

SUPPORTING INFORMATION FOR:
ISOTOPICALLY CHIRAL PROBES FOR IN SITU HIGH-THROUGHPUT
ASYMMETRIC REACTION ANALYSIS.

Michael A. Evans and James P. Morken*

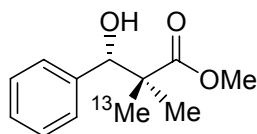
*Department of Chemistry, Venable and Kenan Laboratories
University of North Carolina, Chapel Hill, NC 27599-3290*

General. ^1H NMR spectra were recorded on 300 or 400 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, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. ^{13}C NMR were recorded on a Bruker 400 MHz (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (CDCl_3 : 77.0 ppm).

Liquid chromatography was performed using forced flow (flash chromatography) on Sigma silica gel 60 (SiO_2 , 230-400 mesh). Thin layer chromatography was performed on EM science 0.25 mm silica gel 60 plates. Visualization was achieved with phosphomolybdic acid in ethanol, potassium permanganate in water, or vanillin in sulfuric acid, each followed by heating.

Analytical gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph, a split mode capillary injection system, a flame ionization detector and the indicated column with helium as the carrier gas.

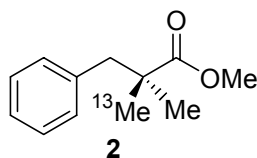
All reactions were conducted in oven and flame dried glassware under an inert atmosphere of dry nitrogen. ^1H NMR samples were prepared in a glovebox under an inert atmosphere of dry nitrogen. Deuterated solvents were used as received. Dichloroethane was sequentially washed with concentrated H_2SO_4 , water, aqueous Na_2CO_3 , and water, then dried with MgSO_4 and fractionally distilled from CaH_2 . Benzene and toluene were distilled over CaH_2 . Diethyl ether was passed through activated basic alumina. THF was distilled from sodium/benzophenone ketyl. Isopropanol was distilled from MgSO_4 and freeze-pump-thaw degassed. All other reagents were purchased from either Lancaster or Aldrich Chemical Companies and used directly.



(2S,3S)-3-Hydroxy-2-methyl-2- ^{13}C -methyl-3-phenyl-propionic acid methyl ester. Using flame-dried glassware and an inert atmosphere, a solution of LDA was made by slowly adding 13.5 ml (31.1mmol) of 2.31 M *n*-butyllithium to 4.41 ml (31.1mmol) diisopropyl amine in 25 ml THF at -78°C . After allowing the reaction to warm to -10°C for 20 minutes, it was chilled to -78°C and 2.88 g

(14.8mmol) of (2R,3R)-3-hydroxy-2-methyl-3-phenyl-propionic acid methyl ester was slowly added by syringe over a period of 5 minutes. To ensure enolate formation, the reaction was again warmed to -10°C for 20 minutes before cooling to -78°C . At this time, a solution of 1.10 ml (22.2mmol) ^{13}C -iodomethane in 5 ml THF and 3.70ml dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (DMPU) at -78°C was transferred into the reaction mixture *via* cannula over a period of 10 minutes. The reaction was warmed to 0°C for 45 minutes before pouring into saturated NH_4Cl . Finally, the organic layer was extracted with

