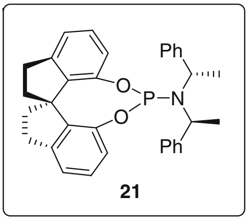


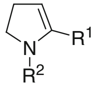
20a R = H
20b R = Br
20c R = 4-OMe-C_6H_4
20d R = C_6H_5
20e R = 2-Naphthyl
20f R = 2,4,6-Me_3-C_6H_2
20g R = 4-F-C_6H_4



R^1	R^2	%ee
Ph	H	93
4-OMe-Ph	H	88
3-OMe-Ph	H	82
2-OMe-Ph	H	64
4-CF_3-Ph	H	70
t-Bu	H	73
Ph	Me	29

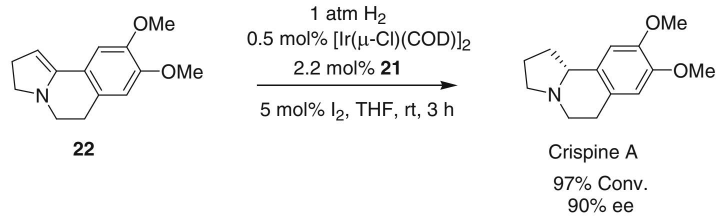
Fig. 17 Summary of the best results obtained in the Ir-catalyzed hydrogenation of enamides using H8-binol-monophosphoroamidite ligands **20c**





R^1	R^2	%ee
Ph	Me	94
Ph	i-Pr	96
4-OMe-C_6H_4	Me	94
4-F-C_6H_4	Me	92

Fig. 18 Summary of the best results obtained in the Ir-catalyzed hydrogenation of cyclic *N*,*N*-dialkyl enamines using spiro-phosphoroamidite ligand **21**



Scheme 2 Synthesis of Crispine **A** through asymmetric hydrogenation

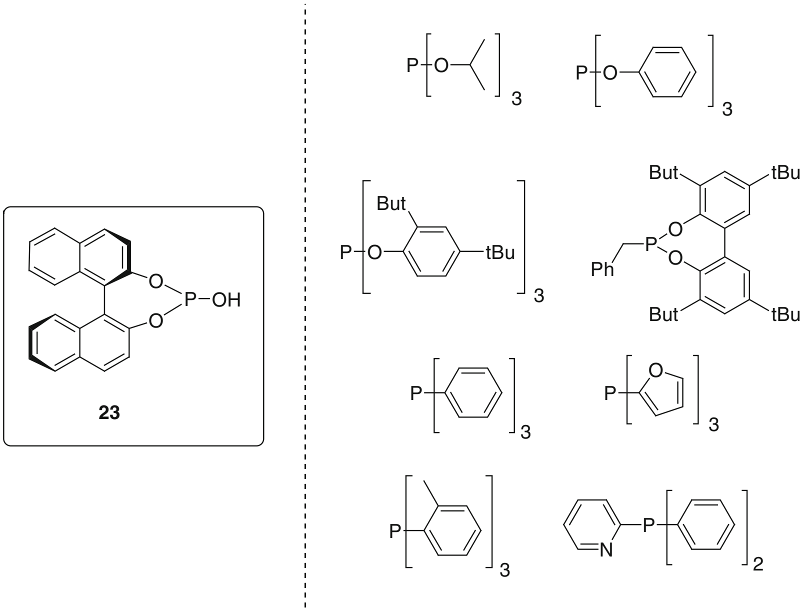
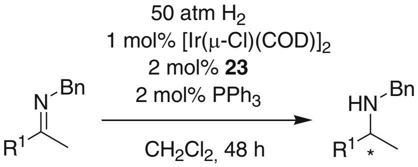


Fig. 19 Combination of ligand **23** with several achiral monodentated P-ligands (phosphites, phosphonites, and phosphines)

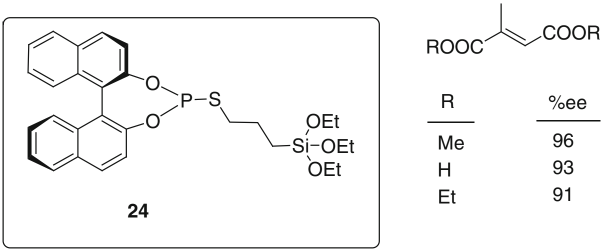
Reetz and coworkers reported the use of ligand **23** in combination with several achiral monodentated P-ligands (phosphites, phosphonites, and phosphines) for the asymmetric Ir-catalyzed hydrogenation of imines (Fig. 19). The combination of ligand **23** with the achiral triphenylphosphine leads to remarkable efficient catalyst system reducing imines with enantioselectivitites up to 92% (Scheme 3) [51].

Binol-derivative monodentate monophosphorothioite (**24**) and its iridium complex was covalently anchored to mesoporous silica supports (i.e., SBA-15, MCM-41, etc.). Among the catalysts investigated, iridium complex immobilized over SBA-15 (IrPSSBA-15) was found to be the ideal heterogeneous catalyst system for the enantioselective hydrogenation of itaconic acid derivatives. High conversions (99%) and excellent enantioselectivities (up to 96% ee) were observed under

Scheme 3 Summary of the best results obtained in the Ir-catalyzed hydrogenation of imines using the combination of ligand **23** and triphenylphosphine



R^1	%ee
Ph	88
4-OMe-Ph	90
4-Cl-Ph	92
2-Naphthyl	92



R	%ee
Me	96
H	93
Et	91

Fig. 20 Monodentate monophosphorothioite ligand **24**

milder reaction conditions (Fig. 20) [52]. It was found that the catalytic activity and enantioselectivity were comparable to its homogenenous analog. The catalyst was reused at least five times and the same activity and selectivity were maintained.

3.2 *Monodentate Phosphines*

Considering the most common ligand, triphenylphosphine iridium(I) cationic systems $[Ir(COD)(PPh_3)_2]X$ were used as catalysts, both homogeneous and heterogenized in smectite clay materials (montmorillonite MK-10, sodium bentonite and lithium hectorite). Both homogeneous and heterogenized $[Ir(COD)(PPh_3)_2]X$ ($X = PF_6^-$, BF_4^-) systems showed high catalytic activity in the hydrogenation of the imine *N*-benzylidene aniline. In particular, the immobilization of the organometallic complex $[Ir(COD)(PPh_3)_2]BF_4$ in the supports studied afforded catalytic systems that could be reused for a large number of runs, with negligible loss of the catalytic activity (>97% conversion) for at least 13 runs [53]. As described above (Sect. 3.1), achiral monophosphines as triphenylphosphine and tri-*ortho*-tolylphosphine have been combined with other monodentate chiral ligand as phosphoroamidite, improving both the conversion and enantioselectivity [51].

4 Conclusions

Iridium complexes containing phosphorus ligands have shown to be active catalysts for hydrogenation reaction. Mono- and bidentate phosphines, phosphinites, phosphites, phosphoroamidites, and a combination of these functionalities have been applied in the iridium-catalyzed hydrogenation. In the early days, diphosphines were the most widely used phosphorus ligands. However, they are generally difficult to synthesize and prone to oxidation. In recent years, chiral phosphites, phosphinites, phosphonites, and phosphoroamidites have emerged as new types of ligands, which present several advantages and high catalytic activity and selectivity. Homogeneous and heterogeneous systems have been studied, allowing the recycling of catalysts. Slight modifications in the electronic and steric properties of the ligands influence the catalytic results, which indicate the potentiality of modular ligands. Imines, including unfunctionalized N–H imines and cyclic imines as quinolines and other substrates, have been transformed in the corresponding chiral amines with ee higher than 95% in many cases. Interestingly mild reaction conditions have been used for these hydrogenations that have been previously performed at high pressures. Binol-derived phosphoroamidite constitute one of the most successful ligands in these asymmetric reaction, achieving, in some cases, practically total enantioselectivity.

Acknowledgments We thank the Spanish Government (Consolider Ingenio CSD2006-0003, 2008PGIR/07 to O. Pàmies, 2008PGIR/08 to M. Diéguez and ICREA Academia award to M. Diéguez) and the Catalan Government (2009SGR116) for financial support.

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Top Organomet Chem (2011) 34:31–76
DOI: 10.1007/978-3-642-15334-1_3

Iridium-Catalyzed Asymmetric Hydrogenation of Olefins with Chiral N,P and C,N Ligands

David H. Woodmansee and Andreas Pfaltz

Abstract Asymmetric hydrogenation is one of the most important catalytic methods for the preparation of optically active compounds. For a long time, chiral rhodium- and ruthenium–diphosphine complexes were the catalysts of choice in this field. However, their application range in the asymmetric hydrogenation of olefins is limited to substrates bearing a coordinating group adjacent to the C=C bond. These limitations were surmounted with the advent of iridium complexes with chiral N,P-ligands. For a wide range of unfunctionalized olefins, excellent enantioselectivities can now be achieved with low catalyst loadings. Moreover, these catalysts also allow highly enantioselective hydrogenation of various functionalized olefins, heterocycles such as furans or indoles, and imines. Research in this field is productive with new catalysts giving high enantioselectivities for difficult substrates appearing at an ever more frequent rate. These methods greatly expand the repertoire of reactions available to synthetic chemists for the preparation of optically active compounds in a reliable and an atom-economical fashion.

Keywords 1,1′-Disubstituted alkenes, Asymmetric catalysis, Asymmetric hydrogenation, Imine, Iridium N,P complexes, Tetrasubstituted alkenes, Trisubstituted alkenes

Contents

D.H. Woodmansee and A. Pfaltz (✉)
Department of Chemistry, St Johanns-Ring 19, 4056 Basel, Switzerland
e-mail: andreas.pfaltz@unibas.ch

1 Introduction

The development of highly enantioselective rhodium–diphosphine catalysts in the early 1970s marked the beginning of a new era in asymmetric synthesis. For the first time, practically useful enantioselectivities could be obtained with synthetic chiral catalysts. The well-known L-Dopa process developed by Monsanto at that time [1] demonstrated that these catalysts can be applied on an industrial scale, and since then, hydrogenation has played a dominant role in industrial asymmetric catalysis [2]. Today, asymmetric hydrogenation remains a corner stone of the modern organic chemists' repertoire of reliable catalytic methods for the construction of optically active compounds [3, 4]. High enantioselectivity, low catalyst loadings, essentially quantitative yields, perfect atom economy, and mild conditions are attractive features of this transformation as evident in the ever growing list of publications using these methods.

A plethora of chiral phosphine ligands which induce very high enantioselectivity in rhodium- and ruthenium-catalyzed hydrogenations are known. However, the range of olefins that can be hydrogenated with high enantiomeric excess is still limited. Both rhodium and ruthenium catalysts require the presence of a coordinating functional group adjacent to the C=C bond, hydrogenation of dehydro amino acid derivatives or allylic alcohols being typical substrate classes. A caveat of this reactivity in regard to unfunctionalized olefins is that these catalysts generally display low reactivity and unsatisfactory enantioselectivity. Thus, their application has been restricted largely to certain classes of properly functionalized substrates.

Some years ago the Pfaltz group discovered a new class of chiral iridium N,P-ligand complexes which overcame the limitations of the rhodium- and ruthenium-based systems [5, 6]. Early transition metal metallocenes catalysts capable of asymmetric hydrogenation of a range of unfunctionalized olefins in excellent enantioselectivities have been reported but under onerous conditions [7–9]. Moreover, iridium N,P-based systems showed exceptionally high activity in the hydrogenation of unfunctionalized tri- and even tetrasubstituted olefins. In this respect, they resembled the Crabtree catalyst, $[Ir(pyridine)(Cy_3P)(COD)]PF_6$ (Cy = cyclohexyl, COD = cyclooctadiene) [10], which provided the stimulus for this work. In addition, promising results were also obtained with certain functionalized alkenes for which no suitable catalysts were available. In this chapter, we discuss the special properties and scope of these catalysts with special emphasis on recent developments [11–14].

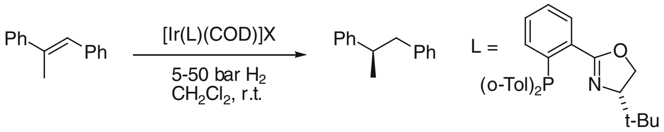
2 Mechanistic Studies

2.1 Initial Studies: An Unexpected Anion Effect

Initial studies with iridium complexes derived from chiral phosphinooxazolines (PHOX ligands) and (*E*)-1,2-diphenyl-1-propene as substrate gave encouraging results (Scheme 1) [5, 15]. With 4 mol% of catalyst ($X = PF_6^-$) at 10–50 bar hydrogen pressure, up to 98% ee could be obtained. However, the turnover numbers were disappointingly low.

Kinetic studies demonstrated that with 4 mol% of catalyst in a 0.3 M solution of olefin at 7 bar hydrogen pressure, the reaction was extremely fast and reached completion within less than 1 min [16]. Lower catalyst loadings resulted in decreased conversion. Although the initial rate was still high at 1 mol% catalyst loading, a rapid and essentially complete deactivation of the catalyst was observed before 50% of the olefin was consumed. Deactivation is a known problem of the Crabtree catalyst, which is attributed to the formation of inactive hydride-bridged trinuclear complexes [10]. In the case of Ir(PHOX) complexes as well, NMR analysis of deactivated reaction mixtures suggested the presence of such hydride-bridged species. In subsequent studies, a trinuclear Ir(PHOX)-hydride complex was isolated and characterized by NMR and X-ray analysis [17]. This complex proved to be remarkably stable, and all experiments to convert it back into a catalytically active species failed.

Attempts to increase conversion by variation of the solvent, hydrogen pressure, or the catalyst and substrate concentration were unsuccessful. Coordinating solvents and additives such as amines, or coordinating anions such as halides, carboxylates,



Scheme 1 Initial screening with PHOX

and even the very weakly coordinating triflate ion were found to deactivate the catalyst. The best results were obtained in anhydrous dichloromethane or 1,2-dichloroethane using cationic Ir-PHOX complexes with hexafluorophosphate as counterion. Rigorous exclusion of moisture and oxygen resulted in increased conversion. When the reaction was set up in carefully dried dichloromethane in a glove box, full conversion could be achieved with only 0.5 mol% of the catalyst. However, reactions at such low catalyst loadings were difficult to reproduce.

After extensive experimentation, a simple solution for avoiding catalyst deactivation was discovered, when testing an Ir-PHOX catalyst with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F^-) as counterion [5]. Iridium complexes with this bulky, apolar, and extremely weakly coordinating anion [18] did not suffer from deactivation, and full conversion could be routinely obtained with catalyst loadings as low as 0.02 mol% [19]. In addition, the BAr_F salts proved to be much less sensitive to moisture than the corresponding hexafluorophosphates. Tetrakis(pentafluorophenyl)borate and tetrakis(perfluoro-tert-butoxy)aluminate were equally effective with very high turnover frequency, whereas catalysts with hexafluorophosphate and tetrafluoroborate gave only low conversion while reactions with triflate were completely ineffective (Fig. 1).

How can these bulky, extremely weakly coordinating anions prevent catalyst deactivation? A comparative kinetic study of catalysts with different anions provided a plausible answer [19]. With PF_6^- as a counterion, the rate dependence on olefin concentration was first order, whereas the rate order observed for the corresponding BAr_F^- complex was close to zero. This striking difference may be explained by the stronger coordination of PF_6^- or formation of a tight anion pair, which slows down the addition of the olefin to the catalyst to such an extent that it becomes rate-limiting. In contrast, the essentially noncoordinating BAr_F^- ion does not interfere with olefin coordination, and the catalyst remains saturated with olefin even at low substrate concentration. The slower reaction of the PF_6^- salt with the olefin could

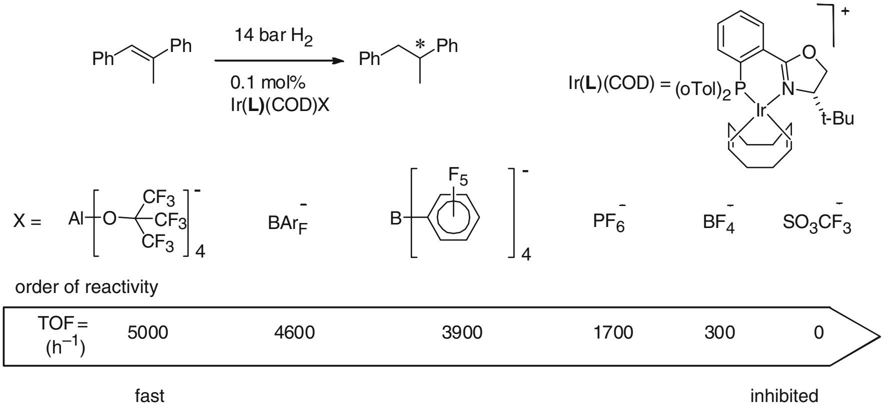


Fig. 1 Order of reactivity of the complexes [Ir(PHOX)(COD)]X by TOF measured at 4°C with E-α-methylstilbene as substrate

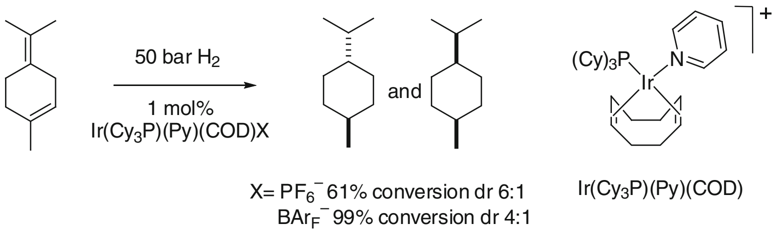


Fig. 2 Comparison of Crabtree catalyst with the BAr_F analog

explain its higher tendency to undergo deactivation. If we assume that deactivation is caused by the formation of hydride-bridged species leading to an inactive trinuclear complex, then the critical step in the catalytic cycle is the reaction of the Ir-hydride intermediate with the olefin. If olefin insertion is very fast, as in case of the BAr_F^- counterion, hydrogenation dominates over the deactivation pathway, whereas with the PF_6^- analog, the olefin reacts more slowly and deactivation becomes a significant competing process.

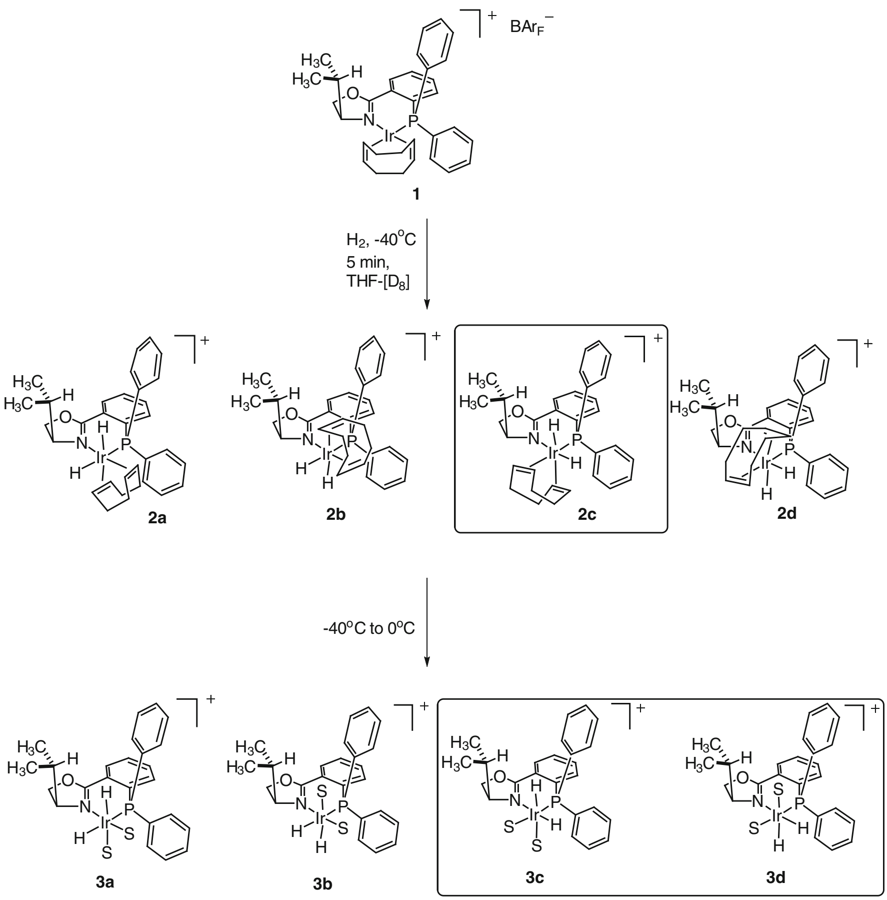
Virtually every iridium catalyst of the formula $[Ir(L^*)(COD)]^+ [X]^-$ for asymmetric olefin hydrogenation that has appeared after the initial counterion effect studies was based on BAr_F^- as the preferred anion [14]. The anion effect is broadly applicable in iridium-catalyzed reductions as experiments with a direct analog of the Crabtree catalyst of the formula $[Ir(pyridine)(Cy_3P)(COD)]BAr_F$ indicates (Fig. 2).

Hydrogenation of δ-terpinene (Fig. 2) proceeded in higher conversion with Crabtree's catalyst with BAr_F counter ion rather than the normal PF_6. The BAr_F counter ion performed better in all instances where the more coordinating PF_6 salt failed to reach complete hydrogenation [20].

2.2 NMR Investigations of Iridium PHOX Hydride Complexes

In an early work of Crabtree and coworkers, olefin dihydride intermediates formed during hydrogenation of cyclooctadiene using $[Ir(pyridine)(PCy_3)(COD)]PF_6$ in dichloromethane at 0°C were detected by NMR spectroscopy [21]. In a more recent complementary study, Mazet et al. found that when $[Ir(PHOX)(COD)]BAr_F$ complex **1** was treated with hydrogen at −40°C for 5 min in $[D_8]$-THF, olefin dihydride intermediates were formed, which were characterized by NMR spectroscopy [22]. Two new signals appeared in the hydride region that were assigned to a single dihydride complex **2c** formulated as $[Ir(PHOX)(H)_2(COD)]BAr_F$ (Scheme 2).

The predominance of isomer **2c** over **2a** or **2b** is consistent with Crabtree's findings, which convincingly demonstrated that in the reaction of H_2 with $[Ir(pyridine)(PR_3)(COD)]PF_6$, the formation of an Ir–H bond *trans* to the N ligand is electronically favored [23]. Highly selective formation of isomer **2c** results from H_2 addition to the



Scheme 2 ^{1}H NMR study of Ir(**5a**) hydride formation

more sterically encumbered face of the starting complex because dihydrogen addition to the sterically more accessible face leading to isomer **2d** would build up steric strain between the chelating COD ligand and the isopropyl group in the oxazoline ring and the pseudoaxial P-phenyl group. When the solution containing complex **2c** was warmed to 0°C under hydrogen, a gradual consumption of isomer **2c** was observed accompanied by the appearance of two new hydride complexes **3c** and **3d** with concomitant formation of cyclooctane.

2.3 *Computational Studies and Additional Experiments*

DFT (density functional theory) calculations on the complete structures of complexes shown in Scheme 2 have been carried out by Mazet et al. [22, 24, 25]. The fully minimized structures of the four possible *cis*-dihydrides formed by oxidative addition of H_2 to $[Ir(PHOX)(COD)]^+$ were calculated. The most stable structure corresponded to the reaction product **2c** that was shown to be formed exclusively in the NMR experiment. Isomers **2a** and **2d** were 10.6 and 4.9 kcal/mol higher in energy, whereas for isomer **2b**, no stable chelate structure could be located due to severe steric interactions, which prevent the formation of an Ir–N bond. The four possible $[Ir(PHOX)(H)_2(solvent)_2]^+$ complexes **3a–d** resulting from the hydrogenation of the cyclooctadiene ligand were also examined, and again, the two most stable structures corresponded to the isomers observed in the NMR experiments. These results show that steric interactions are very important and may dominate over electronic factors. Consequently, computational studies of potential reaction pathways should be based on full catalyst and substrate structures rather than simple model systems.

Unfortunately, attempts to observe and characterize intermediates under catalytic conditions have been unsuccessful so far. When considering which intermediates may be formed during catalysis, one of the first issues that becomes apparent is what ligands are coordinated to iridium during catalysis. An olefin dihydride iridium complex, which incorporates a bidentate N,P ligand, has a sixth coordination site available for an additional ligand. Whereas coordination of a second molecule of olefin seems highly unlikely due to steric hindrance, dihydrogen and dichloromethane may both be effective ligands for iridium.

Thus the two plausible catalytic cycles have been considered, one via an Ir dihydride complex **A** and the other via an $IrH_2(\eta^2\text{-}H_2)$ complex **B** (Fig. 3). The first is analogous to the well-established mechanism for rhodium diphosphine-catalyzed hydrogenation of olefins going through Ir(I) and Ir(III) intermediates [26–29].

Experimental support for an Ir(I)–Ir(III) mechanism was provided by Chen and Dietiker [30]. They reported an elegant experimental investigation of the hydrogenation of styrene with $[Ir(PHOX)(COD)]BAr_F$ in the gas phase by means of electrospray ionization tandem mass spectrometry. By means of reversible deuterium labeling, the investigators found masses corresponding only to intermediates with a mass corresponding to a dihydride complex with no presence of a trihydride species and concluded that no Ir(V) species with PHOX could be present in the catalytic reaction.

Based on DFT calculations Brandt et al. proposed a catalytic cycle via Ir(III) and Ir(V) intermediates, in which an additional dihydrogen molecule coordinated to an Ir-dihydride undergoes oxidative addition during migratory insertion [31]. However, since an extremely truncated model for the ligand and substrate (ethylene) was used which neglected the severe steric interactions present in the actual catalysts it

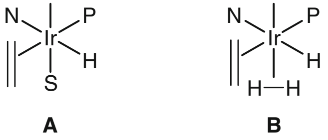


Fig. 3 Possible Ir(III) and Ir(V) hydride intermediates (*S* solvent)

seems premature to rule out an Ir(I)–Ir(III) cycle. From subsequent calculations on the full catalyst and substrate structures, which were based on the postulated Ir(III)–Ir(V) cycle, a simple qualitative quadrant model was derived for rationalizing the observed enantioselectivities. Further studies by the same investigators on a complete complex with stereoelectronic contributions from both *trans* α- and β-methylcinnamic esters were investigated and applied to the model (Fig. 4) [32]. The authors concluded that in the case of the *trans*-β-methylcinnamic ester, electronic and steric factors cooperated in their model to give high enantioselectivity. In the case of the *trans*-α-methylcinnamic ester, steric interactions placed the migrating hydride onto the alpha carbon, which would be electronically disfavored and thus lead to lower selectivities, both substrate selectivity observations being reflected by experimental results.

Fan et al. also reported DFT calculations on the complete ligand and substrate structures with an iridium carbene-based complex for an Ir(III)–Ir(V) catalytic cycle, which reproduced the correct selectivity order for three different substrates [33]. Calculations on complete ligands and real substrates that reproduce experimentally determined enantioselectivities give plausible credence to these authors' computational experiments.

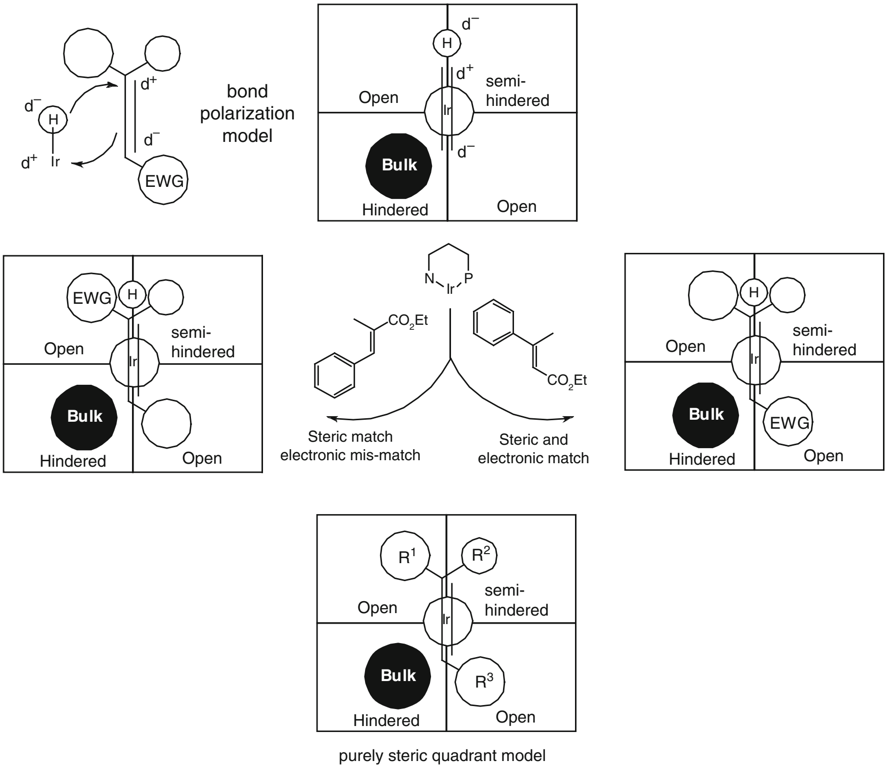


Fig. 4 Anderssons quadrant model

Preliminary studies by Meuwly and Roseblade [24, 25] indicated that calculated pathways beginning from $[Ir(P^{\wedge}N)(H)_2(\eta^2\text{-}H_2)(\eta^2\text{-olefin})]^+$ complexes lead to predicted enantioselectivities which are opposite to the experimentally observed values. While competing pathways involving solvated Ir(I)–Ir(III) intermediates were somewhat higher in energy (by a few kcal/mol), calculated transition states energies were in reasonable agreement with the experimentally observed enantioselectivities. Taking into account that CH_2Cl_2 as the solvent is present in much higher concentration than H_2, the Ir(I)–Ir(III) and Ir(III)–Ir(V) cycles become energetically very similar, making it difficult to distinguish between them based on calculations alone.

Thus, additional experimental and computational studies will be needed to draw definitive conclusions regarding the mechanism of Ir-catalyzed asymmetric hydrogenation. The Ir(I)–Ir(III) and Ir(III)–Ir(V) cycles seem to be similar in energy, so it may well be that depending on the catalyst, substrate, and the hydrogenation conditions, one or the other pathway will be preferred or both cycles could operate in parallel.

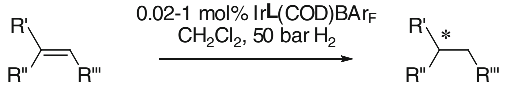
3 Asymmetric Hydrogenation of Trisubstituted Alkenes

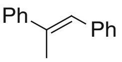
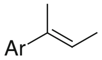
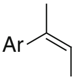
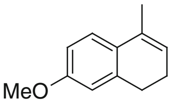
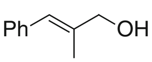
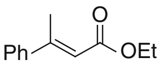
3.1 Asymmetric Hydrogenation of Standard Test Substrates

Largely unfunctionalized trisubstituted olefins are the most commonly investigated hydrogenation substrates in iridium-catalyzed reductions [11–14]. As previously stated, strongly coordinating groups such as basic amines, alcohols, and strongly donating Lewis bases can in general slow the iridium catalysts down to a point where they are not effective. However, a number of olefins with moderately Lewis basic functionalities such as acids, alcohols, esters, ketones, ethers, halogens, and other similar groups adjacent or in proximity to the C=C bond have been successfully reduced with very high functional group tolerance and stereoselectivity. There is an increasing appearance of more coordinating functionalities such as enamines, indoles, imines, and even pyridines, all of which will be touched upon in the later sections of this chapter.

A survey of a list of typical ligands with reasonable asymmetric induction for the reduction of a commonly tested set of trisubstituted olefins (Table 1) reveals several common features (Fig. 5). Virtually, all of the ligands consist of a heterocycle with a sp^2-hybridized nitrogen atom as a hard σ donor and a strong soft donor moiety such as a trisubstituted phosphorus atom or an N-heterocyclic carbene forming the second portion of the chelating ligand. Six-membered metallacycles are the most investigated, with the exception of the seven-membered carbene ligand **9**, the seven-membered spirocycles SpinPHOX **15a**–**c**, and the rigid spiroindanes SiPHOX **16a**–**d**. Stereogenic units have been incorporated with varying degrees of success in all regions of the metallacycle backbone. Although some ligands display a wider

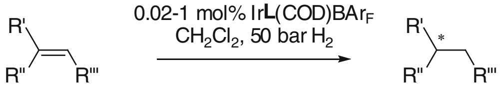
Table 1 Asymmetric hydrogenation of standard substrates with chiral N,P and C,N iridium catalysts

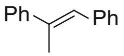
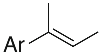
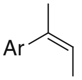
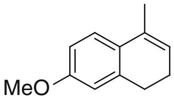
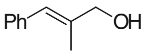
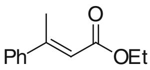


Substrate	Ligand ee %[a]						
	5	**6**	**7**	**8**	**9**	**10**	**11**
 **25a**	**b** 97	**a** 99	**a** 98	**a–c** 99	99	**a–d** 99	**a** 99
 **25b**	**b** 81	**a** 99	**a** 91	**a–c** 99	97	**a–d** 99	**a** 90
 **25c**	**b** 63	**e** 92	**a** 89	**a** 98	80	–	–
 **25d**	**b** 72	**f** 95	**a** 95	**a** 92	–	**b** 55	**b** 94
 **25e**	**b** 96 (95)	**a** 92	**a** 97	**a** 97	93	**b, d** 97	**b** 98 (95)
 **25f**	**b** 84 (96)	**f** 96	**a** 94	**a** 99	–	**b, d** 98	**b** 93

(*continued*)

Table 1 (continued)

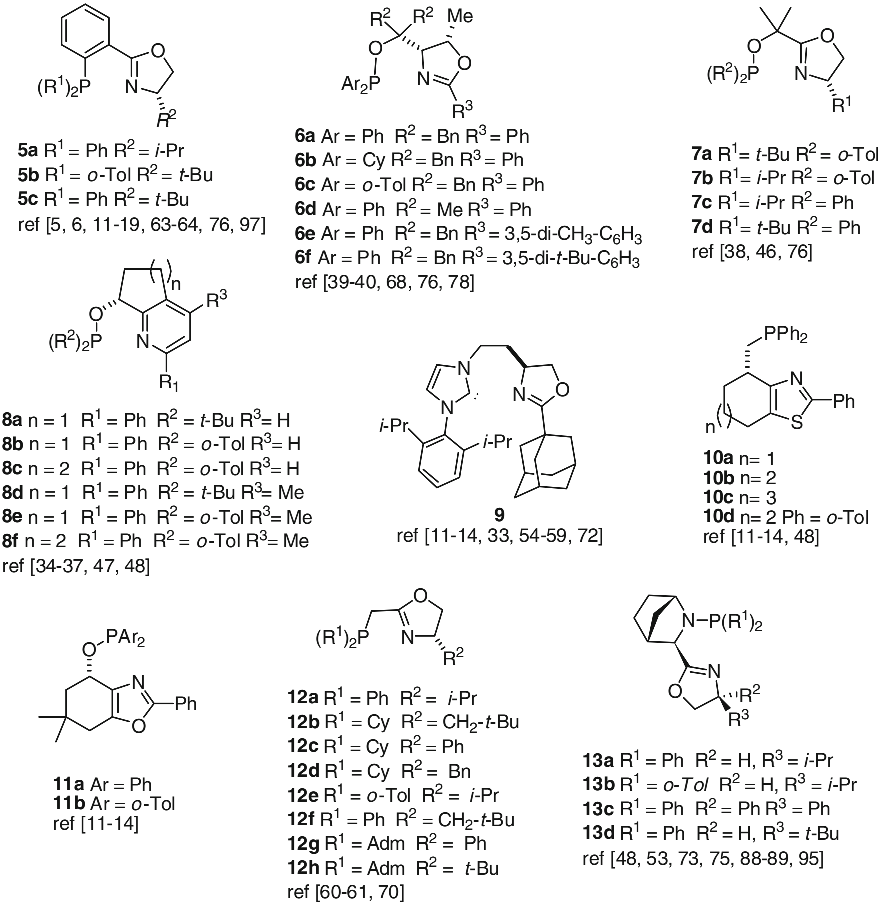


Substrate	Ligand ee %[a]						
	13	**14**	**17**	**18**	**20**	**21**	**24**
 **25a**	**c** 98	**a** 98	99	**a–b** 99	**b,g** 99	**a** 94 (35)	78
 **25b**	**c** 99	**a** 89	99	**b** 99	**d** 94	**a** 94	–
 **25c**	–	**c** 96	92	**a** 95	**f** 88	**a** 43 (18)	–
 **25d**	**c** 95	**b** 96	96	–	**e** 83	**a** 97	89 (95)
 **25e**	–	**b** 96	93	**b** 92	–	**a** 45 (5)	99
 **25f**	**a** 88	**a** 95	99	**b** 99 (85)	**c** 98	**a** 55 (10)	82

[a] All conversions less than 99% are noted under the enantioselectivity in brackets

range of acceptable enantioselectivity, no single catalyst can be said to be generally applicable to all olefins. The current trend is toward good selectivity in a given class of substrates with modifications to many of the existing scaffolds in an attempt to improve selectivity for important targets.

Many similarities to the classic PHOX ligand **5a–c** are clearly visible from the given ligand list in Fig. 5. As indicated by NMR and computational studies (see Sect. 2.2 and 2.3), the coordinated olefin takes a position in a trans orientation from the soft donation moiety (i.e., phosphorus or carbene substituent) and adjacent to the nitrogen atom. In the PHOX system, this places the olefin into close proximity with the stereogenic center of the ligand to create a well-defined chiral environment. Ring size of the metallacycle plays an extremely important role in governing catalyst reactivity. Catalysts derived from ligands **8a–f** and **10a–d** are some of the most selective catalysts known for unfunctionalized trisubstituted olefins [32, 34–37].



5a R^1 = Ph R^2 = *i*-Pr
5b R^1 = *o*-Tol R^2 = *t*-Bu
5c R^1 = Ph R^2 = *t*-Bu
ref [5, 6, 11-19, 63-64, 76, 97]

6a Ar = Ph R^2 = Bn R^3 = Ph
6b Ar = Cy R^2 = Bn R^3 = Ph
6c Ar = *o*-Tol R^2 = Bn R^3 = Ph
6d Ar = Ph R^2 = Me R^3 = Ph
6e Ar = Ph R^2 = Bn R^3 = 3,5-di-CH_3-C_6H_3
6f Ar = Ph R^2 = Bn R^3 = 3,5-di-*t*-Bu-C_6H_3
ref [39-40, 68, 76, 78]

7a R^1= *t*-Bu R^2 = *o*-Tol
7b R^1= *i*-Pr R^2 = *o*-Tol
7c R^1= *i*-Pr R^2 = Ph
7d R^1= *t*-Bu R^2 = Ph
ref [38, 46, 76]

8a n = 1 R^1 = Ph R^2 = *t*-Bu R^3= H
8b n = 1 R^1 = Ph R^2 = *o*-Tol R^3= H
8c n = 2 R^1 = Ph R^2 = *o*-Tol R^3= H
8d n = 1 R^1 = Ph R^2 = *t*-Bu R^3= Me
8e n = 1 R^1 = Ph R^2 = *o*-Tol R^3= Me
8f n = 2 R^1 = Ph R^2 = *o*-Tol R^3= Me
ref [34-37, 47, 48]

9
ref [11-14, 33, 54-59, 72]

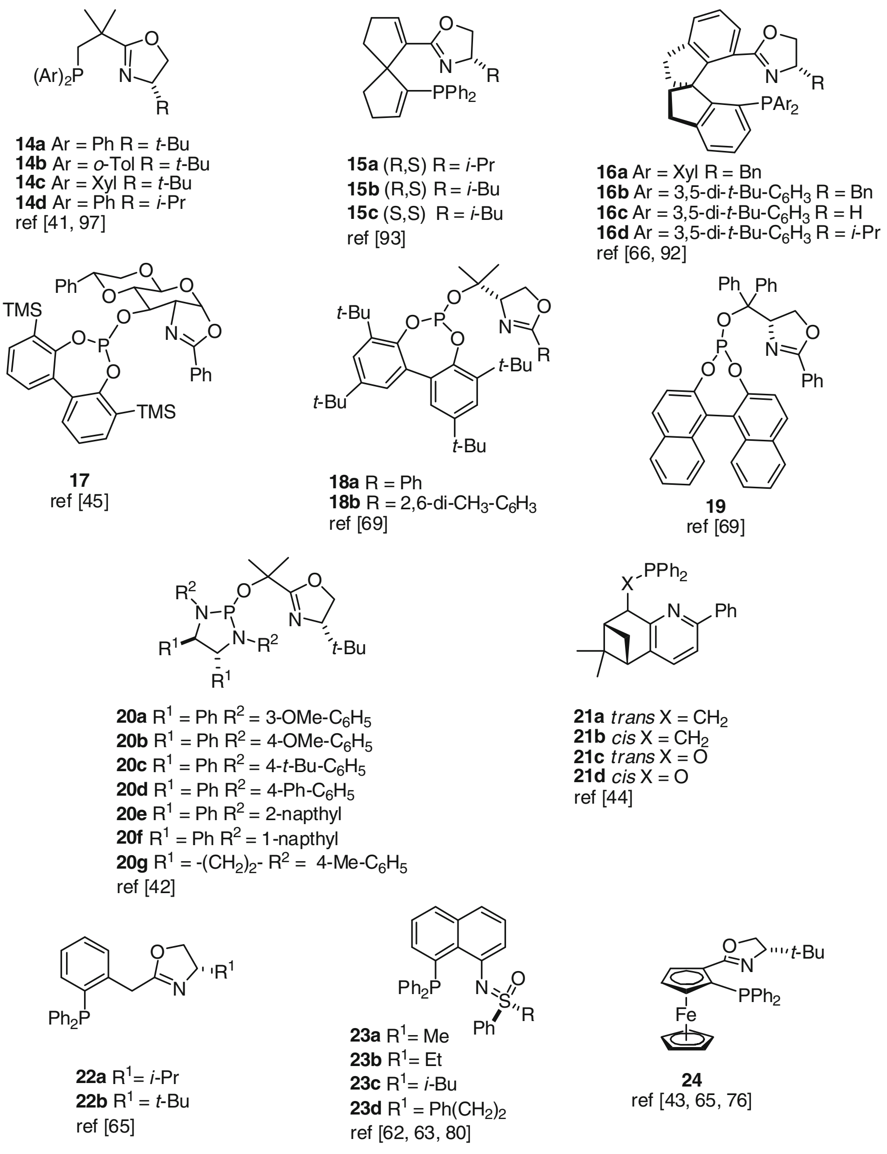
10a n= 1
10b n= 2
10c n= 3
10d n= 2 Ph = *o*-Tol
ref [11-14, 48]

11a Ar = Ph
11b Ar = *o*-Tol
ref [11-14]

12a R^1 = Ph R^2 = *i*-Pr
12b R^1 = Cy R^2 = CH_2-*t*-Bu
12c R^1 = Cy R^2 = Ph
12d R^1 = Cy R^2 = Bn
12e R^1 = *o*-Tol R^2 = *i*-Pr
12f R^1 = Ph R^2 = CH_2-*t*-Bu
12g R^1 = Adm R^2 = Ph
12h R^1 = Adm R^2 = *t*-Bu
ref [60-61, 70]

13a R^1 = Ph R^2 = H, R^3 = *i*-Pr
13b R^1 = *o-Tol* R^2 = H, R^3 = *i*-Pr
13c R^1 = Ph R^2 = Ph R^3 = Ph
13d R^1 = Ph R^2 = H, R^3 = *t*-Bu
ref [48, 53, 73, 75, 88-89, 95]

Fig. 5 continued



14a Ar = Ph R = *t*-Bu
14b Ar = *o*-Tol R = *t*-Bu
14c Ar = Xyl R = *t*-Bu
14d Ar = Ph R = *i*-Pr
ref [41, 97]

15a (R,S) R = *i*-Pr
15b (R,S) R = *i*-Bu
15c (S,S) R = *i*-Bu
ref [93]

16a Ar = Xyl R = Bn
16b Ar = 3,5-di-*t*-Bu-C_6H_3 R = Bn
16c Ar = 3,5-di-*t*-Bu-C_6H_3 R = H
16d Ar = 3,5-di-*t*-Bu-C_6H_3 R = *i*-Pr
ref [66, 92]

17
ref [45]

18a R = Ph
18b R = 2,6-di-CH_3-C_6H_3
ref [69]

19
ref [69]

20a R^1 = Ph R^2 = 3-OMe-C_6H_5
20b R^1 = Ph R^2 = 4-OMe-C_6H_5
20c R^1 = Ph R^2 = 4-*t*-Bu-C_6H_5
20d R^1 = Ph R^2 = 4-Ph-C_6H_5
20e R^1 = Ph R^2 = 2-napthyl
20f R^1 = Ph R^2 = 1-napthyl
20g R^1 = -$(CH_2)_2$- R^2 = 4-Me-C_6H_5
ref [42]

21a *trans* X = CH_2
21b *cis* X = CH_2
21c *trans* X = O
21d *cis* X = O
ref [44]

22a R^1= *i*-Pr
22b R^1 = *t*-Bu
ref [65]

23a R^1= Me
23b R^1= Et
23c R^1= *i*-Bu
23d R^1 = $Ph(CH_2)_2$
ref [62, 63, 80]

24
ref [43, 65, 76]

Fig. 5 Frequently used N,P and C,N ligands

While they have proven very selective for trisubstituted olefins, they fail to produce high selectivity or reactivity with the substrate classes of tetrasubstituted olefins, terminal olefins, and 1,3-dienes.

The catalyst derived from ligand **9** perform well with several classes of olefins albeit with slightly lower enantioselectivities in reduction of trisubstituted olefins, but are remarkably reactive toward 1,3-dienes [11, 33]. Further examples of the size of the iridium metallacycle controlling selectivity and reactivity comes from the substrate profile of the five-membered iridium chelates from ligands **12a–e,** which reduce tetrasubstituted olefins under mild conditions and high conversions but give unacceptable enantioselectivity with less-substituted olefins [13].

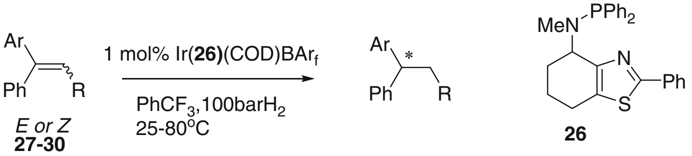
On consultation of Table 1, it becomes apparent that small changes in overall geometry about the metal center as well as the donation capabilities to the metal center can have a drastic effect on the selectivity. PHOX ligand **5b** compared with the later permutation of SimplePHOX ligand **7a** has the same 4-tert-butyl-4,5-dihydrooxazole moiety as a stereo-defining group and nearly the same steric environment about the phosphorus atom, yet they give drastically different enantioselectivity. ThrePHOX **6a–f** ligands are highly selective and active catalysts which incorporate effective modifications on the PHOX progenitor. In comparison to both PHOX and the later derivative SimplePHOX, the stereochemistry of ThrePHOX has been moved to the center of the backbone and transmits chirality to both sides of the chelate [38–40].

Other features of note are observed when the phosphinite group of SimplePHOX is replaced by a phosphine in the newer NeoPHOX ligand **14a–c**, resulting in some small improvements in enantioselectivity but with the added advantages of a phosphine over the more reactive phosphinite [41]. The lack of overall changes to selectivity for these simple substrates may reflect that the alteration in overall geometry, most importantly the bite angle, matters more to reactivity than electronic changes to the soft donor group. Ligands **20a–b** provide reasonable selectivity but actually less than the parent SimplePHOX and at a cost of a more complicated synthesis, a strong indication that optimal interactions were disrupted by the excess chiral and steric encumbrance [42].

Other examples of adding too much bulk in the context of the general substrates come in the form of ligand **24** [43]. While the ligand maintains many of the stereochemical features of ligand **5c,** the added bulk leads to much lower enantioselectivities and conversion by disrupting interactions necessary for substrate binding. Similar effects are seen with ligands **21a–d**, which are closely related to the very active catalysts derived from **8a–c**, **10a–d**, and **11a–b**, with the exception of the deleterious addition of extra ring rigidity and steric encumbrance from the carbon bridge [44].

While Table 1 is an important tool for many of the studies, the current trend is to elaborate more the increasingly difficult substrates within a particular class of olefins. Andersson and coworkers have published several variations of the 1, 2-diaryl substrate **25a** for the fairly more difficult 1,1′diaryl class of trisubstituted olefins (Scheme 3) [45]. The authors note that the products form an important class of compounds that are pharmaceutically relevant and difficult to prepare by other available methods.

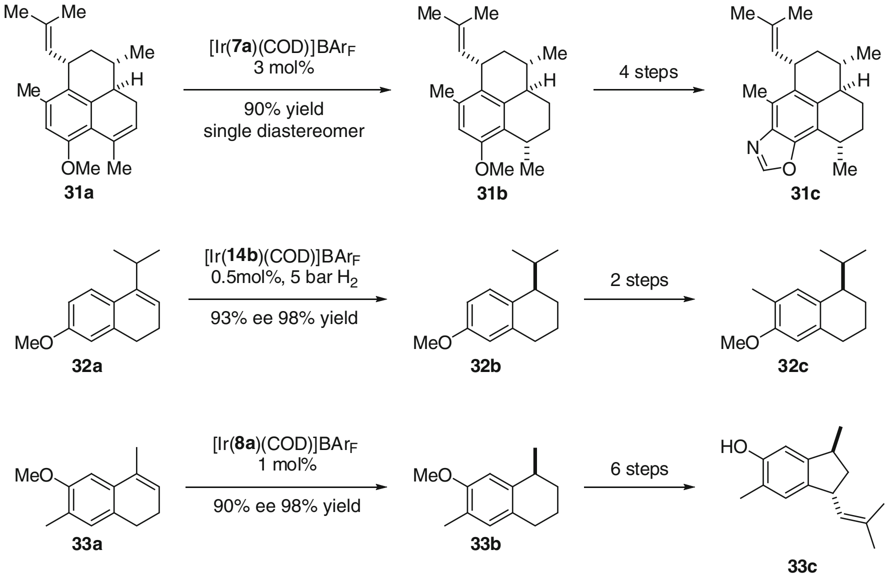
Reduction of all of the reported geminal diaryl substrates was completely under the control of the third stereo defining R-group. Particularly difficult were the sterically demanding **29** and the electron poor olefin **30**, both of which required heating to produce poor to moderate yields.



(*E*)-**27:** Ar = 4-Br-C_6H_4 R=Me: 95% ee (*S*) (*E*)-**28:** Ar = 4-Br-C_6H_4 R=n-pent: 99% ee (+)
(*Z*)-**27:** Ar = 4-Br-C_6H_4 R=Me: 99% ee (*R*) (*Z*)-**28:** Ar = 4-Ph-C_6H_4 R=n-pent: 99% ee (–)

(*E*)-**29:** Ar= 2-Me-C_6H_4 R= Ph: 92%ee (+) 35% Conv L = **10b**
(*E*)-**30:** Ar= 4-CF_3-C_6H_4 R= Ph: 76% ee (*S*) 48% Conv

Scheme 3 Asymmetric hydrogenation of geminal-diaryl substrates



Scheme 4 Use of Ir N, P based asymmetric hydrogenation in total synthesis

The reduction of simple trisubstituted olefins derived from **25d** has found use in the enantioselective total synthesis of pseudopteroxazole **31c**, demethyl methoxycalamenene **32c**, and both enantiomers of mutisianthol **33c** (Scheme 4) [41, 46, 47].

SimplePHOX **7a** proved a useful tool to force the diastereomeric reduction of olefin **31a** to pseudopteroxazole precursor **31b** in perfect diastereoselectivity and 90% yield with only trace amounts of over-reduced product. NeoPHOX catalyst from ligand **14b**, a closely related system to **7a**, furnished product **32b** in 93% ee, which was then easily recrystallized to enantiopure material with 58% recovery. The *R* enantiomer of **33b** was synthesized by the use of catalyst from ligand **8a** in 90% ee and 98% yield with the fully aromatized naphthalene as 2% byproduct. A higher catalyst loading of 2 mol% of catalyst from **7a** was used to produce the

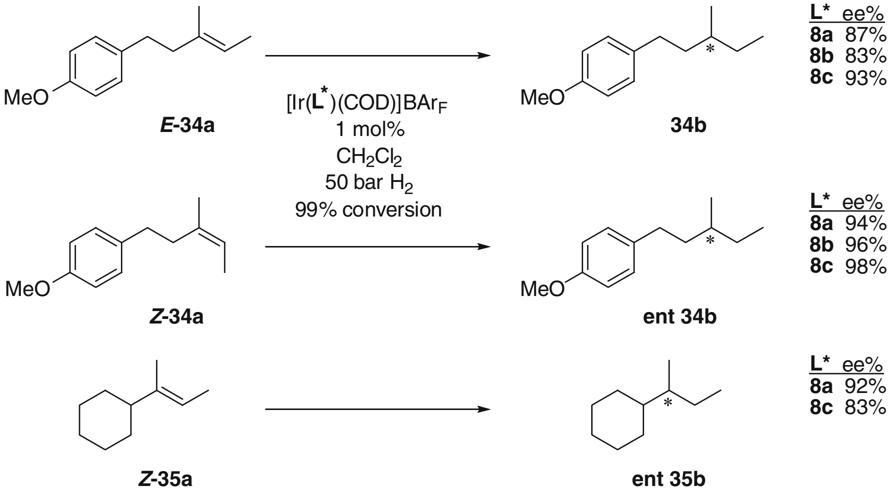
S enantiomer in 80% ee with 13% of the fully aromatized naphthalene byproduct occurring even when using 50 bar of hydrogen pressure. Lower catalyst loadings gave increased amounts of aromatization byproduct and lower enantioselectivity.

Asymmetric hydrogenation of cyclic olefins is not the sole application of this methodology in synthesis, and the current trend in research is to use these catalysts in building more elaborately functionalized molecules.

3.2 Asymmetric Hydrogenation of Purely Alkyl Substituted Olefins

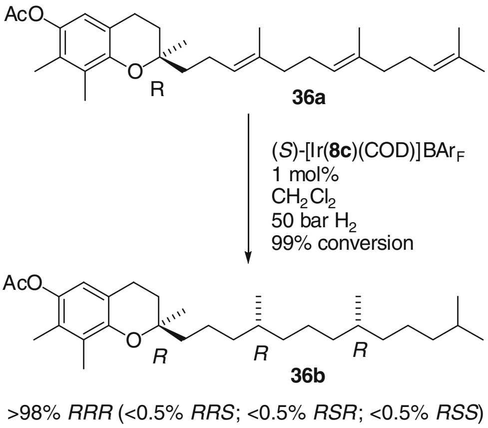
The development of chiral homogeneous catalysts with the capacity to reduce purely alkyl-substituted olefins with high asymmetric induction and yield has been a long-standing problem. Most iridium catalysts that perform well with nothing more coordinating than a phenyl group adjacent to the olefin fail to give good asymmetric induction in the absence of an aromatic substituent in close vicinity to the C=C bond [11–14].

As a first step to solving this problem, Bell et al. started an active screening project utilizing *E* and *Z* isomers of compound **34a** as a model (Scheme 5) [36]. Although **34a** contains an aromatic substituent for analytical purposes, the functional group has been moved three bonds away from the carbon–carbon double bond. If any coordination took place through this remote site the effect was expected to be weak. Out of the screening effort, pyridine phosphinite ligands **8a–c** were identified as excellent ligands giving high enantioselectivity and

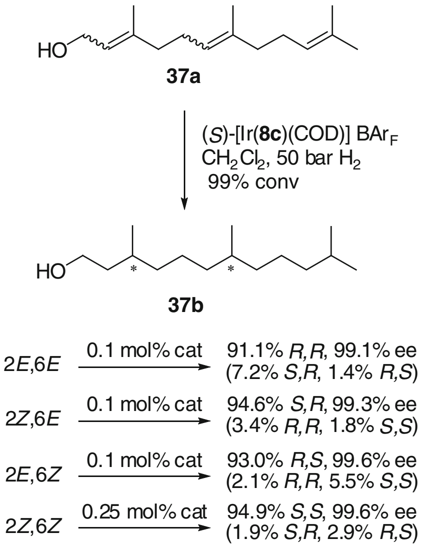


Scheme 5 Test substrates in the asymmetric hydrogenation of purely alkyl substituted alkenes

Scheme 6 Asymmetric synthesis of γ-tocopherol from the triene



Scheme 7 Total stereocontrol in the asymmetric reduction of farnesol isomers



conversion. Both *E* and *Z* isomers gave acceptable enantioselectivity. As observed in other cases, the *E* and *Z* isomers were converted to opposite enantiomers. In order to rule out any small interactions from the distal aromatic ring, the completely alkyl-substituted olefin **35a** was reduced under standard conditions. Fittingly, ligand **8a** provided the branched chiral alkane **35b** in 92% enantioselectivity.

Because *cis* and *trans* olefins are converted to products of opposite configuration, it becomes possible to introduce two or more stereogenic centers with the desired relative and absolute configuration in a single step through hydrogenation of a di- or polyene by adjusting the geometry of the individual C=C bonds. This is demonstrated by the highly enantio- and diastereoselective preparation of γ-tocopherol **36b,** a component of vitamin E, from γ-tocotrienyl acetate **36a** (Scheme 6).

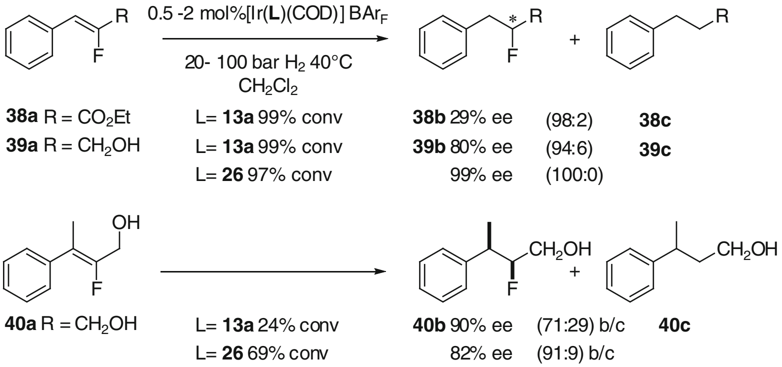
In a subsequent publication, the fully optimized stereospecific synthesis of each individual diastereomer and its corresponding enantiomer with catalyst loadings of **8c** from 0.1 to 0.25 mol% was reported (Scheme 7) [37]. Electron withdrawing protecting groups attached to the allylic alcohol slowed down the reaction rate and higher catalyst loadings were required to achieve full conversion. The authors conducted a grams scale synthesis of (*R*,*R*)-**37b** in comparable yield and enantioselectivity to the test reactions, illustrating the practicality of this approach.

3.3 Asymmetric Hydrogenation of Fluorinated Olefins

Chiral organofluorides are increasingly in demand as the pharmaceutical and materials industries seek to take advantage of the special properties these halides impart. A lack of methods to provide chiral monofluorides and trifluoromethyl groups has given the group of Andersson impetus to create new asymmetric hydrogenation routes to these valuable halides [48, 49].

A brief scope of α-fluorocinnamic acid derivatives with both trisubstituted and tetrasubstituted C=C bonds were reduced with mixed results (Scheme 8) [48]. The vinyl fluorides proved extremely difficult for catalysts that usually perform superbly on more frequently studied substrates. Elevated temperatures and pressures were required to obtain moderate to good conversions with closely related substrates. A struggle with dehalogenation occurred with the harsher conditions required for this difficult reaction. The group noticed that phosphoramide ligands **13a–c** gave lower amounts of dehalogenation and new phosphoramide **26** was developed by the group to incorporate the best of both of their original ligands (Fig. 6). This catalyst gave improved enantioselectivity and less dehalogenation (Scheme 8).

Evidently, vinylfluorides represent a new challenge to iridium asymmetric hydrogenation. It is noteworthy that no examples of asymmetric reduction of



Scheme 8 Asymmetric hydrogenation of vinyl fluorides

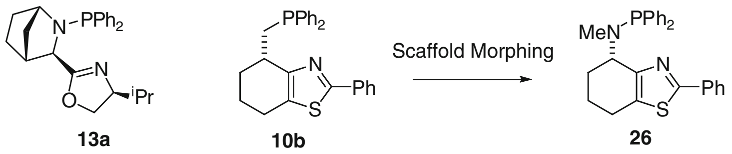
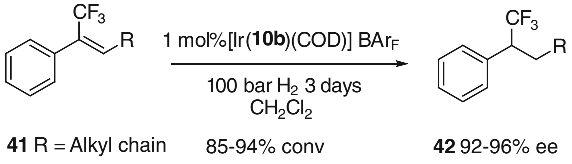
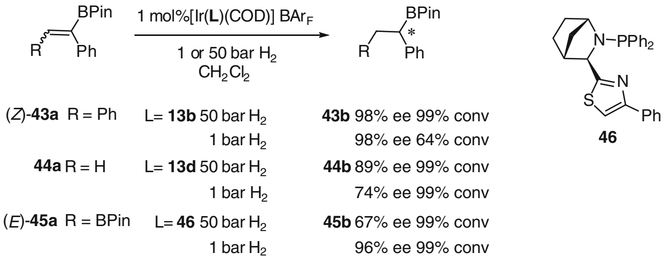


Fig. 6 Scaffold morphing to improve dehalogenation profile

Scheme 9 Asymmetric hydrogenation of trifluoromethyl alkenes





Scheme 10 Asymmetric hydrogenation of vinyl boronic esters

vinyl fluorides without adjacent coordinating groups have been reported in the literature [14].

