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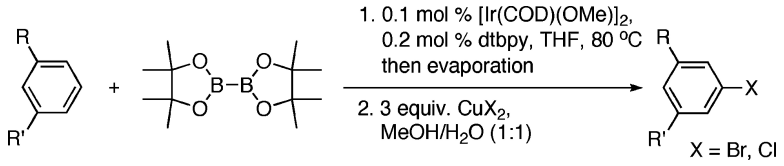

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Meta Halogenation of 1,3-Disubstituted Arenes via Iridium-Catalyzed Arene Borylation

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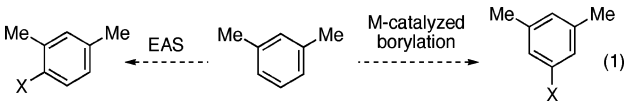
The halogenation of arenes to form aryl halides is a fundamental reaction of organic chemistry. Because electronic effects control the regiochemistry of this process, most substituents that make the arene suitable for electrophilic aromatic substitution (EAS) direct the halogenation to the ortho or para positions (left of eq 1).[1] A combination of directed metalation, followed by halogenation of the resulting aryl anion can alter selectivity, but this process generates ortho-substituted haloarenes.[2] Strategies to prepare meta-substituted haloarenes from aromatic substrates substituted with electron-donating substituents are more limited. For example, the bromination of *m*-xylene using $AlCl_3$ and Br_2 leads to a mixture of products, and 3,5-dimethylphenyl bromide is obtained in only 19% yield.[3]

A highly active catalyst for arene borylation generated from the combination of $[Ir(COD)(OMe)]_2$ (**1**) and 4,4′-di-*t*-butylbipyridine (dtbpy, **2**)[4] (IMH catalyst) was developed by Ishiyama, Miyaura, and the authors' laboratory;[4] less active catalysts based on phosphine ligands were reported by Smith and Maleczka.[5] The regiochemistry of the products from these iridium-catalyzed borylations of arenes results more from steric than electronic control.[5,6] Thus, 1,3-disubstituted arenes form 3,5-disubstituted boronic esters, as shown at the right of eq 1, and this regioselectivity has been used to prepare phenols,[7,8] aminoaryl boronate esters,[8] arylamines,[9] 1,3-substituted arylboronic acids, and trifluoroborates.[10] However, aryl halides are among the most useful aromatic intermediates, and if a reliable method could be identified to convert the arylboronate ester to an aryl halide, then this step could be used in tandem with C−H borylation to create a new strategy for the synthesis of products from meta halogenation of 1,3-disubstituted arenes. We report the development of such a one-pot method for the synthesis of bromoarenes and chloroarenes using the combination of iridium-catalyzed borylation of arenes and halogenation of the resulting aryl boronate esters with copper(II) bromide or copper(II) chloride. The utility of this method is demonstrated by the direct synthesis of a valuable nicotine derivative by direct selective meta halogenation.



The halogenation of arenes via C−H borylation relied on the identification of a method to convert aryl pinacolboronates to the corresponding aryl halides. Dibromodimethylhydantoin, *N*-halosuccinimides, chloramine T/NaBr, and copper(II) halide salts have been employed for the conversion of arylboron compounds to aryl halides,[11−13] and we tested these reagents for the conversion of the pinacol ester of phenylboronic acid to bromobenzene. Although conversions of arylboronic acids to aryl halides were reported with dibromodimethylhydantoin and NaOMe in acetonitrile,[13] the analogous reactions with the phenylboronic ester formed less than 20% of the haloarene. Changing the solvent to THF, MeOH, dioxane, DMSO, or DCM did not improve reaction yields. Treatment of the arylboronate esters with bromine, *N*-bromosuccinimide, and a mixture of chloramine T and NaBr also gave low yields of bromobenzene.

Because arylboronate esters can be converted to aryl trifluoroborates,[10,14] we tested the conversion of aryl trifluoroborates to aryl bromides. The reaction of $K[PhBF_3^-]$ with chloramine T and NaBr at room-temperature provided bromobenzene in 80% yield by GC, but reactions of trifluoroborates containing electron-donating 3,3-dimethyl groups gave mixtures of mono- and dibrominated arenes, and reactions of arenes containing electron-withdrawing 3,5-trifluoromethyl groups occurred to about 30% conversion.

