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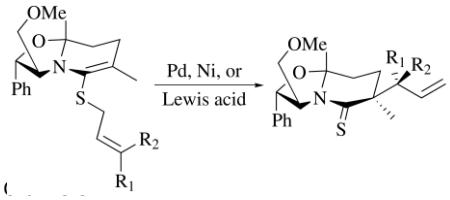


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# Recent Advances in the Generation and Functionalization of C(alkenyl)–Pd Species for Synthesis of Polysubstituted Alkenes

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted

Available online

*Keywords:*
Keyword_1
Keyword_2
Keyword_3
Keyword_4
Keyword_5

ABSTRACT

The synthesis of polysubstituted alkenes represents a formidable challenge in organic synthesis. Over the years, many advances have been made for this purpose, yet challenges persist in terms of selectivity, scope, and efficiency. Palladium-catalyzed methods for alkene synthesis are attractive within this field given that cross-coupling is particularly impactful in the construction of organic molecules due to palladium's ability to facilitate modular carbon–carbon and carbon–heteroatom bond formation. To employ palladium catalysis for alkene synthesis, the generation and subsequent functionalization of C(alkenyl)–Pd intermediates are key steps. In this review, we highlight research advances since 2000 in the area of polysubstituted alkene syntheses involving C(alkenyl)–Pd species.

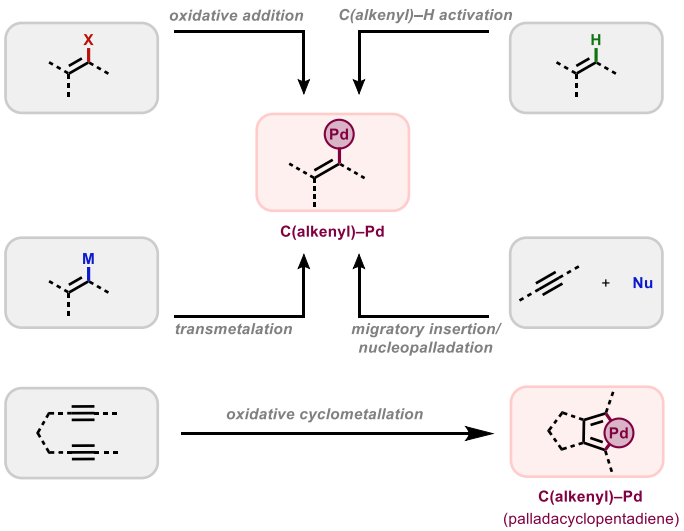


## 1. Introduction

Carbon–carbon double bonds play a unique and indispensable role in organic chemistry. Alkenes are constituent components of both petrochemical and biorenewable feedstocks; as chemical inputs they grant access to plethora of different product motifs. Additionally, there are numerous alkene-containing natural products that are attractive targets for total synthesis. Beyond serving as starting and ending points in multi-step organic synthesis, alkenes are common intermediates *en route* to structurally complex small molecules. Thus, the synthesis and selective functionalization of alkenes represent major themes in organic chemistry.

Alkenes can contain up to four substituents. The presence of two or more substituents gives rise to regio- and stereoisomerism. Though these forms of isomerism add structural and functional diversity, they also introduce new selectivity control challenges that must be addressed through the development of useful synthetic approaches to polysubstituted alkenes.

Methods for alkene synthesis have been actively pursued for more than a century, and three major classes of transformations have emerged: elimination reactions from suitably functionalized alkyl fragments (such as Burgess dehydration[1] and Hofmann elimination[2]), ylide olefinations (such as Wittig and Horner–Wadsworth–Emmons reactions[3]), and metal-mediated reactions. While useful in their own right, elimination reactions often present reactivity and selectivity issues when applied to syntheses of polysubstituted alkenes due to complications in deprotonation step on a branched carbon skeleton. Compared to elimination reactions, ylide olefinations have advantages in the synthesis of polysubstituted alkenes, both in terms of elevated reactivity in congested settings and defined regioselectivity, but stereoselectivity control in ylide olefination remain a complex issue, particularly in the case of tri- and tetrasubstituted alkenes.




**Scheme 1**. Overview of the elementary steps that lead to C(alkenyl)–Pd intermediates.

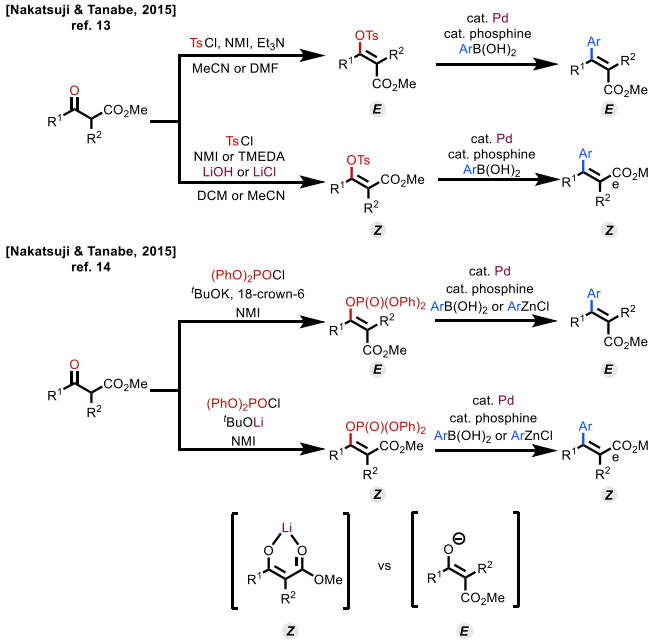
Beyond elimination and ylide olefination, transition metal catalysis has been widely applied in alkene synthesis. Olefin metathesis,[4–5] allylic substitution,[6] and alkyne functionalizations[7–10] are among the most common reactions in this category. Although these approaches are useful in many contexts, applications in polysubstituted alkene synthesis remain underdeveloped. In contrast, palladium-catalyzed cross-coupling reactions are often more effective for preparing polysubstituted alkenes. Palladium-catalyzed cross-coupling requires a pre-functionalized alkenyl coupling partner that reacts with the metal to generate a C(alkenyl)–Pd species, which then engages a second coupling partner to furnish the substituted alkene product. The regioselectivity of the reaction is programmed by the site of pre-functionalization on the alkenyl coupling partner. Moreover, β-

hydride elimination and *E*/*Z*-isomerization of the C(alkenyl)–Pd species are usually less kinetically favored compared to the productive pathway. Thus, high regio- and *E*/*Z*-selectivity selectivity are typically observed.

Given the advantages of palladium-catalysis in polysubstituted alkene synthesis, a number of complementary approaches have been explored to access C(alkenyl)–Pd species. In this review, we summarize progress in this field over the past two decades. Given the breadth of chemistry covered, this review in not intended to be comprehensive. Rather, we discuss only a representative collection of papers that showcase recent breakthroughs and highlight outstanding challenges. This review is organized thematically, with each section covering a different elementary step that leads to C(alkenyl)–Pd species, including oxidative addition, oxidative cyclometallation, transmetalation, migratory insertion, nucleopalladation, and C–H activation. (**Scheme 1**). State-of-the-art strategies to functionalize the resultant C(alkenyl)–Pd species to access polysubstituted alkenes are also discussed.

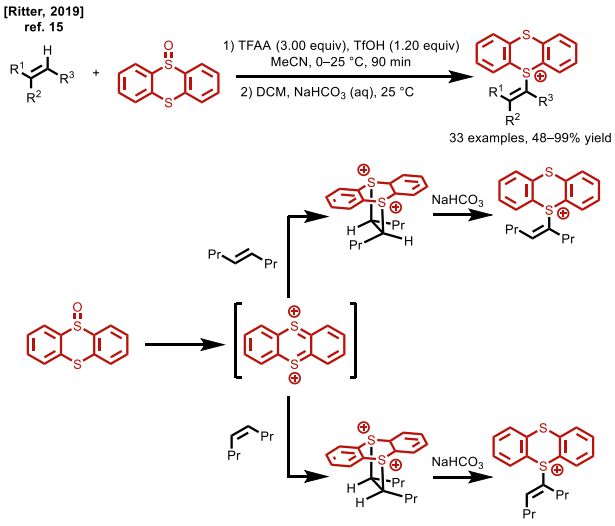
## 2. C(alkenyl)–Pd species generated from the oxidative addition of alkenyl electrophiles

Although alkenyl iodides, bromides, and to a lesser extent chlorides, are effective electrophiles for oxidative addition to Pd(0), alkenyl tosylates, triflates, and phosphates are often used because of their simpler syntheses.[11] These electrophiles are prepared from the corresponding ketone *via* enolate formation and *O*-selective trapping with sulfonylating or phosphonylating reagents. Thus, the key challenge in preparing the corresponding electrophiles is controlling the regio- and stereoselectivity of enolate formation. In an effort to address the selectivity challenge of enolate formation, bases and additives have been evaluated for their ability to control selectivity.[12] For instance, Nakatsuji and Tanabe reported approaches to generate tri- and tetrasubstituted alkenyl phosphates and tosylates in a stereodivergent manner (**Scheme 2**).[13–14] The authors adopted the established *N*-methylimidazole (NMI)-promoted enolate formation strategy to functionalize β-ketoesters, achieving >20:1 *E*/*Z*-selectivity through appropriate selection of the basic additive. Organic bases such as triethylamine and DBU generated the *E*-isomer, whereas coordinating lithium bases such as LiOH or LiCl resulted in the *Z*-isomer.



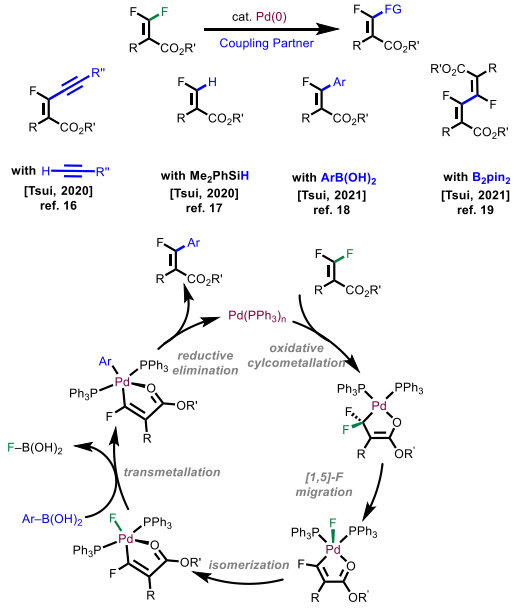

**Scheme 2**. Stereodivergent syntheses of alkenyl tosylate and phosphonate electrophiles and applications in cross-coupling reactions

Though most studies have focused on alkenyl halides, triflates, tosylates, or phosphates as the electrophiles in oxidative addition, other categories of coupling partners have emerged that offer advantages in some contexts. In 2019, the Ritter group reported a regio- and stereoselective thianthrenation of unactive alkenes that grants access to alkenyl electrophiles (**Scheme 3**).[15] In the event, thianthrene-*S*-oxide is activated by TFAA to form the thianthrenium dication. The thianthreniumm dication then undergoes [4+2] cycloaddition with the alkene. Treatment of the resulting [4+2] adduct with base triggers elimination, furnishing the corresponding alkenyl sulfonium salt as the product. The authors demonstrated that this electrophile could participate in palladium-catalyzed Mizoroki–Heck, Sonogashira, and Negishi couplings.



