Palladium Catalysis

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Aerobic Alcohol Oxidation Coupled to Palladium-Catalyzed Alkene Hydroarylation with Boronic Esters**

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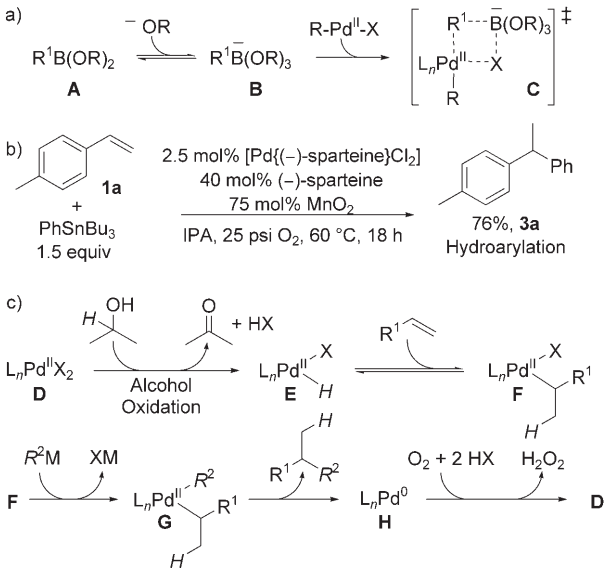
The Suzuki reaction, which couples an organohalide and an organoboron compound,[1] is an attractive cross-coupling reaction for use in the synthesis of natural products[2] and pharmaceuticals.[3] This utility is mainly because of the excellent functional group compatibility, ease of preparation of boronic acid derivatives, and the low toxicity of the boron byproducts.[2] The mechanistic details have been widely investigated and the reaction is thought to proceed through oxidative addition of the organohalide (R–X) to Pd^0 to form R–Pd^{II}–X and then transmetalation of the organoborane (R^1–$B(OR)_2$).[1] The resulting R–Pd^{II}–R^1 intermediate undergoes reductive elimination to form the product. An exogenous base is required to activate the boronic acid derivative for transmetalation, which is proposed to occur through a four-centered transition state (intermediate **C**, Scheme 1 a).[4]

Our group has been developing an alterative route to generate the requisite R–Pd^{II}–X intermediate by using an alkene as a synthon for an alkylhalide. To this end, we have recently reported the coupling of an alcohol oxidation to the functionalization of an alkene.[5] Specifically, styrene derivatives and organostannanes undergo a Pd-catalyzed reductive cross-coupling reaction in isopropyl alcohol (IPA) under an aerobic atmosphere to yield hydroarylation product **3a** in 76% yield (Scheme 1 b). The proposed mechanism proceeds by initial oxidation of the alcoholic solvent to generate Pd^{II}-hydride **E**, which reacts with the alkene to yield Pd-alkyl **F** (Scheme 1 c). Subsequent transmetalation forms **G** and reductive elimination yields the reductive coupling product and Pd^0 (**H**), which is oxidized by O_2 to regenerate the active catalyst (**D**).[6] As discussed above, boronic acids offer significant practical advantages in cross-coupling reactions with respect to organostannane compounds.[1] However, the development of a reductive coupling of alkenes with boronic acid derivatives was thought to be a significant challenge compared to the use of organostannanes because the strong exogenous base needed to facilitate transmetalation[4] will simultaneously affect the rate of the alcohol oxidation[7]



Scheme 1. a) Base facilitated transmetalation with boronic esters. b) Reductive coupling with organostannanes. c) Mechanistic hypothesis.

(Scheme 1 c). The addition of a base can also promote a base-mediated reductive elimination of the proposed Pd^{II}-hydride intermediate (**E**) to form Pd^0.[8] Herein, we report the development of a catalyst system for the reductive coupling of arylboronic esters and styrenes, and studies that highlight the mechanistic complexity of the reaction.

