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C-H Activation

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Aims and Scope

The series *Topics in Current Chemistry* presents critical reviews of the present and future trends in modern chemical research. The scope includes all areas of chemical science, including the interfaces with related disciplines such as biology, medicine, and materials science.

The objective of each thematic volume is to give the non-specialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights of interest to a larger scientific audience are emerging.

Thus each review within the volume critically surveys one aspect of that topic and places it within the context of the volume as a whole. The most significant developments of the last 5–10 years are presented, using selected examples to illustrate the principles discussed. A description of the laboratory procedures involved is often useful to the reader. The coverage is not exhaustive in data, but rather conceptual, concentrating on the methodological thinking that will allow the non-specialist reader to understand the information presented.

Discussion of possible future research directions in the area is welcome.

Review articles for the individual volumes are invited by the volume editors.

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

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Authors and editors wish to dedicate this volume to the memory of Keith Fagnou

Preface

During the past several decades, extensive investigations into transition metal-catalyzed carbon–hydrogen (C–H) bond activation processes have greatly improved our understanding of how to cleave and functionalize inert C–H bonds effectively. In addition to enriching the discipline of organometallic chemistry in a general sense, researchers in this field have made tremendous strides toward harnessing this knowledge to develop novel chemical technologies that will benefit humankind in practical ways. For example, the selective oxidation of methane and related petroleum components is recognized as a significant challenge with wide-ranging commercial implications. In particular, the refinement of this technology would change how bulk chemicals are produced industrially and would enable alternative strategies for utilizing natural energy resources in an economical fashion.

In more recent years, it has become evident that the direct formation of carbon–carbon and carbon–heteroatom bonds from unactivated C–H bonds *via* C–H activation has enormous potential for advancing the field of chemical synthesis. In accordance with the basic principles of retrosynthetic analysis, C–H activation reactions can drastically shorten possible routes to a given natural product by providing unprecedented disconnections in both the early and late stages. This volume contains valuable and insightful contributions from several leading experts in this area. Collectively, these chapters focus on relevant progress during the past 5 years toward the development of increasingly versatile and efficient C–H activation reactions that have the potential to be broadly applicable in the realm of organic chemistry.

Though the recognition that C–H activation could potentially be a uniquely powerful synthetic tool dates back several decades, there has nevertheless been a marked increase in the depth and breadth of research in recent years, including both the development of a diverse array of catalytic C–H activation reactions and the implementation of the novel transformations as key steps in campaigns toward natural products. Although this volume focuses on more recent progress, the authors of each section have attempted to situate these contemporary investigations within the context of previous work by presenting a historical view of the subject that they are discussing. In spite of these efforts, unfortunately not all of the important contributions could be included in this short volume.

The volume begins with a chapter by M. Lautens on a novel class of synthetic transformations built upon the logic of the Catellani reaction, a Pd(0)-catalyzed, norbornene-mediated arene alkylation/olefination. Within this broad theme, this section focuses on recent innovative advances in improving the versatility and overall synthetic usefulness of this reaction. The following chapter by K. Fagnou features insightful discussion of another prominent catalytic system (Pd(0)/ligand and Ar–X) for C–H arylation. This transformation has a relatively long history; however, Fagnou has made numerous new contributions toward better understanding this reaction mechanistically and expanding its synthetic scope. In this chapter, a particular emphasis is placed on the arylation of heterocycles, which may be of special interest to medicinal chemists. In the next chapter, O. Daugulis highlights recent discoveries in the area of C–H arylation using Pd(II) and Cu(II) catalysts. The author is a leading expert on this topic and is responsible for many of the advances in arylation chemistry with ArI during the past 5 years. Subsequently, M.J. Gaunt comprehensively reviews the development of C–H arylation and olefination of indoles and pyrroles. In this section, the discussion of the recent, exciting developments from the Gaunt laboratory demonstrating regiochemical control through careful tuning of protecting groups is especially enjoyable to read. Describing a slightly different strategy for C–H arylation, R.C. Larock relates an interesting story on the development of remote C–H arylation through spatial migration of a preformed aryl–metal bond, many of the examples of which are based on contributions from his own group.

This section is followed by discussion of recent developments in arene/arene coupling, a somewhat ambitious research endeavor to forge biaryl carbon–carbon bonds with high selectivity in the absence of any prefunctionalized substrates. S.L. You, one of the major contributors in this area, provides an exceptionally thorough account on this matter. Although arene/arene homocoupling catalyzed by both Pd and Cu catalysts is well documented, recent advances show promise for coupling two different arene partners to one another. The discussion of Pd-catalyzed C–H functionalization is then closed by a beautiful chapter by G.S. Liu on allylic C–H functionalization, which includes almost every major advancement in the past 5 years, especially some highlights from M.C. White's laboratory.

The volume then shifts direction slightly to discuss C–H functionalization reactions by other transition metal catalysts. L. Ackermann covers many of the most important developments in Ru-catalyzed C–H arylation. Although Ru-catalyzed C–H activation reactions reported by Murai and Kakiuchi are among the earliest catalytic C–H activation reactions for carbon–carbon bond formation, Ackermann focuses on an exciting new development in Ru-catalyzed C–H arylation with the assistance of various ligands reported from his own laboratory and others. Next, K. Itami introduces recent work in catalyst design and highlights synthetic applications of Rh(I)-catalyzed C–H arylation reactions. Seminal work from R.G. Bergman and J.A. Ellman is highlighted. In this chapter, the use of C–H activation in material science speaks to the emerging opportunity for this technology in that research area. In the next chapter, C.J. Li describes an oxidative cross-dehydrogenative coupling (CDC), a process mainly developed in his own laboratory. In this context, the ability to use substrates containing allylic C–H bonds could potentially render this reaction a powerful tool in synthesis.

Finally, this volume closes by covering the most advanced field of C–H functionalization chemistry in terms of synthetic applications in complex settings, namely Rh(II)-catalyzed carbene and nitrene insertion processes. First, H.M.L. Davies gives a comprehensive outlook of the state of the art in carbene insertion chemistry, while providing insights into his trademark donor–acceptor concept and the remarkably efficient Davies catalyst. Early contributions from M.P. Doyle and others are also discussed. Next, J. Du Bois presents a beautiful story concerning the development of stereoselective nitrene insertion and recent advances therein. Highly complex natural products, including landmarks such as (-)-tetrodotoxin, have been made using Du Bois's C–H amination reactions.

As editors of the volume, we hope that 12 chapters herein from leading experts in the field provide an overview of the cutting edge in contemporary C–H functionalization. At the same time, many of the authors have also generously offered their views on future research trends, which we hope will be useful for our colleagues in the field. We are grateful to H. Yamamoto for encouraging us to take on this task. Additionally, we would like to thank graduate student K.M. Engle for his diligent editing efforts. We are deeply indebted to all contributors for providing such incredibly organized and insightful articles. J.-Q. Yu also wishes to thank colleagues in the NSF Center on Stereoselective C–H Functionalization for all of their inspiration and support.

Authors and editors wish to dedicate this volume to the memory of Keith Fagnou.

Spring 2010

Jin-Quan Yu
Zhangjie Shi

Obituary

Keith Fagnou was a man of diverse and exceptional abilities. He was born in Saskatoon, Saskatchewan on June 27, 1971 and attended the University of Saskatchewan where he graduated with a degree in Education. He taught secondary school but realized his true passion lay in research. Keith moved to Toronto and took third and fourth year courses in Chemistry to be accepted into the graduate program. It was in just such a course that I first met Keith.

Keith approached me about working in my laboratory for the summer and as he already had an undergraduate degree, he was not eligible for any summer scholarships. I looked over his transcript and noticed that he was a terrific student and had done particularly well in my course. His alternative was to go back to the Navy where he would be on the high seas navigating huge boats. In spite of some concerns about my finances, I offered him a fully funded position and for both of the rest was, as they, history.

Keith had no research experience so I teamed him up with Tomislav Rovis, now Stille Professor at Colorado State University. Tom was a senior student in my group at that time and about to head off to Harvard and work with Dave Evans. Tom suggested Keith investigated a long-standing problem in our group, namely adding heteroatoms to strained heterobicyclic systems. Tom had come across a paper suggesting rhodium might be a suitable metal and Keith dutifully set out to find out if this was the answer. After a few months, the first results trickled in and not only was rhodium a suitable catalyst, but also the stereochemistry of the addition was opposite to what would have been predicted based on the earlier work. Keith had a project and was on a mission to get results. Coincidently, I had lectured at an OMCOS meeting in Göttingen and met a scientist from Ciba Speciality Chemicals who asked me if we might be interested in trying the Josiphos family of ligands. He sent some for Tom to try: While they failed to improve his reaction, they were available to Keith who showed that they gave excellent selectivity.

Keith was admitted to our graduate program and was keen to stay in Toronto since his wife was a student in the medical school. Her busy schedule gave Keith the maximum time available to undertake his masters and doctoral studies, and he made the most of this time. His first paper, published in *JACS* in 2000 with Tom Rovis, described the enantioselective ring opening of oxabicycles using alcohols as nucleophiles. He followed this up with a paper coauthored by an undergraduate, Mark Taylor, now my colleague at the University of Toronto, on the ring opening with phenols as nucleophiles. Ultimately, Keith published 18 papers while a member of my group – certainly a record. Among the more notable were widely cited reviews on "Rhodium-Catalyzed Carbon–Carbon Bond Forming Reactions with Organometallic Compounds" which appeared in *Chemical Reviews*, "Halide Effects in Transition Metal Catalysis" in *Angewandte Chemie*, and "Transition Metal-Catalyzed Enantioselective Ring-Opening Reactions of Oxabicyclic Alkenes" coauthored with Sheldon Hiebert that appeared in *Accounts of Chemical Research.* In addition to his time in Toronto, Keith spent time at AstraZeneca in Montreal where he got his first taste of life in the pharmaceutical industry and the wonder of Montreal bagels which were his main source of nutrition during this period. Edward Roberts, now at Scripps, and Christopher Walpole were important influences during this stay.

Keith left the group and took up a position at the University of Ottawa, but not before winning many awards in recognition of his success during his PhD. Among the most notable were the NSERC PGS, Boehringer Ingelheim Prize, Governor General's Gold Medal, John Charles Polanyi Prize, and an NSERC PDF to work with Robert Grubbs. A confluence of circumstances led him to seek an academic job immediately following graduation rather than following through on the postdoc, and I had no trouble offering my strongest support. In fact given his interest in C–H activation, it was probably vital that he took an academic job right away: many others were entering this field and Keith might have found himself a bit behind the pack had his start been delayed by 2 years. In any case, Keith certainly made the most of his time in Ottawa.

Over the next 5 years, Keith made a remarkable impact on the field of direct arylation chemistry. The systematic manner in which his group approached one of the "holy grails" of organic synthesis (namely, carbon–carbon bond formation by functionalization of inert C–H bonds) is a testament to the extraordinary "vision" of this young scientist. His group's first paper, published in *JACS* in 2004, describes palladium-catalyzed intramolecular direct arylations under mild conditions. Over the next 5 years, the Fagnou group built upon this result to develop an arsenal of synthetic methods than enable the effective, regioselective construction of C–C bonds from unactivated precursors. One of his most influential papers appeared in *Science* in 2007 and reported on the direct, oxidative cross-coupling of arenes without functionalization of either partner. I remember the day Keith called to share the news that this paper was accepted and the happiness in his voice.

Understanding the mechanistic details of the C–H activation step was a major thrust of Keith's research, and information from these studies played a key role in the methods developed by his coworkers. The Fagnou group's mechanistic studies of C–H arylation reactions are among their most highly cited work, and represent a contribution whose impact will likely be felt for years to come. In total, some 40 papers have or will appear in many of the best journals and will serve to summarize his independent career. His research program was on a rapid upward trajectory: in 2008, his group published five papers in *JACS*. He remained a modest and self-effacing individual even as his international profile rose. He was invited to be a Visiting Professor in Paris in 2008 and we exchanged messages reminiscing on our experiences in the City of Light. One comment stands out as he reported that he felt he should have been born a wealthy Parisian rather than a kid from Saskatoon. I could do nothing but smile and agree having grown up in Hamilton.

Keith managed to make the job of being a professor look easy. He was beloved by his students and began attracting the best students in the country to his group. The "Fagnou Factory" as they called themselves worked hard and enjoyed the environment Keith created and sustained. His first PhD managed a job at Merck Frosst without a postdoc, a remarkable feat attesting to the educational rigor of Keith's labs. Keith was also a superb lecturer (in both English and French); in fact, when I was away I always asked him to fill in for me in spite of knowing the students might have wished I was away more often after hearing him give clear and well-planned lectures. He was equally skilled at research presentations and on one occasion, he lectured for me at Pacifichem in Hawaii and I received a flurry of emails the next day, indicating that his lecture was much appreciated and the symposium organizers were glad he had come in my place! Apparently, I was told he was careful to avoid looking too suntanned on his return but he and Sheldon Hiebert were very grateful I had sent them to Hawaii in December.

Keith was selected for many awards in recent years, including an A.P. Sloan Fellowship, an Eli Lilly Granteeship, Amgen Young Investigator Award, Astra-Zeneca Award, Merck Process Research Award, University of Ottawa Researcher of the Year, and most recently the OMCOS Award. He was the only Canadian to be so honored and the list of prior winners (Kobayashi, Carriera, Fu, Ma, Hartwig, and Nozaki) is a Who's Who of the field of catalysis. At the time of his death, he held the position "University of Ottawa Research Chair in Novel Catalytic Transformations."

Keith began to enjoy the fruits of his labors and everywhere I went I heard Keith had just visited or was coming soon. People who visited our department always mentioned a rising young star in Ottawa who they met at Gordon Conference or international conference. He began to travel regularly and to take his family when he could. The past summer he took his young son Zachary back to Paris for a father–son trip. His wife Danielle Gervais-Fagnou, now an MD in Ottawa, his daughter Clara, and his youngest Samuel were never far from his thoughts and he regularly spoke about coaching his son's hockey team or heading out on an outdoor adventure. Keith paid attention to the needs of his family and still had a life outside the lab and home. He played hockey, jogged, and generally took good care of himself. His unexpected death on November 11, 2009 was a shock to all who knew and cared about this gentle, kind, funny man with an irreverent sense of humor. The reaction of the community speaks to the high regard held for Keith and the number of lives he touched. The world has lost a great person, a warm and loving husband and father, and a scientist whose accomplishments had already put him front and center of an active and important field. Sadly, we will not have the chance to see the full measure of his contributions to science.

December 15, 2009 Mark Lautens and Mark Taylor

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Synthesis in the Key of Catellani: Norbornene-Mediated *ortho* C–H Functionalization

Andrew Martins, Brian Mariampillai, and Mark Lautens

Contents

Keywords Palladium • C-H • Activation • Norbornene

1 Introduction

In the late 1990s Catellani reported a remarkable palladium-catalyzed domino reaction [1] in the presence of norbornene, in which aryl iodides were alkylated at the *ortho* positions by alkyl halides followed by a Mizoroki-Heck reaction to afford

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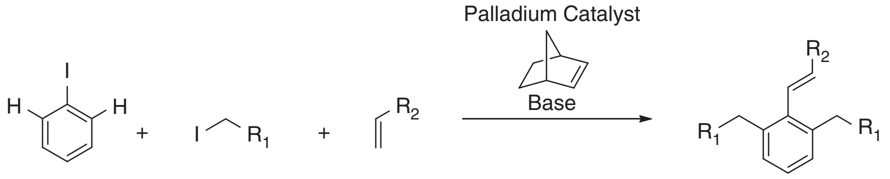
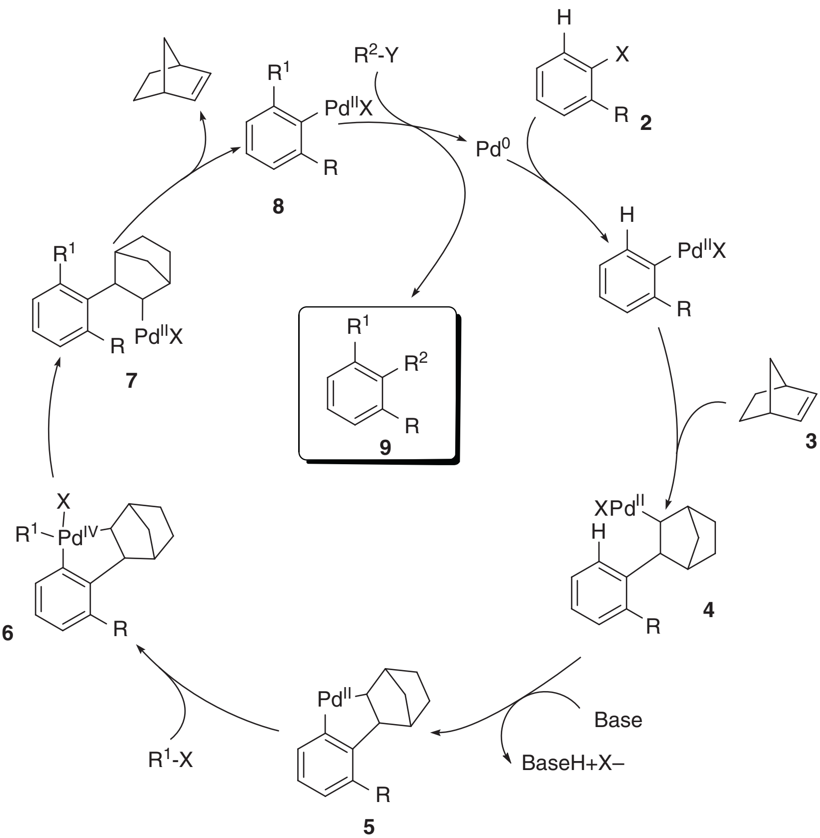
products of type **1** (Scheme 1) [2–4]. The process allowed for the construction of up to three carbon–carbon bonds in a single reaction using simple, commercially available starting materials. We called this process the Catellani reaction, and in the past decade considerable attention has been focused upon unlocking its synthetic potential. This review will primarily focus upon the mechanistic aspects of the Catellani reaction, followed by an overview of the synthetic scope of molecules currently accessible with this technology.



Scheme 1 Initial report of the Catellani reaction

2 Mechanism of the Catellani Reaction

The mechanism of the Catellani reaction revolves around the ability of norbornene to initiate a competitive reaction pathway and form a rigid catalyst scaffold which positions palladium in proximity to a C–H bond. The unique reactivity of norbornene is accompanied by a catalytic cycle involving multiple oxidation state transitions of palladium between (0), (II), and potentially (IV). The proposed mechanism for the Catellani reaction of an aryl iodide containing a pre-existing *ortho* functional group is shown in Scheme 2. Initial oxidative addition of palladium(0) into the mono-*ortho*-substituted aryl iodide (**2**) is followed by carbopalladation of norbornene (**3**) to give norbornylpalladium(II) intermediate **4**. With no possibility of *syn*-*β*-hydride elimination, an electrophilic metalation at the *ortho* position occurs, followed by deprotonation and rearomatization to form palladacycle **5**. This palladium(II) complex can then undergo reaction with alkyl or aryl halides to form palladium(IV) complex **6**. Reductive elimination forms the *ortho* C–C bond and generates norbornylpalladium(II) intermediate **7** (if there is no pre-existing *ortho* substituent, the cycle repeats to alkylate the other *ortho* position). With both *ortho* positions substituted, extrusion of norbornene via de-carbopalladation (β-carbon elimination) is favored due to the increased steric strain of **7**, to form arylpalladium(II) species **8**, which can then undergo a traditional palladium catalyzed coupling reaction to yield the desired product **9** and regenerate the palladium(0) catalyst. Each step of this complex catalytic cycle will explained in further detail in the following sections.



R1 = Alkyl, Aryl
R2 = Aryl, Alkenyl, H, CN
Ligands, solvent molecules and stereochemistry omitted for clarity

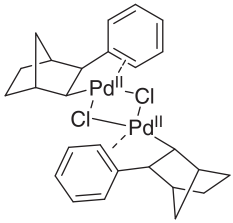
Scheme 2 Generalized reaction mechanism of the Catellani reaction

2.1 Oxidative Addition

The first step of the Catellani reaction involves the oxidative addition of a palladium(0) species into an aryl halide bond to generate an arylpalladium(II) species [5, 6]. Catellani's initial reports employed the pre-formed phenyl-norbornylpalladium(II) dimer [7] (PNP dimer) (**10**, Fig. 1) as a pre-catalyst which could directly enter the catalytic cycle and generate a palladium(0) species after one catalyst turnover [4].

Alternatively, the palladium(0) species may be formed in situ via reaction of a palladium(II) salt with an excess of phosphine [8–10] or other reducing agents

Fig. 1 PNP dimer catalyst



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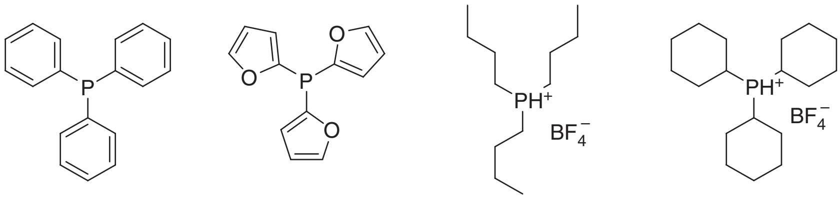


11 **12** **13** **14**

Fig. 2 Phosphine ligands used in the Catellani reaction

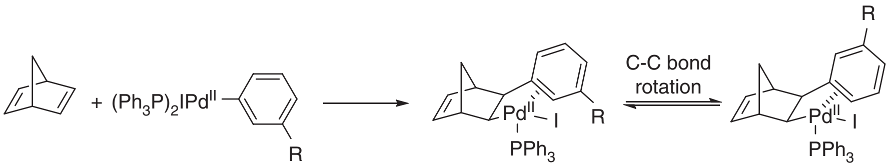
(DMF, DMA) [11]. The use of phosphine ligands in the Catellani reaction was developed by Lautens, and in general shows greater functional group tolerance. Both $Pd(OAc)_2$ and $PdCl_2$ may be used in with a variety of ligands (Fig. 2) including PPh_3 (**11**), TFP (**12**), *n*-Bu_3PHBF_4 (**13**), and Cy_3PHBF_4 (**14**). While **11** and **12** are generally considered air stable, the use of tetrafluoroborate phosphonium salts **13** and **14** developed by Fu [12] provide an ease of handling for the otherwise sensitive alkyl phosphines. Generally, bidentate phosphines show much poorer activity in the reaction. Phosphine-free conditions have also been utilized in the presence of highly coordinative solvents such as DMF. Once a suitably ligated palladium(0) complex has been formed, it can then undergo oxidative addition with aryl and/or heteroaryl iodides, bromides, and chlorides, and continue through the catalytic cycle.

2.2 *Carbopalladation of Norbornene*

After oxidative addition to the aryl iodide occurs, two possibilities exist; the resultant arylpalladium(II) species can (1) undergo a traditional palladium-mediated coupling reaction or (2) perform a carbopalladation of norbornene which would generate norbornylpalladium(II) complex **4** (Scheme 2) and initiate the desired catalytic cycle. Due to the high reactivity associated with norbornene (strain energy = 21.6 kcal mol^{-1}) [13] and its often superstoichiometric quantities, the desired reaction pathway can be favored. As it is not incorporated in the final product, norbornene can be regarded as both a directing group for the functionalization of the *ortho* position(s) and as a temporary protecting group for the *ipso* carbon of the arene.

The reactivity of arylpalladium(II) species with highly strained bicyclic alkenes such as norbornene has been studied over the past three decades. The group of Horino was the first to look at the reaction of arylpalladium(II) complexes with norbornene [7] via carbopalladation as an extension to the pioneering work of Mizoroki [14] and Heck [15]. Their work gave recognition to the fact that, in rotationally restricted systems such as bicycles, β-hydride elimination would be suppressed because of the bicycles' inability to provide a hydrogen atom in a *syn* relationship to palladium(II) [16]. Catellani has examined the η^1 and η^2 bonding modes of the arene with complexes similar to **4** using both experimental and computational methods [17]. By placing methyl substituents at various positions around the aromatic ring and monitoring the changes in bonding, it was found that the palladium center receives π electron density from the arene mainly through the *ipso* carbon atom.

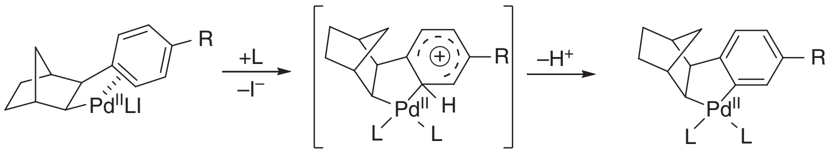
The structures of several palladium-norbornyl complexes were determined by X-ray analysis and NMR spectroscopy [18]. Norbornadienyl complex **15** (R=H) showed that the palladium has a square planar geometry (Scheme 3). The phenyl group and the palladium center are in a *syn* orientation to one another, and palladium is situated on the *exo* face of the norbornenyl group, as would be expected from preferential addition to the least sterically hindered face. Additionally, the phenyl group is bound to the palladium center in a η^2 bonding mode with the C_{ipso}–C_{ortho} linkage being unsymmetric. The Pd–C_{ipso} and Pd–C_{ortho} bond distances were measured to be 2.43 and 2.59 Å, respectively. Solution NMR showed that rotation of the phenyl group is facile at temperatures higher than 40 °C on the NMR time scale, making the two *ortho* and the two *meta* carbons and their hydrogens equivalent. At temperatures lower than −40 °C the rotation is impeded and the spectral patterns are consistent with those of the X-ray structure.



Scheme 3 Carbopalladation of the norbornyl scaffold

2.3 Palladacycle Formation

Due to the inability of the norbornylpalladium(II) species **4** to undergo a *syn* β-hydride elimination, a variety of alternative reactions can take place. Catellani has shown a number of reactions are possible including alkyne addition [19] and carbonylation [20]. In addition, and perhaps the most intriguing reaction of complex **4** is the formation of the five membered palladacycle **5** in the presence of mild bases. The norbornyl scaffold places palladium in the optimal position for a C–H functionalization reaction, which is believed to occur via electrophilic aromatic substitution (EAS) [21] at the *ortho* aromatic carbon of **4**. This process of carbon-palladium bond formation is proposed to occur through a Wheland-type intermediate **16** with temporary loss of aromaticity (Scheme 4) [22]. Catellani examined effect of electron-withdrawing and electron-donating substituents on the rate of palladacycle formation by ^{1}H NMR, and found that 50% conversion of **17** to **18** occurred in 10, 100, and 240 min for R=OMe, H, NO_2, respectively (Scheme 5). This trend is typical for substituent effects in electrophilic aromatic substitution reactions where the rate-determining step is formation of the Wheland-type intermediate [23].



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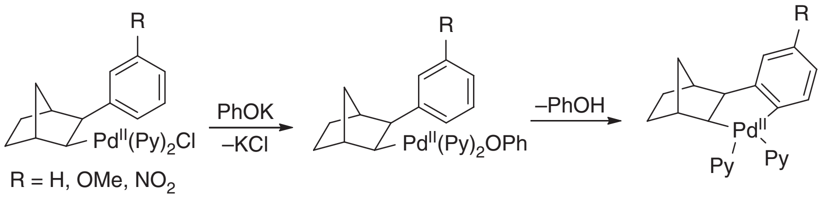
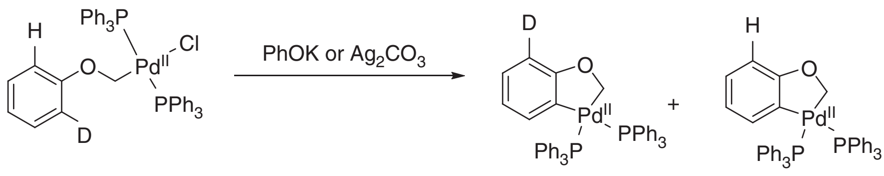
Scheme 4 Palladacycle formation via electrophilic aromatic substitution



17 **18**

Scheme 5 Evidence for electrophilic aromatic substitution

Echavarren has also studied intramolecular *ortho* C–H functionalization of aromatics by alkylpalladium(II) species (Scheme 6). In a system where the aromatic ring is deuterated at one of the *ortho* positions, the production of a statistically equivalent mixture of both deuterated (**19**) and nondeuterated (**20**) products was observed. The absence of a kinetic isotope effect supports an EAS mechanism in which deprotonation is not rate limiting [24]. The EAS mechanism for C–H activation by an alkylpalladium(II) species is in stark contrast to the mechanism of C–H functionalization reactions by vinyl- or arylpalladium(II) species, where proton abstraction has been determined to be rate limiting [25]



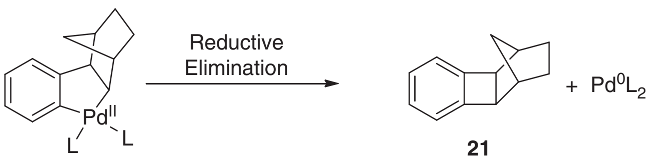
19 **20**

19:**20** = 1:1

Scheme 6 Evidence for a rate-determining Wheland-type intermediate

2.4 Oxidative Addition to Palladacycle

Once palladacycle formation has occurred, a number of possibilities exist for its reaction. A side product often seen in Catellani reactions is cyclobutane (**21**) formation resulting from a reductive elimination of the palladacycle (Scheme 7). In fact, under optimized conditions it is possible to achieve good yields of the cyclobutane products [26]. However, the focus of this section will be to examine the reaction of the palladacycle with alkyl and aryl halides.



21

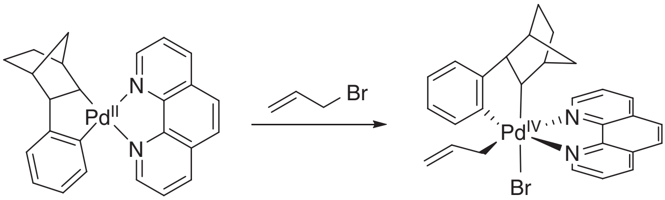
Scheme 7 Cyclobutane formation

2.4.1 Palladacycle Reaction with Alkyl Halides

In the presence of alkyl halides, palladacycle **5** reacts at the C–X bond to generate a proposed palladium(IV) species such as **6**. In recent years, palladium(IV) species have become popular catalytic intermediates in the scientific community, and are generally accessed via oxidation of palladium(II) to palladium(IV) with strong oxidizing agents [27, 28]. The formal oxidation of **5** to **6** using alkyl halides would be one of the mildest methods to accomplish this feat.

Since the first X-ray crystal structure of a palladium(IV) complex was published by Canty [29, 30], a number of groups have undertaken the study of these relatively uncommon intermediates. In an effort to elucidate the role of palladium(IV) and palladium(II) intermediates in the reaction mechanism, Catellani prepared a number of isolable palladacycle complexes in both the (II) and (IV) oxidation states using 1,10-phenanthroline as the ligand (Scheme 8) [31]. Catellani successfully isolated palladium(IV) palladacycle **22**, which was subsequently characterized by

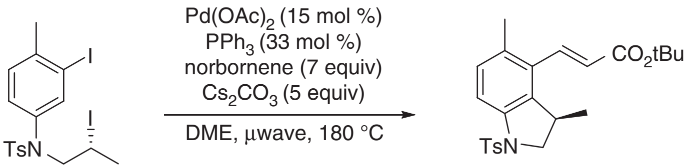
NMR spectroscopy. Complex **22** was formed selectively by oxidative addition of allyl bromide to palladium(II) palladacycle **21**. This structure is believed to result from *cis* oxidative addition of allyl bromide to palladacycle **21**.



21 **22**

Scheme 8 Isolation of palladium(II) and palladium(IV) metallacycles

The stereochemistry of oxidative addition to the palladium(II) palladacycle was studied by Lautens using an enantioenriched secondary alkyl halide (Scheme 9) [32]. From alkyl halide **23**, product **24** was obtained, showing a net inversion of stereochemistry [33–35]. Previous work by Stille showed that reductive elimination from palladium(IV) occurs with retention of stereochemistry [36], suggesting that oxidative addition occurs with an inversion of stereochemistry. This corresponds with the generally accepted S_N2 mechanism for the reaction of palladium(0) with alkyl halides [37, 38].



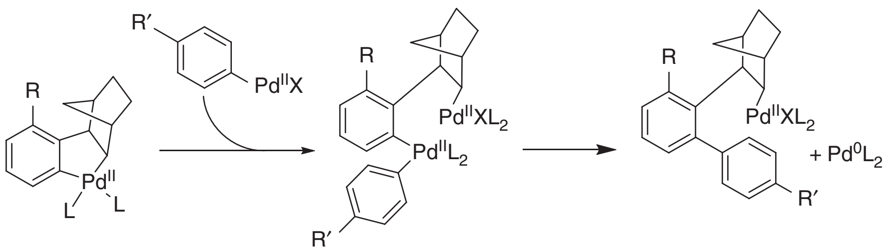
23
80%ee

24
63%ee

Scheme 9 Stereochemistry of oxidative addition

2.4.2 Palladacycle Reaction with Aryl Halides

Catellani found that the interaction of palladacycles such as **5** with aryl halides led to the incorporation of the aryl group in a manner analogous to alkyl halides [39]. A similar mechanism could be proposed for the oxidative addition of aryl halides to palladacycles such as **5** to generate a palladium(IV) species, although to date there is no direct evidence for this pathway. An alternative mechanism has been put forward by Echavarren which involves transmetallation between two palladium centers [40], generating intermediate **25** and avoiding the need for a palladium(IV) species in the arylation reaction (Scheme 10). Computational studies found that a transmetalation between two palladium centers would be a lower energy pathway. However, these results were found to be quite sensitive to the ligands and solvation of the complexes. Nevertheless, the excellent yields and selectivities observed for the *ortho* arylation chemistry suggests that, whichever mechanism is taking place, there seems to be an inherent difference in reactivity between palladium(0) and palladium(II). Based upon observations by Catellani, both electron rich and electron deficient aryl iodides preferentially react with palladium(0), while only electron deficient aryl iodides and bromides react with palladium(II) palladacycles such as **5** [41].

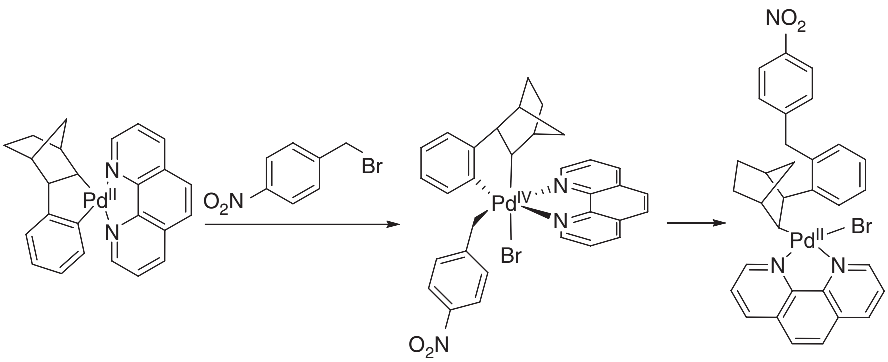


25

Scheme 10 Proposed transmetallation mechanism for aryl transfer

2.5 Reductive Elimination from Palladacycle

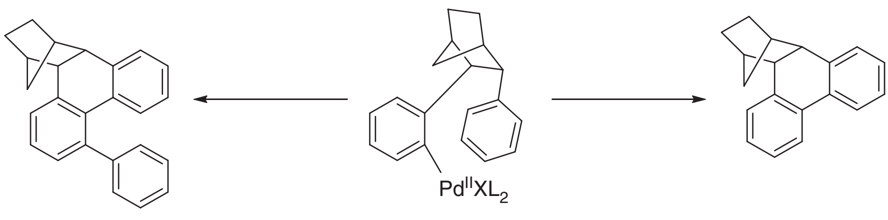
After an alkyl or aryl halide reacts with a palladacycle such as **5**, there is a difference in the selectivity of the reductive elimination step which forms an sp^2–sp^3 bond (*ortho* alkylation) or an sp^2–sp^2 bond (*ortho* arylation). The reductive elimination to form an sp^2–sp^3 bond will be examined first. Catellani has reported the isolation and crystal structure of palladium(II) complex **28**, presumably derived from oxidative addition of *p*-nitrobenzyl bromide to **26** followed by reductive elimination from **27** (Scheme 11) [42]. The reductive elimination step is believed to involve initial rearrangement of the ligands so that the coupling groups are in an axial-equatorial arrangement with respect to the plane containing phenanthroline, rather than an equatorial *cis* position. This rearrangement avoids the need for an unlikely N–Pd–N widening and likely occurs by ejection of the halide followed by its reintroduction in the correct orientation. Although this rearrangement occurs in the model system, the actual catalytic system may be much more flexible due to the presence of monodentate phosphines or solvent molecules as ligands. It should be noted that reductive elimination to form an sp^3–sp^3 bond between the alkyl chain and norbornyl group is disfavored and is not observed.



26 **27** **28**

Scheme 11 Reductive elimination from an alkylaromatic palladium(IV) metallacycle

In the case of sp^2–sp^2 bond formation, the situation is more complicated. In order to favor aryl–aryl (sp^2–sp^2) coupling over norbornyl-aryl (sp^3–sp^2) coupling, a bulky *ortho* substituent on the palladacycle-containing aryl must be present to achieve transfer of the incoming aryl group to the desired (*ortho'*) position. Catellani has coined this observation "the *ortho* effect," and it was a key finding in the development of *ortho* arylation chemistry. If the transmetallation pathway proposed by Echavarren is invoked (Scheme 10) then the selectivity of the reaction is determined during migration of the aryl group between the palladium centers. In cases where there is no pre-existing *ortho* substituent, the reaction would lead to a reductive elimination of the norbornyl–aryl bond (**29**) and further reaction to form products of type **30** and **31** (Scheme 12) [39].

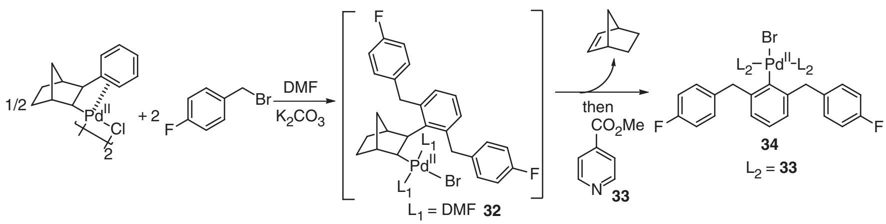


30 **29** **31**

Scheme 12 Arylation products formed in the absence of a pre-existing *ortho* substituent

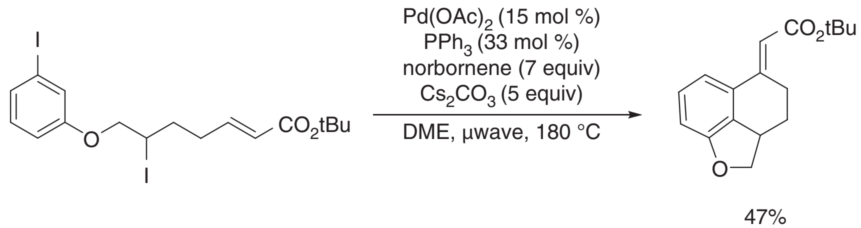
2.6 Norbornene Extrusion

In the case of the *ortho* alkylation chemistry, if no pre-existing *ortho* substituent is present, the species formed after sp^3–sp^2 coupling resembles complex **4** and, through rotation of the norbornylpalladium(II) group, the other *ortho* position can be alkylated, again through palladacycle formation. In the case of the *ortho* arylation, one *ortho* position of the aryl iodide must blocked to achieve the desired outcome of the reaction and achieve a species such as **7**. Norbornene serves as an *ortho* directing group and as a protecting group for the *ipso*-carbon, and thus *β*-carbon elimination (decarbopalladation) of norbornene ensues after these events unfold. Catellani isolated complex **34** and characterized it by NMR; which was accomplished by carrying out the reaction in the absence of a Heck acceptor and by adding methyl isonicotinate (**33**) at the end of the reaction (Scheme 13). Loss of norbornene from intermediate **32** does not occur if the aromatic moiety of phenyl-norbornane is monoalkylated. Therefore, the norbornene extrusion is likely a result of steric factors created by the two benzyl groups [43].



Scheme 13 Norbornene extrusion via β-carbon elimination

Although the belief that steric factors influence norbornene extrusion is reasonable and supported by Catellani's studies, it is entirely possible that norbornene carbopalladation and extrusion are reversible processes. If so, a species related to **4** may be trapped as the mono-*ortho*-alkylated product. Although mono-functionalization has been observed in stoichiometric studies by Catellani [31, 42], catalytic reactions generally do not afford monoalkylated products. Interestingly, Lautens has shown that in some particular systems mono-alkylation is possible, which may occur as a result of a sterically congested system (Scheme 14) [44]. This does lend some evidence to the possibility that norbornene carbopalladation and extrusion are reversible steps, and may occur between *ortho* functionalization steps.



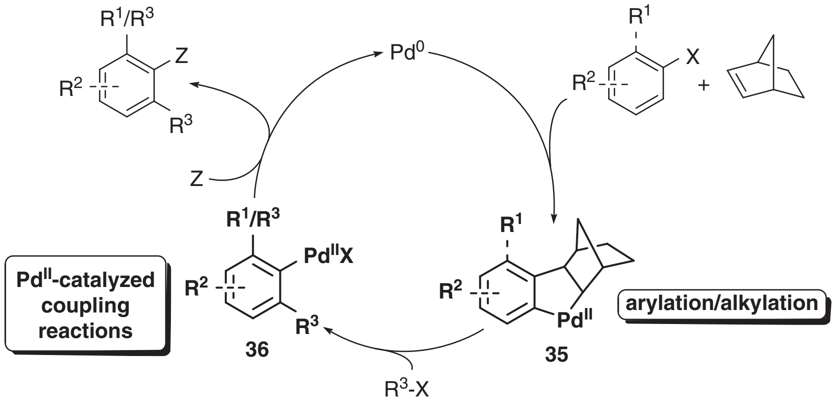
Scheme 14 Monoalkylation of an unblocked substrate

2.7 Terminating Events

The final step of the Catellani reaction involves the reaction of an *ortho*, *ortho'*-disubstituted arylpalladium(II) species such as **8** where palladium is present at the *ipso* position. This arylpalladium(II) species can be subjected to a variety of reactions in order to terminate the reaction, and re-enter the catalytic cycle. These reactions and their applications to synthesis will be discussed in the subsequent sections.

3 Synthetic Applications

Through the mechanistic investigations of Chiusoli and Catellani, a unique catalyst system emerged which can perform unprecedented aromatic transformations. Although the new reactions developed by Catellani were mechanistically and synthetically interesting, the true test of a catalytic system lies in the versatility and broad synthetic applicability it exhibits. As the simplified reaction sequence depicted in Scheme 15 illustrates, the product diversity available via the Catellani reaction stems not simply from the aryl halides used, but from the variety of catalytic reactions which the generalized palladium(II) species **35** and **36** can undergo. While palladacycle species **35** can promote aromatic alkylation and arylation reactions, the variety of palladium(II)-catalyzed reactions which species **36**, the product of *ortho*-functionalization and norbornene extrusion, can undergo is the true pivot of product diversity, and is the main focus of this section. With such a complex catalytic cycle, the reaction proposed to occur with species **36** may occur with any palladium(II) species present in the reaction, requiring the development of reaction conditions which are not only amenable to *ortho* functionalization but also allow a selective terminal coupling reaction to take place.



Scheme 15 Generalized Catellani reaction sequence and key reactive intermediates

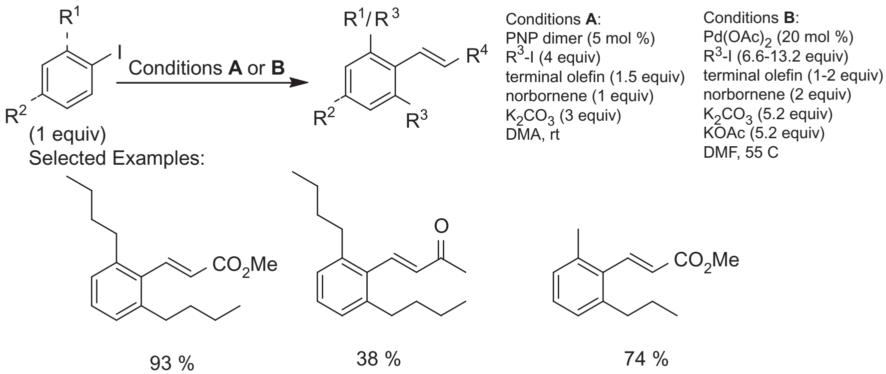
3.1 *Mizoroki–Heck Coupling*

The Mizoroki–Heck reaction [14, 15] is perhaps the most rigorously studied palladium-catalyzed coupling reaction. As the mechanism and selectivities of the Mizoroki–Heck reaction are well known, it is a prime candidate for the termination of the Catellani catalytic cycle. The carbopalladation of electron-deficient terminal alkenes (Heck acceptors) is generally thought to be the rate limiting step of the Mizoroki–Heck reaction [45]. Considering that the carbopalladation of norbornene is quite facile due to it's high bond strain of 21.6 kcal/mol, the catalytic cycle of an *ortho*-functionalization/Mizoroki–Heck reaction should proceed as desired, with low probability of a Heck acceptor reacting with other arylpalladium(II) species. The terminal Mizoroki–Heck coupling could occur either intermolecularly or intramolecularly, enabling the synthesis of a variety of products.

3.1.1 Intermolecular Mizoroki–Heck Coupling

With *ortho*-Alkylation

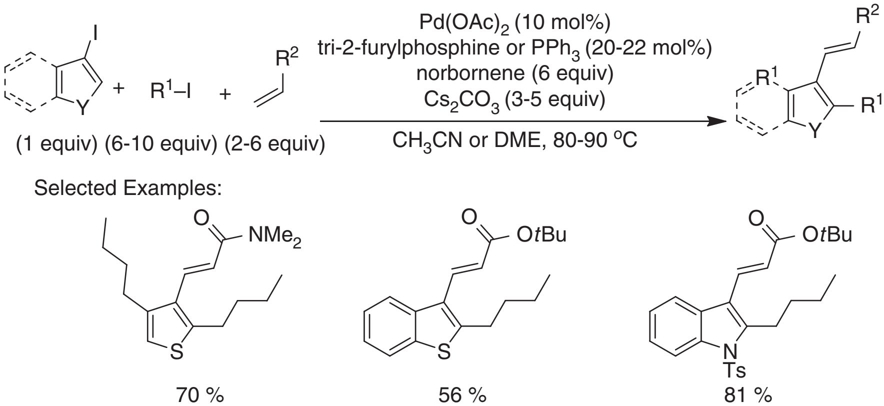
The first example of an *ortho*-alkylation/Mizoroki–Heck coupling was reported by Catellani [4] in 1997. Using the PNP dimer as a catalyst in the presence of an aryl halide, norbornene, an alkyl iodide, a terminal olefin and a base at room temperature, 1,2,3-trisubstituted benzenes (Scheme 16), were synthesized through alkylation of a palladacycle of type **35**, followed by Mizoroki–Heck coupling with an arylpalladium(II) species of type **36**. Although the synthetic scope of the reaction was limited, the importance of the report reveals an unprecedented catalytic transformation where two aryl C–H bonds are converted to sp^2–sp^3 C–C bonds followed by a standard Mizoroki–Heck coupling. The 1,2,3-trisubstitution pattern generated in the products would be very difficult to obtain via conventional methods.



Scheme 16 Synthesis of polysubstituted benzenes via *ortho*-alkylation/Mizoroki–Heck coupling

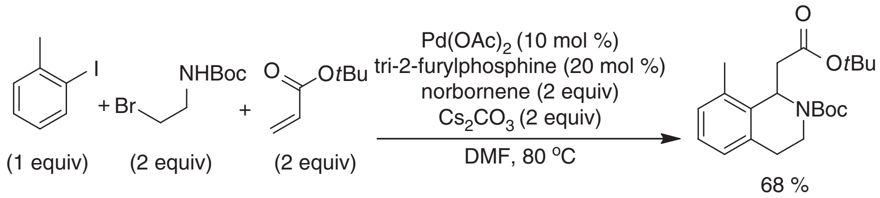
While the PNP dimer was an efficient catalyst for the *ortho*-alkylation/Mizoroki–Heck reaction, the practicality of the transformation is lessened by the fact that the PNP dimer is not commercially available, and can be quite difficult to prepare. Thus, Catellani adapted the reaction conditions to include commercially available and air-stable $Pd(OAc)_2$ as the catalyst source [46]. Under these conditions, the *ortho*-alkylation/Mizoroki–Heck coupling of aryl iodides containing a pre-existing *ortho* substituent could be carried out. The reaction required higher temperatures, and the addition of KOAc to promote the carbopalladation of norbornene [47] and encourage the *ortho*-alkylation pathway vs a direct Mizoroki–Heck coupling.

The above approach of an intermolecular *ortho*-alkylation followed by an intermolecular Mizoroki–Heck coupling was later extended to heteroaryl iodides by Lautens [48]. Using a $Pd(OAc)_2$/triarylphosphine catalyst system, 3-iodothiophene, -benzothiophene, and -indole were transformed to the *ortho*-alkylation/Mizoroki–Heck coupling products in good to excellent yields (Scheme 17). Unfortunately, 2-iodoheteroaryls were found to be poor substrates for the reaction.



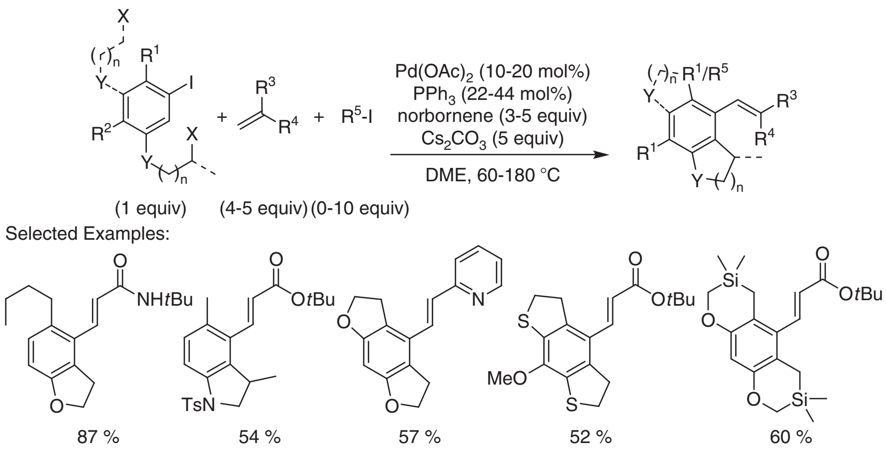
Scheme 17 Polysubstituted heteroaryls synthesized via *ortho*-alkylation/Mizoroki–Heck coupling

Seeing an opportunity to use functionalized alkyl halides which can react with the electron-deficient alkene product of the *ortho*-alkylation/Mizoroki–Heck coupling, Ferraccioli and Catellani reported the use of *N*-Boc-2-bromoalkylamines as bifunctional reagents which could undergo a subsequent intramolecular aza-Michael addition to the electron deficient alkene (Scheme 18) [49]. Although the reaction worked well for the synthesis of tetrahydroisoquinolines, the analogous reaction with a longer alkyl chain to form tetrahydro-2-benzazepines did not undergo the aza-Michael addition in situ, and required the addition of external KO*t*Bu to promote the cyclization.



Scheme 18 *Ortho*-alkylation/Mizoroki–Heck/aza-Michael reaction

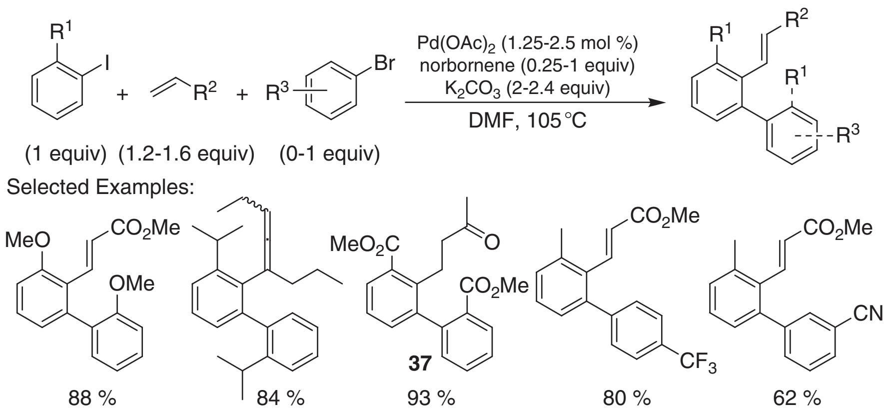
While the approach used by Ferraccioli and Catellani employed a functional group on the alkyl halide to form a heterocycle, Lautens used a different strategy where the alkyl halide is tethered to the aryl iodide through a heteroatom. This strategy effectively employs either one or two intramolecular *ortho*-alkylations, followed by intermolecular Mizoroki–Heck coupling to furnish bi- [32, 50] and tricyclic [51, 52] heterocycles (Scheme 19). Lautens was able to vary the length of, and incorporate several different heteroatoms into, the haloalkyl chain, to generate a wide variety of polycyclic heterocycles in good to excellent yields. In most cases, microwave irradiation proved to be the best heating method, enabling a rapid synthesis of a variety of molecules.



Scheme 19 Polycyclic heterocycles synthesized via intramolecular *ortho*-alkylation/Mizoroki–Heck coupling

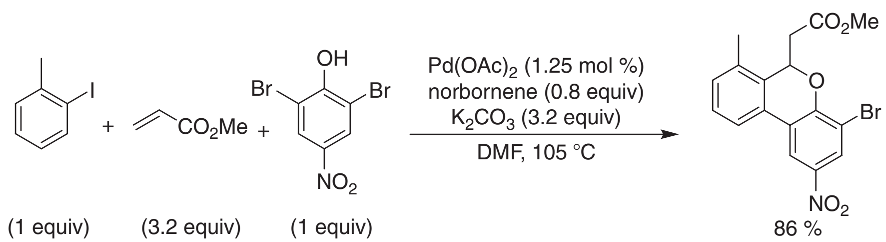
With *ortho*-Arylation

In the mechanistic studies of the reactivity of (arylnorbornyl) palladacycles [39], Catellani observed the *ortho*-arylation of the PNP dimer to generate unsymmetrical homobiaryl products. This *ortho*-arylation was combined with the Mizoroki–Heck termination reaction by Catellani to generate unsymmetrical vinyl homobiaryl products [53] in good to excellent yields (Scheme 20). When dialkylalkynes were used as acceptors, allene products were formed in moderate yields [54]. In order to access homobiaryl alkyl ketone products such as **37**, Catellani and Muzart employed allylic alcohols as the terminal alkene [55]. Catellani later found that electron-deficient aryl bromides, or electron-rich ones with a coordinating *ortho* substituent can undergo a selective, crossed biaryl coupling via *ortho*-arylation in the presence of electron-rich, *ortho* substituted aryl iodides. When combined with the Mizoroki–Heck coupling, this enabled a powerful synthesis of vinyl heterobiaryls in good to excellent yields [41].



Scheme 20 Substituted biaryls synthesized via *ortho*-arylation/Mizoroki–Heck coupling

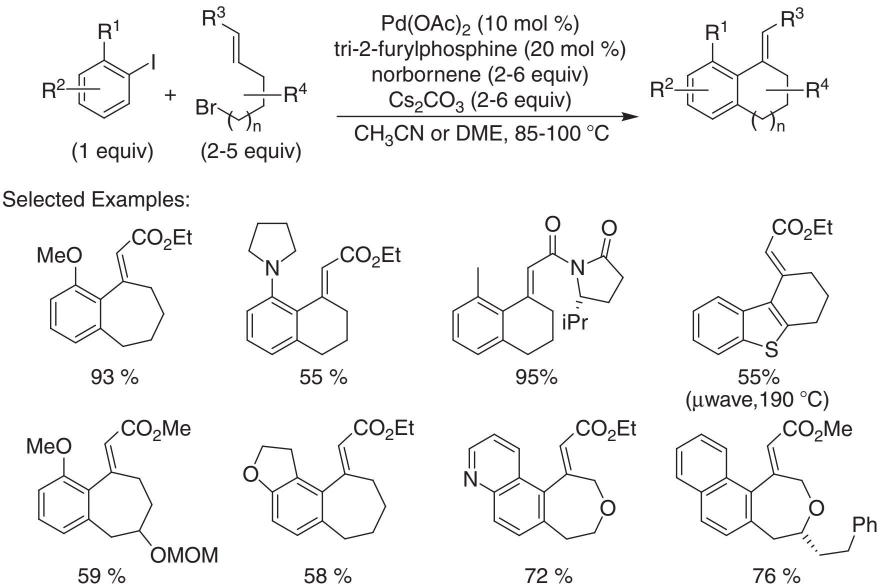
While using *o*-bromophenol as the *ortho*-arylating agent in the above sequence, Catellani found the product to be a 6*H*-dibenzopyran, the product of an *ortho*-arylation/Mizoroki–Heck coupling followed by an oxy-Michael addition of the phenol to the electron-deficient alkene. This was later developed into an efficient method for the synthesis of a variety of 6*H*-dibenzopyrans (Scheme 21) [56, 57], and is one of the most modular and effective methods to construct this interesting heterocyclic framework.



Scheme 21 6*H*-Dibenzopyrans via *ortho*-Arylation/Mizoroki–Heck coupling/oxy-Michael reaction

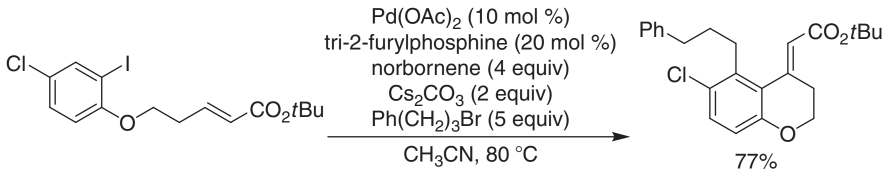
3.1.2 Intramolecular Mizoroki–Heck

The utility of bifunctional substrates as a means to make polycyclic products was explored by Lautens, who first used bromoalkylenoates as coupling partners to generate carbocyclic ring systems via intermolecular *ortho*-alkylation followed by an intramolecular Mizoroki–Heck coupling (Scheme 22) [58, 59]. The carbocyclic products could be obtained in excellent yields, and the reaction conditions showed wide functional group tolerance. Lautens then explored the effect of carbon, and heteroatom-based substituents on the alkyl chain of the bromoalkylenoate [60]. A wide variety of substituents were tolerated; however, the main limiting factor was the reactivity of the bromoalkylenoates with the substituents under basic conditions. Finally, incorporating an oxygen atom into the alkyl chain of the bromoalkylenoate enabled the synthesis of benzoxepines [60, 61].



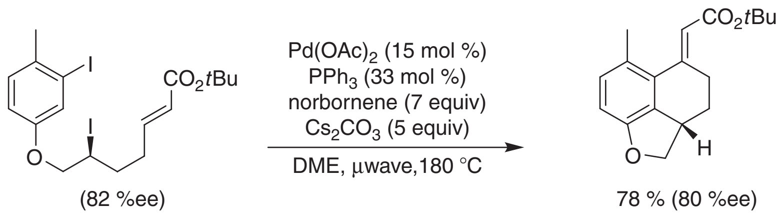
Scheme 22 Aromatic carbocycles and oxepines synthesized via *ortho*-alkylation/Mizoroki–Heck coupling

The success in generating benzoxepines led Lautens to explore the synthesis of other oxygen-containing heterocycles through variation of oxygen atom placement within the chain. α-Halo ethers were not suitable substrates for the reaction, which prompted Lautens to explore the use of an oxygen-tethered Heck acceptor to generate phenol-based heterocycles. Using derivatives of 2-iodophenol, a variety of chromen-4-ylidenes (Scheme 23) and 1-benzoxepin-5-ylidenes were formed via an intramolecular *ortho*-alkylation followed by an intramolecular Mizoroki–Heck cyclization [62]. The length of the tether was crucial to selectivity, as the formation of six- and seven-membered rings was enabled under the reaction conditions (i.e., cyclization was slower than *ortho*-alkylation); however, the desired five-membered benzofuran products could not be synthesized as the 5-*exo*-*trig* Mizoroki–Heck cyclization was much faster than *ortho*-alkylation.



Scheme 23 Synthesis of chromans via *ortho*-alkylation/Mizoroki–Heck reaction

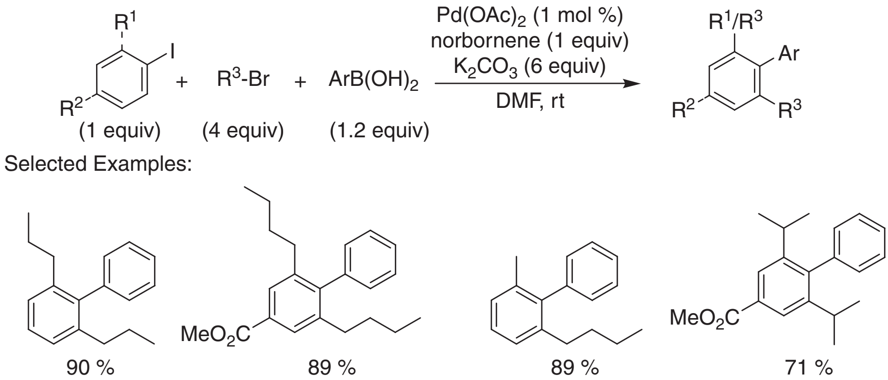
While exploring the use of secondary alkyl halides as partners for *ortho*-alkylation, Lautens reported some very interesting examples where a secondary alkyl halide and Heck acceptor are tethered to an oxygen or nitrogen heteroatom to make several tricyclic molecules in one step (Scheme 24) [32, 44]. This work was instrumental in proving the stereochemical requirements of the oxidative addition of an enantioenriched alkyl halide to the intermediate palladacycle.



Scheme 24 Polycyclic heterocycles from intramolecular *ortho*-alkylation/Mizoroki–Heck coupling

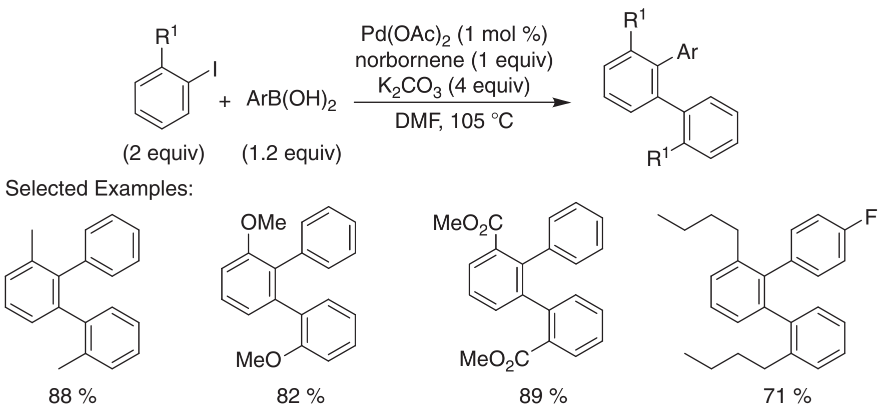
3.2 Suzuki–Miyaura Coupling

The synthesis of biaryl motifs can be achieved through the *ortho*-arylation reaction developed by Catellani, but are more commonly synthesized via Suzuki–Miyaura [63] cross coupling reactions. Catellani reported a method for the selective *ortho*-alkylation reaction terminated with a Suzuki–Miyaura coupling of arylboronic acids (Scheme 25) [64]. Yields were generally high, and several functionalized biaryls were formed. The sequence is highly selective, and there was no reported isolation of by-products from Suzuki–Miyaura coupling with any of the transient palladium(II) intermediates. Interestingly, this is the first catalytic use of a secondary alkyl halide as coupling partner, which was subsequently explored by Lautens [32, 44].



Scheme 25 *Ortho*-alkylation/Suzuki–Miyaura coupling sequence

With success in developing the *ortho*-alkylation/Suzuki–Miyaura coupling sequence, Catellani later reported the *ortho*-arylation variant which forms two aryl–aryl bonds in a single reaction sequence (Scheme 26) [65]. The sequence forms an unsymmetrical aryl dimer through *ortho*-arylation of the aryl iodide, followed by Suzuki–Miyaura coupling. The method works well for *ortho*-substituted aryl iodides with fairly unreactive *ortho* substituents (amines, ethers and hydroxyl groups at the *ortho* position yielded no product). In terms of the arylboronic acid, *o,o*'-disubstitution did not afford product; which is not completely unexpected, as highly hindered Suzuki–Miyaura couplings typically require electron-rich, sterically demanding biphenyl-based ligands [66]. Although not reported, it would be interesting to see if a crossed *ortho*-arylation reaction with electron-deficient aryl bromides, which have been reported recently [41], can be used in conjunction with the Suzuki–Miyaura coupling to generate a wider variety of triaryl products.



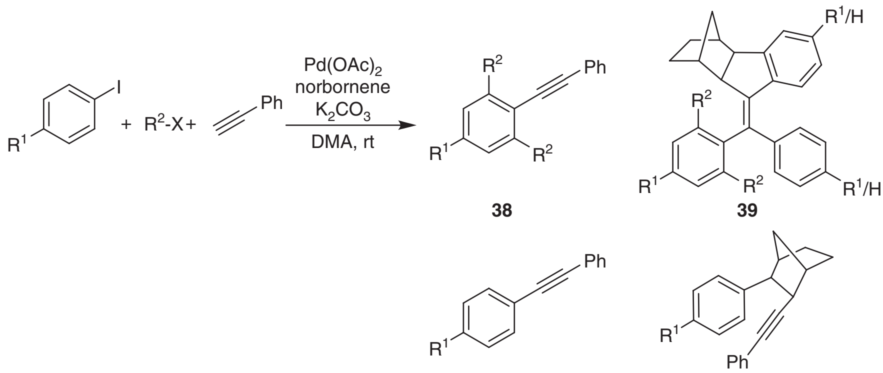
Scheme 26 *Ortho*-arylation/Suzuki–Miyaura coupling sequence

3.3 Cassar–Sonogashira Coupling

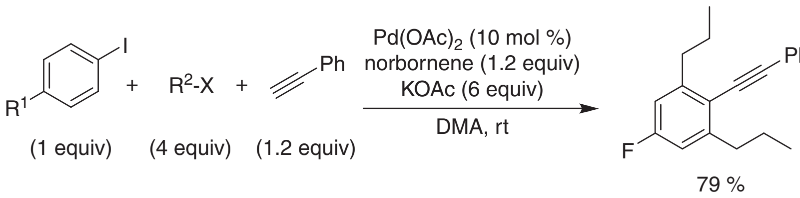
Palladium-catalyzed alkynylation reactions (Cassar–Sonogashira coupling) [67, 68] are well developed and can occur under a wide variety of reaction conditions. Typically, the Cassar–Sonogashira coupling occurs under a bimetallic palladium/copper catalyst system, but more recently, copper-free Cassar–Sonogashira couplings have appeared [69]. Although the bimetallic and copper-free methods occur through different reaction mechanisms, both conditions can be quite efficient and high yielding.

While the termination of the Catellani reaction sequence with a Mizoroki–Heck coupling generates a product containing a fairly unreactive alkene, the termination with a Cassar–Sonogashira coupling generates a highly reactive alkyne product. The reactivity of alkynes towards carbopalladation poses a threat to the target reaction sequence, as alkynes can compete with norbornene for carbopalladation. Taking these issues into account, Catellani worked towards the development of a copper-free *ortho*-alkylation/Cassar–Sonogashira coupling reaction sequence [70].

Under the reaction conditions, phenylacetylene was found to be a much more reactive coupling partner than arylboronic acids in the analogous Suzuki–Miyaura coupling, as in addition to the desired product (**38**), alkynylation and further addition reactions occurred with a variety of transient palladium(II) species (Scheme 27). Despite these undesired side reactions, Catellani was able to fine-tune the reaction conditions to form predominantly product **38** or **39**. The formation of the desired product **38** (and suppression of product **39**) is promoted by acceleration of norbornene carbopalladation by KOAc [47] and by using an excess of alkyl halide; affording several structurally similar unsymmetrical alkyne products in good yields (Scheme 28).



Scheme 27 Observed products of *ortho*-alkylation/Cassar–Sonogashira coupling sequence

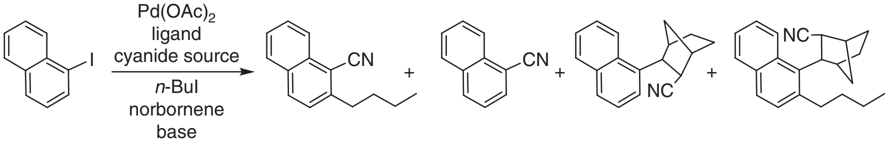


Scheme 28 Optimized o*rtho*-alkylation/Cassar–Sonogashira coupling sequence

3.4 Cyanation

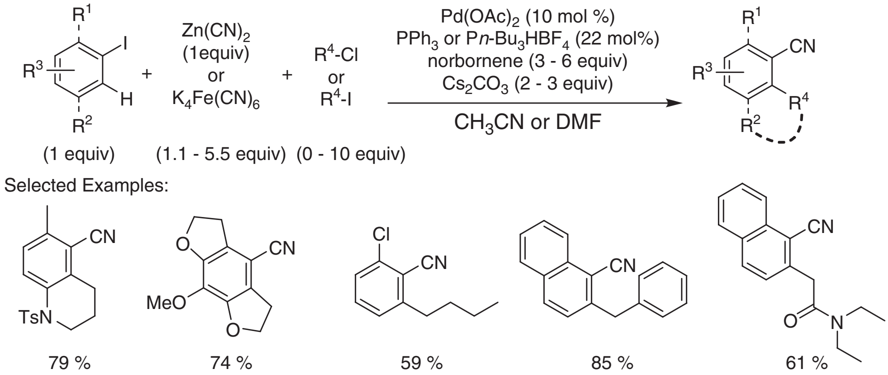
Palladium catalyzed cyanation [71] has recently received a lot of attention in the literature as a cross-coupling which employs cheap, commercially available metal cyanides and incorporates the versatile and synthetically useful cyano group. The development of a domino *ortho*-functionalization/cyanation reaction represents an advance in palladium catalysis as there are very few, if any palladium-catalyzed domino cyanation reactions. The development of the domino *ortho*-functionalization/cyanation [72, 73] by Lautens has led to some of the most significant discoveries of highly functionalized alkyl halides as coupling partners, as well as further development in the selectivity and scope of *ortho*-arylation chemistry.

While optimizing the reaction conditions, Lautens found that cyanation took place with many intermediates in the Catellani reaction sequence, as all non-palladacycle palladium(II) species in the sequence underwent cyanation (Scheme 29). Through optimization experiments, the target product could be obtained in good to excellent yields from either tethered or intermolecular alkyl bromides and iodides (Scheme 30). As alkyl chlorides are more widely commercially available, lower in cost, and more stable than the corresponding alkyl bromides or iodides, Lautens reported a method to incorporate alkyl chlorides as reaction partners. This study eventually led to the use of benzyl chlorides, α-chloroesters, and α-chloroamides as coupling partners, which were far too reactive as the analogous bromides or iodides.

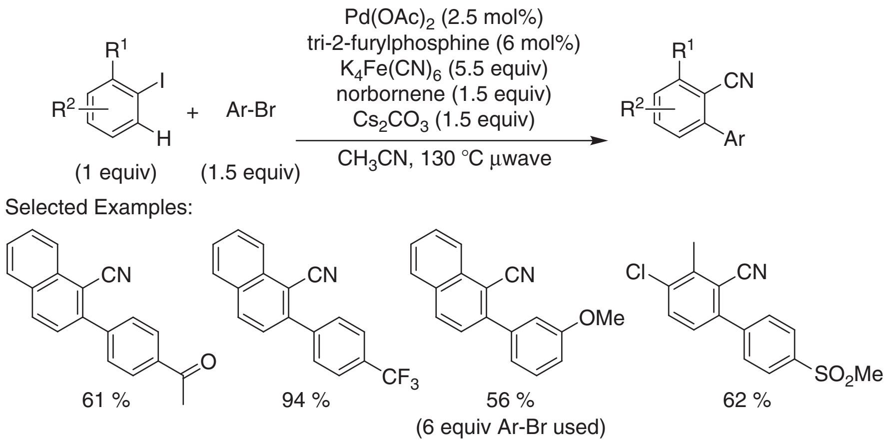


Scheme 29 Products obtained in the *ortho*-alkylation/Cyanation reaction

Using electron-deficient aryl bromides as reagents for *ortho*-arylation, Lautens then expanded the scope of the cyanation reaction to synthesize biaryl cyanides (Scheme 31). As an extension of Catellani's findings that electron-deficient aryl



Scheme 30 Aryl cyanides synthesized via *ortho*-alkylation/Cyanation reaction



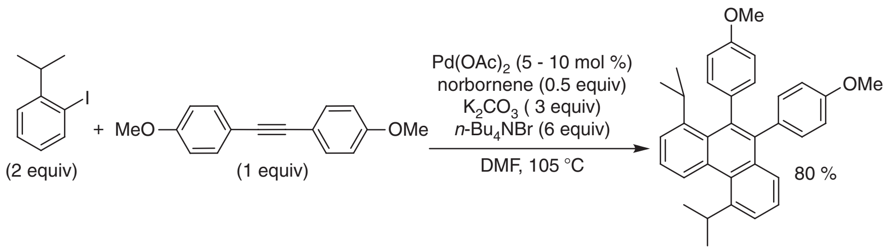
Scheme 31 Aryl cyanides synthesized via *ortho*-arylation/Cyanation reaction

bromides undergo *ortho*-arylation in the presence of electron-rich or electroneutral aryl iodides [41], a variety of electron-deficient aryl bromides with synthetically and medicinally useful functional groups were used in the *ortho*-arylation/cyanation sequence. It was also found that more electron-rich aryl bromides, such as *m*-bromoanisole could be used as a coupling partner when the aryl bromide was used in a large excess.

3.5 Direct Arylation

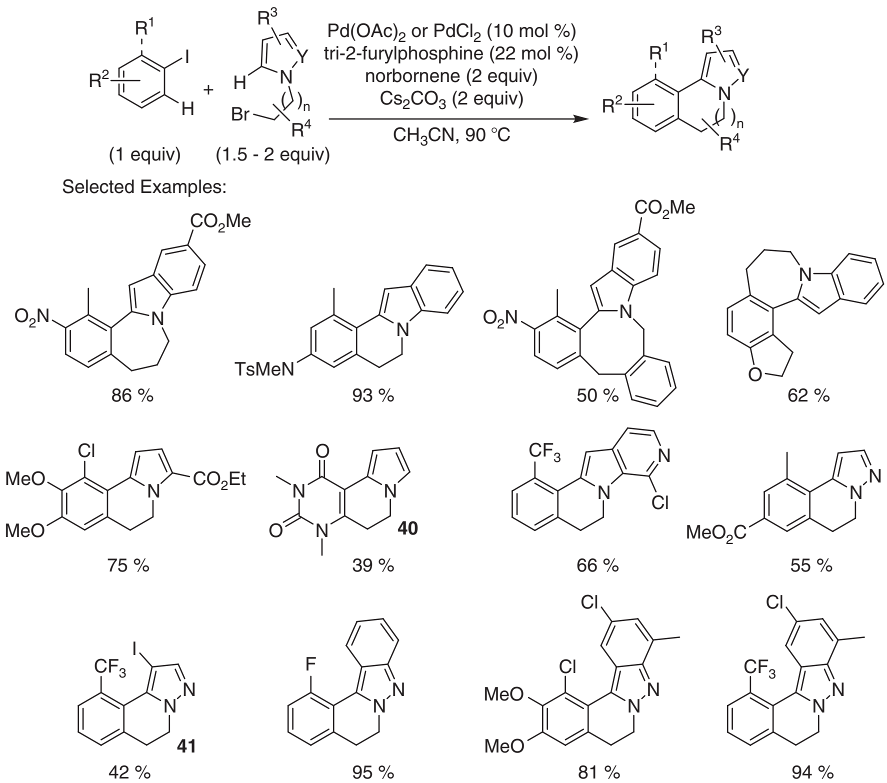
The direct arylation of aryl halides has recently been an area of intense activity in metal catalysis [74]. The ability to form aryl–aryl bonds in the absence of activating functional groups (such as boronic acids or organometallic complexes) is highly atom-economical, and thus has merited a great deal of research. The direct arylation of benzene-based systems has proven difficult, albeit with some exceptions [75]. However, direct arylation processes involving the formation of aryl-heteroaryl bonds have been much more successful, as the reaction is generally easier to perform, and the incorporation of heteroaromatics adds an element of biological activity to the products formed. Mechanistically, there are several possibilities for palladium-catalyzed direct arylation reactions (electrophilic metalation, σ-bond metathesis, C–H insertion, etc.) [76], and while none of the proposed mechanisms are universally applicable, the mechanistic outcome is essentially a C–H functionalization: the formation of a C–C bond from an aryl C–H bond. A coupling of the Catellani reaction with direct arylation would prove to be a powerful strategy for the formation of multiple C–C bonds via multiple C–H functionalization reactions.

Catellani's report for the synthesis of phenanthrenes [54] employs the most difficult of direct arylation reactions, cyclization onto benzene rings, as the terminal coupling. Noting that in the presence of a palladium catalyst and norbornene, aryl iodides in the absence of alkyl halides form unsymmetrical dimeric biphenylyl palladium(II) species, Catellani explored the use of aromatic alkynes as a means to bridge from one aromatic ring to another through alkyne carbopalladation followed by direct arylation. This strategy proved to be quite effective in forming a variety of substituted phenanthrenes in good yields (Scheme 32). The addition of n-Bu_4NBr to the reaction dramatically increased the yield. It was also found that the steric and electronic nature of the *ortho*-substituent greatly impacted the yield, as sterically bulky groups, and electron-withdrawing groups afforded little to no product. The nature of the alkyne was also important, as diaryl alkynes afforded the desired products, alkyl-aryl alkynes afforded a mixture of phenanthrene and allene products, while dialkyl alkynes afforded exclusively allene products.



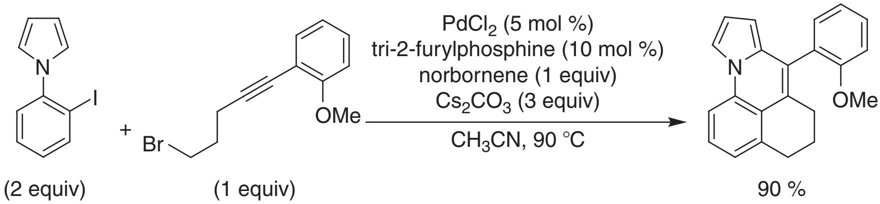
Scheme 32 Synthesis of phenanthrenes

Lautens has applied the direct arylation strategy to enable the coupling of a variety of heteroaromatics as the terminal step of the Catellani reaction sequence. A variety of *N*-bromoalkyl nitrogen heterocycles including indoles [77–79], azaindoles [78], pyrroles [78, 80], pyrazoles [80, 81], and indazoles [81] have successfully undergone an *ortho*-alkylation/direct arylation reaction to afford a wide variety of heterocyclic products in good to excellent yields (Scheme 33). The reaction conditions are tolerant of electron-rich and electron-deficient aryl iodides and a wide variety of functional groups. Some examples in Scheme 33 are worth noting. First, compound **40**, obtained in 39% yield from *N,N'*-dimethyl-5-iodouracil, is the only nucleobase used successfully in a Catellani reaction sequence. Second, compound **41** is also interesting, as it is the only coupling partner reported so far to contain an sp^2-hybridized C–I bond which does not undergo *ortho*-alkylation or -arylation processes and is successfully retained in the product. While neither of these compounds were obtained in excellent yields, the success in their preparation demonstrates the selectivity and synthetic potential of the Catellani reaction sequence.



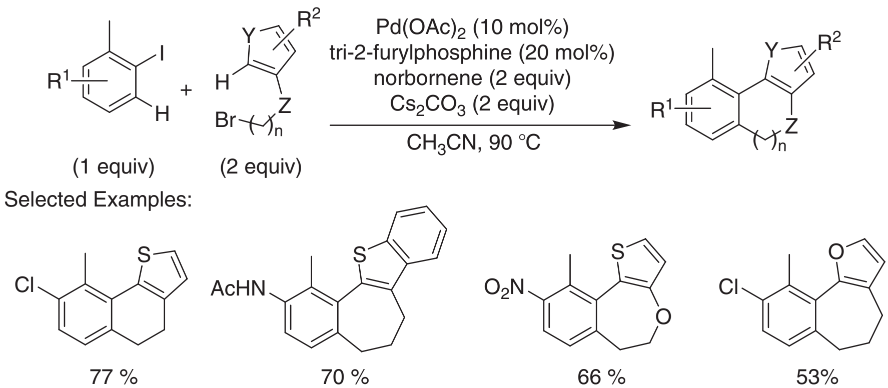
Scheme 33 Nitrogen heterocycles synthesized via *ortho*-alkylation/direct arylation sequence

More recently, Lautens has also employed 1-(2-iodophenyl)-pyrrole as a bifunctional aryl iodide/acceptor for the synthesis of substituted pyrrolo[1,2]quinolines (Scheme 34)[82]. During Catellani's application of the Cassar–Sonogashira reaction to the *ortho*-alkylation sequence [70] it was found that alkynes can undergo further carbopalladation reactions with arylpalladium(II) species. It was this reactivity which led Lautens to explore the use of bromoalkylalkynes as species which can undergo an *ortho*-alkylation, followed by a cyclocarbopalladation onto the alkyne, and termination via direct arylation of the pendant pyrrole. The starting materials are all easily synthesized in very high yields, making this a highly efficient and modular route to substituted pyrrolo[1,2]quinolines.



Scheme 34 Synthesis of pyrrolo[1,2]quinolines

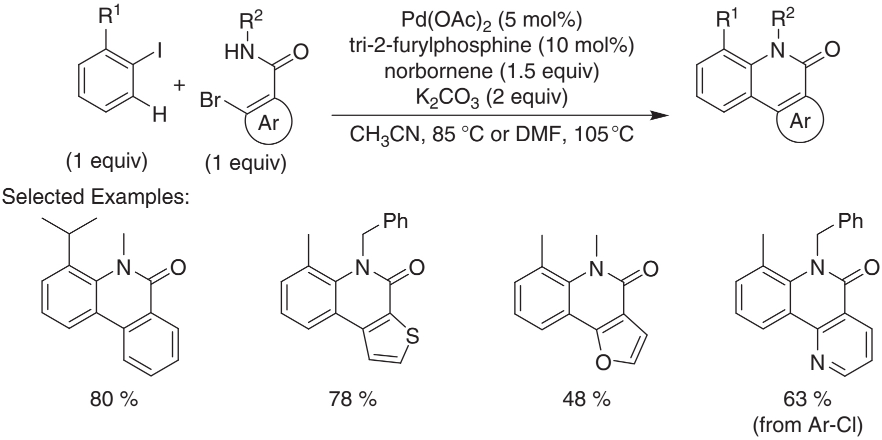
By synthesizing bromoalkyl-sulfur and -oxygen based heterocycles, Lautens was able to extend the strategy to include the synthesis of polycyclic thiophenes and furans [83, 84]. Under similar reaction conditions to those used for nitrogen-based heterocycles, polycyclic products were obtained in good to excellent yields (Scheme 35). The electronic nature of the aryl iodide had a large impact on the observed yields, as electron-deficient aryl iodides worked well, while little to no product was obtained with electron-rich ones. Based upon these results, Lautens proposed that the mechanism of direct arylation of thiophenes occurs through an electrophilic metalation mechanism.



Scheme 35 Sulfur-based and oxygen-based heterocycles synthesized via *ortho*-alkylation/direct arylation sequence

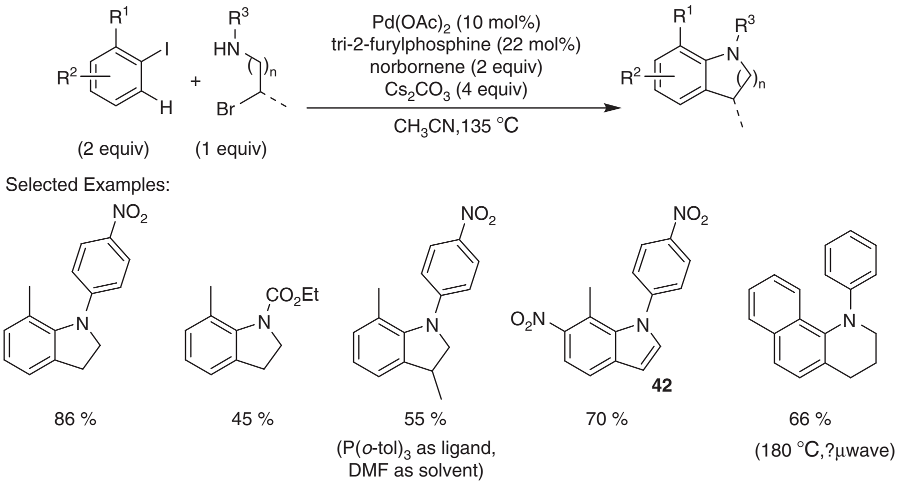
3.6 Amination

The biological significance of nitrogen-containing molecules has made palladium-catalyzed C–N (Buchwald–Hartwig) coupling [85] an essential tool in organic synthesis. Thus the development of a C–N coupling variant of the Catellani reaction would be highly desirable, especially if the products are nitrogen heterocycles. Aiming to make a family of phenanthridone products, Ferraccioli and Catellani employed *o*-bromobenzamides as bifunctional reagents to perform an *ortho*-arylation/amidation reaction (Scheme 36) [86]. The phenanthridone products from both free and secondary amides were obtained in good to excellent yields. Furthermore, the method was extended to heterocyclic *o*-bromobenzamides to generate a variety interesting polycyclic heterocycles. It was found that 2-bromopyridylamides were too reactive under the conditions, but were able to employ a 2-chloropyridylamide in good yield. This is the first example of a chloroarene being employed successfully in a catalytic *ortho*-arylation reaction.



Scheme 36 Phenanthridones synthesized via *ortho*-arylation/amidation reaction sequence

Unlike the *ortho*-arylation/amidation reaction, an *ortho*-alkylation/amination or amidation reaction must address the inherent reactivity of amines and amides toward alkyl halides. As all of the Catellani *ortho*-functionalization reactions take place in polar aprotic solvents with bases present, the potential for S_N2 displacement of the halide by the amine/amide is quite high, and may consume the reagents. With these concerns in consideration, Lautens developed a route towards functionalized indolines, and tetrahydroquinolines using 1° and 2° bromoalkylamines as bifunctional reagents (Scheme 37) [87]. Ferraccioli and Catellani previously used 1° bromoalkylamines as bifunctional reagents in the *ortho*-alkylation/Mizoroki–Heck/aza-Michael sequence [49] but did not explore aryl amination as the terminal step. In order to have bromoalkylamines which are active in the *ortho*-alkylation/amination sequence, but have limited propensity to self-condense or polymerize, Lautens chose nitrogen substituents which diminish the nucleophilicity of nitrogen, namely aryl and carbamyl groups. Using this rationale, both *N*-aryl and *N*-carbamyl indolines were afforded in good yields, with the best nitrogen substituent being a *p*-nitrophenyl group. Interestingly, when an electron-deficient, nitro-substituted aryl iodide was used, the indole product (**42**) was obtained rather than the indoline. While palladium-catalyzed dehydrogenations are known, they generally employ a reductant for palladium, and in this case there is no obvious substrate oxidant nor metal reductant present.

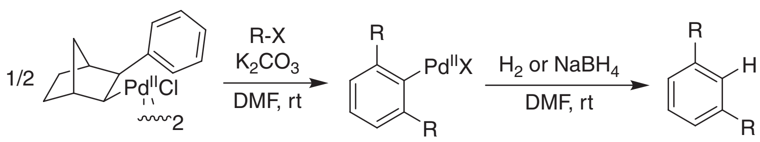


Scheme 37 Nitrogen heterocycles synthesized via *ortho*-alkylation/amination reaction sequence

While Ferraccioli, Catellani, and Lautens had success in developing *ortho*-functionalization/amination reactions, there are still improvements to be made in this area of research. To date, there have been no reports of an intermolecular amination reaction as part of the Catellani reaction sequence. Although challenging, this reaction would allow access to interesting polysubstituted *N*-arylamines, and should be a goal of future research.

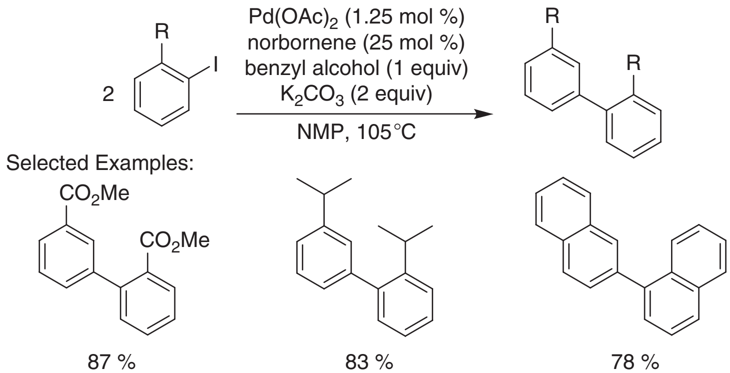
3.7 Hydrogenolysis

The hydrogenolysis of arylpalladium(II) species is a widely used reaction for the dehydrohalogenation of arenes. In combination with the Catellani reaction sequence, hydrogenolysis of a complex of type **36** leads to a *meta*-substituted arene product. In Catellani's stoichiometric investigations of the *ortho*-alkylation [43] and *ortho*-arylation [88, 89] of the PNP dimer, H_2 or $NaBH_4$ were used for reduction of the resultant *o,o'*-disubstituted arylpalladium(II) species (Scheme 38).



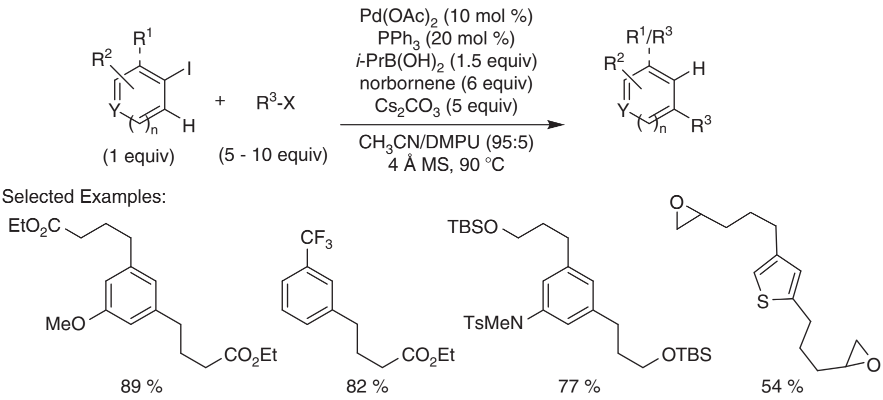
Scheme 38 Hydrogenolysis of complexes of type **36**

To use this approach catalytically, hydrogenolysis must be selective, and only target the arylpalladium(II) species of type **36**. Thus, Catellani proposed that a slow hydrogen transfer reagent must be used to target the terminal arylpalladium(II) species. This method of delayed hydrogenolysis with a variety of transfer reagents proved fruitful when used with *ortho*-arylation to afford a variety of unsymmetrical homobiaryl products (Scheme 39) [90]. Several hydrogen transfer reagents worked well under the reaction conditions, with benzyl alcohol proving to be optimal. Interestingly, when water was added to the reaction in excess (~3 equiv.), a good yield of product was obtained, although no comment on the mechanism of hydrogenolysis with water was made. The limitations of this method preclude the use of halogen atoms *ortho* to the iodide, as a fluorine atom did not undergo *ortho*-arylation (fluorine is presumably too small to contribute to the "*ortho*-effect") and a chlorine atom underwent *ortho*-arylation, but the norbornene adduct cyclized onto the aromatic ring, displacing the chlorine. As with the Suzuki–Miyaura coupling as a terminal step, the recent developments in crossed *ortho*-arylation could transform this reaction into a powerful method for the synthesis of unsymmetrical biaryls.



Scheme 39 Synthesis of unsymmetrical biaryls via *ortho*-arylation/hydrogenolysis reaction

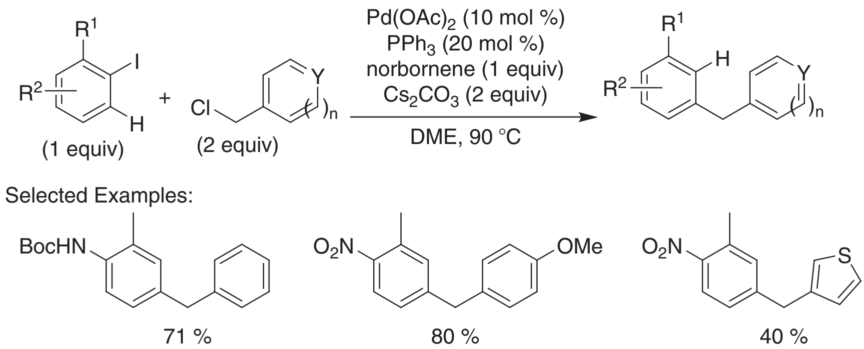
While attempting to expand the scope of the *ortho*-alkylation/Suzuki–Miyaura coupling reaction with alkyl boronic acids, Lautens isolated exclusively the *ortho*-alkylation/hydrogenolysis product, with no alkyl transfer being observed. This observation led Lautens to optimize the reaction, and in the presence of an alkyl halide and isopropyl boronic acid, aryl iodides undergo an *ortho*-alkylation/hydrogenolysis reaction to afford *meta*-substituted benzenes [91] or thiophenes [48] (Scheme 40). Hydrogen transfer from the boronic acid was proposed to occur via β-hydride elimination of an alkylarylpalladium(II) species. Mechanistic studies using deuterium labeling revealed that a second reductive pathway was present. When d_5-iodoethane was used in the presence or absence of isopropyl boronic acid, deuterium was the major atom incorporated at the *ipso* position (>98% D). From these findings, Lautens proposed that the number of β-hydrogens present on the



Scheme 40 Synthesis of *meta*-substituted aromatics via *ortho*-alkylation/hydrogenolysis reaction

alkyl halide is crucial to the success of the hydrogenolysis; as the yield with an alkyl halide with two β-hydrogens is increased in the presence of isopropyl boronic acid, whereas the yield with iodoethane, containing three β-hydrogens is unchanged by the presence of isopropyl boronic acid. Future work in this area should aim to reveal the true role of isopropyl boronic acid as either a reductant, or as a promoter of hydrogenolysis.

Another unexpected hydrogenolysis reaction was discovered by Lautens while attempting to expand the scope of the *ortho*-alkylation/direct arylation of thiophenes. When benzyl chlorides were used as alkylating agents, significant amounts of the *ortho*-benzylation/hydrogenolysis product were obtained. An optimization of the reaction conditions led to an efficient synthesis of diarylmethanes (Scheme 41) [92]. This reaction is unique compared to the aforementioned

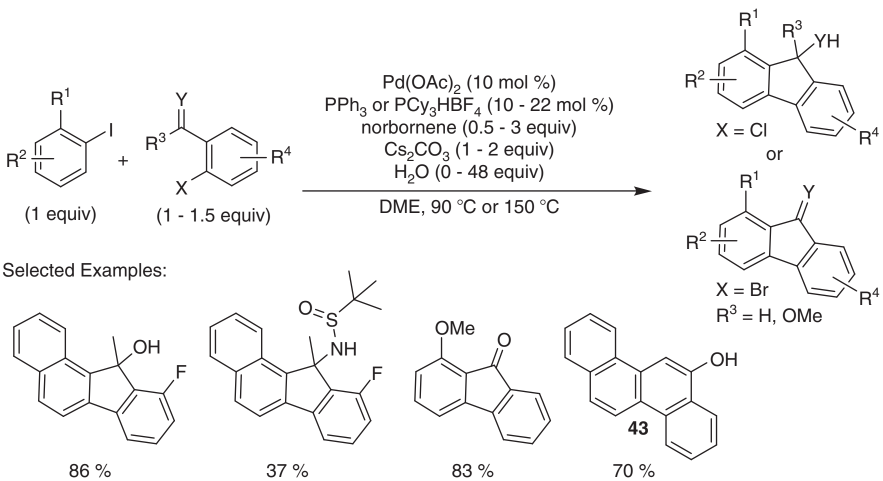


Scheme 41 Synthesis of diarylmethanes via *ortho*-benzylation/hydrogenolysis sequence

ortho-functionalization/hydrogenolysis reactions in that there is no reductant added to the reaction, and the benzyl halide contains no β-hydrogens. Deuterium labeling studies were conducted to find the source of reductant, and found that the main source of deuterium was the α-deuterons of the benzyl chloride. Lautens proposed that the α-deuteron transfer occurs through reaction of the benzyl chloride with the carbonate base, which act as a surrogate for benzyl alcohol, in a manner analogous to Catellani's biaryl synthesis.

3.8 Addition to C=O and C=N Bonds and Enolate Couplings

While studying the *ortho*-arylation/cyanation reaction, Lautens observed an unexpected side product in which no cyano group was incorporated. This product was later found to be a tertiary fluorenol, the result of *ortho*-arylation with a 2'-haloacetophenone, followed by addition of the arylpalladium(II) species of type **36** to the pendant ketone. Conditions were developed to include 2'-haloacetophenone imines, 2-halobenzoates and 2-halobenzaldehydes as reaction partners to generate tertiary fluorenols, fluorenylamines, and fluorenones (Scheme 42) [93]. Water was found to be a key additive to the reaction, as it promoted the formation of the fluorenol product, however, in the absence of water, chrysenol products such as **43** could be obtained. Interestingly, these results show that *ortho*-arylated species of type **36** can act as either nucleophilic (through addition to the C=O bond) or electrophilic (presumably through coupling to an enolate formed in situ) arylpalladium(II) species in the presence or absence of water.



Scheme 42 *Ortho*-arylation/C=O or C=N addition reaction

4 Conclusion

The use of norbornene as a scaffold for aromatic C–H functionalization, a process we dubbed the Catellani Reaction, is a useful and mechanistically interesting method for the polyfunctionalization of aromatic molecules. Through the development and study of palladium complexes with norbornene, a powerful synthetic method has emerged which has been proven useful primarily through the research efforts of Catellani and Lautens. Future studies in this area should focus on expanding the already wide variety of products available, and to develop and/or utilize new reactions which can be performed on either the palladacycle intermediate or terminal arylpalladium(II) species.

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Mechanistic Considerations in the Development and Use of Azine, Diazine and Azole *N*-Oxides in Palladium-Catalyzed Direct Arylation

Keith Fagnou

Abstract Azines, diazines or thiazole *N*-oxides are highly reactive substrates in palladium-catalyzed direct arylation reaction. For these reactions, the results are inconsistent with an SEAr reaction pathway and may best fit with a concerted metalation-deprotonation-like (CMD) mechanism.

Keywords Direct arylation • Palladium • Catalysis • Azines • Azoles

Contents

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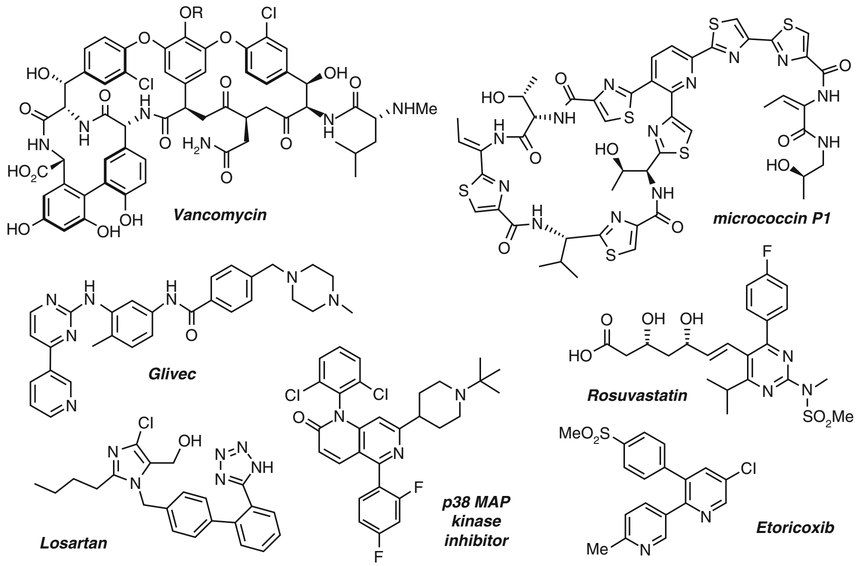
1 Introduction

1.1 Biaryl Compounds in Nature and Medicinal Chemistry

The biaryl structural motif is prevalent in natural products and in pharmaceutical and material sciences ([1–4]; for a review on P, N ligands with pyridyl donors see [5, 6]). While chemists often find inspiration in the methods nature employs to create molecular architectures, the techniques used by nature to form biaryls offer little guidance for the majority of aromatic targets whose synthesis is required of organic chemists. For example, many biaryls found in nature, such as in the antibiotic vancomycin, bear several electron-donating groups such as hydroxy or alkoxy substituents. The presence of these electron-donating groups is linked to the radical cation-type chemistry used by nature to forge the biaryl carbon–carbon bond. Alternatively, when heterocycle-containing biaryls are found in natural products, the carbon–carbon bond of the biaryl core is frequently formed prior to aromatization of the two sides. A comparison of these types of molecules with many of those with industrial application reveals the challenge associated with these compounds, particularly those where electron-donating groups may be absent, or where electron-withdrawing groups may be present (Scheme 1). As a consequence, chemists have been developing new approaches for biaryl synthesis for more than a century, and these efforts have culminated in the establishment of broadly applicable transition metal catalyzed cross-coupling reactions between an aryl halide and an aryl organometallic reagent (for reviews on this topic, see [7]).



Scheme 1 Biaryl molecules in nature and in medicinal chemistry

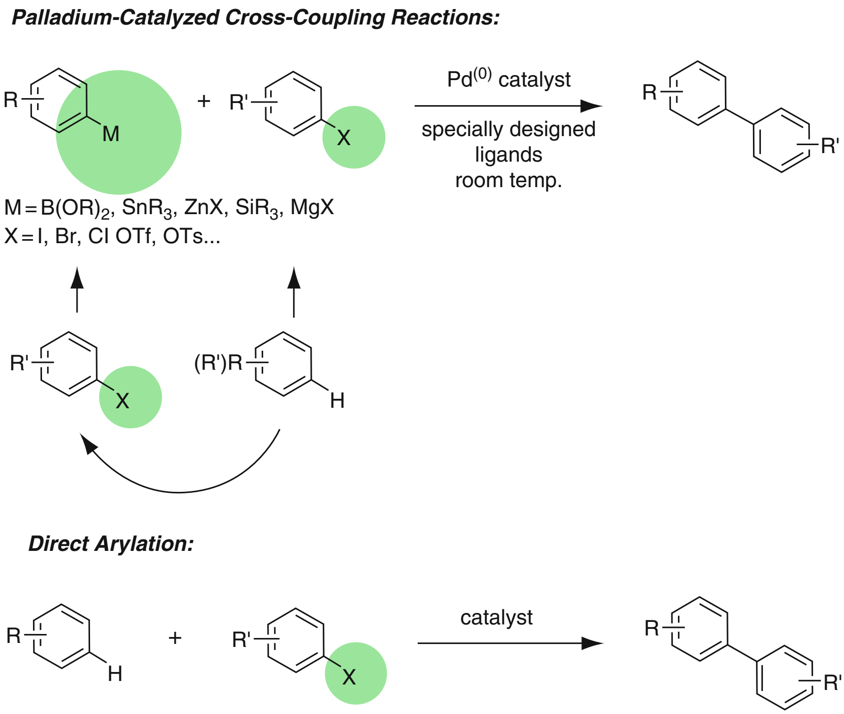
These processes typically occur in very high yield, with high functional group compatibility, under mild conditions and with low catalyst loadings.

1.2 Direct Arylation in Biaryl Synthesis

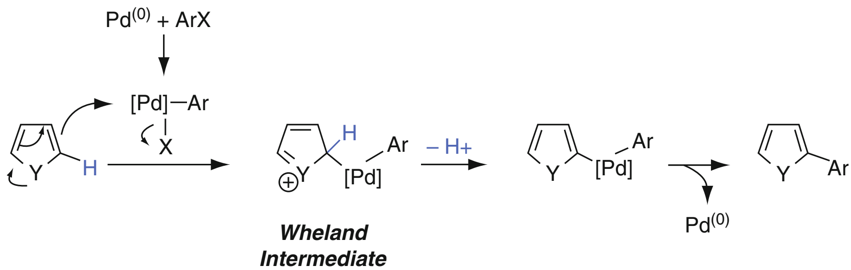
Despite the important advances made over the past 30 years in metal catalyzed cross-coupling methodology, it is important to be mindful of the fact that both the organometallic and halide cross-coupling reagents must be synthesized through one or more steps and that both of these coupling partners will typically come from the corresponding simple arene starting material. The inefficiency associated with this pre-activation is greatest with the organometallic species since it is typically prepared from the corresponding aryl halide that, in turn, is prepared from the simple arene. Depending on the organometallic reagent used, these species may be hydrolytically sensitive, incompatible with prolonged bench top storage and may suffer from functional group intolerance. Thus, there is still ample room for innovation, particularly in areas focused at the minimization of (potentially unnecessary) arene pre-activation.

One reaction class that targets the minimization of arene pre-activation is "direct arylation" wherein one of the arenes (usually the organometallic) is substituted with the simple arene itself (Scheme 2). Several catalysts may be used including palladium, rhodium, ruthenium, copper and others (for selected direct arylation processes with Pd(0)/Pd(II) see [8–14]; for selected analogous C–C bond forming processes initiated with Pd(II) see [15–21]; for oxidative cross-couplings in the absence of substrate pre-activation initiated with Pd(II), see [22–28]; for selected direct arylation processes with Rh, see [29–39]; for selected direct arylation processes with Ru, see [40, 41]; for selected direct arylation processes with other metals see [42–47]). Direct arylation reactions with palladium catalysts were first described with π-excessive heteroaromatic coupling partners (for pioneering work on palladium-catalyzed direct arylation of heteroaromatics, see [48–61]) leading researchers to propose that an electrophilic aromatic substitution (S_EAr) pathway was operative (Scheme 3). Under this reactivity profile, the nucleophilic arene would interact with an electrophilic arylpalladium(II) intermediate via a Wheland-like intermediate. This Wheland intermediate could then undergo a fast deprotonation to produce the heteroleptic biaryl palladium complex that can then undergo reductive elimination to afford the cross-coupled product. Importantly, this reaction profile should be principally governed by the nucleophilicity of the aromatic coupling partner – a notion that fits well with a catalytic cycle where the simple arene must replace the role of the nucleophilic arylorganometallic reagent.

Ongoing research in our group and by others [62–65] on the mechanism of palladium-catalyzed direct arylation has led to the advancement of a second mode of C–H bond cleavage where a Wheland-like intermediate is not involved in the reaction pathway (Scheme 4). This pathway, which we have termed a concerted metalation-deprotonation (CMD) mechanism, appears less dependent on arene

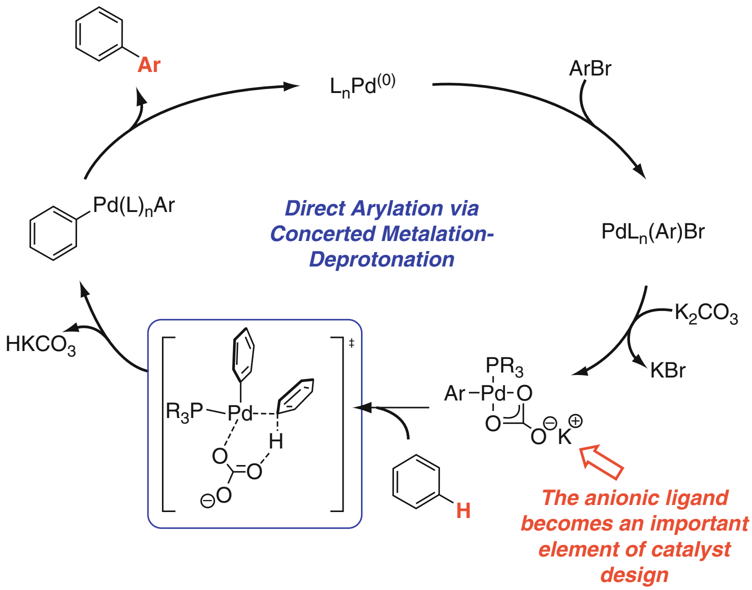


Scheme 2 Biaryl synthesis via palladium-catalyzed cross-coupling and direct arylation reactions



Scheme 3 A plausible electrophilic aromatic substitution mechanism for palladium-catalyzed direct arylation

nucleophilicity and has broad scope with electron-deficient and electron-neutral arenes. Recent results also indicate that this pathway may also extend to several "nucleophilic" heteroatom containing aromatic coupling partners [66]. This review describes the results from our group pointing to the involvement of a nonelectrophilic aromatic substitution pathway. It also outlines the initial steps in reaction development that have been enabled by this new knowledge.

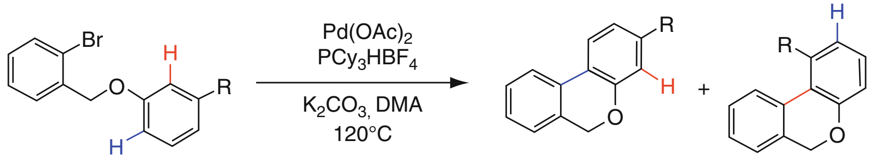


Scheme 4 A prototypical concerted metalation-deprotonation (CMD) direct arylation mechanism

2 Experimental Support of a Nonelectrophilic Aromatic Substitution Pathway in Palladium-Catalyzed Direct Arylation

An indication that non-S_EAr-type reactivity could be at play has emerged from cyclizations. In these reactions, the effect of a *meta*-substituent on regioselectivity was evaluated and, in the majority of cases, reaction was observed at the more sterically accessible *para*-position (Scheme 5) [67]. In contrast, an inversion in selectivity was found to occur when a fluorine substituent was present, leading to preferential *ortho*-direct arylation.

In order to rationalize this reactivity, two different processes were proposed, whereby cleavage of the C–H bond would occur simultaneously with carbon–palladium bond formation: a σ-bond metathesis process involving an anionic ligand on the palladium metal and a bimolecular process whereby a noncoordinated base was inducing deprotonation. In both cases, because the C–H bond is being cleaved as site selectivity is being determined, the C–H acidity may influence transition state accessibility and consequently be a governing parameter in direct arylation. Such selectivity could arise with fluorinated arenes since the *ortho*-C–H bonds are more acidic than those located at a more remote *para*-positions. At the same time, Echavarren also observed similar rate accelerations induced by fluorine substituents and proposed a mechanism similar to σ-bond metathesis where the anionic ligand is a carbonate base [63, 64]. Importantly, Echavarren and Maseras evaluated this



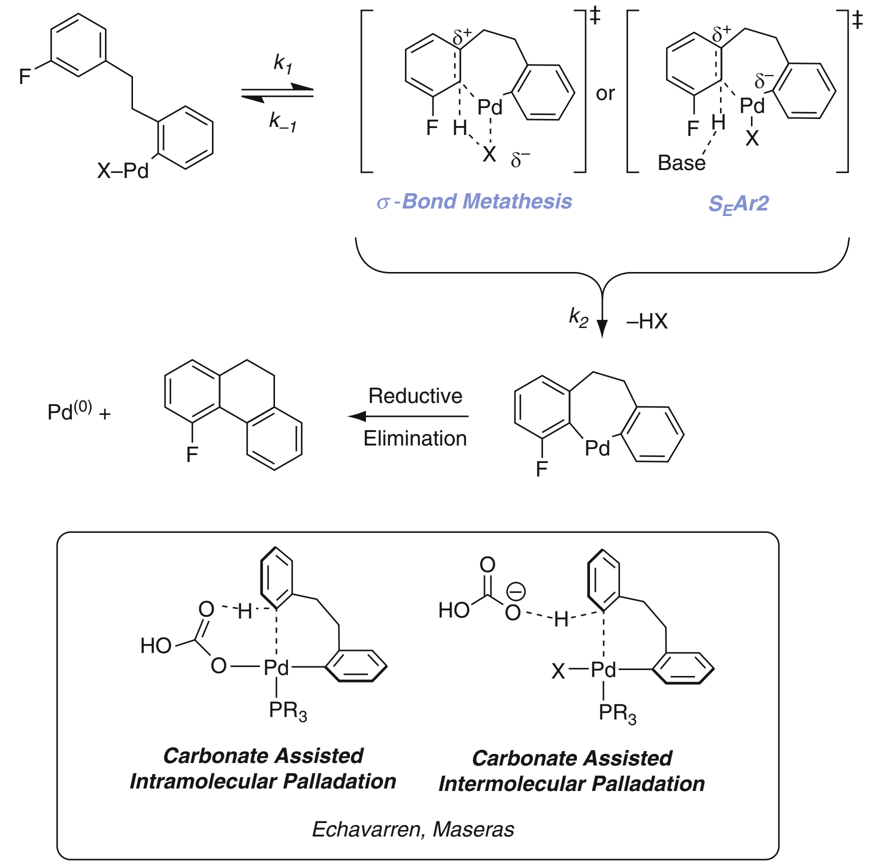
R-Group	Ratio
OMe	10:1
Me	4:1
*i*Pr *t*Bu CF_3	>30:1
CO_2Me	>30:1
Cl	8:1
F	1:4

Scheme 5 Substituent effects on regioselectivity

mechanism via DFT calculations and found that it accurately predicted the experimental outcomes from their studies, constituting the first theoretical support for this type of mechanism in palladium-catalyzed direct arylation (Scheme 6) [63].

Perfluoroarenes were also found to be highly reactive coupling partners in intermolecular direct arylation [68, 69]. A wide range of aryl halides can be employed, including heterocycles such as pyridines, thiophenes, and quinolines. A fluorinated pyridine substrate may also be cross-coupled in high yield and it was also found that the site of arylation preferentially occurs adjacent to fluorine substituents when fewer fluorine atoms are present. Interestingly, the relative rates established from competition studies reveal that the rate of the direct arylation increases with the amount of fluorine substituents on the aromatic ring. In this way, it is inversely proportional to the arene nucleophilicity and therefore cannot arise from an electrophilic aromatic substitution type process (Scheme 7).

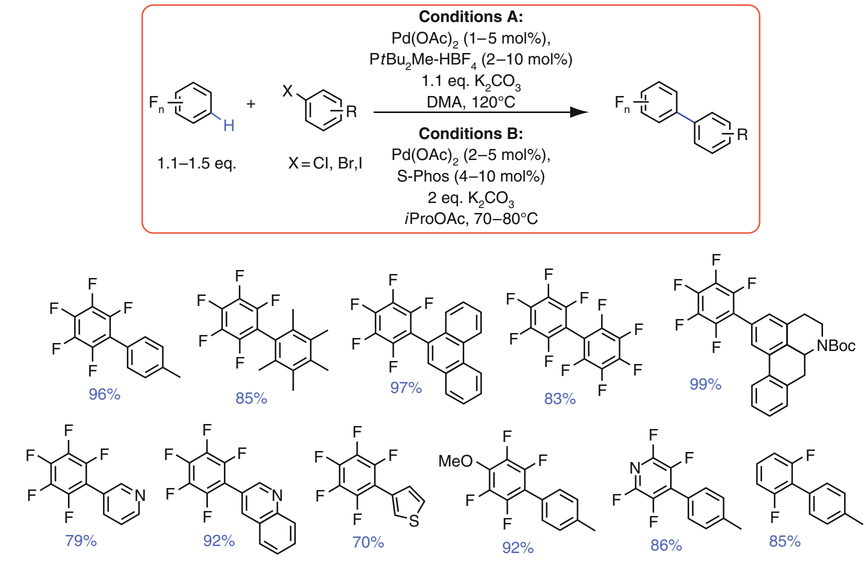
To rationalize this reactivity, DFT calculations were performed to evaluate the lowest energy pathway. Two pathways were found to be energetically accessible. One involves a sigma-bond metathesis where a bromine ligand is inducing deprotonation. In a pathway similar to that proposed by Echavarren and Maseras [63, 64], anionic ligand exchange could also occur at the aryl palladium(II) intermediate to produce a palladium carbonate species. This complex could then follow the CMD pathway via a six-membered transition state. An examination of the energy barriers for these two processes indicates that the pathway arising from carbonate exchange is significantly lower than that occurring via sigma-bond metathesis. This observation may indicate that the reaction should follow the lower energy pathway; however, studies aimed at determining the solubility of the carbonate base under



Scheme 6 Initial hypothesis for the influence of fluorine substituents on regioselectivity

the reaction conditions indicated that very little carbonate base is actually dissolved. In this way, a limiting step in the reaction may actually involve the anion exchange (Scheme 8).

The intermolecular direct arylation of simple benzenes was also evaluated [12]. Under conditions established for the fluorinated substrates, none of the desired cross-coupled product was formed. With the goal of increasing the amount of soluble base in the reaction mixture, varying amounts of different carboxylic acids were added. Both the amount and the type of acid was found to influence significantly the reaction outcome, with larger acids used in substoichiometric amounts providing superior outcomes. For example, as the steric bulk is increased from acetic acid to pivalic acid, an increase in conversion is noted. Under optimal conditions, addition of 30 mol% pivalic acid results in 100% conversion of the aryl bromide and an 82% isolated yield of benzene direct arylation is obtained. To rationalize the reactivity, it was proposed that the potassium pivalate may behave as



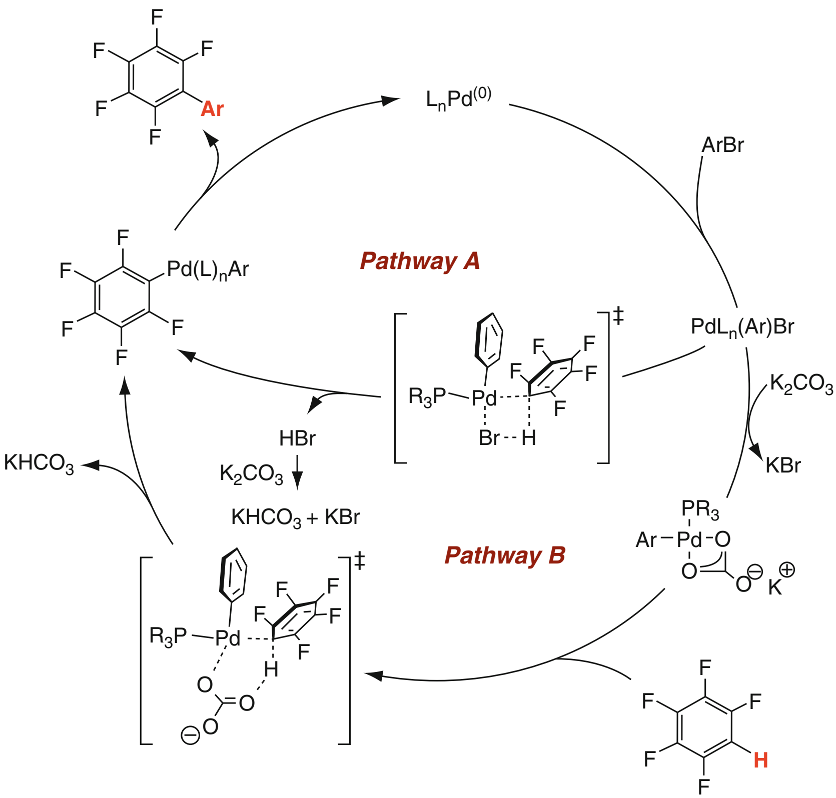
Scheme 7 Scope of perfluoroaromatics in palladium-catalyzed direct arylation

a catalytic proton shuttle from the transition state of the CMD process to the insoluble carbonate base. Importantly, knowledge achieved through the establishment of these reaction conditions should provide new opportunities for reaction development for other non-nucleophilic arenes (Scheme 9).

