

Synthesis of Enantiopure Piperazines via Asymmetric Lithiation-Trapping of N-Boc Piperazines: Unexpected Role of the Electrophile and Distal N-Substituent

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Data is available at: doi 10.15124/04a01ef8-f5aa-4f78-8db1-9c02e3945e69

1. Experimental details

1.1 General

All-non aqueous reactions were carried out under oxygen free Ar or N₂ using flame-dried glassware. Et₂O and THF were freshly distilled from sodium and benzophenone. Alkyllithiums were titrated against *N*-benzylbenzamide before use. All diamines used in lithiation reactions were distilled over CaH₂ before use. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C and was purchased in Winchester quantities. Brine refers to a saturated solution. Water is distilled water.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F₂₅₄ aluminium backed silica plates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in CDCl₃, chemical shifts are quoted in parts per million relative to CHCl₃ (δ _H 7.26) and CDCl₃ (δ _C 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Boiling points give for compounds purified by Kügelrohr distillation correspond to the oven temperature during distillation. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer or a Perkin Elmer UATR Two FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltonics microOTOF spectrometer. Optical rotations were recorded at room temperature on a Jasco DIP-370 polarimeter (using sodium D line, 589 nm) and $[\alpha]$ _D given in units of 10⁻¹ deg cm³ g⁻¹. Chiral stationary phase HPLC was performed on an Agilent 1200 series chromatograph. *In situ* ReactIR™ infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR iC10 spectrometer with a silicon-tipped (SiComp) probe.

The following compounds were synthesised according to the reported procedures: piperazine **4**,¹ (+)-sparteine surrogate² and *tert*-butyl piperazine-1-carboxylate.¹

1.2 General Procedures

General Procedure A: Asymmetric Lithiation/trapping using *s*-BuLi/diamine with pre-mixing of diamine and *s*-BuLi

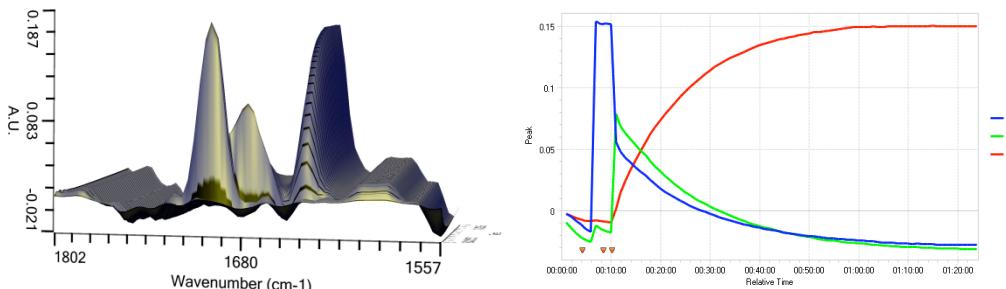
s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine (1.0 eq.) and diamine (1.3 eq.) in Et₂O (4-7 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 10 min to 6 h. Then, the electrophile (1.3-2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated NH₄Cl_(aq) (10 mL) (and saturated NaHCO_{3(aq)} (10 mL) or 20% NaOH_(aq) (10 mL) where used) 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: Asymmetric Lithiation/trapping using *s*-BuLi/diamine without pre-mixing of diamine and *s*-BuLi

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine (1.0 eq.) and diamine (1.3 eq.) in solvent (4-7 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 10 min to 6 h. Then, the electrophile (1.3-2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated NH₄Cl_(aq) (10 mL) (and saturated NaHCO_{3(aq)} (10 mL) or 20% NaOH_(aq) (10 mL) where used) 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

ReactIR™ monitoring of the lithiation of *N*-Boc-*N'*-benzyl piperazine **4** ((-)-sparteine)

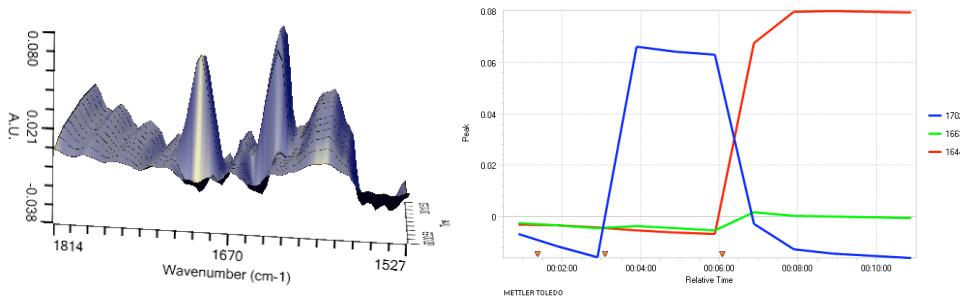


(Scheme 2)

Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to -78°C , (-)-sparteine (305 mg, 299 μL , 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at -78°C for 75 min.

For *N*-Boc-*N'*-benzyl piperazine **4**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{\text{C=O}}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{\text{C=O}}$ in the pre-lithiation complex **5**. A new peak at 1645 cm^{-1} was observed which was assigned to $\nu_{\text{C=O}}$ in the lithiated intermediate **6**. After a lithiation time of 60 min, lithiation of *N*-Boc-*N'*-benzyl piperazine **4** to give the lithiated intermediate **6** was observed. Using the peak at 1645 cm^{-1} , a half-life value, $t_{1/2}$ of ~ 9.5 min was determined. Lab Book Reference: JDF3_238

ReactIR™ monitoring of the lithiation of *N*-Boc-*N'*-benzyl piperazine **4** ((+)-sparteine surrogate)



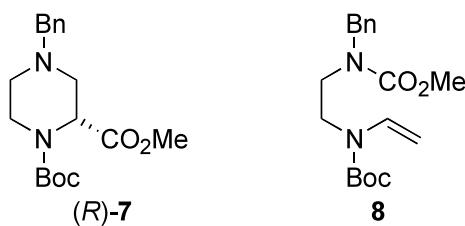
(Scheme 2)

Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to -78°C , a solution of (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi

(1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at -78°C for 5 min.

For *N*-Boc-*N'*-benzyl piperazine **4**, a peak at 1702 cm⁻¹ was observed and assigned to $\nu_{\text{C=O}}$. After addition of *s*-BuLi, a new peak at 1663 cm⁻¹ was observed which was assigned to $\nu_{\text{C=O}}$ in the pre-lithiation complex **5**. A new peak at 1644 cm⁻¹ was observed which was assigned to $\nu_{\text{C=O}}$ in the lithiated intermediate **6**. After a lithiation time of 2 min, complete lithiation of *N*-Boc-*N'*-benzyl piperazine **4** to give the lithiated intermediate **6** was observed. Using the peak at 1644 cm⁻¹, a half-life value, $t_{1/2}$ of ~0.5 min was determined. Lab Book Reference: JDF5_428

(R)-1-tert-butyl 2-methyl 4-benzylpiperazine-1,2-dicarboxylate (R)-7 and tert-Butyl N-[2-[benzyl(methoxycarbonyl)amino]ethyl]-N-ethenylcarbamate 8



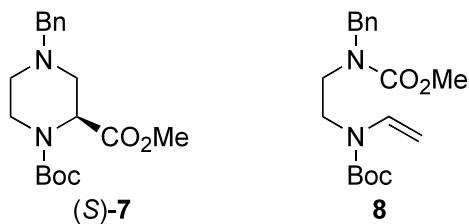
(Scheme 3)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (−)-sparteine (305 mg, 299 μ L, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in Et₂O (7 mL) for 90 min and methyl chloroformate (189 mg, 155 μ L, 2.0 mmol, 2.0 eq.), worked up with 20% NaOH_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*)-**7** (236 mg, 71%, 88:12 er by CSP-HPLC) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.7; IR (CHCl₃) 2979, 1744 (C=O, CO₂Me), 1691 (C=O, Boc), 1408, 1366, 1301, 1169, 1119, 1046, 976, 867 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) (55:45 mixture of rotamers) δ 7.32-7.24 (m, 5H, Ph), 4.71 (br s, 0.55H, NCH), 4.54 (br s, 0.45H, NCH), 3.85 (br d, J = 13.0 Hz, 0.55H, NCH), 3.77-3.75 (m, 0.45H, NCH), 3.73 (s, 1.35H, OMe), 3.71 (s, 1.65H, OMe), 3.58 (d, J = 13.0 Hz, 0.45H, CH_AH_BPh), 3.58 (d, J = 13.0 Hz, 0.55H, CH_AH_BPh), 3.45 (d, J = 13.0 Hz, 0.55H, CH_AH_BPh), 3.41 (d, J = 13.0 Hz, 0.45H, CH_AH_BPh), 3.34-3.27 (m, 1.55H, NCH), 3.18 (td, J = 13.0, 3.0 Hz, 0.45H, NCH), 2.79 (br d, J = 11.0 Hz, 0.45H, NCH), 2.74 (d, J = 11.0 Hz, 0.55H, NCH), 2.18 (td, J = 11.0, 4.0 Hz, 1H, NCH), 2.11 (br d, J = 11.0 Hz, 0.55H, NCH), 2.11 (br d, J = 11.0 Hz, 0.45H, NCH), 1.47 (s, 4.9H, CMe₃), 1.42 (s, 4.1H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 171.3 (CO₂Me), 171.1 (CO₂Me), 155.8 (NC=O), 155.3 (NC=O),

137.6 (*ipso*-Ph), 128.7 (Ph), 128.1 (Ph), 127.2 (Ph), 80.2 (CMe₃), 62.3 (NCH₂), 55.5 (NCH), 54.3 (NCH), 53.5 (NCH₂), 52.4 (NCH₂), 52.3 (NCH₂), 51.9 (OMe), 42.0 (NCH₂), 41.0 (NCH₂), 28.3 (CMe₃); MS (ESI) *m/z* 335 (M + H)⁺; HRMS *m/z* calcd for C₁₈H₂₆N₂O₄ (M + H)⁺ 335.1965, found 335.1974 (−2.7 ppm error); [α]_D +27.5 (c 1.0 in CHCl₃); CSP-HPLC: Chiralcel AD-H (95:5 hexane:*i*-PrOH, 1.0 mL min^{−1}) (*R*)-**7** 5.4 min, (*S*)-**7** 6.3 min, and vinyl carbamate **8** (39 mg, 12%) as a colourless oil, *R*_F (8:2 petrol-EtOAc) 0.4; IR (CHCl₃) 2973, 2934, 1672 (C=O), 1485, 1454, 1430, 1387, 1371, 1346, 1225, 1200, 1148, 769, 725 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) δ 7.34–7.19 (m, 5H, Ph), 7.10–6.94 (br m, 1H, CH=CH₂), 4.58–4.37 (br m, 2.5H, CH=CH₂ + NCH₂), 4.30–4.17 (m, 1.5H, NCH₂), 3.77 (s, 1.5H, OMe), 3.44 (br s, 1.5H, OMe), 3.68–3.59 (br m, 2H, NCH₂), 3.38 (br s, 1H, NCH₂), 3.30 (br s, 1H, NCH₂), 1.49 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 157.6 (C=O), 157.3 (C=O), 156.0 (C=O), 155.8 (C=O), 137.4 (*ipso*-Ph), 128.6 (CH=CH₂), 127.8 (Ph), 127.4 (Ph), 127.1 (Ph), 79.2 (CMe₃), 52.8 (CO₂Me), 50.9 (NCH₂Ph), 50.5 (NCH₂Ph), 46.4 (NCH₂), 45.7 (NCH₂), 39.0 (NCH₂), 28.3 (CMe₃) (CH=CH₂ not resolved), MS (ESI) *m/z* 357 [(M + Na)⁺, 100], 335 [(M + H)⁺, 10], 220 [(M – Boc)⁺, 80], HRMS *m/z* calcd for C₁₈H₂₆N₂O₄ (M + H)⁺ 335.1965, found 335.1972 (−2.6 ppm error). Spectroscopic data of (*R*)-**7** consistent with those reported in the literature.¹

Lab Book Reference: JDF5_451

(S)-1-*tert*-Butyl 2-methyl 4-benzylpiperazine-1,2-dicarboxylate (*S*)-7 and *tert*-Butyl N-[2-[benzyl(methoxycarbonyl)amino]ethyl]-N-ethenylcarbamate 8



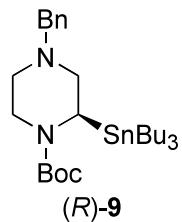
(Scheme 3)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (152 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in Et₂O (7 mL) for 1 h and methyl chloroformate (189 mg, 155 μ L, 2.0 mmol, 2.0 eq.), worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2-7:3 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**7** (295 mg, 88%, 85:15 er by CSP-HPLC) as a colourless oil, [α]_D −28.7 (c 1.0 in CHCl₃); CSP-HPLC: Chiralcel

AD-H (95:5 hexane:*i*-PrOH, 1.0 mL min⁻¹) (*R*)-**7** 5.4 min, (*S*)-**7** 6.3 min, and vinyl carbamate **8** (28 mg, 8%) as a colourless oil.

Lab Book Reference: JDF5_469

(*R*)-*tert*-Butyl 4-benzyl-2-(tributylstannyl)piperazine-1-carboxylate (*R*)-9

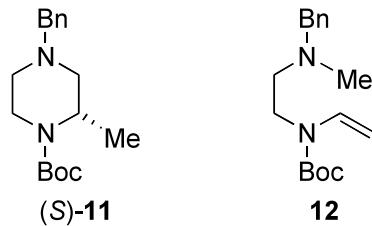


(Scheme 3)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in Et₂O (7 mL) for 10 min and Bu₃SnCl (650 mg, 542 μ L, 2.0 mmol, 2.0 eq.), worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*)-**9** (96 mg, 17%, 77:23 er by CSP-HPLC) as a colourless oil, *R*_F (9:1 petrol-EtOAc) 0.2; IR (CHCl₃) 2961, 2911, 2881, 2827, 1647 (C=O), 1433, 1395, 1395, 1344, 1278, 1231, 1151, 1088, 1055, 1007, 850, 688 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) δ 7.38-7.21 (m, 5H, Ph), 4.13 (s, 0.5H, NCH), 4.03 (br d, *J* = 13.0 Hz, 0.5H, NCH), 3.80-3.16 (m, 4H, NCH), 2.82-2.37 (m, 3H, NCH), 2.21 (br s, 0.5H, NCH), 1.96-1.80 (m, 0.5H, NCH), 1.55-1.35 (m, 15H, CH₂ + CMe₃), 1.35-1.23 (m, 6H, CH₂), 0.99-0.78 (m, 15H, CH₂ + Me); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 154.6 (C=O), 154.2 (C=O), 138.2 (*ipso*-Ph), 129.4 (Ph), 128.3 (Ph), 127.2 (Ph), 79.5 (CMe₃), 79.4 (CMe₃), 63.3 (NCH₂), 58.1 (NCH₂), 53.2 (NCH₂), 53.0 (NCH₂), 46.5 (NCH), 45.5 (NCH), 44.8 (NCH₂), 42.6 (NCH₂), 29.3 (CH₂), 29.3 (CH₂), 28.5 (CMe₃), 27.9 (CH₂), 27.7 (CH₂), 13.8 (Me), 11.1 (CH₂), 10.4 (CH₂); MS (ESI) *m/z* 567 (M + H)⁺; HRMS *m/z* calcd for C₂₈H₅₀N₂O₂Sn (M + H)⁺ 567.2972, found 567.2945 (+3.9 ppm error); $[\alpha]_D$ -26.0 (c 1.0 in CHCl₃); CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min⁻¹) (*S*)-**9** 7.2 min, (*R*)-**9** 7.8 min.

Lab Book Reference: JDF5_468

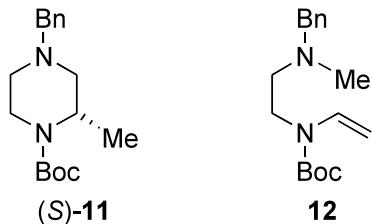
(S)-*tert*-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate (S)-11 and *tert*-butyl 2-(benzyl(methyl)amino)ethyl(vinyl)carbamate 12



(Scheme 3)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine (152 mg, 149 μ L, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (138 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 90 min and methyl iodide (142 mg, 62 μ L, 1.0 mmol, 2.0 eq.), worked up with 20% NaOH_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1:8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**11** (43 mg, 33%, 61:39 er by CSP-HPLC) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.6; IR (ATR) 2973, 1688 (C=O), 1452, 1407, 1392, 1364, 1341, 1322, 1305, 1279, 1247, 1223, 1158, 1107, 1059, 1039, 1028, 740, 700 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.29 (m, 4H, Ph), 7.26-7.22 (m, 1H, Ph), 4.18 (br s, 1H, NCH), 3.80 (br d, J = 12.5 Hz, 1H, NCH), 3.53 (d, J = 13.0 Hz, 1H, CH_AH_BPh), 3.40 (d, J = 13.0 Hz, 1H, CH_AH_BPh), 3.11 (td, J = 12.5, 3.5 Hz, 1H, NCH), 2.77-2.73 (m, 1H, NCH), 2.59 (dt, J = 11.0, 1.5 Hz, 1H, NCH), 2.12 (dd, J = 11.0, 4.0 Hz, 1H, NCH), 2.00 (ddd, J = 12.5, 11.5, 3.5 Hz, 1H, NCH), 1.45 (s, 9H, CMe₃), 1.24 (d, J = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.8 (C=O), 138.4 (*ipso*-Ph), 128.7 (Ph), 128.2 (Ph), 127.0 (Ph), 79.3 (CMe₃), 62.8 (NCH₂), 57.3 (NCH₂), 53.2 (NCH₂), 47.0 (NCH), 39.1 (NCH₂), 28.4 (CMe₃), 15.9 (Me); MS (ESI) *m/z* 291 (M + H)⁺; CSP-HPLC: Chiralcel IC (99:1 hexane:*i*-PrOH, 1.0 mL min^{−1}) (*R*)-**11** 12.3 min, (*S*)-**11** 14.7 min, and vinyl carbamate **12** (19 mg, 13%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.4; IR (CHCl₃) 3019, 2980, 2793, 2399, 1698 (C=O), 1627 (C=C), 1521, 1494, 1423, 1391, 1217, 1152, 1018, 928, 847, 761, 699 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.22 (m, 5H, Ph), 7.10-6.95 (br m, 1H, CH=CH₂), 4.23-4.10 (m, 2H, CH=CH₂), 3.68-3.51 (m, 2H, NCH₂), 3.55 (s, 2H, CH₂Ph), 2.53 (br s, 2H, NCH₂), 2.29 (s, 3H, NMe), 1.45 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 153.1 (C=O), 139.0 (*ipso*-Ph), 132.8 (CH=CH₂), 128.9 (Ph), 128.2 (Ph), 127.0 (Ph), 90.5 (CH=CH₂), 81.1 (CMe₃), 62.7 (NCH₂Ph), 62.5 (NCH₂Ph), 53.3 (NCH₂), 53.1 (NCH₂), 42.7 (NMe), 42.5 (NMe), 41.4 (NCH₂), 40.9 (NCH₂), 28.2 (CMe₃); MS (ESI) *m/z* 291 [(M + H)⁺, 100], 235 [(M - CMe₃)⁺, 20], 191 [(M - Boc)⁺, 10]; HRMS *m/z* calcd for C₁₇H₂₆N₂O₂ (M + H)⁺ 291.2067, found 291.2072 (−1.0 ppm error). Spectroscopic data of (*S*)-**11** consistent with those reported in the literature.³ Lab Book Reference: JDF7_619

(S)-*tert*-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate (S)-11 and *tert*-butyl 2-(benzyl(methyl)amino)ethyl(vinyl)carbamate 12

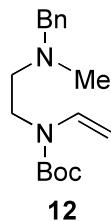


(Scheme 3)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (138 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 90 min and dimethyl sulfate (126 mg, 97 μ L, 1.0 mmol, 2.0 eq.), worked up with 20% NaOH_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**11** (16 mg, 11%, 58:42 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{–1}) (*R*)-**11** 6.8 min, (*S*)-**11** 7.3 min, and vinyl carbamate **12** (63 mg, 43%) as a colourless oil.

Lab Book Reference: JDF5_485

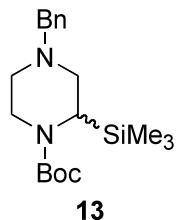
***tert*-Butyl 2-(benzyl(methyl)amino)ethyl(vinyl)carbamate 12**



(Scheme 3)

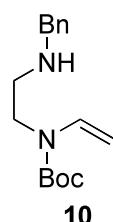
Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in Et₂O (7 mL) for 10 min and dimethyl sulfate (252 mg, 189 μ L, 2.0 mmol, 2.0 eq.), worked up with 20% NaOH_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave vinyl carbamate **12** (145 mg, 50%) as a colourless oil.

Lab Book Reference: JDF5_475

tert-Butyl 4-benzyl-2-(trimethylsilyl)piperazine-1-carboxylate 13

(Scheme 3)

Using general procedure A, *s*-BuLi (1.85 mL of a 1.3 M solution in hexanes, 2.3 mmol, 1.3 eq.), (−)-sparteine (548 mg, 2.3 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (500 mg, 1.8 mmol, 1.0 eq.) in Et₂O (14 mL) for 5 h and Me₃SiCl (330 μ L, 2.6 mmol, 2.0 eq.), worked up with saturated NH₄Cl_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et₂O as eluent gave *N*-Boc piperazine **13** (237 mg, 38%, 52:48 er by CSP-HPLC) as a yellow oil, *R*_F (9:1 petrol-EtOAc) 0.4; IR (CHCl₃) 2977, 2804, 1673 (C=O), 1454, 1420, 1366, 1296, 1168, 1111, 1027, 840 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) (60:40 mixture of rotamers) δ 7.32–7.30 (m, 4H, Ph), 7.27–7.22 (m, 1H, Ph) 4.20 (br s, 0.6H, NCH), 3.80 (br s, 0.4H, NCH), 3.61–3.55 (m, 1H, NCH), 3.44 (d, *J* = 13.0 Hz, 1H, CH_AH_BPh), 3.40 (d, *J* = 13.0 Hz, 1H, CH_AH_BPh), 3.05 (br s, 0.4H, NCH), 2.92 (br s, 0.6H, NCH), 2.80 (d, *J* = 12.0 Hz, 1H, NCH), 2.72 (m, 0.6H, NCH), 2.64 (br s, 0.4H, NCH), 2.24 (br s, 1H, NCH), 1.93 (td, *J* = 12.0, 3.0 Hz, 1H, NCH), 1.46 (s, 9H, CMe₃), 0.12 (s, 9H, SiMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.7 (C=O), 138.3 (*ipso*-Ph), 129.1 (Ph), 128.1 (Ph), 127.0 (Ph), 79.1 (CMe₃), 63.4 (NCH₂), 54.3 (NCH₂), 53.2 (NCH₂), 45.3 (NCH), 41.4 (NCH₂), 28.4 (CMe₃), −0.8 (SiMe₃); MS (ESI) *m/z* 349 (M + H)⁺; HRMS *m/z* calcd for C₁₉H₃₂N₂O₂Si (M + H)⁺ 349.2306, found 349.2297 (+1.7 ppm error); CSP-HPLC: Chiralcel AD (98:2 hexane:*i*-PrOH, 0.4 mL min^{−1}) 21.3 min (minor), 26.9 min (major). Spectroscopic data of **13** consistent with those reported in the literature.¹

tert-Butyl (2-(benzylamino)ethyl)(vinyl)carbamate 10

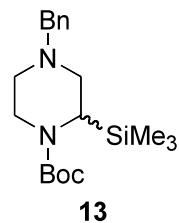
(Scheme 3)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine (152 mg, 149 μ L, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine **4** (138 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 1 h and Me₃SiOTf (222 mg, 181 μ L, 1.0 mmol, 2.0 eq.), worked up with saturated

$\text{NaHCO}_{3(\text{aq})}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 97:3 CH_2Cl_2 -MeOH as eluent gave alkene **10** (71 mg, 51%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.2; IR (ATR) 2978, 2936, 2821, 1702 (C=O), 1625 (C=C), 1452, 1421, 1364, 1327, 1247, 1213, 1163, 1137, 1028, 977, 836, 769, 733 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.29 (m, 4H, Ph), 7.29-7.21 (m, 1H, Ph), 7.04 (br s, 1H, $\text{CH}=\text{CH}_2$), 4.33 (d, J = 16.0 Hz, 1H, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.20 (br s, 1H, $\text{CH}=\text{CH}_\text{A}\text{H}_\text{B}$), 3.82 (s, 2H, CH_2Ph), 3.65 (br s, 2H, NCH_2), 2.83 (t, J = 6.5 Hz, 2H, NCH_2), 1.47 (s, 9H, CMe_3) (NH not resolved); ^{13}C NMR (100.6 MHz, CDCl_3) δ 153.0 (C=O), 140.0 (*ipso*-Ph), 133.0 ($\text{CH}=\text{CH}_2$), 128.3 (Ph), 128.0 (Ph), 127.0 (Ph), 90.8 ($\text{CH}=\text{CH}_2$), 81.2 (CMe_3), 53.9 (CH_2Ph), 46.0 (NCH_2), 42.5 (NCH_2), 28.1 (CMe_3); MS (ESI) m/z 277 [(M + H) $^+$, 100], 221 [(M - CMe_3) $^+$, 20]; HRMS m/z calcd for $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_2$ (M + H) $^+$ 277.1911, found 277.1910 (+0.5 ppm error).

Lab Book Reference: JDF10_941

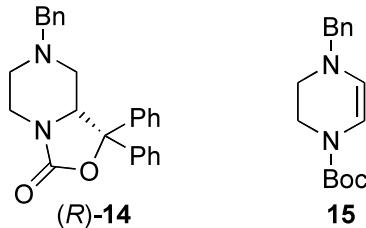
tert-Butyl 4-benzyl-2-(trimethylsilyl)piperazine-1-carboxylate 13



(Scheme 3)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (152 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and Me_3SiCl (217 mg, 253 μL , 2.0 mmol, 2.0 eq.), worked up with saturated $\text{NaHCO}_{3(\text{aq})}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine **13** (186 mg, 53%, 50:50 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 1.0 mL min $^{-1}$) 3.0 min, 3.4 min.

Lab Book Reference: JDF5_474

(R)-7-Benzyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (R)-14

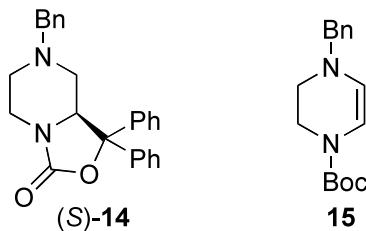
(Scheme 3)

Using general procedure A, *s*-BuLi (1.5 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.), (–)-sparteine (457 mg, 448 μ L, 1.95 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (415 mg, 1.5 mmol, 1.0 eq.) in Et₂O (10 mL) for 1 h and a solution of benzophenone (547 mg, 3.0 mmol, 2.0 eq.) in Et₂O (2 mL), worked up with 20% NaOH_(aq) (10 mL) gave the crude product which contained a 78:22 mixture of (R)-**14** and alkene **15** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave oxazolidinone (R)-**14** (310 mg, 54%, 81:19 er by CSP-HPLC) as a white solid, mp 146–149 °C; *R*_F (7:3 petrol-Et₂O) 0.2; IR (CHCl₃) 3020, 2400, 1751 (C=O), 1422, 1215, 929, 759, 669 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 7.53–7.50 (m, 2H, Ph), 7.40–7.21 (m, 13H, Ph), 4.54 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.80 (ddd, *J* = 13.0, 3.5, 1.5 Hz, 1H, NCH), 3.50 (d, *J* = 13.0 Hz, 1H, CH_AH_BPh), 3.31 (d, *J* = 13.0 Hz, 1H, CH_AH_BPh), 3.09 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.70–2.66 (m, 1H, NCH), 2.55 (ddd, *J* = 11.0, 3.5, 1.5 Hz, 1H, NCH), 1.93 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.57 (t, *J* = 11.0 Hz, 1H, NCH); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.5 (C=O), 142.7 (*ipso*-Ph), 139.1 (*ipso*-Ph), 137.6 (*ipso*-Ph), 129.1 (Ph), 128.8 (Ph), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 127.6 (Ph), 126.2 (Ph), 126.0 (Ph), 85.3 (Ph₂CO), 62.9 (NCH₂), 61.1 (NCH), 55.7 (NCH₂), 50.7 (NCH₂), 41.5 (NCH₂); MS (ESI) *m/z* 385 (M + H)⁺; HRMS *m/z* calcd for C₂₅H₂₄N₂O₂ (M + H)⁺ 385.1911, found 385.1899 (+3.6 ppm error); [α]_D +145.9 (*c* 1.0 in CHCl₃); CSP-HPLC: Chiralcel OD (90:10 hexane:*i*-PrOH, 1.0 mL min^{–1}) (*S*)-**14** 14.4 min, (R)-**14** 18.9 min. Spectroscopic data consistent with those reported in the literature.¹

Diagnostic signals for alkene **15**: ¹H NMR (400 MHz, CDCl₃) (67:33 mixture of rotamers) δ 6.03 (d, *J* = 6.5 Hz, 0.33H, CH=CHNBoc), 5.88 (d, *J* = 6.5 Hz, 0.67H, CH=CHNBoc), 5.49 (d, *J* = 6.5 Hz, 0.33H, CH=CHNBoc), 5.38 (d, *J* = 6.5 Hz, 0.67H, CH=CHNBoc), 3.94 (s, 2H, CH₂Ph).

Lab Book Reference: JDF1_35

(S)-7-Benzyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (S)-14

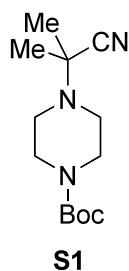


(Scheme 3)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in Et₂O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et₂O (1 mL), worked up with 20% NaOH_(aq) (10 mL) gave the crude product which contained a 41:59 mixture of (*R*)-**14** and alkene **15** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3 petrol-EtOAc as eluent gave oxazolidinone (*S*)-**14** (137 mg, 36%, 75:25 er by CSP-HPLC) as a white solid, $[\alpha]_D -114.9$ (*c* 1.0 in CHCl₃); CSP-HPLC: Chiralcel OD (90:10 hexane:*i*-PrOH, 1.0 mL min⁻¹) (*S*)-**14** 14.4 min, (*R*)-**14** 18.9 min.

Lab Book Reference: JDF1 61

***tert*-Butyl 4-(2-cyanopropan-2-yl)piperazine-1-carboxylate S1**

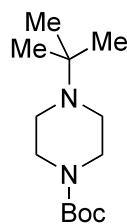


HCl (40.3 mL of a 2.0 M in Et₂O, 80.6 mmol, 1.5 eq.) was added dropwise to a stirred solution of *tert*-butyl piperazine-1-carboxylate (12.6 g, 53.7 mmol, 1.0 eq.) in MeOH (60 mL) and CH₂Cl₂ (60 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h. Then, the solvent was evaporated under reduced pressure and the residue was dissolved in water (150 mL). NaCN (2.63 g, 53.7 mmol, 1.0 eq.) and then a solution of acetone (9.4 g, 11.8 mL, 161.2 mmol, 3.0 eq.) in water (20 mL) were added sequentially. The resulting mixture was stirred at rt under air for 48 h. Then, water (100 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organics were dried (MgSO₄) and evaporated under reduced pressure to give *N*-Boc piperazine **S1** (11.0 g, 81%) as a white solid which was sufficiently pure by ¹H NMR spectroscopy, mp 108–110 °C; IR (CHCl₃) 3018, 1686 (C=O), 1455, 1429, 1391, 1367, 1307, 1290, 1266, 1242, 1215, 1172, 1130, 750, 667 cm^{–1}; ¹H NMR (400

MHz, CDCl₃) δ 3.46 (t, *J* = 5.0 Hz, 4H, NCH₂), 2.59 (t, *J* = 5.0 Hz, 4H, NCH₂), 1.51 (s, 6H, CMe₂), 1.46 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.4 (C=O), 119.8 (CN), 79.9 (CMe₃), 55.8 (CMe₂), 47.3 (NCH₂), 44.0 (NCH₂), 28.4 (CMe₃), 26.1 (CMe₂); MS (ESI) *m/z* 276 [(M + Na)⁺, 40], 254 [(M + H)⁺, 100], 198 [(M - CMe₃)⁺, 50]; HRMS *m/z* calcd for C₁₃H₂₃N₃O₂ (M + H)⁺ 254.1863, found 254.1864 (−0.2 ppm error).

Lab Book Reference: JDF5_447

tert*-Butyl 4-*tert*-butylpiperazine-1-carboxylate **19*

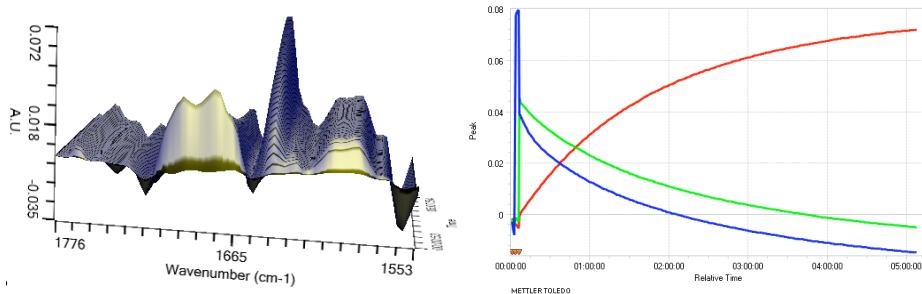


19

Methyl magnesium bromide (31.3 mL of a 3.0 M in Et₂O, 94.0 mmol, 3.0 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine **S1** (7.9 g, 31.3 mmol, 1.0 eq.) in THF (150 mL) at 0 °C under Ar. After being allowed to warm to rt the reaction was allowed to stir at rt for 16 h. Then, the mixture was cooled to 0 °C and water (20 mL) was added dropwise. The mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2-94:6 CH₂Cl₂-MeOH as eluent gave *N*-Boc-*N'*-*tert*-butyl piperazine **19** (6.0 g, 79%) as a white solid, mp 49–51 °C; *R*_F (19:1 CH₂Cl₂-MeOH) 0.3; IR (CHCl₃) 2977, 1682 (C=O), 1429, 1366, 1288, 1267, 1247, 1169, 1128, 953, 864, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.41 (t, *J* = 5.0 Hz, 4H, NCH₂), 2.50 (t, *J* = 5.0 Hz, 4H, NCH₂), 1.46 (s, 9H, OCMe₃), 1.06 (s, 9H, NCMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.6 (C=O), 79.2 (OCMe₃), 53.7 (NCMe₃), 45.8 (NCH₂), 44.6 (NCH₂), 28.3 (CMe₃), 25.7 (CMe₃); MS (ESI) *m/z* 243 (M + H)⁺; HRMS *m/z* calcd for C₁₃H₂₆N₂O₂ (M + H)⁺ 243.2067, found 243.2073 (−1.9 ppm error).

Lab Book Reference: JDF2_183

ReactIR™ monitoring of the lithiation of *N*-Boc-*N'*-*tert*-butyl piperazine **19** ((*–*)-sparteine)

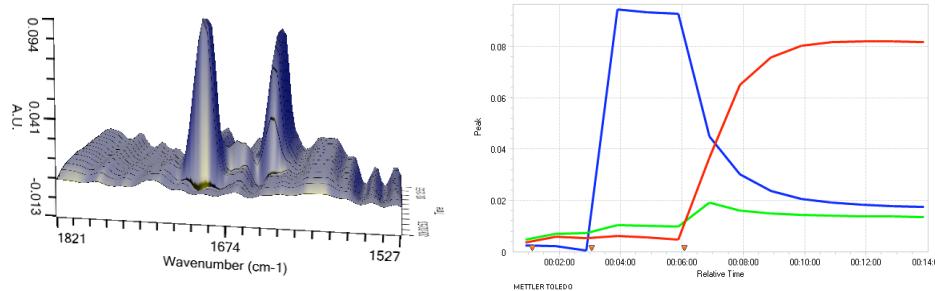


(Scheme 5)

Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to -78°C , (*–*)-sparteine (305 mg, 299 μL , 1.3 mmol, 1.3 eq.) was added followed by a solution *N*-Boc-*N'*-*tert*-butyl piperazine **19** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at -78°C for 5 h. For *N*-Boc-*N'*-*tert*-butyl piperazine **19**, a peak at 1700 cm^{-1} was observed and assigned to $\nu_{\text{C}=\text{O}}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{\text{C}=\text{O}}$ in the pre-lithiation complex **23**. A new peak at 1644 cm^{-1} was observed which was assigned to $\nu_{\text{C}=\text{O}}$ in the lithiated intermediate **24**. After a lithiation time of 5 h, near-complete lithiation of *N*-Boc-*N'*-*tert*-butyl piperazine **19** to give the lithiated intermediate **24** and *N*-Boc-*N'*-*tert*-butyl piperazine **19** was observed. Using the peak at 1644 cm^{-1} , a half-life value, $t_{1/2}$ of ~ 60 min was determined.

Lab Book Reference: JDF6_564

ReactIR™ monitoring of the lithiation of *N*-Boc-*N'*-*tert*-butyl piperazine **19** ((*+*)-sparteine surrogate)



(Scheme 5)

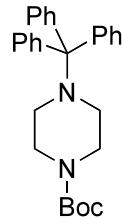
Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to -78°C , a solution of (*+*)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution *N*-Boc-*N'*-*tert*-butyl piperazine **19** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2

mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIRTM). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at -78 °C for 7 min.

For *N*-Boc-*N'*-*tert*-butyl piperazine **19**, a peak at 1701 cm⁻¹ was observed and assigned to $\nu_{\text{C=O}}$. After addition of *s*-BuLi, a new peak at 1665 cm⁻¹ was observed which was assigned to $\nu_{\text{C=O}}$ in the pre-lithiation complex **23**. A new peak at 1646 cm⁻¹ was observed which was assigned to $\nu_{\text{C=O}}$ in the lithiated intermediate **24**. After a lithiation time of 5 min, lithiation of *N*-Boc-*N'*-*tert*-butyl piperazine **19** to give the lithiated intermediate **24** was observed. Using the peak at 1646 cm⁻¹, a half-life value, $t_{1/2}$ of ~1.0 min was determined.

Lab Book Reference: JDF5_427

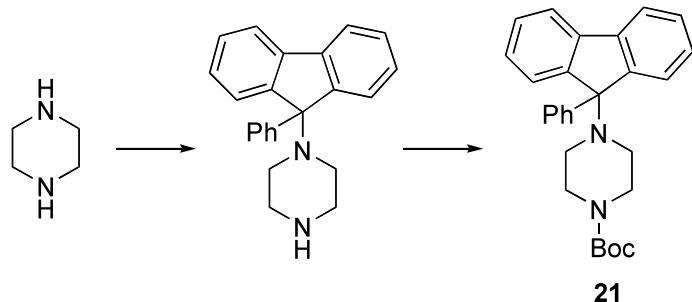
4-Tritylpiperazine-1-carboxylic acid *tert*-butyl ester **20**



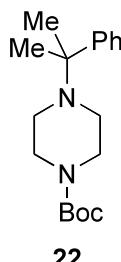
20

Triphenylmethyl chloride (2.06 g, 7.4 mmol 1.1 eq.) was added to a stirred solution of Et₃N (748 mg, 1.03 mL, 7.4 mmol, 1.1 eq.) and *tert*-butyl piperazine-1-carboxylate (1.25 g, 6.7 mmol, 1.0 eq.) in CHCl₃ (40 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. Then, saturated NaHCO_{3(aq)} (50 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 30 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 petrol-Et₂O as eluent gave *N*-Boc-*N'*-trityl piperazine **20** (2.29 g, 80%) as a white solid, mp 137-140 °C, R_F (9:1 petrol-Et₂O) 0.2; IR (CHCl₃) 1693 (C=O), 1410, 1364, 1169, 1115, 1003 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.46 (br s, 6H, Ph), 7.37-7.21 (m, 6H, Ph), 7.15 (t, J = 7.5 Hz, 3H, Ph), 3.54 (br s, 4H, NCH₂), 2.25 (br s, 4H, NCH), 1.38 (s, 9H, CMe₃); ¹³C NMR (400 MHz, CDCl₃) δ 154.9 (C=O), 146.9 (*ipso*-Ph), 127.9 (Ph), 127.6 (Ph), 126.1 (Ph), 79.4 (CMe₃), 76.9 (CPh₃), 47.8 (NCH₂), 44.4 (NCH₂), 28.3 (CMe₃); MS (ESI) m/z 451 (M + na)⁺; HRMS (ESI) m/z calcd for C₂₈H₃₂N₂O₂ (M + Na)⁺ 451.2355, found 451.2356.

