

Development of the First Catalytic Asymmetric Aldol-Tishchenko Reaction. Insight into the Catalyst Structure and Reaction Mechanism.

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General. Infrared (IR) spectra were recorded on Nicolet Magna 560 and Perkin-Elmer 283 spectrophotometers, λ_{max} in cm^{-1} . Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra were recorded on Varian Gemini (300 MHz) and Bruker AC200 (200 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl_3 : 7.24 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constants (Hz), and assignment. ^{13}C NMR were recorded on a Varian Gemini 300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuteriochloroform: δ 77.0 ppm). Microanalyses were performed by Robertson Microlit Laboratories (Madison, NJ). High-resolution mass spectrometry was performed by the University of Minnesota, Department of Chemistry, Mass Spectrometry Facility. Vapor pressure osmometry experiments were performed on a Knauer vapor pressure osmometer.

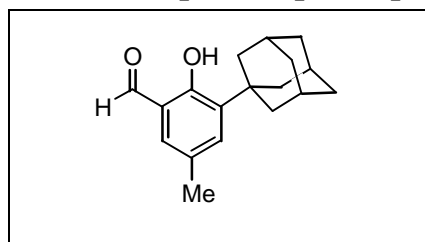
Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Sigma silica gel (SiO_2) 60 (230-400) mesh. Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60 plates. Visualization was obtained with phosphomolybdic acid in ethanol followed by heating.

Analytical gas-liquid chromatography (GLC) was performed on Hewlett-Packard 6890 Series chromatographs equipped with split-mode capillary injection systems and flame-ionization detectors.

Analytical high performance liquid chromatography (HPLC) was performed on a Shimadzu liquid chromatograph equipped with a UV detector. Enantiomeric ratios were determined either by GLC with a Supelco β -DEX 120 fused silica (30m x 0.25mm) capillary column with helium as the carrier, or by HPLC with either a Chiracel OJ or Chiracel OD column.

All reactions were conducted in oven and flame-dried glassware under an inert atmosphere of dry nitrogen. Diethyl ether, toluene and dichloromethane were obtained from filtration stills. Benzene was purified by extraction with sulfuric acid, water and dilute sodium hydroxide followed by drying and distillation from powdered 4 Å molecular sieves (Aldrich). Isobutyraldehyde was distilled under nitrogen from powdered 4 Å molecular sieves (Aldrich) prior to use. Benzaldehyde (99.5+%) was purchased in a Sure/Seal bottle from Aldrich and used in the glove-box without further purification. *p*-Anisaldehyde and cinnamaldehyde were distilled prior to use. All other reagents were purchased and used without further purification. Except for those compounds described below, salicaldehydes and salen ligands were obtained from Aldrich Chemical Co. 3-*t*-Butyl-2-hydroxybenzaldehyde was prepared according to reference 2. 3-hydroxy-2,2-dimethyl-3-phenyl propionaldehyde was prepared according to the method of Mahrwald.⁷

3-Adamantyl-2-hydroxy-4-methylbenzaldehyde.¹



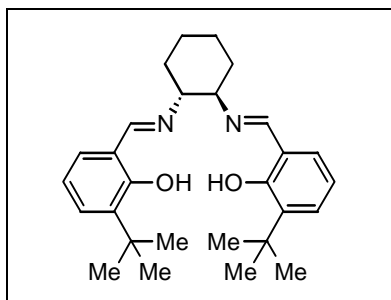
A 50 ml flame-dried flask equipped with stir-bar under nitrogen was charged with 1.26 g (5.2 mmol) 2-(1-adamantyl)-4-methylphenol, 1 mL dry toluene, 245 μ L (2.1 mmol) dry 2,6-lutidine and 60 μ L (0.52 mmol) tin (IV) chloride. After stirring for 20

minutes, 345 mg (11.44 mmol) of paraformaldehyde was added and the mixture heated at 100 °C for 15 hours. The mixture was cooled to room temperature, poured into 30 mL water, acidified with 6 N HCl to a pH of 2 and extracted with diethyl ether (2 x 100 mL). The ether layers were washed with water (75 mL) and brine (75 mL), dried with anhydrous MgSO₄ and concentrated *in vacuo* to yield a pale yellow solid. Passage through a silica gel plug yielded 2.66 g (95%) pure 3-adamantyl-2-hydroxy-4-methylbenzaldehyde. IR (neat): 3420 (br, s), 2930 (m), 1635 (m) cm⁻¹; ¹H NMR: δ 11.61 (1 H, s, RCHO), 9.79 (1 H, s, phenyl), 7.22 (1 H, br s, phenyl), 7.13 (1 H, br s, phenyl), 1.51-2.28 (19H, m,

alkyl); ^{13}C NMR: δ 197.1, 159.4, 138.2, 135.5, 131.4, 128.3, 120.5, 41.1, 40.4, 37.3, 29.2, 20.9.

