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A Dual Palladium and Copper Hydride Catalyzed Approach for Alkyl–Aryl Cross-Coupling of Aryl Halides and Olefins

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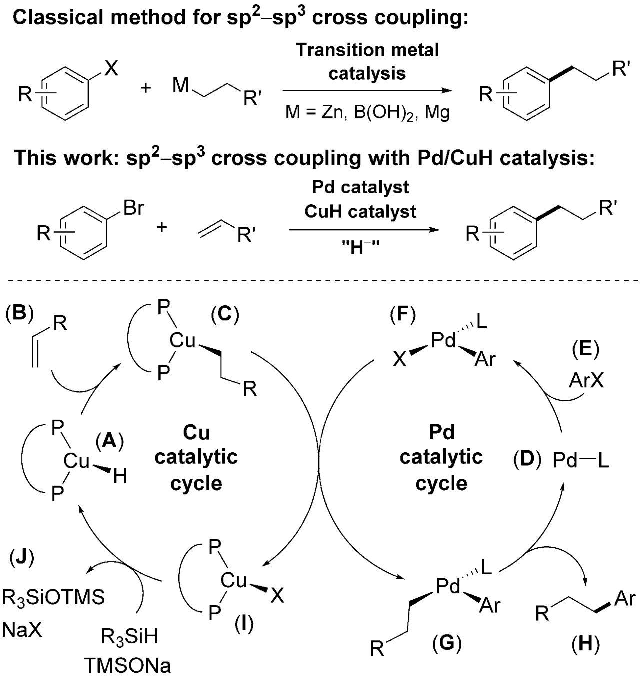
Abstract: *We report an efficient means of sp^2–sp^3 cross coupling for a variety of terminal monosubstituted olefins with aryl electrophiles using Pd and CuH catalysis. In addition to its applicability to a range of aryl bromide substrates, this process was also suitable for electron-deficient aryl chlorides, furnishing higher yields than the corresponding aryl bromides in these cases. The optimized protocol does not require the use of a glovebox and employs air-stable Cu and Pd complexes as precatalysts. A reaction on 10 mmol scale further highlighted the practical utility of this protocol. Employing a similar protocol, a series of cyclic alkenes were also examined. Cyclopentene was shown to undergo efficient coupling under these conditions. Lastly, deuterium-labeling studies indicate that deuterium scrambling does not take place in this sp^2-sp^3 cross coupling, implying that β-hydride elimination is not a significant process in this transformation.*

Transition metal-catalyzed sp^2–sp^3 cross coupling has become a vibrant area of research due to its potential to serve as a strategic C–C bond forming process. Furthermore, this approach provides opportunities for appending fragments to complex, functionalized starting materials, thus expediting the synthesis of their analogs. Classically, a stoichiometric alkyl metal reagent is used as a coupling partner to enable facile transmetalation with a transition metal catalyst.[1] Despite their synthetic utility, many of these methods suffer from promiscuous reactivity of the organometallic reagent and synthesis of the reagent is often nontrivial.

The palladium-catalyzed Suzuki cross coupling with alkylboron reagents is perhaps the most frequently utilized strategy for appending an alkyl fragment to an arene.[2] In general, this approach has proven to be a versatile and reliable method that tolerates a broad range of functional groups. In addition, alkyl boron reagents are often readily accessible from the corresponding olefin via hydroboration.[3] This method, however, suffers from several drawbacks with respect to the requisite boron reagents. In the case of trialkylboranes, the reagent is sensitive to air. Regarding more air-stable alkyl boronic acid/ester or trifluoroborate derivatives, multistep synthetic routes must often be employed for their preparation. Diminished synthetic efficiencies are also sometimes observed due to competitive β-hydride elimination of intermediate alkylpalladium(II) complexes. To address some of these deficiencies, several new strategies for alkyl-aryl cross coupling have been developed. Seminal reports by Fu demonstrated that alkyl halides can readily couple with aryl boronic acids with the use of a trialkylphosphine-supported palladium catalyst or a bipyridyl-supported nickel catalyst.[4] In addition, palladium and nickel-catalyzed cross-electrophile strategies have allowed the coupling of alkyl halides with aryl electrophiles in the presence of an exogenous reductant.[5–8]

