Evaluation of (+)-Sparteine-like Diamines for Asymmetric Synthesis

Michael J. Dearden, Matthew J. McGrath and Peter O'Brien*

Department of Chemistry, University of York, Heslington, York YO10 5DD UK

paobl@york.ac.uk

Supporting Information Available: Full experimental procedures and characterization data, derivatization procedures for determining er of **6**, **10** and **12**, characterization data for lactams **4a-c** and $^1\text{H}/^{13}\text{C}$ NMR spectra of new compounds.

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General Methods. All solvents were distilled before use. Et₂O and THF were freshly distilled from sodium benzophenone ketyl whereas CH₂Cl₂, cumene and toluene were freshly distilled from calcium hydride. Cinnamyl alcohol was freshly distilled before use (bp ~150 °C/2 mmHg). All (+)-sparteine-like diamines **1** and **2a-c** were freshly distilled before use (bp ~190 °C/2 mmHg). All non-aqueous reactions were carried out under oxygen-free N₂ using oven-dried glassware. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C and was purchased in Winchester quantities. Brine refers to a saturated aqueous solution.

Flash column chromatography was carried out using silica 60, 70-200 micron. Thin layer chromatography was carried out using commercially available F₂₅₄ aluminium-backed silica plates. Proton and carbon NMR spectra were recorded on a 270 MHz (67.9 MHz for ¹³C) instrument using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield of tetramethylsilane. Carbon NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT experiments.

Infra-red spectra were recorded on an FT-IR spectrometer. Chemical ionisation and high resolution mass spectra were recorded on an Analytical (VG) Autospec spectrometer. Optical rotations were recorded on a polarimeter (using the sodium D line; 589 nm) and [α]_D are given in units of 10⁻¹ deg cm² g⁻¹.

Cyclohexane-1,3-dicarboxylic anhydride **11**,¹ *N*-pivaloyl-*o*-ethylaniline **13**,² and *t*-butylphenylphosphine-borane **15**³ were prepared according to the literature procedures.

General procedure for *N*-Acylation of cytisine

A solution of acid chloride (1.1 equiv) in CH₂Cl₂ (8 mL) was added dropwise over 30 min to a stirred solution of (–)-cytisine (1.1 g, 5.8 mmol) and 10% w/v NaOH_(aq) (5 equiv) in CH₂Cl₂ (16 mL) at room temperature. The resulting solution was stirred at room temperature for 5 h and then water (10 mL) was added. The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product.

(1*R*,9*R*)-11-Acetyl-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-6-one **3a**

Using the above general procedure, acetyl chloride (1.0 mL, 14.5 mmol), (–)-cytisine (2.5 g, 13.1 mmol) and 10% w/v NaOH_(aq) (26.3 mL, 65.7 mmol) in CH₂Cl₂ (40 mL) gave the crude product. Purification by column chromatography on silica with 9:1 CH₂Cl₂-MeOH as eluent gave acylated pyridone **3a** (1.97 g, 65%) as a white solid, mp 203-205 °C (lit.,⁴ 212 °C); [α]_D –209.9 (*c* 1.0 in CHCl₃) {lit.,⁴ [α]_D –200 (*c* 1 in CHCl₃)}. Spectroscopic data were identical with those reported in the literature.⁴

(1*R*,9*R*)-11-Butyryl-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-6-one **3b**

Using the above general procedure, butyryl chloride (0.6 mL, 6.1 mmol), (–)-cytisine (1.1 g, 5.6 mmol) and 10% w/v NaOH_(aq) (11.1 mL, 27.7 mmol) in CH₂Cl₂ (19 mL) gave the crude product. Purification by column chromatography on silica with 9:1 CH₂Cl₂-MeOH as eluent gave acylated pyridone **3b** (1.21 g, 84%) as a yellow-brown oil, [α]_D –152.0 (*c* 1.0 in CHCl₃); *R*_F(9:1 CH₂Cl₂-MeOH) 0.5; IR (CHCl₃) 2943, 1655, 1576 cm^{–1}; ¹H NMR (270 MHz, CDCl₃) 50:50 mixture of rotamers δ 7.29-7.25 (m, 1H), 6.46 (d, *J* = 7.5, 0.5H), 6.43 (d, *J* = 7.5, 0.5H), 6.08 (d, *J* = 6.0, 0.5H), 6.06 (d, *J* = 6.0, 0.5H), 4.82 (d, *J* = 13.5, 0.5H), 4.70 (d, *J* = 13.0, 0.5H), 4.18-3.81 (m, 3H), 3.38-3.31 (m, 1H), 3.08 (br s, 1H), 2.84 (d, *J* = 13.0, 0.5H), 2.80 (d, *J* = 13.0, 0.5H), 2.53 (br s, 1H), 2.30-2.16 (m, 1H), 2.08-1.80 (m, 3H), 1.57-1.44 (m, 1H), 1.44-1.26 (m, 1H), 0.85 (t, *J* = 7.5, 1.5H), 0.74 (t, *J* = 7.5, 1.5H); ¹³C NMR (67.9 MHz, CDCl₃) 50:50 mixture of rotamers δ 172.06, 172.04, 163.2, 163.2, 148.5, 139.0, 138.3, 138.2, 117.6, 117.00, 105.7, 104.7, 53.3, 52.6, 51.4, 48.7, 48.4, 47.5, 34.8, 34.6, 34.3, 27.4, 27.0, 25.99, 25.97, 18.3, 18.1, 13.54, 13.50; MS (CI, NH₃) *m/z* 261 [(M + H)⁺]; HRMS (CI, NH₃) *m/z* calcd for C₁₅H₂₀N₂O₂ (M + H)⁺ 261.1603, found 261.1601.