General Procedure for the Synthesis of Salen Ligands.³ To a 50 mL flask equipped with stir bar, under nitrogen, was added 2.98 g (11 mmol) 3-adamantyl-2-hydroxy-4-methylbenzaldehyde and 8 mL ethyl alcohol. To this mixture was then added 1.13 g (5.52 mmol) of (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine in 3 mL of ethyl alcohol. The mixture was heated overnight at reflux and subsequently cooled in the freezer and the precipitate filtered off. Purification was achieved by flash chromatography (10:1 hexanes/EtOAc) to yield 2.67g (70%) of pure (*R,R*)-(-)-*N,N*-Bis-(3-Adamantyl-5-methylsalicylidene)-1,2-diphenylethylenediamine (**1f**).

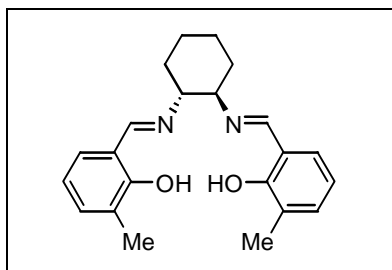
(*R,R*)-(-)-*N,N*-Bis(3-*tert*-butylsalicylidene)1,2-cyclohexanediamine



(1b). IR (neat): 3440 (br, s), 2940 (s), 1620 (s) cm^{-1} ; ^1H NMR: δ 12.70 (1 H, s, OH), 8.26 (2 H, s, ArCHN), 7.23 (2 H, dd, $J=8.0$, 1.0 Hz, phenyl), 6.97 (2 H, dd, $J=8.0$, 1.0 Hz, phenyl), 6.69 (2 H, t, $J=8.0$ Hz, phenyl), 3.31 (2 H, dd, $J=9.1$, 5.0 Hz NCHCHN), 1.23-2.16 (8 H, m, cyclohexyl) 1.35 (18 H, s, C(CH₃)₃); ^{13}C NMR: δ 165.5, 160.3,

137.1, 129.8, 129.3, 118.6, 117.8, 72.5, 34.9, 33.3, 29.5, 24.5. HRMS (FAB) Calc'd for C₂₈H₃₉N₂O₂ (M+H)⁺: 435.3013. Found: 435.3006.

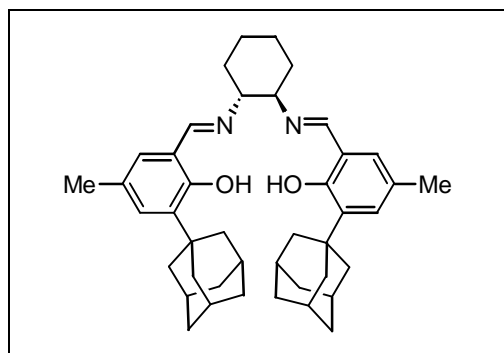
(*R,R*)-(-)-*N,N*-Bis(3-methylsalicylidene)1,2-cyclohexanediamine



(1c). IR (neat): 2940 (s), 2850 (br, s), 1620 (s) cm^{-1} ; ^1H NMR: δ 13.62 (2 H, s, OH), 8.24 (2 H, s, ArCHN), 7.10 (2 H, d, $J=7.0$ Hz, phenyl), 6.97 (2 H, d, $J=7.0$ Hz, phenyl), 6.71 (2 H, t, $J=7.0$ Hz, phenyl), 3.29 (2 H, dd, $J=5.2$, 4.1 Hz, ArcNCH), 2.21 (6 H, s, ArCH₃) 1.39-1.95 (8 H, m, cyclohexyl); ^{13}C NMR: δ 164.8, 159.3, 133.2, 129.2, 125.7, 118.1,

118.0, 72.76, 33.44, 24.44, 15.72. Anal Calc'd for C₂₂H₂₆N₂O₂: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.37; H, 7.38; N, 8.05.

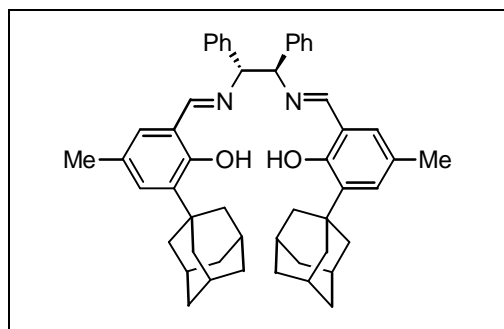
(*R,R*)-(-)-*N,N*-Bis(3-Adamantyl-5-methylsalicylidene)-1,2-



cyclohexanediamine (1d). IR (neat): 3430 (br, s), 2920 (s), 1635 (s) cm^{-1} ; ^1H NMR: δ 13.59 (2 H, s, OH), 8.19 (2 H, s, ArCHN), 6.92 (2 H, d, $J=1.0$ Hz, phenyl), 6.73 (2 H, d, $J=1.0$ Hz, phenyl), 3.26 (2 H, m, ArCHNCH), 1.35-2.15 (44 H, m, alkyl); ^{13}C NMR: δ 165.7, 158.2, 137.0, 130.3, 129.7, 126.6, 118.4, 72.5, 40.5,

37.4, 37.0, 33.3, 29.3, 24.6, 20.8. HRMS (FAB) Calc'd for $\text{C}_{42}\text{H}_{54}\text{N}_2\text{O}_2$: 618.4183. Found (M^+) 618.4136.

