A Facile Direct anti-Selective Catalytic Asymmetric Mannich Reaction of Aldehydes with Preformed N-Boc and N-Cbz Imines

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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 purchased from Daicel Chemical Industries, LTD. ESI HRMS was recorded on a Bruker Apex-2 mass spectrometer in TOF mode.

2. Synthesis of chiral catalysts

Catalysts 1a, 1b, 1c, 2a, 2b have been reported from (L)-4-hydroxyproline, the details of the synthesis method see the reference. Synthetic routine as follows:

The preparations of catalysts 1d-1f were similar to catalyst 1a.
1-(3,5-bis(trifluoromethyl)phenyl)-3-((3R,5S)-5-((triethylsilyloxy)methyl)pyrrolidin-3-yl)thiourea (1d): yellowish foam. $\alpha$D$_{20}^\circ = +17.0$ (c = 1.0, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) : $\delta = 0.58 - 0.66$ (m, 6H), 0.63 - 0.97 (m, 9H), 2.16 - 2.24 (m, 2H), 3.37 - 3.42 (m, 1H), 3.54 - 3.68 (m, 2H), 3.86 - 3.90 (m, 1H), 5.08 (s, 1H), 6.77 (br, 2H), 7.59 (s, 1H), 8.16 (s, 2H), 8.50 (s, 1H) ppm; $^{13}$C NMR (75.5 MHz, CDCl$_3$) : $\delta = -0.06, 6.6, 29.7, 32.9, 51.6, 54.2, 59.3, 61.2, 117.8, 122.6, 131.7, 140.6, 181.3$ ppm; HRMS(ESI-TOF) calcd for C$_{20}$H$_{29}$F$_6$N$_3$OSSi [M+H]$^+$ 502.1783, found 502.1781.

1-(3,5-bis(trifluoromethyl)phenyl)-3-((3R,5S)-5-((tert-butyldimethylsilyloxy)methyl)pyrrolidin-3-yl)thiourea (1e): yellowish foam. $\alpha$D$_{20}^\circ = -1.6$ (c = 1.0, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) : $\delta = 0.095 - 0.099$ (s, 6H), 0.93 (s, 9H), 2.25 - 2.30 (m, 2H), 3.42 - 3.48 (m, 1H), 3.92 - 3.97 (d, $J = 15$ Hz), 4.06 - 4.09 (m, 1H), 5.13 (s, 1H), 5.55 (br, 3H), 7.59 (s, 1H), 8.14 (s, 2H), 8.52 - 8.54 (m, 1H) ppm; $^{13}$C NMR (75.5 MHz, CDCl$_3$) : $\delta = -5.5, 18.2, 25.8, 29.7, 32.8, 51.9, 54.0, 59.5, 61.3, 117.9, 121.3, 122.8, 124.9, 131.7, 140.5, 181.3$ ppm; HRMS(ESI-TOF) calcd for C$_{20}$H$_{29}$F$_6$N$_3$OSSi [M+H]$^+$ 502.1783, found 502.1786.

1-(3,5-bis(trifluoromethyl)phenyl)-3-((3R,5S)-5-((triphenylsilyloxy)methyl)pyrrolidin-3-yl)thiourea (1f): yellowish foam. $\alpha$D$_{20}^\circ = +13.3$ (c = 1.0, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) : $\delta = 1.81 - 1.93$ (m, 1H), 2.01 - 2.08 (m, 1H), 2.92 - 2.98 (m, 1H), 3.11 - 3.15 (m, 1H), 3.58 - 3.69 (m, 2H), 4.77 - 4.87 (m, 1H), 5.34 (br, 2H), 7.30 - 7.59 (m, 17H), 7.94 - 8.01 (m, 2H) ppm; $^{13}$C NMR (75.5 MHz, CDCl$_3$) : $\delta = 33.2, 50.8, 54.4, 59.4, 62.0, 118.1, 121.2, 123.1, 124.8, 127.9, 128.5, 130.8, 131.9, 132.4, 135.1, 140.3, 180.8$ ppm; HRMS(ESI-TOF) calcd for C$_{32}$H$_{32}$F$_6$N$_3$OSSi [M+H]$^+$ 646.1783, found 646.1781.