(1*R*,9*R*)-11-(2,2-Dimethylpropionyl)-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-6-one 3c

Using the above general procedure, pivaloyl chloride (0.9 mL, 7.7 mmol), (–)-cytisine (1.3 g, 6.9 mmol) and 10% w/v NaOH_(aq) (16.7 mL, 41.8 mmol) in CH₂Cl₂ (20 mL) gave the crude product. Purification by column chromatography on silica with 9:1 CH₂Cl₂-MeOH as eluent gave acylated pyridone **3c** (1.33 g, 69%) as a white solid, mp 161-164 °C (lit.,⁴ 163 °C); [α]_D –245.3 (*c* 1.0 in CHCl₃){lit.,⁴ [α]_D –261 (*c* 0.95 in CHCl₃)}. Spectroscopic data were identical with those reported in the literature.⁴

General procedure for hydrogenation-LiAlH₄ reduction of *N*-acylated cytosines

A suspension of pyridone **3a-c** (5.5 mmol) and platinum(IV) oxide (0.1 equiv) in degassed MeOH (25 mL) was stirred at room temperature under a H₂ atmosphere (H₂ balloon) for 24 h. The solids were removed by filtration through Celite and the filter cake was washed with 9:1 CH₂Cl₂-MeOH (100 mL). The filtrate was evaporated under reduced pressure to give the crude product. To this crude product in THF (25 mL) at 0 °C under N₂ was added LiAlH₄ (6 equiv) in one portion. The resulting suspension was heated at reflux for 16 h. After cooling to 0 °C, Et₂O (10 mL) was added followed by the dropwise (CARE) addition of saturated Na₂SO_{4(aq)} until effervescence ceased. The solids were removed by filtration through Celite and the filter cake was washed with 9:1 CH₂Cl₂-MeOH (100 mL). The filtrate was dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product.

(1*R*,2*S*,9*S*)-11-Ethyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane **2a**

Using the above general procedure, pyridone **3a** (792 mg, 3.35 mmol) and platinum(IV) oxide (76 mg, 0.34 mmol) in MeOH (10 mL) followed by reduction with LiAlH₄ (0.68 g, 18.0 mmol) in THF (15 mL) gave the crude product. Purification by Kugelrohr distillation gave diamine **2a** (577 mg, 83%) as a colourless oil, bp 115-120 °C/1 mmHg (oven temp); [α]_D +39.8 (*c* 1.0 in CHCl₃); *R*_F(9:1 CH₂Cl₂-MeOH) 0.3; IR (CHCl₃) 2934 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 3.12 (br d, *J* = 11.0, 1H), 2.93-2.84 (m, 3H), 2.61 (dq, *J* = 12.0, 7.0, 1H), 2.31-2.20 (m, 2H), 2.02-1.45 (m, 12H), 1.36-1.19 (m, 2H), 1.04 (t, *J* = 7.0, 3H); ¹³C NMR (67.9 MHz, CDCl₃) δ 66.4, 60.5, 59.2, 57.5, 53.5, 52.2, 34.8, 34.1, 30.63, 30.57, 25.6, 25.2, 11.9; MS (CI, NH₃) *m/z* 209 [(M + H)⁺]; HRMS (CI, NH₃) *m/z* calcd for C₁₃H₂₄N₂ (M + H)⁺ 209.2018, found 209.2017.

