Articles

Comparison of Stereoselectivity in the Reactions of Crotylmetal Reagents with Dicobalt Hexacarbonyl-Complexed and Uncomplexed Propynals

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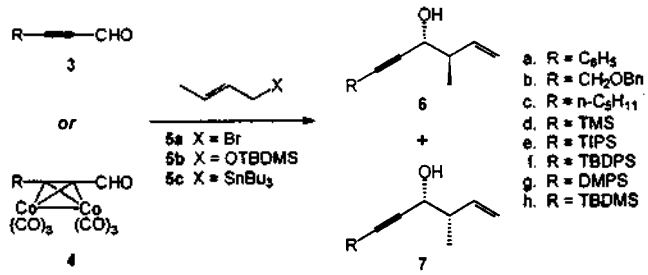
The diastereoselectivity of addition reaction of crotylmetal reagents to cobalt-complexed acetylenic aldehydes and metal-free aldehydes was examined. The *anti*-diastereomer was the predominant product when the crotyl metallics were Cr, Sn, and Zr. In THF, the uncomplexed aldehydes normally gave higher *anti*-diastereoselectivity. However, the cobalt-complex of silicon-substituted propynals with three bulky substituents produced increased proportions of *syn*-diastereomer. In DMF, the selectivity shifted towards *syn*-isomer except in the case of dimethylphenylsilyl substituent. When tributylstannane was used in the presence of BF_3 etherate, moderate *syn*-selectivity was observed with uncomplexed aldehydes, but only decomposed products from complexed aldehydes.

Introduction

Optically active secondary alkynyl alcohols **1** form an important class of compounds. They serve as intermediates for preparation of many natural products including enediyne class antitumor antibiotics[1-2] of recent interest. Conventional methods for the asymmetric synthesis of **1** include reduction of acetylenic ketones,[3] alkynylation of aldehydes,[4] reductive cleavage of acetylenic acetals,[5] and addition of organometal reagents to acetylenic aldehydes.[6] In the course of our study related with enediyne mimics we have been interested in developing highly stereoselective syntheses of acetylenic homoallylic alcohol[7] **2** (Figure 1).

We planned to achieve this goal by allylation of acetylenic aldehydes, since the reactions of substituted allylmetal reagents with carbonyl compounds show high degree of diastereoselectivity.[8] To our surprise, however, only limited information on the allylation of propynal derivatives has so far been available in the literature.[9] The diastereoselectivity of the addition of crotyl metal complexes to aldehydes in some cases reflects the geometry of the allylic moiety (B, Al, Sn), in other cases (Ti, Cr, Zr, Si, and Sn in the presence of Lewis acids) the reactions are *anti*- or *syn*-selective independently of the allyl group geometry.[8a,10] Furthermore, there had been some results[11-14] in which metal-complexed substrates give higher stereoselectivity than uncomplexed substrates. Thus we initiated a comparison study for the reactions of crotylmetal reagents with cobalt-complexed and metal-free propynals (Scheme 1).

Figure 1.



Scheme 1.

Results and Discussion

Since the chair-like cyclic transition state is believed to be involved in the allylation of crotylchromium reagent with aldehydes,[8a] we expected that increase of steric bulkiness of aldehyde would result in better selectivity. However, in all the reactions of crotylchromium reagent generated from crotyl bromide **5a** and chromium(II) chloride in THF,[15] the cobalt-complexed aldehydes showed lower *anti*-selectivity than uncomplexed aldehydes (Table 1, entry 1, 4, 8, 11 *vs* 2, 5, 9, 12).[16] Only in the case of trimethylsilyl-substituted aldehyde, complexation with cobalt resulted in comparable selectivity (entry 11 *vs* 12). Tin(II) fluoride[17] or zirconocene-induced[18] reactions also gave diminished *anti*-selectivity than the reactions with chromium reagents (entries 3, 6, 7, 10 and 14).

Hoping to achieve *syn*-selectivity by changing the solvent to DMF, as shown previously in the case of sterically demanding aldehyde (*e.g.* pivaldehyde),[15b] we investigated the effects of solvent. In these experiments silicon-substituted aldehydes were chosen as the substrates, since the resultant product, after removal of the silyl group, can be connected to any carbon species *via* alkylation or cross-coupling.