The preparations of catalysts 2c were similar to catalyst 2a.

N-((3R,5S)-5-((tert-butyldiphenylsilyloxy)methyl)pyrrolidin-3-yl)-3,5-bis(trifluoromethyl)benzenesulfonamide (2c): brown solid, mp: 106 - 108 °C. $\alpha$D$_{20}^\circ = -5.1$ (c = 1.0, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) : $\delta = 1.03$ (s, 9H), 1.68 - 1.69 (m, 1H), 1.80 - 1.82 (m, 1H), 2.65 - 2.69 (m, 1H), 3.06 - 3.11 (m, 1H), 3.37 - 3.40 (m, 1H), 3.40 - 3.50 (m, 1H), 3.57 - 3.60 (m, 1H), 3.87 (s, 1H), 4.60 (br, 2H), 7.35 - 7.45 (d, 6H, $J = 30$ Hz), 7.60 - 7.62 (d, 4H, $J = 6$ Hz), 8.07 (s, 1H), 8.31 (s, 2H) ppm; $^{13}$C NMR (75.5 MHz, CDCl$_3$) : $\delta = 19.1, 26.8, 35.1, 52.3, 54.2, 57.8, 65.1, 120.6, 124.3, 125.9, 127.8, 127.2, 129.9, 132.3, 135.5, 144.1$ ppm; HRMS(ESI-TOF) calcd for C$_{32}$H$_{32}$F$_6$N$_3$OSSi [M+H]$^+$ 646.1783, found 646.1781.

All the N-Boc protected α-amido sulfones and N-Boc protected imines 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. Determination of diastereomeric ratios and enantiomeric purity:

Chiral HPLC analysis was performed on a WATERS 510 instrument (2487 Dual λ Absorbance Detector and 515 HPLC Pump) using chiral column, Chiralpak columns purchased from Daicel Chemical Industries, Daicel Chiralpak AS-H column with i-PrOH/hexane or ethanol/hexane as the eluent was used (all HPLC performed at 25 °C). HPLC traces were compared to the retention time of the racemic samples prepared by carrying out the reactions with (DL) proline or pyrolidine add HAc as the catalyst.

4. Determination of the absolute configuration of the major diastereomer:

The absolute configuration of the obtained anti-Mannich products have been confirmed by Maruoka group.[4] The absolute configuration of the anti-isomer obtained in the reaction between isovaleraldehyde and N-Boc-imine was determined to be (1S, 2R) by comparison of the HPLC retention times with the literature data.4 HPLC analysis: Daicel Chiralpak AS-H, hexane/i-PrOH = 100/1, flow rate = 1 mL/min, λ = 205 nm, major product: $t_{\text{major}} = 14.9$ min, $t_{\text{minor}} = 12.9$ min, anti: ee $>99\%$, $dr$ 90/10. (Reference: Daicel Chiralpak AS-H, hexane/i-PrOH = 100/1, flow rate = 1 mL/min, λ = 205 nm, retention time; 10.4 min (minor) and 12.2 min (major)).

