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Cross-Coupling

Alkene Carboboration Enabled by Synergistic Catalysis

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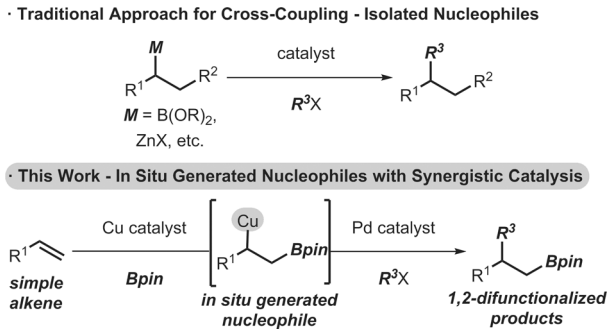
Abstract: A synergistic Pd/Cu system for the coupling of alkenes, $(Bpin)_2$ (pin = pinacolate), and aryl/vinyl bromides is disclosed. This method allows for the catalytic generation of secondary Csp^3–Cu nucleophiles in situ and subsequent Pd-catalyzed cross-coupling.

Palladium-catalyzed cross-coupling reactions have emerged as an indispensable method for chemical synthesis.[1] The majority of these methods rely on the pregeneration, and often isolation, of the nucleophile component (Scheme 1). Synthesis of the requisite nucleophile can often require tedious reaction sequences. Thus, catalytic generation of nucleophiles from simple components and direct cross-coupling would represent an attractive strategy for chemical synthesis.[2,3] Herein, we describe a synergistic Pd/Cu catalytic system that allows in situ generation of Cu-based nucleophiles from simple alkenes and diboron reagents followed by Pd-catalyzed cross-coupling (Scheme 1).[4,5] As will be outlined below, this strategy offers several advantages over traditional cross-coupling methods.

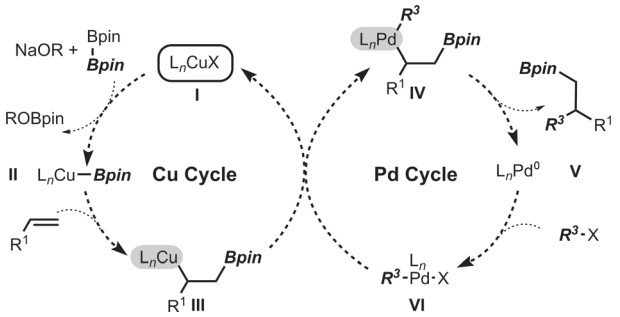
Our approach towards generating nucleophiles in situ was inspired by the pioneering work of Sadighi and co-workers, who demonstrated that Csp^3–Cu complexes could be generated by migratory insertion of NHC–Cu–Bpin (pin = pinacolate) complexes across alkenes.[6,7] Subsequent studies by numerous groups, including ours,[8] have developed catalytic variants that intercept the in situ generated Csp^3- or Csp^2–Cu complexes with various electrophiles (most commonly a proton) to turnover the catalyst.[9–14] Cross-coupling of in situ generated Csp^3- or Csp^2-Cu-complexes with carbon-based electrophiles to formally constitute a carboboration process[15] is significantly more difficult.[8,13] These reactions are largely limited to cases involving in situ generated Csp^2–Cu complexes or allyl–Cu complexes.[8,13] The only examples describing capture of Csp^3–Cu complexes utilize alkyl halides as the electrophilic component.[13a–c,f,h,k]



Scheme 1. Approaches towards cross-coupling.

We became interested in the cross-coupling of in situ generated Csp^3- or Csp^2–Cu complexes with aryl halides, because these processes would give rise to important and versatile motifs for chemical synthesis (see below, for examples). Based on these efforts, we recently reported a method for Cu-catalyzed carboboration of alkynes and allenes.[8] This method entails addition of a Cu–Bpin complex across an alkyne or allene and direct capture of the resulting Csp^2–Cu complex or allyl-Cu-complex, respectively, with aryl iodides. However, efforts to extend this methodology to the coupling of simple alkenes have been met with significant challenges. This is primarily due to the slow reaction between the generated Csp^3–Cu complex and the aryl halide. To circumvent this challenge, we devised a form of synergistic catalysis that merges the Cu-catalyzed migratory insertion of Cu–Bpin complexes across alkenes with Pd-catalyzed cross-coupling reactions of aryl halides (Scheme 1).[4,5,16]