Trifluoromethyl-substituted olefins appear to also be problematic substrates for asymmetric hydrogenation as very long amounts of time and high pressures were required to achieve appreciable yields with ligand **10b** (Scheme 9) [49]. Nevertheless, useful yields and excellent enantioselectivities were obtained for most examples.

3.4 Asymmetric Reduction of Vinylboronates

Boronic esters have been used in a wide range of transformations. These useful reagents have been transformed into numerous functional groups and are essential reagents for several C–C bond-forming reactions. Transition metal-catalyzed hydroboration of olefins often leads to mixtures of branched and linear products. Several groups have reported asymmetric reductions of vinyl boronic esters [50–52] with chiral rhodium P,P complexes; however, the first iridium-catalyzed reduction was reported by Paptchikhine et al (Scheme 10) [53].

In contrast to normal trisubstituted aryl olefins, a strong pressure effect was observed in this case. Interestingly, for substrate **44a** catalysts' hydrogenation with Ir(**13d**) demonstrated opposite pressure-dependant enantioselectivity of substrate **45a** with catalyst Ir(**46**). Poor enantioselectivity was obtained for substrates that did not contain an aromatic ring adjacent to the olefin.

3.5 Diastereoselective Reduction of Alkenes

Although functional group-directed enantioselective hydrogenation tends to fall in the realm of rhodium and ruthenium catalysts, there are many examples of diastereoselective hydrogenations with Crabtree's catalyst that are controlled by coordination of the iridium center to a Lewis basic functional group (Fig. 7). When one considers that iridium catalysts do not require coordinating groups for hydrogenation activity and purely steric interactions suffice for enantioface discrimination, then protection of the directing group with a large noncoordinating moiety could reverse the direction of attack by the catalyst to create the opposite diastereomer-protected equivalent (Fig. 7).

Diastereoselective hydrogenations of this type have been reported by Burgess and coworkers [54–59] using chiral-protected and -unprotected allylic and homo allylic alcohols as substrates with their carbene catalyst Ir(**9**). Catalyst control was found to be dominant, but depending on the position and nature of the oxygen substituents, moderate to strong match/ mismatch effects were observed.

This approach has been used to synthesize a variety of valuable 1,3-deoxypolyketide chirons, 1,3-hydroxymethyl chirons, vicinal dimethyl chirons, and aldol-like products from trisubstituted olefins (Scheme 11). High diastereomeric ratios could be obtained often in greater than 90% for most cases.

A reasonably large difference in diastereomeric excess was observed between product **47b** with an adjacent methyl ester and **48b** with a primary alcohol in the equivalent position [57]. It was noted by the authors that in cases involving a 1,3 system, changing the pendant group from a primary allylic alcohol to a methyl ester caused a reversal of facial selectivity [54, 58]. The same effect was absent in the 1,2 systems **51b** and **52b** studied. The diastereomeric ratio in the latter case was attributed mainly to catalyst control [58].

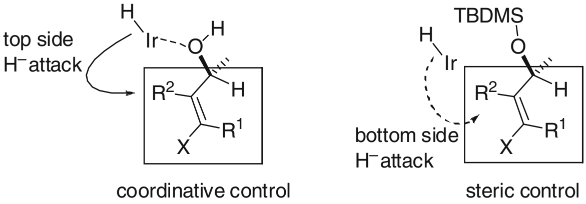
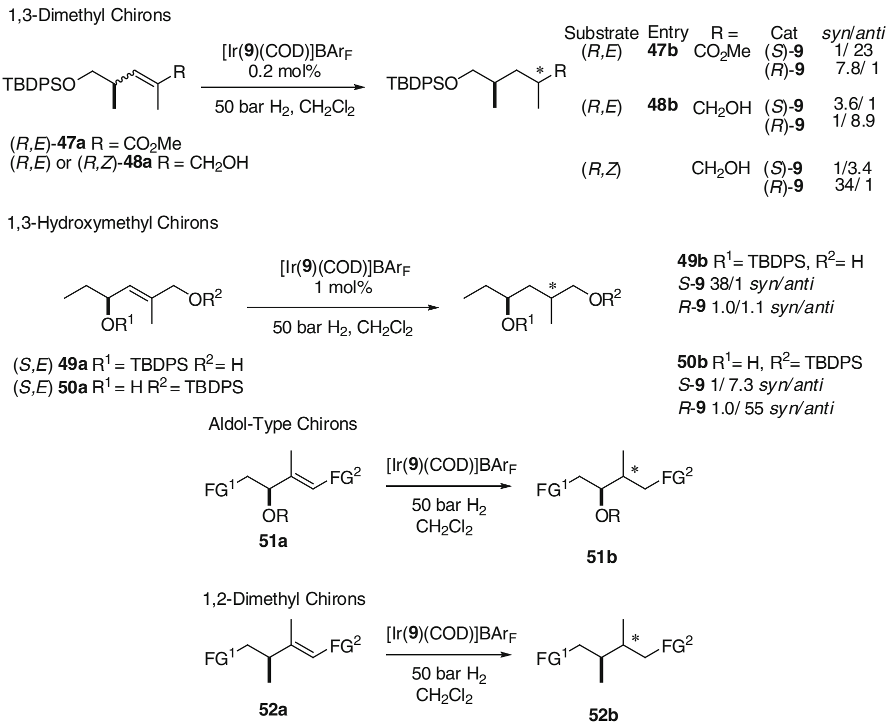
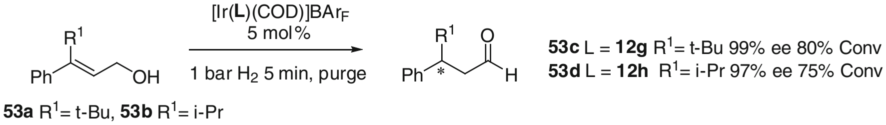


Fig. 7 Diastereoselective hydrogenation based on catalyst and substrate control



Scheme 11 Diastereoselective hydrogenation with Ir(**9**)



Scheme 12 Rearrangement of allylic alcohols

3.6 *Redox Rearrangement of Allylic Alcohols to Chiral Aldehydes*

Mazet et al. have reported an efficient asymmetric isomerization reaction of allylic alcohols [60, 61]. In a preliminary report they utilized the BAr_F analog of Crabtree's complex to efficiently catalyze a hydride transfer from the α position of the allylic alcohol to the β position of the olefin with a concomitant formation of a formyl group. A subsequent report detailed a remarkable enantioselective variant of this process catalyzed with Ir(**12g**) and (**12h**) (Scheme 12).

The iridium catalyst was activated by briefly purging the system with atmospheric pressure of hydrogen to remove the COD ligand followed by degassing the system with vacuum and inert atmosphere to avoid over reduction. High enantioselectivities were obtained in moderate to good yields with a limited range of substrates. The system studied was very sensitive to ligand geometry the five-membered metallacycles were much more efficient than six-membered analogs and bulky substrates with aromatic substituents were required for high selectivity.

3.7 Conjugate Reduction

Catalytic asymmetric conjugate reductions represent one of the most venerable and investigated reaction types in catalysis. Conjugate reductions with rhodium and ruthenium diphosphine-based catalysts have been heavily investigated and substituted α,β-unsaturated acids and esters are frequent substrates for these systems. Iridium N,P-based reductions are more recent and far less investigated but offer chemoselectivity advantages under certain circumstances [62]. Ester **25f** is the most regularly investigated conjugate reduction substrate and has been a general benchmark for evaluating the selectivity and reactivity of iridium N,P-based catalysts for many years. It has also been described that the *trans*-α-methylcinnamic esters have been particularly difficult substrates for reduction, and this has been rationalized by computational methods [32]. Nearly all systems that have been investigated are based on a cinnamic acid core with different substitution patterns about the α and β carbons. Varying degrees of electrophilic groups have been incorporated to the conjugate system such as ketones, esters, acids, amides, diphenylphosphine oxides, and phosphonates [54–59, 62–67].

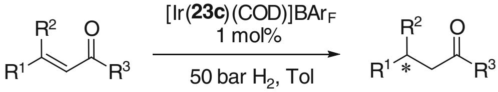
Iridium-catalyzed reduction of α,β-unsaturated ketones has been investigated most recently by the groups of Bolm and Hou, respectively.

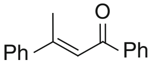
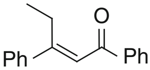
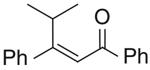
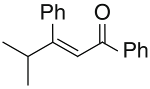
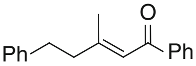
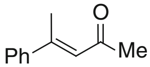
As Table 2 indicates, ligand **23c** proved effective for substrates with large, branched groups on the beta positions. The best selectivity was obtained for **54c**, which was substituted with aromatic groups on both sides of the substrate, and a large branched alkyl attached to the β position [62]. Entries **54e** and **54f** are encouraging and may indicate that this method could be extended to more broadly useful compounds. The investigators performed a solvent study and determined the reaction to be equally selective in toluene and dichloromethane; so the former was used presumably for its industrial attractiveness.

A broader range of substrates have been reduced with substitution at the α position of α,β-unsaturated ketones using ligand **5c** [63, 64].

Table 3 indicates that reduction of α substituted unsaturated ketones is extremely efficient with PHOX **5c**. Unfortunately, substrates lacking any aromatic ring within close proximity to the olefin were reportedly not reduced [64]. However, a wide range of functional groups were shown to be tolerated by Bolm et al. [63]. Most impressively, nitroaromatic compounds were well tolerated under the conditions used, highlighting the extraordinary chemoselectivity that can be obtained with iridium N,P catalysts. Perhaps one of the most productive features of these studies is the ability to create a stereogenic center with high degrees of substitution and

Table 2 Enantioselective hydrogenations of linear α,β-unsaturated ketones

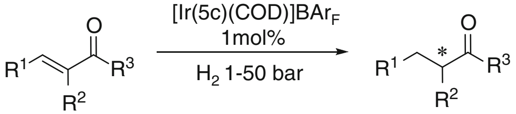


Substrate	Substrate	Yield %	ee %
54a		89	81
54b		94	89
54c		94	97
54d		86	92
54e		93	81
54f		70	79

perfect acyclic stereocontrol while maintaining an unencumbered site α to the carbonyl group for further elaboration.

Substituted α,β-unsaturated amides have also been reduced with high enantioselectivity and conversion with ligand **24** [65]. Here as well, the investigations relied heavily on substrates with adjacent aromatic rings and α substitution. Catalyst loadings were moderately higher than with other systems with 2 mol% used. Table 4 indicates that ligand **24** can tolerate a wide range of substituents on the amide nitrogen but fairs best with the more sterically demanding groups such as isobutyl or benzyl. The use of more coordinating groups such as methoxyethyl **56e** or the versatile Weinreb amide **56f** results in a moderate to severe erosion of enantioselectivity.

Table 3 Enantioselective hydrogenations of α-substituted α,β-unsaturated ketones



Substrate	R^1	R^2	R^3	Yield (Conv) %	ee %
55a	Ph	Me	Me	91[a] (100[b])	98[a] (98[b])
55b	Ph	Me	Et	91[a]	98[a]
55c	Ph	Me	Ph	96[a] (100[b])	99[a] (97[b])
55d	Ph	Ph	Me	94[a]	98[a]
55e	4-MeOC$_6$H$_4$	Et	*n*-Pr	(100[b])	(98[b])
55f	Et	Me	Ph	89[a]	87[a]
55g	H	Bn	Ph	84[a]	86[a]
55h	2-MeC$_6$H$_4$	Me	Me	89[a]	98[a]
55i	2-MeOC$_6$H$_4$	Me	Me	90[a]	99[a]
55j	2-ClC$_6$H$_4$	Me	Me	89[a]	98[a]
55k	3-MeOC$_6$H$_4$	Me	Me	93[a]	99[a]
55l	3-ClC$_6$H$_4$	Me	Me	92[a]	98[a]
55m	3-NO$_2$C$_6$H$_4$	Me	Me	91[a]	98[a]
55n	4-MeOC$_6$H$_4$	Me	Me	97[a]	98[a]
55o	4-ClC$_6$H$_4$	Me	Me	92[a]	99[a]
55p	4-NO$_2$C$_6$H$_4$	Me	Me	88[a]	99[a]

[a] Hydrogenations were carried out in toluene [63]

[b] Hydrogenations were carried out in dichloromethane [64]

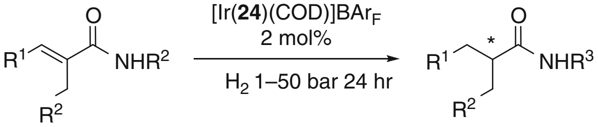
Some of the more sterically demanding substrates such as **56h** were reduced with a moderate loss of enantioselectivity.

Recently developed ligand SIPHOX **16a–d** proved to be a valuable tool in the asymmetric reduction of α,β-unsaturated acids [66]. In a complete break with what is typically observed with iridium-based N,P ligands, SiPHOX catalysts were observed to reduce the strongly coordinating carboxylic acid triethylamine salt of α methylcinnamic acid in excellent enantioselectivity and yield (Table 5). Equally surprising is the use of methanol as a solvent, which normally inhibits reductions mediated by iridium N,P catalysts.

Table 5 indicates an extremely efficient catalyst with very low catalyst loadings for such a highly coordinating environment. Functional group tolerance appears to be excellent with groups as reactive as arylbromides being converted in close to perfect yield.

Cesium carbonate was found to be a far more efficient additive for purely alkyl-derived substrates **57r–w**. Very useful enantioselectivities were obtained for all entries with the exception of a tertiary isobutyl-derived alkene **57u**, which was converted with a respectable 90% ee. The yields were slightly lower for purely alkyl-derived substrates, but full conversions were reported by the authors.

Table 4 Asymmetric hydrogenation of α-substituted α,β-unsaturated amides with ligand **24**



Substrate	R^1	R^2	R^3	ee %
56a	Ph	Me	Ph	96
56b	Ph	Me	n-Bu	84
56c	Ph	Me	*i*-Bu	93
56d	Ph	Me	Bn	95
56e	Ph	Me	$(CH_2)_2OMe$	90
56f	Ph	*t*-Bu	*i*-Bu	96
56g	Ph	Bn	*i*-Bu	97
56h	Ph	2-Napht	*i*-Bu	87
56i	$3\text{-}ClC_6H_4$	Et	*i*-Bu	98
56j	$4\text{-}MeOC_6H_4$	Et	*i*-Bu	96[a]
56k	Ph	Et	*i*-Bu	97
56l	Ph	*i*-Pr	*i*-Bu	96
56m	Ph	*n*-Bu	*i*-Bu	95
56n	Ph	MeO	*i*-Bu	95
56o	*i*-Pr	H	Bn	93
56p	*n*-Pr	H	Bn	84
56q	*i*-Bu	H	Bn	87
56r	Me	H	Ph	95
56s	Ph	Me	OMe, Me	75[b]

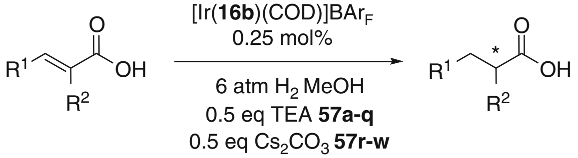
[a] 3 Mol% of catalyst was used
[b] Weinreb amide

Scheme 13 depicts an interesting application of this methodology in the synthesis of a crucial intermediate for the blood pressure-lowering drug Aliskiren with the less-encumbered ligand **16c**. In the presence of excess amounts of triethylamine, **58b** was produced in 96% yield and 98% ee. Catalyst loadings were optimized at 0.016 mol% or S/C ratio of 6,000. At S/C ratio of 10,000, a slight loss of enantioselectivity and yield was noticed.

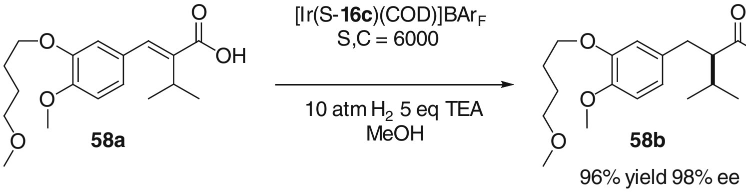
Vinyl phosphine oxides and phosphonates are highly electron-deficient and can undergo conjugate reduction much like their carbonyl counter parts. The group of Andersson has reported an enantioselective reduction of both to yield chiral phosphine oxides and phosphonates (Table 6) [67].

The authors did not report on trisubstituted diphenylphosphine oxides, but apparently, the results are excellent with what is usually a difficult 1,1′ unsubstituted pattern about the olefin. The investigation found near perfect selectivity and yields for most of the reported compounds when using **26** as a ligand. However, a very slow reaction was noted for the *E* olefin **59h** while hydrogenation of *E* configured olefin **59j** preceded smoothly, indicating a delicate balance between structure and reactivity. Other anomalous behavior of the substrates **59h–j** is that both *E*- and *Z*-configured olefins produce the same enantiomer.

Table 5 Asymmetric hydrogenation of cinnamic and tiglic acid derivatives



Substrate	R^1	R^2	Yield %	ee %
57a	Ph	Me	99	99.2
57b	2-MeC$_6$H$_4$	Me	97	99
57c	3-MeC$_6$H$_4$	Me	98	99
57d	4-MeC$_6$H$_4$	Me	98	99
57e	2-MeOC$_6$H$_4$	Me	98	99
57f	3-MeOC$_6$H$_4$	Me	99	98
57g	4-MeOC$_6$H$_4$	Me	97	99
57h	2-ClC$_6$H$_4$	Me	97	96
57i	3-ClC$_6$H$_4$	Me	98	99
57j	4-ClC$_6$H$_4$	Me	97	98
57k	3-BrC$_6$H$_4$	Me	97	99
57l	4-BrC$_6$H$_4$	Me	97	98
57m	4-CF$_3$C$_6$H$_4$	Me	98	97
57n	2-naphthyl	Me	96	99
57o	furan-2-yl	Me	98	98
57p	Ph	*i*-Pr	97	99
57q	Ph	Ph	95	94
57r	Me	Me	92	99.1
57s	Et	Me	93	98
57t	*n*-Pr	Me	89	99
57u	*i*-Bu	Me	97	90
57v	*n*-Pr	Et	89	99.4
57w	Me	*n*-Pr	92	98

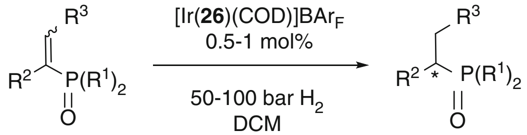


Scheme 13 Asymmetric hydrogenation of an intermediate of aliskiren

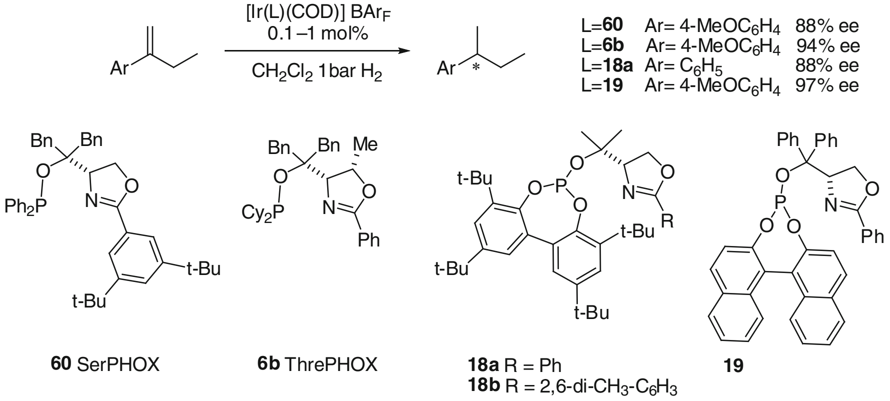
4 Asymmetric Hydrogenation of 1,1′-Disubstituted Olefins

1,1′-Disubstituted olefins are a challenging substrate class when compared to the more widely investigated trisubstituted olefins. Although they react very quickly, obtaining high enantioselectivity with most ligands has been problematic. Blankenstein and Pfaltz reported the first iridium N,P-based catalyst capable of reducing

Table 6 Asymmetric reduction of vinyl diphenylphosphine oxides and phosphonates



Substrate	R^1	R^2	R^3	Conv %	ee %
59a	Ph	Ph	H	99	99
59b	Ph	4-MeOC$_6$H$_4$	H	99	99
59c	Ph	4-CF$_3$C$_6$H$_4$	H	93	99
59d	Ph	2-MeC$_6$H$_4$	H	99	99
59e	Ph	C$_6$H$_{11}$	H	99	99
59f	Ph	*t*-Bu	H	98	90
59g	Ph	CH$_2$CH$_2$OH	H	99	99
59h	OEt	Ph	*E*-CO$_2$Et	10	90
59i	OEt	Ph	*Z*-CO$_2$Et	99	99
59j	OEt	Bn	*E*-CO$_2$Et	99	99
59k	OEt	Ph	H	99	99
59l	OEt	CH$_2$CH$_2$OAc	*E*-CO$_2$Et	99	99

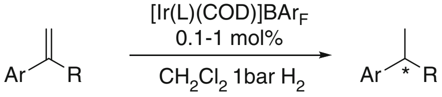


Scheme 14 Reduction of 1,1′ disubstituted alkenes

1,1′-disubstituted olefins in useful selectivity with SerPHOX **60** (Scheme 14) [38]. The authors discovered a very strong dependence on hydrogen pressure with the highest selectivity obtained at atmospheric pressure of hydrogen. The later developed catalyst Ir(**6b**) was found to give higher enantioselectivities and is now commercially available as the BAr$_F$ COD complex [68].

A large combined research effort of the three groups of Diéguez, Andersson, and Börner initiated a combinatorial study utilizing the SerPHOX and ThrePHOX backbones in combination with a chiral biarylphosphinite moiety, ligands **18** and

Table 7 Asymmetric reduction of 1,1′-disubstituted olefins



Substrate	L	Ar	R	Conv %	ee %
61a	**19**	Ph	Et	100	99
61b	**19**	4-MeOC$_6$H$_4$	Et	100	99
61c	**19**	4-CF$_3$C$_6$H$_4$	Et	100	96
61d	**19**	Ph	*n*-Bu	100	94
61e	**19**	Ph	*i*-Bu	100	93
61f	**19**	Ph	neopentyl	100	90
61g	**19**	Ph	i-Pr	100	97
61h	**19**	Ph	cyclohexyl	100	97
61i	**19**	Ph	*t*-Bu	100	99
61j	**18a**	2-furyl	*n*-Bu	100	99
61k	**19**	2-thienyl	*n*-Bu	100	96
61l	**19**	2-pyridyl	Et	100	99
61m	**19**	2-pyridyl	*t*-Bu	100	99
61n	**18b**	Ph	2-naphthyl	100	99[a]
61o	**18b**	Ph	2-MeC$_6$H$_4$	99	99[a]
61p	**19**	4-CF$_3$C$_6$H$_4$	4-MeOC$_6$H$_4$	100	63[a]
61q	**19**	Ph	CH$_2$OH	100	95[a]
61r	**19**	Ph	CH$_2$OAc	100	91[a]
61s	**19**	Ph	CH$_2$TMS	100	96[a]
61t	**19**	4-MeOC$_6$H$_4$	CF$_3$	100	75[a]

[a] Reaction was run at 50 bar hydrogen

19 [69, 94]. A library of 96 possible phosphite oxazoline ligands was synthesized with systematic changes to the backbone and with special attention to the biaryl phosphite group.

Ligand **19** was found to be highly selective for the hydrogenation of 1-aryl, 1′-alkyl alkenes, and ligand **18b** was found to be selective for 1-aryl, 1′-hindered aryl alkenes (Table 7).

Ligand **19** performs excellently with the wide variety of 1,1′-disubstituted olefins reported. Substrates **61a–m** are efficiently reduced at 1 bar of hydrogen in high enantioselectivity with very little dependence on the bulk of the alkyl substituents. Strongly coordinating olefins such as **61l** and **61m** typically perform poorly in iridium-catalyzed hydrogenations, but reduction with **19** clearly breaks this rule and the substrates are reduced in excellent selectivity and yield.

The more sterically demanding **61n–o** were easily reduced by Ir(**18b**), perhaps due to a more open and accommodating catalyst structure. Other changes to note are the higher pressure (50 bar) required to reduce the chelating substrates **61q–r**, the hindered **61s**, and the electron poor **61t**. The diarylmethylene substrate **61p** reveals that enantioface discrimination is also possible based on electronic rather than steric effects. Both aryl groups have very similar steric demands but distinguish themselves by their π donor and π acceptor properties. The remarkable ee of

63% may be explained by the different interaction of the iridium center with the electron-poor and the electron-rich aryl groups and/or alignment of the catalyst dipole with the substrate dipole created by electron donor and acceptor groups.

5 Asymmetric Hydrogenation of Tetrasubstituted Olefins

Tetrasubstituted olefins remain a challenging class of substrate. Buchwald and coworkers have shown that chiral zirconocene complexes can catalyze the hydrogenation of tetrasubstituted olefins with high enantioselectivity [7, 8]. However, high catalyst loadings, long reaction times, and high pressures are a disadvantage of this system.

Schrems et al. identified a number of P,N ligands, which have given encouraging results for this class of substrate [70]. Surprisingly, the structurally simple readily accessible phosphinooxazoline **12a**, originally reported by Sprinz and Helmchen [71], and subsequent analogs **12b–e** proved to be the most efficient ligands for several substrates (Table 8).

For a few select cases, the cyclic alkene **62a–c** with simple primary alkyls as substituents were readily hydrogenated with SimplePHOX ligand **7a** and **7c**. Importantly, no epimerization at the benzylic position was observed, and hydrogenation gave entirely *cis* product with most substrates. Aromatization of the dihydronapthelene substrates **63a–b** was a frequent side reaction, even at high pressures.

For some substrates, a dependence of enantioselectivity on pressure was observed with low to moderate pressures being optimal for many combinations. Ligand **12c** in combination with substrate **62a** gives an enantioselectivity of 92% at 50 bar of pressure and 97% at 1 bar, similar to the trend found in the early studies of the 1,1′-disubstituted substrates.

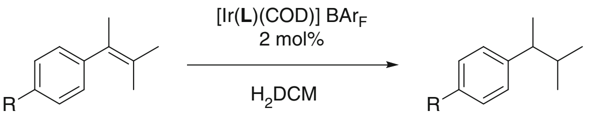
Yet even more important is the observation that ligands with identical configurations gave products of opposite configuration solely on the basis of the substituent on the stereogenic center. For instance, ligand S-**12a** gives the (−) reduction product of **63a** in 65% ee at 50 bar, and changing the ligand to S-**12f** under identical reaction conditions gives the (+) product in 39% ee. Clearly, the critical interactions with these catalysts and substrates are highly subject to the extremely crowded environment about the metal center and very small changes to either the substrate or ligand can lead to large changes in overall selectivity and yield.

Mastery of tetrasubstituted olefins greatly expands the tools available for the synthesis of chiral carbon skeletons and tetrasubstituted olefins have the added value of possibly creating two stereogenic centers simultaneously.

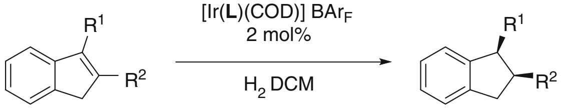
6 Asymmetric Hydrogenation of Trisubstituted Olefins with Heteroatoms

Asymmetric hydrogenation of a C=C bond with a heteroatom substituent leads to highly valued chirons which can often be elaborated into more complex functionalized molecules. Most asymmetric hydrogenation routes to these chirons have

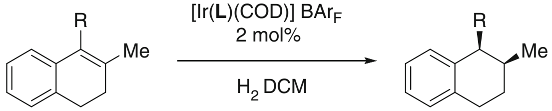
Table 8 Asymmetric reduction of tetrasubstituted olefins



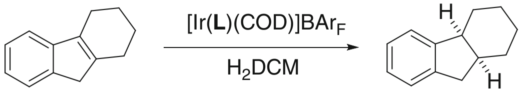
Substrate		R	L	P (bar)	t (h)	ee %	Conv %
61a	–	MeO	**12c**	1	4	97	99
61b	–	F	**12d**	5	4	89	99



Substrate	R^1	R^2	L	P (bar)	t (h)	ee (%)	Conv (%)
62a	Me	Me	**12a**	5	4	94	99
			7c	5	4	95	99
62b	Et	Me	**12a**	50	4	93	99
			7a	50	4	94	98
62c	*n*-Bu	Me	**12a**	50	4	94	99
			7a	50	4	95	97
62d	Ph	Me	**12a**	5	4	95	99
62e	Me	Ph	**12a**	50	4	88	20
62f	Et	Ph	**12a**	50	4	93	23



Substrate		R	L	P (bar)	t (h)	ee %	Conv %
63a	Me	Me	**12a**	50	4	73	99
	Me	Me	**6a**	5	4	77	46
63a	Ph	Me	**12b**	5	4	91	32



Substrate	L	P (bar)	mol%	ee %	Conv %
64	**5a**	50	2.0	94	99
		50	1.0	93	99
		50	0.5	93	99
		50	0.1	90	99
	12e	5	2.0	96	99

relied on ruthenium or rhodium diphosphine complexes [1–4, 11]. Iridium N,P and C,N complexes are the newest addition to catalysts capable of asymmetric hydrogenation of heteroatom-substituted olefins, and in spite of the typical sensitivity of the complexes toward Lewis bases, many successful hydrogenations of such olefins have been reported in the recent literature. Indoles, enamines, enol esters, enol ethers, chromenes, furans, quinolines, and pyridines have all been successfully reduced with useful enantioselectivities using chiral iridium complexes and each shall be touched upon in the following section.

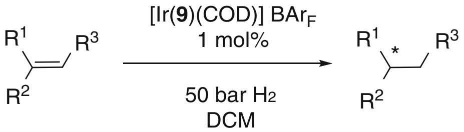
6.1 Enol Esters and Ethers

Zhu and Burgess have reported an asymmetric conjugate reduction of 1,3-enol ether esters (Table 9) and 1,3-enol ether alcohols (Table 10) [72]. Initial reaction conditions reached full conversion of *E*-1-methoxy-1-phenylethene using ligand **9** albeit with a very low enantioselectivity of 29%.

Asymmetric hydrogenation of **65a–h** with ligand **9** indicates a difficult reaction. Enantioselectivities are moderate to good with the best selectivity for the amide **65g**. Strong steric effects were observed with increasing the size of the ester giving an increase in ee. The steric crowding at the alkoxy bearing C atom was also observed to have a large effect on the enantioselectivity. Substituents larger than methoxy groups greatly eroded the selectivity as observed for the ethoxy ether **65e**. Secondary alkyl groups were completely deleterious to hydrogenation activity with an abysmal conversion of 15% for substrate **65f**.

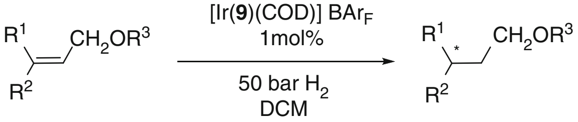
Asymmetric hydrogenation of vinyl ether alcohols proceeded in better selectivity than the ester counterparts, but acid sensitivity was observed for **66a–d**, and a stoichiometric equivalent of potassium carbonate relative to the substrate was

Table 9 Asymmetric hydrogenation of vinyl ether esters



Substrate	R^1	R^2	R^3	Conv %	ee %
65a	Me	OMe	CO_2H	99	63
65b	Me	OMe	CO_2Me	85	60
65c	Me	OMe	CO_2Et	99	78
65d	Me	OMe	CO_2-*t*-Bu	99	88
65e	Me	OEt	CO_2Et	99	66
65f	OMe	*i*-Pr	CO_2Me	15	nd
65g	Me	OMe	$CO_2NEtOMe$	90	90
65h	Me	OMe	COPh	5	nd

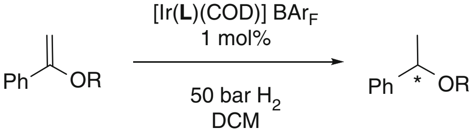
Table 10 Asymmetric hydrogenation of vinyl ether alcohols



Substrate	R^1	R^2	R^3	ee %
66a	Me	OMe	H	96
66b	Me	OEt	H	98
66c	*n*-Bu	OMe	H	93
66d	*i*-Pr	OMe	H	91
66e[a]	Me	OMe	TBDPS	89
66f[a]	Me	OMe	Ac	92

[a] K_2CO_3 was not required for this case

Table 11 Ligand and substrate optimization studies



R	**L 13a**	**L 13b**	**L 11a**	**L 10b**
TMS	[a]	[a]	[a]	[a]
CH_3	[a]	[a]	[a]	[a]
Ac	[a]	Full conv; rac	[a]	No conv
$PO(OEt)_2$	Complex; mixture[b]	Full conv; 65% ee	[a]	No conv
$POPh_2$	30% conv; 82% ee	Full conv; 95% ee	41% conv; 63% ee	No conv

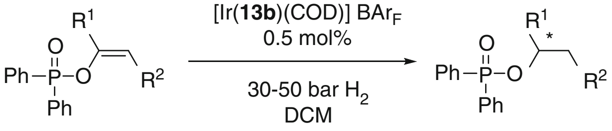
[a] A complex mixture was obtained
[b] Ethylbenzene was the major product

required to neutralize any acidic contaminants. Larger groups on either side of the olefin eroded enantioselectivity but not to the same degree as with substrates **65a–f**.

Cheruku et al. have investigated a series of enol esters [73, 95]. A preliminary experiment to determine the optimal protecting group with a small group of catalysts identified diphenylphosphinates as the optimal esters (Table 11).

Ligand **13b** in combination with diphenylphosphinate as the ester group gave the chiral phenylethyl diphenylphosphinate **67b** with full conversion and high enantioselectivity of 95%. Although it may seem that the diphenylphosphinate ester group is not ideal in terms of atom economy, it should be noted that it is an excellent leaving group and can be readily displaced with a number of good

Table 12 Asymmetric hydrogenation of enol phosphinates



Substrate	R^1	R^2	Conv %	ee %
68a	Ph	H	99	95
68b	4-MeC$_6$H$_4$	H	97	96
68c	4-*t*-BuC$_6$H$_4$	H	93	94
68d	4-MeOC$_6$H$_4$	H	48[a]	98
68e	4-BrC$_6$H$_4$	H	99	99
68f	4-CF$_3$C$_6$H$_4$	H	99	99
68g	4-NO$_2$C$_6$H$_4$	H	99	92
68h	β-naphthyl	H	99	85
68i	cyclohexyl	H	99	92
68j	t-Bu	H	99	99
68k	Ph	Me	99	96
68l	Ph	Et	90	92
68m	Ph	*i*-Pr	89	90
68n	Ph	CO$_2$Et	99	99
68o	4-MeC$_6$H$_4$	CO$_2$Et	99	99
68p	4-CF$_3$C$_6$H$_4$	CO$_2$Et	99	99
68q	4-BrC$_6$H$_4$	CO$_2$Et	99	98
68r	Me	CO$_2$Et	99	99
68s	Et	CO$_2$Et	99	99
68t	*i*-Pr	CO$_2$Et	99	99
68u	ClCH$_2$	CO$_2$Et	95[b]	93[b]
68v	*t*-Bu	CO$_2$Et	98	93
68w	*t*-Bu	Et	99	90
68x	*i*-Pr	Me	99	91

[a] Reaction was run with 2 mol% catalyst and 10 mg poly(vinylpyridine) resin
[b] Run at 2 mol% catalyst

nucleophiles. A study of both 1,1′-disubstituted vinyl phosphinates and trisubstituted vinyl phosphinates was conducted and the results are summarized in Table 12.

Asymmetric hydrogenation of both 1,1′-disubstituted vinyl phosphinates and the trisubstituted phosphinates with ligand **13b** was highly successful. Enantioselectivities were very high for many useful combinations including bulky alkyl groups on the stereogenic center. Substrate **68d** was very acid-sensitive, and an acid scavenger with increased amounts of catalyst was required to obtain reasonable results. Allylic chloride **68u** also required higher catalyst loading but was reduced efficiently and in high enantioselectivity. In many cases, the enantioselectivity was higher than what can be obtained from reduction of the corresponding ketones with ruthenium-based catalysts [95].

6.2 Asymmetric Hydrogenation of Furans and Chromenes

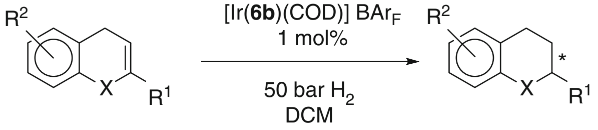
Chiral-reduced heterocycles containing only oxygen are common throughout organic synthesis and are highly sought after compounds. Asymmetric hydrogenation offers an atom-economical approach to these compounds in a single, clean step. However, hydrogenation of prochiral furans and dehydropyrans has proven difficult, mostly attributed to the increased stability of aromatic compounds and the electron-rich nature of these substrates [74]. For a long time, no suitable chiral catalysts were available until iridium N,P catalyst provided a solution for these problematic hydrogenation reactions.

ThrePHOX **6b** proved to be a valuable tool in the reduction of chromenes **71a–k**, all of which were reduced in greater than 90% enantioselectivity. The very electron-rich thiochromene **71h** required higher temperature, and lower conversion was observed, but the enantioselectivity remained in the useful range (Table 13) [96].

A series of furans and benzofurans were reduced in excellent enantioselectivity and conversion using iridium complexes derived from pyridine–phosphinite ligands. Tertiary butyl-derived phosphinites were the preferred donor groups with ligand **8a** giving the highest enantioselectivity most consistently. Higher temperatures and longer reaction times were required to obtain good conversion for all cases; most notably, **69e** reacted very sluggishly at 40°C (Fig. 8).

These results mark the very first successful catalytic reduction of furans in high enantioselectivity and greatly expand the methods available for the synthesis of enantiopure heterocycles.

Table 13 Asymmetric hydrogenation of substituted 4H-chromenes



Substrate	R^1	R^2	X	Conv %	ee %
71a	Me	H	O	93	95
71b	4-MeC_6H_4	H	O	99	98
71c	2-FC_6H_4	H	O	99	99
71d	4-BrC_6H_4	H	O	95	91
71e	4-ClC_6H_4	6-Cl	O	90	97
71f	Ph	7-MeO	O	99	99
71g	2-furyl	H	O	99	97
71h	Ph	H	S	73[a]	91[a]
71i	Ph	H	O	99	99
71j	cyclohexyl	H	O	99	95
71k	Ph	7-$(CH{=}CH)_2$-8	O	99	96

[a] Reaction was conducted at 40°C

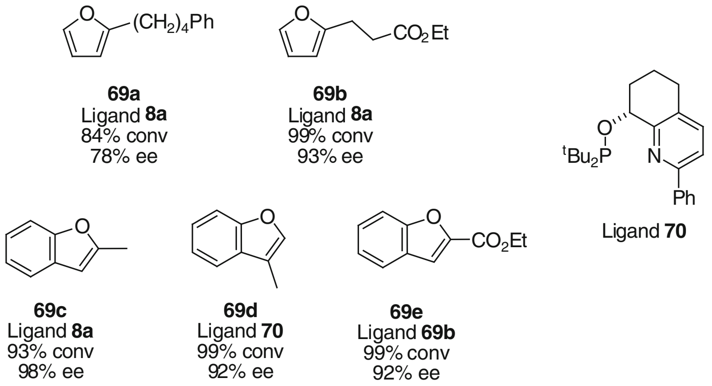


Fig. 8 Asymmetric hydrogenation results for substituted furans

6.3 Asymmetric Hydrogenation of Enamines and Indoles

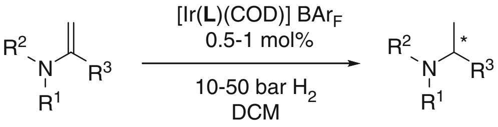
Much like the enol systems discussed in Sect. 6.1, enamines are predictably difficult substrates for most iridium asymmetric hydrogenation catalysts. Both substrate and product contain basic functionalities which may act as inhibitors to the catalyst. Extended aromatic enamines such as indoles may be even more difficult substrates for asymmetric hydrogenation with an additional energetic barrier to overcome. Initial reports by Andersson indicated a very difficult reaction indeed (Table 14) [75]. Higher enantioselectivities were later reported by Baeza and Pfaltz (Table 14) [76].

Moderate enantioselectivities were obtained with ligand **13b** at room temperature. Simply changing from a diethyl amine moiety **72a** to a pyrolidine **72g** caused a precipitous drop in enantioselectivity for both ligands **13b** and ThrePHOX **6b**. An electronic effect was observed for ligand **13b** with a drop from good selectivity with enamine **72b** with a methyl group in the paraposition of the aromatic ring to poor selectivity with the stronger π donating paramethoxy group with **72c**.

Steric interaction was also clearly an issue for all of the systems investigated. Most notable is the large difference in the reactivity between ThrePHOX **6b**- and PHOX **5c**-based catalysts with respect to the substituents bound to the nitrogen atom. ThrePHOX consistently performed best with *N*-methyl-*N*-benzyl enamines while PHOX preferred a *N*-methyl-*N*-phenyl derivative. Lowering the temperature had a favorable outcome on enantioselectivity but slowed the reaction and caused drops in conversion for **5c** and **6b**.

A variety of ligands were used to hydrogenate **73a**, **74a–b**, **75a–b**, and **76a** with moderate results. Steric interactions were magnified and that may explain why nearly all of the substrates in Scheme 15 give less than optimal results. *N*-methyl-*N*-phenyl-amine derived enamines **74a** and **75a** were resistant to hydrogenation where the analogous *N*-methyl-*N*-benzyl-amine-based enamines were completely converted with SimplePHOX ligand **77** with moderate enantioselectivity.

Table 14 Asymmetric reduction of enamines



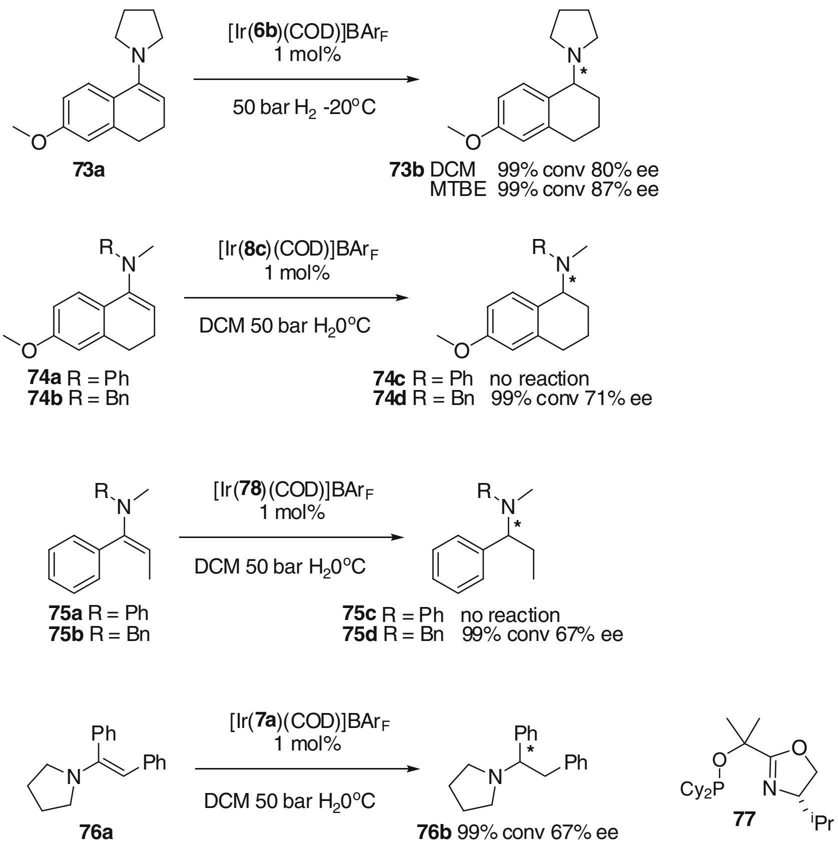
Substrate	R^1	R^2	R^3	Conv %	ee %
72a	Et	Et	Ph	99^a (99^b)	84^a (54^b)
72b	Et	Et	4-MeC_6H_4	99^a	87^a
72c	Et	Et	4-$MeOC_6H_4$	99^a	64^a
72d	Et	Et	4-$CF_3C_6H_4$	99^a	77^a
72e	Et	Et	2-naphthyl	99^a	64^a
72f	Me	Ph	Ph	99^a (98^c)	79^a (91^c)
72g	*N*,*N′*-$(CH_2)_4$		Ph	66^a (99^b)	33^a (8^b)
72h	*N*,*N′*-$(CH_2{-}CH_2)_2O$		Ph	75^a	30^a
72i	Me	4-$MeOC_6H_4$	Ph	99^c	90^c
72j	Me	4-ClC_6H_4	Ph	99^c	90.5^c
72k	Me	Bn	Ph	$99^{b,d}$	$92.5^{b,d}$
72l	Me	Bn	4-$MeOC_6H_4$	93^b	74^b
72m	Me	Bn	4-ClC_6H_4	93^b	74^b
72n	Me	Bn	2-furan	$93^{b,e}$	$74^{b,e}$
72o	Me	Bn	t-Bu	53^c	21^c

[a] Run with 0.5 mol% ligand **13b** at room temperature and 50 bar H_2 [75]
[b] Run with 0.5 mol% ligand **6b** at −20°C [76]
[c] Run with 0.5 mol% ligand **5c** at −20°C [76]
[d] MTBE was used as solvent
[e] Run at 0°C

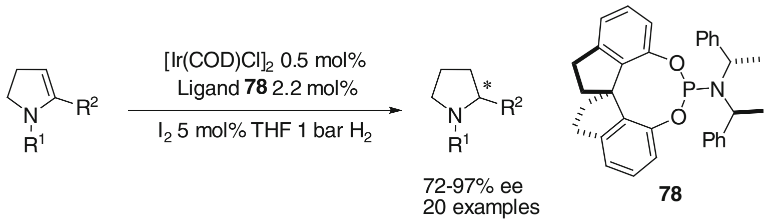
It should also be mentioned that a very active and selective catalyst in the form of a monodentate phosphoramidite in combination with iridium was very successful in the reduction of cyclic enamines, but the discussion of this work is beyond the scope of this chapter (Scheme 16) [77]. Enantioselectivities were reported as excellent with atmospheric pressure sufficing for full conversion in most cases.

Baeza and Pfaltz also investigated indoles which reacted very sluggishly but excellent enantioselectivity could be obtained (Table 15) [78].

Hydrogenation of protected 2-indoles required higher catalyst loading and higher temperatures than used for enamines, but many substrates were hydrogenated in high enantioselectivity and yield. Both electron-donating groups and electron-withdrawing groups interfered with catalysis but the reaction with indole **79b** could be pushed to completion by changing the solvent to chlorobenzene and increasing the temperature to 110°C with very little loss in enantioselectivity. Nitroindole **79d** was completely unreactive and no hydrogenation products were observed. The boc-protecting group was exchanged for acyl or tosyl groups in a few cases and with a beneficial effect to conversion for some indoles. Indole **79i** was extremely difficult to reduce but useful levels of product and enantioselectivity



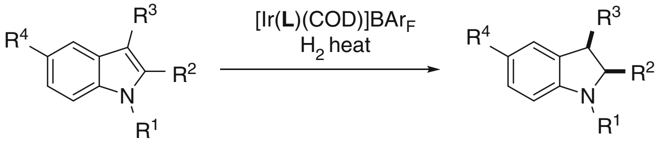
Scheme 15 Asymmetric hydrogenation of cyclic and acyclic enamines

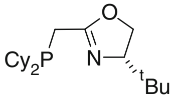


Scheme 16 Asymmetric hydrogenation of enamines with Ir(**78**)

could be obtained with ligand **8a**. Indoles with substitution in the 3 position were very difficult to hydrogenate and reactions with esters in this position completely failed. However, simple methyl derivative **79k** was hydrogenated in excellent ee and yield.

Table 15 Asymmetric hydrogenation of indoles





80

Substrate	mol% (L)	*T* (°C)	R^1	R^2	R^3	R^4	Conv %^{a}	ee %^{a}
79a	4 (**8a**)	60	boc	Me	H	H	89	99
79b	4 (**8a**)	60	boc	Me	H	MeO	68	99
		110^b					85^b	98.5^b
79c	4 (**8a**)	60	boc	Me	H	F	64	98.5
79d	4 (**8a**)	60	boc	Me	H	NO_2	0	nd
79e	1 (**6b**)	25	boc	Ph	H	H	94^c	88^c
79f	1 (**6b**)	25	boc	CO_2Et	H	H	66^c	92^c
							88^d	93^d
79g	2 (**8a**)	60	Ac	CO_2Et	H	H	97	99
79h	2 (**80**)	25	Tosyl	Me	H	H	94	99
79i	4 (**8a**)	110^b	Tosyl	Ph	H	H	70^b	98^b
79j	4 (**8a**)	60	Tosyl	Me	H	H	95	99
79k	2.5 (**8a**)	60	Tosyl	H	Me	H	97	98

[a] Reaction was run at 100 bar unless otherwise noted

[b] Chlorobenzene as solvent, 110°C

[c] Reaction was run at 75 bar

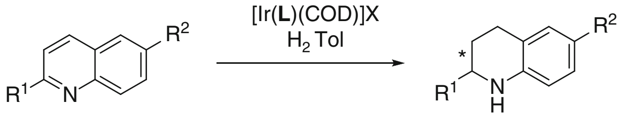
[d] 2 mol% of catalyst, DCM, 25°C

6.4 Asymmetric Hydrogenation of Quinolines and Pyridines

Asymmetric hydrogenation of nitrogen heterocycles is a relatively unexplored and open field. Only a handful of iridium N,P-based systems have been used successfully to hydrogenate substituted quinolines and the more stable pyridines. Lu et al. were the first to report a successful asymmetric hydrogenation of two substituted quinolines with ligand **24** (Table 16) [79]. A few reports using diphosphines and monophos variations followed until Lu and Bolm published a second iridium N,P-based asymmetric hydrogenation of similar quinolines with ligand **23a** (Table 16) [80].

Ligand **24** was surprisingly effective in the presence of 5 mol% iodine without the use of BAr$_F$ as a counterion. Reduction of sterically demanding substrates was a problem for both systems and aromatic substitution on the 2 position of the quinoline abolished the enantioselectivity and poor conversion was obtained. Electron-donating and -withdrawing groups also damaged the enantioselectivity although less for Zhou's system. Nevertheless, useful enantioselectivity and yield could be obtained for simple alkyl derivatives.

Table 16 Asymmetric hydrogenation of quinolines



Substrate	R^1	R^2	Yield %^{a} Conv %^{b}	ee %^{a} ee %^{b}
81a	Me	H	95^a	90^a
			95^b	87^b
81b	Et	H	95^a	91^a
			62^b	77^b
81c	*n*-Pr	H	62^b	80^b
81d	*i*-Bu	H	53^b	75^b
81e	*n*-pentyl	H	94^a	92^a
			90^b	65^b
81f	Me	Me	93^a	92^a
			95^b	75^b
81g	Me	F	86^a	89^a
			43^b	64^b
81h	Me	MeO	95^b	78^b
81i	Ph	H	45^a	3^a
81j	$(CH_2)_2Ph$	H	92^a	72^a

[a]Reaction was conducted at 40 bar H_2, 1 mol% [(**24**)Ir(COD)]Cl and 5 mol% I_2 [79]
[b]Reaction was conducted at 60 bar H_2, 1 mol% [(**23a**)Ir(COD)]BAr_F [80]

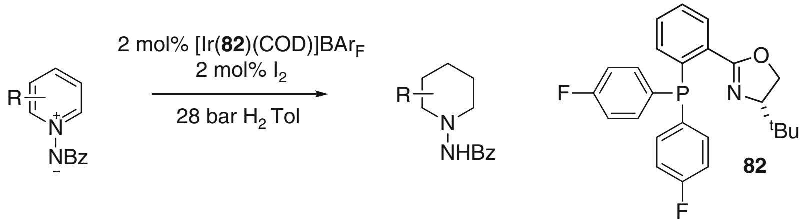
A single paper from Charette and coworkers details the catalytic asymmetric hydrogenation of *N*-iminopyridinium ylides to substituted piperdines using PHOX ligand **82** in combination with iodine (Table 17) [81].

Moderate to good enantioselectivities were obtained for nearly all examples, but the products from **83a–c** could be recrystallized to higher enantiomeric purity. Addition of iodine was critical for catalysis as was the use of a ligand with electron-poor *para*-fluorophenyl groups on the phosphorous atom. Substitution at the 3 position of the pyridine ring was described as being difficult for both the quinolines and pyridine systems. The resulting hydrazine derivatives could be easily converted to piperdines by reduction with Raney nickel or under Birch conditions.

7 Asymmetric Hydrogenation of Imines

Given the importance of chiral amines to synthetic chemistry as well as other fields asymmetric hydrogenation of imines has attracted wide interest but limited success compared to C=C and C=O bond reduction. The first asymmetric hydrogenation of imines was carried out in the seventies with ruthenium- and rhodium-based catalysts, followed later by titanium and zirconium systems [82]. Buchwald found that

Table 17 Asymmetric hydrogenation of *N*-iminopyridinium ylides



Substrate	R	Yield %	ee %
83a	2-Me	90 (84[a])	90 (97[a])
83b	2-Et	96 (78[a])	83 (94[a])
83c	2-*n*Pr	98 (75[a])	84 (95[a])
83d	2-Bn	97	58
83e	2-CH_2OBn	85	76
83f	2-$(CH_2)_3OBn$	88	88
83g	2,3-dimethyl	91 (>95:5 *cis*:*trans*)	54
83h	2,5-dimethyl	92 (57:43 *cis*:*trans*)	86/84

[a] Numbers in parentheses are after a single recrystallization

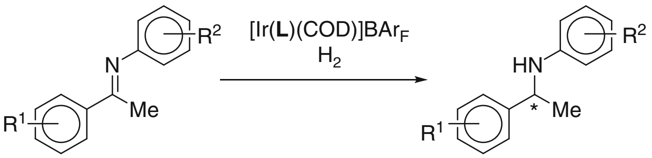
Britzinger-type ansa titanocenes were highly selective for the reduction of cyclic imines, albeit at long reaction times, high catalyst loading, and with high pressures [83]. Crabtree found that pyridine phosphine complexes of iridium were highly active in the reduction of imines [10]. The asymmetric synthesis of Metolachlor, an important agrochemical used in the protection of maize, is the first example of an industrially useful enantioselective reduction of imines catalyzed by an iridium complex with a Josiphos type ligand [84]. The first use of iridium N,P complexes in the asymmetric hydrogenation of imines was reported by Pfaltz and coworkers [85].

Many of the systems studied required high catalyst loadings, very high pressures, elevated temperatures, and long reaction times. Several problems can be encountered with imines such as hydrolysis to starting materials, dimer and trimer formation, and the presence of enamine and syn/anti isomers [82]. Additionally, with the exception of *N*-aryl imines, the resulting amines are far more basic than the imine substrates and may cause a larger degree of product inhibition of the catalyst. Many recent advances have been made with iridium systems other than N,P ligands such as diphosphines and monodentate phosphoramidites [86, 87].

Initial studies with PHOX indicated a lack of an anion effect, replacement of PF_6^- by SbF_6^-, or BF_4^- as counter ion had no apparent effect on the overall reaction. However, nearly all reported catalysts within the last decade utilize BAr_F as a counterion, perhaps for the higher catalyst stability, easier handling, and general reactivity toward a broader range of substrates.

Andersson reported the use of ligand **13a** in the asymmetric hydrogenation of substituted acetophenone-based *N*-aryl imines (Table 18) [88, 89]. New ligands **84** and **85** were reported by the groups of Bolm and Knochel, respectively, for

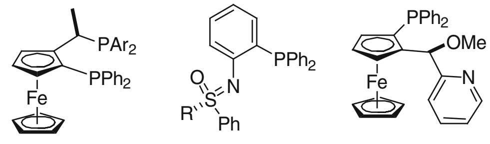
Table 18 Asymmetric hydrogenation of acetophenone based *N*-aryl ketimines



			Ligand ee%							
Imine	R^1	R^2	**5a**[a]	**13a**[b]	**14d**[c]	**15a**[d]	**16a**[e]	**77**[f]	**84**[g]	**85**[h]
86a	H	H	90	90	94	91	93	96	–	84
86b	H	4-MeO	96	89	94	90	–	95	96	85
86c	H	Ar[i]	–	–	–	–	–	–	–	94
87a	2-Me	H	–	83	–	–	–	–	–	–
87b	2-Me	4-MeO	–	–	–	–	–	–	94	–
87c	2-Me	Ar[i]	–	–	–	–	–	–	–	94
88a	3-Me	4-MeO	–	–	–	–	–	–	93	–
88b	3-Me	Ar[i]	–	–	–	–	–	–	–	93
91a	4-Me	H	–	–	–	88	94	–	–	–
91b	4-Me	4-MeO	–	–	–	–	–	–	96	–
92	4-AcO	Ar[i]	–	–	–	–	–	–	–	94
93	4-MeO	H	–	86	90	–	94	94	–	–
94a	4-MeO	4-MeO	–	86	–	–	–	–	94	–
94b	3-MeO	4-MeO	–	–	–	–	–	–	96	–
94c	2-MeO	4-MeO	–	–	–	–	–	–	90	–
95a	3-Cl	H	–	–	–	93	93	–	–	–
95b	3-Br	H	–	–	–	93	92	–	–	–
96a	4-Cl	H	96	–	95	93	90	96	–	–
96b	4-Cl	4-MeO	–	89	–	91	–	–	95	–
96c	4-Cl	Ar[i]	–	–	–	–	–	–	–	92
97a	4-Br	H	–	–	–	91	91	–	–	–
97b	3-Br	H	–	–	–	93	92	–	–	–
98a	4-CF_3	H	–	–	–	92	–	–	–	–
98b	4-CF_3	Ar[i]	–	–	–	–	–	–	–	89
99a	H	4-Cl	89	–	92	–	97	94	–	–
99b	H	4-Br	–	–	–	89	96	–	–	–
100	3,4-Xy	H	–	–	–	95	94	–	–	–

Condition [a]0.5 mol% cat, DCM, 5 bar H_2, 0°C
Condition [b]0.5 mol% cat, DCM, 20 bar H_2
Condition [c]0.5 mol% cat, DCM, 5 bar H_2, −20°C
Condition [d]1.0 mol% cat, DCE, 1 atm H_2, 10°C
Condition [e]1.0 mol% cat, MTBE, 1 atm H_2, 10°C, 4Å MS
Condition [f]0.5 mol% cat, DCM, 5 bar H_2, −20°C
Condition [g]0.5 mol% cat, 2 mol% I_2, tol, 20 bar H_2
Condition [h]1.0 mol% cat, 4:1 toluene: methanol, 10 bar H_2
Condition [i]Ar = 4-MeO-3,5-Me_2-C_6H_2

asymmetric hydrogenation of imines with improved enantioselectivities and yields (Fig. 9) [90, 91]. Two similar chiral spirocycle-based ligands SpinPHOX **15** and SiPHOX **16** proved highly effective in the asymmetric hydrogenation of these difficult substrates [92, 93]. Baeza and Pfaltz reported three structurally similar



Josiphos **84** **85**

Fig. 9 Ligands for asymmetric hydrogenation of imines

catalysts based on PHOX in an expanded look at the earlier work and found excellent selectivity and activity at low catalyst loadings [97].

Essentially, all studies have used acetophenone-based *N*-aryl ketimines as substrates or derivatives thereof. Some of the *N*-aryl groups are easily deprotected to yield branched α-aryl primary amines, which can be further functionalized.

Several authors have conducted investigations of the *N*-aryl moiety to optimize interactions for each individual catalyst. All of the catalysts in Table 18 function well at 1 mol% catalyst loading and with ambient to moderate pressures of hydrogen. Noncoordinating solvents were preferred with the exception of Knochel's ligand **85**, which gave the highest enantioselectivity in a mixture of 25% methanol in toluene.

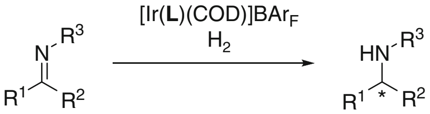
Although all of the substrates tested in Tables 18 and 19 have a very high degree of similarity, some useful trends can be identified for each individual catalyst. Different conditions were used for different catalyst systems, possibly reflecting different mechanisms for each individual system. For instance, addition of iodine was found to give inferior results with PHOX and related ligands, yet Bolm's ligand **84** requires iodine for catalysis, a result more in agreement with iridium diphosphine complexes [82]. Other interesting deviations are the optimal conditions reported by Knochel with ligand **85**, which calls for 25% methanol in toluene as a solvent. This result stands in stark contrast to Zhou's ligand **16a**, which is inhibited by methanol in imine hydrogenations.