(1*R*,2*S*,9*S*)-11-*n*-Butyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane **2b**

Using the above general procedure, pyridone **3b** (1.38 g, 5.2 mmol) and platinum(IV) oxide (120 mg, 0.5 mmol) in MeOH (10 mL) followed by reduction with LiAlH₄ (1.14 g, 30.4 mmol) in THF (18 mL) gave the crude product. Purification by Kugelrohr distillation gave diamine **2b** (1.0 g, 81%) as a colourless oil, bp 130-135 °C/0.6 mmHg (oven temp); [α]_D +42.9 (*c* 1.1 in CHCl₃); *R*_F(9:1 CH₂Cl₂-MeOH) 0.4; IR (CHCl₃) 2935 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 3.10 (br d, *J* = 11.0, 1H), 2.92-2.84 (m, 3H), 2.53-2.43 (m, 1H), 2.32-2.21 (m, 2H), 1.98-1.73 (m, 6H), 1.69-1.15 (m, 12H), 0.90 (t, *J* = 7.0, 3H); ¹³C NMR

(67.9 MHz, CDCl₃) δ 66.3, 60.6, 59.9, 59.3, 57.5, 53.0, 34.9, 34.1, 30.6, 29.0, 25.7, 25.2, 25.1, 14.2; MS (CI, NH₃) m/z 237 [(M + H)⁺]; HRMS (CI, NH₃) m/z calcd for C₁₅H₂₈N₂ (M + H)⁺ 237.2331, found 237.2327.

(1*R*,2*S*,9*S*)-11-(2,2-Dimethylpropyl)-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane 2c

Using the above general procedure, pyridone **3c** (1.1 g, 4.0 mmol) and platinum(IV) oxide (91 mg, 0.4 mmol) in MeOH (8 mL) followed by reduction with LiAlH₄ (0.91 g, 24.2 mmol) in THF (15 mL) gave the crude product. Purification by Kugelrohr distillation gave diamine **2c** (887 mg, 89%) as a colourless oil, bp 135-140 °C/0.6 mmHg (oven temp); $[\alpha]_D^{25} +16.1$ (c 1.1 in CHCl₃); R_F (9:1 CH₂Cl₂-MeOH) 0.5; IR (CHCl₃) 2942 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 2.94-2.71 (m, 4H), 2.48 (br d, J = 9.0), 2.34 (br d, J = 10.0, 1H), 2.19 (br d, J = 11.0, 1H), 1.91-1.86 (m, 3H), 1.80-1.65 (m, 3H), 1.63-1.31 (m, 6H), 1.30-1.09 (m, 2H), 0.87 (s, 9H); ¹³C NMR (67.9 MHz, CDCl₃) δ 70.4, 65.8, 61.0, 60.8, 57.0, 56.1, 36.0, 34.0, 33.7, 31.3, 30.5, 28.0, 26.1, 25.3; MS (CI, NH₃) m/z 251 [(M + H)⁺]; HRMS (CI, NH₃) m/z calcd for C₁₆H₃₀N₂ (M + H)⁺ 251.2487, found 251.2488.

Characterization data for lactams **4a-c**

For characterization of lactams **4a-c**, samples of the crude products from the hydrogenation of pyridones **3a-c** were purified by column chromatography on silica with 9:1 CH₂Cl₂-MeOH as eluent.

(1R,2S,9R)-11-Acetyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecan-6-one **4a**

White solid, mp 155-157 °C; $[\alpha]_D -259.9$ (*c* 1.0 in CHCl₃); *R_F*(9:1 CH₂Cl₂-MeOH) 0.5; IR (CHCl₃) 2930, 1622, 1461 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) 5.07 (dd, *J* = 2.0, 14.0, 1H), 4.90 (td, *J* = 2.0, 14.0, 1H), 3.93 (br dd, *J* = 2.0, 13.0, 1H), 3.52-3.46 (m, 1H), 3.35 (td, *J* = 2.0, 13.5, 1H), 2.82 (br d, *J* = 13.5, 1H), 2.63 (dd, *J* = 2.5, 14.0, 1H), 2.39-2.33 (m, 2H), 2.18-1.50 (m, 8H), 2.03 (s, 3H); ¹³C NMR (67.9 MHz, CDCl₃) 170.0, 169.3, 59.2, 51.2, 45.7, 41.6, 33.4, 32.62, 32.56, 27.9, 27.65, 21.5, 19.7; MS (CI, NH₃) *m/z* 237 [(M + H)⁺]; HRMS (CI, NH₃) *m/z* calcd for C₁₃H₂₀N₂O₂ (M + H)⁺ 237.1603, found 237.1604.

(1R,2S,9R)-11-Butyryl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecan-6-one **4b**

Colourless oil; $[\alpha]_D -139.3$ (*c* 1.0 in CHCl₃); *R_F*(EtOAc) 0.1; IR (CHCl₃) 2932, 1622, 1461 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) 4.99 (dd, *J* = 2.0, 14.0, 1H), 4.76 (td, *J* = 2.0, 14.0, 1H), 3.90 (br dd, *J* = 2.0, 13.0, 1H), 3.45-3.35 (m, 1H), 3.25 (td, *J* = 2.0, 13.5, 1H), 2.73 (br d, *J* = 14.0, 1H), 2.56 (dd, *J* = 2.5, 14.0, 1H), 2.29-1.41 (m, 8H), 0.92 (t, *J* = 7.5, 3H); ¹³C NMR (67.9 MHz, CDCl₃) 171.6, 169.7, 59.1, 50.1, 45.7, 41.7, 34.9, 33.3, 32.6, 32.5, 27.8, 27.5, 19.7, 18.2, 13.8; MS (CI, NH₃) *m/z* 265 [(M + H)⁺]; HRMS (CI, NH₃) *m/z* calcd for C₁₅H₂₄N₂O₂ (M + H)⁺ 265.1916, found 265.1912.

