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The Asymmetric MSPV Reduction of Prochiral Ketones with *i*PrOH Catalyzed by Al Catalysts

E. Joseph Campbell, Hongying Zhou, and SonBinh T. Nguyen*

Department of Chemistry
Northwestern University
2145 Sheridan Rd.
Evanston IL 60208

Supporting Information Available: Experimental procedure, quantitative analysis (including chiral GC traces), plots of conversion and ee vs. time for the reduction of α-bromoacetophenone, and the characterization of the active chiral aluminum alkoxide catalyst (9 pages). This material is available on the WWW under at http://www.angewandte.com or from the author.

General Information and Materials. Toluene was distilled over sodium/benzophenone. 2-propanol was distilled over $Mg(OiPr)_2$. Propiophenone, *iso*valerophenone, *iso*butyrophenone, acetophenone, α-methoxyacetophenone, 4-methylacetophenone, 4-fluoroacetophenone, 4-chloroacetophenone, and 4-bromoacetophenone were dried over CaH_2. All solvents were distilled under nitrogen and saturated with nitrogen prior to use. Ligands **1** and **2** were synthesized according to literature procedure.[1,2] Monomeric chiral (BINOL)AlMe complexes was synthesized following literature precedent.[3] Pure samples of 1-(4-fluorophenyl)ethanol, 1-(4-chlorophenyl)ethanol, and 1-(4-bromophenyl)ethanol were prepared by LAH reduction. Pure samples of α-bromomethylbenzyl alcohol, α-methoxymethylbenzyl alcohol, and 1-phenyl-3-methylbutanol were prepared from the corresponding ketones according literature procedures.[4] All other reagents were purchased from the Aldrich Chemical Company and used without further purification, unless otherwise noted.

GC analyses of reaction mixtures were carried out on a Hewlett Packard 5890A GC equipped with an FID detector and a HP3396A integrator. The column used was a 30-m HP-5 capillary column with 0.32-mm inner diameter and 0.25-μm film thickness. Flow rate = 1.8 mL/min. GC yields of 1-phenylethanol, 1-phenyl-1-propanol, 2-chloro-1-phenylethanol, and 1-*p*-tolylethanol were determined through integration of the product peak against 1,2,4,5-tetramethylbenzene (internal standard) using pre-established response factors. All other yields of the alcohol were determined through the integration of the product peak against that of the starting material. For verification a scale-up MSPV reduction was carried out for α-bromoacetophenone and its isolated yield found to be consistent with GC data (vide infra).

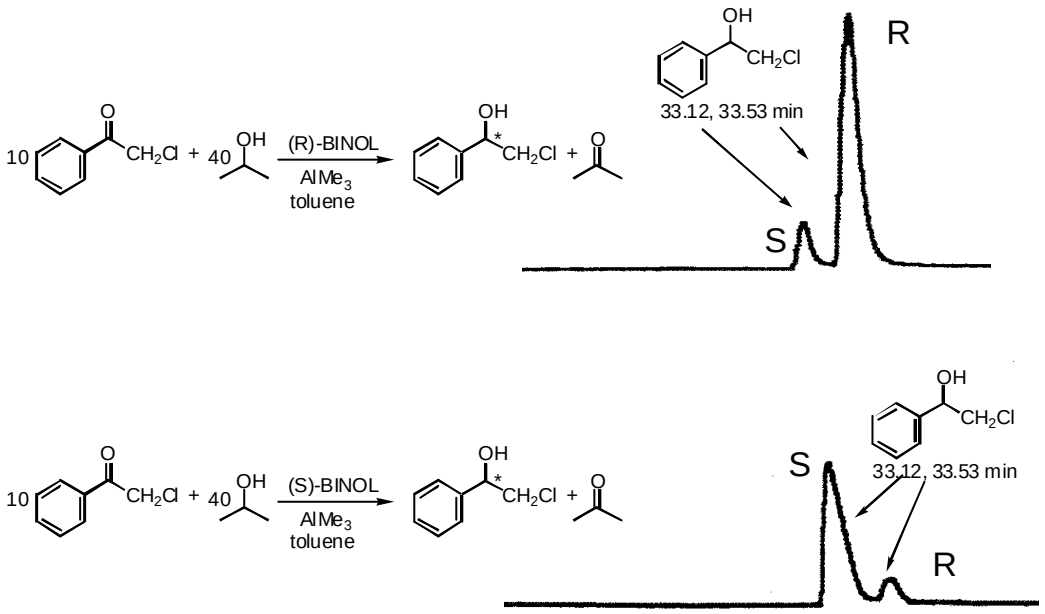
Chiral GC analysis (for Table 1, entries 1,2,5-8 and Table 2, entries 1-5 of manuscript) was performed on a Hewlett Packard 5890A GC equipped with an FID detector and a HP3390A integrator. The chiral column used was a 30-m Supelco β-Dex™ 225 fused silica capillary column with 0.25-mm inner diameter and 0.25-μm film thickness. Flow rate = 1.8 mL/min. Retention times for various components of the reaction mixture were assigned by the injection of a pure sample of each component in the reaction. All other chiral GC analysis (Table 1, entries 3 and 4 of manuscript) was performed on a Hewlett Packard 5890A equipped with a FID detector and an HP3390A integrator. The chiral column used was a 30-m Supelco β-Dex™ 120 fused silica capillary column with 0.25-mm inner diameter and 0.25-μm film thickness. Flow rate = 1.8 mL/min.

