Asymmetric Synthesis Using Diisopropyl Tartrate Modified (*E*)- and (*Z*)-Crotylboronates: Preparation of the Chiral Crotylboronates and Reactions with Achiral Aldehydes

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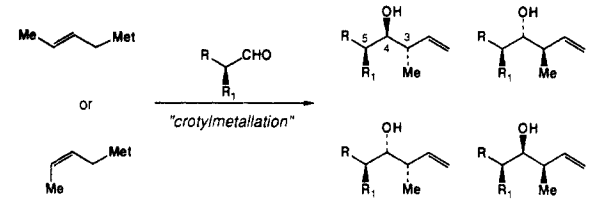
Abstract: Diisopropyl tartrate modified (*E*)- and (*Z*)-crotylboronates **2** and **3** are easily prepared with very high isomeric purity (≥98% *E* for **2**; ≥99% *Z* for **3**) via the metalation of (*E*)- and (*Z*)-2-butene with *n*-BuLi and KOtBu in THF followed by treatment of the (*E*)- and (*Z*)-crotylpotassiums **4** and **5** with (*i*-PrO)$_3$B, aqueous hydrolysis, and esterification with diisopropyl tartrate (DIPT). (*E*)-Crotylboronate **2** has been prepared on 400-mmol scales with excellent results. A procedure for the preparation and standardization of solutions of **2** and **3** is also described. Crotylboronates **2** and **3** undergo highly diastereo- and enantioselective reactions with aliphatic (linear or α-monobranched; 72–91% ee), aromatic and α,β-unsaturated aldehydes (55–74% ee). The reaction diastereoselectivity closely parallels the reagent isomeric purity especially for reactions performed at −78 °C. The enantioselectivity is best in toluene for all substrates except benzaldehyde where best results are obtained in THF. The relative and absolute stereochemistry of 9 of the 14 homoallyl alcohols synthesized in this study were assigned by correlation with epoxyalcohols prepared by the Sharpless asymmetric epoxidation. The results in each case are consistent with the asymmetric crotylboration reaction proceeding preferentially through transition state A. That is, assuming that R of RCHO has priority over the crotyl group that is transferred, (*R,R*)-**2** and (*R,R*)-**3** invariably produce homoallyl alcohols with *S* configuration at the carbinol center. The enantiomeric set of homoallylic alcohols are available simply by using reagents (S,S)-**2** and (S,S)-**3** prepared from (*S,S*)-DIPT.

The reactions of crotylmetal reagents and other propionate enolate equivalents with carbonyl compounds are of considerable interest in the context of acyclic diastereoselective synthesis.[3-5] Four diastereomeric products may be produced in reactions with chiral carbonyl substrates, and considerable effort has been devoted to the development of highly stereoselective syntheses of each isomer.[5b] To do so by using crotylmetal or aldol chemistry requires that two independent stereochemical problems be controlled: (1) the C(3),C(4)-anti or -syn stereochemistry generated in concert with the new C–C bond, and (2) the aldehyde diastereofacial selectivity issue that determines the relationship of the newly formed C(3) and C(4) stereocenters to the center (C(5)) originally present in the chiral carbonyl substrate. The first issue (simple diastereoselectivity) is no longer a major problem as numerous allylmetal and aldol reagents are available that react with aldehydes with very high diastereoselectivity. Indeed, as long as reagents are used that react via closed, cyclic transition states, this problem is reduced to selecting a species with the appropriate double bond or enolate geometry: *E* reagents generate the C(3)–C(4)-anti relationship, while *Z* reagents provide the 3,4-syn diastereomer.[3] Control of aldehyde diastereofacial selectivity is more difficult to achieve, however, and recourse to the strategy of double asymmetric synthesis is generally required.[4-7a]



Over the past several years a number of laboratories have focused on the development of a family of chiral allyl metal reagents as enolate surrogates for application in the aldol-like construction of natural products of propiogenic/acetogenic origin.[7-9] We viewed allylboronates as highly attractive candidates

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(3) For reviews of the reactions of allylmetal compounds and aldehydes, see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (b) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1990; Vol. 2, in press.

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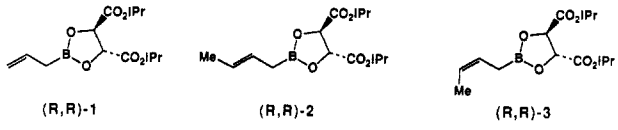
for these purposes since reagents encompassing the (*E*)-crotyl [(*E*)-propionate], (*Z*)-crotyl [(*Z*)-propionate] and allyl [acetate] subgroups are easily prepared in large quantities by similar, simple methods; the aldehyde addition reactions proceed via cyclic transition states with predictable transmission of olefin stereochemistry into the 3,4-anti or -syn relationship in the products, and the boronate unit itself is amenable to asymmetric modification. In addition, allylboronates are stable to storage and can be analyzed by capillary GC analysis before use. They are nonbasic, relatively non-nucleophilic, and hence are highly chemoselective in their reactions. Finally, the product homoallyl alcohols are easily converted by protection and ozonolysis to chiral aldehydes of interest as substrates for subsequent C–C bond forming processes.

We have demonstrated that the tartrate ester modified allylboronates **1–3** are particularly useful reagents for organic synthesis.[9] We describe here the details of preparation of the tartrate crotylboronates **2** and **3** and focus on the stereochemical features of their reactions with representative achiral aldehydes. The reactions of **2** and **3** with several α-methyl chiral aldehydes and applications of this technology in the synthesis of the C(19)–C(29) segment of rifamycin S are discussed in the accompanying manuscript.[10]

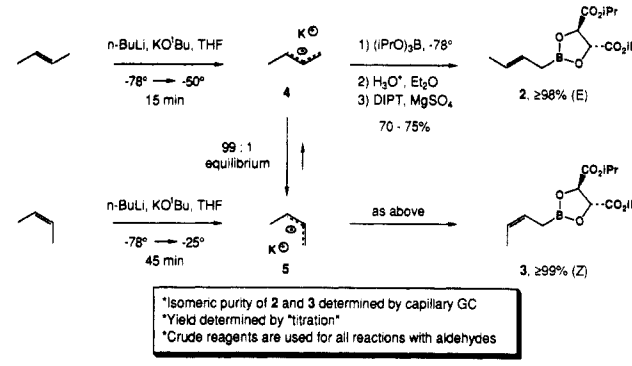


(R,R)-1 (R,R)-2 (R,R)-3

Preparation of Tartrate Crotylboronates 2 and 3

Reagents **2** and **3** are easily prepared via crotylpotassium intermediates by using modifications of Schlosser's crotylboronate synthesis.[11] Although the literature described several different conditions for metalation of (*E*)-butene (*n*-BuLi, KOtBu, THF, −60 °C for 6 h;[11b] −50 °C for 15 h;[11a] −20 °C for 3 min[11d]), we initially elected to perform this step at −78 °C for 12 h out of concern for the thermodynamic instability of (*E*)-crotylpotassium.[6b,12] Thus, a solution of the appropriate crotylpotassium was generated at −78 °C and treated with 1.0 equiv of $FB(OMe)_2$ (neat) at −78 °C for 1 h. This mixture was then quenched with saturated aqueous NaCl solution containing 1 equiv of HCl and extracted with ether to give a solution containing the crude crotylboronic acid. This solution was concentrated on a rotary evaporator, care being taken not to take the solution to dryness since allylic boronic acids are unstable especially when neat. This solution was immediately treated with 1.0 equiv of diisopropyl tartrate (DIPT) in CH_2Cl_2 or Et_2O in the presence of $MgSO_4$ to give reagents **2** and **3** that were contaminated with at least 0.3 equiv of DIPT (GC or NMR analysis); the amount of residual DIPT varied from run to run. Such samples, however, could be enriched in **2** or **3**, but never fully purified, by high vacuum short path distillation. Alternatively, a much purer reagent was obtained by using DIPT (0.4 equiv) as the limiting component of the reaction sequence. When performed on a small scale (up to 100 mmol), the latter method typically provided **2** and **3** in 70–88% yield (based on DIPT) following distillation with isomeric purities of 96–97% for **2** and 97–98% for **3** (capillary GC analysis).

Scheme I. Optimized Procedure for Synthesis of 2 and 3



While our studies of the reactions of **2** and **3** with D-glyceraldehyde acetonide were still in progress,[9b] Professor H. C. Brown informed us that his group was performing the butene metalation step at −45 °C for 15 min.[8a] We subsequently found that this modification did not significantly affect the yield or isomeric purity of **2** or **3**, at least in small scale preparations (vide infra) and consequently adopted it owing to the time that it saved. As a general rule, however, we performed the metalation at −50 °C for 15 min to further minimize the risk of stereochemical leakage via isomerization of the (*E*)-crotylpotassium intermediate.[9b,13]

Reagents prepared in this way were used in all of our initial studies.[9b-d] Several problems were encountered, however, necessitating that an improved procedure be developed. First, the efficiency of the distillation of **2** and **3** decreased with increasing scale owing to the ease of reagent decomposition, especially when the pot temperature exceeds 100 °C. This problem was eliminated by the observation that the enantioselectivity of reactions with both chiral and achiral aldehydes is comparable when crude or distilled tartrate crotylboronates are used, as long as 4-Å molecular sieves are also included. Consequently, use of reagents purified by distillation was no longer required. A more serious problem, however, was that the yield and isomeric purity of the reagents also decreased with increasing scale. For example, the (*E*)-crotyl reagent **2** was obtained in less than 35% yield on a 200-mmol scale, as determined by the titration procedure subsequently described, with an isomeric purity of 94–96%, while on this scale the (*Z*)-crotyl reagent **3** was obtained in yields as low as 14% with an isomeric purity of 92–95%.

These problems were attributed to the exothermicity of the reaction of $FB(OMe)_2$ and the crotylpotassiums **4** and **5** that necessitated that a slow addition of $FB(OMe)_2$ be performed (typically 2 h for a 200-mmol scale experiment, care being taken to maintain the internal temperature below −65 °C).[14] The initially formed ate complex i presumably is not stable under these conditions, and loss of fluoride ion leads to dimethyl crotylboronate (ii) that most certainly reacts with a second equivalent of crotylpotassium (which is present in large excess at least early in the reaction). Repetition of this addition–elimination sequence ultimately leads to the generation of methyl dicrotylborinate (iii) and tricrotylborane (iv). The latter species is expected to be configurationally unstable under these conditions,[15] and both iii

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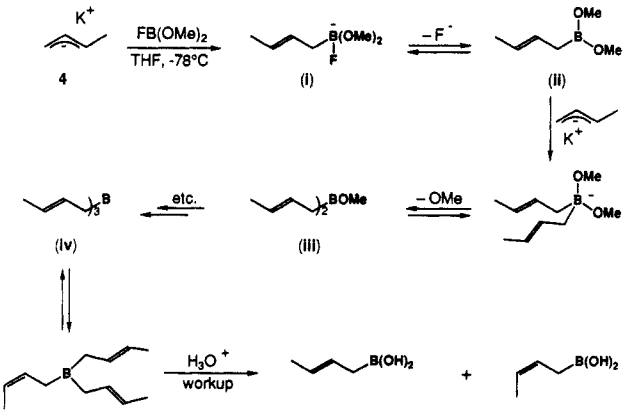
(12) The equilibrium mixture of (*E*)- and (*Z*)-crotylpotassium at −48 °C in THF is 1:99: Schlosser, M.; Hartmann, J. *J. Am. Chem. Soc.* **1976**, *98*, 4674.

(13) The extent of metalation of (*E*)-butene at −50 °C for 15 min is dependent on the reaction concentration and is assessed by the amount of tartrate butylboronate present in **2**. Thus, in experiments where the BuLi–KOtBu concentration is 0.7–0.8 M, 14–20% of the butylboronate is produced. At a BuLi–KOtBu concentration of 0.9 M, however, the amount of butylboronate is 3% or less. While the extent of metalation may be increased by performing the metalation at −50 °C for 30–45 min, or at −45 °C for 15 min as specified by Brown,[8a,b] we have found that both modifications lead to a slightly decreased (1–2%) isomeric purity for **2** (experiments performed with $(i\text{-PrO})_3B$ as the electrophilic boron reagent).

