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Palladium(II)-Catalyzed C–H Activation/C–C Cross-Coupling Reactions: Versatility and Practicality

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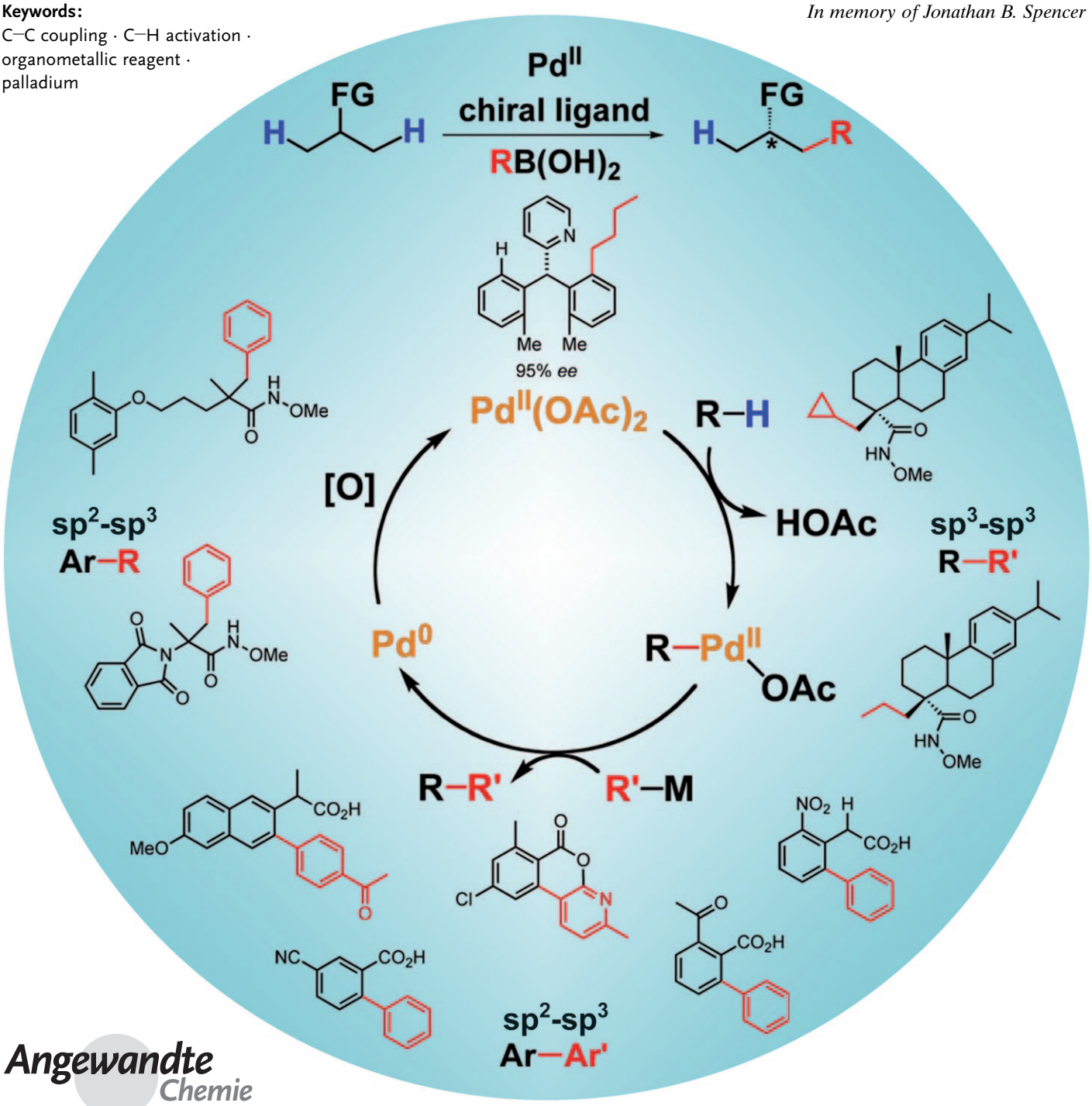
Keywords:
C–C coupling · C–H activation · organometallic reagent · palladium

In memory of Jonathan B. Spencer

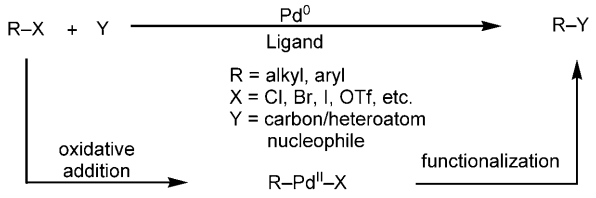


In the past decade, palladium-catalyzed C–H activation/C–C bond-forming reactions have emerged as promising new catalytic transformations; however, development in this field is still at an early stage compared to the state of the art in cross-coupling reactions using aryl and alkyl halides. This Review begins with a brief introduction of four extensively investigated modes of catalysis for forming C–C bonds from C–H bonds: Pd^{II}/Pd^{0}, Pd^{II}/Pd^{IV}, $Pd^{0}/Pd^{II}/Pd^{IV}$, and Pd^{0}/Pd^{II} catalysis. A more detailed discussion is then directed towards the recent development of palladium(II)-catalyzed coupling of C–H bonds with organometallic reagents through a Pd^{II}/Pd^{0} catalytic cycle. Despite the progress made to date, improving the versatility and practicality of this new reaction remains a tremendous challenge.

From the Contents

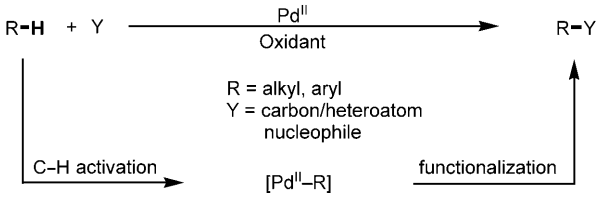
1. Introduction

Among the myriad of important transition metal catalyzed synthetic transformations, palladium-catalyzed Heck coupling, cross-coupling (Kumada, Stille, Negishi, Suzuki–Miyaura, Hiyama), Tsuji–Trost allylation, and Buchwald–Hartwig amination reactions using organohalides and other surrogates are particularly valuable tools in synthetic chemistry.[1,2] A common and critical feature of these catalytic processes is the formation of aryl or alkyl palladium(II) intermediates which can be subsequently functionalized to form carbon–carbon and carbon–heteroatom bonds (Scheme 1).



Scheme 1. Palladium(0)-catalyzed reactions of aryl(alkyl) halides. Tf = trifluoromethanesulfonyl.

The versatility of these C–C and C–heteroatom bond-forming processes ultimately stems from the reactivity of the corresponding aryl and alkyl palladium(II) species. Thus the development of the most straightforward and economical sequences to prepare such intermediates would certainly improve these reactions. In particular there exists, virtually, unlimited opportunities for using unactivated carbon–hydrogen (C–H) bonds,[3] which can readily be cleaved by palladium(II) catalysts, as reaction partners (Scheme 2). From the viewpoint of synthetic analysis, such reactions offer not only complementary reactivity, but also represent novel synthetic disconnections in a given synthetic plan when the regioselective introduction of halides into molecules is not straightforward.



Scheme 2. Palladium(II)-catalyzed functionalization of C–H bonds.

Cyclopalladation of C(aryl)–H bond containing molecules has been extensively documented[4–6] and has been found to proceed along a variety of pathways (Scheme 3).[7] These studies were a major part of the impetus for us to launch our efforts in developing catalytic transformations which are based on a sequence of C–H activation and subsequent cross-coupling reactions with organometallic reagents. In hindsight, the fact that a strongly coordinating nitrogen-containing directing group is typically needed to promote facile cyclopalladation severely limits the substrate scope; nevertheless, such a class of substrates has served as a pivotal platform for our discovery and optimization of this unprecedented mode of catalysis.

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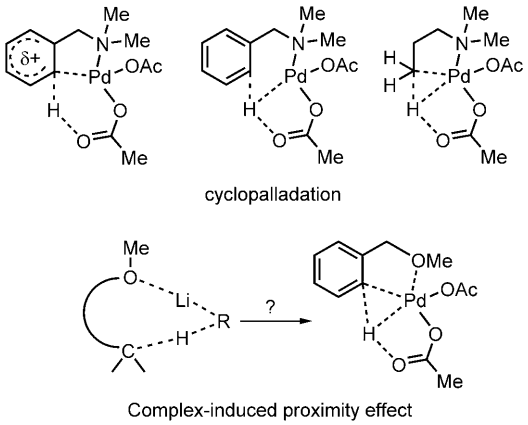

Scheme 3. C–H activation through cyclopalladation or the CIPE.

We envisioned ultimately expanding the scope of these reactions to include more synthetically useful oxygen-containing directing groups (e.g. carboxylic acids, ketones, esters, alcohols, etc.). We were encouraged by studies in which less coordinative oxy-functional groups, such as Boc and OMe, were used to direct lithiation through the complex-induced proximity effect (CIPE), a term originally coined by Beak and Snieckus (Scheme 3).[8] The distinction between the CIPE and directed cyclopalladation is that the thermodynamic stability of the resulting intermediates in the case of the CIPE is generally much lower. As such, these complexes are, in general, not isolable, even though they are incredibly intriguing from a synthetic perspective. Indeed a pioneering example of *ortho* C–H functionalization of acetophenone by a ruthenium(0) catalyst has been reported.[9] Inspired by these precedents, we focused on developing new conditions and reagents that would promote C–H insertion driven not only by traditional cyclopalladation, but also by the CIPE.

After a brief survey of various approaches in palladium-catalyzed C–H activation/C–C bond formation, this Review describes the early adventures and recent developments in palladium-catalyzed coupling of C–H bonds with organometallic reagents to form $C(sp^2)$–$C(sp^2)$, $C(sp^2)$–$C(sp^3)$, and $C(sp^3)$–$C(sp^3)$ bonds. The versatility and practicality of these types of reactions in their current forms are evaluated with respect to the efficiency of catalysis, substrate scope, and operational costs. Key problems and potential solutions in this field are also discussed.

2. Olefination of $C(sp^2)$–H Bonds: Pd^{II}/Pd^0 Catalysis

The past five decades have witnessed noticeable progress in the development of palladium-catalyzed C–H activation/C–C bond-forming processes. Research in this field has largely focused on the discovery of new modes of catalysis and the expansion of substrate scope. One of the earliest examples concerns C–H activation of benzene by $Pd(OAc)_2$ and subsequent carbopalladation and β-hydride elimination to afford olefinated arenes (Scheme 4).[10]

This early report by Moritani and Fujiwara demonstrated the impressive reactivity of palladium(II) in activating aryl C–H bonds; however, two major drawbacks largely hampered

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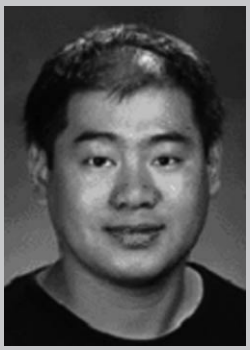
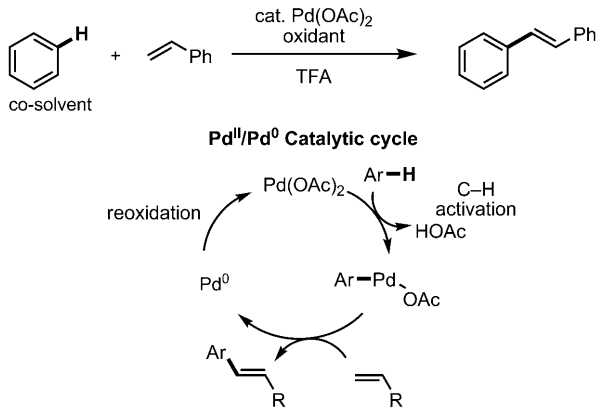


Dong-Hui Wang completed his BSc at Lanzhou University in 2000 then carried out research at the Shanghai Institute of Organic Chemistry under Prof. Zhaoguo Zhang studying palladium-catalyzed cross-coupling reactions of organozinc reagents with carboxylic anhydrides. In 2004, he began graduate studies under Prof. Jin-Quan Yu. He earned his MSc from Brandeis University before relocating to The Scripps Research Institute, where he is currently pursuing his PhD, studying C–H activation/C–C coupling reactions using carboxylic acid directing groups.

Keary Mark Engle received his BSc with Highest Honors from the University of Michigan, where he worked with Prof. Adam Matzger studying self-assembled monolayers. Following graduation, he was awarded a J. William Fulbright Fellowship to study under Prof. Manfred Reetz at the Max-Planck-Institute for Coal Research (Germany) and a scholarship from the European Union IDECAT program to study under Prof. Jan Bäckvall at Stockholm University (Sweden). In 2008, he moved to The Scripps Research Institute to begin graduate studies under the supervision of Prof. Jin-Quan Yu as a NSF and NDSEG predoctoral fellow.

