Supporting Information

Catalytic asymmetric synthesis of cyclic amino acid derivatives
Taichi Kano, Takeshi Kumano, Ryu Sakamoto and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University
Sakyo, Kyoto 606-8502, Japan

General Information: Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. $^1$H NMR spectra were measured on a JEOL JNM-FX400 (400MHz) spectrometer. Chemical shifts were reported in ppm from tetramethyilsilane (in the case of CDCl$_3$) as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quintet, m = multiplet, br = broad, and app = apparent), and coupling constants (Hz). $^{13}$C NMR spectra were recorded on a JEOL JNM-FX400 (100MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using a Daicel CHIRALPAK AD-H, AS-H and CHIRALCEL OD-H 4.6 mm × 25 cm column. The high-resolution mass spectra (HRMS) were performed on Applied Biosystems Mariner 8295 API-TOF and Bruker microTOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF$_254$, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230-400 mesh). Glycine t-butyl ester-benzophenoneimine Shiff base 1, $^1$ alanine t-butyl ester-p-chlorobenzalidimine Shiff base 6, $^2$ chiral phase transfer catalysts (S)-2a, (S)-2b and (S)-2c were prepared according to literature procedure. $^3$ Alkyl halides 3, $^4$-6 8$^4$ and 13$^7$ were prepared according to literature procedure. Cyclic amino esters 5b, $^8$ 5d, $^9$ 5a, $^{10}$ 10e $^{11}$ and 10f $^{11}$ are known compounds. Other simple chemicals were purchased and used as such.

General procedure for asymmetric alkylation under phase-transfer conditions

To a mixture of 1 (30 mg, 0.10 mmol), 3a (209 mg, 1.0 mmol) and (S)-2a (1.5 mg, 0.002 mmol) in toluene (1 mL) was added CsOH (42 mg, 0.25 mmol) at −40 °C, and the reaction mixture was vigorously stirred for 16 h. After the consumption of the starting material, the mixture was diluted with H$_2$O, extracted with dichloromethane. The organic layer was dried over Na$_2$SO$_4$ and purified by chromatography on silica gel (hexane/ethyl acetate = 5/1 as eluent) to afford 4a (36 mg, 0.085 mmol, 85% yield) as an oil. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 6.3 min (major) and 10.0 min (minor)). [α]$^2_{D}$ = 81.1 (c 1.0, CHCl$_3$; 99% ee); $^1$H NMR δ 7.66-7.63 (2H, m), 7.45-7.29 (6H, m), 7.19-7.17 (2H, m), 3.93-3.84 (5H, m),
1.93-1.87 (2H, m), 1.60-1.55 (2H, m), 1.44 (9H, s), 1.40-1.30 (2H, m), 1.27 (3H, s); \[\textsuperscript{13}\text{C NMR } \delta 171.5, 169.9, 139.7, 136.7, 130.1, 128.8, 128.5, 128.4, 127.94, 127.88, 111.0, 80.8, 66.0, 64.6, 38.9, 33.8, 28.1, 23.8, 20.6; IR (neat) 2951, 1732, 1622, 1447, 1368, 1148, 1069 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{29}\)H\(_{34}\)NO\(_4\): 424.2482 ([M + H])\(^+\), Found: 424.2491 ([M + H])\(^+\)].

(R)-\textit{tert}-Butyl 4-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)butanoate (4b): Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL/min, \(\lambda = 254 \text{ nm, retention time: } 9.7\) min (major) and 12.9 min (minor); \([\alpha]_{D}^{20} = 74.3 \text{ (c } 1.0, \text{ CHCl}_3, 90\% \text{ ee)}; \[\text{H NMR } \delta 7.66-7.63 (2H, m), 7.46-7.28 (6H, m), 7.19-7.17 (2H, m), 4.82 (1H, t, \(J = 4.8 \text{ Hz}\), 3.97-3.87 (3H, m), 3.84-3.75 (2H, m), 2.07-1.98 (2H, m), 1.76-1.67 (1H, m), 1.63-1.55 (1H, m), 1.44 (9H, s); \[\textsuperscript{13}\text{C NMR } \delta 171.1, 170.1, 139.6, 136.6, 130.1, 128.7, 128.4, 128.3, 127.9, 127.8, 104.2, 80.8, 65.5, 64.8, 64.7, 30.4, 28.02, 27.98; IR (neat) 2976, 2359, 1732, 1368, 1146 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{29}\)H\(_{34}\)NO\(_4\): 396.2169 ([M + H])\(^+\), Found: 396.2181 ([M + H])\(^+\)].

