N,N'-Bis(2,2,2-trifluoroethyl)-N,N'-ethylenetartramide: An Improved Chiral Auxiliary for the Asymmetric Allylboration Reaction

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N,N-Bis(2,2,2-trifluoroethyl)-*N,N'*-ethylenetartramide (**8**), synthesized by a simple four-step sequence from ethylenediamine and benzylidenetartaric acid, was designed in anticipation that the derived allylboronates **9**–**11** would display enhanced reactivity owing to the inductive effect of the *N*-trifluoroethyl substituents that would increase the Lewis acidity of the boron atom of the *B*-allyl-1,3,2-dioxaborolanes. Reagents **9**–**11** were synthesized by transesterification of **8** with the crystalline and easily purified allylboronate diethanolamine complexes **13**, **19**, and **25**. Allylboronate **9** is ca. 100-fold more reactive than **6** and is also substantially more useful than the previously reported allyboronate **4**, which suffers from very poor solubility in toluene at −78 °C. Most importantly, allylboronates **9**–**11** are significantly more enantioselective than the parent tartrate allylboronates **1**–**3** and rank among the most highly enantioselective allylboron reagents yet reported. Reactions of **9**–**11** with aldehydes are performed in THF at −78 or −55 °C for 5–12 h periods. The enantioselectivity realized in reactions with achiral aldehydes is 92–95% ee (Table 2), and excellent diastereoselectivity is achieved in double asymmetric reactions with chiral aldehydes **15a**, **15b**, and **33** (Tables 3 and 4). For example, **16** and **28** are now available with a minimum selectivity of 92% from reactions of **15a** and **15b** with allylboronate **9**, while the crotylboration products **29**, **30**, and **31** are available with a minimum selectivity of 90% (usually ≥95%) from reactions of **15a** and **15b** with crotylboronates **10** and **11**; the fourth isomer, **32a**, is available with 83% selectivity. Chiral reagents **9**–**11** thus appear well suited for application to complex problems in organic synthesis.

The reaction of allylmetal reagents and carbonyl compounds is an important synthetic method that has found numerous applications in the stereocontrolled synthesis of acyclic molecules.[2-4] Excellent diastereoselectivity occurs in reactions of aldehydes with type I allyl organometallics, which proceed by way of cyclic transition states. However, control of the diastereofacial selectivity in allylmetalation reactions of chiral aldehydes typically requires use of chiral reagents that permit stereochemical control to be achieved via the strategy of double asymmetric synthesis.[3-6] Several families of highly enantioselective allylmetal reagents are now available from the laboratories of Hoffmann,[7-9] Brown,[10-12] Reetz,[13] Masamune,[14,15] Corey,[16] and Duthaler,[17,18] among others.[19] Allylations of chiral aldehydes with allylsilanes or allylstannanes catalyzed by chiral Lewis acids may also ultimately constitute a solution to the aldehyde diastereofacial selectivity problem.[20-23]

We introduced the tartrate allylboronates **1**–**3** in 1985[24] and have subsequently fully documented the enantio- and diastereoselectivity of their reactions with a range of achiral and chiral aldehydes.[25-28] While **1**–**3** are highly practical reagents and have found numerous applications in complex synthetic problems,[28-36] they give

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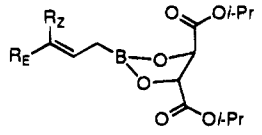
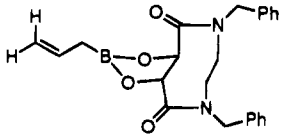
only good to moderate levels of enantioselectivity in reactions with most achiral aldehydes (typically 60–87% ee,[25,27] except for reactions with metal carbonyl-complexed unsaturated aldehydes, which give 83–98% ee).[37,38] Diminished enantioselectivity also frequently occurs with β-alkoxy aldehydes.[26] Moreover, double asymmetric reactions with chiral aldehydes are usually most selective when performed in the matched stereochemical series,[28] especially if the substrate contains a conformationally unconstrained β-alkoxy substituent.[26]



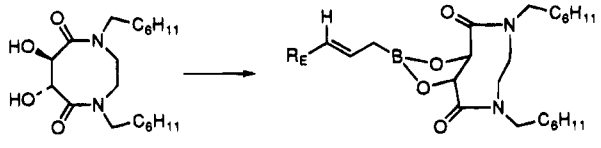
(R,R)-**1**, $R_E = R_Z = H$
(R,R)-**2**, $R_E = Me$, $R_Z = H$
(R,R)-**3**, $R_E = H$, $R_Z = Me$



(R,R)-**4**

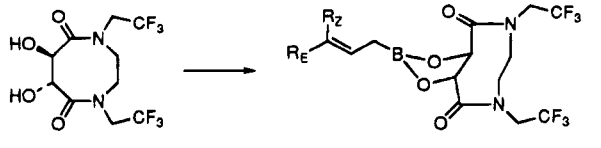
In 1988, we reported the synthesis of allylboronate **4** containing a conformationally rigid tartramide auxiliary.[39] This reagent, designed on the basis of our rationale of the mechanism of asymmetric induction in allylboration reactions of **1**–**3**,[24,40] was found to be substantially more enantioselective than the parent tartrate ester derivative **1** (94–97% ee for most substrates except PhCHO).[39] The Banfi reagent **4** still ranks among the most highly enantioselective allylborating agents in the literature. However, the very poor solubility characteristics of **4** result in impractically long reaction times and poor conversions under conditions which give maximum asymmetric induction (toluene, −78 °C).[39] Thus, reagent **4** has not yet found any applications in organic synthesis.

These problems encouraged us to continue our efforts to develop improved, second-generation allylboron reagents which exhibit high enantioselectivity with a wide range of substrates but which are also useful for preparative purposes in organic synthesis. We report herein the synthesis of allylboronate **6** which has improved solubility characteristics compared to **4**, the design of *N,N'*-bis(2,2,2-trifluoroethyl)-*N,N'*-ethylenetartramide (**8**), and the synthesis of the derived allylboronates **9**–**11** that are significantly more reactive than **4**, **6**, or the corresponding crotylboronates (e.g., **7**). The new chiral auxiliary **8** thus appears to meet the criterion of synthetic utility set at the outset of these investigations.[41]



(R,R)-**5**

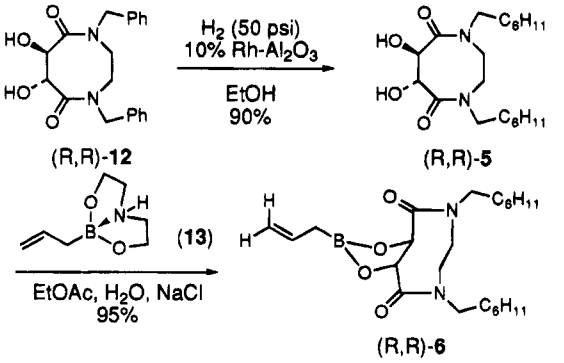
(R,R)-**6**, $R_E = H$
(R,R)-**7**, $R_E = Me$



