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One-Pot Synthesis of Arylboronic Acids and Aryl Trifluoroborates by Ir-Catalyzed Borylation of Arenes

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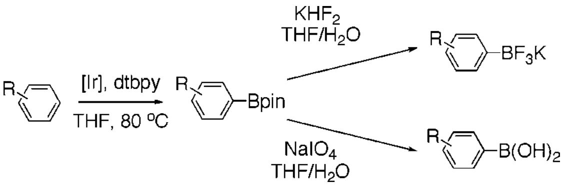
ABSTRACT



The synthesis of arylboronic acids and aryl trifluoroborates in a one-pot sequence by Ir-catalyzed borylation of arenes is reported. To prepare the arylboronic acids, the Ir-catalyzed borylation is followed by oxidative cleavage of the boronic ester with $NaIO_4$. To prepare the aryltrifluoroborate, the Ir-catalyzed borylation is followed by displacement of pinacol by KHF_2. These two-step sequences give products that are more reactive toward subsequent chemistry than the initially formed pinacol boronates.

The chemistry of arylboronic acids and aryltrifluoroborates[1−3] has been developed extensively in the past decade. These reagents are air-stable solids that can be stored for long periods of time without decomposition.[4,5] These reagents undergo a variety of catalyzed and uncatalyzed processes. In addition to the extensive use of arylboronic acids in the Suzuki−Miyaura cross-coupling reaction, these reagents undergo halogenations, oxidative aminations, metal-catalyzed additions to imines and iminium ions, metal-catalyzed 1,2- and 1,4-additions to aldehydes and olefins, and copper-mediated couplings with phenols and amines.[6,7]

Aryl trifluoroborates have been studied as alternatives to boronic acids.[7,8] These reagents[8,9] have been used in palladium-catalyzed cross coupling reactions,[10] rhodium-catalyzed 1,2- and 1,4-additions,[5] and copper-catalyzed couplings with phenols to form diaryl ethers.[7,11] The stability of organotrifluoroborates allows substrate elaboration to precede coupling or addition reactions.[8] In many cases, both boronic acids and trifluoroborates have been shown to be more reactive than boronic esters.

The conventional method for the synthesis of arylboronic acids involves the use of Grignard or organolithium reagents and starts from aryl halides.[1] Addition of the metalated arene to a trialkylborate $B(OR)_3$, followed by hydrolysis of the boronic ester, generates the arylboronic acid. Arylboronic acids have also been prepared by palladium-catalyzed coupling of an aryl halide or triflate with a boron reagent, such as $B_2(OR)_2$ or $HB(OR)_2$, followed by hydrolysis of the

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boronic ester to the boronic acid.[12] The corresponding trifluoroborates have been synthesized by treating the arylboronic acid or the arylboronic ester with potassium hydrogen difluoride.[13] Aryltrifluoroborates can also be synthesized in a one-pot fashion by lithiation of an aryl halide, followed by trapping with a trialkylborate and addition of an aqueous KHF_2 solution.[5]

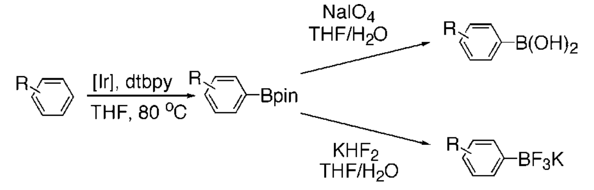
Although these routes to arylboronic acids and aryl trifluoroborates have been used many times, they have several limitations. First, the use of organometallic intermediates can limit the tolerance toward functional groups. Second, the synthesis is limited by the substitution patterns of haloarenes. This substitution pattern is typically controlled by the regioselectivity of electrophilic aromatic substitution. Thus, few 3,5-disubstituted boronic acids are commercially available.