(R)-\textit{tert}-Butyl 5-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)pentanoate (4d): Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL/min, \(\lambda = 254 \text{ nm, retention time: } 7.7\) min (major) and 9.9 min (minor); \([\alpha]_{D}^{20} = 20.1 \text{ (c } 1.0, \text{ CHCl}_3, 99\% \text{ ee)}; \[\text{H NMR } \delta 7.66-7.63 (2H, m), 7.46-7.29 (6H, m), 7.20-7.15 (2H, m), 4.81 (1H, t, \(J = 4.8 \text{ Hz}\), 3.96-3.88 (3H, m), 3.85-3.77 (2H, m), 1.97-1.91 (2H, m), 1.63-1.58 (2H, m), 1.44 (9H, s), 1.42-1.26 (2H, m); \[\textsuperscript{13}\text{C NMR } \delta 171.4, 170.0, 139.7, 136.7, 130.1, 128.7, 128.43, 128.36, 127.9, 127.8, 104.4, 80.8, 65.9, 64.8, 33.7, 33.5, 28.0, 20.6; IR (neat) 2949, 1732, 1622, 1368, 1146 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{29}\)H\(_{34}\)NO\(_4\): 410.2326 ([M + H])\(^+\), Found: 410.2334 ([M + H])\(^+\)].

(R)-\textit{tert}-Butyl 6-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)hexanoate (4e): Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 1.0 mL/min, \(\lambda = 254 \text{ nm, retention time: } 8.1\) min (major) and 10.8 min (minor); \([\alpha]_{D}^{20} = 7.4 \text{ (c } 1.0, \text{ CHCl}_3, 99\% \text{ ee)}; \[\text{H NMR } \delta 7.66-7.63 (2H, m), 7.46-7.29 (6H, m), 7.18-7.16 (2H, m), 4.80 (1H, t, \(J = 4.8 \text{ Hz}\), 3.97-3.88 (3H, m), 3.85-3.77 (2H, m), 1.92-1.87 (2H, m), 1.65-1.60 (2H, m), 1.44 (9H, s), 1.41-1.20 (4H, m); \[\textsuperscript{13}\text{C NMR } \delta 171.4, 169.8, 139.7, 136.7, 130.0, 128.7, 128.4, 128.3, 127.9, 127.8, 104.4, 80.7, 65.9, 64.7, 33.7, 33.5, 28.0, 25.9, 23.8; IR (neat) 2976, 1732, 1622, 1144, 1030 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{29}\)H\(_{34}\)NO\(_4\): 424.2482 ([M + H])\(^+\), Found: 424.2488 ([M + H])\(^+\)].

(R)-\textit{tert}-Butyl 2-(diphenylmethyleneamino)-6-(2-methyl-1,3-dioxolan-2-yl)hexanoate (4f): Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, \(\lambda = 254 \text{ nm, retention time: } 12.0 \text{ min (major) and 15.7 min (minor). }\,[\alpha]_{D}^{20} = 83.6 \text{ (c } 0.5, \text{ CHCl}_3; 98\% \text{ ee)}; \[\text{H NMR } \delta 7.65-7.63 (2H, m), 7.56-7.30 (6H, m), 7.18-7.15 (2H, m), 3.94-3.85 (5H, m), 1.88 (2H, q, \(J = 7.6 \text{ Hz}\), 1.61-1.57 (2H, m), 1.44 (9H, s), 1.37-1.20 (7H, m); \[\textsuperscript{13}\text{C NMR } \delta 171.6, 169.8, 136.8, 135.3, 130.1, 128.8, 128.42, 128.37, 128.0, 127.9, 110.0, 80.8, 66.0, 64.6, 39.1, 34.7, 33.6, 28.1, 26.3, 23.9, 23.7; IR (neat) 2978, 2359, 1732, 1622, 1368, 1152 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{27}\)H\(_{36}\)NO\(_4\): 438.2639 ([M + H])\(^+\), Found: 438.2646 ([M + H])\(^+\)].
General procedure for diastereoselective reductive amination

To a mixture of 4a (67 mg, 0.16 mmol), EtOH (3 mL) and H₂O (1.5 mL) was added TFA (36 μL, 0.48 mmol). After stirring for 1 h, to the mixture was added 10% Pd/C (34 mg) and the mixture was stirred at 40 °C for 24 h under hydrogen atmosphere. After filtration through celite, the filtrate was basified with aqueous NaHCO₃ and extracted with dichloromethane. The organic layer was dried over Na₂SO₄ and purified by chromatography on silica gel (dichloromethane/methanol = 50/1 as eluent) to afford 5a (28 mg, 0.14 mmol 88% yield) as an oil. [α]ᵢ Dü = 7.1 (c 0.7, CHCl₃; 99% ee); ¹H NMR δ 3.22 (1H, dd, J = 11.5, 2.7 Hz), 2.64 (1H, dqd, J = 11.0, 6.4, 2.7 Hz), 1.99-1.94 (1H, m), 1.89-1.83 (1H, m), 1.77 (1H, br), 1.62-1.57 (1H, m), 1.46 (9H, s), 1.44-1.25 (2H, m), 1.12 (3H, d, J = 6.4 Hz), 1.08-0.98 (1H, m); ¹³C NMR δ 172.6, 80.8, 59.8, 51.8, 33.8, 29.0, 28.0, 24.6, 22.8; IR (neat) 2926, 1726, 1368, 1157 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₁H₂₂NO₂: 200.1645 ([M + H]+), Found: 200.1644 ([M + H]+).