In THF, cobalt-complexed aldehydes indeed produced more *syn*-diastereomer, especially in the case of substrates with three large substituents on the silicon atom (compare

Table 1. Reactions of cobalt-complexed propynals and uncomplexed propynals with crotylmetal reagents in THF

Entry	Aldehyde	Allylic reagent	Additive	Yield[a] %	*anti* : *syn* (6 : 7)[b]
1	**3a**	**5a**	$CrCl_2$	75	96 : 4
2	**4a**	**5a**	$CrCl_2$	75	87 : 13
3	**3a**	**5a**	SnF_2	86	74 : 26
4	**3b**	**5a**	$CrCl_2$	70	97 : 3
5	**4b**	**5a**	$CrCl_2$	61	87 : 13
6	**4b**	**5a**	SnF_2	43	82 : 18
7	**4b**	**5b**	$ZrCp_2$	37	86 : 14
8	**3c**	**5a**	$CrCl_2$	72	96 : 4
9	**4c**	**5a**	$CrCl_2$	89	93 : 7
10	**4c**	**5a**	SnF_2	50	82 : 18
11	**3d**	**5a**	$CrCl_2$	77	95 : 5
12	**4d**	**5a**	$CrCl_2$	79	95 : 5
13	**4d**	**5a**	SnF_2	69	82 : 18
14	**4d**	**5b**	$ZrCp_2$	64	91 : 9

[a]Isolated yield. [b]Determined by ^1H NMR analysis.

Table 2. Allylation of silicon-substituted propynals with crotylchromium reagent in THF and DMF

Entry	Aldehyde	Allylic reagent	Solvent	Yield[a] %	*anti* : *syn* (6 : 7)[b]
1	**3e**	**5a**	THF	75	94 : 6
2	**4e**	**5a**	THF	79	54 : 46
3	**3e**	**5a**	DMF	81	71 : 29
4	**4e**	**5a**	DMF	68	62 : 38
5	**3f**	**5a**	THF	76	94 : 6
6	**4f**	**5a**	THF	82	61 : 39
7	**3f**	**5a**	DMF	76	66 : 34
8	**4f**	**5a**	DMF	77	60 : 40
9	**3g**	**5a**	THF	80	93 : 7
10	**4g**	**5a**	THF	84	91 : 9
11	**3g**	**5a**	DMF	75	94 : 6
12	**4g**	**5a**	DMF	79	52 : 48

[a]Isolated yield. [b]Determined by capillary GC analysis.

entry 10 with 2 and 6; Table 2). These results may imply that remote substituents affect some influence on the structure of transition state due to its bented structure.[14b]

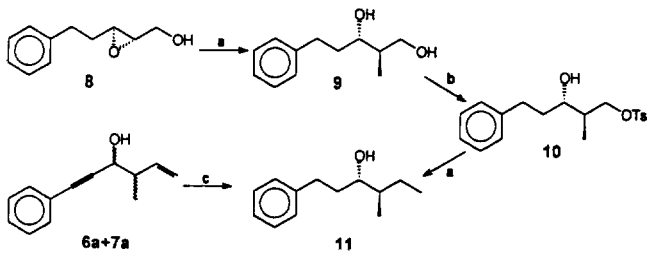
In DMF, all the reactions of cobalt-complexed aldehydes showed much lower *anti*-selectivity (entries 4, 8 and 12), but those of uncomplexed aldehydes exhibited diminished *anti*-selectivity only in the case of triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) groups (entry 11 vs 3 and 7).

To achieve high *syn*-selectivity, Lewis acid catalyzed allylation[19] of silicon-substituted propynals with crotyl tributylstannane was examined (Table 3). Moderate degree of *syn*-selectivity was obtained in the reactions of uncomplexed aldehydes. However, the reactions of cobalt-complexed aldehydes resulted in the unidentifiable decomposed products, presumably due to the other types of Lewis acid catalyzed reactions.

Table 3. Reactions of cobalt-complexed propynals and uncomplexed propynals with crotyltributylstannane in the presence of BF_3

Entry	Aldehyde	Allylic reagent	Additive	Yield[a] %	*anti* : *syn* (6 : 7)[b]
1	**3e**	**5c**	BF_3	82	21 : 79
2	**4e**	**5c**	BF_3	*c*	—
3	**3g**	**5c**	BF_3	90	26 : 74
4	**4g**	**5c**	BF_3	*c*	—
5	**3h**	**5c**	BF_3	90	22 : 78
6	**4h**	**5c**	BF_3	*c*	—

[a]Isolated yield. [b]Determined by capillary GC analysis. [c]Decomposed.



