Enantioselective and Diastereoselective Additions of Allylic Stannanes to Aldehydes Promoted by a Chiral (Acyloxy)borane Catalyst

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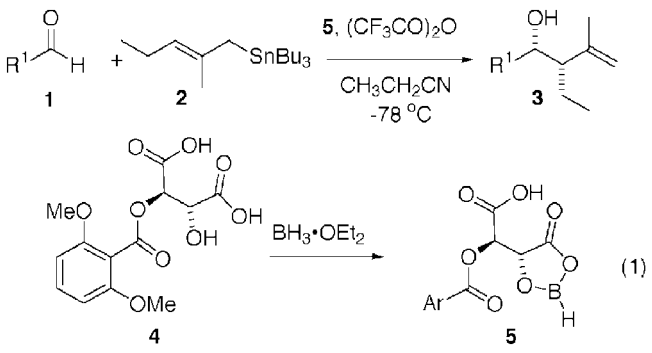
A modified Yamamoto Lewis acid (CAB), prepared from the 2,6-dimethoxybenzoic ester of (*R*,*R*)-tartaric acid, and 1.5 equiv of BH_3•THF was employed in additions of crotyltributyltin (**6**) and allyltributyltin (**9**) to representative achiral aldehydes in the presence of 2 equiv of $(CF_3CO)_2O$. The crotyltin additions proceeded with good to excellent diastereoselectivity and enantioselectivity affording the syn adducts **7a**−**e** of 70−90% ee as major products (78:22−92:8). Addition of allylstannane **9** to cyclohexanecarboxaldehyde (**1a**) afforded the (*R*)-adduct of only 55% ee. In contrast, the use of Keck's BINOL catalyst gave **10**, the allyl adduct of **1a**, of 87% ee. However, addition of the crotylstannane to **1a** with this catalyst led to a 65:35 mixture of syn and anti adducts **7a** and **8a** of 95% and 49% ee. Additions of crotylstannane **6** to (*R*)- and (*S*)-2-methyl-3-ODPS-propanal [(*R*)-**11** and (*S*)-**11**] promoted by the modified CAB Lewis acid afforded the syn,syn and syn,anti products **12** and **14** in large predominance (98:2 and 90:10), indicative of effective complex control in the transition state. The results are consistent with the Corey H-bonded aldehyde transition-state proposal.

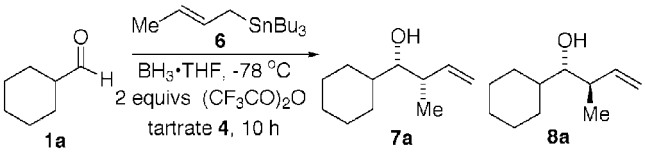
Some years ago, we reported on additions of allylic stannane **2** to various aldehydes in the presence of the chiral (acyloxy)borane (CAB) **5**, first described by Yamamoto (eq 1).[1,2] In the interim, a number of studies on



additions of allylic and allenylstannanes catalyzed by metal complexes of BINOL and BINAP have appeared.[3] Results with crotylstannanes were reported in only one of these.[4] In that investigation, addition of *cis*- and *trans*-crotyltributyltin to methyl glyoxalate afforded mixtures of syn and anti adducts of modest ee in relatively low yield (38% and 53%, respectively).

In the course of developmental work on the synthesis of polypropionate natural products, we had occasion to examine the use of chiral catalysts for additions of crotylstannanes to aldehydes. We were especially interested in employing the Keck binaphthol catalyst[5] for these additions, but our previous experience suggested that such reactions might be too slow for practical applications, especially with hindered branched aldehydes. Accordingly, we decided to conduct a limited survey of the CAB and Keck BINOL methodology with crotyltributyltin. We began by examining a series of additions to cyclohexanecarboxaldehyde (**1a**) with CAB **5** as the promoter/catalyst for the purpose of optimizing reaction conditions (Table 1). We had previously discovered that trifluoroacetic anhydride improved reaction efficiency, although best results were obtained with a stoichiometric amount of the (acyloxy)borane **5**.[1] In the present study, we identified several modifications that allowed the use of 50 mol % of the tartrate precursor **4**. These include (1) slow addition of the crotylstannanes by means of a syringe pump and (2) the use of a 50% excess of BH_3•THF. In all cases, the syn adduct **7a** of at least 90% ee predominated by 9:1 or better.