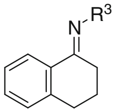
PHOX **5a**, SimplePHOX **77**, and NeoPHOX **14d** are very closely related in bite angle and overall geometry however these catalysts differ in the electronic properties on the phosphine moiety. All of these ligands gave excellent enantioselectivity in close agreement with each other, reflecting the importance of geometry and bite angle over electronic properties. The authors also reported a strong temperature effect on selectivity with lower temperature giving higher enantioselectivity. Catalysts loadings as low as 0.1 mol% were effective for several substrate and catalyst combinations but with an increased pressure requirement to reach useful conversions.

In comparison, ligand **13a** generally gave moderate to good enantioselectivities over a limited range of substrates, and larger substituents were not tolerated well with imine **87a** reaching only 52% conversion albeit at 0.5 mol% catalyst loading. This system appeared to be the most sensitive to the size of the substrate, changing a methyl group such as in imine **86a** with an ee of 90% for an ethyl group as in **101a** decreased the enantioselectivity to 78%.

Ligand **84** gave excellent enantioselectivity for most of the reported substrates but some sensitivity to steric hindrance was also clear. Changing from α-naphthyl

Table 19 Asymmetric hydrogenation of imines



				Ligand ee%				
Imine	R[1]	R[2]	R[3]	**13a**[a]	**14d**[b]	**15b**[c]	**84**[d]	**85**[e]
101a	Ph	Et	Ph	78	82	92	–	–
101b	Ph	Et	4-MeO-C_6H_4	–	–	–	92	–
101c	Ph	Et	Ar[f]	–	–	–	–	94
102	α-napth	Me	4-MeO-C_6H_4	–	–	–	98	–
103a	β-napth	Me	Ph	91	–	–	–	–
103b	β-napth	Me	4-MeO-C_6H_4	–	–	–	69	–
103c	β-napth	Me	Ar[f]	–	–	–	–	93
103c	β-napth	Me	Bn	–	–	93	–	–
104a			Ph	90	–	–	–	–
104b			4-MeO-C_6H_4	–	–	–	91	–
104c			Bn	–	–	96	–	–
104d			Me	–	–	98	–	–
104e			i-Bu	–	–	96	–	–

Condition [a]0.5 mol% cat, DCM, 20 bar H_2
Condition [b]0.5 mol% cat, DCM, 5 bar H_2, −20°C
Condition [c]1.0 mol% cat, DCM, 20 atm H_2, 10°C
Condition [d]0.5 mol% cat, 2 mol% I_2, toluene, 20 bar H_2, 20 h
Condition [e]1.0 mol% cat, 4:1 toluene: methanol, 10 bar H_2, 25°C, 20 h
Condition [f]Ar = 4-MeO-3,5-Me_2-C_6H_2

methyl ketimine **102** with an ee of 98% for β-naphthyl-derived **103b** drops the enantioselectivity to 69%.

Inferior results with *N*-benzyl compared to *N*-aryl imines have been reported for many iridium-based systems [93]. Han et al. compensated for this same negative effect with SpinPHOX **15a** by replacing the pendant isopropyl group with a bulkier *tert*-butyl group in **15b**, demonstrating that the control of the system can be obtained by simple ligand modification. The added bulk of **15b** made it possible to reduce the very challenging *N*-alkyl-substituted imines **104d–e** in excellent enantioselectivity.

Knochel took a different approach by optimizing the substrate *N*-aryl group while investigating ligand **85**. Introduction of two meta-methyl groups in the 4-methoxyphenyl substituent increased the enantioselectivity from 84% with imine **86a** to 94% with **86c**.

Electronic effects seem to have very little influence on the overall enantioselectivity with both electron-donating and- withdrawing groups giving very small changes to the enantioselectivity when all other variables were the same. Substrate geometry seems to play a much more influential role with this particular class of substrates.

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Top Organomet Chem (2011) 34:77–106
DOI: 10.1007/978-3-642-15334-1_4

Iridium-Catalyzed Hydrogen Transfer Reactions

Ourida Saidi and Jonathan M. J. Williams

Abstract This chapter describes the application of iridium complexes to catalytic hydrogen transfer reactions. Transfer hydrogenation reactions provide an alternative to direct hydrogenation for the reduction of a range of substrates. A hydrogen donor, typically an alcohol or formic acid, can be used as the source of hydrogen for the reduction of carbonyl compounds, imines, and alkenes. Heteroaromatic compounds and even carbon dioxide have also been reduced by transfer hydrogenation reactions. In the reverse process, the oxidation of alcohols to carbonyl compounds can be achieved by iridium-catalyzed hydrogen transfer reactions, where a ketone or alkene is used as a suitable hydrogen acceptor. The reversible nature of many hydrogen transfer processes has been exploited for the racemization of alcohols, where temporary removal of hydrogen generates an achiral ketone intermediate. In addition, there is a growing body of work where temporary removal of hydrogen provides an opportunity for using alcohols as alkylating agents. In this chemistry, an iridium catalyst "borrows" hydrogen from an alcohol to give an aldehyde or ketone intermediate, which can be transformed into either an imine or alkene under the reaction conditions. Return of the hydrogen from the catalyst provides methodology for the formation of amines or C–C bonds where the only by-product is typically water.

Keywords Alcohols · Alkenes · Asymmetric transfer hydrogenation · C-alkylation · Imines · Ketones · *N*-alkylation · Oxidation · Reduction · Transfer hydrogenation

Contents

O. Saidi and J.M.J. Williams (✉)
Department of Chemistry, University of Bath, Bath, UK
e-mail: j.m.j.williams@bath.ac.uk

1 Introduction

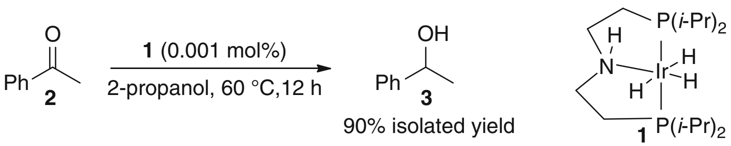
Iridium complexes are amongst the most important for catalyzing hydrogen transfer reactions. Hydrogen transfer from a donor alcohol to an acceptor ketone has seen considerable attention, although other hydrogen donors and acceptors have also been used. In the presence of suitable enantiomerically pure ligands, many of these hydrogen transfer reactions have been performed asymmetrically, with high levels of enantioselectivity achieved in many cases. More recently, iridium catalysts have proved to be popular for the activation of alcohols by the temporary removal of hydrogen, which has allowed alcohols to be used as alkylating agents for nitrogen- and carbon-based nucleophiles.

2 Reduction of Ketones and Aldehydes by Transfer Hydrogenation

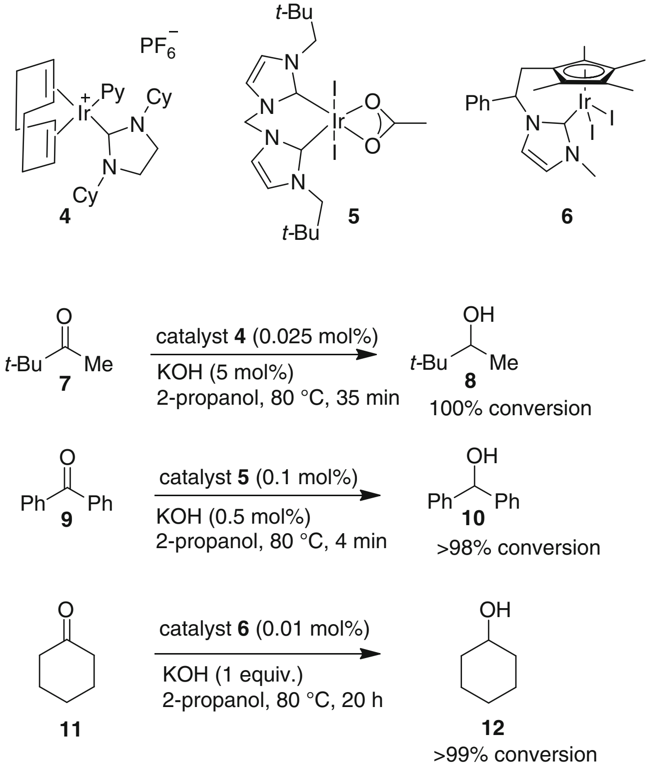
The reduction of ketones and aldehydes into the corresponding secondary and primary alcohols is one of the fundamental functional group transformations. The reaction is usually performed with either a stoichiometric reducing agent such as $NaBH_4$ or by metal-catalyzed reduction. Whilst direct hydrogenation with H_2 is completely atom efficient, transfer hydrogenation from a suitable hydrogen donor means that the use of potentially explosive H_2 gas can be avoided. In many cases, 2-propanol is used as the hydrogen donor, and by using it as the solvent, it is present in sufficient excess that the equilibrium is driven towards the formation of the product.

There have been many reports of the use of iridium-catalyzed transfer hydrogenation of carbonyl compounds, and this section focuses on more recent examples where the control of enantioselectivity is not considered. In particular, recent interest has been in the use of iridium *N*-heterocyclic carbene complexes as active catalysts for transfer hydrogenation. However, alternative iridium complexes are effective catalysts [1, 2] and the air-stable complex **1** has been shown to be exceptionally active for the transfer hydrogenation of ketones [3]. For example, acetophenone **2** was converted into the corresponding alcohol **3** using only 0.001 mol% of this catalyst as shown in Scheme 1. The availability of the hydrogen on the nitrogen donor was believed to be important for reactivity with concerted hydrogen transfer from both the NH and IrH to the ketone.

N-Heterocyclic carbene complexes of Ir(I) and Ir(III) have also demonstrated high reactivity in transfer hydrogenation reactions of ketones (Scheme 2) [4]. Complex **4** catalyzed the reduction of a range of ketones into the corresponding alcohols, including the reduction of pinacolone **7** into alcohol **8** with a low catalyst loading and short reaction time [5]. The chelating bis(*N*-heterocyclic carbene) complex **5** was shown to catalyze the reduction of ketones, and in the case of the reduction of benzophenone **9** to alcohol **10**, the reaction was complete within 4 min [6].



Scheme 1 A highly active iridium catalyst for transfer hydrogenation



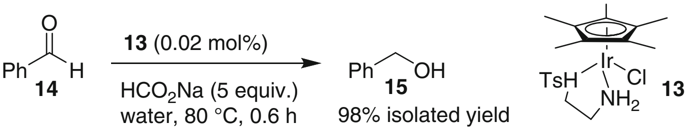
Scheme 2 Use of *N*-heterocyclic carbene complexes of iridium

The same catalyst has also been used for the reduction of aldehydes to primary alcohols [7]. Several other iridium *N*-heterocyclic carbene complexes have been shown to be successful as catalysts for the transfer hydrogenation of ketones [8–12], including the interesting complex **6**, where the cyclopentadienyl ring is tethered to the *N*-heterocyclic carbene. Complex **6** was employed at low catalyst loading for the reduction of a range of ketones including the conversion of cyclohexanone **11** into cyclohexanol **12** [13].

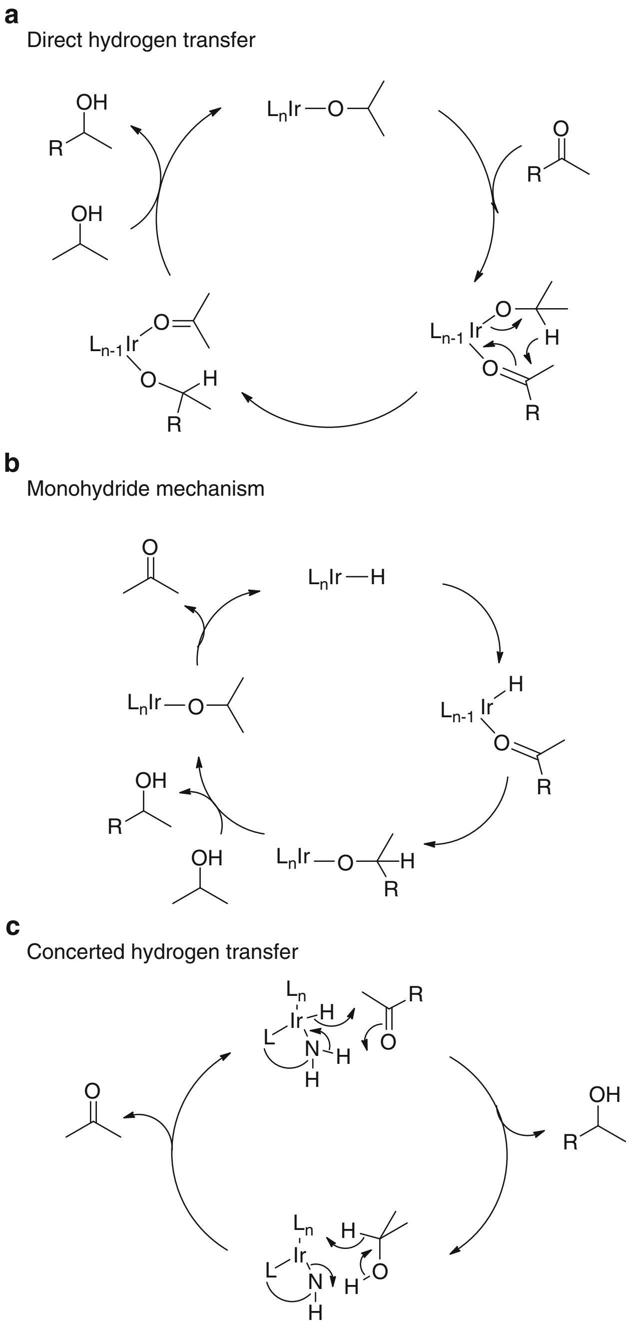
The use of water as a solvent can have environmental advantages for some processes, and iridium-catalyzed transfer hydrogenation of carbonyl compounds has been achieved using water as the medium. The water-soluble hydride complex [Cp*Ir(bipy)H]PF_6 (Cp* = pentamethylcyclopentadienyl, bipy = 2,2′-bipyridine) catalyzes the reduction of ketones with formic acid as the hydrogen donor [14], where the fastest reactions occurred at pH 2–3. Xiao and coworkers have demonstrated that complex **13** formed from $[Cp^*IrCl_2]_2$, and monotosylated ethylenediamine provides a highly active catalyst for the transfer hydrogenation of aldehydes using sodium formate [15, 16]. The reactions were described as being "on water and in air" as the catalyst is not soluble in water, and the presence of air did not appear to cause any problems. For example, the reduction of benzaldehyde **14** to give benzyl alcohol **15** was achieved with only 0.02 mol% catalyst in under an hour (Scheme 3). A polymer-bound variant of catalyst **13** was developed where the transfer hydrogenation of aldehydes occurred at the interface of emulsion droplets [17].

The mechanism for the iridium-catalyzed hydrogen transfer reaction between alcohols and ketones has been investigated, and there are three main reaction pathways that have been proposed (Scheme 4). Pathway (a) involves a direct hydrogen transfer where hydride transfer takes place between the alkoxide and ketone, which is simultaneously coordinated to the iridium center. Computational studies have given support to this mechanism for some iridium catalysts [18].

Alternative reaction pathways, which involve iridium hydride complexes, have also been presented. Bäckvall and coworkers have developed deuterium labeling experiments to probe whether hydrogen transfer reactions proceed through a monohydride or dihydride mechanism. In the case of Ir(I) complexes, the monohydride mechanism (b) is favored [19, 20]. Once an iridium hydride species is formed, the reaction pathway proceeds by coordination of the incoming ketone and hydride transfer. Ligand exchange with the alcohol acting as the hydrogen donor occurs and hydride transfer regenerates the iridium hydride species [21]. The concerted hydrogen transfer pathway (c) is available when the ligand contains an available hydrogen, as seen for complex **1** in Scheme 1. The iridium hydride transfers one hydrogen atom to the carbon of the incoming carbonyl compound, while the associated amine NH



Scheme 3 Transfer hydrogenation of an aldehyde in water



a Direct hydrogen transfer

b Monohydride mechanism

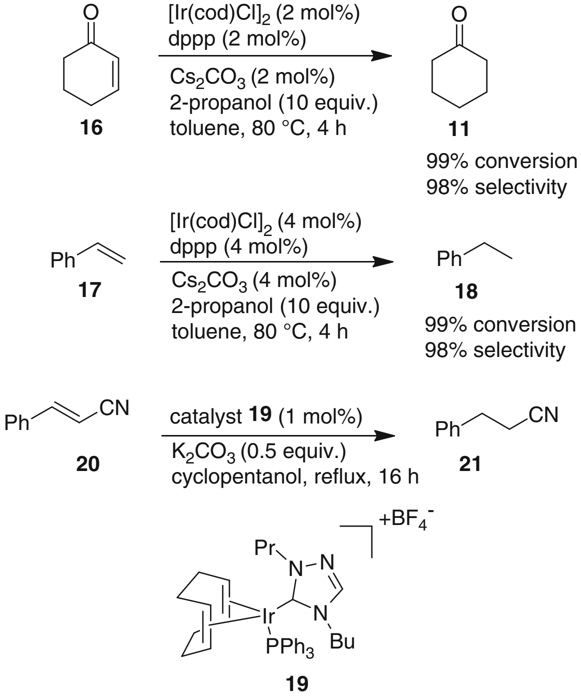
c Concerted hydrogen transfer

Scheme 4 Mechanistic pathways for transfer hydrogenation provides the second hydrogen atom, which is transferred to the oxygen of the carbonyl compound. The catalyst is then restored to the iridium hydride by the reverse process of hydrogen delivery from the donor alcohol.

It seems likely that all three reaction pathways are feasible and the nature of the ligands determines which pathway is favored by a particular iridium catalyst.

3 Reduction of Other Substrates by Transfer Hydrogenation

Iridium catalysts have been used for the transfer hydrogenation of alkenes using alcohols as the hydrogen donor (Scheme 5). Even though the first report of iridium-catalyzed reduction of alkenes by hydrogen transfer appeared as early as 1967 [22], there has been much less attention given to this process in comparison with the reduction of carbonyl compounds. $IrCl(CO)(PPh_3)_2$ has been used to catalyze hydrogen transfer from formic acid to α,β-unsaturated ketones [23], and a polymer–supported variant of this catalyst has also been shown to be effective [24]. Ishii and coworkers have developed the catalyst combination $[Ir(cod)Cl]_2$/dppp/Cs_2CO_3 [cod = 1,5-cyclooctadiene, dppp = 1,3-bis(diphenylphosphino)propane] for the transfer hydrogenation of α,β-unsaturated carbonyl compounds [1].

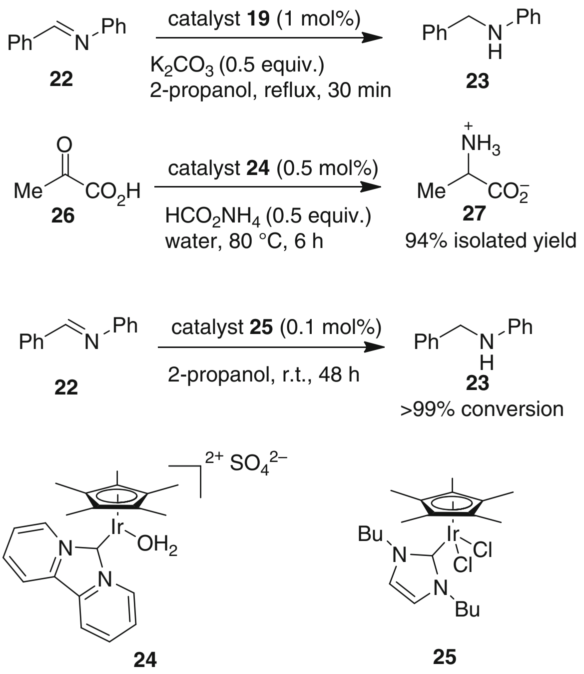


Scheme 5 Reduction of alkenes by transfer hydrogenation

The catalyst is also effective for the reduction of styrenes, ketones, and aldehydes. Cyclohexenone **16** was reduced to cyclohexanone **11** by transfer hydrogenation, and using a higher catalyst loading, styrene **17** was reduced to ethylbenzene **18**. The elaboration of $[Ir(cod)Cl]_2$ into the triazole-derived iridium carbene complex **19** provided a catalyst, which was used to reduce alkene **20** by transfer hydrogenation [25].

The transfer hydrogenation of imines has been achieved using iridium catalysts, with representative examples shown in Scheme 6. The same catalyst **19** was also effective for the transfer hydrogenation of imine **22** to give *N*-benzylaniline **23** after 30 min [25]. The reaction was also successful when the amine and aldehyde were added as separate components and imine formation taking place in situ prior to reduction. An alternative reductive amination procedure using iridium-catalyzed transfer hydrogenation has been achieved using ammonium formate as the nitrogen source and reducing agent. Catalyst **24** was used to convert a range of α-keto acids into α-amino acids, including the conversion of keto acid **26** into alanine **27** in water [26]. Corberan and Peris have shown that catalyst **25** is active for transfer hydrogenation reactions and have applied this to one example of imine reduction, which is achieved at room temperature [27].

Remarkably, complex **25** was also able to reduce CO_2 by transfer hydrogenation in 2-propanol [28]. While there have been many reports using H_2 to reduce CO_2, the work of Peris and coworkers is the only example of a hydrogen transfer reaction to reduce CO_2 with 2-propanol [29]. The reduction is run in the presence of KOH,

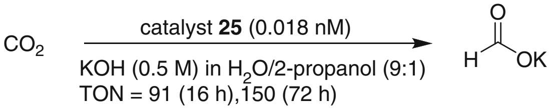


Scheme 6 Reduction of imines by transfer hydrogenation

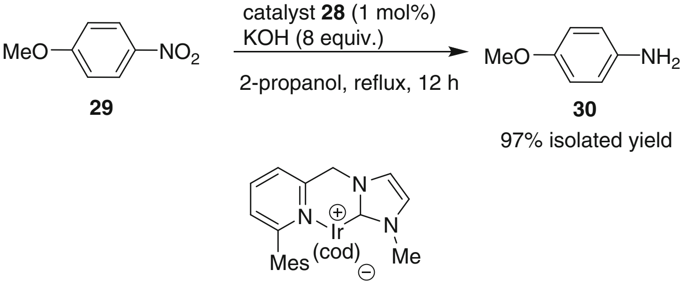
which allows the reduction product to be formed as the stable potassium formate salt (Scheme 7).

The catalytic reduction of nitro groups is usually achieved using heterogeneous catalysts, although the iridium complex **28** has been shown to be effective for the reduction of *p*-nitroanisole **29** to the corresponding aniline **30** using isopropanol as the hydrogen donor (Scheme 8) [30]. In the reduction of some nitroarenes, azo compounds (Ar–N=N–Ar) could be formed as by-products or as the major product by variation of the reaction conditions.

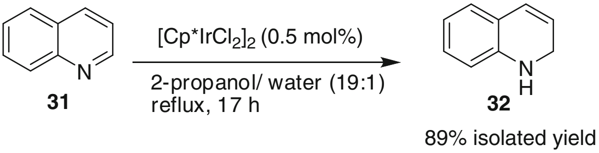
Fujita, Yamaguchi, and coworkers have used iridium-catalyzed transfer hydrogenation for the partial reduction of a range of quinolines (Scheme 9) [31]. For the parent quinoline **31**, $[CpIrCl_2]_2$ catalyzed the reduction to give 1,2,3,4-tetrahydroquinoline **32** in good yield. In some cases, perchloric acid was used as an additive to accelerate the reaction by protonation of the nitrogen atom. Crabtree and coworkers have identified a cationic iridium *N*-heterocyclic carbene complex as an alternative catalyst for partial reduction of quinolines using either 2-propanol or formic acid as the reducing agent [32].



Scheme 7 Reduction of carbon dioxide by transfer hydrogenation



Scheme 8 Reduction of a nitroarene by transfer hydrogenation

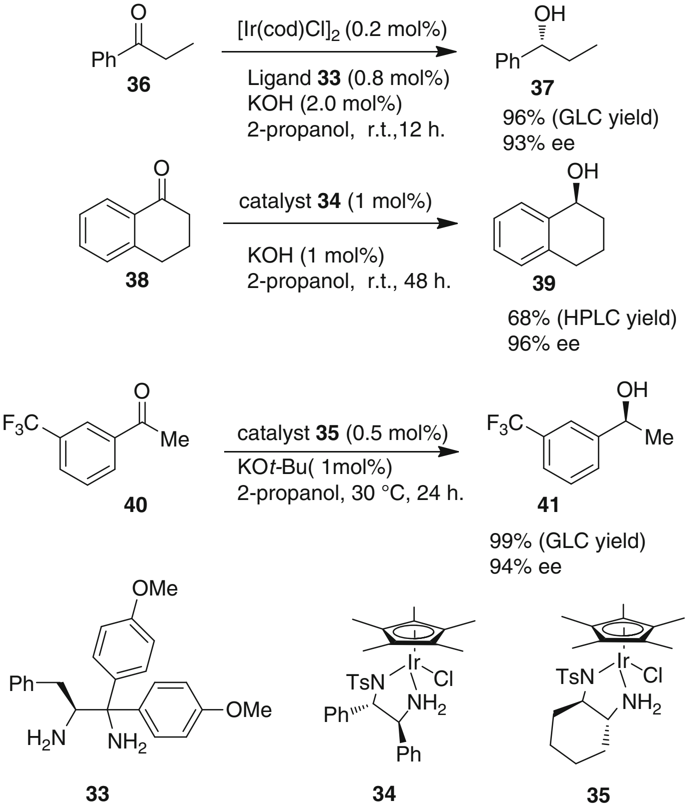


Scheme 9 Partial reduction of quinoline by transfer hydrogenation

4 Asymmetric Transfer Hydrogenation of Ketones

The control of enantioselectivity in the reduction of carbonyl compounds provides an opportunity for obtaining the product alcohols in an enantiomerically enriched form. For transfer hydrogenation, such reactions have been dominated by the use of enantiomerically pure ruthenium complexes [33, 34], although Pfaltz and coworkers had shown by 1991 that high levels of enantioselectivity could be obtained using iridium(I) bis-oxazoline complexes [35].

In the late 1990s, two classes of enantiomerically pure iridium complexes were shown to be effective for the asymmetric transfer hydrogenation of aromatic ketones. Inoue and coworkers used the Ir(I) precursor $[Ir(cod)Cl]_2$ in conjunction with ligand **33** for the reduction of a range of ketones at room temperature with good enantioselectivity [36]. For example, propiophenone **36** was converted into the corresponding alcohol **37** with 93% ee (Scheme 10). Two groups independently reported that the combination of $[Cp^*IrCl_2]_2$ or the analogous rhodium complex with amino sulfonamide ligands was capable of achieving very high enantioselectivities in the transfer

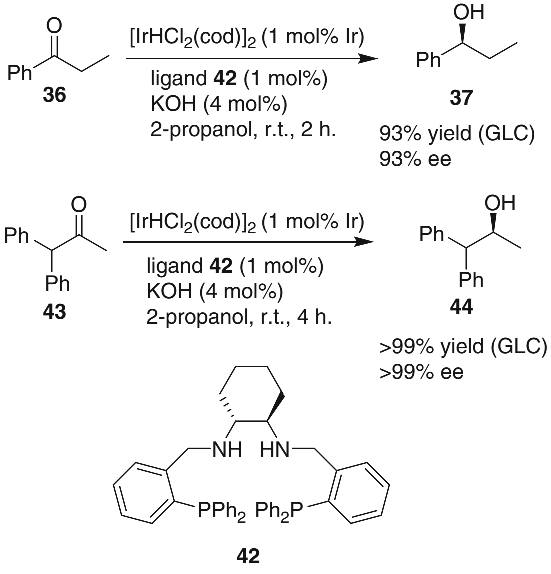


Scheme 10 Asymmetric reduction of ketones with iridium catalysts

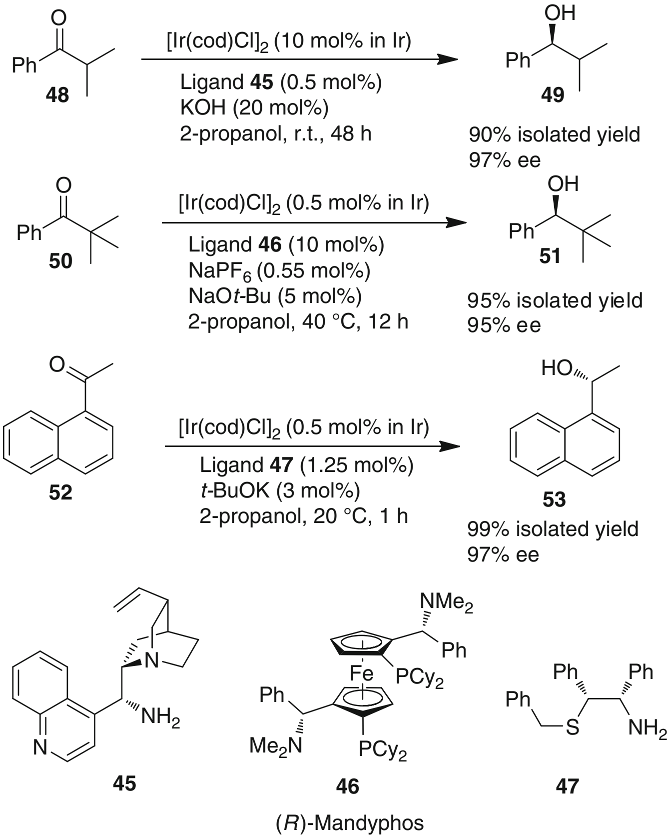
hydrogenation of aryl ketones [37–40]. These catalysts were designed as isoelectronic variants of successful (arene)ruthenium complexes, which had been used in the same reactions. One example from the group of Mashima and coworkers involved the reduction of tetralone **38** to give the alcohol **39** in 96% ee [38]. Ikariya and coworkers reported complex **34** and the related complex **35** for the asymmetric transfer hydrogenation of ketones. For example, ketone **40** was reduced to alcohol **41** with 94% ee [40, 41]. Alternative enantiomerically pure monosulfonated diamines have also been successfully used for the iridium-catalyzed asymmetric transfer hydrogenation of ketones [42–44].

The majority of subsequent research into iridium-catalyzed asymmetric transfer hydrogenation has involved the use of either Ir(cod) or Cp*Ir complexes as catalysts. In the case of reactions using Ir(cod) catalysts, the ligand **42** developed by Gao and coworkers has achieved the highest enantioselectivies across a range of substrates (Scheme 11)[45]. The Ir(III) precursor $[IrHCl_2(cod)]_2$ was complexed in situ to ligand **42** and used for the reduction of ketones **36** and **43** at room temperature with high enantioselectivity to the corresponding alcohols **37** and **44**. In the case of the reduction of propiophenone **36**, the reactions were run at lower catalyst loading. Using only 0.02 mol% of catalyst, a 90% isolated yield of alcohol **37** was obtained with 88.4% ee after 3 h at 55°C [46]. Gao and coworkers subsequently reported that the reactions were also successful in the absence of base [47].

Several other enantiomerically pure bidentate ligands have been screened using $[Ir\,(cod)Cl]_2$, including bis-oxazolines [48, 49], amino oxazolines [50], *N*-heterocyclic carbenes [51], and diamines [52, 53]. Examples where the enantioselectivity was in excess of 90% ee include the use of ligands **45**, **46**, and **47** [54–56]. Selected examples of the use of these ligands with $[Ir(cod)Cl]_2$ are given in Scheme 12 for the reduction of ketones **48**, **50**, and **52**.



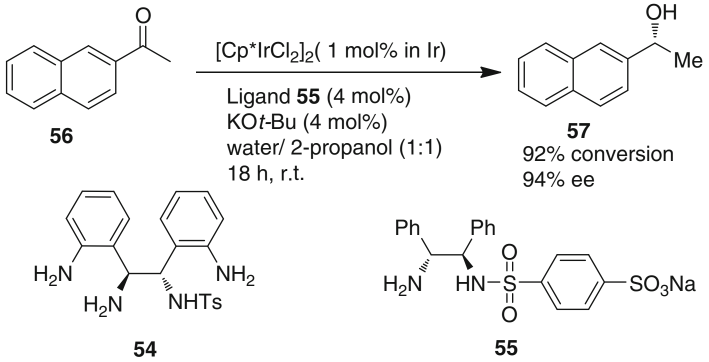
Scheme 11 Use of a bidentate phosphine in asymmetric transfer hydrogenation



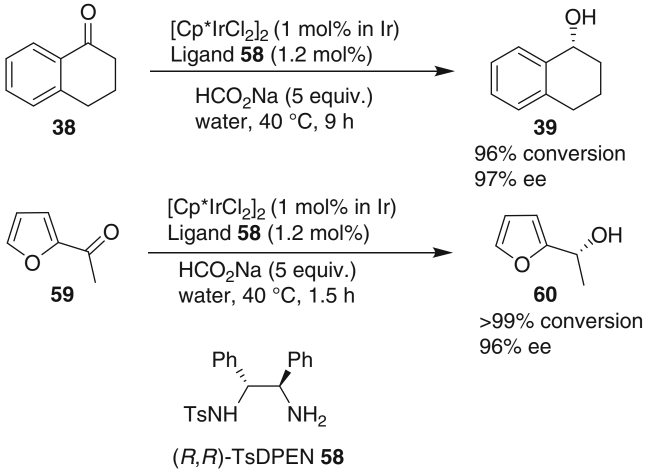
Scheme 12 Further examples of asymmetric transfer hydrogenation with [Ir(cod)Cl]$_2$

There has been a growing interest in the development of aqueous phase asymmetric transfer hydrogenation of ketones [57, 58]. Water-soluble enantiomerically pure ligands **54** and **55** have been prepared [59, 60]. Ligand **54**, although highly successful with [Cp*RhCl$_2$]$_2$, gave low conversions using [Cp*IrCl$_2$]$_2$ but still with good enantioselectivity. Sulfonated ligand **55** was used in a mixture of water and 2-propanol to reduce aromatic ketones including ketone **56** (Scheme 13). The presence of water was found to accelerate the rate of reduction, even though the concentration of 2-propanol was lowered.

Gao and coworkers have developed a tetra-sulfonated version of their ligand **42** and demonstrated that this can be used in 2-propanol/water (2:1) with similar levels of enantioselectivity to those obtained with the nonsulfonated ligand [61]. Xiao and coworkers have demonstrated that it is not necessary for the TsDPEN ligand to be derivatized for asymmetric transfer hydrogenation reactions to be successful in water [62]. They used unmodified TsDPEN **58**, which was precomplexed to [Cp*IrCl$_2$]$_2$ and then used to catalyze the reduction of over twenty aryl ketones using sodium formate as the reducing agent. Especially high enantioselectivities



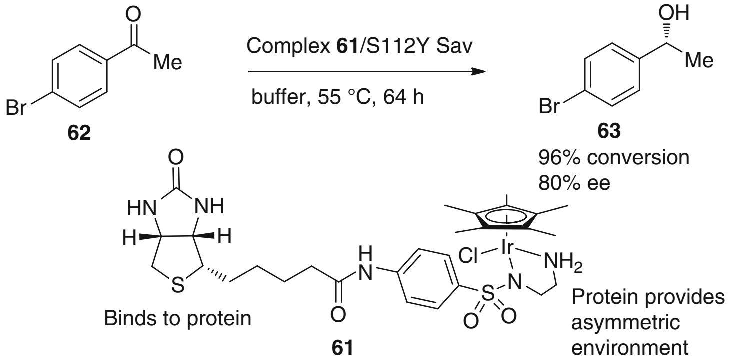
Scheme 13 Further examples of asymmetric transfer hydrogenation with $[Cp^*IrCl_2]_2$



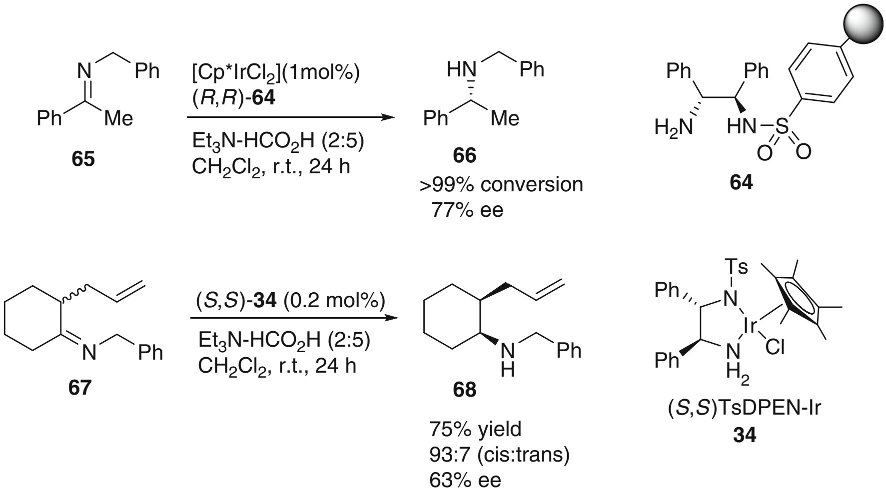
Scheme 14 Asymmetric transfer hydrogenation in water

were obtained in the reduction of tetralone **38** and 2-acetylfuran **59** (Scheme 14). However, in all cases, the analogous rhodium catalysts were found to be more reactive and more selective.

Ward and coworkers have developed an interesting approach to the asymmetric transfer hydrogenation of ketones by designing a series of artificial metalloenzymes [63]. They prepared a range of metal complexes, including the iridium catalyst **61**, which were tethered to the biotin group. The biotin group has a high affinity for the protein Streptavidin, and once the catalyst was docked into the protein, the chiral environment around the iridium was exploited for the asymmetric transfer hydrogenation of ketones. In the case of the iridium complex **61**, a mutant of the wild type Streptavidin, S112Y Sav, was found to give a good level of asymmetric induction for the reduction of bromoacetophenone **62** to the corresponding alcohol **63** (Scheme 15).



Scheme 15 Use of a protein to provide an asymmetric environment



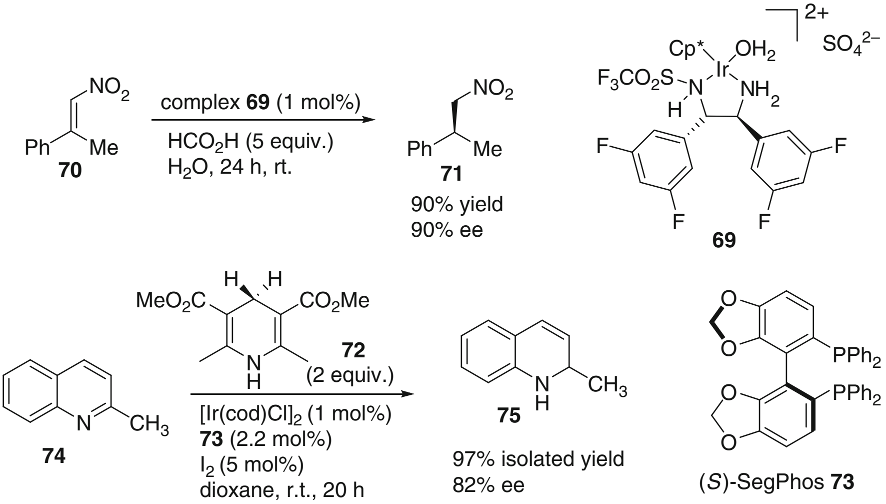
Scheme 16 Asymmetric reduction of imines with iridium catalysts

5 Asymmetric Transfer Hydrogenation of Other Substrates

The asymmetric transfer hydrogenation of imines using iridium catalysts has received less attention than with ruthenium catalysts, and the enantioselectivities appear to be lower for iridium catalysts. Haraguchi and coworkers have used the polymer-supported ligand **64** for the reduction of imine **65** using $Et_3N\text{-}HCO_2H$ (2:5 azeotrope) as the hydrogen source (Scheme 16) [64]. When the catalyst precursor was $[Cp^*IrCl_2]_2$, the product **66** was formed with 77% ee, whereas a higher ee could be obtained using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst precursor. There has been a report of a dynamic kinetic resolution reaction for the reduction of imines using iridium complex **34** [65]. Imine **67** is stereochemically labile under the reaction conditions due to ready tautomerization to the achiral enamine. Iridium complex **34** catalyzed the reduction of imine **67** to give the amine **68** with reasonable enantioselectivity. However, when the isoelectronic Ru(*p*-cymene) complex was used, enantioselectivities of up to 98% ee could be obtained for related substrates.

In spite of the success of asymmetric iridium catalysts for the direct hydrogenation of alkenes, there has been very limited research into the use of alternative hydrogen donors. Carreira and coworkers have reported an enantioselective reduction of nitroalkenes in water using formic acid and the iridium aqua complex **69** [66]. For example, the reduction of nitroalkene **70** led to the formation of the product **71** in good yield and enantioselectivity (Scheme 17). The use of other aryl substrates afforded similar levels of enantioselectivity.

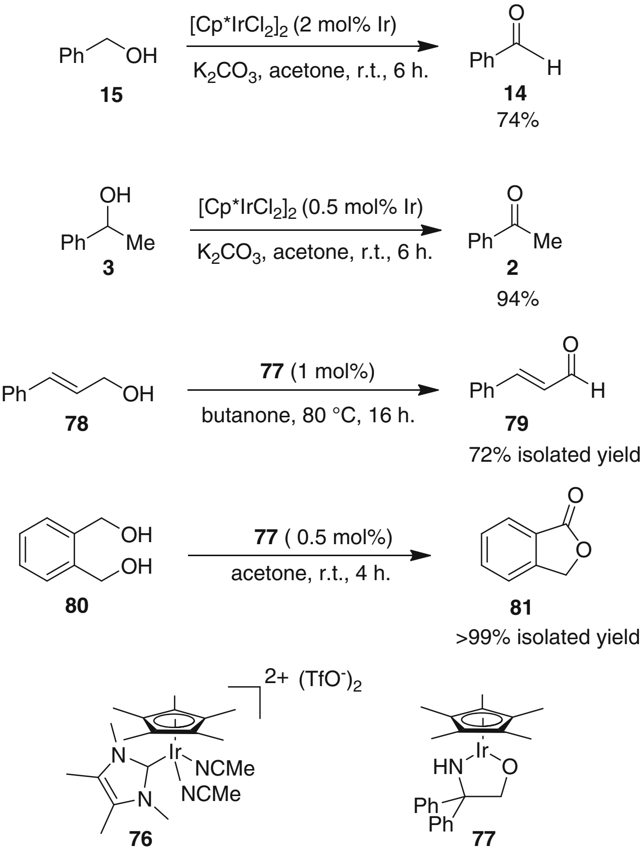
The asymmetric reduction of quinolines has been achieved using Hantzsch esters as the hydrogen donor [67]. Loss of hydrogen from Hantzsch ester **72** leads to the corresponding pyridine, which provides a strong driving force for hydrogen donation. The iridium complex $[Ir(cod)Cl]_2$ is complexed with (*S*)-Segphos **73** and activated with iodine and then used as the catalyst for the transfer hydrogenation of 2-methylquinoline **74** (Scheme 17). The asymmetric reduction of substrate **74** has also been reported using sodium formate as the reducing agent with an in situ catalyst formed from $[Cp^*IrCl_2]_2$ and TsDPEN, although the product **75** was formed with only 11% ee [68]. This contrasts with the corresponding rhodium catalyst where the product was formed with 96% ee.



Scheme 17 Asymmetric reduction of other substrates with iridium catalysts

6 Oxidation of Alcohols

The use of metal-catalyzed hydrogen transfer reactions for alcohol oxidation provides an alternative approach to the use of noncatalytic stoichiometric oxidants. Various alcohols and diols have been oxidized using iridium catalysts in the presence of a ketone as a hydrogen acceptor (Scheme 18). The Oppenauer-type oxidation of primary and secondary alcohols using $[CpIrCl_2]_2$ in the presence of K_2CO_3 has been shown to be effective [69]. Even at room temperature, benzyl alcohol **15** could be converted into benzaldehyde **14** using acetone as both the solvent and hydrogen acceptor (Scheme 18). No over-oxidation to carboxylic acids or esters was observed. Secondary alcohols including 1-phenethyl alcohol **3** were readily converted into the corresponding ketones. Modifications of the $[CpIrCl_2]_2$ complex have been found to give improvements in turnover number in alcohol oxidation reactions. The *N*-heterocyclic carbene complex **76** could be used with

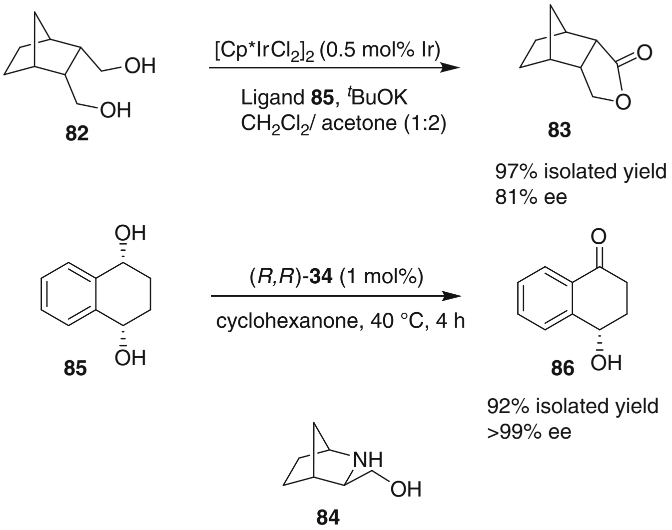


Scheme 18 Oxidation of alcohols by hydrogen transfer

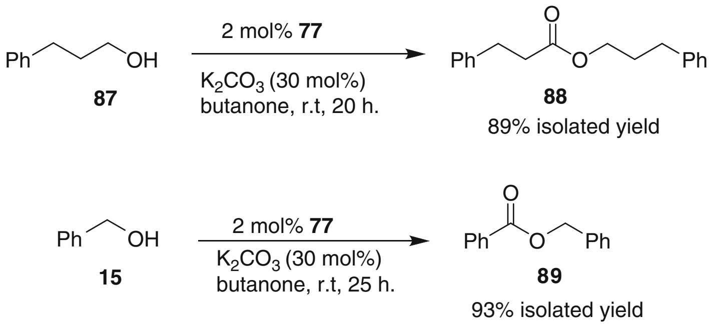
lower catalyst loadings than for the parent complex [70, 71]. The iridium complex **77** has also been used as a catalyst for the oxidation of alcohols (Scheme 18). Using either butanone or acetone as the solvent and hydrogen acceptor, primary alcohols were selectively oxidized to aldehydes. Electron-rich benzylic alcohols were particularly good substrates, with aliphatic alcohols performing less well. The oxidation of cinnamyl alcohol **78** gave cinnamaldehyde **79** in good yield [72], while the oxidation of diols led to the formation of lactones via intermediate hydroxy aldehydes [73]. Cyclization to the lactol and further oxidation led to formation of the lactone. For example, diol **80** was oxidized to give lactone **81** under mild reaction conditions.

Asymmetric variants of alcohol oxidation reactions have been reported, including the desymmetrization of meso diols, to give lactones using $[\mathrm{CpIrCl_2}]_2$ in the presence of an enantiomerically pure amino alcohol. In the best example reported, meso diol **82** was converted into the enantiomerically enriched lactone **83** using $[\mathrm{CpIrCl_2}]_2$/ligand **84**/*t*-BuOK as the catalyst [74]. Related chemistry involving the desymmetrization of meso diol **85** gave the hydroxy ketone **86** with over 99% ee, using the preformed catalyst (*R*,*R*)-**34** (Scheme 19) [75].

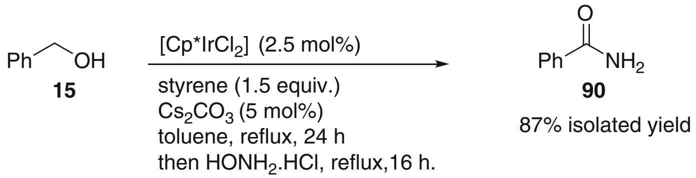
Complex **77** has also been reported to catalyze the oxidative dimerization of alcohols to esters when the reactions are performed in the presence of base [76]. The presence of base presumably encourages the reversible attack of the alcohol onto the initially formed aldehyde to give a hemiacetal, which is further oxidized to give the ester product. Alcohols **87** and **15** were converted into esters **88** and **89** with good isolated yields (Scheme 20). Alternative iridium catalysts have been used for related oxidative dimerization reactions, and the addition of base is not always a requirement for the reaction to favor ester formation over aldehyde formation [77, 78].



Scheme 19 Asymmetric oxidation of diols by desymmetrization



Scheme 20 Oxidative dimerization of alcohols to give esters

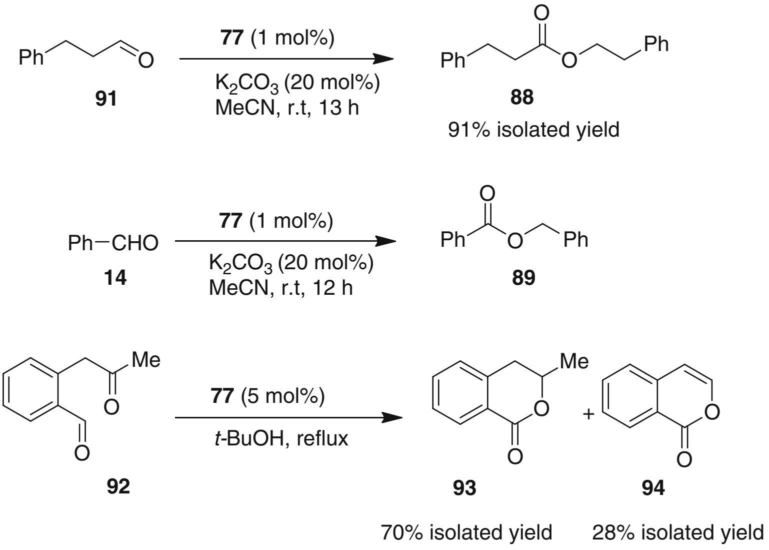


Scheme 21 Iridium catalyzed conversion of an alcohol to a primary amide

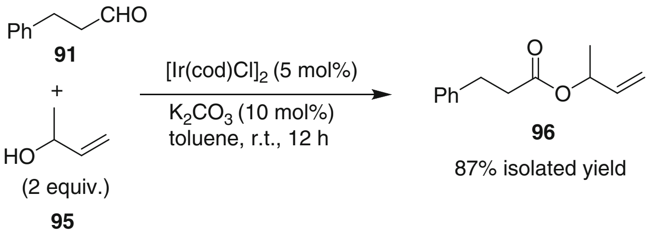
The iridium-catalyzed oxidation of benzylic alcohols has been coupled with an in situ oxime formation. The iridium catalyst then fulfills a second role by catalyzing the rearrangement of the oxime into an amide. For example, benzyl alcohol **15** underwent oxidation to benzaldehyde using styrene as the hydrogen acceptor in the presence of [CpIrCl$_2$]$_2$, as shown in Scheme 21. Addition of hydroxylamine hydrochloride to the reaction mixture rapidly generated benzaldehyde oxime, which after, further heating, rearranged to give benzamide **90** in good isolated yield [79]. The reaction of 2-aminobenzyl alcohol with enolizable ketones has been catalyzed by iridium complexes to give quinolines as the oxidized products [80]. Two equivalents of ketone were used in order to drive the oxidation process.

7 Tishchenko Reaction

The dimerization of aldehydes to form esters is a completely atom-efficient process known as the Tishchenko reaction, which involves no net oxidation or reduction. Suzuki, Katoh, and coworkers have used complex **77** to catalyze the Tishchenko reaction of a range of aldehydes, including dihydrocinnamaldehyde **91** and benzaldehyde **14** (Scheme 22) [81]. The same catalyst has been used for an intramolecular variant of the reaction, where keto-aldehyde **92** isomerizes to lactone **93** via an intramolecular Tishchenko reaction. The oxidized product is formed as a by-product,



Scheme 22 Tishchenko reaction catalysed by irisium complexes



Scheme 23 Oxidation of an aldehyde to an ester

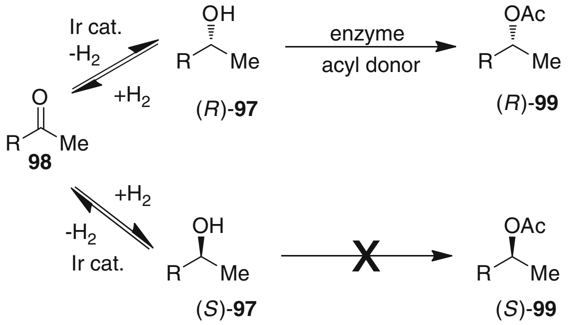
and by running the reaction in the presence of an additional aldehyde as a hydrogen acceptor, the oxidized species **94** is formed as the sole product [82].

A related report has demonstrated that aldehydes can be converted into esters in the presence of allylic alcohols [83]. Dihydrocinnamaldehyde **91** and allyl alcohol **95** undergo a cross-condensation reaction to give ester **96**. The allyl alcohol **95** also serves as a hydrogen acceptor, perhaps via an isomerization/reduction sequence (Scheme 23).

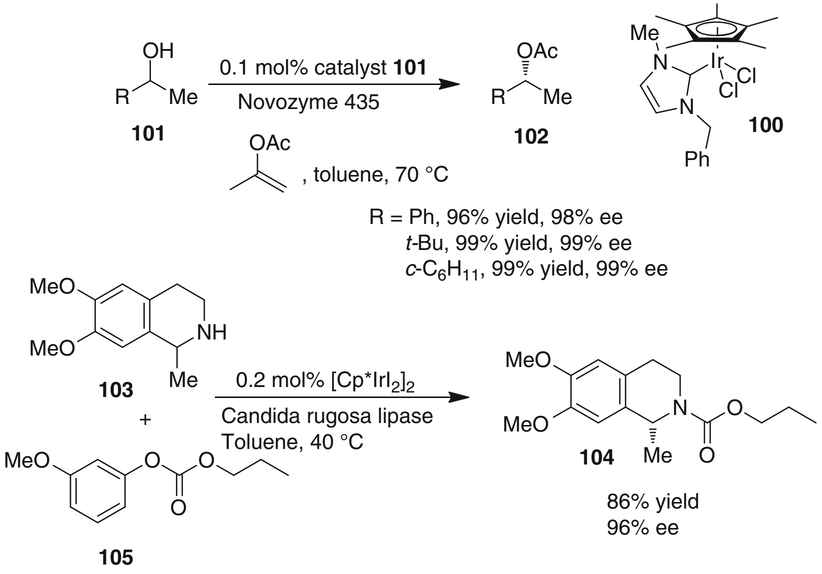
8 Dynamic Kinetic Resolution Processes

The reversibility of hydrogen transfer reactions has been exploited for the racemization of alcohols and amines. By coupling the racemization process with an enantioselective enzyme-catalyzed acylation reaction, it has been possible to achieve dynamic kinetic resolution reactions. The combination of lipases or esterases with various ruthenium catalysts has been widely employed for these reactions [84], although there are also a few reports of combining enzymes with iridium catalysts to achieve dynamic kinetic resolution reactions [85–88]. The general principle of the dynamic resolution process is outlined in Scheme 24. Interconversion of alcohol (*R*)-**97** with its enantiomer (*S*)-**97** can be achieved by the temporary removal of hydrogen via the achiral ketone **98**. The enzyme selectively acylates one enantiomer of the alcohol to give the enantiomerically enriched ester (*R*)-**99**, which is inert to racemization under the reaction conditions.

Marr and coworkers have used the combination of the iridium *N*-heterocyclic carbene complex **100** (0.1 mol%) with the lipase Novozyme 435 to convert racemic alcohols **101** into enantiomerically enriched esters **102** with excellent yield and enantioselectivities (Scheme 25) [85]. Peris and coworkers have used complex **25**



Scheme 24 Dynamic kinetic resolution strategy



Scheme 25 Examples of iridium catalyzed dynamic kinetic resolution

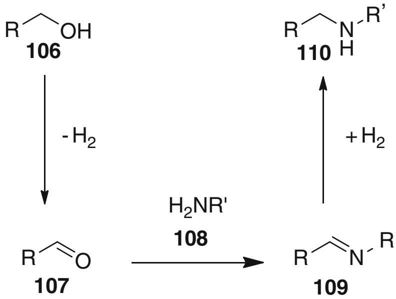
to effect the racemization of a branched primary alcohol and used this in combination with an enzyme-catalyzed acylation in order to perform a dynamic kinetic resolution [27].

$[Cp^*IrI_2]_2$ has been used by Blacker and coworkers as an efficient catalyst for the racemization of amines [86, 87]. The catalyst reversibly converts the amine into an achiral imine in a similar way to that seen for alcohol racemization. Racemic amine **103** underwent dynamic kinetic resolution to form the carbamate **104** with high enantioselectivity in the presence of *Candida rugosa* lipase and the iridium catalyst (Scheme 25). Feringa, deVries, and coworkers have reported that the reaction of $[CpIrI_2]_2$ with benzylic amines generates iridacyclic complexes, which are also competent catalysts for the racemization of alcohols and amines [88].

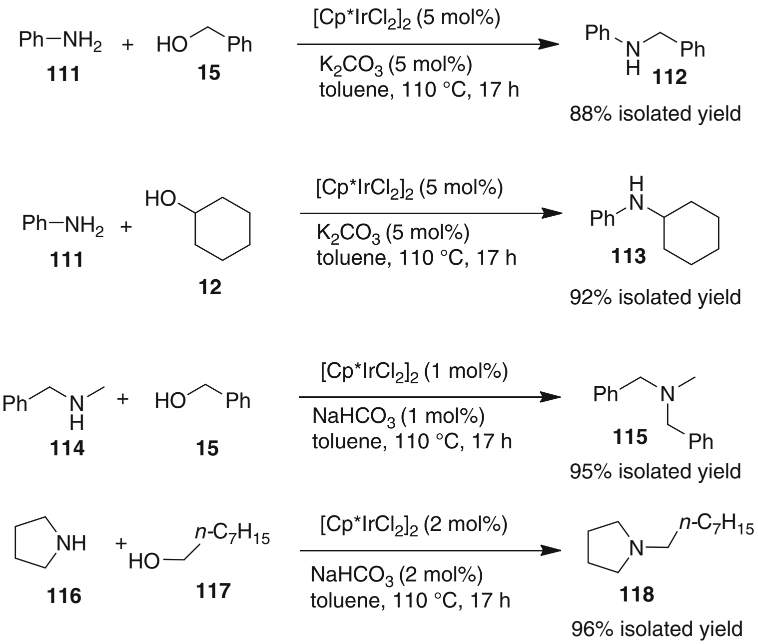
9 Alkylation of Amines with Alcohols

The ability of iridium complexes to interconvert alcohols and carbonyl compounds has been developed to allow alcohols to act as alkylating agents. Alcohols are generally less toxic than the corresponding alkyl halides, and this methodology provides a more environmentally benign approach to the alkylation of amines. The mechanism is believed to proceed via the temporary removal of hydrogen from the alcohol **106** to give an intermediate aldehyde **107** (Scheme 26). The intermediate aldehyde **107** is more electrophilic than the original alcohol and will readily react with an amine **108** to form an imine **109**. Whether the imine formation occurs within the coordination sphere of the metal is debatable and may depend on the particular catalyst that is being used. Return of the hydrogen from the catalyst reduces the imine into the amine **110** with no net oxidation or reduction. The overall process has been termed "borrowing hydrogen," and the area has been reviewed recently [89–93].

The most widely used iridium catalyst for the *N*-alkylation of amines with alcohols is $[Cp^*IrCl_2]_2$, which was identified and developed by Fujita, Yamaguchi, and coworkers [94]. Aniline **111** has been selectively alkylated by a range of



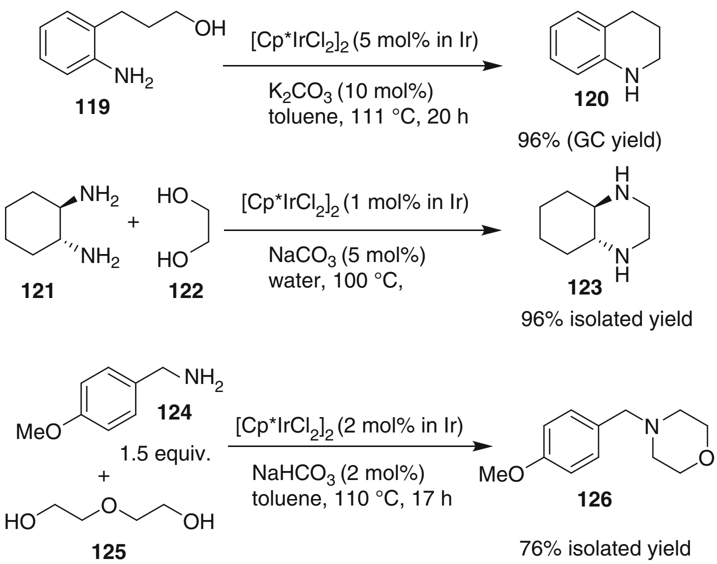
Scheme 26 Alkylation of amines with alcohols by borrowing hydrogen



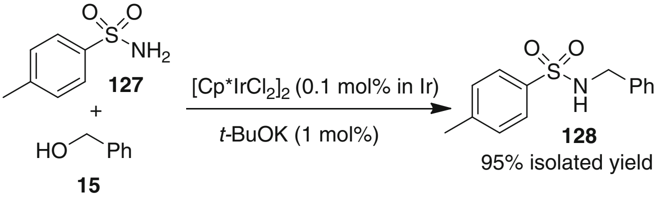
Scheme 27 Examples of amine alkylation reactions

alcohols including benzylic alcohols and primary and secondary alcohols (Scheme 27)[95]. Good isolated yields were generally obtained, including the formation of products **112** and **113** from the reaction of aniline **111** with either benzyl alcohol **15** or cyclohexanol **12**. Secondary amines could also be alkylated under similar reaction conditions. Amine **114** was alkylated with benzyl alcohol **15**, and pyrrolidine **116** was alkylated with octanol **117** to give the corresponding tertiary amine products **115** and **118** [96].

