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 $LiAlH_4$ 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 $LiAlH_4$ 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-valine[2] (3.53 g, 15.2 mmol) in $CHCl_3$ (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 Et_3N (4.23 mL, 30.5 mmol) in $CHCl_3$ (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% $NaHCO_3$ (40 mL). The organic layer was dried (Na_2SO_4), 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 (CH_2Cl_2–*n*-hexane); R_f 0.32 [*n*-hexane–EtOAc (7:3)]; m.p. = 126–128 °C; $[\alpha]^{23}_D$ −172.5 (0.4, $CHCl_3$); ν_{max} /cm^{-1} 2965, 1740, 1670, 1635; ^{1}H NMR (250 MHz, $CDCl_3$) (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, CH_2N), 3.72, 3.71 and 3.68 (3H, 3s, CH_3O), 2.83, 2.82, 2.79, 2.68 and 2.56 (3H, 5s, CH_3N), 2.44–1.75 [5H, m, $(CH_2)_2$ + 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, CH_3), 0.86 and 0.80 (3.2H, 2d, *J* 6.5 and 7.0, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) (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, 18.4 and 18.4; HMRS (ES^+) Found MH^+ = 343.2221, $C_{17}H_{31}N_2O_5$ requires MH^+ = 343.2233; LRMS *m/z* (ES^+) 343 (100%, MH^+), 287 (99); Found C, 59.08; H, 8.99; N, 8.21, $C_{17}H_{30}N_2O_5$ 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 $LiAlH_4$ (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 Na_2SO_4/H_2O 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 Na_2SO_4 and then concentrated and purified by Kugelrohr distillation (155 °C, 4 mm Hg), to give the ligand **7** (1.0 g, 57%); $[\alpha]^{23}_D$ −22.3 (2.1, EtOH); ν_{max} /cm^{-1} 3340, 2950, 2870, 1035; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.46 (1H, dd, *J* 10.5 and 3.5, C*H*OH), 3.27 (1H, dd, *J* 10.5 and 6.5, C*H*OH), 3.20–3.07 (1H, m, CHN), 2.75–2.25 (5H, m, 5 x CHN), 2.23 (6H, s, $N(CH_3)_2$), 2.13–1.60 (4H, m, 4 x CH), 1.64–1.42 (1H, m, CH), 0.91 (3H, d, *J* 7.0, CH_3), 0.90 (3H, d, *J* 7.0, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 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, $C_{12}H_{27}N_2O$ 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:
$[\alpha]^{23}_D$ +116.0 (0.9, EtOH); ν_{max} /cm^{-1} 3335, 2955, 2865, 1043; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.54 (1H, dd, *J* 11.0 and 3.5, C*H*OH), 3.31 (1H, dd, *J* 11.0 and 5.0, C*H*OH), 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, $N(CH_3)_2$), 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, CH_3), 0.86 (3H, d, *J* 7.0, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 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, $C_{12}H_{27}N_2O$ 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:
$[\alpha]^{22}_D$ +59.8 (1.2, $CHCl_3$); ν_{max} /cm^{-1} 3360, 2960, 2910, 1260, 1010; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.43 (1H, dd, *J* 10.5 and 3.5 Hz, CHOH), 3.25 (1H, dd, *J* 10.5 and 7.5 Hz, CHOH), 3.13 (1H, quin, *J* 4.5 Hz, CHN), 2.71–2.37 (5H, m, 5 x CHN), 2.29 (6H, s, $N(CH_3)_2$), 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, CH_3), 0.86 (3H, d, *J* 7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 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; HRMS (ES) Found MH^+ = 229.2291, $C_{13}H_{29}N_2O$ 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:
$[\alpha]^{22}_D$ +50.6 (1.2, $CHCl_3$); ν_{max} /cm^{-1} 3360, 2961, 2910, 1255, 1005; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.31 (1H, br, OH), 3.52 (1H, dd, *J* 11 and 3 Hz, C*H*OH), 3.30 (1H, dd, *J* 11 and 5 Hz, C*H*OH), 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, $N(CH_3)_2$), 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, CH_3), 0.81 (3H, d, *J* 7 Hz, CH_3); ^{13}C NMR (100 MHZ, $CDCl_3$) 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, $C_{13}H_{29}N_2O$ 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:
$[\alpha]^{22}_D$ +48.6 (1.4, $CHCl_3$); υ_{max}/cm^{-1} 3365, 2960, 2870, 2775, 1450, 1045; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.45 (1H, dd, *J* 10.5 and 3.5 Hz, C*H*OH), 3.27 (1H, dd, *J* 10.5 and 7 Hz, C*H*OH), 3.13–3.09 (1H, quin, *J* 4.5 Hz, CHN), 2.87–2.37 (5H, m, 5 x CHN), 2.21 (6H, s, $N(CH_3)_2$), 1.87–1.45 (4H, m, 4 x CH), 0.86 (3H, d, *J* 6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 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, $C_{10}H_{23}N_2O$ 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:

$[\alpha]^{22}_D$ –17.7 (1.5, $CHCl_3$); υ_{max}/cm^{-1} 3365, 2960, 2870, 2775, 1450, 1045; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.22 (1H, br, OH), 3.49 (1H, dd, *J* 11 and 3.5 Hz, C*H*OH), 3.31 (1H, dd, *J* 11 and 5.5 Hz, C*H*OH), 3.27–3.14 (1H, m, CHN), 2.79–2.21 (5H, m, 5 x CHN), 2.21 (6H, s, $N(CH_3)_2$), 1.85–1.55 (4H, m, 4 x CH), 0.82 (3H, d, *J* 6 Hz, CH_3); ^{13}C NMR (100 MHZ, $CDCl_3$) δ = 66.1, 64.4, 59.8, 59.5, 56.1, 40.2, 27.9, 24.1, 10.3; HRMS (ES) Found MH^+ = 187.1806, $C_{10}H_{23}N_2O$ requires MH^+ = 187.1810; LRMS m/z (ES) 187 (100%, MH^+).

Data for ligand **13**, prepared from *N*-Boc-*N*-methyl-L-leucine and L-proline methyl ester hydrochloride:
$[\alpha]^{22}_D$ +56.7 (1.2, $CHCl_3$); υ_{max}/cm^{-1} 3330, 2960, 2860, 2820, 1455, 1260, 1080, 1010; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.41 (1H, dd, *J* 10.5 and 3.5 Hz, C*H*OH), 3.24 (1H, dd, *J* 10.5 and 7.5 Hz, C*H*OH), 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, $CDCl_3$) δ = 65.0, 64.4, 59.1, 57.3, 56.4, 39.3, 34.9, 27.9, 25.6, 24.2, 23.4, 22.3; HRMS (ES) Found MH^+ = 229.2287, $C_{13}H_{29}N_2O$ requires MH^+ = 229.2280; LRMS m/z (ES) 229 (100%, MH^+).

Data for ligand **14**, prepared from *N*-Boc-*N*-methyl-D-leucine and L-proline methyl ester hydrochloride:
$[\alpha]^{22}_D$ –50.0 (1.2, $CHCl_3$); υ_{max}/cm^{-1} 3325, 2955, 2865, 2820, 1460, 1260, 1080, 1010; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.50 (1H, dd, *J* 11 and 3 Hz, C*H*OH), 3.30 (1H, dd, *J* 11 and 5.5 Hz, C*H*OH), 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, $CDCl_3$) δ = 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, $C_{13}H_{29}N_2O$ 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); ν_{max} /cm^{-1} 3375, 2945, 1040; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.60 (1H, dd, *J* 11.0 and 4.0, C*H*OH), 3.36 (1H, dd, *J* 11.0 and 4.0, C*H*OH), 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, $CDCl_3$) δ = 70.1, 65.5, 62.8, 55.3, 52.0, 43.0, 37.3, 28.5, 27.7, 23.9; HMRS (ES) Found MH^+ = 229.2260, $C_{13}H_{29}N_2O$ 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 D-proline methyl ester hydrochloride:
$[\alpha]^{23}_D$ +69.5 (1.05, EtOH); ν_{max} /cm^{-1} 3365, 2950, 2860, 1045; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.62 (1H, dd, *J* 11.0 and 3.5, C*H*OH), 3.34 (1H, dd, *J* 11.0 and 3.5, C*H*OH), 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, $CDCl_3$) δ = 71.1, 65.8, 62.9, 54.6, 53.4, 43.1, 36.6, 28.5, 27.8, 23.9; HMRS (ES) Found MH^+ = 229.2275, $C_{13}H_{29}N_2O$ requires MH^+ = 229.2280; LRMS *m/z* (EI) 171 (4%, $M^+ - C_4H_9$), 114 (100).

