

Direct L-Proline Catalyzed Asymmetric α -Amination of Ketones

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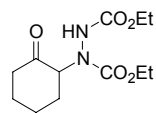
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Supporting Information

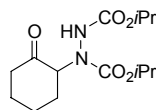
General Methods. The ^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta=0$) for ^1H NMR and relative to the central CDCl_3 resonance ($\delta=77.07$) for ^{13}C NMR. Flash chromatography (FC) was carried out using Merck silica gel 60 (230-400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products were determined by HPLC using a Daicel Chiralpak AS columns with *i*-PrOH/hexane as eluent or by chiral GC using a Chrompack CP-Chirasil Dex C β or Astec G-TA columns in comparison to the corresponding racemic samples (prepared by using racemic proline as catalyst).

Materials. Diethyl-, di-*iso*-propyl- and di-*tert*-butyl azodicarboxylate were purchased from Aldrich and used as received. The ketones, (*DL*)-proline and (*L*)-proline are all commercially available from Aldrich or Lancaster.

General Experimental Procedure for the Catalytic Enantioselective Direct α -Amination of Ketones 1a,b with Azodicarboxylates 2a-c (Table 1): To a stirred solution of the azodicarboxylate (1.0 mmol) and ketone (1.5 mmol for entries 1-8 and 5 mmol for entry 12) in the solvent (3 ml for entries 1-8 and 1 ml for entry 12), L-proline was added and the reaction mixture was stirred at room temperature until the yellow color of the azodicarboxylate had disappeared. The reaction mixture was quenched with water, extracted with diethyl ether and dried over anhydrous Na_2SO_4 . The solvent and the excess ketone were removed *in vacuo*. In the case of entries 9-11, the neat reactions were carried out by treating 2.5 mmol of diethyl azodicarboxylate with butanone (5 mmol) in the presence of L-proline at room temperature. The ee of these products were determined after work-up.

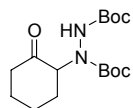


***N',N'*-Bis(ethoxycarbonyl)-2-hydrazino-cyclohexanone (3a).** The ee was determined by chiral GC using a Chrompack CP-Chirasil Dex C β (β -PM) column (τ_{minor} = 25.97 min; τ_{major} = 26.19 min). This compound was purified by Flash Chromatography (20% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$). $[\alpha]_{\text{D}}^{25}$ = -32.1 (c = 1.07 g/100mL, CHCl_3 , 79% ee). ^1H NMR (60°C) δ 6.60 (s br, 1H), 4.85 (s br, 1H), 4.13-4.24 (m, 4H), 2.48-2.51 (m, 1H), 2.30-2.40 (m, 2H), 2.07-2.11 (m, 1H), 1.98-2.00 (m, 1H), 1.75-1.88 (m, 2H), 1.55-1.66 (m, 1H), 1.24-1.30 (m, 6H). ^{13}C NMR (60°C) δ 207.3, 156.5 (2C), 66.1, 62.8, 61.9, 41.4, 30.9, 26.8, 24.5 14.5, 14.4. HRMS $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$ calculated 295.1270 found 295.1273.



***N',N'*-Bis(isopropoxycarbonyl)-2-hydrazino-cyclohexanone (3b).** The ee was determined by chiral GC using a Chrompack CP-Chirasil Dex C β (β -PM) column (τ_{minor} = 30.51 min; τ_{major} = 30.87 min). This compound was purified by Flash Chromatography (20% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$). Yield: 50%. $[\alpha]_{\text{D}}^{25}$ = -15.5 (c = 1.28 g/100mL, CHCl_3 , 55% ee); ^1H NMR (60°C) δ 6.51 (s br, 1H), 4.89-4.97 (m, 2H), 4.82 (s br, 1H), 2.45-2.50

(m, 1H), 2.29-2.38 (m, 2H), 2.03-2.10 (m, 1H), 1.95-2.01 (m, 1H), 1.71-1.88 (m, 2H), 1.53-1.65 (m, 1H) 1.21-1.27 (m, 12H), ^{13}C NMR (60°C) δ 207.2, 156.1 (2C), 70.5, 69.5, 65.6, 41.3, 30.8, 26.8, 24.5, 22.1, 22.0, 21.9 (2C). HRMS $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$ calculated 323.1583 found 323.1582.

