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# Orthogonal Reactivity in Boryl-Substituted Organotrifluoroborates

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Several different strategies utilizing two orthogonally reactive boron species have been used to increase complexity and diversity in organic substructures. Although assorted dibora-substituted organic molecules have been described and utilized in this context,[1] for the most part this approach suffers from a few significant limitations. For example, the two boron species are often functionally identical and both are chemically processed in the same way.[2] In other cases, the ultimate fate of the two organoborons takes advantage of inherent reactivity differences related to the reactive substituent on boron.[3] Lastly, the two boron species may be symmetrically reactive, and reaction at one center leaves an organoboron that is unreactive under similar conditions.[4]

There are a few examples detailing the cross-coupling of electrophilic partners containing protected versions of boronic acids,[5] but to date a single example can be found that generates a dibora compound and sequentially cross-couples the organoborons with selectivity based solely on the nature of the nonparticipating boron substituents.[6]

Herein we report the development of dibora-substituted linchpins allowing bidirectional syntheses of diverse organic substructures. Although cross-couplings of organotrifluoroborates with aryldiazoniums and diaryliodoniums can be carried out under anhydrous conditions,[7] other electrophilic partners (e.g., halides, triflates) require aqueous or protic conditions.[8] Owing to the reactivity of trialkylboranes in the absence of water, we explored their formation and selective cross-coupling in the presence of organotrifluoroborates.

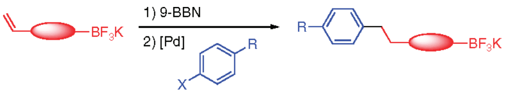
The hydroboration of alkenyl-containing organotrifluoroborates with 9-BBN generates intermediate dibora species. These linchpins undergo selective cross-coupling at the trialkylborane, providing pure, elaborated trifluoroborates. Subsequently, a further increase in molecular complexity can be achieved by cross-coupling the organotrifluoroborate.

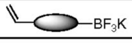
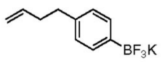
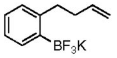
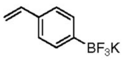
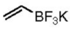
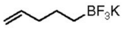
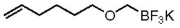
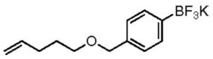
Using 4-bromobenzonitrile as a model electrophile with potassium 4-(but-3-enyl)phenyltrifluoroborate, a brief screening of the cross-coupling step was carried out.[11] Use of 2 mol % $Pd(OAc)_2$, 3 mol % DavePhos,[12] and KF (3 equiv), with stirring overnight at rt, afforded the highest conversion and isolated yield (79%) of the corresponding cross-coupled product (Table 1, entry 1).

With conditions in hand, various alkenyl-containing aryltrifluoroborate substrates were hydroborated and selectively cross-coupled (Table 1, entries 1−8 and 14). Aryl bromides, chlorides, iodides, and triflates were found to cross-couple with complete selectivity at the borane moiety of the dibora intermediate, in each case providing the elaborated potassium aryltrifluoroborate product in good yields. The reaction also proved to be scalable to 5 mmol (Table 1, entry 8).

The reaction of potassium vinyltrifluoroborate also proceeded smoothly in the sequence, cleanly generating the cross-coupled product (Table 1, entries 9−11). Of particular note is the regioselectivity of the initial hydroboration step, creating a reversal in the pattern associated with tricoordinate alkenylborons. The resulting dibora species represents a 1,2-dianion equivalent that is markedly distinct from the 1,1-dibora intermediates traditionally formed when tricoordinate alkenylborons undergo hydroboration.[13]

