Supporting Information

Mechanistic Interrogation of the Asymmetric Lithiation-trapping of N-Thiopivaloyl Azetidine and Pyrrolidine

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Data is available at: doi 10.15124/f6c60051-fd06-4d8e-94b6-7bf91ac2a69f
1. Experimental details

1.1 General

Water is distilled water. Brine refers to a saturated aqueous solution of NaCl. THF was freshly distilled from sodium and benzophenone ketyl or dried using a Grubbs solvent purification system. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C. All reactions were carried out under O₂-free Ar or N₂ using oven-dried and/or flame-dried glassware.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using Merck F₂₅₄ aluminium-backed silica plates. ¹H (400 MHz) and ¹³C (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument with an internal deuterium lock. Chemical shifts are quoted as parts per million and referenced to CHCl₃ (δ_H 7.27) and or CDCl₃ (δ_C 77.0, central line of triplet). ¹³C NMR spectra were recorded with broadband proton decoupling. ¹³C NMR spectra were assigned using DEPT experiments. Coupling constants (J) are quoted in Hertz. IR spectra were recorded on an ATI Matteson Genesis FT-IR spectrometer. Melting points were measured on a Gallenkamp melting point apparatus. Electrospray high and low resolution mass spectra were recorded on a Bruker Daltronics microOTOF spectrometer. Chiral stationary phase HPLC was performed on an Agilent 1200 series instrument and a multiple wavelength, UV/Vis diode array detector; integration was normally performed at 230 nm.

The following compounds were made according to the reported procedures: diamines (R,R)-4 and (S,S)-4¹ and (+)-sparteine surrogate 21.²
1.2 General Procedures

**General Procedure A: s-BuLi/diamine-mediated lithiation-electrophilic trapping of N-thiopivaloyl azetidine 1**

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq.) was added dropwise to a stirred solution of N-thiopivaloyl azetidine 1 (79 mg, 0.50 mmol, 1.0 eq.) and diamine (0.60 mmol, 1.2 eq.) in Et₂O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the electrophile (0.75 mmol, 1.5 eq.) was added dropwise and the solution was stirred at −78 °C for 1 h. 1 M HCl(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product.

**General Procedure B: s-BuLi/diamine-mediated lithiation-electrophilic trapping of N-thiopivaloyl pyrrolidine 9**

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of N-thiopivaloyl pyrrolidine 9 (86 mg, 0.50 mmol, 1.0 eq.) and diamine (0.65 mmol, 1.3 eq.) in Et₂O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, the electrophile (0.75 mmol, 1.5 eq.) was added dropwise and the solution was stirred at −78 °C for 1 h. 1 M HCl(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product.
1.3 Experimental Procedures and Characterisation Data

2,2-Dimethyl-1-azetidinyl-1-ylpropan-1-thione 1

Trimethylacetyl chloride (7.21 mL, 58.6 mmol, 1.1 eq.) was added to a stirred solution of azetidine hydrochloride (5.00 g, 53.3 mmol, 1.0 eq.) and Et₃N (37.1 mL, 266 mmol, 5.0 eq.) in CH₂Cl₂ (75 mL) at 0 °C. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 1 M HCl(aq) (15 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduce pressure to give the crude N-pivaloyl azetidine. The residue was dissolved in pyridine (150 mL) and phosphorous(V) sulfide (14.80 g, 66.6 mmol, 1.25 eq.) was added. The resulting solution was heated to 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M HCl(aq) (150 mL). 1 M HCl(aq) was added until pH 3 was obtained. The resulting solution was stirred at rt for 2 h and then extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with 1 M HCl(aq) (50 mL), water (50 mL) and brine (50 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et₂O as eluent gave thioamide 1 (6.40 g, 78%) as a yellow oil, Rₚ (8:2 petrol-Et₂O) 0.2; ¹H NMR (400 MHz, CDCl₃) δ 4.51 (br t, J = 7.5 Hz, 2H, NCH₂), 4.29 (br t, J = 7.5 Hz, 2H, NCH₂), 2.33-2.25 (m, 2H, CH₂), 1.36 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 209.1 (C=S), 56.6 (NCH₂), 56.0 (NCH₂) 43.1 (CMe₃), 29.8 (CMe₃), 14.6 (CH₂). Spectroscopic data consistent with those reported in the literature.¹

Lab Book Reference: PJR 2/110A
2,2-Dimethyl-1-pyrrolidin-1-yl-propanone S1

Trimethylacetyl chloride (3.87 g, 32.0 mmol, 1.0 eq.) was added to a stirred solution of pyridine (4.30 mL, 54.0 mmol, 1.7 eq.) and pyrrolidine (2.89 mL, 32.0 mmol, 1.0 eq.) in CHCl₃ (28 mL) at 0 °C. The resulting solution was heated at 65 °C and stirred for 16 h. The solution was allowed to cool to rt and then water (50 mL) was added. The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product as a yellow solid. Recrystallisation from CHCl₃ gave amide S1 (5.09 g, 100%) as colourless needles, mp 53-56 °C (lit., 456-59 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.54 (br s, 4H, NCH₂), 1.86 (br s, 4H, CH₂), 1.25 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 176.4 (C=O), 47.8 (NCH₂), 38.9 (CMe₃), 27.5 (CMe₃), 23.0 (CH₂). Spectroscopic data consistent with those reported in the literature.¹

Lab Book Reference: PJR 1/55

2,2-Dimethyl-1-pyrrolidin-1-ylpropan-1-thione 9³

Phosphorous(V) sulfide (17.78 g, 80.0 mmol, 1.25 eq.) was added to a stirred solution amide S1 (10.0 g, 64 mmol, 1.0 eq.) in pyridine (100 mL) at rt under Ar. The resulting solution was heated at 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M HCl(aq) (150 mL). 1 M HCl(aq) was added until pH 3 was obtained. The resulting solution was stirred at rt for 2 h and then extracted with CH₂Cl₂ (3 × 100 mL). The combined organic extracts were washed with 1 M HCl(aq) (100 mL), water (100 mL) and brine (100 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography
on silica with 7:3 petrol-EtOAc as eluent gave thioamide 9 (5.09 g, 100%) as pale yellow needles, mp 32-35 °C (lit., 6 33-35 °C); R_F (7:3 petrol-EtOAc) 0.5; 1H NMR (400 MHz, CDCl_3) δ 3.83 (t, J = 7.0 Hz, 2H, NCH_2), 3.74 (t, J = 7.0 Hz, 2H, NCH_2), 1.95 (quintet, J = 7.0 Hz, 2H, CH_2), 1.81 (quintet, J = 7.0 Hz, 2H, CH_2), 1.29 (s, 9H, CMe_3); 13C NMR (100.6 MHz, CDCl_3) δ 208.4 (C=S), 57.5 (NCH_2), 52.7 (NCH_2) 43.4 (CMe_3), 30.1 (CMe_3), 27.2 (CH_2), 22.8 (CH_2). Spectroscopic data consistent with those reported in the literature. 6

Lab Book Reference: PJR 2/110A

1-[(2R)-2-[(S)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (S,R)-13 and 1-[(2R)-2-[(R)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (R,R)-12

(Scheme 3 and Scheme 4)

Using general procedure A, s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), N-thiopivaloyl azetidine 1 (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine 3 (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) and benzaldehyde (76 µL, 0.75 mmol, 1.5 eq.) gave the crude product which contained an 86:14 mixture of alcohols (R,R)-12 and (S,R)-13 by 1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (S,R)-13 (12 mg, 9%, 58:42 er by CSP-HPLC) as a white solid, mp 151-153 °C; R_F (4:1 petrol-EtOAc) 0.3; IR (CHCl_3) 3203 (OH), 2921, 1441, 1414, 1341, 1242, 1126, 996, 980, 731 cm⁻¹; 1H NMR (400 MHz, CDCl_3) δ 7.46-7.43 (m, 2H, o-Ph), 7.39-7.35 (m, 2H, m-Ph), 7.32 (tt, J = 7.5, 1.5 Hz, 1H, p-Ph), 5.47 (br s, 1H, CHO), 5.28 (dddd, J = 9.5, 5.0, 2.0, 2.0 Hz, 1H, NCH), 4.54 (br s, 1H, OH), 4.23 (ddd, J = 9.5, 5.0, 2.0 Hz, 1H, NCH_2B), 2.19-2.06 (m, 1H, CH_2B), 1.30 (s, 9H, CMe_3); 13C NMR (100.6 MHz, CDCl_3) δ 211.1 (C=S), 139.6 (ipso-Ph), 128.2 (Ph), 127.7 (Ph), 126.7 (Ph), 73.7 (OCH or NCH), 73.5 (OCH or NCH), 56.1 (NCH_2), 43.4 (CMe_3) 29.5 (CMe_3), 17.2 (CH_2); MS (ESI) m/z 286 [(M + Na)^+], 264 [(M + H)^+], 308 (100); HRMS m/z calcd for C_{15}H_{21}NO_3 (M + Na)^+ 286.1414, found 286.1414 (0.0 ppm error); [α]_D +40.9 (c 0.65 in
CHCl₃); CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (S,R)-13 7.4 min, (R,S)-13 10.0 min and alcohol (R,R)-12 (99 mg, 75%, 75:25 er by CSP-HPLC) as a white solid, mp 109-111 °C (lit.,³ 116-117 °C); Rₚ (4:1 petrol-EtOAc) 0.2; ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.43 (m, 2H, Ph), 7.39-7.29 (m, 3H, Ph), 5.32 (d, J = 7.5 Hz, 1H, CHOH), 5.22 (dddd, J = 9.0, 7.5, 5.0, 1.5 Hz, 1H, NCH), 5.17 (br s, 1H, OH), 4.31 (td, J = 10.0, 5.0 Hz, 1H, NCH₂), 4.20-4.13 (m, 1H, NCH₂), 2.20 (dddd, J = 12.0, 10.0, 9.0, 7.5 Hz, 1H, CH₂), 1.86 (ddt, J = 12.0, 9.5, 5.0 Hz, 1H, CH₂), 1.35 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 212.3 (C=S), 139.9 (ipso-Ph), 128.3 (Ph), 128.1 (Ph), 127.3 (Ph), 76.3 (OCH or NCH), 73.8 (OCH or NCH), 56.0 (NCH₂), 43.6 (CMe₃), 29.6 (CMe₃), 18.3 (CH₂); [α]D +74.8 (c 0.75 in CHCl₃); CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (R,R)-12 17.8 min, (S,S)-12 20.4 min. Spectroscopic data for rac-12 is consistent with those reported in the literature.³

Lab Book Reference PJR 8/624

Note: In Hodgson’s paper,³ rac-12 was reported as the only diastereomer generated. In our hands, we always observed two diastereomers, 12 (major) and 13 (minor). Both have been fully characterised, including X-ray crystallography (see Section 2).

1-((R)-2-((S)-Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (S,R)-15 and 1-((R)-2-((R)-hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (R,R)-14

(Scheme 3)

Using general procedure B, s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine 3 (145 µL, 0.65 mmol, 1.3 eq.) and N-thiopivaloyl pyrrolidine 9 (86 mg, 0.50 mmol, 1.0 eq.) in Et₂O (5 mL) and benzaldehyde (76 µL, 0.75 mmol, 1.5 eq.) gave the crude product which contained a 58:42 mixture of diastereomeric alcohols (S,R)-15 and (R,R)-14 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et₂O as eluent gave alcohol (S,R)-15 (55 mg, 40%, 86:14 er by CSP-HPLC) as a white solid, mp 169-174
°C; $R_F$ (7:3 petrol-Et$_2$O) 0.2; IR (CHCl$_3$) 3386 (OH), 2972, 2876, 1604, 1478, 1383, 1365, 1160, 732 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, $J$ = 7.0 Hz, 2H, o-Ph), 7.34 (t, $J$ = 7.0 Hz, 2H, m-Ph), 7.26 (t, $J$ = 7.0 Hz, 1H, p-Ph), 5.90 (br s, 1H, OCH), 5.36-5.32 (m, 1H, NCH$_{A}$H$_{B}$), 2.28 (br s, 1H, OH), 2.12-1.97 (m, 2H, CH), 1.75-1.64 (m, 2H, CH), 1.44 (s, 9H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 210.1 (C=S), 141.9 (ipso-Ph), 128.1 (Ph), 127.2 (Ph), 125.5 (Ph), 71.4 (OCH or NCH), 70.4 (OCH or NCH), 54.7 (NCH$_2$), 44.2 (CMe$_3$), 30.7 (CMe$_3$), 25.0 (CH$_2$), 22.4 (CH$_2$); MS (ESI) $m/z$ 300 [(M + Na)$^+$, 20], 278 [(M + H)$^+$, 100], 260 (30), 125 (40); HRMS $m/z$ calcd for C$_{16}$H$_{23}$NOS (M + H)$^+$ 278.1573, found 278.1570 (1.1 ppm error); $[\alpha]_D$ +7.0 (c 1.0 in CHCl$_3$); CSP-HPLC: Chiracel AD (95:5 Hexane-iPrOH, 1.0 mL min$^{-1}$) ($S$,$R$)-15 11.3 min, ($R$,$S$)-15 14.7 min and alcohol ($R$,$R$)-14 (50 mg, 37%, 82:18 er by CSP-HPLC) as a colourless oil, $R_F$ (7:3 petrol-Et$_2$O) 0.1; IR (film) 3387 (OH), 2973, 2876, 1605, 1452, 1411, 1383, 1365, 1162, 732 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.41-7.29 (m, 5H, Ph), 5.68 (dd, $J$ = 8.0, 8.0, 3.5 Hz, 1H, NCH), 5.29-5.26 (m, 1H, OCH), 4.11 (dd, $J$ = 11.5, , 5.5 5.5 Hz, 1H, NCH$_{A}$H$_{B}$), 3.97 (br d, $J$ = 5.0 Hz, 1H, OH), 3.25-3.18 (m, 1H, NCH$_{A}$H$_{B}$), 1.90-1.73 (m, 4H, CH), 1.45 (s, 9H, CMe$_3$); $^{13}$C NMR rotamers (100.6 MHz, CDCl$_3$) δ 212.6 (C=S), 141.8 (ipso-Ph), 128.3 (Ph), 128.5 (Ph), 128.3 (Ph), 127.8 (Ph), 127.6 (Ph), 127.1 (Ph), 127.0 (Ph), 74.4 (br, OCH), 69.8 (NCH), 65.3 (NCH$_2$), 52.7 (NCH$_2$), 44.3 (CMe$_3$), 30.7 (CMe$_3$), 24.3 (CH$_2$), 24.1 (CH$_2$); MS (ESI) $m/z$ 300 [(M + Na)$^+$, 20], 278 [(M + H)$^+$, 100], 260 (20), 125 (20); HRMS $m/z$ calcd for C$_{16}$H$_{23}$NOS (M + H)$^+$ 278.1573, found 278.1570 (1.1 ppm error); $[\alpha]_D$ +94.2 (c 0.8 in CHCl$_3$); CSP-HPLC: Chiracel AD (90:10 Hexane-iPrOH, 1.0 mL min$^{-1}$) ($R$,$R$)-14 10.6 min, ($S$,$S$)-14 22.4 min.

