Asymmetric Transfer Hydrogenation of Prochiral Ketones in Aqueous Media with New Water-Soluble Chiral Vicinal Diamine as Ligand

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1. General

^{1}H NMR spectra were recorded on Bruker (300 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz). ^{13}C NMR data were collected on Bruker (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0). Elemental analyses were performed on Carlo Erba 1106. Enantiomeric ratio was determined by chiral GLC on CP-cyclodex B-236 M or CP-Chiralsil-*L*-Val or CP-Chirasil-DEX CB column and by chiral HPLC analysis on Daicel Chiralcel OD/OJ column in comparison with the authentic racemates. Optical rotation data were recorded on Perkin-Elmer Polarimeter-341. All ketones were purchased from Acros, Aldrich and Fluka, and used directly without further purification.

2. Synthesis of (*R,R*)-**2**

Compound (*R,R*)-**1** (1.000 g, 4.717 mmol) was added to 2.4 mL of oleum (50% SO_3) at 0 ^{o}C and the mixture was stirred vigorously for 22 hr at 0 ^{o}C to room temperature. Then the viscous mixture was poured onto ca. 50 g crashed ice carefully under vigorous stirring, and excessive solid $BaCO_3$ was added to neutralize to pH = 7-8. The product was purified by RP chromatography, and 1.765 g of white solid was obtained (68% yield). M.p. >280 ^{o}C (decomposed); $[\alpha]_D^{20}$= +48.1° (c= 0.70, H_2O); ^{1}H-NMR (D_2O, 300 MHz, ppm), δ: 7.60-7.57 (m, 4H, aromatic H), 7.32-7.14 (m, 4H, aromatic H), 4.26 (s, 2H, 2 × CH); ^{13}C-NMR (D_2O, 75 MHz, ppm), δ: 142.5, 140.2, 130.5, 129.1, 124.8, 123.8, 60.4; IR (cm^{-1}), υ: 1040.5 (SO_2), 1193.9 (SO_2), 1632.9 (N-H), 3447.4 (N-H); ESI-HRMS (*m/z*): Calcd. for $C_{14}H_{14}BaN_2O_6S_2$ + H 508.9418; obsd. 508.9431.

3. Synthesis of (*R,R*)-**3**

Compound *(R,R)*-**2** (1.715 g, 3.096 mmol) and 1.4 equivalent of NaOH (176 mg, 4.391 mmol) were dissolved in 15 mL of water. 0.2 equivalent of SDS (184 mg, 0.676 mmol) was added as surfactants, and 1.2 equivalent of TsCl dissolving in 30 mL of DCM was added dropwise under vigorously stirring at room temperature for 24 hr to the mixture. After the SDS was filtered, the aqueous layer was separated from DCM and 1.1 equivalent of Na_2SO_4 (433 mg, 3.406 mmol) was added into this aqueous solution to remove the Ba^{2+} ion. The mixture was concentrated and purified by RP chromatography to give 1.353 g of the white product as (*R,R*)-**3** · $2H_2O$ (72% yield). M.p. >280 ^{o}C (decomposed); $[\alpha]_D^{20}$= +66.3° (c=0.64, H_2O); ^{1}H-NMR (D_2O, 300 MHz, ppm), δ: 7.57-7.47 (m, 2H, aromatic H), 7.29-7.11 (m, 6H, aromatic H), 6.91 (m, 3H, aromatic H), 6.76-6.73 (m, 1H, aromatic H), 4.51 (d, *J* = 9.0 Hz, 1H, CH), 4.33 (d, *J* = 9.0 Hz, 1H, CH), 2.10 (S, 3H, CH_3); ^{13}C-NMR (D_2O, 75 MHz, ppm), δ: 145.4, 143.5, 143.3, 140.6, 138.5, 135.8, 131.6, 131.4, 130.5, 129.9, 129.7, 127.4, 125.8, 125.2, 124.9, 124.7, 64.6, 60.4, 21.4; IR (cm^{-1}), υ: 1040.1 (SO_2), 1190.6 (SO_2), 1634.0 (N-H), 3451.3 (N-H); ESI-HRMS (*m/z*): Calcd. for $C_{21}H_{20}N_2Na_2O_8S_3$ + H 571.0250; obsd. 571.0254. Anal. Calcd. for $C_{21}H_{24}N_2Na_2O_{10}S_3$: C, 41.58; H, 3.99; N, 4.62; Found: C, 41.67; H, 3.91; N, 4.58.