5. General procedure for the anti-selective Mannich reaction

anisaldehyde N-Boc imine 4a (0.2 mmol, 1 equiv.) and catalyst 1c (0.01 mmol, 0.05 equiv.) were dissolved in anhydrous CHCl$_3$ (1 mL), subsequently, isovaleraldehyde 3a (1.0 mmol, 5 equiv.) was added at 0 °C. 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 Na$_2$SO$_4$, concentrated in vacuo and the residue was purified by flash column chromatography (5-10% AcOEt/PE) to afford the corresponding Mannich product. The ee and $dr$ were determined by a chiral phase Chiralpak AS-H column (96/4 hexane/i-PrOH, flow rate 0.5 mL/min, $\lambda = 220$ nm, $t_{\text{major}} = 20.9$ min, $t_{\text{minor}} = 18.6$ min, anti: ee $>99\%$, $dr$ = 95/5)
6. Characterization of the Mannich reaction products:

**tert-butyl (1S, 2R)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate**

The title compound was isolated as colorless oil in 94% 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 = 20.9 min, t_minor = 18.6 min, anti: ee >99%, dr = 95/5; [α]D^20 = -7.5 (c = 1.0, CHCl_3). \(^1\)H NMR (300 MHz, CDCl_3): δ = 1.04 - 1.11 (m, 6H), 1.40 (s, 9H), 1.80 - 1.87 (m, 1H), 2.54 - 2.60 (m, 1H), 3.79 (s, 3H), 5.08 (br, 1H), 5.32 (d, 1H, J = 9 Hz), 6.83 (d, 2H, J = 8.4 Hz), 7.14 (d, 2H, J = 8.7 Hz), 9.76 (d, 1H, J = 3.9 Hz) ppm. \(^13\)C NMR (75 MHz, CDCl_3): δ = 18.5, 21.3, 28.1, 52.5, 55.1, 79.7, 114.1, 127.7, 132.8, 155.0, 158.9, 206.1 ppm.

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

The title compound was isolated as colorless oil in 93% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t_major = 19.8 min, t_minor = 16.3 min, anti: ee >99%, dr = 90/10; [α]D^20 = -4.9 (c = 1.0, CHCl_3). \(^1\)H NMR (300 MHz, CDCl_3): δ = 0.98 - 1.00 (d, 3H, J = 6 Hz), 1.05 - 1.07 (d, 3H, J = 6 Hz), 1.43 (s, 9H), 1.80 - 1.87 (m, 1H), 2.33 (s, 3H), 5.08 - 5.13 (m, 1H), 5.33 - 5.35 (d, 1H, J = 6 Hz), 7.10 - 7.27 (m, 4H), 9.75 - 9.77 (d, 1H, J = 6 Hz) ppm. \(^13\)C NMR (75 MHz, CDCl_3): δ = 18.7, 21.0, 21.0, 21.3, 28.1, 52.8, 63.0, 79.7, 129.1, 129.4, 137.2, 137.7, 155.1, 206.2 ppm.

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

The title compound was isolated as colorless oil in 91% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 100/1 hexane/iPrOH, flow rate 1 mL/min, λ = 205 nm, t_major = 14.9 min, t_minor = 12.9 min, anti: ee >99%, dr = 90/10; [α]D^20 = +6.6 (c = 1.0, CHCl_3). \(^1\)H NMR (300 MHz, CDCl_3): δ = 1.0 - 1.08 (m, 6H), 1.38 (s, 9H), 1.84 - 1.90 (m, 1H), 2.60 - 2.65 (m, 1H), 5.15 (m, 1H), 7.26 - 7.36 (m, 5H), 9.75 - 9.76 (d, 1H, J = 3 Hz) ppm. \(^13\)C NMR (75 MHz, CDCl_3): δ = 18.0, 21.3, 28.1, 28.2, 53.0, 62.9, 79.8, 126.5, 127.5, 128.7, 140.8, 155.0, 206.2 ppm.