Lab Book Reference PJR 8/636 and 6/501

**rac-Methyl 1-(2,2-dimethylpropanethioyl)azetidine-2-carboxylate rac-16**

![rac-16](image)

(Racemic standard for Scheme 3)

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added to a stirred solution of N-thiopivaloyl azetidine 1 (79 mg, 0.08 mL, 0.50 mmol, 1.0 eq.) and TMEDA (0.18
mL, 131 mg, 1.2 mmol, 2.4 eq.) in Et₂O (7 mL) at −100 °C under N₂. The resulting solution was stirred at −100 °C for 2 min. Then, methyl chloroformate (0.077 mL, 95 mg, 1.0 mmol, 2.0 eq.) was added and the solution was stirred at −100 °C for 10 min and allowed to warm to rt over the course of 1 h. 2 M HCl (aq) (3 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave methyl ester rac-16 (13.6 mg, 0.063 mmol, 13%) as a pale yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 5.02-4.96 (m, 1H, CHN), 4.68–4.59 (m, 1H, CH₃N), 4.52–4.43 (m, 1H, CH₂N), 3.75–3.73 (m, 3H, CO₂Me), 2.59–2.48 (m, 1H, CH₃), 2.24–2.14 (m, 1H, CH₂), 1.35–1.33 (m, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 211.6 (C=S), 170.0 (CO₂Me), 65.9 (CHN), 56.1 (CH₂N), 52.4 (CO₂Me), 43.1 (CMe₃), 29.6 (CMe₃), 19.1 (CH₂). Spectroscopic data consistent with those reported in the literature.³
Lab Book Reference: JCS-1-102

(R)-Methyl 1-(2,2-dimethylpropanethiol)azetidine-2-carboxylate (R)-16

(Scheme 3)
Using general procedure A, s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), N-thiopivaloyl azetidine 1 (0.08 mL, 79 mg, 0.5 mmol, 1.0 eq), (−)-sparteine 3 (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et₂O (5 mL) and methyl chloroformate (0.06 mL, 71 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 8:2:7:3 hexane-EtOAc as eluent gave (R)-16 (48 mg, 0.225 mmol, 45%, 67:33 er by CSP-HPLC) as a pale yellow oil, [α]₀ +45.5 (c 0.52 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-iPrOH, 1.0 mL min⁻¹) (S)-16 12.7 min, (R)-16 13.8 min.
Lab Book Reference: JCS-5-58
(R)-Methyl 1-(2,2-dimethylpropanethioyl)pyrrolidine-2-carboxylate (R)-17

(Scheme 3)

Using general procedure B, s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), N-thiopivaloyl pyrrolidine 9 (0.084 mL, 86 mg, 0.5 mmol, 1.0 eq), (–)-sparteine 3 (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et₂O (5 mL) and methyl chloroformate (0.06 mL, 71 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave (R)-17 (67 mg, 0.29 mmol, 58%, 76:24 er by CSP-HPLC) as a pale yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 5.11 (dd, J = 8.5, 5.0 Hz, CHN), 4.04–3.90 (m, 2H, CH₂N), 3.71 (s, 3H, CO₂Me), 2.30–2.10 (m, 2H, CH₂), 2.07–1.90 (m, 2H, CH₂), 1.42 (s, 9H, CMe₃); ¹³C NMR δ 211.6 (C=S), 171.5 (CO₂Me), 68.6 (CHN), 53.4 (CH₂N), 52.3 (CO₂Me), 43.8 (CMe₃), 30.4 (CMe₃), 28.0 (CH₂), 26.1 (CH₂); [α]D +25.3 (c 1.08 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-iPrOH, 1.0 mL min⁻¹) (S)-17 10.6 min, (R)-17 11.8 min.

Lab Book Reference: JCS-5-59

rac-1-(2,2-Dimethylpropanethioyl)azetidine-2-carboxylic acid rac-18

(Racemic standard for Scheme 3)

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq) was added to a stirred solution of N-thiopivaloyl azetidine 1 (0.077 mL, 79 mg, 0.5 mmol, 1.0 eq) and TMEDA (145 mg, 0.2 mL, 1.3 mmol, 2.6 eq) in Et₂O (7 mL) at −100 °C under N₂. The resulting solution was stirred at −100 °C for 2 min. Then, dry CO₂ (generated from solid CO₂ flushed through CaCl₂ and added into the reaction via cannula) was bubbled through the reaction mixture for 10 min at −100 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et₂O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M HClₐq and extracted with CH₂Cl₂ (6 x 5 mL). The combined organic extracts were dried (MgSO₄) and
evaporated under reduced pressure to give acid *rac*-**18** (47 mg, 0.23 mmol, 46%) as an off-white solid, IR (ATR) 2968, 2924, 2867, 2638 (CO$_2$H), 2554 (CO$_2$H), 1705 (C=O), 1455, 1421, 1397, 1365, 1339, 1294, 1223, 1198, 1164, 1045, 1031, 1005, 931, 825, 780, 721, 680, 655, 563, 537, 528 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.07 (dd, $J$ = 9.0, 5.0 Hz, 1H, CHN), 4.62 (ddd, $J$ = 9.5, 9.5, 9.5 Hz, 1H, $CH_AH_BN$), 4.49 (ddd, $J$ = 9.5, 9.5, 5.5 Hz, 1H, $CH_AH_BN$), 2.64-2.53 (m, 1H, $CH_AH_B$), 2.46-2.35 (m, 1H, $CH_AH_B$), 1.34 (s, 9H, CMe$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 212.0 (C=S), 173.8 (CO$_2$H), 66.5 (CHN), 56.5 (CH$_2$N), 43.3 (CMe$_3$), 29.6 (CMe$_3$), 19.0 (CH$_3$); MS (ESI) material degraded during analysis.

Lab Book Reference JCS-2-5

**(S)-1-(2,2-Dimethylpropanethiyl)azetidine-2-carboxylic acid (S)-**18

(Scheme 3)

$s$-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq) was added to a stirred solution of *N*-thiopivaloyl azetidine 1 (0.077 mL, 79 mg, 0.5 mmol, 1.0 eq) and (*-)sparteine 3 (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et$_2$O (5 mL) at $-78$ °C under N$_2$. The resulting solution was stirred at $-78$ °C for 30 min. Then, dry CO$_2$ (generated from solid CO$_2$ flushed through CaCl$_2$ and added into the reaction via cannula) was bubbled through the reaction mixture for 10 min at $-78$ °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et$_2$O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH $< 2$ with 2 M HCl$_{(aq)}$ and extracted with CH$_2$Cl$_2$ (6 x 5 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated under reduced pressure to give acid (S)-**18** (97 mg, 0.48 mmol, 96%, 75:25 er by CSP-HPLC of the methyl ester) as an off white solid, mp 126–139 °C; [$\alpha$]$_D$ $-62.2$ (c 0.93 in EtOAc). Acid (S)-**18** was converted into methyl ester (S)-**16** by reaction with Me$_3$SiCHN$_2$ in MeOH/toluene (4:6 v/v, 2 mL), quenching with glacial AcOH and evaporation under reduced pressure. CSP-HPLC of methyl ester (S)-**16**: Chiralcel OD-H (98:2 Hexane-$i$PrOH, 1.0 mL min$^{-1}$) (S)-**16** 14.3 min, (R)-**16** 18.2 min.
Rac-1-(2,2-dimethylpropanethioyl)pyrrolidine-2-carboxylic acid rac-19

(Racemic standard for Scheme 3)

s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq) was added to a stirred solution of N-thiopivaloyl azetidine 9 (0.16 mL, 171 mg, 1.0 mmol, 1.0 eq) and TMEDA (0.20 mL, 155 mg, 1.3 mmol, 1.3 eq) in Et₂O (10 mL) at −78 °C under N₂. The resulting solution was stirred at −78 °C for 30 min. Then, dry CO₂ (generated from solid CO₂ flushed through CaCl₂ and added into the reaction via cannula) was bubbled through the reaction mixture for 10 min at −78 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et₂O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M HCl(aq) and extracted with CH₂Cl₂ (6 x 5 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give acid rac-19 (184 mg, 0.86 mmol, 86%) as an off-white solid, IR (ATR) 2978, 2869 (CO₂H), 2646 (CO₂H), 2553 (CO₂H), 1703 (C=O), 1474, 1416, 1368, 1336, 1297, 1272, 1225, 1173, 1152, 1090, 1058, 1021, 929, 915, 871, 804, 692, 61, 597, 502 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.25-5.13 (m, 1H, CHN), 4.06-3.98 (m, 1H, CH₂N), 3.96-3.88 (m, 1H, CH₂CH₂N), 2.31-1.99 (m, 4H, CH₂CH₂), 1.43 (s, 9H, CMe₃); ¹³C NMR (100 MHz, CDCl₃) 211.8 (C=S), 175.2 (CO₂H), 66.6 (CHN), 53.3 (CH₂N), 43.9 (CMe₃), 30.5 (CMe₃), 27.9 (CH₂), 26.1 (CH₂); MS (ESI) m/z 216 [(M + H)⁺, 55], 238 [(M + Na)⁺, 100]; HRMS m/z calcd for C₁₀H₁₇NO₂S (M + Na)⁺ 238.0872, found 238.0878 (−2.2 ppm error).

(S)-1-(2,2-Dimethylpropanethioyl)pyrrolidine-2-carboxylic acid (S)-19

(Scheme 3)

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq) was added to a stirred solution of N-thiopivaloyl azetidine 9 (0.08 mL, 86 mg, 0.5 mmol, 1.0 eq) and (−)-sparteine 3 (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et₂O (5 mL) at −78 °C under N₂. The resulting solution
was stirred at –78 °C for 1 h. Then, dry CO₂ (generated from solid CO₂ flushed through CaCl₂ and added into the reaction via cannula) was bubbled through the reaction mixture for 10 min at –78 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et₂O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M HCl(aq) and extracted with CH₂Cl₂ (6 x 5 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give acid (S)-19 (79 mg, 0.37 mmol, 74%, 80:20 er by CSP-HPLC of the methyl ester) as an off white solid. Acid (S)-19 was converted into methyl ester (S)-17 by reaction with Me₃SiCHN₂ in MeOH/toluene (4:6 v/v, 2 mL), quenching with glacial AcOH and evaporation under reduced pressure. CSP-HPLC of the methyl ester: Chiralcel OD-H (98:2 Hexane-iPrOH, 1.0 mL min⁻¹) (S)-17 11.6 min, (R)-17 12.9 min.

(R)-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (R)-2

(Scheme 3)

Using general procedure A, s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq.), N-thiopivaloyl azetidine 1 (79 mg, 0.50 mmol, 1.0 eq.) and (−)-sparteine 3 (0.14 mL, 0.60 mmol, 1.2 eq.) in Et₂O (5 mL) and methyl iodide (47 µL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et₂O as eluent gave methylated azetidine (R)-3 (79 mg, 91%, 59:41 er by CSP-HPLC) as a colourless oil, Rf (8:2 petrol-Et₂O) 0.3; ¹H NMR (400 MHz, CDCl₃) δ 4.91-4.82 (m, 1H, NCH), 4.57 (dddd, J = 10.5, 9.0, 7.0, 1.5 Hz, 1H, NCH₂H₃), 4.43 (ddddd, J = 10.5, 10.0, 5.0 Hz, 1H, NCH₂H₂), 2.54 (ddddd, J = 11.0, 10.0, 9.0, 7.0 Hz, 1H, CH₂H₂), 1.85 (ddddd, J = 11.0, 9.5, 5.0, 5.0 Hz, 1H, NCH₂H₂), 1.62 (d, J = 6.0 Hz, 3H, Me), 1.34 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) rotamers δ 209.6 (C=S), 65.7 (NCH), 64.8 (NCH), 55.6 (NCH₂), 53.7 (NCH₂), 43.3 (CMe₃), 30.9 (CMe₃), 29.6 (CMe₃), 23.1 (CH₂), 18.5 (Me); [α]D +0.2 (c 1.0 in CHCl₃) (lit.,³ [α]D −21.3 (c 1.15 in CHCl₃ for (R)-2 of 99:1 er)); CSP-HPLC: Chiralcel OD-H (99:0.1 Hexane-iPrOH, 1.0 mL min⁻¹) (S)-2 11.1 min, (R)-2 11.9 min. Spectroscopic data consistent with those reported in the literature.³
**Note:** Optical rotation data is not consistent with that reported in the literature and the configuration was assigned by CSP-HPLC (see Section 2).

Lab Book Reference PJR 8/649

**rac-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione rac-2**

![Structure of rac-2](image)

(Racemic standard for Scheme 3)

Using general procedure A, s-BuLi (0.46 mL of a 1.3M solution in hexanes, 0.60 mmol, 1.2 eq.), N-thiopivaloyl azetidine 1 (79 mg, 0.50 mmol, 1.0 eq.) and TMEDA (90 µL, 0.60 mmol, 1.2 eq.) in Et₂O (5 mL) and methyl iodide (47 µL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et₂O gave methylated azetidine rac-2 (58 mg, 67%) as a colourless oil.

Lab Book Reference PJR 8/642

**((S)-2,2-Dimethyl-1-(2-methylpyrrolidin-1-yl)propane-1-thione (S)-20**

![Structure of (S)-20](image)

(Scheme 3)

Using general procedure B, s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), N-thiopivaloyl pyrrolidine 9 (86 mg, 0.50 mmol, 1.0 eq.) and (−)-sparteine 3 (0.15 mL, 0.65 mmol, 1.3 eq.) in Et₂O (5 mL) and methyl iodide (47 µL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et₂O as eluent gave methylated pyrrolidine (S)-20 (78 mg, 84%, 58:42 er by CSP-HPLC) as a colourless oil, \(R_f\) (8:2 petrol-Et₂O) 0.3; IR (film) 2975, 2876, 1530, 1458, 1410, 1325, 1116, 730 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) 85:15 mixture of rotamers δ 5.15-5.07 (m, 0.85H, NCH), 4.84-4.78 (m, 0.15H, NCH), 4.21 (ddd, \(J = 14.5, 8.5, 8.5\) Hz, 0.15H, NCHₐH₉), 4.00 (ddd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 3.90 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 3.76 (ddd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 3.51 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 3.31 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 3.13 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 3.02 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 2.84 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 2.70 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 2.57 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 2.35 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 2.24 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 2.11 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 1.98 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 1.86 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 1.71 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 1.59 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 1.47 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 1.35 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 1.24 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 1.13 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 1.03 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 0.91 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 0.80 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 0.70 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 0.60 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 0.49 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 0.38 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 0.28 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 0.18 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.85H, NCH₈H₉), 0.08 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉), 0.00 (dd, \(J = 13.5, 12.0, 7.0\) Hz, 0.15H, NCH₈H₉).
Hz, 0.85H, NCH₂H₃), 3.83-3.76 (m, 0.15H, NCH₂H₃), 3.67 (ddd, J = 13.5, 6.5, 6.5 Hz, 0.85H, NCH₂H₃), 2.13-1.86 (m, 3H, CH), 1.66-1.59 (m, 1H, CH), 1.43 (s, 1.35H, CMe₃), 1.39 (s, 7.65H, CMe₃), 1.33 (d, J = 6.5 Hz, 2.55H, Me), 1.24 (d, J = 6.0 Hz, 0.45H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 208.8 (C=S), 61.8 (NCH), 52.0 (NCH₂), 44.0 (CMe₃), 30.6 (CMe₃), 30.4 (CH₂), 24.9 (CH₂), 17.7 (Me); MS (ESI) m/z 208 [(M + Na)⁺, 100], 186 [(M + H)⁺, 20]; HRMS m/z calcd for C₁₀H₁₉NS (M + Na)⁺ 208.1136, found 208.1131 (−0.5 ppm error); [α]ₒD −10.1 (c 0.95 in CHCl₃); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-iPrOH, 1.0 mL min⁻¹) (S)-20 8.0 min, (R)-20 9.0 min. Lab Book Reference PJR 8/650

**rac-2,2-Dimethyl-1-(2-methylpyrrolidin-1-yl)propane-1-thione rac-20**

(Racemic standard for Scheme 3)

Using general procedure B, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), N-thiopivaloyl pyrrolidine 9 (171 mg, 1.0 mmol, 1.0 eq.) and TMEDA (0.195 mL, 1.3 mmol, 1.3 eq.) in Et₂O (5 mL) and methyl iodide (374 µL, 6.0 mmol, 4.6 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave methylated pyrrolidine rac-20 (425 mg, 77%) as a yellow oil.

