Enantioselective Organocatalytic Aminomethylation of Aldehydes: A Role for Ionic Interactions and Efficient Access to β^2 -Amino Acids

Yonggui Chi, Samuel H. Gellman*

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

gellman@chem.wisc.edu

Supporting Information

General Procedures. Analytical thin-layer chromatography (TLC) was carried out on Whatman TLC plates precoated with silica gel 60 (250 μm thickness). Visualization was performed using a UV lamp or potassium permanganate stain. Column chromatography was performed on EM Science silica gel (230-400 mesh).

Materials. (S)-Diphenylmethyl pyrrolidine (**B**) was purchased from Acros Organics; other commercial reagents were purchased from Sigma-Aldrich. DMF is biotech grade from Sigma-Aldrich. All commercial reagents were used as received. N,O-acetal (**A**) was prepared using literature procedures.¹

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker AC-300 (300 MHz) spectrometers. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AC-300 (75 MHz) spectrometer. Mass spectra (MS) were obtained using an electrospray ionization (ESI) mass spectrometer. Chromatographic enantiomeric excess (ee) determinations were performed on a Shimadzu 10A HPLC using a Chiracel OD or ODH analytical column (detection at 254 nm). Optical rotations were measured using a 5 mL cell with a 1 dm path length on a Perkin-Elmer 241 digital polarimeter and are reported as follows: $[\alpha]_D^{25}$ (c in g per 100 mL solvent).

Stereochemistry Determination:

Absolute configuration of compound **S1** was obtained by X-ray diffraction analysis.² Absolute configuration of β -propyl γ -dibenzylamino alcohol (**S3**) was assigned by comparing the optical rotation of **S4** and **S2**. The absolute configuration of other β -substituted γ -dibenzylamino alcohols from the Mannich reaction was assigned by analogy to **S3**.

¹ (a) Hosomi, A.; Iijima, S.; Sakurai, H. *Tetrahedron. Lett.* **1982**, 23, 547. (b) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem. Int. Ed.* **1996**, 35, 981. (c) Rehn, S.; Ofial, A. R.; Mayr, H. *Synthesis*, **2003**, 1790.

² **S1** were prepared using similar protocol that was used to prepare **S3**. Yonggui Chi, Samuel H. Gellman, manuscript in preparation.

(S)-β-Propyl-γ-(S)-N-benzyl-α-methylbenzylamino alcohol (S1): ^1H NMR (300 MHz, CDCl_3) δ 7.24-7.35 (m, 10H), 5.05 (br, 1H), 4.03 (q, $J = 6.9$ Hz, 1H), 3.92 & 3.97 (s, 1H), 3.58 (m, 1H), 3.33 & 3.38 (s, 1H), 2.94-2.98 (m, 1H), 2.53-2.59 (m, 1H), 2.40-2.48 (m, 1H), 1.89-1.96 (m, 1H), 1.35 (d, $J = 6.9$, 3H), 1.21-1.31 (m, 2H), 0.91-0.99 (m, 3H), 0.85 (t, $J = 7.5$, 3H). ^{13}C NMR (75 MHz, CDCl_3): 142.8, 140.0, 129.5, 128.7, 128.4, 128.3, 127.5, 127.3, 68.5, 56.5, 55.2, 54.9, 36.5, 32.5, 20.6, 14.5, 9.5. TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 312.2, found 312.4. X-ray quality crystals were obtained via slow evaporation of a hexane solution.

(S)-β-Propyl-γ-Bocamino alcohol (S2): NMR (300 MHz, CDCl_3) δ 4.82 (br, 1H), 3.48-3.64 (m, 1H), 3.29-3.44 (m, 3H), 3.04-3.13 (m, 1H), 1.54-1.66 (m, 1H), 1.45 (s, 9H), 1.09-1.41 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): 157.7, 80.0, 62.8, 41.5, 41.0, 31.1, 28.6, 20.5, 14.5. TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 218.2, found 218.4; $[\text{M}+\text{Na}]^+$ calculated 240.2, found 240.4; $[2\text{M}+\text{Na}]^+$ calculated 457.4, found 457.8. Optical rotation: $[\alpha]_D^{25} = +7.0^\circ$ ($c = 0.20$, MeOH).