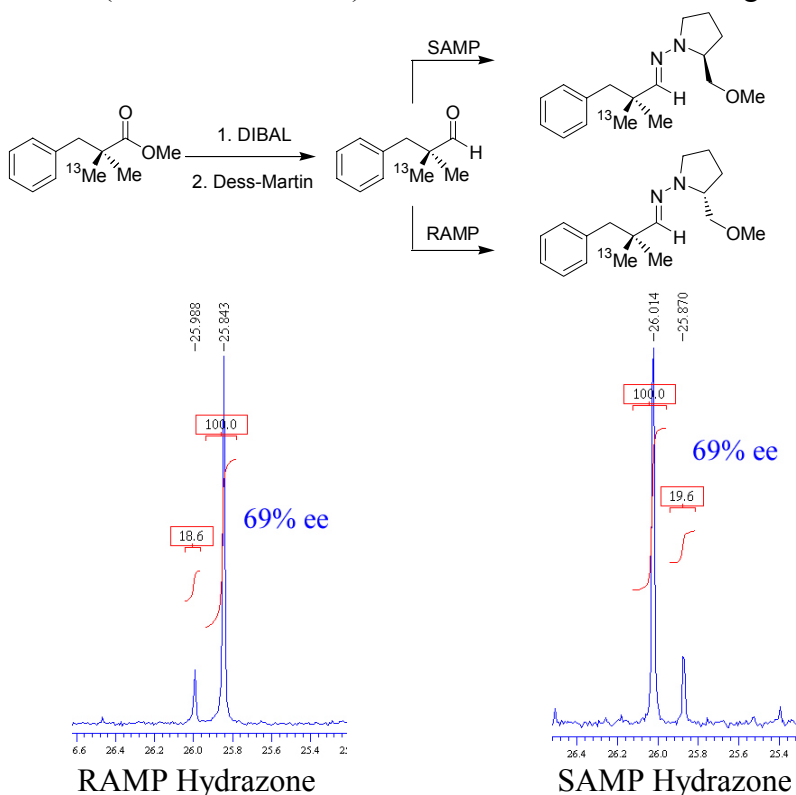
ether and dried with MgSO_4 . The crude material was passed through a silica gel column (6:1 cyclohexane:ethyl acetate) to remove a majority of the impurities prior to recrystallization from pentane. 2.01 g (9.6 mmol, 65%) of fine, white crystals were obtained in a 9:1 diastereomer ratio determined by ^1H NMR analysis. ^1H NMR (400 MHz, CDCl_3): 7.14-7.28 (5H, br m, aryl CH), 4.84 (1H, dd, $^3J_{\text{CH}}=2.3$ Hz, $^3J_{\text{HH}}=4.1$ Hz, CHOH), 3.68 (3H, s, OCH_3), 3.01 (1H, d, $J=4.2$ Hz, OH), 1.12 (3H, d, $^3J_{\text{CH}}=4.7$ Hz, $^{12}\text{CH}_3$), 1.09 (3H, d, $^1J_{\text{CH}}=128.5$ Hz, $^{13}\text{CH}_3$). ^{13}C NMR (100 MHz): 178.1, 139.9, 127.7, 126.6 (2C), 78.7, 52.1, 47.6 (d, $^1J_{\text{CC}}=34.8$), 23.1, 19.1. HRMS Calc'd for $^{12}\text{C}_{11}^{13}\text{C}_1\text{H}_{16}\text{O}_3$ $\text{M}+\text{NH}_4^+$: 227.1476; Found: 227.1490.

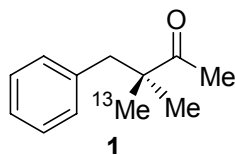


(S)-2-methyl-2- ^{13}C -methyl-3-phenyl-propionic acid methyl ester (2). 1.0 g (4.78 mmol) of labeled Frater alkylation adduct was dissolved in 12 ml (0.4M) dichloromethane, employing a polypropylene vessel with a nitrogen atmosphere. 1.26 ml (9.56 mmol) dimethylethylsilane was then introduced into reaction flask, followed by 1.32 ml (9.56 mmol) tetrafluoroboric acid. After stirring for 30

minutes at 40 $^\circ\text{C}$, the reaction was poured into a saturated sodium bicarbonate solution and was then extracted with ether. After drying and removing the solvent, 0.906 g (4.68 mmol, 98%) of a viscous yellow liquid was obtained. ^1H NMR analysis showed only the desired product, and therefore no further purification was performed. ^1H NMR (400 MHz, CDCl_3): 7.12-7.31 (5H, br m, aryl CH), 3.69 (3H, s, OCH_3), 2.88 (2H, d, $^3J_{\text{CH}}=3.9$ Hz, CH_2), 1.21 (3H, d, $^3J_{\text{CH}}=4.6$ Hz, $^{12}\text{CH}_3$), 1.21 (3H, d, $^1J_{\text{CH}}=127.6$ Hz, $^{13}\text{CH}_3$). ^{13}C NMR (100 MHz) 177.8, 137.8, 130.0, 127.9, 126.4, 51.8, 46.3, 43.5 (d, $^1J=35.2$ Hz), 24.9. HRMS Calc'd for $^{12}\text{C}_{11}^{13}\text{C}_1\text{H}_{16}\text{O}_2$ $\text{M}+\text{NH}_4^+$: 211.1527; Found: 211.1519.

