

A Multistage, One-Pot Procedure Mediated by a Single Catalyst: A New Approach to the Catalytic Asymmetric Synthesis of β -Amino Acids

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SUPPORTING INFORMATION

General: Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions. All reagents used are commercially available from NovaBiochem, Aldrich, Fluka, and Acros Chemicals. All solvents were dried and distilled by standard procedures. All acid chlorides were distilled by standard procedures. Catalysts **3a** and **3b**,¹ and α -chloroglycine **2a**² were made according to literature precedent. Physical data, identity, and absolute configuration of **5a-d** and **6a-c** were consistent with literature precedent.² Polymer supported catalyst **3c** was made according to literature precedence.³ The ¹H, ¹³C, and ¹⁹F NMR spectra were acquired on a Varian Unity Plus 400 MHz instrument in CDCl₃ unless otherwise stated. The ¹H (400 MHz) and ¹³C (101 MHz) chemical shifts are given in parts per million (δ) with respect to internal TMS standard or residual solvent peaks unless otherwise stated. ¹⁹F (376 MHz) chemical shifts are given in parts per million with respect to internal CFCl₃ standard. HPLC analysis was

¹ Pracejus, H.; Maetje, H. *J. Prakt. Chem.* **1964**, *24*, 195-205.

² Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387-390.

³ Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett.* **2000**, *2*, 3963-3965.

performed with a Waters Millipore Model 510 head unit a Regis Technologies (*R,R*) Whelk-01 Chiral, a Waters Millipore Lambda-Max Model 481L spectrophotometer and a Hewlett Packard integrator. Solution phase IR data were recorded on a Bruker Vector 22 FTIR spectrometer.

General procedure for β -substituted aspartic acids **5a-e.**⁴ A 25 mL round-bottom flask equipped with a stir bar was loaded under nitrogen with α -chloroamine **2a** (63 mg, 0.26 mmol), proton sponge **4** (83 mg, 0.39 mmol), and the benzoylquinine catalyst **3a** (6 mg, 0.013 mmol). Toluene (1 mL) was added to the mixture and stirred for 1 h. The solution was diluted with toluene (7 mL) and cooled to -78 °C in a dry ice/acetone bath. Phenylacetyl chloride **1a** (20 mg, 0.13 mmol) in toluene (1 mL) was added to the reaction drop wise. The reaction was allowed to slowly warm to room temperature overnight. Excess methanol (6 mL)⁵ was added and the solution was refluxed.⁶ The reaction was monitored by TLC and stopped when all of the β -lactam had reacted (~ 4 h). The solvent was removed *in vacuo* and the residue was taken up in chloroform (10 mL) and washed with 1 M HCl (3 x 10 mL). The organic layer was dried with MgSO₄ and filtered through Celite. The filtrate was concentrated and the residue was submitted to flash column chromatography to yield **5a** in 62% yield (22 mg) and 95% ee.

General Procedure for Methanolysis of β -lactams. In a 10 mL round-bottom flask equipped with a stir bar and condenser, the N-acyl β -lactam **9a** (15 mg, 0.046 mmol) was suspended in methanol (1.0 mL). Benzoylquinine (2.0 mg, 0.0046 mmol) and scandium (III) triflate (2.3 mg, 0.0046 mmol) suspended in methanol (0.5 mL each) were added to the solution. The reaction was refluxed and continuously monitored by TLC until all of the lactam had been consumed. The solution was concentrated and the residue was eluted through a plug of silica with EtOAc/hexanes (2:5) yielding the desired β -amino acid.

⁴ Ketene **7e** from 4-methoxyphenoxyacetyl chloride was formed at 0 °C in 6 mL of toluene and the imine solution was added to it at -78 °C.

⁵ For the synthesis of **6a-e**, methanol was substituted with 0.26 mmol of the corresponding amine, which was added directly to the reaction mixture at room temperature and stirred until the reaction was complete by TLC.

⁶ The methanolysis of the β -lactam proceeds faster if the toluene is removed and the crude mixture is refluxed in methanol.

