

Copper-Catalyzed Cross-Coupling of Aryl-, Primary Alkyl-, and Secondary Alkylboranes with Heteroaryl Bromides

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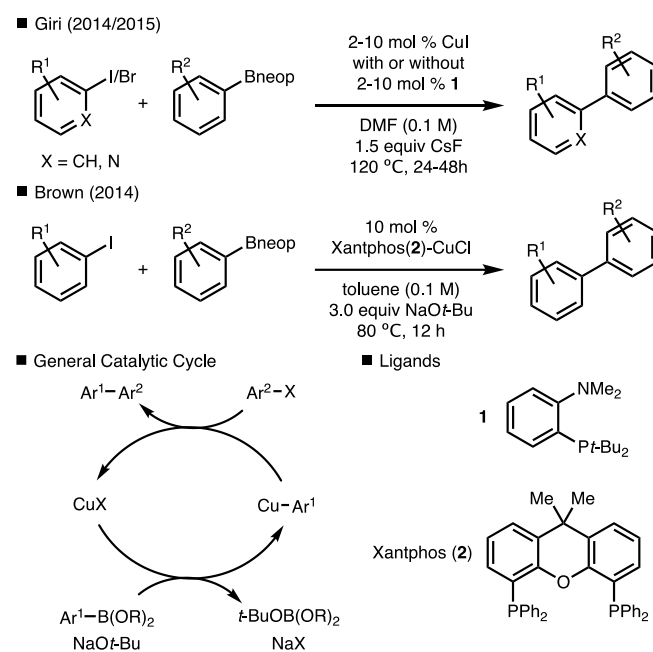
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A method for the Cu-catalyzed cross-coupling of both aryl and alkylboranes with aryl bromides is described. The method employs an inexpensive Cu-catalyst and functions for a variety of heterocyclic as well as electron deficient aryl bromides. In addition, aryl iodides of varying substitution patterns and electronic properties work well.

Copper-catalyzed cross-coupling reactions have enjoyed a rich history over the last several decades.¹ In recent years, a resurgence of effort in this field has been directed towards developing methods for the coupling of organoboronic esters and organohalides.^{1c} This reaction is clearly similar to the well-established and widely used Pd- or Ni-catalyzed Suzuki-Miyaura cross-coupling.² The development of Cu-catalyzed variants of these reactions is significant for two reasons. The first is the development of variants that cannot be carried out readily with Pd- and Ni-catalysis. The second is the use of cheaper and less toxic Cu, especially as compared to Pd, and to a lesser degree Ni.

Early work pertaining to the development of Cu-catalyzed cross-coupling of organoboronic acids and organohalides was reported by Li but does not work well with electron deficient or sterically hindered nucleophiles.³ More recent efforts by Liu led to a method for the coupling of organoboronic esters and alkyl halides.⁴ In 2014, our group reported a method for cross-coupling of arylboronic esters and aryl iodides promoted by XantphosCuCl.⁵ Contemporaneous with our early work, Giri initially reported the coupling of arylboronic esters with aryl iodides⁶ and later with electron deficient arylbromides.⁷ In both our work and Giri's work it is proposed that an aryl copper intermediate is formed by transmetalation with the arylboronic ester followed by reaction with an arylhalide (Scheme 1). Despite Giri's more recent developments,⁷ Cu-catalyzed cross-coupling of organoboranes with arylbromides remains limited and a general method does not exist.⁸ Herein, we disclose a method for Cu-catalyzed cross-coupling of aryl

and alkylboranes and electron deficient aryl bromides and heteroaryl bromides.



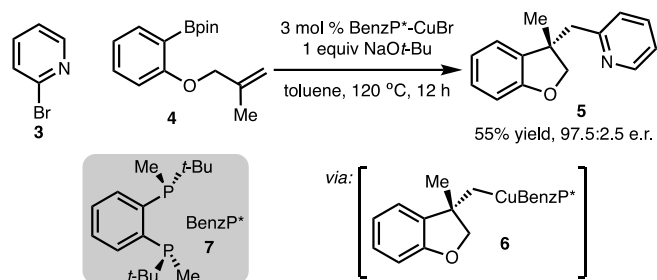
Scheme 1. Cu-Catalyzed Cross-Coupling of Boronic Esters and Arylhalides.

In 2015, our group reported an alkene interrupted cross-coupling reaction (Scheme 2).^{9,10} In particular, it was demonstrated that nitrogen-containing heteroaryl bromides (*e.g.*, **3**) were competent electrophiles in these reactions.^{9b} It is important to note that mechanism studies suggest that alkyl copper intermediate **6** is generated by migratory insertion prior to reaction with an arylhalide. Based on this observation, efforts were directed towards investigating the cross-coupling reaction of arylbromides under the conditions originally developed in our group (Scheme 1).⁵ In addition, the identification of a less expensive ligand than Xantphos, use of fewer equivalents of base, and running the

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reaction at increased concentration (*i.e.*, minimize solvent) were key to the optimization.