General MSPV Reduction Procedure. All reactions were carried out under a dry nitrogen atmosphere unless otherwise noted. Into a 4-mL-vial equipped with a magnetic stir bar was added toluene (500 μL) and enantiopure BINOL (5.8 mg, 0.02 mmol). $AlMe_3$ (1.9 ml, 0.02 mmol) was added to the mixture via syringe

and the reaction was allowed to stir for 5 minutes when a white precipitate formed. The carbonyl substrate (10 equiv) and 2-propanol (40 or 150 equiv) were added and the vial was sealed with a teflon-lined silicone septa. The reaction was stirred at room temperature under nitrogen for 16 hours. Aliquots (20 μL) were passed through a plug of neutral aluminum oxide [activated, Brockmann activity 1, ~150 mesh] and analyzed on GC to determine selectivity and conversion data. The chiral GC traces of the MSPV reductions are provided on the following pages.

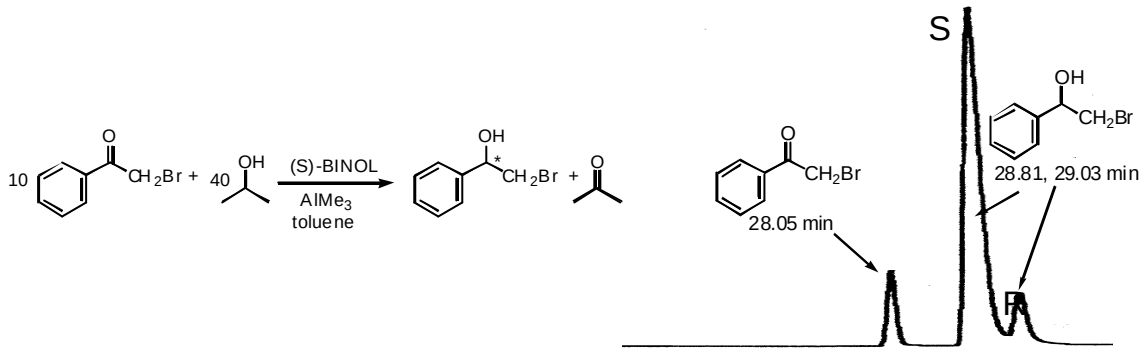
Scale-up Asymmetric MSPV Reduction. In the drybox and into a 20-mL-vial equipped with a magnetic stir bar was added toluene (2 mL) and (*S*)-(-)-BINOL (57.3 mg, 0.2 mmol). $AlMe_3$ (19.7 μL, 0.2 mmol) was added to the mixture via syringe and the reaction was allowed to stir for 5 minutes when a white precipitate formed. α-Bromoacetophenone (0.40 g, 2.0 mmol) and 2-propanol (610 μL, 8.0 mmol) were added and the vial was sealed with a teflon-lined cap, taken out of the drybox, and stirred at room temperature under nitrogen for 16 hours. Flash column chromatography using 230-400 mesh silica gel (purchased from Merck, column dimensions = 2.5 cm x 12 cm) and CH_2Cl_2 eluent, was done on the reaction and a pure sample of α-(bromomethyl)benzyl alcohol was isolated in 93% yield and 79% ee.

The chiral GC traces for the MSPV reduction of a -chloroacetophenone catalyzed by (*R*)- and (*S*)-BINOL and Al Me_3 (Table 1, entry 1).



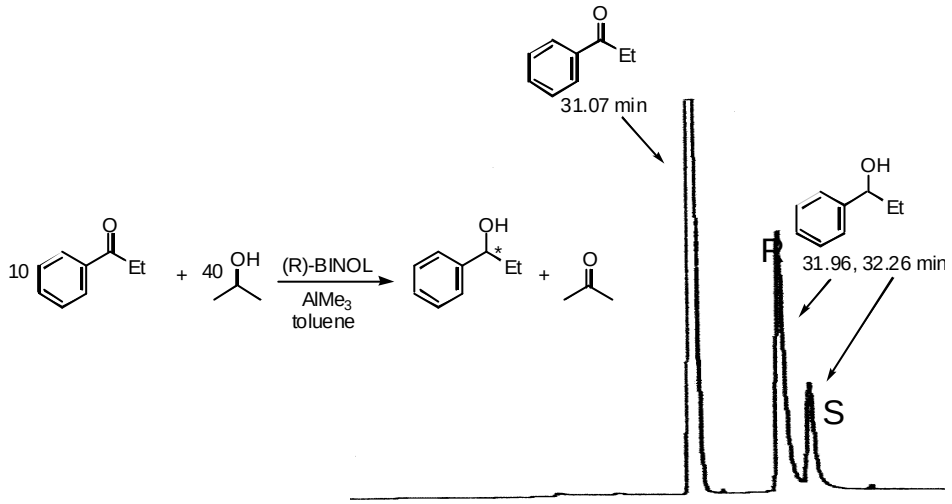
Temp. Program: initial temp. = 80 °C, initial time = 0 min., ramp = 2 °C/min., final temp = 180 °C, final time = 10 min.