(R,R)-**8**

(R,R)-**9**, $R_E = R_Z = H$
(R,R)-**10**, $R_E = Me$, $R_Z = H$
(R,R)-**11**, $R_E = H$, $R_Z = Me$

Use of *N,N'*-Bis(cyclohexylmethyl)-*N,N'*-ethylenetartramide (5) as a Chiral Auxiliary. We first addressed the solubility issue, thinking that this was the main problem associated with poor reactivity characteristics of **4**. After considerable exploratory work on the synthesis of modified diol auxiliaries, we found that *N,N'*-bis(cyclohexylmethyl)-*N,N'*-ethylenetartramide (**5**) was easily prepared by hydrogenation of **12** over Rh on Al_2O_3.[42] Treatment of **5** with the crystalline allylboronate diethanolamine complex **13** in a two-phase mixture of EtOAc and saturated aqueous NaCl then provided **6** in



excellent yield.[27] Significantly, 0.5 M solutions of **6** in toluene were completely homogeneous at −78 °C, and allylborations of simple aldehydes such as *n*-hexanal and cyclohexanecarboxaldehyde proceeded to completion within a 5–7 h period. Interestingly, however, the enantioselectivity of these reactions was dependent on the method of preparation and handling of **6**. For example, when **6** was prepared from **5** by treatment with triallylborane,[39] the best % ee obtained in the reaction with $C_6H_{11}CHO$ was 62% ee (entry 2), whereas the best % ee obtained with **6** prepared from diisopropyl allylboronate was 91% ee (entry 3). Similar results were obtained with the first samples of **6** prepared via the diethanolamine complex **13** (entry 4). Because we suspected that an achiral allylboron species was contaminating **6** (e.g., allylboronic acid), solutions of the reagent were pretreated with 0.1 equiv of acetaldehyde (entry 5) or pivalaldehyde at 23 °C (entry 6) before addition of the aldehydic substrate. The data show that the pivalaldehyde treatment increased the enantioselectivity from 90 to 95% ee (compare entries 4 and 6). This pretreatment was performed in all other allylboration experiments described in this paper.

Comparison of the data in entry 6 versus that of entry 1[39] indicates that **6** is potentially more useful than the Banfi reagent **4** for synthetic applications. However, there was an indication from the reaction with TBDPSO-$(CH_2)_3CHO$ (entry 8) that **6** reacts sluggishly with some substrates. This was also observed in reactions of **6** with chiral aldehydes **15a** and **17**[43] and in the reactions of the (*E*)-crotylboronate (*R,R*)-**7** with c-$C_6H_{11}CHO$ and *n*-C_5H_9CHO. Accordingly, we concluded that further development of *N,N'*-bis(cyclohexylmethyl)-*N,N'*-ethylenetartramide (**5**) as a chiral auxiliary for the allylboration reaction was not warranted.

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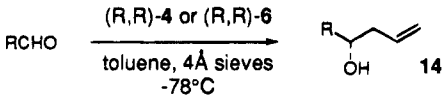
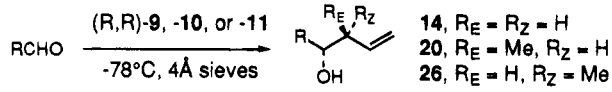
Table 1. Asymmetric Allylborations of Achiral Aldehydes with (*R,R*)-6



entry	reagent	RCHO	conc (M)	time (h)	conv (%)[g]	product	yield[h]	% ee[i]
1[a]	**4**	$C_6H_{11}CHO$	0.03	47	80	**14a**	40	97
2	**6**[b]	$C_6H_{11}CHO$	0.5	5	99	**14a**		62
3	**6**[c]	$C_6H_{11}CHO$	0.5	3	93	**14a**		91
4	**6**[d]	$C_6H_{11}CHO$	0.5	5		**14a**		90
5	**6**[d,e]	$C_6H_{11}CHO$	0.5	5		**14a**		90
6	**6**[d,f]	$C_6H_{11}CHO$	0.5	5	98	**14a**	82	95
7	**6**[d,f]	n-$C_5H_{11}CHO$	0.5	7	99	**14b**	93	97
8	**6**[d,f]	$TBDPSO(CH_2)_3CHO$	0.5	36	85	**14c**	72	94

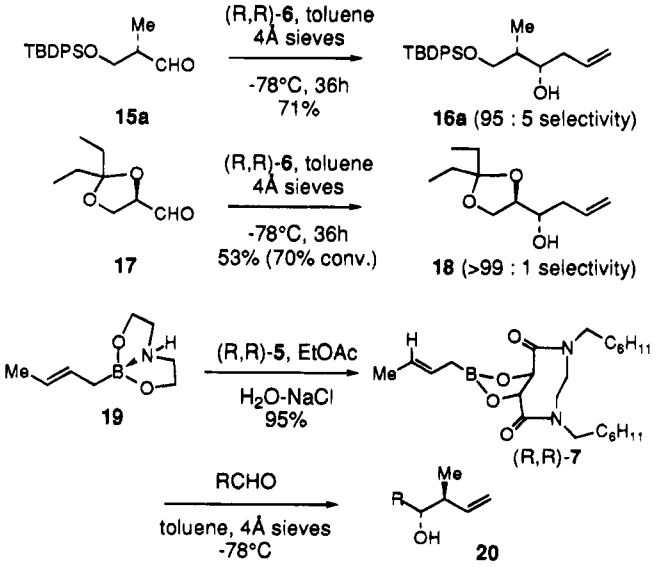
[a] The data for entry 1 are reproduced from ref 39. [b] Reagent **6** was prepared from triallylborane. [c] Reagent **6** was prepared from $(i\text{-PrO})_2BCH_2CH{=}CH_2$. [d] Reagent **6** was prepared *via* **13** as described in text. [e] The solution of (*R,R*)-**6** was treated with 0.1 equiv of CH_3CHO before addition of RCHO. [f] The solution of (*R,R*)-**6** was pretreated with 0.1 equiv of Me_3CCHO (30 min, 23 °C) before addition of RCHO at −78 °C. [g] Reactions were terminated by the addition of excess CH_3CHO, and extent conversion (ratio of RCHO to **14**) was determined by capillary GC analysis. [h] Isolated yields of **14**. [i] Determined by the Mosher ester method for entries 2−8.

