Supplementary Information:

Asymmetric transfer hydrogenation of imines and iminiums catalyzed by a water-soluble catalyst in water

Jiashou Wu, Fei Wang, Yaping Ma, Xin Cui, Linfeng Cun, Jin Zhu*, Jingen Deng* and Bangliang Yu

Key Laboratory of Asymmetric Synthesis & Chirotechnology of Sichuan Province and Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, and Graduate School of Chinese Academy of Sciences, Beijing, China

E-mail: jgdeng@cioc.ac.cn

Table of Contents

1. General procedure

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-300. Chemical shifts in NMR spectra are reported in parts per million from TMS with solvent resonance as the internal standard (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet, br = broad). Optical rotations were measured on a Perkin-Elmer polarimeter-341. Exact mass (HR-MS) spectra were recorded on BioTOF Q. Enantiomeric excess was determined by chiral HPLC analysis on Daicel Chiralcel OD column in comparison with the authentic racemates. Unless otherwise noted, all reagents were purchased from commercial sources and were used without further purification. (*R,R*)-**1**-RuCl(*p*-cymene) complex was synthesized as Noyori's procedure.[1] The water-soluble chiral ligand, (*R,R*)-**2**, was obtained by synthesized as our approach[2] and further purified on HPLC. **3a-3d** were prepared by the Bischler-Napieralski reaction as described in the literature.[3]

2. General procedure for the preparation of imines 5a-e. To a stirred and cooled (0 ºC) solution of tryptamine (3.2 g, 20 mmol) in CH_2Cl_2 (40 mL) and NEt_3 (6 mL) was added a solution of corresponding acyl chloride (1.1 equiv.) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for 2 h, washed with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. The solvents were removed and the resulting amide was reacted directly without purification with $POCl_3$ (10 mL) in toluene (5 mL). The reaction mixture was allowed to reflux for 4 h, then cooled and poured onto ice. The resulting solution was brought to pH 8 with aqueous 40% NaOH and extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated. Purification on silicon gel with ethyl ether afforded desired product.

1-Methyl-4,9-dihydro-3*H*-*β*-carboline (5a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 2.90 (t, J = 8.5 Hz, 2H), 3.90 (t, J = 8.5 Hz, 2H), 7.12-7.63 (m, 4H), 9.51 (br, 1H).

1-Ethyl-4,9-dihydro-3*H*-*β*-carboline (5b): yellow solid; m.p. 162.0-166.9 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.29 (t, *J* = 7.4 Hz, 3H), 2.71 (q, *J* = 7.4 Hz, 2H), 2.87 (t, *J* = 8.4 Hz, 2H), 3.90 (t, *J* = 8.4 Hz, 2H), 7.13-7.62 (m, 4H), 8.80 (br, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ= 10.9, 19.3, 28.4, 48.2, 111.9, 116.8, 120.0, 120.3, 124.4, 125.6, 128.6, 136.6, 161.7 ppm; FT-IR (KBr): ν = 3437, 1621, 1603, 1502, 746 cm^{-1}; HRMS (ESI) for $C_{13}H_{15}N_2$ (M+H): calcd. 199.1230, found: 199.1242.

1-Isopropyl-4,9-dihydro-3*H*-*β*-carboline (5c): off-white solid; m.p. 160.0-169.0 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.28 (br s, 3H), 1.31 (br s, 3H), 2.85 (t, *J* = 8.3 Hz, 2H), 3.02 (m, 1H), 3.88 (t, *J* = 8.3 Hz, 2H), 7.13-7.62 (m, 4H), 8.54 (br, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ= 19.3, 20.3, 28.7, 33.2, 48.1, 111.8, 117.2, 119.9, 120.2, 124.4, 125.6, 128.2, 136.5, 165.1 ppm; FT-IR (KBr): ν = 3438, 1621, 1601, 1506, 750 cm^{-1}; HRMS (ESI) for $C_{14}H_{17}N_2$ (M+H): calcd. 213.1386, found: 213.1375.

