Highly Efficient Asymmetric \textit{anti}-Mannich Reactions of Carbonyl Compounds with \textit{N}-Carbamoyl Imines Catalyzed by Amino-thiourea Organocatalysts †

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1. General methods

All solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial source were used without further purification. Petroleum ether and ethyl acetate for flash column chromatography were distilled before use. All reactions were monitored by TLC with silica gel coated plates. Flash column chromatography was performed on silica gel H (10-40 μ). 1H NMR and 13C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer. Chemical shifts are reported in ppm from tetramethyl silane (TMS) with the solvent resonance as the internal standard. Proton signal multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or a combination of them. J-values are in Hz. Melting points were determined on an X-6 digital melting-point apparatus and were uncorrected. Optical rotations were measured on a Perkin Elmer 341 Polarimeter at λ = 589 nm. Analytical high performance liquid chromatography (HPLC) was carried out on WATERS 510 instrument (2487 Dual λ Absorbance Detector and 515 HPLC Pump) using chiral column. ChiralPak columns were purchased from Daicel Chemical Industries, LTD. ESI HRMS was recorded on a Bruke P-SIMS-Gly FT-ICR mass spectrometer.

2. Synthesis of chiral catalysts

The synthesis of catalysts 2a from (L)-4-hydroxyproline has been reported, the detail of synthetic procedure see the reference,1 the route as follows:

Thiophosgene (1.7 mL, 22 mmol) was added dropwise to the mixture of 20 (4.9 g, 10.8 mmol), CaCO3 (1.41 g, 14.1 mmol) and H2O (6 mL) in CHCl3 (60 mL) at 0°C. The mixture was stirred overnight. After filtration, the organic phase was washed with brine and dried over anhydrous Na2SO4, concentrated under reduced pressure to afford crude product 21. Purification by silica gel column chromatography gave pure compound 22 as colorless oil (4.75 g, yield 88%).

Et3N (0.30 mL, 2.2 mmol) was added to the solution of 2,2,2-trifluoroethanaminium chloride (0.3 g, 2 mmol) in fresh distill CH2Cl2 (10 mL) under ice bath, then, 22 (0.9 g, 2 mmol) was added to the mixture and warmed to 30°C, stirred further for 5 h, dilute with CH2Cl2(30 mL), washed with saturated NH4Cl and brine, dried over anhydrous Na2SO4, concentrated under reduced pressure to afford crude product 23. Purification by silica gel column chromatography gave pure compound 23 (0.5 g, yield 51%).

23 (0.5 g, 1.0 mmol) was added to the mixture of trifluoroacetic acid and CH2Cl2 (6 mL, V/V = 1:5) at 0°C and the solution was stirred for 6 h, concentrated and removed the excess trifluoroacetic acid, diluted...
with water and adjusted the pH of the solution to 8 with aqueous ammonia. Extracted with dichloromethane three times and combined organic layers, dried over anhydrous Na₂SO₄. Concentrated and purified by flash column chromatography to give thiourea catalyst 2d (0.37 g, yield 70%).

**Synthesis of catalyst 2e**

4-nitrophenyl carbonochloridate (0.9 g, 4.5 mmol) was added to the mixture of 3,5-bis(trifluoromethyl)aniline (0.7 mL, 4.5 mmol) and pyridine (0.4 mL, 5.0 mmol) in dry CH₂Cl₂ (20 mL) at room temperature, stirred for 5 minute, then, 20 (1.4 g, 3 mmol) in 10 mL CH₂Cl₂ and DIPEA (0.6 mL, 0.43 mmol) were added to the mixture successively. The resulting mixture was stirred for 5 hours further. Extracted with CH₂Cl₂ three times and combined organic layers, washed with saturated NaHCO₃ and brine, dried over anhydrous Na₂SO₄. Concentrated and purified by flash column chromatography to give the product 24 (1.9 g, yield 92%).