Table 2. Asymmetric Allylborations of Achiral Aldehydes with (*R,R*)-9, (*R,R*)-10, and (*R,R*)-11



entry	reagent[a]	RCHO	solvent	conc (m)	time[b] (h)	product	yield (%)[c]	% ee[d,e]
1	**9**	$C_6H_{11}CHO$	toluene	0.1	1	**14a**	71	94 (87)
2	**9**	$C_6H_{11}CHO$	THF	0.5	5	**14a**	91	94 (78)
3	**9**	n-$C_5H_{11}CHO$	THF	0.5	5	**14b**	95	95 (−)
4	**9**	$TBDPSO(CH_2)_3CHO$	THF	0.5	5	**14c**	80	95 (82)
5	**10**	$C_6H_{11}CHO$	THF	0.3	6	**20a**	85	94 (87)
6	**10**	n-$C_5H_{11}CHO$	THF	0.3	6	**20b**	82	92 (85)
7	**11**	$C_6H_{11}CHO$	THF	0.4	9	**26a**	80	92 (83)
8	**11**	n-$C_5H_{11}CHO$	THF	0.4	9	**26b**	76	92 (82)

[a] Solutions of **9**, **10**, and **11** were pretreated with 0.1 equiv of Me_3CCHO (30 min, 23 °C) before addition of RCHO at −78 °C. [b] Reactions were terminated by addition of excess CH_3CHO at −78 °C. [c] Yields of **14**, **20**, and **26** isolated by chromatography. [d] Enantiomeric excesses were determined by ^1H NMR or capillary GC analysis of the Mosher ester derivatives. [e] Values in parentheses are the % ee values obtained by using the parent tartrate ester modified allylboronates **1**−**3**.



RCHO	Conc.	Time	Conv	Product	Yield	% e.e.
c-$C_6H_{11}CHO$	0.6 M	24 h	96%	**20a**	74%	93%
n-$C_5H_{11}CHO$	0.6 M	22 h	71%	**20b**	70%	88%

Development of *N,N'*-Bis(2,2,2-trifluoroethyl)-*N,N'*-ethylenetartramide (8) as an Auxiliary for the Allylboration Reaction. We have previously suggested that the considerably greater reactivity of the tartrate allylboronates **1**−**3** compared to all other allylboronic esters is due to the inductive effect of the carbalkoxy substituents that decreases the electron density of the dioxaborolane ring oxygens, which in turn increases the Lewis acidity of the boron atom.[44,45] Reagents containing tartramide auxiliaries presumably are less reactive than the parent tartrate ester-derived *B*-allyl-1,3,2-dioxaborolanes, since the inductive effect of the amide nitrogen is less than that of the ester oxygen. This effect is clearly apparent in the relative ^{11}B chemical shifts of the two classes of reagents.[44,45] Accordingly, we reasoned that strongly electron-withdrawing substituents on nitrogen should enhance the Lewis acidity and increase the reactivity of the tartramide-substituted allylboronates and therefore targeted *N,N'*-bis(2,2,2-trifluoroethyl)-*N,N'*-ethylenetartramide (**8**) as a new generation auxiliary for the allylboration reaction.[46]

Auxiliary **8** was synthesized by a simple four-step sequence starting from ethylenediamine (**21**). Thus, acylation of **21** with trifluoroacetic anhydride provided the crystalline bis(trifluoroacetamide) **22**, which was reduced with $LiAlH_4$ in THF at reflux, giving diamine **23** in 93% overall yield. DCC coupling of **23** with benzylidene-(*R,R*)-tartaric acid[39] in dilute CH_2Cl_2 then provided **24** in 38−47% yield. Other condensing agents (e.g., Mukaiyama salt and BOP-Cl, which give 52−65%

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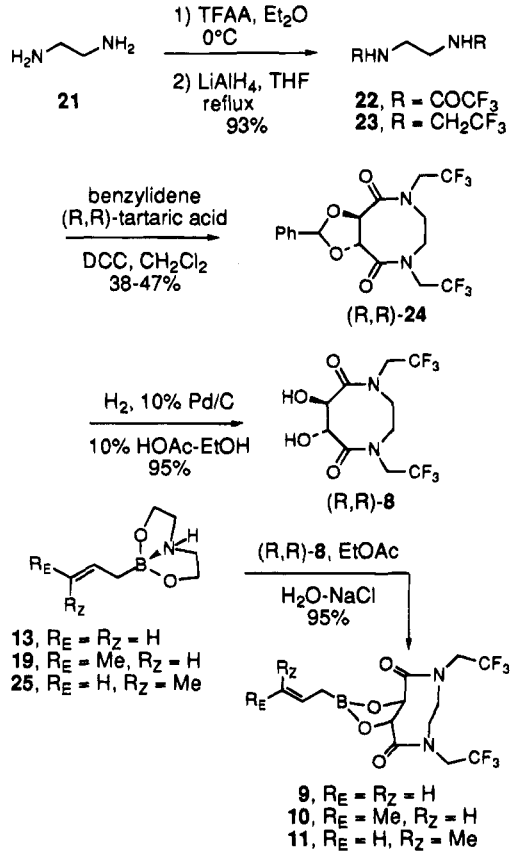
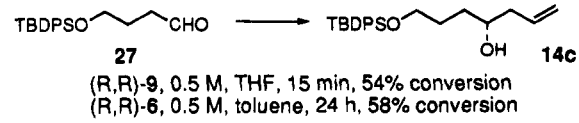
(46) Attempts to synthesize imide, *N*-sulfonyl, or *N*-aryl analogs of **5** were unsuccessful.

yields in the analogous cyclization, leading to the benzylidene acetal precursor to **12**) were much less efficient in this case. Removal of the benzylidene acetal by catalytic hydrogenolysis then provided (*R,R*)-**8** in 95% yield. Multigram quantities of both enantiomers of **8** have been synthesized by this sequence. Finally, transesterification of the crystalline and easily purified allylboronate diethanolamine complexes **13**, **19**, and **25** with (*R,R*)-**8** provided the crude allylboronates **9**–**11** in excellent yield. Because we were unable to purify these reagents by recrystallization, they were used directly in allylboration reactions following preparation of standardized solutions (see Experimental Section).