Table 1. Optimization of Crotylstannane Additions to Cyclohexanecarboxaldehyde in the Presence of CAB 5 and $(CF_3CO)_2O$



4, equiv	BH_3:**4**	**6**:**1a**	yield, %	**7a**:**8a**	ee, % (**7a**)
1.0	1:1	1:1	62	90:10	96[a]
1.0	1:1	1:1[b]	73	93:7	90[a]
0.5	1:1	1:1[b]	55	92:8	91[a]
0.5	1.5:1	1:1[b]	70	92:8	93[a]
0.2	1.5:1	1:1[b]	<50	91:9	ND[c]
0.5	1.5:1	2:1[b]	70	93:7	91[d]

[a] Determined by GC analysis. [b] Stannane added over 3 h by syringe pump. [c] Not determined; sample contained impurities. [d] Estimated from the optical rotation of entry 3.

We next proceeded to compare these results with additions performed with Keck's BINOL−Ti(O-*i*-Pr)$_4$

(1) Marshall, J. A.; Tang, Y. *Synlett* **1992**, 653.
(2) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561.
(3) For a recent review of these additions, see: Marshall, J. A. *Chemtracts-Org. Chem.* **1996**, *9*, 280.
(4) Aoki, S.; Mikami, L.; Terada, M.; Nakai, T. *Tetrahedron* **1993**, *49*, 1783.
(5) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827.

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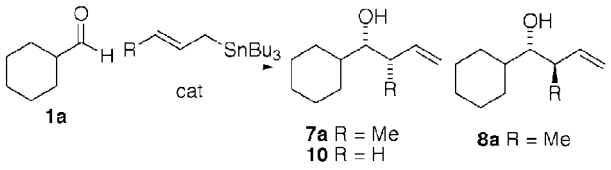
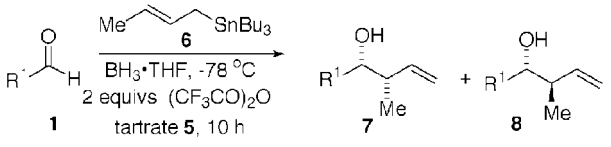
Table 2. Comparative BINOL- and CAB-Promoted Additions of Stannanes 6 and 9 to Cyclohexanecarboxaldehyde



R	cat.	yield, %	**7** (ee):**8** (ee)
Me (**6**)	BINOL[a]	18	65 (95):35 (49)
Me (**6**)	CAB	71	93 (93):7 (80)
H (**9**)	BINOL[a]	53	**10** (87)
H (**9**)	CAB[b]	42	**10** (55)

[a] 20 mol % (*M*)-BINOL, 10 mol % Ti(O-*i*-Pr)$_4$, CH_2Cl_2, 4 A MS, −20 °C, 70 h. [b] Same as Table 3.

Table 3. CAB-Promoted Addition of Crotyl Stannane 6 to Achiral Aldehydes



R^1	yield,[a] %	**7**:**8**[b,c]	ee **7**,[a] %
c-C_6H_{11} (**1a**)	70	92:8 (97:3)	91
C_6H_{13} (**1b**)	74	91:9 (88:12)	92
(*E*)-PrCH=CH (**1c**)	71	78:22 (86:14)	89
$C_6H_{13}C{\equiv}C$ (**1d**)	70[d]	79:21 (79:21)	71
$DPSOCH_2CH_2$ (**1e**)	73	88:12 (94:6)[e]	70[e]

[a] Ratio of tartrate:BH_3:stannane:aldehyde:$(CF_3CO)_2O$ = 0.5:0.75:1.0:1.0:2.0. [b] Determined by GC analysis on an α-DEX or *β*-DEX cyclodextrin GC column. [c] Ratios in parentheses are from additions employing BF_3•OEt_2 as the Lewis acid. [d] The reaction was complete after 6 h. [e] The analysis was performed on the diol after cleavage of the DPS ether.

catalyst (Table 2).[5] Parallel experiments were conducted with cyclohexanecarboxaldehyde (**1a**) and the crotyl- and allylstannanes **6** and **9**. The latter reaction was reported to proceed in 95% yield to afford adduct **10** of 92% ee.[5] Under nonoptimized conditions, we obtained **10** of 87% ee in 53% yield after a reaction time of 70 h. The addition of crotylstannane **6** afforded a 65:35 mixture of syn and anti adducts in less than 20% yield under these reaction conditions. With the CAB catalyst, this addition gave adduct **7a** of 93% ee along with **8a** of 80% ee as a 92:8 mixture in 71% yield after a reaction time of 10 h. Addition of allylstannane **9** to aldehyde **1a** by this procedure was less enantioselective, affording adduct **10** of 55% ee in 35% yield.