24 (0.62 g, 0.87 mmol) was added to the mixture of trifluoroacetic acid and CH₂Cl₂ (5mL, V/V = 1:4) at 0°C and the solution was stirred for 6 h. The mixture was concentrated to remove the excess trifluoroacetic acid, diluted with water and adjusted the pH of the solution to 8 with aqueous ammonia. Extracted with dichloromethane three times and combined organic layers, dried over anhydrous Na₂SO₄. Concentrated and purified by flash column chromatography to give urea catalyst 2e (0.3 g, yield 71%).

**Synthesis of catalyst 3**

The details of synthesis of catechol sulfate 25 see the reference.²

n-BuLi (1 mL, 2.4 mmol) was added dropwise to the solution of 3, 5-bis(trifluoromethyl) aniline (0.46 g, 2 mmol) in CH₂Cl₂ (10 mL) under -78 °C, stirred for 20 minute, then, the solution of catechol sulfate 25 (0.2 g, 1 mmol) in CH₂Cl₂ (5 mL) was added to this mixture, warmed to room temperature, monitored by TLC, stirred until the catechol sulfate disappeared. The reaction was quenched with saturated NH₄Cl, extracted with ethyl acetate three times and combined organic layers, washed with brine, and dried over anhydrous Na₂SO₄. Concentrated and purified by flash column chromatography to give 26 (0.2 g, yield 43%).

20 (1.6 g, 3.5 mmol) was added to the solution of 26 (1.3 g, 3.5 mmol) in dioxane (20 mL) and refluxed for 24 hours, removed the dioxane under reduce pressure, diluted with 50 mL ethyl acetate, washed with brine, dried over anhydrous Na₂SO₄. Concentrated and purified by flash column chromatography to give 27 (1.6 g, yield 70%).

27 (0.7 g, 0.97 mmol) was added to the mixture of trifluoroacetic acid and CH₂Cl₂ (5mL, V/V = 1:4) at 0°C and the solution was stirred for 6 h, concentrated to remove the excess trifluoroacetic acid, diluted with
water and adjusted the pH of the solution to 8 with aqueous ammonia. Extracted with dichloromethane three times and combined organic layers, dried over anhydrous Na2SO4. Concentrated and purified by flash column chromatography to give the catalyst 3 (0.33 g, yield 65%).

**Synthesis of catalyst 4**

3,4-Dimethoxy-3-cyclobutene-1,2-dione (0.2 g, 1.7 mmol) was added to the solution of 3,5-bis(trifluoromethyl)aniline (0.3 mL, 1.7 mmol) in 2 mL MeOH and stirred for 2 days at room temperature. The resulting pale yellow solid was isolated by filtration to give 28 (0.4 g, 67% yield).

28 (0.4 g, 1.1 mmol) was added to the solution of 20 (0.5 g, 1.14 mmol) in MeOH (3 mL) and stirred at room temperature, monitored by TLC until the reaction finished, removed the MeOH under reduce pressure, purified by flash column chromatography to give 29 (0.4 g, 50% yield).

29 (0.3 g, 0.3 mmol) was added to the mixture of trifluoroacetic acid and CH2Cl2 (3mL, V/V = 1:4) at 0 °C and the solution was stirred for 6 h. The reaction mixture was concentrated to remove the excess trifluoroacetic acid, diluted with water and adjusted the pH of the solution to 8 with aqueous ammonia. Extracted with dichloromethane three times and combined organic layers, dried over anhydrous Na2SO4. Concentrated and purified by flash column chromatography to give the squaramide catalyst 4 (0.24 g, 85% yield).

All the *N*-Boc protected *α*-amido sulfones and *N*-Boc protected imines derived from aromatic aldehyde were prepared by the method reported by Jacobsen. All the *N*-Cbz protected *α*-amido sulfones and *N*-Cbz protected imines were prepared by the method reported by Dixon.

**3. Synthesis of *N*-Cbz *α*-amido sulfone 11 derived from ethyl glyoxalate:**

Benzyl carbamate (3.0 g, 20 mmol) was added to the mixture of sodium *p*-tolysulfinate monohydrate (SPTS) (11.8 g, 60 mmol) and ethyl glyoxalate (4.0 mL, 40 mmol) in formic acid (99%, 20 mL). The solution was stirred for two days at room temperature, then poured the mixture into ice water, white solid was precipitated and isolated by filtration, washed with water and ether, dried under reduce pressure to obtain the *N*-Cbz *α*-amido sulfone 11 (6.6 g, 85% yield).

