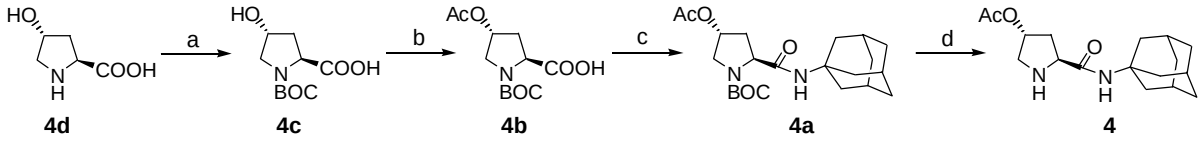
Asymmetric Epoxidation of Olefins Catalyzed by Chiral Iminium Salts Generated in situ from Amines and Aldehydes

Man-Kin Wong,* Lai-Mei Ho, Yan-Song Zheng, Chun-Yu Ho, and Dan Yang*

Department of Chemistry, The University of Hong Kong,
Pokfulam Road, Hong Kong

SUPPORTING INFORMATION

Preparation of amine 4[a]



4d **4c** **4b** **4a** **4**

[a]Reagents and conditions:
a) Boc_2O, Et_3N, MeOH;
b) Ac_2O, pyridine, CH_2Cl_2, rt;
c) 1-adamantanamine hydrochloride, DCC, HOBt, Et_3N, CH_2Cl_2, rt;
d) TFA, CH_2Cl_2.

To a solution of triethylamine (4 mL) and methanol (36 mL) was added *trans*-4-hydroxy-L-proline (**4d**) (5.0 g, 38 mmol) and di-tert-butyl dicarbonate (16.6 g, 79.3 mmol). After heating to 40–50 °C for 1.5 h, the reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure, and the residue was cooled to 0 °C followed by acidification with diluted hydrochloric acid to pH 2. The mixture was stirred at 0 °C for 30 min. Then it was extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, and filtered. Evaporating off the solvent under reduced pressure afforded *trans*-N-(*tert*-butoxycarbonyl)-4-hydroxy-L-proline (**4c**) (9.17 g, 35.7 mmol, 94% yield) as colourless liquid and used directly for next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (br s, 1H), 4.37–4.49 (m, 2H), 3.46–3.58 (m, 2H), 2.28–2.35 (m, 1H), 2.05–2.15 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (75.8 MHz, $CDCl_3$) δ

177.51, 174.97, 156.13, 154.31, 81.54, 81.00, 69.65, 69.27, 57.85, 57.73, 54.62, 54.45, 38.89, 37.60, 28.34, 28.22.

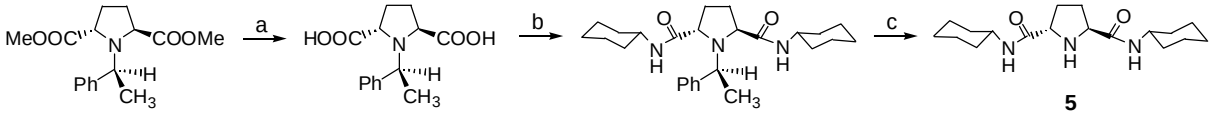
To a solution of **4c** (8.26 g, 35.7 mmol) in CH_2Cl_2 (15 mL) was added acetic anhydride (19.9 mL, 179 mmol) and pyridine (20 mL) under nitrogen at room temperature. The reaction mixture was stirred at room temperature overnight. Then the reaction mixture was washed with 1 M hydrochloric acid (30 mL) and extracted with CH_2Cl_2 (30 mL × 4). The combined organic layers were dried over anhydrous $MgSO_4$. The organic layer was filtered and removed under reduced pressure to provide **4b** (14.28 g, 26.2 mmol, 73% yield) as a white solid (m.p. 95–97 °C) which was directly used for next step without purification. $[\alpha]_D^{20}$ = –70.53° (*c* 1.02 CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (m, 1H), 4.47 (t, *J* = 7.7 Hz, ½ H), 4.36 (t, *J* = 8.0 Hz, ½ H), 3.55–3.77 (m, 2H), 2.26–2.48 (m, 2H), 2.07 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 177.74, 174.67, 170.42, 155.89, 153.59, 81.90, 81.03, 72.18, 71.83, 57.69, 52.37, 51.95, 36.49, 34.63, 28.31, 28.21, 20.99; IR (CH_2Cl_2) 3498, 1741, 1699, 1624 cm^{-1}; LRMS (EI, 20 eV) *m*/*z* 228 (2), 213 (11), 172 (29); HRMS (EI) for $C_{11}H_{18}NO_4$ (M^+–COOH), calcd 228.1236, found 228.1233.