3 Azine and Azole *N*-Oxides in Direct Arylation

3.1 Synthetic Considerations

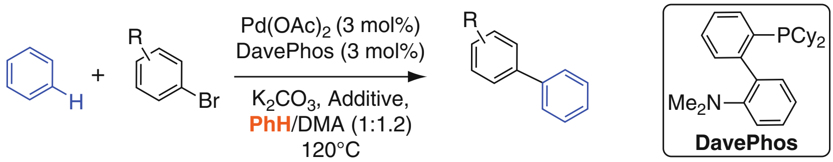
Recognizing the industrial value of nitrogen containing aromatics such as azines and dizines, the knowledge obtained through CMD studies described above was applied to these types of substrates (for an important advance in regioselective azine direct arylation without substrate pre-activation catalyzed by Rh(I), see [70]; for an example of metal-free, base promoted biaryl formation between unactivated azine and diazines and aryl bromides and iodides, see [71]). Alternatives to the use of 2-metallopyridines and diazines were targeted, since these substrates (particularly the pyridylboronic acids) were known to exhibit problematic reactivity (for example, the instability of 2-pyridylboronic acids has long prevented their use in Suzuki cross-couplings and has recently been addressed through the use of pyridylboronates, see [72, 73]). It was rationalized that, by taking advantage of the increased Bronsted acidity of the *ortho*-positions of pyridine *N*-oxides,



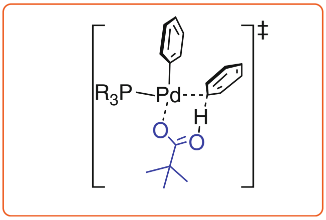
Scheme 8 Plausible CMD-based catalytic cycle for perfluoroarene direct arylation

[74, 75] these substrates may act as surrogates for 2-pyridylboronic acids under a CMD-based direct arylation reaction pathway. Importantly the pyridine *N*-oxide substrates are very easily prepared, handled, and stored, and are increasingly commercially available (for a review on pyridine *N*-oxides and their reactivity see [76]). These substrates are conveniently prepared by treatment of the simple pyridine or diazine substrate with methyltrioxorhenium (MTO) in the presence of hydrogen peroxide [77] or through reaction with *m*CPBA. If desired, the *N*-oxide moiety may easily be removed under mild conditions by treatment with palladium on carbon under a hydrogen atmosphere or with zinc (or other metals) in mildly acidic media.

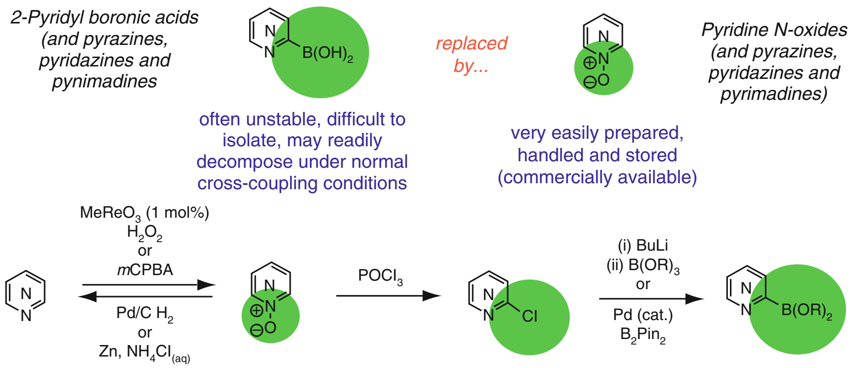
From a reaction efficiency perspective, it is important to recognize that the use of *N*-oxide substrates still necessitates a pre-activation step (the oxidation), and an improvement to the strategy would clearly constitute the ability to achieve similar reactivity and scope with the simple azines and diazines themselves [70]. Since the *N*-oxide is not consumed during the course of the reaction, however, and since the *N*-oxide group may be used to introduce a wealth of other functionalities on the aromatic ring, some additional utility may be gained from this “activation” and



Entry	Additive	Conversion	Yield
1	none	<5	0
2	AcOH (30 mol%)	20	11
3	$EtCO_2H$ (30 mol%)	14	6
4	$^{i}PrCO_2H$ (30 mol%)	32	13
5	**$^{t}BuCO_2H$ (30 mol%)**	**100**	**82**



Scheme 9 Effect of carboxylate additives on palladium-catalyzed direct arylation of benzene

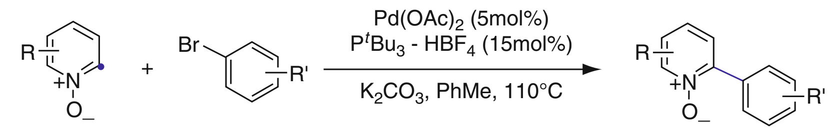


Scheme 10 Pyridyl organometallic reagents and pyridine *N*-oxides as a plausible replacement

minimize the synthetic cost. When a comparison is made to more traditional cross-couplings, however, the use of an *N*-oxide substrate does constitute an improvement in efficiency since most methods to introduce an organometallic component at the 2-position of an azine/diazine involves an *N*-oxide intermediate. For example, most syntheses of 2-pyridyl boronic acids involve a three step procedure whereby the pyridine is transformed to the pyridine *N*-oxide followed by treatment with $POCl_3$ to furnish the corresponding 2-chloropyridine (Scheme 10). This species is then transformed into the pyridyl lithium compound by reaction with BuLi, which is then trapped with a trialkoxyborane and hydrolyzed. By employing the *N*-oxide strategy, not only is there an improvement in step count, but an easily handled reagent also replaces a challenging organometallic.

3.2 *Reactivity with Azine and Diazine* N-*Oxides*

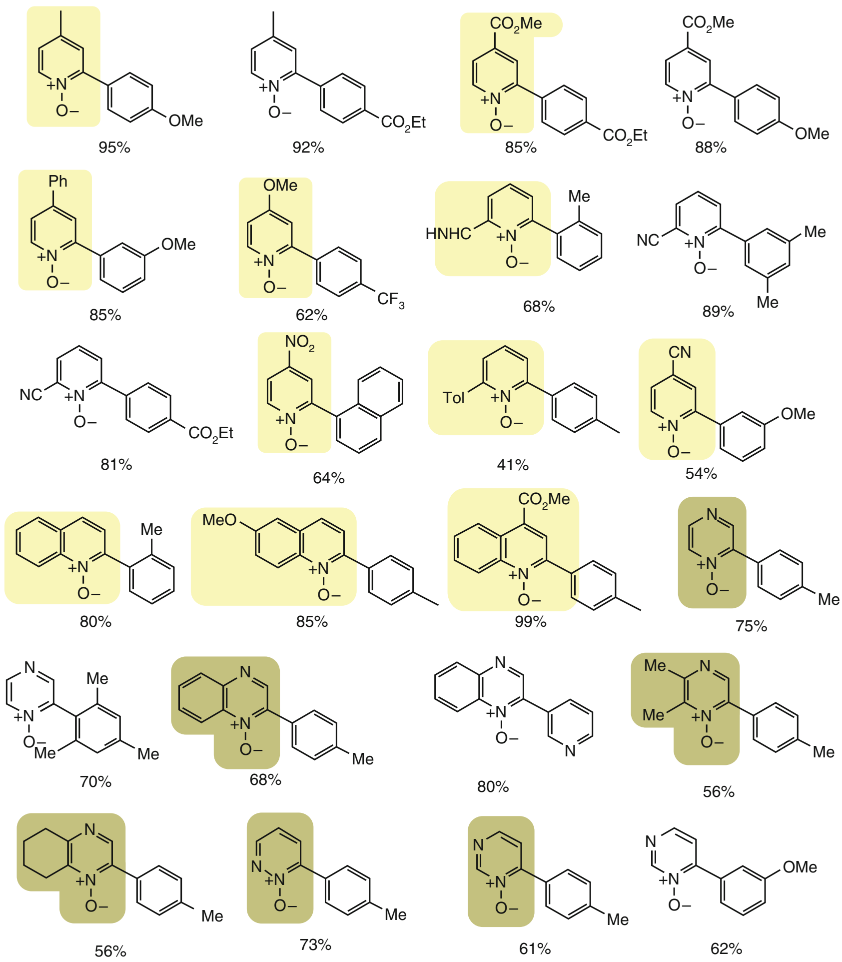
In 2005, the direct arylation of pyridine *N*-oxide compounds was described (for pyridine *N*-oxides see [78, 79]) employing 4 equivalents of the pyridine *N*-oxide substrate in conjunction with an aryl bromide coupling partner, 5 mol% $Pd(OAc)_2$, 15 mol% $PtBu_3HBF_4$, and 1.5–2 equivalents K_2CO_3 in toluene at 110 °C. Under these conditions, the corresponding 2-arylpyridine *N*-oxides are obtained in good to excellent yields as one regioisomer. Subsequent efforts, with the goal of establishing scalability and improving the stoichiometry, revealed that as little as 1.5–2 equivalents of the *N*-oxide may be employed and that the reactions are scalable to greater than 10 g with little change in experimental outcome. On the milligram scale, 5 mol% of the palladium catalyst is typically employed; however, on larger scales 2 mol% palladium may be employed with no decrease in yield. Below this level, incomplete conversions are currently encountered.



(1.5 to 4 equiv.)

70–95%

The scope of these transformations is very broad [78, 79]. A variety of substituents may be present on the pyridine *N*-oxide substrate, including methyl groups, electron-withdrawing groups such as ester, nitrile, or nitro substituents, and electron-donating groups such as methoxy substituents. In some cases lower yields are obtained. For example, 2-aryl pyridine *N*-oxide provides a 41% isolated yield of the direct arylation product, likely due to an increase in steric bulk at the reaction site. 4-Cyanopyridine *N*-oxide also provides diminished yields; however, in this case the lower yields are likely due to technical challenges associated with the sparing solubility of this substrate in the majority of organic solvents. In addition to pyridines, quinoline *N*-oxides may also be employed in high yields as can diazine *N*-oxides. Pyrazine *N*-oxides are excellent substrates providing desired products in very high yields, as are pyridazines. Pyrimidine *N*-oxides remain challenging substrates, providing the desired product in synthetically useful albeit lower yields. In these cases, up to 60% yield may be obtained when a catalytic

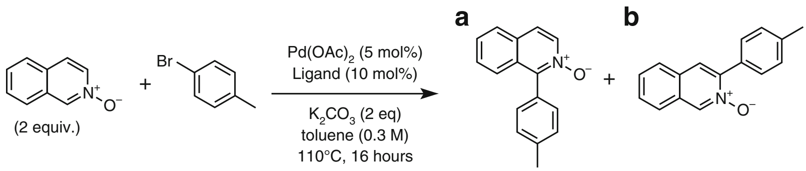


Scheme 11 Scope of azine *N*-oxide direct arylation

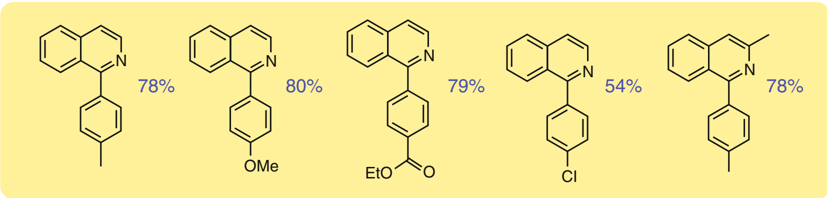
quantity of copper additive is used in conjunction with the palladium catalyst (Scheme 11).

3.3 *Regioselectivity with Nonsymmetrical Azine Substrates*

Treatment of isoquinoline *N*-oxide under a variety of conditions leads to the formation of 2-regioisomers with the major product arising from arylation of the benzylic position. Significantly, the regioselectivity may be tuned by the choice of ligand. For example, the use of sterically encumbered ligands such as tri-*tert*-butyl



Entry	Ligand	**A:B**	Conversion (%)
1	P^{t}Bu$_3$-HBF$_4$	2:1	>99
2	PCy$_3$-HBF$_4$	8:1	90
3	PMe^{t}Bu$_2$-HBF$_4$	13:1	>99



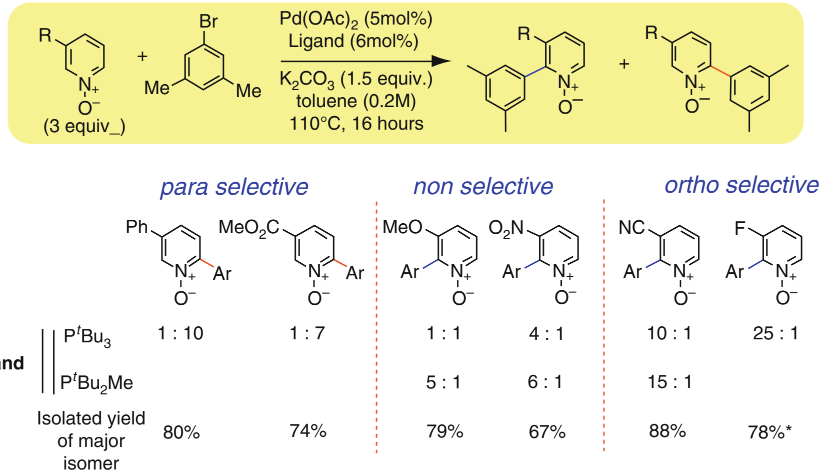
Scheme 12 Ligand effects on isoquinoline *N*-oxide direct arylation

phosphine gives rise to a 2:1 regioisomeric ratio. The use of smaller ligands, such as tricyclohexyl and di-*tert*-butyl methyl phosphine, results in improved regioselectivities. Under optimal conditions, up to 13:1 regioselectivity can be achieved for reaction at the benzylic site with greater than 99% conversion. With these substrates, separation of the regioisomers can be challenging by flash chromatography. Consequently, isolation of desired products may be carried out in a two-pot process of arylation and deoxygenation prior to separation of the isomers (Scheme 12).

With pyridine *N*-oxides, the regioselectivity is also highly influenced by the nature of the pyridyl substituent (Scheme 13). In some cases high *para*-selectivity is observed for reaction at the more sterically accessible position, as is the case with phenyl or ester groups. Other substituents lead to low regioselectivity such as methoxy or nitro substituents. In these cases, by changing the ligand from tri-*tert*-butyl phosphine to the slightly smaller di-*tert*-butyl methyl phosphine, the regioselectivity may be increased favoring reaction at the more sterically encumbered position in synthetically useful yields. Other pyridine *N*-oxides give high *ortho*-selectivity such as when a nitrile or a fluorine substituent is present.

3.4 *Azole* **N**-*Oxides*

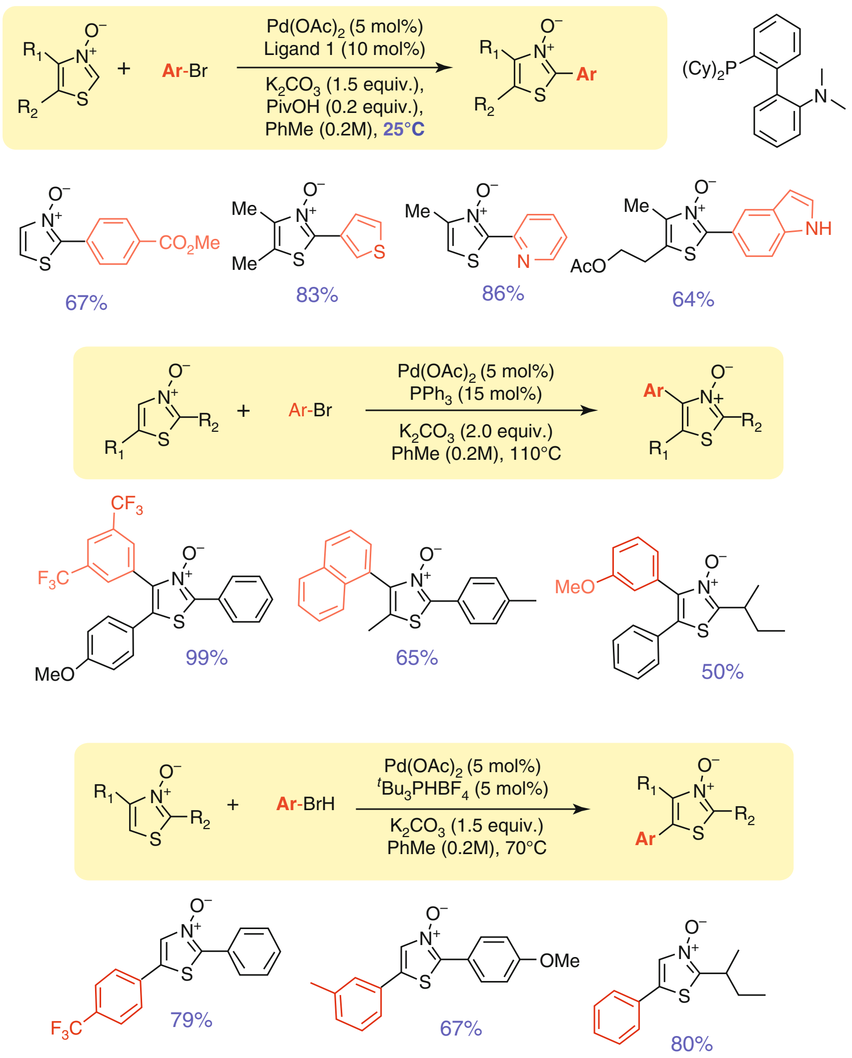
Thiazole *N*-oxides are also highly reactive substrates in direct arylation [80]. For example, the direct arylation of several thiazole *N*-oxides with arylbromides in the presence of a palladium catalyst and a Buchwald ligand can be achieved at 25 °C,



Scheme 13 Ligand and substituent effects on pyridine *N*-oxide direct arylation

constituting rare examples where direct arylation occurs at or near room temperature. As was the case with direct arylation reactions with benzene substrates (see above), the addition of 20 mol% pivalic acid in addition to the stoichiometric potassium carbonate base was found to be optimal. A variety of aryl halide substrates may be employed including thiophenes, pyridines, as well as a free N–H indole that cross couples with a highly functionalized thiazole *N*-oxide substrate in 64% yield. If the arylation is carried out on thiazole *N*-oxide substrates where the C2 position is blocked by the presence of a substituent, the next site to undergo arylation is at C5, adjacent to the sulfur atom. To achieve reactivity at C5 the reaction temperature must be heated to 70 °C and, in these cases, removal of the pivalate additive was found to offer higher regioselectivities. In cases where both the C2 and C5 have been blocked by substituents, arylation may also be induced to occur at C4, leading to rare examples where direct arylation at C4 has been achieved. Because of the diminished reactivity and the increased steric bulk adjacent to the reaction center, the reaction temperature must be heated further to 110 °C (Scheme 14).

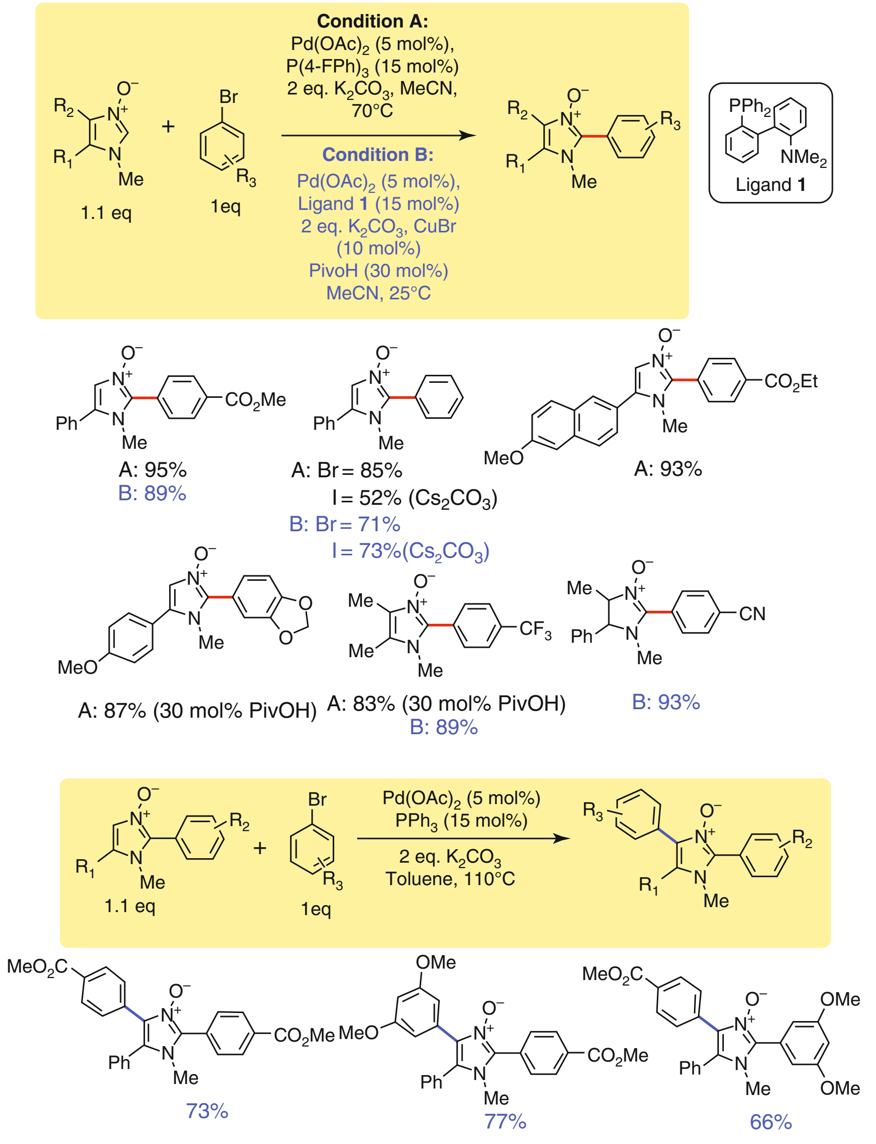
Imidazole *N*-oxide substrates may be used in a similar fashion. Initial investigations revealed that the use of palladium acetate in conjunction with an electron deficient 4-fluorophenylphosphine in acetonitrile at 70 °C provides C2 arylation in high yields. With the goal of achieving the same reactivity at or near room temperature it was determined that the use of palladium acetate in conjunction with a Buchwald ligand, catalytic copper bromide and 30 mol% pivalic acid in acetonitrile could also achieve high yields of C2 arylation at 25 °C. As was the case with thiazole *N*-oxides, if the C2 and C5 positions of the imidazole are blocked C4 arylation may also be achieved in synthetically useful yield (Scheme 15).



Scheme 14 Thiazole *N*-oxides in palladium-catalyzed direct arylation

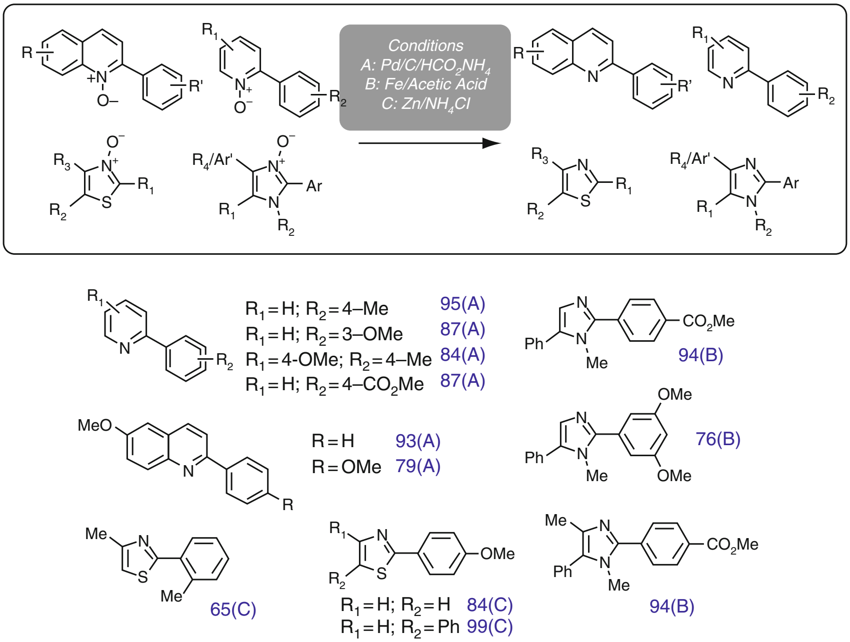
3.5 *Methods for* N-*Oxide Deoxygenation*

The utility of the direct arylation methodology of azine and azole *N*-oxides relies on the ability either to employ the *N*-oxide moiety in other types of azine/azole functionalization or to induce easily *N*-oxide deoxygenation under mild conditions subsequent to direct arylation (for reduction with Fe/acetic acid please see [81]). Three different conditions were typically employed based on the substrate



Scheme 15 Imidazole *N*-oxides in palladium-catalyzed direct arylation

undergoing reaction. Azine *N*-oxides can be readily reduced to the corresponding aryl azine by Pd/C with ammonium formate or under a hydrogen atmosphere. Reactions are run at room temperature, proceed in relatively short reaction times, and provide the products in good to excellent yield. This protocol is not compatible with some functional groups such as aryl halides, however. In these cases, use of Zn



Scheme 16 Illustrative example of *N*-oxide deoxygenation

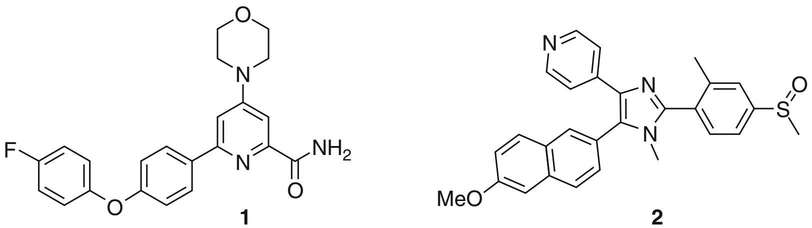
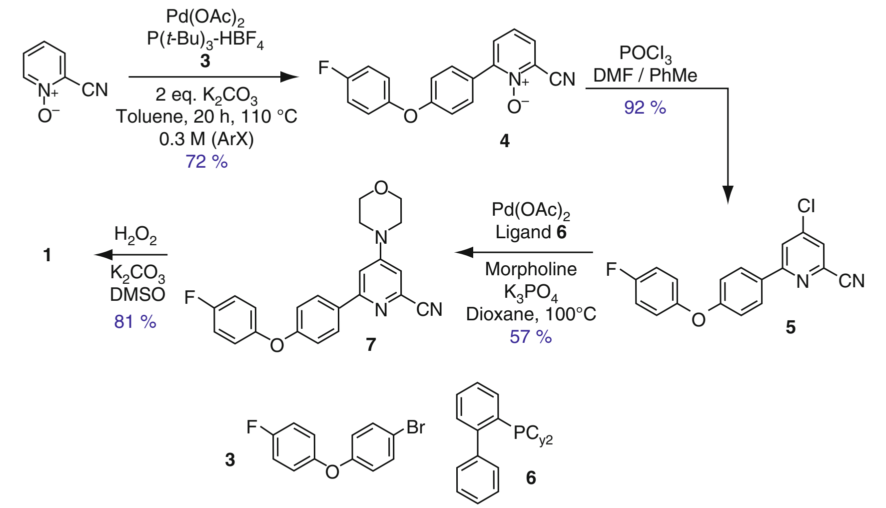


Fig. 1 Medicinal compounds prepared via *N*-oxide direct arylation

dust in aqueous ammonium chloride/THF can selectively achieve deoxygenation without inducing hydrodechlorination. Illustrative examples are shown in Scheme 16.

4 Applications in Medicinal Chemistry

The synthesis of sodium channel inhibitor **1** [82] illustrates the utility of the *N*-oxide strategy by using it not only to form the biaryl carbon–carbon bond, but also to form the C4 carbon–nitrogen bond. Diaryl ether **3**, prepared by a copper catalyzed cross-coupling of 4-fluorophenol and 1-bromo-4-iodobenzene [83], was coupled



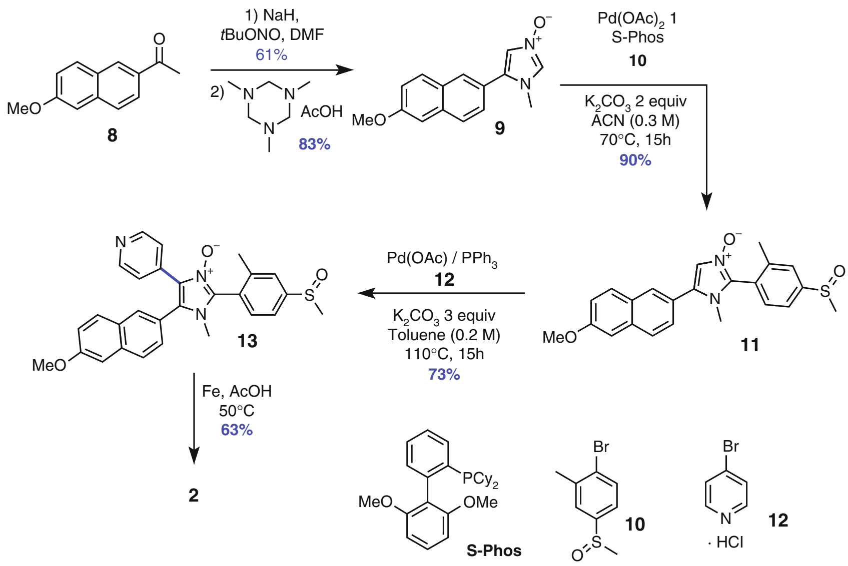
Scheme 17 Synthesis of sodium channel inhibitor **1**

under standard direct arylation conditions with 2-cyanopyridine *N*-oxide, prepared quantitatively by treatment of 2-cyanopyridine with MTO and aqueous hydrogen peroxide in dichloromethane (now commercially available) [77], to afford the 2-aryl-6-cyanopyridine *N*-oxide **4** in 72% yield. With the 2- and 6-positions blocked, treatment of **4** with $POCl_3$ results in deoxygenation and the formation of the C4 carbon–chlorine bond in **5** in 92% yield. A Buchwald–Hartwig amination with morpholine provides **7** [84] and is followed by nitrile hydrolysis to the corresponding amide by treatment with hydrogen peroxide [85] to give **1** in five steps and an overall yield of 31% (Scheme 17).

In the preparation of the tie-2 tyrosine kinase inhibitor **2** [86, 87], *N*-oxide **9** was prepared in two steps from ketone **25**. Likely due to the increased steric encumbrance of aryl bromide **10**, use of the standard C2 direct arylation conditions resulted in lower yields. A rapid reinvestigation of other ligands revealed that the use of S-Phos was superior to the use of tri(4-fluorophenyl)phosphine. Under these modified conditions, direct arylation to give **11** could be achieved in 90% isolated yield. A second direct arylation at C4 using 4-bromopyridine was accomplished with no change to the standard C4 arylation conditions, generating triarylimidazole *N*-oxide **13** in 73% isolated yield. Selective reduction of the *N*-oxide moiety leaving the sulfoxide intact was carried out with iron and acetic acid to furnish the target compound **2** (Scheme 18).

5 Mechanistic Considerations

A detailed mechanistic discussion is beyond the scope of this review. Nonetheless, an important question dealing with the nature of the C–H bond cleaving mechanism may

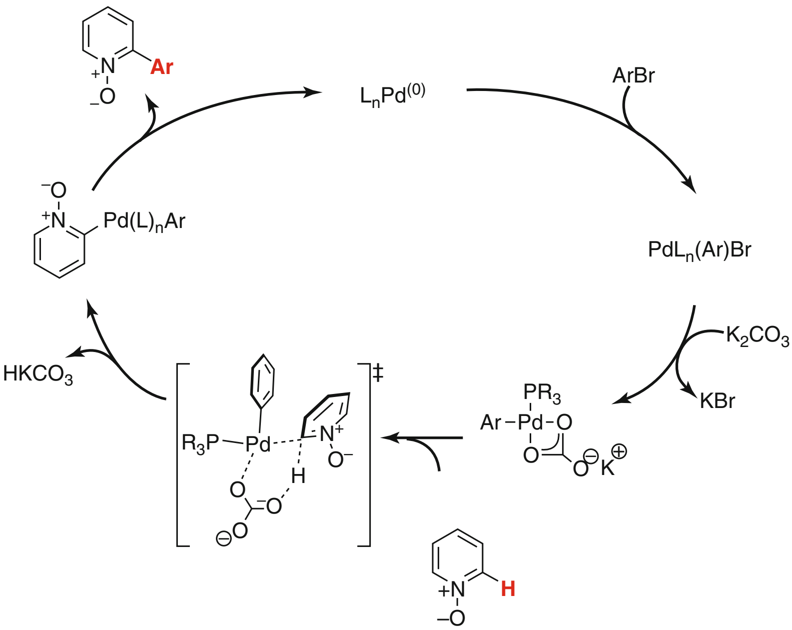


Scheme 18 Synthesis of Tie2 tyrosine kinase inhibitor **2**

be addressed: does experimental evidence support an electrophilic aromatic substitution pathway or is a concerted metallation-deprotonation pathway more likely. In addition to the intriguing regioselectivities described above for 3-substituted pyridine *N*-oxides, relative rates also appear incompatible with common S_EAr outcomes. For example, in competition reactions, 4-nitropyridine *N*-oxide reacts preferentially over 4-picoline *N*-oxide, indicating that it is the more π-electron deficient azine that exhibits higher reactivity. In contrast, when 4-picoline *N*-oxide is reacted with a more π-electron-rich substrate such as 4-methoxypyridine *N*-oxide, it is now the more π-rich substrate that reacts preferentially. These results are inconsistent with an S_EAr reaction pathway and may best fit with a CMD-like mechanism. A potential CMD-based catalytic cycle is illustrated in Scheme 19.

6 Outlook

The past decade has witnessed remarkable growth in the development of catalytic methods for the direct functionalization of aromatic compounds. The rapid growth of metal catalyzed direct arylation processes over this time period is illustrative. Given the importance of the target molecules, and the increased importance given to a consideration of the overall efficiency of chemical processes, the next decade should see equally impressive growth. An important litmus test that this methodology will need to pass in upcoming years is a validation in an industrial/pharmaceutical setting, and perhaps in the more academic pursuit of natural products total synthesis.



Scheme 19 A potential concerted metallation-deprotonation reaction pathway for *N*-oxide direct arylation

This, and other challenges associated with a continued broadening of scope and catalyst development, can only come with a deeper appreciation of the mechanistic underpinnings that govern reactivity and selectivity. As more mechanistic information emerges, new and more exciting advances can be anticipated.

Acknowledgments NSERC, the Research Corporation, the Sloan Foundation, the ACS (PRF AC), Merck Frosst, Merck Inc., Amgen, Eli Lilly, Astra Zeneca, and Boehringer Ingelheim are thanked for financial support of this and our other research programs.

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Palladium and Copper Catalysis in Regioselective, Intermolecular Coupling of C–H and C–Hal Bonds

Olafs Daugulis

Contents

Palladium and copper-catalyzed arylation of C–H bonds by aryl halide reagents is reviewed. The emphasis of the review is on directing-group-containing arene and alkane arylation catalyzed by palladium and on sp^2 C–H bond arylation catalyzed by copper. Literature up to early 2009 is covered.

1 Introduction

Classical methods for creating aryl–aryl bonds involve reactions such as Stille, Suzuki, or Kumada requiring functionalization of both coupling components (Scheme 1A) [1–4]. In contrast, using a carbon–hydrogen bond as a functional group in cross-coupling reactions is beneficial since prefunctionalization of one or both of the coupling components is not required (Scheme 1B,C).

Since aryl halides and aryl metals are typically made in one or more steps from hydrocarbons, carbon–hydrogen bond use as a functional group would result in

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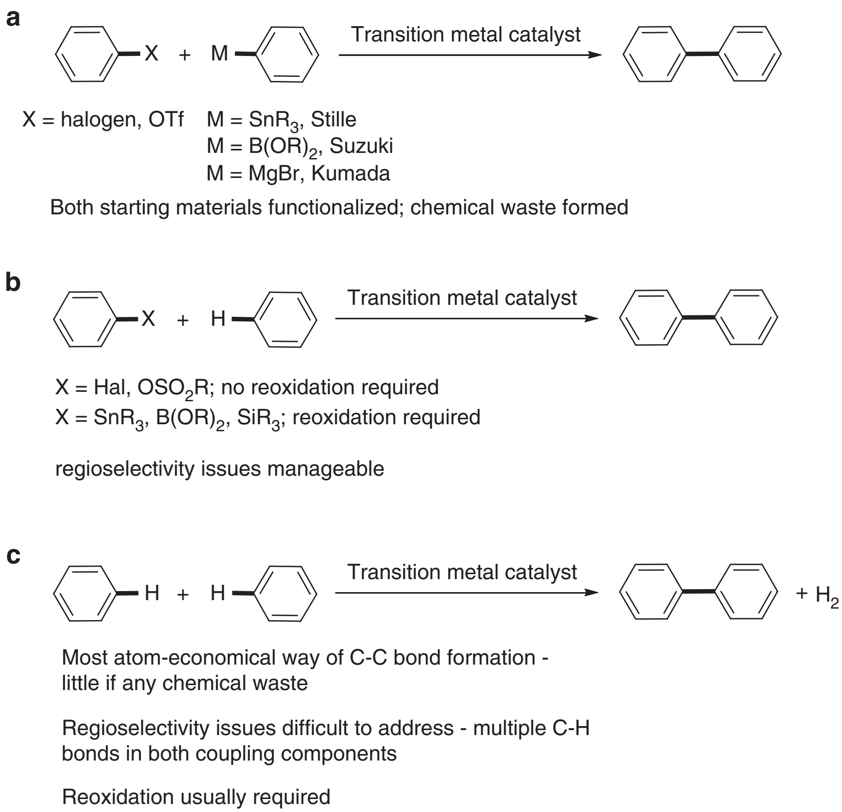


Scheme 1 Carbon–carbon bond formation

shortening of synthetic schemes and overall increased efficiency of chemical processes. One can argue that increased efficiency makes the chemical processes more "green" by reducing the amount of byproducts and solvent waste. The advantages of direct carbon–hydrogen bond functionalization were recognized some time ago [5–8]. Unfortunately, general methods that would be useful in synthetic applications have not been developed until the last decade [9–15]. Additionally, several issues have still not been fully addressed. Unactivated sp^3 (not benzylic or α to heteroatom) C–H bond conversions to C–C bonds are rare. In most cases *tert*-butyl groups are functionalized which is the easiest case due to impossibility of β-hydride elimination from palladated intermediates. Use of nonprecious metals such as copper and iron in C–H bond functionalization is not common, and most widely used catalysts include expensive metals such as palladium, rhodium, and ruthenium.

This review focuses on the synthetic applications of carbon–hydrogen bond arylation by aryl halides, concentrating on palladium and copper catalysis. Mechanistic issues will be covered only briefly. Some examples of carbon–hydrogen bond alkylation by alkyl halides or arylation by aryl metal reagents will also be mentioned. Early work in transition-metal-catalyzed or promoted conversion of C–H bonds to C–C bonds will be described to credit early investigators in the field.

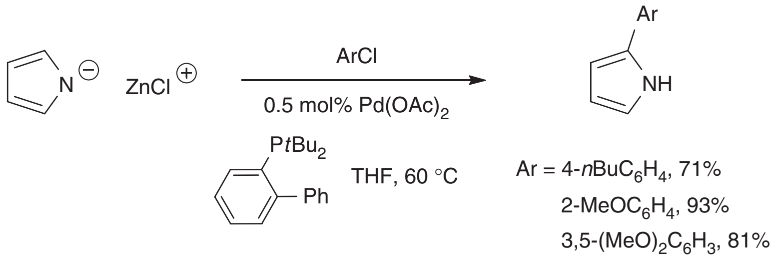
2 Brief Historical Background

The conversion of a nonacidic sp^2 C–H bond to a carbon–metal bond followed by the reaction with a carbon electrophile was first reported by Volhard in 1892 [16]. Volhard showed that thiophene reacts with mercury(II) chloride affording chloromercurythiophene. The arylmercury readily reacts with acid chlorides producing 2-acetyl- and benzoylthiophenes in excellent yields. Thus, the C–H functionalization field is over a century old. The next milestone in C–H activation was described in 1931 by Kharasch [17]. He reported that $AuCl_3$ metalates arenes under mild conditions, demonstrating that transition metals can participate in C–H bond activation reactions. Interestingly, the reactions appear to be highly regioselective. Only *p*-tolylgold dichloride was reported to be formed in the auration of toluene. However, it was not until the 1960s when Kleiman, Dubeck, and Cope reported that Group 10 metal complexes cyclometalate directing-group-containing arenes [18, 19]. The reaction of alkanes such as methane and ethane with a mixture of H_2PtCl_6 and Na_2PtCl_4 was observed by Shilov in 1969 [20]. A mixture of alcohols and alkyl halides is produced. Shilov's report is perhaps the first catalytic transformation where both alkane C–H bond cleavage and functionalization occur at the metal center. Unfortunately, while the reaction is catalytic in Pt(II), it is stoichiometric in Pt(IV). In the early 1980s, Bergman, Graham, and Jones reported the first examples of oxidative addition of unactivated alkane C–H bonds to $Cp^*(PMe_3)M$ (M = Ir, Rh) fragments resulting in observation of alkyl hydride products [21–23]. Following an early report of Ru-catalyzed phosphite *ortho*-arylation [24], Murai developed an efficient, ruthenium-catalyzed method for the *ortho*-alkylation of ketones by alkenes [25]. The advances described above have laid groundwork for the synthetic achievements in C–H bond functionalization field that have occurred in the last 10–15 years.

3 Palladium-Catalyzed C–H Bond Arylation

3.1 Electron-Rich Heterocycle Arylation by Aryl Chlorides

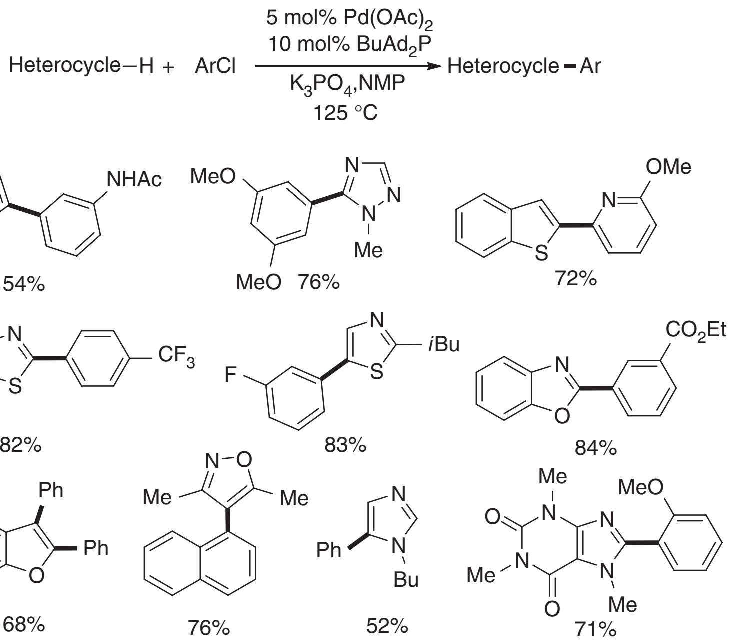
There are now many reports of palladium-catalyzed five-membered heterocycle arylation by aryl iodides and aryl bromides [26–31]. However, only a few reports describe the use of generally cheaper and more accessible aryl chlorides in such reactions. Curiously, the first paper describing aryl chloride use in heterocycle arylation was published in 1985 and is one of the first intermolecular direct heterocycle arylation examples. Ohta showed that chloropyrazines regioselectively arylate *NH*-indoles at C-2 position if $Pd(PPh_3)_4$ catalyst is employed [32]. He also showed that a copper additive improves the arylation yield, a modification that is now widely used for such reactions. In later work, Ohta and coworkers demonstrated that other heterocycles such as furans, thiophenes, pyrroles, oxazoles, imidazoles, and thiazoles also participate in couplings with chloropyrazines [33]. Several examples of intramolecular arene arylation by aryl chlorides have been reported recently [34–36]. The use of nonactivated aryl chlorides for intermolecular reactions was not reported until 2004 when Sadighi disclosed a method for the arylation of zincated pyrroles by aryl halides [37]. 4-Chlorobutylbenzene, 2-chloromethoxybenzene, and 3,5-dimethoxychlorobenzene were shown to couple with pyrrole in excellent yields by employing a combination of catalytic palladium acetate with Buchwald's 2-dialkylphosphinobiphenyl ligands (Scheme 2). Interestingly, use of the phosphine ligand shown in Scheme 2 allows for selective arylation on C-2 of pyrrole; however, the use of a related dicyclohexylphosphine derivative sometimes results in *N*-arylation. Aryl chlorides react at lower temperature than aryl bromides. The reactions are highly regioselective (>19:1) for the arylation at C-2 as opposed to C-3.



Scheme 2 Zincated pyrrole arylation

However, a truly general method for electron-rich heterocycle arylation was not reported until 2007 [38]. Electron-rich, bulky butyl-di-1-adamantylphosphine or *tert*-butyldicyclohexylphosphine in combination with $Pd(OAc)_2$ afforded the best results, and the former was chosen because of cost considerations. Interestingly, electron-rich *N*-heterocyclic carbene ligands that facilitate oxidative addition of aryl chlorides to low-valent transition metals are inefficient in heterocycle arylation. A number of structurally diverse electron-rich heterocycles are reactive (Scheme 3). Thiophene, benzothiophene, 1,2- and 1,3-oxazole derivatives, benzofuran, thiazoles, benzothiazole, 1-alkylimidazoles, 1-alkyl-1,2,4-triazoles, and caffeine can be arylated. Electron-rich, electron-poor, and heteroaryl chlorides can be used.

Some steric hindrance is tolerated on the heterocycle and aryl chloride. Amide substitution is tolerated on both aryl chloride and the heterocycle, and the *NH* group

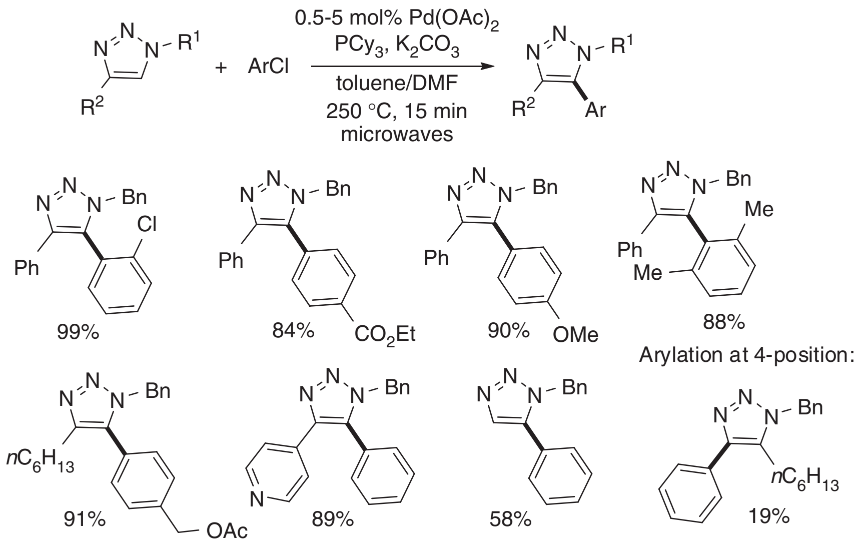


Scheme 3 General method for heterocycle arylation

is not arylated. The limitations of the procedure are as follows: arylation of *NH*-containing heterocycles such as indoles or pyrroles results in *N*-functionalization. Arylation of *N*-substituted indoles does not go to completion and isomer mixtures are usually obtained. Benzofuran monoarylation results in the formation of a mixture of isomers. While the method is very general, additional optimization may be required to maximize reaction yields since the heterocycles that can be arylated are very structurally diverse. For example, the optimized procedure for the phenylation of isobutylthiazole involves decreased amount of phosphine ligand, added sodium acetate reagent, and DMA solvent [39].

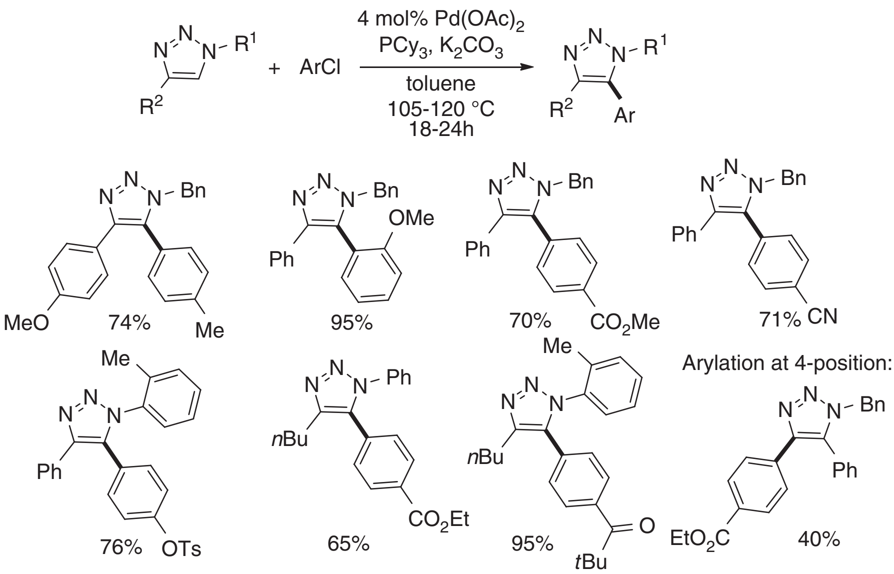
Several other recent papers describe aryl chloride use in direct arylation of heterocycles. Yorimitsu and Oshima have reported that 1,4-disubstituted 1,2,3-triazoles can be treated with aryl chlorides in the presence of K_2CO_3 under palladium catalysis at high temperature under microwave irradiation [40]. Triazoles arylated in 5-position are obtained (Scheme 4). Typically, good to excellent yields are obtained in 15 min. The ligand of choice is tricyclohexylphosphine. Aryl chlorides with electron-withdrawing and -donating groups are reactive. Even highly hindered 2,6-dimethylchlorobenzene is reactive affording the coupling product in 88% yield. However, arylation at 4-position is less efficient. Only 19% yield of product was obtained if 1-benzyl-5-alkyltriazole was arylated by chlorobenzene.

Subsequently, Ackermann reported that 1,2,3-triazoles can be arylated by aryl chlorides even if conventional heating to 105–120 °C is employed [41]. Tricyclohexylphosphine ligand combination with palladium acetate was shown to be the



Scheme 4 Triazole arylation under microwave irradiation

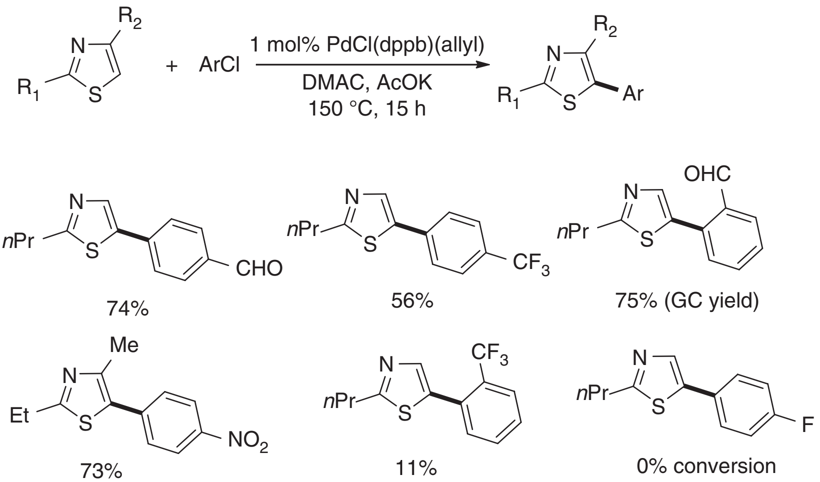
most efficient catalyst. NHC ligands were inefficient, and 2-dialkylphosphinobiphenyl ligands afforded lower conversions to the product. *N*-Alkyl and *N*-aryl 1,2,3-triazoles can be arylated by a variety of electron-poor, electron-rich, and heteroaryl chlorides (Scheme 5). Some hindrance on the aryl chloride is tolerated. Method is functional group tolerant – even 4-chlorobenzonitrile can be used as a coupling partner.



Scheme 5 Triazole arylation under conventional heating

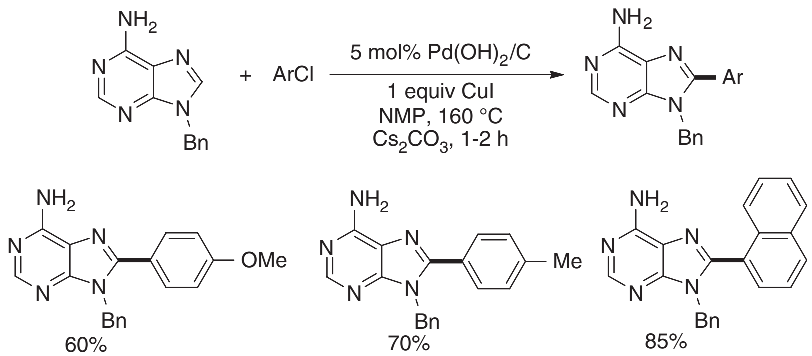
N-Monosubstituted triazole arylation resulted in product mixture. Arylation of 1,5-disubstituted triazole afforded the product in low yield consistent with results reported by Yorimitsu.

Doucet has reported that activated aryl chlorides can be employed in the arylation of thiazoles if PdCl(dppb)C_3H_5 catalyst is used (Scheme 6) [42]. Acetyl, formyl, nitro, cyano, ester, and trifluoromethyl substituted aryl chlorides are reactive. However, 4-chlorofluorobenzene was not reactive. Use of the same catalyst system was shown to be effective for the arylation of oxazole and benzoxazole with activated aryl chlorides [43].



Scheme 6 Activated aryl chlorides in thiazole arylation

In a recent paper, Alami has shown that $Pd(OH)_2/C$ catalyzes arylation of adenine derivatives by aryl halides, including aryl chlorides, under microwave activation (Scheme 7) [44]. Stoichiometric CuI additive is also employed.



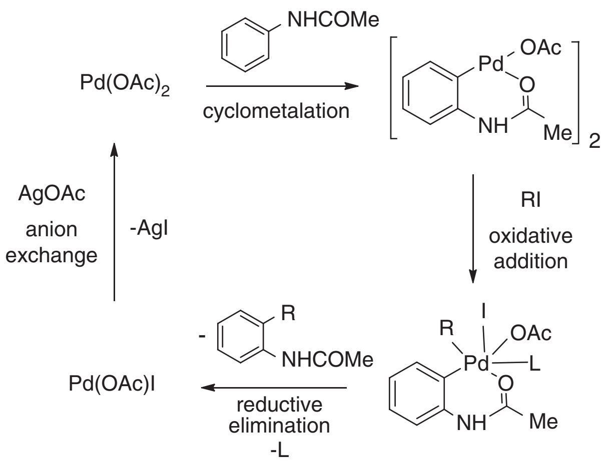
Scheme 7 Pearlman's catalyst in adenine arylation

While most of the examples reported involve arylation by aryl bromides or iodides, four examples of aryl chloride use were described, with arylation product yields ranging from 22% to 85%.

3.2 Directing-Group Containing Arene and Alkane Arylation

3.2.1 Anilide Arylation

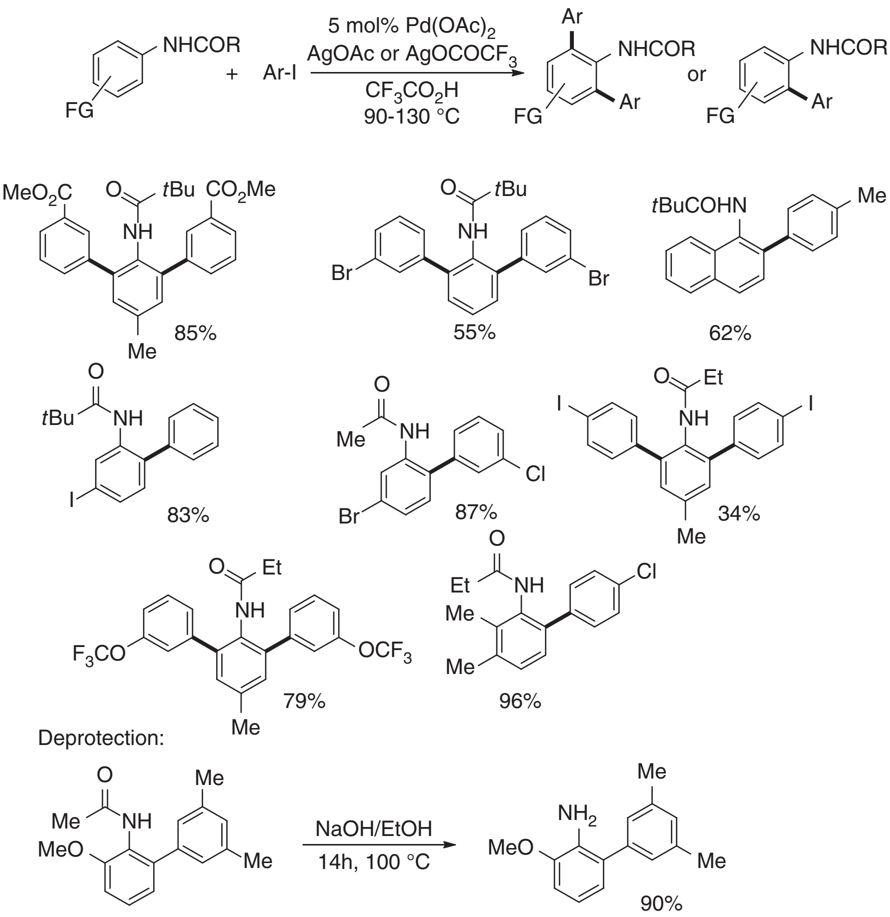
In 1984, Tremont described a procedure for palladium acetate-promoted anilide alkylation by alkyl iodides [45, 46]. He suggested that the reaction proceeds by either a Pd(II)–Pd(IV) catalytic cycle or a sigma-bond metathesis mechanism. A possible Pd(II)–Pd(IV) catalytic cycle is presented in Scheme 8.



Scheme 8 A Pd(II)–Pd(IV) catalytic cycle

Cyclometallation of the anilide is followed by oxidative addition of aryl or alkyl iodide to Pd(II) species affording a high-energy Pd(IV) complex. Fast reductive elimination and anion exchange affords the product and regenerates the catalyst. Since it has been shown that both alkyl and aryl iodides participate in Pd(II)–Pd(IV) catalytic cycles, it should be possible to employ aryl iodides in the reactions [47]. For R = aryl, it should be possible to render reactions catalytic because aryl iodides are compatible with silver salts that are used for iodide removal from palladium coordination sphere. Consequently, a combination of aryl iodide, silver acetate, and catalytic palladium acetate efficiently arylates pivalanilides (Scheme 9) [48]. The reactions are the fastest in trifluoroacetic acid and afford the *ortho*-arylated products in good to excellent yields. Bromide is tolerated both on the aryl iodide and pivalanilide coupling partners. As a result, scaffolds amenable for further functionalization by using Pd(0)–Pd(II) coupling processes can be obtained. While the pivaloylated anilines afford the cleanest results, it is difficult to remove the acyl group from the arylation product. Use of removable directing-groups such as acetyl, propionyl, or trifluoroacetyl would allow a short synthesis of 2-aminobiphenyl- or terphenyl derivatives. Related 2,6-diarylanilines are used in the synthesis of ligands for Brookhart-type transition-metal-catalyzed olefin polymerization [49]. Access to these compounds requires multiple step syntheses from starting materials that may not be readily available.

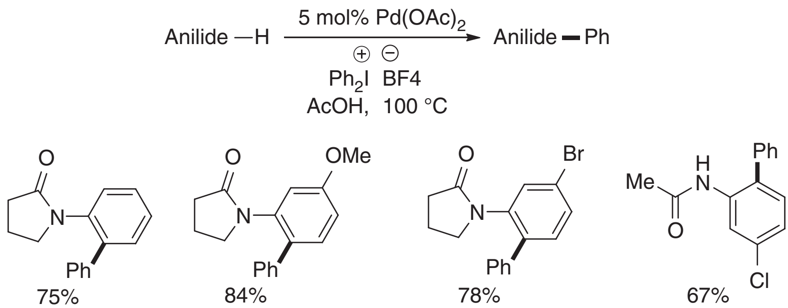
After some optimization, it was found that propionyl and acetyl derivatives of anilines can be efficiently arylated under conditions similar to the ones described above (Scheme 9) [50]. Electron-rich as well as electron-poor anilides are reactive. Aryl iodides of all electronic properties can be used; however, *ortho*-substitution is not tolerated. Propionylanilides are arylated in somewhat higher yields than acetanilides.



Scheme 9 Anilide arylation

Anilides substituted in 2- or 3-positions are monoarylated. 4-Substituted anilides can be either mono- or diarylated. For slower reactions or diarylation, use of silver trifluoroacetate instead of silver acetate is beneficial by increasing the reaction rate. The products can be deprotected by base hydrolysis to afford 2-aryl- or 2,6-diarylanilines.

Sanford has reported a method for palladium-catalyzed anilide arylation by iodonium salts (Scheme 10) [51]. The reactions proceed by a Pd(II)–Pd(IV) couple mechanism. High functional group tolerance, excellent regioselectivity, and good reaction scope was observed. The reactions were carried out at 100 °C in acetic acid solvent.



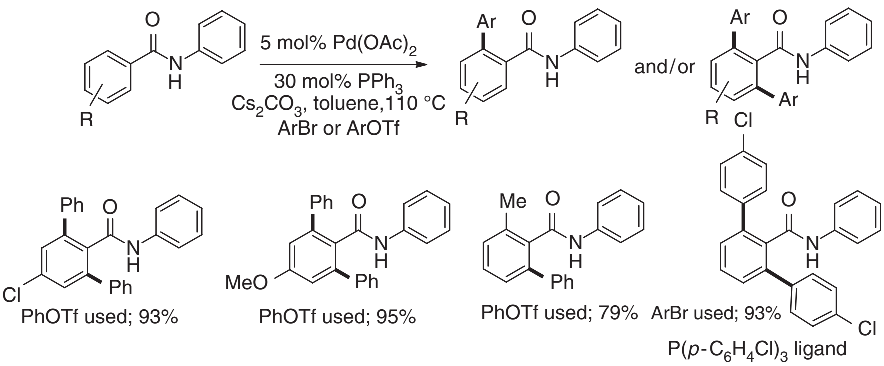
Scheme 10 Anilide arylation by iodonium salts

Several reports have appeared describing anilide arylation by arenes that do not involve coupling of a C–H bond with a C–Hal bond and thus will be discussed only briefly. Buchwald has shown that oxidative arylation of anilides takes place in presence of 5–10 mol% of palladium acetate and catalytic DMSO in trifluoroacetic acid solvent by using oxygen as the terminal oxidant [52]. Pivalanilides afford the best results. Notably, only about four equivalents of the arene component are required for efficient arylation. However, regioisomer mixtures were obtained if monosubstituted arenes were used as the coupling components.

Shi has reported a method for *N*-alkylanilide arylation by simple arenes [53]. The reaction conditions include heating the anilide with excess arene in propionic acid in the presence of catalytic palladium acetate and copper triflate under oxygen atmosphere. Use of monosubstituted arenes leads to the formation of isomer mixtures; however, from the point of atom economy C–H/C–H couplings are the most efficient way for formation of C–C bonds if oxygen is used as the terminal oxidant. Shi has also reported that anilides can be coupled with arylboronic acids and trialkoxyarylsilanes [54, 55]. Silver and copper salts are used as terminal oxidants.

3.2.2 Benzamide Arylation

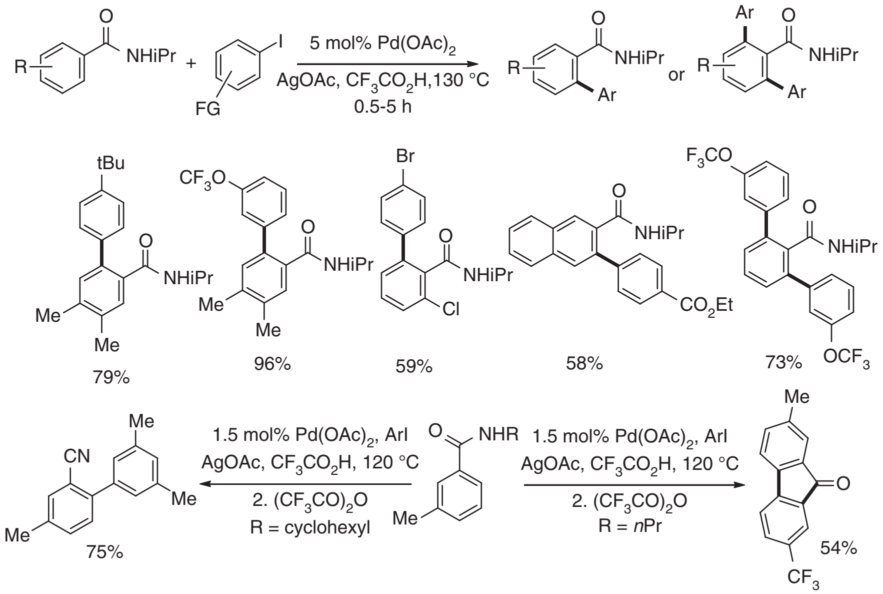
In an early work, Miura and coworkers have demonstrated that benzoic acid phenylamides can be arylated by aryl bromides or triflates (Scheme 11) [56].



Scheme 11 Benzanilide arylation by aryl bromides and triflates

The reactions proceed in DMF or toluene and require the presence of a cesium base. The coordination of an amide anion to an intermediate palladium species is necessary for the *ortho*-palladation/aryl transfer step to occur. Most likely the reaction proceeds by a Pd(0)–Pd(II) mechanistic pathway. Chloride substitution is tolerated on both coupling components. Contamination of phenyl group from phosphine is, however, observed.

We reasoned that the arylation of benzamide derivatives should also be possible under Pd(II)–Pd(IV) couple conditions. Gratifyingly, conditions that were developed for anilide arylation worked well for benzamide arylation (Scheme 12) [57].

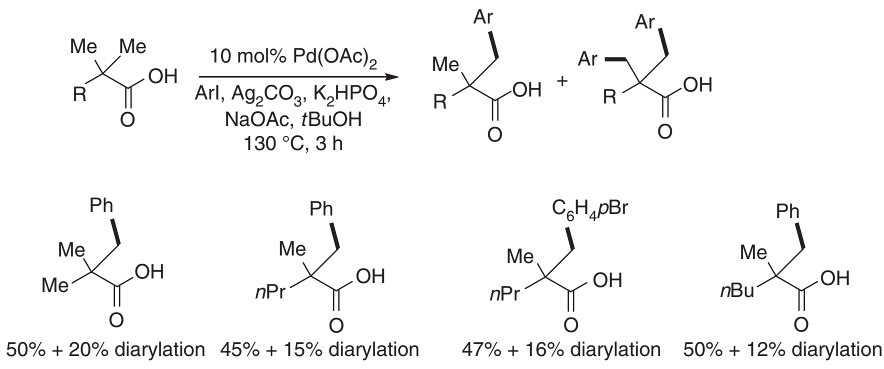


Scheme 12 Benzamide arylation by aryl iodides

The best results were obtained with *n*-propylamide, isopropylamide, and cyclohexylamide derivatives. The reactions proceed well with electron-poor aryl iodides. Electron-rich aryl iodides react faster but are more susceptible to side reactions. Thus, more optimization is needed if electron-rich aryl iodides are used. Arylation products can be further elaborated to fluorenones and nitriles in a one-pot reaction with trifluoroacetic anhydride [58].

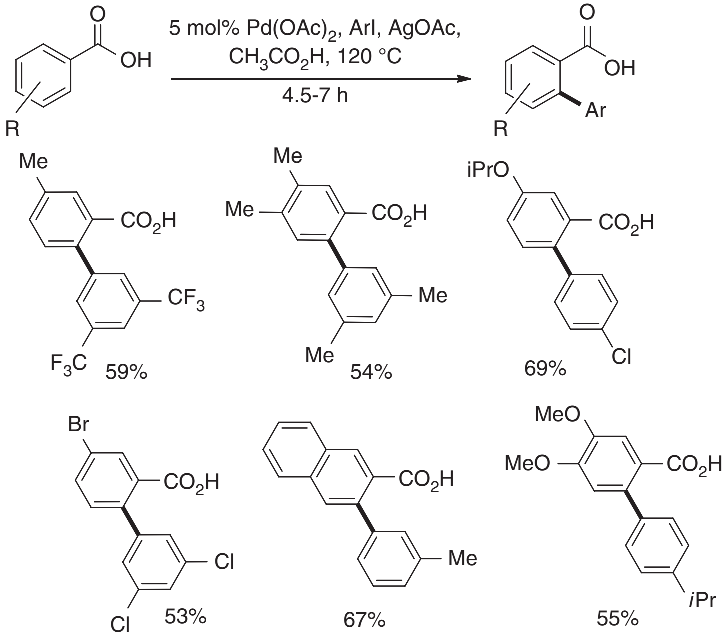
3.2.3 Carboxylic Acid Arylation

Ortho-arylation of benzoic acids is often preferable to *ortho*-arylation of benzamides if conversion of the amide moiety to other functional groups is desired. However, only a few reports have dealt with the *ortho*-functionalization of free benzoic acids due to challenges that involve such transformations. The reactions can be complicated by decarboxylation of the product and the starting material. Despite those difficulties, several methods for direct *ortho*-arylation of benzoic acids have been developed. Yu has shown that arylboronates are effective in arylation of benzoic acids under palladium catalysis [59]. The reactions require the presence of palladium acetate catalyst, silver carbonate oxidant, and benzoquinone. Even more interestingly, the procedure is applicable to the arylation of unactivated sp^3 C–H bonds in tertiary carboxylic acids such as pivalic acid (Scheme 13) if aryl iodide coupling partner is used. Aryl trifluoroborates can also be used [60].



Scheme 13 Carboxylic acid arylation by aryl iodides

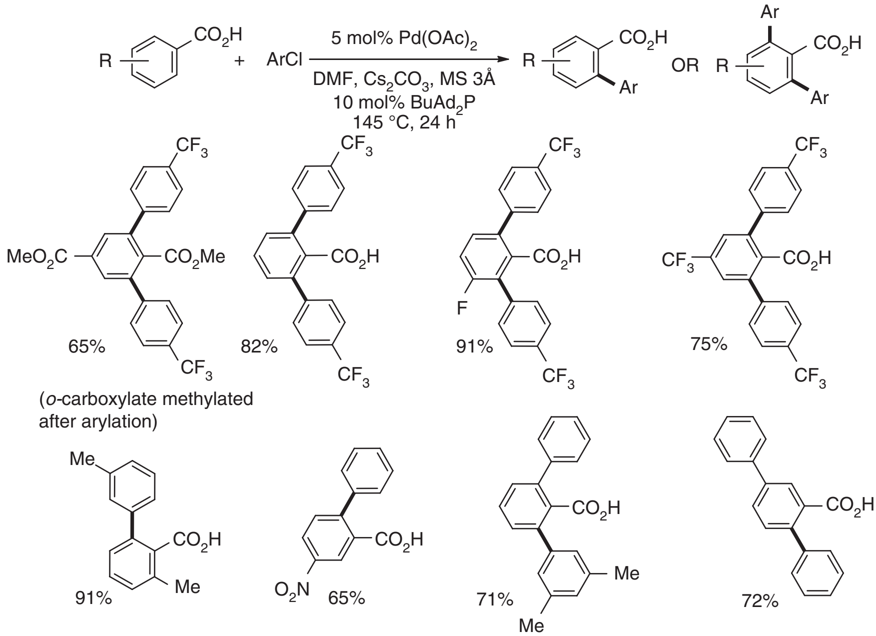
Another method that has been developed for benzoic acid arylation by aryl iodides involves use of a combination of catalytic palladium acetate with stoichiometric silver acetate in acetic acid (Scheme 14) [61]. This method is tolerant of chloride and bromide substitution and most likely proceeds through a Pd(II)–Pd(IV) coupling cycle. Moderately electron-poor to electron-rich benzoic acids are reactive, and aryl iodides of any electronic properties may be used. Reactions generally proceed in lower yields than amide or anilide arylations due to competing solvent arylation. Thus, temperature needs to be controlled carefully for achieving optimal results. Monoarylation of 2- or 3-substitued benzoic acids proceeds with acceptable to good yields. However, clean diarylation of benzoic acids could not be achieved due to formation of mono- and diarylated product mixtures.



Scheme 14 Benzoic acid arylation by aryl iodides

Aryl chlorides are widely used for C–C bond creation under Pd(0)–Pd(II) catalytic cycle conditions [62]. As a consequence, use of cheaper ArCl in benzoic acid arylation should also be possible if appropriate ligands are used and catalytic cycle for the arylation is changed from Pd(II)–Pd(IV) to a Pd(0)–Pd(II) couple. The method involves use of catalytic palladium acetate in combination with butyl-di-1-adamantylphosphine ligand, cesium carbonate base, and an aryl chloride coupling partner [61]. Benzoic acids of any electronic properties are reactive (Scheme 15). Electron-poor benzoic acids react well, and it is possible to couple them with both electron-poor and electron-rich aryl chlorides. Both electron-poor and electron-rich aryl chlorides can be coupled with electron-rich benzoic acids. However, the combination of an electron-rich aryl chloride with an electron-rich benzoic acid is occasionally problematic due to product decarboxylation or aryl halide hydrodehalogenation. The nitro group is compatible with the reaction conditions, as is the ester group.

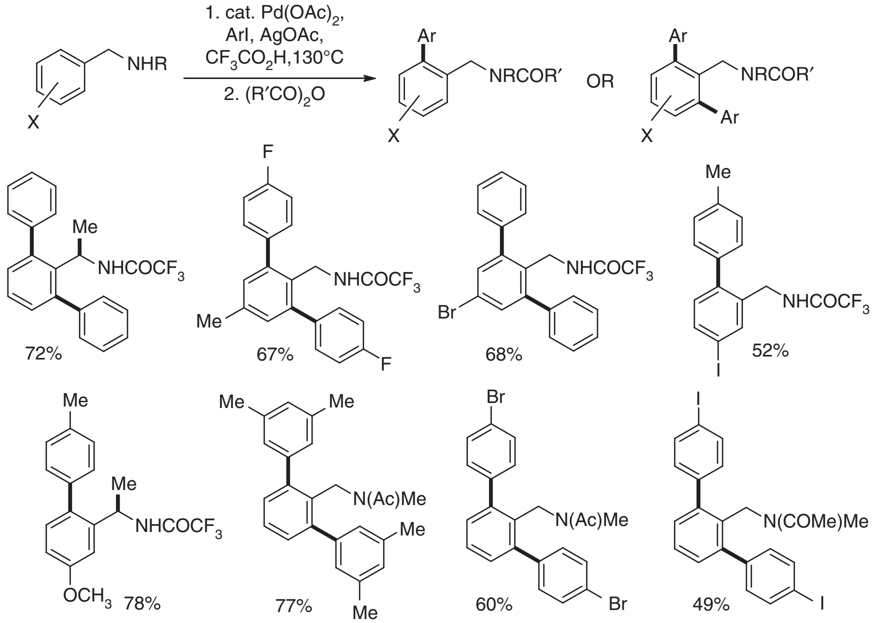
In general, 2- or 3-substituted benzoic acids are monoarylated due to steric interference of the substituent. Halogens other than fluorine are not compatible with the reaction conditions in contrast with the ArI/AgOAc method.



Scheme 15 Benzoic acid arylation by aryl chlorides

3.2.4 Benzylamine Arylation

According to mechanistic considerations of Scheme 8, benzylamine arylation should also be feasible. The palladation of benzylamines in strong acid might be retarded due to protonation of the directing amino group. Employing a limited amount of trifluoroacetic acid solvent allowed efficient benzylamine arylation [63]. Specifically, the benzylamine arylation reactions are the fastest if about five equivalents of trifluoroacetic acid solvent are used. A number of benzylamines and *N*-methylbenzylamines were shown to be reactive under these conditions (Scheme 16). The reactions proceed well with both electron-rich and moderately electron-poor benzylamines. For unsubstituted or 4-substituted benzylamines, 2,6-diarylation is observed. Benzylamines substituted at the 3-position are monoarylated. As in the case of pyridine and anilide arylation, bromine is tolerated on the substrate, and even iodide is compatible with the reaction conditions, although the yield is reduced. The products are acylated after the reaction to facilitate isolation.



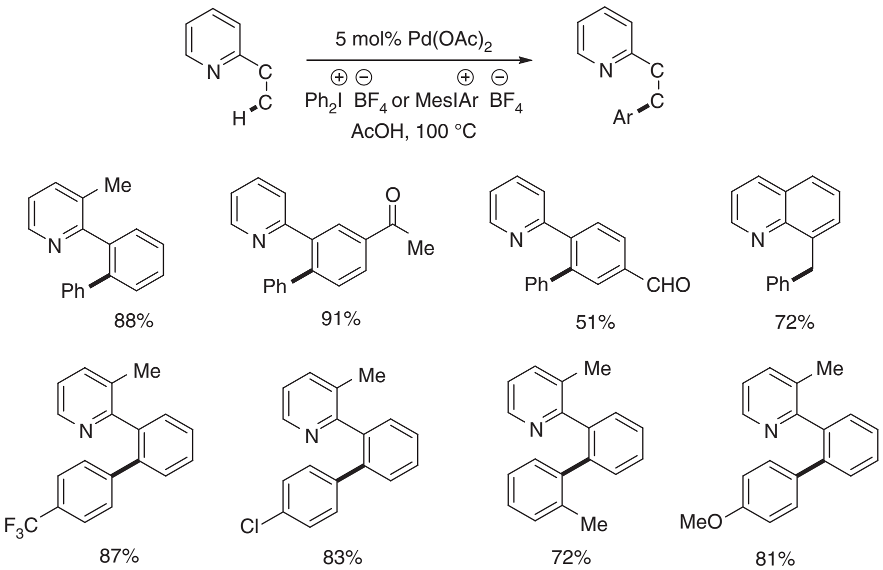
Scheme 16 Benzylamine arylation

3.2.5 Arylation by Employing Other Nitrogen Directing-Groups

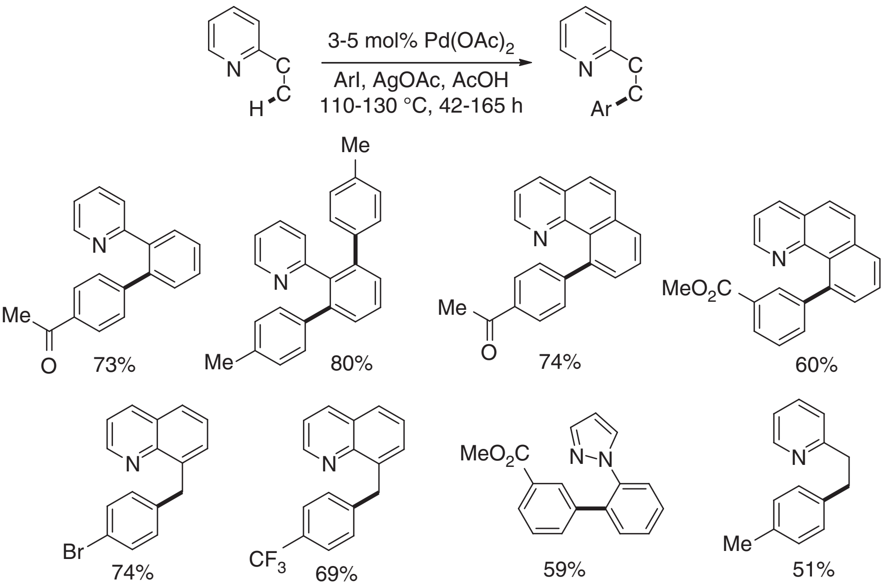
Ruthenium-catalyzed 2-substituted pyridine C–H bond arylation by aryl halides was reported by Oi and Inoue in 2001 [64]. Several other *ortho*-directing groups have been shown to be effective in ruthenium-catalyzed *ortho*-arylation by the same group. A report by Ackermann details an early use of nonactivated aryl chlorides in the arylation of 2-arylpyridines by employing ruthenium catalysis [65]. Subsequently, simple $RuCl_3$ aquacomplex was shown to be reactive in arylation of 2-arylpyridines [66]. Several groups have reported that alkylation of 2-arylpyridines and oxazolines is possible under palladium catalysis by employing peroxides or alkyltin reagents [67, 68]. Even iron catalysts can be used in the arylation of 2-substituted pyridines by diarylzinc species [69]. Charette has described palladium-catalyzed benzylic C–H arylation of 2-alkylsubstituted *N*-iminopyridinium ylides [70]. In a very interesting paper, Bergman and Ellman have shown that pyridines can be arylated in 2-position by aryl bromides under rhodium catalysis [71].

Palladium-catalyzed arylation of nitrogen-directing group containing arenes will be covered in more detail. The first report of palladium catalysis in 2-arylpyridine arylation was published by Sanford [51]. The arylations proceed at 100 °C in acetic acid or aromatic solvents by using diaryliodonium electrophiles (Scheme 17). Selective transfer of the less hindered aryl group from mesitylaryliodonium salts was also demonstrated. Interestingly, arylation of benzylic positions is very facile.

Aryl iodide use in 2-substituted pyridine arylation has also been reported (Scheme 18) [72]. Acetic acid solvent is usually employed, and extended reaction times, typically several days, are required. Interestingly, the most reactive substrate



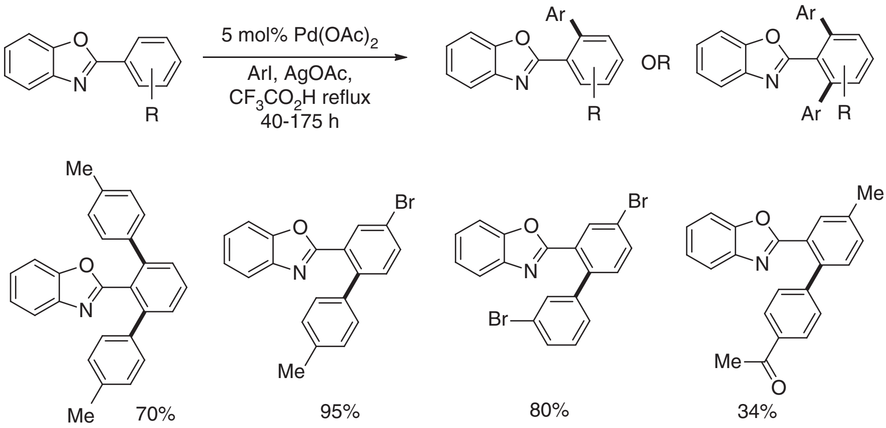
Scheme 17 2-Substituted pyridine arylation by iodonium salts



Scheme 18 Aryl iodides in 2-substituted pyridine arylation

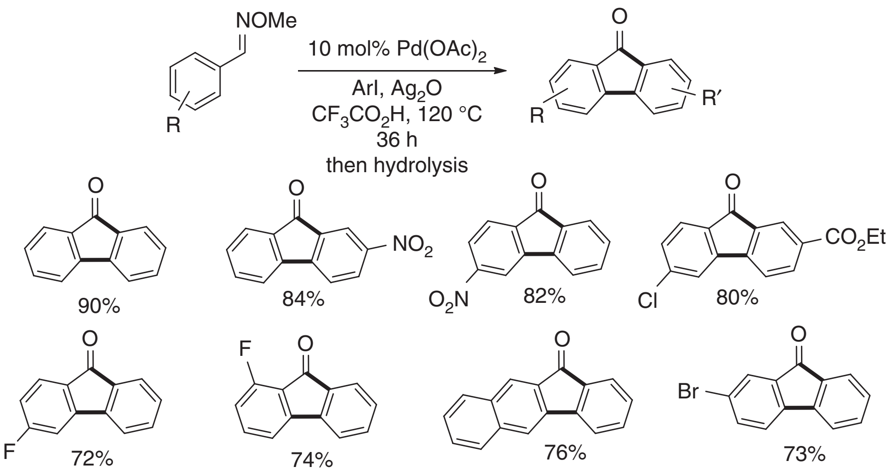
is 8-methylquinoline showing that arylation of benzylic sp^3 C–H bonds is more facile than the arylation of sp^2 C–H bonds. *p*-Tolylation of 2-ethylpyridine affords 2-(*p*-tolylethyl)pyridine in an acceptable yield. This is perhaps the first example of palladium-catalyzed C–C bond formation from an unactivated sp^3 C–H bond that is not a part of a *tert*-butyl group.

Wu has shown that benzoxazole moiety can efficiently serve as the directing group under conditions similar to those developed in [48, 72]. Reactions proceed best in refluxing trifluoroacetic acid and require the presence of silver acetate as the halide removing agent (Scheme 19).



Scheme 19 Benzoxazole directing-group

An interesting extension of palladium-catalyzed arylation of directing-group containing arenes by aryl iodides has been recently described by Cheng [74]. The arylation of aldoxime ethers under standard conditions ($Pd(OAc)_2$ catalyst, CF_3CO_2H solvent, stoichiometric Ag^+ source at elevated T) affords fluorenones by tandem *o*-arylation/palladium-catalyzed cyclization pathway (Scheme 20).



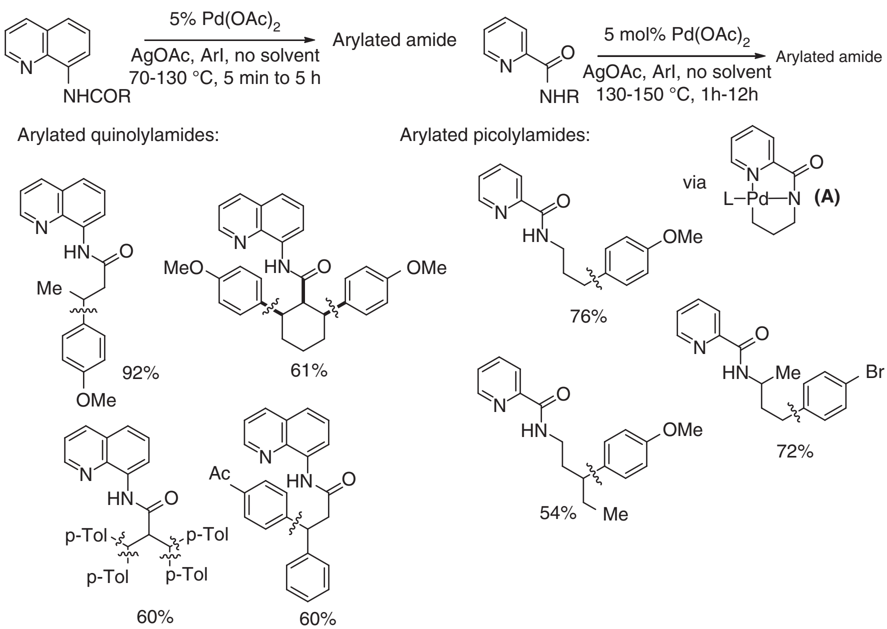
Scheme 20 Fluorenone synthesis by *o*-arylation methodology

Palladium-catalyzed dimerization of 2-arylpyridines by employing oxone as the terminal oxidant has been reported [75]. The reaction was shown to proceed via a Pd(II)–Pd(IV) pathway. A method for cross-coupling of simple arenes with 2-arylpyridine derivatives by using catalytic palladium acetate in the presence of two equivalents of silver carbonate requires use of a large excess of the less reactive arene [76].

3.2.6 Directing-Group-Containing Alkane Arylation

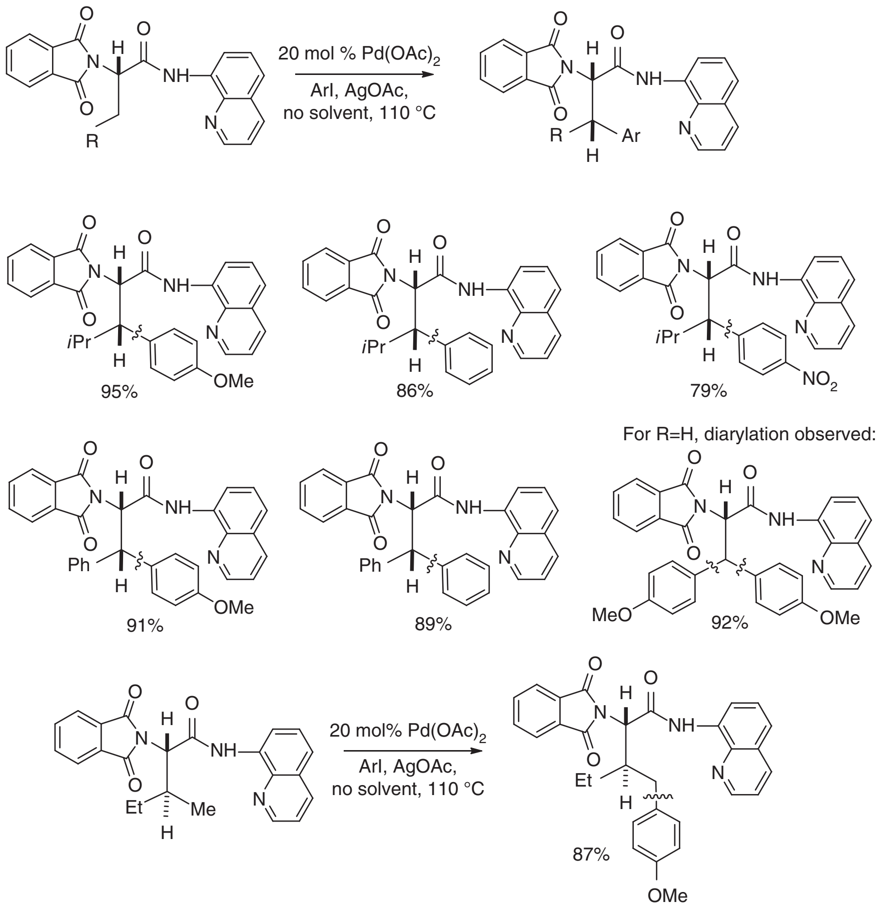
Noncarbene conversions of unactivated (not benzylic or α to heteroatom) sp^3 C–H bonds to C–C bonds are rare. Only a handful of examples have been described, and most of them involve the simplest case – activation of a *tert*-butyl group where β-hydride elimination from the intermediate palladated complex is impossible. Dyker has disclosed 1,2-dihydrocyclobutabenzene derivative synthesis starting from 1-*tert*-butyl-2-iodobenzene [77]. While studying the effect of ligand structure on the efficiency of Suzuki–Miyaura coupling processes, Buchwald and coworkers discovered an interesting C–H bond activation/C–C bond formation sequence [78]. Thus, derivatives of 1-bromo-2,4,6-tri-*tert*-butylbenzene are arylated in the *tert*-butyl groups under Pd catalysis by boronic acids. Baudoin has shown that 2-bromoalkylbenzenes can be cyclized to benzocyclobutenes or dehydrogenated under Pd catalysis [79, 80]. Fagnou has reported that 2-bromophenol *tert*-butyl ethers can be cyclized under palladium catalysis to form dihydrobenzofurans [81]. *N*-Pivaloylated heterocycles can be cyclized intramolecularly by using catalytic palladium acetate with air as the stoichiometric oxidant [82]. A related report by Fujii and Ohno shows that 2-bromo-*tert*-butylaniline derivatives can be cyclized to indolines employing a palladium acetate-tricyclohexylphosphine catalyst [83]. Interestingly, quaternary carbon center is not required for the latter transformation. Yu has developed a procedure for the arylation and alkylation of free pivalic acids and *O*-methylhydroxamic acids by boronates and boronic acids [59, 84].

It has been shown that if pyridine directing-group is employed in palladium acetate-catalyzed arylation by aryl iodides, even sp^3 C–H bonds can be arylated [72]. The generality of the method could be improved if pyridine is employed as a part of a removable auxiliary ligand. The reaction mechanism involves a C–H activation step and, presumably, a step where Pd(II) is converted to Pd(IV). Additional pyridine ligand may stabilize a high-energy Pd(IV) species and presumably increase the rate of its formation [85]. The C–H activation step will also most likely be facilitated by an additional coordination site. β-Hydride elimination should be retarded by saturating the coordination sites on palladium. As a consequence, the logical auxiliary structures are pyridines linked to the group to be arylated by an amide linkage. After the arylation step the auxiliary could be removed by acid or base hydrolysis. The arylation regiochemistry is dictated by five-membered palladated chelate formation (Scheme 21, structure A). Auxiliary-assisted sp^3 C–H bond arylation results are presented in Scheme 21 [86]. Picolinic acid and 8-aminoquinoline were shown to be effective auxiliaries for the arylation of sp^3 C–H bonds. Arylation regiochemistry is dictated by the formation of a double five-membered ring chelate. As expected, carboxylic acid 8-aminoquinoline amides are arylated in β-positions. Aliphatic C–H bonds are arylated extremely easily in this case. The butyramide of 8-aminoquinoline undergoes *p*-methoxyphenylation in the methylene group in less than 5 min at 110 °C. Cyclohexanecarboxylic acid amide is diarylated. The reaction proceeds at 70 °C and is diastereoselective (8:1) for the formation of the all-*cis* product. For a Pd-catalyzed functionalization of secondary aliphatic C–H bonds these are exceptionally mild conditions. Interestingly, secondary C–H bonds react faster than primary bonds, allowing the tetraarylation of isobutyric amide. The transposition of the amide group allows one to arylate alkylamine derivatives by employing picolinic acid as a removable directing-group. This is an unusual remote functionalization reaction that allows selective arylation of the γ-position of an aliphatic amine. The reaction conditions are harsher than for aminoquinoline derivatives, showing that the role of the auxiliary ligand is quite important. The reactions shown above are among the first examples of palladium-catalyzed unactivated sp^3 C–H bond transformation into C–C bonds with no adjacent tertiary centers.



Scheme 21 Auxiliary-assisted arylation of unactivated sp^3 C–H bonds

The method described above has been used by Corey to functionalize α-amino acid derivatives [87]. *N*-Phthaloyl-α-amino acid amides of 8-aminoquinoline can be selectively arylated at the β-carbon. Interestingly, in certain cases γ-arylation is observed if the β-position is tertiary (Scheme 22). A number of unnatural (S)-α-amino acid amides are available by employing this method. The arylations that result in formation of new stereocenters are diastereoselective.



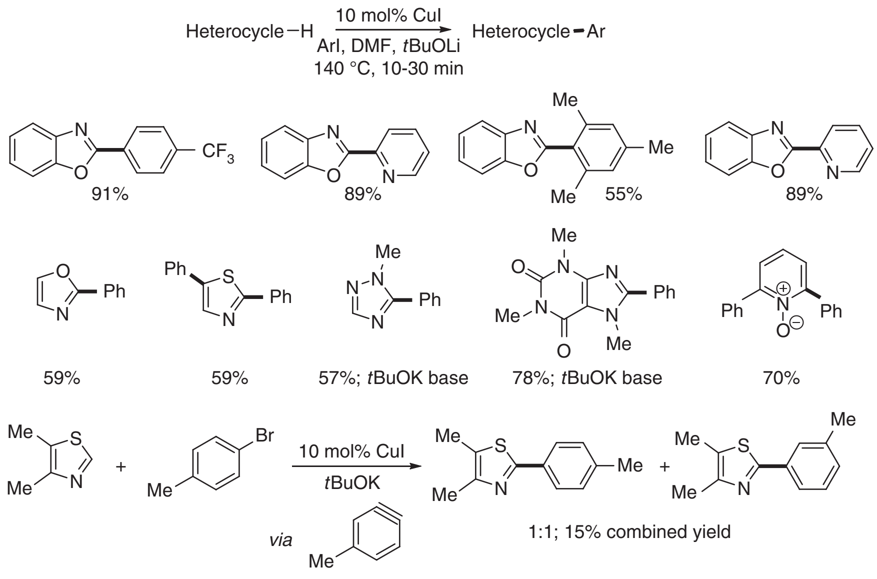
Scheme 22 Amino acid derivative arylation

4 Copper-Catalyzed sp² C–H Bond Arylation

Copper is underutilized as a catalyst for C–H bond functionalization even though it was the first transition metal shown to promote carbon–hydrogen bond arylation. In 1941, Steinkopf, Leitsmann, and Hofmann showed that Ullmann reaction of 2-iodothiophene produces substantial amounts of tritiophene [88]. This reaction necessarily involves one C–H bond arylation step. Subsequently, it has been shown that electron-deficient arenes such as polynitrobenzenes and pentafluorobenzene, and electron-rich thiophene can also be arylated by aryl iodides in the presence of stoichiometric copper(I) oxide under forcing conditions [89–91]. Use of copper(I) *tert*-butoxide in the arylation of 1,3-dinitrobenzene has been reported [92]. Miura has shown that copper(I) salts not only modulate the regioselectivity of palladium-catalyzed electron-rich imidazole arylation by aryl iodides, but that use of overstoichiometric CuI can bring about low-yielding arylation of such species [93]. These observations can be explained by invoking an organocopper intermediate that would react with aryl iodide to form the cross-coupled product. If the presumed arylcopper intermediate could be generated efficiently, a copper-catalyzed method for the carbon–hydrogen bond arylation would be achieved. A logical approach to organocopper species generation involves employing a relatively strong base. This approach was used in developing a general method for copper-catalyzed arylation of acidic sp^2 C–H bonds.

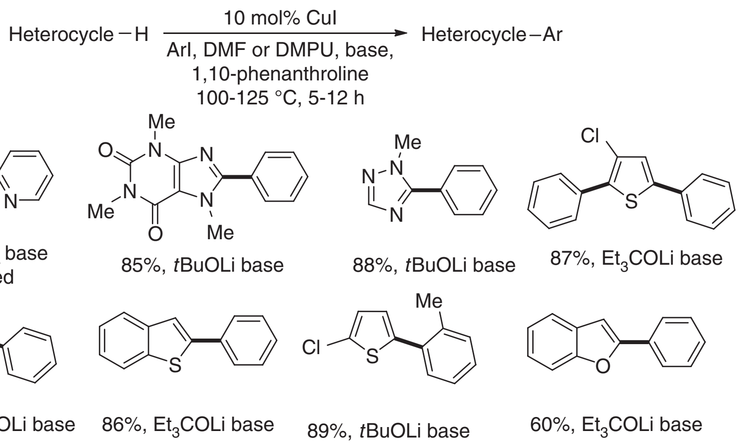
4.1 Electron-Rich Heterocycle Arylation

Two sets of conditions have been developed for electron-rich heterocycle arylation [94, 95]. Most acidic heterocycles such as benzoxazole or benzothiazole may be arylated by employing *t*BuOLi base, aryl iodide, and DMF solvent (Scheme 23). These reactions proceed at 140 °C in minutes. For less acidic imidazole, 1,2,4-triazole, and caffeine derivatives a stronger *t*BuOK base is required, and the reaction proceeds by a benzyne-type mechanism. Formation of regioisomer mixtures was observed if substituted aryl halides were used in combination with *t*BuOK (Scheme 23).



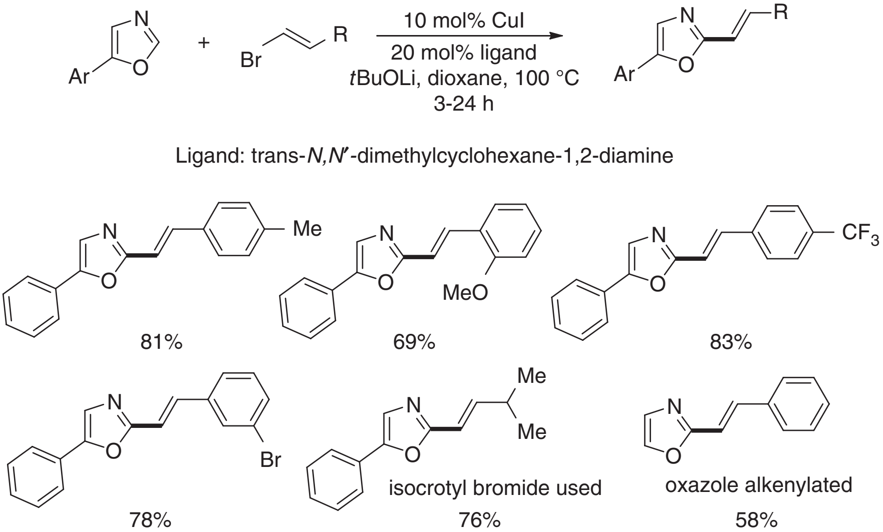
Scheme 23 Arylation of acidic heterocycles

For slower reactions, formation of *tert*-butyl aryl ether by the reaction of *tert*-butoxide base with aryl iodide was observed, resulting in decreased conversion to the arylation products. Therefore, a second set of conditions was developed. Employing phenanthroline ligand as described by Buchwald and Venkataraman [96, 97] should allow for a more efficient heterocycle arylation by stabilizing the copper catalyst and facilitating the halide displacement step. Replacing *t*BuOK with a weaker lithium alkoxide or K_3PO_4 base should shut down the benzyne mechanism, ensuring arylation regioselectivity. Employing hindered Et_3COLi base instead of *t*BuOLi should slow down the nucleophilic substitution of aryl iodide by alkoxide. Addition of phenanthroline ligand allows *t*BuOLi or Et_3COLi base to be used for less acidic heterocycle arylation, avoiding the problems associated with the benzyne mechanism. The modified reaction conditions allow for the arylation of less acidic heterocycles that were not reactive under the previous conditions (Scheme 24). It is possible to employ K_3PO_4 base in the arylation of the most acidic heterocycles with DMSO p*K*as below 27. Thiophenes, caffeine, alkylimidazoles, alkyltriazoles, benzothiophene, and benzofuran can be arylated by employing either *t*BuOLi or Et_3COLi base. The limitations of the method are as follows. Furans and *N*-substituted indoles are unreactive, while heterocycles possessing acidic N–H bonds are arylated on the nitrogen. The following DMSO p*K*as of heterocycle C–H bonds have been reported: *N*-alkylindoles, about 37; furan, 35; *N*-methylimidazole, 33 [98]. Consequently, copper-catalyzed electron-rich heterocycle arylation is successful for compounds possessing p*K*as below 35.



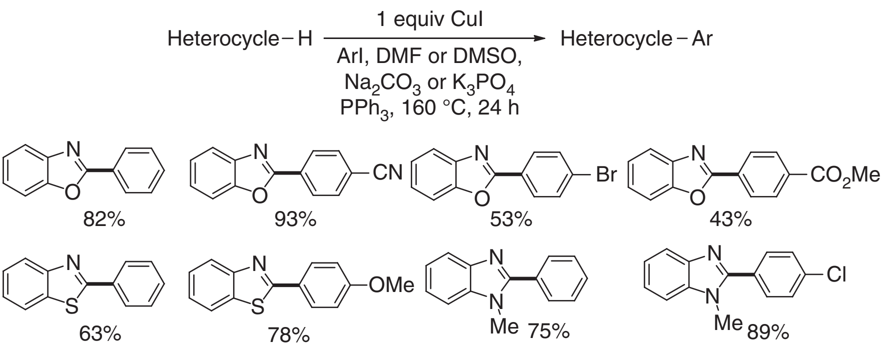
Scheme 24 Electron-rich heterocycle arylation

In a recent work, Piguel has shown that direct alkenylation of various electron-rich heterocycles by alkenyl bromides is possible under copper catalysis [99]. Employing a combination of CuI with *trans*-1,2-*N,N′*-dimethylcyclohexane diamine ligand and *t*BuOLi base, 5-aryloxazoles, benzothiazole, benzoxazole, and unsubstituted oxazole were alkenylated by β-bromostyrenes and isocrotyl bromide in good to excellent yields (Scheme 25). A short, convergent synthesis of a natural product annuloline was also described using copper-catalyzed alkenylation as the key step.



Scheme 25 Oxazole alkenylation

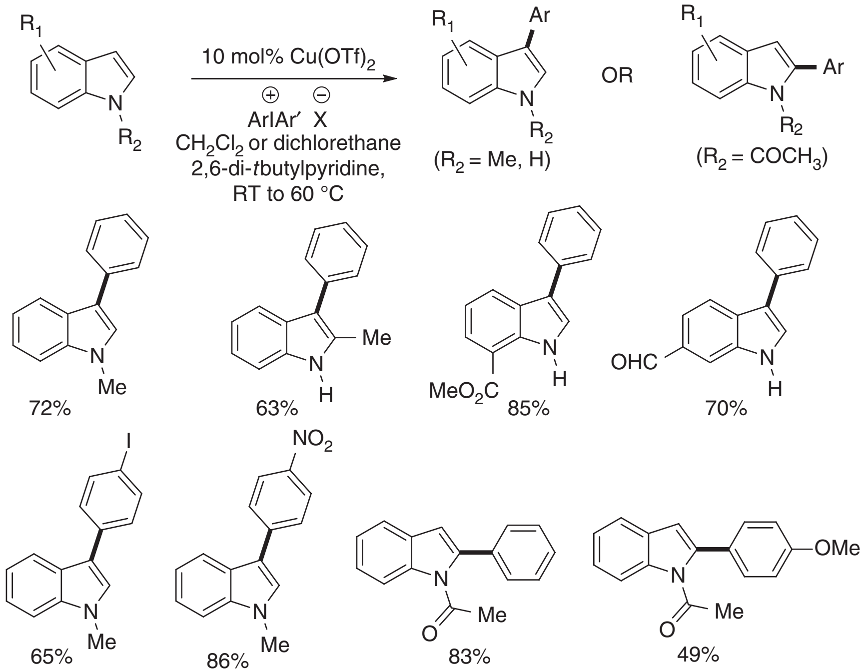
Miura has recently shown that benzoazoles can be arylated by aryl iodides in the presence of catalytic or stoichiometric copper iodide [100]. Sodium carbonate base was found to be optimal, and triphenylphosphine additive was found to increase yields. Benzoxazole, benzothiazole, and *N*-methylbenzimidazole were shown to be reactive (Scheme 26).



Scheme 26 Benzazole arylation

A one-pot, copper-catalyzed formation of fully decorated triazoles was recently demonstrated by Ackermann. In the first step, a copper-catalyzed “click” reaction produces triazoles from alkynes and azides. In the second step, a direct, copper-catalyzed arylation of the triazoles by aryl iodides results in the formation of C-arylated products. Lithium *tert*-butoxide base is employed [101].

Indole arylation by diaryliodine(III) reagents employing $Cu(OTf)_2$ was reported by Gaunt (Scheme 27) [102]. Reactions proceed at very mild conditions and both *NH* and *N*-substituted indoles can be arylated. Interestingly, regioselectivity of arylation is dependent on the substituent on the nitrogen of indole. For *N*-alkyl- and 1-*H* indoles, selective C-3 arylation was observed. For *N*-acylindoles, arylation at 2-position occurs. The finding was explained by invoking a C-2 to C-3 migration of arylcopper(III) intermediate. Mechanism of indole arylation is apparently distinct from the mechanism of Cu(I) catalyzed arylations described above. An initial oxidation of Cu(II) to Cu(III) is proposed, followed by an electrophilic arylation of indole.

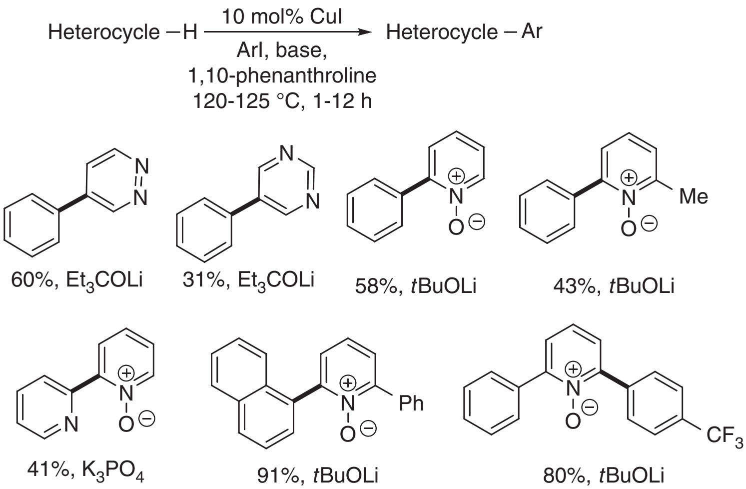


Scheme 27 Indole arylation

Itami has reported that electron-rich arenes can be arylated by arylboronic acids in the presence of stoichiometric copper(II) trifluoroacetate [103]. Trimethoxybenzene, indole, and pyrrole were shown to be reactive. Reactions proceed in dichloromethane in the presence of trifluoroacetic acid.

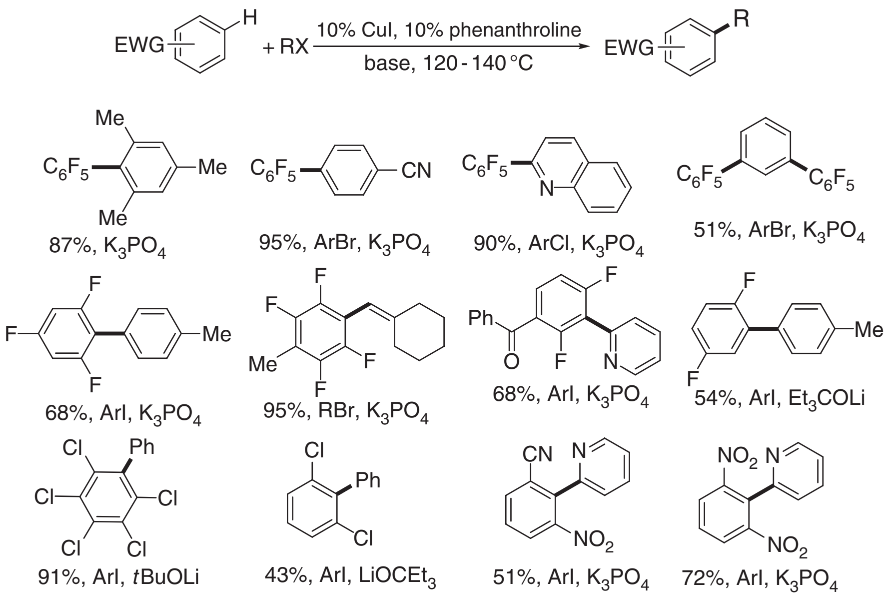
4.2 Electron-Deficient Heterocycle and Benzene Derivative Arylation

The reaction conditions developed for electron-rich heterocycles have been applied for electron-deficient heterocycle and benzene arylation [95, 104]. Pyridine oxides, pyrimidine, and pyridazine can be efficiently functionalized (Scheme 28). The most acidic position of the heterocycle is selectively arylated. Arylation of electron-deficient benzene derivatives also proceeds smoothly (Scheme 29). All polyfluorobenzenes are arylated efficiently. Just like for electron-rich heterocycles, the reactivity parallels the acidity of C–H bonds. The most acidic C–H bonds, those flanked by two electron-withdrawing groups, are arylated preferentially. Potassium phosphate can be used as a base if an arene contains more than two fluorine substituents or two fluorine substituents and an additional electron-withdrawing group. Penta-, tetra-, 1,3,5-tri-, and 1,3-dichlorobenzenes can be arylated in reasonable to excellent yield. 1,3-Dinitrobenzene and 3-nitrobenzonitrile are also reactive, affording the arylation products in moderate yields. Arenes possessing only one electron-withdrawing group, such as nitro-, chloro-, fluoro-, and cyanobenzene, are unreactive and less than 5% conversion to products was observed in those cases.



Scheme 28 Electron-deficient heterocycle arylation

Matsubara and Yoshida have shown that 9,10-di(pentafluorophenyl)anthracene can be synthesized by a copper-catalyzed arylation of pentafluorobenzene with dibromoanthracene [105]. The reaction is only successful if silver oxide base is used.



Scheme 29 Electron-deficient benzene arylation

5 Conclusions

In the last 5–10 years, the direct transition-metal-catalyzed functionalization of carbon–hydrogen bonds has undergone an explosive growth. A number of substrates can now be functionalized in a predictable and controllable fashion. Many directing-group-containing arenes can be arylated or alkylated by employing ruthenium, rhodium, or palladium catalysis. Electron-rich heterocycles can be arylated under palladium or copper catalysis. Acidic sp^2 C–H bonds are arylated by aryl halides if copper(I) catalysts are used. However, despite the developments, the problems still remain. Unactivated sp^3 (not benzylic or α to heteroatom) C–H bond conversion to C–C bonds is rare with most cases involving *tert*-butyl group functionalization. Additionally, most of the examples include use of expensive metals such as palladium, rhodium, and ruthenium. Use of nonprecious metals such as copper and iron in C–H bond arylation is not common. Examples describing use of these metal catalysts have started appearing in literature only in the last few years.

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Pd-Catalyzed C–H Bond Functionalization on the Indole and Pyrrole Nucleus

Elizabeth M. Beck and Matthew J. Gaunt

Abstract This review details recent developments in the Pd-catalyzed C–H bond arylation and alkenylation of indoles and pyrroles, aromatic heterocycles that are frequently displayed in natural products and medicinal agents.

Keywords Palladium • Indole • Pyrrole • C–H activation

Contents

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Abbreviations

Ac	Acyl
Am	Amyl
Ar	Aryl
atm.	Atmospheres
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BQ	Benzoquinone
Bu	Butyl
Bz	Benzoyl
°C	Degrees centigrade
cat.	Catalytic
cod	Cycloocta-1,5-diene
DavePhos	2-(Dicyclohexylphosphino)-2′-(dimethylamino)biphenyl
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DMA	*N,N*-Dimethylacetamide
DMF	*N,N*-Dimethylformylamide
DMSO	Dimethylsulfoxide
DTBP	2,6-Di-*tert*-butylpyridine
dtbpy	4,4′-Di-*tert*-butyl 2,2′-bipyridine
ee	Enantiomeric excess
eq	Equivalent
Et	Ethyl
FG	Functional group
Fmoc	Fluorenylmethyloxycarbonyl chloride
h	Hour
HATU	(*O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HetAr	Heteroaromatic
IMes	1,2-bis(2,4,6-trimethyl phenyl)imidazol-2-ylidene
Kcal	Kilocalories
L	Ligand
M	Metal
Mbs	*p*-Methoxy benzene-sulfonyl
Me	Methyl
Mes	Mesityl
MOM	Methoxymethyl
NHC	*N*-Heterocyclic carbene
[O]	Oxidant
Ph	Phenyl
PIDA	Phenyliodo(III)diacetate
pin	Pinacolato

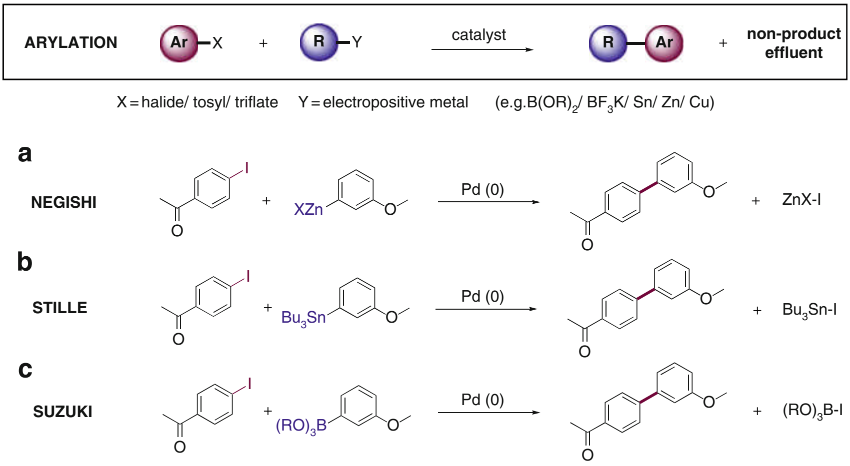
Piv	Pivaloyl
i-Pr	*iso*-Propyl
Py	Pyridine
SEM	2-Trimethylsilyl ethoxymethoxy
Sol	Solvent
S-Phos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TIPS	Triisopropylsilyl
TFA	Trifluoroacetic acid
Tf	Triflate
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TON	Turnover number
Ts	Tosyl
TSE	Trimethylsilylethyl
μw	Microwave
X-Phos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

1 Introduction

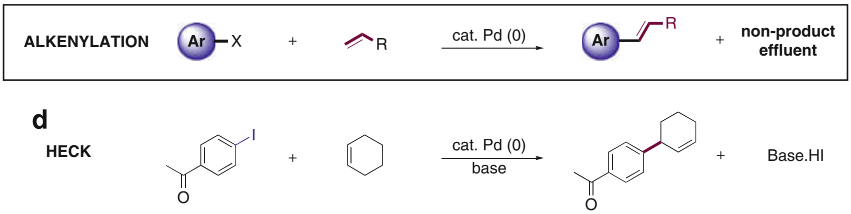
Chemical synthesis has been revolutionized by the development of metal-catalyzed cross-coupling reactions. Palladium-catalyzed reactions such as the Heck [1], Negishi [2], Stille [3], Suzuki [4] and Sonogoshira [5], to name but a few, have become crucial tools for synthetic organic chemists. It is now possible to couple aryl halides, triflates and tosylates with olefins, alkanes or other functionalized arenes in high yield with very low catalyst loading. These tactics rely on strategically installed metal-active groups and such starting materials require additional steps to prepare them from feedstock chemical sources. C–H bonds are ubiquitous in organic molecules but are often unreactive. Introduction of functionality through the direct transformation of C–H bonds would provide the opportunity for distinctly different assemblies of synthetic targets. While this is an attractive concept, achieving selectivity among different C–H bonds remains a major challenge; this means that developing new catalyst systems that display both high reactivity and predictable selectivity is essential in order to increase the efficiency with which complex molecular architectures can be assembled.

1.1 Conventional Palladium-Catalyzed Cross-Coupling

Biaryl C–C bond formation, via metal-catalyzed cross-coupling tactics, is a widely used transformation in the synthesis of both complex natural products and medicinal agents. Efficient catalytic methods have emerged for the union of complex



Scheme 1 Arylation via conventional cross-coupling tactics



Scheme 2 Alkenylation via conventional Heck cross-coupling

molecular fragments together in a highly selective manner. Typically one reaction component bears a metal containing functionality (Y) (nucleophilic component) whilst the other contains a halide atom or pseudo-halogen (X) (electrophilic component) (Scheme 1).

Similarly, the Heck reaction has become one of the most fundamental metal-catalyzed C–C bond forming processes for the synthesis of complex molecules [6]. Heck type reactivity comes from the ability of Pd(0) species to undergo oxidative addition to various C–X bonds and the addition of the RPdX intermediates to unsaturated bonds (Scheme 2).

Metal-catalyzed cross-coupling has had a major impact in the union of complex fragments during natural product synthesis programmes. In many cases structurally and functionally complex molecules can be coupled, often as part of a synthesis endgame, to reveal the architecture of natural products with exquisite control and in high yield. Furthermore, in many of these cases, there would be no alternative method to complete the synthesis.

While it is difficult to find fault in complex examples of conventional cross couplings, when applied to smaller molecules there is room for potential improvement. First, the overall coupling of two fragments in this manner requires two or three discrete steps: (1) pre-functionalization of starting materials, i.e. formation of the aryl halide and/or metallated component, and (2) Pd(0)-catalyzed union of reaction partners. This unfortunately gives rise to loss of material and significant accumulation of waste products, although this is less of an issue when coupling larger fragments together.

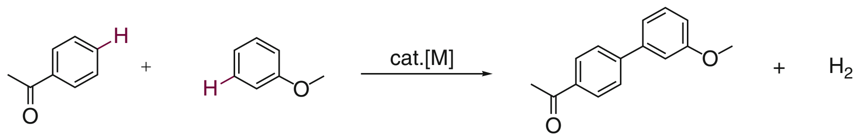
1.2 *Palladium-Catalyzed C–H Bond Functionalization*

The concept of "atom economy" has frequently been used to emphasize the minimal number of reactants, as well as selection of "low energy" starting materials as substrates [7], for example, using substrates that contain a reactive C–H bond rather than a C–X bond. Ideally, a direct catalytic cross-coupling reaction that utilizes "traditionally inert" C–H bonds would underline this concept as only the loss of nontoxic hydrogen gas or water as by-products would be necessitated (Scheme 3).