The chiral GC trace (after 12h) for the MSPV reduction of a -bromoacetophenone catalyzed by (*S*)-BINOL and $AlMe_3$ (Table 1, entry 2).



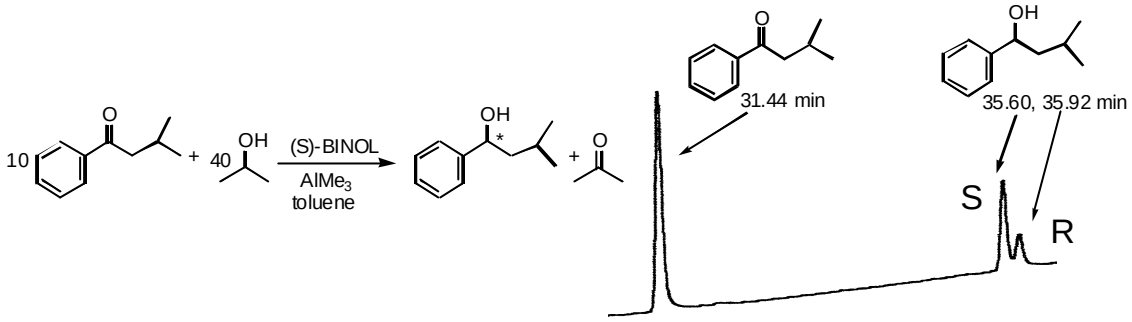
Temp. Program: initial temp. = 100 °C, initial time = 0 min., ramp = 2 °C/min., final temp = 180 °C, final time = 10 min.

The chiral GC trace for the MSPV reduction of propiophenone catalyzed by (*R*)-BINOL and $AlMe_3$ (Table 1, entry 3).



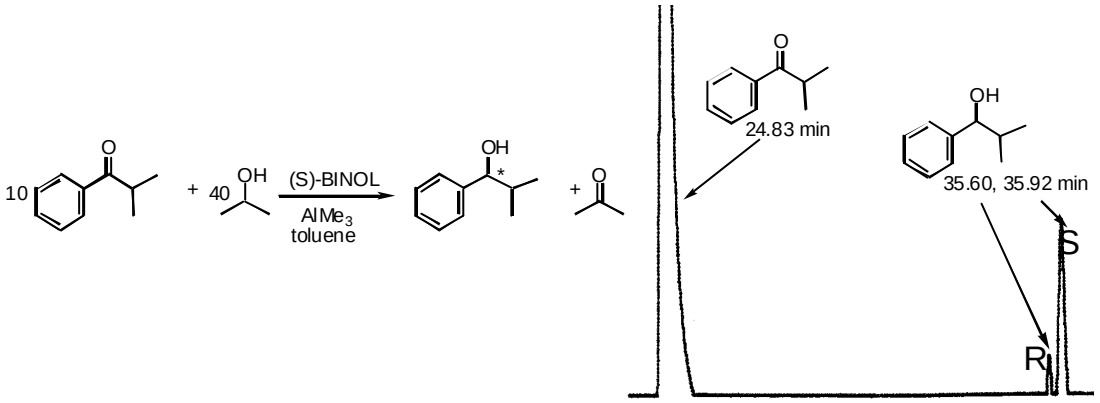
Temp. Program: initial temp. = 100 °C, initial time = 0 min., ramp = 2 °C/min., final temp = 180 °C, final time = 10 min.

The chiral GC trace for the MSPV reduction of *iso*valerophenone catalyzed by (*S*)-BINOL and $AlMe_3$ (Table 1, entry 4).



