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Utilization of Potassium Vinyltrifluoroborate in the Development of a 1,2-Dianion Equivalent

Gary A. Molander* and Deidre L. Sandrock

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

gmolandr@sas.upenn.edu

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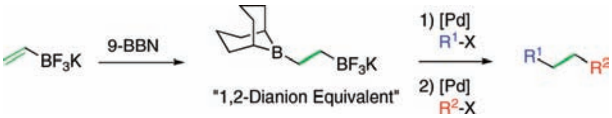
ABSTRACT

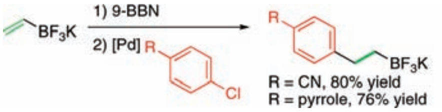


Previous studies of orthogonally reactive dibora species led to the discovery of a unique reactivity pattern associated with potassium vinyltrifluoroborate. Upon hydroboration, the vinyltrifluoroborate generates a 1,2-diboraethane, which is distinct from the 1,1-dibora intermediates generated when traditional alkenyldialkylboron species undergo hydroboration. The 1,2-dianion equivalent thus generated can be envisioned as a building block for the linkage of two different electrophiles via palladium-catalyzed Suzuki−Miyaura cross-couplings.

Orthogonally reactive boron species in dibora compounds have been described as a means of generating functionalized compounds efficiently in a bidirectional manner.[1] We have recently disclosed a strategy for creating boryl-substituted trifluoroborates in situ and subsequently cross-coupling the trialkylborane moiety chemoselectively to provide a functionalized trifluororoborate.[1a] In a one-pot process, these trifluoroborates can be further cross-coupled to increase molecular complexity in a highly efficient manner.

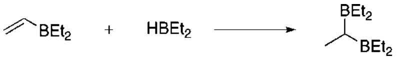
The selectivity seen in this transformation is a result of the fluoride−hydroxyl exchange that must occur for an organotrifluoroborate to be activated for transmetalation.[2] Because protic media are necessary for the cross-coupling of organotrifluoroborates with most electrophilic species (e.g., halides, triflates) and trialkylborane cross-coupling can be effected under anhydrous conditions,[3] selective conditions have been developed that will allow reaction only at the tricoordinate boron.

During the course of our investigations, we examined the ability of potassium vinyltrifluoroborate to undergo the hydroboration/cross-coupling sequence to generate a functionalized trifluoroborate (eq 1). Hydroboration with 9-BBN followed by Pd-catalyzed cross-coupling conditions provided the desired phenethyltrifluoroborate derivative.



(1)

By contrast, hydroboration of vinyldialkylboranes provides the 1,1-dibora compounds (eq 2).[4] This reaction demonstrates that a trifluoroborate inverts the polarity of the double bond. The unique regioselectivity of the hydroboration of vinyltrifluoroborate can be exploited for the development of a 1,2-dianion equivalent (Figure 1).



$$\mathrm{CH_2{=}CH{-}BEt_2} + \mathrm{HBEt_2} \longrightarrow \mathrm{CH_3CH(BEt_2)_2} \qquad (2)$$

A limited number of 1,2-dibora compounds have been described in the literature.[5] They have been generated via

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(1) (a) Molander, G. A.; Sandrock, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 15792. (b) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466.

(2) (a) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (b) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2002**, *42*, 9099. (c) Batey, R. A.; Thadani, A. N. *Org. Lett.* **2002**, *4*, 3827. (d) Hutton, C. A.; Yuen, A. K. *Tetrahedron Lett.* **2005**, *46*, 7899.

(3) (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.

10.1021/ol900822j CCC: $40.75

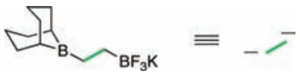


Figure 1. Hydroborated intermediate as a 1,2-ethane dianion equivalent.

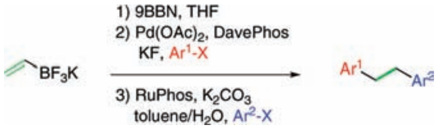
the catalyzed diboration of ethene, the reductive coupling of iodomethylpinacolborane with various metals, and the hydrogenation of the alkynyl 1,2-dibora substrates. However, each of these protocols utilizes chemically equivalent boron species, effectively eliminating the possibility of selective reaction at one boron center.

