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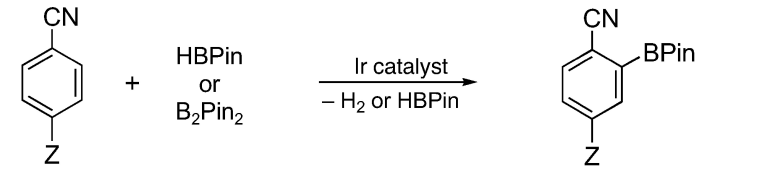

Z = Br, I, CH_3, SMe, NMe_2, CO_2Me, NHAc, CF_3

regioselectivity complements electrophilic aromatic substitutions and orthometallations

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Sterically Directed Functionalization of Aromatic C−H Bonds: Selective Borylation Ortho to Cyano Groups in Arenes and Heterocycles

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Abstract: Ir-catalyzed borylations of 4-substituted benzonitriles are described. In contrast to electrophilic aromatic substitutions and directed ortho metalations, C−H activation/borylation enables functionalization at the 2-position, adjacent to the cyano group, when the 4-subsitutent is larger than cyano. When an excess of borane reagent is used, diborylation can be achieved with a single regioisomer being formed in certain cases. Extension of sterically directed borylation to cyano-substituted, five- and six-membered ring heterocycles is also reported.

Introduction

Aromatic hydrocarbons are fundamental chemical building blocks, and their reactivity is a cornerstone of organic chemistry. Their utility derives largely from the regiochemical fidelity embodied in electrophilic aromatic substitutions.[1] While steric effects can influence electrophilic aromatic substitution, electronic effects typically dominate. For electrophilic aromatic substitution (EAS) reactions, substituents on aromatic rings fall into two classes: ortho, para directors and meta directors. When directing groups are positioned to work in concert, regioselectivity can be complete as in the classic example of nitration at the 3-postion of 4-bromobenzonitrile (Scheme 1, electronically preferred product, FG = NO_2).[2] For most disubstituted benzenes, EAS does not usually offer well-defined regiochemical outcomes. For example, two of the three possible arrangements of directing groups in 1,4-substituted benzenes give poor regioselectivity as shown in Scheme 1.

For the functionalization at positions meta to ortho, para directors and/or ortho to meta directors, alternate methods to electrophilic aromatic substitutions are required. In the case of certain meta directing substituents, directed ortho metalation (D*o*M) constitutes a powerful method for functionalization at the adjacent positions, provided that the substituent is a sufficiently strong directed metalation group (DMG).[3] For disubstituted benzenes, the regioselectivity of D*o*M depends on the positions of the substituents and their ranking in the DMG hierarchy. 1,3-Subsituted benzenes can often be derivatized selectively at the 2-position because DMGs can act in concert to direct metalation.

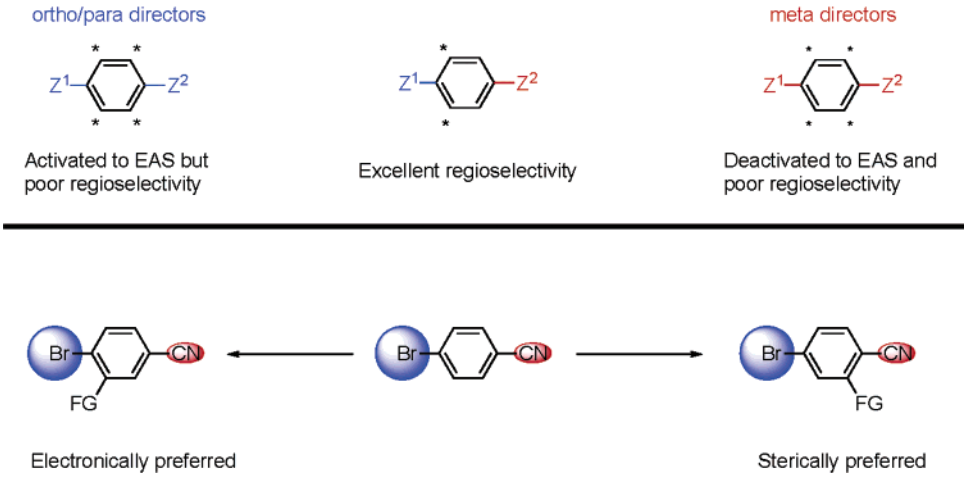
In contrast, DMGs can compete in 1,2- and 1,4-substituted benzenes. Therefore, high regioselectivities are typically realized when there is a substantial difference in relative DMG powers. For example, while D*o*M protocols can be effective for functionalizing ortho to cyano groups in simple aromatic nitriles,[4] the presence of other groups can subvert the selectivity. Sometimes the regiochemical outcome is unexpected. For instance, competitive 2,5-dilithiation of 4-bromobenzonitrile occurs with LDA[5] and deprotonation at the 3-position has been reported with the hindered phosphazene base, P_4-*t*-Bu,[6] even though the DMG ranking of CN is greater than that of Br. In fact, there are no documented transformations of 4-bromobenzonitrile that are selective for the 2-position.[7,8] Moreover, examples of functionalization at the 2-position in other 4-substituted benzonitriles are limited, and there are no general approaches toward this end.[9] This is unfortunate because aryl nitriles have a rich chemistry and are particularly useful entries into heterocyclic systems.[10]

