# Supporting Information

**Stereoselective Organocatalytic One-Pot α,α-Bifunctionalization of Acetaldehyde by a Tandem Mannich Reaction/Electrophilic Amination**

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1. General

$^1$H NMR (200 and 300 MHz) and $^{13}$C (50 and 75 MHz) spectra were recorded with 200 or 300 MHz spectrometers using tetramethylsilane as an internal standard. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values expressed in Hertz. Electrospray ionization (ESI) mass spectra were collected using a Q-TOF instrument. Samples (solubilized in ACN at 1mg/mL and then diluted by 1000) were introduced into the MS via an UHPLC system whilst a Leucine Enkephalin solution was co-injected via a micro pump. Infrared spectra were recorded with a FT spectrometer. Optical rotation values were measured at room temperature. Melting points were determined in open capillary tubes and are uncorrected. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel 60 F$_{254}$. Column chromatography separations were performed using silica gel (0.040-0.060 mm). HPLC analyses were performed with a machine equipped with a UV/Vis detector at 30°C employing chiral AD or AS-H columns. HPLC grade heptane and isopropyl alcohol were used as the eluting solvents. Acetaldehyde was purified by Kugelrohr distillation prior to use. $N$-tert-butoxycarbonyl, $^1$N-benzyloxy carbonyl$^2$ and $N$-benzoyl imines $^3$ were prepared using the literature procedure.

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2. General procedure for organocatalytic Mannich reaction of acetaldehyde

To a solution of N-protected-N-benzylidenamine 1a (0.3 mmol, 61.6 mg) at 0 °C in tetrahydrofuran, dichloromethane or acetonitrile (0.65 mL) was successively added (S)-2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsiloxyethyl]pyrrolidine 2 (0.03 mmol, 17.9 mg), p-nitrobenzoic acid (0.03 mmol, 5.0 mg) and acetaldehyde (0.45 mmol, 25 µL). After the reaction mixture was stirred for 16 h, 96% EtOH (1.3 mL) and NaBH₄ (0.6 mmol, 22.7 mg) were added. The resulting mixture was stirred for additional 15 min at 0 °C, before being quenched with saturated aqueous NH₄Cl solution. The organic materials were extracted with ethyl acetate three times, dried over anhydrous Na₂SO₄, and concentrated in vacuo after filtration. In the case of N-benzoylimine 1a, purification by chromatography on silica gel (pentane/EtOAc, 2/1) gave (S)-3-benzoylamino-3-phenylpropanol 3 as a pure compound. Enantiometric excesses have been determined by HPLC analysis employing chiral AS-H column (heptane/2-propanol, 90/10, 1.0 mL/min), tᵣ = 16.9 min for (R) and tᵣ = 27.5 min for (S) according to the conditions described by Hayashi et al.⁴ All the spectroscopic data for 3 were in complete agreement with those reported.⁴

3. General procedure for one-pot Mannich reaction/electrophilic amination

3.1 Experimental procedure by sequential addition of reagents

To a solution of N-benzoyl-N-benzylidenamine 1a (0.3 mmol, 61.6 mg) at 0 °C in acetonitrile (0.65 mL) was successively added (S)-2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsiloxyethyl]pyrrolidine 2 (0.03 mmol, 17.9 mg), p-nitrobenzoic acid (0.03 mmol, 5.0 mg) and acetaldehyde (0.45 mmol, 25 µL). After the reaction mixture was stirred for 16 h, di-tert-butyl azodicarboxylate (0.45 mmol, 103.6 mg) was added and the reaction mixture was allowed to warm to room temperature and stirred for 24 h. 96% EtOH (1.3 mL) and NaBH₄ (0.6 mmol, 22.7 mg) were then added and the resulting mixture was stirred for additional 15 min at 0 °C, before being quenched with saturated aqueous NH₄Cl solution. The organic materials were extracted with ethyl acetate three times, dried over anhydrous Na₂SO₄, and concentrated in vacuo after filtration. Diastereomeric ratio was determined at this stage by UHPLC-ESI of the crude product (syn/anti : 90.5/9.5). Two careful purifications were required to yield pure compound 4a in 54% yield. The first one was carried out by column chromatography on silica gel with the solvent mixture: pentane/EtOAc, 80/20 and the second one by using the solvent mixture DCM/Et₂O, 95/5.

3.2 Experimental procedure for the full one-pot transformation

To a solution of N-benzoyl-N-benzylidenamine 1 (0.3 mmol) at 0 °C in acetonitrile (0.65 mL) was successively added (S)-2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsiloxyethyl]pyrrolidine 2 (0.03 mmol, 17.9 mg), p-nitrobenzoic acid (0.03 mmol, 5.0 mg) and acetaldehyde (0.45 mmol, 25 µL). After the reaction mixture was stirred for 16 h, di-tert-butyl azodicarboxylate (0.45 mmol, 103.6 mg) was added and the reaction mixture was allowed to warm to room temperature and stirred for 24 h. 96% EtOH (1.3 mL) and NaBH₄ (0.6 mmol, 22.7 mg) were then added and the resulting mixture was stirred for additional 15 min at 0 °C, before being quenched with saturated aqueous NH₄Cl solution. The organic materials were extracted with ethyl acetate three times, dried over anhydrous Na₂SO₄, and concentrated in vacuo after filtration. Diastereomeric ratio was determined at this stage by UHPLC-ESI of the crude product (syn/anti : 90.5/9.5). Two careful purifications were required to yield pure compound 4a in 54% yield. The first one was carried out by column chromatography on silica gel with the solvent mixture: pentane/EtOAc, 80/20 and the second one by using the solvent mixture DCM/Et₂O, 95/5.