Scheme 2.

The stereochemical assignment was ascertained unequivocally by correlation with epoxy alcohol **8** prepared via the Sharpless asymmetric epoxidation (Scheme 2).[20] Treatment of epoxy alcohol **8** with Me_2CuLi,[21] followed by $NaIO_4$ treatment[22] to cleave any 1,2-diol that may have been produced, provided 1,3-diol **9**. The primary hydroxyl group of **9** was selectively monotosylated and then displaced with Me_2CuLi to give *anti*-alcohol **11** that was correlated with the major product of the reaction of aldehyde **3** and crotylchromium reagent after hydrogenation.

Experimental

General Methods

^1H NMR spectra were recorded on a JEOL JNM-EX400 (400 MHz) spectrometer using TMS as an internal standard. ^{13}C NMR spectra were obtained at 100.5 MHz with $CDCl_3$ as solvent and internal reference. All the peak assignments were made by employing two-dimensional phase-sensitive homo- and heteronuclear shift correlation methods.[23] IR spectra were taken on a Nicolet 50DXB FT-IR spectrophotometer.

All reactions were carried out under the argon atmosphere. Diethyl ether, THF were distilled from benzophenone ketyl solutions. Dichloromethane was distilled from CaH_2 and trifluoroacetic acid was dried over P_2O_5 prior to distillation.

Analytical gas chromatography (GC) was carried out on a Varian Star 3600 Gas Chromatograph equipped with a

flame ionization detector (FID) and a capillary column (DB-5; 0.25 mm×0.25 μm×30 m) at 80 psi N_2 pressure. Diastereomer ratios were determined by (a) NMR integration, or (b) integration of GC traces (assuming equivalent response factors for diastereomers).

Substituted propynals were prepared as described in the literature,[24-25] by condensation of anion of alkynes with 1-formylpiperidine or by silylation of propargyl aldehyde diethyl acetal. Crotyltributylstannane was prepared according to the recently published procedure.[26]

3-(Triisopropylsilyl)-2-propynal-Dicobalt Hexacarbonyl Complex (4e). Representative Formation of Cobalt-Complexed Propargyl aldehydes

$Co_2(CO)_8$ (2.1 g, 6 mmol) was transferred under nitrogen to a dry, preweighed flask. Et_2O (25 mL) was introduced *via* syringe followed by an ether solution (5 mL) of 3-(triisopropylsilyl)-2-propynal (1.26 g, 6 mmol). The solution was stirred for 0.5 h until CO evolution was no longer visible. The solvent was removed under reduced pressure and the residue subjected to flash chromatography. Elution, first with straight hexanes to remove cobalt derived impurities, followed by 5% EtOAc/Hexanes afforded 2.68 g (90%) of the desired cobalt complex: ^{1}H NMR ($CDCl_3$) δ 10.36 (br s, 1H, CHO), 1.17 (br s, 21H, *i*-Pr); ^{13}C NMR ($CDCl_3$) δ 198.75 (br, CO's), 189.10 (CHO), 104.52, 74.38 (C_2, C_3), 18.85 (CH_3), 13.26 (SiCH).

Representative Procedure for the Reactions of Aldehydes with Crotyl bromide in the presence of $CrCl_2$

To a suspension of $CrCl_2$ (0.49 g, 4 mmol) in THF (5 mL was added a solution of aldehyde 3 (1 mmol) and *E*-crotyl bromide **5a** 240 μL, 2 mmol) in THF (5 mL) at 0 ℃ under an argon atmosphere. After being stirred for 2 h at room temperature, the mixture was poured into a mixture of brine, water and ether (1 : 1 : 1, 75 mL), and the whole mixture was stirred for 30 min. The organic layer was separated and the remainder was extracted with ether (3×10 mL). The combined extract was dried ($MgSO_4$) and concentrated to provide an oil, which was purified by column chromatography on silica gel (eluant : 5% EtOAc/Hexanes).