(*R,R*)-(-)-*N,N*-Bis-(3-Adamantyl-5-methylsalicylidene)-1,2-



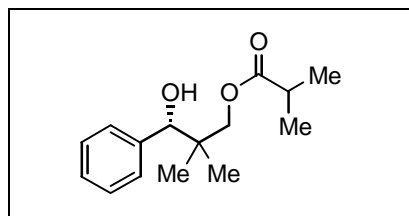
diphenylethylenediamine (1f). IR (neat): 3440 (br, m), 2910 (s), 1630 (s) cm^{-1} ; ^1H NMR: δ 13.43 (2 H, s, OH), 8.27 (2 H, s, ArCHN), 7.17 (10 H, m, aromatic), 6.95 (2 H, d, $J=2.0$ Hz, phenyl), 6.72 (2 H, d, $J=2.0$ Hz, phenyl), 4.65 (2 H, s, NCHPh), 1.76-2.14 (36 H, m, alkyl); ^{13}C

NMR: δ 167.2, 158.2, 139.6, 137.1, 130.7, 130.0, 128.3, 128.2, 127.5, 126.7, 118.4, 80.2, 40.5, 37.4, 37.1, 29.4, 20.8. HRMS (FAB) Calc'd for $\text{C}_{50}\text{H}_{57}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 717.4422. Found (M^+): 717.4466.

General Procedure for Catalytic Asymmetric Aldol-Tishchenko Reaction with $\text{Y}_5\text{O}(\text{O}i\text{-Pr})_{13}$ as the Catalyst. A 25 ml flask equipped with stir bar and 100 mg of 4 Å powdered molecular sieves was heated with a heat-gun under vacuum for a few minutes to activate the sieves, then taken into an inert atmosphere glove box. To the flask was then added 12.2 mg (0.046 mmol) of $\text{Y}_5\text{O}(\text{O}i\text{-Pr})_{13}$, 42.6 mg (0.059 mmol) of salen **1f** and 9.2 mL of dry dichloromethane. The mixture was stirred for 15 hours, at which point 47 μL (0.46 mmol) benzaldehyde was added. After 5 minutes, 250 μL (2.76 mmol) of freshly-distilled isobutyraldehyde was added dropwise, with stirring. After 5 hours, the mixture was quenched with 1 M HCl and extracted with dichloromethane (2 x 100

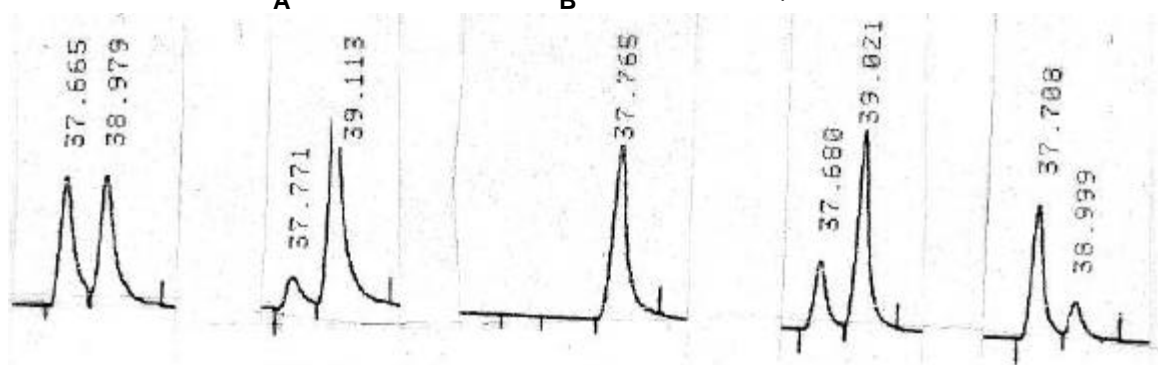
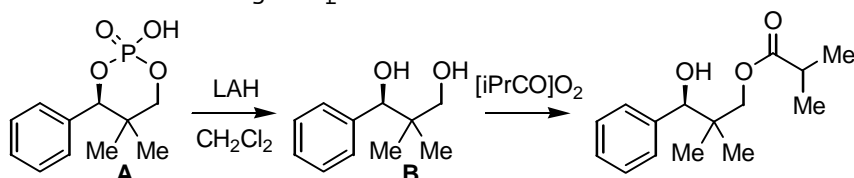
mL). The organic layer was washed with brine (75 mL), dried with MgSO_4 and concentrated *in vacuo* to yield a pale yellow oil. Purification by flash chromatography (14:1 dichloromethane:ethyl acetate) yielded 76.3 mg of **2a** (68% yield).

(1S) 1-Hydroxy-1-phenyl-2,2-dimethylprop-3-yl Isobutanoate (2a).