Data for ligand **17**, prepared from *N*-Boc-*N*-methyl-L-valine and L-pipecoline methyl ester hydrochloride:
$[\alpha]_D^{23}$ +20.7 (1.1, EtOH); ν_{max} /cm^{-1} 3400, 2920 ; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.39 (1H, dd, *J* 11.5 and 9.0, C*H*OH), 3.34 (1H, dd, *J* 11.5 and 5.0, C*H*OH), 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,

J 14.5 and 3.0, CHN), 2.26 (6H, s, 2 x CH_3), 2.24–2.16 (1H, m, CHN), 1.81 (1H, spd, *J* 7.0 and 5.0, CH), 1.70–1.50 (1H, m, CH), 1.52–1.20 (4H, m, 4 x CH), 1.14–0.97 (1H, m, CH), 0.87 (3H, d, *J* 7.0, CH_3), 0.84 (3H, d, *J* 7.0, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 68.8, 62.6, 61.2, 51.1, 46.4, 41.3, 26.1, 24.2, 23.6, 22.4, 21.1, 19.6; HRMS (ES) Found MH^+ = 229.2275, $C_{13}H_{29}N_2O$ requires MH^+ = 229.2280; LRMS *m*/z (ES) 229 (100%, MH^+).

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, EtOH); ν_{max} /cm^{-1} 3380, 2930 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.84 (1H, dd, *J* 12.0 and 3.5, C*H*OH), 3.25 (1H, dd, *J* 12.0 and 2.0, C*H*OH), 2.90 (1H, dt, *J* 12.0 and 3.5, CHN), 2.71 (1H, dd, *J* 14.5 and 9.5, CHN), 2.34 (6H, s, $N(CH_3)_2$), 2.26–2.13 (3H, m, 3 x CHN), 1.97–1.81 (2H, m, CHN and CH), 1.80–1.65 (2H, m, 2 x CH), 1.60–1.36 (3H, m, 3 x CH), 1.34–1.19 (1H, m, CH), 0.95 (3H, d, *J* 7.0, CH_3), 0.87 (3H, d, *J* 7.0, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 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, $C_{13}H_{29}N_2O$ 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 below (see procedure for compound **26**):
$[\alpha]_D^{23}$ +9.1 (0.9, EtOH); ν_{max} /cm^{-1} 3432, 2935; ^{1}H NMR (400MHz $CDCl_3$) δ = 3.38 (1H, dd, *J* 9.5 and 4.5, CH), 3.30 (1H, dd, *J* 10 and 5, 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 x CH_3), 2.27–2.22 (1H, m, CH), 1.80–1.57 (4H, m, 2 x CH_2), 1.09 (6H, d, *J* 13, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 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:
$[\alpha]^{23}_D$ –131.0 (0.06, EtOH); ν_{max} /cm^{-1} 3255, 2945, 2780, 1035; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 4.65 (1H, br, OH), 3.57 (2H, t, *J* 5.5, C*H*$_2$OH), 3.20–3.11 (1H, m, CHN), 3.66–2.20 (6H, m, 3 x CH_2N), 2.44 (3H, s, CH_3), 2.29 (3H, s, CH_3), 2.00–1.50 (4H, m, 2 x CH_2); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 64.2, 61.5, 59.9, 59.0, 57.4, 43.2, 41.7, 30.0, 22.7; HMRS (ES) Found MH^+ = 173.1661, $C_9H_{21}N_2O$ 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:
$[\alpha]^{23}_D$ –81.2 (1.6, EtOH); ν_{max} /cm^{-1} 3265, 2935, 2825, 1065; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.90 (1H, br s, OH), 3.55 (1H, dd, *J* 10.5 and 5, C*H*OH), 3.23 (1H, t, *J* 10.5, C*H*OH), 3.06–2.97 (1H, m, CHN), 2.85 (1H, dd, *J* 13.5 and 5, CHN), 2.47 (1H, dd, *J* 13.5 and 7, CHN), 2.40–2.15 (2H, m, 2 x CHN), 2.36 (3H, s, CH_3N), 2.35 (3H, s, CH_3N), 2.23–2.12 (1H, m, CHN), 2.0–1.88 (1H, m, CH), 1.87–1.61 (3H, m, CH_2 + CH), 1.58–1.45 (1H, m, CH), 0.93 (3H, d, *J* 7, CH_3), 0.80 (3H, d, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 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, $C_{12}H_{27}N_2O$ 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:
$[\alpha]^{23}_D$ +83.7 (0.9, EtOH); ν_{max} /cm^{-1} 3150, 2950, 2870, 1055; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 (1H, br s, OH), 3.53 (1H, dd, *J* 10.5 and 5, C*H*OH), 3.16 (1H, t, *J* 10.5, C*H*OH), 3.07–2.98 (1H, m, CHN), 2.75 (1H, dd, *J* 13 and 4.5, CHN), 2.56–2.48 (1H, m, CHN), 2.40 (3H, s, CH_3N), 2.38–2.27 (2H, m, 2 x CHN), 2.34 (3H, s, CH_3N), 2.24–2.14 (1H, m, CHN), 2.04–1.90 (1H, m, CH), 1.88–1.62 (3H, m, CH_2 + CH), 1.59–1.46 (1H, m, CH), 0.97 (3H, d, *J* 6.5, CH_3), 0.81 (3H, d, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 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, $C_{12}H_{27}N_2O$ 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, $CHCl_3$); ν_{max} /cm^{-1} 3340, 2945, 2870, 2830, 1630, 1455, 1040; ^1H NMR (400 MHz $CDCl_3$) δ = 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, $N(CH_3)_2$), 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, $CDCl_3$) δ = 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, $C_{15}H_{25}N_2O$ 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, $CHCl_3$); ν_{max} /cm^{-1} 3355, 2945, 2860, 2820, 1645, 1455, 1040; ^1H NMR (400 MHz $CDCl_3$) δ = 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, $N(CH_3)_2$), 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, $CDCl_3$) δ = 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, $C_{15}H_{25}N_2O$ requires MH^+ = 249.1967; LRMS (ES) *m/z* 249 (100%, MH^+).