Several cyclizations of amino alcohols have been reported (Scheme 28) [97], including the ring closure of aniline **119** to give tetrahydroisoquinoline **120** [98]. Interestingly, when the reaction was run on the substrate with one less methylene group in the tether, the five-membered ring product was formed as the indole with loss of hydrogen. Cyclization reactions involving diols and either amines or diamines have been reported. Nordstrøm and Madsen cyclized diamine **121** with ethylene glycol **122** to give the bicyclic piperazine **123** [99]. The reactions could be run in water, and although the presence of base was beneficial for these reactions, it was not essential. In a separate study, Williams and coworkers showed that base was generally not needed for amination reactions catalyzed by $[Cp^*IrCl_2]_2$ when they were run in water or ionic liquids [100]. Cyclization reactions of primary amines with diols provide an interesting approach to the synthesis of *N*-heterocycles. In one example, the formation of morpholine **126** was achieved by the reaction of amine **124** with diol **125** [101, 102].



Scheme 28 The use of diols to give cyclic amines

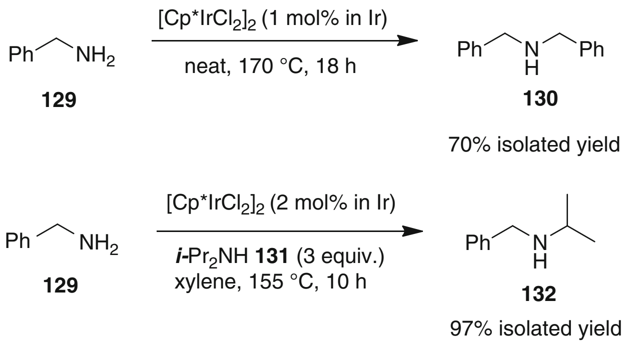


Scheme 29 Alkylation of sulfonamides with alcohols

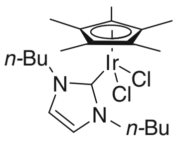
Recently, the *N*-alkylation of sulfonamides using $[Cp^*IrCl_2]_2$ as the catalyst has been reported using either water [100] or toluene [103] as the solvent (Scheme 29). *p*-Toluenesulfonamide **127** was alkylated with a range of over 20 alcohols. When benzylic alcohols were used, it was possible to use a low catalyst loading in order to achieve reaction. The catalytic species formed in the reactions was a bridged iridium dimer complex, $[(Cp^*Ir)(\mu\text{-}NTs)_2]$. Eisenstein, Crabtree, and coworkers briefly examined the alkylation of *p*-toluenesulfonamide **127** in the context of a mechanistic investigation [104]. Computational studies had shown that while alcohol and imine complexation to iridium were requirements for *N*-alkylation reactions, the basic amines coordinate more strongly, lowering the rate of reaction. The faster reaction observed using *p*-toluenesulfonamide, which is less basic than conventional amines, provided experimental support for the theoretical calculations.

Under more forcing reaction conditions, $[Cp^*IrCl_2]_2$ has been reported to convert primary amines into secondary amines with loss of ammonia [105]. At 170°C, benzylamine **129** was converted into dibenzylamine **130**, with only trace amounts of tertiary amines being formed (Scheme 30). The cross-coupling of two amines has been achieved with high selectivity where the iodide complex $[Cp^*IrI_2]_2$ was found to be more reactive [106]. Thus, benzylamine **129** reacted with diisopropylamine **131** to give the secondary amine **132**. These reactions are believed to proceed via oxidation of the diisopropylamine **131** to an imine, which is then attacked by the primary amine with loss of isopropylamine and subsequent reduction to give the amine product.

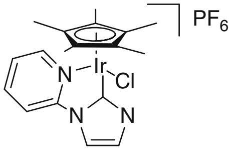
Complexation of $[Cp^*IrCl_2]_2$ with *N*-heterocyclic carbenes has led to complexes such as **25**, developed by Peris and coworkers [107, 108], and **133**, developed by Crabtree and coworkers [12]. Complex **24** is activated by the addition of silver triflate and is effective for the *N*-alkylation of amines with alcohols and for the *N*-alkylation of anilines with primary amines. Complex **25** has also been shown to couple benzyl alcohol **15** with a range of alcohols, including ethanol **134**, to give ether products such as ether **135** (Scheme 31). Complex **133** was an active hydrogen transfer catalyst for the reduction of ketones and imines, using 2-propanol as the hydrogen source. It was also an effective catalyst for the *N*-alkylation of amines



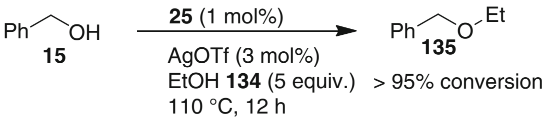
Scheme 30 Iridium catalyzed amine coupling



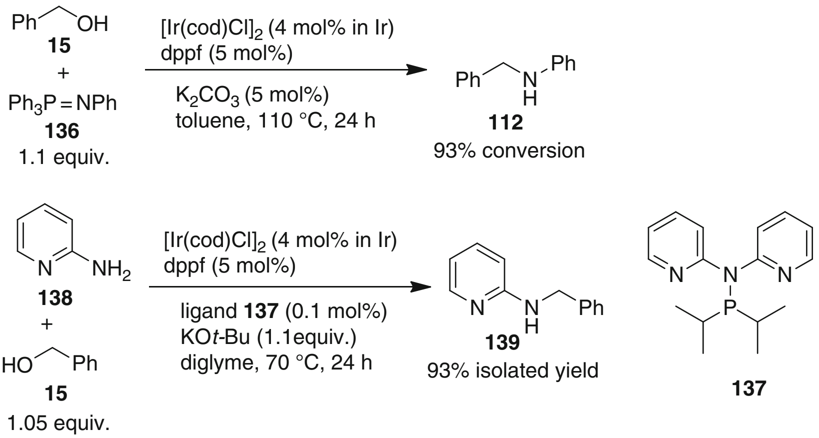
25



133



Scheme 31 Conversion of alcohols into ethers



Scheme 32 Further examples of amine formation from alcohols

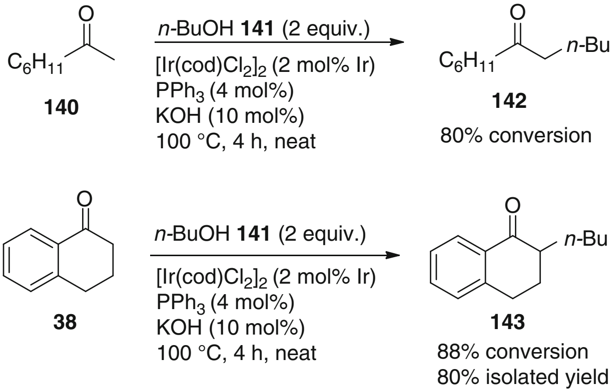
with alcohols and the β-alkylation of secondary alcohols with primary alcohols (see Sect. 10).

Other iridium complexes that do not contain the Cp* ligand have also been found to be capable of catalyzing *N*-alkylation reactions (Scheme 32). Liu and coworkers have reported that *N*-heterocyclic carbene complexes of the type (NHC)Ir(CO)(PPh_3)Cl are effective catalysts [109]. The *N*-alkylation of amines with alcohols has been catalyzed by $[Ir(cod)Cl]_2$ in the presence of dppf (bis(diphenylphosphino) ferrocene) [110]. The same catalyst combination was also used for the formation of alkylated anilines using iminophosphorane **136** as the nitrogen source [111]. In the reaction with benzyl alcohol **15**, the reaction was believed to proceed by oxidation to benzaldehyde followed by imine formation via an aza-Wittig reaction with iminophosphorane **136** and return of hydrogen to generate the amine product **112**. Kempe and coworkers have found that ligand **137** greatly enhanced the activity of $[Ir(cod)Cl]_2$ and was an effective catalyst even at 70°C for the alkylation of aniline **111** with benzyl alcohol **15** to give *N*-benzyl aniline **112** [112]. In particular, the combination of $[Ir(cod)Cl]_2$ with ligand **137** was effective for the monoalkylation of 2-aminopyridine **138** with a range of alcohols, including benzyl alcohol **15**, at low catalyst loading.

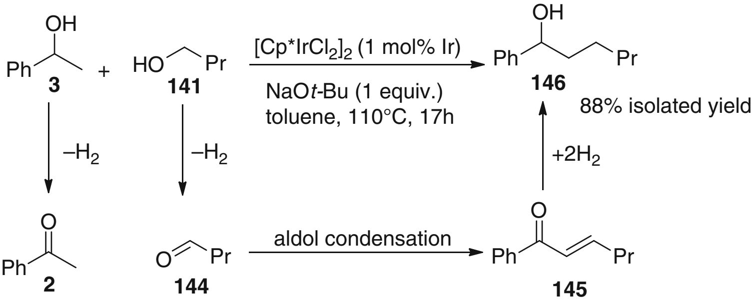
10 C-Alkylation Reactions of Alcohols

The activation of alcohols by iridium-catalyzed borrowing hydrogen reactions has also been applied to the formation of C–C bonds [113]. Reactions proceed by temporary removal of hydrogen from an alcohol to give an aldehyde (or ketone), which is transformed into an alkene with subsequent return of the hydrogen to provide a new C–C bond. Ishii and coworkers have used $[Ir(cod)Cl]_2$ with triphenylphosphine and potassium hydroxide to catalyze the α-alkylation of ketones with alcohols [114]. Typical examples include the reaction of ketones **140** and **38** with 1-butanol **141** to give the butylated products **142** and **143** (Scheme 33). For the reaction with ketone **140**, the alkylation was completely selective for reaction on the less substituted side of the ketone. Related iridium-catalyzed α-alkylation of ketones with alcohols has been reported where the product ketone is reduced in situ by transfer hydrogenation with an enantiomerically pure ruthenium complex [115].

Fujita, Yamaguchi, and coworkers have coupled secondary alcohols with primary alcohols using $[Cp^*IrCl_2]_2$ as the catalyst [116]. The reaction occurs by removal of hydrogen from the secondary alcohol **3** and the primary alcohol **141** to give ketone **2** and aldehyde **144** intermediates (Scheme 34). An aldol condensation of these intermediates leads to the α,β-unsaturated ketone **145**, which is reduced to the saturated alcohol **146** by the return of two equivalents of hydrogen. An alternative iridium(III) catalyst, $(terpy)IrCl_3$ (terpy = 2,2′:6′,2″-terpyridine), was found to have higher activity with reaction times as low as 1 h under otherwise



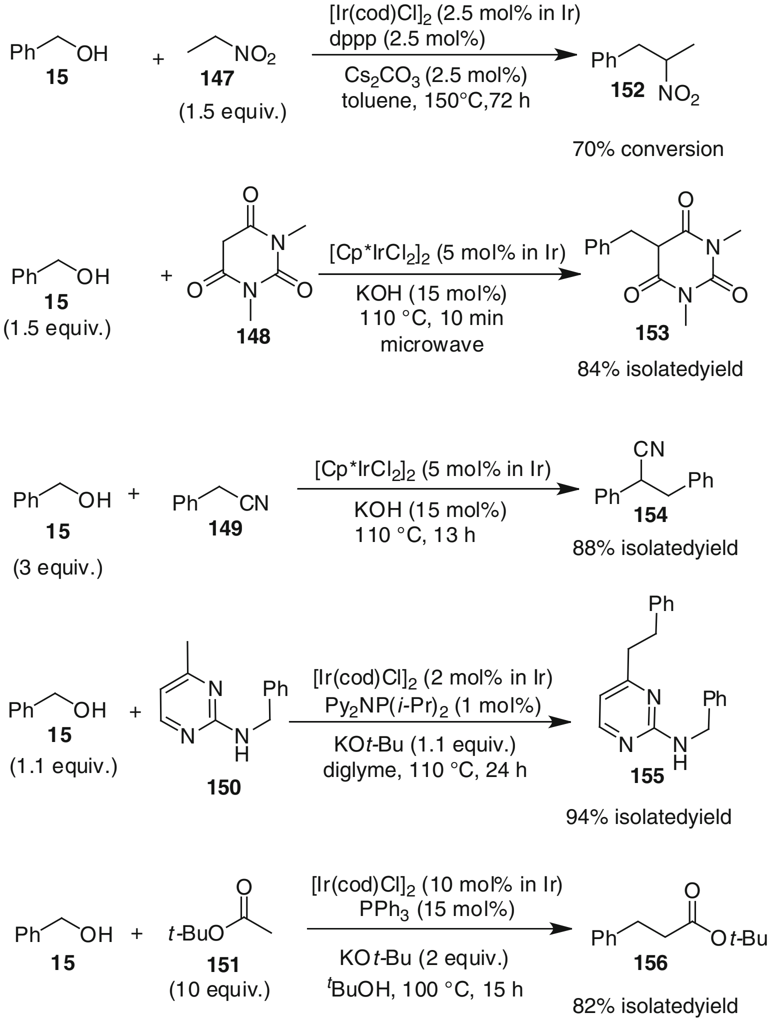
Scheme 33 Formation of C-C bonds using alcohols



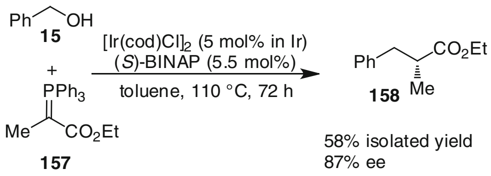
Scheme 34 Alcohol coupling reactions by borrowing hydrogen

similar reaction conditions [117]. A selfcondensation of primary alcohols has also been reported using either $[Ir(cod)Cl]_2$ or $[Cp^*IrCl_2]_2$ [118].

A variety of other carbon nucleophiles have been alkylated with alcohols including malonate esters, nitroalkanes, ketonitriles [119, 120], barbituric acid [121], cyanoesters [122], arylacetonitriles [123], 4-hydroxycoumarins [124], oxindoles [125], methylpyrimidines [126], indoles [127], and esters [128]. Selected examples are given in Scheme 35. Thus, benzyl alcohol **15** could be alkylated with nitroethane **147**, 1,3-dimethylbarbituric acid **148**, phenylacetonitrile **149**, methylpyrimidine **150**, and even *t*-butyl acetate **151** to give the corresponding alkylated products **152–156**.



Scheme 35 Further examples of alcohols as alkylating agents



Scheme 36 Enantioselective variant of borrowing hydrogen

The formation of C–C bonds from alcohols using iridium-catalyzed borrowing hydrogen chemistry has also been reported using Wittig reagents and Horner Wadsworth Emmons reagents for the alkene-forming step in the reaction pathway [129, 130]. In the example in Scheme 36, the reaction was performed using an enantiomerically pure iridium catalyst, which was used to couple phosphonium ylid, **157** with benzyl alcohol **15** to give the product **158** with reasonably good control of enantioselectivity [131].

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Top Organomet Chem (2011) 34:107–138
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Formation of C–C Bonds via Iridium-Catalyzed Hydrogenation and Transfer Hydrogenation

John F. Bower and Michael J. Krische

Abstract The formation of C–C bonds via catalytic hydrogenation and transfer hydrogenation enables carbonyl and imine addition in the absence of stoichiometric organometallic reagents. In this review, iridium-catalyzed C–C bond-forming hydrogenations and transfer hydrogenations are surveyed. These processes encompass selective, atom-economic methods for the vinylation and allylation of carbonyl compounds and imines. Notably, under transfer hydrogenation conditions, alcohol dehydrogenation drives reductive generation of organoiridium nucleophiles, enabling carbonyl addition from the aldehyde or alcohol oxidation level. In the latter case, hydrogen exchange between alcohols and π-unsaturated reactants generates electrophile–nucleophile pairs en route to products of hydro-hydroxyalkylation, representing a direct method for the functionalization of carbinol C–H bonds.

Keywords Iridium, Enantioselective, Hydrogenation, Transfer hydrogenation, Allylation, Vinylation

Contents

J.F. Bower
Department of Chemistry and Biochemistry, University of Texas at Austin, 1 University Station – A5300, Austin, TX 78712-0165, USA
and
Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford 1 3TA, UK

M.J. Krische (✉)
Department of Chemistry and Biochemistry, University of Texas at Austin, 1 University Station – A5300, Austin, TX 78712-0165, USA
e-mail: mkrische@mail.utexas.edu

1 Introduction

The majority of chemical commodities (plastics, foams, pharmaceuticals, agrochemicals) are made from rapidly depleting petrochemical feedstocks. Consequently, there is a growing need to develop catalytic methods for the direct manufacture of chemical products from abundant renewable resources in the absence of stoichiometric byproducts [1]. In the specific case of carbonyl and imine addition, a departure from the use of premetallated nucleophiles represents a particularly important focus. Progress in this area will depend largely upon the discovery of new chemical reactivity.

Catalytic hydrogenation is the cleanest and most cost-effective method available for the reduction of organic molecules. Accordingly, chemical processes such as the Haber–Bosch reaction[1] [2, 3], alkene hydroformylation[2] [4–7], and enantioselective hydrogenation[3] [8–10], all of which provide materials essential to humanity, are practiced on a vast scale. The industrialization of these processes is assisted by the fact that such hydrogen-mediated transformations do not generate stoichiometric byproducts, which facilitate product purification and waste stream management. Interestingly, although catalytic hydrogenation and the Grignard reaction are both reductive transformations, a union between catalytic hydrogenation and carbonyl addition chemistry failed to materialize after the emergence of alkene hydroformylation, which may be viewed as the prototypical C–C bond-forming hydrogenation.

The collective studies from our laboratory establish metal-catalyzed hydrogenation and transfer hydrogenation as general methods for C–C bond formation.[4,5,6]

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[1] The catalytic hydrogenation of atmospheric nitrogen, accounts for the annual production of over 100,000,000 metric tons of ammonia, which is the limiting nutrient in terrestrial plant growth. The Haber–Bosch process is estimated to sustain one-third of the Earth's population. Approximately half the nitrogen in our bodies is nitrogen fixed through the Haber–Bosch reaction.

[2] The prototypical C–C bond forming hydrogenation, hydroformylation combines basic feedstocks (α-olefins, carbon monoxide, and hydrogen) with perfect atom economy and accounts for the production of over 10 million metric tons of aldehyde annually, making it the largest volume application of homogeneous metal catalysis.

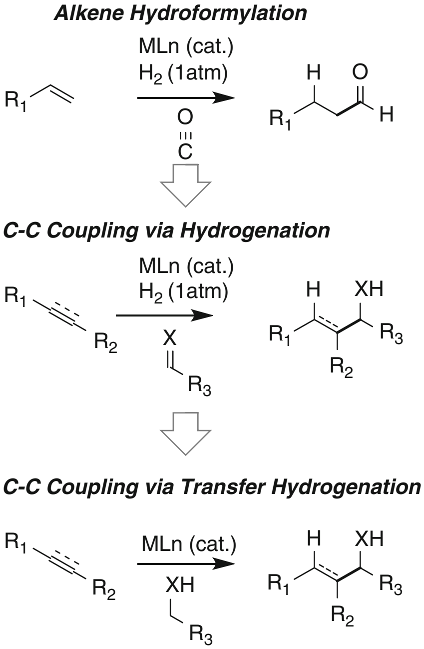
[3] The asymmetric hydrogenation of $C{=}X$ π-bonds ($X = O$, NR) is estimated to account for over half the chiral drugs manufactured industrially, withstanding physical and enzymatic resolution.

[4] For selected reviews on C–C bond forming hydrogenation and transfer hydrogenation, see [11–17].

[5] Prior to our systematic studies, two isolated reports of hydrogen mediated C–C coupling were reported, see [18, 19].

[6] Side products of reductive C–C bond formation have been observed in catalytic hydrogenation on rare occasions, see [20, 21].

Scheme 1 Catalytic C–C coupling via hydrogenation and transfer hydrogenation (X=O, NR_2)



These processes exploit π-unsaturated reactants as surrogates to moisture sensitive organometallic reagents, enabling carbonyl and imine addition under essentially neutral conditions in the absence of stoichiometric organometallic reagents and resulting metallic byproducts. Remarkably, under transfer hydrogenation conditions, hydrogen exchange between alcohols and π-unsaturated reactants generates electrophile–nucleophile pairs en route to products of hydro-hydroxyalkylation, representing a direct method for the functionalization of carbinol C–H bonds.[7,8,9] For such “carbonyl additions from the alcohol oxidation level,” preactivation is not required as both the nucleophile and electrophile are generated catalytically from simple and stable precursors (Scheme 1). In this review, iridium-catalyzed C–C bond-forming hydrogenations and transfer hydrogenations are surveyed. Related hydrogen-mediated C–C couplings employing rhodium and ruthenium catalysts

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[7] The alcohol-unsaturate couplings developed in our laboratory provide products of carbonyl addition. In contrast, related hydrogen auto-transfer processes provide products of alcohol substitution via pathways involving oxidation–condensation–reduction and the use of preactivated nucleophiles. For recent reviews, see [22–25].

[8] Processes that enable direct catalytic C–C functionalization of carbinol C–H bonds are highly uncommon. Rh-catalyzed alcohol-vinylarene C–C coupling has been described. The requirement of BF_3 and trends in substrate scope suggest these processes involve alcohol dehydrogenation-reductive Prins addition: [26–29].

[9] For radical mediated C–C functionalization of carbinol C–H bonds, see [30, 31].

are not covered in this account but are described in several recent monographs (see footnote 4, [11–17]).

2 Iridium-Catalyzed Hydrogenation for C–C Bond Formation

2.1 Alkynes as Vinylmetal Surrogates via Iridium-Catalyzed Hydrogenation

Allylic alcohols and allylic amines are highly versatile building blocks for organic synthesis, and methods for their preparation in enantiomerically enriched form are the subject of intensive investigation.[10,11] The majority of established protocols rely upon metal-catalyzed allylic substitution employing *O*- and *N*-nucleophiles (For reviews on metal catalyzed allylic amination and alkoxylation, see: [37–43]). An alternative approach to allylic alcohols and allylic amines involves the catalytic enantioselective vinylation of aldehydes and imines. Based upon the seminal studies of Oguni [44] and Noyori [45] on the enantioselective addition of dialkylzinc reagents to aldehydes (For reviews encompassing catalytic enantioselective addition of organozinc reagents to carbonyl compounds, see: [46–51]), Oppolzer (see footnote 12, [52]) devised the first catalytic enantioselective aldehyde vinylations.[12,13] In this process, vinylzinc reagents are generated in situ by alkyne hydroboration followed by transmetallation from boron to zinc using $ZnMe_2$. A conceptually related approach was developed subsequently by Wipf, in which hydrozirconation-transmetallation is used to generate the vinylzinc reagent (see footnote 12, [55]). These studies, along with catalytic enantioselective alkyl- and aryl-zinc-mediated ketone additions described by Yus [73, 74] and Fu [75], set the stage for catalytic enantioselective ketone vinylations, as described by Walsh (For catalytic enantioselective ketone vinylation using organozinc reagents, see: [76–78]). Catalytic methods for carbonyl vinylation continue to emerge, as demonstrated by recent reports on rhodium-catalyzed aldehyde additions employing vinylboron reagents [79].

Enantioselective vinylzinc-mediated imine additions reveal additional challenges (For reviews encompassing the catalytic enantioselective addition of organozinc reagents to imines, see: [80–84]). After the seminal report of Soai [85], several enantioselective catalysts for the addition of organozinc reagents to imines were developed. However, highly activated *N*-acyl and *N*-(diphenylphosphinoyl) imines are required (For enantioselective catalytic addition of organozinc reagents

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[10] For reviews encompassing the synthesis of allylic alcohols, see [32, 33].

[11] For reviews encompassing the synthesis of allylic amines, see [34–36].

[12] For enantioselective catalytic addition of vinylzinc reagents to aldehydes, see [52–70].

[13] For reviews encompassing catalytic enantioselective aldehyde vinylation using organozinc reagents, see [71, 72].

to imines, see: [85–96]). To address the issue of reactivity, Tomioka (see footnote 14, [97]) disclosed an enantioselective copper catalyst for organozinc-mediated imine addition.[14] In addition to late transition metals (Cu, Rh) (see footnote 14) [117, 118], early transition metal catalysts (Ti, Zr, Hf) (For enantioselective zirconium, titanium and hafnium catalyzed addition of organozinc reagents to imines, see: [119–124]) are found to promote the highly enantioselective addition of organozinc reagents to imines. The enantioselective addition of organolithium reagents to imines promoted or catalyzed by chiral chelating agents also has been described (For reviews encompassing catalytic enantioselective addition of organolithium reagents to carbonyl compounds and imines, see: [125–132]). Finally, under the conditions of rhodium catalysis, organotin, organotitanium, and organoboron reagents participate in catalytic asymmetric imine addition (For enantioselective rhodium catalyzed addition of organometallic reagents to imines, see: Organotin reagents [133–134], Organotitanium reagents [135] and Organoboron reagents [136]). Despite these efforts, highly enantioselective imine additions employing vinylmetal reagents remain elusive (Catalyzed addition of vinylzirconocenes to imines is known, but enantioselective variants have not been developed: [147, 148]).[15]

The direct metal-catalyzed reductive coupling of alkynes to carbonyl compounds or imines provides an alternative to the use of discrete vinylmetal reagents (For a compilation of reviews on the subject of metal catalyzed reductive C–C coupling, see: [150]).[16] Catalytic intramolecular carbonyl vinylation was first reported by Ojima (1994), who employed a rhodium catalyst in combination with a silane as the terminal reductant [159]. Related cyclizations using titanium or nickel catalysts later were reported by Crowe [160] (For an aligned study, see: [161]) and Montgomery [162–167], respectively. Finally, in an adaptation of Montgomery's cyclization protocol, intermolecular nickel-catalyzed alkyne–aldehyde reductive couplings were reported by Jamison [168–171]. Subsequently, improved nickel catalysts for this process were devised by Takai [172] and Montgomery [165]. However, while direct alkyne–carbonyl reductive couplings circumvent the use of discrete vinylmetal reagents, they nevertheless employ terminal reductants such as hydrosilanes, hydrostannanes, organozinc reagents, organoboron reagents or chromium(II) chloride, which generate stoichiometric quantities of byproduct.

Under the conditions of iridium-catalyzed hydrogenation, alkyne–carbonyl and alkyne–imine reductive coupling occurs in the absence of stoichiometric byproducts. For example, iridium-catalyzed hydrogenation of nonconjugated alkynes in the presence of α-ketoesters delivers the corresponding α-hydroxy esters in

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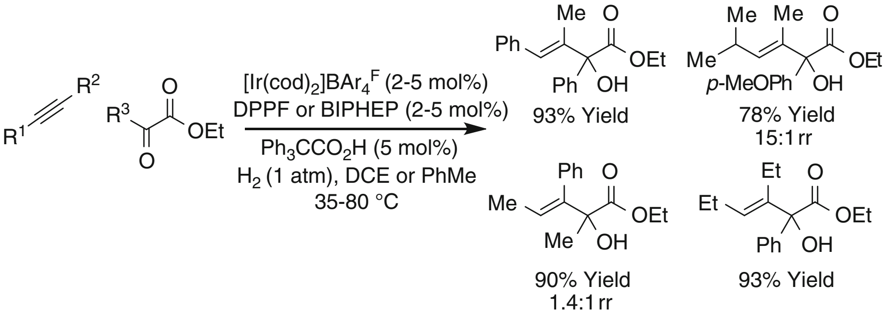
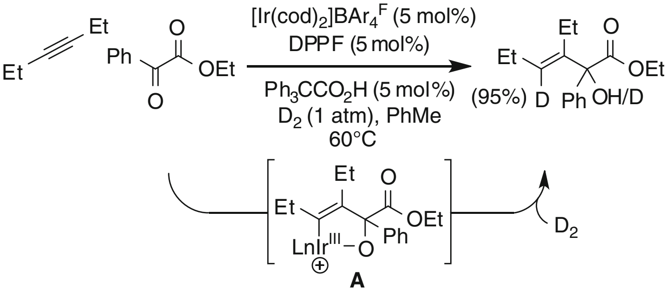
[14] For enantioselective copper catalyzed addition of organozinc reagents to imines, see [97–116].

[15] Enantioselective Ni-catalyzed alkyne, imine, triethylborane 3-component coupling has been reported, but modest selectivities (51–89% ee) are observed. For this method, vinylation is accompanied by ethyl transfer: [149]

[16] For selected reviews encompassing intra- and intermolecular direct reductive coupling of alkynes to carbonyl partners, see [151–158]



Scheme 2 Iridium-catalyzed hydrogenation of alkynes in the presence of α-ketoesters to furnish α-hydroxy esters



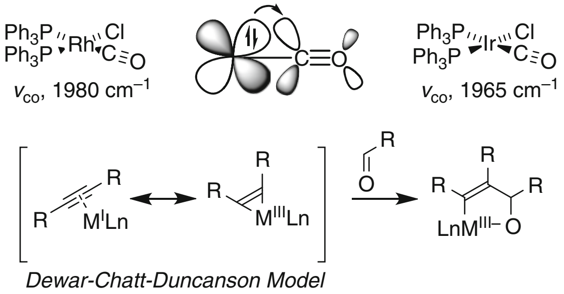
Scheme 3 Alkyne-carbonyl reductive coupling via iridium-catalyzed hydrogenation under a deuterium atmosphere

excellent yield [173]. Notably, nonsymmetric alkynes engage in highly regioselective reductive coupling (Scheme 2).

Deuterium labeling studies are consistent with a mechanism involving alkyne–carbonyl oxidative coupling to furnish iridacycle **A** followed by Brønsted acid-assisted hydrogenolysis of this species to deliver the product. Deuterium at oxygen is removed through exchange in the course of chromatographic isolation but is observed via EI–MS analysis of reaction mixtures. Although mechanisms involving alkyne hydrometallation cannot be excluded on the basis of deuterium labeling studies alone, regioselectivity trends observed in response to variation of the steric features of both the alkyne and carbonyl partners strongly suggest that oxidative coupling pathways are operative (Scheme 3).

Cationic rhodium complexes also catalyze alkyne–carbonyl and alkyne–imine reductive coupling under hydrogenation conditions [174–178]. The rhodium-catalyzed processes are applicable to the reductive coupling of conjugated alkynes (1,3-enynes, 1,3-diynes) to activated ketones [174], aldehydes [175–177], or imines [178]. The rhodium-catalyzed reductive coupling of acetylene to carbonyl compounds or imines also is described [179–182]. For reactions of conjugated alkynes, the observed trends in substrate scope suggest π-backbonding at the stage of the

Scheme 4 Significance of π-backbonding at the stage of the alkyne–metal complex



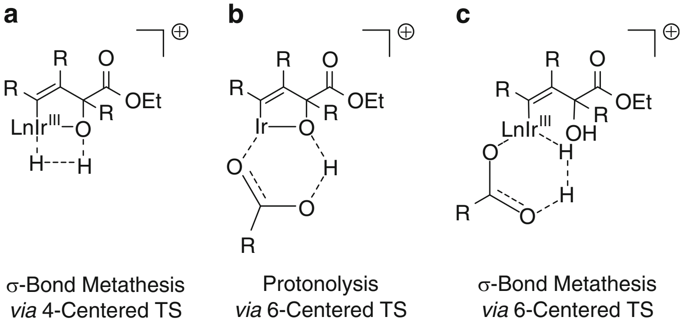


Fig. 1 Carboxylic acid-assisted hydrogenolysis of oxa-iridacyclic intermediates that arise via alkyne–carbonyl oxidative coupling

metal–alkyne complex facilitates alkyne-C=X (X=O, NR) oxidative coupling [183–185]. As rhodium is a relatively weak π-donor, conjugated alkynes and activated carbonyl and imine partners, which embody lower lying LUMOs, are required for oxidative coupling. Due to relativistic effects, iridium is a stronger π-donor than rhodium [186–189] and, therefore, can promote oxidative coupling of nonconjugated alkynes, which have higher lying LUMOs (Scheme 4).[17]

Regarding the role of the Brønsted acid cocatalyst, computational studies by Musashi and Sakaki suggest that carboxylic acid additives accelerate coupling by circumventing highly energetic four-centered transition structures for hydrogenolysis of metallacyclic intermediates **A** [195]. In the presence of carboxylic acid, protonolysis of oxa-iridacyclic intermediates **A** provide iridium carboxylates, which engage in hydrogenolysis through lower energy six-centered transition structures **C**. Protonolysis itself may occur through six-centered transition structures **B**. This interpretation is consistent with recently reported ESI–MS and DFT studies on the rhodium-catalyzed reductive coupling of acetylene to carbonyl and imine partners under hydrogenation conditions (Fig. 1) [182].

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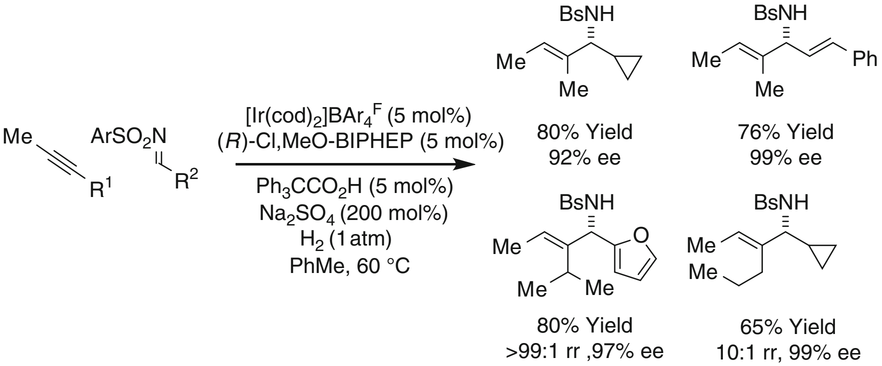
[17] Alkyne complexation by iridium(I) results in substantial deviation from linearity, as revealed by single crystal X-ray diffraction analysis: [190–194].



Scheme 5 Enantioselective iridium-catalyzed hydrogenation of alkynes in the presence of *N*-arylsulfonyl imines to furnish trisubstituted allylic amines

Cationic iridium complexes modified by chiral phosphine ligands promote highly enantioselective alkyne–imine reductive coupling under hydrogenation conditions to furnish trisubstituted allylic amines as single geometrical isomers [196, 197]. Carboxylic acid cocatalysts are required to enforce high levels of conversion. Additionally, Na_2SO_4 facilitates coupling by serving as a desiccant, thus mitigating imine hydrolysis by adventitious water. A remarkable feature of these transformations involves high levels of contrasteric regioselectivity observed in reductive couplings of nonsymmetric alkynes (Scheme 5).

As corroborated by deuterium labeling, the observed contrasteric regiocontrol appears to be a consequence of the oxidative coupling pathway. Specifically, formation of aza-iridacycle **A** via alkyne–imine oxidative coupling occurs such that nonbonded interactions between the large alkyne substituent and the sterically demanding iridium center are minimized. Carboxylic acid-assisted hydrogenolysis (via **B** and **C**) delivers the allylic amine. Formation of the iridacyclic intermediate **A** is the enantiodetermining event. Here, square planar iridium(I) binds the alkyne and imine at adjacent coordination sites. In accordance with the Dewar–Chatt–Duncanson model [183–185], the bound alkyne exhibits iridacyclopropene character (Alkyne complexation by iridium(I) results in substantial deviation from linearity, as revealed by single crystal X-ray diffraction analysis: (see footnote 17) [190–194]). Bidentate coordination of the *N*-arylsulfonyl imine to the iridium center is anticipated[18] [198]. Insertion of the imine into the iridium–carbon bond of the iridacyclopropene then delivers the indicated aza-iridacyclopentene **A**. Minimization of nonbonded interactions between the *N*-arylsulfonyl group and the phenylphosphino moieties accounts for the observed sense of stereoinduction (Scheme 6).

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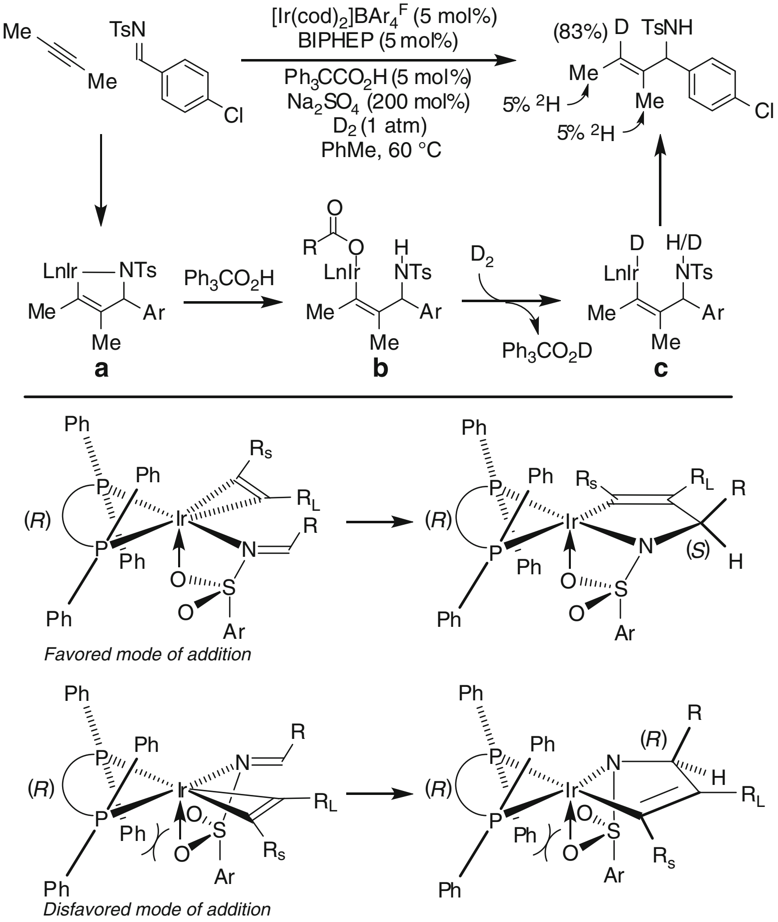
[18] The bidentate κ2-mode of binding has been observed by single crystal X-ray diffraction analysis for a related palladium *N*-arylsulfonamidate complex.



Scheme 6 Proposed mechanism for hydrogenative imine vinylation and proposed enantiodetermining transition states

2.2 Allenes as Allylmetal Surrogates via Hydrogenation

Enantioselective carbonyl allylation is one of the most broadly utilized transformations in synthetic organic chemistry (For reviews on enantioselective carbonyl allylation, see: [199–204]). Shortly after the first reports of carbonyl allylation employing isolable allylboron and allylsilicon reagents by Mikhailov and Bubnov [205] and Hosomi and Sakurai [206], respectively, enantioselective carbonyl allylations were reported by Hoffmann (see footnote 19, [207]). While the design of increasingly effective chiral allylmetal reagents continues[19] 207–220], this

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[19] For selected examples of chirally modified allyl metal reagents, see [207–220].

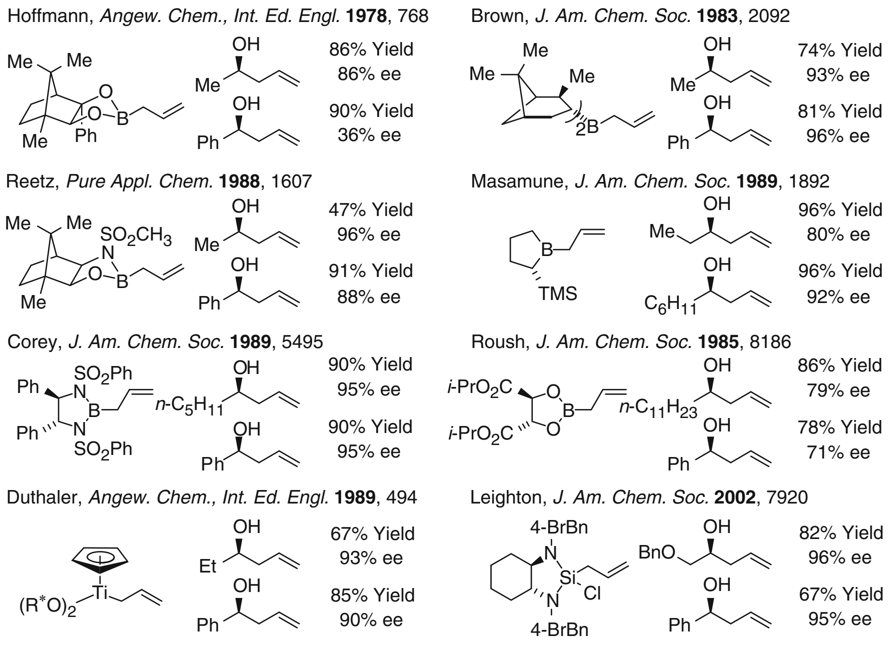

Fig. 2 Selected examples of chiral allylmetal reagents for enantioselective carbonyl allylation

approach only can be viewed as an interim solution as the use of stoichiometric chiral-inducing elements invariably leads to molar quantities of byproduct, diminishing prospects for large-volume applications (Fig. 2).

This limitation is addressed, in part, by the groundbreaking work of Yamamoto [221] and subsequent studies by Umani-Ronchi [222] and Keck [223] on chiral Lewis acid catalysts for enantioselective carbonyl allylation. Chiral Lewis base-catalyzed enantioselective carbonyl allylations soon followed, as reported by Denmark [224].[20] Although these methods avoid the stoichiometric use of chiral modifiers, they employ molar quantities of allylmetal reagent and, consequently, generate stoichiometric quantities of metallic byproducts. Furthermore, preparation of the allylmetal reagent itself is often beset by excessive waste production. For example, allylstannanes employed in the Umani-Ronchi–Keck process are prepared from the corresponding organomagnesium reagents, which, in turn, are prepared from the allylic halides [222, 223]. Thus, preactivation in the form of three stoichiometric operations is required in advance of C–C coupling (Scheme 7).

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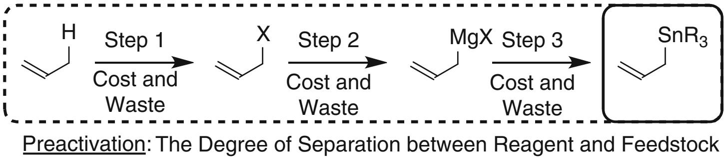
[20] For selected examples of catalytic asymmetric carbonyl allylation employing allylmetal reagents, see [221–224].



Scheme 7 Preactivation often accompanies the use of stoichiometric organometallic reagents

The reductive generation of transient allylmetal species from allylic alcohols, allylic carboxylates,[21,22] or allylic halides[23,24] represents an approach to carbonyl allylation that avoids discrete allylmetal reagents. However, with a few exceptions, (see footnote 21, [235–238]) such processes require stoichiometric quantities of metallic reductants, such as SmI_2, $SnCl_2$, and Et_2Zn. Finally, the carbonyl–ene reaction enables carbonyl allylation in the absence of stoichiometric byproducts by employing simple olefins as allyl donors; however, enantioselective variants are limited to highly activated electrophiles, and general protocols remain a distant goal.[25,26]

Carbonyl allylation in the absence of metallic reagents is achieved under the conditions of iridium-catalyzed hydrogenation or transfer hydrogenation employing 1,2-dienes, 1,3-dienes, or allyl acetates as precursors to transient allylmetal species (see footnote 4, [16]). Here, hydrogen or isopropanol may serve as reductant. For transfer hydrogenative processes, isopropanol dehydrogenation drives reductive generation of allylmetal nucleophiles from unsaturates. Of greater significance is the fact that hydrogen exchange between reactant alcohols and π-unsaturated partners occurs to generate electrophile–nucleophile pairs en route to products of C–C coupling. In this way, carbonyl allylation is achieved directly from the alcohol oxidation level, availing a method for the hydro-hydroxyalkylation of unsaturates via functionalization of carbinol C–H bonds (Scheme 8) (see footnotes (7, 8, 9), [22–31]).

Hydrogen-mediated carbonyl allylation was first demonstrated under the conditions of iridium-catalyzed hydrogenation in studies of allene–carbonyl reductive coupling [269]. Using a cationic iridium catalyst, hydrogenation of commercially available 1,1-dimethylallene in the presence of carbonyl electrophiles delivers products of carbonyl *tert*-prenylation as single regioisomers in good to excellent

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[21] For selected examples of carbonyl allylations employing nucleophilic π-allyls derived from allylic acetates and carboxylates, see: *Palladium* [225–233], *Rhodium* [234, 235], *Ruthenium* [236–238], *Iridium* [239–241].

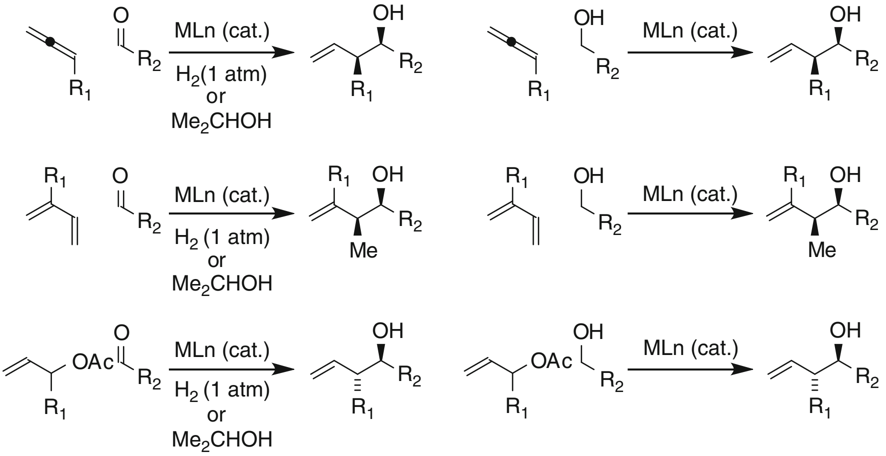
[22] For selected reviews on carbonyl allylation via umpolung of π-allyls, see [242–247].

[23] For catalytic enantioselective carbonyl allylation and crotylation via Nozaki-Hiyama coupling, see [248–257].

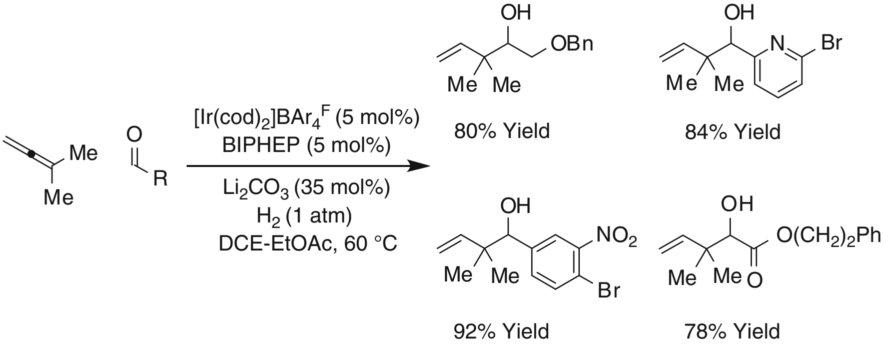
[24] For recent reviews of catalytic Nozaki-Hiyama coupling, see [258–261].

[25] For reviews on carbonyl-ene reactions, see [262–265].

[26] For Nickel catalyzed carbonyl-ene reactions, see [266–268].



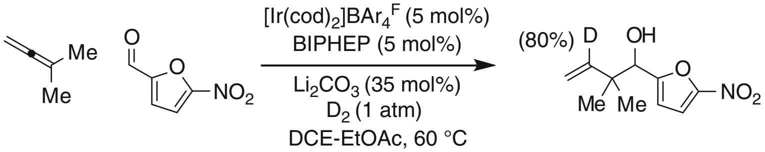
Scheme 8 Carbonyl allylation via hydrogenation and transfer hydrogenation



Scheme 9 Catalytic carbonyl addition via iridium-catalyzed hydrogenative coupling of dimethylallene

yield. Note that functional groups typically considered "hydrogen-labile," such as aryl halides, benzylic ethers, alkenes, and nitroarenes, are tolerated under these conditions. Unlike conventional allylation protocols, all reactant atoms, including hydrogen, are incorporated into the product and so no stoichiometric byproducts are generated (Scheme 9).

Reductive coupling of 1,1-dimethylallene and 5-nitro-2-furancarboxaldehyde under a deuterium atmosphere provides the product of *tert*-prenylation incorporating deuterium at the interior vinylic position (80% ^{2}H). This result is consistent with a mechanism involving allene–aldehyde oxidative coupling. However, alternate pathways involving allene hydrometallation to furnish allyliridium species cannot be excluded on the basis of these data (Scheme 10).



Scheme 10 Iridium-catalyzed reductive coupling of 1,1-dimethylallene to an aldehyde under an atmosphere of deuterium

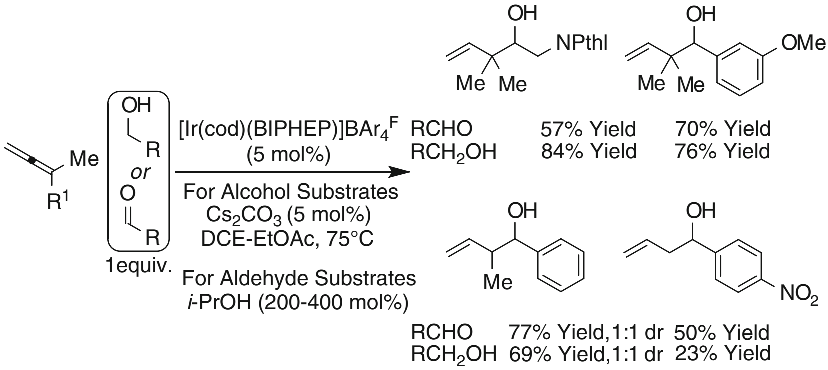
3 Iridium-Catalyzed Transfer Hydrogenation for C–C Bond Formation

3.1 Allenes as Allylmetal Surrogates via Transfer Hydrogenation

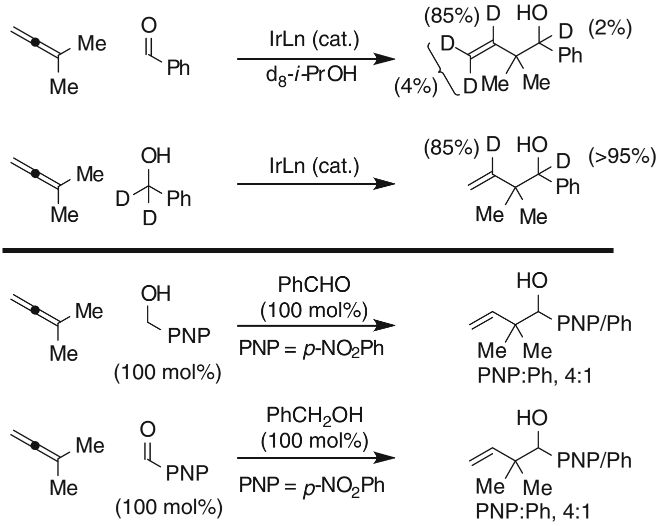
Although carbonyl *tert*-prenylation occurs efficiently upon iridium-catalyzed hydrogenation of 1,1-dimethylallene in the presence of aldehydes, attempted crotylations and allylations employing methylallene or allene gas, respectively, suffer from competing conventional hydrogenation of the olefinic C–C coupling product. Corresponding iridium-catalyzed transfer hydrogenations overcome this limitation [270]. Under nearly identical conditions, by simply substituting isopropanol (200 mol%) for hydrogen as the terminal reductant, 1,1-dimethylallene reductively couples to aldehydes to furnish products of *tert*-prenylation in good to excellent yield across a broad range of substrates. Remarkably, it was found that alcohol reactants serve dually as reductants and aldehyde precursors, enabling formation of identical products. Thus, carbonyl addition occurs with equal facility from the aldehyde or alcohol oxidation levels. This chemistry is also applicable to carbonyl crotylation and allylation employing methylallene or allene gas, respectively. However, the volatility of these reagents contributes to diminished efficiencies (Scheme 11).

The coupling of 1,1-dimethylallene to benzaldehyde employing d_8-isopropanol as reductant delivers the product of *tert*-prenylation, incorporating deuterium primarily at the internal vinylic position (85% ^{2}H). Similar results are obtained when the reaction is conducted from the alcohol oxidation level employing d_2-benzyl alcohol. Further mechanistic insight comes from crossover experiments in which 1,1-dimethylallene is exposed to equimolar quantities of *p*-nitrobenzyl alcohol and benzaldehyde. The *p*-nitrophenyl- and phenyl-containing adducts are obtained in a 4:1 ratio, respectively. An identical product distribution is obtained upon exposure of 1,1-dimethylallene to equimolar quantities of *p*-nitrobenzaldehyde and benzyl alcohol under otherwise identical conditions. These data are consistent with fast and reversible alcohol dehydrogenation to form nonmetal-bound aldehyde in advance of C–C coupling (Scheme 12).

Highly enantioselective variants of these processes employ a cyclometallated iridium *C*,*O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid, and

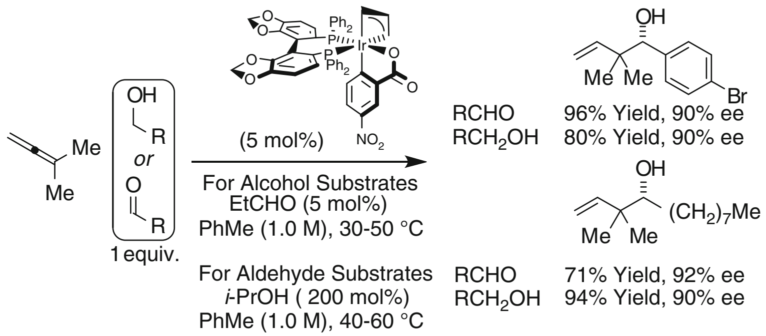


Scheme 11 Carbonyl *tert*-prenylation, crotylation, and allylation from the aldehyde or alcohol oxidation level under the conditions or iridium-catalyzed transfer hydrogenation

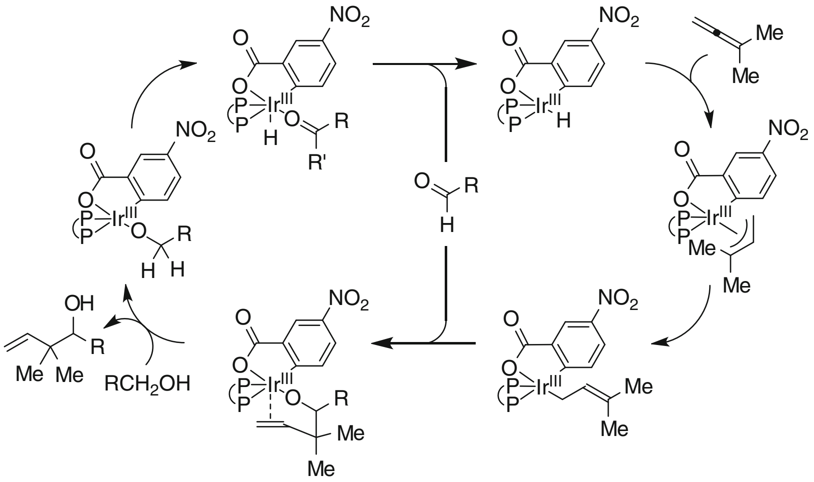


Scheme 12 Isotopic labeling and crossover experiments in iridium-catalyzed couplings of 1,1-dimethylallene under transfer hydrogenation conditions

(*S*)-SEGPHOS [271, 272]. Using this complex as a precatalyst, transfer hydrogenation of 1,1-dimethylallene in the presence of diverse aldehydes mediated by isopropanol delivers products of *tert*-prenylation in good to excellent yield and with excellent levels of enantioselectivity. In the absence of isopropanol, enantioselective carbonyl reverse prenylation is achieved directly from the alcohol oxidation level to furnish an equivalent set of adducts. Notably, enantioselective *tert*-prenylation is achieved under mild conditions (30–50°C) in the absence of stoichiometric metallic reagents. Indeed, for reactions conducted from the alcohol oxidation level, stoichiometric byproducts are completely absent (Scheme 13).



Scheme 13 Enantioselective carbonyl *tert*-prenylation from the alcohol or aldehyde oxidation level via iridium-catalyzed C–C bond-forming transfer hydrogenation



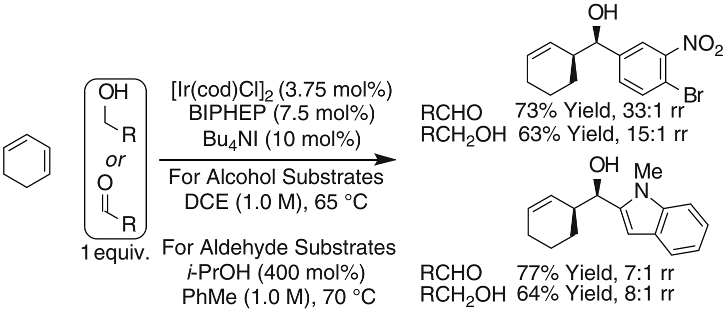
Scheme 14 Proposed catalytic mechanism for carbonyl *tert*-prenylation from the alcohol oxidation level via iridium-catalyzed C-C bond-forming transfer hydrogenation

Our collective mechanistic studies are consistent with the indicated catalytic cycle. Notably, the catalyst engages primary alcohols in rapid and reversible dehydrogenation, yet the coupling products, which are homoallylic alcohols, are not subject to oxidation as coordination of the homoallylic olefin to the catalyst provides a hexa-coordinate 18-electron complex lacking an open coordination site for β-hydride elimination (Scheme 14).

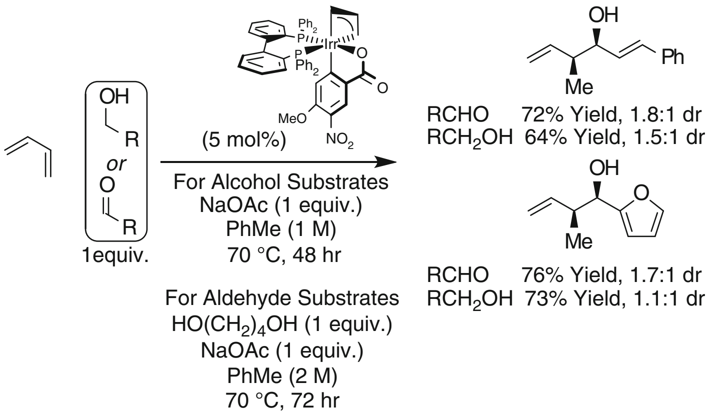
3.2 Dienes as Allylmetal Surrogates via Transfer Hydrogenation

Under the conditions of iridium-catalyzed transfer hydrogenation employing isopropanol as reductant, 1,3-cyclohexadiene couples to aryl aldehydes to provide products of carbonyl cyclohexenylation in good to excellent yield and with high levels of diastereocontrol. Under nearly identical conditions, but in the absence of isopropanol, corresponding alcohols couple directly to 1,3-cyclohexadiene to furnish identical products of carbonyl cyclohexenylation (Scheme 15) [273].

More recently, using the cyclometallated iridium *C*,*O*-benzoate derived from allyl acetate, 4-methoxy-3-nitrobenzoic acid and BIPHEP, catalytic carbonyl crotylation employing 1,3-butadiene from the aldehyde, or alcohol oxidation was achieved under transfer hydrogenation conditions [274]. Carbonyl addition occurs with roughly equal facility from the alcohol or aldehyde oxidation level. However, products are obtained as diastereomeric mixtures. Stereoselective variants of these processes are under development. It should be noted that under the conditions of ruthenium-catalyzed transfer hydrogenation, conjugated dienes, including butadiene, couple to alcohols or aldehydes to provide either products of carbonyl crotylation or β,γ-enones (Scheme 16) [275, 276].



Scheme 15 Iridium-catalyzed couplings of 1,3-cyclohexadiene under transfer hydrogenation conditions (ratio refers to 1,4-olefinic versus 1,5-olefinic alcohols)

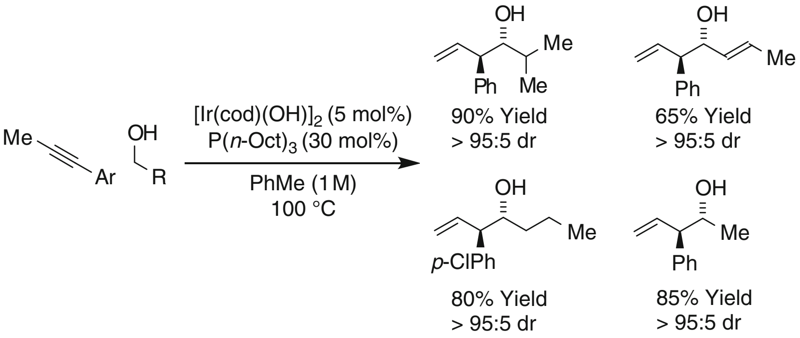


Scheme 16 Iridium-catalyzed C–C couplings of 1,3-butadiene under transfer hydrogenation conditions

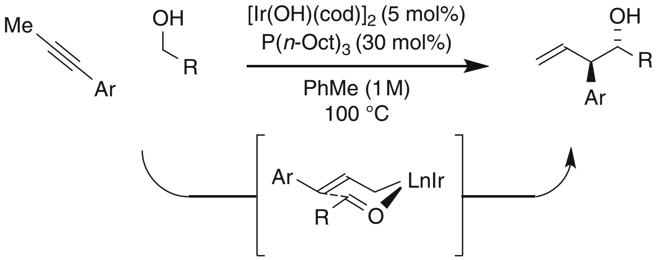
3.3 Alkynes as Allylmetal Surrogates via Transfer Hydrogenation

As demonstrated in recent work by Obora and Ishii, alkynes serve as allyl donors in carbonyl allylations from the alcohol oxidation level [277]. Specifically, upon exposure to an iridium catalyst generated in situ from $[Ir(OH)(cod)]_2$ and $P(n\text{-Oct})_3$, 1-aryl-2-methylalkynes couple to primary alcohols to furnish homoallylic alcohols with complete branched regioselectivity and excellent levels of diastereoselectivity (Scheme 17).

