J|A|C|S
COMMUNICATIONS

Cyanation of Arenes via Iridium-Catalyzed Borylation

Carl W. Liskey, Xuebin Liao, and John F. Hartwig*

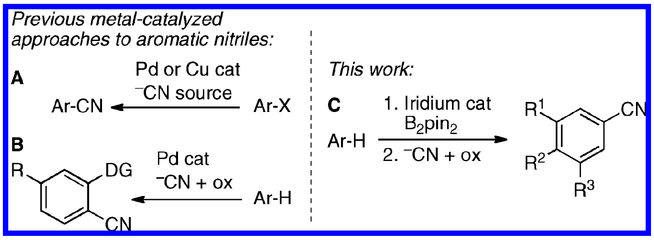
Department of Chemistry, University of Illinois, 600 South Matthews Avenue, Urbana, Illinois 61801-3602

Received May 22, 2010; E-mail: jhartwig@illinois.edu

Abstract: We report a method to conduct one-pot meta cyanation of arenes by iridium-catalyzed C−H borylation and copper-mediated cyanation of the resulting arylboronate esters. This process relies on a method to conduct the cyanation of arylboronic esters, and conditions for this new transformation are reported. Conditions for the copper-mediated cyanation of arylboronic acids are also reported. By the resulting sequence of borylation and cyanation, 1,3-disubstituted and 1,2,3-trisubstituted arenes and heteroarenes containing halide, ketone, ester, amide, and protected alcohol functionalities are converted to the corresponding meta-substituted aryl nitriles. The utility of this methodology is demonstrated through the conversion of a protected 2,6-disubstituted phenol to 4-cyano-2,6-dimethylphenol, which is an intermediate in the synthesis of the pharmaceutical etravirine. The utility of the method is further demonstrated by the conversion of 3-chloro-5-methylbenzonitrile, produced through the one-pot C−H borylation and cyanation sequence, to the corresponding 3,5-disubstituted aldehydes, ketones, amides, carboxylic acids, tetrazoles, and benzylamines.

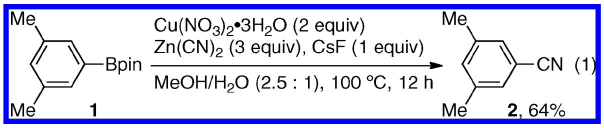
Aromatic and heteroaromatic nitriles are in dyes, herbicides, pharmaceuticals, and natural products.[1] Such nitriles have been formed by the Rosenmund−von Braun[2] or Sandmeyer[3] reaction involving stoichiometric copper(I) cyanide and aryl halides or diazonium salts, respectively, or with palladium-[1,4] or copper-catalyzed[5] reactions of cyanide with aryl halides (Scheme 1A). Palladium-catalyzed, copper-mediated reactions of arylboronic acids with benzylthiocyanate[6] and oxidative cyanations of azoles with hypervalent iodine reagents[7] have also been reported recently. A few palladium-catalyzed cyanations of arenes that contain a directing group (Scheme 1B)[8] or of heteroarenes that have an acidic C−H bond have been reported recently,[9] but a method to conduct cyanations of arenes that lack a functional group at the point of reaction or at a position to direct the C−H bond cleavage are unknown.

Scheme 1



We envisioned a method for the cyanation of arenes that exploits the iridium-catalyzed borylation of arenes.[10−12] The discovery of a method to convert an arylboronate ester to an aryl nitrile, in conjunction with the iridium-catalyzed borylation of C−H bonds, would create a new route to aromatic nitriles in which the regioselectivity would result from the steric effects that control the C−H borylation process (Scheme C). We describe such a cyanation of arenes by C−H borylation and copper-mediated conversion of the intermediate arylboronate ester to the corresponding aryl nitrile. The selectivity of this undirected C−H cyanation process complements that from conventional halogenation followed by cyanation of the resulting aryl halide. The utility of our new process extends beyond the synthesis of aromatic nitriles because aromatic nitriles are readily converted to the corresponding aldehydes, ketones, amides, carboxylic acids, and benzylamines.[13]

A C−H cyanation based on arene borylation requires the conversion of arylboronate esters to aromatic nitriles. To identify conditions for this transformation, a series of copper reagents and cyanide sources were tested. The reaction of the pinacol ester of 3,5-dimethylphenylboronic acid (**1**) with $Zn(CN)_2$ in the presence of CsF or KOH with 1.5 equiv of added $Cu(OAc)_2$, which has commonly been employed in Chan−Lam coupling reactions, generated the corresponding benzonitrile product in less than 10% yield. However, this reaction with 1.5 equiv of copper(II) nitrate in place of copper acetate formed the product in 64% yield after 12 h at 100 °C (eq 1).

