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Facile Synthesis of 2-Bromo-3-fluorobenzonitrile: An Application and Study of the Halodeboronation of Aryl Boronic Acids

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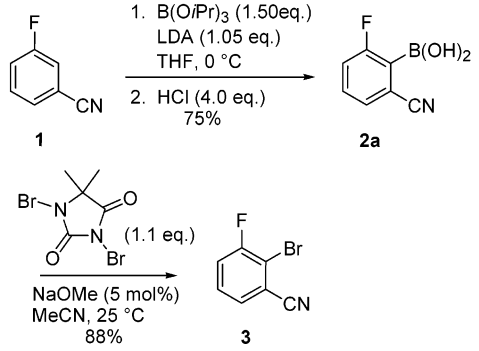
Abstract: A scaleable synthesis of 2-bromo-3-fluorobenzonitrile via the NaOMe-catalyzed bromodeboronation of 2-cyano-6-fluorophenylboronic acid was developed. The generality of this transformation was demonstrated through the halodeboronation of a series of aryl boronic acids. Both aryl bromides and aryl chlorides were formed in good to excellent yields when the corresponding aryl boronic acid was treated with 1,3-dihalo-5,5-dimethylhydantoin and 5 mol % NaOMe.

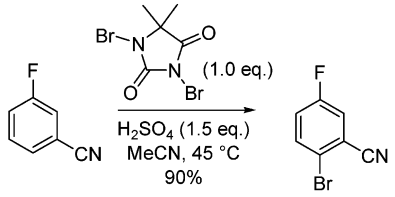
Aryl halides are important synthetic intermediates that have been used extensively in various carbon−carbon and carbon−heteroatom bond-forming reactions. Although a plethora of aryl halides are commercially available, the regioselective introduction of the carbon−halogen bond into advanced synthetic intermediates can be a challenging problem in organic synthesis, and the extensive literature concerning carbon−halogen bond formation exemplifies the importance of this transformation.[1] The most common means of aromatic halogenation include electrophilic aromatic substitution, conversion of an amine to a halide via the diazonium salt (i.e., the Sandmeyer reaction), and to a lesser extent, the halogenation of an arylmetallic species.[2] Recently, our research efforts required the use of multi-kilogram quantities of 2-bromo-3-fluorobenzonitrile (**3**) as an intermediate. Herein, we describe a practical and facile synthesis of **3** (Scheme 1) from 3-fluorobenzonitrile (**1**) via the bromodeboronation of electron-poor aryl boronic acid **2a**. The scope and limitations of this transformation were determined by the synthesis of several aryl bromides and aryl chlorides from the corresponding aryl boronic acids under our reaction conditions.

While many aryl bromides can be easily accessed by electrophilic bromination using bromine and a Lewis acid catalyst, this approach is usually limited to electron-rich systems with ring halogenation occurring ortho and para to the directing group.[3] Nevertheless, fluorobenzenes have been shown to undergo electrophilic aromatic substitution.[4] Treatment of compound **1** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) for 8 h at 45 °C (Scheme 2) resulted in the selective formation of 2-bromo-5-fluorobenzonitrile (**4**) in high yield (90%).[5] Since the regioselectivity of electrophilic bromination of **1** was governed by the para directing effect of the fluorine substituent, another method for the synthesis of **3** was clearly required.

SCHEME 1. Synthesis of 2-Bromo-3-fluorobenzonitrile



SCHEME 2. Electrophilic Bromination of 3-Fluorobenzonitrile



Our next approach to **3** relied upon deprotonation of **1**, followed by bromination of the resulting aryl anion intermediate. While organolithium bases such as *n*-butyllithium, lithium diisopropylamide (LDA), or lithium bis(trimethylsilyl)amide readily added to the nitrile and resulted in undesired ketone and amide products,[6] milder bases, such as Grignard or alkyl zinc halide reagents, did not deprotonate **1**. A directed metalation using Kondo's triorganozincate complex **6**[7] allowed access to **3** in 75% yield and excellent regioselectivity via treatment of intermediate **5** with bromine (Scheme 3). However, this chemistry was not amenable to kilo-scale processing due to a considerable exotherm exhibited during the bromine addition, byproducts associated with the reaction and difficulties with product isolation.[8]

We envisioned that the use of a less reactive intermediate, such as an aryl silane[9] or an aryl boronic acid,[10]

* Corresponding author.