Lab Book Reference JCS 2-33
1-[(2S)-2-][(R)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (R,S)-13 and 1-[(2S)-2-][(S)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (S,S)-12

(Scheme 4)

Using general procedure A, s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), N-thiopivaloyl azetidine 1 (79 mg, 0.5 mmol, 1.0 eq.), (+)-sparteine surrogate 21 (116 mg, 0.6 mmol, 1.2 eq.) in Et₂O (5 mL) and benzaldehyde (76 µL, 0.75 mmol, 1.5 eq.) gave the crude product which contained an 86:14 mixture of alcohols (S,S)-12 and (R,S)-13 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (R,S)-13 (9 mg, 7%, 54:46 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (S,R)-13 7.5 min, (R,S)-13 10.2 min and alcohol (R,R)-12 (91 mg, 70%, 54:46 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (R,R)-12 18.2 min, (S,S)-12 20.4 min.

Lab Book Reference PJR 8/660

1-[(2S)-2-][(R)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (R,S)-13 and 1-[(2S)-2-][(S)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (S,S)-12

(Scheme 4)

Using general procedure A, s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), N-thiopivaloyl azetidine 1 (79 mg, 0.5 mmol, 1.0 eq.), diamine (S,S)-4 (186 mg, 0.6 mmol, 1.2 eq.) in Et₂O (5 mL) and benzaldehyde (76 µL, 0.75 mmol, 1.5 eq.) gave the crude product which
contained a 77:23 mixture of alcohols \((S,S)-12\) and \((R,S)-13\) by \(^1\)H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol \((R,S)-13\) (26 mg, 20\%, 65:35 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min\(^{-1}\)) \((S,R)-13\) 7.5 min, \((R,S)-13\) 10.2 min and alcohol \((R,R)-12\) (96 mg, 73\%, 53:47 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min\(^{-1}\)) \((R,R)-12\) 18.7 min, \((S,S)-12\) 20.9 min.

**2,2-Dimethyl-1-(2-(trimethylstannyl)azetidin1-yl)propane-1-thione 22**

![2,2-Dimethyl-1-(2-(trimethylstannyl)azetidin1-yl)propane-1-thione 22](image)

Using general procedure A, s-BuLi (1.38 mL of a 1.3 M solution in hexanes, 1.8 mmol, 1.2 eq.), \(N\)-thiopivaloyl azetidine 1 (236 mg, 1.5 mmol, 1.0 eq.) and (−)-sparteine 3 (0.41 mL, 1.8 mmol, 1.2 eq.) in Et\(_2\)O (8 mL) and Me\(_3\)SnCl (2.25 mL of a 1.0 M solution in hexane, 2.25 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5-9:1 petrol-Et\(_2\)O as eluent gave stannane \((S)-22\) (263 mg, 55\%, 68:32 er by CSP-HPLC) as a colourless oil, \(R_f\) (9:1 petrol-Et\(_2\)O) 0.3; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.65-4.47 (m, 3H, NCH), 2.57-2.48 (m, 1H, CH), 2.26-2.18 (m, 1H, CH), 1.33 (s, 9H, CMe\(_3\)), 0.15 (s, 9H, SnMe\(_3\)); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 202.4 (C=S), 61.6 (NCH), 56.8 (NCH\(_2\)), 42.4 (CMe\(_3\)), 29.9 (CMe\(_3\)), 18.3 (CH\(_2\)), −7.7 (SnMe\(_3\)); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-iPrOH, 1.0 mL min\(^{-1}\)) 5.4 min (major), 8.1 min (minor). Spectroscopic data consistent with those reported in the literature.\(^3\)

Lab Book Reference PJR 8/629, 8/637, 8/629
2,2-Dimethyl-1-(2-(trimethylstannyl)azetidin1-yl)propane-1-thione rac-22

Using general procedure A, s-BuLi (1.38 mL of a 1.3 M solution in hexanes, 1.8 mmol, 1.2 eq.), \(N\)-thiopivaloyl azetidine 1 (236 mg, 1.5 mmol, 1.0 eq.) and TMEDA (0.27 mL, 1.8 mmol, 1.2 eq.) in Et\(_2\)O (8 mL) and Me\(_3\)SnCl (2.25 mL of a 1.0 M solution in hexane, 2.25 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5-9:1 petrol-Et\(_2\)O as eluent gave stannane rac-22 (284 mg, 60%) as a colourless oil.

Lab Book Reference: PJR 8/680

(S)-2,2-Dimethyl-1-(2-(trimethylstannyl)pyrrolidin-1-yl)propane-1-thione 23

Using general procedure B, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.), \(N\)-thiopivaloyl pyrrolidine 9 (171 mg, 1.00 mmol, 1.0 eq.) and (−)-sparteine 3 (296 μL, 1.30 mmol, 1.3 eq.) in Et\(_2\)O (7 mL) and trimethyltin chloride (1.50 mL of a 1.0 M solution in hexanes, 1.5 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave stannane 23 (228 mg, 68%, 78:22 er by CSP-HPLC) as a colourless oil, \(R_F\) (95:5 petrol-EtOAc) 0.3; IR (film) 2978, 1500, 1482, 1448, 1390, 1246, 1074, 1036, 912, 809, 730 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.37-4.28 (m, 1H, NCH), 3.91-3.78 (m, 2H, NCH\(_2\)), 2.20-2.09 (m, 2H, CH\(_2\)), 2.07-2.01 (m, 1H, CH), 1.98-1.88 (m, 1H, CH), 1.40 (s, 9H, CMe\(_3\)), 0.07 (s, 9H, SnMe\(_3\)); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 201.0 (C=S), 63.7 (NCH), 53.1 (NCH\(_2\)), 43.1 (CMe\(_3\)), 30.7 (CMe\(_3\)), 28.2 (CH\(_2\)), 27.6 (CH\(_2\)), −6.7 (SnMe\(_3\)); MS (ESI) \(m/z\) 336 [(M\(^{120}\)Sn + H)\(^+\), 100], 334 [(M\(^{118}\)Sn + H)\(^+\), 70], 332 [(M\(^{116}\)Sn + H)\(^+\), 30]; HRMS \(m/z\) calcd for C\(_{12}\)H\(_{25}\)NS\(^{120}\)Sn (M + Na\(^+\)) 336.0803 (−1.0 ppm error), found 336.0806; [\(\alpha\)]\(_D\) +290.89 (c 0.70 in CHCl\(_3\)); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-\(t\)PrOH, 1.0 mL min\(^{-1}\)) (S)-18 4.9 min, (R)-18 6.4 min. Lab Book Reference: PJR 8/630A
**rac-2,2-Dimethyl-1-(2-(trimethylstannyl)pyrrolidin-1-yl)propane-1-thione rac-23**

Using general procedure B, s-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.), N-thiopivaloyl pyrrolidine 9 (171 mg, 1.00 mmol, 1.0 eq.) and TMEDA (194 µL, 1.30 mmol, 1.3 eq.) in Et₂O (7 mL) and trimethyltin chloride (1.50 mL of a 1.0 M solution in hexanes, 1.5 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave stannane rac-23 (254 mg, 76%) as a colourless oil.

Lab Book Reference PJR 8/699

**1-[2-[Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione rac-13 and 1-[(2-[hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione rac-12**

(Scheme 5)

n-BuLi (0.06 mL of a 2.5 M solution in hexanes, 0.14 mmol, 1.1 eq.) was added dropwise to a stirred solution of enantioenriched stannane 22 (43 mg, 0.13 mmol, 1.0 eq., 68:32 er) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (16 µL, 0.16 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M HCl(aq) (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture of alcohols rac-12 and rac-13 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol rac-13 (9 mg, 26%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralce AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (S,R)-13 7.3 min, (R,S)-13 9.8 min and alcohol rac-12 (20 mg, 58%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiralce AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (S,R)-13 7.3 min, (R,S)-13 9.8 min.
er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min\(^{-1}\)) \((R,R)-12\) 18.0 min, \((S,S)-12\) 20.3 min.

Lab Book Reference PJR 8/628

(Scheme 5)

\(n\)-BuLi (0.06 mL of a 2.5 M solution in hexanes, 0.14 mmol, 1.1 eq.) was added dropwise to a stirred solution of enantioenriched stannane 22 (43 mg, 0.13 mmol, 1.0 eq., 68:32 er) and TMEDA (21 µL, 0.14 mmol, 1.1 eq.) in Et\(_2\)O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (16 µL, 0.16 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M HCl\(_{aq}\) (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et\(_2\)O (3 x 10 mL). The combined organic layers were dried (MgSO\(_4\)) and evaporated under reduced pressure to give the crude product which contained a 76:24 mixture of alcohols \(rac\)-12 and \(rac\)-13 by \(^1\)H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol \(rac\)-13 (8 mg, 24%, 50:50 er by CSP-HPLC) as a white solid CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min\(^{-1}\)) \((S,R)-13\) 7.4 min, \((R,S)-13\) 10.1 min and alcohol \(rac\)-12 (21 mg, 61%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min\(^{-1}\)) \((R,R)-12\) 18.5 min, \((S,S)-12\) 20.4 min.

Lab Book Reference PJR 8/629

1-(2-(Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione \(rac\)-15 and 1-(2-(hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione \(rac\)-14

(Scheme 5)

\(n\)-BuLi (26 µL of a 2.5 M solution in hexanes, 0.066 mmol, 1.1 eq.) was added to a stirred solution of enantioenriched stannane 23 (20 mg, 0.06 mmol, 1.0 eq., 78:22 er) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (7 µL, 0.07 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10
min and 1 M HCl\(_{\text{aq}}\) (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et\(_2\)O (3 x 10 mL). The combined organic layers were dried (MgSO\(_4\)) and evaporated under reduced pressure to give the crude product which contained a 60:40 mixture of alcohols *rac*-14 and *rac*-15 by \(^1\)H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *rac*-15 (7 mg, 42\%, 51:49 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min\(^{-1}\)) (*S*,*R*)-15 11.2 min, (*R*,*S*)-15 14.6 min and alcohol *rac*-14 (9 mg, 52\%, 51:49 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min\(^{-1}\)) (*R*,*R*)-14 10.6 min, (*S*,*S*)-14 23.1 min.

Lab Book Reference PJR 8/634

(Scheme 5)
n-BuLi (26 µL of a 2.5M solution in hexanes, 0.066 mmol, 1.1 eq.) was added to a stirred solution of enantioenriched stannane 23 (20 mg, 0.06 mmol, 1.0 eq., 78:22 er) and TMEDA (10 µL, 0.066 mmol, 1.1 eq.) in Et\(_2\)O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (7 µL, 0.07 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M HCl\(_{\text{aq}}\) (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et\(_2\)O (3 x 10 mL). The combined layers were dried (MgSO\(_4\)) and evaporated under reduced pressure to give the crude product which contained a 76:24 mixture of alcohols *rac*-14 and *rac*-15 by \(^1\)H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *rac*-15 (8 mg, 24\%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min\(^{-1}\)) (*S*,*R*)-15 11.3 min, (*R*,*S*)-15 14.7 min and alcohol *rac*-14 (21 mg, 61\%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min\(^{-1}\)) (*R*,*R*)-14 10.6 min, (*S*,*S*)-14 23.0 min.

Lab Book Reference PJR 8/635
1-[(2R)-2-[(S)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (S,R)-13 and 1-[(2R)-2-[(R)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (R,R)-12

(Scheme 6)

A solution of stannane rac-22 (50 mg, 0.16 mmol, 1.0 eq.) in Et₂O (3 mL) was added dropwise to a stirred solution of n-BuLi (0.07 mL of a 2.5 M solution in hexanes, 0.18 mmol, 1.1 eq.) and (−)-sparteine 3 (42 µL, 0.18 mmol, 1.1 eq.) in Et₂O (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (19 µL, 0.19 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M HCl (aq) (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained an 87:13 mixture of alcohols (R,R)-12 and (S,R)-13 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (S,R)-13 (4 mg, 10%, 62:38 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (S,R)-13 7.6 min, (R,S)-13 10.3 min and alcohol (R,R)-12 (37 mg, 88%, 73:27 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (R,R)-12 18.7 min, (S,S)-12 20.8 min.

Lab Book Reference PJR 8/685
1-((R)-2-((S)-Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (S,R)-15 and 1-((R)-2-((R)-hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (R,R)-14

(Scheme 6)
A solution of stannane rac-23 (100 mg, 0.30 mmol, 1.0 eq.) in Et₂O (3 mL) was added to a stirred solution of n-BuLi (0.13 mL of a 2.5 M solution in hexane, 0.33 mmol, 1.1 eq.) and (-)-sparteine 3 (77 µL, 0.33 mmol, 1.1 eq.) in Et₂O (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (46 µL, 0.45 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 1 h and 1 M HCl (aq) (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained a 55:45 mixture of diastereomeric alcohols (S,R)-15 and (R,R)-14 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et₂O as eluent gave alcohol (S,R)-15 (32 mg, 39%, 88:12 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (S,R)-15 11.7 min, (R,S)-15 15.2 min and alcohol (R,R)-14 (29 mg, 35%, 82:18 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel AD (90:10 Hexane-iPrOH, 1.0 mL min⁻¹) (R,R)-14 9.8 min, (S,S)-14 18.8 min.

Lab Book Reference PJR 8/700
s-BuLi (0.23 mL of a 1.3 M solution in hexanes, 0.3 mmol, 1.2 eq.) was added dropwise to a stirred solution of N-thiopivaloyl azetidine 1 (40 mg, 0.25 mmol, 1.0 eq.) in Et₂O (5 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min. Then, benzaldehyde (38 µL, 0.38 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred at −40 °C for 10 min and 1 M HCl (aq) (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained a 62:38 mixture of alcohols rac-12 and rac-13 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc gave alcohol rac-13 (14 mg, 21%) as a white solid and alcohol rac-12 (27 mg, 42%) as a white solid.

Lab Book Reference PJR 8/640
resulting solution was stirred for 30 min. Benzaldehyde (38 µL, 0.38 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred for 10 min at −78 °C and 1 M HCl(aq) was added. The two layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture of alcohols rac-12 and rac-13 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol rac-13 (12 mg, 19%) as a white solid and alcohol rac-12 (28 mg, 43%) as a white solid.

