Dynamic Resolution of N-Boc-2-lithiopiperidine

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Electronic Supplementary Information

Experimental procedures and spectroscopic data:

The preparation of the ligands is described below.

In general:
Ligands 4–18 and 21–23 were prepared by coupling two amino-acid derivatives (using dicyclohexylcarbodiimide and hydroxybenzotriazole or using HATU) then LiAlH₄ reduction.

Ligands 19 and 24–29 were prepared by treatment of a β-(dimethyl)amino-alcohol with methanesulfonyl chloride then addition of proline methyl ester, followed by LiAlH₄ reduction.

In detail:
The ligands 4–6 and 20 were prepared according to the literature.¹

As a representative procedure, the ligand 7 was prepared as follows:

To a stirred solution of N-Boc-N-methyl-L-valine² (3.53 g, 15.2 mmol) in CHCl₃ (50 mL) was added dicyclohexylcarbodiimide (3.15 g, 15.2 mmol) and hydroxybenzotriazole (2.06 g, 15.2 mmol). The suspension was stirred for 10 min and L-proline methyl ester hydrochloride (2.52 g, 15.2 mmol) and Et₃N (4.23 mL, 30.5 mmol) in CHCl₃ (30 mL) was added. After 18 h, the solvents were removed under reduced pressure, EtOAc (50 mL) was added and the mixture was stirred for 30 min. The solids were removed by filtration, the organic layer was washed with 10% citric acid (40 mL), and 10% NaHCO₃ (40 mL). The organic layer was dried (Na₂SO₄), concentrated under reduced pressure and purified by column chromatography on silica gel, eluting with petrol−EtOAc (1:4), to give the amide (2.86 g, 55%) as needles after recrystallisation from (CH₂Cl₂−n-hexane); R_f 0.32 [n-hexane−EtOAc (7:3)]; m.p. = 126–128°C; [α]²³_D −172.5 (0.4, CHCl₃); ν max /cm⁻¹ 2965, 1740, 1670, 1635; ¹H NMR (250 MHz, CDCl₃) (mixture of rotamers) δ = 4.59 (0.8H, d, J 11.0, CH), 4.50−4.39 (1.2H, m and d, J 11.0, CH), 3.95−3.52 (2H, m, CH₂N), 3.72, 3.71 and 3.68 (3H, 3s, CH₃O), 2.83, 2.82, 2.79, 2.68 and 2.56 (3H, 5s, CH₃N), 2.44−1.75 [5H, m, (CH₂)_5 + CH], 1.45, 1.44 and 1.43 (9H, 3s, t-Bu), 0.96 and 0.93 (2.8H, 2d, J 6.5 and 6.5, CH₃), 0.86 and 0.80 (3.2H, 2d, J 6.5 and 7.0, CH₃); ¹³C NMR (125 MHz, CDCl₃) (mixture of rotamers) δ = 172.6, 170.1 and 169.1, 156.5, 80.2 and 79.8, 62.3 and 61.5, 61.2 and 60.6, 58.9, 52.2 and 52.1, 47.3, 46.7 and 46.3, 29.2 and 29.1, 28.5, 28.4 and 28.3, 27.6 and 27.4, 25.0 and 24.9, 19.4 and 19.0, 18.5 and 18.4; HRMS (ESⁿ) Found MH⁺ = 343.2221, C₁₇H₃₁N₂O₅ requires MH⁺ = 343.2233; LRMS m/z (ESⁿ) 343 (100%, MH⁺), 287 (99); Found C, 59.08; H, 8.99; N, 8.21, C₁₇H₃₀N₂O₅ requires C, 59.63; H, 8.83; N, 8.18. This compound has been reported in the literature,³ but no spectroscopic data were given.

To a stirred suspension of LiAlH₄ (1.86 g, 49 mol) in THF (30 mL) cooled to 0°C was added dropwise a solution of the amide above (2.8 g, 8.2 mmol) in THF (15 mL). The mixture was stirred for 10 min at room temperature and then was heated under reflux for 5 h. The mixture was cooled to 0°C and was carefully quenched by slow addition of EtOAc. A slurry of Na₂SO₄/H₂O was added while the...
mixture was vigorously stirred until all the salts appeared white. The solvent was decanted, and the remaining white solid was washed several times with EtOAc. The combined organic layers were washed with HCl (aq) (2 M, 250 mL). The aqueous layer was extracted with EtOAc (2 x 200 mL) and then basified with NaOH pellets and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated and purified by Kugelrohr distillation (155 °C, 4 mm Hg), to give the ligand 7 (1.0 g, 57%). [α]²³_D −22.3 (2.1, EtOH); v max /cm⁻¹ 3340, 2950, 2870, 1035; ¹H NMR (400 MHz, CDCl₃) δ = 3.46 (1H, dd, J 10.5 and 3.5, CHO), 3.27 (1H, dd, J 10.5 and 6.5, CHO), 3.20−3.07 (1H, m, CHN), 2.75−2.25 (5H, m, 5 x CHN), 2.23 (6H, s, N(CH₃)₂), 2.13−1.60 (4H, m, 4 x CH), 1.64−1.42 (1H, m, CH), 0.91 (3H, d, J 7.0, CH₃), 0.90 (3H, d, J 7.0, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ = 66.1, 64.6, 64.5, 56.2, 52.9, 40.7, 27.8, 26.9, 24.1, 21.9, 19.5; HMRS (ES) Found MH⁺ = 215.2128, C₁₂H₁₇N₂O requires MH⁺ = 215.2123; LRMS m/z (ES) 215 (100%, MH⁺).