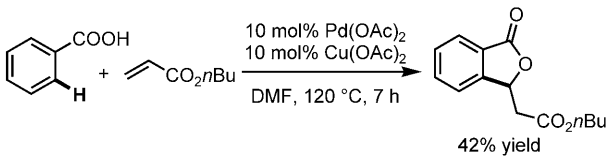
Jin-Quan Yu received his BSc in Chemistry from East China Normal University and his MSc from the Guangzhou Institute of Chemistry. In 2000, he obtained his PhD at the University of Cambridge with Prof. J. B. Spencer. After serving as a junior research fellow at Cambridge, he joined the laboratory of Prof. E. J. Corey at Harvard University as a postdoctoral fellow. He then began his independent career at Cambridge (2003–2004), before moving to Brandeis University (2004–2007), and finally to The Scripps Research Institute, where he is currently an Associate Professor of Chemistry. His group studies palladium catalyzed C–H activation.



Scheme 4. Palladium(II)-catalyzed olefination of arenes: Pd^{II}/Pd^{0} catalysis (Moritani and Fujiwara, **1967**).[10]

the application of this catalytic reaction.[10] First, a large excess of the arene was required (often used as the solvent). Second, there was a lack of control of the regioselectivity when monosubstituted benzene was used as the substrate. Addressing this latter shortcoming, an early attempt of using benzoic acid to achieve *ortho* selectivity represented an encouraging step forward (Scheme 5).[12]

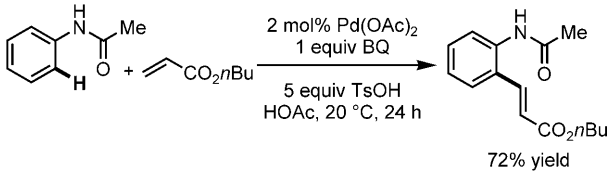
In response to this regioselectivity problem, an instrumental development using a directing group was reported by de Vries and co-workers (Scheme 6).[13] The use of an anilide substrate afforded high *ortho* selectivity and allowed the



Scheme 5. Directed *ortho* olefination of benzoic acid (Miura et al., **1998**).[12]

arene to be used as the limiting reagent. In this reaction, benzoquinone is believed to be crucial for the C–C bond-forming step, and the use of TsOH was also found to be beneficial.

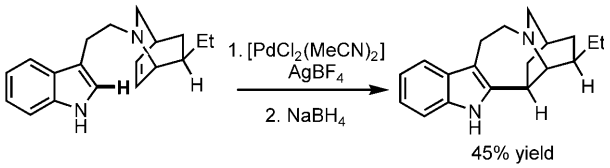
Notably, the mechanism of the C–H cleavage step for this electron-rich arene may be distinct from that of the reaction with benzene. Among the three known reaction mechanisms,[7] the cleavage of the C–H bonds in the anilide substrate is likely to proceed by electrophilic palladation of the electron-rich arene and subsequent loss of the *ortho* proton ($S_{Ar}E$). This mechanism is consistent with the relatively electron-rich nature of this substrate and is additionally supported by kinetic data collected for a series of substituted anilides.[13,14]



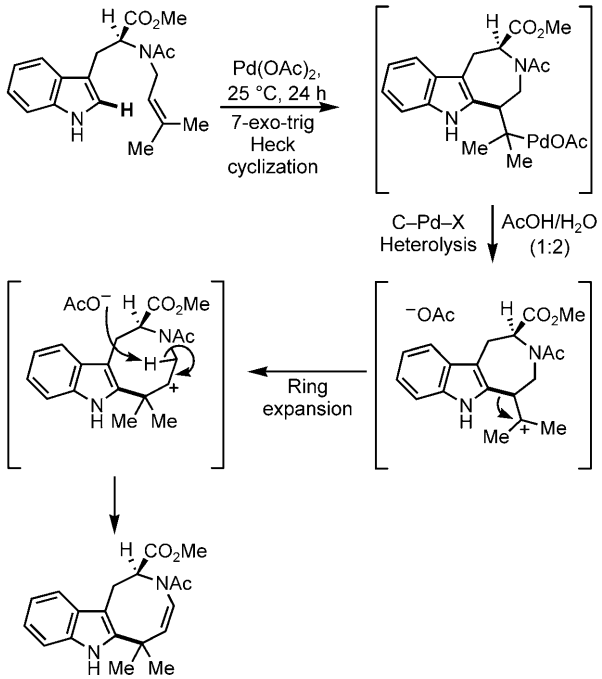
Scheme 6. *ortho*-Selective olefination of arenes (de Vries et al., **2002**).[13] BQ = 1,4-benzoquinone, Ts = *para*-toluenesulfonyl.

Importantly, this study together with Fujiwara's early work has spurred recent studies on C–H activation/Heck coupling reactions using arenes possessing either high electron density or directing groups.[15] Notably, two elegant synthetic applications using an indole olefination have further inspired efforts towards improving this reaction (Scheme 7 and Scheme 8).[16] In the synthesis of ibogamine the carbon–palladium bond was reduced by $NaBH_4$ to give the desired product. An unexpected ring expansion of the alkylpalladium intermediate served extraordinarily well in the synthesis of (+)-austamide.

Although catalytic olefination of indoles using $Pd(OAc)_2$, and Ag^{I} and Cu^{II} salts as the reoxidants was reported as early as 1983 by Itahara et al. (Scheme 9),[17] several recent studies have greatly advanced this chemistry. Notably, the work of

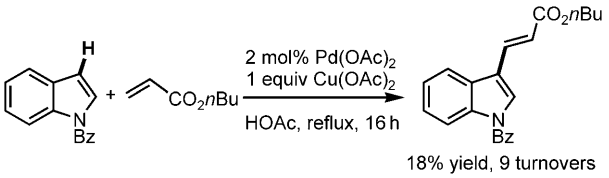


Scheme 7. Synthesis of ibogamine (Trost et al., **1978**).[16a]



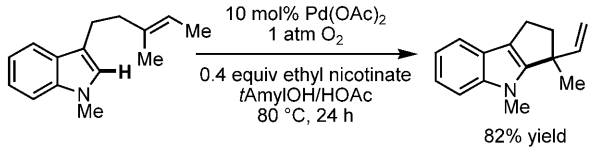
Scheme 8. Synthesis of (+)-austamide (Baran and Corey, **2002**).[16b]

Ferreira and Stoltz, in which molecular oxygen is used as the reoxidant in the intramolecular olefination of indoles, was a significant development (Scheme 10).[18] In contrast, by using allylic acetates as the olefin partner, Ma and Yu cleverly avoided the need for an oxidant (Scheme 11).[19] In this latter



Scheme 9. Catalytic olefination of indoles by electrophilic palladation (Itahara et al., **1983**).[17b] Bz = benzoyl.

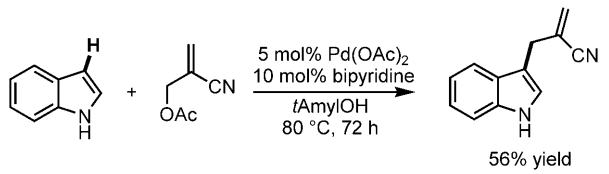
study, the authors put forth a mechanism whereby palladium(II)-catalyzed C–H activation takes place as the first step, followed by intermolecular carbopalladation of the allylic



Scheme 10. Intramolecular olefination of indoles using O_2 as the oxidant (Ferreira and Stoltz, **2003**).[18] *t*AmylOH = 2-methylbutan-2-ol.

acetate. β-acetate elimination then regenerates the active catalyst, $Pd(OAc)_2$, without formal reduction to palladium(0) during the catalytic cycle.

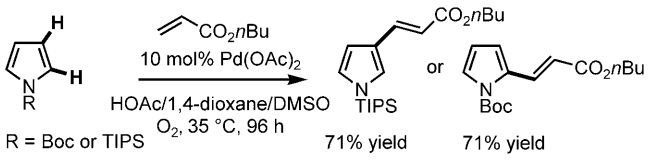
Achieving regioselective functionalization at either the 2- or 3-position of pyrroles through the use of different protecting groups is also synthetically useful (Scheme 12).[20] In this case, the agreement of the observed regioselectivity



Scheme 11. Oxidant-free olefination of indoles (Ma and Yu, **2004**).[19]

with that of the electrophilic bromination reaction of protected pyrroles[21] lends valuable evidence to the hypothesis that an electrophilic palladation process is involved in these olefination reactions.

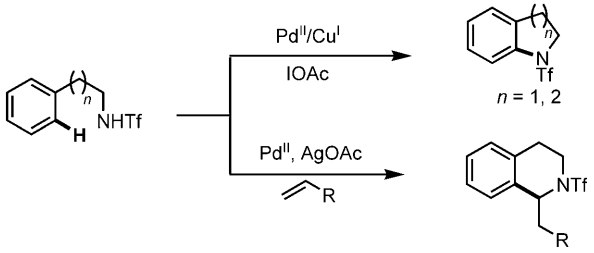
To expand the synthetic utility of directed C–H activation/olefination, a concise and general route for the preparation of heterocyclic compounds from trifluoromethanesulfonyl-protected arylalkylamines has recently been developed using



Scheme 12. Regioselective olefination of pyrroles (Gaunt et al., **2006**).[20b] Boc = *tert*-butyloxycarbonyl, TIPS = triisopropylsilyl, DMSO = dimethylsulfoxide.

highly acidic triflamide groups to direct C–H activation (Scheme 13).[22]

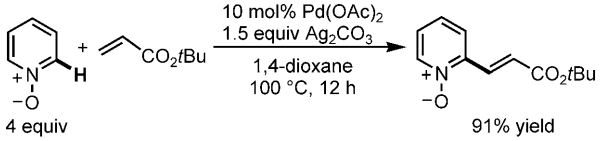
A recent report by Chang and co-workers describes a useful olefination of pyridine *N*-oxides (Scheme 14).[23] The reactivity of palladium catalysts with pyridine *N*-oxides was



Scheme 13. Heterocycle synthesis by the olefination of arenes (Yu et al., **2008**).[22]

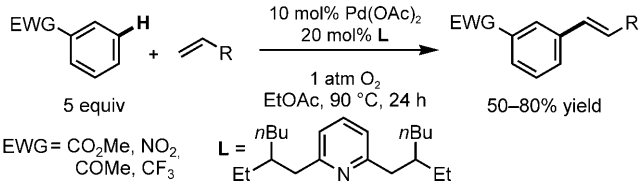
also documented previously by Fagnou and co-workers in arylation reactions.[24]

Finally, efforts in establishing a *meta* C–H activation/olefination process have yielded unprecedented reactivity (Scheme 15).[25] The use of a rationally designed mutually



Scheme 14. Olefination of pyridine *N*-oxides (Chang et al., **2008**).[23]

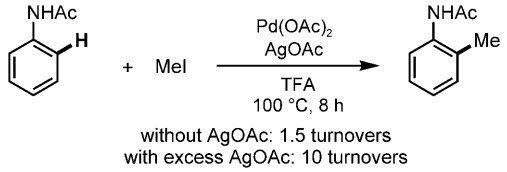
repulsive ligand was crucial for C–H activation of electron-deficient arenes, which were previously found to be unreactive. Owing to the electron-poor nature of the substrates and the observed distribution of products (roughly 4:1 *meta*/*para* isomers), an electrophilic palladation mechanism[15] in this case is unlikely. Rather, a combination of C–H acidity and steric hinderance seem to govern the reactivity of the different sites, suggesting a concerted mechanism whereby acetate serves as an internal base (Scheme 3). This novel ligand also allowed 1 atm O_2 to be used as the sole oxidant, which represents a potentially important step forward in developing highly practical C–H functionalization reactions.



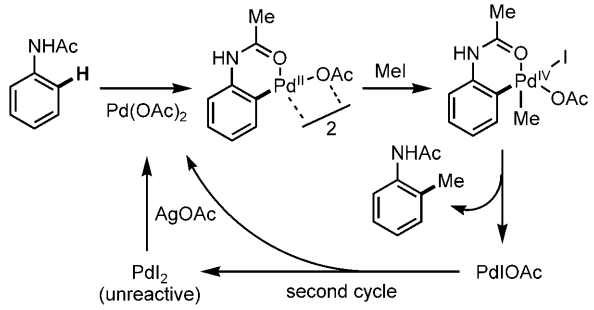
Scheme 15. *meta*-Selective olefination of electronic-deficient arenes (Yu et al., **2009**).[25] EWG = electron-withdrawing group.