We have studied the direct, catalytic functionalization of C−H bonds to form boronate esters.[14] With Ishiyama and Miyaura, we have published the most active catalysts for the conversion of arenes to arylboronic esters.[15−17] This catalyst, herein called the IMH catalyst, is based on the combination of $[Ir(COD)(OMe)]_2$ and di-*tert*-butylbipyridine (dtbpy), and it catalyzes the borylation of both electron-rich and electron-deficient arenes and heteroarenes with bispinacolatodiboron (B_2pin_2) as the boron source. Smith has published catalysts containing bisphosphine ligands that operate at higher temperatures.[18] The C−H borylation processes with both catalysts tolerate a variety of functional groups, such as alkoxides, nitriles, esters, and halogens, and the regioselectivity of the borylation processes complements that of electrophilic substitutions. The regioselectivity of the arene borylation is largely determined by steric factors rather than by the electron distribution in the arene.[15,19]

Unfortunately, the C−H borylation processes have required the use of pinacol-substituted boron reagents and form pinacol-substituted boronic esters. These products are convenient to handle, but they are often less reactive than boronic acids or trifluoroborates in the transformations described in the first paragraph.[7,20] This lower reactivity results, in part, from the unfavorable hydrolysis of the pinacolboronates to boronic acids.

Thus, a convenient method to directly convert the arenes to arylboronic acids or to aryltrifluoroborates would enhance the utility of this C−H activation chemistry. We report a one-pot method to convert arenes to arylboronic acids and a similar one-pot method to convert arenes to aryl trifluoroborates (Scheme 1). These transformations occur by C−H bond activation with pinacolboronates, followed by conversion of the esters to acids and trifluoroborates in situ using aqueous sodium periodate and potassium hydrogen difluoride, respectively.

Scheme 1



To develop a route to arylboronic acids by C−H activation of arenes, it was necessary to find a method that would convert the arylboronic esters to arylboronic acids in the presence of the iridium catalyst and in the solvent of the catalytic process. Arylboronic esters have been shown to be converted to the arylboronic acids by an oxidative cleavage of the pinacol group by $NaIO_4$.[21] This oxidative process drives the equilibrium for hydrolysis to the boronic acid by oxidation of the pinacol to acetone, and this oxidant does not convert the boronic acid to the corresponding phenol. Thus, a protocol based on this conversion of the pinacol ester to the acid should involve a C−H activation step with low loadings of iridium and a solvent that is both inert to the C−H activation chemistry and suitable for the oxidation step. Because the arene borylations are known to be efficient in THF,[19] we tested this medium for the hydrolysis of pinacolatoboronic esters.

The compatibility of the oxidation and C−H activation methods to the remaining iridium catalyst and the THF medium was first tested using crude arylboronic esters produced by arene borylation in the presence of the IMH catalyst and evaporation of all of the THF solvent. The crude arylboronic esters were subjected to the oxidative hydrolysis procedure with $NaIO_4$ as oxidant in a 4:1 mixture of THF/H_2O. The boronic acids were isolated after the reaction by addition of aqueous HCl solution and extraction of the boronic acid into ethyl acetate. As shown in Table 1, the conversion of the crude boronic ester to the acid occurs with systems containing electron-rich and electron-poor aryl

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(12) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447. (c) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813. (d) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458. (e) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164. (f) Euzenat, L.; Horhant, D.; Ribourdouille, Y.; Duriez, C.; Alcaraz, G.; Vaultier, M. *Chem. Commun.* **2003**, 2280.

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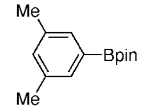
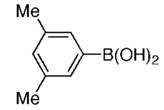
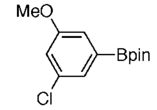
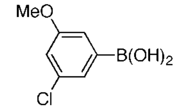
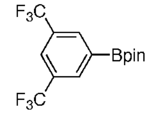
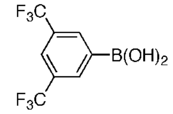
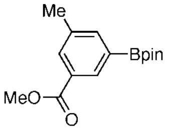
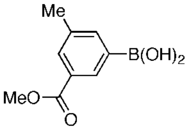
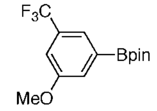
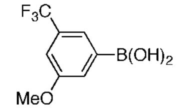
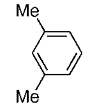
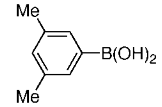
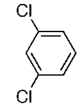
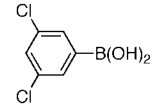
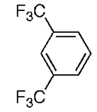
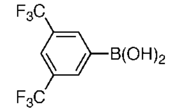
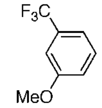
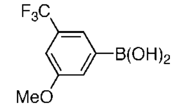
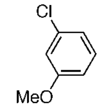
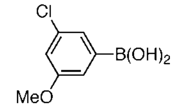
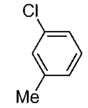
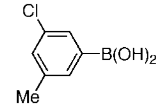
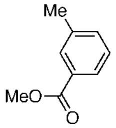
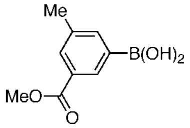
(21) (a) Falck, J. R.; Bondlela, M.; Venkataraman, S. K.; Srinivas, D. *J. Org. Chem.* **2001**, *66*, 7148. (b) Coutts, S. J.; Adams, J.; Krolikowski, D.; Snow, R. J. *Tetrahedron Lett.* **1994**, *35*, 5109.

