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Arenes to Anilines and Aryl Ethers by Sequential Iridium-Catalyzed Borylation and Copper-Catalyzed Coupling

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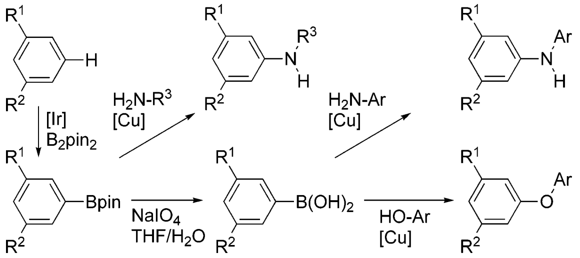
ABSTRACT



***N*-Alkyl- and *N*-arylanilines were synthesized from arenes by a two-step sequence of iridium-catalyzed borylation and copper-catalyzed coupling with amines. Diaryl ethers were obtained by a related sequence of arene borylation, followed by coupling with phenols. In particular, 3,5-disubstituted arylamines and aryl ethers were prepared by initiating this sequence with meta-substituted arenes.**

The iridium-catalyzed borylation of arenes[1−8] is a one-step method to generate aryl boronates, which are convenient synthetic intermediates. The most active catalyst (referred to herein as the IMH catalyst) for the conversion of arenes to arylboronic esters is generated from di-*tert*-butylbipyridine and $[Ir(COD)(OMe)]_2$ and was developed jointly by the Ishiyama and Miyaura group and our group.[1a,2−4]

The direct conversion of arenes to arylamines is limited.[9] We envisioned a route from arenes to arylamines by the combination of C−H borylation of arenes and conversion of the arylboronic ester to the arylamine. Chan and Lam first reported the copper-mediated conversion of arylboronic acids to arylamines,[10,11] and numerous systems for this process have now been reported.[10−14] A similar route to biaryl ethers by the borylation of arenes, followed by copper-mediated coupling of arylboronic acids with phenols,[10b,15] can be envisioned.

Although many methods for the functionalization of arenes by electrophilic aromatic substitution are known, and some of these electrophilic substitutions generate precursors to

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(2) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056.

(3) (a) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, *2003*, 2924. (b) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263.

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(9) (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (c) Hoffmann, N.; Muhler, M. *Catal. Lett.* **2005**, *103*, 155. (d) Yamamoto, M.; Matsubara, S. *Chem. Lett.* **2007**, *36*, 172. (e) Yu, T.; Hu, C.; Wang, W. *Chem. Lett.* **2005**, *34*, 406.

(10) (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (b) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.

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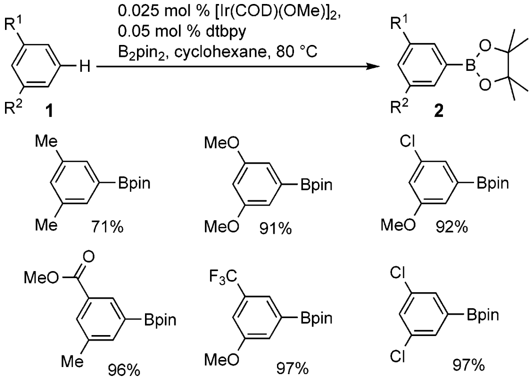
arylamines, access to 1,3,5-trisubstituted arenes remains a synthetic challenge. Many substituents direct electrophilic aromatic substitution to the ortho and para positions, and most meta-directing substituents deactivate arenes toward this process. Thus, 1,3,5-trisubstituted arenes containing three different substituents are often difficult to access.

The selectivity of arene borylation typically complements the selectivity of electrophilic aromatic substitutions. Because the position of the boronate group in the product is dictated more by steric effects than by electronic effects, the C−H activation occurs faster at positions meta and para to existing substituents than at positions ortho to them. As a result, reactions of meta-disubstituted arenes lead to 3,5-disubstituted arylboronates.[1,5,6,16] This feature has been exploited to synthesize 3,5-disubstituted phenols by the borylation of arenes with the IMH catalyst and subsequent oxidation[6,7] and has also been used to synthesize 1,3,5-substituted arylamino boronates by catalytic borylation of halogenated arenes using the IMH catalyst, followed by Pd-catalyzed amination of the halides.[7,8] The products of the C−H borylation have also been used in situ for Suzuki−Miyaura cross coupling.[4,5,17]