(R)-tert-Butyl azepane-2-carboxylate (5e): [α]ᵢ Dü = -6.3 (c 1.2, CHCl₃; 99% ee); ¹H NMR δ 3.42 (1H, dd, J = 8.8, 5.2 Hz), 3.10-3.04 (1H, m), 2.75-2.68 (1H, m), 2.57 (1H, br), 2.09-2.02 (1H, m), 1.76-1.54 (7H, m), 1.46 (9H, s); ¹³C NMR δ 172.0, 82.1, 59.9, 45.8, 31.3, 29.5, 28.0, 27.4, 25.0; IR (neat) 2928, 1728, 1368, 1155 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₁H₂₂NO₂: 200.1645 ([M + H]+), Found: 200.1648 ([M + H]+).

(2R,7R)-tert-Butyl 7-methyazepane-2-carboxylate (5f): [α]ᵢ Dü = 15.0 (c 0.5, CHCl₃; 98% ee); ¹H NMR δ 3.39 (1H, dd, J = 9.8, 5.1 Hz), 2.79-2.71 (1H, m), 2.07-1.98 (1H, m), 1.88 (1H, br), 1.61-1.76 (5H, m), 1.46 (9H, s), 1.44-1.40 (1H, m), 1.34-1.26 (1H, m), 1.12 (3H, d, J = 6.6 Hz); ¹³C NMR δ 174.1, 80.9, 61.0, 54.5, 39.6, 33.6, 28.0, 25.3, 25.0, 23.9; IR (neat) 2926, 2359, 1726, 1368, 1157 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₂H₂₅NO₂: 214.1802 ([M + H]+), Found: 214.1799 ([M + H]+).

(2R,6R)-tert-Butyl 2,6-dimethylpiperidine-2-carboxylate (7)

To a mixture of 6 (161 mg, 0.60 mmol), 3a (1.25 g, 6.0 mmol) and (S)-2a (9 mg, 0.012 mmol) in toluene (6 mL) was added CsOH (280 mg, 1.5 mmol) at –20 °C, and the reaction mixture was vigorously stirred for 20 h. After the consumption of the starting material, the mixture was concentrated under reduced pressure, and to the residue were added EtOH (3mL), H₂O (3mL), and TFA (245 μL, 3.3 mmol). After stirring for 1 h, to
the mixture was added 10% Pd/C (80 mg) and the mixture was stirred at 40 °C for 36 h under hydrogen atmosphere. After filtration through celite, the result solution was basified with aqueous NaHCO₃ and extracted with dichloromethane. The organic layer was dried over Na₂SO₄ and purified by chromatography on silica gel (dichloromethane/methanol = 30/1 as eluent) to afford 7 (79 mg, 0.37 mmol, 61% yield) as an oil. [α]°₂⁰ = 18.3 (c 1.0, CHCl₃; 96% ee); ¹H NMR δ 2.91-2.86 (1H, m), 1.73-1.49 (6H, m), 1.46 (9H, s), 1.35 (3H, s), 1.07 (3H, d, J = 6.4 Hz), 1.02-0.91 (1H, m); ¹³C NMR δ 175.7, 80.4, 58.1, 45.5, 34.0, 32.8, 27.8, 22.9, 20.6, 20.1; IR (neat) 2974, 1732, 1622, 1447, 1368, 1150 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₇H₂₃NO₅: 214.1802 ([M + H]+), Found: 214.1794 ([M + H]+).

### Determination of the enantiomeric excess of (R)-tert-butyl 2-amino-2-methyl-5-(2-methyl-1,3-dioxolan-2-yl)pentanoate

![Chemical structure](image)