Data for ligand 8, prepared from N-Boc-N-methyl-l-valine and d-proline methyl ester hydrochloride: [α]²³_D +116.0 (0.9, EtOH); v max /cm⁻¹ 3335, 2955, 2865, 1043; ¹H NMR (500 MHz, CDCl₃) δ = 3.54 (1H, dd, J 11.0 and 3.5, CHO), 3.31 (1H, dd, J 11.0 and 5.0, CHO), 3.22−3.16 (1H, m, CHN), 2.75 (1H, dd, J 14.0 and 10.5, CHN), 2.62 (1H, ddt, J 8.5, 5.0 and 4.0, CHN), 2.35 (6H, s, N(CH₃)₂), 2.40−2.28 (3H, m, 3 x CH), 1.98−1.75 (2H, m, 2 x CH), 1.75−1.65 (2H, m, 2 x CH), 1.65−1.56 (1H, m, CH), 0.93 (3H, d, J 7.0, CH₃), 0.86 (3H, d, J 7.0, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ = 69.5, 65.8, 63.9, 55.3, 53.8, 41.4, 27.9, 26.6, 24.0, 22.5, 19.7; HMRS (ES) Found MH⁺ = 215.2114, C₁₂H₁₂N₂O requires MH⁺ = 215.2123; LRMS m/z (ES) 215 (100%, MH⁺).

Data for ligand 9, prepared from N-Boc-N-methyl-l-isoleucine and l-proline methyl ester hydrochloride: [α]²³_D +59.8 (1.2, CHCl₃); v max /cm⁻¹ 3360, 2960, 2910, 1260, 1010; ¹H NMR (400 MHz, CDCl₃) δ = 3.43 (1H, dd, J 10.5 and 3.5 Hz, CHO), 2.35 (1H, dd, J 10.5 and 7.5 Hz, CHO), 3.13 (1H, quin, J 4.5 Hz, CHN), 2.71−2.37 (5H, m, 5 x CHN), 2.29 (6H, s, N(CH₃)₂), 1.86−1.63 (5H, m, 5 x CH), 1.50−1.10 (3H, m, 3 x CH), 0.88 (3H, t, J 7 Hz, CH₃), 0.86 (3H, d, J 7 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ = 65.1, 64.3, 64.1, 56.5, 53.0, 40.5, 32.4, 28.7, 27.9, 24.2, 16.2, 12.1; HMRS (ES) Found MH⁺ = 229.2291, C₁₃H₂₉N₂O requires MH⁺ = 229.2280; LRMS m/z (ES) 229 (100%, MH⁺).

Data for ligand 10, prepared from N-Boc-N-methyl-l-isoleucine and d-proline methyl ester hydrochloride: [α]²³_D +50.6 (1.2, CHCl₃); v max /cm⁻¹ 3360, 2961, 2910, 1255, 1005; ¹H NMR (400 MHz, CDCl₃) δ = 4.31 (1H, br, OH), 3.52 (1H, dd, J 11 and 3 Hz, CHO), 3.30 (1H, dd, J 11 and 5 Hz, CHO), 3.19−3.13 (1H, m, CHN), 2.77 (1H, dd, J 13.5 and 10.5 Hz, CH), 2.64−2.39 (2H, m, 2 x CHN), 2.33−2.20 (2H, m, 2 x CHN), 2.29 (6H, s, N(CH₃)₂), 1.71−1.50 (5H, m, 5 x CH), 1.30−1.08 (2H, m, 2 x CH), 0.87 (3H, t, J 7 Hz, CH₃), 0.81 (3H, d, J 7 Hz, CH₃); ¹³C NMR (100 MHZ, CDCl₃) δ = 67.2, 65.9, 64.0, 55.4, 53.6, 41.3, 31.6, 29.0, 27.9, 24.0, 16.2, 11.8; HRMS (ES) Found MH⁺ = 229.2272, C₁₃H₂₉N₂O requires MH⁺ = 229.2280; LRMS m/z (ES) 229 (100%, MH⁺).

Data for ligand 11, prepared from N-Boc-N-methyl-l-alanine and l-proline methyl ester hydrochloride: [α]²³_D +48.6 (1.4, CHCl₃); v max/cm⁻¹ 3365, 2960, 2870, 2775, 1450, 1045; ¹H NMR (400 MHz, CDCl₃) δ = 3.45 (1H, dd, J 10.5 and 3.5 Hz, CHO), 3.27 (1H, dd, J 10.5 and 7 Hz, CHO), 3.13−3.09 (1H, quin, J 4.5 Hz, CHN), 2.87−2.37 (5H, m, 5 x CHN), 2.21 (6H, s, N(CH₃)₂), 1.87−1.45 (4H, m, 4 x CH), 0.86 (3H, d, J 6.6 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ = 64.9, 64.4, 59.8, 56.9, 56.3, 39.4, 27.9, 24.2, 9.7; HRMS (ES) Found MH⁺ = 187.1817, C₁₀H₁₇N₂O requires MH⁺ = 187.1810; LRMS m/z (ES) 187 (100%, MH⁺).

