The Stereoselective Cyclopropanation of Chiral Allylic Alcohols Using a Chiral Dioxaborolane Ligand: A New Route to *anti*-Cyclopropylmethanol Derivatives

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Abstract: The diastereoselective cyclopropanation reaction of allylic alcohols in the presence of the chiral dioxaborolane ligand **1** was studied. Unprecedently high *anti*-selectivities were obtained with *E*-olefins when 2.2 equivalents of bis(iodomethyl)zinc and 1.1 equivalent of **1** were used. © 1999 Elsevier Science Ltd. All rights reserved.

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Recently, we described a highly enantioselective process for the cyclopropanation of allylic alcohols using a bifunctional chiral dioxaborolane ligand derived from (R,R)-(+)-N,N,N',N'-tetramethyltartaric acid diamide (**1**).[1] Substituted cyclopropylmethanol derivatives could be produced in high yields (≥80%) and enantioselectivities (≤94% ee).
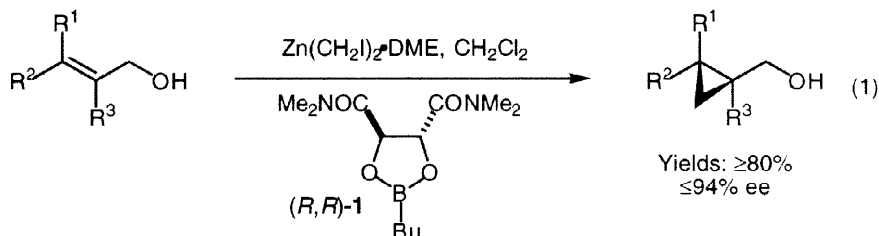
Concurrently to this work, we have also studied the diastereoselective cyclopropanation of chiral, acyclic allylic alcohols and we have reported efficient conditions for the relative stereocontrol.[2] When EtZnCH$_2$I[3] in CH$_2$Cl$_2$ was used, unprecedently high *syn*-selectivities were obtained with *E*- and *Z*-olefins (Scheme 1). Other methods using the Simmons Smith reagent[4] and the iodomethylsamarium carbenoid[5] have also been reported for the cyclopropanation of chiral allylic alcohols but the level of diastereoselection was highly dependent on the substitution pattern of the allylic alcohol.
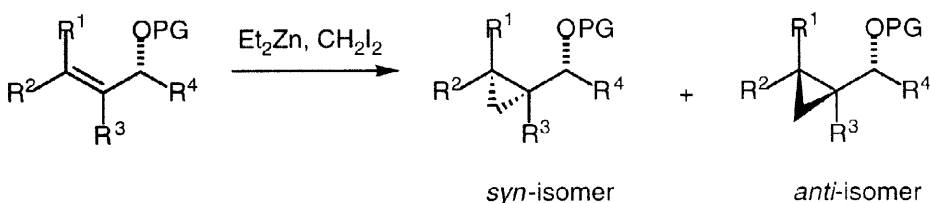
Scheme 1
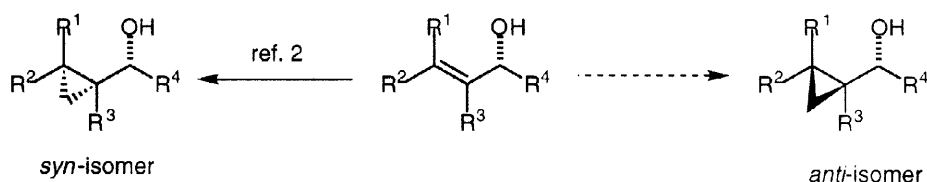
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Conversely, the direct access to the *anti* isomer with good diastereoselection is a much more difficult task. Lautens has shown[6] that some of these compounds are accessible by the reduction of the corresponding cyclopropylketone but high *anti*-selectivity was observed only when $R^1 \neq H$. In this paper, we now report the first example of double stereodifferentiation for a reagent-based diastereoselective cyclopropanation reaction that can provide access to the *anti* isomer with good to excellent selectivities for *E*-substituted allylic alcohols.

Diastereoselective Cyclopropanation of Allylic Ethers. During our initial studies on the diastereoselective cyclopropanation of allylic alcohols,[2] we noticed that benzyl protected *E*-disubstituted allylic alcohols could lead, in some cases, to the formation of the *anti* isomer with good ratios. These results prompted us to further investigate the effect of the substitution pattern and of the nature of the protecting group on the level of *anti* diastereoselection. These results are presented in Table 1.

**Table 1. Cyclopropanation of protected chiral allylic alcohols**

Entry	R^1	R^2	R^3	R^4	PG	Yield[a]	Ratio[b] syn : anti
1	H	Ph	H	Me	Bn	94%	1 : 9
2	H	Ph	H	Me	Me	95%	1 : 1.6
3	H	Ph	H	Et	Bn	97%	1 : 2
4	H	Ph	H	Et	Me	93%	3.4 : 1
5	H	Ph	H	*i*-Pr	Bn	82%[c]	19 : 1
6	H	Ph	H	*i*-Pr	Me	94%[c]	>20 : 1[d]
7	H	*n*-Pr	H	Et	Bn	88%	1 : 2
8	H	Ph	Me	Me	Bn	98%	1 : 7
9	Ph(CH₂)₃	H	H	Me	Bn	85%	15 : 1[d]
10	Ph(CH₂)₃	H	H	Me	Me	80%[c]	17 : 1[d]

[a] Isolated yield of the diastereomeric mixture. [b] Determined by capillary GC analysis of the crude reaction mixture. [c] Isolated yield of the syn-isomer. [d] Determined by ¹H NMR analysis of the crude reaction product.

