Catalytic Enantioselective Sulfinyl Transfer Using Cinchona Alkaloid Catalysts

Hillary M. Peltier, Jared W. Evans, Jonathan A. Ellman*

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, California 94720

Supporting Information

Reagents and General Methods. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. 1,8-Bis(dimethylamino)naphthalene was recrystallized from absolute EtOH. *tert*-Butylsulfinyl chloride was prepared using the previously published method.¹ Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. CH₂Cl₂, acetonitrile (CH₃CN), and triethylamine (Et₃N) were distilled from CaH₂ immediately prior to use. Toluene was distilled from Na. The concentration of commercially available solutions of phenyllithium in cyclohexane-ether was determined by titration with 2,6-di-*tert*-butyl-4-methylphenol and 1,10-phenanthroline. Reactions were carried out in flame- or oven- dried glassware under a N₂ atmosphere. Extracts were dried over Na₂SO₄ and concentrated using a Buchi rotary evaporator under reduced pressure. Chromatography was carried out with Merck 60 Å 230-400 mesh silica gel. IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory and only partial data are listed. ¹H and ¹³C NMR spectra were obtained in CDCl₃ at room temperature. Chemical shifts in NMR spectra are expressed in ppm relative to CDCl₃. Coupling constants are reported in Hz. Enantiopurities were determined by HPLC using Diacel CHIRALCEL OD, CHIRALCEL AD, and CHIRALCEL AS (4.6 x 250 mm) columns with UV detection at 210 and 254 nm. Elemental analyses were performed by the University of California at Berkeley Micro-Mass Facility. Spectroscopic data of sulfinate esters **19a** and **19c** is consistent with previously published data.¹

General Procedure A: Enantioselective formation of sulfinate esters (2, 19a-g). A solution of proton sponge (54.0 mg, 0.250 mmol, 2.50 equiv), alcohol (0.500 mmol, 5.00 equiv), catalyst (0.0100 mmol, 0.100 equiv), and internal standard, 2,6-dimethoxytoluene (15.2 mg, 0.100 mmol, 1.00 equiv) in the indicated solvent (0.500 mL, 0.200 M) was cooled to the indicated temperature and sulfinyl chloride **1** (50.0 μ L, 0.100 mmol, 2.00 M) was added as a solution in toluene over a period of 5 min. At the indicated time, 2.00 mL of NEt₃/CD₃OD (0.20 mL of NEt₃/10 g CD₃OD) was added to quench any remaining **1** and 0.300 mL of the mixture was transferred to an NMR tube containing 1.00 mL of CDCl₃. After yield determination by NMR integration relative to the internal standard, the solvents were removed *in vacuo* and the residue was diluted with hexanes (ca. 3.00 mL) and filtered for HPLC analysis. (For yields and ee, see Tables 1-4. See experimental procedures for the preparation, characterization, and chiral HPLC conditions for the racemic sulfinate esters listed below.)

General Procedure B: Formation of racemic sulfinate esters (2, 19b, 19d, 19e, 19f, 19g). A solution of the alcohol (4.45 mmol, 5.00 equiv) and NEt₃ (0.186 mL, 1.33 mmol, 1.50 equiv) in THF (4.45 mL, 0.200 M) was cooled to -78 °C. Sulfinyl chloride **1** (0.404 mL, 0.889 mmol, 2.20 M, 1.00 equiv) was added as a solution in toluene, and after 2 h the reaction vessel was removed from the cold bath. Once the reaction mixture warmed to room temperature, it was stirred for 1 h, diluted with EtOAc (50 mL), and washed with 1N HCl (50 mL), NaHCO₃ (50 mL), brine (50 mL), and then dried and filtered. The EtOAc was removed *in vacuo*, and the residue was purified via silica gel chromatography to afford pure sulfinate ester.

2-Methylpropane sulfinic acid benzyl ester (2). Reaction of 0.461 mL (4.45 mmol) of benzyl alcohol according to General Procedure B yielded pure **2** (0.162 g, 86%) as a colorless oil after chromatography (10% EtOAc/hexanes) with spectral data corresponding to the literature

report.¹ HPLC (Diacel Chiralpak OD column, 96:04 hexanes/IPA; 1.0 mL/min) $t_1 = 7.6$ min, $t_2 = 8.7$ min. ¹H NMR (400 MHz) δ 1.20 (s, 9H), 4.99 (d, 1H, $J = 11.8$ Hz), 5.13 (d, 1H, $J = 11.8$ Hz), 7.31 (m, 5H).