The use of CuX_2 as halogenating agent was more successful. In 2004, Huffman and co-workers published the conversion of phenols to the corresponding aryl bromides using a reaction sequence in which arylboronate esters were converted to aryl bromides in the final step with $CuBr_2$.[11] We tested this halogenation procedure with a series of arenes that are electron-rich and electron poor, and these transformations occurred in acceptable yields.

Using this reactivity of arylboronate esters with $CuBr_2$, we developed the one-pot conversion of the arene to the aryl bromide depicted in the equation of Table 1. Reaction of 1,3-disubstituted arenes with *bis*(pinacolate)diboron (B_2pin_2) in the presence of $[Ir(COD)(OMe)_2]$ (**1**) and dtbpy (**2**) in THF for 16 h at 80 °C,[4,10] followed by evaporation of solvent, dissolution of the crude arylboronic acid in MeOH, and addition of an aqueous solution of copper(II) bromide formed the desired bromoarene in good yields after heating for 4−6 h.

The scope of the conversion of 1,3-disubstituted arenes to 3,5-disubstituted bromoarenes is summarized in Table 1. A variety of 1,3-disubstituted arenes were converted to bromoarenes in good to excellent yields. Entries 1 and 2 show formation of the bromoarene from relatively electron-rich arenes, while entries 3 and 4 show reactions with more electron-poor bromoarenes. Entries 5 and 6 show that the reactions occur in the presence of a chloride, while entries 7−11 show the tolerance of these reactions toward nitriles, esters, amides, and alcohols protected with pivaloyl or silyl groups. Finally, entries 12 and 13 show regioselective halogenation of 2,6-disubstituted and 3-substituted pyridines.

The conversion of arenes to chloroarenes was achieved under similar conditions, except that copper(II) chloride was used to convert the arylboronic esters to the aryl chlorides. Examples of this transformation are summarized in Table 2. The observed scope and yields that were obtained for the chlorination of arenes via arylboronic esters were comparable to those for the bromination of arenes via arylboronic esters. Again, electron-poor and electron-rich arenes underwent this transformation, along with arenes containing nitrile, ester, silyl-, and pivaloyl-protected alcohols. Pyridines substituted in the 2,6- or 3-positions were also converted to the corresponding heteroaryl halide.

The utility of the boronic ester-mediated halogenation of arenes was demonstrated by the direct synthesis of 5-bromonicotine, which

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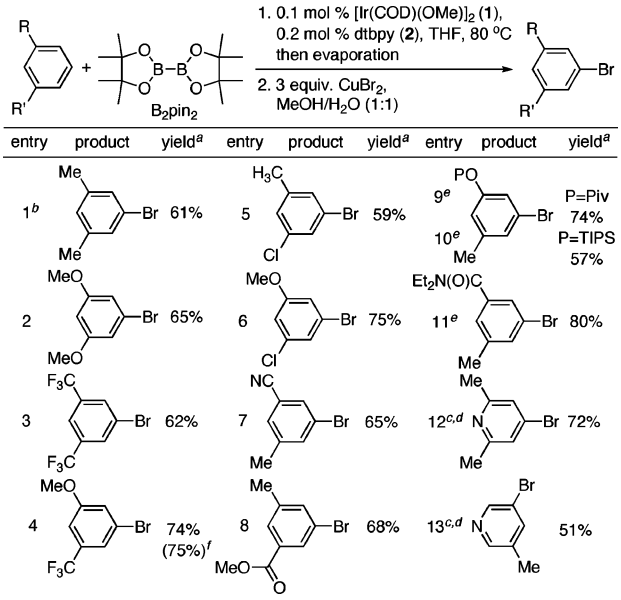
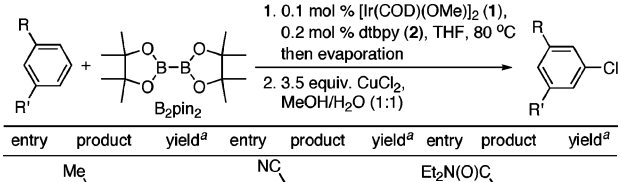
Table 1. Conversion of Arylboronic Esters to Aryl Bromides



entry	product	yield[a]	entry	product	yield[a]	entry	product	yield[a]
1[b]		61%	5		59%	9[e]		P=Piv 74% P=TIPS 57%
2		65%	6		75%	11[e]		80%
3		62%	7		65%	12[c,d]		72%
4		74% (75%)[f]	8		68%	13[c,d]		51%