Data for ligand 12, prepared from N-Boc-N-methyl-d-alanine and l-proline methyl ester hydrochloride:
Data for ligand 13, prepared from N-Boc-N-methyl-L-leucine and L-proline methyl ester hydrochloride:

$[\alpha]^{23}_{D} +56.7$ (1.2, CHCl$_3$); $\nu_{\text{max}}$/cm$^{-1}$ 3330, 2960, 2860, 2820, 1455, 1260, 1080, 1010; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.41 (1H, dd, J 10.5 and 3.5 Hz, CHOH), 3.24 (1H, dd, J 10.5 and 7.5 Hz, CHOH), 3.21–3.16 (1H, quin, J 4.5 Hz, CHN), 2.72–2.41 (4H, m, 4 x CHN), 2.38 (1H, q, J 8.5 Hz, CHN), 2.17 (6H, s, N(CH$_3$)$_2$), 1.83–1.25 (6H, m, 5 x CH, OH), 0.97–0.80 (8H, m, 2 x CH, 2 x CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 66.1, 64.4, 59.8, 59.5, 56.1, 40.2, 27.9, 24.1, 10.3; HRMS (ES) Found MH$^+$ = 187.1806, C$_{10}$H$_{23}$N$_2$O requires MH$^+$ = 187.1810; LRMS m/z (ES) 187 (100%, MH$^+$).

Data for ligand 14, prepared from N-Boc-N-methyl-L-leucine and L-proline methyl ester hydrochloride:

$[\alpha]^{23}_{D}$ +50.0 (1.2, CHCl$_3$); $\nu_{\text{max}}$/cm$^{-1}$ 3325, 2955, 2865, 2820, 1460, 1260, 1080, 1010; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.50 (1H, dd, J 11 and 3 Hz, CHOH), 3.30 (1H, dd, J 11 and 5.5 Hz, CHOH), 3.21–3.16 (1H, m, CHN), 2.79–2.53 (3H, m, 3 x CHN), 2.40–2.33 (1H, m, CHN), 2.27–2.23 (1H, m, CHN), 2.20 (6H, s, N(CH$_3$)$_2$), 1.83–1.39 (5H, m, 4 x CH, OH), 1.23–1.14 (1H, m, CH), 0.91–0.81 (2H, m, 2 x CH), 0.89 (3H, d, J 6.5 Hz, CH$_3$), 0.86 (3H, d, J 6.5 Hz, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 66.1, 64.6, 62.8, 57.1, 56.0, 40.0, 34.3, 27.9, 25.7, 24.1, 23.8, 22.0; HRMS (ES) Found MH$^+$ = 229.2287, C$_{13}$H$_{29}$N$_2$O requires MH$^+$ = 229.2280; LRMS m/z (ES) 229 (100%, MH$^+$).

Data for ligand 15, prepared from N-Cbz-N-methyl-L-tert-butylglycine$^2$ and L-proline methyl ester hydrochloride:

$[\alpha]^{23}_{D}$ +41.2 (0.85, EtOH); $\nu_{\text{max}}$/cm$^{-1}$ 3375, 2945, 1040; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 3.60 (1H, dd, J 11.0 and 4.0, CHOH), 3.36 (1H, dd, J 11.0 and 4.0, CHOH), 3.24–3.14 (1H, m, CHN), 2.73 (1H, dd, J 13.5 and 5.5, CHN), 2.58–2.57 (1H, m, CHN), 2.54 (1H, dd, J 13.5 and 7.0, CHN), 2.44 (6H, s, 2 x CH$_3$), 2.40–2.33 (2H, m, 2 x CHN), 1.93–1.80 (1H, m, CH) 1.77–1.61 (3H, m, 3 x CH), 0.94 (9H, s, t-Bu); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 70.1, 65.5, 62.8, 55.3, 52.0, 43.0, 37.3, 28.5, 27.7, 23.9; HRMS (ES) Found MH$^+$ = 229.2260, C$_{13}$H$_{29}$N$_2$O requires MH$^+$ = 229.2280; LRMS m/z (ES) 229 (100%, MH$^+$).

Data for ligand 16, prepared from N-Cbz-N-methyl-L-tert-butylglycine$^2$ and L-proline methyl ester hydrochloride:

$[\alpha]^{23}_{D}$ +69.5 (1.05, EtOH); $\nu_{\text{max}}$/cm$^{-1}$ 3365, 2950, 2860, 1045; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 3.62 (1H, dd, J 11.0 and 3.5, CHOH), 3.34 (1H, dd, J 11.0 and 3.5, CHOH), 3.28–3.23 (1H, m, CHN), 2.90 (1H, dd, J 13.0 and 11.0, CHN), 2.64–2.54 (1H, m, CHN), 2.51 (6H, s, 2 x CH$_3$), 2.38 (1H, dd, J 11.0 and 2.0, CHN), 2.36 (1H, dd, J 13.0 and 2.0, CHN), 2.31–2.23 (1H, m, CHN), 1.96–1.80 (1H, m, CH) 1.77–1.65 (3H, m, 3 x CH), 0.93 (9H, s, t-Bu); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 71.1, 65.8, 62.9, 54.6, 53.4, 43.1, 36.6, 28.5, 27.8, 23.9; HRMS (ES) Found MH$^+$ = 229.2275, C$_{13}$H$_{29}$N$_2$O requires MH$^+$ = 229.2280; LRMS m/z (EI) 171 (4%, M$^+$ – C$_4$H$_4$O), 114 (100).