1-Cyclohexyl-4,9-dihydro-3*H*-*β*-carboline (5d): yellow solid; m.p. 189.3-191.9 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.26-2.04 (m, 10), 2.80-2.85 (m, 1H), 2.88 (t, *J* = 8.3 Hz, 2H), 3.91 (t, *J* = 8.3 Hz, 2H), 7.13-7.63 (m, 4H), 9.50 (br, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ= 19.3, 26.0, 26.4, 30.8, 43.3, 47.9, 111.9, 117.0, 119.8, 120.1, 124.3, 125.5, 128.4, 136.7, 165.3 ppm; FT-IR (KBr): ν = 2925, 2852, 1617, 1595, 1500, 746 cm^{-1}; HRMS (ESI) for $C_{17}H_{21}N_2$ (M+H): calcd. 253.1699, found: 253.1688.

1-Phenyl-4,9-dihydro-3*H*-*β*-carboline (5e): ^{1}H NMR (300 MHz, d^6-DMSO): δ= 2.86 (t, *J* = 8.2 Hz, 2H), 3.89 (t, *J* = 8.2 Hz, 2H), 7.07-7.10 (m, 1H), 7.18-7.21 (m, 1H), 7.42-7.63 (m, 5H), 7.75-7.78 (m, 2H), 11.11 (br, 1H) ppm.

3. General Procedure for the synthesis of iminiums. A solution of 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline **3d** (1.0 g, 3.74 mmol) in acetone (20 mL) was added 1.60 g (9.36 mmol) benzyl bromide. The mixture was stirred at room temperature for 3 d. The product was obtained by direct filtration.

Iminium 11a: Yellow solid; 50% yield (crude); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.10 (s, 3H), 3.18 (t, J = 7.7 Hz, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 4.08 (t, J = 7.7 Hz, 2H), 5.49 (s, 2H), 6.85 (s, 1H), 7.32-7.41 (m, 6H) ppm; FT-IR (KBr): ν = 2944, 1612, 1600, 1559, 1467, 1453 cm^{-1}; HRMS (ESI) for $C_{19}H_{22}NO_2$ (M-Br): calcd. 296.1645, found: 296.1640.

Iminium 11d: Yellow solid; 67% yield; m.p. 170.6-172.0 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.25 (t, J = 7.8 Hz, 2H), 3.57 (s, 3H), 3.99 (s, 3H), 4.43 (t, J = 7.8 Hz, 2H), 5.35 (s, 2H), 6.40 (s, 1H), 6.89 (s, 1H), 7.25-7.37 (m, 5H), 7.64-7.66 (m, 3H), 7.88-7.91 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 49.7, 56.0, 56.9, 60.8, 110.9, 115.8, 119.9, 128.2, 128.9, 129.2, 129.4, 129.9, 132.0, 132.7, 134.3, 148.3, 157.1, 173.6 ppm; FT-IR (KBr): ν = 3033, 1604, 1596, 1549, 1451 cm^{-1}; HRMS (ESI) for $C_{24}H_{24}NO_2$ (M-Br): calcd. 358.1802, found: 358.1813.

4. Typical procedure for asymmetric transfer hydrogenation of iminiums catalyzed by RuCl[(*1R,2R*)-TsDPEN](η^6-*p*-cymene) (Noyori catalyst) in organic solvent: To a solution of iminium (0.5 mmol) and the Noyori catalyst (0.005 mmol) in acetonitrile (0.8 mL) was added a 5:2 formic acid-triethylamine azeotropic mixture (0.125 mL). The mixture was stirred at 28 °C for a certain period of time, made basic by addition of aqueous Na_2CO_3, and then extracted with CH_2Cl_2. Purification on silicon gel afforded desired product.

5. Typical procedure for asymmetric transfer hydrogenation of imines and iminiums in aqueous media: $[RuCl_2(p\text{-cymene})]_2$ (1.5 mg, 0.0025 mmol), water-soluble chiral ligand (*R,R*)-**2** (3.3 mg, 0.0055) and 50 mol % CTAB (91.3 mg, 0.25 mmol) were dissolved in 1.5 mL of degassed water. After the solution was stirred at 40 ºC for 1 hr, 5 equivalents of $HCOONa{\cdot}2H_2O$ (260 mg, 2.5 mmol) and imine or iminium (0.5 mmol) were added to the solution. Following degassing three times, the

mixture was allowed to react at 28 °C for 10 hr, and then CH_2Cl_2 (3 × 3 ml) was added to extracted organic materials. Purification on silicon gel afforded desired product.