(14) When $FB(OMe)_2$ was added as a precooled (−78 °C) solution in THF, the addition could be performed much more rapidly and the isomeric purity of **2** and **3** increased to 96–97% on 200–300 mmol scales.

and iv will react with water upon reaction workup to provide crotylboronic acid. Thus, generation of iii and iv accounts for the decreased yield and isomeric purity that accompany scale up. In addition, production of small amounts of tricrotylborane is expected to have a greater affect on the isomeric purity of **3** since an (*E*)-crotylborane is more stable than the *Z* isomer.

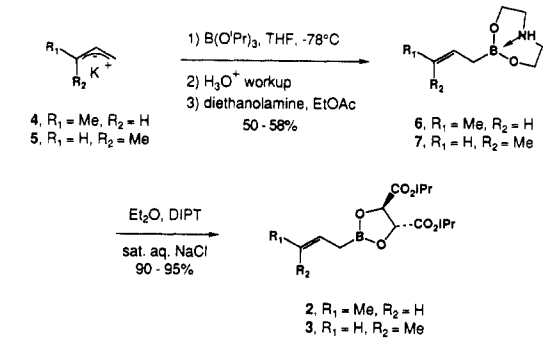


Both problems were solved by using B(O-*iPr*)$_3$ in place of FB(OMe)$_2$ as the electrophilic reagent. Brown has previously shown that B(O-*i*-Pr)$_3$ gives superior results in the synthesis of alkylboronic esters from alkyllithium reagents.[16] Thus, the preferred method of synthesis of **2** now involves treatment of the (*E*)-crotylpotassium solution, generated at −50 °C for 15 min,[13] with 1.0 equiv of B(O-*i*-Pr)$_3$ at −78 °C (Scheme I). Because (*Z*)-crotylpotassium is significantly more stable than the *E* isomer,[12] we now perform the metalation of (*Z*)-butene at −25 °C for 30 min in the preparation of **3**. The (*Z*)-crotylpotassium solution is then also treated with B(O-*i*-Pr)$_3$ at −78 °C. The reactions are quenched with 1 N HCl and *extracted with Et$_2$O containing 1.0 equiv of tartrate ester.*[17] The extracts are dried over MgSO$_4$ for 2 h, filtered, and concentrated in vacuo to give the crude reagents. The yield (usually at least 70–75%; yields in excess of 85% have been obtained on several occasions) and isomeric purity (≥98% *E* for **2**; ≥99% *Z* for **3**) are much improved with this new procedure, and the results appear to be independent of scale: (*E*)-crotylboronate **2** has been prepared on 100–425-mmol scales with excellent results using this new procedure.

(*E*)-Crotylboronate **2** prepared by this new procedure has been purified by distillation (temperatures below 100 °C) on a ca. 20-mmol scale without the decomposition problems noted above—perhaps because the purity of the crude product is greater than from the original FB(OMe)$_2$ route—but with some erosion of isomeric purity (96% *E*).

Reagents **2** and **3** are reasonably stable and have been stored neat in a −20 °C freezer under argon for several months with little noticeable deterioration. Because crude **2** and **3** are routinely used in aldehyde addition reactions, however, we have found it most convenient to store the reagents as solutions in toluene (or THF). This provides a means of determining the yield and also facilitates transfer of known quantities for individual experiments. Thus, the crude reagent is dissolved in toluene (or THF) and then the concentration is determined by treatment of a known volume with a known excess of cyclohexanecarboxaldehyde at 25 °C for 30 min. This reaction ("titration") is quenched with NaBH$_4$ in EtOH, and the ratio of $C_6H_{11}CH_2OH$ to **9d** and/or **10d** is determined by capillary GC analysis. From this ratio one calculates the concentration, and hence also the yield of reagent if the total volume is known. We have stored such solutions for 3–4 months at −20 °C and routinely titrate them before use.

Before we had solved the reagent isomeric purity problem via the optimization studies discussed above, we developed an indirect method involving the crystalline diethanolamine complexes **6** and **7**.[18] These materials are prepared in 50–58% yield by treating the crude crotylboronic acids with 0.7–0.8 equiv of diethanolamine in EtOAc and can be recrystallized to very high isomeric purity (>99% in each case). Tartrate crotylboronates are then generated in 90–95% yield by extracting a mixture of DIPT and **6**/**7** in Et$_2$O with saturated aqueous NaCl. While this method is not recommended for use on a routine basis, it is ideal for preparing reagents with isomeric purities much greater than that possible by the direct method (**2** and **3** have been prepared with >99.8% isomeric purity by way of **6** and **7**). It also is likely to find application in the preparation of chiral crotylboronates incorporating auxiliaries more valuable than the commercial tartrate esters (vide infra).[19]



Reactions with Achiral Aldehydes

We initiated the present study by assuming that the behavior of **1**–**3** would be very similar and consequently have relied extensively on data for the reactions of allylboronate **1** and achiral aldehydes which have been fully optimized with respect to the influence of various experimental variables (tartrate ester, solvent, temperature, etc.) on enantioselectivity.[9i] This work established that the aldehyde addition reactions of **1** are most selective in toluene, except with aromatic substrates for which THF gives best results, that enantioselectivity is significantly better at −78 °C than at higher reaction temperatures (e.g., ambient) and that essentially identical results are obtained when any of the commercially available tartrate esters (Me, Et, *i*-Pr) are used as the auxiliary. The selection of DIPT as the auxiliary in **2** and **3** is thus arbitrary. While we have not studied the reactions of achiral aldehydes and the diethyl tartrate (DET) derived chiral crotylboronates, we have employed the DET analogue of **2** in reactions with several chiral substrates to take advantage of the chromatographic mobility of DET in cases where the separation of a chemically sensitive reaction product and DIPT is difficult. The performance of the DET-derived reagents in these double asymmetric reactions has been essentially indistinguishable from that of **2**, as would be expected on the basis of our results with **1**.[9i]

The asymmetric crotylboration reactions were performed by adding a solution of aldehyde to 1.1–1.5 equiv of **2** or **3** in toluene (0.2 M) at −78 °C containing 4-Å molecular sieves (typically 15–20 mg/mL). It should be noted that the observed enantioselectivity was generally somewhat lower if neat RCHO was added to **2** or **3**. All reactions were complete within several hours, with the exception of those involving pivaldehyde which are significantly slower. Workup consisted of addition of excess aqueous 1 N NaOH to hydrolyze diisopropyl tartrate. Reaction products were then isolated by extraction and purified either by chromatography or distillation.

Ratios of diastereomers **9** and **10** were measured in many cases by using high-field ^{1}H NMR or capillary GC analysis. It proved convenient in several instances, however, to determine this ratio after conversion of unseparated mixtures to the corresponding methyl ethers (NaH, CH_3I, DMF). Analysis of such samples on

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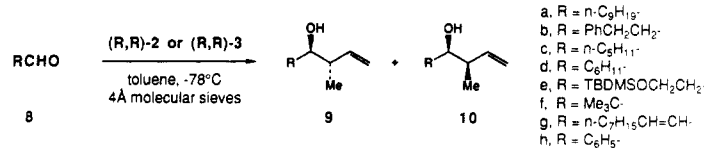
(16) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316.

(17) The yield of reagent decreases somewhat if DIPT is added to the extracts, and significantly so if DIPT is added after the extracts containing crotylboronic acid are dried and concentrated as described in our initial publications (refs 9a,b). The crotylboronic acids are much less stable than originally suspected.

(18) Brown, H. C.; Vara Prasad, J. V. N. *J. Org. Chem.* **1986**, *51*, 4526.

(19) Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

Table I. Reactions of Chiral Crotylboronates **2** and **3** With Achiral Aldehydes



entry	RCHO	reagent	isomeric purity	reaction time (yield)[a,b]	anti:syn (9:10)[c]	% ee[d] 9	% ee[d] 10
1	**8a**	**2**	99.4	3 h (87%)	>99:1	88[C,M,e]	–
2	**8a**	**2**	96	–	97:3	84[C,e]	–
3	**8a**	**2**	94	3 h (90%)	95:5	86[C,e]	–
4	**8a**	**3**	>99.6	6 h (70%)	1:>99	–	77[M,f]
5	**8a**	**3**	98	6 h (80%)	3:97	–	82[M,f]
6	**8a**	**3**	98	9 h (69%) (−95 °C)[g]	3:97	–	86[M]
7	**8b**	**2**	99	3 h (86%)	>99:1	84[C]	–
8	**8b**	**2**	–	3 h (89%)	93:7	85[M]	–
9	**8c**	**2**	–	4 h (84%)	>99:1	85[C]	–
10	**8d**	**2**	99.3	3 h (94%)	>99:1	86[C,h]	–
11	**8d**	**2**	94	3 h (85%)	96:4	87[C,h]	–
12	**8d**	**2**	98	4 h (100%) (−95 °C)[g,i]	>99:1	91[C]	–
13	**8d**	**2**	99	1 h (96%) (23 °C)[g]	>99:1	46[C]	–
14	**8d**	**2**	99.3	3 h (87%) (Et_2O)[j]	>99:1	77[C]	–
15	**8d**	**2**	99.3	3 h (88%) (THF)[j]	>99:1	70[C]	–
16	**8d**	**2**	99.3	3 h (87%) (CH_2Cl_2)[j]	>99:1	62[C]	–
17	**8d**	**3**	99	6 h (90%)	2:98	–	83[M]
18	**8d**	**3**	97	6 h (91%)	6:94	–	83[M]
19	**8e**	**2**	98	4 h (71%)	≥98:2	85[M]	–
20	**8e**	**3**	98	4 h (68%)	2:≥98	–	72[M]
21	**8f**	**2**	99	6 d (41%)	95:5	73[C]	–
22	**8f**	**3**	99.5	7 d (66%)	1:>99	–	70[C]
23	**8g**	**2**	99	4 h (91%)	>99:1	74[C]	–
24	**8g**	**2**	–	– (Et_2O)[j]	–	67[C]	–
25	**8g**	**2**	–	– (THF)[j]	–	65[C]	–
26	**8g**	**3**	98	6 h (83%)	3:97	–	62[M]
27	**8h**	**2**	99.3	3 h (91%) (THF)[j]	>99:1	66[C,P,k]	–
28	**8h**	**2**	96	3 h (94%)	96:4	65[C,P,l]	–
29	**8h**	**3**	99	6 h (94%) (THF)[j]	2:98	–	55[P]
30	**8h**	**3**	98	6 h (90%)	5:95	–	28[P]
31	**8h**	**3**	–	– (Et_2O)[j]	–	–	25[P]

[a] All reactions were performed in toluene at −78 °C in the presence of 15–20 mg/mL of 4-Å molecular sieves unless indicated otherwise (changes in this protocol are indicated in parentheses). [b] Isolated yield of **9** or **10**. [c] Ratios determined by capillary GC or ^1H NMR analysis of the crude reaction product, or by capillary GC after conversion of unseparated mixtures to the corresponding methyl ethers (ref 20). [d] Enantiomeric purity was determined by three methods as indicated by C (Ni-R-Cam GC analysis of methyl ethers), P (Ni-4-Pin GC analysis of methyl ethers), M (^1H and/or ^{19}F NMR analysis of Mosher's ester derivatives). Methyl ether formation was not required for the enantiomeric purity determination of **9f** and **10f**. [e] Enantioselectivity ranges from 84–88% ee and averages 87% ee for 6 runs with different batches of **2** under these conditions. [f] Enantioselectivity ranges from 77–82% ee, with an average value of 80% ee. [g] Reaction performed at the indicated temperature. [h] Enantioselectivity ranges from 85–87% ee and averages 86% ee for 6 runs with different batches of **2**. [i] The yield in this case was determined by GC analysis following $NaBH_4$/MeOH quench; no $C_6H_{11}CH_2OH$ was detected. [j] These experiments were performed in the indicated solvent (Et_2O, THF, or CH_2Cl_2) rather than toluene. [k] The % ee listed here is the average value of 5 runs (range 64–69% ee). [l] % ee listed here is the average value of 6 runs (range 62–66% ee).

25 m × 0.25 mm Ni-R-Cam or Ni-4-Pin chiral capillary columns enabled the anti–syn ratio as well as the enantiomeric purity of the ether derivatives to be determined in a single experiment.[20] Homoallyl alcohols **9f** and **10f** (deriving from pivalaldehyde) could be analyzed by chiral capillary GC without prior methyl ether formation. The Mosher ester technique was used for all % ee determinations where the chiral GC method failed.[20,21] Results of these experiments are summarized in Table I.