We reasoned that a complementary approach for sp^2-sp^3 cross coupling reactions using α-olefins as starting materials would allow us to overcome some of the shortcomings associated with the use of organoboron reagents and the limited commercial availability of alkyl halide coupling partners. Encouraged by a recent report from our lab[9] and previous work utilizing Pd and Cu catalysis in a synergistic fashion,[10] we envisioned that aryl halides and α-olefins could be brought together to form sp^2-sp^3 cross coupled products using a similar dual catalytic approach (Scheme 1). In particular, we rationalized that we could employ olefins as latent nucleophiles and, due to their stability and commercial availability, would serve as an attractive starting material for



Scheme 1. Pd- and CuH-catalyzed reductive cross coupling of terminal olefins with aryl electrophiles.

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sp^2-sp^3 cross coupling. This formal reductive Heck reaction would thus provide access to useful compounds, albeit with perfect selectivity for the linear product.[11]

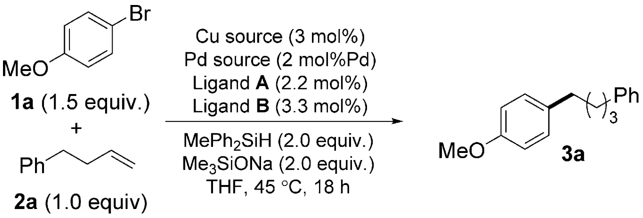
A detailed postulated mechanism of our strategy is shown in Scheme 1. Olefin insertion should readily occur in the presence of alkene **B** and CuH catalyst **A** to generate Cu^I-alkyl **C**. In line with previous work,[12] we believed that olefin insertion should occur in an *anti*-Markovnikov fashion with a simple α-olefin. Concomitant oxidative addition of Pd^0 **D** into aryl electrophile **E** would generate Pd^{II} aryl complex **F**. Transmetalation between Cu^I-alkyl **C** and Pd^{II}-aryl **F** should furnish (alkyl)(aryl)palladium(II) complex **G**, which upon reductive elimination, would form the desired product and close the catalytic cycle for palladium. Base mediated regeneration of phosphine ligated CuH species **A** then closes the catalytic cycle for copper. For this proposed synergistic process to be successful, the rates of these two catalytic cycles would need to be matched to enable efficient catalysis to take place. In addition, palladium-catalyzed reduction/silylation of the aryl electrophile could also affect the overall efficiency of this process.

The optimization of this cross coupling protocol is detailed in Table 1. A series of ligands typically employed for Cu-catalyzed reactions were examined (entries 1–5), and a significant yield was observed only with DTBM-SEGPHOS (entry 5, 53% yield). Dialkylbiarylphosphine ligands have previously shown excellent activity as supporting ligands for Pd-catalyzed cross coupling reactions.[13] Examination of several ligands of this family (entries 5–8) showed BrettPhos to be the most promising supporting ligand examined. CuCl was found to give the highest yield out of a variety of Cu^I and Cu^{II} salts tested (entries 5 and 9–11) (entry 11, 63% yield). A variety of Pd sources were also tested, with $[Pd(cinnamyl)Cl]_2$ providing the best reactivity (entry 11–14). Increasing the reaction temperature above 45 °C was not beneficial for product formation (entry 15, 56% yield). However, the use of Me_2PhSiH as the silane provided a significant increase in the yield of the desired product, largely due to a decreased propensity for unproductive aryl halide reduction (entry 16, 78% yield). Importantly, we found that this reaction could be set up outside of the glovebox using air-stable DTBM-SEGPHOS-ligated CuCl precatalyst **P1** when the loading of silane was increased slightly (entry 17, 75% isolated yield). This precatalyst retained full catalytic activity when stored for prolonged periods of time (> 1 month) in a desiccator outside of the glovebox.[14]