(1) (a) Hudlicky, M.; Hudlicky, T. Formation of Carbon−Halogen Bonds. In *Supplement D*: *The Chemistry of Halides, Pseudohalides and Azides*; Patai, S., Rappoport, Z., Eds.; The Chemistry of Functional Groups; Wiley & Sons: Chichester, U.K., 1983; Chapter 22, pp 1021−1172. (b) Sasson, Y. Formation of Carbon−Halogen Bonds (Cl, Br, I). In *Supplement D*: *The Chemistry of Halides, Pseudohalides and Azides*; Patai, S., Rappoport, Z., Eds.; The Chemistry of Functional Groups; Wiley & Sons: Chichester, U.K., 1995; Chapter 11, pp 535−628.

(2) Urch, C. J. Vinyl and Aryl Halides. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Ley, S. V., Eds.; Elsevier: Oxford, U.K., 1995; Vol. 2, pp 605−633.

(3) March, J. Aromatic Electrophilic Substitution. *Advanced Organic Chemistry*, 4th ed.; Wiley & Sons: New York, 1992; pp 507−511.

(4) (a) Schiemann, G.; Pillarsky, R. *Ber.* **1931**, 1340−1345. (b) Suter, C.; Weston, A. *J. Am. Chem. Soc.* **1941**, *63*, 602−605. (c) Olah, G.; Pavlath, A.; Varsanyi, G. *J. Chem Soc.* **1957**, 1823−1829. (d) Black, W. C.; Guay, B. *Synthesis* **1998**, *8*, 1101−1103.

(5) Compound **4** was isolated by column chromatography in 90% yield. The identity of **4** was confirmed by NMR by comparison against an authentic sample obtained from a commercial source.

(6) (3-Fluorophenyl)pentan-1-one, 3-fluoro-*N*,*N*-diisopropylbenzamide, and 3-fluoro-*N*,*N*-bis(trimethylsilyl)benzamide were identified by NMR of the crude reaction mixtures from the reaction of **1** with *n*-BuLi, LDA, and LHMDS, respectively.

(7) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539−3540.

10.1021/jo035184p CCC: $27.50
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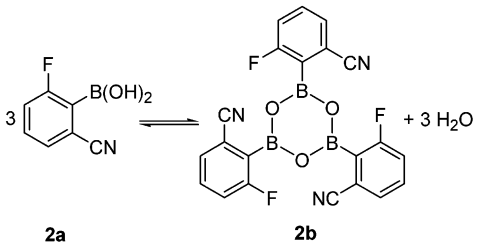
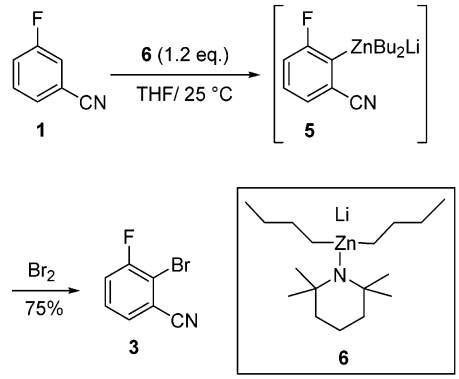


FIGURE 1.

