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Asymmetric Alkyldifluoroboranes and Their Use in Secondary Amine Synthesis

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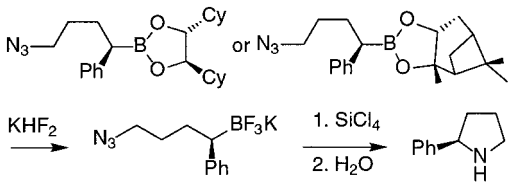
ABSTRACT



Asymmetric diol boronic esters with potassium bifluoride form the corresponding alkyltrifluoroborate and free diol under mild conditions. Defluoridation with tetrachlorosilane produces an alkyldifluoroborane intermediate. This conversion of relatively unreactive boronic esters to derivatives that are strong Lewis acids opens new synthetic opportunities, as illustrated by the preparation of (*R*)-2-phenylpyrrolidine in 98% ee from a pinanediol or 1,2-dicyclohexyl-1,2-ethanediol boronic ester via potassium (2-phenyl-4-azidobutyl)trifluoroborate.

We have found a mild, efficient route from asymmetric boronic esters via alkyltrifluoroborates to reactive alkyldifluoroborane intermediates, which are converted to asymmetric secondary amines via reaction with organic azides. Vedejs and co-workers reported that arylboronic acids react with potassium bifluoride to form aryltrifluoroborates, which are converted to aryldifluoroborane intermediates by trimethylsilyl chloride.[1,2] Organotrifluoroborates prepared by the Vedejs route have been found useful by others,[3] but organodifluoroboranes remain relatively unexplored.[4]

Our method of asymmetric synthesis based on α-halo boronic ester chemistry provides a wide variety of functionalized boronic ester intermediates in very high enantiomeric and diastereomeric purity,[5] but the scope of displacements of boron from carbon has been limited by the low reactivity of boronic esters. Thermodynamics disfavors hydrolysis of the pinanediol or 1,2-dicyclohexylethanediol (DICHED) esters used in our synthetic method. Separation of the diol group from boron requires an exothermic reaction[6] or separation of the diol and the organoboron units into separate phases,[7] which is not always practical. Glass-catalyzed reaction of boronic esters with thionyl chloride and imidazole has provided good recovery of the chiral diols, but efficient hydrolysis of the chloroborane imidazole derivatives has proved elusive.[8]

The direct reaction of pinanediol or DICHED boronic esters with potassium bifluoride under the Vedejs conditions

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(2) It has been reported that the ethanolamine ester of diphenylborinic acid was converted to potassium (difluoro)(diphenyl)borinate by KHF_2: Thierig, D.; Umland, F. *Naturwissenschaften* **1967**, *54*, 563. Vedejs et al. speculated that boronic esters might also react but did not test the possibility.

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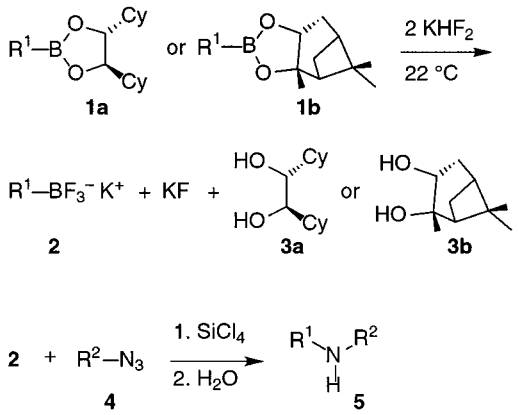
Scheme 1. Conversion of Boronic Esters to Secondary Amines via Trifluoroborates



has proved to be generally facile (Scheme 1). DICHED esters (**1a**) are usually >90% converted to the trifluoroborate salts (**2**) and free DICHED (**3a**), and pinanediol esters (**1b**) can usually be cleaved to **2** and free pinanediol (**3b**) to the extent of ~70%. Reactions usually reach equilibrium within 0.5−2 h at 22 °C.[9] Treatment of **2** with azido compounds (**4**) and tetrachlorosilane results in nitrogen evolution and, after hydrolysis, yields secondary amines (**5**).

The scope of the conversion of DICHED boronic esters **1a** to trifluoroborates (**2**) has been explored briefly with simple substrates, summarized in Table 1.

Table 1. Conversion of DICHED Boronic Esters **1a** to Trifluoroborates **2** and DICHED **3a**[a]

trifluoroborate **2**	δ ^{19}F[b]	**2**, %	**3**, %
Ph-BF_3K	−141	91	86
c-C_6H_{11}-BF_3K[c]	−146	90	86
$CH_3(CH_2)_5$-BF_3K	−139	70	96
(*S*)-PhCH(Cl)-BF_3K	−148	77	88
(*R*)-PhCH(OBn)-BF_3K[c]	−145	87	94
(*R*)-$N_3(CH_2)_3$CH(Ph)-BF_3K[d]	−146	85	90
(*S*)-C_6H_{13}CH(Me)-BF_3K	−145	75	95

[a] Conditions: **1a** (1 mmol) in MeOH (8.5 mL), KHF_2 (7 mmol) in H_2O (~1.5 mL), mixed at ~22 °C, 0.5−2 h; concentrated (vac) until MeOH removed; CH_3CN (10 mL), KHF_2 + KF filtered; **1a** and **3a** extracted with pentane, **3a** crystallized; concentration of CH_3CN sol. yielded **2**. Traces of KHF_2 (^{19}F δ −151) remained in some samples. [b] 282 MHz; broadened by ^{11}B quadrupole; KHF_2 <1%. [c] Anal. C, H, B, F. [d] Anal. C (0.56% high), H, B (0.45% low), K.

