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Asymmetric Synthesis of Tertiary Alcohols from α-Halo Boronic Esters

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ABSTRACT

Reaction of pinanediol boronates with (1,1-dichloroethyl)lithium generated in situ at −78°C followed by rearrangement of the resulting borate complex **2S** *in the presence of zinc chloride at 25°C has resulted in chirally biased insertion of the 1-chloroethyl group into the carbon–boron bond.* (s)-*Pinanediol phenylboronate* (**7**) *produced* (s)-*pinanediol* (*1*S)-(*1-chloro-1-phenylethyl)boronate* (**8S**) *in 92% DE. Nonstereospecific reaction with ethylmagnesium bromide to form* (s)-*pinanediol* (*1*S)-(*1-phenyl-1-methylpropyl)boronate* (**5S**) *reduced the DE to 88%. Peroxidic deboronation yielded* (R)-(+)-*2-phenyl-2-butanol* (**6R**) (*84% EE*). (s)-*Pinanediol ethylboronate* (**4**) *with (1,1-dichloroethyl)lithium showed the opposite chiral preference, yielding* (s)-*pinanediol* (*1*R)-(*1-chloro-1-methylpropyl)boronate* (**3R**) (*89% DE*), *which was converted by phenylmagnesium bromide followed by hydrogen peroxide to* **6R** (*76% EE*). *Diastereoselections were small in reactions of (1,1-dichloroethyl)-lithium with* n-*alkylboronates* **9a** *and* **13** *and with cyclohexylboronate* **9c.** *The* **13** *was converted to the enantiomer of the insect pheromone frontalin* (**17**) (*21% EE*). *Good diastereoselections were found with α-substituted alkylboronates* **9b** *and* **18,** *but the configurations of the products could not be determined.* (s)-*Pinanediol (1,1-dichloroethyl)boronate* (**1**) *reacts with Grignard reagents via an intermediate borate* **2R** *with negligible diastereoselection.*

INTRODUCTION

The reaction of pinanediol boronic esters with (dichloromethyl)lithium in tetrahydrofuran (THF) at −100°C results in borate complexes that rearrange at 0–25°C in the presence of zinc chloride to form α-chloroboronic esters, usually in ≥97% diastereometric excess [DE, defined as $100(x_1 - x_2)$, where x_1 and x_2 are the mole fractions of the two diastereomers] [1, 2]. A hydrogen atom has always been one of the ligands on the carbon in such processes, and the small size of hydrogen must be a major factor in the stereoselectivity. In the present work it is shown that reactions of some types of pinanediol boronic esters with (1,1-dichloroethyl)-lithium can provide levels of asymmetric induction up to 80–90% DE, enough to be synthetically useful.

RESULTS

(s)-*Pinanediol (1,1-Dichloroethyl)boronate* (1)

Our first problem was to find a good preparative route to (1,1-dichloroethyl)lithium and conditions for reacting this very labile species with boronic esters. This problem was first solved by adding lithium diisopropylamide (LDA) to 1,1-dichloroethane in tetrahydrofuran (THF) in the presence of trimethyl borate at −78°C, followed by treatment of the resulting borate complex with anhydrous hydrogen chloride to form dimethyl (1,1-dichloroethyl)boronate [3]. Transesterification with (*s*)-pinanediol [4,5] then yielded (*s*)-pinanediol (1,1-dichloroethyl)boronate (**1**).

The stereoselective step in the synthesis of α-haloboronic esters is the rearrangement of a borate

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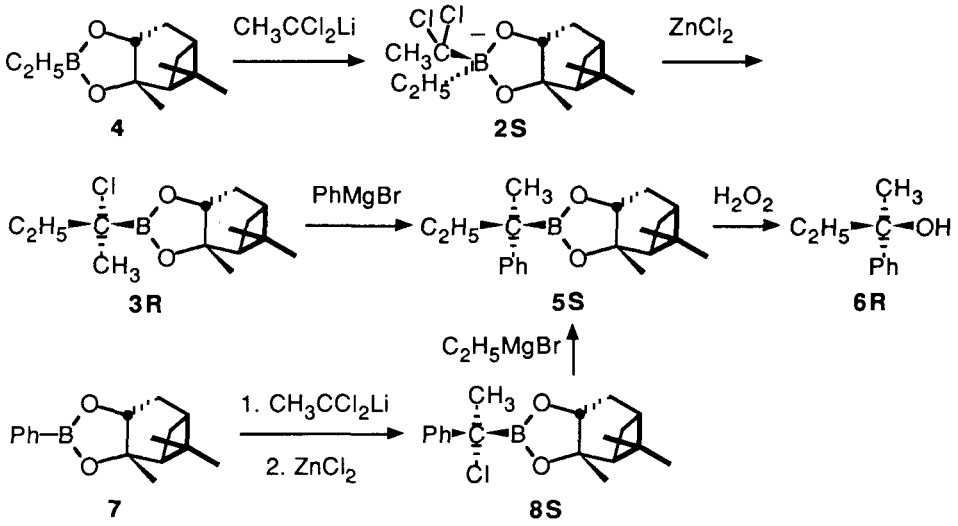
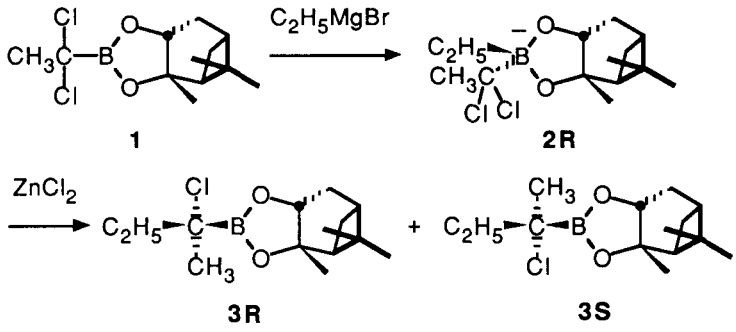


SCHEME 1

complex. With (*s*)-pinanediol as chiral director, there are two diastereomeric borates which result from different synthetic routes [6]. Ethylmagnesium bromide was expected to add to the less hindered face of (*s*)-pinanediol (1,1-dichloroethyl)-boronate (**1**) to form intermediate borate **2R**, in which the boron atom has the *R* configuration. Rearrangement of **2R** in the presence of zinc chloride has yielded a 37 : 63 mixture of (*s*)-pinanediol (1*R*)-(1-chloro-1-methylpropyl)boronate [7] (**3R**) (^{1}H NMR, δ 1.191, d, J = 11 Hz, pinyl C*H* [1]) and its diastereomer (**3S**) (δ 1.203, d, J = 11 Hz). This low diastereoselection has precedent in the reactions of (*s*)-pinanediol (dichloromethyl)boronate with various Grignard or lithium reagents [6].