SCHEME 3. Orthometalation−Bromination of 3-Fluorobenzonitrile



would permit greater control over the exothermic bromination. Although synthesis of the requisite 3-fluoro-2-(trimethylsilyl)benzonitrile was accomplished,[11] treatment of the aryl silane with elemental bromine or DBDMH gave only traces of **3**.[12] Similar results were anticipated for the halodeboronation of 2-cyano-6-fluorophenylboronic acid, since bromination of electron-deficient aryl boronic acids typically result in formation of the aryl bromide in poor yields.[10d] 2-Cyano-6-fluorophenylboronic acid was prepared as an indeterminable mixture of monomer **2a** and trimer **2b** (Figure 1)[13] in 75% yield by the addition of LDA to a THF solution of **1** and B(O-*i*-Pr)$_3$ at 0 °C.[14,15] Since the bromodeboronation of **2a**/**2b** failed in THF, other solvents were evaluated and acetonitrile was the solvent of choice. After a solvent switch to acetonitrile via constant volume distillation, bromide **3** was formed in good yield (65%) by the slow addition of DBDMH to the boronic acid/anhydride mixture at 25 °C.[16,17]

Upon scale-up of this chemistry, nitrile hydrolysis products **7** and **8** formed occasionally and unpredictably at the expense of **3**.[18] In the absence of any distinguishable differences of a successful reaction that generates **3** to a failed reaction producing hydrolysis products **7** and **8**, we proposed that the ratio of monomer **2a** to trimer **2b** might be critical to the halodeboronation reaction. Solutions of arylboronic acids are known to exist in equilibrium with their cyclic anhydrides;[19] however, we were unable to determine the ratio of **2a**/**2b** by ^{1}H, ^{13}C, ^{19}F, or ^{11}B NMR due to the reaction complexity. A simplified model system using commercially available 4-fluorophenylboronic acid (**9a**) and tris(4-fluorophenyl)boroxine (**9b**) was used to evaluate our hypothesis (Scheme 4).[20] A clear difference in reactivity was observed between **9a** and **9b** toward halogenation under our reaction conditions. 4-Bromofluorobenzene (**10**) was formed in only 24% yield when trimer **9b** was brominated with DBDMH versus an 88% yield of **10** for the bromination of boronic acid **9a**. Chlorination of **9a** and **9b** with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) gave 4-chlorofluorobenzene (**11**) in 70% and 14% yield, respectively. We then reasoned that the use of a base should increase the reactivity of the trimer toward bromination by formation of the more nucleophilic borate.[21] Indeed, addition of stoichiometric NaOMe to trimer **9b** increased the yield of **10** to 55% and **11** to 25% after 8 h. Since compound **2a**/**2b** has shown particular instability in solutions with a basic pH (≥ 8.0), catalytic NaOMe was examined in the halodeboronation of **9b** and found to promote the formation of **10** and **11** in remarkably high yields.[22]

Application of the base-catalyzed procedure to the **2a**/**2b** mixture reproducibly afforded an 85−90% yield of bromide **3**.[23−25] More importantly, acetonitrile solutions of **2a**/**2b** that previously gave hydrolysis products **7** and **8** now provide bromide **3** in 85−90% yield. Based on these

(8) The alkylhalide byproducts formed in the reaction were difficult to remove by distillation and inhibited the crystallization of **3**.

(9) (a) Felix, G.; Dunoguès, J.; Pisciotti, F.; Calas, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 488−489. (b) Bennetau, B.; Rajarison, F.; Dunoguès, J.; Babin, P. *Tetrahedron* **1993**, *49*, 10843−10854. (c) Coe, P.; Stuart, A.; Moody, D. *J. Fluorine Chem.* **1998**, *92*, 27−32.

(10) (a) Ainley, A. D.; Challenger, F. *J. Chem. Soc.* **1930**, 2171−2180. (b) Melnikoff, N. N. *J. Gen. Chem. U.S.S.R.* **1936**, *6*, 636. (c) Kabalka, G. W.; Sastry, K. A. R.; Sastry, U.; Somayaji, V. *Org. Prep. Proced. Int.* **1982**, *14*, 359−362. (d) Thiebes, C.; Prakash, G. K. S.; Petasis, N.; Olah, G. *Synlett* **1998**, *2*, 141−142.

(11) Fluoro-2-(trimethylsilyl)benzonitrile was prepared by the slow addition of LDA to a THF solution of **1** and chlorotrimethylsilane at 0 °C.

(12) To a solution of 3-fluoro-2-(trimethylsilyl)benzonitrile in THF or acetonitrile was added either bromine or DBDMH. The reaction was heated to 40 °C, aged for several hours, and monitored by HPLC.