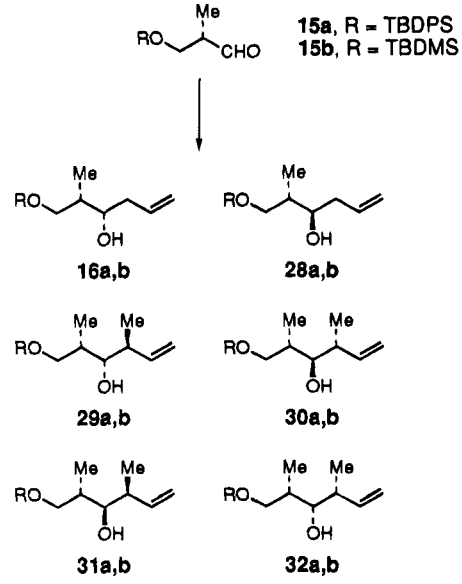


Results of allylborations of achiral aldehydes with **9**–**11** are summarized in Table 2. To our considerable disappointment, we quickly discovered that allylboronate **9** is only sparingly soluble in toluene at room temperature (ca. 0.1 M) and considerably less so at −78 °C. However, we were encouraged by the results of initial experiments which showed that a 71% yield of **14a** was obtained from a 1 h reaction with a heterogeneous 0.1 M solution of **9** in toluene (87% conversion by GC analysis; Table 2, entry 1). We also found that 0.5 M solutions of **9** in THF remained homogeneous at −78 °C and, unlike our experience with **1**–**3**,[25,27] that the allylboration reactions were comparably enantioselective in both THF and toluene (entries 1 and 2). The only drawback to the use of THF as the reaction solvent is that allylborations are intrinsically slower than in toluene.[25] Nevertheless, the data summarized in Table 2 show that the allylborations of **9**–**11** with simple aldehydes proceed to completion within 5–9 h periods. Moreover, in all cases, the enantioselectivity was significantly improved (92–95% ee) relative to results obtained using **1**–**3**.

We estimate that **9** is at least 100-fold more reactive than **6** (discounting the effect of solvent on rate) since the reaction of **9** (0.5 M in THF) and **27** proceeded to 54% completion within 15 min at −78 °C, whereas the reaction with **6** (0.5 M in toluene) proceeded to 58% completion in a 24 h period at −78 °C. Thus, while the reactions of **9** would be expected to be even faster in toluene, the increased reactivity due to the trifluoroethyl substituents and the greater solubility in THF more than compensate for the negative effect on rate by the solvent.



Results of double asymmetric reactions of **9**, **10**, and **11** with α-methyl-β-alkoxypropionaldehydes **15a,b** are summarized in Table 3. These data show that, in virtually all cases, the new chiral reagents lead to a substantial improvement in diastereoselectivity compared to the results previously obtained in reactions of



these aldehydes with the parent tartrate allylboronates **1**–**3**.[26,27,47] Thus, for example, the reaction of matched double-asymmetric reaction of **15a** and (*R,R*)-**9** provides a 92:8 mixture of **16a** and **28a** (Table 3, entry 1), compared to a 79:21 mixture in the reaction with (*R,R*)-**1**, while in the mismatched reaction with (*S,S*)-**9** diastereomer, **28a** is favored, with 97:3 selectivity (Table 3, entry 2), compared to the 87:13 mixture that is obtained when (*S,S*)-**1** is used.[28] Similarly, diastereomers **29a**, **30a**, and **31a** are now available with 95, 96, and >99% selectivity, from the crotylboration reactions of **15a** with (*R,R*)-**10**, (*S,S*)-**10**, and (*S,S*)-**11**, respectively (Table 3, entries 5, 6, and 9). Previously, the dipropionate diastereomers **29a**, **30a**, and **31a** were available with only 82, 90, and 85% selectivity, respectively, from reactions involving the appropriate enantiomers of tartrate crotylboronates **2** and **3**. The new auxiliary functioned well even in the problematic (*Z*)-crotylboronate mismatched double-asymmetric reactions of **15a** and **15b**; for example, selectivity for **32a** improved to 83:12 in the reaction of **15a** and (*R,R*)-**11** from the previous level of 63:32 with **3** (Table 3, entry 10).

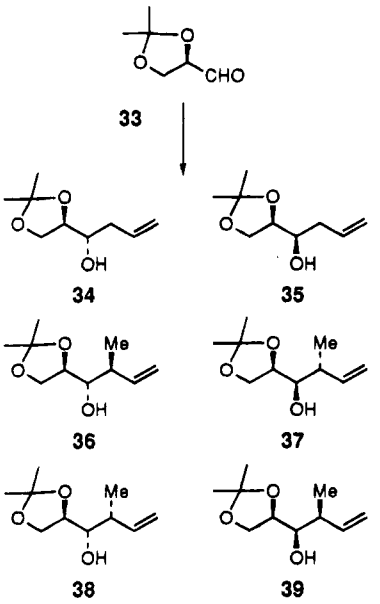
(47) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.

Table 3. Double Asymmetric Reactions of α-Methyl-β-alkoxypropionaldehydes 15a and 15b with 9-11

entry	RCHO	reagent	conditions	yield (%)	product ratios 16	28	29	30	31	32	selectivity with 1-3
1	**15a**	(*R,R*)-**9**	THF, −78 °C, 8 h	82	92	8					79:21 (**16:28**)
2	**15a**	(*S,S*)-**9**	THF, −78 °C, 8 h	83	3	97					13:87 (**16:28**)
3	**15b**	(*R,R*)-**9**	THF, −78 °C, 9 h	72	95	5					89:11 (**16:28**)
4	**15b**	(*S,S*)-**9**	THF, −78 °C, 9 h	76	6	94					19:81 (**16:28**)
5	**15a**	(*R,R*)-**10**	THF, −55 to 0 °C, 12 h	87			95	5			82:16 (**29:30**)
6	**15a**	(*S,S*)-**10**	THF, −55 to 0 °C, 12 h	80			4	96			10:90 (**29:30**)
7	**15b**	(*R,R*)-**10**	THF, −55 to 0 °C, 10 h	85			>97	3			97:3 (**29:30**)
8	**15b**	(*S,S*)-**10**	THF, −55 to 0 °C, 10 h	78			10	90			18:82 (**29:30**)
9	**15a**	(*S,S*)-**11**	THF, −78 to 23 °C, 10 h	74					>99	1	85:12 (**31:32**)
10	**15a**	(*R,R*)-**11**	THF, −78 to 23 °C, 12 h	90			5		12	83	32:63 (**31:32**)
11	**15b**	(*S,S*)-**11**	THF, −78 to 23 °C, 10 h	83				4	95	1	95:1 (**31:32**)
12	**15b**	(*R,R*)-**11**	THF, −78 to 23 °C, 10 h	82			1		37	62	41:45 (**31:32**)

Table 4. Double Asymmetric Reactions of D-Glyceraldehyde Acetonide (33) with 9-11

entry	reagent	conditions	yield (%)	product ratios 34	35	36	37	38	39	selectivity with 1-3
1	(*R,R*)-**9**	THF, −78 °C, 8 h	73	99.4	0.6					96:4
2	(*S,S*)-**9**	THF, −78 °C, 8 h	86	5	95					8:92
3	(*R,R*)-**10**	THF, −78 °C, 9 h	77			95	5			90:10
4	(*S,S*)-**10**	THF, −78 °C, 7 h	84			1	>99			2:98
5	(*R,R*)-**11**	THF, −78 to 23 °C, 10 h	95					>99	1	99:1
6	(*S,S*)-**11**	THF, −78 to 23 °C, 12 h	58					39	61	16:84



Results of double asymmetric reactions of **9-11** with D-glyceraldehyde acetonide (**33**) are summarized in Table 4. These results show that allyl- and crotylboration products **34-38** are now available with a minimum selectivity of 95% via this new methodology described herein. Although the (*Z*)-crotyl boronate **11** was not capable of overriding the intrinsic diastereofacial bias of **33** (97:3 favoring **38**, as determined in reactions with pinacol (*Z*)-crotylboronate),[26,48] the new reagent did a better job in this demanding mismatched double-asymmetric reaction (**38:39** = 39:61) than did the parent tartrate (Z)-crotylboronate **3** (**38:39** = 16:84; Table 4, entry 6). The only circumstances under which reagents **9-11** did not exhibit a significant increase in selectivity were in cases in which the parent tartrate allylboronates had already given outstanding selectivity (e.g., Table 3, entry 11, and Table 4, entries 4 and 5).