(3*R*,4*R*)-2-Benzoylamino-3-(*p*-methoxy)-phenoxy-succinic acid 1-ethyl ester 4-methyl ester (5e). White crystalline solid recrystallized from Et₂O/hexanes: mp = 147-148°C; [α]_D = +21.1° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) δ 7.82 (d, 2H), 7.52 (m, 1H), 7.46 (m, 2H), 7.38 (m, 2H), 7.00 (t, 1H), 6.95 (brd, 1H), 6.90 (d, 2H), 5.51 (dd, 1H), 5.23 (d, 1H), 4.24 (q, 2H), 3.78 (s, 6H) 1.24 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 169.6, 169.4, 168.7, 158.2, 155.2, 134.5, 135.6, 128.7, 127.4, 117.9, 115.3, 80.3, 77.1, 62.7, 55.4, 53.9, 15.0 ppm; IR (CHCl₃) 1377, 1475, 1660, 1793, 1824, 2251 cm⁻¹; HPLC (5% *i*PrOH/1.0% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 30.1, (*R,S*) = 28.4, (*S,R*) = 33.7, (*S,S*) = 39.3 min. Anal Calcd for C₂₁H₂₃N₃O₇: C, 62.8; H, 5.78; N, 3.49. Found C, 62.5; H, 5.81; N, 3.46.

[2-Benzoylamino-3-(methoxycarbonylmethyl-carbamoyl)-3-phenyl-propionylamino]-acetic acid methyl ester (10). White crystalline solid recrystallized from Et₂O/hexanes: mp = 156-158°C; [α]_D = +20.2° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) δ 7.81 (m, 2H), 7.54-7.43 (m, 4H), 6.98 (brd, 1H), 6.89 (brm, 2H), 6.80 (m, 4H), 5.46 (dd, 1H), 5.14 (d, 1H), 4.10-4.20 (m, 4H), 3.74 (s, 3H), 3.68 (s, 3H) ppm; ¹³C NMR (CDCl₃) δ 173.1, 171.5, 170.7, 169.9, 168.1, 136.8, 134.9, 133.0, 129.9, 129.8, 129.4, 129.3, 128.0, 62.1, 61.9, 56.7, 56.3, 53.7, 53.4 ppm; IR (CHCl₃) 1215, 1422, 1570, 1666, 1724, 1750, 2385 cm⁻¹; HPLC (10% *i*PrOH/1.0% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 9.32, (*R,S*) = 7.58, (*S,R*) = 8.01, (*S,S*) = 11.42 min. Anal Calcd for C₂₃H₂₅N₃O₇: C, 60.6; H, 5.53; N, 9.23. Found C, 60.4; H, 5.51; N, 9.28.

1-[(3-Benzoylamino-3-ethoxycarbonyl-2-phenyl-propionylamino)-acetyl]-pyrrolidine-2-carboxylic acid methyl ester (6d). White crystalline solid recrystallized from Et₂O/hexanes: mp = 142-144°C; [α]_D = +19.4° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) δ 8.02 (d, 1H), 7.78 (d, 2H), 7.48 (m, 1H), 7.42 (m, 2H) 7.38-7.30 (m, 2H), 7.30-7.22 (m, 2H), 6.70 (bs, 1H), 5.20 (m, 1H), 4.50 (m, 2H), 4.20 (m, 2H), 4.15 (m, 2H), 3.78 (m, 1H), 3.70 (s, 3H), 3.58 (m, 1H), 3.45 (m, 1H), 2.20 (m, 1H), 2.04 (s, 3H), 1.25 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 172.3, 172.2, 171.0, 167.3, 166.3, 135.5, 134.1, 131.7, 129.1, 128.7, 128.6, 128.3, 127.3, 61.9, 59.0, 55.6, 52.6, 46.1, 42.3, 29.9 ppm; IR (CHCl₃) 1220, 1402, 1576, 1673, 1725, 2280 cm⁻¹; HPLC (10% *i*PrOH/1.0% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 12.41, (*R,S*) = 9.92, (*S,R*) = 11.25, (*S,S*) = 14.93 min. Anal Calcd for C₃₄H₃₉N₃O₇: C, 67.8; H, 6.53; N, 6.98. Found C, 67.6; H, 6.53; N, 6.91.

