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P-Directed Borylation of Phenols

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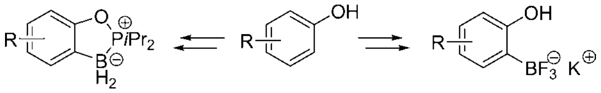
ABSTRACT



Internal borylation occurs upon activation of aryl di-isopropylphosphinite boranes with HNTf$_2$ to give heterocyclic intermediates that can be reductively quenched to afford 6 or treated with KHF$_2$ to give the phenolic potassium aryl trifluoroborate salts 10. The latter salts are useful for Pd-catalyzed coupling with aryl iodides under Molander conditions, provided that precautions are taken to remove the KNTf$_2$ byproduct from the preceding KHF$_2$ step.

Arylboron derivatives are valuable intermediates in organic synthesis due to their important potential for C–C bond formation.[1] Simple arylboronic acid derivatives are usually prepared by treating an arylmagnesium or -lithium reagent with $(RO)_3B$ (R = Me, *i*Pr)[2] or by the reaction of electrophilic boranes with electron-rich arenes.[3] In the case of the highly electrophilic BCl$_3$, modified Friedel–Crafts procedures are effective using aluminum metal (Muetterties borylation)[3b,c] or a carefully selected amine additive[3d] to scavenge the HCl byproduct and to help generate reactive electrophilic intermediates *in situ*. Recently, transition metal catalyzed borylation procedures have also become important.[4] These methods are sensitive to steric effects or internal complexation effects and often allow efficient borylation with complementary regioselectivity compared to the electrophilic borylations.

Intramolecular adaptations of Muetterties borylation directed by tethered heteroatom substituents have long been known, including interesting cases of nitrogen- or oxygen-directed borylation.[5,6] Surprisingly, examples of this chemistry have been reported over a very broad range of temperatures (ranging from 0[5f] to 200 °C[5a]). We became intrigued by this variation in borylation conditions and suspected that the difference between facile and difficult borylations may reflect differences in reagents and activation procedures that influence the relative ease of borenium cation formation.[7] Accordingly, a program was initiated in our laboratory to investigate heteroatom-directed borylation under conditions expected to promote the generation of tethered borenium cations as potential borylation intermediates. We have already reported relevant *N*-directed borylations[8]

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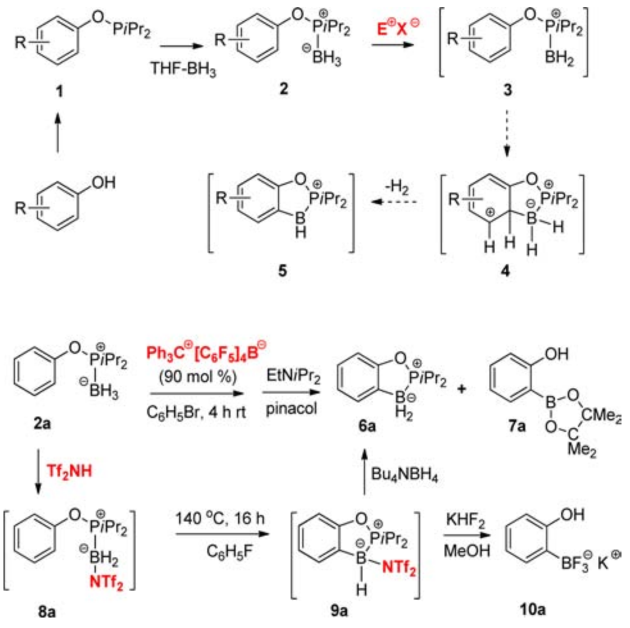
and now describe key features of an analogous P-directed borylation from phosphinite boranes. This approach allows the net conversion of suitable phenols into *ortho*-borylated products using the inexpensive THF−borane as the boron source. The same net conversion has recently been reported by Hartwig et al. using iridium catalysis and bis-pinacolatodiboron as the boron source.[4c]