To a mixture of 6 (54 mg, 0.20 mmol), 3a (418 mg, 2.0 mmol) and (S)-2a (3 mg, 0.004 mmol) in toluene (2 mL) was added CsOH (93 mg, 0.50 mmol) at −20 °C, and the reaction mixture was vigorously stirred for 24 h. After the consumption of the starting material, the mixture was concentrated under reduced pressure, and to the residue were added MeOH (1mL), H₂O (1mL), and TFA (53 μL, 0.7 mmol). After stirring for 0.5 h, the solution was basified with aqueous NaHCO₃, extracted with dichloromethane, dried over Na₂SO₄ and concentrated. To a solution of the residue and triethylamine (56 μL, 0.40 mmol) in dichloromethane (2 mL) was added benzoyl chloride (34 μL, 0.24 mmol) at 0 °C. After stirring for 3 h at 0 °C, the mixture was quenched with H₂O and extracted with dichloromethane. The organic layer was dried over Na₂SO₄ and purified by chromatography on silica gel (hexane/ethylacetate = 5/1 as eluent) to afford 8 (37, 31.3, 28.0, 27.9, 13.7; IR (neat) 2974, 1732, 1622, 1447, 1368, 1150 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₂₃H₃₄NO₄: 424.2482 ([M + H]+), Found: 424.2469 ([M + H]+).
Diastereomixture of (R)-tert-butyl 5-methylpiperidine-2-carboxylate (10b): (2R,5R)/(2R,5S) = 1.2/1. ¹H NMR δ 3.45-3.42 (0.55H, m), 3.11 (0.45H, dd, J = 11.6, 2.8 Hz), 3.08-3.04 (0.45H, m), 2.80 (0.55H, dd, J = 11.6, 3.6 Hz), 2.52 (0.55H, dd, J = 11.6, 9.2 Hz), 2.30 (1H, br), 2.22 (0.45H, app t), 2.04-1.96 (1H, m), 1.86-1.62 (3H, m), 1.48 (4.95H, s), 1.46 (4.05H, s), 1.15-1.01 (1H, m), 0.88 (1.65H, d, J = 6.4 Hz), 0.82 (1.35H, d, J = 6.8 Hz); ¹³C NMR δ 173.2, 172.6, 80.7, 63.4, 59.2, 56.5, 53.5, 50.3, 33.2, 31.5, 30.1, 30.0, 29.7, 28.0, 27.9, 26.0, 19.2, 18.8; IR (neat) 2930, 1728, 1456, 1368, 1155 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₁H₁₂NO₂: 200.1645 ([M + H]⁺), Found: 200.1654 ([M + H]⁺).

Determination of the enantiomeric excess of (R)-tert-butyl 5-methylpiperidine-2-carboxylate (10b):

The enantiomeric excess of 10b was determined by HPLC analysis after conversion to the corresponding benzamide. (2R,5R)/(2R,5S) = 1.2 (98% ee)/1(96% ee). Daicel Chiralpak OD-H, hexane/2-propanol = 200/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: (2R,5R: 56.2 min (major) and 102.7 min (minor)), (2R,5S: 62.5 min (major) and 78.9 min (minor)); ¹H NMR (toluene-d₈, 80 °C) δ 7.48-7.46 (2H, m), 7.15-7.05 (3H, m), 5.07 (0.45H, br), 3.60 (0.55H, br), 3.35 (0.45H, d, J = 13.2 Hz), 2.85 (0.55H, br), 2.22-2.17 (1.55H, m), 2.01-1.98 (0.45H, m), 1.83-1.80 (0.55H, m), 1.69-1.48 (2.45H, m), 1.43 (4.05H, s), 1.41 (4.95H, s), 1.24-1.21 (0.45H, m), 1.14-1.04 (0.55H, m), 0.87 (3.5H, d, J = 6.8 Hz), 0.65 (1.65H, br); ¹³C NMR δ 174.6, 173.6, 173.2, 171.3, 140.40, 140.35, 132.3, 132.1, 131.3, 130.4, 130.0, 84.2, 83.8, 61.2, 55.4, 55.2, 49.7, 34.5, 33.7, 33.2, 30.8, 30.3, 29.9, 24.4, 22.2, 21.8, 19.2; IR (neat) 2930, 1728, 1638, 1420, 1225, 1142 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₈H₁₆NO₄: 304.1907 ([M + H]⁺), Found: 304.1915 ([M + H]⁺).

(R)-tert-Butyl 5-(1,3-dioxolan-2-yl)-2-(diphenylmethyleneamino)-5-phenylpentanoate (9c): [α]₂⁰⁺⁺ = 41.5 (c 1.3, CHCl₃); ¹H NMR δ 7.64-7.61 (2H, m), 7.43-7.10 (13H, m), 4.96 (0.5H, d, J = 4.8 Hz), 4.94 (0.5H, d, J = 4.4 Hz), 3.88-3.87 (1H, m), 3.80-3.74 (4H, m), 2.80-2.76 (1H, m), 1.83-1.70 (4H, m), 1.44 (4.5H, s), 1.39 (4.95H, s); ¹³C NMR δ 171.4, 171.2, 169.8, 169.7, 140.0, 139.9, 139.74, 139.69, 136.69, 136.65, 130.08, 130.06, 128.9, 128.78, 128.75, 128.44, 128.41, 128.38, 128.36, 128.3, 128.20, 128.17, 128.0, 127.93, 127.87, 127.85, 126.7, 126.6, 111.6, 106.8, 80.8, 80.7, 66.2, 65.9, 65.10, 65.07, 65.0, 49.9, 49.7, 33.9, 31.5, 28.02, 28.01, 26.3, 26.2, 20.9; IR (neat) 2976, 1732, 1368, 1146 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₃₁H₂₆NO₄: 486.2639 ([M + H]⁺), Found: 486.1632 ([M + H]⁺).