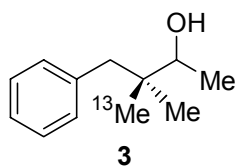
Determination of Enantiopurity. The carboxylic ester was reduced to the primary alcohol followed by Dess-Martin oxidation and conversion to the derived hydrazone with both *S*- and *R*- 1-amino-2-(methoxymethyl)pyrrolidine (SAMP and RAMP) allowed for calculation of original ester enantiopurity.





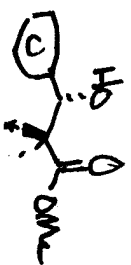
(S)-3-methyl-3-¹³methyl-4-phenyl-butan-2-one (1). Using flame-dried glassware, 158.3 mg (0.819 mmol) of ester **2** was dissolved in 3.9 ml dry pentane. The flask was cooled to 0 °C and 2.05 ml (2.05 mmol) of trimethylsilylmethyl lithium (1.0M in pentane) was slowly syringed in. After 6 hours at 0 °C, 4.1 ml of dry methanol was introduced, and the reaction stirred at room temperature for 1 hour. The reaction was then poured into saturated sodium bicarbonate and was extracted with ether. The organic layer was dried and purified by column chromatography (silica gel, 15:1 hexanes:ethyl acetate). 85.3 mg (0.481 mmol, 59%) of a clear yellow liquid product was obtained. ¹H NMR (400 MHz, CDCl₃): 7.10-7.28 (5H, br m, aryl CH), 2.84 (2H, d, ³J_{CH}=4.1 Hz, CH₂), 2.15 (3H, s, COCH₃), 1.16 (3H, d, ³J_{CH}=4.7 Hz, ¹²CH₃), 1.16 (3H, d, ¹J_{CH}=127.1 Hz, ¹³CH₃). ¹³C NMR (100 MHz) δ ppm: 213.8, 137.7, 130.2, 127.9, 126.3, 48.5 (d, ¹J=35.4), 45.3, 26.1, 24.4. IR: 2966 (br m), 1704 (s), 1358 (m), 1112 (m). HRMS Calc'd for ¹²C₁₁¹³C₁H₁₆O₁ M+NH₄⁺: 195.1578; Found: 195.1583.

High-Throughput Screen of the Reduction of (1): A 3x10 array was set up in 1 ml vials fitted with micro-size stir bars. Using stock solutions, 0.56 μmol of each dimeric metal arene complex and 2.24 μmol (2:1 ligand:metal) were transferred to each reaction vial and diluted to 0.28 mL with isopropanol. All vials were sealed and heated simultaneously at 82 °C for 30 minutes. Then 0.21 mL of a 0.26 M stock solution on **1** (56 μmol **1**) was added to each vial followed by 67 μL of 0.084 M KOH in isopropanol (5.6 μmol). Each sample was then transferred to an NMR tube and sealed for the duration of the experiment. To analyze each reaction by ¹³C NMR, an inverse-gated experiment was employed in which each acquisition required one 90° pulse. The samples were not locked and were not spun. Shimming was only done on the first sample, and the same shim values were then used throughout the experiment.



