Conference paper

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The strategic generation and interception of palladium-hydrides for use in alkene functionalization reactions[1]

Abstract: We review methods that our lab has developed for the generation of Pd-hydrides and the manipulation of these useful intermediates via β-hydride elimination and migratory insertion steps. For a given alkene functionalization reaction, careful understanding of the dynamics of β-hydride elimination, migratory insertion, and transmetallation have allowed for the selective functionalization of Pd-alkyl intermediates. This has afforded us a means by which to transpose palladium to a desired position on a substrate for subsequent functionalization, empowering a number of useful C–H, C–O, and C–C bond-forming reactions.

Keywords: alkenes; Pd-hydride; OMCOS-17; oxidation.

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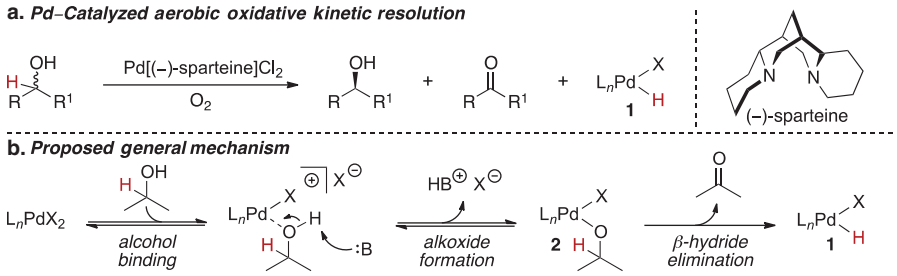
Introduction

β-Hydride elimination is a fundamental organometallic step that occurs as a result of the kinetic instability of a variety of organo-transition metal complexes. Although this intriguing mechanistic process is instrumental in many reactions (such as the Shell higher olefin process and Ziegler–Natta polymerization), the inability to predictably suppress β-hydride elimination in other organometallic transformations often leads to low yields and undesired olefinic mixtures [1]. This is clearly illustrated in the field of sp^3–sp^3 cross-coupling, where such reactions have been designed to avoid β-hydride elimination through the use of ligand control [1–5]. Conversely, an emerging concept in organometallic chemistry has been to embrace a metal's propensity to undergo β-hydride elimination, thereby gaining access to a metal-hydride useful for further reaction. To this end, our group has been interested in exploring palladium's tendency towards facile β-hydride elimination as a way to furnish Pd-hydrides that may be intercepted for a variety of new transformations. Herein, we describe our progress on Pd-catalyzed alkene hydroalkoxylation, hydroarylation, hydroalkenylation, hydroalkylation, and three-component bond-forming reactions. This work has culminated in both new bond-forming strategies and an improved understanding of the factors that control β-hydride elimination.

Results and discussion

Alkene hydrofunctionalization

Over a decade ago, our group became interested in developing Pd-catalyzed oxidation reactions as a means by which to achieve the kinetic resolution of racemic alcohols, thereby delivering an enantiomerically-enriched alcohol and a carbonyl compound (Scheme 1a) [6–21]. The mechanism of this reaction is believed to initiate with alcohol coordination to the Pd(II) catalyst, followed by deprotonation to furnish Pd-alkoxide **2**



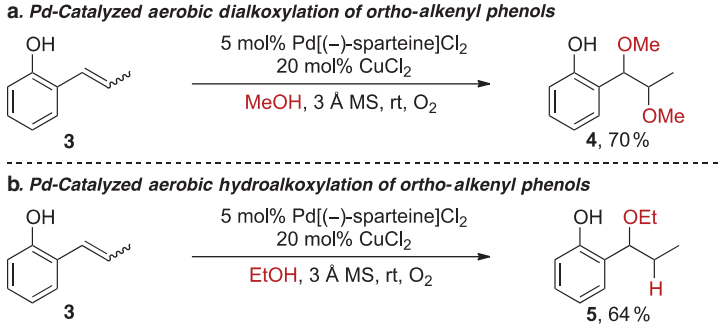
Scheme 1 Pd-catalyzed aerobic oxidative kinetic resolution and proposed general mechanism.

(Scheme 1b). This Pd-alkoxide is then set to undergo β-hydride elimination, producing a carbonyl compound and Pd-hydride **1**. Such a Pd-hydride is typically considered a byproduct that is ultimately converted to an equivalent of acid; however, we became intrigued by the possibility of intercepting this potentially useful intermediate via trapping with an alkenyl substrate.

The prospect of developing new alkene functionalization reactions by integrating Wacker-type processes and cross-coupling technologies via Pd-hydride chemistry was an appealing concept that we were interested in exploring. We envisioned that the development of this reaction class could lead to new and interesting bond disconnections, as well as the ability to gain insight into the mechanistic intricacies of such transformations.

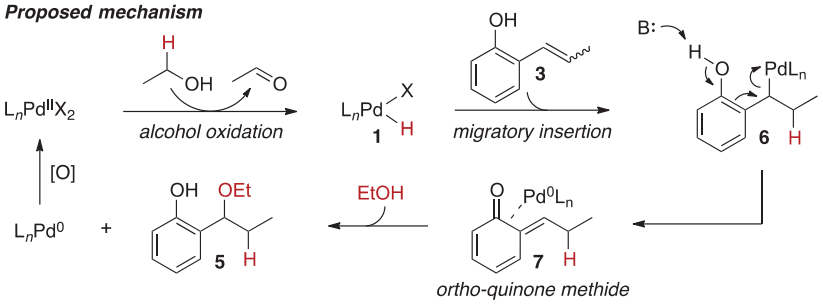
Pd-catalyzed hydroalkoxylation reactions

In the course of investigating Pd[(–)-sparteine]Cl_2-catalyzed Wacker-type aerobic transformations of styrenes, an interesting dimethoxylation product (**4**) of *ortho*-propenyl phenol **3** was observed (Scheme 2a) [22, 23]. This outcome was unanticipated since the initial alkoxypalladation was expected to afford an enol ether intermediate upon β-hydride elimination from non-phenolic styrenes, leading to Wacker-type products. To add further intrigue, when the reaction was carried out in ethanol instead of methanol, a 64 % yield of the hydroethoxylation product **5** was observed (Scheme 2b) [24]. These disparate outcomes in seemingly similar solvents have been attributed to a much faster rate of β-hydride elimination from ethanol compared to methanol [25, 26].



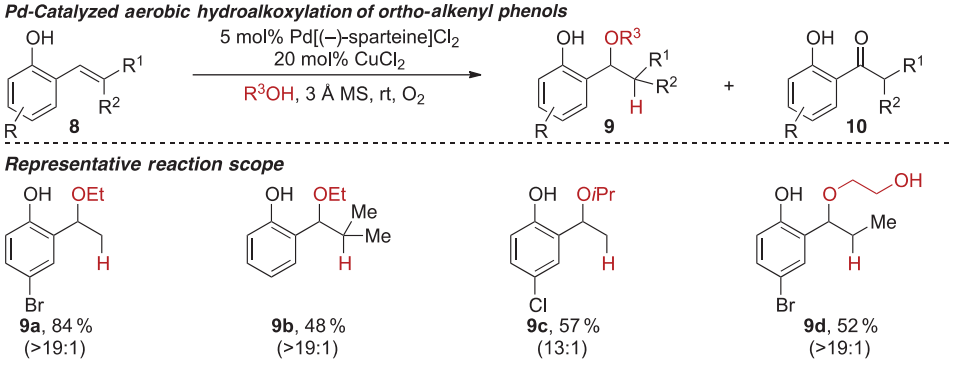
Scheme 2 (a) Pd-catalyzed dimethoxylation of *ortho*-propenyl phenol. (b) Pd-catalyzed hydroethoxylation of *ortho*-propenyl phenol.

