Mechanistically Guided Survey of Enantioselective Palladium-Catalyzed Alkene Functionalization

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Glossary

Oxidative addition: A reaction that cleaves an A–B bond forming two new covalent bonds between a metal center (M) and the A and B residues (A–M–B). During this process the metal is formally oxidized by two electrons and the coordination number of the metal center increases. This is often the first step of organometallic catalytic cycles.

Reductive elimination: Opposite reaction of oxidative addition where two metal-ligand bonds are cleaved and a new bond between those ligands is formed. During this process the metal is formally reduced by two electrons and the coordination number of the metal center decreases. This is typically the last step of organometallic catalytic cycles.

Chain walking: Sequence of β-hydrogen eliminations and migratory insertions that isomerizes an unsaturation through an aliphatic system.

Heck redox-relay: Palladium-catalyzed arylation or alkenylation of alkenols to yield remotely functionalized aldehydes or ketones. The process is initiated by a migratory insertion into the alkene moiety and a series of β-hydrogen eliminations and migratory insertions to transfer the unsaturation to the alcohol moiety. The final oxidation of the alcohol into a carbonyl group serves as a "thermodynamic sink" for terminating the chain-walking process.

Nucleopalladation: Addition across a π-bond of a palladium complex and a heteroatom, the latter of which may or may not be coordinated to the palladium.

Abstract

Palladium-catalyzed alkene functionalization was discovered more than 60 years ago and is a commonly used strategy for the synthesis of pharmaceuticals and materials. The development of asymmetric variants of this reaction is described in this short review. This manuscript is organized around the mechanistic challenges that have hampered the development of these transformations for various substrate classes, as well as the strategies, ligand classes, and additives that have been introduced to overcome them. New methodologies for Heck, oxidative Heck, dehydrogenative Heck, and Wacker type reactions are highlighted, with a special focus on the progression from cyclic to acyclic to electronically unbiased olefin substrates.

Introduction

Palladium-catalyzed methodologies are ubiquitous in synthetic chemistry, and key to their successful implementation has been obtaining detailed mechanistic understanding of these reactions. Specifically, the two-electron nature of oxidative addition and reductive elimination, facile β-hydrogen elimination, and high π-Lewis acidity have enabled the organometallic community to rationally design a myriad of Pd-catalyzed strategies for efficiently building molecular complexity.[1-8] The versatility of Pd catalysis has been described in many reviews,[9-14] but herein we will focus on Pd-mediated enantioselective functionalization of alkenes. In particular, this review will highlight different strategies developed to control the regio- and stereoselectivity of the key elementary steps in these processes.

The discovery of the Pd(II)-catalyzed water addition to ethylene to give acetaldehyde by researchers in Wacker Chemie in 1959[15,16] inspired numerous chemists to study the use of transition-metal complexes to catalyze organic transformations. Shortly after, in 1970, the laboratories of Mizoroki and Heck reported the use of Pd(0) complexes to promote olefin arylations and alkylations.[17,18] The general mechanism of Heck-type transformations is outlined (Figure 1, Key Figure), where a Pd(0) complex (**A**) engages in oxidative addition with an alkenyl or aryl halide to generate Pd(II) intermediate **B**. Migratory insertion of the alkene into the Pd–C bond forges the new C–C bond and yields Pd-alkyl intermediate **C**. Subsequently, a β-

hydrogen elimination delivers the alkene product **3**, and a base-mediated reductive elimination of the Pd-hydride species (**D**) regenerates the Pd(0) catalyst to restart the cycle.