It is interesting to notice that the size of the protecting group has a direct influence on the level of enantioselection in these reactions. For example, the diastereoselectivity decreases from 9 to 2 : 1 favoring the *anti* isomer when going from benzyl- to methyl-protected alcohol (entries 1-2).[7] An increase of the size of the R^4 substituent leads to the formation of larger amounts of the *syn* isomer (entries 3-6). Conversely, a larger substituent at the R^3 position favors the formation of the *anti* isomer. As expected, the *syn* isomer

was formed with very high diastereoselectivities when $R^1 \neq H$ due to the strong preference to minimize $A^{1,3}$ interactions in the transition state. If we assume that this reaction is directed by the ether group, these observations are consistent with the two competitive transition state models shown in Figure 1 (A and B).[8] We believe that several interactions must be compared in order to predict the outcome of the stereochemical induction in these reactions. When $R_1 \neq H$ then the minimization of the $A^{1,3}$ strain is predominant regardless of the other substituents and excellent *syn*-selectivities are observed. When large protecting groups are used, the minimization of the non-bonded interaction between the protecting group and R^4 leads to the preferential formation of the *anti* isomer. Finally, the presence of an alkyl group at R^3 does not appear to play a significant role in dictating the stereochemical outcome (entry 1 vs 8).

Figure 1. Transition state model for the formation of the *syn* and *anti* isomer.
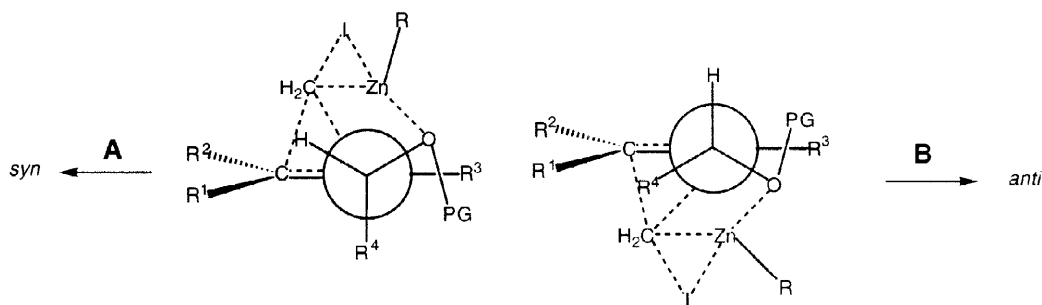
Diastereoselective cyclopropanation of chiral allylic alcohols in the presence of the chiral dioxaborolane ligand 1. In order to study the effect of the chiral dioxaborolane on the cyclopropanation reaction of chiral allylic alcohols, we initially tested whether it would be possible to achieve kinetic resolution of a racemic allylic alcohol. In that respect, **2** was treated with 1.5 equiv of
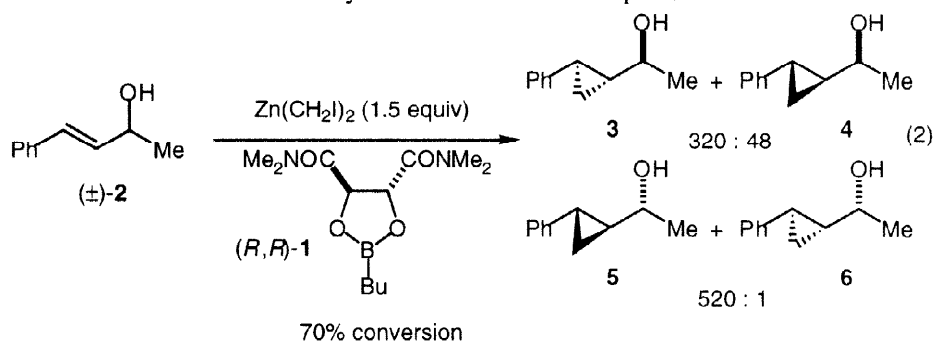
bis(iodomethyl)zinc and 1.1 equiv of **1** using the cyclopropanation reaction and the reaction was stopped after 70% conversion (eq 2).

The capillary GC analysis of the crude reaction product indicated that a mixture of 3 stereoisomeric compounds were obtained. It became obvious that both enantiomers of the starting material reacted at a very similar rate since the residual enantiomeric excess of unreacted **2** was only *ca.* 40%. Quite

interestingly, the major diastereomer produced with both antipodes was the *anti* isomer. More importantly, the diastereomeric ratio was very high. This observation prompted us to develop a general process to generate the *anti* diastereomer from chiral allylic alcohols.

Several enantioenriched allylic alcohols (≥98% ee) were prepared by the Sharpless kinetic resolution method[9] or by an enantioselective dialkylzinc addition to the corresponding aldehyde derivative.[10,11] These substrates were then submitted to cyclopropanation conditions and the effect either antipode of the dioxoborolane addition on the selectivity was examined. The yields and diastereoselectivities observed in different systems are illustrated in Table 2. The reaction of chiral allylic alcohols in the presence of chiral ligand 1 and $Zn(CH_2I)_2$ produced the desired compound in most cases with very high level of induction favoring the *anti* isomer.

**Table 2. Diastereoselective cyclopropanation of chiral, non-racemic allylic alcohols**

1. $Zn(CH_2I)_2$ (2.2 equiv)/CH_2Cl_2, -10 °C
2. 1 (1.2 equiv), CH_2Cl_2, -10 °C to rt, 12 h