Scheme 2. Preliminary Results for Cross-Coupling with Arylbromide

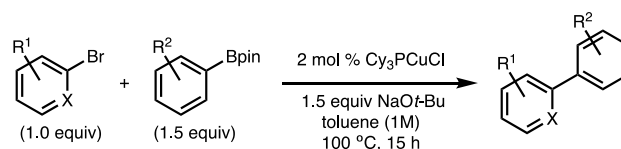
Table 1. Change From Standard Conditions.

entry	HetAr/Ar-Br	change from standard conditions	yield (%) ^[a]
1		no change	94
2		XantphosCuCl instead of Cy ₃ PCuCl	95
3		0.5 mol % Cy ₃ PCuCl	84 ^[b]
4		CuCl instead of Cy ₃ PCuCl	46
5		<i>p</i> -tolBneop (12) instead of <i>p</i> -tolBpin (7)	82
6		<i>p</i> -tolboroxine (13) instead of <i>p</i> -tolBpin (7)	91
7		<i>p</i> -tolBF ₃ K (14) instead of <i>p</i> -tolBpin(7)	<2
8		<i>p</i> -tolB(OH) ₂ (15) instead of <i>p</i> -tolBpin(7)	<2
9		120 °C instead of 100 °C	60
10		XantphosCuCl instead of Cy ₃ PCuCl	50
11		CuCl instead of Cy ₃ PCuCl	6

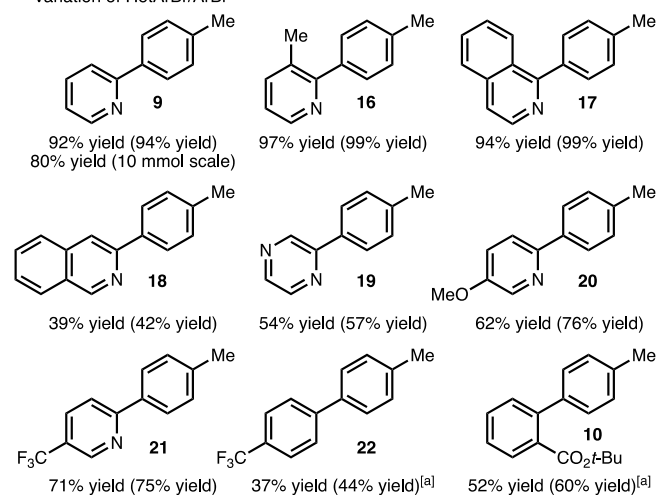
[a] Yield determined by analysis of the crude ¹H NMR spectrum with an internal standard. [b] Reaction run for 24 h. 53% yield after 12 h.

As illustrated in Table 1, we have identified a set of conditions for the cross-coupling of 2-bromopyridine (**3**) and *p*-tolboronic ester **8**. Several points regarding the optimized conditions merit further discussion: 1) Cy₃PCuCl was found to be a suitable and inexpensive catalyst for the cross-coupling. The previously utilized, but significantly more expensive XantphosCuCl also functioned well in the reaction (Table 1, entry 2). 2) The reaction can be performed at high concentrations (1M in toluene). Reactions carried out at higher concentrations than 1M were difficult to stir on 0.5-1 mmol scale. 3) While the reaction performed well with only 0.5 mol % Cy₃PCuCl, evaluation of substrates in Scheme 1 were carried out with 2 mol % Cy₃PCuCl (Table 1, entry 3). 4) Other boronic esters can be used (Table 1, entries 5-6). Importantly, boroxine **13** (0.5

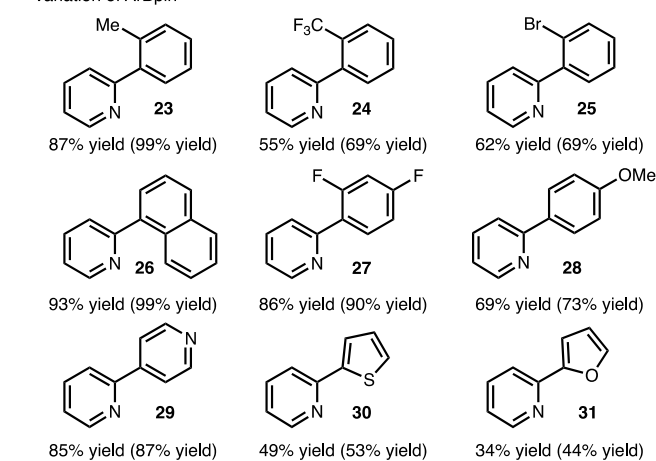
equiv) was suitable for this process (Table 1, entry 6). Potassium trifluoroborate **14** and boronic acid **15** were not suitable in the process likely due to slow transmetalation and protodeboronation, respectively (Table 1, entries 7-8). 4) Other electron deficient aryl bromides such as **11** work in this reaction (Table 1, entry 9). 5) While CuCl could serve as the catalyst in the reaction of 2-bromopyridine as noted by Giri and coworkers, Cy₃PCuCl was superior in this system (compare Table 1, entries 1 and 4). This is especially evident in the reaction of aryl bromide **11** in which CuCl was ineffective (compare Table 1, entries 9 and 11).