IR (neat): 3503 (br, s), 2973 (s), 2880 (m), 1717 (s) cm^{-1} ; ^1H NMR: δ 7.20 - 7.35 (5 H, m, phenyl), 4.50 (1 H, d, $J=3.0$ Hz, PhCHOH), 4.14 (1 H, d, $J=10.9$ Hz, $\text{CH}_a\text{H}_b\text{O}$), 3.69 (1 H, d, $J=10.8$ Hz, $\text{CH}_a\text{H}_b\text{O}$), 2.55 (1 H, m, $\text{CH}(\text{CH}_3)_2$), 2.38 (1 H, d, $J=3.0$ Hz, OH) 1.15 (6 H, d, $J=7$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.88 (3 H, s, CH_3), 0.79 (3 H, s, CH_3); ^{13}C NMR: δ 177.3, 141.0, 127.8, 127.7, 127.6, 78.1, 70.6, 39.5, 34.4, 21.7, 19.6, 19.4, 19.3. Anal Calc'd for $\text{C}_{15}\text{H}_{22}\text{O}_3$: C, 71.97; H, 8.86. Found: C, 72.18; H, 8.92.

Proof of Stereochemistry. Product stereochemistry was determined through comparison with the independently prepared enantiomer. LAH reduction⁵ of the commercially available enantiopure phosphate ester (**A**) afforded 1,3-diol (**B**). Subsequent acylation of the primary alcohol with isobutyric anhydride yielded the **1R** enantiomer of **2b**. GLC comparison of the enantiomers (Supelco β -dex column) was then used to confirm configuration of the major product.



racemic

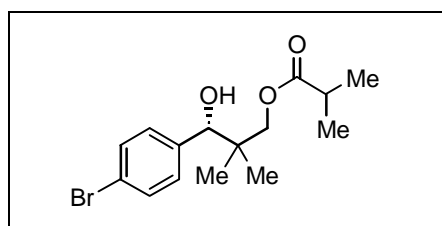
catalytic

authentic

racemic+cat.

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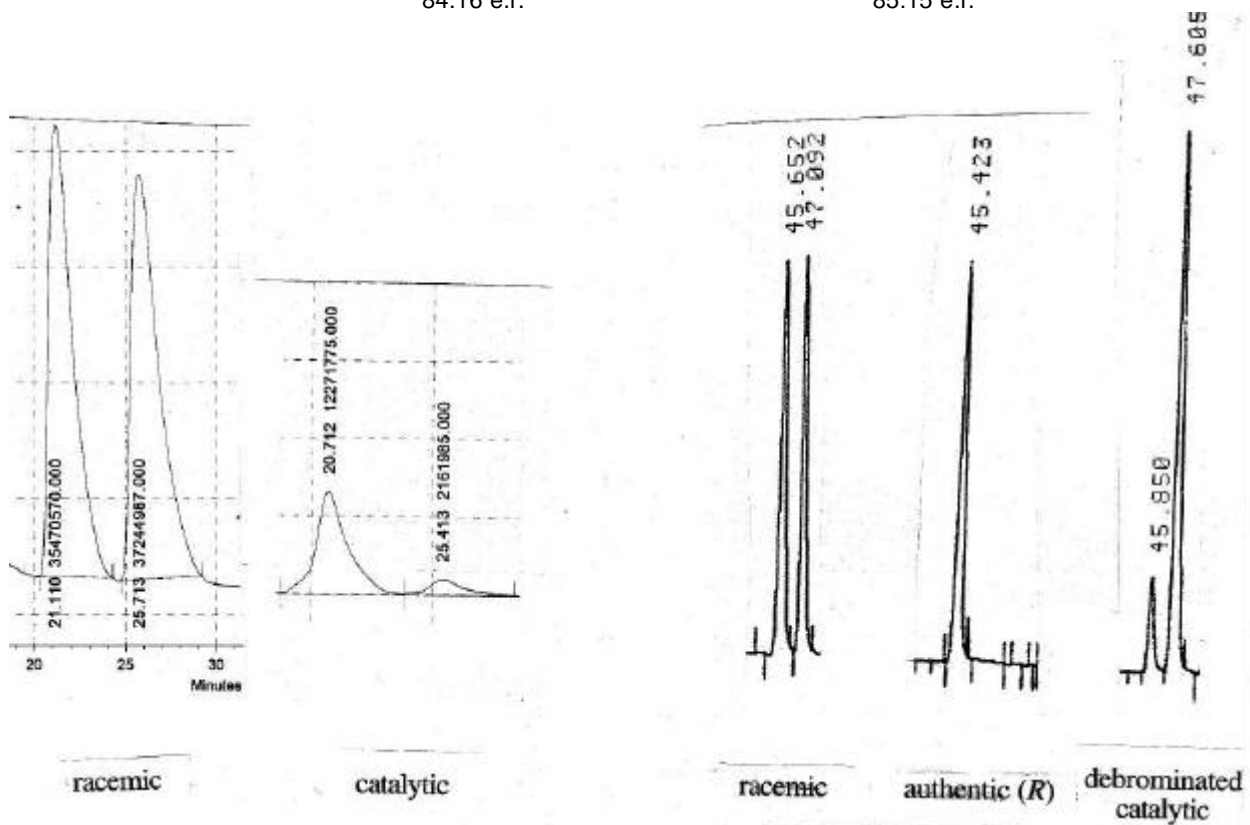
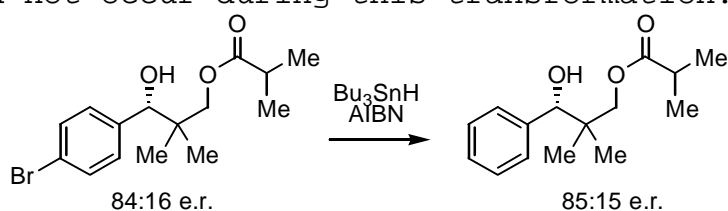
(1S)-1-Hydroxy-1-(4-bromophenyl)-2,2-dimethylprop-3-yl