(2R,5S)-tert-Butyl 5-phenylpiperidine-2-carboxylate ((2R,5S)-10e): Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 25.1 min (major) and 28.9 min (minor); [α]₂⁰⁺⁺ = 1.0 (c 0.4, CHCl₃, 92% ee); ¹H NMR δ 7.31-7.27 (2H, m), 7.21-7.18 (3H, m), 3.58 (1H, dd, J = 5.2, 3.2 Hz), 3.01-2.92 (2H, m), 2.80-2.73 (1H, m), 2.28-2.23 (1H, m), 1.93-1.81 (3H, m), 1.52 (9H, s), 1.48-1.41 (1H, m); ¹³C NMR δ 173.4, 144.6, 128.4, 127.2, 126.3, 81.0, 55.9, 49.6, 42.5, 28.8, 28.2, 26.8; IR (neat) 2932, 1724, 1368, 1150 cm⁻¹; HRMS (ESI-TOF) Calcd. for C₁₈H₁₆NO₂: 262.1802 ([M + H]⁺), Found: 262.1794 ([M + H]⁺).
Diastereomixture of (2R,5R)-tert-butyl 2-(diphenylmethyleneamino)-5-(2-methyl-1,3-dioxolan-2-yl) hexanoate (9d): (2R,5R)/(2R,5S) = 1/1. $^1$H NMR $\delta$7.16-7.19 (2H, m) 7.65-7.63 (2H, m), 7.46-7.30 (6H, m), 3.93-3.79 (5H, m), 2.10-1.97 (1H, m), 1.88-1.69 (1H, m), 1.65-1.51 (2H, m), 1.45 (4.5H, s), 1.44 (4.5H, s), 1.19 (3H, s), 1.11-0.99 (1H, m), 0.93 (1.5H, d, $J$ = 7.1 Hz), 0.91 (1.5H, d, $J$ = 6.8 Hz); $^{13}$C NMR $\delta$ 14.5, 14.6, 20.2, 20.3, 28.06, 28.12, 31.4, 31.8, 32.0, 32.1, 41.3, 41.4, 47.5, 47.6, 47.8, 48.9, 64.49, 65.54, 66.3, 66.6, 80.76, 80.81, 112.29, 112.34, 127.89, 127.90, 127.94, 128.35, 128.37, 128.43, 128.77, 128.82, 129.9, 130.1, 136.78, 136.82, 139.80, 139.83, 169.7, 169.9, 171.5, 171.6, 171.9, 169.9, 139.83, 139.80, 136.82, 136.78, 130.1, 129.9, 128.82, 128.77, 128.43, 128.37, 128.35, 127.94, 127.90, 127.89, 112.34, 112.29, 80.81, 80.76, 66.6, 66.3, 65.54, 64.49, 48.9, 48.8, 47.6, 47.5, 41.4, 41.3, 32.1, 32.0, 31.8, 31.4, 28.12, 28.06, 20.3, 20.2, 14.6, 14.5; IR (neat) 2976, 1732, 1368, 1150 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{27}$H$_{36}$NO$_5$: 438.2639 ([M + H]$^+$), Found: 438.2622 ([M + H]$^+$).

Diastereomixture of (2R,6R)-tert-butyl 5,6-dimethylpiperidine-2-carboxylate (10d): (2R,5R,6R)/(2R,5S,6R) = 2.5/1. $^1$H NMR (toluene-d$_6$, 80 °C) $\delta$ 3.26-3.21 (1H, m), 2.85 (0.71H, dq, $J$ = 2.9, 6.6 Hz), 2.24 (0.29H, dq, $J$ = 8.8, 6.4 Hz), 2.00-1.95 (0.29H, m), 1.81-1.78 (0.29H, m), 1.71-1.47 (5.42H, m), 1.46 (9H, s), 1.11 (0.86H, d, $J$ = 6.4 Hz), 1.03 (2.14H, d, $J$ = 6.6 Hz), 0.89 (2.14H, d, $J$ = 7.1 Hz), 0.85 (0.86H, d, $J$ = 6.1 Hz); $^{13}$C NMR $\delta$ (2R,5R,6R)/(2R,5S,6R) 172.9/172.6, 80.7/80.6, 60.2/59.7, 57.9/53.6, 33.8/37.7, 31.5/32.0, 28.01/28.00, 23.6/29.9, 20.0/20.3, 10.9/18.4; IR (neat) 1730, 1368, 1233, 1155 cm$^{-1}$; HRMS (ESI-TOF) Calcd. for C$_{13}$H$_{24}$NO$_2$: 214.1802 ([M + H]$^+$), Found: 214.1807 ([M + H]$^+$).