To a solution of **4b** (0.82 g, 1.83 mmol) and 1-adamantanamine hydrochloride (0.52 g, 2.75 mmol) in CH_2Cl_2 (30 mL) was added triethylamine (0.75 mL, 5.49 mmol) and 1-hydroxybenzotriazole hydrate (0.32 g, 2.38 mmol) under nitrogen at room temperature. After 1-hydroxybenzotriazole hydrate was dissolved, *N*,*N*'-dicyclohexylcarbodiimide (0.49 g, 2.38 mmol) was added. After stirring at room temperature overnight, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 1 M hydrochloric acid (25 mL), water (25 mL), saturated $NaHCO_3$ solution (30 mL), and brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (40% ethyl acetate in *n*-hexane) to afford (2*S*,4*R*)-4-acetoxy-2-

(adamantan-1-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**4a**) (0.58 g, 1.42 mmol, 78%) as a white solid: M.p. 124–125 °C; analytical TLC (silica gel 60), 50% ethyl acetate in *n*-hexane, R_f = 0.37; $[\alpha]_D^{25}$ = –42.14° (*c* 1.38 CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (br s, ½ H), 5.58 (br s, ½ H), 5.21–5.26 (m, 1H), 4.11–4.23 (m, 1H), 3.48–3.75 (m, 2H), 2.07–2.60 (m, 5H), 2.04 (s, 3H), 1.98 (s, 6H), 1.68 (s, 6H), 1.48 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.25, 169.95, 155.26, 80.72, 72.49, 60.23, 59.01, 53.32, 52.27, 51.64, 41.47, 36.23, 33.25, 29.32, 28.23, 20.85; IR (KBr) 3679, 1738, 1690, 1603 cm^{-1}; LRMS (ESI) *m/z* 407 (M^++1, 100); HRMS (EI) for $C_{22}H_{34}N_2O_5$ (M^+), calcd 406.2468, found 406.2478.

To a solution **4a** (0.27 g, 0.66 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added trifluoroacetic acid (3 mL). The reaction mixture was stirred at 0 °C for 35 min and warmed up to room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was azeotroped with toluene twice. The residue was basified with 2 M NaOH followed by extraction with CH_2Cl_2 (15 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to afford (2*S*,4*R*)-4-acetic acid 5-(adamantan-1-ylcarbamoyl)-pyrrolidin-3-yl ester (**4**) (0.21 g, 0.66 mmol, 100% yield) as a white solid: M.p. 114–116 °C; analytical TLC (silica gel 60), 80% ethyl acetate in *n*-hexane, R_f = 0.66; $[\alpha]_D^{25}$ = –12.33° (*c* 0.94 CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.5 Hz, 1H), 5.20–5.30 (m, 1H), 3.81 (t, *J* = 8.2 Hz, 1H), 3.10 (d, *J* = 13.1 Hz, 1H), 2.91 (dd, *J* = 13.1, 3.7 Hz, 1H), 2.24–2.34 (m, 2H), 2.06–2.10 (m, 4H), 2.04 (s, 3H), 1.99 (br s, 6H), 1.68 (br s, 6H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 172.73, 170.40, 76.39, 60.31, 52.83, 50.76, 41.43, 36.68, 36.25, 29.29, 21.13; IR (KBr) 3328, 1734, 1666 cm^{-1}; LRMS (ESI) *m/z* 307 (M^++1, 100); HRMS (EI) for $C_{17}H_{26}N_2O_3$ (M^+), calcd 306.1943, found 306.1948.

Preparation of amine 5[a]



[a]Reagents and conditions:
a) NaOH, MeOH, reflux;
b) cyclohexylamine, EDCI, HOBt, DMF, rt;
c) Pd/C, H_2, rt;

Diester **5c** was prepared according to a literature procedure. (Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis* **1993**, 298.)

To a solution of NaOH (96 mg, 2.4 mmol) in methanol (10 mL) was added **5c** (150 mg, 0.52 mmol). After refluxing for 10 h, the reaction mixture was cooled to room temperature, and acidified with dilute hydrochloric acid to pH 4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (50% methanol in ethyl acetate) to afford **5b** (130 mg, 0.49 mmol, 96% yield) as a white solid: M.p. 220 °C (dec); analytical TLC (silica gel 60), 50% methanol in ethyl acetate, R_f = 0.45; $[\alpha]_D^{25}$ = –56.1° (*c* 1.6 CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.65 (m, 5H), 5.28 (q, *J* = 6.9 Hz, 1H), 3.88–4.05 (m, 2H), 2.30–2.55 (m, 2H), 1.93–2.20 (m, 2H), 1.59 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.67, 142.04, 128.30, 127.49, 127.29, 65.47, 59.21, 29.17, 21.44; IR (KBr) 3397, 1657, 1620, 1456, 1385 cm^{-1}; LRMS (EI, 20 eV) *m*/*z* 218 (52), 173 (29), HRMS (EI) for $C_{13}H_{16}NO_2$ (M^+–COOH), calcd 218.1181, found 218.1166.