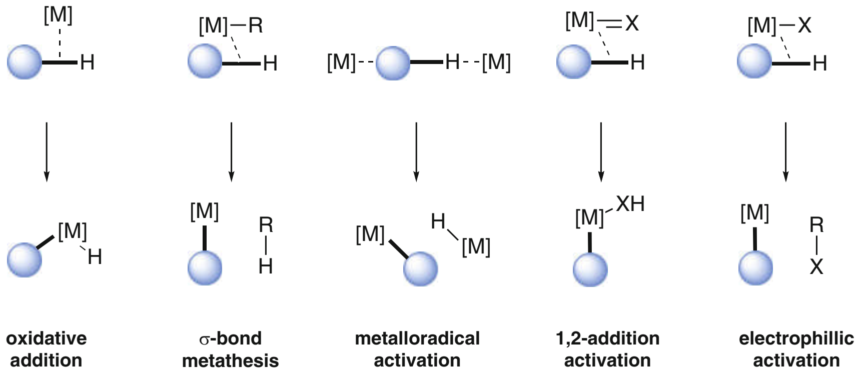
The ability to activate a specific "inert" C–H bond and utilize it as a more versatile functional group is an emerging area in chemistry [8]. Activation of C–H bonds with metal catalysts and further functionalization of these intermediates to valuable products has the potential to replicate the utility of reactions such as the Suzuki or Heck whilst also satisfying the high atom and step efficiency demanded by environmental constraints. This would result in a more efficient transformation and also allow us to look at new approaches in the synthesis of complex molecules that are free from the restraints of functional group manipulation.

Despite many advantages, there are still significant challenges posed by this concept. First, the synthetic challenge arising from the high strength of C–H bonds in alkanes and arenes (e.g. CH_3–H, 105 kcal mol^{-1}; Ar–H, 110 kcal mol^{-1}) relative to the C–X bonds activated in traditional cross-coupling (e.g. Ar–I, 65 kcal mol^{-1}). Often C–H bond activation processes require harsh reaction conditions which severely impinge from their use in complex molecule synthesis. Second, whilst the ubiquitous nature of C–H bonds in organic molecules gives it the potential to become a highly general process, one of the greatest limitations of this type of chemistry is the ability to activate the desired C–H bond in a chemoselective manner.

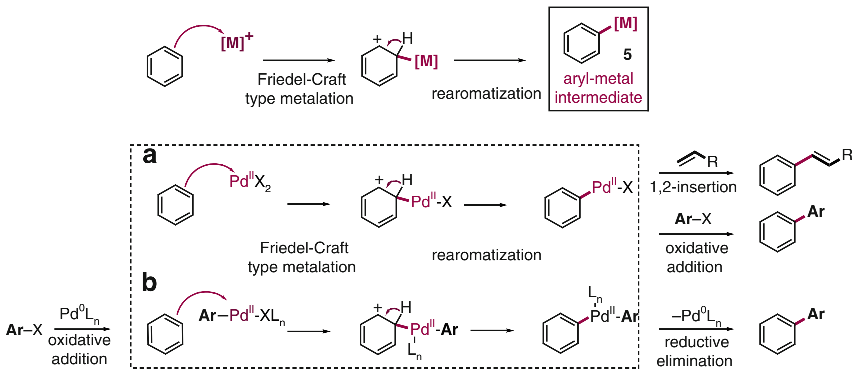
Over the past 30 years there has been a massive effort to achieve selective C–H bond activation by transition metal catalysis and there now exists a variety of mechanisms for the activation of C–H bonds using a range of transition metal catalysts (Scheme 4) [8–18].



Scheme 3 Direct cross-coupling by C–H activation



Scheme 4 Various mechanism for the activation of C–H bonds

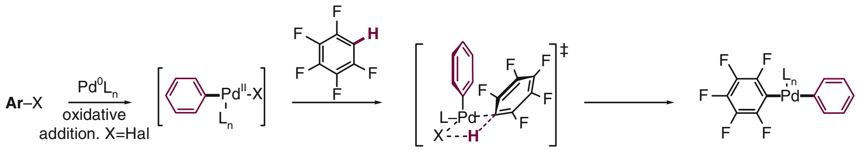


Scheme 5 Electrophilic C–H bond activation at Pd(II) centres

1.3 *Activation Mechanisms of the C–H Bond*

1.3.1 Electrophilic C–H Bond Activation at Palladium(II) Centres

The most common means of activating aromatic C–H bonds via palladium catalysis is by electrophilic C–H activation. This proceeds more like a Freidel-Craft type metallation mechanism, followed by rearomatization to form versatile aryl-metal intermediates (Scheme 5) [19]. It can occur with electrophilic palladium(II) catalysts such as $Pd(OAc)_2$, $PdCl_2$, $Pd(TFA)_2$ (Scheme 5a) or on electrophilic aryl-palladium(II) complexes, that result from oxidative addition of palladium(0) into an aryl halide (Scheme 5b). The resultant aryl-palladium(II) complexes are analogous to those observed in conventional cross-coupling reactions and as such are versatile intermediates in the formation of new C–C bonds.



Scheme 6 Proton-transfer metallation

1.3.2 Proton-Transfer Metallation Pathway

Mechanistically proton-transfer metallation is thought to proceed via a concerted arene-metallation and C–H bond cleaving process, which depends on the acidity of the C–H bond being cleaved (Scheme 6). The reaction shows complete inversion of reactivity relative to the electrophilic C–H activation pathway with electron deficient arenes reacting preferentially [20, 21].

1.4 Regiocontrol in the C–H Bond Functionalization Event

As discussed previously, another major challenge relates to achieving selectivity in the C–H bond functionalization step. The prevalence of C–H bonds in organic molecules means that it is necessary to activate C–H bonds specifically, usually amongst similar C–H environments. In terms of reactions at Pd(II) centres, described above, there are four main factors used to control the regioselectivity of the C–H functionalization.

1. *Intramolecular reactions*: tethered reacting groups are employed to limit the degrees of freedom in a system, thereby controlling the regioselectivity of the reaction.
2. *Directing groups*: auxiliary groups usually containing Lewis basic heteroatoms, coordinate palladium and bring the metal centre into close proximity of a specific C–H bond allowing formation of palladacycles.
3. *Electronic properties of the substrate*: often "activated" C–H bonds are targeted, for example, with electron rich heteroarenes; electrophilic palladation is favored at the most nucleophilic position and relies on the inherent reactivity of the system. Similarly if a proton-transfer pathway is under operation, activation is favoured on the most acidic C–H bond.
4. *Steric properties of the substrate*: depending on substrate structure, certain C–H bonds may be more accessible to the catalyst than others.

2 Pd-Catalyzed C–H Bond Functionalization on the Indoles and Pyrrole Nucleus

This review will cover recent advances in the palladium-catalyzed C–H activation of the indole and pyrrole nucleus, specifically for the formation of new C–C bonds via arylation and alkenylation. Most commonly, activation is achieved through

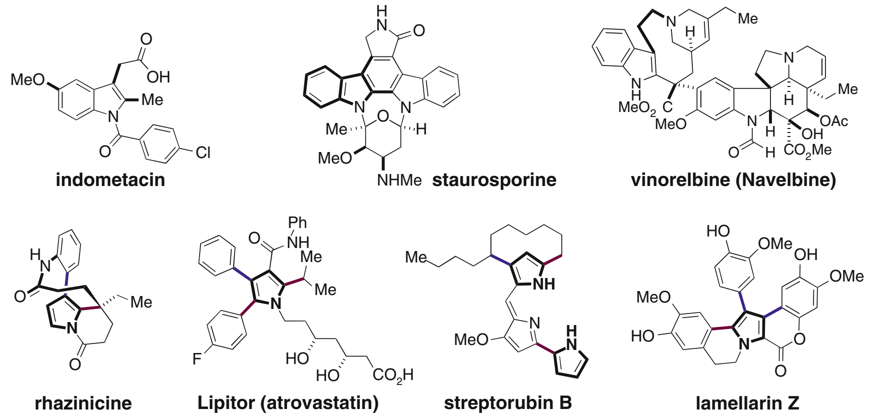


Fig. 1 Indole and pyrrole containing natural products and therapeutics

mechanisms based on electrophilic substitution of aromatic C–H bonds by a palladium(II) species. In particular, we will discuss the effects of mechanistic differences on substrate reactivity and how various levels of regioselectivity can be achieved within aromatic and heteroaromatic systems.

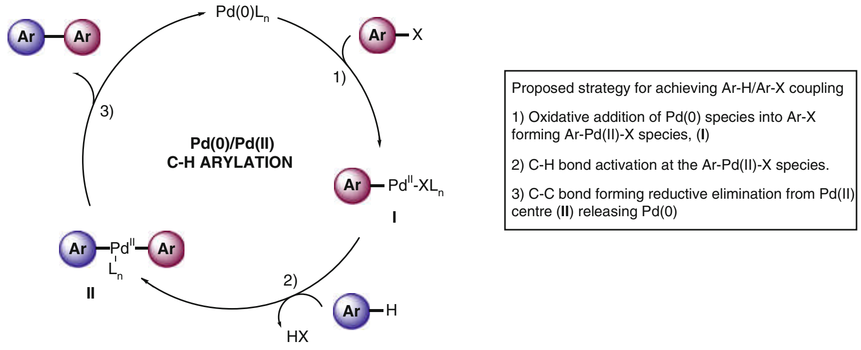
The indole and pyrrole nucleus are common structural motifs in a range of natural products and medicinal agents (Fig. 1). Therefore, methods for their selective and efficient functionalization are important targets for chemical synthesis. The inherent reactivity of these heteroarenes has attracted widespread interest as ideal substrates for direct metal-catalyzed C–H bond functionalization reactions. However, related to their intrinsic reactivity is their sensitivity to harsh aerobic reaction conditions, and so methods to enable direct transformations on these heteroarenes must take this into account.

A common strategy employed to effect selectivity is exploitation of inherent substrate reactivity and utilization of "activated" C–H bonds. Heteroaromatic compounds represent common motifs in both natural products and medicinal agents and contain certain C–H bonds that are intrinsically more reactive than others. By using heteroaromatic motifs as the Ar–H unit, the inherent differences in reactivity of C–H bonds around the motif can be exploited to achieve selectivity.

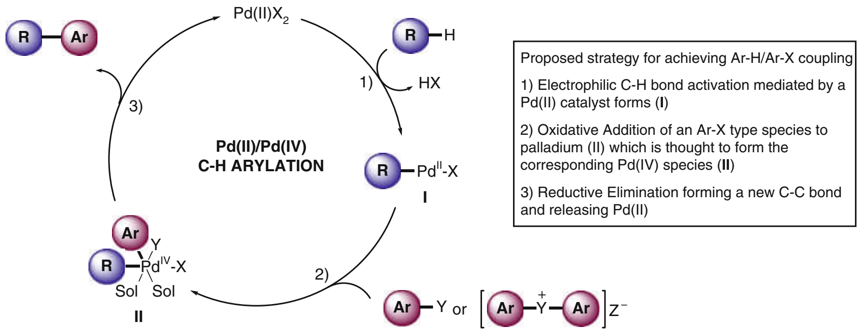
3 Pd-Catalyzed C–H Bond Arylation on Indole and Pyrrole

3.1 Mechanisms of Pd-Catalyzed C–H Bond Arylation

In terms of palladium-catalyzed direct arylation reactions, there are three general mechanisms that are commonly applied (Scheme 7).



Scheme 7 Proposed Pd(0)/Pd(II) catalytic cycle for direct arylation

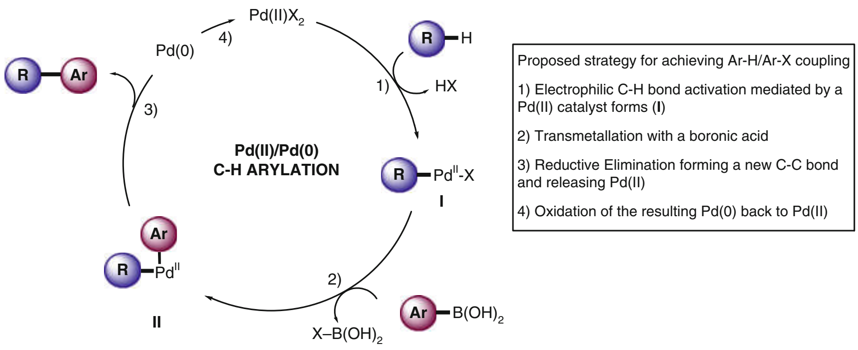


Scheme 8 Proposed Pd(II)/Pd(IV) catalytic cycle for direct arylation

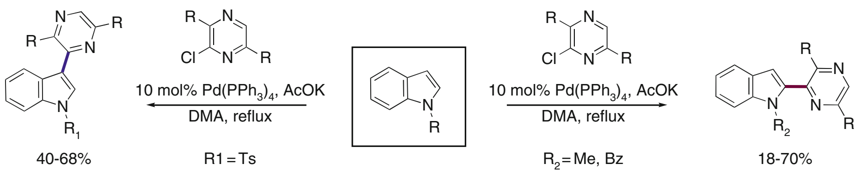
The first case involves direct arylation of arenes with aryl halides via a Pd(0)/Pd(II) cycle (Scheme 8). After initial oxidative addition of Pd(0) into the aryl halide, the C–H bond activation event takes place at the Ar–Pd(II)–X species **4** and is followed by C–C bond forming reductive elimination and regeneration of Pd(0).

More recently, direct arylations have been developed that are proposed to proceed via a Pd(II)/Pd(IV) cycle (Scheme 9). In this case the C–H bond functionalization takes place first, at the highly electrophilic Pd(II) catalyst species, and is followed by oxidative addition of an Ar–X type compound, generating the corresponding Pd(IV) species **II**. Reductive elimination would then form a new C–C bond and release Pd(II) back into the cycle.

A final common arylation mechanism also involves C–H bond palladation with a Pd(II) catalyst, but then a transmetallation with an organometallic such as a boronic acid. Reductive elimination to form the desired product also releases Pd(0) and this species must be oxidized back to the active Pd(II) catalyst. A key aspect of this process is developing an oxidative system that does not result in homo-coupling of the aryl boronic acid (Scheme 9).



Scheme 9 Proposed Pd(II)/Pd(IV) catalytic cycle for direct arylation



Scheme 10 Ohta's regioselective heteroarylation of indoles

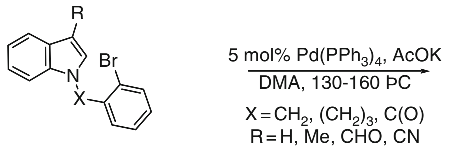
3.2 Regioselective Pd-Catalyzed C–H Bond Arylation on Indole and Pyrrole

Initial work in the area focussed on applying Pd(0)/Pd(II) manifolds to electron rich and nucleophilic heterocycles such as imadazoles, indoles and various other azoles. For an overview of this particular aspect of C–H bond functionalizations, the reader is directed to other excellent reviews of this field [17].

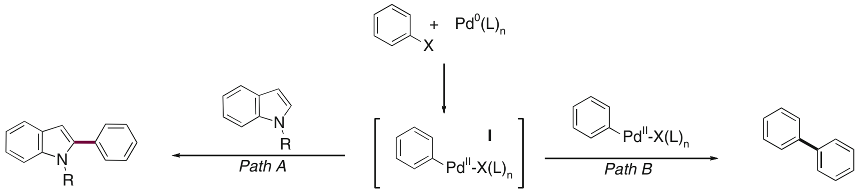
In the context of this review, the indole motif, in particular, has attracted a great deal of attention in the development of C–H functionalization processes. Some of the earliest studies were reported in 1989 by Ohta, who investigated palladium-catalyzed coupling of 2-chloro-3,6-dialkyl pyrazines with protected indoles [22]. Despite requiring highly elevated temperatures they were able to affect selective C2 or C3 heteroarylation of the indole core in moderate yields. Use of 1-tosyl-indole led, predominantly, to 3-heteroaryl indoles whilst 1-alkyl analogues were shown to undergo substitution at C2 (Scheme 10).

Shortly after this, palladium-catalyzed intramolecular cyclizations on indole were also reported. Work by Grigg [23], Kozikowski [24] and Merour [25] showed that under analogous Pd(0) conditions, at high temperature, a variety of polycyclic indoles could be made (Scheme 11).

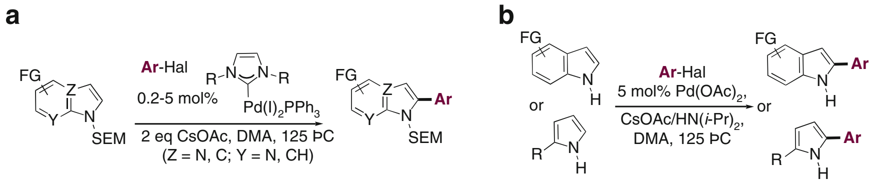
In 2004, Sames reported a practical method by which *N*-substituted indoles could be selectively arylated at the C-2 position with a range of aryl iodides [26]. The investigations found two competitive processes in operation (Scheme 12),



Scheme 11 Intramolecular arylation of indoles



Scheme 12 Sames' strategy towards regioselective intermolecular arylation of indoles



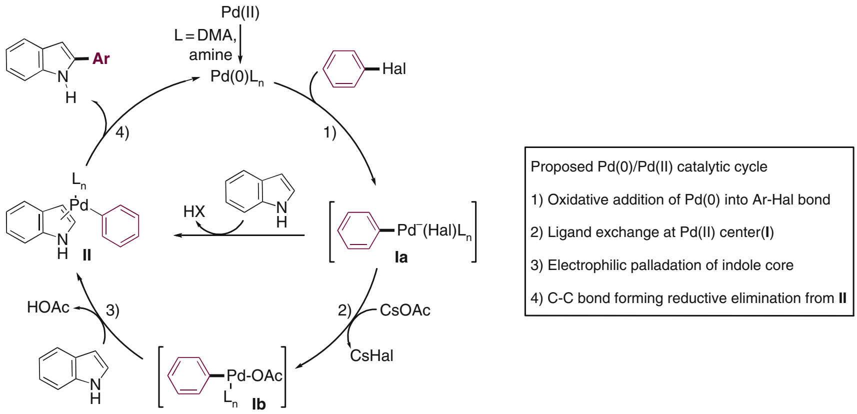
Scheme 13 Sames' intermolecular C2-arylation of indoles

namely the desired cross-coupling *(Path A)* and biphenyl formation *(Path B)*, caused by palladium-catalyzed Ullmann type coupling. It was found that decreased catalyst loading favored production of the desired product due to requirement for bimolecular transmetallation of the aryl-palladium species **I** for biphenyl formation.

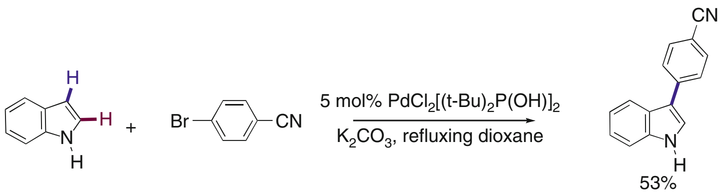
A more robust process, suitable for the production of a greater scope of heterocycle, was later developed using SEM-protected azoles that could be readily converted to the *N*–H counterparts under a variety of conditions (Scheme 13a) [27]. Palladium complexes containing imidazyl carbene ligands were utilized to improve the stability of palladium throughout the catalytic cycle, modulate reactivity and disfavour biphenyl formation.

Sames' discovery that phosphine ligands inhibited the reaction has lead to the development of a new phosphine-free arylation for *N*–H indoles and pyrroles (Scheme 13b) [28]. Increased indole concentration makes possible the coupling of sterically demanding arene donors and indole motifs.

In general these methods, developed by Sames for C–H arylation of indoles, do not follow the expected "electrophilic" regiochemistry, instead showing high C2 selectivity (Scheme 14). Sames described how their mechanistic experiments point towards a mechanism involving electrophilic C–H activation [29]. First, the reaction was shown to be first order in both substrate and catalyst. Moreover, a Hammett



Scheme 14 Proposed catalytic cycle for Sames' intermolecular C2-arylation of indoles

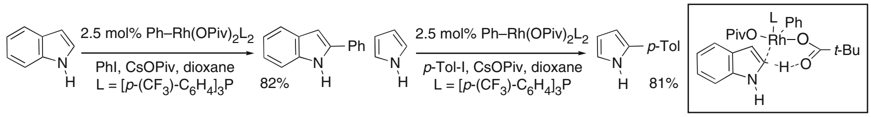


Scheme 15 He's C3 selective arylation of indole

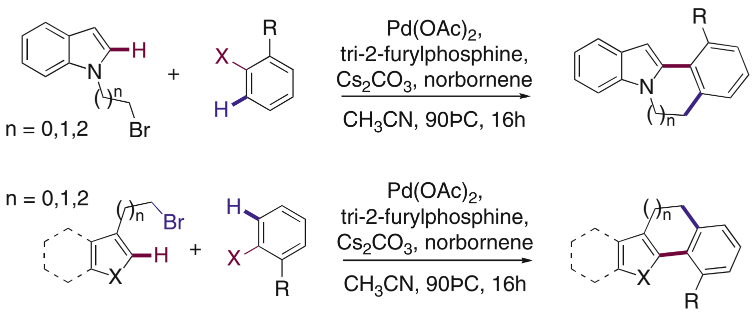
plot indicated a positive charge accumulated at the 3-position of indole and a larger KIE was obtained for the 3-position, where the substitution does not occur. This evidence provides support for an electrophilic palladation mechanism at C3 suggesting, perhaps, that it is then followed by a 1,2-migration of palladium. It should be noted that Fagnou et al. recently reported that a number of reactions that were thought to proceed via electrophilic metalation could in fact be explained by a proton-transfer (concerted metalation deprotonation) mechanism. They reported that the free energy of activation for the direct arylation would be lower at the C2 position, hence explaining the regiochemical outcome of the reaction [30, 31].

A related example from He and co-workers demonstrated that phosphinous ligands on Pd(0) are also able affect an indole arylation reaction. A small selection of C3 arylated indoles can be realized using this method. Of particular note is the C3 selectivity observed in this reaction, when compared to the work of Sames who observed C2 selectivity (Scheme 15).

Sames and co-workers also demonstrated that rhodium(I) catalysts also facilitate a C–H arylation of indole at the C-2 position (Scheme 16). While not explicitly described in their paper, they infer that the pivolate ligand may be involved in an internal proton-transfer, and it seems likely that this is in line with a CMD type activation step reported by Fagnou and Echaverran [20, 21] (opinion of Gaunt and



Scheme 16 Rh-catalyzed C2-arylation of indoles



Scheme 17 Lautens' norbornene-mediated tandem alkylation/Heck reaction

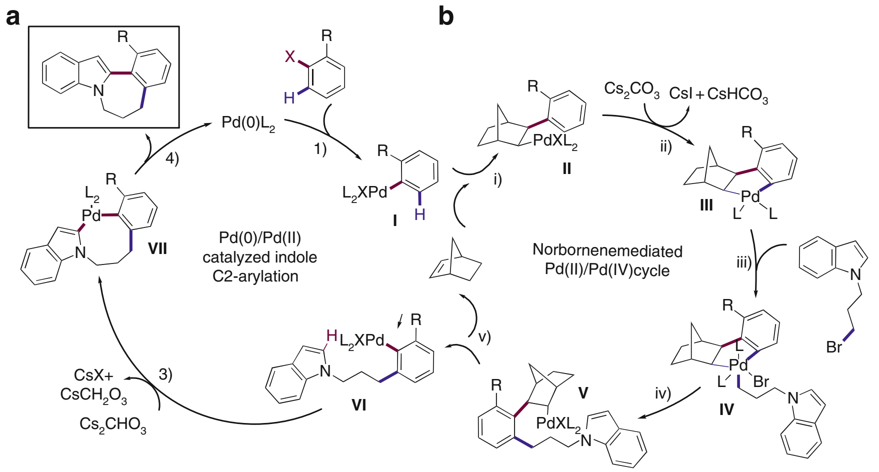
Beck). The arylation was demonstrated on a range of indole and pyrrole molecules in good yields. In all cases arylation was observed at the C2 position of the heteroarene [30].

An extension of the palladium(0) catalyzed direct arylation reactions was reported by Lautens et al. in 2005. Based on the Catellani reaction [32], a direct intramolecular arylation of indole (C2) followed *ortho*-alkylation, via a norbornene-mediated tandem aromatic alkylation/Heck reaction (Scheme 17) [33]. An analogous process was later developed for thiophenes and furans, allowing formation of a range of interesting hetero-aryl polycyclic products (Scheme 17) [34].

This unusual strategy is thought to make use of the different reactivities of palladium(0), palladium(II) and palladium(IV) intermediates. Mechanistically, the reaction is proposed to occur via initial oxidative addition of palladium(0) to the aryl iodide, followed by carbopalladation with norbornene to afford alkyl palladium species **II** (Scheme 18).

Intermediate **II** is incapable of β-hydride elimination and therefore directed *ortho*-palladation on the arene takes place generating intermediate **III**. This Pd(II) complex (**III**) is proposed to add oxidatively to the alkyl halide tether containing indole moiety. The proposed palladium(IV) intermediate **IV** undergoes reductive elimination to form an alkyl–aryl bond (**V**). If the *ortho* position is blocked the norbornyl-palladium species **V** undergoes decarbopalladative expulsion of norbornene to regenerate an aryl-palladium species **VI**. This intermediate can then undergo intramolecular cyclization onto the indole to give a variety of 6- or 7-membered annulated indole products.

As well as those discussed, Pd(0)/Pd(II) catalyst systems have also been used to affect arylation on a range of other heterocycles including imidazopyrimidines,



a Proposed Pd(0)/Pd(II) catalytic cycle

1) Oxidative addition of Pd(0) into Ar-X bond

2) Norbornene mediated Pd(II)-Pd(IV) cycle generates arylpalladium(II) intermedaite **VI**

3) Fast intramolecular palladation to **VII**

4) C-C bond forming reductive elimination from **VII**

b Norbornene mediated Pd(II)/Pd(IV) cycle

i) Heck reaction between arylpalladium(II) complex **I** and norbornene generates **II**

ii) Directed ortho-palladation on arene forms **III**

iii) Oxidative addition of alkyl halide forms Pd(IV) complex **IV**

iv) C-C bond forming reductive elimination generates **V**

v) Reverse Heck reaction releases norbornene and **VI**

Scheme 18 Proposed mechanism for the norbornene-mediated alkylation/Heck reaction

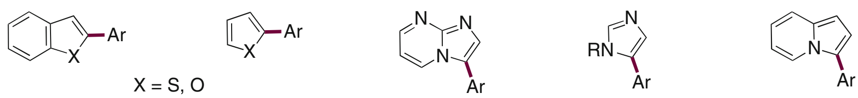
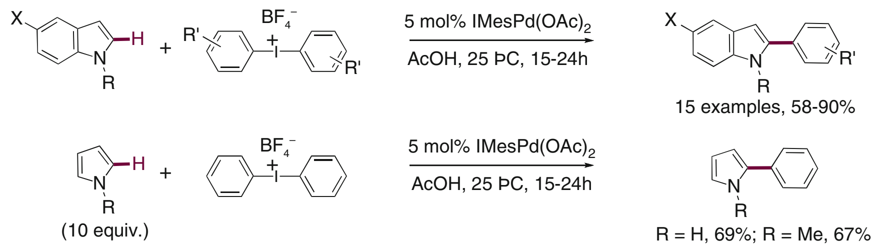


Fig. 2 Observed regioselectivities for direct arylation of heterocycles

indolizines, furans, thiophenes and related benzo-analogs (Fig. 2) [18, 35–41]. In almost all cases regioselectivity and mechanistic studies support the suggestion that arylation proceeds via an electrophilic mechanism.

While synthetically useful, the Pd(0)/Pd(II) catalyst systems generally suffer from a couple of notable disadvantages. In particular, high temperatures and long reaction times (125–150 °C for 12–48 h) are often required to achieve reactivity that can results in moderate scope and functional group tolerance as well as high sensitivity to ambient air and moisture.

More recently, there has been an emphasis on designing direct arylation reactions that occur under milder conditions and lower temperatures. Since the initial findings concerning the use of Pd(II) catalysts in oxidative Heck type transformations and directed palladations, it has been shown that utilization of these highly electron deficient Pd(II) catalysts can enhance the rate of the key electrophilic

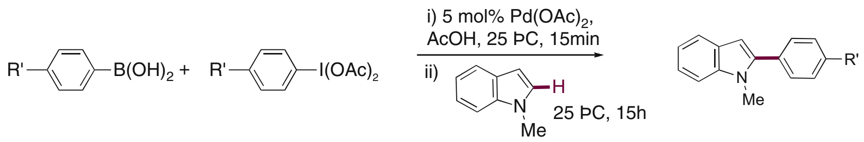


Scheme 19 Sanford's oxidative C2-arylation of indoles and pyrroles

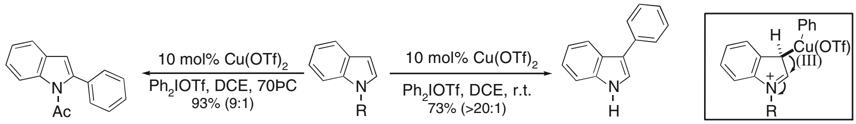
palladation step, allowing arylation of nucleophilic arenes under much milder and tolerant conditions. Heteroaromatics such as indole and pyrrole are particularly suited to such transformations, due to their electron rich and highly nucleophilic character. The strategy most often applied in order to effect oxidative palladium(II) catalyzed C–H bond arylation with Ar–X type species is proposed to proceed via a Pd(II)/Pd(IV) catalytic cycle. An oxidant that simultaneously creates a carbon–palladium bond and oxidizes palladium(II) to palladium(IV) is used. This also benefits from avoiding generation of Pd(0), which often causes problems in terms of catalyst turnover due to precipitation of palladium black.

Using this concept the Sanford group found that direct C2-arylation of indoles and pyrroles could be effected under remarkably mild conditions with aryl iodonium salts and palladium(II) catalysts (Scheme 19) [42]. The high C2 selectivity of the functionalization is attributed to a mechanism involving initial palladation at C3 followed by fast palladium migration to C2 under acidic conditions as initially proposed by Gaunt [43] and Sames [29]. The reaction also works well for simple pyrroles, again with C2 selectivity.

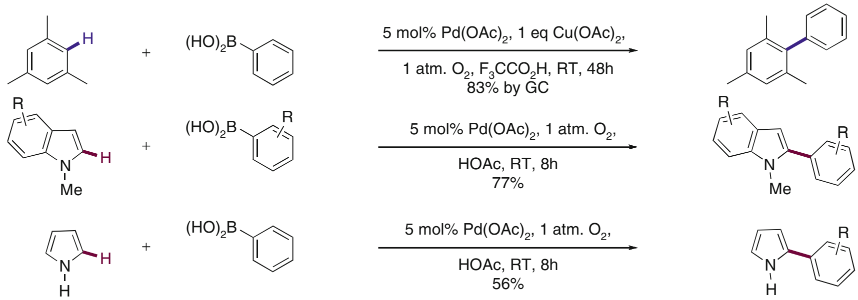
The mild reaction conditions and compatibility with ambient air/moisture are features attributed to be a consequence of the proposed Pd(II)/ Pd(IV) pathway operating in these systems. Whilst C2-phenylation was observed under extremely mild conditions in the presence of catalytic $Pd(OAc)_2$ (5 min, room temperature), only moderate yields were obtained, presumably due to catalyst deactivation. Palladium(II) complexes containing stabilizing ancillary ligands (e.g. IMesPd $(OAc)_2$) resulted in significantly improved performance, albeit slower rate caused, by the more electron rich palladium(II) catalyst). Phenylation could be extended to a variety of electronically diverse indole substrates as well as pyrroles and notably both *N*–H and *N*–Me indole were comparably reactive. As with the previous arylations a range of aryl groups could be installed via [Mes-I–Ar]BF_4 salts; however superior yields were obtained with symmetrical iodine(III) compounds ([Ar–I–Ar]BF_4). Having identified a potential limitation as being the requirement for independent synthesis of the iodonium salt arylating reagents, a one-pot approach to the transformation starting with $ArI(OAc)_2$ and commercially available $ArB(OH)_2$ reagents was developed. Combining $PhB(OH)_2$ and $PhI(OAc)_2$ in AcOH for 15 min at room temperature in the presence of 5 mol% $Pd(OAc)_2$ followed by



Scheme 20 One-pot strategy for C2-arylation of indole



Scheme 21 Controllable and selective Cu-catalyzed C–H bond arylation of indole

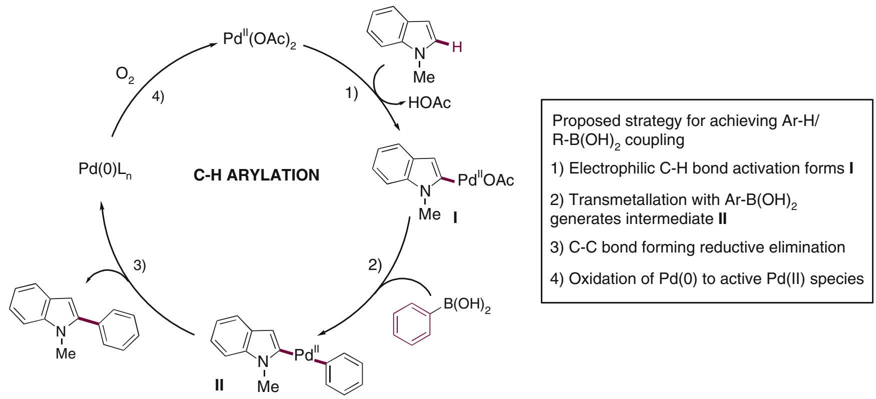


Scheme 22 Shi's direct coupling of arenes and aryl boronic acids

addition of the 1-methyl indole resulted in formation of the C2-phenylation product in excellent yield (Scheme 20).

Interestingly, a related copper catalyzed reaction enables controllable formation of either the C3 or C2 indole arylation products (Scheme 21). Gaunt et al. showed that when free (NH)-indole was treated with diaryliodonium triflates in the presence of copper(II)triflate at room temperature the C3 arylation product was observed in excellent selectivity and high yields [44]. However, if *N*–Ac indole is used then the product of the reaction is the C2 arylation product. The mechanism is proposed to proceed through a Cu(III)–aryl intermediate via an electrophilic metalation pathway. The origin of the C3/C2 selectivity is reasoned to arise form the ability of the metalated indole intermediate to undergo C3 to C2 migration, with the 1,2-shift favored on *N*–Ac indoles. A broad range of indole arylations has been demonstrated with this method. In comparison to the C2 selectivity displayed by palladium catalysts, it is interesting to note the complimentary selectivity displayed by copper catalysts.

Shi described a palladium(II) catalyzed cross-coupling of electron rich (hetero) arenes with aryl boronic acids (Scheme 22) [45]. A major strategic challenge was avoiding homo-coupling of the aryl boronic acids in the presence of palladium(II).



Scheme 23 Proposed catalytic cycle for coupling of arenes and aryl boronic acids

Scheme 24 Larrosa's C2-arylation of indoles with aryl iodides

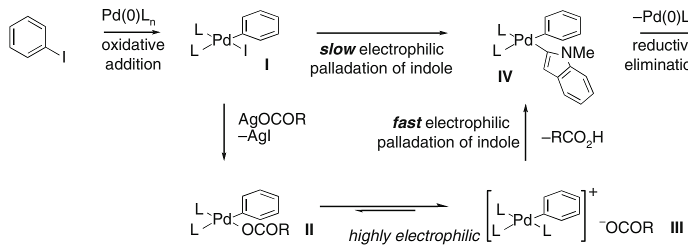
However, it was found that acidic conditions helped to facilitate fast electrophilic attack and hindered the transmetallation of the aryl boronic acids to palladium(II).

Various aromatic rings show good selectivities without requiring directing groups and a range of substituted boronic acids are tolerated. Electron rich heterocycles such as indole and pyrrole are readily employed in the coupling reaction and selectivity appears to be controlled by the electronic properties of the arenes.

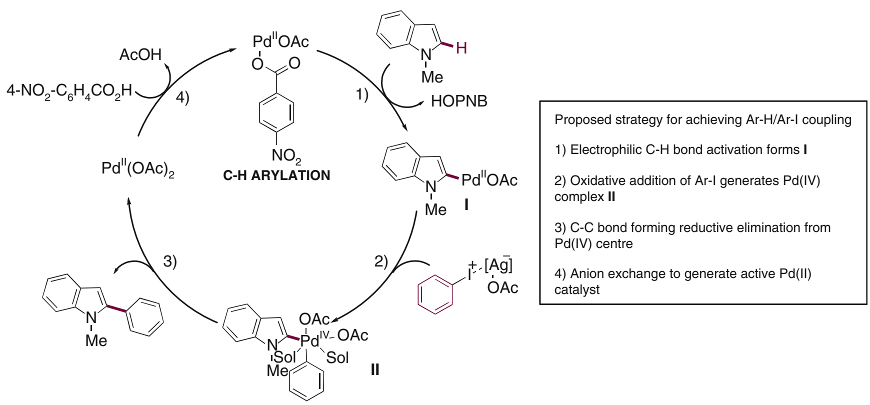
These preliminary studies suggest a catalytic cycle initiated by electrophilic attack of palladium(II) on the indole, followed by transmetallation with a boronic acid and reductive elimination to produce the desired arylated products (Scheme 23).

Larrosa reported the direct C2-arylation of indoles with aryl iodides at room temperature (Scheme 24) [46]. The mild conditions allow a broad range of functionalities on both coupling partners and the method is particularly advantageous due to the large pool of commercially available aryl iodides.

Interestingly, they propose a mechanism that proceeds via a Pd(0)/Pd(II) cycle (Scheme 36). Silver carboxylates, generated in situ from Ag_2O and the corresponding carboxylic acid, are thought to have an important role in the reaction. The limiting step in the arylation of indoles via a Pd(0)/Pd(II) cycle is thought to be the necessary electrophilic palladation of the electron rich Pd(II) species **I**. It was proposed that after oxidative addition of Pd(0) into the aryl halide, the silver salt removed the iodide from the Pd(II) complex **I** forming a cationic Pd(II) species **II** which would be more electrophilic towards the indole unit thus increasing the rate of this palladation step. A poorly coordinating counter ion would allow dissociation to cationic species **II**, forming **III**, and also could act as a base in the palladation step (Scheme 25).



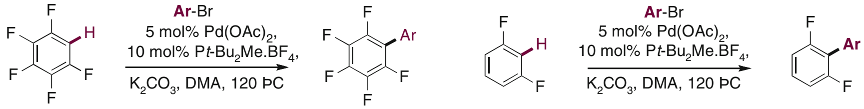
Scheme 25 Proposed catalytic cycle for arylation of indoles with aryl iodides



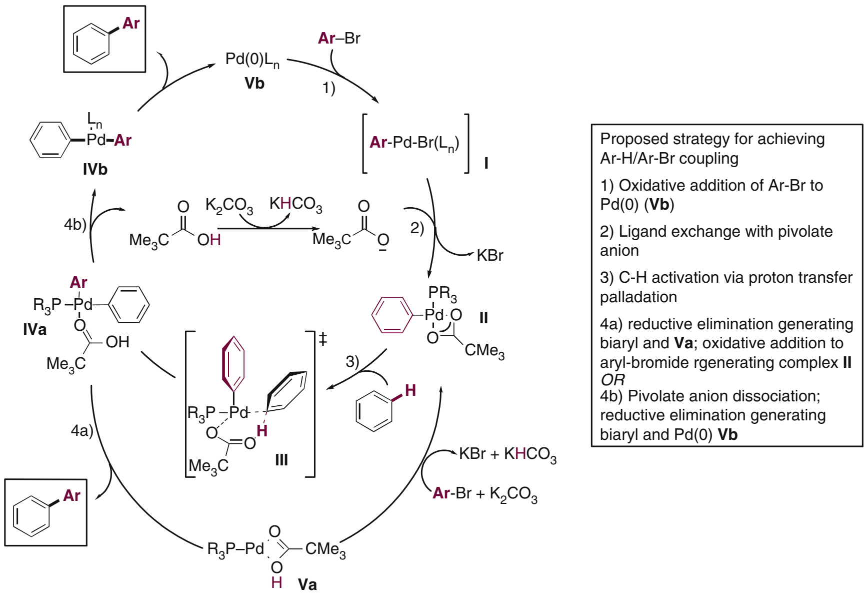
Scheme 26 Alternative proposed catalytic cycle for oxidative coupling of indoles and aryl iodides (Gaunt and Beck)

However, it is not clear how the proposed Pd(0) is formed from Pd(OAc)$_2$ under these reaction conditions and so a mechanism more similar to that proposed by Sanford [42] or Daugulis [47], involving a Pd(II)/Pd(IV) reaction manifold, cannot be ruled out (opinion of Gaunt and Beck). Rapid electrophilic attack from the Pd(II) catalyst would be expected with nucleophilic indole substrates, under the acidic conditions reported. The silver salt could then facilitate oxidative addition to the resulting palladium(II) species **I** by complexing the aryl iodide. Subsequent reductive elimination from the Pd(IV) centre **II** followed by ligand exchange with the silver carboxylate could then remove iodide from the reaction mixture and regenerate the active Pd(II) catalyst (Scheme 26).

The most common mechanism of C–H bond cleavage in the arylation examples discussed above has been assumed to be electrophilic aromatic substitution involving reaction of an electrophilic palladium catalyst with an electron rich, nucleophilic aromatic ring. In order to effect direct arylation on simple, electron deficient arenes, a basic directing group or intramolecular reaction is usually necessary to enable formation of a metalocycle. As a brief introduction to the effect of this area on the functionalization of indoles and pyrroles, we provide an overview of the mechanistic



Scheme 27 Alternative proposed catalytic cycle for oxidative coupling of indoles and aryl iodides



Scheme 28 Proposed catalytic cycle for direct arylation via proton-transfer palladation

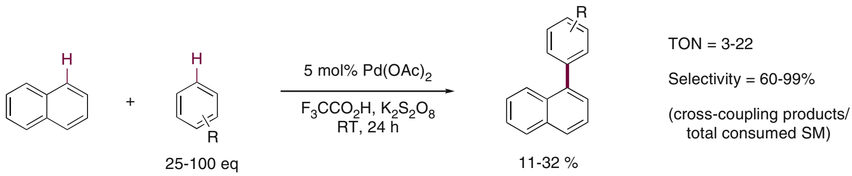
rationale for this mode of activation. The reader is also directed to the seminal contributions [20, 21]. These studies investigated the effect of various electronically biased substituents on aromatic C–H donors, shown in Scheme 27. Notably, the results of the reactions were inconsistent with an electrophilic palladation mechanism. In conjunction with computational studies, a mechanism for Pd-catalyzed arylation was proposed, involving proton abstraction by a carbonate, or related ligand.

In 2006 Fagnou described the direct intermolecular arylation of perfluoro benzene derivatives via the proposed proton-transfer pathway (Scheme 6). The reaction shows complete inversion of reactivity relative to the electrophilic C–H activation pathway and is thought to proceed via a concerted arene-metallation and C–H bond cleaving process, which depends on the acidity of the C–H bond being cleaved.

They were able to extend the scope of the direct arylation to simple, completely unactivated arenes, such as benzenes by development of a palladium-pivalic acid co-catalyst system (Scheme 28) [48].

The pivalate anion is a key component in the C–H bond cleaving step, lowering the energy of the C–H bond cleavage *(Step 3)* and acting as a catalytic proton shuttle from benzene to the stoichiometric carbonate base. Competition experiments

Scheme 29 Direct arylation via double C–H activation



Scheme 30 Lu's intermolecular cross-coupling of simple arenes by double C–H activation

indicate that electron deficient arenes react preferentially (fluoro benzene > benzene > anisole) with C–H acidity influencing the regioselectivity and reactivity correlating with the proposed proton-transfer pathway.

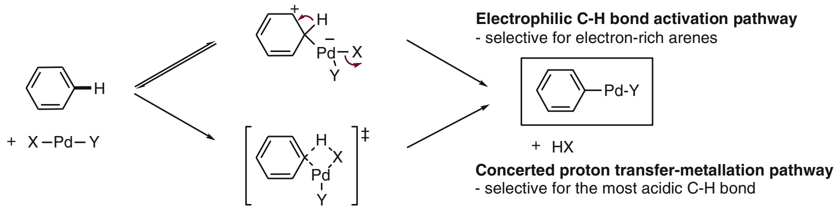
The formation of a C–C bond resulting from the coupling of two C–H bonds is a particularly attractive target, since the only formal by-product would be hydrogen, or water in an oxidative system. However, substantial hurdles impede the conception of a catalytic arene cross-coupling process that does not involve any substrate pre-activation at all. Aside from issues of reactivity and regioselectivity, the prevention of homo-coupling is a key factor for the development of this important class of reaction. The catalyst must be able to react with one arene in the first step of the catalytic cycle and then invert its selectivity in the second step to react exclusively with a different arene (Scheme 29).

One of the first reports of unsymmetrical biaryl formation via a double C–H activation event was published in 2006 by Lu et al. (Scheme 30) [49].

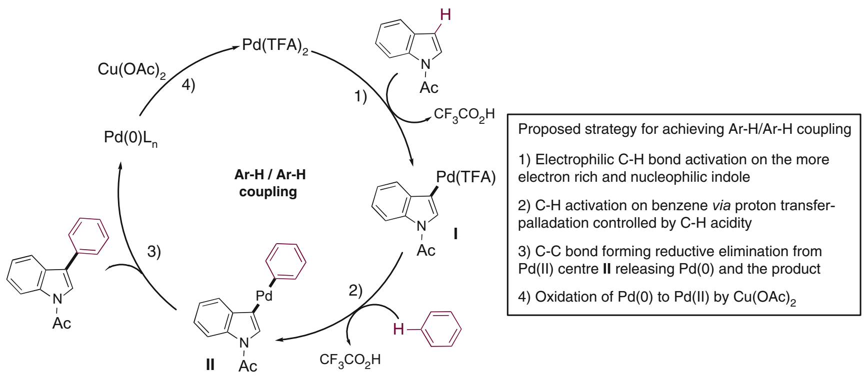
In 2007, the Fagnou group achieved a much more practical and selective Ar–H/Ar–H cross-coupling [50]. Electron deficient palladium(II) complexes can react via an electrophilic C–H activation mechanism with good selectivity for electron rich arenes. In contrast, Fagnou [51] recently showed that complimentary reactivity to this is displayed by some ArPd(II) complexes that react through a proton-transfer-palladation mechanism, and that they depend on arene C–H acidity rather than arene nucleophilicity (Scheme 31).

Fagnou et al. were able to exploit these two complimentary reactivity modes within a single catalytic cycle to achieve a highly selective Ar–H/Ar–H cross-coupling (Scheme 32).

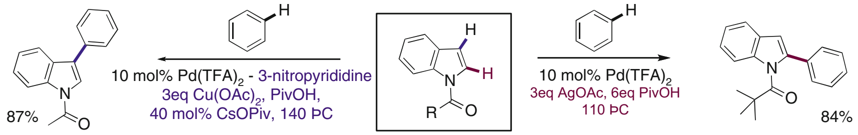
In the first step, it was proposed that the highly electrophilic $Pd^{II}(TFA)_2$ catalyst affected selective electrophilic C–H bond activation exclusively on the electron rich indole. This generated an indole–Pd(II) complex **I**, which was able to selectively activate the benzene via a transfer-palladation pathway, which is controlled by C–H acidity. Reductive elimination afforded biaryl C–C bond formation and released Pd(0) which required oxidation to regenerate the active Pd(II) catalyst.



Scheme 31 Complimentary mechanisms for C–H bond activation

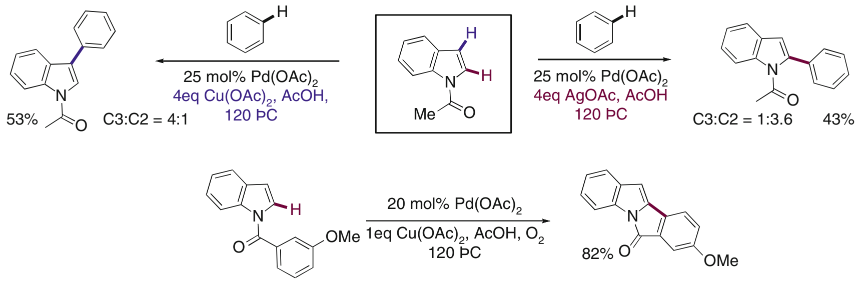


Scheme 32 Fagnou's proposed catalytic cycle for direct coupling of indoles and arenes



Scheme 33 Regioselective coupling of indoles and arenes via double C–H activation

The palladium-catalyzed oxidative cross-coupling process allows access to both C3 and C2 arylindoles as well as displaying a degree of regioselectivity at the benzene component (Scheme 33) [51, 52]. C3 selectivity was achieved on *N*–Ac indoles using a stoichiometric copper(II) oxidant and catalytic $Pd(TFA)_{2.}$ Optimal catalytic activity was observed with 3-nitropyridine and cesium pivolate as additives. It is presumed the pyridine additive may stabilize the palladium(0) prior to reoxidation preventing formation of palladium black that precipitates out of the reaction. Switching to AgOAc as oxidant produced an inversion in selectivity, favouring C2-arylation. These conditions were optimized by switching to *N*–pivalyl indole and removing the additives and resulted in 100% conversion and a 1:25 C3: C2 ratio. Selectivity studies have indicated it is most likely the acetate base, not the metal counter ion, that imparts C2 selectivity; perhaps due to carboxylate-induced cleavage of higher order Pd clusters and the formation of monomeric Pd species.



Scheme 34 Regioselective coupling of indoles and arenes via double C–H activation

Pd–Cu complexes, analogous to trinuclear Pd carboxylate clusters seen at high [Pd], are thought to cause the pronounced C3 selectivity.

DeBoef and co-workers have reported a similar reaction, wherein direct C–H to C–H indole-arene cross-coupling can be controlled through the use of a particular oxidant (Scheme 34) [53, 54]. The basis of their selectivity concept is the formation of different polyvalent clusters between the $Pd(OAc)_2$ and the AgOAc or $Cu(OAc)_2$ oxidants respectively, and the subsequent reactivity of these complex in the arylation reaction. The same group also demonstrated the utility of an intermolecular C–H to C–H coupling reaction.

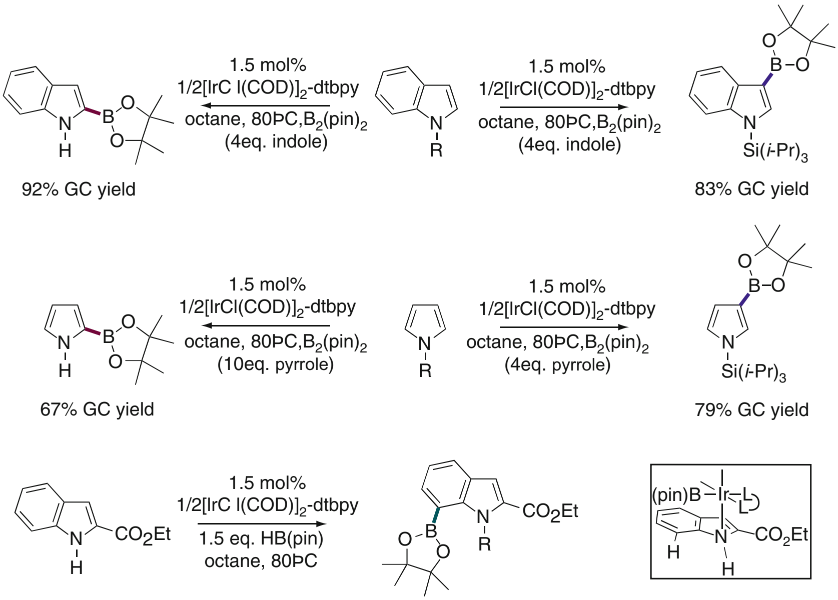
Although not directly relevant to this review, it should be noted that Sanford, Shi and Buchwald have also reported a palladium-catalyzed reaction for the chemo- and regioselective oxidative cross-coupling between ligand coordinated L–C_{Ar}–H substrates and simple arenes (Ar–H) [55–57].

Although not a palladium-catalyzed reaction, the Ir(I)-catalyzed C–H borylation reaction developed independently by Smith and Malezcka [58] and Hartwig and Miyaura [59] deserves some mention in the context of indole and pyrrole functionalization. Based on the original studies, indoles and pyrroles can be borylated (and hence cross coupled under Suzuki conditions) to form either the C2 or C3 functionalised products (Scheme 35) [60, 61]. Free (NH)-indoles and pyrroles react exclusively at the C2, whereas *N*-TIPS indole and pyrroles are borylated at the C3 positions. Interestingly, Smith, Maleczka and co-workers also demonstrated that when the C2 position of indole is blocked, then the borylation reaction takes place at the C7-position of the indole nucleus [62]. They propose that an *N*-chelation to Ir (or B) is responsible for the observed selectivity.

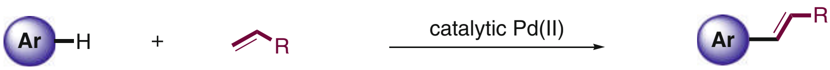
4 Pd-Catalyzed C–H Alkenylation of Indole and Pyrrole

4.1 Mechanisms of Pd-Catalyzed C–H Bond Alkenylation

Indoles and pyrroles have also been shown to undergo C–H alkenylation reactions. In these cases the process involves the coupling of the unfunctionalized (hetero) arene with an olefin (Scheme 36).



Scheme 35 Regioselective Ir(I)-catalyzed C–H borylation of indoles and pyrroles

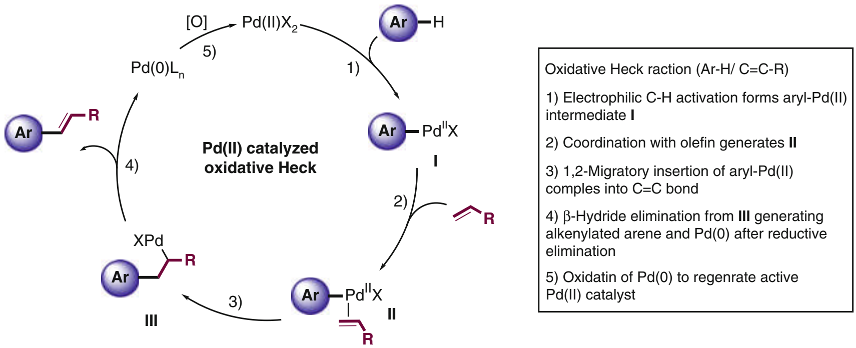


Scheme 36 C–H bond alkenylation of arenes

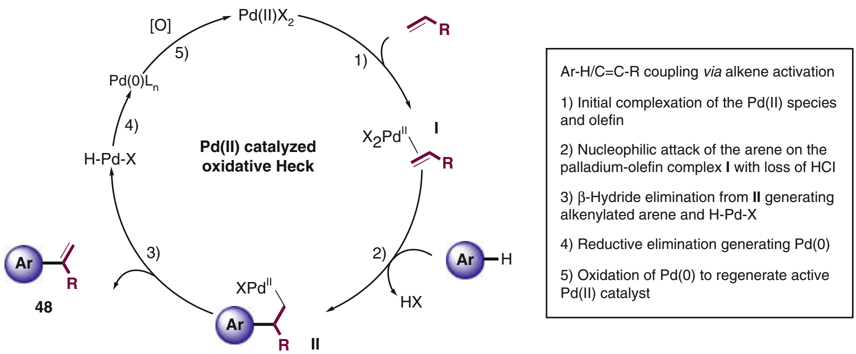
There are two typical mechanisms generally applied for palladium-catalyzed C–H alkenylation. First, the oxidative Heck mechanism, initially proposed by Fujiwara and Moritoni [63].

σ-Aryl–Pd complexes such as **I**, formed via electrophilic substitution of aromatic C–H bonds by Pd(II) species, are thought to be key intermediates in the catalytic cycle (Scheme 37). It is then proposed that a standard Heck arylation pathway is followed. The olefin coordinates to the unstable σ-aryl–palladium complex **I** and subsequently undergoes 1,2-migratory insertion into the aryl–palladium bond to form **III.** This species then rapidly decomposes, via β-hydride elimination, to the arylated olefin and palladium hydride. The latter subsequently reductively eliminates to generate HX and palladium(0), which can be reoxidized to the active palladium(II) source. Second, C–H alkenylation of arenes can occur through initial olefin activation, via coordination to palladium(II) (**I**), followed by subsequent nucleophilic attack from a electron rich (hetero)arene (Scheme 38).

Fujiwara and Moritoni carried out seminal work in the area of C–H alkenylation; they reported that palladium(II) complexes could mediate the coupling of unfunctionalized arenes with olefins in refluxing acetic acid [64]. The initial reactions used stoichiometric quantities of palladium salts; however the reaction was subsequently



Scheme 37 Proposed catalytic cycle for Pd(II) catalyzed oxidative Heck reaction

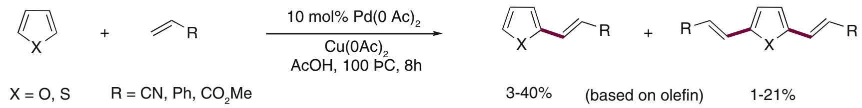


Scheme 38 Proposed catalytic cycle for Pd(II) catalyzed alkenylation via alkene activation

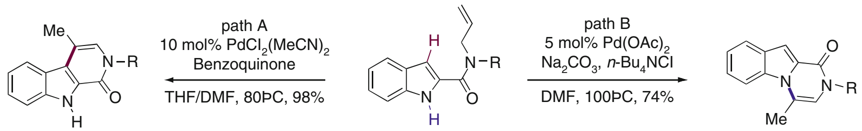
made catalytic using oxidants such as Ag(I) or Cu(II) in the presence of oxygen, *t*-BuOOH, *t*-BuOOBz or benzoquinone [65]. Analogous to the limitations described for direct arylations, C–H alkenylation was restricted in its utility due to the inability to effect single and selective functionalization of simple substituted arenes. The initial work with simple benzene derivatives indicated that electron donating substituents (e.g. Me, Et, OMe) directed *ortho*/*para,* where as electron withdrawing groups (e.g. NO_2) tended to give *meta* products. However, reactions were never completely selective on the arene coupling partner and typically gave mixtures of regioisomers.

4.2 Regioselective C–H Bond Alkenylation of Indole and Pyrrole

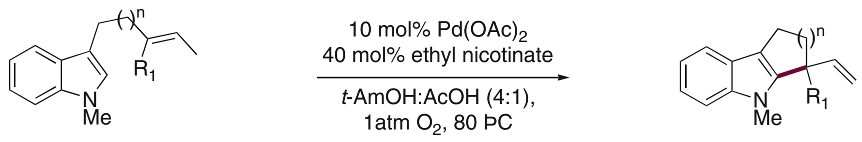
Utilization of "activated" C–H bonds in heteroaromatic compounds is particularly suited to these transformations, where the key C–H activation step involves electrophilic palladation at an electron deficient Pd(II) catalyst. Fujiwara et al.



Scheme 39 Fujiwara's application of the oxidative Heck reaction to various heterocycles



Scheme 40 Beccalli's chemoselective cyclization of indole carboxamide derivatives



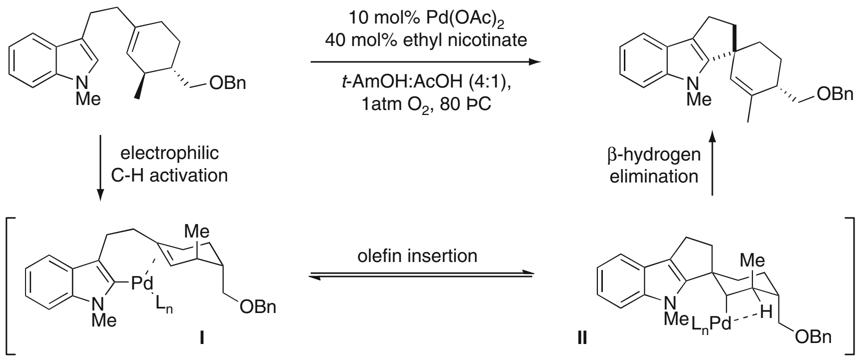
Scheme 41 Stoltz's intramolecular annulation of indoles

investigated the application of the oxidative Heck chemistry to various heterocycles (furan, thiophene, benzofuran, indole) (Scheme 39) [66, 67].

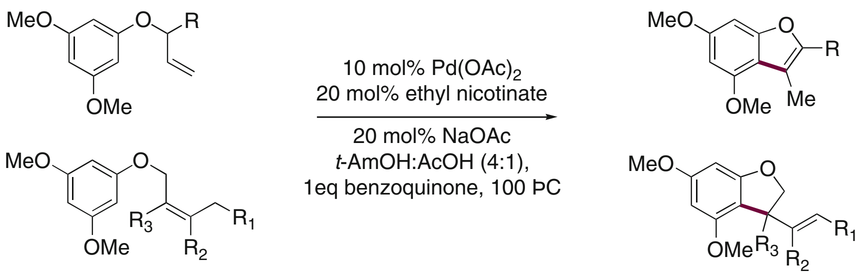
The reaction gave mono- and bis-alkenylated products on furan and thiophene, regioselective for the 2 and 5 positions, although limiting reaction to a single alkenylation was not addressed. In the reaction of 2-substituted furans bearing electron withdrawing or donating groups, the reaction selectively occurred at the 5-position. In an isolated example, reaction with indole occurred at the naturally more nucleophilic C3 position. As with the benzenoid examples, for heteroaromatics Fujiwara et al. and Tsuji et al. both reported more efficient catalytic systems using small amounts of palladium acetate and benzoquinone in the presence of *tert*-butyl peroxybenzoate as an inexpensive reoxidant [66, 67]. Various heteroaromatics and olefins undergo coupling reaction with high TON (up to 280) albeit with limited regioselectivity and substrate scope.

In 2003, Beccalli et al. reported an intramolecular variant, allowing chemoselective cyclization of indole carboxamide derivatives into β-carbolinones (path A) or pyrazino[1,2-*a*]indoles (path B) (Scheme 40) [68]. The chemoselectivity of the cyclization could be controlled by the reaction conditions. $PdCl_2(MeCN)_2$ and benzoquinone in DMF/THF made possible C–H functionalization at the C3 position of indole, whilst $Pd(OAc)_2$ in Na_2CO_3 and *n*-Bu_4NCl in DMF resulted in intramolecular amination of the double bond (N–H functionalization).

Stoltz et al. also reported an intramolecular reaction where C–H bond cyclization of indoles onto unactivated olefins was possible using palladium(II) and molecular oxygen as the sole stoichiometric oxidant (Scheme 41) [69]. They found the C2



Scheme 42 Proposed mechanism for intramolecular alkenylation of indoles

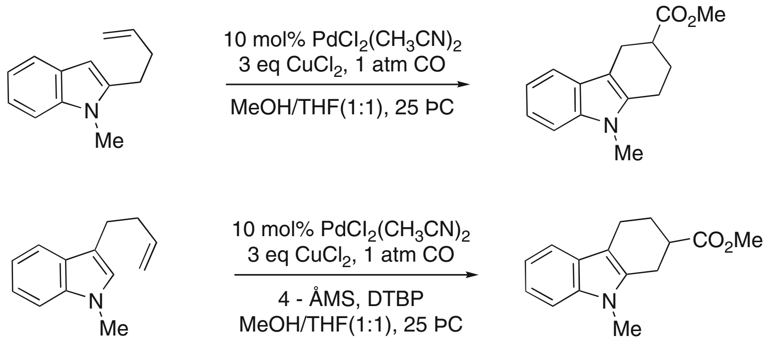


Scheme 43 Intramolecular alkenylation of aromatic rings

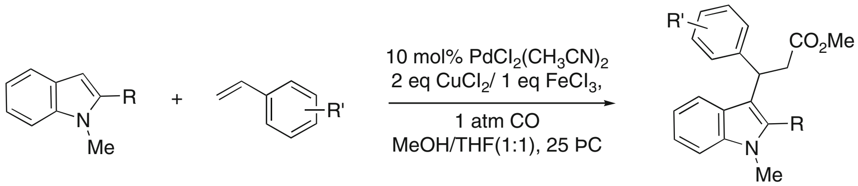
position on indole could be activated if the more nucleophilic C3 position was blocked.

Following work from Uemura [70], research focused on the use of palladium-pyridine systems, which had the potential for modification with chiral ligands to catalyze enantioselective processes. A correlation between the electronic nature of the pyridine ligand and its ability to facilitate the cyclization was observed. More electron withdrawing ligands resulted in a more electrophilic, and therefore more reactive, palladium catalyst; however, if too electron deficient, they were unable to ligate palladium sufficiently and as a result hampered both reactivity and Pd(0) oxidation. The mechanism is consistent with the previously discussed oxidative Heck process involving initial electrophilic palladation followed by olefin insertion and β-hydride elimination). This was indicated by subjecting a designed indole to the annulation conditions (Scheme 42). The observed stereochemistry of the product supports the mechanism if the requirements for *syn* migratory insertion and *syn* β-hydrogen elimination are operative.

The group have also developed an analogous process for direct C–H functionalization of electron rich aromatic rings and cyclization with unactivated alkenes to access substituted benzofuran and dihydrobenzofuran derivatives (Scheme 43) [71].



Scheme 44 Widenhoefer's cyclization/carboxylation of alkenyl indoles

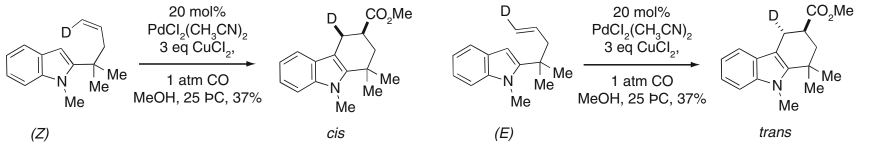


Scheme 45 Intermolecular alkylation/carboxylation of indoles with styrene derivatives

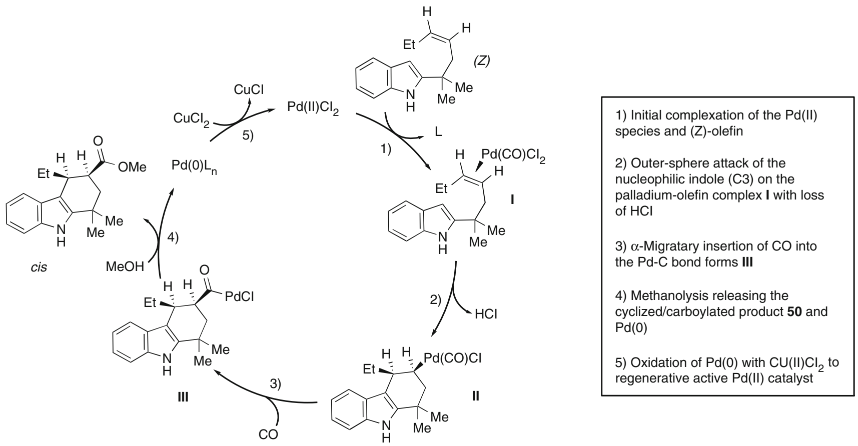
Interestingly, Widenhoefer reported a similar palladium(II) catalyzed cyclization of indoles onto alkenes (Scheme 58) [72]. This mild protocol for cyclization/carboxylation of 2-alkenyl indoles makes possible catalytic addition of a carbon-nucleophile and carbonyl group across a C=C bond. The mechanism, however, is thought to involve outer-sphere attack of indole onto a palladium–olefin complex rather than the electrophilic C–H activation of the indole C(3)–H bond, exhibited by the Stoltz carbocyclization.

Copper(II) chloride was found to be the best oxidant for the system and a range of esters could be formed if ten equivalents of the corresponding alcohol was added to a THF solution. A range of substituted indoles were subjected to the reaction conditions and furnished both 6- and 7-membered annulation products, in good to excellent yields, 58–91%. 3-Alkenyl indoles were also effective substrates, under going cyclization onto the less nucleophilic C2 position in good yield albeit requiring extended reaction time (Scheme 44).

It was also possible to carry out an analogous intermolecular version of the alkylation/carboxylation process between 2-substituted indoles and styrenes (Scheme 45) [73]. While sterically and electronically diverse styrene derivatives reacted with moderate to good yields (40–78%), indoles without substitution at C2 failed to undergo efficient reaction. The reactions were always selective for the indole C3-position (as C2 was blocked) and produced products substituted to the phenyl ring.



Scheme 46 Mechanistic investigations of the cyclization/carboxylation reaction

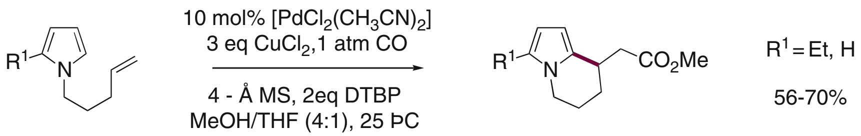


Scheme 47 Proposed catalytic cycle for the cyclization/carboxylation of alkenyl indoles

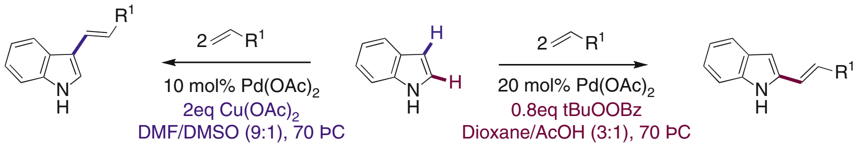
The stereochemistry of the reaction was investigated for both (*Z*) and (*E*) 3-(4-deuterio-3-butenyl)indoles. Treatment of *(Z)*-deuterated alkene with a catalytic quantity of $PdCl_2(CH_3CN)_2$ in the presence of $CuCl_2$ gave the *cis*-product as a single diastereomer whilst treatment of corresponding *(E)*-isomer with the same conditions gave *trans*-product also as a single diastereomer. This indicated the palladium-catalyzed cyclization/carboalkoxylation was stereospecific and that the indole and carbomethoxy group add in an *anti* fashion across the C=C bond of the olefin (Scheme 46).

The stereochemical outcome was in agreement with a mechanism for the palladium-catalyzed cyclization/carboalkoxylation of a substituted alkene (Scheme 47) that involves outer-sphere attack of the indole on the palladium-olefin complex **I** which, coupled with loss of HCl, would form the alkylpalladium intermediate **II**. 1,1-Migratory insertion of CO into the Pd–C bond of **II** with retention of stereochemistry would form the acyl–palladium complex **III**, which could undergo methanolysis to release *cis*-product and form a palladium(0) complex. Oxidation with Cu(II) would then regenerate the active Pd(II) catalyst.

Widenhoefer has also reported two isolated examples of C2-cyclization/carboxylation on *N*-alkenyl pyrrole substrates (Scheme 48) [73]. In order to achieve moderate to good yields, addition of molecular sieves and dropwise addition of



Scheme 48 C2 C–H cyclization/carboxylation on *N*-alkenyl pyrroles



Scheme 49 Gaunt's regioselective intermolecular C–H alkenylation of indoles

a Brønsted base was required to counteract the competitive acid promoted pyrrole polymerization.

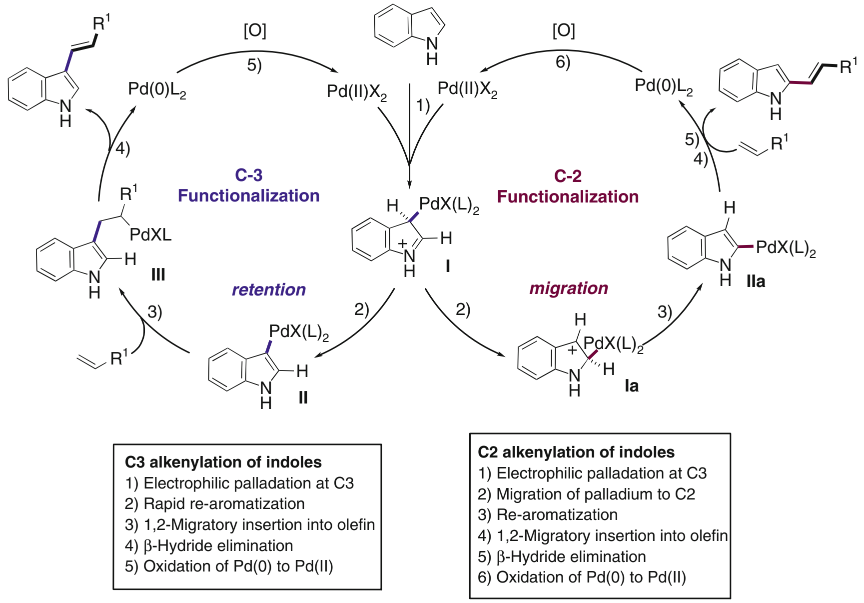
Although much has been learnt about the reactivity and regioselectivity in direct functionalization of heteroarenes, the ability to manipulate and controllably switch the selectivity is extremely rare. In 2005, a method for direct and selective C2 or C3 elaboration of free-(NH) indoles using palladium-catalyzed C–H functionalization was developed by Gaunt and co-workers (Scheme 49) [43].

This relatively mild and highly regioselective process allowed C–H alkenylation with both electron deficient acrylates and more unactivated alkenes. Switchable regioselectivity was achieved by varying the reaction media and chemical oxidant.

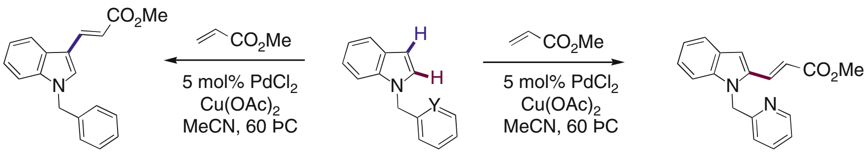
It is proposed that, for both pathways, indole initially undergoes electrophilic palladation at the more nucleophilic C3 position via intermediate **I** (Scheme 50). Under neutral conditions the acetate ion, formed from the attack of indole on Pd $(OAc)_2$, will readily remove a proton from intermediate **I** to form palladated species **II** (Scheme 50*, retention pathway*). This species undergoes 1,2-migratory insertion with the olefin, and subsequent β-hydride elimination then affords C3-alkenylated products. In contrast, under acidic conditions (*t*-BuOOBz, AcOH/dioxane) it is thought that rearomatization is slowed, allowing a migration pathway to dominate (Scheme 50*, migration pathway*). The C3-PdX bond in **I** is proposed to shift to the highly activated C2 position of the iminium intermediate to give species **Ia** and ultimately **IIa**. Subsequent 1,2-migratory olefin insertion and β-hydride elimination would then generate the corresponding C2-alkenylated products.

Concurrent with these studies, Brown and co-workers reported a regioselective C–H functionalization of indoles via directing group control (Scheme 51) [74]. When a benzyl group was attached to the indole nitrogen, alkenylation took place selectively at the more nucleophilic C3 position (in agreement with Fujiwara's observations). Alternatively *N*-pyridyl protected indoles directed alkenylation to the more unusual C2 position via coordination to the protecting group.

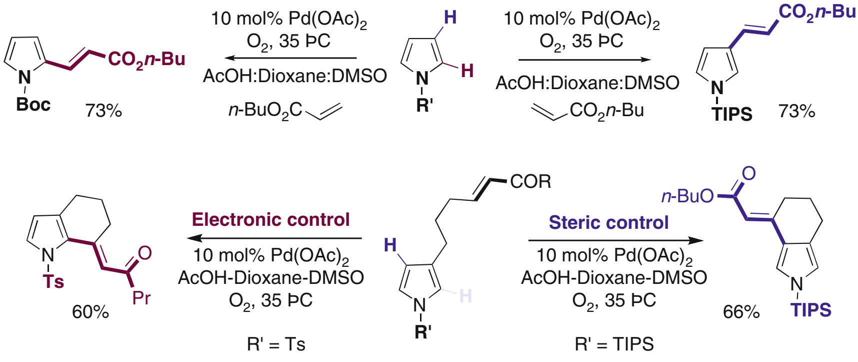
Gaunt and co-workers have also developed an efficient palladium(II) oxidation system for C–H functionalization of pyrroles under ambient conditions (Scheme 52)



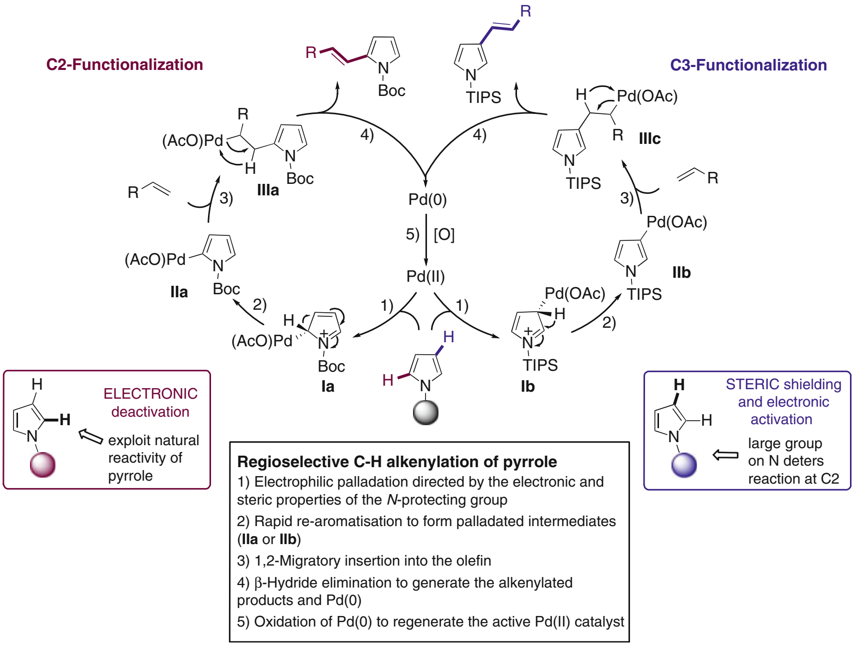
Scheme 50 Proposed catalytic cycle for regioselective C–H alkenylation of indoles



Scheme 51 Brown's directing group controlled intermolecular alkenylation of indoles



Scheme 52 Gaunt's regioselective inter- and intramolecular C–H bond functionalization of pyrroles



Scheme 53 Proposed regioselectivity concept and catalytic cycle for C–H alkenylation

[75]. It is possible to control the position of reaction via simple steric and electronically tuned *N*-pyrrole protecting groups to form products with either C-2 or C-3 elaboration. *N*-Boc pyrroles react at the C2 position, exploiting the inherent reactivity of this heteroarene. In contrast, *N*-TIPS pyrrole is shielded from reacting at the C2 position by the sterically demanding silyl group and so instead undergoes the C–H bond alkenylation at the C3 position. This method can be used to generate a range of alkenylated products. The regioselectivity concept can also be applied in an intramolecular sense forming different pyrrole architectures depending on the group on the pyrrole nitrogen. Despite the high propensity of pyrroles to oxidation and polymerization, this mild C–H functionalization method affords excellent yields of either C2 or C3 derived products.

In terms of the mechanism, both reactions are thought to proceed via an electrophilic palladation step followed by Heck type coupling with the olefin (*oxidative Heck mechanism*) (Scheme 53). For C2 palladation, a slightly electron withdrawing group on nitrogen deactivates the ring sufficiently that the natural C2 selectivity controls the electrophilic palladation. In the case of C3 elaboration, the TIPS group is extremely bulky and slightly electron donating. Presumably, the steric bulk deters reaction at the adjacent C2 position whilst the highly activated nature of the pyrrole allows palladation at the less nucleophilic C3 even under these mild catalytic conditions. After regioselective palladation on pyrrole it is thought that the respective aryl–palladium intermediates (**IIa** and **IIb**) undergo a 1,2-migratory insertion with the alkene, which after β-hydride elimination gives the alkenylated products and palladium(0).

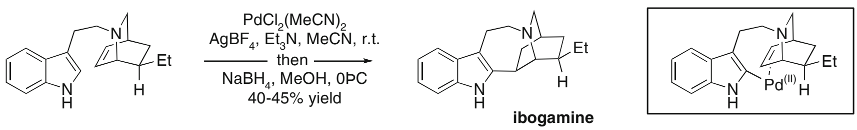
5 Pd-Catalyzed C–H Bond Functionalization of Indoles and Pyrroles in Complex Molecule Synthesis

In terms of making natural products, synthetic strategies have been revolutionized by the development of cross-coupling reactions, which are particularly useful for uniting complex molecular fragments. The successful assembly of complex molecules via cross-coupling tactics exploits the reactivity of strategically installed "metal-active" functional groups in the key bond forming events. In recent years the advance of metal-catalyzed C–H bond activation technology has suggested that similar transformations are possible without the need to pre-functionalize the parent molecules. There has been a wealth of methodological advances that have highlighted the potential efficacy of these processes in synthesis. However, there are few examples of the application of such catalytic tactics in total synthesis. This is possibly due to complications with the harsh reaction conditions often required and the selectivity and stability issues associated with the more complex substrates inevitably needed for these purposes. In spite of this, direct C–H functionalization tactics could have a huge impact in streamlining natural product synthesis and so further development in this area represents an important goal for synthetic chemists.

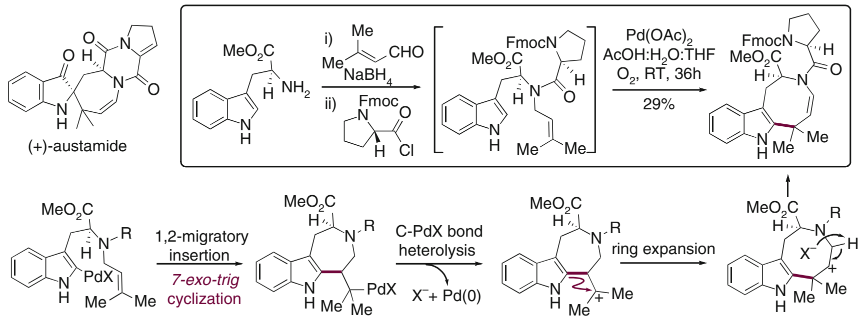
The following section looks at how palladium-catalyzed C–H functionalization has been successfully applied in synthetic strategies enabling rapid and elegant routes to complex natural products containing the indole and pyrrole nucleus. There are a number of metal-mediated examples where stoichiometric quantities of transition metals are employed to affect the desired transformation; however, there are very few cases of catalytic functionalization with in the context of complex molecule synthesis.

An early example of a natural product synthesis featuring an indole C–H bond alkenylation was report by Trost and co-workers (Scheme 54). Using stoichiometric Pd(II)-salts in combination with silver(I) tetrafluoroborate, they were able to mediate a oxidative Heck process onto the bicyclic amino-alkene. Using a reductive work-up to reduce the Pd–C bond, they were able to complete a synthesis of ibogamine [76].

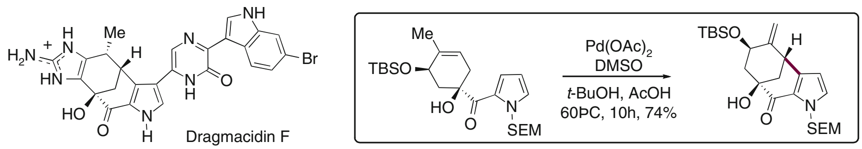
In 2002 Corey and Baran employed a similar palladium-mediated indole-dihydroindoloazocine cyclization to construct the core 8-membered ring in their



Scheme 54 Trost's synthesis of ibogamine featuring a Pd(II)-mediated carbocyclization



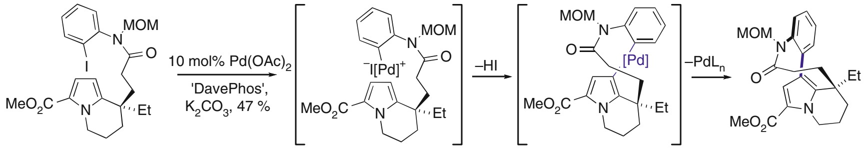
Scheme 55 Corey's synthesis of (+)-austamide featuring a Pd(II)-mediated carbocyclization



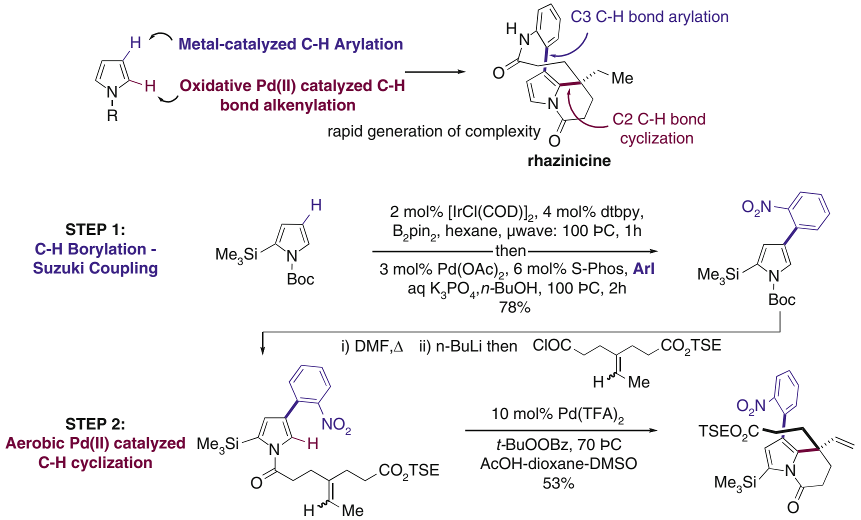
Scheme 56 Stoltz's synthesis of dragmacidin F featuring a Pd(II)-mediated carbocyclization

synthesis of (+)-austamide, (Scheme 55) [77, 78]. Treatment with $Pd(OAc)_2$ in 1:1:1 THF–H_2O–AcOH at 23 °C under 1 atm of O_2 for 36 h allowed conversion of an *N*-prenylated tryptophan derivative to the dihydroindoloazocine tricyclic architecture in one step (29%) making possible a impressively short route to the natural product. The proposed carbocyclization mechanism involved initial C2 indole palladation followed by intramolecular *7-exo-trig* Heck type cyclization. It was thought that the aqueous acetic acid solvent system subsequently caused C–PdX bond heterolysis and Pd(0) which produced a cationic intermediate that by migration of the electron rich β-[2-indolyl] group resulted in ring enlargement and formation of the dihydroindoloazocine product.

Similarly, in 2004, the Stoltz group employed a heteroarene/olefin oxidative C–C coupling transformation as a key step in their synthesis of pyrrole alkaloid (+)-dragmacidin F (Scheme 56) [79, 80]. They found that exposure of the key pyrrole fragment to $Pd(OAc)_2$ under a variety of conditions led to carbocyclization and after optimization they were able to isolate the desired fused pyrrole-bicyclic structure as a single stereo- and regio-isomer in 74% yield. The transformation is noteworthy since it results in functionalization of the electronically deactivated C3 position. They were, however, unable to effect catalytic turnover of palladium with a stoichiometric oxidant, which they presumed was due to extensive oxidative decomposition of both starting material and product. This Pd(II)-mediated strategy did, however, provide the desired cyclized product in around twice the yield of the conventional Heck route, using equivalent amounts of palladium, which highlights the positive influence of C–H functionalization processes.



Scheme 57 Trauner's application of direct C–H arylation in the synthesis of (±)-rhazinilam



Scheme 58 Iterative C–H bond functionalization strategy for the synthesis of (±)-rhazinicine

Trauner applied a C–H bond activation approach to the synthesis of rhazinilam [81]. The synthetic power of direct C–H arylation on nucleophilic heteroarenes was demonstrated through formation of the strained 9-membered ring using intramolecular coupling to an unactivated pyrrole (Scheme 57).

Conditions first described by Fagnou were used to affect the C–H to C–H bond cyclization, which proceeded in 47% yield. Mechanistically the direct coupling reaction is thought to proceed via intramolecular nucleophilic attack of the pyrrole moiety onto the Pd(II) centre. It was postulated that the electron rich "DavePhos" ligand facilitates both oxidative addition and forms a more reactive cationic Pd(II) species by dissociation of the halide. Following a deprotonation step, reductive elimination of Pd(0) then resulted in formation of the biaryl bond, completing the core framework. Application of this "direct" palladium-catalyzed biaryl coupling facilitates a very efficient and concise synthesis of rhazinilam as a racemate.

Gaunt and co-workers have also completed the first total synthesis of rhazinicine, a related natural product to rhazinilam, achieved in 11 steps from commercial materials using a short synthetic strategy that demonstrates how iterative metal-catalyzed C–H bond functionalizations can positively influence complex molecule assembly (Scheme 58) [82].

They found that combination of the Ir(I) catalyzed C–H borylation and Suzuki coupling sequence led to a two-step, one-pot "C–H Suzuki" arylation that enabled direct transformation of the *N*-Boc pyrrole to the C3 arylated intermediate in 78% yield. Following installation of the required acyl group, an application of their oxidative Pd-catalyzed C–H alkenylation reaction enabled formation of the key structural architecture of the natural deliver the natural product. The orthogonal selectivity characteristics displayed by these C–H functionalization processes makes possible iterative functionalization of the heteroaromatic pyrrole core. Utilization of the highly versatile C–H borylation – Suzuki coupling to install the aromatic functionality opens up possibilities of facile analogue synthesis via this route.

C–H functionalization is an area of rapid growth that pushes the limits of chemical reactivity. Even within the subsection of palladium-catalyzed C–H bond functionalization of indole and pyrrole, many new modes of reactivity and strategies for controlling selectivity have emerged over the past 5–10 years. Discovery of new catalytic species and reaction conditions with novel selectivity modes will be crucial to the future utility of C–H activation within the context of complex molecule synthesis. Achieving selectivity among different C–H bonds remains a major challenge and so the development of new catalyst systems that are both highly reactive and predictably selective is essential to significantly increase the efficiency with which carbon frameworks can be constructed. Combining various mechanisms of activation should allow us to selectively functionalize at a variety of different positions around an aromatic system. Such an ability to transform a variety of C–H bonds with high levels of selectivity would unlock an entirely new perspective in complex molecule synthesis and should lead to major simplifications of synthetic sequences.

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Remote C–H Activation via Through-Space Palladium and Rhodium Migrations

Feng Shi and Richard C. Larock

Abstract The catalytic activation of a C–H bond is a fundamentally important organic transformation. There are now numerous reports of palladium-mediated C–H activation by the through-space interaction of a palladium center with a neighboring C–H bond. This type of C–H activation can lead to a net "palladium migration" from the carbon atom where the palladium is first introduced to a remote carbon atom where C–H activation occurs. This process provides a novel method to introduce a palladium moiety into a position where direct palladium introduction may not be straightforward. This process is accompanied by concurrent migration of a hydrogen atom in the direction opposite to that of the palladium migration. Analogous rhodium migrations have also been reported. In this account, different types of palladium and rhodium migrations are reviewed and the reaction mechanism is discussed.

Keywords Atom economy • C–H Activation • Palladium catalysis • Rhodium catalysis

Contents

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Abbreviations

Ac	Acetyl
acac	Acetylacetonate
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Boc	*tert*-Butoxycarbonyl
Bz	Benzoyl
cod	1,5-Cyclooctadiene
dba	Di(benzylidene)acetone
DMAc	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
dppb	1,4-Bis(diphenylphosphino)butane
dppm	Bis(diphenylphosphino)methane
dppp	1,3-Bis(diphenylphosphino)propane
Ms	Methanesulfonyl
Piv	Pivaloyl
TBAB	Tetrabutylammonium bromide
TBAC	Tetrabutylammonium chloride
TES	Triethylsilyl
Tol	Tolyl
Tol-BINAP	2,2′-Bis[di(*o*-tolyl)phosphino]-1,1′-binaphthyl
S-phos	2,6-Dimethoxy-2′-(diphenylphosphino)biphenyl

1 Introduction

The activation of a C–H bond is a highly challenging yet fundamentally important process in organic chemistry [1–4], since C–H bonds are known to be strong, lack polarity, and are generally unreactive. These features render C–H activation a demanding task. On the other hand, successful C–H activation can dramatically impact organic synthesis. Adding the C–H bond to the list of “functional groups” fundamentally changes retrosynthetic analysis [5], and significantly transforms synthetic organic chemistry in terms of the synthetic pathways available, plus overall reaction efficiency. Considering that essentially all chemicals ultimately derive from fossil resources that contain only C–H and C–C bonds, the success of C–H activation can potentially revolutionize the industrial manufacture of fine chemicals and thus more efficiently use these nonrenewable resources.

Through the years, reports on C–H activation have increased exponentially. Many transition metals have been discovered to catalyze C–H activation. Palladium, arguably the most powerful and most widely used transition metal in organic synthesis [6], has been found to be capable of catalyzing various C–H activation processes in recent years [7–23]. Such palladium-catalyzed C–H activation processes have considerable intrinsic advantages over processes catalyzed by other metals, because the resultant C–Pd bond can participate in a number of subsequent transformations and lead to a number of different products, thus making the greatest use and diversification of this C–H activation process. An interesting feature of palladium-catalyzed C–H activation is that palladium, in most cases, only activates C–H bonds that are in close vicinity to a chelation-directing group, such as an amido group [9]. While such a directing effect affords outstanding selectivity in such C–H activation processes, it also significantly limits their synthetic utility. Therefore, methods have been sought using palladium to activate, and thus functionalize, certain "remote" C–H bonds that are not in proximity to a directing group.

This problem is solved by a two-step approach termed through-space palladium migration [24]. In this approach, palladium is first introduced to a certain carbon atom using standard methods, such as oxidative addition or alkyne insertion. This stage is similar to the aforementioned chelation-directed C–H activation in the sense that palladium is introduced into the molecule and has a nearby C–H bond to interact with. In the second stage, the through-space interaction of palladium with a nearby C–H bond becomes strong enough to lead to the cleavage of the C–H bond, and relocation of the palladium to this carbon atom. The net effect is a "palladium migration." Simultaneous to the migration of palladium, the hydrogen atom residing on this carbon atom undergoes a concurrent migration in the opposite direction to the carbon atom that used to carry palladium. This migration process activates the C–H bond without requiring a neighboring directing group and introduces a palladium moiety to a remote site where direct introduction of palladium may be difficult. This migration of palladium may occur one or more times, depending on the exact environment. Typically, such a through-space palladium migration occurs much more efficiently on a C–H bond that is four or five bonds away from palladium, presumably facilitated by the formation of a five- or six-membered ring palladacycle. After migration of the palladium, further reaction ensues, removing the palladium moiety from the molecule and functionalizing the activated C–H bond. This functionalization can be achieved through standard synthetic processes, such as elimination, ligand exchange, transmetalation, and nucleophilic displacement of Pd(II).

Palladium migration is a mechanistically interesting and synthetically useful process, because it provides an indirect approach to introduce palladium to a specific location in an organic molecule. It also allows C–H activation to occur on a remote site whose direct functionalization may not be easily achieved. Through the years, palladium migration processes have been applied to the construction of a variety of important heterocycles, such as carbazoles [25, 26], indoles [26], xanthones [27], and fluoren-9-ones [27, 28]. They have also received special attention from computational chemists, who have conducted theoretical studies on the mechanism and transition state [29–31].

Other than palladium, rhodium is also known to perform similar migrations. Representative examples will also be briefly discussed. The palladium migration along alkyl chains via reversible β-hydride elimination/reinsertion processes will not be covered [32–36].

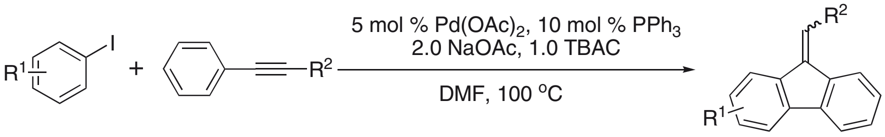
2 One-Step 1,4-Palladium Migrations

Among all palladium migrations, the 1,4-migration is the most commonly seen. In this situation, palladium shifts from one carbon atom to another carbon atom that is separated by two additional atoms. The process may be favored by the formation of a relatively strain-free five-membered ring palladacycle, as well as the close proximity of the palladium to the C–H bond. A variety of palladium 1,4-migration examples have been reported. It has been established that palladium can migrate from vinylic, aryl, and alkyl (benzylic or homobenzylic) positions, to aryl, alkyl (benzylic or homobenzylic), acyl, and imidoyl positions. Both single-substrate rearrangements and multiple-substrate coupling reactions are known. Depending upon the specific reaction system, the palladium sources and ligands may vary, yet cesium pivalate (CsOPiv) seems to be a universal additive that is necessary to assure high yields of the migration products in most cases [37]. The exact role of this additive remains elusive, but its relatively good solubility in DMF, a common solvent for palladium migration, has been shown to be one of the key reasons [38, 39].

2.1 Vinylic to Aryl Palladium Migrations

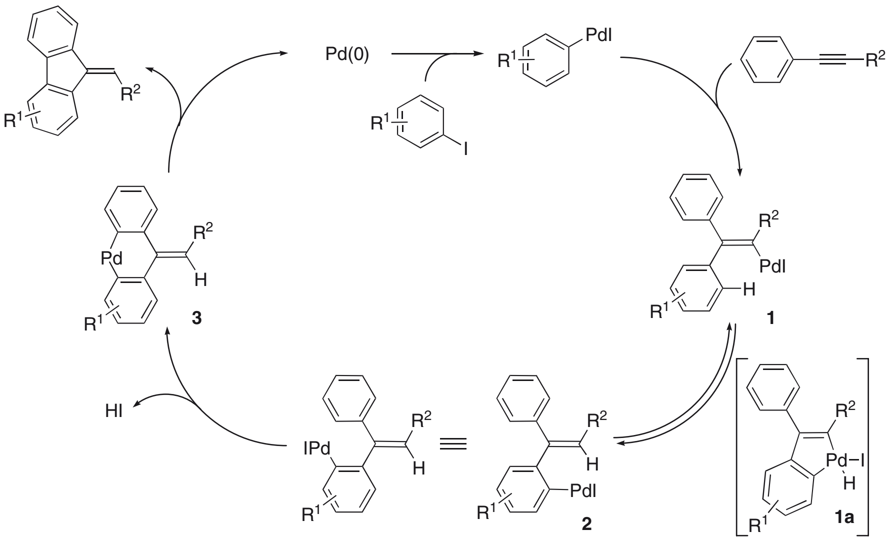
In 2000, a novel annulation process involving iodobenzene and diphenylacetylene under palladium-catalyzed conditions was reported to afford 9-benzylidene-9*H*-fluorene in a 62% yield (Scheme 1) [40, 41]. A further survey of the reaction led to the first well-studied example of palladium migration in terms of substrate scope, reaction conditions, and mechanism. The reaction proceeds through a relatively new catalytic cycle (Scheme 2). Thus, Pd(0) first oxidatively inserts into the aromatic C–I bond, followed by migratory insertion of the alkyne to afford intermediate **1** (Pd introduction stage). In this intermediate, the vinylic Pd is in close proximity to a neighboring aromatic C–H bond that is five bonds away, resulting in activation of this remote C–H bond and migration of palladium to form a second intermediate **2**, possibly via the five-membered ring intermediate **1a** (Pd migration stage). The net effect of the palladium migration is the activation and the cleavage of the remote C–H bond, as well as the formation of another C–H bond where the palladium originally resided. Intermediate **2** can then undergo a single bond rotation, followed by an arylation step to afford intermediate **3**, which then reductively eliminates the desired product and regenerates the Pd(0) catalyst (termination stage). The arylation step, mechanistically, may parallel electrophilic aromatic substitution [42–44], although recent studies have pointed to other possible mechanistic pathways, such as proton abstraction [45–50]. Control of the geometry of the exocyclic olefin is not achieved in this reaction.

An extension of this vinylic to aryl palladium migration was reported later using *N*-aryl-3-iodoaniline, instead of iodobenzene, as the substrate under improved reaction conditions (Scheme 3) to afford 4-vinylcarbazoles [25]. For reasons not understood, this reaction is limited to substrates whose N–H bonds are not substituted. Overall, the reaction offers a quick synthetic approach to carbazoles, which involves the



R^1 = H, R^2 = Ph	62%
R^1 = H, R^2 = *t*-Bu	61%
R^1 = H, R^2 = CMe_2OH	55%
R^1 = 2-CN, R^2 = Ph	63% (*E*)
R^1 = 2-MeO, R^2 = Ph	45% (2:3 *E*:*Z*)
R^1 = 4-MeO, R^2 = Ph	25% (2:3 *E*:*Z*)

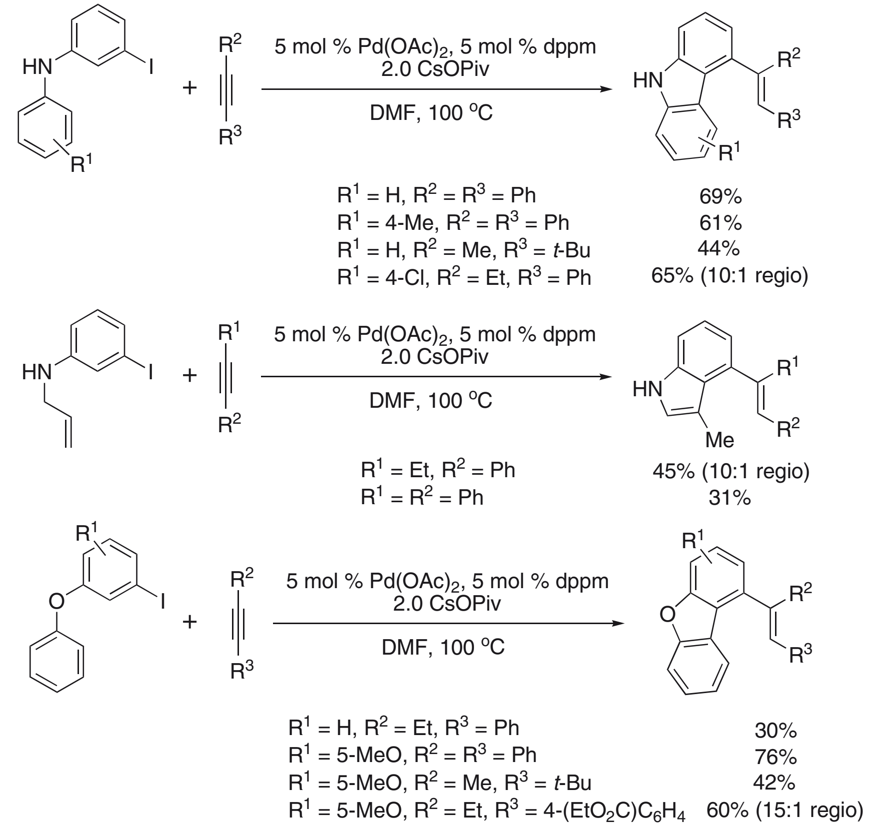
Scheme 1 Vinylic to aryl palladium migration in the synthesis of 9-benzylidene-9*H*-fluorenes



Scheme 2 Proposed mechanism for the annulation involving vinylic to aryl palladium migration

cleavage of two C–H bonds, and formation of two C–C bonds and one C–H bond all in a single step. The same principle was then used to synthesize indoles and dibenzofurans starting from the appropriate substrates (Scheme 3) by simply varying the groups used to trap the migrated palladium [26].

The reaction mechanism of these reactions parallels the aforementioned palladium migration and has been strongly supported by isotope labeling experiments. Interestingly, in this reaction, palladium selectively migrates to the position *ortho* to the nitrogen, rather than the less sterically congested *para* position, and does not migrate further to the allylic positions when R^2 is an alkyl group (see Sect. 3.2 for the consecutive vinylic to aryl to allylic migration). A possible explanation for this observation is that the *ortho* heteroatom may weakly chelate the palladium center, thus stabilizing the *ortho* migration regioisomer, leading to the regio-discrimination observed, as well as the absence of the consecutive double migration. It is also possible that the



Scheme 3 Vinylic to aryl palladium migration in the synthesis of vinylic carbazoles, indoles, and dibenzofurans

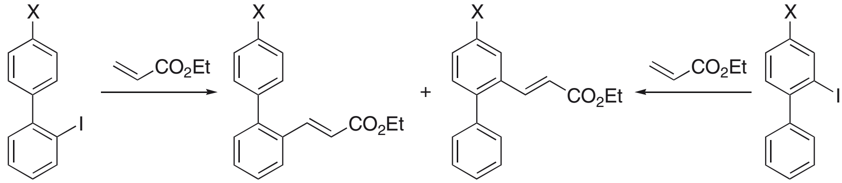
inductive effect of the nitrogen and oxygen atom favors migration of palladium to the *ortho* position (see the later discussion of the mechanism of the aryl to aryl palladium migration in Sect. 2.2).

2.2 Aryl to Aryl Palladium Migrations

Besides vinylic to aryl migrations, aryl to aryl palladium migrations have also been studied. Although it may seem that the aryl to aryl migration should be a reversible process, which is indeed observed in some cases, reactions of this type may be driven in one direction by introduction of an intramolecular palladium trap to selectively react with the palladium after migration.

The first aryl to aryl migrations were observed between the *o*-position and the *o*′-position in a biphenyl system [51] and an analogous phenylpyridine system [52] (Table 1). While studying the Heck reaction of *o*-iodobiphenyls and analogues,

Table 1 Aryl to aryl palladium migration in biphenyls terminated by Heck coupling



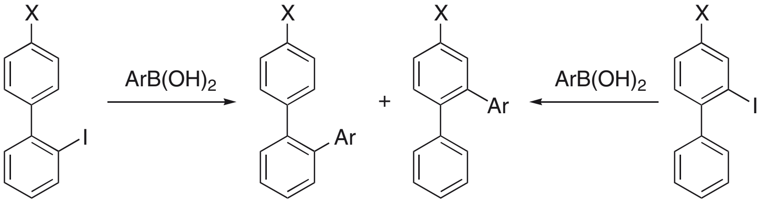
Entry	Case	Substrate	Procedure[a]	% Yield	Ratio **6**:**7**
1	1	**4a** (X=Me)	A	100	100:0
	2		C	88	50:50
	3	**5a** (X=Me)	C	86	49:51
	4		A	93	0:100
2	1	**4b** (X=NMe_2)	A	80	100:0
	2		C	90	55:45
	3	**5b** (X=NMe_2)	C	93	49:51
	4		A	100	0:100
3	1	**4c** (X=NO_2)	B	85	100:0
	2		D	46	39:61
	3	**5c** (X=NO_2)	D	37	33:67
	4		B	89	0:100

[a]Procedure A: 5 mol% $Pd(OAc)_2$, 1.0 equiv of TBAC, 2.0 equiv of $NaHCO_3$, 4.0 equiv of ethyl acrylate, 0.25 M in DMF, 100 °C; Procedure B: same as procedure A, but replacing $NaHCO_3$ with Et_3N; Procedure C: 5 mol% $Pd(OAc)_2$, 5 mol% dppm, 2.0 equiv of CsOPiv, 1.0 equiv of ethyl acrylate, 0.063 M in DMF, 100 °C; Procedure D: same as procedure C, but replacing 5 vol% of DMF with H_2O

Jeffery found that under classical conditions (procedures A and B) [53], all Heck couplings afforded products with the olefin incorporated at the positions where the iodide originally resided (cases 1 and 4 in each entry). However, under modified conditions (procedures C and D), unsymmetrical *o*-iodobiphenyls gave not only *o*-olefinated, direct Heck coupling products, but also *o′*-olefinated, migrated products in essentially equilibration ratios (cases 2 and 3 in each entry). The product distribution is dependent more on the electronic and steric nature of the starting *o*-iodobiphenyls than on the location of the iodide in the starting materials. This is clear evidence that there exists an equilibration between the two *o*-palladated biphenyl intermediates prior to olefin trapping, which suggests a palladium migration between the *o*-position and the *o′*-position. The similar, but unequal, product ratios from different substituted biphenyls, particularly from electronically perturbed substrate pairs, such as **4b/5b** and **4c/5c** (compare cases 2 and 3 for entries 2 and 3), suggests that such an equilibration is not always completely satisfied and that olefin trapping is not substantially slower than the palladium migration.

Trapping the palladium species by transmetalation in a Suzuki-Miyaura coupling shows a very similar trend (Table 2) [38]. By modifying the original Suzuki-Miyaura conditions [54] by the addition of water and pivalic acid [37], the palladium can migrate between the two *o*-positions before being trapped by

Table 2 Aryl to aryl palladium migration in biphenyls terminated by Suzuki-Miyaura coupling[a]



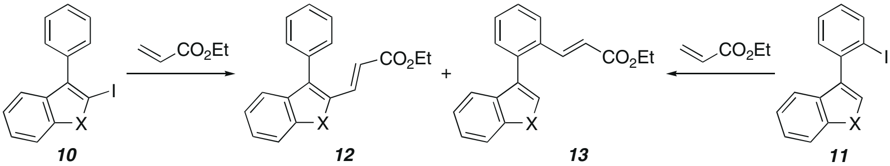
Entry	Case	Substrate	Ar	% Yield	Ratio **8**:**9**
1	1	**4a** (X=Me)	4-$MeO_2CC_6H_4$	78	51:49
	2	**5a** (X=Me)		83	49:51
2	1	**4a** (X=Me)	4-$MeOC_6H_4$	93	52:48
	2	**5a** (X=Me)		90	49:51
3	1	**4d** (X=OMe)	4-$MeO_2CC_6H_4$	85	42:58
	2	**5d** (X=OMe)		75	39:61
4	1	**4c** (X=NO_2)	4-$MeO_2CC_6H_4$	61	23:77
	2	**5c** (X=NO_2)		75	16:84

[a]Reaction conditions: 5 mol% $Pd(OAc)_2$, 5 mol% dppm, 2.0 equiv of CsOPiv, 2.0 equiv of PivOH, 20 equiv of H_2O, 1.4 equiv of boronic acid, 0.063 M in DMF, 100 °C

transmetalation. Again, the observed product distribution is more dependent on the electronic nature of the starting material than the location of the iodide, a result very similar to the previously discussed palladium migration/Heck reaction. In addition, the results also imply that equilibration of the palladium migration is not completely satisfied and that transmetalation is not substantially slower than the palladium migration, because once more, the product distribution from electronically perturbed starting materials is similar, but unequal.

Note that in both the Heck and Suzuki-Miyaura processes, electronics have a strong influence on the distribution of the products. Results from similar reactions using 4-phenylpyridines as the substrates show a similar trend [52, 55]. Although it appears that palladium tends to reside on or migrate to the more electron-poor aromatic ring, computational studies have indicated that it is the acidity of the C–H bond, rather than the electronics of the aromatic ring, that dictates the selectivity. The palladium moiety tends to migrate to or reside on a carbon atom that is more stable as an anion [38]. Such an explanation is in agreement with several other studies involving palladium-catalyzed aromatic C–H functionalizations in C–C bond forming processes, where a proton abstraction step is believed to take place as a key step [37, 45–50]. This is also supported by similar reactions carried out on other biaryl systems (Table 3) [38]. Thus, reactions with 3-phenylindoles and 3-phenylbenzofurans clearly show that the palladium has a very high tendency to reside on or migrate to the relatively electron-rich 2-positions of the five-membered heteroaromatic rings, where the acidity of the C–H bonds is the greatest.

Table 3 Aryl to aryl palladium migration in other biaryls terminated by Heck coupling



Entry	Case	Substrate	Procedure[a]	% Yield	Ratio **12**:**13**
1	1	**10a** (X=O)	C	85	100:0
	2	**11a** (X=O)	C	83	~94:6
	3	**11a**	A	75	0:100
2	1	**10b** (X=NMe)	C	94	100:0
	2	**11b** (X=NMe)	C	90	~86:14
	3	**11a**	A	95	0:100

[a]Procedure A: 5 mol% $Pd(OAc)_2$, 1.0 equiv of TBAC, 2.0 equiv of $NaHCO_3$, 4.0 equiv of ethyl acrylate, 0.25 M in DMF, 100 °C; Procedure C: 5 mol% $Pd(OAc)_2$, 5 mol% dppm, 2.0 equiv of CsOPiv, 1.0 equiv of ethyl acrylate, 0.063 M in DMF, 100 °C

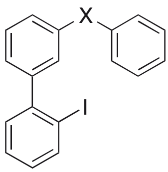
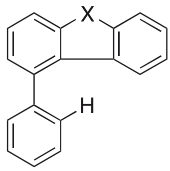
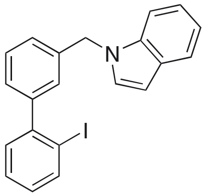
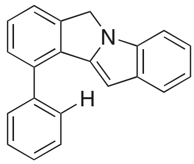
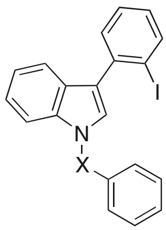
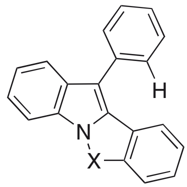
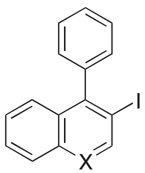
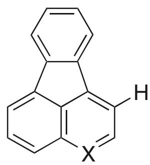
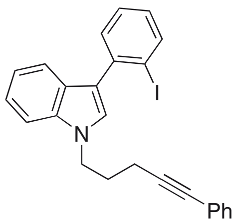
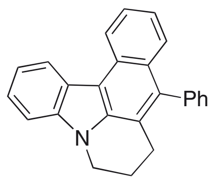
Other than using Heck and Suzuki-Miyaura couplings to trap the migrated palladium, aryl to aryl palladium migration can also be terminated by simple intramolecular arylation or migratory insertion. Since an intramolecular trap can be placed at a specific location in a molecule, which will only allow reaction with palladium after migration, such termination steps allow the aryl to aryl migration to occur under nonequilibrium conditions and thereby render products of a "complete" migration (Table 4) [39, 56]. The arylation by palladium intermediates gives best results when a five-membered ring is formed. However, in rare cases, trapping the palladium to form a six-membered ring may be marginally successful. Intramolecular alkyne insertion also works well for the formation of a six-membered ring (Table 4, entry 9). The selectivity of the migration of palladium seems to follow the aforementioned trend of C–H acidity, as the reaction provides better yields of the product if the palladium is migrating to the more acidic position (compare entries 1 and 2, and entries 7 and 8). The nature of the trap also affects the yield of the reaction. Apparently the more electron-rich arene traps the palladium intermediate better (compare entries 5 and 6).

2.3 Alkyl to Aryl Palladium Migrations

Among palladium 1,4-migrations, palladium can migrate from an alkyl to an aryl position in two different ways. One way is to migrate from a 1-naphthylmethyl position to a neighboring 8-naphthyl position in a naphthalene system. The other is to migrate from a homobenzylic position to an *ortho* phenyl position. Both processes have been observed.

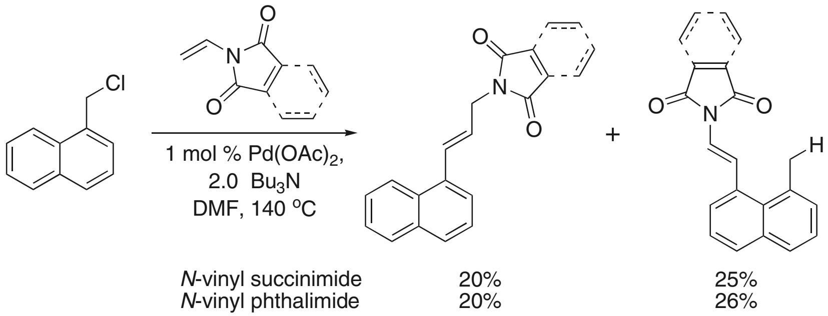
The 1-naphthylmethyl to 8-naphthyl palladium migration was discovered as a side reaction in a Heck reaction of 1-(chloromethyl)naphthalene with olefins

Table 4 Aryl to aryl palladium migration terminated by arylation/insertion[a]

Entry	Substrate		Product	Yield/%
1 2 3		X=CH_2 X=O X=CH_2O		40 89 45[b]
4				70
5 6		X=CH_2 X=C(O)		92 33
7 8		X=CH X=N		81 54
9				65

[a]Reaction conditions: 5 mol% $Pd(OAc)_2$, 5 mol% dppm, 2.0 equiv of CsOPiv, DMF, 100–110 °C
[b]Inseparable products formed with 30% hydrodeiodination side-product evident

(Scheme 4) [57]. In this case, when *N*-vinyl imides were used as the olefin component, the predominant Heck product resulted from palladium migration. Other olefins, including vinyl esters, did not afford palladium migration products. While the reason for the success with *N*-vinyl imides is unclear, it has been pointed that these olefins may serve as ligands to stabilize the palladium and slow down the migratory insertion,



Scheme 4 Benzylic to aryl palladium migration and Heck trapping in a naphthalene system

thus allowing the palladium species after oxidative addition to have ample time to undergo migration. It should be noted that the reverse process, namely palladium migration from the 8-naphthyl position to the 1-naphthylmethyl position, is also known (see Sect. 2.4.1). A detailed investigation of this reaction, including the driving force and the role that the olefin substitution plays, remains to be carried out.

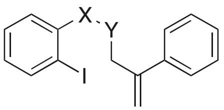
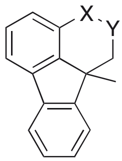
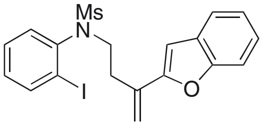
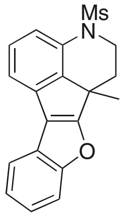
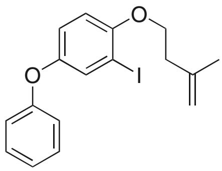
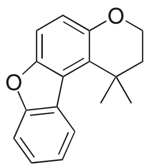
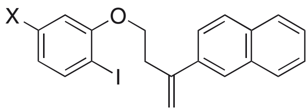
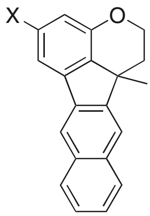
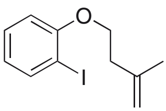
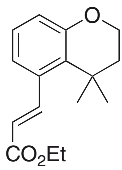
The first detailed study of alkyl to aryl palladium migrations, reported in 2004, involved homobenzylic to phenyl migration (Table 5) [58]. The process was demonstrated using aryl iodides tethered to an olefin. An additional trap, either intramolecular arylation or intermolecular Heck olefination, was used to trap the migrated palladium. The reaction gives high yields of the desired polycyclic products.

The mechanism of this reaction is worth additional discussion (Scheme 5). Intermediate **14** generated by this process has two hydrogens, namely H^a and H^b, available for C–H activation. Activation of C–H^a results in formation of intermediate **15a** with simultaneous migration of palladium from the alkyl position to the aromatic ring originally bearing the iodide, while activation of C–H^b results in formation of intermediate **15b** with palladium migration to the pendent aromatic ring. Either intermediate can lead to a common palladacycle **16** through an arylation step, which then reductively eliminates the observed product. The steric congestion around the palladium in intermediate **14** may serve as the driving force for the palladium migration. It remains to be determined which C–H bond (C–H^a vs C–H^b) is actually activated and which intermediate (**15a** vs **15b**) is actually involved in the catalytic cycle.