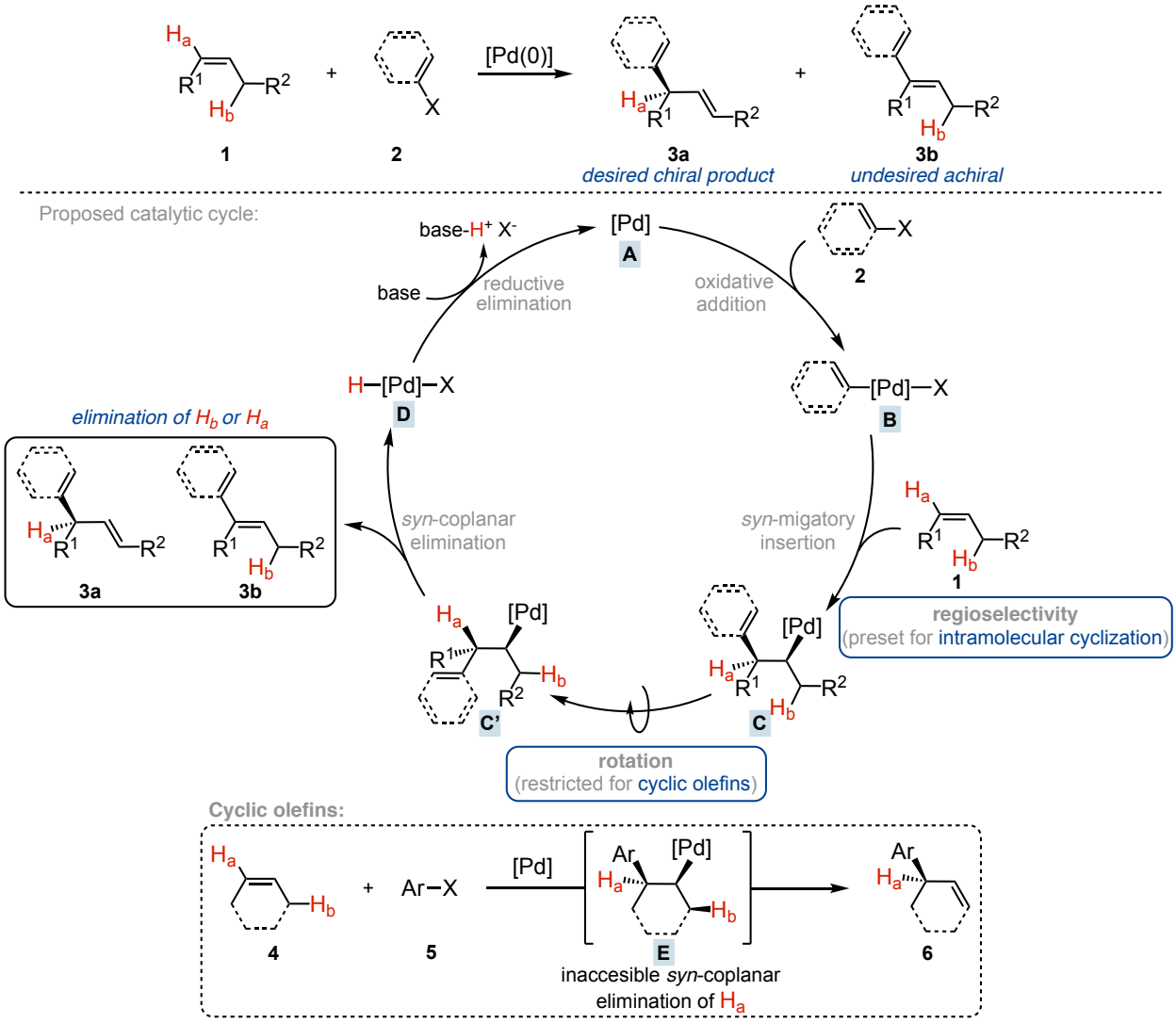
Key to the development of asymmetric variants of this transformation is to favor the β-hydrogen elimination of H_b, away from the newly formed stereocenter to render chiral product **3a**, over H_a, which would deliver achiral product **3b**. Although early Heck reaction development attracted the attention of numerous research groups, asymmetric variants of these methodologies remained elusive until 1989, when the groups of Overman and Shibasaki described the use of bisphosphine ligands to promote alkylation and arylation reactions with moderate enantioselectivity (up to 46% ee).[19,20] While the discovery of these transformations was a major breakthrough, these reactions are intramolecular cyclizations where the regioselectivity of olefin functionalization is dictated by the substrate rather than being under catalyst control. Additionally, these examples were initially limited to cyclic olefins, which, due to conformational restrictions (*vide infra*), are predisposed to preserve the stereochemical information of migratory insertion by preventing an undesired β-hydrogen elimination towards the newly formed stereocenter (Figure 1). The strategies developed to control the regioselectivity in intramolecular reactions and expand the scope to acyclic olefins will serve as the outline for this review.

Controlling β-hydrogen elimination: cyclic and acyclic olefins

As described, early reports of asymmetric Pd-catalyzed olefin functionalization employed cyclic alkenes. These systems are less sterically demanding than their acyclic analogs, which facilitates initial coordination of the olefin to the metal and accelerates the migratory addition step. Additionally, cyclic systems present high barriers for rotation about their C–C bonds, which impedes the formation of achiral products via β-hydrogen elimination towards the newly formed stereocenter. Upon migratory insertion, Pd-alkyl intermediate **E** is formed (Figure 1), where the Pd and aryl groups are added to the same face of the olefin. Subsequently, elimination of H_b renders the final product. Elimination of H_a, which would yield an achiral product, is prevented as a *syn*-coplanar conformation between the Pd complex and H_a cannot be adopted (see Box 1).

The intermolecular arylation of cyclic enol ethers is an example of this process. The arylation of 2,3-dihydrofuran (**4a**) was first reported by Hayashi employing (*R*)-BINAP as chiral ligand (Figure 2a).[21] A mixture of two olefins, **6a** and **6b**, was obtained in a 89:11 ratio with 93% and 67% ee,

Figure 1. Catalytic cycle highlighting the main challenges of asymmetric Heck reactions



Catalytic cycle for Heck-type reactions depicting the formation of chiral product **3a** or achiral product **3b** via β-hydrogen elimination of H_b or H_a, respectively. Bottom: arylation of acyclic olefin **4** depicting unlikely β-hydrogen elimination to yield achiral product.

respectively. Under these conditions the more thermodynamically favored product, generated upon reinsertion of the Pd-hydride intermediate and a subsequent β-hydrogen elimination, is obtained as the major product. A kinetic resolution was found to accounts for the higher enantiopurity of the major product rather than a highly enantioselective initial migratory insertion. Utilizing a non-symmetric phosphine-oxazoline ligand, Pfaltz and coworkers were able to invert the selectivity to favor the formation of **6c** (**L1**, Figure 2b).[22,23] Interestingly, under