trimethylsiloxyethyl]pyrrolidine 2 (0.03 mmol, 17.9 mg), \( p \)-nitrobenzoic acid (0.03 mol, 5.0 mg), di-\( \text{tert} \)-butylazodicarboxylate (0.45 mmol, 103.6 mg) and acetaldehyde (0.45 mmol, 25 \( \mu \)L). After 16 h of stirring, the reaction mixture was allowed to warm to room temperature and stirred for additional 24 h. 96\% EtOH (1.3 mL) and NaBH\(_4\) (0.6 mmol, 22.7 mg) were then added and the resulting mixture was stirred for 15 min at 0 °C, before being quenched with saturated aqueous NH\(_4\)Cl solution. The organic materials were extracted with ethyl acetate three times, dried over anhydrous Na\(_2\)SO\(_4\), and concentrated \textit{in vacuo} after filtration. Diastereoisomeric ratio was determined at this stage by UHPLC-ESI of the crude product. Two careful purifications were required to yield pure compound 4. The first one was carried out by column chromatography on silica gel with the solvent mixture: pentane/EtOAc, 80/20 and the second one by using the solvent mixture DCM/Et\(_2\)O, 95/5.

3.3 Characterization data of the hydrazine derivatives 4

\[ \text{N-[}(1R,2S)-2-(1,2-di-\text{tert}-\text{butyloxy} \text{carbonyl} \text{hydrazino})-3-hydroxy-1-phenylpropyl]benzamide 4a} \]

\[
\begin{aligned}
\text{Ph} &\quad \text{NH} \quad \text{BocN} \quad \text{OH} \\
\text{NHBz} &\quad \text{NH} \quad \text{Boc}
\end{aligned}
\]

TLC: \( R_f = 0.24 \) (pentane/EtOAc, 80/20); m.p. 86-88 °C; \( [\alpha]_D^{20} = -68.1 \) (c 1.11, CHCl\(_3\)) for 96\% ee; \(^1\)H NMR (300 MHz, CDCl\(_3\), 25 °C, TMS): \( \delta = 1.26 \) ppm (s, 9H), 1.50 (s, 9H), 3.14 (dd, \( J(H,H)= 3.4 \) and \( J(H,H)= 12.2 \) Hz, 1H), 3.45 (app. t, \( J(H,H)= 2J(H,H)= 12 \) Hz, 1H), 4.84 (dt, \( J(H,H)= 3.4 \) and \( J(H,H)= 11.0 \) Hz, 1H), 4.97 (app. t, \( J(H,H)= 10 \) Hz, 1H), 6.39 (br. d, \( J(H,H)= 9.2 \) Hz, 1H), 7.29-7.51 (m, 9H), 7.70 (d, \( J(H,H)= 7.1 \) Hz, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\), 25 °C, TMS): 28.1 ppm (3C), 28.3 (3C), 53.6, 59.3, 62.3, 81.8, 82.2, 127.1 (2C), 127.4 (2C), 128.7 (2C), 128.9, 129.7 (2C), 131.9, 134.2, 137.6, 156.3, 158.0, 168.0. IR (neat): \( \nu = 3445, 3284, 2979, 2930, 1709, 1647, 1525, 1481, 1393, 1366, 1253, 1150, 1059, 1028, 842, 759, 701 \); HRMS (ESI) Calcd for C\(_{26}\)H\(_{36}\)N\(_3\)O\(_6\) [M + H]\(^+\) : 486.2604, Found: 486.2616. Diastereoisomeric ratio has been determined by UHPLC-ESI analysis, \( t_r = 3.70 \) min for the minor diastereoisomer and \( t_r = 3.99 \) min for the major diastereoisomer. Enantiomeric excess of 4a has been determined by HPLC analysis employing a chiral AD column (heptane/2-propanol, 90/10, 1.0 mL/min), \( t_r = 7.32 \) min for the minor enantiomer and \( t_r = 16.07 \) min for the major enantiomer.
**N-[(1R,2S)-1-(4-chlorophenyl)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxypropyl]benzamide 4b**

![Structure of 4b](image)

