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Supporting Information

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Gold(I)-Catalyzed Intramolecular Enantioselective Hydroalkoxylation of Allenes

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Experimental procedures, analytical and spectroscopic data for products of catalytic reactions (25 pages).

Experimental

General Methods. Catalytic reactions were performed in sealed glass tubes under an atmosphere of dry nitrogen unless noted otherwise. NMR spectra were obtained on a Varian spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in $CDCl_3$ unless otherwise noted. IR spectra were obtained on a Bomen MB-100 FT IR spectrometer. Gas chromatography was performed on a Hewlett-Parkard 5890 gas chromatograph equipped with a 25 m polydimethylsiloxane capillary column. Chiral HPLC was performed on a Hewlett-Parkard chromatograph equipped with a 25 cm Chiralpak AD-H column. Chiral GC was performed on a Hewlett-Parkard 5890 gas chromatograph equipped with a 20 m × 0.25 mm Chiraldex GTA column (Advanced Separation Technologies). Flash column chromatography was performed employing 200-400 mesh silica gel (EM). Thin layer chromatography (TLC) was performed on silica gel 60 F254. Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ).

Diisopropylamine, CuBr, $LiAlH_4$, acetic anhydride, pyridine, palladium(II) acetate, benzoyl chloride, 4-(dimethylamino)pyridine, methyl isobutyrate, (*R*)-tetrahydrofurfuryl alcohol (Aldrich), tetrahexylammonium chloride (Sigma-Aldrich), *n*-BuLi (2.5 M solution in hexanes), anhydrous dioxane (Acros), and $Pd_2(dba)_3$ (Strem) were used as received. 2,2-Diphenyl-4,5-hexadien-1-ol (**1**), *rac*-**5**, (*R*)-**5**, *rac*-**7**, *rac*-**9**, **11**, 2,2-diphenyl-5,6-dodecadien-1-ol, 4-methyl-2,2-diphenyl-5,6-heptadien-1-ol, 1-phenyl-5,6-heptadien-1-ol, and 2,3-pentadienyl benzoate were synthesized employing published procedures.[1]

2,2-Dimethyl-4,5-heptadien-1-ol (Table 2, entry 4; S1). A solution of methyl isobutyrate (0.82 g, 8.0 mmol) in THF (10 mL) was added dropwise over 30 min to a solution of LDA (9.6 mmol) in THF (30 mL) at –78 °C and stirred for 30 min [mixture **A**]. A solution of $Pd_2(dba)_3$ (0.22 g, 0.24 mmol) and triphenylphosphine (0.76 g, 2.9 mmol) in THF (20 mL) were stirred at room temperature for 20 min. To this, a solution of 2,3-pentadienyl benzoate (1.8 g, 9.6 mmol) in THF (5 mL) was added and the resulting mixture was stirred at room temperature for 10 min [mixture **B**]. Mixture **B** was added to mixture **A** via cannula at –78 °C and the resulting mixture was warmed slowly to room temperature, stirred overnight, and treated with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated under vacuum. Chromatography of the residue (pentane–ether = 20:1) gave a 1:1 mixture of methyl isobutyrate and methyl 2,2-dimethyl-4,5-heptadienoate that was used in the subsequent step without further purification. A solution of this 1:1 mixture (1.06 g) in ether (20 mL) was added dropwise to a suspension of $LiAlH_4$ (0.48 g, 13 mmol) in ether (30 mL) at 0 °C and the resulting suspension was stirred for 1 h. The reaction mixture was treated with aqueous NaOH and filtered through Celite. The filtrate was concentrated under vacuum. Chromatography of the residue (hexanes–EtOAc = 30:1 $\rightarrow$ 5:1) gave **S1** (320 mg, 29%, from methyl isobutyrate) as a colorless oil.

For S1: TLC (hexanes–EtOAc = 5:1): $R_f = 0.30$. ^1H NMR: δ 5.02-4.94 (m, 2 H), 3.31 (s, 2 H), 1.92-1.89 (m, 2 H), 1.72 (br s, 1 H), 1.61 (dd, $J = 4.0, 6.4$ Hz, 3 H), 0.86 (s, 3 H), 0.85 (s, 3 H). $^{13}C\{^1H\}$ NMR: δ 206.2, 86.4, 84.7, 71.6, 38.8, 36.0, 23.9, 23.8, 14.6. IR (neat, cm^{-1}): 3437, 3051, 2969, 1953, 1641, 1498, 1112, 1020, 841, 734. Anal. calcd (found) for $C_9H_{16}O$: C, 77.09 (76.98); H, 11.50 (11.46).

Hydroalkoxylation of allenyl alcohols

Optimization studies for the Au-catalyzed enantioselective conversion of **1** to **3** are depicted in Tables S1-S6 and in Scheme S1. Cyclic ethers **3**,[1] **6**,[1] **8**,[1] 4,4-dimethyl-2-(1-propenyl)tetrahydrofuran (**S2**),[2] **10**,[1] **12**,[1] 2-(1-heptenyl)-5,5-diphenyltetrahydropyran (**S3**), 3-methyl-5,5-diphenyl-2-vinyltetrahydropyran (**S4**), 2-phenyl-6-vinyltetrahydropyran (**S5**), and 2-heptyl-4,4-diphenyltetrahydrofuran (**S6**) have been previously reported.[1] Racemic samples of cyclic ethers were prepared according to published procedures.[1] An authentic sample of (*R*)-**10** (Z:E = 25:1, 84% ee) was synthesized in two steps from commercially available (*R*)-tetrahydrofurfuryl alcohol employing a published procedure.[3]

4,4-Diphenyl-2-vinyltetrahydrofuran (3).[1] A mixture of $Au_2[(S)\text{-}\mathbf{4}]Cl_2$ (5.1 mg, 3.1×10^{-3} mmol) and AgOTs (1.7 mg, 6.3×10^{-3} mmol) in toluene (0.4 mL) was stirred at room temperature for 10 min, cooled to –20 °C, treated with a solution of **1** (31.3 mg, 0.125 mmol) in toluene (0.6 mL), and the resulting suspension was stirred at –20 °C for 18 h. Column chromatography of the reaction mixture (hexanes–EtOAc = 50:1 → 20:1) gave **3** (20.9 mg, 67%) as a colorless oil. The enantiomeric excess of **3** was determined by chiral HPLC analysis (Figure S1).

All remaining enantioselective hydroalkoxylations were performed in an analogous manner. Chiral HPLC or GC analyses for enantiomerically enriched and racemic oxygen heterocycles are shown below.

Control experiments

In one experiment, a mixture of **11** (26.4 mg, 0.10 mmol), AgOTs (1.4 mg, 5.0×10^{-3} mmol), and (*S*)-**4** (2.9 mg, 2.5×10^{-3} mmol), in toluene (1.0 mL) was stirred at –20 °C for 24 h. GC analysis of the crude reaction mixture indicated no detectable formation of **12**. In a second experiment, a mixture of **11** (26.4 mg, 0.10 mmol), AgOTs (1.4 mg, 5.0×10^{-3} mmol), and (*S*)-**4** (2.9 mg, 2.5×10^{-3} mmol) in toluene (1.0 mL) was stirred at room temperature for 24 h. GC analysis of the crude reaction mixture indicated no detectable formation of **12**. In a third experiment, a mixture of **11** (39.6 mg, 0.15 mmol), TsOH (2.1 mg, 7.5×10^{-3} mmol), and (*S*)-**4** (4.3 mg, 3.8×10^{-3} mmol) in toluene (1.0 mL) was stirred at –20 °C for 24 h. GC analysis of the crude reaction mixture indicated no detectable formation of **12**.

Figure S1. Chiral HPLC trace of *rac*-**3** (left trace) and enantiomerically enriched **3** (right trace).

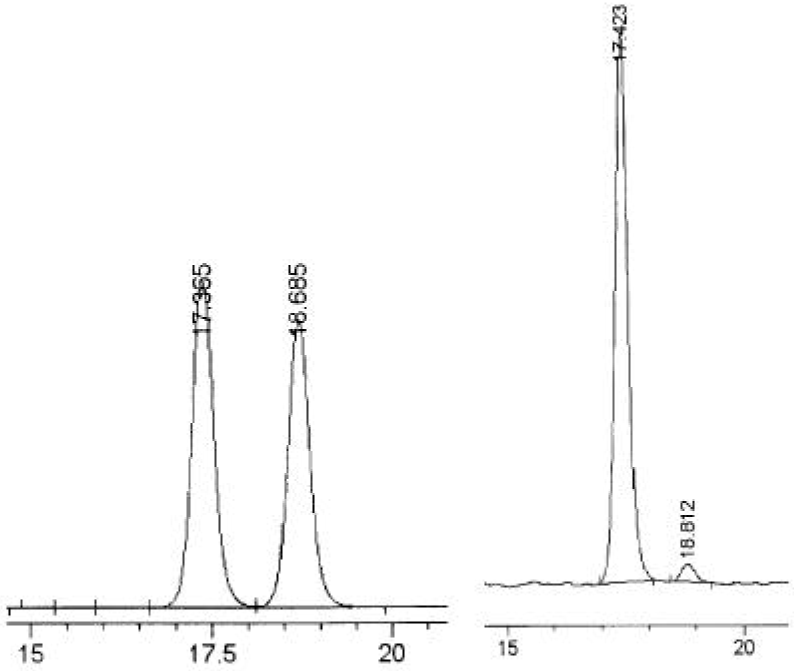


Figure S2. Chiral HPLC trace of racemic (*E*)-**6** (left trace) and of a racemic 1:1 mixture of (*E*)- and (*Z*)-**6** (right trace).