Generally, we envisioned the catalytic cycle illustrated in Scheme 2 would proceed as follows: The Csp^3–Cu complex **III** would be generated by reaction of a Cu–Bpin complex (**II**) with an alkene. Subsequent reaction with an $[PdL_nArX]$ complex (**VI**) (generated by oxidative addition of $[Pd^0L_n]$ (**V**) to an ArX) will provide a new Csp^3–Pd complex **IV**, as well as regenerate the starting Cu complex **I**. Reductive elimination of Pd



Scheme 2. Mechanistic idea to enable carboboration with synergistic catalysis.

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complex **IV** would provide the product and regenerate Pd^0L_n (**V**).

The approach outlined in Scheme 1 is particularly attractive, because: 1) simple alkenes are used as the chemical input; 2) both positions of the alkene are functionalized, thus allowing two new bonds to be generated in a single operation; 3) due to the presence of the Bpin substituent, further functionalization is possible; and 4) this process would allow the cross-coupling of secondary Csp^3 nucleophiles, a recognized challenge in the cross-coupling field.[1c,17,18]

We initiated our studies by examining the carboboration of styrenes, aryl bromides, and $(Bpin)_2$. Our choice to begin our studies herein was largely motivated by two factors: 1) the migratory insertion of Cu–Bpin complexes across styrenes is well established;[6,12] and 2) this method would provide efficient and, perhaps more importantly, modular access to the 1,1-diarylalkane motif.[19] Numerous biologically relevant molecules contain this structural pattern; two pertinent examples are illustrated in Figure 1 (**1**–**2**).[20]

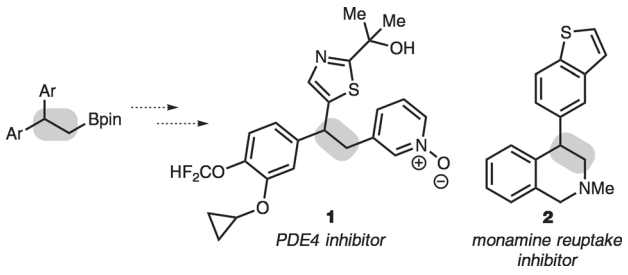
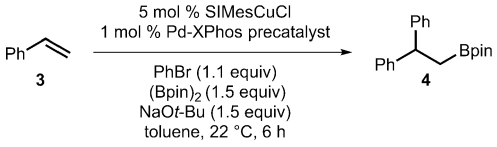


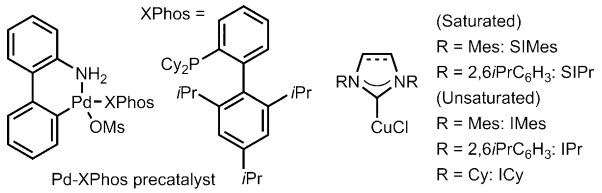
Figure 1. Representative 1,1-diarylalkanes.

After evaluation of numerous reaction parameters, we identified that 1,1-diarylalkane **4** could be generated in >98% yield (GC) by treatment of styrene (**3**), PhBr, and $(Bpin)_2$ in the presence of 5 mol% SIMesCuCl and 1 mol% Pd-2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) precatalyst (Table 1, entry 1).[21] Several points regarding our optimized reaction conditions are noteworthy: 1) the reaction operates well under mild conditions (22 °C) and short reaction time (6 h); and 2) use of phosphine-based Cu complexes provided **4** in low yield (Table 1, entries 2 and 3). Previous reports have detailed that phosphine Cu–Bpin complexes undergo slower migratory insertion than NHC–Cu–Bpin complexes;[10a] and 3) Sterically hindered NHC–Cu complexes IPrCuCl and SIPrCuCl are less efficient than SIMesCuCl (Table 1, entries 5 and 6) likely due to slower rates of migratory insertion and transmetalation. IMesCuCl performs with a similar level of efficiency to that of SIMesCuCl. 4) Other Pd complexes gave **4**, albeit in reduced yield (Table 1, entries 8 and 9). The use of Pd–PCy_3 pre-catalyst led to the formation of a regioisomeric product.[22] Use of the Pd–XPhos pre-catalyst (as opposed to in situ generated complexes) is not necessary and was only employed for simplicity. 5) Reactions with PhI work in moderate yield (62%);[23] however, use of PhCl did not lead to formation of the desired product (Table 1, entries 10–11). 6) Both the Cu and Pd complexes are necessary for this process (Table 1, entries 12 and 13).