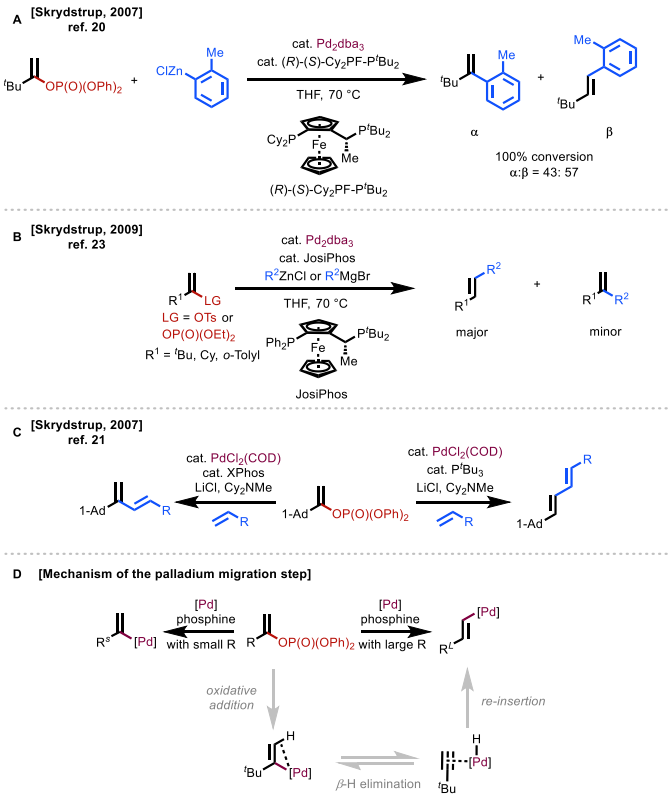

**Scheme 3**. Generation of alkenyl thianthrenium

Alkenyl fluorides represent another special class of precursors for oxidative addition, offering a unique opportunity to transform organofluoride compounds. The Tsui group reported a series of C(alkenyl)–F functionalizations of *gem*-difluoroalkenes, including alkynylation,[16] hydrodefluorination,[17] arylation,[18] and dimerization (*via* a cascade borylation/alkenylation sequence)[19] **(Scheme 4)**. Based on their experimental and computational studies on α-benzyl substituted *gem*-difluoroacrylate,[18] a plausible mechanism is proposed for the formation of a C(alkenyl)–Pd species: the reaction is initiated by a formal [4+1] oxidative cyclometallation to produce a significantly weakened C–F bond compared to the C(alkenyl)–F bond in *gem*-difluoroalkenes. Subsequent turnover-limiting 1,5-fluoride migration leads to the generation of the C(alkenyl)–Pd intermediate. After isomerization, the *trans*-bistriphenylphosphine alkenylpalladium(II) intermediate is generated. In a series of stoichiometric experiments, the authors were able to isolate the alkenylpalladium(II) oxidative addition complex and convert it to the corresponding product. In the same study, the authors also conducted kinetic studies on α-aryl substituted *gem*-difluoroacrylates. Substrates with electron-withdrawing *para*-substituents showed significantly lower reaction rates. This observation runs counter to the proposed mechanism in which [4+1] oxidative cyclometallation is the turnover-limiting step, indicating that an alternative mechanism may be at play.



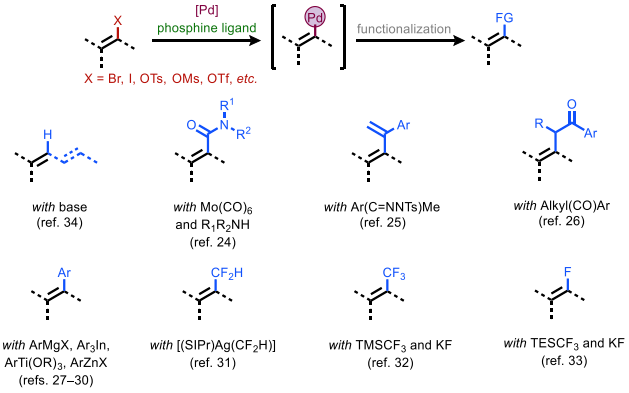
**Scheme 4**. C(alkenyl)–F functionalization of *gem*-difluoroalkenes and the mechanism of C(alkenyl)–F arylation

In traditional alkenyl cross-coupling reactions, the C(alkenyl)–Pd bond is generated at the same position as the C(alkenyl)–X bond. However, when sterically bulky phosphine ligands, such as P$^t$Bu$_3$, dppf, or diakylbiaryl phosphines (*i.e.* Buchwald ligands), are employed, structurally isomeric alkenyl palladium species can be generated through reversible β-H elimination/reinsertion. The specific conditions, however, need to be finely tuned for specific pairings of substrates and nucleophiles. In 2007, the Skrydstrup group reported a Negishi coupling reaction between 1,1-disubstituted alkenyl phosphates and aryl- or alkylzinc reagents.[20] Dppf was found to be the optimal ligand for this reaction. During the course of their study, the authors discovered that when a sterically bulky group was present on the alkenyl electrophile, the corresponding 1,2-disubstituted alkene product was generated instead of the expected 1,1-disubstituted alkene. To explain this phenomenon, the authors proposed a mechanism involving the 1,2-migration of palladium. Isotope labeling experiments revealed that the 1,2-migration pathway proceeds *via* β-hydride elimination from the 1,1-disubstituted C(alkenyl)–Pd intermediate. Re-insertion of the resulting Pd–H species to the corresponding alkyne results in the 1,2-disubstituted C(alkenyl)–Pd intermediate (**Scheme 5D**).[21–22] The authors were able to tune the structure of the phosphine ligand to control regioselectivity. Specifically, they discovered that JosiPhos and analogs can promote the 1,2-migration in Negishi- or Kumada-type arylations.[23] Skrydstrup and co-workers also took advantage of this effect to achieve regiodivergent 1,3-diene synthesis in a Mizoroki–Heck coupling. While XPhos led to 1,1-selectivity, P$^t$Bu$_3$ afforded 1,2-selectivity.[21] In general, C(alkenyl)–Pd(L$_n$) species containing a bulky group at the C1-position and a sterically encumbered ligand were found to be unstable. The steric repulsion between the ligand and alkenyl substitution strengthens the agostic interactions between the palladium center and the C(alkenyl)–H bond at the C2-position. As a result, β-hydride elimination is facile and leads to a thermodynamically favored 1,2-migration (**Scheme 5**).

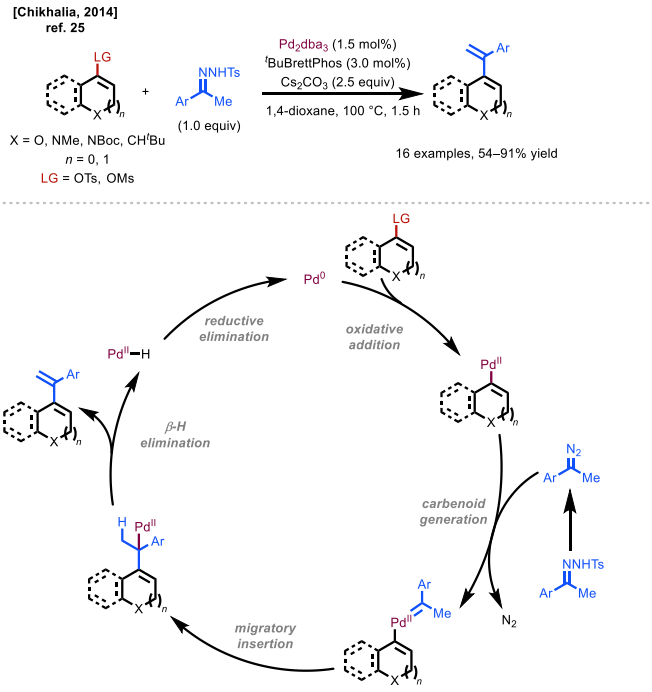



**Scheme 5**. Synthetic applications of the C(alkenyl)–Pd migration

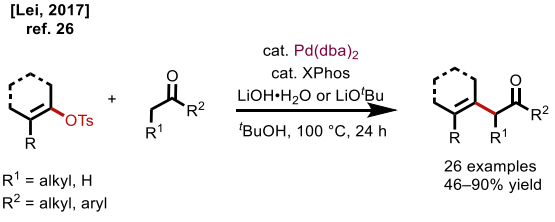
In parallel to the advances in the synthesis of alkenyl electrophiles and controlled isomerization of the resulting C(alkenyl)–Pd species, the utility of oxidative-addition-based approaches for the formation of C(alkenyl)–Pd bonds has been enhanced by the expansion of competent coupling partners (**Scheme 6**). Larhed and co-workers reported a catalytic three-component aminocarbonylation with Mo(CO)$_6$ as the CO source that proceeds *via* a C(alkenyl)–Pd intermediate.[24] CO coordination to the C(alkenyl)–Pd species followed by 1,1-migratory insertion generates an acylpalladium intermediate. This step is followed by nucleophilic attack of the amine to afford the corresponding acrylamide product. The Chikhalia group reported that a C(alkenyl)–Pd(BrettPhos) intermediate can react with a benzyl diazo compound to generate a palladium–carbenoid (**Scheme 7**). 1,1-Migratory insertion of the alkenyl moiety into the carbenoid then generates a new C–C bond. The catalytic cycle is closed by β-hydride elimination and reductive elimination to generate the 1,3-diene product.[25] The Lei group discovered that C(alkenyl)–Pd species react with lithium enolates that are formed *in situ* from alkyl aryl ketones in the presence of LiOH. This reaction affords β,γ-enone products in the presence of XPhos ligand (**Scheme 8**).[26] Notably the β,γ-enone product possesses acidic α-protons that make isomerization to the α,β-enone relatively facile. Nevertheless, this reaction affords the β,γ-enone products with high yield in preference to the potential α,β-enone byproducts.