2.4 Aryl to Alkyl Palladium Migrations

Aryl to alkyl palladium migration is the apparent reverse of the alkyl to aryl migration process mentioned in the previous section. However, compared with the alkyl to aryl migration process, examples of such aryl to alkyl migration processes are more common. One should note that, unlike other migrations, this aryl to alkyl palladium migration results in a species with the palladium residing on an sp^3-carbon, which is expected to exhibit significantly different reactivity from a species resulting from migrations that generate a palladium on an sp^2-carbon. Hence, the termination steps

Table 5 Homobenzylic to aryl palladium migration in the synthesis of polycycles[a]

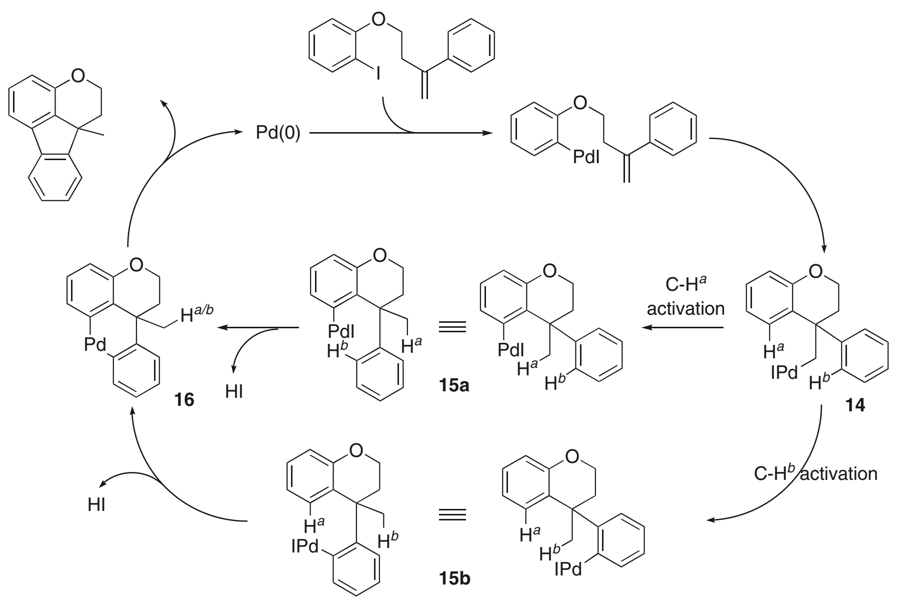
Entry	Substrate		Product	% Yield
1		X=O, Y=CH_2		88
2		X=NMs, Y=CH_2		95
3		X=CH_2, Y=$C(CO_2Et)_2$		82
4				76
5				83
6		X=H		84
7		X=OMe		91
8		X=NO_2		21
9				62[b]

[a]Reaction conditions: 5 mol% $Pd(OAc)_2$, 5 mol% dppm, 2.0 equiv of CsOPiv, DMF, 90–100 °C
[b]The reaction was carried out in the presence of 1.5 equiv of ethyl acrylate

available to such palladium species may be quite different from other palladium species. The most commonly seen termination step is direct β-hydride elimination. Nucleophilic displacement of Pd(II) has also been observed. However, cross-coupling reactions commonly seen in the previous cases are less common.

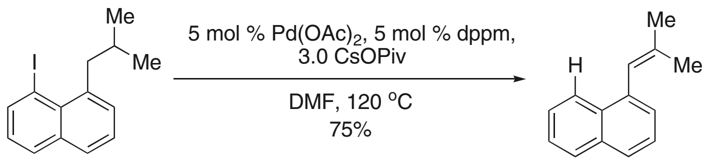
2.4.1 Aryl to Benzylic Migrations

Aryl to benzylic palladium migration [59] is the reverse of the aforementioned 1-naphthylmethyl to 8-naphthyl migration (see Scheme 4). This reverse process

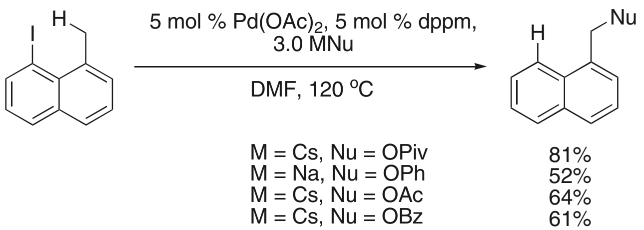


Scheme 5 Mechanism of the homobenzylic to aryl palladium migration

takes place under entirely different reaction conditions. The migrated palladium can react further by either of the following two processes. In the presence of a β-hydrogen, β-hydride elimination can occur to afford a styrene product, which has been reported (1). An alternative process involves displacement of the palladium by an external nucleophile (Scheme 6). However, for reasons that are not completely clear, only cesium phenoxides and carboxylates have proven to be effective nucleophiles in such displacements. While sodium phenoxides also work, carboxylates having



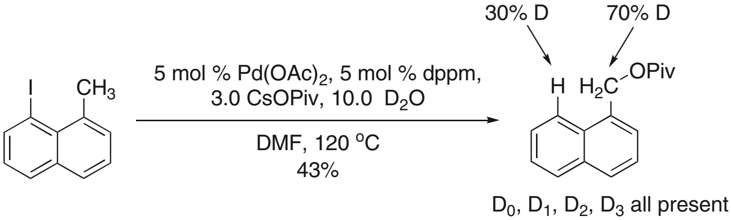
(1)



Scheme 6 Aryl to benzylic palladium migration, followed by β-hydride elimination or nucleophilic displacement, in a naphthalene system

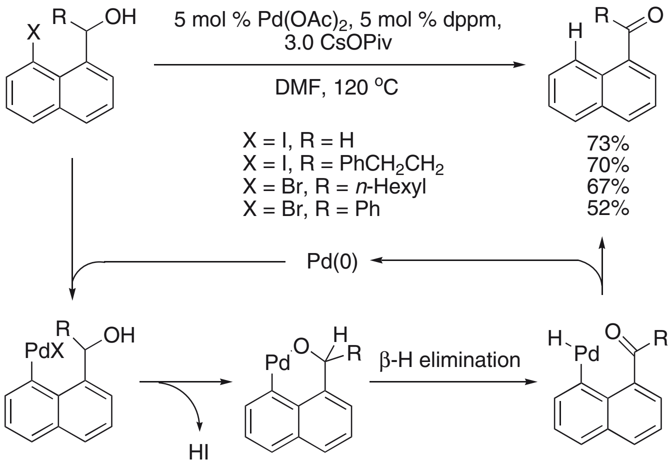
counter ions other than cesium are much less reactive. All other nucleophiles tested, including alkoxides and various carbon and nitrogen nucleophiles, proved ineffective.

A detailed mechanistic investigation using isotope-labeling techniques has been carried out on this process (2). A near statistical distribution of deuterium was found at the 8-naphthyl position and the 1-naphthylmethyl position, and multiple deuterium atoms have been introduced. This result indicates that this palladium migration is completely reversible, and the palladium may migrate back and forth between these two positions before being trapped by the nucleophile. These results not only suggest that this type of palladium migration is a kinetically faster process than the nucleophilic displacement of Pd(II), but also implies that the reverse 1-naphthylmethyl to 8-naphthyl migration may also have a low energy barrier.



(2)

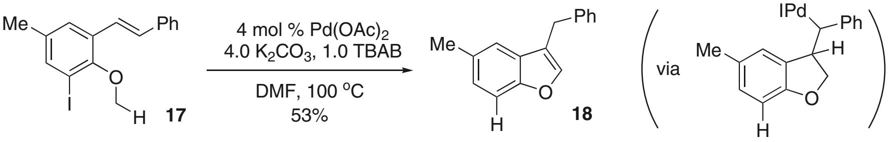
β-Hydride elimination for the removal of palladium after migration also provides a novel route to generate carbonyl products from the corresponding alcohols. In fact, naphthaldehydes or naphthyl ketones have been generated in this manner from 8-halo naphthyl alcohols (Scheme 7). In this reaction, oxidation of the alcohol is accompanied by simultaneous reduction of the halide, and thus the overall reaction is redox neutral. The oxidation is no doubt achieved by a β-hydride elimination step. However, isotope labeling studies suggest that the palladium does not necessarily "migrate" to the benzylic position before the β-hydride elimination step occurs. Thus, this reaction is only a formal C–H activation process and may not be a true "palladium migration."



Scheme 7 Alcohol oxidation in the naphthalene system and a possible mechanism

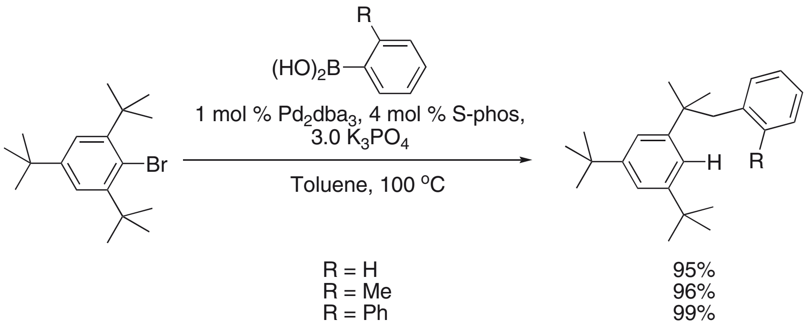
2.4.2 Aryl to Homobenzylic Migrations

A number of examples of aryl to homobenzylic palladium migration have been reported. The first example was reported in 1994 [60]. During an investigation of the Pd-catalyzed C–H activation of methyl ether C–H bonds in *o*-iodoanisoles [61–63], Dyker found that compound **17** could undergo Pd-catalyzed cyclization to afford a 53% yield of benzofuran **18** (3). The benzofuran ring is presumably formed by the olefin trapping a migrated palladium in a Heck-type migratory insertion, followed by a β-hydride elimination to furnish an exocyclic olefin, which then isomerizes to afford the observed product.



(3)

Another example of a similar palladium migration process was reported by Buchwald as a side reaction in the Suzuki-Miyaura coupling of 2,4,6-tri-*tert*-butylbromobenzene (Scheme 8) [64]. Contrary to expectations, Suzuki-Miyaura

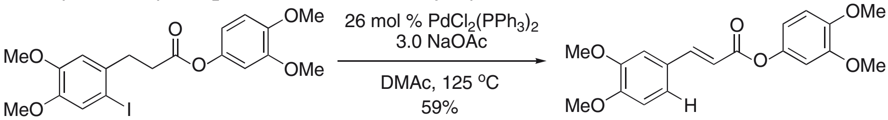


Scheme 8 Alcohol oxidation in the naphthalene system and a possible mechanism

coupling does not occur on the aryl group where the bromide originates, but rather on one of the methyl groups of the *o*-*tert*-butyl moieties. Clearly, the palladium species after oxidative addition is so sterically congested that direct transmetalation is not viable. Thus, this palladium moiety activates one of the homobenzylic C–H bonds that are close by and numerous, resulting in a 1,4-migration to one of the methyl carbons. The steric relief by this palladium migration is critical in this reaction, as replacement of either *o*-*tert*-butyl group with a methyl group results in direct cross-coupling without migration. The high yields of the migration products are not only indicative of the efficiency of the S-phos ligand, but also indicative of the efficiencies of the migration process.

Other than cross-coupling reactions, β-hydride elimination has also been used as a termination step for the removal of palladium after migration. Two examples have been reported [65–67]. However, in these two examples, some mechanistic ambiguity remains.

When studying the Pd-catalyzed reaction of a substituted aryl 2-iodophenylpropionate [65], Ung and Pyne observed exclusive formation of an aryl cinnamate (4). The mechanism proposed involves a palladium migration from the aryl position to the α-position of the carbonyl, which is homobenzylic, followed by subsequent β-hydride elimination. Note that the palladium intermediate after migration can potentially undergo either β-hydride elimination or arylation with the pendent electron-rich arene of the ester moiety, but only the product derived from β-hydride elimination is observed.

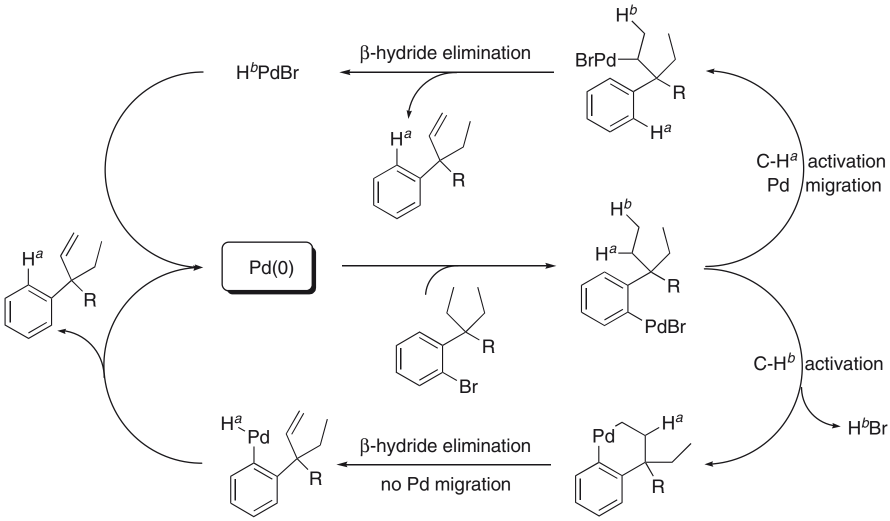


(4)

The exact mechanism of this process, however, remains unclear. It should be noted that the C–H activation in this case involves a C–H bond that is fairly acidic due to the carbonyl group, and the palladium-catalyzed α-arylation of esters by aryl halides is a well known process [68–71]. Thus, one might argue that activation of this specific homobenzylic C–H bond may involve formation of a five-membered ring palladacycle, which undergoes β-hydride elimination, rather than palladium migration.

A more thoroughly studied example of apparent palladium migration has been reported by Baudoin [66, 67]. Reaction of highly congested α,α,α-trisubstituted *o*-tolyl iodides or bromides under Pd-catalyzed conditions results in the formation of olefin products by simultaneous dehydrogenation and hydrodehalogenation (Table 6). The reaction is highly dependent on the steric bulk of the benzylic center, as deletion of even one substituent at that position no longer leads to olefin formation, and a decrease in the size of the alkyl substituent also leads to substantially lowered yields. The reaction provides a mixture of isomers if the α-substituent has alkyl chains longer than an ethyl group. In addition, when there is a choice, the reaction chemoselectively activates the less hindered homobenzylic C–H bond.

Again, the exact mechanism for this process remains uncertain. While the mechanism could simply involve the process described in the top cycle of Scheme 9, the authors suggest the involvement of a palladacycle by a 1,5-C–H activation without any migration of palladium (Scheme 9 bottom cycle). While both pathways lead to the same product with H^a incorporated in the aromatic moiety, which has been confirmed by isotope labeling experiments, the scarcity of such 1,5-C–H activation processes, or the preferential formation of a five-membered ring palladacycle over a six-membered ring counterpart would seem to disfavor the latter mechanism. Moreover, aligning the palladium with the β-hydrogen in such cyclic structures so as to provide a geometry ideal for β-hydride elimination is much more difficult compared with analogous open-chain structures, especially in the bicyclic intermediate which would be required in the example described in entry 7 of Table 6. Thus, it is not hard to imagine that at least in the case of entry 7, the top mechanistic cycle should



Scheme 9 Possible mechanisms for olefin formation via β-hydride elimination [*top cycle*: a 1,4-palladium migration pathway; *bottom cycle*: a 1,5-C–H activation pathway]

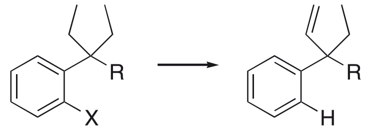
be the favored path for the reaction to proceed. The products of olefin transposition (entries 5–8) are probably best accounted for by further reversible hydropalladation/β-hydride elimination processes along the chain after the first β-hydride elimination has taken place.

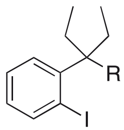
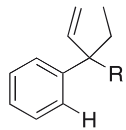
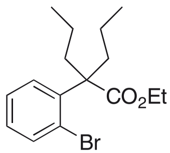
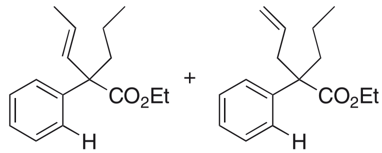
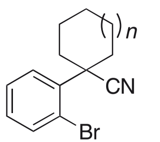
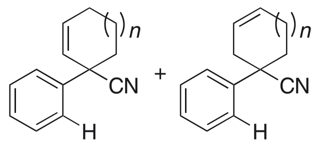
For substrates that have a methyl group in the benzylic position, C–H activation of this methyl group can be chemoselectively achieved. In this event, β-hydride elimination is impossible, and the formation of benzocyclobutene products is observed instead (Table 7) [66]. However, even if there is a choice between methyl C–H bonds and methylene C–H bonds (the latter allowing for β-hydride elimination), steric factors favor methyl C–H activation, leading to the formation of benzocyclobutenes. That being said, this reaction may not mechanistically involve a complete migration of palladium. The product may simply be formed by reductive elimination from a five-membered palladacycle intermediate.

2.5 Aryl to Imidoyl Palladium Migrations

To date, palladium migration to vinylic positions remains unknown. Thus, palladium migration to sp^2 carbons has been largely limited to aryl carbons. However, in addition to vinylic and aryl carbons, aldehydic and imidoyl carbons also possess sp^2 hybridization and carry a C–H bond. This special type of sp^2 C–H bond has also been subjected to palladium migration studies and preliminary success has been achieved. Currently, aryl to imidoyl [27] and aryl/alkyl to acyl [72] palladium migrations are known. Migrations from other types of carbons to imidoyl and acyl positions are

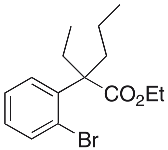
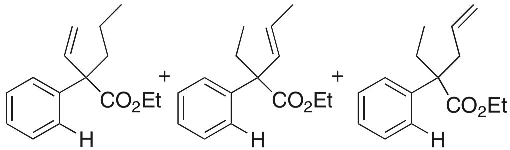
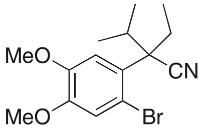
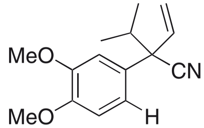
Table 6 Olefin formation via aryl to homobenzylic palladium migration[a]



Entry	Substrate		Product	% Yield
1		R=CH_2OTIPS		82
2		R=CH_2OTES		12
3		R=CO_2Et		62
4		R=CO_2Me		47
5				74 (81:19) 68[b] (93:7)
6		$n = 0$		63[b]
7		$n = 1$		85[b] (55:45)

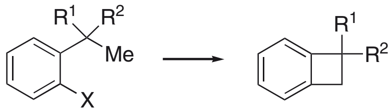
(continued)

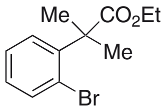
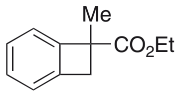
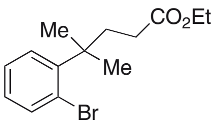
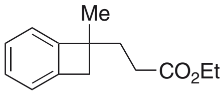
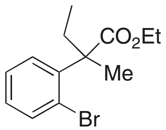
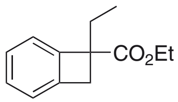
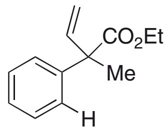
Table 6 (continued)

Entry	Substrate	Product	% Yield
8			75 (73:19:8)
9			82[c]

[a]Reaction conditions: 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-Tol)$_3$, 2.0 equiv of K_2CO_3, DMF, 150 °C [b]Reaction conditions: 5 mol% $Pd(OAc)_2$, 10 mol% P(2-Me-5-$FC_6H_3)_3$, 2.0 equiv of K_2CO_3, DMF, 100 °C [c]Reaction conditions: 5 mol% $Pd(OAc)_2$, 20 mol% P(2-Me-5-$FC_6H_3)_3$, 2.0 equiv of K_2CO_3, DMF, 100 °C

Table 7 Formation of benzocyclobutenes by homobenzylic C–H activation[a]



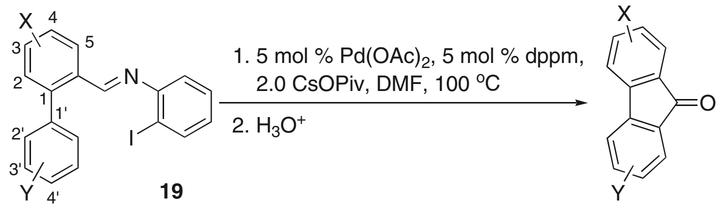
Entry	Substrate	Product	% Yield
1			60
2			78
3		 + 	71 (95:5)

[a]Reaction conditions: 10 mol% $Pd(OAc)_2$, 20 mol% $P(o\text{-}Tol)_3$, 2.0 equiv of K_2CO_3, DMF, 150 °C

still unknown. It is also unknown whether palladium can migrate from imidoyl or aldehydic positions to other types of carbons.

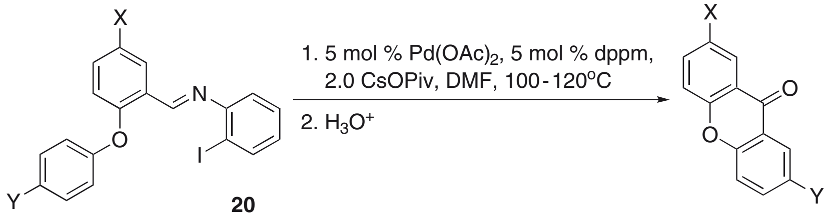
Studies using imines **19** under palladium-catalyzed conditions result in a smooth formation of fluoren-9-one derivatives after hydrolysis of the imine moiety (Scheme 10). The reaction proceeds in excellent yields with a variety of substituents and functional groups. The same reaction applied to imines **20** furnishes xanthone derivatives (Scheme 11). While electronics have minimal effects on construction of the fluoren-9-ones, the xanthone synthesis seems to be highly dependent on electronics, as electron-withdrawing groups on either ring significantly retard the reaction and give much lower yields. This trend seems to be consistent with electrophilic aromatic substitution during the arylation step in these processes.

The mechanisms of these two cyclization reactions appear fairly different. While the xanthone synthesis would appear to follow a simple palladium migration/arylation mechanism, the fluoren-9-one synthesis has been subjected to isotope labeling experiments (Scheme 12), which indicate that more than one mechanistic pathway may apply. It turns out that the deuterium that replaces the iodide after palladium migration comes not only from the imidoyl position, but also from the pendent aromatic ring used to trap the migrated palladium via arylation. Such results can



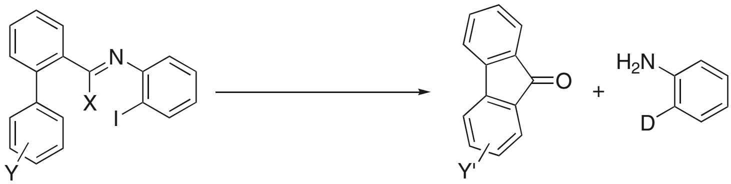
X = Y = H	95%
X = 4-OMe, Y = H	90%
X = H, Y = 4'-NO_2	100%
X = H, Y = 4'-Me	97%

Scheme 10 Aryl to imidoyl palladium migration in the synthesis of 9-fluorene-9-ones



X = Y = H	72%
X = OMe, Y = H	77%
X = H, Y = OMe	77%
X = NO_2, Y = H	38%
X = H, Y = CO_2Me	10%

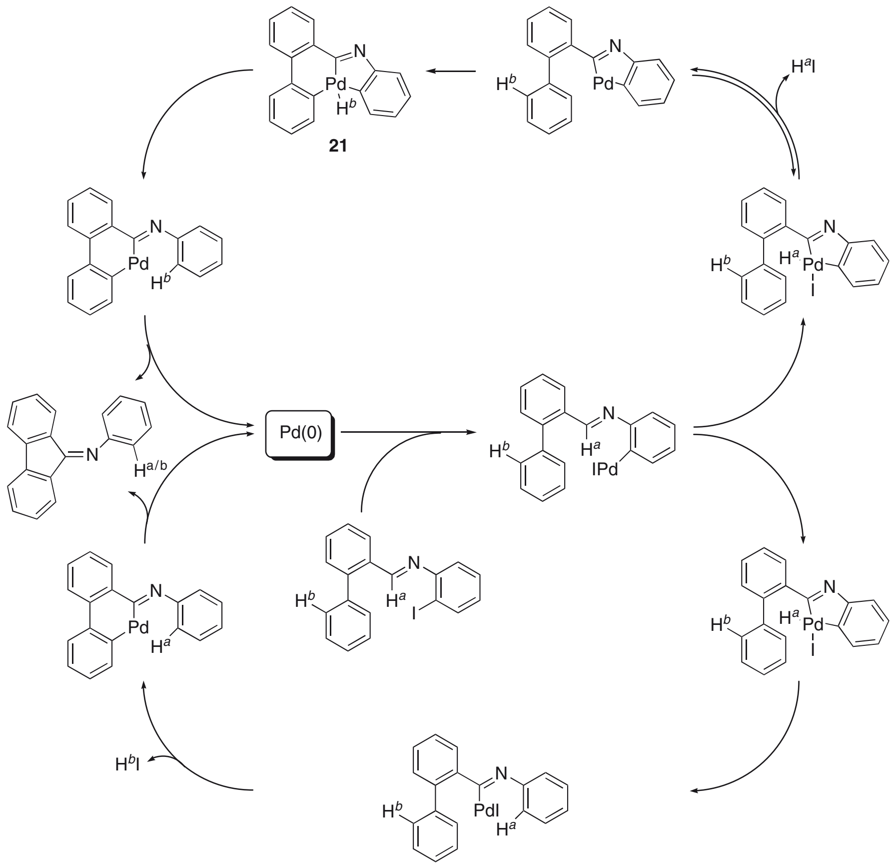
Scheme 11 Aryl to imidoyl palladium migration in the synthesis of xanthones



X = D, Y = H_5	Y' = H_4	35% D
X = H, Y = D_5	Y' = D_4	35% D
X = D, Y = D_5	Y' = D_4	75% D

Scheme 12 Isotope labeling experiments for the aryl to imidoyl palladium migration in the synthesis of fluoren-9-ones

only be explained by the dual mechanism proposed in Scheme 13. The bottom mechanistic cycle of this scheme is the standard palladium migration/arylation pathway, where palladium migrates from the position of the iodide to the imidoyl position, while the imidoyl hydrogen migrates in the opposite direction. The top mechanistic cycle, on the other hand, involves a novel intermediate **21**, which



Scheme 13 Dual mechanisms for the aryl to imidoyl palladium migration in the synthesis of fluoren-9-ones [*top*: dual C–H activation; *bottom*: single C–H activation]

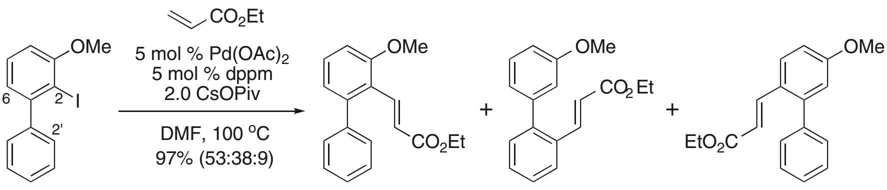
results from a second C–H activation of the pendent aromatic ring. Reductive elimination of this intermediate transfers H^b to the position where the iodide originally resided. The concurrent, dual mechanistic cycles offer a reasonable explanation for the isotope labeling results, and indicate that more complicated mechanistic pathways are possible in these palladium migration processes, although they have not been shown to operate in other processes so far. In addition to this new mechanism, the isotope labeling studies also indicate that this aryl to imidoyl palladium migration is likely an irreversible process, since otherwise deuterium should have been incorporated in both of the *ortho* positions of the aniline.

3 Consecutive 1,4-Palladium Migrations

Consecutive migration refers to a process in which palladium migrates more than once in a molecule. This process, in theory, should represent a potentially powerful tool to introduce palladium to an even more remote site of a molecule through multiple relays. Although consecutive palladium migration has not been studied extensively, it has been demonstrated that given a suitable environment, palladium can indeed migrate twice. The two known cases are aryl to aryl to aryl migration and vinylic to aryl to allylic migration. To date, triple migration of palladium remains unknown.

3.1 Aryl to Aryl to Aryl Palladium Migrations

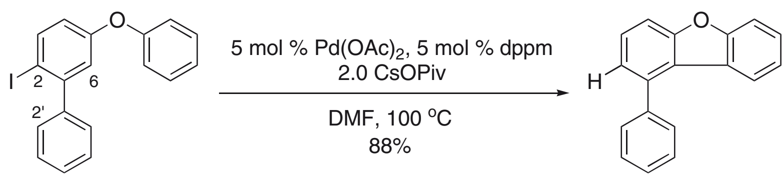
Palladium has been found to migrate twice between aromatic positions in a suitable substrate. In a study of aryl to aryl palladium migration in the biphenyl system mentioned in Sect. 2.2 [38], it was observed that the unsymmetrical substrate **22** afforded three different Heck products **23**, **24**, and **25** in a 53:38:9 distribution (5). The "retention" product **23** comes from direct Heck coupling without palladium migration, while the product **24** comes from a single aryl to aryl palladium migration from the 2-position to the 2′-position. The product **25** can only be derived from a double migration of palladium from the 2-position to the 2′-position, and then to the 6-position on the original ring after a single bond rotation. Although the double migration is not very efficient and the yield of olefin **25** is low, it does occur to a significant extent. The low yield of this double migration product might in part be because the palladium migration equilibrium is not reached.



22 **23** **24** **25**

(5)

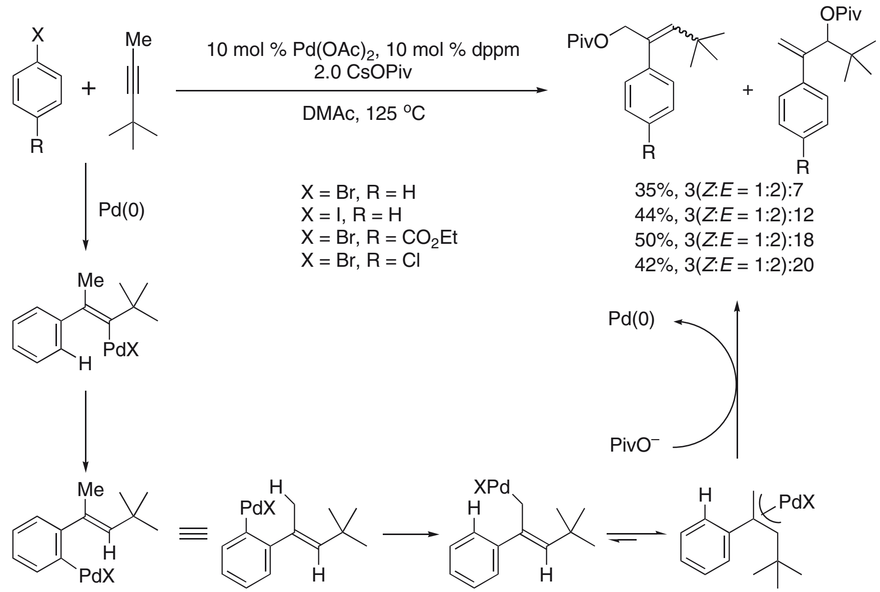
Another double migration process has been reported to occur in a similar system. Once again palladium is observed to migrate from 2-position to 2′-position, and finally to 6-position (6) [39, 56]. In this case, the migrated palladium is trapped not by an intermolecular Heck coupling, but by intramolecular arylation, which cannot occur until the palladium has migrated to the final position. Therefore, it favors a higher yield of the migration product and the apparent irreversibility of the entire migration process.



(6)

3.2 Vinylic to Aryl to Allylic Palladium Migrations

A detailed study has been reported on a double migration of palladium from a vinlyic to an aryl and then to an allylic position where it is trapped [73]. The overall reaction is a three-component coupling between an aryl halide, an internal alkyne that has propargylic hydrogens, and the pivalate base added to the reaction system (Scheme 14). Three isomeric olefin products with an allylic pivalate moiety are formed. Clearly, all three isomeric products can be derived from a common π-allylpalladium species, which presumably originates according to the mechanism proposed in Scheme 14. The mechanism is supported by isotope labeling experiments,



Scheme 14 Vinylic to aryl to allylic palladium migration followed by pivalate displacement

and the second migration, while still reversible, is driven by formation of the π-allylpalladium species. Other nucleophiles known to displace Pd(II) [59] in such π-allylpalladium intermediates have not yet been examined in this reaction.

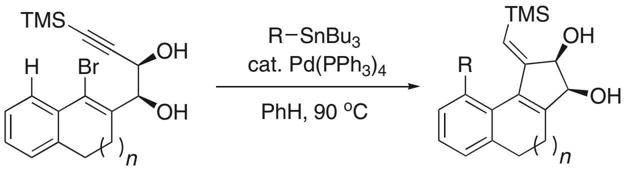
4 One-Step 1,5-Palladium Migrations

Compared with 1,4-palladium migrations, far fewer examples of 1,5-migrations exist. This is probably due to the difficulty in forming the six-membered ring palladacycle, as well as the greater distance between the palladium and the C–H bond. Another major problem is that a 1,5-arrangement of Pd and H can often lead to direct five-membered ring formation rather than migration. Although seriously limited, reports of 1,5-palladium migration, or Pd-catalyzed C–H activation based on a 1,5-interaction, have been reported. Examples are currently limited to: vinylic to aryl migration, aryl to bis(homo)benzylic C–H activation, and aryl to imidoyl C–H activation. Among these, only the vinylic to aryl migration is a true 1,5-palladium migration. The other two cases can be more strictly categorized as Pd-catalyzed C–H activation based on 1,5-interactions. It has not been demonstrated that palladium can migrate more than once by a 1,5-migration.

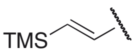
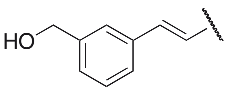
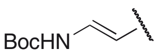
A 1,5-vinylic to aryl palladium migration was first reported by Suffert using a Stille coupling (transmetalation) as a termination step [74]. It is reported that when benzosuberone-derived bromide **26** reacts with vinyl, allyl, or heteroarylstannanes, instead of the direct Stille product, migrated product **27** is formed, incorporating the stannane moiety on the aromatic ring (Table 8). Alkynyl stannanes do not promote palladium migration, and the dihydronaphthalene system (n = 1 in structure **26**) also fails to undergo palladium migration. Exactly how the nature of the stannane affects the palladium migration is unclear. However, the mechanism proposed [29] for this reaction is quite novel and worth mentioning (Scheme 15).

While all previous 1,4-migrations appear to proceed through a five-membered palladacyclic intermediate where the palladium covalently binds to both the original carbon and the carbon to which it is migrating by a Pd(IV) intermediate, this 1,5-migration has been proposed to proceed through an entirely different pathway. It is the first proposed mechanism in which activation of the C–H bond proceeds through a proton-channeling process where direct proton transfer occurs. Unlike

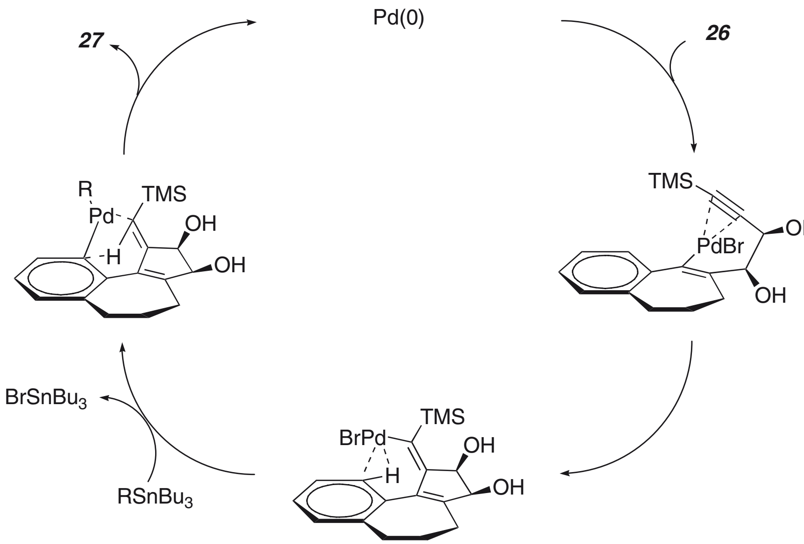
Table 8 The 1,5-vinylic to aryl palladium migration in a Stille coupling



26, n = 2 **27**, n = 2

Entry	R	Procedure[a]	% Yield
1	allyl	A	52
2	2-furyl	A	48
3	vinyl	A	70
4		B	70
5		A	61
6		A	65

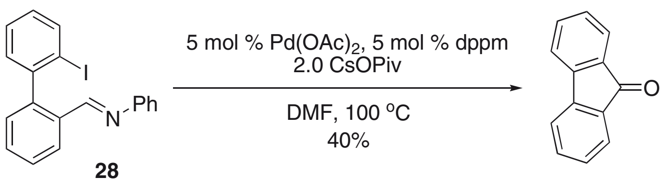
[a]Procedure A: 10 mol% $Pd(PPh_3)_4$, benzene, 90 °C; Procedure B: same as A, except under microwave irradiation for 5 min at 100 °C (100 W), then 5 min at 100 °C (200 W) and finally 8 min at 120 °C (220 W)



Scheme 15 1,5-Vinylic to aryl palladium migration in a Stille coupling involving a direct proton transfer

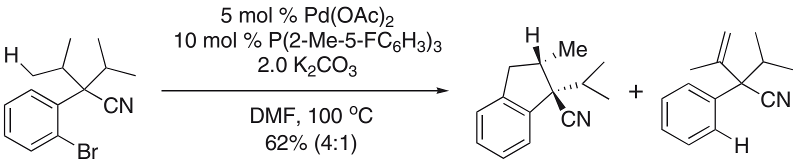
the oxidative addition pathway involving a palladacycle, the oxidation state of palladium remains +2 and a single transition state exists during the entire process. Neither a Pd(IV) intermediate nor a Pd(IV) transition state is involved. Cleavage of the C–H bond is believed to proceed through a strong agostic interaction, followed by "channeling" of the proton from the aryl position to the vinylic position with concurrent palladium shift to the aryl position. This palladium migration very likely takes place after, or at least concurrently with, the transmetalation step, since only in this case can we explain the stannane-dependency of the migration process. A detailed description of this mechanism and a comparison with Pd(IV) mechanistic pathways will be discussed in Sect. 5.

Other palladium-catalyzed 1,5-C–H activation processes reported are extensions of known work. In these examples, palladium activates the C–H bond, but whether the migration occurs or not is still debatable. An aryl to imidoyl C–H activation takes place in substrate **28** (7) under the same reaction conditions that promote the 1,4-palladium migration. However, this reaction affords a much lower yield (compare with Scheme 10), which implies a relatively low efficiency for this 1,5-C–H activation. Mechanistically, the reaction can either go through a direct C–H activation to form a six-membered palladacycle, followed by reductive elimination, or a proton channeling-based palladium migration, followed by an arylation with the original aromatic ring. The exact path has not been established experimentally or computationally.

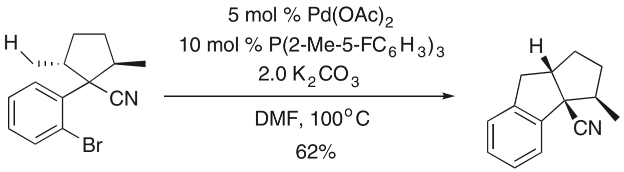


(7)

Another case of an apparent 1,5-C–H activation is the aryl to homobenzylic migration mentioned before in Sect. 2.4.2 [67]. When both the alkyl substitutions on the benzylic carbon are secondary alkyl groups, the steric bulkiness leads to a reduction in homobenzylic 1,4-C–H activation and affords instead a product apparently arising by a 1,5-C–H activation on the bis(homo)benzylic positions (8 and 9). Again, the exact nature of the mechanism has yet to be investigated.



(8)



(9)

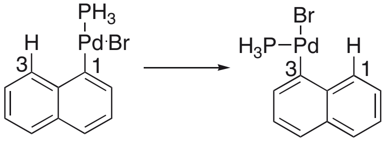
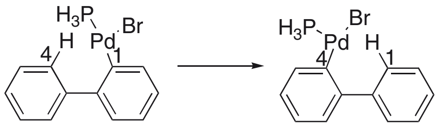
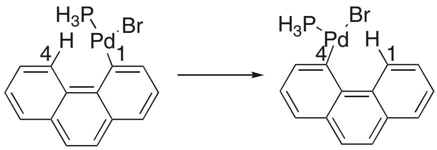
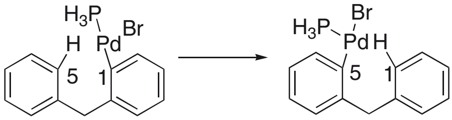
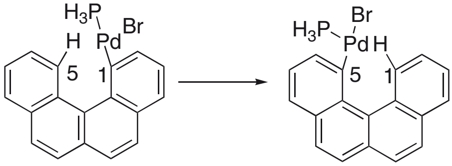
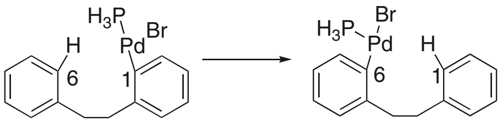
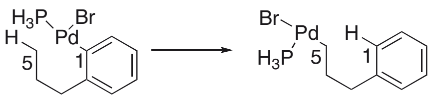
5 Computational Studies of the Palladium Migration Mechanism

The exact mechanism of the migration step has been subjected to computational studies using DFT on a BL3YP level [29–31]. The general aryl to aryl migration [31], aryl to alkyl migration [30], and the specific 1,5-vinylic to aryl migration [29] mentioned in Sect. 4 have been studied. Computational studies suggest that actually three different mechanisms are possibly at work. The first mechanism, abbreviated as Int^{IV}, is a two-step pathway involving a *hydridopalladium(IV) intermediate*, which proceeds by a C–H bond oxidative addition/reductive elimination sequence; the second mechanism, abbreviated as TS^{II}, is a one-step pathway involving a *palladium(II) transition state* where the hydrogen is channeled from one carbon to the other concurrent with palladium migration; the third mechanism, abbreviated as TS^{IV}, is another one-step pathway involving a *hydridopalladium(IV) transition state*. While the first two pathways can be clearly differentiated by the number of steps and the oxidation state of Pd, the second and third pathways are somewhat ambiguous and need further discussion. We will use the aryl to aryl palladium migration and the aryl to alkyl palladium migration as examples to illustrate the three mechanisms and discuss the favored mechanism for different reactions.

5.1 Aryl to Aryl Palladium Migrations

The aryl to aryl palladium migration has been studied computationally on a variety of systems, ranging from 1,3-migration to 1,∞-migration [31]. The energetically favored process for each reaction system is summarized in Table 9. Somewhat

Table 9 Energetically favored pathways for different types of aryl to aryl palladium migrations

Entry	Migration type	Description of migration	Favored pathway
1	1,3-Migration: naphthalene		TS^{IV}
2	1,4-Migration: biphenyl		TS^{II} and TS^{IV}
3	1,4-Migration: phenanthrene		TS^{IV}
4	1,5-Migration: benzylbenzene		TS^{II}
5	1,5-Migration: benzophenan-threne		TS^{II}
6	1,6-Migration: dibenzyl		TS^{II}
7	1, ∞-Migration: intermolecular		TS^{II}

counterintuitively, although the Int^{IV} mechanism seems more straightforward and understandable, it is the less favored process in reality, and almost all favored pathways involving Pd(IV) are actually TS^{IV} pathways.

The different pathways can be better understood by a comparison. Taking the 1,5-migration in the benzylbenzene system into account (entry 4), the Int^{IV} pathway is about 13 kcal mol^{-1} higher in enthalpy than the corresponding TS^{II} pathway (Fig. 1) and thus is much less favorable. While the TS^{II} pathway involves a single

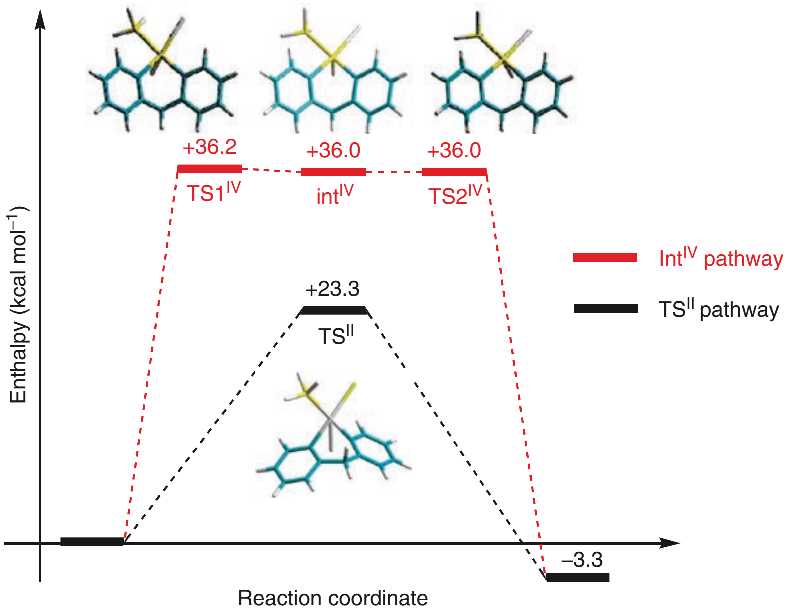


Fig. 1 Energy profiles for the 1,5-palladium migration in a benzylbenzene system (the zero of energy corresponds to the starting material). Reprinted with permission from [31]. Copyright (2006) American Chemical Society

transition state during the entire migration, there are two transition states between the starting material, the intermediate, and the product in the Int^{IV} pathway. Note that there are distinct differences between the Pd(IV) intermediate (top middle structure) and the TS^{II} transition state (bottom structure).

The Pd(IV) intermediate has a much shorter distance between Pd and H (ca. 1.5 Å vs ca. 2.1 Å in the TS^{II} transition state), indicating a bonding interaction between them. However, it has much longer distances between C_1 and H, as well as C_5 and H (ca. > 2 Å vs 1.3–1.5 Å in the TS^{II} transition state), indicating the absence of bonding interactions between the carbons and H in the Pd(IV) intermediate. These data are consistent with the classic bonding models of these two structures. Other than these differences, the Pd–C_1–C_2–C_3 dihedral angle is close to zero in this Pd(IV) intermediate, indicating that Pd lies in the same plane as the organic moiety. However, a 29° dihedral angle in the TS^{II} transition state clearly shows the more out-of-plane geometry, indicating a "migrating" motion of palladium taking place in this structure. Other differences include a smaller C_1–Pd–C_5 angle in the TS^{II} transition state, a smaller Pd–C_1–C_2 angle, and a shorter distance between C_1 and C_5.

A comparison of the TS^{II} and TS^{IV} pathways is illustrated for the 1,4-migration in the biphenyl system (Table 9, entry 2). The two pathways are close in energy and thus are competing (Fig. 2). Both pathways are single transition state, single step in nature and no intermediate is involved. Although the structures of the two transition states look very similar, the imaginary frequencies of the transition states differ

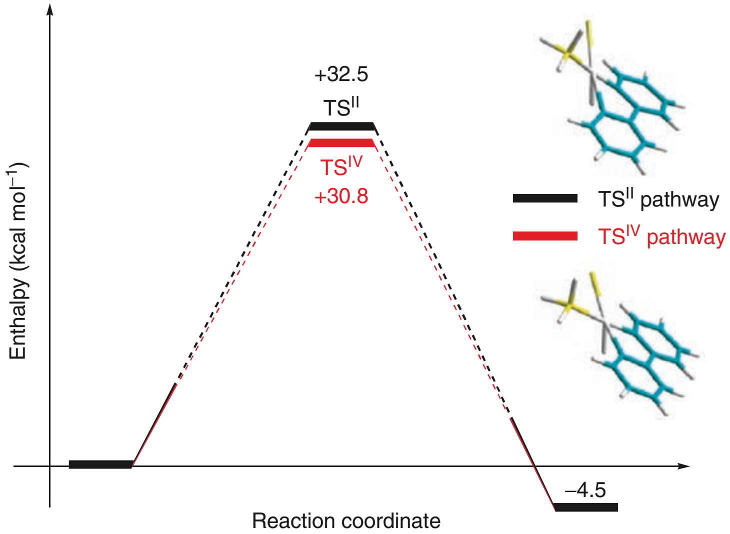


Fig. 2 Energy profiles for the 1,4-palladium migration in a biphenyl system (the zero of energy corresponds to the starting material). Reprinted with permission from [31]. Copyright (2006) American Chemical Society

greatly. A 1372*i* cm^{-1} frequency was found for the TS^{II} transition state and a 409*i* cm^{-1} frequency was found for the TS^{IV} transition state. Compared with a general 200–600*i* cm^{-1} imaginary frequency for the two transition states in the Int^{IV} mechanism, this 409*i* cm^{-1} frequency indicates much greater Pd(IV) character.

The geometry of the TS^{IV} transition state (bottom right) again shows a shorter Pd–H distance (1.54 Å vs 1.66 Å in the TS^{II} transition state, the top right structure in Fig. 2), a longer C_1–H distance (1.86 Å vs 1.62 Å in the TS^{II} transition state), and a longer C_4–H distance (1.85 Å vs 1.60 Å in the TS^{II} transition state), indicating that the hydrogen binds tighter to the palladium and looser to the two carbons. It also shows a shorter Pd–C distance (2.05 Å vs 2.12 Å in the TS^{II} transition state), indicating a stronger interaction between Pd and the carbons. These data point to a higher oxidation state for Pd. The Pd–C_1–C_2–C_3 dihedral angle is again close to zero in the TS^{IV} transition state, compared with a 25° dihedral angle in the TS^{II} transition state. In addition, there is a smaller C_1–Pd–C_5 angle in the TS^{II} transition state and a shorter distance between C_1 and C_5. Clearly, the TS^{IV} transition state represents a palladium center closer to Pd(IV) as indicated by the coplanarity of Pd with its four ligands, namely C_1, C_4, Br, and P, the stronger interaction between Pd and H, a stronger interaction between Pd and C_1, and Pd and C_4, and a weaker interaction between H and C_1, and H and C_4. The TS^{II} transition state represents a palladium center closer to Pd(II) as indicated by the location of the Pd well above the aromatic rings, and the weaker interaction between Pd and H, a weaker interaction between Pd and C_1, and Pd and C_4, and a stronger interaction between H and C_1, and H and C_4. A side view (Fig. 3) shows this more clearly. In the TS^{II} transition state, the hydrogen is much more linear with C_1 and C_4, indicating a direct channeling

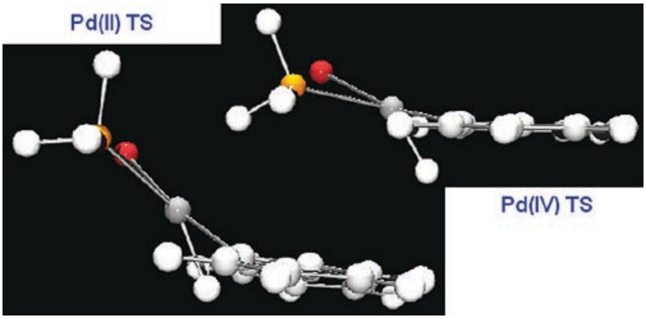


Fig. 3 Side view of the TS^{II} and TS^{IV} transition states [*top*: TS^{IV} transition state; *bottom*: TS^{II} transition state]. Reprinted with permission from [31]. Copyright (2006) American Chemical Society

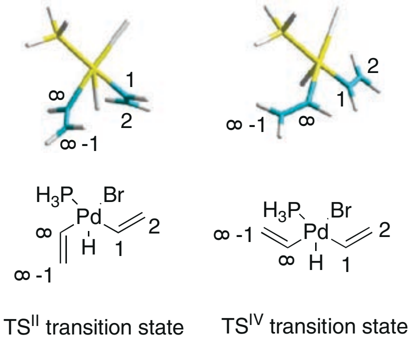


Fig. 4 TS^{II} and TS^{IV} transition states of the 1 ∞-vinylic to vinylic palladium migration. Reprinted with permission from [31]. Copyright (2006) American Chemical Society

movement from one carbon to the other. However, in the TS^{IV} transition state, the hydrogen is no longer aligned with these two carbon atoms, indicating that the hydrogen is temporarily "carried" by the palladium center, resulting in a higher oxidation state for palladium.

The difference between the TS^{II} and TS^{IV} transition states can be better understood in an extreme example, the 1,∞-vinylic to vinylic migration (Table 9, entry 7). This migration shows a more dramatic difference in structure between the TS^{II} transition state and the TS^{IV} transition state (Fig. 4). The TS^{II} transition state is an *s-trans*, *s-cis* geometry (*s-trans* represents the relative location of C_{∞} and C_2 with respect to the Pd–C_1 single bond, and *s-cis* represents the relative location of C_1 and $C_{\infty-1}$ with respect to the Pd–C_{∞} single bond), whereas the TS^{IV} transition state is an *s-trans*, *s-trans* geometry. The geometry of the hydrogen and the two carbon atoms is also much more linear in the TS^{II} transition state, indicating a direct hydrogen transfer, whereas in the TS^{IV} transition state, the hydrogen is undoubtedly located partially on palladium. The "clamping" geometry of the two organic moieties in the TS^{II} transition state is a characteristic feature.

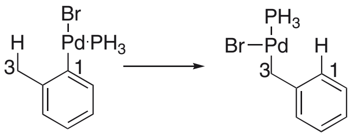
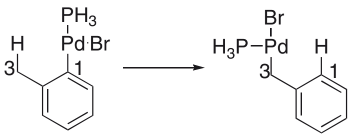
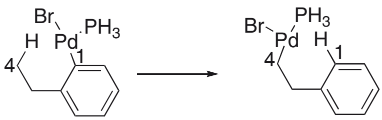
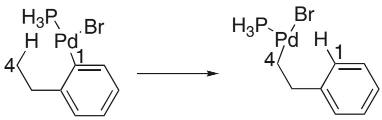
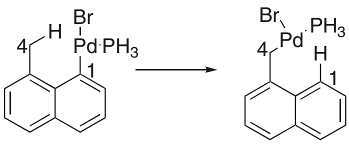
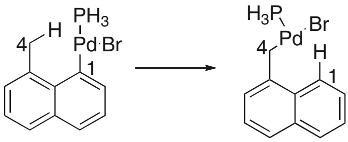
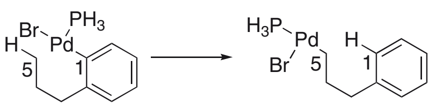
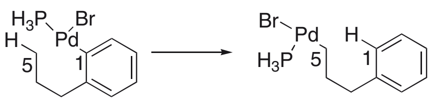
In conclusion, there appear to be three operative mechanistic pathways for the palladium migration step. The Int^{IV} pathway is a two-step process involving a Pd(IV) intermediate and is high in energy in almost all aryl to aryl palladium migrations. The TS^{IV} pathway is a one-step process involving a Pd(IV) transition state and is believed to proceed in intimate palladium migrations, such as some 1,4-palladium migrations and the unprecedented 1,3-migration. The TS^{II} pathway is another one-step process involving a Pd(II) transition state and is believed to proceed in distant palladium migrations, such as some other 1,4-palladium migrations and the 1,*n*-migration, where *n* is 5 or greater. These two latter transition states differ in the structures of the transition states, and are dependent upon the geometrical constraints of the molecule.

5.2 Aryl to Alkyl Palladium Migrations

The aryl to alkyl palladium migration has also been studied computationally on systems ranging from 1,3-migration to 1,5-migration [30] and the results are summarized in Table 10. Unlike the aryl to aryl migration, this aryl to alkyl migration is much more complicated. First, the products can undergo reversible β-hydride elimination/reinsertion to relocate the palladium along the alkyl chain. In fact, the 1,5-migration shown in Table 10, entry 8 has three additional competing mechanisms corresponding to 1,4-C–H activation, followed by a β-hydride elimination/reinsertion, which relocates palladium to C_5, rather than a direct 1,5-migration (for ease of discussion, we will omit the routes involving secondary palladium shifts along alkyl chains via β-hydride elimination/reinsertion.) Second, different geometric isomers in the starting aryl palladium species can lead to different energetically favored pathways, as clearly shown in Table 10, entries 5 and 6. These two features dramatically complicate the migration profile. Third, the aryl to alkyl migration data are calculated in the absence of additional ligands, so that the palladium center remains three-coordinate throughout the process. While this may be important to initiate the agostic Pd–H interaction and commence the C–H activation, the lack of a fourth ligand in the product may substantially favor energetically η^2-coordination of the arene to the palladium center. Taking the 1,3-migration in a toluene system as an example (Table 10, entries 1 and 2), the reaction is shown to be highly exothermic and therefore largely irreversible if an η^3-product is formed, but the same reaction becomes energetically neutral and completely reversible when a benzene molecule is present as a ligand to ensure η^1-product formation. Considering that in reality many of the reactions are in fact carried out with more than one ligand per palladium center, this aryl to alkyl calculation may not reflect the actual energy profiles compared with the previous aryl to aryl calculation, at least as far as the overall ΔH values and the reversibility of the reaction are concerned.

While it remains true that Pd(IV) is more involved in the intimate migrations (1,3- and 1,4-), and Pd(II) is more involved in the distant migrations (1,4- and 1,5-),

Table 10 Energetically favored pathways for different types of aryl to alkyl palladium migration

Entry	Migration type	Description of migration	Favored pathway[a]
1	1,3-Migration: toluene		TS^{IV} and Int^{IV}
2			***TS^{IV}***
3	1,4-Migration: ethylbenzene		TS^{II}, TS^{IV} and Int^{IV}
4			***Int^{IV}***
5	1,4-Migration: naphthalene		TS^{IV}
6			***Int^{IV}***
7	1,5-Migration: propylbenzene		TS^{II}
8			***TS^{II}*** and Int^{IV}

[a]The bold and italic emphasis represents the pathway with the lowest activation enthalpy, if one neglects the geometry of the reactant

the overall trend is rather convoluted when the aforementioned complications are introduced. The Int^{IV} pathway even starts to compete in a more distant 1,5-migration (entry 8), and in certain 1,4-migration (entry 3), all three pathways are in play.

The energy profile of the 1,4-migration in the naphthalene system is illustrated in Fig. 5. Obviously, the two geometric isomers of the aryl palladium starting materials lead to different mechanistic pathways. For the *cis*-isomer (bromide and aryl group on neighboring positions of palladium), the Int^{IV} pathway is more energetically favored, while for the *trans*-isomer (bromide and aryl group on opposite positions of palladium), the TS^{IV} pathway is more energetically favored. Nonetheless, since the activation enthalpy for the *cis*-isomer is much less than that of the *trans*-isomer, the more likely mechanism should first convert the *trans*-isomer to the *cis*-isomer, followed by an Int^{IV} pathway, rather than a direct TS^{IV} pathway from the *trans*-isomer itself. It should also be noted that, according to the assumption of a three-coordinate palladium center, the products in both cases are much lower in energy than the starting materials due to η^2-coordination of the arene to the palladium center in the products and the overall reaction should go in a single direction. That is obviously incorrect, because this migration is known to go both ways, either forward or backward. Therefore, the assumption of a three-coordinate palladium center seems not to be particularly reliable. However, should one discount the added stabilization energy introduced by the η^2-coordination, the actual migration might be more energetically neutral and therefore allow the migration to occur in both directions.

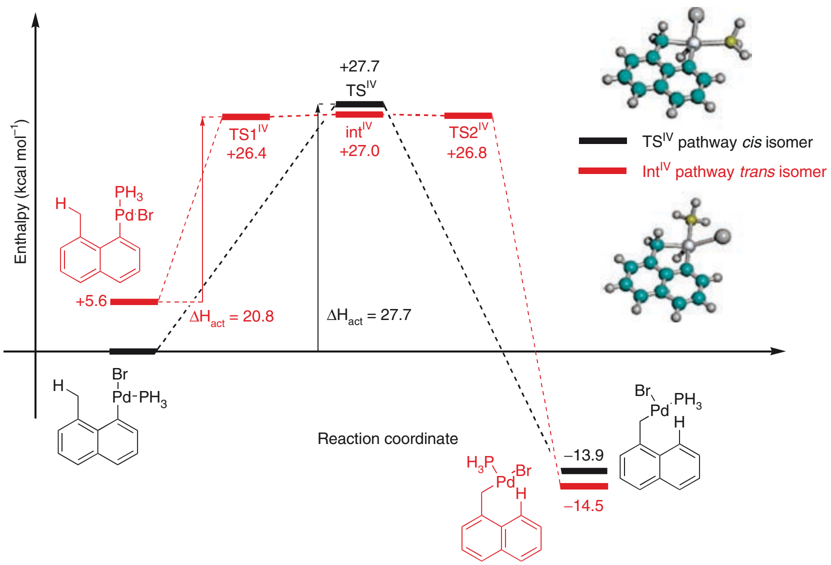


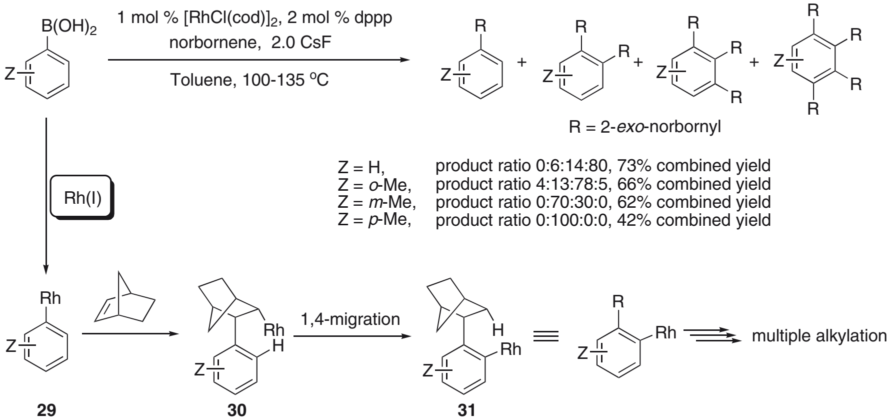
Fig. 5 Energy profiles for the 1,4-palladium migration in a naphthalene system (the zero of energy corresponds to the *trans*-starting material). Reprinted with permission from [30]. Copyright (2007) American Chemical Society

6 Rhodium Migrations

In addition to palladium, rhodium is also known to migrate from one carbon to another under suitable conditions. However, compared with palladium migration processes, rhodium migration is scarce. To date, only a few examples are reported, all involving 1,4-alkyl/vinylic to aryl migrations.

6.1 Alkyl to Aryl Rhodium Migrations

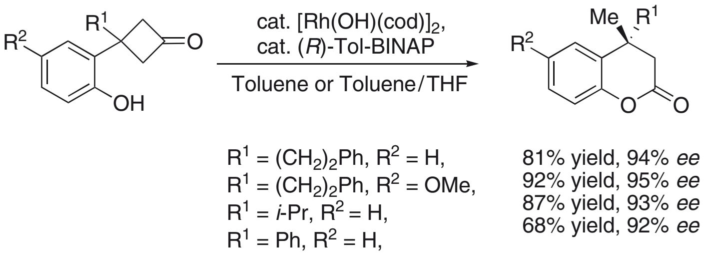
There are two reports of an alkyl to aryl rhodium migration process. The first example was reported in 2000 by Miura [75]. It was discovered that, upon reaction of phenyl boronic acid with norbornene under rhodium-catalyzed conditions, a “merry-go-around type” sequential alkylation occurred up to four times on the aromatic ring, resulting in a 1,2,3,4-tetranorbornylated benzene as the final product (Scheme 16). Mechanistically, this reaction involves an alkyl to aryl migration of rhodium. Thus, aryl rhodium intermediate **29**, generated via an initial transmetalation step,



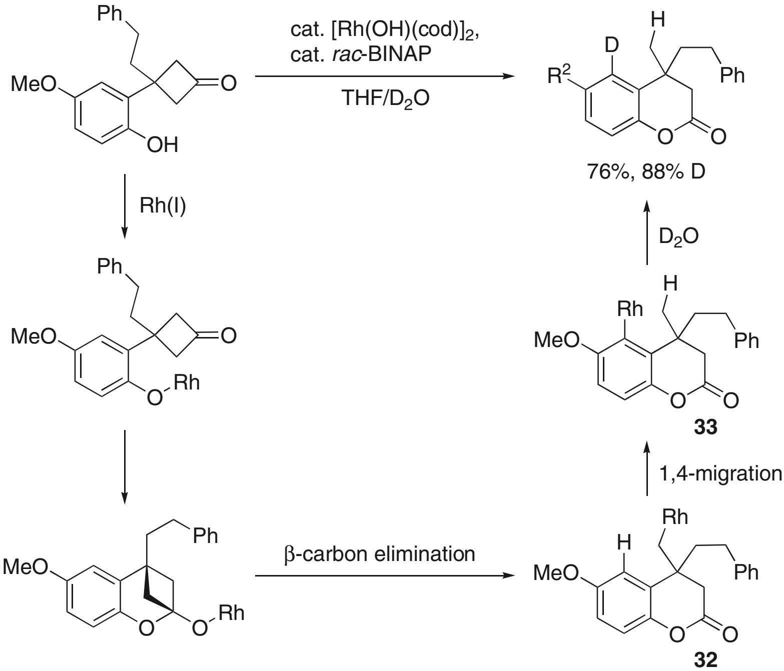
Scheme 16 Sequential alkylation of an aromatic boronic acid by norbornene under rhodium migration conditions

undergoes an insertion with norbornene in an *exo*-fashion to afford intermediate **30**. The structure of this intermediate resembles the intermediate during the alkyl to aryl palladium migration processes. An analogous 1,4-alkyl to aryl rhodium migration occurs, relocating the rhodium moiety on the aromatic ring to furnish intermediate **31**. Intermediate **31** can undergo either a protonolysis to afford the monoalkylation product, or a further insertion/migration to introduce a second norbornyl group. In this manner, the “merry-go-around” reaction continues multiple times.

The other example of a rhodium migration was discovered when 3-substituted-3-(2-hydroxyphenyl)cyclobutanones were subjected to rhodium-catalyzed conditions (Scheme 17) [76]. The reaction generates dihydrocoumarin derivatives in high yields with high enantioselectivity. The rhodium migration was confirmed by an isotope labeling experiment (Scheme 18), which indicated that protonolysis of the rhodium occurs at the aromatic position after rhodium migration (intermediate **33**), rather than at the aliphatic position where rhodium is located after β-carbon elimination (intermediate **32**). It should be noted that the 3-substituent of the cyclobutanone is



Scheme 17 Rhodium-catalyzed asymmetric synthesis of dihydrocoumarins

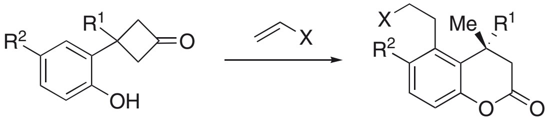


Scheme 18 Isotope labeling experiment and the proposed mechanism for the rhodium migration

crucial for the rhodium migration ($R^1 \neq H$), since deletion of this substituent allows intermediate **32** to undergo the more common β-hydride elimination pathway to remove the rhodium moiety.

This migration process has been further manipulated to use an electron-poor olefin to trap the migrated rhodium (Table 11). Thus, intermediate **33** after rhodium

Table 11 Rhodium migration process trapped by Heck coupling in the synthesis of dihydrocoumarins[a]



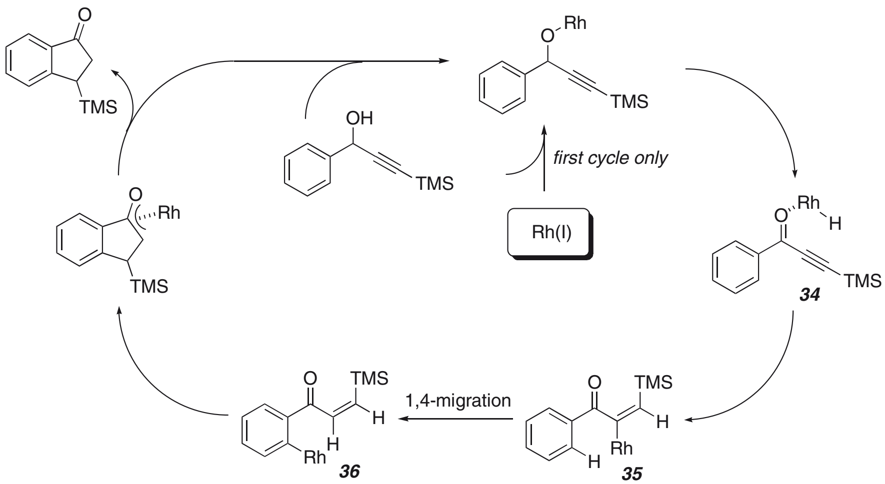
Entry	R^1	R^2	X	% Yield	% *ee*
1	$(CH_2)_2Ph$	OMe	CN	93	95
2	$(CH_2)_2Ph$	OMe	COMe	65	96
3	$(CH_2)_2Ph$	OMe	CO_2Me	76	95
4	Et	H	COMe	75	97
5	*i*-Pr	H	CN	89	91

[a]Reaction conditions: 3.5 mol% $[Rh(OH)(cod)]_2$, 8 mol% (*R*)-Tol-BINAP, 10 equiv of alkene added slowly, THF, 50–60 °C, 10–17 h

migration reacts with the external olefin to furnish a 5-alkylated dihydrocoumarin product in good to excellent yield. Again, the starting material must have a substitution at the 3-position of the cyclobutanone moiety ($R^1 \neq H$).

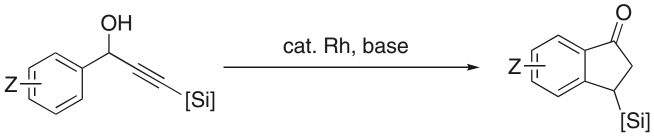
6.2 *Vinylic to Aryl Rhodium Migrations*

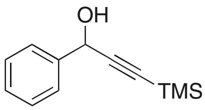
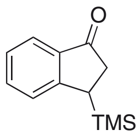
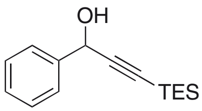
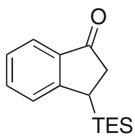
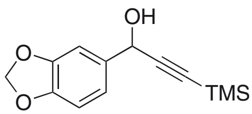
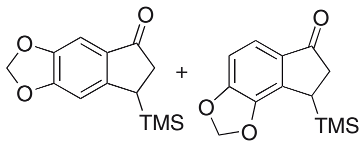
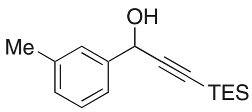
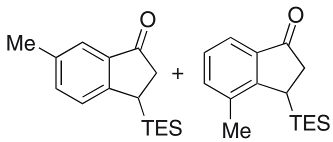
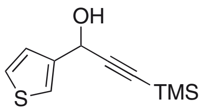
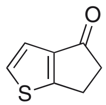
A few examples of vinylic to aryl rhodium migration have also been observed. One such example was discovered independently by two groups almost at the same time [77, 78]. In this reaction, aryl propargyl alcohols undergo a rhodium-catalyzed isomerization to furnish indanone products (Table 12). The reaction proceeds by a fairly complicated mechanism shown in Scheme 19. Thus, after base-promoted ligand



Scheme 19 Proposed mechanism for the rhodium-catalyzed isomerization with vinylic to aryl migration

Table 12 Rhodium-catalyzed isomerization of aryl propargyl alcohols under rhodium migration conditions

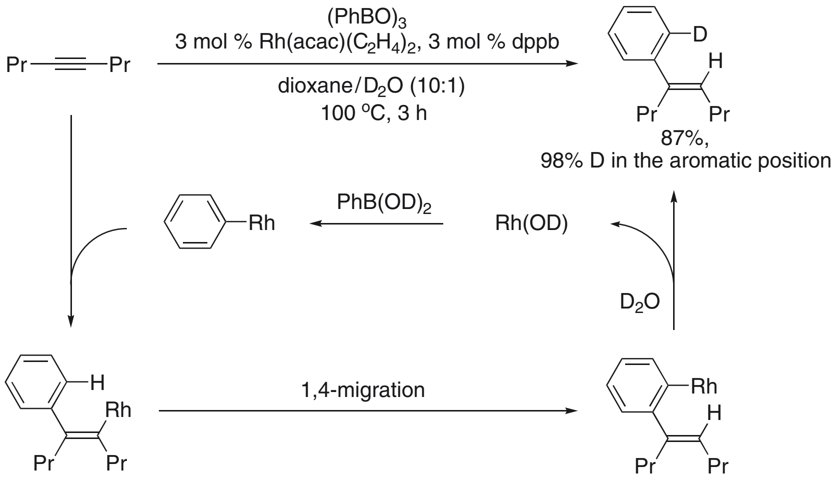


Entry	Substrate	Procedure[a]	Product	% Yield
1		A		86
2		B		92
3		A		88 (1:1)
4		B		76 (>20:1)
5		A		95

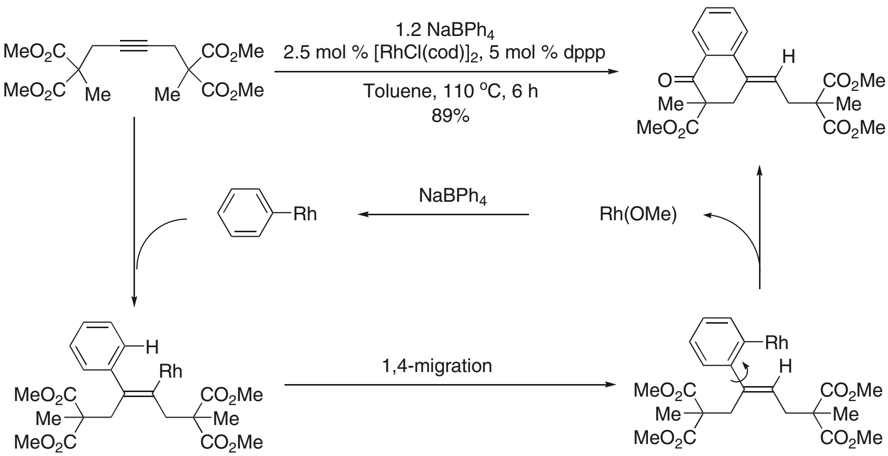
[a]Procedure A: 10 mol% $[Rh(cod)_2](BF_4)$, 40 mol% $P(p\text{-tolyl})_3$, 1.0 equiv of 2,2,6,6-tetramethylpiperidine, 67 °C or 90 °C; procedure B: 5–10 mol% $RhCl(PPh_3)_3$, 15 mol% KOH (0.6 M aqueous), THF, 60 °C

exchange, β-hydride elimination occurs to afford intermediate **34**, which undergoes hydrorhodation to afford intermediate **35**. A crossover experiment has confirmed that this insertion is strictly an intramolecular process and no dissociation of rhodium hydride occurs from intermediate **34**. Next, intermediate **35** undergoes a 1,4-vinylic to aryl rhodium migration to relocate the rhodium on the aromatic moiety, resulting in the formation of **36**. A final cyclization and subsequent protonolysis afford the indanone product. Although desilylation readily occurs with certain substrates, the original conditions do not work well without the terminal silyl group, as substituting the TMS group by a phenyl group when using procedure A only affords a 39% yield of indanone. In this case, RhCl(dppb)(PPh_3) was found to be an effective catalyst.

Rhodium migration has also been observed in the rhodium-catalyzed reaction of aryl boronic acids (or equivalents) with alkynes or enynes. Three reports have been disclosed in the literature [79–81]. The first is an alkyne hydroarylation method reported by Hayashi and coworkers (Scheme 20) [79]. It was observed that under the standard rhodium-catalyzed hydroarylation conditions, protonolysis does not occur on the rhodium-bearing vinylic site, but rather on the aromatic ring after an apparent rhodium migration.



Scheme 20 Rhodium-catalyzed hydroarylation of alkynes with vinylic to aryl rhodium migration



Scheme 21 Rhodium-catalyzed hydroarylation/cyclization

Murakami and coworkers reported a further use for this rhodium migration [80, 81]. Instead of protonolysis, they noticed that the aryl rhodium species after the vinylic to aryl migration is nucleophilic enough to attack an ester moiety in an intramolecular fashion to afford a cyclic ketone. Thus, an internal alkyne equipped with ester groups at a specific place was subjected to the rhodium-catalyzed hydroarylation conditions (Scheme 21). Indeed, the desired ketone was obtained in an 89% yield. Not only methyl esters can serve as acylation agents; ethyl esters and isopropyl esters are also suitable substrates.

7 Conclusions and Outlook

Palladium migrations, although still in their infancy, have been demonstrated as a successful and powerful tool in palladium-catalyzed reactions, especially in the efficient construction of heterocycles and carbocycles. This chemistry has opened up a new chapter in C–H activation research and contributed a great deal to the functionalization of remote C–H bonds where direct functionalization is difficult to achieve. These palladium migrations are broad in scope, and the efficiency of the reaction in consecutive, multiple migrations shows considerable potential for the functionalization of even more remote C–H bonds. Computational studies reveal three major mechanistic pathways for the migration step, and a novel hydrogen-channeling pathway has been proposed. Considerable recent success and a promising future for this palladium migration chemistry are likely to expand the synthetic utility of palladium catalysis and contribute even more to efficient, green organic transformations.

Despite the great success and potential of this palladium migration chemistry, a number of issues still exist. From a practical viewpoint, the yields of the products in quite a few reactions remain low and the overall efficiency needs to be optimized. Detailed studies of the reaction mechanism and substrate scope in certain reactions remain to be carried out, including measurements of the kinetic isotope effect. From a strategic point of view, the dependency of the migration upon the nature of the substrate structure, the reaction conditions, and/or the nature of the palladium trap remain to be elucidated before it is possible to predict palladium migrations in any given specific case. Applications of palladium migration in natural product total synthesis can also be expected.

Fewer examples of rhodium migration chemistry have been reported. Other than palladium and rhodium, platinum [82] is also known to migrate from one position to another under suitable reaction conditions. A better understanding of the migration in these metal-catalyzed reactions in terms of substrate scope and mechanism is needed. Extensions of this migration chemistry to other metals, such as perhaps ruthenium and iridium, can be expected.

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Palladium-Catalyzed Aryl–Aryl Bond Formation Through Double C–H Activation

Shu-Li You and Ji-Bao Xia

Abstract Aryl–aryl bond formation constitutes one of the most important subjects in organic synthesis. The recently developed direct arylation reactions for the formation of aryl–aryl bond have emerged as very attractive alternatives to traditional cross-coupling reactions. Particularly, the direct arylation through double C–H activation using the simple arenes as both coupling partners is a highly economic and attractive method. In this chapter, the recent progress of Pd-catalyzed aryl–aryl oxidative coupling reactions through double C–H activation is presented.

Keywords Arene • Palladium • C–H activation • Oxidative coupling • Biaryl synthesis

Contents

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Abbreviations

Ac	Acetyl
acac	Acetylacetonyl
atm	Atmosphere
Bn	Benzyl
BQ	Benzoquinone
Bz	Benzoyl
Piv	Pivalyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TON	Turnover number
Ts	*p*-Toluenesulfonyl

1 Introduction

This chapter focuses on the palladium-catalyzed aryl–aryl bond formation reaction through double C–H activation. Biaryl structural units are broadly found in biologically important natural products, synthetic pharmaceuticals, agrochemicals, and functional molecules in material sciences [1, 2]. Some of these examples are depicted in Fig. 1, such as the antihypertensive drug Losartan, the natural product Biphenomycin [3, 4], the agrochemical agent Boscalid [5], and the liquid crystal

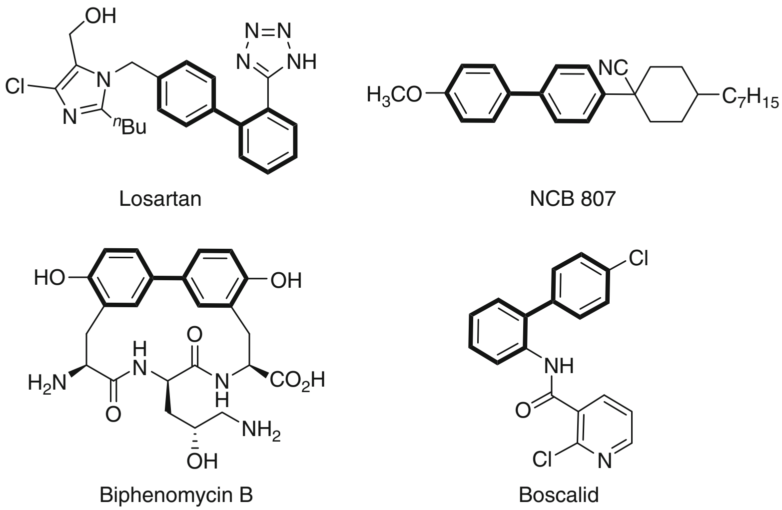


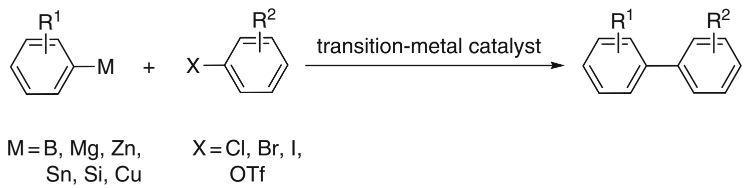
Fig. 1 Examples of important biaryl-containing compounds

material NCB 807 [6]. As a consequence, extensive efforts have been devoted to the discovery of efficient methods for biaryl synthesis.

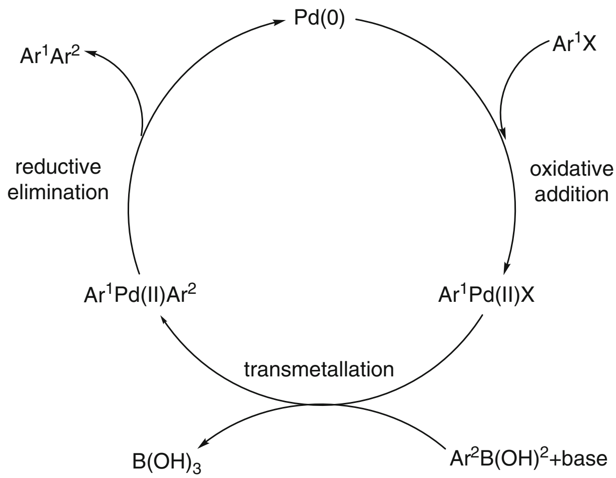
Over the past century, several methods have been developed for the synthesis of biaryl compounds [7]. Among these are the Ullmann-type coupling [8, 9], the Scholl reaction [10], the Gomberg–Bachmann reaction [11], and recently transition-metal-catalyzed cross-coupling reactions [12]. In particular, palladium-catalyzed cross-coupling reactions have been successfully applied to the synthesis of biaryls due to their generally high yields and excellent selectivities.

In general, in the traditional palladium-catalyzed cross-coupling reactions to synthesize biaryls, both coupling partners need to be preactivated compared to simple arenes. Typically, one partner is an organometallic compound (or aromatic carboxylate via decarboxylative coupling [13, 14]), and the other is an aryl halide or pseudohalide (Scheme 1). Several efficient transition-metal-catalyzed reactions, such as the Suzuki–Miyaura [15, 16], Kumada [17], Stille [18, 19], and Negishi couplings [20, 21], have been developed to afford biaryls in high yields from these preactivated coupling partners. Among these, the Suzuki–Miyaura coupling between boronic acids and halides in the presence of a palladium catalyst is the most widely used method in both academic and industrial laboratories. However, in addition to high yield and selectivity, modern organic chemistry adds more criteria for a perfect catalytic reaction, such as robustness of catalyst, mild reaction conditions, affordability of starting materials, atom economy, and a low environmental impact. In this regard, the above-mentioned cross-coupling reactions still have many fundamental drawbacks. Even the powerful Suzuki–Miyaura reaction requires aryl halides (pseudohalides) and a stoichiometric quantity of the relatively expensive boronic acids. Preparation of both coupling partners often requires additional synthetic operations starting from simple aromatic compounds, generating waste from reagents, solvents, and purifications. Moreover, a stoichiometric amount of metal waste is produced from the arene-activating groups upon completion of the cross-coupling reaction. When organometallic reagents are insufficiently stable to participate in the coupling reaction, more efficient methods for the preparation of biaryls are needed.

A quite obvious solution to this problem is to replace both partners of the cross-coupling reaction with simple arenes by the cleavage of C–H bond during the coupling reaction. To assess this possibility, the catalytic cycle of the Suzuki–Miyaura reaction is depicted in Scheme 2. Palladium-catalyzed Suzuki–Miyaura reaction follows a similar catalytic cycle to those of many other cross-coupling



Scheme 1 Biaryl synthesis via traditional transition-metal-catalyzed cross-coupling reactions



Scheme 2 Catalytic cycle of the Suzuki–Miyaura reaction

reactions, involving: (I) oxidative addition of aryl halides or pseudohalide to a palladium(0) complex yielding Ar^1PdX; (II) transmetallation between Ar^1PdX and $Ar^2B(OH)_2$ generating $Ar^1Pd(II)Ar^2$; (III) reductive elimination of Ar^1PdAr^2 to give biaryl compound and regenerate the Pd(0) complex. An important step in this catalytic cycle is the generation of ArPd(II)X intermediate from aryl halide. Therefore, replacement of Ar–X with Ar–H in the coupling reaction requires the generation of the ArPd(II)X intermediate directly from Ar–H compound as one possibility. Fortunately, the ArPd(II)X species can be generated from the aryl C–H in the presence of Pd(II) salts. In 1965, Cope and Siekman reported that Pd(II) salts promoted aryl C–H bond cleavage to afford palladacyclic product with the aid of a directing group [22]. In their report, the reaction of palladium(II) dichloride with azobenzene gave the palladacyclic complex in which a nitrogen atom was coordinated with the Pd center and the C–H bond *ortho* to the azo linkage was cleaved by palladium(II) dichloride forming Pd–carbon bond.

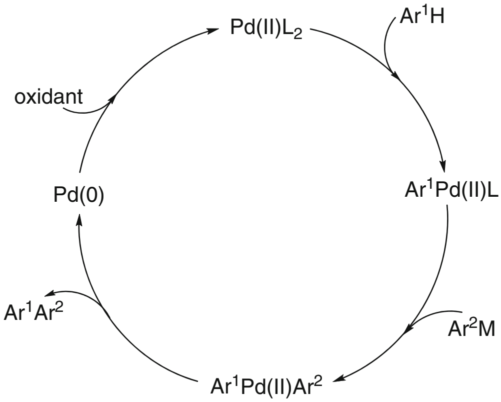
In the cross-coupling reaction, starting from the simple arene (with directing group), palladation by a Pd(II) salt would lead to the formation of the palladacyclic complex ($Ar^1Pd(II)L$) (Scheme 3). After the transmetallation and reductive elimination processes, the biaryl product is obtained together with Pd(0). If the Pd(0) can be further oxidized to Pd(II) catalyst, a catalytic cycle will be formed. By accomplishing this, arenes (C–H) are used to replace the aryl halides (C–X). Similarly, arenes (C–H) can be used to replace the aryl metals (C–M).

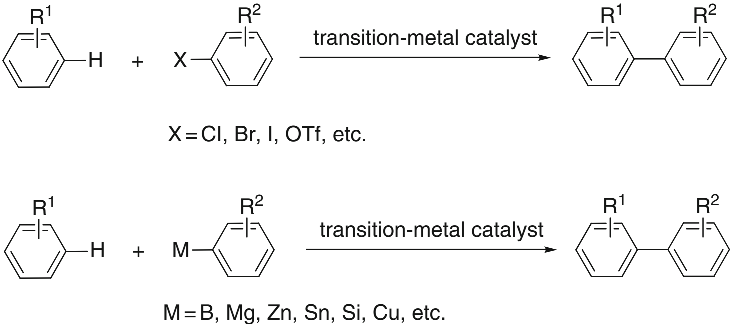
Over the past decade, significant advances have been made in the transition-metal-catalyzed aryl–aryl bond formation through C–H activation (for reviews see [23–32]). In this direct arylation reaction one of the preactivated reaction partners is replaced by a simple arene. This direct arylation process is not only just of academic interest but also attractive for industrial applications, since only one preactivated reaction partner is needed. Obviously, the cost of the reaction will be reduced by using the cheap starting material, and the waste of the reaction can also be greatly reduced to benefit the environment.

Various transition metals (Pd, Rh, Ru, Cu, Fe, etc.) have been shown to be effective for cross-coupling reactions involving C–H bond activation in recent years (for copper, see [33–38]; for iron, see [39, 40]). Pd(II) salts have emerged as the preferred catalysts to promote the C–H bond cleavage in catalytic direct arylation reactions. This process can be classified into two parts, the organometallic reagent is replaced by a simple arene in one case, and the aryl halide is replaced by a simple arene in another (Scheme 4).

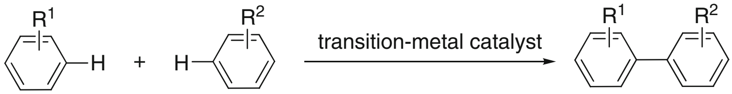
With the success of transition-metal-catalyzed aryl–aryl cross-coupling reactions through C–H activation of one of the coupling partners, obviously, a more economic and attractive alternative is the coupling reaction via double C–H activation of two arenes, neither of which needs to be preactivated (Scheme 5). However, the development of such a process is very challenging because many difficulties remain to be solved. For instance, the control of selectivity when two coupling partners have more than one type of aromatic C–H bond is a challenge.

Scheme 3 Cross-coupling reaction via C–H activation





Scheme 4 Transition-metal-catalyzed aryl–aryl bond formation through C–H activation



Scheme 5 Transition-metal-catalyzed aryl–aryl bond formation through double C–H activation

In this chapter, the recent progress of Pd-catalyzed aryl–aryl bond formation reactions through double C–H activation is presented.

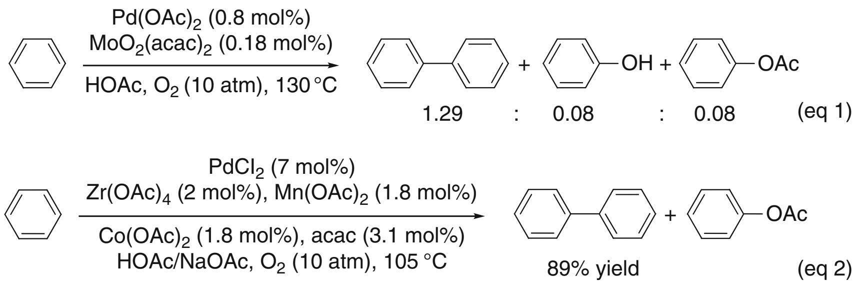
2 Pd-Catalyzed Aryl–Aryl Bond Formation via Oxidative Homocoupling Reaction

2.1 Homocoupling Reaction Without Directing Group

Palladium-catalyzed oxidative homocoupling of benzene to biphenyl is the simplest version for the synthesis of biaryl via double C–H activation. The oxidative coupling of benzene to biphenyl using stoichiometric amounts of $PdCl_2$ in the presence of sodium acetate and acetic acid was first described by van Helden and Verberg in 1965 [41]. Although the phenomenon that the presence of oxygen during the reaction increased the yield was observed and hypothesized as the result of oxidizing the Pd(0) to Pd(II), the authors failed to render this reaction catalytic. Later, Davidson and Triggs described a similar biphenyl formation by palladium acetate, and the yield of biphenyl was increased up to 55% when perchloric acid was used [42]. In 1970, Fujiwara and coworkers found that the oxidative coupling of benzene in the presence of an olefin-palladium chloride complex and silver nitrate gave biphenyl in quantitative yield [43]. Neither the $PdCl_2$ nor $AgNO_3$ effects the reaction alone, and $AgNO_3$ is the most effective cocatalyst among metal salts such as mercuric and copper salts. Since then, the oxidative of benzene to biphenyl by Pd(II) has attracted considerable interest. Several catalytic processes for this coupling have been reported. However, the turnover number of Pd(II) in the biphenyl synthesis is still low (up to 85) even when the reactions are carried out under higher pressure of oxygen [44, 45].

Recently, Yamaji and coworkers reported that the $Pd(OAc)_2$-catalyzed oxidative coupling of benzene in the presence of O_2 and acetic acid gave high selectivity of biphenyl (88%) when $MoO_2(acac)_2$ was used as a cocatalyst, but the turnover number remained low (up to 10) (Eq. 1, Scheme 6) [46].

Sasson and coworkers reported that the oxidative coupling of benzene in the presence of catalytic amount of $PdCl_2$ (7 mol%) together with Zr(IV), Mn(II), and Co(II) acetates led to biphenyl in 89% yield in HOAc/NaOAc under air (10 atm). The combination of several oxygen-binding catalysts such as Zr(IV), Mn(II), and Co(II) acetates increased the concentration of oxygen in solution and therefore



Scheme 6 Pd-catalyzed oxidative homocoupling of benzene

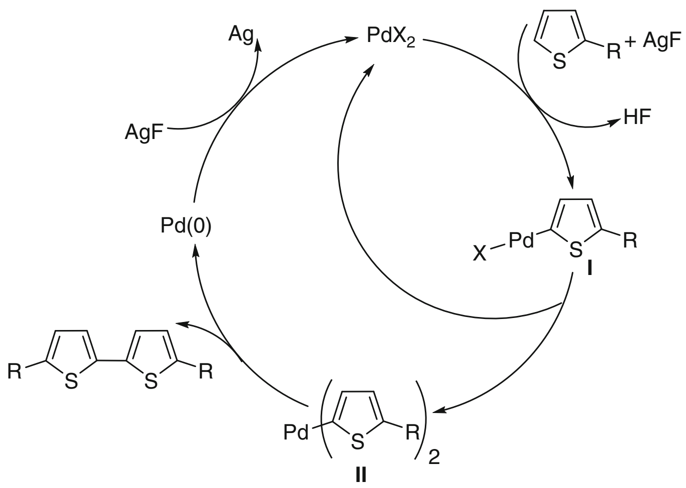
allowed the fast generation of the active Pd(II) species (Eq. 2, Scheme 6). By doing this, the reaction proceeded well even at lower oxygen (and/or air) pressures [47].

In 2002, the Kozhevnikov group and the Ishii group independently reported the catalytic oxidative coupling of benzene to biphenyl using a $Pd(OAc)_2$/heteropoly acids system in acetic acid with oxygen [48, 49]. In the report by Ishii and coworkers, the oxidative coupling of benzene to biphenyl with O_2 (1 atm) can be efficiently achieved by $Pd(OAc)_2$ using a 1/1 mixture of $HPMo_{11}V_1$ and $HPMo_{12}$ as the reoxidation catalyst. The turnover number of the biphenyl formation step can be obtained up to 109, but the conversion based on benzene is still low.

In addition to benzene, different electron-rich heterocycles have also been demonstrated to undergo the oxidative coupling smoothly. In 1976, Kozhevnikov reported the oxidative coupling of furan derivatives to bifurans catalyzed by Pd(II) salts. With $Cu(OAc)_2$ as oxidant, good turnover number (up to 82) was realized for Pd-catalyzed bifuran synthesis [50–52]. The reactivity of 2-substituted furan derivatives in oxidative coupling by Pd(II) salts decreases in the following order of substituents: -H, $-CH_3$, -CHO > $-COOCH_3$, $-COOC_2H_5$, $-CH(OOCCH_3)_2$ > -COOH. This order corresponds to the influence of substituents in the electrophilic substitution of heteroaromatic compounds. Subsequently, Kozhevnikov also realized the catalytic oxidative coupling of thiophenes with low turnover number (<6) [51].

In 1980, Itahara reported the 2,2′-dimerization of pyrroles with palladium acetate in acetic acid [53]. With a substoichiometric amount of palladium acetate (0.34 equiv.), heating the pyrroles in acetic acid at 100 °C for 10 h produced 2,2′-dimerized pyrroles in 38–56% yield.

In 2004, Mori and coworkers reported the palladium-catalyzed homocoupling of 2-substituted thiophenes in the presence of AgF as an activator through double C–H bond activation under mild conditions [54]. Various 2-substituted thiophenes **1** gave the homocoupling products **2** smoothly using 2 mol% $PdCl_2(PhCN)_2$ and 2 equiv. of AgF. Interestingly, 2-(4-methoxyphenyl)thiazole **1h** also underwent the homocoupling smoothly at the 5-position. A catalytic cycle is proposed as depicted in Scheme 7. Electrophilic C–H substitution of $Pd(II)X_2$ with thiophene gives intermediate **I**, which leads to **II** following disproportionation. AgF serves as an effective promoter in forming the intermediate **I** and the oxidant to regenerate the Pd(II) catalyst from a Pd(0) species.



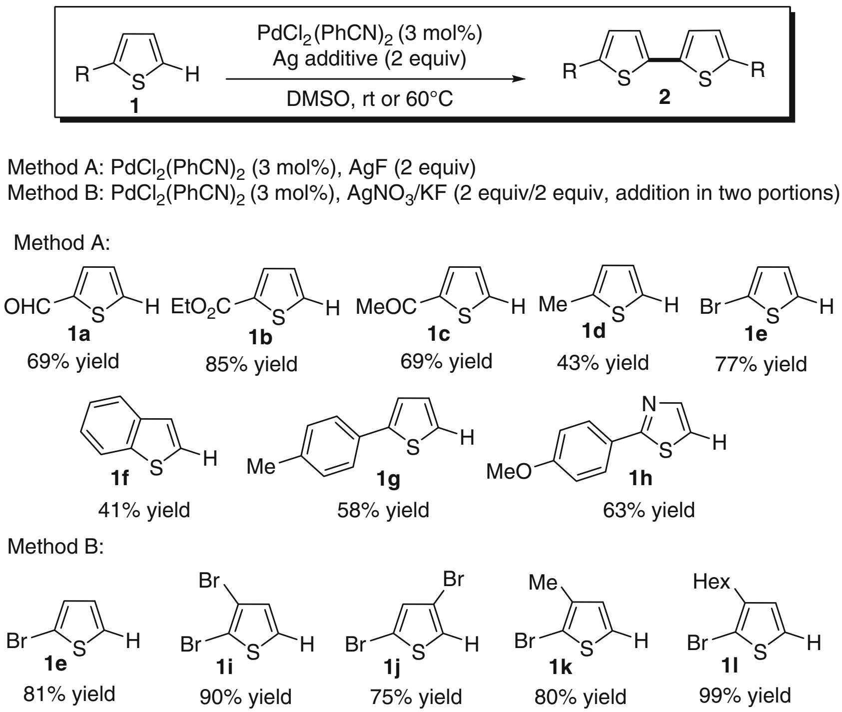
Scheme 7 Plausible mechanism of homocoupling of thiophene

Further studies revealed that the yields of homocoupling of 2-substituted thiophenes can be improved using 2 equiv. of $AgNO_3$ and KF, which were added in two portions [55, 56] (Scheme 8).

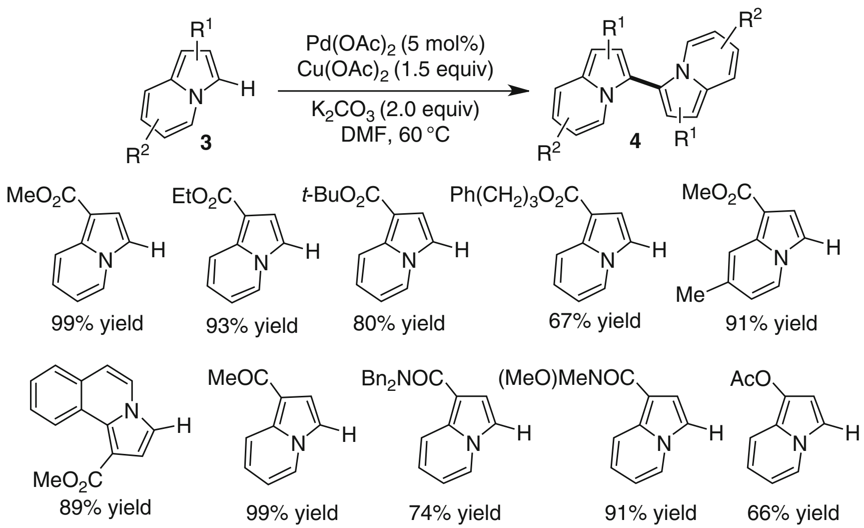
Very recently, You and coworkers developed a palladium-catalyzed highly regioselective homocoupling of indolizines to synthesize biindolizines [57]. Using $Pd(OAc)_2$ as catalyst, $Cu(OAc)_2$ as oxidant, and K_2CO_3 as base, biindolizines were synthesized in good to excellent yields (up to 99% yield) under mild conditions (Scheme 9). The reaction is very general and works for a wide range of indolizine substrates bearing different substituents. In addition, this methodology was demonstrated to be suitable for the synthesis of 18-membered macrobiindolizines with moderate yields (Scheme 10).

2.2 Homocoupling Reaction with Directing Group

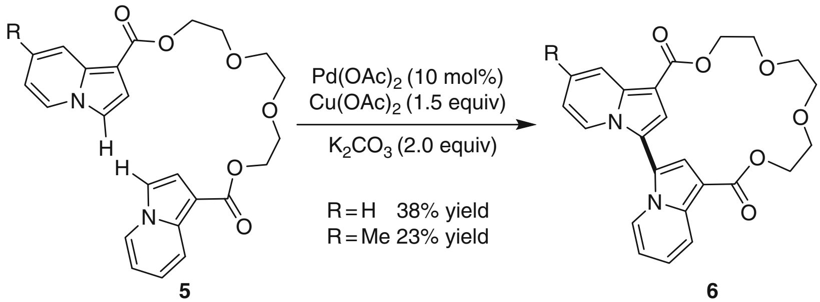
In 2006, Sanford and coworkers reported a Pd-catalyzed homocoupling reaction of 2-arylpyridines [58]. Using 5 mol% $Pd(OAc)_2$ as catalyst and, 2 equiv. of oxone as oxidant, the homocoupling products were obtained in good yields with high regioselectivity (Scheme 11). The aryl C–H bond was cleaved by pyridine-directed palladation. Substituents such as Me, OMe, F, and Br on the phenyl ring were all well tolerated. The lack of side reaction with *ortho*-Br substrate **7c** distinguishes the current reaction from the traditional Ullmann-type reaction. Notably, although thiophene normally proceeds in coupling reactions via C–H activation at the α-position, here the regioselectivity is controlled by the 2-pyridine moiety leading to the C–H activation at the β-position (**7f**). Furthermore, the moderate



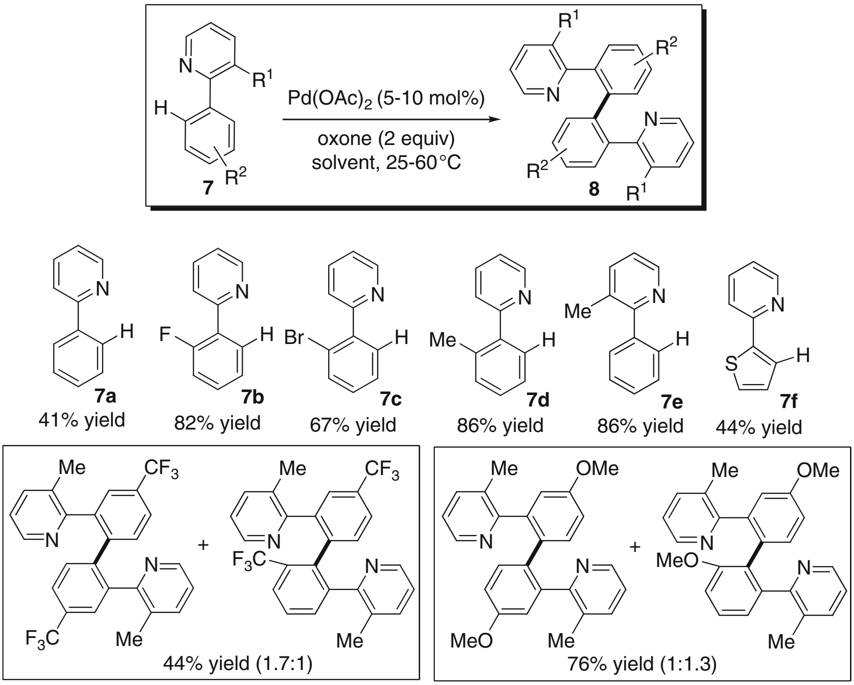
Scheme 8 Pd-catalyzed oxidative homocoupling of 2-substituted thiophenes



Scheme 9 Pd-catalyzed oxidative homocoupling of indolizines



Scheme 10 Construction of cyclophanes by intramolecular oxidative coupling reactions



Scheme 11 Pd-catalyzed oxidative homocoupling of 2-arylpyridines

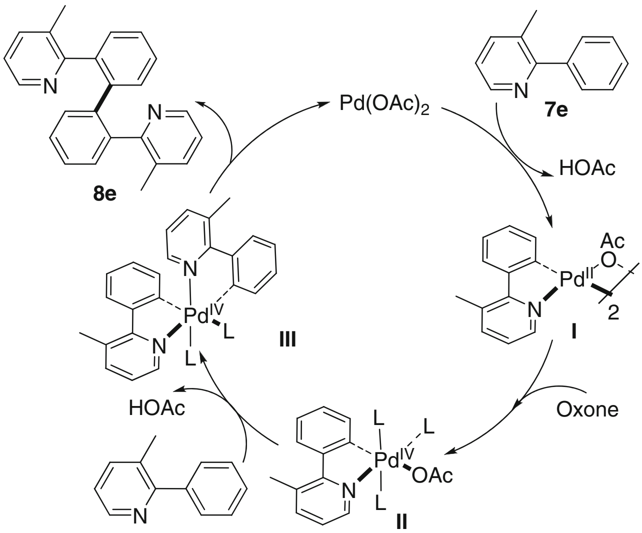
regioselectivities with the substrates containing *meta*-substituents are also in sharp contrast to the previous studies with Pd(II)-mediated direct C–H activation.

A hypothesis of sequential C–H bond activation reactions at Pd(II) and Pd(IV) was proposed after extensive mechanistic studies. As shown in Scheme 12, the catalytic cycle begins with palladation of the 2-arylpyridine substrate to produce the Pd(II) complex **I**. Oxidation of complex **I** with oxone affords the Pd(IV) species **II**, which occurs another C–H activation to give the intermediate **III**. Reductive elimination of **III** leads to the coupling product and regeneration of Pd(II) salts.

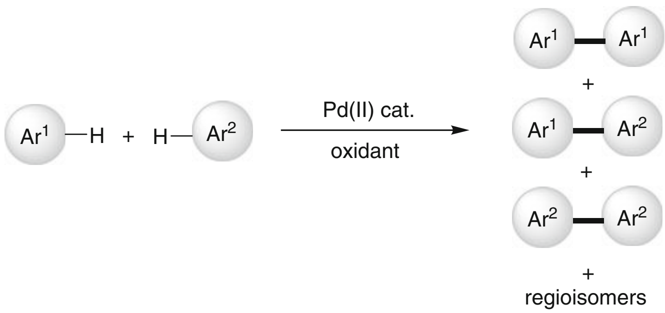
3 Pd-Catalyzed Aryl–Aryl Bond Formation via Oxidative Cross-Coupling Reaction

3.1 Cross-Coupling Reaction Without Directing Group

In comparison to the homocoupling reaction, the cross-coupling reaction has to face a bigger challenge with selectivities. For example, as shown in Scheme 13, theoretically there are at least three different coupling products including two formed from homocoupling reaction. How to avoid the homocoupling reaction represents a great challenge for an efficient cross-coupling reaction via double C–H activation.



Scheme 12 Plausible mechanism of homocoupling of 2-arylpyridines



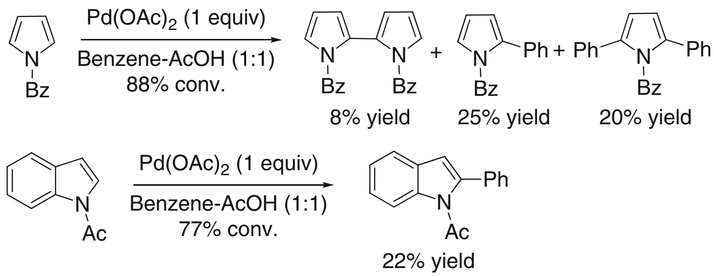
Scheme 13 Pd-catalyzed oxidative cross-coupling reaction

In 1976, during a study on the oxidative homocoupling of furan or thiophene, Kozhevnikov found that the cross-coupling of furan and thiophene in the presence of $Pd(OAc)_2/Cu(OAc)_2/CaCl_2$ led to a high yield of 2-(2-furyl)-thiophene together with regioisomers and homocoupling byproducts [50].

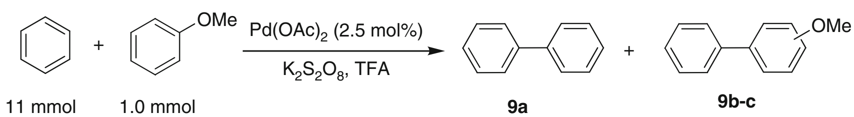
In 1981, Itahara reported the palladium acetate-mediated direct arylation of pyrroles and indoles with arenes [59]. With (sub)stoichiometric $Pd(OAc)_2$ in benzene and acetic acid, arylation of 1-benzoylpyrrole and 1-acetylindole occurred with moderate to excellent conversions, but gave generally low yields of the desired cross-coupling products (Scheme 14). Direct arylation of isoxazole in the presence of stoichiometric amount of $Pd(OAc)_2$ was also reported by Nakamura et al. [60].

In 2006, the synthesis of unsymmetrical biaryls from simple arenes was achieved successfully in a catalytic system of $Pd(OAc)_2/TFA/K_2S_2O_8$ by tuning the concentrations of arenes and TFA, reported by Lu and coworkers (Scheme 15) [61]. Although the yield of cross-coupling reaction is not practical (11–50% based on the limiting arene), it provides valuable information on the Pd-catalyzed cross-coupling reaction via double aromatic C–H activation.

The concentration of the TFA and ratio between the two arenes were found to play important roles in the cross-coupling reaction. A possible catalytic cycle involving four steps was proposed for the formation of unsymmetrical biaryl (Scheme 16): (1) a first electrophilic attack of Pd(II) on the excess arene (high concentration), Ar^1H; (2) a second electrophilic attack of $Ar^1Pd(II)L$ on the electron-rich arene (high electrophilic activity), Ar^2H; (3) Ar^1Ar^2 formed after the reductive elimination, generating Pd(0); (4) regeneration of Pd(II) via oxidation of the Pd(0).



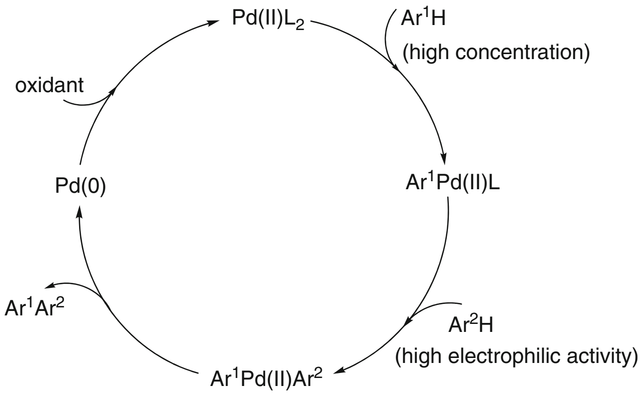
Scheme 14 Pd-mediated arylation of 1-benzoylpyrrole and 1-acetylindole



when TFA = 6.3 mmol, **9a**/**9b-c** = 56/44; **9b**/**9c** (*p*:*o*) = 71/29; TON for **9b-c** = 5.8

when TFA = 0.63 mmol, **9a**/**9b-c** = 21/79; **9b**/**9c** (*p*:*o*) = 69/31; TON for **9b-c** = 2.8

Scheme 15 Pd-catalyzed oxidative cross-coupling between simple arenes



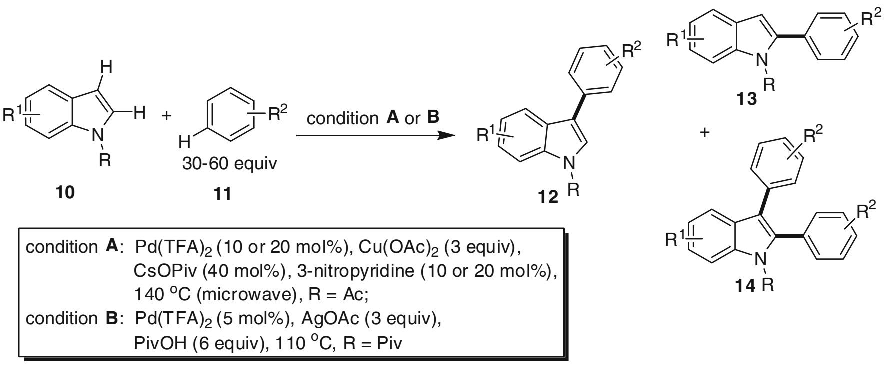
Scheme 16 Plausible mechanism for Pd-catalyzed cross-coupling between simple arenes

Interestingly, subsequent work from Lu's group showed that tuning the concentration of TFA would allow the regioselective homocoupling of *p*-xylene to generate a biaryl or diarylmethane in the presence of the $Pd(OAc)_2/TFA/K_2S_2O_8$ system [62].

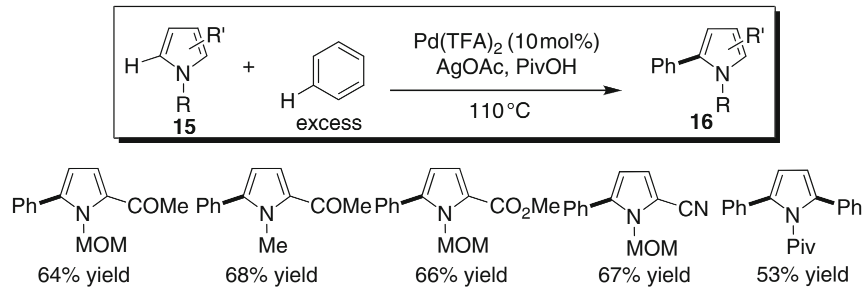
Recently, Fagnou and coworkers reported the palladium-catalyzed oxidative cross-coupling reactions of indoles with simple arenes [63, 64]. Comparing to Itahara's report [59], the catalytic efficiency is highly improved. More interestingly, they found that the direct arylation can selectively occur at C2-indole or C3-indole under different conditions. The detailed results are summarized in Table 1. Using 10 or 20 mol% $Pd(TFA)_2$, 3 equiv. of $Cu(OAc)_2$, 10 or 20 mol% 3-nitropyridine, and 40 mol% CsOPiv, 3-aryl *N*-acetyl indole can be obtained as a major product in moderate to good yields by microwave heating at 140 °C. The reactions work well for indoles with different electronic properties. Interestingly, using 5 mol% Pd $(TFA)_2$, 3 equiv. of AgOAc, and 6 equiv of PivOH, 2-aryl *N*-pivalyl indole can be obtained as a major product in moderate to good yields by heating at 110 °C. Under the similar reaction conditions, the oxidative cross-coupling of pyrroles with benzene gave 2-phenylpyrroles in good yields (Scheme 17). Their experiments indicate that the inversion in C2/C3 selectivity of arylation of indole may be affected by the Pd concentration and acetate additives. In the cross-coupling of *N*-pivalyl indole and benzene, the C3 selectivity increases dramatically from 52 to 99% when the $Pd(TFA)_2$ loading is increased from 20 to 300 mol% in the absence of oxidant and additive under otherwise identical conditions. Furthermore, the addition of 2 equiv. of CsOAc to reactions performed with 20 mol% $Pd(TFA)_2$ in the absence of oxidants induces 99% C2 selectivity. The authors proposed that, when AgOAc or CsOAc is added, C2 selectivity is increased due to carboxylate-induced cleavage of higher-order Pd clusters to form monomeric Pd species. On the other hand, mixed Pd–Cu clusters, favoring the C3 selectivity, may be formed upon the addition of $Cu(OAc)_2$.

Soon after, DeBoef and coworkers reported similar work on oxidative cross-coupling reactions. In the presence of 10 mol% of $Pd(OAc)_2$, 10 mol% of

Table 1 Pd-catalyzed oxidative cross-coupling of indoles with simple arenes

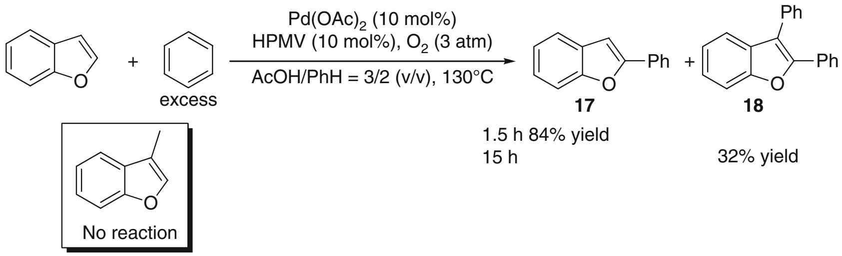


Indole	Arene	Condition **A** Yield of **12** (**12**:**13**:**14**)	Condition **B** Yield of **13** (**13**:**12**:**14**)
R^1 = H	R^2 = H	87 (8.9:1:0.3)	84 (25:1:0.7)
R^1 = 5-OMe	R^2 = H	84 (11.2:1:0.4)	90 (46:1:1)
R^1 = 6-Me	R^2 = H	81 (10:1:0.6)	88 (31:1:1)
R^1 = 5-Cl	R^2 = H	63 (6.5:1:0)	86 (31:1:trace)
R^1 = 6-Cl	R^2 = H	61 (5.7:1:0)	–
R^1 = 6-OMe	R^2 = H	74 (10.5:1:0.3)	76 (26:1: trace)
R^1 = 6-CO_2Me	R^2 = H	54 (2.8:1:0)	86 (31:1:trace)
R^1 = H	R^2 = 1,4-dimethyl	45 (10.4:1:0.4)	58 (31:1:trace)
R^1 = H	R^2 = 1,4-dimethoxy	52 (3.7:1:0)	–
R^1 = H	R^2 = 1,4-difluoro	42 (9.9:1:0)	–
R^1 = H	R^2 = 1,2-dimethyl	–	75 (30:1:trace)



Scheme 17 Pd-catalyzed direct arylation of pyrroles

$H_4PMo_{11}VO_{40}$, and 3 atm of O_2, the oxidative cross-coupling of benzofuran and benzene gave 84% yield of 2-phenylbenzofuran after 1.5 h (Scheme 18) [65]. When the reaction time was prolonged to 15 h, 32% yield of 2,3-diphenylbenzofuran was isolated. Subjecting 3-methylbezofuran to the reaction conditions resulted in the recovery of the starting materials, suggesting the 2-substituted product might result from palladation at the 3-position followed by migration to the 2-position. When



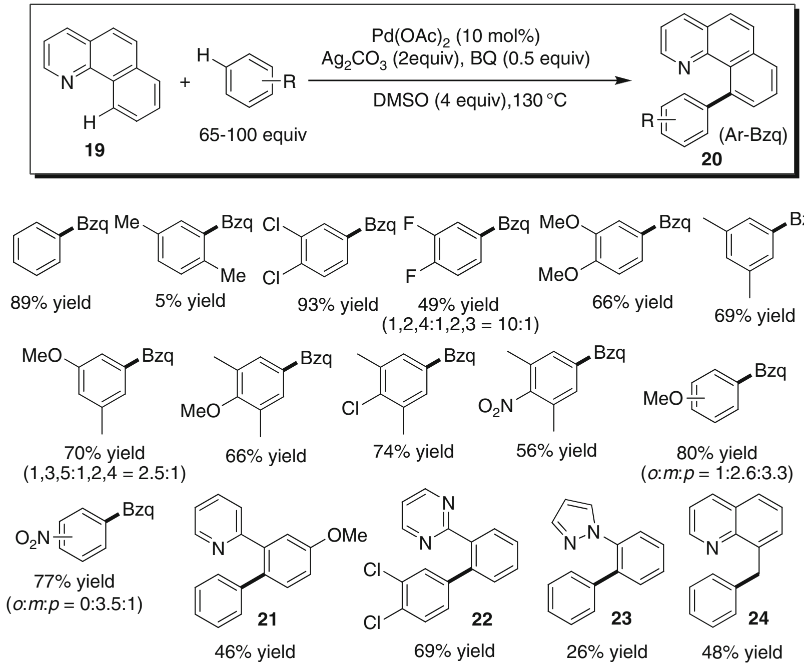
Scheme 18 Pd-catalyzed oxidative cross-coupling of benzofuran with benzene

1 equiv. of $Cu(OAc)_2$ instead of $H_4PMo_{11}VO_{40}$ was used as oxidant, the cross-coupling of *N*-acetyl indole with benzene gave moderate yield with 5:1 (C3/C2) selectivity. They also found that the regioselectivity in the arylation of *N*-acetyl indole can be controllable depending on the oxidant, with $Cu(OAc)_2$ favoring the 3-position or AgOAc the 2-position [66].

3.2 Cross-Coupling Reaction with Directing Group

One useful method to reach an efficient cross-coupling reaction via double C–H bond activation is the introduction of a directing group. The directing group can coordinate with palladium to effect the first C–H activation regioselectively. Then the resulting aryl palladium species will react with another arene, generally present in large excess, to lead to the second C–H activation. The introduction of a directing group and its removal after the coupling reaction generally reduce the synthetic practicality of this approach. However, in many cases, these directing groups are very useful and needed in the synthesis, which makes the cross-coupling reaction with directing group very attractive.

