

Supporting Information

Asymmetric Strecker Synthesis of α -Amino Acids via a Crystallization-Induced Asymmetric Transformation Using (*R*)-Phenylglycine Amide as Chiral Auxiliary

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General. Reagents were purchased from Aldrich Chemical Company and were used without further purification. (*R*)-Phenylglycine amide **1** was available from DSM (Geleen, The Netherlands) NMR spectra were recorded on either a Varian VXR-300 spectrometer (300 MHz) or a Bruker Spectrometer (200 MHz). Chemical shifts are denoted in ppm and were referenced to residual solvent.

2-[1-(*S*)-cyano-2,2-dimethyl-propyl]amino]-2-(*R*)-phenyl-acetamide **3**.

To a stirred suspension of (*R*)-phenylglycine amide **1** (60.3 g, 400 mmol) in H₂O (400 mL) was added pivaldehyde **2** (37.2 g, 419 mmol) at room temperature. Simultaneously, 30 % aqueous NaCN (68.8 g, 420 mmol) and glacial

acetic acid (25.4 g, 423 mmol) were added in 30 minutes, whereby the temperature increased from 23 to 28°C. The mixture was stirred for 2h at 30°C, followed by stirring for 20 h at 70°C. After cooling to 30°C, the amino nitrile was isolated by filtration and washed with H₂O (500 mL). After drying the amino nitrile (*R,S*)-**3** was obtained as a nearly colorless solid (92.4%, dr > 99/1).

(*R,S*)-**3**: m.p. 141°C. $[\alpha]_{589}^{20} = -32.8^{\circ}$ (c = 1.0, CHCl₃).

¹H NMR (200 MHz, CDCl₃): δ 7.38-7.46 (m, 5H), 5.55 (bs, 1H), 5.40 (bs, 1H), 4.49 (s, 1H), 2.87 (d, *J* = 12.7 Hz, 1H), 2.76 (d, *J* = 12.7 Hz, 1H), 1.05 (s, 9H).

¹³C NMR (50 MHz, CDCl₃) δ 170.6, 134.4, 126.9, 126.7, 126.0, 116.3, 62.0, 55.9, 31.7, 23.7.

(*R,R*)-**3**: ¹H NMR (200 MHz, CDCl₃): δ 7.36-7.46 (m, 5H), 6.85 (bs, 1H), 6.15 (bs, 1H), 4.49

(s, 1H), 3.31 (d, $J = 12.3$ Hz, 1H), 1.89 (d, $J = 12.3$ Hz, 1H), 1.15 (s, 9H).

2-[1-(*S*)-aminocarbonyl-2,2-dimethyl-propyl)-amino]-2-(*R*)-phenyl-acetamide **5**

A solution of (*R,S*)-amino nitrile **3** (940 mg, 4.0 mmol, dr 98/1) in CH_2Cl_2 (5.0 mL) was added slowly to conc. H_2SO_4 (5.6 mL, 96%), at such a rate that the temperature was 15–20°C. After the addition was complete, stirring is continued for 30 minutes at room temperature and then the mixture is stirred for 2 h at 40°C. After cooling to 20°C, the mixture was poured on ice and neutralized with 25% aqueous NH_3 to pH = ~9. The oily product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried on Na_2SO_4 and concentrated under vacuum to give 950 mg (94%) of diamide **5**.

M.p. 69°C. $[\alpha]_{589}^{20} = -139.5^\circ$ ($c = 1.0$, CHCl_3).

^1H NMR (300 MHz, CDCl_3) δ 7.30 – 7.40 (m, 5H), 6.51 (bs, 1H), 6.40 (bs, 2H), 6.35 (bs, 1H), 4.08 (s, 1H), 2.53 (bs, 1H), 2.46 (bs, 1H), 0.97 (s, 9H).

^{13}C NMR (50 MHz, CDCl_3) δ 173.3, 172.4, 135.6, 126.4, 125.9, 125.5, 66.0, 62.5, 30.9, 24.5.

(*S*)-2-amino-3,3-dimethylbutanamide **6 ((*S*)-*tert*-leucine amide)**

The diamide **5** (0.90 g, 3.7 mmol) was dissolved in EtOH (96%, 25 mL) and 10% Pd/C (50 mg) was added. The mixture was shaken under pressurized H_2 (2 bar) for 20 h and then filtered through celite. The celite was washed with EtOH (3 x 10 mL). The combined filtrate and washings were concentrated and the crude reaction mixture was separated via SiO_2 chromatography with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1) as eluent to give first the side product phenylacetamide ($R_f = 0.5$) and then 0.49 g (90%) of pure (*S*)-*tert*-leucine amide **6** ($R_f = 0.10$).