**Scheme 6**. Summary of alkene syntheses initiated by the oxidative addition to alkenyl electrophiles

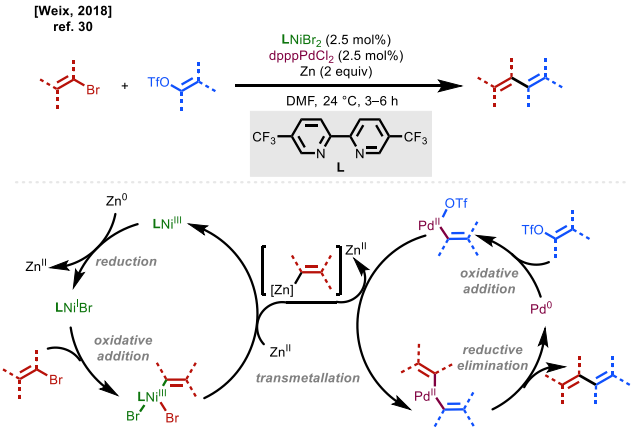



**Scheme 7**. 1,3-Diene synthesis *via* 1,1-migratory insertion of a palladium–carbenoid into a C(alkenyl)–Pd bond

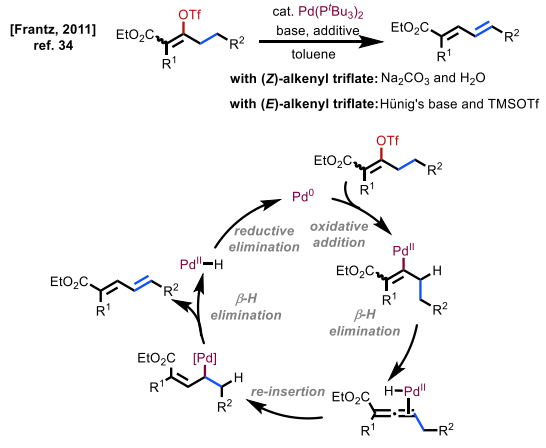


**Scheme 8** Pd(0)-catalyzed coupling between alkenyl tosylates and lithium enolates

Other C–C bond-forming reactions that couple C(alkenyl)–Pd species with aryl nucleophiles have also been investigated. The Skrydstrup group reported a method for the Kumada coupling of alkenyl phosphates that proceeds in the absence of a phosphine ligand.[27] One hypothesis for the fact that no ligand is needed is that palladium nanoparticles are generated *in situ* in the presence of the Grignard reagent, though additional studies are needed to rule out alternative explanations. In addition, the Wu group reported a similar ligand-free arylation with triarylindium coupling partners.[28] Several research groups have reported expanded scopes of organometallic nucleophiles in alkenyl couplings. In 2020, Kwong and colleagues reported a solvent- and base-free arylation using aryltitanium reagents.[29] In this manner, tri- and tetrasubstituted alkenes could be generated. Beyond reactions that couple a nucleophile and an electrophile, the Weix group reported a reductive coupling between alkenyl triflates and alkenyl bromides by Pd and Ni dual catalysis (**Scheme 9**).[30] Mechanistic studies showed that the reaction involves zinc-mediated transmetalation from Ni to Pd. The C–C bond-forming step is proposed to take place from the palladium center. In addition, C(alkenyl)–Pd intermediates can engage fluorine-containing coupling partners to furnish organofluorides. For instance, the Shen group reported difluoromethylation of a dppf-ligated C(alkenyl)–Pd species with a SIPr-stabilized $F_2HC$–Ag coupling partner.[31] Difluoromethylated alkenes with a variety of substitution patterns could thus be obtained in good to high yield. The Buchwald group reported fluorination and trifluoromethylation reactions of alkenyl electrophiles.[32–33] Interestingly, the combination of fluoride and the Ruppert–Prakash reagent or its analogs (*i.e.* $R_3SiCF_3$) was found to be necessary in the two transformations. In the trifluoromethylation system, the fluoride anion is necessary to activate the Ruppert–Prakash reagent for the *in situ* formation of $CF_3^-$. However, it was found that the Ruppert–Prakash reagent also improved regioselectivity in the fluorination reaction. In terms of the chemoselectivity, the identity of the phosphine ligand controlled whether fluoride or $CF_3^-$ was incorporated into the product.




**Scheme 9**. 1,3-Diene synthesis by Ni/Pd dual catalysis

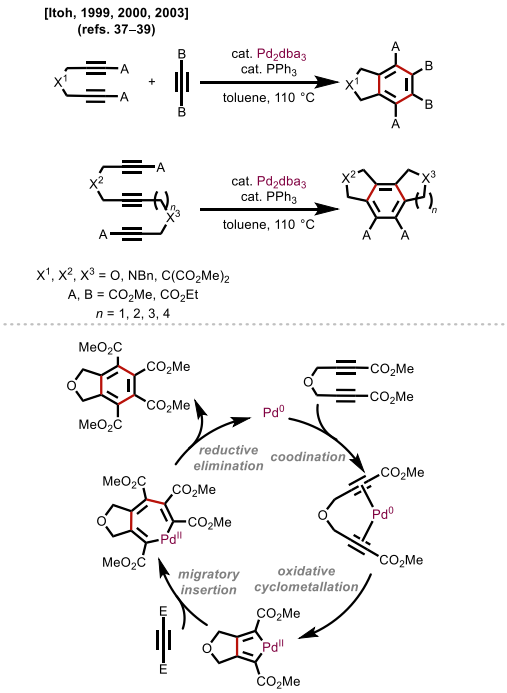



**Scheme 10**. 1,3-Diene synthesis *via* tandem elimination/isomerization from a C(alkenyl)–Pd intermediate.

In a related approach, it has been found that by combining an oxidative addition step with the subsequential allylic β-hydride elimination and reinsertion steps, 1,3-dienes can be conveniently synthesized (**Scheme 10**).[34] In 2011, Frantz and co-workers treated an α,β-unsaturated enol triflate with $Pd(P^tBu_3)_2$ to generate the C(alkenyl)–Pd intermediate. They discovered that the intermediate undergoes β-hydride elimination in the presence of a Lewis base, affording the corresponding allene and a Pd–H intermediate. Hydride re-insertion forms a C(allyl)–Pd species, which undergoes β-hydride elimination to generated the 1,3-diene products.

### 3. C(alkenyl)–Pd species generated from oxidative cyclometallation

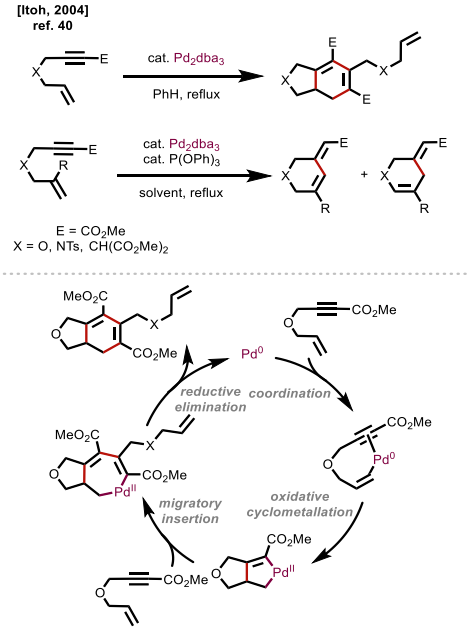
Oxidative cyclometallation most commonly involves a formal [2+2+1] cycloaddition reaction between a low-valent transition metal and two π-systems (*e.g.*, alkene and/or alkyne) to generate a five-membered metallacycle. In this process, three new σ bonds are formed, including one new C–C bond and two new C–M bonds, and the oxidation state of the transition metal increases from $M^n$ to $M^{n+2}$.[35–36] When Pd(0) reacts with one or more alkyne component in oxidative cyclometallation, it leads to formation of a palladacyclopentene or palladacyclopentadiene intermediate, which can react in downstream steps to furnish cyclic alkene-containing products. Although this strategy offers straightforward routes to structurally complex carbo- and heterocyclic structures, mixtures of products often arise from such reactions due to the difficulty of achieving selective incorporation of each of the π-components at the appropriate juncture along the reaction coordinate. Overcoming this challenge is critical for unlocking the full synthetic potential of this mode of reactivity.




**Scheme 11**. Substituted benzene syntheses *via* palladium-catalyzed [2+2+2] cycloaddition of diynes

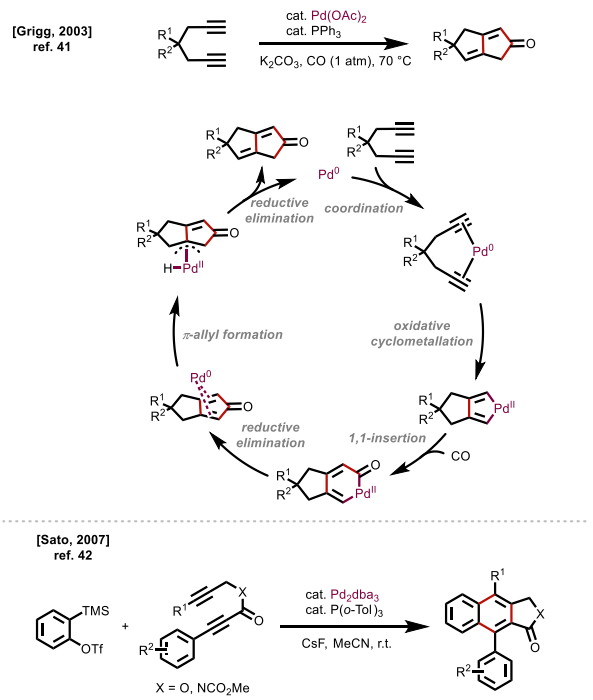
Traditionally, dimethyl acetylenedicarboxylate (DMAD) inserts rapidly into C–Pd bonds, and indeed often functions as an effective dienophile in reactions with palladacyclopentadiene species. Nevertheless, when coupling of DMAD and electron-neutral alkynes is attempted, DMAD outcompetes the electron-neutral alkynes in the reaction, resulting in homotrimerization. The Itoh group addressed this challenge by engineering the alkyne precursor as a non-conjugated diyne substrate, dimethyl nona-2,7-diyn-1,9-dioate, which promotes the selectivity in the oxidative cyclometallation step (**Scheme 11**).[37] The rationale for this design is that dimethyl nona-2,7-diyn-1,9-dioate binds more strongly to Pd(0), which entropically favors the formation of the bicyclic intermediate. The palladacyclopentadiene intermediate is then trapped by DMAD, affording a 5-6 bicyclic benzene. It is noteworthy that this reaction system only allows the formation of 5-6

bicycles, while attempts to form the analogous 6-6 bicyclic product by introducing one more methylene spacer to the diyne substrate were unsuccessful.[37] In later studies, a series of palladacyclopentadiene complexes bearing appropriate ancillary ligands were prepared via oxidative cyclometallation.[38–39]




**Scheme 12**. Cyclohexene/Cyclohexadiene syntheses *via* palladium-catalyzed [2+2+2] cycloaddition of enynes

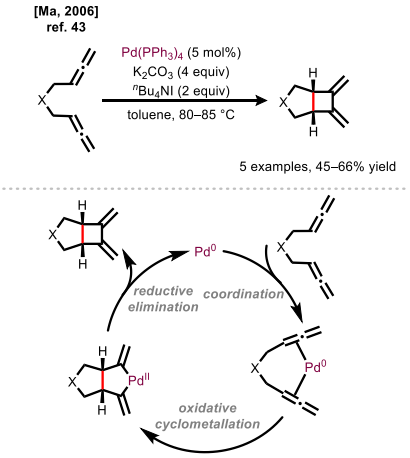
Oxidative cyclopalladation was later performed with an enyne precursor, resulting in a palladacyclopentene intermediate (**Scheme 12**).[40] Instead of being trapped with DMAD, this intermediate reacted with the alkyne moiety of another molecule of the enyne, resulting in the formation of an enyne dimerization product. In contrast, substituted alkenes did not dimerize. Alternatively, β-hydride elimination was found to be the productive pathway for palladacyclopentenes that contain α-substituents.