When the cobalt-complex was used in the reaction, the crude product dissolved in MeOH (5 mL) was added dropwise to a solution of $Fe(NO_3)_3$ (2 g, 5 mmol) in MeOH (2 mL) at room temperature (CO evolution!). After gas evolution had been ceased, the mixture was further stirred for 1 h. Water (5 mL) was then added and the mixture was extracted with ether (3×20 mL). The combined extract was dried ($MgSO_4$), concentrated, and purified by column chromatography on silica gel (eluant : 5% EtOAc/Hexanes).

Representative Procedure for the Reactions of Aldehydes with Crotyl bromide in the presence of SnF_2

To a white grey suspension of SnF_2 (0.63 g, 4 mmol) in THF (5 mL) was added a solution of cobalt-complexed aldehyde **4** (1 mmol) and *E*-crotyl bromide **5a** (240 μL, 2 mmol) in THF (5 mL) at 0 ℃ under an argon atmosphere. After being stirred for 12 h, the mixture was poured into a mixture of brine, water and ether (1 : 1 : 1, 75 mL) and the whole mixture was stirred for 30 min. The reaction mixture was worked up as above.

Representative Procedure for the Reactions of Aldehydes with Crotyl TBS ether in the presence of Cp_2Zr

Under argon atmosphere, a solution of *n*-BuLi (2.05 M in hexane, 2.5 mL, 5.1 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (730 mg, 2.5 mmol) in THF (7 mL) at −78 ℃ and stirred at the same temperature for 1 h. To the reaction mixture was added a solution of crotyl TBS ether **5b** (373 mg, 2 mmol) in THF (4 mL) at −78 ℃. After stirring at room temperature for 3 h, a solution of cobalt-complexed aldehyde 4 (2 mmol) in THF (4 mL) was added at 0 ℃ and the mixture was stirred for 2 h. The reaction mixture was worked up as above.

4-Methyl-1-phenyl-5-hexen-1-yn-3-ol

***anti*-isomer (6a).** IR (film) 3416 (br s), 2249 (w), 1025 (m), 906 (vs), 737 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45-7.30 (m, 5H, Ph), 5.89 (ddd, 1H, *J*=17.4, 10.4, 7.6 Hz, C_5-H), 5.22 (d, 1H, *J*=17.4 Hz, C_6-H), 5.19 (d, 1H, *J*=10.4 Hz, C_6-H), 4.43 (d, 1H, *J*=6.4 Hz, C_3-H; after exchanging with D_2O), 2.57 (sextet, 1H, *J*=6.7 Hz, C_4-H), 1.98 (d, 1H, *J*=5.5 Hz, O<u>H</u>), 1.21 (d, 3H, *J*=6.7 Hz, C_4-C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 139.20 (C_5), 131.69 (*o*-Ph), 128.39 (*p*-Ph), 128.24 (*m*-Ph), 122.56 (*i*-Ph), 116.78 (C_6), 88.44 (C_2), 85.77 (C_1), 66.60 (C_3), 44.53 (C_4), 15.31 (C_4-<u>C</u>H$_3$); ***syn*-isomer (7a)**: 5.94 (ddd, *J*=16.8, 10.4, 7.9 Hz, C_5-H), 5.22-5.16 (m, C_6-H), 4.49 (d, *J*=6.4 Hz, C_3-H; after exchanging with D_2O), 2.57 (m, C_4-H), 2.02 (d, *J*=7.6 Hz, O<u>H</u>), 1.19 (d, *J*=6.7 Hz, C_4-CH_3).