Data for ligand 17, prepared from N-Boc-N-methyl-L-valine and L-pipeoline methyl ester hydrochloride:

$[\alpha]^{23}_{D}$ +20.7 (1.1, EtOH); $\nu_{\text{max}}$/cm$^{-1}$ 3400, 2920; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.39 (1H, dd, J 11.5 and 9.0, CH$_3$), 3.34 (1H, dd, J 11.5 and 5.0, CHOH), 2.79 (1H, ddt, J 13.5, 4.0 and 1.0, CHN), 2.74–2.64 (1H, m, CHN), 2.60–2.50 (1H, m, CHN), 2.45 (1H, dd, J 14.5 and 8.0, CHN), 2.36 (1H, dd,
Data for ligand 18, prepared from N-Boc-N-methyl-L-valine and d-pipecoline methyl ester hydrochloride:

\([\alpha]_D^{23} +78.3 (1.0, \text{EtOH}); \nu_{\max} / \text{cm}^{-1} 3380, 2930; \) \(1^H \text{NMR (} 400 \text{ MHz, CDCl}_3 \) \(\delta = 3.84 (1H, \text{dd, } J 12.0 \text{ and } 3.5, \text{CH}_2, 3.25 (1H, \text{dd, } J 12.0 \text{ and } 2.0, \text{CH}_2OH), 2.90 (1H, dt, } J 12.0 \text{ and } 3.5, \text{CHN}), 2.71 (1H, dd, } J 14.5 \text{ and } 9.5, \text{CHN}), 2.34 (6H, s, N(CH_2)_2), 2.26–2.13 (3H, m, 3 \times \text{CHN}), 1.97–1.81 (2H, m, \text{CHN and CH}), 1.80–1.65 (2H, m, 2 \times \text{CH}), 1.60–1.36 (3H, m, 3 \times \text{CH}), 1.34–1.19 (1H, m, CH), 0.95 (3H, d, J 7.0, CH3), 0.87 (3H, d, J 7.0, CH3); \) \(1^3\text{C NMR (} 100 \text{ MHz, CDCl}_3 \) \(\delta = 69.6, 62.9, 61.4, 53.6, 51.3, 41.3, 28.8, 25.7, 25.4, 24.0, 22.9, 19.5); \) HRMS (ES) Found MH\(^+\) = 229.2281, C_{13}H_{20}N_2O requires MH\(^+\) = 229.2280; LRMS m/z (ES) 229 (100%, MH\(^+\)).

Data for ligand 19, prepared from 2-dimethylamino-2-methylpropan-1-ol and L-proline methyl ester hydrochloride followed by LiAlH\(_4\) reduction, according to the procedure described above (see procedure for compound 26):

\([\alpha]_D^{23} +9.1 (0.9, \text{EtOH}); \nu_{\max} / \text{cm}^{-1} 3432, 2935; \) \(1^H \text{NMR (} 400 \text{MHz CDCl}_3 \) \(\delta = 3.38 (1H, \text{dd, } J 9.5 \text{ and } 4.5, \text{CH}), 3.30 (1H, dd, } J 10 \text{ and } 5, \text{CH}), 3.27–3.21 (1H, m, CH), 2.98–2.89 (1H, m, CH), 2.87–2.79 (1H, m, CH), 2.40–2.35 (1H, m, CH), 2.32 (6H, s, 2 \times \text{CH}_3), 2.27–2.22 (1H, m, CH), 1.80–1.57 (4H, m, 2 \times \text{CH}_2), 1.09 (6H, d, J 13, 2 \times \text{CH}_2); \) \(1^3\text{C NMR (} 100 \text{ MHz, CDCl}_3 \) \(\delta = 68.9, 66.6, 58.0, 47.9, 47.8, 30.8, 25.0, 24.1, 23.7); \) HRMS (ES) Found MH\(^+\) = 201.1969, C_{11}H_{25}N_2O requires MH\(^+\) = 201.1967; LRMS m/z (ES) 227 (100%, MH\(^+\)).

