Asymmetric Protonation of Ketone Enolates Using Chiral β -Hydroxyethers:

Acidity-tuned Enantioselectivity

Supporting Information

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Experimental

Compound **1a** was prepared according to the literature procedure,¹³ Compounds **1b-f** were prepared following methods used for the preparation of **1a** and their physical data are listed below.

Synthetic scheme

Characterization data

Compound **1a**: IR (KBr, cm^{-1}) 3430.0, 3037.8, 2933.0, 2868.2, 1458.4; $[\alpha]_{\text{D}}^{25} = +9.3$ (c 1.0, CHCl_3); ^1H NMR (300MHz, CDCl_3) δ 2.20-3.10 (br, s, 1H), 4.66 (d, 1H, $J=6.8$ Hz) 5.05 (d, 1H, $J=12.8$ Hz) 5.18 (ABq, $J=12.8$ Hz, 2H), 5.33 (d, 1H, $J=6.8$ Hz), 6.46 (d, 1H, $J=7.5$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 73.1, 77.4, 88.5, 121.3, 123.2, 127.4, 128.2, 128.4, 128.8, 128.8, 138.0, 139.6, 140.1 ; CI Mass m/z 209 ($\text{M}+\text{H}-\text{H}_2\text{O}$) $^{+}$

Compound **1b**: IR (KBr) 3436.8, 3018.90, 2914.4, 2861.9, 1605.4, 1462.9, 1033.9; $[\alpha]_{\text{D}}^{26} = -19.3$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 2.32 (s, 6H), 2.83 (br, s, 1H), 4.59 (d, $J=6.8$ Hz, 1H), 5.11 (d, $J=12.3$ Hz, 1H), 5.20 (ABq, $J=12.23$ Hz, 2H), 5.32 (d, $J=6.8$ Hz, 1H), 6.47 (d, $J=7.6$ Hz, 1H), 6.98-7.29 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.8, 77.3, 88.4, 121.3, 123.2, 125.9, 126.3, 127.3, 128.4, 130.4, 138.2, 138.3, 139.5, 140.1; HRMS (EI) m/z calcd 254.1307 for $\text{C}_{17}\text{H}_{18}\text{O}_2[\text{M}]^{+}$, found 254.1316 .

Compound **1c**: IR (KBr) 3347.5, 3070.5, 2880.6, 1589.8, 1568.4, 1426.6, 1198.1, 1041.2; (*S,S*)-**1c**: $[\alpha]_D^{28} = +25.1$ [*c* 1.0, CHCl₃]; (*R,R*)-**1c** $[\alpha]_D^{28} = -21.8$ [*c* 1.0, CHCl₃]; ¹H NMR (300 MHz, CDCl₃) δ 2.88 (br, s, 1H), 4.69 (d, *J*=5.7 Hz, 1H), 5.17 (ABq, *J*=12.4 Hz, 2H), 5.29 (d, *J*=5.6, 1H), 6.75 (d, *J*=4.8 Hz, 1H), 7.11-7.44 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 73.4, 76.0, 87.9, 121.6, 122.7, 126.5, 127.7, 128.6, 128.8, 135.3, 137.3, 140.1, 143.5; EA calcd for C₁₅H₁₂Cl₂O₂; C,61.04; H,4.10; Cl,24.02; O,10.84. found: C, 60.81; H, 4.06.

Compound **1d**: IR (KBr) 3411.3, 3034.0, 2928.3, 2867.9, 1490.6, 1400.0, 1067.9; $[\alpha]_D^{18} = -12.2$ (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 2.95 (br, s, 1H), 4.66 (d, *J*=5.7 Hz, 1H), 5.12 (ABq, *J*=12.3 Hz, 2H), 5.28 (d, *J*=5.7 Hz, 1H), 6.54 (d, *J*=7.5 Hz, 1H), 7.11-7.36 (m, 6H); ¹³C NMR (75MHz, CDCl₃) δ 73.2, 76.6, 88.3, 121.4, 123.0, 127.5, 128.6, 128.9, 129.5, 134.4, 137.6, 138.2, 140.1; EA calcd for C₁₅H₁₃ClO₂; C,69.10; H,5.03; Cl,13.60; O,12.27. found: C, 69.01; H, 5.01.

Compound **1e**: IR (KBr) 3368.1, 2870.7, 1372.3, 1285.1, 1166.2, 1122.0; $[\alpha]_D^{19} = +36.6$ (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 2.90 (d, *J*=3.5 Hz, 1H), 4.93 (d, *J*=5.0 Hz, 1H), 5.09 (s, 2H), 5.35 (d, *J*=5.2 Hz, 1H), 6.80 (d, *J*=7.7, 1H), 7.21-7.34 (m, 6H), 7.83 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 73.5, 75.8, 87.7, 121.6, 122.3, 122.6, 125.5, 127.8, 128.1, 129.0, 131.8, 137.0, 140.1, 142.7; EA calcd for C₁₇H₁₂F₆O₂; C,56.36; H,3.34; F,31.47; O,8.83. found: C, 56.65; H, 3.30 .

Compound **1f**: IR (KBr) 3418.5, 3078.1, 2865.0, 1619.8, 1325.6, 1164.1, 1123.1, 1067.7; $[\alpha]_D^{19} = +18.3$ (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 3.00 (d, *J*=3.1 Hz, 1H), 5.16 (ABq, *J*=12.2 Hz, 2H), 5.35 (d, *J*=5.8 Hz, 1H), 6.52 (d, *J*=7.5 Hz, 1H), 7.17-7.34 (m, 3H), 7.51 (d, *J*=8.1 Hz, 2H), 7.65 (d, *J*=8.2 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 73.3, 76.6, 88.1, 121.5, 122.8, 125.6, 126.3, 127.6, 128.3, 128.7, 130.8, 137.5, 140.1, 143.9; EA calcd for C₁₆H₁₃F₃O₂; C, 65.30; H, 4.45; F, 19.37; O,10.87. found C, 65.40; H, 4.41.

A representative procedure for the enantioselective protonation of lithium enolates prepared from 4, 6, 7, and 8: TMS enol ether **4** prepared from ketone **5** (23 mg, 0.10 mmol) in diethyl ether (1.0 mL) at 0°C was treated with a solution of methyl lithium in diethyl ether (1.40 M, 110 μ L, 0.15 mmol). The mixture was stirred at room temperature for 30 min and then cooled to -78°C . Then the lithium enolate solution at -78°C was added to a solution of β -hydroxyether **1a** (36 mg, 0.16 mmol) in dichloromethane (1.6 mL) at the same temperature. The mixture was stirred for 1 h and then gradually warmed up to 0°C. The reaction mixture was treated with phosphate buffer (pH 7.2) and extracted with ethyl acetate. The residue was purified through column chromatography to give 2-methyl-1-tetralone as a pale red oil (16 mg, 99% yield) and **1a** (36 mg, 99% recovery). HPLC analysis to determine the ee of the product ketone was carried out on Hewlett Packard 1100 series HPLC equipped with diode array detector using Chiralcel OD-H column and eluting with hexane/*i*-PrOH 99:1 (v/v).