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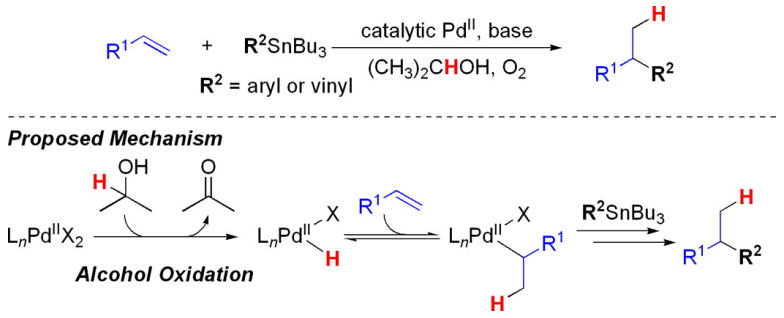

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Palladium-Catalyzed Reductive Coupling of Styrenes and Organostannanes under Aerobic Conditions

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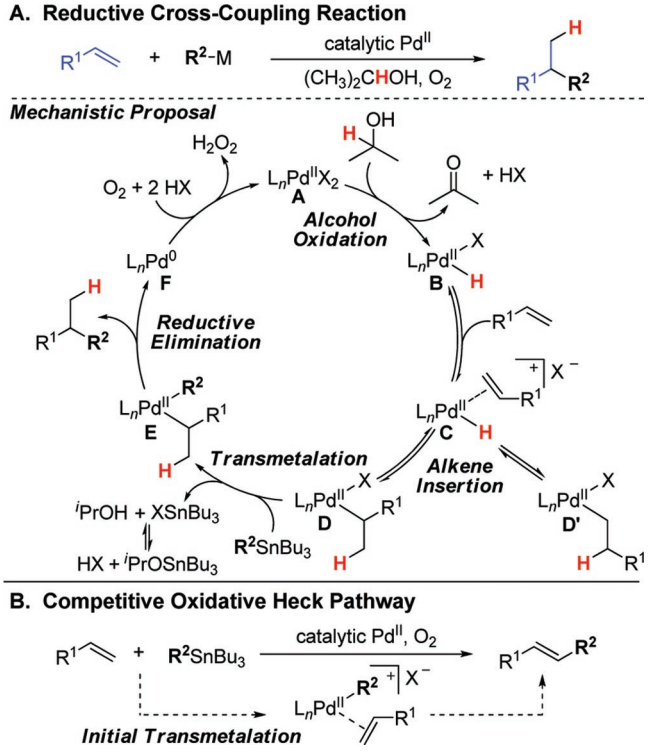
The Pd^0-catalyzed cross-coupling of an electrophilic organic compound (generally compounds containing carbon−halogen bonds) and a nucleophilic organometallic reagent has emerged as a powerful method to construct carbon−carbon bonds.[1] In fact, cross-coupling reactions have significantly impacted chemists' strategies for the synthesis of materials,[2] pharmaceuticals,[3] and natural products.[4] Mechanistically, these reactions are thought to proceed by initial oxidative addition of the electrophilic organic compound (R−X) to Pd^0, yielding an oxidized species $R-Pd^{II}-X$.[1] This step is typically independent of the organometallic cross-coupling partner. In traditional cross-coupling, the R−X coupling partner must be able to oxidize Pd^0 to Pd^{II}, thereby limiting the potential scope of these ubiquitous transformations. Thus, the ability to access $R-Pd^{II}-X$ intermediates via an alternative pathway, specifically eliminating the need for the substrate to oxidize Pd^0 to Pd^{II}, will considerably enhance the versatility of Pd-catalyzed cross-coupling reactions by expanding the types of functional groups that can be used as cross-coupling partners.

