Acyclic Amino Acid-Catalyzed Direct Asymmetric Aldol Reactions: Alanine the Simplest Stereoselective Organocatalysts

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Supporting Information

General. Chemicals and solvents were either purchased puriss p.A. from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), Ce(SO$_4$)$_2$·H$_2$O (10 g), conc. H$_2$SO$_4$ (60 mL), and H$_2$O (940 mL) followed by heating or by treatment with a solution of p-anisaldehyde (23 mL), conc. H$_2$SO$_4$ (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm), $^1$H NMR and $^{13}$C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants $J$ are given in Hz. The spectra were recorded in CDCl$_3$ as solvent at room temperature, TMS served as internal standard (δ = 0 ppm) for $^1$H NMR, and CDCl$_3$ was used as internal standard (δ = 77.0 ppm) for $^{13}$C NMR. HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. GC was carried out using a Varian 3800 GC Instrument. Chiral GC-column used: CP-Chirasil-Dex CB 25m x 0.32mm. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter ($\lambda$ = 589 nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

Typical experimental procedure for the alanine and acyclic amino acid-catalyzed direct asymmetric aldol reactions. A catalytic amount of L-amino acid or chiral amine (0.15 mmol, 30 mol%) was added to a vial containing acceptor aldehyde (0.5 mmol), donor ketone 2 (1.5 mmol), H$_2$O (5 mmol, 90µL) in DMSO (2 mL). After 3-4 days of vigorously stirring at room temperature the reaction mixture was poured into an extraction funnel that contained brine (5.0 mL), which was diluted with distilled H$_2$O (5.0 mL) and EtOAc (15 mL). The reaction vial was also washed with 2 mL of EtOAc, which was poured into the extraction funnel. The aqueous phase was extracted with EtOAc (2x15.0 mL). The combined organic phases were dried with Na$_2$SO$_4$ and the solvent removed under reduced pressure. The reaction can also be quenched by directly putting the reaction mixture on a silica-gel column. The crude aldol product was purified by silica-gel column chromatography (EtOAc:pentane-mixtures) to furnish the desired aldol product 2. The ee of the aldol products 2 were determined by chiral-phase HPLC analysis or chiral-phase GC analyses.
2a: $^1$H-NMR (400 MHz, CDCl$_3$) δ (ppm): 1.30 (s, 3H, CH$_3$), 1.40 (s, 3H, CH$_3$), 3.9 (m, 1H), 4.13-4.50 (m, 3H), 5.01 (d, $J = 7.8$ Hz, 1H, CHOH), 7.70 (d, $J = 8.4$ Hz, 2H, ArH), 8.22 (d, $J = 8.4$ Hz, 2H, ArH); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ (ppm): 23.3, 23.4, 66.6, 71.7, 75.8, 101.4, 123.2, 127.9, 138.3, 146.5, 210.6; HPLC (Daicel Chiralpak AD, iso-hexanes/i-PrOH = 96:4, flow rate 0.5 mL/min, $\lambda = 254$ nm): major isomer: $t_R = 52.12$ min; minor isomer: $t_R = 57.02$ min; $[\alpha]_D^{25} = -131.1$ (c = 1.2, CHCl$_3$).

2b: $^1$H NMR (CDCl$_3$, 400 MHz): 1.52-2.14 (m, 6H), 2.33-2.52 (m, 2H), 2.59 (m, 1H), 3.15 (bs, 1H), 4.90 (d, $J = 8.6$ Hz, 1H), 7.49 (d, $J = 8.7$ Hz, 2H), 8.20 (d, $J = 8.7$ Hz, 2H); $^{13}$C NMR (100 MHz): δ =24.6, 27.6, 30.7, 42.6, 57.1, 73.9, 123.5, 127.8, 147.5, 148.4, 214.7; HPLC (Daicel Chiralpak AD, iso-hexanes/i-PrOH = 80:20, flow rate 0.5 mL/min, $\lambda = 254$ nm): major isomer: $t_R = 31.12$ min; minor isomer: $t_R = 24.14$ min; $[\alpha]_D = +12.8$ (c = 1.1, CHCl$_3$); MALDI-TOF MS: 272.0897; C$_{13}$H$_{15}$NO$_4$ (M+Na$: $\text{calcd}$ 272.0899).

2c: $^1$H NMR (CDCl$_3$, 400 MHz): δ = 1.08 (t, 3H, $J = 7.3$ Hz, CH$_3$CH$_2$), 2.48 (s, 2H, CH$_2$CH$_2$CO), 2.81-2.87 (m, 2H, CHOHCH$_2$CO), 3.64 (s, 1H, OH), 5.26 (m, 1H, CHOH), 7.54 (d, $J = 8.7$ Hz, 2H), 8.21 (d, $J = 8.7$ Hz, 2H); HPLC (Daicel Chiralpak AS, iso-hexanes/i-PrOH = 80:20, flow rate 0.5 mL/min, $\lambda = 254$ nm): major isomer: $t_R = 22.46$ min; minor isomer: $t_R = 29.80$ min; $[\alpha]_D^{25} = +45.1$ (c = 0.9, CHCl$_3$).