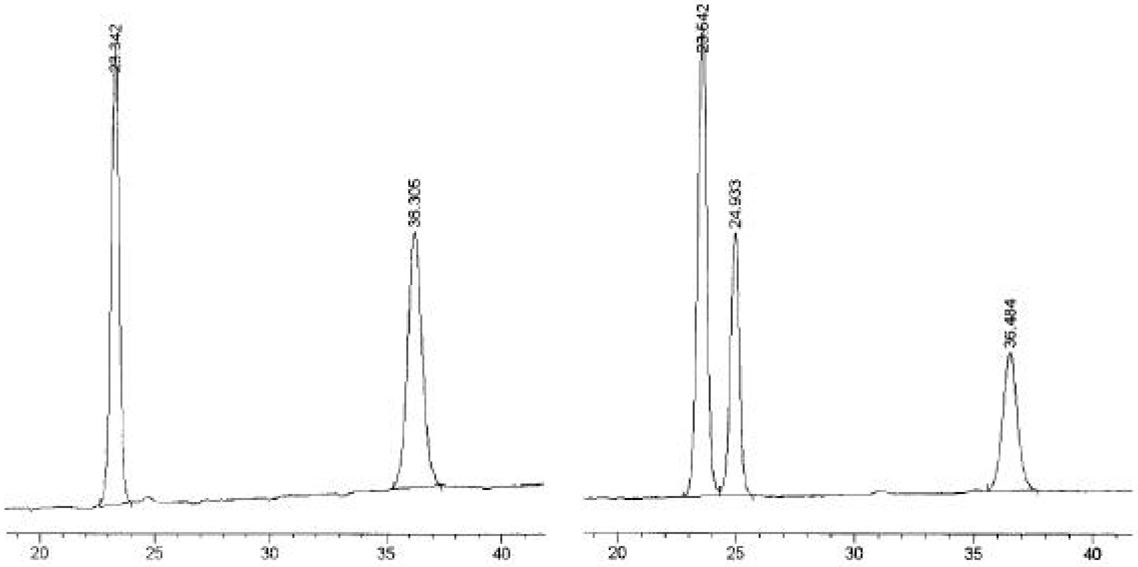


Figure S3. Chiral HPLC trace of a 1:1 mixture of enantiomerically enriched (*E*)-**6** and (*Z*)-**6** generated from *rac*-**5** (left trace) and enantiomerically enriched (*Z*)-**6** generated from (*R*)-**5**.

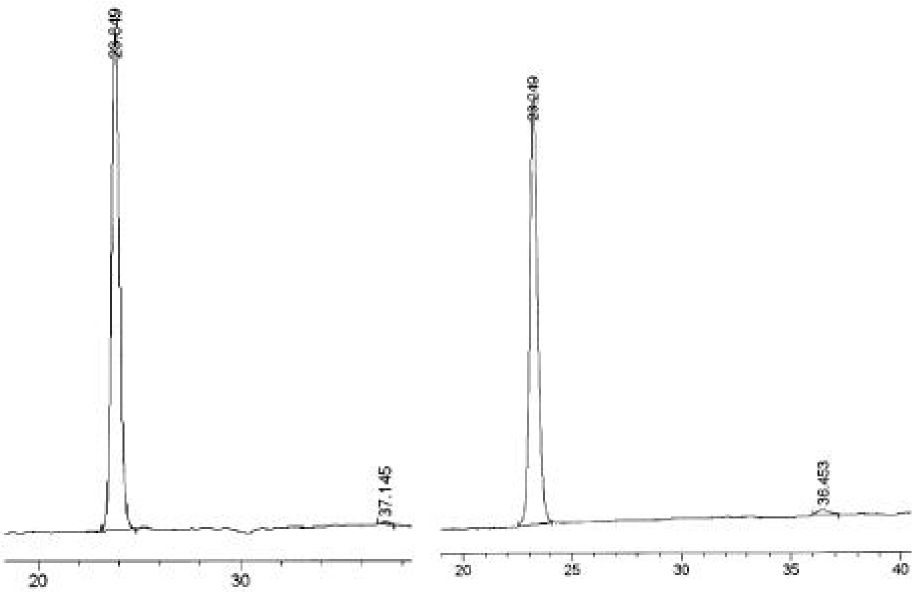


Figure S4. Chiral HPLC trace of *rac*-**S6** (left trace) and enantiomerically enriched **S6** (right trace) .

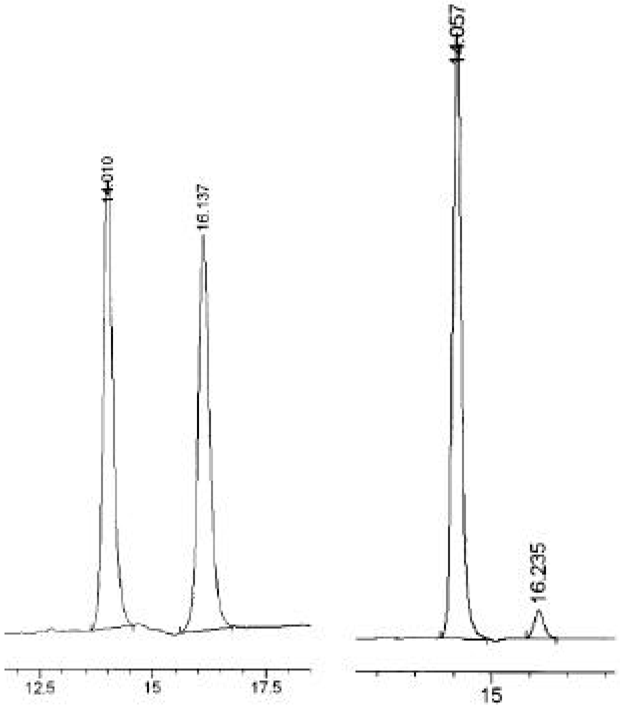


Figure S5. Chiral HPLC traces of a 6.1:1 E/Z mixture of *rac*-**8** (left trace) and a 1:1 E/Z mixture of enantiomerically enriched **8** (right trace).

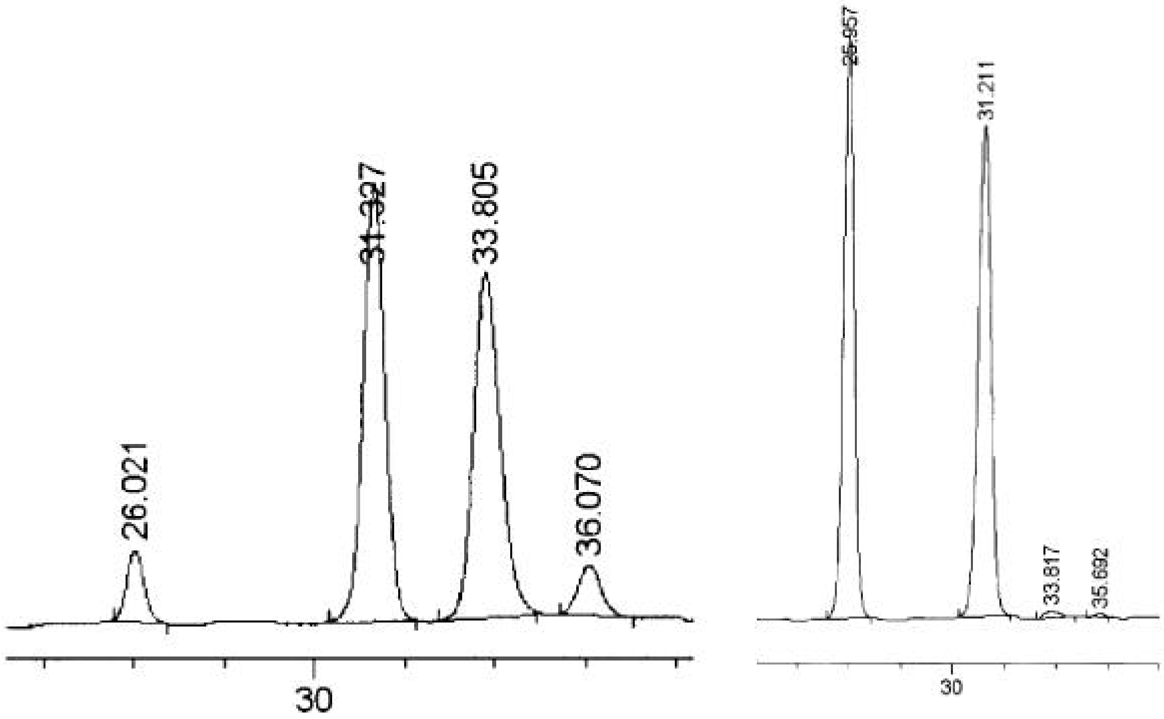


Figure S6. Chiral GC trace of a 5.5:1 E/Z mixture of racemic **S2**.