(S)-β-Propyl-γ-dibenzylamino alcohol (S3): ^1H NMR (300 MHz, CDCl_3) δ 7.24-7.37 (m, 10H), 5.60 (br, 1H), 4.04 & 4.00 (s, 2H), 3.66-3.70 (m, 1H), 3.20-3.26 (m, 1H), 3.16 & 3.11 (s, 2H), 2.50-2.58 (m,

1H), 2.44-2.46 (m, 1H), 1.99-2.10 (m, 1H), 1.25-1.33 (m, 1H), 0.96-1.02 (m, 1H), 0.84-0.89 (t, J = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): 138.2, 129.5, 128.8, 127.6, 69.3, 60.4, 59.4, 36.4, 32.5, 20.6, 14.6. TOF-MS-ESI: [M+H]⁺ calculated 298.2, found 298.5, [M+Na]⁺ calculated 320.2, found 320.5; [2M+Na]⁺ calculated 617.4, found 618.1. Optical rotation: [α]_D^{rt} = +18.0° (c = 0.25, MeOH; as HCl salt). 49% ee [Chiracel OD column; 95/5 hexane/isopropanol; flow rate = 1 mL/min; T_R 1: 7.8 min (minor), T_R 2: 8.9 (major)].

(S)-β-Propyl-γ- Boc amino alcohol (S4): Optical rotation: [α]_D^{rt} = +3.4° (c = 0.20, MeOH).

Table 1. Salt effect:

entry ^a	catalyst	salt	time	ee ^b	favored enantiomer ^c
1	L-proline	--	24 h	49	S
2	L-proline	LiCl	24 h	<5	--
3	C -HOAc	--	2 h	67	R
4	C -HOAc	LiCl	2 h	80	R
5	B -HOAc	--	2h	22	R
6	B -HOAc	LiCl	2h	29	R
7	F -HOAc	--	2 h	83	R
8	F -HOAc	LiCl	2 h	92	R

^a Yield of all reactions > 80% as measured by ¹H NMR of the crude reaction mixture before *in situ* reduction; the reduction is quantitative. ^b Ee of amino alcohol determined by chiral phase HPLC. ^c determined as discussed above.

General Procedures: To 0.1 mmol catalyst dissolved in 1 mL biotech grade DMF (or **1 M LiCl** DMF solution³) in an 8 mL vial at -25 °C was added 110 μL (1 mmol) pentanal. The mixture was stirred for a few minutes, and 127 μL (0.5 mmol) N,O-acetal **A** was added. The vial was capped and the mixture was stirred at -25 °C for 2 or 24 hours. Yield of the reaction was determined by ¹H NMR analysis of the crude reaction mixture.⁴ Excess NaBH₄ (0.06 g, 1.5 mmol) was added, followed by the addition of 1 mL MeOH, and the mixture was stirred for a few minutes. The -25 °C cooling bath was replaced by an ice bath, and the mixture was stirred for another 20 minutes. The mixture was then slowly poured into a 24 mL vial containing 5 mL saturated NH₄Cl at 0 °C and extracted with 10 mL Et₂O. The Et₂O layer was collected, washed with 5 mL water and then 5 mL brine, dried over MgSO₄, filtered and concentrated to give a colorless oil. The oil was dissolved in a mixture of hexane/isopropanol (v/v; 90/10) and used for ee determination without further purification. The corresponding racemic Mannich product was obtained by using D,L-proline as catalyst for ee assay development. The ee determination was performed on a Shimadzu 10A HPLC using a Chiracel OD column. Mobile phase: hexane/isopropanol (v/v: 95/5, premixed); flow rate = 1 mL/min; retention time: ~7.8 minutes and ~8.9 minutes. Shown below are selected HPLC chromatograms:

³ Concentration of LiCl refers to room temperature concentration. At -25 °C, LiCl partially precipitates.

⁴ ¹H NMR analysis: 50 μL crude reaction mixture was mixed with 650 μL CDCl₃ for NMR analysis. NMR condition: RG (gain) = 1, NS = 32.