Here, we report the conversion of arenes to arylamines and aryl ethers by a sequence of arene borylation, followed by copper-mediated amination and etherification. This sequence forms 3,5-disubstituted arylamines and aryl ethers from commercially available meta-substituted arenes. The synthesis of arylamines by this method complements the classical synthesis of arylamines by nitration, reduction and alkylation, or the more recently developed synthesis of arylamines by the coupling of amines with haloarenes that would have been generated by electrophilic aromatic halogenation.

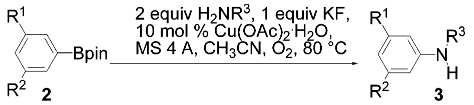
Scheme 1 and Table 1 show the general strategy by which 3,5-disubstituted boronic esters were generated for conversion to 1,3,5-substituted arylamines. The arenes were first converted to the arylboronic ester by reaction with bispinacolatodiboron (B_2pin_2), 0.025 mol % of $[(COD)Ir(OMe)]_2$, and 0.05 mol % of 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) in cyclohexane (Scheme 1).[2,4,18] The arylboronate esters were formed in high yields with this low loading of 0.05 mol % of the iridium. These reactions were conducted with arenes containing halogens, carbomethoxy, trifluoromethyl, and alkoxo groups.

Scheme 1. Borylation of Arenes for Conversion to Arylamines[a]



[a] Yields given are for crude product recovered after the removal of volatile materials under vacuum.

Table 1. Coupling of Alkylamines with Arylboronate Esters Generated by Ir-Catalyzed Arene Borylation



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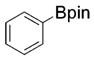
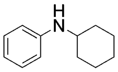
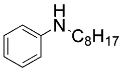
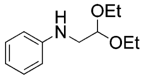
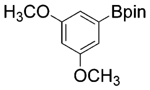
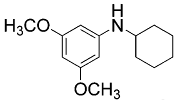
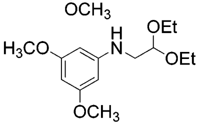
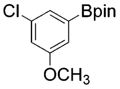
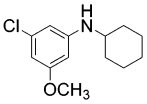
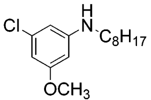
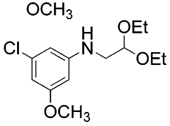
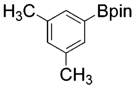
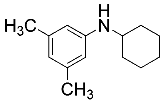
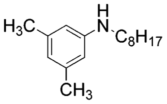
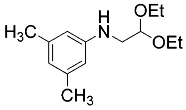
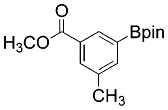
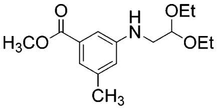
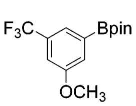
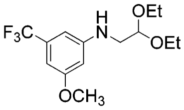
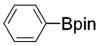
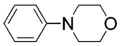
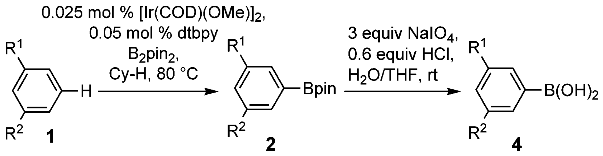
1			67
2			49
3			64
4			64
5			57
6			56
7			47
8			57
9			39
10			34
11			31
12			66
13			57
14			50[b]

[a] Isolated yields after column chromatography based on the amount of ArBpin in the crude arylboronate ester, as judged by NMR spectroscopy of the crude material from the C−H borylation process. [b] 1 equiv $Cu(OAc)_2{\cdot}H_2O$ was used.

Scheme 2. Arylboronic Acids by C−H Borylation and Oxidative Hydrolysis with Aqueous $NaIO_4$

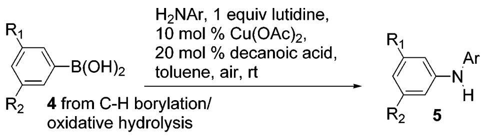


After this C−H bond functionalization process, the solvent was removed from the reaction mixture, and the crude arylboronic esters were converted to arylamines by a copper-mediated process (Table 1, top). This conversion of arylboronates esters to arylamines was not straightforward by existing literature.