Our initial experiments followed the *N*-directed borylation analogy[8] but replaced the benzylic amine borane substrates with the isosteric phosphinite boranes **2**, readily available from the corresponding phenols and commercial ClP(iPr)$_2$/Et$_3$N via the precedented di-isopropyl arylphosphinites **1**.[9] Without isolation, crude **1** were treated with excess THF−BH$_3$ to afford **2** in a one-pot procedure (typically 78−95% overall after chromatography). For the subsequent activation and intramolecular borylation, the benzylamine analogy suggested that typical hydride acceptors E$^+$ might generate transient borenium cations **3** or equivalent electrophilic species.[7] Electrophilic cyclization might then give a transient intermediate **4**, and loss of hydrogen should afford the stabilized borenium cation **5**. Indeed, activation of the simplest example **2a** using 90 mol % of the trityl salt Ph$_3$C$^+$(C$_6$F$_5$)$_4$B$^-$ in bromobenzene, the conditions previously developed for generation of borenium cation equivalents in our *N*-directed borylations,[8] resulted in partial conversion of the substrate at rt according to the ^{1}H NMR assay of the aromatic region. However, attempts to detect the presumed intermediate borenium cation **3a** or the hypothetical cationic product of electrophilic borylation **5a** were inconclusive. Attempted derivatization of the borylation products with pinacol/Hünig's base gave variable mixtures of the isolable neutral complex **6a** as well as a second product that could not be purified. The latter product was tentatively assigned as the expected pinacol ester **7a** based on ^{1}H NMR data of the product mixture, the recovery of small amounts of catechol after exposure of crude **7a** to air, and the formation of a deeply colored insoluble byproduct from attempts to separate **7a** via extraction with aqueous base.[10] These initial studies encountered significant material losses apparently due to partial decomposition of **6a** as well as **7a**, but subsequent experiments demonstrated that **6a** is quite stable when prepared using an optimized borylation procedure.

Activation of **3** with other electrophiles gave no borylation products at rt. However, treatment with 60 mol % of molecular iodine at 100 °C in bromobenzene for 24 h followed by quenching with Bu$_4$NBH$_4$ returned sufficient **6a** for NMR detection at ca. 5% conversion of **3**. A similar experiment with 1.1 equiv of TfOH as the activating electrophile gave only traces of the borylation product **6a** after 24 h in bromobenzene at 100 °C, but Tf$_2$NH under the same conditions gave better conversion (50−60% by NMR assay). A small improvement (to 60−70% conversion) was observed when the amount of Tf$_2$NH was limited to 90 mol %, and this procedure also gave a cleaner product. Similar results were obtained in *o*-dichlorobenzene, but the reaction was somewhat slower in toluene (30−35% conversion after 24 h). After further optimization, consistently good yields of the boryation product **6a** were obtained with 90 mol % of Tf$_2$NH in fluorobenzene using a thick-walled Schlenk tube at 140 °C (16 h), followed by quenching with borohydride. When phosphinite-borane **2a** was reacted with 90 mol % of triflimide for 1 h at room temperature, the activated intermediate **8a** was observed according to the ^{11}B signal at $\delta = -18.9$ ppm in C$_6$D$_5$Br (Scheme 1). Stirring this mixture for 16 h at 140 °C led to the conversion of **8a** into an intermediate assigned as **9a**, ^{11}B $\delta = -9.5$ ppm. The ^{1}H NMR spectrum showed two new multiplets corresponding to the two diastereotopic isopropyl methines at $\delta = 2.04$ and 2.84 ppm (1:1 integral ratio) as expected for a structure containing a stereogenic boron. In addition, the downfield shift of the broad B−H proton signal at $\delta = 3.9$ ppm relative to $\delta = 2.8$ ppm for **8a** supports the proposed structure of **9a**. This evidence is consistent with **8a** acting as an equivalent (or a source) of the transient borenium cation **3a** which undergoes electrophilic cyclization, but neither **3a** nor related borocations were detected.

Scheme 1. Directed Borylation of Aryl Diisopropylphosphinites



Structure **6a** is an example of a previously unknown heterocycle family, but we were more interested in access to the related trifluoroborate salt **10a** due to its utility in palladium catalyzed Suzuki coupling chemistry.[11] Initial attempts to convert **6a** to **10a** using standard conditions (KHF$_2$/MeOH)[12] did not give significant conversion after 16 h at 65 °C. On the

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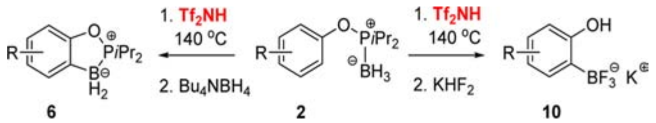
(9) Bedford, R. B.; Hazelwood, S. L.; Horton, P. N.; Hursthouse, M. B. *Dalton Trans.* **2003**, 4164.