In 2007, Hull and Sanford reported that the oxidative cross-coupling of benzo[*h*]quinoline and simple arenes (as solvent) in the presence of 10 mol% $Pd(OAc)_2$, 2 equiv. of Ag_2CO_3, 0.5 equiv. of benzoquinone, and 4 equiv. of DMSO at 130°C afforded products in up to 93% yield (Scheme 19). The regioselectivity of the first C–H activation was predominantly controlled by proximity to a ligand (benzo[*h*]quinoline). The regioselectivity of the second C–H activation was controlled by steric effects of arenes. For 1,2-disubstituted arenes, cross-coupling proceeded with high selectivity at the less hindered 4-position. In the case of 1,3-di and 1,2,3-trisubstituted arenes, cross-coupling proceeded with high selectivity at the less hindered 5-position. For *p*-xylene, the cross-coupling reaction gave only 5% yield, which may be due to steric hindrance. Pyridine, pyrimidine, and pyrazole can also be used as directing groups to control the first C–H activation (**21**–**24**). Further studies disclosed that the yield and regioselectivity of the reaction were affected significantly by the structure of BQ (benzoquinone). The bulkier BQ, by

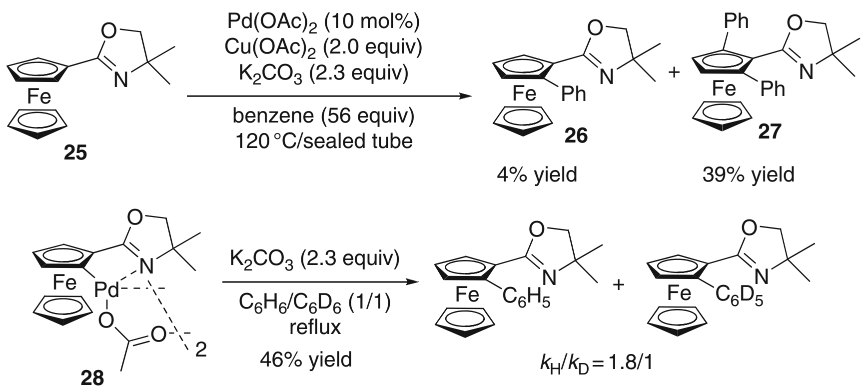


Scheme 19 Pd-catalyzed oxidative cross-coupling of benzo[*h*]quinoline with simple arenes

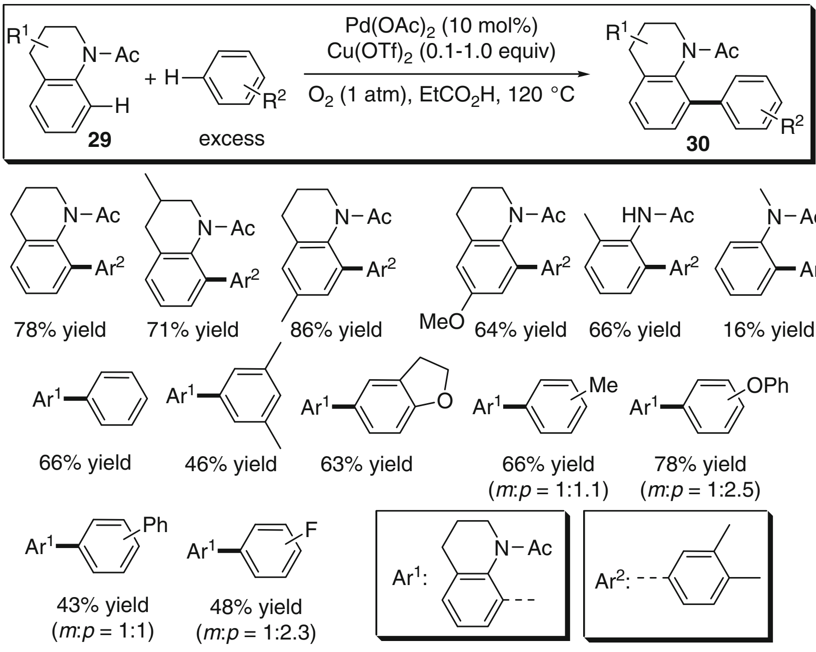
installing methyl group on the BQ, led to a dramatic decrease in coupling at the *ortho*-position of the anisole and a concomitant increase in reaction at the *meta*- and *para*-positions. These results suggest that the BQ ligand is bound to the Pd center during the C–H activation process [67].

Almost at the same time, Xia and You developed a palladium-catalyzed double C–H activation process to synthesize 2-arylferrocenyl oxazoline derivatives [68]. Here the oxazoline was used as a directing group and the oxidative cross-coupling reaction occurred between ferrocenyl oxazoline and a simple arene. In the presence of stoichiometric amounts of $Pd(OAc)_2$, the oxidative cross-coupling of ferrocenyl oxazoline with simple arenes led to products with up to 70% yield. Palladium-catalyzed oxidative cross-coupling of ferrocenyl oxazoline and benzene gave a total 43% yield with the diarylated ferrocene as the major product (Scheme 20). An interesting feature of this method is the excellent diastereoselectivity obtained when enantiopure ferrocenyl oxazolines are used, which introduces the planar chirality easily. Oxazoline is a highly useful functionality in organic synthesis, making this methodology very attractive. Refluxing the ferrocenyl oxazoline palladium acetate dimer complex in benzene led to the coupling product in good yield, suggesting the first C–H activation occurs on the Cp ring. The isotope effect experiment led to the second C–H activation of benzene with a k_H/k_D of 1.8/1.

Simultaneously, Shi and coworkers used an amide as a directing group in the oxidative cross-coupling reaction. Amide was used as a directing group to control

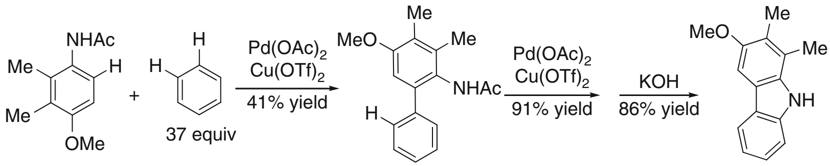


Scheme 20 Pd-catalyzed oxidative cross-coupling of ferrocenyl oxazoline with simple arenes

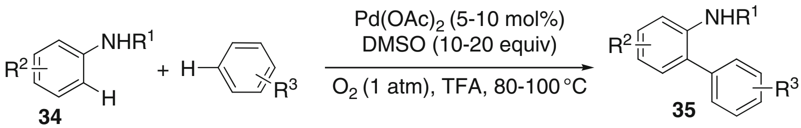


Scheme 21 Pd-catalyzed oxidative cross-coupling of *N*-acetanilides with simple arenes

the first C–H activation [69]. The regioselectivity of the second C–H activation was dependent on the steric hindrance of the arene. Using 10 mol% of $Pd(OAc)_2$ as catalyst, 10–100 mol% of $Cu(OTf)_2$ and oxygen (O_2, 1 atm) as oxidants, and propionic acid as co-solvent, the oxidative cross-coupling product could be isolated in moderate to good yields with high regioselectivities (Scheme 21). This catalytic



Scheme 22 Synthesis of 4-deoxycarbazomycin B from substituted acetanilide and benzene via sequential C–H activation



Scheme 23 Pd-catalyzed oxidative cross-coupling of *N*-acetanilides with simple arenes

system displays an excellent substrate scope with respect to both coupling partners. Remarkably, when NHAc was used as the directing group, a multiple C–H activation process was realized to afford the carbazole structure. As an efficient demonstration, 4-deoxycarbazomycin B (**33**), a degradation product of the natural product carbazomycin B, was synthesized via a sequential oxidative cross-coupling reaction and C–H activation/C–N coupling reaction (Scheme 22).

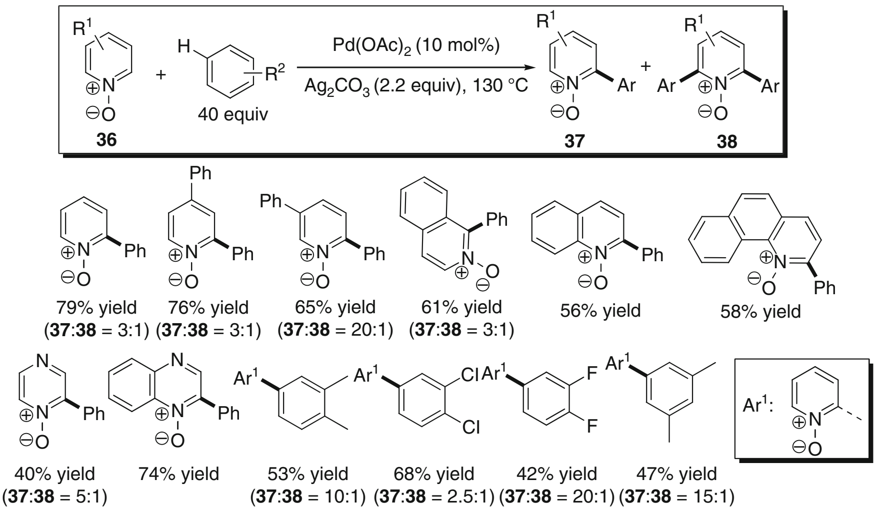
Soonafterward, Buchwald and coworkers reported an efficient Pd-catalyzed oxidative cross-coupling of *N*-acetanilides with simple arenes in a similar manner [70]. In the presence of 5–10 mol% $Pd(OAc)_2$ and 10–20 mol% DMSO, the cross-coupling reaction took place smoothly between anilides and 4–11 equiv. of simple arenes in TFA under an oxygen atmosphere (Scheme 23). The reaction conditions could tolerate a wide range of substrates. The metal-free oxidant represents a great advantage of the current catalytic system.

Recently, Chang and coworkers reported the palladium-catalyzed oxidative cross-coupling reaction between pyridine *N*-oxides and simple arenes [71]. It is debatable to assign pyridine *N*-oxides to the category of directing group despite the fact that a palladium complex bound to oxygen has been isolated after treatment of $PdCl_2(PPh_3)_2$ with pyridine *N*-oxide. Nevertheless, during their studies on the Pd-catalyzed alkenylation of pyridine *N*-oxide, 2-phenylpyridine *N*-oxide was produced as a side product when the reaction was carried out in benzene at 130°C. After screening various conditions, they found general oxidative cross-coupling conditions: arenes (40 equiv.), $Pd(OAc)_2$ (10 mol%), and Ag_2CO_3 (2.2 equiv.) at 130°C. Under these conditions, the oxidative cross-coupling products were obtained with high regioselectivity in good yields (Scheme 24).

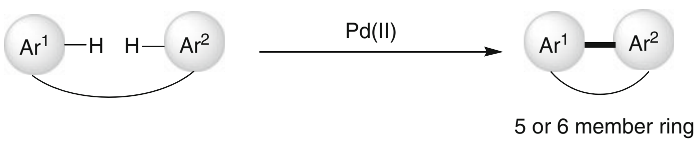
4 Pd-Catalyzed Intramolecular Aryl–Aryl Bond Formation via Double C–H Activation

The intermolecular oxidative coupling of two different arenes has to face the challenge of regioselectivity. Strategies to solve this issue include the introduction of a directing group with the proximal control and the use of substrates with preferential position towards electrophilic attack. Nevertheless, the regioselectivity is still a big challenge for the intermolecular oxidative cross-coupling reaction. However, the aryl–aryl bond formation reaction via intramolecular double C–H activation would have a much better situation due to the favorable formation of five (or six) member ring that directs the regioselectivity (Scheme 25). In this regard, the Pd-catalyzed aryl–aryl bond formation reaction via intramolecular double C–H activation provides a very efficient method for the synthesis of dibenzofurans and carbazoles.

Since the intermolecular oxidative coupling of benzene to biphenyl using stoichiometric amounts of $PdCl_2$ was first described by van Helden and Verberg in 1965 [41], the intramolecular oxidative coupling of two arenes mediated by a palladium catalyst to synthesize cyclic compounds has also attracted great attention.



Scheme 24 Pd-catalyzed oxidative cross-coupling of pyridine *N*-oxides with simple arenes



Scheme 25 The synthesis of cyclic structures via oxidative cross-coupling reaction

More than three decades ago, Itanani and coworkers reported that the intramolecular oxidative coupling of diphenyl ether in the presence of $Pd(OAc)_2$, acetylacetone, and oxygen afforded dibenzofurans along with dimers of diphenyl ether [72, 73]. The yield of dibenzofuran obtained was up to 10,400% based on the reacted palladium acetate (104 TON). In 1975, Åkermark and coworkers reported that the corresponding intramolecular oxidative coupling products were obtained in high yields when diphenyl ether, diphenylamine, benzophenone, and benzanilide were heated in acetic acid with a stoichiometric amount of $Pd(OAc)_2$ [74]. However, diphenyl sulfide failed to yield the cyclized product.

Since then, a series of intramolecular oxidative coupling reactions between two arenes have been reported. This method was extensively used to synthesize many naturally occurring carbazoles (for reviews see [75, 76]), as shown in Table 2. However, most of these transformations are carried out in the presence of stoichiometric or substoichiometric amounts of palladium acetate.

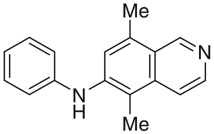
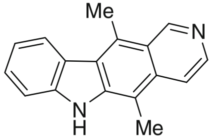
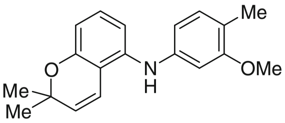
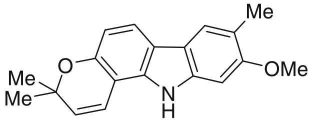
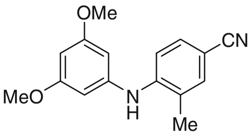
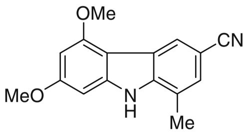
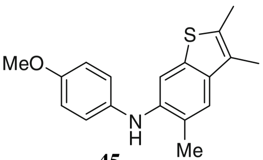
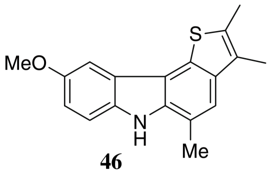
In 1999, Åkermark and coworkers reported an efficient Pd-catalyzed intramolecular oxidative coupling reaction with oxygen as the sole oxidant. A series of heterocyclic compounds were synthesized in moderate to good yields under mild conditions. The oxidative coupling of very reactive substrates such as diphenylamine requires only palladium acetate as catalyst, while a more electrophilic catalyst such as palladium trifluoroacetate together with tin(II) acetate is necessary for less reactive systems like diphenyl ether and benzanilide [86]. The ring closure of benzanilide led to the formation of six-membered ring in a reasonable yield (60%, entry 7, Table 3). This catalytic system works also well for the intramolecular oxidative coupling of 2-arylamino-1,4-quinones to carbazoloquinones in good yields, which will not be discussed in detail in this chapter (see also [87–91]).

Rebeccamycin (**59**) and its family members are potent antitumor agents. Wang and coworkers have developed a practical synthesis of the rebeccamycin aglycone and related analogs by an intramolecular oxidative cyclization of bisindolylmaleimides ([92]; see also [93, 94]). Using air as the stoichiometric oxidant, with 5 mol% $Pd(OAc)_2$ and 100 mol% $Cu(OAc)_2$, the oxidative cyclization of the corresponding bisindolylmaleimides provided the rebeccamycin aglycone and related indolo[2,3-a]pyrrolo[3,4-c]carbazoles in 58–88% yields (Scheme 26). The method was operationally simple with very general substrate scope. In addition, the practicality of the current method was proved by the synthesis of **61a** over 3 kg in 81% yield from readily available starting materials.

In 2007, Fujii, Ohno and their coworkers developed an efficient one-pot Buchwald–Hartwig *N*-arylation and oxidative coupling reaction to synthesize carbazoles (Scheme 27) [95]. Typically, Pd-catalyzed *N*-arylation of anilines with aryl triflates was conducted in toluene under the standard conditions. After completion of the *N*-arylation as determined by TLC, acetic acid was added and an oxygen balloon was connected to the reaction flask (oxygen conditions) or it was subjected to air by an open system (air conditions). The protocol afforded various types of functionalized carbazoles in good to excellent yields (46–>99%).

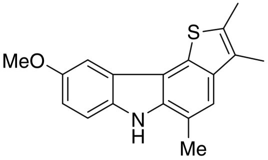
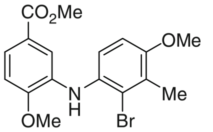
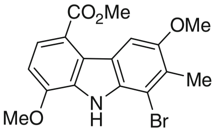
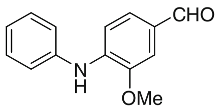
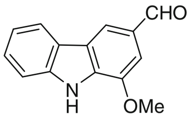
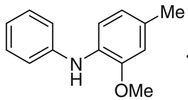
Since 1979, Itahara and coworkers have reported that the $Pd(OAc)_2$-mediated intramolecular oxidative coupling of *N*-aroylindole and *N*-aroylpyrrole gave

Table 2 Synthesis of carbazoles via intramolecular oxidative coupling of two arene C–H bonds

Substrates	Conditions	Products	Yield (%)	References
 **39**	$Pd(OAc)_2$ 10% TFA/HOAc	 ellipticine **40**	15–25	[77]
 **41**	$Pd(OAc)_2$ DMF, reflux	 pyrayafoline A **42**	–	[78]
 **43**	2.0 equiv. $Pd(OAc)_2$ AcOH, reflux, 1 h	 **44**	55	[79]
 **45**	0.5 equiv. $Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, 120 °C, 7 h	 **46**	30	[80]

(*continued*)

Table 2 (continued)

Substrates	Conditions	Products	Yield (%)	References
 **47**	$Pd(OAc)_2$ dioxane/HOAc (3:1) 100 °C, 40 h	 **48**	43	[81, 82]
 **49**	1.5 equiv. $Pd(OAc)_2$ HOAc 160 °C, 12 h	 **50**	73	[83]
 murrayanine **51**	1.2 equiv. $Pd(OAc)_2$ HOAc 140 °C, 10 h	 **52**	71	[83]
51	2.0 equiv. $Pd(OAc)_2$ DMF (3 drops) microwave, 600 W, 1 min	**52**	71	[84]

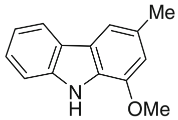
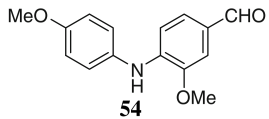
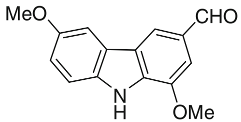
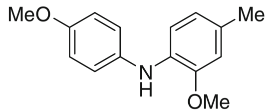
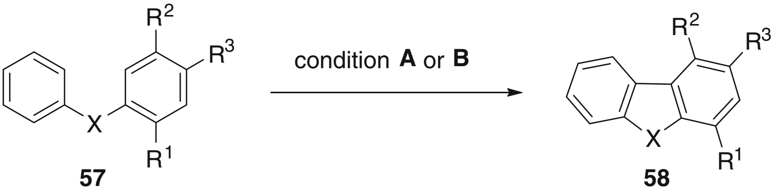
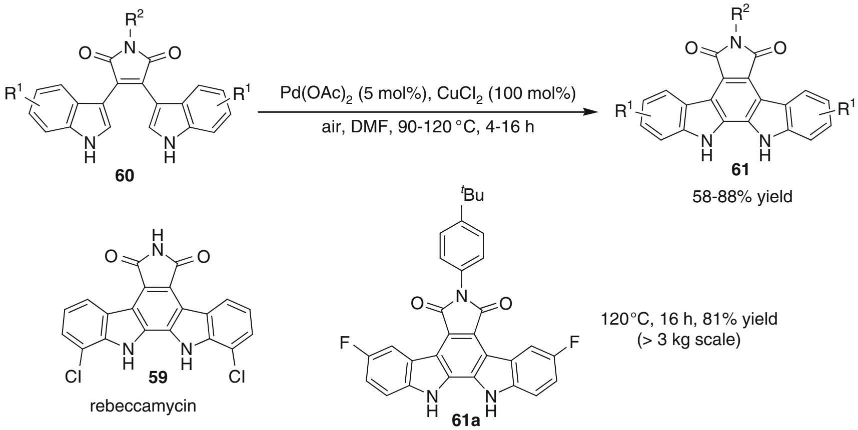
 murrayafoline A **53**	1.2 equiv. $Pd(OAc)_2$ HOAc (3:1) 90 °C, 36 h	 **54**	80	[85]
 6-methoxymurrayanine **55**	1.2 equiv. $Pd(OAc)_2$ HOAc 140 °C, 10 h	 **56**	72	[85]

Table 3 Pd-catalyzed oxidative cyclization of aryl amines, aryl ethers, and benzanilide[a]



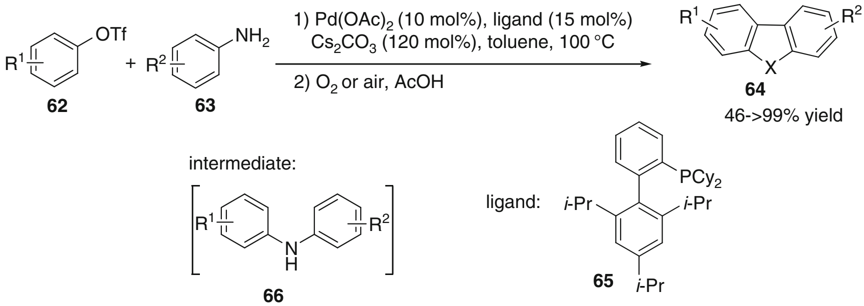
Entry	R^1	R^2	R^3	X	Condition[a]	T(°C)/t(h)	Yield (%)
1	H	H	H	NH	**A**	90/14	61
2	H	H	H	NH	**B**	87/14	66
3	H	H	H	O	**B**	116/48	60
4	NO_2	H	H	NH	**B**	116/50	80
5	H	CHCHCHCH		NH	**B**	85/12	30
6	OEt	H	H	NMe	**B**	25/10	–[b]
7	H	H	H	CONH	**B**	116/60	60

[a]Condition **A**: 5 mol% $Pd(OAc)_2$ in acetic acid under oxygen atmosphere; Condition **B**: 5 mol% $Pd(TFA)_2$ and 10 mol% $Sn(OAc)_2$ in acetic acid under oxygen atmosphere
[b]The product is unstable under the reaction conditions

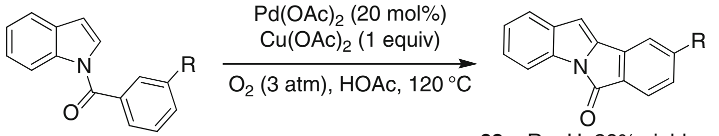


Scheme 26 Pd-catalyzed intramolecular oxidative cyclization of bisindolylmaleimides

relatively low yields [96–99]. Notably, Boger and Patel successfully completed the total synthesis of prodigiosin by utilizing a Pd(II)-promoted intramolecular oxidative coupling of pyrroles [100]. Polymer-supported $Pd(OAc)_2$ was found to be most effective to conduct the cyclization. In 2007, DeBoef and coworkers reported a catalytic version of this reaction (Scheme 28). The oxidative cyclization of *N*-benzoylindole led to the isolation of the product in only 29% yield. However, when an electron-donating group was added to the tethered arene, 82% yield of the cross-coupling product was obtained [65].



Scheme 27 Pd-catalyzed one-pot *N*-arylation and oxidative cyclization



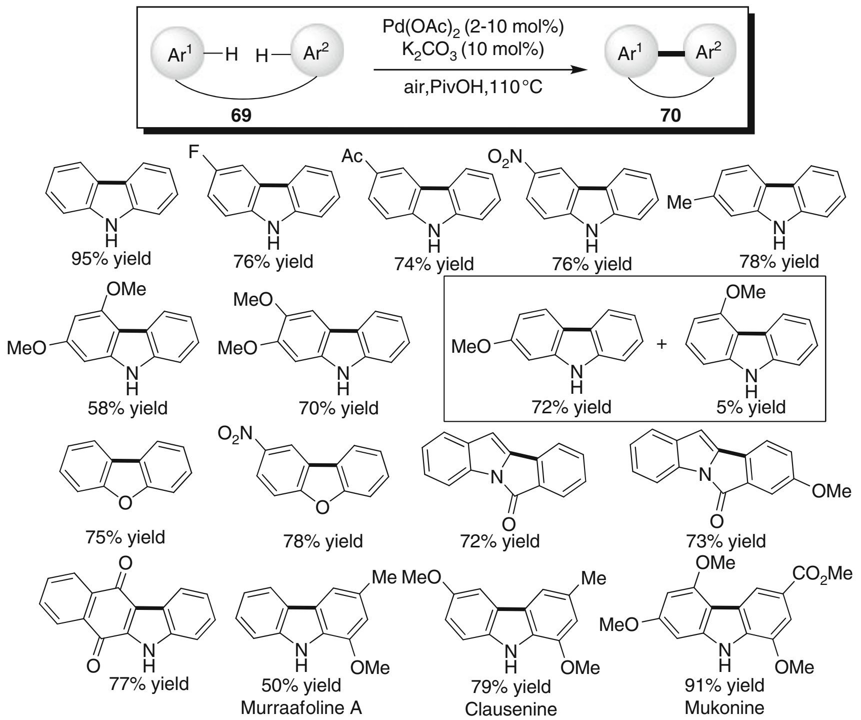
Scheme 28 Pd-catalyzed oxidative cyclization of *N*-aroylindole

More recently, Fagnou and coworkers developed an efficient catalytic system to synthesize carbazoles through a Pd(II)-catalyzed intramolecular oxidative coupling reaction [101]. In the presence of 2–10 mol% $Pd(OAc)_2$ and 10 mol% K_2CO_3, biaryls were obtained in good to excellent yields under air at ambient pressure (Scheme 29). The use of pivalic acid as the reaction solvent, instead of acetic acid, resulted in greater reproducibility, higher yields, and broader substrate scope. Detailed mechanistic studies disclosed some of the side reactions in acetic acid that result in low yields for electron-rich arenes. With the newly developed reaction conditions, three natural carbazoles, Murrayafoline A, Clausenine, and Mukonine, were synthesized in good yields.

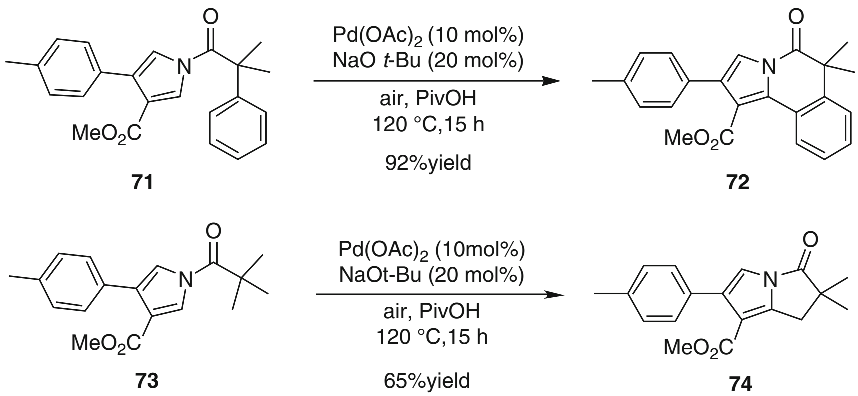
Very recently, Liégault and Fagnou reported that intramolecular oxidative coupling of compound **71** afforded the six-membered heterocyclic compound **72** in 92% yield using 10 mol% $Pd(OAc)_2$ and NaO*t*-Bu (Scheme 30). The reaction proceeded through the coupling between pyrrole C–H and benzene C–H, offering the facile synthesis of six-membered ring. Interestingly, under the same conditions, oxidative coupling of compound **73** gave compound **74** in which a new sp^2–sp^3 bond was formed through double C–H activation [102].

5 Conclusion and Perspective

Biaryl synthesis constitutes one of the most important subjects in organic synthesis. The recently developed direct arylation reactions for the formation of aryl–aryl bonds have emerged as very attractive alternatives to traditional cross-coupling



Scheme 29 Pd(II)-catalyzed intramolecular oxidative cyclization for the synthesis of carbazoles



Scheme 30 Pd(II)-catalyzed intramolecular oxidative coupling of pyrrole derivatives

reactions. Particularly, the direct arylation through double C–H activation allows the use of the simple arenes as both coupling partners. The aryl–aryl bond formation via double C–H activation is superior to the traditional transition-metal-catalyzed cross-coupling by using much cheaper starting materials, reducing waste, and featuring high atom economy. With enormous efforts from many research groups, Pd-catalyzed biaryl synthesis via double C–H activation has led to very efficient methods such as the homocoupling biaryl synthesis, cross-coupling biaryl synthesis of substrates with directing group, and intramolecular oxidative coupling, particularly for carbazole synthesis.

Despite of the promising features of palladium-catalyzed biaryl synthesis via double C–H activation, there remain many difficulties to be solved. To date, all the reported processes have relatively low turnover number. Some of the reactions are even reported with (sub)stoichiometric palladium catalyst and are at the proof of concept stage, which leaves the current methods a long way to go to reach the practicality required for industrial application. In addition to the low reactivity, regioselectivity is another big challenge for the intermolecular oxidative coupling of two arenes. Although this can be partially solved by using a directing group with the proximal control or the use of substrates with a preferential position towards electrophilic attack, a general strategy to control the regioselectivity with respect to both the coupling partners is still highly desirable but unknown. Moreover, the use of excess metal salts as the oxidant leaves the reaction with heavy wastes and difficulties to workup.

The development of C–H activation for cross-coupling reactions has been advanced rapidly. Extensive efforts have been devoted to the mechanistic studies in this field to shed light on the mechanism. The use of oxygen or air as sole oxidant has been successfully realized in a palladium-catalyzed cross-coupling reaction involving C–H activation. We have the right to believe that palladium-catalyzed double C–H activation would be a good alternative for the synthesis of biaryls. With further improvements in catalyst turnover, selectivity, and oxidant, the method should ultimately be able to find industrial applications.

6 Experimental: Selected Procedures

Synthesis of Compound 1-(8-(3,4-Dimethylphenyl)-3,4-dihydroquinolin-1(2*H*)-yl)-ethanone [69]

$Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $Cu(OTf)_2$ (22.0 mg, 0.06 mmol), and *N*-acetyl-1,2,3,4-tetrahydroquinoline (52.5 mg, 0.3 mmol) were weighed in air and added to an oven-dried 25-mL Schlenk tube. The septum-sealed tube was evacuated and refilled with O_2 three times. EtCOOH (1.5 mL) and *o*-xylene (191.0 mg, 1.8 mmol) were added, and the mixture was stirred at 120 °C under oxygen (1 atm) until the substrate was completely consumed. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (80 mL). The organic phase was washed with water (2 × 30 mL) and saturated Na_2CO_3 (30 mL) and dried over $MgSO_4$. The solvent was removed, and the residue was subjected to flash column chromatography with ethyl acetate/petroleum ether (1:10) as eluent to obtain the desired product 1-(8-(3,4-dimethylphenyl)-3,4-dihydroquinolin-1(2*H*)-yl)-ethanone (65.0 mg, 78% yield).

6.1 Synthesis of Compound 2,3-Dimethoxycarbazole [101]

3,4-Dimethoxydiphenylamine (0.5 mmol), $Pd(OAc)_2$ (3 mol%), K_2CO_3 (10 mol%), and pivalic acid (450 mg) are weighed in air and transferred into a test tube (1.2 × 10 cm^2). The uncapped test tube is placed in an oil bath and the mixture is stirred under air at the indicated temperature and for the required time. The solution is then cooled to rt, diluted with CH_2Cl_2, washed with a saturated aqueous solution of Na_2CO_3, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product is purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:4) as eluent to afford the corresponding coupling product 2,3-dimethoxycarbocarbazole (79.5 mg, 70% yield).

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Palladium-Catalyzed Allylic C–H Bond Functionalization of Olefins

Guosheng Liu and Yichen Wu

Abstract Transition metal-mediated carbon–hydrogen bond cleavage and functionalization is a mechanistically interesting and synthetically attractive process. One of the important cases is the removal of a allylic hydrogen from an olefin by a Pd^{II} salt to yield a π-allylpalladium complex, followed by nucleophilic attack to efficient produce allylic derivatives. In contrast to the well-known allylic acetoxylation of cyclohexene, the reaction of open-chain olefins is fairly poor until recent several years. Some palladium catalytic systems have been reported to achieve allylic C–H functionalization, including acetoxylation, amination and alkylation of terminal alkenes. In the most of cases, ligand is crucial to the success of the transformation. This review surveys the recent development of palladium-catalyzed allylic C–H functionalziation of alkenes. These results promise a significant increase in the scope of olefin transformation.

Keywords Palladium-catalyzed • Allylic C–H bond activation • Unactivated olefin • π-allylpalladium • Oxidative functionalization

Contents

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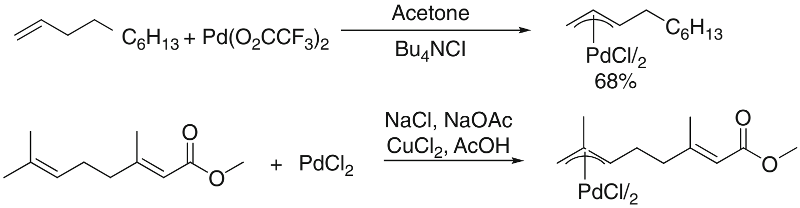
1 Introduction and Background

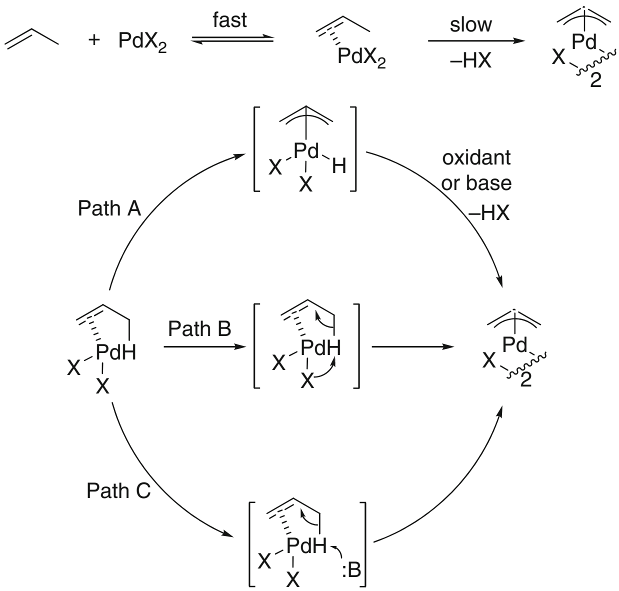
Transition metal-mediated carbon–hydrogen bond cleavage and functionalization is a mechanistically interesting and synthetically attractive process. One of the early examples is the removal of an allylic hydrogen from an olefin by a Pd^{II} salt to yield a π-allylpalladium complex, which most often serves as an electrophilic intermediate in catalytic reactions to form new allylic carbon–carbon and carbon–heteroatom bonds. A large number of reaction conditions have been described for the direct conversion of alkenes into π-allylpalladium complexes, the most direct and versatile route [1, 2]. Among them, one of the most useful methods for the formation of π-allylpalladium complexes was reported by Trost and coworkers, which involve treatment at room temperature of an acetone solution of the equal amount of alkene and $Pd(O_2CCF_3)_2$ [3]. The initially generated relatively unstable trifluoroacetate complex is converted into the chloride by tetrabutylammonium chloride. Alternatively, unactivated alkene treated by $PdCl_2$, sodium chloride, sodium acetate and $CuCl_2$ could also provide the corresponding π-allylpalladium complexes. The weak oxidant $CuCl_2$ has been proved to be an important role to enhance the reaction yield (Scheme 1) [4].

Generally, it is accepted that the formation of π-allylpalladium complexes proceeds through fast, reversible π-complexation of the alkenes to Pd, and subsequent rate-determining allylic hydrogen abstraction (Scheme 2) [5]. Several different pathways have been proposed and debated for the hydrogen removal step [4, 6–9]. For instance, Trost and coworkers suggested that insertion of palladium into the allylic C–H bond gives a π-allylpalladium hydride intermediate, which could react with oxidant or base to produce π-allylpalladium (path a) [4]. However, this mechanism (path a) was not consistent with the studies of the kinetic isotopic effect, reported by Beak and coworkers [7, 8]. The large KIE values (3.5–5.45) imply that the reaction prefers a mechanism involving the removal hydrogen of allyl by internal base (path b) [6–8]. In addition, the conversion of π-alkene palladium species to π-allylpalladium by external weak inorganic base, carried out by Ketley and Braatz, indicates that the abstraction of allylic hydrogen by external base is also possible (path c) [9].

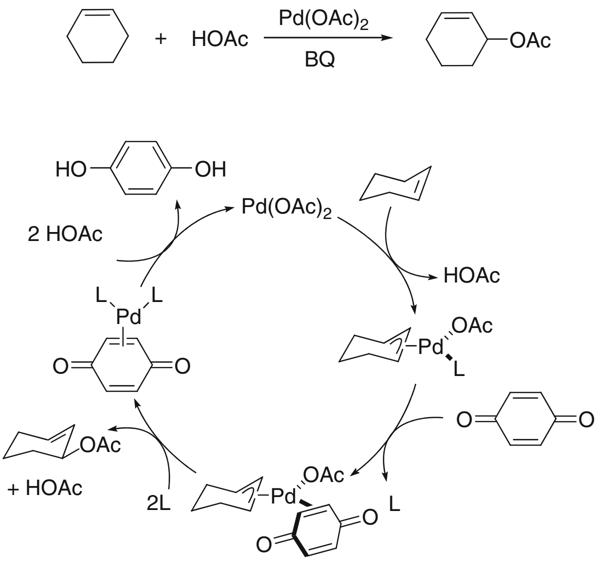
Since the first example of catalytic reaction of palladium-catalyzed allylic acetoxylation was reported by Haszeldine and coworkers in 1966 [10], cyclohexene has been a benchmark substrate for this kind of reactions under different oxidative conditions, which are well documented in reviews and books [11, 12]. The proposed mechanism for allylic acetoxylation of cyclohexene is illustrated in



Scheme 1 π-allylpalladium complexes from Pd-mediated Allyl C–H activation of alkenes



Scheme 2 Proposed mechanism for π-allylpalladium complexes formation



Scheme 3 Proposed mechanism for Pd-catalyzed allylic acetoxylation of cyclohexene

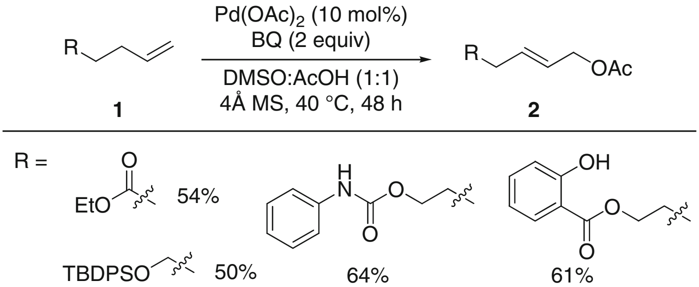
Scheme 3: Pd^{II}-mediated activation of the allylic C–H bond of alkenes generates a π-allylpalladium intermediate. Coordination of benzoquinone (BQ) to the Pd^{II} center promotes nucleophilic attack by acetate on either end of the allylic fragment, which yields cyclohexenyl acetate and releases a Pd^0 species. In this catalytic cycle, BQ is required as an oxidant for the Pd^0 reoxidation, as well as a promoter (a π-acid) for the nucleophilic attack reaction [13]. However, the earlier palladium-catalyzed allylic C–H carboxylation reactions have been limited to cyclic olefins until the selective allylic acetoxylation of terminal alkenes was reported. This chapter surveys the development of homogenous palladium-catalyzed allylic C–H functionalization to construct C–C and carbon–heteroatom bonds.

2 Oxidative Conditions for Allylic C–H Functionalization of Alkenes

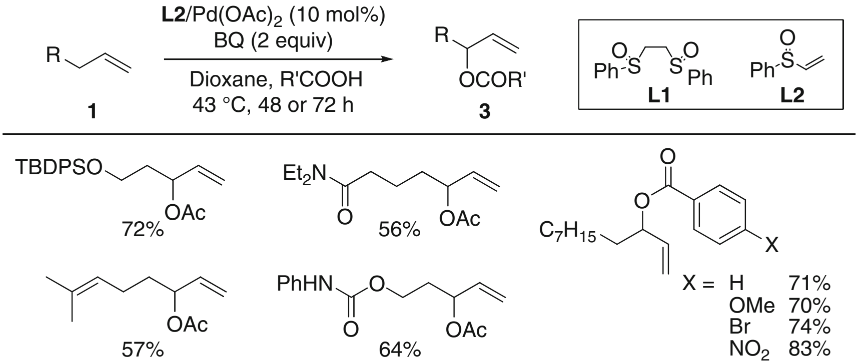
Although the palladium-catalyzed allylic acetoxylation of cyclic alkenes has been extensively studied, reactions of open-chain internal alkenes afforded allylic acetates with fairly poor selectivity, and terminal alkenes predominantly underwent Wacker oxidation to yield ketones or vinyl acetates. Recent studies show that the addition of a ligand to the previous Pd^{II}/BQ system dramatically switches the reactivity and selectivity of terminal alkenes. Several efficient catalytic systems have been reported to perform palladium-catalyzed allylic acetoxylation reactions of terminal alkenes, as well as oxidative allylic amination and alkylation. Those reactions proceed very well to give corresponding allylic C–H functionalized products with good to excellent selectivity. Mechanistic studies suggest that those ligands are crucial for the allylic C–H bond activation to generate π-allylpalladium complex.

3 Pd^{II}/BQ System for Allylic Acetoxylation

In the palladium-catalyzed aerobic oxidation, dimethyl sulfoxide (DMSO) is demonstrated as an important additive/solvent to promote the reoxidation of Pd^0 species (for palladium catalyzed aerobic cyclization in DMSO, see [14–17]; for the mechanistic studies, see [18, 19]). White and coworkers recently found that when DMSO was introduced to the typical Pd^{II}/BQ catalytic system, the reaction of monosubstituted alkenes **1** afforded the corresponding linear (*E*)-allylic acetates **2** with high regio- and stereoselectivity (Scheme 4) [20]. The reaction is proposed to proceed via a π-allyl intermediate, and the addition of DMSO suppresses the Wacker oxidation via sulfoxide ligation to palladium. Further ligand screening revealed when sulfoxide **L1** was used as ligand in dioxane, the reactions of **1** dramatically switched the regioselectivity to give the branched allylic ester **3** with high regioselectivity. After the decomposition of **L1** to generate **L2** *in situ* was discovered, the **L2**/Pd^{II} was tested and found to be another effective catalytic system to promote the oxidation reaction (Scheme 5) [21]. For monosubstituted olefins with various functional groups, the reaction can selectively afford branched allylic acetate products with excellent regioselectivity. Mechanistic studies suggest



Scheme 4 DMSO promoted intermolecular allylic acetoxylation of terminal alkenes

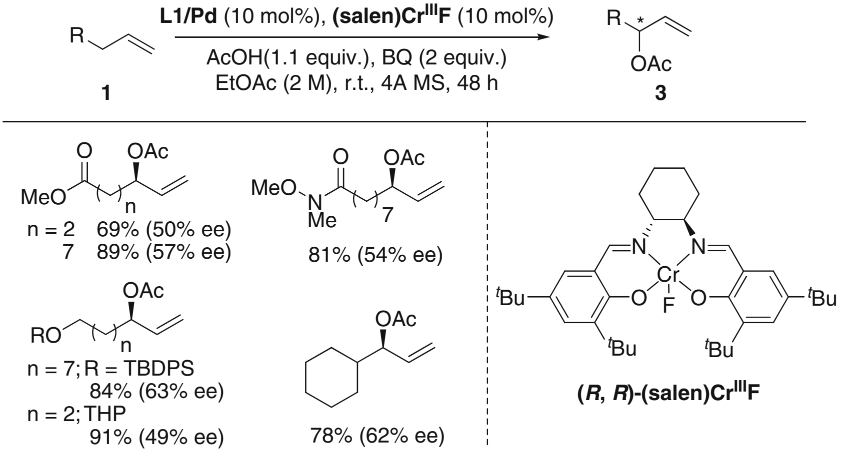


Scheme 5 Pd-catalyzed intermolecular allylic acetoxylation of terminal alkenes

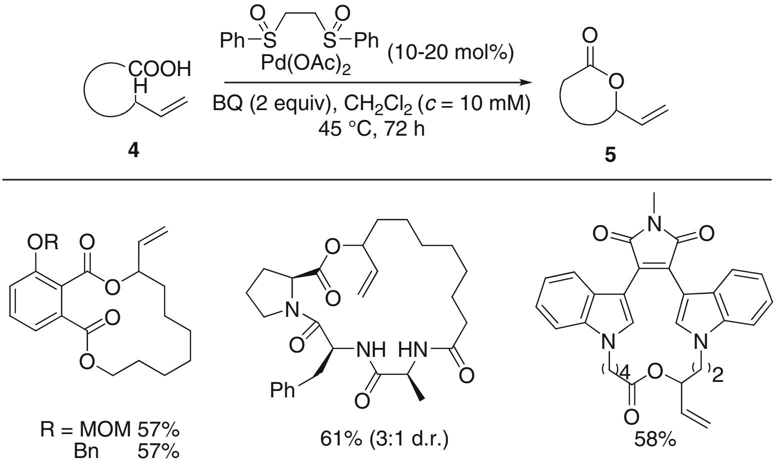
that sulfoxide and vinyl moieties of **L2** are essential to promote the C–H activation. Similar to the early studies, BQ plays not only the role of an oxidant but also that of a π-acid in effecting the reductive elimination.

Very recently, White and coworkers introduced the chiral Lewis acid Cr^{III}(salen) as cocatalyst into **L1**/Pd^{II} catalytic system. The oxidative allylic acetoxyaltion of terminal olefins **1** afforded the corresponding branched allylic acetates **3** in high regioselectivity and moderate enantio-selectivities (up to 63% *ee*) (Scheme 6) [22]. The asymmetric induction possibly results from the coordination between Cr^{III}(salen) and BQ, and the adduct of Cr^{III}(salen)·BQ promotes the acetoxylation of π-allyl-palladium complex to form enantioenriched branched allylic acetates.

After exploring intermolecular reactions, White and coworkers utilized complex **L1**/Pd^{II} to catalyze the intramolecular oxidative cyclization of **4** to synthesize the macrolide **5** with moderate yield and good regioselectivity (Scheme 7) [23]. Further studies on substrate scope demonstrated that this catalytic system was compatible with various carboxylic acids as nucleophiles, such as aryl acids, vinylic and alkyl acids, leading to the generation of 14- to 19-membered macrolides with remarkable levels of selectivity.

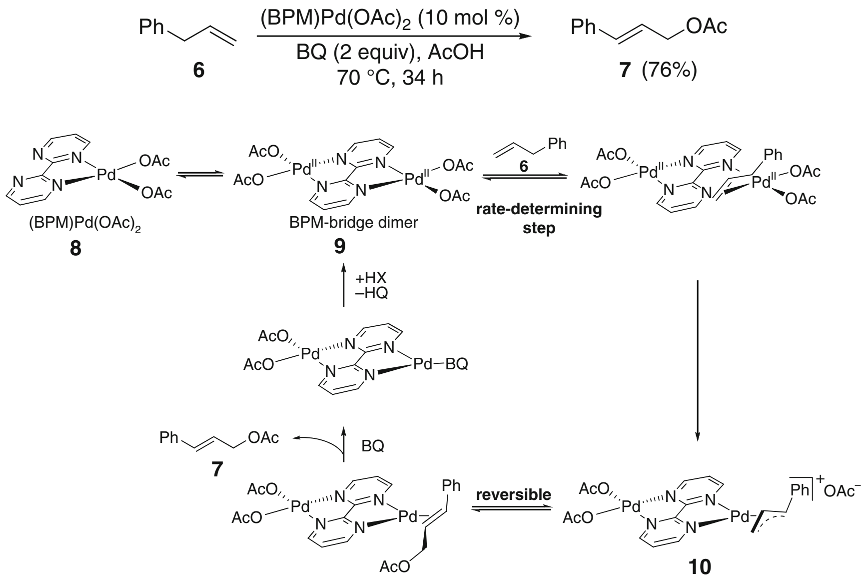


Scheme 6 Pd-catalyzed enantioselective allylic acetoxylation of terminal alkenes

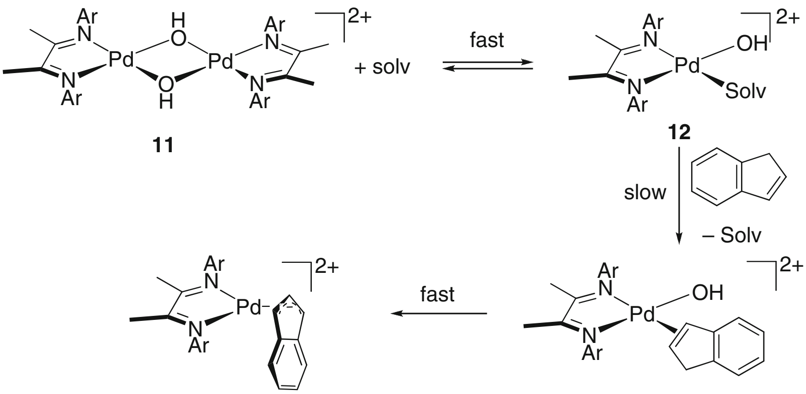


Scheme 7 Pd-catalyzed intramolecular allylic acetoxylation for macrolides synthesis

Bercaw and coworkers reported that bipyrimidine (BPM) could also improve the $Pd(OAc)_2$-catalyzed allylic acetoxylation in acetic acid solution (Scheme 8) [24]. For terminal olefins **6**, the reactions gave the linear allylic acetates **7** as major product in good yields. The mechanistic investigations suggest that the bipyrimidine-bridged dimer **9** generated from disproportionation of $(BPM)Pd(OAc)_2$ **8** would be expected to weaken a Pd–N bond and thus faciliate the coordination to olefin; the Pd-olefin adduct subsequently undergoes allylic C–H activation to form the π-allylpalladium intermediate **10**, followed by a reversible acetate attack to generate the linear allylic acetoxylated product **7**. In this reaction, olefin coordination rather than C–H activation is the rate-determining step.



Scheme 8 (BMP)Pd(OAc)$_2$-catalyzed intermolecular acetoxylation of terminal alkenes



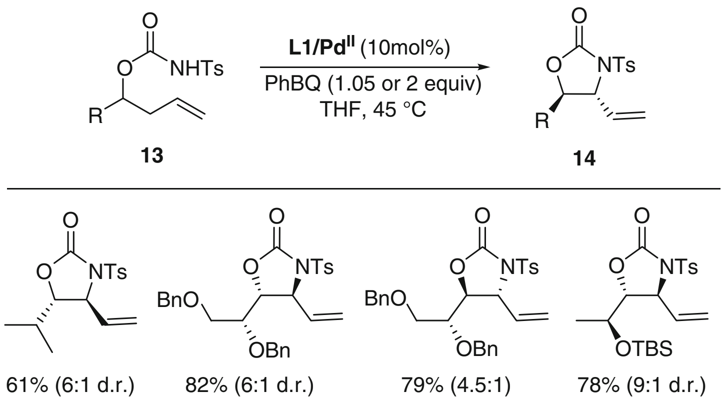
Scheme 9 Proposed mechanism for Pd-catalyzed C–H bond activation of indene

Similar to the bipyrimidine palladium complex, Bercaw and coworkers demonstrated that hydroxy-bridged dimers $[\{(\text{diimine})\text{Pd(OH)}\}_2]^{2+}$ **11** could also effect activation of the allylic C–H bond [25]. Mechansitic studies revealed that the solvent (trifluoroethanol or MeOH) assisted dissociation of dimer **11** to monocationic monomer **12**, followed by the rate-limiting π-coordination of indene to palladium center, and finally by fast C–H activation (Scheme 9).

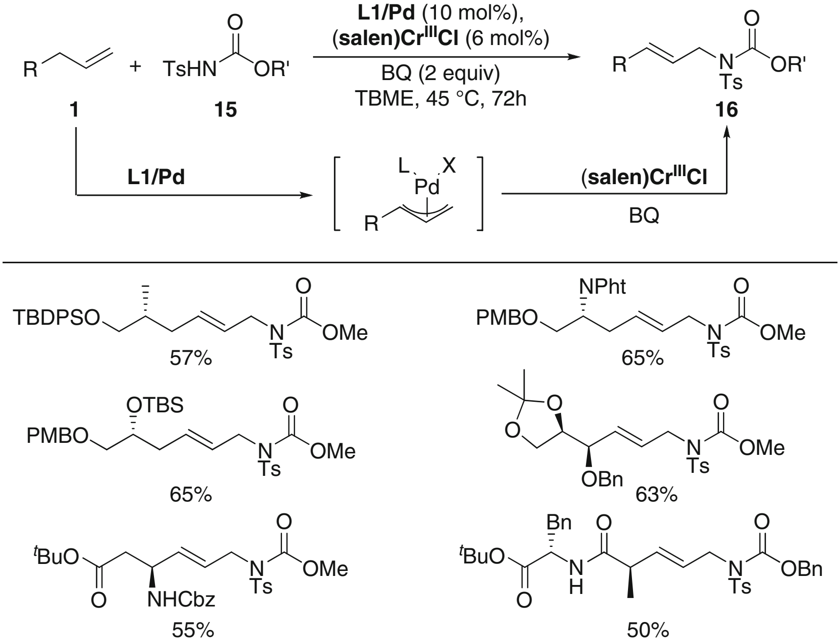
4 Sulfoxide/Pd^{II}/BQ System for Allylic Amination

In comparison to the oxidative allylic carboxylation, the palladium-catalyzed allylic amination has been less successful in previous studies. This is because the oxidative amination of alkenes almost exclusively proceeds through an aminopalladation pathway due to the strong coordination between Pd^{II} and amines or amides. Only a single example of palladium-catalyzed oxidative intramolecular allylic C–H amination was reported by Larock and coworkers [26]. Recently, the **L1**/Pd catalytic system was also demonstrated for oxidative allylic amination. White and coworkers reported a palladium-catalyzed intramolecular allylic amination with weak nitrogen nucleophiles (*N*-tosyl carbamates) as key to avoid the aza-Wacker products. A variety of chiral homoallylic *N*-tosyl carbamate substrates **13** reacted in the presence of the sulfoxide/Pd^{II} catalyst to give the corresponding chiral oxazolidinone products **14** with good selectivities (Scheme 10) [27]. Those products could be easily converted to useful *syn*-1,2-amino alcohols and other derivatives in a few steps.

Employing a similar strategy, the *N*-tosyl carbamate nucleophile **15** was tested in the intermolecular reaction. White and coworkers found that the linear (*E*)-allylamine products **16** were obtained with high regioselectivity in the intermolecular reaction of **1** catalyzed by a heterobimetallic system **L1**/Pd/Cr^{III}(salen) (Scheme 11) [28]. Using BQ as the oxidant, both **L1**/Pd and Cr^{III}(salen) are essential in this allylic oxidative amination. Cr^{III}(salen) is proposed to enhance the π-acidity of BQ in order to promote the functionalization after C–H cleavage by the **L1**/Pd complex. Chiral substrates could also undergo this type of amination to afford the corresponding product with no erosion in *ee*.



Scheme 10 Pd-catalyzed intramolecular allylic oxidative amination



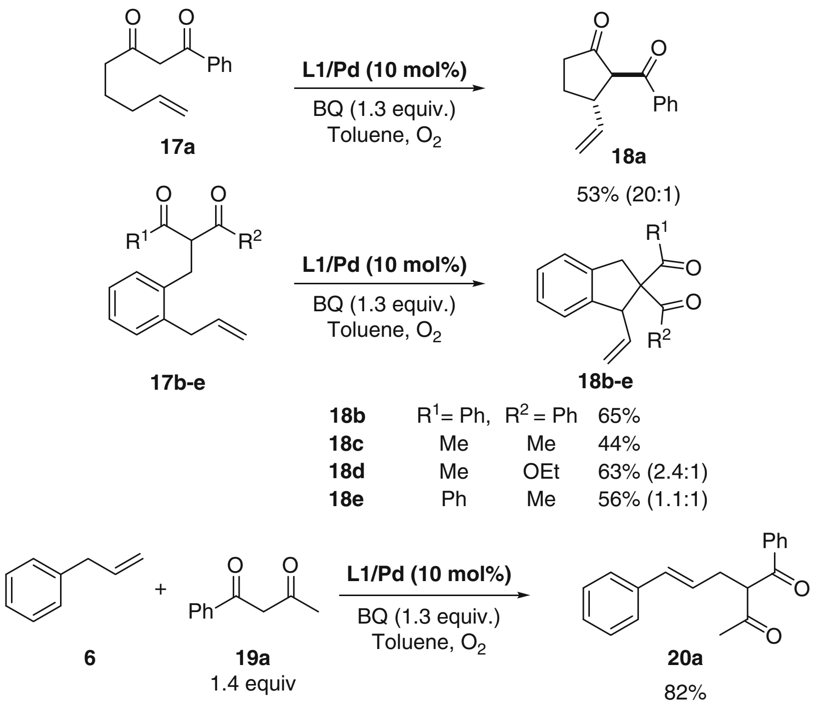
Scheme 11 Heterobimetallic system for intermolecular allylic oxidative amination

5 Sulfoxide/Pd^{II}/BQ System for Allylic Alkylation

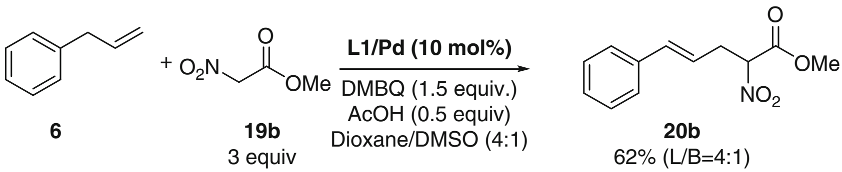
Following the streamlining of allylic oxidation, Shi and coworkers demonstrated that the direct coupling of a carbon nucleophile with a terminal olefin via allylic C–H alkylation could be achieved with the bis(sulfoxide)/Pd^{II}/BQ catalyst system [29]. Intramolecular reactions were performed using aromatic and aliphatic allylic substrates **17a–e**. However, only aromatic allylic substrates could give the good results in the intermolecular reactions with **19a** (Scheme 12). Simultaneously, White and coworkers reported an intermolecular allylic alkylation of allylarene with an excess of nitro-based carbon nucleophile **19b** [30]. It is worth noting that either omitting AcOH or adding stoichiometric Bu_4NOAc significantly diminishes the reactivity (Scheme 13).

6 Pd^{II}/O_2 System for Allylic Functionalization

As mentioned above, BQ is required for the promotion of nucleophilic attack on the Pd-allyl fragment, as well as for the reoxidation of Pd^0, which implies that the reaction might not proceed via the direct dioxygen-coupled turnover without BQ.



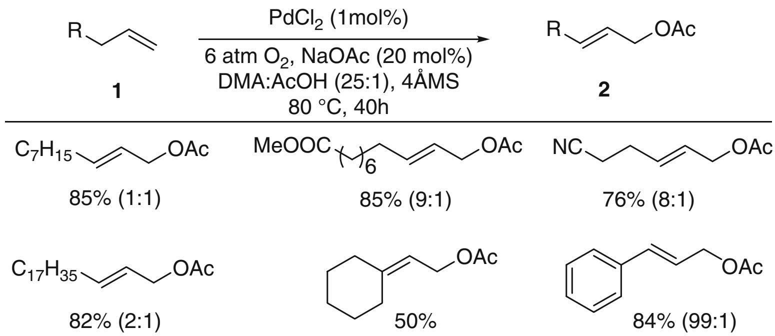
Scheme 12 Pd-catalyzed intra- and intermolecular allylic alkylation



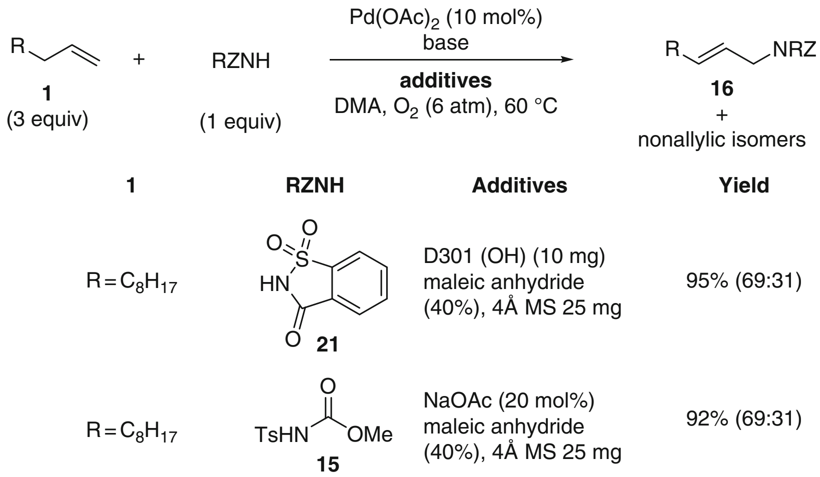
Scheme 13 Pd-catalyzed intermolecular allylic alkylation

Kaneda and coworkers reported the catalytic system for the aerobic oxidative allylic acetoxylation of terminal alkenes **1** under BQ-free condition (Scheme 14) [31]. *N*,*N*-Dimethylacetamide (DMA) is proved to be the best solvent to improve the reoxidation of Pd^0 by dioxygen due to the amide ligation to palladium, which is similar to DMSO. In this catalytic system, many olefins **1** with sensitive functional groups (ester, nitrile, or acetal groups) could give the linear allylic acetates **2** in good yields with high regioselectivity. High pressure of O_2 (6 atm) was required to achieve these results due to the rate-determining reoxidation of Pd^0. Very importantly, those results revealed that BQ is not required for functionalization of π-allylpalladium intermediates.

This BQ-free aerobic catalytic system also worked well for the allylic amination reported by Liu and coworkers (Scheme 15) [32]. The palladium-catalyzed



Scheme 14 Pd-catalyzed intermolecular aerobic allylic acetoxylation of terminal alkenes
*Values in parenthesis are the ratios of E/Z isomer

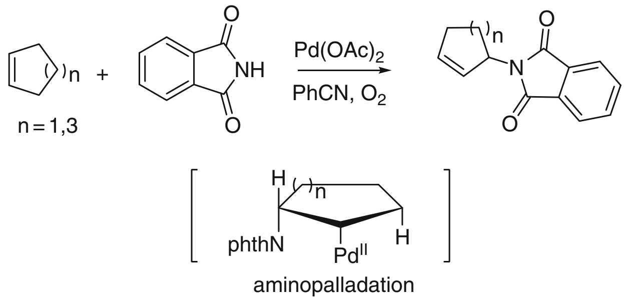


Scheme 15 Pd-catalyzed intermolecular aerobic allylic amination of terminal alkenes

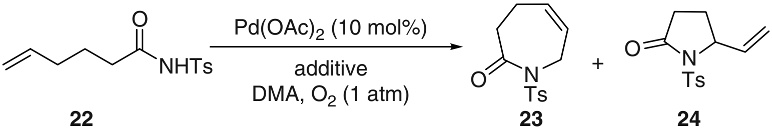
intermolecular aerobic oxidative allylic amination of terminal alkenes **1** with *N*-tosyl carbamate **15** (or saccharin **21**) afforded the linear allylamine derivatives **16** with high regioselectivities, combined with nonallylic isomers as minor products. The fact that the addition of maleic anhydride increased the reaction yield suggests that maleic anhydride plays a role as a ligand similar to that of BQ to promote the nucleophilic attack. It is also noteworthy that both amide-type solvent and the high pressure O_2 are essential for achieving high catalytic turnover.

Furthermore, Stahl and coworkers reported the oxidative amination of cyclic olefin (such as cyclopentene, cycloheptene) to afford cyclic allylic amine product. However, this reaction proceeds via *cis*-aminopalladation/β-hydride elimination pathway, rather than allylic C–H activation (Scheme 16) [33].

Very recently, Liu and coworkers reported a palladium-catalyzed intramolecular aerobic oxidative allylic amination of unactivated alkenes [34]. The reaction of **22**



Scheme 16 Pd-catalyzed aerobic oxidative amination of cyclic olefins



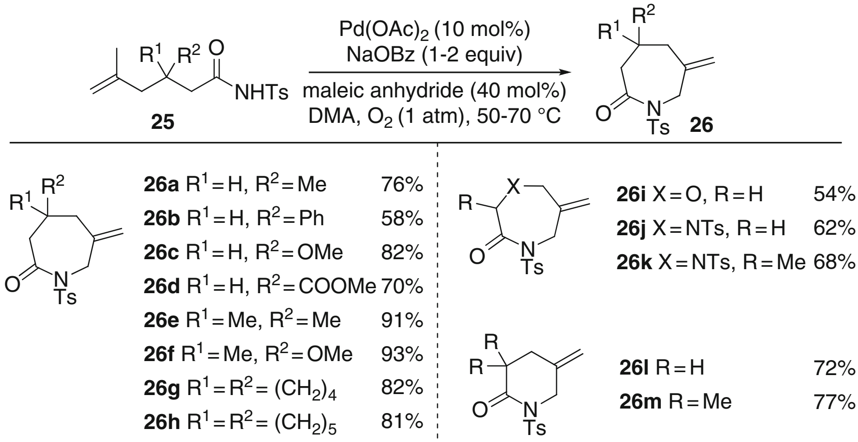
entry	additive	yield (**23**:**24**)
1	none	20% (<3:97)
2	NaOBz (100 mol%)	44% (82:18)
3	NaOBz (100 mol%), 4 Å MS (15 mg), MA (40 mol%)	91% (86:14)
4	(salen)Cr(III)Cl (10 mol%)	65% (<3:97)
5	NaOBz (100 mol%), (salen)Cr(III)Cl (10 mol%)	54% (80:20)

Scheme 17 Pd-catalyzed intramolecular aerobic oxidative allylic amination

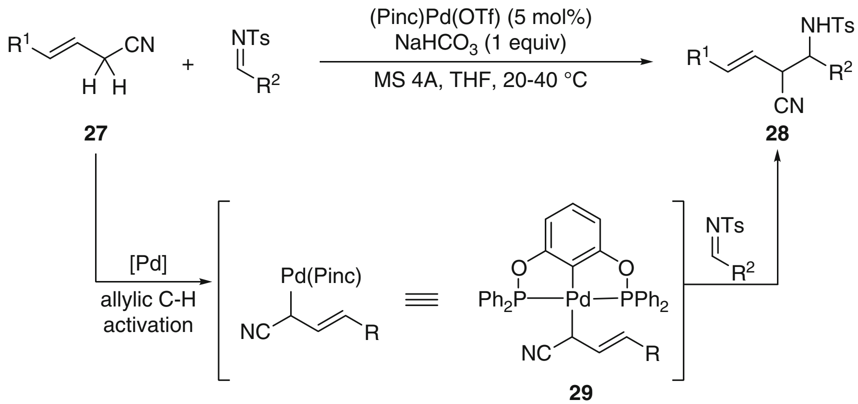
afforded five-membered cyclic amide **24** with good yield in the presence of Cr (salen). Interestingly, the addition of Brønsted base significantly modulated the reaction's regioselectivity to give seven-membered ring **23** as the major product (Scheme 17). Furthermore, substrate **25**, which features one methyl group at internal carbon of olefin, afforded seven-member products **26** as sole product with good yield (Scheme 18). Evidence obtained from the reaction of deuterium labeled substrates strongly supports the fact that the reaction proceeds through a rate-determining allylic C–H activation/irreversible reductive elimination pathway to form the C–N bond.

7 Nonoxidative Conditions for Allylic C–H Functionalization

All of the reactions described above were conducted under oxidative conditions, because the reoxidation of Pd^0, product from nucleophilic attack, is needed to complete the catalytic cycle. However, Szabó and coworkers reported a



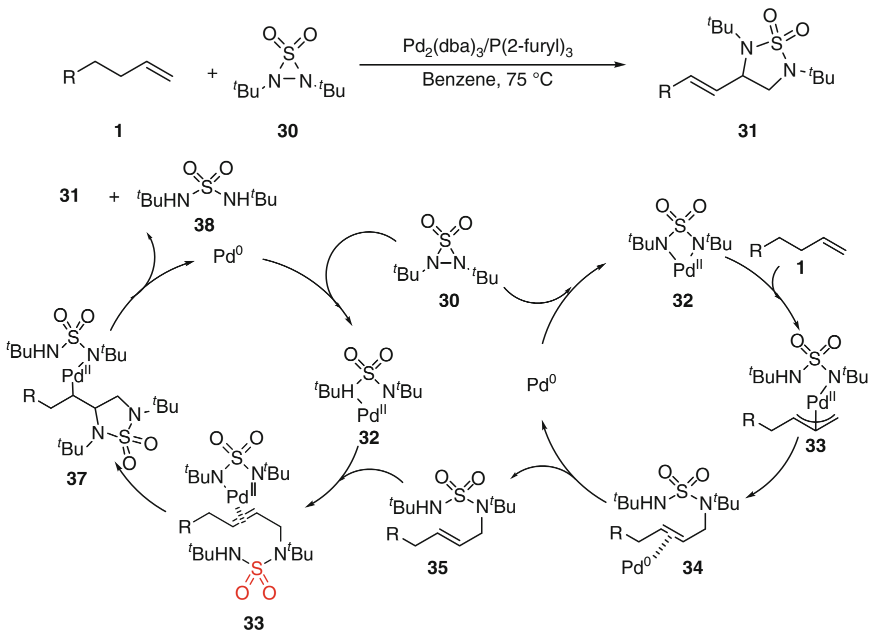
Scheme 18 Pd-catalyzed regioselecitve allylic amination



Scheme 19 Pd-catalyzed coupling reaction between allylic nitrile and imine

palladium-pincer complex that acts as catalyst for C–C coupling of allyl nitriles **27** with tosyl imines under nonoxidative conditions. The reaction proceeds with high regioselectivity to afford homoallylic amine derivatives **28**. The coupling reaction was proposed to involve the coordination of the allyl cyanide to the pincer complex giving rise to the η^1-allylpalladium complex **29** with tridentate pincer architecture, which serves as a nucleophile to react with imines (Scheme 19) [35].

In addition, Shi and coworkers demonstrated that the allylic C–H bond of terminal alkenes **1** could be activated by the Pd^{II} complex generated from oxidative addition of Pd^0 to di-*tert*-butyldiaziridinone **30** [36]. The subsequent nucleophilic attack at [(π-allyl)Pd] complex **33** gives allyl sulfamide **34** and regenerates the Pd^0 catalyst after reductive elimination. Coordination between **32** and **35** formed **36**,



Scheme 20 Pd-catalyzed diamination of terminal alkenes

which then undergoes a Pd^{II}-catalyzed cyclization and β-hydride elimination to afford **31** and release the Pd^0 species (Scheme 20).

8 Conclusion

Palladium-catalyzed oxidative allylic C–H functionalization provides attractive methods for the transformations of olefins, and their utility can be further enhanced by the development of more effective ways to use molecular oxygen (or air) to promote the catalytic cycle. The results outlined in this chapter summarize significant progress in the coupling reaction between terminal alkene and various types of nucleophiles. Further studies will be directed to explorations of the scope of nucleophilic reagents and olefins, and elucidation of the mechanisms of those reactions. Such studies will play an important role in the ongoing development of Pd-catalyzed C–H bond activations.

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Ruthenium-Catalyzed Direct Arylations Through C–H Bond Cleavages

Lutz Ackermann and Rubén Vicente

Abstract Stoichiometric cycloruthenation reactions of substrates containing Lewis-basic functionalities set the stage for efficient ruthenium-catalyzed C–H bond functionalization reactions. Thereby, selective addition reactions of C–H bonds across alkenes or alkynes enabled atom-economical synthesis of substituted arenes. More recently, ruthenium-catalyzed direct arylation reactions were examined, which display an unparalleled scope and, hence, represent economically and environmentally benign alternatives to traditional cross-coupling chemistry.

Keywords Arylations • Catalysis • C–H bond functionalization • Chelation • Hydroarylation • Ruthenium

Contents

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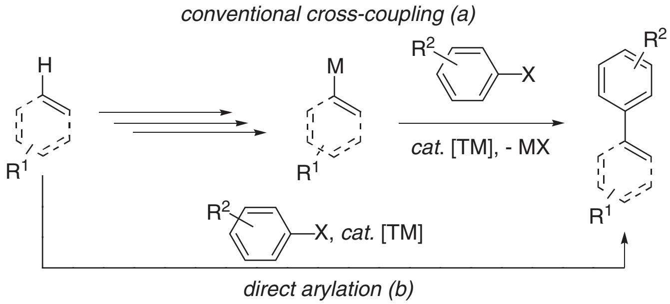
Abbreviations

Ac	Acetyl
Ad	Adamantyl
Bz	Benzoyl
cat	Catalytic
cod	1,4-Cyclooctadiene
Cp	Cyclopentadienyl
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DG	Directing group
DMA	*N*,*N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
dr	Diastereomeric ratio
equiv	Equivalent
(HA)SPO	(Heteroatom substituted) secondary phosphine oxide
i-Pr	*Iso*-propyl
Mes	Mesityl
NMP	*N*-Methyl-2-pyrrolidinone
rac	Racemic
t-Bu	*tert*-Butyl
THF	Tetrahydrofuran
TM	Transition metal
Ts	4-Methyl benzenesulfonyl

1 Introduction

Biaryls are key substructures of compounds with activities of relevance to various research areas, ranging from synthetic chemistry and biology to material sciences. Their syntheses rely strongly on transition metal-catalyzed coupling reactions, which have matured to being among the most powerful tools for the formation of $C(sp^2)–C(sp^2)$ bonds [1–3]. These methodologies proceed regioselectivity because, predominantly, two functionalized starting materials are employed, namely organic (pseudo)halides as electrophiles and organometallic reagents as nucleophiles (Scheme 1a). However, the use of organometallic nucleophiles in stoichiometric amounts gives rise to the formation of stoichiometric amounts of undesired byproducts, which ought to be avoided from an ecological and economical viewpoint. Furthermore, these organometallic reagents are often not commercially available or rather expensive, and their syntheses from arenes involve further chemical transformations, which generate additional byproducts. Consequently, focus has shifted in recent years to the development of direct functionalization reactions of C–H bonds for more sustainable arylation strategies [4–19]. Indeed, the organometallic starting materials can be replaced by unfunctionalized nucleophilic (hetero)arenes (Scheme 1b) in



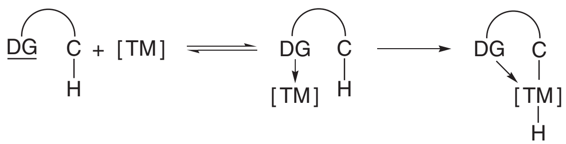
Scheme 1 Conventional cross-coupling (**a**) vs direct arylation (**b**)

these transformations, which overall constitutes an ecological sound alternative to traditional cross-coupling chemistry.

In contrast to conventional cross-coupling strategies, substrates for direct arylations commonly do not bear a single reactive functionality, but display various C–H bonds with comparable dissociation energies. Therefore, the regioselective functionalization of a specific C–H bond in any given substituted arene represents one of the prime challenges for achieving synthetically meaningful intermolecular direct arylations [20].

When electronic effects dominate the reactivity of an aromatic substrate, regioselectivities can be accomplished in intermolecular direct arylation reactions. Thus far, this approach proved predominantly applicable to the functionalization of heteroarenes with the aid of either palladium- [21], copper-, or rhodium-catalysts [22–27].

An alternative strategy for controlling regioselectivity in direct arylations in an overall intermolecular fashion is based on the use of, potentially removable, directing groups (DG). Here, Lewis-basic functionalities coordinate to transition metal complexes, which sets the stage for entropically favored intramolecular C–H bond cleavages, leading to cyclometalated intermediates (Scheme 2) [28–30]. It should, however, be kept in mind that some of these transformations do not necessarily proceed through precoordination by the functional group to the transition metal, but might be the result of thermodynamic reaction control [31].

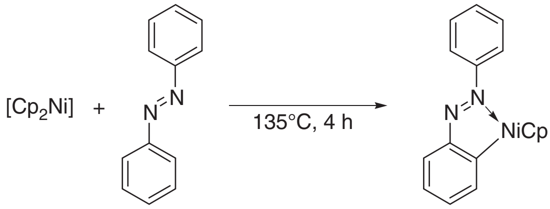


Scheme 2 Regioselective intermolecular C–H bond functionalization through the use of directing groups (DG)

1.1 Stoichiometric Cyclometalation Reactions

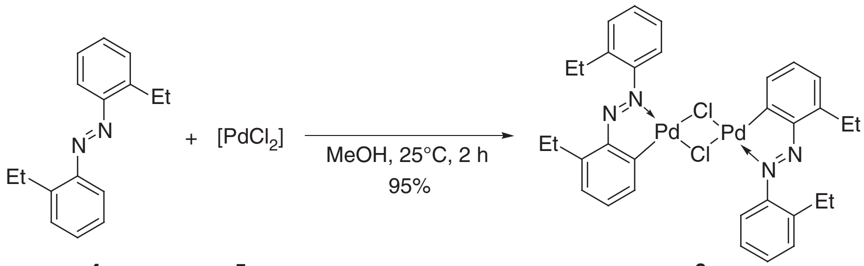
In 1963, an early example [32] of the stoichiometric metalation of a specific C–H bond via the direction by a Lewis-basic functionality was disclosed by

Kleiman and Dubeck at Ethyl Corporation Research Laboratories [33]. Thus, dicyclopentadienylnickel (**1**) was shown to give rise to cyclometalated complex **3**, when being heated in the presence of diazobenzene (**2**) (Scheme 3).



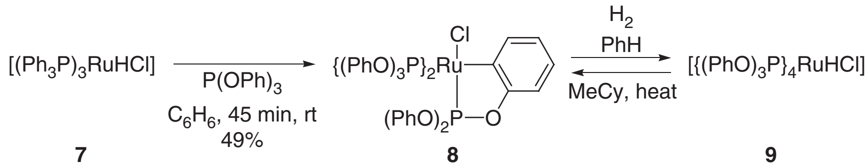
Scheme 3 Synthesis of cyclonickelated complex **3**

Subsequently, Cope and coworkers studied the use of palladium and platinum compounds for chelation-assisted stoichiometric C–H bond functionalizations [34, 35]. Importantly, cyclometalations of diazobenzene derivatives proceeded readily at ambient temperature (Scheme 4). Furthermore, competition experiments revealed that C–H bond functionalizations with tertiary *N*,*N*-dimethyl amines occurred even more rapidly than the ones of diazobenzenes.



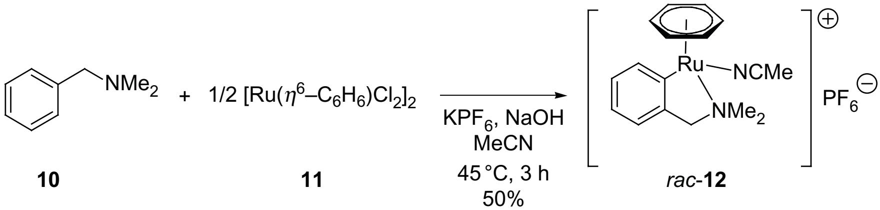
Scheme 4 Preparation of homobimetallic palladium complex **6** via C–H bond functionalization

During the 1960s, a number of transition metal complexes derived from tertiary phosphines were reported to exhibit interactions between the metal atom and C–H bonds of the phosphine ligands ([28]; for a selected example, see [36]). In contrast, an example of cycloruthenation of relevance for catalytic processes made use of phosphite ruthenium complexes. Thus, Knoth and Schunn [37, 38] as well as Robinson and coworkers [39, 40] disclosed independently that ruthenium hydrido complex **7** and a triaryl phosphite yielded cyclometalated species **8** at ambient temperature through elimination of molecular hydrogen (Scheme 5). Interestingly, the formation of [{(PhO)$_3$P}$_4$RuHCl] (**9**) and its selectively deuterated analog [{(2,6-D$_2$C$_6$H$_3$O)$_3$P}$_4$RuDCl] using H_2 or D_2, respectively, was briefly exploited for a catalytic deuteration of phenol [38].



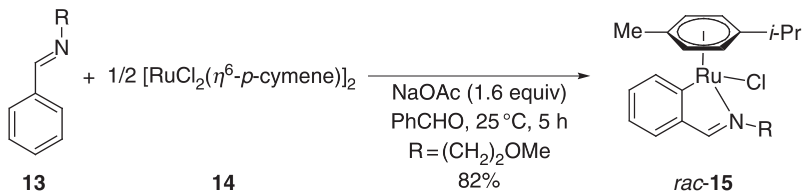
Scheme 5 Formation of cyclometalated ruthenium complex **8**

Cyclometalations with ruthenium complexes proved not to be restricted to phosphorus-based Lewis-basic functionalities, but a variety of nitrogen-containing substrates were employed as starting materials for stoichiometric metalation reactions as well [28]. For example, diazobenzene (**2**) was regioselectively functionalized through chelation-assistance in high yields employing $[Ru(CO)_3Cl_2]_2$ [41, 42]. Further, particularly the use of 2-pyridyl-substituted arenes attracted significant attention for the preparation of cycloruthenated complexes because of their valuable photochemical and photophysical properties ([43–45]; for representative additional examples of the preparation of ruthenacycles, see [46, 47]). During studies directed towards the application of cyclometalated ruthenium complexes to organic synthesis [48], Pfeffer and coworkers disclosed results on optimization studies for effective intermolecular metalation reactions with various Lewis-basic DGs [49]. Specifically, the addition of KPF_6 in stoichiometric amounts was found to be beneficial, since it gave rise to monocationic solvent-stabilized complex $[RuCl(\eta^6\text{-}C_6H_6)(MeCN)_2]^+$. The improved reactivity of this species in stoichiometric metalation reactions was reflected by efficient cyclometalations of various arenes (Scheme 6), as well as stoichiometric functionalizations of $C(sp^3)$–H bonds.



Scheme 6 Efficient preparation of monocationic ruthenacycle *rac*-**12**

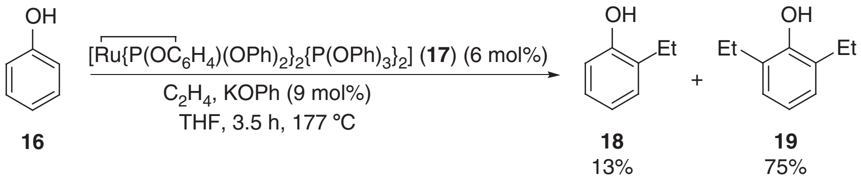
Furthermore, a protocol for base-assisted metalation reactions proved viable through the use of stoichiometric amounts NaOAc, which enabled the synthesis of cyclometalated iridium, rhodium and ruthenium complexes (Scheme 7) [50].



Scheme 7 Base-assisted formation of ruthenacycle *rac*-**15**

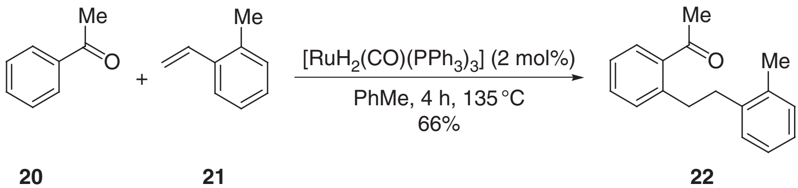
1.2 Ruthenium-Catalyzed Hydroarylation Reactions

Stoichiometric cycloruthenation reactions, as well as the early example of catalytic deuteration of phenol (see above) [38] served for the development of efficient catalytic strategies for C–C bond formations through C–H bond functionalizations. Indeed, ruthenium-catalyzed atom-economical [51] addition reactions of arenes onto C–C multiple bonds, hydroarylations [52–57], were found to be very useful. In an early example, Lewis and Smith disclosed a regioselective alkylation of phenol through in situ formation of its phosphite, and subsequent directed C–H bond functionalization (Scheme 8) [58].



Scheme 8 Ruthenium-catalyzed alkylation of phenol (**16**)

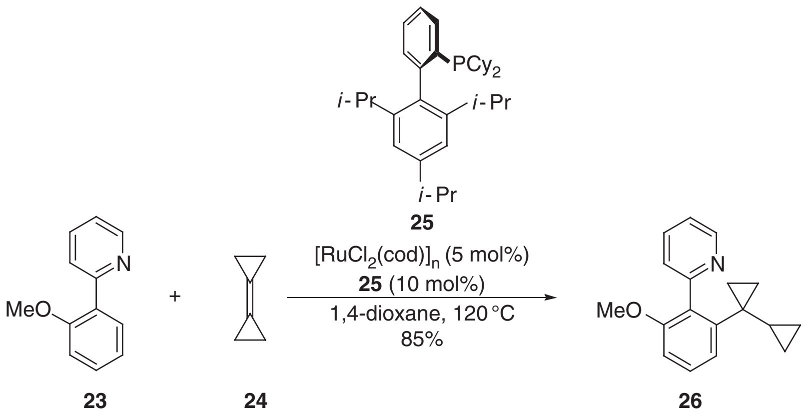
While this protocol relied on the in situ generation of the relevant phosphite for catalytic hydroarylation reactions, Murai and coworkers developed effective methodologies for the direct use of Lewis-basic substrates, such as acetophenone **20** (Scheme 9) [18, 59]. Thereby, regioselective ruthenium-catalyzed anti-Markovnivkov alkylations and alkenylations were accomplished using alkenes or alkynes [60] as substrates, respectively. Recently, an extension of this protocol to terminal alkynes was reported, which involved a phosphine ligand-free catalytic system (see below), along with stoichiometric amounts of a peroxide [61].



Scheme 9 Ruthenium-catalyzed alkylation of ketone **20**

The remarkable selectivity of ruthenium complexes in catalytic addition reactions of C–H bonds onto C–C multiple bonds was recently highlighted by hydroarylations of highly strained methylenecyclopropanes, which occurred with ring conservation. Hence, a catalytic system comprising $[RuCl_2(cod)]_n$ and ligand **25** enabled highly selective additions of arenes, and proved even applicable to the use of bicyclopropylidene (**24**) as substrate (Scheme 10) [62].

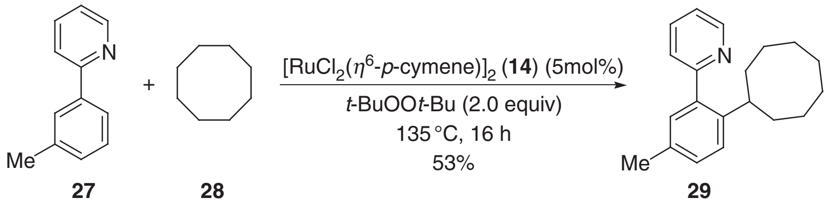
In contrast, stoichiometric amounts of peroxides were recently employed by Li and coworkers to accomplish ruthenium-catalyzed oxidative functionalizations of



Scheme 10 Ruthenium-catalyzed hydroarylation of bicyclopropylidene (**24**)

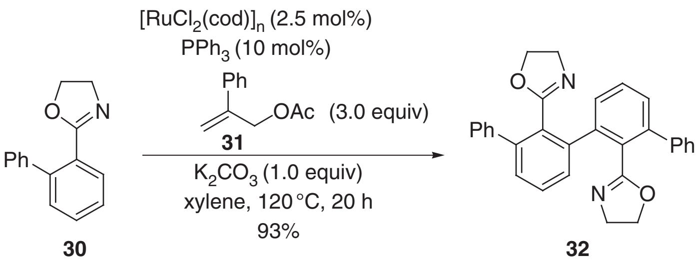
arenes (Scheme 11). This chelation-assisted alkylation represents a promising alternative to hydroarylation chemistry, and constitutes a less common example of ruthenium-catalyzed functionalizations of challenging C(sp^3)–H bonds [63].

Oxidative arylations were also achieved with stoichiometric amounts of allylic acetates as terminal oxidants. Interestingly, the nature of the DG as well as of the allylic



Scheme 11 Ruthenium-catalyzed oxidative alkylation of arene **27**

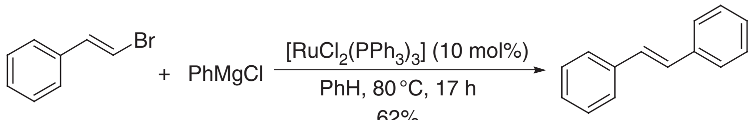
acetate strongly affected the outcome of this process. Thus, 2-pyridyl-substituted arenes yielded predominantly the cross-coupling product [64], whereas oxazolines and azoles were oxidatively homocoupled in the presence of phenallyl acetate **31** as terminal oxidant (Scheme 12) [65].



Scheme 12 Ruthenium-catalyzed oxidative homocoupling with phenallyl acetate (**31**) as oxidant

2 Ruthenium-Catalyzed Direct Arylation Reactions

The formation of $C_{(hetero)aryl}$–$C_{(hetero)aryl}$ bonds through catalytic cross-coupling chemistry is largely dominated by the use of palladium and nickel complexes, while catalysts derived from, among others, copper, cobalt or iron salts, can be applied for select transformations [1]. In contrast, ruthenium-catalyzed traditional cross-coupling reactions between organometallic reagents and organic halides are scarce, with Murahashi's report on cross-couplings between Grignard reagents and alkenyl bromide **33** representing one such example (Scheme 13) [66].

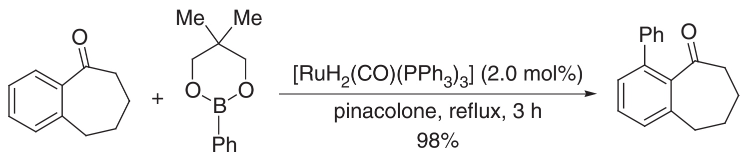


Scheme 13 Ruthenium-catalyzed traditional cross-coupling with Grignard reagent **34**

2.1 Direct Arylations with Organometallic Reagents

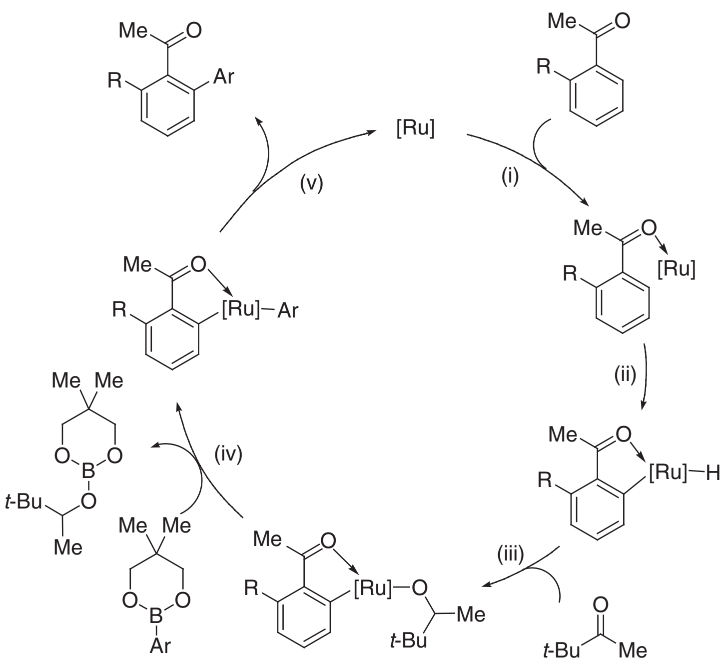
A ruthenium-catalyzed chelation-assisted approach for direct arylations was achieved with boronates as arylating reagents [67]. Thereby, a regioselective ruthenium-catalyzed functionalization of substrates containing oxygen-based DGs was accomplished. A variety of aromatic ketones was efficiently converted with boronates bearing both electron-donating, as well as electron-withdrawing substituents, when employing pinacolone as reaction medium (Scheme 14).

Mechanistic studies revealed that pinacolone acts both as solvent and the reactions mandatory oxidizing agent. Further, inter- and intramolecular competition experiments with isotopic-labeled ketones provided evidence for a precoordination



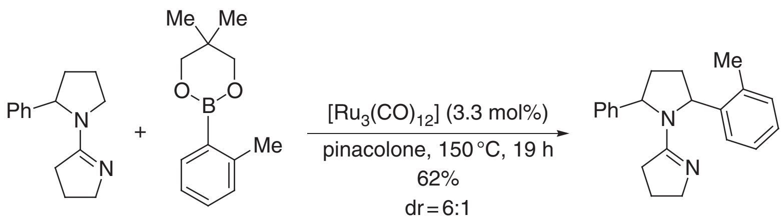
Scheme 14 Ruthenium-catalyzed arylation of ketone **36** in pinacolone

of the ruthenium catalyst by the Lewis-basic oxygen of the ketone [68]. Therefore, a mechanism was proposed comprising (a) coordination by the substrate, (b) regioselective oxidative addition to yield an *ortho*-metalated ruthenacycle, (c) insertion of pinacolone into the [Ru]–H bond, (d) transmetalation, and, finally, (e) reductive elimination (Scheme 15).



Scheme 15 Proposed mechanism for ruthenium-catalyzed arylations of ketones with boronates

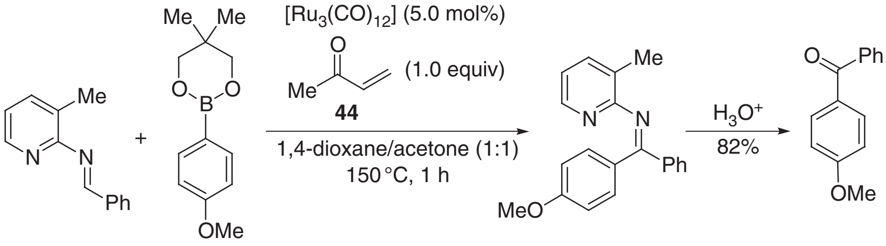
An extension of this methodology to the functionalization of C(sp^3)–H bonds in saturated *N*-heterocycles was reported subsequently [69]. Thereby, pyrrolidines and piperidines were regioselectively arylated with substituted boronates in the α-position to the heteroatom (Scheme 16) [30].



39 40 41

Scheme 16 Ruthenium-catalyzed functionalization of pyrrolidine **39**

A somewhat related strategy for ruthenium-catalyzed arylations of aldimines was reported by Jun and coworkers [70]. Here, a pyridyl-substituent allowed for regioselective funtionalizations employing boronates as arylating reagents. Methyl vinyl ketone (**44**) as oxidant led to high isolated yields of the corresponding ketones after

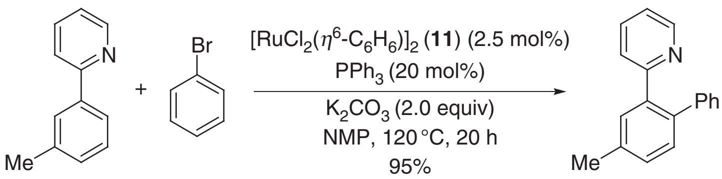


Scheme 17 Ruthenium-catalyzed direct arylation of aldimine **42**

hydrolysis (Scheme 17). Furthermore, a chelation-assisted arylation of aldehydes with aryl iodides or organostannanes as arylating reagents was accomplished with a catalytic system consisting of [$Ru_3(CO)_{12}$] and [$Pd_2(dba)_3 \cdot CHCl_3$] [71].

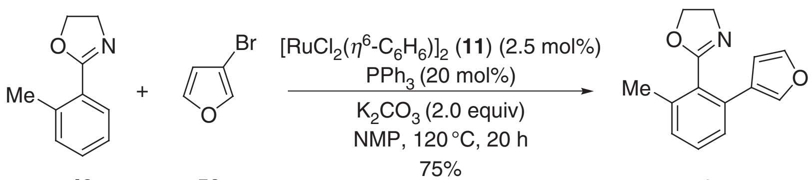
2.2 *Direct Arylations with Organic (Pseudo)Halides*

A catalytic system comprising $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (**11**) and PPh_3 was disclosed by Oi, Inoue and coworkers for direct arylations of pyridine derivatives using aryl bromides as electrophiles (Scheme 18) [72].



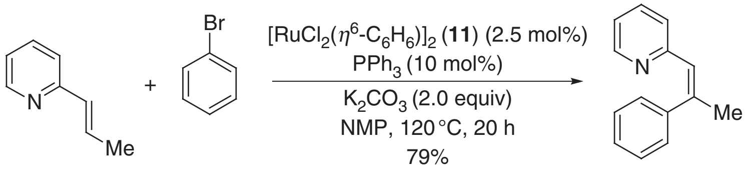
Scheme 18 Ruthenium-catalyzed direct arylation with phenyl bromide (**47**)

This protocol also proved applicable to directed arylations of imines [73], imidazolines, oxazolines (Scheme 19) [74, 75], as well as further arylazoles [76] as pronucleophilic starting materials. The use of 2-oxazolinyl moieties as DG is particularly noteworthy, since they can be easily converted into a variety of valuable functionalities [77].



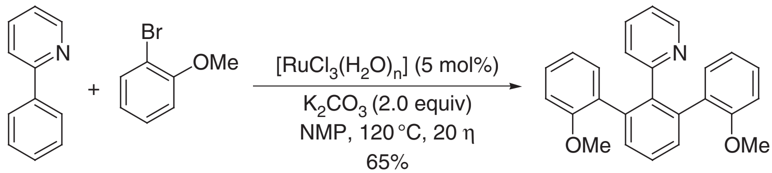
Scheme 19 Ruthenium-catalyzed direct arylation with heteroaryl bromide **50**

Alkenylic C–H bonds could also be directly functionalized with aryl bromides using these reaction conditions, yielding selectively the corresponding substituted alkenes (Scheme 20) [78].



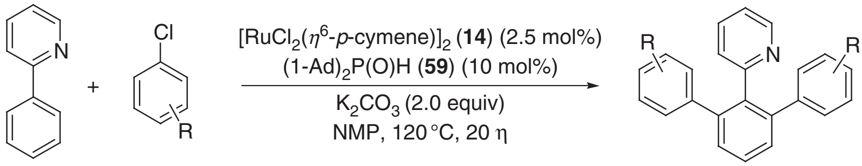
Scheme 20 Ruthenium-catalyzed direct arylation of alkene **52** with aryl bromide **47**

More recently, a phosphine ligand-free ruthenium-catalyzed direct arylation with aryl bromides as electrophiles was disclosed. Notably, the use of inexpensive $RuCl_3(H_2O)_n$ as catalyst in NMP as solvent allowed for economically attractive C–H bond functionalizations of pyridine, oxazoline and pyrazole derivatives, also with more sterically hindered *ortho*-substituted aryl bromides as electrophiles (Scheme 21) [79, 80].



Scheme 21 Ruthenium-catalyzed phosphine ligand-free direct arylation

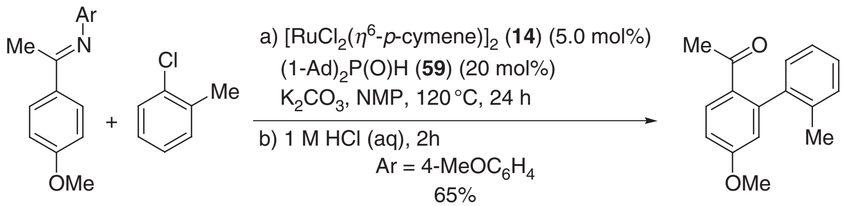
Among aryl halides, chlorides are arguably the most useful single class of electrophilic substrates, due to their lower costs and a wide diversity of commercially available compounds. For traditional cross-coupling reactions the development of stabilizing ligands allowed for the use of these inexpensive electrophiles. In contrast, generally applicable methods for regioselective direct arylation reactions employing aryl chlorides were until recently only reported for intramolecular palladium-catalyzed direct arylation reactions [21]. Therefore, the author's research group set out to probe transition metal-catalyzed direct arylations employing aryl chlorides as readily available electrophiles [12]. As a result, direct C–H bond functionalizations were achieved with a ruthenium complex derived from secondary phosphine oxide (SPO) [81] $(1\text{-Ad})_2P(O)H$ (**59**) [82]. Thus, pyridine [82] and pyrazole [83] derivatives were efficiently arylated with a variety of functionalized aryl chlorides, including electronically-deactivated ones (Scheme 22).



54 R = 3-CN: **57**
R = 4-OMe: **58**
R = 3-CN: **60** 81%
R = 4-OMe: **61** 87%

Scheme 22 Ruthenium-catalyzed direct arylation with aryl chlorides

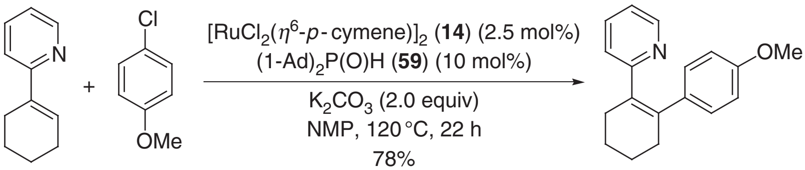
In addition, *ortho*-substituted aryl chlorides could be used, which should prove valuable for further functionalization reactions of the corresponding products (Scheme 23) [82].



62 **63** **64**

Scheme 23 Ruthenium-catalyzed direct arylation with *ortho*-substituted aryl chloride **63**

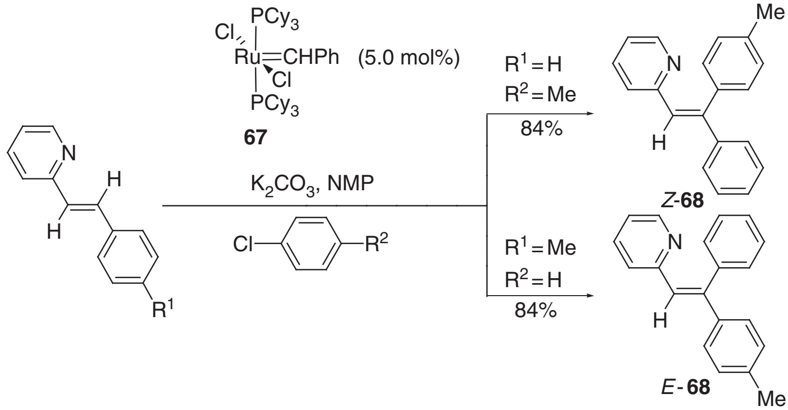
Direct arylations of alkenyl pronucleophiles with readily available chlorides as electrophiles occurred with high efficacy and excellent diastereoselectivity using either ruthenium alkylidene complexes or a ruthenium catalyst derived form air-stable SPO preligand $(1\text{-Ad})_2P(O)H$ (**59**) (Scheme 24) [84].



65 **58** **66**

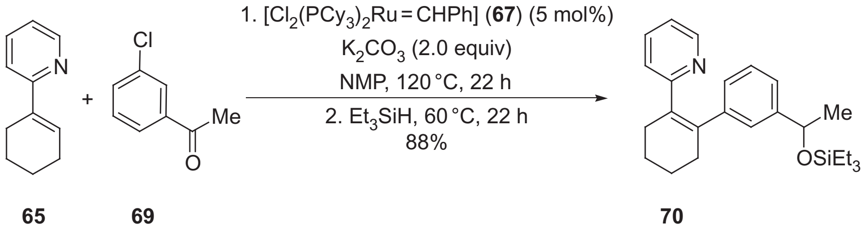
Scheme 24 Ruthenium-catalyzed direct arylation of alkene **65** with SPO preligand **59**

It is worth noting that the diastereoselectivity of these direct arylations turned out to be complementary to palladium-catalyzed Mizoroki–Heck reactions (Scheme 25).



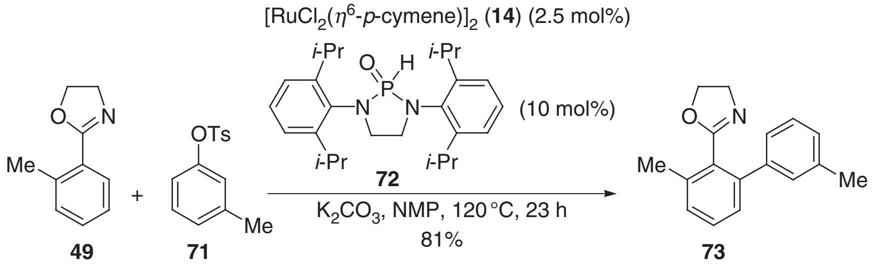
Scheme 25 Ruthenium-catalyzed diastereoselective direct arylation with complex **67**

Based on this C–H bond functionalization protocol, a ruthenium-catalyzed sequence consisting of a direct arylation and a subsequent hydrosilylation reaction was developed using ruthenium carbene **67** as sole catalyst for two mechanistically distinct transformations (Scheme 26) [84].



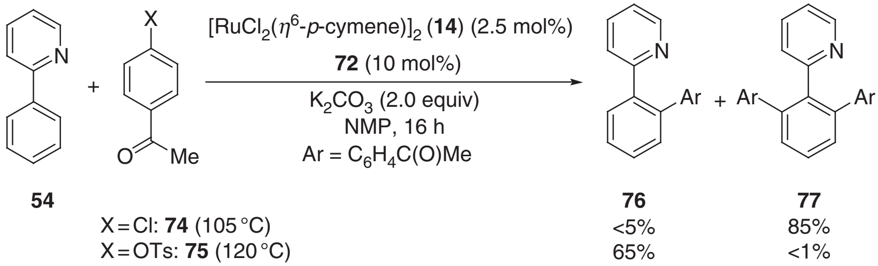
Scheme 26 Ruthenium-catalyzed direct arylation/hydrosilylation sequence

The use of aryl tosylates as electrophiles is attractive, since they can be synthesized from readily available phenols with less expensive reagents than those required for the preparation of the corresponding triflates. More importantly, tosylates are more stable towards hydrolysis than are triflates. However, this greater stability renders tosylates less reactive in transition metal-catalyzed coupling reactions. As a result, protocols for traditional cross-coupling reactions of these electrophiles were only recently developed [1]. In contrast, catalytic direct arylations with aryl tosylates were not reported previously. However, a ruthenium complex derived from heteroatom substituted secondary phosphine oxide (HASPO) preligand **72** [81] allowed for direct arylations with both electron-deficient, as well as electron-rich aryl tosylates (Scheme 27) [83]. As pronucleophiles, pyridine, oxazoline and pyrazole derivatives could be efficiently functionalized.



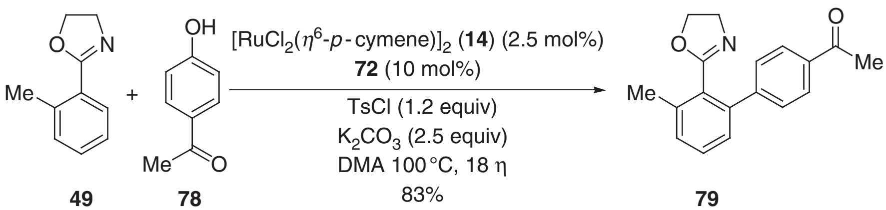
Scheme 27 Ruthenium-catalyzed direct arylation with tosylate **71**

Notably, selective arylation reactions were accomplished through the judicious choice of the electrophile. Hence, aryl chloride **74** yielded predominantly the product of diarylation **77**, whereas the corresponding aryl tosylate **75** gave exclusively rise to the monofunctionalized compound **76** (Scheme 28).



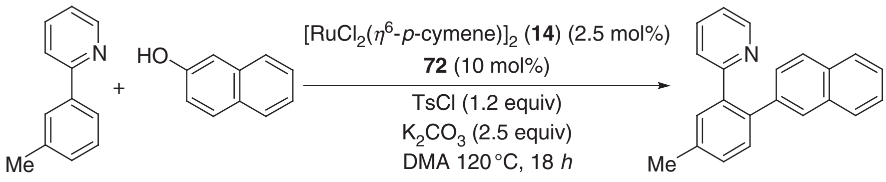
Scheme 28 Ruthenium-catalyzed direct arylations with chloride **74** and tosylate **75**

The remarkable stability of ruthenium complexes could, further, be exploited for direct arylations between simple arenes as pronucleophiles and inexpensive, broadly available phenols as proelectrophiles. Notably, this operationally simple dehydrative direct arylation was achieved with a highly chemo- and regioselective ruthenium catalyst, along with a sulfonyl chloride, and proceeded overall through the functionalizations of both C–H as well as C–OH bonds (Scheme 29) [85].



Scheme 29 Ruthenium-catalyzed dehydrative direct arylation with oxazoline **49**

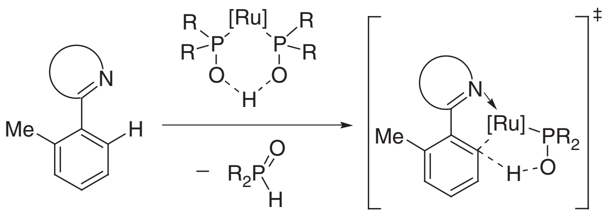
The protocol proved generally applicable, and allowed for the functionalization of arenes with different DGs, such as pyridine **27** (Scheme 30), employing both electron-deficient as well as electron-rich phenols as proelectrophile [85].



27 **80** **81**

Scheme 30 Ruthenium-catalyzed dehydrative direct arylation with naphthol **80**

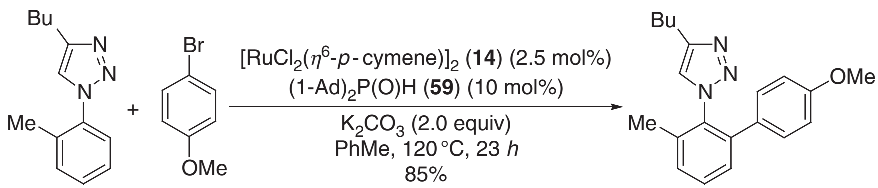
Unfortunately, experimental studies on the working mode of ruthenium-catalyzed direct arylations with organic (pseudo)halides are scarce. However, a beneficial effect of NaOAc on stoichiometric syntheses of ruthenacycles at ambient temperature was reported (see above) [49, 50], and suggested a cooperative deprotonation/metalation mechanism [7, 30, 86] for the C–H bond activation step. Furthermore, recent computational DFT-calculations provided support for such a mechanistic rationale [87]. Moreover, a transition state **83** was independently proposed to account for the high efficacy observed with (HA)SPO preligands in ruthenium-catalyzed direct arylation reactions (Scheme 31).



82 **83**

Scheme 31 Concerted deprotonation/metalation with (HA)SPO preligands

Consequently, ruthenium-catalyzed direct arylations with aryl halides in less coordinating apolar solvents, such as toluene, were probed. Notably, a catalytic system derived from SPO preligand **59** enabled regioselective C–H bond functionalizations at the aromatic moieties of *N*-aryl substituted 1,2,3-triazoles (Scheme 32) [88].

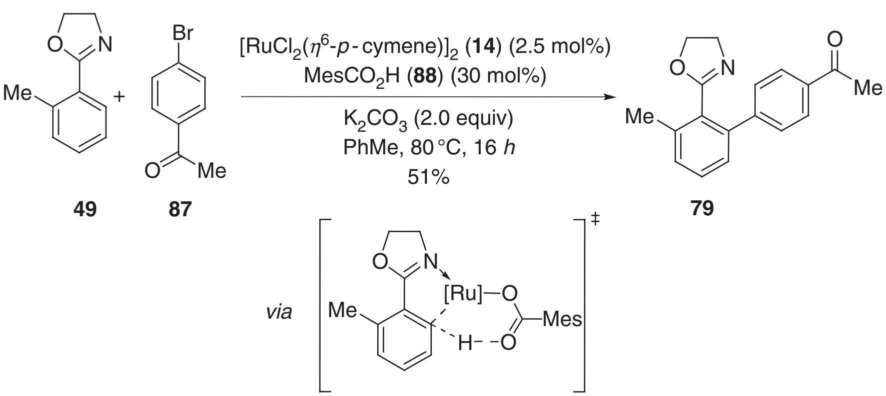


84 **85** **86**

Scheme 32 Ruthenium-catalyzed direct arylation of 1,2,3-triazole **84** in an apolar solvent

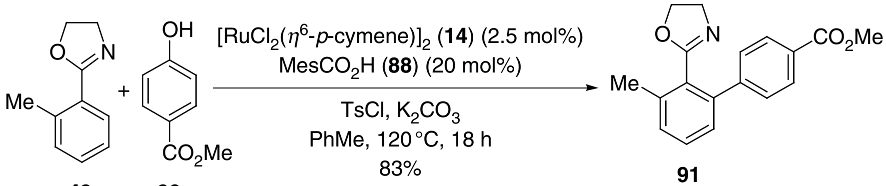
It is noteworthy that the regioselectivity of this ruthenium-catalyzed transformation proved complementary to the one observed when applying either palladium [89, 90] or copper [91] catalysts to the conversion of these substrates.

Recently the beneficial effect of carboxylic acids as additives in palladium-catalyzed direct arylations through a concerted deprotonation/metalation mechanism was put forward [92, 93]. The author's research group, in contrast, tested their application to ruthenium-catalyzed C–H bond functionalizations. Thus, a ruthenium complex derived from carboxylic acid $MesCO_2H$ (**88**) displayed an exceptionally broad scope and allowed for efficient directed arylations of 1,2,3-triazoles, pyridines, pyrazoles or oxazolines among others [88]. With respect to organic electrophiles, aryl bromides, chlorides, and tosylates, including *ortho*-substituted derivatives, were found to be suitable starting materials. Interestingly, these phosphine (pre)ligand-free direct arylations could be performed at a lower reaction temperature of 80 °C, and likely proceeded though transition state **89** (Scheme 33).



Scheme 33 Ruthenium-catalyzed direct arylation using carboxylic acid **88** as cocatalyst

Furthermore, aromatic carboxylic acid $MesCO_2H$ (**88**) enabled dehydrative direct arylations with phenols as proelectrophiles to occur in apolar toluene as solvent as well (Scheme 34) [85].



Scheme 34 Ruthenium-catalyzed dehydrative direct arylation in apolar toluene as solvent

Considering these experimental observations [85, 88], along with recent computational DFT-calculations [87], a mechanism based on a concerted deprotonation/metalation is likely to be operative.

Conclusions

Chelation-assistance has enabled the development of regioselective ruthenium-catalyzed C–H bond functionalization reactions. Thus, valuable C–C bond formations were accomplished through atom-economical hydroarylations of alkenes or alkynes during the last two decades. In contrast, ruthenium-catalyzed direct arylations were reported only relatively recently. These regioselective C–H bond functionalizations proved to be rather broadly applicable. Thus, they allowed, among other things, for intermolecular direct arylations with aryl chlorides, aryl tosylates or phenols as (pro)electrophilic starting materials. Given the unparalleled scope and highly regioselective nature of ruthenium-catalyzed direct arylations, the development of further useful protocols in this rapidly evolving research area is expected.

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Rhodium-Catalyzed C–H Bond Arylation of Arenes

Jean Bouffard and Kenichiro Itami

Abstract A review is presented of synthetic methods for the preparation of biaryls by the rhodium-catalyzed C–H bond arylation of arenes with aryl halides (C–H/C–X couplings), arylmetal reagents (C–H/C–M couplings) and arenes (C–H/C–H couplings), with an emphasis on postulated mechanisms and their implications on reactivity, selectivity and substrate scope.

Keywords Biaryls • Catalysis • C–H activation • Cross-coupling • Rhodium

Contents

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1 Introduction

1.1 *Biaryls, Cross-Coupling and the Promise of C–H Functionalization Methods*

The biaryl motif is ubiquitous in areas of chemistry that include natural products [1–3], pharmaceuticals [8–13], ligands and catalysts [4–7], polymers and materials for molecular electronics, light-emissive materials, organic solar cells, and liquid crystals [14–16]. This broad appeal has led to tremendous efforts being directed at the development of methods for the formation of the biaryl C–C bond [17]. The development of cross-coupling methodologies over the past decades has been especially significant, with current methods allowing for the palladium-catalyzed (or less commonly nickel, copper, iron, and other metals) coupling of unactivated aryl halides, including chlorides or pseudo-halides such as triflates and other sulfonates, with arylmagnesium (Tamao–Kumada–Corriu), arylzinc (Negishi), aryltin (Migita–Kosugi–Stille), arylboron (Suzuki–Miyaura), and arylsilicon (Hiyama) reagents at low temperatures and low catalyst loadings ([18–20]; rare examples of Rh-catalyzed cross-couplings (and/or addition-elimination) [21–24]). The importance of the Suzuki–Miyaura cross-coupling in medicinal chemistry, in particular for the preparation of heterocyclic biaryls, cannot be understated [25].

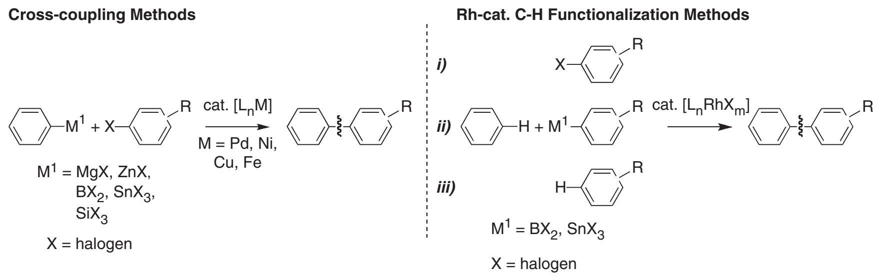
Despite tremendous advances, these powerful, efficient and selective reactions suffer from significant and inherent drawbacks. The two aryl nuclei to be coupled must be independently preactivated through halogenation and metalation, lengthening the synthetic routes and invariably resulting in increased waste generation. Many organometallic substrates are unstable towards normal atmospheric conditions (moisture, oxygen, etc.), and therefore may not be easily handled, purified, weighed, or stored indefinitely. In other instances, organometallic substrates – especially in the case of organotin derivatives – are highly toxic and represent a risk both to the chemist using them and to the environment. Finally, even in the best of circumstances, a stoichiometric equivalent of metal halide (or pseudohalide) waste is generated in the coupling reactions, something not only highly undesirable from an atom economy standpoint, but also with respect to the sometimes tedious workup and purification steps that follow. By contrast, in catalytic C–H functionalization/C–C coupling lies the promise of inherently more efficient processes, and therefore more powerful yet economical ones. Biaryl formation through C–H functionalization may directly operate with unfunctionalized substrates that can originate directly either from the renewable biomass or from petrochemical feedstock.

Nevertheless, current, state-of-the-art methods for aryl–aryl C–C bond formation through C–H functionalization still often suffer from a number of drawbacks by comparison with other synthetic methods. The catalysts employed suffer from limited activity and/or short lifetime, leading to the requirement for high catalyst loadings, elevated reaction temperatures, or both. Lower effective substrate-to-catalyst ratios (S/C) lead to more difficult workup and purification. This is of great concern in the manufacture of pharmaceuticals where the residual transition metals content in a drug must be exceptionally low due to toxicity concerns [26–33]. Moreover, low substrate-to-catalyst ratios also pose an economical concern when the cost of the transition metals and ligands may be prohibitive on a commercial production scale. The requirement for high reaction temperatures may itself induce catalyst deactivation or decomposition, in addition to being incompatible with highly functionalized and/or thermally sensitive substrates. Operations at higher temperatures are also detrimental to the general selectivity of a reaction, increasing the rate of by-product formation, and thus sometimes being detrimental to the workup and purification stages. The issue of selectivity is of particular importance in C–H functionalization, as organic substrates will present a large number of potentially reactive positions. The majority of existing C–H functionalization methods must rely on special subsets of organic substrates possessing either a directing group capable of chelation to the metal center of the catalyst [34] (Sects. 2.3 and 3.1) or the ability to form stable metal-carbene complexes (Sect. 2.2) in order to reach acceptable levels of chemoselectivity. Overall, these drawbacks make current C–H functionalization methodologies promising though not yet adequate for applications involving the predictable, routine intermolecular coupling of late-stage, highly functionalized intermediates.

It is in this context that the field of biaryl formation through C–H functionalization has been the object of great interest, resulting in explosive growth in the past decade [35–41]. Among new methods, palladium-catalyzed transformations have to date achieved the greatest successes. By contrast, while rhodium complexes were among the first to demonstrate the catalytic cleavage of aryl C–H bonds, tandem C–H cleavage/C–C bond formation schemes have met a much slower development in comparison to their palladium counterparts.

In this review, the use of rhodium complexes[1] in the catalytic arylation of arenes through C–H functionalization will be described, with a specific emphasis on their mechanistic underpinnings and associated advantages and drawbacks as they relate to the practicality and scope of these reactions. First, a quick overview of historical landmarks in the rhodium-mediated cleavage of arene C–H bonds will be given. Second, methods for rhodium-catalyzed C–H arylation of arenes will be presented. This section has been divided according to the following reaction formalism (Scheme 1):

[1] The use of elemental rhodium (e.g., rhodium surfaces, rhodium on carbon, rhodium nanoparticles) will not be discussed in this review.