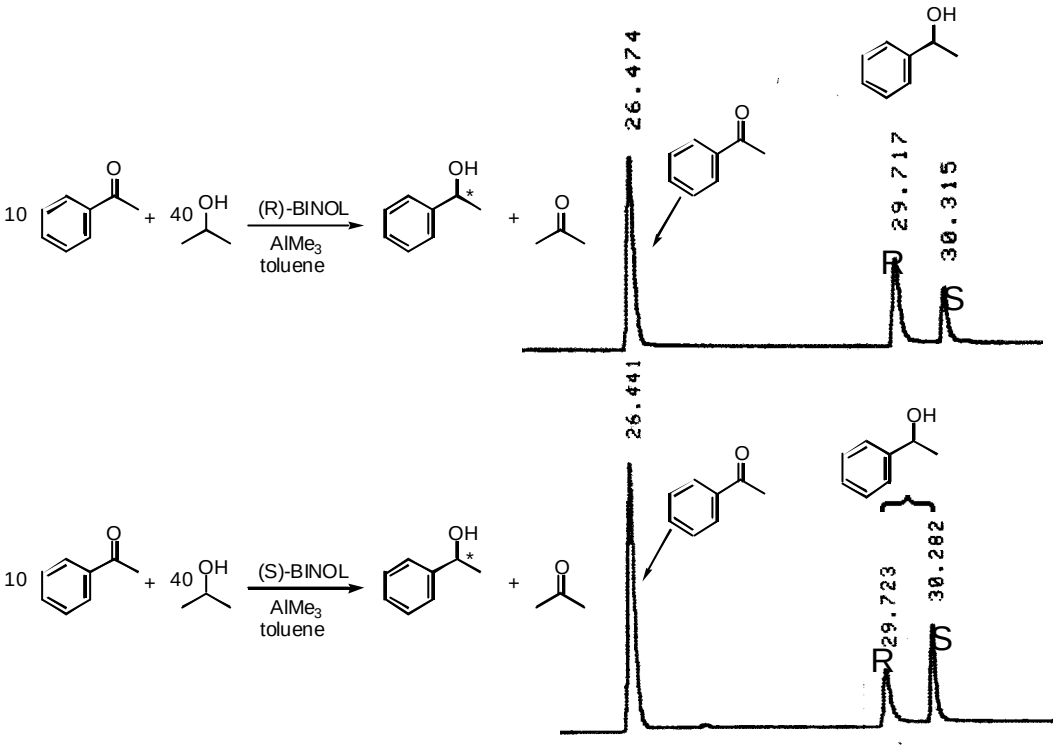
Temp. Program: initial temp. = 100 °C, initial time = 0 min., ramp = 2 °C/min., final temp = 180 °C, final time = 10 min.

The chiral GC trace for the MSPV reduction of *iso*butyrophenone catalyzed by (*S*)-BINOL and $AlMe_3$ (Table 1, entry 5).



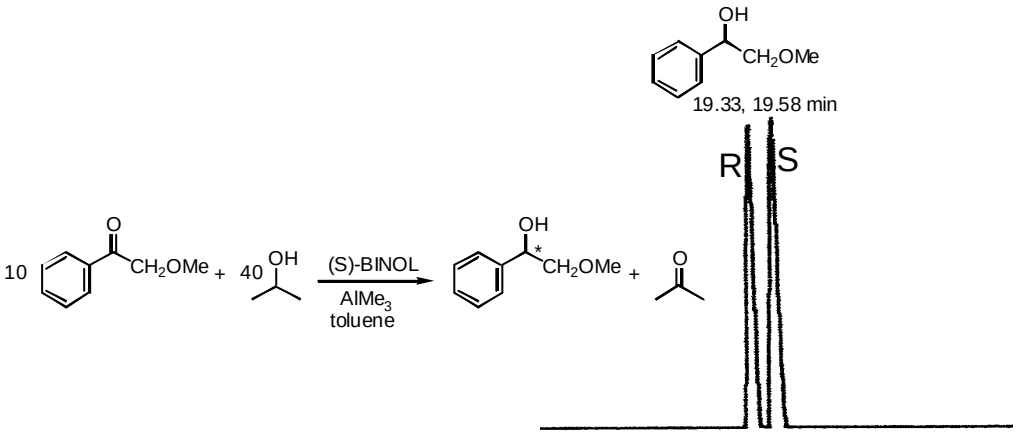
Temp. Program: initial temp. = 100 °C, initial time = 0 min., ramp = 2 °C/min., final temp = 180 °C, final time = 10 min.

The chiral GC trace for the MSPV reduction of acetophenone catalyzed by (*R*)-and (*S*)-BINOL and $AlMe_3$ (Table 1, entry 6).