(1)

Reaction of 63 : 37 **3S**/**3R** with phenylmagnesium bromide in THF yielded a 45 : 55 mixture of (*s*)-pinanediol (1*S*)-(1-phenyl-1-methylpropyl)boronate (**5S**) (δ 1.013, 4.258) and its (1*R*) diastereomer (δ 1.008, 4.278) (**5R**, not illustrated). This failure of stereospecificity in the displacement of chloride by migrating phenyl was unexpected. Oxidation by hydrogen peroxide yielded slightly nonracemic 2-phenyl-2-butanol, 6% EE (enantiomeric excess) of the (*S*)-(−) isomer [8] (**6S**, enantiomer of illustrated **6R**).

(1,1-Dichloroethyl)lithium with Pinanediol Boronates

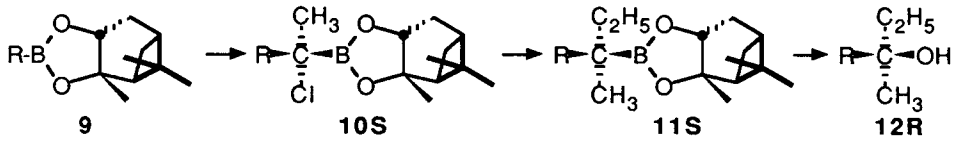
The other diastereomeric borate complex **2S**, in which the configuration at boron is *S*, should arise from addition of (1,1-dichloroethyl)lithium to the less hindered face of (*s*)-pinanediol ethylboronate (**4**) (Scheme 1). There is precedent for much higher diastereoselection in this diastereomeric series of borate complexes [2, 6]. The (1,1-dichloroethyl)-lithium was generated in the presence of **4**, and rearrangement of the resulting **2S** in the presence of enough zinc chloride to complex with the diisopropylamine from the LDA as well as the chloride ion from the rearrangement–displacement process, the resulting ratio of **3R** (δ 1.191) to **3S** (δ 1.203) was 89 : 11 (78% DE). The absolute configuration was proved by reaction of **3R** (78% DE) with phenylmagnesium bromide in THF to produce (*s*)-pinanediol (1*S*)-(1-phenyl-1-methylpropyl)boronate (**5S**) (δ 4.277) in 70% DE over the (1*R*) diastereomer (**5R**) (δ 4.258). Oxidation by hydrogen peroxide

yielded (*R*)-(+)-2-phenyl-2-butanol (**6R**), 70% EE (enantiomeric excess). When the reaction of **3R** with phenylmagnesium bromide was carried out in ether, there was negligible loss of chiral purity as indicated by the EE of the derived (*R*)-(+)-2-phenyl-2-butanol (**6R**), 76%.

The best diastereoselectivity was obtained when (*s*)-pinanediol phenylboronate (**7**) reacted with (1,1-dichloroethyl)lithium to produce (*s*)-pinanediol (1*S*)-(1-chloro-1-phenylethyl)boronate (**8S**) in 92% DE [^{1}H NMR, δ 1.171, d, J = 11 Hz; (1*R*) isomer **8R**, δ 1.107, 4%]. The NMR absorptions of the minor isomer **8R** were identified by epimerization of a sample of **8S** with lithium chloride in THF [10], which produced a nearly equimolar mixture. The absolute configuration was proved by treatment of **8S** with ethylmagnesium bromide in diethyl ether to form **5S**, DE 88% based on ^{1}H NMR multiplets at δ 4.258 (**5R**) and 4.278 (**5S**), followed by oxidation with hydrogen peroxide to **6R**, EE 84%.

It was unexpected that **4** and **7** would insert the CH_3CCl group in opposite chiral directions, and the preferential formation of **8S** is contrary to all precedent set by the (dichloromethyl)borate rearrangements [2]. The most unfortunate feature of this unexpected result is that the diastereoselection in the migration of normal alkyl substituents longer than ethyl turns out to be uselessly poor as well as unpredictable in direction. Branched chains tend to yield useful diastereoselection, but it has not yet been proved whether the absolute configuration of the newly introduced chiral center is entirely predictable.

An example of a normal alkyl group is provided by (*s*)-pinanediol butylboronate (**9a**), which was converted to (*s*)-pinanediol (1*S*)- and (1*R*)-(1-chloro-1-methylpentyl)boronate [**10Sa** (illustrated) and **10Ra** (not illustrated)] in ~49 : 51 ratio, as indicated by further conversion to (*s*)-pinanediol (1-ethyl-1-methylpentyl)boronate (**11Sa/11Ra**) and 3-methyl-3-heptanol (**12Ra/12Sa**) having ~2% EE of **12Sa**, assuming the rotation in ether is of the same sign and general magnitude of that of the neat liquid.



(2)

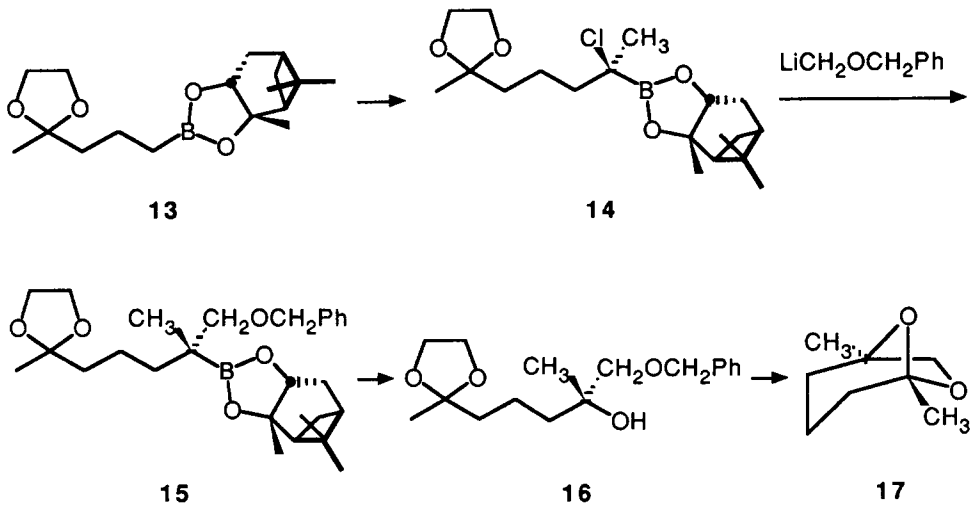
where R for **a** = *n*-butyl; for **b**, isopropyl (**9** and **10** only); for **c**, cyclohexyl.

For an example of a branched chain, (*s*)-pinanediol isopropylboronate (**9b**) was treated with (1,1-dichloroethyl)lithium to form **10Sb** or possibly its (1*R*) diastereomer. We did not find any possible derivative of **10b** in the literature that could be used to prove its configuration. However, the DE of **10b** appeared to be ~95% as indicated by ^{1}H NMR δ 1.23 (d, J = 11 Hz, pinyl C*H* of **10b**), δ 1.25 (d, partially obscured, pinyl C*H* of diastereomer). When **10b** was prepared by the unselective route from (*s*)-pinanediol (1,1-dichloroethyl)boronate (**1**) and isopropylmagnesium chloride, these NMR peaks appeared in the ratio of 1 : 2, with the diastereomer the predominant species.