3. Arylation of $C(sp^2)$–H and $C(sp^3)$–H Bonds: Pd^{II}/Pd^{IV} Catalysis

Owing to their versatility, Pd^0/Pd^{II} catalysis and Pd^{II}/Pd^0 catalysis have both been extensively exploited for the development of catalytic reactions. In contrast, redox chemistry involving palladium(IV) is studied far less often, despite the early proposal of the existence of this oxidation state[26,27] and the unambiguous supporting evidence obtained subsequently.[28] Tremont and Rhaman reported the first intriguing methylation of *ortho* C–H bonds in anilide (Scheme 16). In this work, the reactivity of the cyclopalladated intermediate with MeI was established, and a plausible Pd^{II}/Pd^{IV} mechanism was presented (Scheme 17).[29]



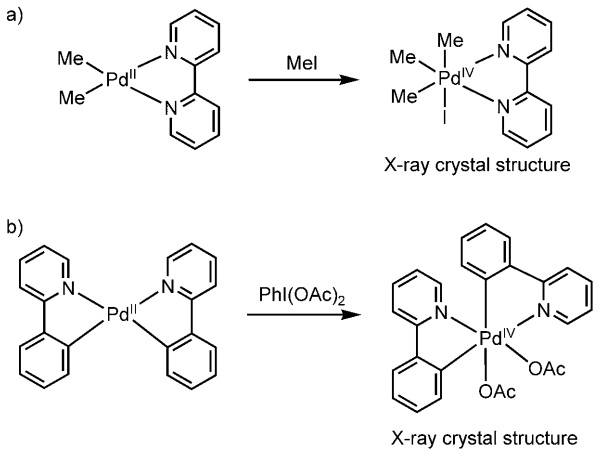
Scheme 16. *ortho* Methylation of anilides (Tremont and Rahman, **1984**).[29]



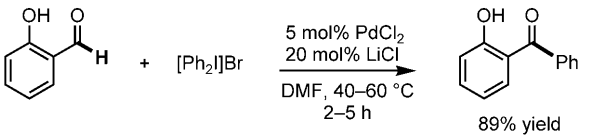
Scheme 17. Proposed Pd^{II}/Pd^{IV} catalytic cycle.

The proposed oxidation of palladium(II) into palladium(IV) by MeI was conclusively supported by X-ray crystallography, the first crystal structure being obtained by Canty and co-workers (Scheme 18).[28] Recently, additional corroborative physical evidence has been obtained by Sanford and co-workers through X-ray crystallographic studies of palladium(IV) intermediates generated in their acetoxylation reaction.[30] Furthermore, the isolation of quantitative amounts of PdI_2 after the completion of the asymmetric catalytic iodination reaction developed in our laboratory,[31] and an earlier example of azo-directed iodination[32] are also important pieces of evidence in support of Pd^{II}/Pd^{IV} redox chemistry.

This early alkylation reaction proceeding by a Pd^{II}/Pd^{IV} cycle was additionally exploited to develop catalytic arylation reactions. In 2000, an intriguing report from Xia and Chen described a palladium-catalyzed arylation of aldehydic C–H bonds using a hypervalent iodine reagent, $[Ph_2I]Br$ (Scheme 19).[33] In seeking to explain the observed reactivity, the authors invoked a Pd^0/Pd^{II} catalytic cycle; however, given the strength of $[Ph_2I]Br$ as an oxidant, a Pd^{II}/Pd^{IV} catalytic



Scheme 18. X-ray crystallographic structures of Pd^{IV} complexes. a) Canty et al., **1986**;[28a] b) Sanford et al., **2005**.[30c]

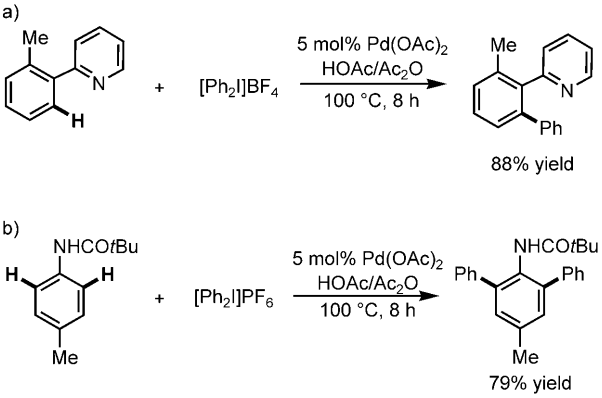


Scheme 19. Palladium-catalyzed arylation of aldehydic C–H bonds (Xia and Chen, **2000**).[33] DMF = *N*,*N*′-dimethyl formamide.

cycle cannot conclusively be ruled out, particularly when considering more recent literature on C–H activation involving hypervalent iodine reagents.

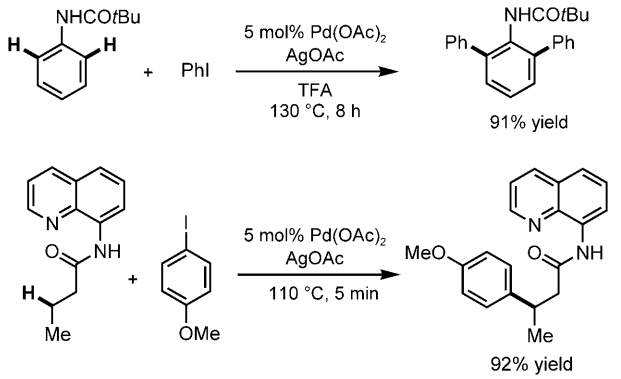
Sanford and co-workers and Daugulis et al. independently developed a more general approach using directed C–H activation and $[Ph_2I]PF_6$ and $[Ph_2I]BF_4$ for arylation of C–H bonds (Scheme 20).[34] It is believed that this reaction proceeds through a Pd^{II}/Pd^{IV} mechanism, whereby $[Ph_2I]PF_6$ and $[Ph_2I]BF_4$ play a similar role to that of MeI in the earlier studies mentioned above. Building on this work, Sanford and co-workers have also successfully extended this chemistry to the arylation of indoles at room temperature.[35]

Especially noteworthy is the discovery by Daugulis and Zaitsev that the arylation of C–H bonds can be performed using cheap and practical ArI under neat conditions or using



Scheme 20. Arylation of C–H bonds by Pd^{II}/Pd^{IV} catalysis. a) Sanford et al., **2005**;[34a] b) Daugulis and Zaitsev, **2005**.[34b]

CF_3COOH (TFA) as the solvent (Scheme 21).[34b] This protocol represents the most efficient arylation reaction proceeding through Pd^{II}/Pd^{IV} catalysis to date. These conditions have also been applied to the arylation of $C(sp^3)$–H bonds by linking a pyridyl group to carboxylic acids through an amide bond (Scheme 21).[36]



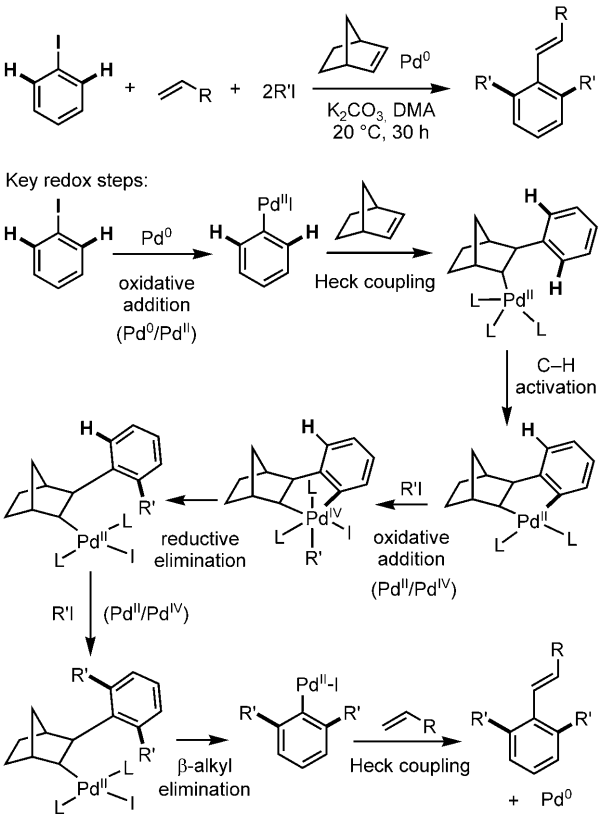
Scheme 21. Arylation of C–H bonds using ArI (Daugulis et al., **2005**).[36a] TFA = trifluoroacetic acid.

4. *Sequential* ortho *Alkylation and Olefination of Aryl Iodides: $Pd^0/Pd^{II}/Pd^{IV}$ Catalysis*

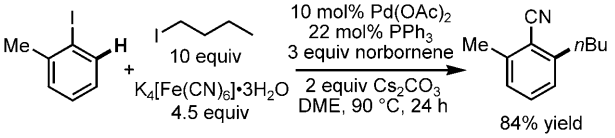
A highly complex yet efficient catalytic reaction involving Pd^0, Pd^{II}, and Pd^{IV} in the reaction pathway was discovered by Catellani et al. in 1997 after her early studies on Pd^{IV} complexes in 1988 (Scheme 22).[37] The key feature of this reaction is the dialkylation of both *ortho* C–H bonds of the aryl iodide substrate. The final Heck coupling of the aryl–Pd^{II} intermediate with an olefin serves as a critical step for closing the catalytic cycle. The advantage of this catalytic cycle is that no external oxidant is needed. As a demonstration of the flexibility and power of palladium redox chemistry, this complex and elegant catalytic cycle is unparalleled.

Despite the many merits of this transformation, the lack of simplicity (because of the formation of multiple bonds, some of which may not be desired in a synthetic application) constitutes a noticeable limitation. Efforts from Lautens and co-workers and others to overcome this drawback and make this transformation more amenable for synthesis have yielded substantial improvements.[38] For example, the interception of aryl–palladium intermediates by a cyanation event is a significant departure from the early alkylation/olefination sequence, affording valuable versatility for synthetic applications (Scheme 23).[39] The use of an alkyl halide containing a tethered acetylene has also led to route to tetrasubstituted helical alkenes (Scheme 24).[40]

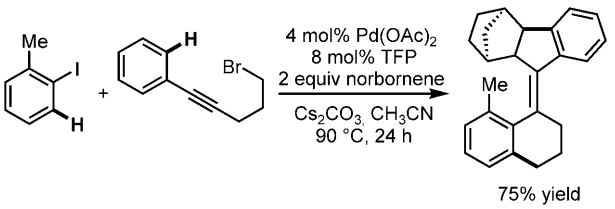
Interestingly, an analogous form of "cascade catalysis" for arylation without using norbornene as the mediator, was also achieved by Carretero and co-workers (Scheme 25).[41]



Scheme 22. *ortho* Alkylation of C–H bonds by $Pd^0/Pd^{II}/Pd^{IV}$ catalysis (Catellani et al., **1997**).[37c] DMA = *N*,*N*-dimethylacetamide.



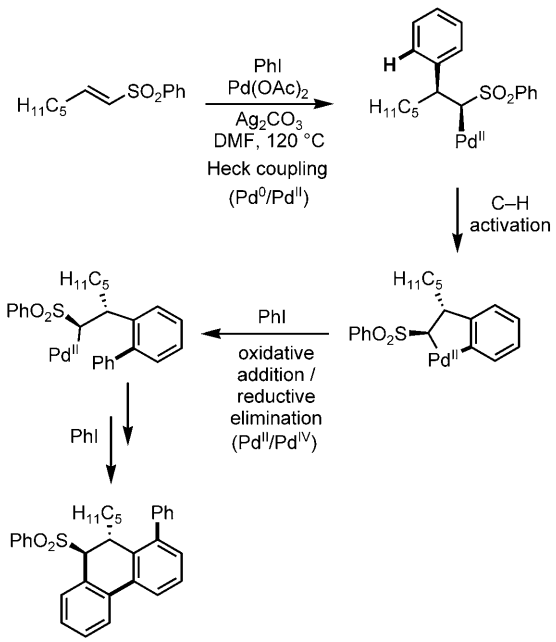
Scheme 23. *ortho* Alkylation and cyanation of arenes (Lautens et al., **2007**).[39] DME = dimethoxyethane.



Scheme 24. Synthesis of tetrasubstituted helical alkenes (Lautens et al., **2009**).[40] TFP = tri-(2-furyl)phosphine.