Lab Book Reference PJR 8/643

(Scheme 7)
s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of N-thiopivaloyl azetidine 1 (79 mg, 0.50 mmol, 1.0 eq.) in Et₂O (5 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min. Then, (−)-sparteine 3 (0.14 mL, 0.60 mmol, 1.2 eq.) was added and the resulting solution was stirred for 15 min. The solution was then cooled to −78 °C and stirred at −78 °C for 30 min. Benzaldehyde (38 µL, 0.38 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M HCl(aq) was added. The two layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained an 81:19 mixture of alcohols (R,R)-12 and (S,R)-13 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (S,R)-13 (9 mg, 7%, 59:41 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (S,R)-13 7.5 min, (R,S)-13 10.1 min and alcohol (R,R)-12 (76 mg, 57%, 71:29 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (R,R)-12 18.2 min, (S,S)-12 20.2 min.

Lab Book Reference PJR 8/665
2. Assignment of Stereochemistry

2.1 Assignment of the Configuration of \((R,R)\)-12 and \((S,R)\)-13

Relative stereochemistry:
The relative stereochemistry of racemic \((R^*,R^*)\)-12 and \((S^*,R^*)\)-13 (generated from a s-BuLi/TMEDA reaction, described below) were assigned by X-ray crystallography.

1-\([(2S^*)-2-[(R^*)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione \((R^*,S^*)\)-13 and 1-\([(2S^*)-2-[(S^*)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione \((S^*,S^*)\)-12

Using general procedure A, s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), N-thiopivaloyl azetidine 1 (79 mg, 0.5 mmol, 1.0 eq.), TMEDA (0.2 mL, 151 mg, 1.3 mmol, 2.5 eq.) in Et₂O (5 mL) and benzaldehyde (100 µL, 1.0 mmol, 2.0 eq.) gave the crude product which contained a 65:35 mixture of alcohols \((S^*,S^*)\)-12 and \((R^*,S^*)\)-13 by \(^1\)H NMR spectroscopy. Purification by flash column chromatography on silica with 95:5-8:2 petrol-EtOAc as eluent gave alcohol \((R^*,S^*)\)-13 (25 mg, 19%) as a white solid and alcohol \((R^*,R^*)\)-12 (49 mg, 37%) as a white solid.

Lab Book Reference JCS2-26
X-ray crystallography:

(R\textsuperscript{\text{*}, R\textsuperscript{\text{*}})-12: CCDC number 1417067

(S\textsuperscript{\text{*}, R\textsuperscript{\text{*}})-13: CCDC number 1417066
**Absolute stereochemistry:**

The absolute stereochemistry of \((R,R)-12\) and \((S,R)-13\) was assigned by conversion into \(N\)-Boc azetidine alcohols \((R,R)-S2\) and \((S,R)-S3\) respectively (Scheme S1). The thiopivaloyl group in each of \((R,R)-12\) and \((S,R)-13\) was removed using MeLi and Boc protection then gave \((R,R)-S2\) and \((S,R)-S3\) respectively. The enantiomeric \(N\)-Boc azetidine alcohols \((S,S)-S2\) and \((R,S)-S3\) were independently synthesised from commercially available amino acid \((S)-S4\) (Scheme S1). Comparison of the optical rotation and CSP-HPLC data of the products generated from each of these routes allowed the assignment of configuration.

\[
\begin{align*}
\text{Scheme S1}
\end{align*}
\]
Experimental for Scheme S1:

(S)-1-(tert-Butoxycarbonyl)azetidine-2-carboxylic acid (S)-S5

![Structure of (S)-S5]

NaOH (420 mg, 10.5 mmol, 1.05 eq.) was added to a stirred solution of (S)-2-azetidine carboxylic acid (S)-S4 (1.00 g, 10.0 mmol, 1.0 eq.) and di-tert-butyl dicarbonate (2.83 g, 12.5 mmol, 1.25 eq.) in 2:1 EtOH-water (30 mL) at rt. The resulting solution was stirred at rt for 16 h. Then, the volatiles were evaporated under reduced pressure and the remaining suspension was acidified with 1 M HCl (aq) (20 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give acid (S)-S5 (1.96 g, 99%) as a white solid, mp 97-99 °C (lit., 97-98 °C); ¹H NMR (400 MHz, CDCl₃) δ 9.03 (br s, 1H, OH), 4.77 (br s, 1H, NCH), 3.96-3.85 (m, 2H, NCH₂), 2.46 (br s, 2H, CH₂), 1.46 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 181.5 (C=O, COOH), 156.6 (C=O, Boc), 82.7 (CMe₃), 60.7 (br, NCH), 47.1 (NCH₂), 28.2 (CMe₃), 19.7 (CH₂); [α]D −168.1 (c 0.7 in CHCl₃). Spectroscopic data consistent with those reported in the literature.⁷

Lab Book Reference PJR 7/512

tert-Butyl 2S-benzoylazetidine-1-carboxylate (S)-S6⁹

![Structure of (S)-S6]

N-Me morpholine (0.62 mL, 5.6 mmol, 1.2 eq.), HOBt (870 mg, 5.6 mmol, 1.2 eq.) and EDC (0.98 mL, 5.6 mmol, 1.2 eq.) were added sequentially to a stirred solution of acid (S)-S5 (1.00 g, 4.6 mmol, 1.0 eq.) and N,O-dimethylhydroxylamine.HCl (550 mg, 5.6 mmol, 1.2 eq.) in DMF (10 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2 h and then allowed to warm to rt and stirred at rt for 16 h. Then, EtOAc (30 mL) was added and the solution was washed with 1 M HCl (aq) (10 mL), 2 M NaOH (aq) (2 x 10 mL) and brine (3 x 10 mL), dried
(MgSO₄) and evaporated under reduced pressure to give the crude Weinreb amide (565 mg, 50%) as a pale yellow solid, ¹H NMR (400 MHz, CDCl₃) δ 5.04 (dd, J = 8.5, 5.5 Hz, 1H, NCH), 4.04 (ddd, J = 9.0, 8.0, 6.0 Hz, 1H, NCHₐHₖ), 3.87 (ddd, J = 9.0, 8.0, 6.0 Hz, 1H, NCHₐHₖ), 3.71 (s, 3H, OMe), 3.22 (s, 3H, NMe), 2.51-2.42 (m, 1H, CHₐHₖ), 2.12 (dddd, J = 11.0, 9.0, 5.5, 5.5 Hz, 1H, CHₐHₖ), 1.43 (s, 9H, CMe₃). PhMgCl (1.72 mL of a 2.0 M solution in THF, 3.44 mmol, 1.5 eq.) was added dropwise to a stirred solution of the crude Weinreb amide (565 mg, 2.3 mmol, 1.0 eq.) in THF (10 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 2 h. Then, saturated NH₄Cl (aq) (15 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1-3:1 petrol-EtOAc as eluent gave ketone (S)-S₆ (430 mg, 36% over two steps) as a white solid, mp 77-79 °C; Rₛ (3:1 petrol-EtOAc) 0.3; IR (CHCl₃) 2981, 1720 (C=O, PhCO), 1675 (C=O, Boc), 1426, 1375, 1210, 1010, 920, 815, 730 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.85-7.83 (m, 2H, o-Ph), 7.52 (d, J = 7.5 Hz, 1H, p-Ph), 7.41 (t, J = 7.5 Hz, 2H, m-Ph), 5.50 (dd, J = 9.5, 5.5 Hz, 1H, NCH), 3.99-3.87 (m, 2H, NCH₂), 2.61 (ddddd, J = 11.0, 9.5, 9.0, 6.0 Hz, 1H, CHₐHₖ), 2.06 (ddddd, J = 11.0, 9.0, 5.5, 5.5 Hz, 1H, CHₐHₖ), 1.34 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 195.7 (C=O, PhCO), 155.8 (C=O, Boc), 134.4 (ipso-Ph), 133.6 (Ph), 128.9 (Ph), 128.2 (Ph), 79.8 (CMe₃), 63.6 (br, NCH), 46.9 (br, NCH₂), 28.32 (CMe₃), 21.3 (CH₂); MS (ESI) m/z 284 [(M + Na)⁺, 100]; HRMS m/z calcd for C₁₅H₁₉NO₃ (M + Na)⁺ 284.1257, found 284.1249 (+3.0 ppm error); [α]D −140.9 (c 0.65 in CHCl₃).

Lab Book Reference PJR 7/524


NaBH₄ (73 mg, 1.93 mmol, 1.2 eq.) was added to a stirred solution of ketone (S)-S₆ (420 mg, 1.61 mmol, 1.0 eq.) in MeOH (5 mL) at 0 °C. The resulting solution was stirred at rt for 30 min. Then, the solution was cooled to 0 °C and saturated NH₄Cl (aq) (5 mL) was added dropwise. The
resulting solution was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained an 85:15 mixture of alcohols (S,S)-S2 and (R,S)-S3 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave alcohol (S,S)-S2 (330 mg, 78%, 99:1 er by CSP-HPLC) as a colourless oil, Rₛ (4:1 petrol-EtOAc) 0.3; IR (CHCl₃) 3348 (OH), 2976, 2952, 1687 (C=O), 1445, 1424, 1375, 1246, 1045, 1025, 915, 800, 730 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.36 (m, 2H, o-Ph), 7.34-7.25 (m, 3H, Ph), 5.75 (br s, 1H, OH), 4.75 (d, J = 8.0 Hz, 1H, OCH), 4.34 (ddd, J = 8.0, 8.0, 8.0 Hz, 1H, NCH), 3.83-3.72 (m, 2H, NCH₂), 1.93-1.80 (m, 2H, CH₂), 1.48 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 158.1 (C=O), 139.2 (ipso-Ph), 128.3 (Ph), 127.9 (Ph), 127.0 (Ph), 80.1 (OCH), 79.1 (CMe₃), 67.8 (NCH), 46.1 (NCH₂), 28.3 (CMe₃), 18.7 (CH₂); MS (ESI) m/z 286 [(M + Na)⁺, 100], 264 [(M + H)⁺, 50], 208 (100), 190 (90); HRMS m/z calcd for C₁₅H₂₁NO₃ (M + Na)⁺ 286.1414, found 286.1408 (+2.1 ppm error); [α]D +1.0 (c 1.3 in CHCl₃); CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (R,R)-S2 11.1 min, (S,S)-S2 24.0 min and alcohol (R,S)-S3 (65 mg, 15%, 99:1 er by CSP-HPLC) as a colourless oil, Rₛ (4:1 petrol-EtOAc) 0.2; IR (film) 3421 (OH), 2970, 1692 (C=O), 1446, 1420, 1378, 1186, 1050, 1040, 910, 730 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, OH not visible) δ 7.29-7.36 (m, 2H, o-Ph), 7.34-7.25 (m, 3H, Ph), 4.94 (d, J = 2.5 Hz, 1H, OCH), 4.57 (ddd, J = 7.5, 7.5, 2.5 Hz, 1H, NCH), 3.73 (ddd, J = 8.5, 1.5, 1.5 Hz, 1H, NCH₂H₅), 3.48-3.43 (m, 1H, NCH₂H₅), 2.16-2.04 (m, 1H, CH₂H₅), 1.93 (ddd, J = 11.5, 8.5, 7.5 5.0 Hz, 1H, CH₂H₅), 1.48 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 157.4 (C=O), 139.6 (ipso-Ph), 128.3 (Ph), 127.6 (Ph), 80.4 (CMe₃), 75.3 (OCH), 66.8 (NCH), 46.7 (NCH₂), 16.2 (CH₂); MS (ESI) m/z 286 [(M + Na)⁺, 100]; HRMS m/z calcd for C₁₅H₂₁NO₃ (M + Na)⁺ 286.1414, found 286.1398 (+5.3 ppm error); [α]D −88.5 (c 1.05 in CHCl₃); CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (R,R)-S3 14.3 min, (S,S)-S3 15.8 min.

Lab Book Reference PJR 7/527
**tert-Butyl (2R)-2-[(R)-hydroxy(phenyl)methyl]azetidine-1-carboxylate (R,R)-S2**

![Chemical structure](image)

MeLi (0.94 mL of a 1.6 M solution in Et₂O, 1.50 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol (R,R)-12 (65 mg, 0.25 mmol, 1.0 eq., 75:25 er.) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 5 h. Then, 1 M HCl(aq) (5 mL) was added dropwise. The resulting solution was extracted with Et₂O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M NaOH(aq) and extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH₂Cl₂ (5 mL) and di-tert-butyl dicarbonate (60 mg, 0.28 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M HCl(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (R,R)-S2 (47 mg, 71%, 74:26 er by CSP HPLC) as a colourless oil, [α]D −1.56 (c 1.1 in CHCl₃); CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (R,R)-S2 11.1 min, (S,S)-S2 25.5 min.

Lab Book Reference PJR 7/526

**tert-Butyl (2R)-2-[(S)-hydroxy(phenyl)methyl]azetidine-1-carboxylate (S,R)-S3**

![Chemical structure](image)

MeLi (0.38 mL of a 1.6 M solution in Et₂O, 0.60 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol (S,R)-13 (26 mg, 0.25 mmol, 1.0 eq., 58:42 er) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 5 h. Then, 1 M HCl(aq) (5 mL) was added dropwise. The resulting solution was extracted with Et₂O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M NaOH(aq) and extracted with Et₂O (3 x 10 mL).
The combined organic layers were dried (MgSO$_4$) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH$_2$Cl$_2$ (5 mL) and di-tert-butyl dicarbonate (60 mg, 0.28 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M HCl$_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (S,R)-S$_3$ (20 mg, 76%, 57:43 er by CSP HPLC) as a colourless oil, [$\alpha$]$_D$ +14.2 (c 0.60 in CHCl$_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-$i$PrOH, 0.5 mL min$^{-1}$) (S,R)-S$_3$ 14.9 min, (R,S)-S$_3$ 15.8 min.

Lab Book Reference PJR 8/684

CSP-HPLC of (R,R)-S$_2$ of 74:26 er

CSP-HPLC of (S,S)-S$_2$ of 99:1 er

CSP-HPLC of (S,R)-S$_3$ of 57:43 er

CSP-HPLC of (R,S)-S$_3$ of 99:1 er
2.2 Assignment of the Configuration of \((R,R)-14\) and \((S,R)-15\)

The absolute stereochemistries of \((R,R)-14\) and \((S,R)-15\) were assigned by conversion into known\(^{10}\) alcohols \((R,R)-S7\) and \((S,R)-S8\) respectively (Scheme S2). The thiopivaloyl group in each of \((R,R)-14\) and \((S,R)-15\) was removed using MeLi and Boc protection then gave \((R,R)-S7\) and \((S,R)-S8\) respectively.