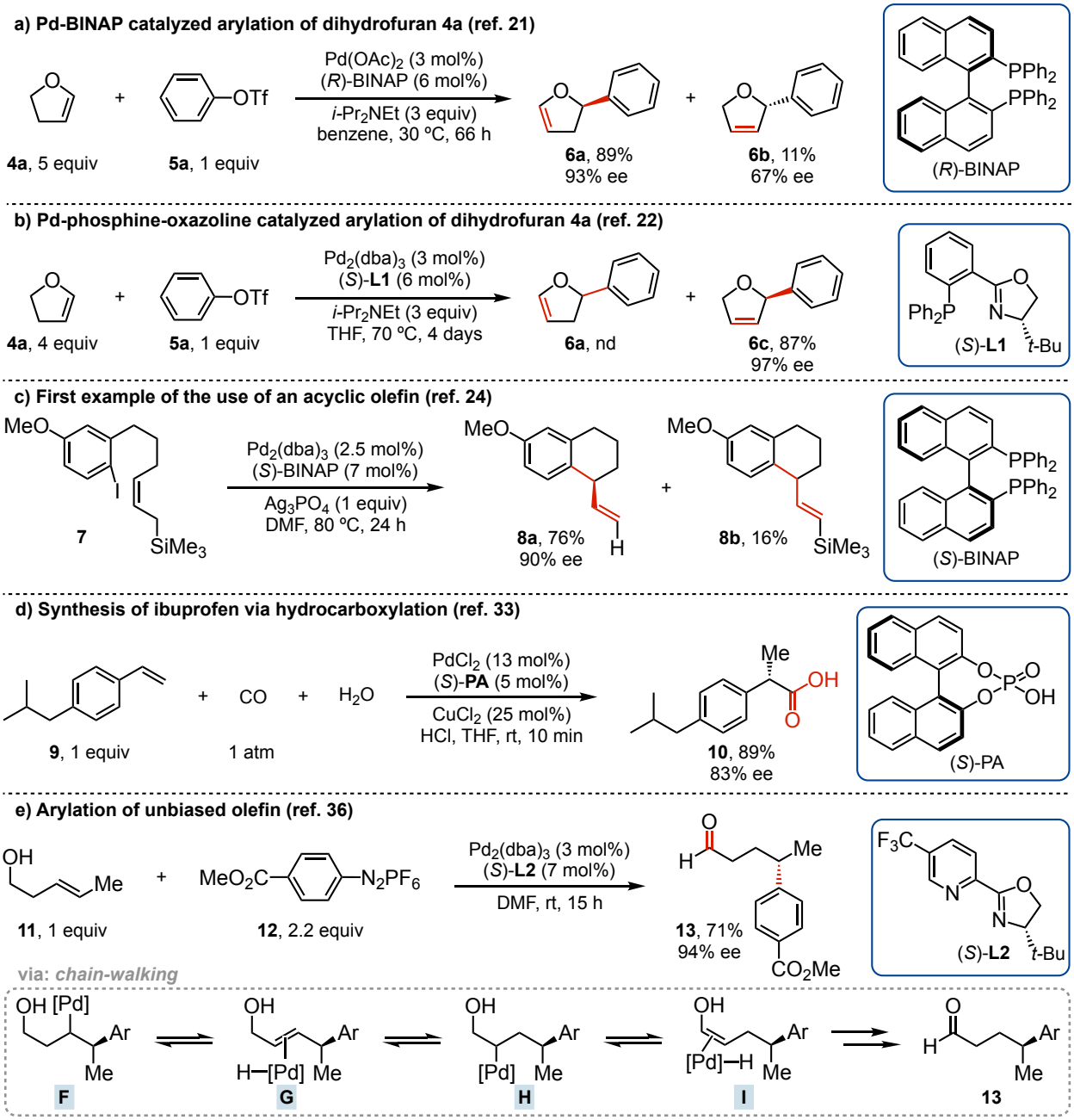
these reaction conditions, the more thermodynamically favored isomerized product, **6a**, was not detected. These examples show how subtle tuning of ligand properties influences the relative rates of β-hydrogen elimination, more facile in the first example, and reductive elimination, which is promoted by the non-symmetric ligand **L1**, leading to different product ratios.

The expansion of this methodology to the use of acyclic olefins is not trivial, as the Pd-alkyl intermediate **C** generated after migratory insertion can easily undergo C–C bond rotation to afford conformer **C'**. Thus, the development of asymmetric processes for acyclic olefins requires the Pd complex to discriminate between the elimination of H_b over H_a to render a chiral product. Most strategies circumvent this challenge by employing a biased olefin that drives β-hydrogen elimination away from the newly formed stereocenter. The first example of enantioselective functionalization of an acyclic olefin was reported by Tietze for an olefin bearing a trimethylsilyl group at the allylic position (Figure 2c).[24] The elimination of this electrofuge group is favored over the elimination towards the newly formed stereocenter, rendering the desilylated chiral compound **8a** as the major product.

This reaction is carried out in the presence of a super stoichiometric amount of Ag(I) salt to scavenge the iodide generated upon oxidative addition, which is a common feature for enantioselective Heck reactions. Although the use of aryl iodides facilitate oxidative addition at Pd, it has been reported that the presence of iodide ions in solution in many cases reduces the enantioselectivity of the overall process.[10] Typically, iodides are exchanged by non-coordinating counterions to facilitate the dissociation of X-type ligands from Pd complex **B**, allowing the generation of cationic 16-electron square planar species (Figure 1). Overman and coworkers have extensively studied the effect of the counterion in the overall kinetics of the process.[10] The ion exchange serves two main purposes, first it opens a coordination position on the Pd complex where the olefin will subsequently bind. Additionally, the cationic nature of the complex favors stronger olefin binding as a consequence of the increased positive charge on Pd that induces enhanced σ-donation from the alkene HOMO. This, in turn, often results in increased olefin activation and accelerates migratory insertion. Significant effects of the counterion on the enantioselectivity of the process have also been observed, with the optimal

counterion found to be case dependent. Interestingly, different achiral counterions can sometimes lead to the formation of enantiomeric products using the same chiral ligand.[25,26]

Figure 2. Arylation of cyclic and acyclic olefins



(a-b) Enantioselective arylation of 2,3-dihydrofuran (**4a**). (c) First example of Pd-catalyzed enantioselective intramolecular arylation of acyclic olefin (**7**). (d) Enantioselective synthesis of ibuprofen (**10**) via hydrocarboxylation of styrene **9**. (e) Enantioselective arylation of homoallylic alcohol **11** to yield remotely functionalized aldehyde **13**.

Controlling the regio- and enantioselectivity of the bond formation

The next reaction development milestone was to control the regioselectivity of migratory insertion. The first examples reported successfully sidestepped this challenge by employing electronically biased olefins or focusing on intramolecular cyclizations (*vide supra*).[27,28] The regioselectivity of migratory insertion is dictated by the charge distribution across the olefin in the transition state,[29] and consequently, the use of polarized alkenes facilitates discrimination between both sp^2-carbons.