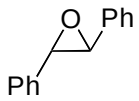
To a solution of **5b** (130 mg, 0.5 mmol) in DMF (15 mL) were added cyclohexylamine (298 mg, 3 mmol) and HOBt (175 mg, 1.3 mmol). The reaction mixture was stirred at room temperature for 10 min, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (249 mg, 1.3 mmol) was added. After stirring at room temperature overnight, the reaction mixture was diluted with CH_2Cl_2 (60 mL). The organic phase was washed with water, dried over anhydrous magnesium sulfate, and concentrated

under reduced pressure. The residue was purified by flash column chromatography (50% ethyl acetate in n-hexane) to afford (2*S*,5*S*)-1-[(*S*)-1-phenylethyl]-pyrrolidine-2,5-dicarboxylic acid bis-cyclohexylamide (**5a**) (130 mg, 61% yield) as a white solid: M.p. 202–203 °C; analytical TLC (silica gel 60), 30% ethyl acetate in *n*-hexane, R_f = 0.4; $[\alpha]_D^{25}$ = –85.9° (*c* 1.0 $CHCl_3$); ^{1}H NMR (300MHz, $CDCl_3$) δ 7.26–7.31 (m, 5H), 6.00 (d, *J* = 8.2 Hz, 2H), 4.10 (q, *J* = 6.7 Hz, 1H), 3.74 (m, 2H), 3.53 (d, *J* = 7.7 Hz, 2H), 2.32–2.39 (m, 2H), 1.85–1.90 (m, 4H), 1.60–1.77 (m, 6H), 1.36–1.41 (m, 4H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.04–1.19 (m, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 173.92, 145.03, 128.54, 127.29, 65.36, 60.24, 47.50, 33.23, 33.10, 30.20, 25.52, 24.86, 23.97; IR ($CHCl_3$) 3430, 3354, 1655, 1513 cm^{-1}; FABMS *m*/*z* 426 (M^++1, 80), 299 (100), 195 (60); HRMS (EI) for $C_{26}H_{39}N_3O_2$ (M^+), calcd 425.3042, found 425.3044.

To a solution of **5a** (150 mg, 0.35 mmol) in methanol (20 mL) was added 10% palladium on activated carbon (30 mg). The mixture was stirred at room temperature under hydrogen atmosphere for 15 h. The catalyst was removed by filtering through a short pad of celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (50% methanol in ethyl acetate) to afford (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid bis-cyclohexylamide (**5**) (94 mg, 83% yield) as a white solid: M.p. 159–160 °C; analytical TLC (silica gel 60), 50% methanol in ethyl acetate, R_f = 0.7; $[\alpha]_D^{25}$ = –90.2° (*c* 0.6 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, *J* = 7.8 Hz, 2H), 3.62–3.91 (m, 4H), 2.81 (br s, 1H), 2.12 (m, 2H), 1.60–1.89 (m, 12H), 1.30–1.37 (m, 4H), 1.10–1.21 (m, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.97, 61.18, 47.81, 32.95, 32.85, 31.27, 25.33, 24.69, 24.67; IR ($CHCl_3$) 3428, 3329, 1656, 1519 cm^{-1}; LRMS (EI, 20 eV) *m*/*z* 321 (M^+, 5), 195 (100); HRMS (EI) for $C_{18}H_{31}N_3O_2$ (M^+), calcd 321.2416, found 321.2418.

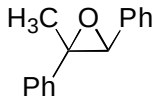
References for the determination of enantiomeric excesses of epoxides:

(*S*,*S*)-*trans*-Stilbene oxide



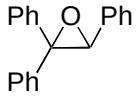
Wang, Z. W.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328.

(*S*,*S*)-*trans*-β-Methylstilbene oxide



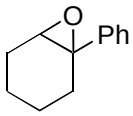
Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

(*S*)-2,2,3-Triphenyloxirane



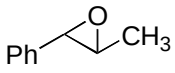
Wang, Z. X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622.

(*S*,*S*)-1-Phenylcyclohexene oxide



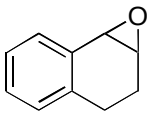
Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 491.

(*S*,*S*)-*trans*-β-Methylstyrene oxide



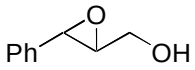
Wang, Z. W.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328.

3,4-Dihydronaphthalene oxide



Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 491.

(*R*,*R*)-*trans*-3-Phenyloxiranemethanol



Wang, Z. W.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099.