(see experimental section)
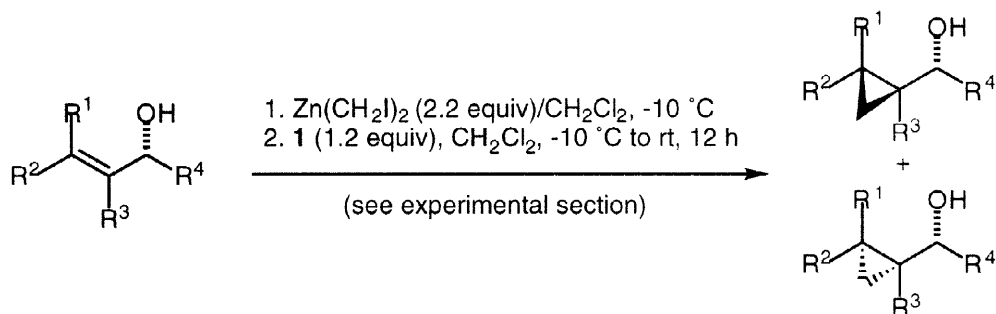
Entry	R^1	R^2	R^3	R^4	1 [b]	Yield [c]	Ratio [d] syn : anti
1	H	Ph	H	Me	R,R	98%	<1 : 200
2	H	Ph	H	Me	S,S	74% (80%)	1 : 12
3	H	Ph	Me	Me	R,R	92%	<1 : 200
4	H	Ph	Me	Me	S,S	57% (60%)	1 : 20
5[e]	H	Ph	H	Et	R,R	83%	1 : 28
6[e]	H	Ph	H	Et	S,S	54%	1 : 12
7	H	n-Pr	H	Et	R,R	84%	1 : 32
8	H	n-Pr	H	Et	S,S	54% (59%)	1 : 12
9	H	Ph	H	i-Pr	R,R	40% (63%)	1 : 1.8
10	H	Ph	H	i-Pr	S,S	16% (37%)	1.6 : 1
11[e]	$Ph(CH_2)_3$	H	H	Me	R,R	20%[f]	>20 : 1[g]
12[e]	$Ph(CH_2)_3$	H	H	Me	S,S	30%[f]	>20 : 1[g]

[a] The starting allylic alcohols were prepared by known method (ref. 9-11) and they were ≥98% ee. [b] Absolute configuration of the chiral ligand. [c] Isolated yield of the pure anti isomer. [d] Determined by capillary GC analysis of the crude reaction mixture. [e] The other enantiomer of the starting chiral allylic alcohol was used. [f] Conversion determined by ^1H NMR. [g] Only one diastereomer could be detected by ^1H NMR.

This method nicely presents the only available protocol for generating *anti*-cyclopropylmethanol derivatives since the highest level of induction were observed with *E*-allylic alcohols. As expected, the cyclopropanation of Z-allylic alcohols produced almost exclusively the *syn*-cyclopropylmethanol. When both, R^2 and R^4 are bulky groups (Ph, *i*-Pr), the chiral ligand could not overwhelm the *syn*-directing propensity of the substrate and low selectivities were observed.

The double stereodifferentiation observed is consistent with our previously postulated transtion state model.[1c] In the matched pair series, the only disfavorable interaction is an $A^{1,3}$ strain between the R^4 group at allylic position and ß-hydrogen (when $R^3 = H$). In the mismatched pair, the severe *syn*-pentane interaction between R^4 and the butyl group of the dioxaborolane disfavors this transition state.

Figure 2. Transition state models (Chem3D) for the double stereodifferentiation reaction
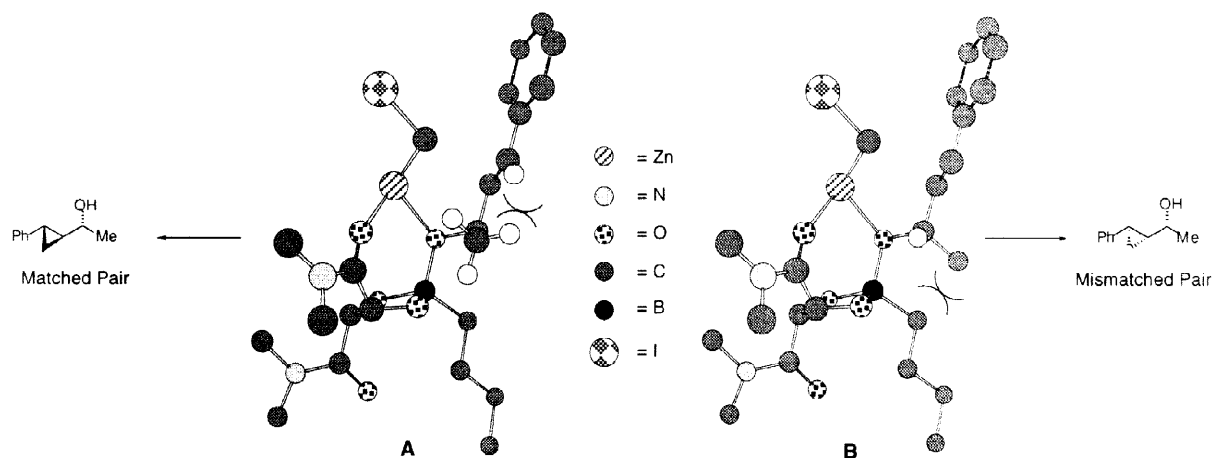
Experimental Section

General procedure for the cyclopropanation of chiral allylic ethers (Table 1). **(1S*,2S*,1'S*)- and (1R*,2R*,1'S*)-1-(1-Methoxyethyl)-2-phenylcyclopropane (Table 1, entry 2).**To a solution of (±)-(E)-3-methoxy-1-phenyl-1-butene (200 mg, 1.23 mmol) in anhydrous CH₂Cl₂ (12 mL) at -10 °C was added dropwise diethylzinc (630 µL, 6.16 mmol) followed by diiodomethane (500 µL, 6.16 mmol). The bath was allowed to warm to rt over 3 h and the mixture was stirred for an additional 1 h. Sat. aq. NH₄Cl (10 mL) was added and the mixture was diluted with ether (80 mL) and 10% aq. HCl (10 mL). The layers were separated and the organic layer was then successively washed with sat. aq. Na₂SO₃ (20 mL), sat. aq. NaHCO₃ (20 mL) and sat. aq. NaCl (20 mL). The organic layer was dried over MgSO₄, and concentrated under reduced pressure. The desired cyclopropylethers (206 mg, 95%) were obtained as a mixture of diastereoisomers after flash chromatography on silica gel (3% EtOAc/hexanes): IR (film) 3064, 3027, 3001, 1604, 1498, 1466, 1202,

1180, 1103 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.24 (m, 4H), 7.19-7.06 (m, 6H), 3.42 (s, 3H),
3.40 (s, 3H), 3.00-2.90 (m, 2H), 1.96-1.90 (m, 1H), 1.74-1.68 (m, 1H), 1.30 (d, J = 6 Hz, 3H), 1.29
(d, J = 6 Hz, 3H), 1.24-1.04 (m, 2H), 0.91 (dt J = 9, 5 Hz, 2H), 0.84-0.77 (m, 2H); ¹³C NMR (100
MHz, CDCl₃) δ 142.7, 142.6, 128.3, 125.9, 125.7, 125.5, 80.1, 80.0, 56.3, 56.2, 28.1, 22.9, 19.9,
19.85, 19.79, 19.4, 15.2, 11.6. Anal. Calcd for C₁₂H₁₆O: C, 81.77; H, 9.15. Found: C. 81.70; H. 9.35.
The diastereomeric ratio (1:1.6 syn:anti) was determined by GC analysis. Conditions: Column: DB-1701,
0.25 mm x 30 m. Pressure 25 psi. Isotherm: 140°C. Tᵣ (major) 4.95 min, Tᵣ (minor) 5.08 min.