An alternate strategy for functionalizing benzonitriles that can potentially complement electrophilic aromatic substitutions and D*o*Ms is to differentiate positions based on steric effects

(1) For an overview see: Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley and Sons: New York, 1990.
(2) Schopff, M. *Ber.* **1890**, *23*, 3435−3440.
(3) D*o*M has recently been reviewed within the context of complex induced proximity effects. See the following article and references therein: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206−2225.
(4) (a) Kristensen, J.; Lysen, M.; Vedso, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435−1437. (b) Pletnev, A. A.; Tian, Q. P.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276−9287.
(5) Lulinski, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68*, 9384−9388.
(6) Imahori, T.; Kondo, Y. *J. Am. Chem.* Soc. **2003**, *125*, 8082−8083.
(7) The deprotonation at the 2-position of 4-bromobenzonitrile is cited as an unpublished result in ref 6.
(8) Alternatively, the nitrile group could be converted to a DMG, such as an amide or ester. Subsequent D*o*M and reformation of the nitrile group could give 2-substituted nitriles.
(9) Examples include additions of hindered alkyl radicals[9a,b] and the addition of vinylsilanes to 4-$CF_3C_6H_4CN$[c]: (a) Wang, C.; Russell, G. A.; Trahanovsky, W. S. *J. Org. Chem.* **1998**, *63*, 9956−9959. (b) Kim, B. H.; Jeon, I.; Han, T. H.; Park, H. J.; Jun, Y. M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2035−2039. (c) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117−3128.
(10) (a) Meyers, A. I.; Sircar, J. C. *The Chemistry of the Cyano Group*. In *The Chemistry of the Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley & Sons: New York, 1970; Chapter 8. (b) Fatiadi, A. J. In *Supplement C: The Chemistry of the Triple-bonded Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley & Sons: New York, 1983; Chapter 26.

10.1021/ja0428309 CCC: $30.25

Scheme 1. Regiochemical Trends in Electrophilic Aromatic Substitution (EAS) for 1,4-Substituted Benzenes



(Scheme 1). Since the first report by Ittel and co-workers in 1976,[11] there have been several reports of transition metal mediated C−H activations where steric, not electronic, effects are the overriding factors in regioselection. More recently, significant progress has been made in coupling C−H activation with subsequent transformations of the nascent M−C bond to design new catalytic processes.[12] Since 1999, we[13] and others[14] have been particularly interested in utilizing Ir-catalyzed borylations of arenes to tap the unique regioselectivities available to sterically directed C−H activations. We reasoned that borylation ortho to nitrile groups should be possible for appropriate substrates since the cyano group is only slightly larger than fluoride (vide infra). Our initial attempts to borylate benzonitriles with pinacolborane (HBPin) using Ir phosphine systems at elevated temperatures gave complex mixtures due to competitive reduction of the nitrile. More active Ir catalysts developed by Hartwig, Ishiyama, and Miyaura overcome this problem. These Ir dipyridyl catalysts operate at room temperature, and examples have been reported showing that the nitrile group is compatible with the borylation conditions.[14d,e] However, data is available for only three substrates, none of which addressed our regiochemical hypothesis. Herein, we describe results for the borylations ortho to cyano groups of benzonitriles.