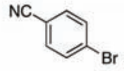
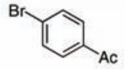
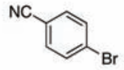
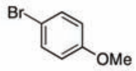
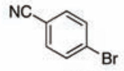
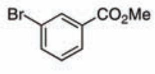
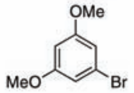
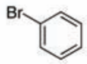
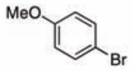
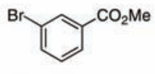
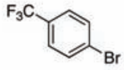
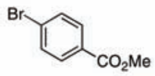
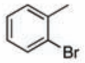
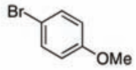
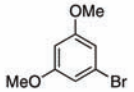
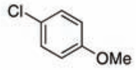
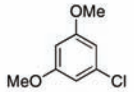
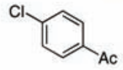
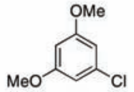
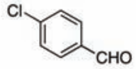
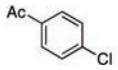
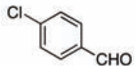
The 1,2-dibora intermediate from potassium vinyltrifluoroborate, on the other hand, can be differentially reacted and therefore serves as a new linchpin building block for the linkage of two different electrophilic partners. Herein we report a comprehensive examination of the unique applications of this protocol, demonstrating its utility as a linker to connect aryl, heteroaryl, and alkenyl electrophiles, generating a diverse library of ethyl-bridged subunits via sequential processes.

Initially, we examined the scope and limitations of this one-pot generation/cross-coupling of the 1,2-diboraethane with a variety of aryl electrophiles (Table 1). After hydroboration of potassium vinyltrifluoroborate with 9-BBN in THF, the resulting dibora intermediate was subjected to a variety of electrophiles using the conditions previously optimized for the chemoselective cross-coupling of the trialkylborane moiety [2 mol % of Pd(OAc)$_2$, 3 mol % of DavePhos,[6] and 3 equiv of KF].[1a] After the reaction was stirred at rt overnight, the solvent was removed in vacuo, and each was subjected to conditions optimized for the cross-coupling of primary alkyltrifluoroborates with aryl chlorides [4 mol % of RuPhos,[7] 3 equiv of K$_2$CO$_3$, and 10:1 toluene/H$_2$O (0.2 M)].[8]

A variety of chloride and bromide electrophiles were tolerated under these conditions including those containing ketones, aldehydes, nitriles, and esters. Specifically, all combinations of electron-rich and electron-poor electrophiles underwent reaction to generate the corresponding cross-coupled products in good yield. The system also proved tolerant of sterically hindered substrates, generating the product in only slightly reduced yield (Table 1, entry 7). Additionally, the reaction proved to be scaleable to 5 mmol (Table 1, entry 4). Of note, the second cross-coupling step of each example proceeded readily without the need of additional Pd(OAc)$_2$.

Table 1. One-Pot Generation/Cross-Coupling of a 1,2-Diboraethane with Aryl Electrophiles[a]



entry	Ar^1-X	Ar^2-X	% isolated yield
1			77
2			71
3			82
4			73 (75[b])
5			72
6			76
7			59
8			75
9			78
10			81
11			79

[a] General conditions: RBF$_3$K (1.0 equiv), 9-BBN (1.0 equiv), and THF (0.25 M) followed by Pd(OAc)$_2$ (2 mol %), DavePhos (3 mol %), Ar^1-X (1.0 equiv), and KF (3 equiv), rt, overnight. After solvent removal, RuPhos (4 mol %), Ar^2-X (1.0 equiv), K$_2$CO$_3$ (3 equiv), and 10:1 toluene/H$_2$O (0.25 M), 24 h, 80 °C. [b] Reaction scaled to 5 mmol.

1-Bromo-3,5-dimethoxybenzene was then chosen as a model electrophile to probe the system's tolerance of a variety of heteroaryl halide substrates (Table 2). Again, subjecting vinyltrifluoroborate to the hydroboration/cross-coupling sequence with the optimized conditions, the fully elaborated products were obtained in excellent yield over the three-step process with pyridine, pyrimidine, isoquinoline, furan, and thiophene derivatives.