(*S*)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (4a): $[\alpha]_D^{23}$ –51.2 (*c* = 1.69, EtOH) (lit. (*S*)-isomer, $[\alpha]_D^{21}$ –51.2 (*c*, = 1.69, EtOH), A. R. Battersby and T. P. Edwards, *J. Chem. Soc.*, 1960, 1214-1221), 95% ee by HPLC analysis (Chiralcel OD, hexane/2-propanol/diethylamine = 90: 10: 0.1, 1.0 mL/min, 254 nm, major isomer 11.9 min, minor isomer 15.5 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 6.7 Hz, 3H), 1.90 (br, 1H), 2.59-2.66 (m, 1H), 2.74-2.76 (m, 1H), 2.92-2.99 (m, 1H), 3.18-3.24 (m, 1H), 3.817 (s, 3H), 3.823 (s, 3H), 4.02 (q, *J* = 6.7, 1H), 6.54 (s, 1H), 6.60 (s, 1H) ppm.

(*S*)-6,7-Dimethoxy-1-ethyl-1,2,3,4-tetrahydroisoquinoline (4b): $[\alpha]_D^{20}$ –50.9 (*c* = 0.55, CH_2Cl_2), (lit. (*S*)-isomer, $[\alpha]_D^{20}$ –51.9 (*c* = 2.1, CH_2Cl_2), R. P. Polniaszek and C. R. Kaufman, *J. Am. Chem. Soc.*, 1989, **111**, 4859-4863), 92% ee by HPLC analysis (Chiralcel OD, hexane/2-propanol/diethylamine = 90: 10: 0.1, 1.0 mL/min, 254 nm, major isomer 12.9 min, minor isomer 18.6 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.4 Hz, 3H), 1.65-1.68 (m, 1H), 1.83-1.86 (m, 1H), 1.94 (br, 1H), 2.63-2.71 (m, 2H), 2.93-2.94 (m, 1H), 3.16-3.20 (m, 1H), 3.77-3.86 (m, 1H), 3.80 (s, 6H), 6.53 (s, 1H), 6.58 (s, 1H) ppm.

(*S*)-6,7-Dimethoxy-1-isopropyl-1,2,3,4-tetrahydroisoquinoline (4c): $[\alpha]_D^{20}$ –98.9 (*c* = 1.80, CH_2Cl_2), (lit. (*S*)-isomer, $[\alpha]_D$ –104.3 (*c* = 0.9, CH_2Cl_2), R. P. Polniaszek and C. R. Kaufman, *J. Am. Chem. Soc.*, 1989, **111**, 4859-4863), 90% ee by HPLC analysis (Chiralcel OD, hexane/2-propanol/diethylamine = 90: 10: 0.1, 1.0 mL/min, 254 nm, minor isomer 10.5 min, major isomer 8.6 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.82 (br, 1H), 2.28-2.30 (m, 1H), 2.54-2.59 (m, 1H), 2.77-2.91 (m, 2H), 3.24-3.29 (m, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 3.87 (d, *J* = 3.2 Hz, 1H), 6.55 (s, 1H), 6.63 (s, 1H) ppm.

(*S*)-1-Methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6a): $[\alpha]_D^{25}$ –62.1 (*c* = 1.36, EtOH), (lit. (*S*)-isomer, $[\alpha]_D^{25}$ –56.8 (*c* = 2.0, EtOH), P. Roszkowski, K. Wojtasiewicz, A. Leniewski, J. K. Maurin, T. Lis and Z. Czarnocki, *J. Mol. Catal. A: Chem.*, 2005, **232**, 143-149), 99% ee by HPLC analysis (Chiralcel OD, hexane/2-propanol/diethylamine = 80: 20: 0.1, 1.0 mL/min, 254 nm, minor isomer 16.6 min, major isomer 22.6 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.7 Hz, 3H), 2.49-2.59 (m, 2H), 2.83-2.86 (m, 1H), 3.14-3.19 (m, 1H), 4.02 (q, *J* = 6.7 Hz, 1H), 6.90-7.03 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 10.69 (s, 1H) ppm.