4. A typical procedure for catalytic reactions

Ruthenium complexes $[RuCl_2(p\text{-cymene})]_2$ (3.1 mg, 0.005 mmol) and water-soluble chiral ligand **3** (5.6 mg, 0.011 mmol) were dissolved in 1 mL of water. After the solution was stirred at 40 °C for 1 hr, $HCO_2Na \cdot 2H_2O$ (520 mg, 5 mmol), 4 mol% SDS (11 mg, 0.040 mmol) and 4'-methylacetophenone (0.314 mL, 1 mmol) were added to the solution. The resulting solution was allowed to react at 40 °C for 24 hr. Then, a mixture solvent (3 × 3 mL) of *n*-hexane and diethyl ether (v/v, 1:1) was added to extract organic materials. GC analysis of a sample aliquot then determined the conversion rate and the enantioselectivity. The pure product was obtained by flash chromatography.

5. A procedure for recycling reaction using (*R,R*)-**3**-Ru(II) as catalyst.

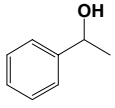
The *firs*t use: Ruthenium complexes $[RuCl_2(p\text{-cymene})]_2$ (3.1 mg, 0.005 mmol) and water-soluble chiral ligand **3** (5.6 mg, 0.011 mmol) were dissolved in 1 mL of water. After the solution was stirred at 40 °C for 1 hr, $HCO_2Na \cdot 2H_2O$ (1040 mg, 10 mmol), 4 mol% SDS (11 mg, 0.040 mmol) and acetophenone (0.118 mL, 1 mmol) were added to the solution. The resulting solution was allowed to react at 40 °C for 24 hr. Then, a mixture solvent (3 × 3 mL) of *n*-hexane and diethyl ether (v/v, 1:1) was added to extract organic materials. GC analysis of a sample aliquot then determined the conversion rate and the enantioselectivity.

The *recycling* use: HCO_2H (40 μL, 1 mmol), 4 mol% SDS (11 mg, 0.040 mmol) and acetophenone (0.118 mL, 1 mmol) were added to the aqueous solution. The resulting solution was allowed to react at 40 °C for 24 hr. Then, a mixture solvent (3 × 3 mL) of *n*-hexane and diethyl ether (v/v, 1:1) was added to extract organic materials. GC analysis of a sample aliquot then determined the conversion rate and the enantioselectivity.

6. A typical procedure for asymmetric transfer hydrogenation of ω-bromo acetophenones.

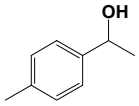
Ruthenium complexes $[RuCl_2(p\text{-cymene})]_2$ (1.5 mg, 0.0025 mmol) and water-soluble chiral ligand (*R,R*)- **3** (3.3 mg, 0.0055 mmol) were dissolved in 0.5 mL of water. After the solution was stirred at 40 °C for 1 hr, 5 equivalent of $HCO_2Na \cdot 2H_2O$ (260 mg, 2.5 mmol), 4 mol% SDS (5.5 mg, 0.020 mmol), ω-bromo acetophenone (**14a**) (99.5 mg, 0.5 mmol) and 0.5 mL of DCM were added to the solution. The resulting mixture was allowed to react at 28 °C for 24 hr. Then, DCM (3 × 3 mL) was added to extract organic materials. The obtained extraction was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The pure product was obtained in 87% isolated yield with 94% ee by flash chromatography. The enantiomeric excess was determined by GLC on CP-cyclodex B-236 M column.