(1R,2S,9R)-11-(2,2-Dimethylpropionyl)-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecan-6-one 4c

White solid, mp 161-164 °C; $[\alpha]_D^{25}$ -204.8 (*c* 1.0 in CHCl₃); *R*_F(EtOAc) 0.15; IR (CHCl₃) 2933, 1621, 1445 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) 5.02 (br qd, *J* = 2.5, 14.0, 1H), 4.70 (td, *J* = 2.5, 14.0, 1H), 4.24 (br dd, *J* = 2.0, 13.0, 1H), 3.42 (td, *J* = 3.5, 10.5, 1H), 3.30 (td, *J* = 2.5, 12.5, 1H), 2.83 (br d, *J* = 14.0, 1H), 2.66 (dd, *J* = 2.0, 14.0, 1H), 2.39-1.51 (m, 10H), 1.20 (s, 9H); ¹³C NMR (67.9 MHz, CDCl₃) 176.7, 169.7, 59.4, 51.3, 45.7, 43.8, 39.0, 33.3, 33.1, 32.9, 28.6, 28.5, 28.1, 20.3; MS (CI, NH₃) *m/z* 279 [(M + H)⁺]; HRMS (CI, NH₃) *m/z* calcd for C₁₆H₂₆N₂O₂ (M + H)⁺ 279.2073, found 279.2070.

General procedure for rearrangement of cyclooctene oxide

s-Butyllithium (1.22 M solution in cyclohexane, 2.4 equiv) was added dropwise over 10 min to a stirred solution of diamine (2.4 equiv) in Et₂O (5 mL) at -78 °C under N₂. The resulting solution was stirred at -78 °C for 15 min and then a solution of cyclooctene oxide **5** (261 mg, 2.07 mmol) in Et₂O (5 mL) was added dropwise via a cannula. After stirring for 4 h at -78 °C, the reaction mixture was allowed to warm to room temperature over 4 h and stirred at room temperature for 12 h. After cooling to 0 °C, 2 M HCl_(aq) (10 mL) was added and the organic layer was extracted with Et₂O (3 × 10 mL). The combined organic extracts were washed with saturated NaHCO_{3(aq)} (2 × 10 mL), brine (10 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica with 4:1 petrol-Et₂O as eluent gave alcohol (-)-**6** or (+)-**6** as a colourless oil, *R*_F(3:7 Et₂O-petrol) 0.1. Spectroscopic data were identical with those reported in the literature.⁵ The enantiomer ratio was determined by chiral HPLC of the corresponding 2,4-dinitrobenzoate. HPLC for 2,4-dinitrobenzoate: Daicel Chiralpak AD, 40% hexane in *i*PrOH, 1.0 mL min⁻¹, 254 nm, 6.0 min [ester from (-)-**6**], 7.1 min [ester from (+)-**6**].

The diamine could be recovered by the dropwise addition of 20% w/v NaOH_(aq) to the combined aqueous layers until pH 9 was obtained. Then, the aqueous layers were extracted with Et₂O (3 × 5 mL) and the combined organic extracts were dried (K₂CO₃) and evaporated under reduced pressure to give the crude diamine (65-80% recovery) as a yellow oil.

(1*R*,3*aS*,6*aS*)-Octahydropentalen-1-ol (-)-**6**

Using the general procedure, *s*-butyllithium (1.91 mL of a 1.31 M solution in cyclohexane, 2.50 mmol), (-)-sparteine (586 mg, 2.50 mmol) and cyclooctene oxide **5** (126 mg, 1.00 mmol) in Et₂O (7.5 mL) gave alcohol (-)-**6** (106 mg, 84%, 83:17 er) as a colourless oil, [α]_D -12.7 (*c* 1.0 in CHCl₃)(lit.,⁵ [α]_D -19.0 (*c* 1.0 in CHCl₃) for (-)-**6** of 84%ee).

(1*S*,3*aR*,6*aR*)-Octahydropentalen-1-ol (+)-**6**

Using the general procedure, *s*-butyllithium (1.58 mL of a 1.30 M solution in cyclohexane, 2.06 mmol), diamine **1** (400 mg, 2.06 mmol) and cyclooctene oxide **5** (108 mg, 0.86 mmol) in Et₂O (10 mL) gave alcohol (+)-**6** (76 mg, 70%, 19:81 er) as a colourless oil, [α]_D +12.8 (*c* 1.0 in CHCl₃).