Intermolecular reactions of potassium trifluoroborates with tetrachlorosilane and azides have been explored briefly (Table 2).

Although chlorotrimethylsilane as used by Vedejs and coworkers[1] is an effective defluoridating agent, tetrachlorosilane was observed to result in faster nitrogen evolution from the azide reactions and was adopted as the standard reagent for this purpose. A known asymmetric secondary amine, R^1 = 2-octyl, R^2 = $PhCH_2$,[10] was chosen as a test target to demonstrate feasibility.

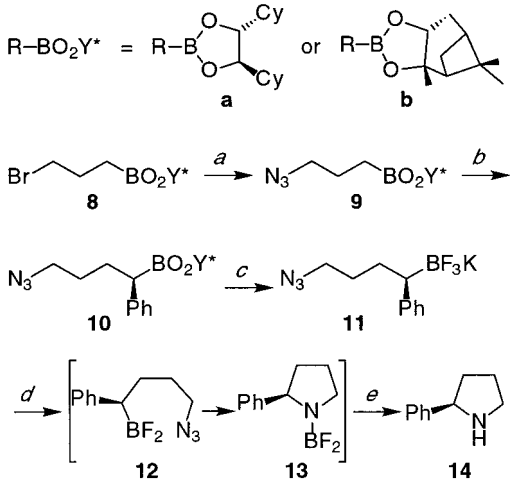
Table 2. Conversion of Trifluoroborates (**2**) and Azides (**4**) to Secondary Amines (**5**)[a]

R^1 of **2**	R^2 of **4**	R_3SiCl	mmol	*T*, °C	**5**, %
Ph	$PhCH_2$	$SiCl_4$	5	80	82
Ph	*n*-C_5H_{11}	TMSCl	7	90	70
Ph	H	$SiCl_4$	5	80	73
c-C_6H_{11}[b]	$PhCH_2$	$SiCl_4$	1.5	70	70
$CH_3(CH_2)_5$	$PhCH_2$	$SiCl_4$	1.5	80	85
(*S*)-C_6H_{13}CH(Me)[c]	$PhCH_2$	$SiCl_4$	1.5	80	75

[a] Borate **2** (1 mmol), $SiCl_4$, or Me_3SiCl (mmol tabulated), and azide **4** (1.3 mmol) were heated and stirred in toluene (~7.5 mL), and the product was recovered by aqueous workup and finally chromatography. [b] CH_3CN added to solubilize **2**. [c] $[\alpha]^{22}_{546}$ = +12.4 (*c* 0.24, CH_2Cl_2).

The preparation of an asymmetric pyrrolidine (**14**) was chosen as a demonstration of the potential utility of the trifluoroborate salts for asymmetric synthesis (Scheme 2).

Scheme 2. Preparation of (*R*)-2-Phenylpyrrolidine[a]



[a] (*a*) **8** (0.11 mol), NaN_3 (1.1 mol), $Bu_4N^+Br^-$ (0.05 mol), EtOAc (250 mL), H_2O (75 mL), 80 °C, 8 h. (*b*) (1) $LiCHCl_2$, −100 °C; $ZnCl_2$, −100 to +22 °C, 15 h; (2) $PhMgBr$.[5] (*c*) KHF_2, MeOH/H_2O. (*d*) **11** (5 mmol), $PhCH_3$ (40 mL),CH_3CN (5 mL), $SiCl_4$ (26 mmol), 22 °C, 10 h. (*e*) Concentrated (vac), H_2O.

Formation of secondary amines (**5**) from alkylchloroboranes is well-known,[11] but the use of fluoroboranes for this purpose has not been investigated previously. Trialkylboranes have also been used with azides for secondary amine synthesis.[12] Only one of three alkyl groups is utilized in the synthesis, and for practical utility the trialkylborane has to be an isomer accessible by hydroboration. If differing alkyl groups are present, selectivity can become a problem, though ring closures tend to supersede competing alkyl migrations.

A significant advantage of the new route includes the recovery of DICHED or pinanediol intact after trifluoroborate formation. The destruction of pinanediol by boron trichloride was discovered previously,[6b] and in the present work we have found that DICHED is recovered in low yield (~10%) if

trichloroborane is used to generate a reactive chloroborane from a boronic ester **1a**. Furthermore, the acid-sensitive benzyloxy substituent survives alkyltrifluoroborate formation. It is also significant that the reaction with potassium bifluoride is the most efficient and generally useful method that has been found to date for converting sterically hindered asymmetric boronic esters to more reactive classes of organoboranes.

The synthesis of the required boronic ester intermediates followed well-established procedures.[5] Bromopropylboronic esters **8** are derived from the hydroboration of allyl bromide.[13] Azide substitution to form **9** was done according to a recently improved phase transfer procedure,[14] and asymmetric homologation to boronic ester **10** has ample precedent.[5,14] The azide group is unaffected by formation of trifluoroborate **11** (^{19}F δ −146), but generation of postulated difluoroborane **12** with tetrachlorosilane results in ring closure to **13** (perhaps dimeric with tetracoordinate boron, ^{19}F δ −151), which is readily hydrolyzed to (*R)*-2-phenylpyrrolidine (**14**).

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Supporting Information Available: Preparative details for trifluoroborates, secondary amines, compounds **9**−**14**; enantiomeric analysis of **14**; ^{1}H, ^{13}C, ^{19}F NMR spectra of **11** and of potassium 1-benzyloxy-2-phenylethyltrifluoroborate. This material is available free of charge via the Internet at http://pubs.acs.org.

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