2-Methylpropane-2-sulfinic acid 4-chlorobenzyl ester (19b). Reaction of 0.635 g (4.45 mmol) of 4-chlorobenzyl alcohol according to General Procedure B yielded pure **19b** (0.217 g, 99%) as a colorless oil after chromatography (25% EtOAc/hexanes). HPLC (Diacel Chiralpak OD column, 96:04 hexanes/IPA; 1.0 mL/min) $t_1 = 7.9$ min, $t_2 = 9.9$ min. IR 3053, 2959, 1599, 1493, 1393, 1127 cm^{-1} . ¹H NMR (400 MHz) δ 1.20 (s, 9H), 4.95 (d, 1H, $J = 12.0$ Hz), 5.09 (d, 1H, $J = 12.0$ Hz), 7.33 (m, 4H). ¹³C NMR (100 MHz) δ 21.4, 57.4, 69.8, 128.5, 129.3, 134.1, 134.4. Anal. Calcd for $\text{C}_{11}\text{H}_{15}\text{ClO}_2\text{S}$: C, 53.54; H, 6.13. Found: C, 53.94; H, 6.27.

2-Methylpropane-2-sulfinic acid naphthalen-1-ylmethyl ester (19d). Reaction of 0.703 g (4.45 mmol) of 1-naphthylmethanol according to General Procedure B yielded pure **19d** (0.200 g, 86%) as a colorless oil after chromatography (2:1 hexanes/EtOAc). HPLC (Diacel Chiralpak OD column, 96:04 hexanes/IPA; 1.0 mL/min) $t_1 = 11.6$ min, $t_2 = 13.7$ min. IR 3053, 2963, 2869, 1600, 1510, 1477, 1362, 1119 cm^{-1} . ¹H NMR (500 MHz) δ 1.14 (s, 9H), 5.36 (d, 1H, $J = 11.8$), 5.62 (d, 1H, $J = 11.8$), 7.43-7.46 (m, 1H), 7.50-7.58 (m, 3H), 7.85-7.88 (m, 2H), 8.08 (d, 1H, $J = 8.5$ Hz). ¹³C NMR (125 MHz) δ 21.6, 57.5, 69.1, 123.8, 125.2, 126.0, 126.6, 127.7, 128.6, 129.7, 131.5, 131.6, 133.7. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2\text{S}$: C, 68.67; H, 6.92. Found: C, 68.93; H, 7.14.

2-Methylpropane-2-sulfinic acid 2,6-dichlorobenzyl ester (19e). Reaction of 0.787 g (4.45 mmol) of 2,6-dichlorobenzyl alcohol according to General Procedure B yielded pure **19e** (0.232 g, 93%) as a white crystalline solid after chromatography (25% EtOAc/ hexanes). HPLC (Diacel Chiralpak AD column, 96:04 hexanes/IPA 1.0mL/min) $t_1 = 7.6$ min, $t_2 = 8.1$ min. IR

3027, 2959, 1591, 1363, 1125 cm^{-1} . ^1H NMR (500 MHz) δ 1.16 (s, 9H), 5.32 (d, 1H, J = 11.3 Hz), 5.37 (d, 1H, J = 11.3 Hz), 7.25-7.37 (m, 3H). ^{13}C NMR (100 MHz) δ 21.4, 57.6, 65.3, 128.4, 130.7, 131.7, 136.8. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{O}_2\text{S}$: C, 46.98; H, 5.02. Found: C, 47.08; H, 5.20.

2-Methylpropane-2-sulfinic acid 2,6-methylbenzyl ester (19f). Reaction of 0.606 g (4.45 mmol) of 2,6-dimethylbenzyl alcohol² according to General Procedure B yielded pure **19f** (0.210 g, 98%) as a colorless oil after chromatography (3:1 hexanes/EtOAc). HPLC (Diacel Chiralpak OD column, 99:01 hexanes/IPA; 1.0 mL/min) t_1 = 9.3 min, t_2 = 10.8 min. IR 3075, 2958, 1562, 1438, 1123 cm^{-1} . ^1H NMR (400 MHz) δ 1.15 (s, 9H), 2.42 (s, 6H), 5.08 (d, 1H, J = 11.1 Hz), 5.17 (d, 1H, J = 11.1 Hz), 7.06 (d, 2H, J = 7.5 Hz), 7.17 (t, 1H, J = 7.6 Hz). ^{13}C NMR (100 MHz) δ 19.6, 21.5, 57.3, 65.1, 128.2, 128.9, 132.2, 138.3. Anal. Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2\text{S}$: C, 64.96; H, 8.39. Found: C, 64.99; H, 8.67.

2-Methylpropane-2-sulfinic acid 2,4,6-trichlorobenzyl ester (19g). Reaction of 0.940 g (4.45 mmol) of 2,4,6-trichlorobenzyl alcohol according to General Procedure B yielded **19g** (0.224 g, 80%) as a white crystalline solid after chromatography (3:1 hexanes/EtOAc). HPLC (Diacel Chiralpak AD column, 96:04 hexanes/IPA; 1.0 mL/min) t_1 = 6.5 min, t_2 = 7.0 min. IR 3064, 2959, 1582, 1550, 1459, 1380, 1131 cm^{-1} . ^1H NMR (500 MHz) δ 1.15 (s, 9H), 5.25 (d, 1H, J = 11.4 Hz), 5.30 (d, 1H, J = 11.4 Hz), 7.36 (s, 2H). ^{13}C NMR (125 MHz) δ 21.5, 57.8, 64.7, 128.5, 130.6, 135.8, 137.4. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{Cl}_3\text{O}_2\text{S}$: C, 41.86; H, 4.15. Found: C, 42.23; H, 4.27.