(1*S*,3*aR*,6*aR*)-Octahydropentalen-1-ol (+)-6

Using the general procedure, *s*-butyllithium (1.91 mL of a 1.31 M solution in cyclohexane, 2.50 mmol), diamine **2a** (521 mg, 2.50 mmol) and cyclooctene oxide **5** (126 mg, 1.00 mmol) in Et₂O (7.5 mL) gave alcohol (+)-**6** (90 mg, 72%, 18:82 er) as a colourless oil, $[\alpha]_D^{25} +10.7$ (*c* 1.0 in CHCl₃).

(1*S*,3*aR*,6*aR*)-Octahydropentalen-1-ol (+)-6

Using the general procedure, *s*-butyllithium (1.91 mL of a 1.31 M solution in cyclohexane, 2.50 mmol), diamine **2b** (591 mg, 2.50 mmol) and cyclooctene oxide **5** (126 mg, 1.00 mmol) in Et₂O (7.5 mL) gave alcohol (+)-**6** (67 mg, 53%, 27:73 er) as a colourless oil, $[\alpha]_D^{25} +8.9$ (*c* 1.0 in CHCl₃).

(1*S*,3*aR*,6*aR*)-Octahydropentalen-1-ol (+)-6

Using the general procedure, *s*-butyllithium (1.91 mL of a 1.31 M solution in cyclohexane, 2.50 mmol), diamine **2c** (616 mg, 2.50 mmol) and cyclooctene oxide **5** (126 mg, 1.00 mmol) in Et₂O (7.5 mL) gave alcohol (+)-**6** (67 mg, 53%, 34:66 er) as a colourless oil, $[\alpha]_D^{25} +7.7$ (*c* 1.0 in CHCl₃).

Representative procedure⁶ for the er determination of alcohol (–)- or (+)-**6**

2,4-Dinitrobenzoic acid (169 mg, 0.80 mmol) was added to a stirred solution of alcohol (+)-**6** (67 mg, 0.53 mmol), DMAP (6 mg, 0.05 mmol) and DCC (131 mg, 0.64 mmol) in CH₂Cl₂ (5 mL) at 0 °C under N₂. The resulting mixture was stirred at room temperature for 16 h and then, *n*-pentane (5 mL) was added. The solids were removed by filtration and the filter cake was washed with CH₂Cl₂ (5 mL). The filtrate was evaporated to give the crude product. Purification by column chromatography on silica with petrol-Et₂O (6:4) as eluent gave the 2,4-dinitrobenzoate ester (144 mg, 80%, 18:82 er by chiral HPLC) as a colourless oil, *R*_F(cyclohexane-EtOAc) 0.8; ¹H NMR (270 MHz, CDCl₃) 8.77 (d, *J* = 2.0, 1H), 8.54 (dd, *J* = 2.0, 8.5, 1H), 7.96 (d, *J* = 8.5, 1H), 5.45-5.32 (m, 1H), 2.82-2.68 (m, 1H), 2.59-2.46 (m, 1H), 1.99-1.22 (m, 10H); HPLC: Daicel Chiralpak AD, 40% hexane in *i*PrOH, 1.0 mL min^{–1}, 254 nm, 6.0 min [ester from (–)-**6**], 7.1 min [ester from (+)-**6**].

General procedure for the oxidative kinetic resolution of 1-indanol

Powdered molecular sieves (3 Å, 500 mg) were added to a 25 mL round bottomed flask equipped with a magnetic stirrer bar and a condenser. The apparatus was flame-dried under vacuum and allowed to cool under a flow of N₂. Then, Pd(nbd)Cl₂ (0.05 equiv), toluene (8 mL) and the diamine (0.20 equiv) were added. The flask was then evacuated and filled with O₂ (□ 3, balloon) and the reaction mixture was heated to 60 °C over 10 min. Then, a solution of racemic 1-indanol **7** (134 mg, 1.0 mmol) in toluene (2 mL) was added dropwise and the resulting reaction mixture was heated at 60 °C for 54 h. After allowing the reaction mixture to cool to room temperature, it was filtered through a short pad of silica using EtOAc as eluent and evaporated under reduced pressure to give the crude product. Analysis of the crude product by ¹H NMR spectroscopy enabled the % conversion (C) to ketone **8** to be determined. The enantiomer ratio of 1-indanol **7** was determined by chiral HPLC: Daicel Chiralcel OJ-R, 3% EtOH in hexane, 1.0 mL min⁻¹, 254 nm, 6.2 min [(*S*)-**7**], 7.5 min [(*R*)-**7**]. The major alcohol enantiomer was identified by comparison of HPLC retention times with those in the literature and by comparison of optical rotation data of isolated alcohols with the literature values.⁷⁻⁹