5. *Arylation and Alkylation of $C(sp^2)$–H and $C(sp^3)$–H Bonds: Pd^0/Pd^{II} Catalysis*

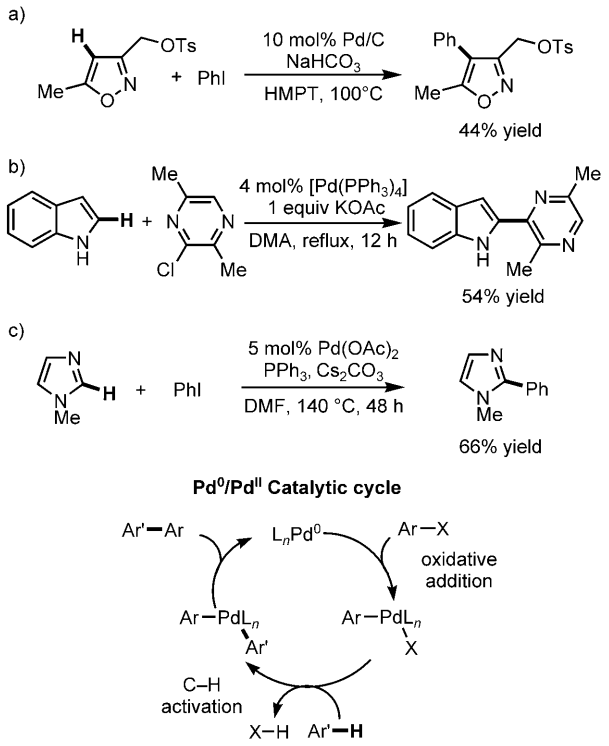
Oxidative addition of aryl halides to palladium(0) is one of the most important modes of reactivity in modern palladium chemistry because it serves as the first step in the Heck coupling, cross-coupling, and Buchwald–Hartwig amination reactions. This reactivity has also been drawn upon extensively in the development of C–H activation/arylation reactions in the past three decades. The initial proof of



Scheme 25. Early arylation of C–H bonds involving $Pd^0/Pd^{II}/Pd^{IV}$ catalysis (Carretero et al., **2001**).[41]

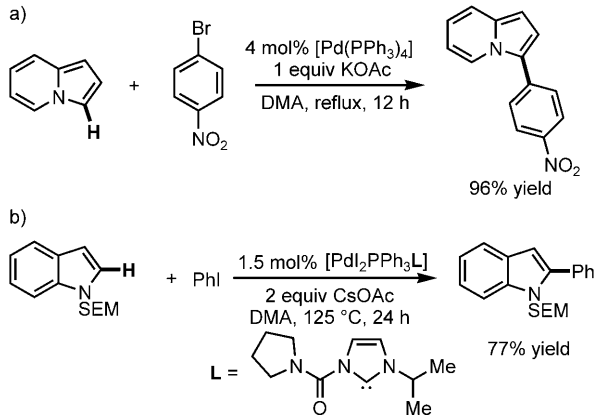
concept was established using electron-rich (hence, more reactive) heterocycles as substrates (Scheme 26).[42]

Among the numerous examples showcasing the arylation of various heterocycles,[43] the subtle effects of the choice of the catalyst, aryl halide, and N-protecting groups on both



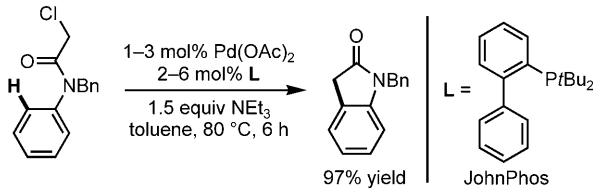
Scheme 26. Arylation of electron-rich heterocycles by Pd^0/Pd^{II} catalysis. a) Sakai et al., **1982**;[42a] b) Ohta and Akita, **1982**;[42b] c) Miura et al., **1998**.[42c] HMPT = hexamethylphosphoric triamide.

reactivity and selectivity have been observed.[44] Understanding these trends is important for synthetic applications (Scheme 27).



Scheme 27. Regioselective arylation of heterocycles. a) Gevorgyan et al., **2004**;[44a] b) Sames et al., **2006**.[44b] SEM = 2-(trimethylsilyl)ethoxymethyl.

The arylation and alkylation of non-heterocyclic arenes was initially limited to intramolecular reactions.[45] An elegant and useful development of this reaction is the synthesis of oxindoles initiated by the oxidative addition of alkyl halides to palladium(0) (Scheme 28).[46]

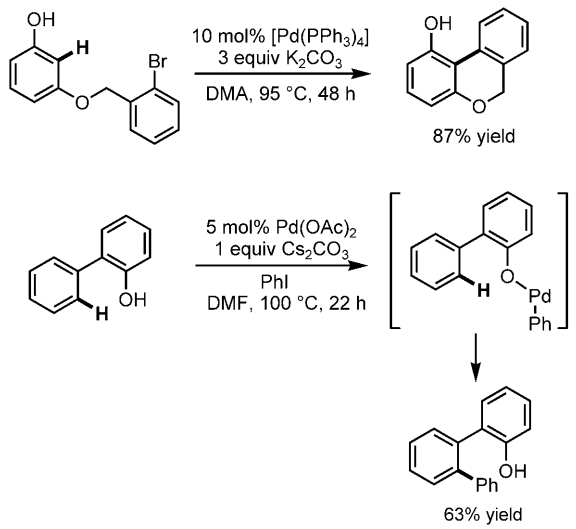


Scheme 28. Alkylation of arenes by alkyl halides (Buchwald and Hennessy, **2003**).[46] Bn = benzyl.

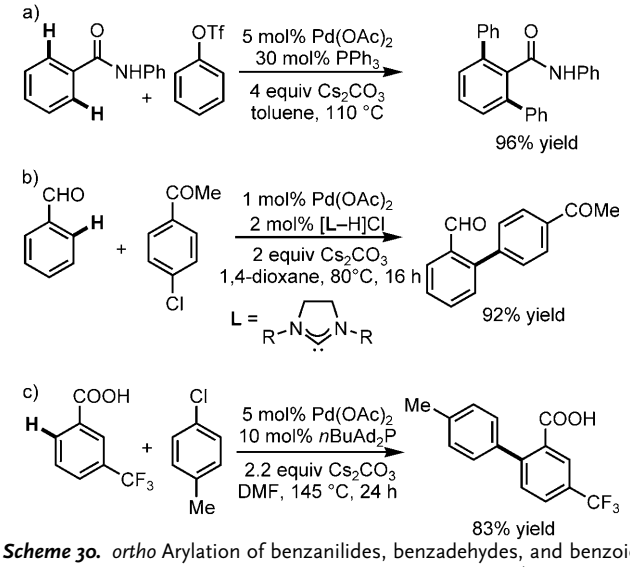
An important early observation was made by Rawal and co-workers was that phenolic OH groups promote *ortho* arylation from an ether tethered aryl bromide (Scheme 29).[47] This reaction appears to be the first example of the arylation of non-heterocyclic arenes since the discovery by Sakai and co-workers, and Akita and Ohta in 1982.[42a,b] Within the same year, intermolecular arylation of 2-phenylphenol was demonstrated.[48] Together, these two results constitute a significant contribution towards the development of intermolecular arylation reactions with non-heterocyclic arenes using Pd^0/Pd^{II} catalysis.

Impressive *ortho* coupling of broadly useful substrates, including benzanilides, benzaldehydes, and benzoic acids, has since been reported (Scheme 30).[49]

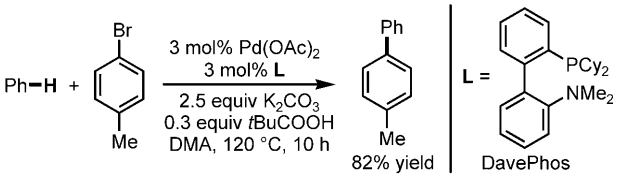
In exploiting the reactivity of palladium(II) with excess benzene,[10] a major advance was made by adding pivalic acid to the reaction system, allowing coupling of benzene with aryl bromides (Scheme 31).[7i] However, the long-standing problems associated with nondirected arene C–H activation (see



Scheme 29. Development of intermolecular arylation reactions with arenes. a) Rawal et al., **1997**;[47] b) Miura et al., **1997**.[48]



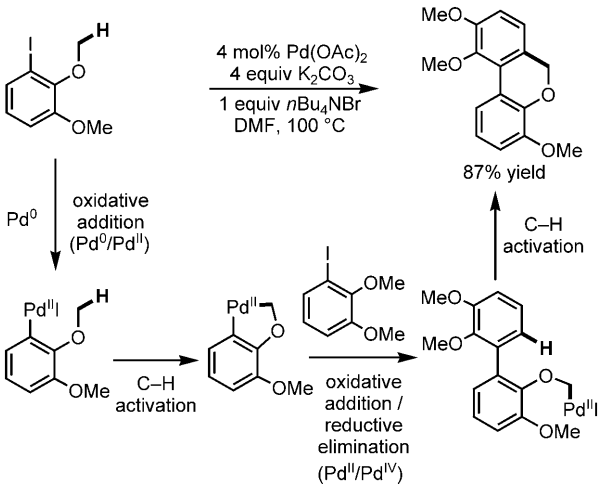
Scheme 30. *ortho* Arylation of benzanilides, benzadehydes, and benzoic acids. a) Miura et al., **2000**;[49a] b) Çetinkaya et al., **2005**;[49b] c) Daugulis et al., **2007**.[49c] Ad = adamantyl.



Scheme 31. Arylation of benzene with aryl bromides (Fagnou and Lafrance, **2006**).[7i] Cy = cyclohexyl.

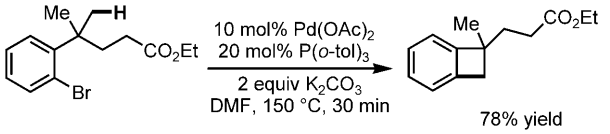
Section 2) still persist in this case: the arene is used as a co-solvent, and there is a lack of regioselectivity with mono-substituted arenes.

Finally, research towards the intramolecular arylation of $C(sp^3)$–H bonds has also progressed during the last fifteen years, albeit with far fewer examples. The first example reported by Dyker impressively encompasses both Pd^0/Pd^{II} and Pd^{II}/Pd^{IV} redox chemistry (Scheme 32).[50]



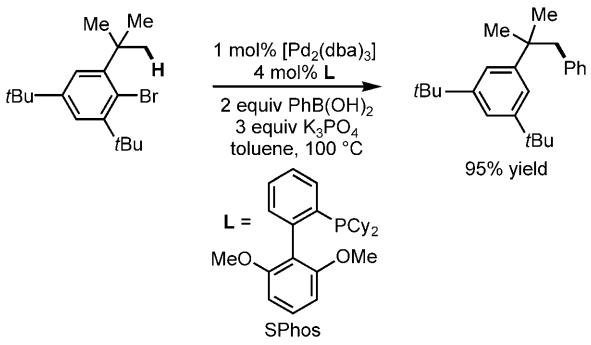
Scheme 32. Intramolecular Arylation of $C(sp^3)$–H bonds (Dyker, **1992**).[50]

An intriguing and useful carbocyclization reaction was developed by Baudoin and co-workers in which this redox chemistry was used to give a strained benzocyclobutene (Scheme 33). This chemistry has also recently been applied to the synthesis of complex natural products by the same group.[51]



Scheme 33. Carbocyclization through arylation of C–H bonds (Baudoin et al., **2003**).[51]

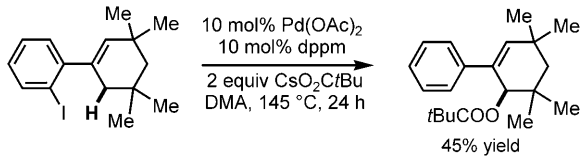
In another case, this Pd^0/Pd^{II} chemistry was beautifully combined with a Suzuki–Miyaura coupling reaction to perform the arylation of $C(sp^3)$–H bonds with an external phenylboronic acids (Scheme 34).[52] In fact, this finding



Scheme 34. Arylation of $C(sp^3)$–H bonds with external $ArB(OH)_2$ (Buchwald et al., **2005**).[52] dba = *trans*,*trans*-dibenzylideneacetone.

inspired our own recent studies concerning the direct coupling of C–H bonds with organoboron reagents, the main subject of this review (see Section 6).

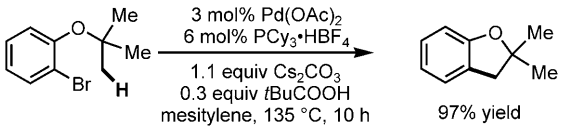
In an insightful mechanistic study of a related process, intramolecular C(sp^3)–H bonds were pivalated in the presence of CsO_2CtBu (Scheme 35).[53] The use of a bulky



Scheme 35. Reaction involving the migration of an aryl-appended palladium center to an allylic carbon center (Larock et al., **2005**).[53] dppm = 1,2-bis(diphenylphosphino)methane.

carboxylate group such as pivalate was believed to be beneficial for the reaction. This observation supports a "through space" migration of palladium from an aryl to an allylic carbon atom. However, one could argue that the activation of the allylic C(sp^3)–H bond by the [ArPdI] species can not necessarily be ruled out in the absence of additional evidence.