Table 2. Enantioselective aminomethylation of aldehydes

entry	product #	R	TLC R _f (v/v, EtOAc/Hexane)	isolated yield (%) ^a	ee (%) ^b
1	S5	Et	0.12 (1/5)	84	90
2	<i>(R)</i> - S3	Pr	0.14 (1/5)	87	92
3	S6	<i>i</i> -Pr	0.13 (1/5)	86	91
4	S7	Bn	0.081 (1/5)	81	92
5	S8	MeO ₂ CCH ₂	0.36 (1/2)	65	90

^a Yield of isolated amino alcohol after column chromatography on silica gel. ^b Ee of amino alcohol determined by chiral phase HPLC.

General Procedures: To 0.33 g (1 mmol) ⁵ catalyst **F** dissolved in 9 mL 1 M LiCl DMF in a 100 mL round bottom flask at -25 °C was added 57 μL (1 mmol) HOAc (in 1 mL 1M LiCl DMF). Aldehyde (neat, 10 mmol) was added, and the mixture was stirred for a few minutes. N,O-acetal **A** (neat, 1.27 mL, 5 mmol) was added. The flask was capped, and the mixture was stirred at -25 °C for 2 hours. Excess NaBH₄ (0.57 g, 15 mmol) was added, followed by the addition of 10 mL MeOH, and the mixture was stirred for a few minutes. The -25 °C cooling bath was replaced by an ice bath, and the mixture was stirred for another 20 minutes. The mixture was then slowly poured into a 250 mL beaker containing 50 mL saturated NH₄Cl at 0 °C and extracted with Et₂O (about 3 x 100 mL). Complete extraction of the product to the organic phases was monitored by TLC analysis. The Et₂O layers were collected, washed with 50 mL water and then 50 mL brine, dried over MgSO₄, filtered and concentrated to give crude β-substituted γ-amino alcohols, which were purified via flash column chromatography eluted with EtOAc/Hexane (1:10; v/v)⁶ to give the desired products as colorless viscous oils. This oil was used directly for ee determination and NMR characterizations (no recrystallization).⁷

(*R*)-β-Ethyl-γ-dibenzylamino alcohol (S5) (Table 2, entry 1): ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.37 (m, 10H), 5.59 (br, 1H), 4.05 & 4.00 (s, 2H), 3.68-3.74 (m, 1H), 3.21-3.28 (m, 1H), 3.13 & 3.17 (s, 2H), 2.51-2.59 (m, 1H), 2.43-2.48 (m, 1H), 1.98 (m, 1H), 1.06 (td, J = 6.3, 7.5 Hz, 2H), 0.88 (t, J = 7.5 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): 138.1, 129.5, 128.7, 127.6, 68.9, 60.1, 59.3, 38.4, 23.1, 12.1. TOF-MS-ESI: [M+H]⁺ calculated 284.2, found 284.5; [M+Na]⁺ calculated 306.2, found 306.5; [2M+Na]⁺ calculated 589.4, found 590.0. Optical rotation: [α]_D²⁰ = +16.8° (c = 0.13, MeOH; as HCl salt). 90% ee [Chiracel OD column; 95/5 hexane/isopropanol; flow rate = 1 mL/min; T_R 1: 8.0 min (major), T_R 2: 10.8 min (minor)].

(*R*)-β-Ppropyl-γ-dibenzylamino alcohol [(*R*)-S3] (Table 2, entry 2): Optical rotation: [α]_D²⁰ = -32.4° (c = 0.25, MeOH; as HCl salt). 92% ee [Chiracel ODH column; 95/5 hexane/isopropanol; flow rate = 1 mL/min; T_R 1: 7.26 min (major), T_R 2: 8.20 min (minor)].

⁵ The reaction scale in Table 2 is larger than the scale in Table 1 in order to get accurate isolated yield and demonstrate reaction scope. It should be noted that the Mannich reaction gave comparable yield and ee at different reaction scales.

⁶ We used 1:5 or 1:2 (v/v) EtOAc/hexane for TLC analysis and 1:10 EtOAc/hexane for column chromatography.

⁷ Optical rotation measurements were performed using the HCl salt of the amino alcohol before recrystallization.