(*R*)-(−)-2-Cyclohexyl-2-butanol (**12Rc**) is of known absolute configuration [11]. Application of the illustrated reaction sequence to (*s*)-pinanediol cyclohexylboronate (**9c**) yielded (*s*)-pinanediol (1*S*)-(1-chloro-1-cyclohexylethyl)boronate (**10Sc**). The ^{1}H NMR spectrum did not indicate the presence of two diastereomers, but no alternative synthesis was carried out in order to find out whether these diastereomers would be distinguishable. With ethylmagnesium bromide, **10Sc** formed (*s*)-pinanediol (1*S*)-(1-cyclohexyl-1-methylpropyl)-boronate (**11Sc**), which on oxidation yielded **12Rc** in only ~20% EE, assuming that the rotation of our small sample in benzene approximates that of the neat liquid.

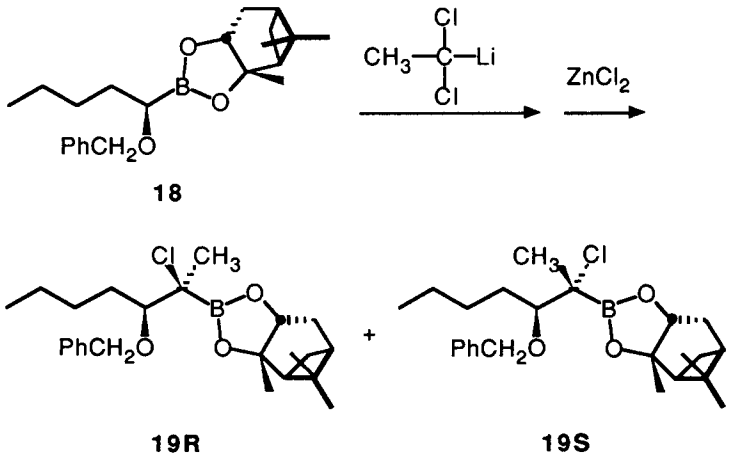
Functionalized Pinanediol Boronates

(1*S*)-(−)-Frontalin, a pheromone of pine beetles [12], was chosen as a target for a natural product synthesis. The reaction of (*s*)-pinanediol [4-(ethylenedioxy)pentyl]boronate [1] (**13**) with (1,1-dichloroethyl)lithium resulted in a modest diastereomeric excess of (*s*)-pinanediol (1*R*)-[1-chloro-1-methyl-5-(ethylenedioxy)hexyl]boronate (**14**). The sense of stereodirection is the same as observed with the ethylboronate **4**. We first tried the reaction of **14** with lithium benzyloxide in order to make the α-benzyloxy boronic ester, which might have served as a precursor to (1*S*)-(−)-frontalin via further chain extension, but we obtained only the α,β-unsaturated boronic esters resulting from abstraction of hydrogen chloride from **14**. These compounds were not characterized beyond the ^{1}H NMR evidence. Treatment of **14** with [(benzyloxy)-methyl]lithium led to (*s*)-pinanediol (1*S*)-[1-(benzyloxymethyl) - 1 - methyl - 5 - (ethylenedioxy)hexyl]boronate (**15**). Oxidative deboronation yielded (2*R*)-1-benzyloxy-2-methyl-6-(ethylenedioxy)-2-heptanol (**16**), which was hydrogenated to form (1*R*)-(+)-frontalin (**17**) in 21% EE, the enantiomer of natural (1*S*)-(−)-frontalin [12].



(3)

As a further test of the diastereoselectivity of the process, we undertook the reaction of (*s*)-pinanediol (1*R*)-[(1-benzyloxy)pentyl]boronate (**18**) with (1,1-dichloroethyl)lithium, which yielded a 10:1 mixture of the diastereomers (*s*)-pinanediol (1*R*,2*S*)- and (1*S*,2*S*)-(2-benzyloxy-1-chloro-1-methylhexyl)boronate (**19R** and **19S**) as indicated by ^{1}H NMR data. Although the doublet at δ 1.23, J = 11 Hz, showed no difference between these two diastereomers, distinctive benzyl proton AB patterns were seen for the major isomer at δ 4.68 and 4.95, J = 11.0 Hz, and the minor isomer at δ 4.70 and 4.80, J = 11.6 Hz. These diastereomers were found to be easily separable by chromatography. By analogy to the reactions of (1,1-dichloromethyl)lithium with the phenylboronic ester **7** and the cyclohexylboronic ester **9c**, the major isomer is postulated to be **19S**, but no characterization of these compounds beyond the NMR data has been carried out.



(4)

Further evidence that the ^{1}H NMR data on the benzyl protons distinguish diastereomers was obtained by reacting the pinacol ester analog of **18**, $C_4H_9CH(OCH_2Ph)BO_2C_2(CH_3)_4$, with (1,1-dichloroethyl)lithium. The two diastereomers from this reaction were produced in approximately equal amounts, as indicated by the benzyl AB patterns at δ 4.66 and 4.96, J = 11.0 Hz (analog of major isomer of **19**), and at δ 4.68 and 4.77, J = 11.6 Hz (analog of minor isomer of **19**).

DISCUSSION

The information obtained from this study falls into two categories. First, some synthetically useful levels of diastereoselectivity have been found with arylboronic and α-substituted alkylboronic esters, and some of the practical problems that need to be solved before this chemistry can be applied to synthesis have at least been defined. Second, the

results put some constraints on speculation about the mechanism of the diastereoselective step.

With (*s*)-pinanediol *n*-alkylboronates (**4, 13**), (1,1-dichloroethyl)lithium tends to produce chain extended (1*R*)-(1-chloro-1-methylalkyl)boronates (**3R, 14**). The apparent exception, conversion of *n*-butylboronate **9a** to α-chloro boronic ester **10a,** is essentially unselective. The conversion of **4** to **3R** is selective enough (≥75% DE) that it could be useful for assembling quaternary chiral centers of the type $(CH_3)(C_2H_5)CR^1R^2$, especially if $R^1:R^2$ contains an additional chiral center that might help with purification to a single chiral species. Ethylene glycol *tert*-butylboronate is known to react with (dichloromethyl)lithium in the normal manner [13], but the chain extension of other *tert*-alkylboronic esters has not been explored.

The more hindered (*s*)-pinanediol phenylboronate (**7**) and α-substituted alkylboronates (**9b, 9c, 18**) appear to be generally more suitable candidates for synthetic applications. The conversion of **7** to **8S** in apparently ≥90% DE promises a practical general route to $(CH_3)(Ar)CR^1R^2$ of known absolute configuration.

There are several unsolved problems. The loss of chiral purity during subsequent conversions of **3R** and **8S** is disconcerting. The loss appeared to be greater when **3R** or **8S** reacted with a Grignard reagent in THF than in diethyl ether. Inasmuch as **3R** and **8S** resemble tertiary alkyl chlorides, perhaps epimerization [10] is exceptionally facile, possibly via carbocations, possibly via boron-stabilized radicals [14].