2d: $^1$H-NMR (400 MHz, CDCl$_3$) δ (ppm): 1.46-1.53 (m, 1H), 1.69-1.76 (m, 2H), 1.97-2.05 (m, 1H), 2.42-2.48 (m, 1H), 2.66-2.75 (m, 1H), 2.94-3.01 (m, 1H), 3.86-3.89 (m,
2H), 3.92-3.95 (m, 2H), 4.04 (m, 1H), 4.92 (m, 1H), 7.49 (d, *J* = 8.6 Hz, 2H), 8.19 (d, *J* = 8.7 Hz, 2H); \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm): 34.50, 37.9, 38.9, 53.4, 64.9, 65.2, 74.0, 107.2, 123.9, 128.0, 128.8, 148.4, 214.0; HPLC (Daicel Chiralpak AD, iso-hexanes/i-PrOH = 80:20, flow rate 0.5 mL/min, \(\lambda = 254\) nm): major isomer: \(t_R = 35.71\) min; minor isomer: \(t_R = 44.03\) min.

![O-O-O-H]

\(\text{O}-\text{O}-\text{N}-\text{CN}\)

\(2e\) \(^1^H\)-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm): 1.20 (s, 3H, CH\(_3\)), 1.37 (s, 3H, CH\(_3\)) 3.78 (bs, 1H), 4.06 (d, *J* = 17.3, 1H), 4.19-4.29 (m, 2H), 4.93 (d, *J* = 7.8 Hz, 1H, CHOH), 7.51 (d, *J* = 8.4, 2H, ArH), 7.63 (d, *J* = 8.4, 2H, ArH); \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm): 23.2, 23.5, 66.6, 72.0, 76.0, 101.2, 128.2, 128.4, 133.7, 137.8, 210.9; HPLC (Daicel Chiralpak OJ, iso-hexanes/i-PrOH = 90:10, flow rate 0.5 mL/min, \(\lambda = 254\) nm): major isomer: \(t_R = 34.50\) min; minor isomer: \(t_R = 36.52\) min; \([\alpha]_{D}^{25} = -101.3\) (\(c = 1.0, \text{CHCl}_3\)).

![O-O-O-B]

\(\text{O}-\text{O}-\text{N}-\text{Br}\)

\(2f\) \(^1^H\)-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm): 1.20 (s, 3H, CH\(_3\)), 1.37 (s, 3H, CH\(_3\)) 3.78 (bs, 1H), 4.06 (d, *J* = 17.3, 1H), 4.19-4.29 (m, 2H), 4.93 (d, *J* = 7.8 Hz, 1H, CHOH), 7.51 (d, *J* = 8.4, 2H, ArH), 7.63 (d, *J* = 8.4, 2H, ArH); \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm): 23.2, 23.5, 66.6, 72.0, 76.0, 101.2, 128.2, 128.4, 133.7, 137.8, 210.9; HPLC (Daicel Chiralpak AS, iso-hexanes/i-PrOH = 97:3, flow rate 0.5 mL/min, \(\lambda = 254\) nm): major isomer: \(t_R = 24.10\) min; minor isomer: \(t_R = 30.32\) min; \([\alpha]_{D}^{25} = -110.9\) (\(c = 1.0, \text{CHCl}_3\)).

![O-O-O-Cl]

\(\text{O}-\text{O}-\text{N}-\text{Cl}\)

\(2g\) \(^1^H\)-NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm): 1.26 (s, 3H, CH\(_3\)), 1.36 (s, 3H, CH\(_3\)) 3.62 (bs, 1H), 4.03 (d, *J* = 17.4 Hz, 1H), 4.19-4.29 (m, 2H), 4.86 (d, *J* = 7.8 Hz, 1H, CHOH), 7.21-7.42 (4H, ArH); \(^1^3\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm): 23.4, 23.7, 66.8, 72.1, 76.0, 101.6, 112.0, 119.0, 128.0, 132.0, 144.8, 210.8; HPLC (Daicel Chiralpak AS, iso-hexanes/i-PrOH = 97:3, flow rate 0.5 mL/min, \(\lambda = 254\) nm): major isomer: \(t_R = 23.41\) min; minor isomer: \(t_R = 28.9\) min; \([\alpha]_{D}^{25} = -178.8\) (\(c = 1.0, \text{CHCl}_3\)).
2h: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.45 (s, 3H), 1.48 (s, 3H), 3.16 (d, $J$ = 4.2 Hz, 1H), 3.70-3.67 (m, 2H), 4.03 (d, $J$ = 17.2 Hz, 1H), 4.21 (m, 1H), 4.27 (d, $J$ = 17.2 Hz, 1H), 4.45 (d, $J$ = 6.2 Hz, 1H), 4.56-4.63 (m, 2H), 7.27-7.37 (m, 5H); $^1$H NMR (100 MHz, CDCl$_3$): $\delta$ = 23.5, 24.2, 66.9, 69.9, 70.2, 73.7, 74.0, 101.1, 127.9, 128.5, 129.2, 138.1, 210.0; HPLC (Daicel Chiralpak AD, hexanes/i-PrOH = 96:4, flow rate 0.5 mL/min, $\lambda$ = 254 nm): major isomer: $t_R$ = 46.02 min; minor isomer: $t_R$ = 40.73 min; $[\alpha]_D^{23}$ = -129.7 (c = 3.3, CHCl$_3$) [Literature: $[\alpha]_D^{25}$ = -106.7 (c = 1.0, CHCl$_3$)].