Lab Book Reference: JDF5_433

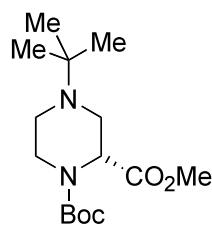
tert-Butyl 4-(9-phenyl-9H-fluoren-9-yl)piperazine-1-carboxylate 21

A mixture of 9-bromo-9-phenyl fluorene (3.21 g, 10 mmol, 1.0 eq.), piperazine (4.31 g, 50 mmol, 5.0 eq.), $\text{Pb}(\text{NO}_3)_2$ (3.97 g, 12 mmol, 1.2 eq.) and K_3PO_4 (3.18 g, 15 mmol, 1.5 eq.) in MeCN (40 mL) was stirred at rt under Ar for 48 h. The solids were removed by filtration through Celite® and washed with MeCN (50 mL), EtOAc (100 mL) and CH_2Cl_2 (100 mL). The filtrate was evaporated under reduced pressure. Then, CH_2Cl_2 (50 mL) and water (50 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure to give the crude *N*-fluorophenyl piperazine (2.70 g, 83%) as a beige solid, ^1H NMR (400 MHz, CDCl_3) δ 7.70-7.67 (m, 2H, Ar), 7.51 (br s, 2H, Ar), 7.41-7.32 (m, 5H, Ar), 7.27-7.22 (m, 4H, Ar), 2.84 (t, J = 5.0 Hz, 4H, NCH_2), 2.42 (br s, 4H, NCH_2), 1.72 (br s, 1H, NH). The crude product was used in the next step without further purification ($\geq 95\%$ purity by ^1H NMR spectroscopy). Then a solution of di-*tert*-butyl dicarbonate (2.17 g, 9.93 mmol, 1.2 eq.) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of crude *N*-fluorophenyl piperazine (2.0 g, 8.27 mmol, 1.0 eq.) in CH_2Cl_2 (80 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred for at rt for 16 h. Then, water (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 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 19:1 as eluent gave *N*-Boc piperazine **21** (3.24 g, 92%) as a white solid, mp 198-201 °C; R_F (9:1 petrol-EtOAc) 0.2; IR (CHCl_3) 3008, 1681 (C=O), 1451, 1429, 1429, 1366, 1287, 1253, 1169, 1129, 1000, 756 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.69-7.67 (m, 2H, Ar), 7.49 (br s, 2H, Ar), 7.39-7.34 (m, 4H, Ar), 7.28-7.23 (m, 5H, Ar), 3.39 (br s, 4H, NCH_2), 2.40 (br s, 4H, NCH_2), 1.39 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 154.7 (C=O), 146.6 (*ipso*-Ar), 142.6 (*ipso*-Ar), 140.6 (*ipso*-Ar), 128.4 (Ar), 128.2 (Ar), 127.4 (Ar), 127.3 (Ar), 127.0 (Ar), 126.1 (Ar), 119.9 (Ar), 79.3 (CMe_3 or NCPH), 77.9 (CMe_3 or NCPH), 47.3 (NCH_2), 28.4 (CMe_3) (one NCH_2 resonance not resolved); MS (ESI) m/z 427 ($\text{M} + \text{H}$)⁺; HRMS m/z calcd for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 427.2380, found 427.2391 (-1.7 ppm error). Lab Book Reference: JDF6_528 and JDF6_529

tert-Butyl 4-(2-phenylpropan-2-yl)piperazine-1-carboxylate 22**22**

Phenyl magnesium chloride (26.6 mL of a 2.0 in THF, 53.3 mmol, 3.0 eq.) was added dropwise to a stirred solution of nitrile **S1** (4.5 g, 17.8 mmol, 1.0 eq.) in THF (100 mL) at 0 °C under Ar. The reaction was allowed to warm to rt and stirred at rt for 16 h. Then, the mixture was cooled to 0 °C and water (20 mL) was added dropwise. The mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 Et₂O-petrol and then with 98:2-94:6 CH₂Cl₂-MeOH as eluent gave *N*-Boc-*N'*-cumyl piperazine **22** (4.2 g, 77%) as a colourless viscous oil, R_F (8:2 petrol-Et₂O) 0.2; IR (CHCl₃) 2932, 1655 (C=O), 1404, 1370, 1345, 1283, 1268, 1245, 1228, 1152, 1109, 989, 949, 850, 745, 691 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.55-7.49 (m, 2H, Ph), 7.34-7.27 (m, 2H, Ph), 7.24-7.17 (m, 1H, Ph), 3.36 (t, J = 4.5 Hz, 4H, NCH₂), 2.41 (br s, 4H, NCH₂), 1.44 (s, 9H, CMe₃), 1.33 (s, 6H, CMe₂Ph); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.8 (C=O), 148.8 (*ipso*-Ph), 128.0 (Ph), 126.2 (Ph), 126.0 (Ph), 79.3 (CMe₃), 59.7 (CMe₂Ph), 46.0 (NCH₂), 44.3 (NCH₂), 28.4 (CMe₃), 24.0 (CMe₂Ph); MS (ESI) *m/z* 305 (M + H)⁺; HRMS *m/z* calcd for C₁₈H₂₈N₂O₂ (M + H)⁺ 305.2224, found 305.2230 (−1.1 ppm error).

Lab Book Reference: JDF7_623

(R)-1-tert-Butyl 2-methyl 4-tert-butylpiperazine-1,2-dicarboxylate (R)-25**(R)-25**

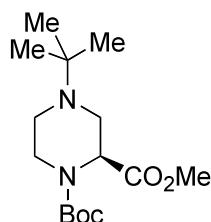
(Table 1, entry 1)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine (152 mg, 149 μ L, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-tert-butyl piperazine **19** (121 mg, 0.5 mmol,

1.0 eq.) in Et_2O (5 mL) for 6 h and methyl chloroformate (95 mg, 77 μL , 1.0 mmol, 2.0 eq.), worked up with saturated $\text{NaHCO}_{3(\text{aq})}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*)-**25** (108 mg, 72%, 89:11 er by CSP-HPLC) as a pale yellow oil, R_F (7:3 petrol-EtOAc) 0.4; IR (CHCl_3) 2976, 1745 (C=O, CO_2Me), 1689 (C=O, Boc), 1455, 1393, 1367, 1304, 1253, 1170, 1119, 1041, 965, 865, 761 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (50:50 mixture of rotamers) δ 4.70 (br s, 0.5H, NCH), 4.53 (br s, 0.5H, NCH), 3.83 (br d, J = 12.5 Hz, 0.5H, NCH), 3.75-3.73 (m, 0.5H, NCH), 3.73 (s, 1.5H, OMe), 3.72 (s, 1.5H, OMe), 3.52-3.45 (m, 1H, NCH), 3.13 (td, J = 12.5, 3.5 Hz, 0.5H, NCH), 3.03 (td, J = 12.5, 3.5 Hz, 0.5H, NCH), 2.92 (br d, J = 11.0 Hz, 0.5H, NCH), 2.84 (br d, J = 11.0 Hz, 0.5H, NCH), 2.28-2.23 (m, 1H, NCH), 2.11 (td, J = 11.0, 3.5 Hz, 1H, NCH), 1.46 (s, 4.5H, OCMe_3), 1.42 (s, 4.5H, OCMe_3), 0.96 (s, 9H, NCMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) (mixture of rotamers) δ 171.6 (CO_2Me), 171.3 (CO_2Me), 155.8 (NC=O), 155.4 (NC=O), 80.0 (OCMe_3), 56.3 (NCH), 55.0 (NCH), 53.3 (NCMe_3), 51.9 (OMe), 47.6 (NCH₂), 45.2 (NCH₂), 42.9 (NCH₂), 42.0 (NCH₂), 28.3 (CMe_3), 25.8 (CMe_3); MS (ESI) m/z 301 ($\text{M} + \text{H}$)⁺; HRMS m/z calcd for $\text{C}_{15}\text{H}_{28}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$)⁺ 301.2122, found 301.2122 (+0.3 ppm error); $[\alpha]_D$ +22.2 (*c* 1.0 in CHCl_3); CSP-HPLC: Chiralcel AD (99:1 hexane:*i*-PrOH, 1.0 mL min⁻¹) (*R*)-**25** 16.0 min, (*S*)-**25** 21.8 min.

Lab Book Reference: JDF2_153

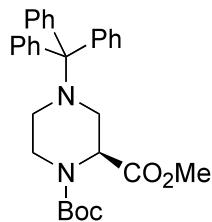
(*S*)-1-*tert*-Butyl 2-methyl 4-*tert*-butylpiperazine-1,2-dicarboxylate (*S*)-25



(*S*)-**25**

(Table 1, entry 2)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-*tert*-butyl piperazine **19** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 10 min and methyl chloroformate (190 mg, 155 μL , 2.0 mmol, 2.0 eq.) worked up with 20% $\text{NaOH}_{(\text{aq})}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**25** (270 mg, 90%, 89:11 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel AD (99:1 hexane:*i*-PrOH, 1.0 mL min⁻¹) (*R*)-**25** 14.6 min, (*S*)-**25** 23.4 min. Lab Book Reference: JDF5_470

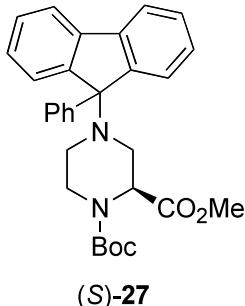
(S)-1-*tert*-Butyl 2-methyl 4-tritylpiperazine-1,2-dicarboxylate (S)-26

(S)-26

(Table 1, entry 3)

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-trityl piperazine **20** (214 mg, 0.5 mmol, 1.0 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et₂O (7 mL) for 1 h and methyl chloroformate (95 mg, 77 μ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et₂O as eluent gave *N*-Boc piperazine (S)-**26** (196 mg, 81%, 81:19 er by CSP-HPLC) as a white solid, mp 189-192 °C; R_F (4:1 petrol-Et₂O) 0.3; IR (CHCl₃) 3020, 2399, 1746 (C=O, CO₂Me), 1688 (C=O, Boc), 1410, 1215, 1120, 1010, 762, 669 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (60:40 mixture of rotamers) δ 7.42 (br s, 6H, Ph), 7.29-7.20 (m, 6H, Ph), 7.17 (br s, 3H, Ph), 4.61 (br s, 0.6H, NCH), 4.46 (br s, 0.4H, NCH), 3.92 (s, 3H, OMe), 3.82 (d, *J* = 12.0 Hz, 0.4H, NCH), 3.74-3.62 (m, 1.6H, NCH), 3.59-3.44 (m, 2H, NCH), 3.09 (d, *J* = 11.0 Hz, 0.4H, NCH), 3.02 (d, *J* = 11.0 Hz, 0.6H, NCH), 1.88-1.80 (m, 1H, NCH), 1.43 (s, 5.4H, CMe₃), 1.39 (s, 3.6H, CMe₃); ¹³C NMR (400 MHz, CDCl₃) (mixture of rotamers) δ 172.1 (CO₂Me), 171.9 (CO₂Me), 155.8 (NC=O), 155.2 (NC=O), 137.9 (*ipso*-Ph), 129.2 (Ph), 127.5 (Ph), 126.3 (Ph), 80.2 (CMe₃), 76.9 (CPh₃), 55.4 (NCH or OMe), 54.2 (NCH or OMe), 51.9 (NCH or OMe), 51.8 (NCH or OMe), 48.9 (NCH₂), 48.8 (NCH₂), 47.8 (NCH₂), 47.8 (NCH₂), 42.5 (NCH₂), 41.5 (NCH₂), 28.3 (CMe₃); MS (ESI) *m/z* 509 (M + Na)⁺; MS (ESI) *m/z* 509 (M + Na)⁺; HRMS *m/z* calcd for C₃₀H₃₃N₂O₄Na (M + Na)⁺ 509.2411, found 509.2417 (-0.9 ppm error); $[\alpha]_D$ -24.0 (*c* 1.0 in CHCl₃); CP-HPLC: Chiralcel AD (95:5 hexane:*i*-PrOH, 0.2 mL min⁻¹) (*R*)-**26** 38.4 min, (S)-**26** 50.4 min.

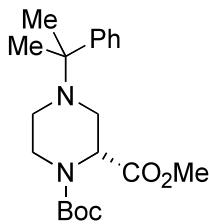
Lab Book Reference: JDF5_416

(S)-1-*tert*-Butyl 2-methyl 4-(9-phenyl-9H-fluoren-9-yl)piperazine-1,2-dicarboxylate (S)-27

(Table 1, entry 4)

Using general procedure B, *s*-BuLi (0.39 mL of a 1.3 M solution in hexanes, 0.50 mmol, 1.3 eq.), *N*-Boc piperazine **21** (165 mg, 0.39 mmol, 1.0 eq.), (+)-sparteine surrogate (99 mg, 0.50 mmol, 1.3 eq.) in Et₂O (7 mL) for 1 h and methyl chloroformate (74 mg, 60 μ L, 0.78 mmol, 2.0 eq.), worked up with saturated NaHCO₃(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et₂O as eluent gave *N*-Boc piperazine (S)-**27** (129 mg, 68%, 84:16 er by CSP-HPLC) as a white solid, mp 165-167 °C; R_F (7:3 petrol-Et₂O) 0.2; IR (CHCl₃) 3018, 2980, 1745 (C=O, CO₂Me), 1691 (C=O, Boc), 1451, 1408, 1367, 1304, 1216, 1170, 1119, 746, 668 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (60:40 mixture of rotamers) δ 7.72-7.67 (m, 2H, Ar), 7.40-7.35 (m, 4H, Ar), 7.30-7.22 (m, 7H, Ar), 4.56 (br s, 0.6H, NCH), 4.39 (br s, 0.4H, NCH), 3.83-3.78 (m, 0.4H, NCH), 3.80 (s, 3H, OMe), 3.70 (br d, J = 12.5 Hz, 0.6H, NCH), 3.41 (td, J = 12.5, 3.5 Hz, 0.6H, NCH), 3.30 (td, J = 12.5, 3.5 Hz, 0.4H, NCH), 3.15 (br d, J = 11.5 Hz, 0.6H, NCH), 3.07 (br d, J = 11.5 Hz, 0.4H, NCH), 2.94 (br d, J = 11.0 Hz, 0.4H, NCH), 2.84 (br d, J = 11.0 Hz, 0.6H, NCH), 2.26-2.16 (m, 2H, NCH), 1.42 (s, 5.4H, CMe₃), 1.37 (s, 3.6H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 171.4 (CO₂Me), 155.9 (NC=O), 155.3 (NC=O), 146.9 (*ipso*-Ar), 146.6 (*ipso*-Ar), 145.7 (*ipso*-Ar), 145.4 (*ipso*-Ar) 142.3 (*ipso*-Ar), 141.1 (*ipso*-Ar), 141.0 (*ipso*-Ar), 140.4 (*ipso*-Ar), 140.3 (*ipso*-Ar), 128.5 (Ar), 128.4 (Ar), 127.6 (Ar), 127.4 (Ar), 127.3 (Ar), 127.0 (Ar), 126.4 (Ar), 126.2 (Ar), 126.1 (Ar), 126.0 (Ar), 120.2 (Ar), 120.0 (Ar), 80.1 (CMe₃), 77.6 (NCPh), 55.7 (NCH or OMe), 54.6 (NCH or OMe), 51.8 (NCH or OMe), 48.6 (NCH₂), 48.5 (NCH₂), 47.5 (NCH₂), 47.3 (NCH₂), 42.7 (NCH₂), 41.7 (NCH₂), 28.3 (CMe₃), 28.2 (CMe₃); MS (ESI) *m/z* 485 (M + H)⁺; HRMS *m/z* calcd for C₃₀H₃₂N₂O₄ (M + H)⁺ 485.2435, found 485.2442 (-1.4 ppm error); $[\alpha]_D$ -100.7 (c 1.0 in CHCl₃); CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 1.0 mL min⁻¹) (S)-**27** 25.1 min, (S)-**27** 30.4 min.

Lab Book Reference: JDF5_417

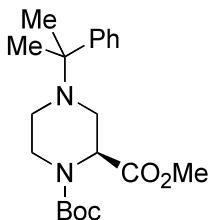
(R)-1-*tert*-Butyl 2-methyl 4-(2-phenylpropan-2-yl)piperazine-1,2-dicarboxylate (R)-28

(R)-28

(Table 1, entry 5)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine (152 mg, 149 μ L, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-cumyl piperazine **22** (152 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 6 h and methyl chloroformate (95 mg, 77 μ L, 1.0 mmol, 2.0 eq.) worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-8:2 CH₂Cl₂-Et₂O as eluent gave *N*-Boc piperazine (R)-**28** (128 mg, 71%, 90:10 er by CSP-HPLC) as a colourless oil, R_F (19:1 CH₂Cl₂-Et₂O) 0.2; IR (CHCl₃) 2972, 2933, 1718 (C=O, CO₂Me), 1662 (C=O, Boc), 1469, 1452, 1391, 1369, 1346, 1331, 1310, 1284, 1195, 1155, 1101, 1016, 951, 736, 692 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) (55:45 mixture of rotamers) δ 7.42–7.37 (m, 2H, Ph), 7.31–7.25 (m, 2H, Ph), 7.23–7.17 (m, 1H, Ph), 4.66 (br s, 0.55H, NCH), 4.50 (br s, 0.45H, NCH), 3.80 (d, J = 11.0 Hz, 0.55H, NCH), 3.72 (s, 1.35H, OMe), 3.70 (s, 1.65H, OMe), 3.72–3.69 (m, 0.45H, NCH), 3.35–3.19 (m, 1.55H, NCH), 3.13 (td, J = 12.0, 3.0 Hz, 0.45H, NCH), 2.74 (d, J = 10.5 Hz, 0.45H, NCH), 2.67 (d, J = 10.5 Hz, 0.55H, NCH), 2.37 (dd, J = 11.5, 3.5 Hz, 1H, NCH), 2.18 (td, J = 11.5, 3.5 Hz, 1H, NCH), 1.46 (s, 5H, CMe₃), 1.41 (s, 4H, CMe₃), 1.31 (s, 6H, CMe₂Ph); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 171.6 (CO₂Me), 171.4 (CO₂Me), 156.0 (NC=O), 155.4 (NC=O), 148.4 (*ipso*-Ph), 148.3 (*ipso*-Ph), 127.9 (Ph), 126.3 (Ph), 125.9 (Ph), 80.1 (CMe₃), 59.2 (CMe₂Ph), 56.0 (NCH), 54.9 (NCH), 51.8 (OMe), 47.8 (NCH₂), 45.7 (NCH₂), 42.7 (NCH₂), 41.7 (NCH₂), 28.3 (CMe₃), 28.2 (CMe₃), 24.0 (CMe₂Ph), 23.9 (CMe₂Ph), 23.7 (CMe₂Ph); MS (ESI) *m/z* 363 (M + H)⁺; HRMS *m/z* calcd for C₂₀H₃₀N₂O₄ (M + H)⁺ 363.2278, found 363.2277 (0.0 ppm error); $[\alpha]_D$ +39.0 (*c* 0.85 in CHCl₃); CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min^{−1}) (R)-**28** 11.5 min, (S)-**28** 19.5 min.

Lab Book Reference: JDF7_603

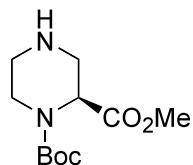
(S)-1-*tert*-Butyl 2-methyl 4-(2-phenylpropan-2-yl)piperazine-1,2-dicarboxylate (S)-28

(S)-28

(Table 1, entry 6)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (126 mg, 0.5 mmol, 1.3 eq.), *N*-Boc-*N'*-cumyl piperazine **22** (152 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 1 h and methyl chloroformate (95 mg, 77 μ L, 1.0 mmol, 2.0 eq.) worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-8:2 CH₂Cl₂-Et₂O as eluent gave *N*-Boc piperazine (S)-**28** (151 mg, 83%, 88:12 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ -36.1 (*c* 1.0 in CHCl₃); CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min⁻¹) (*R*)-**28** 11.5 min, (S)-**28** 19.3 min.

Lab Book Reference: JDF7_646

Determination of the absolute configuration of (S)-28: conversion into (S)-S3**(S)-1-*tert*-Butyl 2-methyl piperazine-1,2-dicarboxylate (S)-S2**

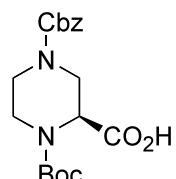
(S)-S2

20% Pd(OH)₂/C (5 mg) was added to a stirred solution of *N*-Boc-piperazine (S)-**28** (35 mg, 0.097 mmol, 1.0 eq.) and ammonium formate (30 mg, 0.48 mmol, 5.0 eq.) in EtOH (5 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 2 h. After cooling to rt, the mixture was filtered through Celite[®] and washed with EtOH (20 mL). The filtrate was evaporated under reduced pressure to give *N*-Boc piperazine (S)-**S2** (23 mg, 97%) as a colourless oil, $[\alpha]_D$ -45.9 (*c* 0.95 in CHCl₃); IR (ATR) 3352 (NH), 2975, 1743 (C=O, CO₂Me), 1692 (C=O), 1454, 1391, 1364, 1340, 1317, 1290, 1252, 1223, 1201, 1112, 1072, 1038, 975, 917, 862, 829, 776, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) δ 4.66 (s, 0.5H, NCH), 4.49 (s, 0.5H, NCH), 3.81 (br d, *J* = 13.0 Hz, 0.5H, NCH), 3.72-3.82 (m, 0.5H, NCH), 3.77 (s, 3H, CO₂Me), 3.46 (br t, *J* = 13.0 Hz, 1H, NCH), 3.10 (td, *J* = 12.5, 2.5 Hz, 0.5H, NCH), 2.86-3.08 (m, 2.5H, NCH), 2.65-2.79 (m, 1H, NCH), 1.61 (br s,

1H, NH), 1.44 (s, 4.5H, CMe₃), 1.40 (s, 4.5H, CMe₃) ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 171.8 (CO₂Me), 171.6 (CO₂Me), 155.9 (NC=O), 155.5 (NC=O), 80.4 (CMe₃), 55.5 (NCH), 54.2 (NCH), 52.3 (CO₂Me), 47.3 (NCH₂), 47.1 (NCH₂), 45.3 (NCH₂), 42.7 (NCH₂), 41.5 (NCH₂), 28.4 (CMe₃); MS (ESI) *m/z* 267 [(M + Na)⁺, 30], 245 [(M + H)⁺, 50], 189 [(M - CMe₃)⁺, 100], 145 [(M - Boc)⁺, 80]; HRMS *m/z* calcd for C₁₁H₂₀N₂O₄ (M + H)⁺ 245.1493, found 245.1496 (+1.7 ppm error).

Lab Book Reference: JDF10_1053

(S)-4-(Benzylloxycarbonyl)-1-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (S)-S3



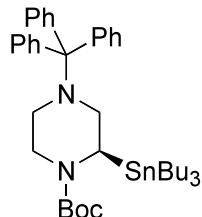
(S)-S3

Benzyl chloroformate (15 mg, 12 μL, 0.086 mmol, 1.5 eq.) was added to a stirred solution of *N*-Boc piperazine (S)-S2 (14 mg, 0.055 mmol, 1.0 eq.) and Et₃N (9 mg, 12 μL, 0.086 mmol, 1.5 eq.) in CH₂Cl₂ at rt. The resulting solution was stirred for 16 h. Water (5 mL) was added and the layers separated. The aqueous was extracted with CH₂Cl₂ (2 x 5 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 7:3 petrol-EtOAc as eluent gave the CBz-methyl ester (16 mg, 74%) as a colourless oil, *R*_F (7:3 petrol-EtOAc) 0.3; [α]_D -3.4 (c 0.75 in CHCl₃); IR (CHCl₃) 2973, 1718 (C=O, CO₂Me), 1672 (C=O), 1492, 1409, 1346, 1302, 1203, 1193, 1094, 1025, 914, 776, 741, 721, 659 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (45:55 mixture of rotamers) δ 7.28-7.40 (5H, m, Ph), 5.17 (br d, *J* = 12.0 Hz, 1H, CH_AH_BPh), 5.08 (d, *J* = 12.0 Hz, 1H, CH_AH_BPh), 4.76 (br s, 0.45H, NCH), 4.65 (br d, *J* = 13.5 Hz, 0.55H, NCH), 4.58 (br d, *J* = 12.0 Hz, 1H, NCH), 3.98-4.17 (m, 1H, NCH), 3.80-3.93 (m, 1H, NCH), 3.71 (br s, 1.35H, OMe), 3.59 (br s, 1.65H, OMe), 3.04-3.32 (m, 2H, NCH), 2.89 (br s, 1H, NCH), 1.47 (s, 5H, CMe₃), 1.43 (s, 4H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 170.5 (CO₂Me), 170.3 (CO₂Me), 155.5 (NC=O), 155.0 (NC=O), 136.3 (*ipso*-Ph), 128.4 (Ph), 128.0 (Ph), 127.8 (Ph), 80.9 (CMe₃), 67.4 (CH₂Ph), 54.8 (NCH), 53.4 (CO₂Me), 52.3 (CO₂Me), 44.7 (NCH₂), 43.2 (NCH₂), 42.9 (NCH₂), 40.0 (NCH₂), 28.2 (CMe₃); MS (ESI) *m/z* 401 [(M + Na)⁺, 100], 323 [(M - Boc)⁺, 30]; HRMS *m/z* calcd for C₁₉H₂₆N₂O₆Na (M + Na)⁺ 401.1683, found 401.1670 (+3.1 ppm error). Then, LiOH (3 mg, 0.13 mmol, 3.0 eq.) was added to a stirred solution of the CBz-methyl ester (16 mg, 0.042 mmol, 1.0 eq.) in 4:1:1 THF-MeOH-water (2 mL) at rt under air. The reaction was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure. The residue was partitioned

between 1M HCl (5 mL) and CH_2Cl_2 (5 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×5 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 66:33:1 CH_2Cl_2 -EtOAc-AcOH as eluent gave carboxylic acid (S)-**S3** (14 mg, 84%) as a pale yellow oil. R_F (66:33:1 CH_2Cl_2 -EtOAc-AcOH); 0.2; $[\alpha]_D -14.9$ (c 0.7 in CHCl_3) (lit.,⁴ $[\alpha]_D -17.5$ (c 1.02 in CHCl_3); ^1H NMR (400 MHz, CDCl_3) (45:55 mixture of rotamers) δ 7.27-7.40 (5H, m, Ph), 5.07-5.21 (m, 2H, CH_2Ph), 4.82 (br s, 0.45H, NCH), 4.63-4.72 (m, 1.55H, NCH), 4.60-4.74 (m, 2H, NCH), 3.09-3.27 (m, 2H, NCH), 2.93 (br s, 1H, NCH), 1.48 (s, 5H, CMe_3), 1.44 (s, 4H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) (mixture of rotamers) δ 187.6 (COOH), 155.8 (NC=O), 155.4 (NC=O), 155.1 (NC=O), 136.0 (*ipso*-Ph), 128.6 (Ph), 128.2 (Ph), 128.0 (Ph), 81.2 (CMe_3), 67.8 (NCH), 54.6 (CH_2Ph), 53.4 (CH_2Ph), 44.5 (NCH₂), 44.5 (NCH₂), 44.3 (NCH₂), 43.2 (NCH₂), 41.4 (NCH₂), 40.2 (NCH₂), 28.3 (CMe_3). Spectroscopic data consistent with those reported in the literature.⁴

Lab Book Reference: JDF7_682 and JDF7_693

(R)-*tert*-Butyl 2-(tributylstannylyl)-4-tritylpiperazine-1-carboxylate (R)-29



(R)-29

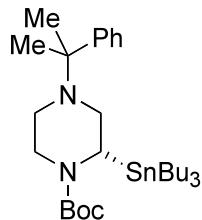
(Table 1, entry 7)

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-trityl piperazine **20** (214 mg, 0.5 mmol, 1.0 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and Bu_3SnCl (325 mg, 271 μL , 1.0 mmol, 2.0 eq.), worked up with saturated $\text{NaHCO}_{3\text{(aq)}}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1:7:3 petrol- Et_2O as eluent gave *N*-Boc piperazine (R)-**29** (265 mg, 74%, 82:18 er by CSP-HPLC) as a pale yellow oil, R_F (19:1 petrol-EtOAc) 0.4; IR (CHCl_3) 2911, 2879, 1646 (C=O), 1465, 1428, 1402, 1344, 1277, 1232, 1196, 1134, 1092, 987, 744, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (75:25 mixture of rotamers) δ 7.46 (br s, 6H, Ph), 7.32-7.20 (m, 6H, Ph), 7.20-7.06 (m, 3H, Ph), 4.06 (s, 0.25H, NCH), 3.82 (s, 0.75H, NCH), 3.50-2.46 (m, 4H, NCH), 2.09-1.48 (m, 2H, NCH), 1.49-1.29 (m, 15H, $\text{CH}_2 + \text{CMe}_3$), 1.29-1.14 (m, 6H, CH_2), 0.95-0.61 (m, 15H, $\text{CH}_2 + \text{Me}$); ^{13}C NMR (100.6 MHz, CDCl_3) δ 155.6 (C=O), 142.8 (*ipso*-Ph), 129.3 (Ph), 127.4 (Ph), 126.0 (Ph), 79.3 (CMe_3), 77.1

(CPh₃), 52.4 (NCH₂), 48.5 (NCH₂), 46.6 (NCH₂), 45.4 (NCH), 29.2 (CH₂), 28.2 (CMe₃), 27.6 (CH₂), 13.7 (Me), 11.9 (CH₂); MS (ESI) *m/z* 719 (M + H)⁺; HRMS *m/z* calcd for C₄₀H₅₈N₂O₂Sn (M + H)⁺ 719.3601, found 719.3605 (−0.6 ppm error); [α]_D −27.4 (*c* 1.1 in CHCl₃); CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min^{−1}) (*R*)-**29** 6.7 min, (*S*)-**29** 7.6 min.

Lab Book Reference: JDF6_505

(S)-*tert*-Butyl 4-(2-phenylpropan-2-yl)-2-(tributylstannylyl)piperazine-1-carboxylate (*S*)-30



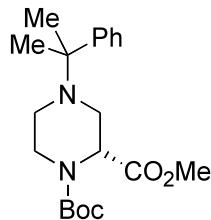
(*S*)-30

(Table 1, entry 8)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine (152 mg, 149 μL, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-cumyl piperazine **22** (152 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 6 h and Bu₃SnCl (325 mg, 271 μL, 1.0 mmol, 2.0 eq.) worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-**30** (180 mg, 61%, 88:12 er by CSP-HPLC of a derivative (*R*)-**28**) as a yellow oil, *R*_F (19:1 petrol-EtOAc) 0.3; IR (CHCl₃) 2971, 2913, 2881, 2827, 1645 (C=O), 1432, 1397, 1344, 1280, 1197, 1152, 1090, 1002, 947, 908, 849, 743, 691, 658 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) δ 7.49 (d, *J* = 7.5 Hz, 2H, Ph), 7.29 (t, *J* = 7.5 Hz, 2H, Ph), 7.23–7.16 (m, 1H, Ph), 4.21–4.12 (m, 0.5H, NCH), 3.97 (br d, *J* = 12.0 Hz, 0.5H, NCH), 3.60–3.25 (m, 1.5H, NCH), 2.86–2.52 (m, 2.5H, NCH), 2.31 (br s, 1H, NCH), 2.06–1.84 (m, 1H, NCH), 1.55–1.37 (m, 15H, CMe₃ + CH₂), 1.33–1.22 (m, 12H, CMe₂Ph + CH₂), 0.95–0.83 (m, 15H, CH₂ + Me); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 154.6 (C=O), 153.9 (C=O), 148.3 (*ipso*-Ph), 148.2 (*ipso*-Ph), 128.0 (Ph), 126.3 (Ph), 79.3 (CMe₃), 79.0 (CMe₃), 60.0 (CMe₂Ph), 50.2 (NCH₂), 46.9 (NCH₂), 45.9 (NCH₂), 45.6 (NCH₂), 43.0 (NCH), 29.2 (CH₂), 28.4 (CMe₃), 27.9 (CH₂), 27.8 (CH₂), 27.6 (CH₂), 27.3 (CH₂), 26.8 (CH₂), 25.7 (CH₂), 22.1 (CMe₂Ph), 20.7 (CMe₂Ph), 13.7 (Me), 11.1 (CH₂), 10.4 (CH₂); MS (ESI) *m/z* 595 (M + H)⁺; HRMS *m/z* calcd for C₃₀H₅₄N₂O₂Sn (M + H)⁺ 595.3285, found 595.3261 (+3.6 ppm error); [α]_D +32.6 (*c* 1.0 in CHCl₃).

Lab Book Reference: JDF7_626

Determination of er of stannane (*S*)-30: tin-lithium exchange to form (*R*)-1-*tert*-Butyl 2-methyl 4-(2-phenylpropan-2-yl)piperazine-1,2-dicarboxylate (*R*)-28

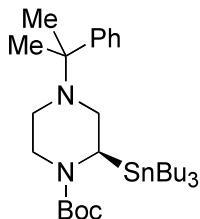


(*R*)-28

n-BuLi (35 μ L of a 2.2 M solution in hexanes, 0.08 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannane (*S*)-30 (35 mg, 0.06 mmol, 1.0 eq.) and TMEDA (9 mg, 12 μ L, 0.08 mmol, 1.3 eq.) in Et₂O (3 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 10 min. Then, methyl chloroformate (11 mg, 9 μ L, 0.12 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at -78 °C for 15 min and then allowed to warm to rt over 30 min. Then, saturated NH₄Cl_(aq) (5 mL) and saturated NaHCO_{3(aq)} (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 \times 5 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 petrol-Et₂O as eluent gave *N*-Boc piperazine (*R*)-28 (15 mg, 69%, 88:12 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min⁻¹) (*R*)-28 11.2 min, (*S*)-28 18.7 min.

Lab Book Reference: JDF7_661

(*R*)-*tert*-Butyl 4-(2-phenylpropan-2-yl)-2-(tributylstannylyl)piperazine-1-carboxylate (*R*)-30



(*R*)-30

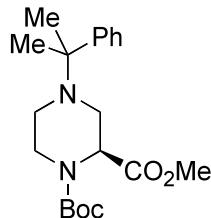
(Table 1, entry 9)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-cumyl piperazine 22 (152 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 1 h and Bu₃SnCl (325 mg, 271 μ L, 1.0 mmol, 2.0 eq.) worked up with saturated NaHCO_{3(aq)} (10 mL) gave the crude product. Purification by flash column chromatography on

silica with 19:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*R*)-**30** (294 mg, 99%, 86:14 er by CSP-HPLC of a derivative (*S*)-**28**) as a yellow oil, $[\alpha]_D -32.8$ (*c* 1.0 in CHCl_3);

Lab Book Reference: JDF7_648

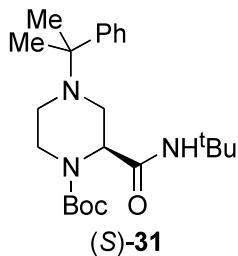
Determination of er of stannane (*R*)-30**: tin-lithium exchange to form (*S*)-1-*tert*-Butyl 2-methyl 4-(2-phenylpropan-2-yl)piperazine-1,2-dicarboxylate (*S*)-**28****



(*S*)-**28**

n-BuLi (35 μL of a 2.2 M solution in hexanes, 0.08 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannane (*R*)-**30** (35 mg, 0.06 mmol, 1.0 eq.) and TMEDA (9 mg, 12 μL , 0.08 mmol, 1.3 eq.) in Et_2O (3 mL) at -78°C under Ar. The resulting solution was stirred at -78°C for 10 min. Then, methyl chloroformate (11 mg, 9 μL , 0.12 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at -78°C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) and saturated $\text{NaHCO}_3_{(\text{aq})}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×5 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 8:2 petrol- Et_2O as eluent gave *N*-Boc piperazine (*S*)-**28** (15 mg, 69%, 86:14 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min^{-1}) (*R*)-**28** 11.2 min, (*S*)-**28** 18.7 min.

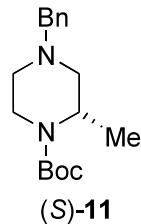
Lab Book Reference: JDF7_660

(S)-*tert*-Butyl 2-(*tert*-butylcarbamoyl)-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate (S)-31

(Table 1, entry 10)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-cumyl piperazine **22** (152 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 1 h and *tert*-butyl isocyanate (64 mg, 74 μ L, 0.65 mmol, 1.3 eq.) worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 17:3-1:1 petrol-Et₂O as eluent gave *N*-Boc piperazine (S)-**31** (108 mg, 54%, 87:13 er by CSP-HPLC) as a white solid, mp 61-64 °C; R_F (8:2 petrol-EtOAc) 0.3; IR (CHCl₃) 2933, 1651 (C=O), 1524, 1488, 1430, 1371, 1345, 1283, 1152, 1102, 951, 742 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.42 (m, 2H, Ph), 7.31-7.24 (m, 2H, Ph), 7.23-7.17 (m, 1H, Ph), 5.88 (br s, 1H, NH), 4.47 (br s, 1H, NCH), 3.86 (br s, 1H, NCH), 3.59 (d, J = 11.5 Hz, 1H, NCH), 2.92 (br s, 1H, NCH), 2.49 (br s, 1H, NCH), 2.30 (dd, J = 11.5, 4.0 Hz, 1H, NCH), 2.09 (td, J = 11.5, 3.5 Hz, 1H, NCH), 1.45 (s, 9H, CMe₃), 1.41 (s, 9H, CMe₃), 1.35 (s, 3H, CMe₂Ph), 1.33 (s, 3H, CMe₂Ph); ¹³C NMR (100.6 MHz, CDCl₃) δ 169.4 (C=O, CONH), 155.1 (C=O, Boc), 148.5 (*ipso*-Ph), 128.1 (Ph), 126.5 (Ph), 126.1 (Ph), 80.6 (OCMe₃), 59.7 (CMe₂Ph), 57.3 (br, NCH), 51.8 (NCH₂), 51.2 (NCMe₃), 46.5 (NCH₂), 42.1 (br, NCH₂), 28.9 (OCMe₃), 28.4 (OCMe₃), 27.8 (NCMe₃), 20.3 (CMe₂Ph); MS (ESI) *m/z* 404 (M + H)⁺; HRMS *m/z* calcd for C₂₃H₃₇N₃O₃ (M + H)⁺ 404.2908, found 404.2914 (+2.2 ppm error); $[\alpha]_D$ -33.2 (c 1.0 in CHCl₃); CSP-HPLC: Chiralcel OD-H (98:2 hexane:*i*-PrOH, 0.5 mL min⁻¹) (*R*)-**31** 14.3 min, (S)-**31** 16.6 min.