***Table 1.*** Hydroboration and Suzuki−Miyaura Cross-Coupling of Alkenyl-Containing Potassium Organotrifluoroborates[a]



| entry |  | R | X | % isolated yield |
|---|---|---|---|---|
| 1 |  | CN | Br | 79 |
| 2 | | CN | Cl | 82 |
| 3 | | CN | I | 69 |
| 4 | | CN | OTf | 72 |
| 5 | | pyrrole | Cl | 71 |
| 6 |  | pyrrole | Cl | 70 |
| 7 |  | CN | Br | 86 |
| 8 | | CN | Cl | 87 (87[b]) |
| 9 |  | CN | Br | 67 |
| 10 | | CN | Cl | 80 |
| 11 | | pyrrole | Cl | 76 |
| 12 |  | pyrrole | Cl | 95 |
| 13 |  | pyrrole | Cl | 65 |
| 14 |  | pyrrole | Cl | 65 |

[a] General conditions: $RBF_3K$ (1.0 equiv), 9-BBN (1.0 equiv) and THF (0.25 M) then $Pd(OAc)_2$ (2 mol %), DavePhos (3 mol %), aryl electrophile (1.0 equiv), and KF (3 equiv), rt, overnight. [b] Reaction scaled to 5 mmol.

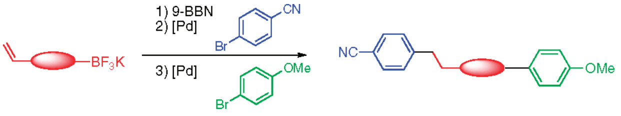
Alkenyl-containing alkyltrifluoroborates were found to be suitable substrates in the reaction sequence (Table 1, entries 12−13). The limited solubility of potassium alkoxymethyltrifluoroborates[14] in THF (Table 1, entry 13) required more dilute reaction conditions and a significantly longer reaction time for the hydroboration step to occur.

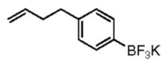
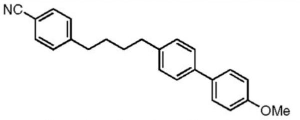
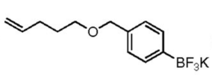
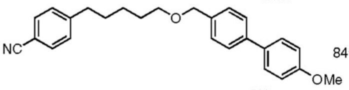
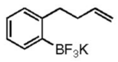
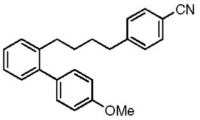
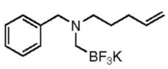
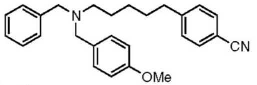
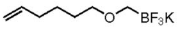
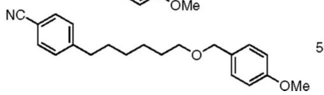
With the ultimate goal of bidirectional functionalization, we turned our attention to a one-pot hydroboration/bidirectional cross-coupling sequence (Table 2). After subjecting the substrates to the first hydroboration/cross-coupling sequence, reaction with a second electrophile under conditions previously optimized for aryltrifluoroborates (entries 1−3),[15] *N*,*N*-dialkylaminomethyltrifluoroborates (entry 4),[16] and alkoxymethyltrifluoroborates (entry 5)[14] generated the desired products.

We then investigated the cross-coupling of trialkylborane reagents with electrophiles containing the organotrifluoroborate moiety.

10.1021/ja807076d CCC: $40.75

***Table 2.*** One-Pot Hydroboration and Bidirectional Suzuki−Miyaura Cross-Coupling of Alkenyl-Containing Organotrifluoroborates[a]

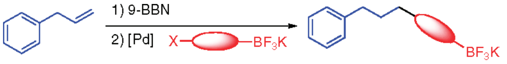


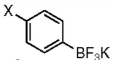
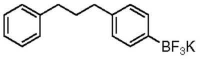
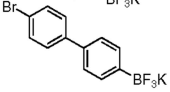
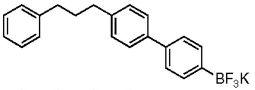
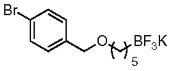
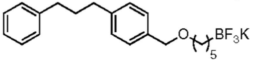
| entry |  | product | % isolated yield |
|---|---|---|---|
| 1 |  |  | 82[b] |
| 2 |  |  | 84[b] |
| 3 |  |  | 70[b] |
| 4 |  |  | 71[c] |
| 5 |  |  | 50[d] |