**4. Determination of diastereomeric ratios and enantiomeric purity:**

The diastereomeric ratios were determined by integration of one set of 1H NMR signal (CHO) or by chiral HPLC. Chiral HPLC analysis was performed on an WATERS 510 instrument (2487 Dual λ Absorbance Detector and 515 HPLC Pump) using chiral column, ChiralPak columns purchased from Daicel Chemical Industries, Daicel ChiralPak AD-H or AS-H column with i-PrOH/hexane or ethanol/hexane as the eluent was used. HPLC traces were compared to the retention time of the racemic samples prepared by carrying out the reactions with pyrolidine add H2OAc as the catalyst.

The absolute configuration of the obtained *anti*-Mannich products have been confirmed by Maruoka group. The absolute configuration of the *anti*-isomer obtained in the reaction between isovaleraldehyde and *N*-Boc-imine 14r was determined to be (*IS, 2R*) by comparison of the HPLC retention times with the literature data. HPLC analysis: Daicel ChiralPak AS-H, hexane/i-PrOH = 100/1, flow rate = 1 mL/min, λ = 205 nm, major product: *t*major = 12.15 min, *t*minor = not fond, *anti: ee* >99%, *dr* 90/10. (Reference: Daicel...
5. General procedure for the anti-selective Mannich reaction of imine and aldehyde

N-PMP imine 6 (or N-Boc imine 9) (0.2 mmol, 1 equiv.) and catalyst 2a (0.01 mmol, 0.05 equiv.) were dissolved in anhydrous 1, 2-dichloroethane (or CHCl₃) (1 mL), subsequently, isovaleraldehyde (1.0 mmol, 5 equiv.) was added at designated temperature. The mixture was stirred and monitored by TLC until the imine was completely disappearance. The mixture was worked up by addition of aqueous saturated ammonium chloride solution and extracted with AcOEt (three times). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo and the residue was purified by flash column chromatography (5-10% AcOEt/PE) to afford the corresponding anti-Mannich product 7 or 10. The ee and dr of anti-Mannich product 7 were determined by a chiral phase ChiralPak AS-H column (hexane / i-PrOH = 90/10, 90/10, 254 nm, 0.5 mL / min, t (major) = 15.40 min, t (minor) = 25.90 min, ee > 99%, dr = 98/2). The ee and dr of anti-Mannich product 10 were determined by a chiral phase ChiralPak AS-H column (96/4 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, tmajor = 20.9 min, tminor = 18.6 min, anti: ee > 99%, dr = 95/5)

6. General procedure for the anti-selective Mannich reaction of α-amido sulfone and aldehyde

To the mixture of α-amido sulfone 11 (0.2 mmol, 1 equiv.), KF (1 mmol, 5 equiv.), catalyst 2a (0.01 mmol, 0.05 equiv.) in 1 mL CHCl₃, isovaleraldehyde (1.0 mmol, 5 equiv.) was added under -20°C, the mixture stirred for additional 11 hours, quenched with saturated NH₄Cl, extract with CH₂Cl₂ (3×10 mL), the mixture stirred for additional 11 hours, quenched with saturated NH₄Cl, extract with CH₂Cl₂ (3×10 mL), combined organic phase and washed with brine, dried over anhydrous Na₂SO₄, concentrated in vacuo and the residue was purified by flash column chromatography to give the anti-selective Mannich product in 90% yield (58 mg). The ee and dr were determined by a chiral phase Daicel ChiralPak AD-H column: 90/10 hexane/iPrOH, flow rate 0.7 mL/min, λ = 214 nm, 254 nm, tmajor = 18.61 min, tminor = 27.35 min, anti: ee > 99%, dr = 99/1.