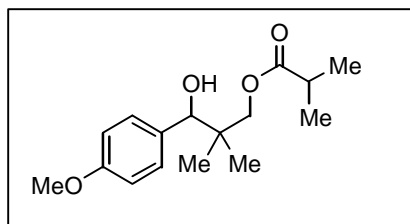
Isobutanoate. IR (neat): 3501 (br, s), 2973 (s), 2870 (m), 1717 (s) cm^{-1} ; ^1H NMR: δ 7.42 (2 H, d, $J=8$ Hz, phenyl), 7.15 (2 H, d, $J=8$ Hz, phenyl), 4.49 (1

H, d, $J=3.0$ Hz, PhCH(OH)), 4.21 (1 H, d, $J=11.1$ Hz, $\text{CH}_a\text{H}_b\text{OR}$), 3.70 (1 H, d, $J=11.1$ Hz, $\text{CH}_a\text{H}_b\text{OR}$), 2.51 (1 H, m, $\text{CH}(\text{CH}_3)_2$), 2.50 (1 H, d, $J=3.0$ Hz, OH), 1.21 (3 H, d, $J=1.4$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.18 (3 H, d, $J=1.4$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.88 (3 H, s, CH_3), 0.82 (3 H, s, CH_3); ^{13}C NMR: δ 177.3, 140.0, 130.9, 129.4, 121.4, 77.3, 70.5, 39.4, 34.4, 21.7, 19.3 (3 carbons). Anal Calc'd for $\text{C}_{15}\text{H}_{21}\text{BrO}_3$: C, 54.72; H, 6.43; Br, 24.27. Found: C, 55.01; H, 6.44; Br, 24.40.

Proof of Stereochemistry. Separation of the enantiomers of **3a** was accomplished through HPLC, using a Chiracel OD column. The stereochemistry of the major enantiomer was determined by conversion of product **3a** to product **2a** through debromination, following the method of Glover⁵ with subsequent analysis by GLC. Racemization did not occur during this transformation.



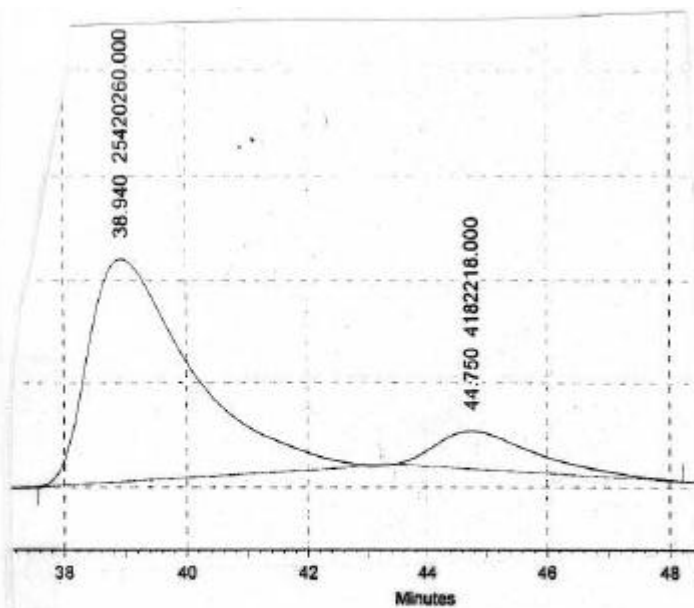
1-Hydroxy-1-(4-methoxy)-2,2-dimethylprop-3-yl Isobutanoate. IR (neat): 3020 (br,s), 3000