It is noteworthy also that at least half of the reactions summarized in Tables 3 and 4 were performed at −55 °C rather than −78 °C. We noticed that the crotylborations of **10** and **11** (Table 3) were relatively sluggish at −78 °C, and therefore we performed the (*E*)-crotylborations of **15** at −55 °C for 10-12 h and the reaction mixtures were allowed to warm to 0 °C before workup (Table 3, entries 5-8). The (*Z*)-crotylborations of **15** and **17** were similarly allowed to warm from −78 °C to ambient temperature before workup (Table 3, entries 9-12; Table 4, entries 5 and 6). Since we have previously established that the enantioselectivity of Banfi reagent **4** is moderately temperature dependent,[39] it is likely that the diastereoselectivity obtained under these "elevated temperature" experiments is not fully optimized. It does, however, reflect the level of selectivity that is achievable in preparative scale experiments.

Summary. We have demonstrated that *N,N*-bis(2,2,2-trifluoroethyl)-*N,N'*-ethylenetartramide (**8**) is an excellent auxiliary for the asymmetric allylboration reaction. The derived allylboronate **9** is ca. 100-fold more reactive than **6**, which we attribute to the inductive effect of the *N*-trifluoroethyl substituents, and is substantially more useful than the original Banfi reagent **4** which suffers from very poor solubility properties. Most importantly, allylboronate **9** and the related crotylboronates **10** and **11** are significantly more enantioselective than the parent tartrate allylboronate **1** and crotylboronates **2** and **3**; the new reagents **9-11** rank among the most highly enantioselective allylboron reagents yet reported.[4] Chiral auxiliary **8** is easily synthesized by a four-step sequence from ethylenediamine and benzylidenetartaric acid and is also easily recovered from the allylboration reaction mixtures.[49] Thus, chiral reagents **9-11** appear to be well suited for application to complex problems in organic synthesis.

Experimental Section

General. All reactions were conducted in flame-dried glassware under dry nitrogen or argon. All solvents were purified before use: Et_2O, THF, and toluene were distilled from sodium benzophenone ketyl; CH_3CN, CH_2Cl_2, and Et_3N were distilled from CaH_2; and MeOH was distilled from magnesium turnings. Low-temperature reactions were maintained by using a Neslab Cryocool CC-100 II cooling apparatus.

NMR and IR spectra were measured on commercially available instruments. High-resolution mass spectra were

measured at 70 eV. Analytical HPLC was performed with a system composed of a Waters 6000A solvent delivery system, a Waters R401 differential refractometer, and a Shimadzu CR601 recorder using either a Rheodyne Dynamax 60A or Whatman Partisil M9 silica column. Capillary GC analyses were performed on a Shimadzu GC-9A instrument. Analytical TLC was performed with the use of plates coated with a 0.25 mm thickness of silica gel containing PF254 indicator (Analtech). Flash chromatography was performed as described by Still[50] with kieselgel 60 (230–400 mesh). Unless otherwise noted, all compounds isolated by chromatography were sufficiently pure (>95% by NMR analysis) for use in subsequent preparative reactions.

(*R,R*)-*N,N'*-Bis(cyclohexylmethyl)-*N,N'*-ethylenetartramide (5). A mixture of (*R,R*)-*N,N'*-dibenzyl-*N,N'*-ethylenetartramide (**12**)[39,51] (3.58 g, 10.1 mmol) and 10% Rh/Al_2O_3 (3.0 g) in EtOH (80 mL) was hydrogenated under 50 psi of H_2 in a Parr hydrogenator until complete. The resulting mixture was filtered through Celite to remove catalyst and concd *in vacuo*. The crude product was purified by flash chromatography (2:1:1 EtOAc:$CHCl_3$:Et_2O) to give 3.22 g (90%) of diol **5**: mp 145–147 °C; $[\alpha]^{20}_D$ −43.5° (*c* 1.0, $CHCl_3$) for the (*R,R*) isomer; ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (br s, 2 H), 4.04 (br s, 2 H), 3.66 (br s, 2 H), 3.56 (br s, 2 H), 3.30 (br s, 2 H), 3.17 (br s, 2 H), 2.17–0.94 (m, 22 H); IR ($CHCl_3$) 3550–3100 (br), 1655 cm^{-1}; HRMS calcd for $C_{20}H_{35}O_4N_2$ (M^+ + 1) 367.2597, found 367.2567. Anal. Calcd for $C_{20}H_{34}O_4N_2$: C, 65.54; H, 9.35. Found: C, 65.58; H, 9.70.

***N,N'*-Bis(trifluoroacetyl)ethylenediamine (22).** To a solution of ethylenediamine (3.86 mL, 48.2 mmol) in 20 mL of dry Et_2O at 0 °C was added a solution of trifluoroacetic anhydride (17.8 mL, 106.1 mmol) in 20 mL of Et_2O dropwise. After being stirred for 1 h, the mixture was concd *in vacuo*, and the resulting white solid was washed with water, filtered, and dried *in vacuo* to provide 11.7 g (97%) of the diamide **22**: mp 189–191 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.33 (s, 4 H), 1.93 (s, 2 H); IR ($CHCl_3$) 1705, 1565, 1185, 900 cm^{-1}; HRMS calcd for $C_6H_6O_2N_2F_6$ (M^+) 252.0334, found 252.0342. Anal. Calcd for $C_6H_6O_2N_2F_6$: C, 28.58; H, 2.39. Found: C, 28.48; H, 2.37.