**tert-butyl (1S, 2R)-1-(4-fluorophenyl)-2-formyl-3-methylbutylcarbamate**

The title compound was isolated as colorless oil in 92% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/ethanol, flow rate 0.5 mL/min, λ = 220 nm, t_major = 22.3 min, t_minor = 24.9 min, anti: ee 98%, dr = 90/10; [α]D^20 = +14.8 (c = 1.0, CHCl_3). \(^1\)H NMR (300 MHz, CDCl_3): δ = 1.01 - 1.03 (d, 3H, J =
6 Hz), 1.06 - 1.08 (d, 3H, J = 6 Hz), 1.39 (s, 9H), 1.85 - 1.90 (m, 1H), 2.60 - 2.61 (m, 1H), 5.1 (m, 1H), 5.46 - 5.49 (d, 1H, J = 9 Hz), 6.99 - 7.28 (m, 4H), 9.75 - 9.76 (d, 1H, J = 3 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ = 18.9, 21.3, 28.2, 52.4, 62.8, 79.9, 115.4, 115.7, 128.1, 128.2, 136.7, 155.0, 160.3, 163.6, 206.0 ppm; HRMS(ESI-TOF) calcd for C17H24FNO3 [M+Na]+ 332.1638, found 332.1245.

tert-butyI (1S, 2R)-1-(4-chlorophenyl)-2-formyl-3-methylbutylcarbamate

The title compound was isolated as colorless oil in 84% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t_major = 16.1 min, t_minor = 15.6 min, anti: ee = 98%, dr = 95/5; [α]D20 = + 4.5 (c = 1.0, CHCl3). 1H NMR (300 MHz, CDCl3): δ = 1.02 - 1.08 (m, 6H), 1.39 (s, 9H), 1.87 - 1.93 (m, 1H), 2.60 (s, 1H), 5.08 (m, 1H), 5.50 - 5.53 (d, 1H, J = 9 Hz), 7.19 - 7.22 (d, 2H, J = 9 Hz), 7.29 - 7.32 (d, 2H, J = 9 Hz), 9.73 - 9.74 (d, 1H, J = 3 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ = 19.0, 21.2, 28.2, 52.5, 62.6, 79.9, 127.9, 128.8, 133.2, 139.6, 155.0, 205.8 ppm.

tert-butyI (1S, 2R)-2-formyl-3-methyl-1-(naphthalen-2-yl)butylcarbamate

The title compound was isolated as colorless oil in 81% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t_major = 23.6 min, t_minor = 27.0 min, anti: ee >99%, dr = 92/8; [α]D20 = - 1.6 (c = 0.75, CHCl3). 1H NMR (300 MHz, CDCl3): δ = 1.02 - 1.04 (d, 3H, J = 6 Hz), 1.08 - 1.10 (d, 3H, J = 6 Hz), 1.39 (s, 9H), 1.84 - 1.93 (m, 1H), 2.71 - 2.76 (m, 1H), 5.3 (m, 1H), 5.50 - 5.53 (d, 1H, J = 9 Hz), 7.35 - 7.84 (m, 7H), 9.78 - 9.79 (d, 1H, J = 3 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ = 14.1, 18.9, 21.0, 21.3, 28.2, 53.2, 60.3, 62.7, 79.9, 124.3, 125.6, 126.0, 126.3, 127.6, 127.9, 128.7, 132.7, 133.3, 138.1, 155.1, 171.1, 206.0 ppm; HRMS(ESI-TOF) calcd for C21H27NO3 [M+Na]+ 364.1889, found 364.1885.

tert-butyI (1S, 2R)-2-formyl-1-(furan-2-yl)-3-methylbutylcarbamate

The title compound was isolated as colorless oil in 89% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t_major = 16.0 min, t_minor = 15.5 min, anti: ee >99%, dr = 91/9; [α]D20 = - 18.6 (c = 0.5, CHCl3). 1H NMR (300 MHz, CDCl3): δ = 1.02 - 1.07 (t, 6H, J = 6 Hz), 1.42 (s, 9H), 1.91 - 1.93 (m, 1H), 2.73 - 2.78 (m, 1H), 5.23 - 5.31 (m, 2H), 6.20 - 6.22 (d, 1H, J = 6 Hz), 6.30 - 6.31 (m, 1H), 7.33 (s, 1H), 9.80 - 9.82 (d, 1H, J = 6 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ = 19.1, 21.1, 27.9, 28.3, 47.3, 60.3, 80.0, 106.7, 110.4, 141.9, 153.3, 155.1, 205.1 ppm; HRMS(ESI-TOF) calcd for C15H23NO4 [M+Na]+ 304.1525, found 304.1527.