As a representative procedure,[5] the ligand **26** was prepared as follows:

To a solution of (1*R*,2*S*)-(–)-*N*-methylephedrine (0.5 g, 2.78 mmol) in dry THF (10 mL) was added Et_3N (1.16 mL, 8.36 mmol) at 0 °C followed by dropwise addition of methanesulfonyl 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_3N (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_2Cl_2 (2 x 25 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), evaporated and purified by column chromatography on silica, eluting with CH_2Cl_2–MeOH (19:1), to give the ester (583 mg, 72%) as an oil; R_f 0.53 [CH_2Cl_2–MeOH (9:1)]; $[\alpha]^{21}_D$ –144.7 (1.0, $CHCl_3$); ν_{max} /cm^{-1} 2965, 1745; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.12 (5H, m, Ph), 3.77 (3H, s, CH_3O), 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, $N(CH_3)_2$), 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, $CDCl_3$) δ = 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, $C_{17}H_{27}N_2O_2$ 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_2SO_4/H_2O 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_2SO_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); ν_{max} /cm^{-1} 3380, 2910,

2810; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.07 (5H, m, Ph), 3.86 (1H, dd, *J* 10.5 and 3, C*H*OH), 3.62 (1H, d, *J* 10.5, CHN), 3.39 (1H, dd, *J* 10.5 and 1, C*H*OH), 3.31–3.21 (1H, m, CHN), 2.88–2.80 (1H, m, CHN), 2.71–2.63 (1H, m, CHN), 2.42–2.33 (1H, m, CHN), 2.09 (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, $CDCl_3$) δ = 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 MH^+ = 263.2114, $C_{16}H_{27}N_2O$ requires MH^+ = 263.2123; LRMS (ES) *m*/*z* 263 (32%, MH^+), 162 (100).