Results

We first examined borylations of 4-substituted benzonitriles. As most substrates were poorly soluble in saturated hydrocarbons, borylations were typically carried out in thf solvent using the catalyst constituted from a 1:2 ratio of $[Ir(OMe)(COD)]_2$ (COD = 1,5-cyclooctadiene) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) as indicated in Scheme 2. The results for monoborylation reactions are given in Table 1. The reaction times roughly correspond to relative reactivities, and yields are for isolated products with respect to the limiting reagent. Either HBPin or B_2Pin_2 can be used with shorter reaction times required for the latter reagent. Diborylation can be significant when the benzonitrile is the limiting reagent. For these substrates, a benzonitrile:borane reagent ratio of 4:1 was used to minimize diborylation.

Scheme 2

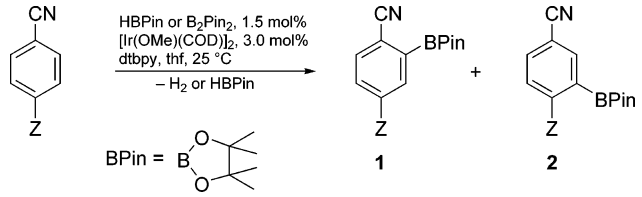


Table 1. Regioselectivities of 4-substituted Benzonitrile Borylations[a]

entry	Z	borane (equiv)	time (h)	% yield[b]	%**1**:%**2**[c]
1	F	HBPin (0.25)	8	71	11:89 (8:92)
2	Cl	HBPin (0.25)	36	76	80:20 (81:19)
3	Br	HBPin (0.25)	48	73	95:5 (97:3)
4	I	B_2Pin_2 (1.0)	40	70	>99:1 (>99:1)
5[d]	CH_3	HBPin (0.25)	72	64	94:6 (92:8)
6	OMe	HBPin (0.25)	24	65	67:33 (67:33)[e]
7[f]	SMe	B_2Pin_2 (0.25)	18	55	90:10 (87:13)[e]
8[d]	NMe_2	B_2Pin_2 (1.0)	72	58	>99:1 (>99:1)
9	CO_2Me	B_2Pin_2 (0.8)	48	65	>99:1 (>99:1)
10[g]	NHAc	B_2Pin_2 (1.6)	18	62	>99:1 (>99:1)
11[h]	CF_3	HBPin (1.1)	24	68	>99:1 (>99:1)

[a] Unless otherwise noted, all reactions were run in thf solution at 25 °C with [Ir] = 3 mol %. [b] Yields are for isolated products based on the limiting reagent. [c] The major isomer was assigned by NMR, and ratios were determined from crude reaction mixtures by GC integration. Isomer ratios for isolated products are in parentheses. [d] [Ir] = 6 mol %. [e] Isomer ratio was determined from NMR integration. [f] Reaction run at 80 °C. [g] [Ir] = 8 mol %. [h] Reaction run in *n*-hexane.

For 4-halobenzonitriles, the extent of borylation at the 3-position (isomer **2**) diminishes in the order F > Cl > Br > I. This trend is consistent with the ordering of steric energies for substituents on a benzene ring F < CN < Cl < Br < I (vide infra). However, the regioselectivities are also consistent with the thermodynamic ordering of *o*-C−H acidities is F > CN > Cl from the literature.[15] Thus, rationalization of the regiochemical outcome is shackled with the age-old dilemma of definitively

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(12) Goldberg, K. I.; Goldman, A. S. *Activation and Functionalization of C-H Bonds*; American Chemical Society: Washington, DC, 2004.
(13) (a) Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **1999**, *121*, 7696−7697. (b) Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **2000**, *122*, 12868-12869. (c) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305−308. (d) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III. *J. Am. Chem. Soc.* **2003**, *125*, 7792−7793.
(14) (a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390−391. (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056−3058. (c) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649−5651. (d) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924−2925. (e) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103−1106. (f) Mertins, K.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chem.* **2004**, *207*, 21−25.