Data for ligand 21, prepared from N-Boc-L-proline and N-methyl-glycine ethyl ester hydrochloride:

\([\alpha]_D^{23} –131.0 (0.6, \text{EtOH}); \nu_{\max} / \text{cm}^{-1} 3255, 2945, 2780, 1035; \) \(1^H \text{NMR (} 250 \text{ MHz, CDCl}_3 \) \(\delta = 4.65 (1H, \text{br, OH}), 3.57 (2H, t, } J 5.5, \text{CH}_2OH), 3.20–3.11 (1H, m, CHN), 3.66–2.20 (6H, m, 3 \times \text{CH}_2N), 2.44 (3H, s, \text{CH}_3), 2.29 (3H, s, \text{CH}_3), 2.00–1.50 (4H, m, 2 \times \text{CH}_2); \) \(1^3\text{C NMR (} 63 \text{ MHz, CDCl}_3 \) \(\delta = 64.2, 61.5, 59.9, 59.0, 57.4, 43.2, 41.7, 30.0, 22.7); \) HMRS (ES) Found MH\(^+\) = 173.1661, C_{9}H_{21}N_2O requires MH\(^+\) = 173.1654; LRMS m/z (ES) 173 (100%, MH\(^+\)).

Data for ligand 22, prepared from N-Boc-L-proline and N-methyl-L-valine methyl ester hydrochloride:

\([\alpha]_D^{23} –81.2 (1.6, \text{EtOH}); \nu_{\max} / \text{cm}^{-1} 3265, 2935, 2825, 1065; \) \(1^H \text{NMR (} 400 \text{ MHz, CDCl}_3 \) \(\delta = 3.90 (1H, \text{br s, OH}), 3.55 (1H, dd, } J 10.5 \text{ and } 5, \text{CHOH}), 3.23 (1H, t, J 10.5, \text{CHOH}), 3.06–2.97 (1H, m, CHN), 2.81 (1H, dd, } J 13.5 \text{ and } 5, \text{CHN}), 2.47 (1H, dd, } J 13.5 \text{ and } 7, \text{CHN}), 2.40–2.15 (2H, m, 2 \times \text{CHN}), 2.36 (3H, s, \text{CH}_3N), 2.35 (3H, s, \text{CH}_2N), 2.23–2.12 (1H, m, CHN), 2.0–1.88 (1H, m, CH), 1.87–1.61 (3H, m, \text{CH}_2 + \text{CH}), 1.58–1.45 (1H, m, CH), 0.93 (3H, d, J 7, \text{CH}_3), 0.80 (3H, d, J 7, \text{CH}_3); \) \(1^3\text{C NMR (} 100 \text{ MHz, CDCl}_3 \) \(\delta = 72.3, 64.9, 60.4, 59.9, 57.2, 42.0, 36.8, 29.8, 28.2, 23.0, 21.9, 19.9); \) HMRS (ES) Found MH\(^+\) = 215.2128, C_{12}H_{25}N_2O requires MH\(^+\) = 215.2123; LRMS m/z (ES) 215 (100%, MH\(^+\)).

Data for ligand 23, prepared from N-Boc-d-proline and N-methyl-L-valine methyl ester hydrochloride:

\([\alpha]_D^{23} +83.7 (0.9, \text{EtOH}); \nu_{\max} / \text{cm}^{-1} 3150, 2950, 2870, 1055; \) \(1^H \text{NMR (} 400 \text{ MHz, CDCl}_3 \) \(\delta = 4.12 (1H, \text{br s, OH}), 3.53 (1H, dd, } J 10.5 \text{ and } 5, \text{CHOH}), 3.16 (1H, t, J 10.5, \text{CHOH}), 3.07–2.98 (1H, m, CHN), 2.75 (1H, dd, } J 13 \text{ and } 4.5, \text{CHN}), 2.56–2.48 (1H, m, CHN), 2.40 (3H, s, \text{CH}_3N), 2.38–2.27 (2H, m, 2 \times \text{CHN}), 2.34 (3H, s, \text{CH}_3N), 2.24–2.14 (1H, m, CHN), 2.04–1.90 (1H, m, CH), 1.88–1.62 (3H, m, \text{CH}_2 + \text{CH}), 1.59–1.46 (1H, m, CH), 0.97 (3H, d, J 6.5, \text{CH}_3), 0.81 (3H, d, J 7, \text{CH}_3); \) \(1^3\text{C NMR (} 100 \text{ MHz, CDCl}_3 \) \(\delta = 71.6, 65.0, 59.9, 59.1, 57.2, 41.8, 38.2, 30.1, 27.9, 22.7, 22.3, 19.9; \)
HMRS (ES) Found MH\(^+\) = 215.2124, C\(_{12}H_7N_3O\) requires MH\(^+\) = 215.2123; LRMS m/z (ES) 215 (100%, MH\(^+\)).

Data for ligand 24, prepared from (R)-styrene oxide and dimethylamine,\(^4\) followed by L-proline methyl ester hydrochloride then LiAlH\(_4\) reduction, according to the procedure described below (see procedure for compound 26):

[\(\alpha\)]\(_D\)\(^{24} = -81.2 \) (1.1, CHCl\(_3\)); \(\nu_{\text{max}} \) /cm\(^{-1}\) 3340, 2945, 2890, 2830, 1630, 1555, 1040; \(^1\)H NMR (400 MHz CDCl\(_3\)) \(\delta\) = 7.42–7.25 (3H, m, Ph), 7.22–7.15 (2H, m, Ph), 4.08 (1H, dd, J 11 and 4, CH), 3.75 (1H, dd, 11 and 3.5, CH), 3.41 (1H, dd, J 11 and 4.5, CH), 3.14–3.07 (1H, m, CH), 2.96 (1H, dd, 12.5 and 10, CH), 2.91–2.85 (1H, m, CH), 2.51 (1H, dd, J 12.5 and 4, CH), 2.36 (6H, s, N(CH\(_2\)_2)), 2.30–2.20 (1H, m, CH), 1.75–1.60 (3H, m, 3 x CH), 1.57–1.48 (1H, m, CH); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) = 138.6, 128.5, 128.1, 127.2, 64.1, 62.8, 61.5, 60.9, 46.6, 46.4, 27.9, 23.7; HRMS (ES) Found MH\(^+\) = 249.1960, C\(_{13}H_{25}N_3O\) requires MH\(^+\) = 249.1967; LRMS m/z (ES) 249 (100%, MH\(^+\)).