The proposed mechanism of the latter hydroethoxylation reaction initiates with the oxidation of ethanol to produce Pd-hydride **1**, into which *ortho*-propenyl phenol **3** can insert to afford Pd-alkyl intermediate **6** (Scheme 3). Base-promoted *ortho*-quinone methide formation followed by the nucleophilic attack of ethanol affords the hydroalkoxylation product and releases Pd(0), which is reoxidzed to Pd(II) using O_2 and $CuCl_2$. The *ortho*-quinone methide intermediate diverts the reaction to the hydroalkoxylation product by arising faster than β-hydride elimination from **6**. This is one of our earliest examples of exploiting substrate control for the selective functionalization of styrenes.



Scheme 3 Proposed mechanism for the Pd-catalyzed hydroethoxylation of *ortho*-propenyl phenol.

The reaction scope of both *ortho*-alkenyl phenols and alcohols was found to be very broad. For example, in addition to *ortho*-propenyl phenol, the reaction can be used to functionalize terminal- and trisubstituted alkenes (**9a**, **9b**, Scheme 4). Commodity alcohols, specifically isopropanol (**9c**) and ethylene glycol (**9d**), are also competent hydride sources and nucleophiles. In the isopropanol example, an inseparable 13:1 mixture of hydroalkoxylation (**9c**) and ketone products (**10c**) is obtained. The ketone byproduct is presumed to originate from the hydrolysis of the Wacker-type acetal product [22]. Additionally, useful aryl halide functional groups are also tolerated (**9a**, **9c**, **9d**).

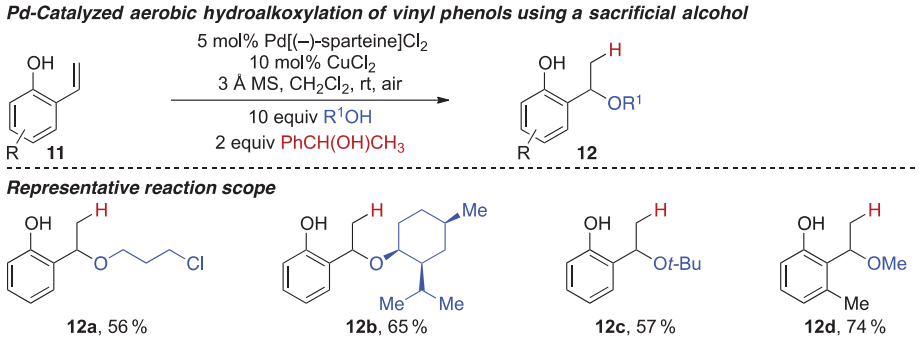


Scheme 4 Pd-catalyzed hydroalkoxylation of *ortho*-alkenyl phenols.

In the aforementioned hydroalkoxylation reactions, the nucleophile and Pd-hydride are both derived from the reaction solvent. This limited the scope of nucleophiles to commodity solvents capable of facile β-hydride elimination. To address this shortcoming, we sought out a sacrificial hydride source, specifically *sec*-phenethyl alcohol, which is both an excellent substrate for Pd-catalyzed alcohol oxidation and is also sufficiently hindered to avoid competing nucleophilic attack. This permits the use of just two equivalents of *sec*-phenethyl alcohol and ten equivalents of the desired alkoxylating alcohol to access more complex hydroalkoxylation products in good yields (Scheme 5) [27]. For example, the scope now includes an alcohol containing a primary chloride (**12a**), and sterically-hindered alcohols, including menthol (**12b**) and *tert*-butanol (**12c**). In terms of the alkenyl phenol substrate, a methyl substituent positioned *ortho* to the vinyl group is well-tolerated, affording **12d**. Finally, *para*-vinyl phenol is also capable of undergoing hydromethoxylation, presumably through a *para*-quinone methide intermediate (not shown).

Pd-catalyzed hydroarylation and hydroalkenylation reactions

Driven by our ability to construct C–O bonds using Pd-catalyzed alkene hydroalkoxylation, we sought to develop an alkene hydroarylation reaction as a means to C–C bond formation. Whereas C–O bond formation

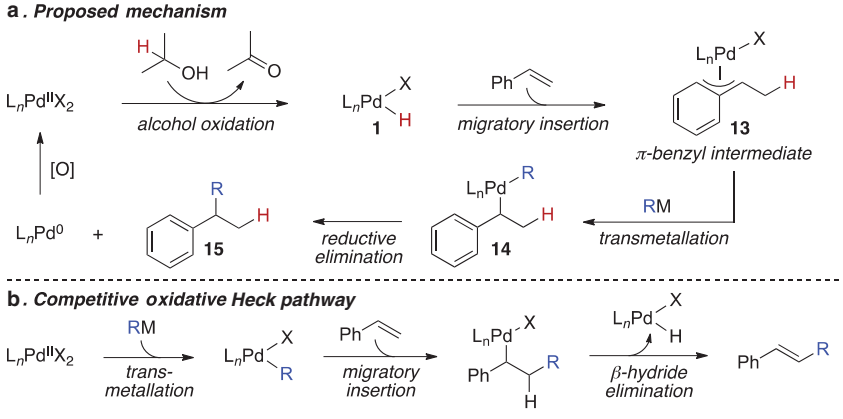


Scheme 5 Pd-catalyzed hydroalkoxylation of *ortho*-vinyl phenols using a sacrificial hydride source.

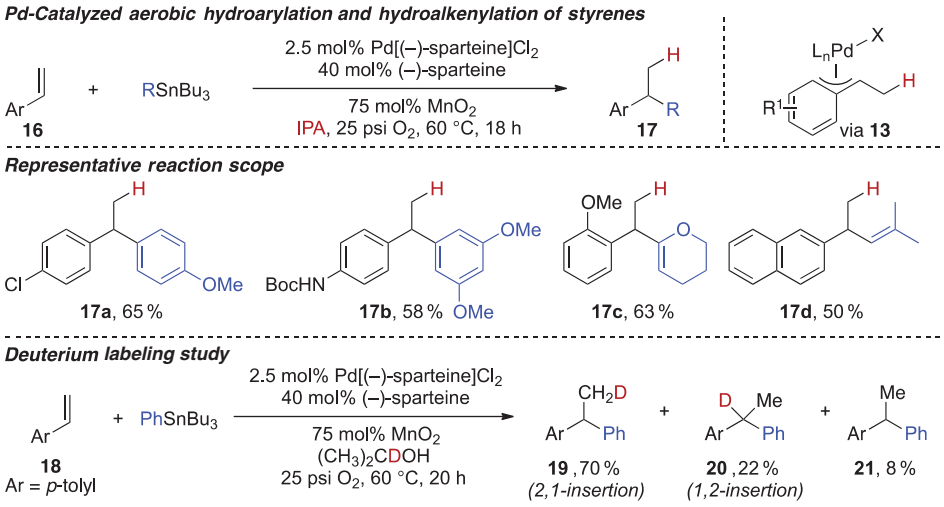
arose from alcohol attack onto a Pd(0)-quinone methide intermediate, we envisioned C–C bond formation resulting from transmetallation and reductive elimination (cross-coupling) from a stabilized Pd(II)-π-benzyl species (**13**, Scheme 6a). Benzylic C–C bonds, like that present in **15**, are accessible from cross-coupling chemistry, wherein an alkyl electrophile is used to oxidize Pd(0) to furnish the required Pd(II)-alkyl intermediate [28]. However, this necessitates a pre-functionalized (halogenated) substrate, and the oxidative addition typically requires bulky, electron-rich, air-sensitive phosphine ligands [29]. In contrast, our proposed tandem alcohol oxidation/cross-coupling approach was designed to avoid oxidative addition and enable the use of alkenes as alkyl electrophile synthons [30].