(1R*,2R*,1'S*)-1-(1-Benzyloxyethyl)-2-phenylcyclopropane (Table 1, entry 1).

The title compounds were prepared from (±)-(E)-3-benzyloxy-1-phenyl-1-butene (480 mg, 2.01 mmol) by
the standard procedure described above. The desired cyclopropylethers (477 mg, 94%) were obtained as a
mixture of diastereoisomers after flash chromatography on silica gel (2.5% ether/hexanes): IR (film) 3130,
3090, 3060, 3040, 2990, 2920, 1635, 1525, 1480, 1400, 1230, 1200, 1130 (br), 1050, 950, 930, 900,
760, 715 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.10 (m, 10H), 4.68 (d, J = 12 Hz, 1H), 4.59 (d, J
= 12 Hz, 1H), 3.17 (dq, J = 8, 6 Hz, 1H), 1.93-1.90 (m, 1H), 1.35 (d, J = 6 Hz, 3H), 1.29-1.26 (m,
1H), 0.96-0.90 (m, 1H), 0.85-0.81 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 142.9, 139.2, 128.5,
128.4, 127.6, 127.5, 125.9, 125.7, 77.9, 70.3, 28.6, 23.0, 20.5, 12.2. Anal. Calcd for C₁₈H₂₀O: C,
85.67; H, 7.99. Found: C, 85.78; H, 8.20. The diastereomeric ratio (1:9 syn:anti) was determined by
GC. Conditions: Column: DB-1701, 0.25 mm x 30 m. Pressure 25 psi. Isotherm: 235 °C. Tᵣ (major) 3.9
min, Tᵣ (minor) 4.1 min.

**(1S*,2S*,1'S*)- and (1R*,2R*,1'S*)-1-(1-Benzyloxypropyl)-2-phenylcyclopropane
(Table 1, entry 3).**

The title compounds were prepared from (±)-(E)-3-benzyloxy-1-phenyl-1-pentene (140 mg, 0.554 mmol)
by the standard procedure described above. The desired cyclopropylethers (144 mg, 97%) were obtained
as a mixture of diastereoisomers after flash chromatography on silica gel (2% ether/hexanes): IR (film)
3130, 3090, 3070, 3030, 2990, 2940, 1640, 1525, 1480, 1140, 1115, 1090, 1050, 755, 720 cm⁻¹; ¹H
NMR (300 MHz, CDCl₃) δ 7.39-7.06 (m, 20H), 4.74 (d, J = 12Hz, 1H), 4.71 (d, J = 12Hz, 1H), 4.60
(d, J = 12Hz, 1H), 4.57 (d, J = 12Hz, 1H), 2.93 (dt, J = 8, 6 Hz, 2H), 1.95-1.87 (m, 1H), 1.80-1.66
(m, 5H), 1.28-1.18 (m, 2H), 1.04 (t, J = 7 Hz, 3H), 1.01 (t, J = 7 Hz, 3H), 1.09-0.84 (m, 4H); ¹³C
NMR (100 MHz, CDCl₃) δ 142.7, 139.1, 128.3, 128.2, 127.6, 127.5, 127.4, 127.3, 125.8, 125.7,
125.5, 83.2, 83.0, 70.6, 70.4, 28.0, 26.7, 22.5, 19.8, 15.1, 12.0, 10.1. Anal. Calcd for C₁₉H₂₂O: C,
85.67; H, 8.32. Found: C, 85.66; H, 8.69. The diastereomeric ratio (1:2 syn:anti) was determined by GC
analysis. Conditions: Column: DB-1701, 0.25 mm x 30 m. Pressure 25 psi. Isotherm: 235 °C. Tᵣ (major)
4.5 min, Tᵣ (minor) 4.8 min.

(1S*,2S*,1'S*)-   and   (1R*,2R*,1'S*)-1-(1-Methoxypropyl)-2-phenylcyclopropane (Table 1, entry 4).

The title compounds were prepared from (±)-(E)-3-methoxy-1-phenyl-1-pentene (200 mg, 1.13 mmol) by the standard procedure described above. The desired cyclopropylethers (201 mg, 93%) were obtained as a mixture of diastereoisomers after flash chromatography on silica gel (3% EtOAc/hexanes): IR (film) 3064, 3010, 2971, 2938, 2819, 1604, 1499, 1460, 1361, 1198, 1172, 1080 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31-7.26 (m, 4H), 7.20-7.15 (m, 2H), 7.11-7.07 (m, 4H), 3.46 (s, 3H), 3.42 (s, 3H), 2.75-2.68 (m, 2H), 1.96-1.92 (m, 1H), 1.75-1.64 (m, 5H), 1.23-1.02 (m, 8H), 0.99 (t, J = 7 Hz, 3H), 0.85-0.79 (m, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.7, 142.6, 128.24, 128.22, 125.7, 125.6, 125.5, 125.4, 85.4, 85.3, 56.68, 56.67, 27.6, 27.5, 26.4, 26.3, 22.5, 19.6, 14.8, 11.7, 9.87, 9.80. Anal. Calcd for C$_{13}$H$_{18}$O: C, 82.06; H, 9.53. Found: C, 81.91; H, 9.61. The diastereomeric ratio (3.4:1 syn:anti) was determined by GC. Conditions: Column: DB-1701, 0.25 mm x 30 m. Pressure 25 psi. Isotherm: 140°C. T$_r$ (minor) 6.84 min, T$_r$ (major) 6.99 min.