TLC: Rf = 0.28 (pentane/EtOAc, 80/20); m.p. 129-131 °C; [α]D = -66.5 (c 1.05, CHCl3) for 98% ee; 1H NMR (300 MHz, CDCl3, 25 °C, TMS): δ= 1.26 ppm (s, 9H), 1.50 (s, 9H), 3.10-3.22 (m, 1H), 3.45 (t, 3J(H,H)= 2J(H,H)= 11.3 Hz, 1H), 4.51 (br. s, 1H), 4.75-4.87 (m, 1H), 4.92-5.05 (m, 1H), 6.44 (br. d, 3J(H,H)= 8.7 Hz, 1H), 7.21 (br. s, 1H), 7.30-7.55 (m, 7H), 7.70 (d, 3J(H,H)= 7.4 Hz, 2H); 13C NMR (75 MHz, CDCl3, 25 °C, TMS): 28.0 ppm (3C), 28.3 (3C), 52.9, 59.2, 82.0, 82.4, 127.2 (2C), 128.7 (2C), 128.9 (2C), 132.1, 133.9, 134.7, 136.3, 156.3, 157.9, 167.9. IR (neat): ν = 3452, 3286, 2978, 2931, 1704, 1680, 1644, 1522, 1487, 1341, 1274, 1254, 1152, 1061, 824, 580; HRMS (ESI) Calcd for C26H35ClN3O6 [M + H]+: 520.2214, Found: 520.2217. Diastereoisomeric ratio has been determined by UHPLC-ESI analysis, tR = 3.93 min for the minor diastereoisomer and tR = 4.20 min for the major diastereoisomer. Enantiomeric excess of 4b has been determined by HPLC analysis employing a chiral AD column (heptane/2-propanol, 90/10, 1.0 mL/min), tR = 10.63 min for the minor enantiomer and tR = 44.30 min for the major enantiomer.

**N-[(1R,2S)-1-(3-chlorophenyl)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxypropyl]benzamide 4c**

![Structure of 4c](image)

TLC: Rf = 0.22 (pentane/EtOAc, 80/20); m.p. 130-131 °C; [α]D = -62.4 (c 1.00, CHCl3) for 98% ee; 1H NMR (300 MHz, CDCl3, 25 °C, TMS): δ= 1.26 ppm (s, 9H), 1.50 (s, 9H), 3.15 (app. d, 3J(H,H) ~ 9.9 Hz, 1H), 3.40-3.52 (m, 1H), 4.81 (app. t, 3J(H,H) ~ 10.2 Hz, 1H), 4.90-5.02 (m, 1H), 6.45 (br. d, 3J(H,H)= 8.3 Hz, 1H), 7.19 (br. s, 1H), 7.27-7.54 (m, 7H), 7.71 (d, 3J(H,H)= 7.6 Hz, 2H); 13C NMR (75 MHz, CDCl3, 25 °C, TMS): 28.1 ppm (3C), 28.3 (3C), 53.2, 59.2, 82.1, 82.4, 125.6, 127.2, 127.7, 128.7 (2C), 129.1, 130.9, 133.1, 133.9, 135.5, 139.7, 156.3, 157.9, 167.9. IR (neat): ν = 3432, 3286, 2970, 2927, 1708, 1526, 1475, 1392, 1365, 1278, 1250, 1148, 1053, 789, 580; HRMS (ESI) Calcd for C26H35ClN3O6 [M + H]+: 520.2214, Found: 520.2215. Diastereoisomeric ratio has been determined by UHPLC-ESI analysis, tR = 3.96 min for the minor diastereoisomer and tR = 4.20 min for the major diastereoisomer. Enantiomeric excess of 4c has been determined by HPLC analysis employing a chiral AD column (heptane/2-propanol, 90/10, 1.0 mL/min), tR = 5.58 min for the minor enantiomer and tR = 13.43 min for the major enantiomer.
**N-[(1R,2S)-2-(1,2-di-tert-butylxycarbonylhydrazino)-3-hydroxy-1-(4-methylphenyl)-propyl]benzamide 4d**

![Structure of 4d]

TLC: Rf= 0.20 (pentane/EtOAc, 80/20); m.p. 74-76 °C; [α]D20 = 88.1 (c 1.00, CHCl₃) for 90% ee; ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ= 1.26 ppm (s, 9H), 1.50 (s, 9H), 2.35 (s, 3H), 3.15 (dd, 3J(H,H)= 3.4 and ²J(H,H)= 12.3 Hz, 1H), 3.43 (m, 1H), 4.82 (dt, 3J(H,H)= 3.4 and ³J(H,H)= 10.4 Hz, 1H), 4.93 (dd, ³J(H,H)= 10.4 and ³J(H,H)= 9.0 Hz, 1H), 6.39 (br. d, 3J(H,H)= 9.0 Hz, 1H), 7.19 (d, ³J(H,H)= 8.1 Hz, 2H), 7.28 (d, ³J(H,H)= 8.1 Hz, 2H), 7.33-7.41 (m, 3H), 7.42-7.50 (m, 1H), 7.69 (d, ³J(H,H)= 7.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): 21.3 ppm, 28.0 (3C), 28.3 (3C), 53.3, 59.3, 62.3, 81.8, 82.1, 127.1 (2C), 127.2 (2C), 128.7 (2C), 130.3 (2C), 131.9, 134.2, 134.6, 138.8, 156.3, 157.9, 168.0. IR (neat): υ= 3480, 3282, 2974, 2923, 1704, 1698, 1633, 1487, 1365, 1278, 1152, 1061, 710, 580; HRMS (ESI) Calcd for C₂₇H₃₈N₃O₆ [M + H]+ : 520.2761, Found: 520.2761. Diastereoisomeric ratio has been determined by UHPLC-ESI analysis, tᵣ = 3.87 min for the minor diastereoisomer and tᵣ = 4.18 min for the major diastereoisomer. Enantiomeric excess of 4d has been determined by HPLC analysis employing a chiral AD column (heptane/2-propanol, 90/10, 1.0 mL/min), tᵣ = 8.72 min for the minor enantiomer and tᵣ = 29.38 min for the major enantiomer.