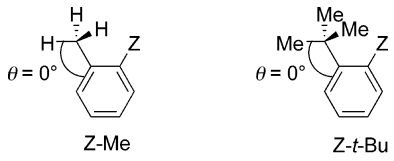
separating steric and electronic effects. Nevertheless, a compelling case can be made for steric directing effects as outlined below.

There are several approaches for evaluating steric effects.[16] Following a course recommended by Ingold,[17] Taft developed a parameter, E_s, to account for steric effects on hydrolysis and esterification rates of *o*-benzoate esters.[18] It was later shown that E_s values could be quantitatively related to van der Waals radii,[19] and values have been calculated for substituents absent in Taft's original work.[20] Dubois later revised Taft's definition, introducing the Taft−Dubois steric parameter, E'_s.[21] Despite their demonstrated utility, E_s and E'_s values are nonetheless empirical, and the database of values is still limited. Alternatively, the energy difference between equatorial and axial conformers of monosubstituted cyclohexanes (the *A* value) has been invoked as a measure of steric effects.[22] Although the equatorial site is indeed favored from a steric standpoint, cyclohexane conformational energies are not immune to electronic effects. Hence, *A* values are poor predictors of steric differences for electronically disparate substituents. For our purposes, although there is no E'_s value in the literature for CN, the E_s value that is typically quoted places CN between F and Cl, which seems reasonable.[23] Unfortunately, the value does not appear in the primary literature that is cited.[20] *A* values are of little help as the value for CN is lower than that of F,[24] and general agreement between *A* and E_s values is poor.

Calculations of steric energies have been addressed using modern computational methods. We felt that a good, albeit crude, model for our purposes was that employed by Fujita and co-workers for evaluating the steric effects in the acid-catalyzed hydrolysis of *o*-benzamides.[25] In essence, their approach involves calculating the difference in enthalpies for 2-substituted toluenes and *tert*-butylbenzenes relative respectively, to toluene and *tert*-butylbenzene, to extract steric enthalpies, denoted as $\Delta\Delta H_s(Z)$, for substituents Z, relative to that of hydrogen. For consistency, the dihedral angles for the methyl and *tert*-butyl groups were constrained as shown in Chart 1.[25a] Since CN and other substituents in Table 1 were not included in the previous report, we recalculated the series.[26] Table 2 lists these $\Delta\Delta H_s(Z)$ values along with calculated and experimental ratios of 2- and 3-borylated benzonitriles.[27]

Agreement between the calculated and experimental isomer ratios is surprisingly good. The halide data correlates best, while

Chart 1



Z-Me Z-*t*-Bu

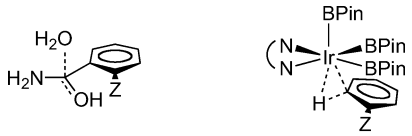
$$\Delta\Delta H_s(Z) = [\Delta H_f°(Z\text{-}t\text{-Bu}) - \Delta H_f°(H\text{-}t\text{-Bu})] - [\Delta H_f°(Z\text{-Me}) - \Delta H_f°(H\text{-Me})]$$

Table 2. Calculated Steric Enthalpies ($\Delta\Delta H_s$) for *o*-Benzene Substituents Z and Isomer Ratios for Borylation[a]

Z	$\Delta\Delta H_s$(Z) kcal·mol^{-1}	%**1**:%**2** calcd[b]	%**1**:%**2** observed[c]
H	0	−	−
CN	3.211	−	−
F	1.535	6:94	8:92
Cl	4.133	83:17	81:19
Br	5.405	98:2	97:3
I	7.759	>99:1	>99:1
CH_3	5.532	98:2	92:8
OMe	2.013	31:69	67:33[d]
SMe	3.682	66:34	87:13[d]
NMe_2	5.039	96:4	>99:1
CO_2Me	4.856	94:6	>99:1
NHAc	5.166	96:4	>99:1
CF_3	8.845	>99:1	>99:1

[a] $\Delta\Delta H_s(Z)$ values computed according to method in ref 25a. [b] Reference 26. [c] GC-FID ratios from Table 1. [d] Isomer ratio was determined by NMR integration.