Because of the ubiquity of heterocycles in many biologically active molecules, we also investigated whether two heterocycles could be linked via this diboraethane subunit. A literature search shows various conditions for the cross-

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(4) (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.

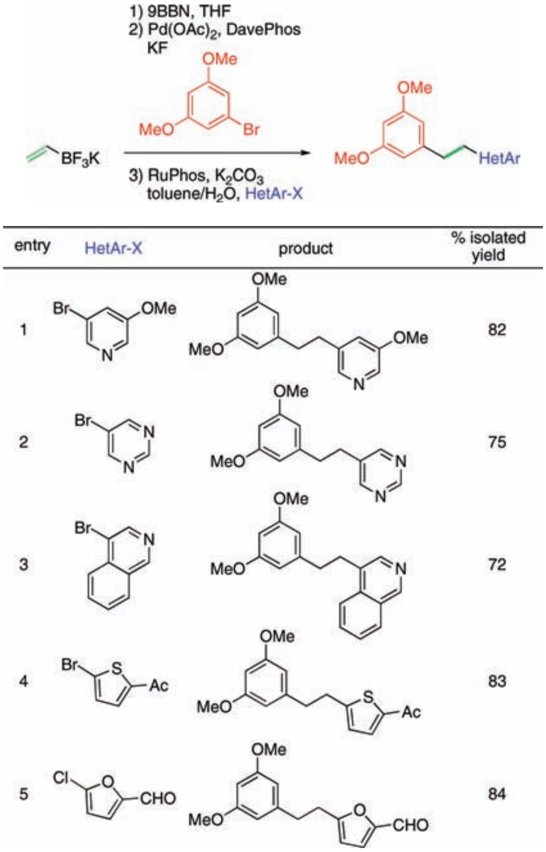
(5) (a) Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 1178. (b) Ali, H. A.; Goldberg, I.; Srebnik, M. *Organometallics* **2001**, *20*, 3962. (c) Eisch, J. J.; Kotowicz, B. W. *Eur. J. Inorg. Chem.* **1998**, 761. (d) Iverson, C. N.; Smith, M. R. *Organometallics* **1997**, *16*, 2757.

(6) 2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl.

(7) 2-Dicyclohexylphosphino-2′6′-diisopropoxy-1,1′-biphenyl.

(8) Dreher, S. D.; Lim, S.-E.; Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* **2009**, DOI: 10.1021/jo900152n.

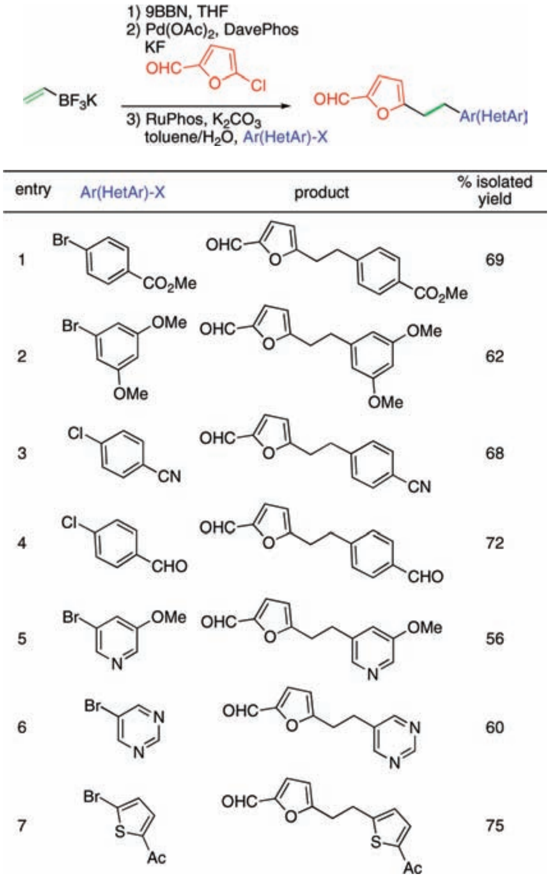
Table 2. One-Pot Generation/Cross-Coupling of a 1,2-Diboraethane with 1-Bromo-3,5-dimethoxybenzene and Heteroaryl Halides[a]



entry	HetAr-X	product	% isolated yield
1			82
2			75
3			72
4			83
5			84

[a] General conditions: RBF_3K (1.0 equiv), 9-BBN (1.0 equiv), and THF (0.25 M) followed by $Pd(OAc)_2$ (2 mol %), DavePhos (3 mol %), Ar-Br (1.0 equiv), and KF (3 equiv), rt, overnight. After solvent removal, RuPhos (4 mol %), HetAr-X (1.0 equiv), K_2CO_3 (3 equiv), and 10:1 toluene/H_2O (0.25 M), 24 h, 80 °C.