7. Analytical data for chiral aromatic alcohols and related compounds

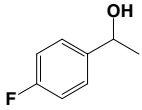


$[\alpha]_D^{23}$= +55.9° (c= 0.78, $CHCl_3$); ee % = 94.9%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 7.42-7.30 (m, 5H), 4.94 (q, J = 6.3 Hz, 1H), 1.52 (d, J = 6.3 Hz, 3H). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 115 °C

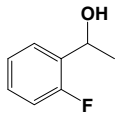
(isothermal), inject temprature = 220 °C, detector temprature = 240 °C, inlet pressure = 10.5 psi; t_1 = 5.0 min, t_2 = 5.3 min.



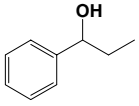
$[\alpha]_D^{23}$= +52.2° (c= 0.96, $CHCl_3$); ee % = 93.7%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 7.39 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.97 (q, *J* = 6.5 Hz, 1H), 2.49 (s, 3H), 2.27 (s, 1H), 1.61 (d, *J* = 6.5 Hz, 3H). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 120 °C (isothermal), inject temprature = 220 °C, detector temprature = 260 °C, inlet pressure = 10 psi; t_1 = 7.5 min, t_2 = 8.0 min.



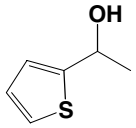
$[\alpha]_D^{23}$= +43.1° (c= 0.73, $CHCl_3$); ee % = 92.3%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 7.59-7.53 (m, 2H), 7.29-7.23 (m, 2H), 5.10 (q, *J* = 6.5 Hz, 1H), 2.38 (s, 1H), 1.71 (d, *J* = 6.5 Hz, 3H). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 115 °C (isothermal), inject temprature = 220 °C, detector temprature = 230 °C, inlet pressure = 10 psi; t_1 = 7.3 min, t_2 = 7.9 min.



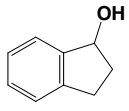
$[\alpha]_D^{23}$= +42.2° (c= 0.78, $CHCl_3$); ee % = 86.8%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 7.61-7.58 (m, 1H), 7.37-7.26 (m, 2H), 7.17-7.10 (m, 1H), 5.31 (q, *J* = 6.5 Hz, 1H), 2.26 (s, 1H), 1.63 (d, *J* = 6.5 Hz, 3H). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 115 °C (isothermal), inject temprature = 220 °C, detector temprature = 230 °C, inlet pressure = 10 psi; t_1 = 6.4 min, t_2 = 6.5 min.



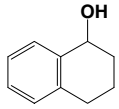
$[\alpha]_D^{23}$= +33.4° (c= 0.28, $CHCl_3$); ee % = 79.6%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 7.48-7.39 (m, 5H), 4.73 (t, *J* = 6.5 Hz, 1H), 1.96-1.88 (m, 3H), 1.05 (t, *J* = 7.5 Hz, 3H). GC analysis: CP-Chirasil-DEX CB, 0.25 mm × 25 m, column temprature = 140 °C (isothermal), inject temprature = 240 °C, detector temprature = 260 °C, inlet pressure = 11 psi; t_1 = 4.8 min, t_2 = 5.0 min.



$[\alpha]_D^{23}$= +20.4° (c= 0.56, $CHCl_3$); ee % = 94.7%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm) δ: 7.26-7.22 (m, 1H), 6.97-6.94 (m, 2H), 5.12 (q, *J* = 6.4 Hz, 1H), 2.27 (br, 1H), 1.59 (d, *J* = 6.4 Hz, 3H). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 130 °C (isothermal), inject temprature = 220 °C, detector temprature = 260 °C, inlet pressure = 11 psi; t_1 = 3.6 min, t_2 = 3.7 min.