7-Benzyloxy-3-methyl-1-hepten-5-yn-4-ol

***anti*-isomer (6b).** IR (film) 3416 (br s), 2250 (w), 1068 (vs), 1025 (vs), 920 (s), 744 (s), 695 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38-7.30 (m, 5H, Ph), 5.84 (ddd, 1H, *J*=17.1, 10.4, 7.6 Hz, C_2-H), 5.183 (d, 1H, *J*=17.1 Hz, C_1-H), 5.175 (d, 1H, *J*=10.4 Hz, C_1-H), 4.60 (s, 2H, Ph-C<u>H</u>$_2$), 4.28 (dt, 1H, *J*=6.4, 1.2 Hz, C_4-H; after exchanging with D_2O), 4.23 (d, 2H, *J*=1.2 Hz, C_7-H), 2.49 (sextet, 1H, *J*=6.7 Hz, C_3-H), 1.90 (d, 1H, *J*=5.5 Hz, O<u>H</u>), 1.15 (d, 3H, *J*=6.7 Hz, C_3-C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 139.03 (C_2), 137.35 (*i*-Ph), 128.44 (*m*-Ph), 128.07 (*o*-Ph), 127.88 (*p*-Ph), 116.85 (C_1), 85.94 (C_6), 81.74 (C_5), 71.56 (Ph<u>C</u>H$_2$O), 66.17 (C_4), 57.35 (C_7), 44.29 (C_3), 15.26 (C_3-<u>C</u>H$_3$); ***syn*-isomer (7b)**; 5.87 (ddd, *J*=17.7, 10.1, 7.9 Hz, C_2-H), 5.21-5.16 (m, C_1-H), 4.33 (dd, *J*=3.5, 1.3 Hz, C_4-H; after exchanging with D_2O), 4.22 (d, *J*=1.2 Hz, C_7-H), 1.94 (d, *J*=7.6 Hz, O<u>H</u>), 1.14 (d, *J*=6.7 Hz, C_3-C<u>H</u>$_3$).

3-Methyl-1-undecen-5-yn-4-ol

***anti*-isomer (6c).** IR (film) 3409 (br s), 2207 (w), 1053 (s), 1018 (s), 913 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, 1H, *J*=17.1, 10.4, 7.6 Hz, C_2-H), 5.15 (d, 1H, *J*=17.1 Hz, C_1-H), 5.14 (d, 1H, *J*=10.4 Hz, C_1-H), 4.18 (dt, 1H, *J*=6.4, 1.8 Hz, C_4-H; after exchanging with D_2O), 2.42 (sextet, 1H, *J*=6.7 Hz, C_3-H), 2.21 (dt, 2H, *J*=7.0, 1.8 Hz, C_7-H), 1.80 (d, 1H, *J*=5.2 Hz, O<u>H</u>), 1.51 (sextet, 2H, C_8-H), 1.40-1.27 (m, 4H, C_9C_{10}-H), 1.12 (d, 3H, *J*=6.7 Hz, C_3-C<u>H</u>$_3$), 0.89 (t, 3H, *J*=7.0 Hz, C_{11}-H); ^{13}C NMR ($CDCl_3$) δ 139.54 (C_2), 116.46 (C_1), 86.59 (C_6), 79.38 (C_5), 66.36 (C_4), 44.70 (C_3), 30.98 (C_9), 28.31 (C_8), 22.14 (C_{10}), 18.62 (C_7), 15.24 (C_3-<u>C</u>H$_3$), 13.95 (C_{11}); ***syn*-isomer (7c)**; 4.25 (br d, *J*=6.4, 1.8 Hz, C_4-H; after exchanging with D_2O), 1.81 (d, *J*=6.4 Hz, O<u>H</u>).

4-Methyl-1-trimethylsilyl-5-hexen-1-yn-3-ol

***anti*-isomer (6d).** IR (film) 3367 (br s), 2966 (s), 2171 (w), 1250 (s), 1025 (s), 913 (m), 850 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (ddd, 1H, J=17.5, 11.1, 7.7 Hz, C_5-H), 5.164 (d, 1H, J=17.5 Hz, C_6-H), 5.156 (d, 1H, J=11.0 Hz, C_6-H), 4.18 (d, 1H, J=6.9 Hz, C_3-H; after exchanging with D_2O), 2.44 (sextet, 1H, J=7.0 Hz, C_4-H), 1.86 (d, 1H, J=5.5 Hz, OH), 1.13 (d, 3H, J=7.0 Hz, C_4-CH_3), 0.17 (s, 9H, $SiMe_3$); ^{13}C NMR ($CDCl_3$) δ 139.12 (C_5), 116.76 (C_6), 104.98 (C_2), 90.48 (C_1), 66.50 (C_3), 44.37 (C_4), 15.28 (C_4-CH_3), −0.18 ($SiMe_3$); ***syn*-isomer (7d)**: 4.25 (d, J=4.8 Hz, C_3-H; after exchanging with D_2O), 1.90 (d, J=7.7 Hz, OH).