For alkyne-mediated allylation, alcohol dehydrogenation generates an iridium hydride that hydrometallates the alkyne to form a vinylmetal species, which, in turn, isomerizes to generate the primary σ-allyliridium intermediate. Carbonyl addition through a closed six-centered transition state accounts for the observed *anti*-diastereoselectivity (Scheme 18). Interestingly, under the conditions of ruthenium-catalyzed transfer hydrogenation, alkynes couple to alcohols or aldehydes to provide products of carbonyl vinylation [278]. Here, isomerization of the vinylruthenium intermediate to the σ-allylruthenium intermediate is not observed.



Scheme 17 Carbonyl arylallylation from the alcohol oxidation level via iridium-catalyzed transfer hydrogenation employing alkynes as allyl donors



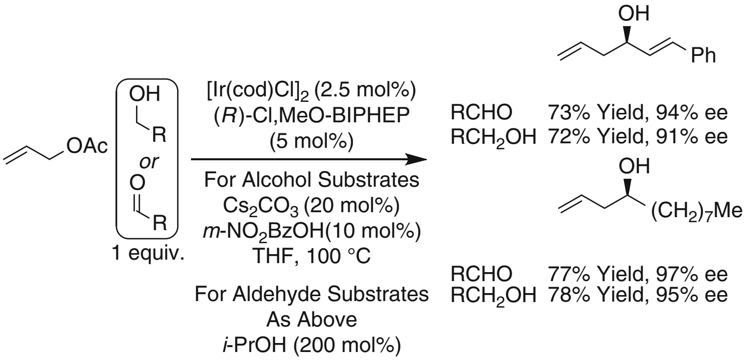
Scheme 18 Plausible stereochemical model for *anti*-diastereoselective iridium-catalyzed allylation of alcohols employing alkynes as allyl donors

3.4 Allylic Acetates as Allylmetal Surrogates via Transfer Hydrogenation

Using allyl acetate as the allyl donor, enantioselective variants of the parent carbonyl allylation process are achieved under the conditions of iridium-catalyzed transfer hydrogenation employing the cyclometallated iridium *C*,*O*-benzoate derived from allyl acetate, 3-nitrobenzoic acid, and a chiral *bis*-phosphine ligand, which is generated in situ [279, 280]. Allyl acetate couples to diverse alcohols to furnish products of carbonyl allylation with exceptional levels of enantioselectivity. Identical products of carbonyl allylation are produced from the corresponding aldehydes upon use of isopropanol as terminal reductant. Thus, enantioselective carbonyl allylation is achieved from the alcohol or aldehyde oxidation level in the absence of metallic reagents or metallic reductants. The reactivity embodied by these processes is remarkable in light of the fact that iridium-catalyzed allylic substitution (*O*-allylation) employing alcohol nucleophiles is a well-established mode of reactivity (Scheme 19) [281–283].[27]

The results of deuterium labeling are consistent with intervention of a symmetric iridium π-allyl intermediate or rapid interconversion of σ-allyl haptomers through the agency of a symmetric π-allyl (Scheme 20) [280]. Competition experiments akin to those previously described (see Scheme 12) again demonstrate rapid and reversible dehydrogenation of the carbonyl partner in advance of C–C coupling.

The BINAP derivative of the *ortho*-cyclometallated iridium catalyst has been characterized by single crystal X-ray diffraction analysis [280]. Remarkably, although the reaction sequence depends upon oxidation of either the reactant alcohol or isopropanol, the enantiomeric purity of the homoallylic alcohol product



Scheme 19 Enantioselective carbonyl allylation from the alcohol or aldehyde oxidation level via iridium-catalyzed C–C bond-forming transfer hydrogenation

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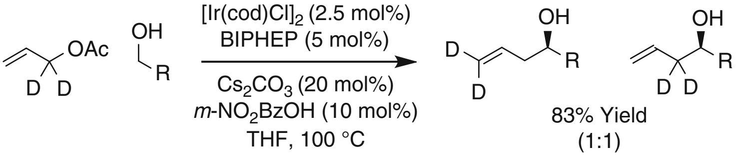
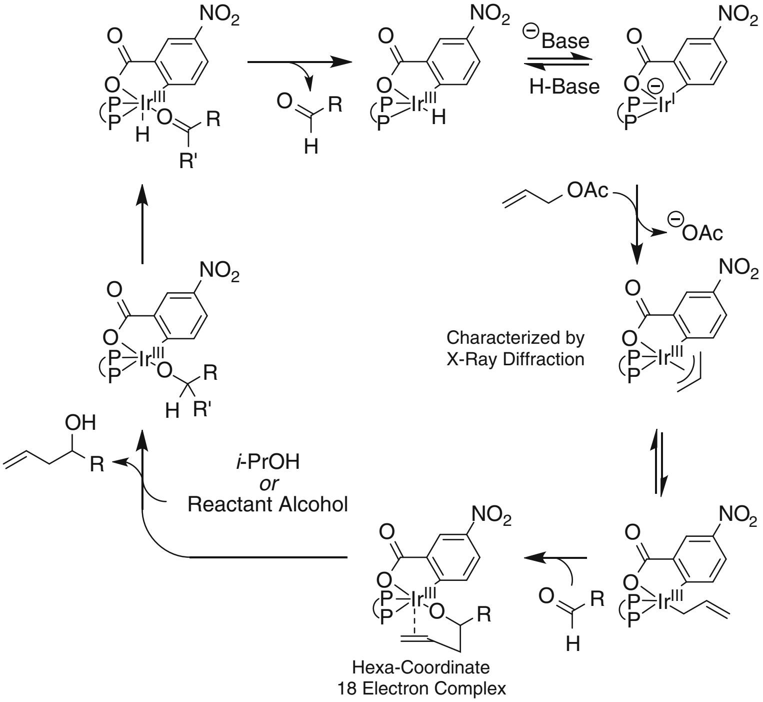
[27] Under the conditions of ruthenium catalysis, alcohols and allylic acetates couple to form enones, see [284].



Scheme 20 Carbonyl allylation from the alcohol oxidation level employing isotopically labeled allyl acetate [R = p-(CO$_2$Me)C$_6$H$_4$]



Scheme 21 Proposed catalytic mechanism for carbonyl allylation from the alcohol oxidation level via iridium-catalyzed C–C bond-forming transfer hydrogenation

is not subject to erosion through reversible dehydrogenation as the pendant alkene of the product prevents dehydrogenation by occupying the single remaining vacant coordination site on iridium, as required for β-hydride elimination (Scheme 21).

A model accounting for the observed sense of absolute stereoinduction is based upon the coordination mode revealed in the crystal structure of the cyclometallated *C*,*O*-benzoate complex [280]. It is postulated that aldehyde binding by the σ-allyl haptomer occurs such that the allyl moiety is placed between the naphthyl and phenyl moieties of the ligand, allowing the aldehyde to reside in a more open environment. In the favored mode of addition, the aldehyde C–H bond projects into

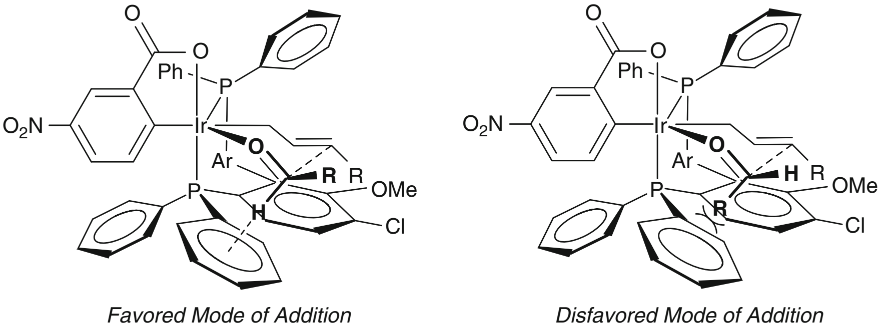


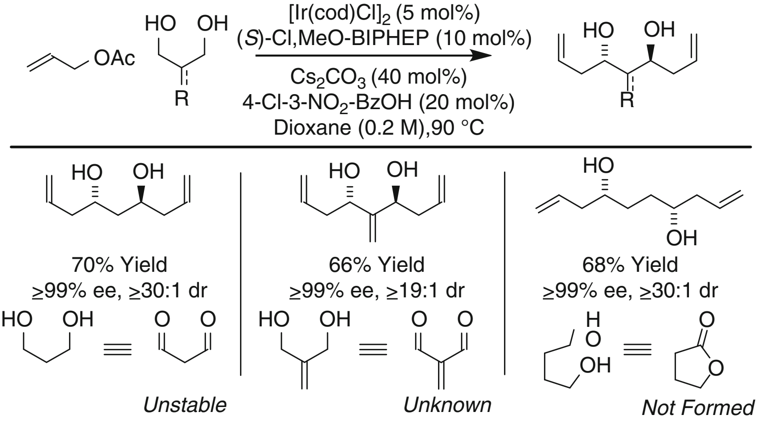
Fig. 3 Proposed stereochemical model accounting for the observed sense of absolute stereoinduction (chiral ligand = (*S*)-Cl,MeO-BIPHEP)

the π-face of a phenyl moiety of the ligand, potentially resulting in a weakly attractive aldehyde C–H–π interaction. The disfavored mode of addition requires the aldehyde substituent to project into the π-face of the ligand phenyl moiety, resulting in a severe nonbonded interaction (Fig. 3).

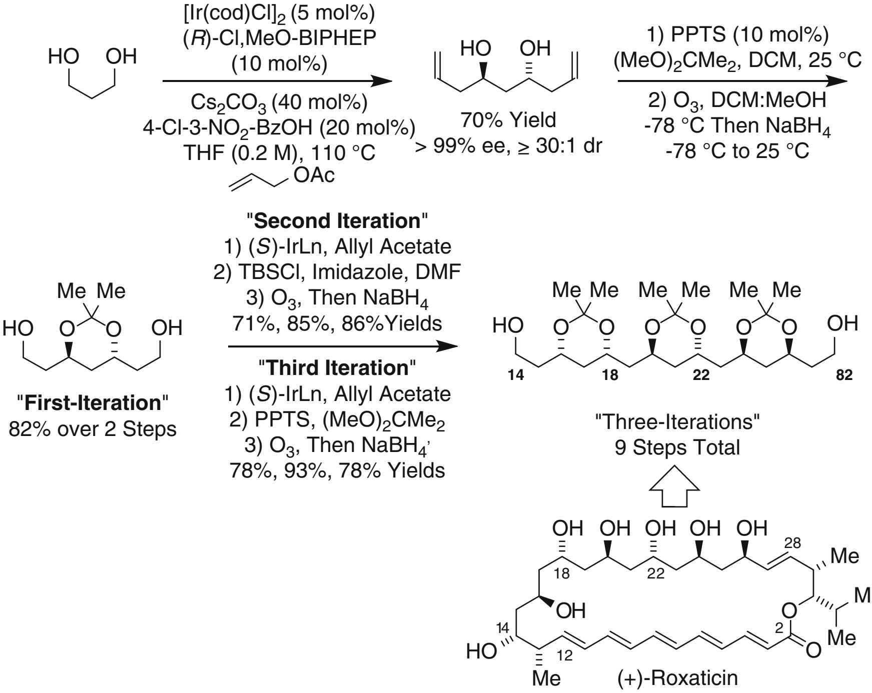
Direct asymmetric carbonyl allylation from the alcohol oxidation level potentially streamlines synthesis by circumventing discrete alcohol oxidation as well as enabling carbonyl allylation processes that are unattainable using conventional allylmetal reagents. For example, two-directional chain elongation via double allylation of 1,3-dialdehydes has not been achieved due to the instability of the requisite 1,3-dicarbonyl precursors (For a review on two-directional chain synthesis, see: [285]). However, propane-1,3-diol and related glycols are highly tractable and participate in bidirectional allylation via sequential generation and capture of transient monoaldehydes to provide C_2-symmetric adducts in good yield [286]. In these processes, the minor enantiomer of the monoallylated intermediate is transformed to the *meso*-stereoisomer of the product, thus amplifying the level of enantiomeric enrichment (Scheme 22) (This mechanism for enantiomeric enrichment is documented by Eliel and Midland: [287, 288]).

Iterative two-directional chain elongation enables rapid construction of 1,3-polyols (Scheme 23). For example, the polyol substructure that appears in the oxopolyene macrolide (+)-roxaticin is available in nine steps from propane-1,3-diol upon three iterations of double carbonyl allylation [286]. Notably, high levels of catalyst-directed stereoselectivity are observed (For selected examples of catalyst directed diastereoselectivity, see: [289–296]). Analogous 1,3-polyol syntheses via iterative homologation in one direction also are reported [297].

This carbonyl allylation strategy is extended to crotylation through the use of α-methyl allyl acetate as a crotylmetal surrogate [298]. Here, after screening several *ortho*-cyclometallated *C*,*O*-benzoates, the iridium complex derived from 4-cyano-3-nitrobenzoic acid and (*S*)-SEGPHOS [272] was found to provide good levels of *anti*-diastereoselectivity accompanied by uniformly high levels of enantioselectivity across a broad range of substrates. Notably, complete branch-regioselectivity is observed in all cases. The observed regio- and *anti*-diastereoselectivity suggest that

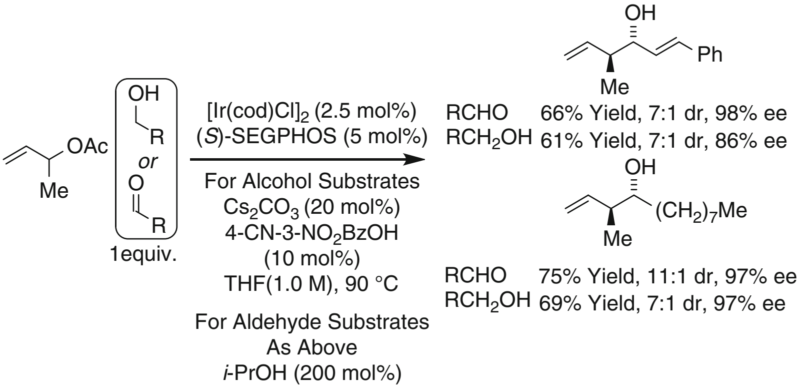


Scheme 22 1,n-Glycols as dialdehyde equivalents in iridium-catalyzed enantioselective carbonyl allylation from the alcohol oxidation level

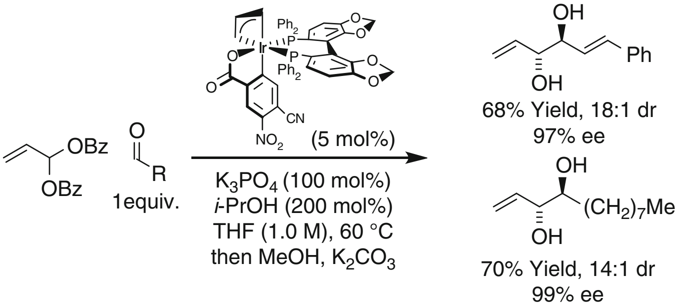


Scheme 23 Synthesis of the 1,3-polyol substructure of the polyene macrolide (+)-roxaticin

aldehyde addition occurs from the primary (*E*)-σ-allyliridium haptomer. As before, carbonyl crotylation is achieved with equal facility from the aldehyde or alcohol oxidation level (Scheme 24).



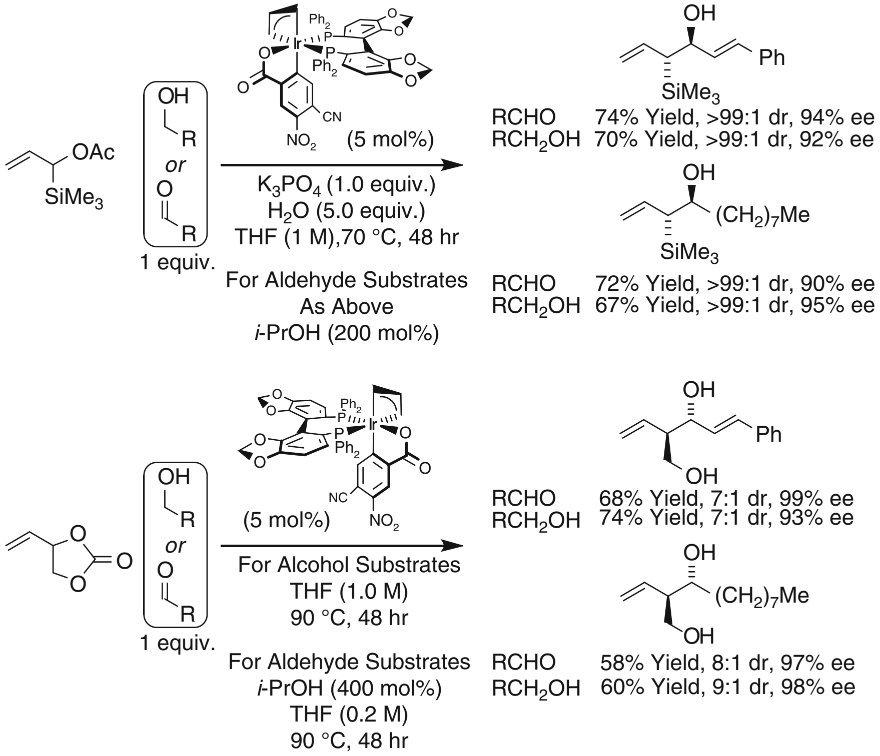
Scheme 24 Enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level via iridium-catalyzed C–C bond-forming transfer hydrogenation



Scheme 25 Diastereo- and enantioselective *anti*-(hydroxy)allylation employing allylic *gem*-dicarboxylates as allyl donors via iridium-catalyzed transfer hydrogenation

Allylic *gem*-dibenzoates derived from acrolein serve as (alkoxy)allylmetal surrogates under the conditions of iridium-catalyzed transfer hydrogenation [299]. In this case, generation of the catalytic complex in situ failed to provide the desired products in good yield, requiring use of the isolated complex prepared from [Ir(cod)Cl]$_2$, 4-cyano-3-nitrobenzoic acid, allyl acetate, and the chiral phosphine ligand (*R*)-SEGPHOS [272]. To achieve high levels of *anti*-diastereoselectivity, efficient partitioning of transient (*E*)- and (*Z*)-σ-allyliridium intermediates is required. It was found that the allylic *gem*-dibenzoate derived from acrolein is unique in its ability to combine high levels of *anti*-diastereoselectivity and favorable reactivity. Under the reported conditions, iridium-catalyzed aldehyde *anti*-(hydroxy)allylation occurs under transfer hydrogenation conditions to provide *anti*-1-ene-3,4-diols with excellent relative and absolute stereocontrol. Corresponding carbonyl additions from the alcohol oxidation level are currently under development (Scheme 25).

New catalytic allylation methodologies continue to emerge. For example, iridium-catalyzed transfer hydrogenation of α-(trimethylsilyl)allyl acetate in the presence of aldehydes mediated by isopropanol and employing the iridium catalyst



Scheme 26 Enantioselective carbonyl (trimethylsilyl)allylation and (hydroxymethyl)allylation from the alcohol or aldehyde oxidation level via iridium-catalyzed C–C bond-forming transfer hydrogenation

modified by (*R*)-SEGPHOS [272] delivers products of (trimethylsilyl)allylation in good isolated yields and with exceptional levels of *anti*-diastereo and enantiocontrol [300]. In the absence of isopropanol, carbonyl (trimethylsilyl)allylation is achieved directly from the alcohol oxidation level to furnish an equivalent set of adducts (Scheme 26, top). Similarly, using the enantiomeric iridium complex, the indicated cyclic carbonate engages in carbonyl (hydroxymethyl)allylation from the alcohol or aldehyde oxidation level with good *anti*-diastereoselectivities and exceptional levels of enantiocontrol [301]. Notably, stereoselective (hydroxymethyl) allylation protocols employing conventional allylmetal reagents are unknown (Scheme 26, bottom).[28],[29],[30]

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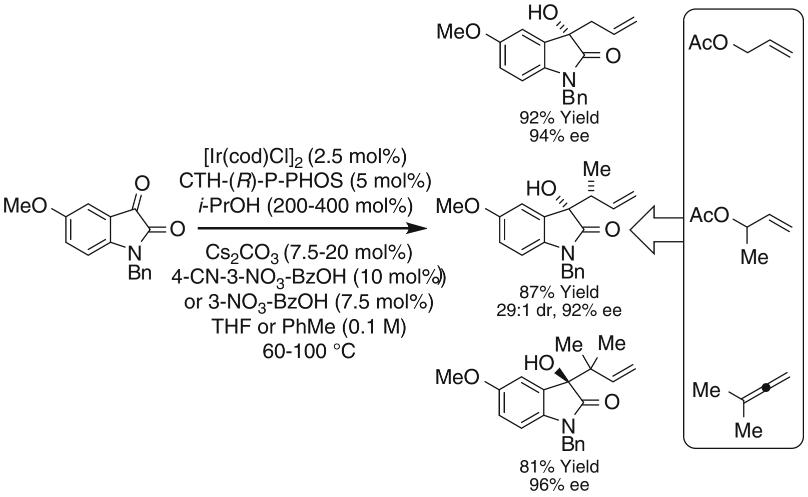
[28] For (hydroxymethyl)allylation via palladium catalyzed reductive coupling of allylic carboxylates, see [302–304].

[29] For (hydroxymethyl)allylation via palladium catalyzed reductive coupling of vinyl epoxides, see [305, 306].

[30] For catalytic enantioselective (hydroxymethyl)allylation, see [307, 308].

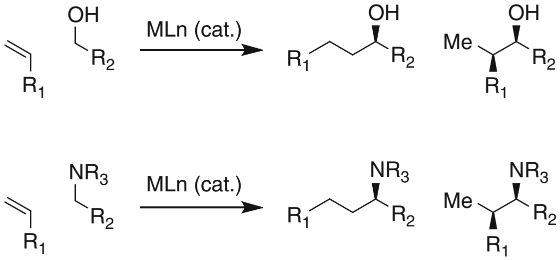


Scheme 27 Enantioselective allylation, crotylation, and *tert*-prenylation of substituted isatins via iridium-catalyzed transfer hydrogenation

Enantioselective ketone addition is one of the many challenging extensions in scope that remains. In a preliminary step toward this goal, the allylation, crotylation, and *tert*-prenylation of substituted isatins was examined using the cyclometallated iridium *C*,*O*-benzoate generated in situ from [Ir(cod)Cl]$_2$, 4-chloro-3-nitrobenzoic acid and CTH-(*R*)-P-PHOS [309]. Isopropanol-mediated transfer hydrogenation of allyl acetate, α-methyl allyl acetate or 1,1,-dimethylallene as allyl donors, in the presence of the substituted isatins delivered the anticipated products of allylation, crotylation, and *tert*-prenylation, respectively, in highly enantiomerically enriched form. Notably, highly enantioselective allylation, crotylation, and reverse prenylation of isatins employing conventional allylmetal reagents have not been reported (Scheme 27) (For enantioselective catalytic allylation of isatins, see: [310]).

4 Conclusion

Organic molecules are defined as compounds of carbon and hydrogen. Hence, the formation of C–C bonds under the conditions catalytic hydrogenation and transfer hydrogenation is a natural endpoint in the evolution of strategies for the synthesis of organic molecules. The use of unsaturates as surrogates to premetallated nucleophiles under hydrogenation conditions represents a departure from the use of stoichiometric organometallic reagents in carbonyl and imine addition that circumvents generation of stoichiometric byproducts. This concept is extended further via C–C bond-forming transfer hydrogenation – processes in which alcohol reactants



Scheme 28 Examples of two aspirational processes: byproduct-free couplings of α-olefins to (renewable) alcohols and amines with linear or branch regiocontrol

serve dually as hydrogen donors and carbonyl precursors, enabling carbonyl addition directly from the alcohol oxidation level in the absence of stoichiometric byproducts and premetallated nucleophiles.

As highlighted in this review, iridium complexes are especially versatile catalysts for C–C bond-forming hydrogenation and transfer hydrogenation. And now, based on these studies, many aspirational transformations are placed within reach (Scheme 28). However, to fully realize the potential of hydrogen-mediated C–C coupling, alternate metal catalysts should be developed and applied to processes beyond those described herein. This challenge will ultimately evoke catalytic methods for the sustainable manufacture of pharmaceutical ingredients, bulk chemicals, and fuels from renewable feedstocks.

Acknowledgments Acknowledgment is made to the Robert A. Welch Foundation (F-0038), NIH-NIGMS (RO1-GM69445), and the ACS-GCI Pharmaceutical Roundtable for partial support of the research described in this account. Dr Oliver Briel of Umicore is thanked for the generous donation of iridium salts. Dr Wataru Kuriyama and Dr Yasunori Ino of Takasago are thanked for the generous donation of (*R*)- and (*S*)-SEGPHOS.

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Top Organomet Chem (2011) 34:139–168
DOI: 10.1007/978-3-642-15334-1_6

Ir-Catalyzed Functionalization of C–H Bonds

Jongwook Choi and Alan S. Goldman

Abstract The ability to selectively functionalize C–H bonds holds enormous potential value in virtually every sphere of organic chemistry, from fuels to pharmaceuticals. Transition metal complexes have shown great promise in this context. Iridium provided the first examples of oxidative addition of C–H bonds; this addition is key to iridium's leading role in alkane dehydrogenation and related reactions. Catalysts based on iridium have also proven highly effective for valuable borylations of C–H bonds and, to a lesser extent, for C–Si coupling. Compared with other platinum group metals, iridium chemistry has not been developed as extensively for the elaboration of C–C bonds from C–H bonds, but significant promise is indicated, particularly for coupling with simple hydrocarbons which lack functionalities that can act as directing groups.

Keywords Alkane metathesis · Borylation · C–H bond activation · Dehydrogenation · Hydroarylation · Iridium catalyst · Silylation

Contents

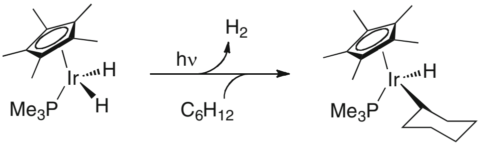
J. Choi and A.S. Goldman (✉)
Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, New Brunswick, NJ 08903, USA
e-mail: alan.goldman@rutgers.edu

1 Introduction and Background Stoichiometric Chemistry

Given the ubiquitous nature of carbon–hydrogen bonds, the ability to selectively catalyze their transformation is one of the most attractive goals of modern synthetic chemistry [1–9]. The potential applications of such chemistry range in scale from synthesis of the most complex fine chemicals to the development of new routes to transportation fuels.

In the realm of C–H bond transformations applied toward the synthesis of fine chemicals, iridium has not achieved the prominence attained in recent years by the second-row platinum group metals, particularly palladium [10]. A notable exception, however, has been the leading role of iridium in the valuable chemistry of arene borylation [11].

With respect to reactions of the simplest of organic molecules, alkanes, iridium has earned a special place. Indeed, iridium has played a particularly important role in the development and mechanistic understanding of the reactions of organometallic complexes with simple molecules in general. Vaska's complex, Ir(Cl)(CO)$(PPh_3)_2$, offered the archetype of the oxidative addition reaction with the discovery of addition of H_2 to give what is formally an Ir(III) complex (in contrast with organic chemical formalisms wherein addition of H_2 is a reduction) [12]. The same complex offered the archetypal oxidative addition of C–X bonds with the report of addition of methyl iodide [13]. Undoubtedly, it is not a coincidence that the first example of oxidative addition of an alkane C–H bond was to an iridium center: the seminal report by Bergman in which photogenerated Cp*Ir(PMe_3) was found to add a wide range of alkane C–H bonds [14].



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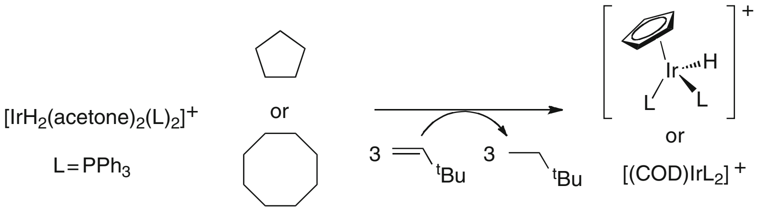
As in the case of the H–H and C–I addition to Vaska's complex, reaction 1 proceeds via addition to Ir(I) to give a stable formally six-coordinate Ir(III) complex.

The first example of dehydrogenation of alkanes by a transition metal complex was also achieved with iridium. The cationic iridium(III) complex, $[IrH_2(acetone)_2(PPh_3)_2]^+ BF_4^-$, with TBE (3,3-dimethyl-1-butene or *t*-butylethene) as a hydrogen acceptor dehydrogenates cyclopentane or cyclooctane (COA) to give the cyclopentadienyl and cyclooctadiene adducts, respectively (2) [15].



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Presumably, TBE first accepts H_2, thereby generating yet another example of an Ir(I) species that undergoes C–H bond oxidative addition. As in the example of 1, the resulting Ir product strongly binds the transformed hydrocarbon. Indeed, the ability of Ir to give stable complexes generally reflects a mixed blessing, valuable for the purposes of characterization of complexes and mechanism, but often leading to species too stable to permit catalytic reactivity. There are, however, many exceptions to the tendency of iridium to give species too stable for catalysis, and as we shall see, the first well-characterized examples of catalytic alkane functionalization were dominated by iridium.

In this review, the recent developments in catalytic functionalization of C–H bonds by iridium complexes will be emphasized. For more information on previous work and their details, there are excellent reviews published recently on C–H bond functionalization by transition metal complexes generally [1–9], as well as with an emphasis on iridium [11, 16].

2 Catalytic Dehydrogenation

2.1 Dehydrogenation of Alkanes

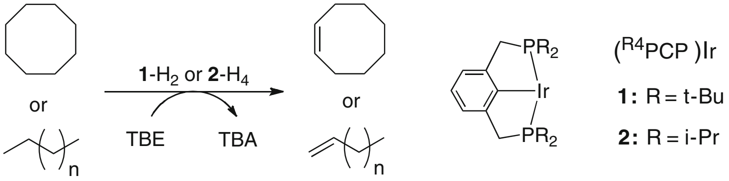
The dehydrogenation of unactivated alkanes to olefins by the removal of two hydrogen atoms is in principle an elegant way to introduce a valuable functionality. This transformation has great potential value considering the importance of olefin intermediates in the commodity and petrochemical industries and the great versatility of olefins as reagents in organic synthesis.

As noted above, the first stoichiometric dehydrogenation of alkanes by soluble homogeneous metal complexes, reported by Crabtree et al. [15], was a reaction of an iridium complex, $[IrH_2(PPh_3)_2(Me_2CO)_2]^+$. The closely related bis-P(p-$FC_6H_4)_3$ complex was subsequently reported to catalytically dehydrogenate COA using TBE as hydrogen acceptor, in the presence of a base that was found to deprotonate the complex [17]. Felkin and coworkers later used the neutral iridium (and ruthenium) polyhydride systems, $(^iPr_3P)_2IrH_5$, $[(p\text{-}F\text{-}C_6H_4)_3P]_2IrH_5$, and $[(p\text{-}F\text{-}C_6H_4)_3P]_3RuH_4$, for catalytic COA/TBE transfer dehydrogenation [18–20]. Using $(^iPr_3P)_2IrH_5$, up to

70 catalytic turnovers were obtained. Soon thereafter, $[(p\text{-F-C}_6H_4)_3P]_2IrH_2(\kappa^2\text{-}O_2CCF_3)$ was found to effect dehydrogenation of linear and cyclic alkanes, both thermally (with TBE as acceptor) and photochemically (without hydrogen acceptor) [21, 22]. This study laid the mechanistic groundwork for future alkane dehydrogenation chemistry, in particular highlighting the importance of the key 14-electron IrL_2X unit (in this case, X being the dechelated κ^1-carboxylate ligand).

The systems discussed above suffered from limited turnover numbers ($\leq$70), presumably due to catalyst degradation; species active enough to react with alkanes could be expected to react, intra- or intermolecularly, with their own ligands. The first molecular catalysts to circumvent this limitation were complexes based on the closest possible analog of IrL_2X, specifically $Rh(PMe_3)_2Cl$. Eisenberg had demonstrated that $M(PPh_3)_2Cl(CO)$ (M = Rh or Ir) catalyzed the photochemical carbonylation of benzene [23, 24]. Tanaka, observing that PMe_3 was more favorable than PPh_3 for C–H activation in the case of 1, found that $Rh(PMe_3)_2Cl(CO)$ was accordingly more efficient for photochemical carbonylation [25, 26], and this same complex was soon found to be even more effective for photochemical alkane dehydrogenation [27–30]. It was later reported by Goldman and coworkers that species $Rh(PMe_3)_2ClL$ (L = CO or phosphine) were excellent alkane transfer-dehydrogenation catalysts although (quite surprisingly) only in the presence of dihydrogen [31, 32]. The requirement of H_2 atmosphere, although mechanistically interesting, was a practical drawback because the system hydrogenated more than one mol acceptor per mol dehydrogenated product.

In 1996, Jensen and Kaska reported that the pincer-ligated iridium complex, $(^{tBu4}PCP)IrH_2$ (**1**-H_2) ($^{tBu4}PCP = \kappa^3\text{-}C_6H_3\text{-}2,6\text{-}[CH_2P(t\text{-}Bu)_2]_2$), shows excellent catalytic activity for transfer dehydrogenation of cycloalkanes (3) and long-term stability at high temperatures (up to 200°C) [33, 34]. The high thermal stability was exploited toward the first efficient example of catalytic acceptorless dehydrogenation [35]. The *i*-propyl analog, $(^{iPr4}PCP)IrH_4$ (**2**-H_4), displayed even higher catalytic activity, achieving close to 1,000 turnovers in the dehydrogenation of cyclodecane without acceptor (4) [36]. Most notably perhaps, Jensen and Goldman reported that complexes **1**-H_2 and **2**-H_4 selectively dehydrogenate the terminal position of *n*-alkanes to give α-olefin, although subsequent isomerization leads to the formation of the thermodynamically more stable internal olefins [37].



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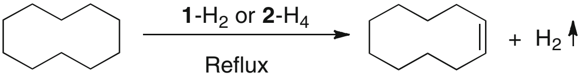

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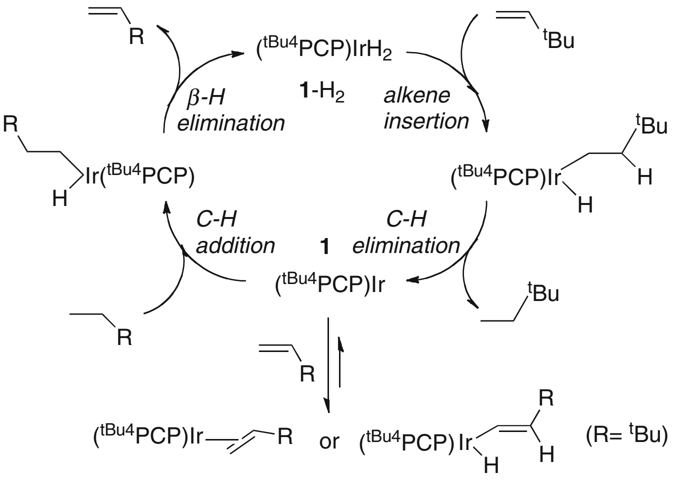
The proposed mechanism of *n*-alkane dehydrogenation by (^{tBu4}PCP)Ir is shown in Scheme 1 [38]. The reactive 14e (^{tBu4}PCP)Ir species (**1**) is generated from the hydrogenation of TBE by **1**-H_2 and undergoes oxidative addition of terminal C–H bonds. β-hydride elimination then affords α-olefin and regenerates **1**-H_2. In the case of acceptorless dehydrogenation, instead of transferring hydrogen to an acceptor, the active species **1** is generated via thermolytic loss of H_2 from **1**-H_2 [39]. Unfortunately, catalytic activity is inhibited by the buildup of olefin product due to the formation of complexes, (^{tBu4}PCP)Ir(olefin). In the case of TBE, the species of this composition is the vinyl hydride shown in Scheme 1, while linear olefins give π-complexes, and 1-alkenes in particular bind very strongly [40, 41].

The success of derivatives of **1** and **2** as dehydrogenation catalysts has led to the investigation of numerous different pincer ligands for iridium-catalyzed alkane dehydrogenation. The "Anthraphos" pincer iridium complex (**3**-H_2) was expected to afford even greater thermal stability (Fig. 1), and indeed, the catalyst can tolerate reaction temperatures up to 250°C [42]. The catalytic activity of **3**-H_2, however, is much less than that of **1**-H_2 under comparable conditions.



Scheme 1 Proposed mechanism of alkane dehydrogenation with acceptors

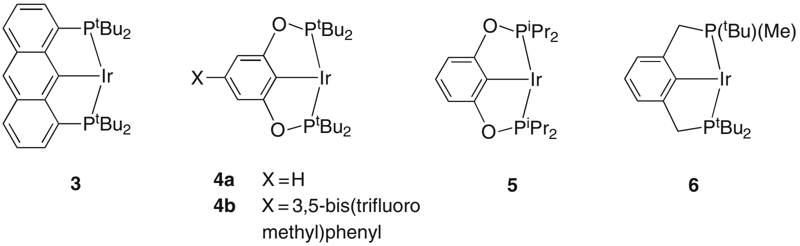


Fig. 1 Various pincer-ligated Ir complexes

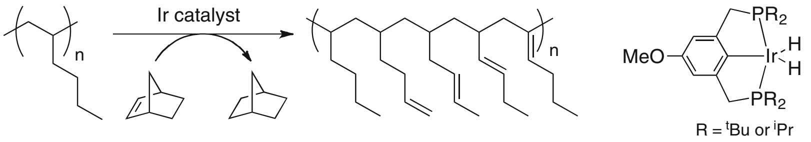
The effect of varying substituents at the *para* position of pincer ligands was investigated both computationally and experimentally [43, 44]. DFT calculations reveal that electron-donating substituents such as methoxy (OMe) favor the oxidative addition of R–H (or H_2) to 14-electron **1** and derivatives; experimentally, the MeO substituent engenders a modest increase in catalytic activity for acceptorless dehydrogenation. The bis-phosphinite complex, (^{R4}POCOP)Ir (^{R4}POCOP = κ^3-2,6-$C_6H_3(OPR_2)_2$), reported by the Brookhart group (**4**, R = ^{t}Bu) [45–47] and Jensen group (**5**, R = ^{i}Pr) [48] shows greater activity for the "benchmark" COA/TBE transfer-dehydrogenation than does **1** under similar conditions [45–47]. The ν_{CO} stretching frequency exhibited by the CO adduct of **4a** is greater than that of **1**, which appears to suggest that **4a** is less electron-rich than **1**. DFT calculations, however, show that oxygen substitution for CH_2 *increases* electron donation to aryl ring in the ^{tBu4}POCOP ligand, similarly to a methoxy substituent at the *para* position [44]. However, **4a** shows much less reactivity for the transfer-dehydrogenation of linear alkanes than does **1** [41], particularly in the case of 1-alkene hydrogen acceptors.

Brookhart and coworkers found significant differences between **1** and **4** when investigating the mechanism of COA dehydrogenation by precursors of **4** [45–47]. In particular, the rate of TBE hydrogenation by **4b**-H_2 is much faster than by **1**-H_2. For example, **4b**-H_2 hydrogenates TBE at −70°C with a rate comparable to that by **1**-H_2 at 55°C. Recent DFT calculations indicate that these differences are attributable to the fact that **4** is significantly less crowded at the metal center than **1** [41]. Thus, **1** undergoes oxidative addition of the unhindered vinyl C–H bond of TBE trans to the t-butyl group, rather than formation of the π-coordinated complex as seen in the case of **4** [45–47]. Both simple coordination and hydrogenation of TBE are clearly very sterically demanding, much more so than addition of the TBE C–H vinylic bond.

As indicated above, steric factors very significantly impact the catalytic efficiency of the pincer-iridium complexes. In this context, Goldman, Brookhart, and Krogh-Jespersen conducted a combined computational–experimental study of the effect on catalytic activity achieved by substituting *t*-butyl groups with methyl groups on phosphorus [40]. DFT calculation showed that a single methyl for *t*-butyl substitution on **1**, to give (^{tBu3Me}PCP)Ir (**6**), has a large favorable effect on the kinetics of the β-hydride elimination step (see Scheme 1), which is calculated to be the rate-determining step in the alkane dehydrogenation cycle. Experimentally, **6** dehydrogenates *n*-alkanes more efficiently than does **1** or even the presumably less crowded (^{iPr4}PCP)Ir (**2**); DFT calculations are in accord with these results [40]. After the first methyl for *t*-butyl substitution, further substitutions of this type are not calculated to result in a significant increase of activity because energies of the olefin-bound resting state and the rate-determining TS (generally β-hydride elimination) are lowered by approximately equal amounts. Experimentally, (^{tBuMe}PCP^{tBuMe})IrH_4 was synthesized and found to give lower turnovers than **6**; this was attributed to cluster formation, a hypothesis supported by the isolation of dimeric species bearing the (^{tBuMe}PCP^{tBuMe}) ligand [40].

Dehydrogenation of saturated polyolefins by pincer-iridium complexes has also been reported. Coates and Goldman have reported that (MeO-^{iPr4}PCP)IrH_4

dehydrogenates poly-1-hexene with up to 18% conversion based on C_6-units (5) [49]. Dehydrogenation selectively takes place at the branches, not the backbone, in accord with the observations that the (^{R4}PCP)Ir complexes (R = ^{t}Bu and ^{i}Pr) have a strong preference for terminal dehydrogenation to give α-olefin, although this is followed by double-bond isomerization.



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Recently, Scott, Brookhart, Goldman and coworkers have heterogenized (^{tBu4}PCP)Ir and (^{tBu4}POCOP)Ir derivatives by supporting them on γ-Al_2O_3. This was most successful with derivatives in which the pincer aryl group had a Lewis-basic *para*-substituent, e.g., NH_2, or a group that could be hydrolyzed and thus react with the alumina surface, e.g., -C(O)(OMe) or -OP(^{t}Bu)$_2$ [50].

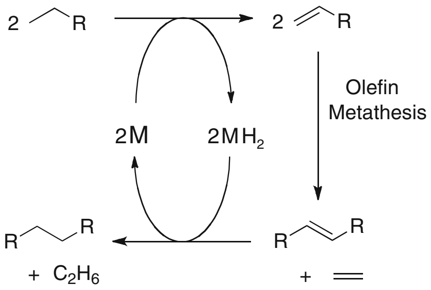
2.2 Alkane Metathesis

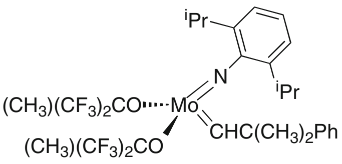
Alkane metathesis (AM; shown for *n*-alkanes in 6), which has also been referred to as “disproportionation” or “redistribution of alkane chains,” has great potential in the context of petroleum refining.

$$H_3C\text{-}(CH_2)_n\text{-}CH_3 + H_3C\text{-}(CH_2)_m\text{-}CH_3 \longrightarrow H_3C\text{-}(CH_2)_{n-x}\text{-}CH_3 + H_3C\text{-}(CH_2)_{m+x}\text{-}CH_3 \quad (6)$$

A particularly intriguing potential application of this reaction is the upgrading of the products of Fischer–Tropsch catalysis to increase the eventual yield of desirable *n*-alkane chain lengths (typically C9–C19). FT catalysis, already practiced on a large scale commercially, may prove to be a key route to the future utilization of coal, biomass, or other nonpetroleum carbon sources (including CO_2 reduction powered by solar, wind, or nuclear energy) [51, 52].

Early work by Burnett and Hughes [53] and later by the Basset group [54, 55] demonstrated the feasibility of alkane metathesis by heterogeneous catalysts. However, these heterogeneous systems did not yield products with any selectivity for molecular weight. In 2006, Brookhart, Goldman, and coworkers reported alkane metathesis using a combination of two homogeneous catalysts, pincer-ligated iridium complexes (**1** or **4a**), and a molybdenum-based Schrock olefin metathesis catalyst (**7**) under relatively mild conditions [56]. The proposed pathway is shown in Scheme 2 for the very desirable case in which *n*-alkane $H_3C(CH_2)_nCH_3$ is disproportionated to $H_3C(CH_2)_{2n}CH_3$ and C_2H_6. The pincer iridium complex dehydrogenates the *n*-alkane to give α-olefin. The olefin metathesis catalyst then effects conversion of two C_n olefins to C_{2n-2} olefin and ethylene. The dihydride complexes





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Scheme 2 Alkane metathesis of linear alkanes

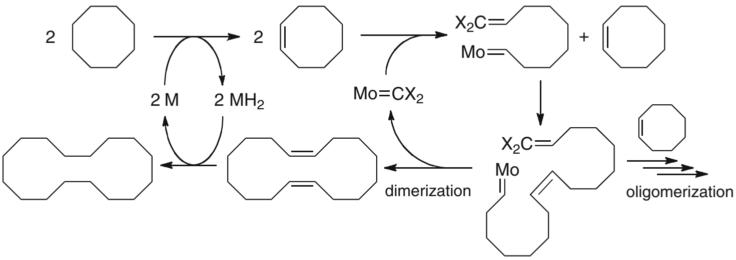
formed in the initial step then hydrogenate these olefins to afford C_{2n-2} n-alkane and ethane. Thus, the overall role of the iridium complex is to transfer hydrogen from n-alkane to the metathesized olefins.

Using **1**-H$_2$ or **4a**-H$_2$ as the transfer-dehydrogenation catalysts, 1.25 and 2.05 M total product concentrations, respectively, were obtained from 7.6 M n-hexane after 1 day at 125°C. In accord with the proposal illustrated in Scheme 2, exclusively linear n-alkanes were formed (in contrast with the Basset systems). But in contrast with the idealized cycle depicted in Scheme 2, the mixtures were not restricted to C_{2n-2} alkane and ethane as products.

Interestingly, the nature of the product mixture was very dependent upon the iridium catalyst. **1**-H$_2$ gave at least moderate selectivity for n-decane as the heavy product from n-hexane, while **4a**-H$_2$ gave successively decreasing amounts of linear heptane, octane, nonane, and decane. A priori, the low selectivity obtained using **4a**-H$_2$ could be explained by faster isomerization of olefin intermediate prior to olefin metathesis and hydrogenation. Recent experimental evidence, however, indicates that **4a** can directly dehydrogenate n-alkane to give the *internal* olefin [57], unlike **1** that shows high kinetic selectivity for the terminal position of n-alkanes.

It was observed that turnover numbers for AM using **1** or **4a** and **7** are limited by the decomposition of **7**. The use of the more thermally stable, heterogeneous, olefin-metathesis catalyst Re_2O_7/Al_2O_3 in place of **7** was therefore investigated for this purpose. The resulting system was less active, requiring higher temperature (175°C) to achieve even rates that were comparable, though still slower. However, catalytic activity was maintained for a longer time and higher turnover numbers were ultimately obtained. In more recent work, using Re_2O_7/Al_2O_3 and pincer-iridium catalysts supported on Al_2O_3 through *para*-substituents (e.g., t-Bu$_2$PO-), even higher turnover numbers (>2,000) were ultimately achieved [58].

Schrock and coworkers have generated and tested more than forty molybdenum and tungsten imido complexes with pincer iridium complex for AM [59]. In general, tungsten complexes perform better than molybdenum complexes, presumably due to



Scheme 3 Alkane metathesis of cyclic alkanes

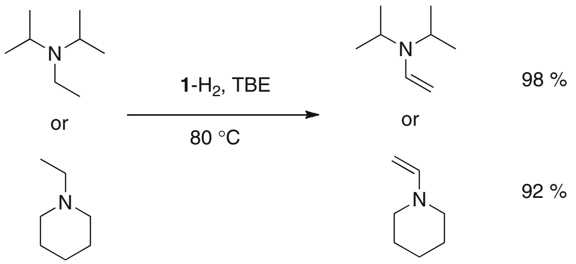
greater stability of the former at the high temperatures required for dehydrogenation. The tungsten imido complex, W(NAr)(CHR)(OSiPh$_3$)$_2$ (Ar = 2,6-diisopropylphenyl, R = CMe$_2$Ph) gave the best product yield, about double that reported with the originally used molybdenum catalyst **7**.

Scott and coworkers [60] have also investigated applications of AM to cycloalkanes. They found, for example, that cyclooctane undergoes metathesis by **7** in tandem with **1**, **4a,** or **6**, to give a range of cyclic products, including (surprisingly) cycloheptane, but mostly low cyclooligomers in which the carbon number is a multiple of 8. The proposed mechanism is shown in Scheme 3.

2.3 Dehydrogenation of Alkyl Groups in Molecules Containing Heteroatoms

Examples of iridium-catalyzed dehydrogenation of alkyl moieties (H–C–C–H linkages) in heteroatom-containing molecules are relatively scarce although stoichiometric reactions have been reported in several cases [61, 62]. Jensen, Kaska and coworkers reported that **1-H$_2$** catalyzes transfer-dehydrogenation of tetrahydrofuran to produce dihydrofuran as well as furan [63]. The catalytic activity was significantly lower than with cycloalkanes under comparable conditions. It was suggested that the oxygen coordination to the metal center inhibits the reaction. Knapp, Goldman and coworkers reported that dehydrogenation of tertiary amines to give enamines (7) occurs in high yield and with good selectivity, particularly in the case of *N*-ethyl amines [64]. The resulting terminal enamines are difficult to synthesize by conventional synthetic routes.

Several iridium-catalyzed dehydrogenations of HCXH (X = O, N) linkages have been reported by pincer-iridium complexes. While these dehydrogenations are not generally considered as C–H bond activations or functionalizations, it is generally not known if they proceed via initial activation of the X–H or C–H bond [65, 66].



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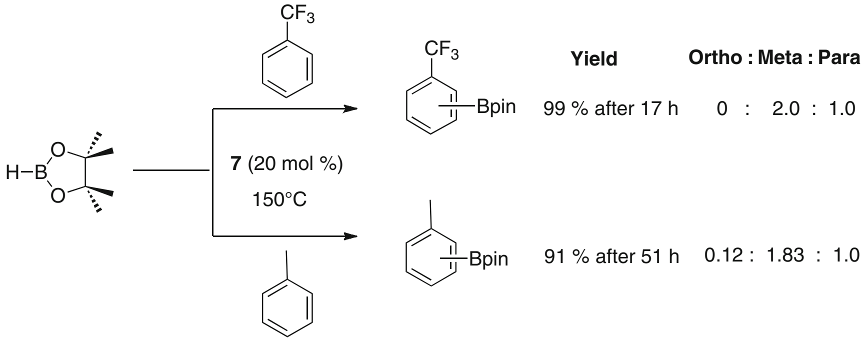
3 Borylation of Arenes

Arylboronate esters are widely used synthons in organic transformations such as C–C or C–X bond forming reaction, thanks to their low toxicity, good functional group tolerance, and high stability toward atmospheric oxidation. Traditionally, they have been prepared from aryl halides via conversion to Grignard or lithium reagents followed by reaction with trialkyl borates. The possibility of direct borylation via C–H bond cleavage was first hinted at by Rablen and Hartwig, who computationally predicted the bond dissociation energies of B–H and B–C bonds and suggested that conversion of C–H to C–B bonds is thermodynamically favorable [67, 68]. Shortly thereafter, the first examples of metal-catalyzed borylations of alkane and arene C–H bonds were discovered, initially photochemical [69–72] and subsequently thermochemical [73, 74]. Since then, numerous stoichiometric and catalytic borylation of C–H bonds have been reported, particularly of arenes [11, 75, 76]. While many transition metal complexes including Rh, Ru, Re, Fe, W, and Pd have been studied in this context, iridium complexes have proven the most effective for the more practical thermocatalytic transformations, affording high reactivity as well as regioselectivity.

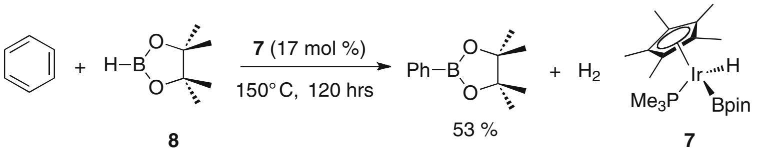
Iridium-catalyzed formation of B–C bonds from arene C–H bonds was first reported by Smith and coworkers [73]. They demonstrated that the archetypal C–H activation products, Cp*Ir(PMe$_3$)(H)(R), could mediate B–C bond formation (R = Ph, cyclohexyl) and were able to effect the catalytic borylation of benzene with HBpin (**8**) to produce C_6H_5Bpin and H_2 at 150°C (8).

Subsequent reports showed that a wide range of arene substrates could be borylated, with regioselectivity predominantly dictated by steric factors [77]. In the case of monosubstituted arenes, borylation generally occurs predominantly at the *meta* and *para* positions, with a near-statistical ratio while substitution at the *ortho* position is minor (Scheme 4). In the case of 1,3-disubstituted arenes, borylation occurs exclusively at 5-position. The selectivity was reversed in favor of the *ortho* position in the case of diethylbenzamide, presumably due to chelation [77].



Scheme 4 Regioselectivity in monosubstituted arenes

Smith also found that catalytic activity is dramatically increased by generating the active catalyst in situ from (Ind)Ir(COD) (Ind = η^5-C_9H_7) in the presence of PMe_3 or chelating phosphines such as 1,2-bis(diphenylphosphino)ethane (dppe) or 1,2-bis(dimethylphosphino)ethane (dmpe) [76]. Moreover, these systems show remarkable functional group tolerance, allowing, for example, borylation of aryl halides, esters and heteroarenes. The selectivity for C–H over C–X (X = halogen) bonds in particular allowed the group to develop one-pot biaryl syntheses via borylation/Pd-catalyzed Miyaura-Suzuki coupling (9) [76].



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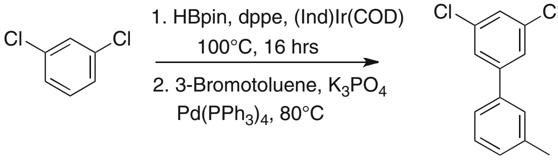

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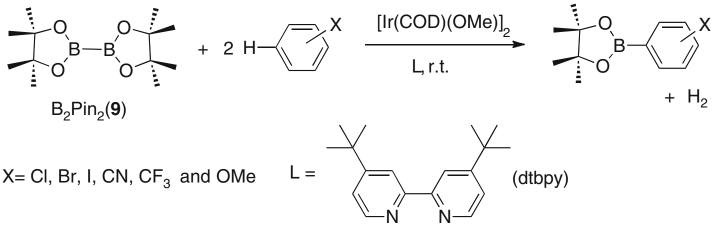
One of the most active and well-studied catalytic borylation systems is that generated from iridium(I) precursors such as $[Ir(COD)Cl]_2$ or $[Ir(COD)(OMe)]_2$ and bipyridine type ligands such as 2,2′-bipyridine or 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy). In 2002, Ishiyama, Miyaura, and Hartwig et al. reported that the combination of $[Ir(COD)Cl]_2$ and 2,2′-bipyridine catalyzes arene borylation in the presence of excess arene under mild conditions (80°C). When the catalyst is generated from $[Ir(COE)_2Cl]_2$ and dtbpy, the reaction proceeds even at room temperature [78, 79]. The same groups optimized conditions and found that the combination of [Ir(COD) (OMe)]$_2$ and dtbpy (10) is a highly effective catalyst in the borylation of arenes so that reactions can be successfully performed with equimolar ratio of arenes and

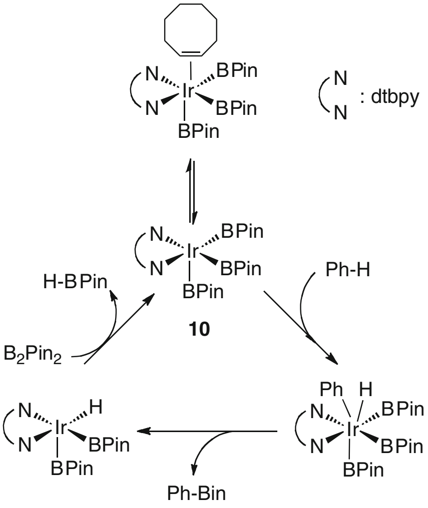
B_2Pin_2 [79] or HBpin [80] at room temperature in nonpolar solvents. The reactions tolerate a wide range of functional groups including Br, I, CO_2Me, and CN.



(10)

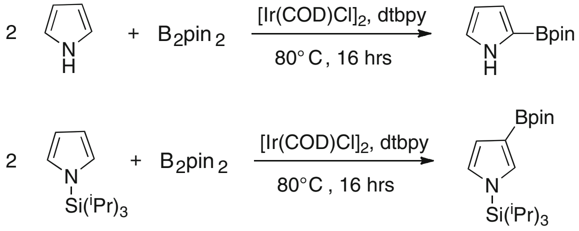
Extensive studies of kinetics and isotope effects by Hartwig and coworkers support the mechanism shown in Scheme 5 for the Ir(I)/dtbpy catalyzed borylation [81]. In particular, these studies indicate that the iridium(III) trisboryl bipyridine complex (**10**) is the species that activates the arene C–H bond; this is in agreement with DFT calculations by Sakaki et al. predicting the key intermediacy of the trisboryl complex and the seven-coordinated Ir(V) species resulting from C–H addition [82]. C–H addition to Ir(III) was also proposed in the (Ind)Ir(COD)/ phosphine-catalyzed borylation by Smith et al. [76].

The iridium-catalyzed direct borylation has been applied to a wide variety of heteroaromatics including thiophene, pyrrole, furan, indole, and pyridine, with good yield under relatively mild conditions [83]. Again, the combination of [Ir(COD)(OMe)]$_2$ and dtbpy yielded a highly efficient system, catalyzing borylation at room temperature in high yield [84]. In the case of five-membered heteroarenes, the reactions are highly selective for borylation at the α-position of the heteroaromatic ring. However, the regioselectivity can be controlled by imposing sufficient steric bulk at the heteroatom (e.g., 11). Interestingly, borylation of six-membered

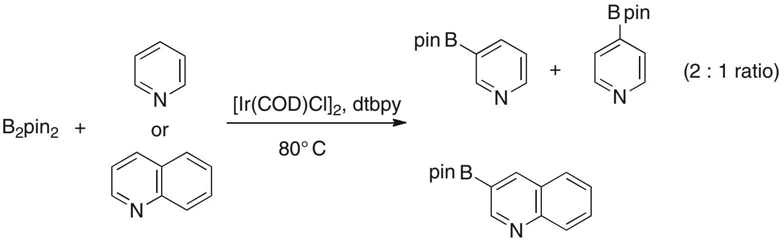


Scheme 5 Proposed mechanism for borylation by bipyridine ligated iridium complexes

heteroaromatic rings shows different regioselectivity. Borylation of pyridine occurs at the 3- and 4-postion with a statistical ratio and the reaction of quinoline selectively gives the 3-borylated product (12). Although the reason for different regioselectivity was not determined, one possibility proposed by the authors is that the reversible coordination at nitrogen (by either iridium or boron) blocks borylation at the 2-position while perhaps activating the 3-position [83].



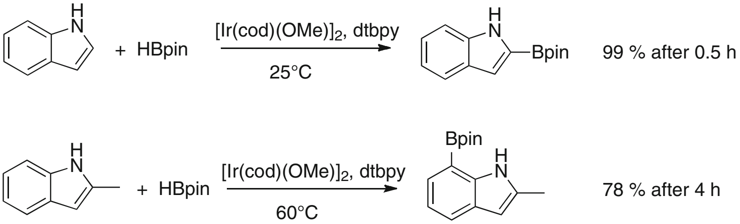
(11)



(12)

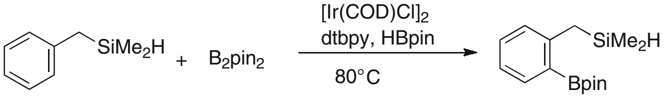
The $[Ir(OMe)(COD)]_2$/dtbpy catalytic system borylates indole selectively at the 2-position (Scheme 6). Smith and coworkers reported that borylation of N-unprotected 2-substituted indoles exclusively occurs at 7-position (Scheme 6) [85, 86]. It has been suggested that nitrogen interaction with the iridium center or possibly the empty p-orbital of boron in a boryl ligand induces the observed regioselectivity. Borylation of other heteroarenes have been reported using the same or similar Ir(I) and bipyridine combination [85, 87–90].