Table 1. Alkene carboboration: effect of changing reaction parameters.[a]



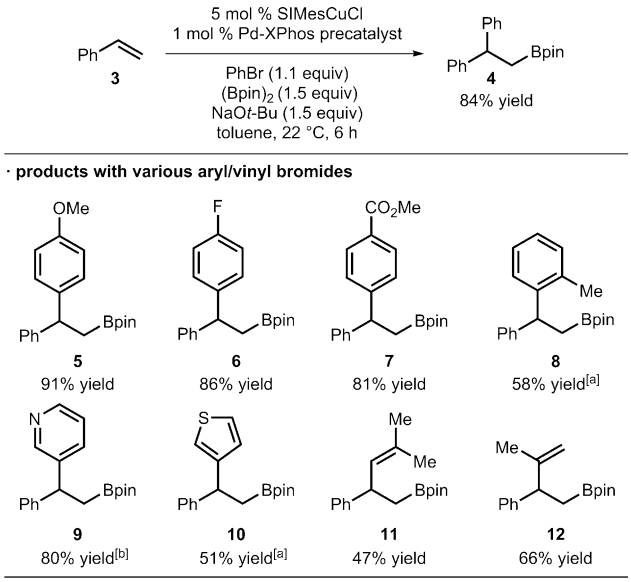
Entry	Change from optimized conditions	Yield [%][b]
1	none	>98
2	Cy_3P CuCl instead of SIMesCuCl	11
3	tBu_3P CuCl instead of SIMesCuCl	39
4	IMesCuCl instead of SIMesCuCl	>98
5	SIPrCuCl instead of SIMesCuCl	10
6	IPrCuCl instead of SIMesCuCl	73
7	ICyCuCl instead of SIMesCuCl	<5
8	Pd–PCy_3 precatalyst instead of Pd-XPhos precatalyst	62[c]
9	Pd–$PtBu_3$ precatalyst instead of Pd-XPhos precatalyst	91
10	PhCl instead of PhBr	<2
11	PhI instead of PhBr	68
12	no Pd-XPhos precatalyst	<2
13	no SIMesCuCl	<2



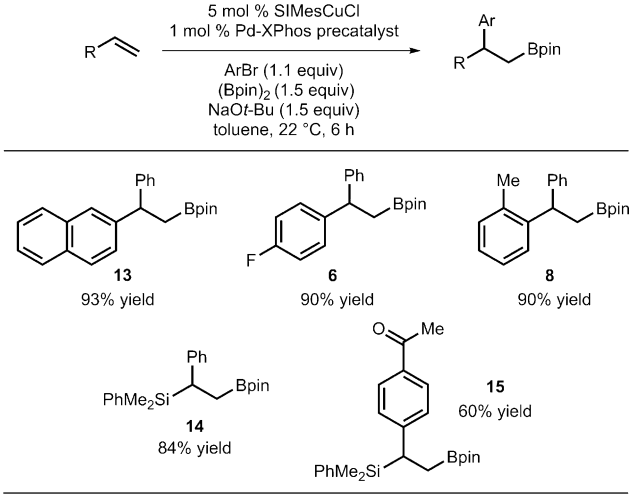
[a] See the Supporting Information for experimental details. [b] Yield determined by GC analysis with a calibrated internal standard (dodecane). [c] Regioisomeric product was formed in 23% yield, see the Supporting Information for details.

7) Under the optimized set of conditions, <2% of products derived from β-hydride elimination of either the putative Csp^3–Cu complex **III** or the Csp^3–Pd complex **IV** was observed. 8) The primary by-product from these reactions was Ph–Bpin resulting from cross-coupling of PhBr and $(Bpin)_2$. Under the optimized set of conditions, the formation of this compound was limited to ≤5%.