7. Characterization of the Mannich reaction products:

(2S, 3R)-ethyl 2-(benzoxycarbonylamino)-3-formylpentanoate

The title compound was isolated as colorless oil in 85% yield. HPLC analysis on a Daicel ChiralPak AD-H column: 90/10 hexane/iPrOH, flow rate 0.75 mL/min, λ = 254 nm, tmajor = 11.35 min, tminor = 16.82 min, anti: ee = 97%, dr = 80/20; [α]D²⁰ = +60.7 (c = 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 9.60 (s, 1H), 7.35 (s, 5H), 5.55 (d, J = 8.9 Hz, 1H), 5.13 (d, J = 3.6 Hz, 2H), 4.66 (d, J = 8.9 Hz, 1H), 4.18 (q, J = 6.9 Hz, 2H), 3.04 (s, 1H), 1.82 (dd, J = 13.9, 6.9 Hz, 1H), 1.53 (dd, J = 14.4, 7.2 Hz, 1H), 1.24 (t, J = 7.0 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 202.45, 170.91, 156.57, 136.21, 128.37, 128.00, 67.16, 61.92, 53.49, 52.54, 27.12, 20.64, 13.93 ppm.

(2S, 3R)-ethyl 2-(benzoxycarbonylamino)-3-formylhexanoate

The title compound was isolated as colorless oil in 83% yield. HPLC analysis on a Daicel ChiralPak AD-H column: 90/10 hexane/iPrOH, flow rate 0.7 mL/min, λ = 214 nm, 254 nm, tmajor = 19.02 min, tminor = 20.9 min, anti: ee > 99%, dr = 99/1.
(2S, 3R)-ethyl 2-(benzoxycarbonylamino)-3-formylheptanoate

The title compound was isolated as colorless oil in 76% yield. HPLC analysis on a Daicel ChiralPak AD-H column: 94/6 hexane/iPrOH, flow rate 0.5 mL/min, λ = 254 nm, t_major = 29.81 min, t_minor = 46.82 min, anti: ee >99%, dr = 89/11; [α]D²⁰ = +58.6 (c = 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 9.60 (s, 1H), 7.46 - 7.25 (m, 5H), 5.66 - 5.69 (d, J = 9 Hz, 1H), 5.12 - 5.14 (m, 1H), 5.10 - 5.11 (m, 2H), 2.61 - 2.66 (m, 1H), 2.32 (s, 3H), 1.80 - 1.88 (m, 1H), 1.10 - 1.09 (m, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 206.14, 158.95, 155.60, 136.20, 132.44, 128.44, 128.07, 127.99, 127.69, 114.11, 66.88, 62.62, 55.22, 28.22, 21.35, 18.70 ppm.

(2S, 3R)-ethyl 2-(benzoxycarbonylamino)-3-formyloctanoate

The title compound was isolated as colorless oil in 67% yield. HPLC analysis on a Daicel ChiralPak AD-H column: 95/5 hexane/iPrOH, flow rate 0.6 mL/min, λ = 254 nm, t_major = 25.65 min, t_minor = 41.83 min, anti: ee = 97%, dr = 83/17; [α]D²⁰ = +53.2 (c = 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 9.60 (s, 1H), 7.46 - 7.25 (m, 5H), 5.56 (d, J = 9.4 Hz, 1H), 5.13 (s, 2H), 4.66 - 4.56 (m, 1H), 2.61 - 2.63 (m, 1H), 2.32 (s, 3H), 1.80 - 1.88 (m, 3H), 0.89 (t, J = 5.8 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 202.45, 170.91, 156.13, 136.17, 128.71, 128.00, 67.08, 61.86, 53.64, 52.50, 31.59, 26.77, 24.88, 22.24, 13.87, 10.73 ppm.