Arylboronic esters are much less reactive than arylboronic acids toward the copper-mediated amination and etherification chemistry. For example, the Cu-mediated oxidative coupling of aryl boronic acids with 10 mol % of $Cu(OAc)_2 \cdot H_2O$, 20 mol % of DMAP, and molecular sieves in methylene chloride reported by Batey[14] does not occur with arylboronic esters. Nevertheless, we found that reactions of the crude arylboronates with 2 equiv of alkylamine and 1 equiv of potassium fluoride in the presence of 10−20 mol % of $Cu(OAc)_2 \cdot H_2O$ and powdered molecular sieves in acetonitrile in an oxygen atmosphere occurred to form the desired arylamine at 80 °C. Potassium fluoride might be aiding in the transmetalation of the aryl group from boron to copper, and molecular sieves were added to remove water liberated from the copper precursor. The arylalkylamines were then isolated by column chromatography.

A summary of the formation of arylamines from crude boronic esters, which were generated from meta-substituted arenes, is provided in Table 1. Reactions of primary amines occurred with the arylboronic esters to generate 3,5-disubstituted *N*-alkylanilines. The reactions occurred with a linear and a cyclic primary alkylamine, as well as a protected aminoaldehyde. Although the yields were modest in some cases, reactions of the more electron-poor arylboronic esters usually occurred in acceptable yields.

Table 2. Coupling of Arylamines with Arylboronic Acids Generated by Ir-Catalyzed Arene Borylation and Oxidative Hydrolysis



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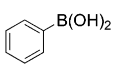
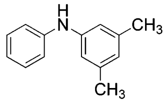
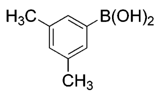
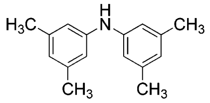
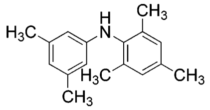
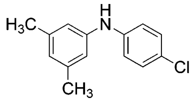
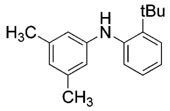
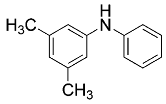
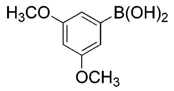
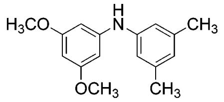
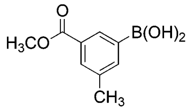
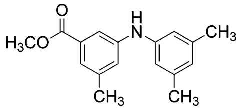
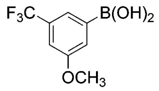
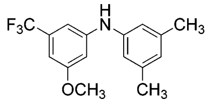
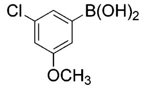
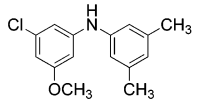
1			95
2			84
3			94
4			89
5			92
6			90
7			81[b]
8			70
9			71[b]
10			79[b]

[a] Isolated yields after column chromatography based on arylamine. [b] 30 mol % $Cu(OAc)_2$ and 60 mol % decanoic acid were used.

In contrast to the reactions of primary alkylamines, the reactions of secondary alkylamines formed the coupled product in low yields. Even the use of stoichiometric amounts of $Cu(OAc)_2 \cdot H_2O$ generated the dialkylaniline products in modest yields. Further, the coupling of the arylboronic esters with arylamines did not occur under Batey's conditions, our modified reaction conditions, or Buchwald's conditions for the coupling of arylboronic acids with arylamines in the presence of copper and myristic acid.[13]

Considering these limitations, we used a reaction sequence described in detail in the accompanying paper in which

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(12) (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, *5*, 674. (b) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415. (c) Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett.* **2003**, *44*, 1691. (d) Chan, D. M. T.; Monaco, K. L.; Li, R. H.; Bonne, D.; Clark, C. G.; Lam, P. Y. S. *Tetrahedron Lett.* **2003**, *44*, 3863. (e) Thomas, A. W.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *115*, 5558.