Determination of the enantiomeric excess of 10d

The enantiomeric excess of 10d was determined by HPLC analysis after conversion to the corresponding benzamide. (2R,5R,6R)/(2R,5S,6R) = 2.5 (99% ee)/1(99% ee). Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, $\lambda$ = 254 nm, retention time: (2R,5S,6R: 9.8 min (minor), 10.9 min (major)). (2R,5R,6R: 12.1 min (major), 20.7 min (minor)). $^1$H NMR (toluene-d$_{6}$s, 80 °C) $\delta$ 7.19-7.13 (2H, m), 6.90-6.82 (3H, m), 4.69-3.76 (2H, m), 1.96 (0.71H, d, $J$ = 13.2 Hz), 1.88-1.85 (0.71H, m), 1.80-1.74 (0.29H, m), 0.81 (2.14H, d, $J$ = 7.1 Hz), 1.64-1.55 (0.29H, m), 1.49-1.09 (11H, m), 0.95 (0.86H, d, $J$ = 7.6 Hz), 0.93 (0.71H, m), 0.79-0.77 (0.29H, m), 0.61 (0.86H, d, $J$ = 6.4 Hz).
7.1 Hz), 0.38 (2.14H, d, J = 6.6 Hz); \(^{13}\)C NMR \(\delta (2R,5R,6R,2R,5S,6R)\) 174.8/175.5, 174.1/174.4, 141.4/141.5, 140.4/140.7, 131.2/131.9, 130.0/129.9, 84.0/83.8, 56.9/55.4, 56.1/55.1, 37.8/37.7, 36.17/36.15, 30.9/29.3, 27.3/26.1, 21.5/21.4, 15.6/23.1; IR (neat) 2976, 2361, 1726, 1641, 1412, 1155 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{19}\)H\(_{32}\)NO\(_3\): 318.2064 ([M + H]\(^{+}\)), Found: 318.2048 ([M + H]\(^{+}\)).

6-(2-Bromoethyl)-1,4-dioxaspiro[4.4]nonane (8e): The title compound was prepared by a similar method described in literature.\(^{4}\) \(^{1}\)H NMR \(\delta 3.95-3.87 (4H, m), 3.52-3.42 (1H, m), 3.40-3.35 (1H, m), 2.12-2.05 (2H, m), 1.95-1.91 (1H, m), 1.84-1.63 (5H, m), 1.36-1.31 (1H, m); \(^{13}\)C NMR \(\delta 117.8, 64.5, 64.4, 44.6, 35.5, 32.8, 32.6, 28.9, 20.6; IR (neat) 2876, 2957, 2876, 1738, 1315, 1260, 1206, 1139, 1026 cm\(^{-1}\).

Diastereomixture of (2R)-tert-butyl 2-(diphenylmethyleneamino)-4-(1,4-dioxaspiro[4.4]nonan-6-yl)butanoate (9e): \([\alpha]_{D}^{22}\) = 91.6 (c 1.0, CHCl\(_3\)); \(^{1}\)H NMR \(\delta 7.65-7.63 (2H, m), 7.44-7.29 (6H, m), 7.19-7.17 (2H, m), 3.91-3.81 (5H, m), 1.94-1.81 (4H, m), 1.74-1.57 (4H, m), 1.44 (9H, s), 1.42-1.21 (3H, m); \(^{13}\)C NMR \(\delta 171.6, 169.8, 139.8, 136.8, 130.1, 128.8, 128.4, 128.3, 127.9, 118.2, 80.7, 66.3, 64.6, 64.4, 46.0, 35.8, 32.5, 31.6, 29.4, 28.1, 25.4, 20.6; IR (neat) 2953, 1732, 1148, 1030 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{33}\)H\(_{56}\)NO\(_4\): 450.2639 ([M + H]\(^{+}\)), Found: 450.2619 ([M + H]\(^{+}\)).

Determination of the enantiomeric excess of 10e

The enantiomeric excess of 10e was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, \(\lambda = 254\) nm, retention time: 16.4 min (major) and 22.3 min (minor). \([\alpha]_{D}^{22}\) = 41.6 (c 0.7, CHCl\(_3\); 99% ee); \(^{1}\)H NMR (toluene-\(d_8\), 80 °C) \(\delta 7.15-7.13 (2H, m), 6.89-6.86 (3H, m), 4.68 (1H, br), 4.04 (1H, br), 1.88-1.84 (1H, m), 1.73-1.65 (2H, m), 1.57-1.51 (1H, m), 1.27 (3H, br), 1.12 (9H, s), 1.06-0.92 (4H, m); \(^{13}\)C NMR \(\delta 174.6, 174.4, 141.6, 140.4, 131.2, 129.9, 83.8, 60.2, 57.2, 39.6, 33.1, 31.8, 30.9, 28.1, 27.7, 24.4; IR (neat) 1726, 2972, 1726, 1603, 1414, 1368, 1153 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{35}\)H\(_{58}\)NO\(_4\): 330.2064 ([M + H]\(^{+}\)), Found: 330.2069 ([M + H]\(^{+}\)).