The simple diastereoselectivity realized in these asymmetric crotylboration reactions is excellent in the vast majority of cases, with the diastereoselectivity closely paralleling the isomeric purity of the chiral crotylboronates. As a general rule, the diastereoselectivity of the reactions of **2** is better than the isomeric purity (refer to entries 1–3 and 10–11), while with the (*Z*)-crotyl reagent **3** the diastereoselectivity is generally slightly less than the isomeric purity (see entries 4–6 and 17–18). Thus, by use of (*E*)-crotyl reagent **2** of 98% isomeric purity it is possible to prepare anti homoallyl alcohols **9** with 99% diastereoselectivity, while 99% pure **3** generally provides syn homoallyl alcohols **10** with 97–98% diastereoselectivity. This reflects the well-precedented tendency of the (*E*)-crotylboronates to be more reactive than their *Z* isomers;[6b,22] hence a kinetic fractionation is expressed in the data. The one exception is the reaction of 99% pure (*E*)-crotylboronate **2** with pivalaldehyde that provides a 95:5 mixture of **9f** and **10f** (entry 21). It turns out that **3** is more reactive toward pivalaldehyde than **2**. For example, when a 2:1 mixture of **2** and **3** was treated with 0.5 equiv of pivalaldehyde for 2 h at −78 °C, the ratio of **9f** to **10f** was 2:9. Thus, the poor diastereoselectivity in the reaction of **2** and pivalaldehyde probably reflects the complete consumption of the small amount of **3** present as a contaminant in **2** in an otherwise incomplete reaction (pivalaldehyde is a very unreactive substrate).

The enantioselectivity of the asymmetric (*E*)-crotylborations using **2** closely parallels the selectivity and reactivity pattern previously established for the asymmetric allylborations with **1**.[9a,i] Thus, the reactions of **2** and linear unbranched or α-branched aliphatic aldehydes in toluene at −78 °C provide anti homoallyl

(20) Halterman, R. L.; Roush, W. R.; Hoong, L. K. *J. Org. Chem.* **1987**, *52*, 1152.

(21) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. The *R*-(+) acid was used for all enantiomeric purity determinations.

(22) (a) Hoffmann, R. W.; Zeiss, H.-J. *J. Org. Chem.* **1981**, *46*, 1309. (b) Hoffmann, R. W.; Kemper, B. *Tetrahedron* **1984**, *40*, 2219. (c) Moret, E.; Schlosser, M. *Tetrahedron Lett.* **1984**, *25*, 4491.

alcohols **9** in 85–88% ee, with enantioselectivity decreasing when the reactions are performed in solvents such as Et_2O, THF, or CH_2Cl_2 (entries 10–16). The enantioselectivity of the (*E*)-crotylboration of cyclohexanecarboxaldehyde **8d** increases to 91% ee when the reaction is performed at −95 °C (entry 12) and decreases to 46% when performed at 23 °C (entry 13). Somewhat lower levels of enantioselectivity (66–74% ee) are realized with aromatic and α,β-unsaturated aldehydes, a tendency also previously noted with **1**.[9a,i] Like **1**, the selectivity of the reaction of **2** and benzaldehyde is somewhat greater in THF than in toluene. Interestingly, the enantioselectivity of the reaction of **2** and β-alkoxy aldehyde **8e** is very good (85% ee), in contrast to the poor results obtained in the reactions of **1** and several β-alkoxyaldehydes.[9j] (*E*)-Crotylboronate **2** also gives significantly better results compared to **1** in reactions with chiral β-alkoxy aldehydes.[10] Thus, the detrimental "alkoxy effect", discussed in detail elsewhere,[9j,10] is least problematic in the asymmetric crotylborations of **2**, an observation that has important ramifications especially in mismatched double asymmetric reactions with chiral aldehydes.[10]

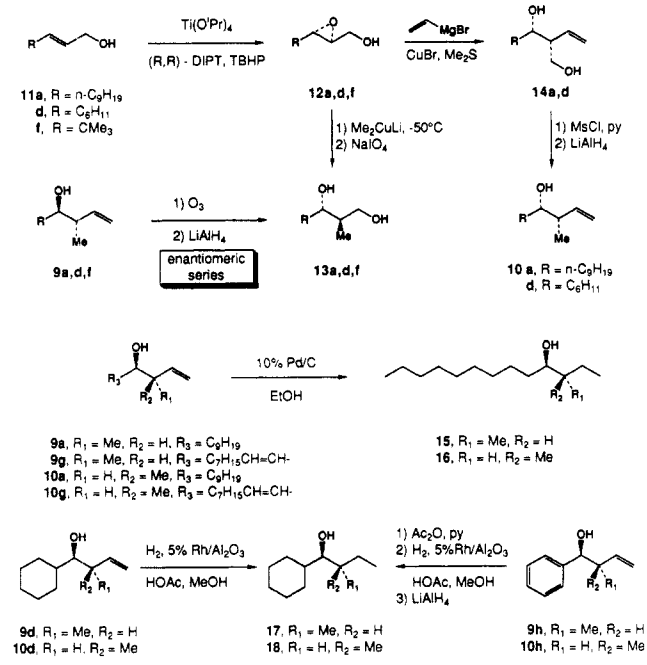
(*Z*)-Crotyl reagent **3** is the least enantioselective of this family of tartrate allyl- and crotylboronates. All other factors being equal, the reactions of **3** are typically 3–13% ee less enantioselective than **2**. This effect is least significant with aliphatic aldehydes (e.g., decanal, cyclohexanecarboxaldehyde—entries 10, 11 and 17, 18), but a significant drop in selectivity occurs with β-alkoxyaldehyde **8e** (entries 19, 20), (*E*)-decenal (entries 23, 26), and benzaldehyde (entries 27–29). A reduction in reaction temperature may be beneficial in these cases, as indicated in the reaction of **3** and decanal that provides **10a** with 86% ee at −95 °C and 77–82% ee at −78 °C (entries 4–6). Factors responsible for the decreased enantioselectivity of **3** comparable to **2** are unclear at present.

Stereochemical Assignments

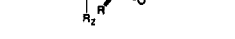
The relative and absolute configurations of nine of the compounds reported in Table I (**9a**, **9d**, **9f–h**, **10a**, **10d**, **10g**, and **10h**) have been assigned by correlation with epoxyalcohols prepared via the Sharpless asymmetric epoxidation.[23] Authentic samples of syn homoallylic alcohols **10a** and **10d** and the anti-1,3-diols **13a**, **13d**, and **13f** were synthesized as shown below. Thus, treatment of epoxyalcohols **12** (≥95% ee) with Me_2CuLi in Et_2O at −50 °C,[24] followed by $NaIO_4$ treatment to cleave any 1,2-diol that may have been produced, provided 1,3-diols **13a,d,f** that proved to be identical, with the exception of enantiomeric purity and absolute configuration, with samples prepared by a standard ozonolytic degradation of homoallyl alcohols **9a**, **9d**, and **9f** prepared from *R,R*-**2**. Identical syntheses of **13d** and **13f** were subsequently reported by Masamune.[25] Alternatively, treatment of epoxyalcohols **12** with $H_2C{=}CHMgBr$ and $CuBr{\cdot}Me_2S$ according to the procedure of Tius provided diols **14a** and **14d**.[26] These compounds were selectively monomesylated (MsCl, pyridine, 0 °C) and then reduced with $LiAlH_4$ (THF, 0 °C) to give syn homoallyl alcohols **10a** and **10d** that were identical, again with the exception of enantiomeric purity and absolute configuration, with the major products of the reactions of *R,R*-**3** and decanal and cyclohexanecarboxaldehyde, respectively.

Homoallyl alcohols in the decanal and (*E*)-decenal series were correlated via hydrogenation (H_2, Pd/C) to the 3-methyltridecan-4-ols **15** and **16**: anti diastereomers **9a** and **9g** each provided **15** while the syn diastereomers **10a** and **10g** converged to **16**. Products in the cyclohexanecarboxaldehyde and benzaldehyde series were similarly correlated by hydrogenation (1 atm H_2, 5% Rh/Al_2O_3) to saturated alcohols **17** (from anti homoallyl alcohols **9d** and **9h**) and **18** (from the syn isomers **10d** and **10h**). Interestingly, best results were obtained in the benzaldehyde series when adducts **10d** and **10h** were acylated before the hydrogenation step (Scheme II).

Scheme II. Correlation Chemistry



These results show that the absolute configurations of **9a,d,f–h** and **10a,d,f,g** prepared from reagents (*R,R*)-**2** and (*R,R*)-**3** (incorporating (*R,R*)-DIPT) are the same as **10a,d** and **13a,d,f** prepared from epoxyalcohols **12** only when (*S,S*)-DIPT is used in the asymmetric epoxidation. The stereostructures of **9** and **10** therefore are correct as formulated in Table I.[27] *Thus, assuming that R of RCHO has priority over the crotyl group that is transferred, R,R reagents 2 and 3 produce homoallyl alcohols with S configuration at the carbinol center.* The stereochemistry induced by the tartrate chiral auxiliary, as defined by transition-state paradigm A, is in complete agreement with the stereochemical course previously established for the reactions of tartrate allylboronate **1** with achiral aldehydes and in the reactions of **1–3** with chiral aldehydes.[9] Of course, the enantiomeric set of homoallyl alcohols are available simply by using reagents (*S,S*)-**2** or (*S,S*)-**3** prepared from (*S,S*)-DIPT.[28]



Summary

We have shown that tartrate ester modified crotylboronates **2** and **3** are easily prepared in high isomeric purity and undergo highly diastereo- and enantioselective reactions with aliphatic (linear or α-monobranched; 72–91% ee), aromatic and α,β-unsaturated aldehydes (55–74% ee). Selectivity in the best cases is comparable to that realized with the crotyl(diisopinocampheyl)boranes.[8a,b,f,k,l] Several other classes of highly enantioselective chiral crotylmetal compounds have been developed in recent years, but in general these reagents or their auxiliaries require multistep syntheses and therefore are less attractive for preparative purposes in spite of their superior enantioselectivity.[8] In short, the stability, selectivity, and ease of preparation and

(23) (a) Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye, R. *Org. Syn.* **1984**, *63*, 66. (c) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 193. (d) Finn, M. G.; Sharpless, K. B. *Ibid.*; Vol. 5, p 247.

(24) (a) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(25) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. The supplementary material accompanying this paper includes physical data for anti 1,3-diols **13d** (cyclohexanecarboxaldehyde series) and **13f** (pivalaldehyde series).

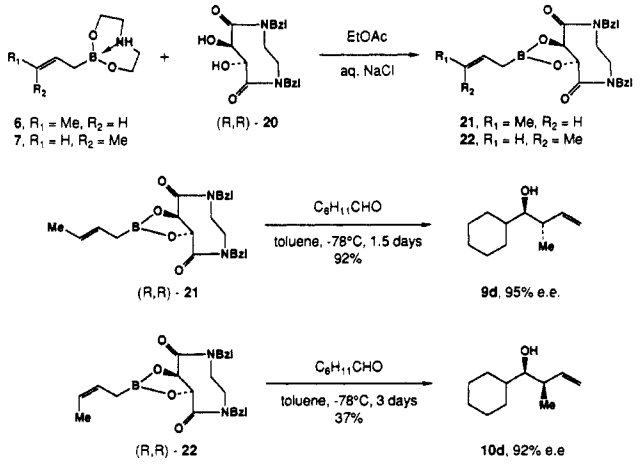
(26) Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131.

(27) The relative and absolute stereochemistries of **9b,c,e** and **10e,f** are assigned by analogy to the cases discussed in text.