To this end, we envisioned a reductive cross-coupling reaction, in which $R-Pd^{II}-X$ would originate from an alkene, a common and attractive starting material in organic synthesis that typically reacts as a nucleophile, instead of from an electrophilic organic reagent (Scheme 1A). On the basis of our recent work in Pd^{II}-catalyzed alcohol and alkene oxidations, we hypothesized that a tandem alcohol oxidation/alkene functionalization sequence would yield the desired $R-Pd^{II}-X$ intermediate.[5] Specifically, oxidation of the alcohol solvent (in this case 2-propanol) with a Pd catalyst **A** will lead to the formation of a Pd^{II}−hydride **B**. Coordination and insertion of the alkene into the Pd^{II}−hydride yields a Pd^{II}−alkyl intermediate **D** (or **D′**) similar to that formed via oxidative addition of an organic electrophile.[1] Transmetalation to form **E** and subsequent reductive elimination generates the reductive coupling product as well as the reduced catalyst **F**. Aerobic oxidation of Pd^0 to Pd^{II} completes the catalytic cycle.[6] In the overall reaction, the sp^2-hybridized carbon atoms of the alkene will be reduced to sp^3 atoms. Incorporation of sp^3 carbon atoms in cross-coupling reactions is significantly more challenging than sp- or sp^2-hybridized carbons.[7] Herein, we describe the design and development of a Pd^{II}-catalyzed reductive cross-coupling reaction of alkenes and organostannanes coupled to the aerobic oxidation of a simple alcohol.

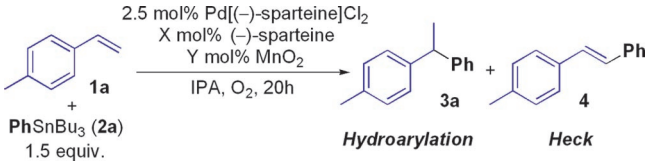
To initiate the investigation, careful selection of the catalyst and solvent was necessary to facilitate alcohol oxidation and to avoid undesired side reactions, such as the oxidative Heck reaction.[8] Therefore, Pd[(−)-sparteine]Cl_2, which our laboratory has shown to be a robust catalyst for both alkene and alcohol oxidations, was selected as the catalyst.[5a−e] The inexpensive solvent, 2-propanol, was chosen since secondary alcohols are excellent substrates for alcohol oxidation and are less nucleophilic than primary alcohols. Thus, they are less likely to undergo Pd-catalyzed reactions with alkenes directly.[9] A styrene substrate was initially evaluated due to the inability of the alkene to isomerize,[10a] and $PhSnBu_3$ was used as the initial cross-coupling partner because additives are generally not required to facilitate transmetalation of organostannanes.[10b]

Scheme 1. (A) Envisioned Reductive Cross-Coupling Reaction and Proposed Mechanism and (B) Competitive Oxidative Heck Reaction



Using this combination of reagents under aerobic conditions similar to those used in other Pd-catalyzed alkene functionalization reactions developed in our laboratory,[5a−e] we were delighted to observe the desired hydroarylation product **3a** as a >25:1 mixture of regioisomers albeit in low yield (Table 1, entry 1).[11] As expected, the major byproduct **4** is formed via an oxidative Heck reaction, which is proposed to originate from initial transmetalation of the Pd^{II} catalyst (Scheme 1B).[8b] Therefore, a decrease in the relative rate of initial transmetalation with respect to the rate of alcohol oxidation was desired to improve the selectivity of the reaction for hydroarylation. Since addition of Cu salts to Pd^0-catalyzed Stille couplings has been shown to facilitate transmetalation,[10b] $CuCl_2$ was removed leading to a decrease in conversion presumably due to catalyst decomposition (Table 1, entry 2).[1] However, as the ratio of the hydroarylation product to Heck was improved (2.4:1), Cu-free conditions were pursued. Without $CuCl_2$ to help facilitate catalyst regeneration, we turned to previous mechanistic studies performed by our group on the aerobic Pd[(−)-sparteine]Cl_2-catalyzed oxidation of alcohols, which revealed a significant rate enhancement and improved catalyst stability when exogenous (−)-

Table 1. Optimization for the Reductive Coupling Product **3a**



entry	scale[a]	X	Y	O_2	temp	% conv[b]	% **3a**[c]	**3a**:**4**[d]
1[e]	0.2	0	0	balloon	rt	85	23	1.3:1
2	0.2	0	0	balloon	rt	67	23	2.4:1
3	0.2	40	0	balloon	rt	40	17	28:1
4	0.2	40	0	balloon	60 °C	63	45	27:1
5[f]	0.2	20	0	balloon	60 °C	37	30	12:1
6[f]	0.2	40	0	balloon	60 °C	30	22	7.4:1
7	0.2	40	75	balloon	60 °C	>99	81	35:1
8[f]	0.2	40	75	balloon	60 °C	26	19	7.7:1
9	1.0	40	0	balloon	60 °C	40	24	16:1
10[g]	1.0	40	0	25 psi	60 °C	63	46	26:1
11[g]	1.0	40	75	25 psi	60 °C	94	86	22:1

[a] Scale in mmol. [b] Percent conversion measured by GC using an internal standard. [c] GC yield. [d] Ratio of GC yields. [e] $CuCl_2$ (7.5 mol %) was added. [f] (−)-Sparteine-*N*-oxide (20 mol %) was added. [g] Reaction was performed in a sealed thick-wall glass pressure vessel.