Numerous studies have focused on developing catalytic systems to functionalize terminal alkenes that favor the formation of branched over terminal products. This strategy has been successfully applied for the copolymerization of terminal olefins and carbon monoxide, yielding optically active materials with high isotacticity utilizing chiral bisphosphines and bisoxazolines as ligands.[30,31] An industrially relevant example of these reactions is the Pd-catalyzed regioselective carbonylation of styrene **9** (Figure 2d).[32] Alper and coworkers reported the use of a Pd(II)/binol-derived phosphoric acid system to enable the enantioselective synthesis of widely distributed anti-inflammatory drugs like ibuprofen (**10**) and naproxen.[33] It should be noted that the asymmetric induction is controlled by phosphoric acid **PA**, which acts as chiral counterion rather than a chiral ligand. This strategy is less common than using chiral ligands, but it has been widely applied in different enantioselective organometallic reactions.[34] There are also examples of Heck-type processes where chiral anions function both as phase transfer catalysts, which help solubilize a reactant, and as chiral counterions to cationic Pd intermediates, thereby impacting the rate, enantioselectivity, and regioselectivity of the process.[35]

The regioselective functionalization of electronically unbiased internal olefins was pioneered by the Sigman lab.[36] In 2012, the arylation of homoallylic and bishomallylic alcohols (**11**) with excellent levels of regio- and enantioselectivity to yield remotely functionalized ketones (**13**) was reported (Figure 2e). These type of transformations have come to be known as Heck redox-relay reactions, where a *chain-walking* process featuring a series of β-hydrogen eliminations and migratory insertions leads to the thermodynamically-driven formation of a ketone or an aldehyde product.[37] Key to the development of this transformation is to maintain the Pd complex coordinated to the substrate during the *chain-walking* process.[38-40] The use of an

electronically non-symmetric pyridine-oxazoline ligand **L2** that acts as a weak σ-donor ligand toward Pd was found to be optimal to strengthen olefin binding. Additionally, hexafluorophosphate aryldiazonium salts (**12**) were use as electrophiles to provide non-coordinating counterions. The use of arene diazonium salts as electrophiles in Pd-catalyzed alkene functionalization is a commonly used strategy that was pioneered by Matsuda in 1977.[41,42]

From oxidative addition to nucleopalladation

Palladium-catalyzed alkene functionalizations are not limited to the formation of C–C bonds, as oxygen and nitrogen-based nucleophiles can also be coupled to olefins to forge new C–O and C–N bonds.[11] Due to the mechanistic resemblance to the Wacker oxidation reaction, discussed in the introduction of this review, these transformations are known as Wacker- and aza-Wacker-type reactions respectively.

The previously discussed Heck-type strategies follow a Pd(0) $\rightarrow$ Pd(II) $\rightarrow$ Pd(0) sequence that regenerates the active Pd (0) catalyst **A**, whereas Wacker-type reactions are promoted by Pd(II) complexes (**K**, Figure 3a). As a result, Wacker-type reactions necessitate the use of an oxidant to regenerate the Pd(II) complex after each turnover. Aerobic conditions, often in the presence of Cu complexes, and other oxidants like *p*-benzoquinone (BQ) are commonly used to fulfill this requirement.[43] Finding a catalytic system where the oxidant, substrate, and ligand are compatible is one of the key challenges for the development of these reactions.[44]

The development of enantioselective Wacker-type reactions often poses more formidable challenges than those previously discussed Heck-type chemistry. In addition to oxidant compatibility issues, β-hydrogen elimination towards the newly formed stereocenter is generally thermodynamically favored because the achiral products generated, analogous to **3b**, would be enol ethers or enamines. As a consequence, many reported systems are only amenable for biased substrates to prevent the formation of these achiral products. The large majority of Wacker and aza-Wacker reports focus on the development of intramolecular cyclizations, where the undesired β-hydrogen elimination towards the C–heteroatom bond is disfavored, as it would render a strained exocyclic double bond.