Table 3. One-Pot Generation/Cross-Coupling of a 1,2-Diboraethane with 5-Chloro-2-furaldehyde and Various Aryl and Heteroaryl Halides[a]



entry	Ar(HetAr)-X	product	% isolated yield
1			69
2			62
3			68
4			72
5			56
6			60
7			75

[a] General conditions: RBF_3K (1.0 equiv), 9-BBN (1.0 equiv), and THF (0.25 M) followed by $Pd(OAc)_2$ (2 mol %), DavePhos (3 mol %), HetAr-Cl (1.0 equiv), and KF (3 equiv), rt, overnight. After solvent removal, RuPhos (4 mol %), Ar(HetAr)-X (1.0 equiv), K_2CO_3 (3 equiv), and 10:1 toluene/H_2O (0.25 M), 24 h, 80 °C.

coupling of some heteroaryl halides to trialkylborane substrates. However, most examples require conditions not amenable to the system described herein (aqueous or unsuitable reaction solvents).[9]

Although other heteroaryl electrophiles proceeded to a limited extent with our optimized system, for the most part, these conditions seemed restricted to the coupling of 5-chloro-2-furaldehyde as the first electrophilic partner. Further investigations are currently underway to find more general conditions for effecting anhydrous cross-couplings of trialkylboranes with heteroaryl halides.

Using the $Pd(OAc)_2$/DavePhos conditions and 5-chloro-2-furaldehyde, we were able to generate a functionalized trifluoroborate intermediate that could be cross-coupled with various electron-rich and electron-poor aryl chlorides and bromides (Table 3). A number of heteroaryl bromides worked well in this reaction sequence, generating the desired diheteroarylethane substrates in good yield.

Using conditions that were previously described for the cross-coupling of primary alkyltrifluoroborates with alkenyl bromides,[10] the cross-coupling of the 1,2-diboraethane equivalent with 1-bromo-3,5-dimethoxybenzene and a variety of alkenyl bromides was demonstrated (Table 4). The functionalized trifluoroborate intermediate was shown to cross-couple with various alkenyl bromide electrophiles in good yield.

Interestingly, when 2-bromo-3-methylcyclopenten-2-one was used as the electrophilic coupling partner, the desired product was obtained in a 32% yield with an isomerized byproduct in 44% yield (Table 4, entry 3). A similar observation has been made previously for the cross-coupling of 4-phenylbutyltrifluoroborate and potassium 2-phenyleth-

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(9) (a) Gonzalez, A. Z.; Roman, J. G.; Gonzalez, E.; Martinez, J.; Medina, J. R.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 9218. (b) Valente, C.; Baglione, S.; Candito, D.; O'Brien, C. J.; Organ, M. G. *Chem. Commun.* **2008**, 735.

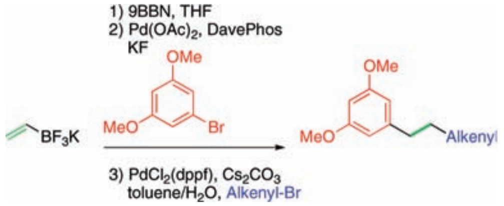
(10) Molander, G. A.; Ham, J.; Seapy, D. G. *Tetrahedron* **2007**, *63*, 768.

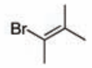
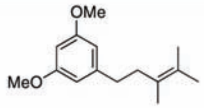
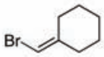
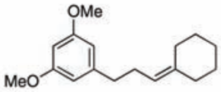
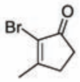
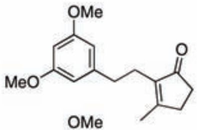
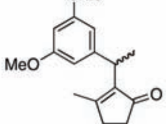
(11) (a) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538. (b) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549. (c) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *J. Org. Chem.* **2003**, *68*, 7733. (d) Abe, S.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2863.