In the borylation of nonheteroaromatic rings, sterics are generally the most important factor influencing regioselectivity so that boronate is generally introduced at the sterically less hindered sites (e.g., *meta* or *para* in monosubstituted

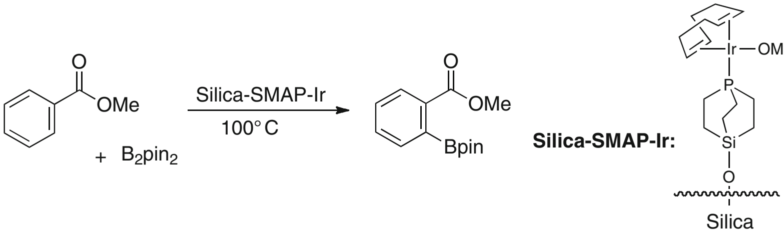


Scheme 6 Borylation of indoles

arenes). However, it was shown that selective borylation of an *ortho* position is possible with the proper directing group [91]. Using hydrosilyl groups, benzylic silanes, phenols, and anilines have been successfully boronated with high regioselectivity for the *ortho* position (13). Although the mechanism has not yet been fully investigated, evidence supports the formation of an Ir–Si bond in the course of the reaction. Recently, Sawamura and coworkers reported a silica-supported iridium monophosphine catalyst that efficiently catalyzes selective *ortho* borylation of arenes possessing directing groups (e.g., methyl benzoate or chlorobenzene) [92]. The high *ortho* selectivity was attributed to the fact that the catalytically active iridium species possesses only a single phosphine ligand; presumably, this allows the directing group to coordinate while still maintaining the degree of coordinative unsaturation required for catalytic activity (14).



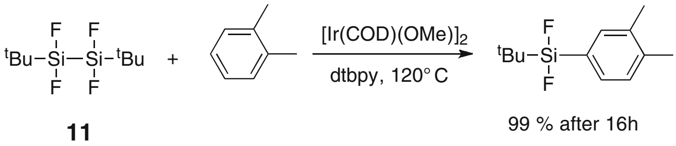
(13)



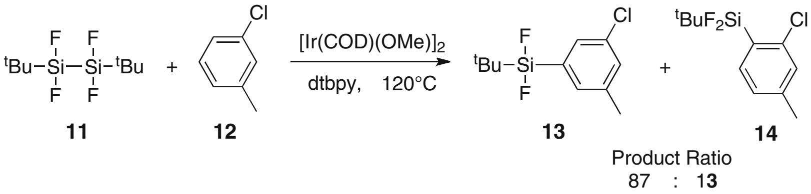
(14)

4 Silylation of Arenes

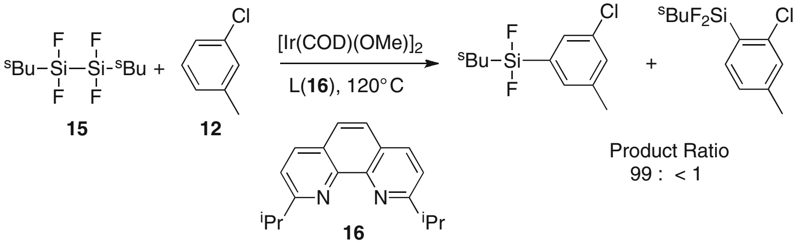
In 1982, Curtis reported one of the earliest examples of catalytic functionalization that appeared to proceed via activation of a simple hydrocarbon C–H bond. Pentamethyldisiloxane was observed to undergo dehydrogenative coupling with benzene in the presence of Vaska's complex, $Ir(CO)(Cl)(PPh_3)_2$, to yield phenyl-pentamethyldisiloxane along with other redistribution products [93]. The reaction required long reaction time at relatively high temperature and gave a variety of redistribution products along with the Ph–Si coupling product in low yield (~20% after 49 days at 100°C); nevertheless, precedent for catalytic formation of aryl–silyl coupling was established. Two decades later, Ishiyama and Miyaura et al. developed an efficient iridium-catalyzed aromatic silylation system [94]. $[Ir(COD)(OMe)]_2$ and dtbpy, which also comprises an efficient system for aromatic borylation, catalyzes aromatic silylation with fluorinated disilanes, $(t\text{-BuF}_2Si)_2$ (**11**), to give the corresponding aryl difluorosilanes (15). Steric factors appear to influence the regioselectivity of the coupling, similar to borylation of arenes, but the silylations in some cases afford lower regioselectivity. For example, *o*-xylene gives exclusively 4-silylated products, but silylation of 3-chlorotoluene (**12**) gave a mixture of products (**13** and **14**) (16). The nature of the substituents on silicon is critical; (^{t}BuCl$_2$Si)$_2$ or (Me$_3$Si)$_2$ do not undergo the analogous reaction. Subsequently, the same group found significant improvement in regioselectivity by using 2,9-diisopropyl-1,10-phenanthroline (**16**) as the chelating ligand, and 1,2-di-sec-butyl-1,1,2,2-tetrafluorodisilane (**15**) as the silyl coupling substrate (17) [95].



(15)



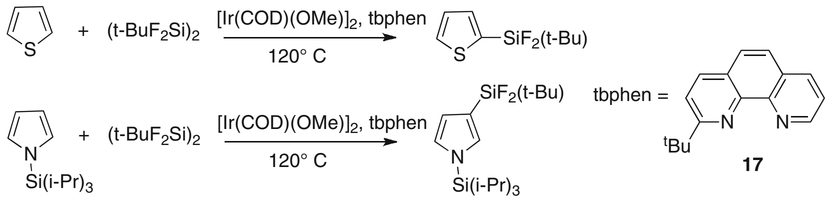
(16)



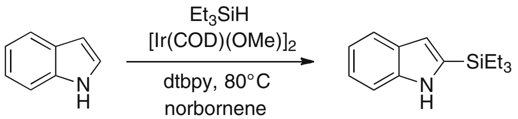
(17)

The silylation of heteroarenes was also reported [96]. Silylation of thiophene or furan with **11** occurs selectively at the α-position in the presence of [Ir(COD)(OMe)]$_2$/2-*tert*-butyl-1,10-phenanthroline (tbphen, **17**). Silylation of pyrrole or indole under the same conditions was unsuccessful presumably due to the presence of the acidic N–H bond. Accordingly, N-substituted pyrrole and indole undergo silylation with **11**, to selectively give 3-substituted products (Scheme 7).

Falck has recently reported dehydrogenative silylation of heteroarenes with triethylsilane (18) [97]. Coupling with the Si–H bond of triethylsilane, rather than the disilane Si–Si bond, in conjunction with the use of norbornene that presumably acts as a hydrogen acceptor, gives good yields with indoles, thiophenes, and furans, under relatively mild condition (80°C). Unlike the reaction shown in Scheme 7, silylation of indole did not require protection of the N–H group.



Scheme 7 Regioselectivity in silylation of heteroarenes

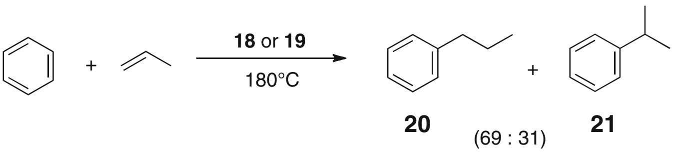


(18)

5 C–C Bond Formation

5.1 Hydroarylation and Hydrovinylation of C–C Multiple Bonds

Periana and coworkers reported in 2000 that the binuclear iridium (III) complex [Ir(μ-acac-O,O,C^3)(acac-O,O)(acac-C^3)]$_2$ (**18**) catalyzes olefin hydroarylation with benzene and unactivated alkenes [98]. In the reaction of 1-alkenes, weak selectivity for anti-Markovnikov addition to yield *n*-alkyl arenes is observed, in sharp contrast with Friedel–Crafts arene alkylations, which essentially only afford branched products. For example, iridium-catalyzed alkylation of benzene with propylene produces *n*-propylbenzene (**20**) and cumene (**21**) in 69 and 31% yield, respectively, whereas the AlCl$_3$-catalyzed reaction gives entirely cumene (**21**) (19). Unlike Friedel–Crafts reactions, in which ethylene reacts more slowly than substituted olefins due to lesser stability of the respective carbonium ion, ethylene is more reactive than propene for the iridium-catalyzed hydroarylation. The reaction is sensitive to steric effects so that alkylation of toluene with ethylene gives only *meta* and *para* substituted products in an approximately statistical ratio (63:37). No *ortho* product was observed. These observations constitute compelling evidence that **18**-catalyzed hydroarylation does not involve free carbonium ions, and are consistent with a C–H activation mechanism. Monomeric iridium complexes, Ir(acac-O,O)$_2$(R)(L) (**19**) where R is Ph or (acac-C^3) and L is pyridine or H$_2$O, were also reported to catalyze the reactions [99]. The use of dimer **18** or four different monomers **R-19-L** (including R = Ph or acac-C3 and L = pyridine or H$_2$O) all gives comparable turnover frequencies and, most importantly, identical ratios of linear to branched product for reaction 19, thus strongly indicating that these species all give rise to the same catalytically active intermediate [99]. Kinetic studies indicate that the active catalyst is monomeric [99–102].



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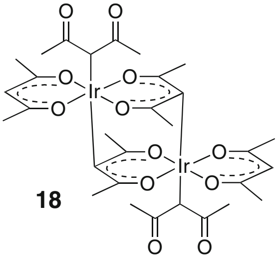

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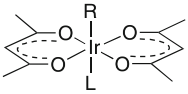
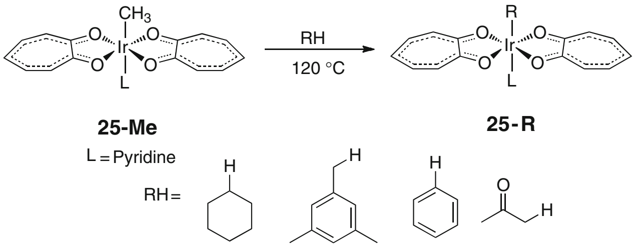


R = Ph, acac-C^3
L = pyridine, H_2O

R-19-L

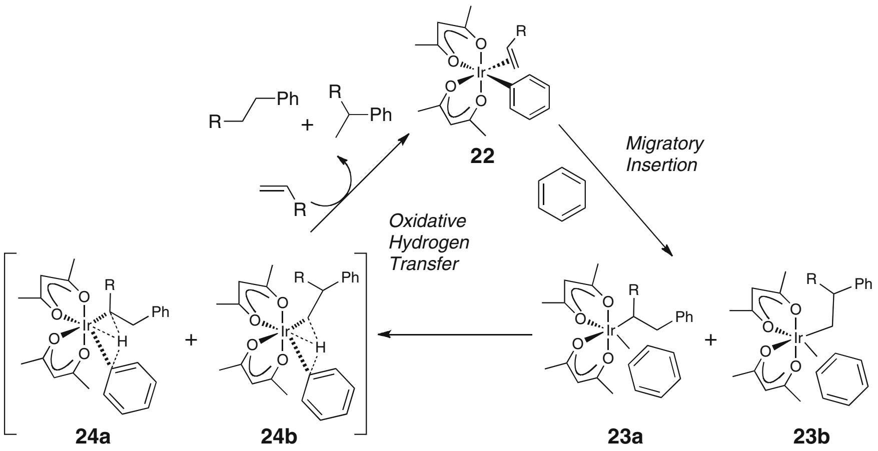
When **acac-C^3-19-Py** is used as the precatalyst for reaction 19, the iridium containing species recovered (65% yield) is **Ph-19-Py**. Displacement of pyridine by olefin can presumably generate **22**. Based on extensive experimental and theoretical study by Periana and Goddard, the mechanism proposed for the hydroarylation is that shown in Scheme 8. *Cis*-bis(acac-O,O) Ir complex (**22**) undergoes olefin insertion into the Ir–aryl bond, followed by arene coordination to generate **23a** and **23b**. Aromatic C–H bond activation then takes place via “oxidative hydrogen migration”, a step which may be viewed as proceeding via a transition state – but not an intermediate – that is essentially Ir(V) in character [100–103]. This step, followed by olefin coordination, yields the coupled organic product and regenerates **22**. DFT calculations show that regioselectivity in olefin arylation is determined by the relative energetics of the transition states for formation of **23a** and **23b**.

In 2005, the same authors reported that the iridium(III) complex with tropolonato ligands (**25**) shows faster C–H bond activation rates than the analogs with acetato ligands (20)[104]. For example, **25-Me** catalyzes H/D exchange with a mixture of C_6H_6/ toluene-d_8 50 times faster than the acetato analog. However, hydroarylation catalyzed by **25-Ph** is slightly less effective than with the acetato analog [105].



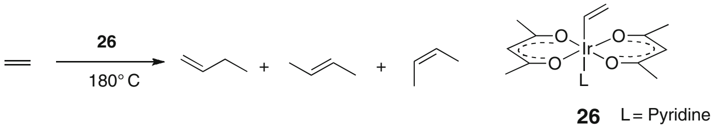
(20)

Periana and Goddard et al. also found that the iridium(III) vinyl bis-acetylacetonate complex (**Vinyl-Ir-Py**, **26**) catalyzes dimerization of olefins (e.g., 21) [106, 107]. Analogously to the hydroarylation of Scheme 8, the mechanism is proposed to



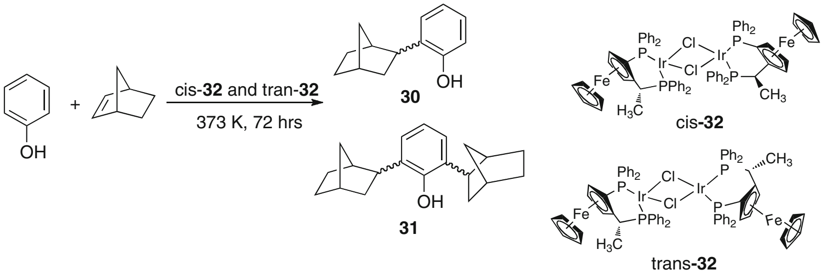
Scheme 8 Proposed mechanism for hydroarylation

involve insertion of olefin into an Ir–vinyl bond followed by vinyl C–H bond activation (Scheme 9).



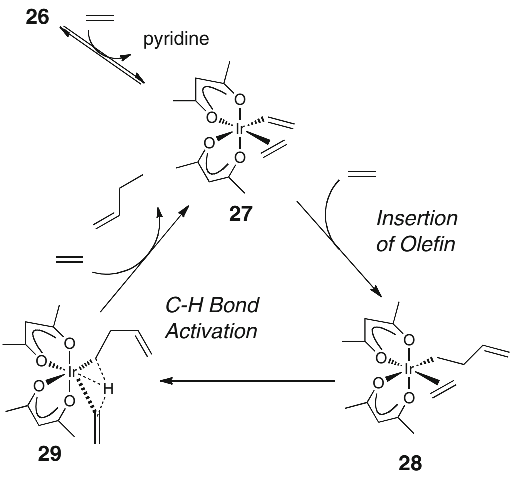
(21)

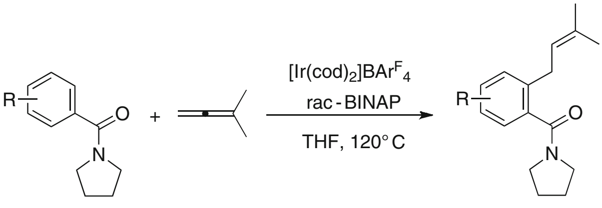
Several arylations involving reactive alkenes such as norbornene or allenes have been reported. Togni and coworkers have shown that norbornene is selectively added to the *ortho* positions of phenols to produce a mixture of **30** and **31** in 69% and 13% yield, respectively, after 72 hours at 100°C (22) [108, 109]. 1,1-dimethylallene also reacts with aromatic carboxamides (**33**) to produce prenylation products (**34**) in the presence of cationic iridium complexes (23) [110]. In both cases, initial *ortho* C–H bond activation in arenes directed by coordinating groups followed by olefin insertion has been proposed.



(22)

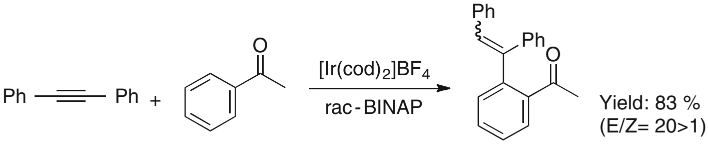
Scheme 9 Proposed mechanism of hydrovinylation





33 **34** (23)

Insertion of alkynes into aromatic C–H bonds has been achieved by iridium complexes. Shibata and coworkers found that the cationic complex [Ir(COD)$_2$]BF$_4$ catalyzes the hydroarylation of internal alkynes with aryl ketones in the presence of BINAP (24) [111]. The reaction selectively produces *ortho*-substituted alkenated-aryl products. Styrene and norbornene were also found to undergo hydroarylation under similar condition. [Cp*IrCl$_2$]$_2$ catalyzes aromatization of benzoic acid with two equivalents of internal alkyne to form naphthalene derivatives via decarboxylation in the presence of Ag$_2$CO$_3$ as an oxidant (25) [112].



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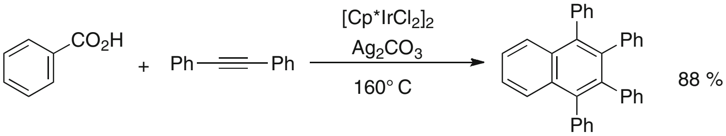
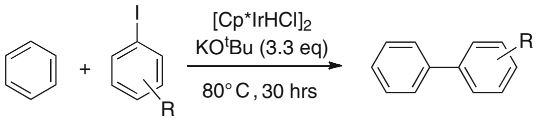


(25)

5.2 Aryl–Aryl Coupling Reactions

Relatively few examples have been reported of iridium-catalyzed arylation of arenes via C–H bond cleavage. The scope of the reactions has been, to date, limited to iodoarenes as coupling partners. The Yamaguchi group reported Cp*Ir-catalyzed benzene coupling with iodoarenes in the presence of excess of KO^{t}Bu (26) [113]. Various types of methyl or methoxy substituted iodoarenes undergo arylation with benzene in moderate yield. The reaction of anisole or toluene with iodobenzene gives poor regioselectivity. These limitations notwithstanding, this was a notable example of arylation of an aryl C–H bond that did not require any "directing group" adjacent to the C–H bond substrate. The mechanism is proposed to involve a phenyl radical intermediate based on the following (1) The regioselectivity shown in 27 is similar to that observed in radical substitution reactions. (2) In the presence of radical scavenger, the authors observed a significant decrease in reaction yield [113].



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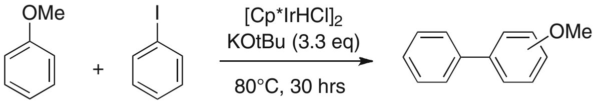
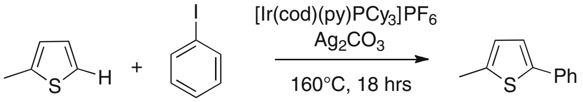


2-OMe : 3-OMe : 4-OMe
72 : 16 : 12 (27)

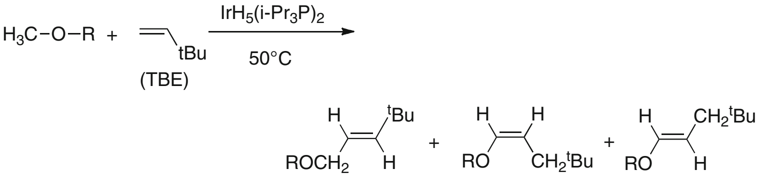
The report by Yamaguchi et al. revealed the first example of iridium-catalyzed direct arylation of aromatic C–H bonds. Subsequently, the Itami group reported that $[Ir(COD)(py)PCy_3]PF_6$, Crabtree's catalyst [114], mediates direct arylation of a broad range of heteroarenes including thiophene and furan in good yield (28) [115]. The choice of additive turns out to be crucial in that only Ag_2CO_3 promotes the reaction among those investigated including AgOTf, AgOAc, Na_2CO_3, K_2CO_3, and KO^{t}Bu. The system shows good functional group tolerance; bromo, nitro, and ester group substituted iodoarenes were used as coupling partners.



87 % (28)

5.3 Coupling with sp³ C–H Bonds

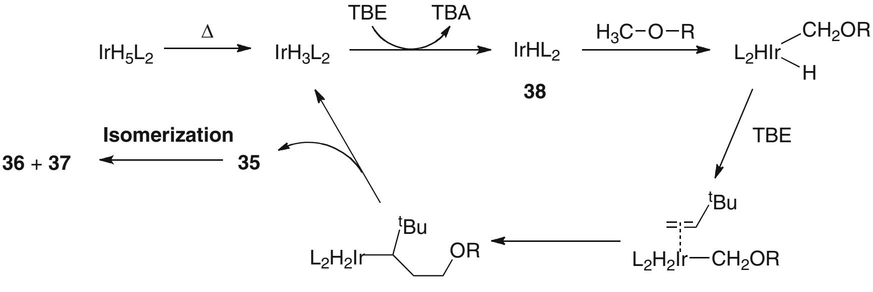
Examples of catalytic formation of C–C bonds from sp^3 C–H bonds are even more scarce than from sp^2 C–H bonds and, in general, are limited to C–H bonds adjacent to heteroatoms. A remarkable iridium-catalyzed example was reported by the group of Lin [116] the intermolecular oxidative coupling of methyl ethers with TBE to form olefin complexes in the presence of $(P^iPr_3)_2IrH_5$ (29). In their proposed mechanism, the reactive 14e$^-$ species **38** undergoes oxidative addition of the methyl C–H bond in methyl ethers followed by olefin insertion to generate the intermediate **39**. β-hydride elimination affords **35**, which can isomerize to products **36** and **37** (Scheme 10). The reaction proceeds under mild condition (50°C) but suffers from poor selectivity as well as low yield (TON of 12 after 24 h).



35 **36** **37** (29)

Sames et al. have reported the intramolecular cyclization of alkene–amide substrates catalyzed by $[Ir(COE)_2Cl]_2$ and the *N*-heterocyclic carbene ligand, *N*, *N′*-bis-(2,6-diisopropylphenyl)-imidazolyl, via olefin insertion following oxidative addition of an sp^3 C–H bond (Scheme 11) [117].

Recently, Shibita et al. reported catalysis of alkyne insertion into an arylamide sp^3 C–H bond to give allylamides (**42**) by a cationic iridium complex [118]. An interesting aspect of this work is the unusually selective cleavage of an sp^3 C–H bond over sp^2 aromatic C–H bonds so that the alkenyl arylamide (**43**) is only a very minor product (30). The carbonyl group is required for the reaction as no coupling



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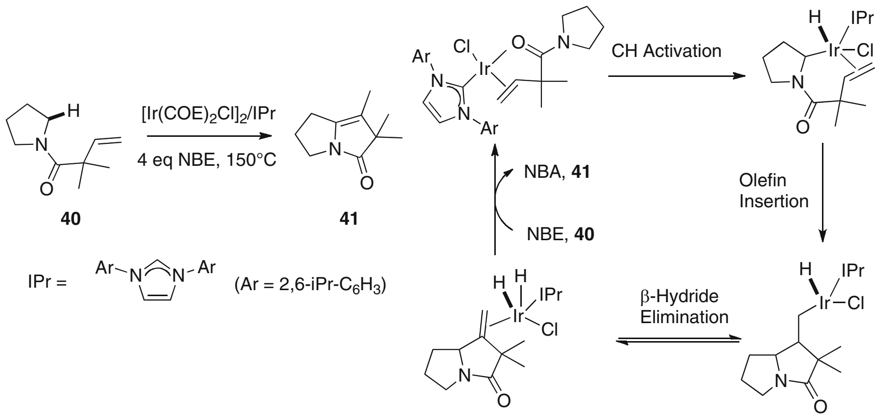
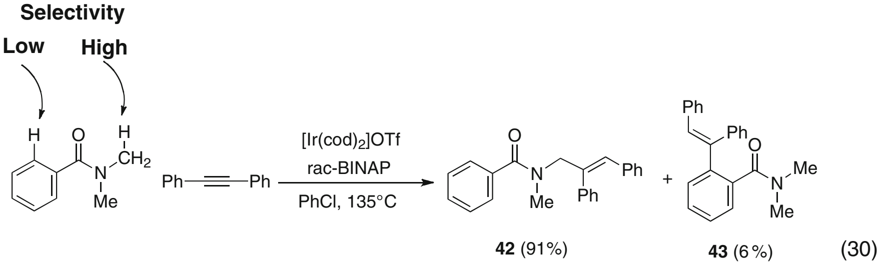
Scheme 10 Proposed mechanism for C–C bond coupling via sp^3 C–H bond cleavage



Scheme 11 Cyclization of alkene–amide via sp^3 C–H Bond cleavage

was observed with *N*,*N*-dimethylbenzylamine under the same conditions. This was tentatively proposed to be due to carbonyl coordination directing C–H addition of the amido sp^3 C–H bond (although the same functionality is well known to result in functionalization of *ortho*-aryl-C–H bonds [119]). Alkyne insertion presumably follows C–H addition to give the allylamides.



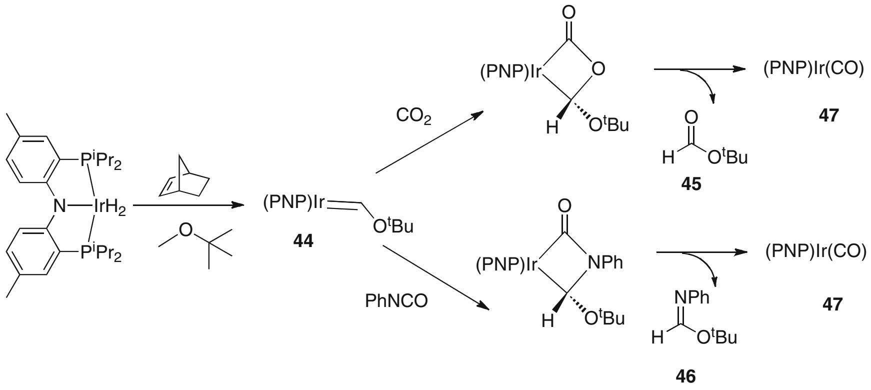
In an unusual example of C–C coupling, the benzylation of a bromofullerene, $C_{60}Me_5Br$, with toluene, has been reported to be catalyzed by $[Ir(COE)_2Cl]_2$ in the presence of triethylamine [120].

6 Others

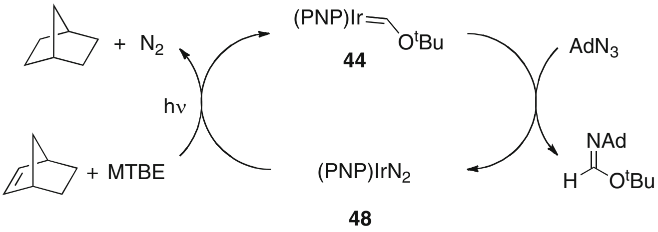
6.1 α,α-Dehydrogenation and Reactions with Heterocumulenes

Initiating a remarkable series of papers in 2008–2009, Grubbs and Whited reported the formation of an Ir(I) carbene complex, **44**, from the reaction of methyl *t*-butyl ether (MTBE) with Ozerov's $(PNP)IrH_2$ ($PNP = [N(2\text{-}P^iPr_2\text{-}4\text{-}Me\text{-}C_6H_3)_2]^-$) and NBE [121–127]. C–H addition to (PNP)Ir presumably occurs followed by α-H-elimination and loss of H_2, which is scavenged by a second mol of NBE; the overall result can be considered an α,α-dehydrogenation. Carbene complex **44**, although formally a Fischer carbene, does not display typical electrophilic activity at the carbene carbon. Rather, the characteristic reactivity elucidated of **44** was with heterocumulenes, particularly CO_2 to give t-Bu formate (**45**) and (PNP)Ir(CO) (**47**) (Scheme 12). Analogous reactions were found with carbonyl sulfide and phenyl isocyanate to give **47** and the thioester and formimidate **46**. Attempts to incorporate these reactions into catalytic cycles were not successful, no doubt due to the very strong Ir–CO bond [128] in **47**.

In order to avoid formation of **47**, the use of diazo reagents (E=N=N) was investigated in place of the analogous carbonyls and indeed the organic products **45** was produced from N_2O, along with the dinitrogen complex **48**. However, even dinitrogen proved too strongly bound to allow incorporation into a thermal catalytic cycle. Dinitrogen could be extruded photochemically, however, allowing the authors to achieve the photocatalytic formation of *N*-adamantyl *t*-butylformimidate shown in Scheme 13 [121–127].



Scheme 12 Reactions (PNP)Ir=CH(O^{t}Bu) with heterocumulenes



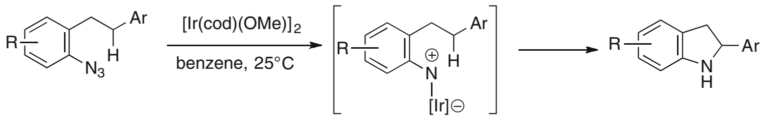
Scheme 13 Catalytic cycle for *t*-butylformimidate synthesis

6.2 C–H Bond Activation by Metal Carbenoids or Nitrenoids

Functionalization of C–H bonds by metal carbenoid or nitrenoid insertions represents a promising alternative to the more “traditional” approach of direct activation by a metal center. Carbenoids and nitrenoids show unusual regio- and stereoselectivity in insertions into C–H bonds, and unlike insertions of metal centers, these are intrinsically “functionalizations” rather than “activations,” which must be followed by functionalization (although in either case, loss of the functionalized group, to regenerate the active metal complex, is still required for catalysis) [129]. The use of dimeric Rh(II) complexes in this area has been extensively developed [129].

Recent studies show that iridium complexes are also capable of catalyzing C–C or C–N bond coupling via carbenoid or nitrenoid insertion into C–H bonds. Katsuki et al. reported that iridium(III)–salen complexes catalyze asymmetric C–H insertion of carbenes at the α-position of THF and the allylic position of 1,4-cyclohexadiene [130]. In both cases, the reactions are highly enantioselective and in the case of THF, highly diastereoselective (Scheme 14). Importantly, while previous related work was limited to the use of α-aryl-α-diazoacetates, this study gave comparably good results with simple α-methyl-α-diazoacetate (R=Me, Scheme 14); this may be due to inhibition of β-H-elimination as a result of the salen ligand precluding access to a coordination site cis to the site of the carbene.

Intramolecular C–N bond coupling in arylazides via C–H bond activation catalyzed by $[Ir(COD)(OMe)]_2$ was recently reported [131]. The intermediate iridium nitrenoid complex (**50**) formed after the extrusion of dinitrogen is proposed as a reactive species, which can cleave the benzylic C–H bond to yield indoline derivatives (31).



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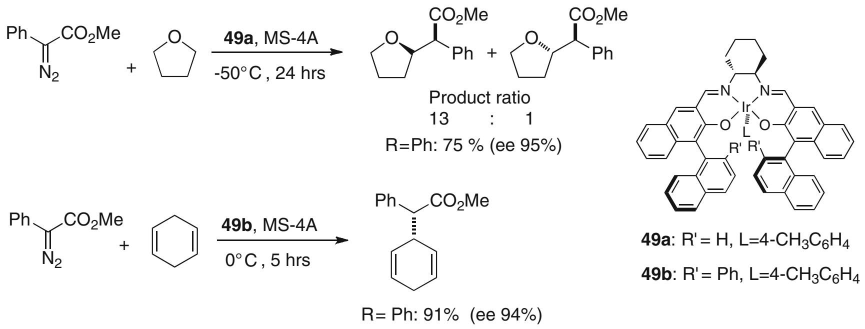
(31)



Scheme 14 Stereoselective C–H functionalization by Ir(III)–salen

7 Concluding Remarks

Extensive research over the past two decades on the catalytic functionalization of C–H bonds by complexes of iridium, as with other transition metals, has begun to pay significant dividends. Nevertheless, only a small fraction of the great potential offered by such chemistry has been realized, and there seems little doubt that progress will continue at a steady pace at least.

Iridium has a tendency to form very stable – and catalytically inactive – Ir(III) complexes. The metal, however, has proven particularly effective for some hydrocarbon functionalizations, the first of which to be discovered was alkane dehydrogenation. Key to this reactivity is (a) the ability of three-coordinate Ir(I) to undergo facile oxidative addition of alkyl–H bonds, an addition that is generally quite unfavorable thermodynamically, and (b) the fact that the products of such additions are coordinatively unsaturated and therefore able to undergo β-hydrogen elimination. The other well-developed C–H bond functionalization in which iridium plays a leading role is borylation. In contrast with dehydrogenation, the key oxidative couple for borylation, and perhaps silylation, arylation, and other couplings as well, appears to be Ir(III)/Ir(V). These reactions involve bonds much more prone to oxidative addition than alkyl–H, including aryl–H, B–H, B–B, and Si–H (For some relevant examples of Ir(V) complexes and discussions of factors stabilizing them, see [132–138]). This may explain why the Ir(III)/Ir(V) couple is accessible with these substrates, although even with such substrates the Ir(V) oxidation state is certainly not so stable that catalytic activity is precluded. None of this however is understood definitively, and any generalizations are still highly speculative. Thus, although iridium provides some of the most classic examples in mechanistic organometallic chemistry, there seems to be great room for growth in its applications in C–H bond functionalization, which will probably be coupled with commensurate growth in our mechanistic understanding of this chemistry.

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DOI: 10.1007/978-3-642-15334-1_7

Iridium-Catalyzed Allylic Substitution

John F. Hartwig and Mark J. Pouy

Abstract Iridium-catalyzed asymmetric allylic substitution has become a valuable method to prepare products from the addition of nucleophiles at the more substituted carbon of an allyl unit. The most active and selective catalysts contain a phosphoramidite ligand possessing at least one arylethyl substituent on the nitrogen atom of the ligand. In these systems, the active catalyst is generated by a base-induced cyclometalation at the methyl group of this substituent to generate an iridium metalacycle bound by the COD ligand of the $[Ir(COD)Cl]_2$ precursor and one additional labile dative ligand. Such complexes catalyze the reactions of linear allylic esters with alkylamines, arylamines, phenols, alcohols, imides, carbamates, ammonia, enolates and enolate equivalents, as well as typical stabilized carbon nucleophiles generated from malonates and cyanoesters. Iridium catalysts for enantioselective allylic substitution have also been generated from phosphorus ligands with substituents bound by heteroatoms, and an account of the studies of such systems, along with a description of the development of iridium catalysts is included.

Keywords Allylic substitution · Asymmetric catalysis · Heterocycles · Iridium · Phosphoramidite

Contents

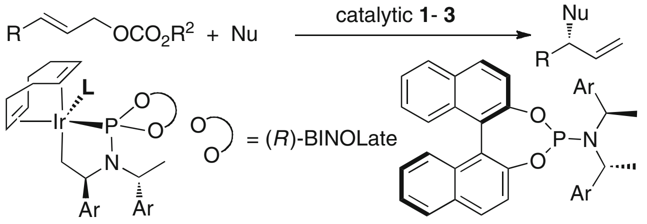
J.F. Hartwig (✉) and M.J. Pouy
Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, IL 61801, USA
e-mail: jhartwig@illinois.edu

1 Introduction

A wide range of carbon, nitrogen, and oxygen nucleophiles react with allylic esters in the presence of iridium catalysts to form branched allylic substitution products. The bulk of the recent literature on iridium-catalyzed allylic substitution has focused on catalysts derived from $[Ir(COD)Cl]_2$ and phosphoramidite ligands. These complexes catalyze the formation of enantiomerically enriched allylic amines, allylic ethers, and β-branched γ-δ unsaturated carbonyl compounds. The latest generation and most commonly used of these catalysts (Scheme 1) consists of a cyclometalated iridium-phosphoramidite core chelated by 1,5-cyclooctadiene. A fifth coordination site is occupied in catalyst precursors by an additional κ^1-phosphoramidite or ethylene. The phosphoramidite that is used to generate the metalacyclic core typically contains one BINOLate and one bis-arylethylamino group on phosphorus.

Iridium-catalyzed allylic substitution has undergone rapid development since it was first reported [1]. What began as a reaction of malonate nucleophiles catalyzed by complexes containing achiral ligands to form racemic product has become a valuable method for the enantioselective formation of carbon–carbon, –nitrogen, and –oxygen bonds. Mechanistic investigations have slowly increased our understanding of the inner workings of the catalytic cycle, and experimentally grounded proposals for the origins of enantioselectivity can now be made.

This chapter describes the development of iridium-catalyzed, enantioselective allylic substitution. It is organized to focus on how modifications to the catalyst, combined with mechanistic insights, have provided the foundation for a steady



L = κ^1-**L1**: [Ir(COD)(κ^2-**L1**)(**L1**)] (**1a**)
L = ethylene: [Ir(COD)(κ^2-**L1**)(C_2H_4)] (**1b**)
L = κ^1-**L2**: [Ir(COD)(κ^2-**L2**)(**L2**)] (**2a**)
L = ethylene: [Ir(COD)(κ^2-**L2**)(C_2H_4)] (**2b**)
L = κ^1-**L3**: [Ir(COD)(κ^2-**L3**)(**L3**)] (**3a**)
L = ethylene: [Ir(COD)(κ^2-**L3**)(C_2H_4)] (**3b**)

Ar = Ph (R_a,R,R)-**L1**
Ar = 2-anisyl (R_a,R,R)-**L2**
Ar = 1-naphthyl (R_a,R,R)-**L3**

Scheme 1 Asymmetric allylic substitution catalyzed by metalacyclic iridium-phosphoramidite complexes

increase in substrate scope, yield, and selectivity. Ultimately, this review describes how these advances have led to the most recently reported generation of metalacyclic iridium-phosphoramidite catalysts.

2 Background

2.1 An Overview of Allylic Substitution

Metal-catalyzed allylic substitution (Fig. 1) leads to the displacement of an ester, halide, or other leaving group by a nucleophile in an allylic position. Substitution occurs in a formal S_N2 or S_N2' fashion, depending on the identity of the two reactants and the catalyst. However, the mechanism is not similar to uncatalyzed S_N2 or S_N2' reactions of purely organic systems. Instead, the metal catalyst initially displaces the leaving group to form an η^3-allyl complex, which is subsequently attacked by the nucleophile at one terminus of the allyl ligand over the other to form the product. Nucleophilic attack on the substituted terminus of an allyl ligand can produce a chiral product. Thus, the use of an appropriate chiral, non-racemic ligand can result in the formation of this product in enantiomerically enriched form.

2.2 Nucleophilic Attack on η^3-Allyl Metal Complexes

Iridium-catalyzed allylic substitution was first investigated after many years of development of allylic substitution reactions catalyzed by a variety of complexes of other metals, particularly those containing palladium. While iridium-catalyzed

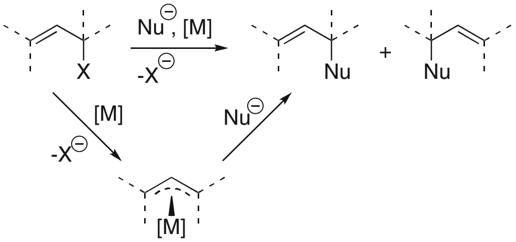


Fig. 1 Metal-catalyzed allylic substitution

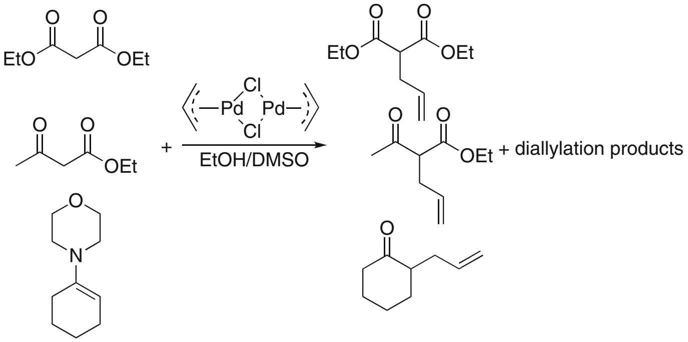


Fig. 2 Stoichiometric nucleophilic attack on the terminus of an allyl ligand

allylic substitution dates back to 1997, the addition of nucleophiles to π-allyl metal complexes has been known since 1965, when Tsuji demonstrated that the carbon nucleophiles ethyl malonate, ethyl acetoacetate, and 1-morpholino-1-cyclohexene react with the terminus of the π-allyl ligand of allylpalladium chloride to form mixtures of mono- and diallylation products (Fig. 2) [2].

2.3 Early Metal-Catalyzed Allylic Substitution

2.3.1 First Metal-Catalyzed Allylic Substitution

After the initial demonstration of stoichiometric nucleophilic attack on π-allyl ligands, catalytic allylic substitution reactions were pursued. In 1970, groups from Union Carbide [3, 4], Shell Oil [5], and Toray Industries [6] published or patented examples of catalytic allylic substitution. All three groups reported allylic amination with palladium catalysts. The Toray Industries report also demonstrated the exchange of aryl ether and ester leaving groups, and the patent from Shell Oil includes catalysts based on rhodium and platinum.

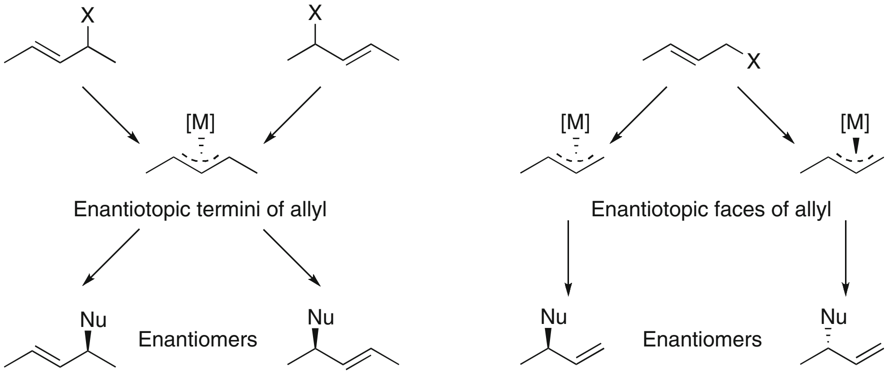


Fig. 3 Enantiotopic termini or faces of η^3-allyl ligands

2.3.2 The Selectivity of Allylic Substitution

Many of the enantioselective allylic substitution reactions are based on the two reaction manifolds in Fig. 3. In the first manifold, enantioselection can result from nucleophilic attack at one of two enantiotopic termini of a symmetrical π-allyl ligand. In the second manifold, enantioselection can result from attack at one of the two enantiotopic faces of an allyl ligand that is substituted at only one of the two termini. Thus, initial selective addition of the metal fragment to one face of the allyl or unselective addition to both faces followed by isomerization to form one stereoisomer selectively will lead to the formation of one enantiomer of product over the other when nucleophilic attack occurs at the more substituted terminus of the allyl ligand. Palladium-catalyzed reactions that generate π-allyl intermediates containing one unsubstituted terminus typically lead to reaction at the unsubstituted terminus, forming to products lacking a stereocenter at the electrophilic carbon. Thus, the formation of enantioenriched branched products from π-allyl intermediates containing one unsubstituted terminus required the development of a new type of catalyst.

2.4 The State of Allylic Substitution in 1997

The first iridium catalysts for allylic substitution were published in 1997. Takeuchi showed that the combination of $[Ir(COD)Cl]_2$ and triphenylphosphite catalyzes the addition of malonate nucleophiles to the substituted terminus of η^3-allyliridium intermediates that are generated from allylic acetates. This selectivity for attack at the more substituted terminus gives rise to the branched allylic alkylation products (Fig. 4), rather than the linear products that had been formed by palladium-catalyzed allylic substitution reactions at that time [7]. The initial scope of iridium-catalyzed allylic substitution was also restricted to stabilized enolate nucleophiles, but it was quickly expanded to a wide range of other nucleophiles.

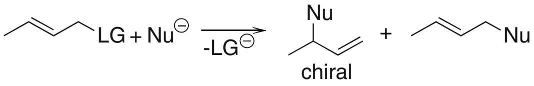


Fig. 4 Branched and linear products formed from η^3-allyl intermediates that have one unsubstituted terminus

2.4.1 Contemporaneous Metal-Catalyzed Allylic Substitution

Most allylic substitution reactions catalyzed by other metals are selective for the formation of branched products. Although this had been demonstrated for a large portion of the d-block before Takeuchi's work with iridium, most of the progress in this area was restricted to stabilized enolate nucleophiles.

Prior to the initial disclosure of iridium-catalyzed allylic substitution, catalysts based on complexes of molybdenum [8–18], tungsten [19–24], iron [25–28], ruthenium [11, 29, 30], cobalt [27], rhodium [11, 31], nickel [11, 32–37], and platinum[38] had all been shown to favor the formation of branched products from substrates that generate π-allyl intermediates that are unsubstituted at one terminus. In fact the widely recognized selectivity of palladium catalysts for the formation of linear products is actually an anomaly among transition metals. Some reactions catalyzed by rhodium and iron catalysts exhibit regiochemical "memory effects," meaning that the nucleophile adds to the same terminus of the allyl group originally occupied by the leaving group. Branched starting materials led to branched products, and linear starting materials led to linear products [39, 40]. Catalysts based on ruthenium, cobalt, and nickel complexes were reported to form branched products selectively, but this regioselectivity was not typically high. Only catalysts based on molybdenum and tungsten formed branched products from allylic substitution with high selectivity. However, these early reactions typically required catalyst loadings of 10 mol% or more, and their use with nitrogen or oxygen nucleophiles had not yet been reported.

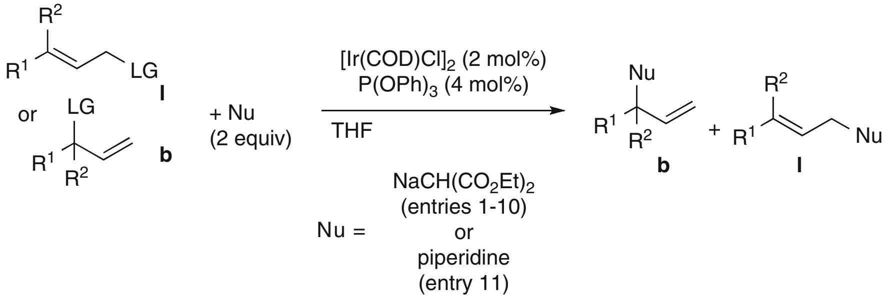
Thus, a catalyst for allylic substitution that is highly active and selective for the formation of products from addition to the more substituted terminus from a variety nucleophiles and allylic esters was unknown. Iridium catalysts have now been developed that begin to fill this void.

3 Early Iridium-Catalyzed Allylic Substitutions

3.1 *Allylic Substitution Catalyzed by $[Ir(COD)Cl]_2$ and Triphenylphosphite*

The first examples of iridium-catalyzed allylic substitution [1] occurred between stabilized carbon nucleophiles and both alkyl- and aryl-substituted allylic alcohol derivatives with exceptional selectivity for the branched substitution product.

Table 1 Allylic substitution catalyzed by $[Ir(COD)Cl]_2$ and $P(OPh)_3$



Entry	b or l/R^1/R^2	LG	T (°C)	Time (h)	Yield (%)	b:l or b:(E)-l:(Z)-l
1	l/Ph/H	OAc	rt	3	98	99:1
2	b/Ph/H	OAc	rt	3	91	99:1
3	l/H/C_3H_7	OAc	65	5	85	7:3:90
4	l/Ph/H	OH	65	1	98	99:1
5	l/Me/Me	OAc	65	24	n.r.[a]	
6	l/Me/Me	$OPO(OEt)_2$	rt	4	81	96:4
7	b/Me/Me	OAc	rt	2	80	100:0
8	l/C_3H_7/H	OAc	rt	3	89	96:4
9[b]	l/C_3H_7/H	OAc	65	9	90	95:5
10[c]	l/C_3H_7/H	OAc	65	16	6	24:48:28
11	l/Ph/H	OCO_2Me	50	3	95	95:5

[a] No reaction

[b] Conducted with $Ir(COD)_2BF_4$

[c] Conducted with PPh_3 (4 mol%)

In this and subsequent studies [41–44], Takeuchi and coworkers described the scope and selectivity of catalysts derived from $[Ir(COD)Cl]_2$ and achiral phosphorus ligands. Many of the trends that they uncovered have also been observed with more recently developed catalyst systems derived from chiral phosphoramidite ligands (Table 1).

Stabilized enolate and amine nucleophiles add to both branched and (*E*)-linear allylic alcohol derivatives to form products in high yield and over 95% selectivity for the branched product when catalyzed by a combination of $[Ir(COD)Cl]_2$ and $P(OPh)_3$. In contrast, substitution of (*Z*)-allylic alcohol derivatives results in formation of (*Z*)-linear products, especially for alkyl-substituted allylic esters. Based on the net retention of configuration observed for allylic substitution of a cyclic allylic carbonate, such substitutions were proposed to occur through a "double-inversion mechanism" in which both oxidative addition of the allylic ester and reaction of the allyl intermediate with the nucleophilic reagent occur with inversion of configuration. Later work by Helmchen and coworkers supported a double inversion mechanism by showing that hindered allylic acetates that are unable to undergo an inversion of configuration were unreactive toward allylic substitution in the presence of iridium catalysts, whereas analogous reactions of unhindered cyclopentenyl acetates proceeded to full conversion [45]. Finally, as discussed in Sect. 5, recent studies on discrete, isolated allyliridium intermediates by Hartwig and coworkers support a mechanism for nucleophilic attack on allyliridium intermediates that proceeds by inversion of configuration [46].

Although most of these early reactions were conducted with allylic acetates, reactions of allylic carbonates, trifluoroacetates, and phosphates also occur. Sodium diethylmalonate also reacts with allylic alcohols in the presence of the iridium-triphenylphosphite catalyst. However, the alcohol itself does not act as a leaving group. Instead, transesterification occurs with one equivalent of malonate nucleophile to form a more labile ester leaving group.

Addition to linear 1,1-disubstituted allylic acetates is slower than addition to monosubstituted allylic esters. Additions to allylic trifluoroacetates or phosphates are faster than additions to allylic carbonates or acetates, and reactions of branched allylic esters are faster than additions to linear allylic esters. Aryl-, vinyl, alkynyl, and alkyl-substituted allylic esters readily undergo allylic substitution. Amines and stabilized enolates both react with these electrophiles in the presence of the catalyst generated from an iridium precursor and triphenylphosphite.

3.1.1 Iridium Precursor and Ligands

Branched allylic substitution products were obtained with the highest yields and selectivities when the reactions were conducted with the combination of $[Ir(COD)Cl]_2$ and $P(OPh)_3$ as catalyst. Other iridium precursors were tested, but they all required higher reaction temperatures, and most of these catalyst systems produced allylic substitution products in lower yield and branched-to-linear selectivity. The use of a π-accepting ligand such as $P(OPh)_3$ proved to be necessary in most cases to obtain high branched selectivity. Reactions conducted with catalysts containing less π-accepting ligands occurred with lower selectivity for the branched isomer.

Catalysts lacking phosphorus ligands have also been used as catalysts for allylic substitutions. $[Ir(COD)Cl]_2$ itself, which contains a π-accepting diolefin ligand, catalyzes the alkylation of allylic acetates, but the formation of branched products was only favored when the substitution reaction was performed with branched allylic esters. Takemoto and coworkers later reported the etherification of branched allylic acetates and carbonates with oximes catalyzed by $[Ir(COD)Cl]_2$ without added ligand [47]. Finally, as discussed in Sect. 6, Carreira reported kinetic resolutions of branched allylic carbonates from reactions of phenol catalyzed by the combination of $[Ir(COE)_2Cl]_2$ and a chiral diene ligand [48].

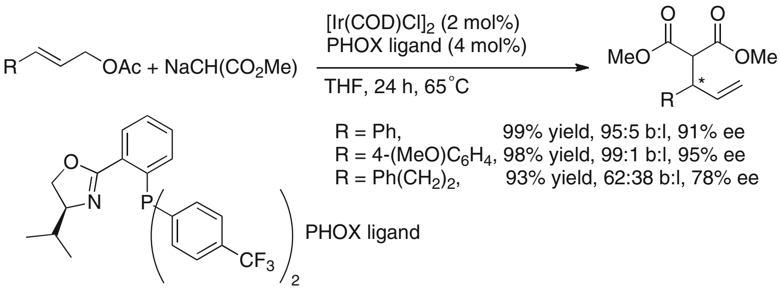
One notable deviation from this trend of increased branched selectivity with increased π-accepting character has been reported. Nomura and coworkers reported allylic substitution reactions catalyzed by $[Ir(COD)Cl]_2$ and triphenylphosphine to form polymers linked by branched 1,1′-(1,4-phenylene)diprop-2-enyl units [49]. Despite this exception, most iridium-catalyzed allylic substitution reactions have been conducted with complexes derived from $[Ir(COD)Cl]_2$ and an electron-accepting ligand.

3.2 *Asymmetric Iridium-Catalyzed Allylic Substitution: A Survey of Ligands*

The formation of chiral products from nucleophilic addition to the more substituted terminus of monosubstituted allyl groups in the presence of iridium catalysts containing achiral π-accepting phosphorus ligands led to efforts to conduct these reactions with related enantioenriched ligands that control the absolute stereochemistry. Catalysts generated from phosphoramidite ligands have been used most commonly for this process, and complexes of these ligands catalyze allylic substitution reactions with broad substrate scope, high activity, and high regio- and enantioselectivity. However, catalysts containing several other families of ligands have also been studied. Reactions catalyzed by complexes of the other families of ligands will be reviewed first.

3.2.1 Reactions Catalyzed by Iridium Complexes of PHOX Ligands

The first enantioselective, iridium-catalyzed allylic substitution was reported by Helmchen and coworkers soon after the initial report by Takeuchi. Helmchen studied catalysts generated from phosphinooxazoline (PHOX) ligands and $[Ir(COD)Cl]_2$ for the reactions of sodium dimethylmalonate with cinnamyl acetates (Scheme 2) [50]. The alkylation products were isolated in nearly quantitative yield and were formed with ratios of branched-to-linear products up to 99:1 and with enantioselectivities up to 95% ee. In this and subsequent studies with PHOX ligands [51, 52], Helmchen et al. demonstrated that the highest yields and selectivities were obtained with a PHOX ligand containing electron-withdrawing substituents and



Scheme 2 Allylic alkylation catalyzed by $[Ir(COD)Cl]_2$ and a PHOX ligand

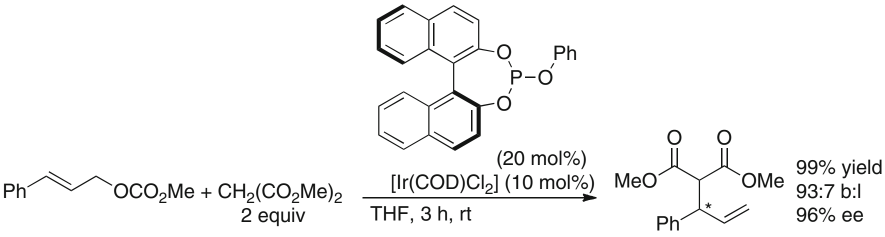
with additives such as LiF. Mark, This is not shown in Scheme 2. Although substitution of only two allylic carbonates was reported, this work showed that iridium complexes could catalyze allylic substitution reactions with high enantioselectivity. However, intramolecular allylic amination catalyzed by complexes of the PHOX ligand [53] occurred with low enantioselectivity, and the regioselectivity was lower for the reactions of alkyl-substituted allylic esters than for the reactions of aromatic allylic esters. Thus, further studies on iridium-catalyzed allylic substitution with complexes of PHOX ligands have not been reported.

3.2.2 Reactions Catalyzed by Iridium Complexes of Chiral Phosphite Ligands

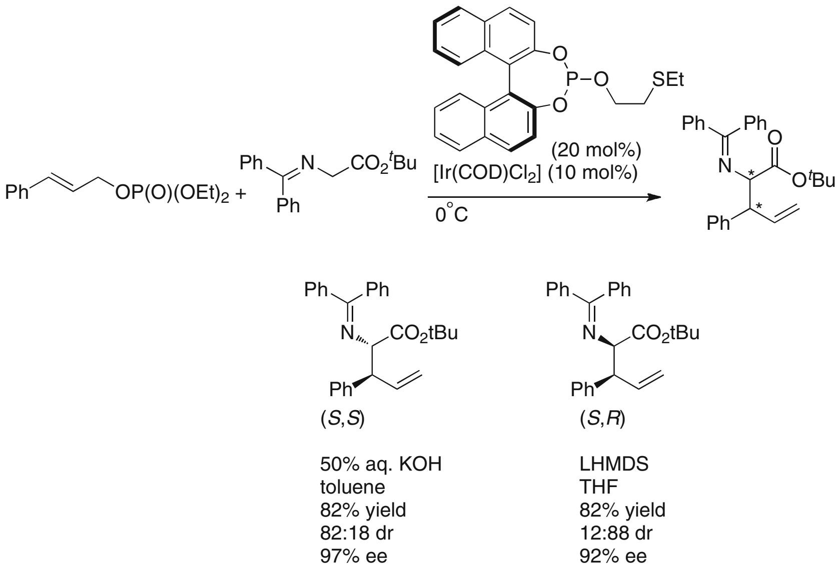
Iridium complexes containing chiral phosphite ligands also catalyze allylic alkylation. Fuji and coworkers reported reactions of dimethylmalonate with cinnamyl methyl carbonate catalyzed by complexes of a BINOL-derived phosphite (Scheme 3) [54, 55]. With *n*BuLi as base and $ZnCl_2$ as additive, the alkylation product was isolated in 99% yield with 93% branched selectivity and 96% ee. Iridium complexes of another BINOL-derived phosphite containing a thioether substituent were shown to catalyze the alkylation of cinnamyl phosphates with a protected glycine nucleophile (Scheme 4) [56, 57]. This reaction is particularly noteworthy because it occurs with high diastereoselectivity. Such high diastereoselectivity has not been achieved when using other iridium catalysts. Furthermore, varying the solvent and base led to the formation of one diastereomer over the other, with the major diastereomer formed in excellent enantiomeric excess in both cases. Less than 1% of linear products were detected in these reactions.

3.2.3 Reactions Catalyzed by Iridium Complexes of Pybox Ligands

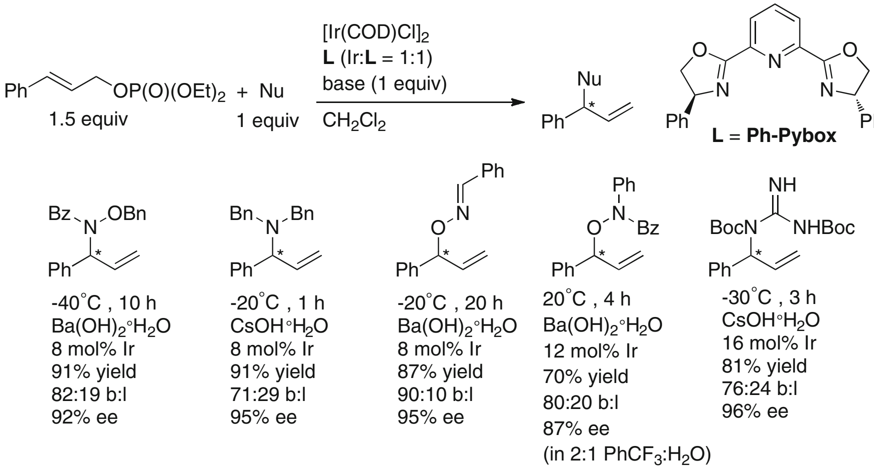
Complexes derived from the oxazolinylpyridine ligand Ph-Pybox and $[Ir(COD)Cl]_2$ catalyze allylic substitution reactions of several oxygen and nitrogen nucleophiles



Scheme 3 Allylic alkylation catalyzed by $[Ir(COD)Cl]_2$ and a chiral phosphite ligand



Scheme 4 Diastereoselective allylic alkylation with protected glycine



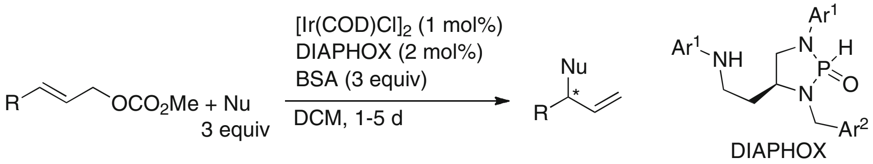
Scheme 5 Allylic substitution catalyzed by $[Ir(COD)Cl]_2$ and **Ph-Pybox**

that have not been used in systems catalyzed by metalacyclic iridium phosphoramidite complexes (Scheme 5). Reactions of amines [58], hydroxylamines [58, 59], oximes [58, 60], and guanidines [61] with cinnamyl phosphates occur in good to excellent yield, branched selectivity, and enantiomeric excess. *O*-substituted hydroxylamines react at nitrogen. However, hydroxylamines react preferentially at oxygen when the hydroxylamine possesses an electron-withdrawing group on nitrogen.