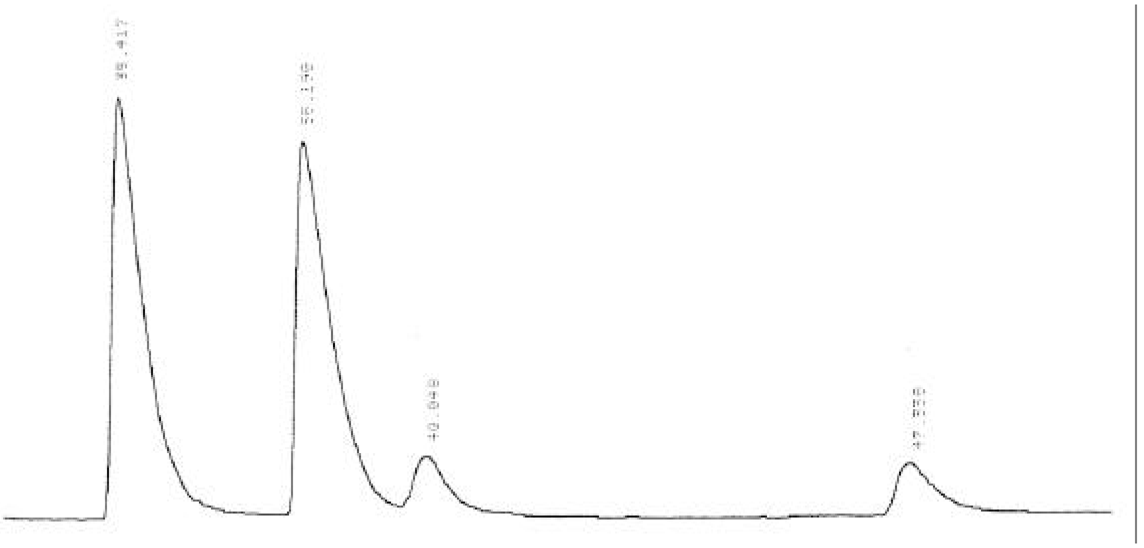
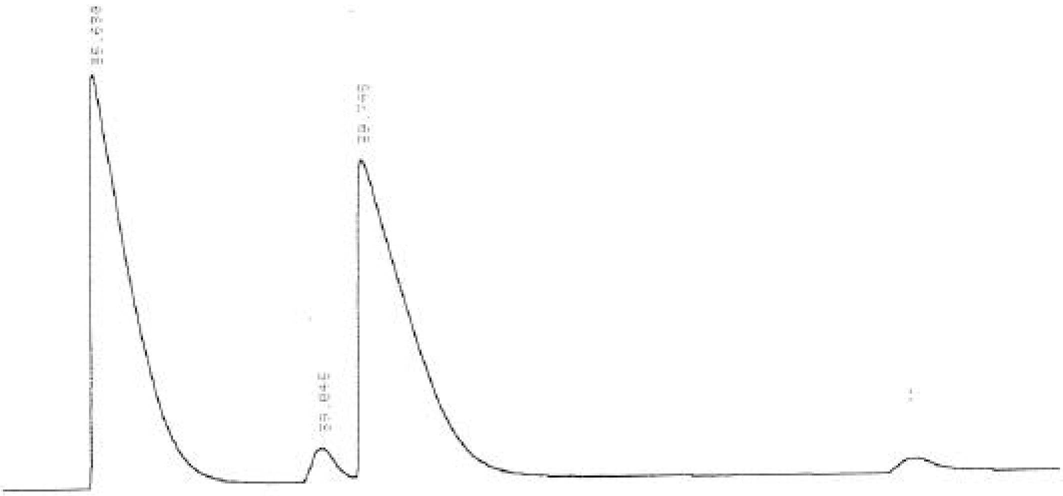


Figure S7. Chiral GC trace of a 1:1 E/Z mixture of enantiomerically enriched **S2**.



Enantioselective hydroalkoxylation of *rac*-9. A mixture of $Au_2[(S)\text{-}\mathbf{4}]Cl_2$ (5.1 mg, 3.1 × 10^{-3} mmol) and AgOTs (1.7 mg, 6.3 × 10^{-3} mmol) in toluene-d_8 (0.4 mL) was stirred at room temperature under N_2 for 10 min, cooled to –20 °C, and treated with a solution of *rac*-**9** (17.5 mg, 0.125 mmol) in toluene-d_8 (0.6 mL). The resulting mixture was stirred at –20 °C for 24 h and filtered through short plug of silica gel. ^{1}H NMR analysis revealed formation of a 1.5:1 mixture of (*E*)-**10** and (*Z*)-**10** in 94% yield versus DMSO internal standard.

Figure S8. Chiral GC trace of a 5.3:1 E/Z mixture of *rac*-**10**.

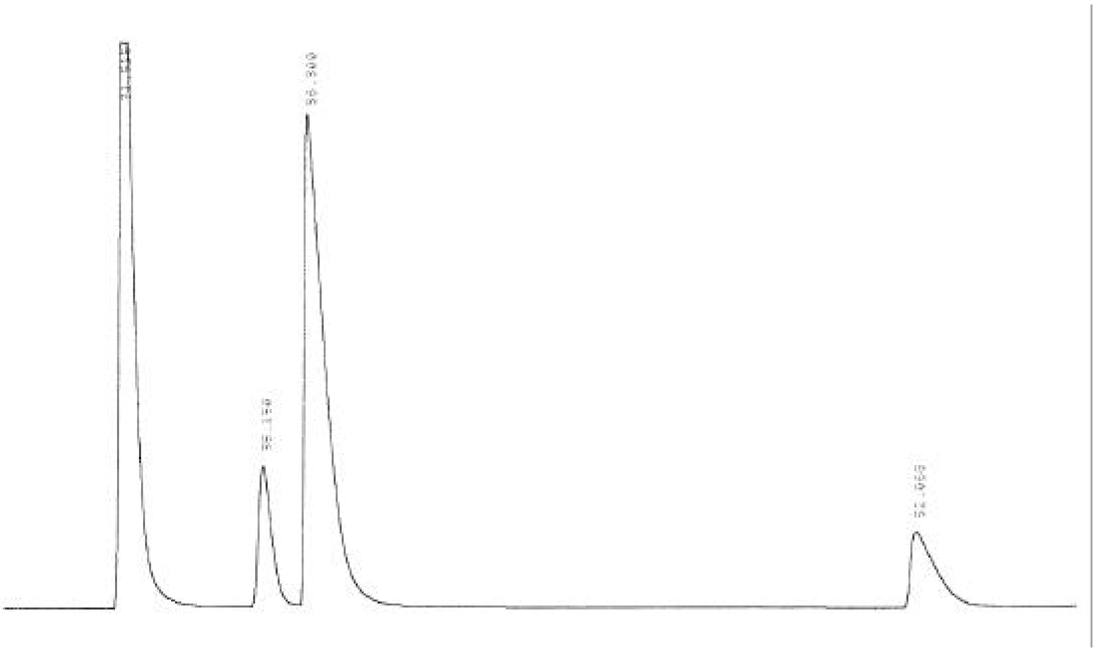


Figure S9. Chiral GC trace of an authentic sample of a 25:1 Z/E mixture of (*R*)-**10** (84% ee).