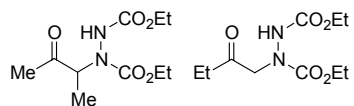


***N',N'*-Bis(*tert*-butoxycarbonyl)-2-hydrazino-cyclohexanone (3c).** The ee was determined by chiral GC using a Chrompack CP-Chirasil Dex C β (β -PM) column (τ_{minor} = 27.63 min; τ_{major} = 27.87 min). This compound was purified by Flash Chromatography (20% Et₂O/CH₂Cl₂). Yield = 67%. $[\alpha]_D^{25}$ = -14.9 (c = 1.08 g/100mL, CHCl₃, 56% ee); ^1H NMR (60°C) δ 6.42 (s br, 1H), 4.83 (s br, 1H), 2.42-2.50 (m, 1H), 2.25-2.36 (m, 2H), 2.01-2.08 (m, 1H), 1.93-2.00 (m, 1H), 1.69-1.86 (m, 2H), 1.50-1.64 (m, 1H) 1.45 (s, 18H), ^{13}C NMR (60°C) δ 207.4, 155.5 (2C), 81.6, 80.7, 65.2, 41.4, 30.8, 28.3(3C), 28.2(3C), 26.8, 24.6. HRMS $\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$ calculated 351.1896 found 351.1892.

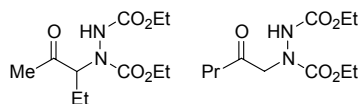
Experimental Procedure for the L-Proline Catalyzed Enantioselective Direct α -Amination of Ketones 1a-f with Diethyl Azodicarboxylate 2a (DEAD) (Table 2):

Procedure for 3a: To a stirred solution of diethyl azodicarboxylate (2 mmol, 314 μL) and cyclohexanone (3 mmol, 0.31 mL) in 1,2-dichloroethane (4 mL) L-proline (10 mol%, 0.2 mmol, 23 mg) was added and the reaction mixture was stirred at room temperature until the yellow color of DEAD **2a** had disappeared. Then the reaction mixture was quenched with water, extracted with diethyl ether and dried over anhydrous Na₂SO₄. The solvent and the excess ketone were removed *in vacuo*. The crude product was purified by Flash Chromatography (20% Et₂O/CH₂Cl₂).

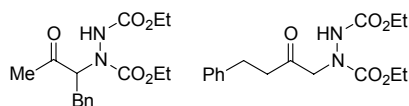
Procedure for 3d-3h. L-Proline (10 mol%, 0.2 mmol, 23 mg) was added to a stirred solution of diethyl azodicarboxylate **2a** (2 mmol, 314 μL) and the ketones **1b-f** (10 mmol) in CH₃CN (1 mL) at room temperature. After disappearing of the yellow color of DEAD, the reaction was quenched with water, extracted with diethyl ether and dried over anhydrous Na₂SO₄. The solvent and the excess ketone were removed *in vacuo*. The crude product was purified to give an inseparable mixture of regioisomers (except for **3h**) by Flash Chromatography (20% Et₂O/CH₂Cl₂).



***N',N'*-Bis(ethoxycarbonyl)-3-hydrazino-2-butanone (3d).** The ee was determined by chiral GC using Astec G-TA column (τ_{major} = 24.11 min; τ_{minor} = 24.53 min). ^1H NMR (60°C) δ 6.63 (s br, 1H), 4.76 (s br, 1H), 4.09-4.21 (m, 4H), 2.15 (s, 3H), 1.37 (d, J = 7.6 Hz, 3H), 1.20-1.25 (m, 6H), ^{13}C NMR (60°C) δ 206.7, 156.7, 156.4, 62.9 (2C), 62.0, 26.5, 14.5, 14.4, 13.1. HRMS $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$ calculated 269.1113 found 269.1117. Minor regioisomer: ^1H NMR (60°C) δ 6.89 (s br, 1H), 4.31 (s br, 2H), 4.09-4.21 (m, 4H), 2.38 (q, J = 7.6 Hz, 2H), 1.20-1.25 (m, 6H), 1.06 (t, J = 7.6 Hz, 3H).