**Scheme 13**. Annulation reactions involving reactions of palladacyclopentadiene with benzyne or CO

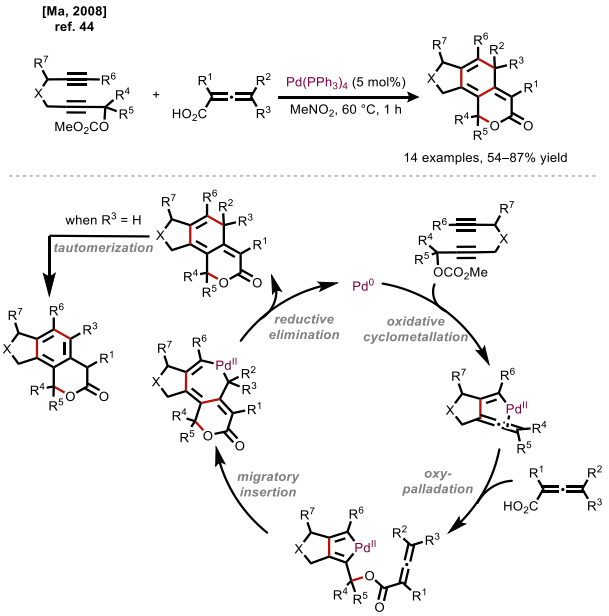
Beyond DMAD, palladacyclopentadiene intermediates have been found to react with other electrophiles. Grigg and co-authors described a [2+2+1] cycloaddition by intercepting a palladacyclopentadiene intermediate with carbon monoxide **(Scheme 13)**.[41] Mechanistically, CO reacts *via* coordination to the metal center followed by 1,1-insertion and reductive elimination to furnish the corresponding cyclopentadienone. Lastly, isomerization of one of the alkenes take place to give the more stable product. Diynes composed of terminal alkynes were used in this case. Sato and co-workers also successfully trapped a catalytically generated palladacyclopentadiene intermediate with benzyne.[42] This method allows for the synthesis of substituted naphthalenes.

In 2006, the Ma group described a formal [2+2] cycloaddition of bisallenes (**Scheme 14**).[43] Oxidative cyclometallation with the bisallene substrate affords an α,α-dimethylidene-substituted palladacyclopentane, a structurally unique C(alkenyl)–Pd intermediate. Subsequent reductive elimination furnishes the 5-4 bicyclic product.




**Scheme 14**. Palladium-catalyzed formal [2+2] cycloaddition of bisallenes

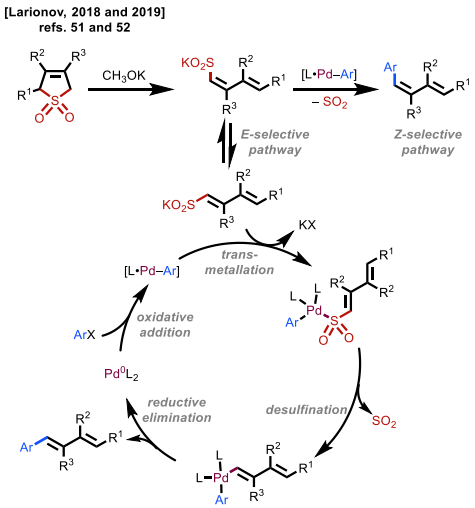
A special case within this category of reactions was discovered by installing a leaving group at one of the propargyl positions of a diyne substrate (**Scheme 15**).[44] The intermediate generated from the reaction between this substrate and Pd(0) is an C(alkenyl)–Pd species tethered to an allene rather than a classical palladacyclopentadiene. This is due to the fact that the propargyl carbonate moiety of the substrate is transformed into an allene *via* β-O elimination. The Pd(II)-bound allene moiety is then attacked by a nucleophilic allenyl carboxylic acid in the solution. This oxypalladation step transforms the C(alkenyl)–Pd intermediate into a palladacyclopentadiene. In the following steps, the palladacyclopentadiene undergoes migratory insertion to the allene coupling partner followed by the reductive elimination. This cascade annulation process furnishes a 5-6-6 tricyclic structure.



**Scheme 15**. Generation of a π-allene-coordinated C(alkenyl)–Pd intermediate by oxidative cyclometallation and its reaction with an allenyl acid

### 4. C(alkenyl)–Pd species generated from the alkenyl transfer

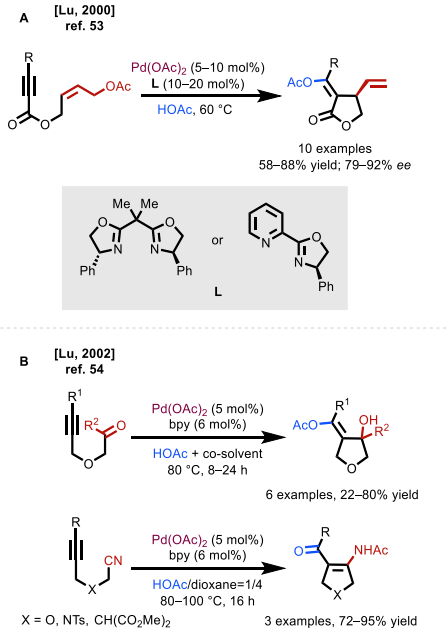
In classical cross-coupling reactions, an organometallic reagent serves as the nucleophilic coupling partner reacts *via* transmetalation, which results in transfer of the carbogenic ligand from a more electropositive metal to a less electropositive metal. Common organometallic reagents include those of boron,[45–46] zinc,[48] tin,[50] silicon,[47] and magnesium.[49] Such alkenyl organometallic reagents have been widely applied in palladium-catalyzed alkenyl cross-coupling reactions. Here we highlight a recent discovery of alkenyl group transfer with alkenyl sulfinates. The Larionov group reported that sulfolenes reacted with a strong base to afford dienyl sulfinates *via* deprotonation and subsequent ring opening (**Scheme 16**).[51–52] Dienyl sulfinates are competent dienyl nucleophiles that can undergo formal transmetalation to Pd(II) with the concomitant loss of $SO_2$. Larionov and co-workers demonstrated that aryl chlorides, bromides, iodides, and triflates were effective electrophiles that could couple with the dienyl group generated *via* sulfolene ring opening, affording aryl-substituted dienes. The reaction has good regio- and stereoselectivity. However, the preferred stereochemical configuration of the product is affected by the substitution pattern of the sulfolene.



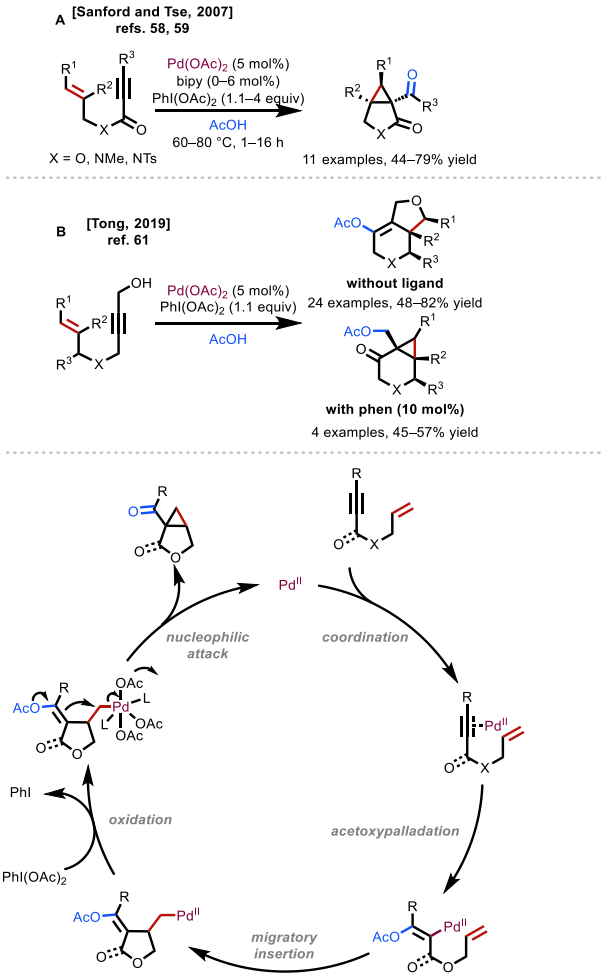

**Scheme 16**. Catalytic generation and functionalization of dienylpalladium species from sulfolene

### 5. C(alkenyl)–Pd species generated from migratory insertion and nucleopalladation

Migratory insertion and nucleometallation are both organometallic 1,2-addition reactions in which a nucleophile adds to an alkene or alkyne to form a new C–M bond. This process can proceed *via* either an outer-sphere or inner-sphere pathway depending on the nature of the nucleophile and the reaction conditions. The outer-sphere pathway occurs when the nucleophile does not bind to the metal center and instead directly attacks the backside of the π-bond, which is activated *via* the π-Lewis acidity of the metal, resulting in the simultaneous formation of C(alkenyl)–nucleophile and C(alkenyl)–M σ-bonds. The outer-sphere pathway is *anti*-stereospecific, though in some cases inner- and outer-sphere additions are competitive processes. In contrast, in the inner-sphere pathway the nucleophile is coordinated as a ligand to the metal center prior to engaging the alkyne. In this scenario, the nucleophile adds to the π-bond by migrating from the metal center. Thus, the inner-sphere pathway is *syn*-stereospecific. In palladium-catalyzed alkyne addition reactions, these two elementary steps are both viable pathways to generate C(alkenyl)–Pd species. The prominent challenge associated with this strategy is regioselectivity control, especially in the cases in which asymmetric disubstituted alkynes are employed. Here, there are two potential regiosomeric transition states for the π-bond addition process, which must be energetically differentiated to avoid the formation of intractable regioisomeric mixtures. Palladium-catalyzed alkyne addition reactions have been widely applied in organic synthesis, and many papers have been published in this area. As discussed above, the purpose of this review is not to cover this topic in a comprehensive manner. Rather, we highlight notable progress that has been made to integrate new classes of nucleophiles/migrating groups and trapping agents for the resultant C(alkenyl)–Pd species, and we discuss examples with unique mechanistic features or those that exemplify key strategies in selectivity control.



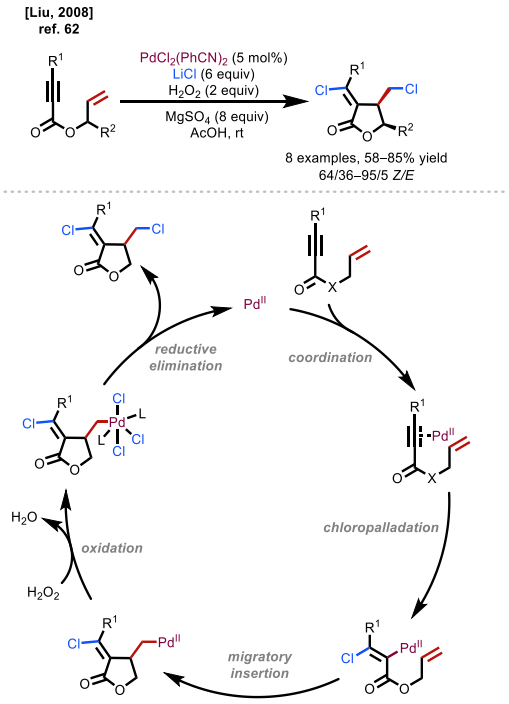

**Scheme 17**. Selected transformations initiated by acetoxypalladation of alkynes




**Scheme 18**. Cyclopropane formation from enynes *via* Pd(II)/Pd(IV) catalysis

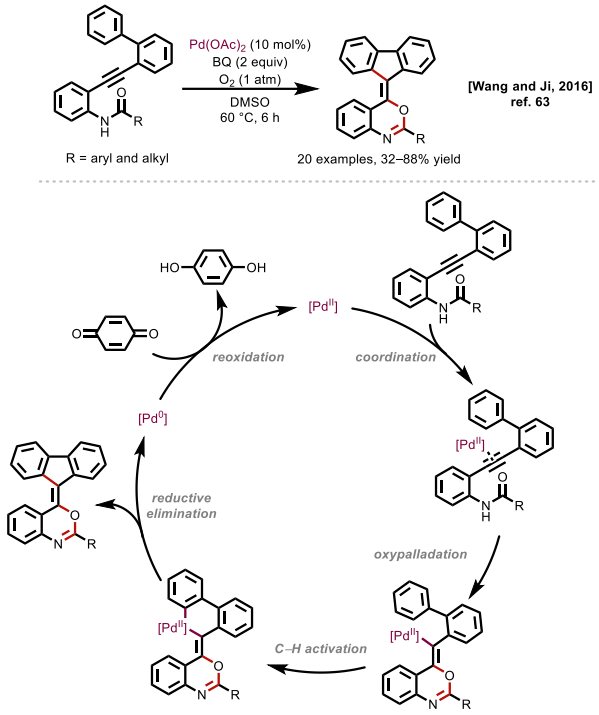
Halides and carboxylates are representative nucleophiles that generally engage in outer-sphere nucleopalladation. Since the mid-1990s, Lu has pioneered this mode of reactivity in a number of elegant cascade processes. Representative examples are depicted in **Scheme 17**, in which the C(alkenyl)–Pd intermediate is generated by the attack of acetate anion and subsequently trapped by the intramolecular addition to a tethered aldehyde or allyl acetate group.[53–54] Beyond these transformations, C(alkenyl)–Pd intermediates can react with electrophiles including allyl alcohols, vinyl ketones, ynamides, *etc.* in an intramolecular or intermolecular fashion. This strategy allows for an efficient route to assemble structurally complex carbon skeletons from simple starting materials.[55–57]