(2R,3S)- and (2S,3S)-3-methyl-3-¹³methyl-4-phenyl-butan-2-ol (3). Sample **A-10** from the assay was concentrated and analyzed by ¹H NMR. The unpurified reaction mixture contains >90% purity reduction product. ¹H NMR (400 MHz, CDCl₃): Diastereomer 1: 7.15-7.27 (5H, br m, aromatic CH), 3.52 (1H, br m, CHOH), 2.68 (1H, dd, ²J_{HH} = 13.2 Hz, ³J_{CH} = 4.8 Hz C₆H₅CH₂), 2.50 (1H, dd, 13.2 Hz, ³J_{CH} = 4.4 Hz C₆H₅CH₂), 1.16 (3H, d, J=6.4 Hz CHCH₃), 0.85 (3H, d, ¹J_{HC}=128.8 Hz, ¹³CH₃), 0.78 (3H, d, ³J_{CH} = 4.8 Hz, ¹²CH₃). Diastereomer 2: 7.15-7.27 (5H, br m, aromatic CH), 3.52 (1H, br m, CHOH), 2.68 (1H, dd, ²J_{HH} = 13.2 Hz, ³J_{CH} = 4.8 Hz C₆H₅CH₂), 2.50 (1H, dd, 13.2 Hz, ³J_{CH} = 4.4 Hz C₆H₅CH₂), 1.16 (3H, d, J=6.4 Hz CHCH₃), 0.86 (3H, d, ³J_{CH} = 4.8 Hz, ¹²CH₃), 0.79 (3H, d, ¹J_{HC}=125.2 Hz, ¹³CH₃).

Procedure for Asymmetric Transfer Hydrogenations Depicted in Table 2. The procedure followed for asymmetric transfer hydrogenation of 3-methyl-2-butanone and acetophenone with catalysts **C-6** and **C-8** is identical to that carried out in the arrayed catalyst evaluation. Enantiopurity, conversion and enantiomer identification were performed by chiral GLC analysis (β-dex 120 by Supelco) in comparison to commercially available racemates and authentic enantiomers.



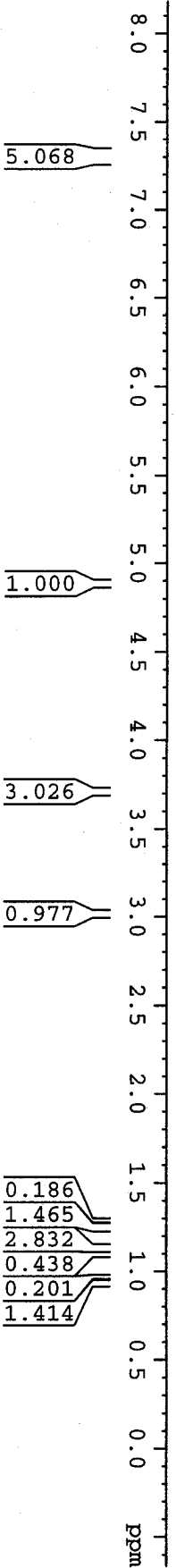
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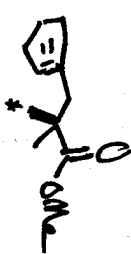