Benzoylamino- α -chloroglycine 2,2,2-trifluoro-ethyl ester (2b). To a solution of 2,2,2-trifluoroethanol (12.4 mL, 171.5 mmol) in CH_2Cl_2 was added triethylamine (13.7 mL, 98.1 mmol). The resulting solution was cooled to $-78\text{ }^\circ\text{C}$ and fumaryl chloride (5.3 mL, 49.0 mmol) was added drop wise. The reaction was allowed to warm to room temperature and then washed with 1M HCl followed by saturated sodium bicarbonate. The organic layer was then dried with MgSO_4 and concentrated. The oily residue was placed on a plug of silica gel and eluted with EtOAc/hexanes yielding 2,2,2-trifluoroethylfumarate as a white solid (10.17 g). A flask containing 2,2,2-Trifluoroethylfumarate (5.0 g, 17.9 mmol) dissolved in a 50/50 mixture of EtOAc/MeCN (225 mL) was cooled to $0\text{ }^\circ\text{C}$. Ruthenium trichloride (0.26 g, 1.25 mmol) and sodium periodate (5.7 g, 26.9 mmol) were combined in 37.5 mL of water and added to the reaction which then stirred at $0\text{ }^\circ\text{C}$ for 1 hour. It was then quenched with 175 mL of saturated sodium sulfite and the aqueous layer was extracted three times with EtOAc. The organics were combined, dried with MgSO_4 , and concentrated. The resulting brown solid was recrystallized from CH_2Cl_2 /hexanes yielding 2,2,2-trifluoroethyltartrate as a pale yellow solid (2.5 g, 7.96 mmol). This was dissolved in diethyl ether (25 mL) and cooled to $0\text{ }^\circ\text{C}$. Periodic acid (1.81 g, 7.96 mmol) was added and the reaction was allowed to warm to room temperature. To the flask was added 4 Å mol. sieves and the resulting mixture stirred for 1 hour. The sieves were filtered from the reaction and the solvent was removed in vacuo. yielding 2,2,2-trifluoroethyl glyoxalate hydrate as an orange oil. This was combined with benzamide (1.15 g, 9.48 mmol) in ethyl acetate (30 mL) and refluxed for 12 hours. The solvent was removed in vacuo and the residue was recrystallized with EtOAc/hexanes yielding a white solid. The resulting *N*-acyl- α -hydroxyamine (0.83 g, 3.0 mmol) was combined with oxalyl chloride (0.58 g, 4.5 mmol) and 2 drops of *N,N*-dimethylformamide in CH_2Cl_2 (15 mL) and stirred at $0\text{ }^\circ\text{C}$ for 6 hours. The solution was then concentrated in vacuo yielding **2b** as a pale yellow solid. The solid was refrigerated and would polymerize upon standing at room temperature. ^1H NMR (CDCl_3); δ 9.08 (brd,1H), 7.98 (d, 2H), 7.63 (m, 1H), 7.50 (m, 2H), 6.78 (d, 1H), 4.88 (m, 2H) ppm. **2b** was used as is and was not further characterized.

***p*-Fluorobenzoylamino- α -chloroglycine ethyl ester (2c).** mp = 68-70 °C; ^1H NMR (CDCl_3); δ 7.88 (m, 2H), 7.35 (brd, 1H), 7.19 (m, 2H), 6.45 (d, 1H), 4.38 (m, 2H), 1.34 (t, 3H) ppm; ^{13}C NMR (CDCl_3) δ 166.5, 166.0, 135.5, 132.2, 128.7, 128.4, 127.4, 63.2, 60.5 ppm. Anal Calcd for $\text{C}_{11}\text{H}_{11}\text{ClFNO}_3$: C, 50.9; H, 4.27; Cl, 13.6, N, 5.39. Found C, 51.2; H, 4.22; Cl, 13.8; N, 5.33.

(*p*-Phenyl)-benzoylamino- α -chloroglycine benzyl ester (2d). mp = 72-73 °C; ^1H NMR (CDCl_3); δ 7.88 (d, 2H), 7.49-7.46 (m, 8H), 7.40 (m, 2H), 7.18 (d, 2H), 6.78 (brd, 1H), 6.37 (d, 1H), 5.31 (s, 2H) ppm; ^{13}C NMR (CDCl_3) δ 167.6, 167.0, 146.7, 140.7, 135.3, 131.8, 130.1, 129.6, 129.3, 129.0, 128.5, 128.4, 128.3, 128.1, 70.5, 61.7 ppm. Anal Calcd for $\text{C}_{22}\text{H}_{18}\text{ClNO}_3$: C, 69.6; H, 4.78; Cl, 9.33; N, 3.69. Found C, 69.6; H, 4.77; Cl, 9.30; N, 3.72.

NMR Experiment. A ^{19}F NMR of *N*-4-fluorobenzoyl- α -chloroamine **2c** (62 mg, 0.26 mmol) in (0.5 mL) benzene- d_6 containing CFCl_3 as an internal standard was obtained. To the sample was added in one portion benzene- d_6 solution (0.4 mL) of proton sponge **4** (64 mg, 0.26 mmol). The mixture was monitored by ^{19}F NMR over the course of 30 minutes during which time no noticeable changes in the spectrum were noted. To the mixture was added BQ (6 mg, 0.013 mmol) as a solution (0.1 mL) in benzene- d_6 and the reaction monitored by ^{19}F NMR until the starting *N*-4-fluorobenzoyl- α -chloroamine **2c** had been completely consumed (approximately 30 minutes).