6-(2-Bromoethyl)-1,4-dioxaspiro[4.5]decane (8f): The title compound was prepared by a similar method described in literature.\(^{4}\) \(^{1}\)H NMR \(\delta 3.99-3.91 (4H, m), 3.55-3.49 (1H, m), 3.45-3.38 (1H, m), 2.28-2.15 (1H, m), 1.81-1.76 (3H, m), 1.72-1.59 (3H, m), 1.49-1.43 (1H, m), 1.39-1.25 (3H, m); \(^{13}\)C NMR \(\delta 110.4, 64.7, 64.5, 43.2, 34.5, 32.9, 32.3, 29.1, 24.5, 23.6; IR (neat) 2978, 3335, 2978, 1713, 1524, 1221, 1117 cm\(^{-1}\).

Diastereomixture of (2R)-tert-butyl 2-(diphenylmethyleneamino)-4-(1,4-dioxaspiro[4.5]decan-6-yl)butanoate (9f): \((2R,4R)/(2R,4S) = 1/1. [\alpha]_{D}^{22}\) = 87.9 (c 1.0, CHCl\(_3\)); \(^{1}\)H NMR \(\delta 7.66-7.63 (2H, m), 7.44-7.29 (6H, m), 7.20-7.16 (2H, m), 3.93-3.81 (5H, m), 2.00-1.97 (1H, m), 1.81-1.65 (3H, m), 1.62-1.59 (2H, m), 1.50-1.47 (1H, m), 1.45 (4.5H, s), 1.44 (4.5H, s), 1.44-1.41
Determination of the enantiomeric excess of 10f

The enantiomeric excess of 10f was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 1.0 mL/min, λ = 254 nm, retention time: 13.6 min (major) and 16.5 min (minor). 

\[ [\alpha]_o^D = 67.1 \text{ (c 1.0, CHCl}_3 \text{); 99% ee} \]

\[ ^1H NMR \text{ (toluene-d}_6, 80 ^\circ \text{C}) \delta 7.59-7.57 (1H, m), 7.30-7.23 (3H, m), 7.17-7.15 (1H, m), 5.05 (1H, br), 4.45 (1H, br), 2.46 (1H, d, J = 12.4 Hz), 2.28-2.27 (1H, m), 2.12-2.01 (2H, m), 1.88-1.73 (3H, m), 1.67-1.54 (2H, m), 1.51 (9H, s), 1.33-1.23 (4H, m); \]

\[ ^13C NMR \delta 174.2, 174.1, 141.4, 140.4, 131.2, 129.9, 83.9, 58.0, 55.9, 39.3, 38.0, 35.8, 34.9, 30.9, 30.1, 29.3, 24.7; IR (neat) 2930, 1724, 1638, 1411, 1368, 1325, 1153 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{29}H\text{38}NO\text{4}_2\): 464.2795 ([M + H]^+), Found: 464.2785 ([M + H]^+).

6-(3-Bromopropyl)-1,4-dioxaspiro[4.4]nonane (8g): The title compound was prepared by a similar method described in literature. 

\[ ^1H NMR \delta 3.94-3.86 (4H, m), 3.45-3.36 (2H, m), 1.95-1.82 (4H, m), 1.80-1.54 (5H, m), 1.40-1.30 (2H, m); \]

\[ ^13C NMR \delta 118.0, 64.5, 64.4, 45.4, 35.7, 34.1, 31.6, 29.5, 27.7, 20.6; IR (neat) 2876, 2953, 2876, 1450, 1209, 1142, 1110, 1028 cm\(^{-1}\). \]

(R)-tert-Butyl 2-(diphenylmethyleneamino)-5-(1,4-dioxaspiro[4.4]nonan-6-yl)pentanoate (9g): \n
\[ [\alpha]_o^D = 70.2 \text{ (c 0.7, CHCl}_3 \text{); 99% ee} \]

\[ ^1H NMR \delta 7.65-7.63 (2H, m), 7.46-7.29 (6H, m), 7.18-7.16 (2H, m), 3.92-3.79 (5H, m), 1.94-1.80 (4H, m), 1.74-1.58 (4H, m), 1.44 (9H, s), 1.42-1.40 (1H, m), 1.30-1.15 (4H, m); \]

\[ ^13C NMR \delta 171.57, 171.56, 169.68, 169.66, 139.73, 139.71, 136.78, 136.75, 130.1, 130.0, 128.7, 128.37, 128.35, 128.32, 127.90, 127.85, 127.83, 127.82, 118.17, 118.15, 80.8, 66.1, 66.0, 64.52, 64.47, 64.4, 46.04, 45.96, 35.7, 34.0, 33.9, 29.4, 29.3, 28.7, 28.5, 28.0, 24.71, 24.67, 20.6; IR (neat) 2947, 1732, 1622, 1368, 1287, 1150 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{29}H\text{38}NO\text{4}_2\): 464.2795 ([M + H]^+), Found: 464.2796 ([M + H]^+).