Benzyl (1S, 2R)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate

The title compound was isolated as colorless oil in 97% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 90/10 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t_major = 30.2 min, t_minor = 36.8 min, anti: ee >99%, dr = 97/3; [α]D²⁰ = +5.7 (c = 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 9.75 - 9.76 (d, J = 3 Hz, 1H), 7.14 - 7.30 (m, 9H), 5.66 - 5.69 (d, J = 9 Hz, 2H), 7.13 (s, 5H), 6.84 - 6.87 (d, J = 9 Hz, 2H), 5.09 - 5.14 (m, 1H), 5.04 - 5.05 (m, 2H), 2.61 - 2.62 (m, 1H), 3.87 (s, 3H), 1.82 - 1.87 (m, 1H), 0.99 - 1.01 (m, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 206.14, 158.95, 155.60, 136.20, 132.44, 128.44, 128.07, 127.99, 127.69, 114.11, 66.88, 62.62, 55.22, 28.22, 21.35, 18.70 ppm.

Benzyl (1S, 2R)-2-formyl-3-methyl-1-p-tolylbutylcarbamate

The title compound was isolated as colorless oil in 95% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 92/8 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t_major = 21.2 min, t_minor = not found, anti: ee >99%, dr = 96/4; [α]D²⁰ = +14.2 (c = 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 9.75 - 9.76 (d, J = 3 Hz, 1H), 7.14 - 7.30 (m, 9H), 5.66 - 5.75 (d, J = 9 Hz, 1H), 5.16 - 5.18 (m, 1H), 4.99 - 5.12 (m, 2H), 2.61 - 2.64 (m, 1H), 2.32 (s, 3H), 1.80 - 1.89 (m, 1H), 0.90 - 1.09 (m, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 206.15, 155.63, 137.39, 137.33, 136.20, 129.42, 128.42, 128.04, 127.99, 126.44, 66.86, 62.55, 53.33, 28.20, 21.34, 21.00, 18.74 ppm.

Benzyl (1S, 2R)-2-formyl-3-methyl-1-phenylbutylcarbamate

The title compound was isolated as colorless oil in 95% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 92/8 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t_major = 21.2 min, t_minor = not found, anti: ee >99%, dr = 96/4; [α]D²⁰ = +14.2 (c = 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 9.75 - 9.76 (d, J = 3 Hz, 1H), 7.14 - 7.30 (m, 9H), 5.66 - 5.75 (d, J = 9 Hz, 1H), 5.16 - 5.18 (m, 1H), 4.99 - 5.12 (m, 2H), 2.61 - 2.64 (m, 1H), 2.32 (s, 3H), 1.80 - 1.89 (m, 1H), 0.90 - 1.09 (m, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 206.15, 155.63, 137.39, 137.33, 136.20, 129.42, 128.42, 128.04, 127.99, 126.44, 66.86, 62.55, 53.33, 28.20, 21.34, 21.00, 18.74 ppm.
The title compound was isolated as colorless oil in 97% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 90/10 hexane/iPrOH, flow rate 0.5 mL/min, \( \lambda = 220 \) nm, \( t_{\text{major}} = 21.2 \) min, \( t_{\text{minor}} = \) not found, \( \alpha = \) ee <99%, \( dr = 95/5 \); [\( \alpha \)]\(_{D}^{20} = +24.5 \) (c = 1, CHCl\(_3\)). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 9.75 - 9.76 \) (d, \( J = 3 \) Hz, 1H), 7.25 - 7.27 (m, 10H), 5.76 - 5.79 (d, \( J = 9 \) Hz, 1H), 5.16 - 5.21 (m, 1H), 5.01 - 5.10 (m, 2H), 2.67 - 2.68 (m, 1H), 1.84 - 1.96 (m, 1H), 0.95 - 1.08 (m, 6H) ppm. 13C NMR (75 MHz, CDCl\(_3\)): \( \delta = 206.02, 155.66, 140.53, 136.24, 136.21, 128.77, 128.46, 128.09, 127.62, 126.52, 66.94, 62.58, 53.57, 28.38, 21.29, 19.17 \) ppm.