tert-butyI (IS, 2R)-1-(4-methoxyphenyl)-2-methyl-3-oxopropylcarbamate

The title compound was isolated as colorless oil in 89% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t_major = 16.0 min, t_minor = 15.5 min, anti: ee >99%, dr = 91/9; [α]D20 = - 18.6 (c = 0.5, CHCl3). 1H NMR (300 MHz, CDCl3): δ = 1.02 - 1.07 (t, 6H, J = 6 Hz), 1.42 (s, 9H), 1.91 - 1.93 (m, 1H), 2.73 - 2.78 (m, 1H), 5.23 - 5.31 (m, 2H), 6.20 - 6.22 (d, 1H, J = 6 Hz), 6.30 - 6.31 (m, 1H), 7.33 (s, 1H), 9.80 - 9.82 (d, 1H, J = 6 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ = 19.1, 21.1, 27.9, 28.3, 47.3, 60.3, 80.0, 106.7, 110.4, 141.9, 153.3, 155.1, 205.1 ppm; HRMS(ESI-TOF) calcd for C15H23NO4 [M+Na]+ 304.1525, found 304.1527.
The title compound was isolated as a white solid in 88% 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 = 24.1 min, t_minor = 17.9 min, anti: ee >99%, dr = 91/9; mp: 102.3 °C - 105.5 °C, [α]D20 = -33.2 (c = 1.0, CHCl3). 1H NMR (300 MHz, CDCl3): δ = 1.00 - 1.02 (d, 3H, J = 6 Hz), 1.39 (s, 9H), 2.76 - 2.80 (m, 1H), 3.80 (s, 3H), 4.81 (s, 1H), 5.11 - 5.14 (d, 1H, J = 9 Hz), 6.86 - 6.89 (d, 2H, J = 9 Hz), 7.16 - 7.19 (d, 2H, J = 9 Hz), 9.65 - 9.66 (d, 1H, J = 3Hz) ppm.

13C NMR (75 MHz, CDCl3): δ = 11.8, 28.3, 52.3, 55.3, 79.9, 114.1, 127.9, 131.9, 155.1, 159.1, 203.5 ppm; HRMS(ESI-TOF) calcd for C16H23NO4 [M+Na]+ 316.1525, found 316.1526.

tert-butyl (1S, 2R)-2-formyl-1-(4-methoxyphenyl)butylcarbamate

The title compound was isolated as a white solid in 94% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 94/6 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, t_major = 24.3 min, t_minor = 18.7 min, anti: ee >99%, dr = 90/10; mp: 105.2 °C - 106.9 °C, [α]D20 = -18.8 (c = 1.0, CHCl3). 1H NMR (300 MHz, CDCl3): δ = 0.87 - 0.92 (t, 3H, J = 15 Hz), 1.39 (s, 9H), 1.57 - 1.64 (m, 1H), 2.54 - 2.58 (m, 1H), 3.80 (s, 3H), 4.84 - 4.87 (m, 1H), 5.15 - 5.17 (d, 1H, J = 6 Hz), 6.86 - 6.89 (d, 2H, J = 9 Hz), 7.17 - 7.20 (d, 2H, J = 9 Hz), 9.61 ppm.