In view of these findings, we decided to continue our studies with the CAB catalyst **5**, crotylstannane **6**, and various aldehydes under the optimized conditions (Table 3). In all cases, syn/anti product ratios were comparable to or only slightly lower than those obtained from additions promoted by BF_3•OEt_2. TLC analysis of reactions in progress indicated that mixtures of alcohols and the derived trifluoroacetates were formed. The esters were cleaved in the workup by brief treatment with methanolic K_2CO_3. Those reactions that produced the smallest amounts of trifluoroacetates afforded adducts of lowest ee and vice versa. Although quantification of this phenomenon was beyond the scope of this study, these observations suggest that trifluoroacetic anhydride is assisting catalyst turnover.

(6) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.

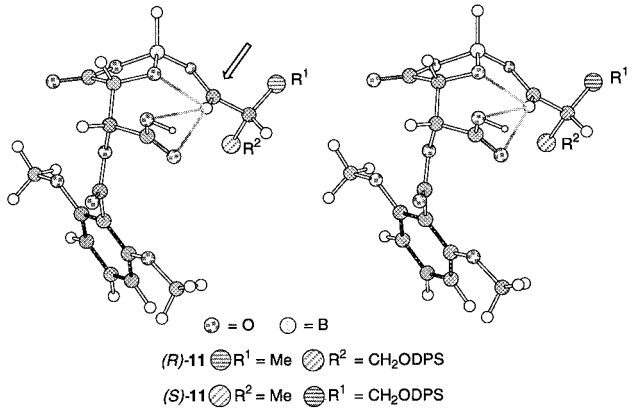


Figure 1. Chem 3D representation of a possible CAB complex with aldehydes (*R*)- and (*S*)-**11**.

Assignment of configuration to adducts **7a**−**e** is based on our previous findings (eq 1).[1] Independent verification came from ^{1}H NMR analysis of the *O*-methylmandelate derivatives of adducts **7a**,**b**,**e**.[7] Furthermore, the optical rotation of **7a** was equal and opposite to that reported for the enantiomer.[8]

As an initial application of the CAB/crotylstannane methodology for assemblage of polypropionate subunits, we examined additions to the nonracemic α-methyl *β*-ODPS aldehydes (*R*)- and (*S*)-**11** (eq 2, DPS = Ph_2-*t*-BuSi). Keck and Abbott have carried out the BF_3-promoted addition of crotylstannane **6** to racemic aldehyde **11**.[6] They obtained a 90:10 mixture of syn,syn (*rac*-**12**) and syn,anti (*rac*-**14**) products. Roush and co-workers obtained a roughly 2.5:1 mixture of syn,syn (ent-**12**) and syn,anti (**14**) products along with small amounts of the corresponding anti adducts upon addition of their (*R*,*R*)-tartrate (*Z*)-crotylboronate to aldehyde (*S*)-**11**.[9] The (*S*,*S*) enantiomer gave a 7:1 mixture favoring **14** over *ent*-**12**. We repeated the BF_3 reaction with aldehyde (*R*)-**11** and obtained a 90:10 mixture of adducts **12** and *ent*-**14**. Aldehydes (*R*)- and (*S*)-**11** proved less reactive than **1a**−**e** in the CAB-promoted additions. No reaction was observed at −78 °C under the conditions described in Table 3. When the reaction temperature was increased to −10 °C after an initial period at −78 °C, the adduct **12** from aldehyde (*R*)-**11** was secured as a 98:2 mixture of diastereomers **12**/*ent*-**14** in 53% yield. An increase in the amount of CAB employed to a full equivalent improved the yield to 68%.