By using the reaction conditions developed for the Pd-catalyzed reductive coupling with organostannanes[5] and the commercially available boronic acid ($PhB(OH)_2$) the desired hydroarylation product (**3a**) was observed in 11% yield (GC) as a greater than 25:1 ratio of regioisomers (Table 1, entry 1).[9] However, we observed catalyst decomposition and competitive initial transmetalation, which generates the oxidative Heck product (**4**).[10] The poor stability of [Pd{(−)-sparteine}Cl_2] under these conditions prompted us to identify a more robust catalyst system. Previously, our group demonstrated that Pd complexes with *N*-heterocyclic carbene (NHC) ligands are excellent catalysts for alcohol oxidation in which high turnover numbers are achieved at low concentrations of O_2.[11] Also, Pd(NHC) complexes have been widely employed in a variety of cross-coupling reactions.[12] Thus, [{Pd(**I*i*Pr**)Cl_2}$_2$] was evaluated by using (−)-sparteine (**sp**) as an exogenous base and an improved ratio of hydroarylation to Heck reaction was observed with only a 63% conversion of the substrate (Table 1, entry 2). Stronger bases are often used in Suzuki reactions,[4] prompting us to evaluate the addition of *t*BuOK, which led to additional improvement in the ratio of

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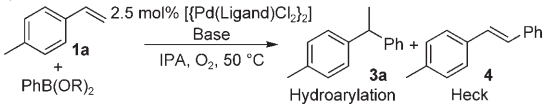
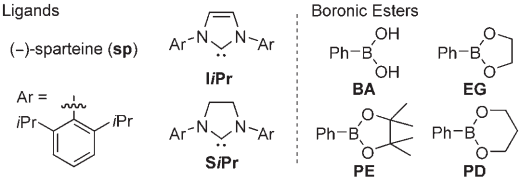
Table 1: Optimization for the reductive coupling product with boronic esters/acids.



Entry	Ligand	$PhB(OR)_2$ (equiv)	Base (mol%)	Conv. [%][a] (*t* [h])	**3a** [%][b] (**3a**:**4**)[c]
1[d]	**sp**	**BA** (1.3)	**sp** (40)	35 (24)	11 (1.4:1)
2	**I*i*Pr**	**BA** (1.3)	**sp** (20)	63 (24)	13 (3.2:1)
3	**I*i*Pr**	**BA** (1.3)	**sp** (20), *t*BuOK (5)	18 (24)	8 (6.4:1)
4	**I*i*Pr**	**PE** (1.3)	**sp** (5), *t*BuOK (5)	99 (24)	30 (2.7:1)
5	**I*i*Pr**	**PE** (2.5)	**sp** (7.5), *t*BuOK (7.5)	>99 (24)	64 (17:1)
6	**I*i*Pr**	**EG** (2.5)	**sp** (7.5), *t*BuOK (7.5)	>99 (4)	49 (27:1)
7	**S*i*Pr**	**EG** (2.5)	**sp** (7.5), *t*BuOK (7.5)	>99 (8)	68 (>30:1)
8	**S*i*Pr**	**PD** (2.5)	**sp** (7.5), *t*BuOK (7.5)	46 (24)	32 (>30:1)
9[e]	**S*i*Pr**	**EG** (3)	**sp** (6), *t*BuOK(6)	>99 (24)	91 (>30:1)
10[e]	**I*i*Pr**	**EG** (3)	**sp** (6), *t*BuOK(6)	>99 (24)	89 (>30:1)
11[f]	**sp**	**EG** (3)	**sp** (6), *t*BuOK(6)	>99 (24)	89 (>30:1)
12[e]	**S*i*Pr**	**EG** (3)	*t*BuOK (6)	2 (24)	1 (4.3:1)
13[e]	**S*i*Pr**	**EG** (3)	**sp** (6)	>99 (24)	78 (23:1)

[a] Percent conversion determined with GC methods by using an internal standard. [b] Yield determined by GC methods. [c] Ratio of yields determined by GC methods. [d] 2.5 mol% [Pd(**sp**)Cl_2]. [e] 0.75 mol% [{Pd(Ligand)Cl_2}$_2$] and 55 °C. [f] 1.5 mol% [Pd(**sp**)Cl_2] and 55 °C.



3a to **4**. The low conversion of these reactions may arise from $PhB(OH)_2$ inhibiting the catalysis; exogenous acid can decrease the rate of alcohol oxidation.[7] Therefore, the pinacol-derived phenylboronic ester (**PE**) was submitted to the reaction conditions with both **sp** and *t*BuOK, which led to a 30% yield (GC) of **3a** (Table 1, entry 4). The reaction was monitored by GC methods and **PE** was fully consumed before the reaction of the olefin was complete, suggesting that remaining **1a** undergoes an undesired reaction that does not involve the boronic ester. On the basis of this hypothesis the amount of **PE** was increased to 2.5 equivalents to produce **3a** in 64% yield (GC) with a 17:1 ratio of **3a** to **4** (Table 1, entry 5).