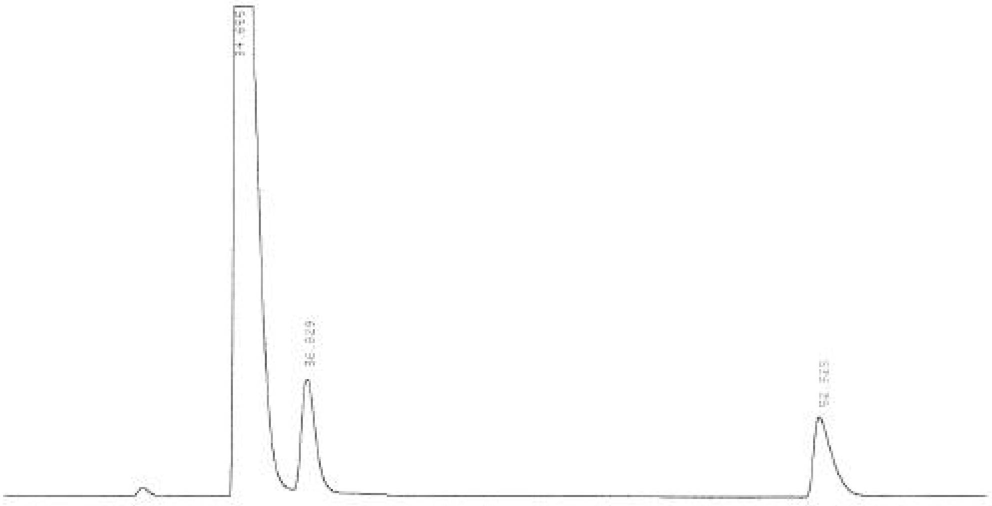


Figure S10. Chiral GC trace of a 1.5:1 E/Z mixture of enantiomerically enriched **10** generated via Au-catalyzed enantioselective hydroalkoxylation of *rac*-**9**.

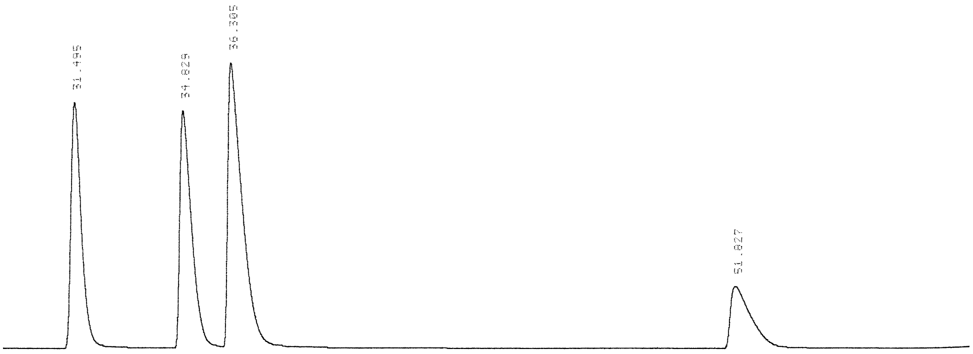


Figure S11. Chiral HPLC trace of *rac*-**12** (left trace) and enantiomerically enriched **12** (right trace).

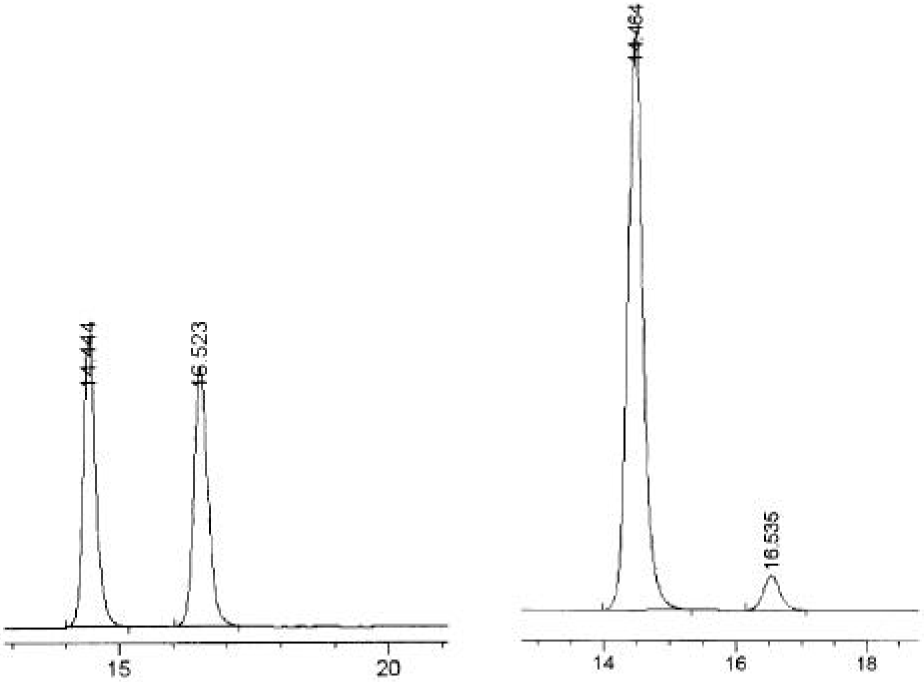


Figure S12. Chiral HPLC trace of a 20:1 E/Z mixture of racemic **S3** (left trace) and a 1.5:1 E/Z mixture of enantiomerically enriched **S3** (right trace).

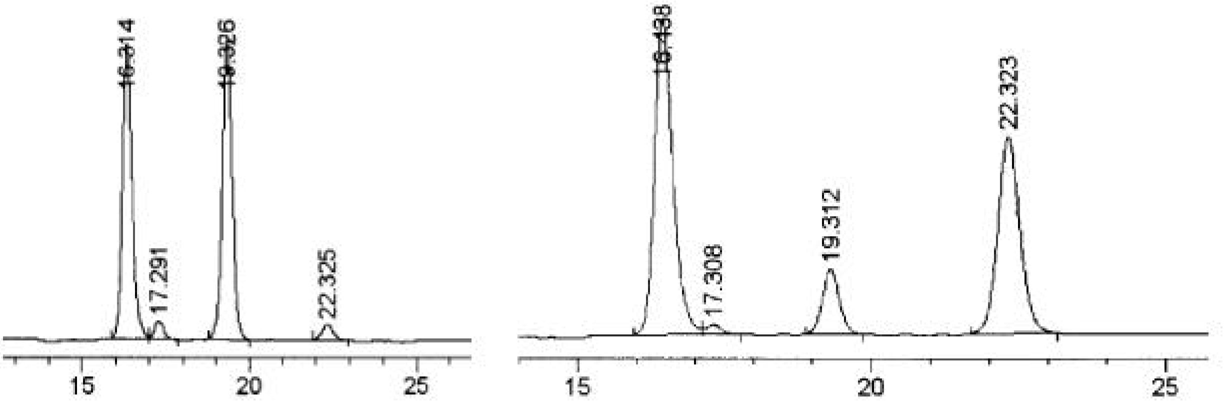
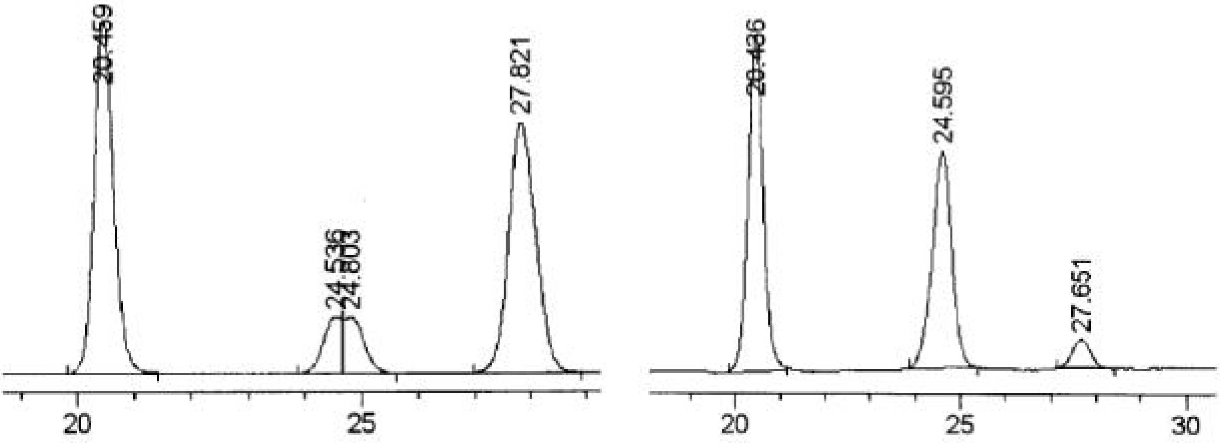


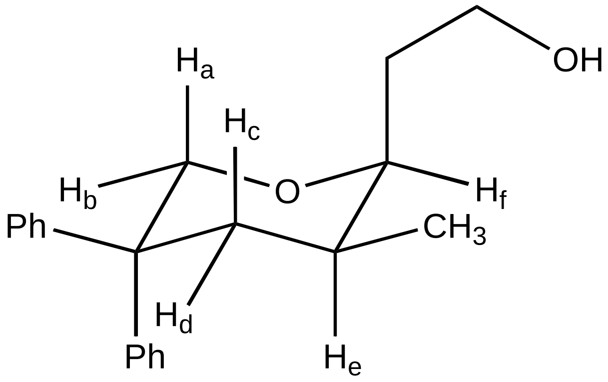
Figure S13. Chiral HPLC trace of a 5.6:1 trans/cis mixture of racemic **S4** (left trace) and a 1.3:1 trans:cis mixture of enantiomerically enriched **S4** (right trace).