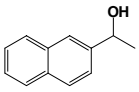


$[\alpha]_D^{23}$= -36.1° (c= 0.05, $CHCl_3$); ee % = 82.9%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 7.37-7.31 (m, 1H), 7.21-7.15 (m, 3H), 5.19 (t, *J* = 5.8 Hz, 1H), 3.05-2.95 (m, 1H), 2.81-2.71 (m, 1H), 2.49-2.38 (m, 1H), 1.94-1.84 (m, 1H), 1.18 (br, 1H). GC analysis: CP-Chirasil-DEX CB, 0.25 mm × 25 m, column temprature = 130 °C (isothermal), inject temprature = 220 °C, detector temprature = 240 °C, inlet pressure = 11.5 psi; t_1 = 9.9 min, t_2 = 10.2 min.

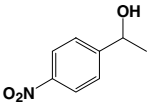


$[\alpha]_D^{23}$= -33.2° (c= 0.31, $CHCl_3$); ee % = 97.7%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 7.45-7.42 (m, 1H), 7.26-7.19 (m, 2H), 7.13-7.11 (m, 1H), 4.78 (t, *J* = 5.0 Hz, 1H), 2.87-2.75 (m, 2H), 2.02-1.79 (m, 5H). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 130 °C (isothermal), inject temprature =

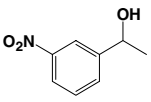
220 °C, detector temprature = 260 °C, inlet pressure = 11 psi; t_1 = 13.3 min, t_2 = 13.6 min.



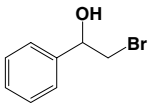
$[\alpha]_D^{23}$= +46.7° (c= 1.04, $CHCl_3$); ee % = 92.0%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 7.86-7.80 (m, 4H), 7.54-7.47 (m, 3H), 5.04 (q, *J* = 6.5 Hz, 1H), 2.26 (s, 1H), 1.59 (d, *J* = 6.5 Hz, 3H). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 160 °C (isothermal), inject temprature = 240 °C, detector temprature = 280 °C, inlet pressure = 11.5 psi; t_1 = 15.2 min, t_2 = 15.6 min.



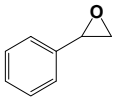
$[\alpha]_D^{23}$= + 35.1° (c= 1.46, $CHCl_3$); ee % = 88.4%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 8.10 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 4.95 (q, *J* = 6.5 Hz, 1H), 2.83 (br., 1H), 1.45 (d, *J* = 6.5 Hz, 3H). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 170 °C (isothermal), inject temprature = 240 °C, detector temprature = 260 °C, inlet pressure = 12 psi; t_1 = 10.7 min, t_2 = 11.1 min.



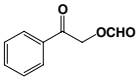
$[\alpha]_D^{23}$= + 33.2° (c= 0.86, $CHCl_3$); ee % = 83.3%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 8.22 (m, 1H), 8.21-8.07 (m, 1H), 7.71-7.68 (m, 1H), 7.52-7.47 (m, 1H), 4.99 (q, *J* = 6.5 Hz, 1H), 2.34 (s, 1H), 1.52 (d, *J* = 6.5 Hz, 3H). GC analysis: CP-Chirisil-*L*-Val, 0.25 mm × 25 m, column temprature = 130 °C (isothermal), inject temprature = 220 °C, detector temprature = 260 °C, inlet pressure = 11 psi; t_1 = 10.9 min, t_2 = 11.1 min.



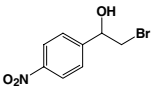
$[\alpha]_D^{23}$= + 49.4° (c= 1.03, $CHCl_3$); ee % = 93.7%; ^{1}H-NMR ($CDCl_3$, 300M Hz, ppm), δ: 7.40-7.29 (m, 5H), 4.94-4.91 (m, 1H), 3.67-3.52 (m, 2H), 2.69 (s, 1H). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 130 °C (isothermal), inject temprature = 200 °C, detector temprature = 220 °C, inlet pressure = 10 psi; t_1 = 17.4 min, t_2 = 18.2 min.