(28) Most of the examples reported in Table I have been duplicated by using the set of enantiomeric reagents (*S,S*)-**2** and (*S,S*)-**3**. The enantiomers of **9** and **10** were obtained with enantioselectivities in all cases falling within experimental error of the values obtained with (*R,R*)-**2** and (*R,R*)-**3**.

handling of the tartrate crotylboronates **2** and **3** makes these reagents highly attractive candidates for application as chiral propionate enolate equivalents in organic synthesis. Indeed, several applications of this technology in the synthesis of stereochemically complex molecules have appeared and others are in progress.[9c,f,g,h,29]

In spite of the many favorable attributes of **2** and **3**, it is clear that considerable room for improvement exists in terms of enantioselectivity and substrate generality. In preliminary studies towards this goal, we have prepared chiral crotylboronates **21** and **22** by the exchange reaction of diethanolamine complexes **6**/**7** and (*R*,*R*)-N,N'-dibenzyl-N,N'-ethylenetartramide (**20**).[19] The reaction of (*R*,*R*)-**21** and cyclohexanecarboxaldehyde at −78 °C provided anti homoallyl alcohol **9d** in 95% ee, while the (*Z*)-crotyl isomer (*R*,*R*)-**22** led to the syn diastereomer **10d** in 92% ee. These



results indicate that it will be possible to prepare chiral crotylboronates that are substantially more enantioselective than **2** and **3**. Reagents **21** and **22**, like the corresponding allyl reagent,[19] however, are unattractive for large scale preparative experiments owing to their poor solubility and reactivity characteristics. Work continues on the development of a chiral auxiliary with the enantioselectivity of (*R*,*R*)-**20** but with the reactivity of the DIPT derived reagents **1**–**3**.

Experimental Section

General. ^{1}H NMR spectra were measured in $CDCl_3$ on Varian XL-300, XL-400, or Bruker AM 500 instruments operating at 300, 400, or 500 MHz, respectively. Residual chloroform (7.26 ppm) was used as internal reference. ^{13}C NMR spectra were recorded at 75.4 MHz on the XL-300 and were referenced with the 77.0 ppm resonance of $CDCl_3$. ^{19}F NMR spectra were obtained at 376.3 or 282.2 MHz on the XL-400 or XL-300 instruments and were referenced with external TFA (0.0 ppm). ^{11}B NMR spectra were recorded at 115.8 MHz on a Bruker AM 360 MHz instrument and were referenced with external BF_3–Et_2O (0.0 ppm). Infrared spectra were recorded on a Perkin–Elmer Model 1420 infrared spectrophotometer and were referenced by the 1601 cm^{-1} absorption of polystyrene. Optical rotations were measured on a Rudolph Autopol III Automatic Polarimeter using a 1 cm^{-3} quartz cell (10-cm path length). Mass spectra were measured at 70 eV on a Varian MAT 44 or a Finnegan MAT 8200 instrument. High-resolution mass spectra were measured at 70 eV on the Finnegan MAT 8200. Elemental analyses were performed by Robertson Laboratory, Inc., of Florham Park, NJ, or Midwest Microlab, Inc., of Indianapolis, IN.

All reactions were conducted in oven-dried (125 °C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, THF, benzene, and toluene were distilled from sodium benzophenone ketyl. Hexane was distilled from sodium benzophenone ketyl in the presence of tetraglyme (Aldrich). Methylene chloride was distilled from CaH_2.

Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm × 10 cm plates coated with a 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin-layer chromatography (PTLC) was performed by using 20 cm × 20 cm plates coated with 0.25- or 0.5-mm thickness of silica gel containing PF 254 indicator (Analtech). Compounds were visualized by charring with ethanolic vanillin/H_2SO_4, phosphomolybdic acid, or *p*-anisaldehyde/H_2SO_4, or by staining with iodine vapor. Unless noted otherwise, all compounds purified by chromatography are sufficiently pure (>95% by ^{1}H NMR analysis) for use directly in subsequent preparative reactions.

Preparation of (*R*,*R*)-Diisopropyl Tartrate (*E*)-Crotylboronate (2). An oven-dried 1-L three-neck round-bottom flask equipped with a magnetic stir bar and a −100 °C thermometer is charged with 350 mL of anhydrous THF and KOtBu (48.0 g, 425 mmol). This mixture is flushed with Ar and cooled to −78 °C, and then *trans*-2-butene (42.0 mL, 450 mmol), condensed from a gas lecture bottle into a rubber-stoppered 25-mL graduated cylinder immersed in a −78 °C dry ice–acetone bath, is added via cannula. *n*-BuLi (2.5 M in hexane, 170 mL, 425 mmol) is then added dropwise via cannula at a rate such that the internal temperature does not rise above −65 °C. After completion of the addition (roughly 2 h on this scale), the cooling bath is removed and the reaction mixture is allowed to warm until the internal temperature reaches −50 °C. The solution is maintained at −50 °C for exactly 15 min and then is immediately recooled to −78 °C.[13]

Triisopropylborate (80.0 g, 98.2 mL, 425 mmol) is then added dropwise via cannula to the (*E*)-crotylpotassium solution at a rate such that the internal temperature does not rise above −65 °C. On this scale the addition time was approximately 2 h. After the addition is complete, the reaction mixture is maintained at −78 °C for 10 min and then rapidly poured into a 2-L separatory funnel containing 800 mL of 1 N HCl saturated with NaCl. The aqueous layer is adjusted to pH 1 by using 1 N HCl, and then a solution of (*R*,*R*)-diisopropyl tartrate (100 g, 425 mmol) in 150 mL of Et_2O is added.[17] The phases are separated, and the aqueous layer is extracted with additional Et_2O (4 × 200 mL). The combined extracts are dried with $MgSO_4$ for at least 2 h at room temperature and then vacuum filtered through a fritted glass funnel under a N_2 blanket into an oven-dried round-bottom flask. The filtrate is concentrated on the rotary evaporator to a colorless thick liquid, and then is pumped to constant weight (125 g) at 0.5–1.0 mmHg. It is necessary for the neat reagent to be stirred for residual volatile materials, especially residual THF, to be removed efficiently. Analysis of the crude product by capillary GC [50 m × 0.25 mm fused quartz SE-54 column (0.2 μm polydiphenylvinyldimethylsiloxane), 170 °C isotherm; retention time for **2** is 10.9 min; **3**, 11.3 min; butylboronate 10.5 min] indicated that the isomeric purity of this batch of reagent was 99%; 12% of tartrate butylboronate was also present, reflecting incomplete metalation of (*E*)-butene in this experiment.[13] The yield of this batch of reagent, determined by the titration procedure described below, was 60%.

The amount of butylboronate is suppressed, and the yield of reagent improved, by performing the butene metalation at a higher concentration (0.9 M).[13] Thus, in several recent runs on 200–300-mmol scales, the yield of **2** has been 82–89% (≥98% isomeric purity) with a butylboronate content of <3%. A portion (ca. 20 mmol) of the product from one such experiment was distilled through a short path apparatus (95 °C, 0.01 mmHg) but with some erosion of isomeric purity (96% *E*).

Tartrate crotylboronate **2**, prepared from initial experiments [FB-$(OMe)_2$ procedure] in which the crude crotylboronic acid (theoretically 1.0 equiv) was treated with 0.4–0.5 equiv of DIPT, was purified by Kugelrohr distillation (80 °C, 0.1 mmHg). Reagent (*S*,*S*)-**2** prepared from (*S*,*S*)-DIPT had $[\alpha]^{25}_D$ +36.5° (neat). This compound is moisture sensitive, and we now prefer to handle it as a solution in toluene or THF: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53–5.63 (m, 1 H), 5.37–5.48 (m, 1 H), 4.83–5.00 (m, 2 H), 4.89 (s, 2 H), 1.86 (br d, *J* = 6.4 Hz, 2 H), 1.53 (br d, *J* = 6.3 Hz, 3 H), 0.90 (d, *J* = 6.3 Hz, 12 H); ^{13}C NMR (75.4 MHz, C_6D_6) δ 169.0, 126.1, 125.3, 78.4, 69.6, 21.6, 18.1; ^{11}B NMR (115.8 MHz, C_6D_6) δ 34.8; IR (thin film) 3500 (br), 2980 (s), 2935 (s), 2880 (s), 1745 (s), 1375 (s), 1220 (s), 1105 (s), 965 (m) cm^{-1}; mass spectrum (CI, NH_3), *m*/*z* 299 (M^+ + 1); high-resolution mass spectrum for $C_{14}H_{23}{}^{10}BO_6$ calcd 297.1617, found 297.1618; high-resolution mass spectrum for $C_{14}H_{23}{}^{11}BO_6$ calcd 298.1581, found 298.1683.

Preparation of (*R*,*R*)-Diisopropyl (*Z*)-Crotylboronate 3. The preparation of (*Z*)-crotylboronate **3** from (*Z*)-2-butene is analogous to that described for the *E* reagent with the following modification: upon completion of the *n*-BuLi addition, the reaction mixture is warmed to −20 to −25 °C for 30–45 min before being recooled to −78 °C. This ensures near quantitative formation of the (*Z*)-crotylpotassium. Temperature control is less critical here since the (*Z*)-crotylpotassium is highly favored at equilibrium (99:1). The remainder of this preparation is the same as that described above for the synthesis of **2**. On a 100-mmol scale, the yield of (*Z*)-crotylboronate is 70–75% (1–2% of butylboronate) and the isomeric purity is >98% (generally >99%).

Tartrate crotylboronate **3**, prepared from initial experiments [FB-$(OMe)_2$ procedure] in which the crude crotylboronic acid (theoretically 1.0 equiv) was treated with 0.4–0.5 equiv of DIPT, was purified by Kugelrohr distillation (92 °C, 0.6 mmHg). Reagent (*R*,*R*)-**3** prepared from (*R*,*R*)-DIPT had $[\alpha]^{25}_D$ −80.2° (*c* = 2.42, $CHCl_3$); ^{1}H NMR (300

(29) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117; *Ibid.* **1989**, *111*, 2967.

MHz, $CDCl_3$) δ 5.67–5.76 (m, 1 H), 5.48–5.55 (m, 1 H), 4.99–5.05 (m, 2 H), 4.92 (s, 2 H), 1.91 (br d, J = 7.8 Hz, 2 H), 1.56 (br d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.3 Hz, 12 H); ^{13}C NMR (75.4 MHz, C_6D_6) δ 169.0, 124.6, 124.4, 78.4, 69.6, 21.3, 12.7; ^{11}B NMR (115.8 MHz, C_6D_6) δ 34.8; IR (thin film) 3500 (br), 3220 (m), 2980 (s), 1745 (s), 1375 (s), 1220 (s), 1100 (s) cm^{-1}; mass spectrum (CI, NH_3), m/z 298 (M^+); high-resolution mass spectrum for $C_{14}H_{23}{}^{11}BO_6$ calcd 298.1581, found 298.1624.

Preparation of Standardized Solutions of Chiral Crotylboronates 2 and 3. The crude reagent is weighed and then dissolved in sufficient toluene (or THF) to give a 1.0 M solution assuming that the yield of reagent is 100%; if the weight of crude product is less than the theoretical amount, then the purity is assumed to be 100%. One mL of this solution (at most, 1 mmol of reagent) is treated with 1.0 mmol of cyclohexanecarboxaldehyde (112 mg, 121 mL) at room temperature for 30 min. The solution is then cooled to 0 °C and quenched with a solution of $NaBH_4$ (excess) in EtOH. Aqueous NaOH (2 mL, 2 N) is then added and the mixture stirred vigorously for 15 min to hydrolyze the tartrate ester. The phases are separated and the aqueous layer is extraced with ether (2 × 5 mL). The extracts are combined, dried (K_2CO_3), and concentrated in vacuo. The mixture is then analyzed by capillary GC on a 50 m × 0.25 mm Bonded FSOT Carbowax 20 column (temperature program: 100 °C for 4 min then 10 deg/min to a final temperature of 190 °C). Under these conditions cyclohexylmethanol (from reduction of unconsumed aldehyde) elutes at 8.4 min, anti homoallyl alcohol **9d** elutes at 10.7 min, and the syn diastereomer **10d** at 11.2 min. From the ratio of cyclohexylmethanol to homoallyl alcohols (anti and syn) one calculates the concentration and hence also the yield of reagent. Such solutions have been stored under argon in a −20 °C freezer for several months with little noticeable deterioration.