TBDPS-S-(-)-1-Methyl-2-pyrrolidinemethanol (5). To a solution of (*S*)-(-)-1-methyl-2-pyrrolidinemethanol (0.0673 mL, 0.566 mmol) and imidazole (73.2 mg, 1.07 mmol) in DMF (0.210 mL, 2.70 M) at 0 °C was added *tert*-butylchlorodiphenyl silane (0.177 mL, 0.679

mmol). The ice bath was removed after 15 min and the mixture was stirred at rt for 20 h. The reaction mixture was diluted with EtO₂ (10 mL) and washed with H₂O (3 x 10 mL) and brine (1 x 10 mL). The organic layer was dried, filtered, and concentrated. Column chromatography (2:1 hexanes/EtOAc) afforded **5** (69.4 mg, 35%) as a colorless oil. IR 3071, 2930, 2854, 2771 cm⁻¹. ¹H NMR (500 MHz) δ 1.07 (s, 9H), 1.53-1.59 (m, 1H), 1.67-1.78 (m, 2H), 1.89-1.96 (m, 1H), 2.20-2.24 (m, 1H), 2.37-2.42 (m, 1H), 2.39 (s, 3H), 3.01-3.05 (m, 1H), 3.53 (dd, 1H, *J* = 10.1, 6.3), 3.75 (dd, 1H, *J* = 10.1, 5.7), 7.38-7.44 (m, 6H), 7.68-7.70 (m, 4H). ¹³C NMR (125 MHz) δ 19.2, 22.7, 26.8, 28.7, 41.9, 57.9, 66.9, 67.8, 127.6, 129.5, 133.7, 133.8, 135.58, 135.6. MS (FAB): *m/z* 354 (MH⁺). HRMS (FAB) Calcd for (MH⁺): 354.2253. Found 354.2248.

Large scale procedure for the enantioselective formation of sulfinate 19g with 10 mol% of quinidine. A solution of proton sponge (846 mg, 3.95 mmol, 2.50 equiv), 2,4,6-trichlorobenzyl alcohol (1.67 g, 7.90 mmol, 5.00 equiv), and quinidine (51.3 mg, 0.158 mmol, 0.100 equiv) in THF (7.90 mL, 0.200 M) was cooled to -40 °C (internal temperature) and sulfinyl chloride **1** (0.790 mL, 1.58 mmol, 2.00 M) was added as a solution in toluene over a period of 40 min. After 20 h, 10 mL of MeOH and 0.2 mL of Et₃N were added and the reaction solution was stirred for 1 h at -40 °C and then was allowed to warm to rt. The mixture was concentrated under reduced pressure and Et₂O (75 mL) was added. The organic layer was washed with 1N HCl (75 mL), NaHCO₃ (75 mL), and brine (75 mL), and then dried, filtered, and concentrated. The resulting residue was purified by column chromatography using basic alumina (3:1 hexanes/EtOAc) to afford **19g** as a white crystalline solid (458 mg, 92%, 90% ee) with spectral data corresponding to that listed above. A combined 1.03 g of 90% ee material was recrystallized two times from heptane (10 mL) to afford **19g** as a white crystalline solid (742 mg, 72%, 99.6% ee).

Determination of the absolute stereochemistry of sulfinic acid ester 19g. Sulfinic acid ester **19g** (12.1 mg, 0.0383 mmol, 99.6% ee) was added to a flame dried 1-dram vial containing THF (0.200 mL, 0.200 M), and the mixture was cooled to -78°C . PhLi (0.121 mL, 0.115 mmol, 0.950 M in cyclohexane-ether) was added dropwise, and the reaction mixture was stirred for 2 h. After the addition of AcOH (0.121 mL, 1.00 M in THF), the mixture was warmed to rt, diluted with EtOAc (10 mL), and washed with brine. The aqueous layer was washed with EtOAc (3 x 10 mL), and the combined organic extracts were dried and concentrated. The resulting residue was purified by column chromatography (1:1 hexanes/EtOAc) to afford (*R*)-*tert*-butyl phenyl sulfoxide (6.90 mg, 99%, 99.6% ee) with spectral data corresponding to the literature report.³ HPLC (Diacel Chiralpak AS column, 90:10 hexanes/ethanol; 1.0 mL/min) $t(S) = 7.8$ min [minor], $t(R) = 9.3$ min [major]. ^1H NMR (400 MHz) δ 1.17 (s, 9H), 7.47-7.52 (m, 3H), 7.58-7.61 (m, 2H).

---

¹ Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134.

² Soloshonok, V. A.; Tang, X.; Hruby, V. J. *Tetrahedron* **2001**, *57*, 6375.

³ Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.