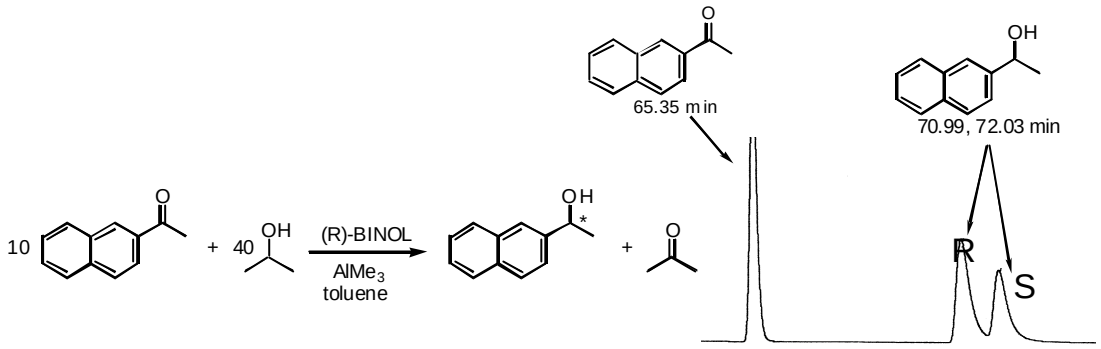
Temp. Program: initial temp. = 80 °C, initial time = 20 min., ramp = 5 °C/min., final temp = 180 °C, final time = 10 min.

The chiral GC trace for the MSPV reduction of a-methoxyacetophenone catalyzed by (*S*)-BINOL and $AlMe_3$ (Table 1, entry 7).



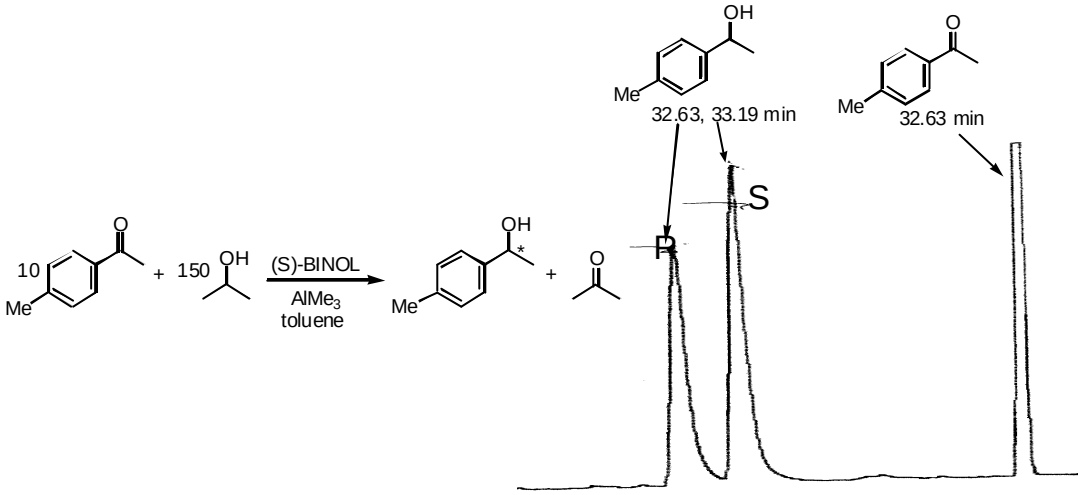
Temp. Program: initial temp. = 100 °C, initial time = 0 min., ramp = 2 °C/min., final temp = 180 °C, final time = 10 min.

The chiral GC trace for the MSPV reduction of acetonaphthenone catalyzed by (*R*)-BINOL and $AlMe_3$ (Table 1, entry 8).



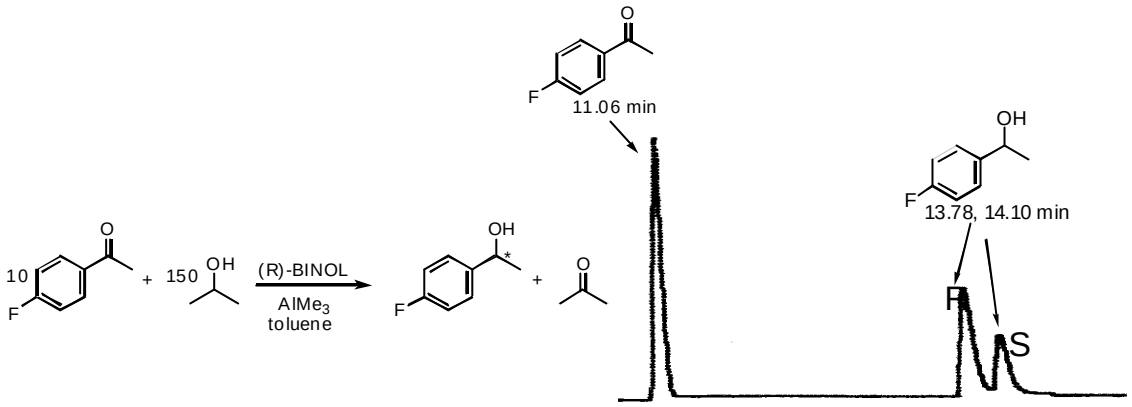
Temp. Program: initial temp. = 100 °C, initial time = 0 min., ramp = 1 °C/min., final temp = 180 °C, final time = 10 min.