(1S*,2S*,1'S*)-1-(1-Benzyloxy-2-methylpropyl)-2-phenylcyclopropane (Table 1, entry 5).

The title compound was prepared from (±)-(E)-3-benzyloxy-4-methyl-1-phenyl-1-pentene (400 mg, 1.50 mmol) by the standard procedure described above. The desired syn-cyclopropylether (345 mg, 82%) was obtained as a colorless oil after flash chromatography on silica gel (1% ether/hexanes): IR (film) 3130, 3090, 3060, 3020, 2990, 2940, 1640, 1530, 1490, 1480, 1410, 1390, 1120, 1090, 1050, 770, 755, 720 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.40-7.05 (m, 10H), 4.76 (d, J = 12 Hz, 1H), 4.60 (d, J = 12 Hz, 1H), 2.79 (dd, J = 8, 5 Hz, 1H), 2.05 (octuplet, J = 7 Hz, 1H), 1.75-1.68 (m, 1H), 1.21-1.29 (m, 1H), 1.09-1.04 (m, 2H), 1.03 (d, J = 7 Hz, 3 H), 1.02 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.7, 139.2, 128.3, 128.2, 127.5, 127.3, 125.7, 125.5, 86.9, 71.2, 32.9, 24.7, 20.3, 18.7, 18.6, 14.7. Anal. Calcd for C$_{20}$H$_{24}$O: C, 85.67; H, 8.63. Found: C, 85.60; H, 8.96. The diastereomeric ratio (19:1 syn:anti) was determined by GC. Conditions: Column: DB-1701, 0.25 mm x 30 m. Pressure 25 psi. Isotherm: 235 °C. T$_r$ (minor) 4.7 min, T$_r$ (major) 5.1 min.

(1S*,2S*,1'S*)-1-(1-Methoxy-2-methylpropyl)-2-phenylcyclopropane (Table 1, entry 6).

The title compound was prepared from (±)-(E)-3-methoxy-4-methyl-1-phenyl-1-pentene (80 mg, 0.420 mmol) by the standard procedure described above. The desired syn-cyclopropylether (81 mg, 94%) was obtained as a colorless oil after flash chromatography on silica gel (2% EtOAc/hexanes): IR (film) 2960, 2930, 2819, 1605, 1498, 1466, 1093 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.30-7.24 (m, 2H), 7.19-7.13 (m, 1H), 7.08-7.05 (m, 2H), 3.46 (s, 3H), 2.54 (dd, J = 8, 5 Hz, 1H), 2.01-1.91 (m, 1H), 1.74-1.68 (m, 1H), 1.21-1.15 (m, 1H), 1.15-1.01 (m, 2H), 0.98 (d, J = 5 Hz, 3H), 0.96 (d, J = 5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.6, 128.3, 125.6, 125.4, 89.1, 57.5, 32.5, 24.3, 20.1, 18.5, 18.4, 14.4. HRMS Calcd for C$_{14}$H$_{20}$O: : 204.15141. Found: 204.15184.The diastereomeric ratio (>20:1 syn:anti) was obtained by the relative integration of signals at 3.45 ppm (major) and 3.40 ppm (minor).

(1S*,2S*,1'S*)-   and   (1R*,2R*,1'S*)-1-(1-Benzyloxypropyl)-2-propylcyclopropane (Table 1, entry 7). The title compounds were prepared from (±)-(E)-3-benzyloxy-4-octene (200 mg. 0.916 mmol) by the standard procedure described above. The desired cyclopropylethers (188 mg. 88%) were obtained as a diastereomeric mixture after flash chromatography on silica gel (2% ether/hexanes): IR (film) 2958, 2920, 2860, 1454, 1103, 1068 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.25 (m. 10H). 4.73 (d, J = 12Hz, 2H), 4.52 (d, J = 12Hz, 2H), 2.69-2.62 (m, 2H), 1.73-1.56 (m. 4H). 1.51-1.11 (m. 8H), 1.05-0.84 (m, 12H), 0.89-0.38 (m, 4H), 0.26-0.21 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 139.3, 128.1, 127.6, 127.4, 127.1, 83.8, 77.1, 70.2, 35.9, 27.9, 22.5, 22.1, 15.0, 13.9, 11.8, 10.0. Anal. Calcd for C₁₆H₂₄O: C, 82.70; H, 10.41. Found: C, 82.37; H, 10.68. The diastereomeric ratio (1:2 syn:anti) was determined by GC. Conditions: Column: DB-1701, 0.25 mm x 30 m. Pressure 25 psi. Isotherm: 190 °C. T_r (major) 3.6 min, T_r (minor) 3.8 min.

(1R*,2R*,1'S*)-   and   (1S*,2S*,1'S*)-1-(1-Benzyloxyethyl)-1-methyl-2-phenylcyclopropane (Table 1, entry 8). The title compounds were prepared from (±)-(E)-3-benzyloxy-2-methyl-1-phenyl-1-butene (200 mg, 0.793 mmol) by the standard procedure described above. The desired cyclopropylethers (207 mg, 98%) were obtained as a diastereomeric mixture after flash chromatography on silica gel as a colorless oil (2% ether/hexanes): IR (film) 3027, 2976, 2931, 1497, 1452, 1371, 1108, 1066, 1028 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.19 (m, 10H). 4.75 (d, J = 12 Hz, 1H), 4.62 (d, J = 12 Hz, 1H), 3.07 (q, J = 6 Hz, 1H). 2.12 (dd, J = 9, 6 Hz, 1H), 1.33 (d, J = 6 Hz, 3H), 0.84 (s, 3H), 0.86-0.77 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 139.09, 138.97, 128.8, 128.3, 127.9, 127.4, 127.3, 125.7, 81.5, 70.4, 29.6, 26.1, 17.8, 13.9, 12.4. Anal. Calcd for C₁₉H₂₂O: C, 85.67; H, 8.32. Found: C, 85.77; H, 8.54. The diastereomeric ratio (1:7 syn:anti) was determined by GC. Conditions: Column: DB-1701, 0.25 mm x 30 m. Pressure 25 psi. Isotherm: 220 °C. T_r (major) 5.8 min, T_r (minor) 6.2 min.