Chart 2



A **B**

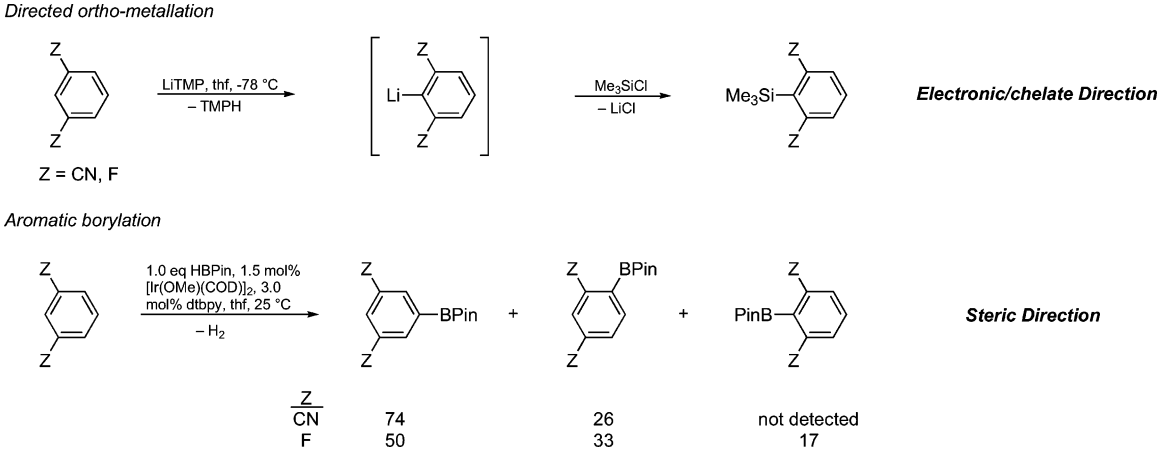
selectivities for CO_2Me, NMe_2, and NHAc substituents are better than the calculated values. To gauge whether aromatic borylation is likely to be more sensitive to steric effects, it is instructive to consider putative transition states for acid-catalyzed hydrolysis of an *o*-benzamide (**A**) and Ir-catalyzed C−H activation (**B**) in Chart 2.

First, transition state **A** more closely resembles the steric model in Chart 1 from which $\Delta\Delta H_s(Z)$ values are calculated. Moreover, transition state **B** should be more sensitive to the sterics of Z because an Ir−C bond ultimately forms ortho to Z, whereas attack by the less hindered water molecule is one carbon removed in transition state **A**.

The poorest agreement between calculated and observed isomer ratios in Table 2 is for Z = OMe, where the borylation is favored at the more hindered position. Although this could simply result from inherent deficiencies in the model, there is reason to believe electronic effects contribute to the regioselectivity. Specifically, while borylation of benzonitrile gives a nearly statistical 2.15:1 ratio of meta to para isomers, anisole borylation favors the meta isomer 4:1. After taking statistics into account, this corresponds to a 2:1 preference for meta vs para borylation.[13b] Given that CN and OMe groups are nearly

(15) Comparisons to the pK_a of benzonitrile[15b] can be made by extrapolating experimental results to estimate pK_a's for fluoro- and chlorobenzene: (a) Stratakis, M.; Wang, P. G.; Streitwieser, A. *J. Org. Chem.* **1996**, *61*, 3145−3150. (b) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155−6157.
(16) The following paper provides an excellent overview: White, D. P.; Anthony, J. C.; Oyefeso, A. O. *J. Org. Chem.* **1999**, *64*, 7707−7716.
(17) Ingold, C. K. *J. Chem. Soc.* **1932**, 1032.
(18) Taft, R. W., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 3120−3128.
(19) Charton, M. *J. Am. Chem. Soc.* **1969**, *91*, 615−618.
(20) Kutter, E.; Hansch, C. *J. Med. Chem.* **1969**, *12*, 647−52.
(21) Macphee, J. A.; Panaye, A.; Dubois, J. E. *Tetrahedron* **1978**, *34*, 3553−3562.
(22) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc*. **1955**, *77*, 5562−5578.
(23) Hansch, C.; Leo, A.; Hoekman, D. *Exploring QSAR: Hydrophobic, Electronic, and Steric Constants*; American Chemical Society: Washington, DC, 1995; p 227.
(24) Jensen, F. R.; Bushweller, C. H.; Beck, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 344−351.
(25) A model for ortho substituent steric effects that correlates strongly with hydrolysis of *o*-substituted benzamides has been reported: (a) Sotomatsu, T.; Murata, Y.; Fujita, T. *J. Comput. Chem.* **1991**, *12*, 135−138. (b) Sotomatsu, T.; Fujita, T. *J. Org. Chem.* **1989**, *54*, 4443−4448.
(26) AM1 calculations were carried out on an SGI Origin 3400 supercomputer using *SPARTAN SGI*, version 5.1.3, Wavefunction, Inc.: Irvine, CA.
(27) Because the isomer ratios reflect differences in relative rates, values were calculated using **1**:**2** = exp(−[$\pi\pi H_s$(Z) − $\pi\pi H_s$(CN)/*RT*]), *T* = values from Table 1. This should not be expected to reproduce the experimental values; however, the net trend should be reflected in the data if a steric model is appropriate.