[Structure image]

3j: $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 1.23-1.32 (m, 1H), 1.49-1.58 (m, 2H), 1.61-1.69 (m, 1H), 1.75-1.81 (m, 1H), 2.03-2.10 (m, 1H), 2.30-2.41 (m, 1H), 2.42-2.48 (m, 1H), 2.50-2.59 (m, 1H), 3.99 (bs, 1H), 4.74 (d, $J$ = 8.3 Hz, 1H), 7.18 (d, $J$ = 8.3 Hz, 2H), 8.45 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz): $\delta$ = 24.9, 27.9, 31.0, 42.8, 57.5, 74.3, 121.9, 128.9, 131.6, 140.3, 215.4; HPLC (Daicel Chiralpak AS, iso-hexanes/i-PrOH = 90:10, flow rate 1.0 mL/min, $\lambda$ = 254 nm): major isomer: $t_R$ = 22.04 min; minor isomer: $t_R$ = 20.36 min; $[\alpha]_D$ = +21.6 (c = 1.0, CHCl$_3$).

[Structure image]

Synthesis of alanine-tetrazole 3: To a solution of Boc$_2$O (2.5 g, 1.3 equiv.) and Cbz-Ala (2.0 g) in MeCN (14 mL) and Py (2.2 mL, 3 equiv.) was added NH$_4$HCO$_3$ (0.89 g, 1.26 equiv.) and the reaction mixture stirred overnight at rt. The solvents were removed by evaporation and the residue dissolved in EtOAc and washed with 2x15 ml water. The water was reextracted with EtOAc and the combined volume of EtOAc dried over MgSO$_4$, filtered and concentrated. The crude product was weakly UV active and had an $R_f$=0.42 (MeOH/DCM 1:9). $^1$H NMR (400MHz, CDCl$_3$) of the crude Cbz-Alanine amide: $\delta$ = 1.41(d, $J$ = 7.1 Hz, 3H), 4.29 (m, 1H), 5.17 (m, 2H), 5.39 (bs, 1H), 6.11 (bs, 1H), 7.27 (m, 5H). Next, to a solution of Cbz-Alanine amide (1.1 g) in Py (10 mL) at -10°C was added drop wise POCl$_3$ (0.55 ml, 1.2 equiv. in DCM (5 mL)) and the resulting
mixture stirred for 3 h. When the starting material was “depleted” by TLC (MeOH/DCM 1:9) the mixture was poured onto ice (~30 g). The organic phase was separated and pyridine removed by repeated washing with a not concentrated CuSO₄ solution. The organic phase was then pre-dried with brine and later dried over MgSO₄. Filtration and concentration afforded the crude product as an oil, TLC Rf = 0.51 (MeOH/DCM 1:9). ¹H NMR (400MHz, CDCl₃) of the crude Cbz-alanine nitrile: δ = 1.41 (d, J = 6.8 Hz, 3H), 4.65 (m, 1H), 5.17 (m, 2H), 5.39 (bs, 1H), 7.28 (m, 5H). To a solution of crude Cbz-alanine nitrile (850 mg) in DMF (13 ml) was simultaneously NaN₃ (300 mg, 1.1 equiv.) and NH₄Cl (256 mg, 1.15 equiv.) added. The reaction was heated to 90-95°C and kept at that temperature (3h) until the TLC (HOAc/EtOAc 1:99) spot at Rf = 0.63 did not increase in strength. The reaction mixture was poured onto ice (30 g), acidified to pH close to 2 with 2M HCl and extracted with CHCl₃ (3x20 mL). The organic phase was washed with water (20 mL), then predried with brine (20 mL) and finally dried over MgSO₄ before filtration and removal of solvent by evaporation. Traces of DMF was removed under reduced pressure. The crude product is a yellowish solid. ¹H NMR (400MHz, CDCl₃) of the crude Cbz-alanine tetrazole: δ = 1.59 (d, J = 6.9 Hz, 3H), 5.07 (m, 2H), 5.22 (m, 1H), 6.19 (bs, 1H), 7.28 (m, 5H). The Cbz-alanine tetrazole (825 mg) was dissolved in MeOH (10 mL) and a catalytic amount of Pd/C was added. After 17h the catalyst was filtered off using celite and the solvent removed under reduced pressure to quantitatively give alanine tetrazole 3 as a white solid. ¹H NMR (400MHz, D₆-DMSO): δ = 1.41 (d, J = 6.8 Hz, 3H), 4.51 (m, 1H). ¹³C NMR (100 MHz, D₆-DMSO): δ = 20.2, 44.4, 161.0.