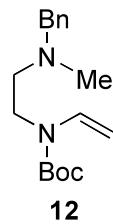
Lab Book Reference: JDF7_651

(S)-*tert*-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate (S)-11

(Scheme 6)

s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of (–)-sparteine (152 mg, 149 μ L, 0.65 mmol, 1.3 eq.) in Et₂O (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, a solution of *N*-Boc-*N'*-benzyl piperazine **4** (138 mg, 0.5 mmol, 1.0 eq.) in Et₂O (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 90 min. Then, TMEDA (280 mg, 375 μ L, 2.5 mmol, 5.0 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 30 min. Then, methyl iodide (142 mg, 62 μ L, 1.0 mmol, 2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated NH₄Cl_(aq) (10 mL) and 20% NaOH_(aq) (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 \times 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 *N*-Boc piperazine (S)-**11** (70 mg, 48%, 87:13 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiralcel IC (99:1 hexane:*i*-PrOH, 1.0 mL min^{–1}) (*R*)-**11** 12.4 min, (S)-**11** 15.3 min.

Lab Book Reference: JDF7_620

tert*-Butyl 2-(benzyl(methyl)amino)ethyl(vinyl)carbamate **12*

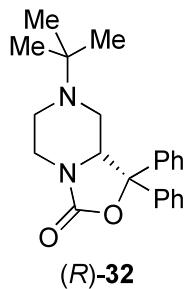
(Scheme 6)

s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of (+)-sparteine surrogate (126 mg, 0.5 mmol, 1.3 eq.) in Et₂O (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, a solution of *N*-Boc-*N'*-benzyl piperazine **4** (138 mg, 0.5 mmol, 1.0 eq.) in Et₂O (1 mL) was added dropwise. The resulting solution was stirred at –

78 °C for 10 min. Then, TMEDA (280 mg, 375 μ L, 2.5 mmol, 5.0 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 30 min. Then, dimethyl sulfate (126 mg, 97 μ L, 1.0 mmol, 2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL) and 20% $\text{NaOH}_{(\text{aq})}$ (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 \times 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 8:2 petrol-EtOAc as eluent gave vinyl carbamate **12** (50 mg, 34%) as a colourless oil.

Lab Book Reference: JDF5_480

(R)-7-*tert*-Butyl-1,1-diphenyltetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (R)-32



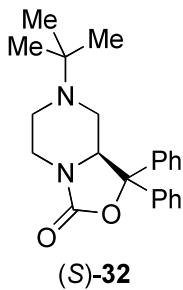
(Table 2, entry 3)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (–)-sparteine (305 mg, 299 μ L, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-*tert*-butyl piperazine **19** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 6 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) worked up with saturated $\text{NaHCO}_{3(\text{aq})}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1-97:3 CH_2Cl_2 -MeOH as eluent gave oxazolidinone (R)-**32** (252 mg, 72%, 90:10 er by CSP-HPLC) as a white solid, mp 193–195 °C; R_F (99:1 CH_2Cl_2 -MeOH) 0.2; IR (CHCl_3) 2975, 1750 (C=O), 1449, 1363, 1302, 1255, 1203, 1036, 984 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.53–7.50 (m, 2H, Ph), 7.39–7.24 (m, 8H, Ph), 4.43 (dd, J = 11.0, 3.5 Hz, 1H, NCH), 3.85 (ddd, J = 13.0, 3.5, 1.0 Hz, 1H, NCH), 3.08 (ddd, J = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.92–2.88 (m, 1H, NCH), 2.62 (ddd, J = 12.0, 3.5, 1.0 Hz, 1H, NCH), 2.06 (td, J = 12.0, 3.5 Hz, 1H, NCH), 1.51 (t, J = 11.0 Hz, 1H, NCH), 0.93 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 156.1 (C=O), 142.4 (*ipso*-Ph), 138.8 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 128.2 (Ph), 127.8 (Ph), 126.0 (Ph), 125.7 (Ph), 85.4 (Ph_2CO), 61.9 (NCH), 54.3 (CMe_3), 48.8 (NCH₂), 44.8 (NCH₂), 42.6 (NCH₂), 26.0 (CMe_3); MS (ESI) m/z 351 ($\text{M} + \text{H}$)⁺; HRMS m/z calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 351.2067, found 351.2062 (+0.7 ppm)

error); $[\alpha]_D +184.1$ (*c* 1.0 in CHCl_3); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min⁻¹) (*S*)-**32** 13.4 min, (*R*)-**32** 16.5 min.

Lab Book Reference: JDF4_392

(*S*)-7-*tert*-Butyl-1,1-diphenyltetrahydro-1*H*-oxazolo[3,4-a]pyrazin-3(5*H*)-one (*S*)-32

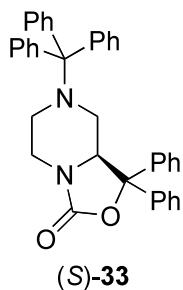


(Table 2, entry 4)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-*tert*-butyl piperazine **19** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL) worked up with saturated $\text{NaHCO}_{3(\text{aq})}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1-97:3 CH_2Cl_2 -MeOH as eluent gave oxazolidinone (*S*)-**32** (265 mg, 76%, 86:14 er by CSP-HPLC) as a white solid, $[\alpha]_D -179.3$ (*c* 1.0 in CHCl_3); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min⁻¹) (*S*)-**32** 13.4 min, (*R*)-**32** 17.7 min.

Lab Book Reference: JDF4_400

(*S*)-1,1-Diphenyl-7-trityltetrahydro-1*H*-oxazolo[3,4-a]pyrazin-3(5*H*)-one (*S*)-33



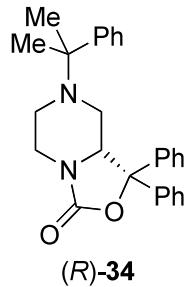
(Table 2, entry 5)

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-trityl piperazine **20** (214 mg, 0.5 mmol, 1.0 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $\text{NaHCO}_{3(\text{aq})}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol- Et_2O as eluent gave *N*-Boc piperazine (*S*)-**33** (215

mg, 80%, 73:27 by CSP-HPLC) as a white solid, mp 238-241 °C (decomposed); R_F (8:2 petrol-Et₂O) 0.1; IR (CHCl₃) 2964, 1743 (C=O), 1467, 1426, 1398, 1341, 1280, 1214, 1164, 1107, 1017, 973, 929, 889, 747, 700, 690 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.53-7.48 (m, 2H, Ph), 7.44-7.28 (m, 9H, Ph), 7.25-7.20 (m, 6H, Ph), 7.18-7.12 (m, 6H, Ph), 7.05-7.02 (m, 2H, Ph), 4.74 (dd, J = 11.0, 3.5 Hz, 1H, NCH), 3.86-3.75 (m, 1H, NCH), 3.38 (td, J = 12.0, 3.5 Hz, 1H, NCH), 3.10-3.01 (m, 1H, NCH), 2.88-2.81 (m, 1H, NCH), 1.38 (td, J = 12.0, 3.5 Hz, 1H, NCH), 0.82-0.74 (m, 1H, NCH); NMR (100.6 MHz, CDCl₃) δ 156.1 (C=O), 142.2 (*ipso*-Ph), 138.6 (*ipso*-Ph), 128.8 (Ph), 128.5 (Ph), 128.4 (Ph), 127.9 (Ph), 127.7 (Ph), 127.7 (Ph), 126.4 (Ph), 126.0 (Ph), 125.6 (Ph), 85.3 (Ph₂CO), 77.2 (CPh₃), 62.0 (NCH), 52.0 (NCH₂), 47.0 (NCH₂), 42.0 (NCH₂); MS (ESI) *m/z* 559 (M + Na)⁺; HRMS *m/z* calcd for C₃₇H₃₂N₂O₂ (M + Na)⁺ 559.2356, found 559.2376 (-3.6 ppm error); $[\alpha]_D$ -121.8 (*c* 1.0 in CHCl₃); CSP-HPLC: Chiralcel AD-H (95:5 hexane:*i*-PrOH, 1.0 mL min⁻¹) (*S*)-**33** 5.6 min, (*R*)-**33** 6.7 min.

Lab Book Reference: JDF6_504

(*R*)-1,1-Diphenyl-7-(2-phenylpropan-2-yl)tetrahydro-1*H*-oxazolo[3,4-a]pyrazin-3(5*H*)-one (*R*)-34



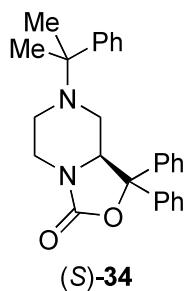
(Table 2, entry 6)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (-)-sparteine (152 mg, 149 μ L, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-cumyl piperazine **22** (152 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 6 h and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et₂O (1 mL) worked up with saturated NaHCO_{3(aq)} (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-8:2 petrol-EtOAc as eluent gave oxazolidinone (*R*)-**34** (110 mg, 53%, 91:9 er by CSP-HPLC) as a white solid, mp 122-124 °C; R_F (7:3 petrol-EtOAc) 0.1; IR (CHCl₃) 2963, 2931, 1723 (C=O), 1470, 1426, 1390, 1342, 1282, 1241, 1159, 1100, 1059, 1016, 971, 895, 690 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.43 (m, 4H, Ph), 7.39-7.19 (m, 11H, Ph), 4.42 (dd, J = 11.0, 3.5 Hz, 1H, NCH), 3.83-3.72 (m, 1H, NCH), 3.04 (td, J = 12.0, 4.0 Hz, 1H, NCH), 2.69-2.63 (m, 1H, NCH), 2.56 (ddd, J = 11.5, 3.5, 2.0 Hz, 1H, NCH), 2.09 (td, J = 11.5, 3.5 Hz, 1H, NCH), 1.55 (t, J = 11.0 Hz, 1H, NCH), 1.24 (s, 3H, CMe₂Ph), 1.18 (s, 3H, CMe₂Ph); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.2 (C=O), 148.3 (*ipso*-Ph), 142.5 (*ipso*-Ph), 138.9 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 128.2 (Ph),

128.1 (Ph), 127.8 (Ph), 126.5 (Ph), 125.9 (Ph), 125.8 (Ph), 125.7 (Ph), 88.3 (Ph₂CO), 62.4 (NCH), 60.2 (CMe₂Ph), 49.3 (NCH₂), 45.3 (NCH₂), 42.5 (NCH₂), 25.0 (CMe₂Ph), 23.3 (CMe₂Ph); MS (ESI) *m/z* 413 (M + H)⁺; HRMS *m/z* calcd for C₂₇H₂₈N₂O₂ (M + H)⁺ 413.2224, found 413.2216 (+2.6 ppm error); [α]_D +144.7 (*c* 1.0 in CHCl₃); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min⁻¹) (*S*)-**34** 19.7 min, (*R*)-**34** 27.7 min.

Lab Book Reference: JDF7_625

(S)-1,1-Diphenyl-7-(2-phenylpropan-2-yl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (S)-34

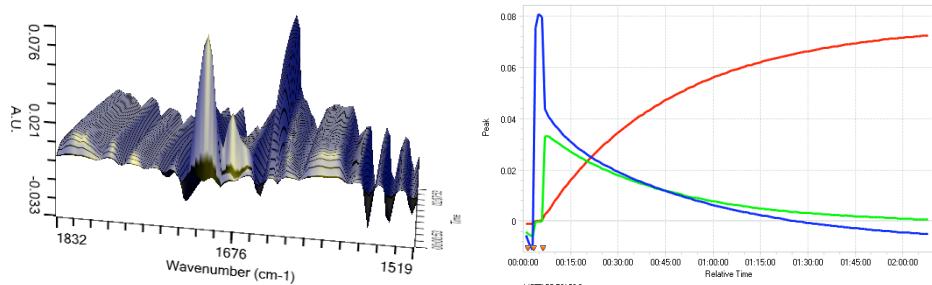


(Table 2, entry 7)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-cumyl piperazine **22** (152 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 1 h and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et₂O (1 mL) worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-EtOAc as eluent gave oxazolidinone (S)-**34** (150 mg, 73%, 87:13 er by CSP-HPLC) as a white solid, [α]_D -106.0 (*c* 1.0 in CHCl₃); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min⁻¹) (S)-**34** 19.7 min, (*R*)-**34** 28.9 min.

Lab Book Reference: JDF7_647

ReactIR™ monitoring of the lithiation of *N*-Boc-*N'*-(*S*)- α -methylbenzyl piperazine (*S*)-36 ((*-*)-sparteine)



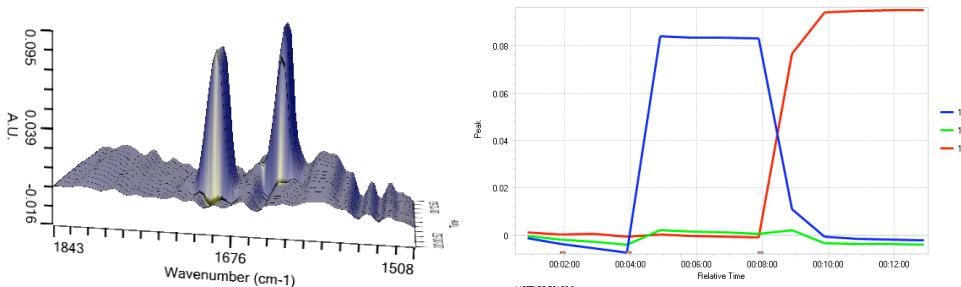
(Scheme 7)

Et₂O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to -78 °C, (-)-sparteine (305 mg, 299 μ L, 1.3 mmol, 1.3 eq.) was added followed by a solution *N*-Boc-*N'*-(*S*)- α -methylbenzyl piperazine (*S*)-36 (290 mg, 1.0 mmol, 1.0 eq.) in Et₂O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at -78 °C for 2 h.

For *N*-Boc-*N'*-(*S*)- α -methylbenzyl piperazine (*S*)-36, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{\text{C=O}}$. After addition of *s*-BuLi, a new peak at 1679 cm^{-1} was observed which was assigned to $\nu_{\text{C=O}}$ in the pre-lithiation complex 37. A new peak at 1645 cm^{-1} was observed which was assigned to $\nu_{\text{C=O}}$ in the lithiated intermediate 38. After a lithiation time of 2 h, near-complete lithiation of *N*-Boc-*N'*-(*S*)- α -methylbenzyl piperazine (*S*)-36 to give the lithiated intermediate 38 and *N*-Boc-*N'*-(*S*)- α -methylbenzyl piperazine (*S*)-36 was observed. Using the peak at 1645 cm^{-1} , a half-life value, $t_{1/2}$ of ~26 min was determined.

Lab Book Reference: JDF4_365

ReactIR™ monitoring of the lithiation of *N*-Boc-*N'*-(*S*)- α -methylbenzyl piperazine (*S*)-36 ((+)-sparteine surrogate)

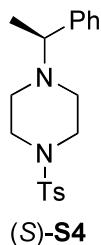


(Scheme 7)

Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to -78°C a solution of (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution *N*-Boc-*N'*-(*S*)- α -methylbenzyl piperazine (*S*)-36 (290 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at -78°C for 5 min.

For *N*-Boc-*N'*-(*S*)- α -methylbenzyl piperazine (*S*)-36, a peak at 1701 cm^{-1} was observed and assigned to $\nu_{\text{C=O}}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{\text{C=O}}$ in the pre-lithiation complex 37. A new peak at 1645 cm^{-1} was observed which was assigned to $\nu_{\text{C=O}}$ in the lithiated intermediate 38. After a lithiation time of 2 min, lithiation of *N*-Boc-*N'*-(*S*)- α -methylbenzyl piperazine (*S*)-36 to give the lithiated intermediate 38 was observed. Using the peak at 1645 cm^{-1} , a half-life value, $t_{1/2}$ of ~ 0.5 min was determined. Lab Book Reference: JDF5_430

(*S*)-1-(1-Phenylethyl)-4-methylbenzenesulfonylpiperazine (*S*)-S4

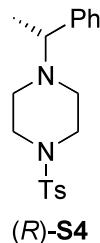


A mixture of *N,N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide (17.8 g, 60.0 mmol, 1.1 eq.), (*S*)-(-)- α -methylbenzylamine (6.6 g, 7.0 mL, 54.5 mmol, 1.0 eq., $>99.5:0.5$ er) and *i*-Pr₂NEt (15.5 g, 20.9 mL, 120 mmol, 2.2 eq.) was stirred and heated at 120°C for 16 h. After being allowed to cool to rt, 7:3 H_2O -EtOH (200 mL) was added and the suspension was stirred for 16 h at rt. Then, the solids were removed by filtration and washed with 1:1 H_2O -EtOH (2 \times 100 mL) and then cyclohexane (3 \times 50 mL)

to give *N*-tosyl piperazine (*S*)-**S4** (17.9 g, 84%) as an off white solid that was used without further purification, ¹H NMR (400 MHz, CDCl₃) δ 7.63-7.60 (m, 2H, Ar), 7.32-7.20 (m, 8H, Ar), 3.35 (q, *J* = 6.5 Hz, 1H, CHMe), 2.97 (br s, 4H, NCH), 2.58-2.53 (m, 2H, NCH), 2.47-2.43 (m, 2H, NCH), 2.43 (s, 3H, ArMe), 1.31 (d, *J* = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.6 (*ipso*-Ar), 143.2 (*ipso*-Ar), 132.4 (*ipso*-Ar), 129.6 (Ar), 128.3 (Ar), 127.9 (Ar), 127.4 (Ar), 127.1 (Ar), 64.4 (NCHPh), 49.5 (NCH₂), 46.3 (NCH₂), 21.5 (Me), 19.4 (Me).

Lab Book Reference: JDF5_422

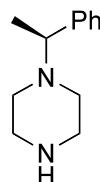
(R)-1-(1-Phenylethyl)-4-methylbenzenesulfonylpiperazine (R)-S4



Using the above procedure, a mixture of *N,N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide (4.0 g, 13.3 mmol, 1.1 eq.), (*R*)-(-)- α -methylbenzylamine (1.47 g, 1.56 mL, 12.1 mmol, 1.0 eq., >98:2 er) and *i*-Pr₂NEt (3.4 g, 4.7 mL, 26.7 mmol, 2.2 eq.) gave *N*-tosyl piperazine (*R*)-**S4** (3.5 g, 83%) as an off-white solid that was used without further purification.

Lab Book Reference: JDF6_533

(S)-1-(1-Phenylethyl)piperazine (S)-S5

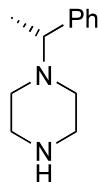


A suspension of tosyl piperazine (*S*)-**S4** (17.9 g, 52 mmol, 1.0 eq.) and 4-hydroxybenzoic acid (21.6 g, 156 mmol, 3.0 eq.) in HBr (33 wt. % in AcOH, 125 mL) was stirred for at rt for 3 d under air. Then, H₂O (150 mL) was added and the mixture was stirred for 2 h. The resulting white precipitate was removed by filtration and washed with H₂O (200 mL). The aqueous filtrate was extracted with toluene (3 \times 100 mL). The aqueous layer was cooled to 0 °C and basified with solid KOH. Then, the basic solution was extracted with EtOAc (3 \times 100 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give piperazine (*S*)-**S5** (9.4 g, 95%) as a pale yellow oil, $[\alpha]_D$

–31.8 (*c* 1.0 in CHCl₃); IR (CHCl₃) 2985, 2363, 1498, 1428, 1301, 1214, 1180, 1012, 913, 801, 692, 650, 616 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.20 (m, 5H, Ph), 3.34 (q, *J* = 6.5 Hz, 1H, CHMe), 2.86 (t, *J* = 5.0 Hz, 4H, NCH), 2.40 (br s, 2H, NCH), 2.37–2.33 (m, 2H, NCH), 1.94 (br s, 1H, NH), 1.35 (d, *J* = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 143.8 (*ipso*-Ph), 128.1 (Ph), 127.6 (Ph), 126.8 (Ph), 65.3 (NCHPh), 51.8 (NCH₂), 46.3 (NCH₂), 19.5 (CHMe); MS (ESI) *m/z* 191 (M + H)⁺; HRMS *m/z* calcd for C₁₂H₁₈N₂ (M + H)⁺ 191.1543, found 191.1549 (–1.9 ppm error).

Lab Book Reference: JDF5_424

(*R*)-1-(1-Phenylethyl)piperazine (*R*)-S5

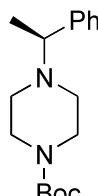


(*R*)-S5

Using the above procedure, tosyl piperazine (*R*)-S4 (3.5 g, 10 mmol, 1.0 eq.) and 4-hydroxybenzoic acid (4.1 g, 30 mmol, 3.0 eq.) in HBr (33 wt. % in AcOH, 30 mL) gave piperazine (*R*)-S5 (1.5 g, 80%) as a pale yellow oil, [α]_D +32.6 (*c* 1.0 in CHCl₃).

Lab Book Reference: JDF6_537

(*S*)-*tert*-Butyl 4-(1-phenylethyl)piperazine-1-carboxylate (*S*)-36



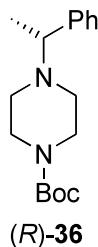
(*S*)-36

A solution of di-*tert*-butyl dicarbonate (14.0 g, 64.2 mmol, 1.3 eq.) in CH₂Cl₂ (50 mL) was added dropwise to a stirred solution of piperazine (*S*)-S5 (9.4 g, 49.4 mmol, 1.0 eq.) in CH₂Cl₂ (100 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, saturated NaHCO_{3(aq)} (100 mL) was added and the two layers were separated. 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. Purification by flash column chromatography on silica with 9:1:1:1 petrol-EtOAc as eluent gave *N*-Boc piperazine (*S*)-36 (13.4 g, 93%) as a pale yellow oil, *R*_F (7:3 petrol-EtOAc) 0.2; [α]_D –40.3 (*c* 1.0 in CHCl₃) (lit.,⁵ [α]_D –32 (*c* 1.04 in CHCl₃) for (*S*)-36 of >99:1 er);

¹H NMR (400 MHz, CDCl₃) δ 7.33-7.20 (m, 5H, Ph), 3.39 (t, *J* = 5.0 Hz, 4H, NCH₂), 3.37 (q, *J* = 6.5 Hz, 1H, CHMe), 2.44-2.41 (m, 2H, NCH), 2.35-2.31 (m, 2H, NCH), 1.43 (s, 9H, CMe₃), 1.36 (d, *J* = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.7 (C=O), 143.6 (*ipso*-Ph), 128.2 (Ph), 127.6 (Ph), 127.0 (Ph), 79.4 (CMe₃) 64.7 (NCHPh), 50.2 (NCH₂); 44.0 (NCH₂), 28.4 (CMe₃), 19.6 (CHMe). Spectroscopic data consistent with those reported in the literature.⁵

Lab Book Reference: JDF5_426

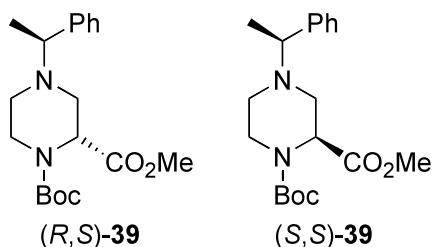
(R)-*tert*-Butyl 4-(1-phenylethyl)piperazine-1-carboxylate (R)-36



Using the above procedure, di-*tert*-butyl dicarbonate (1.9 g, 8.7 mmol, 1.1 eq.) and piperazine (R)-S5 (1.5 g, 7.9 mmol, 1.0 eq.) in CH₂Cl₂ (30 mL) gave *N*-Boc piperazine (R)-36 (2.2 g, 96%) as a pale yellow oil, [α]_D +43.5 (c 1.0 in CHCl₃) (lit.⁵ [α]_D -32 (c 1.04 in CHCl₃) for (S)-36 of >99:1 er); Spectroscopic data consistent with those reported in the literature.⁵

Lab Book Reference: JDF6_538

(R)-1-*tert*-Butyl 2-methyl 4-((S)-1-phenylethyl)piperazine-1,2-dicarboxylate (R,S)-39, (S)-1-*tert*-butyl 2-methyl 4-((S)-1-phenylethyl)piperazine-1,2-dicarboxylate (S,S)-39



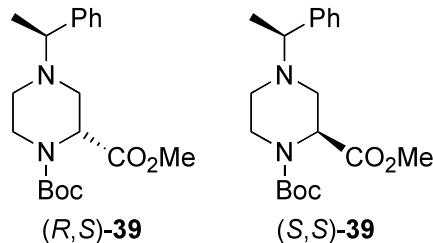
(Scheme 8)

Using general procedure A, *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol, 1.3 eq.), (+)-sparteine surrogate (505 mg, 2.6 mmol, 1.3 eq.), *N*-Boc piperazine (S)-36 (581 mg, 2.0 mmol, 1.0 eq.) in Et₂O (10 mL) for 10 min and methyl chloroformate (378 mg, 309 μL, 4.0 mmol, 2.0 eq.), worked up with saturated NaHCO₃(aq) (10 mL) gave the crude product which contained a 95:5 mixture of (S,S)-39 and (R,S)-39 (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et₂O as eluent gave *N*-Boc piperazine (R,S)-39 (31 mg, 4%) as a colourless oil, *R*_F (4:1

petrol-Et₂O) 0.2; $[\alpha]_D$ +23.4 (*c* 1.1 in CHCl₃); IR (CHCl₃) 1717 (C=O, CO₂Me), 1660 (C=O, Boc), 1498, 1453, 1398, 1346, 1199, 1101, 999, 913, 760 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (55:45 mixture of rotamers) δ 7.34-7.16 (m, 5H, Ph), 4.73 (s, 0.55H, NCH), 4.56 (s, 0.45H, NCH), 3.74 (s, 1.65H, CO₂Me), 3.72 (s, 1.35H, CO₂Me), 3.82-3.63 (m, 1H, CHMe), 3.52-3.36 (m, 2H, NCH), 3.18 (td, *J* = 12.5, 3.5 Hz, 0.55H, NCH), 3.07 (td, *J* = 12.5, 3.5 Hz, 0.45H, NCH), 2.69 (br d, *J* = 11.0 Hz, 0.45H, NCH), 2.62 (br d, *J* = 11.0 Hz, 0.55H, NCH), 2.23 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH), 2.06-1.94 (m, 1H, NCH), 1.45 (s, 5H, CMe₃), 1.42 (s, 4H, CMe₃), 1.31 (d, *J* = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 171.6 (CO₂Me), 171.3 (CO₂Me), 155.9 (NC=O), 155.3 (NC=O), 143.6 (*ipso*-Ph), 143.4 (*ipso*-Ph), 128.5 (Ph), 127.4 (Ph), 126.9 (Ph), 80.1 (CMe₃), 63.5 (NCHPh), 63.3 (NCHPh), 55.7 (NCH), 54.6 (NCH), 52.0 (CO₂Me), 50.4 (NCH₂), 50.2 (NCH₂), 50.0 (NCH₂), 42.3 (NCH₂), 41.3 (NCH₂), 28.3 (CMe₃), 18.7 (CHMe), 18.3 (CHMe); MS (ESI) *m/z* 349 (M + H)⁺; HRMS *m/z* calcd for C₁₉H₂₈N₂O₄ (M + H)⁺ 349.2118, found 349.2118 (+0.6 ppm error) and *N*-Boc piperazine (*S,S*)-**39** (623 mg, 90%, >99:1 er by CSP-HPLC) as a colourless oil, *R*_F (4:1 petrol-Et₂O) 0.15; $[\alpha]_D$ -45.7 (*c* 1.5 in CHCl₃); IR (CHCl₃) 1717 (C=O, CO₂Me), 1661 (C=O, Boc), 1431, 1346, 1282, 1197, 1145, 1102, 1051, 959, 743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (55:45 mixture of rotamers) δ 7.34-7.17 (m, 5H, Ph), 4.62 (s, 0.55H, NCH), 4.45 (s, 0.45H, NCH), 3.88 (br d, *J* = 12.5 Hz, 0.45H, NCH), 3.79 (br d, *J* = 12.5 Hz, 0.55H, NCH), 3.71 (s, 1.35H, CO₂Me), 3.69 (s, 1.65H, CO₂Me), 3.41-3.14 (m, 3H, CHMe + NCH), 3.00 (br d, *J* = 11.0 Hz, 0.45H, NCH), 2.94 (br d, *J* = 11.0 Hz, 0.55H, NCH), 2.10-1.98 (m, 2H, NCH), 1.46 (s, 5H, CMe₃), 1.40 (s, 4H, CMe₃), 1.31 (d, *J* = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 171.2 (CO₂Me), 171.0 (CO₂Me), 155.8 (NC=O), 155.3 (NC=O), 143.4 (*ipso*-Ph), 143.2 (*ipso*-Ph), 128.1 (Ph), 127.4 (Ph), 127.1 (Ph), 80.2 (CMe₃), 80.1 (CMe₃), 64.1 (NCHPh), 55.6 (NCH), 54.4 (NCH), 51.8 (CO₂Me), 51.7 (NCH₂), 51.5 (NCH₂), 49.2 (NCH₂), 42.2 (NCH₂), 41.2 (NCH₂), 28.3 (CMe₃), 28.2 (CMe₃), 19.9 (CHMe), 19.7 (CHMe); MS (ESI) *m/z* 349 (M + H)⁺; HRMS *m/z* calcd for C₁₉H₂₈N₂O₄ (M + H)⁺ 349.2118, found 349.2116 (+1.2 ppm error); CSP-HPLC: Chiralcel AD-H (98:2 hexane:*i*-PrOH, 1.0 mL min⁻¹) (*R,R*)-**39** 7.3 min, (*S,S*)-**39** 10.8 min.

Lab Book Reference: JDF8_708

(R)-1-*tert*-Butyl 2-methyl 4-((S)-1-phenylethyl)piperazine-1,2-dicarboxylate (*R,S*)-39, (S)-1-*tert*-butyl 2-methyl 4-((S)-1-phenylethyl)piperazine-1,2-dicarboxylate (*S,S*)-39

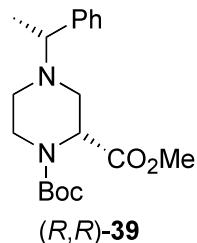


(Scheme 8)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine (152 mg, 149 μ L, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-36 (145 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 3 h and methyl chloroformate (95 mg, 77 μ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product which contained a 37:63 mixture of (*S,S*)-39 and (*R,S*)-39 (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et₂O as eluent gave *N*-Boc piperazine (*R,S*)-39 (85 mg, 49%) as a colourless oil and *N*-Boc piperazine (*S,S*)-39 (47 mg, 27%) as a colourless oil.

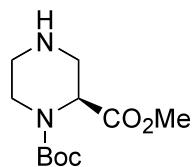
Lab Book Reference: JDF8_710

(R)-1-*tert*-Butyl 2-methyl 4-((R)-1-phenylethyl)piperazine-1,2-dicarboxylate (*R,R*)-39



Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine (152 mg, 149 μ L, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-36 (145 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 1 h and methyl chloroformate (95 mg, 77 μ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product which contained a >95:5 mixture of (*R,R*)-39 and (*S,R*)-39 (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3 petrol-Et₂O as eluent gave *N*-Boc piperazine (*R,R*)-39 (158 mg, 91%, 98:2 er by CSP-HPLC) as a colourless oil; CSP-HPLC: Chiralcel AD-H (98:2 hexane:*i*-PrOH, 1.0 mL min^{−1}) (*R,R*)-39 7.7 min, (*S,S*)-39 10.1 min.

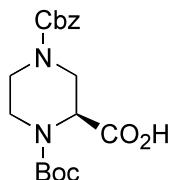
Lab Book Reference: JDF7_621

Determination of the absolute configuration of (S,S)-39: conversion into (S)-S3**(S)-1-*tert*-Butyl 2-methyl piperazine-1,2-dicarboxylate (S)-S2**

(S)-S2

10% Pd/C (5 mg) was added to a stirred solution of *N*-Boc-piperazine (S,S)-39 (20 mg, 0.057 mmol, 1.0 eq.) in MeOH (5 mL). 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 48 h. The mixture was filtered through Celite® and washed with MeOH (20 mL). The filtrate was evaporated under reduced pressure to give *N*-Boc piperazine (S)-S2 (14 mg, quant.) as a pale yellow oil.

Lab Book Reference: JDF7_675

(S)-4-(Benzylloxycarbonyl)-1-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (S)-S3

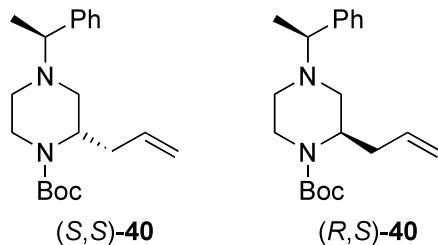
(S)-S3

Benzyl chloroformate (15 mg, 12 μ L, 0.086 mmol, 1.5 eq.) was added to a stirred solution of *N*-Boc piperazine (S)-S2 (14 mg, 0.057 mmol, 1.0 eq.) and Et₃N (9 mg, 12 μ L, 0.086 mmol, 1.5 eq.) in CH₂Cl₂ at rt. The resulting solution was stirred for 16 h. Water (5 mL) was added and the layers separated. The aqueous was extracted with CH₂Cl₂ (2 \times 5 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 7:3 petrol-EtOAc as eluent gave the Cbz-methyl ester (16 mg, 74%) as a colourless oil. Then, LiOH (3 mg, 0.13 mmol, 3.0 eq.) was added to a stirred solution of the Cbz-methyl ester (16 mg, 0.042 mmol, 1.0 eq.) in 4:1:1 THF-MeOH-water (2 mL) at rt under air. The reaction was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure. The residue was partitioned between 1M HCl (5 mL) and CH₂Cl₂ (5 mL) and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 \times 5 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 66:33:1 CH₂Cl₂-EtOAc-AcOH as eluent gave carboxylic acid

(S)-**S3** (14 mg, 84%) as a pale yellow oil, R_F (66:33:1 CH₂Cl₂-EtOAc-AcOH); 0.2; $[\alpha]_D$ -14.3 (*c* 0.7 in CHCl₃) (lit.,⁴ $[\alpha]_D$ -17.5 (*c* 1.02 in CHCl₃).

Lab Book Reference: JDF7_683 and JDF7_694

(S)-*tert*-Butyl 2-allyl-4-((S)-1-phenylethyl)piperazine-1-carboxylate (*S,S*)-40 and (*R*)-*tert*-butyl 2-allyl-4-((S)-1-phenylethyl)piperazine-1-carboxylate (*R,S*)-40



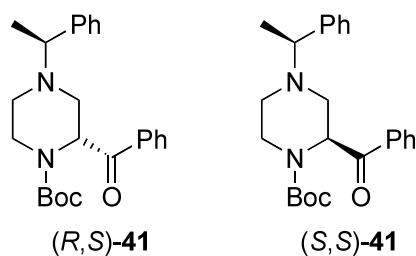
(Scheme 9)

s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of (+)-sparteine surrogate (194 mg, 0.65 mmol, 1.3 eq.) in Et₂O (4 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 15 min. Then, a solution of *N*-Boc piperazine (*S*)-**36** (145 mg, 0.5 mmol, 1.0 eq.), in Et₂O (1 mL) was added dropwise. The resulting solution was stirred at -78 °C for 1 h. Then a solution of CuCN.2LiCl (0.25 mmol, 0.5 eq.) in THF (1 mL) was added dropwise. The resulting solution was stirred at -78 °C for 1 h. Then, allyl bromide (121 mg, 87 μL, 1.0 mmol, 2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated NH₄Cl_(aq) (10 mL) and saturated NaHCO_{3(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 which contained a 5:95 mixture of (*S,S*)-**40** and (*R,S*)-**40** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1 petrol-Et₂O as eluent gave *N*-Boc piperazine (*S,S*)-**40** (8 mg, 5%) as a colourless oil, *R*_F (9:1 petrol-Et₂O) 0.2; [α]_D +7.6 (c 1.4 in CHCl₃); IR (CHCl₃) 2960, 2770, 2323, 2304, 1654 (C=O), 1430, 1397, 1346, 1304, 1282, 1233, 1152, 1092, 1050, 929, 904, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.28 (m, 4H, Ph), 7.27-7.21 (m, 1H, Ph), 5.74 (td, *J* = 17.0, 7.5 Hz, 1H, CH=CH₂), 5.09-5.02 (m, 1H, CH=CH_AH_B), 5.02-4.98 (m, 1H, CH=CH_AH_B), 4.08 (s, 1H, NCH), 3.74 (s, 1H, NCH), 3.34 (q, *J* = 6.5 Hz, 1H, CHMe), 3.04-2.85 (m, 2H, NCH), 2.70-2.40 (m, 3H, NCH + CH₂), 2.08 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 1.91 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.43 (s, 9H, CMe₃), 1.29 (d, *J* = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.8 (C=O), 144.4 (*ipso*-Ph), 135.6 (CH=CH₂), 128.2 (Ph), 127.4 (Ph), 126.8 (Ph), 117.0 (CH=CH₂), 79.3 (CMe₃), 64.0 (CHMe), 51.0 (NCH₂), 50.9 (NCH₂), 39.7 (br, NCH₂), 34.3 (CH₂), 28.3 (CMe₂), 19.0 (CHMe); MS

(ESI) m/z 331 ($M + H$)⁺; HRMS m/z calcd for $C_{20}H_{30}N_2O_2$ ($M + H$)⁺ 331.2380, found 331.2371 (+2.5 ppm error) and (*R,S*)-**40** (130 mg, 79%) as a colourless oil, R_F (9:1 petrol-Et₂O) 0.1; $[\alpha]_D$ -47.3 (c 1.0 in CHCl₃); IR (CHCl₃) 2931, 2323, 2304, 1653 (C=O), 1430, 1390, 1345, 1300, 1282, 1233, 1148, 1092, 1050, 935, 904, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.27 (m, 4H, Ph), 7.26-7.20 (m, 1H, Ph), 5.63 (td, J = 17.0, 7.5 Hz, 1H, CH=CH₂), 5.01 (dd, J = 17.0, 1.5 Hz, 1H, CH=CH_AH_B), 4.95-4.90 (m, 1H, CH=CH_AH_B), 3.90 (br s, 2H, NCH), 3.30 (q, J = 6.5 Hz, 1H, CHMe), 3.07 (br t, J = 12.5 Hz, 1H, NCH), 2.98 (br d, J = 8.0 Hz, 1H, NCH), 2.61 (d, J = 11.0 Hz, 1H, NCH), 2.53-2.31 (m, 2H, CH₂), 1.99 (td, J = 11.5, 6.0 Hz, 1H, NCH), 1.93 (dd, J = 11.5, 3.5 Hz, 1H, NCH), 1.43 (s, 9H, CMe₃), 1.33 (d, J = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.8 (C=O), 144.0 (*ipso*-Ph), 135.5 (CH=CH₂), 128.2 (Ph), 127.5 (Ph), 126.9 (Ph), 117.0 (CH=CH₂), 79.3 (CMe₃), 64.5 (CHMe), 52.8 (NCH₂), 49.8 (NCH₂), 39.3 (br, NCH₂), 34.4 (CH₂), 28.4 (CMe₃), 19.8 (CHMe); MS (ESI) m/z 331 ($M + H$)⁺; HRMS m/z calcd for $C_{20}H_{30}N_2O_2$ ($M + H$)⁺ 331.2380, found 331.2372 (+2.5 ppm error).