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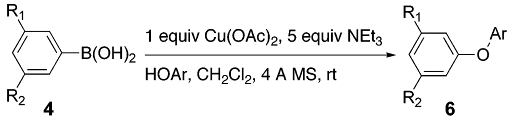
(15) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.

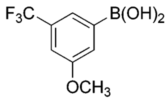
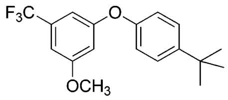
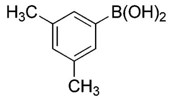
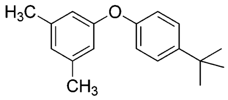
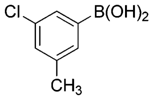
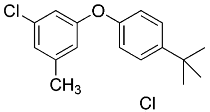
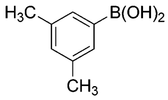
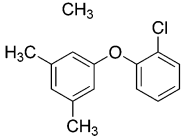
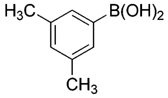
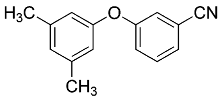
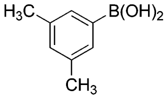
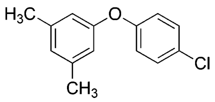
(16) (a) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (b) Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **2000**, *122*, 12868. (c) Tse, M. K.; Cho, J.-Y.; Smith, M. R., III. *Org. Lett.* **2001**, *3*, 2831.

(17) Mkhalid, I. A. I.; Coventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 489.

(18) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103.

Table 3. Coupling of Phenols with Arylboronic Acids Generated by Ir-Catalyzed Arene Borylation and Oxidative Hydrolysis



entry	arylboronic acid	product	yield (%)[a]
1			70%
2			61%
3			94%
4			39%
5			50%
6			84%

[a] Isolated yields after column chromatography.

arylboronic acids are generated by a combination of C−H borylation and oxidative hydrolysis (Scheme 2).[19] The crude aryl boronic acids formed by this procedure and isolated by extraction into EtOAc underwent copper-catalyzed oxidative coupling with arylamines to form diarylamines. These reactions were conducted with 10 mol % of anhydrous $Cu(OAc)_2$, 20 mol % of decanoic acid, and 1 equiv of 2,6-lutidine in toluene under air, as described by Buchwald.[13] After chromatography, the diarylamines were obtained in high yields (Table 2).

The copper-mediated conversion of arylboronic acids to aryl ethers[10,15] also does not occur with pinacol arylboronic esters. For example, reactions of the arylboronic esters with *p-tert*-butylphenol in the presence of catalytic or stoichiometric amounts of $Cu(OAc)_2$ did not form the desired biaryl ether. Thus, our studies on the conversions of arenes to aryl ethers focused on reactions of the arylboronic acids generated by C−H borylation and oxidative hydrolysis of the resulting pinacol boronic ester.

These reactions of the boronic acids are summarized in Table 3. The crude arylboronic acids reacted with phenols to form biaryl ethers. The coupling of an ortho and para-substituted phenol occurred with the crude 3,5-disubstituted arylboronic acids in the presence of 1 equiv of $Cu(OAc)_2$, 5 equiv of triethylamine, and molecular sieves in CH_2Cl_2 at room temperature, as described by Evans.[15] Reaction of the ortho-substituted phenol and the electron-poor cyano-substituted phenol occurred in modest yield, as is typical for these reactions to form biaryl ethers.[20] However, reactions involving the electron-neutral and *p*-chloro-substituted phenols occurred in good yield.

In conclusion, a sequence of Ir-catalyzed borylation and Cu-mediated amination or etherification provides a method to convert arenes to arylamines and aryl ethers. In particular, this method allows the synthesis of 3,5-disubstituted arylamines and aryl ethers from meta-substituted arenes. Although the synthesis of *N*-alkylanilines was accomplished by coupling of primary alkylamines with the arylboronates generated by the C−H activation process, the synthesis of diarylamines and diaryl ethers relied on the accompanying conversion of arenes to arylboronic acids by a sequence of C−H activation and oxidative hydrolysis. Thus, C−H activation, oxidative hydrolysis, and copper-mediated coupling generates 3,5-disubstituted diarylamines and diaryl ethers.

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Supporting Information Available: Experimental procedures and spectral data for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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