(13) While standard instrumental analyses (LC, LC/MS, GC/MS, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, or ^{11}B NMR) only resulted in ambiguous structural assignments of 2-cyano-6-fluorophenylboronic acid, a mixture of monomer **2a**, tris(2-cyano-6-fluorophenyl)boroxine (**2b**), and various oligomers could all be present in solution.

(14) (a) Kristensen, J.; Lysén, M.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435−1437. (b) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054−2055. (c) Li, W.; Nelson, D.; Jensen, M.; Hoerrner, R. S.; Cai, D.; Larsen, R.; Reider, P. *J. Org. Chem.* **2002**, *67*, 5394−5397.

(15) The formation of 3-fluoro-*N*,*N*-diisopropylbenzamide was minimized by this addition sequence. While a one-pot deprotonation/bromination process could be envisioned, an appropriate brominating agent that is unreactive towards LDA, such as 1,2-dibromotetrafluoroethane, was required. 1,2-Dibromotetrafluoroethane is currently prohibited from use by the EPA under the Clean Air Act 1990 because of its adverse effects on stratospheric ozone.

(16) Bromination of the crude diisopropyl boronic ester without an aqueous workup was examined and gave **3** after 2 h at 40 °C in good yield (79%), but poor purity. However, this route was not amenable to large-scale synthesis since ester hydrolysis, followed by acid/base extractions proved necessary to remove the reaction impurities (e.g., ethylbenzene introduced from commercial LDA was polybrominated). Furthermore, a thick, difficult to stir slurry formed upon solvent switch from THF to acetonitrile.

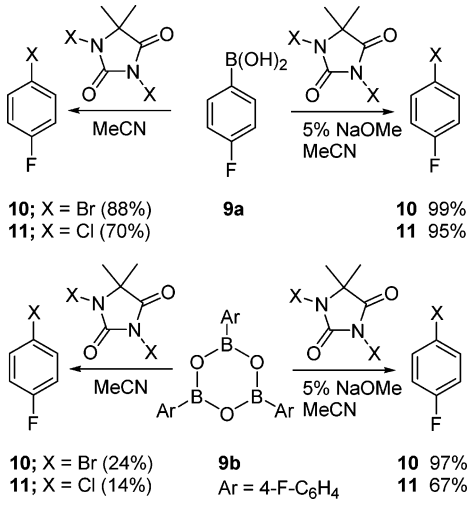
(17) For discussions regarding the mechanism of boron substitution, see: (a) Petasis, N. A.; Zavialov, I. A. *Tetrahedron Lett.* **1996**, *37*, 567−570. (b) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456−6457.

(18) A combined yield of **7** and **8**, as much as 100% with respect to **2**, has been observed. An apparent pH of 5.0−6.5 (pH test strip) and a 2.5−5.0% water content (as determined by Karl Fisher titration) were required of the acetonitrile solution in order to achieve reproducible results in the bromination reaction. Less water required an extended age period for the reaction to go to completion (2−12 h) and resulted in a lower yield of **3** while more water resulted in an increase in decomposition products.

(19) (a) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852−6856. (b) Tokunaga, Y.; Ueno, H.; Shimomura, Y.; Seo, T. *Heterocycles* **2002**, *57*, 787−790.

(20) 4-Fluorophenylboronic acid (**9a**) was obtained from commercial sources as mixture of monomer **9a** (66%) and trimer **9b** (34%). Tris-(4-fluorophenyl)boroxine (**9b**) was obtained from commercial sources and analysis by ^{1}H and ^{11}B NMR showed mostly trimer **9b** (86%) while the remainder of the material is monomer **9a**.

SCHEME 4. Halogenation of Tris(4-fluorophenyl)boroxine and 4-Fluorophenylboronic Acid

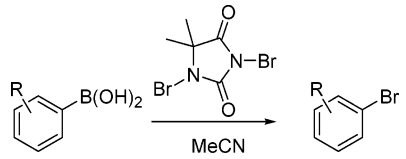


observations, we believe that boroxine **2b** is inert toward bromination with DBDMH and that variations in the **2a**/**2b** ratio, which most likely occur in the solvent switch from THF to acetonitrile, are responsible for an alternate reaction pathway generating **7** and **8** (Scheme 5). In fact, kilogram-scale reactions were typically prone to hydrolysis conceivably due to the prolonged distillation time required which provides favorable conditions for trimer **2b** formation.