Table 1. Conversion of Crude, Isolated Arylboronic Esters to Arylboronic Acids by Aqueous $NaIO_4$[a]

entry	arene	product	%yield[b]
1			66%
2			77%
3			93%
4			81%
5			84%

[a] The arylboronic esters were generated by borylation of arene on a 10 mmol scale using 0.1% $[Ir(COD)(OMe)]_2$ and 0.2% dtbpy in THF at 80 °C. $NaIO_4$ (15.0 mmol) was added to 5 mmol of crude ArBpin in a 4:1 THF/H_2O mixture. [b] Isolated yield.

Table 2. Conversion of Arenes to Arylboronic Acids by C−H Borylation and Oxidative Hydrolysis[a]

entry	arene	product	%yield[b]
1			54%
2			94%
3			81%
4			85%
5			90%
6			89%
7			85%

[a] Borylation of arene was carried out on a 10 mmol scale using 0.1% $[Ir(COD)(OMe)]_2$ and 0.2% dtbpy in THF at 80 °C. $NaIO_4$ (15.0 mmol) was added to 5 mmol of crude ArBpin in a 4:1 THF/H_2O mixture. [b] Isolated yields on a 5 mmol scale of arene. Yields are the average of two reactions.

groups. Moreover, the method tolerates functional groups, such as esters.

The compatibility of the oxidative hydrolysis with residual iridium and a THF/water medium made it feasible to develop a one-pot protocol for the conversions of arenes to arylboronic acids without the need to remove solvent. This sequence was evaluated starting directly with the arene. The catalytic functionalization of the arene was conducted with only 0.2 mol % of the combination of $[Ir(COD)(OMe)]_2$ and dtbpy as catalyst and B_2pin_2 as reagent in THF solvent. Commercial arenes were used as received. The resulting mixture was then diluted with water, and $NaIO_4$ was added. After addition of HCl and extraction into EtOAc, the crude product was isolated. Although more than one catalyst for the borylation of arenes has been reported,[14,15,22] we note that the IMH catalyst used in this work allows the C−H activation to be conducted in an inert solvent, under mild conditions, with low loadings of iridium.[23]

A series of examples of this one-pot protocol is shown in Table 2. The products of these reactions were isolated by simply washing the crude boronic acids with hexanes. This procedure provided products that were judged to be pure by ^1H NMR spectroscopy. As shown in Table 2, the desired arylboronic acids were isolated in excellent yields in most cases. In particular, 3,5-disubstituted arylboronic acids were selectively synthesized from the corresponding meta-substituted arene, in most cases in high yields. This methodology encompassed arenes containing ester and halogen functional groups.

The major limitation of this protocol is the incompatibility of the oxidative hydrolysis to electron-rich heteroarylboronate esters. For example, attempts to conduct the oxidative hydrolysis of the C−H borylation products from furan, thiazole, *N*-methylimidazole, and 2,6-dimethylpyridine led to dark reaction solutions containing mixtures of products, as determined by ^1H NMR spectroscopy. Because of this limitation, we also sought a nonoxidative method to convert arylboronic esters into organoboron reagents that are more reactive than the esters.

To this end, we studied a one-pot preparation of aryl trifluoroborates from arenes. Vedejs reported the conversion of arylboronic acids to the corresponding potassium aryltrifluoroborates by reaction of the esters with KHF_2 in a 5:1 mixture of MeOH and H_2O.[13] A similar reaction of pinacol boronic esters with KHF_2 in a mixture of THF and H_2O

