

Cyanation of Arenes via Iridium-Catalyzed Borylation

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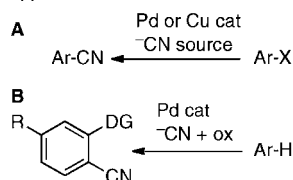
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Abstract: We report a method to conduct one-pot meta cyanation of arenes by iridium-catalyzed C–H borylation and copper-mediated cyanation of the resulting arylboronate esters. This process relies on a method to conduct the cyanation of arylboronic 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.

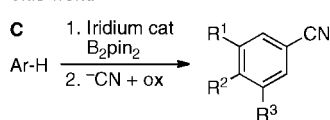
Aromatic and heteroaromatic nitriles are in dyes, herbicides, pharmaceuticals, and natural products.¹ Such nitriles have been formed by the Rosenmund–von Braun² or Sandmeyer³ reaction involving stoichiometric copper(I) cyanide and aryl halides or diazonium salts, respectively, or with palladium-^{1,4} or copper-catalyzed⁵ reactions of cyanide with aryl halides (Scheme 1A). Palladium-catalyzed, copper-mediated reactions of arylboronic acids with benzylthiocyanate⁶ and oxidative cyanations of azoles with hypervalent iodine reagents⁷ 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

Previous metal-catalyzed approaches to aromatic nitriles:



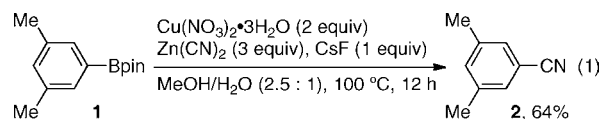
This work:



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

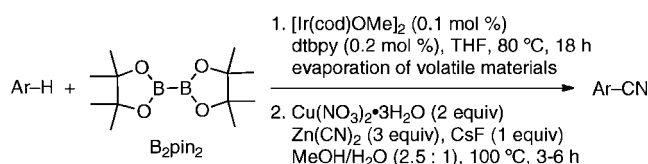
regioselectivity would result from the steric effects that control the C–H borylation process (Scheme C). We describe such a cyanation of arenes by C–H borylation and copper-mediated conversion of the intermediate arylboronate ester to the corresponding aryl nitrile. The selectivity of this undirected 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(NO₃)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 K₄[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 (B₂pin₂), [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

Table 1. Cyanation of Arenes via Iridium-Catalyzed Borylation

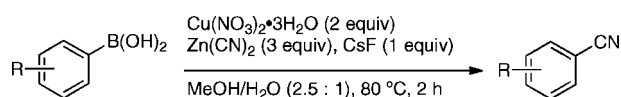
Entry	Product	Yield ^a	Entry	Product	Yield ^a
1 ^b		60%	7		61%
2		55%	8		62%
3		53%	9 ^d		66%
4		63% (59%) ^c	10		65%
5		67%	11 ^d		51%
6 ^d		57%	12 ^e		R = Me 61%
			13 ^e		R = Cl 60%

^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(NO₃)₂·3H₂O, Zn(CN)₂, CsF, and H₂O, 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, alkoxy-carbonyl, 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 aminobenzonitrile products were not generated under the standard conditions.¹⁵

The copper-mediated cyanation of arylboronic compounds also occurred with arylboronic acids (Table 2). The reaction of arylboronic acids with Zn(CN)₂ in the presence of Cu(NO₃)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, syrenyl and pyridyl boronic acids (entries 8 and 9) underwent the coupling reaction in moderate yield.

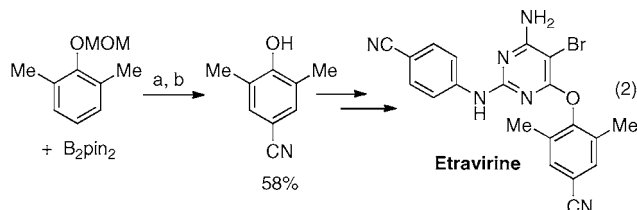
A number of non-nucleoside reverse transcriptase inhibitors that are potent anti-HIV compounds contain arenes possessing cyano

Table 2. Conversion of Arylboronic Acids to Benzonitriles

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

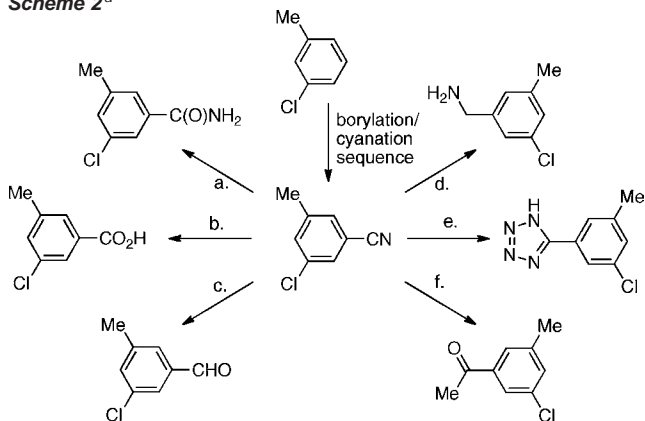
^a Yield of isolated product (0.50 mmol scale). ^b Reaction time was 4 h.

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



^a [Ir(cod)OMe]₂ (1.5 mol %), dtbpy (3.0 mol %), THF, 80 °C, 16 h, evaporation; ^b Cu(NO₃)₂·3H₂O (2 equiv), Zn(CN)₂ (3 equiv), CsF (1 equiv), MeOH/H₂O (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, H₂O, H₂SO₄, reflux, 5 h, 94%. (c) DIBAL-H, Et₂O, 22 °C, 5 h; HCl (10%), 68%. (d) LiAlH₄, Et₂O, 22 °C, 5 h, 86%. (e) ZnBr₂, NaN₃, H₂O, *i*-PrOH, reflux, 30 h; HCl (3 N), 65%. (f) MeMgBr, Et₂O, 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.

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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>.

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