While the enantiomeric excess of *trans*-**S4** was determined directly by chiral HPLC (Figure S13), the peaks for *cis*-**S4** were not resolved by chiral HPLC. Therefore, the enantiomeric excess of *cis*-**S4** was determined by chiral HPLC analysis of the corresponding hydroboration/oxidation product *cis*-2-(3-methyl-5,5-diphenyl-tetrahydropyran-2-yl)ethanol (*cis*-**S7**) (Figure S14).

***cis*-S7**. A solution of 9-BBN in THF (0.23 mL, 0.12 mmol) was added to a solution of a 5.6:1 trans/cis mixture of **S4** (22 mg, 0.078 mmol) in THF (2.5 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3 h, cooled to 0 °C, and treated sequentially with 30% H_2O_2 (96 mg, 0.84 mmol) and 3 M NaOH (0.16 mL, 0.47 mmol). The resulting mixture was stirred at room temperature overnight and treated with brine. The layers were separated and the aqueous layer was extracted with ether (3 × 5 mL). The combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. Chromatography of the residue (hexanes–EtOAc = 15:1 → 2:1) gave *cis*-**S7** (3.0 mg, 14%) as a colorless oil. TLC (hexanes–EtOAc = 5:1): $R_f = 0.14$. ^{1}H NMR (Figure S15): d 7.37-7.12 (m, 10 H), 4.68 (dd, J = 3.2, 12.0 Hz, 1 H), 3.75 (td, J = 4.8, 5.6 Hz, 2 H), 3.49 (d, J = 12.0 Hz, 1 H), 3.26 (dt, J = 2.8, 9.6 Hz, 1 H), 2.83 (t, J = 5.2 Hz, 1 H), 2.39 (td, J = 3.2, 13.2 Hz, 1 H), 2.06 (t, J = 12.4 Hz, 1 H), 1.91-1.85 (m, 1 H), 1.68-1.59 (m, 1 H), 1.47-1.36 (m, 1 H), 0.84 (d, J = 6.8 Hz, 3 H). ^{13}C{^{1}H} NMR (Figure S16): d 146.5, 146.1, 128.7, 128.5, 128.3, 127.0, 126.6, 126.0, 85.0, 74.9, 61.8, 47.0, 43.9, 34.7, 31.5, 18.2. IR (neat, cm^{-1}): 3430, 2974, 2842, 2810, 1586, 1493, 1458, 1403, 1330, 1121, 1080, 748, 701. HRMS calcd (found) for $C_{20}H_{24}O_2$ (M^+): 296.1776 (296.1772).

The stereochemistry of *cis*-**S7** was established from the ^{1}H NMR spectrum. In particular, the large 12.4 Hz coupling between H_c and H_e and the small 2.8 Hz coupling between H_e and H_f established the axial orientation of H_c and H_e and the equatorial relationship between H_e and H_f in a static chair conformer.



cis-**S7**

Figure S14. Chiral HPLC analysis of racemic (left trace) and enantiomerically enriched (right trace, 82% ee) *cis*-**S7**.

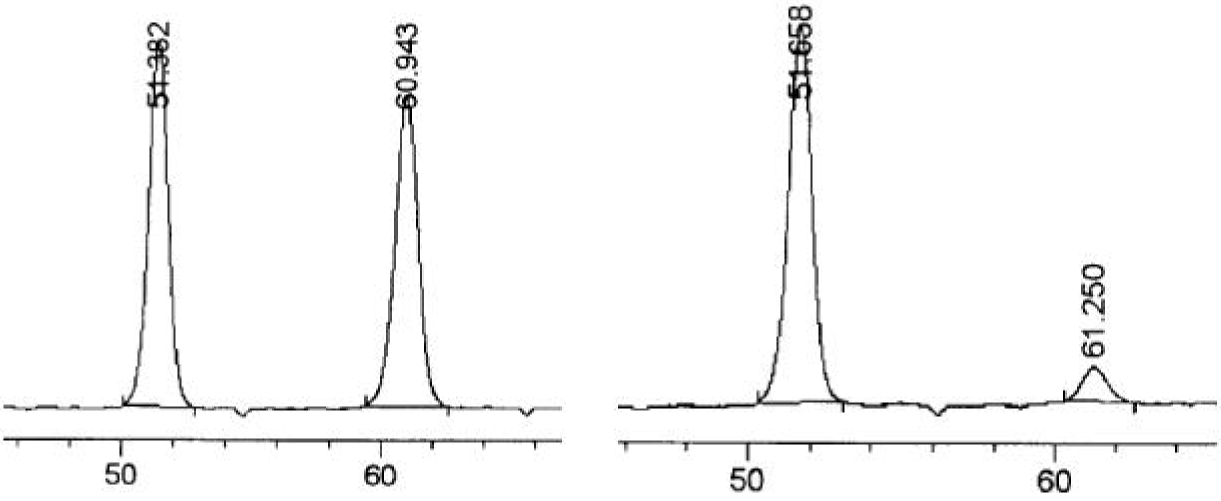


Figure S15. ^{1}H NMR spectrum of *cis*-**S7**.

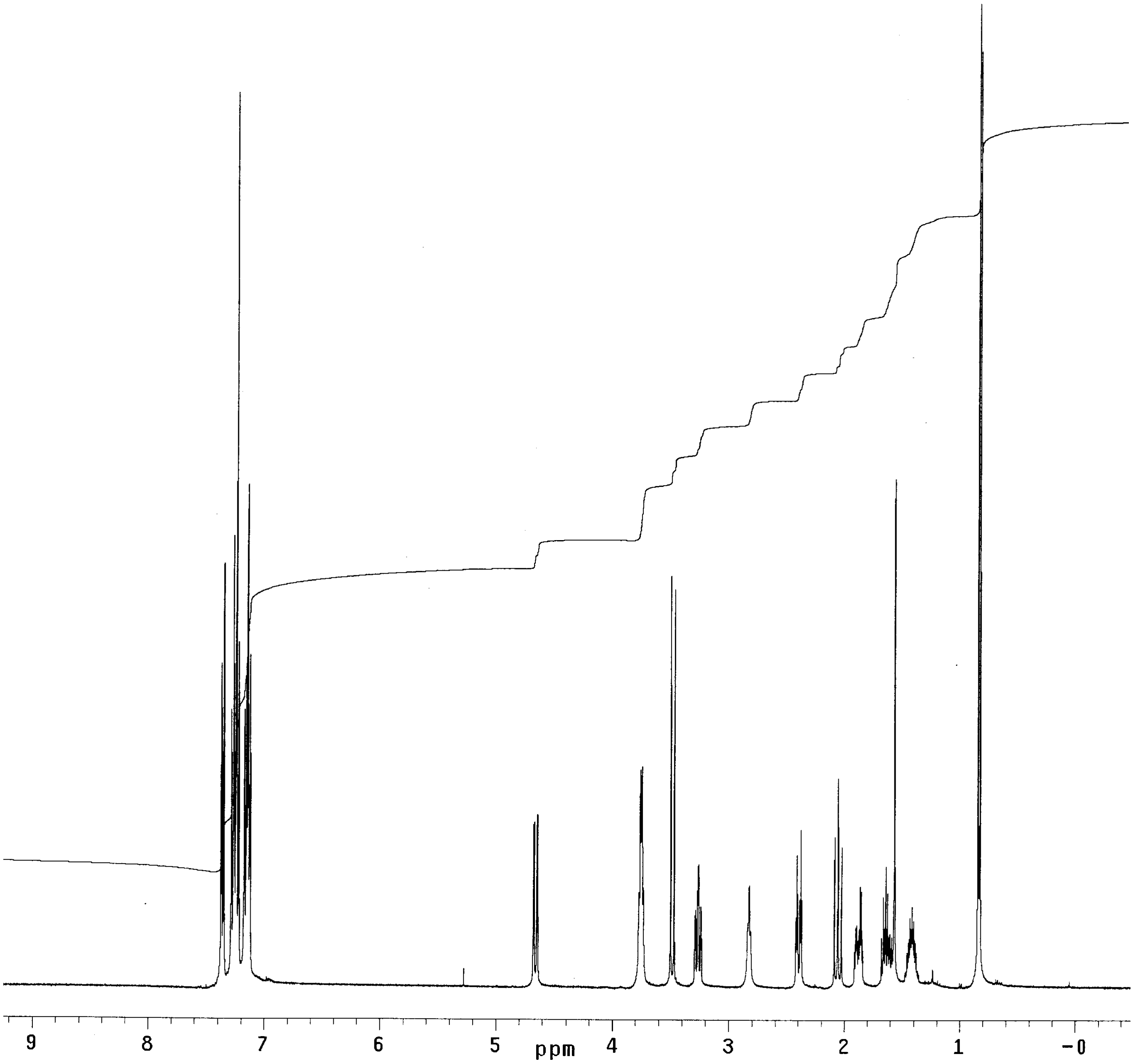


Figure S16. $^{13}C\{^1H\}$ NMR spectrum of *cis*-**S7**.