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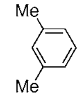
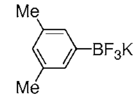
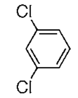
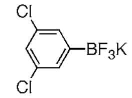
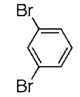
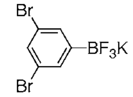
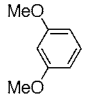
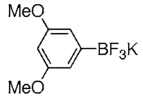
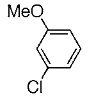
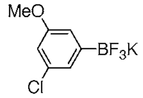
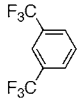
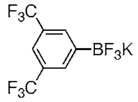
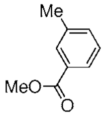
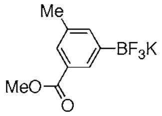
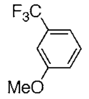
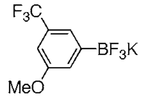
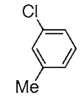
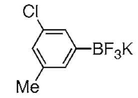
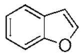
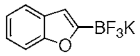
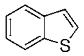
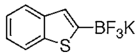
(23) For examples of reactions in neat arene conducted with 0.003 mol % and 0.02 mol % Ir, see refs 17 and 18, respectively.

Table 3. Conversion of Arenes to Potassium Aryltrifluoroborates by C−H Borylation and Displacement of Pinacol by Fluoride[a]

entry	arene	product	%yield[b]
1			61%
2			97%
3			97%
4			93%
5			94%
6			82%
7			75%
8			85%
9			97%
10			78%
11			45%

[a] Borylation of arene was carried out on a 10 mmol scale using 0.1% $[Ir(COD)(OMe)]_2$ and 0.2% dtbpy in THF at 80 °C. KHF_2 (5.7 mmol) was added to 5 mmol of crude ArBpin in a 4:1 THF/H_2O mixture. [b] Isolated yields on a 5 mmol scale of arene.

would allow a one-pot synthesis of the aryl trifluoroborate. However, conversion of a stable aryl pinacolboronate ester to the trifluoroborate was not known.[24]

To test if the pinacolate group would be displaced to form a trifluoroborate in a mixture of THF and water, we treated a solution of PhBpin in THF with an aqueous solution of KHF_2. Complete conversion to the $PhBF_3$ anion was observed, as determined by ^{11}B NMR spectroscopy.

With these data in hand, we combined the borylation of the arene in THF catalyzed by the $[Ir(COD)(OMe)]_2$/dtbpy system with conversion of the arylboronic ester to the corresponding trifluoroborate with 6 equiv of KHF_2 in a 1:3 mixture of H_2O and THF. Removal of the solvent under vacuum, extraction into acetone, and evaporation of the acetone gave a mixture of pinacol and the desired aryltrifluoroborate product.

It was difficult to find one solvent system that would separate the pinacol byproduct from the aryltrifluoroborates. The aryl trifluoroborates are typically purified by recrystallization from acetonitrile or mixtures of acetone and hexanes.[13] However, some of the pinacol crystallized together with the trifluoroborate from these media. Although solvents that separated the two materials could be found, the identity of the solvent depended on the identity of the aryltrifluoroborate. A more general procedure involved sublimation of the pinacol from the crude mixture at 60 °C, and the products from studies on reaction scope were isolated by this method.

The scope of this synthesis of aryl trifluoroborates from arenes by C−H borylation and conversion of the ester to the resulting trifluoroborate is summarized in Table 3. Like our studies on the reactions to form arylboronic acids, our studies on the reactions to form trifluoroborates focused on the synthesis of 3,5-disubstituted products that are lengthy to generate by classical methods. The reactions occurred with the more electron-rich and electron-poor meta-substituted arenes. Like the reactions to form arylboronic acids, they tolerated the presence of halogens on the arene and occurred in high yield with an arene bearing a carbethoxy group.

Because of the absence of any oxidant in the conversion of the boronic esters to the trifluoroborates, this protocol also allowed for the synthesis of heteroaryl trifluoroborates. As shown in entries **10** and **11**, the reaction of benzofuran and benzothiophene selectively formed the 2-substituted heteroaryl trifluoroborates in good to excellent yield.

To summarize, a synthesis of arylboronic acids and potassium aryltrifluoroborates starting from arenes has been developed. This one-pot methodology alleviates the need to initiate the synthesis of boronic acids from halogenated arenes and to use Grignard or organolithium reagents. Moreover, this sequence generates boronic acids with substitution patterns that complement the types of substitution patterns that can be generated from the sequence beginning with the haloarenes. The commercial availability of $[Ir(COD)(OMe)]_2$, dtbpy, and a large number of arenes allows for easy access to a wide range of new arylboronic acids and trifluoroborates.

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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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(24) For an example starting with a different type of boronic ester, see: Matteson, D. S.; Kim, G. Y. *Org. Lett.* **2002**, *4*, 2153.