Scheme 1 Transition metal-catalyzed synthesis of biaryls by cross-coupling and by Rh-Catalyzed C–H functionalization methods

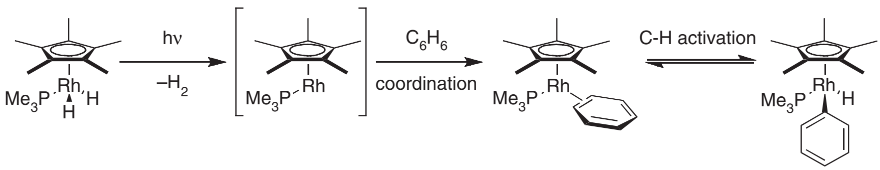
1. C–H/C–X arene arylation methods (Rh-catalyzed condensation methods)
2. C–H/C–M arene arylation methods (Rh-catalyzed oxidative coupling methods)
3. C–H/C–H arene arylation methods (Rh-catalyzed oxidative coupling methods)

Third and finally, a short comparison of rhodium-catalyzed and other arene C–H arylation methods highlighting some of the challenges to overcome in the development of improved arene arylation methods will be given.

1.2 *Rh-Mediated Cleavage of Arene C–H Bonds*

Rhodium complexes were among the first and most thoroughly studied complexes capable of oxidative addition across arene but also alkane C–H bonds [42–46]. Electron-rich, coordinatively unsaturated Rh(I) complexes such as CpRh(PMe_3) or Cp*Rh(PMe_3) can be generated in solution at low temperatures from the irradiation of stable precursors such as CpRh(PMe_3)H_2 or CpRh(PMe_3)(diimide) complexes. These species quickly react with arenes – and alkanes – to generate the C–H oxidative addition product CpRh(PMe_3)(H)R, where R = aryl, alkyl. The arene oxidative addition products are stable, though the arene ligand can exchange with other arenes in solution – or arene solvent – at higher temperatures (Scheme 2).

The mechanism of this reaction has been studied in great detail by the Bergman, Jones, and Perutz groups, among others. A mechanistic proposal that is in



Scheme 2 C–H oxidative addition of arenes by Cp*Rh(PMe_3) [42–54]

agreement with the conclusions of isotope labeling and in situ spectroscopic experiments has emerged [47–54]. Irradiation of the precursor complex results in the expulsion of the photolabile ligand(s) and generates the active coordinatively unsaturated electron-rich Rh(I) complex (e.g., Cp*Rh(PMe_3)). The 16-electron complex rapidly (≤1 μs) forms a stable though short-lived η^2-arene intermediate. The η^2-arene complex then (~150 μs for PhH) rearranges through a reversible C–H oxidative addition that results in the arene C–H oxidative addition product CpRh(H)Ar.

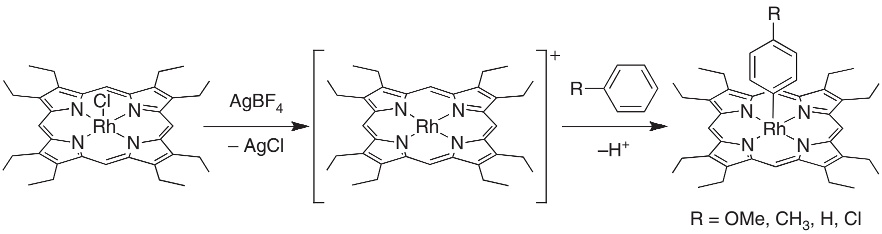
Rhodium(I) hydrotris(3,5-dimethylpyrazolyl)borate (Tp*) complexes bearing a photolabile ligand (CO, carbodiimides) were later demonstrated to participate in the same arene and alkane C–H cleavage reactions [55–58]. Carbodiimide ligands are especially effective because the photoirradiation is rapid and proceeds with high photochemical quantum yields using long-wavelength (>345 nm) sources. A mechanism similar to that proposed for Cp*Rh(PMe_3) is believed to operate in the case of Tp*RhL. However, the hapticity of the Tp* ligand has been found to change throughout the course of the reaction. Following expulsion of the photolabile ligand and substrate coordination, the Tp* ligand undergoes a $\eta^3 \rightarrow \eta^2$ (e.g., Tp* to Bp*) dechelation of one of the three *N*-bound pyrazolyl fragments that precedes the C–H oxidative addition. Rechelation ($\eta^2 \rightarrow \eta^3$) immediately follows the C–H oxidative addition to yield Tp*Rh(H)Ar. The intermediacy of both η^2-C,H ($\sigma_{C\text{-}H}$-bound) and η^2-C,C (π-bound) η^2-Bp*RhL(ArH) arene complexes on the path between the initial complex η^3-Tp*RhL(ArH) and the C–H oxidative addition product η^3-Tp*RhL(H)Ar have been proposed, but only the latter intermediate has been directly observed. Whether the π-bound arene must interconvert to the $\sigma_{C\text{–}H}$-bound arene prior to C–H oxidative addition or whether both species can generate the C–H oxidative addition product could not be unequivocally established, however.

Despite the significance of this chemistry, the applications of this reaction have been limited to stoichiometric reactions and to H/D-exchange of arenes [59]. Most importantly, these advances have, to date, not been found to be promising in catalytic C–C bonding through C–H functionalization, arguably the most desirable application from the standpoint of practical organic synthesis.

2 C–H/C–X Arene Arylation (Rh-Catalyzed Condensation Methods)

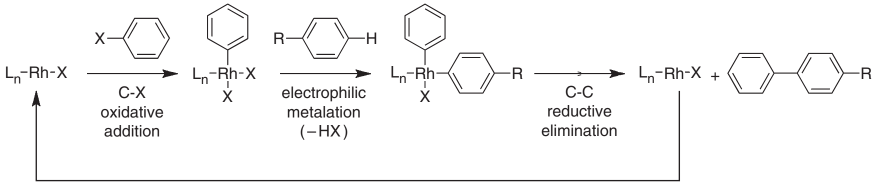
2.1 *Rh-Catalyzed C–H/C–X Arylation of Arenes Through Electrophilic Metalation*

Electron-deficient rhodium(III) complexes participate in the electrophilic metalation of arenes, as originally shown by Aoyama, Ogoshi, and co-workers [60, 61]. Highly electrophilic rhodium(III) complexes have also been employed in other reactions that involve the C–H functionalization of arenes, such as the carboxylation of arenes [62]. Cationic octaethylporphyrinatorhodium(III) [(OEP)Rh]X complexes where X^- is a weakly coordinating anion such as perchlorate (ClO_4^-) or tetrafluoroborate (BF_4^-) are generated by halide abstraction with the corresponding silver(I) salts. These cationic, highly electrophilic Rh(III) species react in turn with arenes to generate the metalated arene complexes [(OEP)RhAr] and a proton. Hammett correlations of reactivity with arene electronics are consistent with an electrophilic metalation process ($\rho = -5.43$). The metalation is highly selective (>99:1; only detected isomer) for the *para* isomer with toluene, anisole and chlorobenzene, while a 92:8 *meta*:*para* ratio is observed for methyl benzoate. The lack of *ortho* metalation has been attributed to the significant steric demands of the octaethylporphyrin ligand. The metalation does not exhibit a significant kinetic deuterium isotope effect, which has been interpreted as signifying that a rate-limiting coordination to form a cationic arene-rhodium intermediate $[(OEP)Rh(ArH)]^+$ (e.g., η^2-arene, or Wheland complex) precedes a rapid deprotonation and σ-aryl bond formation. Photolysis of the [(OEP)RhAr] complexes (where Ar = Ph, 4-$MeOC_6H_4$ or 4-MeC_6H_4) in benzene results in the generation of the corresponding 4-phenylarenes, presumably through homolytic cleavage of the Ar–Rh bond followed by the reaction of benzene with the photogenerated aryl radicals (Scheme 3).



Scheme 3 Electrophilic metalation of arenes by $[(OEP)Rh]^+$ [60–61]

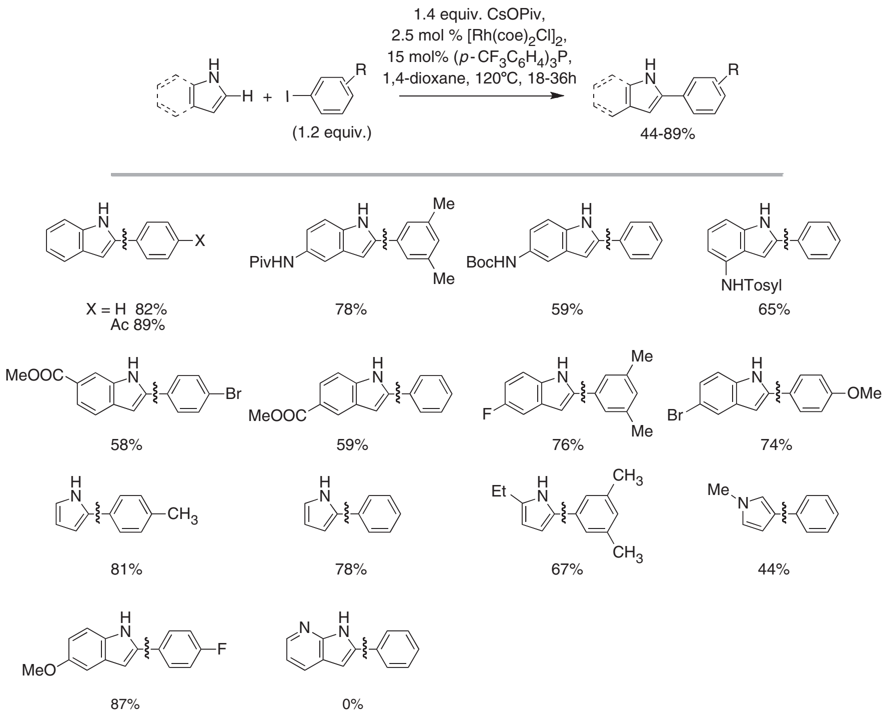
The $[(OEP)Rh]^+$ scaffold, while efficient at the metalation of arenes, is ill-suited for catalytic biaryl bond formation. The generation of an intermediate bearing two aryl groups cis to each other as a typical precursor to biaryls through reductive elimination is impossible due to the ligand-imposed geometry at the metal center. Nonetheless, other highly electron-deficient Rh(III) complexes can offer suitable entries into catalytic routes for electrophilic arene arylation. This is especially the case if the electrophilic Rh(III) center can be accessed in situ from the oxidative addition of Ar–X to a Rh(I) complex (Scheme 4).



Scheme 4 General scheme for C–H/C–X arylation of arenes through electrophilic metalation

In a first report describing this type of catalysis [63], the Sames group has found that the electrophilic complexes ArRh(OPiv)$_2$(L)$_2$, where L is (4-$CF_3C_6H_4$)$_3$P, can catalyze the C-arylation of electron-rich azoles with iodoarenes. The ArRh(OPiv)$_2$(L)$_2$ complexes are conveniently formed in situ by the reaction between [Rh(coe)$_2$Cl]$_2$, (4-$CF_3C_6H_4$)$_3$P, CsOPiv, and an iodoarene, allowing for a simple one-pot catalytic transformation from commercially available reagents (Scheme 5). Under typical reaction conditions, the azole (1 equiv.), ArI (1.2 equiv.), CsOPiv (1.4 equiv.), [Rh(coe)$_2$Cl]$_2$ (0.025 equiv.), and (4-$CF_3C_6H_4$)$_3$P (0.15 equiv.) are dissolved in 1,4-dioxane (1.25 M in azole) and stirred at 120 °C for 18–36 h. Moderate to excellent chemical yields (44–89%) are obtained, and the catalyst loading can be reduced to 2 mol% Rh (6:1 L:Rh) in gram-scale reactions without a significant reduction in yield, but at the expense of longer reaction times (52–56 h). Higher yields were generally observed with combinations of more electron-rich azoles and more electron-deficient iodoarenes. An excellent regioselectivity (>50:1) is observed for the arylation of indoles at the 2-position over the typically more nucleophilic 3-carbon position or *N*-arylation. A reversal of selectivity in disfavor of the more nucleophilic 2-position and in favor of the less sterically hindered 3-position has been observed with an *N*-substituted pyrrole.

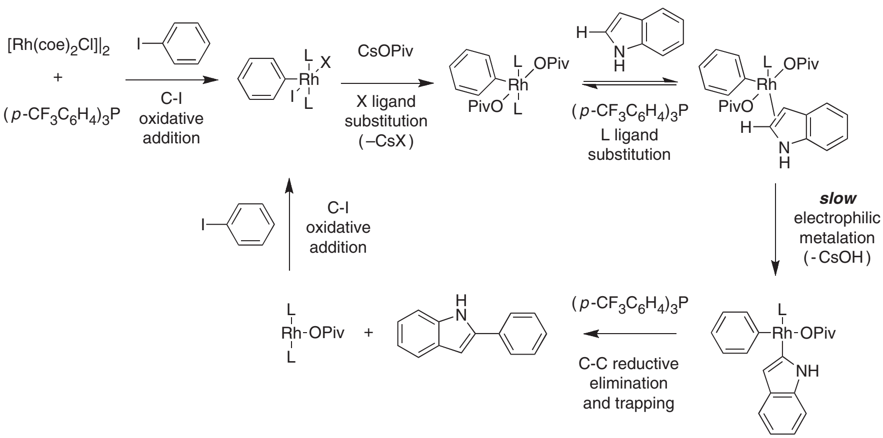
The scope of this reaction is limited to the electron-rich azoles, indoles, and pyrroles as the nucleophilic partners and to electron-deficient to moderately



Scheme 5 Rh-catalyzed arylation of azoles by Wang et al. [63]

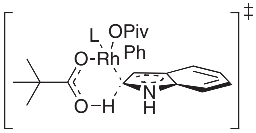
electron-rich substituted iodobenzenes as the electrophilic partners. Aryl halides or pseudohalides that are less reactive towards oxidative addition (Br, Cl, OTf) are not suitable electrophilic partners in this reaction. The reactivity of sterically hindered and/or *ortho* substituted iodoarenes has not been demonstrated. Functional groups including acidic NH (amides, carbamates, sulfonamides), ketones, esters, (hetero) aryl halides (F, Br), and aryl ethers are tolerated under these reaction conditions. The presence of basic sp^2 nitrogens (e.g., pyridines) is not tolerated and resulted in little or no conversion, possibly due to an irreversible coordination to the electrophilic Rh(III) center.

The isolation and structural characterization of the stable electrophilic rhodium(III) species $ArRh(OPiv)_2(L)_2$ where Ar is 4-MeC_6H_4 and L is $(4\text{-}CF_3C_6H_4)_3P$ has facilitated mechanistic experiments. This rhodium(III) complex was found to be a kinetically competent catalyst and, on the basis of initial-rate kinetics, the reaction was found to be first order in $ArRh(OPiv)_2(L)_2$, first order in indole, inverse first order in phosphine ligand, and zeroth order in iodoarene. Furthermore, a large kinetic deuterium isotope effect of $k_H/k_D = 3.0$ observed at the 2-position of indole indicates that C–H (or C–D) bond breaking is taking place at (or prior to) the rate-limiting step of the catalytic cycle. A mechanistic proposal that is consistent with these experimental results is shown in Scheme 6. Coordination of the phosphine ligand(s) to $[Rh(coe)_2Cl]_2$ likely precedes oxidative addition to the iodoarene, and is followed by anionic ligand exchange with cesium pivalate to generate the key resting state of the catalytic cycle, the electrophilic rhodium(III) complex $ArRh(OPiv)_2(L)_2$. Dissociation of one phosphine ligand and coordination to the substrate azole is followed by the rate-limiting insertion of the rhodium complex into the C–H bond at the 2-position. Finally, reductive elimination of the 2-arylated azole, trapping with a phosphine, oxidative addition of iodoarene, and anionic ligand exchange with cesium pivalate regenerate the catalyst.



Scheme 6 Proposed catalytic cycle [63]

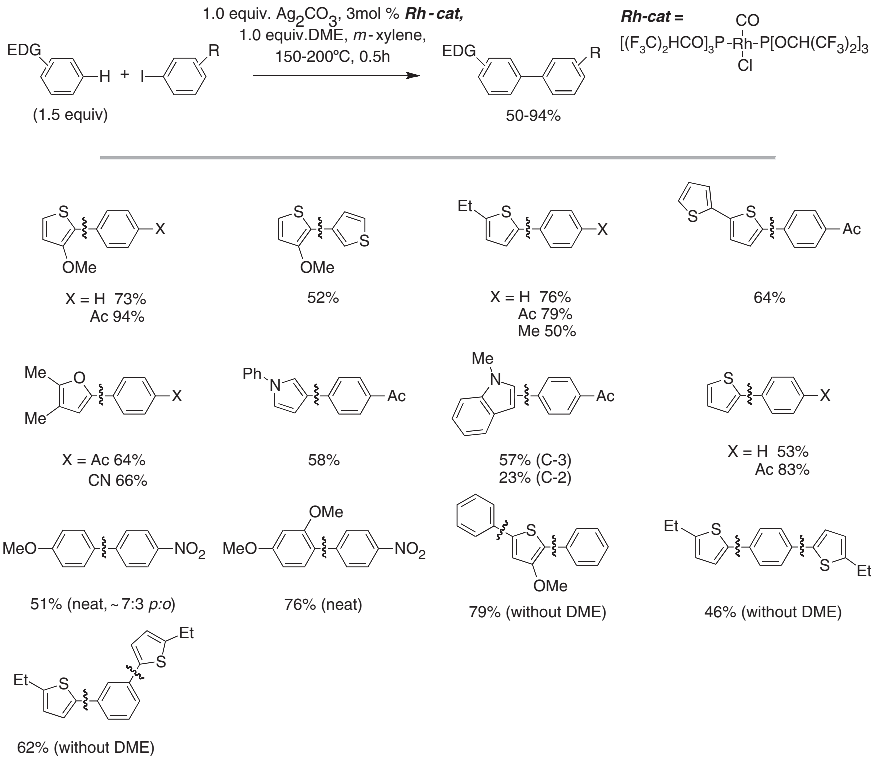
Cesium pivalate plays a key role as a ligand and a base, resulting in catalyst activity far greater than observed with other reagents (carbonates, phosphates, amines). In addition, the excellent regioselectivity for the less nucleophilic 2-carbon position of indoles and the significant kinetic deuterium isotope effect are indications that a purely electrophilic metalation mechanism is probably not involved in this reaction, in contrast with the case for the cationic octaethylporphirinatorhodium(III) complex (see above). The coordination of $(4\text{-}CF_3C_6H_4)_3P$, pivalate and a σ-aryl ligands, especially in the most successful couplings where the aryl ligand bears electron-withdrawing groups, can clearly play a role in increasing the electrophilicity of the rhodium(III) intermediate. The assistance of the pivalate ligand as an internal base or proton shuttle during the rate-limiting C–H cleavage has been suggested (Scheme 7). Parallels have been drawn with arene C–H arylation catalysts that employ palladium(II) pivalates or other carboxylates as anionic ligands and where the involvement of the carboxylate ligand acting as an internal base in the deprotonation and σ-aryl bond formation has been proposed [64–72].



Scheme 7 Postulated participation of the pivalate ligand as an internal base

A second catalyst for the rhodium-catalyzed C–H arylation of arenes through electrophilic metalation has been reported by the Itami group [73, 74]. The $L_2Rh(CO)Cl$ complex bearing the strongly π-accepting carbonyl and phosphite ligand $L = P[OCH(CF_3)_2]_3$ was found to catalyze the C–H arylation of nucleophilic arenes with iodoarenes in the presence of a stoichiometric amount of silver(I) carbonate (Scheme 8). The catalyst is easily prepared in quantitative yields from $[Rh(CO)_2Cl]$ and the phosphite ligand by mixing in warm toluene, to result in a crystalline catalyst that is stable under ambient conditions (air, moisture) for extended periods (>10 months). Under typical reaction conditions, the nucleophilic arene (1.5 equiv.), ArI (1 equiv.), $L_2Rh(CO)Cl$ (0.03 equiv.), Ag_2CO_3 (1 equiv.; 2 equiv. Ag), and dimethoxyethane (DME, 1 equiv.) are suspended in *m*-xylene (0.2 M in iodoarene) and stirred at 150 °C for 12 h. Alternatively, the reaction can be performed under microwave irradiation at 200 °C for 30 min. Moderate to excellent chemical yields (50–94%) are obtained. As for the previous reaction developed by the Sames group, higher yields are generally observed with combinations of more nucleophilic arenes and iodoarenes bearing electron-withdrawing groups.

The regioselectivity observed with many nucleophilic arenes is moderate to excellent, and generally follows the pattern expected for aromatic electrophilic substitution (e.g., nitration, bromination, etc.) of the arenes. 3-Methoxythiophene reacts first at the 2-position but double arylation at the 2- and 5-positions is achieved in the absence of DME additive. 2-Ethylthiophene, 2,3-dimethylfuran, and 2,2′-bithiophene react at the expected 5-position and, similarly, thiophene reacts at the 2-position. 1,3-Dimethoxybenzene reacts exclusively at the 4-position while



Scheme 8 Rh-catalyzed arylation of electron-rich arenes by Yanagisawa et al. [73, 74]

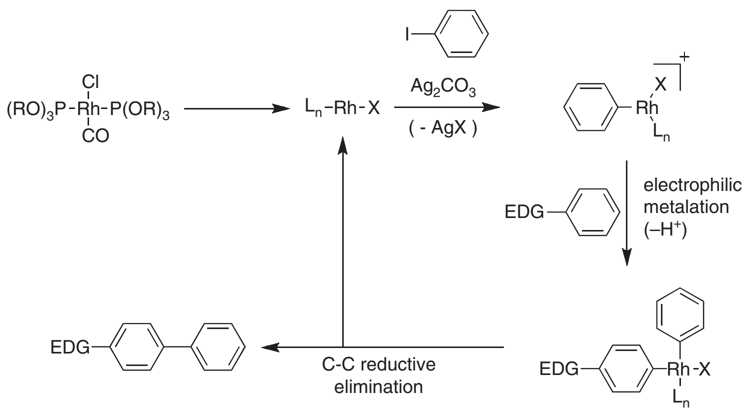
methoxybenzene results in a 7:3 *para*:*ortho* selectivity. *N*-Methylindole results in a ~2.5:1 ratio of the 3- to 2-arylated indoles when reacted with *p*-iodoacetophenone. Finally, the reaction of *N*-phenylpyrrole with *p*-iodoacetophenone unexpectedly results in the 3-arylated product exclusively. While the 2-position is generally preferred in simple electrophilic aromatic substitution of pyrroles, the steric demands of the *N*-phenyl substituent may affect the outcome of the reaction.[2]

The scope of this reaction is limited to electron-rich arenes and heteroarenes such as thiophenes, pyrroles, furans, indoles, and alkoxybenzenes as nucleophilic partners, corresponding to a Mayr π-nucleophilicity parameter $N \geq -1$ [75–78]. Electron-neutral to electron-deficient iodo(hetero)arenes are suitable electrophilic partners. Aryl halides or pseudohalides that are less reactive towards oxidative addition (Br, Cl, OTf) are not sufficiently reactive partners in this reaction. The reactivity of sterically hindered and/or *ortho* substituted iodoarenes has not been demonstrated. However biaryls bearing one *ortho* substituent of relatively small steric demand (e.g., from methoxybenzene or *N*-methylindole) have been prepared.

[2] Erosion of 2-selectivity in favor of the 3-position with *N*-substituted pyrroles has also been reported by Wang et al. in the Rh-catalyzed arylation of nitrogen heterocycles [63].

Functional groups including ketone, nitrile, aryl ether, and nitro groups are tolerated under these reaction conditions. Double arylation at the 2,5-positions of thiophenes is efficient in the absence of DME as an additive and, conversely, the arylation of 2-ethylthiophene with *m*- or *p*-diiodobenzene results in the double arylation products in moderate to good yields (46–62%).

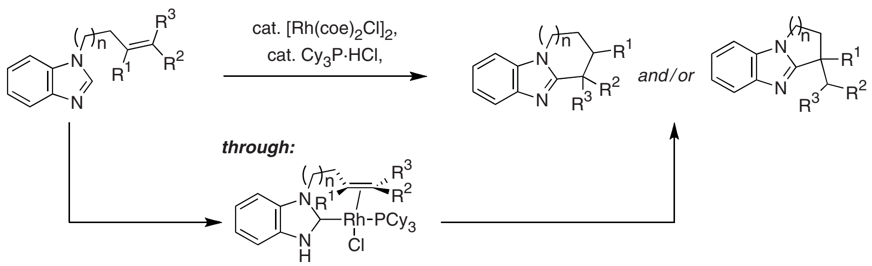
In addition to the scope and selectivity of the reaction, a number of additional experiments were performed to understand better the mechanism of this reaction. A series of rhodium(I) complexes of structure $RhCl(CO)L_2$ with $L = PPh_3$, $P[OCH(CH_3)_2]_3$, $P(OPh)_3$, $PhP[OCH(CF_3)_2]_2$, and $P[OCH(CF_3)_2]_3$ were prepared and tested in the catalytic arylation of 3-methoxythiophene with *p*-iodoacetophenone. Significant conversion to the 2-arylated thiophene was observed only in the case of the most π-acidic ligands ($PhP[OCH(CF_3)_2]_2$, 31%; $P[OCH(CF_3)_2]_3$, 94%), and a correlation was established between the electron-withdrawing character of the ligand as measured by the C≡O stretch frequency and the catalytic efficiency of the rhodium(I) complex in this reaction. The absence of a significant kinetic deuterium isotope effect, as established in an intramolecular competition experiment for the arylation of 2-deuteriothiophene with iodobenzene, indicates that cleavage of the C–H (or C–D) bond does not occur in the rate determining step of the catalytic cycle, and is consistent with an electrophilic metalation process analogous to that observed in cationic rhodium(III) porphyrin complexes. The presence of a stoichiometric amount of silver(I) carbonate is required for efficient catalytic reactions, but the specific role(s) of this reagent has not been established. The formation of cationic rhodium(III) complexes in situ by halide abstraction, inhibition of catalyst inactivation by iodide anions [79–82], and assistance in the oxidative addition step are among the plausible roles of silver(I) in this reaction. The addition of DME to the reaction mixture was also found to be critical for the suppression of undesired multiple arylation products, but the nature of the interaction responsible for this result has not been established. A tentative mechanism for this catalytic cycle has been proposed on the basis of these experiments and DFT calculations (Scheme 9) [83].



Scheme 9 Proposed catalytic cycle [73, 74]

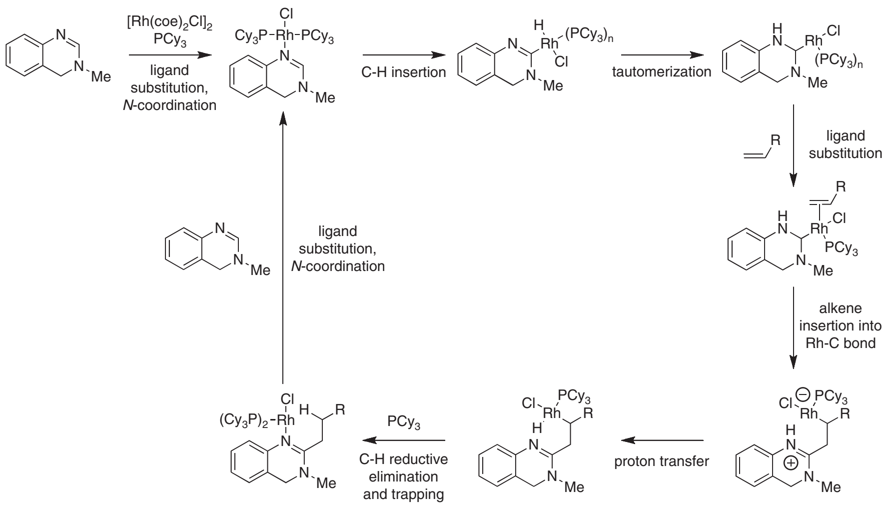
2.2 *Rhodium-Catalyzed C–H/C–X Arylation of Arenes Through N-Heterocyclic Carbene Formation*

Tan, Bergman, and Ellman have reported the discovery a new type of rhodium catalysis for the functionalization of C–H bonds based on the insertion of a rhodium(I) center in the C–H bond of a nitrogen heterocycle that result in the formation of a stable rhodium *N*-heterocyclic carbene (NHC) complex as a reaction intermediate (Scheme 10) [84, 85]. These were first applied to the intramolecular and then the intermolecular addition of nitrogen heterocycles to alkenes via C–H functionalization [86–96]. For these reactions, the combination of $[Rh(coe)_2Cl]_2$ (5–10 mol% Rh) with PCy_3 as a ligand (1.0-1.5 L:Rh) in the presence of catalytic amount of a weak acid additive, such as $Cy_3P{\cdot}HCl$, lutidinium chloride or $MgBr_2$, at elevated temperatures (150–200 °C) in THF was generally found to be the optimal conditions.

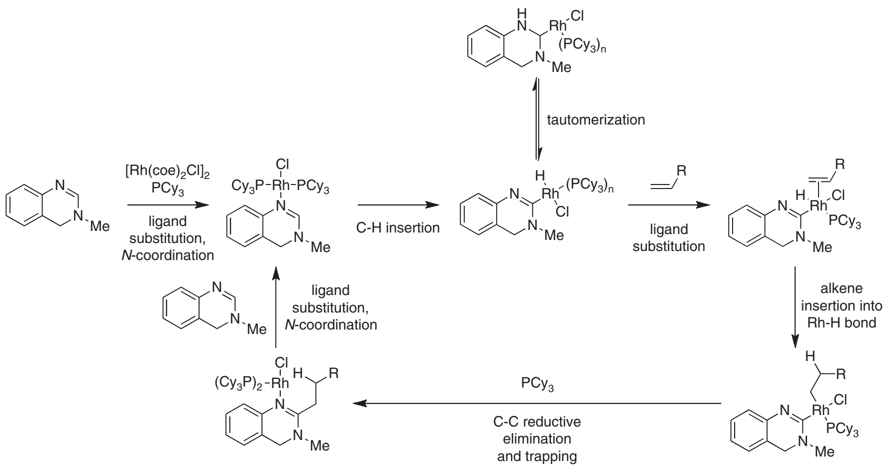


Scheme 10 Rh-catalyzed C–H addition of heterocycles to alkenes [84–96]

Detailed mechanistic experiments that include the preparation, isolation, and structural characterization of postulated intermediates, isotope labeling experiments, rate studies, and computational modeling have led to an attractive mechanistic proposal (Scheme 11). First, the rhodium(I) precursor exchanges ligands and is coordinated by the phosphines and the sp^2 nitrogen of the heterocycle to yield a *trans* square planar (*N*-heterocycle)$Rh(PCy_3)_2Cl$ complex. Insertion of the rhodium center into the adjacent C–H bond and intramolecular H-transfer results in the formation of a rhodium(I) NHC complex. Ligand exchange with an alkene is followed by insertion into the Rh-C bond, intramolecular proton transfer and C–H reductive elimination affording the product of direct C–H addition to the alkene. Finally, ligand exchange regenerates the catalyst. An alternative pathway involving the insertion of the alkene in an Rh–H bond followed by C–C reductive elimination has also been hypothesized (Scheme 12) [96]. The rhodium hydride could originate either from the reversible tautomerization of the NHC Rh(I) complex to a C-bonded σ-heteroaryl Rh(III) hydride or from the oxidative addition of a Brønsted acid additive (e.g., HCl) to a Rh(I) intermediate, providing a rationale for the rate acceleration in the presence of acid.



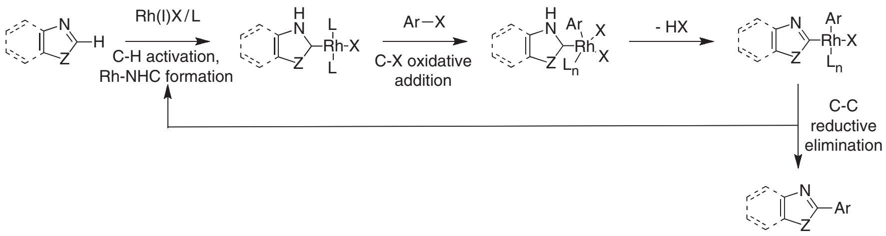
Scheme 11 Proposed catalytic cycle [84–96]



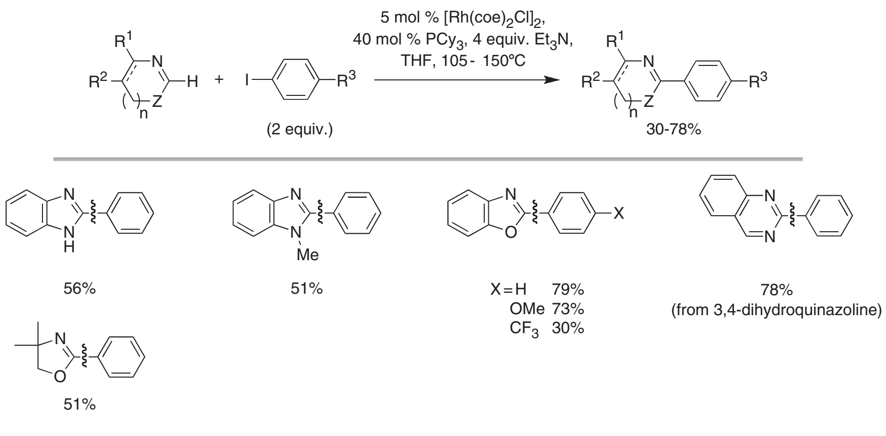
Scheme 12 A possible alternate catalytic cycle [96]

N-Heterocyclic carbenes being excellent σ-donor ligands, the electron-rich rhodium(I) complex can be expected to add oxidatively to aryl halides (or pseudo-halides), leading to a precursor to arylated heterocycles through reductive elimination of the NHC and σ-aryl ligand (Scheme 13) [97–101]. Shortly after their initial report of alkylation of heterocycles with alkenes, the Bergman and Ellman groups reported the catalytic arylation of certain nitrogen heterocycles capable of forming rhodium-NHC intermediates, such as benzimidazole, benzoxazole, 3,4-dihydroquinazoline, and oxazolines with iodoarenes [102].

The Rh(I)/PCy_3 catalytic system that was found to be optimal for the C–H addition of heterocycles to alkenes was also identified as an ideal first-generation catalyst for the arylation of nitrogen heterocycles with iodoarenes in the presence of a tertiary amine base. Under typical reaction conditions, the heterocycle (1 equiv.), ArI (2 equiv.), Et_3N (4 equiv.), $[Rh(coe)_2Cl]_2$ (0.05 equiv.), and PCy_3 (0.4 equiv.) are heated (105–150 °C) in THF (~0.11 M in heterocycle) for 6–18 h. Moderate to good chemical yields (30–78%) are obtained. The reaction is stereoselective for the position that is amenable to NHC formation in all cases (e.g., the 2-position in benzimidazole). Higher yields were obtained with more electron rich iodoarenes, but only a limited number of examples (2) with iodoarenes other than iodobenzene were presented (Scheme 14).



Scheme 13 General catalytic cycle for the C–H arylation of arenes through *N*-heterocyclic carbene formation [97–104]

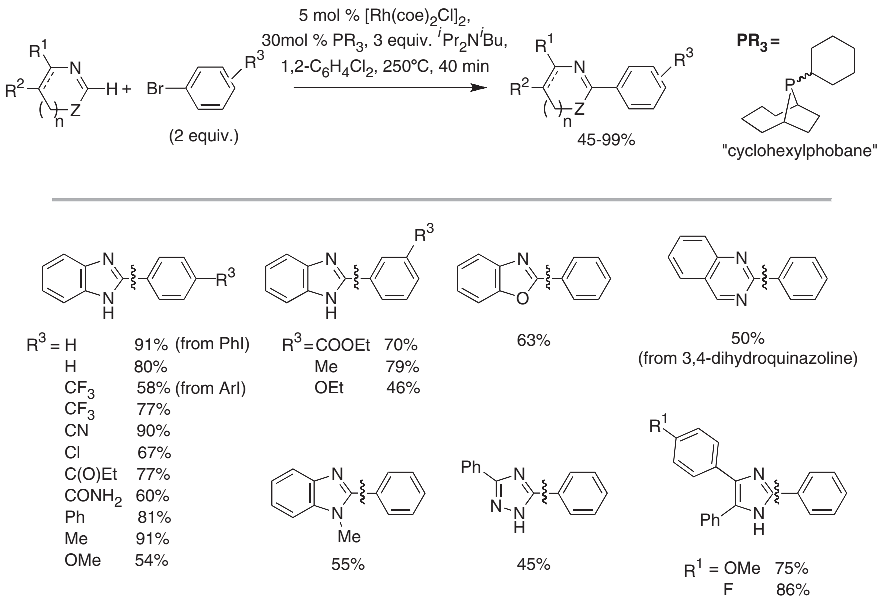


Scheme 14 First-generation Rh-catalyzed C–H arylation of heterocycles by Lewis et al. [102].

The scope of the reaction includes 1*H*-benzimidazole, 1-methylbenzimidazole, benzoxazole, 4,4-dimethyloxazoline, and 3,4-dihydroquinazoline as the heterocyclic partners, but in the latter case only the dehydrogenated product 2-arylquinazoline was isolated. Iodobenzene, *p*-iodoanisole, and *p*-iodotrifluoromethylbenzene are suitable coupling partners. Limited reactivity was observed with bromobenzene, and other aryl halides and pseudohalides (Cl, OTf) were unreactive. The reactivity of sterically hindered and/or *ortho* substituted substrates has not been demonstrated, and functional group compatibility for this procedure was not described in detail.

NMR analysis of the reaction mixture for the catalytic arylation of *N*-methylbenzimidazole with iodobenzene has revealed that an (NHC)Rh(PCy_3)$_2$Cl complex forms rapidly and is then gradually depleted from the reaction mixture. This complex was independently prepared and structurally characterized from the reaction of the heterocycle with stoichiometric amounts of [Rh(coe)$_2$Cl]$_2$ and PCy_3, and found to be a kinetically competent catalyst for this reaction. While a 4:1 L:Rh (L = PCy_3) ligand to rhodium ratio was found to give optimal yields in catalytic runs, the addition of excess phosphine in the stoichiometric reaction of the (NHC)Rh(PCy_3)$_2$Cl complex with iodobenzene was found to lower the reaction rate. This indicates both that dissociation of a phosphine occurs prior to oxidative addition and that excess ligand might be required to extend the catalyst lifetime against decomposition. A significant side-reaction and possible catalyst deactivation pathway was identified as the rhodium-mediated dehydrogenation of the PCy_3 ligand, leading to the formation of rhodium hydrides that participate in the hydrodehalogenation of iodoarenes and the requirement for an excess of iodoarene for the reaction to reach completion.

In a second report, the Bergman and Ellman groups improved on their original procedure for the arylation of heterocycles with aryl halides [103]. The key improvements over the previous method were three-fold: (1) the use of the hindered tertiary amine base ^{i}Pr$_2$N^{i}Bu in replacement of Et_3N; (2) microwave irradiation for rapid (<1 h), high temperature (250 °C) reactions in 1,2-dichlorobenzene; (3) the use of bulky bicyclic trialkylphosphine ligands of the phobane family in replacement of PCy_3 (Scheme 15). Under typical reaction conditions, the heterocycle



Scheme 15 Second-generation Rh-catalyzed C–H arylation of heterocycles by Lewis et al. [103]

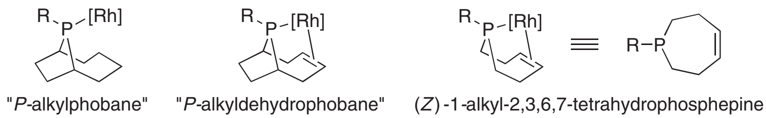
(1 equiv.), ArX (2 equiv.), $^{i}Pr_2N^{i}Bu$ (3 equiv.), $[Rh(coe)_2Cl]_2$ (0.05 equiv.), and 9-cyclohexylbicyclo[4.2.1]-9-phosphanonane ("cyclohexylphobane," as a mixture of *exo* and *endo* isomers, 0.3 equiv.) are heated under microwave irradiation (250 °C), in 1,2-dichlorobenzene (~0.05–0.3 M in heterocycle) for 40 min. Moderate to excellent (45–99%) chemical yields are obtained. Conventional heating (150 °C in THF, ~0.06 M in heterocycle) in sealed tubes is also possible at the expense of longer reaction times (24 h) and depressed yields. The reaction selectivity remains consistent with a mechanism based on the formation of a NHC-rhodium complex as an intermediate.

In addition to heterocycles that were successfully arylated under first-generation procedure, the reaction scope is broadened to include bis(aryl)imidazoles and triazoles, but benzothiazole was found to be incompatible. As previously observed, 3,4-dihydroquinazoline is a reactive coupling partner but only the dehydrogenated product 2-arylquinazoline is obtained. Furthermore, in addition to iodoarenes, bromoarenes are reactive under these reaction conditions. The reaction is tolerant of a large number of functional groups and haloarene substituents, including nitrile, chloro, primary amide, ketone, and ester. Both electron-poor and electron-rich bromoarenes showed good reactivity. Both *para*- and *meta*-substituents were well tolerated, but *ortho*-substituents (OMe, CF_3) shut down the reaction.

The use of the phobane ligand with its rigid bicyclic structure was shown to reduce significantly, though not completely suppress, the hydrodehalogenation of the haloarenes that occurred when PCy_3 is employed as ligand, even with less reactive coupling partners. Among the tested ligands, 9-cyclohexylbicyclo[4.2.1]-9-phosphanonane ("cyclohexylphobane") was identified as a better catalyst than other bicyclic trialkylphosphines such as 9-cyclohexylbicyclo[3.3.1]-9-phosphanonane. While cyclohexylphobane is easily prepared as a mixture of *exo* and *endo* isomers, their separation is tedious. Nevertheless, since under the reaction conditions (microwave irradiation) the mixture of isomers entirely converts to the *exo* isomer, little difference was found between the use of either isomer or that of the mixture of isomers as ligand in catalytic reactions.

Further investigations of the reaction aimed at an understanding of the origins of the parasitic hydrodehalogenation reaction and providing a rationale for the higher efficiency of cyclohexylphobane ligands led to an interesting discovery and to the development of a third-generation catalytic system [104]. NMR analysis of reaction mixtures of $[Rh(coe)_2Cl]_2$ and *exo*-cyclohexylphobane (2:1 L:Rh) heated at 125 °C in THF indicated that first a chlorobis(phosphine)rhodium(I) complex forms, but that one of the two ligands is selectively dehydrogenated and leads to the formation of a new chlororhodium(I) complex bearing one monodentate cyclohexylphobane and one bidentate phosphine-alkene cyclohexyldehydrophobane (Scheme 16). This new complex was also identified in the crude catalytic reaction mixtures for the arylation of heterocycles. The complex was independently prepared, structurally characterized, and its catalytic activity was found to be indistinguishable from that of Rh(I)/cyclohexylphobane, suggesting that an identical active catalytic species is formed in both reactions.

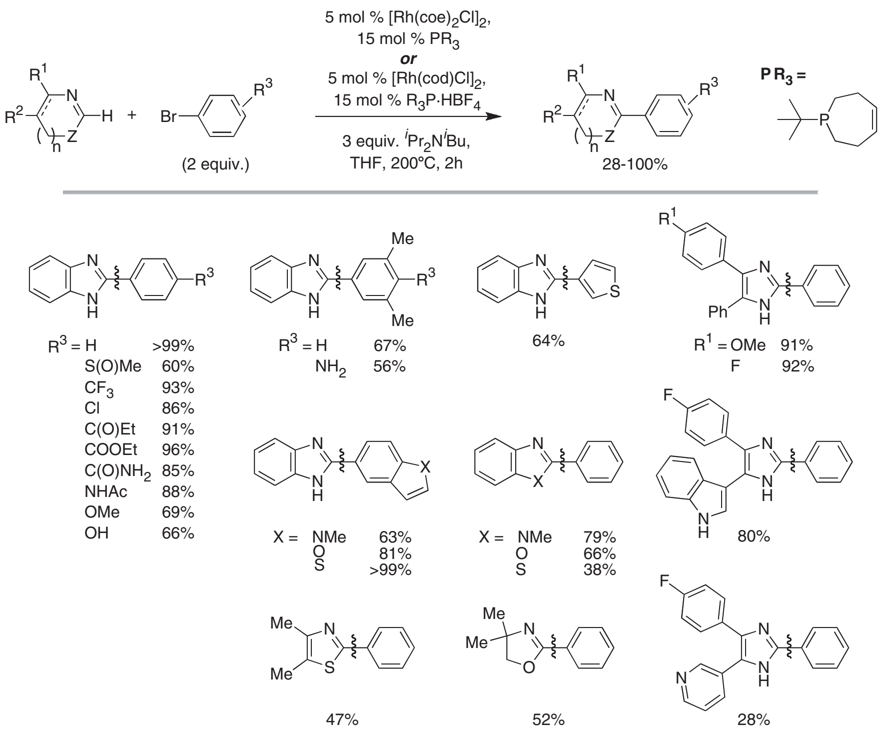
Structure-property relationship studies of bidentate phosphine-alkene ligands in the catalytic arylation of heterocycles were pursued with the synthesis of a



Scheme 16 Evolution of ligands in the Rh-catalyzed C–H arylation of heterocycles by Lewis et al. [104]

series of (*Z*)-1-substituted 2,3,6,7-tetrahydrophosphepine ligands. The *P*-*tert*-butyl substituted tetrahydrophosphepine ligand was found to have excellent catalytic properties when employed in a 1.5:1 L:Rh with $[Rh(coe)_2Cl]_2$. Other substituents including *P*-aryl resulted in fast initial reaction rates but more rapid catalyst deactivation. Structural characterization of an independently synthesized chloro(phosphine)rhodium(I) dimer where the ligand is (*Z*)-1-cyclohexyl-2,3,6,7-tetrahydrophosphepine established the close relationship with that of the cyclohexylphobane-derived complex, and the fact that a bicyclic structure is not required for high catalytic activity.

The use of (*Z*)-1-*tert*-butyl-2,3,6,7-tetrahydrophosphepine ligand was thus identified as a superior catalytic system for the arylation of heterocycles with bromoarenes, with higher conversions and low incidence of hydrodehalogenation (Scheme 17). Under typical reaction conditions, the heterocycle (1 equiv.), ArBr

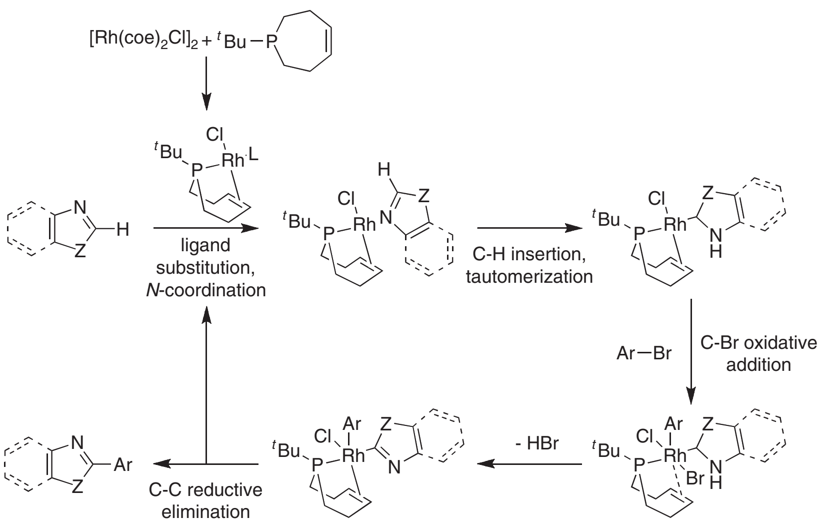


Scheme 17 Third-generation Rh-catalyzed C–H arylation of heterocycles by Lewis et al. [104]

(2 equiv.), $^{i}Pr_2N^{i}Bu$ (3 equiv.), $[Rh(coe)_2Cl]_2$ (0.05 equiv.), and (*Z*)-1-*tert*-butyl-2,3,6,7-tetrahydrophosphepine (0.15 equiv.) are heated under microwave irradiation (200 °C) in THF (~0.1–0.3 M in heterocycle) for 2 h. Alternatively, the commercially available (Aldrich) and air-stable tetrafluoroborate salt of the phosphine ligand can be used in replacement of the free phosphine [105], and 1,4-dioxane may be used as replacement for THF. Moderate to excellent (28-100%) chemical yields are obtained, and the catalyst loading can be reduced to 2 mol% Rh (1.5:1 L:Rh) without significant reduction of yield but at the expense of longer reaction times (24-120 h) under conventional heating (165–175 °C). As previously observed, the selectivity for the arylation reaction remains consistent with the formation of a rhodium-carbene intermediate.

The scope of the reaction is broadened by the use of the tetrahydrophosphepine ligand. In addition to heterocycles that were reactive with PCy_3 or cyclohexylphobane as ligands, 4,5-dimethylthiazole can be arylated. The scope with respect to the bromoarene partner is also broadened to include electron-rich bromoarenes and heteroaryl bromides such as 3-bromothiophene, 5-bromo-*N*-methylindole, 5-bromobenzofuran, and 5-bromobenzothiophene. Functional groups including sulfoxides, chlorides, fluorides, ketones, esters, primary and secondary amides, phenols, anilines, and pyridines can be tolerated under these conditions. Sterically hindered and/or *ortho* substituted substrates are unreactive, but *meta* and *para* substituted substrates are well-tolerated.

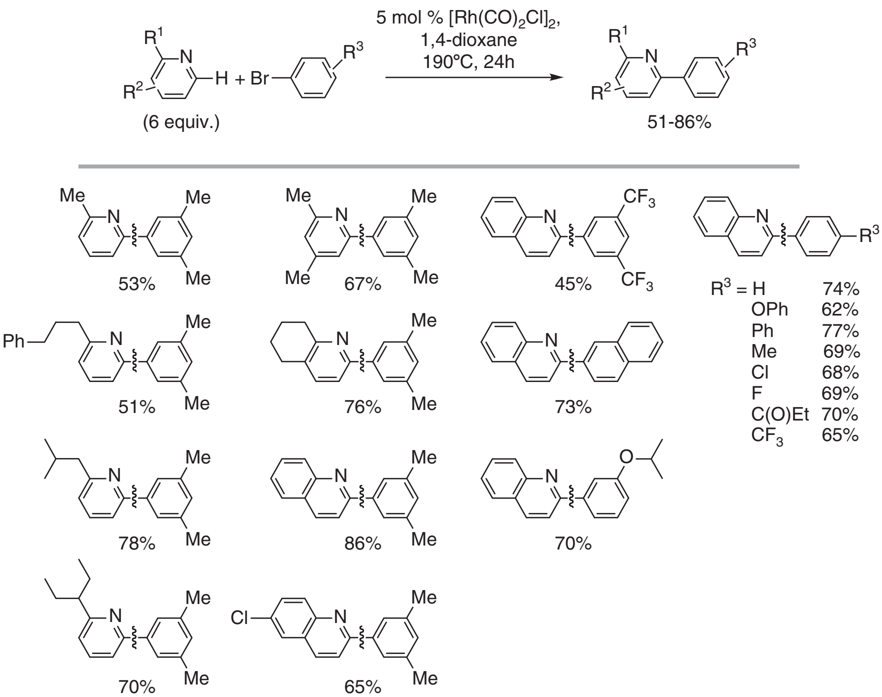
The mechanism for heterocycle arylation is likely analogous to that postulated with monodentate trialkylphosphine ligands (Scheme 18). The higher reactivity and extended catalyst lifetime observed with bidentate phosphine-alkene ligand might



Scheme 18 Proposed catalytic cycle for the C–H arylation of arenes through *N*-heterocyclic carbene formation with tetrahydrophosphepine ligands [104]

be provided by the easily reversible hemilability of the alkene ligand. In contrast, trialkylphosphines can stabilize the catalyst in the presence of an excess phosphine, but only at the expense of a reduced reaction rate due to the required ligand dissociation at a critical step in the catalytic cycle.

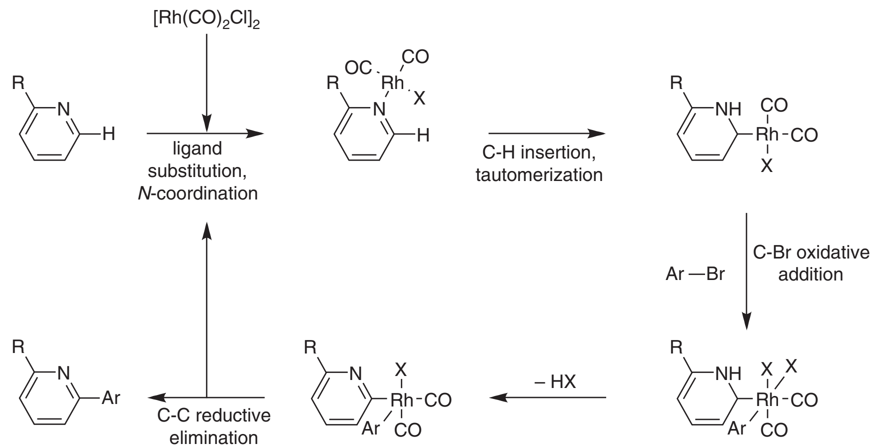
The Bergman and Ellman groups have earlier demonstrated the rhodium-catalyzed C–H addition of pyridines and quinolines to alkenes resulting in 2-alkylated heterocycles under conditions (Rh(I), $PCy_3/Cy_3P{\cdot}HCl$) similar to those required for the alkylation of 5-membered heterocycles (benzimidazoles, benzoxazoles, benzothiazoles, oxazolines, etc.) and 3,4-dihydroquinazolines [94]. By contrast, the catalytic arylation of pyridines and quinolines under conditions (Rh(I), trialkylphosphine or dehydrophosphepine, hindered tertiary amine base) effective for the arylation of 5-membered heterocycles and 3,4-dihydroquinazolines did not proceed. Extensive screening of catalysts and reaction conditions led to the discovery that, while electron-rich rhodium(I) catalysts were inefficient, the electron-deficient $[Rh(CO)_2Cl]_2$ in the absence of other ancillary ligands is a good precatalyst for the 2-position selective direct arylation of pyridines and quinolines with bromoarenes (Scheme 19)[176]. Various additives such as phosphines, phosphites, Brønsted or Lewis acid and bases did not result in improved yields and in certain cases completely suppressed the catalytic activity.



Scheme 19 Rh-catalyzed C–H arylation of pyridines by Berman et al. [176]

Under typical reaction conditions, the pyridine or quinoline (3–6 equiv.), ArBr (1 equiv.), and $[Rh(CO)_2Cl]_2$ (0.05 equiv.) are heated (175–190 °C) in 1,4-dioxane (0.3 M in ArBr) for 24 h. Moderate to good (51–86%) chemical yields are obtained, and the catalyst loading can be reduced to 2 mol% Rh while maintaining good yields by conducting the reaction in neat substrates. Comparable yields were obtained for electron-rich and electron-poor bromoarenes. The reaction is however limited in scope to pyridines substituted (or fused) at the 2-position and quinolines. This requirement is consistent with that observed for the rhodium(I) catalyzed C–H addition of pyridines and quinolines to alkenes and for other processes involving the formation of a pyridine- or quinoline-derived metal-NHC complex [106–108]. Sterically hindered and/or *ortho* substituted electrophiles are unreactive, but *meta* and *para* substituted electrophiles are well tolerated. Functional group compatibility includes aryl chlorides and fluorides, ketones and ethers. Interestingly, the reactivity of 2-trialkylsilyl (e.g., TIPS) substituted pyridines, good precursors to functionalized 2*H*-pyridines after protodesilylation, has been demonstrated for alkylation reactions [94], and may also be applicable to the C–H arylation of pyridines.

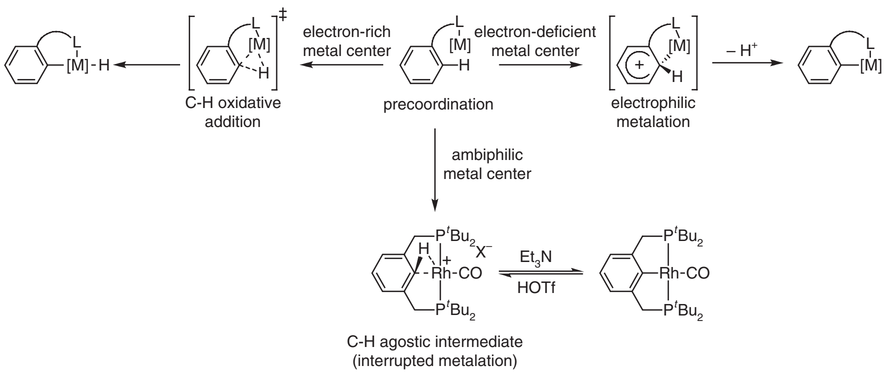
No rationale is provided for the particular catalytic efficiency of the $[Rh(CO)_2Cl]_2$ for this transformation, or for the suppression of catalytic activity in the presence of ligands that improve the reactivity in closely related reactions [176]. Nevertheless, this reaction is likely to share a common mechanism with other heterocyle arylation processes that include heterocycle coordination, C–H insertion and tautomerization to the rhodium(I) NHC complex, oxidative addition to the bromoarene, and reductive elimination of the arylated heterocycle (Scheme 20).



Scheme 20 Proposed catalytic cycle for the C–H arylation of pyridines through *N*-heterocyclic carbene formation [176]

2.3 Rh-Catalyzed C–H/C–X Arylation of Arenes Through Directed Metalation

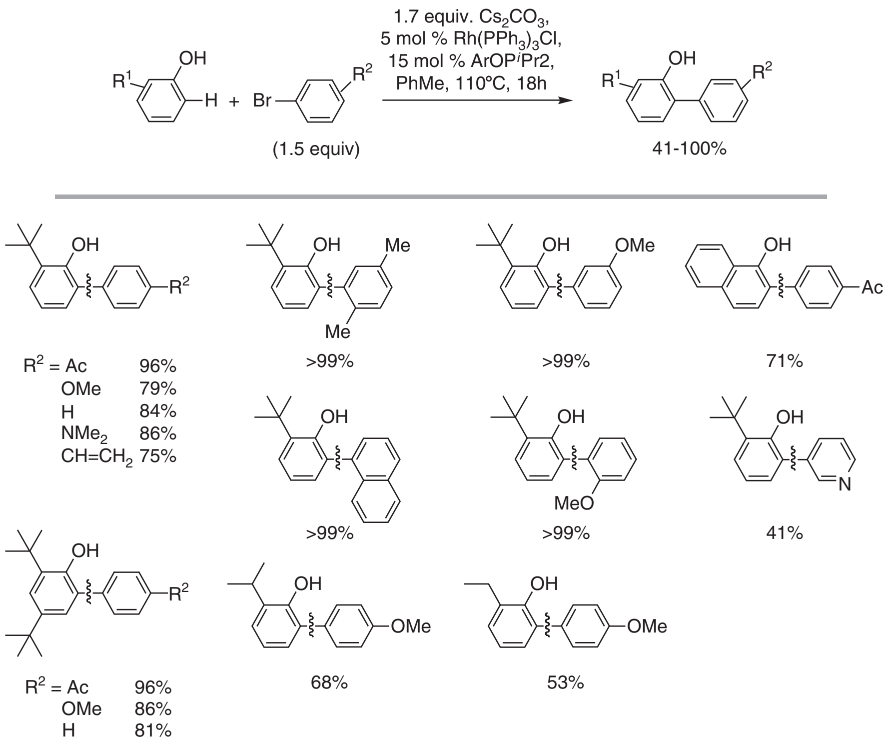
Arene substrates bearing a basic site that can coordinate to transition metal complexes can facilitate arene C–H cleavage when the geometry and electronics of the resulting complex, or the entropic advantage associated with precoordination ("effective molarity"), favor intramolecular C-H cleavage and metalation [34, 109–111]. Directed metalation is thus one of the most effective ways to increase the rates and/or to control the regioselectivity of catalytic cycles that involve arene C–H cleavage. Several pathways are possible for the metalation step depending on the electronic properties of the transition metal centers, with formal C–H oxidative addition being more likely with electron-rich metal centers and electrophilic metalation being more likely for electron-deficient metal centers (Scheme 21). Rhodium complexes have been shown to participate in these processes, as well as alternate and/or intermediate metalation pathways. In a particularly interesting example, the Milstein group has reported that a cationic, relatively electron-poor rhodium(I) complex of a pincer-type PCP ligand forms a stable agostic interaction with an arene σ C–H bond [112, 113]. The electronics of the complex are such that oxidative addition of the C–H bond by the electron-deficient rhodium(I) center does not occur, but yet that the rhodium center is not sufficiently electrophilic to undergo electrophilic metalation. Nonetheless, electron-donation from the σ C–H bond to the rhodium center dramatically increases the acidity of the aromatic C–H bond, to the degree where weak amine bases can abstract this proton and trigger the reversible metalation of the arene.



Scheme 21 Directed metalation pathways [109–113]

A number of research groups have developed rhodium-catalyzed methods for the C–H bond arylation of arenes that likely proceed through cyclometalated intermediates. Aryl phosphites and phosphinites undergo facile orthometalation with rhodium complexes leading to the five-membered metalacycles. The research groups of Bedford and Oi have exploited this reactivity to develop rhodium-catalyzed methods for the direct *ortho* arylation of phenols with haloarenes that rely on the reversible transesterification of phosphorus(III) esters, amides, and halides with phenols and/or phenoxides [114–117].

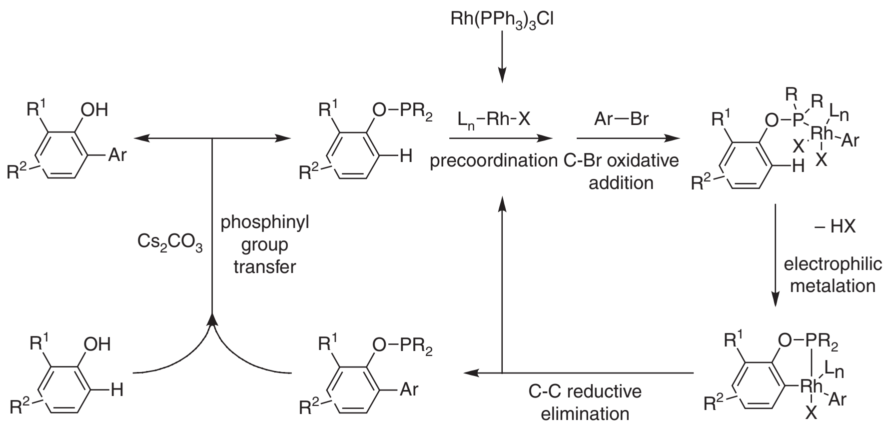
In a first report, the Bedford group reported that Wilkinson's catalyst ($RhCl(PPh_3)_3$) can catalyze the *ortho* arylation of phenols with haloarenes in the presence of a base and of a catalytic amount of an aryl dialkylphosphinite (Scheme 22). Other ligands such as bulky triarylphosphites can also be employed, but are less efficient and require a large excess of the bromoarene. Under typical conditions, the phenol (1 equiv.), ArBr (1.5 equiv.), Cs_2CO_3 (1.7 equiv.), $RhCl(PPh_3)_3$ (0.05 equiv.), and a matched aryl diisopropylphosphinite ($ArOP^iPr_2$, 0.15 equiv.) are refluxed (~110 °C) in toluene (0.1 M in phenol) for 18 h. Good to excellent (68–100%) yields are obtained for the reaction of bromoarenes with phenols bearing a bulky *ortho* substituent (e.g., *tert*-butyl, *iso*-propyl or 1-naphthol). Phenols without *ortho* substituents are unreactive, and less bulky *ortho* substituents (e.g., ethyl, methyl) lead to depressed yields. Both electron-rich and electron-poor bromoarenes are reactive, while chloroarenes give much lower yields. In all cases the arylation was found



Scheme 22 Rh-catalyzed C–H *ortho* arylation of phenols by Bedford et al. [114, 116]

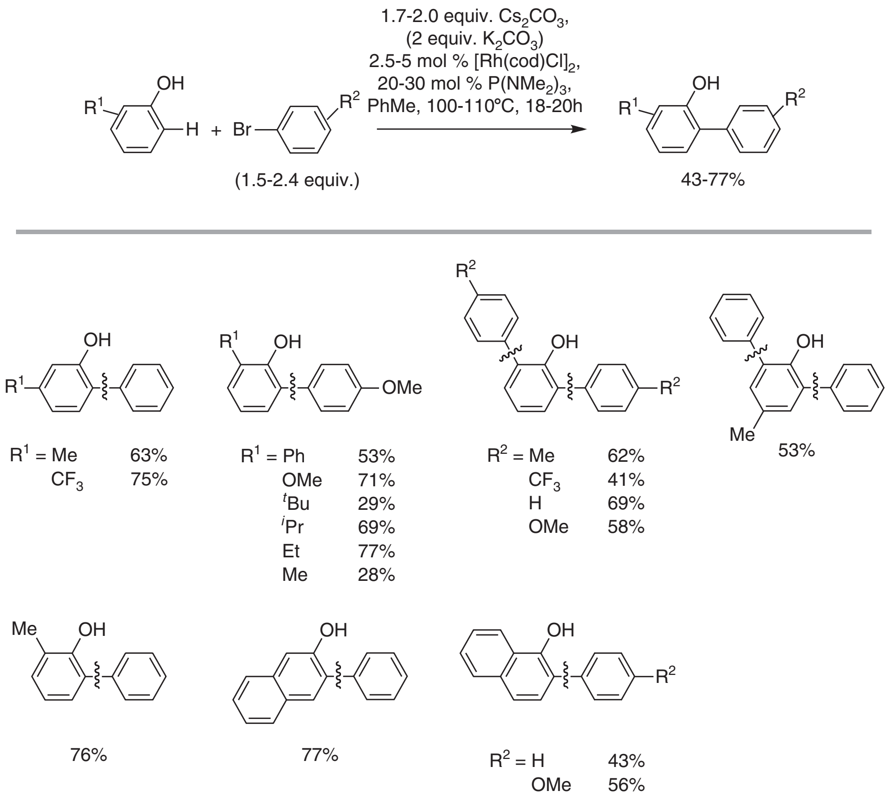
to be *ortho* selective, but multiple arylation can occur with suitable substrates. The reaction scope with respect to the haloarene also includes *ortho* substituted substrates, and ketones and ethers are tolerated functional groups.

The high selectivity for *ortho* arylation constitutes evidence that the reaction proceeds through cyclometalation of a phenol incorporated within the phosphinite ligand. Preliminary mechanistic studies and the requirement for a bulky *ortho* substituent on the phenol, which may restrict the conformational freedom of the phosphinite to a more favorable geometry, suggest that orthometalation may be the rate-determining step of the catalytic cycle when bromoarenes are employed as electrophilic coupling partners. A possible reaction mechanism involving oxidative addition of the bromoarene, coordination of the aryl dialkylphosphinite, electrophilic orthometalation by rhodium(III), and reductive elimination in parallel with a base-catalyzed transesterification of the phosphinic esters with phenoxides was suggested, but an alternative pathway that involves cyclometalation by C–H oxidative addition to a rhodium(I) center could not be ruled out (Scheme 23).



Scheme 23 Proposed catalytic cycle for the C–H *ortho* arylation of phenols [114–117]

Independently, the Oi group reported an analogous rhodium-catalyzed *ortho* arylation of phenols with bromoarenes [115]. In their procedure, hexamethylphosphotriamide (HMPT) acts as the phosphinyl group transfer agent that enables the orthometalation of a rhodium-bound aryl phosphite or phosphoramidate (Scheme 24). Under typical conditions, the phenol (1 equiv.), ArBr (2.4 equiv.), K_2CO_3 (2 equiv.), Cs_2CO_3 (2 equiv.), $P(NMe_2)_3$ (0.2 equiv.), and $[Rh(cod)Cl]_2$ (0.025 equiv.) are heated (100 °C) in toluene (reaction molarity unspecified) for 20 h. Moderate to good yields are obtained (43–77%), and the use of HMPT as a ligand and phosphinyl group transfer agent allows for the arylation of phenols that do not bear an *ortho* substituent, including phenol itself. In addition, the use of HMPT circumvents the problem of having to use an aryl dialkylphosphinate ligand



Scheme 24 Rh-catalyzed C–H *ortho* arylation of phenols by Oi et al. [115] or Bedford et al. [116]

that matches the phenol substrate. The reactivity of electron-poor and electron-rich phenols and bromoarenes has been demonstrated. Multiple arylation occurs and is predominant with most phenols that do not possess *ortho* substituents. This is indicative of the positive influence of *ortho* substituents on the rates of cyclometalation, as previously observed by the Bedford group [114, 116]. Mixtures of K_2CO_3 and Cs_2CO_3 were empirically found to perform slightly more efficiently than Cs_2CO_3 alone, but a rationale for this observation has not been forthcoming.

In a follow-up paper, the Bedford group performed a comparative study of the two methods [116]. In agreement with the previous results, it was established that the use of $RhCl(PPh_3)_3$/$ArOP^iPr_2$ gave superior yields for the arylation of phenols bearing large substituents at the 2-position and $[Rh(cod)Cl]_2$/$P(NMe_2)_3$ was more effective for the arylation of phenols that do not have *ortho* substituents. Interestingly, the direct arylation of 3-substituted phenols favors the 6-position selective arylation in the $[Rh(cod)Cl]_2$/$P(NMe_2)_3$ system. Further optimization of the $RhCl(PPh_3)_3$/

ArOP^{i}Pr$_2$ system allows for a reduction of the catalyst loading to 3 mol% Rh without a significant reduction in yields, and the use of less expensive K_3PO_4 as a base in certain cases. An extended survey of the substrate scope identified that a number of 2,6-disubstituted bromoarenes and heteroaryl halides including pyridines and thiophenes are reactive substrates. 2-Bromopyridine and 2-bromothiophene are poor substrates however, possibly due to the formation of catalytically inactive stable metal chelates. Finally, additional functional groups including anilines, alkenes, and chloroarenes are tolerated.

A major disadvantage of the preferred RhCl(PPh$_3$)$_3$/ArOP^{i}Pr$_2$ catalytic system is the need for the preparation of an aryl diisoprolylphosphinite ligand that matches the phenolic substrate to avoid product contamination with ligand-derived arylated by-products. In a recent report, chlorodialkylphosphines were identified as practical, commercially available ligands that can, in combination with [Rh(cod)Cl]$_2$, replace RhCl(PPh$_3$)$_3$/ArOP^{i}Pr$_2$ to achieve identical results while circumventing this drawback [117]. Presumably, the phenolic substrate reacts with the chlorodialkylphosphine in the presence of a base to generate the aryl dialkylphosphinite in situ. This hypothesis is consistent with the observation that, as for aryl dialkylphosphinites, the diisopropylchlorophosphine gave the best results among the screened dialkylchlorophosphines.

In addition to phosphorus, basic nitrogens can act as binding sites to direct the metalation of arenes in catalytic C–H arylations. In fact, the precoordination of nitrogen heterocycles to rhodium complexes prior to C–H insertion and tautomerization to the Rh-carbenes described by the Bergman and Ellman groups (see above) can be considered a particular subset of nitrogen-directed C–H metalations. Nevertheless, directed metalation through cyclometalation remains more common, and has also been employed in the Rh-catalyzed C–H arylation of arenes. Pyridines were found to be efficient directing groups for the Rh-catalyzed decarbonylative arylation of heterocyclic arenes with acyl chlorides, as recently reported by Zhao and Yu [118]. Under typical reaction conditions, the 2-substituted pyridine or fused pyridine (1 equiv.), ArCOCl (1.5–4 equiv.), [Rh(cod)Cl]$_2$ (0.05–0.10 equiv.), Na_2CO_3 (2–4 equiv.), and 4 Å molecular sieves are heated (145 °C) in “xylene”[3] (~0.15 M in pyridine substrate) for 16 h. In general, good to excellent yields (60-95%) are obtained with aromatic acid chlorides (Scheme 25).

In all cases, the regioselectivity observed is consistent with a cyclometalated intermediate. Multiple arylation also occurs with substrates bearing more than one C–H bond susceptible to cyclometalation. The efficiency of the reaction is dependent on the directing ability of the substituted or fused pyridine substrate. Rigid substrates such as benzo[*h*]quinoline afford higher yields than freely rotating 2-arylpyridines. Heterocycles that afford 5-membered metalacyclic intermediates (benzo[*h*]quinoline, 2-arylpyridines) are more reactive than those that afford 6-membered metalacyclic

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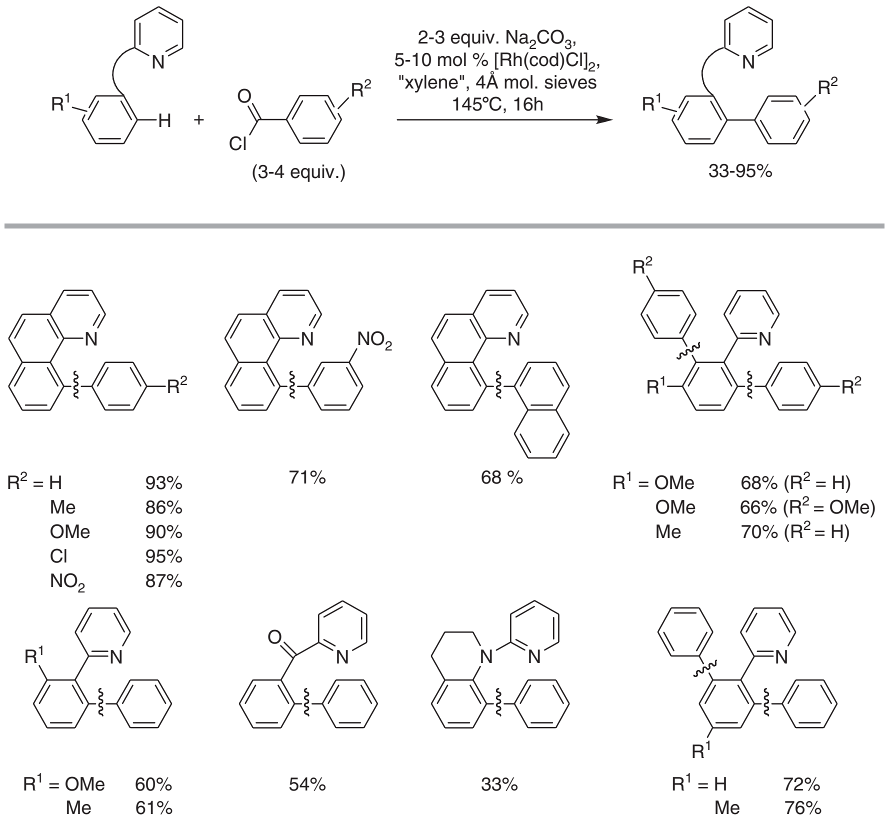
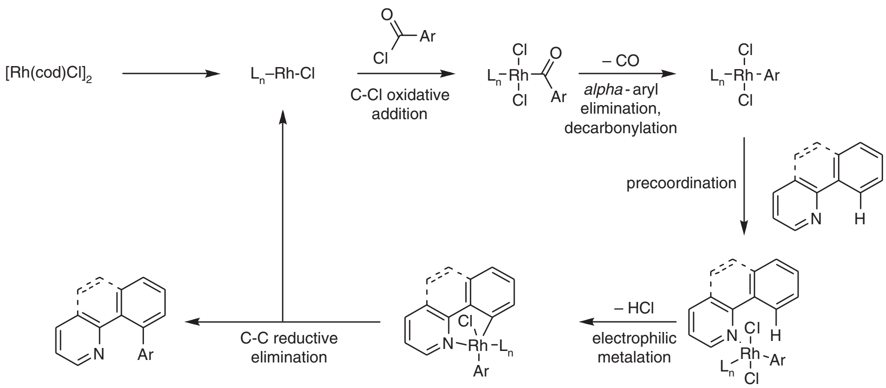
[3] The authors do not specify whether *o*-, *m*-, *p*-xylene, or a mixture of xylenes isomers is employed as solvent.



Scheme 25 Rh-catalyzed decarbonylative directed C–H arylation of arenes by Zhao and Yu [118]

intermediates (2-benzoylpyridine, 1-(pyridin-2-yl)-1,2,3,4-tetrahydroquinoline). Electron-rich or electron-poor benzoyl chlorides and cinnamoyl chlorides offer comparable reactivity, while aliphatic acid chlorides offer at best modest reactivity. Phenylglyoxalyl chloride also undergoes double decarbonylation to afford arylated products. Interestingly, the presence of a phosphine ligand greatly suppressed the catalytic activity. The reaction is compatible with ethers, ketones, chloroarenes, nitroarenes, and alkenes. Only one example of arylation between sterically hindered and/or *ortho* substituted arylation partners (benzo[*h*]quinoline and 1-naphthoyl chloride, 68% yield) has been demonstrated.

The reaction mechanism is proposed to consist of oxidative addition of the acyl chloride to a rhodium(I) center, decarbonylation, coordination to the substrate and cyclometalation followed by reductive elimination, affording the arylated product and regenerating the rhodium(I) catalyst (Scheme 26). Alternative proposals in which certain elementary steps are interchanged are also plausible.

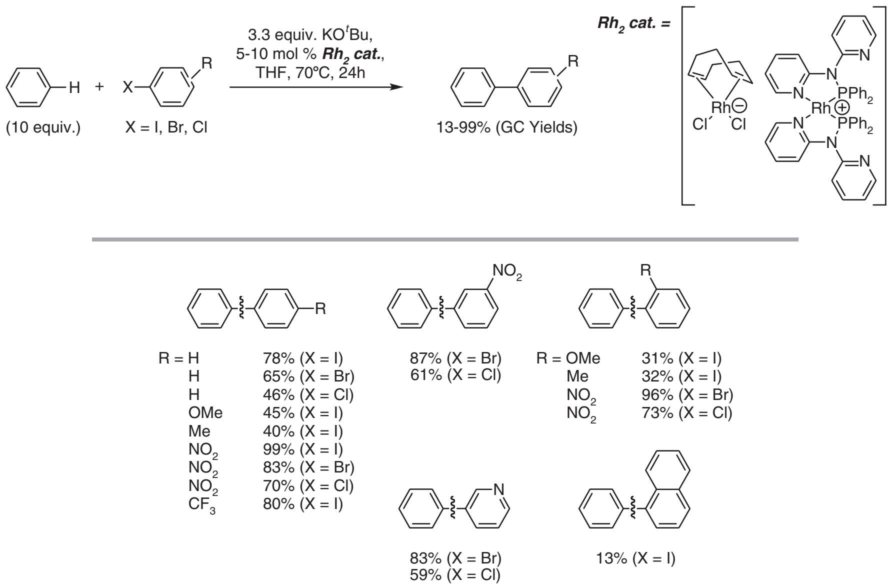


Scheme 26 Proposed catalytic cycle for the decarbonylative directed C–H arylation of arenes [118]

2.4 *Rh-Catalyzed C–H/C–X Arylation of Arenes Through Other or Unknown Mechanisms*

Rh-catalyzed methods for the C–H/C–X arylation of arenes do not always fall within the previously described general categories with respect to the mode and regioselectivity of C–H cleavage (electrophilic metalation, NHC-Rh complex formation, directed metalation). In particular, an interesting and powerful catalyst that does not appear to belong to one of these categories has been reported by Proch and Kempe [119]. Mixing of $[Rh(cod)Cl]_2$ with the P∩N ligand [bis(2-pyridyl)amino]diphenylphosphine in a 1:1 L:Rh ratio results in a bimetallic salt-like complex composed of a $[Rh(cod)Cl_2]^-$ anion and a doubly P∩N ligated rhodium(I) cation. This bimetallic complex is a remarkably efficient catalyst for the arylation of unactivated arenes (e.g., benzene) with iodoarenes in the presence of KO^{t}Bu as a base. The arylation can proceed at comparatively low temperatures (70 °C), and can reach TONs as high as 780 (Scheme 27).

Under typical conditions, the arene (10 equiv.), ArX (1 equiv.), KO^{t}Bu (3.3 equiv.), $[Rh(cod)Cl]_2$ (0.001–0.10 equiv.), and [bis(2-pyridyl)amino]diphenylphosphine (0.002–0.2 equiv.) are heated (70 °C) in THF (~0.4 M in ArX) for 24 h. Poor to good yields (13–83%; GC yields) are obtained for the arylation of benzene and toluene with iodoarenes at low catalyst loadings (0.2-2 mol% Rh); good to excellent yields (65–97%; GC) for the arylation of benzene with bromoarenes (with 10 mol% Rh) and moderate to good yields (46–73%; GC) for the arylation of benzene with chloroarenes (with 20 mol% Rh) are also reported. The scope of this reaction with respect to the arene partner has been demonstrated only for benzene and toluene. In the latter case, poor regioselectivity (~7:2:1 *o*:*m*:*p*) is observed. The reaction scope with respect to haloarene is broad and includes



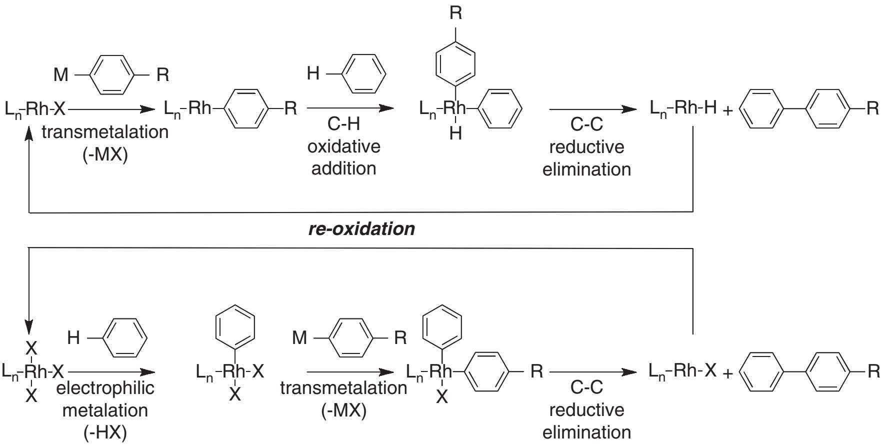
Scheme 27 Rh-catalyzed C–H arylation of benzene by Proch and Kempe [119]

electron-rich, electron-poor, *ortho* substituted and heterocyclic (3-bromopyridine and 3-chloropyridine) substrates. Functional group compatibility also includes nitroarenes and ethers.

A number of control and kinetic experiments were conducted to help establish a mechanistic proposal. Catalytic arene arylation occurs only in the presence of both the anion and cation of the bimetallic complex, and the reaction is suppressed when one of the ionic components is replaced by a weakly interacting counter-ion (Et_4N^+ or $B(Ar_F)_4^-$ where $Ar_F = 3,5\text{-}C_6H_3(CF_3)_2$). Kinetics of the stoichiometric reaction between the bimetallic complex and chlorobenzene in THF were established to be pseudo-first-order in chlorobenzene. However, since the identity of the reaction product has not been established, and since this reaction is conducted in the absence of arene or base, direct relevance to the catalytic cycle is unclear. The regioselectivity observed in the arylation of toluene (~7:2:1 *o*:*m*:*p*) with iodobenzene might be indicative of a radical aromatic substitution pathway. Hammett correlation of the direct arylation of benzene with iodoarenes shows only a modest electronic susceptibility ($\rho = 1.33$), which may be construed as additional evidence for radical pathways, but may instead originate from the fact that the rate-determining step of the catalytic cycle does not involve the cleavage of the Ar–X bond when iodoarenes are employed as coupling partners. Hence, the mechanistic complexity and superior catalytic activity of the bimetallic rhodium catalyst in the challenging C–H arylation of unactivated arenes warrants further investigation.

3 C–H/C–M Arene Arylation (Rh-Catalyzed Oxidative Coupling Methods)

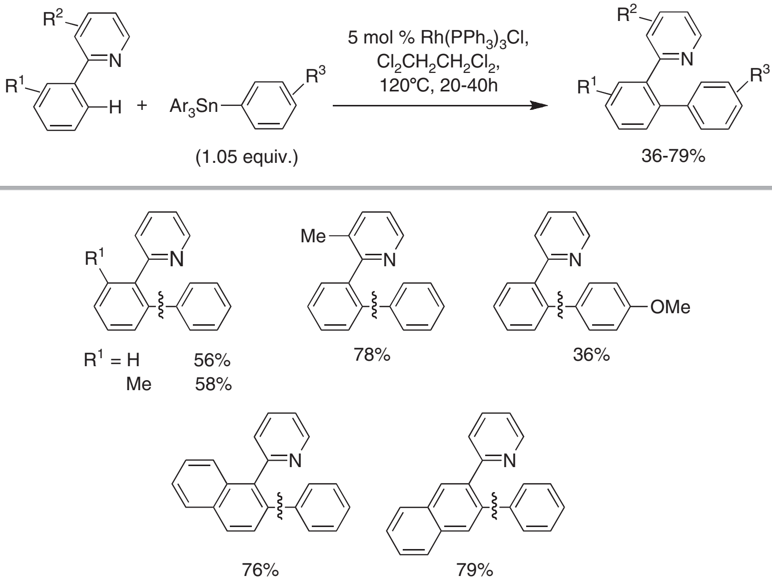
Rh-catalyzed C–H arene arylation are generally believed to proceed through a *cis* bis(σ-aryl)rhodium(III) intermediate that reductively eliminates to yield the desired arylated arene. In the preceding section, methods in which one of the σ-aryl ligands is introduced by C–H cleavage and the other by the oxidative addition of a haloarene to a rhodium(I) center (C–H/C–X coupling) have been described. The second σ-aryl ligand can instead be introduced on the key catalytic intermediate by the transmetalation of a suitable organometallic reagent to the rhodium center. In addition, catalytic cycles in which transmetalation precedes C–H oxidative addition are possible. Provided that a re-oxidation of the rhodium center can occur under reaction conditions, a catalytic C–H/C–M arene arylation process can be established (Scheme 28).



Scheme 28 General schemes for C–H/C–M arylation of arenes

3.1 Rh-Catalyzed C–H/C–M Arylation of Arenes Through Directed Metalation

In a first report describing the C–H/C–M arylation of arenes, the Oi group disclosed that 2-arylpyridines can be arylated at the *ortho* positions of the 2-aryl substituent with tetraarylstannanes as organometallic coupling partners, in the presence of a catalytic amount of a Rh(I)/PPh_3 catalyst such as Wilkinson's catalyst, and with a chlorinated solvent acting as the oxidizing agent (Scheme 29) [120]. Among the catalysts tested, Rh(I)/PPh_3 catalysts (e.g., $RhCl(PPh_3)_3$ or $[RhCl(coe)_2]_2$ and PPh_3) were superior to systems with more electron-rich and sterically hindered (PCy_3), electron-deficient ($P(OPh)_3$), or bidentate (dppe) ligands. Under typical reaction



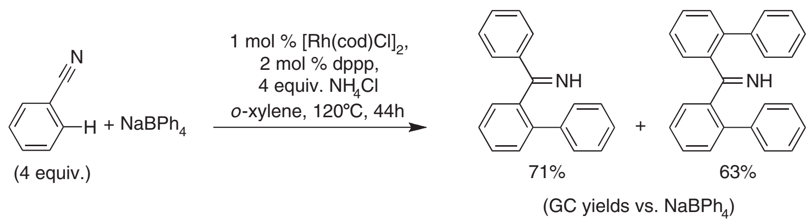
Scheme 29 Rh-catalyzed C–H arylation of 2-arylpyridines with arylstannanes by Oi et al. [120]

conditions, the 2-arylpyridine (1 equiv.), Ar_4Sn (1.05 equiv.), and $RhCl(PPh_3)_3$ (0.05 equiv.) are stirred in 1,1,2,2-tetrachloroethane (~0.3 M in arylpyridine) at 120 °C for 20 h. The arylation is selective for the *ortho* positions of the 2-aryl substituent, and moderate to good yields (36–79%) of *ortho* arylated products are obtained. Multiple arylation can occur with substrates having more than one unsubstituted *ortho* positions, such as 2-phenylpyridine.

The scope of this reaction with respect to the 2-arylpyridine includes substrates with *ortho* substituents such as 3-methyl-2-phenylpyridine, 2-(2-methylphenyl) pyridine, and 2-(1-naphthyl)pyridine that result in singly arylated C–H/C–M coupling products. The sensitivity of this reaction to sterics is further evidenced by the selective phenylation of 2-(2-naphthyl)pyridine at the 3-naphthyl position while the more sterically hindered 8-naphthyl position is unreactive. Both electron-neutral (Ph_4Sn) and electron-rich ($(4\text{-}MeOC_6H_4)_4Sn$) tetraarylstannanes have been shown to participate in this reaction, but the reaction with *ortho* substituted and/or sterically hindered stannanes has not been demonstrated. Functional group tolerance for groups other than aryl ethers has not been reported.

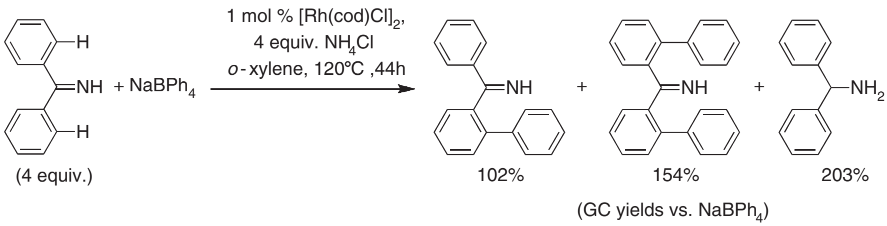
The mechanism of the coupling was not explored in detail, but likely involves ligand exchange at the rhodium center and coordination by the pyridine substrate, directed cyclometalation, transmetalation of the organotin reagent, and reductive elimination to afford the *ortho* arylated products (Scheme 28). The nature of the reoxidation process is more equivocal. Trichloroethylene is generated during the reaction when 1,1,2,2-tetrachloroethane is chosen as solvent, which may be indicative of an oxidation process that includes C–Cl oxidative addition followed by *β*-hydride elimination and subsequent rhodium hydride-mediated disproportionation reactions. Alternately, oxidative addition of tetrachloroethane followed by *β*-chloride elimination may also occur [121, 122]. However, other chlorinated solvents including chloroform, 1,2-dichloroethane, and 1,1,1-trichloroethane also promote this reaction, albeit less efficiently. Furthermore, trichloroethylene may not be an innocent side-product, for its use as an additive (0.25 equiv.) was shown to promote the *ortho*-phenylation of 2-arylpyridines in a non-chlorinated solvent (THF).

In addition to organotin reagents, organoboron reagents, which benefit from a broader commercial availability and low toxicity, were demonstrated to participate in Rh-catalyzed C-H/C–M oxidative couplings through directed metalation pathways. Imines have been identified as competent directing groups in the arylation of arenes using organoboron reagents. The Miura group first disclosed serendipitous results in which benzophenone imines generated in situ from the Rh-catalyzed addition of an organoboron reagent ($NaBPh_4$) to benzonitriles were found to participate in directed *ortho* arylation reactions to afford a mixture of arylated products (Scheme 30) [123]. In this experiment, $NaBPh_4$ (1 equiv.), PhCN (4 equiv.), $[Rh(cod)Cl]_2$ (0.01 equiv.), bis(diphenylphosphino)propane (dppp, 0.02 equiv.), and NH_4Cl (4 equiv.) are heated (120 °C) in *o*-xylene (0.1 M in $NaBPh_4$) for 44 h to afford a ~1.6:1 ratio of the mono and bis *ortho* arylated benzophenone imines (134% overall yield with respect to $NaBPh_4$). In the absence of NH_4Cl, the reaction does not reach this stage of completion and a mixture of benzophenone imine, mono and bis *ortho* arylated benzophenone imines are obtained (68% overall yield with respect to $NaBPh_4$).



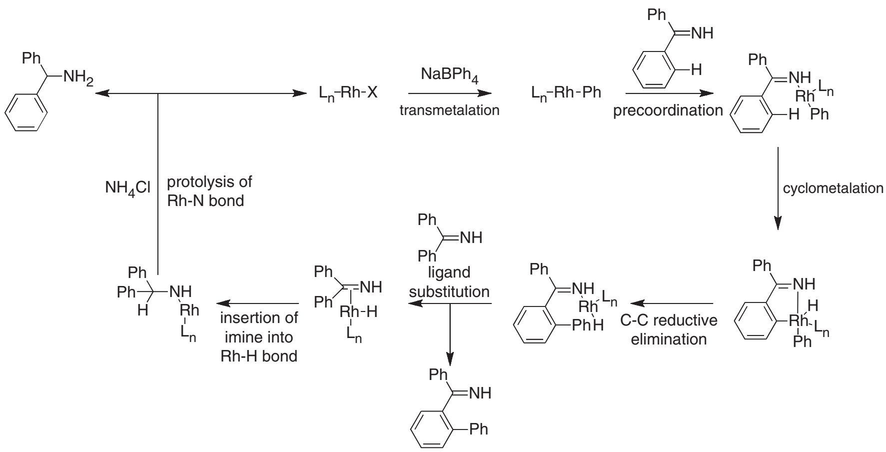
Scheme 30 Rh-catalyzed tandem addition/directed C–H arylation with $NaBPh_4$ by Ueura et al. [123]

Interestingly, when benzophenone imine itself is employed as substrate, higher reaction efficiency is observed in the absence of ancillary ligand (Scheme 31). Under identical reaction conditions, a ~1.3:1 ratio of the mono and bis *ortho* arylated benzophenone imine is obtained (256% overall yield with respect to $NaBPh_4$). Under these reaction conditions, the excess of benzophenone imine participates in the reoxidation of the catalyst as a formal dihydrogen acceptor, resulting in the concomitant formation of diphenylmethaneamine.



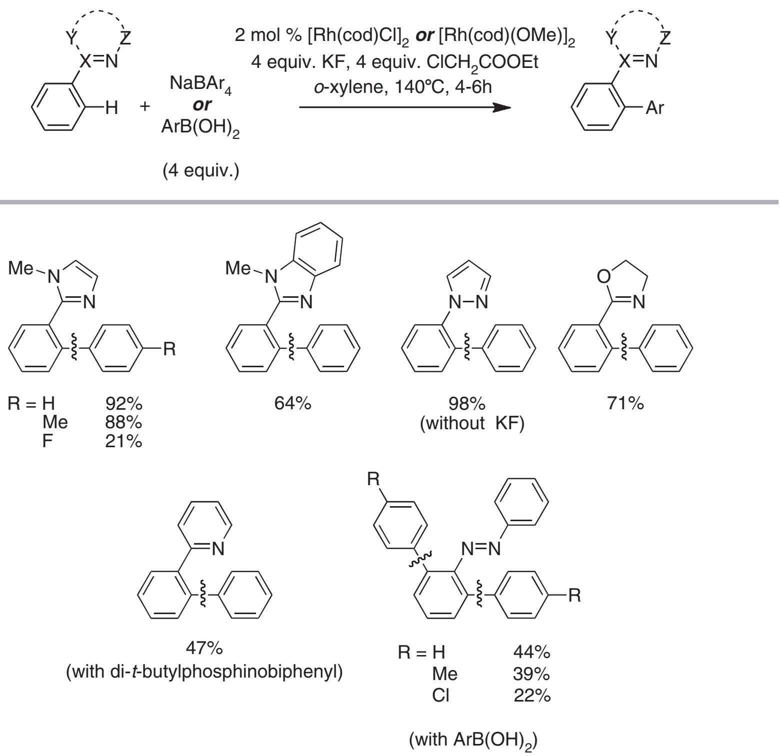
Scheme 31 Rh-catalyzed directed C–H arylation of benzophenone imine with $NaBPh_4$ by Ueura et al. [123]

The mechanism of this transformation was not investigated, however a possible mechanism was proposed (Scheme 32). Transmetalation of the organoboron reagent to a rhodium(I) center could be followed by coordination of the imine, oxidative addition of the *ortho* C–H bond and reductive elimination to afford the *ortho* arylated product and a rhodium(I) hydride. Reoxidation would then follow through insertion of the imine in to the Rh–H bond followed by protonation with NH_4Cl.



Scheme 32 Proposed catalytic cycle for the directed C–H arylation of imines with $NaBPh_4$ [123]

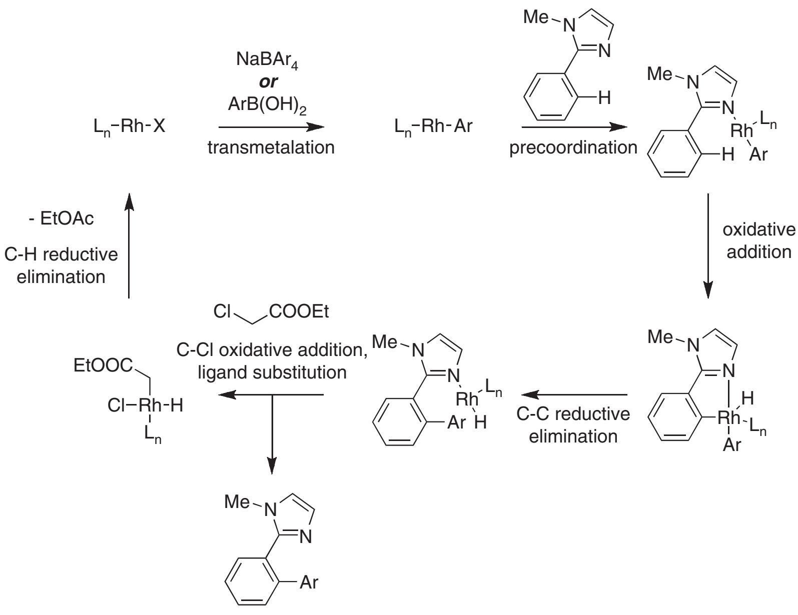
While the complete mechanistic picture for this transformation remains to be elucidated, the high efficiency of *ortho* arylation with a comparatively low catalysts loading (2 mol% Rh) and the implication that under these conditions more than two aryl groups can be successfully transferred from $NaBPh_4$ make this chemistry unusual and remarkable. In a follow-up paper, the Miura group reported further improvements of this reaction through the use of a more suitable reoxidant and an extension of the substrate scope with respect to the directing group (Scheme 33) [124]. Although optimal reaction conditions and catalytic efficiency vary greatly between substrates, for most substrate pairs, the combination of $[Rh(cod)Cl]_2$ (0.02 equiv.) and $NaBAr_4$ (4 equiv.) with ethyl α-chloroacetate (4 equiv.) [125, 126] and KF (4 equiv.) in *o*-xylene (0.05 M in $NaBAr_4$) at 120 °C was found to maximize the yields of *ortho* arylation.



Scheme 33 Rh-catalyzed directed C–H arylation of arenes with arylboron reagents by Miyamura et al. [124]

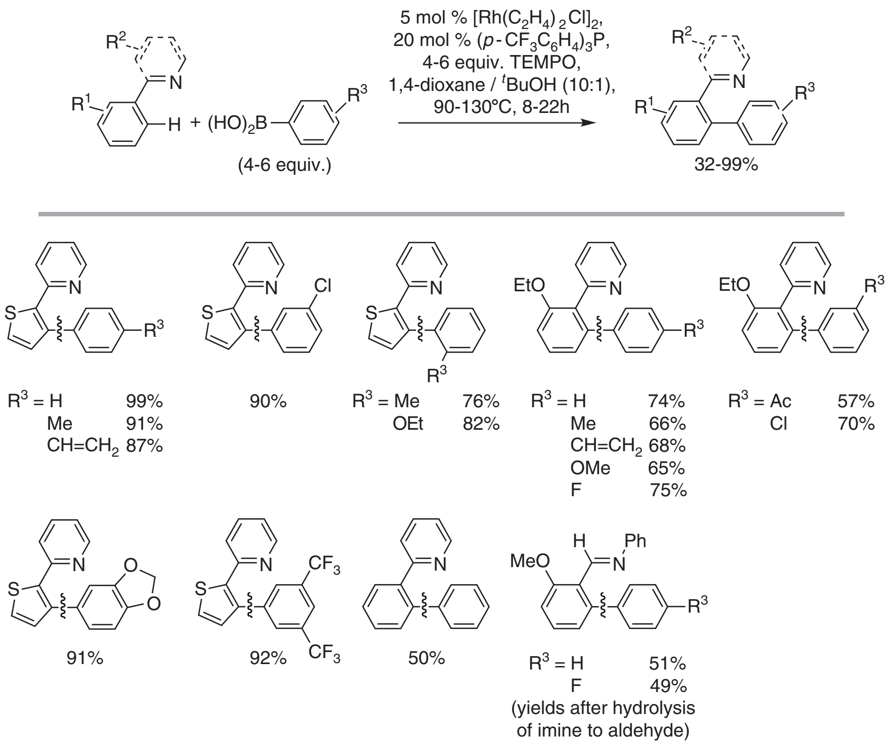
The catalytic *ortho* arylation was found to be applicable to a number of aryl azoles including, in decreasing order of reactivity, 1-phenylpyrazole, 1-methyl-2-phenylimidazole, 2-phenyl-2-oxazoline, 1-methyl-2-phenylbenzimidazole, and 2-phenylpyridine. This last substrate required the addition of di-*tert*-butylphosphinobiphenyl as ligand (2:1 L:Rh) to achieve acceptable yields. Azobenzene was a poor substrate under typical reaction conditions (15% yield) but replacement of $NaBPh_4$ with $PhB(OH)_2$ as the organometallic coupling partner and of $[Rh(cod)Cl]_2$ with $[Rh(cod)OMe]_2$ as catalyst significantly improved reactivity. *Ortho* arylation with organoboron reagents bearing *para* substituents was demonstrated, and a significant electronic sensitivity is observed, with electron-neutral (H) and electron-donating substituents (CH_3) leading to significantly higher yields than electron-withdrawing groups (F, Cl).

A revised mechanistic proposal to include reoxidation by ethyl α-chloroacetate has been proposed (Scheme 34). Following transmetalation of the organometallic reagent to a rhodium(I) center, coordination of the substrate and C–H oxidative addition, reductive elimination affords the arylated substrate and a rhodium(I) hydride. The latter then oxidatively adds to the C–Cl bond of ethyl α-chloroacetate, and reductive elimination of ethyl acetate regenerates the catalyst. The role of KF as an additive remains undetermined, and in the absence of supporting evidence the proposed mechanism remains speculative. While the use of ethyl α-chloroacetate is a significant improvement over the previous procedure, the potential for side-reactions such as *N*-alkylation of the azoles with this potent carbon electrophile may not always be insignificant. A comparison with other oxidizing agents would provide useful insight into what may be a significant step for catalyst turnover.



Scheme 34 Proposed catalytic cycle for the directed C–H arylation of arenes with arylboron reagents [124]

Vogler and Studer have reported that a Rh(I)/(4-$CF_3C_6H_4)_3P$ catalyst analogous to that previously reported by the Sames group for electrophilic C–H/C–X coupling can also participate in the oxidative directed *ortho* arylation (or alkenylation) of 2-pyridylarenes with boronic acids in the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) as the oxidant (Scheme 35) [127]. Under typical reaction conditions, the 2-pyridylarene (or imine, 1 equiv.), boronic acid (4–6 equiv.), TEMPO (4-6 equiv.), $[Rh(C_2H_4)_2Cl]_2$ (0.05 equiv.), and $(4\text{-}CF_3C_6H_4)_3P$ (0.20 equiv.) are stirred in 10:1 1,4-dioxane/*tert*-butanol (~0.2 M in 2-pyridylarene) at 90–130 °C for 8–22 h. The reaction is selective for the *ortho* positions of the arene. Good to excellent yields (57–99%) are obtained for the *ortho* arylation of 2-arylpyridines. Benzaldimines can also act as substrates, but the reaction is less efficient (32–51%). Multiple arylation can occur with substrates having more than one unsubstituted *ortho* positions, such as 2-phenylpyridine.

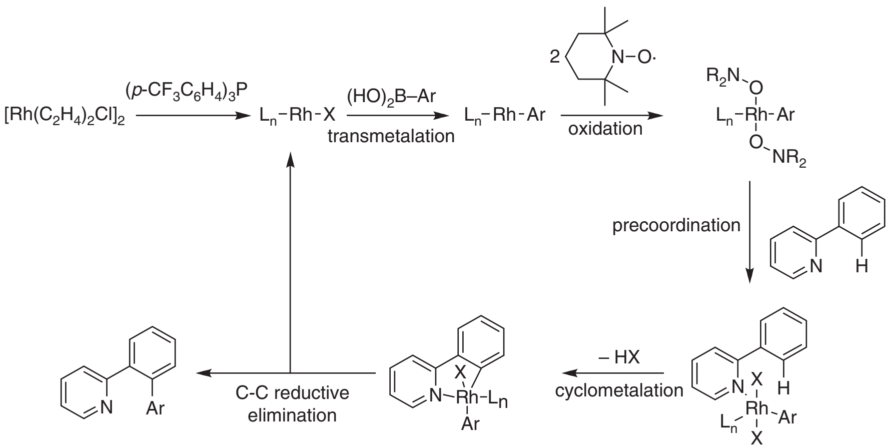


Scheme 35 Rh-catalyzed directed C–H arylation with boronic acids by Vogler and Studer [127]

Among the catalysts tested, systems using electron-deficient triarylphosphines ($(4\text{-}CF_3C_6H_4)_3P$) were superior to electron-neutral (PPh_3), electron-rich ($(4\text{-}MeOC_6H_4)_3P$) and bidentate (dppb) ligands, and $[Rh(C_2H_4)_2Cl]_2$ was identified as the preferred rhodium precursor. These observations are consistent with an electrophilic C–H metalation process requiring a highly electron-deficient Rh(III) center, but could also relate to the ease of phosphine dissociation and ligand-exchange with the substrate, or to ligand stability under oxidative conditions.

Reduced TEMPO can be re-oxidized in situ with air or dioxygen (1 atm), which allows the reaction to proceed catalytically in that reagent (20 mol %), albeit at the expense of somewhat depressed yields. The scope of the reaction includes 2-(2-thienyl)pyridine and 2-(2-ethoxyphenyl)pyridine, but some less electron-rich substrates such as 2-phenylpyridine exhibit comparable reactivity. *N*-Phenyl benzaldimines were also demonstrated as reactive substrates. A drawback of this methodology is the requirement for large excesses (4–6 equiv. per arene) of the comparatively expensive organoboron reagent, possibly due to its competing oxidation (hydroxylation or oxidative dimerization). However, a broad range of boronic acids show good reactivity, including electron-rich, electron-poor, *para-* and *meta-* substituted substrates. Boronic acids bearing *ortho* substituents (Me, OEt) are less efficiently coupled, but are nonetheless sufficiently reactive with less sterically demanding arene substrates (e.g., 2-(2-thienyl)pyridine) to afford arylated derivatives in acceptable yields. The lack of electronic sensitivity with respect to the organoboron substrate suggests that transmetalation is unlikely to be the rate-limiting step in the catalytic cycle. Functional groups including certain heterocycles (thiophene), alkenes, ethers, aryl halides (F, Cl) and ketones are tolerated under these reaction conditions.

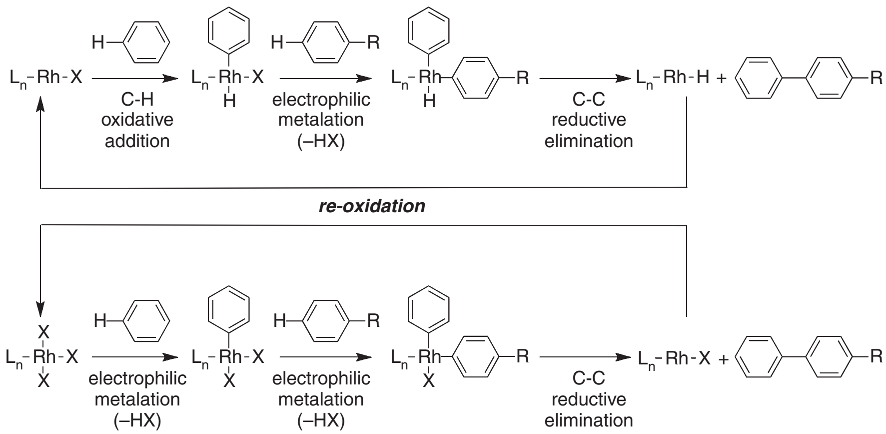
The mechanism of the coupling was not explored in detail, but a catalytic cycle that is consistent with the observed reactivity has been proposed (Scheme 36). An arylrhodium(I) intermediate formed by transmetalation of the organoboron reagent is likely oxidized by TEMPO to give a rhodium(III) complex ligated to the TEMPO anion. Dissociation of a phosphine and coordination of the 2-pyridylarene preactivates the substrate for a C–H cleavage step in which the coordinated TEMPO anion may act as an internal base. Finally, reductive elimination regenerates the rhodium(I) precursor.



Scheme 36 Proposed catalytic cycle for the directed C–H arylation with boronic acids [127]

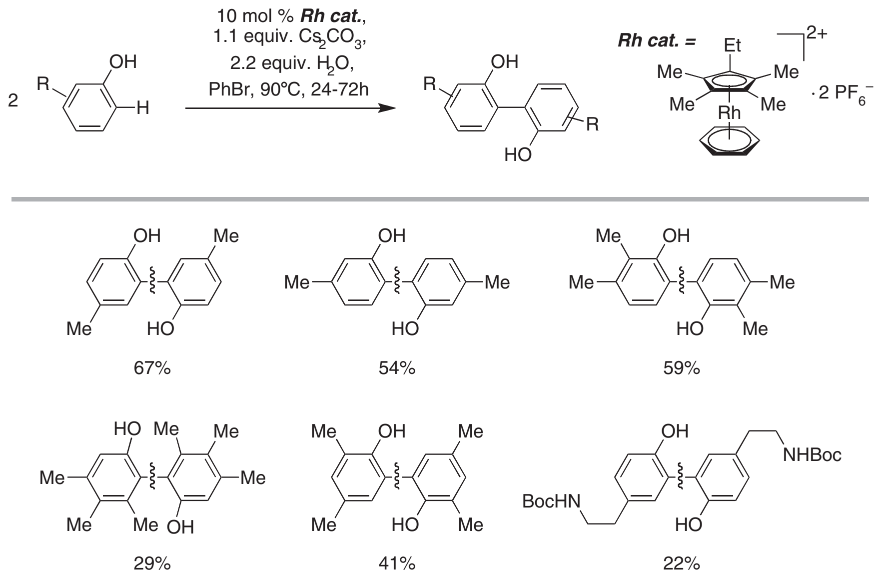
4 C–H/C–H Arene Arylation (Rh-Catalyzed Oxidative Coupling Methods)

In all of the preceding arene arylation reactions, at least one of the arenes to be coupled must first be preactivated either by halogenation or stoichiometric metalation prior to the key catalytic biaryl bond formation. In principle, if both arenes can be activated by catalytic C–H metalation, a more efficient and economical synthesis of biaryls can be achieved (Scheme 37). Significant challenges need to be met for successful C–H/C–H arene arylation by transition metal-catalyzed oxidative coupling methods. In addition to the control of regioselectivity for arene C–H metalation (e.g., by selective electrophilic metalation, NHC-metal formation or directed metalation), selectivity for the desired cross-coupled product over homocoupled products is particularly difficult to achieve. Additional issues such as selectivity for *mono* arylation over multiple arylation and/or product stability can be of concern since the resulting biaryls generally possess additional aryl C–H bonds that are available for further functionalization. In spite of significant recent methodological developments in this field [128–141], in particular with Pdcatalysts, the vast majority of these reactions remain confined to special cases such as intramolecular coupling, intermolecular homocoupling, or the use of large excesses of one of the substrates to be cross-coupled. A rare exception is the coupling of phenols and other electron-rich arenes through radical pathways that are of considerable importance in a number of biosynthetic pathways. However, in the absence of the appropriate enzyme to control the reactivity and selectivity, these reactions are of limited synthetic practicality.



Scheme 37 General scheme for C–H/C–H arylation of arenes

Reports of Rh-catalyzed C–H/C–H arene arylations are rare and provide limited scope and mechanistic data. In a first report, the Barrett group describes the oxidative *o,o'*-dimerization of phenols in the presence of a rhodium(III) catalyst

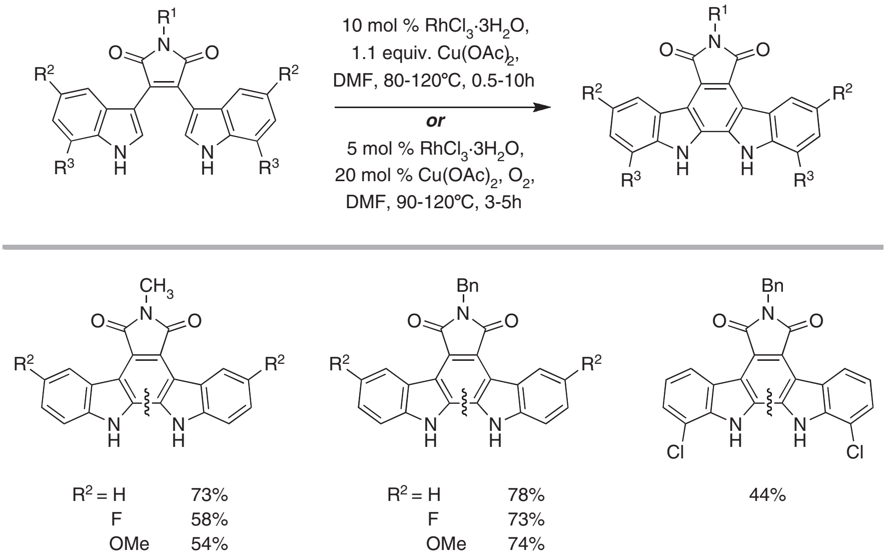


Scheme 38 Rh-catalyzed oxidative *ortho* dimerization of phenols by Barrett et al. [142]

(10 mol% (η^6-benzene)(η^5-ethyltetramethylcyclopentadienyl)rhodium(III) hexafluorophosphate), a base (Cs_2CO_3), bromobenzene and water as solvent and additives, respectively (Scheme 38) [142]. Under typical reaction conditions, a phenol (1 equiv.), the rhodium precatalyst (0.1 equiv.), Cs_2CO_3 (1.1 equiv.), and H_2O (2.2 equiv.) are heated (90 °C) and stirred in PhBr (1 M in phenol) for 24–72 h. Moderate yields (22–59%) are obtained for unhindered substrates but more sterically demanding phenols can also be coupled at the expense of longer reaction times and depressed yields.

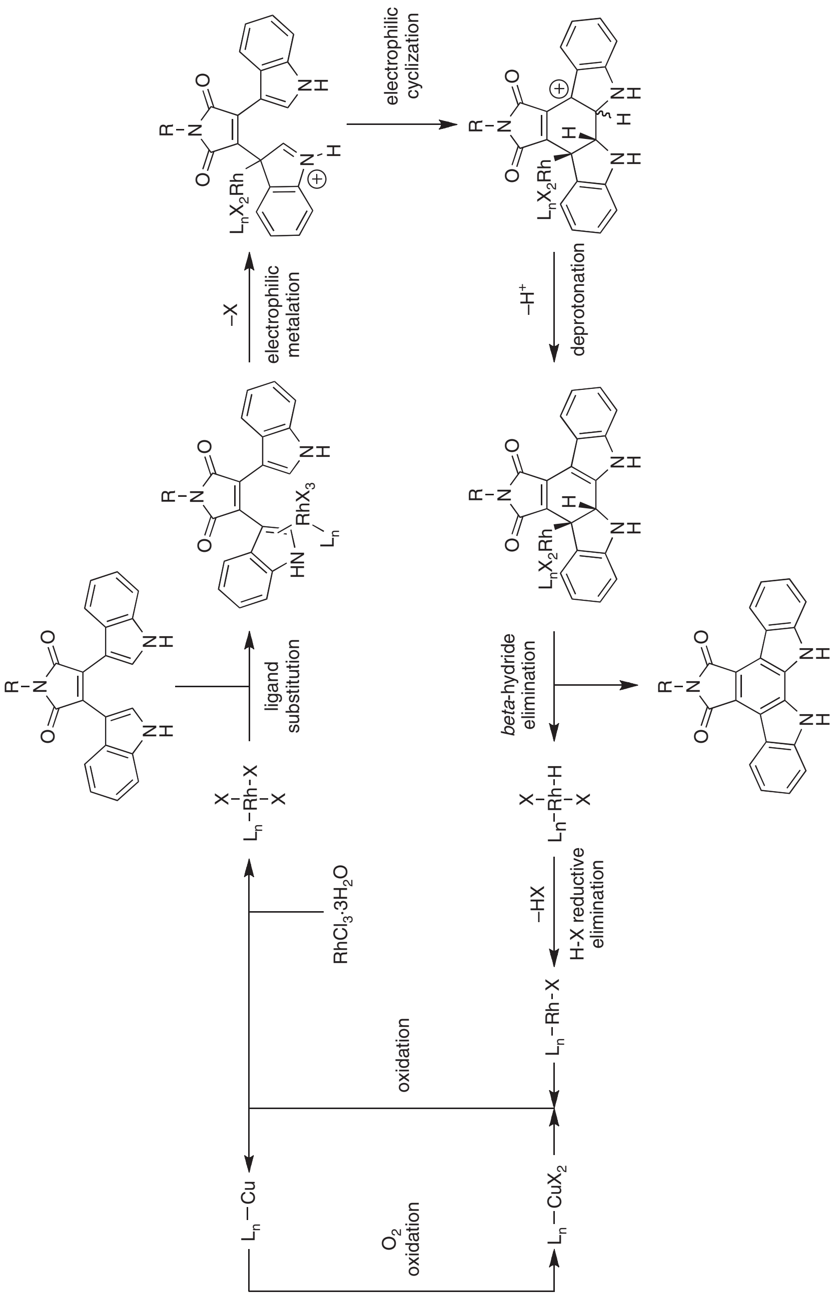
The precatalyst employed by the Barrett group is not the only rhodium precursor that can promote the oxidative dimerization of phenols. In their investigation of the Rh-catalyzed *ortho* arylation of phenols with bromoarenes through orthometalation in the presence of a phosphorus ligand capable of phosphinyl group transfer (Sect. 2.3), the Bedford group noted that the oxidative dimerization of the phenolic substrate was a significant side-reaction when a rhodium(I)/bulky triarylphosphite catalyst system is employed [114–117]. Neither the specific role of each reagent nor mechanistic details were established, but bromobenzene likely participate in the reoxidation of the rhodium catalyst through oxidative addition and hydrodebromination pathways.

A rhodium(III) catalyst was also shown by Witulski and Schweikert to promote the intramolecular oxidative cyclization of bisindolylmaleimides to indolocarbazoles as a key step in the synthesis of cytotoxic agents of the indolocarbazole family (Scheme 39) [143]. Under typical reaction conditions, the bisindolylmaleimide substrate (1 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1.1 equiv.), and $RhCl_3 \cdot 3H_2O$ (0.1 equiv.) are heated (80–120 °C) and stirred in DMF (~0.01 M in substrate) for 0.5-10 h. Moderate to good yields (44-78%) are obtained, with substrates bearing electron-donating groups showing greater reactivity than those bearing electron-withdrawing groups.



Scheme 39 Rh-catalyzed oxidative cyclization of bisindolylmaleimides by Witulski and Schweikert [143]

The reaction is tolerant of a number of substituents on the indolyl groups, including methoxy, fluoro, and chloro. Since the use of stoichiometric amounts of copper(II) salts as the terminal oxidant is impractical, the oxidative cyclization can alternately be conducted with a catalytic loading of Cu(II) (20 mol%) by continually sparging oxygen in the reaction mixture. Copper is then believed to act as a redox shuttle between the rhodium catalyst and oxygen as the terminal oxidant. Slightly lower yields are obtained with the second procedure, but workup and purification are greatly facilitated. The reaction mechanism was not probed in detail, and may include multiple pathways to the indolocarbazole products since the reaction also proceeds with stoichiometric $Cu(OAc)_2$ in the absence of a rhodium catalyst, albeit less efficiently. The authors propose a mechanism in which electrophilic metalation of an indolyl substituent initiates a cationic cyclization resulting in the indolocarbazole after rearomatization upon the loss of a proton (Scheme 40).