Recently, this reactivity was elegantly utilized by Fagnou and co-workers to develop a general method for the preparation of dihydrobenzofurans (Scheme 36).[54] In this



Scheme 36. Synthesis of dihydrobenzofurans (Fagnou et al., **2007**).[54]

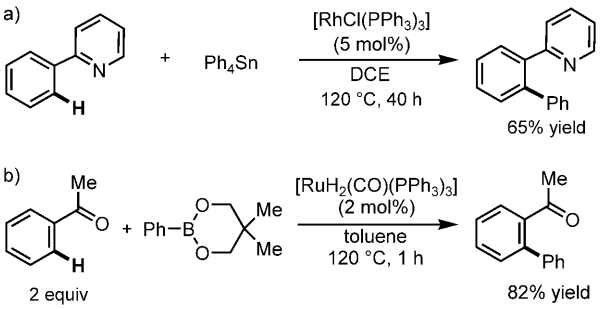
case, the presence of bulky carboxylate anions was found to dramatically improve the yield.

With respect to the simplicity and cost of the catalytic system, intermolecular arylation using Pd^0/ArI/ligand is the closest to conventional Heck coupling and cross-coupling reactions. A major challenge that still remains for this mode of catalysis is to address its relatively limited scope and versatility.

6. Arylation and Alkylation of C(sp^2)–H and C(sp^3)–H Bonds with Organometallic Reagents: Pd^{II}/Pd^0 Catalysis

6.1. Rhodium(I)- and Ruthenium(II)-Catalyzed Arylation of C(sp^2)–H Bonds

Although the development of C–H activation/C–C bond-forming reactions using other metals is beyond the scope of this Review,[55–57] we wish to illustrate two coupling reactions using organometallic reagents, which are catalyzed by rhodium(I) and ruthenium(II) catalysts, to highlight the significant advancements in the field (Scheme 37).[58]



Scheme 37. Rhodium(I)- and ruthenium(II)-catalyzed *ortho* C–H coupling. a) Oi et al., **1998**;[58a] b) Murai et al., **2003**.[58b] DCE = 1,2-dichloroethane.

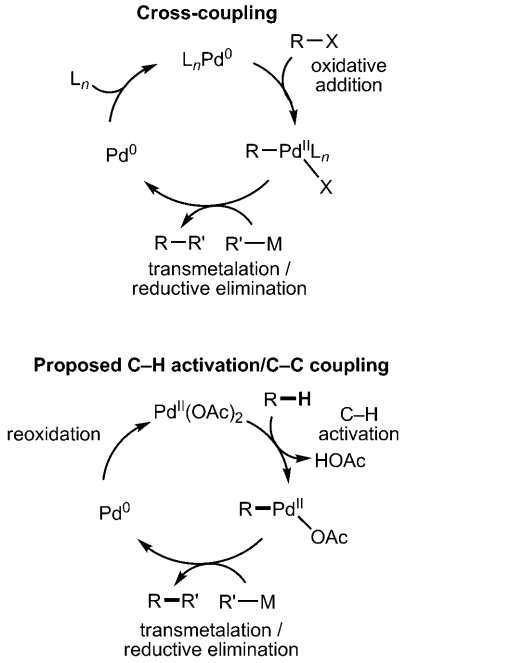
Conceptually, it is important to distinguish the palladium(II)-catalyzed C–H activation/C–C coupling reactions developed in our laboratory from this chemistry. In using palladium rather than other transition metals, we sought to build our chemistry upon the established reactivity of aryl-(alkyl) halides with palladium(0). In doing so, we endeavored to access the reactivity of known catalytic cycles of palladium from new entry points, rather than using the various redox manifolds of other transition metals.

6.2. Establishment of the First Catalytic Cycle for a Palladium(II)-Catalyzed C–H Activation/C–C Coupling Reaction

After our initial development of diastereoselective iodination and acetoxylation of C–H bonds of oxazoline substrates through Pd^{II}/Pd^{IV} catalysis,[31] we attempted to harness the reactivity of the oxazoline directing group to establish the proof of concept for an unprecedented coupling process proceeding through Pd^{II}/Pd^0 catalysis. The choice of organotin reagents as the coupling partners was inspired by the observation of a transmetalation process between a cyclopalladated complex and Me_3SnPh, reported by Louie and Hartwig.[59]

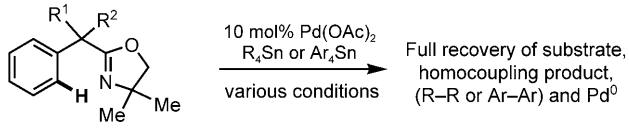
A brief comparison of the proposed C–H activation/C–C coupling process to the palladium(0)-catalyzed cross-coupling reactions[60] of aryl halide and alkyl halides was helpful in identifying potential problems in our early attempts (Scheme 38). The proposed catalytic cycle has two differences from that of the cross-coupling reactions: a) an oxidation system is required for the reoxidation of palladium(0); b) the ligands commonly used to promote the desired transmetalation and reductive elimination steps are not compatible with the C–H activation step.

The most challenging obstacle for establishing this new catalytic cycle, however, was the fact that the palladium(II) species tend to react preferentially with organometallic reagents rather than the more inert C–H bonds, resulting in rapid precipitation of palladium(0). Indeed, reactions of oxazoline substrates with $Pd(OAc)_2$ and organotin reagents under various conditions consistently resulted in full recovery



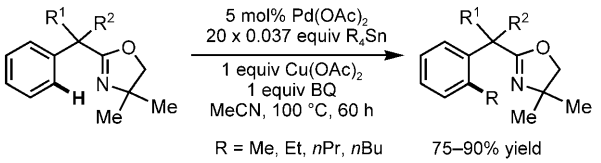
Scheme 38. Comparison of conventional cross-coupling with C–H activation/C–C coupling.

of palladium(0) precipitate, despite the fact that each individual step in the potential catalytic cycle had precedent (Scheme 39).



Scheme 39. Problematic homocoupling of organometallic reagents in the presence of palladium(II) (Chen and Yu, **2004–2006**).

The results of our exploratory studies were frustrating because no meaningful information could be extracted from our extensive screening experiments. To facilitate a progressive screening process, we added the organotin reagents batchwise, which we expected would slow down the reaction of $Pd(OAc)_2$ with the organotin reagents. This simple operational change was vital for us to begin to observe the desired coupling products and to establish a meaningful assay. The resulting data allowed a more rational screening to be performed; ultimately the combination of $Cu(OAc)_2$, benzoquinone, and CH_3CN gave the best results for this new coupling reaction (Scheme 40).[61]

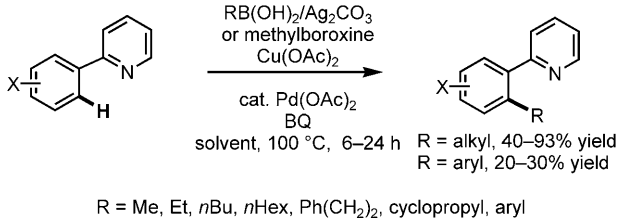


Scheme 40. C–H coupling with organotin reagents (Yu et al., **2006**).[61]

Although benzoquinone is a well-established oxidant for palladium(0) and a promoter for C–C bond formation in a wide range of palladium-catalyzed reactions,[62] our studies on the formation of cyclopalladated intermediates and their subsequent reaction with organotin reagents revealed an additional role for benzoquinone: promoting C–H activation. In particular, the previously reported use of benzoquinone to promote C–C bond formation[13] in an arene C–H activation/olefination reaction was most relevant to our study (Scheme 6).

6.3. Expanding the Scope of the Coupling Partner: Versatility

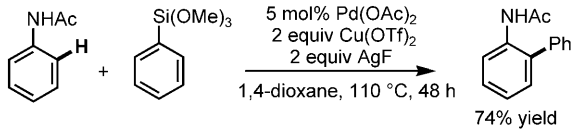
Having established the proof of concept, we moved forward to test if organoboronic acids, the most widely used coupling partners,[1] could be used for this reaction. As described in Scheme 34, the Pd^0/ArI initiated C–H coupling with phenyl boronic acid reported by Buchwald and co-workers was encouraging.[52] A single example of stoichiometric coupling of a cyclopalladated complex with vinyl boronic acid had also been previously reported by Sames and co-workers.[63] Our preliminary results showed that coupling of oxazoline substrates with organoboronic acids gave products in approximately 10% yield. By exploring other directing groups, we found that coupling of pyridine substrates with alkylboronic acids was successful (Scheme 41).[64]



Scheme 41. C–H coupling with organoboron reagents (Yu et al., **2006**).[64]

The use of silver(I) oxidants was critical for both transmetalation and catalytic turnover in this case. Additionally, we found that arylboronic acids could also be used in this reaction (20–30% yields). However, rather than optimizing this coupling protocol with 2-phenylpyridine, we sought applications with more synthetically applicable substrates and thus focused our efforts on developing this reaction using a carboxylic acid directing group (see Section 6.4).

The potential generality of palladium(II)-catalyzed C–H activation/C–C coupling with organometallic reagents has been further demonstrated by Shi and co-workers in the coupling of anilides with arylsilanes (Scheme 42).[65] These highly reactive anilide substrates can also be *ortho* coupled with arylboronic acids.[66] As discussed in Section 2, the early study by de Vries and co-workers[13] suggested that reaction of this anilide with $Pd(OAc)_2$ proceeds by electrophilic palladation.

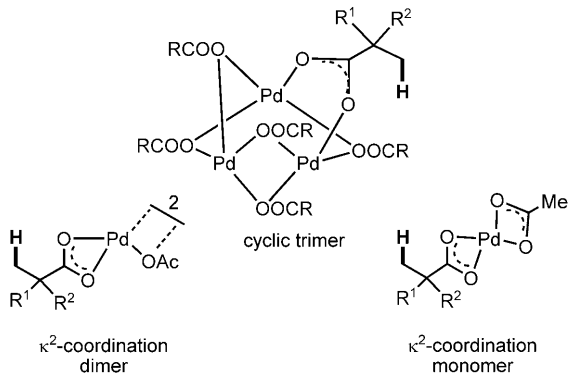


Scheme 42. C–H coupling with organosilane reagents (Shi et al., **2007**).[65]

6.4. Expanding the Substrate Scope: A Significant Challenge

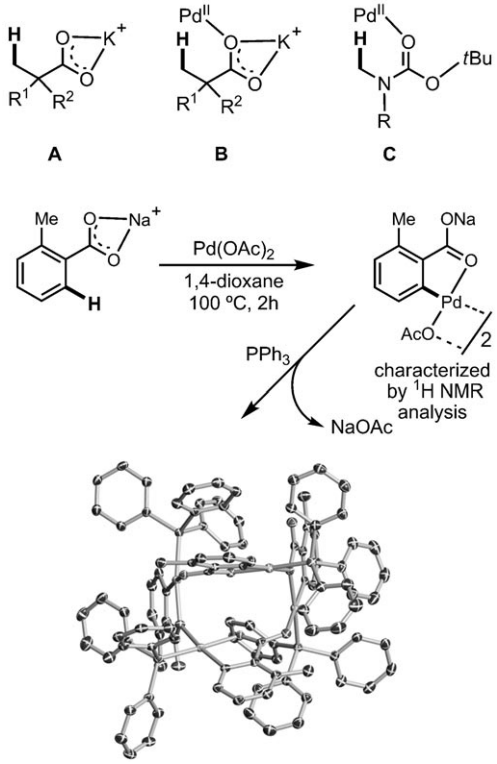
As discussed in Section 6.2, one of the major problems in these coupling reactions is the undesired reaction between the palladium(II) catalysts and the organometallic reagents. This side reaction becomes predominant if C–H activation of the substrates is not rapid. The aforementioned coupling reactions benefited greatly from the use of electron-rich aryl rings or from the presence of strongly coordinating groups to ensure rapid binding of the substrate with the palladium(II) catalysts. Typically, nitrogen-containing directing groups are used to aid coordination, however, the presence of such groups severely restricts the substrate scope, preventing potential broad synthetic applications. Therefore, expanding the scope to include simple substrates, such as carboxylic acids and alcohols, was a major hurdle to general applicability. Compared to the classical nitrogen atom directed cyclopalladation reactions, palladium(II) insertion into C–H bonds promoted by oxygen atom coordination to the palladium (through CIPE)[8] is rather rare.

Considerable difficulties have been met during our effort to promote palladium(II) insertion into inert C–H bonds in both aliphatic and aryl carboxylic acids. We hypothesized that the observed lack of reactivity of carboxylic acids with palladium(II) catalysts was a result of the presence of several possible known coordination modes (Scheme 43). In these complexes, the CIPE is absent because the palldium center is locked away from the β-C–H bonds by κ^2 coordination.



Scheme 43. Coordination modes of palladium(II) with carboxylic acids.