Representative Procedure for the Reactions of Aldehydes with Crotyl Tributylstannane (5c)

To a stirred solution of the aldehyde (1 mmol) in CH_2Cl_2 (15 mL) was added BF_3 etherate (0.31 mL, 2.5 mmol) at −78 ℃, followed by a solution of crotyltributylstannane (690 mg, 2 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at −78 ℃ for 2 h, quenched with saturated aqueous $NaHCO_3$ solution and allowed to warm to room temperature. The layers were separated, and the aqueous phase was extracted with ether. The combined extract was washed with brine, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give *syn*-homoallylic alcohol as the major diastereomer.

4-Methyl-1-triisopropylsilyl-5-hexen-1-yn-3-ol

***syn*-isomer (7e).** ^1H NMR ($CDCl_3$) δ 5.88 (ddd, 1H, J=16.1, 12.5, 8.1 Hz, C_5-H), 5.172 (d, 1H, J=16.1 Hz, C_6-H), 5.168 (d, 1H, J=12.5 Hz, C_6-H), 4.28 (d, 1H, J=5.1 Hz, C_3-H; after exchanging with D_2O), 2.47 (sextet, 1H, J=7.0 Hz, C_4-H), 1.92 (d, 1H, J=8.1 Hz, OH), 1.13 (d, 3H, J=6.6 Hz, C_4-CH_3), 1.07 (s, 21H, *i*-Pr); ^{13}C NMR ($CDCl_3$) δ 138.76 (C_5), 117.26 (C_6), 106.56 (C_2), 86.71 (C_1), 66.52 (C_3), 44.42 (C_4), 18.56 (*i*-Pr), 15.83 (C_4-CH_3), 11.15 (SiCH); ***anti*-isomer (6e)**: ^1H NMR ($CDCl_3$) δ 5.83 (ddd, J=17.6, 10.3, 7.3 Hz, C_5-H), 5.16 (d, 1H, J=17.6 Hz, C_6-H), 5.14 (d, 1H, J=10.3 Hz, C_6-H), 4.25 (d, J=6.6 Hz, C_3-H; after exchanging with D_2O), 2.48 (sextet, 1H, J=7.0 Hz, C_4-H), 1.87 (d, J=5.1 Hz, OH), 1.15 (d, 3H, J=8.1 Hz, C_4-CH_3); ^{13}C NMR ($CDCl_3$) δ 139.27 (C_5), 116.51 (C_6), 106.91 (C_2), 86.63 (C_1), 66.65 (C_3), 44.42 (C_4), 17.68 (*i*-Pr), 15.05 (C_4-CH_3), 12.27 (SiCH).

4-Methyl-1-(*tert*-butyldiphenyl)silyl-5-hexen-1-yn-3-ol

***syn*-isomer (7f).** ^1H NMR ($CDCl_3$) δ 7.80-7.35 (aromatic), 5.96 (ddd, 1H, J=16.8, 10.3, 8.1 Hz, C_5-H), 5.23 (d, 1H, J=16.8 Hz, C_6-H), 5.22 (d, 1H, J=10.3 Hz, C_6-H), 4.43 (d, 1H, J=6.6 Hz, C_3-H; after exchanging with D_2O), 2.58 (sextet, 1H, J=7.3 Hz, C_4-H), 1.22 (d, 3H, J=6.6 Hz, C_4-CH_3), 1.09 (s, 27H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 138.65 (C_5), 117.50 (C_6), 108.99 (C_2), 86.01 (C_1), 66.68 (C_3), 44.45 (C_4), 27.04 (*t*-Bu), 18.50 (SiC), 15.88 (C_4-CH_3); ***anti*-isomer (6f)**: 5.90 (ddd, J=16.8, 10.3, 7.5 Hz, C_5-H), 5.22 (d, 1H, J=16.8 Hz, C_6-H), 5.19 (d, 1H, J=10.3 Hz, C_6-H), 4.40 (d, J=5.9 Hz, C_3-H; after exchanging with D_2O), 2.50 (sextet, 1H, J=7.0 Hz, C_4-H), 1.23 (d, 3H, J=6.6 Hz, C_4-CH_3); ^{13}C NMR ($CDCl_3$) δ 139.03 (C_5), 116.80 (C_6), 109.26 (C_2), 85.85 (C_1), 66.78 (C_3), 44.34 (C_4), 27.04 (*t*-Bu), 18.50 (SiC), 15.16 (C_4-CH_3).