Initial attempts to develop this reaction focused on identifying a suitable catalyst/solvent combination that could achieve selective alcohol oxidation in the presence of a transmetallating reagent. Arylstannanes were selected as the organometallic reagent because, unlike boronic acids, no base is required to promote transmetallation, thus avoiding potential base-induced attenuation of the rate of alcohol oxidation. Avoiding the competing oxidative Heck reaction proved difficult, as Heck products predominate if transmetallation occurs faster than alcohol oxidation (Scheme 6b). Initially, low yields and poor selectivities were observed using Pd[(–)-sparteine]Cl_2 as catalyst in isopropanol (IPA). Eventually, excellent selectivity was realized through the addition of 40 mol% of (–)-sparteine to the reaction (Scheme 7). However, as substrate conversion approached 50 %, a significant reduction in the rate of the reaction was observed. This was attributed to catalyst inhibition by (–)-sparteine-*N*-oxide, formed by the oxidation of (–)-sparteine with adventitious H_2O_2 (a byproduct of the aerobic oxidation). Ultimately, this observation led to the addition of 75 mol% of MnO_2 to the reaction to disproportionate H_2O_2 and allow complete substrate consumption.

The optimized conditions enable the selective construction of a variety of diarylmethine-containing compounds (**17a**, **17b**, Scheme 7). The diarylmethine motif is prevalent in many biologically-active small



Scheme 6 (a) Mechanistic rationale for the proposed hydroarylation of styrene. (b) Mechanistic rationale for a competitive oxidative Heck reaction.

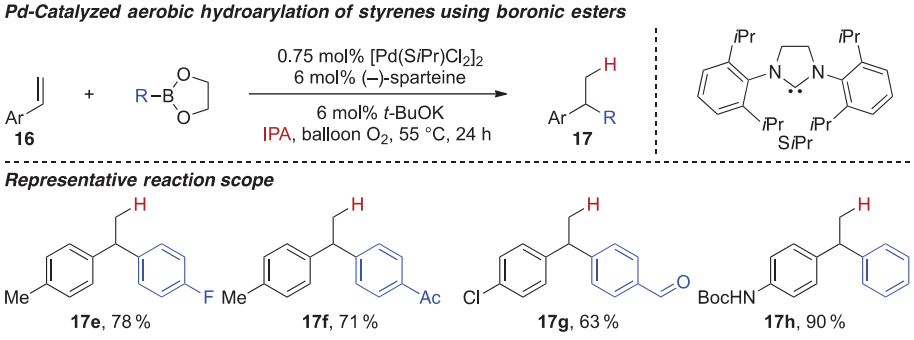


Scheme 7 Pd-catalyzed hydroarylation and hydroalkenylation reactions of styrene derivatives.

molecules [31–34], including compound **17b**, which exhibits selective antiproliferative activity against MCF-7 breast cancer cells [33]. Both electron-rich (**17a**) and electron-poor (**17b**) arylstannanes are effective coupling partners under the reaction conditions. The reaction also tolerates a variety of functional groups on the styrene substrate, including an aryl chloride (**17a**) and a Boc-protected aniline (**17b**). Moreover, this method also permits the use of *ortho*-substituted styrenes as well as a naphthalene derivative, which afford the corresponding products **17c** and **17d** in reasonable yields. Notably, alkenylstannanes are also effective coupling partners for hydroalkenylations (**17c**, **17d**).

To probe the proposed mechanistic hypothesis, an isotopic labeling experiment was performed using $(CH_3)_2CDOH$ as solvent. A 92% yield of hydroarylation products containing a single deuterium atom was observed as a 70:22 mixture of isotopomers **19** and **20**. This data suggests that the Pd-deuteride formed via alcohol oxidation inserts in both 1,2- and 2,1-fashion; however, in the case of the 1,2-insertion, the resultant Pd-alkyl isomerizes to the stabilized π-benzyl intermediate prior to transmetallation. The observation of unlabeled product **21** is consistent with the generation of a Pd-hydride, which could arise from β-hydride elimination of either Pd-alkyl insertion intermediate followed by dissociation from the resultant alkene.

The concept of a tandem alcohol oxidation/cross-coupling sequence was later extended to boronic esters [35, 36], which are appealing transmetallating reagents due to their low toxicity and ease of preparation. Under the conditions just described for arylstannanes, a meager 11% GC yield of a 1.4:1 mixture of hydroarylation to oxidative Heck products was observed when using phenylboronic acid ethylene glycol ester. This prompted the investigation of new catalysts, specifically Pd-*N*-heterocyclic carbene (NHC) complexes, which our group had previously shown to be effective for aerobic alcohol oxidations [11]. Optimization led to the use of a combination of exogenous (–)-sparteine and *t*-BuOK in conjunction with the catalyst $[Pd(SiPr)Cl_2]_2$

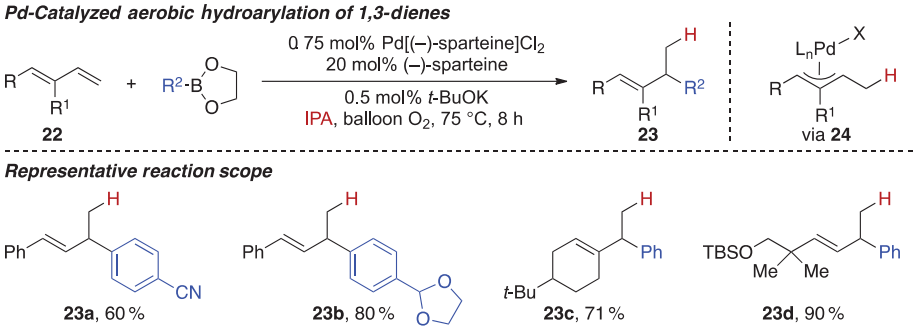


Scheme 8 Pd-catalyzed hydroarylation reactions of styrene derivatives with boronic esters.

(Scheme 8). The addition of (–)-sparteine was found to be crucial to the success of the reaction, presumably serving to break up $[Pd(SiPr)Cl_2]_2$ to the active monomeric form.

The reaction incorporates diverse functionality on the styrene, including a *para*-tolyl group (**17e**, **17f**, Scheme 8), an aryl chloride (**17g**), and a Boc-protected aniline (**17h**). Various functional groups are also tolerated on the boronic ester, including an aryl fluoride (**17e**) and acid-sensitive acetal groups, which, upon acidic workup, furnish ketone **17f** and aldehyde **17g.**

This protocol could also be extended to the use of 1,3-dienes as substrates, which, like styrenes, undergo 1,2-hydroarylation of the terminal alkene, in this case via a π-allyl-stabilized Pd-alkyl intermediate (**24**, Scheme 9) [37]. However, the use of the $[Pd(SiPr)Cl_2]_2$ complex resulted in minimal conversion of the 1,3-diene, prompting the use of Pd[(–)-sparteine]Cl_2. The conditions are otherwise similar to those reported for styrenes. The scope of boronic esters is broad, and includes a benzonitrile (**23a**) and a benzyl acetal (**23b**). In terms of the substrate, a diene containing a trisubstituted double bond (**23c**) is tolerated, as is a TBS-protected alcohol-containing diene (**23d**). However, substrates are limited to those containing sterically-bulky substituents at the 4-position (R group) of the 1,3-diene **22**, which serves to limit σ-π-σ isomerization of the putative Pd-π-allyl intermediate.