We then discovered that the presence of a wide range of cationic counter ions, including Na^+, promoted palladium(II) insertion into the C–H bonds of carboxylic acid substrates. In our working model, the sodium cation coordinates with the carboxylate group in a κ^2 fashion, thereby forcing palladium(II) to coordinate with the unhindered lone pair of electrons on the oxygen atom (Scheme 44). The assembly of this pretransition state is believed to trigger C–H insertion through the CIPE. Subsequent structural studies using X-ray crystallography and ^{1}H NMR spectroscopy have also provided

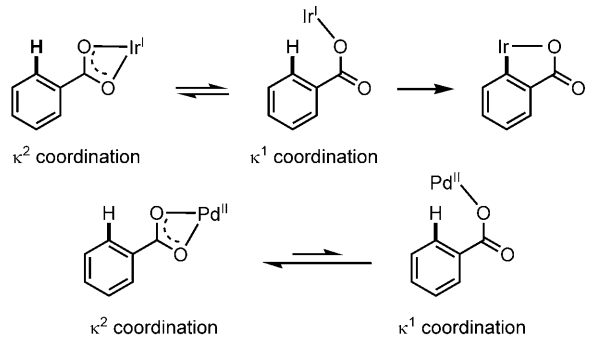


Scheme 44. A working model for table salt promoted C–H insertion.[67]

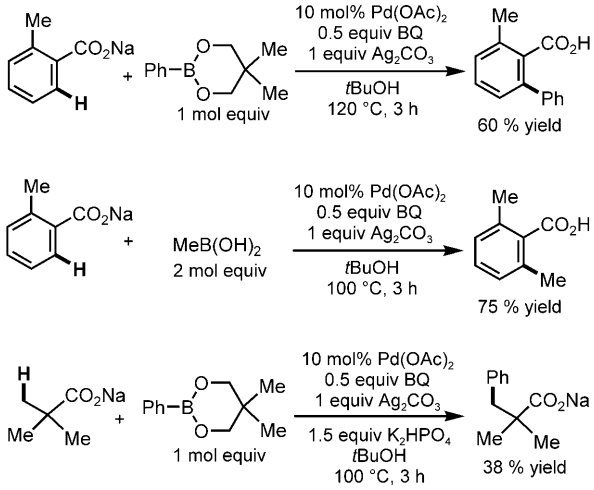
evidence for the formation of such a structure from toluic acid.[67] The dramatic influence of Na^+ or K^+ on the reactivity of carboxylic acids was also later observed in other reactions of these substrates. Strikingly, the mere use of table salt was sufficient for the promotion of C–H insertion.

It is commonly believed that a shift from a κ^2 to a κ^1 metal carboxylate,[68] as has been observed for stoichiometric rhodium(I) and iridium(I) insertions[69] into the *ortho* C–H bonds of benzoic acids, is the operative mechanism for late transition metals in general. However, in the case of palladium, the energetic preference is for the metal to remain in a κ^2 acetate-bound configuration, thereby disfavoring a shift to a κ^1 palladium(II) carboxylate (Scheme 45).[67]

This mode of reactivity made possible the application of our coupling protocol to substrates without strong directing groups (Scheme 46).[70] In this preliminary report, the yields were generally poor and the substrate scope was limited to only a few benzoic acids. The use of boronic acids appended to sp^3-carbon centers was limited to $MeB(OH)_2$, most likely because of a β-hydride elimination, which could occur with other alkylboronic acids after the transmetalation step, was not possible. The use of Ag_2CO_3 as a stoichiometric oxidant was another major practical drawback. Nonetheless, the ability to use a simple functional group to promote C–H insertion by palladium(II) was encouraging. Moreover, the



Scheme 45. Comparison of iridium carboxylates and palladium carboxylates.

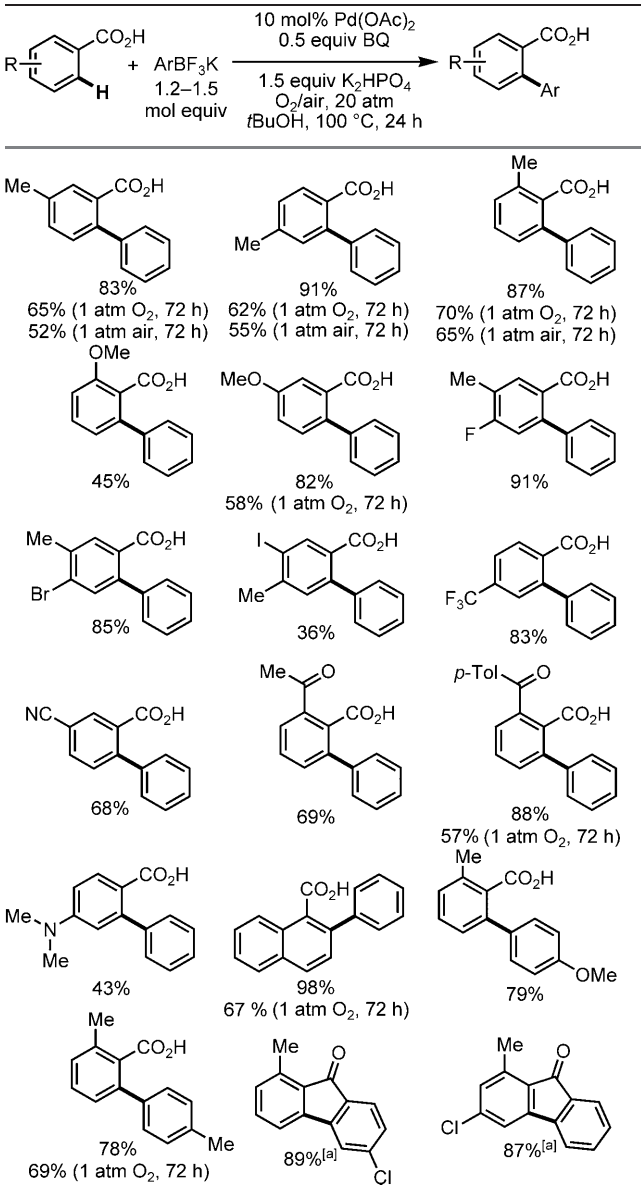


Scheme 46. Coupling of C–H bonds with substrates without a nitrogen-containing directing group (Yu et al., **2007**).[70]

C–H insertion intermediates are different from the commonly obtained cyclopalladated complexes in that the latter have unusually high thermodynamic stability, which is beneficial for the C–H activation step but may also cause difficulties for additional functionalization. This cation-promoted reactivity was additionally demonstrated in the arylation of $C(sp^3)$–H bonds by using Pd^{II}/Pd^{IV} catalysis. Previous conditions developed by Daugulis and co-workers[36] were modified by adding excess NaOAc to improve the yields.

The versatility and practicality of this coupling reaction was then substantially improved by using potassium aryltrifluoroborates as the coupling partners (Table 1).[71,72] Under these new conditions, the use of air or O_2 as the oxidant instead of Ag_2CO_3 was made possible. Although the use of 20 atm of air or O_2 as needed to shorten the reaction time, this coupling reaction could also be performed under 1 atm of air or O_2 over a prolonged reaction time. Most importantly, a wide range of functional groups was tolerated. The compatibility with deactivating electron-withdrawing groups, such as nitro and acetyl groups, is valuable in synthesis. Mechanistically, the reactivity observed with arenes containing both a carboxyl and a nitro group renders an electrophilic palladation pathway unlikely.

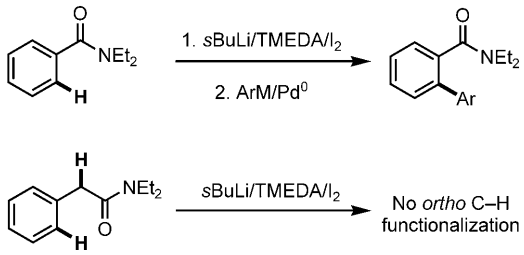
Table 1: Versatile biaryl synthesis through C–H activation/C–C coupling. (Yu et al., **2008**).[71]



[a] Treatment of the coupling product with oxalyl chloride gave the product shown.

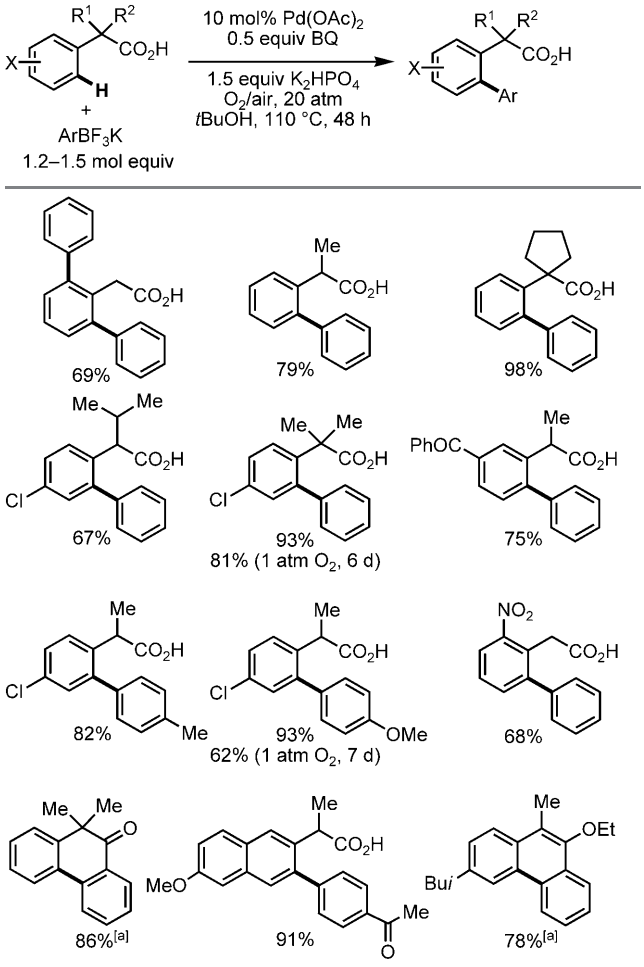
The results obtained with benzoic acid substrates prompted us to test whether this coupling protocol could be applied to phenyl acetic acid substrates as well. Notably, the broadly useful lithiation/iodination/arylation sequence (Scheme 47) is incompatible with this type of substrate because of the presence of the acidic α-hydrogen atom.[73] A direct *ortho* arylation would therefore provide an unprecedented disconnection for biaryl synthesis.

A wide range of phenyl acetic acid substrates were reactive under our C–H activation/C–C coupling conditions (Table 2). Intriguingly, the removal of the silver(I) oxidant was crucial for this reaction to occur. Common functional groups on the aryl boronic acids, including methoxy, carbonyl, and halo groups, were also tolerated. Currently, the scope of heterocyclic boronic acids is still limited (Table 3), and as



Scheme 47. *ortho* Lithiation. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

Table 2: Versatile biaryl synthesis through C–H activation/C–C coupling. (Yu et al., **2008**).[71]

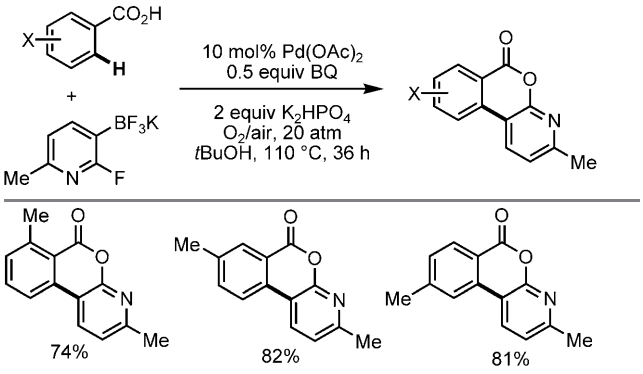


[a] Treatment of the coupling product with oxalyl chloride gave the product shown.

shown for pyridyl boronic acid substrates, 2,6-disubstitution is required to obtain the corresponding product in good yields.

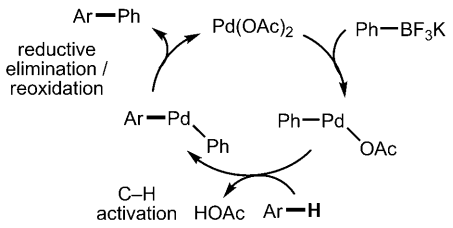
The compatibility of these reaction conditions with either benzoic acid or phenyl acetic acid substrates, which are among the most abundant starting materials in synthesis, makes this aryl–aryl coupling reaction a versatile way to construct biaryl molecules having different carbon skeletons. The only drawback is the requirement for the presence of a carboxyl group; however, the rich chemical reactivity of carboxyl groups also offers opportunity for a wide range of chemical manipulations

Table 3: Coupling with heterocyclic trifluoroborates. (Yu et al., **2008**)[71]



to meet synthetic needs. Furthermore, our ongoing work suggests that other broadly useful substrates are also compatible with this coupling protocol. For instance, trifluoromethanesulfonyl-protected phenylalkyl amines, which have recently been found to be reactive substrates for *ortho* C–H activation,[22] similarly undergo successful *ortho* coupling under identical conditions. The inclusion of a broader range of synthetically useful directing groups will minimize the inherent limitation of directed C–H coupling to a great extent because a particular directing group can be chosen to meet the needs of a desired synthetic application.