To further the optimize the reaction, ethylene glycol-derived boronic ester **EG**, which was expected to undergo faster transmetalation because of its smaller size, was submitted to the reaction conditions and a 49% yield (GC) of **3a** was measured after 4 hours (Table 1, entry 6). Evaluating other NHC ligands revealed that the combination of **S*i*Pr** and **EG** produces **3a** in 68% yield within 8 hours (Table 1, entry 7). Interestingly, when propanediol-derived boronic ester **PD** was used under the same reaction conditions a 32% yield of **3a** was observed, demonstrating the sensitivity of the transformation to the nature of the boronic ester (Table 1, entry 8). Additional optimization of the reaction conditions, including an increase to three equivalents of **EG**, produces **3a** in 91% yield (GC) with [{Pd(**S*i*Pr**)Cl_2}$_2$] as the catalyst; these conditions were found to be the optimal conditions for the transformation (Table 1, entry 9). [{Pd(**I*i*Pr**)Cl_2}$_2$] is also a proficient catalyst under these conditions yielding **3a** in 89% yield (GC) (Table 1, entry 10). Interestingly, under these conditions [Pd{**sp**}Cl_2] is also an effective catalyst (Table 1, entry 11). Finally, the reaction was performed under the optimal conditions without **sp**, leading to rapid Pd^0 metal precipitation with only 2% conversion of **1a** (Table 1, entry 12). In contrast, performing the reaction without *t*BuOK leads to a 78% yield (GC) of **3a**, suggesting that the combination of both **sp** and *t*BuOK is required to achieve excellent catalysis (Table 1, entry 13). However, the use of more *t*BuOK led to diminished yields of **3a**.[16]

Diaryl methine units are prevalent in biologically active small molecules and this method should allow the rapid highly regioselective synthesis of this functionality.[13] To explore the scope of the reductive coupling of boronic esters and styrenes we utilized the optimized conditions to synthesize a variety of diaryl methine-containing products (Table 2). All of the reductive coupling reactions are highly regioselective (>25:1), and the reactions of simple coupling partners give high yields (78–91%) of isolated diaryl methine-containing products (Table 2, entries 1–3). The results demonstrate that substrates containing acid-sensitive functional groups are stable to the reductive coupling reaction conditions;[14] for example, acetal protecting groups, which are readily removed upon work up, are compatible with the reaction conditions (Table 2, entries 5–7). Arylboronic esters containing electron-donating groups react more slowly, thereby requiring a higher catalyst loading (Table 2, entries 8 and 9), and *ortho* substitution on the arylboronic acid is tolerated (Table 1, entry 10). The ester functionality is also compatible, however an increase in [**sp**] is required to achieve a 63% yield of **3k** (Table 2, entry 11). On the basis of our previous mechanistic hypothesis that the formation of a π-benzyl intermediate is responsible for the outstanding regioselectivity,[5,15] a diene substrate, which can form a similar π-allyl species, was evaluated and yielded the reductive coupling product **3l** in 41% yield as a greater than 25:1 mixture of regioisomers (Table 2, entry 12). Under these conditions both vinylboronic esters and simple alkenes, which rapidly isomerize, do not undergo an effective reductive coupling reaction. Even though a chiral additive (**sp**) is used, less than 5% *ee* is observed for the product.[16]

There were three mechanistic questions that we wanted to address: 1) What is the efficiency of alcohol oxidation compared to product formation? 2) Why are 3 equivalents of the arylboronic ester required for good product yields? and 3) Why is exogenous **sp** required for catalysis? To investigate the first question, a higher molecular weight alcohol (*sec*-BuOH) was used as the solvent to enable GC analysis to effectively measure the amount of ketone being formed by alcohol oxidation. A time course analysis of the reaction was performed and the yields (GC) of the hydroarylation product **3a** and butan-2-one (**5**), as well as the percent of styrene **1a** remaining, were plotted as a function of time (Figure 1a).[16]

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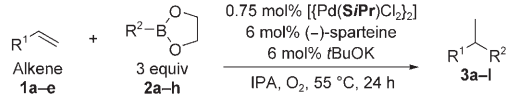
Table 2: Substrate scope of the reductive coupling reaction with boronic esters.