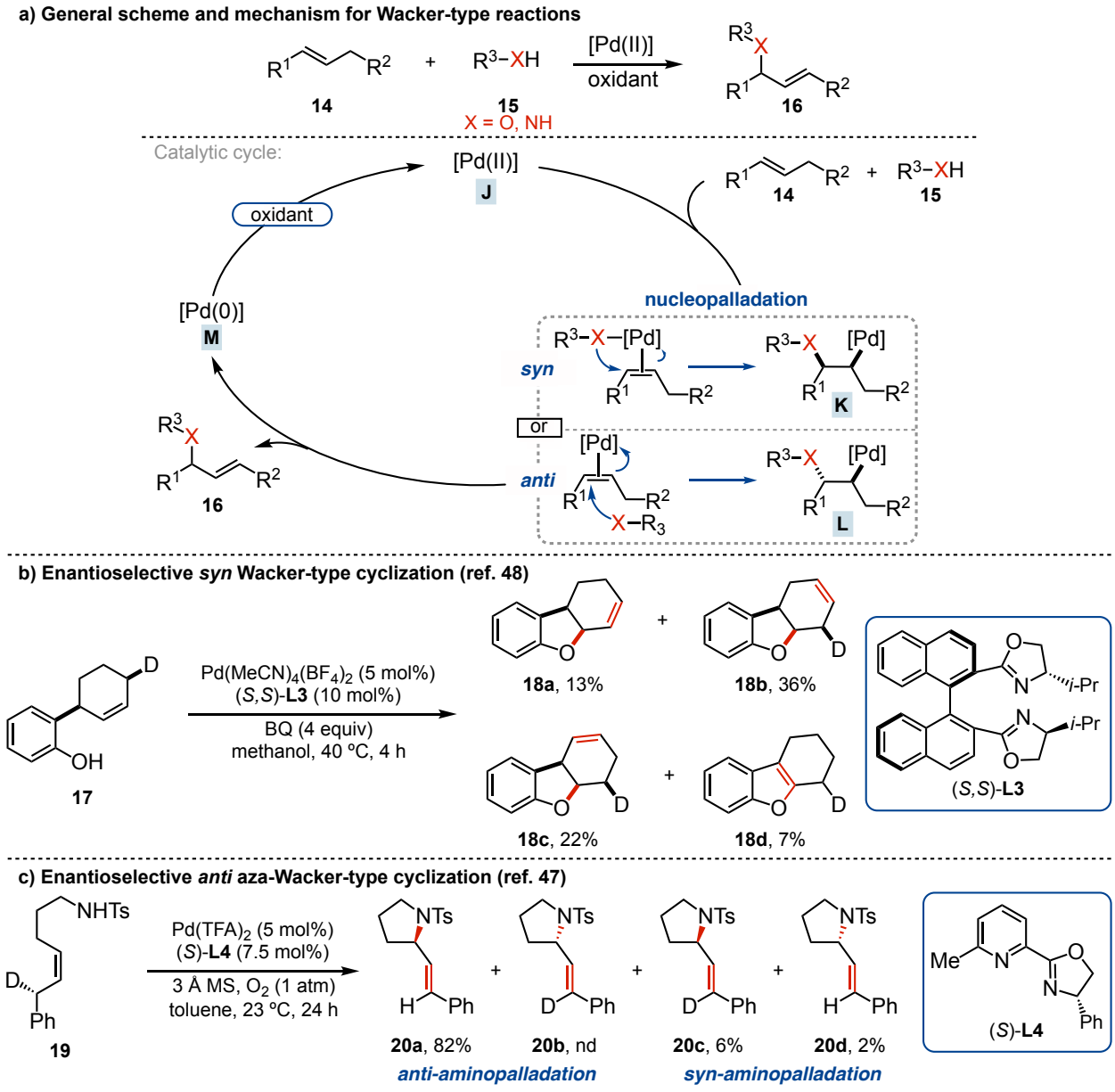
An additional challenge associated with the successful development of an enantioselective Wacker-type transformation is to control the mechanism of the nucleopalladation step that forges the new C–heteroatom bond (Figure 3a). Extensive studies of enantioselective Wacker reactions have shown that nucleopalladation can occur via two different pathways: (1) *syn*-nucleopalladation, where the new bond is generated via migratory insertion of the π-system into a coordinated metal-nucleophile bond (**K**); and (2) *anti*-nucleopalladation, an outer-sphere attack of the nucleophile to the coordinated olefin that renders the new C−heteroatom and Pd–C bond in an *anti*-configuration (**L**).[45]. The mechanism of the bond forming step has been reported to be highly dependent on the reaction conditions, nucleophile, and catalyst employed.[46,47] Exquisite control of the reaction conditions is likely required to achieve high levels of enantioselectivity, as these two pathways may lead to the formation of enantiomeric products.

In 2004, Hayashi reported a mechanistic study of the oxypalladation step in the enantioselective cyclization of deuterated phenol **17** (Figure 3b).[48] Analysis of the products obtained (**18a-18d**) indicated a *syn*-oxypalladation mechanism, in line with other reports by Wolfe[49-51] and Stoltz[44] using both oxygen and nitrogen-based nucleophiles. In contrast, the study of the cyclization of tosylamine **19** utilizing $Pd(TFA)_2$ and **L4** revealed *anti*-aminopalladation as the major pathway.[47] Interestingly, this study also showed that the nature of the aminopalladation is highly dependent on the counterion. A switch from a 91:9 in favor of the *anti*-addition mechanism in the presence of TFA to 10:90 favoring the *syn* pathway when $Pd(OAc)_2$ was used as the catalyst precursor was observed. The counterion effect on the mechanism of this aza-Wacker reaction is not surprising, as extensive studies of the original Wacker oxidation of ethylene to give acetaldehyde also reported a change of oxypalladation pathway depending on the chloride concentration.[52] High concentrations of chloride ions have been shown to outcompete water for coordination to Pd, which disfavors a *syn* addition. Moreover, the concentration of chloride ions has also been shown to affect the mechanism of enantioselective Wacker-type reactions.[53]

Contrasting with the numerous reports of intramolecular Wacker and aza-Wacker transformations, the intermolecular variants of these reactions are scarce.[54-57] There are only

two reports regarding the addition of oxygen nucleophiles.[54,55] Both examples employ phenols as the oxygen source with an allylic trichloroacetimidate coupling partner (**21**) to yield

Figure 3. Enantioselective Wacker-type reactions



(a) Catalytic cycle for enantioselective Wacker-type reactions illustrating both *syn* and *anti* nucleopalladation mechanisms and the role of the oxidant. (b) Intramolecular Wacker cyclization of phenol **17** highlighting the *syn* nature of the oxypalladation step. (c) Intramolecular aza-Wacker cyclization of tosyl amine **19** depicting a mixture of *syn* and *anti* aminopalladation products favoring the *anti* aminopalladation pathway.

enantioenriched ethers (**23**, Figure 3a).[54] The desired β-elimination is facilitated by the presence of the trichloroacetimidate moiety, which serves as the leaving group to enable the formation of chiral ether **23** in good yields and with excellent enantioselectivity.