Kinetic resolution of *rac*-1-indanol **7** using (–)-sparteine

Using the general procedure, powdered molecular sieves (3 Å, 500 mg), Pd(nbd)Cl₂ (13 mg, 0.05 mmol), (–)-sparteine (47 mg, 0.20 mmol) and racemic 1-indanol **7** (134 mg, 1.0 mmol) in toluene (10 mL) gave the crude product which contained a 33:67 mixture (by ¹H NMR spectroscopy) of alcohol (*S*)-**7** (96:4 er; 92 %ee) and ketone **8** (% conversion (C) = 67%). Hence, selectivity factor (s) = 8.0.¹⁰

Kinetic resolution of *rac*-1-indanol **7** using diamine **1**

Using the general procedure, powdered molecular sieves (3 Å, 500 mg), Pd(nbd)Cl₂ (13 mg, 0.05 mmol), diamine **1** (39 mg, 0.20 mmol) and racemic 1-indanol **7** (134 mg, 1.0 mmol) in toluene (10 mL) gave the crude product which contained a 59:41 mixture (by ¹H NMR spectroscopy) of alcohol (*R*)-**7** (72:28 er; 44 %ee) and ketone **8** (% conversion (C) = 41%). Hence, selectivity factor (s) = 6.8.¹⁰

Kinetic resolution of *rac*-1-indanol **7** using diamine **2a**

Using the general procedure, powdered molecular sieves (3 Å, 500 mg), Pd(nbd)Cl₂ (13 mg, 0.05 mmol), diamine **2a** (42 mg, 0.20 mmol) and racemic 1-indanol **7** (134 mg, 1.0 mmol) in toluene (10 mL) gave the crude product which contained a 32:68 mixture (by ¹H NMR spectroscopy) of alcohol (*R*)-**7** (91:9 er; 82 %ee) and ketone **8** (% conversion (C) = 68%). Hence, selectivity factor (s) = 5.3.¹⁰

Kinetic resolution of *rac*-1-indanol **7** using diamine **2b**

Using the general procedure, powdered molecular sieves (3 Å, 500 mg), Pd(nbd)Cl₂ (13 mg, 0.05 mmol), diamine **2b** (43 mg, 0.20 mmol) and racemic 1-indanol **7** (134 mg, 1.0 mmol) in toluene (10 mL) gave the crude product which contained a 36:64 mixture (by ¹H NMR spectroscopy) of alcohol (*R*)-**7** (79:21 er; 58 %ee) and ketone **8** (% conversion (C) = 64%). Hence, selectivity factor (s) = 3.4.¹⁰

(R)-2-Benzylhexan-1-ol 10

n-Butyllithium (2.47 mL of a 1.44 M solution in hexanes, 3.56 mmol, 3.0 equiv) was added dropwise to a stirred solution of diamine **1** (230 mg, 1.19 mmol, 1.0 equiv) in cumene (2 mL) at -15°C under N_2 . The resulting solution was stirred at -15°C for 5 min and then a solution of (*E*)-cinnamyl alcohol **9** (159 mg, 1.19 mmol, 1.0 equiv) in cumene (3 mL) was added dropwise *via* cannula over 15 min. After stirring at 0°C for 1 h, 2 M $\text{HCl}_{(\text{aq})}$ (5 mL) was added and the mixture was extracted with Et_2O (3 $\times$ 10 mL). The combined organic extracts were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by repeated column chromatography on silica with 95:5 cyclohexane-EtOAc as eluent gave alcohol (*R*)-**10** (164 mg, 71%, 87:13 er) as a colourless oil, $[\alpha]_{\text{D}}^{25} +4.0$ (*c* 0.95 in CH_2Cl_2)(lit.,¹¹ $[\alpha]_{\text{D}}^{25} -4.1$ (*c* 0.02 in CH_2Cl_2) for (*S*)-**10** of 83%ee); R_{F} (4:1 petrol-EtOAc) 0.5. Spectroscopic data were identical with those reported in the literature.¹¹ The enantiomer ratio was determined by integration of the signals in the ^1H NMR spectrum of the corresponding Mosher's esters.