The conversion of isopropylboronic ester **9b** to **10b** in ~95% DE seems especially promising, and it is unfortunate that proving the configuration of **10b** was not feasible. The cyclohexylboronic ester **9c** led to alcohol **12c** of apparently low EE (~20%). There is the possibility that the rotation of the small sample, taken in benzene, is grossly different from that of the neat liquid recorded in the literature, and even some possibility that the rotation could change sign with solvent. However, the initial appearance of low stereoselectivity did not encourage further investigation. It is possible that **10Sc** was formed in good DE, there being no ^1H NMR evidence of a mixture at that point, and that the low EE of the derived **12Rc** resulted from accidental epimerization of **10Sc** prior to or during conversion to **11Sc.** If such epimerization occurred, there is no guarantee that the configuration of the **11c** is at all connected to that of **10c,** as an intermediate cation or radical could be slightly biased toward producing either diastereomer.

In contrast, the stereochemistries of the conversions of ethylboronate **4** via **3R** and **5S** to 2-phenyl-2-butanol **6R** and of phenylboronate **7** via **8S** and **5S** to **6R** are firmly established. Even though not fully stereospecific, the conversion of (1,1-dichloroethyl)boronate **1** to **3S:3R** was followed by production of **5R:5S** and ultimately 2-phenyl-2-butanol **6S:6R** of opposite predominant chirality, precluding any possibility that the initial stereochemical biases were leveled by an intermediate equilibrium-controlled step in this case.

One reason for making frontalin (**17**) was to provide another determination of the stereochemical preference in the reaction of an unbranched alkylboronic ester with (dichloroethyl)lithium. Again it can be argued that the EE of the **17** obtained was within the range of possible equilibrium control, and while it appears that the (α*R*) isomer of α-chloroboronic ester **14** predominates, this point has not been proved unequivocally. No inference of stereochemical preference can be drawn for the conversion of butylboronic ester **9a** to α-chloroboronic ester **10a** since the derived alcohol **12a** was essentially racemic.

With regard to mechanistic information, the present results imply that stereochemical control of the chirality-determining intramolecular displacement rests more on the relative sizes of the substituents on the (α,α-dihaloalkyl)borate than on their relative polarities or cation complexing abilities. If the chirality of the rearrangement–displacement process were controlled by some sort of chelation of the zinc chloride between the chlorine atom that is not displaced and the chiral directing group, the preferred chirality direction should remain the same regardless of whether the carbon at which displacement takes place is substituted with H or CH_3 and should also be independent of the migrating group.

The product formed is dependent on which of the two prochiral chlorine atoms lies anti to the migrating group and is thus most easily displaced. The contrast in size and perhaps polarity between chlorine and hydrogen produces consistent behavior in the $CHCl_2$ group [1]. The size difference between chlorine and methyl in the CCl_2CH_3 group is not so clearcut. The methyl group is larger than the chlorine atom by only 11% in estimated volume [15], although the radius of chlorine (1.73 Å [15]) is substantially less than the longest estimated radial dimension of a methyl group (1.094 + 1.45 = 2.544 Å [16]). The relative energies of axial and equatorial substituents in cyclohexanes for chlorine (ΔG° = 0.5 kcal mol^{-1}) are closer to hydrogen (ΔG° = 0) than to methyl (ΔG° = 1.74 kcal mol^{-1}) [17]. In view of the multiplicity of possible modes of neighboring group interaction, it is not too surprising that the preferred orientation of the CCl_2CH_3 group in the transition state for rearrangement of the borate complex is dependent on the migrating alkyl or aryl group, and that the diastereoselections are not large. The thermodynamic difference between transition states which produce 80% DE and 0% DE is only ~1 kcal mol^{-1}, too small to justify further speculation about possible neighboring group interactions.

CONCLUSIONS

The following conclusions may be drawn:

1. Reaction of (*s*)-pinanediol ethylboronate (**4**) with (1,1-dichloroethyl)lithium leads to (*s*)-pinanediol(1*R*)-(1-chloro-1-methylpropyl)boronate (**3R**) (78% DE), which with phenylmagnesium bromide in ether yields (1*S*)-(1-phenyl-1-methylpropyl)boronate (**5S**) (76% DE).
2. Reaction of (*s*)-pinanediol phenylboronate (**7**) with (1,1-dichloroethyl)lithium produces (*s*)-pinanediol (1*S*)-(1-chloro-1-phenylethyl)boronate (**8S**) (92% DE), which with ethylmagnesium bromide in ether yields (1*S*)-(1-phenyl-1-methylpropyl)boronate (**5S**) (88% DE).
3. The chiral direction of insertion of the CH_3CCl group into the carbon–boron bond is therefore opposite for **4** and **7**, and is clearly dependent on the nature of the migrating group.
4. Reactions of pinanediol *n*-alkylboronates with (1,1-dichloroethyl)lithium are only slightly diastereoselective.
5. Reactions of (*s*)-pinanediol 1-substituted alkylboronates with (1,1-dichloroethyl)lithium may yield DEs in the ≥90% range. It is tentatively suggested that the preferred stereochemistry is the same as with phenylboronate **7**, but this is by no means certain.
6. [(Chloro)(dialkyl)methyl] boronic esters, such as **3R** and **14**, have some characteristics in common with tertiary alkyl chlorides. Elimination of hydrogen chloride is sometimes seen as a side reaction of these boronic esters with bases, and some degree of epimerization may occur during reactions with bases.
7. Pinanediol (1,1-dichloroethyl)boronate does not yield useful diastereoselection in its reactions with Grignard reagents, and is similar to pinanediol (dichloro)methylboronate in this regard.

EXPERIMENTAL

General

Reactions involving air-sensitive reagents were run under argon. Tetrahydrofuran (THF) was freshly distilled from benzophenone ketyl. Butyllithium was titrated against 2-propanol with 1,10-phenanthroline as indicator. Liquids were transferred via glass syringes with stainless steel needles or via cannula through rubber septa. Lithium diisopropylamide (LDA) was freshly prepared by adding 1.6 *M* butyllithium in hexane to an equivalent amount of 0.2 *M* diisopropylamine in THF. "Anhydrous zinc chloride" was prepared by stirring granular reagent-grade anhydrous zinc chloride under vacuum at 100°C several hours, resulting in a fine free-flowing powder [1]. Preparative thin layer chromatography was done on Baker 60–200 mesh silica gel, and column chromatography on EM Science 230–400 mesh silica gel. The 90-MHz ^1H and 22-MHz ^{13}C NMR spectra were taken on a JEOL FX90Q Fourier transform instrument, and the 200-MHz ^1H and 50-MHz ^{13}C NMR spectra were taken on a Nicolet NT-200 instrument. Optical rotations were measured with a Jasco DIP-181 digital polarimeter. Melting points were taken in capillary tubes in a Thomas-Hoover liquid bath melting point apparatus and are uncorrected. Boiling points are uncorrected. Microanalyses were by Galbraith Laboratories, Knoxville, Tennessee.