Scheme 3

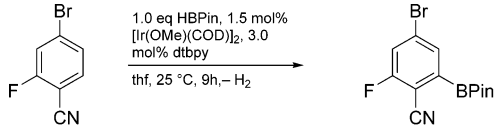


isosteric, the identical 2:1 preference for borylation meta to OMe may have electronic origins.

To strengthen what is a circumstantial case for sterics overriding electronics in borylations of 4-benzonitriles, we turned to 1,3-disubsituted CN and F benzenes, where C−H bonds flanked by 0−2 ortho hydrogens are present. Under D*o*M conditions, 1,3-dicyano and 1,3-difluorbenzene are known to react selectively at the 2-position as shown in Scheme 3.[28] If selectivities of Ir-catalyzed borylations of CN- and F-substituted arenes are sterically directed, the propensity for borylation in the 1,3-disubstituted benzenes should follow the order 5 → 4 → 2-. As indicated in Scheme 3, this is indeed the case. Furthermore, only 1,3-difluorobenzene exhibits significant borylation at the 2-position, consistent with the lower steric requirement for F relative to that for CN. Murai has invoked CN to Ru π-bonding to account for selective C−H activation ortho to CN.[29] However, from the data in Scheme 3, the borylation ortho to H vs CN is favored by a factor of 5.7 in the present system. Thus, sterically directed regioselectivity is the only satisfactory explanation for the regiochemistry in these borylations. On the basis of these results and the data in Table 2, we favor steric directing effects to account for the selectivities in Table 1.

Additional features of the reactions in Table 1 merit comment. First, the 2-borylated products for entries 2−11 are new compounds. In fact, 4-F-2-BPinC_6H_3CN is the only previously reported 2,4-benzonitrile with boron at the 2-position to the best of our knowledge.[30] Moreover, introduction of the BPin group using other methods, such as Miyaura's cross-coupling reactions of alkoxydiboron reagents and aryl halides, are inconvenient because access to the 2-halogenated compounds is extremely limited.[31] Entries 8−10 highlight the complementary nature of sterically directed borylations to D*o*M protocols, where hydrogens ortho to amine, ester, and amide groups react preferentially.[32] Thus, aromatic borylation provides the most general approach to elaborating the 2-positions of 4-substituted benzonitriles. Last, it should be noted that entries 7 and 10 are the first examples of functional group tolerance for SMe and NHAc substituents, respectively.

The regioselectivities in Table 2 are not necessarily limited to disubstituted benzenes. In addition to diborylation of 4-substituted benzonitriles (vide infra), we also note that 4-bromo-2-fluorobenzonitrile is borylated according to eq 1, affording a 5:95 ratio of 5- and 6-borylated products. This is a particularly attractive reaction because 1,2-benzisoxazoles and other heterocycles can be obtained by substitution of fluoride followed by ring-forming condensation with the cyano group.[33] Similarly, borylation of 3,4-dichlorobenzonitrile yields the 5- and 6-borylated isomers in a 20:80 ratio. For both substrates, the selectivity for borylation ortho to CN vs halide is virtually identical to that for the corresponding 4-halobenzonitriles in Table 1.