![Scheme S2](image)

**Experimental for Scheme S2:**

**tert-Butyl \((2R)-2-[(R)-hydroxy(phenyl)methyl]pyrrolidine-1-carboxylate \((R,R)-S7\)**

\((R,R)-S7\)

MeLi (0.58 mL of a 1.6 M solution in Et\(_2\)O, 0.93 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol \((R,R)-14\) (43 mg, 0.16 mmol, 1.0 eq., 82:18 er) in THF (5 mL) at 0 °C under
Supporting Information

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Ar. The resulting solution was stirred at 0°C for 5 h. Then, 1 M HCl(aq) (5 mL) was added dropwise. The resulting solution was extracted with Et₂O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M NaOH(aq) and extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH₂Cl₂ (5 mL) and di-tert-butyl dicarbonate (37 mg, 0.17 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M HCl(aq) (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH₂Cl₂-acetone as eluent gave alcohol (R,R)-S7 (30 mg, 70%, 82:18 er by CSP HPLC) as a colourless oil, [α]D −0.6 (c 0.75 in CHCl₃) (lit., [α]D −1.6 (c 1.0 in CHCl₃ for (R,R)-S7 of 97:3 er)); CSP-HPLC: Chiracel OD (98:2 Hexane-iPrOH, 0.5 mL min⁻¹) (R,R)-S7 28.6 min, (S,S)-S7 35.7 min. Spectroscopic data consistent with those reported in the literature.¹⁰ Lab Book Reference PJR 8/648

tert-Butyl (2R)-2-[(S)-hydroxy(phenyl)methyl]pyrrolidine-1-carboxylate (S,R)-S8

![Chemical Structure](image)

MeLi (0.45 mL of a 1.6 M solution in Et₂O, 0.72 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol (S,R)-15 (33 mg of 86:14 er, 0.12 mmol, 1.0 eq.) in THF (5 mL) at 0°C under Ar. The resulting solution was stirred at 0°C for 5 h. Then, 1 M HCl(aq) (5 mL) was added dropwise. The resulting solution was extracted with Et₂O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M NaOH(aq) and extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH₂Cl₂ (5 mL) and di-tert-butyl dicarbonate (28 mg, 0.13 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M HCl(aq) (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash
column chromatography on silica with 98:2 CH₂Cl₂-acetone as eluent gave alcohol (S,R)-S₈ (17 mg, 50%, 86:14 er by CSP HPLC) as a colourless oil, [α]ᵰ +79.4 (c 1.0 in CHCl₃) (lit., [α]ᵰ +112.7 (c 1.5 in CHCl₃ for (S,R)-S₈ of 96:4 er)); CSP-HPLC: Chiracel OD (99:1 Hexane-iPrOH, 0.5 mL min⁻¹) (S,R)-S₈ 25.7 min, (R,S)-S₈ 28.3 min. Spectroscopic data consistent with those reported in the literature.¹⁰

Lab Book Reference PJR 8/647

2.3 Assignment of the Configuration of (R)-16 and (S)-18

The configuration of (S)-1₈ was assigned by conversion of (S)-1₈ into amido ester (S)-S₉ which was independently synthesised from N-Boc acid (S)-S₅ (Scheme S3).

Scheme S3
**Supporting Information**

**Experimental for Scheme S3:**

(S)-**Methyl 1-pivaloylazetidine-2-carboxylate (S)-S9**

\[
\text{Me}_3\text{SiCHN}_2 (0.15 \text{ mL of a 2.0 M solution in Et}_2\text{O, 0.30 mmol, 1.2 eq}) \text{ was added dropwise to a}
\]

stirred solution of acid (S)-S5 (50 mg, 0.248 mmol, 1.0 eq) in MeOH/toluene (4:6 v/v, 3 mL) at

rt. After 5 min, glacial AcOH (4 mL) was added and the solvent was evaporated under reduced

pressure to give the crude ester (57 mg) as a colourless oil, \(^1\)H NMR (400 MHz, CDCl\(_3\)) 4.60

(dd, \(J = 9.0, 5.5 \text{ Hz}, 1\text{H, CHN}), 4.01 \text{ (ddd, } J = 8.5, 8.5, 6.0 \text{ Hz, 1H, } CH_3H_BN\)), 3.87 \text{ (ddd, } J = 8.5,

8.5, 5.5 Hz, 1H, CH\(_A\)H\(_B\)N), 3.76 (s, 3H, CO\(_2\)Me), 2.54-2.43 (m, 1H, CH\(_A\)H\(_B\)), 2.16 \text{ (ddd, } J =

11.0, 8.5, 5.5, 5.5 Hz, 1H, CH\(_A\)H\(_B\)), 1.40 (s, 9H, CMe\(_3\)). Freshly distilled TFA (0.57 mL, 0.855 g, 7.50 mmol, 30 eq) was added to a stirred solution of the crude methyl ester (57 mg) in CH\(_2\)Cl\(_2\) (5 mL) at rt. The resulting solution was stirred at rt for 48 hours. Then, the solvent was evaporated under reduced pressure to give the crude TFA salt (88 mg) as a yellow o

il, \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 5.11 (dd, \(J = 9.0, 9.0 \text{ Hz}, 1\text{H, CHN}), 4.24 \text{ (ddd, } J = 10.0, 10.0, 10.0 \text{ Hz, 1H, } CH_3H_BN\)), 4.10 \text{ (ddd, } J = 10.0, 10.0, 6.5 \text{ Hz, 1H, } CH_AH_BN\)), 3.84 (s, 3H, CO\(_2\)Me), 2.97-2.86 (m, 1H, CH\(_A\)H\(_B\)), 2.75-2.63 (m, 1H, CH\(_A\)H\(_B\)). Pivaloyl chloride (0.15 mL, 150 mg, 1.24 mmol, 5 eq) was added to a stirred solution of the crude TFA salt (88 mg), Et\(_3\)N (0.35 mL, 251 mg, 2.48 mmol, 10 eq) and DMAP (6.1 mg, 0.05 mmol, 0.2 eq) in CH\(_2\)Cl\(_2\) (5 mL) at rt under N\(_2\). The resulting solution was stirred at rt for 48 hours. Then, 2 M HCl\(_{\text{aq}}\) (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL) and the combined organic layers were dried (MgSO\(_4\)) and evaporated under reduced pressure. The residue was absorbed onto a plug of silica and eluted with 80 mL of EtOAc-pentane (1:1) to give the crude product. Purification by dry column flash chromatography through 13 cm of silica in a 2 cm diameter flash column, eluting with 50 mL aliquots of 5% increasing polarity of EtOAc-pentane (95:5 to 70:30) as eluent gave amido-ester (S)-S9 (6.8 mg, 0.034 mmol, 14% over 3 steps from (S)-S5, 97:3 er by CSP-HPLC) in the sixth fraction as a pale yellow oil, IR (ATR) 2959, 1744 (C=O), 1631 (C=O), 1573, 1435, 1407, 1381, 1362, 1281, 1242, 1199, 1179, 1159, 1135, 1065, 1025,
980, 933, 881, 756, 632 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.70 (br s, 1H, CHN), 4.48 (br s, 1H, CH\(_4\)H\(_9\)N), 4.30 (br s, 1H, CH\(_4\)H\(_9\)N), 3.76 (s, 3H, CO\(_2\)Me), 2.61-2.48 (m, 1H, CH\(_A\)H\(_B\)), 2.22-2.13 (m, 1H, CH\(_A\)H\(_B\)), 1.20 (s, 9H, CMe\(_3\)); \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 172.0 (C=O, CO\(_2\)Me), 123.6 (NC=O), 60.1 (CHN), 52.4 (CO\(_2\)Me), 29.8 (CH\(_2\)N), 27.1 (CMe\(_3\)), 20.4 (CH\(_2\)), 14.3 (CMe\(_3\));

MS (ESI) \(m/z\) 200 [(M + H)\(^+\), 100], 222 [(M + Na)\(^+\), 65]; HRMS \(m/z\) calcd for C\(_{10}\)H\(_{18}\)NO\(_3\) (M + Na)\(^+\) 222.1101, found 222.1097 (+1.7 ppm error); [\(\alpha\)]\(_D\) \(-78.5\) (c 0.34 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane\(-i\)PrOH, 1.0 mL min\(^{-1}\)) (S)-S\(_9\) 26.2 min, (R)-S\(_9\) 48.5 min. A second portion of (S)-S\(_9\) (13.3 mg, 0.0668 mmol, 26.9% over 3 steps of lesser purity) was isolated from the fifth fraction.

Lab Book Reference: JCS-4-80, JCS-4-81, JCS-4-84

Oxone (142 mg, 0.46 mmol, 5.1 eq) was added to a stirred solution of acid (S)-18 (18.6 mg, 0.092 mmol, 1.0 eq, 75:25 er) in MeOH/water (1:1, 5 mL) at rt. The resulting solution was stirred at rt for 72 hours. Then, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (2 x 5 mL), dried (MgSO\(_4\)) and the solvent evaporated under reduced pressure to give the crude product (15.9 mg), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.04 (dd, \(J = 8.5, 7.0\) Hz, 1H, CHN), 4.45–4.29 (m, 2H, CH\(_2\)N), 2.55–2.45 (m, 1H, CH\(_4\)H\(_9\)N), 2.22–2.13 (m, 1H, CH\(_A\)H\(_B\)), 1.23 (s, 9H, CMe\(_3\)). The residues were dissolved in MeOH/toluene (4:6 v/v, 3 mL) and to this stirred solution was added Me\(_3\)SiCHN\(_2\) (2.0 M in Et\(_2\)O) dropwise at rt until the yellow colour persisted (~0.05 mL). The resulting solution was stirred at rt for 5 min. Then, glacial AcOH (5 mL) was added to destroy excess Me\(_3\)SiCHN\(_2\) and the solvent was evaporated under reduced pressure to give (S)-S\(_9\) (6.9 mg, 0.044 mmol, 47% over 2 steps, 76:24 er) as a pale yellow oil that did not require further purification, [\(\alpha\)]\(_D\) \(-79.0\) (c 0.35 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane\(-i\)PrOH, 1.0 mL min\(^{-1}\)) (S)-S\(_9\) 25.6 min, (R)-S\(_9\) 47.4 min.

Lab Book Reference: JCS-5-20, JCS-5-21
CSP-HPLC of (S)-S9 of 97:3 er

![CSP-HPLC of (S)-S9 of 97:3 er](image)

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Totals: 5.3706e+04 598.89092

CSP-HPLC of (S)-S9 of 76:24 er

![CSP-HPLC of (S)-S9 of 76:24 er](image)

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Totals: 1.7216e+04 319.01467

The configuration of acid (S)-18 was also assigned by X-ray crystallography of a sample grown from an enantioenriched sample (of 97:3 er).

**Enantioenrichment of (S)-18**

A stirred solution of acid (S)-18 (60 mg, 75:25 er) in hexane (~ 2 mL) was gently heated to reflux. Then, boiling EtOAc was added until all solid material just dissolved and the solution was allowed to slowly cool to rt. Then, the solution was cooled to 0 °C for 30 min. The formed crystals were collected by filtration to give rac-18 (29 mg). The filtrate was evaporated under reduced pressure to give acid (S)-21 (30 mg, 97:3 er by CSP-HPLC of the methyl ester) as a white solid. Acid (S)-18 was converted into methyl ester (S)-16 by reaction with Me3SiCHN2 in MeOH/toluene (4:6 v/v, 2 mL), quenching with glacial AcOH and evaporation under reduced pressure. CSP-HPLC of methyl ester (S)-16: Chiralcel OD-H (98:2 Hexane-iPrOH, 1.0 mL min−1) (S)-16 13.5 min, (R)-16 17.0 min.

Crystals suitable of (S)-18 for X-ray crystallography were prepared by dissolving (S)-18 (30 mg, 97:3 er) in the minimum amount of EtOAc. The solution was placed into a small glass vial and placed upright in a sealed vessel containing pentane (~ 20 mL). After several days, suitable crystals had precipitated in the glass vial. These were collected and subjected to X-ray analysis.
\((S)-18\): CCDC number 1417069

The configuration of \((R)-16\) was assigned by conversion of acid \((S)-18\) of known configuration into \((S)-16\) and comparison of CSP-HPLC data (Scheme S4).

Scheme S4
2.4 Assignment of the Configuration of (R)-17 and (S)-19

The configuration of acid (S)-19 was assigned by conversion of (S)-19 into amido ester (S)-S10 which was independently synthesised from N-Boc acid (S)-S5 (Scheme S5).
**Experimental for Scheme S5**

**(S)-Methyl 1-pivaloylpyrrolidine-2-carboxylate (S)-S10**

![Chemical Structure](image)

Oxone (18 mg, 0.059 mmol, 5 eq) was added to a stirred solution of acid (S)-19 (5 mg, 0.023 mmol, 1.0 eq, 98:2 er) in MeOH/water (1:1 v/v, 1 mL) at rt. The resulting solution was stirred at rt for 72 h. Then, the reaction was diluted with EtOAc (50 mL) and washed with water (2 x 5 mL), dried (MgSO₄) and the solvent evaporated under reduced pressure to give the crude product (7.2 mg). 

[\(\text{H} \text{NMR (400 MHz, CDCl}_3 \text{)} 4.68-4.61 \text{ (br m, 1H, CHN)} \), 3.74-3.69 (m, 2H, CH₂N), 2.15-1.87 (m, 4H, CH₂CH₂), 1.29 (s, 9H, CMe₃). The residues were redissolved in MeOH/toluene (4:6 v/v, 2 mL) and Me₃SiCH₂N₂ (2.0 M soln in Et₂O) was added dropwise at rt until the yellow colour persisted (~0.03 mL). The resulting solution was stirred at rt for 5 min. Then, glacial AcOH (5 mL) was added to destroy excess Me₃SiCH₂N₂ and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80 mL of 1:1 EtOAc-pentane gave (S)-S10 (2.6 mg, 0.012 mmol, 52% over 2 steps, 98:2 er). 

[\(\text{H} \text{NMR (400 MHz, CDCl}_3 \text{)} 4.52-4.45 \text{ (br m, 1H, CHN)} \), 3.82-3.66 (m, 2H, CH₂N), 3.72 (s, 3H, CO₂Me), 2.17-2.01 (m, 2H, CH₂), 2.00-1.81 (m, 2H, CH₂), 1.23 (s, 9H, CMe₃); \(\text{C} \text{NMR (100.6 MHz, CDCl}_3 \text{)} \delta 176.9 \text{ (C=O)} \), 173.5 (C=O), 60.9 (CHN), 52.1 (CH₂N), 48.2 (CO₂Me), 38.8 (CMe₃), 27.9 (CH₂), 27.3 (CMe₃), 26.1 (CH₂); \(\alpha \) -14.5 (c 0.13 in EtOAc); CSP-HPLC: Chiralcel OD-H (96:4 Hexane-iPrOH, 1.0 mL min⁻¹) (S)-S10 13.1 min, (R)-S10 17.8 min. Spectroscopic data consistent with those reported in the literature.¹¹

Lab Book Reference: JCS-5-4, JCS-4-90

Thionyl chloride (2.53 mL, 4.13 g, 34.8 mmol, 2.0 eq.) was added dropwise to a stirred solution of L-proline (2.0 g, 17.4 mmol, 1.0 eq) in MeOH (18 mL) at 0 °C. The resulting solution was stirred at 0 °C for 2 h. Then, the solvent was evaporated under reduced pressure to give the crude product (2.97 g). A portion of the crude product (0.59 g) was suspended in CH₂Cl₂ (10 mL) and DMAP (74 mg, 0.60 mmol), Et₃N (2.10 mL, 1.53 g, 15.1 mmol) and pivaloyl chloride (0.58 mL, 546 mg, 4.53 mmol) were added sequentially at 0 °C under N₂. The resulting solution was
allowed to warm to rt over 4 h. Then, the reaction was diluted with EtOAc (50 mL) and washed with 2 M HCl (2 x 20 mL), K₂CO₃ (10% w/w, 30 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification through a plug of silica with 8:2 hexane-EtOAc (200 mL) as eluent gave (S)-S₁₀ (509 mg, 2.39 mmol, 69% over 2 steps) as a pale red oil, [α] −47.2 (c 1.025 in EtOAc); CSP-HPLC: Chiralcel OD-H (96:4 Hexane-iPrOH, 1.0 mL min⁻¹) (S)-S₁₀ 13.3 min.