[a] Average isolated yield for the two-step process from two experiments. Reactions were run on a 2.0 mmol scale. [b] Reaction run using 0.5 mol % $[Ir(COD)(OMe)]_2$ and 1.0 mol % dtbpy. [c] Contained 2% pinacol by ^1H NMR spectroscopy. [d] Reaction run using 3.0 mol % **1** and 6.0 mol % **2**. [e] Reaction run using 1.0 mol % **1** and 2.0 mol % **2**. [f] Yield in parentheses was obtained when conducting the reaction without a glove box using Schlenk techniques. See Supporting Information for details.

Table 2. Conversion of Arylboronic Esters to Aryl Chlorides



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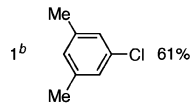
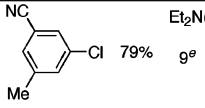
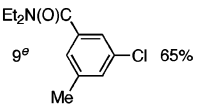
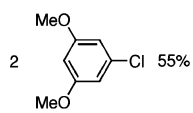
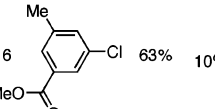
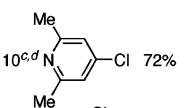
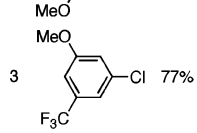
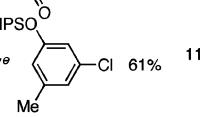
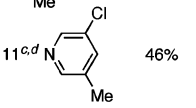
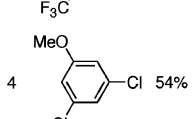
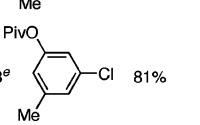
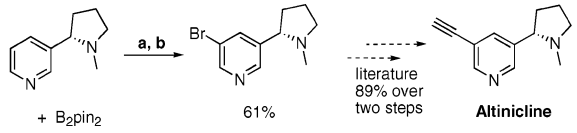
1[b]		61%	5		79%	9[e]		65%
2		55%	6		63%	10[c,d]		72%
3		77%	7[e]		61%	11[c,d]		46%
4		54%	8[e]		81%			

[a] Average isolated yield for the two-step process from two experiments. All reactions were run on a 2.0 mmol scale. [b] Reaction run using 0.5 mol % **1** and 1.0 mol % **2**. [c] Contained 2% pinacol by ^1H NMR spectroscopy. [d] Reaction run using 3.0 mol % **1** and 6.0 mol % **2**. [e] Reaction run using 1.0 mol % **1** and 2.0 mol % **2**.

is an intermediate in the synthesis of a member of a class of compounds that act as neuronal nicotinic acetylcholine receptors,[15] and a precursor to other derivatives by cross-coupling methods. Among the derivatives of 5-substituted nicotine,[16] Altinicline (5-ethynyl-nicotine) has been investigated for the treatment for Parkinson's disease. The most efficient synthesis of Altinicline is a five-step route starting from (*L*)-nicotine with an overall yield of 32%.[17]

Scheme 1



Conditions: *a.* 3.0 mol % $[Ir(COD)(OMe)]_2$, 6.0 mol % dtbpy, THF, 80 °C, evaporation; *b.* 3.5 equiv $CuBr_2$, $MeOH/H_2O$ (1:1).

A formal iridium-catalyzed synthesis of this material is shown in Scheme 1. The iridium-catalyzed borylation of (*L*)-nicotine occurred in high yield with exclusive selectivity for reaction at the 5-position, as determined by ^1H NMR spectroscopy. Treatment of this crude material with aqueous copper(II) bromide at 85 °C for 6 h formed 5-bromonicotine in 61% yield. The conversion of this halide to Altinicline has previously been reported in 89% yield by Sonogashira coupling with 2-methyl-3-butyn-2-ol, followed by deprotection with NaH (Scheme 1).[18]

In summary, we have shown that a variety of 3,5-disubstituted aryl bromides and chlorides can be synthesized in one-pot using a sequence of iridium-catalyzed arene borylation, followed by ipso halogenation with copper(II) salts. Ongoing work is being performed to extend this methodology for the synthesis of aryl iodides and aryl fluorides.

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Supporting Information Available: Complete ref 18. Procedures for synthesis and characterization of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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