Data for ligand **27**, prepared from (1*S*,2*R*)-(+)-*N*-methylephedrine and L-proline methyl ester hydrochloride:
$[\alpha]^{23}_D$ +15.5 (1.1, EtOH); ν_{max} /cm^{-1} 3385, 2930, 2820; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.16 (5H, m, Ph), 3.76 (1H, d, *J* 9.5, CHN), 3.55 (1H, dd, *J* 10.5 and 4, C*H*OH), 3.36 (1H, dd, *J* 10.5 and 3.5, C*H*OH), 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, $CDCl_3$) δ = 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 MH^+ = 263.2117, $C_{16}H_{27}N_2O$ requires MH^+ = 263.2123; LRMS (ES) *m*/*z* 263 (100%, MH^+).

Data for ligand **28**, prepared from (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine and L-proline methyl ester hydrochloride:
$[\alpha]_D^{22}$ = +16.9 (1.4, EtOH); ν_{max} /cm^{-1} 3385, 2935, 2825; ^{1}H NMR (400 MHz $CDCl_3$) δ = 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, $CDCl_3$) δ = 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 MH^+ = 263.2132, $C_{16}H_{27}N_2O$ requires MH^+ = 263.2123; LRMS (ES) *m*/*z* 263 (100%, MH^+), 162 (82).

Data for ligand **29**, prepared from (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine and D-proline methyl ester hydrochloride:
$[\alpha]^{23}_D$ +90.0 (0.5, EtOH); ν_{max} /cm^{-1} 3345, 2970, 2930, 1670, 1410, 1255, 1160; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28–7.10 (5H, m, Ph), 6.29 (1H, br, OH), 3.69 (1H, dd, *J* 11 and 3 Hz, C*H*OH), 3.61 (1H, d, *J* 11 Hz, CH), 3.33 (1H, dd, *J* 11 and 3 Hz, C*H*OH), 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, $CDCl_3$) δ = 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 MH^+ = 263.2120, $C_{16}H_{27}N_2O$ requires MH^+ = 263.2123; LRMS m/z (ES) 263 (100%, MH^+).

For the formation of (*S*)-**3** (51% yield, 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;[6] this was converted to the *p*-bromobenzoate derivative as reported and the er (87:13) was determined by chiral HPLC as reported [(Chiracel OD column, hexane–^{i}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 × 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.[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**, $[\alpha]_D^{24}$ +28 (1.0, $CHCl_3$) [lit.[7] for (*R*)-**30**, er 99:1, $[\alpha]_D^{24}$ –42.2 (1.8, $CHCl_3$)], er 80:20, determined by conversion to the silane **3** (by treatment with *n*-BuLi, Et_2O,

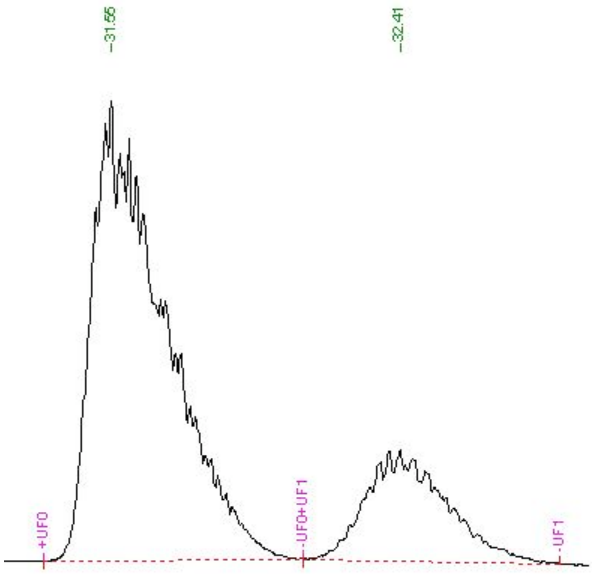
TMEDA, –78 °C then TMSCl) followed by chiral GC as above. Other data in accordance with the literature.[8]