(1)

85% yield,
95% isomeric purity

To avoid diborylation, excess arene was used for several entries in Table 1. We were curious as to how efficiently the diborylated products could be formed and whether compounds with isomeric purities sufficiently high as to be synthetically useful could be obtained. The reactions were typically run in thf with a 4:1 ratio of HBPin to arene at twice the catalyst loading for monoborylation. The results are given in Table 3.

Unlike the situation for 4-bromo-2-fluorobenzonitrile and 3,4-dichlorobenzonitrile, the observed distribution of isomers is much different than a simple extrapolation of selectivities from Table 1 predicts.[34] In all cases the extent of 2,5-diborylation is significantly higher than expected, except for Z = CF_3 where borylation ortho to CF_3 is likely prohibitive. The data suggest that the BPin group has a directing role. To answer this question, we examined the regioselectivity for PhBPin borylation in thf under similar reaction conditions (eq 2). The reaction was

(28) (a) Krizan, T. D.; Martin, J. C. *J. Org. Chem.* **1982**, *47*, 2681−2682. (b) Bennetau, B.; Rajarison, F.; Dunogues, J.; Babin, P. *Tetrahedron* **1993**, *49*, 10843−10854.
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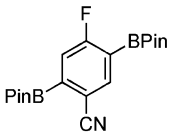
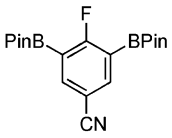
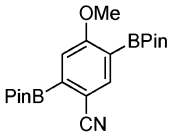
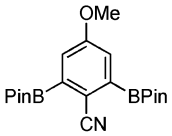
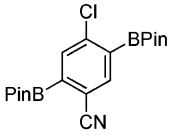
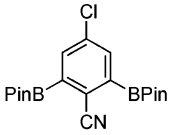
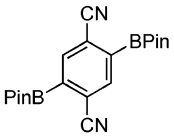
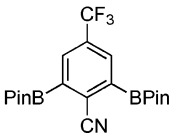
Table 3. Diborylations of 4-substituted Benzonitriles[a]

Z	%yield, time	Products[b]	
F	92, 24h	 46% (14%)	 54% (86%)
OMe	81, 48h[c]	 80% (60%)	 20% (33%)
Cl	82, 48h	 80% (44%)	 20% (54%)
CN	71, 20h[d]		
CF_3	83, 36h		

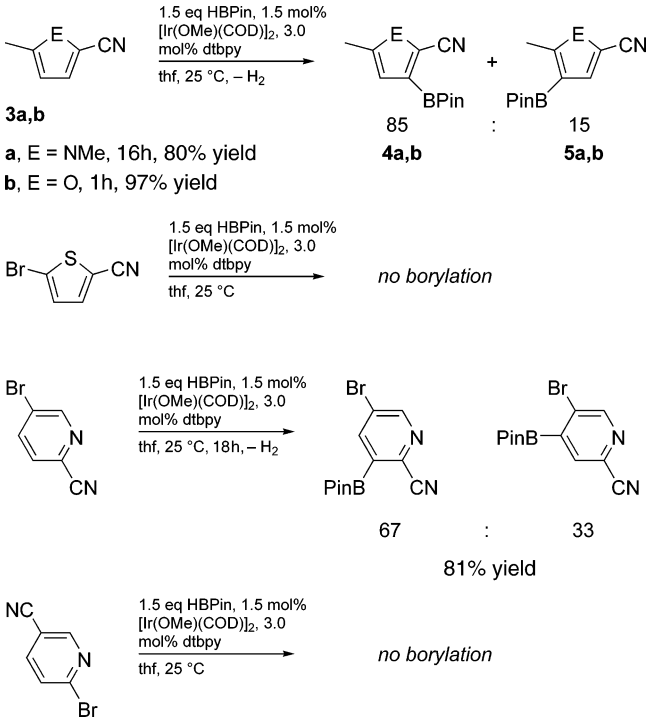
[a] Unless otherwise noted, all reactions were run in thf solution at 25 °C with 4.0 equiv of HBPin and [Ir] = 6 mol %. [b] Isomer distribution determined GC-FID. Calculated values using the selectivities in Table 1 (ref 32) are shown in parentheses. For Z = OMe and Cl, the 3,5-diborylation products are calculated respectively as 7% and 2% of the isomer mixture. [c] Reaction run at 60 °C. [d] Isolated as a single isomer after recrystallization from a 93:7 mixture of 2,5- and 2,6-borylated isomers.