(1S,1'S,2'R)-1-(1-Benzyloxyethyl)-2-(3-phenylpropyl)cyclopropane (Table 1, entry 9). The title compound was prepared from (S)-(Z)-2-benzyloxy-7-phenyl-3-heptene (90 mg. 0.321 mmol) by the standard procedure described above. The desired syn-cyclopropylether (80 mg, 85%) was obtained as a colorless oil after flash chromatography on silica gel (5% ether/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.25 (m, 8H), 7.20-7.17 (m, 2H), 4.64 (d, J = 12, 1H), 4.56 (d, J = 12, 1H), 3.15-3.08 (m, 1H), 2.68-2.60 (m, 2H), 1.79-1.70 (m, 2H), 1.63-1.55 (m, 1H), 1.32 (d, J = 6 Hz, 3H), 1.07-0.90 (m, 1H), 0.89-0.77 (m, 3H), 0.16-0.13 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 142.5, 139.2, 128.3, 128.2, 127.5, 127.2, 125.6, 76.0, 70.1, 35.7, 31.9, 28.5, 21.5, 21.3, 14.3, 11.4; [α]_D -2.70° (c 2.80, CHCl₃). HRMS Calcd for C₂₁H₂₆O: 294.19836. Found: 294.19775. The diastereomeric ratio (15:1 syn:anti) was obtained by the relative integration of multiplets at 0.14 ppm (major) and -0.20 ppm (minor).

(1S,1'S,2'R)-1-(1-Methoxyethyl)-2-(3-phenylpropyl)cyclopropane (Table 1, entry 10).
The title compound was prepared from (S)-(Z)-2-methoxy-7-phenyl-3-heptene (63 mg, 0.308 mmol) by
the standard procedure described above. The desired *syn*-cyclopropylether (56 mg, 80%) was obtained as
a colorless oil after flash chromatography on silica gel (10% ether/hexanes). ^{1}H NMR (400 MHz, CDCl$_3$)
δ 7.32-7.27 (m, 2H), 7.20-7.16 (m, 3H), 3.37 (s, 3H), 2.92-2.86 (m, 1H), 2.72-2.60 (m, 2H), 1.82-
1.68 (m, 2H), 1.66-1.58 (m, 1H), 1.25 (d, J = 6 Hz, 3H), 1.08-0.99 (m, 1H), 0.86-0.74 (m, 3H), 0.18-
0.14 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.5, 128.24, 128.17, 125.6, 77.8, 56.0, 35.7, 31.8,
28.4, 21.2, 20.7, 14.0, 11.1; [α]$_D$ -55.2° (c 0.83, CHCl$_3$). HRMS Calcd for C$_{15}$H$_{22}$O: 218.16707.
Found: 218.16627. The diastereomeric ratio (17:1 *syn:anti*) was obtained by the relative integration of
multiplets at 0.17 ppm (major) and -0.22 ppm (minor).

**General procedure for the cyclopropanation of chiral, non-racemic allylic alcohols
(Table 2).^{12} (1R,1'S,2'S)-1-(2-Phenylcyclopropyl)-1-ethanol** (Table 2, entry 1). To a
solution of diethylzinc (140 μL, 1.35 mmol) in anhydrous CH$_2$Cl$_2$ (4 mL) at -10 °C was added dropwise
diiodomethane (215 μL, 2.70 mmol). The resulting white mixture was stirred at -10 °C for 10 min, after
which time a solution of dioxaborolane R,R-1 (200 mg, 0.742 mmol) in anhydrous CH$_2$Cl$_2$ (2 mL) was
added. After an additionnal 5 min of stirring at -10 °C, a solution of (R)-(E)-4-phenyl-3-buten-2-ol (100
mg, 0.675 mmol) in anhydrous CH$_2$Cl$_2$ (2 mL) was added. The mixture was warmed to rt and stirred for
an additionnal 12 h. Sat. aq. NH$_4$Cl (2 mL) was then added and the mixture was diluted with ether (40
mL) and 10% aq. HCl (10 mL). The layers were separated and the organic layer was washed with sat. aq.
Na$_2$SO$_3$ (10 mL). The aqueous phase was eliminated and the organic phase was stirred vigorously for 6 h
with 2M aq. NaOH (40 mL) and 30% aq. H$_2$O$_2$ (4 mL). The layers were separated and the organic layer
was then successively washed with sat. aq. NH$_4$Cl (3 x 20 mL) and sat. aq. NaCl (20 mL). The organic
layer was dried over MgSO$_4$, and concentrated under reduced pressure. The desired cyclopropylalcohol
(107 mg, 98%) was obtained as a white solid after flash chromatography on silica gel (15%
EtOAc/hexanes): [α]$_D$ +64.2° (c 1.00, CHCl$_3$); IR (film) 3360 (br), 3060, 3000, 2960, 2920, 1600,
1490, 1440, 1410, 1210, 1100, 1070, 1020, 970, 930, 740, 680 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ
7.30-7.08 (m, 5H), 3.40 (qn, J = 6 Hz, 1H), 1.95-1.89 (m, 1H), 1.68 (s, 1H), 1.34 (d, J = 6 Hz, 3H),
1.34-1.25 (m, 1H), 0.98-0.90 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.6, 128.2, 125.7, 125.5,
71.7, 30.7, 22.3, 21.2, 13.2. HRMS calcd for C$_{11}$H$_{14}$O: 162.10446, found 162.10464. Anal. Calcd for
C$_{11}$H$_{14}$O: C, 81.44; H, 8.70. Found: C, 81.10; H, 9.34. The diastereomeric ratio (<1:200 *syn:anti*) was
determined by GC analysis of the corresponding acetate. Conditions: Column: DB-1701, 0.25 mm x 30
m. Pressure 25 psi. Isotherm: 140°C. T$_r$ (major) 10.2 min, T$_r$ (minor) 11.3 min.