Representative procedure for the er determination of alcohol 10

(*S*)- α -Methoxy- β -(trifluoromethyl)phenylacetyl chloride (20 mg, 0.08 mmol) was added to a stirred solution of alcohol (*R*)-**10** (8 mg, 0.04 mmol), Et_3N (14 μL , 0.08 mmol) and DMAP (0.5 mg, 0.005 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 . The resulting solution was stirred at room temperature for 76 h (TLC indicated complete consumption of alcohol (*R*)-**10**) and then Et_2O (5 mL) was added. The solution was washed with 2 M $\text{HCl}_{(\text{aq})}$ (5 mL), saturated $\text{NaHCO}_{3(\text{aq})}$ (2 $\times$ 5 mL) and brine (5 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product (quantitative yield). Analysis by ^1H NMR spectroscopy indicated an 87:13 dr: ^1H NMR (270 MHz, CDCl_3) major diastereomer: 4.20 (dd, $J = 11.0, 5.0$, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{O}$); minor diastereomer: 4.08 (d, $J = 5.0$, 2H, CH_2O).

(1*R*,3*S*)-3-Benzoylcyclohexanecarboxylic acid **12**

Phenylmagnesium chloride (1.11 mL of a 2 M solution in THF, 2.22 mmol, 1.2 equiv) was added dropwise to a stirred solution of diamine **1** (430 mg, 2.22 mmol, 1.2 equiv) in toluene (4.4 mL) at $-78\text{ }^{\circ}\text{C}$ under N_2 . Then, a solution of anhydride **11** (318 mg, 2.06 mmol, 1.0 equiv) in toluene (10 mL) was added dropwise *via* a cannula and the resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 20 h. Saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ solution (4 mL) was added and the resulting white suspension was allowed to warm to room temperature. Then, 2 M $\text{NaOH}_{(\text{aq})}$ (18 mL) was added and the aqueous layer was washed with Et_2O (2 $\times$ 6 mL). The aqueous layer was acidified by the careful addition of 6 M $\text{HCl}_{(\text{aq})}$ (7 mL) and the aqueous layer was then extracted with Et_2O (3 $\times$ 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica with 2:3 hexane-acetone as eluent gave keto acid (1*R*,3*S*)-**12** (360 mg, 78%, 89:11 er) as a colourless oil, $[\alpha]_{\text{D}} -22.2$ (*c* 1.0 in CH_2Cl_2)(lit.,¹² $[\alpha]_{\text{D}} +19.7$ (*c* 1.0 in CH_2Cl_2) for (1*S*,3*R*)-**12** of 82%ee); R_{F} (2:3 hexane-acetone) 0.7. Spectroscopic data were identical with those reported in the literature.¹² The enantiomer ratio was determined by chiral HPLC of the corresponding methyl ester. HPLC for keto ester: Daicel Chiralpak OD, 0.6% *i*PrOH in hexane, 1.0 mL min⁻¹, 254 nm, 13.9 min [(1*S*,3*R*)-**12**], 16.8 min [(1*R*,3*S*)-**12**].

Representative procedure¹² for the er determination of acid (1*R*,3*S*)-12****

DCC (412 mg, 2.0 mmol) was added in one portion to a stirred solution of keto-acid (1*R*,3*S*)-**12** (360 mg, 1.6 mmol), methanol (497 mg, 15.6 mmol) and DMAP (2 mg, 0.07 mmol) in 2:1 CH_2Cl_2 -THF (30 mL) at $0\text{ }^{\circ}\text{C}$ under N_2 . The resulting solution was stirred at room temperature for 16 h and the solvent was evaporated under reduced pressure. Purification of the residue by column chromatography on silica with petrol- Et_2O (3:1) as eluent gave the methyl ester (160 mg, 42%, 89:11 er by chiral HPLC) as a colourless oil, R_{F} (2:1 petrol- Et_2O) 0.5; $[\alpha]_{\text{D}} -20.1$ (*c* 1.1 in CHCl_3)(lit.,¹² $[\alpha]_{\text{D}} +22.4$ (*c* 1.1 in CHCl_3) for (1*S*,3*R*)-**12** of 82%ee). Spectroscopic data were identical with those reported in the literature.¹² HPLC: Daicel Chiralcel OD, 0.6% *i*PrOH in hexane, 1.0 mL min⁻¹, 254 nm, 13.9 min [ester from (+)-**12**], 16.8 min [ester from (–)-**12**].