M.p. 105°C (lit.¹ 98–100°C). $[\alpha]_{589}^{20} +47.1^\circ$ ($c = 1.0$, 5N HCl); (lit.¹ $[\alpha]_{589}^{20} = +41.0^\circ$)

^1H NMR (300 MHz, CDCl_3) δ 6.50, (bs, 1H), 5.49 (bs, 1H), 3.07 (s, 1H), 1.48 (bs, 2H), 0.96 (s, 9H).

^{13}C NMR (50 MHz, CDCl_3) δ 174.0, 61.9, 31.3, 24.1.

(*S*)-2-amino-3,3-dimethylbutanoic acid **7 ((*S*)-*tert*-leucine)**

(*S*)-2-amino-3,3-dimethylbutanamide **6** (200 mg, 1.54 mmol) in 6N HCl (50 mL) was heated at 100°C for 24 h, cooled to room temperature and applied to a Dowex 50 Wx8 ion-exchange column in the NH_4^+ -form. The column was washed with H_2O (25 mL), followed by elution with 10% aqueous NH_3 (40 mL). Concentration and drying gave 174 mg (86%) of pure (*S*)-*tert*-leucine **7** as a white solid.

M.p. 252–256°C (lit.¹ 252–260°C; sublimes). $[\alpha]_{589}^{20} = -10.0^\circ$ ($c = 1.0$, H_2O), (lit.¹ $[\alpha]_{589}^{20} = -10.9^\circ$).

^1H NMR (300 MHz, D_2O) δ 3.44 (s, 1H), 1.06 (s, 9H).

^{13}C NMR (50 MHz, D_2O) δ 174.0, 61.9, 31.3, 24.1.

2-[2-(*S*)-cyano-(3,4-dimethoxyphenyl)propyl)-amino]-2-(*R*)-phenyl-acetamide **9**