Entry	R^2	Product	Yield [%][a]
1	**2a**	**3a**	81
2	**2a**	**3b**	91
3	**2b**	**3c**	78
4	**2a**	**3d**	90
5[b]	**2c**	**3e**	77
6[b]	**2c**	**3f**	68
7[b]	**2d**	**3g**	71
8[c]	**2e**	**3h**	58
9[c]	**2f**	**3i**	65
10[c]	**2g**	**3j**	68
11[d]	**2h**	**3k**	63
12	**2a**	**3l**	41

[a] Average yield of isolated product for two experiments performed on 0.5-mmol scale. [b] Treated with *p*-toluenesulfonic acid in acetone/H_2O upon work up. [c] 1.5 mol% [{Pd(**SiPr**)Cl_2}$_2$] and 65 °C. [d] 15 mol% **sp**.

Initially, the yield of **3a** and **5** are equivalent until approximately 60% conversion; this is consistent with the oxidation of one alcohol directly yielding product, and suggests that the Pd^{II}-hydride species formed by alcohol oxidation reacts with the alkene faster than it reductively eliminates.[8] In contrast, as the reaction progresses to higher substrate conversion, the yield of **5** increases at a rate that differs from that of product formation. This difference implies that as the concentration of the alkene decreases, the Pd^{II}-hydride species can undergo other competitive reactions, including reductive elimination.

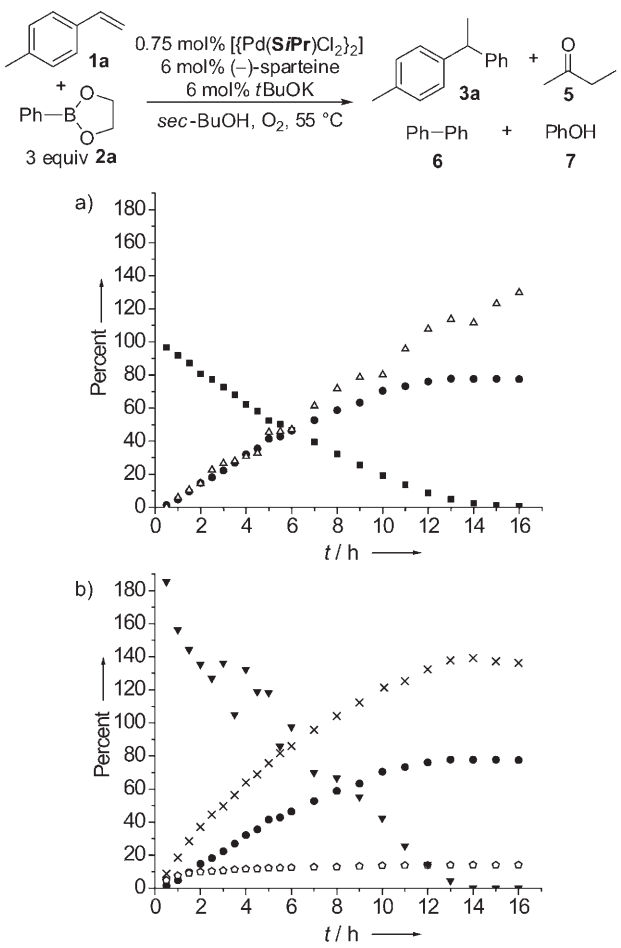


Figure 1. a) The amount of butan-2-one and hydroarylation product generated compared to styrene consumed over time; measured by GC methods based upon 1 equiv of **1a**: ■ = 4-methylstyrene (**1a**), ● = hydroarylation (**3a**), △ = butan-2-one (**5**). b) The quantity of boronic ester consumed compared to phenol, hydroarylation product, and biphenyl (**6**) produced over time: ▼ = boronic ester (**2a**), × = phenol (**7**), ● = hydroarylation (**3a**), ⬠ = biphenyl.

The yield (GC) of **3a** was 78% in *sec*-BuOH compared to 91% in IPA, indicating a modest solvent dependence.