(S)-2,2-Dimethyl-N-[2-(1-trimethylsilyl)ethyl]phenyl]propionamide 14

s-Butyllithium (4.4 mL of a 1.1 M solution in cyclohexane, 4.8 mmol, 2.4 equiv) was added dropwise to a stirred solution of *N*-pivaloyl-*o*-ethylaniline **13** (411 mg, 2.0 mmol, 1.0 equiv) in Et₂O (2 mL) at –25 °C under N₂. The resulting solution was stirred at –25 °C for 2 h and then diamine **1** (1.12 g, 5.8 mmol, 2.9 equiv) was added *via* syringe. The resulting red solution was stirred at –25 °C for 45 min and then cooled to –78 °C. After stirring at –78 °C for 30 min, Me₃SiCl (0.38 mL, 3.0 mmol, 1.5 equiv) was added dropwise and the resulting solution was stirred at –78 °C for 5 h. Then, MeOH (1 mL) was added and the reaction mixture was washed with 5% H₃PO_{4(aq)} (3 × 5 mL). The combined aqueous washings were extracted with Et₂O (3 × 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica with 90:10 hexane-EtOAc as eluent gave silyl adduct (*S*)-**14** (321 mg, 58%, 93:7 er) as a white solid, mp 80-81 °C (lit.,¹³ 96-97 °C); [α]_D +34.5 (*c* 1.0 in CHCl₃)(lit.,¹³ [α]_D –40.7 (*c* 7.7 in CHCl₃) for (*R*)-**14** of 95:5 er); *R*_F(19:1 hexane-EtOAc) 0.2. Spectroscopic data were identical with those reported in the literature.¹³ The enantiomer ratio was determined by chiral HPLC: Daicel Chiralpak AD, 3% *i*PrOH in hexane, 0.5 mL min^{–1}, 254 nm, 11.4 min [(*R*)-**14**], 12.8 min [(*S*)-**14**].

rac*-(2-Methoxyphenylmethyl)-*P*-*tert*-butylphenylphosphine-borane **16*

n-Butyllithium (1.05 mL of a 1.35 M solution in hexanes, 1.42 mmol, 1.0 equiv) was added dropwise to a stirred solution of *t*-butylphenylphosphine-borane **15** (256 mg, 1.42 mmol, 1.0 equiv) and diamine **1** (357 mg, 1.84 mmol, 1.3 equiv) in Et₂O (9 mL) at –78 °C under N₂. The resulting solution was allowed to warm slowly to room temperature over 2 h and then stirred at room temperature for 1 h. *No precipitate formed.* The resulting solution was then cooled to –78 °C and 2-(chloromethyl)anisole (0.26 mL, 1.84 mmol, 1.3 equiv) was added dropwise. The resulting solution was allowed to warm slowly to –25 °C over 3 h and then stored at –25 °C for 24 h (freezer). 5% H₂SO_{4(aq)} (3 mL) was added and the mixture was extracted with Et₂O (3 × 5 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica with 90:10 hexane-EtOAc as eluent gave phosphine-borane *rac*-**16** (160 mg, 38%, 50:50 er) as a white solid, mp 75-77 °C (lit.,¹⁴ 82.6-83.0); [α]_D 0 (*c* 1.0 in CHCl₃)(lit.,¹⁴ [α]_D +88 (*c* 1.0 in CHCl₃) for (*R*)-**16** of 95%ee); *R*_F(4:1 petrol-EtOAc) 0.8. Spectroscopic data were identical with those reported in the literature.¹⁴ The enantiomer ratio was determined by chiral HPLC: Daicel Chiralpak AD, 1% *i*PrOH in hexane, 1.0 mL min^{–1}, 254 nm, 8.2 min [(*R*)-**16**], 9.8 min [(*S*)-**16**].

(R)-1,1'-Binaphthalene-2,2'-diol **17**

A suspension of copper(I) chloride (101 mg, 1.02 mmol, 1.4 equiv) and diamine **1** (396 mg, 2.04 mmol, 2.8 equiv) in MeOH (6.5 mL) was sonicated under air for 30 min. Then, argon was bubbled through the resulting solution for 1 h, whilst continuing to sonicate. At the same time, argon was bubbled through a solution of 1,1'-binaphthalene-2,2'-diol *rac*-**17** (208 mg, 0.72 mmol, 1.0 equiv) in CH₂Cl₂ (16.5 mL) for 1 h. Then, the green copper chloride/diamine solution was added *via* cannula to the binaphthol/CH₂Cl₂ solution and the resulting dark red solution was sonicated under argon for 10 min. The reaction mixture was stirred at room temperature for 8 h in the dark and then stored at -25 °C for 16 h (freezer). Pre-cooled (-25 °C) conc. HCl_(aq) (10 mL) was added dropwise over 5 min to the reaction mixture at -25 °C. The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 25 mL). The combined organic extracts were washed with water (25 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica with 15:1 CH₂Cl₂-hexane as eluent gave BINOL (*R*)-**17** (178 mg, 86%, 99:1 er) as a yellow solid, mp 206-208 °C (lit.,¹⁵ 208-210); [α]_D +31.0 (*c* 1.1 in THF)(lit.,¹⁶ [α]_D -32 (*c* 1.0 in THF) for (*S*)-**17**); *R*_F(16:1 CH₂Cl₂-petrol) 0.25. Spectroscopic data were identical with those reported in the literature.¹⁶ The enantiomer ratio was determined by chiral HPLC: Daicel Chiralpak AD, 20% *i*PrOH in hexane, 1.0 mL min⁻¹, 254 nm, 15.9 min [(*R*)-**17**], 18.2 min [(*S*)-**17**].

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