**N-[(1R,2S)-2-(1,2-di-tert-butylxycarbonylhydrazino)-1-(4-fluorophenyl)-3-hydroxypropyl]benzamide 4e**

![Structure of 4e]

TLC: Rf= 0.15 (pentane/EtOAc, 80/20); m.p. 128-131 °C; [α]D20 = 122.9 (c 1.00, CHCl₃) for 97% ee; ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ= 1.26 ppm (s, 9H), 1.50 (s, 9H), 3.14 (dd, 3J(H,H)= 3.6 and ²J(H,H)= 12.3 Hz, 1H), 3.44 (app. t, ³J(H,H)= 2J(H,H)~ 11.7 Hz, 1H), 4.81 (dt, ³J(H,H)= 3.6 and ³J(H,H)= 11.0 Hz, 1H), 4.96 (app. t, ³J(H,H)~ 9.5 Hz, 1H), 6.42 (br. d, 3J(H,H)= 9.0 Hz, 1H), 7.09 (d, ³J(H,H)= 8.5 Hz, 2H), 7.24 (br. s, 1H), 7.33-7.51 (m, 5H), 7.70 (d, ³J(H,H)= 7.3 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): 28.1 ppm (3C), 28.3 (3C), 52.8, 59.3, 62.3, 81.9, 82.3, 116.6 (2C), 127.1 (2C), 128.7 (2C), 129.1 (2C), 132.1, 133.6, 133.9, 156.3, 157.9, 167.9. ¹⁹F NMR (200 MHz, CDCl₃, 25°C, CFCl₃): δ= -112.9 ppm. IR (neat): □ = 3451, 3294, 2974, 2927, 1708, 1680, 1637, 1507, 1388, 1365, 1278, 1219, 1152, 1057, 828; HRMS (ESI) Calcd for C₂₆H₃₅FN₃O₆ [M + H]+ : 520.2571, Found: 520.2571. Diastereoisomeric ratio has been determined by UHPLC-ESI analysis, tᵣ = 3.75 min for the minor diastereoisomer and tᵣ = 4.03 min for the major diastereoisomer.
Enantiomeric excess of 4e has been determined by HPLC analysis employing a chiral AD column (heptane/2-propanol, 90/10, 1.0 mL/min), \( t_r = 9.88 \) min for the minor enantiomer and \( t_r = 32.88 \) min for the major enantiomer.

\[ \text{N-}[(1R,2S)-2-(1,2-di-\text{tert}-\text{butyloxy} & \text{carbonyl} & \text{hydrazino})-3-hydroxy-1-(2- \text{naphthyl})\text{propyl}]\text{benzamide 4f} \]

TLC: Rf= 0.22 (pentane/EtOAc, 80/20); \([\alpha]_D^{20}=-73.0\) (c 1.00, in CHCl\(_3\)) for 96% ee; \(^1\)H NMR (300 MHz, CDCl\(_3\), 25 °C, TMS): \( \delta = 1.28 \) ppm (s, 9H), 1.52 (s, 9H), 3.18 (app. d, \( ^3\)J(H,H)= 12.2 Hz, 1H), 3.50 (app. t, \( ^3\)J(H,H)= \( ^2\)J(H,H)~ 11.5 Hz, 1H), 5.00 (dt, \( ^3\)J(H,H)= 3.4 and \( ^3\)J(H,H)= 9.0 Hz, 1H), 5.15 (t, \( ^3\)J(H,H)= 9.0 Hz, 1H), 6.54 (br. d, \( ^3\)J(H,H)= 9.0 Hz, 1H), 7.32-7.59 (m, 7H), 7.71 (d, \( ^3\)J(H,H)= 7.2 Hz, 2H), 7.77-7.94 (m, 4H); \(^13\)C NMR (75 MHz, CDCl\(_3\), 25 °C, TMS): 28.1 ppm (3C), 28.3 (3C), 53.7, 59.4, 62.2, 81.9, 82.3, 124.7, 126.8, 126.9, 127.2 (2C), 127.9, 128.0, 128.7 (3C), 129.8, 131.9, 133.2, 133.6, 134.0, 134.8, 156.4, 157.9, 168.0. IR (neat): \( \nu = 3291, 2979, 2930, 1704, 1698, 1643, 1488, 1367, 1246, 1153, 1061, 908, 730; \) HRMS (ESI) Calcd for C\(_{30}\)H\(_{38}\)N\(_3\)O\(_6\) [M + H]\(^+\) : 536.2761, Found: 536.2753. Diastereoisomeric ratio has been determined by UHPLC-ESI analysis, \( t_r = 3.98 \) min for the minor diastereoisomer and \( t_r = 4.29 \) min for the major diastereoisomer. Enantiomeric excess of 4f has been determined by HPLC analysis employing a chiral AD column (heptane/2-propanol, 90/10, 1.0 mL/min), \( t_r = 6.95 \) min for the minor enantiomer and \( t_r = 29.34 \) min for the major enantiomer.