examined at low conversion to avoid skewing the data by borylation of *m*-$C_6H_4(BPin)_2$.[35] The para to meta ratio is 1.8:1, significantly greater than the 1:2 statistical ratio. This translates to a 3.6:1 selectivity for para vs meta borylation after statistical corrections. While we are reluctant to speculate on the origins of this selectivity, BPin clearly has a para directing effect that

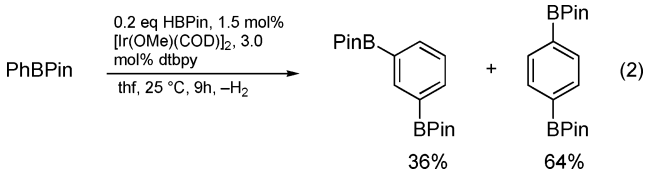
(34) Isomer distributions for diborylation where the BPin group does not affect selectivity were calculated as follows. For 4-chlorobenzonitrile, borylation ortho to CN vs Cl is favored by a factor of 4, giving the 2-borylated isomer as the major product. In the second borylation, selectivity ortho to CN is lowered by half because there are two H's ortho to Cl and only one H ortho to CN in the monoborylated product. Applying analogous arguments to the other monoborylated isomer, the percentages of 2,6-, 2,5-, and 3,5-diborylated isomers can be calculated as 54, 44, and 2%, respectively. Isomer ratios for the other substrates in Table 3 were calculated similarly.

(35) The experiment in eq 2 was performed through the reaction of benzene with 1.2 equiv of HBPin in thf in the presence of Ir catalyst. The first equivalent of borane generates PhBPin in situ, and the remaining 0.2 equiv gives the diborylated isomers.

Scheme 4



likely contributes to the regioselectivities in Table 3. Last, it should be noted that single isomers of diborylated products can readily be obtained for Z = CN, or CF_3.



We have also examined a limited number of heteroaromatic compounds to assess whether the regioselectivities found for arenes will translate to other substrates (Scheme 4). Borylation of 1,5-dimethyl-2-pyrrolecarbonitrile (**3a**) gives an 85:15 ratio of the regioisomers **4a** and **5a** with the major isomer **4a** arising from borylation adjacent to the cyano group. Similarly, 5-methyl-2-furonitrile (**3b**) borylates predominantly at the 3-position to also give an 85:15 ratio of borylated isomers **4b** and **5b**. Borylation of 2-bromo-5-cyanothiophene was unsuccessful. Since the steric interactions between adjacent positions diminish as aromatic rings contract, the decline in selectivity for the five-membered heterocycles is not surprising. Two isomeric cyanopyridines were also examined. 5-Bromo-2-cyanopyridine undergoes borylation to afford an isomer mixture. While borylation ortho to CN accounts for the major product, the degree of borylation ortho to Br is substantially higher than that found for 4-bromobenzonitrile. Somewhat surprisingly, 2-bromo-5-cyanopyridine gave no borylation products. Since halogen-substituted aromatic heterocycles tend to be more reactive than their carbocyclic counterparts, side reactions that deactivate catalytically active species are more likely.

Conclusions

In summary, the steric directing effects that govern the regioselectivities in Ir-catalyzed borylations of aromatic and

heteroaromatic compounds enable functionalization of C−H bonds adjacent to cyano groups, when these positions are the least hindered sites in the substrate. The regioselectivities for borylations complement those found in electrophilic aromatic substitutions and D*o*Ms, and several relatively simple borylated products have been prepared for the first time. Diborylations of 4-substituted benzonitriles favor para-disposed BPin groups when borylation at the 5-position is possible. While it appears that similar trends in regioselectivities can be extended to borylations of heteroaromatic nitriles, the substrate scope is narrower and the regioselectivity is poorer than for carbocyclic aromatic substrates. We are currently focusing on improving regioselectivities by modifying the Ir ligands, as well as sterically differentiating other aromatic substituents.

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Supporting Information Available: Spectral data for all new compounds pictured, as well as general experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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