(2R,5aR,8aR)-tert-Butyl decahydrocyclopenta[b]azepine-2-carboxylate (10g): \n
\[ [\alpha]_o^D = -6.7 \text{ (c 1.2, CHCl}_3 \text{); 99% ee} \]

\[ ^1H NMR \delta 3.59 (1H, app t), 2.75-2.70 (1H, m), 2.44-2.42 (1H, m), 2.04-1.51 (1H, m), 1.45 (9H, s), 1.26-1.15 (1H, m), 1.12-1.02 (1H, m); \]

\[ ^13C NMR \delta 174.3, 80.9, 63.2, 60.5, 50.2, 34.3, 32.6, 32.4, 28.0, 23.7, 21.6; IR (neat) 2930, 1724, 1368, 1225, 1155 cm\(^{-1}\); HRMS (ESI-TOF) Calcd. for C\(_{12}H_{26}NO_2\): 240.1952 ([M + H]^+), Found: 240.1958 ([M + H]^+).

Determination of the enantiomeric excess of (2R,5aR,8aR)-tert-butyl decahydrocyclopenta[b]azepine-2-carboxylate (10g): The enantiomeric excess of 10g
was determined by HPLC analysis after conversion to the corresponding benzamide. Daicel Chiralpak OD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 13.8 min (minor) and 16.8 min (major); [α]D 254 = −5.6 (c 1.1, CHCl3, 90% ee); 1H NMR (toluene-d8, 80 °C) δ 7.51-7.48 (2H, m), 7.19-7.12 (2H, m), 7.08-7.06 (1H, m), 5.04 (1H, br), 4.06-3.99 (1H, m), 2.79 (1H, br), 2.30-1.92 (3H, m), 1.85-1.81 (1H, m), 1.76-1.42 (6H, m), 1.42 (9H, s), 1.29-1.09 (2H, m); 13C NMR δ 175.0, 174.1, 142.1, 140.4, 132.1, 130.0, 84.0, 69.2, 64.1, 46.3, 36.6, 35.5, 35.3, 35.2, 31.0, 27.5, 24.4; IR (neat) 2930, 1728, 1639, 1404, 1327, 1155 cm−1; HRMS (ESI-TOF) Calcd. for C21H18NO3: 344.2220 ([M + H]+), Found: 344.2211 ([M + H]+).

(R,Z)-tert-Butyl 2-(diphenylmethylethenoamino)-6,6-dimethoxy-4-methylhex-4-enoate (14): Daicel Chiralpak OD-H, hexane/2-propanol = 50/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 17.2 min (minor) and 23.4 min (major). [α]D 254 = 82.2 (c 0.9, CHCl3; 92% ee); 1H NMR δ 7.65-7.62 (2H, m), 7.46-7.28 (6H, m), 7.18-7.14 (2H, m), 5.30 (1H, dd, J = 6.4, 0.8 Hz), 4.95 (1H, d, J = 6.4 Hz), 4.07 (1H, dd, J = 8.3, 5.1 Hz), 3.26 (3H, s), 3.15 (3H, s), 2.68-2.56 (2H, m), 1.52 (3H, d, J = 1.2 Hz), 1.45 (9H, s); 13C NMR δ 171.0, 170.0, 139.6, 138.1, 136.4, 130.1, 128.8, 128.5, 128.3, 127.94, 127.91, 124.9, 100.1, 81.2, 64.7, 52.6, 51.5, 43.4, 28.0, 17.1; IR (neat) 2367, 1734, 1150, 1053 cm−1; HRMS (ESI-TOF) Calcd. for C26H34NO4: 424.2482 ([M + H]+), Found: 424.2465 ([M + H]+).

(2R,4S)-tert-Butyl 4-methylpiperidine-2-carboxylate (15): [α]D 254 = 8.8 (c 0.4, CHCl3; 92% ee); 1H NMR δ 3.18 (1H, dd, J = 11.7, 2.7 Hz), 3.16-3.11 (1H, m), 2.60 (1H, td, J = 12.5, 2.7 Hz), 1.99-1.93 (1H, m), 1.63-1.48 (2H, m), 1.46 (9H, s), 1.05-0.95 (2H, m), 0.94 (3H, d, J = 6.4 Hz); 13C NMR δ 172.6, 80.8, 59.6, 45.8, 38.1, 34.7, 31.3, 28.0, 22.4; IR (neat) 2949, 2924, 1732, 1368, 1269, 1161 cm−1; HRMS (ESI-TOF) Calcd. for C11H12NO2: 200.1645 ([M + H]+), Found: 200.1641 ([M + H]+).

References

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is © The Royal Society of Chemistry 2012
Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is © The Royal Society of Chemistry 2012