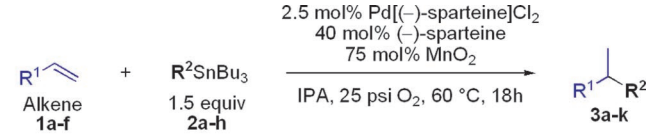
sparteine is used.[5a] Therefore, the addition of exogenous (−)-sparteine was evaluated where 40 mol % was found to significantly increase the selectivity for the hydroarylation product over Heck with a ∼28:1 ratio in modest conversion (entry 3). To increase the reaction rate, the temperature was raised to 60 °C and a 45% GC yield of the hydroarylation product was observed (entry 4).

A time course analysis of the reaction revealed a significant retardation of the rate as the reaction progressed (50% conversion of **1a** at 2 h, 65% conversion at 10 h), suggesting either catalyst decomposition or inhibition. One possible inhibitor is (−)-sparteine-*N*-oxide, which can be formed by oxidation of (−)-sparteine with H_2O_2, a product of O_2 reduction.[6,12] To test our hypothesis, two experiments were performed with added 20 mol % of (−)-sparteine-*N*-oxide at two different concentrations of (−)-sparteine. In both cases, a similar decrease in the conversion of **1a** was observed (compare entries 4−6), which is consistent with a detrimental effect of (−)-sparteine-*N*-oxide (entry 6). Therefore, MnO_2 was evaluated as an additive to disproportionate H_2O_2.[13] Excitingly, addition of 75 mol % of MnO_2 produced **3a** in 81% GC yield at nearly complete conversion (entry 7). Finally, as a control, both MnO_2 and (−)-sparteine-*N*-oxide were added with results similar to the absence of MnO_2 (entry 8). To further probe the role of MnO_2, ESI-MS was used to analyze the reaction mixtures for the presence of (−)-sparteine-*N*-oxide.[14] With added MnO_2, the ratio of peak heights (which are dependent on ionization potential and do not directly reflect the absolute amount of each species) of (−)-sparteine-*N*-oxide to (−)-sparteine was found to be 0.50 compared to 0.64 in the absence of MnO_2, a ∼28% difference. This is consistent with MnO_2 acting as a scavenger of H_2O_2.

Another issue observed upon scaling the reaction was poor conversion of **1a**, which was attributed to catalyst decomposition, presumably due to poor mass transport of O_2 (entry 9).[15] Raising the pressure of O_2 from balloon (∼1.1 atm) to 25 psi (1.7 atm) improved the reaction outcome (entry 10). Even with the increased O_2 pressure, MnO_2 was still required to achieve effective catalysis (compare entries 10 and 11).

With conditions optimized, the initial scope of the Pd^{II}-catalyzed reductive coupling was explored. All of the reactions are highly regioselective (>25:1), which contrasts many of the reported Lewis acid catalyzed hydroarylation reactions.[16] The electronic nature of the arylstannane has minimal impact on the yield of the reaction (Table 2, entries 1−7), and substitution *ortho* on either the styrene

Table 2. Substrate Scope of the Reductive Coupling Reaction



entry	R^2	product	yield (%)[a]
1	**2a**	**3a**	76
2	**2b**	**3b**	70
3	**2c**	**3c**	67
4[b]	**2d**	**3d**	59
5	**2b**	**3e**	65
6[c]	**2e**	**3f**	58
7[b,c]	**2e**	**3g**	55
8[b]	**2f**	**3h**	63
9[b]	**2f**	**3i**	69
10[b,d]	**2g**	**3j**	52
11[b]	**2h**	**3k**	50

[a] Average isolated yield of two experiments performed on 1 mmol scale. [b] Pd[(−)-sparteine]Cl_2 (3.5 mol %) was used. [c] Reaction was performed on 0.5 mmol scale. [d] Treated with HOAc upon workup.