13C NMR (75 MHz, CDCl3): δ = 11.6, 20.4, 28.3, 53.8, 55.2, 59.6, 79.8, 114.1, 127.9, 132.4, 155.0, 159.0, 204.1 ppm; HRMS(ESI-TOF) calcd for C17H25NO4 [M+Na]+ 330.1681, found 330.1684.

tert-butyl (1S, 2R)-2-formyl-1-(4-methoxyphenyl)hexylcarbamate

The title compound was isolated as a white solid 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 = 24.4 min, t_minor = not find, anti: ee >99%, dr = 89/11; mp: 74.2 °C - 76.5 °C; [α]D20 = +2.8 (c = 1, CHCl3). 1H NMR (300 MHz, CDCl3): δ = 0.82 - 0.91 (m, 5H), 1.26 - 1.30 (m, 3H), 1.45 (s, 9H), 2.63 - 2.66 (m, 2H), 3.80 (s, 3H), 4.85 (s, 1H), 5.18 - 5.21 (d, 1H, J = 9 Hz), 6.86 - 6.89 (d, 2H, J = 9 Hz), 7.16 - 7.19 (d, 2H, J = 9 Hz), 9.60 - 9.61 (d, 1H, J = 3 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ = 13.7, 14.0, 22.4, 22.5, 22.8, 25.2, 26.7, 28.3, 29.2, 55.2, 57.9, 79.8, 114.1, 127.9, 132.4, 155.0, 158.9, 204.0 ppm; HRMS(ESI-TOF) calcd for C17H25NO4 [M+Na]+ 330.1681, found 330.1684.

(R)-tert-butyl 1-(4-methoxyphenyl)-2,2-dimethyl-3-oxopropylcarbamate

The title compound was isolated as a white solid in 70% 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 = 15.0 min, t_minor = 12.3 min. ee = 92%; mp: 102.5 °C - 105 °C; [α]D20 = +1.3 (c = 1, CHCl3). 1H NMR (300 MHz, CDCl3): δ = 1.04 (s, 6H), 1.38 (s, 9H), 3.79 (s, 3H), 4.79 - 4.82 (d, 1H, J = 9 Hz), 5.36 - 5.39 (d, 1H, J = 9 Hz), 6.84 - 6.87 (d, 2H, J = 9 Hz), 7.11 - 7.14 (d, 2H, J = 9 Hz), 9.56 (s, 1H). 13C NMR (75 MHz, CDCl3): δ = 17.9, 20.7, 28.2, 50.4, 55.2, 58.7, 79.8, 113.6, 128.8, 130.5, 155.1, 158.9, 205.3 ppm; HRMS(ESI-TOF) calcd for C17H25NO4 [M+Na]+ 330.1681, found 330.1684.
Benzyl (1S, 2R)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate

The title compound was isolated as colorless oil in 86% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 90/10 hexane/iPrOH, flow rate 0.5 mL/min, \( \lambda = 220 \text{ nm} \), \( t_{\text{major}} = 30.2 \text{ min} \), \( t_{\text{minor}} = 36.8 \text{ min} \), \( \text{anti: ee >99%} \), \( \text{dr} = 95/5 \); \([\alpha]_D^{20} = +5.4 \text{ (c = 1, CHCl}_3\text{)}\). \(^1\text{H NMR (300 MHz, CDCl}_3\text{)}: \delta = 0.99 - 1.06 (\text{m, 6H}), 1.82 - 1.87 (\text{m, 1H}), 2.62 - 2.63 (\text{m, 1H}), 3.87 (\text{s, 3H}), 5.04 - 5.05 (\text{m, 2H}), 5.09 - 5.14 (\text{m, 1H}), 5.66 - 5.69 (\text{d, 1H, J = 9 Hz}), 7.17 - 7.20 (\text{d, 2H, J = 9 Hz}), 7.31 (\text{s, 5H}), 9.76 - 9.77 (\text{d, 1H, J = 3 Hz}) \text{ ppm.} \(^{13}\text{C NMR (75 MHz, CDCl}_3\text{)}: \delta = 18.7, 21.4, 28.2, 55.2, 62.6, 66.9, 114.1, 127.7, 127.9, 128.1, 128.4, 136.2, 155.6, 158.9, 206.1 \text{ppm.}\)