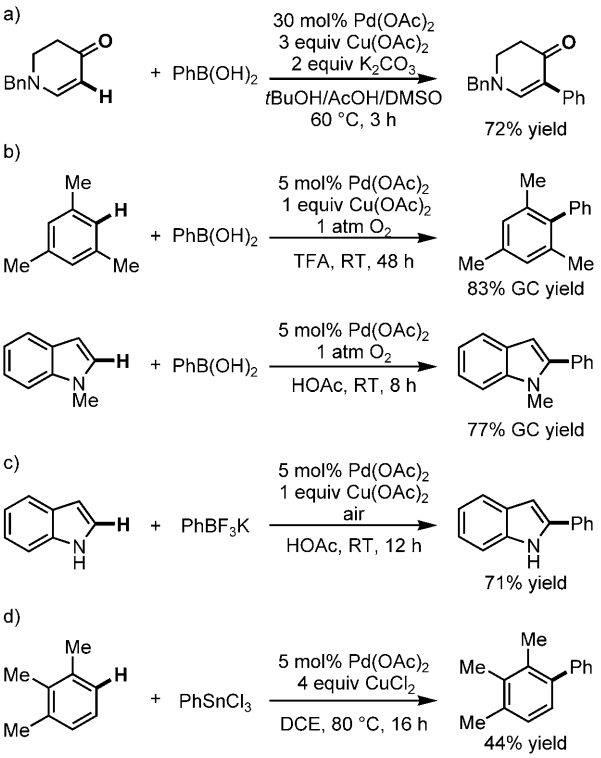
Intrigued by the drastically enhanced reactivity in C–H activation, we are currently investigating whether a different mechanism is operative. For instance, transmetalation between palladium(II) and $ArBF_3K$ could take place as the first step in the catalytic cycle (Scheme 48). If this pathway were to hold, in theory the electron-rich Ph–Pd–OAc species could be oxidized into a palladium(IV) intermediate, which



Scheme 48. An alternative catalytic cycle.

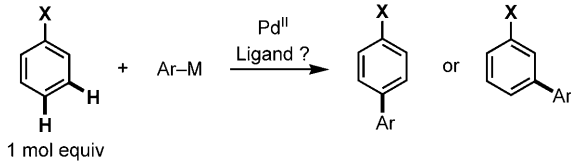
could then cleave C–H bonds more efficiently. However, these hypotheses remain speculative in the absence of comprehensive mechanistic studies and additional structural characterization.

The next major task is to test the applicability of this newly developed C–H activation/C–C coupling reaction for a wide range of substrates containing no proximate chelating functional groups. Whereas it is encouraging to see that the coupling of electron-rich and hence highly activated olefins, arenes, and indoles with organoboron[74] and organotin[75] reagents is feasible (Scheme 49), key challenges in this endeavor remain to be addressed. For example, the reaction of palladium(II) with benzene still requires a large excess of



Scheme 49. Coupling of electron-rich arenes with organometallic reagents. a) Georg et al., **2008**;[74a] b) Shi et al., **2008**;[74b] c) Zhang et al., **2008**;[74c] d) Oi et al., **2008**.[75]

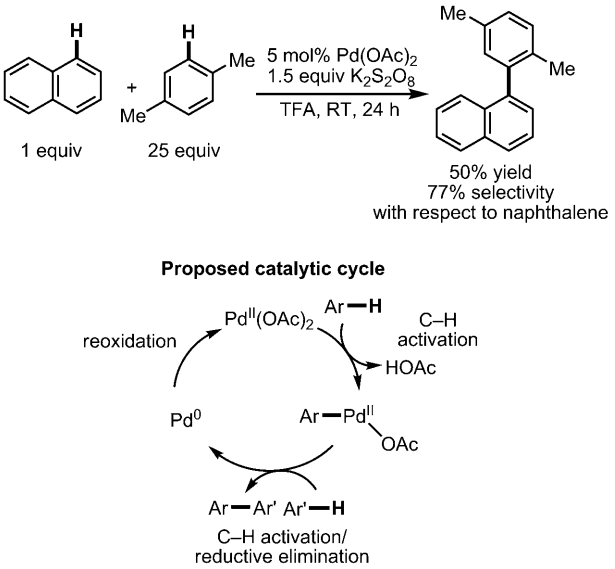
benzene. Additionally, palladium(II) generally reacts with monosubstituted benzene at the *ortho*-, *meta*-, and *para*-positions in an unselective fashion, limiting the potential for synthetic applications. The solution to both of these problems most likely hinges on an innovative design of a new ligand that will impart an appropriate steric and electronic bias on palladium(II) so that selective C–H coupling of monosubstituted arenes can be accomplished. In this respect, our initial report on *meta* C–H activation/Heck coupling represents a promising step forward (Scheme 15),[25] but a significant amount of work remains to be done to attain higher selectivity and efficiency, and to expand this chemistry to C–C cross-coupling. Continued efforts to confront the fundamental challenges of coupling unactivated arenes with organometallic reagents regioselectively are expected to yield both novel ligands and improved catalytic systems (Scheme 50).



Scheme 50. *meta*- and *para*-Selective coupling of monosubstituted arenes with organometallic reagents: a lingering challenge.

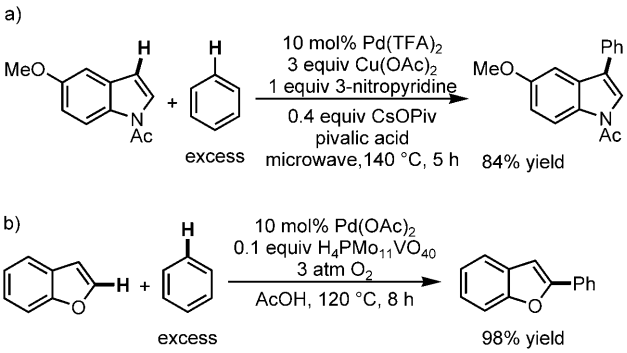
6.5. Coupling of C(aryl)–H Bonds with Arenes: A Related Reaction

Recently, a closely related coupling reaction involving two different arene substrates as the coupling partners has attracted significant attention. Since the early discovery of palladium(II)-catalyzed arene–arene coupling,[76] a great deal of effort has been devoted to eliminating the less desirable arene–arene homocoupling pathway. Substantial progress towards this goal has been made by Lu and co-workers in using Pd^{II}/Pd^{0} catalysis, although the obtained selectivity of the heterocoupling product versus the homocoupling product is not yet high enough for widespread synthetic application (Scheme 51).[77]



Scheme 51. An early example of arene–arene coupling (Lu et al., **2006**).[77]

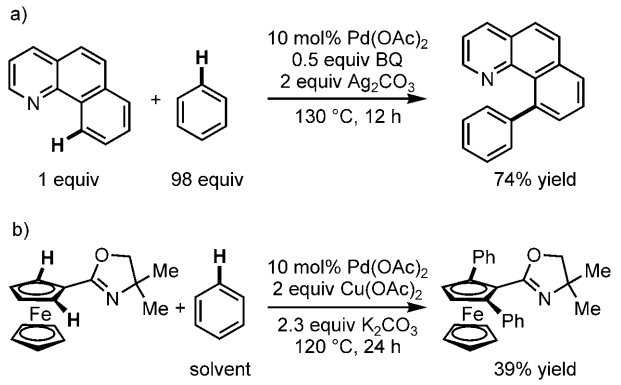
The replacement of one of the arene partners by an electron-rich heterocycle substantially improves the selectivity for the heterocoupling reaction (Scheme 52).[78] Notably, sub-stoichiometric coupling of *N*-acetylindole with benzene was previously reported by Itahara et al.[79] The highly



Scheme 52. Coupling of heterocycles with benzene. a) Fagnou and Stuart, **2007**;[78a] b) DeBoef et al., **2007**.[78b] Piv = pivaloyl.

efficient paladium(II)-catalyzed intramolecular homocoupling of pyrroles was also successfully exploited by Boger and Patel to achieve the total synthesis of prodigiosin.[76c] Recently, Buchwald and co-workers reported a drastically improved protocol which allowed coupling of anilide substrates with 4–11 equivalents of benzene.[80]

The use of a directing group has also been successfully employed to suppress homocoupling (Scheme 53).[81] A highly efficient heterocoupling process was developed by Hull and Sanford using a pyridyl moiety as the directing group.[81a]

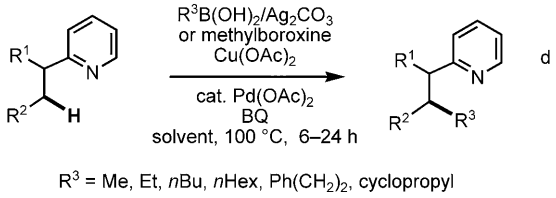


Scheme 53. Heterocoupling using directing groups. a) Sanford and Hull, **2007**;[81a] b) You and Xia, **2007**.[81b]

Similar to the coupling protocol developed in our group,[64] in this case, the use of benzoquinone as a C–H activation promoter and Ag_2CO_3 as the oxidant was also found to be critical. Additionally, concurrent to these studies, Xia and You found that oxazoline was a suitable directing group for this coupling reaction.[81b] Diastereoselective coupling using chiral oxazolines was also found to be possible by the same group. Notably, our group has also used oxazoline groups as auxiliaries to achieve C–H coupling with organotin reagents using $Cu(OAc)_2$ as the oxidant.[61]

6.6. Coupling of $C(sp^3)$–H Bonds with Organometallic Reagents

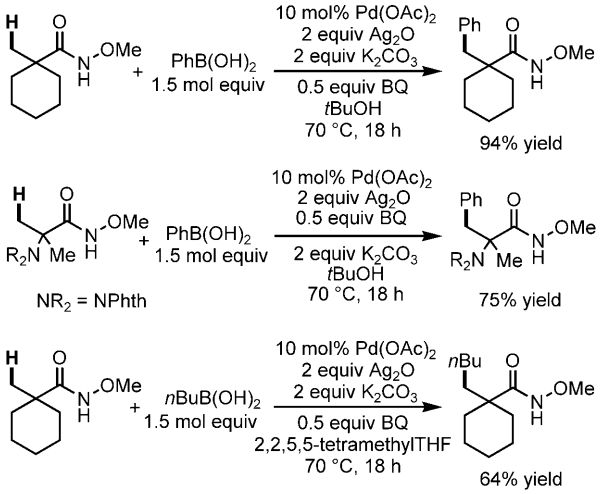
Despite recent impressive progress made in $C(sp^3)$–$C(sp^3)$ cross-coupling using alkyl halides,[82] efforts to couple $C(sp^3)$–H bonds with organometallic reagents have been met with numerous problems, likely because of the lack of assistance from an appropriate ligand. Nevertheless, the feasibility of such a process was first demonstrated in pyridyl-directed C–H activation/C–C coupling (Scheme 54).[64] Although generally,



Scheme 54. An early example of $C(sp^3)$–$C(sp^3)$ C–H activation/C–C coupling (Yu et al., **2006**).[61]

the C–H bonds involved in this process are primary, secondary C–H bonds are also reactive under these conditions, albeit in much lower yields.

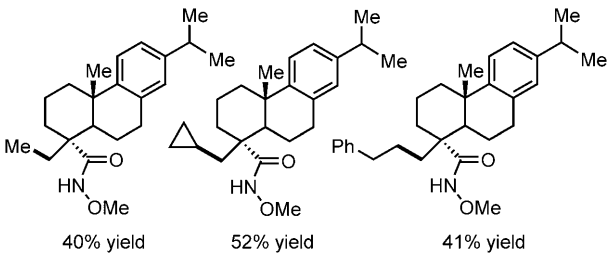
Expansion of this C–C coupling protocol to aliphatic carboxylic acid substrates afforded $C(sp^3)$–$C(sp^3)$ coupling products in poor yields (10–20%). The carboxyl-directed C–H activation inspired us to test structurally analogous hydroxamic acids as substrates (Scheme 55). We envisioned



Scheme 55. $C(sp^3)$–H activation/C–C coupling (Yu et al., **2008**).[83] THF = tetrahydrofuran.

that the CONH moiety could exhibit behavior similar to that of the CO_2H group. We also hypothesized that the methoxy group could provide steric hindrance, which is believed to be important for preventing β-hydride elimination in $C(sp^3)$–$C(sp^3)$ cross-coupling reactions.[82] Extensive screening established conditions for an unprecedented reaction to accomplish β-C–C bond formation with aliphatic acid derivatives.[83] Considering the significance of the classical α lithiation/alkylation of carboxylic acids in chemical synthesis, this newly developed β-C–C bond-forming reaction is likely to find broad utility as a novel synthetic disconnection.