(R)-β-Isopropyl-γ-dibenzylamino alcohol (S6) (Table 2, entry 3): ¹H NMR (300 MHz, CDCl₃) δ 7.24-7.36 (m, 10H), 5.62 (m, 1H), 4.04 & 4.00 (s, 2H), 3.69-3.74 (m, 1H), 3.30-3.34 (m, 1H), 3.17 & 3.13 (s, 2H), 2.64-2.72 (m, 1H), 2.44-2.50 (m, 1H), 1.88-1.94 (m, 1H), 1.44-1.51 (m, 1H), 0.83 & 0.81 (diastereotopic, d, J = 6.7 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 138.1, 129.5, 128.7, 127.6, 67.2, 59.3, 57.9, 42.1, 28.8, 20.4, 20.0. TOF-MS-ESI: [M+H]⁺ calculated 298.2, found 298.5; [M+Na]⁺ calculated 320.2, found 320.5; [2M+Na]⁺ calculated 617.4, found 618.1. Optical rotation: [α]_D^{rt} = -29.5° (c = 0.20, MeOH; as HCl salt). 91% ee [Chiracel OD column; 95/5 hexane/isopropanol; flow rate = 1 mL/min; T_R 1: 7.2 min (major), T_R 2: 8.6 min (minor)].

(R)-β-Benyl-γ-dibenzylamino alcohol (S7) (Table 2, entry 4): ¹H NMR (300 MHz, CDCl₃) δ 7.09-7.35 (m, 15H), 3.95 & 3.90 (s, 2H), 3.64-3.69 (m, 1H), 3.13-3.34 (m, 1H), 3.18 & 3.13 (s, 2H), 2.28-2.58 (m, 5H). ¹³C NMR (75 MHz, CDCl₃): δ 140.1, 138.0, 129.5, 129.1, 128.7, 128.6, 127.6, 126.3, 68.5, 59.2, 59.0, 38.7, 36.6. TOF-MS-ESI: [M+H]⁺ calculated 346.2, found 346.6. Optical rotation: [α]_D^{rt} = -44.1° (c = 0.14, MeOH; as HCl salt). 92% ee [Chiracel OD column; 95/5 hexane/isopropanol; flow rate = 1 mL/min; T_R 1: 13.2 min (major), T_R 2: 19.5 min (minor)].

S8 (Table 2, entry 6): ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.36 (m, 10H), 4.64 (br, 1H), 4.14 & 4.16 (s, 2H), 3.65 (s, 3H), 3.63-3.69 (m, 1H), 3.33-3.39 (m, 1H), 3.26 & 3.22 (s, 2H), 2.42-2.58 (m, 3H), 2.11 (d, 6.0 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 137.1, 128.3, 129.4, 128.7, 127.6, 67.4, 59.1, 57.9, 51.9, 34.9, 34.4. TOF-MS-ESI: [M+H]⁺ calculated 328.2, found 328.5. Optical rotation: [α]_D^{rt} = -24.7° (c = 0.20, MeOH; as HCl salt). ~90% ee [Chiracel OD column; 95/5 hexane/isopropanol; flow rate = 1 mL/min; T_R 1: 16.4 min (major), T_R 2: 19.6 min (minor)].

Scheme 2. Concise synthesis of β²-amino acid:

(R)-S3-HCl: The Mannich reaction/reduction sequence followed the general procedures described above for Table 2; except that 10 mol% catalyst was used in this case (to minimize catalyst quantity). This procedure provided **(R)-S3** as a viscous oil in quantitative yield with ~85% ee. **(R)-S3** was dissolved in 50 mL Et₂O, followed by the slow addition of 50 mL 4N HCl in dioxane. The resulting mixture was stirred for a few minutes and the solvent was removed under reduced pressure to give a viscous oil. To this viscous oil in a 150 mL flask, was added 50 mL EtOAc. The flask was shaken with heating (with a heat gun) until the oil solidified in ethyl acetate to give a milky mixture with white solid. A few drops of MeOH were added to the milky mixture until the solid was just completely dissolved to give a clear solution. The open flask with the EtOAc-MeOH hot solution was then kept in a glass container containing hot Et₂O. The container was sealed and stayed at room temperature for crystallization. Crystals from this procedures were filtered, washed with EtOAc and dried *in vacuo* to afford 9.6 g (72% yield) **(R)-S3-HCl** as white crystals with >98% ee (determined using the free amino alcohol after a base wash of the HCl salt).⁸ Melting point: 135-137 °C. Optical rotation: $[\alpha]_D^{25} = -36.3^\circ$ ($c = 0.25$, MeOH; as HCl salt).