**Benzyl (1S, 2R)-1-(4-chlorophenyl)-2-formyl-3-methylbutylcarbamate**

The title compound was isolated as colorless oil in 98% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 94/6 hexane/iPrOH, flow rate 0.5 mL/min, \( \lambda = 220 \) nm, \( t_{\text{major}} = 31.2 \) min, \( t_{\text{minor}} = 34.2 \) min, \( \alpha = \) ee >99%, \( dr = 99:1 \); [\( \alpha \)]\(_{D}^{20} = +25.6 \) (c = 1, CHCl\(_3\)). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 9.72 - 9.73 \) (d, \( J = 3 \) Hz, 1H), 7.43 - 7.45 (d, \( J = 6 \) Hz, 2H), 7.32 (s, 5H), 7.13 - 7.15 (d, \( J = 9 \) Hz, 2H), 5.89 - 5.92 (d, \( J = 9 \) Hz, 1H), 5.01 - 5.10 (m, 2H), 2.65 (s, 1H), 1.86 - 1.97 (m, 1H), 1.02 - 1.08 (m, 6H) ppm. 13C NMR (75 MHz, CDCl\(_3\)): \( \delta = 205.89, 155.63, 139.17, 136.07, 133.34, 128.86, 128.47, 128.15, 128.02, 127.91, 67.01, 62.26, 52.94, 28.38, 21.29, 19.17 \) ppm.

**Benzyl (1S, 2R)-1-(4-bromophenyl)-2-formyl-3-methylbutylcarbamate**

The title compound was isolated as colorless oil in 85% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 94/6 hexane/iPrOH, flow rate 0.5 mL/min, \( \lambda = 220 \) nm, \( t_{\text{major}} = 29.27 \) min, \( t_{\text{minor}} = 26.37 \) min, \( \alpha = \) ee >99%, \( dr = 99:1 \); [\( \alpha \)]\(_{D}^{20} = +74.7 \) (c = 1, CHCl\(_3\)). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 9.70 \) (d, \( J = 1.1 \) Hz, 1H), 7.53 (d, \( J = 7.9 \) Hz, 1H), 7.40 - 7.18 (m, 6H), 7.16 - 7.04 (m, 1H), 6.26 (t, \( J = 17.2 \) Hz, 1H), 5.49 (dd, \( J = 8.9, 4.5 \) Hz, 1H), 5.15 - 4.98 (m, 2H), 2.96 (d, \( J = 28.0 \) Hz, 1H), 2.13 (dtt, \( J = 27.1, 13.4, 6.7 \) Hz, 1H), 1.10 (dt, \( J = 29.5, 14.8 \) Hz, 6H). 13C NMR (75 MHz, CDCl\(_3\)): \( \delta = 206.56, 155.51, 139.17, 136.33, 133.40, 129.09, 128.59, 128.54, 128.19, 128.11, 127.69, 122.63, 67.02, 59.63, 53.28, 29.15, 21.12, 20.17 \) ppm. HRMS (ESI): calcd. for C\(_{20}\)H\(_{22}\)BrN\(_3\) [M + Na]\(^+\): 426.0681; found 426.0667. IR (neat): \( \nu = 3422, 3326, 3064, 3033, 2963, 2874, 2741, 1716, 1503, 1468, 1341, 1276, 1244, 1112, 1053, 1026, 754, 698, 629, 539 \) cm\(^{-1}\).

**Benzyl (1S, 2R)-1-(4-bromophenyl)-2-formyl-3-methylbutylcarbamate**

The title compound was isolated as colorless oil in 95% yield. HPLC analysis on a Daicel ChiralPak IC column: 90/10 hexane/iPrOH, flow rate 0.5 mL/min, \( \lambda = 220 \) nm, \( t_{\text{major}} = 20.71 \) min, \( t_{\text{minor}} = \) not found, \( \alpha = \) ee >99%, \( dr = 97:3 \); [\( \alpha \)]\(_{D}^{20} = -6.3 \) (c = 1, CHCl\(_3\)). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 9.83 \) (t, \( J = 9.2 \) Hz, 1H), 7.40 - 7.26 (m, 5H), 6.30 (dd, \( J = 3.0, 1.9 \) Hz, 1H), 6.22 (s, 1H), 5.73 (d, \( J = 9.2 \) Hz, 1H), 5.36 - 5.23 (m, 3H), 4.70 (t, \( J = 2.9, 1.4 \) Hz, 1H), 3.20 (dd, \( J = 28.0, 17.2 \) Hz, 1H), 1.82 - 1.91 (m, 1H), 1.00 - 1.07 (m, 6H) ppm. 13C NMR (75 MHz, CDCl\(_3\)): \( \delta = 206.02, 155.66, 140.53, 136.24, 136.21, 128.77, 128.46, 128.09, 127.62, 126.52, 66.94, 62.58, 53.57, 28.30, 21.33, 19.02 \) ppm.
Benzyl (1S, 2R)-2-formyl-1-(4-methoxyphenyl)butylcarbamate