In 2007, the Sanford and the Tse groups independently reported palladium-catalyzed oxidative cyclopropane-forming reactions from non-conjugated enyne starting materials (**Scheme 18**).[58–60] The catalytic cycle for these processes begins in a similar manner to the Lu system where C(alkenyl)–Pd intermediate is formed *via* acetoxypalladation. Following the migratory insertion of the pendant alkene, however, (diacetoxyiodo)benzene then oxidizes the C(alkyl)–Pd(II) intermediate. The oxidation step generates an electrophilic C(alkyl)–Pd(IV) intermediate, which is attacked by the nucleophilic alkenyl acetate in a $S_N2$ fashion, affording a cyclopropane. Later, Tong and co-workers modified the substrate in the Sanford and Tse methods by installing an additional hydroxyl group at the propargylic position.[61] Under similar reaction conditions, the presence of the hydroxyl group perturbs pathway selectivity such that C–O reductive elimination is favored instead of $S_N2$-type nucleophilic attack. In 2008, the Liu group reported an analogous Pd(II)/Pd(IV) catalytic process with chloride as nucleophile. Reductive elimination from the Pd(IV) intermediate furnishes a C($sp^3$)–Cl bond **(Scheme 19)**.[62]



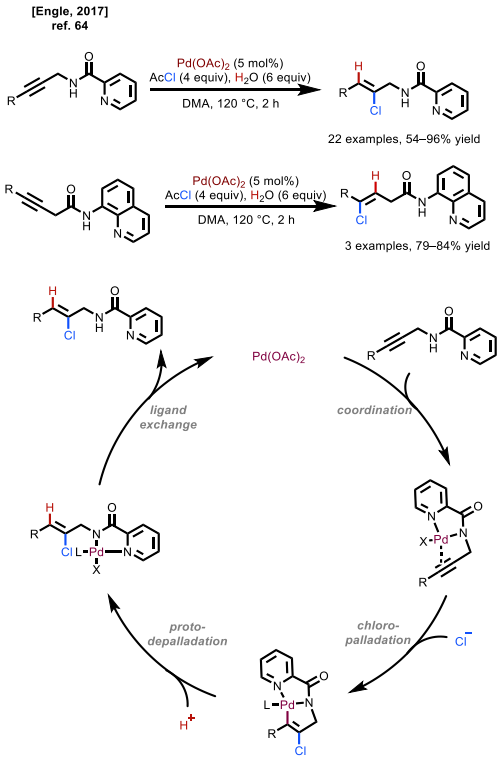

**Scheme 19**. Catalytic cyclative dichlorination of 1,5-enynes

In 2016, Wang and Ji reported an annulation reaction *via* intramolecular oxypalladation across an alkyne. In this reaction, the C(alkenyl)–Pd intermediate that arises from oxypalladation is in close proximity to a phenyl group, allowing for a subsequential C(aryl)–H activation.[63] Reductive elimination then furnishes the product. Overall, this cascade arene/alkyne annulation process affords fluorene-benzoxazine derivatives **(Scheme 20)**.




**Scheme 20**. Catalytic cyclization cascade initiated *via* oxypalladation across an alkyne

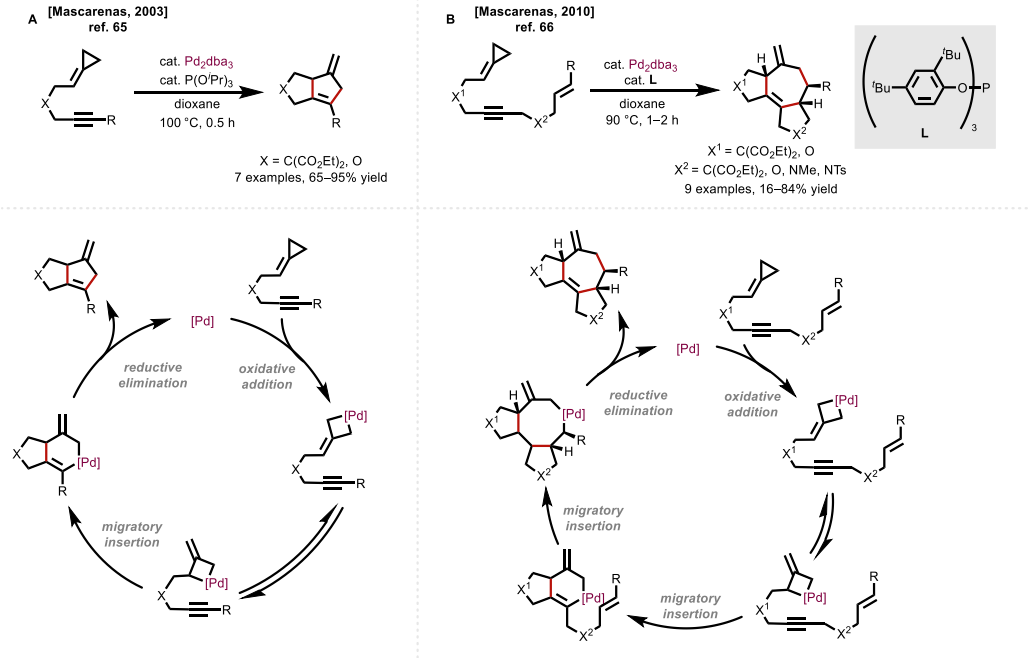
The reactions highlighted so far represent interesting methods for polysubstituted alkene synthesis. In these methods, the regioselectivity is controlled by tethering one or more of the reaction partners to the reactive alkyne moiety and/or by employing conjugated alkynes with electronically differentiated C–C π-systems. Controlling selectivity in intermolecular reactions using non-conjugated alkyne substrates represents a significant challenge, particularly in the cases of dialkyl-substituted substrates. To address this issue, our lab found that a removable bidentate directing auxiliary could be used to control the regioselectivity of hydrochlorination with *in situ* generated HCl. Directed chloropalladation is proposed to furnish a 5,5-palladabicyclic intermediate, which is preferred on kinetic and thermodynamic grounds, allowing a means of controlling regioselectivity in a manner that is largely independent of alkyne substitution (**Scheme 21**).[64] Two families of alkyne substrates were examined, propargyl amine derivatives and 3-butynoic acid derivatives bearing auxiliaries derived from picolinic acid and 8-aminoquinoline, respectively. Both directing groups favor formation of the 5-membered palladacycle intermediate, which leads to opposite regiochemical outcomes with the two substrates due to their different tether lengths between the alkyne and directing group (distal addition of the chloride in the case of 3-butynoic acid, and proximal addition in the case of propargyl amines).




**Scheme 21**. The selective alkyne hydrochlorination with bidentate amide directing groups

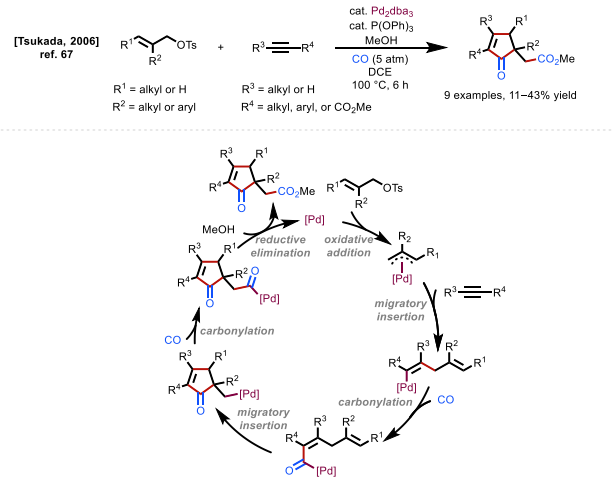
Regarding reactions that proceed *via* the inner-sphere pathway, there have been myriad innovations in terms of novel reactivity to generate the nucleophilic organopalladium species and in terms of selectivity control. As shown in **Scheme 1**, nucleophilic organopalladium species can be generated by oxidative addition with alkenyl electrophiles, C(alkenyl)–H activation, and transmetalation with alkenyl nucleophiles.

A number of advances have been reported that demonstrate unconventional organopalladium progenitors. For example, the Mascareñas group reported an example of intramolecular formal [3+2] cycloaddition between an alkylidenecyclopropane and a tethered alkyne.[65] The reaction is initiated by oxidative addition of Pd(0) to the alkylidenecyclopropane (**Scheme 22A**), which affords a palladacyclobutane intermediate that is then trapped by the alkyne moiety of the substrate through allylic migratory insertion. Subsequent C(alkenyl)–C(allylic) reductive elimination closes the catalytic cycle for this formal cycloaddition process. The same group further extended this reaction to an analogous [3+2+2] addition by tethering an alkene moiety proximal to the alkynes to enable a second migratory insertion following the initial migratory insertion event. In this way, a 5-7-5 tricyclic structures can be accessed (**Scheme 22B**).[66]



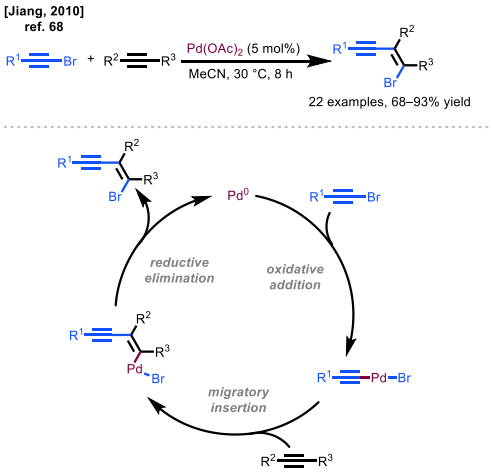

**Scheme 22**. Annulation reactions initiated by alkylidenecyclopropane ring expansion

In addition to the unique C($sp^3$)–C($sp^3$) oxidative addition step showcased in the reactions in **Scheme 22**, the reactivity of the palladacyclobutane intermediate is also notable. The palladacyclobutane intermediate is also a C(allyl)–Pd species, which usually behaves as an electrophile. However, in the Mascareñas studies, the C(allyl)–Pd species reacts as a nucleophile in the migratory insertion step. Beyond these reports, an example of the intermolecular C(allyl)–Pd migratory insertion into an alkyne was reported by the Tsukada group **(Scheme 23)**.[67] This reaction begins with oxidative addition of Pd(0) to an allyl tosylate. The resulting C(allyl)–Pd species undergoes the migratory insertion into 2-butyne, affording a C(alkenyl)–Pd intermediate. Coordination of CO and subsequent 1,1-migratory insertion sets the stage for a second migratory insertion of the tethered alkene moiety. Finally, the resulting C(alkyl)–Pd intermediate is trapped by a second equivalent CO, and ester formation closes the catalytic cycle. This catalytic cascade process provides access to a collection of substituted cyclopent-2-en-1-one products.