\[ \text{N-}[(1R,2S)-2-(1,2-di-\text{tert}-\text{butyloxy} & \text{carbonyl} & \text{hydrazino})-3-hydroxy-1-(3- \text{methoxyphenyl})\text{propyl}]\text{benzamide 4g} \]

TLC: Rf= 0.20 (pentane/EtOAc, 80/20); \([\alpha]_D^{20}=-85.0\) (c 1.00, CHCl\(_3\)) for 96% ee; \(^1\)H NMR (300 MHz, CDCl\(_3\), 25 °C, TMS): \( \delta = 1.26 \) ppm (s, 9H), 1.50 (s, 9H), 3.09-3.24 (m, 1H), 3.40-3.50 (m, 1H), 3.81 (s, 3H), 4.82 (dt, \( ^3\)J(H,H)= 10.5 and \( ^3\)J(H,H)= 3.7 Hz, 1H), 4.90-5.02 (app. t, \( ^3\)J(H,H)~ 9.0 Hz, 1H), 6.40 (app. d, \( ^3\)J(H,H)~ 8.9 Hz, 1H), 6.82-6.93 (m, 2H), 6.98 (d, \( ^3\)J(H,H)= 7.7 Hz, 1H), 7.27-7.52 (m, 5H), 7.70 (d, \( ^3\)J(H,H)= 7.2 Hz, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\), 25 °C, TMS): 28.1 ppm (3C), 28.3 (3C), 53.6, 55.5, 59.3, 62.3, 81.8, 82.2, 112.9, 114.4, 119.3, 127.1 (2C), 128.7 (2C), 130.8, 131.9, 134.1, 139.1, 156.3, 157.9, 160.4, 168.0.
IR (neat): \( \tilde{\nu} = 3450, 3302, 2980, 1643, 1488, 1363, 1048, 905, 727, 708 \); HRMS (ESI) Calcd for \( \text{C}_{27}\text{H}_{38}\text{N}_{3}\text{O}_{7} \) [M + H]\(^+\): 516.2710, Found: 516.2704. Diastereoisomeric ratio has been determined by UHPLC-ESI analysis, \( t_r = 3.77 \) min for the minor diastereoisomer and \( t_r = 4.05 \) min for the major diastereoisomer. Enantiomeric excess of \( 4g \) has been determined by HPLC analysis employing a chiral AD column (heptane/2-propanol, 90/10, 1.0 mL/min), \( t_r = 6.30 \) min for the minor enantiomer and \( t_r = 14.34 \) min for the major enantiomer.

\( \text{N-[(1R,2S)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxy-1-(2-methoxyphenyl)propyl]benzamide} \ 4h \)

TLC: \( R_f = 0.20 \) (pentane/EtOAc, 80/20); m.p. 102-104 °C; \([\alpha]_D^{20} = -61.4 \) (c 0.85, CHCl\(_3\)) for 88% ee; \(^1\)H NMR (300 MHz, CDCl\(_3\), 45 °C, TMS): \( \delta = 1.25 \) ppm (s, 9H), 1.51 (s, 9H), 3.04 (app. d, \( ^2J(H,H) = 10.7 \) Hz, 1H), 3.42 (app. t, \( ^2J(H,H) = ^3J(H,H) = 10.7 \) Hz, 1H), 3.97 (s, 3H), 4.80-5.20 (m, 2H), 6.88-7.00 (m, 2H), 7.19 (d, \( ^3J(H,H) = 7.1 \) Hz, 1H), 7.22-7.50 (m, 5H), 7.71 (d, \( ^3J(H,H) = 7.1 \) Hz, 2H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\), 25 °C, TMS): 28.1 ppm (3C), 28.4 (3C), 52.6, 55.9, 59.9, 61.1, 81.3, 81.9, 111.9, 121.6, 125.6, 127.1 (2C), 128.6 (2C), 129.9, 130.2, 131.6, 134.9, 156.1, 157.8 (2C), 167.6. IR (neat): \( \tilde{\nu} = 3436, 3313, 2982, 2931, 1712, 1645, 1578 \); HRMS (ESI) Calcd for \( \text{C}_{27}\text{H}_{38}\text{N}_{3}\text{O}_{7} \) [M + H]\(^+\): 516.2710, Found: 516.2725. Diastereoisomeric ratio has been determined by UHPLC-ESI analysis, \( t_r = 3.87 \) min for the minor diastereoisomer and \( t_r = 4.15 \) min for the major diastereoisomer. Enantiomeric excess of \( 4h \) has been determined by HPLC analysis employing a chiral AD column (heptane/2-propanol, 90/10, 1.0 mL/min), \( t_r = 8.36 \) min for the minor enantiomer and \( t_r = 14.78 \) min for the major enantiomer.
4. Synthesis of the α,β-diaminocarboxylic acid 5

\[(2S,3R)\text{-methyl-3-benzamido-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-phenylpropanoate} \ 7\]