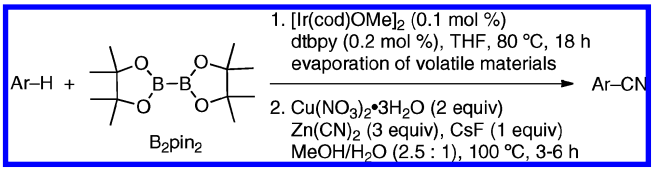


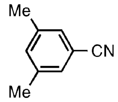
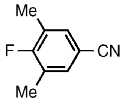
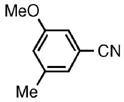
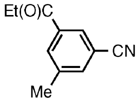
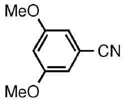
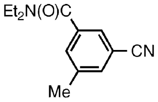
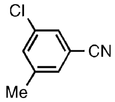
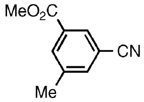
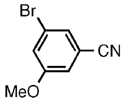
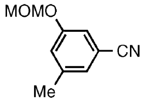
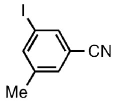
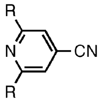
Variation of the reaction conditions showed that the copper and cyanide source, additive, and solvent all have a large effect on the outcome of the cyanation of arylboronates. Copper(II) nitrate was the only copper complex we found to promote this reaction in yields above 40%.[14] Reactions of **1** with $Cu(NO_3)_2$ and acetone cyanohydrin or $Zn(CN)_2$ as the cyanide source in the presence of CsF or KOH occurred in 60−68% yield, but reactions with $K_4[Fe(CN)_6]$, NaCN, TsCN, and CuCN as the cyanide source gave less than 5% yield of the aromatic nitrile. A fluoride or hydroxide base was needed, presumably to activate the arylboronate ester by generating an intermediate borate. Reactions conducted in a solvent combination of MeOH and water generated the product in higher yields than those conducted in other polar solvents, such as DMSO, DMF, or *t*-BuOH (43−55%). The major side products of these reactions resulted from protodeborylation, coupling with the aqueous methanol solvent to form phenol and anisole, and homocoupling to form biaryls.

With the conditions just described for the cyanation of arylboronate esters, we developed a one-pot sequence to convert 1,3-disubstituted or 1,2,3-trisubstituted arenes and heteroarenes to aromatic and heteroaromatic nitriles (Table 1). The borylation of 1,3-disubstituted arenes in the presence of bis(pinacolato)diboron (B_2pin_2), $[Ir(cod)OMe]_2$, and di-*tert*-butylbipyridine (dtbpy) in THF at 80 °C over 18 h produced arylboronate esters, which were converted to the aromatic nitriles by evaporation of the volatile materials, dissolution of the residue in MeOH, addition of

10.1021/ja104442v

Table 1. Cyanation of Arenes via Iridium-Catalyzed Borylation



Entry	Product	Yield[a]	Entry	Product	Yield[a]
1[b]		60%	7		61%
2		55%	8		62%
3		53%	9[d]		66%
4		63% (59%)[c]	10		65%
5		67%	11[d]		51%
6[d]		57%	12[e] 13[e]		R = Me 61% R = Cl 60%

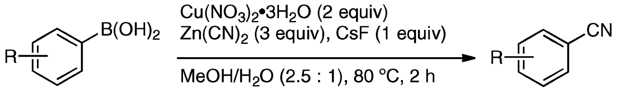
[a] Yield of isolated product from the one-pot procedure (0.50 mmol scale). [b] Borylation with 0.50 mol % [Ir(cod)OMe]$_2$ and 1.0 mol % dtbpy. [c] Reaction performed on 10.0 mmol scale. [d] Borylation with 1.5 mol % [Ir(cod)OMe]$_2$ and 3.0 mol % dtbpy. [e] Borylation with 3.0 mol % [Ir(cod)OMe]$_2$ and 6.0 mol % dtbpy.