A study of the base-catalyzed halodeboronation reaction was conducted by bromination of a series of aryl boronic acids under our reaction protocol (Table 1). We observed that reactions typically gave the desired halogenated product in good to excellent yield and tolerated a range of functionality. Only when a strong electron-donating group was present (entry 5, Table 1) did electrophilic aromatic halogenation compete with displacement of the boron. As seen in Scheme 6, in addition to 2-bromoanisole (**13e**), 5-bromo-2-methoxyphenylboronic acid (**14**) and 2,4-dibromoanisole (**15**) were formed in a combined yield of 23% when **12e** was subjected to DBDMH in the presence of 5 mol % NaOMe. Optimization of the reagent stoichiometries (0.52 equiv of DBDMH; 0.3 equiv of NaOMe) led to the selective conversion of **12e** to **13e** in 94% yield. This is a novel result since only electrophilic aromatic bromination of **12e** has been reported.[21f]

As seen with the bromination of **2a**/**2b**, addition of a catalytic amount of base to the reaction mixture resulted

TABLE 1. Bromination of Aryl Boronic Acids Using DBDMH and DBDMH/NaOMe[a,b]



entry	boronic acid[c]	R	yield (%) (DBDMH)	yield (%) (DBDMH/NaOMe)
1	**12a**	2-F	95	98
2	**12b**	3-NO_2	21	96
3	**12c**	H	96	99
4	**12d**	2-Me	97	99
5	**12e**	2-OMe	45[d]	77[e]
6	**12f**	3-$C(O)CH_3$	95	95
7	**12g**	4-$C(O)CH_3$	83	99

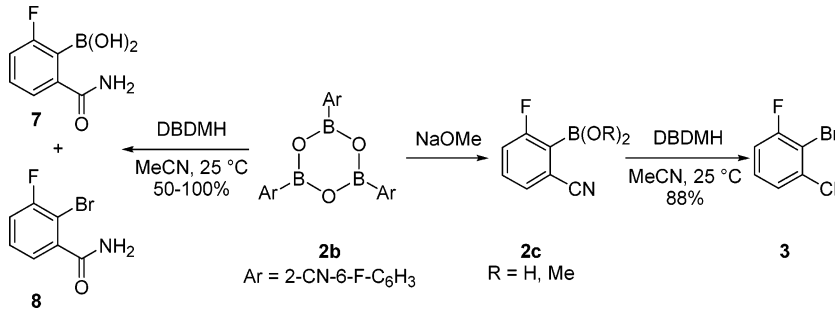
[a] Yields were determined by HPLC analysis vs a standard prepared from commercially available authentic material. [b] Product yields have not been optimized. [c] The acetonitrile solution of aryl boronic acid prior to DBDMH addition typically had a water content of 2−4% as determined by Karl Fisher titration and a pH of 4−6. [d] Electrophilic aromatic bromination products were also formed: 5-bromo-2-methoxyphenylboronic acid (34%) and 2,4-dibromoanisole (18%). [e] Electrophilic aromatic bromination products were also formed: 5-bromo-2-methoxyphenylboronic acid (5%) and 2,4-dibromoanisole (18%).

in an increase in yield of the product (entries 1−7). The effects of base catalysis can be best exemplified by the bromination of 3-nitrophenylboronic acid (entry 2) since 3-bromonitrobenzene (**13b**) was formed in 96% yield when methoxide was present versus 21% yield in the absence of base.