Lab Book Reference: JCS-6-38, JCS-6-39

**CSP-HPLC of (S)-S₁₀ of 98:2 er**

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Totals : 1433.76232 45.91179

**CSP-HPLC of (S)-S₁₀ of 100:0 er**

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Totals : 4951.46973 102.84155

In a separate experiment, a sample of (S)-S₁₀ of 61:39 er was also prepared.

**CSP-HPLC of (S)-S₁₀ of 61:39 er**

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Totals : 1.497054 335.37031
The configuration of acid (S)-19 was also assigned by X-ray crystallography of a sample grown from an enantioenriched sample (of 98:2 er).

**Enantioenrichment of (S)-19**

A stirred solution of acid (S)-19 (80 mg, 80:20 er) in hexane (~ 2 mL) was gently heated to reflux. Then, boiling EtOAc was added until all solid material just dissolved and the solution was allowed to slowly cool to rt. Then, the solution was cooled to 0 °C for 30 min. The formed crystals were collected by filtration to give rac-19 (21 mg). The filtrate was evaporated under reduced pressure to give acid (S)-19 (59 mg, 90:10 er by CSP-HPLC of the methyl ester) as a white solid. This procedure was repeated again to give rac-19 (9.9 mg) and (S)-19 (49.5 mg, 96:4 er by CSP-HPLC of the methyl ester). This procedure was repeated once more to give rac-19 (4.4 mg) and (S)-19 (44.1 mg, 98:2 er by CSP-HPLC of the methyl ester) as a white solid. [α]_D <sup>-23.9</sup> (c 0.095 in EtOAc of 98:2 material). Acid (S)-19 was converted into methyl ester (S)-17 by reaction with Me₃SiCHN₂ in MeOH/toluene (4:6 v/v, 2 mL), quenching with glacial AcOH and evaporation under reduced pressure. CSP-HPLC of the methyl ester: Chiralcel OD-H (98:2 Hexane-iPrOH, 1.0 mL min⁻¹) (S)-17 11.6 min, (R)-17 12.9 min.

Crystals suitable of (S)-19 for X-ray crystallography were prepared by dissolving (S)-19 (44.1 mg, 98:2 er) in the minimum amount of EtOAc. The solution was placed into a small glass vial and placed upright in a sealed vessel containing pentane (~ 20 mL). After several days, suitable crystals had precipitated in the glass vial. These were collected and subjected to X-ray analysis.

Lab Book Reference: JCS-2-28, JCS-3-72, JCS-2-29

(S)-22: CCDC number 1417068
The configuration of (R)-17 was assigned by conversion of acid (S)-19 of known configuration into (S)-17 and comparison of CSP-HPLC data (Scheme S6).

\[
\text{1.} \text{BuLi, (-)-sparteine 3} \\
\text{Et}_2\text{O, -78\degree C, 30 min} \\
\text{2. MeOCOCl}
\]

\[
(R)-17, 58\%, 76:24 \text{ er} \\
[\alpha]_D^{25} +25.3 \text{ (c 1.08 in EtOAc)}
\]

\[
\text{Me}_3\text{SiCHN}_2 \\
\text{MeOH/Toluene} \\
\text{rt, 5 min}
\]

\[
(S)-17, 98:2 \text{ er}
\]

Scheme S6

**CSP-HPLC of (R)-20 of 76:24 er**

**CSP-HPLC of (S)-20 of 98:2 er**
2.5 Assignment of the Configuration of \((R)-2\)

The configuration of \((R)-2\) was assigned by comparison to \((R)-2\) which was independently synthesised from \(N\)-Boc acid \((S)-S5\) (Scheme S7).

Scheme S7
Experimental for Scheme S7

(S)-\textit{tert}-Butyl 2-(hydroxymethyl)azetidine-1-carboxylate (S)-S11

\[
\begin{align*}
\text{\(\text{HO} \quad \text{Boc}\)} & \\
\text{(S)-S11} & \\
\end{align*}
\]

Borane dimethyl sulfide complex (0.51 mL, 5.42 mmol, 1.3 eq.) was added dropwise to a stirred solution of N-Boc acid (S)-S5 (840 mg, 4.17 mmol, 1.0 eq.) in THF (10 mL) at 0 °C under Ar. After gas evolution ceased, the resulting solution was stirred and heated at 66 °C for 1 h. Then, the solution was cooled to rt and MeOH (5 mL) was added dropwise. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4-1:1 petrol-EtOAc as eluent gave alcohol (S)-S11 (725 mg, 93%) as a colourless oil, \(R_F\) (1:1 petrol-EtOAc) 0.2, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.42 (br s, 1H, NCH), 4.25 (br s, 1H, OH), 3.88-3.82 (m, 1H, NCH\(_A\)H\(_B\)), 3.79-3.68 (m, 3H, NCH\(_A\)H\(_B\) + OCH\(_2\)), 2.16 (dddd, \(J = 11.5, 11.5, 9.0, 5.0\) Hz, 1H, CH\(_A\)H\(_B\)), 1.91 (br s, 1H, CH\(_A\)H\(_B\)), 1.43 (s, 9H, CMe\(_3\)); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 157.5 (C=O), 80.3 (CMe\(_3\)), 67.0 (OCH\(_2\)), 63.6 (NCH), 46.7 (NCH\(_2\)), 28.3 (CMe\(_3\)), 17.9 (CH\(_2\)); \([\alpha]_D\) −19.8 (c 0.45 in CHCl\(_3\)) (lit., \(^3\) \([\alpha]_D\) −21.5 (c 0.83 in CHCl\(_3\))). Spectroscopic data consistent with those reported in the literature.\(^3\)

Lab Book Reference PJR 8/686

(S)-\textit{tert}-Butyl 2-(iodomethyl)azetidine-1-carboxylate (S)-S12\(^{12}\)

\[
\begin{align*}
\text{\(\text{I} \quad \text{Boc}\)} & \\
\text{(S)-S12} & \\
\end{align*}
\]

Iodine (1.28 g, 5.06 mmol, 1.5 eq.) was added in three portions to a stirred solution of imidazole (459 mg, 6.74 mmol, 2.0 eq.) and triphenylphosphine (1.33 g, 5.06 mmol, 1.5 eq.) in CH\(_2\)Cl\(_2\) (15 mL) at 0 °C over 30 min. The resulting solution was allowed to warm to rt and then stirred at rt for 10 min. Then, a solution of alcohol (S)-S11 (630 mg, 4.17 mmol, 1.0 eq.) in CH\(_2\)Cl\(_2\) (5 mL) was added dropwise and the resulting solution was stirred at rt for 16 h. The solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was
dissolved in Et₂O (25 mL) and the solids were removed by filtration. The organic layer was washed with sat. Na₂S₂O₃(aq) (15 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave iodide \((S)\)-S12 (851 mg, 85%) as a colourless oil, \(R_F\) (9:1 petrol-EtOAc) 0.4; IR (CHCl₃) 2975, 2968, 1695 (C=O), 1510, 1446, 1420, 1278, 1190, 1035, 915, 815, 731 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) δ 4.21-4.15 (m, 1H, NCH), 3.81-3.69 (m, 2H, NCH), 3.51 (br d, \(J = 9.0\) Hz, 1H, \(CH_AH_B\)), 3.37 (dd, \(J = 9.0, 9.0\) Hz, 1H, \(CH_AH_B\)), 2.29 (dddd, \(J = 11.5, 9.0, 8.0, 5.5\) Hz, 1H, \(CH_AH_B\)), 1.89 (dddd, \(J = 11.5, 9.0, 6.5, 6.0\) Hz, 1H, \(CH_AH_B\)), 1.43 (s, 9H, CMe₃); \(^1^3\)C NMR (100.6 MHz, CDCl₃) δ 155.6 (C=O), 79.7 (CMe₃), 61.1 (NCH), 44.9 (NCH₂), 28.3 (CMe₃), 23.4 (CH₂), 11.6 (CH₂I); MS (ESI) m/z 320 [(M + Na)⁺, 60], 241 (100); HRMS m/z calcd for \(C_9H_{16}INO_2\) (M + Na)⁺ 320.0118, found 320.0108 (+3.0 ppm error); \([\alpha]_D\) −88.7 (c 0.95 in CHCl₃).

(R)-tert-Butyl-2-methylazetidine-1-carboxylate (R)-S13

\[(R)\]-S13

5% Pd/C (65 mg, 10 wt% of \((S)\)-S12) was added to a stirred solution of iodide \((S)\)-S12 (650 mg, 2.18 mmol, 1.0 eq.) and Et₃N (0.30 mL, 2.18 mmol, 1.0 eq.) in MeOH (10 mL) at rt. Then, the reaction flask evacuated under reduced pressure and back-filled with Ar three times. After a final evacuation, a balloon of H₂ was attached and the reaction mixture was stirred vigorously at rt under H₂ for 16 h. The solids were removed by filtration through Celite® and washed with CH₂Cl₂ (15 mL). Then, the filtrate was evaporated under reduced pressure and the residue was dissolved in CH₂Cl₂ (15 mL) and washed with 1 M HCl(aq) (10 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et₂O as eluent gave methyl azetidine (R)-S13 (280 mg, 75%) as a colourless oil, \(R_F\) (4:1 petrol-Et₂O) 0.3; \(^1\)H NMR (400 MHz, CDCl₃) δ 4.26 (dq, \(J = 6.5, 6.5\) Hz 1H, NCH), 3.81-3.77 (m, 2H, NCH₂), 2.30-2.21 (m, 1H, \(CH_AH_B\)), 1.74 (dddd, \(J = 11.0, 8.0, 8.0, 6.0\) Hz, 1H, \(CH_AH_B\)), 1.42 (s, 9H, CMe₃), 1.35 (d, \(J = 6.5\) Hz, Me); \(^1^3\)C NMR (100.6 MHz, CDCl₃) δ 156.4 (C=O), 78.9 (CMe₃), 57.9 (br, NCH), 45.7 (br, NCH₂), 28.4
(CMe$_3$), 23.6 (CH$_2$), 21.5 (Me); [$\alpha$]$_D$ = 38.1 (c 1.0 in CHCl$_3$) (lit.,$^3$ [$\alpha$]$_D$ = 40.5 (c 0.80 in CHCl$_3$)). Spectroscopic data consistent with those reported in the literature.$^3$

Lab Book Reference: PJR 8/688A

(R)-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (R)-2

Trimethylsilyliodide (16 $\mu$L, 0.11 mmol, 1.2 eq.) was added dropwise to a stirred solution of N-Boc methyl azetidine (R)-S13 (16 mg, 0.09 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (5 mL) under N$_2$ at rt. The resulting solution was stirred at rt for 30 min. Then, Et$_3$N (18 $\mu$L, 0.14 mmol, 1.5 eq.) and trimethylacetylchloride (17 $\mu$L, 0.14 mmol, 1.5 eq.) were added sequentially and the resulting solution was stirred at rt for 2 h. 1 M HCl$_{aq}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were dried (MgSO$_4$) and evaporated under reduced pressure. The residue was dissolved in pyridine (20 mL) and phosphorus(V) sulfide (32 mg, 0.14 mmol, 1.5 eq.) was added. The resulting solution was stirred heated at 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M HCl$_{aq}$ (15 mL). Conc. HCl was added until pH 3 was obtained. The resulting solution was stirred at rt for 2 h and then extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic extracts were washed with 1 M HCl$_{aq}$ (100 mL), water (100 mL) and brine (100 mL), dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 hexane-Et$_2$O as eluent gave methylazetidine (R)-2 (7.6 mg, 48%, 100:0 er by CSP-HPLC) as a pale yellow oil, $R_F$ (8:2 petrol-Et$_2$O) 0.3; [$\alpha$]$_D$ $+$20.03 (c 0.45 in CHCl$_3$) (lit.,$^3$ [$\alpha$]$_D$ $-$21.3 (c 1.15 in CHCl$_3$ for (R)-2 of $>$99:1 er)); CSP-HPLC: Chiracel OD-H (99.9:0.1 Hexane-iPrOH, 1.0 mL min$^{-1}$) (R)-2 19.2 min.

Note: Optical rotation data is not consistent with that reported in the literature and the absolute stereochemical configuration was assigned by CSP-HPLC.
CSP-HPLC of (S)-2 of 69:31 er

![CSP-HPLC of (S)-2 of 69:31 er](image1)

### CSP-HPLC of (S)-2 (69:31 er) doped with (R)-2 (>99:1 er)

![CSP-HPLC of (S)-2 (69:31 er) doped with (R)-2 (>99:1 er)](image2)

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Totals: 3.8757e4 1.1979e4

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Totals: 3.4481e4 767.1560

2.6 Assignment of the Configuration of (S)-20

The configuration of (S)-20 was assigned by comparison to (R)-20 which was independently synthesised from commercially available (R)-(−)-methylpyrrolidine (R)-S14 (Scheme S8).

![Scheme S8](image3)

\[
\begin{align*}
\text{1. } & \text{ BuLi, } (-)\text{-sparteine} \\
& \text{Et}_2\text{O, } -78 \degree \text{C, 1 h} \\
\text{2. } & \text{ Mel}
\end{align*}
\]

\[(S)-20, 84\%\text{, 58:42 er} [\alpha]_\text{D}^0 - 10.1 \text{ (c 0.95 in CHCl}_3]\]

\[
\begin{align*}
\text{1. } & \text{ Me}_3\text{CCOCl, Et}_3\text{N} \\
& \text{CH}_2\text{Cl}_2, \text{ rt, 2 h} \\
\text{2. } & \text{ P}_2\text{S}_5, \text{ pyridine,} \\
& 75 \degree \text{C, 6 h}
\end{align*}
\]

\[(R)-20, 66\%\text{, 100:0 er} [\alpha]_\text{D}^0 + 72.4 \text{ (c 1.20 in CHCl}_3]\]

Scheme S8
**Experimental for Scheme S8**

**(R)-2,2-Dimethyl-1-(2-methylpyrrolidin-1-yl)propane-1-thione (R)-20**

Trimethylacetyl chloride (320 µL, 2.6 mmol, 1.3 eq.) was added to a stirred solution of (R)-(-)-methylpyrrolidine (202 µL, 2.0 mmol, 1.0 eq.) and Et₃N (338 µL, 2.6 mmol, 1.3 eq.) in CH₂Cl₂ (10 mL) at 0 °C. The resulting solution was allowed to warm to rt and stirred at rt for 2 h. Then, 1 M HCl (aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude N-pivaloyl pyrrolidine. The residue was dissolved in pyridine (35 mL) and phosphorous(V) sulfide (556 mg, 2.50 mmol, 1.25 eq.) was added. The resulting solution was heated to 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M HCl (aq) (30 mL). 1 M HCl (aq) was added until pH 3 was obtained. The resulting solution was stirred at rt for 2 h and then extracted with CH₂Cl₂ (3 x 15 mL). The combined organic extracts were washed with 1 M HCl (aq) (50 mL), water (50 mL) and brine (50 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et₂O as eluent gave methylated pyrrolidine (R)-20 (243 mg, 66%, 100:0 er by CSP-HPLC) as a colourless oil, Rₚ (8:2 petrol-Et₂O) 0.2; [α]D +72.4 (c 1.20 in CHCl₃); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-iPrOH, 1.0 mL min⁻¹) (R)-20 13.9 min.
3. Additional Experiments

Having established that a dynamic resolution of diastereomeric lithiated intermediates was responsible for the enantioselectivity in the lithiation-trapping of 1, we briefly explored different temperatures and additional electrophiles with azetidine 1 (Table S1).