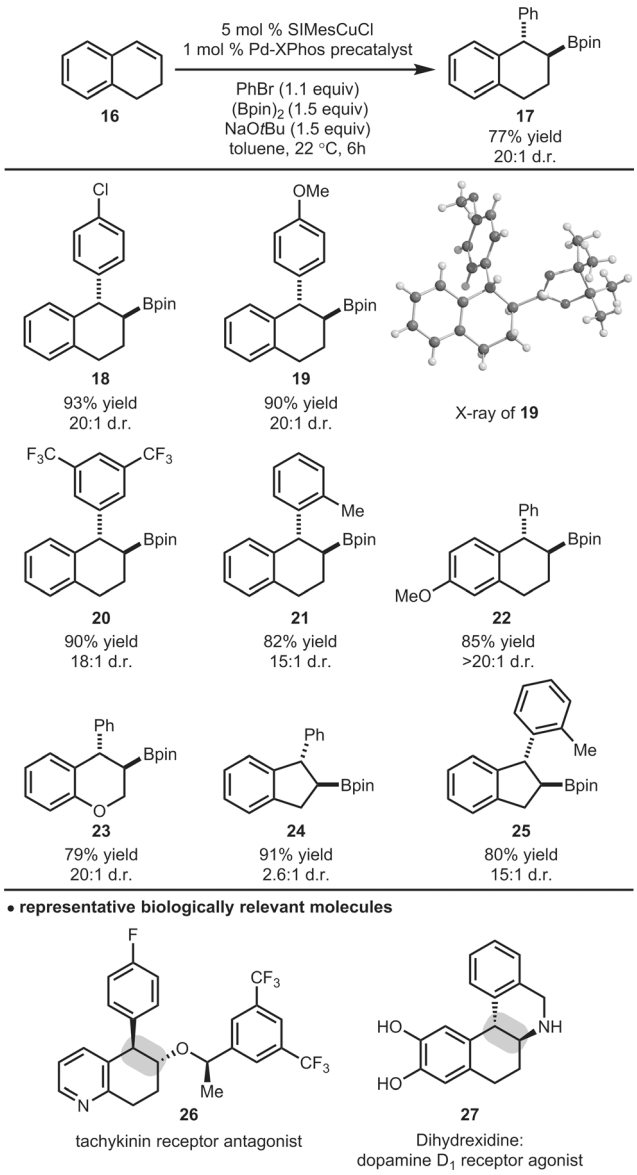
With an optimized set of conditions in hand, we explored the scope and limitations of this process. Several points regarding the range of electrophiles are noteworthy (Scheme 3): 1) Electron-deficient (see products **6**–**7**), electron-rich (see products **5**, **8**), and sterically hindered (product **8**) aryl bromides undergo reaction in good yield. 2) Reaction with vinyl bromides led to formation of **11** and **12** in 47 and 66% yields, respectively. These examples are particularly noteworthy, because there is potential for migratory insertion of SIMesCu–Bpin across the vinyl bromide. Reactions with less hindered vinyl bromides (e.g., 1-bromo-1-propene) did not lead to product formation, likely because of competitive migratory insertion pathways. 3) Reactions with heterocyclic aryl bromides also worked well (see products **9**–**10**). These examples are especially relevant to the preparation of biologically active compounds.[24] 4) Due to the mild reaction conditions, transesterification of methyl esters with NaO*t*Bu did not occur (**7**). 5) Approximately 10% of a product derived from β-hydride elimination was observed only in the cases of 2-bromotoluene and 3-bromothiophene.[22] 6) Mesityl bromide did not work in this process, likely due to severe steric interactions (not shown).



Scheme 3. Reactions with aryl/vinyl bromides and styrene. Yields reported as the average of two experiments. [a] Approximately 10% of products derived from β-hydride elimination were observed. [b] Yield was determined by ^{1}H NMR analysis with an internal standard.



Scheme 4. Reactions with aryl bromides and alkenes. Yields reported as the average of two experiments.

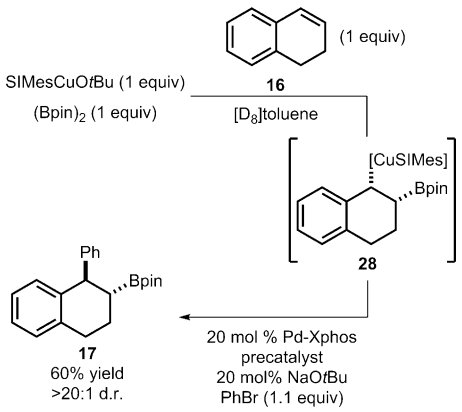


Scheme 5. Reactions with disubstituted alkenes. Yields reported as the average of two experiments.