***N,N'*-Bis(2,2,2-trifluoroethyl)ethylenediamine (23).** To a stirred suspension of $LiAlH_4$ (3.95 g, 98.8 mmol) in dry THF (75 mL) in a 500 mL round-bottom flask equipped with a reflux condenser was added a solution of **22** (10 g, 39.7 mmol) in THF (75 mL) at such a rate as to maintain gentle reflux, over approximately 1 h. The mixture was then heated to reflux for 15 h and then was cooled in an ice bath. H_2O (30 mL) was added slowly with vigorous stirring. The resulting suspension was stirred for 30 min; then EtOAc (150 mL) was added, and the salts were removed by filtration. The filtrate was dried ($MgSO_4$) and concd *in vacuo* to give 8.88 g (95%) of the volatile diamine **23**: bp 110 °C, 3 Torr; ^1H NMR (300 MHz, $CDCl_3$) δ 3.19 (q, *J* = 9.3 Hz, 4 H), 2.83 (s, 4 H), 1.58 (s, 2 H); IR ($CHCl_3$) 3500–3120, 2900, 2840, 1460, 1400, 1270, 1150 cm^{-1}; HRMS calcd for $C_6H_{11}N_2F_6$ (M^+ + 1) 225.0827, found 225.0877.

(*R,R*)-2,3-*O*-Benzylidene-*N,N'*-bis(2,2,2-trifluoroethyl)-*N,N'*-ethylenetartramide (24). A solution of benzylideneetartaric acid (33.2 g, 139.0 mmol)[39] and *N,N'*-bis(2,2,2-trifluoroethyl)ethylenediamine (**23**) (31.3 g, 139.0 mmol) in CH_2Cl_2 (2 L) was added to a solution of DCC (86.1 g, 417 mmol) and DMAP (8.5 g, 69.3 mmol) in dry CH_2Cl_2 (2.5 L). The solution was stirred at rt overnight. The mixture was then concd *in vacuo*, and the crude product was purified by flash silica chromatography (1:1:1 hexane:CH_2Cl_2:EtOAc) to provide 38.8 g (65%) of impure macrolactam **24**. This material was recrystallized from CH_2Cl_2–hexane before the next step to provide 22.3 g (38%) of pure **24**: mp 86–88 °C; $[\alpha]^{20}_D$ −5.5° (*c* 2.92, $CHCl_3$) for the (*R,R*) isomer; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 2 H), 7.40 (m, 3 H), 6.11(s, 1 H), 4.99 (d, *J* = 6.1 Hz, 1 H), 4.86 (d, *J* = 6.1 Hz, 1 H), 4.74 (m, 2 H), 3.77 (bs, 4 H), 3.51 (m, 2 H); IR ($CHCl_3$) 2950, 2865, 1700 cm^{-1}; HRMS calcd for $C_{17}H_{16}O_4N_2F_6$ (M^+) 426.1015, found 426.0990. Anal. Calcd for $C_{17}H_{16}O_4N_2F_6$: C, 48.23; H, 3.82. Found: C, 48.60; H, 4.21.

(*R,R*)-*N,N'*-Bis(2,2,2-trifluoroethyl)-*N,N'*-ethylenetartramide (8). H_2 gas was bubbled through a solution of tartramide **24** (16.0 g, 37.5 mmol) and 10% Pd–C (1.0 g) in EtOH:HOAc (10:1, 330 mL) until the reaction was judged complete by TLC analysis. The reaction mixture was filtered through a pad of Celite, and the filtrate was concd *in vacuo*. The crude product was purified by flash silica chromatography (1:1:1 Et_2O:CH_2Cl_2:EtOAc) to provide 12.0 g (97%) of pure diol **8** as a white solid: mp 73–75 °C; $[\alpha]^{20}_D$ −28.9° (*c* 1.34, $CHCl_3$) for the (*R,R*) isomer; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42 (s, 2 H), 4.19 (m, 2 H), 4.02 (m, 1 H), 3.83 (s, 2 H), 3.73 (m, 2 H), 3.47 (m, 1 H); IR ($CHCl_3$) 3550–3150 (br), 1725, 1680 cm^{-1}; HRMS calcd for $C_{10}H_{13}O_4N_2F_6$ (M^+ + 1) 339.0778, found 339.0776. Anal. Calcd for $C_{10}H_{12}O_4N_2F_6$: C, 35.51; H, 3.57. Found: C, 35.60; H, 3.92.

Synthesis of Allylboronate Diethanolamine Complex 13. Solutions of triisopropyl borate (80 mL) in dry Et_2O (20 mL) and allylmagnesium bromide in Et_2O (62.5 mL, 80.0 mmol, 1.0 M) were added dropwise simultaneously, but separately, to a flask containing 20 mL of dry Et_2O at −78 °C. This mixture was stirred for 0.5 h at −78 °C, allowed to warm to rt, and stirred for an additional 3 h. The slurry was cooled to 0 °C, and then 80 mL of aqueous HCl–brine (1 N solution saturated with NaCl, 80 mmol) was added dropwise over a 15 min period. The mixture was warmed to rt, and stirring was continued for 10 min. The organic layer was separated and directly treated with 50 mmol of diethanolamine. The aqueous phase was extracted with 5:1 Et_2O:CH_2Cl_2 (3 × 50 mL). The combined organic layers were stirred over anhydrous $MgSO_4$ for 2.5 h and then concd *in vacuo*. The solids were triturated with CH_2Cl_2 and filtered. The filtrate was concd *in vacuo* to give a white solid, which was recrystallized twice from benzene–hexane to give 5.86 g (75%, based on diethanolamine) of pure **13**: mp 132–134 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (m, 1 H), 4.83 (m, 2 H), 4.34 (br s, 1 H), 4.03 (m, 2 H), 3.89 (m, 2 H), 3.21 (m, 2 H), 2.81 (m, 2 H), 1.50 (d, *J* = 8.4 Hz, 2 H); IR (KBr) 3380 (br), 3111, 1625 cm^{-1}; HRMS calcd for $C_4H_9O_2B_1N_1$ ($M^+ - C_3H_5$)$^+$ 114.0726; found 114.0721.

The (*E*)- and (*Z*)-crotylboronate diethanolamine complexes **19** and **25** were prepared according to the literature procedure in yields of 66 and 61%, respectively.[27]

Synthesis of Allylboronate (*R,R*)-6 from Diol (*R,R*)-5 and Diethanolamine Complex 13. A suspension of diethanolamine complex **13** (230 mg, 1.36 mmol) and (*R,R*)-diol **5** (500 mg, 1.36 mmol) in EtOAc (30 mL) was treated with saturated aqueous NaCl (51 mL) as described for the preparation of (*R,R*)-**9**. The crude product (312 mg, 99%, a white foam) was dried overnight under high vacuum (1.0 mmHg) before use. The yield was determined to be 89% by the titration method described subsequently: ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (m, 1 H), 5.06 (m, 1 H), 4.97 (s, 2 H), 4.93 (m, 1 H), 3.56 (m, 4 H), 3.42 (dd, *J* = 10.8, 5.4 Hz, 2 H), 3.15 (dd, *J* = 10.8, 6.2 Hz, 2 H), 1.96 (m, 2 H), 1.72–0.97 (m, 22 H).