Synthesis of (*E*)-Crotylboronate Diethanolamine Complex 6. (*E*)-Crotylboronic acid (100 mmol, theoretical amount) was prepared in the usual manner from 125 mmol of (*E*)-butene and 100 mmol of *n*-BuLi, KOtBu, and B(*i*-OPr)$_3$. The reaction was quenched with 1 N HCl and then was extracted with EtOAc (3 × 120 mL). The combined organic fractions were treated with diethanolamine (8.41 g, 80 mmol) and stirred over 4-Å molecular sieves under nitrogen for 3 h. Filtration and concentration of the solution in vacuo produced an oil, which upon treatment with 50 mL of benzene afforded 14.7 g of a pale yellow solid. Recrystallization of this material from CH_2Cl_2–Et_2O yielded 8.4 g (50%) of **6** as a white crystalline solid: mp 120–121 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (m, 1 H), 5.33 (m, 1 H), 4.15 (br s, 1 H), 4.00 (m, 2 H), 3.88 (m, 2 H), 3.22 (m, 2 H), 2.80 (m, 2 H), 1.62 (dd, J = 6.6, 2.1 Hz, 3 H), 1.46 (d, J = 9.0 Hz, 2 H); ^{11}B NMR (115.8 MHz, $CDCl_3$) δ 11.26; mass spectrum (EI), m/z 114 (M^+ − crotyl). Anal. Calcd for $C_8H_{16}BNO_2$: C, 56.85; H, 9.54. Found: C, 56.79; H, 9.69.

(*Z*)-Crotylboronate Diethanolamine Complex 7. (*Z*)-Crotylboronic acid (100 mmol, theoretical amount) was converted to 9.8 g (59%) of **7** by using the procedure described for preparation of **6**: mp 156–157 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.64 (m, 1 H), 5.32 (m, 1 H), 4.32 (br s, 1 H), 4.00 (m, 2 H), 3.88 (m, 2 H), 3.21 (m, 2 H), 2.79 (m, 2 H), 1.62 (dd, J = 7.2, 2.0 Hz, 3 H), 1.43 (d, J = 7.2 Hz, 2 H); ^{11}B NMR (115.8 MHz, $CDCl_3$) δ 12.01; IR (KBr) 3140 (br), 3000 (s), 2860 (s), 1640 (s), 1355 (s), 1272 (s), 1210 (s) cm^{-1}; mass spectrum (EI), m/z 114 (M^+ − crotyl). Anal. Calcd for $C_8H_{16}BNO_2$: C, 56.85; H, 9.54. Found: C, 56.62; H, 9.46.

Synthesis of Tartrate (*E*)-Crotylboronate 2 from the Diethanolamine Complex 6. A suspension of **6** (444 mg, 2.62 mmol) and (*R*,*R*)-diisopropyl tartrate (615 mg, 2.62 mmol) in Et_2O (10 mL) was treated with saturated aqueous NaCl (10 mL) and stirred under nitrogen for 5 min. The phases were separated and the aqueouslayer extracted with Et_2O (2 × 15 mL). The organic layer was washed with aqueous saturated NaCl (15 mL). Organic extracts were combined and dried over anhydrous $MgSO_4$. Filtration and concentration of the solution in vacuo afforded 0.77 g (99%) of **2**. The yield was determined to be 92% by the titration method described earlier.

Representative Procedure for Reactions of 2 and 3 with Aldehydes. Preparation of (3*S*,4*R*)-4-Cyclohexyl-3-methyl-1-buten-4-ol (9d). A solution of (*E*)-crotylboronate **2** (3.19 g, 10.7 mmol, crude reagent, 99.3% isomeric purity) in 32 mL of dry toluene under N_2 was treated with powdered 4-Å molecular sieves (600 mg) and then cooled to −78 °C. A solution of freshly distilled cyclohexanecarboxaldehyde (1.00 g, 8.92 mmol) in 10 mL of toluene was then added dropwise over 30 min. The reaction mixture was stirred over −78 °C for 3 h and then was treated with 10 mL of 2 N NaOH to hydrolyze DIPT. The two-phase mixture was warmed to 0 °C and stirred for 20 min before being filtered through a pad of Celite. The aqueous layer was extracted with Et_2O (4 × 10 mL). The combined organic extracts were dried over K_2CO_3, filtered, and chromatographed through flash silica gel (60 × 150 mm column) with use of 6:1 hexane–ether as eluant to provide 1.41 g (94%) of **9d** that was >99% diastereomerically pure (capillary GC analysis: Carbowax 20 column; 70 °C for 4 min then 10 deg/min to a final temperature of 150 °C) and had an enantiomeric purity of 86% ee as determined by the chiral capillary GC analysis of the methyl ether.[20]

Data for homoallyl alcohols **9** and **10** are summarized below. Homoallyl alcohols **9c**,[30a] **9d**,[30b,c] **9f**,[8g,30] **9h**,[8b,22a,30] **10c**,[30a] **10d**,[30b,c] **10f**,[8b,30] and **10h**[8b,22a,30] are previously known compounds.

(3*S*,4*R*)-3-Methyl-1-tridecen-4-ol (9a) (prepared from the reaction of **8a** and (*R*,*R*)-**2**): R_f 0.43 (2:1 hexane–ether); $[\alpha]^{25}_D$ +0.56° (c = 0.89, $CHCl_3$); $[\alpha]^{28}_{336}$ −6.6° (c = 0.89, $CHCl_3$; data obtained on a sample of **9a** that was >99.5% diastereomerically pure and 88% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (ddd, J = 16.2, 11.3, 8.0 Hz, 1 H), 5.14 (br d, J = 11.3 Hz, 1 H), 5.12 (br d, J = 16.2 Hz, 1 H), 3.37 (m, 1 H), 2.17 (m, 1 H), 1.15–1.65 (m, 17 H), 1.00 (d, J = 6.8 Hz, 3 H), 0.85 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 140.4, 116.2, 74.7, 44.1, 34.3, 31.9, 29.7, 29.6, 29.5, 29.3, 25.8, 22.7, 16.3, 14.1; IR (thin film) 3385, 3078, 2928, 2858, 1637, 1460, 999, 911 cm^{-1}; mass spectrum (CI, NH_3), m/z 212 (M^+), 196, 157; high-resolution mass spectrum for $C_{14}H_{28}O$ calcd 212.2140, found 212.2106. Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 78.81; H, 13.04.

(3*S*,4*R*)-3-Methyl-6-phenyl-1-hexen-4-ol (9b) (prepared from the reaction of **8b** and (*R*,*R*)-**2**): $[\alpha]^{25}_D$ +13.8° (c = 1.13, $CHCl_3$; data obtained on material that is >99.5% diastereomerically pure and 86% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.14–7.30 (m, 5 H), 5.73 (ddd, J = 18.0, 11.5, 8.5 Hz, 1 H), 5.09–5.16 (m, 2 H), 3.40 (m, 1 H), 2.84 (m, 1 H), 2.67 (m, 1 H), 2.22 (m, 1 H), 1.55–1.90 (m, 3 H), 1.02 (d, J = 6.8 Hz, 3 H); IR (thin film) 3395, 3067, 3030, 2974, 2932, 2876, 1640, 1605, 1497, 1456, 1145, 999, 913, 748, 699 cm^{-1}; high-resolution mass spectrum for $C_{13}H_{18}O$ calcd 190.1358, found 190.1352. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.00; H, 9.62.

(3*R*,4*S*)-3-Methyl-1-nonen-4-ol (9c) (prepared from the reaction of **8c** and (*S*,*S*)-**2**): R_f 0.38 (2:1 hexane–ether); $[\alpha]^{25}_D$ −3.3° (c = 5.3, $CHCl_3$; data obtained on a 99:1 mixture of diastereomers); ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17, 10, 8 Hz, 1 H), 5.07 (br d, J = 10 Hz, 1 H), 5.05 (br d, J = 17 Hz, 1 H), 3.46 (m, 1 H), 2.18 (m, 1 H), 1.20–1.70 (m, 9 H), 1.00 (d, J = 6.8 Hz, 3 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 140.3, 116.0, 74.7, 44.0, 34.2, 31.9, 25.4, 22.6, 16.2, 13.9; IR (thin film) 3410, 3078, 2932, 2863, 1640, 1462, 1419, 1380, 1336, 1145, 999, 912 cm^{-1}; high-resolution mass spectrum for $C_{10}H_{18}$ ($M^+ - H_2O$) calcd 138.1409, found 138.1411. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 77.00; H, 12.49.

(3*S*,4*R*)-4-Cyclohexyl-3-methyl-1-buten-4-ol (9d) (prepared from the reaction of **8d** and (*R*,*R*)-**2**): R_f 0.34 (3:1 hexane–ether); $[\alpha]^{25}_D$ −15.8° (c = 1.02, $CHCl_3$; data obtained on a >99% diastereomerically pure sample, 86% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddd, J = 18.0, 10.9, 7.2 Hz, 1 H), 5.10–5.15 (m, 2 H), 3.11 (dd, J = 5.1, 5.1 Hz, 1 H), 2.39 (m, 1 H), 1.60–1.85 (m, 5 H), 1.35–1.48 (m, 2 H), 1.06–1.28 (m, 5 H), 1.04 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ 140.4, 116.0, 78.8, 40.5, 40.3, 30.0, 27.0, 26.5, 26.4, 26.1, 17.0; IR (thin film) 3420, 2925, 2858, 1640, 1451, 1396, 1332, 1114, 999, 912 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O$: C, 78.52; H, 11.98. Found: C, 78.22; H, 12.20.

(3*S*,4*R*)-3-Methyl-6-[(*tert*-butyldimethylsilyl)oxy]-1-hexen-4-ol (9e) (prepared from the reaction **8e** and (*R*,*R*)-**2**): $[\alpha]^{25}_D$ +8.2° (c = 2.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddd, J = 17.0, 11.0, 7.8 Hz, 1 H), 5.08–5.04 (m, 2 H), 3.97–3.79 (m, 2 H), 3.75–3.66 (m, 1 H), 3.25 (d, J = 7.0 Hz, 1 H), 2.22–2.33 (m, 1 H), 1.63–1.69 (m, 2 H), 1.07 (d, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.11 (s, 6 H); IR (thin film) 3600–3200 (br), 2950, 2920, 2350, 1470, 1455, 1250, 1080, 900, 830, 770 cm^{-1}; high-resolution mass spectrum for $C_{13}H_{29}O_2Si$ (M^+ + 1) calcd 245.193, found 245.193.

(3*S*,4*S*)-3,5,5-Trimethyl-1-hexen-4-ol (9f) (prepared from the reaction of **8f** and (*R*,*R*)-**2**): $[\alpha]^{25}_D$ −7.6° (c = 1.02, $CHCl_3$; data obtained on an 95:5 mixture of diastereomers); ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (ddd, J = 16.6, 11.2, 7.0 Hz, 1 H), 5.04–5.09 (m, 2 H), 3.14 (dd, J = 4.5, 2.2 Hz, 1 H), 2.52–2.64 (m, 1 H), 1.45 (d, J = 6.6 Hz, 1 H), 1.12 (d, J = 7.0 Hz, 3 H), 0.94 (s, 9 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 140.3, 115.3, 82.7, 39.4, 26.9, 26.7, 20.7; IR (thin film) 3470, 3079, 2961, 2875, 1639, 1481, 1463, 1365, 1108, 994, 909 cm^{-1}; mass spectrum (CI, NH_3), m/z 125 (M^+ − OH), 87 (M^+ − crotyl); high-resolution mass spectrum for C_9H_{17} (M^+ − OH) calcd 125.1330, found 125.1329.

(*E*)-(3*S*,4*S*)-3-Methyl-1,5-tridecadien-4-ol (9g) (prepared from the reaction of **8g** and (*R*,*R*)-**2**): $[\alpha]^{25}_D$ −14.2° (c = 0.92, $CHCl_3$; data obtained on >99% diastereomerically pure material); ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17, 10, 8 Hz, 1 H), 5.61 (m, 1 H), 5.38 (m, 1 H), 5.12–5.19 (m, 2 H), 3.77 (m, 1 H), 2.20 (m, 1 H), 2.02 (m,

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2 H), 1.83 (br s, 1 H), 1.15–1.40 (m, 10 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 140.6, 133.6, 130.6, 116.0, 76.2, 44.5, 32.2, 31.8, 29.2, 29.1 (2 C), 22.6, 16.0, 14.0; IR (thin film) 3395, 3080, 2925, 2879, 1671, 1640, 1460, 1380, 999, 968, 911 cm^{-1}; high-resolution mass spectrum for $C_{14}H_{26}O$ calcd 210.1984, found 210.1978.