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

The title compound was isolated as colorless oil in 84% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 92/8 hexane/iPrOH, flow rate 0.5 mL/min, \( \lambda = 220 \text{ nm} \), \( t_{\text{major}} = 21.2 \text{ min} \), \( t_{\text{minor}} = \text{not found} \), \( \text{anti: ee >99%} \), \( \text{dr} = 93/7 \); \([\alpha]_D^{20} = +13.8 \text{ (c = 1, CHCl}_3\text{)}\). \(^1\text{H NMR (300 MHz, CDCl}_3\text{)}: \delta = 0.90 - 1.09 (\text{m, 6H}), 1.80 - 1.89 (\text{m, 1H}), 2.32 (\text{s, 3H}), 2.61 - 2.64 (\text{m, 1H}), 4.99 - 5.12 (\text{m, 2H}), 5.16 - 5.18 (\text{m, 1H}), 5.72 - 5.75 (\text{d, 1H, J = 9 Hz}), 7.14 - 7.30 (\text{m, 9H}), 9.75 - 9.76 (\text{d, 1H, J = 3 Hz}) \text{ ppm.} \(^{13}\text{C NMR (75 MHz, CDCl}_3\text{)}: \delta = 18.7, 21.0, 21.3, 28.2, 53.3, 62.5, 66.9, 126.4, 127.9, 128.0, 128.4, 129.4, 136.2, 137.3, 137.4, 155.6, 206.2 \text{ppm.}\)

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

The title compound was isolated as colorless oil in 88% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 90/10 hexane/iPrOH, flow rate 0.5 mL/min, \( \lambda = 220 \text{ nm} \), \( t_{\text{major}} = 21.2 \text{ min} \), \( t_{\text{minor}} = \text{not found} \), \( \text{anti: ee >99%} \), \( \text{dr} = 92/8 \); \([\alpha]_D^{20} = +23.2 \text{ (c = 1, CHCl}_3\text{)}\). \(^1\text{H NMR (300 MHz, CDCl}_3\text{)}: \delta = 0.95 - 1.08 (\text{m, 6H}), 1.84 - 1.96 (\text{m, 1H}), 2.67 - 2.68 (\text{m, 1H}), 5.01 - 5.10 (\text{m, 2H}), 5.16 - 5.21 (\text{m, 1H}), 5.76 - 5.79 (\text{d, 1H, J = 9 Hz}), 7.25 - 7.27 (\text{m, 10H}), 9.75 - 9.76 (\text{d, 1H, J = 3 Hz}) \text{ ppm.} \(^{13}\text{C NMR (75 MHz, CDCl}_3\text{)}: \delta = 19.0, 21.3, 28.3, 53.6, 62.6, 66.9, 126.5, 127.6, 128.0, 128.5, 128.8, 136.2, 136.2, 140.5, 155.7, 206.0 \text{ppm; HRMS(ESI-TOF) calcd for C}_{20}\text{H}_{23}\text{NO}_3 [M+Na]^+ 348.1576, found 348.1574.}\)