(-)-1-Ethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6b): $[\alpha]_D^{23}$ –87.9 (*c* = 1.61, EtOH), (lit. $[\alpha]_D$ –62.6 (CH_3COCH_3), C. Gremmen, B. Willemse, M. J. Wanner and G.-J. Koomen, *Org. Lett.*, 2000, **2**, 1955-1958), 99% ee by HPLC analysis (Chiralcel OD, hexane/2-propanol/diethylamine = 80: 20: 0.1, 1.0 mL/min, 254 nm, major isomer 8.9 min, minor isomer 11.0 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.4 Hz, 3H), 1.69-1.74 (m, 1H), 1.88-2.08 (m, 1H), 2.72-2.78 (m, 2H), 2.99-3.06 (m, 1H), 3.34-3.40 (m, 1H), 4.00-4.03 (m, 1H), 7.07-7.18 (m, 2H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.77 (br, 1H) ppm.

(-)-1-Isopropyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6c): $[\alpha]_D^{23}$ –112.8 (*c* = 1.00, EtOH), 99% ee by HPLC analysis (Chiralcel OD, hexane/2-propanol/ diethylamine = 80: 20: 0.1, 1.0 mL/min, 254 nm, major isomer 6.5 min, minor isomer 8.6 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 2.18-2.27 (m, 1H), 2.73-2.78 (m, 2H), 2.95-3.02 (m, 1H), 3.39-3.44 (m, 1H), 4.01-4.03 (m, 1H), 7.11-7.17 (m, 2H), 7.32 (dd, *J* = 1.3, 7.2 Hz, 1H), 7.51 (dd, *J* = 1.5, 7.3 Hz, 1H), 7.85 (br, 1H) ppm.

(-)-1-Cyclohexyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6d): $[\alpha]_D^{20}$ –85.4 (*c* = 1.67, EtOH), (lit. $[\alpha]_D$ –68.5 (CH_3COCH_3), C. Gremmen, B. Willemse, M. J. Wanner

and G.-J. Koomen, *Org. Lett.*, 2000, **2**, 1955-1958), 98% ee by HPLC analysis (Chiralcel OD, hexane/2-propanol/diethylamine = 80: 20: 0.1, 1.0 mL/min, 254 nm, major isomer 7.0 min, minor isomer 10.9 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16-1.87 (m, 11H), 2.71-2.76 (m, 2H), 2.99-3.02 (m, 1H), 3.36-3.40 (m, 1H), 3.99 (d, J = 1.6 Hz, 1H), 7.07-7.18 (m, 2H), 7.32 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.77 (br, 1H) ppm.

(*S*)-1-Phenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6e): $[\alpha]_D^{23}$ +0.92 (c = 0.97, $CHCl_3$), (lit. (*R*)-isomer, $[\alpha]_D^{23}$ –3.9 (c = 1.03, $CHCl_3$), N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916-4917), 99% ee by HPLC analysis (Chiralcel OD, hexane/2-propanol/diethylamine = 80: 20: 0.1, 1.0 mL/min, 254 nm, minor isomer 16.8 min, major isomer 11.9 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.84-2.94 (m, 2H), 3.09-3.16 (m, 1H), 3.34-3.39 (m, 1H), 5.15 (s, 1H), 7.12-7.19 (m, 3H), 7.31-7.36 (m, 5H), 7.56-7.59 (m, 1H), 7.65 (br, 1H) ppm.