The chiral GC trace for the MSPV reduction of 4-methylacetophenone catalyzed by (*S*)-BINOL and $AlMe_3$ (Table 2, entry 2).



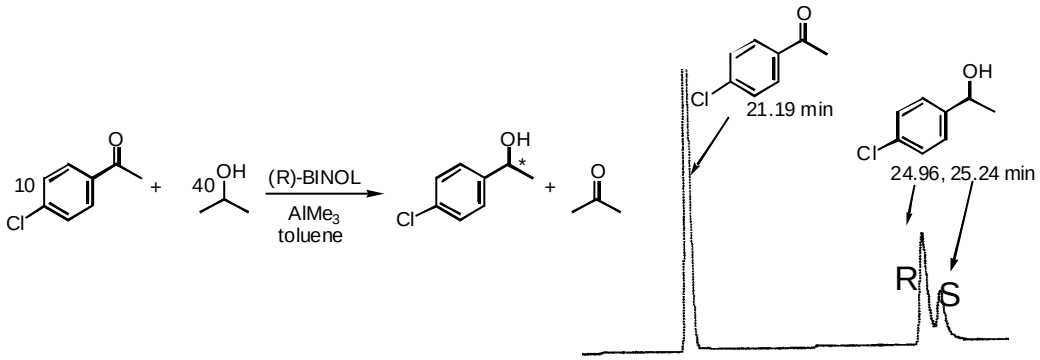
Temp. Program: initial temp. = 80 °C, initial time = 20 min., ramp = 5 °C/min., final temp = 180 °C, final time = 10 min.

The chiral GC trace for the MSPV reduction of 4-fluroacetophenone catalyzed by (*R*)-BINOL and $AlMe_3$ (Table 2, entry 3).



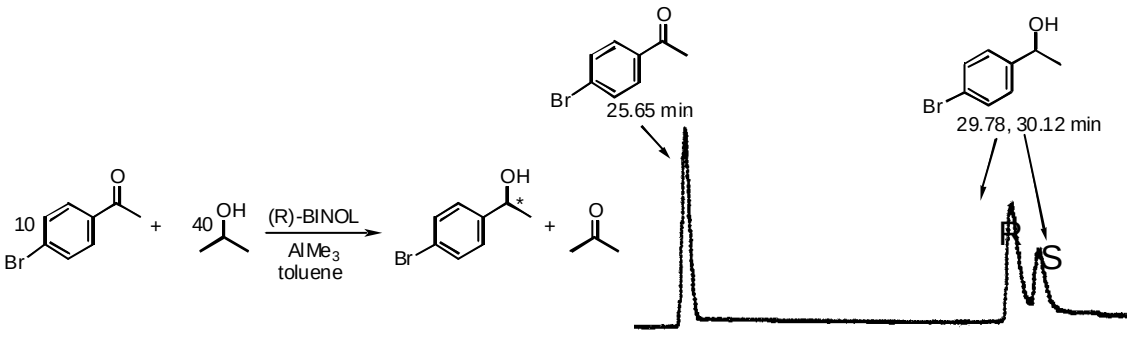
Temp. Program: initial temp. = 80 °C, initial time = 20 min., ramp = 5 °C/min., final temp = 180 °C, final time = 10 min.

The chiral GC trace for the MSPV reduction of 4-chloroacetophenone catalyzed by (*R*)-BINOL and $AlMe_3$ (Table 2, entry 4).



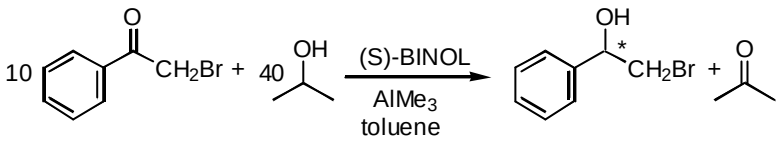
Temp. Program: initial temp. = 80 °C, initial time = 20 min., ramp = 5 °C/min., final temp = 180 °C, final time = 10 min.