Recently, much attention has been placed upon aryl chlorides and their application in palladium-catalyzed cross-coupling reactions.[26] Under our standard reaction conditions, aryl chlorides are easily synthesized from aryl boronic acids by using DCDMH as the halogenating reagent (see Table 2). Trends in yield similar to those described above were observed when the reactions were base catalyzed (entries 2−7). Notable results were again obtained for 3-nitrophenylboronic acid (entry 2) since chlorination did not occur in any appreciable extent in the absence of base, but proceeded in 43% yield when methoxide was present. Unlike the bromination of **12e** to give 2-bromoanisole, selective preparation of 2-chloroanisole (**16e**) by simple adjustment of reagent stoichiometries was never achieved (entry 5).

It has been previously reported that the chlorodeboronation of aryl boronic acids gave only trace amounts of product when *N*-chlorosuccinimide (NCS) was used as the halogen source.[10d] As an extension of our study, the

SCHEME 5. Proposed Reactivity of Tris(2-cyano-6-fluorophenyl)boroxine



SCHEME 6. Bromination of 2-Methoxyphenylboronic Acid

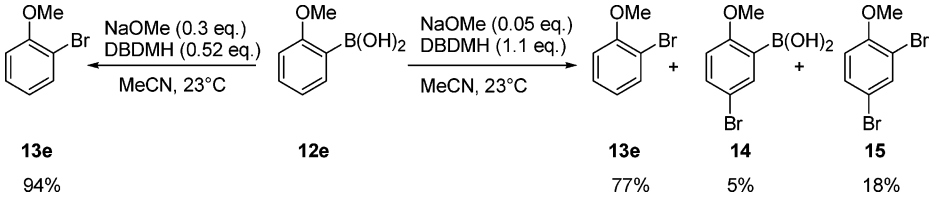
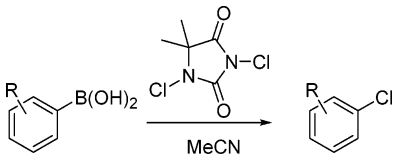


TABLE 2. Chlorination of Aryl Boronic Acids Using DCDMH and DCDMH/NaOMe[a,b]

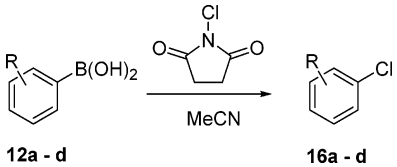


12a - g 16a - g

entry	boronic acid[c]	R	yield (%) (DCDMH)	yield (%) (DCDMH/NaOMe)
1	**12a**	2-F	91	88
2	**12b**	3-NO_2	1.6	43
3	**12c**	H	42	73
4	**12d**	2-Me	88	97
5	**12e**	2-OMe	11[d]	18[e]
6	**12f**	3-$C(O)CH_3$	79	79
7	**12g**	4-$C(O)CH_3$	36	55

[a] Yields were determined by HPLC analysis vs a standard prepared from commercially available authentic material. [b] Product yields have not been optimized. [c] The acetonitrile solution of aryl boronic acid prior to DCDMH addition typically had a water content of 2−4% as determined by Karl Fisher titration and a pH of 4−6. [d] Major product formed: 5-chloro-2-methoxyphenylboronic acid (84%). [e] Major product formed: 5-chloro-2-methoxyphenylboronic acid (67%).

TABLE 3. Chlorination of Aryl Boronic Acids Using NCS and NCS/NaOMe[a,b]



12a - d 16a - d

entry	boronic acid	R	yield (%) (NCS)	yield (%) (NCS/NaOMe)
1	**12a**	2-F	95	61
2	**12b**	3-NO_2	<0.5	3.7
3	**12c**	H	28	22
4	**12d**	2-Me	79	63

[a] Yields were determined by HPLC analysis vs a standard prepared from commercially available authentic material. [b] Product yields have not been optimized.

chlorination of several aryl boronic acids using NCS and NCS/NaOMe was briefly investigated (Table 3). In contrast to published results, NCS affected the desired transformation in our hands.[27] While aryl chlorides **16a** and **16d** were formed in excellent yields (95% and 79%, respectively) when NCS was employed in the reaction, addition of catalytic NaOMe to these substrates actually hindered the formation of product (entries 1, 3−4). In the case of **12a** (entry 1), a >30% decrease in yield was observed when 5 mol % NaOMe was added to the reaction.[28] Observation of greater amounts of unreacted starting material under base-catalyzed conditions suggests that NaOMe had deleterious effects toward NCS.