(s)-*Pinanediol (1,1-Dichloroethyl)boronate* (**1**)

Dimethyl (1,1-dichloroethyl)boronate [3] (26.5 g, 155 mmol) and (*s*)-pinanediol (98% EE) (26.4 g, 155 mmol) were stirred in 200 mL of diethyl ether and washed with three 50-mL portions of water. The organic phase was dried over magnesium sulfate and concentrated under vacuum to 42 g (98%) of solid **1**, mp 73–75°C. The material was recrystallized from methanol–water (3:1 ratio, 15 mL methanol per gram of **1**), mp 77.5–78.5°C, 57%, with additional material recoverable from the mother liquor; $[\alpha]^{25}_{577}$ + 35.4°; $[\alpha]^{25}_{546}$ + 40.5°; $[\alpha]^{25}_{435}$ + 69.8°; $[\alpha]^{25}_{365}$ + 111.6° (c, 4.1, benzene); 200-MHz ^1H NMR ($CDCl_3$), δ 0.86 (s, 3 pinyl CCH_3), 1.24 (d, J = 11 Hz, 1, pinyl CH), 1.31 (s, 3, pinyl CCH_3), 1.47 (s, 3, pinyl CCH_3), 1.90–2.02 (m, 2, pinyl CH_2), 2.15 (s, 3, CH_3CCl_2), 2.22–2.50 (m, 2, pinyl CH_2), 4.48 (dd, 1, OCH). Analysis, calculated for $C_{12}H_{19}BCl_2O_2$, C, 52.03; H, 6.91; B, 3.90; Cl, 25.60; found, C, 52.21; H, 6.95; B, 4.27; Cl, 25.78.

(s)-*Pinanediol (1-Phenyl-1-methylpropyl)boronate* (**5S/5R**) *and 2-Phenyl-2-butanol* (**6S/6R**) *from* **1**

A solution of 4.16 g (15 mmol) of (*s*)-pinanediol (1,1-dichloroethyl)boronate (**1**) in 25 mL of THF was stirred at −78°C during the addition of 15 mmol of ethylmagnesium bromide (2 *M* in ether). After 15 min, 1.36 g (10 mmol) of zinc chloride was added and the reaction was allowed to warm to room temperature overnight. The crude product **3R/3S** was isolated via "Workup with Magnesium Sulfate" (see next section); 200-MHz ^1H NMR ($CDCl_3$) δ 1.191 (d, J = 11 Hz, 0.37, pinyl CH of minor isomer), 1.203 (d, J = 11 Hz, 0.63, pinyl CH of major isomer). The crude **3R/3S** in 50 mL of THF at −78°C was stirred during the addition of 15 mmol of phenylmagnesium bromide (3 *M* in ether) from a syringe. The mixture was stirred 1 h at −78°C, than allowed to warm to room temperature. Concentration and treatment with magnesium sulfate and ether–petroleum ether in the usual manner [3] (see next

paragraph for details) yielded an oil which was purified by flash chromatography with 5% ether in petroleum ether, R_f 0.6, 3.65 g (78%); 200-MHz ^{1}H NMR ($CDCl_3$), δ 1.008 [d, J = 11 Hz, 0.45, pinyl C*H* of (*S*) isomer], 1.013 [d, J = 11 Hz, 0.55, pinyl C*H* of (*R*) isomer], 4.258 (dd, pinyl OC*H* of (*R*) isomer), 4.278 (dd, pinyl OC*H* of (*S*) isomer). Oxidation with hydrogen peroxide yielded 1.8 g (93%) of (*S*)-(−)-2-phenyl-2-butanol, $[\alpha]_{546}^{22}$ −0.94° (c, 4.1, acetone), EE 6%.

Workup with Magnesium Sulfate

The mixture was concentrated on a rotary evaporator to a viscous liquid. Petroleum ether (bp 30–60°C, 5–10 mL mmol^{-1} of boronic ester) was added and the two-phase system was stirred. The petroleum ether phase was decanted into a stirring slurry of magnesium sulfate (~1 g mmol^{-1} of boronic ester) in petroleum ether (10–20 mL mmol^{-1}). The gummy residue of lithium (or magnesium) and zinc halides and residual THF was extracted with three or four additional portions of petroleum ether (until evaporation of a drop on a watch glass left no residue) and these extracts were added to the magnesium sulfate slurry. A fritted glass filter was prepared with a slurry of fresh magnesium sulfate and petroleum ether, and the extracts from the reaction mixture were filtered through this bed of magnesium sulfate and the magnesium sulfate was rinsed with additional petroleum ether. The petroleum ether extracts were concentrated under vacuum (rotary evaporator) to yield a residue of the oily crude product.

(s)-*Pinanediol* (*1*S)-(*1-Chloro-1-phenylethyl*)*boronate* (**8S**)

A solution of lithium diisopropylamide was prepared by addition of 1 mmol of 1.6 *M* butyllithium in hexane to 0.14 mL (1 mmol) of diisopropylamine in 5 mL of THF. This solution was added via cannula to a solution of 0.255 g (1 mmol) of pinanediol phenylboronate (**7**) and 0.17 mL (2 mmol) of 1,1,-dichloroethane in 5 mL of THF stirred at −78°C. After 15 min, 0.23 g (1.7 mmol) of anhydrous zinc chloride was added in one portion [1]. The cooling bath was removed and the mixture was allowed to warm to 20–25°C. Workup with magnesium sulfate (see previous section) yielded 0.30 g (93%) of crude **8S**; 200-MHz ^{1}H NMR ($CDCl_3$), δ 0.832 (s, 3, pinyl CC*H*$_3$), 1.107 (d, J = 11 Hz, 0.04, pinyl C*H* of minor isomer), 1.171 (d, J = 11 Hz, 0.96, pinyl C*H* of major isomer), 1.281 (s, 3, pinyl CC*H*$_3$), 1.415 (s, 3, pinyl CC*H*$_3$), 1.97 (s, 3, C*H*$_3$CCl), 1.7–2.5 (m, 6, pinyl C*H*), 4.394 (dd, 1, pinyl OC*H*), 7.2–7.6 (m, 5, C$_6$*H*$_5$). A computer line fit of the doublets centered at δ 1.107 and 1.171 indicated that the isomer ratio was 1 : 22.