(10) "Dark polymeric material" forms upon exposure of *o*-hydroxyphenyl trifluoroborate to basic aqueous conditions: Yuen, A. K. L.; Hutton, C. A. *Tetrahedron Lett.* **2005**, *46*, 7899.

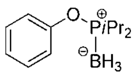
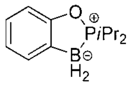
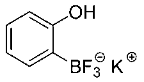
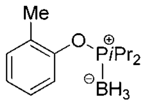
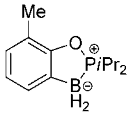
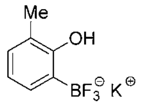
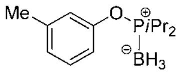
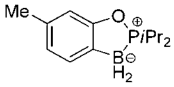
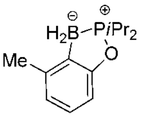
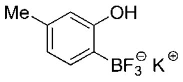
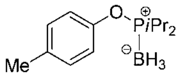
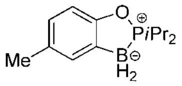
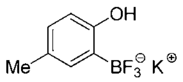
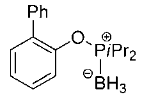
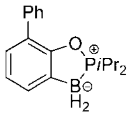
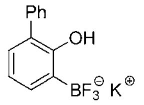
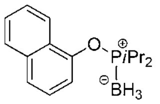
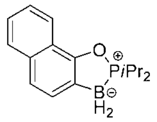
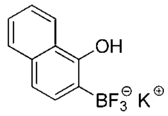
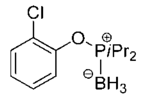
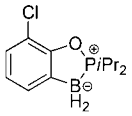
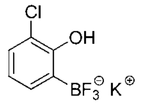
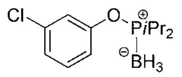
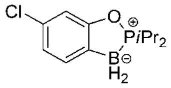
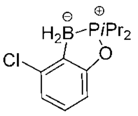
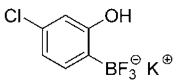
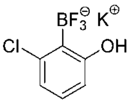
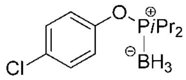
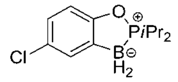
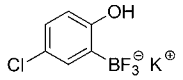
(11) Review: Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240.

(12) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027.

Table 1. Activation of Aryl Di-isopropylphosphinites



6 **2** **10**

entry	2	product 6[a]	yield[b]	product 10[c]	yield[b]
1	 **2a**	 **6a**	80%	 **10a**	75%
2	 **2b**	 **6b**	84%	 **10b**	88%
3	 **2c**	 **6c**  **6c'**	84% (1:1)[d]	 **10c**	39%
4	 **2d**	 **6d**	72%	 **10d**	94%
5	 **2e**	 **6e**	78%	 **10e**	57%
6	 **2f**	 **6f**	66%	 **10f**	56%
7	 **2g**	 **6g**	56%	 **10g**	62%
8	 **2h**	 **6h**  **6h'**	41% (1.1:1)[d]	 **10h**  **10h'**	61% (1.3:1)[d]
9	 **2i**	 **6i**	56%	 **10i**	34%

[a] Conditions: Aryl di-isopropylphosphinites (0.2 mmol), Tf_2NH (0.18 mmol), PhF (1 mL), 140 °C, 16 h, sealed tube, quenched with n-Bu_4NBH_4. [b] Isolated yields. [c] Conditions: Aryl di-isopropylphosphinites (0.5 mmol), Tf_2NH (0.45 mmol), toluene (2 mL), 140 °C, 16 h, sealed tube, quenched with KHF_2. [d] Mixture of two regioisomers.

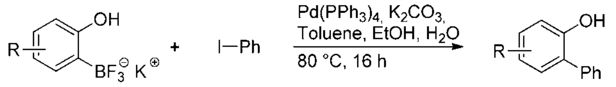
other hand, similar KHF_2 treatment of the crude borylation product **9a** *without any* reductive quenching resulted in smooth conversion to **10a**, identified by NMR comparison with known material.[10] The crude **10a** obtained after solvent removal contained $KNTf_2$ according to the ^{19}F signal at $\delta = -79.8$ ppm, but the contaminant could be removed by extracting **10a** with hot acetone, followed by crystallization from minimal methanol (Table 1, entry 1, 71% of **10a** isolated).