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

The title compound was isolated as colorless oil in 90% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 94/6 hexane/iPrOH, flow rate 0.5 mL/min, \( \lambda = 220 \text{ nm} \), \( t_{\text{major}} = 31.2 \text{ min} \), \( t_{\text{minor}} = 34.2 \text{ min} \), \( \text{anti: ee >99%} \), \( \text{dr} = 94/6 \); \([\alpha]_D^{20} = +21.6 \text{ (c = 1, CHCl}_3\text{)}\). \(^1\text{H NMR (300 MHz, CDCl}_3\text{)}: \delta = 1.02 - 1.08 (\text{m, 6H}), 1.85 - 2.14 (\text{m, 1H}), 2.62 - 2.66 (\text{m, 1H}), 5.01 - 5.04 (\text{m, 2H}), 5.14 - 5.18 (\text{m, 1H}), 5.72 - 5.77 (\text{d, 1H, J = 9 Hz}), 7.08 - 7.30 (\text{m, 10H}), 9.75 - 9.78 (\text{d, 1H, J = 3 Hz}) \text{ ppm.} \(^{13}\text{C NMR (75 MHz, CDCl}_3\text{)}: \delta = 1.02 - 1.08 (\text{m, 6H}), 18.7, 21.0, 21.3, 28.3, 53.6, 62.6, 66.9, 126.5, 127.6, 128.0, 128.5, 128.8, 136.2, 136.2, 140.5, 155.7, 206.0 \text{ppm; HRMS(ESI-TOF) calcd for C}_{20}\text{H}_{23}\text{NO}_3 [M+Na]^+ 349.1576, found 349.1574.\)
1.88 - 1.95 (m, 1H), 2.65 (s, 1H), 5.01 - 5.16 (m, 3H), 5.88 - 5.91 (d, 1H, J = 9 Hz), 7.18 - 7.32 (m, 9H), 9.73 - 9.74 (d, 1H, J = 3 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ = 19.1, 21.3, 28.4, 52.9, 62.3, 67.0, 127.9, 128.0, 128.1, 128.2, 128.5, 133.3, 136.1, 139.2, 155.6, 205.9 ppm; HRMS(ESI-TOF) calcd for \( C_{20}H_{22}ClNO_3 \) [M+Na]⁺ 383.1264, found 383.1340.

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

The title compound was isolated as colorless oil in 82% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 94/6 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm; \( t_{\text{major}} = 31.2 \text{ min, } t_{\text{minor}} = 34.2 \) min, anti: ee >99%, dr = 94/6; [α]D²⁰ = + 21.6 (c = 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.02 - 1.10 (m, 6H), 1.86 - 1.97 (m, 1H), 2.65 (s, 1H), 5.01 - 5.14 (m, 3H), 5.89 - 5.92 (d, 1H, J = 9 Hz), 7.13 - 7.15 (d, 1H, J = 9 Hz), 7.32 (s, 5H), 8.97 - 9.07 (d, 1H, J = 3 Hz) ppm. 13C NMR (75 MHz, CDCl₃): δ = 19.1, 21.3, 28.4, 53.0, 62.2, 67.0, 121.5, 128.0, 128.1, 128.3, 128.5, 131.8, 136.1, 139.8, 155.6, 205.8 ppm; HRMS(ESI-TOF) calcd for \( C_{20}H_{22}BrNO_3 \) [M+Na]⁺ 427.0759, found 427.0716.

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

The title compound was isolated as white solid in 95% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 94/6 hexane/iPrOH, flow rate 0.5 mL/min, λ = 220 nm, \( t_{\text{major}} = 13.6 \) min, \( t_{\text{minor}} = 18.2 \) min, anti: ee >99%, dr = 95/5; mp: 88.4°C - 89.5°C, [α]D²⁰ = + 4.0 (c = 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.02 - 1.10 (m, 6H), 1.17 - 1.22 (m, 3H), 1.86 - 1.92 (m, 1H), 2.64 - 2.7 (m, 1H), 4.03 - 4.10 (m, 2H), 5.15 - 5.20 (m, 1H), 5.67 - 5.70 (d, 1H, J = 9 Hz), 7.23 - 7.36 (m, 5H), 9.76 - 9.77 (d, 1H, J = 3 Hz) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 14.4, 18.9, 21.3, 28.2, 53.4, 61.0, 62.6, 126.5, 127.6, 128.7, 140.6, 155.9, 206.2 ppm; HRMS(ESI-TOF) calcd for \( C_{15}H_{21}NO_3 \) [M+Na]⁺ 286.1619, found 286.1416.

7. Reference:


Supplementary Material (ESI) for Chemical Communications

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8. NMR spectra and HPLC for catalysts and part of the Mannich products
Supplementary Material (ESI) for Chemical Communications
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![Graph 1](image1)

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