Lab Book Reference: JDF8 706

(R)-tert-butyl 2-benzoyl-4-((S)-1-phenylethyl)piperazine-1-carboxylate (*R,S*)-41 and (S)-tert-butyl 2-benzoyl-4-((S)-1-phenylethyl)piperazine-1-carboxylate (*S,S*)-41



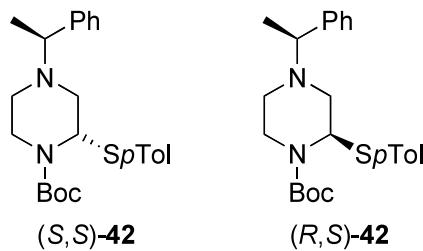
(Scheme 9)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**36** (145 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 1 h and *N*-methoxy-*N*-methylbenzamide (107 mg, 99 μ L, 0.65 mmol, 1.3 eq.), worked up with saturated NaHCO_{3(aq)} (10 mL) gave the crude product which contained a 7:93 mixture of (*R,S*)-**41** and (*S,S*)-**41** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 99:1-97:3 CH₂Cl₂-Et₂O as eluent gave *N*-Boc piperazine (*R,S*)-**41** (12 mg, 6%) as a white solid, mp 104-105 °C; R_F (98:2 CH₂Cl₂-Et₂O) 0.2; $[\alpha]_D$ +1.9 (*c* 0.65 in CHCl₃); IR (CHCl₃) 2967, 2933, 2772, 1674 (C=O, PhCO), 1661 (C=O, Boc), 1429, 1385, 1345, 1283, 1234, 1144, 1102, 1051, 931, 848 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (55:45 mixture of rotamers) δ 7.83-7.69 (m, 2H, Ph), 7.56-7.46 (m, 1H, Ph), 7.46-7.37 (m, 2H, Ph), 7.22-7.07 (m, 5H, Ph), 5.48 (br s, 0.55H, NCH), 5.31 (br s, 0.45H, NCH), 3.78 (br d, *J* = 11.0 Hz, 0.45H, NCH), 3.69 (br d, *J* = 11.0 Hz, 0.55H, NCH), 3.50-3.23 (m, 3H, NCH).

CHMe + *NCH*), 2.78-2.56 (m, 1*H*, *NCH*), 2.49-2.34 (m, 1*H*, *NCH*), 2.14-1.97 (m, 1*H*, *NCH*), 1.45 (s, 4.95*H*, *CMe*₃), 1.37 (s, 3.05*H*, *CMe*₃), 1.02 (d, *J* = 6.5 Hz, 3*H*, *CHMe*); ¹³C NMR (100.6 MHz, *CDCl*₃) (mixture of rotamers) δ 199.4 (COPh), 156.1 (NC=O), 143.4 (*ipso*-Ph), 136.6 (*ipso*-Ph), 136.5 (*ipso*-Ph), 132.3 (Ph), 128.6 (Ph), 128.6 (Ph), 128.5 (Ph), 128.5 (Ph), 127.8 (Ph), 127.7 (Ph), 127.5 (Ph), 127.2 (Ph), 126.8 (Ph), 80.1 (*CMe*₃), 64.5 (*CHMe*), 59.0 (*NCH*), 58.0 (*NCH*), 52.9 (*NCH*₂), 50.4 (*NCH*₂), 42.5 (*NCH*₂), 41.7 (*NCH*₂), 28.3 (*CMe*₃), 28.3 (*CMe*₃), 18.4 (*CHMe*), 18.3 (*CHMe*); MS (ESI) *m/z* 395 (M + H)⁺; HRMS *m/z* calcd for *C*₂₄*H*₃₀*N*₂*O*₃ (M + H)⁺ 395.2329, found 395.2312 (+4.3 ppm error) and *N*-Boc piperazine (*S,S*)-**41** (170 mg, 86%) as a white solid, mp 127-129 °C; *R*_F (98:2 *CH*₂*Cl*₂-*Et*₂*O*) 0.1; [α]_D -2.6 (*c* 0.8 in *CHCl*₃); IR (*CHCl*₃) 2967, 2933, 2772, 1674 (C=O, PhCO), 1661 (C=O, Boc), 1430, 1385, 1346, 1281, 1234, 1150, 1102, 1051, 931, 848 cm⁻¹; ¹H NMR (400 MHz, *CDCl*₃) (55:45 mixture of rotamers) δ 7.75-7.59 (m, 2*H*, Ph), 7.55-7.43 (m, 1*H*, Ph), 7.41-7.31 (m, 2*H*, Ph), 7.06-6.78 (m, 5*H*, Ph), 5.39 (br s, 0.55*H*, *NCH*), 5.21 (br s, 0.45*H*, *NCH*), 3.91 (br d, *J* = 12.0 Hz, 0.45*H*, *NCH*), 3.82 (br d, *J* = 12.0 Hz, 0.55*H*, *NCH*), 3.62-3.43 (m, 1*H*, *CHMe*), 3.24-3.02 (m, 2.45*H*, *NCH*), 2.98 (br d, *J* = 10.0 Hz, 0.55*H*), 2.22 (dd, *J* = 12.0, 4.5 Hz, 1*H*, *NCH*), 2.04 (br s, 1*H*, *NCH*), 1.47 (s, 4.95*H*, *CMe*₃), 1.36 (s, 3.05*H*, *CMe*₃), 1.17 (d, *J* = 6.5 Hz, 3*H*, *CHMe*); ¹³C NMR (100.6 MHz, *CDCl*₃) (mixture of rotamers) δ 200.0 (COPh), 156.2 (NC=O), 155.6 (NC=O), 143.2 (*ipso*-Ph), 143.1 (*ipso*-Ph), 136.1 (*ipso*-Ph), 136.1 (*ipso*-Ph), 132.6 (Ph), 128.6 (Ph), 128.5 (Ph), 128.0 (Ph), 127.7 (Ph), 127.0 (Ph), 126.7 (Ph), 80.2 (*CMe*₃), 64.5 (*CHMe*), 58.9 (*NCH*), 57.9 (*NCH*), 52.3 (*NCH*₂), 52.3 (*NCH*₂), 49.7 (*NCH*₂), 42.6 (*NCH*₂), 41.8 (*NCH*₂), 28.5 (*CMe*₃), 28.3 (*CMe*₃), 20.2 (*CHMe*); 20.1 (*CHMe*); MS (ESI) *m/z* 395 (M + H)⁺; HRMS *m/z* calcd for *C*₂₄*H*₃₀*N*₂*O*₃ (M + H)⁺ 395.2329, found 395.2311 (+4.3 ppm error).

Lab Book Reference: JDF8 723

(S)-*tert*-Butyl 4-((S)-1-phenylethyl)-2-(*p*-tolylthio)piperazine-1-carboxylate (*S,S*)-42 and **(R)-*tert*-butyl 4-((S)-1-phenylethyl)-2-(*p*-tolylthio)piperazine-1-carboxylate (*R,S*)-42**



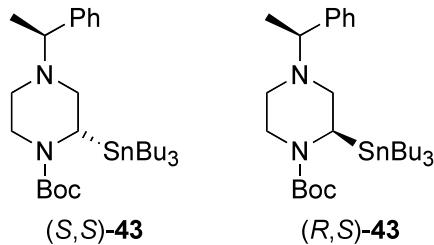
(Scheme 9)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**36** (145 mg, 0.5 mmol, 1.0 eq.)

in Et_2O (5 mL) for 1 h and *p*-tolyl disulfide (246 mg, 1.0 mmol, 2.0 eq.), worked up with saturated $\text{NaHCO}_{3(\text{aq})}$ (10 mL) gave the crude product which contained a 5:95 mixture of (*S,S*)-**42** and (*R,S*)-**42** (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica (prewashed with 99:1 $\text{CH}_2\text{Cl}_2\text{-Et}_3\text{N}$) with CH_2Cl_2 as eluent gave *N*-Boc piperazine (*S,S*)-**42** (8 mg, 4%) as a pale yellow oil, R_F (CH_2Cl_2) 0.2; $[\alpha]_D$ -46.5 (*c* 0.4 in CHCl_3); IR (CHCl_3) 2931, 2881, 1661 (C=O), 1469, 1429, 1387, 1347, 1283, 1283, 1253, 1146, 1101, 1001, 930, 846, 801 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (65:35 mixture of rotamers) δ 7.44-7.30 (m, 6H, Ar), 7.29-7.23 (m, 1H, Ar), 7.08 (br d, J = 7.0 Hz, 2H, Ar), 5.76 (br s, 0.35H, NCH), 5.56 (br s, 0.65H, NCH), 3.86 (br d, J = 12.0 Hz, 0.65H, NCH), 3.69 (br s, 0.35H, NCH), 3.60-3.38 (m, 2H, NCH + CHMe), 3.27 (br d, J = 10.5 Hz, 1H, NCH), 2.77 (br s, 1H, NCH), 2.41 (br d, J = 9.5 Hz, 1H, NCH), 2.32 (s, 3H, ArMe), 2.00 (br s, 1H, NCH), 1.36 (d, J = 6.5 Hz, 3H, CHMe), 1.29 (br s, 3.2H, CMe_3), 1.10 (br s, 5.8H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) (mixture of rotamers) δ 153.4 (C=O), 143.5 (*ipso*-Ph), 142.4 (*ipso*-Ph), 135.1 (Ph), 135.0 (Ph), 131.1 (*ipso*-Ph), 129.6 (Ph), 128.2 (Ph), 127.6 (Ph), 127.0 (Ph), 80.0 (CMe_3), 65.0 (NCH), 63.8 (CHMe), 54.8 (NCH₂), 50.5 (NCH₂), 42.0 (NCH₂), 38.5 (NCH₂), 27.7 (CMe_3), 21.1 (ArMe), 19.0 (CHMe); MS (ESI) *m/z* 413 (M + H)⁺; HRMS *m/z* calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_2\text{S}$ (M + H)⁺ 413.2257, found 413.2268 (-3.0 ppm error) and *N*-Boc piperazine (*R,S*)-**42** (178 mg, 86%) as a pale yellow oil, R_F (CH_2Cl_2) 0.1; $[\alpha]_D$ +37.9 (*c* 1.0 in CHCl_3); IR (CHCl_3) 2934, 2776, 1662 (C=O), 1469, 1429, 1388, 1346, 1287, 1196, 1149, 1101, 1047, 998, 921, 844, 764 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (65:35 mixture of rotamers) δ 7.34 (br d, J = 4.0 Hz, 6H, Ar), 7.29-7.22 (m, 1H, Ar), 7.06 (br d, J = 7.0 Hz, 2H, Ar), 5.67 (br s, 0.35H, NCH), 5.46 (br s, 0.65H, NCH), 3.98 (br d, J = 11.5 Hz, 0.65H, NCH), 3.80 (br s, 0.35H, NCH), 3.62 (br t, J = 11.5 Hz, 1H, NCH), 3.43 (br s, 1H, CHMe), 3.15-2.95 (m, 2H, NCH), 2.30 (s, 3H, ArMe), 2.32-2.22 (m, 1H, NCH), 2.08 (br t, J = 10.0 Hz, 1H, NCH) 1.40 (br d, J = 6.5 Hz, 3H, CHMe), 1.29 (br s, 3.2H, CMe_3), 1.08 (br s, 5.8H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) (mixture of rotamers) δ 153.3 (C=O), 142.8 (*ipso*-Ph), 137.9 (*ipso*-Ph), 137.7 (*ipso*-Ph), 135.1 (Ph), 134.3 (Ph), 130.7 (*ipso*-Ph), 130.2 (*ipso*-Ph), 129.6 (Ph), 128.3 (Ph), 127.6 (Ph), 127.0 (Ph), 79.9 (CMe_3), 64.6 (NCH), 64.3 (CHMe), 55.4 (NCH₂), 54.5 (NCH₂), 50.0 (NCH₂), 39.8 (NCH₂), 38.4 (NCH₂), 28.1 (CMe_3), 27.6 (CMe_3), 21.0 (ArMe), 19.8 (CHMe); MS (ESI) *m/z* 413 (M + H)⁺; HRMS *m/z* calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_2\text{S}$ (M + H)⁺ 413.2257, found 413.2247 (+2.5 ppm error).

Lab Book Reference: JDF8_723

(S)-*tert*-Butyl 4-((S)-1-phenylethyl)-2-(tributylstannyl)piperazine-1-carboxylate (*S,S*)-43 and (*R*)-*tert*-butyl 4-((S)-1-phenylethyl)-2-(tributylstannyl)piperazine-1-carboxylate (*R,S*)-43



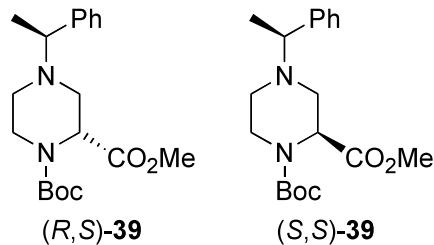
(Scheme 9)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**36** (145 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 1 h and Bu₃SnCl (325 mg, 271 μ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO_{3(aq)} (10 mL) gave the crude product which contained). Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave a 7:93 mixture (by derivatisation to (*R,S*)-**39** and (*S,S*)-**39**) of *N*-Boc piperazines (*S,S*)-**43** and (*R,S*)-**43** (272 mg, 94%) as a pale yellow oil, *R*_F (19:1 petrol-EtOAc) 0.2; ¹H NMR (400 MHz, CDCl₃) (50:50 mixture of rotamers) δ 7.19-7.35 (m, 5H, Ph), 3.97-4.16 (m, 1H, CHMe), 3.60 (br s, 0.5H, NCH), 3.45 (br s, 0.5H, NCH), 3.21-3.38 (m, 1.5H, NCH), 2.94 (br d, *J* = 9.5 Hz, 0.5H, NCH), 2.65-2.77 (m, 0.5H, NCH), 2.56-2.68 (m, 1H, NCH), 2.39-2.46 (m, 1H, NCH), 2.18-2.32 (m, 1H, NCH), 1.93-2.04 (m, 0.5H, NCH), 1.32-1.7 (m, 18H, CH₂ + CHMe + CMe₃), 1.21-1.34 (m, 6H, CH₂), 0.79-0.97 (m, 15H, CH₂ + Me).

Lab Book Reference: JDF8_725

Determination of the diastereomeric ratio of *N*-Boc piperazines (*S,S*)-43 and (*R,S*)-43 via conversion into (*R,S*)-39 and (*S,S*)-39:

(R)-1-tert-Butyl 2-methyl 4-((S)-1-phenylethyl)piperazine-1,2-dicarboxylate (R,S)-39, (S)-1-tert-butyl 2-methyl 4-((S)-1-phenylethyl)piperazine-1,2-dicarboxylate (S,S)-39

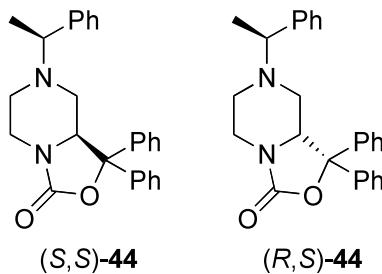


n-BuLi (51 μ L of a 2.2 M solution in hexanes, 0.11 mmol, 1.3 eq.) was added dropwise to a stirred solution of diastereomeric stannanes (*S,S*)-43 and (*R,S*)-43 (50 mg, 0.09 mmol, 1.0 eq.) and TMEDA (13 mg, 17 μ L, 0.11 mmol, 1.3 eq.) in Et₂O (3 mL) at -78 °C under Ar. The resulting solution was

stirred at -78°C for 10 min. Then, methyl chloroformate (16 mg, 13 μL , 0.17 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at -78°C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) and saturated $\text{NaHCO}_{3(\text{aq})}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were dried (MgSO_4) and evaporated under reduced pressure gave the crude product which contained a 7:93 mixture of $(R,S)\text{-39}$ and $(S,S)\text{-39}$ (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 19:1 petrol-EtOAc as eluent gave a mixture of diastereomeric *N*-Boc piperazines $(R,S)\text{-39}$ and $(S,S)\text{-39}$ (19 mg, 64%).

Lab Book Reference: JDF8_727

(S)-1,1-Diphenyl-7-((S)-1-phenylethyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (S,S)-44 and (R)-1,1-diphenyl-7-((S)-1-phenylethyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (S,S)-44



(Scheme 9)

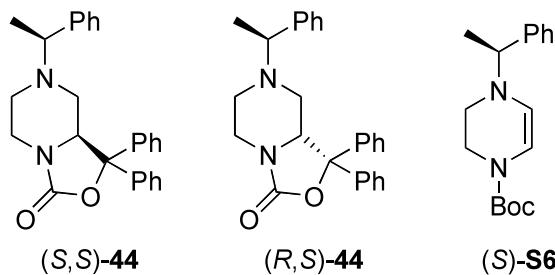
Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (152 mg, 1.3 mmol, 1.3 eq.), *N*-Boc piperazine $(S)\text{-36}$ (290 mg, 1.0 mmol, 1.0 eq.) in Et_2O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $\text{NaHCO}_{3(\text{aq})}$ (10 mL) gave the crude product which contained a 90:10 mixture of $(S,S)\text{-44}$ and $(R,S)\text{-44}$ (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3-1:1 petrol- Et_2O as eluent gave *N*-Boc piperazine $(S,S)\text{-44}$ (122 mg, 31%) as a white solid, mp 139-140 $^{\circ}\text{C}$; R_F (7:3 petrol-EtOAc) 0.2; $[\alpha]_D -244.9$ (*c* 1.0 in CHCl_3) (lit.,⁵ $[\alpha]_D +213$ (*c* 0.108 in CHCl_3) for $(S,S)\text{-44}$ of >99:1 er); ^1H NMR (400 MHz, CDCl_3) δ 7.54-7.51 (m, 2H, Ph), 7.40-7.22 (m, 11H, Ph), 7.18-7.16 (m, 2H, Ph), 4.51 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.74 (ddd, *J* = 13.0, 3.5, 1.0 Hz, 1H, NCH), 3.34 (q, *J* = 7.0 Hz, 1H, CHMe), 3.04 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.72-2.60 (m, 2H, NCH), 1.86 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.46 (t, *J* = 11.0 Hz, 1H, NCH), 1.22 (d, *J* = 7.0 Hz, 3H, CHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 156.0 (C=O), 142.7 (*ipso*-Ph), 142.3 (*ipso*-Ph), 138.7 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 127.8 (Ph), 127.3 (Ph), 127.2 (Ph),

126.0 (Ph), 125.8 (Ph), 85.3 (Ph₂CO), 64.3 (CH), 61.4 (CH), 52.5 (NCH₂), 49.1 (NCH₂), 41.9 (NCH₂), 19.2 (CHMe) and *N*-Boc piperazine (*R,S*)-**44** (15 mg, 4%) as a white solid, mp 127-129 °C; *R*_F (7:3 petrol-EtOAc) 0.1; [α]_D +187.7 (*c* 1.0 in CHCl₃) (lit.⁵ [α]_D -132 (*c* 0.11 in CHCl₃) for (*R,S*)-**44** of >99:1 er); ¹H NMR (400 MHz, CDCl₃) δ 7.48-7.45 (m, 2H, Ph), 7.38-7.20 (m, 11H, Ph), 7.18-7.14 (m, 2H, Ph), 4.43 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 3.81 (ddd, *J* = 13.0, 3.5, 1.0 Hz, 1H, NCH), 3.48 (q, *J* = 7.0 Hz, 1H, CHMe), 3.10 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 2.82-2.70 (m, 1H, NCH), 2.43 (ddd, *J* = 12.0, 3.5, 1.0 Hz, 1H, NCH), 2.02 (td, *J* = 12.0, 3.5 Hz, 1H, NCH), 1.49 (t, *J* = 11.0 Hz, 1H, NCH), 1.26 (d, *J* = 7.0 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.8 (C=O), 142.0 (*ipso*-Ph), 141.8 (*ipso*-Ph), 138.3 (*ipso*-Ph), 128.1 (Ph), 128.0 (Ph), 127.9 (Ph), 127.8 (Ph), 127.4 (Ph), 127.1 (Ph), 126.8 (Ph), 125.6 (Ph), 125.4 (Ph), 84.9 (Ph₂CO), 63.3 (CH), 61.2 (CH), 52.8 (NCH₂), 47.1 (NCH₂), 41.6 (NCH₂), 16.7 (CHMe); Spectroscopic data for (*S,S*)-**44** and (*R,S*)-**44** consistent with those reported in the literature.⁵

Lab Book Reference: JDF4 399

Characterisation of alkene by-product S6 – from a (–)-sparteine reaction with (S)-36

(S,S)-1,1-Diphenyl-7-((S)-1-phenylethyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (S,S)-44,
 (R)-1,1-diphenyl-7-((S)-1-phenylethyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (R,S)-44
 and (S)-*tert*-butyl 4-(1-phenylethyl)-3,4-dihydropyrazine-1(2H)-carboxylate (S)-S6

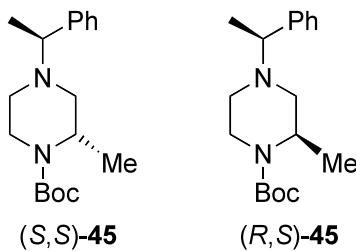


Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (−)-sparteine (305 mg, 299 μ L, 1.3 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**36** (290 mg, 1.0 mmol, 1.0 eq.) in Et₂O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et₂O (1 mL), worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product which contained a 40:60 mixture of (*S,S*)-**44** and (*R,S*)-**44** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2:1:1 petrol-Et₂O as eluent gave *N*-Boc piperazine (*S,S*)-**44** (67 mg, 16%) as a white solid, *N*-Boc piperazine (*R,S*)-**44** (113 mg, 29%) as a white solid and alkene (*S*)-**6** as a clear oil (29 mg, 10%), *R*_F (8:2 petrol-Et₂O) 0.2; IR (CHCl₃) 2971, 1664 (C=O), 1505, 1471, 1430, 1371, 1347, 1203, 1189, 1147, 914, 774, 722, 691 cm^{−1}; ¹H NMR (400 MHz, CDCl₃) (70:30 mixture of rotamers) δ 7.41–

7.21 (m, 5H, Ph), 6.00 (d, J = 6.5 Hz, 0.3H, $CH=CH$), 5.85 (d, J = 6.5 Hz, 0.7H, $CH=CH$), 5.64 (d, J = 6.5 Hz, 0.3H, $CH=CH$), 5.50 (d, J = 6.5 Hz, 0.7H, $CH=CH$), 4.11-4.00 (m, 1H, $CHMe$), 3.69-3.58 (m, 1H, NCH), 3.57-3.47 (m, 1H, NCH), 2.95 (t, J = 5.0 Hz, 1.4H, NCH), 2.91 (t, J = 5.0 Hz, 0.6H, NCH), 1.48 (s, 2.7H, CMe_3), 1.46 (s, 6.3H, CMe_3), 1.44 (s, 3H, $CHMe$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mixture of rotamers) δ 151.7 (C=O), 143.8 (*ipso*-Ph), 142.2 (*ipso*-Ph), 128.4 (Ph), 128.3 (Ph), 127.5 (Ph), 127.2 (Ph), 127.0 (Ph), 126.5 (Ph), 118.0 ($CH=CH$), 117.1 ($CH=CH$), 102.9 ($CH=CH$), 102.7 ($CH=CH$), 80.1 (CMe_3), 61.3 (NCHPh), 44.1 (NCH₂), 42.1 (NCH₂), 40.8 (NCH₂), 28.4 (CMe_3), 18.3 (CHMe); MS (ESI) m/z 289 [(M + H)⁺, 100] 233 [(M - CMe_3)⁺, 20]; HRMS m/z calcd for $C_{17}H_{24}N_2O_2$ (M + H)⁺ 289.1906, found 289.1911 (+1.6 ppm error).

Lab Book Reference: JDF4_394

(S)-*tert*-Butyl 2-methyl-4-((S)-1-phenylethyl)piperazine-1-carboxylate (*S,S*)-45 and (*R*)-*tert*-butyl 2-methyl-4-((S)-1-phenylethyl)piperazine-1-carboxylate (*R,S*)-45

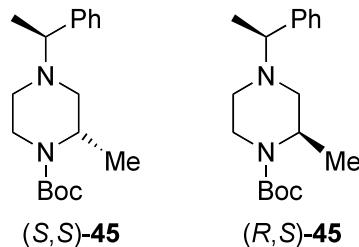


(Scheme 9)

Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (152 mg, 1.3 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**36** (290 mg, 1.0 mmol, 1.0 eq.), in Et₂O (7 mL) for 1 h and methyl iodide (284 mg, 125 μ L, 2.0 mmol, 2.0 eq.), worked up with saturated NaHCO₃(aq) (10 mL) gave the crude product which contained a 24:76 mixture of (*S,S*)-**45** and (*R,S*)-**45** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1:1:1 petrol-Et₂O as eluent gave *N*-Boc piperazine (*S,S*)-**45** (46 mg, 15%) as a colourless oil, *R*_F (4:1 petrol-Et₂O) 0.2; $[\alpha]_D$ +24.2 (*c* 1.0 in CHCl₃); IR (CHCl₃) 2961, 2889, 2769, 1654 (C=O), 1430, 1394, 1346, 1301, 1258, 1212, 1196, 1147, 1112, 1068, 1015, 744 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.28 (m, 4H, Ph), 7.25–7.21 (m, 1H, Ph), 4.20 (br s, 1H, NCH), 3.70 (br d, *J* = 13.0 Hz, 1H, NCH), 3.34 (q, *J* = 6.5 Hz, 1H, CHMe), 3.00 (td, *J* = 13.0, 3.5 Hz, 1H, NCH), 2.77 (dt, *J* = 11.0, 2.0 Hz, 1H, NCH), 2.64–2.60 (m, 1H, NCH), 2.16 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 1.89 (ddd, *J* = 13.0, 12.0, 3.5 Hz, 1H, NCH), 1.44 (s, 9H, CMe₃), 1.31 (d, *J* = 6.5 Hz, 3H, CHMe), 1.26 (d, *J* = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.7 (C=O), 144.4 (*ipso*-Ph), 128.8 (Ph), 127.5 (Ph), 126.8 (Ph), 79.2 (CMe₃), 64.0 (NCHPh), 53.9 (NCH₂), 51.1 (NCH₂), 47.2 (NCH), 39.3 (NCH₂), 28.4 (CMe₃), 19.2 (CHMe), 16.0

(CHMe); MS (ESI) m/z 305 (M + H) $^+$; HRMS m/z calcd for C₁₈H₂₈N₂O₂ (M + H) $^+$ 305.2224, found 305.2238 (−3.4 ppm error) and *N*-Boc piperazine (*R,S*)-**45** (161 mg, 53%) as a colourless oil, R_F (4:1 petrol-Et₂O) 0.1; $[\alpha]_D$ −92.8 (c 1.0 in CHCl₃); IR (CHCl₃) 2933, 2770, 1645 (C=O), 1430, 1394, 1346, 1297, 1268, 1196, 1149, 1114, 1067, 1014, 743 cm $^{-1}$; ¹H NMR (400 MHz, CDCl₃) δ 7.32–7.20 (m, 5H, Ph), 4.07 (br s, 1H, NCH), 3.83 (br d, J = 13.0 Hz, 1H, NCH), 3.29 (q, J = 6.5 Hz, 1H, CHMe), 3.12 (td, J = 13.0, 3.5 Hz, 1H, NCH), 3.01–2.96 (m, 1H, NCH), 2.50 (dt, J = 11.0, 2.0 Hz, 1H, NCH), 2.02–1.94 (m, 2H, NCH), 1.43 (s, 9H, CMe₃), 1.33 (d, J = 6.5 Hz, CHMe), 1.17 (d, J = 6.5 Hz, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 154.7 (C=O), 144.4 (*ipso*-Ph), 128.2 (Ph), 127.3 (Ph), 126.8 (Ph), 79.2 (CMe₃), 64.5 (NCHPh), 55.6 (NCH₂), 49.9 (NCH₂), 47.1 (NCH), 39.4 (NCH₂), 28.4 (CMe₃), 20.0 (CHMe), 15.6 (CHMe); MS (ESI) m/z 305 (M + H) $^+$; HRMS m/z calcd for C₁₈H₂₈N₂O₂ (M + H) $^+$ 305.2224, found 305.2223 (+0.6 ppm error). Lab Book Reference: JDF5_420

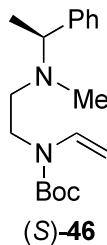
(S)-*tert*-Butyl 2-methyl-4-((S)-1-phenylethyl)piperazine-1-carboxylate (*S,S*)-45 and (*R*)-*tert*-butyl 2-methyl-4-((S)-1-phenylethyl)piperazine-1-carboxylate (*R,S*)-45



(Scheme 10)

Using general procedure B, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**36** (145 mg, 0.5 mmol, 1.0 eq.), TMEDA (74 mg, 97 μ L, 0.65 mmol, 1.3 eq.) in Et₂O (5 mL) for 1 h and methyl trifluoromethanesulfonate (164 mg, 113 μ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO_{3(aq)} (10 mL) gave the crude product which contained a 28:72 mixture of (*S,S*)-**45** and (*R,S*)-**45** (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 17:3-7:3 petrol-Et₂O as eluent gave *N*-Boc piperazine (*S,S*)-**45** (33 mg, 23%) as a colourless oil, and *N*-Boc piperazine (*R,S*)-**45** (104 mg, 72%) as a colourless oil.

Lab Book Reference: JDF10_976

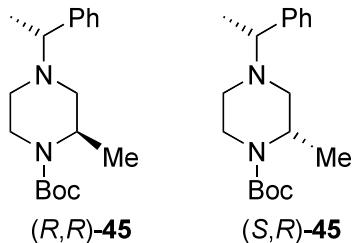
(S)-*tert*-Butyl (2-(methyl(1-phenylethyl)amino)ethyl)(vinyl)carbamate (S)-46

(Scheme 10)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (S)-36 (145 mg, 0.5 mmol, 1.0 eq.) in Et₂O (5 mL) for 1 h and methyl trifluoromethanesulfonate (164 mg, 113 μ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1-1:1 petrol-Et₂O as eluent gave alkene (S)-46 (71 mg, 46%) as a colourless oil, R_F (4:1 petrol-Et₂O) 0.2; $[\alpha]_D$ -21.0 (*c* 1.1 in CHCl₃); IR (CHCl₃) 2973, 2930, 2851, 2779, 1707 (C=O), 1623 (C=C), 1453, 1419, 1360, 1324, 1247, 1205, 1150, 1060, 863, 832, 769 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.27 (m, 4H, Ph), 7.25-7.18 (m, 1H, Ph), 7.08-6.82 (br m, 1H, CH=CH₂), 4.17-3.92 (m, 2H, CH=CH₂), 3.70-3.36 (m, 3H, NCH + CHMe), 2.59-2.53 (m, 1H, NCH), 2.46-2.32 (m, 1H, NCH), 2.30 (br s, 3H, NMe), 1.45 (br s, 9H, CMe₃), 1.35 (d, *J* = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) (mixture of rotamers) δ 153.2 (C=O), 152.4 (C=O), 143.9 (*ipso*-Ph), 132.7 (CH=CH₂), 128.2 (Ph), 127.5 (Ph), 126.8 (Ph), 90.3 (CH=CH₂), 81.0 (CMe₃), 63.9 (CHMe), 63.7 (CHMe), 50.4 (NCH₂), 49.9 (NCH₂), 41.5 (NCH₂), 41.0 (NCH₂), 28.1 (CMe₃), 18.6 (CHMe), 18.4 (CHMe); MS (ESI) *m/z* 305 (M + H)⁺; HRMS *m/z* calcd for C₁₈H₂₈N₂O₂ (M + H)⁺ 305.2224, found 305.2224 (+0.3 ppm error).

Lab Book Reference: JDF10_977

(R)-*tert*-Butyl 2-methyl-4-((R)-1-phenylethyl)piperazine-1-carboxylate (*R,R*)-45 and (S)-*tert*-butyl 2-methyl-4-((R)-1-phenylethyl)piperazine-1-carboxylate (*S,R*)-45

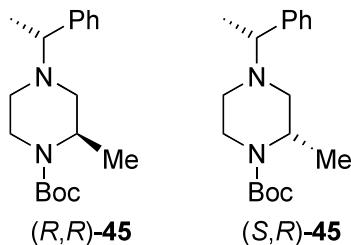


(Scheme 10)

s-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of (–)-sparteine (152 mg, 149 μ L, 0.65 mmol, 1.3 eq.) in Et₂O (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, a solution of *N*-Boc piperazine (*R*)-36 (145 mg, 0.5 mmol, 1.0 eq.) in Et₂O (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 3 h. Then, TMEDA (240 mg, 375 μ L, 2.5 mmol, 5.0 eq.) was added dropwise, and the resulting solution was stirred at –78 °C for 30 min. Then, methyl iodide (142 mg, 62 μ L, 1.0 mmol, 2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated NH₄Cl_(aq) (10 mL) and saturated NaHCO_{3(aq)} (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et₂O (3 \times 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude products in which contained a 10:90 mixture of (*R,R*)-45 and (*S,R*)-45 (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et₂O as eluent gave *N*-Boc piperazine (*R,R*)-45 (5 mg, 3%) as a colourless oil and *N*-Boc piperazine (*S,R*)-45 (106 mg, 70%) as a colourless oil.

Lab Book Reference: JDF6_578

(R)-*tert*-Butyl 2-methyl-4-((R)-1-phenylethyl)piperazine-1-carboxylate (*R,R*)-45 and (S)-*tert*-butyl 2-methyl-4-((R)-1-phenylethyl)piperazine-1-carboxylate (*S,R*)-45

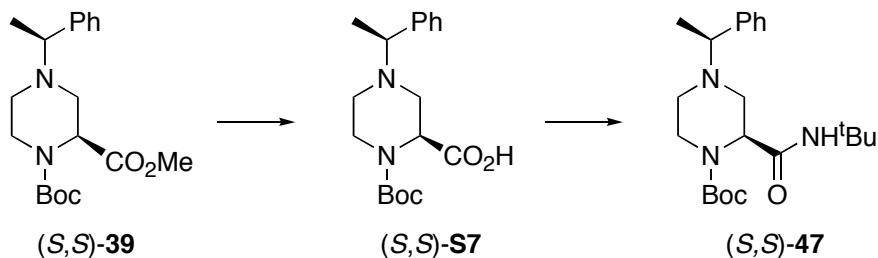


(Scheme 10)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine (152 mg, 149 μ L, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*R*)-36 (145 mg, 0.5 mmol, 1.0 eq.), in Et₂O (5 mL) for 3 h and methyl iodide (142 mg, 62 μ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO₃_(aq) (10 mL) gave the crude product which contained a 45:55 mixture of (*R,R*)-45 and (*S,R*)-45 (by ¹H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1:1:1 petrol-Et₂O as eluent gave *N*-Boc piperazine (*R,R*)-45 (41 mg, 27%) as a colourless oil, $[\alpha]_D$ −7.8 (*c* 1.6 in CHCl₃) and *N*-Boc piperazine (*S,R*)-45 (48 mg, 32%) as a colourless oil, $[\alpha]_D$ +80.2 (*c* 1.0 in CHCl₃).

Lab Book Reference: JDF6_577

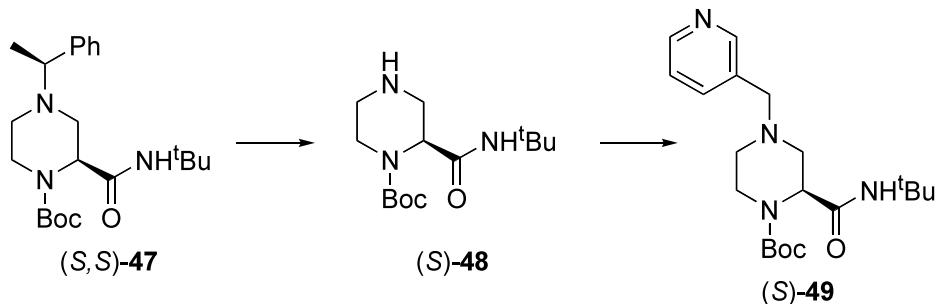
(S)-*tert*-Butyl 2-(*tert*-butylcarbamoyl)-4-((S)-1-phenylethyl)piperazine-1-carboxylate (*S,S*)-47



Lithium hydroxide (4 mg, 0.17 mmol, 3.0 eq.) was added to a stirred solution of methyl ester (*S,S*)-39 (20 mg, 0.06 mmol, 1.0 eq.) in THF/MeOH/water (4:1:1, 3 mL) under air. The resulting solution was stirred at room temperature for 48 h. The volatiles were removed under reduced pressure. Then, water (5 mL) was added and the pH was adjusted to pH 4–5 with 1M HCl_(aq). The aqueous was extracted with CH₂Cl₂ (3 \times 5 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give *N*-Boc piperazine (*S,S*)-S7 (21 mg, 99%) as a white gum, ¹H NMR (400 MHz, CDCl₃) (55:45 mixture of rotamers) δ 7.29–7.60 (m, 6H, Ph + CO₂H), 4.75 (br s, 0.45H, NCH), 4.60 (br s, 0.55H, NCH), 4.12 (q, *J* = 7.0 Hz, 1H, CHMe), 3.97 (br d, *J* = 14.0 Hz, 0.55H, NCH), 3.85 (br d, *J* = 14.0 Hz, 0.45H, NCH), 3.76 (t, *J* = 11.0 Hz, 1H, NCH), 3.41–3.64 (m, 1H, NCH), 3.29 (br d, *J* = 10.5

Hz, 0.55H, NCH), 3.21 (br d, J = 10.5 Hz, 0.45H, NCH), 2.47 (dd, J = 11.5, 4.0 Hz, 1H, NCH), 2.28-2.38 (m, 1H, NCH), 1.56-1.69 (m, 3H, CHMe), 1.41 (s, 9H, CMe₃). The crude product was used in the next step without further purification ($\geq 90\%$ purity by ¹H NMR spectroscopy). HATU (36 mg, 0.094 mmol, 1.5 eq.) was added in one portion to a stirred solution of acid (*S,S*)-**S7** (21 mg, 0.06 mmol, 1.0 eq.), *tert*-butylamine (7 mg, 10 μ L, 0.094 mmol, 1.5 eq.) and DIPEA (16 mg, 22 μ L, 0.126 mmol, 2.0 eq.) in DMF (2 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Saturated NaHCO_{3(aq)} (5 mL) was added and the aqueous layer was extracted with Et₂O (3 \times 5 mL). The combined organic layers were washed with brine (3 \times 5 mL), dried (MgSO₄) 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 *N*-Boc piperazine (*S,S*)-**47** (21 mg, 92%) as a white solid, mp 91-93 °C; R_F (7:3 petrol-EtOAc) 0.3; $[\alpha]_D$ -61.1 (*c* 0.8 in CHCl₃); IR (CHCl₃) 2974, 2932, 1653 (C=O), 1490, 1431, 1394, 1346, 1194, 1148, 1101, 1015, 914, 769, 731, 658 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.20-7.35 (m, 5H, Ph), 6.18 (br s, 1H, NH), 4.37 (br s, 1H, NCH), 3.94 (br s, 1H, NCH), 3.45 (q, J = 6.5 Hz, 1H, CHMe), 3.20 (br d, J = 11.5 Hz, 1H, NCH), 3.09 (br s, 1H, NCH), 2.89 (br d, J = 9.5 Hz, 1H, NCH), 1.94-2.12 (m, 2H, NCH), 1.44 (s, 9H, CMe₃), 1.36 (s, 9H, CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 168.9 (Me₃CNC=O), 155.0 (OC=O), 142.4 (*ipso*-Ph), 128.2 (Ph), 127.7 (Ph), 127.2 (Ph), 80.5 (OCMe₃), 64.1 (CHMe), 56.4 (NCH), 51.0 (NCMe₃), 50.7 (NCH₂), 49.2 (NCH₂), 41.4 (NCH₂), 28.7 (CMe₃), 28.3 (CMe₃), 18.2 (CHMe); MS (ESI) *m/z* 390 (M + H)⁺; HRMS *m/z* calcd for C₂₂H₃₅N₃O₃ (M + H)⁺ 390.2739, found 390.2751 (+3.5 ppm error). Lab Book Reference: JDF8_759 and JDF8_762

(S)-*tert*-Butyl 2-(*tert*-butylcarbamoyl)-4-(pyridin-3-ylmethyl)piperazine-1-carboxylate (*S*)-49****



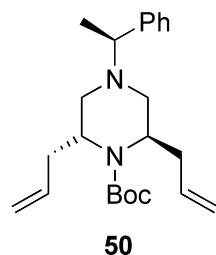
(Scheme 11)

1-Chloroethylchloroformate (27 mg, 20 μ L, 0.189 mmol, 3.0 eq.) was added to a stirred solution of *N*-Boc piperazine (*S,S*)-**47** (25 mg, 0.063 mmol, 1.0 eq.) in 1,2-dichloroethane (3 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 3 h. After cooling to rt, the solvent was evaporated under reduced pressure. The intermediate bis-carbamate was purified by flash column

chromatography on silica with 4:1 to 7:3 petrol-EtOAc as eluent, R_F (7:3 petrol-EtOAc) 0.2. A solution of bis-carbamate in MeOH (3 mL) was stirred and heated at reflux for 2 h. After cooling to rt, the solvent was evaporated under reduced pressure to give the *N*-Boc piperazine hydrochloride (*S*)-**48** as a white gum (17 mg, 84%), ^1H NMR (400 MHz, CDCl_3) δ 11.28 (br s, 1H, NH_2^+), 7.99 (br s, 1H, NH_2^+), 6.36 (br, s, 1H, CONH), 4.69 (br s, 1H, NCH), 4.07 (br s, 1H, NCH), 3.83 (br s, 1H, NCH), 3.60 (br d, J = 11.0 Hz, 1H, NCH), 3.30 (t, J = 13.0 Hz, 1H, NCH), 3.10 (br s, 2H, NCH), 1.48 (s, 9H, CMe_3), 1.31 (s, 9H, CMe_3). The crude product was used in the next step without further purification ($\geq 90\%$ purity by ^1H NMR spectroscopy). Then, 3-(chloromethyl)pyridine hydrochloride (13 mg, 0.077 mmol, 2.5 eq.) was added to a stirred solution of *N*-Boc piperazine hydrochloride (*S*)-**48** (10 mg, 0.031 mmol, 1.0 eq.) and Et_3N (16 mg, 22 μL , 0.155 mmol, 5.0 eq.) in CH_2Cl_2 (2 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 20% $\text{NaOH}_{(\text{aq})}$ (3 mL) was added and the layers were separated. The aqueous was extracted with CH_2Cl_2 (3×5 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 19:1 CH_2Cl_2 :MeOH as eluent gave *N*-Boc piperazine (*S*)-**49** (8 mg, 69%) as a pale yellow oil, $[\alpha]_D$ -35.5 (c 0.3 in CHCl_3); IR (CHCl_3) 2924, 2883, 1652 (C=O), 1487, 1432, 1372, 1346, 1283, 1145, 1102, 961 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.51 (s, 1H, Ar), 7.70 (br s, 1H, Ar), 7.25-7.32 (m, 2H, Ar), 5.91 (br s, 1H, NH), 4.49 (br s, 1H, NCH), 3.98 (br s, 1H, NCH), 3.57 (d, J = 13.5 Hz, 1H, $\text{CH}_A\text{H}_B\text{Ar}$), 3.49 (d, J = 13.5 Hz, 1H, $\text{CH}_A\text{H}_B\text{Ar}$), 3.41 (dt, J = 11.5, 1.5 Hz, 1H, NCH), 3.05 (s, 1H, NCH), 2.71 (d, J = 10.5 Hz, 1H, NCH), 2.12-2.21 (m, 1H, NCH), 2.07 (td, J = 11.5, 2.5 Hz, 1H, NCH), 1.47 (s, 9H, CMe_3), 1.36 (s, 9H, CMe_3); MS (ESI) m/z 377 ($\text{M} + \text{H}$) $^+$; HRMS m/z calcd for $\text{C}_{20}\text{H}_{32}\text{N}_4\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 377.2547, found 377.2535 (+2.6 ppm error).