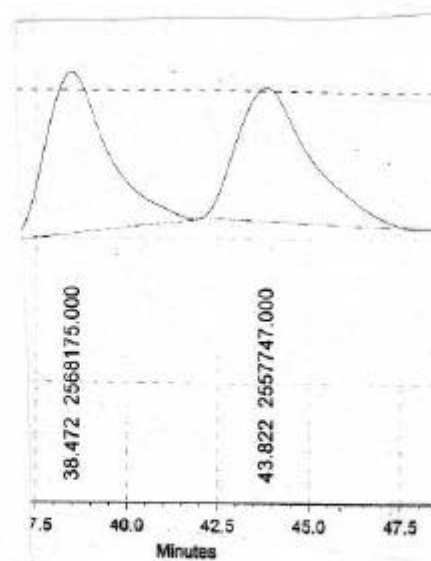
(s), 1730 (s), 1270 (s) cm^{-1} ; ^1H NMR: δ 7.20 (2 H, dd, $J=9$, 2 Hz, phenyl), 6.83 (2 H, dd, $J=9$, 2 Hz, phenyl), 4.51 (1 H, d, $J=2.3$ Hz, PhCHOH), 4.16 (1 H, d, $J=11$ Hz, $\text{CH}_a\text{H}_b\text{OR}$), 3.78 (3 H, s, PhOCH_3), 3.73 (1 H, d, $J=11$ Hz, $\text{CH}_a\text{H}_b\text{OR}$), 2.59 (1

H, m, $\text{CH}(\text{CH}_3)_2$), 2.30 (1 H, d, $J=2.5$ Hz, OH), 1.21 (3 H, d, $J=7.7$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.19 (3 H, d, $J=7.7$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.91 (3 H, s, CH_3), 0.82 (3 H, s, CH_3); ^{13}C NMR: δ 177.2, 159.0, 133.1, 128.7, 113.2, 77.7, 70.7, 55.4, 39.5, 34.4, 21.6, 19.6, 19.3, 19.3. HRMS (CI) Calc'd for $\text{C}_{16}\text{H}_{28}\text{N}_1\text{O}_4$ ($\text{M}+\text{NH}_4$) $^+$: 298.2019. Found ($\text{M}+\text{NH}_4$) $^+$: 298.2019.

Enantiomeric excess was determined via HPLC separation of the stereoisomers on a Chiralcel OD column:

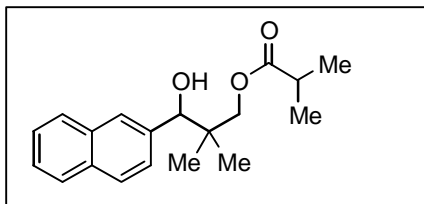


catalytic



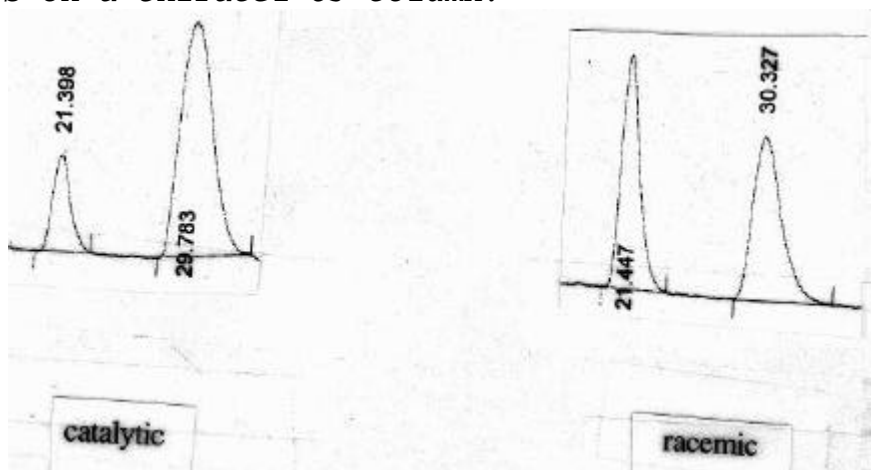
racemic

1-Hydroxy-1-(2-naphthyl)-2,2-dimethylprop-3-yl Isobutanoate. IR

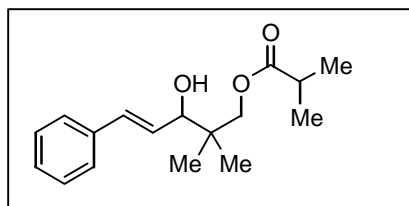


(neat): 3496 (br, s), 3057 (m), 2973 (s), 2876 (m), 1717 (s) cm^{-1} ; ^1H NMR: δ 7.75 (4 H, m, naphthyl), 7.43 (3 H, m, naphthyl), 4.70 (1 H, d, $J=3.1$ Hz, naphthylCH(OH)), 4.27 (1 H, d, $J=11.1$ Hz, $\text{CH}_a\text{H}_b\text{OR}$), 3.76 (1 H, d, $J=11.1$ Hz, $\text{CH}_a\text{H}_b\text{OR}$), 2.64 (1 H, m, $\text{CH}(\text{CH}_3)_2$), 2.48 (1 H, d, $J=3.5$ Hz, OH), 1.20 (6 H, d, $J=7.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.95 (3 H, s, CH_3), 0.87 (3 H, s, CH_3); ^{13}C NMR: δ 177.3, 159.1, 138.6, 133.0, 132.9, 128.0, 127.7, 127.3, 126.5, 126.1, 125.9, 78.1, 70.7, 39.8, 34.4, 21.8, 19.6, 19.4, 19.3. Anal Calc'd for $\text{C}_{19}\text{H}_{24}\text{O}_3$: C, 75.97; H, 8.05. Found: C, 76.11; H, 8.03.