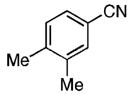
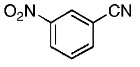
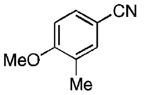
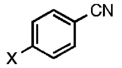
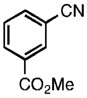
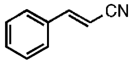
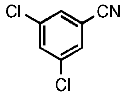
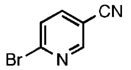
$Cu(NO_3)_2 \cdot 3H_2O$, $Zn(CN)_2$, CsF, and H_2O, and heating at 100 °C for 3−6 h. The reaction sequence occurred with alkyl- and alkoxy-substituted arenes (entries 1−3). Arenes containing chloride, bromide, iodide, or fluoride (entries 4−7) afforded the product without detectable amounts of side product from dehalogenation. In addition, the reaction occurred with arenes containing alkylcarbonyl, aminocarbonyl, alkoxycarbonyl, or protected phenolic hydroxyl groups (entries 8−11). Finally, the reaction of 2,6-disubstituted pyridines produced 4-cyanopyridine products. Reactions of a variety of protected anilines were also studied, but the corresponding protected aminobenzontrile products were not generated under the standard conditions.[15]

The copper-mediated cyanation of arylboron compounds also occurred with arylboronic acids (Table 2). The reaction of arylboronic acids with $Zn(CN)_2$ in the presence of $Cu(NO_3)_2$ and CsF formed the aromatic nitriles at lower temperatures and within shorter times than the reactions of pinacol boronate esters with the same reagents. Under these conditions, arylboronic acids containing electron-donating (entries 1 and 2) or electron-withdrawing (entries 3−5) groups formed benzonitriles in 67−70% yield. This oxidative coupling provides a method for the preparation of aromatic nitriles that complements palladium-catalyzed cyanation. For example, the copper-mediated cyanation of boronic acids containing chloride, bromide, and iodide formed the corresponding halogenated benzonitriles in good yield. In addition, sytrenyl and pyridyl boronic acids (entries 8 and 9) underwent the coupling reaction in moderate yield.

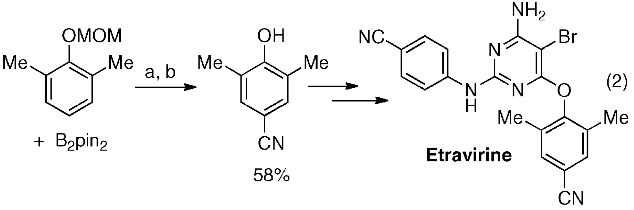
A number of non-nucleoside reverse transcriptase inhibitors that are potent anti-HIV compounds contain arenes possessing cyano groups located meta to the other substituents. For example, etravirine (eq 2) is a recently approved drug for the treatment of HIV that is prepared from 4-cyano-2,6-dimethylphenol.[16] By the one-pot C−H cyanation sequence reported here, a protected 2,6-dimethylphenol was converted to 4-cyano-2,6-dimethylphenol in 58% isolated yield.[17]

Table 2. Conversion of Arylboronic Acids to Benzonitriles



Entry	Product	Yield[a]	Entry	Product	Yield[a]
1		68%	5		67%
2		70%	6 7		X = Br 58% X = I 62%
3		68%	8[b]		65%
4		69%	9		61%

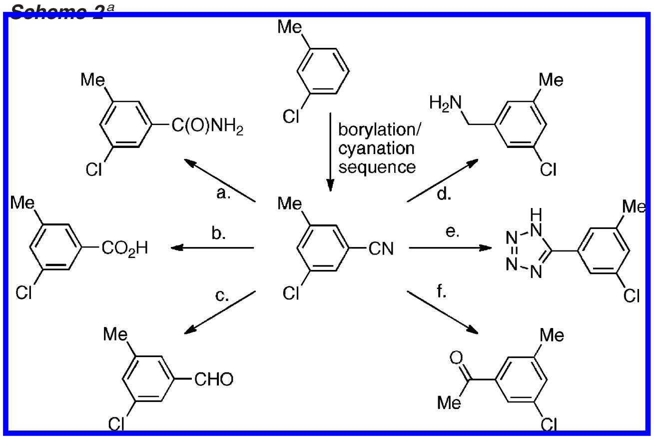
[a] Yield of isolated product (0.50 mmol scale). [b] Reaction time was 4 h.