(R)-S4: **(R)-S3-HCl** (5.0 g, 15 mmol) and wet 10% Pd/C (1.0 g) were added to 50 mL MeOH in a hydrogenation flask. The heterogeneous mixture was put under 40-60 psi H₂ at room temperature overnight. After the hydrogenolysis was completed as indicted by TLC analysis, the mixture was diluted by 50 mL CH₂Cl₂, and DIEA (26 mmol, 6.4 mL) and Boc₂O (18 mmol, 4.0 g) were added. The mixture was stirred at room temperature overnight and filtered through a pad of celite to remove Pd/C, and the celite was washed with MeOH extensively. The filtrate was collected, concentrated and applied to a silica chromatography column eluted with EtOAc/Hexane (1/5, v/v, TLC R_f = 0.07) to give 3.1 g (96% yield) **(R)-S4** as a colorless oil. Optical rotation: $[\alpha]_D^{25} = -7.0^\circ$ ($c = 0.20$, MeOH).

(R)-Boc-β²-Homonovaline-OH (S9): To 2.8 g (13 mmol) **(R)-S4** dissolved in 130 mL acetone at 0 °C was added 19.5 mmol H₂Cr₂O₇ (39 mL Jones reagent).⁹ The mixture was stirred for 12 h, during which time the mixture warmed to room temperature. Excess isopropanol was added, and the mixture was stirred overnight. The mixture was filtered, and the solution was concentrated to about 20 mL under reduced pressure at room temperature. The concentrated mixture was diluted with 20 mL 2 N HCl and extracted with Et₂O. Complete extraction of the product into the Et₂O phase was monitored by TLC. The Et₂O layers were collected, combined and concentrated to about 50 mL. This concentrated Et₂O solution was extracted with 2 M NaOH (monitored by TLC). The basic aqueous extracts were collected, combined and washed with 2 x 10 mL Et₂O. The basic aqueous solution was then acidified with 2 N HCl and extracted with Et₂O (monitored by TLC). The Et₂O layers were combined, washed with saturated NaCl, dried over MgSO₄, filtered and concentrated under reduced pressure to give **Boc-β²-Homonovaline-OH** as a viscous colorless oil that is pure by TLC and NMR analysis (present as rotamers on the NMR time scale). ¹H NMR (300 MHz, CDCl₃) δ 10.10 (br, 1H), 6.61 & 4.95 (br, 1H), 3.16-3.36 (m, 2H), 2.54-2.56 (m, 1H), 1.18-1.57 (m, 13H), 0.86 (t, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 180.7 & 179.3, 158.2 & 156.2, 81.3 & 79.8, 45.9 & 45.6, 42.9 & 41.6, 31.9, 28.6, 20.5, 14.1. TOF-MS-ESI: [M-H]⁺ calculated 230.2, found 230.5; [2M-H]⁺ calculated 461.3, found 462.0. Optical rotation: $[\alpha]_D^{25} = -17.5^\circ$ ($c = 0.33$, MeOH).

⁸ A second recrystallization may be needed to get >98% ee because the crystallization process is not exactly reproducible. It is highly recommended to check the ee of each recrystallization product before further use.

⁹ Jones reagent preparation: To 50 mmol Na₂Cr₂O₇ dissolved in 50 mL H₂O, was slowly added 200 mol concentrated H₂SO₄. The solution was then diluted to 100 mL to give the Jones reagent (0.5 M H₂Cr₂O₇).

Selected NMR Spectrum:

S1-¹H NMR

S1-¹³C NMR:

S2-¹H NMR:

S2-¹³C NMR:

(*R*)-**S3**-1H NMR:

(*R*)-**S3**-¹³C NMR:

S9-¹H NMR:

¹H NMR in CDCl₃ (exist as rotamers)

S9- ^{13}C NMR

HPLC Chromatograph of ee determination (Table 2 & Recrystallized (*R*)-S3):

Table 2, entry 1:

Table 2, entry 2:

Scheme 2:

Table 2, entry 3:

Table 2, entry 4:

Table 2, entry 5: