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A NEW PROCESS FOR THE GENERATION OF 1,3,2-OXAZABOROLIDINES, CATALYSTS FOR ENANTIOSELECTIVE SYNTHESIS

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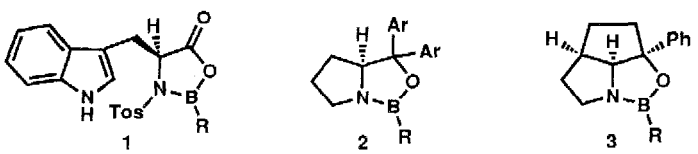
Summary: *A simple and easily reproducible procedure for the formation of 1,3,2-oxazaborolidines from β-amino alcohols and bis(trifluoroethyl) alkylboronates, is reported along with a new synthesis of the latter.*

Several chiral 1,3,2-oxazaborolidines have recently gained prominence as catalysts for a variety of highly enantioselective reactions. For example, the catalyst **1** is useful for enantioselective Diels–Alder reactions[1] and catalysts **2** and **3** are important in the reduction of carbonyl compounds (CBS reduction).[2] These catalysts (or their enantiomers) have been used in key steps to produce the following synthetically useful or biologically active compounds and classes of compounds with typically > 20 : 1 enantioselectivity: prostaglandin intermediates,[1,2b] α-amino acids,[3] anti-PAF diarylfurans,[4] trifluoromethyl carbinols,[5] oxiranes,[2c,6] allylic alcohols,[2f] 1-deuterated primary alcohols,[2e] α-hydroxy acids,[2f,7] β-agonists isoproterenol[8a] and denopamine,[8b] the anti-depressant fluoxetine,[9] and the natural products ginkgolide B,[10] bilobalide,[11] forskolin,[12] and antheridic acid.[13] The expanding utility and potential of oxazaborolidines has created a need for improved methods for boro-heterocycle formation. Herein we describe a simple synthesis of bis(trifluoroethyl) alkylboronates and their use as reagents for the *in situ* formation of catalytic oxazaborolidines such as **2**. Thus, the process of CBS catalyst formation using a bis(trifluoroethyl) alkylboronate reagent and an amino alcohol, followed by reduction of an achiral ketone, isolation of pure chiral alcohol, and amino alcohol•HCl recovery can be accomplished in about one hour.

Previously, we have synthesized 1,3,2-oxazaborolidines from amino alcohols (or amido acids) and BH_3•THF or substituted boronic acids. Although these methods easily and reproducibly afford effective oxazaborolidine catalysts, the reaction times required are somewhat long (3-10 h for the reaction of (*S*)-2-(diphenylhydroxymethyl)-pyrrolidine **4** with an alkylboronic acid,[2b,c] 48 h for reaction with BH_3•THF[2c]) and efficient removal of water from the reaction mixture is essential. Further, structural analogs of **4** which are less nucleophilic or which lead to strained oxazaborolidines can be much less reactive toward alkylboronic acids and harder to prepare. Therefore, a more reactive alkylboronic acid equivalent was sought in order to speed catalyst formation and to provide access to a wider range of boro-heterocyclic structures.

We now report that bis(trifluoroethyl) alkylboronates are outstanding reagents for oxazaborolidine formation (**Scheme 1**). Simply mixing bis(trifluoroethyl) *n*-butylboronate **5** with (*S*)-2-(diphenylhydroxymethyl)-pyrrolidine (**4**) (Aldrich Co.) in toluene, removing toluene, trifluoroethanol and excess boronate reagent **5** *in vacuo*, and heating (110 °C) at 0.07 torr for 30 min affords clean conversion of **4** to CBS



R = H, alkyl, phenyl Ar = phenyl or β-naphthyl

catalyst **2** (Ar = Ph, R = *n*-butyl).[14] This rapid and simple procedure allows *in situ* catalyst generation for enantioselective reductions. **Table 1** details the use of bis(trifluoroethyl) *n*-butylboronate and bis(trifluoroethyl) ethylboronate in catalyst formation and subsequent CBS reductions with BH_3•THF or catecholborane as stoichiometric reductant. The enantioselectivities of reductions conducted by this new procedure are comparable to those observed with catalyst derived by dehydration of a mixture of (*S*)-2-(diphenylhydroxymethyl)-pyrrolidine and an alkylboronic acid.

Scheme 1.

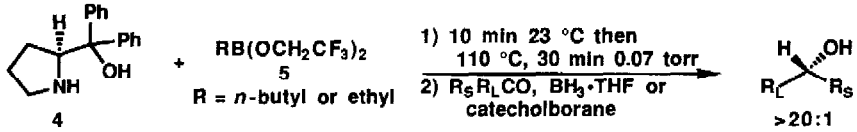


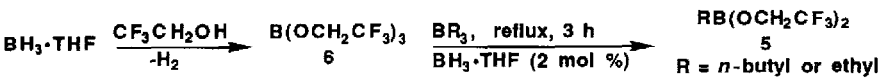
Table 1. CBS catalyzed ketone reductions

ketone	R in catalyst **2**	stoichiometric reductant	temp. °C (time (h))	ee% (configuration)	comparison ee%[d] (configuration)
acetophenone	*n*-butyl[a]	BH_3•THF	23 (0.1)	96 (*R*)	96 (*R*)
acetophenone	ethyl[a]	BH_3•THF	23 (0.1)	96 (*R*)	96 (*R*)
1,1,1-trichloro-4-phenylbutan-2-one	*n*-butyl[b]	catecholborane/ toluene	-78 (12)	94 (*R*)	95 (*R*)
1,1,1-trichloro-heptan-2-one	ethyl[a]	catecholborane/ toluene	-60[c] (12)	96 (*R*)	95 (*R*)

[a]The catalyst was generated *in situ* just prior to use. [b]The catalyst was generated, stored, and used as a stock solution. [c]This reaction was initiated at -78 °C and then warmed to -60 °C after 1 h. [d]These comparison reactions were run with catalyst **2** (Ar = Ph, R = *n*-butyl) generated from (*S*)-2-(diphenylhydroxymethyl)-pyrrolidine and *n*-butylboronic acid. The comparison reactions were run under identical reaction conditions as their counterparts (i.e., temperature, time, stoichiometric reductant and solvent).

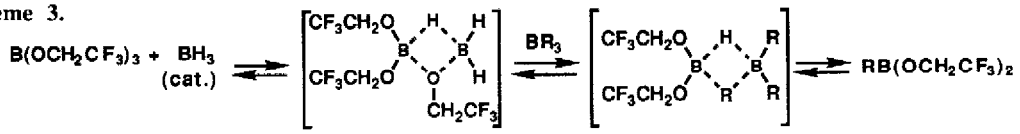
Consequent to the finding that bis(trifluoroethyl) alkylboronates **5** are extremely useful reagents, it became essential to devise a simple and effective procedure for their synthesis.[15] The new synthesis of bis(trifluoroethyl) alkylboronates which has resulted takes advantage of the facile redistribution of borate esters and trialkylboranes with BH_3•THF as catalyst.[16] We have found that BH_3•THF reacts quantitatively with dry trifluoroethanol to form tris(trifluoroethyl) borate, which then can be converted efficiently to **5**. The synthesis and distillation of bis(trifluoroethyl) *n*-butylboronate (**Scheme 2**) is carried out from a single flask as follows. Dry trifluoroethanol is added dropwise to BH_3•THF at 0 °C, the mixture is warmed to 23 °C and THF is removed by distillation at 1 atm. To the resultant neat tris(trifluoroethyl) borate **6** is added tributylborane[17] and BH_3•THF (2 mol%, redistribution catalyst) and the mixture is heated at reflux for 3 h. Distillation affords bis(trifluoroethyl) *n*-butylboronate **5** in 82% yield as a colorless non-viscous liquid, unchanged by storage at ambient temperature (with rigorous exclusion of water) for at least 6 months as measured by ^{11}B and ^1H NMR. A reasonable pathway for this borane-catalyzed conversion of tris(trifluoroethyl) borate **6** and a trialkylborane to a bis(trifluoroethyl) alkylboronate **5** involving bridged hydride intermediates is depicted in **Scheme 3**.[16b]

Scheme 2.



In conclusion, we have developed a new and simple synthesis of pure bis(trifluoroethyl) alkylboronates and have demonstrated their use as effective reagents for *in situ* oxazaborolidine catalyst formation. The high reactivity of these boronates allows fast and reproducible catalyst formation and provides ready access to a wide range of boro-heterocyclic structures. The following experimental details illustrate the preparative procedures.[18]

Scheme 3.