To a solution of \(N\)-benzoyl-\(N\)-benzylidename 1a (1.08 mmol, 225 mg) at 0 °C in acetonitrile (2.25 mL) was successively added (S)-2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsiloxymethyl]pyrrolidine 2 (0.108 mmol, 64.5 mg), p-nitrobenzoic acid (0.108 mmol, 18.0 mg), di-\(\text{tert}\)-butylazodicarboxylate (1.62 mmol, 373 mg) and acetaldehyde (1.62 mmol, 90.5 µL). After 16 h of stirring, the reaction mixture was allowed to warm to room temperature and stirred for additional 24 h. The mixture was then diluted with acetonitrile (9 mL) and a 1/1 mixture of MeOH/H\(_2\)O (11.2 mL) was then added, followed by addition of KH\(_2\)PO\(_4\) (4.37 mmol, 595 mg), NaClO\(_2\) (4.2 mmol, 380 mg) and 30% H\(_2\)O\(_2\) (4 mL). The reaction mixture was stirred at room temperature for 2 h. The solution was acidified with a 2 M HCl aqueous solution until pH = 3. Saturated Na\(_2\)SO\(_4\) aqueous solution (2.75 mL) was added at 0 °C and the mixture was acidified with a 2 M HCl aqueous solution until pH = 3 if necessary. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over MgSO\(_4\) and concentrated under reduced pressure. Diastereomeric ratio was determined at this stage by UHPLC-ESI of the crude product (\(\text{syn:anti}\) = 94/6, \(t_r\) = 3.76 min for the major diastereoisomer and \(t_r\) = 4.54 min for the minor diastereoisomer). The crude was purified over a pad of silica (DCM/MeOH, 95/5 then DCM/MeOH, 90/10) to remove the unreacted amination reagent and to lead to 6 (257 mg).

To a solution of 6 (257 mg) in toluene/MeOH (2/1, 4.4 mL) was added dropwise a solution of TMSCHN\(_2\) (2 M in hexanes, 1.03 mmol, 515 µL) at room temperature. The solution was stirred for 15 min and the excess of TMSCHN\(_2\) was quenched with a few drops of AcOH. The solvent was removed under reduced pressure and the crude was purified by chromatography on silica gel (pentane/EtOAc, 9/1 then 8/2) to furnish 7 (144 mg) in 26% yield from 1a.

TLC: Rf = 0.25 (pentane/EtOAc, 80/20); m.p. 111-113 °C; \([\alpha]_D^{20}\) = -71.9 (c 1.00, CHCl\(_3\)); \(^1\)H NMR (300 MHz, CDCl\(_3\), 50 °C, TMS): \(\delta = 1.34 \text{ ppm (s, 9H), 1.47 (s, 9H), 3.61 (s, 3H), 5.18 (br. s, 1H), 5.81 (t, 1H, \(^3\)J(H,H)= 8.7 Hz), 7.10 (s, 1H), 7.23-7.55 (m, 9H), 7.79 (d, \(^3\)J(H,H)= 7.2 Hz, 2H); \(^13\)C NMR (50 MHz, CDCl\(_3\), 25 °C, TMS): 27.9 ppm (3C), 28.1 (3C), 52.6, 52.9, 62.0, 80.9, 82.3, 127.3 (2C), 127.8 (2C), 128.6 (2C), 129.2 (2C), 131.9, 133.2, 134.1, 137.7, 154.8, 155.5, 166.7, 167.8. IR (neat): \(\square = 3309, 3002, 2978, 2923, 1741, 1700, 1641, 1526, 1479, 1393, 1361, 1314, 1251, 1149, 753, 694; HRMS (ESI) Calcd for C\(_{27}\)H\(_{36}\)N\(_3\)O\(_7\) [M + H]\(^+\): 514.2553, Found: 514.2459.
**Procedure A:** Cleavage of the hydrazine under sonication

To a solution of ester 7 (0.1 mmol, 51 mg) in dichloromethane (0.5 mL) was added trifluoroacetic acid (0.5 mL) at 0 °C. After 2 h, the volatiles were evaporated under reduced pressure. To a solution of the crude deprotected hydrazine in MeOH (1 mL) was added Raney Ni (50 mg) and the reaction mixture was sonicated for 4 h at 0 °C under hydrogen atmosphere. The suspension was filtered through a pad of celite, washed with MeOH and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc, washed with 10% aq. Na₂CO₃, dried over anhydrous MgSO₄, and concentrated *in vacuo* after filtration. Diastereoisomeric ratio was determined at this stage by ¹H NMR of the crude product (*syn/anti* = >95/5). Purification was carried out by column chromatography on silica gel with the solvent mixture: EtOAc/pentane, 3/2 to afford amine 8 (23 mg) in 77% yield as a single diastereoisomer.