To investigate why 3 equivalents of **2a** are required, the fate of the boronic ester was observed as the reaction progressed (Figure 1b). More than one equivalent of **2a** was consumed within 30 minutes and then a relatively linear decrease in concentration was observed (the scatter can be attributed to hydrolysis of **2a** on silica gel before GC analysis). In addition to hydroarylation product **3a**, two major byproducts, biphenyl (**6**) and phenol (**7**), were observed. A 10% yield (GC) of biphenyl, the product of oxidative boronic acid homocoupling,[17] is formed within 2 hours, but a 14% yield of biphenyl (ca. 0.28 equiv of **2a** consumed) is observed overall. Phenol is the major byproduct that is formed consistently throughout the reaction (ca. 1.3 equiv of **2a** consumed); it is likely to be formed from the reaction of the boronic ester with H_2O_2 produced from the reduction of O_2 during catalyst regeneration.[10b,18] Together these data account for the undesired pathways that consume the excess arylboronic ester required.

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The final mechanistic question addressed the role(s) of **sp** since performing the reaction without exogenous **sp** leads to poor catalysis. Several functions of **sp** can be envisioned, including performing as a ligand to stabilize Pd^0 during catalyst regeneration, acting as a ligand on Pd^{II} during the reductive coupling process, or breaking up the dimeric $[\{Pd(\mathbf{Si}\mathbf{Pr})Cl_2\}_2]$ complex. The first two roles are difficult to probe directly, however, an experiment was performed to investigate the feasibility of **sp** breaking up the dimer complex. The experiment involved dissolving $[\{Pd(\mathbf{Si}\mathbf{Pr})Cl_2\}_2]$ and 2 equivalents of **sp** in 1,2-dichloroethane (DCE) and heating the resulting mixture to reflux for 2 hours (Figure 2).

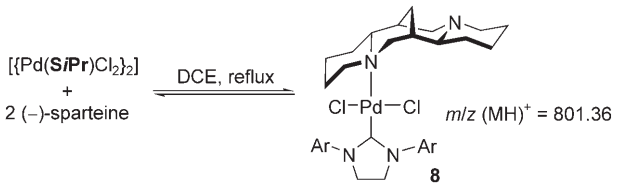

Figure 2. Reaction of $[\{Pd(\mathbf{Si}\mathbf{Pr})Cl_2\}_2]$ and **sp** yields complex **8** $[(MH)^+ = 801.36]$ characterized by ESI-MS methods.[16]

An aliquot of the mixture was analyzed by ESI-MS methods. Excitingly, the major Pd complex observed in solution corresponds to $[Pd(\mathbf{Si}\mathbf{Pr})(\mathbf{sp})Cl_2]$ $[m/z\ (MH)^+ = 801.3]$. On the basis of the *trans* geometry of related [Pd(NHC)(pyridine)Cl_2] complexes,[19] we propose that complex **8** is formed and that the NHC ligand is *trans* to the monodendate **sp** ligand. Unfortunately, attempts to isolate complex **8** only led to the $[\{Pd(\mathbf{Si}\mathbf{Pr})Cl_2\}_2]$ complex and free **sp**, suggesting that complex **8** is in equilibrium with the dimer. Notably, $[Pd\{\mathbf{sp}\}Cl_2]$ is not observed by ESI-MS methods. Other simple amine bases do not lead to an effective catalytic system for reductive coupling,[16] possibly because the large size of **sp** facilitates ligand dissociation or the free nitrogen center of **sp** acts as an intramolecular base.[7]

In conclusion, we have developed a catalyst system for a highly regioselective reductive coupling of arylboronic esters and styrenes under aerobic conditions to yield a variety of diaryl methine-containing products. The proposed mechanism couples an alcohol oxidation with C–C bond formation, in which an alkene can be thought of as an alkyl halide that is used in classic cross-coupling reactions. Careful analysis of the reaction progress reveals that excess arylboronic ester is required for effective catalysis because there is some oxidation of the boronic ester, by H_2O_2 from O_2 reduction, to generate phenol as the major by-product. Also, the requirement of two bases, **sp** and *t*BuOK, was explored and revealed that **sp** may promote the formation of a monomeric catalyst. Future efforts will be focused upon expanding the scope of this new transformation, exploring new Pd-catalyzed reductive coupling processes integrated with alcohol oxidation, and extending the method to include asymmetric catalytic variants.

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