(*R*)-3-Methyl-2,3-dihydrobenzo[*d*]isothiazoline 1,1-Dioxide (8a): $[\alpha]_D^{20}$ +19.1 (c = 1.50, $CHCl_3$), (lit. (*S*)-isomer, $[\alpha]_D^{20}$ –30 (c = 1.21, $CHCl_3$), W. Oppolzer, M. Wills, C. Starkeman and G. Bemardinelli, *Tetrahedron. Lett.*, 1990, **29**, 4117-4120), 65 % ee by HPLC analysis (Chiralcel OD, hexane/2-propanol = 80: 20, 1.0 mL/min, 254 nm, major isomer 10.9 min, minor isomer 9.2 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (d, J = 6.7 Hz, 3H), 4.72 (q, J = 6.7 Hz, 1H), 7.32(dd, J = 0.7, 7.8 Hz, 1H), 7.42-7.47 (m, 1H), 7.53-7.58 (m, 1H), 7.69 (d, J = 7.7 Hz, 1H) ppm.

(*R*)-3-*tert*-Butyl-2,3-dihydrobenzo[*d*]isothiazoline 1,1-Dioxide (8b): $[\alpha]_D^{20}$ +55.3 (c = 1.87, $CHCl_3$), (lit. (*R*)-isomer, $[\alpha]_D^{20}$ +37 (c = 1.87, $CHCl_3$), J. Mao and D. C. Baker, *Org. Lett.*, 1999, **1**, 841-843), 94 % ee by HPLC analysis (Chiralcel OD, hexane/ 2-propanol = 80: 20, 1.0 mL/min, 254 nm, major isomer 25.2 min, minor isomer 8.6 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 9H), 4.46 (d, J = 5.0 Hz, 1H), 5.03 (br, 1H), 7.53-7.65 (m, 3H), 7.81-7.84 (m, 1H) ppm.

(*S*)-2-Benzyl-1-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (12a): $[\alpha]_D^{20}$ +8.9 (*c* = 2.40, CH_2Cl_2), (lit. racemate, M. Ferrari, M. Furlanut, I. Maragno, E. Santi-Soncin and E. Toth, *Arch. Int. Pharmacodyn. Ther.*, 1972, **200**, 40), 90% ee by HPLC analysis (Chiralcel OJ, hexane/2-propanol = 99: 1, 1.0 mL/min, 254 nm, minor isomer 20.6 min, major isomer 36.9 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 5.0 Hz, 3H), 2.57-2.85 (m, 3H), 3.04-3.09 (m, 1H), 3.69-3.89 (m, 9H), 6.54 (s, 1H), 6.59 (s, 1H), 7.24-7.42 (m, 5H) ppm.

(+)-2-Benzyl-1-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (12d): off-white solid; m.p. 131.9-132.9 ºC; $[\alpha]_D^{20}$ +71.0 (*c* = 1.00, CH_2Cl_2), 95% ee by HPLC analysis (Chiralcel OD, hexane/2-propanol = 99: 1, 1.0 mL/min, 254 nm, minor isomer 10.2 min, major isomer 11.4 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.51-2.54 (m, 1H), 2.68-2.73 (m, 1H), 2.96-3.10 (m, 2H), 3.29 (d, *J* = 13.5 Hz, 1H), 3.61 (s, 3H), 3.80 (d, *J* = 13.5 Hz, 1H), 3.85 (s, 3H), 4.55 (s, 1H), 6.21 (s, 1H), 6.61 (s, 1H), 7.22-7.38 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 47.0, 55.8, 58.7, 68.1, 110.8, 111.7, 126.8, 126.9, 127.2, 128.1, 128.2, 128.7, 129.5, 130.1, 139.6, 144.3, 147.0, 147.3 ppm; FT-IR (KBr): ν = 3027, 1607, 1512, 1451, 699 cm^{-1}; HRMS (ESI) for $C_{24}H_{26}NO_2$ (M+H): calcd. 360.1958, found: 360.1969.

References

1. K. J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem. Int. Ed.*, 1997, **36**, 285.
2. Y.-P. Ma, H. Liu, L. Chen, J. Zhu and J.-G. Deng, *Org. Lett.*, 2003, **5**, 2103.
3. P. N. Craig, F. P. Nabenhauer, P. M. Williams, E. Macko and J. Jones, *J. Am. Chem. Soc.*, 1952, **74**, 1316-1317.