The HNTf$_2$ procedure was then applied to several other derivatives **3** (Table 1, entries 2–9). The borylation products **6** and **10** were usually obtained in yields of 50–75% for the more electron-rich aryl substrates (entries 2–6). However, no borylation was detected with electron-withdrawing substituents (CO$_2$Me, CN) attached to the aromatic ring. Furthermore, regioselectivity was near 1:1 starting with *m*-substituted substrates (entries 3, 8). Unexpectedly, the KArBF$_3$ salt **10c** (entry 3) was isolated as a single regioisomer even though the corresponding **6c** was obtained as a mixture of isomers. This discrepancy results from the lower solubility of **10c** compared to the regioisomer (not shown) and isolation by crystallization. We note that the most valuable reagent in these experiments is the 90 mol % of HNTf$_2$ used for the activation step. Accordingly, the yields in Table 1 are reported based on HNTf$_2$ as limiting reagent.

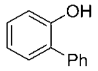
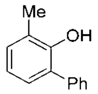
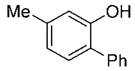
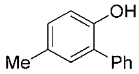
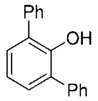
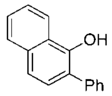
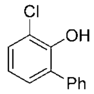
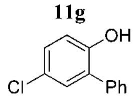
Having established an *O*-directed borylation route to phenolic trifluoroborate salts, we were interested in evaluating their suitability for palladium-catalyzed coupling with iodobenzene as the test substrate. Using classical conditions[13] for this coupling, we encountered difficulties and poor reactivity in early experiments. This problem resulted from rate inhibition by KNTf$_2$, a contaminant that was present because **10** had been isolated without crystallization. Supporting evidence was obtained by conducting the reaction of **10b** with iodobenzene using Pd(PPh$_3$)$_4$ as catalyst (K$_2$CO$_3$/toluene/EtOH–H$_2$O, 80 °C) in the presence of varying amounts of KNTf$_2$. Thus, the yield of coupled product **11** increased from $<2\%$ to 91% when the amount of KNTf$_2$ contaminant decreased from 100 mol % to <1 mol % (^{19}F NMR assay). In view of these results, all yields for coupling products **11** in Table 2 are reported using **10** that contains $<1\%$ of KNTf$_2$.

The findings presented above demonstrate access to *ortho*-borylated phenols from substrates containing donor substituents. Although cationic intermediates **3** could not be detected, the phosphorus-directed borylation probably involves borenium equivalents as the active borylating agents.[7,8] In terms of cost for laboratory scale synthesis, we believe that the method reported here for the preparation of potassium aryltrifluoroborates **10** derived from simple, monofunctional phenols is competitive with reported alternatives due to the low cost of the boron source (THF–BH$_3$). However, the conditions are relatively harsh compared to the method of Hartwig et al.[4c] The latter procedure is likely to perform better with polyfunctional substrates and may also have advantages with *meta*-substituted phenols, judging from the two examples reported to date. In terms of practicality from a broader perspective, we note that several plausible alternatives to the corrosive and expensive HNTf$_2$ as the activating electrophile and "hydridophile" remain to be explored. A catalytic variation of the current method would also be a desirable goal for future work.[14]

Table 2. Suzuki Coupling[a]



10 **11**

entry	10	product	yield[b]
1	**10a**	 **11a**	89%
2	**10b**	 **11b**	91%
3	**10c**	 **11c**	74%
4	**10d**	 **11d**	84%
5	**10e**	 **11e**	80%
6	**10f**	 **11f**	68%
7	**10g**	 **11g**	89%
8	**10i**	 **11i**	86%

[a] Condition: Iodobenzene (1.5 equiv), Pd(PPh$_3$)$_4$ (5 mol %), toluene/EtOH/H$_2$O (3/1/1, 1.25 M), 80 °C, 16 h. [b] Isolated yields.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at at http://pubs.acs.org.

The authors declare no competing financial interest.

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(14) An attempt to perform a catalytic reaction with 10 mol % of Tf$_2$NH gave $<10\%$ conversion to **6a** after 16 h at 140 °C.