CAB-promoted addition of crotylstannane **6** to aldehyde (*S*)-**11** afforded a 90:10 mixture of adducts favoring the syn,anti diastereomer **14**. This adduct was the minor isomer from the BF_3-promoted addition of crotylstannane **6** to aldehyde (*S*)-**11**. Approximate ratios of diastereomers could be estimated from the ^{1}H NMR spectra of reaction mixtures. A more exact ratio was secured by GC analysis of the derived diols **13** and **15** (TBAF). Care was taken to avoid separation of the diastereomeric diols during removal of the silyl byproducts on silica gel.

On the basis of the results summarized in eq 2, we conclude that the CAB-promoted additions are strongly

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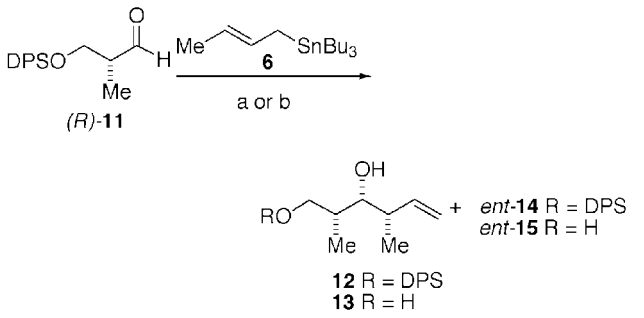
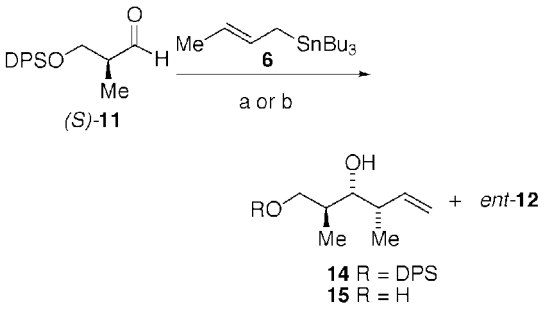
complex controlled, essentially overriding the intrinsic facial preference of the aldehyde substrate. These findings are in accord with the H-bonded transition states proposed by Corey as an explanation for enantioselective additions to certain aldehyde−Lewis acid complexes (Figure 1).[10] A syn-selective addition to such a complex would account for the observed stereochemical preferences.



a) BF_3•OEt_2, CH_2Cl_2, -78 °C, (71%) **12**:*ent*-**14** = 90:10
b) tartrate **4**, BH_3•THF, $(CF_3CO)_2O$, -78 °C to -10 °C (68%); **12**:*ent*-**14** = 98:2

(2)



a) BF_3•OEt_2, CH_2Cl_2, -78 °C, (75%); *ent*-**12**:**14** = 90:10
b) tartrate **4**, BH_3•THF, $(CF_3CO)_2O$, -78 °C to -10 °C (65%); *ent*-**12**:**14** = 10:90

Our results indicate that the modified CAB Lewis acid gives better syn/anti selectivity than the Keck BINOL/Ti catalyst[5] in additions of crotyltributyltin to aldehydes. However, allylations are more enantioselective with the Keck catalyst. Additions to the CAB−aldehyde complex, as pictured in Figure 1, are relatively insensitive to Felkin−Ahn control in the case of the α-chiral aldehydes (*R*)- and (*S*)-**11**. The diminished selectivity of additions to alkynal **1d** may result from the smaller size of the alkynyl substituent, leading to lower syn/anti product ratios, and the greater electrophilicity of the aldehyde, favoring reactions via non-H-bonded complexes. At present, we are unable to account for the relatively lower selectivity observed for the β-ODPS aldehyde **1e**. Roush has also noted that β-oxygen substituents can lower the enantioselectivity of additions of chiral crotylboronates to aldehydes.[9]

Experimental Section

GC analyses were performed on α-DEX or β-DEX cyclodextrin columns with temperature programming starting at 100 °C with a ramp of 1°/min.