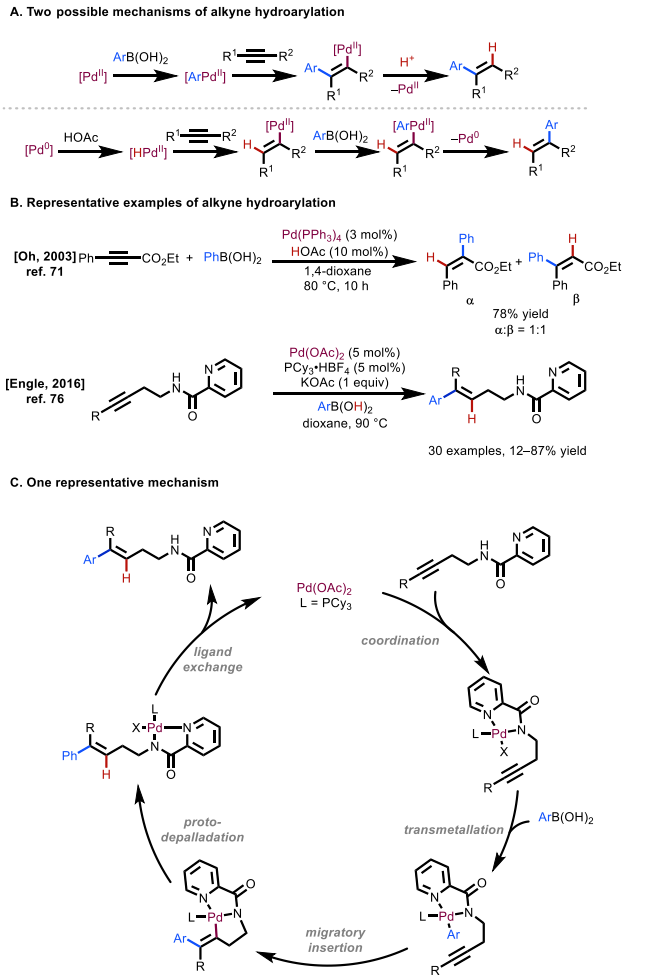



**Scheme 23**. Three-component coupling with a nucleophilic C(allyl)–Pd(II) species

Incorporating greater than one functional group to an alkyne moiety can be achieved by reacting an alkyne with an organohalide. This type of reaction can integrate all the fragments of the coupling partner to the alkyne, without generating any byproducts. In 2010, Jiang and coworkers reported that a Pd(0) pre-catalyst can react with an alkynyl bromide to furnish C(alkynyl)–Pd(II) species, which can add to another alkyne substrate. The resulting C(alkenyl)–Pd(II) species undergoes C($sp^2$)–Br reductive elimination to form the *cis*-bromo-1,3-enyne product (**Scheme 24**).[68] Later in the same year, a related reaction with an alkynyl chloride was reported.[69]




**Scheme 24.** The palladium-catalyzed bromoalkynylation of alkynes



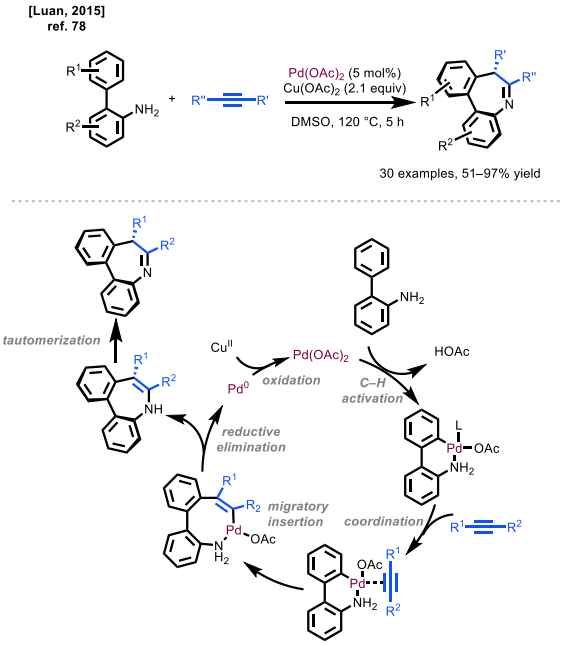

**Scheme 25**. Hydroarylation on alkynes *via* inner-sphere migratory insertion.

C(aryl)–Pd species are one of the most commonly encountered organopalladium species that react with alkynes *via* inner-sphere insertion to yield C(alkenyl)–Pd intermediates. C(aryl)–Pd species can be accessed for this purpose *via* transmetalation, oxidative addition, or C–H activation with an appropriate aryl precursor, and numerous catalytic alkyne functionalization reactions have been developed using these approaches, which have been reviewed elsewhere.[70] Here, we focus on one representative family of reactions, alkyne hydroarylation reactions with arylboron reagents.

Different mechanisms for this type of coupling have been proposed depending on the reaction conditions and the precatalyst employed, of which two are most commonly invoked (**Scheme 25**). In one pathway, a Pd(II) catalyst reacts with the arylboron reagents to generate C(aryl)–Pd species *via* transmetalation. Next, migratory insertion of the C(aryl)–Pd species across an alkyne takes place to form a C(alkenyl)–Pd intermediate, which then undergoes protodepalladation. Alternatively, in the second proposed mechanism, oxidative addition of Pd(0) to HX (e.g., HOAc) takes place, followed by the insertion of the Pd–H species, transmetalation with the arylboronic nucleophiles, and finally the C–C bond-forming reductive elimination. Though the mechanistic details remain unclear in many of the published systems, several research groups have made significant progress in inner-sphere insertion of C(aryl)–Pd species. The Oh group pioneered the *syn*-hydroarylation of alkynes with arylboronic acids under the combined action of $Pd(PPh_3)_4$ and HOAc, invoking a hydropalladation pathway.[71] Later on, the method was expanded to include alkynes with synthetically useful functional groups, including propargyl alcohols, propargyl amines, propargylic carboxylates, and ynamides.[72–75] One limitation of the aforementioned methods is the formation of regioisomers in many cases, which arise from the two possible regiochemical outcomes of the migratory insertion step. Our lab found that a removable bidentate directing auxiliary could be used to control the regioselectivity of aryl addition using $Pd(OAc)_2$ as catalyst, $PCy_3$ as ligand, and KOAc as base.[76] Using this method, regio- and

stereoselective hydroarylation of a series of conjugated and non-conjugated internal alkynes was achieved. A transmetalation-first mechanism was proposed on the basis of a series of mechanistic experiments.

Beyond transmetalation, C(aryl)–Pd species can also be generated from simple arene coupling partners by C–H activation. This approach has been prominently applied by Fujiwara to achieve catalytic hydroarylation of alkynes with arenes, where the catalytic cycle is closed by C(alkenyl)–Pd protonolysis.[77] Rather than undergoing protodepalladation, the key C(alkenyl)–Pd intermediate can instead participate in other C–C and C–heteroatom bond forming steps to bring about 1,2-difunctionalization. For instance, the Luan group reported a [5+2] oxidative annulation initiated by aniline-directed C(aryl)–H activation (**Scheme 26**).[78] The resulting palladacycle undergoes migratory insertion with diphenylacetylene. The catalytic cycle is terminated by C–N reductive elimination from the Pd(alkenyl)(amino) intermediate. The enamine product tautomerizes to form the imine-containing heterocycle. The unusual 5-7-5 tricyclic backbone structure of the product is a notable aspect of this method.

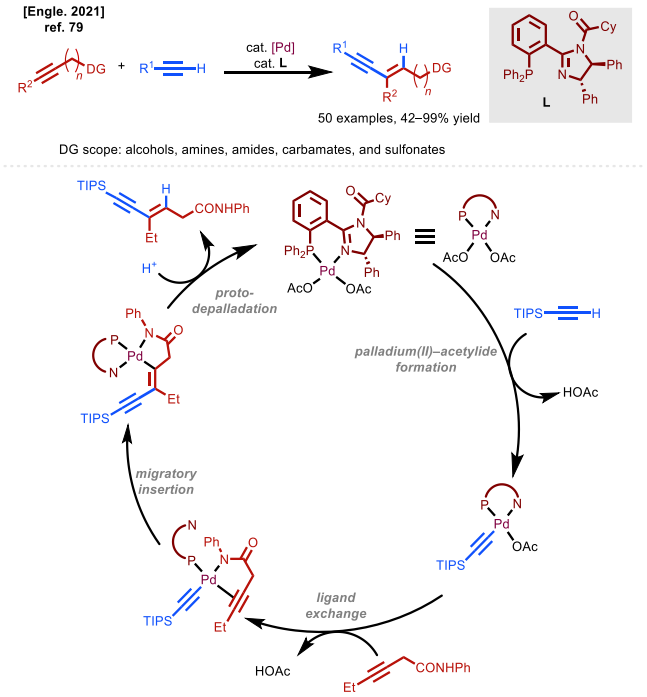



**Scheme 26**. Alkyne difunctionalization *via* C(aryl)–H activation, alkyne migratory insertion and C–N reductive elimination

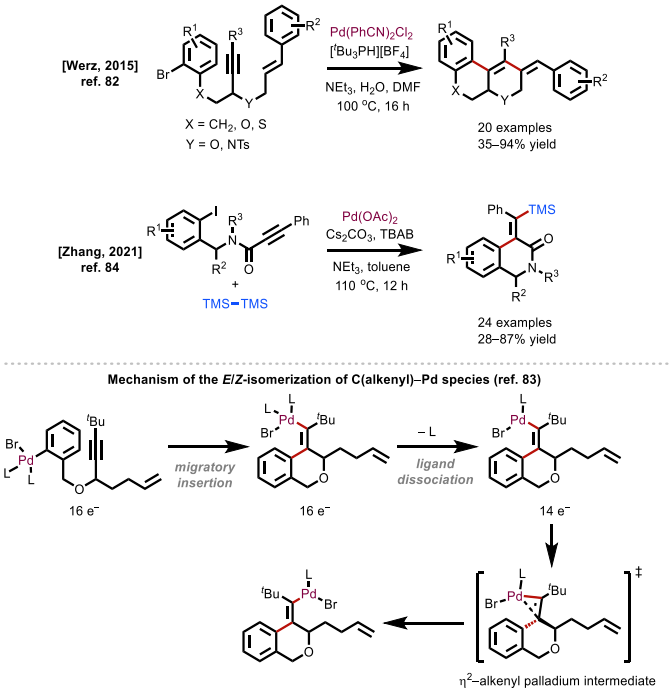
As shown in the examples described in earlier in this section, the regiochemical outcome of palladium-catalyzed alkyne functionalizations is controlled by a combination of factors, including the properties of the alkyne substrate, the nature of nucleophilic coupling partner, and the nature of palladium catalyst (including the identity of the ancillary ligand). Building on our success using removable directing auxiliaries to control the regioselectivity of alkyne functionalization (**Scheme 21 and 25c**), our research group sought to further develop this directing group strategy using only native functionality without the need for auxiliary incorporation and removal steps (**Scheme 27**). Protic functional groups, such as alcohols, amides, and sulfonamides, induce regio- and stereoselective hydroalkynylation across an alkyne to furnish 1,3-enynes. A tailored phosphoimidazoline (BIPI) ligand was essential for high regio- and *E*/*Z*-selectivity (the latter by suppressing secondary *E*/*Z* isomerization of the product).[79]