Bis(trifluoroethyl) Ethylboronate. A dry short path distillation apparatus having a septum in place of a thermometer was filled with N_2 and charged with BH_3•THF (35 mL, 35 mmol, 1 *M*) and trifluoroethanol (dropwise) (6.95 mL, 95 mmol, distilled from CaH_2) at 0 °C over 10 min (rapid gas evolution). After stirring at 23 °C for 20 min the septum was replaced with a thermometer and THF was removed by distillation at 1 atm (N_2) (70-74 °C). The mixture was cooled and the still head was replaced with a reflux condenser fitted with a septum with maintenance of the N_2 atmosphere. Triethylborane (2.76 mL, 19.1 mmol) was added followed by BH_3•THF (0.95 mL, 0.95 mmol, 1 *M*) and the mixture was heated at reflux for 3 h. The condenser was replaced with a dry distillation head. Distillation at 1 atm afforded a forerun (bp 70-80 °C). After cooling, the pressure was lowered to 50 torr and distillation was continued to give a forerun (40-47 °C), followed by bis(trifluoroethyl) ethylboronate as a colorless liquid boiling at 47-52 °C (6.92 g, 61%, based on CF_3CH_2OH), (containing *ca.* 2% of **6**; ^{11}B NMR (96 MHz, $CDCl_3$) δ 16.4 ppm). The receiving flask was fitted with a three-way stopcock for storage of the moisture sensitive bis(trifluoroethyl) ethylboronate; ^1H NMR (300 MHz, $CDCl_3$) δ 4.2 (q, J = 9 Hz, 4H) 0.9 (t, J = 8 Hz, 3H), 0.8 (q, J = 8 Hz, 2H); ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.2 ppm; d = 1.18 g/mL.

Bis(trifluoroethyl) *n*-Butylboronate was prepared by the procedure above; distillation at 1 atm afforded a forerun (bp 70-80 °C); after cooling, the pressure was lowered to 50 torr and bis(trifluoroethyl) *n*-butylboronate was distilled at 80-89 °C (8.95 g, 82%) as a colorless liquid: ^1H NMR (270 MHz, $CDCl_3$) δ 4.2 (q, J = 8 Hz, 4H), 1.4 (m, 4H), 0.9 (m, 5 H); ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.0 ppm; d = 1.12 g/mL.

(*R*)-1-Phenylethanol. To a dry flask fitted with a three-way stopcock (one inlet to N_2 or vacuum, the other a septum) containing (*S*)-2-(diphenylhydroxymethyl)-pyrrolidine (210 mg, 0.83 mmol, azeotropically dried with toluene) was added toluene (4 mL) and bis(trifluoroethyl) *n*-butylboronate (238 μL, 1.0 mmol) with stirring. After 10 min at 23 °C the toluene was removed *in vacuo* and the colorless oil was heated to 110 °C at 0.07 torr for 30 min. After cooling to 23 °C and returning to 1 atm (N_2), BH_3•THF (5.0 mL, 5.0 mmol, 1 *M*) was added to the neat catalyst with stirring. To this solution was added acetophenone (1.0 g, 8.3 mmol, in 7.3 mL THF) dropwise over 5 min. Reaction was complete upon addition, and the mixture was decomposed by the addition of HCl (1.92 mL, 1.0 mmol, 0.5 *M* in methanol). The solution was partially concentrated *in vacuo* and the resultant (*S*)-2-(diphenylhydroxymethyl)-pyrrolidine•HCl was recovered by filtration. The filtrate was diluted with ether and washed with sat. aqueous KH_2PO_4 and brine, concentrated, and passed through a short plug of silica gel with 6:1 20-40 pet. ether–ether to afford (*R*)-1-phenylethanol (960 mg, 7.9 mmol, 95% yield) of 96% ee analyzed by HPLC (Daicel Co. Chiracel OD, 5% *i*-PrOH in hexane, 8.9 min (*R*) major, 10.6 min (*S*) minor, 1 mL/min).