**Procedure B:** Cleavage of the hydrazine without sonication

To a solution of ester 7 (0.15 mmol, 77 mg) in dichloromethane (0.75 mL) was added trifluoroacetic acid (0.75 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 2 h and the volatiles were evaporated under reduced pressure. To a solution of the crude deprotected hydrazine in MeOH (1.5 mL) was added Raney Ni and the reaction mixture was stirred 24 h at room temperature under hydrogen atmosphere. The suspension was filtered through a pad of celite, washed with MeOH and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc, washed with 10% aq Na₂CO₃, dried over anhydrous MgSO₄, and concentrated *in vacuo* after filtration. Diastereoisomeric ratio was determined at this stage by ¹H NMR of the crude product (*syn/anti* = 87/13). Purification was carried out by column chromatography on silica gel with the solvent mixture: EtOAc/pentane, 3/2 to afford amine 8 (15 mg) in 33% yield as an inseparable mixture of diastereoisomers (*dr* 87/13).

---

(2S,3R)-methyl-2-amino-3-benzamido-3-phenylpropanoate 8

![Chemical Structure](image-url)
The spectroscopic data for the minor diastereoisomer was in complete agreement with those reported for 8 with an anti-configuration of the amine groups. Therefore, this confirms the selective formation of 4-syn from α,α-bifunctionalization of acetaldehyde with N-Bz 1 and di-tert-butyl azodicarboxylate.

(2S,3R)-methyl 3-benzamido-2-(tert-butoxycarbonyl)-3-phenylpropanoate 9

To a solution of amino ester 8 (0.04 mmol, 12 mg) in 1,4-dioxane were added Et₃N (0.06 mmol, 8µL) and Boc₂O (0.08 mmol, 17.5 mg) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 0.5 h and diluted in EtOAc. The organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated in vacuo after filtration. Purification was carried out by column chromatography on silica gel with the solvent mixture: CH₂Cl₂/Et₂O, 95/5 to afford compound 9 (14 mg) in 88% yield. TLC: Rf= 0.20 (CH₂Cl₂/Et₂O, 95/5); [α]D°=+26.0 (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ= 1.37 ppm (s, 9H), 3.56 (s, 3H), 4.73 (t, ³J(H,H)= 8.4 Hz, 1H), 5.32-5.47 (m, 2H), 7.26-7.63 (m, 9H), 7.82 (d, ³J(H,H)= 7.2 Hz, 2H); ¹³C NMR (50 MHz, CDCl₃, 25° C, TMS): 28.3 ppm (3C), 52.6, 57.4, 58.3, 80.9, 127.1 (2C), 127.3 (2C), 128.4, 128.7 (2C), 128.9 (2C), 131.8, 133.9, 138.2, 156.3, 166.9, 170.6. IR (neat): υ = 3354, 3057, 2978, 2946, 1740, 1694, 1637, 1519, 1266, 1168, 703; HRMS (ESI) Calcd for C₂₂H₂₇N₂O₅ [M + H]⁺: 399.1920, Found: 399.1922.

(2S,3R)-3-benzamido-2-(tert-butoxycarbonyl)-3-phenylpropanoic acid 5

Ester 9 (0.035 mmol, 14 mg) was treated with lithium hydroxide (0.21 mmol, 4.8 mg) for 1 h at 0 °C in aqueous THF (1/1, 1.25 mL), and then acidified with formic acid (a few drops). The solution was extracted with EtOAc three times and the combined organic layers were dried over MgSO₄ and concentrated to afford crude acid. Purification was carried out by column chromatography on silica gel with the solvent mixture: CH₂Cl₂/MeOH, 9/1 to afford compound 5 (10 mg) in 74% yield.

---

TLC: Rf = 0.17 (CH₂Cl₂/MeOH, 9/1); the comparison of the optical rotation measured for 5, [α]D²₀ = +61.9 (c 0.95, MeOH) with that reported for ent-5, [α]D²₀ = -66.4 (c 1.0, MeOH)⁶ confirmed the stereoselective formation of the (2S,3R) diastereoisomer. All the spectroscopic data for 5 were in complete agreement with those reported.⁶

5. Catalytic cycle: HRMS analysis of detected intermediates

ESI-MS measurements were conducted to support the catalytic cycle described below.

Preparation of ESI-MS sample (one-pot α,α-bifunctionalization of acetaldehyde with di-tert-butylazodicarboxylate and N-benzoil imine 1b, R=4-ClC₆H₄): Once the reaction mixture was allowed to room temperature, an analytical sample (30 µL) was taken after 15 min of reaction. The sample was then diluted and injected.

Table 1. HRMS analysis of detected intermediates[a]

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[a] Calibration using internal standard (Leucine Enkephalin). It is important to note that relative ratio of the intermediates cannot be determined from this method.
HRMS analysis allowed us to characterize all the intermediates of the catalytic cycle except for enamine \textbf{A}. Nevertheless, oxazolidine \textbf{A}' probably due to desilylation/cyclization of \textbf{A} was intercepted. The characterization of the different intermediates provided substantial experimental support to the proposed catalytic cycle.
6. $^1$H and $^{13}$C NMR spectra