(1R,1'S,2'S)-1-(1-Methyl-2-phenylcyclopropyl)-1-ethanol (Table 2, entry 3).   The title
compound was prepared from (R)-(E)-3-methyl-4-phenyl-3-buten-2-ol (100 mg, 0.616 mmol) by the
standard procedure described above. The desired cyclopropylalcohol (100 mg, 92%) was obtained as a
colorless oil after flash chromatography on silica gel (15% EtOAc/hexanes): [α]$_D$ +27.7° (c 1.28, CHCl$_3$):

IR (film) 3420 (br), 3120, 3080, 3030, 2990, 2930, 1635, 1530, 1475, 1400, 1330, 1130, 1100, 1050, 950, 800, 760, 720 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.18 (m, 5H), 3.38 (q, J = 6 Hz, 1H), 2.09 (dd, J = 9, 6 Hz, 1H), 1.63 (s (br), 1H), 1.30 (d, J = 6 Hz, 3H), 0.93-0.90 (m, 1H), 0.85-0.82 (m, 1H), 0.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 139.0, 129.0, 127.9, 125.7, 74.7, 28.2, 27.7, 19.6, 14.9, 12.8. HRMS Calcd for C₁₂H₁₆O: 176.12012. Found: 176.11939. The diastereomeric ratio (<1:200 *syn:anti*) was determined by GC analysis of the corresponding acetate. Conditions: Column: DB-1701, 0.25 mm x 30 m. Pressure 25 psi. Isotherm: 160°C. Tᵣ (major) 6.0 min, Tᵣ (minor) 6.3 min.

(1S,1'R,2'R)-1-(2-Phenylcyclopropyl)-1-propanol (Table 2, entry 5). The title compound was prepared from (S)-(E)-1-phenyl-1-penten-3-ol (100 mg, 0.616 mmol) by the standard procedure described above. Unreacted allylic alcohol was destroy by dihydroxylation reaction: the crude mixture in acetone:H₂O (4:1) was stirred overnight with 100 μL of 0.16 M solution of OsO₄ in water and 100 μL of 60% NMO in water. Then sol. NaHSO₃ (500 mg) was added, and the mixture was extracted with EtOAc (2 x 30 mL); the organic layer was washed with sat. aq. NaCl (20 mL), then dried with MgSO₄ and concentrated under reduced pressure. The desired cyclopropylalcohol (90 mg, 83%) was obtained as a colorless oil after flash chromatography on silica gel (15% EtOAc/hexanes): [α]ᴅ -69.6° (c 0.97, CHCl₃): IR (film) 3420 (br), 3090, 3060, 3030, 2990, 2940, 1640, 1530, 1490, 1140, 1120, 1050, 990, 950, 770, 720 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.07 (m, 5H), 3.13 (dt, J = 7, 6 Hz, 1H), 1.94-1.88 (m, 1H), 1.76-1.60 (m, 2H), 1.58 (s (br), 1H), 1.32-1.23 (m, 1H), 1.03 (t, J = 7 Hz, 3H), 0.99-0.92 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 142.7, 128.2, 125.8, 125.4, 76.7, 29.9, 29.1, 20.6, 13.6, 9.93. HRMS Calcd for C₁₂H₁₆O: 176.12012. Found: 176.12027. The diastereomeric ratio (1:28 *syn:anti*) was determined by GC analysis of the corresponding acetate. Conditions: Column: DB-1701, 0.25 mm x 30 m. Pressure 25 psi. Isotherm: 160°C. Tᵣ (major) 7.0 min, Tᵣ (minor) 7.6 min.

(1R,1'S,2'S)-1-(2-Propylcyclopropyl)-1-propanol (Table 2, entry 7). The title compound was prepared from (R)-(E)-4-octen-2-ol (100 mg, 0.780 mmol) by the standard procedure described above. Unreacted allylic alcohol was destroy by dihydroxylation reaction like preceeding specified. The desired cyclopropylalcohol (94 mg, 84%) was obtained as a colorless oil after flash chromatography on silica gel (15% ether/hexanes): [α]ᴅ +25.3° (c 1.25, CHCl₃); IR (film) 3430 (br), 3020, 2990, 2940, 1495, 1410, 1140, 1050, 990, 940, 760 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.85 (ddd, J = 8, 7, 6 Hz, 1H), 1.67-1.51 (m, 2H), 1.47 (s (br), 1H), 1.46-1.37 (m, 2H), 1.26-1.13 (m, 2H), 0.97 (t, J = 7 Hz, 3H), 0.92 (t, J = 7 Hz, 3H), 0.70-0.59 (m, 2H), 0.40-0.35 (m, 1H), 0.33-0.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 77.4, 35.8, 29.8, 24.9, 22.7, 16.1, 13.8, 9.9, 9.8. The diastereomeric ratio (1:32 *syn:anti*) was determined by GC analysis of the corresponding acetate. Conditions: Column: DB-1701, 0.25 mm x 30 m. Pressure 25 psi. Isotherm: 100°C. Tᵣ (major) 6.5 min, Tᵣ (minor) 7.5 min.

(1R,1'S,2'S)- and (1R,1'R,2'R)-1-(2-Phenylcyclopropyl)-2-methyl-1-propanol (Table 2, entry 9). The title compounds were prepared from (R)-(E)-4-methyl-1-phenyl-1-penten-3-ol (100 mg, 0.567 mmol) by the standard procedure described above. Unreacted allylic alcohol was destroy by