The rate dependency of imine formation on the concentration of proton sponge was determined as follows: Three separate NMR samples containing the same quantities of catalyst BQ (6 mg, 0.1 eq), *N*-4-fluorobenzoyl- α -chloroamine **2c** (1 eq), and solvent (0.5 mL) benzene- d_6 were prepared. To each sample was added a different quantity of proton sponge as a solution in benzene- d_6 (0.2 mL). The addition of proton sponge to the samples was as follows: sample 1 (64 mg, 2 eq), sample 2 (128 mg, 4 eq), and sample 3 (192 mg, 6 eq). The rate of imine formation and the corresponding consumption of the starting *N*-4-fluorobenzoyl- α -chloroamine **2c** were monitored by ^{19}F NMR. Under these conditions no discernable rate difference between the three samples was apparent.

1-[(Biphenyl-4-carbonyl)-3-(4-methoxy-phenoxy)-4-oxo-azetidine-2-carboxylic acid benzyl ester (9g). A 25 mL round-bottom flask equipped with a stir bar was loaded under nitrogen with α -chloroamine **2d** (87 mg, 0.26 mmol), proton sponge **4** (83 mg, 0.39 mmol), and the benzoylquinine catalyst **3a** (6 mg, 0.013 mmol). Toluene (1 mL) was added to the mixture and stirred for 0.5 h. The solution was diluted with toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. A prepared solution of 4-methoxyphenoxyketene **7g** (26 mg, 0.13 mmol) in toluene (2 mL) was added to the reaction drop wise. The reaction was allowed to slowly warm to room temperature overnight. The solvent was removed in vacuo and the residue was taken up in chloroform (10 mL) and washed with 1 M HCl (3 x 10 mL), saturated NaHCO₃ (3 x 10 mL), dried with MgSO₄ and filtered. The filtrate was concentrated and the residue was submitted to flash column chromatography the fractions containing the product were pooled and concentrated. The product was recrystallized from Et₂O/hexane yielding **9g** in 48% yield (32 mg) and 95% ee as the major cis diastereomer (dr 11:1): mp = 151-154° C; [a]^D = -24.3° (c = 0.010, CHCl₃); ¹H NMR (CDCl₃) 8.13 (d, 2H), 7.69 (d, 2H), 7.62 (d, 2H), 7.46 (t, 2H), 7.41-7.35 (m, 2H), 7.31 (brd, 1H), 7.29 (d, 2H), 7.24 (d, 2H), 6.87 (d, 2H), 6.76 (d, 2H), 5.39 (d, 1H), 5.20 (dd, 1H), 5.12 (brs, 2H), 3.64 (s, 3H) 3.35 (s, 2H) ppm; ¹³C NMR (CDCl₃) 166.9, 166.5, 161.7, 156.6, 152.1, 147.7, 140.8, 135.9, 131.7, 130.1, 130.0, 129.7, 129.6, 129.5, 129.4, 128.4, 128.1, 118.2, 115.7, 80.7, 68.9, 58.1, 56.7 ppm; IR (CHCl₃) 3024, 2963, 1801, 1749, 1368, 1265, 1217, 1169, 1085, 1010 cm⁻¹. HPLC (5% *i*-PrOH/ 1% HOAc/hexanes, 1.0 mL/min) (R,R) = 18.2, (R,S) = 15.7, (S,R) = 22.4, (S,S) = 27.9 min. Anal Calcd for C₃₁H₂₅NO₆ C, 73.36; H, 4.96; N, 2.76. Found C, 73.35; H, 4.94; N, 2.77.

2-Amino-3-(4-methoxy-phenoxy)-succinamic acid (13). Dry liquid ammonia cooled to -78° C with the aid of a dry ice/acetone bath was added a solution of *cis*- β -lactam **9g** (100 mg, 0.20 mmol) in CH₂Cl₂ (1 mL) drop wise over the course of 5 min. The resulting yellow solution was gradual warmed to room temperature and the ammonia allowed to evaporate. The white heterogeneous mixture was concentrated by reduced pressure rotary evaporation and the residue subjected to column chromatography (80% EtOAc/hexanes) on a short plug of silica gel (1.0 cm x 5 cm) the fractions containing the product were pooled and concentrated to afforded a white solid which was recrystallized from (EtOAc/Ether/Hexanes: 1/3/8) giving pure product **11** (88%, 92 mg). mp = 212-215° C; ¹H NMR (DMSO-d₆) 8.13 (d, 2H), 7.69