Synthesis of Allylboronate (*R,R*)-9 from Diol (*R,R*)-8 and Diethanolamine Complex 13. A suspension of diethanolamine complex **13** (125 mg, 0.806 mmol) and diol (*R,R*)-**8** (300 mg, 0.887 mmol) in EtOAc (14 mL) was treated with saturated aqueous NaCl (28 mL) and stirred under N_2 for 15 min. The reaction mixture was poured into a separatory funnel containing brine (18 mL), EtOAc (18 mL), and 1 N $NaHSO_4$ (2 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$ and allowed to stir for 4 h. Filtration and concentration of the solution *in vacuo* afforded 312 mg (99%) of allylboronate **9** as

(48) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.

(49) Samples of (*R,R*)-**8** and (*S,S*)-**8** recovered from allylboration reactions were pooled and purified by chromatography over silica gel using EtOAc (37 parts), Et_2O (24 parts), CH_2Cl_2 (19 parts), and hexane (10 parts) as the solvent system. The yield of recovered **8** was typically 70–80%.

(50) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(51) Cyclic tartramide **12** was synthesized by a slight modification of the literature method. Specifically, the cyclization of benzylideneetartaric acid and *N,N'*-dibenzylethylenediamine was performed by adding BOP-Cl (4 equiv) and *i*-Pr_2NEt (6 equiv) in $CHCl_3$ and refluxing overnight, which gave the benzylidene acetal of **12** in 65% yield.

a white foam (crude), which was dried under vacuum (1.0 mmHg) overnight. The yield was determined to be 99% by the titration method described subsequently. Partial data for **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (m, 1 H), 5.09 (s, 2 H), 5.04 (m, 2 H), 4.79 (m, 2 H), 3.94 (s, 4 H), 3.75 (m, 2 H), 2.08 (d, J = 5.6 Hz, 2 H); ^{11}B NMR (115.8 MHz, $CDCl_3$) δ 34.33; IR ($CHCl_3$) 3060, 2980, 1680 cm^{-1}; HRMS calcd for $C_{13}H_{16}BO_4N_2F_6$ (M^+ + 1), 389.1106; found, 389.1096.

Synthesis of (*E*)-Crotylboronate (*R,R*)-10 from (*R,R*)-8 and Diethanolamine Complex 19. A suspension of diethanolamine complex **19**[27] (113 mg, 0.67 mmol) and diol (*R,R*)-**8** (250 mg, 0.73 mmol) in EtOAc (12 mL) was stirred with saturated aqueous NaCl (24 mL) under N_2 for 15 min. The reaction mixture was poured into a separatory funnel containing brine (18 mL), EtOAc (18 mL), and 1 N $NaHSO_4$ (2 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$ for 4 h with stirring. Filtration and concentration of the solution *in vacuo* afforded 270 mg (95%) of **10** as a white foam (crude), which was dried under high vacuum (1.0 mmHg) overnight. The yield was determined to be 92% by the titration method described subsequently. Partial data for **10**: $[\alpha]^{20}_D$ +4.2° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (m, 2 H), 5.04 (s, 2 H), 4.75 (dq, J = 18.8, 9.5 Hz, 2 H), 3.79 (s, 4 H), 3.54 (dq, J = 16.8, 8.7 Hz, 2 H), 1.90 (dd, J = 3.1, 3.1 Hz, 2 H), 1.63 (d, J = 3.8 Hz, 3 H); IR ($CHCl_3$) 3000, 2960, 2935, 1700 cm^{-1}; HRMS calcd for $C_{14}H_{18}BO_4N_2F_6$ (M^+ + 1) 403.1263, found 403.1282.

Synthesis of (*Z*)-Crotylboronate (*R,R*)-11 from (*R,R*)-8 and Diethanolamine Complex 25. A suspension of diethanolamine complex **25**[27] (341 mg, 2.49 mmol) and diol (*R,R*)-**8** (750 mg, 2.21 mmol) in EtOAc (25 mL) was treated with saturated aqueous NaCl (50 mL) under N_2 for 15 min according to the procedure described for the synthesis of (*R,R*)-**10**. Crude reagent **11** (855 mg, 95%) so produced was dried under high vacuum (1.0 mmHg) overnight before use. The yield was determined to be 95% by the titration method described subsequently. Partial data for **11**: $[\alpha]^{20}_D$ +1.5° (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (m, 2 H), 5.05 (s, 2 H), 4.77 (dq, J = 18.3, 8.9 Hz, 2 H), 3.79 (s, 4 H), 3.55 (dq, J = 16.9, 8.7 Hz, 2 H), 1.96 (d, J = 7.3 Hz, 2 H), 1.63 (d, J = 5.1 Hz, 3 H); IR ($CHCl_3$) 3020, 1700 cm^{-1}; HRMS calcd for $C_{14}H_{18}BO_4N_2F_6$ (M^+ + 1) 403.1263, found 403.1258.

Preparation of Standardized Solutions of Chiral Allylboronates 6 and 9–11. The crude reagent is weighed and then dissolved in sufficient THF to give a 0.6 M solution assuming 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%. An aliquot of this solution (0.068 mL, at most 0.041 mmol of reagent) is treated with 0.041 mmol of cyclohexanecarboxaldehyde (4.6 mg, 5.0 μL) at rt for 2 h. The solution is then cooled to 0 °C, and the reaction is 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. The phases are separated and the aqueous layer is extracted with ether (2 × 5 mL). The extracts are combined, dried (K_2CO_3), and concd *in vacuo*. The mixture is then analyzed by capillary GC on a 50 m × 0.25 mm bonded FSOT Carbowax 20M column (temperature program: 100 °C for 4 min and 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, homoallylic alcohol **14a** elutes at 9.6 min, anti homoallyl alcohol **20a** elutes at 10.7 min, and the syn diastereomer **26a** elutes at 11.2 min. From the ratio of cyclohexylmethanol to homoallyl alcohols, one calculates the approximate concentration and hence also the yield of reagent.