Determination of the Stereochemistry of the Allylation Products. (A) (*S,S*)-3-(2-Phenylethyl)-oxiranemethanol (8)

An oven-dried 100 mL round-bottomed flask equipped with a magnetic stirbar was charged with 400 mg of 4 Å powdered, activated molecular sieves and 30 mL of dry CH_2Cl_2. The flask was cooled to −20 ℃. L-(+)-Diisopropyl tartrate (130 μL, 0.62 mmol), $Ti(O$-*i*-$Pr)_4$ (150 μL, 0.53 mmol) and TBHP (3 mL, 15.6 mmol, 5.2 M in isooctane) were added sequentially with stirring. The resulting mixture was stirred at −20 ℃ for 1 h. (*E*)-5-Phenyl-2-penten-1-ol (1 g, 6.15 mmol), dissolved in 10 mL of CH_2Cl_2 was then introduced *via* canula. The mixture was stirred for an additional 3 h at −20 ℃. The cold reaction mixture was quenched with 0.5 mL of a 10% aqueous solution of sodium hydroxide saturated with sodium chloride, then ether was added. After addition of $MgSO_4$ and Celite, filtration through a pad of Celite, the concentrated crude product was purified by column chromatography on silica gel to give epoxy alcohol **8** (1 g, 91.3%): IR (film) 3416 (br s), 1496 (m), 1454 (s), 1236 (m), 1089 (s), 1025 (vs), 737 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32-7.28 (m, 2H, Ph), 7.22-7.19 (m, 3H, Ph), 3.84 (ddd, 1H, J=12.7, 5.4, 2.5 Hz, C_1-H), 3.56 (ddd, 1H, J=12.7, 7.3, 4.4 Hz, C_1-H), 2.99 (dt, 1H, J=5.6, 2.5 Hz, C_3-H), 2.86 (ddd, 1H, J=4.4, 2.4, 2.5 Hz, C_2-H), 2.84 (ddd, 1H, J=13.8, 8.5, 6.0 Hz, $PhCH_2$), 2.74 (dt, 1H, J=13.8, 8.1 Hz, $PhCH_2$), 1.97-1.83 (m, 2H, $PhCH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 141.01 (*i*-Ph), 128.44 (*o*-Ph), 128.33 (*m*-Ph), 126.08 (*p*-Ph), 61.44 (C_1), 58.68 (C_2), 55.33 (C_3), 33.29 ($PhCH_2CH_2$), 32.14 ($PhCH_2$).

(*R,S*)-2-Methyl-5-phenyl-1,3-pentanediol (9)

A slurry of copper iodide (3.3 g, 16.8 mmol) in ether (10 mL) under argon was cooled to −78 ℃. Methyllithium (25 mL, 1.5 M in ether, 33.5 mmol) was added *via* syringe and the resulting pale brown solution stirred for 20 min. A solution of the epoxy alcohol **8** (1.2 g, 6.7 mmol) in dry ether (10 mL) was then added dropwise and further stirred for 4 h. After the reaction was quenched with NH_4OH saturated with NH_4Cl, the crude product was treated with excess $NaIO_4$ in THF/water (5 : 1) for 1 h. After the usual workup, the crude product was purified by flash chromatography (30% EtOAc/Hexanes) to afford 1,3-diol **9** (530 mg, 40.5%): IR (film) 3360 (br s), 2924 (s), 1454 (m), 1025 (s), 913 (s), 737 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31-7.18 (m, 5H, Ph), 3.75 (dd, 1H, J=10.8, 3.7 Hz, C_1-H), 3.58 (dd, 1H, J=10.8, 7.4 Hz, C_1-H), 3.57 (m, 1H, C_3-H), 2.83 (ddd, 1H, J=13.7, 10.2, 5.3 Hz, C_5-H), 2.65 (ddd, 1H, J=13.7, 10.0, 5.3 Hz, C_5-H), 1.89 (dddd, 1H, J=13.7, 10.2, 6.5, 3.1 Hz, C_4-H), 1.78 (dddd, 1H, J=13.7, 10.0, 8.9, 5.3 Hz, C_4-H), 1.74 (m, 1H, C_2-H), 0.89 (d, 3H, J=7.0 Hz, C_2-CH_3); ^{13}C NMR ($CDCl_3$) δ 142.12 (*i*-Ph), 128.38 (*o*-Ph), 128.31 (*m*-Ph), 125.80 (*p*-Ph), 76.54 (C_3), 67.56 (C_1), 39.81 (C_2), 37.06 (C_4), 31.63 (C_5), 13.78 (C_2-CH_3).