Data for ligand 25, prepared from (R)-styrene oxide and dimethylamine,\(^4\) followed by D-proline methyl ester hydrochloride then LiAlH\(_4\) reduction, according to the procedure described below (see procedure for compound 26):

[\(\alpha\)]\(_D\)\(^{24} = -31.1 \) (1.1, CHCl\(_3\)); \(\nu_{\text{max}} \) /cm\(^{-1}\) 3355, 2945, 2860, 2820, 1645, 1455, 1040; \(^1\)H NMR (400 MHz CDCl\(_3\)) \(\delta\) = 7.42–7.27 (5H, m, Ph), 3.96 (1H, dd, J 11.5 and 5.5, CH), 3.80–3.75 (1H, m, CH), 3.45–3.30 (2H, m, CH\(_2\)), 3.17 (1H, dd, J 12.5 and 11.5, CH), 3.09–3.01 (1H, m, CH), 2.84–2.76 (1H, m, CH), 2.33 (6H, s, N(CH\(_2\)_2)), 2.26–2.18 (1H, m, CH), 1.64–1.55 (1H, m, CH), 1.45–1.26 (3H, m, 3 x CH); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) = 128.5, 128.4, 127.5, 65.9, 62.7, 61.3, 58.6, 52.4, 44.5, 28.7, 24.2; HRMS (ES) Found MH\(^+\) = 249.1960, C\(_{15}H_{25}N_3O\) requires MH\(^+\) = 249.1967; LRMS m/z (ES) 249 (100%, MH\(^+\)).

As a representative procedure,\(^5\) the ligand 26 was prepared as follows:

To a solution of (1R,2S)-(--)-N-methylephedrine (0.5 g, 2.78 mmol) in dry THF (10 mL) was added Et\(_3\)N (1.16 mL, 8.36 mmol) at 0 °C followed by dropwise addition of methanesulfonfyl chloride (0.43 mL, 5.57 mmol). After 1 h, the solvent was removed under reduced pressure. The residue was dissolved in toluene (8 mL) and a solution of L-proline methyl ester hydrochloride (554 mg, 3.34 mmol) and Et\(_3\)N (0.77 mL, 5.57 mmol) in toluene (5 mL) was added and the mixture was heated at 90 °C. After 12 h, aqueous NaOH (2 N) was added (to pH 12) and the mixture was extracted with CH\(_2\)Cl\(_2\) (2 x 25 mL). The organic layer was washed with brine (20 mL), dried (Na\(_2\)SO\(_4\)), evaporated and purified by column chromatography on silica, eluting with CH\(_2\)Cl\(_2\)-MeOH (19:1), to give the ester (583 mg, 72%) as an oil; R\(_f\) 0.53 [CH\(_2\)Cl\(_2\)-MeOH (9:1)]; [\(\alpha\)]\(_D\) = -144.7 (1.0, CHCl\(_3\)); \(\nu_{\text{max}} \) /cm\(^{-1}\) 2965, 1745; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) = 7.39–7.12 (5H, m, Ph), 3.77 (3H, s, CH\(_3\)O), 3.75 (1H, d, J 10.5, CHN), 3.35–3.25 (1H, m, CHN), 3.21 (1H, dd, J 9 and 5.5, CHN), 2.92–2.86 (1H, m, CHN), 2.38–2.28 (1H, m, CHN), 2.14 (6H, s, N(CH\(_2\)_2)), 1.90–1.67 (3H, m, 3 x CH), 1.65–1.54 (1H, m, CH), 1.20 (3H, d, J 6.5, CH\(_3\)); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) = 175.1, 135.9, 129.3, 127.6, 126.8, 66.5, 61.7, 58.7, 51.5, 44.9, 40.1, 28.5, 23.2, 8.2; HRMS (ES) Found MH\(^+\) = 291.2076, C\(_{11}H_{17}N_2O_2\) requires MH\(^+\) = 291.2073; LRMS (ES) m/z 313 (11%, MNa\(^+\)), 291 (100, MH\(^+\)).