Lab Book Reference: JDF8_765 and JDF8_776

(2*R*,6*R*)-*tert*-Butyl 2,6-diallyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*R,R,S*)-50****



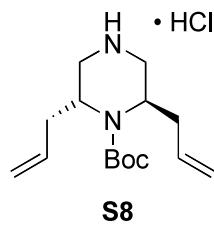
(Scheme 12)

s-BuLi (0.15 mL of a 1.3 M solution in hexanes, 0.20 mmol, 1.3 eq. was added dropwise to a stirred solution of *N*-Boc piperazine (*R,S*)-**40** (50 mg, 0.15 mmol, 1.0 eq.) and TMEDA (23 mg, 29 μL , 0.20 mmol, 1.3 eq.) in Et_2O (3 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 1 h.

Then, a solution of CuCN.2LiCl (0.076 mmol, 0.5 eq.) in THF (0.5 mL) was added dropwise. The resulting solution was stirred at -78°C for 1 h. Then, allyl bromide (37 mg, 26 μL , 0.3 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at -78°C for 15 min and then allowed to warm to rt over 30 min. Then, saturated $\text{NaHCO}_{3(\text{aq})}$ was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3×10 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 19:1 petrol- Et_2O as eluent gave *N*-Boc piperazine (*R,R,S*)-**50** (32 mg, 57%) as a colourless oil, R_F (9:1 petrol- Et_2O) 0.2; $[\alpha]_D -35.9$ (c 1.5 in CHCl_3); IR (CHCl_3) 2972, 2932, 2886, 2774, 1665 (C=O), 1430, 1370, 1346, 1301, 1196, 1151, 980, 906, 840, 747, 692, 658 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.27 (m, 4H, Ph), 7.25-7.20 (m, 1H, Ph), 5.75-5.62 (m, 2H, $\text{CH}=\text{CH}_2$), 5.05-4.94 (m, 4H, $\text{CH}=\text{CH}_2$), 3.74-3.68 (m, 2H, NCH), 3.34 (q, $J = 6.5$ Hz, 1H, CHMe), 2.66-2.42 (m, 6H, CH_2 + NCH), 2.36 (br d, $J = 6.0$ Hz, 1H, CH_2 or NCH), 2.33 (br d, $J = 6.0$ Hz, 1H, CH_2 or NCH), 1.44 (s, 9H, CMe_3), 1.34 (d, $J = 6.5$ Hz, 3H, CHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 156.0 (C=O), 144.0 (*ipso*-Ph), 135.6 ($\text{CH}=\text{CH}_2$), 128.2 (Ph), 127.5 (Ph), 126.9 (Ph), 116.9 ($\text{CH}=\text{CH}_2$), 79.6 (CMe_3), 64.4 (CHMe), 53.1 (NCH), 52.5 (NCH₂), 36.7 (CH_2), 28.4 (CMe_3), 19.9 (CHMe); MS (ESI) m/z 371 ($\text{M} + \text{H}$)⁺; HRMS m/z calcd for $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 371.2693, found 371.2689 (+0.7 ppm error).

Lab Book Reference: JDF8_743

(2*R*,6*R*)-*tert*-Butyl 2,6-diallylpiperazine-1-carboxylate hydrochloride (*R,R*)-S8****

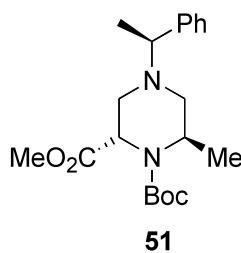


1-Chloroethylchloroformate (36 mg, 27 μL , 0.25 mmol, 3.0 eq.) was added to a stirred solution of *N*-Boc piperazine (*R,R,S*)-**50** (31 mg, 0.08 mmol, 1.0 eq.) in 1,2-dichloroethane (3 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 3 h. After cooling to rt, the solvent was evaporated under reduced pressure. The intermediate bis-carbamate was purified by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent, R_F (9:1 petrol-EtOAc) 0.2. A solution of bis-carbamate in MeOH (3 mL) was stirred and heated at reflux for 2 h. After cooling to rt, the solvent was evaporated under reduced pressure to give the *N*-Boc piperazine hydrochloride (*R,R*)-**S8** as a hydroscopic solid (14 mg, 55%), $[\alpha]_D -34.9$ (c 0.7 in CHCl_3); IR (CHCl_3) 2933, 2666 (NH_2^+), 1664 (C=O), 1564, 1438, 1366, 1347, 1313, 1240, 1196, 1150, 1103, 1047, 894, 741 cm^{-1} ; ^1H NMR (400

MHz, CDCl_3) δ 10.17 (s, 2H, NH_2^+), 5.84-5.72 (m, 2H, $\text{CH}=\text{CH}_2$), 5.41 (d, $J = 17.0$ Hz, 2H, $\text{CH}=\text{CH}_A\text{CH}_B$), 5.17 (d, $J = 10.0$ Hz, 2H, $\text{CH}=\text{CH}_A\text{CH}_B$), 4.01-3.90 (m, 2H, NCH), 3.45-3.23 (m, 4H, NCH), 2.59-2.48 (m, 2H, CH_2), 2.48-2.38 (m, 2H, CH_2), 1.47 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 153.8 (C=O), 133.0 ($\text{CH}=\text{CH}_2$), 120.0 ($\text{CH}=\text{CH}_2$), 81.1 (CMe_3), 48.9 (NCH), 40.7 (NCH₂), 37.8 (CH_2), 28.3 (CMe_3); MS (ESI) m/z 267 ($\text{M} + \text{H}$)⁺; HRMS m/z calcd for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$)⁺ 267.2067, found 267.2055 (+4.3 ppm error).

Lab Book Reference: JDF8_777

(2*S*,6*R*)-1-*tert*-Butyl 2-methyl 6-methyl-4-((*S*)-1-phenylethyl)piperazine-1,2-dicarboxylate (*S,R,S*)-51

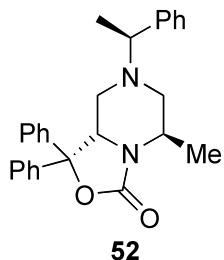


(Scheme 12)

Using general procedure B, *s*-BuLi (0.16 mL of a 1.3 M solution in hexanes, 0.21 mmol, 1.3 eq.), *N*-Boc piperazine (*R,S*)-45 (50 mg, 0.16 mmol, 1.0 eq.), TMEDA (25 mg, 32 μL , 0.21 mmol, 1.3 eq.) in Et_2O (3 mL) for 1 h and a methyl chloroformate (31 mg, 25 μL 0.33 mmol, 2.0 eq.), worked up with saturated $\text{NaHCO}_{3(\text{aq})}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1:7:3 petrol- Et_2O as eluent gave *N*-Boc piperazine (*R,R,S*)-51 (46 mg, 77%) as pale yellow oil, R_F (8:2 petrol- Et_2O) 0.2; $[\alpha]_D -45.2$ (c 1.1 in CHCl_3); IR (CHCl_3) 2932, 2777, 1716 (C=O, ester), 1665 (C=O, Boc), 1468, 1431, 1347, 1298, 1235, 1151, 1068, 1011, 895, 847 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.20 (m, 5H, Ph), 4.20 (dd, $J = 7.5, 4.0$ Hz, 1H, NCH), 3.99-3.88 (m, 1H, NCH), 3.72 (s, 3H, CO_2Me), 3.32 (q, $J = 6.5$ Hz, 1H, CHMe), 2.86 (br s, 1H, NCH), 2.45 (br s, 2H, NCH), 2.31 (br s, 1H, NCH), 1.42 (s, 9H, CMe_3), 1.32 (d, $J = 6.5$ Hz, 3H, CHMe), 1.26-1.20 (m, 3H, CHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 172.1 (CO_2Me), 155.6 (NC=O), 143.5 (*ipso*-Ph), 128.2 (Ph), 127.4 (Ph), 127.0 (Ph), 80.6 (CMe_3), 64.1 (CHMe), 56.1 (br, NCH₂), 52.2 (NCH₂), 52.0 (CO_2Me), 49.0 (NCH), 28.1 (CMe_3), 19.7 (CHMe), 17.9 (CHMe) (NCH not resolved); MS (ESI) m/z 363 ($\text{M} + \text{H}$)⁺; HRMS m/z calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_4$ ($\text{M} + \text{H}$)⁺ 363.2278, found 363.2272 (+1.2 ppm error).

Lab Book Reference: JDF8_749

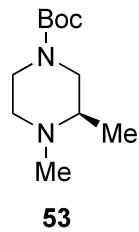
(5*R*,8a*S*)-5-Methyl-1,1-diphenyl-7-((S)-1-phenylethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (*R,S,S*)-52



(Scheme 12)

Using general procedure B, *s*-BuLi (0.16 mL of a 1.3 M solution in hexanes, 0.21 mmol, 1.3 eq.), *N*-Boc piperazine (*R,S*)-**45** (50 mg, 0.16 mmol, 1.0 eq.), TMEDA (25 mg, 32 μ L, 0.21 mmol, 1.3 eq.) in Et₂O (3 mL), with a solution of benzophenone (60 mg, 0.33 mmol, 2.0 eq.) in Et₂O (0.5 mL), worked up with saturated NaHCO_{3(aq)} (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et₂O as eluent gave oxazolidinone (*R,S,S*)-**52** (33 mg, 49%) as a white solid, mp 116-119 °C; *R*_F (8:2 petrol-Et₂O) 0.2; [α]_D -177.1 (*c* 1.6 in CHCl₃); IR (CHCl₃) 2983, 2963, 1718 (C=O), 1469, 1428, 1397, 1298, 1216, 1184, 1054, 1017, 986, 691, 654 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.53-7.46 (m, 2H, Ph), 7.42-7.17 (m, 13H, Ph), 4.67 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 4.06-3.98 (m, 1H, NCH), 3.28 (q, *J* = 6.5 Hz, 1H, CHMe), 2.70 (ddd, *J* = 11.0, 3.5, 1.5 Hz, 1H, NCH), 2.51 (br d, *J* = 11.5 Hz, 1H, NCH), 1.99 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH), 1.42 (t, *J* = 11.0 Hz, 1H, NCH), 1.31 (d, *J* = 6.5 Hz, 3H, CHMe), 1.20 (d, *J* = 6.5 Hz, 3H, CHMe); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.6 (C=O), 143.3 (*ipso*-Ph), 142.3 (*ipso*-Ph), 138.9 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 128.3 (Ph), 128.2 (Ph), 127.8 (Ph), 127.2 (Ph), 127.0 (Ph), 126.1 (Ph), 125.9 (Ph), 85.3 (CMe₃), 64.1 (CHMe), 58.0 (NCH), 54.3 (NCH₂), 52.8 (NCH₂), 46.4 (NCH), 19.5 (CHMe), 16.3 (CHMe); MS (ESI) *m/z* 413 (M + H)⁺; HRMS *m/z* calcd for C₂₇H₂₈N₂O₂ (M + H)⁺ 413.2224, found 413.2216 (+1.7 ppm error).

Lab Book Reference: JDF8_740

(R)-*tert*-Butyl 3,4-dimethylpiperazine-1-carboxylate (R)-53

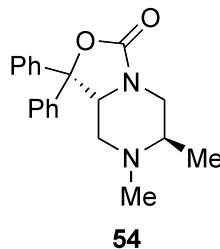
(Scheme 12)

A solution of *N*-Boc piperazine (*R,S*)-**45** (244 mg, 0.80 mmol, 1.0 eq.) in THF (5 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (122 mg, 3.2 mmol, 4.0 eq.) in THF (5 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at reflux for 16 h. After cooling to 0 °C, the mixture was diluted with Et₂O (10 mL). Water (122 μL), 20% NaOH_(aq) (244 μL) and water (122 μL) were sequentially added dropwise and the mixture stirred for 15 min. Then, anhydrous MgSO₄ was added and the mixture stirred for 30 min. The solids were removed by filtration through Celite® and washed with Et₂O (10 mL). The filtrate was concentrated under reduced pressure to give the crude amine (153 mg, 88%) as a pale yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 7.27-7.33 (m, 4H, Ph), 7.19-7.25 (m, 1H, Ph), 3.33 (q, *J* = 6.5 Hz, 1H, CHMe), 2.92 (br d, *J* = 11.0 Hz, 1H, NCH), 2.67-2.77 (m, 1H, NCH), 2.58-2.67 (m, 1H, NCH), 2.28 (s, 3H, NMe), 2.09-2.28 (m, 3H, NCH), 1.91 (m, 1H, NCH), 1.36 (d, *J* = 6.5 Hz, 3H, CHMe), 1.08 (d, *J* = 6.5 Hz, 3H, CHMe). The crude product was used in the next step without further purification (≥90% purity by ¹H NMR spectroscopy). Then, 10% Pd/C (20 mg) was added to a stirred solution of the crude amine (153 mg, 0.70 mmol, 1.0 eq.) in MeOH (10 mL) and conc. HCl (5 drops). 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 mixture was filtered through Celite® and washed with MeOH (20 mL). The filtrate was evaporated under reduced pressure to give crude secondary amine hydrochloride. A solution of di-*tert*-butyl dicarbonate (183 mg, 0.84 mmol, 1.2 eq.) in CH₂Cl₂ (20mL) was added dropwise a stirred solution of secondary amine hydrochloride (max. 0.7 mmol, 1.0 eq.) in CH₂Cl₂ (3 mL) and Et₃N (354 g, 488 mL, 3.5 mmol, 5.0 eq.) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 20% NaOH_(aq) (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 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 19:1 CH₂Cl₂-MeOH as eluent gave *N*-Boc piperazine (R)-**53** (130 mg, 87%) as a pale yellow oil, *R*_F (19:1

$\text{CH}_2\text{Cl}_2\text{-MeOH}$ 0.1; $[\alpha]_D$ -0.3 (c 0.9 in CHCl_3); IR (CHCl_3) 2934, 2889, 2809, 2755, 1659 (C=O), 1435, 1406, 1370, 1345, 1319, 1270, 1252, 1227, 1135, 1093, 1070, 1049, 1024, 964, 868 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.66-3.97 (m, 2H, NCH), 3.00 (br t, J = 11.0, 1H, NCH), 2.71 (br d, J = 11.5 Hz, 1H, NCH), 2.59 (br s, 1H, NCH), 2.27 (s, 3H, NMe), 2.15 (td, J = 11.5, 3.0 Hz, 1H, NCH), 1.96-2.07 (m, 1H, NCH), 1.42 (s, 9H, CMe_3), 1.04 (d, J = 6.0 Hz, 3H, CHMe); ^{13}C NMR (100.6 MHz, CDCl_3) (mixture of rotamers) δ 154.5 (C=O), 79.6 (CMe_3), 57.5 (NCH), 54.9 (NCH₂), 50.2 (NCH₂), 49.2 (NCH₂), 44.0 (NCH₂), 43.2 (NCH₂), 42.4 (NMe), 28.2 (CMe_3), 16.3 (CHMe); MS (ESI) m/z 215 [(M + H)⁺, 100], 159 [(M - CMe_3)⁺, 20]; HRMS m/z calcd for $\text{C}_{11}\text{H}_{22}\text{N}_2\text{O}_2$ (M + H)⁺ 215.1754, found 215.1746 (+3.9 ppm error).

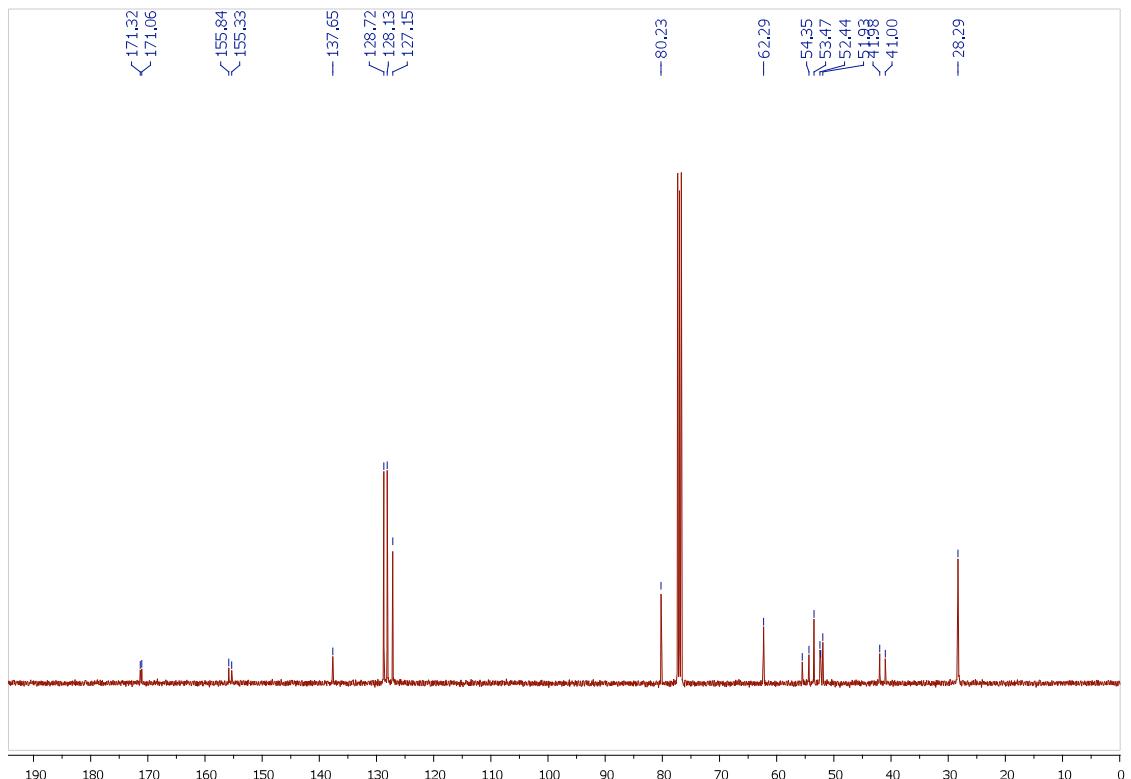
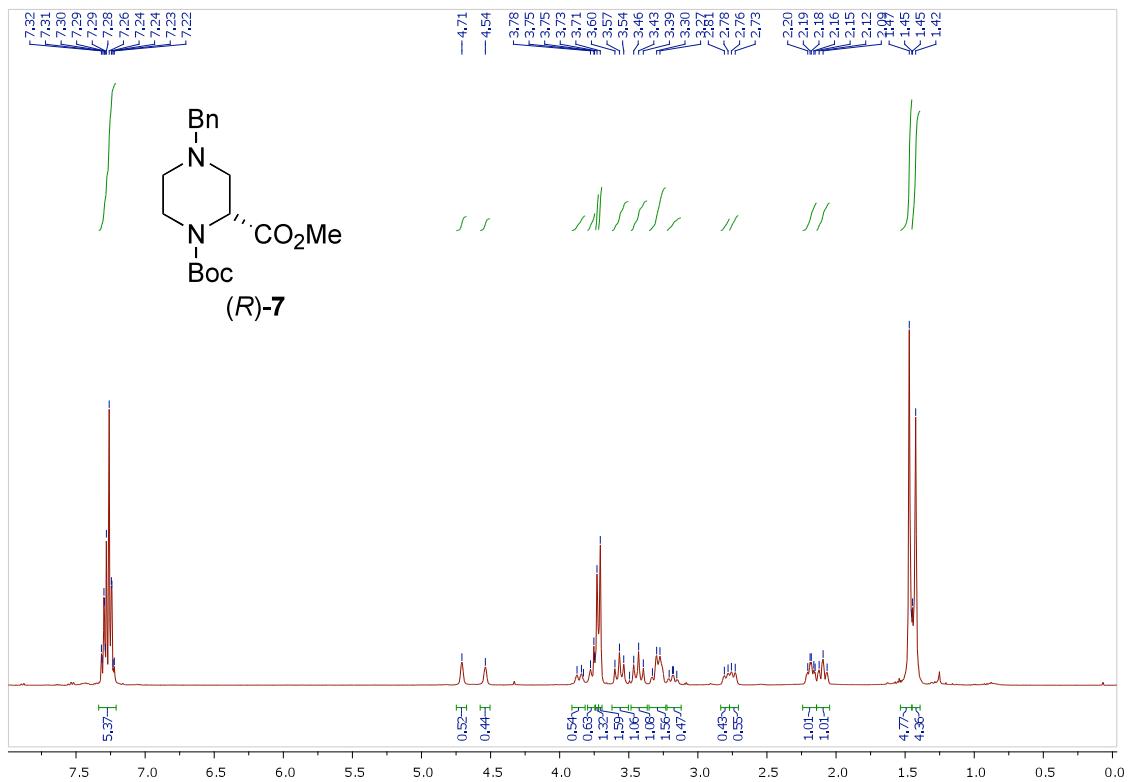
Lab Book Reference: JDF9_810 and JDF9_812

(6*R*,8*R*)-6,7-Dimethyl-1,1-diphenyltetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (*R,R*)-54

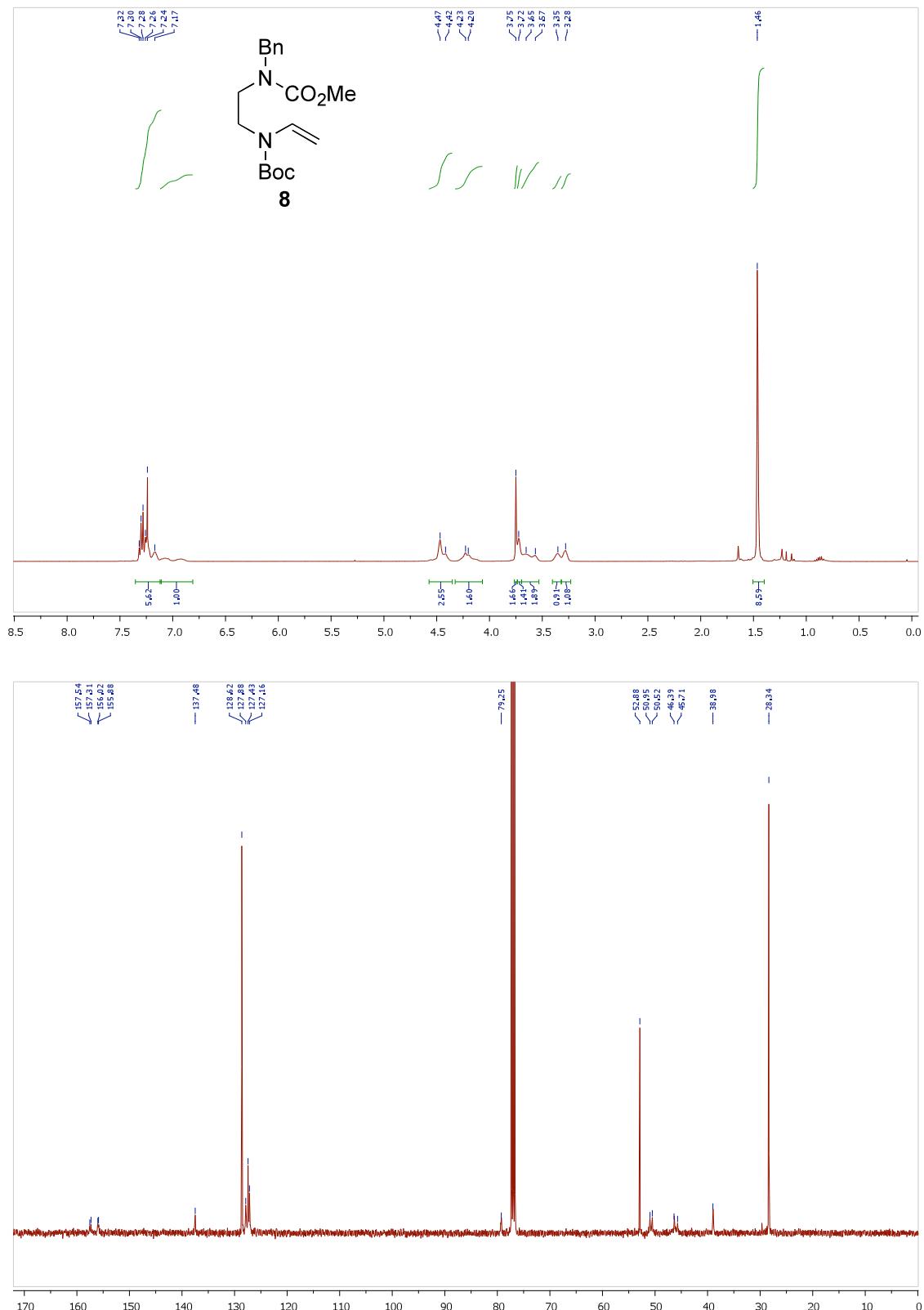


(Scheme 12)

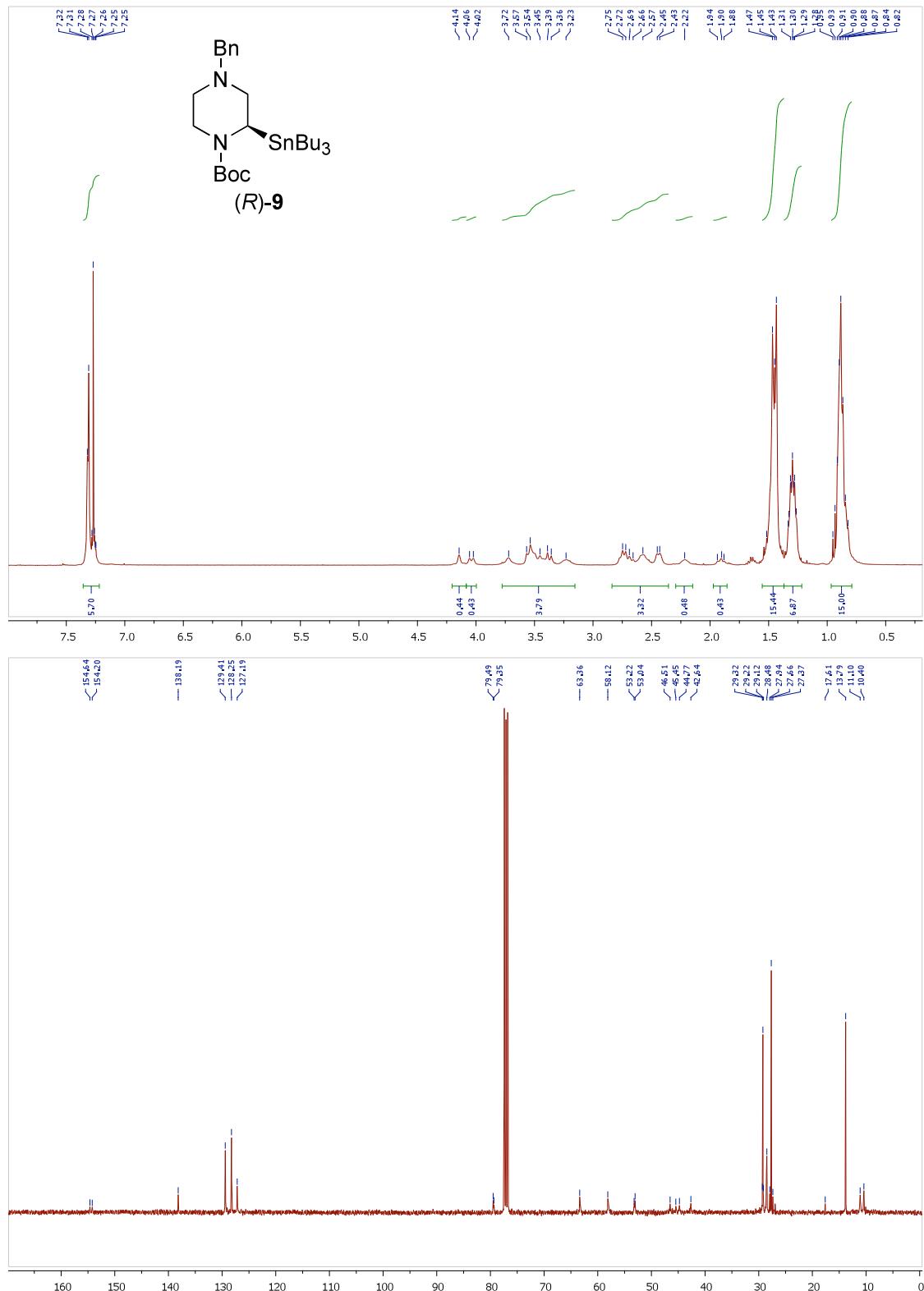
Using general procedure B, *s*-BuLi (0.14 mL of a 1.3 M solution in hexanes, 0.18 mmol, 1.3 eq.), *N*-Boc piperazine (*R*)-**53** (30 mg, 0.14 mmol, 1.0 eq.), TMEDA (21 mg, 27 μL , 0.18 mmol, 1.3 eq.) in Et_2O (3 mL) for 1 h and a solution of benzophenone (51 mg, 0.28 mmol, 2.0 eq.) in Et_2O (1 mL), worked up with saturated $\text{NaHCO}_{3\text{(aq)}}$ (10 mL) gave the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave oxazolidinone (*R,R*)-**54** (24 mg, 53%) as a white solid, mp 184-187 $^{\circ}\text{C}$; R_F (EtOAc) 0.2; $[\alpha]_D$ +151.4 (c 1.2 in CHCl_3); IR (CHCl_3) 2972, 2885, 2813, 1724 (C=O), 1471, 1427, 1322, 1196, 1069, 996, 949, 915, 746 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.47-7.55 (m, 2H, Ph), 7.26-7.42 (m, 8H, Ph), 4.63 (dd, J = 11.0, 3.0 Hz, 1H, NCH), 3.76 (dd, J = 13.5 Hz, 3.5, 1H, NCH), 2.79 (dd, J = 13.0, 11.5 Hz, 1H, NCH), 2.46 (dd, J = 11.5, 3.5 Hz, 1H, NCH), 2.21 (s, 3H, NMe) 1.99-2.11 (m, 1H, NCH), 1.70 (t, J = 11.5 Hz, 1H, NCH), 1.08 (d, J = 6.5 Hz, 3H, CHMe); ^{13}C NMR (100.6 MHz, CDCl_3) δ 155.9 (C=O), 142.2 (*ipso*-Ph), 138.5 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 127.9 (Ph), 125.9 (Ph), 125.7 (Ph), 85.2 (Ph_2CO), 60.8 (NCH), 57.6 (NCH₂), 56.9 (NCH), 47.8 (NCH₂), 42.7 (NMe), 16.5 (CHMe); MS (ESI) m/z 323 (M + H)⁺; HRMS m/z calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$ (M + H)⁺ 323.1754, found 323.1741 (+3.7 ppm error). Lab Book Reference: JDF9_817

2 $^1\text{H}/^{13}\text{C}$ NMR Spectra and CSP-GC/HPLC Data400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