The scope of this process has also been extended to other classes of activated alkenes. As illustrated in Scheme 4, various substituted styrene derivatives, including the sterically hindered 2-methyl styrene, operated well in this reaction (see products **6**, **8**, and **13**). Dimethylphenyl vinylsilane is also a competent substrate (Scheme 4).[13f] These products (**14** and **15**) are notable, because both the silyl and boron units can be differentially functionalized. Preparation of **15** also represents that ketones are tolerated under the reaction conditions.[25]

Reactions with cyclic 1,2-substituted styrene derivatives were also investigated (Scheme 4). These substrates offer the additional challenge, as well as opportunity, of diastereocontrol.[18,26] Furthermore, the products of these reactions are related to the structure of biologically significant molecules after oxidation or amination[27] of the resulting Bpin unit (Scheme 5, **26** and **27**).[28]

Under the optimized conditions, 1,2-dihydronaphthalene (**16**) was converted to **17** in 20:1 diastereomeric ratio (d.r.) and 77% yield (Scheme 5). Reactions of 1,2-dihydronaphthalene (**16**) with other sterically and electronically modified aryl bromides also provided the products (**18**–**21**) in uniformly good yields and diastereoselectivities. 2*H*-Chromene, as well as 6-methoxy-1,2-dihydronaphthalene, led to formation of **23** and **22**, respectively, in good yields and diastereoselectivities. Remarkably, reaction of indene with PhBr provided **24** in low d.r. (2.6:1 d.r.), but the same reaction with 2-bromotoluene generated **25** in high d.r. (15:1 d.r.).[29] In all cases, the stereochemical relationship between the Ar and Bpin substituents was determined to be *trans* for the major diastereomer.[22]



Scheme 6. Mechanistic studies (see the Supporting Information for experimental details). Yield and d.r. of **17** determined by GC analysis with a calibrated internal standard (dodecane).

To provide evidence for the plausibility of the catalytic cycle illustrated in Scheme 2, we have carried out the carboboration reaction in a stepwise manner. (Scheme 6). Thus, treatment of 1,2-dihydronaphthalene (1.0 equiv) with SIMesCuO*t*-Bu (1.0 equiv), and $(Bpin)_2$ (1.0 equiv) led to the formation of a new complex in <5 min at 22 °C. Due to the low stability of this new complex, full characterization was not possible.[22,30] Based on literature precedent, the product is likely from a *syn*-migratory insertion of SIMesCuBpin across 1,2-dihydronaphthalene as illustrated by structure **28**. After five minutes, treatment of putative Cu complex **28** with 20 mol% Pd-Xphos precatalyst (preactivated with 20 mol%NaO*t*Bu) and PhBr (1.1 equiv) led to the formation of **17** in 60% yield and >20:1 d.r. within 30 min at 22 °C. We expect that the transmetalation of the Csp^3–Cu complex to generate the Csp^3–Pd complex likely proceeds with inversion of stereochemistry to ultimately provide the *trans*-diastereomer after a stereoretentive reductive elimination.[31] This is largely due to the known configurational stability of related Csp^3–Cu complexes[6] and Csp^3–Pd complexes,[32] especially given the time frame of the experiment ($<$ 30 min). However, at the present time, a pathway that involves epimerization of the alkyl metal intermediates as an explanation for *trans*-diastereomer formation is still possible.[18a] Future studies will be aimed at unravelling the subtle details of this process.

In conclusion, we have developed a synergistic Pd/Cu catalytic system that allows the cross-coupling of in situ generated secondary Csp^3–Cu nucleophiles. The method functions well with a variety of substrates and provides efficient access to molecules that contain medicinally relevant scaffolds. We have also demonstrated that high levels of diastereocontrol can be achieved for many examples. We expect that due to the high modularity of this method, a variety of useful processes can be developed.

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Keywords: carboboration · copper · cross-coupling · palladium · synergistic catalysis

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