(s)-*Pinanediol* (*1*S)-(*1-Phenyl-1-methylpropyl*)*boronate* (**5S**) *and* (R)-(+)-*2-Phenyl-2-butanol* (**6R**) *from* **7**/**8S**

To a solution of 1.48 g (4.64 mmol) of (*s*)-pinanediol (1*S*)-(1-chloro-1-phenylethyl)boronate in 15 mL of ether stirred at −78°C was added dropwise 4.64 mmol of 2 M ethylmagnesium bromide in ether. The cooling bath was removed and the mixture was stirred overnight at 20–25°C. Workup with magnesium sulfate yielded 1.36 g of **5S**; 200-MHz ^{1}H NMR ($CDCl_3$), δ 1.008 (d, J = 11 Hz, 1, pinyl C*H* of major isomer), 1.013 (d, J = 11 Hz, 0, pinyl C*H* of minor isomer), 4.258 (dd, 0.05–0.06, OC*H*), 4.278 (dd, 0.95–0.96, OC*H*). This crude **5S** was dissolved in 25 mL of THF and treated with a tenfold excess of hydrogen peroxide and potassium hydroxide and stirred overnight. (*R*)-(+)-2-Phenyl-2-butanol (**6R**) was isolated by extraction and distillation; $[\alpha]_{589}^{22}$ +15.68°, $[\alpha]_{546}^{22}$ +17.87° (neat); $[\alpha]_{589}^{22}$ +13.0°, $[\alpha]_{546}^{22}$ +15.7° (c, 1.0, acetone) [lit. [8] $[\alpha]_{589}^{22}$ +18.4° (neat)]; EE 85%.

(s)-*Pinanediol* (*1*R)-(*1-Chloro-1-methylpropyl*)*boronate* (**3R**)

Lithium diisopropyl amide (5 mmol) was added to a solution of 1.04 g (5 mmol) of (*s*)-pinanediol ethylboronate (**4**) and 0.84 mL (10 mmol) of 1,1-dichloroethane in 25 mL of THF stirred at −78°C. After 15 min, 1.155 g (8.5 mmol) of anhydrous zinc chloride was added in one portion. The cooling bath was removed and the mixture was allowed to warm to room temperature overnight. Workup with magnesium sulfate yielded 1.18 g (87%) of impure **3R**; 200-MHz ^{1}H NMR ($CDCl_3$), δ 0.851 (s, 3, pinyl CC*H*$_3$), 1.007 (t, 2, CHC*H*$_3$), 1.191 (d, J = 11 Hz, 0.88, pinyl C*H* of major isomer), 1.203 (d, J = 11 Hz, 0.12, pinyl C*H* of minor isomer), 1.298 (s, 3, pinyl CC*H*$_3$), 1.413 (s, 3, pinyl CC*H*$_3$), 1.565 (s, 3, C*H*$_3$CCl), 1.8–2.45 (m, 8, pinyl C*H* and CH$_3$C*H*$_2$), 4.369 (dd, 1, pinyl OC*H*); MS *m/e* (relative intensity), 270 (2), 234 (12), 214 (23), 185 (35), 145 (80), 118 (54), 93 (53), 83 (69), 69 (68), 58 (100); exact mass calculated for $C_{14}H_{24}BClO_2$, 270.1558; found, 270.1326. A computer line fit of the doublets centered at δ 1.191 and 1.203 indicated an 8 : 1 isomer ratio.

(s)-*Pinanediol* (*1*S)-(*1-Phenyl-1-methylpropyl*)*boronate* (**5S**) *and* (R)-(+)-*2-Phenyl-2-butanol* (**6R**) *from* **4**/**3R**

A solution of 1.04 g (4.64 mmol) of (*s*)-pinanediol (1*R*)-(1-chloro-1-methylpropyl)boronate (**3R**) in 15 mL of THF at −78°C was stirred during the dropwise addition of 4.64 mmol of 2 *M* phenylmagnesium bromide in ether. The cooling bath was removed and the mixture was stirred at 20–25°C overnight. Workup with magnesium sulfate yielded

1.31 g (97%) of **5S**; 200-MHz ^{1}H NMR ($CDCl_3$), δ 0.91 (s, 3, pinyl CCH_3), 0.96 (t, 3, CCH_3), 1.01 (d, J = 11 Hz, ~1, pinyl CH of major isomer), 1.013 (d, not well enough resolved to estimate quantity of minor isomer), 1.32 (s, 3, pinyl CCH_3), 1.42 (s, 3, pinyl CCH_3), 1.60–2.40 (m, 6, pinyl CH), 4.258 (dd, 0.15, pinyl OCH of minor isomer), 4.278 (dd, 0.85, pinyl OCH of major isomer), 7.10–7.37 (m, 5, C_6H_5); mass spectrum *m/e* (relative intensity), 312 (100), 297 (12), 283 (50), 269 (8), 257 (10), 243 (11), 229 (8), 213 (13), 187 (19), 173 (24); exact mass calculated for $C_{20}H_{29}BO_2$, 312.2260; found, 312.2290. Analysis, calculated for $C_{20}H_{29}BO_2$, C, 76.93; H, 9.36; B, 3.46; found, C, 76.93; H, 9.44; B, 3.53. Crude **5S** (4.6 mmol) in 25 mL of THF was treated with a tenfold excess of hydrogen peroxide and potassium hydroxide and stirred overnight. (*R*)-(+)-2-Phenyl-2-butanol was isolated by extraction with ether and distillation, $[\alpha]_{546}^{22}$ +14.9° (neat) (71% EE). Repetition of the preparation of **3R** with ether instead of THF as solvent led to (*R*)-(+)-2-phenyl-2-butanol, $[\alpha]_{546}^{22}$ +16.1° (neat) (77% EE).

(s)-*Pinanediol* (*1*R)- *and* (*1*S)-(*1-Chloro-1-methylpentyl*)*boronate* (**10Ra/10Sa**)

The procedure described for the preparation of **3R** was followed, except that (*s*)-pinanediol butylboronate (**9a**) was used in place of **4.** The crude **10Ra/10Sa** contained <5% **9a** according to 90-MHz NMR analysis. Since it was unstable toward elimination of hydrogen chloride on chromatography, it was used without further purification; 200-MHz ^{1}H NMR ($CDCl_3$), δ 0.85 (s, 3, pinyl CCH_3), 0.93 (t, 3, CH_2CH_3), 1.19 (d, J = 11 Hz, 1, pinyl CH), 1.29 (s, 3, pinyl CCH_3), 1.45 (s, 3, pinyl CCH_3), 1.58 (s, 3, CH_3CCl), 1.20–1.45 (m, butyl CH_2), 1.80–2.45 (m, 8, pinyl CH), 4.37 (dd, 1, pinyl OCH); MS *m/e* (relative intensity), 262 (14), 221 (16), 167 (27), 134 (36), 101 (37), 83 (61), 67 (51), 57 (100); exact mass calculated for $C_{16}H_{27}BO_2$ (loss of HCl from $C_{16}H_{28}BClO_2$), 262.2104; found, 262.2096. Overlapping absorptions near δ 1.2 interfered with any determination of the diastereomer ratio from ^{1}H NMR data.