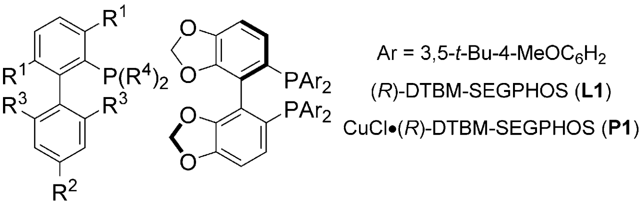
After optimization of our model reaction was completed, we examined the substrate scope of this protocol (Table 2).[15] A variety of functional groups were tolerated, including: ethers (such as **3b**), an amide (**3c**), a carbamate (**3c**), esters (such as **3e**), an alkyl chloride (**3d**), thioethers (such as **3g**), amines (**3g**, **3h**, and **3o**), and silyl ethers (such as **3l**). A free alcohol was tolerated (**3m**), but excess silane was required and the efficiency of the process was significantly diminished. The coupling of **2f** displaying both a terminal and internal alkene proved highly selective for the more reactive α-olefin.

A series of heterocycles were also tolerated, including quinolines (**3f**, **3m**, and **3o**), an indazole (**3h**), an electron-rich pyridine (**3j**), a benzothiophene (**3k**), and electron-rich pyrimidines (**3l** and **3n**). Electron-neutral and electron-rich aryl bromides generally perform well in this chemistry, while more electron-poor aryl and heteroaryl bromides proved to be problematic. For these substrates, the reduced aryl bromide was observed as a major side-product. We reasoned that electron-deficient aryl chlorides would be more recalcitrant to reduction in this chemistry, and could complement the aryl electrophile scope. In line with this rationale, 2-chloro-6-methylpyridine showed an enhanced efficiency in product formation over the corresponding bromide in the *anti*-Markovnikov hydroarylation of terminal olefins (Scheme 2A). This trend also applied to vinylarenes, with 2-chloroquinoline providing higher yield and enantioselectivity compared to 2-bromoquinoline in the hydroarylation of 2-vinylanisole (Scheme 2B).[16]

Table 1: Optimization of the Pd/Cu-catalyzed reductive cross coupling of terminal alkenes with aryl bromides.



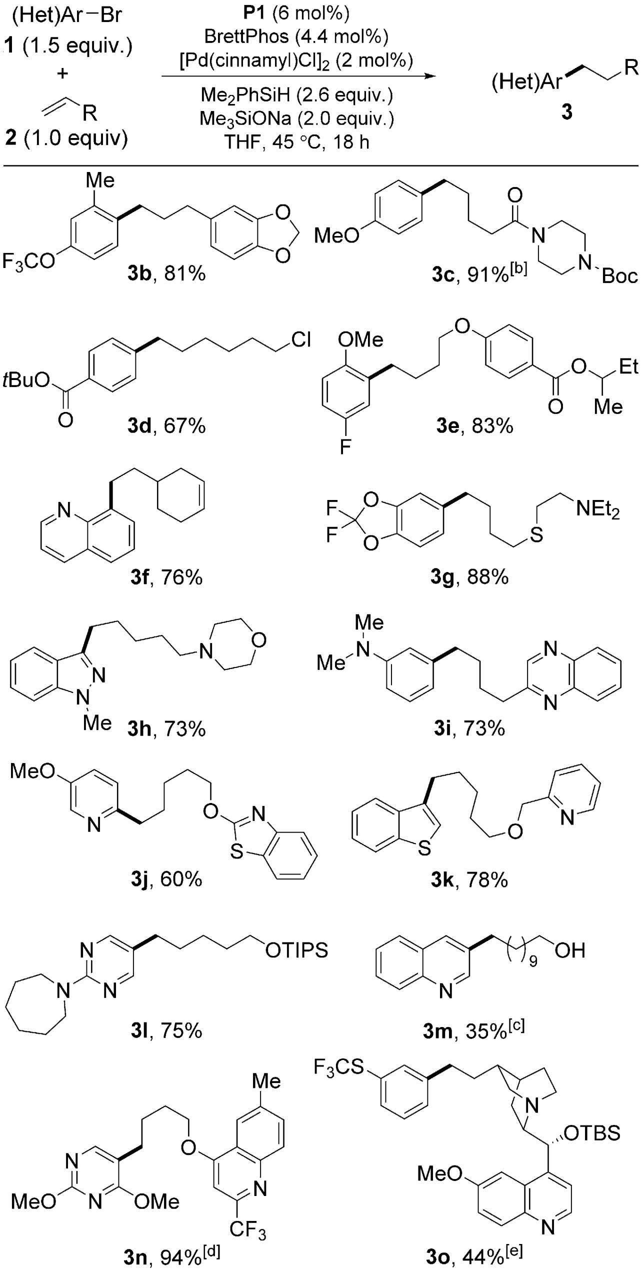
Entry	Pd source[a]	Ligand A	Cu source	Ligand B	Yield,%[b]
1	$[Pd(cin)Cl]_2$	BrettPhos	CuOAc	XantPhos	5
2	$[Pd(cin)Cl]_2$	BrettPhos	CuOAc	BINAP	6
3	$[Pd(cin)Cl]_2$	BrettPhos	CuOAc	PPh_3	4
4	$[Pd(cin)Cl]_2$	BrettPhos	IPrCuCl	–	0
5	$[Pd(cin)Cl]_2$	BrettPhos	CuOAc	**L1**	53
6	$[Pd(cin)Cl]_2$	*t*BuBrettPhos	CuOAc	**L1**	26
7	$[Pd(cin)Cl]_2$	XPhos	CuOAc	**L1**	40
8	$[Pd(cin)Cl]_2$	CPhos	CuOAc	**L1**	9
9	$[Pd(cin)Cl]_2$	BrettPhos	$Cu(OAc)_2$	**L1**	33
10	$[Pd(cin)Cl]_2$	BrettPhos	CuBr	**L1**	61
11	$[Pd(cin)Cl]_2$	BrettPhos	CuCl	**L1**	63
12	$Pd(OAc)_2$	BrettPhos	CuCl	**L1**	35
13	Pd_2dba_3	BrettPhos	CuCl	**L1**	15
14	$Pd(cod)Cl_2$	BrettPhos	CuCl	**L1**	23
15[c]	$[Pd(cin)Cl]_2$	BrettPhos	CuCl	**L1**	56
16[d]	$[Pd(cin)Cl]_2$	BrettPhos	CuCl	**L1**	78
17[e]	$[Pd(cin)Cl]_2$	BrettPhos	**P1**	–	79 (75)