The only two examples of enantioselective intermolecular aza-Wacker reactions have been recently reported by the Sigman group. N–alkylation of Indoles via an Intermolecular Aza-Wacker-Type Reaction.[56,57] Carbamates have been added to allylic alcohols to afford β-amino aldehydes in moderate yields with moderate to good enantioselectivity, albeit with the requirement of high ligand loadings due to the poor stability of the Pd-PyrOx complex under the reaction conditions.[57] This reaction is the only example of an intermolecular Wacker-type reaction that enables the formation of fully substituted, enantioenriched chiral centers. A Markovnikov *syn*-aminopalladation to trisubstituted olefins was shown to afford otherwise synthetically elusive α-tertiary amines (**26**). Additionally, a regioselective *N*-alkylation of indole derivatives was achieved under similar conditions.[56] The heterocycles were successfully coupled to allylic and homoallylic alcohols yielding remotely substituted aldehydes.

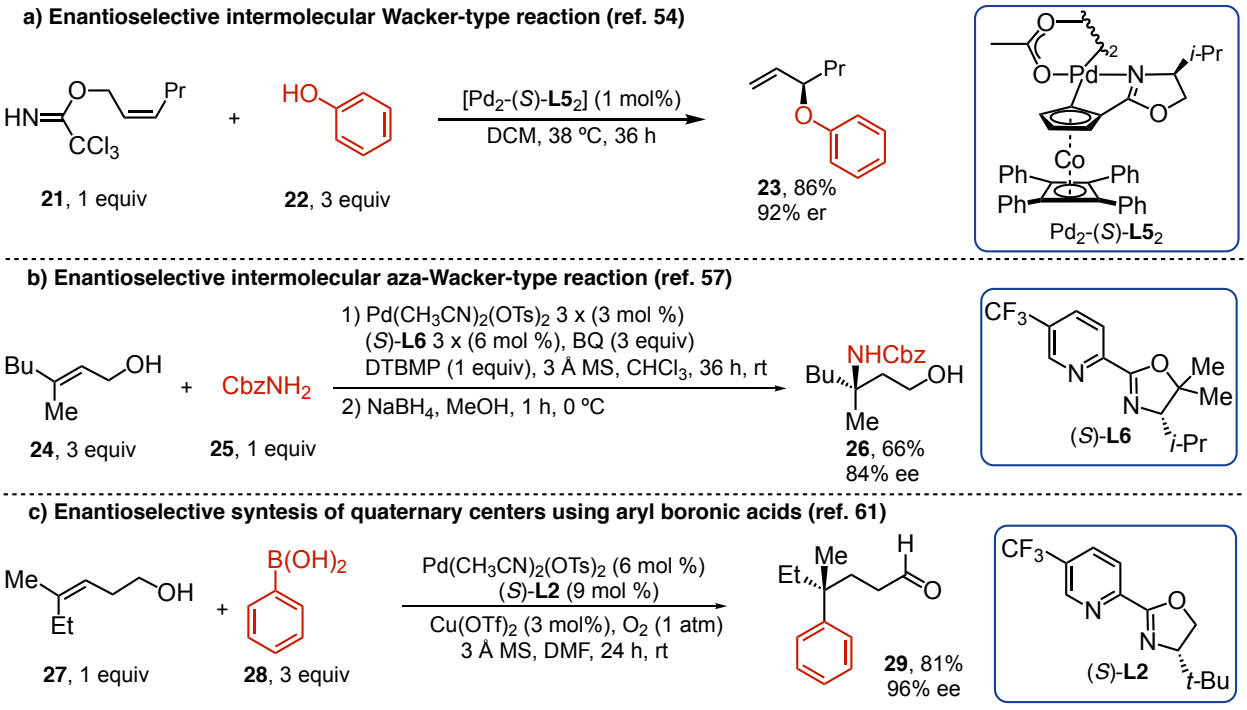
Alternative Pd(0)/(II)-catalyzed strategies for the formation of enantioenriched C−heteroatom bonds are also known. Aza-Heck reactions where oxidative addition into an O−N bond of an oxime ester generates a Pd–N species that can undergo migratory insertion with a π-system also allows for the synthesis of chiral amines.[58] However, the enantioselective variants of this reaction are limited to intramolecular cyclizations.[59] Additionally, an attractive alternative for the formation of enantioenriched alcohols is Pd-mediated alkene hydrosilylation. The oxidative addition of Pd(0) complexes into the Si−H bond of trichlorosilane, followed by migratory insertion with an olefin has been reported to forge a new C−Si bond in high yields and enantioselectivity. These compounds can be further functionalized by cross-coupling, as well as readily oxidized to render chiral alcohols.[60]

Pd(II) catalysis beyond nucleopalladation

The use of Pd(II) catalysis to mediate asymmetric additions of alkenes, alkynes and aryl groups to olefins has also been explored. Analogous Pd−alkyl intermediates to those obtained via oxidative addition (**B**, Figure 1) can be generated via transmetalation to a Pd(II) complex from another organometallic species. Aryl boronic acids are the most commonly used transmetalating agents

to generate Pd-aryl complexes, providing a complementary strategy to oxidative addition into aryl halides. As shown in Figure 4c, this strategy was used for the construction of quaternary centers with excellent levels of enantiomeric excess using trisubstituted olefins.[61] In a similar manner to the *chain-walking* process described in Figure 2d, but under oxidative conditions, homoallylic alcohols and other alkenols with varied methylene units separating the olefin and the alcohol were employed to render remotely functionalized aldehydes as final products. Additionally, it was shown that the Pd catalyst could *walk through* a preexisting stereocenter without any erosion of chiral information, yielding the final product with >99:1 enantiomeric excess. Interestingly, the outcome is independent of the enantiomer of ligand used, indicating that the Pd complex does not dissociate from the alkene intermediates during the *chain-walking* process.