The utility of this coupling reaction was additionally demonstrated in the alkylation of the hydroxamic acid derived from dehydroabietic acid, a natural product identified to efficiently open voltage-dependent K^+ (BK) channels (Scheme 56).[84] Because of their bioactivity, molecules of this type could ultimately be used for treatments of diseases such as acute stroke, epilepsy, and asthma. Generally, however,



Scheme 56. Derivatives of a biologically active natural product. Yields shown are for the isolated product. (Yu et al., **2008**).[83]

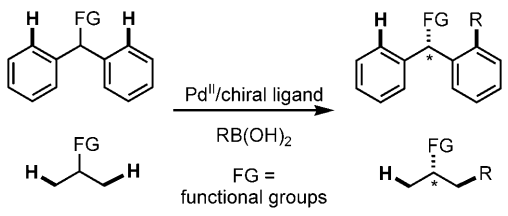
diversification of such core structures is difficult because of the lack of reactive chemical functional groups, aside from the carboxylic acid moiety, which is essential for biological activity. Masking the carboxylic acid as the hydroxamic acid allows functionalization at the methyl β C–H bond, affording a novel class of analogues that could ultimately display improved pharmacokinetic properties.

6.7. Enantioselective C–H Activation/C–C Coupling

To date, asymmetric catalysis is largely based on chiral recognition of a π face (*re* versus *si*) possessed by olefins or carbonyl compounds.[85] Only a few examples involve chiral recognition of sp^3-carbon centers,[86–88] including asymmetric Heck cyclization, asymmetric metathesis, and kinetic resolution of alcohols.[89] Nonetheless, research concerning enantioselective carbene insertion into C(sp^3)–H bonds has made impressive progress during the past few decades.[90] Recently, an enantioselective nitrene insertion process has also emerged as a promising asymmetric C–H amination method.[91]

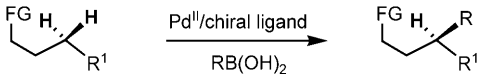
Despite the remarkable success in developing palladium-catalyzed asymmetric catalysis more generally, studies towards the enantioselective functionalization of C–H bonds through palladium insertion have been largely unsuccessful.[92–95] On the basis of our experience, it seems that two pervasive problems have historically plagued research in this field. Firstly, the relatively high reaction temperatures required in C–H activation reactions make chiral recognition of sp^3 carbon centers challenging. Secondly, most commonly used chiral ligands are problematic. Typically, effective chiral induction in asymmetric catalysis occurs as a result of the chiral ligands promoting the favored reaction pathway. However, in the case of C–H insertion processes, these ligands either outcompete the substrate for binding to the palladium(II) center or deactivate palladium(II) for cleavage of the desired C–H bond, even if the required [L(substrate)PdX_2] complex is formed.

Encouraged by the recent progress in palladium-catalyzed C–H activation/C–C coupling, we sought to develop enantioselective variants of these reactions (Scheme 57). Our initial efforts focused on desymmetrization of prochiral C–H bonds on geminal aryl or methyl groups. In choosing such systems for early investigation, we envisioned that any insights into the stereoselection model for these substrates would be directly applicable to the desymmetrization of other C–H bonds. In particular, we looked towards desymmetrization of geminal C–H bonds of methylene groups as a long-term goal (Scheme 58), though the reactivity of methylene C–H bonds is usually markedly lower.[64]



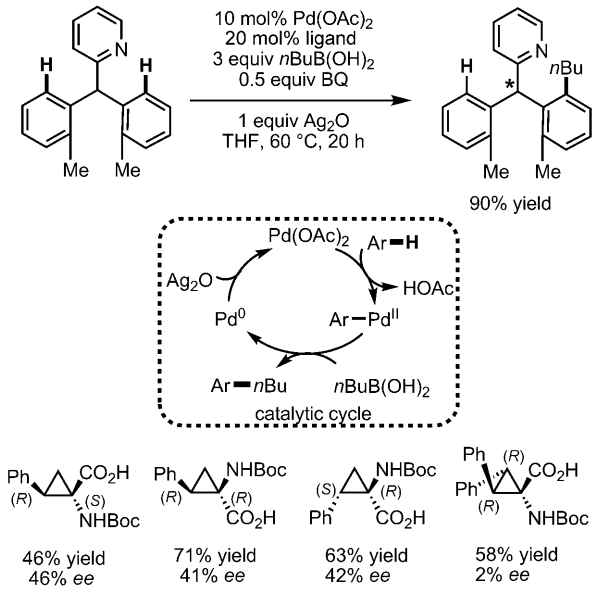
Scheme 57. Desymmetrization of germinal aryl and methyl groups.

By using a highly efficient C–H activation/C–C coupling reaction at a relatively mild temperature (60 °C) as an assay,



Scheme 58. Desymmetrization of methylene C–H bonds.

we were able to establish a proof of concept for palladium(II)-catalyzed enantioselective C–H activation using chiral carboxylic acids with constrained conformations (Scheme 59).[96] Analysis of these data revealed that only the α-chiral center is important for chiral recognition.



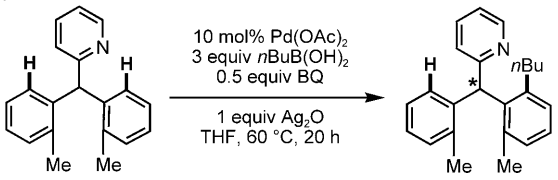
Scheme 59. Proof of concept (Yu et al., **2008**).[96]

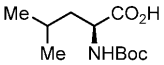
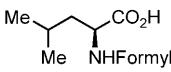
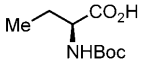
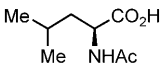
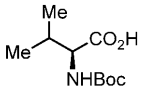
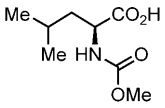
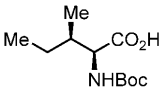
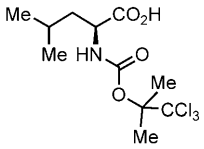
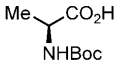
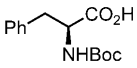
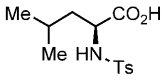
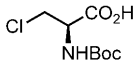
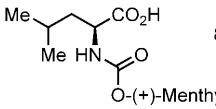
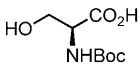
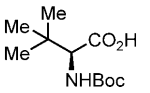
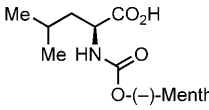
Upon additional investigation, it was found that a wide range of monoprotected amino acids were effective chiral ligands for this enantioselective coupling reaction (Table 4). Of particular importance was the finding that mono-N-protection of the amino acid ligands is crucial for chiral recognition.

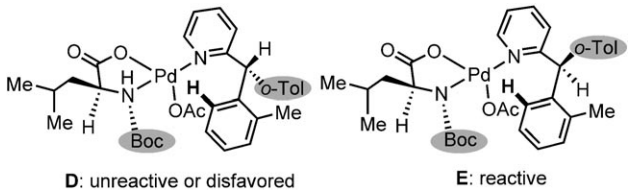
Analysis by ^{1}H NMR spectroscopy and X-ray crystallography led us to propose the involvement of a key reactive intermediate **E** (Scheme 60). The interaction between bound substrate and the monoprotected chiral amino acid ligand on the palladium center results in the assembly of an intermediate complex **E** in which C–H cleavage is not retarded to a noticeable degree. Contrasting this favorable pre-transition state with the unfavorable pre-transition state formed from **D**, it is clear that the steric interactions in **D** decrease the efficiency of this pathway, leading to the high enantioselectivity of this process (Scheme 60).

In hindsight, monoprotection of the nitrogen atom in the amino acid ligands offers a tremendous advantage for chiral

Table 4: Palladium-catalyzed enantioselective C–H coupling. (Yu et al., **2008**)[96]



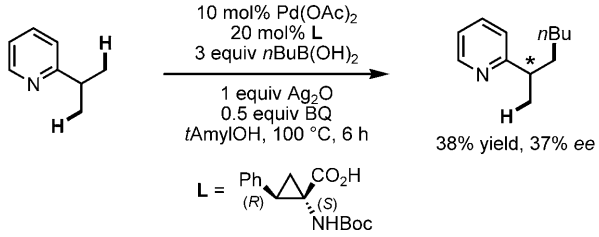
Ligand	Yield [%]	*ee* [%]	Ligand	Yield [%]	*ee* [%]
	63	90		53	6
	47	85		74	80
	69	70		88	79
	85	72		89	85
	60	80			
	66	81		89	60
	83	83		87	85
	65	88			
	60	52		91	87



Scheme 60. A simplified stereomodel for asymmetric C–H insertion. (Yu et al., **2008**).[83]

control in metal-mediated reactions. With this modification, the chirality on the α carbon (which is spatially remote) is relayed to the nitrogen atom attached to the metal center, a process that hinges upon the bisdentate coordination of the ligand. This chiral relay can be thought of as a "gearing effect." Notably, this concept is closely related to the pioneering work by Evans et al. on the rational design of a chiral mixed phosphorus/sulfur ligand for asymmetric hydrogenation in which the chiral sulfur center is assembled through a "gearing effect".[97]

In an effort to expand the scope of this reaction, we explored the coupling of prochiral C(sp^3)–H bonds. Use of the ligands listed in Table 4 gave poor enantioselectivity (10–15% *ee*). A significant improvement was made by using a more rigid ligand to give 37% *ee* (Scheme 61). The sensitive



Scheme 61. Enantioselective coupling of C(sp^3)–H bonds.

response of enantioselectivity to the ligand structure suggests that there is vast opportunity for additional tuning of existing ligand structures, as well as for the design of entirely new ligand architectures to achieve enantioselective C–H activation reactions with more general substrate scope. To this end, we are currently synthesizing a wide range of chiral amino acid ligands[98] with the aim of applying this new asymmetric C–C bond-forming reaction to broader classes of substrates.

7. Conclusions and Outlook

Recently, palladium-catalyzed C–H activation/C–C bond-forming reactions have emerged as a promising set of synthetic transformation for the assembly of carbon–carbon bonds. Various catalytic cycles have been developed to accomplish the olefination, arylation, and alkylation of unactivated C–H bonds, including Pd^{II}/Pd^{0}, Pd^{II}/Pd^{IV}, $Pd^{0}/Pd^{II}/Pd^{IV}$, and Pd^{0}/Pd^{II} catalytic cycles. Our group developed the first protocol for successful C–H activation/C–C coupling with organometallic reagents using Pd^{II}/Pd^{0} catalysis. Since its initial discovery, this mode of catalysis has been expanded to include a broad range of coupling partners, including organotin, organoboron, and organosilicon reagents. Importantly, C(sp^2)–C(sp^2), C(sp^2)–C(sp^3), and C(sp^3)–C(sp^3) coupling reactions have all been demonstrated. One major goal, the use of simple substrates with this Pd^{II}/Pd^{0} coupling such as carboxylic acids and amines, has been achieved. Because of the ubiquity of these functional groups, this catalytic reaction will likely find immediate synthetic applications, especially in the early stages of a synthesis and in medicinal chemistry.

Despite these advancements, C–H activation/C–C coupling still falls short of the remarkably high standards for efficiency and practicality set by palladium-catalyzed cross-coupling reactions of aryl and alkyl halides. In this context, a number of major challenges must still be overcome before these reactions will find broad applicability:

- Air as the oxidant: Development of an efficient catalytic system that uses 1 atm of air as the sole oxidant, rather than co-oxidants such as copper(II) and silver(I) salts, or benzoquinone would make this new process more comparable to conventional cross-coupling reactions in terms of costs and practicality.

- Reduced catalyst loading: In many cases, C–H activation reactions with palladium require 5–10 mol% catalyst. Thus, from the standpoint of atom economy and overall cost, discovering more efficient catalytic systems with improved turnover is paramount.
- Regioselective arene C–H activation: The design of novel ligands to promote C–H activation of monosubstituted benzene regioselectively at the *meta*-[25] or *para*-positions would represent a new paradigm in reactivity and would greatly expand the scope of this new C–C bond-forming reaction.
- Enantioselective C–H activation of C(sp^3)–H bonds: Although, this goal may seem elusive based on the results of our laboratory to date, continued efforts will eventually lead to a general asymmetric C–H activation/C–C coupling protocol, a reaction that would deliver a completely new disconnection for asymmetric C–C bond formation. These reactions will greatly simplify target synthesis by allowing overarching strategies that start from simpler and more abundant starting materials. Furthermore, the understanding gleaned from the development of chiral ligands will greatly facilitate the design of new ligands to promote catalysis and to control the regioselectivity of C–H activation.

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