Table S1. Asymmetric lithiation-PhCHO trapping of N-thiopivaloyl azetidine 1 at different temperatures.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp 1 / °C&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Temp 2 / °C&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield/%&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Er&lt;sup&gt;d&lt;/sup&gt;</th>
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<td>59:41</td>
</tr>
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</table>

<sup>a</sup> Temp 1 = lithiation temperature.  
<sup>b</sup> Temp 2 = incubation temperature.  
<sup>c</sup> % Yield after purification by chromatography.  
<sup>d</sup> Er determined by CSP-HPLC after purification by chromatography (see Supporting Information).  
<sup>e</sup> Reaction cooled to –78 °C for 30 min before addition of PhCHO.
Experimental for Table S1

1-[(2R)-2-[(S)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (S,R)-13 and 1-[(2R)-2-[(R)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (R,R)-12

(Table S1, entry 1)

$s$-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of $N$-thiopivaloyl azetidine 1 (79 mg, 0.5 mmol, 1.0 eq.) and (-)‐sparteine 3 (0.14 mL, 0.6 mmol, 1.2 eq.) in $Et_2O$ (5 mL) at −100 °C under Ar. The resulting solution was stirred at −100 °C for 30 min. Then, benzaldehyde (76 µL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −100 °C for 1 h. Then, 1 M HCl\textsubscript{(aq)} (10 mL) was added and the two layers were separated. The aqueous layer was extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were dried (MgSO\textsubscript{4}) and evaporated under reduced pressure to give the crude product which contained an 87:13 mixture of alcohols (R,R)-12 and (S,R)-13 by $^1$H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (S,R)-13 (9 mg, 7%, 57:43 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-/iPrOH, 1.0 mL min\textsuperscript{-1}) (S,R)-13 7.4 min, (R,S)-13 10.0 min and alcohol (R,R)-12 (87 mg, 66%, 77:23 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-/iPrOH, 1.0 mL min\textsuperscript{-1}) (R,R)-12 18.4 min, (S,S)-12 20.8 min.

Lab Book Reference PJR 8/625

(Table S1, entry 3)

$s$-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of $N$-thiopivaloyl azetidine 1 (79 mg, 0.5 mmol, 1.0 eq.) and (-)‐sparteine 3 (0.14 mL, 0.6 mmol, 1.2 eq.) in $Et_2O$ (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −50 °C and stirred for 1 h. Benzaldehyde (76 µL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −50 °C for
10 min. Then, 1 M HCl\textsubscript{(aq)} was added. The two layers were separated and the aqueous layer was extracted with Et\textsubscript{2}O (3 x 10 mL). The combined organic layers were dried (MgSO\textsubscript{4}) and evaporated under reduced pressure to give the crude product which contained an 80:20 mixture of alcohols \((R,R)-12\) and \((S,R)-13\) by \textsuperscript{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol \((S,R)-13\) (17 mg, 13\%, 58:42 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-\textsuperscript{i}PrOH, 1.0 mL min\textsuperscript{-1}) \((S,R)-13\) 7.5 min, \((R,S)-13\) 10.2 min and alcohol \((R,R)-12\) (108 mg, 82\%, 68:32 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-\textsuperscript{i}PrOH, 1.0 mL min\textsuperscript{-1}) \((R,R)-12\) 18.4 min, \((S,S)-12\) 20.9 min.

Lab Book Reference PJR 8/657

(Table S1, entry 4)

\(\text{-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of } N\text{-thiopivaloyl azetidine 1 (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine 3 (0.14 mL, 0.6 mmol, 1.2 eq.) in Et\textsubscript{2}O (5 mL) at } −78 °C \text{ under Ar. The resulting solution was stirred at } −78 °C \text{ for 30 min. Then, the solution was warmed to } −40 °C \text{ and stirred for 1 h. Benzaldehyde (76 \textmu L, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at } −40 °C \text{ for 10 min. Then, 1 M HCl\textsubscript{(aq)} was added. The two layers were separated and the aqueous layer was extracted with Et\textsubscript{2}O (3 x 10 mL). The combined organic layers were dried (MgSO\textsubscript{4}) and evaporated under reduced pressure to give the crude product which contained an 80:20 mixture of alcohols \((R,R)-12\) and \((S,R)-13\) by \textsuperscript{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol \((S,R)-13\) (19 mg, 14\%, 56:44 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-\textsuperscript{i}PrOH, 1.0 mL min\textsuperscript{-1}) \((S,R)-13\) 7.5 min, \((R,S)-13\) 10.1 min and alcohol \((R,R)-12\) (111 mg, 84\%, 62:38 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-\textsuperscript{i}PrOH, 1.0 mL min\textsuperscript{-1}) \((R,R)-12\) 18.2 min, \((S,S)-12\) 20.8 min.

Lab Book Reference PJR 8/656
s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of N-thiopivaloyl azetidine 1 (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine 3 (0.14 mL, 0.6 mmol, 1.2 eq.) in Et₂O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −30 °C and stirred for 1 h. Benzaldehyde (76 µL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −30 °C for 10 min. Then, 1 M HCl(aq) was added. The two layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture of alcohols (R,R)-12 and (S,R)-13 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (S,R)-13 (15 mg, 11%, 55:45 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (S,R)-13 7.5 min, (R,S)-13 10.2 min and alcohol (R,R)-12 (100 mg, 76%, 59:41 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (R,R)-12 18.5 min, (S,S)-12 20.5 min.

Lab Book Reference PJR 8/658

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of N-thiopivaloyl azetidine 1 (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine 3 (0.14 mL, 0.6 mmol, 1.2 eq.) in Et₂O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −30 °C and stirred for 1 h. The solution was then cooled to −78 °C and stirred at −78 °C for 30 min. Benzaldehyde (76 µL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −30 °C for 10 min. Then, 1 M HCl(aq) was added. The two layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product which contained a 86:14 mixture of alcohols (R,R)-12 and (S,R)-13 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (S,R)-13 (9 mg, 7%, 59:41 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min⁻¹) (S,R)-13 7.4 min, (R,S)-13 10.1 min and alcohol (R,R)-12 (95 mg, 72%, 75:25 er by CSP-HPLC) as a white solid,
CSP-HPLC: Chiracel AD-H (95:5 Hexane-iPrOH, 1.0 mL min\(^{-1}\)) \((R,R)\)-12 18.3 min, \((S,S)\)-12 20.5 min.

Lab Book Reference PJR 8/664

In an attempt to explore the dynamic resolution mechanism further, we briefly explored two other carbonyl electrophiles and Me\(_3\)SiCl. In these cases, we have been unable to determine the absolute configuration of the major enantiomers of the products, \(S15-S17\).

Table S2. Asymmetric lithiation-trapping of \(N\)-thiopivaloyl azetidine 1 with different electrophiles.

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<th>Entry</th>
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<th>Electrophile</th>
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<th>Er(^b)</th>
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<td>Ph(_2)C=O</td>
<td>(S16)</td>
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<td>3</td>
<td>Me(_3)SiCl</td>
<td>(S17)</td>
<td>56</td>
<td>56:44</td>
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<td>((S,S))-4</td>
<td>Me(_3)SiCl</td>
<td>(S17)</td>
<td>45</td>
<td>47:53</td>
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</tbody>
</table>

\(^a\) % Yield after purification by chromatography. \(^b\) Er determined by CSP-HPLC after purification by chromatography (see Supporting Information).

**Experimental for Table S2**

\(rac\)-1-(2-(2-hydroxypropan-2-yl)azetidin-1-yl)-2,2-dimethylpropane-1-thione \(S15\)

(Racemic standard for Table S2, entry 1)

\(s\)-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added to a stirred solution of \(N\)-thiopivaloyl azetidine 1 (79 mg, 0.08 mL, 0.50 mmol, 1.0 eq.) and TMEDA (0.18
mL, 131 mg, 1.2 mmol, 2.4 eq.) in Et₂O (7 mL) at −100 °C under N₂. The resulting solution was stirred at −100 °C for 2 min. Then, distilled, dry acetone (0.073 mL, 58 mg, 1.0 mmol, 2.0 eq.) was added and the solution was stirred at −100 °C for 10 min and allowed to warm to rt over the course of 1 h. 2 M HCl (aq) (3 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2-7:3 hexane-EtOAc as eluent gave alcohol *rac*-S₁₅ (40 mg, 0.187 mmol, 37%) as a brown solid, mp 74–77 °C; IR (ATR) 3264 (OH), 2967, 2924, 1464, 1433, 1402, 1362, 1300, 1255, 1173, 1136, 986, 948, 541, 474 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.00 (br s, 1H, OH), 4.96 (dd, J = 10.0, 6.0 Hz, 1H, CHN), 4.46–4.40 (m, 2H, CH₂N), 2.52–2.41 (m, 1H, CH₂H₂), 1.97–1.87 (m, 1H, CH₂H₂), 1.36 (s, 9H, CMe₃), 1.30 (s, 3H, Me), 1.15 (s, 3H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 212.5 (C=S), 79.1 (CHN), 73.3 (C(Me)₂OH), 56.3 (CH₂N), 43.8 (CMe₃), 29.8 (CMe₃), 25.7 (Me), 23.2 (Me), 19.5 (CH₂); MS (ESI) m/z 238 [(M+Na)⁺, 85] 216 [(M+H)⁺, 100]; HRMS m/z calcld for C₁₁H₂₂NOS (M+Na)⁺ 238.1236, found 238.1229 (+3.0 ppm error). Spectroscopic data consistent with those reported in the literature.³

Lab Book Reference: JCS-2-6

1-(2-(2-Hydroxypropan-2-yl)azetidin-1-yl)-2,2-dimethylpropane-1-thione S₁₅

(Table S2, entry 1)

Using general procedure A, s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), N-thiopivaloyl azetidine 1 (0.08 mL, 79 mg, 0.5 mmol, 1.0 eq), (–)-sparteine 3 (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et₂O (5 mL) and freshly distilled, dry acetone (0.06 mL, 48 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 8:2-7:3 hexane-EtOAc as eluent gave S₁₅ (23 mg, 0.107 mmol, 22%, 60:40 er by CSP-HPLC) as a brown solid, mp 70–75 °C; [α]₁₀⁻⁷.5 (c 0.95 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-PrOH, 1.0 mL min⁻¹) 13.0 min (major), 14.1 min (minor).

Lab Book Reference: JCS-2-14
**Rac-1-(2-(Hydroxydiphenylmethyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione S16**

(Racemic standard for Table S2, entry 2)

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added to a stirred solution of N-thiopivaloyl azetidine 1 (79 mg, 0.08 mL, 0.50 mmol, 1.0 eq.) and TMEDA (0.18 mL, 131 mg, 1.2 mmol, 2.4 eq.) in Et₂O (7 mL) at −100 °C under N₂. The resulting solution was stirred at −100 °C for 2 min. Then, a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et₂O (0.5 mL) was added and the solution was stirred at −100 °C for 10 min and allowed to warm to rt over the course of 1 h. 2 M HCl (aq) (3 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5-8:2 hexane-EtOAc as eluent gave alcohol rac-S16 (55 mg, 0.16 mmol, 32%) as a white solid, mp 191–193 °C; Rₚ (8:2 petroleum ether-EtOAc) 0.4; IR (ATR) 3163 (O–H), 2961, 2929, 1467, 1395, 1366, 1316, 1287, 1247, 1214, 1060, 1013, 767, 704, 587 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.45 (m, 2H, Ph), 7.38–7.30 (m, 6H, Ph), 7.27–7.24 (m, 2H, Ph), 5.93 (ddd, J = 9.5, 5.0, 1.5 Hz, 1H, CHN), 4.16 (ddd, J = 10.0, 10.0, 4.5 Hz, 1H, CH₁H₂N), 3.41–3.32 (m, 1H, CH₁H₂N), 2.72–2.61 (m, 1H, CH₁H₂), 2.11–2.02 (m, 1H, CH₁H₂), 1.18 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 212.6 (C=S), 144.6 (ipso-Ph), 142.6 (ipso-Ph), 128.5 (m-Ph), 128.1 (m-Ph), 127.8 (p-Ph), 127.7 (p-Ph), 127.5 (o-Ph), 127.3 (o-Ph), 82.8 (C(Ph)₂OH), 77.3 (CHN), 56.7 (CH₂N), 43.7 (CMe₃), 29.7 (CMe₃), 21.0 (CH₂); MS (ESI) m/z 340 [(M + H)+, 100]; HRMS m/z calcd for C₂₁H₂₆NOS (M+H)+ 340.1730, found 340.1723 (+2.0 ppm error).

Lab Book Reference: JCS-2-2
1-(2-(Hydroxydiphenylmethyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione S16

(Table S2, entry 2)

Using general procedure A, s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq), N-thiopivaloyl azetidine 1 (0.08 mL, 79 mg, 0.5 mmol, 1.0 eq), (−)-sparteine 3 (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et2O (7 mL) and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq) in Et2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica eluting with 95:5-8:2 hexane-EtOAc as eluent gave alcohol S16 (61 mg, 0.18 mmol, 36%, 56:44 er by CSP-HPLC) as a white solid, mp 179–183 °C; [α]D +23.6 (c 0.85 in CHCl3). CSP-HPLC: Chiralcel OD-H (98:2 Hexane-iPrOH, 1.0 mL min–1) 8.0 min (minor), 12.9 min (major).

Lab Book Reference: JCS-2-10

rac-2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione rac-S17

(Racemic standard for Table S2, entries 3 and 4)

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added to a stirred solution of N-thiopivaloyl azetidine 1 (79 mg, 0.08 mL, 0.50 mmol, 1.0 eq.) and TMEDA (0.18 mL, 131 mg, 1.2 mmol, 2.4 eq.) in Et2O (5 mL) at −100 °C under N2. The resulting solution was stirred at −100 °C for 2 min. Then, trimethylsilyl chloride (0.133 mL, 109 mg, 1.0 mmol, 2.0 eq.) was added and the solution was stirred at −100 °C for 10 min and allowed to warm to rt over the course of 1 h. 2 M HCl(aq) (3 mL) was added and the two layers were separated. The aqueous layer was extracted with CH2Cl2 (3 × 10 mL). The combined organic layers were dried (MgSO4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 petrol-EtOAc as eluent gave silane rac-S17 (73 mg, 0.32 mmol, 64%) as a white solid, Rf (8:2 petrol ether–EtOAc) 0.46; IR (ATR) 2950, 1474, 1441,
1361, 1244, 1134, 1016, 945, 833, 752, 687, 645, 496 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.61 (ddd, \(J = 11.0, 6.5, 2.0\) Hz, 1H, CHN), 4.52–4.39 (m, 2H, CH\(_2\)N), 2.47–2.35 (m, 1H, CH\(_{\alpha}\)H\(_{\beta}\)), 2.10–2.00 (m, 1H, CH\(_{\alpha}\)H\(_{\beta}\)), 1.33 (s, 9H, CMe\(_3\)), 0.18 (s, 9H, SiMe\(_3\)); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 206.1 (C=S), 62.2 (CHN), 57.1 (CH\(_2\)N), 42.9 (CMe\(_3\)), 30.0 (CMe\(_3\)), 17.1 (CH\(_2\)), –1.30 (SiMe\(_3\)); MS (ESI) \m/z\) 230 [(M + H)+, 100]; HRMS \m/z\) calcd for C\(_11\)H\(_{24}\)NSSi (M+H)+ 230.1393, found 230.1388 (+2.3 ppm error). Spectroscopic data consistent with those reported in the literature.\(^3\)

Lab Book Reference: JCS-1-103

2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione S17

![Structure S17](image)

(Time S2, entry 3)

Using general procedure A, s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), N-thiopivaloyl azetidine 1 (0.08 mL, 79 mg, 0.5 mmol, 1.0 eq), (–)-sparteine 3 (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et\(_2\)O (5 mL) and trimethylsilyl chloride (95 \(\mu\)L, 81 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave silane S17 (64 mg, 0.28 mmol, 56%, 56:46 er by CSP-HPLC) as a white solid, mp 49–52 °C; [\(\alpha\)]\(_D\) +15.6 (c 0.52 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-iPrOH, 1.0 mL min\(^{-1}\)) 4.7 min (major), 5.9 min (minor).