(3*S*,4*S*)-3-Methyl-4-phenyl-1-buten-4-ol (9h) (prepared from the reaction of **8h** and (*R*,*R*)-**2**): R_f 0.23 (3:1 hexane–ether); $[\alpha]^{25}_D$ −73.4° (c = 2.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.35 (m, 5 H), 5.81 (ddd, J = 17.1, 10.0, 8.2 Hz, 1 H), 5.21 (br d, J = 17 Hz, 1 H), 5.19 (br d, J = 10 Hz, 1 H), 4.37 (dd, J = 7.7, 2.8 Hz, 1 H), 2.49 (m, 1 H), 2.13 (d, J = 2.8 Hz, 1 H), 0.88 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 142.5, 140.6, 128.1, 127.6, 126.8, 116.6, 77.8, 46.1, 16.4; IR (thin film) 3430, 3068, 3035, 2979, 2878, 1640, 1605, 1496, 1455, 1195, 1018, 911, 760, 734, 702 cm^{-1}; high-resolution mass spectrum for $C_{11}H_{13}$ (M^+ − OH) calcd 145.1017, found 145.1024. Anal. Calcd for $C_{11}H_{14}O$: C, 81.40; H, 8.70. Found: C, 81.66; H, 8.42.

(3*R*,4*R*)-3-Methyl-1-tridecen-4-ol (10a) (prepared from the reaction of **8a** and (*R*,*R*)-**3**): $[\alpha]^{25}_D$ +25.2° (c = 1.17, $CHCl_3$; data obtained on >99.5% diastereomerically pure material); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddd, J = 17.3, 9.7, 7.3 Hz, 1 H), 5.07 (br d, J = 17.3 Hz, 1 H), 5.05 (br d, J = 9.7 Hz, 1 H), 3.46 (m, 1 H), 2.25 (m, 1 H), 1.20–1.52 (m, 19 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.86 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.1, 115.0, 74.7, 43.4, 34.0, 31.9, 29.7, 29.6, 29.5, 29.3, 26.1, 22.6, 14.1, 14.0; IR (thin film) 3378, 2930, 2858, 1640, 1462, 1379, 995, 911 cm^{-1}; mass spectrum (CI, NH_3), m/z 212 (M^+), 195, 157; high-resolution mass spectrum for $C_{14}H_{28}O$ calcd 212.2140, found, 212.2127. The acetate derivative gave a correct C, H analysis. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.81; H, 11.75.

(3*R*,4*R*)-4-Cyclohexyl-3-methyl-1-buten-4-ol (10d) (prepared from the reaction of **8d** and (*R*,*R*)-**3**): R_f 0.18 (3:1 hexane–ether); $[\alpha]^{25}_D$ +28.0° (c = 0.61, $CHCl_3$; data obtained on >99% diastereomerically pure material); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddd, J = 17.3, 10.0, 7.0 Hz, 1 H), 5.08 (br d, J = 17.3 Hz, 1 H), 5.06 (br d, J = 10.0 Hz, 1 H), 3.18 (ddd, J = 5.0, 5.0, 4.3 Hz, 1 H), 2.38 (m, 1 H), 1.91 (br d, J = 13.0 Hz, 1 H), 1.73 (m, 2 H), 1.64 (m, 1 H), 1.58 (m, 1 H), 1.41 (m, 1 H), 1.35 (d, J = 4.3 Hz, 1 H), 1.00–1.30 (m, 5 H), 0.97 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 142.0, 114.4, 78.6, 40.2, 39.8, 29.6, 27.8, 26.4, 26.2, 25.9, 13.1; IR (thin film) 3400, 3078, 2925, 2855, 1681, 1450, 995, 911 cm^{-1}; mass spectrum, m/z 113 (M^+ − crotyl). Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.33; H, 12.03.

(3*R*,4*R*)-3-Methyl-6-[(*tert*-butyldimethylsilyl)oxy]-1-hexen-4-ol (10e) (prepared from the reaction of **8e** and (*R*,*R*)-**3**): $[\alpha]^{26}_D$ +5.6° (c = 2.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddd, J = 15.6, 9.9, 7.9 Hz, 1 H), 5.02–5.10 (m, 2 H), 3.90 (m, 1 H), 3.86 (m, 1 H), 3.68 (m, 1 H), 3.40 (d, J = 2.2 Hz, 1 H), 2.27 (m, 1 H), 1.70–1.60 (m, 2 H), 1.07 (d, J = 7.2 Hz, 3 H), 0.91 (s, 9 H), 0.09 (S, 6 H); IR (thin film) 3600–3300 (br), 2950, 2920, 2850, 1470, 1460, 1300, 1080, 905, 830, 770 cm^{-1}; high-resolution mass spectrum (CI) for $C_{13}H_{29}O_2Si$ (M^+ + 1) calcd 245.198, found, 245.194.

(3*R*,4*S*)-3,5,5-Trimethyl-1-hexen-4-ol (10f) (prepared from the reaction of **8f** and (*R*,*R*)-**3**): $[\alpha]^{25}_D$ +5.1° (c = 0.86, $CHCl_3$; data obtained on >99% diastereomerically pure material); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, J = 17.2, 10.0, 7.0 Hz, 1 H), 5.02 (br d, J = 17.2 Hz, 1 H), 4.99 (br d, J = 10.0 Hz, 1 H), 3.24 (dd, J = 5.0, 1.3 Hz, 1 H), 2.43–2.55 (m, 1 H), 1.41 (d, J = 5.0 Hz, 1 H), 1.05 (d, J = 6.5 Hz, 3 H), 0.96 (s, 9 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.3, 113.0, 81.3, 39.6, 35.7, 26.8, 14.7; IR (thin film) 3480 (br), 3078 (s), 2957 (s), 2874 (s), 1647 (s), 1475 (s), 1364 (s), 1100 (m), 998 (m), 909 (s) cm^{-1}; mass spectrum, m/z 125 (M^+ − OH); high-resolution mass spectrum (EI) for C_9H_{16} (M^+ − H_2O), calcd 124.1252, found, 124.1253. Anal. Calcd for $C_9H_{18}O$: C, 75.98; H, 12.75. Found: C, 75.62; H, 11.73.

(*E*)-(3*R*,4*S*)-3-Methyl-1,5-tridecadien-4-ol (10g) (prepared from the reaction of **8g** and (*R*,*R*)-**3**): $[\alpha]^{25}_D$ +1.8° (c = 1.0, $CHCl_3$; data obtained on a 99.4:0.6 mixture of diastereomers); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (ddd, J = 17.4, 10.0, 7.5 Hz, 1 H), 5.62 (m, 1 H), 5.41 (br dd, J = 15.3, 6.7 Hz, 1 H), 5.05 (m, 2 H), 3.94 (br dd, J = 6.0, 5.8 Hz, 1 H), 2.31 (m, 1 H), 2.01 (m, 2 H), 1.55 (br s, 1 H), 1.20–1.40 (m, 10 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.86 (t, J = 6.8 Hz, 3 H); IR (thin film) 3400 (br), 3080, 2961, 2925, 2855, 1640, 1456, 968, 911 cm^{-1}; mass spectrum, m/z 192 (M^+ − H_2O); high-resolution mass spectrum for $C_{14}H_{26}O$ calcd 210.1984, found 210.1935. The acetate derivative gave a correct combustion analysis. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.85; H, 11.27.

(3*R*,4*S*)-3-Methyl-4-phenyl-1-buten-4-ol (10h) (prepared from the reaction of **8h** and (*R*,*R*)-**3**): R_f 0.34 (2:1 hexane–ether); $[\alpha]^{25}_D$ −15.0° (c = 0.93, $CHCl_3$; data obtained on a 98:2 mixture of diastereomers); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.37 (m, 5 H), 5.77 (ddd, J = 17.5, 10.0, 7.0 Hz, 1 H), 5.06 (br d, J = 10 Hz, 1 H), 5.05 (br d, J = 17.5 Hz, 1 H), 4.62 (dd, J = 5.5, 3.5 Hz, 1 H), 2.59 (m, 1 H), 1.93 (d, J = 3.5 Hz, 1 H), 1.01 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 142.6, 140.3, 127.9, 127.2, 126.5, 115.3, 77.2, 44.6, 14.1; IR (thin film) 3420, 3065, 3034, 2976, 2952, 2879, 1640, 1605, 1495, 1454, 1015, 912, 762, 700 cm^{-1}; mass spectrum, m/z 145 (M^+ − OH), 107 (M^+ − crotyl); high-resolution mass spectrum (EI) for $C_{11}H_{13}$ (M^+ − OH) calcd 145.1017, found 145.1021. Anal. Calcd for $C_{11}H_{14}O$: C, 81.43; H, 8.70. Found: C, 81.30; H, 8.82.

Representative Procedure for Synthesis of Epoxy Alcohols 12a, 12d, and 12f. To a solution of Ti(O-*i*-Pr)$_4$ (1.35 g, 4.75 mmol) in CH_2Cl_2 (40 mL) containing powdered 4-Å molecular sieves (50 mg) at −78 °C was added (*R*,*R*)-(+)-DIPT (2.5 g, 64 mmol) in CH_2Cl_2 (2 mL). After 10 min, allylic alcohol **11d** (0.561 g, 4.00 mmol) in CH_2Cl_2 (1 mL) was added followed by dropwise addition of TBHP (3.3 mL of a 3.64 M solution in toluene, 12.0 mmol). After 30 min at −78 °C, the reaction mixture was maintained at −5 °C overnight. This solution was poured into a 0 °C solution of tartaric acid (5 g) and ferrous sulfate(12.9 g) in water (50 mL) and stirred for 30 min at room temperature. The aqueous phase (green) was extracted with ether (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered through Celite, and concentrated by rotary evaporation. The tartrate ester was hydrolyzed at 8 °C for 2 h in a mixture of ether (75 mL) and NaOH saturated with NaCl (50 mL). The aqueous portion was extracted with ether (2 × 50 mL). The combined organic extracts were dried and concentrated by rotary evaporation. The product was purifed by flash chromatography (1:1 hexane–ether) to yield **12d** (0.560 g, 90% yield). The enantiomeric purity was 95% ee as determined by Mosher ester analysis: $[\alpha]^{24}_D$ −24.6 (c = 7.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (br d, J = 12.5 Hz, 1 H), 3.59 (dd, J = 12.5, 4.5 Hz, 1 H), 2.96 (br s, 1 H), 2.74 (dd, J = 6.5 Hz, 1 H), 2.10 (br s, 1 H), 1.60–1.85 (m, 5 H), 1.00–1.30 (m, 6 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 62.0, 60.3, 57.6, 39.5, 29.5, 28.8, 26.1, 25.5, 25.4; IR (thin film) 3400, 2880, 2810, 1740, 1460, 1090 cm^{-1}; mass spectrum, m/z (rel intensity), 138 (0.1, 25 (0.6)), 113 (4.8), 95 (100), 81 (71), 67 (60), 55 (56), 41 (45).

Epoxide **12a** (95% ee) was prepared in 75% yield by the asymmetric epoxidation ((*R*,*R*)-DIPT) of allylic alcohol **11a**: mp 62.5–63.0 °C (recrystallized from 10:1 hexane–ether); $[\alpha]^{24}_D$ −29.4° (c = 6.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (br d, J = 12.5 Hz, 1 H), 3.65 (br d, J = 4.3 Hz, 1 H), 2.94 (br d, J = 16.6 Hz, 2 H), 1.58 (t, J = 1.2 Hz, 2 H), 1.44 (m, 2 H), 1.28 (s, 13 H), 0.88 (t, J = 1.2 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 61.8, 58.7, 56.3, 31.9, 31.6, 29.5, 26.0, 22.7, 14.1; IR (thin film) 3500 (br), 2890 (s), 2825 (m), 1500 (m), 1250 (s), 1095 (s) cm^{-1}; mass spectrum, m/z 169 (M^+ − CH_2OH).

Epoxy alcohol **12f** was similarly prepared in 82% yield by the asymmetric epoxidation of **11f** using (*R*,*R*)-DIPT as the chiral auxiliary: $[\alpha]^{24}_D$ −20.0° (c = 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (m, 1 H), 3.60 (m, 1 H), 3.04 (dt, J = 4.2, 1.6 Hz, 1 H), 2.76 (br s, 1 H), 1.88 (t, J = 6.3 Hz, 1 H), 0.93 (s, 9 H); IR (thin film) 3430 (br), 2995 (s), 2920 (s), 1515 (m), 1475 (w), 1380 (m), 1090 (m), 1045 (m), 900 (m) cm^{-1}.