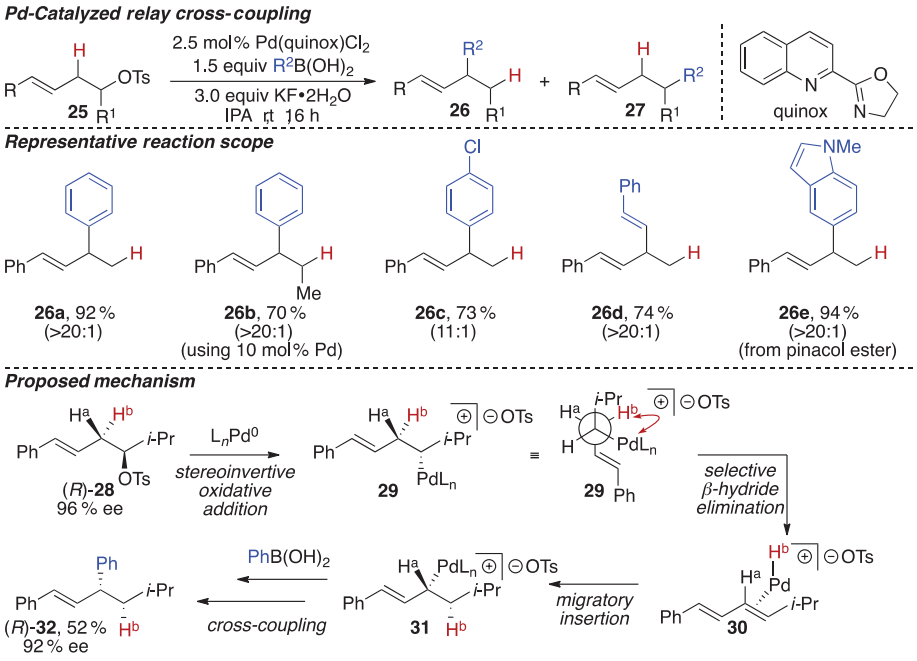


Scheme 9 Pd-catalyzed 1,2-hydroarylation of 1,3-dienes with boronic esters.

Relay Suzuki reactions

We saw the propensity for β-hydride elimination from Pd-alkyl intermediates as an opportunity to develop a relay Suzuki reaction of alkyl halides containing a distal alkene, wherein cross-coupling would occur in the allylic position rather than the carbon atom bearing the halide [38]. This was realized by employing homoallylic tosylates (**25**) as substrates to access products **26** (Scheme 10) [39]. This method is complementary to the just-mentioned hydroarylation of dienes as it accesses similar product scaffolds through the intermediacy of an *in situ*-generated 1,3-diene.

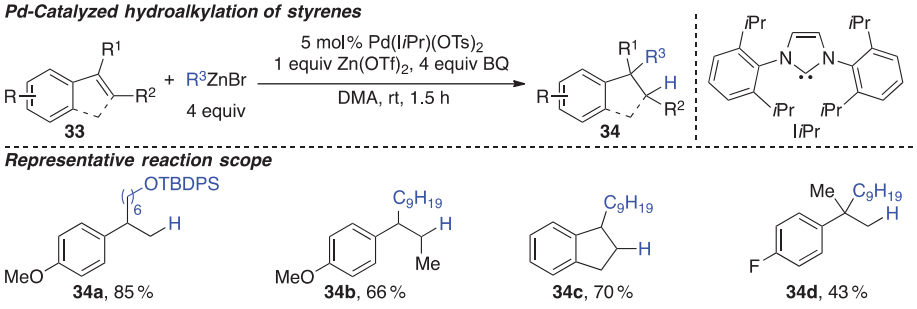
At ambient temperature in the presence of the air-stable *N,N*-ligated Pd(quinox)Cl_2 precatalyst, both primary (**26a**) and secondary (**26b**) homoallylic electrophiles undergo allylic relay cross-coupling with phenylboronic acid. The boronic acid scope is very broad, as a variety of useful aryl- and alkenyl groups are coupled to the allylic position with high yield and selectivity, including a *para*-chlorophenyl group (**26c**), a styrene (**26d**), and an indole (**26e**). Efforts are underway to develop an asymmetric catalytic variant of this reaction, an endeavor requiring a difficult enantioselective β-hydride elimination [40]. Enantiomerically-enriched products can currently be obtained via chirality transfer, which occurs smoothly from the enriched secondary tosylate (*R*)-**28**, affording product (*R*)-**32**. A number of mechanistic implications have been drawn from this result. Foremost, a rare example of oxidative addition of a secondary alkyl tosylate to Pd(0) [41] affords **29** through an invertive S_N2-type process. Then, conformationally controlled β-hydride elimination and face-selective migratory insertion lead, via diene complex **30**, to π-allyl-stabilized Pd-alkyl **31**, which undergoes cross-coupling to give (*R*)-**32**.



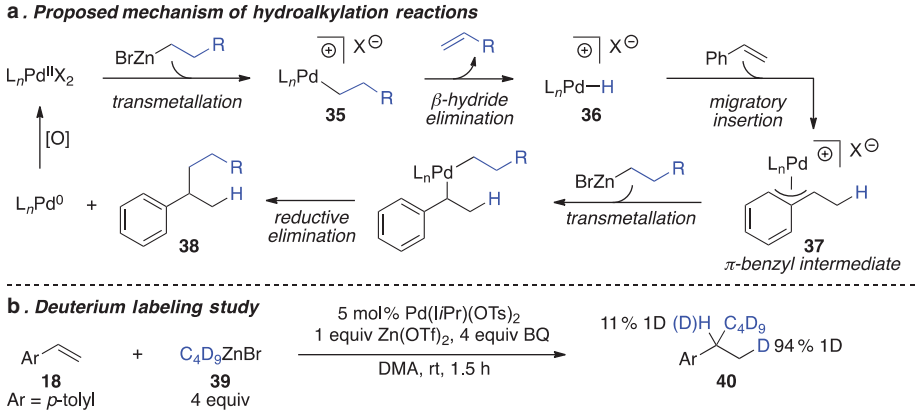
Scheme 10 Pd-catalyzed relay Suzuki cross-couplings of homoallylic tosylates.

Pd-catalyzed hydroalkylation reactions

In contrast to our hydroarylation and hydroalkenylation reactions, we hypothesized that a Pd-hydride could be produced via β-hydride elimination from an unstabilized Pd-alkyl (rather than a Pd-alkoxide) intermediate. This approach would enable the formation of an sp^3–sp^3 C–C bond if an alkyl organometallic could function as both the sacrificial hydride source and the coupling partner. As such, we turned our attention to the potential for alkylzinc reagents to afford hydroalkylation products. Initial attempts to develop an alkene hydroalkylation reaction under an atmosphere of O_2 were unsuccessful. Alternative oxidants, such as benzoquinone (BQ), led to a promising 30 % GC yield of the hydroalkylation product. While BQ-mediated oxidations typically require Brønsted acids to facilitate the oxidation of Pd(0) to Pd(II) by activating BQ, they are not compatible with alkylzinc reagents. Hence, a variety of Lewis-acids were evaluated and $Zn(OTf)_2$ was found to significantly enhance the performance of the reaction. Further optimization revealed that the reaction was best catalyzed by Pd-(NHC) catalysts in polar solvents, namely *N*,*N*-dimethylacetamide (DMA) (Scheme 11) [42]. A variety of functionalized alkylzinc reagents are compatible with the reaction conditions, including a TBDPS-protected alcohol (**34a**). The reaction is not limited to terminal styrenes, as β-methyl anisole (**34b**), indene (**34c**), and 4-fluoro-α-methyl styrene (**34d**) are all competent substrates, with the latter leading to the



Scheme 11 Pd-catalyzed hydroalkylation reactions of styrene derivatives.