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**, $[\alpha]_D^{21}$ +37.0 (0.55, $CHCl_3$) [lit.[9] for (*S*)-**31**, er 100:0, $[\alpha]_D$ –77.4 (1.4, $CHCl_3$)], er 77:23, determined by chiral stationary phase GC [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 8.1 min (minor) and 8.4 min (major) (at 120 °C)]. Other data in accordance with the literature.[8]

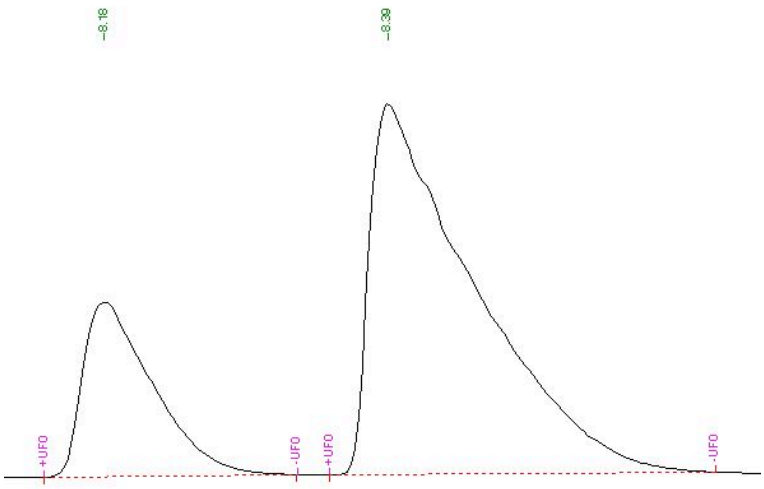
The piperidine **32** was prepared as follows:
N-Boc-piperidine (580 mg, 3.1 mmol) and TMEDA (0.52 mL, 3.4 mmol) in Et_2O (6 mL) were treated with *sec*-BuLi (2.46 mL, 3.4 mmol, 1.4 M in hexane) at –78 °C. After 3 h, the deprotonated ligand **7** [prepared by adding *sec*-BuLi (2.80 mL, 3.9 mmol, 1.4 M in hexane) to **7** (0.80 g, 3.8 mmol) in Et_2O (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_4Cl was added. The organic layer was dried (Na_2SO_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, $CHCl_3$) [lit.[10] for (*S*)-**32**, er 100:0, $[\alpha]_D$ –49.2 (0.9, $CHCl_3$)], er 79:21, determined by chiral stationary phase GC [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)]. Other data in accordance with the literature.[10]

GC and HPLC traces:

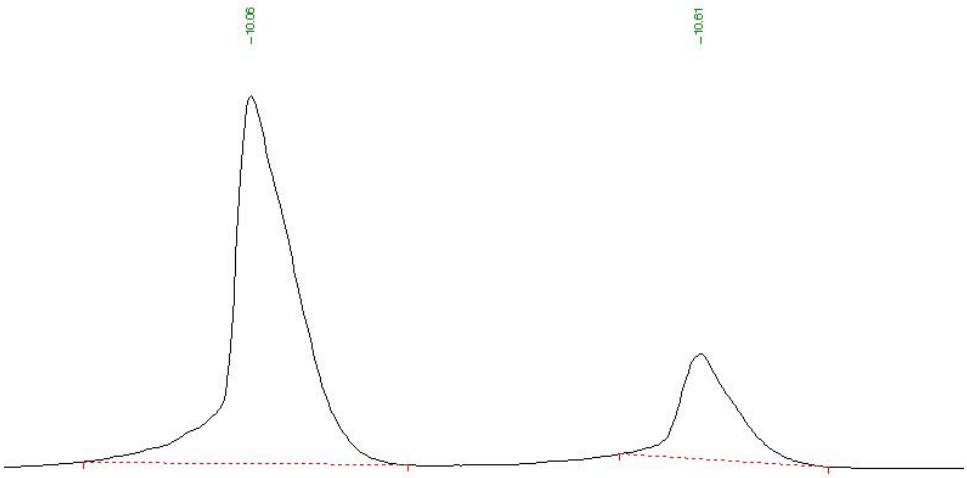
Piperidine (*S*)-**3** (er 79:21) prepared by dynamic thermodynamic resolution using ligand **7**.
GC column: β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 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 × 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).



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