(s)-*Pinanediol* (*1-Ethyl-1-methylpentyl*)*boronate* (**11Ra/11Sa**) *and 3-Methyl-3-heptanol* (**12Sa/12Ra**)

The procedure described for the preparation of **5S** from **8S** was followed, except that (*s*)-pinanediol (1-chloro-1-methylpentyl)boronate (**10Ra/10Sa**) was used in place of **8S.** The **11Ra/11Sa** was chromatographed with 5% ether in petroleum ether, R_f 0.7, 82%; 200-MHz ^{1}H NMR ($CDCl_3$), δ 0.84 (s, 3, pinyl *CCH*$_3$), 0.91 (s, *CH*$_3$CB), 1.14 (*d, J* = 11 Hz, 1, pinyl *CH*), 1.28 (s, 3, pinyl *CCH*$_3$), 1.36 (s, 3, pinyl *CCH*$_3$), 1.15–2.45 (m, alkyl and pinyl *CH*), 4.26 (dd, 1, pinyl OCH); MS *m/e* (relative intensity), 292 (31), 277 (40), 251 (16), 223 (80), 196 (40), 179 (24), 152 (30), 135 (100), 111 (32), 83 (58), 67 (53); exact mass calculated for $C_{18}H_{33}BO_2$, 292.2574; found, 292.2598. Analysis calculated for $C_{18}H_{33}BO_2$, C, 73.97; H, 11.38; B, 3.56; found, C, 73.88; H, 11.41; B, 3.56. Oxidation of **11Ra/11Sa** with 10 equiv hydrogen peroxide and 20 equiv potassium hydroxide in aqueous THF yielded 83% 3-methyl-3-heptanol (**12Sa/12Ra**), EE of (*S*)-(−) isomer ~2% based on $[\alpha]_{589}^{22}$ −0.015° (c, 3, ether) [lit. [9] (*R*) enantiomer, $[\alpha]_{589}^{22}$ +0.67° (neat)].

(s)-*Pinanediol* (*1-Chloro-1,2-dimethylethyl*)*boronate* (**10b**)

The procedure described for the preparation of **3R** was followed, except that (*s*)-pinanediol isopropylboronate (**9b**) was used in place of **4.** The **10b** was chromatographed with 5% ether in petroleum ether, R_f 0.45, 89%; 200-MHz ^{1}H NMR ($CDCl_3$), δ 0.84 (s, 3, pinyl CCH_3), 1.00–1.10 [dd, 6, CH(CH_3)$_2$], 1.23 (d, J = 11 Hz, 0.98, pinyl CH, major isomer), 1.25 (d, J assumed to be 11 Hz but partially obscured, 0.02, pinyl CH, minor isomer), 1.31 (s, 3, pinyl CCH_3), 1.42 (s, 3, pinyl CCH_3), 1.57 (s, 3, CH_3CCl), 1.75–2.47 (m, 7, pinyl CH and CH_3CH), 4.40 (dd, 1, pinyl OCH); MS *m/e* (relative intensity), 248 (7), 233 (5), 214 (8), 199 (11), 179 (15), 134 (28), 109 (12), 93 (23), 83 (35), 70 (49), 58 (100); exact mass calculated for $C_{15}H_{26}BClO_2$, 284.1714; found, 284.2680. Preparation of **10b** from (*s*)-pinanediol (1,1-dichloroethyl)boronate (**1**) and isopropylmagnesium chloride resulted in material having two pinyl doublets, δ 1.23 and, partially obscured, 1.25. From the ratios of the peaks at 242 and 246 Hz from tetramethylsilane, the isomer ratio was 1 : 2. For **10b** prepared from **9b,** the corresponding ratio was ~50 : 1.

(s)-*Pinanediol* (*1*S)-(*1-Chloro-1-cyclohexylethyl*)*boronate* (**10Sc**)

The procedure described for the preparation of **3R** was followed, except that (*s*)-pinanediol cyclohexylboronate (**9c**) was used in place of **4.** The **10Sc** was chromatographed with 5% ether in petroleum ether, R_f 0.6, 93%; 200-MHz ^{1}H NMR ($CDCl_3$), δ 0.85 (s, 3, pinyl CCH_3), 1.23 (d, J = 11 Hz, 1, pinyl CH) (minor isomer not identified), 1.29 (s, 3, pinyl CCH_3), 1.40 (s, 3, pinyl CCH_3), 1.52 (s, 3, CH_3CCl), 1.05–1.35 (m, cyclohexyl CH), 1.60–2.45 (m, pinyl CH), 4.37 (dd, 1, pinyl OCH); MS *m/e* (relative intensity), 288 (13), 262 (5), 247 (9), 214 (12), 193 (20), 166 (13), 135 (45), 110 (83), 93 (39), 83 (85), 59 (100); exact mass calculated for $C_{18}H_{29}BO_2$ (loss of HCl from $C_{18}H_{30}BClO_2$), 288.2260; found, 288.3282.

(s)-*Pinanediol* (*1*S)-(*1-Cyclohexyl-1-methylpropyl)boronate* (**11Sc**) *and* (R)-(−)-*2-Cyclohexyl-2-butanol* (**12Rc**) *from* **9c/10Sc**

The procedure described for the preparation of **5S** from **8S** was followed, except that (*s*)-pinanediol (1*S*)-(1-chloro-1-cyclohexylethyl)boronate (**10Sc**) was used in place of **8S.** The **11Sc** was chromatographed with 5% ether in petroleum ether, R_f 0.9, 75%; 200-MHz ^{1}H NMR ($CDCl_3$), δ 0.84 (s, 3, pinyl CCH_3), 0.86 (s, CH_3CB), 1.18 (d, J = 11 Hz, 1, pinyl CH) (minor isomer not identified), 1.28 (s, 3, pinyl CCH_3), 1.36 (s, 3, pinyl CCH_3), 1.0–2.4 (m, cyclohexyl and pinyl CH), 4.27 (dd, 1, pinyl OCH); MS *m/e* (relative intensity), 318 (14), 304 (9), 249 (20), 236 (20), 222 (16), 179 (12), 152 (16), 135 (83), 125 (21), 109 (30), 93 (55), 83 (44), 67 (41), 58 (100); exact mass calculated for $C_{20}H_{35}BO_2$, 318.2730; found, 318.2691. Oxidation of **11Sc** with 10 equiv hydrogen peroxide and 20 equiv potassium hydroxide in aqueous THF yielded 86% (*R*)-(−)-2-cyclohexyl-2-butanol (**12Rc**), $[\alpha]_{589}^{22}$ −0.70° (c, 1, benzene) [lit. [11] α_{589}^{24} −3.52° (neat)].

(s)-*Pinanediol* (*1*R)-[*1-Chloro-1-methyl-5-(ethylenedioxy)hexyl*]*boronate* (**14**)

The procedure described for the preparation of **3R** was followed, except that (*s*)-pinanediol [4-(ethylenedioxy)pentyl]boronate (**13**) [1] was used in place of **4.** Conversion of **13** to **14** was only 55–60%, and attempted chromatography yielded only unsaturated products corresponding to elimination of hydrogen chloride.