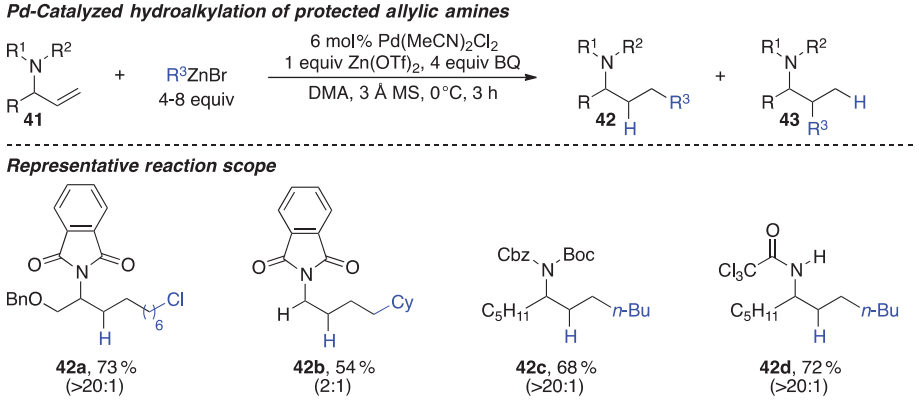
Scheme 12 (a) Proposed mechanism for the Pd-catalyzed hydroalkylation of styrene. (b) Dueterium-labeling experiment.

formation of an all-carbon quaternary center. It should be noted that no constitutional isomers are observed as byproducts in this reaction.

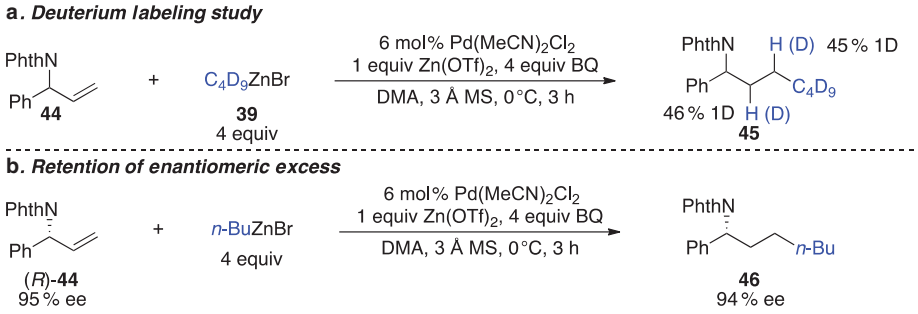
Mechanistically, it is postulated that initial transmetallation affords an unstabilized Pd-alkyl intermediate **35** that is prone to β-hydride elimination (Scheme 12a). The resultant Pd-hydride can be intercepted by styrene, producing a π-benzyl-stabilized Pd-alkyl intermediate **37**, which undergoes transmetallation and reductive elimination to afford the hydroalkylation product **38**. The isotopic scrambling observed when using the deuterated alkylzinc reagent **39** suggests that the alkene migratory insertion occurs in both 1,2- and 2,1-fashion, but the 1,2-insertion Pd-alkyl intermediate isomerizes to the benzylic position (Scheme 12b). In contrast, the π-benzyl-stabilized Pd-alkyl intermediate **37** resists β-hydride elimination, allowing selective transmetallation to occur, thereby affording the Markovnikov hydroalkylation product **38** exclusively. The formation of sp^3–sp^3 C–C bonds using palladium catalysis is non-trivial; this method provides an important complement to traditional Pd(0) cross-coupling approaches to this bond construction.

In an effort to expand the substrate scope of our hydrofunctionalization reactions, we began to explore the ability of alkenes other than styrenes or 1,3-dienes to effectively stabilize Pd-alkyl intermediates. Inspired by a 2009 report from Feringa and coworkers [43], we found that allylic phthalimides are able to deliver hydroalkylation products with excellent anti-Markovnikov selectivity (Scheme 13) [44].

In terms of the scope, several protected allylic amines bearing Lewis basic functional groups, such as those containing a benzyl ether (**42a**) and a thiophene (not shown), are tolerated under the reaction conditions. A variety of functionalized alkylzinc reagents, including a primary alkyl chloride (**42a**), are also able to deliver the corresponding hydroalkylation products in good yields and excellent selectivities. A significant decrease in selectivity is observed when the substrate lacks additional substitution at the amine-bearing



Scheme 13 Pd-catalyzed anti-Markovnikov hydroalkylation reactions of allylic amine derivatives.

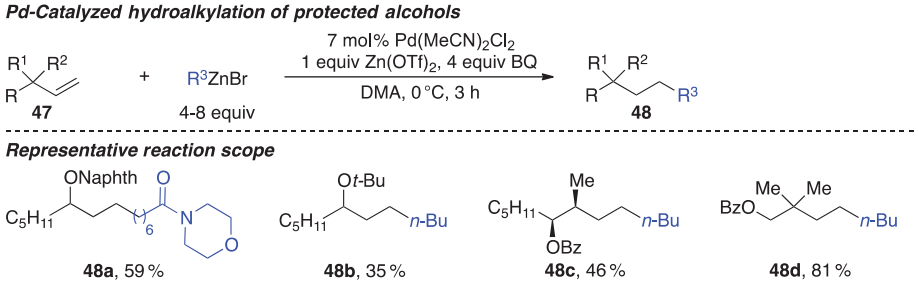


Scheme 14 Experiments to probe the mechanism of the hydroalkylation of allylic phthalimides.

carbon (**42b**). Upon probing a variety of amine protecting groups, the reaction proved to be more general than originally anticipated. For example, a di-protected *N*-Cbz-*N*-Boc amine affords 68 % yield and >20:1 anti-Markovnikov selectivity (**42c**). Interestingly, electron-poor protecting groups, including a trichloroacetamide, are able to deliver the hydroalkylation products in >20:1 selectivity (**42d**), suggesting that coordination of the carbonyl functional group to the palladium catalyst (common for phthalimide, Cbz, and Boc) is not responsible for the high anti-Markovnikov selectivity.

Perdeuterated alkylzinc reagent **39** was evaluated in order to interrogate the reaction mechanism, and 91 % deuterium incorporation was observed upon reaction with **44**, with a near-equal amount of deuterium found at both the 1- and 2-position (Scheme 14a). This suggests that, once the Pd-deuteride is formed, both 1,2- and 2,1-insertion occur, with the primary Pd-alkyl intermediate selectively undergoing transmetallation to give the anti-Markovnikov product **45**. This stands in contrast to the hydroarylation of styrenes, which affords only Markovnikov products. Importantly, no deuterium incorporation is observed in the allylic position, suggesting that β-hydride elimination does not occur at the amine-bearing carbon. In further support of this hypothesis, when an entantiomerically-enriched allylic phthalimide, (*R*)-**44**, was submitted to the reaction conditions, the product was obtained with virtually full retention of enantiomeric excess (Scheme 14b). This mechanistic feature allows access to compounds containing a stereocenter in regions devoid of functional groups.