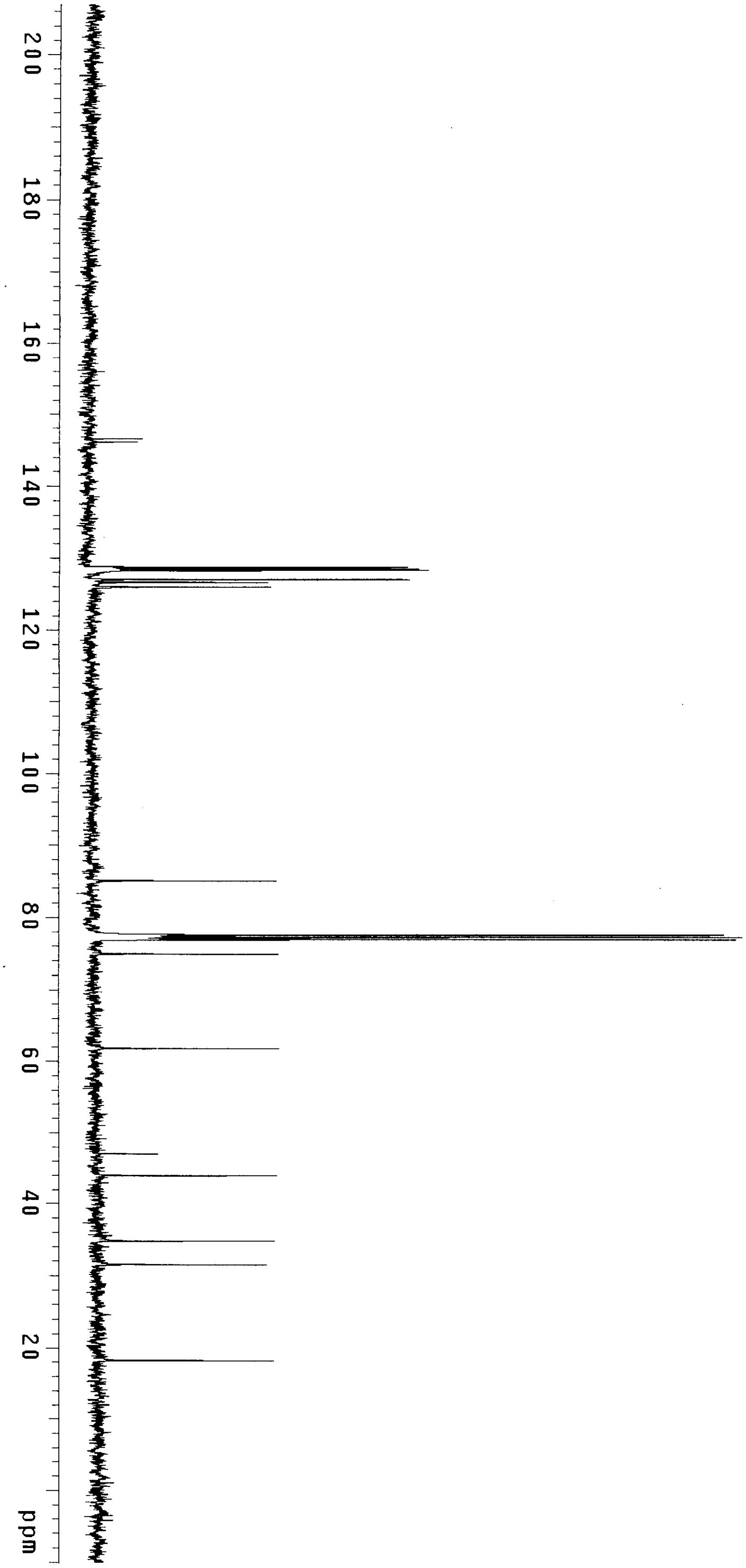
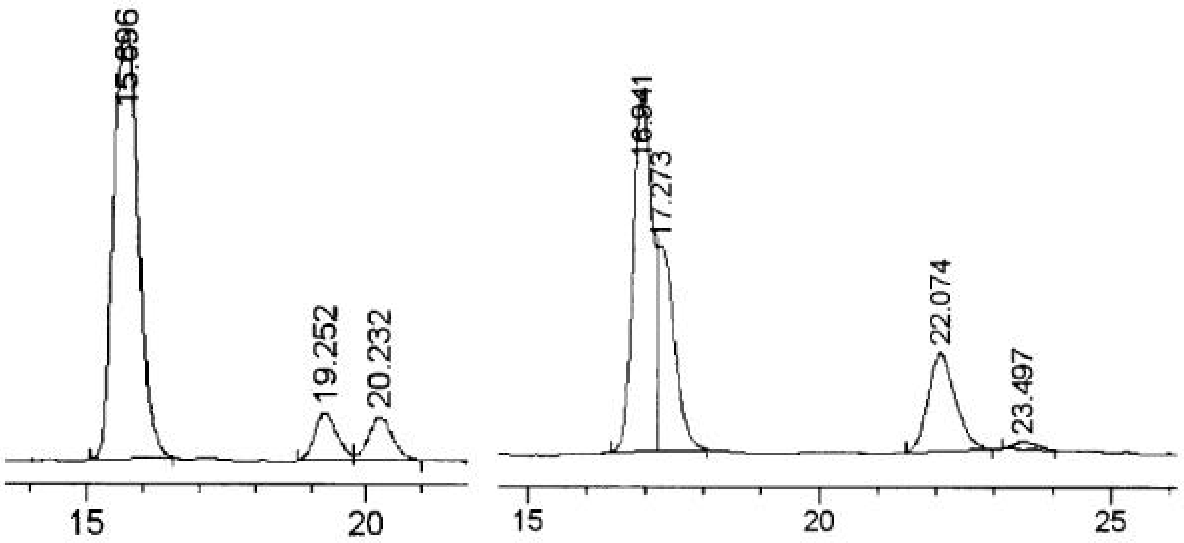


Figure S17. Chiral HPLC trace of a 7.2:1 cis:trans mixture of racemic **S5** (left trace) and a 1:3.3 trans:cis mixture of enantiomerically enriched **S5** (right trace).



The enantiomeric excess of *trans*-**S5** was directly determined by chiral HPLC (Figure S17). However, because the peaks of *cis*-**S5** were not resolved by chiral HPLC, the enantiomeric excess of *cis*-**S5** was determined by chiral HPLC analysis of *cis*-2-(6-phenyl-tetrahydro-2H-pyran-2-yl)ethanol (*cis*-**S8**; Figure S18), generated via hydroboration/oxidation of *cis*-**S5** employing a procedure analogous to that described for the conversion of *cis*-**S4** to *cis*-**S7**.

For *cis*-S8. Colorless oil, 56%. TLC (hexanes–EtOAc = 5:1): $R_f = 0.11$. ^{1}H NMR (Figure S19): d 7.30-7.20 (m, 5 H), 4.38 (dd, J = 2.0, 11.6 Hz, 1 H), 3.79-3.72 (m, 3 H), 2.84 (br s, 1 H), 1.95-1.23 (m, 8 H). ^{13}C{^{1}H} NMR (Figure S20): d 143.3, 128.5, 127.5, 125.9, 80.3, 79.4, 61.9, 38.3, 33.8, 31.5, 24.0. IR (neat, cm^{-1}): 3379, 3033, 2977, 2931, 1958, 1499, 1450, 1367, 1113, 843, 749, 699. HRMS calcd (found) for $C_{13}H_{18}O_2$ (M^+): 206.1307 (206.1305).

Figure S18. Chiral HPLC traces of racemic (left trace) and enantiomerically enriched (right trace, 45% ee) *cis*-**S8**.