Representative Procedure for Reactions of Epoxides 12a, 12d, and 12f with Me_2CuLi. MeLi (6.1 mL of a 1.48 M solution in hexane, 9.0 mmol) was added dropwise over 10 min to a slurry of CuI (0.760 g, 4.0 mmol) in Et_2O (6 mL) at −10 °C. After 30 min, the solution was cooled to −50 °C. Epoxy alcohol **12d** (0.156 g, 1.0 mmol) in ether (5 mL) was then added dropwise. After being stirred for 2 h at −50 °C, the solution was allowed to warm to room temperature over 3 h and was stirred overnight. The solution was then poured into saturated aqueous NH_4Cl and 1 N NaOH (50 mL). The mixture was stirred for 2 h, and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried and concentrated in vacuo. This material was treated with $NaIO_4$ (0.239 g, 1.12 mmol) in THF/H_2O (5:1) for 1 h. The mixture was diluted with saturated brine solution and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated. The crude diol was purified by preparative TLC (0.5 mm silica gel plate, 1:2 hexane–ether) to yield an authentic sample of anti diol **13d** (0.143 g, 83%).[25] This material had $[\alpha]^{24}_D$ −20.4° (c = 7.1, $CHCl_3$) and was identical in all other respects (except absolute configuration and enantiomeric purity) to diol (+)-**13d** prepared via the ozonolysis of anti homoallylic alcohol (−)-**9d** (deriving ultimately from (*R*,*R*)-**2**). The absolute configuration of (−)-**13d** prepared from epoxy alcohol (−)-**12d** was further verified by preparation of the bis-MTPA derivatives and comparison of the data with that obtained from (+)-**13d**.

Epoxy alcohol (−)-**12a** ((*R*,*R*)-DIPT derived) was converted to anti 1,3-diol (−)-**13a** ($[\alpha]^{24}_D$ −23.2° (c = 6.2, $CHCl_3$)) that is enantiomeric to (+)-**13a** prepared by ozonolysis of anti homoallylic alcohol **9a** ((*R*,*R*)-**2** derived).

Finally, epoxy alcohol (−)-**12f** ((*R*,*R*)-DIPT derived) was converted to anti 1,3-diol (+)-**13f** ($[\alpha]^{24}_D$ −6.4°; c = 5.0, $CHCl_3$) that again was

enantiomeric to (−)-**13f** prepared by ozonolysis of (−)-**9f** ((*R,R*)-**2** derived).[25]

Representative Procedure for Conversion of Anti Homoallyl Alcohols 9 to 1,3-Diols 13. Preparation of (1*R*,2*S*)-1-Cyclohexyl-2-methyl-1,3-propanediol (13d). A solution of (−)-**9d** (100 mg, 0.594 mmol, ((*R,R*)-**2** derived) in 20 mL of CH_2Cl_2 at −78 °C was treated with a stream of ozone in O_2 until the reaction was complete by TLC (10 min). The resulting blue solution was purged with nitrogen until colorless. The solvent was removed in vacuo and the residue dissolved in 10 mL of dry THF. A slurry of $LiAlH_4$ (67 mg, 1.8 mmol) in 5 mL of THF was added dropwise to the mixture at 0 °C. After 2 h the excess $LiAlH_4$ was quenched with 0.1 mL of water in THF, followed by 0.1 mL of 1 N NaOH, and an additional 0.3 mL of water. The mixture was stirred at 0 °C for 2 h and then filtered, concentrated in vacuo, and chromatographed through flash silica (20- × 150-mm column) with 4:1 hexane–Et_2O as eluant to afford 74 mg (72%) of pure **13d**:[25] $[\alpha]^{25}_D$ +14.8° (*c* = 0.79, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$); δ 3.76 (dd, *J* = 10.7, 3.6 Hz, 1 H), 3.64 (dd, *J* = 10.7, 7.0 Hz, 1 H), 3.34 (dd, *J* = 7.6, 4.2 Hz, 1 H), 1.80–1.89 (m, 1 H), 1.74–1.80 (m, 3 H), 1.66–1.69 (br d, 1 H), 1.53–1.56 (br d, 1 H), 1.38–1.49 (m, 2 H), 1.08–1.30 (m, 6 H), 0.89 (d, *J* = 7 Hz, 3 H); IR (thin film) 3350, 2922, 2852, 1450, 1038, 973, 891 cm^{-1}; mass spectrum, *m/z* 154 ($M^+ - H_2O$). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.66; H, 11.70.

(2*S*,3*R*)-2-Methyl-1,3-dodecanediol (13a): $[\alpha]^{25}_D$ −20.3° (*c* = 10.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (m, 1 H), 3.59 (m, 1 H), 3.51 (m, 1 H), 2.85 (br s, 1 H), 2.61 (br s, 1 H), 1.68 (m, 1 H), 1.25–1.55 (m, 16 H), 0.85 (m, 6 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 76.9, 67.3, 39.7, 35.1, 31.8, 29.7, 29.6 (2 C), 29.3, 25.2, 22.6, 14.0, 13.8; IR (thin film) 3340 (br), 2930 (s), 2860 (s), 1460 (m), 1378 (w), 1028 (m) cm^{-1}; mass spectrum (of acetate derivative) *m/z* 259 ($M^+ - 41$). An acceptable combustion analysis was obtained on the diacetate derivative. Anal. Calcd for $C_{17}H_{32}O_4$: C, 67.96; H, 10.74. Found: C, 67.90; H, 10.48.

(2*S*,3*S*)-2,4,4-Trimethyl-1,3-pentanediol (13f):[25] Homoallylic alcohol **9f** was converted to the corresponding 1,3-diol **13f** in 64% yield: $[\alpha]^{25}_D$ −4.4° (*c* = 0.87, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (m, 1 H), 3.63 (m, 1 H), 3.24 (dd, *J* = 4.8, 4.1 Hz, 1 H), 2.78 (br s, 1 H), 2.57 (br s, 1 H), 1.91 (m, 1 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 0.95 (s, 9 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 84.8, 66.5, 35.8, 35.0, 26.1, 18.3; IR (thin film) 3390 (br), 2940 (s), 2860 (s), 2225 (w), 1450 (m), 1355 (m), 1065 (m), 965 (m) cm^{-1}; mass spectrum (CI, NH_3), *m/z* 129 (M^+ − OH, parent ion); high-resolution mass spectrum for $C_8H_{17}O$ (M^+ − OH) calcd 129.1279, found 129.1279. Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.74; H, 12.74.

(1*S*,2*S*)-2-Methyl-1-phenyl-1,3-propanediol (13h): Homoallylic alcohol **9h** was converted to the 1,3-diol **13h** in 83% yield: R_f 0.1 (1:1 hexane–ether); $[\alpha]^{25}_D$ −32.8° (*c* = 0.68, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.38 (m, 5 H), 4.55 (dd, *J* = 6.0, 8.4 Hz, 1 H), 3.73–3.83 (m, 2 H), 2.80–2.85 (m, 2 H, OH), 2.06 (m, 1 H), 0.71 (d, *J* = 7.0 Hz, 3 H); mass spectrum (CI, NH_3), *m/z* 166 (M^+). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.60; H, 8.77.

Representative Procedure for Reaction of Epoxides 12 with $H_2C{=}CHMgBr$ and CuBr–Me_2S. To a mixture of CuBr–Me_2S (1.64 g, 8.0 mmol), Me_2S (1.5 mL), and ether (10 mL) at −25 °C was added dropwise vinylmagnesium bromide (20.0 mL, 1.0 M in THF, 260 mmol). After 10 min, epoxide **12d** (0.312 g, 2.0 mmol) was added. The mixture was stirred between −20 and −30 °C for 5 h and then was allowed to warm to room temperature and stirred overnight. The solution was poured into pH 8.5 aqueous NH_4Cl/NaOH solution and stirred vigorously for 2 h. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was treated with excess $NaIO_4$ in THF/water (5:1) for 3 h. Saturated brine solution was added and the solution extracted with EtOAc. After being dried over Na_2SO_4 and concentrated in vacuo, the product was purified by flash silica gel chromatography (1:1 hexane–ether) to yield diol **14d** (0.287 g, 77%): $[\alpha]^{24}_D$ −23.3° (*c* = 5.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (ddd, *J* = 17.0, 11.0, 7.0 Hz, 1 H), 5.16 (d, *J* = 17.0 Hz, 1 H), 5.15 (d, *J* = 11.0 Hz, 1 H), 3.89 (dd, *J* = 10.5, 6.0 Hz, 1 H), 3.71 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.45 (dd, *J* = 8.5, 3.5 Hz, 1 H), 2.46 (m 1 H), 1.74 (br s, 2 H), 1.00–1.70 (m, 11 H); ^{13}C NMR (7.54 (MHz, $CDCl_3$) δ 136.4, 117.6, 79.0, 65.6, 46.2, 40.7, 30.2, 26.4 (2 C), 26.1, 25.5; IR (thin film) 3350, 2920, 2850, 1450, 1060, 900 cm^{-1}; mass spectrum, *m/z* (rel intensity) 149 (0.2), 136 (4), 111 (15), 95 (23), 83 (60), 67 (15), 54 (100).

Epoxy alcohol **12a** ((*R,R*)-DIPT derived) was similarly converted to diol **14a** in 75% yield: $[\alpha]^{24}_D$ −15.0° (*c* = 1.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (ddd, *J* = 16.3, 10.7, 8.8 Hz, 1 H), 5.17 (br d, *J* = 10.7 Hz, 1 H), 5.16 (br d, *J* = 16.3 Hz, 1 H), 3.74 (m, 2 H), 3.70 (d, *J* = 6.7 Hz, 2 H), 2.56 (br s, 1 H), 2.29 (m, 1 H), 1.15–1.58 (m, 16 H), 0.86 (t, *J* = 7.4 Hz, 3 H); IR (thin film) 3350 (br), 2935 (s), 2855 (s), 1450 (w) cm^{-1}; mass spectrum (CI, NH_3), *m/z* 197 ($M^+ - CH_2OH$).

Procedure for Conversion of 1,3-Diols 14 to Syn Homoallyl Alcohols 10. Preparation of an Authentic Sample of 10d. A solution of 240 mg (1.3 mmol) of diol (−)-**14d** in 10 mL of pyridine was treated at 0 °C with 114 mg (1.4 mmol) of methanesulfonyl chloride. This solution was then placed in a −50 °C freezer for 48 h. The solution was then diluted with aqueous $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was then coevaporated twice from heptane to remove pyridine.

The crude monomesylate was then dissolved in Et_2O (2 mL) and transferred via cannula to a 0 °C solution of 38 mg (2.6 mmol) of $LiAlH_4$ in 10 mL of Et_2O. The solution was stirred at 0 °C for 2 h and at room temperature overnight. The mixture was then quenched by the sequential addition of 1.3 mL of H_2O, 4 mL of 5 N NaOH, and 1.5 mL of H_2O. The mixture was filtered and the residue washed with EtOAc. The crude product was then purified by preparative TLC (0.5-mm silica gel plate, 2:1 hexane–ether) to provide 116 mg (53% of syn homoallyl alcohol (−)-**10d** ($[\alpha]^{24}_D$ −37.1° (*c* = 4.1, $CHCl_3$)) that was enantiomeric but otherwise identical to (+)-**10d** prepared from cyclohexanecarboxaldehyde and (*R,R*)-**3**. The absolute stereochemical assignment for (−)-**10d** was verified by preparation of the pair of diastereomeric MTPA esters using (+)- and (−)-MTPA–Cl.

Diol **14a** was converted to syn homoallyl alcohol **10a** ($[\alpha]^{24}_D$ −30.0° (*c* = 1.1, $CHCl_3$)) in 44% yield according to this procedure. Here again, (−)-**10a** prepared from **14a** was enantiomeric to (+)-**10a** obtained from the reaction decanal and (*R,R*)-**3**.