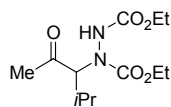


***N',N'*-Bis(ethoxycarbonyl)-3-hydrazino-2-pentanone (3e).** The ee was determined by HPLC using Chiralpak AS column (hexane/*i*-PrOH (95:05); flow rate 1.0 mL/min; τ_{minor} = 14.68 min; τ_{major} = 16.08 min). ^1H NMR (60°C) δ 6.54 (s br, 1H), 4.61 (s br, 1H), 4.14-4.23 (m, 4H), 2.20 (s, 3H), 1.84-1.92 (m, 1H), 1.70-1.78 (m, 1H), 1.25-1.29 (m, 6H), 1.09 (t, J = 7.2 Hz, 3H), ^{13}C NMR (60°C) δ 206.6, 157.0, 156.5, 69.2, 63.0, 62.1, 27.5, 20.9, 14.49, 14.47, 11.3. HRMS $\text{C}_{11}\text{H}_{20}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$ calculated 283.1270 found 283.1272. Minor regioisomer: ^1H NMR (60°C) δ 6.77 (s br, 1H), 4.34 (s br, 2H), 4.14-4.23 (m, 4H), 2.37 (t, J = 7.2 Hz, 2H), 1.62-1.67 (m, 2H), 1.25-1.50 (m, 6H), 0.94 (t, J = 7.2 Hz, 3H).



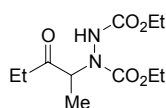
***N',N'*-Bis(ethoxycarbonyl)-3-hydrazino-4-phenyl-2-butanone (3f).** The ee was determined by HPLC using Chiralpak AS column (hexane/*i*-PrOH (96:04); flow

rate 1.0 ml/min; $\tau_{\text{minor}} = 19.85$ min; $\tau_{\text{major}} = 25.65$ min). ^1H NMR (60°C) δ 7.07-7.25 (m, 5H), 6.13 (s br, 1H), 4.79 (s br, 1H), 4.04-4.12 (m, 4H), 2.99-3.10 (m, 2H), 2.11 (s, 3H), 1.13-1.20 (m, 6H), ^{13}C NMR (60°C) δ 205.6, 156.3 (2C), 137.6, 129.1 (2C), 128.9 (2C), 127.0, 68.8, 63.1, 62.3, 33.9, 28.2, 14.5 (2C). HRMS $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$ calculated 345.1426 found 345.1425. Minor regioisomer: ^1H NMR (60°C) δ 7.07-7.25 (m, 5H), 6.64 (s br, 1H), 4.23 (s br, 2H), 4.04-4.12 (m, 4H), 2.85 (t, $J = 8.0$ Hz, 2H), 2.64 (t, $J = 8.0$ Hz, 2H), 1.13-1.20 (m, 6H).



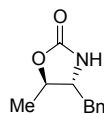
***N',N'*-Bis(ethoxycarbonyl)-3-hydrazino-4-methyl-2-pentanone (3g)** The ee was determined by HPLC using Chiralpak AS column (hexane/*i*-PrOH (97:03); flow rate 1.0 ml/min; $\tau_{\text{minor}} = 19.14$ min; $\tau_{\text{major}} = 21.48$ min). ^1H NMR (60°C) δ 6.69 (s br, 1H), 4.38 (s br, 1H), 4.05-4.15 (m, 4H), 2.20-2.28 (m, 1H), 2.18 (s, 3H), 1.15-1.20 (m, 6H),