To a stirred suspension of LiAlH\(_4\) (0.588 g, 15.5 mmol) in THF (10 mL) cooled to 0 °C was added dropwise a solution of the amide above (1.5 g, 5.17 mmol) in THF (10 mL). The mixture was stirred for 10 min at room temperature and then was heated under reflux for 5 h. The mixture was cooled to 0 °C and was carefully quenched by slow addition of EtOAc. A slurry of Na\(_2\)SO\(_4\)/H\(_2\)O was added while the mixture was vigorously stirred until all the salts appeared white. The solvent was decanted, and the remaining white solid was washed several times with EtOAc. The combined organic layers were washed with HCl (aq) (2 M, 150 mL). The aqueous layer was extracted with EtOAc (2 x 200 mL) and then basified with NaOH pellets and extracted with EtOAc (3 x 80 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and then concentrated and purified by Kugelrohr distillation (220 °C, 5 mm Hg), to give the ligand 26 (1.25 g, 92%) as an oil; [\(\alpha\)]\(_D\)\(^{23} = -121.3 \) (0.75, EtOH); \(\nu_{\text{max}} \) /cm\(^{-1}\) 3380, 2910,
The absolute $\Delta^h$; $\gamma$ conversion to the $\Delta^h$; $\gamma$-S$_2$H-\--H$^-$\text{ate} 0.5 mL per min, detection at 254 nm, $\text{R}$ configuration was verified by X-$\text{max}$N). 2.14 (6H, s, N(CH$_3$)$_2$), 1.74--1.40 (4H, m, 4 x CH), 1.12 (3H, d, J 6.5, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 136.1, 129.3, 127.6, 126.9, 64.8, 60.8, 59.1, 58.8, 45.5, 40.1, 27.2, 23.3, 8.9; HRMS (ES) Found $\text{MH}^+$ = 263.2114, C$_{16}$H$_{27}$N$_2$O requires $\text{MH}^+$ = 263.2123; LRMS (ES) m/z 263 (32%, $\text{MH}^+$), 162 (100).

Data for ligand 27, prepared from (1S,2R)-(+)\-N-methylamphetamine and L-proline methyl ester hydrochloride:

$[\alpha]_D^{23} +15.5$ (1.1, EtOH); $\nu_{\text{max}}$/cm$^{-1}$ 3385, 2930, 2820; $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.40--7.16 (5H, m, Ph), 3.76 (1H, d, J 9.5, CHN), 3.55 (1H, dd, J 10.5 and 3.5, CHOH), 3.39--3.11 (2H, m, 2 x CHN), 3.10--2.80 (3H, m, 2 x CHN), 2.14 (6H, s, N(CH$_3$)$_2$), 1.80--1.50 (4H, m, 4 x CH), 1.15 (3H, d, J 6.5, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 140.2, 128.6, 127.7, 126.5, 68.3, 64.9, 59.8, 59.7, 51.4, 40.3, 29.4, 24.2, 9.2; HRMS (ES) Found $\text{MH}^+$ = 263.2117, C$_{16}$H$_{27}$N$_2$O requires $\text{MH}^+$ = 263.2123; LRMS (ES) m/z 263 (100%, $\text{MH}^+$).

Data for ligand 28, prepared from (1S,2S)-(+)\-N-methylpseudoephedrine and L-proline methyl ester hydrochloride:

$[\alpha]_D^{22} +16.9$ (1.4, EtOH); $\nu_{\text{max}}$/cm$^{-1}$ 3385, 2935, 2825; $^1$H NMR (400 MHz CDCl$_3$) $\delta =$ 7.40--7.19 (5H, m, Ph), 3.56 (1H, d, J 11.5, CH), 3.45 (1H, dd, J 10.5 and 3.5, CH), 3.36--3.25 (2H, m, 2 x CH), 3.24--3.16 (1H, m, CH), 3.11--3.04 (1H, m, CH), 2.85--2.75 (1H, m, CH), 2.32 (6H, s, N(CH$_3$)$_2$), 1.57--1.47 (1H, m, CH), 1.35--1.09 (3H, m, 3 x CH), 0.64 (3H, d, J 6.5, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 138.3, 128.8, 128.3, 127.3, 69.6, 65.5, 58.7, 58.4, 53.1, 38.7, 28.4, 23.9, 8.1; HRMS (ES) Found $\text{MH}^+$ = 263.2132, C$_{16}$H$_{27}$N$_2$O requires $\text{MH}^+$ = 263.2123; LRMS (ES) m/z 263 (100%, $\text{MH}^+$), 162 (82).

Data for ligand 29, prepared from (1S,2S)-(+)\-N-methylpseudoephedrine and D-proline methyl ester hydrochloride:

$[\alpha]_D^{23} +90.0$ (0.5, EtOH); $\nu_{\text{max}}$/cm$^{-1}$ 3345, 2970, 2930, 1670, 1410, 1255, 1160; $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.28--7.10 (5H, m, Ph), 6.29 (1H, br, OH), 3.69 (1H, dd, J 11 and 3 Hz, CHOH), 3.61 (1H, d, J 11 Hz, CH), 3.33 (1H, dd, J 11 and 3 Hz, CHOH), 3.21--3.19 (1H, m, CHN), 2.92 (1H, t, J 6.5 Hz, CHN), 2.79--2.69 (1H, m, CHN), 2.40--2.15 (1H, m, CHN), 2.32 (6H, s, N(CH$_3$)$_2$), 1.69--1.12 (4H, m, 4 x CH), 0.64 (3H, d, J 6.5 Hz, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 136.1, 129.5, 127.9, 127.0, 65.0, 62.5, 60.1, 59.6, 46.2, 40.7, 27.8, 23.6, 9.9; HRMS (ES) Found $\text{MH}^+$ = 263.2120, C$_{16}$H$_{27}$N$_2$O requires $\text{MH}^+$ = 263.2123; LRMS m/z (ES) 263 (100%, $\text{MH}^+$).