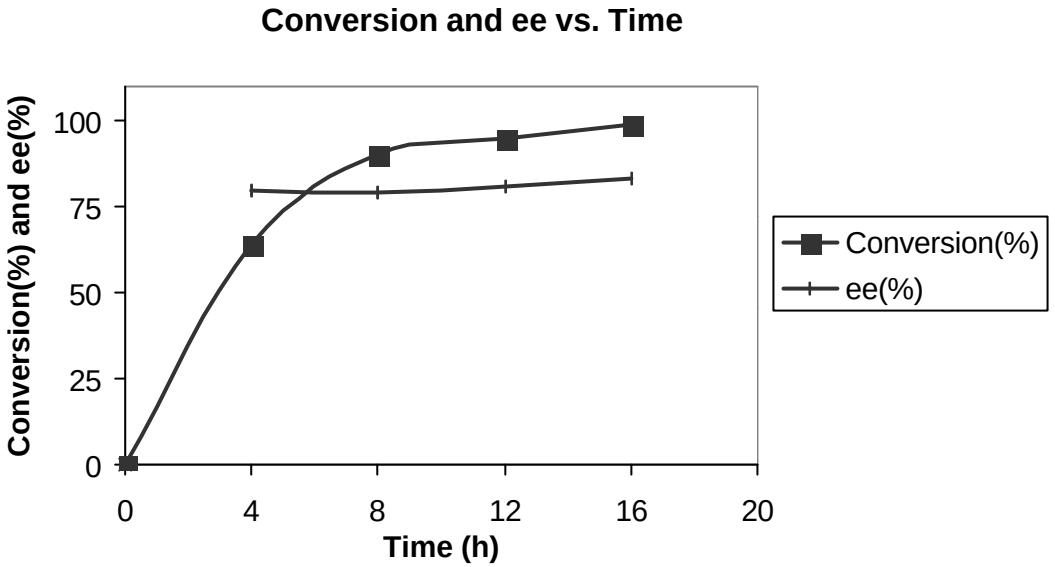
The chiral GC trace for the MSPV reduction of 4-bromoacetophenone catalyzed by (*R*)-BINOL and $AlMe_3$ (Table 2, entry 5).



Temp. Program: initial temp. = 80 °C, initial time = 20 min., ramp = 5 °C/min., final temp = 180 °C, final time = 10 min.

The time evolution of the selectivity and conversion for the asymmetric MSPV reduction of a -bromoacetophenone.