As seen in the preceding examples, most catalytic alkyne functionalization reactions involving inner-sphere migratory insertion proceed with overall *syn*-stereoselectivity, as a consequence of the *syn*-stereospecific nature of 1,2-migratory insertion of C–Pd species into π-bonds. However, net *anti*-selective C–Pd additions have been discovered in some cases.[80–81] This unusual stereoselectivity results from a secondary *E*/*Z*-isomerization of the C(alkenyl)–Pd intermediate that is formed upon inner-sphere *syn*-stereospecific migratory insertion. For instance, the Werz group reported the *anti*-addition of a C(aryl)–Pd species to a tethered alkyne. The resulting C(alkenyl)–Pd species is intercepted by a pendant alkene, furnishing 1,3-diene products (**Scheme 28**).[82] Later in 2021, Zhang *et al.* reported an alkenylsilane synthesis in which an alkyne-containing aryl iodide undergoes an analogous palladium-mediated cyclization and *E*/*Z* isomerization sequence.[84] In this case, the C(alkenyl)–Pd intermediate transmetalates with hexamethyldisilane, and subsequent C(alkenyl)–Si reductive elimination results in the corresponding *anti*-1,2-arylsilylated product.

The discovery of a net *anti*-selective inner-sphere migratory insertion challenges the prevailing dogma that the stereoselectivity is programmed by the mechanism of elementary step involved. The origin of this special stereochemical outcome of migratory insertion has been investigated by experimental and computational studies. The Werz group proposed that *E*/*Z*-isomerization of a C(alkenyl)–Pd species takes place through the η²-C(alkenyl)–Pd transition state.[82] To initiate the isomerization process, one L-type ligand on the 16-e⁻ C(alkenyl)–Pd species dissociates, resulting in a 14-e⁻ C(alkenyl)–Pd species. Then, the alkene moiety of the 14-e⁻ C(alkenyl)–Pd species coordinates to palladium in a η²-coordination mode, generating the transition state for the C=C bond rotation. Finally, the alkene moiety dissociates from palladium to complete the *E*/*Z*-isomerization process, furnishing the thermodynamically more stable *anti*-intermediate.[83]




**Scheme 27**. Selective alkyne cross-coupling of terminal and internal alkyne enabled by native directing groups

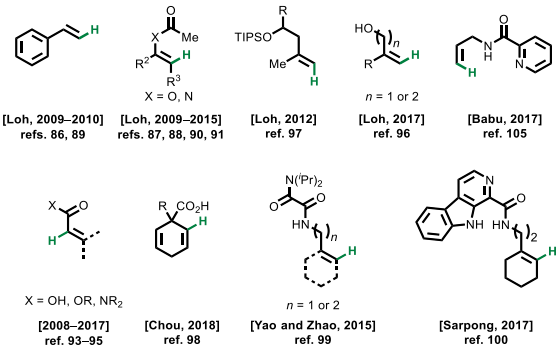



**Scheme 28**. Inner-sphere migratory insertion followed by *E*/*Z*-isomerization

### 6. C(alkenyl)–Pd species generated from C(alkenyl)–H activation

In principle, palladium-catalyzed C(alkenyl)–H activation is the most straightforward strategy to generate C(alkenyl)–Pd species **(Scheme 29)**.[85] However, compared to C(alkyl)–H and C(aryl)–H activation methods, which have been actively explored, C(alkenyl)–H activation remains in its infancy. Several unique challenges arise with alkenes as C–H activation substrates, including alkene isomerization side reactions and issues with C–H bond site selectivity (*e.g.* C(alkenyl)–H bond vs C(allyl)–H bond or different C(alkenyl)–H bonds on the same alkene). Pioneering work by Loh established Pd(II)-catalyzed C(alkenyl)–H functionalization of styrene,[86, 89] enol ester,[87] and enamide substrates[88, 90, 91]. C(alkenyl)–H activation of these three classes of substrates takes place with excellent regio- and stereoselectivity. The alkenyl proton at the β-position *cis* to the pendant functional group is activated. The resulting C(alkenyl)–Pd intermediate undergoes transmetalation with an aryl coupling partner or migratory insertion with an accepter alkene to afford C(alkenyl)–H arylation or alkenylation products.[86–91] Later in an elegant study, Iwasawa and co-workers described a C(alkenyl)–H carboxylation reaction of α-phenyl-2-hydroxystyrene with $CO_2$ to furnish coumarin analogues.[92]

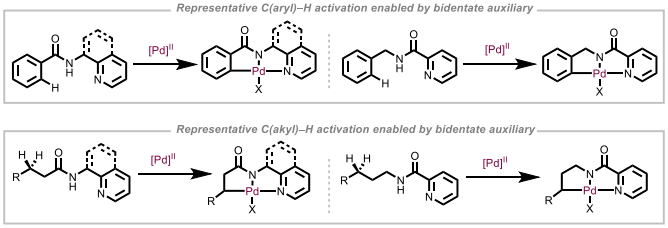
C(alkenyl)–H activation reactivity was then extended to a variety of conjugated alkenes, including acrylic acids[94] and acrylamides,[95] *etc*. In this section, we highlight a selection of transformations with unique mechanisms. In 2016, the Yu group described a reaction in which *N*-methoxycinnamamide reacts with $^t$butyl isocyanide to generate 4-imino-β-lactams *via* a Pd(II)/Pd(0) catalytic cycle.[93] This process is initiated by the attack of deprotonated *N*-OMe amide on $^t$butyl isocyanide to form an imido-palladium intermediate. The ensuing acyl migration brings palladium in close proximity to the C(alkenyl)–H bond at the α-position. A five-membered palladacycle is formed by C(alkenyl)–H activation. Finally, a C(alkenyl)–C(imidyl) bond is formed by reductive elimination.




**Scheme 29**. Representative substrates employed in palladium-catalyzed C(alkenyl)–H activation

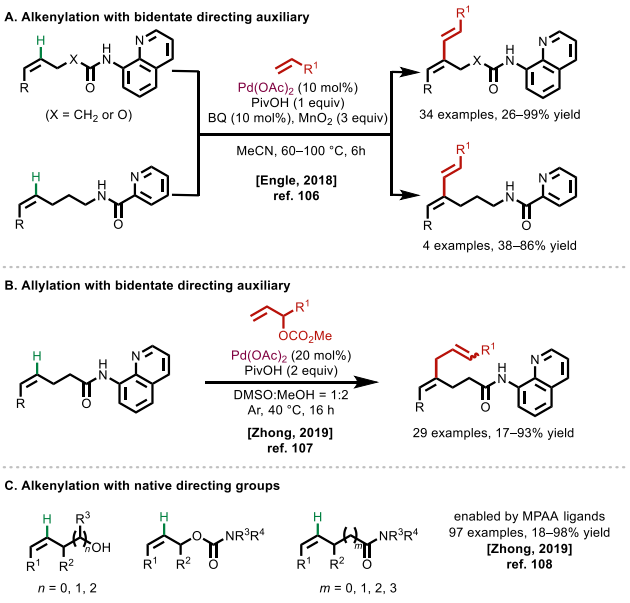
Later, non-conjugated acyclic C(alkenyl)–H bonds were successfully activated by palladium catalysts (**Scheme 29**). The Loh group described 1,3-diene syntheses by C(alkenyl)–H activation of 1,1-disubstituted alkenyl alcohols.[96–97] A silyl ether protecting group controlled stereoselectivity. Free alcohol substrates favor *Z*-selectivity due to a proposed chelation effect, while the steric bulk of the silyl ether protected alcohol results in reaction at the less hindered site, resulting in *E*-selectivity. Cyclic alkenes have been successfully applied in the C(alkenyl)–H activation as well for various transformations, including alkenylation,[98] alkenyl lactamization,[99] alkynylation,[100] and acetoxylation.[101]

In addition to facilitating C(alkyl)–H and C(aryl)–H bond activation (**Scheme 30**),[102–104] N,N-bidentate amide auxiliaries have also been found to enable otherwise challenging C(alkenyl)–H functionalizations. Shao and He reported the picolinamide (PA)-directed C(alkenyl)–H acetoxylation of cyclohexene derivatives.[101] C(alkenyl)–H bond cleavage at the *δ*-position results in a six-membered palladacycle that then undergoes Pd(II)/Pd(IV) oxidization facilitated by $PhI(OAc)_2$. Finally, C–O reductive elimination affords alkenyl acetate products. In another study, PA was used to facilitate *γ*-C(alkenyl)–H arylation of an acyclic alkene at the terminal position *via* the intermediacy of a five-membered palladacycle.[105]

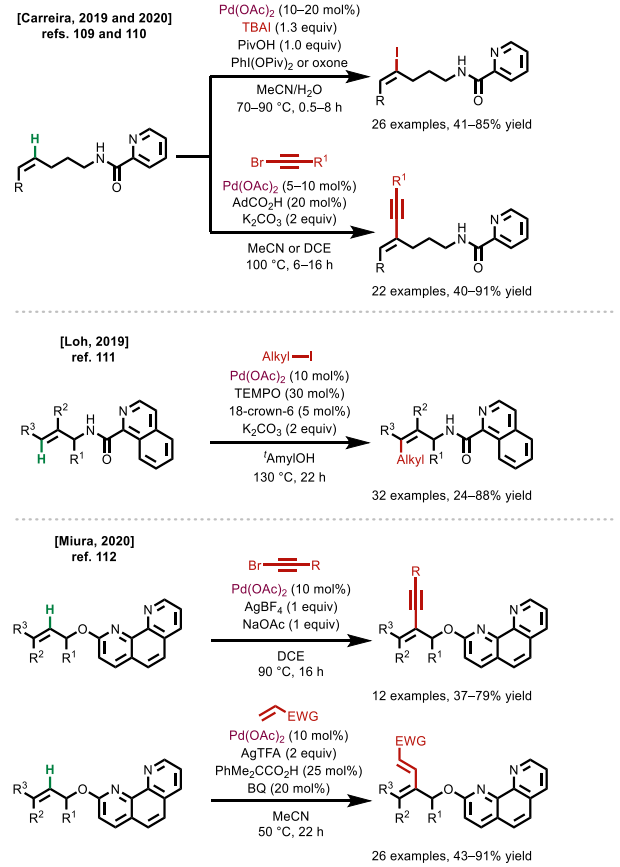



**Scheme 30.** C(alkyl)–H and C(aryl)–H activation facilitated by bidentate amide auxiliaries

In 2018, our group discovered that 8-aminoquinoline (8-AQ) and PA directing groups could promote C(alkenyl)–H activation of non-activated, acyclic alkenes through a six-membered palladacycle (**Scheme 31A**). In contrast to the previous studies, the reaction system exhibits unique C(alkenyl)–H site selectivity by virtue of proceeding through an *exo* six-membered palladacycle intermediate. Starting with stoichiometric $Pd(OAc)_2$, a dimeric C(alkenyl)–Pd complex was synthesized, supporting the proposed C(alkenyl)–H activation step. This selective C(alkenyl)–H activation process was leveraged in a catalytic method for 1,3-diene synthesis through reaction with a second alkene coupling partner.[106]