BrettPhos: R^1 = OMe, R^2 = R^3 = *i*Pr, R^4 = Cy
***t*BuBrettPhos:** R^1 = OMe, R^2 = R^3 = *i*Pr, R^4 = *t*Bu
XPhos: R^1 = H, R^2 = R^3 = *i*Pr, R^4 = Cy
CPhos: R^1 = H, R^2 = H, R^3 = NMe_2, R^4 = Cy

[a] cin = π-cinnamyl. [b] Yields determined by GC analysis of the crude reaction mixture using tetradecane as an internal standard, isolated yield is in parenthesis and is an average of two runs performed with 1 mmol of olefin. [c] Reaction run at 55 °C. [d] Me_2PhSiH used as the silane.
[e] Reaction was run outside of the glovebox and with 2.6 equiv of Me_2PhSiH as the silane.

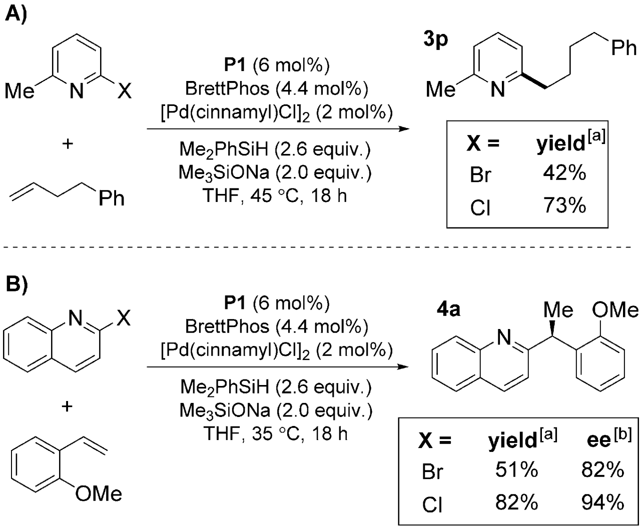
Table 2: Substrate scope for the Pd/Cu-catalyzed reductive cross coupling of monosubstituted olefins with aryl bromides.[a]