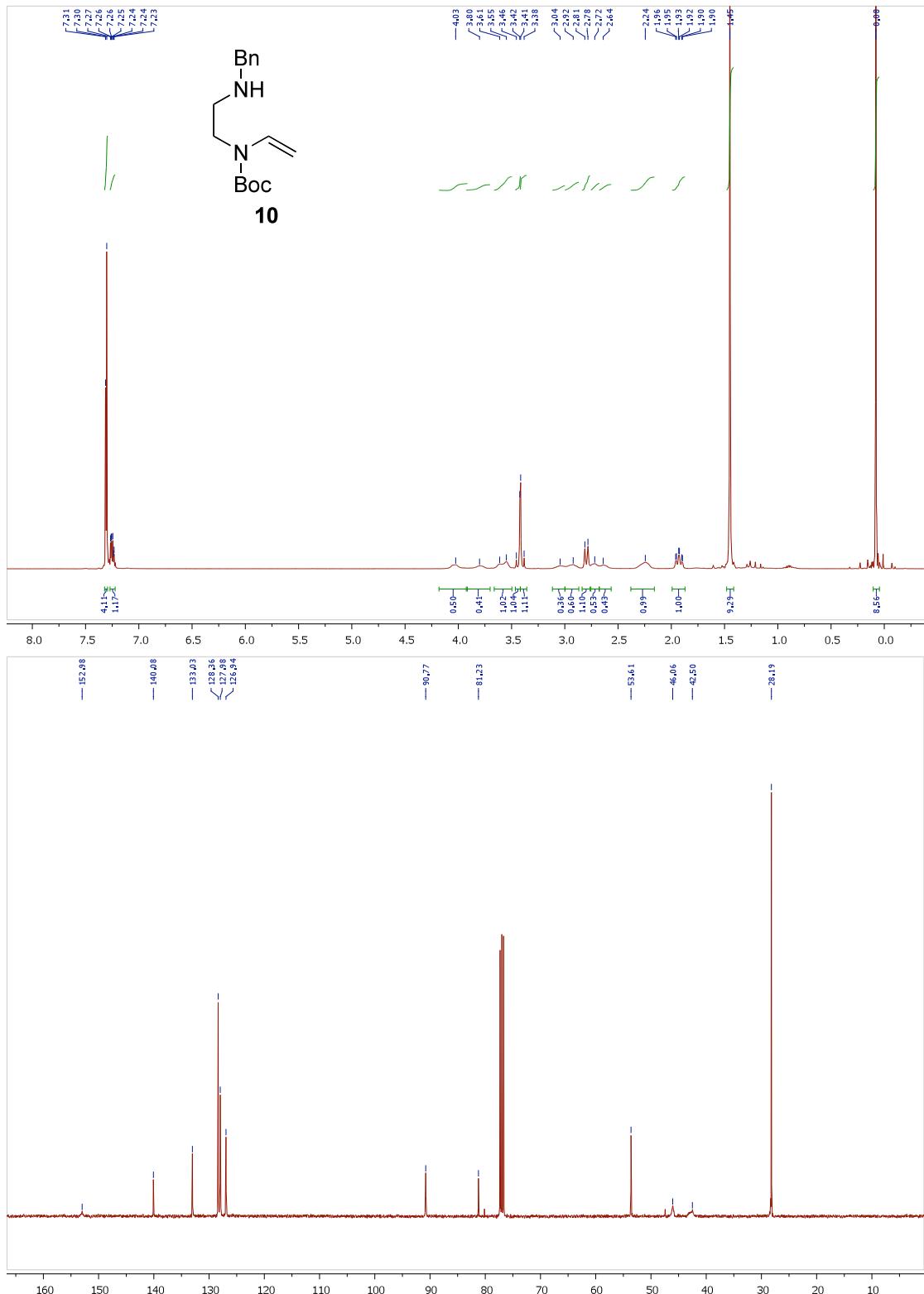
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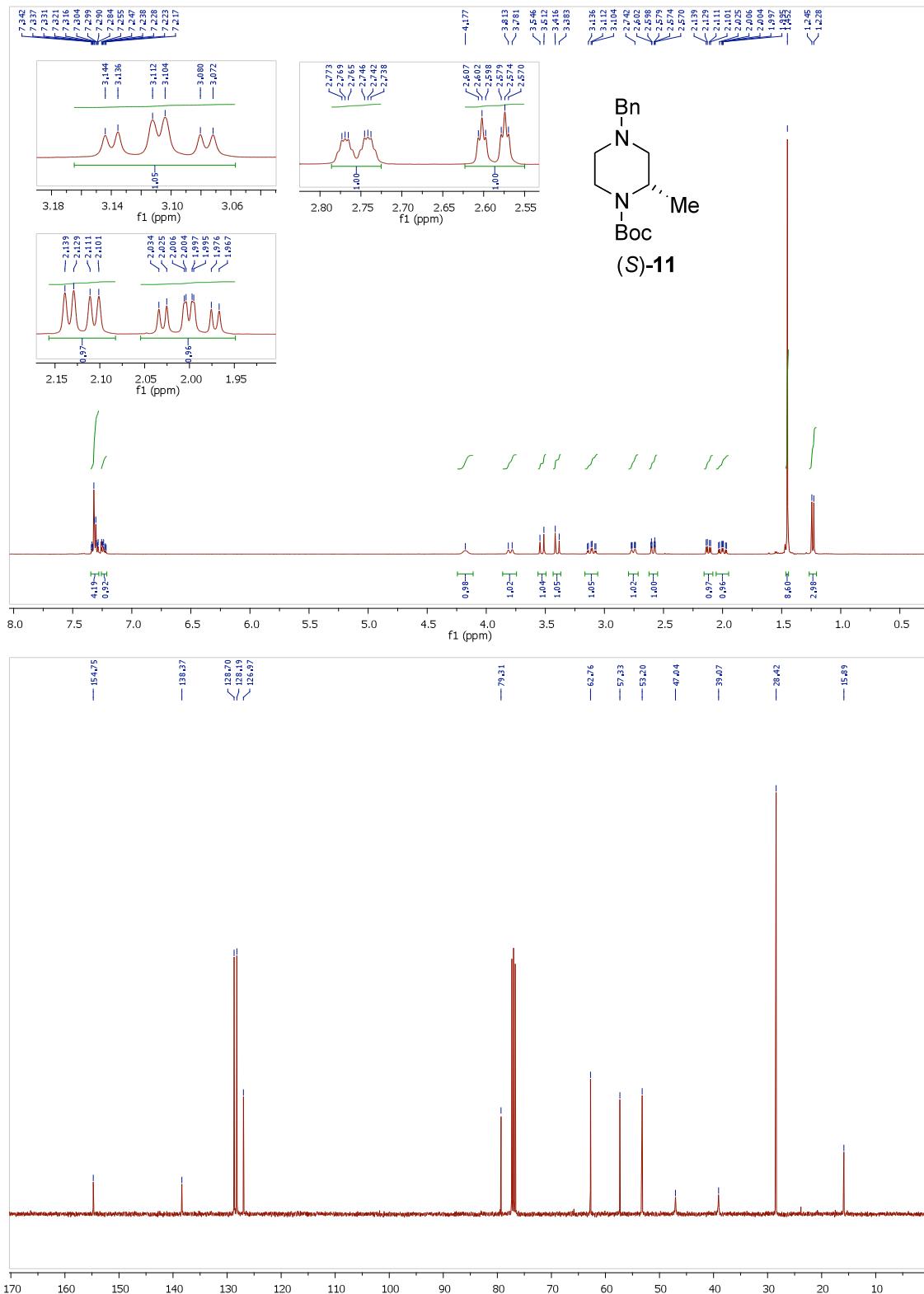
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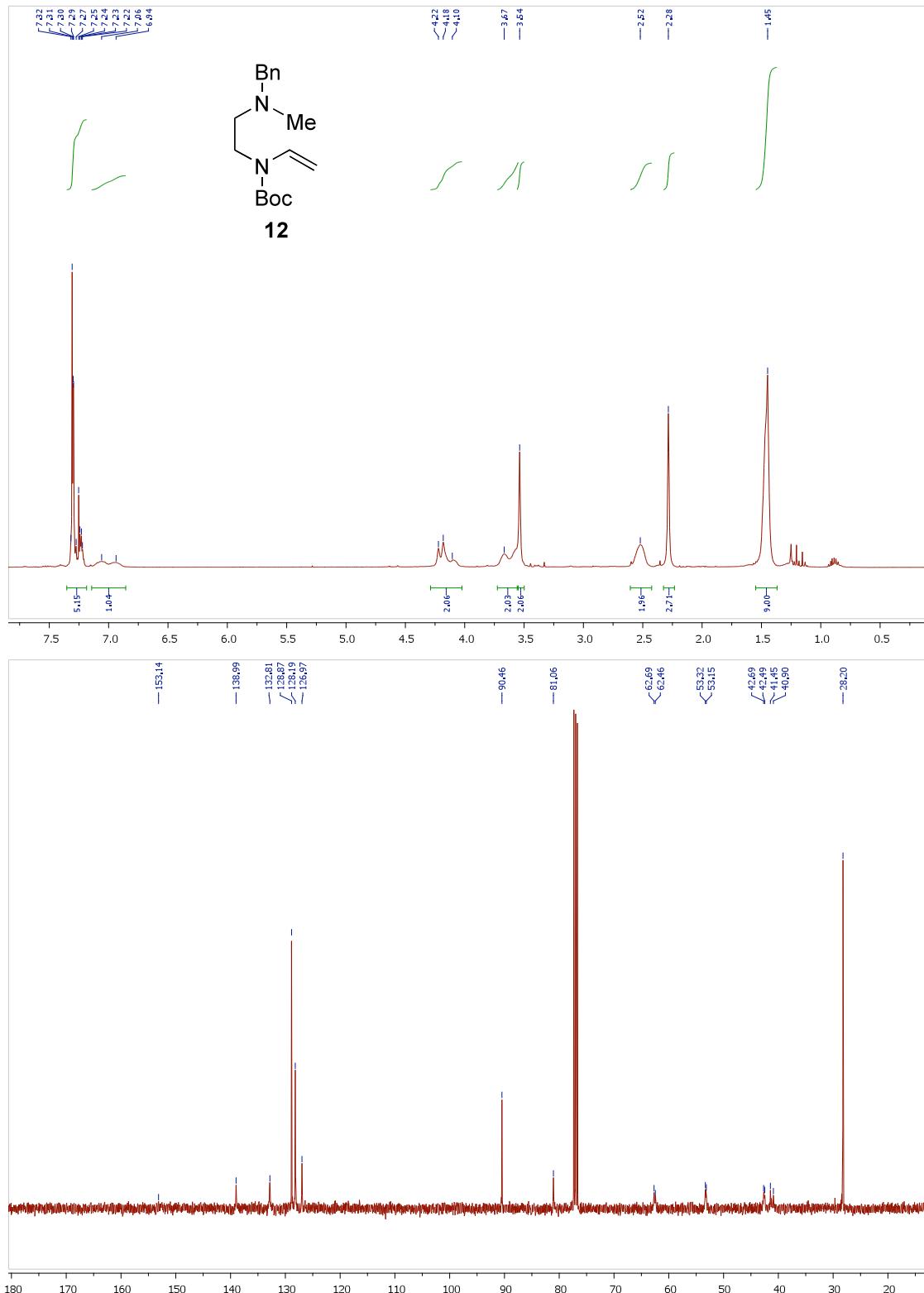
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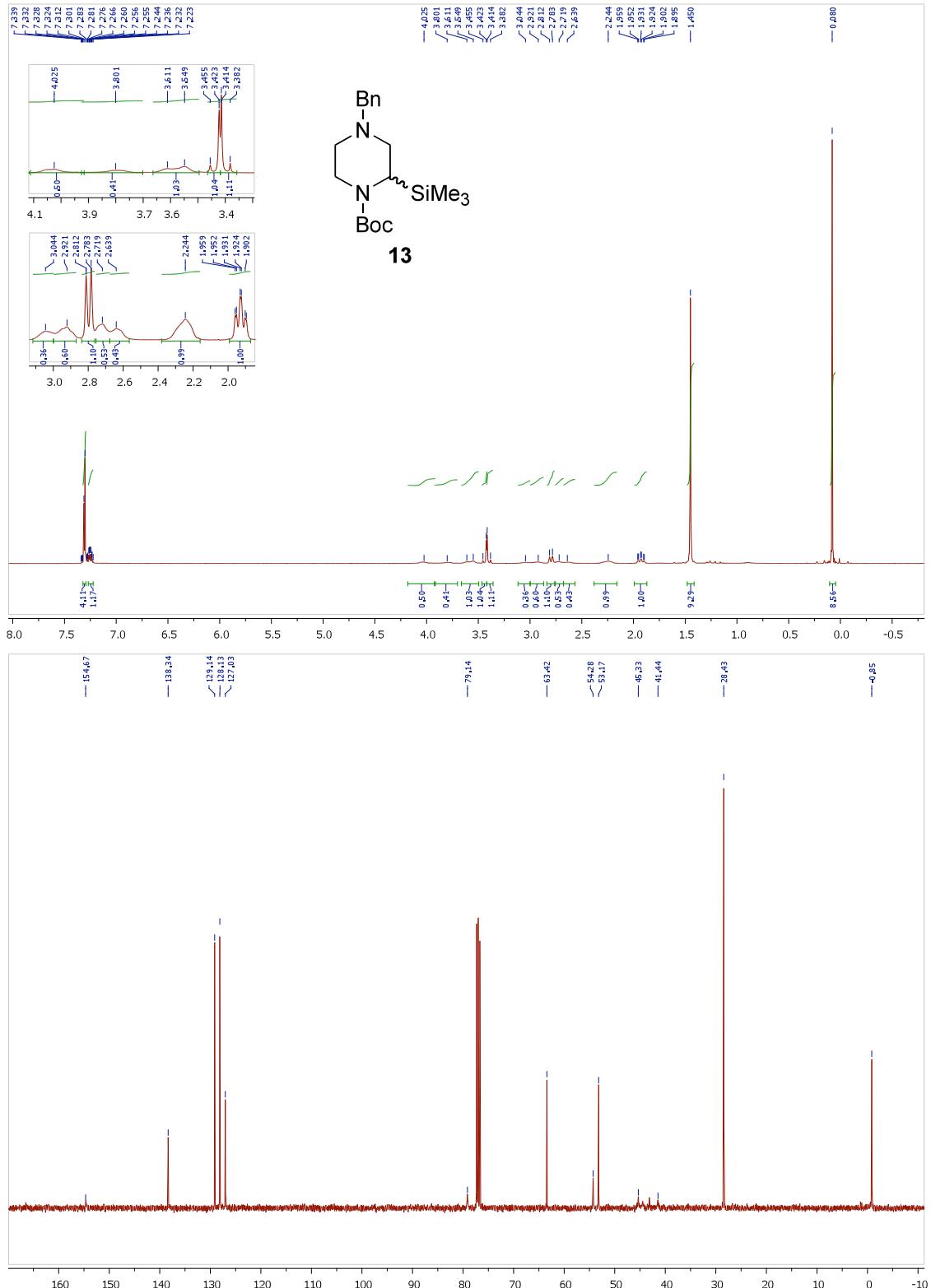


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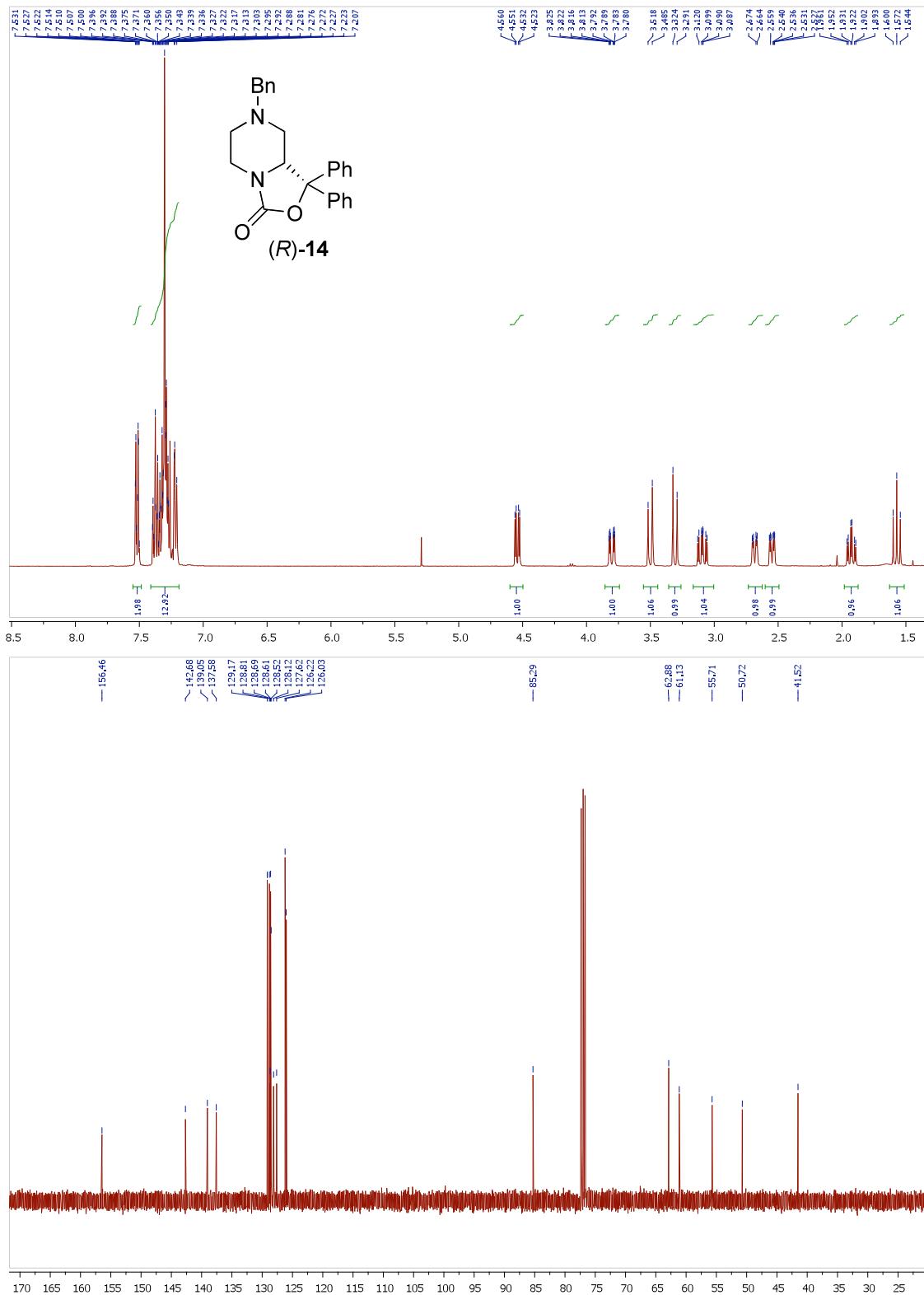


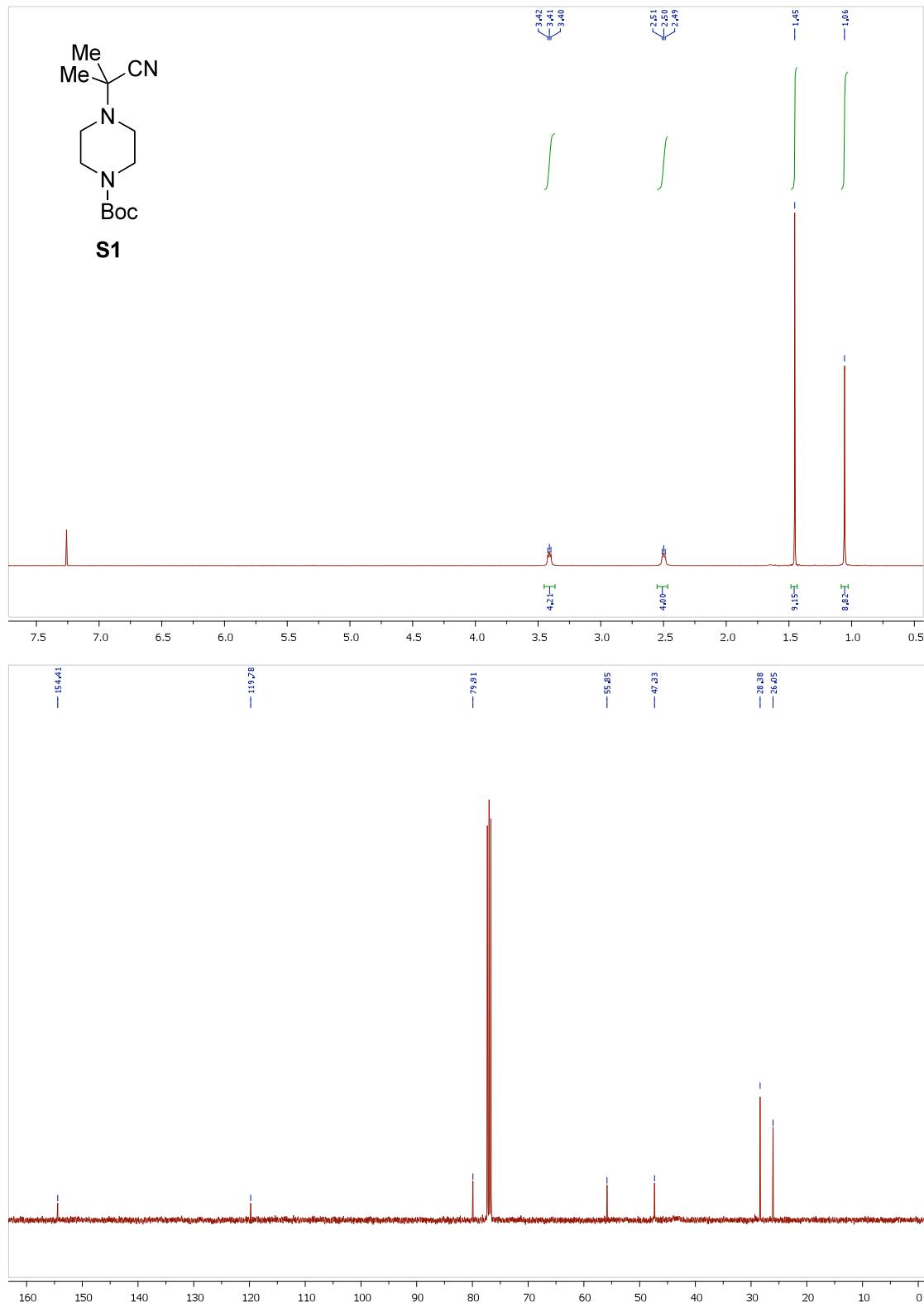
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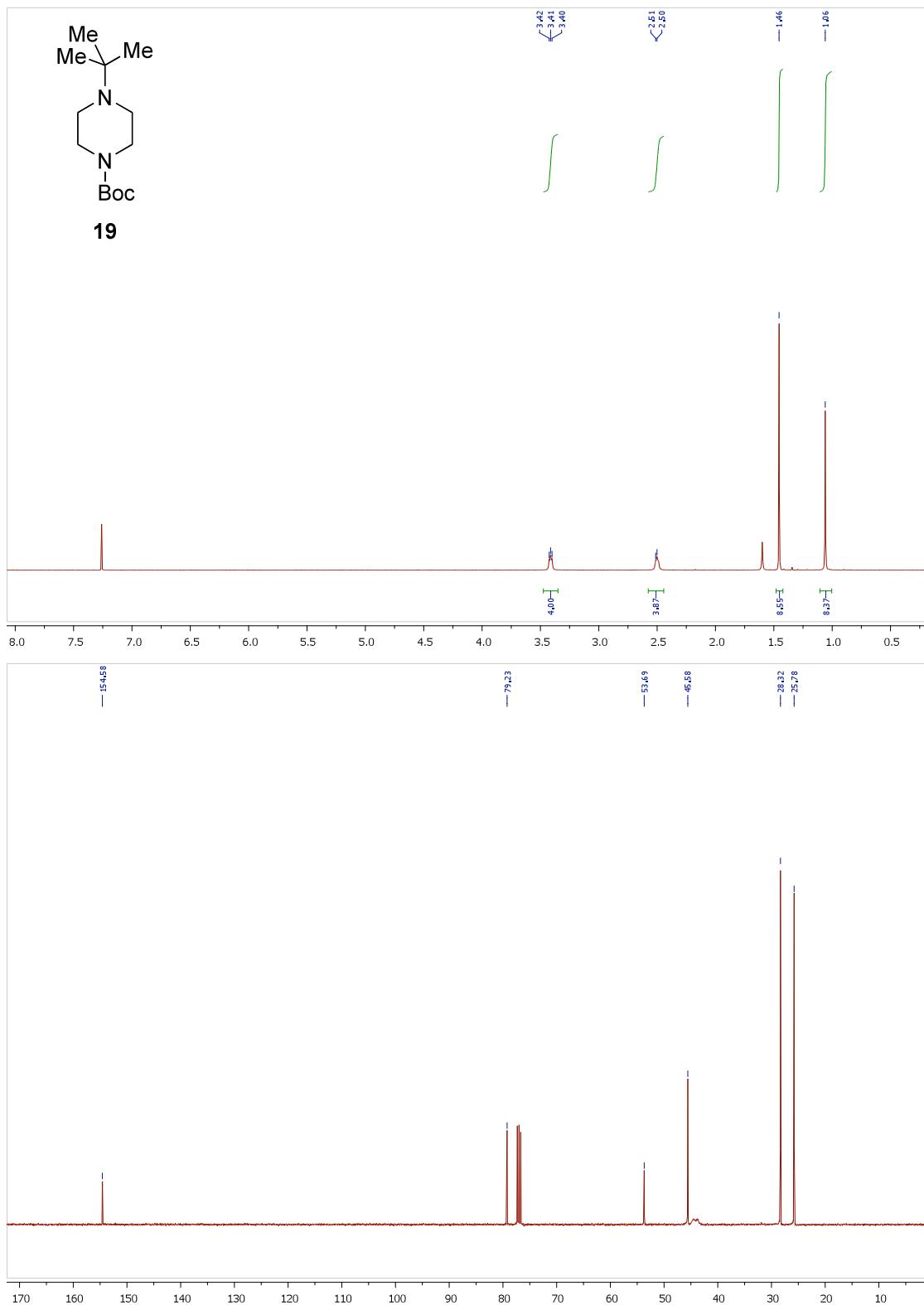


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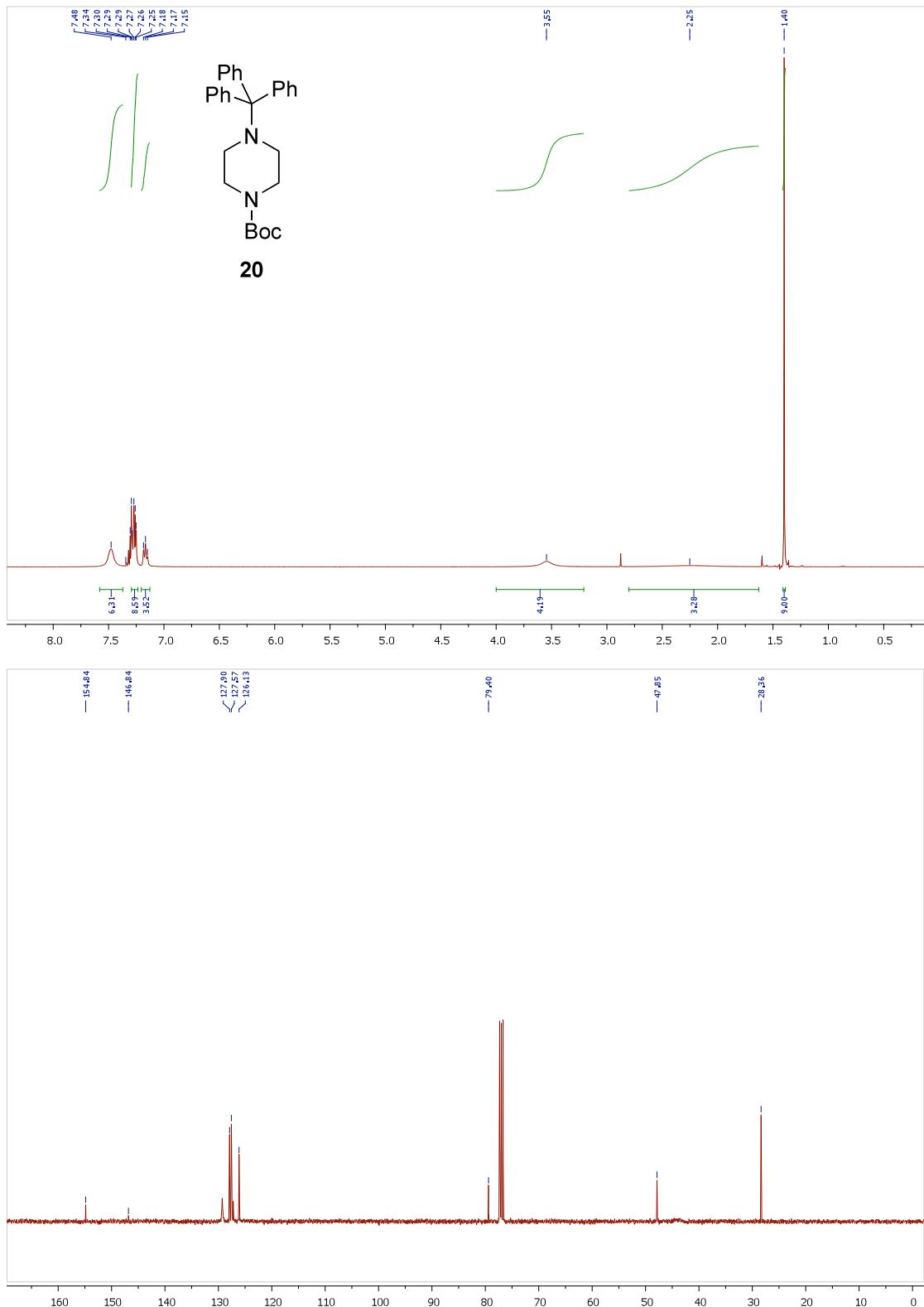
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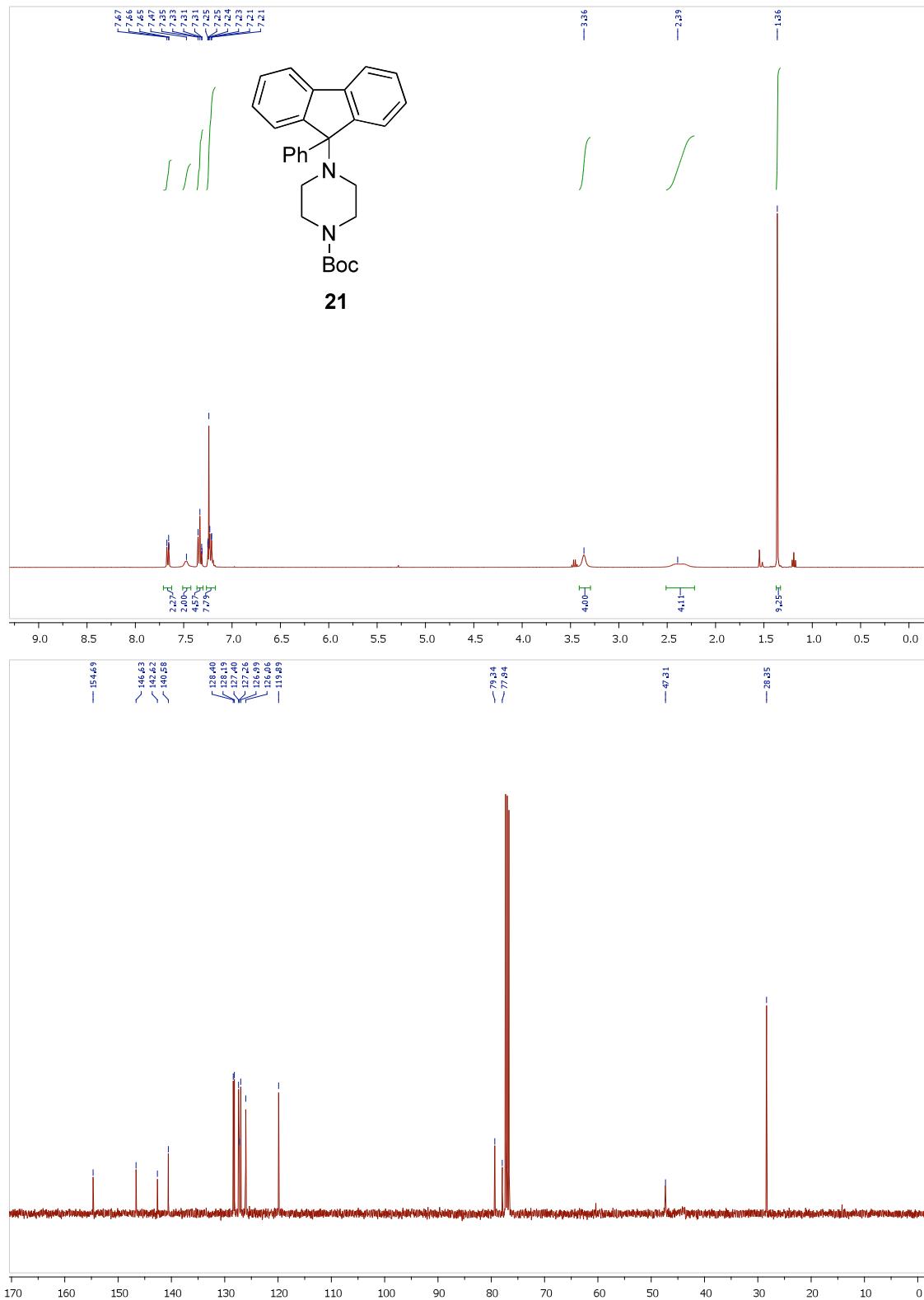


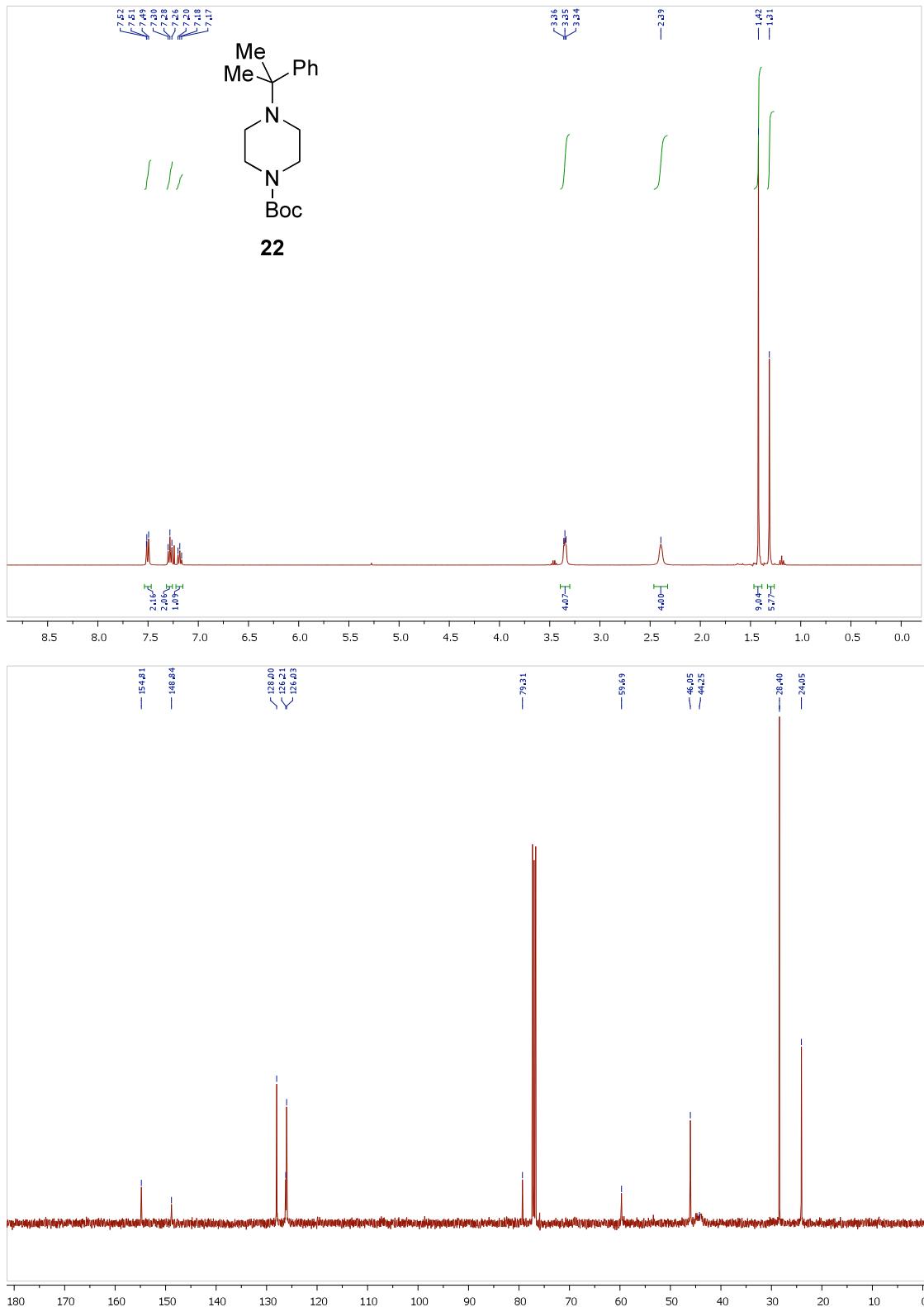
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

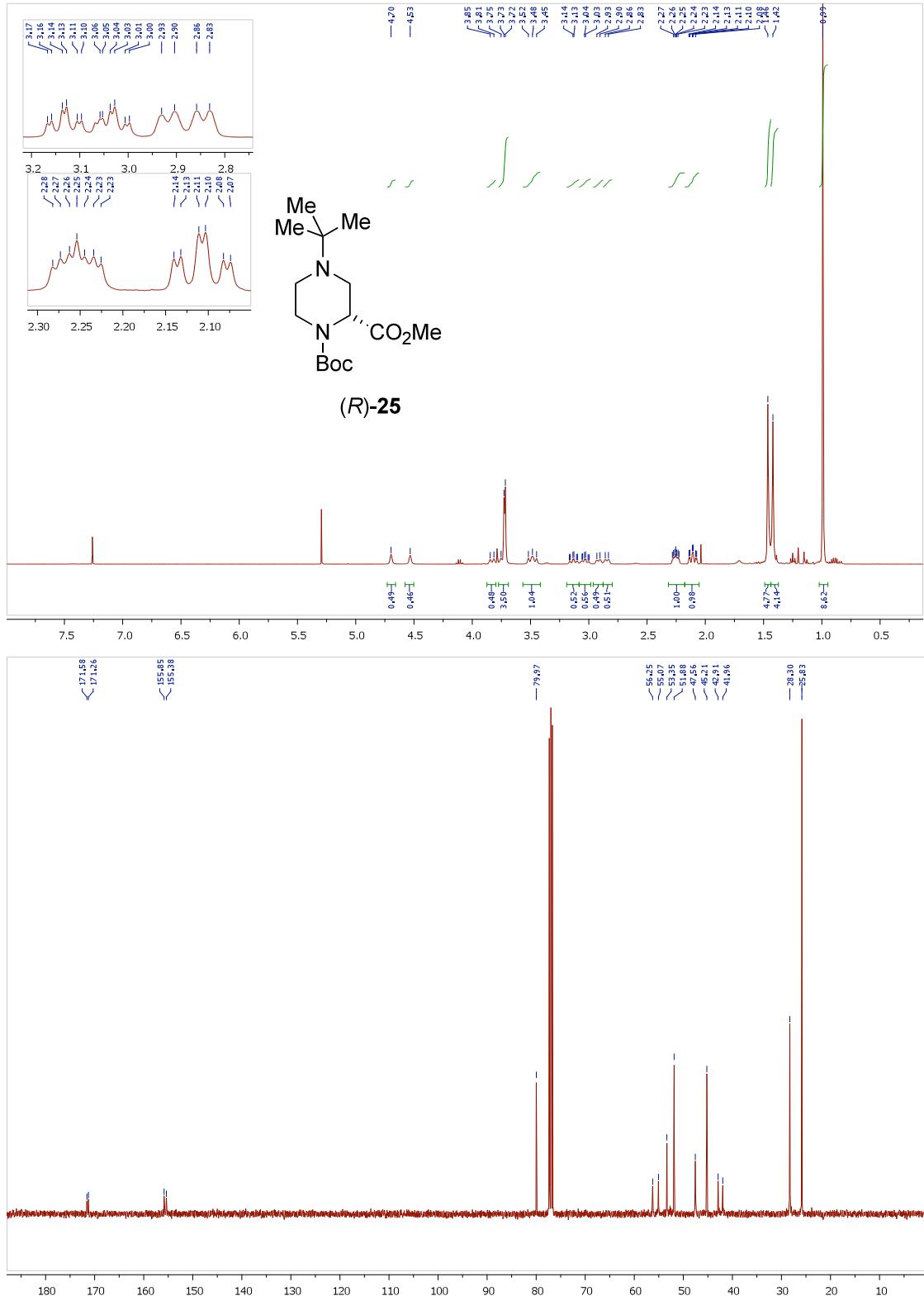
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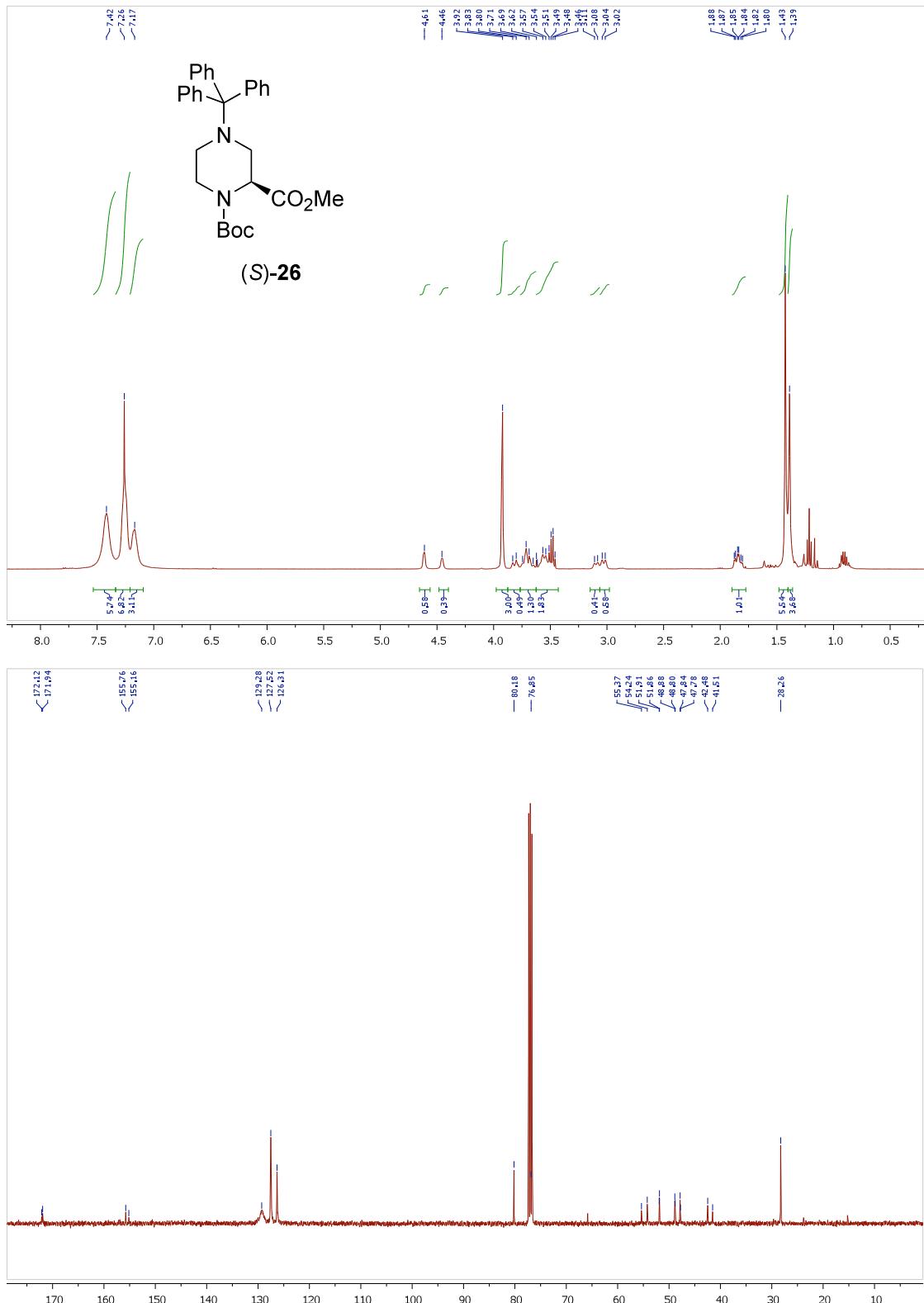
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400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