(1*S*,2*S*)-(−)-1-Cyclohexyl-2-methyl-3-buten-1-ol (7a). A. CAB Catalyst. To a solution of tartrate **4** (58.0 mg, 0.206 mmol) in propionitrile (0.40 mL) at 0 °C was added 1.0 M BH_3•THF in THF (0.310 mL, 0.310 mmol).[1,2] After 1 h, the reaction was cooled to −78 °C, and cyclohexanecarboxaldehyde (**1a**) (0.050 mL, 0.413 mmol) was added followed by trifluoroacetic anhydride (0.120 mL, 0.826 mmol). After 5 min, crotyltributyltin (0.140 g, 0.413 mmol) in propionitrile (1 mL) was added over a period of 3 h with a syringe pump. After 7 h, the reaction was quenched with a saturated $NaHCO_3$ solution (1 mL) and extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. This was diluted with MeOH (5 mL), and a catalytic amount of K_2CO_3 was added. After 1 h at room temperature, the mixture was quenched with water and extracted with ether. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. The crude product was chromatographed on silica gel (5% ethyl acetate in hexanes) to give 49.5 mg (71%) of alcohols **7a**/**8a** as a 92:8 mixture of diastereomers of 93 and 80% ee, respectively (GC analysis, α-DEX column): $[\alpha]_D = -28.1$ (*c* 1.52, $CHCl_3$) [lit.[8] $[\alpha]_D = +28.0$ (*c* 0.61, $CHCl_3$) for the enantiomer]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89−5.72 (m, 1H), 5.17−4.98 (m, 2H), 3.20 (dd, *J* = 5.9, 5.5 Hz, 1H), 2.41 (m, 1H), 2.01−0.81 (m, 11H), 1.00 (d, *J* = 6.6 Hz, 3H).

B. BINOL−Ti(O-*i*-Pr)$_4$ Catalyst. A solution of (*R*)-BINOL (24.0 mg, 0.083 mmol), Ti(O-*i*-Pr)$_4$ (0.012 mL, 0.041 mmol), and trifluoromethanesulfonic acid (0.004 mL, 0.041 mmol) in CH_2Cl_2 (2.5 mL) in the presence of 4 Å molecular sieves (0.2 g) was heated at reflux for 1 h.[5] The mixture was cooled to room temperature, and aldehyde **1a** (0.050 mL, 0.41 mmol) was added. After 30 min, the mixture was cooled to −78 °C, and crotyltributyltin (0.43 g, 1.24 mmol) was added. After 10 min, the mixture was warmed to −20 °C. After 73 h, the reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. The crude product was chromatographed on silica gel (5% ethyl acetate in hexanes) to give 14.0 mg (18%) of alcohols **7a**/**8a** as a 65:35 mixture of diastereomers of 95 and 49% ee, respectively (GC analysis, α-DEX column).

(*S*)-1-Cyclohexyl-3-buten-1-ol (10).[5,11] **A. CAB Catalyst.** The procedure for **7a** was followed with tartrate **4** (0.058 g, 0.10 mmol), BH_3•THF (0.31 mL, 0.31 mmol), aldehyde **1a** (0.050 mL, 0.41 mmol), trifluoroacetic anhydride (0.12 mL, 0.83 mmol), and allyltributyltin **9** (0.13 g, 0.41 mmol) in propionitrile (0.5 mL) at −78 °C for 10 h to give 22 mg (35%) of alcohol **10** of 55% ee (α-DEX column): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92−5.76 (m, 1H), 5.20−5.07 (m, 2H), 3.39 (m, 1H), 2.39−2.27 (m, 1H), 2.20−2.00 (m, 1H), 1.92−1.58 (m, 5H), 1.44−0.95 (m, 6H).

B. BINOL−Ti(O-*i*-Pr)$_4$ Catalyst. The procedure for **7a** was followed with (*R*)-BINOL (25.0 mg, 0.089 mmol), Ti(O-*i*-Pr)$_4$ (0.013 mL, 0.045 mmol), trifluoromethanesulfonic acid (0.004 mL, 0.045 mmol), aldehyde **1a** (0.050 mL, 0.41 mmol), crotyltributyltin (0.42 g, 0.13 mmol), and molecular sieves (0.2 g) in CH_2Cl_2 (2.5 mL) at −20 °C for 70 h to give 36 mg (53%) of alcohol **10** of 87% ee (α-DEX column).