Lab Book Reference: JCS-2-11

(Time S2, entry 4)

Using general procedure A, s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), N-thiopivaloyl azetidine 1 (0.08 mL, 79 mg, 0.5 mmol, 1.0 eq), diamine (S,S)-4 (186 mg, 0.6 mmol, 1.2 eq) in Et\(_2\)O (5 mL) and trimethylsilyl chloride (95 \(\mu\)L, 81 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave silane S17 (51 mg, 0.22 mmol, 45%, 47:53 er by CSP-HPLC) as a white
solid, mp 46–49 °C; [α]D +19.2 (c 1.145 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-
-iPrOH, 1.0 mL min⁻¹) 4.7 min (minor), 5.5 min (major).

Lab Book Reference: JCS-2-12

Experiments were also conducted using alternative ligand/electrophile combinations and the
experimental detail is reported below.

\((S)-1-(2,2\text{-Dimethylpropanethioyl})azetidine-2\text{-carboxylic acid (S)--18}\)

\(\text{s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq) was added to a solution of N-}\)

\(-\text{thiopivaloyl azetidine 1 (0.077 mL, 79 mg, 0.5 mmol, 1.0 eq) and (S,S)-diamine 4 (178 mg, 0.6}\)

\(\text{mmol, 1.2 eq) in Et}_2\text{O (5 mL) at } -78 \degree \text{C under N}_2. \text{The resulting solution was stirred at } -78 \degree \text{C for}\)

30 min. Then, dry CO₂ (generated from solid CO₂ flushed through CaCl₂ and added into the
reaction via cannula) was bubbled through the reaction mixture for 10 min at –78 °C and then
allowed to warm to rt over 1 h. The reaction mixture was diluted with Et₂O (10 mL) and
extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M HCl (aq)
and extracted with CH₂Cl₂ (6 x 5 mL). The combined organic extracts were dried (MgSO₄)
and evaporated under reduced pressure to give acid (S)-18 (71 mg, 0.36 mmol, 71%, 57:43 er by
CSP-HPLC of the methyl ester) as an off-white solid. Acid (S)-18 was converted into methyl
ester (S)-16 by reaction with Me₃SiCHN₂ in MeOH/toluene (4:6 v/v, 2 mL), quenching with
glacial AcOH and evaporation under reduced pressure. CSP-HPLC of methyl ester (S)-16:
Chiralcel OD-H (98:2 Hexane-/iPrOH, 1.0 mL min⁻¹) (S)-16 14.5 min, (R)-16 18.3 min.

Lab Book Reference: JCS-2-15, JCS-3-69
(S)-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (S)-2

Using general procedure A, s-BuLi (0.46 mL of a 1.3M solution in hexanes, 0.60 mmol, 1.2 eq.), N-thiopivaloyl azetidine 1 (79 mg, 0.50 mmol, 1.0 eq.) and diamine (S,S)-4 (186 mg, 0.60 mmol, 1.2 eq.) in Et₂O (5 mL) and methyl iodide (47 µL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et₂O gave methylated azetidine (S)-2 (76 mg, 88%, 69:31 er by CSP-HPLC) as a colourless oil, [α]D –2.0 (c 0.95 in CHCl₃) (lit., [α]D −21.3 (c 1.15 in CHCl₃ for (R)-2 of 99:1 er)); CSP-HPLC: Chiracel OD-H (99.9:0.1 Hexane-iPrOH, 1.0 mL min⁻¹) (S)-2 14.0 min, (R)-2 15.4 min.

Note: Optical rotation data is not consistent with that reported in the literature³ and the configuration was assigned by CSP-HPLC (see Section 2).

Lab Book Reference PJR 8/668

1-((S)-2-((R)-Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (R,S)-15 and 1-((S)-2-((S)-hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (S,S)-14

Using general procedure B, s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate 21 (120 mg, 0.65 mmol, 1.3 eq.) and N-thiopivaloyl pyrrolidine 9 (86 mg, 0.50 mmol, 1.0 eq.) in Et₂O (5 mL) and benzaldehyde (76 µL, 0.75 mmol, 1.5 eq.) gave the crude product which contained a 78:22 mixture of diastereomeric alcohols (R,S)-15 and (S,S)-14 by ¹H NMR spectroscopy. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et₂O as eluent gave alcohol (R,S)-15 (86 mg, 62%, 85:15 er by CSP-HPLC) as a white solid,
CSP-HPLC: Chiracel AD (95:5 Hexane-iPrOH, 1.0 mL min\(^{-1}\)) (S,R)-15 11.2 min, (R,S)-15 14.6 min and alcohol (S,S)-14 (33 mg, 24%, 92:8 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel AD (90:10 Hexane-iPrOH, 1.0 mL min\(^{-1}\)) (R,R)-14 10.8 min, (S,S)-14 19.8 min.

Lab Book Reference PJR 8/662
4. $^1$H/$^{13}$C NMR Spectra

(R)-2

\[ \text{H, Me, S} \]
5. CSP-HPLC Data

CSP-HPLC of (S)-2 of 69:31 er

![Graph showing CSP-HPLC of (S)-2 with retention times and areas]

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Totals: 3.07974e4 1165.72696

CSP-HPLC of rac-2 of 50:50 er

![Graph showing CSP-HPLC of rac-2 with retention times and areas]

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Totals: 306.02238 10.21277
CSP-HPLC of (R,R)-12 of 75:25 er

![HPLC chromatogram of (R,R)-12](image)

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Totals: 6.15895e4 1835.89966

CSP-HPLC of rac-12 of 50:50 er

![HPLC chromatogram of rac-12](image)

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Totals: 2906.33447 91.34246
CSP-HPLC of (S,R)-13 of 58:42 er

![Graph of CSP-HPLC of (S,R)-13 of 58:42 er]

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Totals: 6.0406e4 3780.88977

CSP-HPLC of rac-13 of 50:50 er

![Graph of CSP-HPLC of rac-13 of 50:50 er]

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Totals: 2469.56482 171.52319
CSP-HPLC of (S,S)-S2 of 99:1 er

![CSP-HPLC of (S,S)-S2 of 99:1 er](image)

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CSP-HPLC of (R,R)-S2 of 75:25 er

![CSP-HPLC of (R,R)-S2 of 75:25 er](image)

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CSP-HPLC of (R,S)-S3 of 99:1 er

CSP-HPLC of (S,R)-S3 of 57:43 er
CSP-HPLC of (R,R)-14 of 82:18 er

![Graph showing CSP-HPLC data for (R,R)-14]

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Totals: 2.15190e4 433.90915

CSP-HPLC of rac-14 of 50:50 er

![Graph showing CSP-HPLC data for rac-14]

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<td>MM</td>
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<td>3.352.35986</td>
<td>32.08914</td>
<td>50.4365</td>
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</table>

Totals: 6646.68750 102.78968
CSP-HPLC of (S,R)-15 of 86:14 er

CSP-HPLC of rac-15 of 50:50 er
CSP-HPLC of (R)-16 of 67:33 er

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.798</td>
<td>RS</td>
<td>0.3563</td>
<td>7852</td>
<td>21632</td>
<td>324.5020</td>
</tr>
<tr>
<td>2</td>
<td>16.273</td>
<td>RS</td>
<td>0.4887</td>
<td>1,560,368</td>
<td>512.7361</td>
<td>55.5665</td>
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<tr>
<td>Totals:</td>
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CSP-HPLC of rac-16 of 50:50 er

<table>
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<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
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<td>1</td>
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<td>RS</td>
<td>0.3574</td>
<td>5703.45072</td>
<td>289.41261</td>
<td>50.0292</td>
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<td>2</td>
<td>17.336</td>
<td>RS</td>
<td>0.4039</td>
<td>5695.85855</td>
<td>217.30383</td>
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### CSP-HPLC of (R)-17 of 76:24 er

![CSP-HPLC of (R)-17 of 76:24 er](image)

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.59</td>
<td>SE</td>
<td>0.288</td>
<td>580.77</td>
<td>50.37</td>
<td>34.49</td>
</tr>
<tr>
<td>2</td>
<td>11.92</td>
<td>SE</td>
<td>0.326</td>
<td>1799.99</td>
<td>81.29</td>
<td>75.36</td>
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Totals: 2371.35952 113.67181

### CSP-HPLC of rac-17 of 54:46 er

![CSP-HPLC of rac-17 of 54:46 er](image)

<table>
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<th>Peak</th>
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<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.54</td>
<td>SE</td>
<td>0.267</td>
<td>1032.00</td>
<td>59.25</td>
<td>53.54</td>
</tr>
<tr>
<td>2</td>
<td>11.90</td>
<td>SE</td>
<td>0.296</td>
<td>887.54</td>
<td>46.16</td>
<td>46.46</td>
</tr>
</tbody>
</table>

Totals: 1910.45825 105.41398
CSP-HPLC of (S)-20 of 58:42 er

![Graph of CSP-HPLC of (S)-20](image)

<table>
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<tr>
<th>Peak RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BV</td>
<td>8.031</td>
<td>0.2329</td>
<td>3.24516e4</td>
<td>2140.43945</td>
<td>57.8625</td>
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<tr>
<td>2</td>
<td>VB</td>
<td>9.025</td>
<td>0.1609</td>
<td>2.36324e4</td>
<td>2442.75171</td>
<td>42.1375</td>
</tr>
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Totals: 5.60840e4 4583.19116

CSP-HPLC of (R)-20 of 100:0 er

![Graph of CSP-HPLC of (R)-20](image)

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BBA</td>
<td>13.900</td>
<td>1.0214</td>
<td>1.03801e5</td>
<td>1299.89954</td>
<td>100.0000</td>
</tr>
</tbody>
</table>

Totals: 1.03801e5 1299.89954
**CSP-HPLC of 22 of 68:32 er**

![CSP-HPLC of 22 of 68:32 er](image1)

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.436</td>
<td>1.2728E4</td>
<td>1394.87549</td>
<td>67.5019</td>
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<tr>
<td>2</td>
<td>8.111</td>
<td>6.2728E2</td>
<td>400.98623</td>
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Totals: 1.0056E4 1795.76172

**CSP-HPLC of rac-22 of 50:50 er**

![CSP-HPLC of rac-22 of 50:50 er](image2)

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.178</td>
<td>1.8386E3</td>
<td>213.35065</td>
<td>50.0619</td>
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<tr>
<td>2</td>
<td>7.608</td>
<td>1.8341E3</td>
<td>172.38014</td>
<td>49.9381</td>
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Totals: 3672.76050 385.73079
**CSP-HPLC of 23 of 78:22 er**

![CSP-HPLC of 23 of 78:22 er](image)

<table>
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<tr>
<th>Peak</th>
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<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.860</td>
<td>VV</td>
<td>0.1216</td>
<td>2382.31567</td>
<td>296.87918</td>
<td>77.8709</td>
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<tr>
<td>2</td>
<td>6.422</td>
<td>BB</td>
<td>0.2091</td>
<td>676.99817</td>
<td>50.27295</td>
<td>22.1291</td>
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</table>

Totals:

3059.31384 347.15213

---

**CSP-HPLC of rac-23 of 50:50 er**

![CSP-HPLC of rac-23 of 50:50 er](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.705</td>
<td>BB</td>
<td>0.1331</td>
<td>1.56368e4</td>
<td>1840.94458</td>
<td>47.5946</td>
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<tr>
<td>2</td>
<td>6.023</td>
<td>VB</td>
<td>0.2891</td>
<td>1.72174e4</td>
<td>988.85254</td>
<td>52.4054</td>
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</table>

Totals:

3.29542e4 2829.79712
CSP-HPLC of S15 of 60:40 er

<table>
<thead>
<tr>
<th>Peak RetTime Type Width Area Height Area</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 12.991 BV 0.3409 9157.42285 409.49518 39.6060</td>
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</tr>
<tr>
<td>2 14.121 VB 0.3810 1.39639e4 555.09570 50.3940</td>
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</tr>
<tr>
<td>Totals: 2.31213e4 965.59088</td>
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</tr>
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CSP-HPLC of rac-S15 of 50:50 er

<table>
<thead>
<tr>
<th>Peak RetTime Type Width Area Height Area</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 13.074 BV 0.3565 6233.15082 284.94638 49.9182</td>
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</tr>
<tr>
<td>2 14.341 VB 0.3896 6253.57422 243.53642 50.0818</td>
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</tr>
<tr>
<td>Totals: 1.24857e4 508.48280</td>
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</tr>
</tbody>
</table>
CSP-HPLC of 16 of 56:44 er

<table>
<thead>
<tr>
<th>Peak</th>
<th>Ret Time</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>0.394</td>
<td>2554.07158</td>
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<tr>
<td>2</td>
<td>12.913</td>
<td>BB</td>
<td>0.4519</td>
<td>3407.83398</td>
<td>111.08730</td>
<td>56.2028</td>
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</table>

Totals: 6062.70537 247.71593

CSP-HPLC of rac-S16 of 50:50 er

<table>
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<tr>
<th>Peak</th>
<th>Ret Time</th>
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<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>0.3037</td>
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<tr>
<td>2</td>
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<td>BB</td>
<td>0.4796</td>
<td>3017.87456</td>
<td>95.99203</td>
<td>49.6652</td>
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</table>

Totals: 5872.31555 246.70918
CSP-HPLC of S17 of 53:47 er

![CSP-HPLC of S17 of 53:47 er](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area (min)</th>
<th>Height (min)</th>
<th>[mAU]</th>
<th>[mAU]</th>
<th>[%]</th>
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</thead>
<tbody>
<tr>
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<td>BB</td>
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</tr>
<tr>
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<td>BB</td>
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</table>

CSP-HPLC of rac-S17 of 50:50 er

![CSP-HPLC of rac-S17 of 50:50 er](image)

<table>
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<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area (min)</th>
<th>Height (min)</th>
<th>[mAU]</th>
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<th>[%]</th>
</tr>
</thead>
<tbody>
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6. References for Supporting Information