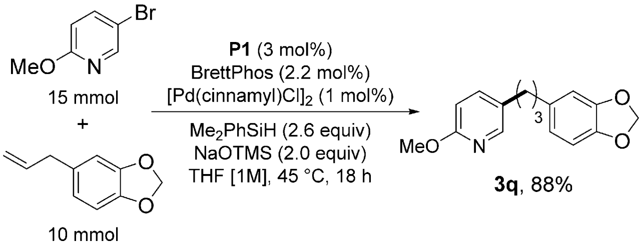
[a] All yields represent the average of isolated yields from two runs performed with 1 mmol of olefin. [b] Reaction was run with 1 mol% $[Pd(cinnamyl)Cl]_2$, 2.2 mol% BrettPhos, and 3 mol% **P1**. [c] Reaction run with 3.6 equiv of Me_2PhSiH. [d] Reaction was run at 0.25 M. [e] Reaction was run at 0.5 M.

To highlight the practical utility of this transformation, a reaction was performed on a 10 mmol scale again without the aid of a glovebox. Even with lowered catalyst loadings (3 mol% Cu, 2 mol% Pd), the reaction exhibited excellent efficiency, providing the desired product **3q** in a consistently high yield (Scheme 3, 2.4 grams, 88%).

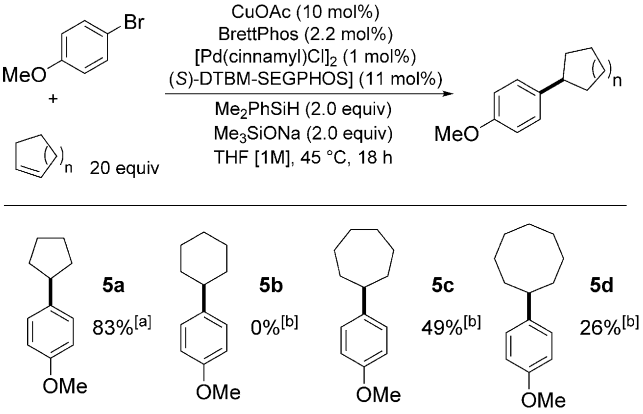
We were also interested in further exploring this chemistry with other classes of olefins. In particular, we investigated the use of cheap, readily available cyclic alkenes that could be used in excess for the synthesis of cross-coupled products containing cycloalkyl groups (Scheme 4). This strategy would



Scheme 2. Comparison of electron-deficient aryl chlorides and bromides in Pd/CuH-catalyzed reductive cross coupling reactions. A) Anti-Markovnikov reductive cross coupling with α-olefins. B) Enantioselective Markovnikov hydroarylation of vinylarenes. [a] All yields represent the average of isolated yields from two runs performed with 1 mmol of olefin. [b] Enantiomeric excess determined by chiral HPLC.



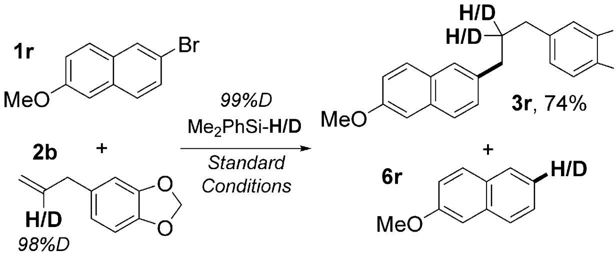
Scheme 3. Scale-up of the reductive cross coupling. Yields represent the average of isolated yields from two runs performed with 10 mmol of olefin.



