P-Directed Borylation of Phenols

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ABSTRACT

Internal borylation occurs upon activation of aryl di-isopropylphosphinite boranes with HNTf₂ to give heterocyclic intermediates that can be reductively quenched to afford 6 or treated with KHF₂ 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 KNTf₂ byproduct from the preceding KHF₂ 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 $(RO)_3B (R = Me, iPr)^2$ or by the reaction of electrophilic boranes with electron-rich arenes.³ In the case of the highly electrophilic BCl₃, 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

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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 $200 \circ C^{5a}$). 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 borylations⁸

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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 analogy⁸ but replaced the benzylic amine borane substrates with the isosteric phosphinite boranes 2, readily available from the corresponding phenols and commercial $ClP(iPr)_2/Et_3N$ via the precedented di-isopropyl arylphosphinites 1.9 Without isolation, crude 1 were treated with excess THF-BH₃ 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 $Ph_3C^+(C_6F_5)_4B^-$ 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 ¹H NMR assay of the aromatic region. However, attempts to detect the presumed intermediate borenium cation 3a or the hypothetical cationic product of electrophilic borvlation 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 ¹H 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_4NBH_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 Tf₂NH 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 Tf₂NH was Scheme 1. Directed Borylation of Aryl Diisopropylphosphinites



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 Tf₂NH 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 ¹¹B signal at $\delta = -18.9$ ppm in C_6D_5Br (Scheme 1). Stirring this mixture for 16 h at 140 °C led to the conversion of 8a into an intermediate assigned as 9a, ¹¹B $\delta = -9.5$ ppm. The ¹H 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.

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 (KHF₂/MeOH)¹² did not give significant conversion after 16 h at 65 °C. On the

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^{*a*} Conditions: Aryl di-isopropylphosphinites (0.2 mmol), Tf₂NH (0.18 mmol), PhF (1 mL), 140 °C, 16 h, sealed tube, quenched with *n*-Bu₄NBH₄. ^{*b*} Isolated yields. ^{*c*} Conditions: Aryl di-isopropylphosphinites (0.5 mmol), Tf₂NH (0.45 mmol), toluene (2 mL), 140 °C, 16 h, sealed tube, quenched with KHF₂. ^{*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 KNTf₂ according to the ¹⁹F 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 HNTf₂ 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 borvlation was detected with electron-withdrawing substituents (CO₂Me, CN) attached to the aromatic ring. Furthermore, regioselectivity was near 1:1 starting with *m*-substituted substrates (entries 3, 8). Unexpectedly, the KArBF₃ 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 HNTf₂ used for the activation step. Accordingly, the yields in Table 1 are reported based on HNTf₂ 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 conditions¹³ for this coupling, we encountered difficulties and poor reactivity in early experiments. This problem resulted from rate inhibition by KNTf₂, 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-(PPh₃)₄ as catalyst (K₂CO₃/toluene/EtOH-H₂O, 80 °C) in the presence of varying amounts of KNTf₂. Thus, the yield of coupled product 11 increased from < 2% to 91%when the amount of KNTf2 contaminant decreased from 100 mol % to <1 mol % (¹⁹F NMR assay). In view of these results, all yields for coupling products 11 in Table 2 are reported using 10 that contains < 1% of KNTf₂.

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–BH₃). 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

Table 2. Suzuki Coupling^a



^{*a*} Condition: Iodobenzene (1.5 equiv), Pd(PPh₃)₄ (5 mol %), toluene/ EtOH/H₂O (3/1/1, 1.25 M), 80 °C, 16 h. ^{*b*} Isolated yields.

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 HNTf₂ 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

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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.

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The authors declare no competing financial interest.