0.85-0.92 (m, 6H), ^{13}C NMR impossible to obtain, even at 60°C, due to rigid structure. HRMS $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$ calculated 297.1426 found 297.1430. Minor regioisomer: ^1H NMR (60°C) δ 6.94 (s br, 1H), 4.23 (s br, 2H), 4.05-4.15 (m, 4H), 2.51 (br, 2H), 2.05-2.11 (m, 1H), 1.15-1.20 (m, 6H), 0.85-0.92 (m, 6H),



***N',N'*-Bis(ethoxycarbonyl)-2-hydrazino-3-pentanone (3h)** The ee was determined by chiral GC using Astec G-TA column ($\tau_{\text{major}} = 26.16$ min; $\tau_{\text{minor}} = 26.45$ min). $[\alpha]_D^{25} = -29.9$ ($c = 1.04$ g/100mL, CHCl_3 , 93% ee); ^1H NMR (60°C) δ 6.55 (s br, 1H), 4.83 (s br, 1H), 4.17-4.20 (m, 4H), 2.46-2.50 (m, 2H), 1.41 (d, $J = 7.6$ Hz, 3H), 1.26 (q, $J = 7.0$ Hz, 6H), 1.08 (t, $J = 7.2$ Hz, 3H), ^{13}C NMR (60°C) δ 209.7, 156.6, 156.4,

62.8, 62.0 (2C), 32.3, 14.5, 14.4, 13.3, 7.6. HRMS $\text{C}_{11}\text{H}_{20}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$ calculated 283.1270 found 283.1271.



(4*R*,5*R*)-4-Benzyl-5-methyl-2-oxazolidinone (5). 2.5 mmol of a mixture of regioisomers of **3f** was dissolved in

15 mL MeOH and cooled to 0°C. 180 mg NaBH_4 was added slowly and the mixture was stirred 0.5h at 0°C. The reaction mixture was then warmed to room temperature and 15 mL 0.5 N NaOH was added and stirring was continued for 2h. MeOH was removed *in vacuo* and 100 mL water was added. The aqueous suspension was extracted with 3x50 mL EtOAc. The organic phase was dried with MgSO_4 and concentrated *in vacuo*. The crude product mixture was dissolved in 5 mL acetonitrile and added to a acetonitrile (10 mL) solution of iodotrimethylsilane (prepared *in situ* from 1.5 mL hexamethyldisilane and 1.3 g iodine). This solution was stirred for 4h at 70°C. The solution was cooled to room temperature and quenched with 10 mL MeOH. The solvents were removed *in vacuo* and the residue was dissolved in 10 mL acetone and stirred for 5 min. Acetone was removed *in vacuo* and 10 mL of acetic acid was added together with 1 g of Zn and 100 μL of acetone. After 2h another 1 g of Zn and 100 μL of acetone was added and the mixture was stirred over night at 50°C. The suspension was filtered and most of the acetic acid was removed *in vacuo*. The residue was suspended in CH_2Cl_2 and extracted with sat. NaHCO_3 . The organic phase was dried with MgSO_4 and concentrated. The crude product was purified by FC (20% EtOAc in CH_2Cl_2) to give 126 mg of **5** (26% yield based on DEAD **2a**). $[\alpha]_D^{25} = +71^\circ$ ($c = 1.0$ g/100mL, CHCl_3). The optical rotation was equal to a literature value for the same compound.¹ ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.15 (m, 5H), 5.81 (s, 1H), 4.40 (k, $J = 6$ Hz, 1H), 3.63 (q, $J = 7$ Hz, 1H), 2.86 (dd, $J = 14, 7$ Hz, 1H), 2.82 (dd, $J = 14, 7$ Hz, 1H), 1.29 (d, $J = 6$ Hz, 1H, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.8, 136.0, 129.04 (2C), 129.00 (2C), 127.2, 78.4, 60.8, 41.1, 20.1. HRMS $\text{C}_{11}\text{H}_{13}\text{NO}_2$ $[\text{M}+\text{Na}]^+$; calculated: 214.0844 found: 214.0845.

¹ Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S.; *Chem.Pharm.Bull.*, **1988**, *36*, 3341.