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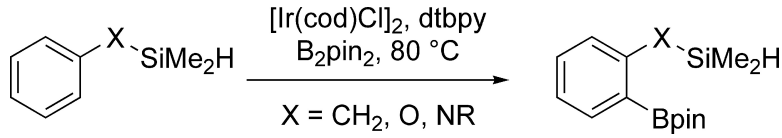

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Silyl-Directed, Iridium-Catalyzed *ortho*-Borylation of Arenes. A One-Pot *ortho*-Borylation of Phenols, Arylamines, and Alkylarenes

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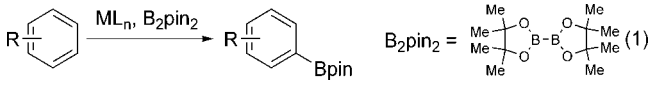
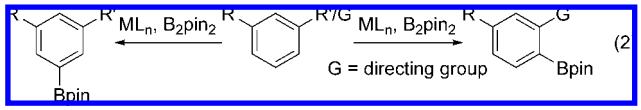
Arylboron reagents are versatile synthetic intermediates in chemical synthesis.[1] The traditional route to these reagents involves the addition of organolithium or magnesium species to borates. More recently, a direct route to arylboronic esters from arenes has been developed using metal-catalyzed functionalization of aromatic C−H bonds with bis(pinacolato)diboron (B_2pin_2) (eq 1).[2] The most efficient catalyst for this transformation is generated from 4,4′-di-*tert*-butylbipyridine (dtbpy), $[Ir(cod)X]_2$ (X = Cl, OMe), and the boron reagents.[3–5]



(1)

The regioselectivity of this catalytic C−H borylation of arenes has typically been governed by steric factors; functionalization occurs at the least hindered aryl C−H bond, not at the most electron-rich or electron-poor C−H bond. Thus, the functionalization of 1,3-disubstituted arenes leads to 1,3,5-trisubstituted products (eq 2, left), and *ortho*-substituted boronic esters are usually formed only from 1,4-disubstituted arenes.[6] The *ortho*-substituted boronic esters can be produced using directed *ortho*-metalation with organolithium reagents,[7] but a direct, *ortho*-borylation of C−H bonds could be a milder synthetic method. Such a process would require strategies to override the underlying steric control of regioselectivity (eq 2, right).



(2)

We describe a method to conduct *ortho*-C−H borylation that makes use of a new directing group for *ortho*-functionalization, a dimethylhydrosilyl group. By this method, arenes undergo iridium-catalyzed borylation at the C−H bond *ortho* to a hydrosilylmethyl, siloxide, or silylamine substituent. Using the formation of siloxides and silylamines from phenols and amines, we have developed this reaction into a one-pot directed borylation of free phenols and *N*-alkylanilines.

These studies began with consideration of reaction sequences in which a hydrosilyl group would direct *ortho*-functionalization. In one sequence, a hydrosilyl group could undergo borylation to form a silylborane, and this event could trigger an intramolecular borylation of the arene. In a second sequence, a silyl group could serve as a temporary attachment to the metal that would trigger cleavage of the *ortho*-C−H bond[8] and subsequent functionalization.

Initial studies to use a hydrosilyl moiety to direct arene borylation are summarized in eqs 3 and 4. The reaction of phenyldimethylsilane (**1**) with B_2pin_2 and pinacolborane (HBpin)[9] in the presence of the combination of $[Ir(cod)Cl]_2$ and dtbpy as ligand at 80 °C in THF solvent (eq 3) formed a series of products, some resulting from redistribution of the arylsilane.[10] However, reactions of aromatic hydrosilanes lacking a direct aryl−Si bond occurred in higher yields (eq 4). Benzyldimethylsilane (**2**) reacted with B_2pin_2 in the presence of 0.25 mol % of $[Ir(COD)Cl]_2$ and 0.5 mol % of dtbpy to form a 2.3:1 mixture of mono- and di-*ortho*-functionalized arylboronic esters

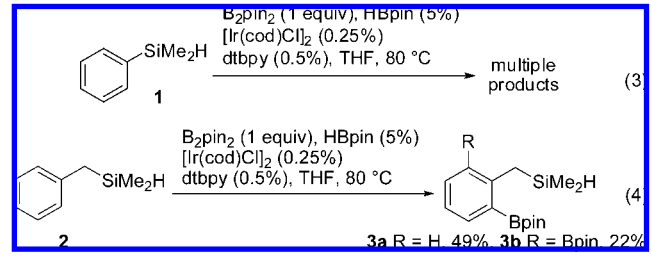
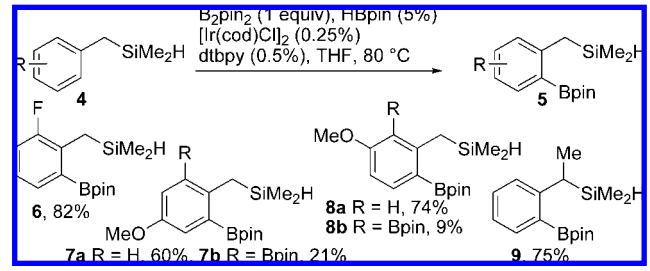