[a.] $[Ir(cod)OMe]_2$ (1.5 mol %), dtbpy (3.0 mol %), THF, 80 °C, 16 h, evaporation; [b.] $Cu(NO_3)_2 \cdot 3H_2O$ (2 equiv), $Zn(CN)_2$ (3 equiv), CsF (1 equiv), $MeOH/H_2O$ (2.5 : 1), 100 °C, 4 h, 58% yield.

In some cases benzonitriles are the desired final product, but in many cases they are used as intermediates to generate products containing functionality resulting from reaction of the cyano group. The series of reactions shown in Scheme 2 for a prototypical 3,5-

Scheme 2[a]



[a] Reaction conditions: (a) KOH, t-BuOH, 60 °C, 4 h, 94%. (b) AcOH, H_2O, H_2SO_4, reflux, 5 h, 94%. (c) DIBAL-H, Et_2O, 22 °C, 5 h; HCl (10%), 68%. (d) $LiAlH_4$, Et_2O, 22 °C, 5 h, 86%. (e) $ZnBr_2$, NaN_3, H_2O, i-PrOH, reflux, 30 h; HCl (3 N), 65%. (f) MeMgBr, Et_2O, 48 h, reflux; HCl (10%), 74%.

disubstituted aromatic nitrile prepared by C−H borylation to form 1,3,5-trisubstituted arene products underscores the versatility of the cyanation process. As shown, 3-chloro-5-methylbenzonitrile was converted in a straightforward fashion to the corresponding primary benzamide, benzoic acid, benzaldehyde, benzylamine, and aromatic ketone. In addition, this sequence leads to products with a tetrazole, which can function as bioisosteric replacement for a carboxylic acid,[18] in the mutually meta position of a 1,3-disubstituted arene.

In summary, we have demonstrated the first copper-mediated oxidative cyanation of arylboronate esters and arylboronic acids and the use of this procedure to create a route to meta-substituted benzonitriles containing a variety of functional groups. The development of other copper-mediated oxidative reactions of arylboronate esters is in progress.

Acknowledgment. We thank the NSF (CHE-0910641) for support of this work, Johnson Mathey for [Ir(cod)OMe]$_2$, and AllyChem for B$_2$pin$_2$. C.W.L. thanks Abbott Laboratories for a graduate fellowship.

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

References

(1) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513.

(2) (a) von Braun, J.; Manz, G. *Justus Liebigs Ann. Chem.* **1931**, *488*, 111. (b) Rosenmund, K. W.; Struck, E. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 1749.

(3) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2650.

(4) (a) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50. (b) Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C. Y. *Org. Lett.* **2004**, *6*, 3723. (c) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388.

(5) (a) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890. (b) Cristau, H. J.; Ouali, A.; Spindler, J. F.; Taillefer, M. *Chem.—Eur. J.* **2005**, *11*, 2483. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(6) Zhang, Z. H.; Liebeskind, L. S. *Org. Lett.* **2006**, *8*, 4331.

(7) (a) Dohi, T.; Morimoto, K.; Kiyono, Y.; Tohma, H.; Kita, Y. *Org. Lett.* **2005**, *7*, 537. (b) Katritzky, A. R.; Scriven, E. F. V.; Majumder, S.; Tu, H.; Vakulenko, A. V.; Akhmedov, N. G.; Murugan, R. *Synthesis* **2005**, 993.

(8) (a) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Jia, X. F.; Yang, D. P.; Zhang, S. H.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716.

(9) Do, H.-Q.; Daugulis, O. *Org. Lett.* **2010**, *12*, 2517.

(10) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(11) (a) Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (c) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263.

(12) (a) Cho, J. Y.; Iverson, C. N.; Smith, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 12868. (b) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305.

(13) (a) Rappoport, Z. *The Chemistry of the Cyano Group*; Interscience Publishers: London, 1970. (b) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1988.

(14) See the Supporting Information for experimental details, including a table of parameters tested.

(15) Reactions of other heteroarenes that undergo C−H borylation reactions to form 2- or 3-borylheteroarenes were conducted under these conditions, but large amounts of products from homocoupling or protodeborylation of the pinacol arylboronate esters occurred.

(16) De Clercq, E. *Antiviral Res.* **2010**, *85*, 19.

(17) In situ cleavage of the MOM group occurred.

(18) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379.

JA104442V