With minimal reoptimization, this method was extended to protected allylic alcohols (Scheme 15) [45]. As with protected amines, a variety of alcohol protecting groups afford anti-Markovnikov hydroalkylation products in good yields and high selectivity, including 1-naphthoyl- (**48a**), *tert*-butyl- (**48b**), and benzoyl-protecting groups (**48c**, **48d**). The competence of the *tert*-butyl ether substrate **47b** supports the hypothesis that the allylic heteroatom does not dictate the high anti-Markovnikov selectivity through catalyst coordination, although enhanced yields are typically observed when Lewis basic groups are present. Further, aliphatic substrates (such as dodecene) do not afford selective hydroalkylations. Instead, only alkene isomerization is observed (not shown). This exemplifies the importance of substitution at the allylic position, which is required to sufficiently slow β-hydride elimination in order for selective transmetallation to occur. Even methyl substitution at the allylic position gives a sufficient 46 % yield and >20:1 selectivity for the anti-Markovnikov product **48c**. Not surprisingly, a geminal dimethyl group at the allylic position



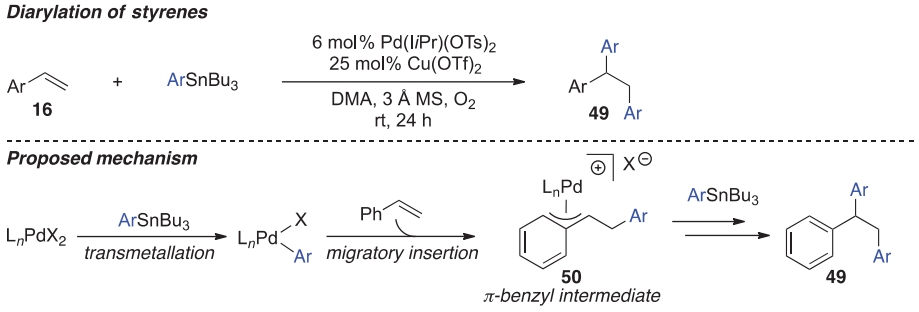
Scheme 15 Pd-catalyzed anti-Markovnikov hydroalkylation reactions of allylic alcohol derivatives.

results in even higher yields and >20:1 selectivity (**48d**). Finally, the scope of alkylzinc reagents is broad, as illustrated by the use of a morpholine-derived amide (**48a**). Recently, Lin and Qing have shown that geminal difluorination of the allylic position also selectively furnishes the anti-Markovnikov products [46]. It is hypothesized that the high anti-Markovnikov selectivity arises from a combination of the retardation of β-hydride elimination at the allylic position (due to substitution) and a relatively fast transmetallation of the less sterically-hindered primary Pd-alkyl intermediate.

Alkene difunctionalization

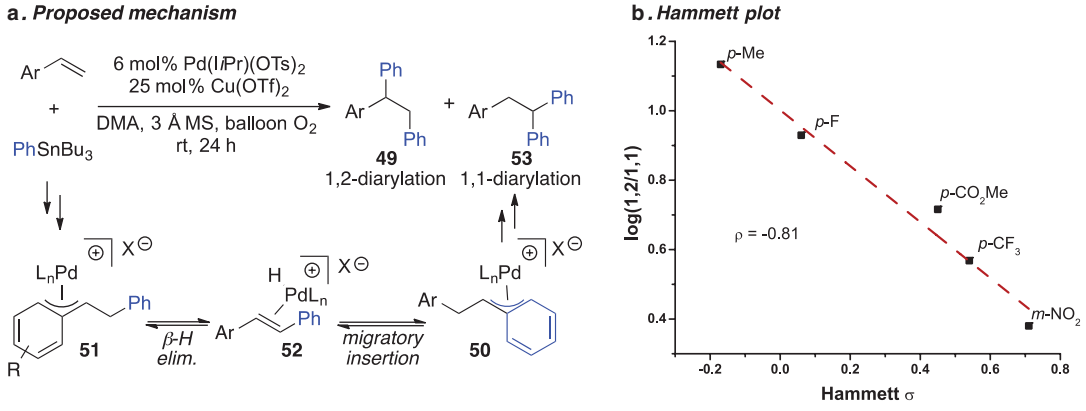
Pd-catalyzed alkene diarylation reactions

Our interest in alkene difunctionalization reactions stemmed from a desire to rapidly increase molecular complexity by constructing two new C–C bonds in a single reaction. It also arose from the observation of an alkene diarylation byproduct in the aforementioned Pd-catalyzed hydroarylation of styrenes using arylstannanes. This byproduct was believed to result from initial transmetallation of the aryl stannane followed by styrene insertion into the Pd-aryl bond, affording the stabilized π-benzyl intermediate **50** to which cross-coupling occurs to give the diarylation product **49** (Scheme 16). This results in the installation of two new C–C bonds across an alkene in a 1,2-fashion, providing access to a diverse array of diarylated products in the presence of catalytic Pd(I*i*Pr)(OTs)$_2$ [47, 48].



Scheme 16 Pd-catalyzed diarylation reactions of styrenes.

When electron-deficient styrenes are used as substrates, a mixture of 1,2- and 1,1-diarylation products is observed. The selectivity correlates to the Hammett σ-values of the substrate's arene substituent with a ρ of −0.81 [47] (Scheme 17). This suggests that when π-benzyl intermediate **51** is electron-deficient, isomerization



Scheme 17 (a) Proposed mechanism for the 1,1-diarylation of styrenes. (b) Linear free energy relationship between styrene Hammett electronic parameters and product selectivity.

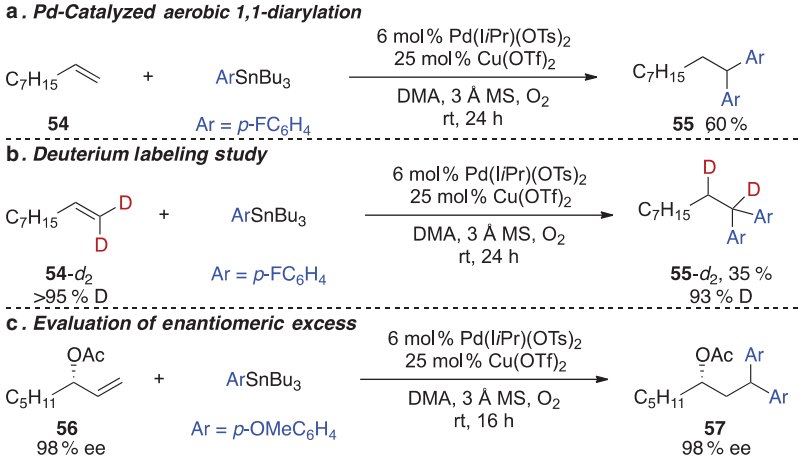
to the more electron-rich π-benzyl intermediate **50** (which better stabilizes the cationic Pd complex) is possible. The product distribution therefore depends upon the relative rates of β-hydride elimination and interception of the π-benzyl intermediate by the second equivalent of stannane.

Based on this observation, we began investigating non-conjugated terminal alkenes under the assumption that β-hydride elimination and reinsertion would lead to the substrate-stabilized π-benzyl intermediate and allow a second transmetallation to occur. This was indeed the case for 1-nonene **54**: the 1,1-diarylation product **55** was isolated in 60 % yield, and no other isomers were detected (Scheme 18a). In an isotopic labeling experiment, both deuterium atoms of substrate **54**-d_2 were conserved in the product **55**-d_2, with one deuterium atom transposed to the internal carbon (Scheme 18b). This is consistent with our mechanistic hypothesis, as after the initial migratory insertion, β-hydride elimination and reinsertion would be expected to transpose a deuterium atom to the internal carbon while leading to a π-benzyl intermediate. Finally, enantiomerically-enriched allylic acetate **56** affords the 1,1-diarylation product **57** with complete retention of enantiomeric excess under the reaction conditions [48]. This suggests that either β-hydride elimination does not occur in the allylic position, or if it does occur, the resultant internal alkene inserts into the Pd-hydride with exquisite facial fidelity.