Chart 1. Regioselective Borylation of Benzylic Hydrosilanes



(**3**) in a combined 71% isolated yield. No accompanying products resulting from C−H borylation at the *meta*- or *para*-positions of **3** were detected by ^1H NMR spectroscopy.

Chart 1 summarizes the reactions of several hydrodimethylbenzylsilanes. Reactions of 2-, 3-, and 4-substituted arenes (**4**) provided *ortho*-functionalized products (**5**). Reactions of the methoxy-substituted arenes show the dominance of the silylmethyl group over the methoxy group as an *ortho*-director for this catalytic process. This directing effect of the silylmethyl group contrasts with the strong directing effect of an alkoxo group toward *ortho*-lithiations.[11] In addition, an α-silylethylarene formed the *ortho*-borylated product in good yield, and this reaction was more selective for monoborylation than the reaction of the benzyl dimethylhydrosilane.

Although benzylsilanes can be cleaved with fluoride to form methylarenes,[12] or oxidized to form aryl alcohols,[13] methods to use more readily cleavable silicon linkers would be valuable. Thus, we studied reactions of aryl hydrosilyl ethers derived from phenols. Treatment of an aryl alcohol (**10**) with 1.5 equiv of diethylsilane (Et_2SiH_2) in the presence of 0.5 mol % of $[Ir(cod)Cl]_2$ as catalyst in hydrocarbon solvent formed the silyl ether **11** and H_2 (Chart 2).[14] After evaporation of the volatile materials and dissolution of the residue in THF in the same pot, addition of the boron reagents and the combination of $[Ir(cod)Cl]_2$ and dtbpy as catalyst led to the product of *ortho*-borylation (**12**).[15,16]

Purification of the initial products was complicated by facile protodeborylation, but treatment of the crude product with excess aqueous potassium hydrogen fluoride (KHF_2) formed the more stable, isolable trifluoroborate salt **13**.[17,18] Using this procedure, borylation of both electron-rich and electron-poor phenols formed the *ortho*-trifluoroborylated aryl alcohols in Chart 2.

This strategy was also followed to effect a similar one-pot, regioselective functionalization of anilines. Dehydrogenative coupling

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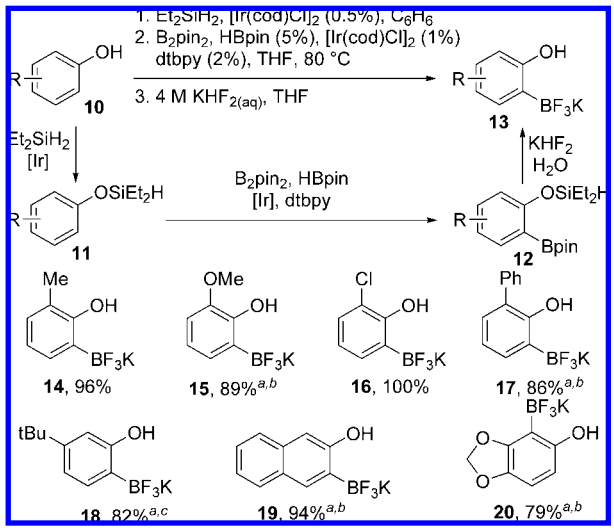
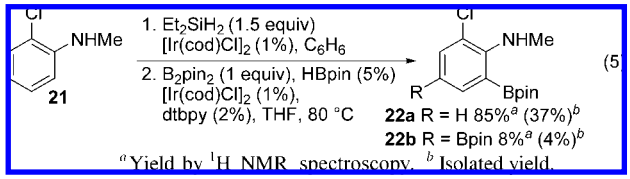
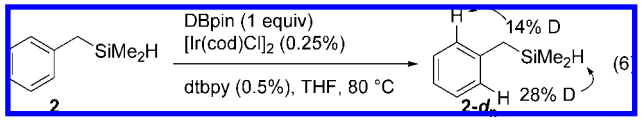
Chart 2. One-Pot *ortho*-Borylation of Phenols[a]



[a] Yields corrected for the presence of small quantities of KBF_4 and $K[HOBF_3]$ contaminants in isolated products. [b] Isolated with 2−5% contaminants. [c] Isolated with 12% contaminants.

of diethylsilane with *N*-methyl-2-chloroaniline (**21**, eq 5) catalyzed by $[Ir(cod)Cl]_2$, followed by reaction of the silylamine with B_2pin_2 catalyzed by $[Ir(cod)Cl]_2$, and dtbpy formed the *ortho*-borylated aniline **22a** in high yield. A small amount of diborylated product (**22b**) was also formed.