Enantiomeric excess was determined via HPLC separation of the stereoisomers on a Chiralcel OJ column:

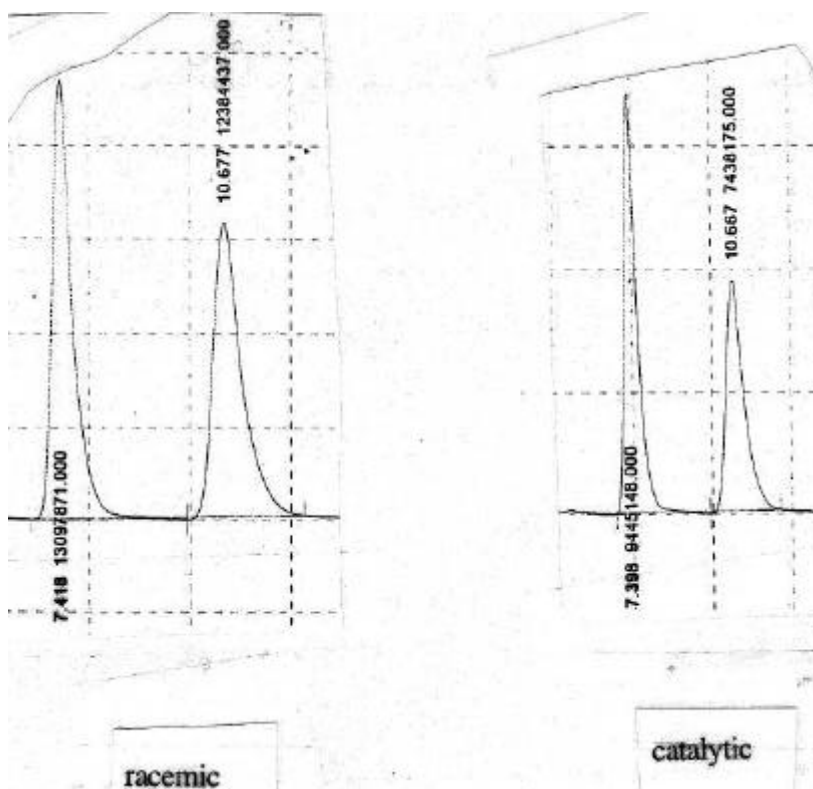


1-Hydroxy-1-(trans-cinnamyl)-2,2-dimethylprop-3-yl Isobutanoate



(6a). IR (neat): 3480 (br, s), 2990 (s), 1725 (s) cm^{-1} ; ^1H NMR: δ 7.25-7.42 (5 H, m, phenyl), 6.62 (1 H, d, $J=16$ Hz, $\text{PhCH}=\text{CH}$), 6.30 (1 H, dd, $J=15, 7$ Hz, $\text{PhCH}=\text{CH}$), 4.20 (1 H, d, $J=11.1$ Hz, $\text{CH}_a\text{H}_b\text{OR}$), 4.11 (1 H, m, PhCHCHCHOH), 3.85 (1 H, d, $J=10.8$ Hz, $\text{CH}_a\text{H}_b\text{OR}$), 2.64 (1 H, m, $\text{CH}(\text{CH}_3)_2$), 2.25 (1 H, d, $J=4.1$ Hz, OH), 1.21 (6 H, d, $J=7.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.99 (6 H, s, CH_3); ^{13}C NMR: δ 177.3, 136.7, 132.3, 128.7, 128.3, 127.8, 126.6, 76.9, 70.4, 39.2, 34.4, 21.8, 19.8, 19.4, 19.3. Anal Calc'd for $\text{C}_{17}\text{H}_{24}\text{O}_3$: C, 73.88; H, 8.75. Found: C, 73.60; H, 8.60.

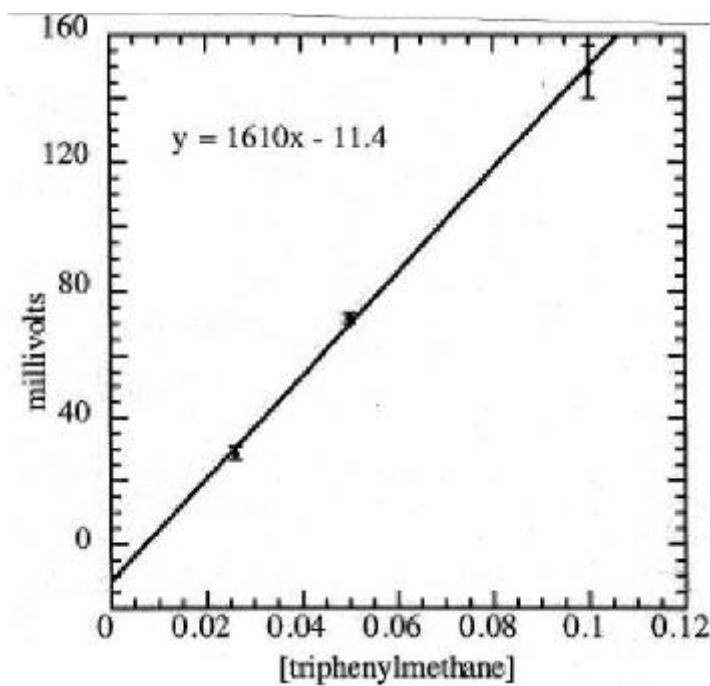
Enantiomeric excess was determined via HPLC separation of the stereoisomers on a Chiracel OD column:



General Procedure for Preparation of Catalyst for Vapor Pressure Osmometry (VPO) Study. Stock solutions of triphenylmethane in dichloromethane were made up at different concentrations, several VPO measurements obtained for each stock solution, and a linear relationship between mV and monomer concentration was observed (see graph below). To calculate the aggregation state of the $Y_5O(Oi-Pr)_{13}$ -**1a** complex, a mixture was prepared as follows: to a 50 mL flask equipped with stir-bar was added 80 mg (0.3 mmol) $Y_5O(Oi-Pr)_{13}$, 213 mg (0.39 mmol) of salen ligand **1a** and 6 mL dry dichloromethane and the mixture stirred for 24 hours to form a 0.050 M stock solution of catalyst in dichloromethane. Multiple VPO measurements for the catalyst solution were then obtained and the solute concentration determined from the calibration curve for triphenylmethane.

Calibration Curve

[triphenylmethane], M	current, mV
0.026	28.8 ± 2.2
0.050	71.3 ± 1.6
0.10	148.6 ± 8.4



Analysis of $1a-Y_5O(Oi-Pr)_{13}$ Complex

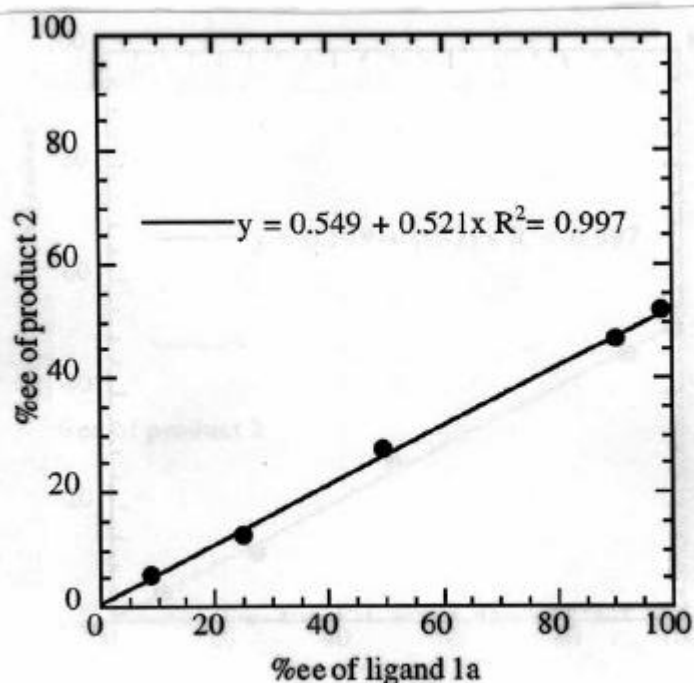
current (mV) measured for a 0.050 M solution each in metal and ligand **1a**: 72.7, 78.3, 80.8, 80.8, 88.1 (ave.: 80.1 ± 6.9)

[solute] = 0.057 ± 0.005 M

Correlation Between Catalyst Optical Purity and Product Optical Purity. The general procedure for catalytic reaction was followed using ligand **1a** of varying optical purity (prepared by mixing authentic enantiomers in different ratios). Analysis of enantioselectivity was performed on Supelco β -dex column.

Dependence of Product ee on Ligand ee

<u>%ee of ligand 1a</u>	<u>ee of 2a</u>
8.9	5.7
24.9	12.4
49.5	27.6
75.1	38.6
90.3	37.2
98.0	52.3



References

- [1] G. Casiraghi, G. Casnati, G. Puglia, G. Sartori, G. Terenghi, *J. Chem. Soc. Perkins I.* **1979**, 1862.
- [2] G. Casiraghi, G. Casnati, M. Cornia, A. Pochini, *Gazetta Chimica Italiana.* **1978**, 108, 79.
- [3] R. G. Konsler, J. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, 120, 10780.
- [4] Y. Jiang, L. Gong, X. Feng, W. Hu, W. Pan, A. Mi, *Tetrahedron* **1997**, 53, 14327.
- [5] R. Hulst, R. W. J. Zijlstra, N. K. de Vries, B. L. Feringa, *Tetrahedron Asym.* **1994**, 5, 1701.
- [6] S. A. Glover, C. A. Rowbottom, A. P. Scott, J. L. Schoonraad *Tetrahedron* **1990**, 46, 7247.
- [7] R. Marhwald, B. Costisella, B. Guendogan *Synthesis* **1998**, 3, 262.