The title compound was isolated as white solid in 86% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 92/8 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm: t_major = 54.46 min, t_minor = 47.63 min, anti: ee > 99%, dr = 88/12; [α]D 20 = + 4.7 (c = 1, CHCl₃). mp 105.8 - 106.5°C. ¹H NMR (300 MHz, CDCl₃) δ 9.77 (d, J = 6 Hz, 1H), 7.40 - 7.19 (m, 2H), 6.89 (dd, J = 6 Hz, 6H). 13C NMR (75 MHz, CDCl₃) δ 156.91, 155.05, 128.99, 128.79, 128.07, 120.73, 110.91, 79.56, 61.33, 206.70, 156.91, 155.05, 128.99, 128.79, 128.07, 120.73, 110.91, 79.56, 61.33, 55.22, 50.79, 28.34, 21.40, 18.39 ppm. HRMS (ESI) calcd. For C₂₀H₂₄N₂O₄ [M + Na]⁺ 364.1528, found 364.1528. IR (KBr): 3445, 3352, 3069, 2965, 2875, 2839, 2728, 2175, 1699, 1560, 1424, 1326, 1244, 1163, 1050, 879, 755, 628, 563 cm⁻¹.

tert-butyl (1S, 2R)-2-formyl-3-methyl-1-p-tolyllbutylcarbamate

The title compound was isolated as colorless oil in 84% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 96/4 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm: t_major = 14.42 min, t_minor = 12.07 min, anti: ee > 99%, dr = 88/12; [α]D 20 = + 5.4 (c = 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 9.74 (d, J = 4.2 Hz, 1H), 7.29 - 7.19 (m, 2H), 6.91 (dd, J = 16.3, 8.0 Hz, 2H), 5.72 (d, J = 9.6 Hz, 1H), 5.35 (t, J = 9.0 Hz, 1H), 3.86 (s, 3H), 2.84 - 2.65 (m, 1H), 1.85 - 1.65 (m, 1H), 1.40 (s, 9H), 1.01 (dd, J = 21.4, 6.9 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 206.70, 156.91, 155.05, 128.99, 128.79, 128.07, 120.73, 110.91, 79.56, 61.33, 55.22, 50.79, 28.34, 21.40, 18.39 ppm. HRMS (ESI) calcd. For C₁₈H₂₇N₂O₄ [M + Na]⁺ 344.1844; found 344.1844. IR (neat): 3450, 3350, 3069, 2935, 2875, 2830, 2728, 2175, 1699, 1562, 1326, 1244, 1163, 1050, 879, 755, 628, 563 cm⁻¹.