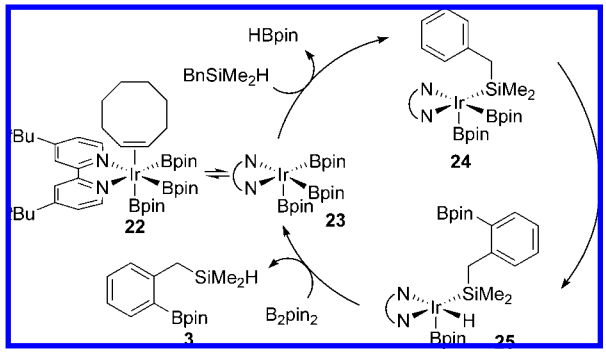




Two sets of experiments imply that the *ortho*-functionalization results from temporary formation of an Ir−Si bond, rather than formation of a silylborane. First, the silylborane $BnMe_2SiBpin$ was not kinetically competent to be an intermediate in the *ortho*-borylation. $BnMe_2SiBpin$ reacted in the presence of $[Ir(cod)Cl]_2$/dtbpy and B_2pin_2 to form an *ortho*-borylarene more slowly than the reaction of **2** under the same conditions.

Second, H/D exchange indicated selective cleavage of the *ortho*-C−H bonds. Benzyldimethylsilane (**2**, eq 6) was treated with DBpin in the presence of $[Ir(cod)Cl]_2$ and dtbpy and heated in a sealed vessel at 80 °C for 20 min in THF. Subsequent ^1H and ^2H NMR spectroscopic analysis of the recovered hydrosilane **2-d_n** indicated the absence of deuterium at the *meta*- or *para*-position during the time in which 14% deuterium incorporation had occurred at the *ortho*-C−H bonds and 28% deuterium incorporation had occurred into the Si−H bond.[19] Thus, we conclude that the *ortho*-substituted product results from selective C−H activation at the *ortho*-position directed by the hydrosilyl group, rather than selective functionalization of product of *ortho*-C−H bond cleavage by a silylborane moiety.

Scheme 1



Scheme 1 shows a proposed mechanism for the *ortho*-borylation that is based on our previous demonstration of the intermediacy of the trisboryl complex **22** in arene borylation. We suggest that the *ortho*-borylation occurs by generation of the bisboryl monosilyl complex **24**, followed by selective *ortho*-C−H bond activation[8] and functionalization to give hydride complex **25** (Scheme 1).[20] Subsequent addition of B_2pin_2 would then extrude the arylboronic ester (**3**) and regenerate the iridium fragment **23**.

In conclusion, we have demonstrated a method to conduct iridium-catalyzed *ortho*-borylation of arenes using a conceptually novel approach based on hydrosilanes as directing groups. This concept has been applied to the development of regioselective functionalization of benzylic silanes, phenols, and anilines. Future studies will exploit this strategy to effect additional regioselective hydrocarbon borylations and related functionalizations.

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Supporting Information Available: Reaction procedures and spectroscopic details for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Substrates containing a single atom between silicon and the arene proved to be more reactive than those with longer linkers. The silyl ether formed from benzyl alcohol did not undergo a similar *ortho*-borylation.
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(18) Despite the enhanced stability of these salts, purification was frequently complicated by the presence of small quantities of KBF_4 and $K[HOBF_3]$.
(19) In contrast, the iridium-catalyzed reaction of toluene-d_8 with HBpin results in non-selective H/D exchange. See Supporting Information.
(20) (a) This C−H bond activation and C−B bond formation could occur by oxidative addition and reduction or by σ bond metathesis. For calculations on an oxidative addition pathway, see: Tamura, H.; Yamazaki, H.; Sato, H.; Sakaki, S. *J. Am. Chem. Soc.* **2003**, *125*, 16114. For evidence of σ bond metathesis in related C−H borylations, see: (b) Webster, C. E.; Fan, Y.; Hall, M. B.; Kunz, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 858. (c) Hartwig, J. F.; Cook, K. S.; Hapke, M.; Incarvito, C. D.; Fan, Y.; Webster, C. E.; Hall, M. B. *J. Am. Chem. Soc.* **2005**, *127*, 2538.

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