3.2.4 Reactions Catalyzed by Iridium Complexes of DIAPHOX and Phosphorodiamidite Ligands

The phosphoramidite ligands that are the focus of the remainder of this chapter have prompted the investigation of ligands containing related structures. Iridium complexes of aspartic acid-derived P-chirogenic diaminophosphine oxides (DIAPHOXs) catalyze the amination [62] and alkylation [63] of allylic carbonates (Scheme 6). With BSA as base and catalytic amounts of $NaPF_6$ as additive, branched amination and alkylation products were obtained from cinnamyl carbonates in excellent yields and enantioselectivities. However, the yields and enantioselectivities were lower for the reactions of alkyl-substituted allylic carbonates. Added LiOAc increased the enantioselectivities of allylic alkylation products.

Catalysts generated from $[Ir(COD)Cl]_2$ and phosphorodiamidite ligands containing a pyrrolo[1,2-*c*] diazaphosphol-1-one backbone catalyze the addition of phenol to methyl cinnamyl carbonate (Scheme 7) [64]. The arrangement of the steric bulk around the ligand determines the configuration of the product; catalysts containing the two ligands in which the *N*-aryl and *O*-aryl groups are reversed form the opposite enantiomers. DFT calculations were performed to determine the origin of this reversal in selectivity, and these studies suggested that reversal of the aryl groups changes the face of the allyl ligand that is preferentially coordinated to the metal center.

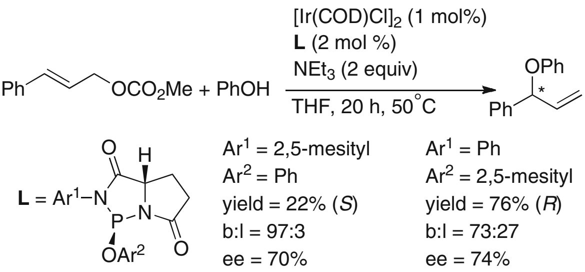


R = Ph
Nu = $BnNH_2$
Ar^1 = 4-$^tBuC_6H_4$
Ar^2 = Ph
5 mol% $NaPF_6$
-20°C
96% yield
92% ee

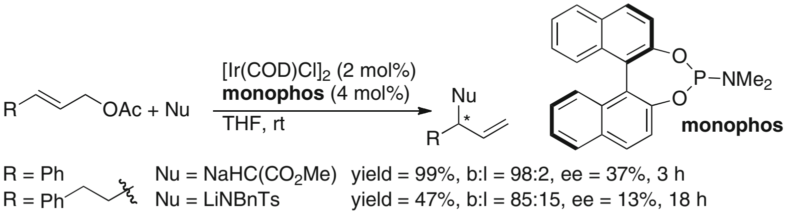
R = CH_2CH_2Ph
Nu = $BnNH_2$
Ar^1 = 4-$^tBuC_6H_4$
Ar^2 = Ph
5 mol% $NaPF_6$
-20°C
74% yield
68% ee

R = Ph
Nu = $CH_2(CO_2Me)$
Ar^1 = Ph
Ar^2 = 3-PhC_6H_4
10 mol% $NaPF_6$
10 mol% LiOAc
rt
93% yield
90% ee

Scheme 6 Allylic substitution catalyzed by $[Ir(COD)Cl]_2$ and DIAPHOX



Scheme 7 Allylic etherification catalyzed by $[Ir(COD)Cl]_2$ and a phosphorodiamidite ligand



Scheme 8 Allylic substitution catalyzed by $[Ir(COD)Cl]_2$ and monophos

3.3 Iridium Catalysts Containing Phosphoramidite Ligands

3.3.1 Reactions Catalyzed by Complexes of Monophos

Although Helmchen et al. showed that asymmetric iridium-catalyzed allylic substitution could be achieved, the scope of the reactions catalyzed by iridium complexes of the PHOX ligands was limited. Thus, they evaluated reactions catalyzed by complexes generated from $[Ir(COD)Cl]_2$ and the dimethylamine-derived phosphoramidite monophos (Scheme 8) [45, 51]. Although selectivity for the branched isomer from addition of malonate nucleophiles to allylic acetates was excellent, the highest enantiomeric excess obtained was 86%. This enantiomeric excess was obtained from a reaction of racemic branched allylic acetate. The enantiomeric excess was lower when linear allylic acetates were used. This system catalyzed addition of the lithium salts of *N*-benzyl sulfonamides to allylic acetates, but the product of the reaction between this reagent and an alkyl-substituted linear allylic acetate was formed with an enantiomeric excess of 13%.

3.3.2 Reactions Catalyzed by Complexes of Bis-Phenethylamine-Derived Phosphoramidite, L1

Amination with **L1**

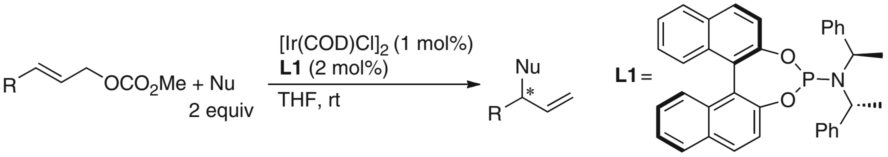
Although reactions catalyzed by $[Ir(COD)Cl]_2$ and the dimethylamine-based monophos occurred with only modest enantioselectivity, a wide variety of reactions catalyzed by iridium complexes of other phosphoramidite ligands have occurred with excellent enantioselectivity. Ohmura and Hartwig reported that the combination of bisphenethylamine-derived phosphoramidite **L1** (Scheme **1**) and [Ir(COD)Cl]$_2$ catalyze the amination of a series of allylic carbonates with primary and secondary amines in excellent yield, branched selectivity, and enantioselectivity (Table 2) [65]. **L1** was originally developed by Feringa and coworkers for use in copper-catalyzed conjugate additions of alkylzinc reagents to α-β-unsaturated ketones [67].

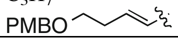
The scope of allylic electrophiles that react with amines was shown to encompass electron-neutral and electron-rich cinnamyl methyl carbonates, as well as furan-2-yl and alkyl-substituted allylic methyl carbonates. An *ortho*-substituted cinnamyl carbonate was found to react with lower enantioselectivity, a trend that has been observed in later studies of reactions with other nucleophiles. The electron-poor *p*-nitrocinnamyl carbonate also reacted, but with reduced enantioselectivity. Allylic amination of dienyl carbonates also occur in some cases with high selectivity for formation of the product with the amino group at the γ-position over the ε-position of the pentadienyl unit [66]. Arylamines did not react with allylic carbonates under these conditions. However, they have been shown to react in the presence of the metalacyclic iridium-phosphoramidite catalysts that are discussed in Sect. 4.

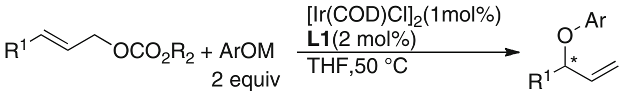
Iridium-Catalyzed Allylic Etherification with Catalysts Derived from **L1**

Hartwig et al. demonstrated that the same combination of iridium precursor and phosphoramidite **L1** also catalyzes allylic etherifications (Scheme **9**) [68]. Lithium and sodium aryloxides were shown to react with cinnamyl and hex-2-enyl carbonates to form the branched allylic ethers in high yield, with high branched-to-linear

Table 2 Allylic amination catalyzed by [Ir(COD)Cl]$_2$ and **L1**



Entry	R	Nu	Yield (%)	b:l	ee (%)	t(h)	Reference
1	Ph	$BnNH_2$	84	98:1	95	10	[65]
2	Ph	n-hexylNH_2	88	98:2	96	9	[65]
3	Ph	pyrrolidine	75	98:2	97	2	[65]
4	$4\text{-(MeO)}C_6H_4$	$BnNH_2$	88	99:1	96	9	[65]
5	$4\text{-(NO}_2\text{)}C_6H_4$	$BnNH_2$	67	83:13	86	12	[65]
6	$2\text{-(MeO)}C_6H_4$	$BnNH_2$	77	95:4	76	16	[65]
7	C_3H_7	$BnNH_2$	66	88:8	95	10	[65]
8		$BnNH_2$	71	96:4	96	14	[66]



R^1	R^2	ArOM	Yield (%)	b:l	ee (%)	t (h)
Ph	Me	PhOLi	86	96/4	96	20
Ph	Me	4-(MeO)C_6H_4OLi	88	98:2	97	8
Ph	Et	4-BrC_6H_4ONa	91	96/4	90	8
Ph	Et	4-(NO_2)C_6H_4ONa	n.r.[a]			
2-(MeO)C_6H_4	Me	PhOLi	79	98/2	75	41
nPr	Me	PhOLi	93	92/8	92	14

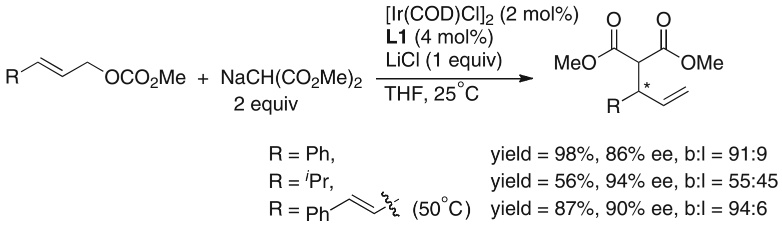
[a] No reaction

Scheme 9 Allylic etherification catalyzed by $[Ir(COD)Cl]_2$ and **L1**

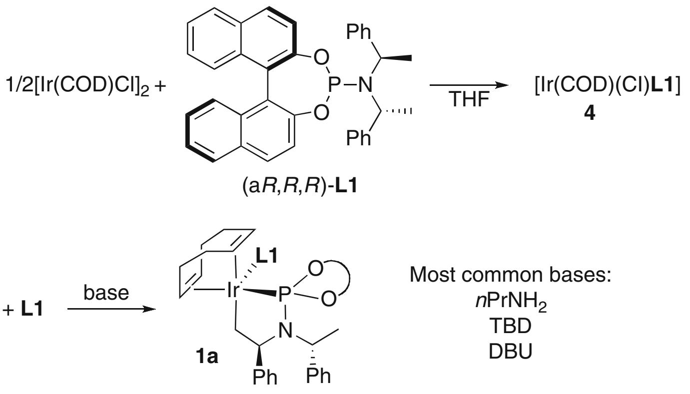
ratios, and enantiomeric excesses of up to 97%. The use of alkali metal aryloxides was necessary to obtain useful reaction rates; reactions of phenols in combination with amine bases occurred in lower yield and enantioselectivity. In some cases, transesterification of the carbonate with the phenoxide competed with the allylic substitution process. In these cases, reactions of ethyl allylic carbonates, rather than methyl allylic carbonates, occurred in high yield. As was observed for iridium-catalyzed allylic amination, the reaction of an *ortho*-substituted cinnamyl carbonate occurred with lower enantioselectivity than reactions of *meta*- and *para*-substituted cinnamyl carbonates. In contrast, the reactivity of *ortho*-substituted aryloxides was comparable to that of less hindered aryloxides. However, reactions of electron-deficient aryloxides occurred with lower branched-to-linear ratios and lower enantioselectivity. The most electron-poor aryloxides derived from 4-(NO_2)C_6H_4OH did not react. The lithium phenoxides were added directly to reaction mixtures, or they were generated in situ from the corresponding phenol and *n*BuLi or Cy_2NLi.

Iridium-Catalyzed Asymmetric Allylic Alkylation with Catalysts Derived from L1

Reactions of allylic electrophiles with stabilized carbon nucleophiles were shown by Helmchen and coworkers to occur in the presence of iridium-phosphoramidite catalysts containing **L1** (Scheme **10**) [66, 69], but alkylations of linear allylic acetates with salts of dimethylmalonate occurred with variable yield, branched-to-linear selectivity, and enantioselectivity. Although selectivities were improved by the addition of lithium chloride, enantioselectivities still ranged from 82–94%, and branched selectivities from 55–91%. Reactions catalyzed by complexes of phosphoramidite ligands derived from primary amines resulted in the formation of alkylation products with higher branched-to-linear ratios but lower enantioselectivities. These selectivities were improved by the development of metalacyclic iridium catalysts discussed in the next section and “salt-free” reaction conditions described later in this chapter.



Scheme 10 Iridium-catalyzed allylic alkylation catalyzed by [Ir(COD)Cl]$_2$ and **L1**



Scheme 11 Formation of the active metalacyclic iridium phosphoramidite catalyst

4 Advances in Mechanistic Understanding and Catalyst Design: Cyclometalation and Modification of the Phosphoramidite Ligand

4.1 *Discovery of the Active Metalacyclic Catalyst*

Although the combination of [Ir(COD)Cl]$_2$ and **L1** was shown to catalyze the alkylation, amination, and etherification of allylic esters to form the branched substitution product in high yield and enantioselectivity, the identity of the active catalyst in these reactions had not been identified. The combination of [Ir(COD)Cl]$_2$ and **L1** forms the square-planar [Ir(COD)(Cl)**L1**] (**4**) (Scheme 11) [45]. However, this complex does not react with allylic carbonates to form an appreciable amount of an allyl complex, and the absence of this reactivity suggested that the mechanism or identity of the active catalyst was more complex than that from simple addition of the allylic ester to the square-planar complex containing a κ^1-phosphoramidite ligand.

Instead of reacting with the allylic ester, the square-planar complex **4** reacts with pyrrolidine to form a new species, **1a**, which contains a cyclometalated

P,*C*-bound κ^2-phosphoramidite in addition to a κ^1-phosphoramidite (Scheme 11). This cyclometalated complex was identified by NMR spectroscopy and X-ray crystallography [70]. A cyclometalated species had been proposed to form in reactions catalyzed by $[Ir(COD)Cl]_2$ and $P(OPh)_3$. However, no complexes were isolated from this mixture or shown to be competent to catalyze allylic substitution [45].

Mechanistic studies showed that metalacycle **1a** is competent to be a catalyst in asymmetric allylic substitution reactions. The reaction of benzylamine with methyl cinnamyl carbonate catalyzed by a mixture of **L1** and $[Ir(COD)Cl]_2$ occurs with an induction period and forms product in 84% yield and 95% ee, whereas the same reaction catalyzed by a mixture of metalacycle **1a** and $[Ir(COD)Cl]_2$ occurs without an induction period in just 2 hours to form the substitution product in 81% yield and 97% ee. The latter reaction was conducted with added $[Ir(COD)Cl]_2$ to trap the κ^1-bound **L1** after dissociation. This ligand must dissociate to provide a site for oxidative addition of the allylic carbonate.

The synthesis of pure metalacycle **1a** from $[Ir(COD)Cl]_2$ and **L1** requires only amine base and heat, followed by precipitation and removal of amine hydrochloride. However, this complex was typically generated in situ during early studies by the treatment of a combination of $[Ir(COD)Cl]_2$ and **L1** with an amine base, such as $n\mathrm{PrNH}_2$, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). If a 1:1 ratio of iridium to ligand is used, a mixture of **1a** and $[Ir(COD)Cl]_2$ is produced. Helmchen et al. have reported that catalyst activation in the presence of tetrahydrothiophene (THT) prevents coordination of the κ^1-phosphoramidite [71].

4.2 Effect of the Phosphoramidite Ligand

Concurrent with studies on cyclometalation, studies on the effects of the structure of phosphoramidite ligand had been conducted. Several groups studied the effect of the structure of ligand on the rate and selectivity of these iridium-catalyzed allylic substitutions. **L1** contains three separate chiral components – the two phenethyl moieties on the amine as well as the axially chiral BINOL backbone. These portions of the catalyst structure can control reaction rates by affecting the rate of cyclometalation, by inhibiting catalyst decomposition, or by forming a complex that reacts faster in the turnover-limiting step(s) of the catalytic cycle.

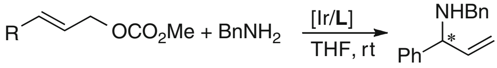
4.2.1 Modification of the Amino Groups on the Phosphoramidite

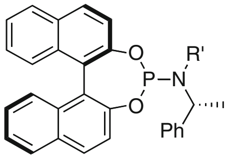
Catalysts containing **L1** were much more reactive and selective than those containing monophos. The conclusion that the cyclometalated core of complex **1a** is present in the active catalyst explains why the complexes of **L1** are more reactive than those of monophos. Complexes containing monophos cannot form a species containing an analogous stable, five-membered metalacycle.

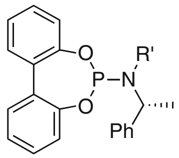
Modifications were made to the arylethyl substituent of the phosphoramidite to identify catalysts that would exhibit even higher reactivity and selectivity than **L1**. Some studies of reactions catalyzed by complexes of different phosphoramidites were performed with preactivated catalyst, but others were performed without activation of the catalyst. Thus, it is not straightforward to determine which ligands form the most active catalysts. Nonetheless, certain modifications to the bisphenethylamine portion of phosphoramidite **L1** improve the rates, yields, and selectivities of allylic substitution reactions catalyzed by the modified ligands and [Ir(COD)Cl]$_2$. Phosphoramidite ligands **L2** or **L3** derived from bisnaphthethylamine or 1-(2-methoxyphenyl)ethylamine, the latter of which is not yet commercially available from typical suppliers (Table 3), generate catalysts that are more reactive or more selective for reactions of certain substrate combinations. Complexes derived from **L2** and **L3** cyclometalate faster than complexes derived from **L1**, leading to a shorter induction period when the catalyst is not formed prior to addition of the reagents [75]. Likewise, the metalacyclic complex **2a** derived from **L2** is more resilient than **1a** to deactivation by acidic pronucleophiles [76].

Additional studies were conducted to determine how further modifications to the amine portion of the phosphoramidite ligand affect iridium-catalyzed allylic substitution. One arylethyl moiety is necessary for the formation of metalacyclic active catalyst, but it was unclear how changes to the structure of the second substituent on nitrogen would affect reactivity and selectivity. A stereocenter on this second

Table 3 Comparison of phosphoramidite ligands







R' = cyclododecyl

L4 **L5**

Entry	R	L	Time (h)	Yield (%)	ee (%)	b:l	Activated prior to adding reagents?	Reference
1	C_3H_7	**L1**	3	58	95	94:6	Yes	[72]
2	C_3H_7	**L3**	0.5	67	98	94:6	Yes	[72]
3	Ph	**L1**	2	81	97	98:2	Yes	[70]
4	Ph	**L1**	12	84	95	98:2	No	[70]
5	Ph	**L2**	16	88	97	98:2	No	[73]
6	Ph	**L4**	3	93	95	99:1	Yes	[74]
7	Ph	**L5**	3	86	94	98:2	Yes	[74]

substituent was shown to be unnecessary to form metalacyclic iridium catalyst that reacted with high enantioselectivies. Phosphoramidites synthesized from C_1-symmetric amines in which one phenethyl group has been replaced by a bulky cycloalkyl group generate catalysts that display reactivity similar to that of the catalysts containing related phosphoramidites synthesized from C_2-symmetric amines (Table 3, entry 6) [74, 77, 78].

4.2.2 Modification of the Diol Backbone of the Phosphoramidite

The configuration of the chiral BINOLate backbone of the phosphoramidite ligand affects the rates and enantioselectivities of allylic substitution reactions. Hartwig and coworkers found that allylic substitution conducted with a catalyst derived from the simplified ligand (S_a,R)-**L4** occurred more slowly than that conducted with a catalyst derived from (R_a,R)-**L4** [74]. Complexes of the “mismatched” (S_a,R)-**L4** undergo cyclometalation slowly. The products formed from reactions catalyzed by complexes of (S_a,R)-**L4** and (R_a,R)-**L4** have the opposite absolute configuration.

The resolved BINOLate backbone of the phosphoramidite ligand is not required for high catalyst activity and selectivity. Catalysts generated from ligands in which the BINOLate backbone has been replaced with an achiral biphenolate catalyze allylic substitution reactions in high yield and selectivity despite rapid room temperature atropisomerism of the biphenolate [74, 77]. Iridium-catalyzed allylic substitution occurs with a catalyst generated from the simplified phosphoramidite containing just one chiral center (one phenethyl group on nitrogen) and no resolved, axially chiral components (Table 3, entry 7).

4.3 Scope of Allylic Substitution Catalyzed by Metalacyclic Iridium-Phosphoramidite Complexes

Metalacyclic iridium-phosphoramidite complexes generated prior to addition of the reagents react with a substantially broader scope than those generated in situ. Some nucleophiles, such as arylamines, are not sufficiently basic to induce cyclometalation and do not react with allylic carbonates in the presence of $[Ir(COD)Cl]_2$ and **L1**. In reactions of some other nucleophiles, catalyst activation by cyclometalation is slow, and a long induction period results. Thus, it is typically advantageous to conduct reactions with the “pre-activated” metalacyclic species generated prior to addition of the reagents Coupled with a set of modified phosphoramidite ligands that lead to improved reactivity and selectivity, these new catalyst systems have been applied quickly to reactions of a variety of nucleophiles, some of which have been commonly used for allylic substitution with catalysts containing other metals and others that have rarely been used with catalysts of any metal.

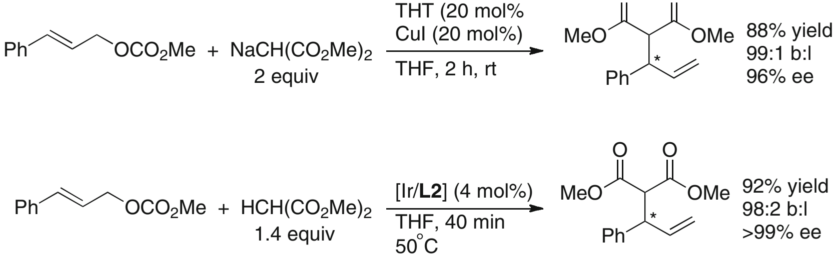
4.3.1 Iridium-Catalyzed Allylic Substitution with Carbon Nucleophiles

Iridium-Catalyzed Allylic Substitution with Stabilized Enolates

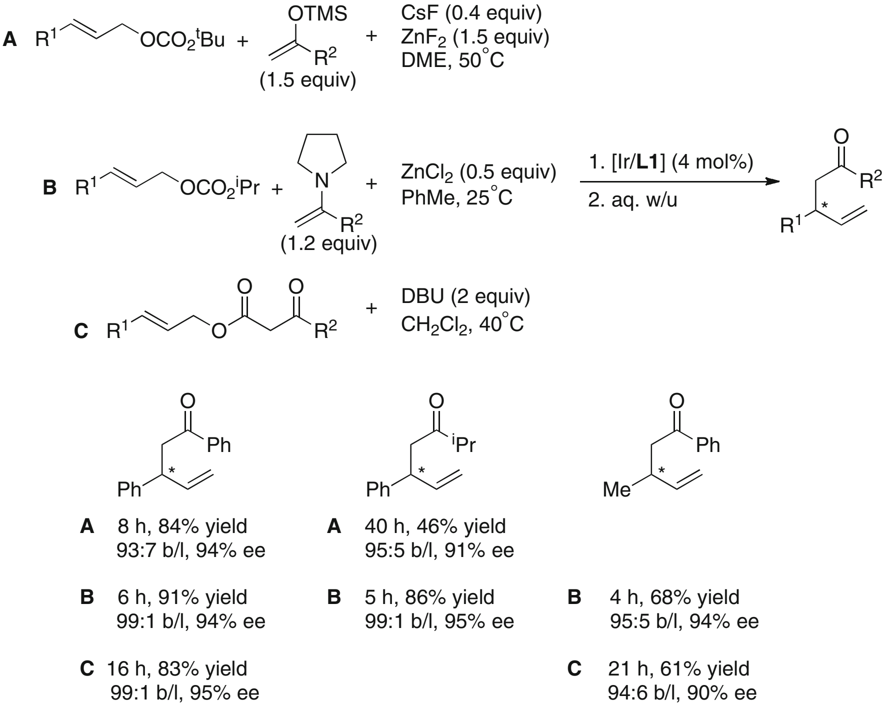
Malonate nucleophiles react with allylic carbonates in the presence of **L1** and $[Ir(COD)Cl]_2$. However, the yields and selectivities of these reactions were lower than those obtained from analogous reactions with nitrogen and oxygen nucleophiles. The use of a preactivated metalacycle increased the selectivities of products formed from iridium-catalyzed allylic alkylation reactions. By forming the active metalacycle from a mixture of **L1** and $[Ir(COD)Cl]_2$ and base, Helmchen et al. demonstrated that products formed from the reaction of sodium dimethylmalonate with linear allylic carbonates were formed with enantioselectivities above 96% (Scheme **12**) [71]. Additional improvements were realized by applying "salt-free" conditions [79]. Rather than deprotonating the malonate nucleophile prior to addition of the other reaction components, the neutral malonate was added; the alkoxide generated from decarboxylation of the carbonate leaving group deprotonates the malonate. By combining "salt-free" conditions with catalysts derived from the more active ligand **L2**, high yields of the branched alkylation product were obtained in excellent enantioselectivity (Scheme **12**).

Allylic Substitution with Unstabilized Enolates

Unstabilized enolates react with allylic carbonates in the presence of metalacyclic iridium-phosphoramidite catalysts. Although ketones and aldehydes have not yet been used directly as pronucleophiles with this catalyst system, silyl enol ethers [80] and enamines [81] react with linear allylic carbonates to form, after workup, β-branched, γ-δ unsaturated ketones (Scheme **13**). Both methods form products in high yield, branched selectivity, and enantioselectivity for a range of cinnamyl and alkyl-substituted allylic carbonates. However, the silyl enol ethers derived from aliphatic ketones reacted in lower yields than enamines derived from the same ketones.



Scheme 12 Allylic alkylation with activated catalyst before and after applying "salt-free" conditions



Scheme 13 Allylic substitution with unstabilized enolate nucleophiles

In addition, unstabilized enolate nucleophiles have been generated by decarboxylation of β-ketocarboxylates. In this case, no additives are required to activate the nucleophile, but the highest yields and selectivities were obtained in the presence of two equivalents of DBU [82]. Although reactions of allylic carbonates containing aromatic, heteroaromatic, and aliphatic substituents occurred, only reactions to form aryl ketone products were published.

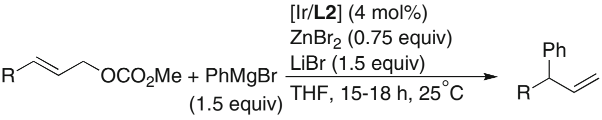
Allylic Substitution with Nitroalkanes

Nitroalkanes react with allylic carbonates in the presence of iridium catalysts [83]. However, nitroalkanes are prochiral, and products are formed with poor diastereoselectivity. Nitroalkanes and other prochiral nucleophiles are discussed further in Sect. 6.

Allylic Substitution with “Hard” Carbon Nucleophiles

Hard carbon nucleophiles that do not contain stabilizing electron-withdrawing substituents have been shown to react with allylic carbonates only recently in the presence of iridium catalysts. Alexakis et al. reported conditions for the reactions of arylzinc reagents with allylic carbonates in the presence of iridium phosphoramidite catalysts [84, 85]. The arylzinc reagents were generated from the corresponding aryl Grignard reagent and $ZnBr_2$. Although regioselectivities were poor, typically around 1:1, the branched-to-linear ratio of this reaction was higher than that of other allylic arylation reactions, which exclusively form linear products. Although the active metalacyclic catalyst in these reactions was not formed prior to addition of the reagents, the high reactivity of the combination of $[Ir(COD)Cl]_2$ and ligand **L2** led to acceptable rates; the organozinc reagent might serve as the base to form the active metalacyclic catalyst (Scheme **14**).

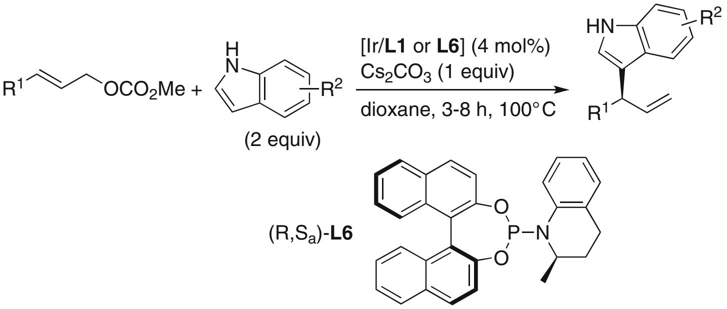
Nitrogen heterocycles undergo *C*-allylation in the presence of metalacyclic iridium-phosphoramidite catalysts. Recently, Yu and coworkers reported the *C*-allylation of indoles with the iridium catalyst derived from **L1** [86] and from phosphoramidites containing 2-methylindoline- and 2-methyl-1,2,3,4-tetrahydroquinoline as the amino group (Table 4) [87]. No *N*-allylation was reported. However,



R = Cy, b:l = 69:31, 72% yield, 74% ee
R = 4-ClC_6H_4, b:l = 55:45, 83% yield, 99% ee
R = 4-$(MeO)C_6H_4$, b:l = 33:67, 78% yield, 91% ee
R = 4-$(CF_3)C_6H_4$, b:l = 56:44, 98% yield, 97% ee

Scheme 14 Addition of aryl zinc reagents to allylic carbonates

Table 4 *C*-allylation of indoles



Entry	R^1	R^2	L	Yield (%)	ee (%)
1	Ph	H	**L1**	49	85
2	4-$(MeO)C_6H_4$	5-MeO	**L1**	85	89
3	4-$(CF_3)C_6H_4$	H	**L1**	63	87
4	nBu	H	**L1**	55	85
5	4-$(CF_3)C_6H_4$	H	**L6**	41	65

N-allylation of indoles and other azoles in the presence of iridium catalysts has been reported recently and is discussed in Sect. 5.3.

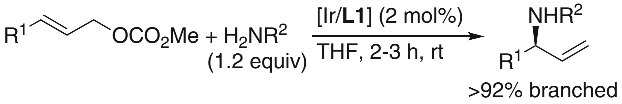
4.3.2 Allylic Substitution with Nitrogen Nucleophiles

Allylic Substitution with Amines and Anilines

As previously discussed, activation of the iridium-phosphoramidite catalyst before addition of the reagents allows less basic nitrogen nucleophiles to be used in iridium-catalyzed allylic substitution reactions [70, 88]. Arylamines, which do not react with allylic carbonates in the presence of the combination of **L1** and $[Ir(COD)Cl]_2$ as catalyst, form allylic amination products in excellent yields and selectivities when catalyzed by complex **1a** generated in situ (Scheme **15**). The scope of the reactions of aromatic amines is broad. Electron-rich and electron-neutral aromatic amines react with allylic carbonates to form allylic amines in high yields and excellent regio- and enantioselectivities as do hindered *ortho*-substituted aromatic amines. Electron-poor aromatic amines require higher catalyst loadings, and the products from reactions of these substrates are formed with lower yields and selectivities.

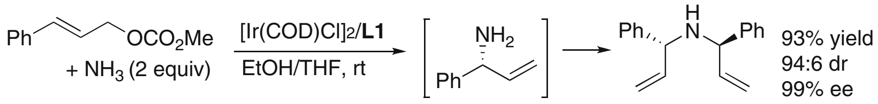
Ammonia, Imides, Carbamates, and Sulfonamides

A diverse group of secondary and tertiary amines are readily synthesized from the reaction of primary and secondary amines with allylic carbonates in the presence of preformed iridium metalacycles, but the direct synthesis of primary amines via iridium-catalyzed allylic amination requires the use of ammonia as a nucleophile. The asymmetric allylation of ammonia had not been reported until very recently, and it is not a common reagent in other metal-catalyzed reactions. Nonetheless, Hartwig and coworkers developed the reactions of ammonia with allylic carbonates in the presence of **1a** generated in situ [89]. Reactions conducted in the initial work led exclusively to the products from diallylation (Scheme **16**). Further advances in



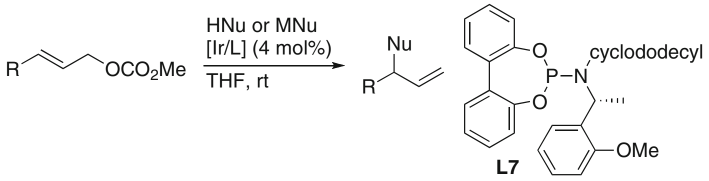
R^1 = Ph, R^2 = 4-MeC_6H_4, 94% yield, 93% ee
R^1 = Ph, R^2 = 4-$(MeO)C_6H_4$, 95% yield, 95% ee
R^1 = Ph, R^2 = 4-ClC_6H_4, 80% yield, 96% ee
R^1 = Ph, R^2 = 3,5-$Me_2C_6H_4$, 82% yield, 96% ee
R^1 = C_3H_7, R^2 = Ph, 93% yield, 92% ee

Scheme 15 Amination of allylic carbonates with arylamines enabled by preactivated catalyst



Scheme 16 Allylic substitution with ammonia to form diallylamines

Table 5 Allylic substitution with ammonia equivalents



Entry	R	Nu	L	Yield (%)	b:l	ee (%)	Time (h)	Reference
1	Ph	o-$NsNH_2$	**L2**	92	90:10	96	3	[91]
2	Ph	phthalimide	**L2**	95	96:4	98	2.5	[91]
3	Ph	HN(Boc)(CHO)	**L2**	96	98:2	99	0.7	[91]
4	Ph	$NaN(Boc)_2$	**L2**	80	97:3	99	0.7	[91]
5[a]	Ph	$HN(Boc)_2$	**L2**	90	99:1	99	1	[94]
6	4-$CF_3(C_6H_4)$	$LiN(Boc)_2$	**L7**	76	85:15	92	4	[89]
7	4-$MeO(C_6H_4)$	KTFAc	**L7**	93	nd	98	12	[89]

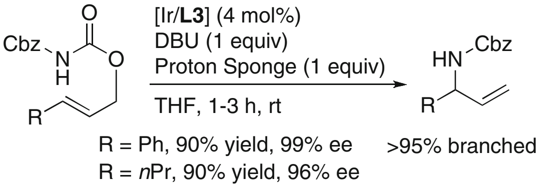
[a] Conducted at 50°C

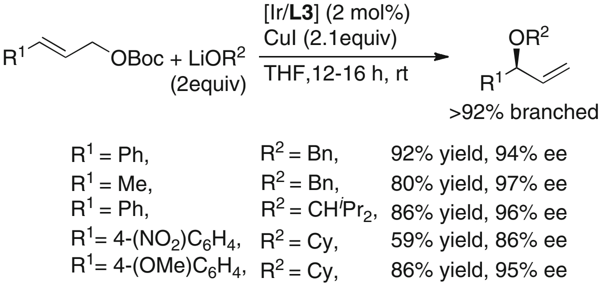
catalyst development led to the selective formation of the monoallylation product, and these reactions are discussed in Sect. 5.3 after introduction of these catalysts that were refined further.

Protected primary allylic amines were generated from allylic carbonates and ammonia equivalents. Iridium-catalyzed allylic substitution has now been reported with sulfonamides [90, 91], imides [89, 91–93], and trifluoroacetamide [89] to form branched, protected, primary allylic amines (Table 5). When tested, yields and selectivities were highest from reactions catalyzed by complexes derived from **L2**. Reactions of potassium trifluoroacetamide and lithium di-*tert*-butyliminodicarboxylate were conducted with catalysts derived from the simplified ligand **L7**. Reactions of nosylamide and trifluoroacetamide form singly-protected amine products. The other ammonia equivalents lead to the formation of doubly protected allylic amine products, but one protecting group can be removed selectively, except when the product is derived from phthalimide.

Allylic substitution with free carbamate nucleophiles was not accomplished until advanced catalyst precursors were developed. However, products from substitution with carbamate nucleophiles were generated by a decarboxylative allylation. In this process, the imidodicarbonate was shown to undergo decarboxylation to form the carbamate nucleophile, and reaction of the resulting carbamate with the π-allyliridium intermediate formed branched allylic carbamate products (Scheme **17**) [92, 95].

Scheme 17 Intramolecular decarboxylative allylic amidation



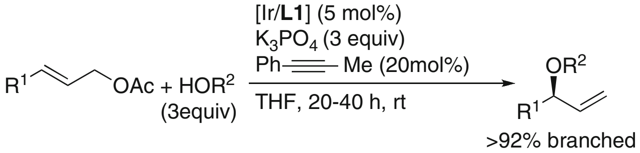


Scheme 18 Allylic substitution reactions between copper alkoxides and allylic carbonates

4.3.3 Allylic Substitution with Oxygen Nucleophiles

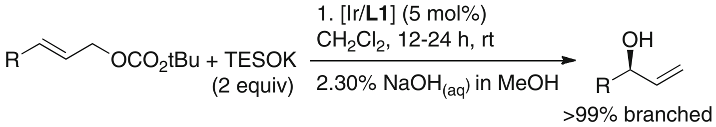
Iridium catalysts generated from modified phosphoramidite ligands prior to addition of the reagents were applied to the allylation of oxygen nucleophiles. As discussed earlier, iridium catalysts derived from $[Ir(COD)Cl]_2$ and **L1** readily catalyze the addition of phenoxides to linear allylic carbonates to form branched allyl aryl ethers with high enantioselectivity. More challenging has been the development of asymmetric allylic substitutions with alkoxide nucleophiles because of their high basicity. The addition of copper salts moderates the basicity of the alkoxides by forming softer copper alkoxides. Thus, Shu and Hartwig developed conditions for asymmetric allylic etherification with copper alkoxides in the presence of iridium-phosphoramidite catalysts. Analogous reactions of alkoxide nucleophiles catalyzed by other transition metals have not been reported to occur with high yield and enantioselectivity [96]. Copper alkoxides, both with and without branching α to the oxygen, were shown to add to electron-rich, electron-neutral, and electron-poor cinnamyl carbonates, as well as alkyl-substituted allylic carbonates. Branched products formed in high yields and enantioselectivities (Scheme **18**). Reactions conducted with ligand **L3** occurred in higher yields, branched-to-linear ratios and enantioselectivities than those conducted with ligand **L1**.

Ueno and Hartwig subsequently improved upon this method by developing conditions for allylic alkoxylation that do not require copper additives [97]. In reactions conducted with **1a** generated in situ as catalyst and K_3PO_4 as base,



R^1 = Ph,	R^2 = Bn,	68% yield, 93% ee
R^1 = Ph,	R^2 = *n*Hex,	71% yield, 91% ee
R^1 = 4-(OMe)C_6H_4,	R^2 = Bn,	82% yield, 92% ee
R^1 = Ph,	R^2 = TBDMS,	85% yield, 98% ee

Scheme 19 Allylic substitution reactions between aliphatic alcohols and allylic carbonates



R = 4-(MeO)C_6H_4,	75% yield, 95% ee
R = 4-(CF_3)C_6H_4,	78% yield, 98% ee
R = C_3H_7,	65% yield, 95% ee (isolated as TES ether)

Scheme 20 Reactions of potassium triethylsiloxide with allylic carbonates to form branched allylic alcohols [98]

aliphatic alcohols reacted with cinnamyl and alkyl-substituted allylic acetates to form allylic ethers in high yield and selectivity (Scheme **19**). An achiral vinyl ether was formed in these reactions from isomerization of the product, but the addition of 1-phenyl-1-propyne minimized this isomerization, presumably by poisoning an isomerization catalyst that forms during the reaction. This method can also be used to synthesize protected allylic alcohols from cinnamyl acetate and TBSOH, which is related to an earlier method developed by Carreira et al. that uses potassium triethylsiloxide (TESOK) as a nucleophile for the formation of branched allylic alcohols [98]. TESOK adds to *tert*-butyl allylic carbonates in the presence of catalytic amounts of **1a** generated in situ (Scheme **20**).

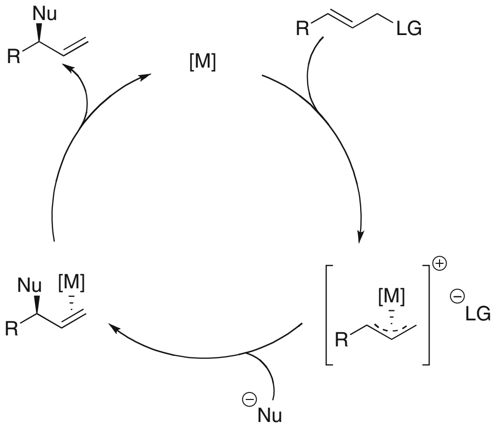
4.3.4 Intramolecular Allylic Substitution Catalyzed by Metalacyclic Iridium Phosphoramidite Complexes

Several types of intramolecular allylic substitution reactions of carbon, nitrogen, and oxygen nucleophiles catalyzed by metalacyclic iridium phosphoramidite complexes have been reported. Intramolecular allylic substitution is much faster than the competing intermolecular process when conducted in the presence of iridium catalysts. Thus, conditions involving high dilution are not required. Intramolecular allylic substitution has been applied to form products that are precursors to natural products via allylic alkylation [79, 99], amination [53, 78], and etherification [78].

5 New Mechanistic Insights: The Isolation of Catalytic Intermediates

5.1 General Mechanism of Metal-Catalyzed Allylic Substitution

Studies of the mechanism of palladium-catalyzed allylic substitution have been aided by the isolation and characterization of allylpalladium complexes that are catalytic intermediates. Related mechanistic studies of iridium-catalyzed allylic substitution were, until recently, hampered by the inability to observe catalytically active allyliridium species. Based on the mechanism of palladium-catalyzed allylic substitution, iridium-catalyzed allylic substitution was assumed to occur by the series of steps shown in Scheme **21**, but information on the relative rates of individual steps, the structures of intermediates, and the origins of enantioselectivity was limited. Soon after the discovery of the iridium-phosphoramidite system that catalyzes allylic substitution with high enantioselectivity, the active catalyst was shown to consist of a metalacyclic iridium fragment that is derived from the phosphoramidite ligand and that contains a coordinated cyclooctadiene. However, this fragment had only been isolated as a species coordinated to an additional ligand, such as a **L1** (**1a**) or ethylene (**1b**). This five-coordinate, 18-electron species presumably lies off of the actual catalytic cycle and requires dissociation of the phosphoramidite or ethylene ligand to form a 16-electron intermediate that lies on the catalytic cycle. No other species shown to lie on the catalytic cycle had been



Scheme 21 General mechanism for metal-catalyzed allylic substitution

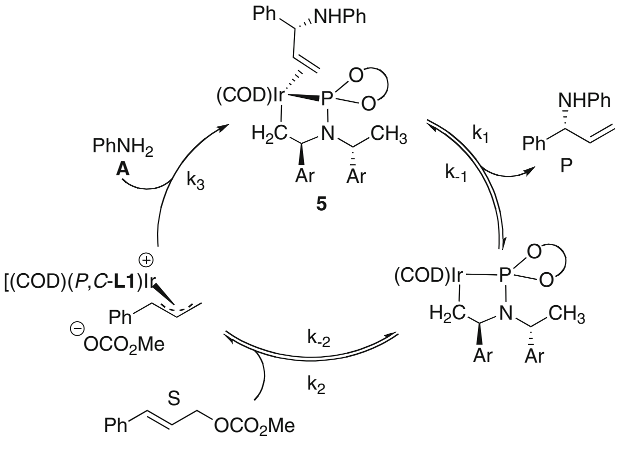
observed or isolated. Attempts to generate a π-allyliridium(III) intermediate from the species containing **L1** or ethylene as ligand led to complexes that neither catalyzed allylic substitution nor produced the expected branched allylation products upon exposure to a stoichiometric quantity of nucleophile [52].

5.2 Isolation and Study of Intermediates in Allylic Substitution Reactions Catalyzed by Metalacyclic Iridium-Phosphoramidite Complexes

5.2.1 Identification and Isolation of the Catalyst Resting State

Marković and Hartwig isolated and characterized the first intermediate in iridium-catalyzed allylic substitution [100]. They isolated the metalacyclic iridium-phosphoramidite fragment containing COD and the olefinic portion of *N*-(1-phenylallyl)aniline, the product of the allylic substitution reaction between cinnamyl carbonate and aniline (**5** in Scheme **22**). This complex containing the product of allylic substitution was first detected by ^{31}P NMR spectroscopy during catalytic reactions. It was then isolated, prepared independently, and shown to be chemically and kinetically competent to be an intermediate in allylic substitutions.

In addition to isolating complex **5**, Marković and Hartwig performed kinetic studies on the amination of methyl cinnamyl carbonate with aniline. The proposed mechanism involves reversible dissociation of product, reversible, endothermic oxidative addition of the allylic carbonate to form a π-allyliridium species, and irreversible nucleophilic attack on the π-allyliridium intermediate, as depicted in



Scheme 22 Catalytic cycle for the reaction of aniline with methyl cinnamyl carbonate catalyzed by a metalacyclic iridium-phosphoramidite complex

Scheme 22. The rate equation for this mechanism is described in (1). The authors determined that the reaction is first-order in allylic carbonate, aniline and catalyst, and inverse first-order in allylamine product. These results are consistent with the proposed mechanism. Thus, iridium-catalyzed allylic substitution is inhibited by product. In addition, the formation of the allyliridium intermediate is disfavored.

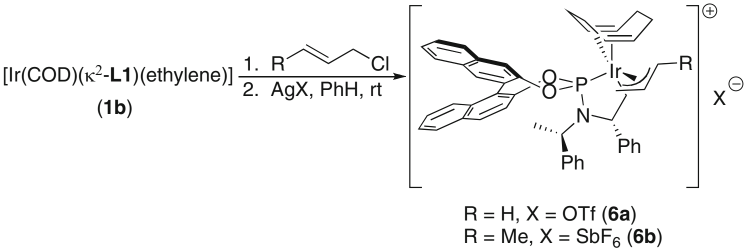
$$\text{rate} = \frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = \frac{K_1 K_2 k_3 [\mathrm{S}][\mathrm{A}][\mathrm{Ir}]_{\mathrm{tot}}}{[\mathrm{P}]}. \tag{1}$$

5.2.2 Isolation of π-Allyliridium Intermediates

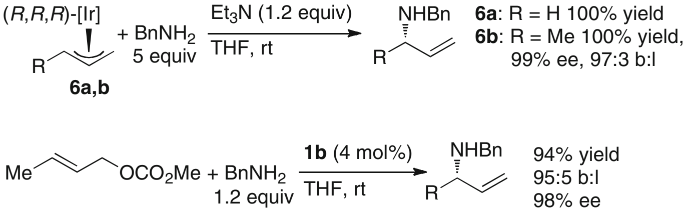
Additional mechanistic insights were gained when Hartwig and coworkers isolated and characterized the first π-allyl complexes that are chemically and kinetically competent to be intermediates in iridium-catalyzed allylic substitution [46]. These complexes were prepared independently from allylic electrophiles that are more reactive than allylic carbonates. The isolation and structural characterization of these species provided a detailed view into the origins of enantioselectivity.

The allyliridium species were formed from allylic chlorides, rather than allylic carbonates. Treatment of complex metalacyclic iridium complex **1b** with allylic methyl carbonates led to no apparent reaction and no accumulation of a new iridium species. The lack of observable product from this reaction is consistent with prior kinetic data indicating that the formation of an allyliridium intermediate from a resting state containing ethylene or allylic amine as ligand was thermodynamically unfavorable. Although the reaction of allylic carbonates with metalacyclic iridium phosphoramidite precursors is thermodynamically unfavorable, the reaction of allylic chlorides with **1b** formed a new species, as determined by ^{31}P NMR spectroscopy. This new species was trapped by addition of AgOTf, isolated as single crystals, and shown to be the intermediate allyiridium species (Scheme 23). The parent π-allyliridium complex **6a** and the analogous crotyl complex **6b** were both isolated and characterized by X-ray diffraction.

Allyliridium complexes **6a** and **6b** reacted with a series of nucleophiles to form products in yields that are similar to those of allylic substitution reactions catalyzed



Scheme 23 Synthesis of η^3-allyliridium intermediates



Scheme 24 The reaction of allyl complexes with benzylamine

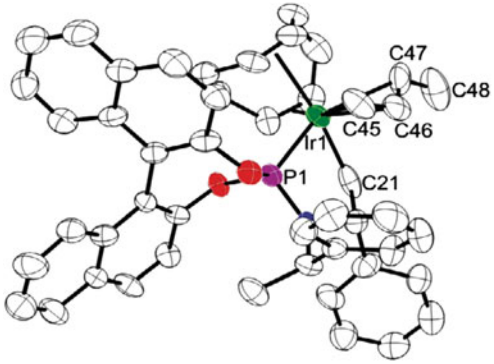


Fig. 5 ORTEP Diagram of Crotyl Complex **6b** [46]

by **1b**. Moroever, nucleophilic attack on the crotyl complex **6b** also resulted in the formation of products with branched-to-linear ratios and enantioselectivities that are similar to those of catalytic reactions with methallyl methyl carbonate (Scheme 24).

Information on the origins of enantioselection by the iridium catalyst can be gleaned from the structure of the crotyl complex **6b** (Fig. 5). The phosphoramidite and COD ligands on iridium create a steric environment that constrains the orientation of the allyl ligand. First, the allyl unit binds in an orientation in which the methyl substituent on the allyl unit lies in solution away from the other ligands. Second, coordination to one face of the allyl ligand is favored over coordination to the other because it minimizes interaction between the COD ligand and the central carbon of the allyl group (C38). Comparison of the configuration of the isolated allyl complex with that of the isolated organic products indicates that nucleophilic attack occurs anti to the metal center [46].

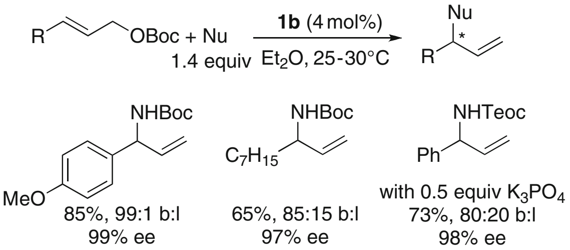
5.3 Reaction Development Based on Mechanistic Insights

These recent mechanistic studies have provided the foundation for the most recent work that has expanded the scope of iridium-catalyzed allylic substitution. The synthesis and characterization of the ethylene-bound complex **1b** resulted directly from studies on the synthesis of catalytic intermediates. This stable adduct of the catalytically active metalacyclic fragment is a convenient, single-component catalyst precursor that does not require an activator to generate the active catalyst. With **1b** this activation occurs by dissociation of the coordinated ethylene.

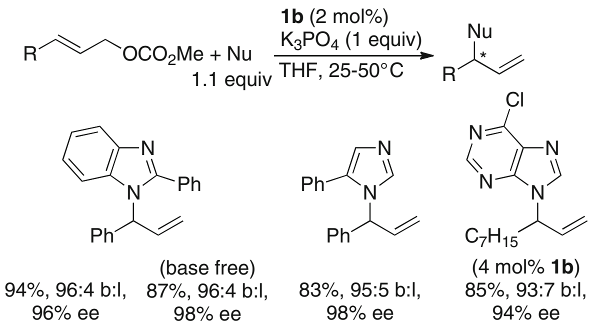
In contrast, reactions catalyzed by **1a** were typically conducted with added $[Ir(COD)Cl]_2$ to trap the κ^1-phosphoramidite ligand after dissociation, and thereby, to leave the unsaturated active catalyst. Under these conductions, as much as half of the iridium in the system is present in an inactive acyclic species. In contrast, when ethylene adduct **1b** is used as the catalyst, all of the iridium belongs to the active metalacyclic species. Hartwig and coworkers have recently taken advantage of the increased availability of the active catalyst generated from **1b** to develop new allylic substitution reactions. These new processes include the reactions of carbamates, nitrogen heterocycles, and ammonia.

Previously, iridium-catalyzed reactions to form *N*-allyl carbamates required the use of allylic imidodicarbonates as reagents that undergo decarboxylative allylation, and the scope of these reactions encompassed only allylic benzyloxycarbamates. Direct allylic substitution with commercially available carbamate nucleophiles would allow the formation of a variety of protected primary amine products without the need to synthesize imidodicarbonates. Hartwig and coworkers have shown that the ethylene complex **2b**, which is the 2-anisyl variant of **1b**, catalyzes the reaction between *tert*-butyl allylic carbonates and $BocNH_2$, fluorenyloxycarbamate ($FmocNH_2$), benzyloxycarbamate ($CbzNH_2$), 2,2,2-trichloroethoxycarbamate ($TrocNH_2$), 2-trimethylsilylethoxycarbamate ($TeocNH_2$), and 2-oxazolidinone (Scheme 25) [101]. Yields and selectivities were high, and the substrate scope encompasses a range of aryl- and alkyl-substituted allylic carbonates. Reactions of $BocNH_2$ occurred without the use of exogenous base.

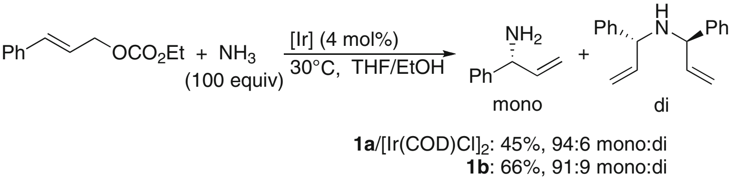
Complex **2b** also catalyzes the addition of imidazoles, benzimidazoles, and several purines to methyl allylic carbonates (Scheme 26) [76]. These reactions occurred with good yields and excellent enantioselectivities. *N*-substituted heterocycles are found in a number of compounds that exhibit a range of biological activity. The syntheses of several pharmacologically active compounds were conducted with yields that were improved over those published previously.



Scheme 25 Allylic substitution with carbamate nucleophiles



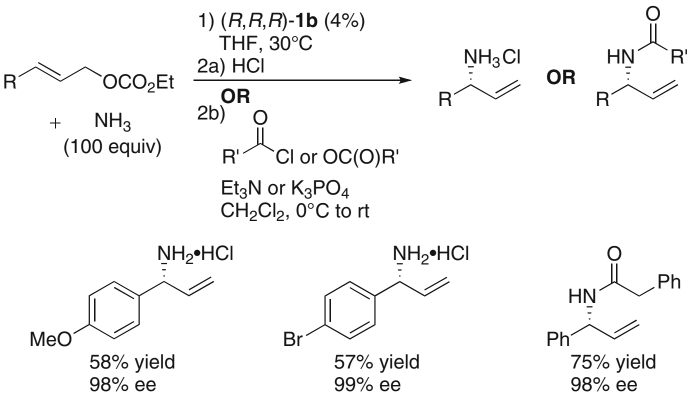
Scheme 26 Allylic substitution with *N*-heterocycles



Scheme 27 Allylic substitution with ammonia catalyzed by **1a** and **1b**

The use of ethylene adduct **1b** is particularly important when the species added to activate catalyst **1a** is incompatible with one of the reaction components. Iridium-catalyzed monoallylation of ammonia requires high concentrations of ammonia, but these conditions are not compatible with the additive [Ir(COD)Cl]$_2$ because this complex reacts with ammonia [102]. Thus, a reaction between ammonia and ethyl cinnamyl carbonate catalyzed by ethylene adduct **1b** produces the monoallylation product in higher yield than the same reaction catalyzed by **1a** and [Ir(COD)Cl]$_2$ (Scheme 27). Ammonia reacts with a range of allylic carbonates in the presence of **1b** to form branched primary allylic amines in good yield and high enantioselectivity (Scheme 28). Quenching these reactions with acyl chlorides or anhydrides leads to a one-pot synthesis of branched allylic amides that are not yet directly accessible by metal-catalyzed allylation of amides.

The high concentration of ammonia that is required for selective formation of primary allylic amines suggests that ammonia is much less reactive toward nucleophilic attack on an allyl ligand than the primary allylic amine products. The reactivity of different nucleophiles toward allyl ligands was assessed by treating the allyliridium complex **6a** with ammonia and 1-phenylprop-2-en-1-amine. No product from allylation of ammonia was detected from this reaction. In addition, the reaction of an allylic carbonate with the combination of ammonia and 1-phenylprop-2-en-1-amine in the presence of **1b** did not produce detectable amounts of the product from allylation of ammonia. These results confirm that the primary amine is much more



Scheme 28 Selective monoallylation of ammonia catalyzed by **1b**

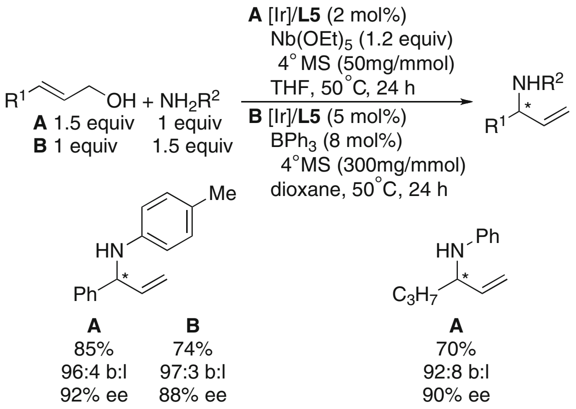
reactive toward the allyliridium species than is ammonia. This greater reactivity of the allylamine explains why iridium-catalyzed allylic substitutions conducted with low concentrations of ammonia selectively form diallylation products over monoallylation products. However, the stability of catalyst **1b** toward ammonia allows the reaction to be conducted with high concentrations of ammonia and to form the primary allylic amine selectively.

6 Challenges in Iridium-Catalyzed Allylic Substitution

The scope of reactions catalyzed by metalacyclic iridium-phosphoramidite complexes is remarkably broad, but reactions with some substrates, such as allylic alcohols, prochiral nucleophiles, branched allylic esters, and highly substituted allylic esters, that would form synthetically valuable products or would lead to simpler synthesis of reactants occur with low yields and selectivities. In addition, iridium-catalyzed allylic substitution reactions are sensitive to air and water and must be conducted with dry solvents under an inert atmosphere. Several advances have helped to overcome some, but not all of these challenges.

6.1 Allylic Substitution of Allylic Alcohols

Most iridium-catalyzed allylic substitutions have been performed with allylic esters, which are typically synthesized from allylic alcohols. Reactions of allylic alcohols as electrophiles would alleviate the need to prepare the esters from the alcohol. In a few cases, however, iridium catalyzed allylic substitutions have been conducted with allylic alcohols as the electrophile. As discussed earlier in this



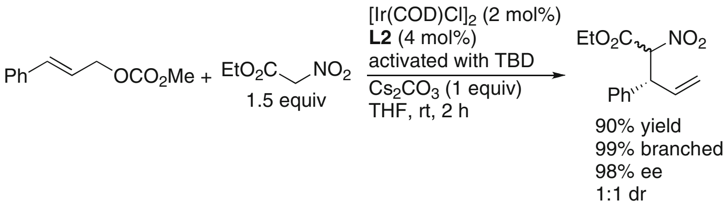
Scheme 29 Allylic substitution with linear allylic alcohols activated by Lewis acids

chapter, Takeuchi found that allylic alkylation reactions between malonate nucleophiles and allylic alcohols occur via transesterification between the allylic alcohol and one equivalent of the nucleophile, there by producing a more reactive leaving group. Thus, allylic substitution occurs in these cases with the allylic alcohol via the formation of an allylic ester.

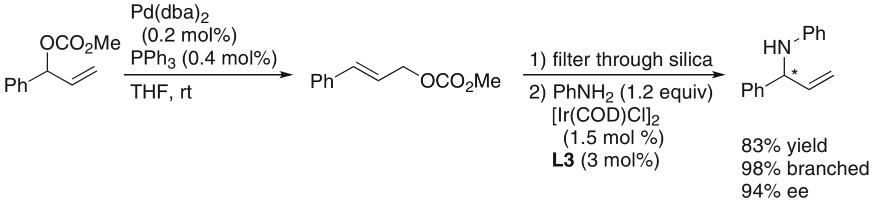
More recently, Hartwig and coworkers reported iridium-catalyzed, asymmetric aminations of allylic alcohols in the presence of Lewis acid activators [103]. The addition of molecular sieves and $Nb(OEt)_5$ or catalytic amounts of BPh_3 activated the allylic alcohol sufficiently to allow allylic amination reactions to occur in high yield, branched-to-linear selectivity, and enantioselectivity (Scheme **29**). Without the activators, only trace amounts of product were observed.

6.2 Diastereoselectivity of Iridium-Catalyzed Allylic Substitution Reactions

Control of diastereoselectivity in allylic substitution reactions remains a significant challenge. Nucleophilic attack by a prochiral nucleophile can produce linear allylic substitution products containing one stereogenic center or branched products containing two stereogenic centers. The diastereoselectivity of reactions of prochiral nucleophiles catalyzed by iridium complexes has been low. For example, nitroalkanes [83], ethyl nitroacetates [83], and malonic amides [104] undergo allylic substitution catalyzed by the metalacyclic iridium complexes in high yield, branched-to-linear selectivity, and enantioselectivity, but the alkylation products form as 1:1 mixtures of diastereomers (Scheme **30**). However, the reactions of allylic esters with glycine derivatives reported by Kanayama and described in Sect. 3 occurred with good diastereoselectivity in the presence of iridium-phosphite catalysts (Sect. 3) [56, 57].