Scheme 40 Proposed catalytic cycle for the oxidative cyclization of bisindolylmaleimides

5 Conclusions and Outlook

In the decade that followed the first report of a Rh-catalyzed C–H arylation of arenes in 1998 [120], tremendous methodological developments have resulted in valuable and practical synthetic methods for the expeditious preparation of a broad range of (hetero)biaryls. Nonetheless, for most target biaryls, these reactions remain to this date unlikely to compete with other modern methods for aryl-aryl C–C bond formation such as the Suzuki-Miyaura cross-coupling. Rhodium-catalyzed methods for the C–H arylation of arenes generally suffer from a comparatively narrow substrate scope, limited functional group tolerance, the need for a high catalyst loading (5–10 mol% Rh) and elevated temperatures (≥100 °C) and/or extended reaction times, making them less suited for the ideal late-stage coupling of highly functionalized intermediates. Even among C–H arylation reactions, the development of rhodium-catalyzed methods appear to lag behind advances in palladium catalysis, often preferred in the arylation of unactivated arenes [35–41], electron-rich [144–149] or electron-deficient heterocycles [150–155], and ruthenium catalysis, arguably the most powerful in many directed (*ortho*) arylation reactions [156–165]. For certain substrate combinations, copper [166] or iridium [167, 168] catalysis may also be adequate.

The development of new rhodium catalysts for the C–H arylation of arenes faces a number of significant challenges. Rhodium(I) is generally less reactive for the oxidative addition of unactivated aryl halides (or pseudohalides) than its palladium(0) counterpart, which contributes to the scarcity of rhodium-catalyzed C–H/C–X arylation methods with substrates other than the most reactive aryl iodides or bromides. Coupling methods that rely on electrophilic metalation are especially affected by this limitation due to the antagonistic electronic requirements at different steps of the catalytic cycle (e.g., strong donor ligands for oxidative addition to Rh(I) and π-acidic ligands for electrophilic metalation at Rh(III)). In that regard, C–H/C–X arylation methods that rely on the formation of a comparatively electron-rich rhodium(I)-NHC intermediate are especially attractive for the superior reactivity and the unique regioselectivity that this mechanism enables. Organometallic reagents are often prepared from halogen-metal exchange and are typically less stable and more costly than the corresponding halide. Nevertheless, provided with suitable stoichiometric reoxidizing agent that does not induce undesired side-reactions such as homocoupling of the organometallic partner and oxidative degradation of the supporting ligands, C–H/C–M couplings that do not require the use of a stoichiometric base can become attractive for cross-coupling of substrates that bear base-sensitive functional groups. Less typical organometallic reagent surrogates such as arylcarboxylic acids are worthy of sustained investigation in this regard [169–175]. The development of rhodium-catalyzed C–H/C–H arene arylation methods remains in its infancy, and significant issues of reactivity and selectivity remain to be addressed.

Palladium catalysis benefits from the colossal body of work that lead to the development of specialized and often commercially available ligands for aryl-aryl bond formation through C-M/C–X cross-coupling chemistry. Since these processes share many elementary steps with the catalytic cycle likely to occur in the C–H arylation of arenes, it is unsurprising that common sets of ligands – bulky biaryldialkylphosphines for instance – can exhibit superior reactivity in both families of reactions. By comparison, the development of specialized ligands for rhodium-catalyzed aryl–aryl bond formation is not equally advanced, but, as recently demonstrated by the Ellman and Bergman groups [103, 104], significant potential may lie in this research endeavor. Similarly, the identification and eradication of catalyst decomposition pathways is essential to achieving high catalyst turnovers under conditions (e.g., excess stabilizing ligands) that do not impede low-temperature reactivity.

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Cross-Dehydrogenative Coupling Reactions of sp^3-Hybridized C–H Bonds

Woo-Jin Yoo and Chao-Jun Li

Abstract New methodologies in cross-coupling reaction using C–H bonds as substrates is of great interest due to the challenges associated with C–H bond activation and the potential to streamline synthesis by the elimination of pre-activation of coupling reagents. In this chapter, recent developments in oxidative cross-coupling reactions will be presented with the focus on the functionalization of sp3 C–H bonds with other C–H bonds

Keywords Copper • Ruthenium • Palladium • C–H functionalization • Oxidative coupling

Contents

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1 Introduction

The development of efficient strategies towards the formation of carbon–carbon (C–C) bonds is of great interest to chemists [1]. Historically, nucleophilic additions, substitutions, and Friedel-Craft type reactions have been the dominant choices for the connection of simple molecules to produce complex ones through the formation of C–C bonds. Furthermore, the development of pericyclic [2] and transition metal-catalyzed reactions [3–5] has increased the efficiency of C–C bond formation processes in modern organic chemistry and has greatly extended its scope. Recently, there has been considerable interest in the utilization of carbon–hydrogen (C–H) bonds as substrates for cross-coupling reactions (for recent reviews on direct arylation reactions, see [6–11]; for reviews on oxidative cross-coupling reactions, see [12, 13]). The direct use of C–H bonds to form C–C bonds is highly desirable since it has the potential to streamline synthetic scheme by eliminating the need for the preparation and isolation of activated substrates prior to the coupling event. This advantage can be best illustrated by the recent progress in biaryl cross-coupling reactions (Fig. 1).

Oxidative coupling reactions with C–H bonds is quite challenging due to the relative strong C–H bond, along with the associated selectivity issues with the myriad of C–H bonds that are available for the coupling reaction. While challenging, chemists have striven to develop new synthetic methodologies that incorporate the use of C–H bonds as substrates for C–C bond formation processes. In this chapter, an overview of the recent developments in oxidative cross-coupling reactions will be presented, with focus on the functionalization of sp^3 C–H bonds with other C–H bonds.

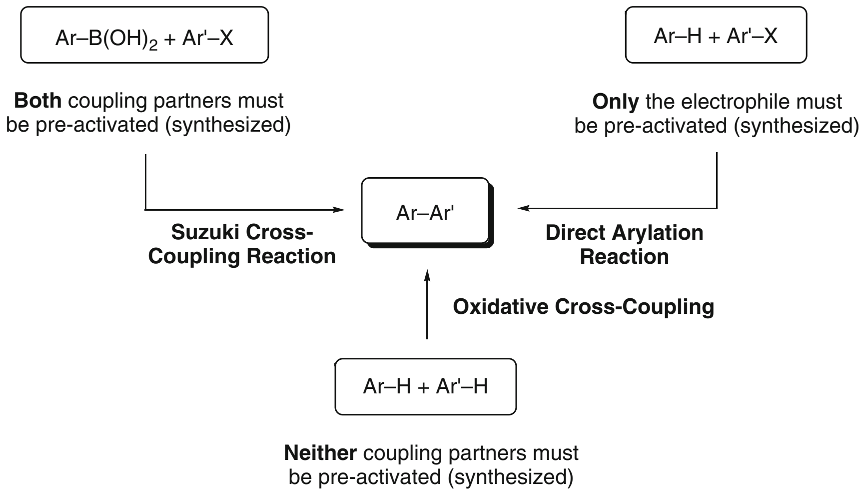


Fig. 1 Various strategies for the synthesis of biaryl compounds

2 Oxidative Coupling of C–H Bonds Adjacent to the Nitrogen in Amines

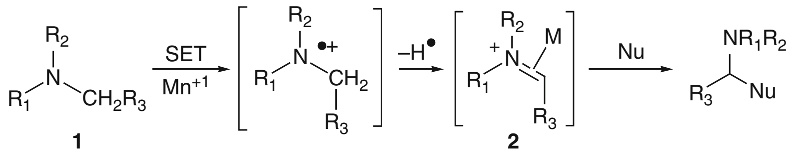
It has previously been established that the sp^3 C–H bond adjacent to nitrogen in tertiary amines **1** can be selectively oxidized to generate an iminium ion **2** through single electron transfer (SET) processes [14] or by transition metals [15, 16]. Conceptually, oxidative C–C bond formation can be achieved with the sp^3 C–H bond through the interception of the resulting reactive intermediate **2** with a variety of nucleophiles (Scheme 1).

In the following section, selective functionalization of the sp^3 C–H adjacent to the nitrogen atom will be presented and classified according to the hybridization of the nucleophiles. In almost all cases, the oxidative coupling reaction occurs through the addition of the C–H nucleophile to the resulting in situ generated iminium ion **2**.

3 Alkylation (sp^3–sp^3 Coupling)

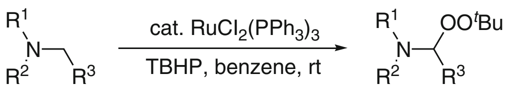
In one of the earliest examples of selective C–H bond functionalization of tertiary amines, Murahashi and co-workers established that the C–H bond adjacent to the nitrogen atom can be selectively oxidized with *tert*-butyl hydroperoxide (TBHP) using catalytic amounts of $RuCl_2(PPh_3)_3$ (Scheme 2) [15].

Murahashi believed that α-*tert*-butyldioxyamines **3** was derived from an iminium ion intermediate that was trapped by a *tert*-butyl peroxyl anion. Similar oxygenated products of tertiary amines have been generated from the action of various peroxides with catalytic amounts of ruthenium [15, 16]. Murahashi and co-workers later demonstrated that selective oxidative C–C bond formation was



1 2

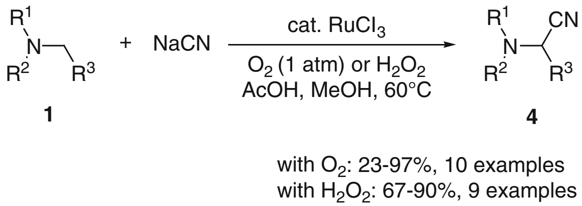
Scheme 1 Selective oxidation of tertiary amines to iminium ions



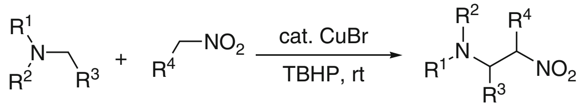
1 3

9 examples
65-97%

Scheme 2 Ruthenium-catalyzed oxidation of tertiary amines with TBHP



Scheme 3 Ruthenium-catalyzed oxidative cyanation of tertiary amines with sodium cyanide



Scheme 4 Oxidative coupling of tertiary amines with nitroalkanes

possible through a ruthenium-catalyzed oxidative cyanation of tertiary amines (Scheme 3) [17–19].

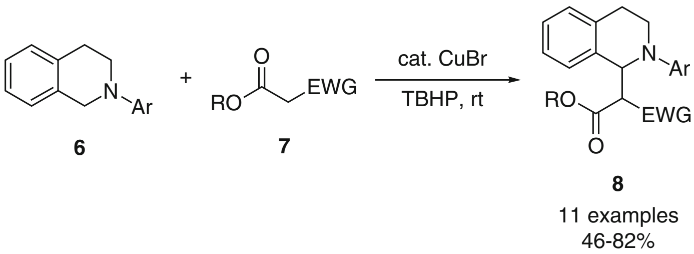
Synthesis of α-aminonitriles **4** was achieved with a simple ruthenium(III) chloride salt as catalyst with either oxygen gas or hydrogen peroxide as the oxidant. While either oxidant can be utilized, in general Murahashi found the hydrogen peroxide system to be superior for substrates that were challenging when using oxygen as the oxidant. The role of the acetic acid was to act as a proton source to generate hydrogen cyanide in situ from sodium cyanide.

Employing a similar strategy, Li and co-workers reported a copper-catalyzed nitro-Mannich type reaction between tertiary amines **1** and nitroalkanes **5** (Scheme 4) [20].

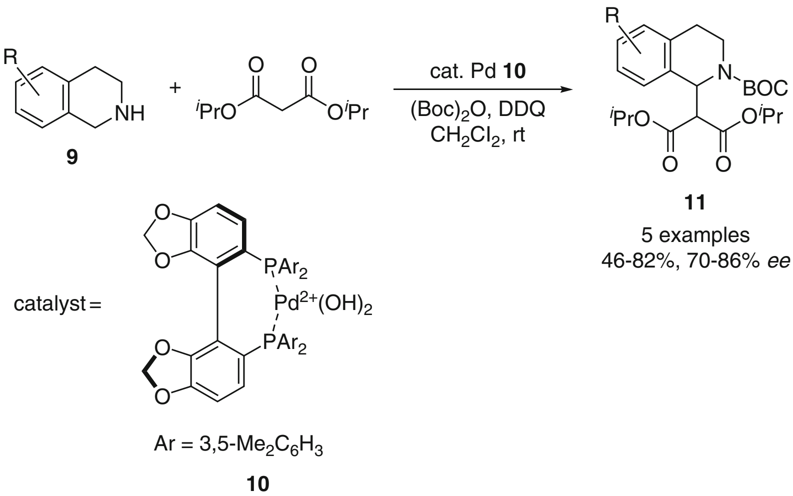
Li and co-workers examined the reaction between 1,2,3,4-tetrahydroisoquinoline and nitromethane, in which the nitromethane was used as a solvent, with various copper(I) and copper(II) salts. The desired aza-Henry product **6** was observed in all cases and CuBr was found to be the catalyst of choice.

Dialkyl malonates are another type of sp^3 C–H bond nucleophile often used in synthesis and Li and co-workers examined its use in the oxidative coupling reactions. The reaction of tetrahydroisoquinolines **6** with a variety of dialkyl malonates **7** in the presence of 5.0 mol% of CuBr and THBP (1–1.2 equiv.) at room temperature provided the desired β-diester amines **8** in high yields (Scheme 5) [21].

Asymmetric oxidative alkylation of free tetrahydroisoquinolines **9** was recently described by Sodeoka and co-workers (Scheme 6) [22, 23]. Through the use of a chiral cationic palladium(II) species **10**, The enantiopure alkylated BOC protected amines **11** were obtained with good yields and enantioselectivity. The alkylation is believed to occur through the initial protection of the amine with $(Boc)_2O$, followed



Scheme 5 Copper-catalyzed oxidative alkylation of tertiary amines with malonates

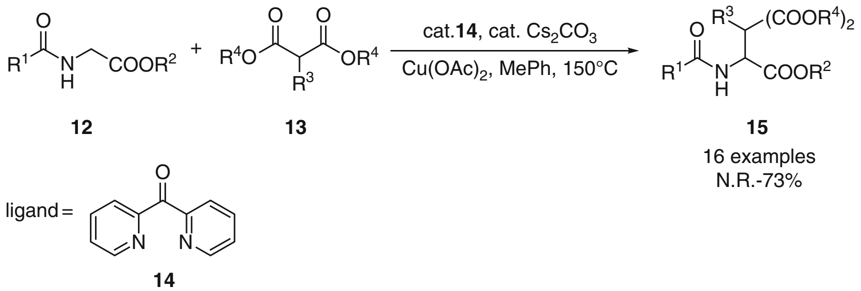


Scheme 6 Palladium-catalyzed asymmetric oxidative alkylation of BOC protected amines

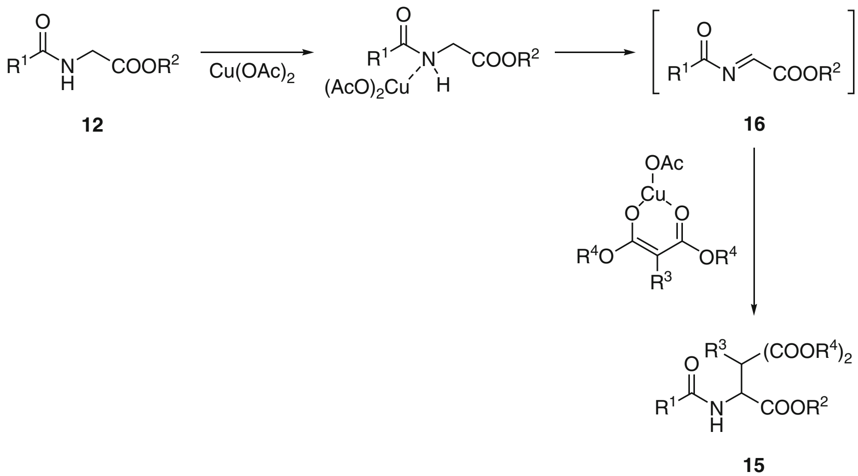
by an in situ generation of the iminium ion achieved by the slow addition of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) dissolved in CH_2Cl_2.

While most examples of oxidative coupling reactions of the α C–H of amines have been tertiary amines, Li and co-workers recently reported the cross-coupling between the α C–H of amides **12** with malonates **13** (Scheme 7) [24].

Li and co-workers initially attempted to use their previously optimized reaction conditions with CuBr and TBHP, but could not obtain the desired product. However, using 2.0 equiv. of $Cu(OAc)_2$, a small amount of the coupled amide **15** was observed. After extensive optimization, the alkylated amide **15** was obtained with moderate to good yields using a catalytic amount of Cs_2CO_3 and bidentate ligand **14**. Li tentatively proposed that the reaction occurs through the initial coordination of the nitrogen of amide **12** to $Cu(OAc)_2$. This is believed to be followed by oxidation of the amide to generate the imino intermediate **16**. Next, the malonate, activated by copper, adds to the imine to furnish the desired product **15**. The ligand in the



Scheme 7 Oxidative alkylation of amides with malonates mediated by $Cu(OAc)_2$



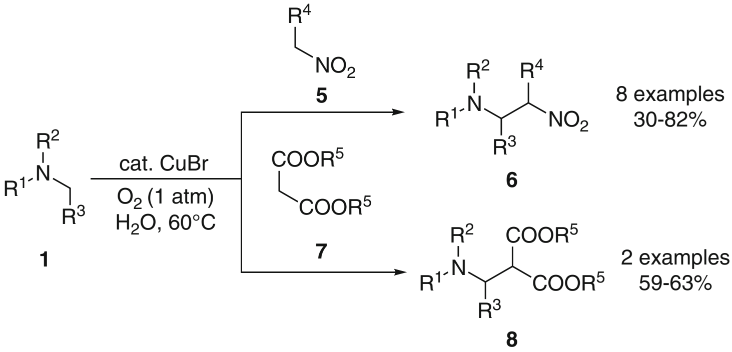
Scheme 8 Proposed mechanism for the oxidative functionalization of glycine derivatives with diethyl malonates

reaction is believed to render the copper species to become more electronegative and to allow the abstraction of the NH proton to occur more easily (Scheme 8).

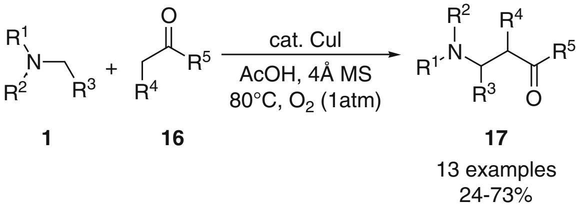
Peroxides are potentially hazardous in large-scale reactions and thus the replacement of these reactive species is of great interest. Molecular oxygen represents one of the most ideal oxidants due to its abundance in nature and its nontoxicity. Interestingly, when water is used as the solvent, molecular oxygen has been shown by Li and co-workers to be an effective hydrogen acceptor for the oxidative alkylation reaction (Scheme 9) [25].

Following the work by Li, Guo, and co-workers recently demonstrated that simple alkyl ketones **16** can undergo oxidative Mannich with tertiary amines **1** using oxygen as the terminal oxidant (Scheme 10) [26].

Unlike the work by Li and co-workers, Guo found that the reaction works best in the absence of solvent and slight improvement in yield of **17** was found when using molecular sieves to remove the presence of water. Acetic acid was found to be an



Scheme 9 Copper-catalyzed oxidative coupling reactions of C–H bonds adjacent to nitrogen using oxygen as the terminal oxidant



Scheme 10 Copper-catalyzed oxidative alkylation of tertiary amines using oxygen as the terminal oxidant

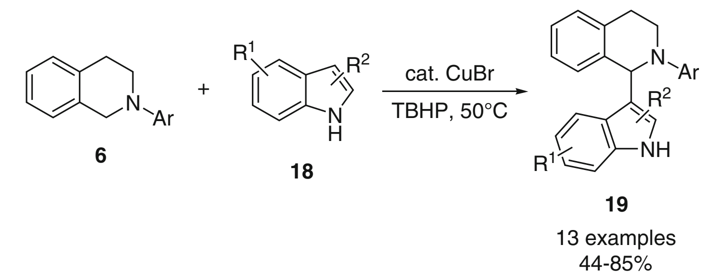
important additive and other carboxylic acids gave poor yields when utilized instead of acetic acid.

4 Alkenylation (sp^3–sp^2 Coupling)

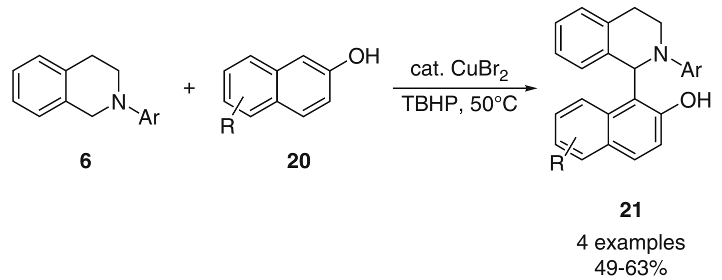
The proposed iminium intermediate **2** in the oxidative alkylation reaction implied that other C–H based nucleophiles could undergo oxidative addition reactions to the C–H bond of tertiary amines. Li and co-workers demonstrated the cross-coupling of indoles **18** with tertiary amines **6** using simple copper salts as catalyst (Scheme 11) [27].

The oxidative coupling reaction proved to be regioselective and occurred selectively at the C3 position of the indole if both C2 and C3 positions on the indole were unoccupied. However, when the C3 position was occupied, C2-substituted products were obtained. Also, indoles that were both electron-rich and electron-poor worked well under the optimized reaction conditions.

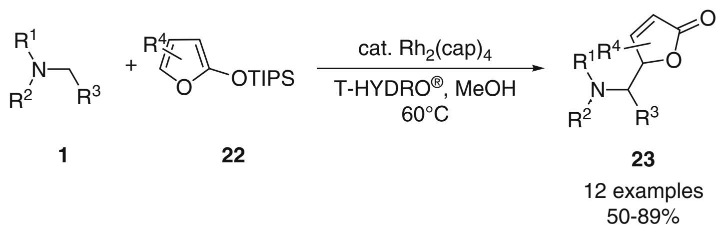
Li and co-workers also showed that an electron-rich aromatic C–H bond could undergo oxidative coupling reactions with tertiary amines. For example, 2-naphthol derivatives **20** were to be good substrates for the oxidative coupling reaction. While



Scheme 11 Copper-catalyzed oxidative coupling of indoles with tetrahydroisoquinolines



Scheme 12 Oxidative coupling of tetrahydroisoquinoline with 2-naphthol derivatives



Scheme 13 Rhodium-catalyzed oxidative Mannich reaction of tertiary amines with 2-siloxyfurans

a variety of copper(I) and copper(II) salts were found to catalyze the reaction, $CuBr_2$ was found to be the best (Scheme 12) [28].

Doyle and co-workers demonstrated the use of 2-siloxyfurans **22** as a nucleophile for the oxidative coupling reaction with tertiary amines **1** using dirhodium caprolactamate ($Rh_2(cap)_4$) as catalyst (Scheme 13) [29].

Instead of the use of an expensive rhodium species, Tan and co-workers showed that $CuBr_2$ could be utilized as an alternative catalyst for the oxidative coupling reaction to generate the oxidative Mannich product **23** [30].

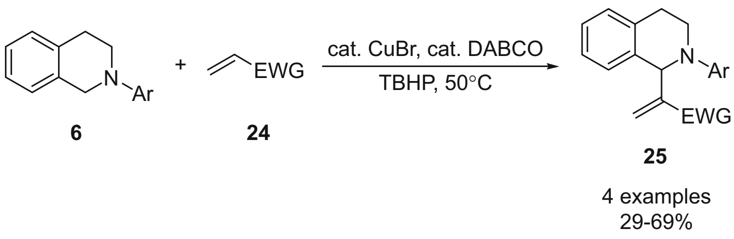
Besides electron-rich sp^2 C–H bonds, Li and co-workers demonstrated that electron-deficient alkenes **24** were shown to undergo oxidative coupling reactions with tertiary amines **6**. With the use of DABCO as a base, oxidative Morita–Baylis–Hillman (MBH) product **25** was obtained using CuBr as catalyst with TBHP as the oxidant (Scheme 14) [28].

5 Alkynylation (sp^3–sp Coupling)

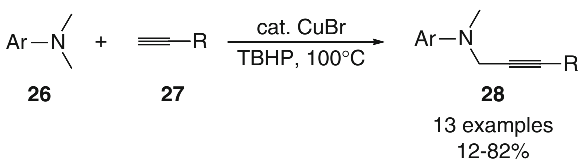
The sp C–H bonds of terminal alkynes are well known to become activated by metal salts in the presence of bases. A variety of research groups have examined the use of terminal alkynes as nucleophiles for the oxidative addition to the C–H bond adjacent to the nitrogen atom of amines. Li and co-workers examined the oxidative coupling of *N*,*N*-dimethylaniline **26** with 1-alkynes **27** (Scheme 15) [31, 32].

Li found that a variety of copper salt could catalyze both the activation of the sp C–H bond of the terminal alkyne and the activation of the peroxide. The nature of the alkyne was shown to have a strong influence upon the success of the reaction. In all cases, aromatic alkynes were found to provide the oxidative alkynylated product **28** in good yields, while aliphatic alkynes resulted in lower yields. The reaction was also shown to tolerate various functional groups such as alcohols and esters.

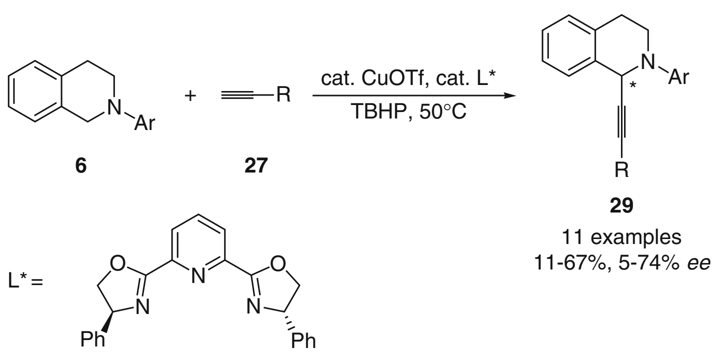
Many asymmetric C–C bond formation processes are based upon the addition of nucleophiles to the prochiral faces of double bonds to create the chiral carbon center. Since the oxidative alkynylation is believed to occur through the addition of the terminal alkyne to an in situ generated iminium ion, Li and co-workers examined the potential for the development of an asymmetric variant to the oxidative alkynylation process (Scheme 16) [33, 34].



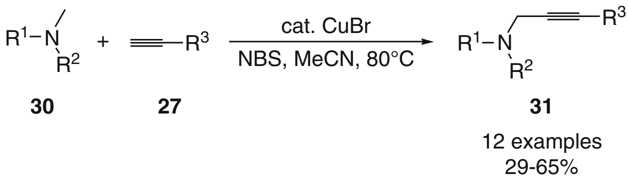
Scheme 14 Copper-catalyzed oxidative MBH-type reaction



Scheme 15 Copper-catalyzed alkynylation of *N*,*N*-dimethylanilines



Scheme 16 Asymmetric alkynylation of tetrahydroisoquinolines with terminal alkynes



Scheme 17 Copper-catalyzed oxidative alkynylation of tertiary amines using NBS as an oxidant

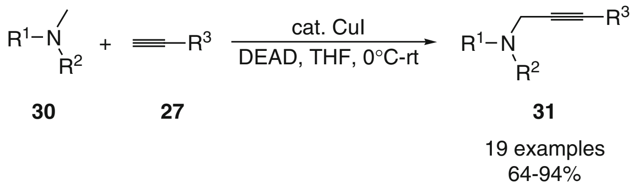
Li and co-workers examined a variety of ligands such as chiral bisoxazolines, Quinap, and Binap as ligands in conjugation with various copper salts. Li found that CuOTf with PyBox provided the best results for **29** and found that aromatic substituted alkynes gave the best yields and enantioselectivity relative to the aliphatic substituted alkynes. Li also found that the presence of an *ortho*-methoxy substituent improved enantioselectivity and attributed the improvement in selectivity to potential coordination of the oxygen atom to the copper/ligand complex.

For many of the oxidative addition reaction of the C–H bond adjacent to tertiary amines, an aromatic group is a necessity for successful coupling with C–H bond nucleophiles. Fu and co-workers recently reported the oxidative alkynylation reaction of tertiary amines without aryl substitutions **30** (Scheme 17) [35].

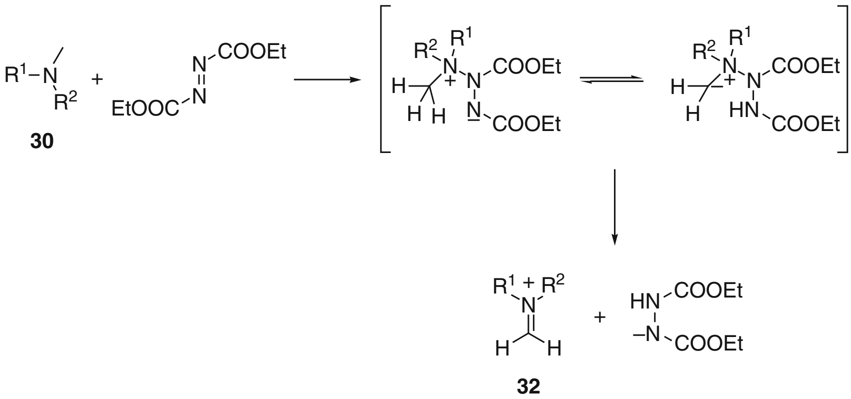
While low to modest yields were obtained for the alkynylated product **31**, high catalyst loading (40 mol%) was required. The work by Fu clearly demonstrates the limitation of the oxidative alkynylation reaction with tertiary amines. The problem with the strict requirement for aryl substituted tertiary amines has been solved recently by Li and co-workers (Scheme 18) [36].

Based upon their previous studies with DEAD prompted dehydrogenation of tertiary amines and tandem reaction with sulfonyl azides, [37] Li believed that DEAD would provide the desired iminium ion intermediate **32** without the need for an aryl substituent (Scheme 19).

Indeed, Li found that DEAD mediates the addition of terminal alkynes **27** to aliphatic tertiary methylamines **30** to provide the desired propargyl amine **31** in



Scheme 18 Copper-catalyzed oxidative alkynylation of aliphatic tertiary amines with terminal alkynes mediated by DEAD

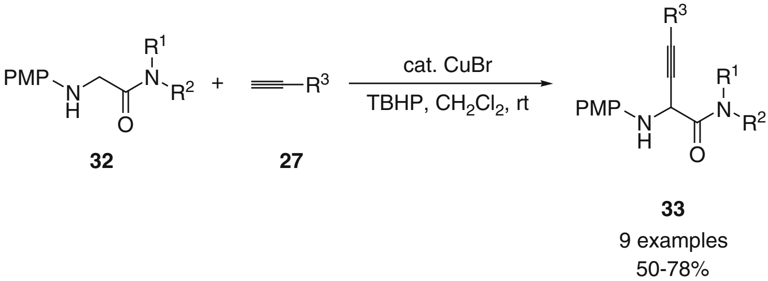


Scheme 19 DEAD-mediated dehydrogenation of aliphatic tertiary methylamines

good to excellent yields under mild conditions. In almost all cases, the methyl C–H bond is functionalized with a mixture of alkynylation products found only when one of the substituents is a benzyl group. Also, it should be noted that this protocol is complementary to the previous oxidative alkynylation reactions since the DEAD-mediate reaction could not couple tertiary amines with aryl substituents.

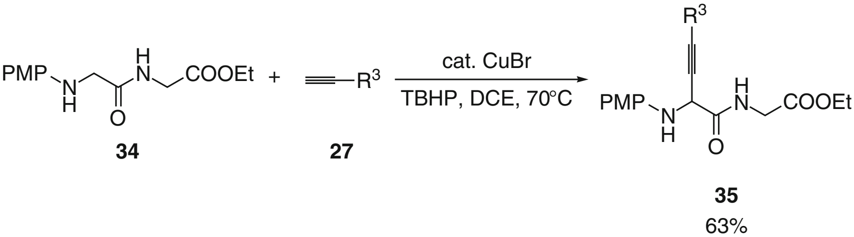
The C–H bond adjacent to PMP-protected amines **32** have been shown by Li and co-workers to undergo oxidative alkynylation using CuBr as catalyst and TBHP as an oxidant (Scheme 20) [24, 38].

It was interesting to note that the oxidative alkynylation of the C–H bond required to be adjacent to both the PMP-protected amine and an amide functional group in order to furnish the desired amide **33** with good yields. For example, Li found that if the amide was replaced with an ester, the desired oxidative coupling product was not observed. While this stringent requirement appeared to limit the applicability of this protocol, Li and co-workers used this to their advantage by demonstrating an oxidative coupling of dipeptide **34** to provide a direct and site-selective approach to alkynylated dipeptide **35** (Scheme 21).



32 **27** **33**

Scheme 20 Direct oxidative alkynylation of glycine amides



34 **27** **35**

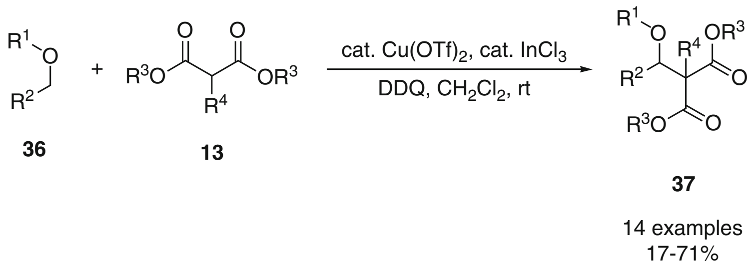
Scheme 21 Site-specific alkynylation of a dipeptide

6 Oxidative Coupling of C–H Bonds Adjacent to the Oxygen in Ethers (sp^3–sp^3)

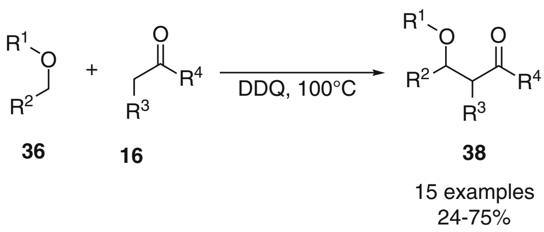
The functionalization of the C–H bond adjacent to oxygen in ethers is more challenging than the functionalization of the C–H bond adjacent to nitrogen in amines due to the higher oxidation potential of ethers. Thus, for successful oxidative coupling of the C–H bond in ethers, a stronger oxidant than TBHP or oxygen would be required. It has been previously established that DDQ can react with benzyl ethers to generate oxonium ions. With a combination of indium and copper as catalysts in the presence of DDQ, oxidative coupling of the sp^3 C–H bond of ethers **36** with malonates **13** was achieved by Li and co-workers (Scheme 22) [39].

Li found that the yields for oxidative alkylation products **37** were best when cyclic benzyl ethers were used as substrates. Li believed that the role of the $InCl_3$ was to activate the DDQ to increase its oxidative potential, while the $Cu(OTf)_2$ activated the malonate for the addition to the in situ generated oxonium ion.

One of the limitations of the copper- and indium-catalyzed oxidative alkylation protocol is the use of a relatively reactive malonate. Li found that simple ketones **16** can undergo oxidative alkylation reactions with benzyl ethers **36** by using DDQ as an oxidant at high temperatures (Scheme 23) [40].



Scheme 22 Copper- and indium-catalyzed oxidative alkylation of benzyl ethers mediated by DDQ



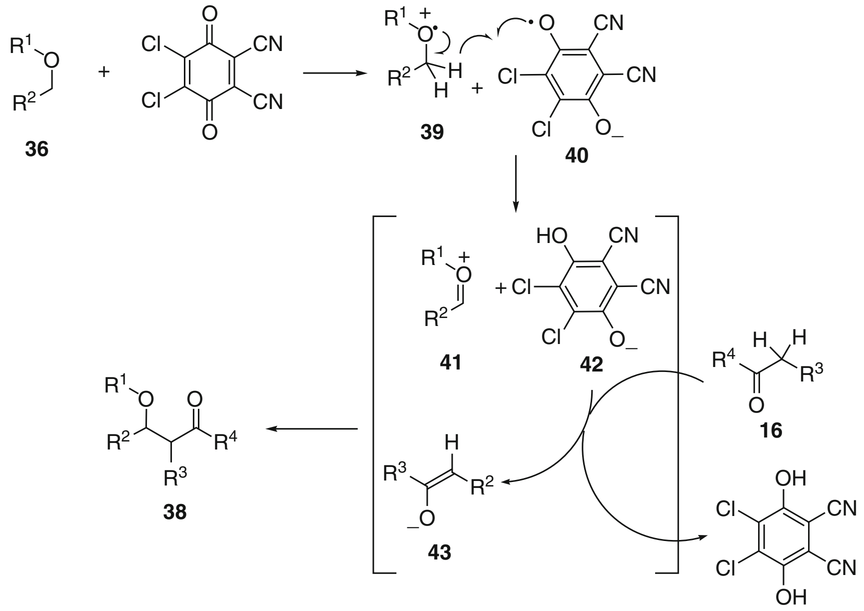
Scheme 23 Oxidative coupling between benzyl ethers and simple ketones mediated by DDQ

Li proposed a tentative mechanism for the oxidative alkylation reaction (Scheme 24).

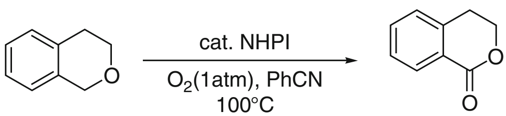
The reaction is believed to proceed through a SET from the benzyl ether **36** to the DDQ to generate benzyl radical cation **39** and a DDQ radial anion **40**. Abstraction of the proton of radical cation **39** by **40** results in the formation of the radical benzyl ether cation **41** and DDQ anion **42**. Deprotonation of ketone **16** by anion **42** generates enolate **43**, which then undergoes addition to **41** to furnish the desired oxidative alkylated ether **38**.

While DDQ was found to be an acceptable oxidant for the alkylation of benzyl ethers, Li and co-workers attempted to use oxygen as an oxidant. However, since oxygen gas itself is not sufficiently strong to generate the oxonium ion from benzyl ethers, an alternative approach was deemed necessary. Indeed, this problem was already solved by Ishii and co-workers who previously demonstrated that isochroman can be oxidized to its corresponding ester using *N*-hydroxyphthalimide (NHPI) as the catalyst and oxygen gas as the terminal oxidant (Scheme 25) [41].

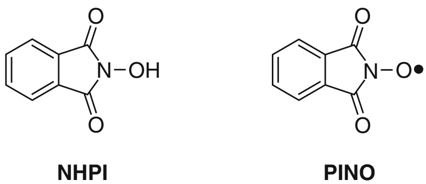
NHPI is a cheap and nontoxic compound that is an effective catalyst for C–H bond activation by hydrogen abstraction. It acts as a precursor of phthalimido-*N*-oxyl (PINO) radical (generated from the abstraction of NHPI by diradical oxygen gas) and this radical is the active species that abstracts hydrogen atoms of C–H bonds (Fig. 2) (for reviews on the use of NHPI as catalyst, see [42–46]).



Scheme 24 Proposed mechanism for the DDQ-mediated oxidative alkylation of benzyl ethers



Scheme 25 Selective C–H bond oxidation using NHPI as catalyst

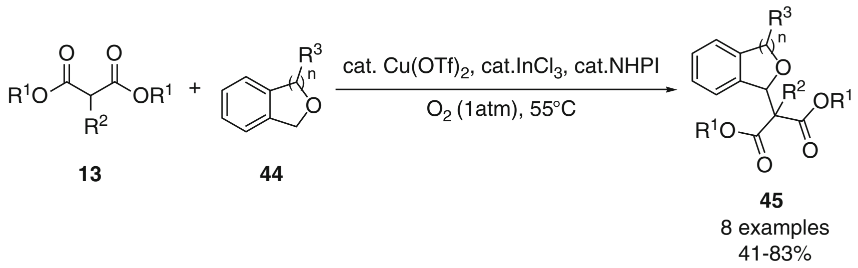


NHPI PINO

Fig. 2 Structures of NHPI and PINO

Using the combination of NHPI and oxygen gas as a DDQ equivalent, Li and co-workers were successful in oxidative coupling cyclic benzyl ethers **44** with malonates **13** using catalytic amounts of $Cu(OTf)_2$ and $InCl_3$ (Scheme 26) [47].

The yields obtained for the oxidative alkylated product **45** was similar to that of the DDQ-mediated reactions. However, due to competing NHPI-catalyzed oxidation of ether **44** to an ester, excess (5.0 equiv.) of **44** was required. Also, Li and co-workers showed that simple ketones can also undergo oxidative alkylation when slightly higher reaction temperatures were employed.



Scheme 26 Oxidative alkylation of cyclic benzyl ethers with malonates using oxygen gas as the terminal oxidant

7 Oxidative Coupling of Allylic and Benzylic C–H Bonds

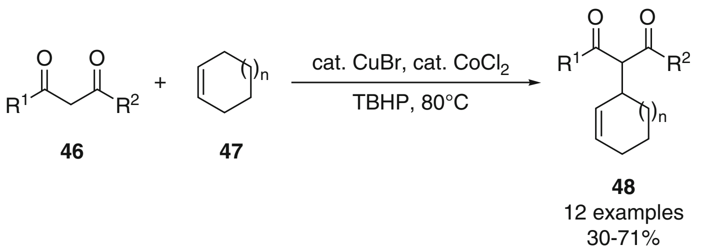
Selective oxidation of allylic and benzylic C–H bonds over aliphatic C–H bonds has been well reported. The selectivity can be attributed to the relative weak bond strength of allylic and benzylic C–H bonds. However, unlike simple oxidation reactions, selective oxidative coupling reactions of allylic and benzylic C–H bonds have only been recently disclosed.

7.1 Allylic Alkylation (sp^3–sp^3)

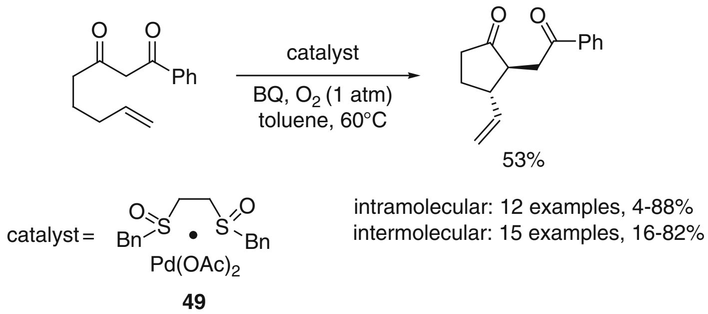
The palladium-catalyzed allylic alkylation (Tsuji–Trost) reaction is an important organic transformation that allows for the formation of a single C–C bond (for a recent reference, see [48]) The methodology was found to be versatile and the chemo-, regio-, and stereoselectivity can be tuned easily. In general, an allylic carboxylate (or another leaving group) is activated by a palladium catalyst during the reaction with a pronucleophile. In theory, the direct utilization of an allylic C–H would improve the synthetic efficiency of the reaction by avoiding the formation of the activated allylic precursor (allylic carboxylate). In their pioneering work, Trost and co-workers reported the allylic alkylation from an allylic C–H bond in two steps [49]. However, due to the difficulty associated with direct re-oxidation of the palladium(0) species to the palladium(II) catalyst, stoichiometric palladium was required.

Following upon their previous experiences with oxidative coupling chemistry with THBP, Li and co-workers recently reported an oxidative allylic alkylation reaction between activated methylene nucleophiles **46** (such as diketones and ketoesters) with cyclic alkenes **47** catalyzed by CuBr and $CoCl_2$ (Scheme 27) [50].

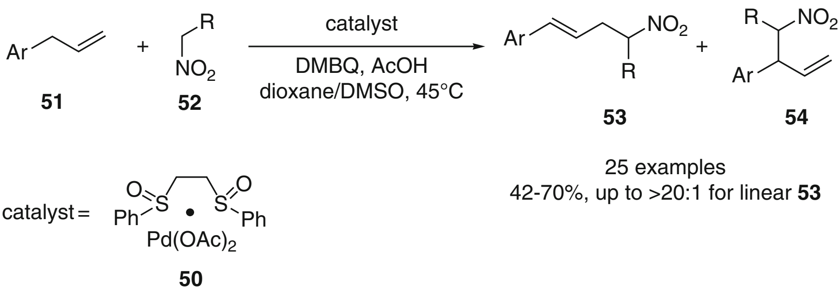
Excess cyclic alkenes **47** were required to furnish the desired alkylated product **48** due to the completing oxidation of **47** to its corresponding allylic alcohol and ketone.



Scheme 27 Oxidative allylic alkylation of cyclic alkenes



Scheme 28 Palladium(II)-catalyzed inter- and intramolecular oxidative allylic alkylation



Scheme 29 Palladium(II)-catalyzed intermolecular oxidative allylic alkylation

Following the work by Li, Shi and co-workers reported both an inter- and intramolecular oxidative allylic alkylation reaction utilizing palladium(II) complex **49** as a catalyst and using benzoquinone (BQ) with oxygen gas as the oxidant (Scheme 28) [51].

White and co-workers also reported an intermolecular oxidative allylic alkylation reaction using a similar palladium(II) complex **50** (Scheme 29) [52].

White found that highly acidic C–H nucleophiles were required for a successful oxidative coupling reaction and used nitroalkanes **52** with electron-withdrawing substituents. In virtually all cases, the oxidative alkylation of **51** resulted in the linear nitroalkanes **53** being the major product. Due to the propensity of soft nucleophiles to undergo addition reactions to BQ, White chose to use 2,6-dimethylbenzoquinone (DMBQ) as the oxidant.

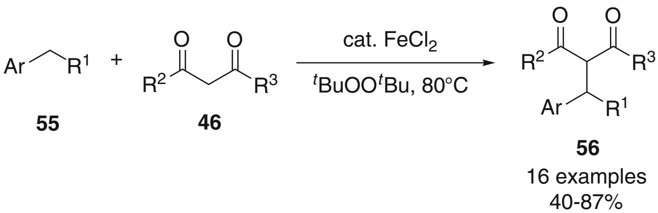
7.2 Benzylic Alkylation (sp^3–sp^3)

Following their earlier success with the oxidative allylic alkylation reaction, Li and co-workers examined the oxidative cross-coupling reaction between activated methylenes **46** with benzylic C–H bonds of **55** (Scheme 30) [53].

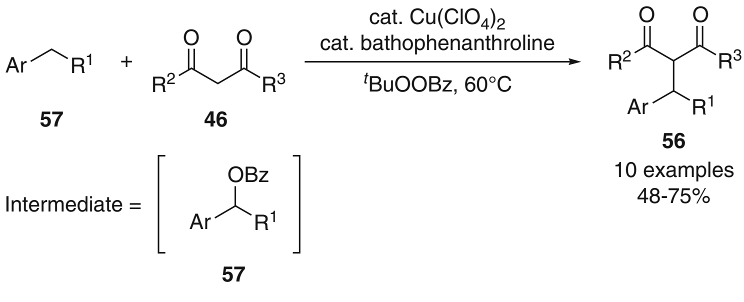
Initially, Li and co-workers utilized their copper/cobalt system and found the alkylated product **56** in low yields. However, through optimization studies, they found that using $FeCl_2$ as catalyst and *tert*-butyl peroxide provided the desired product **56** in moderate to good yields.

Powell and co-workers also demonstrated that peroxides can mediate the oxidative coupling reaction of activated methylenes **46** with benzyl aromatics **55** (Scheme 31) [54].

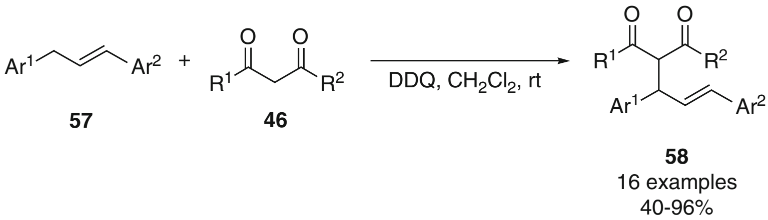
Powell believed that the reaction proceeds through the in situ generation of benzoate **57** which then undergoes a coupling reaction with **46**. The key evidence supporting this hypothesis was the observation of this intermediate in the initial stages of the reaction (via ^{1}H NMR). Furthermore, 1-phenylethyl benzoate **57**



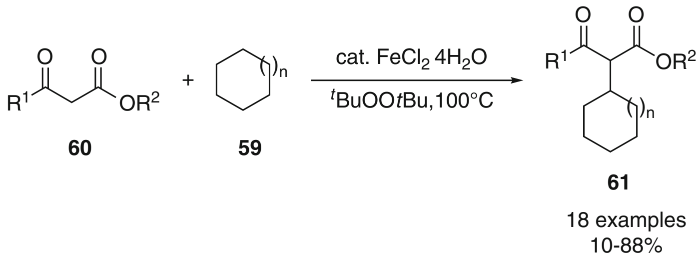
Scheme 30 Iron(II)-catalyzed oxidative alkylation of benzylic C–H bonds



Scheme 31 Copper(II)-catalyzed oxidative benzylic alkylation



Scheme 32 Oxidative alkylation mediated by DDQ



Scheme 33 Oxidative cross-coupling reaction between cyclic alkanes and β-ketoesters

(Ar = Ph, R^1 = Me) was synthesized independently and the benzoate was shown to undergo the cross-coupling reaction to generate the alkylated product **56**.

Bao and co-workers recently reported a metal-free oxidative coupling reaction of benzylic/allylic C–H bonds of **57** with activated methylene **46** using DDQ as the oxidant to generate the alkylated product **58** (Scheme 32) [55].

Furthermore, Bao and co-workers extended this methodology to include benzylic/propargylic C–H bonds as oxidative coupling partners to 1,3-dicarbonyl compounds [56].

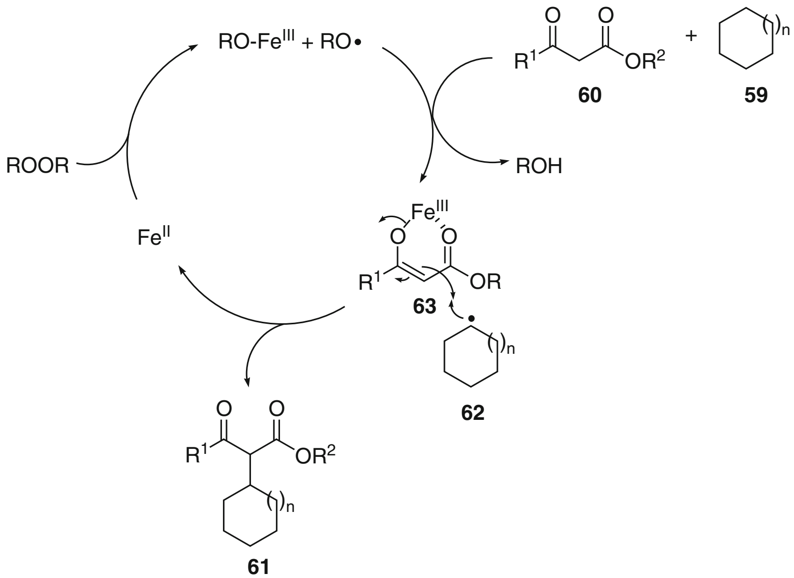
8 Oxidative Coupling of Alkane C–H Bonds

The oxidative cross-coupling reaction of simple aliphatic C–H bonds remains to be quite a challenging problem. However, the Fenton chemistry (for reviews on Fenton chemistry, see [57, 58]) and the Gif processes (for reviews on Gif chemistry, see [59, 60]) has firmly established that simple aliphatic C–H bonds can be converted into C–O bonds under mild conditions by using peroxides catalyzed by various iron salts. With this in mind, Li and co-workers attempted to achieve cross-coupling reactions by adapting these processes to form C–C bonds. Indeed, using iron(II) chloride as a catalyst, simple cyclic alkanes **59** were shown to undergo cross-coupling reactions with various β-ketoesters **60** (Scheme 33) [61].

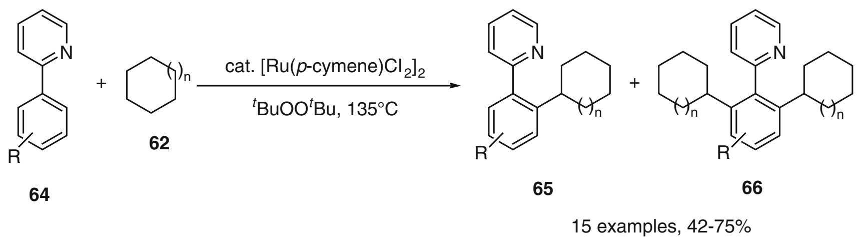
Li believed that a cyclic alkane radical was generated from the hydrogen abstraction by a *tert*-butoxy radical that arose from the iron-catalyzed decomposition of the *tert*-butyl peroxide. The cyclic radical **62** was then believed to react with the iron enolate **63** to form the alkylated product **61** (Scheme 34).

To extend the concept of trapping alkane radicals with other types of C–H bonds, Li and co-workers showed that aromatic C–H bonds of **64**, with the aid of a pyridine directing group, can undergo oxidative cross-coupling reactions with cyclic alkanes **62** in the presence of *tert*-butyl peroxide and catalytic amounts of dichloro (*p*-cymene)ruthenium(II) dimer (Scheme 35) [62].

A mixture of mono- **65** and di- **66** alkylated products were generated with moderate yields from the ruthenium(II)-catalyzed oxidative coupling reaction. However, the dialkylation was shown to be minimized when substituents were present on the aryl ring.



Scheme 34 Proposed mechanism for the iron(II)-catalyzed oxidative alkylation of cyclic alkanes

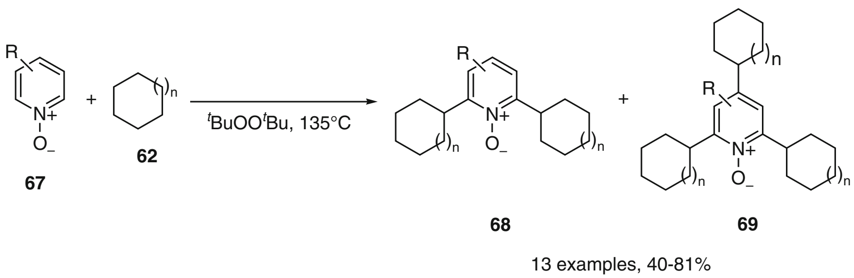


Scheme 35 Ruthenium(II)-catalyzed oxidative alkylation of 2-phenylpyridines with cycloalkanes

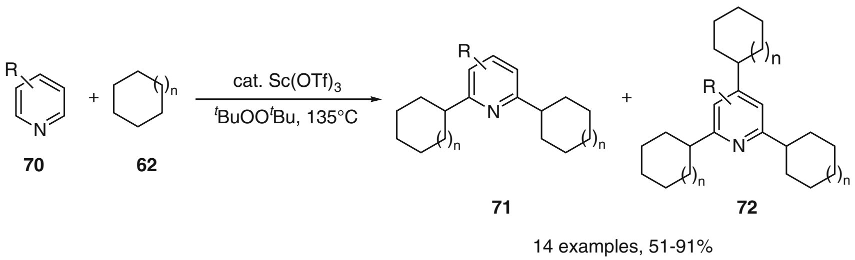
Recently, the C–H bond of nitrogen heteroaromatics has been shown to become activated upon the conversion of the heteroaromatic to its corresponding *N*-oxide derivative (for recent examples of direct functionalization of pyridine *N*-oxides and *N*-iminopyridinium ylides, see [63–67]). Li and co-workers demonstrated that *tert*-butyl peroxides can mediate the oxidative coupling between pyridine *N*-oxides **67** and cycloalkanes **62** (Scheme 36) [68].

Although alkylation was shown to prefer the C–H bond adjacent to the nitrogen atom, the oxidative coupling reaction was not completely selective and trialkylation was also observed. Also, the pyridine *N*-oxides were compared with pyridine itself for the oxidative alkylation reaction and was found to be quite inferior and only provide trace amounts of the desired coupling product. However, Li and co-workers hypothesized that a Lewis acid might coordinate with the nitrogen atom and temporarily polarize the nitrogen heteroaromatic to activate the aryl C–H bond. After screening a variety of Lewis acids, $Sc(OTf)_3$ was found to be the best catalyst for the oxidative coupling of *N*-heteroaromatics **70** with cycloalkanes **62** (Scheme 37) [69].

Similar to the situation with the oxidative coupling of pyridine *N*-oxides, the Sc $(OTf)_3$-catalyzed oxidative alkylation provide both the bis **71** and tri **72** alkylated products.



Scheme 36 Oxidative cross-coupling of pyridine *N*-oxide derivatives with cycloalkanes



Scheme 37 $Sc(OTf)_3$-catalyzed oxidative alkylation of quinolines and pyridines with cycloalkanes

9 Conclusion

As illustrated in this chapter, oxidative cross-dehydrogenative coupling (CDC) has provided the opportunity to simplify organic synthesis by presenting an alternative to the separate steps of prefunctionalization and defunctionalization that have traditionally been part of synthetic design. In the near future, we anticipate the development of CDC reactions that will be more efficient and effective to provide a positive economical and ecological impact on the next generation of C–C bond formation processes.

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Functionalization of Carbon–Hydrogen Bonds Through Transition Metal Carbenoid Insertion

Huw M.L. Davies and Allison R. Dick

Abstract The functionalization of carbon–hydrogen bonds through transition metal carbenoid insertion is becoming a powerful method for the construction of new carbon–carbon bonds in organic synthesis. This chapter will highlight recent developments in this field, while placing it within its historical context. Intramolecular carbenoid C–H insertion will be covered first, focusing on formation of three- and six-membered rings, as well as the use of nontraditional substrates. Additionally, the most recent progress in asymmetric catalysis will be discussed. The bulk of the chapter will concentrate on intermolecular transformations, emphasizing both the effect of substrate structure and the influence of carbene substituent electronics on the regioselectivity of the reactions. Vinyldiazoacetates will be covered as a distinct class of carbenoid precursors, as they have been shown to initiate a variety of unique transformations, such as the combined C–H activation/Cope rearrangement. Finally, the synthetic utility of carbenoid C–H insertion reactions, both intra- and intermolecular, will be displayed through their use in the total syntheses of a number of natural products and pharmaceuticals.

Keywords Asymmetric catalysis • Carbenoids • C–H insertion • Diazo compounds • Rhodium

Contents

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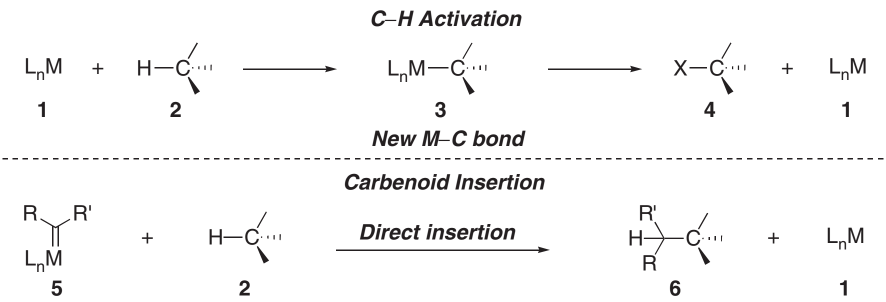
Abbreviations

2,2-DMB	2,2-Dimethylbutane
ad	Adamantyl
BOX	Bis(oxazoline)
cy	Cyclohexyl
de	Diastereomeric excess
dr	Diastereomeric ratio
EDA	Ethyl diazoacetate
EDG	Electron donating group
ee	Enantiomeric excess
EWG	Electron withdrawing group
hfacac	Hexafluoroacetylacetonate
mes	Mesityl (2,4,6-trimethylbenzene)
*p*ABSA	*p*-Acetamidobenzenesulfonyl azide
por*	Chiral porphyrin ligand
TFT	α,α,α-Trifluorotoluene
Tp	Trispyrazolylborate

1 Introduction

The direct functionalization of carbon–hydrogen bonds is becoming a powerful tool in modern organic synthesis. The installation of new functionality where none existed previously allows rapid introduction of complexity into simple molecules. Such methodology has the potential to revolutionize the field of chemical synthesis if certain key requirements are met. First of all, the transformations must be regioselective, since C–H bonds are ubiquitous in organic molecules. Second, they must be stereoselective to be useful in the context of complex molecule synthesis or the synthesis of pharmaceutical targets. Furthermore, the vast majority of these reactions currently rely on transition metals to occur. Both for the sake of cost effectiveness and environmental impact, the amount of the metal utilized must be minimized; that is, the reactions must be catalytic with low catalyst loadings. This is especially important for pharmaceuticals, in which trace metals must be kept to certain strict minima.

Although this entire volume is dedicated to carbon–hydrogen bond activation, a distinction must be made between traditional C–H activation as it is generally thought of and the C–H functionalization by means of metal carbenoid C–H insertion that will be discussed in this chapter (Scheme 1) [1]. The former involves a direct interaction between the transition metal catalyst **1** and the substrate **2**, forming a distinct organometallic intermediate (**3**), which then becomes further functionalized to yield the final product **4** [2]. The insertion of a metallocarbene into a carbon–hydrogen bond, however, is just that: an insertion [3]. The carbon atom of the carbenoid (**5**) interacts with the C–H bond in a three-centered transition state [4], resulting in the breakage of the original C–H bond and the formation of new C–C and C–H bonds in a single step (as in **6**), without forming a metal–carbon bond. The net result in both cases is the same, however: the original C–H bond is transformed into new functionality through the aid of a transition metal.



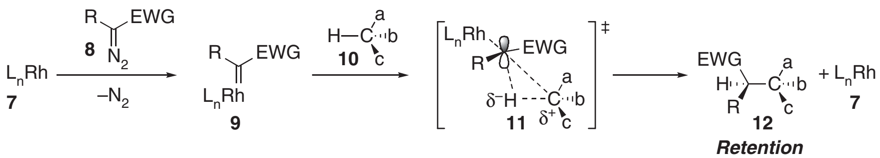
Scheme 1 Comparison of C–H activation and carbenoid insertion

Among the myriad of C–H functionalization methodologies discussed in this volume, carbenoid insertion offers some unique advantages that render it complementary to many other approaches. First, the reactions are often conducted under very mild conditions, at or below room temperature, making them extremely tolerant towards other functional groups within complex molecules such as esters, ethers, carbamates, alkenes and aromatic systems, especially if they are sterically protected [5]. Second, the catalysts are generally quite active and very selective for the decomposition of diazo compounds to generate the carbenoid species [6]. This also enhances compatibility with additional functionality, and furthermore, renders the process as a whole quite catalytic, allowing very low catalyst loadings to be used. Third, the metals are easily modified with chiral ligands to allow asymmetric catalysis to take place, with very high levels of asymmetric induction having already been achieved using this chemistry. Finally, the regioselectivity for C–H functionalization is controlled by a delicate balance of steric and electronic effects, permitting site selective C–H functionalization to occur in fairly elaborate systems.

1.1 The Mechanism of Carbenoid C–H Insertion

The mechanism of carbenoid C–H insertion, although it is considered to take place in a single step, is still not fully understood. Initial clues as to the exact nature of the transition state came from classical Hammett studies. Wang and coworkers examined a series of intramolecular insertion reactions adjacent to *para*-substituted benzene rings and determined that the resultant Hammett ρ values, when plotted vs σ, were −1.39 to −0.66, depending on the catalyst [7, 8]. This suggested a build up of positive charge at the carbon bearing the hydrogen atom undergoing the activation. Davies [9] and Woo [10] conducted Hammett studies with intermolecular C–H insertion reactions. In both cases, the best correlation was obtained vs. σ^+, with ρ values of −1.27 and −1.11, respectively.

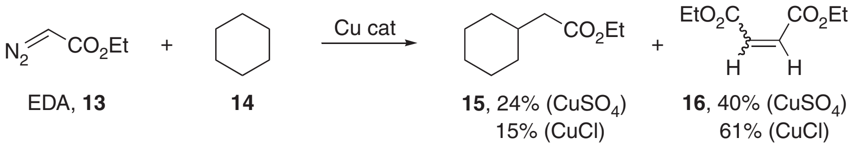
Further support of this experimental evidence was obtained through detailed computational studies conducted by Nakamura and coworkers [11, 12]. They concluded that the overall mechanism for the carbenoid insertion event occurs as shown in Scheme 2. The diazo compound **8** binds to one of the rhodium atoms in the catalyst **7** as an axial ligand, and extrusion of nitrogen gas results. Following approach of the substrate **10**, the actual insertion takes place through a three-centered transition state (**11**), in which the 2p orbital of the carbenoid initiates electrophilic attack onto the σ C–H bonding orbital of the alkane [4]. Specifically, this is thought to involve initial hydride transfer from the substrate to the carbenoid carbon followed by new C–C bond formation, which occurs in a *concerted* but highly *asynchronous* manner. Importantly, this occurs with complete retention of stereochemistry to provide the product **12**. As will be demonstrated throughout this chapter, this mechanism has profound implications for selectivity of the insertion event, catalyst effects, as well as certain side reactions. A thorough understanding of the transition state, then, can help to optimize the chemistry to increase its utility for the synthetic community.



Scheme 2 Mechanism of carbenoid C–H insertion

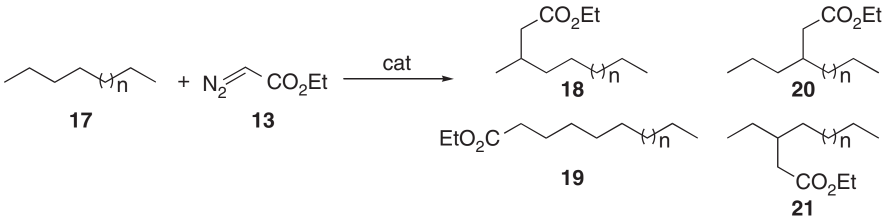
1.2 Historical Survey

The earliest examples of transition metal carbenoid C–H insertion reactions were carried out with ethyl diazoacetate **13** (EDA) and simple alkanes acting as the reaction solvent. In 1974, Scott and DeCicco reported that $CuSO_4$ and CuCl were capable of decomposing EDA in the presence of cyclohexane (**14**) to generate C–H insertion product **15** [13]. Although these results, along with control experiments, provided proof that the copper catalyst was necessary for the transformation to take place, the maximum yield of the product was only 24%, and dimeric byproducts of the diazo compound dominated, even at high dilution (Scheme 3).



Scheme 3 Early example of insertion into cyclohexane with EDA

Callot [14, 15] and Noels [16, 17] examined the reactions of rhodium porphyrins [14, 15] and carboxylates [16, 17] with various alkanes. When *n*-alkanes **17** were utilized, complex mixtures of isomeric products were always obtained (Scheme 4). Functionalization at C2 (as in **18**) was nearly always the major product, and, depending on the catalyst used, C1 (**19**) or C3 (**21**) could be the site of the second most common attack. Branched alkanes also led to multiple products, but C–H insertion at tertiary sites was generally favored.



Scheme 4 Lack of selectivity of EDA insertion into *n*-alkanes

The above examples clearly illustrate that early carbenoid C–H insertion reactions were far from being synthetically useful. Even when conducted on simple substrates, selective transformations were not achieved. In addition, dimerization of the carbenoid was a competing reaction, rendering yields of the desired products low. Both the low selectivity of the insertion events and the facile dimerization reactions suggested that the carbenoids were simply too reactive. In order to

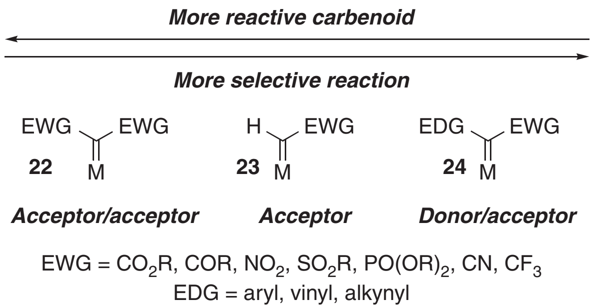


Fig. 1 Classifications of metal carbenoids by substituent electronics

attenuate this high reactivity and achieve more selective reactions, chemists have subsequently turned to three major strategies: (1) intramolecular reactions (see Sect. 2), (2) modification of the carbenoid precursor, and (3) catalyst development.

Diazo compounds are by far the most common precursors for the generation of the transition metal carbenoid intermediates [6]. The resulting carbenoid complexes can be classified into three primary categories based upon the electronics of the substituents on the carbene carbon (Fig. 1) [18]. Acceptor/acceptor carbenoids **22**, as the name implies, contain two electron-withdrawing groups flanking the carbenoid carbon, the most common being ester or keto moieties. These carbenoids are extremely electron deficient, rendering their reactions unselective and often complicated by the formation of side-products derived from zwitterionic intermediates. Acceptor carbenoids **23** are also traditionally unselective in intermolecular reactions, but have been used successfully in the intramolecular manifold. Less frequently encountered are the related alkyl/acceptor carbenoids, in which the hydrogen atom is replaced by an alkyl group. These are most often seen in intramolecular reactions because, unless they are efficiently trapped, they are prone to alkene formation by a 1,2-hydride shift [19].

Donor/acceptor carbenoids **24** were a relatively late arrival to the field of carbenoid chemistry, but have greatly expanded its scope [3]. The addition of the electron-releasing moiety, although decreasing the reactivity of the carbenoid, has been found to enhance greatly the selectivity of a variety of transformations, including C–H insertion. Davies and coworkers found that aryl, vinyl, and, to a lesser extent, alkynyl groups are all suitable donors for these reactions [20].

In addition to modification of the substituents on the carbenoid carbon, the transition metal catalyst itself also offers opportunities for both steric and electronic variation through ligand design [21]. Although early studies in carbenoid C–H insertion focused on copper catalysts and transition metal porphyrins, dirhodium tetracarboxylates and tetracarboxamidates have become by far the most popular catalysts for these transformations (Fig. 2). The simplest, $Rh_2(OAc)_4$ (**25a**, R = Me), is D_{4h}-symmetric, displaying a "paddlewheel" arrangement of the ligands around the dirhodium core, and is widely used when asymmetric induction is not needed. Other achiral carboxylates **25b–f** are also employed that vary both the steric and electronic properties of the ligands.

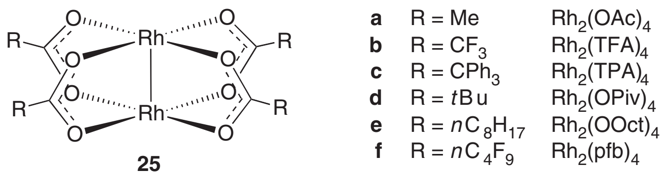


Fig. 2 Common achiral dirhodium catalysts

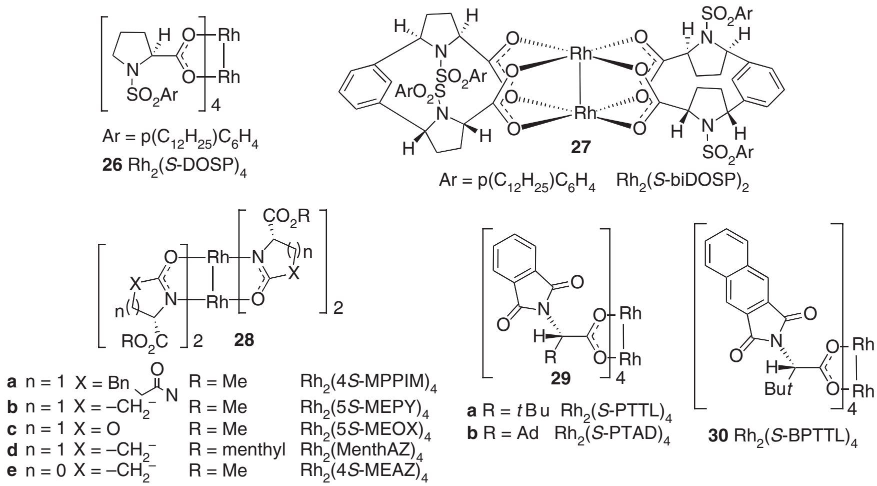


Fig. 3 Chiral dirhodium catalysts discussed in this chapter

These dirhodium catalysts are also ideally suited to chiral variants (Fig. 3). Not only are the ligands easily modified to include stereogenic centers, but the binding site of the carbenoid, at the axial position of one of the rhodium atoms, also offers unique opportunities for asymmetric induction based upon the overall orientation of the four ligands. It has been suggested that certain classes of these catalysts adopt different, distinct conformations in solution [21]. The prolinates Rh_2(*S*-DOSP)$_4$ (**26**) and Rh_2(*S*-biDOSP)$_2$ (**27**), for example, have been proposed to exist preferentially in a D_2 conformation (**27** is locked as such) [22], while the carboxamidates **28** are locked in a C_2 arrangement [23]. The phthalimides Rh_2(*S*-PTTL)$_4$ (**29a**) and Rh_2(*S*-BPTTL)$_4$ (**30**) are also thought to adopt in solution a conformation with C_2 symmetry [24].

The different groups of catalysts are complementary to each other because they tend to be most effective with different classes of carbenoids [5]. Since the carboxamidate catalysts are less electrophilic than the carboxylates, they tend to produce carbenoids that are not as reactive. Therefore, they are better suited for use with more reactive carbenoids such as the acceptor-substituted carbenoids. The phthalimide carboxylate catalysts have been extensively used with acceptor/acceptor carbenoids, while the prolinates have been extremely effective with donor/acceptor-substituted carbenoids.

Other chiral catalysts have also been developed that do not fall into the families shown in Fig. 3 [25–30], but to date they tend to give low enantioselectivities and will not be discussed in this chapter. In addition, chiral auxiliaries are sometimes utilized instead of or in addition to chiral catalysts to control stereoselectivity [31–34], but this is becoming increasingly less popular as the catalysts become more selective.

Although the dirhodium catalysts are the most commonly used today, other metals are still being explored for carbenoid C–H insertion [35]. These include copper [36–45], silver [46, 47], iron [48–50], gold [40], and magnesium [51, 52], and most will be discussed in context, particularly in Sect. 3.1.

1.3 Scope of This Chapter

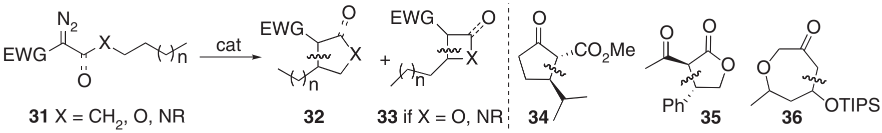
Although this series is entitled *Topics in Current Chemistry*, the reactions of carbenes, and even C–H insertions of carbenes, have been known for many years. As such, this chapter will focus specifically on a few key areas of this topic. First, in keeping with the theme of the series, the remaining material will focus on developments from within the last 5–10 years. Second, intramolecular carbenoid C–H insertion is a more mature area of study and has already been thoroughly reviewed [5, 6, 53–55]. Although this methodology will be briefly summarized and some exciting new results highlighted, the main focus of the chapter will be on intermolecular reactions. Third, only transition metal-catalyzed transformations will be discussed. Finally, the synthetic utility of this methodology will be highlighted through the discussion of its application in a number of total syntheses of natural products and pharmaceuticals.

2 Intramolecular C–H Insertion

Intramolecular carbenoid C–H insertion has been a useful method for the construction of small to medium rings since the early 1980s, and these transformations can occur with good regio-, diastereo-, and enantioselectivity with appropriate choice of catalyst [6]. Taber, Doyle, and Hashimoto have been key players in this area and have also developed a number of chiral catalysts for increasing levels of enantioinduction. Many studies have been conducted concerning the effects of substrate conformation, sterics, stereoelectronics, and catalyst on the regioselectivity, diastereoselectivity, and enantioselectivity of the C–H insertion events, but these are outside the scope of this chapter. For detailed discussion, refer to the reviews cited in Sect. 1.3.

2.1 Summary of Basic Trends Observed Prior to 1998

Despite the vast number of examples of intramolecular carbenoid C–H insertion that have been reported in the literature, a number of general trends have emerged that can be used to predict reactivity and selectivity in new systems (Scheme 5) [6]. By far, the most obvious is that the formation of five-membered rings is preferred in the absence of any other controlling factors, largely due to entropic considerations. This preference can be overridden, however, by the presence of an electron-donating moiety such as a heteroatom, allowing insertion to take place adjacent to this "activating" group (as in **33**). When more than one five-membered ring could possibly be formed, reactivity generally follows in the order 3°>2°>>1°. As far as stereoselectivity is concerned, *trans* disubstituted cyclopentanes are typically generated, and insertion into equatorial C–H bonds is usually favored over their axial counterparts.

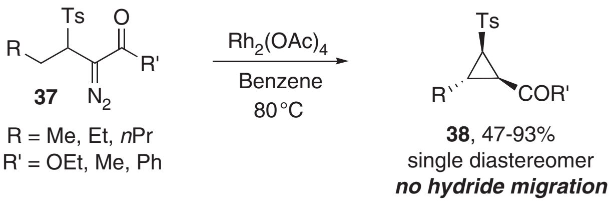


Scheme 5 General scheme of intramolecular carbenoid C–H insertion and representative examples

2.2 Recent Developments

2.2.1 Selective Formation of "Unusual" Ring Sizes

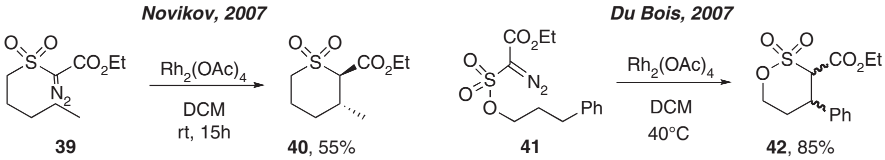
Although the formation of three-membered rings by cyclopropanation of olefins with metal carbenoids is commonplace, the construction of such systems via intramolecular C–H insertion is quite rare. This is because 1,2 migration of any hydride atoms α to the carbenoid center is typically very facile, rendering it inactive toward further transformations [56]. It was found, however, that β-tosyl α-diazo carbonyl compounds **37** are suitable substrates for intramolecular 1,3 C–H insertion reactions catalyzed by achiral rhodium carboxylates **25** (Scheme 6) [57].



Scheme 6 Formation of cyclopropanes through intramolecular C–H insertion

The resulting cyclopropane products **38** were formed in good yield (>70%) when competing five-membered ring formation was not possible, and as a single diastereomer. A similar cyclopropane formation through magnesium carbenoid C–H insertion has been reported by Satoh and coworkers, but the system was set up such that no β hydrogens were present [51, 52].

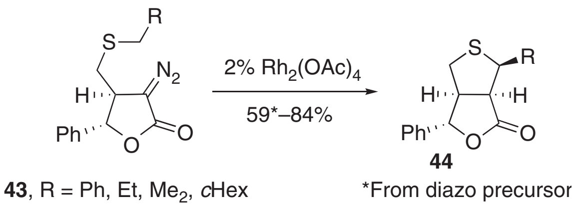
Both Novikov [58] and Du Bois [59] have developed systems involving sulfones (**39**) and sulfonates (**41**) that form six-membered rings selectively (Scheme 7). Novikov takes the traditional approach of preforming the diazo compound (such as **39**), then treating it with $Rh_2(OAc)_4$ (**25a**) at room temperature to generate the cyclized products **40** in 53–80% yield. Du Bois, in addition to this protocol, also forms the carbenoid in situ from the methylene group through the use of PhI=O and cesium carbonate.



Scheme 7 Intramolecular formation of six-membered sulfones and sulfonates

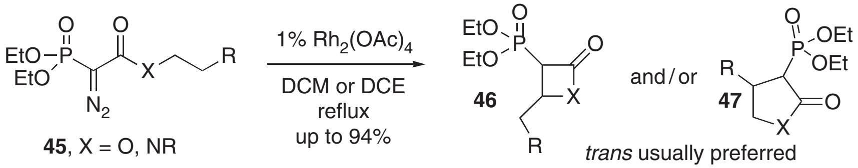
2.2.2 Novel Substrates

In addition to the typical substrates shown in Scheme 5, the scope has begun to be expanded. For instance, although intramolecular insertion α to oxygen and nitrogen atoms is quite commonplace, similar C–H functionalizations adjacent to sulfur are rare due to more facile ylide formation with this heteroatom. However, in 2004, Harrowven, Brown, and coworkers developed a system specifically designed to overcome this competing reaction (Scheme 8) [60]. A number of diazolactones **43** containing a tethered thioether moiety were synthesized and subjected to diazo decomposition with $Rh_2(OAc)_4$ (**25a**). The subsequent thienofuranones **44** were formed in moderate to good yields (59–84%) and excellent diastereoselectivity in most cases.



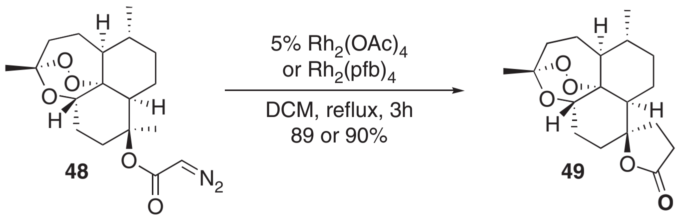
Scheme 8 C–H insertion α to sulfur to produce thienofuranones

In addition to changing the site for the C–H insertion event, the nature of the acceptor group can also be changed from the usual ester, keto, or amide group. In 1995, Minami and coworkers demonstrated that dialkoxyphosphonates (as in **45**) were also possible acceptor groups [61], but the yields of the cyclized products were generally quite low. Gois and Afonso improved upon this system in 2003, providing α-(dialkoxyphosphoryl)lactones and lactams **46** and **47** in yields up to 94% (Scheme 9) [62]. The substituents in the products existed exclusively in the *trans* orientation, which the authors attributed to preferential insertion into pseudoequatorial C–H bonds.



Scheme 9 Intramolecular C–H insertion of diazophosphonates

Another quite fascinating use of intramolecular carbenoid C–H insertion was demonstrated in the synthesis of analogs of artemisinin, which exhibits antimalarial properties (Scheme 10) [63]. Beginning from 10-dihydroartemisinin, diazo ester **48** was constructed. Intramolecular C–H insertion into the adjacent methyl group (C16) occurred in 90% yield with 5% $Rh_2(pfb)_4$ (**25f**) to provide lactone **49**. Importantly, the labile endoperoxide moiety was left untouched throughout the sequence.



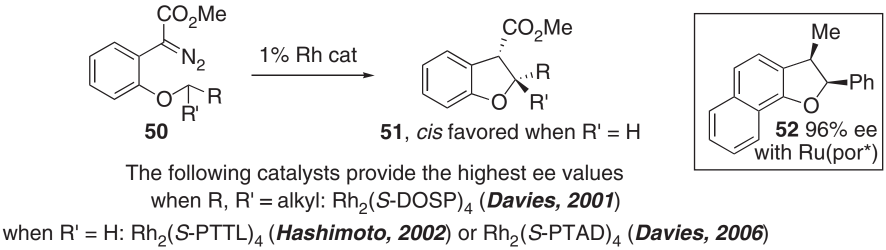
Scheme 10 Intramolecular C–H insertion in the synthesis of an artemisinin analog

2.2.3 Recent Examples of Enantioselective Catalysis

2.2.3.1 Synthesis of Dihydrobenzofurans: Catalyst and Substrate Comparison

A number of groups have successfully synthesized dihydrobenzofurans (**51**) in high enantioselectivity, but the right combination of catalyst and substrate needs to be used [64–66]. In all cases, *ortho*-substituted benzene rings are the precursors for the C–H insertion events. Davies [64] and Hashimoto [66] both used diazoesters **50** as the carbenoid source (Scheme 11). Davies' prolinate catalyst Rh_2(*S*-DOSP)$_4$ (**26**) was found to give high enantioselectivity for insertion into methine C–H bonds (up to 94% ee), but selectivity was low for methylene sites.

In contrast, Hashimoto's phthalimide-based catalysts such as **29a** gave poor selectivity for 3° C–H bonds, but provided superior results for 2° benzylic positions, also



Scheme 11 Asymmetric synthesis of dihydrobenzofurans through intramolecular C–H insertion

providing the cyclized products in up to 94% ee, with the *cis* diastereomer favored in good to excellent ratios. In a subsequent publication, Davies' structurally related Rh_2(*S*-PTAD)$_4$ catalyst (**29b**) also proved remarkably effective for insertion into secondary sites [67]. Yu and Che chose to form their carbenoids by decomposition of aryl tosylhydrazones with ruthenium porphyrin catalysts [65]. Although only one example was reported utilizing a chiral catalyst, the product **52** was obtained in 96% ee. Interestingly, this system also successfully avoided β-hydride migration.

2.2.3.2 Other Recent Enantioselective Examples

Hashimoto and coworkers have reported a highly diastereo- and enantioselective synthesis of 1,2-disubstituted cyclopentanes **53** that also avoids competing 1,2 hydride migration with appropriate choice of catalyst (Fig. 4) [68]. Phthalimide-based Rh_2(*S*-PTTL)$_4$ (**29a**) was found to be the optimal catalyst for insertion into the benzylic position of the precursors to **53**, and was effective for both electron poor and electron rich systems. The diastereoselectivity for the 1,2 *cis* product was excellent as long as the reaction was conducted at −78 °C, and enantioselectivities of up to 95% were achieved. An additional example demonstrated that insertion into a fully aliphatic position could also proceed with high ee (94%), but the resulting product was the *trans* diastereomer.

Hashimoto also developed an enantioselective synthesis of 3-arylindan-1-ones (**54**, Fig. 4) [69]. Although the yields were excellent for these reactions (92–96%), the highest enantioselectivity achieved was only 72% with Rh_2(*S*-PTTL)$_4$. In 2001, Doyle and May reported that aryldiazoacetates are quite selective substrates for

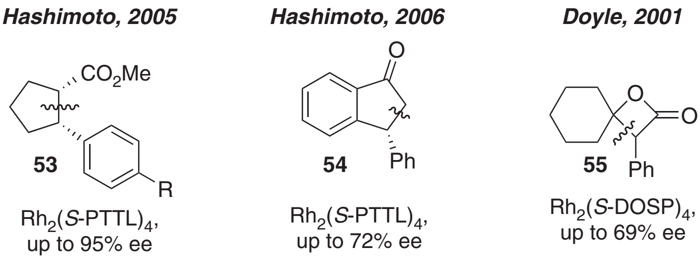
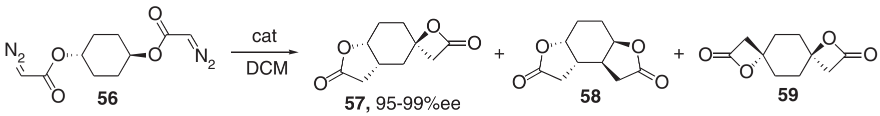


Fig. 4 Classes of compounds recently synthesized through asymmetric intramolecular C–H insertion

formation of β-lactones **55** (Fig. 4) over their five-membered ring counterparts [70]. They examined a number of chiral dirhodium catalysts, and Rh_2(*S*-DOSP)$_4$ (**26**) in refluxing pentane generally provided the best enantioinduction, with enantioselectivities ranging from 41 to 69% ee.

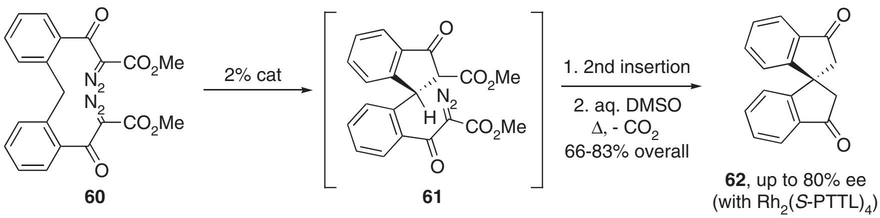
2.2.3.3 Tandem Asymmetric Reactions: Kinetic Amplification and Synthesis of Spiro Systems

One interesting aspect of asymmetric catalysis is that sequential reactions with a chiral catalyst can often lead to an enhancement in the enantioselectivity over a single transformation with the same catalyst in a process called kinetic amplification. Doyle was able to exploit this phenomenon in the synthesis of novel tricyclic products from the bis-diazoacetate of *trans*-1,4-cyclohexanediol (**56**, Scheme 12) [71]. Although formation of C_2-symmetric product **58** was expected, resulting from the typically preferred five-membered insertion event, it was found that **57** could be produced preferentially with appropriate choice of catalyst, and with very high ee (95–99%). Bis-β-lactone **59** was never the major product, but could be formed as up to 34% of the product mixture. Notably, similar catalyst-controlled mixtures of β- and γ-lactone products were also obtained with diazoacetates derived from cholesterol derivatives [72].



Scheme 12 Amplification of asymmetric induction through sequential C–H insertion events

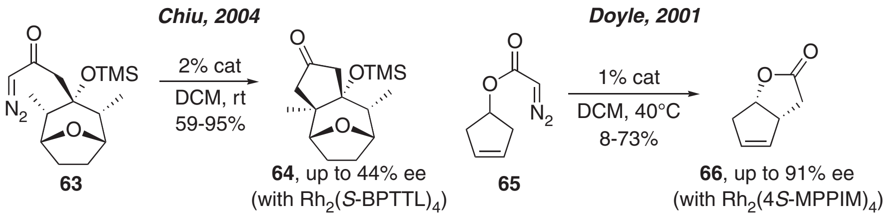
Similar tandem reactions have been utilized to construct all-carbon spirocyclic ring systems. Initially, achiral studies were conducted by Undheim and coworkers using $Rh_2(OAc)_4$ (**25a**) as the catalyst [73, 74]. Although they provided proof of concept, the yields were generally low, and multi-step procedures were often necessary to obtain the final products. Additionally, the methodology was not extended to asymmetric catalysis. In 2001, Hashimoto and coworkers optimized conditions by which spirocyclic product **62** could be obtained in one pot from bis-diazo compound **60** in good yield and up to 80% ee with phthalimide catalyst Rh_2(*S*-PTTL)$_4$ (**29a**, Scheme 13) [75].



Scheme 13 Synthesis of spirocyclic compounds through tandem C–H insertions

2.2.3.4 Desymmetrization Reactions

Desymmetrization is a powerful method by which *meso* substrates can be converted to chiral nonracemic materials through the use of a chiral catalyst and appropriate reaction conditions. Carbenoid C–H insertions, like many other areas of organic chemistry, have found uses for this technique. Chiu chose to study an elaborate oxabicylic system **63** (Scheme 14, left), and obtained the best results with benzo extended phthalimide Rh_2(*S*-BPTTL)$_4$ (**30**) as catalyst. Utilizing substrates containing methyl groups at the site of the insertion event and a single electron withdrawing group on the diazo compound, **64** was produced in up to 44% ee [76]. Doyle, on the other hand, obtained superior results with simpler 3-substituted cyclopentene system **65** (Scheme 14, right) [77]. When heteroatom-rich Rh_2(4*S*-MPPIM)$_4$ (**28a**) was used as the catalyst, **66** was obtained in 91% ee. A similar system (lacking the ester oxygen atom) was utilized by Fukuyama and coworkers toward the asymmetric synthesis of the bicyclo[3.3.0] octane ring system [32]. In this case, both a chiral auxiliary and Rh_2(*S*-DOSP)$_4$ (**26**) were used, and the highest diastereoselectivity obtained was still only 78% de.



Scheme 14 Desymmetrization through rhodium-catalyzed C–H insertion

As shown in the sections above, intramolecular carbenoid C–H insertion is beginning to branch out from the traditional formation of five-membered rings in a diastereo- or enantioselective manner. Three- and six-membered rings are now capable of being formed in certain systems, and kinetic amplification and desymmetrization using chiral catalysts have both been achieved. Additionally, the methodology is being applied to increasingly elaborate systems, and acceptor groups other than esters and ketones have been found to be compatible with this chemistry. Due to the mild conditions and low catalyst loadings typically utilized for formation of C–C bonds through this chemistry, it will likely continue to find use in new contexts in organic synthesis.

3 Intermolecular C–H Insertion

Unlike intramolecular reactions, the selectivity challenges associated with intermolecular C–H insertions are related more to steric considerations, bond strengths, and electronics rather than ring size, entropic, or stereoelectronic issues. Without the driving influence of ring size, however, the number of available C–H bonds within the substrate with which the carbenoid can react becomes much larger. Thus the other controlling factors must be finely balanced to allow a selective reaction to occur.

Rhodium carbenoids, especially the donor/acceptor carbenoids, act as very sterically demanding electrophiles. Hence, based on size alone, the favored order of reactivity of C–H bonds would be 1°>2°>3°, yet carbenoids are also very electrophilic, so they would prefer to react with more electron rich C–H bonds, thus 1°<2°<3°. So, in practice, secondary C–H bonds tend to be the most active overall, because they possess the proper balance between these steric and electronic requirements [5]. Furthermore, when the C–H bond is adjacent to an electron donating group such as a heteroatom or an aromatic ring, it becomes even further activated towards functionalization. Based upon these few general trends, a surprising level of control of reactivity can be achieved in carbenoid reactions with complex molecules, especially when their reactivity is attenuated with proper substituents on the carbenoid.

3.1 Ethyl Diazoacetate

Although the early examples of carbenoid C–H insertion with EDA demonstrated both low yields of the desired product and poor selectivity, recent catalyst development has begun to address these issues [36–43, 46, 47]. Interestingly, the catalysts most commonly employed for use with EDA are generally not rhodium-based, with copper and silver tending to be the most prevalent (Fig. 5). Trispyrazolylborate (Tp) ligands, the homoscorpionate ligands, have been found to be very effective at stabilizing the metals to provide effective reactivity. Additionally, a family of *N*-heterocyclic carbene precatalysts **68** displays unique selectivity in many instances.

As with the earliest examples of C–H insertion, cyclohexane has been a common substrate for evaluation of the effectiveness of new catalysts (Table 1). In contrast to the simple copper catalysts utilized in Scheme 3, the new homoscorpionate ligands of **67** and **69b**, developed for this purpose by Dias, Lovely and Pérez,

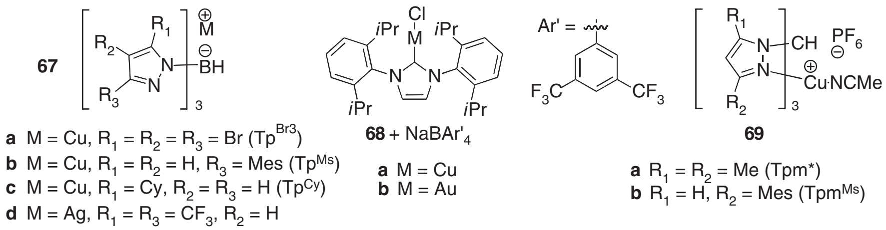
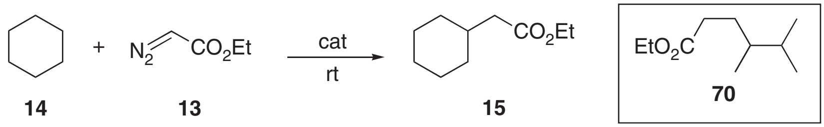


Fig. 5 Common catalysts for intermolecular C–H insertions with EDA

Table 1 Best results for insertion of EDA into cyclohexane with various catalysts



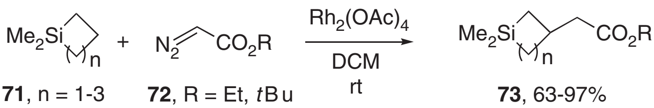
Entry	Catalyst	Yield (%)	Reference	Entry	Catalyst	Yield (%)	Reference
1	5% **67d**·THF	88	[47]	5	5% **68b**	84	[40]
2	5% **67a**·NCMe	90	[37]	6	1% **25b**	78	[16]
3	5% **69b**	77	[42]	7	1% **25b**	90[a]	[16]
4	5% **68a**	80	[40]				

[a]At reflux

provided **15** in up to 90% isolated yield at room temperature (entries 1–3). The copper and gold *N*-heterocyclic carbene catalysts **68** also provided product yields in the 80% range (entries 4–5) [40]. It is worth mentioning, however, that even in 1981 Noels found that $Rh_2(TFA)_4$ (**25b**) was an effective catalyst for this reaction, providing excellent yields at low catalyst loadings (entries 6, 7) [16].

Not only did the *reactivity* improve with these new catalysts, but the *selectivity* also increased in certain instances. One example is compound **70**, shown in the box above Table 1. Although it was noted in Sect. 1.2 that branched alkanes typically led to insertion products at tertiary C–H bonds, this compound was formed in 83% yield with gold catalyst **68b**, displaying a remarkable increase in primary selectivity [40].

One unique class of substrates that displays remarkably high reactivity with EDA is silacycloalkanes **71** [78]. Perhaps due to the electronic stabilizing effect of the silicon atom, C–H insertion occurs exclusively β to the silyl group, and good to excellent yields of the products **73** are obtained (Scheme 15).



Scheme 15 Intermolecular carbenoid insertion into silacycloalkanes

3.2 Aryldiazoacetates

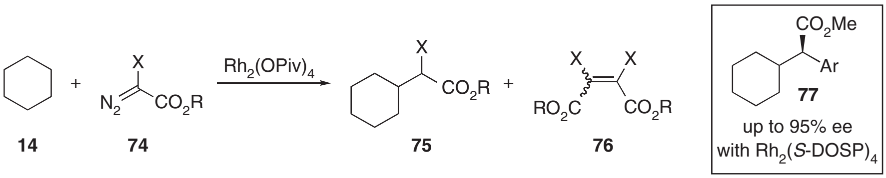
Aryldiazoacetates constitute an effective class of donor/acceptor diazo compounds in the realm of intermolecular carbenoid transformations [79]. Because of their electronic profile, they were expected to display increased chemoselectivity for the desired C–H insertion event, while suppressing unwanted side reactions such as carbene dimerization. Additionally, the regioselectivity was expected to be enhanced in more complex systems due to the attenuated reactivity of the carbenoid.

3.2.1 Reactions with Cyclohexane and Simple Alkanes

When the chemoselectivity hypothesis was tested with cyclohexane as the substrate and $Rh_2(OPiv)_4$ (**25d**) as the catalyst, it was shown to be true (Table 2) [80]. Although the reaction with EDA produced predominantly carbene dimer **76** (entry 1), 94% of the C–H insertion product **75** was isolated with methyl phenyldiazoacetate as the carbenoid precursor under identical reaction conditions (entry 3). This simple comparison indicated that the donor/acceptor carbenoids are indeed more stable and less prone towards undesired dimerization events. Another feature of the donor/acceptor carbenoids that is not shared by EDA is the fact that the carbenoid carbon possesses two substituents. This opens up the opportunity for asymmetric catalysis to occur. Indeed, when a number of aryldiazoacetates **74** were decomposed with Rh_2(*S*-DOSP)$_4$ (**26**) in the presence of cyclohexane, up to 95% ee was achieved for **77** [79, 81]. A fluorous prolinate catalyst was also developed to facilitate purification, but the enantioselectivities were not as high [82].

The results above clearly demonstrate that donor/acceptor carbenoids (specifically those derived from aryldiazoacetates) are capable of better reactivity than their acceptor or acceptor/acceptor counterparts with certain catalysts. Cyclohexane, however, is not appropriate for examining the *selectivity* of intermolecular carbenoid C–H insertion reactions. In order to achieve selective transformations on more complex substrates, it would be crucial to determine what level of differentiation could be obtained between different types of C–H bonds. Thus Davies and coworkers studied the relative rate of insertion of methyl phenyldiazoacetate into a number of simple substrates through competition studies (Fig. 6) [81].

Table 2 C–H insertion into cyclohexane with a variety of diazo compounds



Entry	R	X	Yield **75** (%)	Yield **76** (%)
1	Et	H	10	67
2	Me	COMe	65	0
3	Me	Ph	94	0

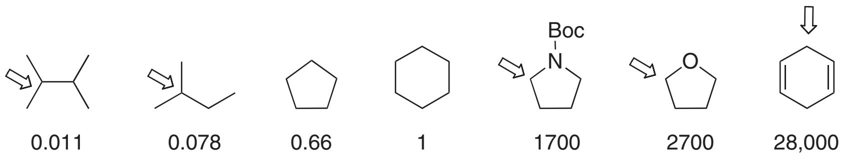
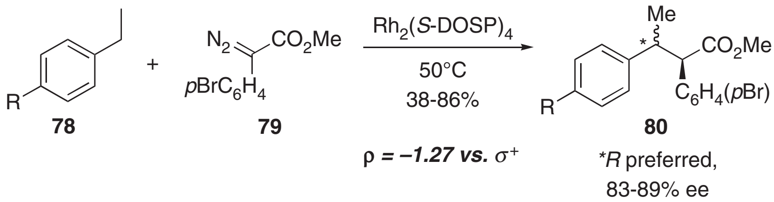


Fig. 6 Relative rates and sites of insertion of methyl phenyldiazoacetate into various substrates at rt

The rates span several orders of magnitude, indicating that selectivity should be possible in more elaborate substrates. The least favorable is insertion into the unactivated tertiary position of 2,3-dimethylbutane. The secondary C–H bonds of cyclohexane are intermediate in reactivity, but those adjacent to heteroatoms are much more reactive. The steric bulk of the Boc group slows the rate of insertion of this substrate relative to THF. Finally, the double activation of 1,4-cyclohexadiene makes this the most reactive substrate. By comparison, cyclopropanation of styrene and Si–H insertion into Ph_2*t*BuSi–H both had relative rates of 24,000, so the majority of the C–H insertion processes are relatively "slow" by carbenoid standards. Notably, these studies were conducted at ambient temperature, and even greater differences in reactivity, and hence better selectivity, might be expected under milder conditions.

3.2.2 Benzylic C–H Insertion

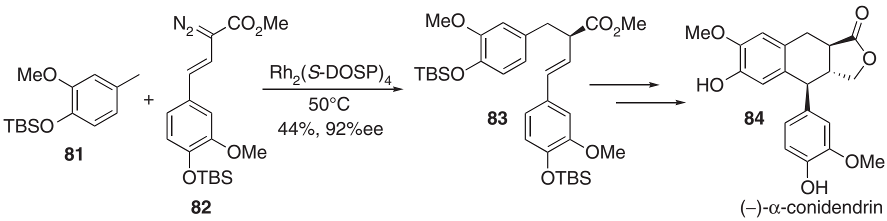
One specific type of activated C–H bond that was not examined above, but seemed as though it might be prone toward facile intermolecular carbenoid insertion, was that of benzylic positions [9, 10, 83]. Initially, Davies and coworkers examined reactions of substituted ethylbenzenes **78** with methyl *para*-bromophenyldiazoacetate **79** (Scheme 16) [9]. The benzylic C–H insertion products **80** were obtained in yields ranging from 38 to 86%, with the higher values obtained for more electron rich substrates. The *R* stereoisomer of the methyl group predominated in all reactions, with diastereomeric ratios of about 2:1 to 4:1, and the ee of the major diastereomer was usually in the high 80s. As noted in Sect. 1.1, a Hammett ρ value of −1.27 was obtained vs σ^+.



Scheme 16 Benzylic C–H insertion

In addition to ethylbenzene, indane and tetrahydronaphthalene derivatives were found to be suitable substrates for benzylic C–H insertion, providing products in good ee, but only low to moderate de. Toluene and isopropyl benzene were also examined; however, cyclopropanation of the ring became a major competing side reaction under rhodium catalysis [9]. However, aromatic ring cyclopropanation is sterically blocked if the aromatic ring is at least 1,4-disubstituted. Isopropyl benzene was functionalized in good yield with an achiral iron porphyrin [83], and similar catalysts were also used to functionalize the methyl group of mesitylene, but with nearly equal amounts of aromatic substitution [10].

Despite the unexpected challenges associated with benzylic carbenoid C–H insertion, the Davies group successfully employed this methodology toward the concise total syntheses of (+)-imperanene and (−)-α-conidendrin [84]. Although the imperanene synthesis will be discussed in a later context (Sect. 4.2), the route to conidendrin **84** is outlined below (Scheme 17). The key carbenoid insertion took place between vinyldiazoester **82** and substituted toluene **81** in moderate yield, but provided the precursor (**83**) to the tricyclic structure in 92% ee.



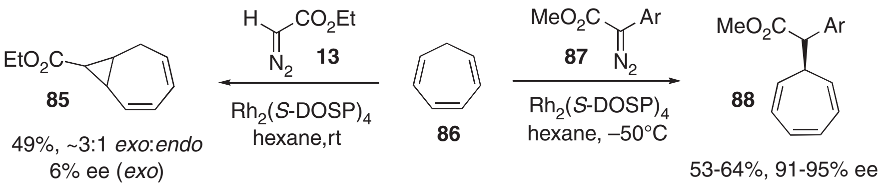
Scheme 17 Concise synthesis of (−)-α-conidendrin via intramolecular C–H insertion

3.2.3 Allylic C–H Insertion

Similar to benzylic C–H bonds, allylic sites also offer a degree of electronic activation that could lead to selective reactions in complex substrates. This system is slightly more complex, however, because cyclopropanation of the olefin can become a major competing pathway, and reaction conditions often must be finely tuned to maximize the insertion event (see below).

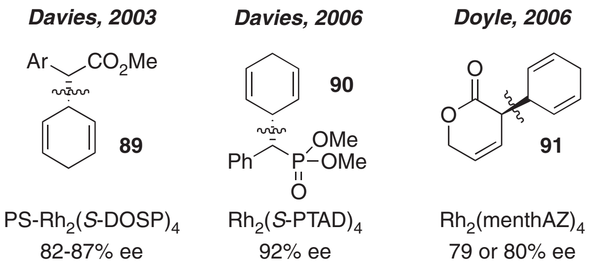
3.2.3.1 Insertion into Doubly Allylic Sites

An early example that suggested donor/acceptor carbenoids might be ideally suited to allylic C–H insertion was the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of cycloheptatriene (**86**) with either EDA or methyl aryldiazoacetates **87** (Scheme 18) [85]. With EDA as the carbenoid precursor, the monocyclopropanated product **85** was formed in 49% yield (~3:1 *exo*:*endo*) and 6% ee. The outcome of the reaction changed dramatically with carbenoids derived from aryldiazoacetates. In these cases, less than 5% of the cyclopropane was observed, and 53–64% yield of the C–H insertion product **88** was isolated in 91–95% ee.



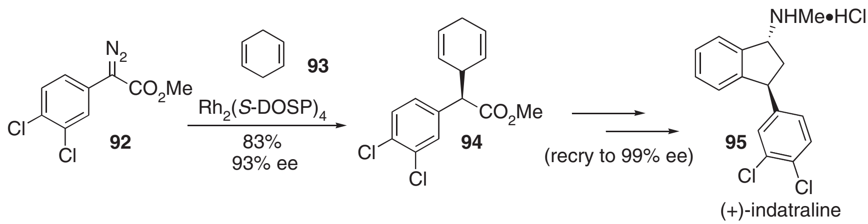
Scheme 18 Differential reactivity of carbenoid classes with cycloheptatriene

Fig. 7 Examples of carbenoid insertion into cyclohexadiene

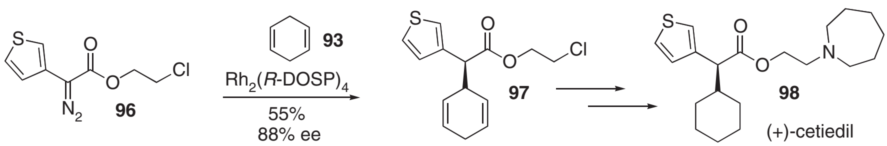


Davies [67, 86], Doyle [87], and Hilt [88, 89] have developed systems for selective C–H insertion into 1,4-cyclohexadiene derivatives (Fig. 7). A number of aryldiazoacetates were shown to be effective carbenoid precursors to **89** when a recyclable polystyrene-supported prolinate Rh_2(*S*-DOSP)$_4$ was used as the catalyst [86]. With a diazophosphonate, Davies found phthalimide Rh_2(*S*-PTAD)$_4$ (**29b**) to be the best catalyst, furnishing the desired products **90** in 83% yield and 92% ee [67]. Doyle utilized a unique vinyldiazolactone as the carbenoid precursor, and obtained varying ratios of insertion to cyclopropanation depending on catalyst, with the best result (9:1) obtained with carboxamidates Rh_2(4*S*-MEAZ)$_4$ (**28e**) or Rh_2(menthAZ)$_4$ (**28d**, two different diastereomers) [87]. Furthermore, **28d** provided the insertion product **91** in the highest ee of about 80%.

Davies and coworkers exploited the utility of the cyclohexadiene system in short total syntheses of (+)-indatraline (**95**, Scheme 19) [90] and (+)-cetiedil (**98**, Scheme 20) [91]. In each case, an aryldiazoacetate (**92** or **96**) was used as the carbenoid precursor, Rh_2(DOSP)$_4$ as the catalyst, and unsubstituted 1,4-cyclohexadiene **93** as the substrate. The ultimate fate of the diene differed in each case; in the indatraline synthesis it was ultimately oxidized to a benzene ring with DDQ, and in the preparation of cetiedil it was reduced to a cyclohexane with H_2 and Pd/C.

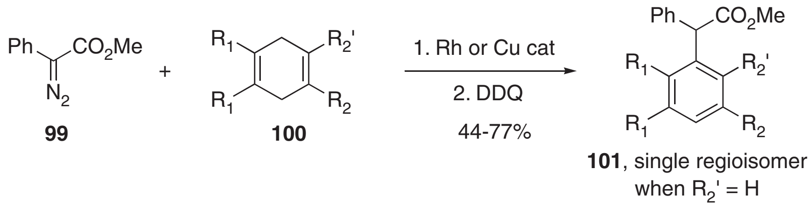


Scheme 19 Synthesis of (+)-indatraline



Scheme 20 Synthesis of (+)-cetiedil

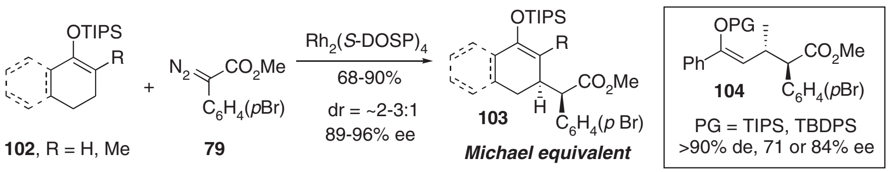
Hilt took a slightly different approach toward the functionalization of cyclohexadienes [88, 89]. He reasoned that subsequent DDQ oxidation of the insertion products would provide facile access to substituted benzene derivatives **101** that would be difficult to obtain by traditional means (Scheme 21). These sequential reactions typically took place in moderate to good yields with $Rh_2(OAc)_4$ (**25a**) or Cu(hfacac) (hfacac = hexafluoroacetylacetonate) as the catalyst, thus generating racemic products. Notably, when differentially substituted 1,4-cyclohexadienes (**100**, R_2' = H) were used as the substrates, the insertion event occurred exclusively at the less sterically hindered site.



Scheme 21 One pot synthesis of highly substituted benzenes from 1,4-cyclohexadienes

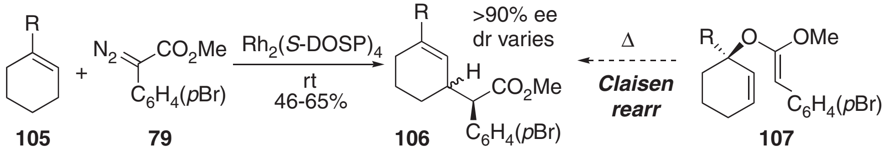
3.2.3.2 Allylic C–H Insertion as Equivalents to Traditional Organic Reactions

One unique aspect of the carbenoid C–H insertion chemistry is its ability to form products that are typically obtained from more classical organic reactions. One example is the allylic insertion into silyl enol ethers **102** to form products equivalent to those from an asymmetric Michael reaction (Scheme 22) [92]. Cyclic substrates provided the desired "Michael" adducts **103** in the highest ee values for the major isomer (89–96%), but with only moderate de, favoring the diastereomer shown about 1.5:1 to 3:1. The diastereoselectivity was markedly improved to >90% de with acyclic substrate **104** with sterically differentiated substituents, but the enantioselectivity dropped to below 85% ee. Notably, this transformation was limited to aryldiazoacetates. When EDA was utilized as the carbene precursor, cyclopropanation of the olefin was the major reaction pathway, and only small amounts of the desired C–H insertion were observed.



Scheme 22 Allylic C–H insertion as an equivalent to the asymmetric Michael reaction

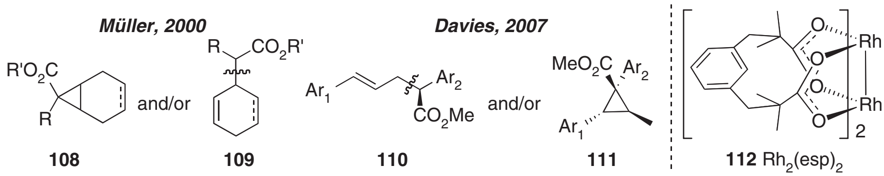
Another classical organic reaction that found a carbenoid equivalent was the Claisen rearrangement (Scheme 23), eliminating the need to preform more elaborate substrate **107**, including defined olefin geometry and quaternary stereochemistry [93]. In order to suppress cyclopropanation of the olefin, 1-substituted cyclohexenes **105** were utilized as substrates. In most cases, a single regioisomer of allylic C–H insertion (**106**) was observed at the site distal to the substituent. The enantioselectivities were above 90% ee in all but one case, but the diastereoselectivity varied dramatically. Interestingly, the favored diastereomer was found to change based upon the substitution on the olefin. Small substituents led preferentially to the *erythro* isomer, while increasing size produced greater amounts of the *threo* product, until it became the major diastereomer when R = *t*Bu or Cl.



Scheme 23 Allylic C–H insertion as an equivalent to the Claisen rearrangement

3.2.3.3 Balance Between Allylic C–H Insertion and Cyclopropanation

As noted throughout this section, substrates intended for allylic C–H activation are also capable of undergoing facile intermolecular cyclopropanation reactions. Both Davies [94] and Müller [45] have carried out systematic studies to determine the controlling factors that govern the selectivity between these two competing pathways (Scheme 24).



Scheme 24 Substrates that can undergo cyclopropanation and/or C–H insertion

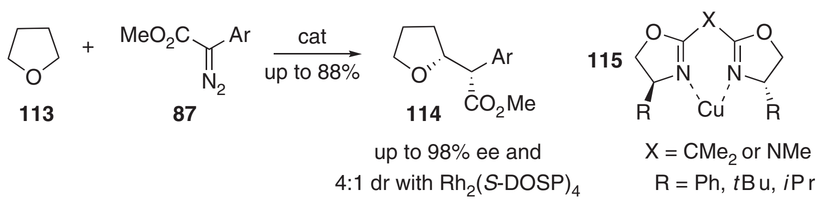
Müller chose to examine cyclohexene and 1,4-cyclohexadiene (ten equivalents relative to diazo compound) as model systems, and screened a variety of carbenoid precursors and catalysts (Scheme 24, left). All reactions were conducted in DCM at 25 °C. The results with 1,4-cyclohexadiene were quite clear-cut. With acceptor-substituted carbenes, selectivity was >95:5 in favor of cyclopropanation **108** for Cu^0 or $Rh_2(OAc)_4$ catalysts. For acceptor/acceptor carbenoid precursors, CuCl still favored cyclopropanation >95:5, but with $Rh_2(OAc)_4$ insertion **109** now became the major product in a 66:34 ratio. Finally, with either alkyl/acceptor or donor/acceptor (methyl phenyldiazoacetate) carbenoids, the allylic C–H insertion was overwhelmingly favored (>98:2) with a number of rhodium catalysts. The same general trends were observed for cyclohexene, but selectivity was generally not as high, especially for the acceptor/acceptor carbene precursors. In these cases, even with rhodium catalysts, cyclopropanation tended to dominate, although not to the same extent.

Davies studied acyclic systems strictly with aryldiazoacetates (Scheme 24, right). Knowing from prior studies that *trans* olefins are generally less prone to cyclopropanation, experiments were initiated with *trans* anethole ($Ar_1 = p\mathrm{OMeC_6H_4}$) as the substrate. When Rh_2(*S*-DOSP)$_4$ **26** was used as the catalyst, allylic C–H insertion **110** was always the favored product, but the ratio varied with the electronics of the aryl substituent on the carbenoid. Electron donating substituents increased the amount of insertion product formed, while electron withdrawing groups led to additional cyclopropanation **111**. In contrast to the effect of electronics on the carbenoid, increased electron donation on the *substrate* actually favored cyclopropanation. Additionally, it was discovered that the catalyst had a remarkable effect on the product ratio. When sterically demanding $Rh_2(TPA)_4$ (**25c**) was used in place of Rh_2(*S*-DOSP)$_4$, allylic insertion became the exclusive reaction pathway. Alternatively, Du Bois' catalyst, $Rh_2(esp)_2$ (**112**), [95] favored cyclopropanation to a much greater extent, and it became the sole product in appropriate systems.

3.2.4 C–H Insertion α to Oxygen

3.2.4.1 Insertion into Tetrahydrofuran

As shown in Fig. 6, THF is a very active substrate for carbenoid C–H insertion adjacent to the oxygen atom. A number of catalysts have been used for this transformation, with varying results (Scheme 25). Davies and coworkers have used Rh_2(*S*-DOSP)$_4$ (**26**) as the catalyst, obtaining **114** in yields ranging from 48 to 74%, diastereoselectivities from 1.6:1 to 4.0:1, and up to 98% ee [79, 81]. It was noted that the highest enantioselectivity was obtained not in neat THF, but when the reactions were conducted in hexanes at −50 °C with two equivalents of THF.

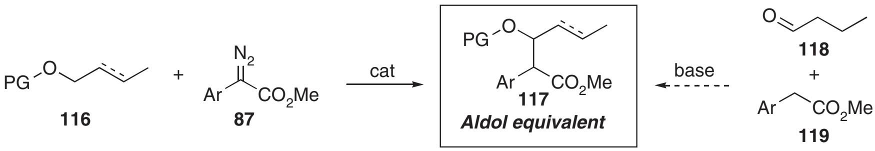


Scheme 25 Carbenoid insertion into THF

Fraile, Mayoral, and coworkers utilized copper BOX catalysts (**115**), both homogeneous and immobilized on a laponite support, for their C–H insertion reactions [96]. They obtained similar yields and diastereoselectivities to the Rh_2(*S*-DOSP)$_4$ catalyst (up to about 3:1), but the highest enantioselectivity was 88% ee. Woo [10] and Che [83] chose to use achiral iron porphyrin catalysts. Woo obtained the products in 62–82% yield in about 3.5:1 dr, and Che in 88% yield, but only 2:1 dr. By way of comparison, Pérez obtained excellent yields for this insertion reaction with EDA (95–99%) utilizing copper homoscorpionate catalysts **67a** and **67b**, [36, 39] but the transformations were not asymmetric.

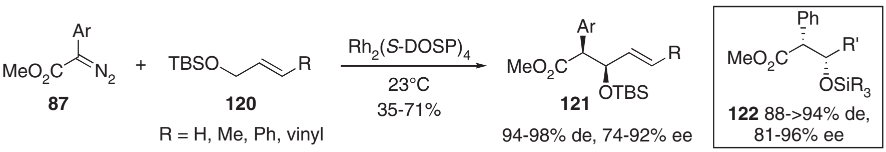
3.2.4.2 Insertion α to Oxygen as a Surrogate to the Aldol Reaction

Although the reactions with THF demonstrated that C–H insertion α to oxygen could occur with good enantioselectivity, the diastereoselectivity was still low. Thus other suitable substrates were sought that would yield products with both high enantioselectivity and high diastereoselectivity. Additionally, it was noted that such insertion reactions between substrates **116** and aryldiazoacetates **87** would provide structures that are commonly accessed through aldol chemistry (Scheme 26) [31, 97–99]. Notably, this chemistry also *extends* the scope of traditional aldol chemistry. Structures **117** containing the olefin could not be easily accessed from α, β unsaturated aldehydes, because Michael addition would be a competing reaction.