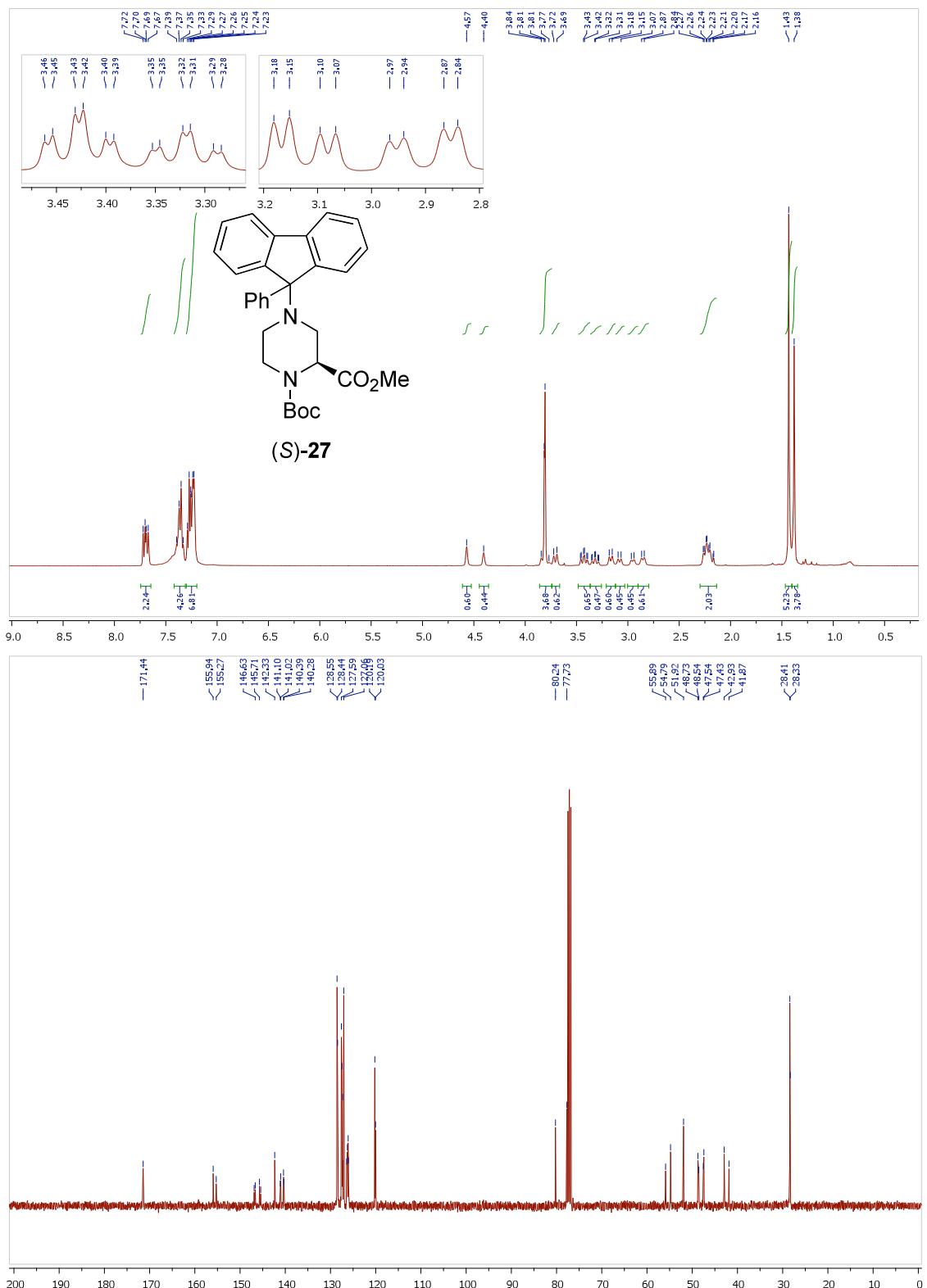
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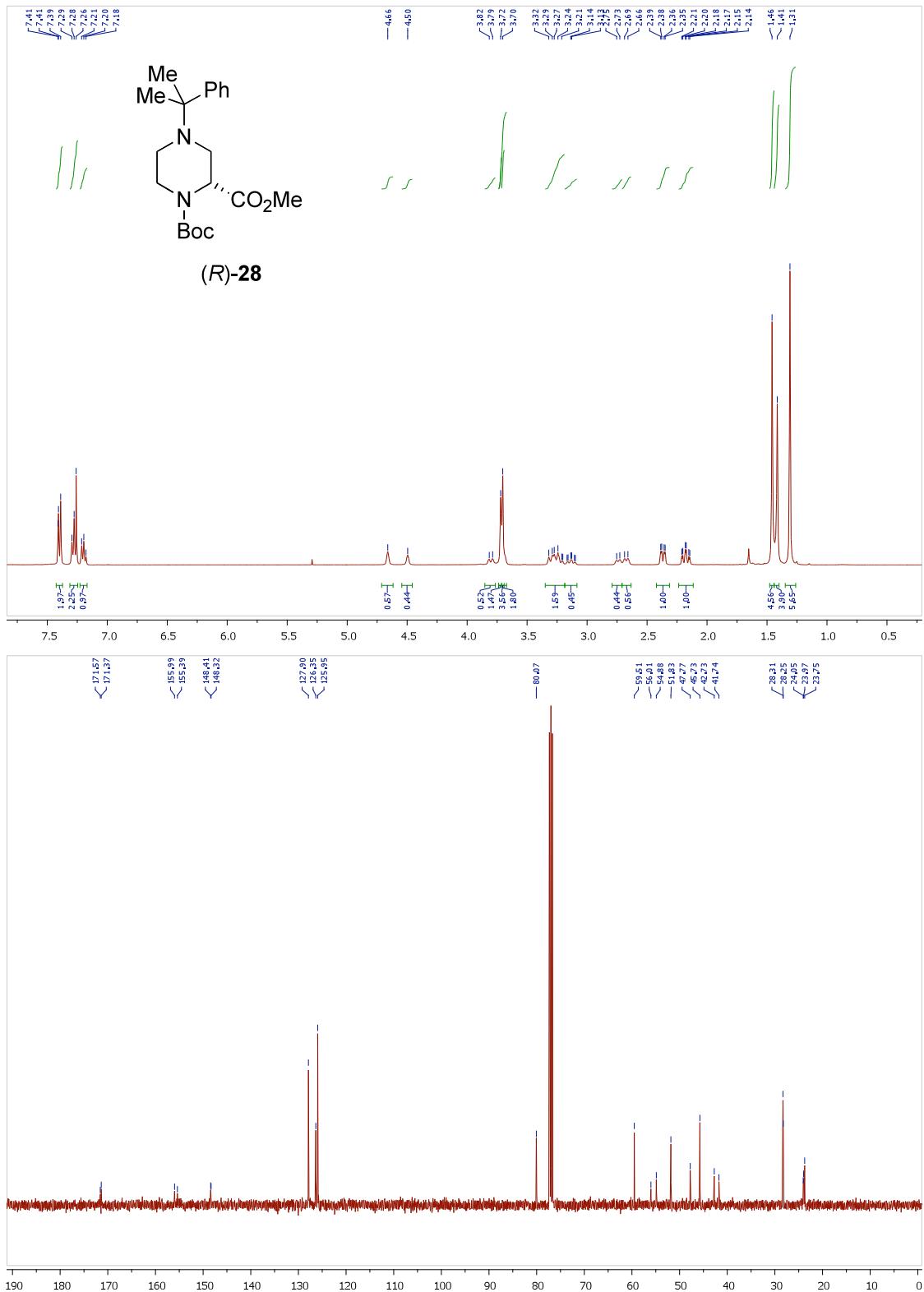
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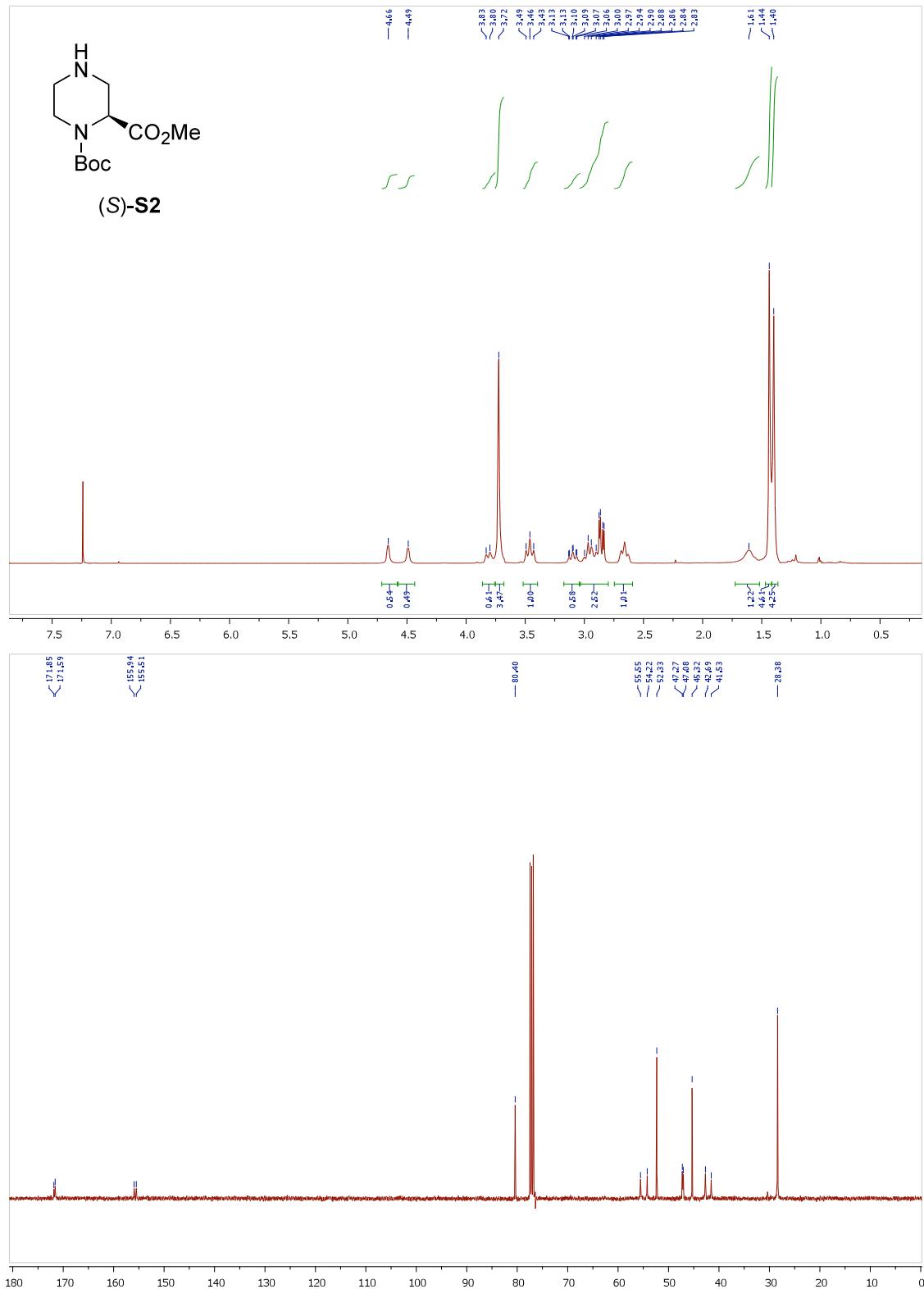
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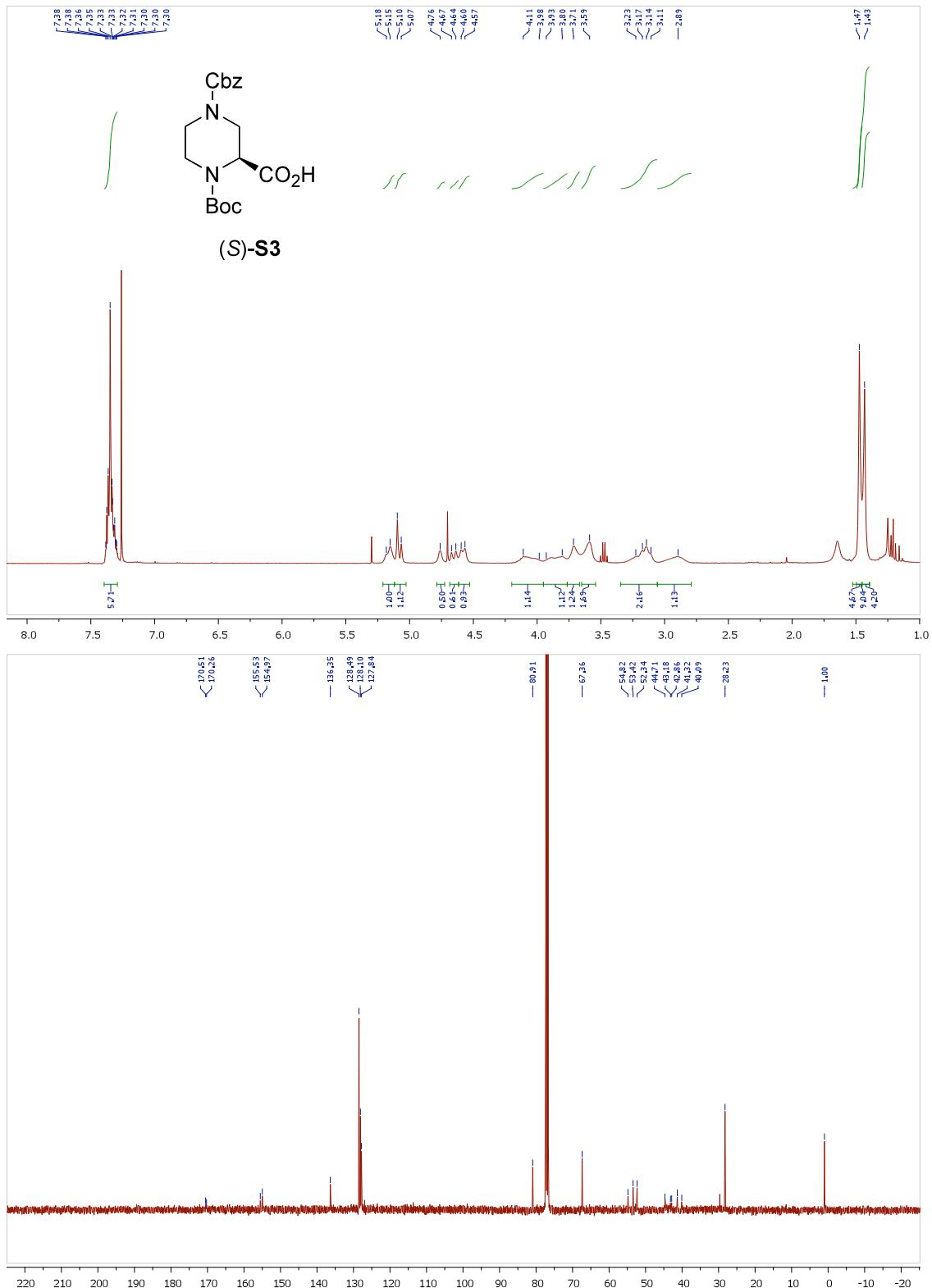
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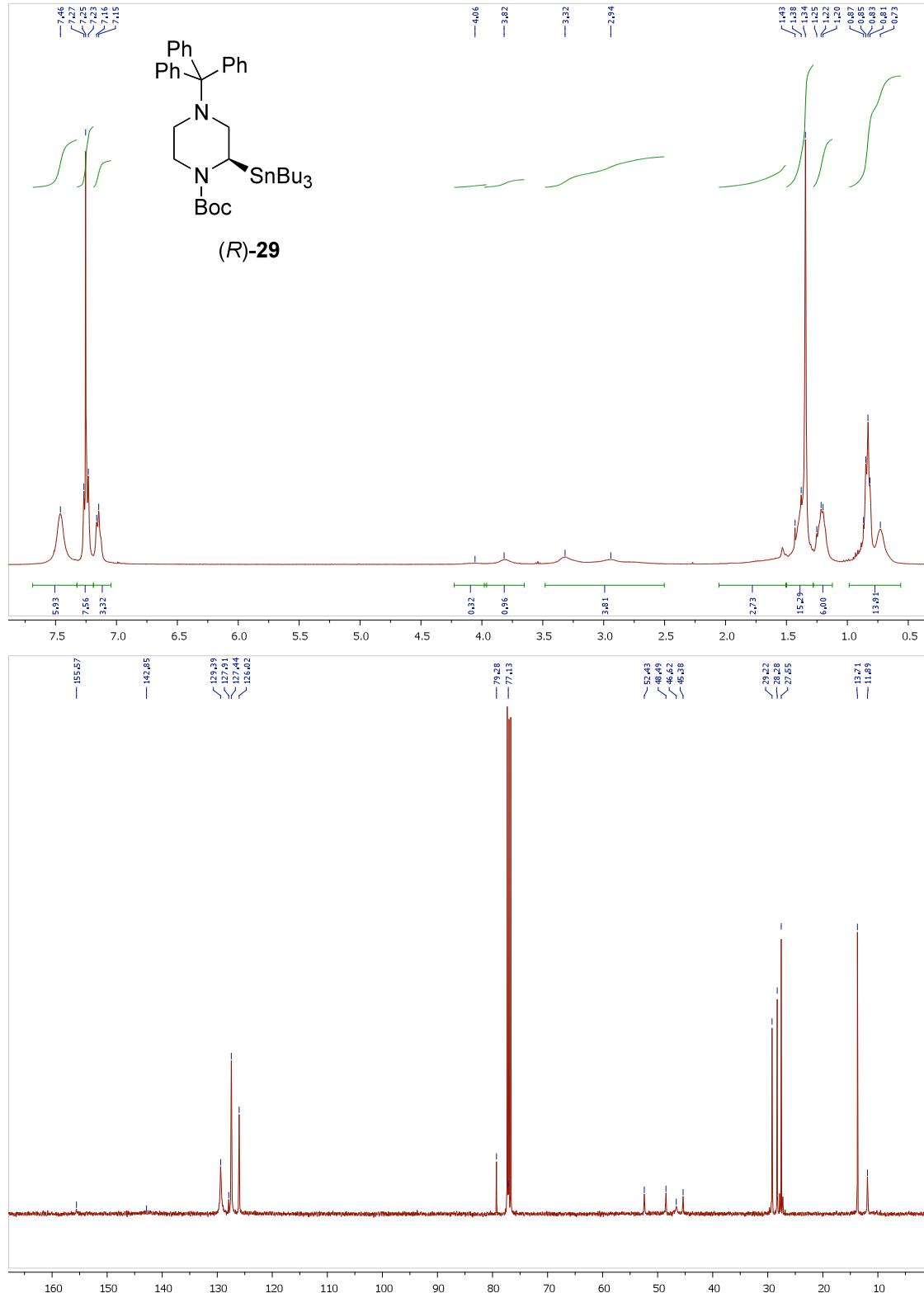
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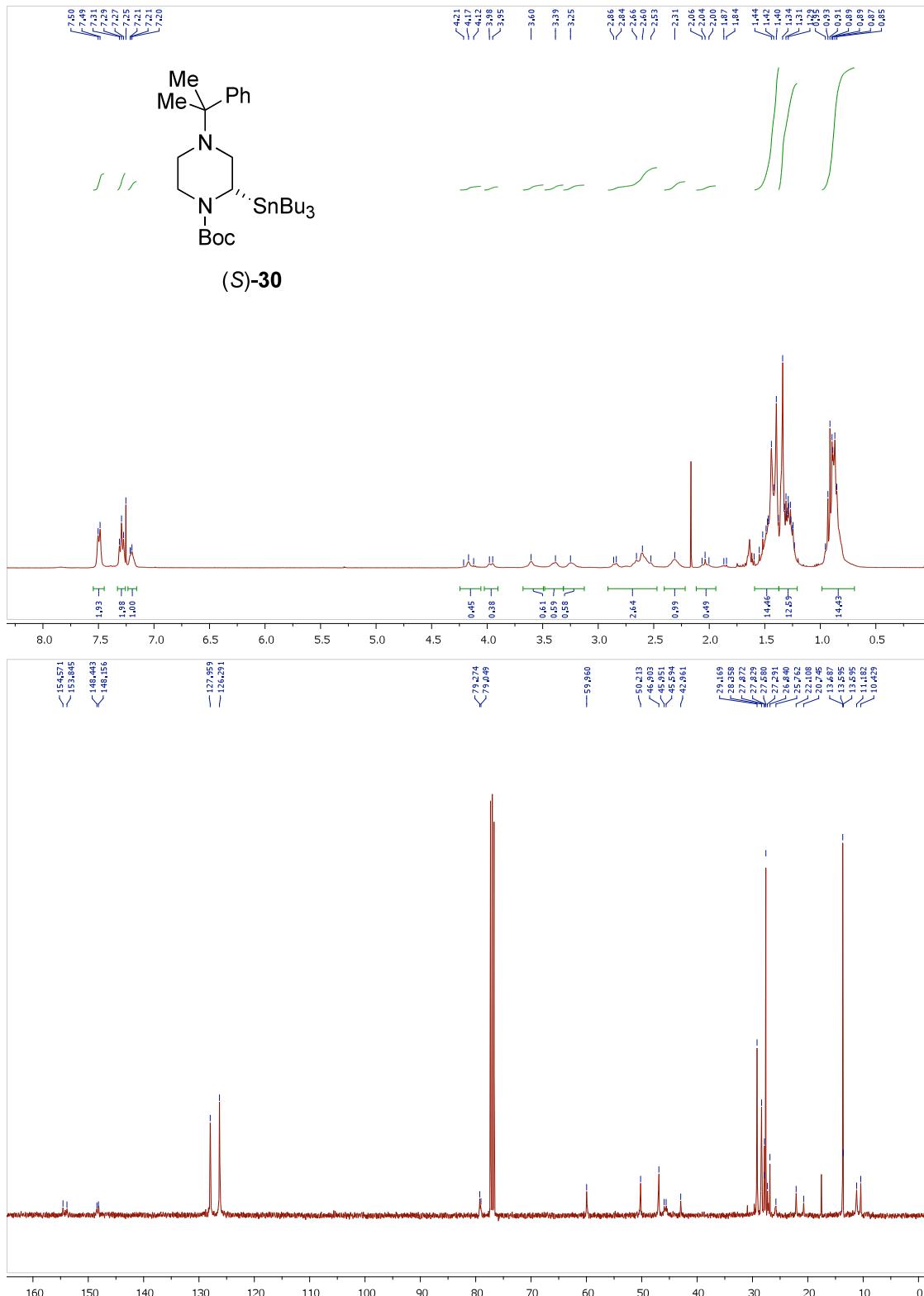
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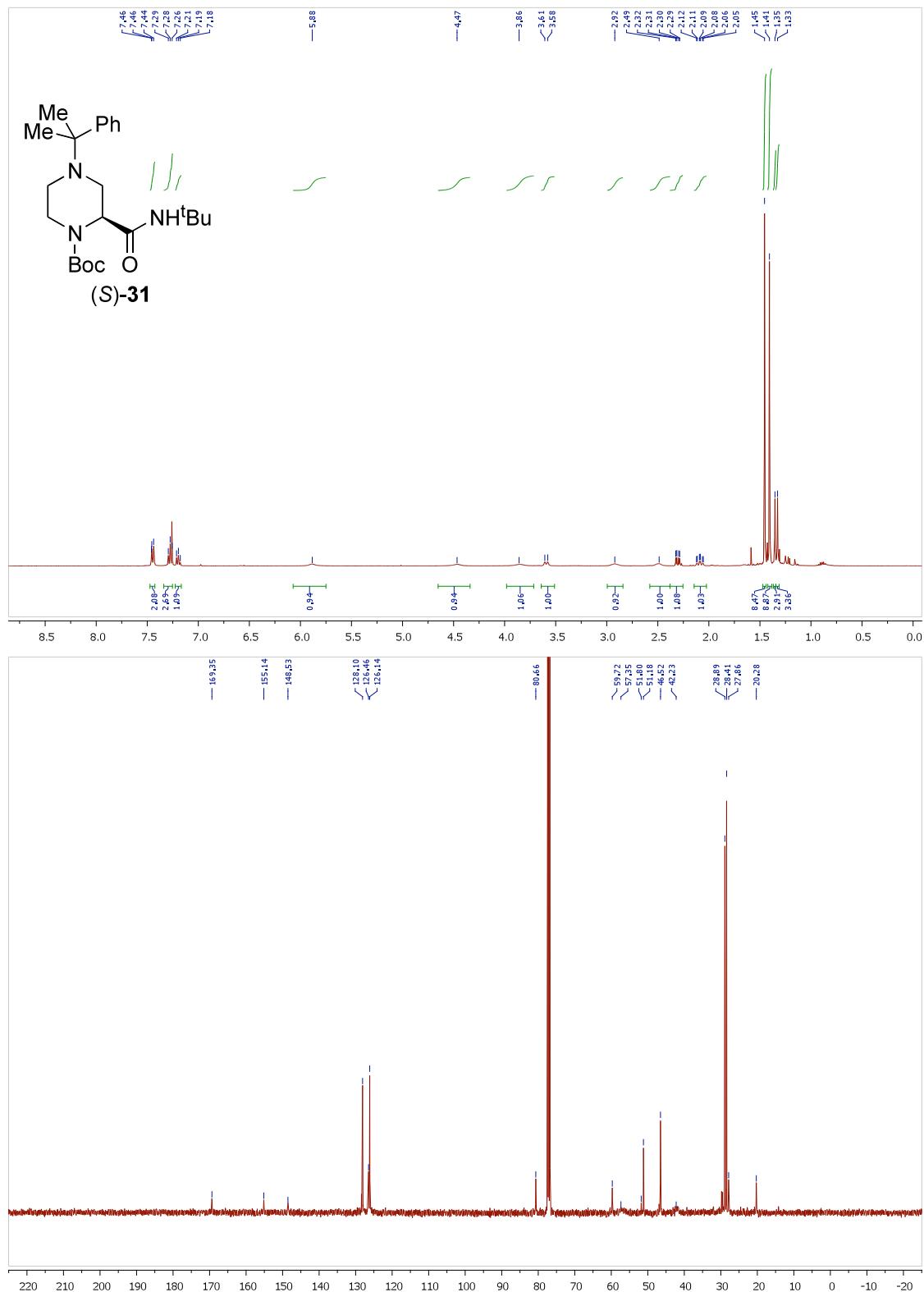
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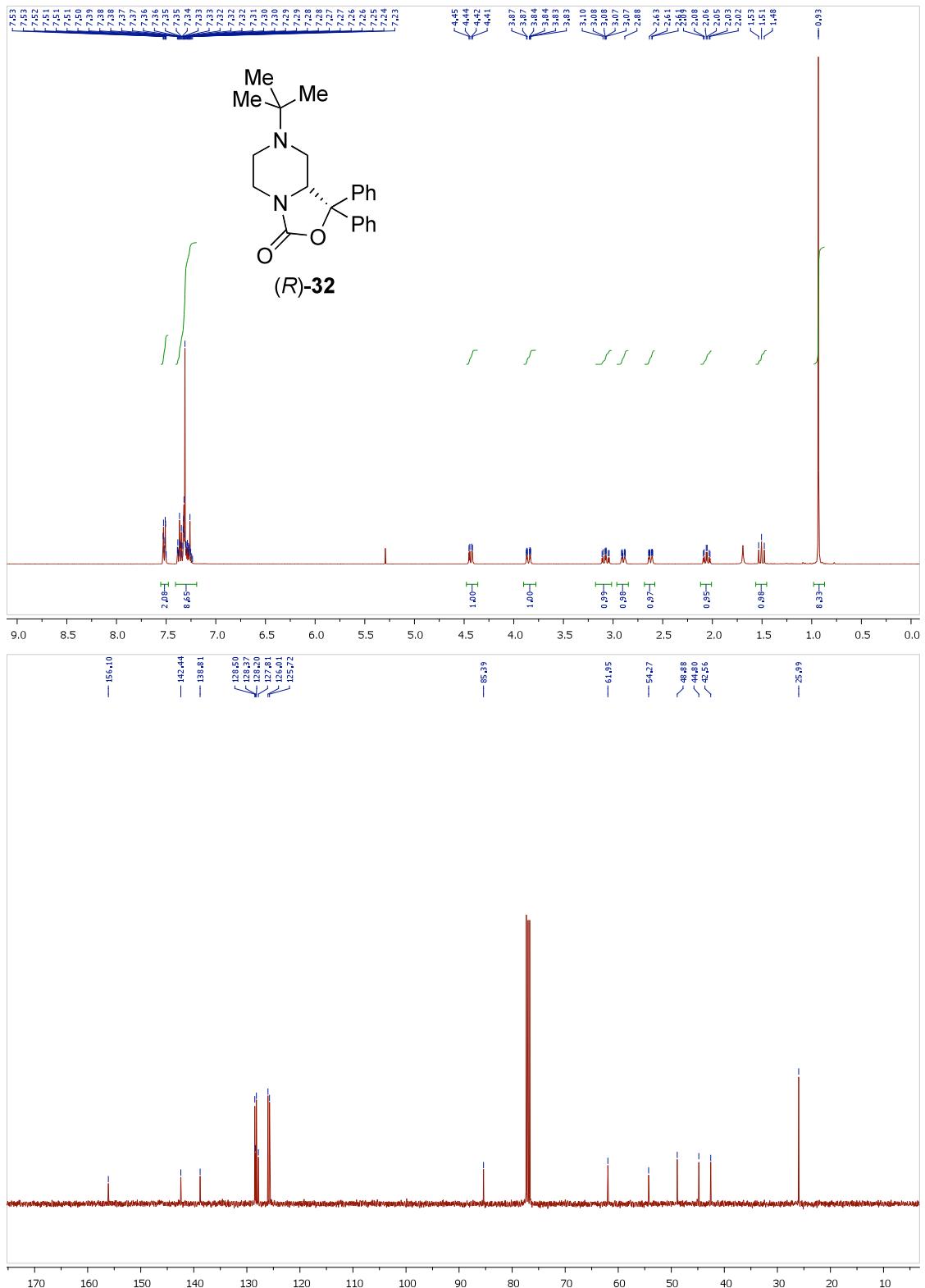
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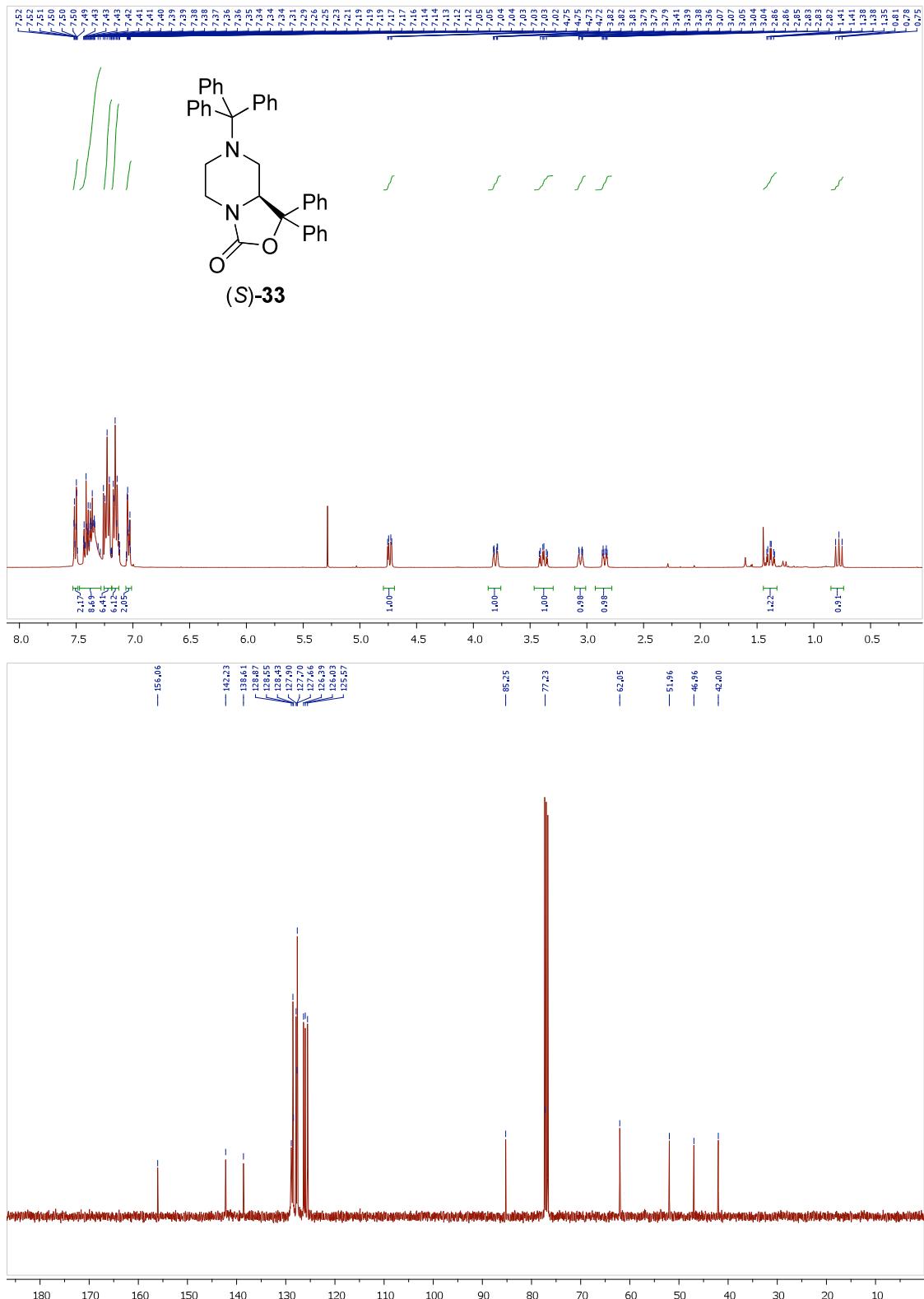
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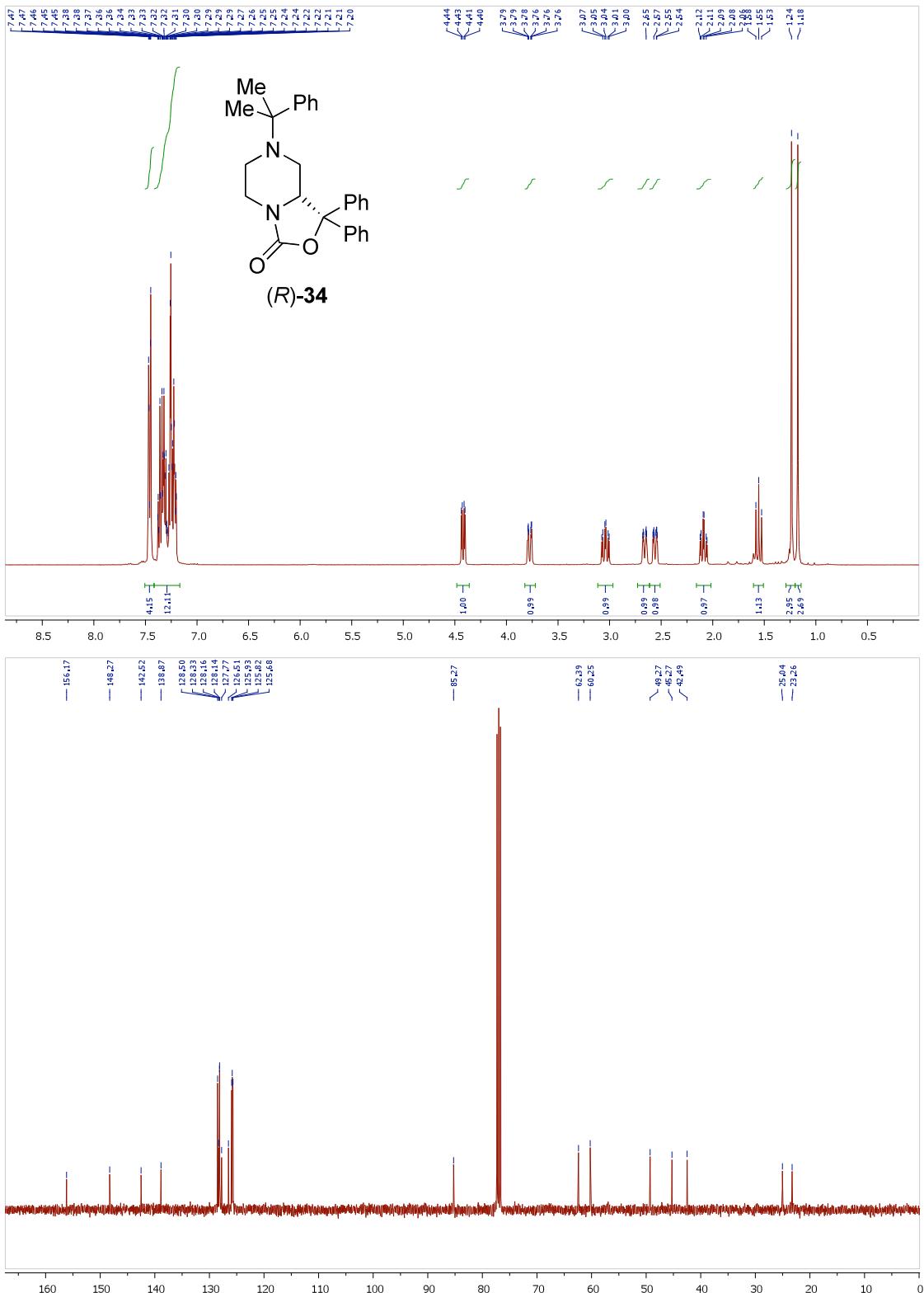
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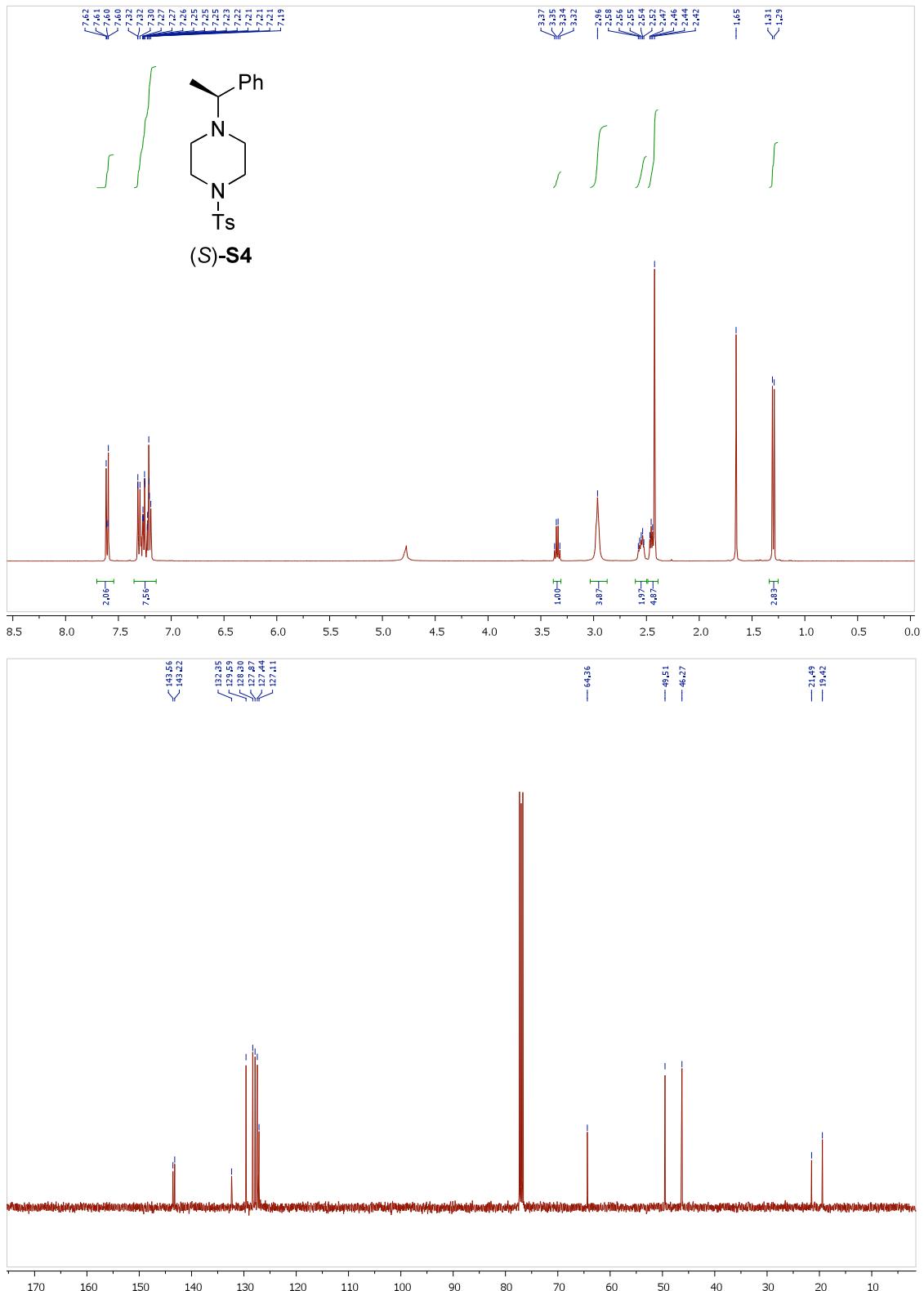