Scheme 4. Investigation of cyclic alkenes as substrates in the Pd/CuH-catalyzed reductive cross-coupling. [a] Yield represents the average of isolated yields from two runs performed with 1 mmol of aryl bromide. [b] Yield determined by analysis of the crude reaction mixture via ^1H-NMR spectroscopy using 1,3-benzodioxole as an internal standard.

serve to both obviate the need for expensive cycloalkyl zinc reagents as required for the corresponding Negishi reactions while also simplifying the reaction setup.[17] In this context, cyclopentene was found to couple in excellent efficiency with *para*-bromoanisole to afford product **5a**. A high concentration of cyclopentene and copper catalyst was required for productive reactivity, presumably due to a more challenging hydrocupration step. Application of this protocol to alkenes of larger ring size led to reduced efficiency in the case of cycloheptene and cyclooctene, while cyclohexene was unreactive. We hypothesize that this trend is due to the decreased ring strain of the larger cyclic olefins, which reduces the propensity for the olefin to undergo hydrocupration with the CuH catalyst.[18,19]

As mentioned above, aryl halide reduction constitutes the major unproductive side-reaction of this transformation. To this end, deuterium-labeling studies were pursued in this dual-catalyzed CuH/Pd protocol. We believed this could clarify two aspects of this chemistry: 1) the mechanism of aryl electrophile reduction and 2) whether the transient Cu^I-alkyl or Pd^{II}-alkyl aryl complex presumed to form during the course of the reaction undergo β-hydride elimination at any point (Scheme 1, **C** and **G**). The results of our study, using the four combinations of labeled and unlabeled silane and alkene, are displayed in Scheme 5. First, use of deuterated silane resulted in formation of deuterated arene **6r**. We believe this implies that reduction of the aryl bromide occurs through a transmetalation event with the silane as the hydride source, rather than a β-hydride elimination/ aryl-hydrogen reductive elimination sequence with the alkyl group as the ultimate source of the hydride (Scheme 1, **G**). Further confirming this hypothesis, deuterium scrambling was not observed when using a deuterated alkene, which indicates that β-hydride elimination from an organometallic alkyl complex is likely not taking place in this reaction.



Silane 2b	H	D
H	**3r** - 0%D **6r** - 0%D	**3r** - 48%D **6r** - 96%D
D	**3r** - 50%D **6r** - 0%D	**3r** - 93%D **6r** - 96%D

Scheme 5. Deuterium-labeling studies for the Pd/CuH-catalyzed reductive cross coupling of terminal alkenes with aryl bromides. Deuterium incorporation was quantified by ^{1}H-NMR spectroscopy of the purified products.

In conclusion, we report the Cu/Pd-catalyzed reductive coupling of α-olefins and aryl electrophiles to form sp^2-sp^3 cross-coupled products. This protocol tolerates a broad range of functional groups and heterocycles, and does not require the preparation of any sensitive or specialized coupling partners. In addition, electron-deficient heteroaryl chlorides were shown to be effective in this reaction as well, complementing the efficiency observed for electron-rich and electron-neutral aryl bromides. The synthetic utility of this system was highlighted in a scale-up of the reaction to a 10 mmol scale using air-stable Cu and Pd precatalysts at reduced catalyst loadings. Studies using cyclic alkenes demonstrate that cyclopentene is also an effective coupling partner for this chemistry, likely due to the relief of ring-strain via hydrocupration. Finally, deuterium-labeling studies clarify the mechanism for aryl halide reduction and discount β-hydride elimination as a significant process in the protocol.

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Conflict of interest

MIT has or has filed patents on ligands/precatalysts that are described in the paper from which SLB and former/current coworkers receive royalty payments.

Keywords: alkenes · copper · cross-coupling · homogeneous catalysis · palladium

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Communications

Homogeneous catalysis

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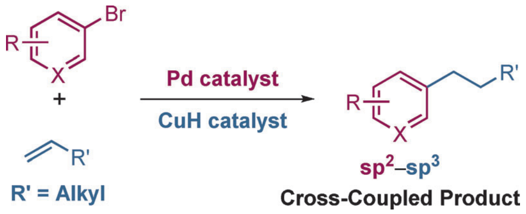
A Dual Palladium and Copper Hydride Catalyzed Approach for Alkyl–Aryl Cross-Coupling of Aryl Halides and Olefins



Cross-coupling: A protocol for sp^2–sp^3 cross-coupling of terminal alkenes and aryl halides is reported. A broad substrate scope based on air-stable precatalysts is detailed. This reaction is shown on a 10 mmol scale, along with preliminary studies with cyclic alkenes that highlight cyclopentene as an effective coupling partner.