Correlation of 9a and 9g. Synthesis of (3*S*,4*R*)-3-Methyltridecan-4-ol (15). A solution of 159 mg (0.75 mmol) of **9a** (75% ee) in 2 mL of ethanol was hydrogenated over Pd/C (30 mg) under a hydrogen atmosphere. When complete, the reaction mixture was filtered through a plug of Celite, concentrated in vacuo, and chromatographed on a short flash silica gel column to give 120 mg (75%) of **15** ($[\alpha]^{23}_D$ +7.7° (*c* = 1.9, $CHCl_3$)). This compound was identical with **15** ($[\alpha]^{23}_D$ +9.2° (*c* = 1.4, $CHCl_3$)) prepared by hydrogenation of **9g** (75% ee): ^1H NMR (300 MHz, $CDCl_3$) δ 3.46 (m, 1 H), 1.58–1.40 (m, 5 H), 1.29–1.25 (br s, 14 H), 1.10 (m, 1 H), 0.96–0.88 (m, 9 H); IR (thin film) 3600–3200 (br), 2960, 2920, 2850, 1460, 1375 cm^{-1}; mass spectrum (CI, NH_3), *m/z* 213 (M^+ − 1), 197, 157; high-resolution mass spectrum, calcd for $C_{14}H_{30}O$ (M^+) 214.2300, found 214.2297. Anal. Calcd for $C_{14}H_{30}O$: C, 78.43; H, 14.10. Found: C, 78.55; H, 14.08.

Correlation of 10a and 10g. Synthesis of (3*R*,4*R*)-3-Methyltridecan-4-ol (16). Syn homoallyl alcohols **10a** and **10g** were hydrogenated by using the procedure described for preparation of **15**. Alcohol **16** prepared from **10a** ((*R,R*)-**3** derived) had $[\alpha]^{24}_D$ +13.4° (*c* = 1.84, $CHCl_3$) and **16** prepared from **10g** ((*R,R*)-**3** derived) had $[\alpha]^{24}_D$ +9.4° (*c* = 1.88, $CHCl_3$): ^1H NMR (300 MHz, $CDCl_3$) δ 3.53 (m, 1 H), 1.59–1.34 (m, 5 H), 1.29–1.20 (br s, 14 H), 1.20 (d, 5.6 Hz, 1 H); 0.96–0.88 (m, 9 H); IR (thin film) 3600–3200 (br), 2960, 2920, 2850, 1460, 1380 cm^{-1}; mass spectrum (CI, NH_3), *m/z* 213 (M^+ − 1), 197, 157; high-resolution mass spectrum (EI) for $C_{14}H_{29}O$ (M^+ − 1), calcd 213.2221, found 213.2223.

Correlation of 9d and 9h. Synthesis of (1*S*,2*S*)-1-Cyclohexyl-2-methylbutan-1-ol (17). (a) From 9d. A solution of 25 mg (0.15 mmol) of **9d** ((*R,R*)-**2** derived) in 1 mL of MeOH containing one drop of HOAc was hydrogenated over 5 mg of 5% Rh/Al_2O_3 under a hydrogen atmosphere. The reaction was stirred overnight and then was filtered through a short column of silica gel. Removal of solvent in vacuo gave 25 mg (98%) of pure **17**: R_f 0.55 (1:1 hexane–ether); $[\alpha]^{23}_D$ +0.61° (*c* = 0.66, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (dd, *J* = 11.3, 5.4 Hz, 1 H), 1.72–1.85 (m, 3 H), 1.39–1.69 (m, 5 H), 0.96–1.34 (m, 7 H), 0.88–0.92 (m, 6 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.8, 139.7, 138.9, 128.0, 127.7, 127.0, 115.4, 78.8, 43.4, 20.9, 16.2; IR (thin film) 3380 (br), 2920 (s), 2843 (s), 1705 (w), 1440 (s), 1375 (m), 1075 (m), 970 (s) cm^{-1}; mass spectrum (CI, NH_3), *m/z* 170 (M^+); high-resolution mass spectrum (CI) calcd for $C_{11}H_{22}O$ (M^+) 170.1671, found 170.1662. Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 76.84; H, 13.14.

(b) From 9h. A solution of 26 mg (0.16 mmol) of **9h** ((*R,R*)-**2** derived) in 0.5 mL of dry pyridine was treated with Ac_2O (0.045 mL, 0.48 mmol) and DMAP (5 mg). The solution was stirred at room temperature for 3 h until complete by TLC analysis. Pyridine was then removed by coevaporation with heptane, and the residue was chromatographed through a short plug of flash silica gel (5:1 hexane–Et_2O), affording 31 mg (97%) of pure (3*S*,4*S*)-3-methyl-4-phenyl-1-buten-4-yl acetate: $[\alpha]^{25}_D$ +68.8° (*c* = 0.94, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.34 (m, 5 H), 5.74 (ddd, *J* = 17.6, 11.2, 7.6 Hz, 1 H), 5.58 (d, *J* = 8.1 Hz, 1 H), 5.03 (br d, *J* = 17.6 Hz, 1 H), 5.02 (br d, *J* = 11.2 Hz, 1 H), 2.63 (m, 1 H), 2.03 (s, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.8, 139.7, 138.9, 128.0, 127.7, 127.0, 115.4, 78.8, 43.4, 20.9, 16.2; IR (thin film) 2974, 1739, 1456, 1371, 1233, 1019, 914, 758, 699 cm^{-1}; mass spectrum, *m/z* 149 (M^+ − crotyl), 144

(M^+ - HOAc). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.78; H, 8.23.

A solution of the above acetate (89 mg, 0.44 mmol) in 0.5 mL of MeOH containing 0.05 mL of HOAc was hydrogenated over 13 mg of 5% Rh/Al_2O_3 under atmospheric hydrogen. When complete as indicated by TLC analysis, the mixture was filtered through a pad of Celite and then chromatographed through a 30 × 150 mm flash silica gel column (3:1 hexane-ether) to afford 91 mg (98%) of (1*S*,2*S*)-1-cyclohexyl-2-methyl-1-butyl acetate that was used directly in the following experiment: R_f 0.35 (3:1 hexane-ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (dd, J = 9.0, 9.0 Hz, 1 H), 2.12 (br s, 3 H), 1.57-1.78 (m, 6 H), 1.36-1.50 (m, 1 H), 1.02-1.35 (m, 6 H), 0.91-0.99 (m, 1 H), 0.80-0.90 (m, 6 H).

The acetate prepared above (75 mg, 0.35 mmol) was dissolved in 5 mL of Et_2O and treated with $LiAlH_4$ (15 mg, 0.38 mmol) at 0 °C. The reacion was complete within a few minutes and quenched according to the method described for the preparation of **10d**. The crude product was filtered through a short plug of flash silica gel, yielding 51 mg (86%) of **17** that was identical with the sample prepared from **9d**. Because the $[\alpha]^{25}_D$ value is so small and, therefore potentially unreliable, the absolute configuration of **17** prepared from **9h** was verified by preparing the (*R*)- and (*S*)-MTPA esters, which were indistinguishable from those prepared from the **9d** derived sample of **17**.

Correlation of 10d and 10h. Synthesis of (1*S*,2*R*)-1-Cyclohexyl-2-methylbutan-1-ol (18). Syn homoallyl alcohols **10d** and **10h** were converted to **18** by using the methods described for the synthesis of **17**. Compound **18** prepared from (*R*,*R*)-**3** derived **10d** had $[\alpha]^{25}_D$ +4.8° (c = 0.81, $CHCl_3$) while that from (*R*,*R*)-**3** derived **10h** had $[\alpha]^{25}_D$ +5.0° (c = 1.12, $CHCl_3$). The absolute configurations of these compounds was further verified by the Mosher ester analysis. Data for **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.18 (dd, J = 7.6, 3.8 Hz, 1 H), 1.96 (br d, J = 12.8 Hz, 1 H), 1.72-1.78 (m, 2 H), 1.59-1.67 (m, 2 H), 1.52-1.54 (m, 1 H), 1.37-1.42 (m, 2 H), 1.13-1.29 (m, 5 H), 0.93-1.01 (m, 2 H), 0.90 (dd, J = 7.7, 7.2 Hz, 3 H), 0.85 (d, J = 6.2 Hz, 3 H); IR (thin film) 3380 (br), 2910 (s), 2840 (s), 1445 (s), 1370 (m), 1115 (m), 1075 (m), 975 (s) cm^{-1}; mass spectrum (CI, NH_3), m/z 169 (M^+ - 1). Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.40; H, 13.15.

(3*R*,4*S*)-3-Methyl-4-phenyl-1-butenyl acetate (acetate derivative of **10h**): R_f 0.36 (3:1 hexane-ether); $[\alpha]^{25}_D$ -31.9° (c = 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.33 (m, 5 H), 5.63 (ddd, J = 17.5, 10.5, 7.4 Hz, 1 H), 5.62 (d, J = 7.1 Hz, 1 H), 4.94 (d, J = 10.5 Hz, 1 H), 4.93 (d, J = 17.5 Hz, 1 H), 2.67 (dq, J = 7.4, 6.8 Hz, 1 H), 2.07 (s, 3 H), 1.03 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.0, 139.0, 138.9, 127.9, 127.6, 127.0, 115.5, 78.8, 42.8, 21.0, 15.2; IR (thin film) 2978, 1741, 1456, 1374, 1233, 1020, 918, 757, 700 cm^{-1}; mass spectrum, m/z 149 (M^+ - crotyl), 144 (M^+ - HOAc). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.73; H, 7.87.

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Acyclic Diastereoselective Synthesis Using Tartrate Ester Modified Crotylboronates. Double Asymmetric Reactions with α-Methyl Chiral Aldehydes and Synthesis of the C(19)-C(29) Segment of Rifamycin S

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Abstract: Double asymmetric reactions of the tartrate ester modified crotylboronates **1** and **2** and α-methyl chiral aldehydes are described. The reactions of the appropriate enantiomers of **1** and **2** with β-alkoxy-α-methylpropionaldehydes **11** provide adducts **12**, **13**, and **14** with a minimum diastereoselectivity of 90%, provided that the optimal hydroxyl protecting group is selected for **11**. Thus, TBDMS protected aldehyde **11a** is the optimal substrate for the matched double asymmetric reactions leading to **12a** and **14a**, while the TBDPS protected **11b** is the optimal precursor to **13b** and **15b** via mismatched double asymmetric reactions. A similar dependence of stereoselectivity on the protecting group is seen in the reactions of **11** and chiral allylboronate **16**. It is inferred from these and other data (c.f., $\sum\Delta\Delta G^{\ddagger}$ data provided in Table IV) that β-alkoxy aldehyde substituents have a significant, negative impact on the diastereoselectivity of the double asymmetric reactions of the tartrate allylboronates, especially those involving **2** and **16**. Additional insight into the existence of the "alkoxy effect" is provided by the double asymmetric reactions of **1**, **2**, and **16** with aldehyde **20** that lacks an offending β-alkoxy group. These experiments (Table V) show that the diastereoselectivity of the reactions of **20** especially with **2** and **16** ($\sum\Delta\Delta G^{\ddagger}$ = 1.7-1.8 kcal mol^{-1}) are significantly improved relative to those with **11** (typically $\sum\Delta\Delta G^{\ddagger}$ = 1.1-1.4 kcal mol^{-1}). Improvements in stereoselectivity of the allyl- and (*E*)-crotylborations of both **11** and **20** are also possible by using reagents **28** and **29** incorporating the more highly enantioselective *N*,*N*′-dibenzyl-*N*,*N*′-ethylenetartramide auxiliary previously developed in these laboratories (Table VI). Adduct **23** deriving from these studies has been converted into lactone **27**, a known precursor of the Prelog-Djerassi lactonic acid. An empirical model is presented that enables one to predict the situations in which **1** and **2** will be maximally effective in complex synthetic problems. Thus, dipropionate substructures **7** and **9** with anti relationships between branching methyl groups can be prepared with very high diastereoselectivity via matched double asymmetric reactions with the appropriate α-methyl chiral aldehyde substrate, while substructures **8** and **10** with syn relationships between methyl branches are more difficult to prepare via mismatched double asymmetric reactions. Moreover, the ease of preparation of **7** and **9**, and the difficulty with **8** and **10**, is expected to increase as the intrinsic diastereofacial preference of the chiral aldehyde increases. Accordingly, the number of bond constructions leading to 1,3-anti branching methyl relationships should be maximized when applying this technology in total synthesis, and the more difficult 1,3-syn branching methyl units should be introduced as early as possible. These principles are illustrated in a highly diastereoselective synthesis of the C(19)-C(29) segment of the ansa bridge of rifamycin S. This synthesis features four C-C bond forming reactions involving the chiral crotyl- and allylboronate technology and proceeds in 15% yield and with 78% stereoselectivity for the 16-step sequence originating from (*S*)-**11b**.

In the preceding paper we described the synthesis of tartrate ester modified crotylboronates **1** and **2** and defined the stereochemistry of their reactions with achiral aldehydes.[3] Our motivation to initiate synthetic studies in this area derived from the

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