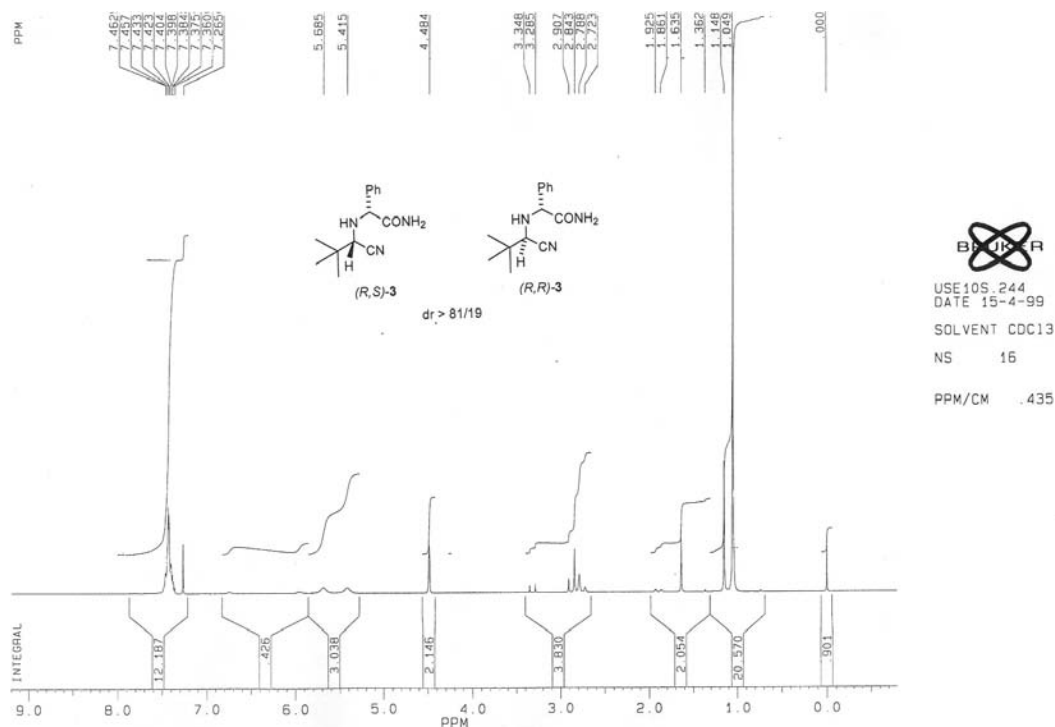
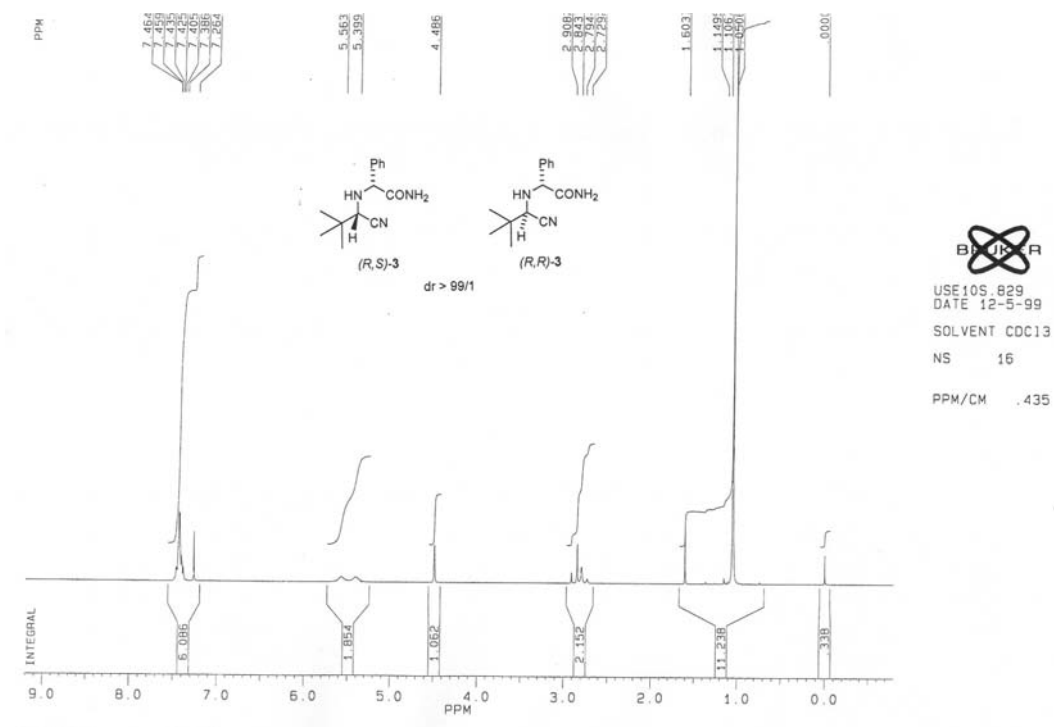
To a stirred suspension of (*R*)-phenylglycine amide **1.HCl** salt (18.6 g, 100 mmol) in MeOH (150 mL) and H_2O (25 mL) was added 3,4-dimethoxyphenylacetone **8** (19.3 g, 100 mmol) at room temperature. Then, 30 % aqueous NaCN (16.5 g, 100 mmol) was added and the now clear solution stirred for 96 h at room temperature. The precipitated amino nitrile (*R,S*)-**9** was isolated by filtration and washed with $\text{H}_2\text{O}/\text{MeOH}$ (3 x 15 mL, v/v 70:30). After drying, the amino nitrile (*R,S*)-**9** was obtained as a nearly colorless solid (76% yield, dr >99/1).

(*R,S*)-**9**: ^1H NMR (200 MHz, CDCl_3): δ 7.26–7.38 (m, 5H), 6.79 (s, 3H), 6.58 (bs, 1H), 5.70 (bs, 1H), 4.49 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.85 (s, 2H), 2.56 (s, 1H), 1.50 (s, 3H).

(*R,R*)-**9**: ^1H NMR (200 MHz, CDCl_3): δ 7.26–7.43 (m, 5H), 6.78–6.91 (m, 3H), 6.64 (bs, 1H), 5.78 (bs, 1H), 4.49 (s, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 2.85–2.98 (m, 2H), 1.15 (s, 3H). NH could not be assigned

NMR spectrum of (*R,R*)-**9** also contains the imine

¹ Speelman, J.C.; Talma, A.G.; Kellogg, R.M.; Meetsma, A.; de Boer, A.; Beurskens, P.T.; Bosman, W.P. *J. Org. Chem.* **1989**, *54*, 1055.



The diastereomeric ratio of (*R,S*)-**3** and (*R,R*)-**3** is based on the integration of the tert-butyl signals at 1.05 ppm and 1.15 ppm in the spectrum shown. A ratio of 81/19 is calculated.