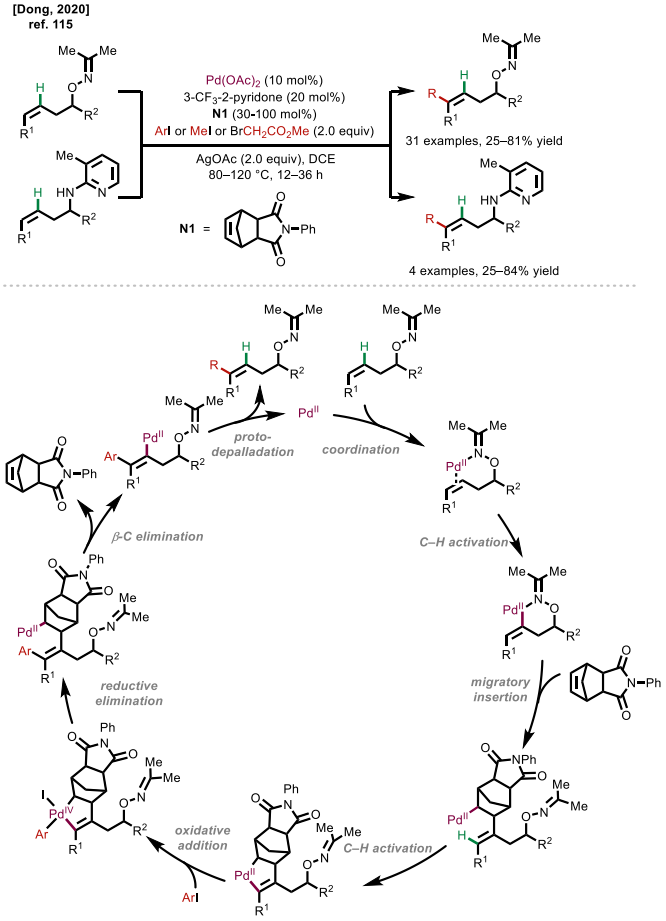



**Scheme 31**. *endo*-C(alkenyl)–H activation *via* Pd(II)/Pd(0) catalytic cycle




**Scheme 32**. The C(alkenyl)–H activations *via* Pd(II)/Pd(IV) catalytic cycle

Following these reports, a number of directed C(alkenyl)–H functionalization methods have been developed by other research groups. In 2019, the Zhong group described C–H allylation assisted by the 8-AQ auxiliary (**Scheme 31B**). Allyl carbonate was found to be an effective coupling partner, presumably because the good leaving group ability of carbonate allows β-O elimination to outcompete β-H elimination. A solvent mixture of DMSO and methanol was found to be important for obtaining good yields.[107] In an important study, the same research group was able to develop a method for proximal-selective C(alkenyl)–H olefination directed by native functional groups, including alcohols, amides, and carbamates (**Scheme 31C**).[108] Mono-*N*-protected amino acid (MPAA) ligands and pentafluoroethanol additive are necessary to promote C(alkenyl)–H activation without the assistance of the typically used bidentate amide directing auxiliaries.




**Scheme 33**. Alkenyl Catellani reaction

The Carreira group employed alkenyl amines containing the PA auxiliary and successfully achieved C(alkenyl)–H iodination and alkynylation *via* a Pd(II)/Pd(IV) catalytic cycle (**Scheme 32**).[109] In the first study, $PhI(OPiv)_2$ was shown to be effective in oxidizing the C(alkenyl)–Pd(II) intermediate to the corresponding C(alkenyl)–Pd(IV) species. Association of iodide then sets the stage for C(alkenyl)–I bond formation through reductive elimination. Alkynylbromide is another effective reagent capable of generating an analogous Pd(IV) intermediate through oxidative addition, giving rise to C(alkenyl)–H alkynylation products.[110] The Loh and Miura groups found that isoquinoline[111] and phenanthroline-based[112] directing groups can also facilitate C(alkenyl)–H activation *via* Pd(II)/Pd(IV) redox processes (**Scheme 32**). In particular, the isoquinoline-based directing auxiliary successfully facilitated C(alkenyl)–H alkylation with 1° and 2° alkyl iodides, allowing access to stereochemically defined trialkyl- (and in one case, tetraalkyl-) substituted alkene products.

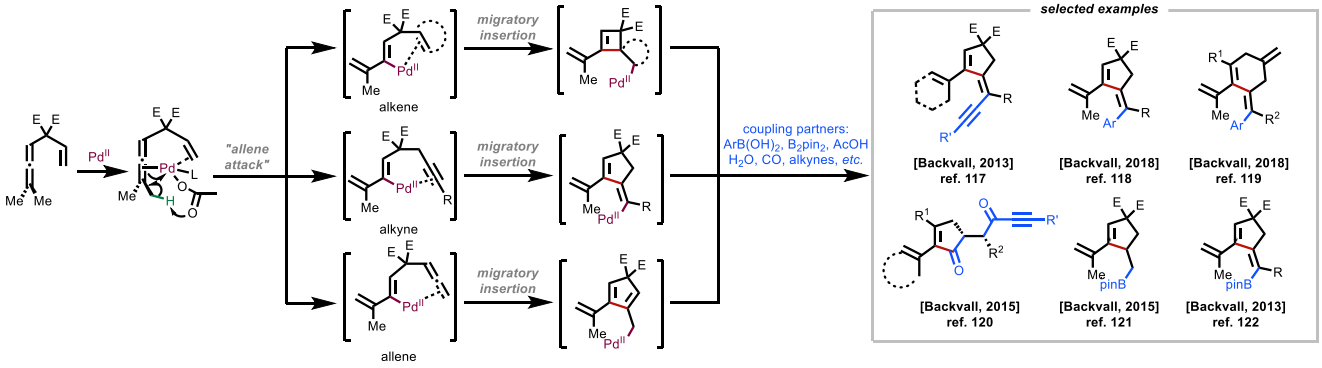
The Dong group reported an alkenyl Catellani reaction in which an oxime auxiliary and a pyridone additive allow proximal-selective C(alkenyl)–H activation (**Scheme 33**).[113–114] The intermediate is then trapped with norbornyl imide, which transposes palladium to the distal C(alkenyl)–H bond through migratory insertion and a secondary C(alkenyl)–H activation step. The C,C-palladacyles reacts with aryl or alkyl iodides via Pd(II)/Pd(IV) oxidative addition and reductive elimination. Lastly, norbornene is regenerated by β-carbon elimination, and the product is liberated by C(alkenyl)–Pd protonolysis. In the overall design norbornene functions as a traceless directing group to a extend C(alkenyl)–H activation site selectivity to remote sites.[115]

### 7. Miscellaneous pathways for forming C(alkenyl)–Pd species

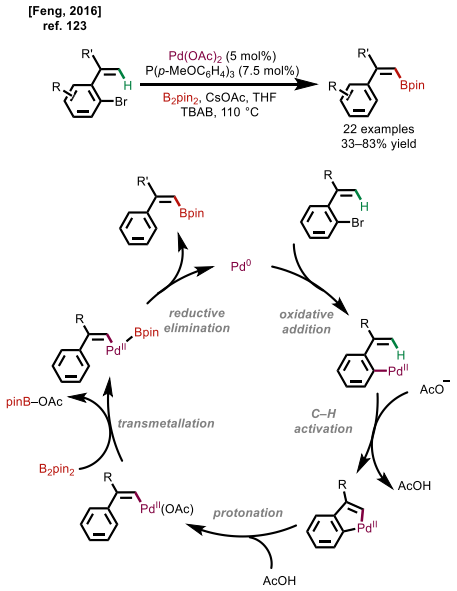
In a series of publications, the Bäckvall group reported an elegant collection of oxidative allene–alkene and allene–alkyne cyclizations.[116] C(alkenyl)–Pd species are generated by allene C–H activation. The

C(alkenyl)–Pd intermediate then undergoes intramolecular migratory insertion with a tethered alkene/alkyne moiety. The catalytic cycle is terminated by the functionalization of the resulting C–Pd intermediate. Alkynylation,[117] arylation,[118–119] carbonylation,[120] borylation,[121–122] and other reactions. have been successfully demonstrated using this reaction platform **(Scheme 34)**.

In the C(alkenyl)–H activation reactions discussed in above in Section 6, the palladium catalyst is brought into proximity of the targeted C(alkenyl)–H bond through coordination to a Lewis basic functional group. An alternative way to achieve colocalization of the catalyst and C(alkenyl)–H bond of interest is to generate a C–Pd species via oxidative addition (or another elementary step) the vicinity of the targeted C(alkenyl)–H bond. C(alkenyl)–H activation can then take place by intramolecular palladium migration. In 2016, the Feng group described the first example of such a process involving palladium 1,4-migration from an aryl group to an alkenyl group.[123] In this study, the C–Pd bond initiator is generated by oxidative addition to an arylbromide. C(alkenyl)–H activation then proceeds *via* a concerted metalation-deprotonation (CMD) pathway, resulting in the 5-membered C,C-palladacycle intermediate. The following protodepalladation of the C(aryl)–Pd bond completes the 1,4-palladium shift from the aryl group to the alkenyl group. Finally, the C(alkenyl)–Pd intermediate proceeds in a Miyaura-type borylation to afford the alkenyl boronic ester product. While both the C(aryl)–Pd species and the C(alkenyl)–Pd species can potentially react with $B_2pin_2$, the use of CsOAc was found to enable high selectivity for C(alkenyl)–B bond formation, while maintaining a good overall yield **(Scheme 35)**.




**Scheme 34**. Palladium(II)-Catalyzed Oxidative Functionalization of Allenes




**Scheme 35**. C(alkenyl)–H activation *via* palladium 1,4-migration

## 8. Conclusion

Palladium catalysis represents a promising strategy for synthesizing polysubstituted alkenes through selective generation and functionalization of C(alkenyl)–Pd intermediates. In this review, we have attempted to provide an overview of different elementary steps that furnish C(alkenyl)–Pd species and their application in alkene syntheses. For each category of reaction, we have discussed unique characteristics that stem from the underlying mechanism and have highlighted recent progress from the literature. We hope that this review will inspire further developments in alkene syntheses *via* transition metal catalysis with focus on methods that are selective, modular, and versatile., focusing on ways to enable highly selective transformations. We are optimistic that continued efforts in this direction will yield a toolkit of transformations that enable convenient access to alkenes bearing any substitution pattern and any combination of functional groups.

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## Acknowledgments

This work was financially supported by National Science Foundation (CHE-2046286). We appreciate Camille Z. Rubel for detailed proofreading and helpful discussion.

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