(12) 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

(13) 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

Table 4. One-Pot Generation/Cross-Coupling of a 1,2-Diboraethane with 1-Bromo-3,5-dimethoxybenzene and Alkenyl Bromides[a]

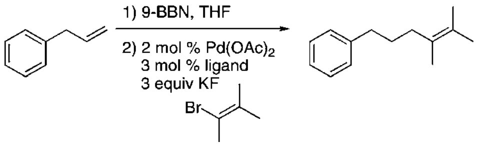


entry	Alkenyl-Br	product	% isolated yield
1			72
2			74
3			32
			44

[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 %), Ar−Br (1.0 equiv), and KF (3 equiv), rt, overnight. After solvent removal, $PdCl_2(dppf)•CH_2Cl_2$ (10 mol %), alkenyl bromide (1.0 equiv), Cs_2CO_3 (3 equiv), and 3:1 toluene/H_2O (0.17 M), 24 h, 80 °C.

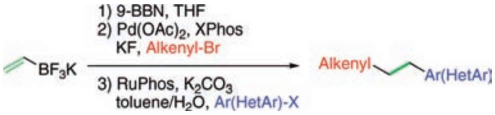
yltrifluoroborate to this same bromide. This isomerization is undoubtedly a result of a β-hydride elimination/reinsertion process.[10]

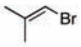
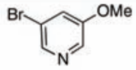
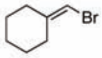
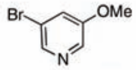
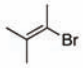
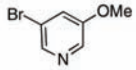
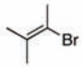
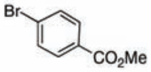
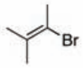
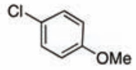
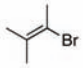
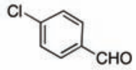
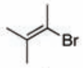
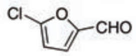
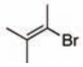
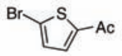
Lastly the cross-coupling of the 1,2-diboraethane intermediate first to an alkenyl bromide and then to various aryl and heteroaryl electrophiles was investigated. There is limited precedent for the anhydrous cross-coupling of trialkylboranes to alkenyl bromides,[9a,11] so a very brief ligand screen was carried out to identify conditions capable of facilitating this transformation. To screen reaction conditions for this step, allylbenzene was subjected to hydroboration with 9-BBN (eq 3) and then to cross-coupling using 2 mol % of $Pd(OAc)_2$, 3 mol % of a ligand (RuPhos, DavePhos, XPhos,[12] and SPhos[13]) and 3 equiv of KF.



(3)

Table 5. One-Pot Generation/Cross-Coupling of a 1,2-Diboraethane with Alkenyl Bromides and Various Aryl and Heteroaryl Halides[a]



entry	Alkenyl-Br	Ar(HetAr)-X	% isolated yield
1			69
2			81
3			80
4			80
5			62
6			62
7			79
8			79

[a] General conditions: RBF_3K (1.0 equiv), 9-BBN (1.0 equiv), and THF (0.25 M) followed by $Pd(OAc)_2$ (2 mol %), XPhos (3 mol %), alkenyl bromide (1.0 equiv), and KF (3 equiv), rt, overnight. After solvent removal, RuPhos (4 mol %), Ar(HetAr)-X (1.0 equiv), K_2CO_3 (3 equiv), and 10:1 toluene/H_2O (0.25 M), 24 h, 80 °C.

For this system with 2-bromo-3-methylbut-2-ene as the electrophile, XPhos emerged as the best ligand to promote the transformation. Applying these new conditions to the reaction sequence, the cross-coupling of three different alkenyl bromides as the first electrophilic partner with diverse aryl and heteroaryl halides was demonstrated (Table 5).

The 1,2-diboraethane generated from the hydroboration of potassium vinyltrifluoroborate allows sequential reactivity at chemically inequivalent boron moieties. To the best of our knowledge, this reagent is the only ethyl dianion equivalent to be used in this context, and its unique reactivity pattern gives rise to a new protocol for the multicomponent construction of libraries of ethyl-linked subunits in a one-pot process.

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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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