[a] General conditions: $RBF_3K$ (1.0 equiv), 9-BBN (1.0 equiv) and THF (0.25 M) then $Pd(OAc)_2$ (2 mol %), DavePhos (3 mol %), aryl electrophile (1.0 equiv), and KF (3 equiv), rt, overnight. [b] $RBF_3K$ coupling: $Pd(OAc)_2$ (0.5 mol %), electrophile (1.0 equiv), $K_2CO_3$ (3 equiv) and MeOH (0.125 M), 65 °C, 2 h. [c] $RBF_3K$ coupling: $Pd(OAc)_2$ (3 mol %), XPhos[9] (6 mol %), electrophile (1.0 equiv), $Cs_2CO_3$ (3 equiv) and 10:1 THF/$H_2O$ (0.25 M), 80 °C, 24 h. [d] $RBF_3K$ coupling: $Pd(OAc)_2$ (3 mol %), RuPhos[10] (6 mol %), electrophile (1.0 equiv), $Cs_2CO_3$ (3 equiv) and 10:1 dioxane/$H_2O$ (0.25 M), 100 °C, 24 h.

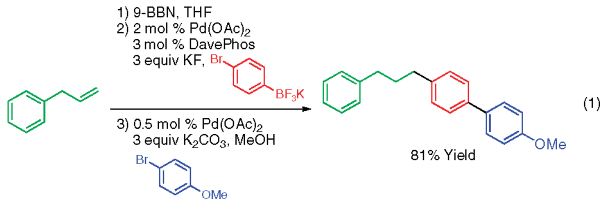
Treatment of allylbenzene with 9-BBN followed by exposure to the conditions previously described for the cross-coupling of dibora substrates provided the elaborated aryl- and alkyltrifluoroborate products in good yields (Table 3). This method can be extended to bidirectional functionalization as well. This one-pot sequence provided the fully elaborated product in excellent yield (eq 1).

***Table 3.*** Hydroboration of Allylbenzene and Suzuki−Miyaura Cross-Coupling with Halo-Containing Trifluoroborates[a]



| entry |  | product | % isolated yield |
|---|---|---|---|
| 1 |  |  | X = Br; 91<br>X = Cl; 85 |
| 2 |  |  | 81 |
| 3 |  |  | 71 |

[a] General conditions: 9-BBN (1.1 equiv), allylbenzene (1.1 equiv), and THF (0.25 M), then $Pd(OAc)_2$ (2 mol %), DavePhos (3 mol %), $RBF_3K$ (1.0 equiv), and KF (3 equiv), rt, 4 h.



(1)

Taking into consideration the reactivity differences between organotrifluoroborates and trialkylboranes, a method was developed to hydroborate alkenyl-containing organotrifluoroborates. Conditions were found for reaction of the borane moiety of these dibora-intermediates in a highly chemoselective fashion, leaving the trifluoroborate intact for subsequent transformation. The stability of the trifluoroborate moiety to these metal catalyzed reactions allows simple and efficient strategies for multicomponent complex molecule construction.

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**Supporting Information Available:** Experimental procedures, compound characterization data, and NMR spectral data of all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.
(10) 2-Dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl.
(11) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9772. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
(12) 2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl.
(13) (a) Colberg, J. C.; Rane, A.; Vaquer, J.; Soderquist, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 6065. (b) Wrackmeyer, B.; Schanz, H.-J. *Collect. Czech. Chem. Commun.* **1997**, *62*, 1254.
(14) Molander, G. A.; Canturk, B. *Org. Lett.* **2008**, *10*, 2135.
(15) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867.
(16) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, *9*, 1597.

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