(d, 2H), 7.62 (d, 2H), 7.46 (t, 2H), 7.41-7.33 (m, 2H), 7.29 (d, 2H), 7.24 (d, 2H), 6.87 (d, 2H), 6.76 (d, 2H), 5.39 (d, 1H), 5.20 (qt, 2H), 5.12 (d, 1H), 3.74 (s, 3H) ppm; ^{13}C NMR (DMSO- d_6) 166.9, 166.5, 161.7, 156.6, 152.1, 147.7, 140.8, 135.9, 131.7, 130.1, 130.0, 129.7, 129.6, 129.5, 129.4, 128.4, 128.1, 118.2, 115.7, 80.7, 68.9, 58.1, 56.7 ppm. Anal Calcd for $\text{C}_{31}\text{H}_{28}\text{N}_2\text{O}_6$ C, 70.9; H, 5.38; N, 5.34. Found C, 71.1; H, 5.41; N, 5.33.

Compound **11** (86 mg, 0.16 mmol) was dissolved in (10 mL) of a (EtOH/DMF:5/1) mixture and Pd/C (10 mg) was added. The resulting slurry was evacuated and an atmosphere of hydrogen gas reestablished with the aid of a balloon filled with hydrogen. The reaction was stirred for 5 h under an atmosphere of hydrogen and then filtered through a plug of Celite. The filter cake was washed with EtOH and the organics combined and concentrated. The resulting solid was thoroughly dried yielding a white solid **12** (99%, 69 mg). (Note: The product could be purified by column chromatography using silica gel and a gradient solvent system of (Hex:EtOAc/3:1) followed by (EtOAc) and finally (EtOAc:MeOH/4:1) if necessary. : mp = 138-141° C; ^1H NMR (DMSO- d_6) 8.71 (d, 1H), 7.97 (d, 2H), 7.75 (d, 2H), 7.70 (d, 2H), 7.59 (s, 1H), 7.46 (t, 2H), 7.37 (t, 1H), 6.85 (q, 4H), 5.23-5.20 (m, 1H), 5.11 (s, 2H), 4.99 (d, 1H), 3.64 (s, 3H) ppm; ^{13}C NMR (DMSO- d_6) 172.4, 172.1, 167.9, 155.7, 153.1, 144.6, 140.6, 137.0, 133.8, 130.6, 129.9, 129.6, 128.4, 118.5, 116.1, 80.2, 68.1, 56.9 ppm; Anal Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_6$ C, 66.35; H, 5.10; N, 6.45. Found C, 66.17; H, 5.08; N, 6.48.

A 10 mL round-bottom flask equipped with a stir bar was charged with (67 mg, 0.15 mmol) and 3% NaHg amalgam (45 mg). The solids were suspended in (3 mL) of methanol and vigorously stirred for 2 h under a nitrogen atmosphere. The yellow solution was filtered to remove the solids and cooled to 0 °C and the solution acidified with 2 N HCl. The methanol was removed by reduced pressure rotary evaporation and the aqueous solution washed with EtOAc (4 mL). The aqueous layer was concentrated to afford a white solid **13** that was sufficiently pure yield (67%, 26 mg). (Note: To obtain a sample of higher purity the product could be recrystallized from aqueous EtOH or alternatively purified by ion exchange chromatography. mp = 208-211° C; ^1H NMR (D_2O) 6.89 (d, 2H), 6.823 (d, 2H), 5.13 (d, 1H), 5.05 (brs, 2H), 4.34 (d, 1H), 3.66 (s, 3H) ppm; ^{13}C NMR (D_2O) 172.5, 169.9, 130.15, 127.9, 118.5, 116.1, 77.6, 56.8, 55.7 ppm; Anal Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_5$ C, 51.97; H, 5.55; N, 11.02. Found C, 52.10; H, 5.54; N, 10.98.

Threo- β -hydroxy-succinamic acid (14). Compound **13** (26 mg, 0.10 mmol) was dissolved in CH₃CN (3 mL). Cerium ammonium nitrate (60 mg, 0.11 mmol) was added to the solution at 0 °C. The solvent was removed yielding **14** in 82% yield. The compound was converted to the HCl salt for further characterization and to prevent decomposition. White crystalline solid : $[\alpha]_D = -28.1^\circ$ (c = 0.01, 1M HCl). All other data consistent with literature precedent.⁷

⁷ (a) Singerman, A.; Liwschitz, Y. *Tetrahedron Lett.* **1986**, 9, 4733-4734. (b) Okai, H.; Izumiya, N.; *Bull Chem Soc. Jpn.* **1969**, 42, 3550-3555.