In conclusion, an easily scaleable, reproducible synthesis of 2-bromo-3-fluorobenzonitrile from 2-cyano-6-fluorophenylboronic acid was achieved using DBDMH as the brominating reagent. Furthermore, the generality of this chemistry has been demonstrated by the clean transformation of a variety of aryl boronic acids, especially those with electron-withdrawing substituents, to the corresponding aryl bromides and aryl chlorides in good to excellent yields. Addition of a catalytic amount of NaOMe has beneficial effects on the rate and yield of the reaction in almost all of the examples studied. The data collected thus far indicates that base aids in the breakdown of less reactive trimeric boronic acid anhydrides to a more reactive monomeric form.

Acknowledgment. We thank Dr. John Limanto for insightful discussions. We also thank Dr. Peter Dormer for assistance with ^{11}B NMR data.

Supporting Information Available: Experimental procedures for the synthesis of compounds **2a**/**2b** and **3**, as well as characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035184P

(21) (a) Kuivila, H. G.; Easterbrook, E. K. *J. Am. Chem. Soc.* **1951**, *73*, 4629−4632. (b) Kuivila, H. G.; Hendrickson, A. R. *J. Am. Chem. Soc.* **1952**, *74*, 5068−5070. (c) Kuivila, H. G.; Soboczenski, E. J. *J. Am. Chem. Soc.* **1954**, *76*, 2675−2678. (d) Kuivila, H. G.; Williams, R. M. *J. Am. Chem. Soc.* **1954**, *76*, 2679−2682. (e) Kuivila, H. G.; Benjamin, L. E. *J. Am. Chem. Soc.* **1955**, *77*, 4834−4837. (f) Kuivila, H. G.; Benjamin, L. E.; Murphy, C. J.; Price, A. D.; Polevy, J. H. *J. Org. Chem.* **1962**, *27*, 825−829. (g) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(22) Addition of 5 mol % NaOMe to trimer **9b** yielded a new compound that corresponds to the mixed boronic acid/monomethyl ester as determined by ^1H and ^{13}C NMR.

(23) Of the several bases screened for the halodeboronation reaction (NaOMe, NaOtBu, NaOH, KF, KOAc, or K_3PO_4), NaOMe gave the highest yield of products **3**, **16b**, and **16c**. Interestingly, a stoichiometric amount of $B(OH)_3$ also promoted the bromodeboronation of **2a**/**2b**. Multi-kilogram quantities of **3** have been prepared using the NaOMe-catalyzed reaction.

(24) Addition of a full equivalent of NaOMe to the reaction resulted in product formation in only 43% yield.

(25) The effect of methoxide charge was also examined in the halogenation of compounds **12a**, **12b**, and **12e**. A full equivalent of methoxide (vs 5 mol %) resulted in a decrease in rate and yield of the reactions. No product was observed if these reactions were carried out in MeOH or NaOMe/MeOH.

(26) (a) Littke, A.; Dai, C.; Fu, G. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J.; Yin, J.; Buchwald, S. *J. Org. Chem.* **2000**, *65*, 1158−1174. (c) Dia, C.; Fu, G. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724. (d) LeBlond, C.; Andrews, A.; Sun, Y.; Sowa, J. R., Jr. *Org. Lett.* **2001**, *3*, 1555−1557. (e) Littke, A.; Fu, G. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000. (e) Klapars, A.; Huang, X.; Buchwald, S. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428. (f) Littke, A.; Schwarz, L.; Fu, G. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348.

(27) The bromodeboronation of compounds **12b** and **12c** with NBS and NBS/NaOMe was also examined. The desired aryl bromides were formed both in the presence and absence of base in comparable yields and in agreement to the values reported in the literature.[10d]

(28) This trend was further demonstrated by increasing the NaOMe charge to 25 mol % since 1-chloro-2-fluorobenzene was formed in only 12% yield. The reaction was aged for a total of 36 h with no further increase in product yield observed.