$[\alpha]_D^{23}$= + 23.6° (c= 0.83, $CHCl_3$); ee % = 94.4% ; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 7.38-7.28 (m, 5H), 3.88 (dd, *J* = 2.6 Hz, *J* = 4.1 Hz, 1H), 3.16 (dd, *J* = 2.6 Hz, *J* = 4.1 Hz, 1H), 2.82 (dd, *J* = 2.6 Hz, *J* = 4.1 Hz, 1H). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 90 °C (isothermal), inject temprature = 200 °C, detector temprature = 220 °C, inlet pressure = 10 psi; t_1 = 7.0 min, t_2 = 7.3 min.

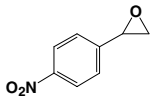


^{1}H-NMR ($CDCl_3$, 300M Hz, ppm), δ: 8.18 (s, 1H), 7.86-7.83 (m, 2H), 7.58-7.52 (m, 1H), 7.45-7.39 (m, 2H), 5.38 (s, 2H).

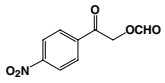


$[\alpha]_D^{23}$= + 29.6° (c= 1.03, $CHCl_3$); ee % = 84.2% ; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 8.24 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 5.06 (m, 1H), 3.68 (m, 1H), 3.54 (m, 1H), 2.93 (s, 1H); EI-MS (*m/z*): 247 (M+2, 4), 245 (4), 154 (48), 153 (100), 122 (24), 96 (17), 77(42), 75 (16), 66 (34). GC analysis: CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 145 °C, hold 14 minutes, 10 °C /minute

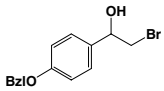
to 200 °C, hold 20 minute, inject temprature = 240 °C, detector temprature = 260 °C, inlet pressure = 11.5 psi; t_1 = 32.2 min, t_2 = 32.7 min.



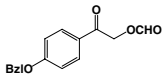
$[\alpha]_D^{23}$= + 32.5° (c= 0.39, $CHCl_3$); ee % = 83.9%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 8.21 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H), 3.97 (dd, *J* = 2.4 Hz, *J* = 4.2 Hz, 1H), 3.24 (dd, *J* = 2.4 Hz, *J* = 4.2 Hz, 1H), 2.79 (dd, *J* = 2.4 Hz, *J* = 4.2 Hz, 1H); EI-MS (*m/z*): 165 (M, 22), 150 (100), 118 (89), 91 (42), 88 (91), 96 (17), 76(14). GC analysis; CP-cyclodex B-236 M, 0.25 mm × 25 m, column temprature = 145 °C, hold 14 minutes, 10 °C /minute to 200 °C, hold 20 minute, inject temprature = 240 °C, detector temprature = 260 °C, inlet pressure = 11.5 psi; t_1 = 15.3 min, t_2 = 15.7 min.



^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 8.36 (d, *J* = 8.1 Hz, 2H), 8.26 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 2H), 5.47 (s, 2H); IR (cm^{-1}), υ: 1728 (C=O), 1701 (C=O).



$[\alpha]_D^{23}$= + 26.9° (c= 1.19, $CHCl_3$); ee % = 91.8%; ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm), δ: 7.57-7.39 (m, 7H), 7.11 (d, *J* = 8.8 Hz, 2H), 5.20 (s, 2H), 5.03-4.96 (m, 1H), 3.76-3.62 (m, 2H), 2.29 (br, 1H). HPLC analysis: Chiralcel OD, *iso*-PrOH/n-hexane = 10/90 (v/v), 1.0 mL/min, 23 °C, 230 nm; t_1 = 13.8 min, t_2 = 15.7 min.



^{1}H-NMR ($CDCl_3$, 300M Hz, ppm), δ: 8.25 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.44-7.35 (m, 5H), 7.04 (d, *J* = 8.8 Hz, 2H), 5.39 (s, 2H), 5.13 (s, 2H).