$N$-[(1R,2S)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxy-1-phenylpropyl]benzamide 4a
N-[(1R,2S)-1-(4-chlorophenyl)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxypropyl]benzamide 4b
$N$-[(1$R,2S$)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxy-1-(4-methylphenyl)-propyl]benzamide 4d
$N\cdots[(1R,2S)-2\cdots(1,2\cdots\text{di-}1R,2S\cdots\text{tert-butyl}2\cdots\text{oxycarbonyl}2\cdots\text{hydrazino})\cdots1\cdots(4\cdots\text{fluorophenyl})\cdots3\cdots\text{hydroxypropyl}]\cdots\text{benzamide 4e}$
$N\{1R,2S\}-2-(1,2\text{-}\text{di-}tert\text{-}\text{butyloxycarbonylhydrazino})\text{-}3\text{-}\text{hydroxy}\text{-}1\text{-}(2\text{-}naphthyl)\text{propyl} \text{benzamide} \ 4f$
$N-[(1R,2S)-2-(1,2-di-\text{tert}-\text{butyloxycarbonylhydrazino})-3-hydroxy-1-(3-\text{methoxyphenyl})propyl]benzamide \ 4g$
N-[(1R,2S)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxy-1-(2-methoxyphenyl)propyl]benzamide 4h
(2S,3R)-methyl 3-benzamido-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-phenylpropanoate 7
(2S,3R)-methyl 2-amino-3-benzamido-3-phenylpropanoate 8
(2S,3R)-methyl 3-benzamido-2-(tert-butoxycarbonyl)-3-phenylpropanoate 9
7. UHPLC-ESI data

\[ \text{Crude reaction mixture} \]

\[ \text{syn/anti} = 94/6 \]

\[ \text{Pure syn-diastereoisomer} \]
N-[(1R,2S)-1-(4-chlorophenyl)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxypropyl]benzamide 4b

Crude reaction mixture

\textit{syn/anti} = 92/8

Pure \textit{syn}-diastereoisomer
**N-[(1R,2S)-1-(3-chlorophenyl)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxypropyl]benzamide 4c**

![Chemical structure of 4c]

**Crude reaction mixture**

\[\text{syn/anti} = 90.5/8.5\]

**Pure syn-diastereoisomer**

S38
Crude reaction mixture

\[ \text{syn/anti} = 93.5/6.5 \]

Pure \textit{syn}-diastereoisomer
N-[(1R,2S)-2-(1,2-di-tert-butylxycarbonylhydrazino)-1-(4-fluorophenyl)-3-hydroxypropyl]benzamide 4e

Crude reaction mixture

syn/anti = 88/12

Pure syn-diastereoisomer
**N-[(1R,2S)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxy-1-(2-naphthyl)propyl]benzamide 4f**

Crude reaction mixture

\[ \text{syn/anti} = 88/12 \]

Pure \( \text{syn-diastereoisomer} \)
**N-[(1R,2S)-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxy-1-(3-methoxyphenyl)propyl]benzamide 4g**

![Chemical structure of 4g](image)

**Crude reaction mixture**

\[ \text{syn/anti} = 91/9 \]

**Pure syn-diastereoisomer**

---

Date: 27-May-2011

- TOF MS ES+
  - 516.271 0.05Da
  - 8.80e3 Area
  - 91.12 Area%  

Date: 06-Jun-2011

- TOF MS ES+
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  - 100.00 Area%
\[N-[(1R,2S)-2-(1,2-di-\text{tert}-\text{butyloxy}carbonylhydrazino)-3-hydroxy-1-(2-methoxyphenyl)propyl]benzamide \text{ 4h}\]

Crude reaction mixture

\[\text{syn/anti} = 96/4\]

Pure \text{syn-diastereoisomer}
(3R)-benzamido-2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-phenylpropanoic acid
8. HPLC data

\[ N-[2-(1,2-di-\text{tert-}\text{-butyloxy}c\text{arbonylhydr}azino)-3-hydroxy-1-\text{phenylpropyl}]\text{benzamide}\ 4a \]

- **Racemic**

- **Enantioenriched**

### Racemic

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$N$-[1-(4-chlorophenyl)-2-(1,2-di-tert-butyloxy carbonylhydrazino)-3-hydroxypropyl]benzamide 4b

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$N\text{-}[1\text{-}(3\text{-chlorophenyl})-2\text{-}(1,2\text{-di-}tert\text{-butyloxy} \text{carbonylhydrazino})\text{-}3\text{-hydroxypropyl}] \text{benzamide 4c}$

- **Racemic**

- **Enantioenriched**
*N*-\[\text{2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxy-1-(4-methylphenyl)-propyl} \]benzamide 4d

- **Racemic**

- **Enantioenriched**

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N-[2-(1,2-di-tert-butyloxycarbonylhydrazino)-1-(4-fluorophenyl)-3-hydroxypropyl]benzamide 4e

- Racemic

- Enantioenriched
$N$-[2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxy-1-(2-naphthyl)propyl]benzamide 4f

- **Racemic**

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- **Enantioenriched**

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**N-[2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxy-1-(3-methoxyphenyl)propyl]benzamide 4g**

![Chemical Structure]

- **Racemic**

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$N$-[2-(1,2-di-tert-butyloxycarbonylhydrazino)-3-hydroxy-1-(2-methoxyphenyl)propyl]benzamide 4h

- **Racemic**

![Racemic Peaks Chart](chart1.png)

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- **Enantioenriched**

![Enantioenriched Peaks Chart](chart2.png)

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