Representative Procedure for Reactions of Allylboronates 9–11 with Aldehydes: (*S*)-1-Cyclohexylbut-3-en-1-ol (14a). A mixture of (*R,R*)-**9** in THF (1.25 mL, 0.67 mmol, 0.54 M) and 600 mg of powdered 4 Å molecular sieves was stirred for 30 min at rt under argon and then was cooled to −78 °C. A solution of pivaldehyde (2.4 μL, 0.02 mmol) in dry THF (200 μL) was then added dropwise. After the addition was complete, the solution was allowed to warm to ambient temperature and stirred for 30 min. The mixture was recooled to −78 °C, and a solution of cyclohexanecarboxaldehyde (54 μL, 0.45 mmol) in 0.20 mL of dry THF was then added dropwise down the side of the flask. After the addition was complete, the solution was maintained at −78 °C for 5 h. Excess acetaldehyde was then added dropwise *via* syringe, the cooling bath was removed, and the solution was warmed to rt. The mixture was filtered through a plug of Celite and concd under reduced pressure to yield a crude oil that was purified by flash silica chromatography (9:1 hexane:ether) to give 56 mg (91%) of the known homoallylic alcohol **14a** as a colorless oil.[27] The column was washed with EtOAc to recover auxiliary **8**; the appropriate fractions were set aside for recycle.[49] The enantiomeric purity of **14a** was determined to be 94% ee by capillary GC analysis of the (*R*)-Mosher ester (MTPA) derivative[52] [0.25 in. × 10 ft 4.1% Carbowax on Chrom G column, 200 °C isotherm; t_R = 21.6 and 22.1 for the two diastereomers].

With the exception of **18** and **26b**, all other allyl- and crotylboration reaction products reported in this paper are known compounds. Enantiomeric or diastereomeric purities were determined as summarized below:

The enantiomeric purity of homoallylic alcohol **14b**,[16] prepared by allylboration of *n*-hexanal with (*R,R*)-**9**, was determined by ^{1}H NMR analysis integration of the vinylic protons of the two diastereomeric (*R*)-MTPA esters: δ 5.75 (m, 1 H for one isomer) and 5.65 (m, 1 H for the second diastereomer).

The enantiomeric purity of homoallylic alcohol **14c**,[26,39] prepared by the asymmetric allylboration of **27** with (*R,R*)-**9**, was determined by ^{1}H NMR integration of the vinylic resonances of the diastereomeric (*R*)-MTPA esters: δ 5.82 (m, 1 H for one isomer) and 5.70 (m, 1 H for the second diastereomer).

The enantiomeric purity of **20a**,[27] prepared by the (*E*)-crotylboration of c-$C_6H_{11}CHO$ with (*R,R*)-**10**, was determined by capillary GC analysis of the (*R*)-MTPA ester derivative: [0.25 in. × 10 ft 4.1% Carbowax on Chrom G column, 200 °C isotherm; t_R = 29.6 and 30.2 min for the two diasteromeric MTPA esters].

The enantiomeric purity of **20b**,[27] prepared by the (*E*)-crotylboration of *n*-$C_5H_{11}CHO$ with (*R,R*)-**10**, was determined by capillary GC analysis of the (*R*)-MTPA ester derivative [0.25 in. × 10 ft 4.1% Carbowax on Chrom G column, 200 °C isotherm; t_R = 8.1 and 9.0 min for the two MTPA ester diastereomers].

The enantiomeric purity of **26a**,[27] prepared by the (*Z*)-crotylboration of c-$C_6H_{11}CHO$ with (*R,R*)-**11**, was determined by capillary GC analysis of the (*R*)-MTPA ester derivative [0.25 in. × 10 ft 4.1% Carbowax on Chrom G column, 200 °C isotherm; t_R = 22.1 and 22.5 min for the two MTPA ester diastereomers].

The enantiomeric purity of **26b**,[53] prepared by the (*Z*)-crotylboration of *n*-$C_5H_{11}CHO$ with (*R,R*)-**11**, was determined by capillary GC analysis of the (*R*)-MTPA ester derivative [0.25 in. × 10 ft 4.1% Carbowax on Chrom G column, 200 °C isotherm; t_R = 13.4 and 13.8 min for the two MTPA ester diastereomers].

Mixtures of **16a** and **28a**, prepared by the allylborations of **15a** with **9**, were analyzed by HPLC as previously described.[26]

Mixtures of **16b** and **28b** derived from the allylboration of **15b** were determined by capillary GC analysis (0.25 in. × 10 ft 4.1% Carbowax on Chrom G column, 160 °C isotherm; t_R (**28b**) = 9.70 min, t_R (**16b**) = 10.05 min).

Mixtures of **29a,b–32a,b**, prepared by the crotylborations of **15a** or **15b**, were determined by HPLC as previously described.[28]

Mixtures of **34** and **35** derived from the allylborations of **33** were analyzed by capillary GC (0.25 in. × 10 ft 4.1% Carbowax on Chrom G column, 150 °C isotherm; t_R (**35**) = 9.0 min, t_R (**34**) = 10.5 min[48]).

Mixtures of **36–39** derived from the crotylborations of **33** were determined by GC analysis as previously described.[48]

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***erythro*-1,2-*O*-Pentylidenehex-5-en-1,2,3-triol (18).** A mixture of (*R,R*)-**6** (1.0 mL, 0.66 mmol, 0.66 M solution in THF) and 600 mg of 4 Å powdered molecular sieves was stirred for 30 min at rt and then the mixture was cooled to −78 °C. A solution of pivaldehyde (5.2 μL, 0.044 mmol) in dry THF (200 μL) was then added dropwise. After the addition was complete, the solution was warmed to rt and stirred for 30 min. The mixture was recooled to −78 °C and then a solution of D-glyceraldehyde pentylidene ketal **17**[43] (0.069 g, 0.44 mmol) in 0.20 mL of dry THF was then added dropwise down the side of the flask. After the addition was complete, the solution was maintained at −78 °C for 36 h. Excess acetaldehyde was then added dropwise via syringe, the cooling bath was removed, and the solution was warmed to rt. The mixture was filtered through a plug of Celite and concd under reduced pressure to yield the crude product that was purified by flash silica chromatography (hexane:ether 9:1) to give 0.047 g (53%) of the homoallylic alcohol **18** with 99.4:0.6 diastereoselectivity. Diastereoselectivities were determined by capillary GC analysis (0.25 in. × 10 ft 4.1% Carbowax on Chrom G column, 150 °C isotherm); t_R (**18**) = 16.15 min; t_R (threo diastereomer) = 16.60 min. The stereochemical assignment for **18** follows from spectroscopic comparison with the well-characterized acetonide analog **34**.[48] Data for **18**: $[\alpha]^{23}_D$ +10.3° (c = 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.89−5.77 (m, 1 H), 5.19−5.06 (m, 2 H), 4.05−3.76 (m, 4 H), 2.36−2.02 (m, 2 H), 1.71−1.52 (m, 4 H), 0.95−0.78 (m, 6 H); IR ($CHCl_3$) 3580, 3420, 3000 cm^{-1}; HRMS calcd for $C_{11}H_{21}O_3$ (M^+ 1) 201.1490, found 201.1481. Anal. Calcd for $C_{11}H_{20}O_3$: C, 66.62; H, 8.55. Found: C, 66.93; H, 8.82.

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Supplementary Material Available: ^1H NMR spectra of **6**, **9**−**11**, **13**, and **23** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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