(2*S*,3*R*,4*S*)-2,4-Dimethyl-5-hexene-1,3-diol (13).[9] **A. CAB-Promoted Addition.** The standard procedure was followed with tartrate **4** (92.0 mg, 0.327 mmol), BH_3•THF (0.330 mL, 0.327 mmol), aldehyde (*R*)-**11** (0.107 g, 0.327 mmol), trifluoroacetic anhydride (0.092 mL, 0.65 mmol), and crotyltributyltin (0.110 g, 0.327 mmol) in propionitrile (1.3 mL) at −78 °C for 10 h and then −10 °C for an additional 12 h to give 85.2 mg (68%) of alcohol as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.60 (m, 1H), 7.49−7.31 (m, 6H), 5.60 (m, 1H), 5.00 (m, 2H), 3.80−3.58 (m, 3H), 2.29 (m, 1H), 1.79 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.06 (s, 9H), 0.96 (d, *J* = 7.0 Hz, 3H).

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The above alcohol (58.3 mg, 0.152 mmol) in THF (1.0 mL) at 0 °C was treated with 1 M TBAF in THF (0.23 mL, 0.23 mmol), and the mixture was allowed to warm to room temperature. After 1.5 h, the mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel (50% ethyl acetate in hexanes) to give 20.1 mg (92%) of the diol as a 98:2 mixture of syn,syn (**13**) and syn,anti (*ent*-**15**) diastereomers as determined by GC on an α-DEX column: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (m, 1H), 5.04 (m, 2H), 3.80−3.54 (m, 3H), 2.32 (m, 1H), 1.84 (m, 1H), 1.10 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H).

B. BF_3·OEt_2 Promoted Addition. The standard procedure was followed with aldehyde (*R*)-**11** (57.5 mg, 0.176 mmol), crotyltributyltin (0.073 g, 0.211 mmol), and BF_3·OEt_2 (0.045 mL, 0.352 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C for 6 h to give 48.2 mg (71%) of alcohol adducts.

The above alcohol (46.0 mg, 0.12 mmol) and TBAF (0.20 mL, 0.18 mmol) in THF (1.0 mL) were stirred for 2 h to give 15.9 mg (92%) of diol as a 90:10 mixture of syn,syn (**13**) and syn,anti (*ent*-**15**) diastereomers.

(2*R*,3*S*,4*R*)-2,4-Dimethyl-5-hexene-1,3-diol (*ent*-13). The standard procedure was followed with aldehyde (*S*)-**11** (80 mg, 0.24 mmol), crotyltributyltin (0.100 g, 0.294 mmol), and BF_3·OEt_2 (0.062 mL, 0.49 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C for 3 h to give 71 mg (75%) of alcohol adducts.

The above alcohol (71.0 mg, 0.18 mmol) and TBAF (0.27 mL, 0.18 mmol) in THF (1.0 mL) were stirred for 1 h to give 24 mg (90%) of a 90:10 mixture of syn,syn and syn,anti diastereomers *ent*-**13** and **15**.

(2*R*,3*R*,4*S*)-2,4-Dimethyl-5-hexene-1,3-diol (15).[9] The standard procedure was followed with tartrate **4** (0.110 g, 0.385 mmol), BH_3·THF (0.385 mL, 0.385 mmol), aldehyde (*S*)-**11** (0.126 g, 0.385 mmol), trifluoroacetic anhydride (0.110 mL, 0.770 mmol), and crotyltributyltin (0.132 g, 0.385 mmol) in propionitrile (1.5 mL) at −78 °C for 10 h and then −10 °C for an additional 12 h to give 95.8 mg (65%) of alcohol **14** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.61 (m, 4H), 7.50−7.33 (m, 6H), 5.86 (m, 1H), 5.03 (m, 2H), 3.87−3.42 (m, 3H), 2.34 (m, 1H), 1.83 (m, 1H), 1.06 (s, 12H), 0.91 (d, J = 7.0 Hz, 3H).

The alcohol (70.0 mg, 0.183 mmol) and TBAF (0.27 mL, 0.27 mmol) in THF (1.0 mL) were stirred for 1 h to give 25.6 mg (97%) of diol as a 90:10 mixture of syn,anti (**15**) and syn,syn (*ent*-**13**) diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.13 (m, 2H), 3.80−3.43 (m, 3H), 2.46 (m, 1H), 1.85 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H).

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Supporting Information Available: Experimental procedures for **7b**−**e** and racemic-**7a**−**e** and ^{1}H NMR spectra and GC traces for all compounds and derivatives (42 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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