(*R,S*)-2-Methyl-5-phenyl-1-toluenesulfonyloxy-3-pentanol (10)

A solution of the diol **9** (480 mg, 2.46 mmol) in 10 mL of dry pyridine was treated with *p*-toluenesulfonyl chloride (552 mg, 2.9 mmol) at 0 ℃ for 7 h. The solution was then diluted with aqueous $NaHCO_3$ and extracted with EtOAc (3× 20 mL). The combined extracts were dried over $MgSO_4$, filter-

ed, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel to give tosylate **10** (680 mg, 80%): IR (film) cm^{-1} 3550 (br s), 1349 (vs), 1180 (vs), 962 (s), 913 (s), 730 (vs); ^1H NMR ($CDCl_3$) δ 7.78 (d, 2H, J=8.3 Hz, Ts-*o*), 7.34 (d, 2H, J=8.3 Hz, Ts-*m*), 7.30-7.16 (m, 5H, Ph), 4.16 (dd, 1H, J=9.7, 5.1 Hz, C_1-H), 4.04 (dd, 1H, J=9.7, 4.2 Hz, C_1-H), 3.51 (ddd, 1H, J=9.2, 7.4, 2.8 Hz, C_3-H), 2.81 (ddd, 1H, J=13.8, 10.2, 5.1 Hz, C_5-H), 2.62 (ddd, 1H, J=13.8, 10.2, 6.5 Hz, C_5-H), 2.44 (s, 3H, Ts-CH_3), 1.84 (m, 1H, C_2-H), 1.82 (m, 1H, C_4-H), 1.66 (ddd, 1H, J=18.9, 9.7, 5.1 Hz, C_4-H), 0.93 (d, 3H, J=6.9 Hz, C_2-CH_3); ^{13}C NMR ($CDCl_3$) δ 144.81 (C-CH_3), 141.76 (*i*-Ph), 132.83 (SO_2-C), 129.85 (C-C-CH_3), 128.46 (*o*-Ph), 128.35 (*m*-Ph), 127.88 (SO_2-C-C), 125.94 (*p*-Ph), 72.39 (C_1), 71.97 (C_3), 38.98 (C_2), 36.05 (C_4), 31.99 (C_5), 21.64 (Ts-CH_3), 13.58 (C_2-CH_3).

(*S*,*R*)-4-Methyl-1-phenyl-3-hexanol (11)

After a solution (0.3 M, 3.4 mL, 1 mmol) of lithium dimethylcuprate was prepared as above, a solution of tosylate **10** (80 mg, 0.23 mmol) in dry ether (2 mL) was added dropwise. The resulting mixture was further stirred for 4 h. After usual workup, the crude product was purified by column chromatography on silica gel to give alcohol **11** (40 mg, 91%): IR (film) 3310 (s), 2959 (vs), 1454 (s), 1032 (s), 906 (m), 737 (s), 695 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32-7.18 (m, 5H, Ph), 3.57 (ddd, 1H, J=9.3, 5.1, 3.0 Hz, C_3-H), 2.95 (ddd, 1H, J=13.7, 10.0, 5.3 Hz, C_1-H), 2.74 (ddd, 1H, J=13.7, 9.7, 6.9 Hz, C_1-H), 1.78 (dddd, 1H, J=14.3, 9.3, 6.9, 5.3 Hz, C_2-H), 1.69 (dddd, 1H, J=14.3, 10.0, 9.7, 5.1 Hz, C_2-H), 1.50 (m, 1H, C_5-H), 1.50 (m, 1H, C_4-H), 1.23 (m, 1H, C_5-H), 0.984 (t, 3H, J=7.3 Hz, C_6-H), 0.977 (d, 3H, J=6.8 Hz, C_4-CH_3); ^{13}C NMR ($CDCl_3$) δ 142.36 (*i*-Ph), 128.41 (*o*-Ph), 128.35 (*m*-Ph), 125.74 (*p*-Ph), 75.14 (C_3), 40.70 (C_4), 35.19 (C_2), 32.47 (C_1), 24.66 (C_5), 14.64 (C_4-CH_3), 11.68 (C_6).

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