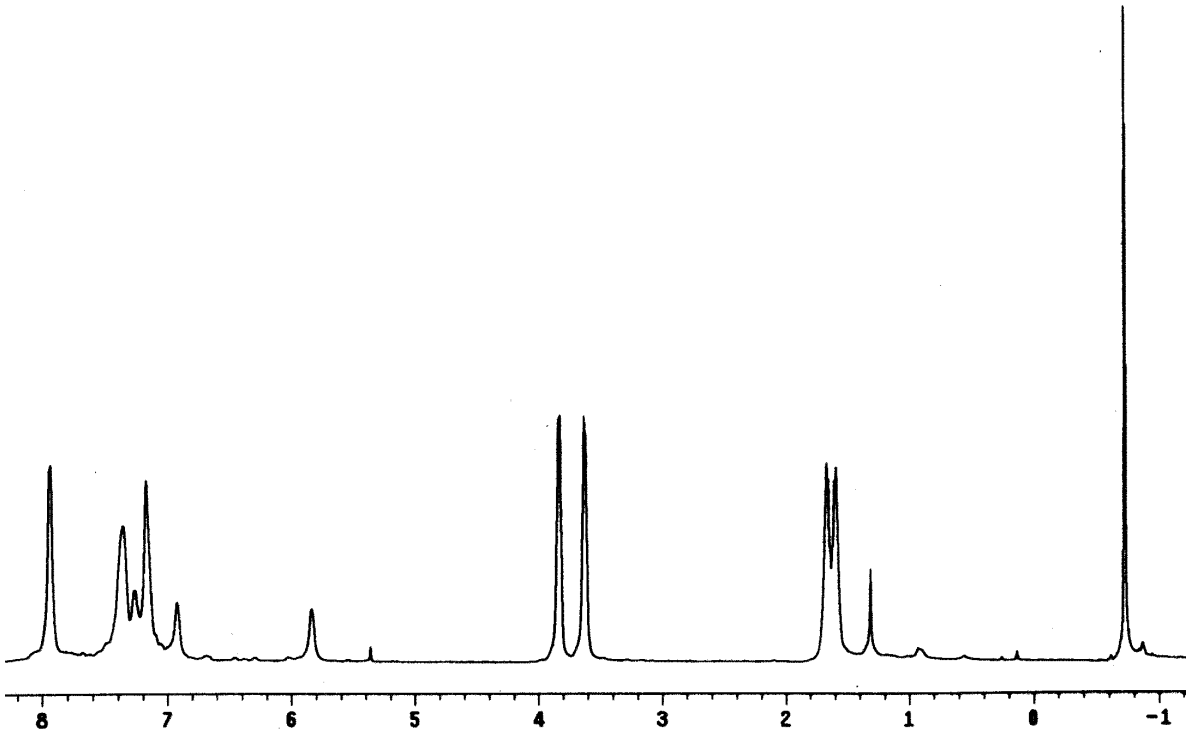




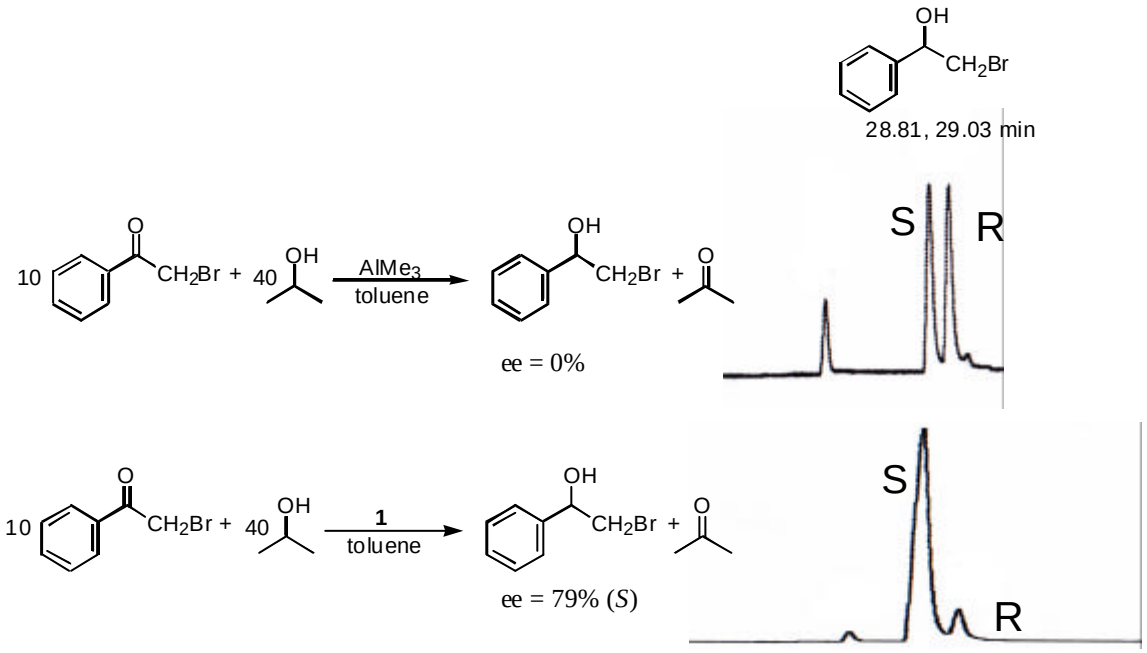
Time evolution study of chirally pure (*R*)-1-phenylethanol. Into a 4-mL-vial equipped with a magnetic stir bar was added toluene (500 μL) and enantiopure (*R*)-BINOL (5.8 mg, 0.02 mmol). $AlMe_3$ (1.9 ml, 0.02 mmol) was added to the mixture via syringe and the reaction was allowed to stir for 5 minutes when a white precipitate formed. (*R*)-1-phenylethanol (24 μL, 10 equiv), Acetone (31 μL, 20 equiv) and 2-propanol (30 μL, 20 equiv) were added and the vial was sealed with a teflon-lined silicone septa. The reaction was stirred at room temperature under nitrogen for 16 hours. Aliquots (20 μL) were passed through a plug of neutral aluminum oxide [activated, Brockmann activity 1, ~150 mesh] and analyzed on GC to determine selectivity and conversion data.

Synthesis of ((*S*)-BINOL)AlMe•THF (1). In the drybox and into a 50-mL Schlenk flask equipped with a magnetic stir bar was added Toluene (10 mL) THF (160 μL, 2 equiv) and (*S*)-(-)-BINOL (0.287 g, 1 mmol). $AlMe_3$ (96.5 μL, 1 mmol) was added to the mixture via syringe and the reaction was allowed to stir for 3 h. The solvent was removed under vacuum and a white solid was collected, yield = 350 mg (88%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.92 (b, 3H, naphthyl), 7.32-6.85 (b, 8H, naphthyl), 5.81 (b, 1H, naphthyl), 3.82 (m, 2H, OCH_2), 3.59 (m, 2H, OCH_2), 1.60 (m, 2H, OCH_2CH=CH), -0.76 (s, 3H, Al-CH_3). ^{13}C NMR (500 MHz, DMSO-d_6): δ 157.69, 150.03, 134.40, 133.96, 130.64, 128.98, 128.67, 127.68, 126.10, 125.85, 125.19, 124.39, 123.86, 122.81,122.21, 117.02, 70.63, 25.53, –11.12 (Al-CH_3).

The ^{1}H NMR spectra of complex 1 in DMSO-d_6 .



The chiral GC trace for the MSPV reduction of a -bromoacetophenone catalyzed by ((*S*)-BINOL)AlMe•THF.



References.

(1) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**; *65*, 6319-6337.
(2) Pirkle, W. H.; Schreiner, J. L. *J. Org. Chem.* **1981**, *46*, 4988-4991.
(3) Ko, B.-T.; Chao, Y.-C.; Lin, C.-C. *Inorg. Chem.* **2000**, *39*, 1463-1469.
(4) Campbell, E. J.; Zhou, H.; Nguyen, S. T. *Org. Lett.* **2001**, *3*, 2391-2393.