Scheme 30 Allylic alkylation with ethyl nitroacetate



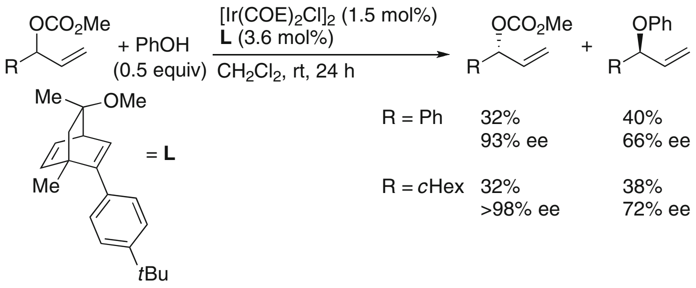
Scheme 31 Sequential Pd-catalyzed isomerization and Ir-catalyzed allylic substitution

6.3 Allylic Substitution of Branched Allylic Esters

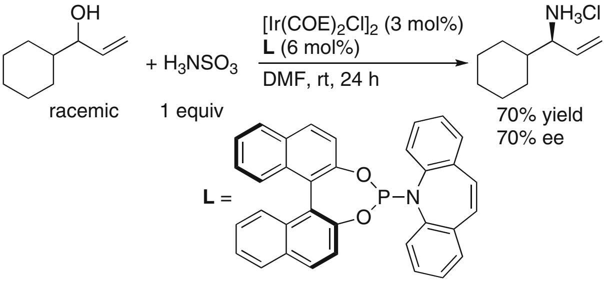
Allylic substitution reactions catalyzed by metalacyclic iridium-phosphoramidite complexes form branched products from linear allylic esters with high regioselectivity. However, reactions with racemic, branched allylic esters would be particularly valuable because they are readily accessible from a wide array of aldehydes and vinylmagnesium halides. However, iridium-catalyzed allylic substitution reactions of branched allylic esters have so far occurred with low enantioselectivities [45, 75].

Hartwig and coworkers reported an approach to address this limitation involving tandem catalytic reactions. In this tandem process, sequential palladium-catalyzed isomerization of the branched isomer to the linear isomer, followed by iridium-catalyzed allylic substitution leads to the branched product with high enantiomeric excess [105]. More specifically, treatment of branched allylic esters with catalytic amounts of the combination of $Pd(dba)_2$ and PPh_3 led to rapid isomerization of the branched allylic ester to the linear isomer, and the linear isomer underwent allylic substitution after addition of the iridium catalyst and nucleophile (Scheme **31**).

Carreira et al. reported the kinetic resolution of branched allylic carbonates catalyzed by an iridium complex derived from a chiral [2.2.2]-bicyclooctadiene [48]. Reactions of allylic carbonates with phenol were run to 50% conversion of the carbonate, leaving unreacted allylic carbonate in high enantiomeric excess (Scheme **32**). The phenyl ether products were also isolated in mid-to-high enantiomeric excess.



Scheme 32 Kinetic resolution of branched allylic carbonates

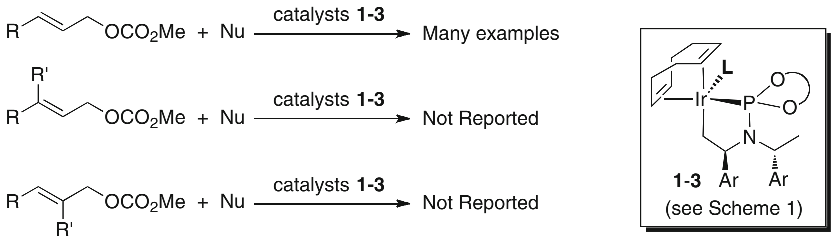


Scheme 33 The reaction of sulfamic acid with a branched allylic alcohol

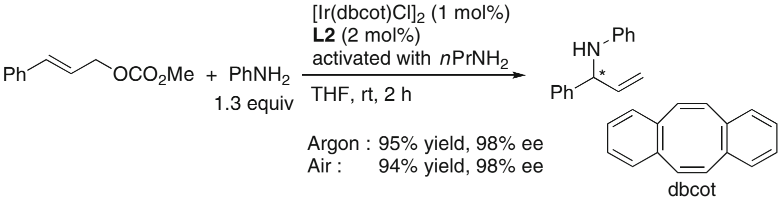
More recently, Carreira and coworkers reported the reactions of sulfamic acid with branched allylic alcohols to form branched primary allylic amines [106]. One enantioselective reaction was disclosed, and the product was isolated in 70% ee when using a 5*H*-dibenzo[*b*, *f*]azepine-derived phosphoramidite with [Ir(COE)$_2$Cl]$_2$ (Scheme 33). This reaction occurs under acidic conditions, which is incompatible with the metalacyclic catalysts.

6.4 Allylic Substitution with Highly Substituted Allylic Esters

No examples have been reported of enantioselective, iridium-catalyzed allylic substitutions of linear allylic esters to generate 1,1-disubstituted or 2-substituted π-allyl intermediates. Takeuchi published reactions in which the proposed allyliridium intermediates are 1,1- or 1,3-disubstituted, but these substrates have not been shown to undergo reactions catalyzed by chiral iridium complexes. No reactions of 1,2-disubstituted substrates have been published (Scheme 34).



Scheme 34 The reaction of highly substituted allylic carbonates have not been catalyzed by metalacyclic iridium-phosphoramidite complexes



Scheme 35 Air-stable allylic substitution catalyzed by $[Ir(dbcot)Cl]_2$ and **L2**

6.5 Stability of Iridium-Phosphoramidite Catalysts to Air and Water

Except for one recent example, all iridium-catalyzed allylic substitution reactions have been performed under an inert atmosphere with dry solvent and reagents. The iridium metalacycle is sensitive to protonation, which opens the metalacycle and results in the formation of a less-active complex containing a κ^1-phosphoramidite ligand. A paper by Helmchen et al. addressed this issue [107]. Nearly all iridium catalysts used for allylic substitution consist of an iridium fragment chelated by COD. In the presence of a catalyst containing dibenzo[*a*,*e*]cyclooctatetraene (dbcot) in place of COD, allylic substitution reactions occur in air with results that are comparable to those of reactions performed under an inert atmosphere (Scheme 35).

7 Conclusion

Takeuchi's initial report on iridium-catalyzed allylic substitution demonstrated that the allylation of carbon nucleophiles forms branched, racemic substitution products. Chiral catalysts were quickly developed that led to methods to prepare the products of allylic substitution at the more substituted position of mono-substituted allylic carbonates with high enantioselectivities. Since these initial reports, the scope of iridium-catalyzed asymmetric allylic substitution has grown to include reactions of a wide range of carbon, nitrogen, and oxygen nucleophiles. Substitution products are now typically formed in excellent enantiomeric excess. Only recently have studies begun to reveal the mechanism of iridium-catalyzed allylic substitution, but these mechanistic insights are now aiding in the development of new catalyst precursors that further improve reaction scope and catalyst activity.

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Top Organomet Chem (2011) 34:209–230
DOI: 10.1007/978-3-642-15334-1_8

Iridium-Catalyzed 1,3-Dipolar Cycloadditions

Daniel Carmona and Luis A. Oro

Abstract 1,3-Dipolar cycloaddition reactions (DCR) are atom-economic processes that permit the construction of heterocycles. Their enantioselective versions allow for the creation of up to four adjacent chiral centers in a concerted fashion. In particular, well-defined half-sandwich iridium (III) catalysts have been applied to the DCR between enals or methacrylonitrile with nitrones. Excellent yield and stereoselectivities have been achieved. Support for mechanistic proposals stems from the isolation and characterization of the true catalysts.

Keywords 1,3-Dipolar cycloadditions · Enals · Iridium catalysts · Methacrylonitrile · Nitrones

Contents

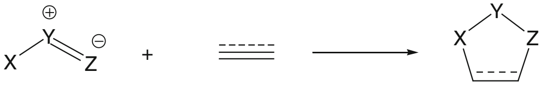
D. Carmona (✉) and L.A. Oro
Instituto de Ciencia de Materiales de Aragón, University of Zaragoza-CSIC, Pedro Cerbuna 12, 50009 Zaragoza, Spain
e-mail: dcarmona@unizar.es

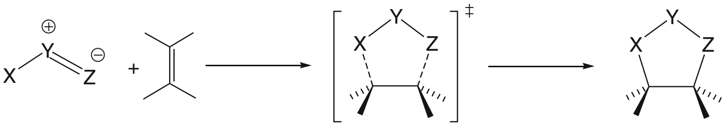
1 Introduction

Cycloaddition reactions are a fundamental class of processes in synthetic chemistry. Within this class, the 1,3-dipolar cycloaddition reaction (DCR) has found extensive use as an efficient method for the synthesis of different heterocyclic compounds. These type of reactions involve the addition of a 1,3-dipole to a multiple π-bond system (dipolarophile) leading to five-membered heterocycles (Scheme 1) [1].

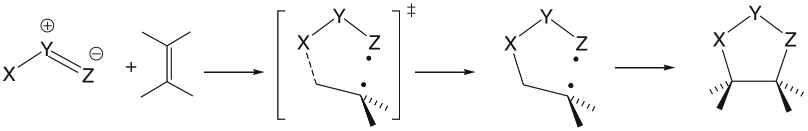
Huisgen in the 1960s undertook a systematic study that led to the generalization and classification of DCR [2] and to the proposal of a concerted synchronous mechanism (Scheme 2) [3]. However, Firestone considered the DCR to proceed via a stepwise diradical mechanism. Stereochemistry would be retained for short-lived diradical intermediates but may be destroyed for longer-lived diradicals (Scheme 3) [4]. Currently, the most widely accepted mechanism is a concerted process with both new bonds being formed at the same time but not necessarily to the same extent. Additionally, very recently, Houk et al. have found an unambiguous correlation between the calculated activation barriers and the distortion energies, the latter being "the energy required to distort the 1,3-dipole and the dipolarophile from their equilibrium geometries into the transition-state geometries without allowing any interaction between them" [5]. These findings provide a new way of understanding the DCR that cannot be neglected in accurate computational studies [6–8].

Scheme 1 1,3-Dipolar cycloadddition reaction





Scheme 2 Concerted mechanism for DCR



Scheme 3 Stepwise diradical mechanism for DCR

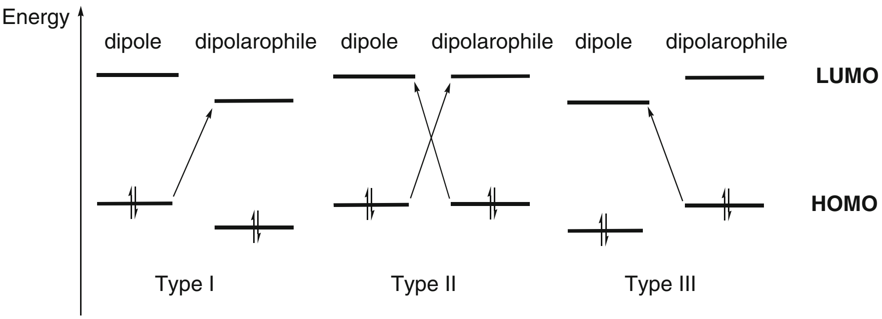


Fig. 1 Sustmann's classification of DCR

1.1 The Frontier Molecular Orbital Theory

The most successful qualitative model for DCR is based on frontier molecular orbital (FMO) theory. According to this theory, reaction takes place by maximizing overlap between the HOMO and LUMO of the reagents. Sustman applied FMO theory to the reactivity of concerted DCR and classified them into three types depending on the interactions established between the FMO of the dipole and dipolarophile (Fig. 1) [9–12]. Type I reactions involve dipoles with high-lying HOMO and dipolarophiles with low-lying LUMO. The most favorable FMO interaction will imply transference of charge from the nucleophilic dipole to the electrophilic dipolarophile. In this case, the reaction rate may be increased, for example, introducing electron-withdrawing groups on the dipolarophile. By the contrary, type III reactions involve dipoles with low-lying LUMO and dipolarophiles with high-lying HOMO. The dominant FMO interaction will take place between the HOMO of the dipolarophile and the LUMO of the dipole. Reactions of this type can be accelerated by using dipolarophiles with electron-donating groups. Finally, type II reactions involve dipoles and dipolarophiles with similar energy gaps between the HOMO and LUMO. These reactions are called ambiphilic, and, in particular, reactions of nitrones with alkenes belong to this type. Introduction of electron-donating or electron-withdrawing substituents on the dipolarophile or the dipole can alter the relative FMO energies resulting in a change to type I or III reaction.

Interestingly, the presence of metallic Lewis acids in the reaction media may substantially affect reactions. When coordinating to the dipolarophile, the Lewis acid lowers the energy of its frontier orbitals. This lowering reduces the energy gap between the LUMO of the dipolarophile and the HOMO of the dipole (Fig. 2) leading to an acceleration of the cycloaddition. Similarly, coordination to the dipole reduces the energy difference between the HOMO of the dipolarophile and the LUMO of the dipole, this reduction resulting in an increment of the reaction rate. Notably, the efficiency of this Lewis acid interaction relies not only on the fastening of the reaction but also on the capability of metallic complexes to control the selectivities of the cycloaddition. Thus, a variety of Lewis acids based on metals have been employed as catalysts in stereoselective DCR often providing excellent results [13–22].

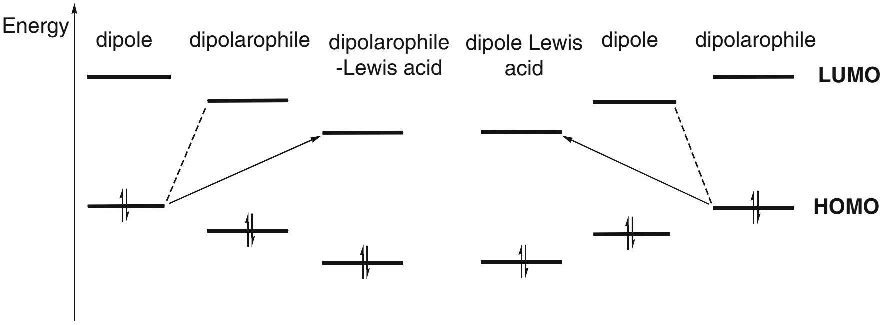
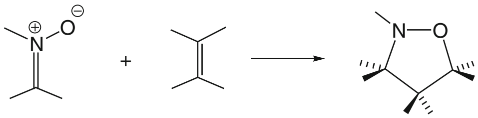


Fig. 2 Changes in FMO by coordination to a Lewis acid

Scheme 4 DCR between nitrones and alkenes



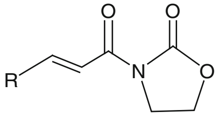
2 DCR of Nitrones with Alkenes

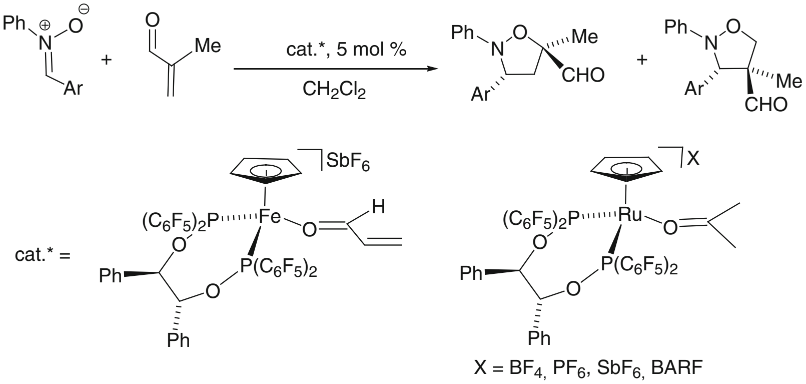
Over the last years, one of the most studied DCR has been the asymmetric version of the cycloaddition of nitrones with alkenes. This reaction leads to the construction of up to three contiguous asymmetric carbon centers (Scheme 4). The resulting five-membered isoxazolidine derivatives may be converted into amino alcohols, alkaloids, or β-lactams. Several chiral metal complexes have been used as catalysts for this process [13–15, 18–22]. However, the employment of iridium derivatives is very scarce.

2.1 DCR of Nitrones with Enals

Due to the presence of an electron-withdrawing group on the dipolarophile, these processes are classified as type I reactions. The process involves the transference of charge from the dipole to the dipolarophile. When catalyzed by metallic compounds, coordination of the dipolarophile is highly desired. Usually, coordination of a nitrone to the Lewis acid is more feasible than coordination of a carbonyl compound. For this reason, alkenes that enable a bidentate coordination to the Lewis acid, such as 3-alkenoyl-oxazolidinones (Scheme 5), have been frequently employed as a model system to study the metal-catalyzed 1,3-dipolar cycloaddition

Scheme 5 3-Alkenoyl-oxazolidinones





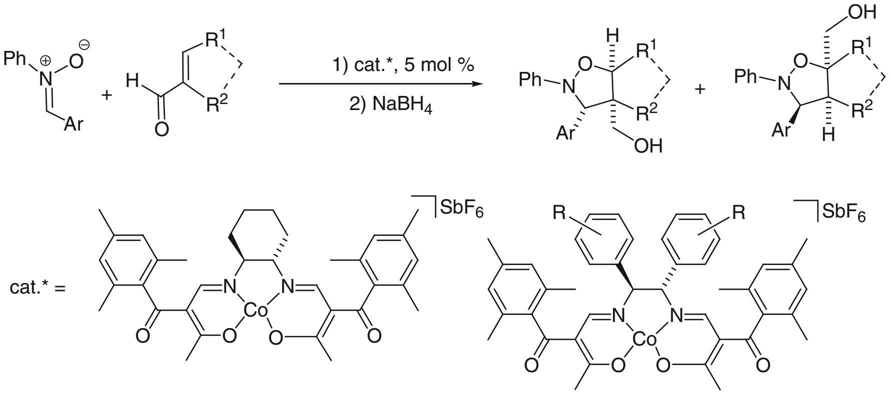
Scheme 6 DCR catalyzed by Binop-F complexes

of nitrones [14, 15, 18, 20]. In contrast, examples of one point binding catalysts for the activation of electron-deficient monofunctionalized alkenes, such as enals, are scarce [18, 20]. Only recently has it been possible to find a few examples in the literature.

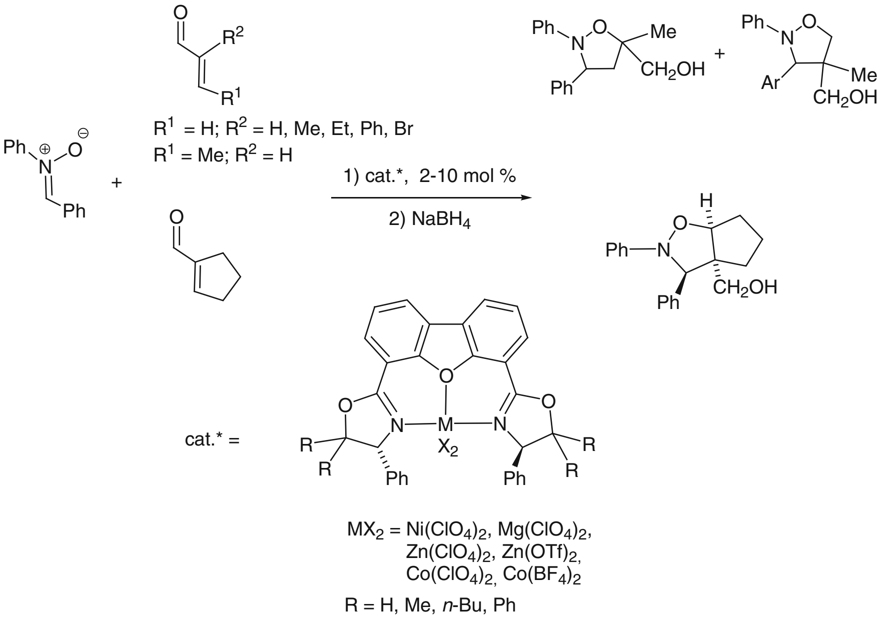
In 2002, Kündig et al. [23, 24] developed catalytic DCR between diaryl nitrones and α,β-unsaturated aldehydes in the presence of Binop-F iron and ruthenium complexes as chiral Lewis-acid catalysts (Scheme 6). The corresponding cycloadducts were obtained in good yields with complete *endo* selectivity and up to 94% ee. The isoxazolidine products were obtained as a mixture of regioisomers in molar ratios varying from 96:4 to 15:85. Experimental and computational data show that the regioselectivity correlates directly with the electronic properties of the nitrone.

Yamada and coworkers [25–27] have employed chiral β-ketoiminato cobalt (III) complexes as catalysts for the same type of reaction. The cycloadducts were obtained with complete *endo* selectivity and in moderate to high ee (Scheme 7).

Complexes of nickel(II) or magnesium(II) with the chiral ligand DBFOX (Scheme 8) catalyze the DCR of nitrones with α-alkyl- and arylacroleins rendering preferentially the 5-carbaldehyde cycloadducts. However, the reactions with α-bromoacrolein catalyzed by the zinc(II) complex of the same ligand afford isoxazoline-4-carbaldehydes. The corresponding cobalt(II) complex is also active for the cycloaddition between cyclopenten-1-carbaldehyde and diphenylnitrone.



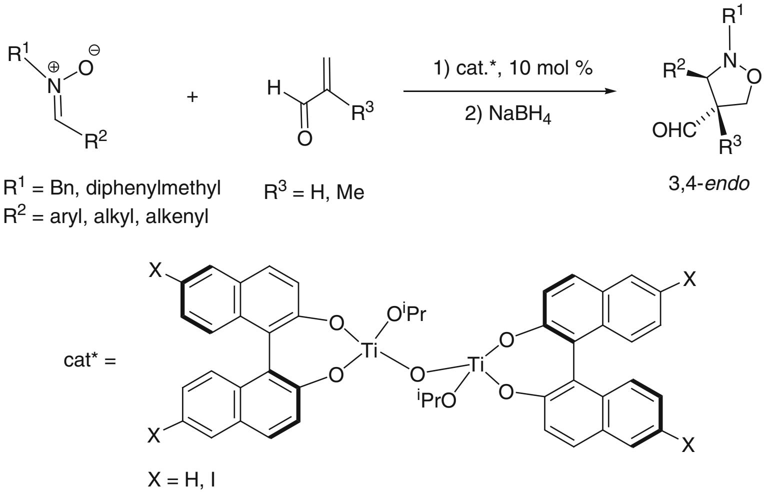
Scheme 7 Cycloadditions catalyzed by β-ketoiminato complexes of Co(III)



Scheme 8 DCR catalyzed by DBFOX complexes

The adducts are characterized as alcohols after reduction with $NaBH_4$. Enantioselectivities up to 99.5 ee were achieved at room temperature [28, 29].

The chiral dinuclear titanium complexes depicted in Scheme 9 have been utilized as catalysts for the DCR between *N*-benzyl and *N*-diphenylmethyl nitrones and



Scheme 9 Cycloaddition catalyzed by bis-titanium chiral catalysts

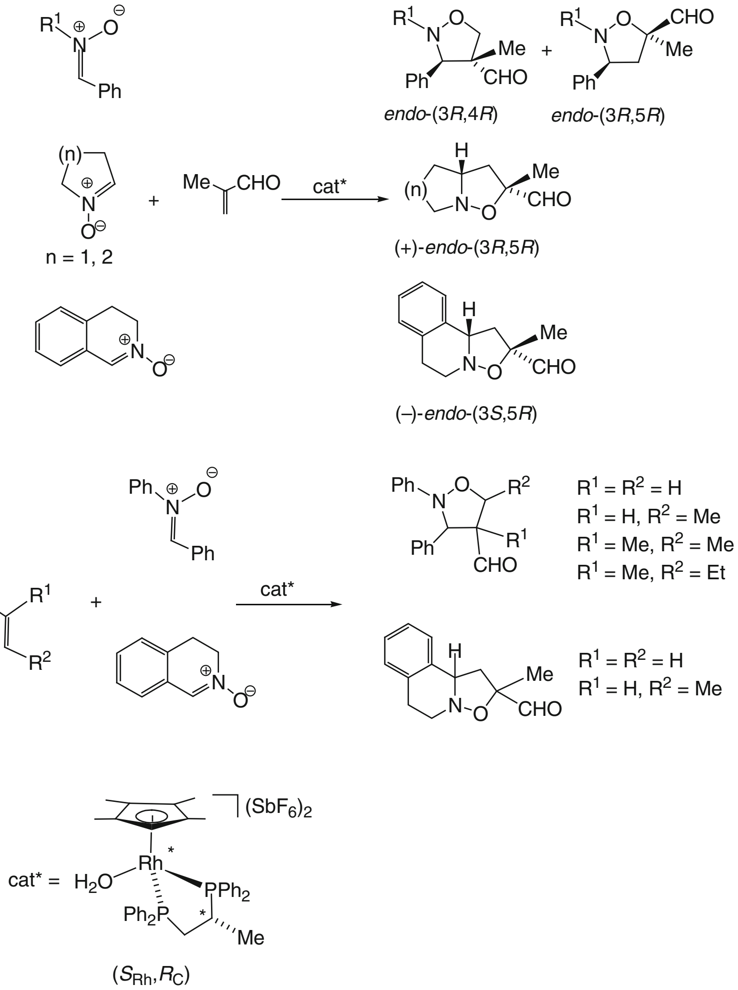
acrolein or methacrolein. Interestingly, the 3,4-*endo* adduct was the major product. Several *N*-benzyl and *N*-diphenylmethyl nitrones with aromatic rings with different electronic properties, alkyl groups such as *tert*-butyl or cyclohexyl, and 1-cyclopentenyl or 1-methyl-1-propenyl have been investigated. In general, good yields and enantoselectivities up to 99% ee with a catalytic loading of 10 mol% were achieved [30–32].

The enantioselective catalytic 1,3-dipolar cycloaddition of linear or cyclic nitrones to enals was accomplished using the half-sandwich rhodium(III) complex (S_{Rh},R_{C})-[(η^5-C_5Me_5)Rh{(*R*)-Prophos}(H_2O)](SbF_6)$_2$ as catalyst precursor [33, 34]. At −25°C, quantitative conversions to the cycloadducts, with up to 95% ee, were achieved (Scheme 10). The intermediate with the dipolarophile coordinated to the rhodium has been isolated and completely characterized, including the X-ray determination of its molecular structure [33, 34].

The same rhodium precursor, (S_{Rh},R_{C})-[(η^5-C_5Me_5)Rh{(*R*)-Prophos}(H_2O)](SbF_6)$_2$, promotes the reaction between the nitrones *N*-benzylideneaniline *N*-oxide or 3,4-dihydroisoquinoline *N*-oxide with other enals different from methacrolein (Scheme 10). The cycloadducts were prepared with excellent regioselectivity, perfect *endo* selectivity, and enantiomeric excesses up to 94% [35].

Cationic chiral Rh_2^{5+} carboxamidates show catalytic activity for the DCR between diaryl nitrones and methacrolein (Scheme 11). Cycloadducts were obtained as 3,4-*endo*/3,5-*endo* mixtures with molar ratios ranging from 13/87 to 90/10. The enantioselectivity of the 3,4 isomers is higher than that of the 3,5 adducts and increases when the steric bulk of the ligand ester group increases [36].

Ruthenium complexes of formula [(η^6-arene)Ru(LL*)(H_2O)](SbF_6)$_2$ (arene = C_6H_6, *p*-$MeC_6H_4{}^{i}Pr$, C_6Me_6; LL* = bidentate chelate chiral ligand with PN, PP, or

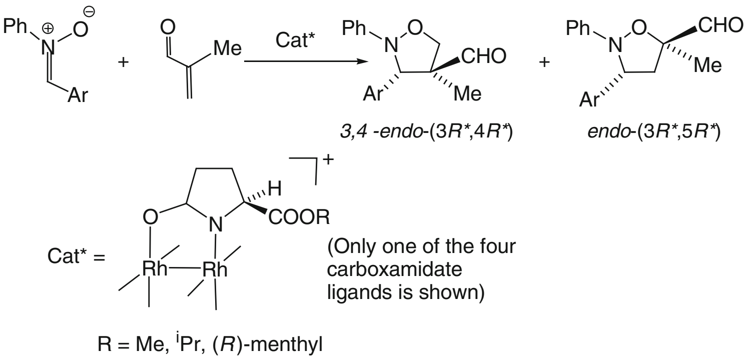


Scheme 10 DCR catalyzed by chiral half-sandwich complexes of rhodium

NN donor atoms) efficiently catalyze the DCR of methacrolein with a series of nitrones (Scheme 12). Typically, quantitative conversions are achieved at −25°C, in a few hours. Perfect diastereoselectivity for the *endo* adducts is observed, but only low to moderate enantioselectivity is obtained [37].

3 DCR of Nitrones with Enals Catalyzed by Iridium Complexes

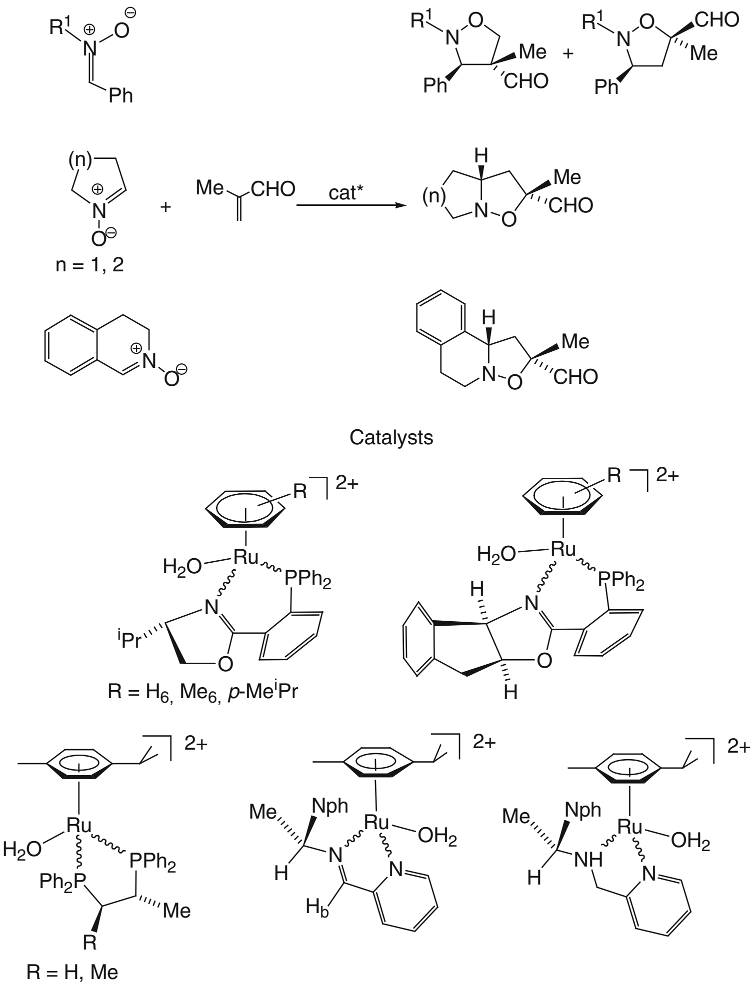
Methacrolein is the enal most studied in DCR catalyzed by iridium complexes.



Scheme 11 DCR between diaryl nitrones and methacrolein catalyzed by cationic Rh_2^{5+} carboxamidates

3.1 DCR of Nitrones with Methacrolein

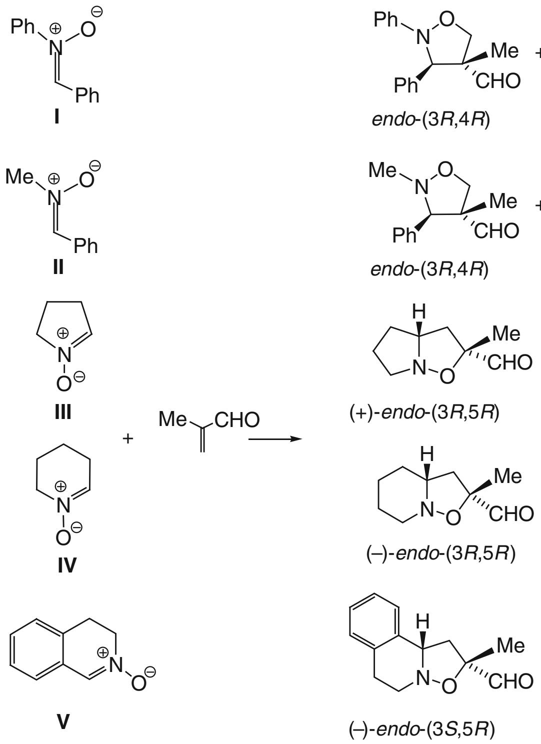
The enantioselective DCR of nitrones **I**–**V** to methacrolein catalyzed by $(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}$ (Prophos = 1,2-bis(diphenylphosphino)propane) containing complexes (Scheme 13) was published in 2005 [34]. As a catalyst precursor, the aqua-complex $(S_{Ir},R_C)\text{-}[(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(H_2O)](SbF_6)_2$ (**1**), prepared by treating the tris(solvento) complex [38] in acetone with an equimolar amount of (*R*)-Prophos in the presence of traces of water (Scheme 14), was employed. Complex **1** is prepared in a completely diastereoselective manner: only one of the two possible epimers at metal was spectroscopically detected, in solution from −90°C to RT, and an X-ray determination showed that it was the *S* at metal isomer. Methacrolein displaces coordinated water from **1** affording, also diastereoselectively, the enal complex $(S_{Ir},R_C)\text{-}[(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(\text{methacrolein})]$ $(SbF_6)_2$ (**2**) (Scheme 15) [34]. The presence of an electron-withdrawing group on the dipolarophile (CHO) together with the coordination to the metal makes the DCR process a Sustmann's type I reaction and, accordingly, electronic density will be transferred from the nitrone to the methacrolein. In such a process, to achieve good yield, coordination of the dipole (nitrone) has to be avoided. Nitrones may coordinate metals through their oxygen atom and, in fact, while acyclic nitrones **I** and **II** do not displace methacrolein from complex **2**, the cyclic ones **III**–**V** readily substitute the coordinated dipolarophile even at a low temperature. Thus, for example, ^{31}P NMR spectra of dichloromethane solutions of the methacrolein complex $(S_{Ir},R_C)\text{-}[(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(\text{methacrolein})]$ $(SbF_6)_2$ (**2**) remained unchanged for hours, in the −90°C to RT range of temperatures, after the addition of 20 equivalents of nitrone **I**. However, immediately after addition, at −60°C, of the same amount of the cyclic nitrone **V**, the ^{31}P NMR spectrum showed the formation of the nitrone complex $[(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(\mathbf{V})]^{2+}$. In fact, the related nitrone complex $[(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(\mathbf{III})](SbF_6)_2$ has been



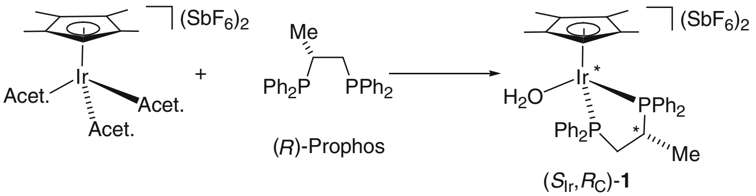
Scheme 12 DCR catalyzed arene-ruthenium complexes

isolated and characterized by addition of the corresponding cyclic nitrone to the water complex (S_{Ir},R_C)-[(η^5-C_5Me_5)Ir{(*R*)-Prophos}(H_2O)](SbF_6)$_2$, in the presence of molecular sieves, according to Scheme 16. When the nitrone complex was prepared and isolated at −25°C, the two epimers at metal, in ca. 50/50 molar ratio, were obtained. In dichloromethane, complete and irreversible epimerization occurs to the thermodynamically preferred S_{Ir},R_C isomer. The latter was the sole isolated isomer when the preparation was carried out at room temperature.

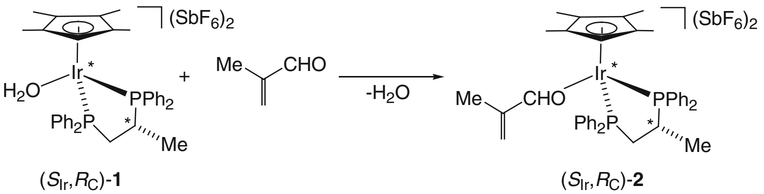
In summary, when the iridium complex **2** is used as catalyst for the DCR reaction between cyclic nitrones and methacrolein, coordination of the nitrone to the metal is likely, to the detriment of methacrolein coordination. As we will see later, to avoid



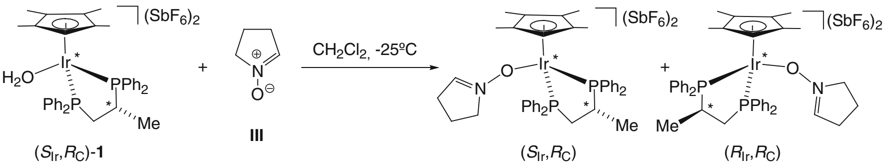
Scheme 13 Major adducts for the DCR between nitrones **I**–**V** and methacrolein



Scheme 14 Preparation of the catalyst Precursor (S_{Ir},R_C)-**1**



Scheme 15 Preparation of the methacrolein complex(S_{Ir},R_C)-**2**



Scheme 16 Preparation of nitrone complexes

Table 1 Enantioselective DCR of methacrolein with nitrones **I**–**V**

Entry	Nitrone	t (h)	Yield (%)	3,4-*endo*	3,5-*endo*	ee (%)
1	**I**	10	100	82	18	95/85.5
2	**II**	24	78	2	98	–/93
3	**III**	15	100	–	100	86
4	**IV**	15	100	–	>99	92
5	**V**	15	100	–	100	93
6	**III**	16	75	–	>99	76

this negative effect, concentration of cyclic nitrones has to be maintained low during catalysis.

3.1.1 Catalytic Reactions

Complex **2** efficiently catalyzes the cycloaddition reaction of methacrolein with the nitrones **I**–**V**. Table 1 lists some results obtained. The reactions were performed in CH_2Cl_2 in the presence of 4 Å molecular sieves, with 5 mol% of catalyst loading and a 1/140/20 catalyst/methacrolein/nitrone molar ratio. Typically, quantitative yields are obtained after a few hours at −25°C. The acyclic nitrone **II** generates the less active system but, even so, 78% conversion was achieved after 24 h at −10°C (entry 2). Enantiomeric excesses greater than 90% were achieved in most cases. A greater excess of methacrolein improves both rate and enantioseletivity (compare entry 6 with a catalyst/methacrolein/nitrone molar ratio 1/28/20 with entry 3 with a 1/140/20 molar ratio). To avoid undesired nitrone coordination, addition of the cyclic nitrones **III**–**V** was accomplished over 10 h.

Temperature variation slightly affected both product distribution and enantioselectivity, the latter smoothly increases as temperature decreases (Table 2). Thus, for example, the ee of the 3,4-*endo* adduct of the DCR between methacrolein and nitrone **I** gradually increases from 85 to 96% when temperature decreases from +5 to −35°C (entries 1–5). A similar trend was observed for the 3,5-adduct as well as for the DCR involving other nitrones (Table 2).

Ab initio calculations carried out by Tanaka and Kanemasa conclude that, under Lewis acid-catalyzed conditions, the formation of *endo*-cycloadducts is preferred and that the attack of nucleophilic nitrone oxygen should become more favored to occur at the β-position of the enal rendering 3,4-cycloadducts [39]. In the iridium

Table 2 Effect of the temperature

Entry	Nitrone	T (°C)	t (h)	Yield (%)	3,4-*endo*	3,5-*endo*	ee (%)
1	**I**	+5	6	100	58	42	85/79
2	**I**	−5	7	100	71	29	91/81
3	**I**	−15	8	100	78	22	93.5/82
4	**I**	−25	10	100	82	18	95/85.5
5	**I**	−35	24	100	86.5	13.5	96/87
6	**II**	0	15	78	5	95	–/88
7	**II**	−10	24	78	2	98	–/93
8	**III**	−25	15	100	–	100	86
9	**III**	−35	24	55	–	100	91
10	**V**	−25	15	100	–	>99	93
11	**V**	−35	24	53	–	100	95

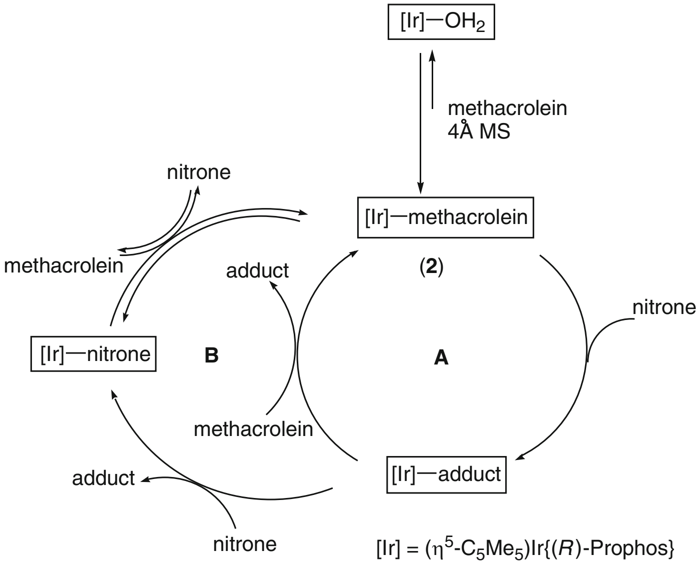
system that we are referring to, reactions occur with perfect *endo* selectivity. With respect to the regioselectivity, while the uncatalyzed reaction of nitrone **I** with methacrolein gives the 3,5-*endo* adduct, the major product of the catalyzed reaction is the 3,4-*endo* cycloadduct, in good agreement with Tanaka and Kanemasa calculations. On the other hand, cyclic nitrones **III**–**V**, which are more sterically demanding in their *endo*-approach to coordinated methacrolein, render 3,5-cycloadducts in all cases [23, 40].

3.1.2 The Catalytic Cycle

The catalytic cycle that has been proposed [34] is depicted in Scheme 17. At −25°C, the resting state of the catalyst is the [Ir]-methacrolein complex **2** that is the true catalyst. Its reaction with the nitrone is the key step of the productive cycle **A**: it is the rate- and enantioselectivity-determining step, at this temperature. For cyclic nitrones, path **B** becomes operative diminishing the concentration of the active species and, therefore, decreasing the rate. Lowering nitrone concentration (slow addition) hinders this undesired side reaction and, although it also slows down the rate of formation of the [Ir]-adduct intermediate, it favors the catalytic process overall. It has been experimentally shown that the catalytic rate increases when methacrolein concentration increases. Scheme 17 explains this effect because increasing this concentration favors the adduct elimination in path **A** and it recuperates the inactive metallic concentration, present as [Ir]-nitrone in path **B**, by shifting the [Ir]-nitrone/[Ir]-methacrolein equilibrium toward the enal complex, which restarts the cycle.

3.1.3 Origin of the Enantioselectivity

The (η^5-C_5Me_5)Ir{(*R*)-Prophos} system is very selective for the DCR of nitrones and methacrolein with enantioselectivity up to 96% ee. A few structural features of



Scheme 17 Proposed catalytic cycle

the cation of the catalyst, $[(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(\text{methacrolein})]^{2+}$, account for the encountered selectivity. First, in spite of (*R*)-Prophos being a C_1 symmetric ligand, the *S* at metal epimer of the catalyst is formed with complete diastereoselectivity. Moreover, although, in some instances, epimerization at the metal in chiral half-sandwich transition metal complexes is a low-demanding energy process [41], this isomerization is not observed for this complex. Second, all the diffractometric and spectroscopic data support a λ conformation for the Ir–P–C–C–P five-membered metallacycle formed on coordination of the (*R)*-Prophos ligand. The bulky C_5Me_5 ring constrains this conformation forcing the methyl substituent to occupy the less hindered pseudoequatorial position. This conformation, together with the *S* configuration at the metal, determines the chiral bias of the catalyst pocket in which catalysis takes place. Third, methacrolein coordinates to the metallic fragment in the *E* geometry and adopts an *s-trans* conformation [42–44]. This conformation, which is also preferred for uncomplexed methacrolein [45], is reinforced by coordination and retained in catalytic conditions. Fourth, CH/π-attractive interactions between the CHO aldehyde proton and the *pro-S* phenyl ring of the (*R*)-Prophos ligand (Fig. 3) establish the methacrolein rotamer around the M–O bond both in the solid state and in the solution. Overall, the geometry of the methacrolein is set and, in the chiral environment in which it is located, its *Re*-face becomes much more accessible to the nitrone than its *Si*-face, which is shielded by the phenyl rings of the (*R)*-Prophos ligand. This situation seems also to apply for the transition-state assembly of the DCR and accounts for the outcome of the catalytic reaction.

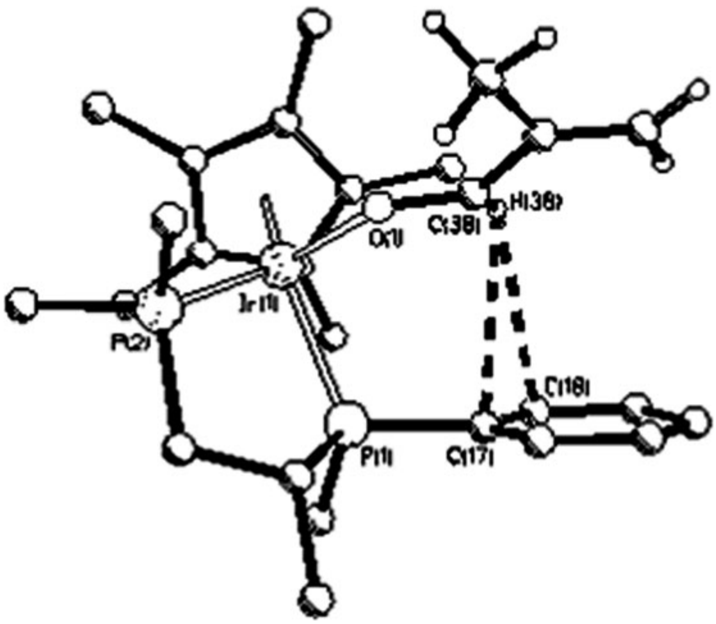
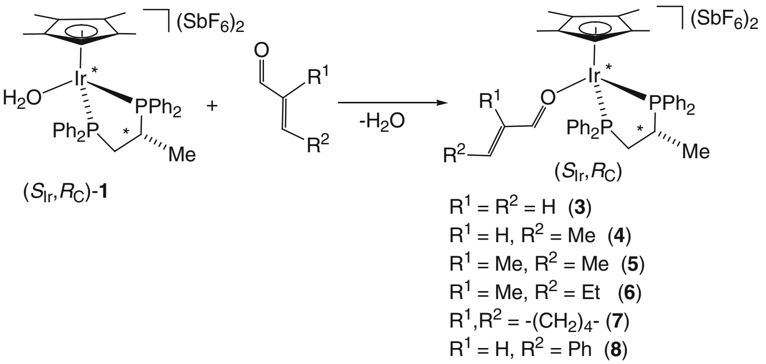


Fig. 3 Schematic view of the CH/π interactions in the cation of complex **2**

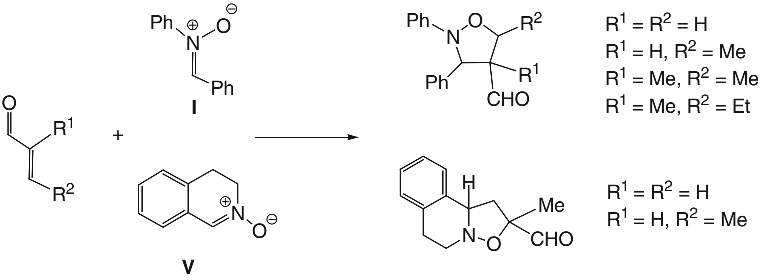
3.2 DCR of Nitrones with Other α,β-Unsaturated Aldehydes

Complexes of the formula (S_{Ir},R_{C})-[(η^5-C_5Me_5)Ir{(*R*)-Prophos}(enal)](SbF_6)$_2$ (**3**–**8**) can be diastereoselectively prepared by addition of the appropriate enal to the water complexes (S_{Ir},R_{C})-[(η^5-C_5Me_5)Ir{(*R*)-Prophos}(H_2O)](SbF_6)$_2$ in the presence of 4Å molecular sieves (Scheme 18).

One interesting feature of the ^{1}H NMR spectra of these complexes is the strong shielding of the aldehyde proton resonance after coordination. At −25°C in CD_2Cl_2 solution, this proton resonates in the range 6.93–7.50 ppm, about 2.3 ppm shifted to higher field with respect to the corresponding free enals. It has been shown that a comparable shift, measured in the related (S_{Ir},R_{C})-[(η^5-C_5Me_5)Ir{(*R*)-Prophos}(methacrolein)](SbF_6)$_2$ complex, is concomitant to the existence of CH/π interactions between the CHO proton and one of the phenyl rings of the Profos ligand [34]. Therefore, it is likely that these interactions are also operating in complexes **3**–**8**. In addition, NOESY experiments show enhancement patterns compatible only with an *s-trans* conformation for the coordinated enal and a λ conformation for the Ir–P–C–C–P five-membered metallacycle. In summary, the NMR data indicate that the conformation of both metallic fragment and enal are significantly hampered when the enal is coordinated to the metal into the chiral pocket defined by the (C_5Me_5)Ir{(*R*)-Prophos} moiety. Thus, they are excellent candidates to be tested as catalyst for DCR: the enals present a restricted conformation and, furthermore, they



Scheme 18 Preparation of the enal complexes



Scheme 19 1,3-Dipolar cycloaddition reactions

Table 3 Enantioselective DCR of enals with nitrones **I** and **V**

Entry	Catalyst	Nitrone	T (°C)	t (h)	Yield (%)	ee (%)
1	**3**	**I**	−25	16	100	90
2	**4**	**I**	−25	25	100	84.5
3	**5**	**I**	−25	72	96.5	92
4	**6**	**I**	−10	72	100	84.5
5	**6**	**I**	−25	72	55	94
6	**3**	**V**	−25	25	69	66
7	**4**	**V**	−25	25	100	70

are activated by coordination to the metal. In fact, most of them efficiently catalyze the cycloaddition reaction of the nitrones *N*-benzylidenphenylamine *N*- oxide (**I**) and 3,4-dihydroisoquinoline *N*-oxide (**V**) to the corresponding enal (Scheme 19). Table 3 lists a selection of the results. Catalysts were prepared *in situ* by treating the aqua precursors $(S_{\mathrm{Ir}},R_{\mathrm{C}})$-$[(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(H_2O)](SbF_6)_2$ with the corresponding enal in the presence of 4Å MS. The reactions were performed in CH_2Cl_2, in the presence of 4 Å molecular sieves, with 10 mol% of catalyst loading and a 1/70/10 catalyst/enal/nitrone molar ratio. The 1-cyclohexen-1-carboxaldehyde (**7**) and *trans*-cinnamaldehyde (**8**) derivatives were not active. The cyclic nitrone **V** was added slowly to avoid undesired nitrone coordination (see above). Perfect diastereoselectivity for the *endo* isomer was observed in all cases, and the 3,4 regioisomer was the sole adduct (nitrone **I**) or the major one (more than 90%, nitrone **V**). The ee values achieved ranged from 66 to 94%, enantioselectivity increases as temperature decreases (compare entries 4 and 5).

The absolute configuration of the major adduct obtained from the reaction of *trans*-crotonaldehyde with nitrone **I** was determined as the 3*S*,4*R*,5*S* isomer by derivatization with (*R*)-(-)-α-methylbenzylamine [45]. Accordingly, the *Re*-face of the coordinated *trans*-crotonaldehyde has to be much more accessible to the nitrone than its *Si*-face during the chirality induction step.

4 DCR of Nitrones with Methacrylonitrile Catalyzed by Iridium Complexes

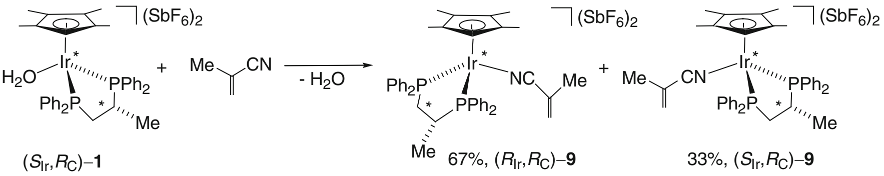
The problem of the competitive coordination between the nitrone and the alkene can be circumvented by using alkenes with a good coordinating functionality such as a cyano group. Thus, the DCR between nitrones **IV** and **V** (see Scheme 13) and methacrylonitrile was carried out using the aqua-complex (S_{Ir},R_{C})-[(η^5-C_5Me_5)Ir{(*R*)-Prophos}(H_2O)]$(SbF_6)_2$ (**1**) as the catalyst precursor [46, 47]. The reactions were performed in CH_2Cl_2, with 10 mol% of catalyst loading and a 1/70/20 catalyst/methacrylonitrile/nitrone molar ratio. In both cases, quantitative conversion to the 3,5-*endo*-cycloadduct are achieved but the system is not enantioselective (Table 4).

Interesting information about the catalytic systems was obtained by studying the stereochemistry of the reaction of the catalyst precursor **1** with methacrylonitrile. The water molecule of complex **1** is readily displaced by methacrylonitrile rendering complex [(η^5-C_5Me_5)Ir{(*R*)-Prophos}(methacrylonitrile)] $(SbF_6)_2$ (**9**) as a mixture of the two possible epimers at metal, namely, R_{Ir},R_{C} and S_{Ir},R_{C}, in 34% diastereomeric excess in the former (Scheme 20). In acetone, at 50°C, the R_{Ir},R_{C} isomer slowly epimerizes to the thermodynamically preferred S_{Ir},R_{C} epimer. From the solution, pure samples of the latter can be isolated that have been employed as *stoichiometric* catalysts for the DCR between methacrylonitrile and nitrones **IV** and **V**.

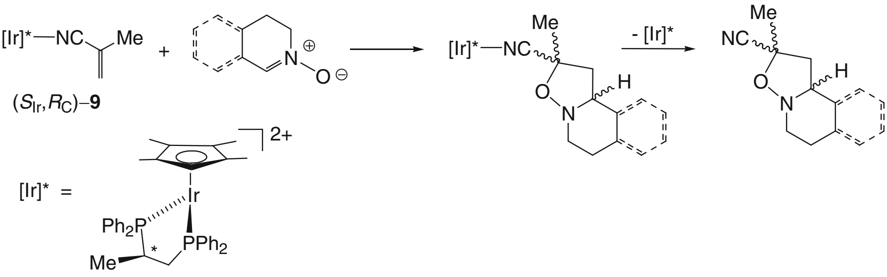
Reaction of pure (S_{Ir},R_{C})-**9** with nitrones **IV** or **V** followed by the addition of an excess of *n*-Bu_4NBr (Scheme 21) gives the corresponding 3,5-*endo*-isoxazolidines in quantitative yield. Table 5 collects the ee values obtained for the two nitrones. Comparison of the results of Table 5 with those of Table 4 indicates that, whereas a mixture of epimers complex **9** (67% R_{Ir},R_{C}/33% S_{Ir},R_{C}, molar ratio) reacts with nitrones 2,3,4,5-tetrahydropyridine *N*-oxide (**IV**) or 3,4-dihydroisoquinoline

Table 4 Catalytic DCR of methacrylonitrile

Entry	Nitrone	Yield	3,5-*endo* (%)	ee (%)
1	**IV**	91	100	1
2	**V**	100	100	0



Scheme 20 Preparation of the methacrylonitrile complex **9**



Scheme 21 Stoichiometric DCR between complex (S_{Ir},R_C)−**9** and nitrones **IV** and **V**

Table 5 Stoichiometric reactions

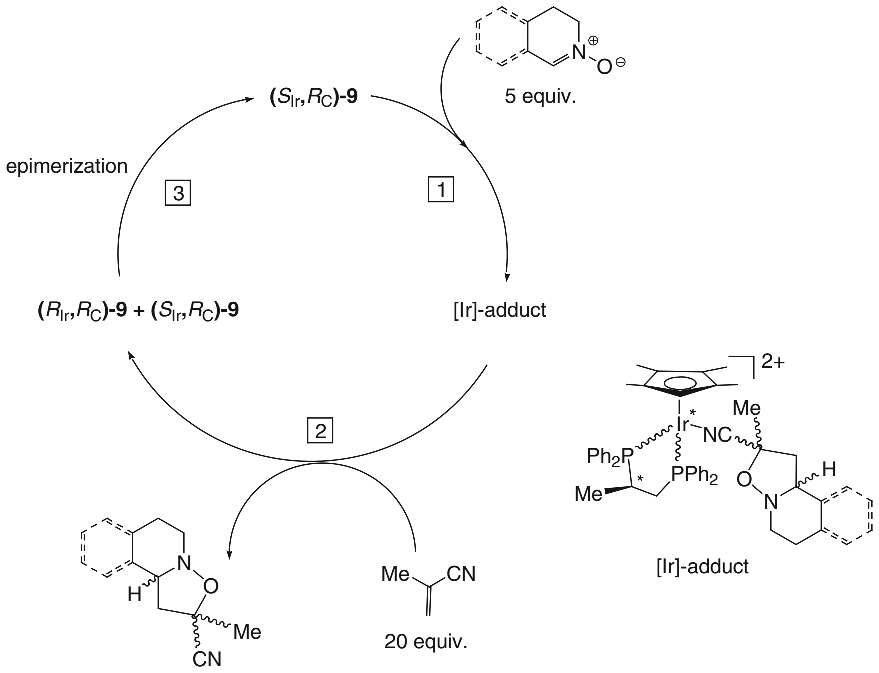
Entry	Nitrone	Temp.	ee (%)
1	**IV**	RT	84
2	**V**	RT	74
3	**IV**	0°C	93.5

N-oxide (**V**) rendering regio- and diastereoselectively racemates of the corresponding 3,5-cycloadducts (Table 4), pure (S_{Ir},R_C)-**9** stoichiometrically catalyzes these reactions with 84 and 74% ee, respectively, (Table 5) at room temperature. At lower temperatures, greater ee are obtained (entry 3, 0°C, 93.5% ee).

The impressive increase in the ee values achieved in stoichiometric reactions compared to those in catalytic runs strongly indicates that the configuration at the metal correlates with the stereochemistry of the catalytic outcome: only if (R_{Ir},R_C)-**9** and (S_{Ir},R_C)-**9** diverge in enantioselection, it is possible to achieve zero ee working with R_{Ir},R_C/S_{Ir},R_C mixtures and up to 93.5% ee using pure (S_{Ir},R_C)-**9** as catalyst.

4.1 Recycling Experiments

Pure (S_{Ir},R_C)-**9** is a highly enantioselective catalyst for the DC reaction between methacrylonitrile and nitrones **IV** and **V**, but only stoichiometric amounts of the



Scheme 22 Recycling experiments

product can be prepared in high enantioselectivity. To increase the ratio adduct/catalyst without loss of ee, recycling experiments in repetitive batch mode have been carried out. Scheme 22 shows the three steps of the procedure developed. In the first step, 5 equivalents of nitrone were added to diastereopure (S_{Ir},R_{C})-**9**. After the required reaction time, excess of nitrone was extracted in Et_2O/CH_2Cl_2 to avoid the simultaneous presence of nitrone, alkene, and catalyst in the reaction medium. Adduct was dissociated from the iridium complex by adding 20 equivalents of alkene in the second step. Simultaneously, a (R_{Ir},R_{C}, S_{Ir},R_{C})-**9** mixture was formed. The adduct and the excess of nitrile were extracted in Et_2O/CH_2Cl_2, and from the extract, the adduct was recovered. In the third step, the (R_{Ir},R_{C}, S_{Ir},R_{C})-**9** mixture was allowed to epimerize to (S_{Ir},R_{C})-**9**, which restarts a further catalytic run. Following these procedure, in a second catalytic run, (S_{Ir},R_{C})-**9** renders the cycloadduct in 93.5% yield and 92% ee. As it can be seen, both yield and ee are essentially maintained.[1]

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[1] With the homologous rhodium complex (S_{Rh},R_{C})-[(η^5-C_5Me_5)Rh{(*R*)-Prophos}(methacrylonitrile)]$(SbF_6)_2$ as catalyst, up to ten consecutive catalytic runs have been performed for the reaction between methacrylonitrile and the nitrone 3,4-dihydroisoquinoline *N*-oxide (**V**). Yield decreases from 97% (first run) to 84% (tenth run) and enantioselectivity remains essentially constant at 90% ee.

5 Conclusions

Diastereomerically pure iridium complexes of the formula $[(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(\text{activated alkene})](SbF_6)_2$ (activated alkene = enal, methacrylonitrile) are active, and selective catalysts for the DCR between one point binding activated alkenes and nitrones. Enals coordinate to the metal in a completely diastereoselective way with a restricted geometry. From the point of view of the selectivity, a key point in enal coordination is the establishment of CH/π-attractive interactions between the CHO aldehyde proton and one (*R*)-Prophos phenyl group. This interaction fixes the methacrolein rotamer around the M–O bonds and renders the system enantioselective.

The above-mentioned complexes are the sole iridium derivatives applied to DCR, and the cycloaddition of nitrones to enals or methacrylonitrile, the unique process studied. We think that iridium-based catalysts are underrepresented in 1,3-dipolar cycloaddition chemistry. For example, no iridium (I) systems have been developed to this end. It can be anticipated that the (bidentate ligand)Ir(I) fragment could be active (and stereoselective if chiral bidentate ligands are used) in DCR such as those involving azomethine ylides.

In summary, the development of 1,3-dipolar cycloadditions will continue during the next years and the potential of iridium-based catalysts in this field is far from being exhausted.

Acknowledgments The authors thank financial support from Ministerio de Ciencia e Innovación (MICINN, Spain) and FEDER (Grant CTQ2009/10303BQU) and MULTICAT, Consolider Ingenio-2010 (CSD2009-00050).

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