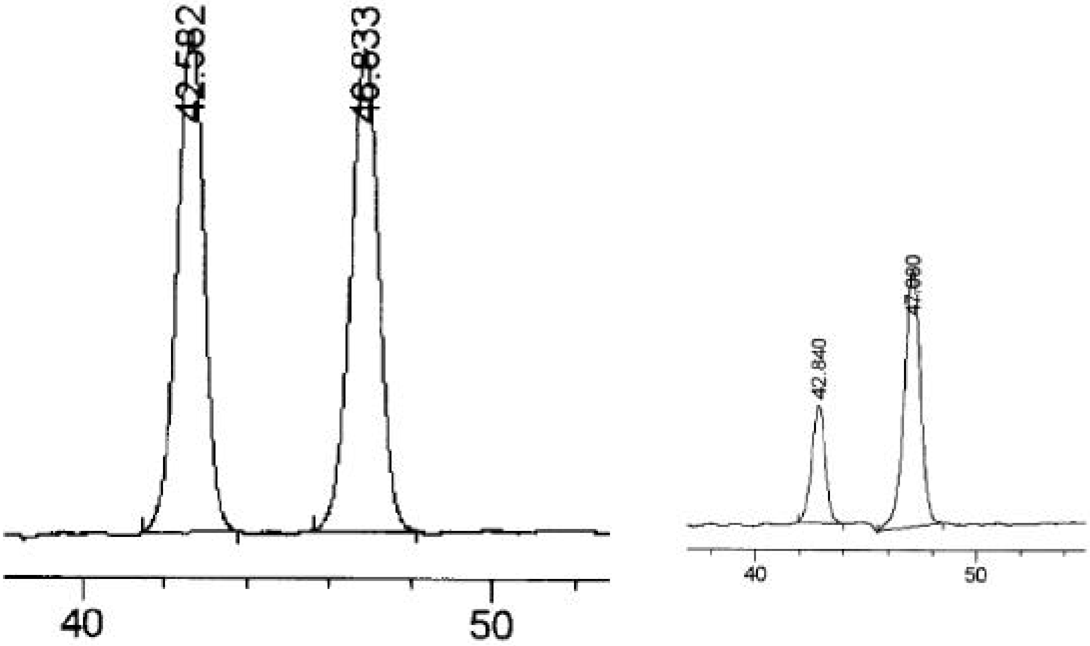


Figure S19. ^{1}H NMR spectrum of *cis*-**S8**.

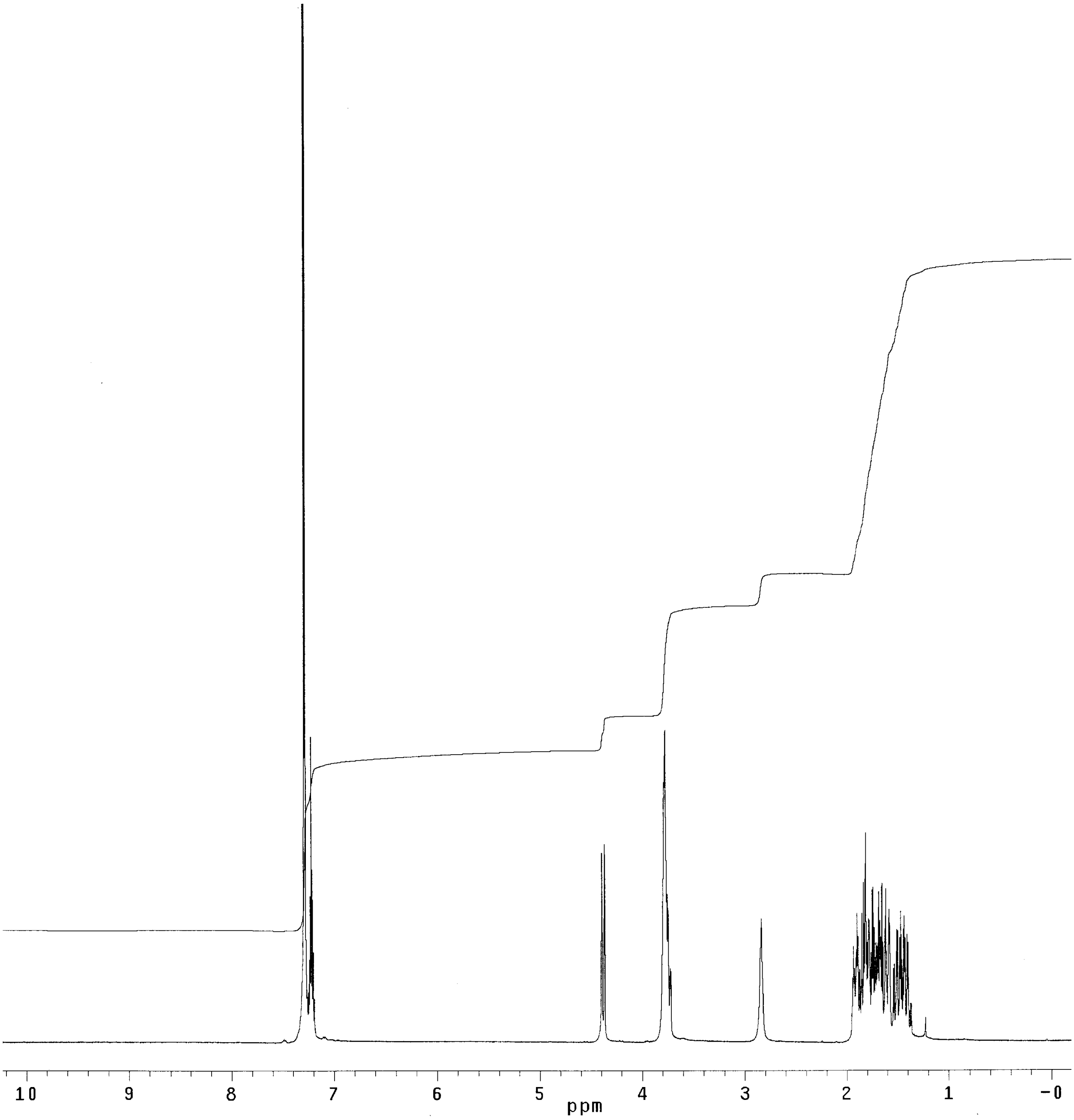


Figure S20. $^{13}C\{^1H\}$ NMR spectrum of *cis*-**S8**.

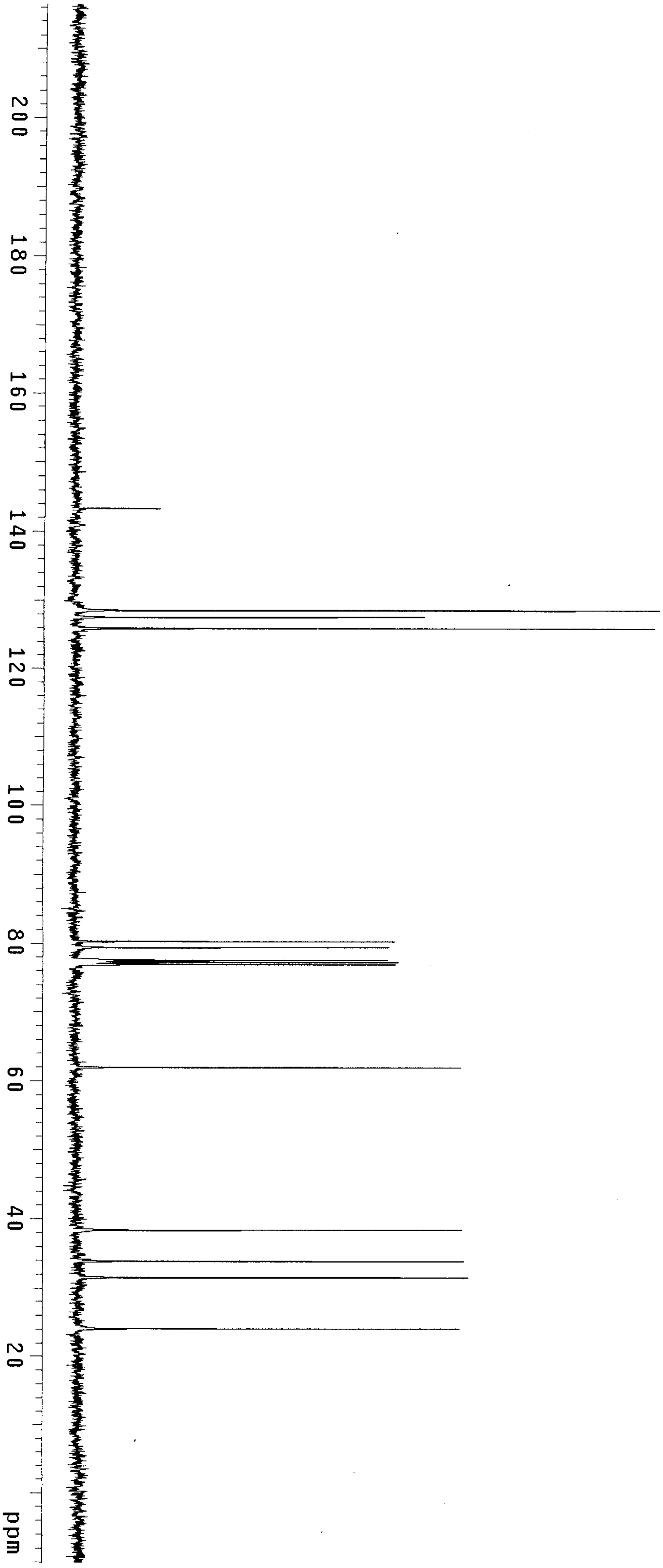
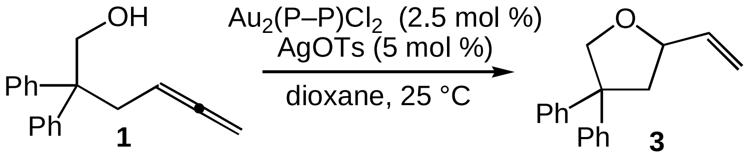