(s)-*Pinanediol* (*1*S)-[*1-(Benzyloxymethyl)-1-methyl-5-(ethylenedioxy)hexyl*]*boronate* (**15**)

A solution of 6.34 g (11 mmol) of (tributylstannyl)methyl benzyl ether in 100 mL of ether was stirred at −78°C during the dropwise addition of 11 mmol of 1.6 *M* butyllithium in hexane. After 15 min, the cold mixture was added via cannula to a stirred solution of 4.34 g of crude (*s*)-pinanediol (1*R*)-[1-chloro-1-methyl-5-(ethylenedioxy)hexyl]-boronate (**14**) (containing ~40% **13**) in 100 mL of ether stirred at −78°C. The mixture became very viscous, but on warming to 20–25°C the mixture thinned and a white precipitate formed. After workup with magnesium sulfate, the residual oil was purified by flash chromatography with 30:70 ether–petroleum ether, 1.57 g (29%) of 15, R_f 0.31; 200-MHz ^{1}H NMR ($CDCl_3$), δ 0.83 (s, 3, pinyl CCH_3), 1.208 (d, J = 11 Hz, 0.63, pinyl CH of major isomer), 1.223 (d, J = 11 Hz, 0.37, pinyl CH of minor isomer), 1.26 (s, 3, CCH_3), 1.29 (s, 3, CCH_3), 1.34 (s, 3, CCH_3), 1.4–2.4 (m, alkyl and pinyl CH), 3.35 (m, 2, CCH_2O), 3.90 (m, 4, OCH_2CH_2O), 4.26 (dd, 1, pinyl OCH), 4.49 (s, 2, $C_6H_5CH_2$), 7.33 (m, 5, C_6H_5); 22.5-MHz ^{13}C NMR, δ 19.61, 20.44, 23.72, 24.02, 26.34, 27.11, 28.72, 35.16, 35.70, 35.99, 38.14, 39.57, 39.99, 51.31, 59.95, 64.54, 73.18, 77.77, 78.13, 85.51, 110.13, 127.05, 127.23, 128.06; MS *m/e* (relative intensity), 456 (7), 443 (33), 287 (10), 135 (40), 109 (50), 91 (100), 69 (20), 55 (23); exact mass calculated for $C_{27}H_{41}BO_5$, 456.3047; found, 456.3089.

(2R)-*1-Benzyloxy-2-methyl-6-(ethylenedioxy)-2-heptanol* (**16**)

A solution of 1.57 g (3.4 mmol) of (*s*)-pinanediol (1*S*)-[1-(benzyloxymethyl)-1-methyl-5-(ethylenedioxy)hexyl]boronate (**15**) in 20 mL of THF was cooled in an ice bath and treated with 1.56 g (24 mmol) of potassium hydroxide in 30 mL of water and 2.2 mL (22 mmol) of 30% hydrogen peroxide. The mixture was stirred overnight. The mixture was extracted with ether and the **16** was distilled in a kugelrohr at 140°C (0.01 torr) and chromatographed with ether, R_f 0.4, 0.87 g (86%); 200-MHz ^{1}H NMR ($CDCl_3$), δ 1.20 (s, 3, CCH_3), 1.34 (s, 3, CCH_3), 1.40–1.70 [m, 6, $(CH_2)_3$], 2.38 (s, 1, OH), 3.35 (dd, 2, CCH_2O), 3.94 (s, 4, OCH_2CH_2O), 4.57 (s, 2, $C_6H_5CH_2$), 7.34 (m, 5, C_6H_5); 22.5-MHz ^{13}C NMR, δ 18.35, 23.78, 39.27, 39.69, 64.60, 72.11, 73.48, 77.41, 110.01, 127.53, 128.36, 138.25; MS *m/e* (relative intensity), 291 (21), 233 (43), 169 (9), 141 (17), 125 (15), 107 (11), 91 (100), 81 (8), 71 (20), 55 (16).

(*1*R)-(+)-*Frontalin* (**17**)

(2*R*)-1-Benzyloxy-2-methyl-6-(ethylenedioxy)-2-heptanol (**16**) (0.77 g, 2.6 mmol) was hydrogenated at 1 atm with 200 mg of 10% palladium on charcoal catalyst in 20 mL of ethanol overnight. The product **17** was passed through a short column of silica with the aid of petroleum ether, then isolated by distillation, 0.21 g (57%); 200-MHz ^{1}H NMR ($CDCl_3$), δ 1.36 (s, 3, CCH_3), 1.45 (s, 3, CCH_3), 1.50–2.00 [m, 6, $(CH_2)_3$], 3.48 (dd, 1, *exo*-CH), 3.93 (dd, 1, *endo*-CH); $[\alpha]_{589}^{22}$ +11.15° (c, 1.8, ether) (21% EE) [lit. [12] natural (1*S*)-(−) enantiomer, $[\alpha]_{589}^{22}$ −52° (c, 1.65, ether)].

(s)-*Pinanediol* (*1*R, *2*S)- *and* (*1*S, *2*S)-(*2-Benzyloxy-1-chloro-1-methylhexyl)boronate* (**19R, 19S**)

The procedure described for the preparation of **3R** was followed, except that (*s*)-pinanediol (1*R*)-[(1-benzyloxy)pentyl]boronate (**18**) (DE ~97%) (1.68 g, 4.72 mmol) was used in place of **4,** which yielded **19R** and **19S,** 1.52 g; 200-MHz ^{1}H NMR ($CDCl_3$), δ 0.84 (s, 3, pinyl CCH_3), 0.88 (t, 3, CH_2CH_3), 1.23 (d, J = 11 Hz, 1, pinyl CH), 1.29 (s, 3, pinyl CCH_3), 1.39 (s, 3, pinyl CCH_3), 1.61 (s, 3, CH_3CCl), 1.50–2.45 (m, pinyl and heptyl CH), 3.79 (dd, 1, OCH), 4.36 (dd, 1,

pinyl OC*H*), 4.678 (d, J = 11.0 Hz, 0.91, C_6H_5CHH, major isomer), 4.697 (d, J = 11.6 Hz, 0.09, C_6H_5CHH, minor isomer), 4.795 (d, J = 11.6 Hz, 0.09, C_6H_5CHH, minor isomer); 4.946 (d, J = 11.0 Hz, 0.91, C_6H_5CHH, major isomer), 7.20–7.50 (m, 5, C_6H_5). An earlier sample of **19R/19S** prepared from **18** of ~76% DE showed ~12% minor isomer in the NMR spectrum. This sample was chromatographed with 10% ether in petroleum ether and yielded two fractions, R_f 0.22, 1.28 g, and R_f 0.3, 0.23 g, which had ^{1}H NMR spectra corresponding to the major and minor diastereomers. Similar reaction of pinacol [(1-benzyloxy)pentyl]boronate with (1,1-dichloroethyl)lithium yielded a 1 : 1 mixture of diastereomeric pinacol (2-benzyloxy-1-chloro-1-methylhexyl)boronates; 200-MHz ^{1}H NMR ($CDCl_3$), δ 4.660 (d, J = 11.0 Hz, 1, C_6H_5CHH, analog of major isomer), 4.677 (d, J = 11.6 Hz, 1, C_6H_5CHH, analog of minor isomer), 4.769 (d, J = 11.6 Hz, 0.11, C_6H_5CHH, analog of minor isomer); 4.964 (d, J = 11.0 Hz, 1, C_6H_5CHH, analog of major isomer).

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