Figure 4. Enantioselective intermolecular Wacker-type reactions and use of boronic acids

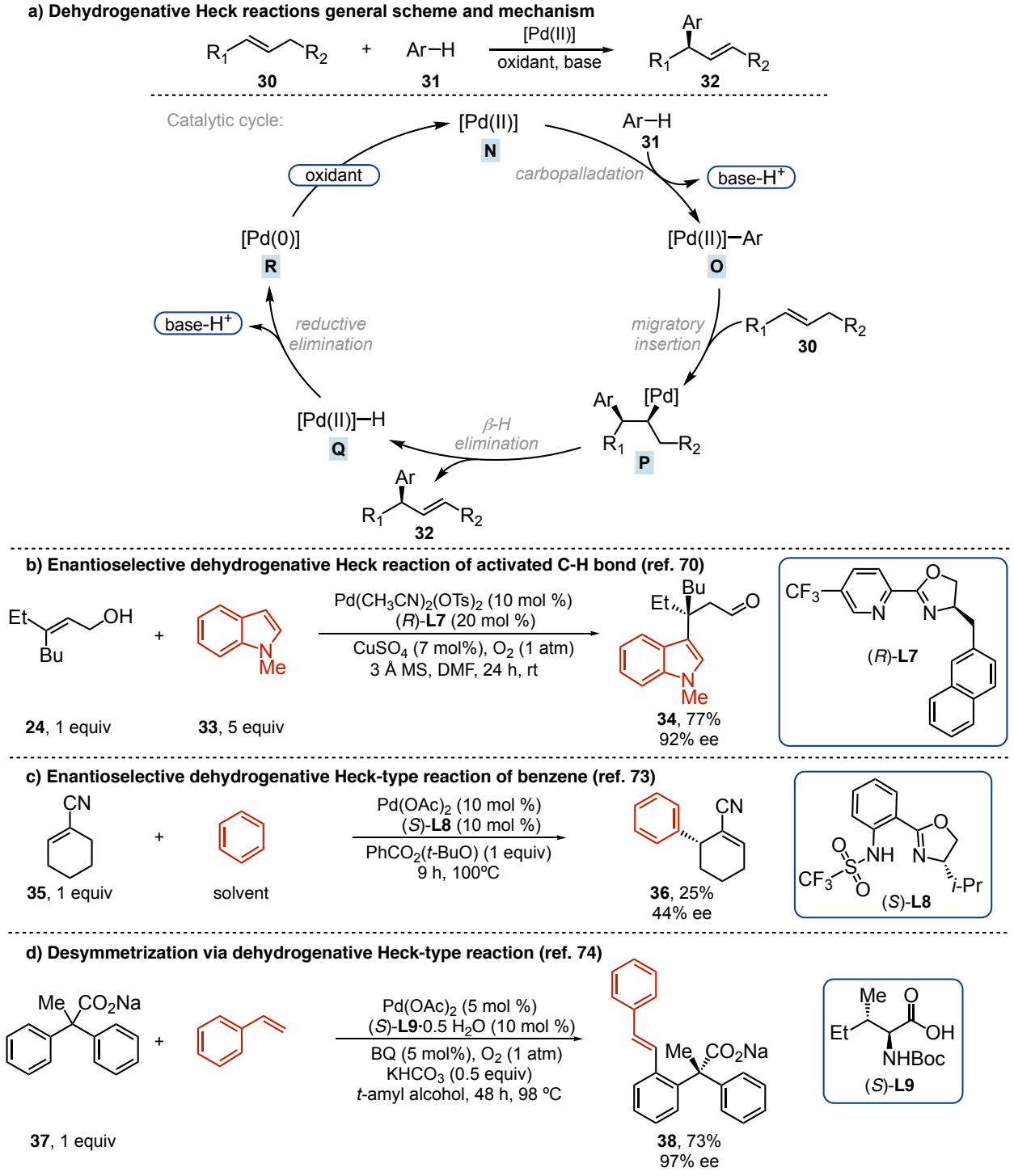


(A) First example of enantioselective intermolecular Wacker: addition of phenol to allylic trichloroacetimidates (**21**). (B) Addition of benzyl carbamate (**25**) to trisubstituted alkenol **24** to yield enantioenriched α-tertiary amine **26**. (C) Enantioselective formation of aldehyde **29** bearing a quaternary stereocenter via arylation of homoallylic alcohol **27**.

The development of *chain-waking* processes relies on the thermodynamic stability of the final product, usually refer to as the "thermodynamic sink" for the reaction. The oxidation of alcohols to aldehydes and ketones is the most commonly used strategy for Heck redox-relay processes. However, other thermodynamic driving forces like the formation of α,β-unsaturated carbonyl groups or other Michael acceptors[62,63], styrene derivatives [64], or cyclopropane ring openings[65,66] have been reported.[37] Recently, the Sigman group has reported the use of homoallylic phthalimides and other electron-poor amine protecting groups in an interrupted Heck redox-relay process. These substrates undergo an enantioselective Heck reaction analogous to that depicted in Figure 4c, but instead of the expected ene amide products the chain walking process is interrupted and allylic phthalimides are obtained. DFT calculations, together with isotopic labeling studies, showed that the observed selectivity is due to the instability of the Pd-hydride intermediate that would yield the ene amide.[67,68]

Pd(II) complexes can also promote dehydrogenative Heck reactions where a C−H bond of the substrate is functionalized. This approach circumvents the necessity of using coupling partners bearing a leaving group or an organometallic species, thereby reducing the amount of waste generated. Together with the unsaturated product **32**, two protons and two electrons are generated in these processes. As depicted in Figure 5, a base is required to control the pH of the mixture, and a stoichiometric oxidant is required to regenerate the Pd(II) catalyst (**N**) after each turnover.[69] Few examples of enantioselective dehydrogenative Heck reactions have been reported. In 2013, it was shown that *N*-methyl indoles (**33**) could be successfully alkylated at the nucleophilic C-3 position to afford pharmaceutically relevant compounds.[70] Trisubstituted allylic and homoallylic alcohols were coupled to the heterocycle to generate quaternary centers at the β- and γ-positions from an aldehyde, which can serve as a synthetic handle for further functionalization. Mechanistic studies suggest that C−C bond formation proceeds via a *syn*-migratory insertion process and that C−H bond cleavage is likely to proceed via an electrophilic aromatic substitution mechanism. Intramolecular variants of this reaction where a C-2 alkylation was afforded have also been reported, although the use of C-3 substituted indoles was required to achieve C-2 attack in these examples.[71,72]

Figure 5. Oxidative Heck-type reactions



(A) Catalytic cycle for dehydrogenative Heck reactions highlighting the role of base and oxidant. (B) C3-alkylation of *N*-methyl indole (**33**) to yield aldehyde **34** bearing a quaternary stereocenter in the β-position. (C) First example of enantioselective intermolecular dehydrogenative Heck: alkylation of benzene with moderate enantioselectivity. (D) Desymmetrization of diphenylacetate **37** via C-H activation at the *ortho* position.