■ Variation of HetAr/ArBr



■ Variation of ArBpin

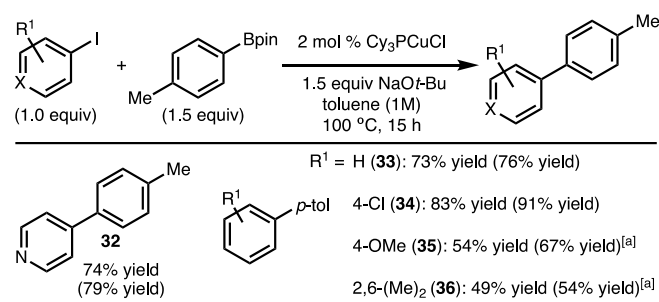


Scheme 3. Cu-Catalyzed Cross-Coupling of Boronic Esters and Arylbromides. Yield of product after purification by silica gel column chromatography. Yield in parentheses determined by analysis of the crude ¹H NMR with an internal standard. [a] Reaction carried out at 120 °C.

The substrate scope of the reaction was explored and illustrated in Scheme 3. A variety of 2-substituted bromo pyridine derivatives underwent cross-coupling in good yield. 3-bromo and 4-bromopyridines are not suitable substrates for this process. While

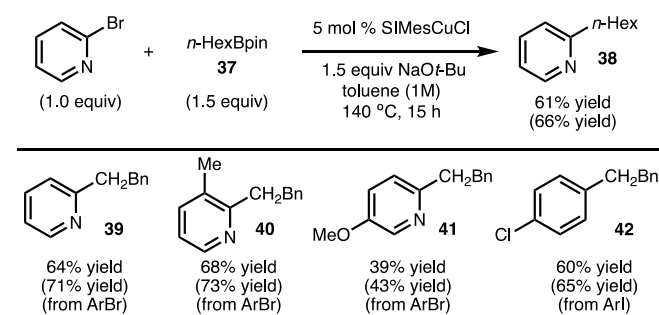
other electron deficient arylbromides (products **10** and **22**) were tolerated, a current limitation is the use of neutral or electron rich aryl bromides (not shown). With respect to the boronic ester component, electron rich (product **28**), electron poor (products **24** and **27**), sterically hindered (products **23**, **24** and **25**), and heterocyclic (products **29**, **30**, and **31**) were compatible.¹¹ While esters were tolerated, substrates with ketones and nitriles did not allow for product formation.

For comparison to our prior studies with cross-coupling of aryl iodides and Cu-Xantphos,⁵ the newly developed conditions also function well. For all major substrate classes (electron rich, electron poor, sterically hindered, heterocyclic), the products were generated in moderate to good yield (Scheme 4).



Scheme 4. Cu-Catalyzed Cross-Coupling of Boronic Esters and Aryliodides. Yield of product after purification by silica gel column chromatography. Yield in parentheses determined by analysis of the crude ¹H NMR with an internal standard. [a] Reaction carried out at 120 °C.

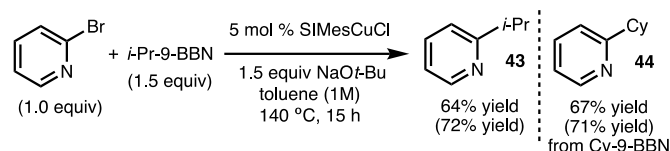
To extend this reaction to the coupling of the more difficult alkyl boronic ester required a change in catalyst and conditions.¹² In particular, it was identified that use of SIMesCuCl at elevated temperatures allowed for coupling of alkylBpin **37** and 2-bromopyridine (Scheme 5). These conditions could also be applied to the coupling of an aryl iodide (product **42**). These results are notable in that Cu-catalyzed reactions of alkyl boron reagents are largely limited to the more sensitive alkyl-9-BBN derivatives.^{13,14}



Scheme 5. Cu-Catalyzed Cross-Coupling of Primary Alkylboronic Esters. Yield of product after purification by silica gel column chromatography. Yield in parentheses determined by analysis of the crude ¹H NMR with an internal standard.

Furthermore, the cross coupling could be extended to secondary nucleophiles (Scheme 6). In these examples, use of the alkyl-9-BBN derivatives was crucial as the analogous alkyl-Bpin was

unreactive.^{15,16} It should be noted that for cross-coupling of *i*-Pr-9-BBN (product **43**), formation of *n*-alkyl products that might result from β -hydride elimination/reinsertion pathways was not observed. Extension of the cross-coupling to secondary alkyl boranes to aryl iodides was unsuccessful. To the best of our knowledge, this method represents the first example of Cu-catalyzed cross-coupling with a secondary alkyl borane.



Scheme 6. Cu-Catalyzed Cross-Coupling of Secondary Alkylboranes. Yield of product after purification by silica gel column chromatography. Yield in parentheses determined by analysis of the crude ¹H NMR with an internal standard.

In summary, a method for the cross coupling of electron deficient aryl bromides and organoboranes is presented. The method utilizes a readily available and inexpensive Cu-catalyst and was found to be compatible with not only arylboranes, but primary and secondary alkylboranes.

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Conflicts of interest

There are no conflicts to declare.

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