(*S*)-*B*-*n*-Butyl Catalyst 2 (Ar = Ph) formed as above; ^1H NMR (270 MHz, $CDCl_3$) δ 7.7-7.2 (m, 10H), 4.4 (dd, J = 9.9, 5.0 Hz, 1H), 3.4 (m, 1H), 3.1 (m, 1H), 1.8 (m, 2H), 1.6 (m, 3H), 1.4 (m, 2H), 1.0 (m, 5H), 0.8 (m, 1H); ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.7 ppm.

(*R*)-1,1,1-Trichloro-2-heptanol. To a dry flask fitted with a three-way stopcock (one inlet to N_2 or vacuum, the other a septum) containing (*S*)-2-(diphenylhydroxymethyl)-pyrrolidine (263 mg, 1.04 mmol, azeotropically dried with toluene) was added toluene (2.5 mL) and bis(trifluoroethyl) ethylboronate (253 μL, 1.25 mmol) with stirring. After 10 min at 23 °C the toluene was removed *in vacuo* and the colorless oil was heated to 110 °C at 0.07 torr for 30 min. After cooling to 23 °C and returning to 1 atm (N_2), toluene (5.2 mL) was added to the colorless CBS catalyst **2** (Ar = Ph, R = ethyl) followed by addition of 1,1,1-trichloroheptan-2-one (2.25 g, 10.4 mmol) and the mixture was cooled to -78 °C. Freshly distilled catecholborane (1.73 mL,

15.5 mmol, in 7.1 mL of toluene) was added dropwise over 10 min directly into the reaction mixture with vigorous stirring. A white precipitate formed and after 1 h the mixture was warmed to -60 °C (becoming homogeneous), and maintained at -60 °C for 12 h. The mixture was decomposed by addition of methanolic HCl (2.5 mL, 1.25 mmol, 0.5 *M*) and allowed to warm to 23 °C. Partial concentration *in vacuo* afforded a fine white precipitate ((*S*)-2-(diphenylhydroxymethyl)-pyrrolidine • HCl) which was recovered by filtration. The filtrate was diluted with ether, washed with pH 13 buffer until the aqueous washings were colorless (7 x 5 mL), then brine (3 x 10 mL), and dried over magnesium sulfate and concentrated *in vacuo* to afford 2.13 g (94% yield) of (*R*)-1,1,1-trichloro-2-heptanol as a colorless oil after sg chromatography (10 : 1 hexane–ethyl acetate). Chiracel HPLC analysis revealed the alcohol had an ee of 96% (OD column; 1.5% *i*-PrOH–hexane, 8.1 min minor, 8.7 min major, refractive index detector); ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.0 (ddd, *J* = 9.7, 5.6, 1.5 Hz, 1H) 2.7 (d, *J* = 5.6 Hz, 1H, -OH), 2.05 (m, 2H) 1.7-1.2 (m, 6H), 0.9 (br t, *J* = 5.4 Hz, 3H); IR (neat) 3400, 2960 cm^{-1}; CIMS (triethylsilyl ether): 350 $[M+NH_4]^+$; HRMS (triethylsilyl ether): calcd. for $[C_{13}H_{27}OCl_3Si+NH_4]^+$: 350.1240; found: 350.1227.

(*S*)-*B*-Ethyl Catalyst 2 (Ar = Ph) formed as above; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6-7.2 (m, 10H), 4.4 (dd, *J* = 9.5, 4.0 Hz, 1H), 3.4 (m, 1H), 3.1 (m, 1H), 1.8 (m, 2H), 1.7 (m, 1H), 1.2 (m, 3H), 1.0 (m, 2H), 0.8 (m, 1H); ^{11}B NMR (96 MHz, $CDCl_3$) δ 33.9 ppm.

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14. Initially bis(trifluoroethyl) alkylboronates react rapidly (< 5 min, 23 °C) with amino alcohols such as **4** with loss of 1 equiv of trifluoroethanol to form a mixed boronate ester (^{11}B NMR *ca.* 7 ppm). Heating *in vacuo* affords the oxazaborolidine.
15. The bis(trifluoroethyl) alkylboronates initially used in this research were prepared by a cumbersome two-step sequence, (1) reaction of a 1-alkene with Br_2BH•Me_2S and (2) distillation of the resulting alkyl dibromoborane, reaction with trifluoroethanol (HBr evolution) and distillation.
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17. Commercially available tributylborane contains 94% *n*-butyl and 6% *sec*-butyl groups. This isomer distribution has not interfered with catalyst selectivity (**Table 1**).

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