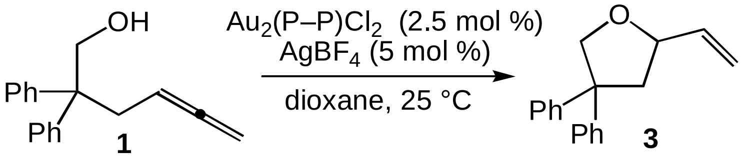
Table S1. Gold/AgOTs-catalyzed enantioselective hydroalkoxylation of **1** ([**1**]$_{\text{initial}}$ = 0.125 M) as a function of ligand.



entry	P–P	time (h)[a]	yield (%)[b]	ee (%)
1	MOP	1	93	17.8
2	BINAP	2	93	18.7
3	Xylyl-BINAP	4	84	24.5
4	MeO-BIPHEP	2	95	41.0
5	(*S*)-**4**	2	75	86.1

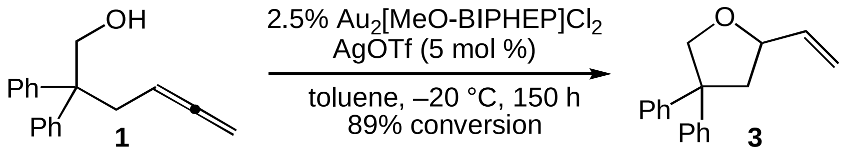
[a] Time required for complete (=98%) consumption of **1**. [b] Yield determined by GC analysis versus internal standard.

Table S2. Gold/AgBF$_4$-catalyzed enantioselective hydroalkoxylation of **1** ([**1**]$_{\text{initial}}$ = 0.125 M) as a function of ligand.



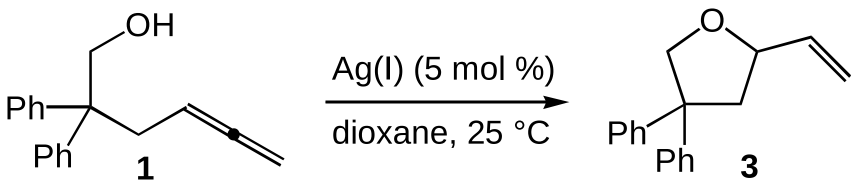
entry	P–P	time (h)[a]	yield (%)[b]	ee (%)
1	MOP	4.5	64	12.6
2	BINAP	74[c]	—	—
3	Xylyl-BINAP	3	84	12.8
4	MeO-BIPHEP	N/A	N/A	N/A
5	(*S*)-**4**	1	33	62.2

[a] Time required for complete (=98%) consumption of **1**. [b] Yield determined by GC analysis versus internal standard. [c] 50% conversion.



Scheme S1

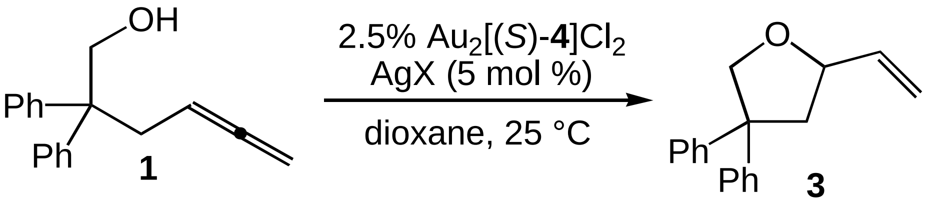
Table S3. Silver-catalyzed hydroalkoxylation of **1**.



entry	silver salt	time (h)	conversion (%)[a]
1	AgOTs	46	0
2	$AgAsF_6$	16.5	0
3	$AgSbF_6$	16.5	0
4	AgOCN	18	0
5	Ag_2CO_3	21	0
6	CH_3COOAg	21	0
7	$AgClO_4$	16	0
8	$AgNO_3$	15.5	14
9	CF_3COOAg	14	17
10	$[CH_3COCH{=}C(O\text{-})CH_3]Ag$	21	6
11	$AgBF_4$	46	45
12	AgOTf	46	38

[a] Determined by GC analysis versus internal standard.

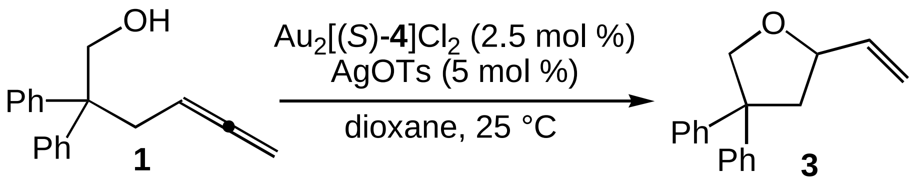
Table S4. Enantioselective hydroalkoxylation of **1** ([**1**]$_{\text{initial}}$ = 0.125 M) catalyzed by Au_2[(*S*)-**4**]Cl_2 as a function of silver source.



entry	silver salt	time (h)[a]	yield (%)[b]	ee (%)
1	AgOTs	2	75	86.1
2	$AgClO_4$	1	38	27.7
3	$AgAsF_6$	1	36	25.7
4	$AgSbF_6$	0.1	47	31.0
5	AgOCN	15	—[c]	—
6	Ag_2CO_3	14	—[c]	—
7	CH_3COOAg	17	—[c]	—

[a] Time required for complete (=98%) consumption of **1**. [b] Yield determined by GC analysis versus internal standard. [c] No reaction.

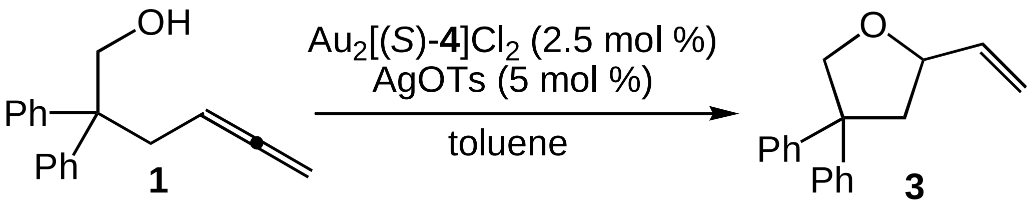
Table S5. Enantioselective hydroalkoxylation of **1** ([**1**]$_{\text{initial}}$ = 0.125 M) catalyzed by Au$_2$[(*S*)-**4**]Cl$_2$/AgOTs as a function of solvent.



entry	solvent	time (h)[a]	yield (%)[b]	ee (%)
1	THF	4	75	83.1
2	MeOH	47	91	21.7
3	acetone	1	93	41.1
4	EtOAc	2	75	81.4
5	CH_3CN	2	90	44.1
6	dioxane	2	75	86.1
7	toluene	< 0.1	73	86.4

[a] Time required for complete (=98%) consumption of **1**. [b] Yield determined by GC analysis versus internal standard.

Table S6. Enantioselective hydroalkoxylation of **1** catalyzed by $Au_2[(S)$-**4**$]Cl_2$/AgOTs as a function of temperature and concentration.



entry	temp	[**1**] (M)	time (h)	yield (%)[a]	ee (%)
1	25 °C	0.125	0.1	73	86.4
2	25 °C	0.013	4	73	90.2
3	25 °C	0.013 (by syringe pump)	4	76	88.5
4	0 °C	0.025	6	71	90.7
5	–20 °C	0.125	4.5	59	94.0
6	–20 °C	0.063	18	76	93.2
7	–20 °C	0.013	61	73	92.5

[a] Yield determined by GC analysis versus internal standard.

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