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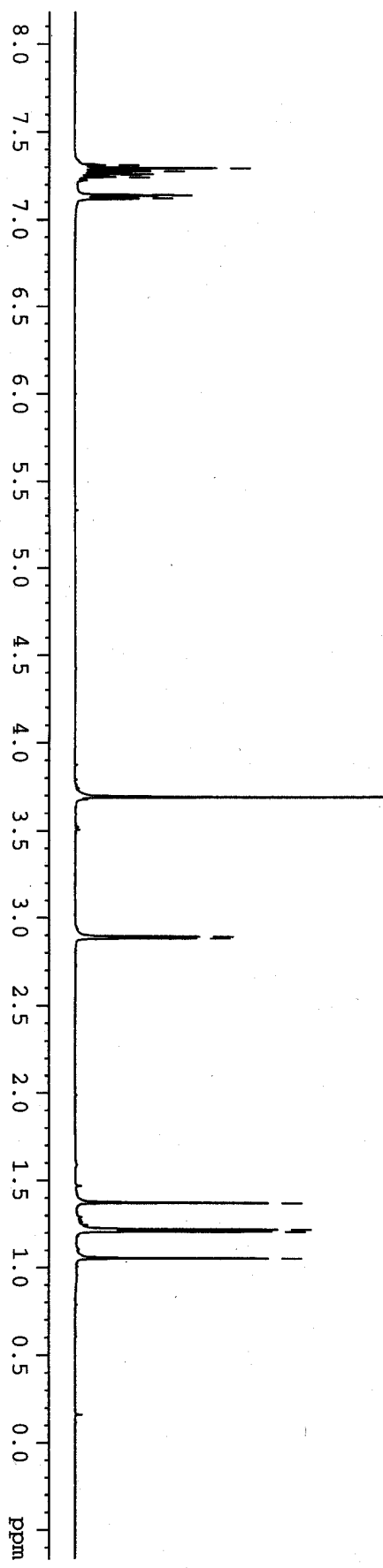
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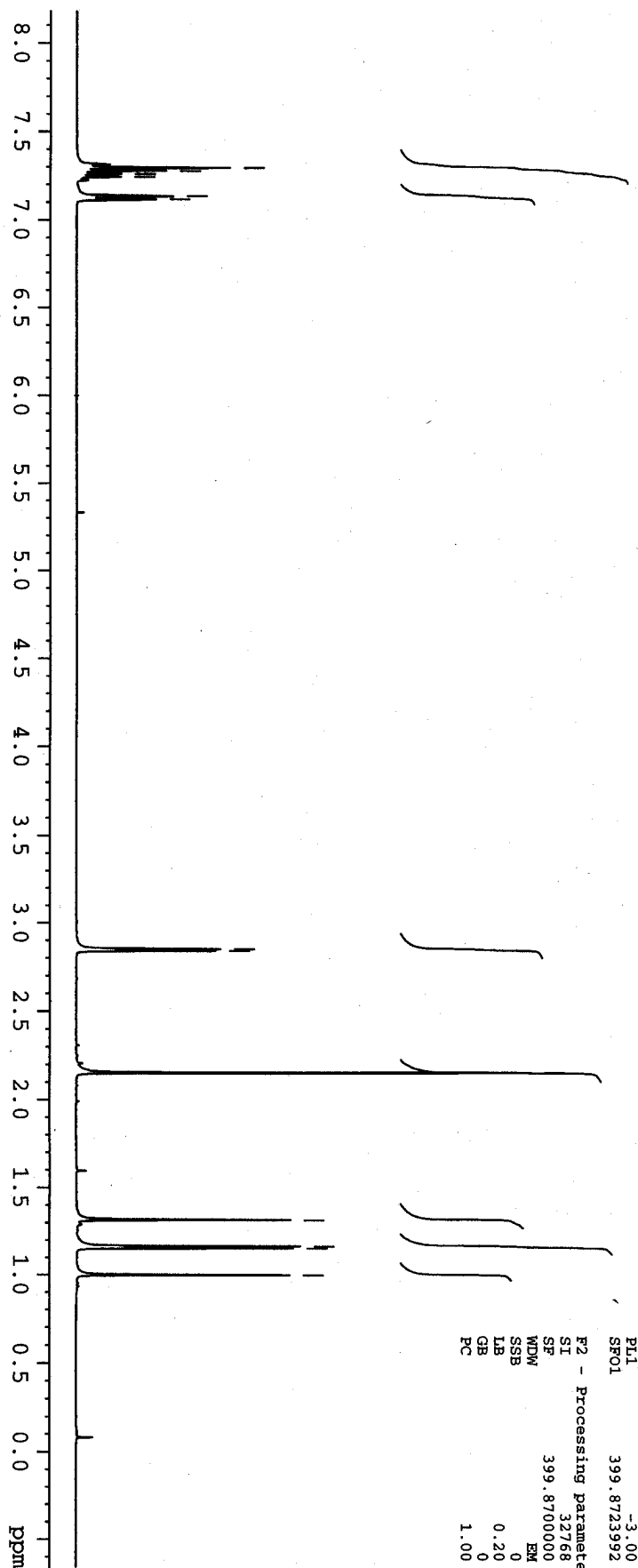
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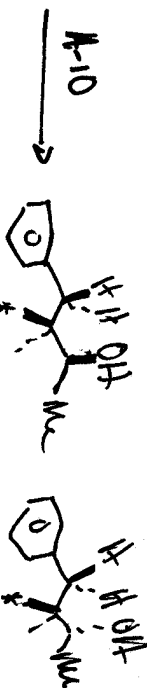
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PROCNO 1

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