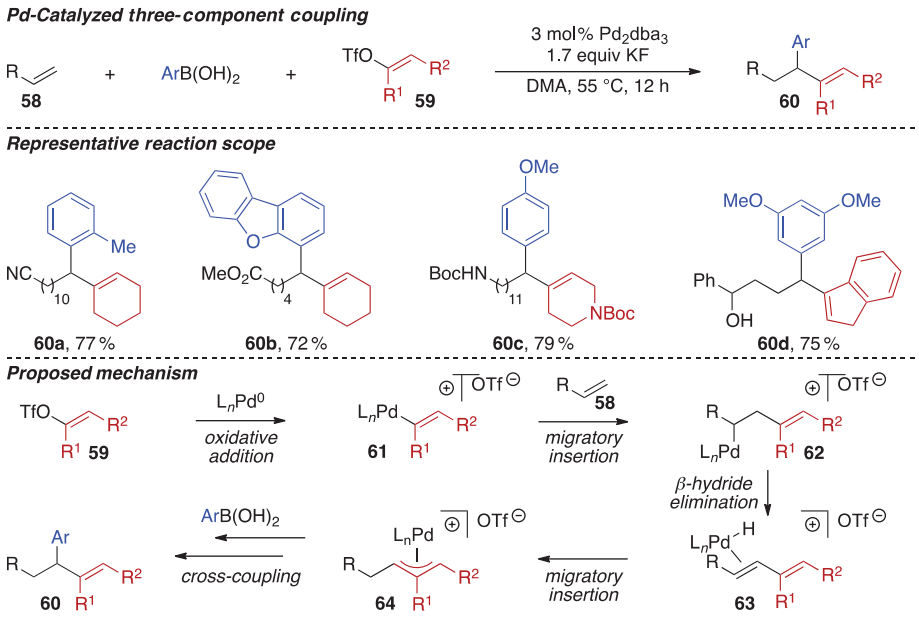
Pd-catalyzed alkenylarylation reactions of alkenes

A clear limitation of our Pd(II)-catalyzed diarylation reactions is that two identical aryl groups are added to the alkene. In an effort to generate even greater molecular complexity, we envisioned a Pd(0)-catalyzed three-component coupling strategy [49] to combine a non-conjugated terminal alkene, an oxidant (alkenyl triflate), and a transmetallating reagent. This would be initiated by the oxidative addition of the alkenyl triflate (**59**) to Pd(0) to furnish the Pd-alkenyl species **61** (Scheme 19). The terminal alkene **58** could then insert into the Pd-alkenyl bond to deliver the Pd-alkyl intermediate **62**. This kinetically unstable intermediate could then undergo β-hydride elimination and migratory insertion to arrive at the stabilized π-allyl intermediate **64**, to which a boronic acid could cross-couple [50].

This reaction delivers 1,1-alkenylarylation products in good yield and selectivity (Scheme 19). Some functional groups incorporated include a nitrile (**60a**), a methyl ester (**60b**), a Boc-protected amine (**50c**) and an unprotected secondary alcohol (**60d**). A variety of boronic acids are also well-tolerated, including those containing *ortho*-tolyl- (**60a**), dibenzofuranyl- **(60b)**, electron-rich *para*-methoxyphenyl- (**60c**), and eletron-poor 3,5-dimethoxyphenyl- (**60d**) groups. This reaction is limited to the use of cyclic alkenyl triflates as the oxidant because of the ease with which they undergo oxidative addition, and because the resultant cationic Pd-alkenyl species **61** is predisposed to the necessary substrate insertion.

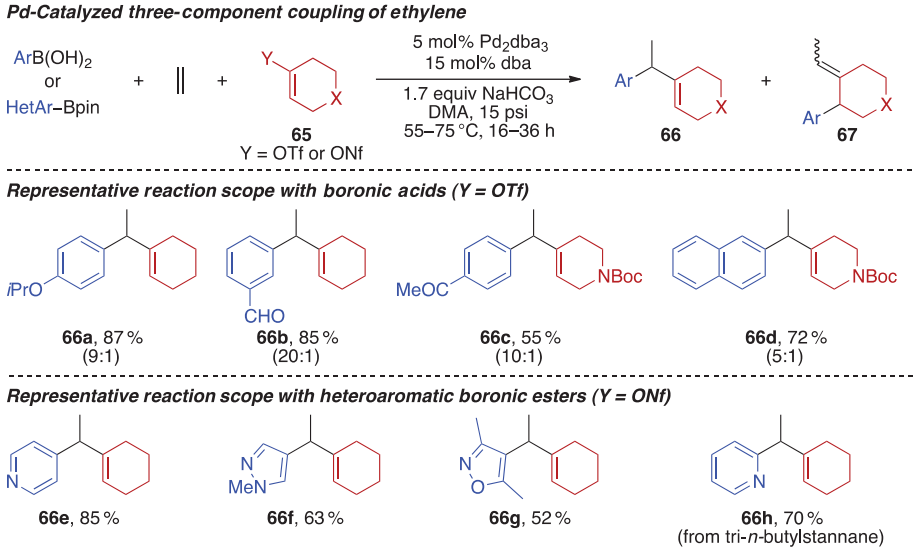


Scheme 18 Key Pd-catalyzed 1,1-diarylation reactions of terminal alkenes.



Scheme 19 Pd-catalyzed three-component alkenylarylation reactions.

Ethylene, the simplest alkene, may also be used in three-component couplings with aryl- or heteroaryl boronic acids or esters and cyclic alkenyl triflates or nonaflates (Scheme 20) [51–53]. Both electron-rich (**66a**) and electron-deficient (**66b**, **66c**) phenylboronic acids afford good yields and good 1,1-selectivities. This method also works well for 2-naphthyl boronic acid (**66d**), leading to product **66d** in good yield and 5:1 selectivity for the thermodynamically stable endocyclic alkene. Additonally, heteroaromatic pinacol boronic esters (**66e–66g**) make good coupling partners. This is a noteworthy achievement since the use of these heteroaromatic organometallic reagents poses a great challenge in Suzuki reactions due to their Lewis basicity and propensity to decompose via protodeborylation. Examples include a 4-pyridyl group (**66e**), an *N*-methylpyrazole (**66f**), and a substituted isoxazole group (**66g**). Additionally, a 2-pyridyl group can be coupled from the corresponding tri-*n*-butyl tin reagent (**66h**). The scope of electrophiles is again limited to cyclic alkenyl triflates and nonaflates, the latter of which are less costly to prepare.



Scheme 20 Pd-catalyzed three-component alkenylarylation reactions of ethylene.