dihydroxylation reaction like preceding specified. Two diastereoisomers were separated by flash chromatography on silica gel (10% EtOAc/hexanes) to produce 43 mg (40%) of *anti* isomer (major) as colorless oil: $[\alpha]_D$ +64.6° (c 1.02, $CHCl_3$); IR (film) 3394 (br), 3027, 2959, 2868, 1604, 1498, 1467, 1417, 1367, 1091, 999 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.07 (m, 5H), 2.94 (dd, J = 8, 6 Hz, 1H), 1.93-1.82 (m, 2H), 1.52 (s (br), 1H), 1.31-1.23 (m, 1H), 1.02 (d, J = 7 Hz, 3H), 0.99 (d, J = 7 Hz, 3H), 1.05-0.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 128.2, 125.7, 125.5, 80.4, 34.3, 27.4, 20.3, 18.6, 18.0, 14.3. 25 mg (23%) of *syn* isomer was isolated as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.06 (m, 5H), 2.90 (dd, J = 8, 6 Hz, 1H), 1.89-1.81 (m, 2H), 1.56 (s (br), 1H), 1.29-1.20 (m, 1H), 1.02 (d, J = 7 Hz, 3H), 0.99 (d, J = 7 Hz, 3H), 1.03-0.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 128.3, 125.6, 125.5, 80.7, 34.4, 27.5, 21.9, 18.6, 18.3, 12.9; $[\alpha]_D$ -99.3° (c 0.64, $CHCl_3$). HRMS Calcd for $C_{13}H_{18}O$: 190.13577. Found: 190.13530. The diastereomeric ratio (1:1.8 *syn:anti*) was determined by GC analysis of the corresponding acetate. Conditions: Column: DB-1701, 0.25 mm x 30 m. Pressure 25 psi. Isotherm: 180°C. T_r (major) 4.8 min, T_r (minor) 5.1 min.

(1S,1'S,2'R)-1-[2-(3-Phenylpropyl)cyclopropyl]-1-ethanol (Table 2, entry 11). The title compound was prepared from (S)-(Z)-7-phenyl-3-hepten-2-ol (50 mg, 0.262 mmol) by the standard procedure described above. The analysis of the crude ^1H NMR indicated a conversion of 30% to *syn*-isomer. The *syn*-isomer was separated from the starting materiel by flash chromatography on silica gel (20% EtOAc/hexanes): $[\alpha]_D$ -26.3° (c 1.24, $CHCl_3$); IR (film) 3420 (br), 3120, 3090, 3020, 2990, 2920, 1635, 1530, 1470, 1440, 1400, 1200, 1130, 1100, 1050, 1020, 940, 770, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.20-7.12 (m, 3H), 3.38-3.30 (m, 1H), 2.71-2.59 (m, 2H), 1.83-1.68 (m, 2H), 1.61-1.53 (m, 1H), 1.47 (s (br), 1H), 1.31 (d, J = 6 Hz, 3H), 1.18-1.09 (m, 1H), 0.94-0.83 (m, 2H), 0.76-0.70 (m, 1H), 0.07 (q, J = 5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 128.23, 128.19, 125.6, 69.1, 35.6, 31.8, 28.4, 24.3, 23.6, 16.2, 9.78. HRMS Calcd for $C_{14}H_{20}O$: 204.15141. Found: 204.15089.

References and Notes

1. (a) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651-2652. (b) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081-1083. (c) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943-11952.

2. Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966-2967.

3. Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 2647-59.

4. (a) Ratier, M.; Castaing, M.; Godet, J.-Y.; Pereyre, M. *J. Chem. Res. (M).* **1978**. 2309-2318. (b) Groth, U.; Schöllkopf, U.; Tiller, T. *Liebigs Ann. Chem.* **1991**, 857-860. (c) Schöllkopf. U.; Tiller, T.; Bardenhagen, J. *Tetrahedron* **1988**, *44*, 5293-5305. (d) Zhao, Y.; Yang, T.-F.; Lee, M.; Chun, B. K.; Du, J.; Schinazi, R. F.; Lee, D.; Newton, M. G.; Chu, C. K. *Tetrahedron Lett.* **1994**. *35*, 5405-5408. (e) Mohamadi, F.; Still, W. C. *Tetrahedron Lett.* **1986**, *27*, 893-896.

5. (b) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525-3532. (c) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942-3944. (d) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1995**, *60*, 2474-2487. (e) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1992**. *57*, 798-800.

6. Indirectly, *anti-Z*-cyclopropane are accessible by reduction of Z-cyclopropyl ketones: Lautens. M.; Delanghe, P. H. M. *Tetrahedron Lett.* **1994**, *35*, 9513-9516.

7. The triisopropylsilylether produced the *anti* isomer with 91% diastereoselectivity (60% yield. 5 equiv of Et_2Zn and CH_2I_2). In this case, it is not very probable that this reaction is directed by the silyl ether. The minimization of the A-1,3 strain and attack by the reagent *anti* to the TIPS ether explains the stereochemical outcome of this reaction.

8. (a) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**. *104*, 7162-7166. (b) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**. *40*, 2257-2274. (c) Mareda, J.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1983**. *105*, 6997-6999.

9. Allylic alcohols used in entries 1-4, 7-10 were prepared by a Sharpless kinetic resolution: Gao. Y.; Hanson, R. M.; Kunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

10. The allylic alcohol used in entry 5 and 6 was prepared in 90% ee according to the following procedure and then further enriched by a Sharpless kinetic resolution (ref. 9): Takahashi. H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**. *48*, 5691-5700.

11. The allylic alcohol used in entries 11 and 12 was prepared from ethyl lactate by the following 7-step procedure: 1. TIPSCl, 2,6-lutidine, CH_2Cl_2, 1h, rt (98%); 2. DIBAL-H, CH_2Cl_2, -78 °C, 1h. (98%); 3. CBr_4, PPh_3 CH_2Cl_2, 0 °C, 15 min (90%); 4. BuLi, THF, -78 °C, 1h (98%); 5. BuLi. THF. -78 °C, 5 min then $PhCH_2CH_2CH_2I$, THF/HMPA; rt, 16 h; 6. TBAF, THF, rt. 2h (55%. 2 steps); 7. H_2, $NaBH_4$, $Ni(OAc)_2{\cdot}4H_2O$ (59%). McKew, J. C.; Kurth M. J. *Org. Prep. Proc. Int.* **1993**. *25*, 125-130.

12. Similar yields and selectivities were obtained when these reactions were carried on 5 mmole-scale but. in these cases, the $Zn(CH_2I)_2{\cdot}DME$ complex must be used. See ref. 1c for the procedure.