or the arylstannane is tolerated (entries 4 and 8). A styrene containing a chlorine atom exhibits high chemoselectivity for the reductive coupling process wherein no products arising from a Stille-type coupling are observed (entry 5).[1] Acid-sensitive protecting groups can be incorporated (entries 6 and 7), which would not likely be stable under Lewis acid catalyzed hydroarylation reaction conditions.[16] An exciting aspect of this type of alkene reductive coupling with an organostannane is expansion to reaction types not accessible using reported hydroarylation methods.[16] To this end, several vinylstannanes were tested under the optimized conditions with a slight increase of catalyst loading (entries 8−11).[17] Stannanes containing enol ethers were good coupling agents for the reductive

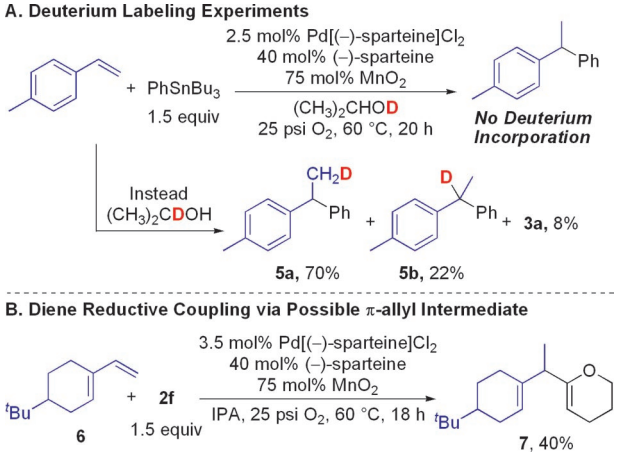


Figure 1. Mechanistic experiments.

coupling as is highlighted by the ability to perform an overall hydroacylation reaction (entry 10).[18] Even though a chiral catalyst is used in these reactions, no appreciable asymmetric induction is observed.[14]

To explore the validity of our initial mechanistic hypothesis, two isotopic labeling experiments were performed to determine the origin of the proton incorporated into the product (Figure 1A). When using $(CH_3)_2CHOD$ as solvent, no deuterium is incorporated into the product, ruling out the involvement of acidic protons in the process.[14] However, when using $(CH_3)_2CDOH$ as solvent, 92% of the hydroarylation products contain a single deuterium atom as a mixture of isotopomers **5a** and **5b**.[19] These data support our original mechanistic hypothesis that a Pd−hydride is formed via alcohol oxidation and the alkene subsequently inserts into the Pd−hydride (Scheme 1A).[5] The production of two isotopomers supports the reversible formation of both intermediates **D** and **D′** from **C**, which equilibrate via β-hydride elimination. During the course of the reaction, deuterium is incorporated into the styrene, which suggests the alkene can dissociate from **C**. The observation of a single product regioisomer suggests that only **D** leads to product. A possible explanation is that intermediate **D** can be stabilized by a π-benzyl species when using a styrenyl substrate.[20] This hypothesis provoked us to test a diene substrate, where the Pd−alkyl intermediate can be similarly stabilized via a possible π-allyl species (Figure 1B). This reaction proceeds modestly to yield the reductive coupling product as a single regioisomer and 1:1 mixture of diastereomers. Unfortunately, simple alkenes such as decene do not undergo reductive coupling under these conditions.

In conclusion, we have disclosed a fundamentally different approach to Pd-catalyzed cross-coupling reactions. In this process, Pd^0 is not oxidized by the organic substrate, but the requisite Pd^{II} organometallic species is accessed via a Pd^{II}-catalyzed alcohol oxidation to produce a Pd−hydride followed by alkene insertion. This contrasting approach allows for the facile and highly regioselective formation of sp^3−sp^2 carbon−carbon bonds from various alkenes and organostannane derivatives where an alkene can now be thought of as a synthon for aliphatic halides in cross-coupling reactions. It is also important to point out that this reductive coupling reaction is performed under aerobic conditions wherein the reduction of O_2 is necessary to complete the catalytic cycle. Current efforts are focused on exploiting this unique approach to alkene functionalization by expanding the scope of these processes to other cross-coupling partners and asymmetric catalysis.

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Supporting Information Available: Experimental procedures and characterization data for substances. This material is available free of charge via the Internet at http://pubs.acs.org.

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