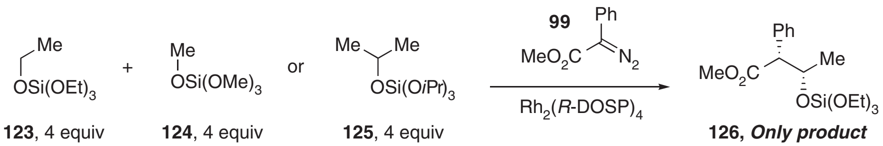
Scheme 26 C–H insertion α to oxygen as an aldol equivalent

Ultimately, it was determined that protected allyl alcohols, tetralkoxy silanes, and silyl ethers were the best substrates for these transformations. Alkyl or allyl silyl ethers (**120**) provided products such as **121** in >85% de and good 74–92% ee with Rh_2(*S*-DOSP)$_4$ as the catalyst (Scheme 27) [98]. Extension of the reaction to alkoxysilanes, generated **122** in 88 to >94% de and 81–96% ee. Interestingly, this catalyst did not seem to be compatible with benzyl silyl ethers, and the products were formed with low selectivity (<40% ee). It was found that the use of either a chiral auxiliary or phthalimide Rh_2(PTTL)$_4$ resulted in improved results [31].



Scheme 27 C–H insertion into allyl silyl ethers as an equivalent to the aldol reaction

The use of silyl ethers also provided a good glimpse into the steric effects of the C–H insertion [98]. Relative rates were obtained for insertion α to the oxygen atom in silyl protected *n*-butanol. It was found that the reaction rate increased dramatically as the size of the silyl protecting group decreased, with a 100-fold rate difference between TBDPS and TMS. Complementary steric and electronic effects were observed with the tetralkoxy silane substrates [97, 98]. In competition experiments, it was found that the carbenoid derived from diazo ester **99** reacted solely with tetraethoxy silane **123** to form product **126**, and not the corresponding tetramethoxy or tetraisopropoxy derivatives **124** or **125** (Scheme 28). Thus, the secondary C–H bonds appear to possess the right balance between steric and electronic requirements for the insertion.

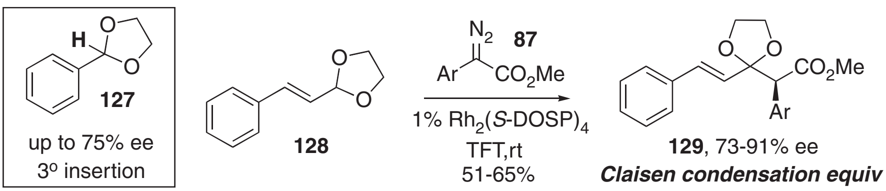


Scheme 28 Competition study demonstrates preference for secondary C–H insertion

Protected allyl alcohols provided further opportunities to study the electronic requirements of the C–H insertion [98, 99]. It was found that if the oxygen atom is protected with a silyl group, it serves as an activating substituent, and insertion occurs adjacent to the oxygen. If, however, the alcohol is protected as an acetoxy group, it effectively deactivates the proximal C–H bonds, causing other reactions to occur. Depending on the substrate, these could include cyclopropanation of the olefin, or C–H insertion at a site distal to the oxygen atom.

3.2.4.3 Insertion α to Oxygen as a Surrogate to the Claisen Condensation

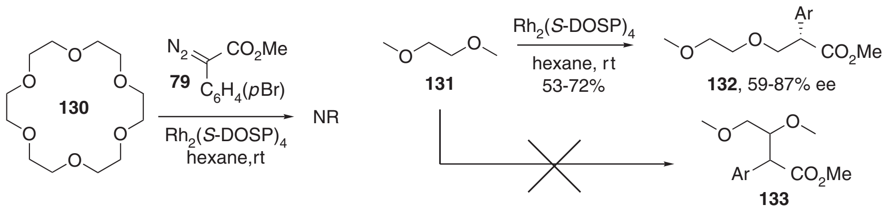
Not only could C–H insertion α to oxygen be applied to the synthesis of *syn* aldol products, but insertion into acetals followed by deprotection would also serve as a Claisen condensation equivalent (Scheme 29) [100]. The insertion into a substrate such as **127** would present an additional challenge for regioselectivity. Although the desired tertiary site is doubly activated by the two oxygen atoms, it is also more sterically hindered. It was found, however, that insertion into this position was generally favored. Furthermore, the positioning of an olefin or an alkyne adjacent to the acetal as in **128** increased the selectivity by decreasing the steric requirement at that site. The products (**129**) were generally formed in moderate yield and good ee.



Scheme 29 Carbenoid insertion into acetals as an equivalent to the Claisen condensation

3.2.4.4 Influence of a β Oxygen Substituent

As demonstrated in the above sections, an oxygen atom has a favorable activating effect on its α C–H bonds. Davies and coworkers found, however, quite the opposite to be true for the β position [101]. In an attempt to access rapidly chiral crown ethers through asymmetric C–H insertion, they were surprised to discover that 18-crown-6 **130** failed to react with diazo ester **79** in the presence of Rh_2(*S*-DOSP)$_4$ to form any insertion product, even adjacent to the activating oxygen atom (Scheme 30, left). Similarly, 1,2-dimethoxyethane **131** led exclusively to products of insertion at the methyl group (**132**), rather than the typically favored methylene site to give **133** (Scheme 30, right). These results combined are indicative of the β oxygen destabilizing positive charge build up during the transition state through inductive electron withdrawal, rendering alternative reaction pathways more favorable.

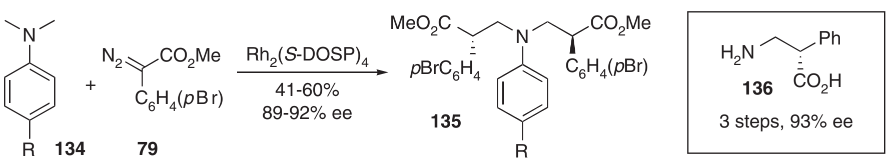


Scheme 30 Influence of a β oxygen substituent on carbenoid C–H insertion

3.2.5 C–H Insertion α to Nitrogen

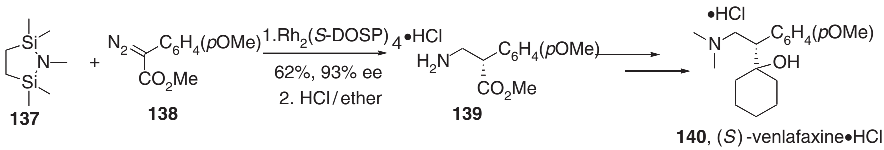
3.2.5.1 Acyclic Substrates

Nitrogen atoms are also highly electronically activating for adjacent C–H bonds, making them reactive toward carbenoid insertion. Interestingly, the degree of activation is so strong that it led to one of the rare synthetically useful examples of insertion into primary C–H bonds in the synthesis of C_2-symmetric anilines (Scheme 31) [102]. In this transformation, substituted *N*,*N*-dimethylanilines **134** were treated with two equivalents of aryldiazoacetate **79** and Rh_2(*S*-DOSP)$_4$, providing products **135** in moderate yields and good enantioselectivities (85–92% ee). It was also found that the reaction of suitably protected *N*-methyl-*N*-benzyl amines with aryl diazoacetates provided the immediate precursors to β^2 amino acids such as **136** in moderate yields and good enantioselectivities, also through primary C–H insertion [103].



Scheme 31 Synthesis of C_2-symmetric anilines and β-amino acids

This unique reactivity of *N*-methyl C–H bonds was exploited in a short total synthesis of the antidepressant venlafaxine (**140**, Scheme 32) [104]. In the key event, substrate **137** was treated with aryldiazoacetate **138** and Rh_2(*S*-DOSP)$_4$, providing product **139** in 62% yield and 93% ee. Dimethylation of the amine followed by addition of a bis-Grignard to the ester afforded the HCl salt of (*S*)-venlafaxine.

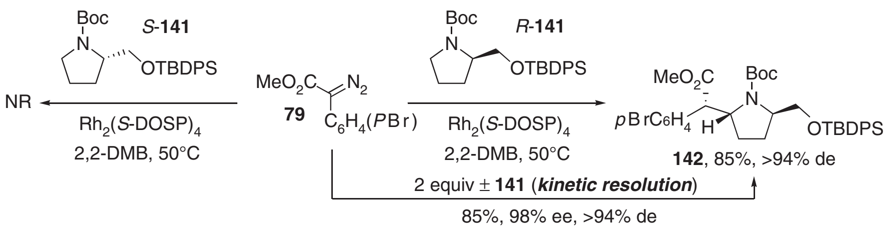


Scheme 32 Synthesis of (*S*)-venlafaxine

3.2.5.2 Cyclic Substrates

Carbenoid C–H insertion α to nitrogen is certainly not limited to *N*-methyl amines. Cyclic amines such as *N*-Boc-pyrrolidine and *N*-Boc-piperidine are also suitable substrates for this transformation, giving rise to products that would traditionally be formed from a Mannich reaction [86, 105–107]. The regioselectivity is excellent in these reactions, giving exclusive insertion adjacent to the nitrogen atom. The diastereoselectivity is generally very high for pyrrolidines, favoring the *erythro* products, but can be much lower for their six-membered counterparts. Interestingly, the selectivity increases again for seven- and eight-membered rings.

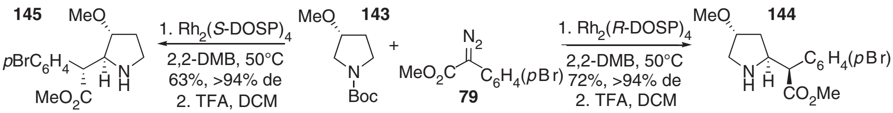
When chiral substituted pyrrolidines are utilized as substrates, opportunities exist for double stereodifferentiation, kinetic resolution, and catalyst differentiation. A striking example of double stereodifferentiation was provided by substrate **141**, in which the *R* enantiomer underwent smooth C–H insertion in 85% yield and >94% de to afford product **142**, but no observable reaction occurred with the *S* enantiomer (Scheme 33).



Scheme 33 Kinetic resolution through carbenoid C–H insertion

The above result suggested that kinetic resolutions would also be possible with appropriate substrates. When an excess of racemic 2-substituted pyrrolidines were treated with a rhodium catalyst and an aryldiazoacetate, only a single enantiomer of each starting material reacted efficiently with the carbenoid to afford the product in both good ee and good de, providing an example of kinetic resolution (Scheme 33). Similar reactivity was observed for 3-substituted pyrrolidines.

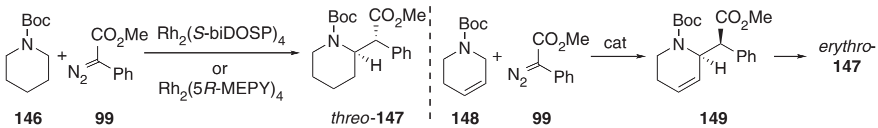
An even more interesting transformation was observed with substrate **143**, which formed two different products with the two enantiomers of the same catalyst (Scheme 34). In the "matched" case, the expected insertion α to the nitrogen atom was observed to provide **144**. With the "mismatched" catalyst, however, insertion occurred at the more sterically congested center between the nitrogen and the oxygen atoms to yield **145**, clearly demonstrating the role the chiral catalyst can play on the regioselectivity of carbenoid C–H insertions.



Scheme 34 Differential reactivity with enantiomeric catalysts and a chiral substrate

3.2.5.3 Synthesis of Methylphenidate Analogs

Despite the fact that piperidines seem to yield less selective reactions than pyrrolidines, they have been successfully used as substrates for the synthesis of *threo*-methylphenidate (Ritalin) and analogs (Scheme 35) [108–110]. For the synthesis of Ritalin itself, *N*-Boc-piperidine **146** was treated with methyl phenyldiazoacetate **99** and a chiral catalyst. Davies and coworkers found that bridged prolinate Rh_2(*S*-biDOSP)$_4$ (**27**) provided the desired product in 86% ee, although in moderate diastereoselectivity, providing *threo*-**147** in 52% yield [109]. Winkler obtained the same product in a maximum of 69% ee (recrystallized to 95%), but with 94% de using carboxamidate Rh_2(5*R*-MEPY)$_4$ (5*R*-**28b**) in 44% yield, 26% after recrystallization [108].



Scheme 35 Synthesis of methylphenidate (Ritalin)

Davies also found that *erythro*-**147** could be preferentially obtained if tetrahydropyridine **148** was used as the substrate [109]. The Davies group then synthesized a number of analogs of methylphenidate, both *threo* and *erythro*, by varying the aryl component of the diazo compound. Their binding affinities for both serotonin and dopamine transporters were evaluated, and some were found to be up to 15 times more potent than Ritalin itself [110].

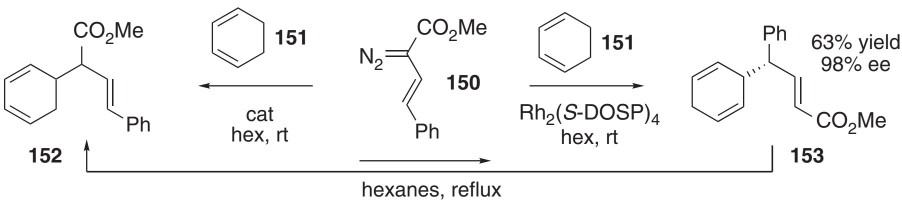
3.3 *Vinyldiazoacetates*

3.3.1 Examples of C–H Insertion

The first examples of C–H insertion with vinylcarbenoids were reported by Davies and coworkers in 1997 and 1998 [79, 80]. In these studies, it was found that vinylcarbenoids reacted with cyclohexane in higher yield and with much higher enantioselectivity than carbenoids derived from EDA or acceptor/acceptor diazo compounds. However, in the absence of suitable traps, they also reacted with themselves to form polycyclic products.

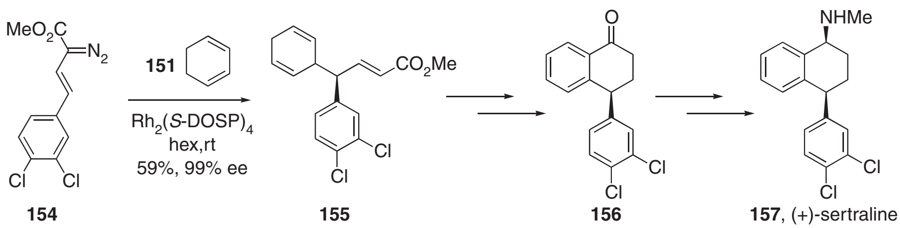
3.3.2 Discovery of the Combined C–H Activation/Cope Rearrangement

A breakthrough in the use of vinyldiazoacetates as carbenoid precursors came about when examining 1,3-cyclohexadiene **151** as the substrate [111]. When vinyldiazoacetate **150** was decomposed in the presence of **151**, the expected direct C–H insertion product **152** did not result. Instead, rearranged 1,4-cyclohexadiene **153** was isolated in 63% yield and 98% ee (Scheme 36).



Scheme 36 Discovery of the combined C–H insertion/Cope rearrangement

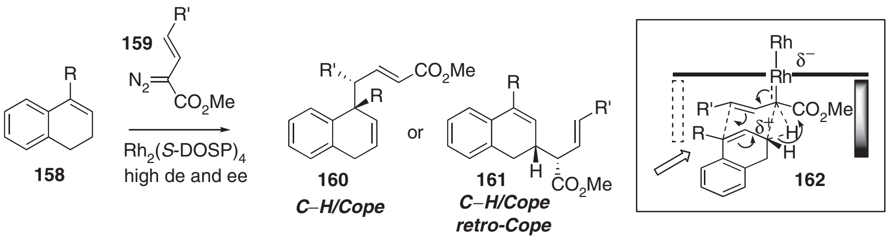
It seemed reasonable to conclude that **153** was formed by C–H insertion followed by a Cope rearrangement, yet thermolysis of **153** in refluxing hexane showed that the equilibrium actually lay in the opposite direction: **152** was cleanly formed. Thus the formation of **153** was more likely due to a *concerted* reaction, in which the initial C–H activation is interrupted by a rearrangement that resembles a Cope rearrangement. This transformation was ideally suited to a short formal synthesis of (+)-sertraline (**157**, Scheme 37).



Scheme 37 Formal synthesis of (+)-sertraline

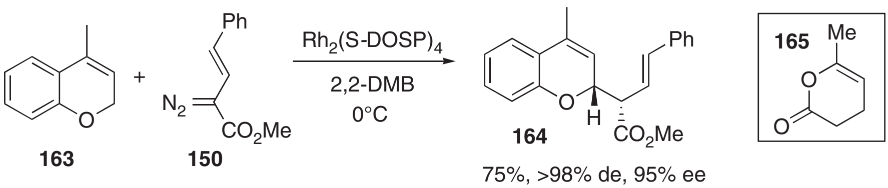
3.3.3 Scope of the Combined C–H Activation/Cope Rearrangement

After the discovery of this unique transformation, the scope was explored. When certain 1,2-dihydronaphthalene substrates **158** were utilized, it was found that the direct C–H insertion products **161** were formed in extraordinarily high diastereoselectivity and enantioselectivity (>98 de and >95 ee, Scheme 38), much higher than was typically observed for insertion reactions with aryldiazoacetates (see Sect. 3.2). Thus, it was reasoned that these compounds were actually being produced via a combined C–H activation/Cope rearrangement, through a transition state such as **162**, followed by a retro-Cope. Furthermore, appropriate substrate modification allowed isolation of the C–H activation/Cope adduct **160**, providing products in >98% de and up to >99% ee [112, 113]. In certain cases, a double C–H insertion into dihydronaphthalene substrates was also observed [112].



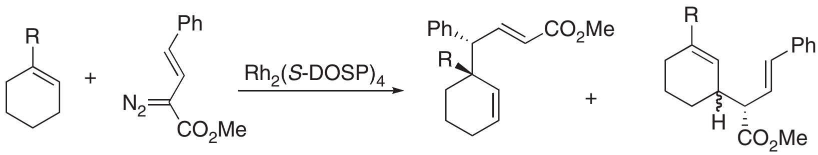
Scheme 38 Combined C–H activation/Cope applied to dihydronaphthalene substrates

Although dihydronaphthalenes seem to be the best substrates for the combined C–H activation/Cope rearrangement, the transformation is not limited to that family. When an oxygen atom was introduced into the nonaromatic ring, forming 2*H*-chromene **163**, it was still a viable substrate, yielding 75% of the formal C–H insertion product **164** in >98% de and 95% ee (Scheme 39) [113]. Another interesting oxygenated system was dihydropyranone **165** [114]. It reacted with a number of different carbenoids to form the C–H activation/Cope products in good yield, >98% de, and 99% ee.



Scheme 39 Oxygenated substrates for the combined C–H activation/Cope rearrangement

Furthermore, 1-substituted cyclohexenes **105** were also determined to be suitable substrates, providing the C–H/Cope products **166** in 31–68% yield, >98% de and 95–99% ee (Scheme 40) [114]. A major competing side reaction seen with this system, however, was the direct C–H insertion to provide **167**. When the transformation was extended to 1-substituted cyclopentenes, the yields dropped off even further due to undesired competing reactions, including both the direct C–H insertion as well as cyclopropanation of the olefin. The product ratios seem to be sensitive to sterics and electronics of both the olefin and the reacting C–H bonds, and further optimization studies will be needed.

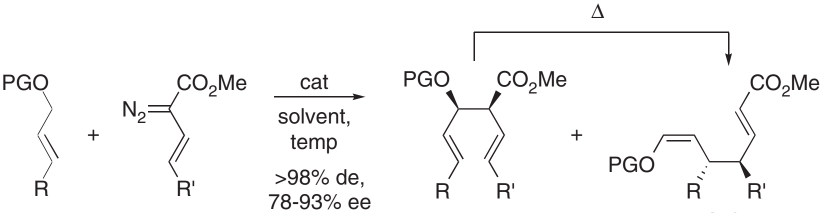


105 **150** **166**, 31-68% >98% de, 95-99% ee **167**

Scheme 40 Combined C–H activation/Cope applied to cyclohexenes

3.3.4 C–H Activation/Siloxy-Cope Rearrangement

The C–H activation/siloxy-Cope rearrangement is another variation on the oxygenated substrates that can provide both the direct insertion and the rearranged products in >98% de and good to excellent ee (Scheme 41) [115]. A number of optimization studies were conducted for this transformation, and optimal conditions were found to be $Rh_2(S\text{-DOSP})_4$ as catalyst and 2,2-dimethylbutane (DMB) as solvent. The ratio between the two products **169** and **170** varied with the substituents on both the diazo compound **159** and the silyl allyl ether **168**. It was also found that the siloxy-Cope reaction would reach an equilibrium mixture if R and/or R′ were aryl groups. Replacing them with alkyl groups removed conjugation from **169**, however, driving the reaction to completion.



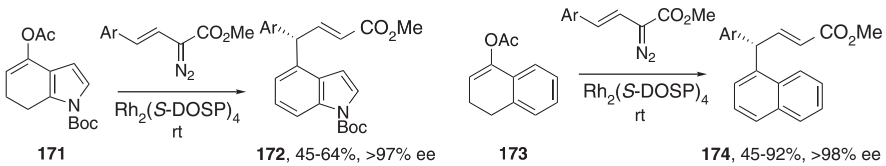
168 **159** **169** **170**

Scheme 41 The C–H activation/siloxy-Cope rearrangement

3.3.5 C–H Activation/Cope Rearrangement Followed by Elimination

Tandem reactions are always of interest to the organic chemistry community, since molecular complexity can be developed in minimal synthetic steps. It was envisioned, then, that the positioning of a leaving group at a suitable location on the substrates for the C–H activation/Cope rearrangement could lead to subsequent aromatization in a single step, generating new substituted aromatics that would be difficult to access by traditional means.

One way this goal was realized was in the synthesis of a variety of 4-substituted indoles from a single 4-acetoxy-6,7-dihydroindole precursor (**171**, Scheme 42) [116]. In this transformation, the C–H activation/Cope rearrangement took place as usual, but the intermediate quickly underwent loss of the acetoxy group with concomitant aromatization to give the desired indole **172** in 45–65% yield. This methodology was suitable for a variety of arylvinyldiazoacetates, including electron poor and electron rich, and the enantioselectivities of the products were all above 97%.



Scheme 42 Synthesis of 4-substituted indoles and 1-substituted naphthalenes through C–H/Cope followed by elimination

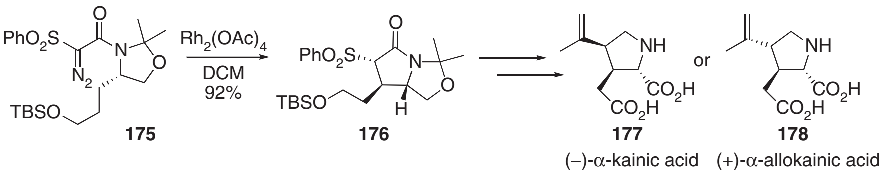
A second example of this tandem reaction sequence was in the synthesis of 4-aryl-4-(1-naphthyl)-2-butenoates **174** (Scheme 42, right) [113, 117]. As in the indole synthesis, an acetoxy group was lost following the C–H activation/Cope rearrangement, providing the aromatized products. Thirteen examples of this transformation were provided, with yields ranging from 45 to 92%, and enantioselectivities all >98%.

4 Carbenoid C–H Insertion in the Synthesis of Pharmaceuticals and Natural Products

As has been demonstrated throughout the previous sections of this chapter, transition metal carbenoids, particularly those of dirhodium carboxylates, are quite capable of selective C–H insertions on complex substrates. As such, these transformations have been applied as key C–C bond-forming steps in several syntheses of natural products and pharmaceuticals. In addition to their use in the total syntheses discussed in the following sections, they have also recently been applied to the construction of key building blocks of natural products as well as partial syntheses [118–123]. The application of carbenoid C–H insertion in this milieu is a testament to its growing value to the synthetic community, and more activity in this area is expected in the future.

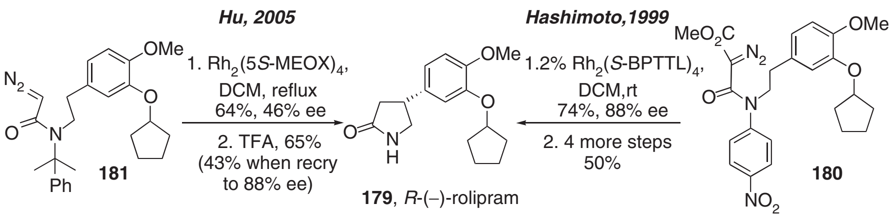
4.1 Intramolecular Examples

One demonstration of nontraditional carbenoid precursors being utilized in the context of total synthesis was highlighted in the syntheses of (−)-α-kainic acid **177** and (+)-α-allokainic acid **178** published by Jung and coworkers in 2007 (Scheme 43) [124]. In the preparation of these molecules, advanced intermediate **175** was constructed, containing a phenylsulfonyl group as an acceptor moiety. $Rh_2(OAc)_4$-mediated cyclization proceeded in 92% yield to form bicyclic structure **176** as a single diastereomer. Elaboration to the final products, including dephenylsulfonylation, could then be accomplished.



Scheme 43 Synthesis of (−)-α-kainic acid and (+)-α-allokainic acid

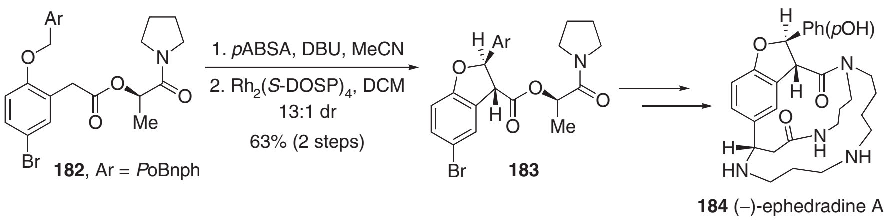
Examples of more "basic," but enantioselective intramolecular carbenoid C–H insertion reactions were displayed in two very similar total syntheses of the phosphodiesterase type IV inhibitor *R*-(−)-rolipram (**179**, Scheme 44) [125, 126]. In 1999, Hashimoto and coworkers utilized acceptor/acceptor diazo compound **180**, with the nitrogen atom protected with a *p*-nitrophenyl moiety, as the carbenoid precursor. After screening a number of phthalimide-based dirhodium catalysts, $Rh_2(S\text{-BPTTL})_4$ (**30**) was found to give the optimal results, providing the cyclized product in 74% yield and 88% ee.



Scheme 44 Syntheses of *R*- (−)-rolipram

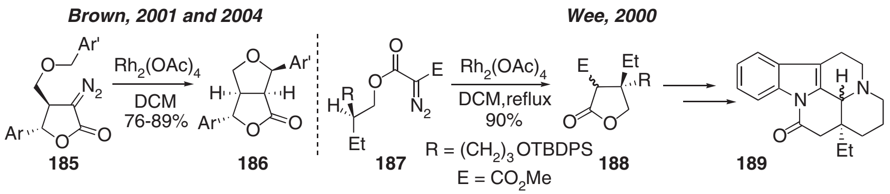
Hu and coworkers utilized a very similar cyclization precursor **181** in 2005, with the main differences being the lack of a second acceptor group on the diazo and the protecting group on the nitrogen atom. They also chose to screen not the phthalimide-based catalysts, but the prolinates and carboxamidates, and Rh_2(5*S*-MEOX)$_4$ (**28c**) provided the best enantioselectivity, but still only 46% ee. After two recrystallizations of the final product, the enantiomeric purity was increased to 88% ee, but Hashimoto's protocol was clearly superior.

In certain cases, a chiral catalyst alone is not sufficient to impart the necessary asymmetric induction. An impressive example of stereoselective C–H insertion through the use of a chiral auxiliary combined with a chiral catalyst was provided by Fukuyama and coworkers in the total synthesis of (−)-ephedradine A (**184**, Scheme 45) [33, 34]. Substrate **182** was treated with diazo transfer reagent *p*ABSA and DBU to afford the requisite diazo ester. When treated with Rh_2(*S*-DOSP)$_4$, a 13:1 mixture of diastereomers of the C–H insertion product (**183**) was formed, in 63% yield from **182**. Removal of the chiral auxiliary was easily accomplished, and recrystallization of the resulting acid provided enantiomerically pure product in 90% yield, which was ultimately taken on to **184**. A similar cyclization procedure was used by Rodríguez-García and coworkers for the synthesis of dihydrodehydrodiconiferyl alcohol, but without the aid of a chiral auxiliary, resulting in much lower selectivities [127].



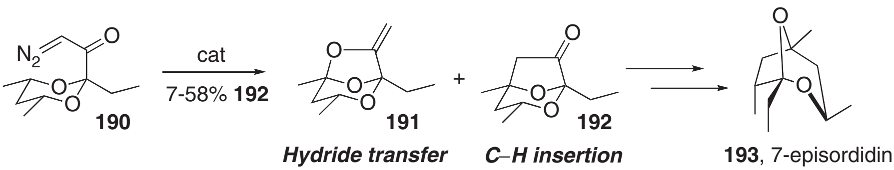
Scheme 45 Synthesis of (−)-ephedradine A

In systems that already contain stereogenic centers near the site of C–H insertion, that is often enough to control the stereoselectivity of the key carbenoid transformation without the use of a chiral catalyst. That was certainly the case in the synthesis of a variety of *endo*, *exo*-furofuranone lignans **186** by Brown and coworkers (Scheme 46, left) [128, 129]. Following the synthesis of substrates such as **185** (either racemic or enantioenriched), $Rh_2(OAc)_4$-mediated cyclization furnished a single diastereomer of the bicyclic products **186** in moderate to good yields. Wee also demonstrated the stereospecificity of the C–H insertion event in the total synthesis of (−)-eburnamonine and (+)-epi-eburnamonine (**189**). As shown below (Scheme 46, right), the cyclization occurred in 90% yield with full retention of stereochemistry [130].



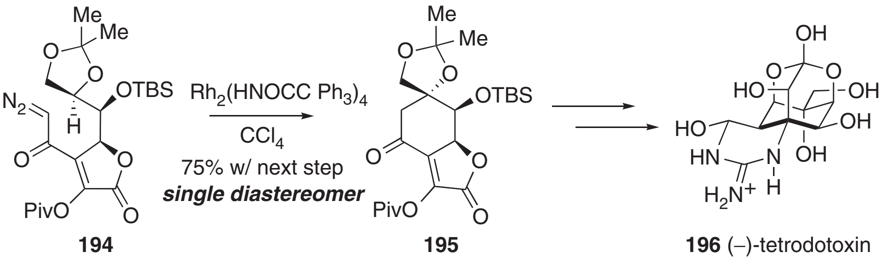
Scheme 46 Syntheses of furofuranone lignan lactones and eburnamonine

Other rigid systems also seem ideally set up for intramolecular C–H insertion, but competing reactions can sometimes interfere. Wardrop and coworkers found this to be the case during the synthesis of (±)-7-episordidin, **193** (Scheme 47) [131, 132]. The key diazo intermediate en route to the natural product was **190**. Although the favored chair conformation should leave the carbenoid nicely poised for insertion into one of the axial C–H bonds, the desired cyclic ketone **192** was obtained in only low to moderate yields, depending on the catalyst used. A major side product **191** was also observed, resulting from oxygen atom-assisted hydride transfer to the electrophilic carbenoid center. Less electron rich rigid systems do not seem to suffer from this unwanted reaction. One family of natural products based on the isotwistane carbon skeleton, synthesized from carvone by Srikrishna and coworkers, exemplify this fact [133–138]. Another interesting feature of some of these synthetic sequences is that, in certain cases, the key carbenoid insertion took place α to an electron withdrawing carbonyl moiety, a transformation that is usually disfavored.



Scheme 47 Synthesis of 7-episordidin and competitive hydride transfer

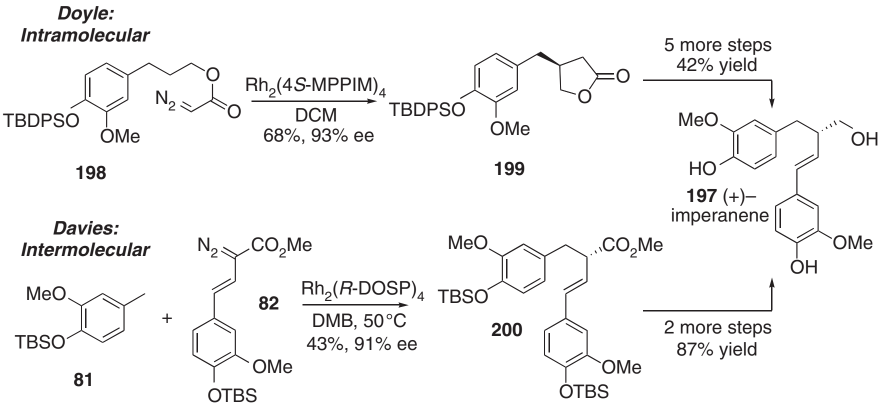
Arguably the most complex natural product in which carbenoid C–H insertion has recently been applied as a key step is (−)-tetrodotoxin, **196**, synthesized by Du Bois and coworkers in 2003 (Scheme 48) [139]. In this example of carbenoid insertion α to the oxygen atom of **194**, $Rh_2(HNOCCPh_3)_4$ (**25c**) was found to be the best catalyst for this diastereospecific transformation. Notably, this total synthesis also employs a rhodium-mediated nitrene insertion at a later point in the route.



Scheme 48 Synthesis of (–)-tetrodotoxin

4.2 (+)-Imperanene: One Small Molecule, Two Complementary Approaches

Two syntheses of the bioactive small molecule (+)-imperanene (**197**), isolated from *Imperata cylindrica*, demonstrate that intra- and intermolecular carbenoid C–H insertion can be used as two different means to the same end. The Doyle group reported an intramolecular approach toward this natural product, with diazoester **198** as the cyclization precursor (Scheme 49, top) [140]. In the key event, Rh_2(4*S*-MPPIM)$_4$-catalyzed carbenoid insertion led to lactone **199** in 68% yield and 93% ee. Other rhodium catalysts were found to give inferior yields and enantioselectivities. Elaboration of **199** to (+)-imperanene provided the natural product in 12 steps and approximately 16% overall yield.



Scheme 49 Complementary routes to (+)-imperanene

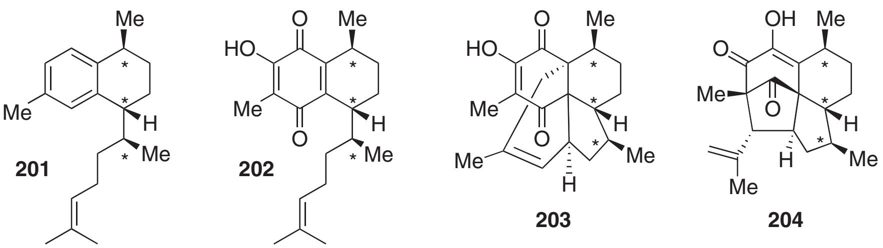
The Davies group took an alternative approach with an intermolecular route to the same small molecule (Scheme 49, bottom) [84]. In this case, the carbenoid C–H insertion event took place on trisubstituted benzene **81**. With Rh_2(*R*-DOSP)$_4$ as the catalyst, the transformation occurred in 91% ee, but only 43% yield, likely due to the fact that carbenoid insertion is typically disfavored at primary positions. Nevertheless, following the rhodium-catalyzed reaction, all that remained to unmask the natural product was LAH reduction of the ester and TBAF deprotection of the TBS groups. Thus the Davies synthesis proved to be much shorter, but the carbenoid step in the Doyle route gave a higher yield.

4.3 Intermolecular Examples

As was demonstrated in Sect. 3.2, the major drawback of intermolecular carbenoid C–H insertion is often its low diastereoselectivity. The combined C–H insertion/Cope rearrangement, however, generally proceeds with excellent diastereocontrol, rendering this transformation much more useful in the context of complex molecule synthesis.

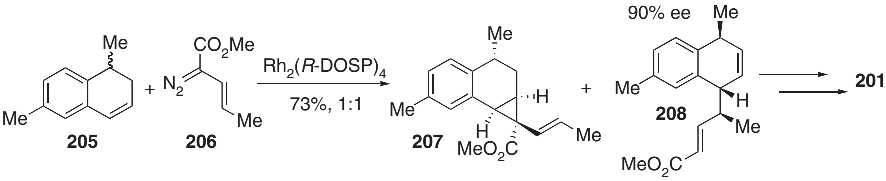
In 2004, it was discovered that dihydronaphthalenes are excellent substrates for the combined C–H insertion/Cope rearrangement (see Sect. 3.3.3). Because of the unique bond-forming features and high diastereo- and enantioselectivity of this reaction, the Davies group was eager to apply it to the total synthesis of natural products. A family of marine diterpenes isolated from *Pseudopterogorgia elisabethae* possessed a core that would easily be derived from carrying out this key transformation on suitably substituted dihydronaphthalene precursors (Fig. 8). Furthermore, it was envisioned that the three stereocenters marked with asterisks, locations for which stereocontrol has been difficult in prior syntheses [141], could all be set in this single operation.

The first natural product in this family to be synthesized with this methodology was (+)-erogorgiaene (**201**) [142], and provided an excellent proof of concept for the more complex structures to follow (Scheme 50). Importantly, this synthesis began with racemic dihydronaphthalene precursor **205**, and included a powerful enantiodivergent carbenoid transformation. In this key step, one enantiomer of the substrate was poised to react with the rhodium carbenoid to form the desired C–H



(+)-Erogorgiaene ***(+)-Elisabethadione*** ***(–)-Colombiasin A*** ***(–)-Elisapterosin B***

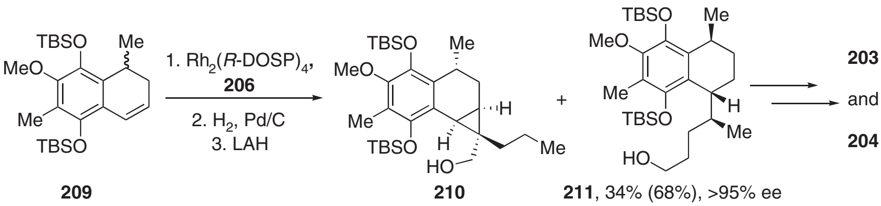
Fig. 8 Natural products derived from *Pseudopterogorgia elisabethae*



Scheme 50 Key enantiodivergent step in (+)-erogorgiaene synthesis

insertion/Cope rearrangement product **208** in 36% yield (64% from the matched enantiomer) and 90% ee. The other enantiomer of the substrate was mismatched for this transformation, and instead underwent a cyclopropanation reaction to form **207** in 36% yield. Global hydrogenation, reduction of the ester, PCC oxidation of the primary alcohol, and Wittig olefination completed the synthesis of (+)-erogorgiaene in short order.

Two even more impressive examples of the utility of the combined C–H insertion/Cope rearrangement towards the total synthesis of marine diterpenes were demonstrated in the completion of (−)-colombiasin A and (−)-elisapterosin B (Scheme 51) [143]. The construction of both molecules began with racemic, highly substituted dihydronaphthalene **209**. The enantiodivergent carbenoid transformation took place as in the erogorgiaene synthesis to form the desired product and cyclopropane in a 1:1 ratio. After hydrogenation and LAH reduction, **211** was isolated in 34% yield (68% from the matched enantiomer) as a single diastereomer in >95% ee. This common intermediate was used to complete the syntheses of both (−)-colombiasin A and (−)-elisapterosin B.



Scheme 51 Enantiodivergent step in the syntheses of (−)-colombiasin A and (−)-elisapterosin B

The use of the combined C–H insertion/Cope rearrangement towards the synthesis of this broad family of natural products has also aided in some possible structural reassignments of some of its members [144, 145]. After completing the synthesis of the assigned structure of (+)-elisabethadione, it was determined that the structural data of the synthetic product did not match the originally reported spectroscopic data for the isolated material. In an attempt to resolve this discrepancy, a related *p*-benzoquinone natural product was also synthesized through an identical route. In this case, the proton and carbon NMR data for the synthetic and natural material were in excellent agreement. This implied that either the structure of (+)-elisabethadione was misassigned, or that there were errors in the originally reported spectroscopic data for this compound.

5 Summary, Conclusions, and Future Outlook

The functionalization of C–H bonds by means of carbenoid insertion is a highly effective method of introducing new C–C bonds into organic substrates in both a regio- and a stereoselective manner with an appropriate catalyst. Although early reactions were carried out with EDA as the carbenoid source, donor/acceptor carbenes are quickly becoming key players in this field due to their enhanced selectivity in many instances. Rhodium carboxylates and carboxamidates remain the catalysts of choice for most transformations, particularly those requiring asymmetric induction, although significant advances have been made in the development of achiral silver and copper homoscorpionate catalysts for use with EDA.

Although intramolecular carbenoid C–H insertion is a more mature field, progress continues to be made in this area as it is applied to increasingly complex substrates. It is within the realm of intermolecular C–H insertion that enormous growth has been seen in recent years. Catalyst development has allowed such transformations to occur with increasing levels of regio- and enantioselectivity, rendering these reactions quite synthetically useful. Many of these carbenoid systems have also been shown to be equivalents to traditional organic transformations such as aldol, Michael, Mannich, or Claisen chemistry. The remaining key hurdle that must be overcome is the low diastereoselectivity in many of these systems. This is not a concern, however, in the case of vinylcarbenoids when engaged in the combined C–H activation/Cope rearrangement.

As a testament to the utility of the carbenoid C–H insertion methodology, it has already been utilized as a key component of many partial and total syntheses of natural products and pharmaceuticals. Several were highlighted in this chapter, and many more instances will likely emerge on the scene in the coming years as the chemistry continues to improve. In the future, research will continue to focus on development of new and more selective chiral catalysts, as well as expanding the scope of the acceptable donor and acceptor groups compatible with the carbenoids themselves. With continued advancements, this area of "C–H activation" will remain a synthetically important part of organic chemistry for decades to come.

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Metal-Catalyzed Oxidations of C–H to C–N Bonds

David N. Zalatan and J. Du Bois

Abstract This chapter offers a general review of selective methods for the oxidative conversion of C–H to C–N bonds. Special focus has been given to the many disparate catalyst types that are capable of promoting this unique transformation.

Keywords Amination • Transition metal catalysis • Nitrene

Contents

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1 Introduction

To the synthetic chemist, Nature's exacting ability to promote chemo- and stereoselective C–H bond oxidation on architecturally complex molecules stokes the imagination and inspires the inventive mind. Myriad reports now describe catalytic processes designed to convert C–H bonds into value-added functional groups. Some of these reaction types, namely C–H borylation, C–H amination, and C–H iodination, are without enzymatic parallel, and thus speak to the power of small molecule, chemical catalysis to extend beyond Nature's capabilities. The amination process – that is, the select conversion of C–H to C–N bonds – has been intensively investigated and is now the subject of several treatises [1–10]. The upsurge in activity in this arena over the past 10 years is driven in part by utilitarian pursuits given the prevalence of nitrogen-based functional groups in chemical, biological, and materials science and, as such, the oft-desire to access natural and non-natural nitrogenous structures. The preparative difficulties in assembling amines and amine derivatives can be generally ascribed to two factors: (1) the need for preoxidized carbon functional groups from which displacement and reductive exchange reactions result in C–N bond formation; (2) the reliance on protection/deprotection strategies to mask the polar and sometimes acidic nature of most nitrogen-based functional groups. Both issues conspire to complicate synthetic planning and to increase the overall time, effort, and waste associated with preparing nitrogen-containing compounds. Accordingly, highly controlled oxidative methods that enable site-selective conversion of C–H to C–N bonds offer to transform the practice of chemical synthesis.

This chapter will highlight recent efforts to develop metal-mediated processes for selective C–H amination. Other excellent, comprehensive reviews can be found on this topic [3, 8–10]. To distinguish this discourse from prior works, we have opted to focus attention on the diversity of catalysts that are now known to mediate racemic and asymmetric intra- and intermolecular oxidation reactions. Where possible, mechanistic insights that elucidate the role of the metal catalyst and the details of the defining bond-forming event will be presented. It is our hope that this analysis will serve to inspire additional inventive discoveries in this rapidly progressing field – advances that may change the art and practice of complex molecule assembly.

2 Background

The history of C–H amination can be traced to the earliest work of Hofmann involving the reactivity of *N*-bromoamines, chemistry later recognized by Löffler and Freytag for its potential to facilitate pyrrolidine synthesis from simple acyclic precursors [11]. The intermediacy of both haloamine and aminyl radical in this stepwise oxidation reaction is now generally accepted, as is the hyper-reactivity of the radical oxidant and the difficulties associated with its control. Photolytic and thermal reactions of organic azides are plagued by similar issues of chemo-promiscuity, a problem for all intents and purposes intrinsic to nitrenes no matter the spin state (i.e., singlet vs triplet). The unconstrained reactivities of both aminyl radicals and nitrenes have no doubt dissuaded most practitioners of fine chemicals synthesis from exploiting tactics in which these species would necessarily intercede. Nonetheless, it is possible to find more than one spectacular demonstration of the application of such tactics in the annals of natural products synthesis [12–14]. These works underscore the potential transformative power of C–H amination reactions as tools for molecule construction.

Control over nitrene reactivity has been achieved with the utilization of transition metal catalysts. Seminal reports by the groups of Kwart and Kahn [15], D. Breslow [16], and Turner [17] highlight reactions of benezenesulfonyl azide and chloramine-T (TsNClNa) with Cu and Zn powder to give products of alkane C–H insertion. While these findings are of historical note, general methods for metal-mediated nitrene transfer did not emerge until the advent of *N*-sulfonyl iminoiodinane ($ArSO_2N{=}IPh$) reagents. The earliest studies with these reagents and transition metal catalysts, as systematically investigated in the labs of R. Breslow and Mansuy, illustrated the unique reactivity of such oxidants for alkene aziridination and C–H amination [18, 19]. A contemporaneous report by Barton, like the prior discovery of Turner, pointed to the use of chloramine-T as a nitrene equivalent [20]. Although these early works generally involved reactions with Mn- and Fe-based catalysts, the uniqueness of dirhodium tetracarboxylates, exemplified by $Rh_2(OAc)_2$, for C–H amination, was noted in a singular example by R. Breslow [21] and later exploited by Müller (Fig. 1) [22–24]. The discovery by Evans that numerous metal ion complexes, including non-redox active salts such as $Zn(OTf)_2$, could induce alkene aziridination with $ArSO_2N{=}IPh$ as the terminal oxidant reignited interest in these iodoimine reagents [25, 26]. This work also marks the first time Cu salts were shown to be particularly capable catalysts for promoting aziridination.

Today, the application of hypervalent iodine reagents still dominates the reaction landscape of electrophilic N-atom transfer processes, a testament to the unique reactivity of such oxidants. Nevertheless, the past decade has witnessed a flurry of activity aimed at the invention of new reagents and protocols that enable amine and amine derivative synthesis through selective C–H bond modification. We have attempted to highlight many of these recent discoveries, with apologies in advance

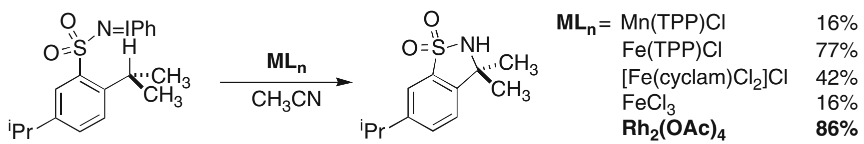

Fig. 1 The seminal report of intramolecular C–H amination by Gellman and R. Breslow

to any researchers whose work we may have accidentally and regrettably overlooked.

3 Copper Catalysis

3.1 Nitrenoid Reactions

The demonstration by Evans in 1991 that both Cu^{+} and Cu^{2+} salts could catalyze alkene aziridination using PhI=NTs as the nitrene source fueled interest in this methods problem [25]. Subsequent studies by Evans and Jacobsen using chiral Cu^{+} complexes would underscore the potential for such reagent combinations to elicit asymmetric N-atom transfer to prochiral alkenes [26–28]. Mechanistic studies by both laboratories have given support for a process involving a nitrenoid oxidant. For aziridination reactions conducted under asymmetric catalysis, large steric substitutions of the ArI-moiety in ArI=NTs appear to have no discernible influence of product enantiomeric excess (%ee). These data seemingly rule out an electrophilic, Lewis acid-type mechanism of an ArI=NTs•CuL_n complex in the selectivity-determining step. Additional evidence for a nitrene-type oxidation reaction comes from a comparative study of an asymmetric aziridination performed with either PhI=NTs or $TsN_3/h\nu$, in which the product is formed with the same level of optical purity irrespective of the conditions used. Both Evans and Jacobsen note, however, that aziridination of certain aryl- or diaryl-substituted *cis*-olefins (e.g., stilbene) with select Cu catalysts affords *cis*/*trans* product mixtures. The lack of stereospecific N-atom transfer in these cases does not accord with a concerted aziridination mechanism.

Density functional theory (DFT) calculations have provided additional important insights into the Cu-promoted aziridination process [29]. These data offer a picture for the putative sulfonylnitrene species that is bound in a two-point pose (i.e., coordination occurs through both the N- and one of the sulfonyl O-atoms) to a Cu^{+} center. Theory suggests that the mode of N-atom transfer will differ depending on the choice of substrate and the nature of the Cu^{+} counterion, a finding consistent with the aforementioned results and a Hammet analysis performed by Pérez, et al. [30]. These calculations argue for an active Cu(I) catalyst and show how Cu^{2+} salts can enter into a Cu(I)–Cu(III) catalytic cycle. Three different low energy pathways for N-atom transfer are suggested: (1) a closed shell singlet pathway that leads directly to aziridine through a concerted asynchronous transition state; (2) an open-shell singlet pathway involving a short-lived biradical intermediate; and (3) a triplet surface leading to a longer-lived radical species that must undergo spin crossover. The location of nearly isoenergetic singlet and triplet Cu-nitrene intermediates on the reaction coordinate is consistent with a process that is highly dependent on the nature of the copper complex as well as the alkene.

Although it is not the intent of this review to provide a comprehensive discussion of metal-mediated alkene aziridination, the mechanistic parallels between the

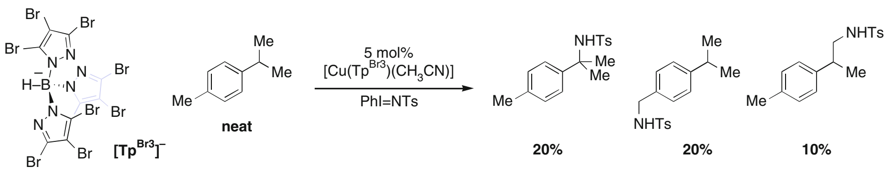

Fig. 2 Cu(I) homoscorpionate complexes catalyze benzylic C–H amination

Cu-promoted reaction and Cu-catalyzed C–H amination merit some analysis of the former process. From the standpoint of reaction utility, the work of Dauban and Dodd [31, 32] and, more recently, Lebel [33] has advanced Cu-catalyzed alkene aziridination to a state-of-the-art synthetic method. In particular, Dauban and Dodd have shown that pre-formation of sulfonyliodoimines is not required and that such species can be generated in situ from the corresponding sulfonamide and PhI=O. These conditions greatly expand the number and type of sulfonamide derivatives that will engage in olefin aziridination processes.

Examples of secondary and benzylic C–H amination have been documented using Cu(I) homoscorpionate complexes with either PhI=NTs or chloramine-T as the nitrogen source (Fig. 2) [30, 34–37]. A rare example of a formal C–H insertion reaction into an aromatic C–H center has also been observed with this reagent combination. A downside to these processes is that they are typically performed neat in substrate. The somewhat indiscriminate reactivity observed in Cu(I) homoscorpionate-catalyzed C–H amination reactions contrasts other metal-nitrene processes and is suggestive of a nitrenoid oxidant having significant radical character. Hammett analysis of Cu(homoscorpionate)-promoted alkene aziridination is consistent with a Cu-bound nitrogen-centered radical operating as the active oxidant. Theoretical calculations are warranted to understand how the enforced tetrahedral geometry of the homoscorpionate ligand influences the electronic ground state of the reactive nitrenoid species. This particular catalyst system is unique to the amination literature, as most examples of Cu-mediated C–H amination involve complexes derived from bidentate ligands.

Although the combination of $[Cu(Tp^{Br3})(CH_3CN)]$ and PhI=NTs will oxidize benzene, aniline products are typically not observed in reactions of substituted aromatic derivatives with this catalyst system. In more general terms, it appears that electrophilic metal-nitrene species show very little predilection to oxidize aromatic C–H bonds. An exception appears from the work of Sadighi, who has observed amination of 1,3-dimethoxybenzene by employing an electron-poor Cu(2,9-diarylphenanthroline)SbF_6 complex with PhI=NTs as the nitrogen source (Fig. 3) [38]. Use of a sterically encumbered phenanthroline ligand gives exclusively a 1:1 Cu^+/phenanthroline adduct and forces the Cu center to adopt a three coordinate geometry. Given the sterically crowded nature of the putative nitrenoid intermediate, it is somewhat remarkable that a productive reaction ensues with a substrate the size of dimethoxybenzene. Although no mechanistic information is provided in this report, the observed reactivity with an electron-rich arene is suggestive of a mechanism

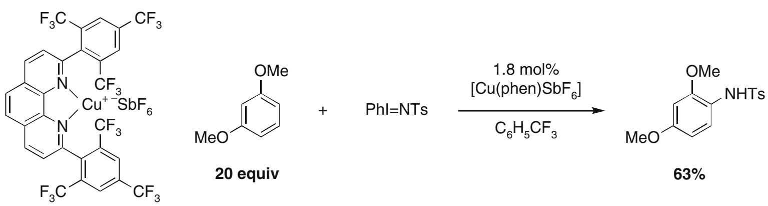

Fig. 3 A rare example of a metal-catalyzed aromatic C–H amination reaction

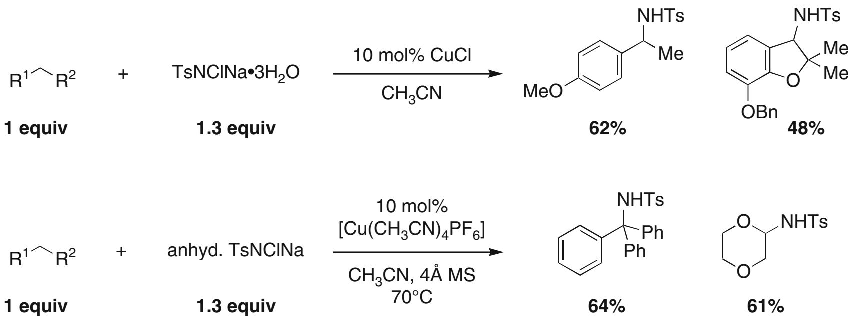

Fig. 4 Copper salts catalyze amination reactions with chloramine-T as the nitrogen source

involving electrophilic aromatic substitution. The authors do not indicate whether this catalyst is capable of effecting aliphatic C–H amination.

Recent successes in C–H amination have been recorded using Cu-based catalysts and chloramine-T as nitrogen sources. An initial report by Taylor and coworkers in 1998 showed that Cu^+ complexes derived from *N*-alkyl-2-pyridylcarboxaldimines would promote aziridination of unfunctionalized olefins and, in certain cases, the amination of allylic and benzylic C–H centers [39]. Subsequent investigations by the same lab found that CuCl can serve as an effective promoter for hydrocarbon oxidation under conditions that employed chloramine-T and substrate as the limiting reagent (Fig. 4) [40]. This latter feature is of particular note as most intermolecular alkane C–H insertion reactions are conducted with excess substrate to achieve high product yields. The exceptional performance of such a simple copper catalyst is remarkable, particularly when one considers the number of alternative Cu-ligand complexes that have been investigated for this same purpose. Surprisingly, no additional reports have come forth that further detail the scope and limitations of this process. The substrate profile is indicative of a reaction that works optimally with and, in fact, may be limited to electron-rich benzylic substrates. Nevertheless, this method is particularly attractive for preparative scale synthesis given the low cost of CuCl and chloramine-T. A related protocol for amination of 1°, 2°, and 3° benzylic C–H bonds uses anhydrous chloramine-T and the commercially available catalyst, $[Cu(CH_3CN)_4]PF_6$, and appears to be quite effective (Fig. 4) [41]. Similarly, simple copper salts such as $Cu(OTf)_2$ in

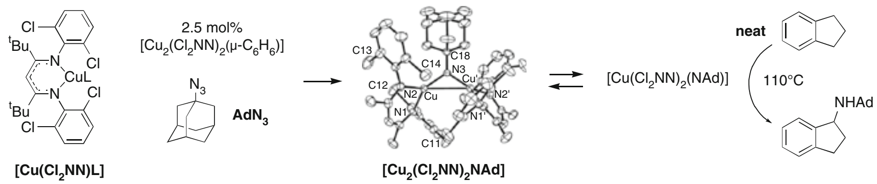

Fig. 5 Isolation of a discrete copper-nitrene precursor competent for C–H amination reactions

combination with $TsNH_2$ and $PhI(OAc)_2$ have found application for intermolecular oxidation of ethereal C–H centers to give isolable N,O-acetal products [42].

Despite the widespread interest in the development of efficient and, in several cases, asymmetric Cu-mediated methods for alkane amination and olefin aziridination, few reports detail efforts to explore experimentally the stepwise details of the reaction process and/or to characterize the putative Cu-nitrene oxidant. Seminal work by Warren, Cundari, and coworkers detailing reactivity, mechanistic, and computational studies of a β-diketiminate-derived Cu^+ complex for C–H amination has afforded terrific insight into the structural and electronic configuration of the nitrenoid oxidant [43–45]. Treatment of the [Cu_2(β-diketiminate)$_2$(μ-toluene)] complex with 1 equiv. of an aryl azide generates a μ-aza-bridged dicopper complex, which has been crystallographically characterized (Fig. 5). The stoichiometric reaction of this adduct with either ^{t}BuNC or Me_3P results in facile nitrogen group transfer. Mixing two unique homodimeric [Cu(β-diketiminate)$_2$(μ-NAd)] complexes generates heterodimeric products, suggesting that the aza-bridged complex can dissociate to two mononuclear species. The dimer-monomer equilibrium is not unique to the arylnitrene complex, and is also suggested for a nitrenoid species derived from adamantyl azide. The latter complex reacts efficiently with ethylbenzene and other simple hydrocarbons to generate adamantyl amine products. This same oxidation can be performed with catalytic amounts of the Cu^+ complex (2.5 mol%) in neat hydrocarbon substrate. The use of fewer equivalents of hydrocarbon results in competitive formation of the adamantyl diazene, AdN=NAd. Interestingly, the formation of related diazene products has seldom been indicated in other reported nitrenoid processes.

Warren and coworkers have determined a kinetic isotope effect of 5.3 for the catalytic amination of ethylbenzene, which is identical to the value obtained using stoichiometric [Cu_2(β-diketiminate)$_2$NAd]. In addition, the rate of C–H amination with this complex is nicely correlated with homolytic C–H bond strengths. These two pieces of data are consistent with a mechanism for C–H insertion involving initial C–H abstraction followed by radical recombination. Although prior DFT calculations have indicated that related Cu^+ nitrenes should favor a triplet ground state, calculations performed using complete active space self-consistent field (CASSCF) multiconfigurational techniques favor a singlet nitrenoid having biradical character [46]. This spin state is calculated to be 18 kcal mol^{-1} lower in energy than that of the triplet. The observed reactivity (i.e., C–H abstraction/radical rebound) of the mononuclear nitrenoid, [Cu(β-diketiminate)NAd], is in line with the predicted open shell electronic configuration. Such studies raise questions as to the accuracy of DFT calculations for modeling metallonitrene species.

3.2 Non-Nitrenoid Amination Processes

Recent reports describe Cu catalyzed C–H amination through pathways that likely involve the intermediacy of amidyl radical species as opposed to discrete nitrenoids. Cuprous complexes derived from phenanthroline will react with ^{t}BuOOAc and 1° or 2° sulfonamides to convert benzylic hydrocarbons – indan, ethylbenzene, tetrahydronaphthalene – to the corresponding sulfonamide products (Fig. 6) [47]. The fact that 2° sulfonamide starting materials can engage in this process discounts a Cu nitrene species as the active oxidant. Owing to the observed formation of benzylic acetate derivatives and the fact that these products prove competent as intermediates in the amination reaction, the authors suggest that this reaction proceeds through initial C–H acetoxylation followed by copper-catalyzed exchange with the starting sulfonamide. An alternative mechanistic proposal involving sulfonamide radical generation is also possible. A related process uses peroxide oxidants for the amidation of sp^3 C–H bonds adjacent to a nitrogen atom [48].

Shi and coworkers have described reactions of diaziridinones with both saturated and unsaturated starting materials to give amine and diamine products, respectively. Nitrenoid-promoted amination of C–H centers adjacent to strong electron withdrawing groups (i.e., carbonyl moieties) is generally quite inefficient. By contrast, di-*tert*-butyldiaziridinone reacts with aryl acetic esters in the presence of a Cu^+ catalyst to afford the corresponding di-*tert*-butylated hydantoins (Fig. 7) [49]. The possible role of an organo-copper intermediate species has been suggested to account for this unique oxidation event. Deprotonation of an α-C–H bond or C–H

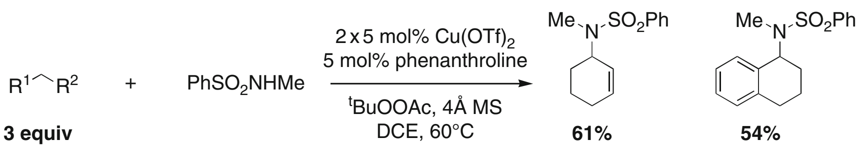

Fig. 6 Allylic and benzylic C–H amination promoted by peroxide oxidants

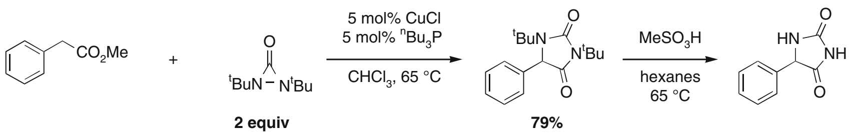

Fig. 7 α-Amination of esters by di-*tert*-butyldiaziridinone

abstraction by an N-centered radical is thought to give rise to a Cu(III) species that reductively eliminates to give product.

A final example of an allylic C–H amination process involves a mechanism that does not fall into the classification of either a Cu-bound nitrene or N-centered radical-type process. In this case, *N*-Boc-hydroxylamine serves as the nitrogen source and is converted to the acylnitroso species via a disproportionation mechanism facilitated by $P(OEt)_3$ and CuBr [50]. Such compounds will react with olefin substrates through a thermal ene-like rearrangement to give *N*-Boc-*N*-hydroxy allylic amines. The Cu catalyst is not believed to play a specific role in the actual C–H oxidation event.

4 Silver and Gold Catalysis

Despite the prevalence of Cu-based catalysts for electrophilic N-atom transfer reactions, reports describing the use of silver complexes in nitrenoid processes are conspicuously few [51, 4]. A dimeric Ag(I) complex derived from 4,4′,4″-tri-*tert*-butylterpyridine (*t*Bu_3tpy) and $AgNO_3$ is capable of catalyzing intramolecular C–H amination of both carbamates and sulfamates under conditions analogous to those described for the equivalent Rh-promoted process. He and coworkers have suggested that this reaction involves nitrenoid formation and transfer on the intact, dinuclear Ag(I) adduct. This conclusion is based on mass spectrometric evidence and on the fact that the dimeric catalyst can be recovered from a spent reaction mixture. A related disilver complex formed from 4,7-diphenyl-1,10-phenanthroline and AgOTf has also been characterized by X-ray crystallography [52]. This catalyst appears to be more effective than the terpyridine system for promoting intramolecular carbamate C–H amination (Fig. 8). In addition, the phenanthroline-derived complex can mediate intermolecular C–H amination with PhI=NNs (Ns = *p*-nitrobenzenesulfonyl) as the oxidant. Lower product yields are obtained when the iminoiodinane is replaced with $PhI(OAc)_2$ and $NsNH_2$. The reaction performs with modest efficiency on simple, unfunctionalized hydrocarbons used in 5- or 10-fold excess relative to PhI=NNs. The authors suggest that the performance of the

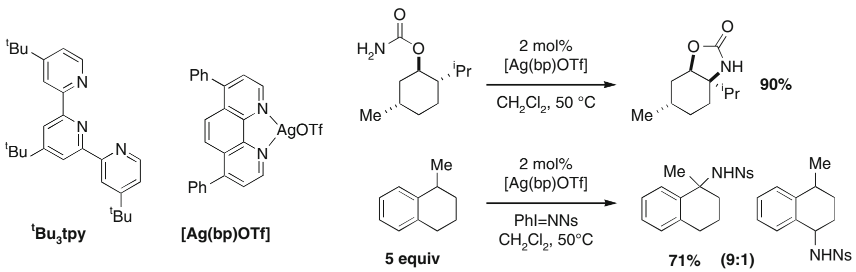

Fig. 8 Silver catalyzed intra- and intermolecular C–H amination

disilver complexes relative to the Cu-system for catalytic C–H amination is related to the higher oxidation potential of Ag, and the inability of such complexes to engage in deleterious one-electron oxidation pathways. In accord with recent findings of Warren (see Section Copper Catalysis), one wonders whether a dimer-monomer equilibrium exists for a μ-aza bridged disilver-nitrene adduct, giving rise to a reactive mononuclear Ag(I)-nitrene species. Additional mechanistic and computational studies are warranted to answer such questions. Covalently linking two phenanthroline units could prove telling if indeed catalytic activity is arrested with such systems.

Mononuclear Ag(I) complexes derived from Tp^{Br3} (Tp^{Br3} = hydrotris(3,4,5-tribromo)pyrazolyl borate) and related scorpionate ligands display activity as catalysts for intermolecular C–H amination [53]. Complexes of this type were first highlighted by Dias and Lovely for carbenoid reactions with diazo starting materials [54, 55]. By analogy to this work and previous reports of [Cu(Tp^{Br3})(CH_3CN)] catalyzed C–H amination, Díaz-Requejo, Pérez, and coworkers have found that Ag trispyrazolylborate catalysts will oxidize neat hydrocarbon with 20-fold excess PhI=NTs to afford isomeric mixtures of sulfonamidated products. Amination is favored to some extent for 3° sites over 2° and 1° C–H bonds. The observation of 1° methyl functionalization is unusual for these types of nitrenoid processes and suggestive of a hydrogen abstraction-type reaction, possibly via a triplet nitrenoid oxidant. The formation of chloroalkanes when CCl_4 is used as solvent as well as the inhibition of this reaction by BHT both point to a mechanism involving transient radical species.

A AuOTf complex derived from *t*Bu_3tpy can effect aziridination of simple olefins using $NsNH_2$ and $PhI(OAc)_2$ [56]. We include this finding as part of the discussion, as it represents the only report of which we are aware of an N-atom transfer reaction with a discrete Au coordination complex. He and coworkers, drawing analogy to their earlier work with disilver(I) complexes, suggest that the active Au catalyst is dimeric, a proposition that is supported by mass spectrometry data. Interestingly, this catalyst has yet to be shown competent for C–H amination, and there are evident differences in reactivity between the isostructural Au and Ag systems.

In a recent report, $AuCl_3$ has been found to catalyze the intermolecular amination of both benzylic and aromatic C–H bonds using PhI=NNs as a nitrene equivalent (Fig. 9) [57]. Mechanistic studies by these authors indicate that the Au(III) catalyst acts first to metalate the aromatic ring. The resulting arylgold species subsequently exchanges with PhI=NNs to give the arylsulfonamide product and to regenerate a reactive auric catalyst. In some sense, this mechanism is

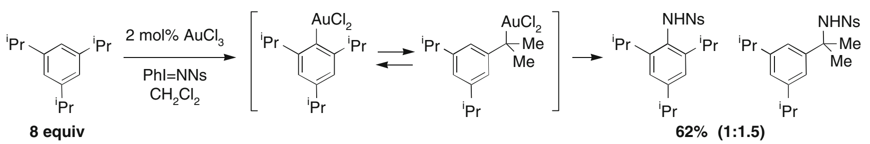

Fig. 9 An unusual amination reaction involving Au(III) catalysis

reminiscent of aryl amination chemistry using Pd catalysts. The amination step, however, may simply involve nucleophilic attack of the organoaurate on the imino-iodinane reagent. Formation of benzylic sulfonamides is thought to proceed by way of a mechanistically intriguing isomerization process from the arylated Au(III) species. The current scope of the reaction, like most Ag and Au-catalyzed amination processes, appears to be limited.

5 Ruthenium Catalysis

Many successful examples of selective and efficient intra- and intermolecular C–H amination have been recorded using Ru-based catalysts. Che and coworkers have scripted seminal reports in this arena and have contributed greatly to our overall understanding of the mechanism by which Ru complexes promote N-atom transfer to sp^3 and sp^2 substrates [58]. The electron-withdrawn pentafluorophenyl-substituted Ru^{2+} porphyrin, [Ru(TPFPP)(CO)], has proven one of the most effective catalysts for amination reactions of benzylic, allylic, and α-ethereal C–H bonds (Fig. 10) [59–61]. In many instances, only a slight excess of substrate (e.g., 2 equiv.) is needed to achieve high levels of product conversion. Moreover, the combination of 1° sulfonamide or sulfamate and $PhI(OAc)_2$ can serve in place of the more capricious iminoiodinane oxidants. Useful mechanistic insights have been obtained from reactions with unsymmetrical allylic substrates. In these instances, regioisomeric product mixtures are formed. These results seem to indicate an operative stepwise mechanism as opposed to a concerted C–H oxidation pathway (see below). The catalyst itself is clearly associated with the active oxidant in the bond-determining step, as optically active Ru(porphyrin)(CO) complexes have been shown to effect asymmetric sulfamate ester insertion with product enantiomeric excess as high as 88% in select cases.

Reaction of [Ru(TPP)(CO)] (TPP = tetraphenylporphyrin) with PhI=NTs generates a Ru(VI) bis-imido complex, which has been crystallographically characterized [62]. This species is chemically competent as an N-centered oxidant, and will react with olefin, benzylic, and adamantyl substrates to form sulfonylaziridine and sulfonamide products, respectively (Fig. 11). The availability of this meta-stable adduct has offered a unique opportunity to study directly the mechanism of the C–H

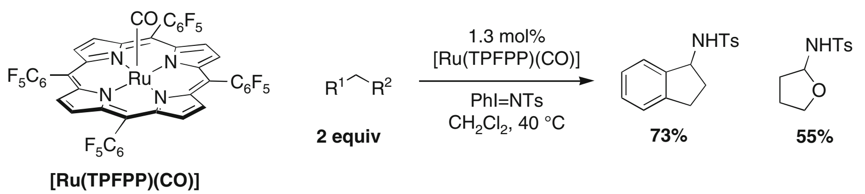

Fig. 10 Efficient intermolecular C–H amination using an electron-deficient Ru porphyrin catalyst

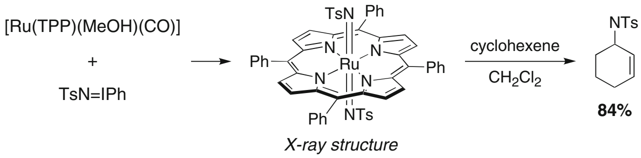

Fig. 11 An isolable Ru(VI) bis-imido complex competent for N-atom transfer

insertion event. Still, it remains unclear whether the Ru(VI) oxidation state is indeed accessed under the typical catalytic conditions of the amination reaction, particularly when one is employing the strongly electron-withdrawn perfluorinated porphyrin complex. It is equally uncertain whether all Ru complexes (see below) catalyze C–H amination in a manner analogous to the porphyrin systems.

Mechanistic studies by Che have revealed a large primary deuterium KIE of 11 for the amination of ethylbenzene with $[Ru(TPP)(NTs)_2]$. An excellent correlation between the rate of N-atom transfer and TE (total effect), a parameter that correlates substituent effects with C–H bond dissociation energy, is also noted. Both pieces of data speak to a process that involves rate-limiting C–H abstraction followed by a radical rebound event. A more recent study gives further evidence for a stepwise oxidation mechanism by revealing a close correlation between the rates of C–H insertion and C–H homolytic bond strength [63]. These investigations also demonstrate that the rate of C–H amination can be influenced by the electronic characteristics of the sulfonyl substituent on the imido ligand. Consistent with an electrophilic mechanism for C–H functionalization, the rate of oxidation increases as the sulfonyl group is made more electron withdrawn. The Ru(VI)/(V) redox potentials for these individual complexes, as measured by cyclic voltammetry, are also sensitive to the nature of the sulfonyl unit.

Density functional theory calculations by Che and Phillips have provided an alternative mechanistic model for Ru-catalyzed amination reactions that does not involve a Ru(VI) bis-imido species [64]. These newest findings posit that the active oxidant is a Ru(IV) mono-imido complex and that the lowest energy pathway for C–H amination follows a concerted singlet nitrenoid insertion event. Although the calculated energy gap between the singlet and triplet spin states of the Ru(IV) imido is small (<1 kcal mol^{-1}), the closed shell singlet configuration is favored. There appears to be some inconsistency between theory and experiment, as a concerted insertion mechanism should be regiospecific in reactions with unsymmetrical allylic derivatives. Catalytic amination reactions performed with [Ru(TPFPP)(CO)] and PhI=NTs, however, afford mixtures of allylic sulfonamide products. At this time, more mechanistic work is warranted on the Ru-catalyzed process to reconcile these ostensible discrepancies.

Nonporphyrin-derived Ru catalysts for C–H amination have seen limited utility as compared to their porphyrin counterparts [65]. A recent report by Blakey and coworkers, however, is likely to shift this imbalance [66]. As this lab has demonstrated, use of the Nishiyama Ru(II)-pybox complex, $[Ru(pybox)(H_2C{=}CH_2)Br_2]$,

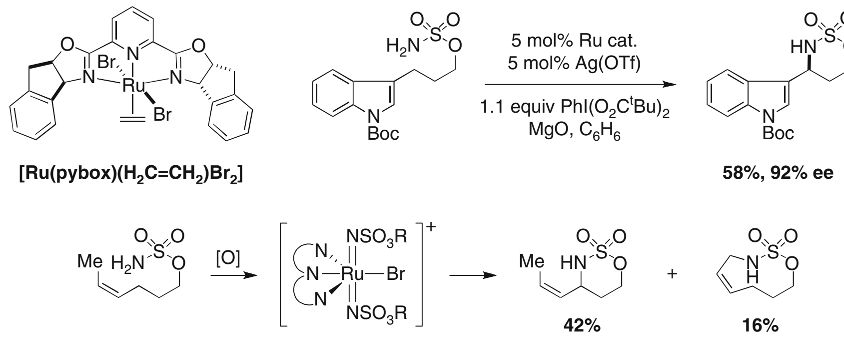

Fig. 12 Enantioselective Ru-pybox catalyzed intramolecular sulfamate C–H amination

in combination with AgOTf affords an active catalyst, which is capable of promoting intramolecular sulfamate C–H insertion in good yields and with high levels of asymmetric control (Fig. 12). The amination reaction proceeds optimally with sulfamate ester substrates, $PhI(O_2C^tBu)_2$, and MgO, conditions also described for the analogous Rh-catalyzed process. The structure and reactivity of the active oxidant in the Ru-pybox process is particularly intriguing, as it shows a high bias for allylic C–H insertion over alkene aziridination. Based on the observed chemoselectivity and the work of Che, the authors speculate that the reactive oxidant in this catalytic process is a cationic Ru(VI) bis-imido species. Reactions performed with Ru complexes having an ethylene (H_2C=CH_2), CO, or PPh_3 ancillary ligand give comparable product yields and selectivities. Accordingly, the authors propose that such ligands are free of the active Ru catalyst. A potentially fruitful investigative opportunity is to understand the differences between the mononuclear Ru-pybox and dinuclear Rh-tetracarboxylate catalysts for effecting sulfamate C–H insertion. The high chemoselectivity displayed by the Ru-pybox system for allylic C–H bonds is particularly intriguing, and contrasts that of most dimeric Rh catalysts [67]. A mechanism for the Ru-pybox-catalyzed oxidation involving stepwise radical formation appears consistent with the current available data and could explain the proclivity of this system for allylic amination.

Ruthenium-based catalysts display some utility for electrophilic amination of heteroaromatic substrates. Che and coworkers have found that [Ru(TTP)(CO)] in combination with PhI=NTs will oxidize arenes such as furan, indole, and pyrrole (Fig. 13) [68]. Reactions occur optimally under the action of ultrasound, a rather unusual addendum to the standard protocol for C–H amination. More intriguingly still, *N*,*N*-ditosylated products are isolated in most instances, a finding that is not easily resolved mechanistically. As the substrate profile for this amination process involves only electron-rich heteroaromatics, aziridination of the arene nucleus would seem a likely step along the reaction coordinate. Interestingly, no amination product is observed when stoichiometric [Ru(TMP)$(NTs)_2$] (TMP = tetra(2,4,-6-trimethylphenyl)porphyrin) is mixed with either furan or *N*-phenylpyrrole, though a reduction of the starting Ru(VI) complex to a Ru(IV) species is noted

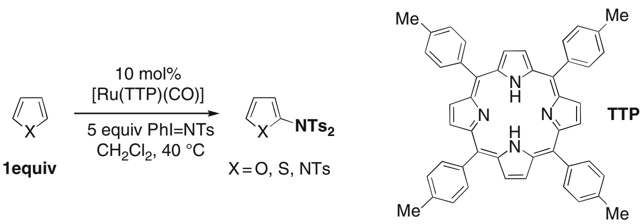

Fig. 13 Electrophilic amination of electron-rich heteroaromatic substrates

by UV/vis spectroscopy. The involvement of a Ru(VI) bis-imido intermediate as the active oxidant in this process is, therefore, precluded. Additional mechanistic studies are needed to understand further the stepwise details of this unusual reaction.

6 Iron Catalysis

Despite its unique place as one of the first metals to be recognized for effecting C–H amination of hydrocarbon substrates, only a small number of ensuing reports have appeared detailing the use of novel Fe-catalysts for this process. Contemporaneous discoveries by Breslow and Barton highlight iron-mediated amination reactions with iminoiodinane and chloramine-T oxidants, respectively [18, 20, 21]. Breslow has also shown that natural cytochrome P450s catalyze both intra- and intermolecular C–H amination with $ArSO_2N{=}IPh$ oxidants [69]. Additionally, Mansuy and coworkers have utilized Fe(III)-porphyrin complexes to mediate allylic amination and alkene aziridination – in most cases, mixtures of products are generated with isomeric distributions indicative of a H-atom abstraction/radical rebound mechanism [19, 70, 71].

Recent DFT calculations on high-valent Fe(IV)=NR porphyrin oxidants support a non-concerted stepwise mechanism for C–H amination. Two reaction surfaces of doublet (low spin) and quartet (high spin) reactivity are found to represent the lowest energy pathways from starting material to product [72]. These calculations further suggest that the R group on nitrogen can have a very large influence on the barrier for imido ligand transfer to the substrate. Unfortunately, such insights have not yet translated to the invention of a general, all-purpose catalyst for C–H amination.

To date, some of the more interesting examples of N-atom transfer from Fe-based complexes involve the oxidative modification of C–H bonds that comprise the ligand framework (Fig. 14). Que and coworkers have shown that a trispyridyl Fe(II) complex will react in the presence of PhI=NTs to oxidize an arene C–H bond that is positioned proximally to the metal center [73]. Such sp^2 amination

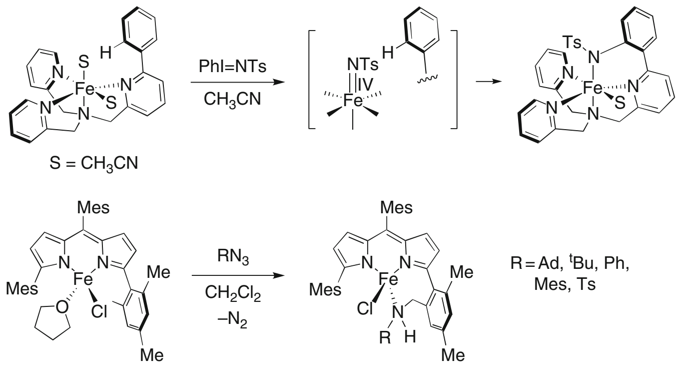

Fig. 14 Ligand amination observed for select Fe complexes

Fig. 15 Fe-catalyzed benzylic amination with sulfonamide and carboxamide nitrogen sources

events of unactivated arene C–H bonds are quite rare. An observed NIH shift and measured KIE of 1.3 for this reaction are in accord with an electrophilic aromatic substitution mechanism. A similar ortho-arene C–H amination reaction has been noted using a mixed-valent diiron(II/III) complex [74]. In this case, a reaction conducted with 2 equiv. of ArI=NTs (Ar = 2-*t*-$BuSO_2C_6H_4$) gave a bis-sulfonamide product, a result that hints at the potential of the dinuclear iron complex for catalytic reactions. A third example of ligand amination, in which an Fe(II) dipyrromethene complex is found to react with an alkyl-, aryl-, or sulfonylazide derivative, has appeared recently from the Betley lab [75]. Irrespective of the substitution on the azide nitrogen source, a 1° benzylic C–H bond positioned adjacent to the ferrous center undergoes selective amination. The authors postulate that the active oxidant is an Fe(IV) imido species and that the insertion event follows an H-atom abstraction/radical rebound pathway.

A remarkably efficient $FeCl_2$-catalyzed intermolecular amination of simple benzylic substrates has been described (Fig. 15) [76]. These same authors have also noted the ability of CuBr to operate in a similar capacity [77]. *N*-Bromosuccimide (NBS) is used as the oxidant together with either a carboxamide or sulfonamide starting material. The *N*-brominated amide purportedly reacts with $FeCl_2$ to generate an Fe nitrene species that is capable of oxidizing benzylic C–H bonds, though evidence for such a mechanism is absent from the discussion. If a nitrenoid pathway is indeed operative, one might expect isocyanate formation to compete with C–H insertion in reactions for which carboxamide is employed as the nitrogen source. Isocyanate formation is apparently not observed. An alternative pathway for C–H amination could involve Fe-mediated benzylic halogenation followed by S_N2 displacement by the nitrogen source, a process in some sense reminiscent of the Hofmann-Löffler-Freytag reaction. Zalatan and Du Bois have reported a metal-catalyzed HLF-type reaction of sulfamate esters using a halogen-based oxidant (NaOCl/NaBr) [78]. Interestingly, a number of different metal complexes and salts, including $FeCl_2$ and $CuCl_2$, prove effective for this transformation.

7 Manganese Catalysis

Early work by Breslow and Mansuy demonstrated the efficacy of Mn(III) porphyrin catalysts for promoting alkene aziridination and C–H amination reactions [18, 19, 21, 72]. Subsequent findings by Che have indicated that the performance of these Mn systems is in many ways comparable to related Ru(II) complexes [60]. By employing [Mn(TPFPP)Cl], Che has shown that $PhI(OAc)_2$ and 1° sulfonamides ($TsNH_2$, $NsNH_2$, $MeSO_2NH_2$) can be combined in situ with simple hydrocarbon substrates to promote C–H amination (Fig. 16). Contemporaneous work by the Du Bois lab using Rh-based catalysts resulted in a similar find. The porphyrin catalyst operates with high turnover numbers using limiting amounts of the starting substrate to afford the products of intermolecular amination in yields >75%.

Investigations by both Katsuki and Che have highlighted the application of chiral Mn(III) salen complexes for asymmetric N-atom transfer reactions (Fig. 17) [79–81]. In the former case, the use of [Mn(salen)PF_6] together with PhI=NTs affords modest product yields and enantiomeric ratios for amination of simple benzylic and allylic starting materials. A high-valent Mn imido species is presumed to be the active oxidant. Methodological and mechanistic studies conducted by Che have found that the same types of Mn(III) salen complexes will induce oxidative cyclization of sulfamate esters. Although these catalysts afford

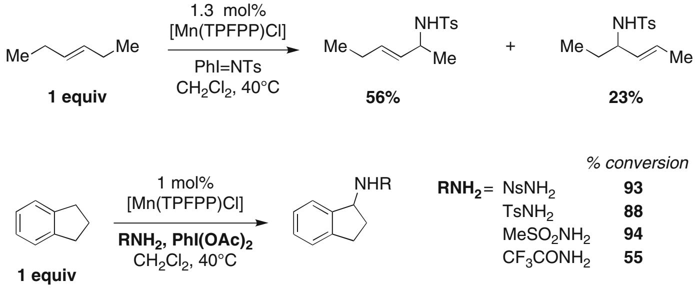

Fig. 16 Early examples of Mn(III)-catalyzed C–H amination

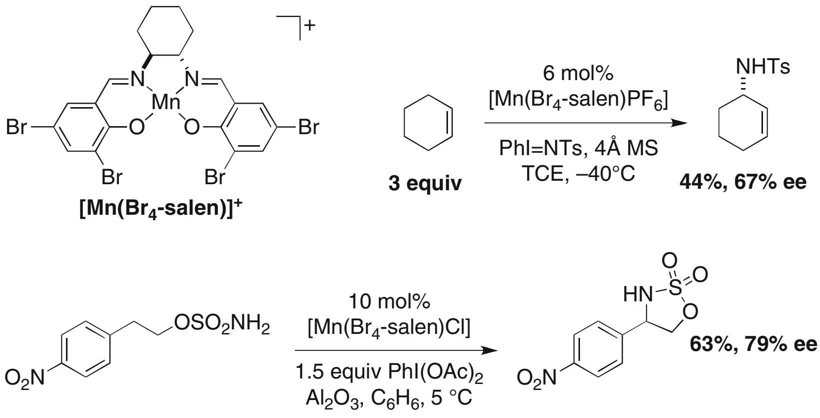

Fig. 17 Mn(salen)-catalyzed asymmetric C–H amination

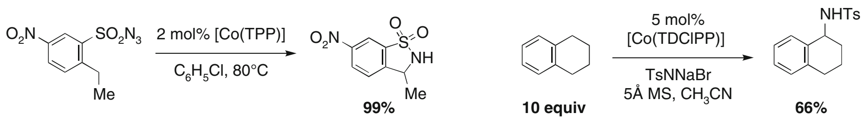

Fig. 18 [Co(TPP)]-mediated amination proceeds efficiently with disparate nitrogen sources

only moderate levels of asymmetric induction, yields are generally reasonable for five- and six-membered ring cyclic sulfamate formation. The reaction operates using a combination of sulfamate and $PhI(OAc)_2$ rather than the preformed iodoimine. Results from Hammett analysis and an insertion reaction with an optically pure 3° C–H substrate are used to argue for a concerted asynchronous reaction mechanism. Additional studies with cyclopropyl clock substrates are warranted to support this conclusion. Other high valent Mn(V) imido oxidants are believed to react with unsaturated substrates in a stepwise fashion [82, 83].

8 Cobalt Catalysis

Until recently, Co-based complexes had been seemingly dismissed as catalysts for C–H amination. Findings by Zhang and coworkers, however, have revealed the marked performance of Co(II) porphyrin complexes, [Co(TPP)] in particular, for promoting N-atom transfer reactions (Fig. 18). A striking feature of this catalyst system is its ability to engage effectively with different nitrogen sources including sulfonylazides [84], phosphorylazides [85, 86], and bromamine-T [87]. Intramolecular C–H insertion of aryl-substituted sulfonylazides can be conducted with 2 mol% of the catalyst to afford high yields of the five-membered sultam products.

The Co(II) catalyst outperforms analogous TPP complexes of V, Mn, Fe, Ru, Ni, and Zn. A similar intermolecular process using TsNBrNa and catalytic [Co(TDClPP)] (TDClPP = tetra(2,6-dichlorophenyl)porphyrin) occurs with excess (10 equiv.) benzylic hydrocarbons to give the corresponding 2° sulfonamides.

Arylazides will decompose in the presence of [Co(TPP)] and unsaturated hydrocarbons to generate both aziridine and allylic amine product mixtures [88–90]. Such a process is capable of oxidizing benzylic C–H bonds as well, though poor catalytic efficiency and problems with product over-oxidation limit the utility of these reactions [91, 92]. Detailed kinetics analysis and Hammett studies have led Cenini and coworkers to propose a mechanism that does not involve a Co imido complex, as had been previously suggested. The observation of a Co(III) species by UV/vis spectroscopy strongly implicates a one-electron pathway for this particular amination method.

9 Rhodium Catalysis

Dirhodium tetracarboxylate complexes are among the most successful and well-studied catalysts for C–H amination. Early work by Müller provided support for a concerted asynchronous reaction mechanism for intermolecular amination reactions using $Rh_2(OAc)_4$ and NsN=IPh [22–24]. Du Bois and coworkers have shown that carbamate and sulfamate esters can engage in oxidative cyclization reactions promoted by these same types of Rh complexes using $PhI(OAc)_2$ as the terminal oxidant [93–96]. Mechanistic studies, which include Hammett analysis ($\rho = -0.55$ vs σ^+), KIE measurements (1.9 ± 0.1), and cyclopropane clock experiments using sulfamate derivatives give additional weight to a proposed concerted asynchronous C–H insertion mechanism involving a Rh-nitrene intermediate [68]. These findings are bolstered by DFT calculations on the carbamate insertion reaction [97]. Kinetics analysis and catalyst labeling studies confirm the lability of Rh-bound carboxylate ligands and indicate that ligand exchange occurs within 60 s of initiating a reaction. Accordingly, these mechanistic findings have led to advances in catalyst design, namely the formulation of a chelating bis-dicarboxylate complex, $Rh_2(esp)_2$ [98]. This new catalyst greatly expands the scope of the amination process and makes possible high yielding and selective intramolecular oxidation reactions with carbamate, urea, guanidine, sulfamate, sulfamide, sulfonamide, and phosphoramidate derivatives (Fig. 19) [99, 100]. Effective methods for intermolecular C–H amination have also been enabled through the advent of new reagent and catalyst designs (Fig. 20).

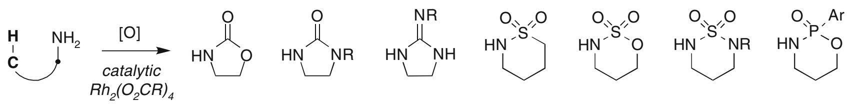

Fig. 19 A general method for heterocycle formation through Rh-catalyzed C–H amination

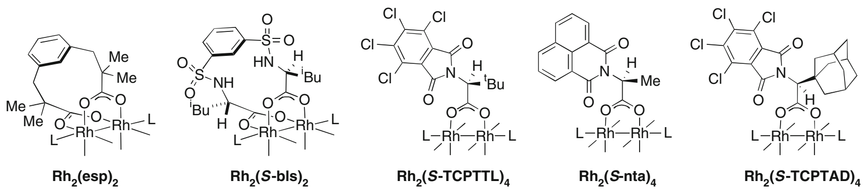

Fig. 20 A collection of dirhodium tetracarboxylate catalysts for C–H amination

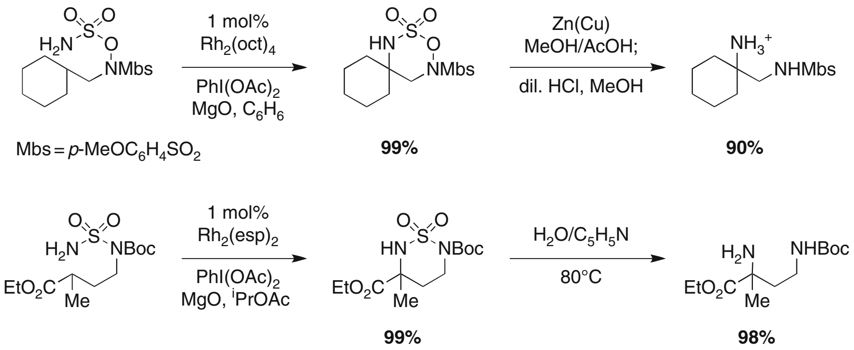

Fig. 21 Selective methods for 1,2- and 1,3-diamine synthesis

The application of intramolecular C–H amination technologies for the synthesis of 1,2- and 1,3-diamine derivatives has seen recent progress with the discovery of two novel methods (Fig. 21). Sulfamate esters derived from *N*-alkyl hydroxyl amines are easily prepared using either Mitsunobu or Pd-catalyzed π-allyl chemistries [101, 102]. Oxidative cyclization of these substrates affords the unusual [1,2,3,6]-oxathiadiazinane-2,2-dioxide products in good yields and, like other sulfonyl substrates, with a strong bias for six-membered ring formation. Subsequent reduction of the N–O bond in this heterocycle with Zn(Cu) couple reveals a differentially protected 1,2-diamine. A related process utilizes *N*-Boc-*N*-alkylsulfamide starting materials, which perform with exceptional efficiency as substrates for Rh-catalyzed C–H amination [103]. The products from these reactions can be ring-opened under mild conditions (aqueous pyridine, 80 °C) to furnish mono-Boc protected 1,3-diamines.

While the majority of Rh-catalyzed C–H amination processes employ hypervalent iodine oxidants and sulfonamide derivatives, Lebel and coworkers have demonstrated that *N*-tosyloxycarbamates will engage with catalytic $Rh_2(O_2CCPh_3)_4$ and K_2CO_3 to afford products of intramolecular C–H insertion (Fig. 22) [104, 5, 105]. Similar to Du Bois' earlier work involving oxidative cyclization with 1° carbamates [94], the *N*-tosyloxy derivatives display a strong bias for oxazolidinone formation. Selectivity trends and other mechanistic data support a reaction pathway involving a Rh-nitrene oxidant. Intermolecular amination of simple benzylic substrates

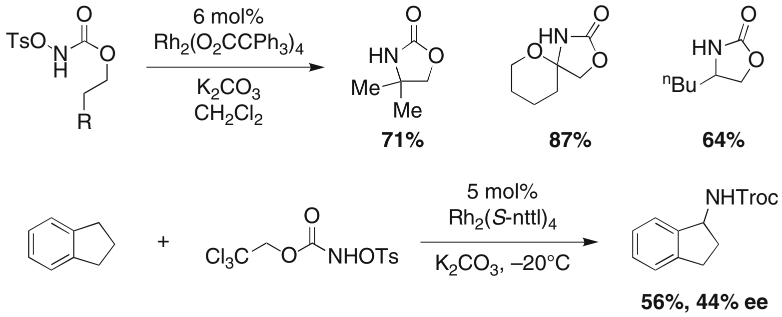

Fig. 22 Tosyloxycarbamate derivatives as nitrene precursors

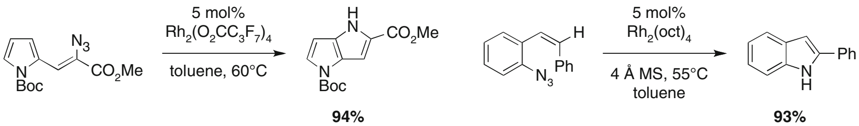

Fig. 23 Intramolecular aromatic C–H amination with vinyl azide starting materials

(5–15 equiv.) can be conducted in an analogous fashion using *N*-Troc-*N*-tosyloxycarbamate (Fig. 22) [106]. Notably, the 1° C–H bonds of toluene and mesitylene are oxidized under these conditions, a reaction that is not observed with other Rh-catalyzed amination protocols (i.e., $Cl_3CCH_2OSO_2NH_2$, $PhI(OAc)_2$, $Rh_2(esp)_2$). The lack of fragmentation of a fast radical clock and a small, negative ρ value of -0.47 are both suggestive of a nitrenoid pathway for C–H oxidation. The measured KIE of 5, however, is larger than that observed for other Rh-catalyzed processes (a KIE of 3.5 was recorded by Müller for intermolecular amination of adamantane using $Rh_2(OAc)_4$ and PhI=NNs) [23].

Demonstrations of C–H amination with $ArSO_2N_3$ and Ru, Co, and Cu catalysts notwithstanding, productive reactions with these types of nitrene precursors and the analogous carbonylazides and dirhodium systems have not been described. Recent reports by Driver and coworkers, however, have identified vinylazides as useful substrates for intramolecular sp^2 C–H functionalization (Fig. 23) [107–110]. Interestingly, this amination method is the only one of which we are aware in which the most productive reactions are achieved using the most electron deficient perfluorocarboxylate-derived Rh complexes. Such catalysts have never before proven effective in combination with hypervalent iodine reagents. In addition, this vinylazide process is the only known Rh-mediated reaction that enables sp^2 C–H amination. The putative mechanism involves electrophilic aromatic substitution by a Rh-nitrene intermediate, a theory supported in part by a kinetic isotope effect of 1.0 and the observation of products derived from concerted 1,2-migrations. A similar C–H amination reaction involving vinylazide substrates and $[Ir(cod)Cl]_2$ was recently disclosed by these same authors [111].

A growing interest in asymmetric methods for C–H amination has spurred the development of a number of different chiral dirhodium complexes, which have proven valuable for both intra- and intermolecular oxidation reactions. Tetracarboxylate complexes derived from unnatural α-amino acids, in particular *tert*-leucine and adamantylglycine, function in combination with sulfonamides or sulfamates and $PhI(OAc)_2$ to give aryl-substituted sultams and [1,2,3]-oxathiazinane-2,2-dioxide products, respectively, with up to 66% ee [112–114]. These same types of catalysts have also proven effective for intermolecular C–H amination reactions (see below). The performance of such complexes is rather remarkable given the rapid rate of ligand exchange that appears to take place for bridging carboxylate ligands in simple complexes such as $Rh_2(OAc)_4$. In fact, studies by the Du Bois lab using threonine-derived chiral Rh catalysts have established that % ee decreases as a function of product conversion [99, 115]. Presumably the rate of exchange for different amino acid-based ligands is dependent on the substituent groups and on the overall topology of the complex. Perhaps the favored bowl-like tertiary structure, previously described for a dirhodium catalyst derived from *tert*-leucine, is somehow responsible for mitigating these deleterious ligand exchange processes [116]. Interestingly, chiral strapped dicarboxylate complexes have proven largely unsuccessful for mediating enantioselective amination reactions.

A chiral lactamate complex has proven effective for enantioselective, intramolecular amination of benzylic-derived substrates (Fig. 24) [117]. Reactions with this catalyst afford substituted aryl-oxathiazinane products with enantiomeric ratios that are among the highest recorded for C–H amination. With the exception of perfluorinated acetamides, the catalyst, Rh_2(*S*-nap)$_4$, is, to date, the only known carboxamidate system that functions under the oxidizing conditions of the C–H amination reaction. Other complexes fashioned from strongly donating carboxamidate ligands (e.g., $Rh_2(acam)_4$, $Rh_2(cap)_4$) undergo rapid one-electron oxidation to an inactive dirhodium(II/III) form. With Rh_2(*S*-nap)$_4$, turnover numbers in excess of 40 can be achieved prior to catalyst arrest. The higher oxidation potential for this complex relative to other carboxamidate Rh dimers is believed to be an important design criterion, which allows amination to compete favorably with the catalyst deactivation process. Another unique feature of the Rh_2(*S*-nap)$_4$ system is its propensity to favor intramolecular allylic C–H amination over aziridination, a property generally not observed for Rh tetracarboxylate catalysts [68].

The invention of selective and efficient protocols for intermolecular C–H amination remains one of the great challenges in methods development. With the

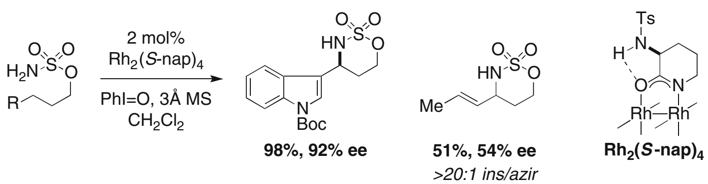

Fig. 24 Enantioselective C–H amination catalyzed by the chiral lactamate complex, Rh_2(S-nap)$_4$

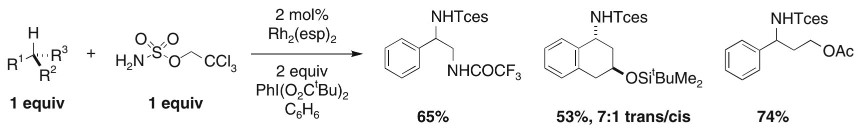

Fig. 25 Efficient intermolecular C–H amination with limiting amounts of substrate

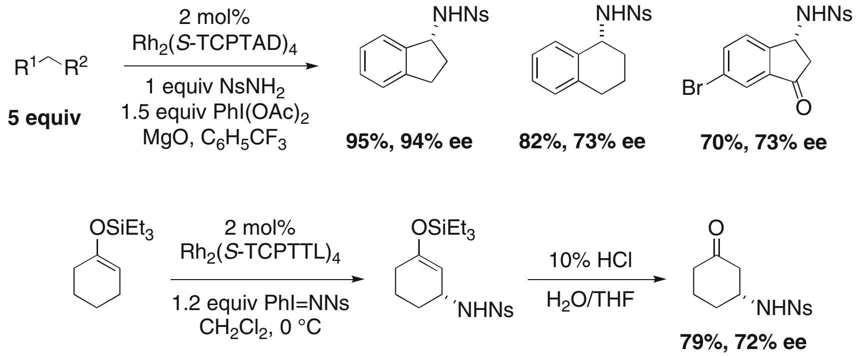

Fig. 26 Asymmetric intermolecular C–H amination with chiral Rh tetracarboxylate catalysts

advent of $Rh_2(esp)_2$, it is now possible to conduct C–H insertion reactions using limiting amounts of substrate (Fig. 25) [118]. The reaction employs Cl_3CCH_2O-SO_2NH_2 as the nitrogen source and $PhI(O_2C^tBu)_2$ as the oxidant, the latter being added as a solution dropwise over a 2- to 3-h period. Optimal reaction performance in terms of both product yield and chemoselectivity occurs with benzylic derivatives. In several cases, attendant functional groups such as silyl ethers, esters, and amides have been shown to be compatible with the reaction conditions.

Analogous intermolecular C–H amination reactions using chiral Rh tetracarboxylate complexes have been described, although these processes generally rely on the use of excess hydrocarbon substrate (Fig. 26) [115, 119, 120]. Oxidation of indan and tetralin are among the most effective starting materials for these reactions; in the best cases reported to date, aminated products are obtained using a catalyst derived from adamantylglycine, Rh_2(*S*-TCPTAD)$_4$ with enantiomeric excesses exceeding 70% [121].

The most impressive examples of asymmetric intermolecular C–H amination have been established through the collaborative work of Müller, Dodd, and Dauban [122, 123]. Using 3 mol% of Rh_2(*S*-nta)$_4$, a catalyst derived from *tert*-leucine, and an optically active sulfonimidamide as the nitrogen source, amination of limiting amounts of prochiral benzylic substrates can be achieved with yields >90% and with outstanding diastereocontrol (up to 99:1 dr) (Fig. 27). Remarkably, the insertion reaction performs at subambient temperature (−35°C), suggesting that the sulfonimidamide and the corresponding nitrenoid species have properties that are

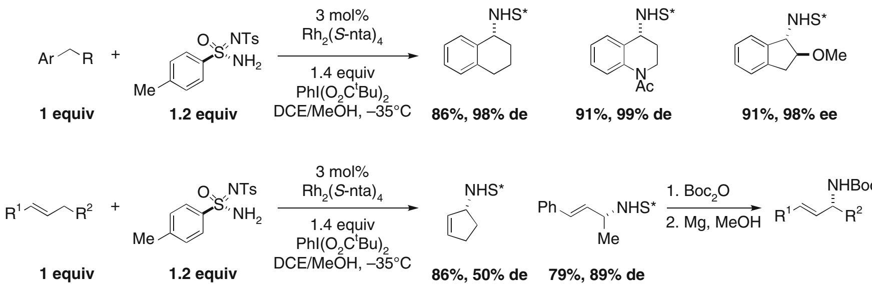

Fig. 27 An efficient and highly diastereoselective method for intermolecular C–H amination

distinct from other amide reagents. Under the same conditions, $Cl_3CCH_2OSO_2NH_2$ gives no reaction [120]. The uniqueness of the sulfonimidamide nitrogen source warrants further examination of this reagent with other dirhodium catalyst systems. Finally, we note that products obtained via diastereoselective C–H amination may be easily converted to the corresponding amines by simple reductive removal of the sulfonyl group (e.g., Li naphthalenide, Mg with sonication).

A feature common to all intermolecular amination reactions is the superior performance of benzylic substrates as compared to all other types of hydrocarbon derivatives, including those having a 3° C–H bond. This fact is somewhat surprising, in light of the high intrinsic reactivity for intramolecular amination of 3° C–H centers by electrophilic Rh-nitrene oxidants (as demonstrated by intramolecular competition experiments) [68]. Efforts to improve the overall efficiency of intermolecular benzylic amination and to expand the substrate scope to include 3° C–H derivatives have motivated studies to understand the factors responsible for catalyst arrest in these types of processes. It should be noted that studies to reveal the nature of the active oxidant in these intermolecular reactions give evidence for a concerted asynchronous C–H insertion mechanism, analogous in all aspects to the intramolecular chemistry. Most importantly, intermolecular insertion into stereogenic 3° C–H bonds occurs with absolute stereochemical retention of configuration, a defining characteristic of the Rh-catalyzed amination process that has potentially powerful implications for fine chemical synthesis.

Analysis of product mixtures from inefficient intermolecular amination reactions conducted with $Cl_3CCH_2OSO_2NH_2$ and $PhI(O_2C^tBu)_2$ as the stoichiometric oxidant has revealed the presence of 2,2-dimethyl-*N*-(2′,2′,2′-trichloroethoxysulfonyl)aziridine. Apparently, a pathway for decarboxylation of the pivalic acid byproduct is available, which affords isobutylene and subsequently its aziridination product. Color changes to the reaction solution also give indication for a one-electron oxidation of the emerald green $Rh_2(esp)_2$ dimer to a bright red, mixed-valent Rh(II/III) form. The stability of the $[Rh_2(esp)_2]^+$ species under the reaction conditions is considerably greater than that of other simple tetracarboxylate complexes (e.g., $Rh_2(O_2C^tBu)_4$), and is likely a critical factor contributing to the differential performance of the esp complex vis-à-vis other catalysts for amination reactions [124]. Electrochemical and spectroscopic measurements confirm the generation of the one-electron oxidized Rh(II/III) species and support a mechanism in which the pivalic acid functions as a reducing agent to restore the dirhodium complex to its favored (II/II) oxidation state. Presumably, one-electron oxidation of pivalic acid is followed by rapid CO_2 extrusion and subsequent formation of isobutylene, thus explaining the unusual aziridine product. It is possible to capitalize on these findings to improve overall reaction performance. Accordingly, PhI $(O_2CCMe_2Ph)_2$ has been used in place of the $PhI(O_2C^tBu)_2$, and has been shown to give a considerable boost to catalyst turnover numbers due to the more favorable and kinetically faster reducing ability of $PhMe_2CCO_2H$ relative to $^tBuCO_2H$. This discovery has led to the formulation of a new protocol for intermolecular amination, which no longer requires slow addition of reagents and which gives products of 3° C–H oxidation in yields up to 68% using limiting substrate amounts [125]. These findings together with the aforementioned work of Müller, Dodd, and Dauban should elevate the standing of the intermolecular amination chemistry as a general tool for chemical synthesis. The application of such methods for the single-step modification of complex structures of pharmacological or medicinal import may hold significant value.

10 Palladium Catalysis

In contrast to other transition metals, only a small number of reports describe formation of nitrenoid intermediates with Pd-based catalysts [126, 127]. Crystallographic analysis of the products obtained from treatment of a dimeric Pd(I) complex, $[Pd_2(dppm)_2Cl_2]$, with $ArSO_2N_3$ (Ar = 2,4,6-triisopropylbenzene) has revealed two intriguing structures (Fig. 28) [128]. In both cases, the dppm ligands (dppm = bis-(diphenylphosphanyl)methane) bridge two Pd(I) centers. The $ArSO_2N_3$ also links the Pd nuclei through a μ,η^1-bridge. The second structure

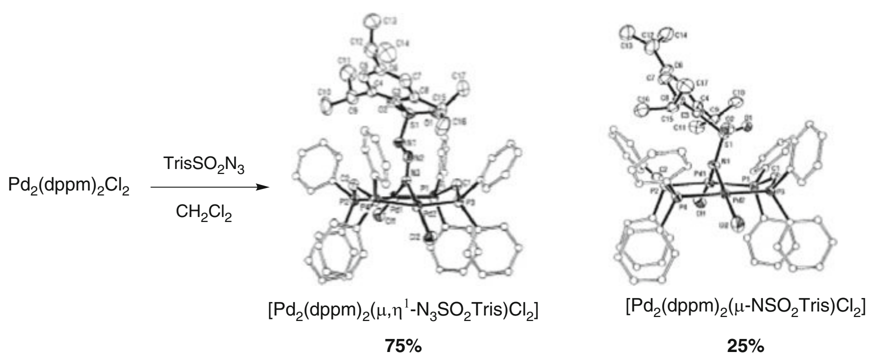

Fig. 28 Crystallographic characterization of an unusual dimeric Pd(I) nitrene complex

is best described as a dimeric Pd(I) nitrene complex. The stability of this adduct is rather remarkable given the electron deficient nature of the μ-ArSO_2N ligand and is ascribed, in part, to the shielding effect of the sterically bulky isopropyl groups of the arenesulfonyl moiety. Other, less substituted, arenesulfonylazides will react with [Pd_2(dppm)$_2$$Cl_2$] and CO to form isocyanates [129–132]. No examples of aziridination or C–H insertion with this reagent combination have been documented. It is intriguing, however, to note the similarity of the dipalladium μ-ArSO_2N complex with that of the dimeric Cu(I) complex described by Warren (see Section 3 Copper Catalysis). Perhaps the bridging nature of the dppm ligands is responsible for restricting dimer dissociation to form a reactive mononuclear Pd-nitrene species.

C–H Amination by way of an organo-metal intermediate offers an alternative reaction mode from that of metal-nitrene chemistry through which to form C–N bonds. In this regard, Pd catalysis has proven decidedly unique. Sanford and coworkers have demonstrated that cyclopalladated species can be oxidized with PhI(OAc)$_2$ under conditions that enable catalytic turnover to afford acetoxylated products [133]. Che and coworkers have exploited this type of reaction manifold and have described an oxime-directed amination process that uses Pd(OAc)$_2$ as a catalyst, acyl- or sulfonamide nitrogen sources, and peroxysulfate ($K_2S_2O_8$) as the terminal oxidant (Fig. 29) [134]. This process is quite efficient for aryl C–H bond amination and, with aliphatic substrates, is selective for 1° methyl functionalization. Mechanistic studies by Sanford on an isolable cyclopalladated adduct suggest the possible intermediacy of a Pd(IV) imido species, which reductively eliminates to regenerate the Pd(II) catalyst and to afford the aminated product [135]. Other mechanisms involving dimeric Pd(III) intermediates or the direct insertion of PhI=NTs into the Pd–C bond cannot be discounted [136, 137].

Electrophilic, nitrenoid-mediated amination processes are often challenged to discriminate between alkene aziridination and C–H insertion in substrates possessing some degree of unsaturation. Alkene aziridination is typically favored owing to the greater nucleophilicity of an ordinary π bond vis-à-vis a σ-C–H center. White and coworkers have found an elegant solution to this difficult problem of chemoselectivity with the advent of a selective Pd(II) catalyst for allylic C–H functionalization [138, 139]. In these examples, allylic C–H activation of terminal alkenes

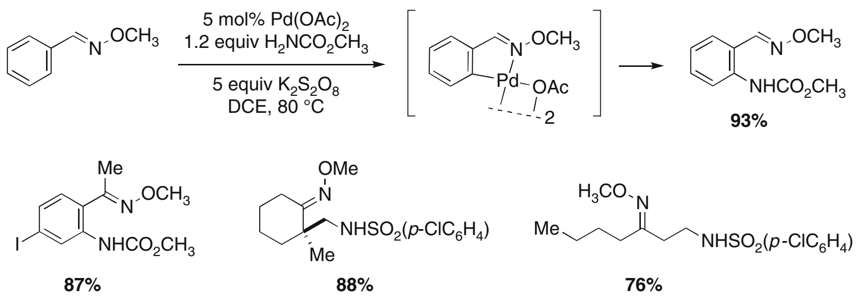

Fig. 29 Oxime-directed Pd(II)-catalyzed C–H amination reactions

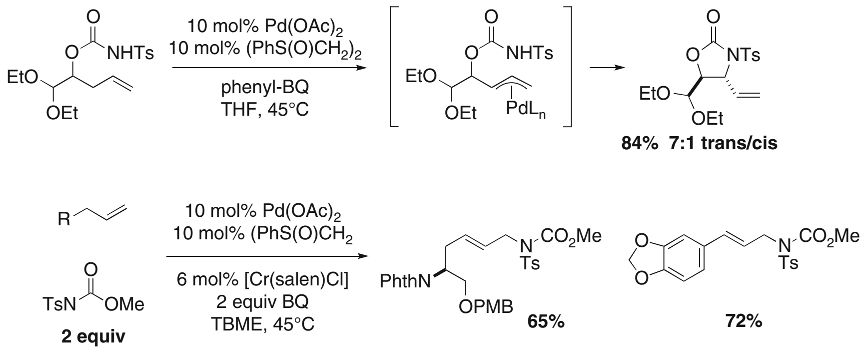

Fig. 30 Highly chemoselective methods for intra- and intermolecular allylic C–H oxidation

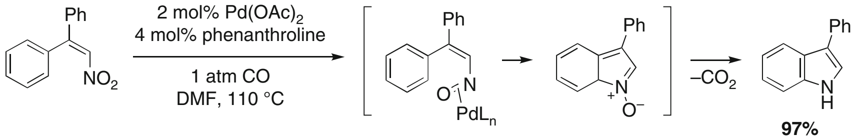

Fig. 31 Pd-catalyzed indole synthesis with nitroalkene substrates

occurs under the action of a chelating bis-sulfoxide Pd(OAc)$_2$ complex. The intermediate Pd^{2+} π-allyl species is then intercepted by a nucleophilic acylsulfonamide nitrogen source (Fig. 30) [140, 141]. Catalysis is made possible by reoxidation of the transient Pd(0) species with benzoquinone (BQ). This process can beconducted in both an intramolecular format to generate vinyl-substituted oxazolidinones or as an intermolecular reaction to yield linear allylic amine derivatives. In the former case, diastereocontrol of the disubstituted oxazolidinone products is generally quite high (up to 18:1). A recent report by Liu mimics White's intermolecular reaction by replacing the bis-sulfoxide ligand with maleic anhydride and by employing O_2 as the terminal oxidant in place of benzoquinone [142]. These methods are nicely complementary to the chemistry of metallonitrenes.

Investigations by Dong have highlighted a unique process for 3-arylindole formation that involves a [Pd(phenanthroline)(OAc)$_2$] catalyst, 1 atm CO, and a nitroalkene substrate (Fig. 31) [143]. This procedure has been described as a reductive activation of the nitro moiety and a formal C–H amination of an arene C–H bond. The authors speculate, however, that the mechanism for indole synthesis is likely an electrocyclization event, which takes place by way of a Pd-bound nitrosoalkene. The application of nitrosoalkenes (and, for that matter, vinylnitrenes or -nitrenoids) for amination reactions has enjoyed little prior art. Thus, the Dong process offers an important tactic for generating such species from a convenient class of starting material. Finding reagents alternative to the traditional iminoiodinanes, haloamines, and azides that react with metal catalysts to furnish electrophilic nitrogen species is a potentially promising avenue for future research.

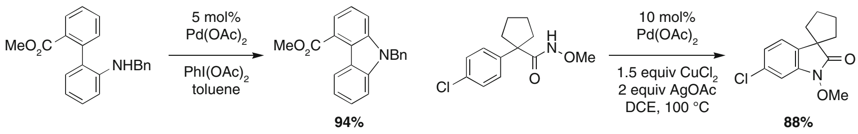

Fig. 32 Heterocycle synthesis via directed C–H palladation

Among the earliest reports of aromatic C–H amination under Pd catalysis are those detailed by Buchwald and coworkers for carbazole assembly (Fig. 32) [144–146]. Such heterocycles can be made efficiently from *N*-protected *o*-aminobiphenyl starting materials in a process that is thought to involve either a Heck- or Wacker-like addition of a Pd(II)-amidate across a pendant aromatic ring. Catalysis is achieved with $Cu(OAc)_2$ or DMSO/O_2 serving as an effective reoxidant of the Pd(0) intermediate. A related method for *N*-alkylcarbazole synthesis has been outlined by Gaunt, which operates at ambient temperatures through a putative Pd(II/IV) cycle [147]. Two-electron oxidation of an aryl-Pd(II) species by $PhI(OAc)_2$ is thought to trigger a subsequent reductive elimination event to form product. By way of an analogous cyclometalation pathway, supported Pt catalysts operating in aqueous solvent have also been shown to promote carbazole synthesis, albeit at temperatures exceeding 200 °C [148]. Contemporaneous with these other works, studies by Yu and coworkers have highlighted a clever synthesis of oxindole derivatives from *N*-methoxyamide starting materials. This process is believed to occur through a Pd(II/IV) cycle with $CuCl_2$ functioning as the terminal oxidant (Fig. 32) [149]. A more recent disclosure by this same lab has revealed a cyclopalladation/oxidation strategy for preparing substituted indolines and tetrahydroquinolines [150].

11 Miscellaneous

The vast majority of C–H amination protocols utilize redox active transition metals as catalysts. Recent discoveries have highlighted, however, the performance of redox inactive metal complexes and metal free conditions for effecting C–H to C–N bond conversion.

Nicholas and coworkers have described a $ZnBr_2$-catalyzed amination process that employs either chloramine-T or PhI=NTs as the nitrogen source [151]. Modest product yields are recorded with the hydrocarbon substrate as the limiting reagent. Although the substrate scope appears restricted to rather uncomplicated arylalkanes, the very observation of sulfonamide product is rather striking. Remarkably, other salts such as $ZnCl_2$, ZnI_2, $CdCl_2$, and $HgCl_2$, as well as catalytic HBr are reported to promote benzylic C–H amination with varying degrees of efficiency. A finding that the reaction is inhibited by *p*-methoxyphenol has led the authors to propose a radical-based mechanism, though one might expect PhI=NTs to react directly with such an inhibitor. The possibility of a Lewis acid-activated pathway in which the electrophilicity of the iminoiodinane is increased by coordination with $ZnBr_2$ is intriguing. In this context, it bears mentioning that Evans has also observed Lewis acid catalysis (e.g., $Mg(OTf)_2$, $Zn(OTf)_2$) in the aziridination of alkenes with this same hypervalent iodine reagent [25].

Reactive borylnitrene species, generated via photolysis of the corresponding borylazide, have been shown to effect C–H amination of simple alkane and cycloalkane substrates [152]. These reactions are conducted in neat substrate with light of 254 nm wavelength. The authors suggest that the high product yields (>75%) are indicative of a singlet nitrene C–H insertion process, which is fast relative to the rate of intersystem crossing to the triple ground state of the borylnitrene.

The combination of an aryl- or alkylsulfonamide, 3 equiv. $PhI(OAc)_2$ and substoichiometric I_2 is able to promote C–H amination of simple hydrocarbons in the absence of any metal catalyst [120]. These reactions are best performed neat (10-fold excess of substrate relative to RSO_2NH_2) at 50°C and appear to operate with reasonable selectivity to give benzylic sulfonamide products. Over-oxidation to the sulfonylimine is noted in some cases. A proposed reaction mechanism posits the intermediacy of a sulfonamidyl radical, formed from the *N*-iodosulfonamide. This pathway parallels in many ways the mechanism invoked for the Hofmann-Löffler-Freytag process.

12 Conclusions

General and effective methods for the selective amination of C–H bonds have evolved in parallel with the discovery of new catalyst complexes that promote such transformations. Looking forward, the many formidable challenges presented by such a problem in reaction development should continue to serve as a wellspring for creative invention. Next-generation catalyst designs would profit from a unified understanding of the elements held in common by the disparate metal complexes of Cu, Ag, Ru, Mn, Fe, Co, and Rh that mediate nitrenoid-type C–H insertion events. Detailed knowledge of the pathways that underlie catalyst arrest will also benefit such pursuits. Undoubtedly, the reach of C–H amination technologies will continue to expand with the advent of new, higher performance catalyst systems. However, the truly innovative designs will also prove capable of exercising some degree of control over the site of oxidation in a given substrate; in this regard, it seems there is no shortage of inspiration from Nature.

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