The functionalization of unactivated C−H bonds has also been accomplished utilizing this strategy. An early example by Terada shows the alkylation of benzene in low yield and ee (Figure 5c).[73] The desymmetrization of diphenylacetic acids (**37**) using a carboxylate as a directing group is another rare example of an asymmetric dehydrogenative Heck reaction targeting unactivated C−H bonds (Figure 5d).[74] The transformation utilizes a boc-protected amino acid (**L9**) as a chiral ligand and promotes the formation of the final products in high enantiomeric excess and yields in most cases. Both of these reactions likely undergo C−H cleavage via a concerted metalation deprotonation (CMD) mechanism, where an initial agostic interaction with the metal weakens the C−H bond and allows for subsequent deprotonation by a base.[75]

Holy grail of Heck chemistry: alkyl groups as coupling partners

The main limitation of enantioselective Heck-type reactions arises from the propensity of Pd to promote β-hydrogen elimination. The development of Heck-type alkene functionalizations has been possible due to this Pd characteristic, but it is also the main obstacle that hampers the use of alkyl groups with hydrogens in the β-position as coupling partners. In other to successfully develop a Heck-type reaction that couples alkyl groups, the Pd-alkyl complex generated prior to migratory insertion (analogous to **B**) should be stable enough to favor olefin migratory insertion over β-hydrogen elimination. Resultingly, this would require to accelerate an intermolecular, and typically rate-limiting, step over an intramolecular process.

The first enantioselective Heck-type reaction was reported in 2012 by Zhou and coworkers where benzylic electrophiles, lacking β-hydrogens, were used.[76] A limited number of reports have described Pd-catalyzed intermolecular processes to enable the formation of either racemic or achiral products coupling of alkyl groups bearing hydrogens β-position to alkenes.[77] These reports have tackled the previously described problem by bypassing the formation of a Pd-alkyl complex. Alternatively, these reactions are believed to proceed via formation of carbon-centered radicals that are subsequently trapped by the olefin.[78,79]

Concluding Remarks and Future Perspectives

A primary limitation hampering the further development of Pd-catalyzed alkene functionalization, especially carbon-heteroatom couplings, is the stability of the known ligands to the required oxidative conditions. As a result, these reactions require high ligand loadings and

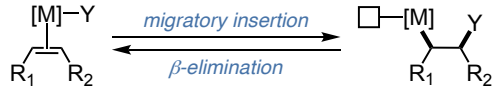
typically require the use of stoichiometric oxidants or cocatalysts that aide Pd re-oxidation under aerobic conditions. The ideal solution would be the development of robust systems that allow for reduced Pd loadings, which may be generally enabled by the use of greener oxidants such as molecular oxygen in the absence of a cocatalyst (see Outstanding Questions). One of the most prominent contributors to this line of research, albeit in the context of Pd-mediated oxidation reactions, is the Stahl group.[80-83]

From a broader perspective, current efforts for the development of alkene functionalization reactions have focused on the use of Earth-abundant transition metals, with Ni catalysts becoming much more prominent in the recent literature.[84-86] Interests in exploring this new area is motivated not only by the low cost of Earth abundant metals, but also by the potential for orthogonal reactivity that they may promote. Indeed, a new range of mechanistic opportunities is enabled by the single-electron reactivity of first-row transition metals rather than the two-electron steps characteristic of second- and third-period metals.

Box 1: Migratory insertion and β-elimination (400 words max per box current 296)

Migratory insertion is a fundamental organometallic step in which a metal (**M**) and a ligand (**Y**) are added in a *syn*-fashion to a π-system that is coordinated to the metal (Figure I). As a result of this reaction, the M–Y bond is cleaved and new metal–C and Y–C σ-bonds are formed. Upon migratory insertion, there is no change in the oxidation state of the metal and an empty coordination site is generated. The reverse reaction, β-elimination, can also be facilitated by transition metals. A *syn*-coplanar conformation between the metal and Y, a group in the β position, is required for β-elimination, which affords the coordinated π-system together with a new M–Y bond. β-Eliminations are known for a wide variety of groups, but β-hydrogen elimination is the most common due to the reduced steric demand and lower directionality of the C–H bond with respect to other groups. During this process, the oxidation state of the metal is not altered and an empty coordination site is required. In most cases, an interaction between the metal and the C–Y bond weakens the bond and precedes the elimination (for β-hydrogen elimination this is known as an agostic interaction).

Figure I. Migratory insertion and β-elimination



Palladium (II) complexes are known to promote these two steps with high efficiency. Migratory insertion is facilitated by the high π-Lewis acidity of Pd(II). This step is often the turnover-limiting and stereo-determining step of the reactions discussed herein, and it is generally thermodynamically favored. On the other hand, β-hydrogen elimination is typically thermodynamically less favorable. Control of β-hydrogen elimination to yield the desired product is often challenging due to fast kinetics. Strategies developed to favor the desired β-hydrogen elimination are discussed in this review, including those utilizing conformational constraints or biasing of the substrates and catalyst.

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