tert-butyl (1S, 2R)-2-formyl-3-methyl-1-phenylbutylcarbamate

The title compound was isolated as colorless oil in 86% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 100/1 hexane/iPrOH, flow rate 1 mL/min, λ = 205 nm, t_major = 12.15 min, t_minor = not found, anti: ee > 99%, dr = 89/11; [α]D 20 = + 6.2 (c = 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 9.75 - 9.76 (d, J = 3 Hz, 1H), 7.26 - 7.36 (m, 5H), 5.41 - 5.44 (d, J = 9 Hz, 1H), 5.13 (m, 1H), 2.60 - 2.65 (m, 1H), 1.11 - 0.96 (m, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 156.89, 155.05, 128.99, 128.79, 128.07, 120.73, 110.91, 79.56, 61.33, 55.22, 50.79, 28.34, 21.40, 18.39 ppm. HRMS (ESI) calcd. For C₁₈H₂₇N₂O₄ [M + Na]⁺ 344.1844; found 344.1844. IR (neat): 3444, 3352, 3069, 2965, 2875, 2830, 2728, 2175, 1699, 1562, 1326, 1244, 1163, 1050, 879, 755, 628, 563 cm⁻¹.
The title compound was isolated as colorless oil in 85% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 98/2 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t\textsubscript{major} = 21.56 min, t\textsubscript{minor} = 16.68 min, \textit{anti}: ee = 99%, dr = 85:15; [\textalpha]\textsubscript{D}\textsuperscript{20} = +16.0 (c = 1, CHCl\textsubscript{3}). \textit{1}H NMR (300 MHz, CDCl\textsubscript{3}): \textit{δ} 9.73 - 9.63 (m, 1H), 7.29 - 7.32 (d, J = 9 Hz, 2H), 7.19 - 7.22 (d, J = 9 Hz, 2H), 5.50 - 5.53 (d, J = 9 Hz, 1H), 5.08 (m, 1H), 2.60 (s, 1H), 1.87 - 1.93 (m, 1H), 1.39 (s, 9H), 1.02 - 1.04 (d, J = 6 Hz, 3H) ppm. \textit{13}C NMR (75 MHz, CDCl\textsubscript{3}): \textit{δ} 205.82, 155.01, 138.72, 127.59, 127.37, 126.81, 126.62, 79.98, 62.60, 52.46, 28.25, 21.24, 19.07 ppm.

tert-butyl (1S, 2R)-2-formyl-1-phenylhexylcarbamate\textsuperscript{5b, 7b}

The title compound was isolated as white solid in 95% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 96/4 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t\textsubscript{major} = 13.64 min, t\textsubscript{minor} = 12.59 min, \textit{anti}: ee >99%, dr = 85:15; [\textalpha]\textsubscript{D}\textsuperscript{20} = +12.0 (c = 1, CHCl\textsubscript{3}). mp 79 - 83°C. \textit{1}H NMR (300 MHz, CDCl\textsubscript{3}) \textit{δ} 9.78 - 9.70 (m, 2H), 5.50 - 5.53 (d, J = 6 Hz, 3H), 1.02 - 1.04 (d, J = 6 Hz, 3H) ppm. \textit{13}C NMR (75 MHz, CDCl\textsubscript{3}) \textit{δ} 203.94, 155.15, 140.32, 128.73, 127.62, 126.70, 79.82, 57.77, 54.46, 29.20, 28.25, 26.70, 22.46, 13.70 ppm.

tert-butyl (1S, 2R)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate\textsuperscript{7b, 8}

The title compound was isolated as colorless oil in 90% yield. HPLC analysis on a Daicel ChiralPak AS-H column: 96/4 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t\textsubscript{major} = 20.9 min, t\textsubscript{minor} = 18.6 min, \textit{anti}: ee = 99%, dr = 92:8; [\textalpha]\textsubscript{D}\textsuperscript{20} = -8.7 (c = 1.0, CHCl\textsubscript{3}). \textit{1}H NMR (300 MHz, CDCl\textsubscript{3}) \textit{δ} 203.94, 155.15, 140.32, 128.73, 127.62, 126.70, 79.82, 57.77, 54.46, 29.20, 28.25, 26.70, 22.46, 13.70 ppm.
9.76 (d, 1H, J = 3.9 Hz), 7.14 (d, 2H, J = 8.7 Hz), 6.83 (d, 2H, J = 8.4 Hz), 5.32 (d, 1H, J = 9 Hz), 5.08 (br, 1H), 3.79 (s, 3H), 2.54 - 2.60 (m, 1H), 1.80 - 1.87 (m, 1H), 1.40 (s, 9H), 1.04 - 1.11 (m, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 206.14, 158.87, 155.00, 132.82, 127.68, 114.08, 79.70, 63.00, 55.18, 28.06, 21.31, 18.54 ppm.
8. References:


9. NMR spectra and HPLC for catalysts and part of the Mannich products
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