For the formation of (S)-3 (51% yield, $\text{er}$ 79:21) by dynamic thermodynamic resolution, see the main paper: Notes and references section.

An authentic sample of (S)-3 was prepared according to the literature;\textsuperscript{6} this was converted to the p-bromobenzoate derivative as reported and the $\text{er}$ (87:13) was determined by chiral HPLC as reported [(Chiracel OD column, hexane--PrOH 99.5:0.5, flow rate 0.5 mL per min, detection at 254 nm, retention times: 22.8 min (major) and 24.9 min (minor)] and by GC [β-cyclodextrin-permethylated 120 fused silica capillary column 30 m $\times$ 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 27.5 min (major) and 28.2 min (minor) (at 85 °C)]. The absolute configuration was verified by X-ray crystal structure analysis of the p-bromobenzoate derivative and was in line with that reported.\textsuperscript{6}

The piperidine 30 was prepared in the same way as the piperidine 3 (see main paper: Notes and references section).

Data for the piperidine (S)-30, [\(\alpha\)]\_D\textsuperscript{24} +28 (1.0, CHCl$_3$) \[lit.\] for (R)-30, er 99:1, [\(\alpha\)]\_D\textsuperscript{24} --42.2 (1.8, CHCl$_3$)], er 80:20, determined by conversion to the silane 3 (by treatment with $n$-BuLi, Et$_2$O, SI page 6.
TMEDA, –78 °C then TMSCl) followed by chiral GC as above. Other data in accordance with the literature.\textsuperscript{8}

The piperidine 31 was prepared in the same way as the piperidine 3, except that the reaction was quenched at –78 °C with water prior to warming to room temperature. Data for the piperidine \((R)-31\), \([\alpha]_D^{21} \pm 37.0\) (0.55, CHCl\(_3\)) \([\text{lit.}\textsuperscript{9} \text{for} \((S)-31\), \text{er} 100:0, [\alpha]_D \pm 77.4 \text{ (1.4, CHCl\(_3\))}, \text{er} 77:23]\), determined by chiral stationary phase GC [\(\beta\)-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d., 20% permethylated \(\beta\)-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 8.1 min (minor) and 8.4 min (major) (at 120 °C)]. Other data in accordance with the literature.\textsuperscript{8}

The piperidine 32 was prepared as follows: \(N\)-Boc-piperidine (580 mg, 3.1 mmol) and TMEDA (0.52 mL, 3.4 mmol) in Et\(_2\)O (6 mL) were treated with sec-BuLi (2.46 mL, 3.4 mmol, 1.4 M in hexane) at –78 °C. After 3 h, the deprotonated ligand 7 [prepared by adding sec-BuLi (2.80 mL, 3.9 mmol, 1.4 M in hexane) to 7 (0.80 g, 3.8 mmol) in Et\(_2\)O (6 mL) at 0 °C] was added. The mixture was warmed to –40 °C. After 90 min the mixture was cooled to –78 °C and a solution of ZnCl\(_2\) (0.56 mg, 4.1 mmol) in THF (5 mL) was added slowly. After 30 min a solution of CuCN·2LiCl [prepared from CuCN (340 mg, 3.8 mmol) and LiCl (325 mg, 7.6 mmol)] in THF (12 mL) was added. After 30 min allyl bromide (0.81 mL, 9.4 mmol) was added. The mixture was allowed to warm slowly (over 18 h) to room temperature and a solution of NH\(_4\)Cl was added. The organic layer was dried (Na\(_2\)SO\(_4\)) and evaporated. Purification by column chromatography on silica, eluting with petrol (b.p. 40–60 °C)–EtOAc (98:2) gave the piperidine 32 (376 mg, 47%) as an oil; \([\alpha]_D^{24} +40.0\) (0.85, CHCl\(_3\)) \([\text{lit.}\textsuperscript{10} \text{for} \((S)-32\), \text{er} 100:0, [\alpha]_D \pm 49.2 \text{ (0.9, CHCl\(_3\))}, \text{er} 79:21]\), determined by chiral stationary phase GC [\(\beta\)-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d., 20% permethylated \(\beta\)-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 10.0 min (major) and 10.6 min (minor) (at 110 °C)]. Other data in accordance with the literature.\textsuperscript{10}
GC and HPLC traces:

Piperidine (S)-3 (er 79:21) prepared by dynamic thermodynamic resolution using ligand 7. GC column: β-cyclodextrin-permethylated 120 fused silica capillary column 30 m x 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 31.5 min (major) and 32.4 min (minor) (at 85 °C).

Piperidine (R)-31: er 77:23
GC column: β-cyclodextrin-permethylated 120 fused silica capillary column 30 m x 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 8.1 min (minor) and 8.4 min (major) (at 120 °C).
Piperidine (R)-32: er 79:21
GC column: β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 10.0 min (major) and 10.6 min (minor) (at 110 °C).