Conclusion

We have highlighted a portion of our efforts towards selective alkene functionalization reactions involving Pd-hydride intermediates. Pd-hydrides may originate from alcohol oxidations or Pd-alkyl β-hydride eliminations from reagents or substrates. Taking advantage of our improved understanding of the dynamics of β-hydride elimination, migratory insertion, and transmetallation, we have developed selective functionalization reactions of stabilized Pd-alkyls. More than a decade's worth of research has revealed that Pd-catalyzed alkene hydrofunctionalization chemistry is a powerful tool for selective C–H, C–O, and C–C bond-forming processes. Our hydroarylation, hydroalkenylation, and hydroalkylation reactions provide attractive alternatives to cross-coupling by using alkenes as synthons for alkyl halides in sp^3–sp^2 and sp^3–sp^3 C–C bond constructions. Highly selective and predictable hydrofunctionalizations of *ortho*-alkenylphenols, styrenes, and 1,3-dienes can be achieved through the interception of *ortho*-quinone methide-, π-benzyl-, and π-allyl intermediates, respectively. Substituted allylic substrates, such as allylic amines and alcohols, have also been shown to enable selective C–C bond constructions without the need for formal substrate stabilization. Finally, alkene difunctionalization reactions have been shown to expedite the assembly of highly complex products from simple chemical feedstocks, including ethylene. Substantial ongoing effort is being devoted to the realization of asymmetric variants of these reactions

References

[1] R. Jana, T. P. Pathak, M. S. Sigman. *Chem. Rev.* **111**, 1417 (2011).
[2] M. R. Netherton, C. Dai, K. Neuschütz, G. C. Fu. *J. Am. Chem. Soc.* **123**, 10099 (2001).
[3] M. R. Netherton, G. C. Fu. *Angew. Chem. Int. Ed.* **41**, 3910 (2002).
[4] J. Zhou, G. C. Fu. *J. Am. Chem. Soc.* **125**, 12527 (2003).
[5] A. C. Frisch, M. Beller. *Angew. Chem. Int. Ed.* **44**, 674 (2005).
[6] E. M. Ferreira, B. M. Stoltz. *J. Am. Chem. Soc.* **123**, 7725 (2001).
[7] D. R. Jensen, J. S. Pugsley, M. S. Sigman. *J. Am. Chem. Soc.* **123**, 7475 (2001).
[8] D. R. Jensen, M. S. Sigman. *Org. Lett.* **5**, 63 (2002).
[9] J. A. Mueller, D. R. Jensen, M. S. Sigman. *J. Am. Chem. Soc.* **124**, 8202 (2002).
[10] J. T. Bagdanoff, E. M. Ferreira, B. M. Stoltz. *Org. Lett.* **5**, 835 (2003).
[11] D. R. Jensen, M. J. Schultz, J. A. Mueller, M. S. Sigman. *Angew. Chem. Int. Ed.* **42**, 3810 (2003).
[12] S. K. Mandal, D. R. Jensen, J. S. Pugsley, M. S. Sigman. *J. Org. Chem.* **68**, 4600 (2003).
[13] S. K. Mandal, M. S. Sigman. *J. Org. Chem.* **68**, 7535 (2003).
[14] J. A. Mueller, M. S. Sigman. *J. Am. Chem. Soc.* **125**, 7005 (2003).
[15] J. T. Bagdanoff, B. M. Stoltz. *Angew. Chem. Int. Ed.* **43**, 353 (2004).
[16] D. D. Caspi, D. C. Ebner, J. T. Bagdanoff, B. M. Stoltz. *Adv. Synth. Catal.* **346**, 185 (2004).
[17] J. A. Mueller, C. P. Goller, M. S. Sigman. *J. Am. Chem. Soc.* **126**, 9724 (2004).
[18] R. J. Nielsen, J. M. Keith, B. M. Stoltz, W. A. Goddard. *J. Am. Chem. Soc.* **126**, 7967 (2004).
[19] B. M. Stoltz. *Chem. Lett.* **33**, 362 (2004).
[20] R. M. Trend, B. M. Stoltz. *J. Am. Chem. Soc.* **126**, 4482 (2004).
[21] M. J. Schultz, S. S. Hamilton, D. R. Jensen, M. S. Sigman. *J. Org. Chem.* **70**, 3343 (2004).
[22] A. M. Balija, K. J. Stowers, M. J. Schultz, M. S. Sigman. *Org. Lett.* **8**, 1121 (2006).
[23] M. J. Schultz, M. S. Sigman. *J. Am. Chem. Soc.* **128**, 1460 (2006).
[24] K. M. Gligorich, M. J. Schultz, M. S. Sigman. *J. Am. Chem. Soc.* **128**, 2794 (2006).
[25] W. G. Lloyd. *J. Org. Chem.* **32**, 2816 (1967).
[26] T. Nishimura, N. Kakiuchi, T. Onoue, K. Ohe, S. Uemura. *J. Chem. Soc., Perkin Trans. 1*, 1915 (2000).
[27] Y. Zhang, M. S. Sigman. *Org. Lett.* **8**, 5557 (2006).
[28] N. Kambe, T. Iwasaki, J. Terao. *Chem. Soc. Rev.* **40**, 4937 (2011).
[29] M. R. Netherton, G. C. Fu. *Org. Lett.* **3**, 4295 (2001).
[30] K. M. Gligorich, S. A. Cummings, M. S. Sigman. *J. Am. Chem. Soc.* **129**, 14193 (2007).
[31] J. Kischel, I. Jovel, K. Mertins, A. Zapf, M. Beller. *Org. Lett.* **8**, 19 (2005).
[32] B. L. H. Taylor, E. C. Swift, J. D. Waetzig, E. R. Jarvo. *J. Am. Chem. Soc.* **133**, 389 (2010).
[33] K. Gligorich, R. Vaden, D. Shelton, G. Wang, C. Matsen, R. Looper, M. Sigman, B. Welm. *Breast Cancer Res.* **15**, R58 (2013).
[34] H. M. Wisniewska, E. C. Swift, E. R. Jarvo. *J. Am. Chem. Soc.* **135**, 9083 (2013).

[35] Y. Iwai, K. M. Gligorich, M. S. Sigman. *Angew. Chem. Int. Ed.* **47**, 3219 (2008).
[36] S. M. Podhajsky, Y. Iwai, A. Cook-Sneathen, M. S. Sigman. *Tetrahedron* **67**, 4435 (2011).
[37] L. Liao, M. S. Sigman. *J. Am. Chem. Soc.* **132**, 10209 (2010).
[38] S. Aspin, A.-S. Goutierre, P. Larini, R. Jazzar, O. Baudoin. *Angew. Chem. Int. Ed.* **51**, 10808 (2012).
[39] B. J. Stokes, S. M. Opra, M. S. Sigman. *J. Am. Chem. Soc.* **134**, 11408 (2012).
[40] I. T. Crouch, R. K. Neff, D. E. Frantz. *J. Am. Chem. Soc.* **135**, 4970 (2013).
[41] B. Xiao, Z.-J. Liu, L. Liu, Y. Fu. *J. Am. Chem. Soc.* **135**, 616 (2013).
[42] K. B. Urkalan, M. S. Sigman. *J. Am. Chem. Soc.* **131**, 18042 (2009).
[43] B. Weiner, A. Baeza, T. Jerphagnon, B. L. Feringa. *J. Am. Chem. Soc.* **131**, 9473 (2009).
[44] R. J. DeLuca, M. S. Sigman. *J. Am. Chem. Soc.* **133**, 11454 (2011).
[45] R. J. DeLuca, M. S. Sigman. *Org. Lett.* **15**, 92 (2012).
[46] X. Lin, F.-L. Qing. *Org. Lett.* **15**, 4478 (2013).
[47] K. B. Urkalan, M. S. Sigman. *Angew. Chem. Int. Ed.* **48**, 3146 (2009).
[48] E. W. Werner, K. B. Urkalan, M. S. Sigman. *Org. Lett.* **12**, 2848 (2010).
[49] M. S. McCammant, L. Liao, M. S. Sigman. *J. Am. Chem. Soc.* **135**, 4167 (2013).
[50] L. Liao, R. Jana, K. B. Urkalan, M. S. Sigman. *J. Am. Chem. Soc.* **133**, 5784 (2011).
[51] V. Saini, M. S. Sigman. *J. Am. Chem. Soc.* **134**, 11372 (2012).
[52] V. Saini, B. J. Stokes, M. S. Sigman. *Angew. Chem. Int. Ed.*, **52**, 11206 (2013).
[53] V. Saini, L. Liao, Q. Wang, R. Jana, M. S. Sigman. *Org. Lett.* **15**, 5008 (2013).