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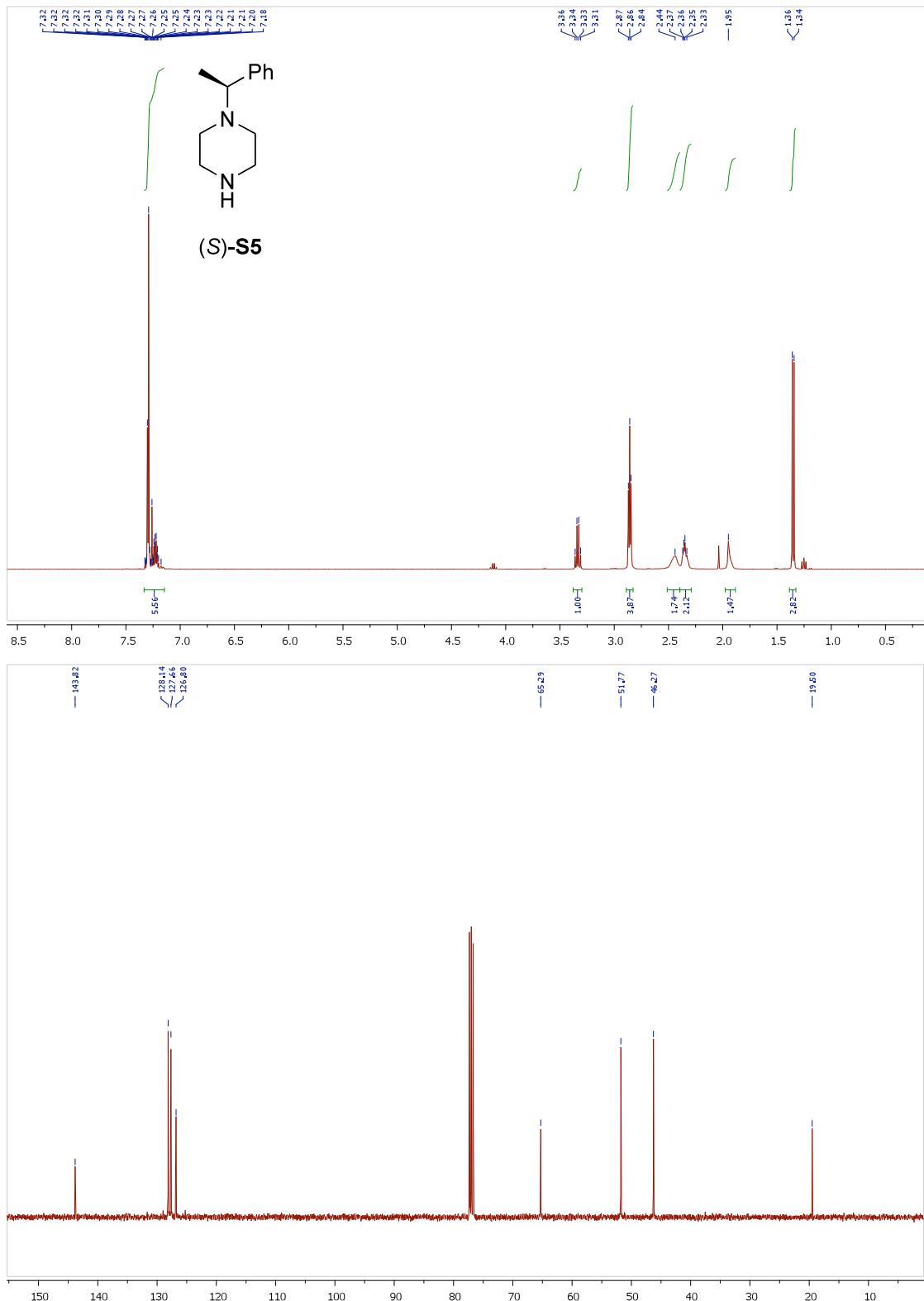
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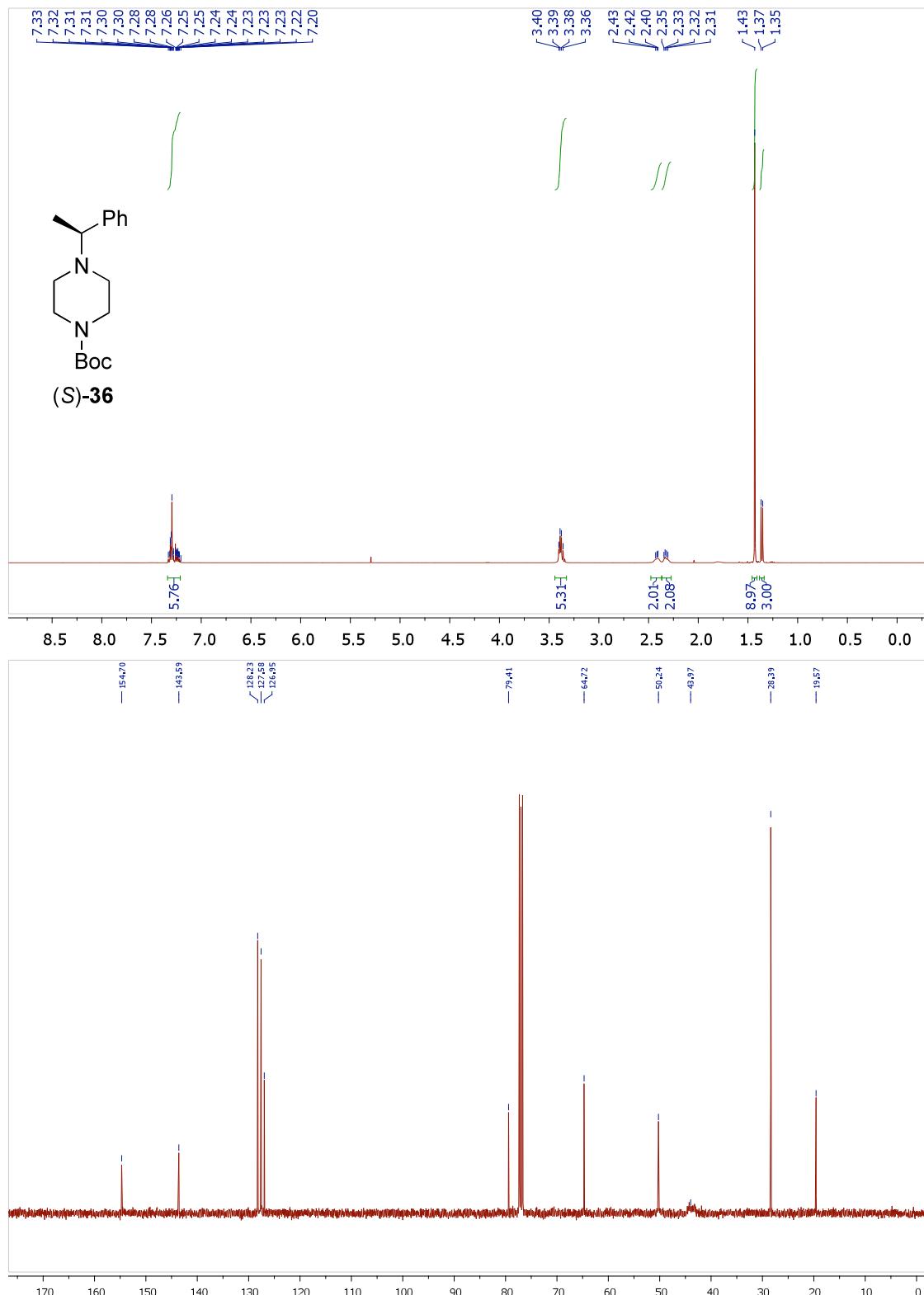
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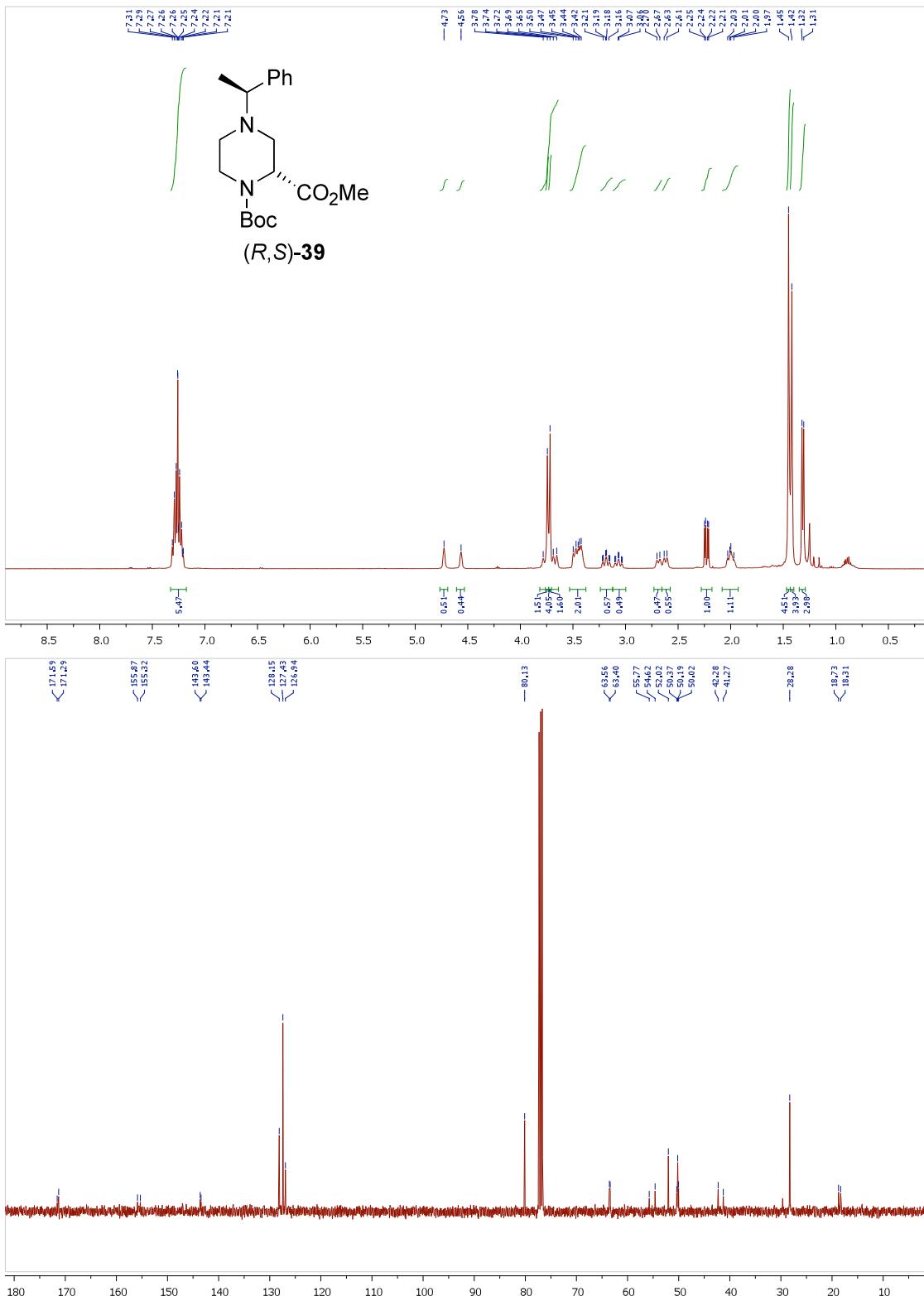
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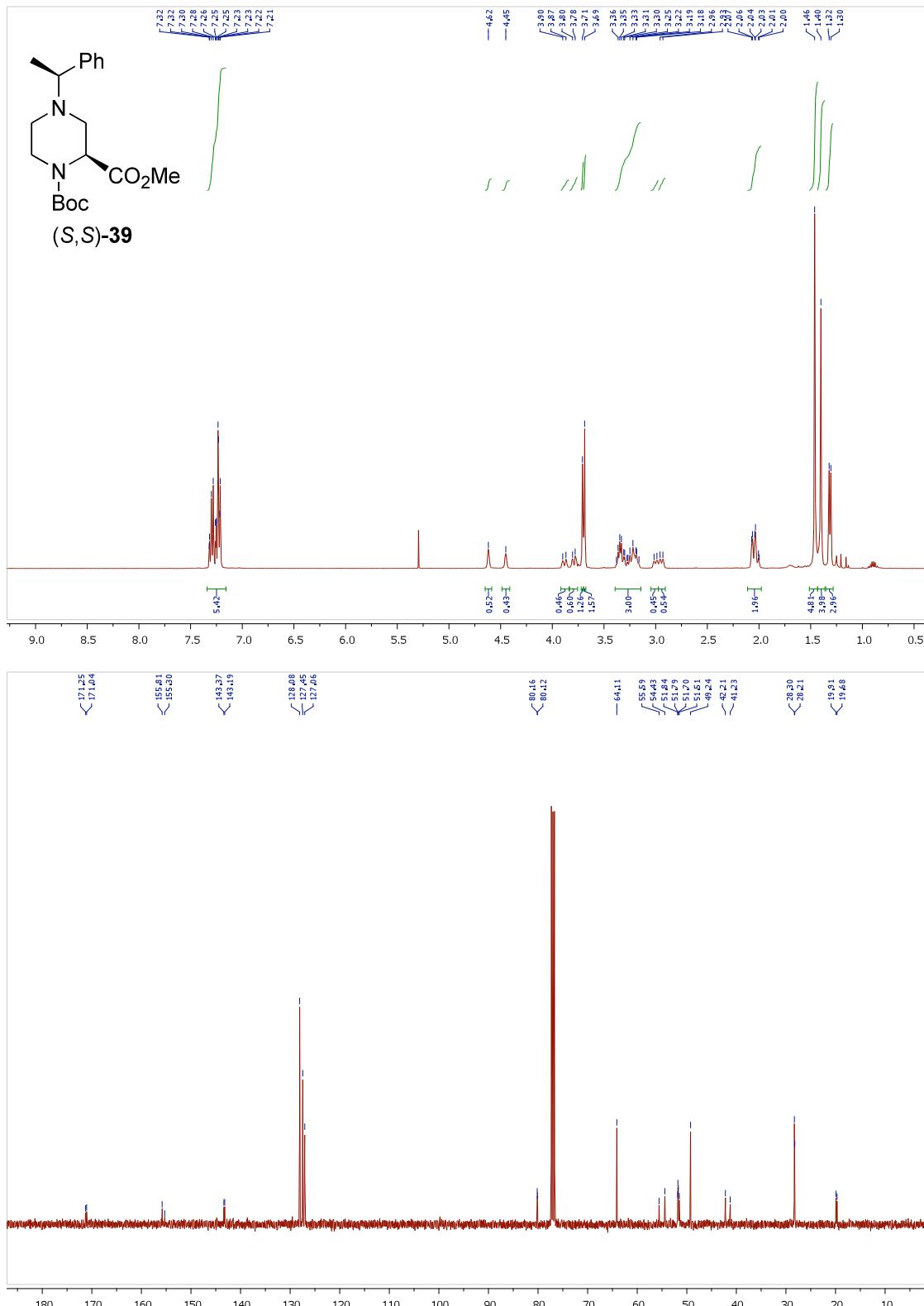
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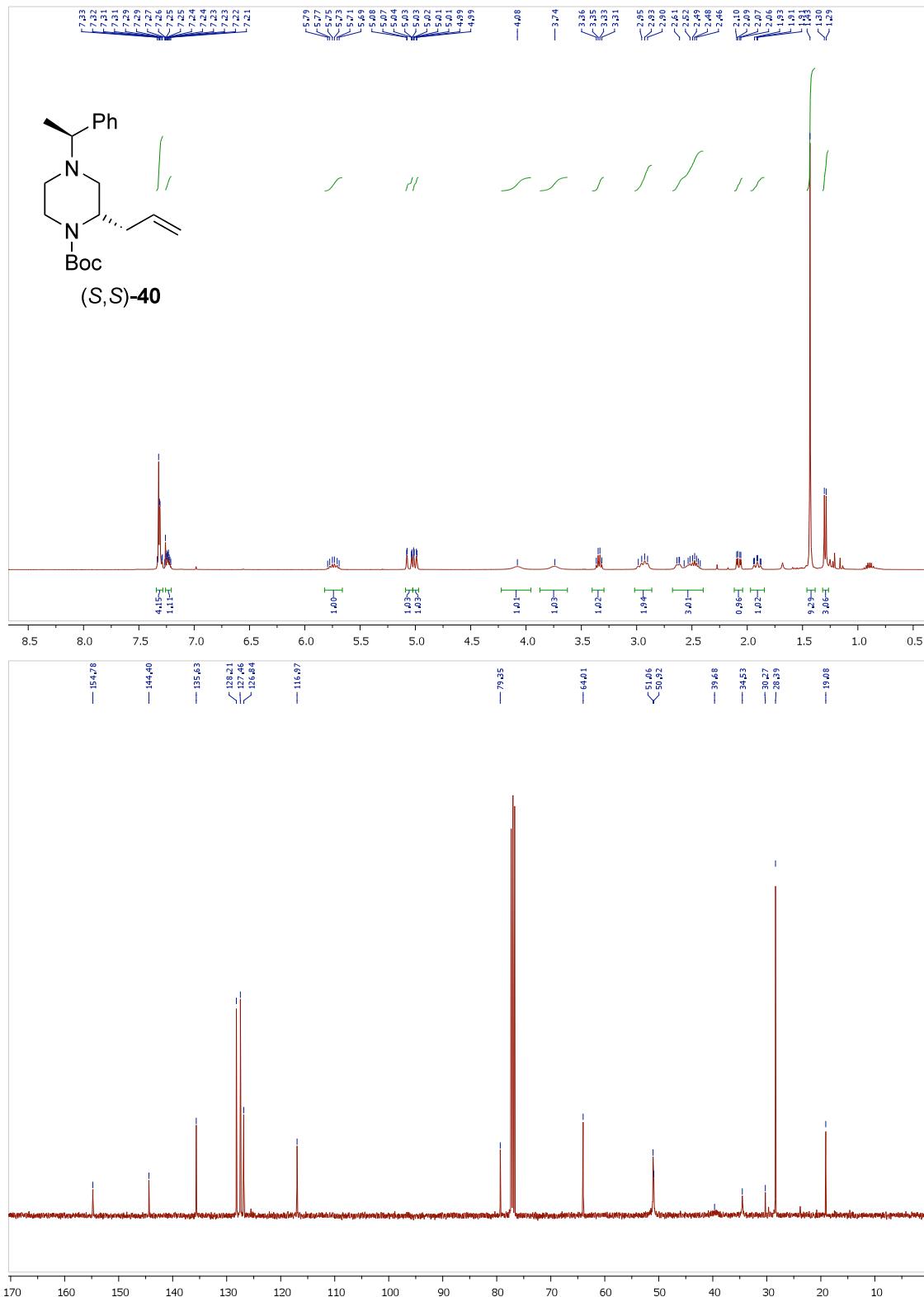
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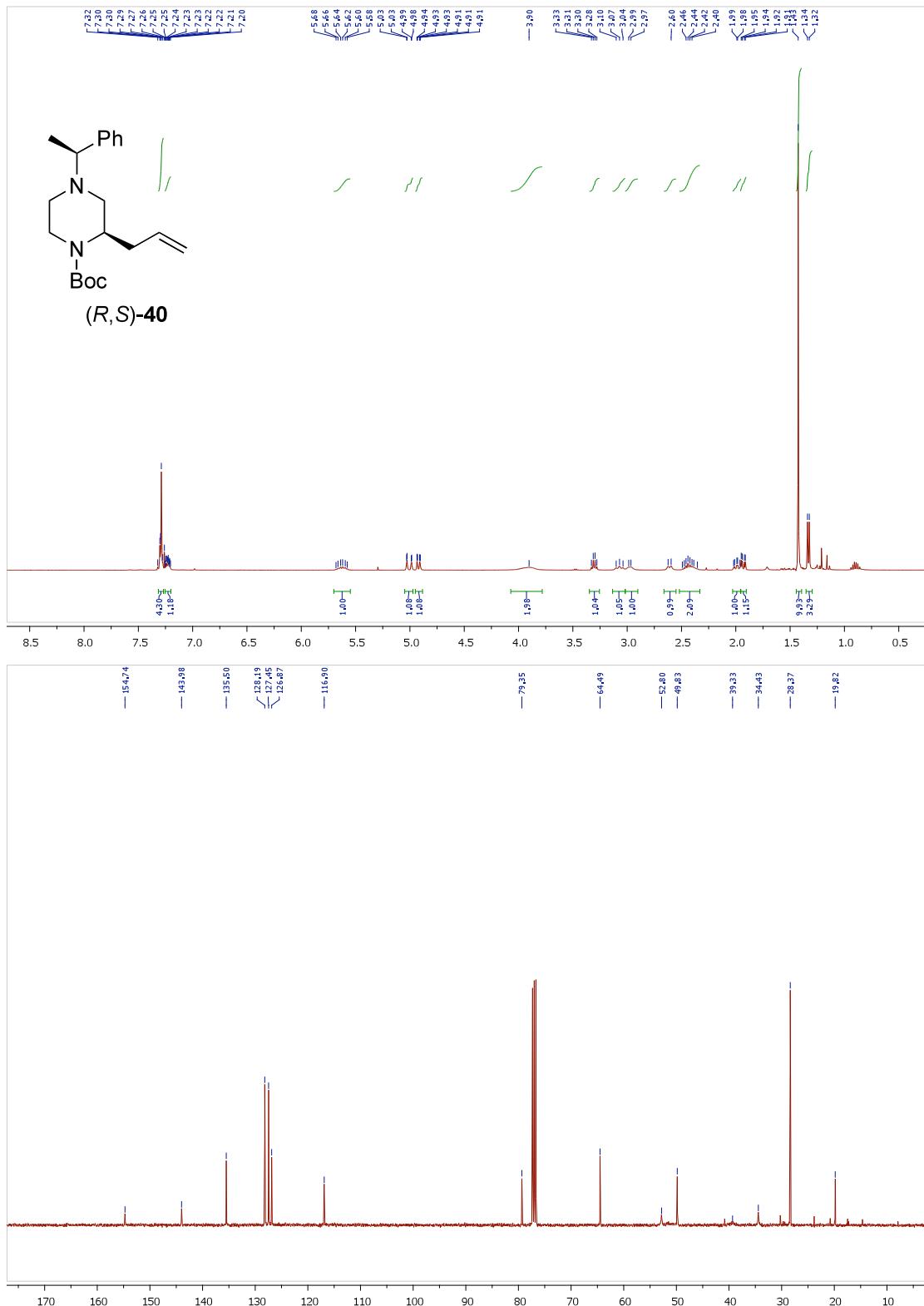
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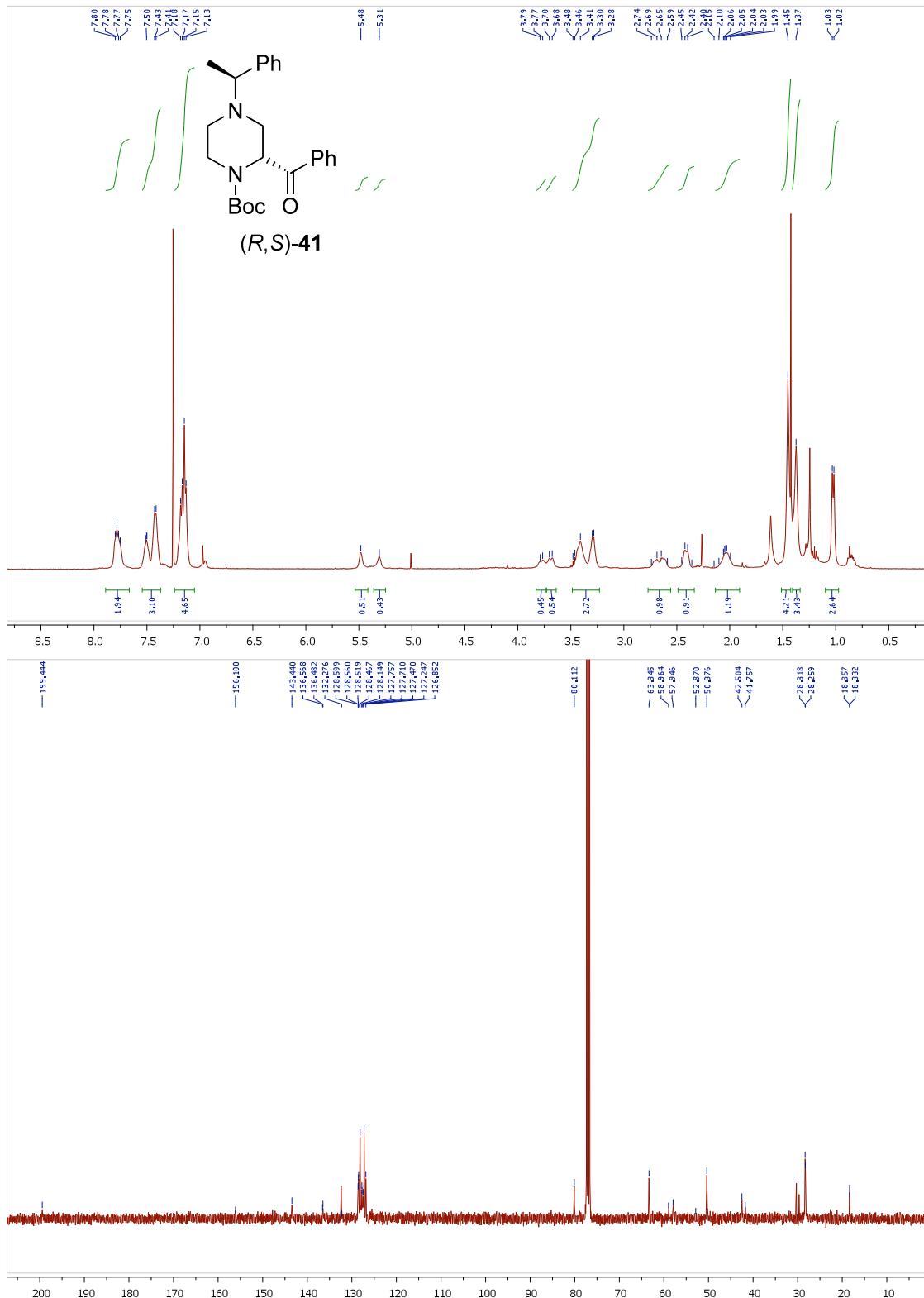
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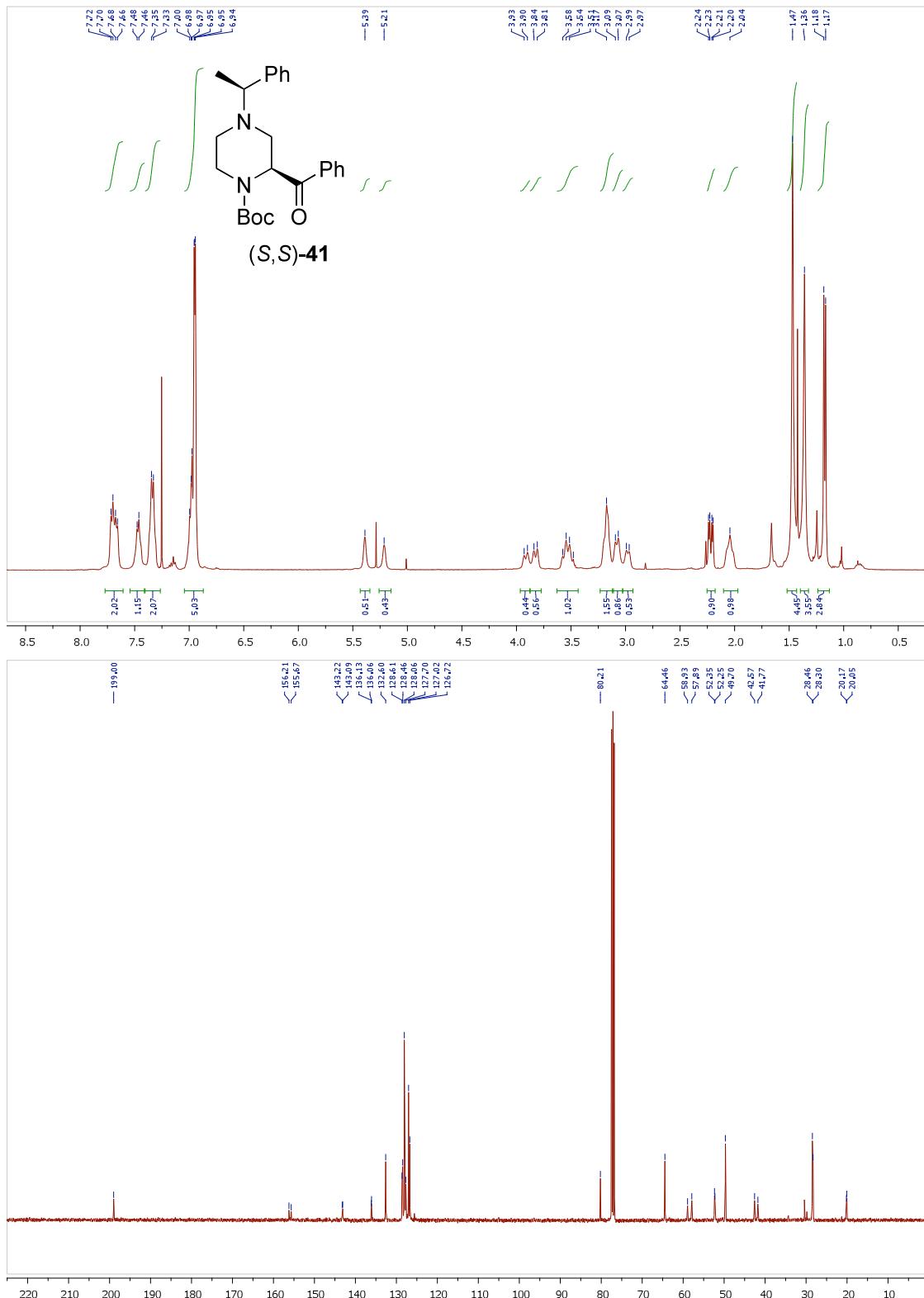
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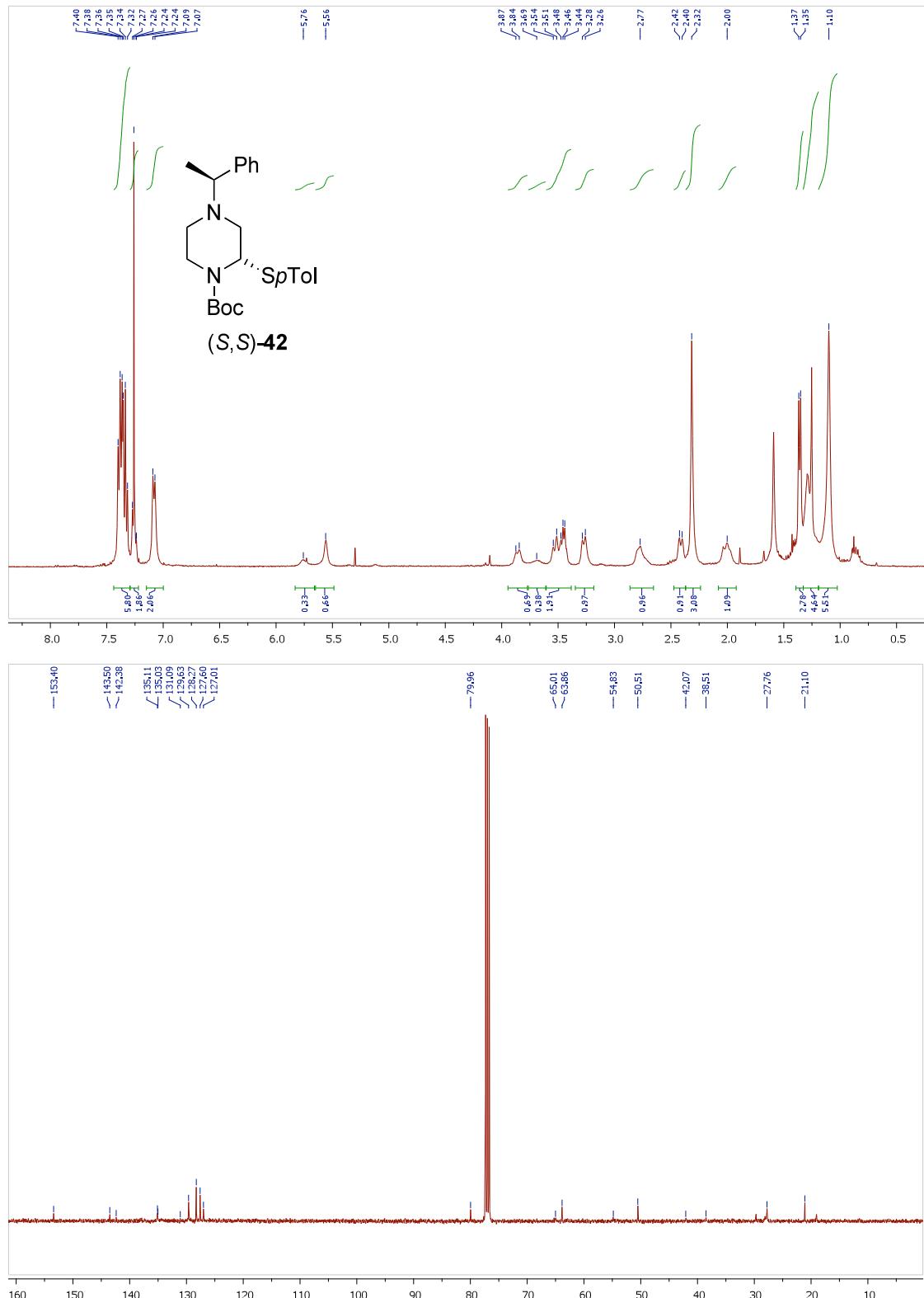
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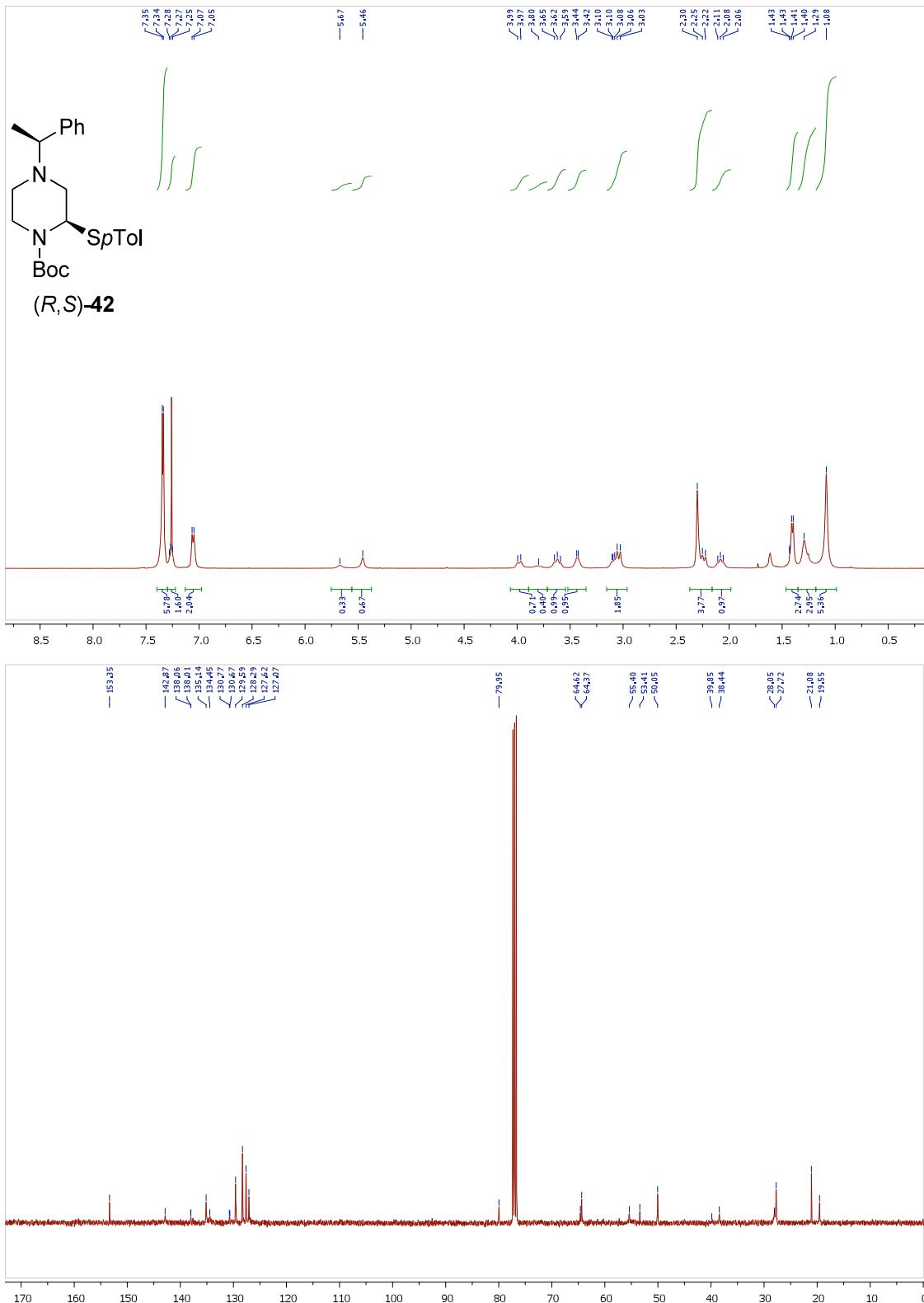
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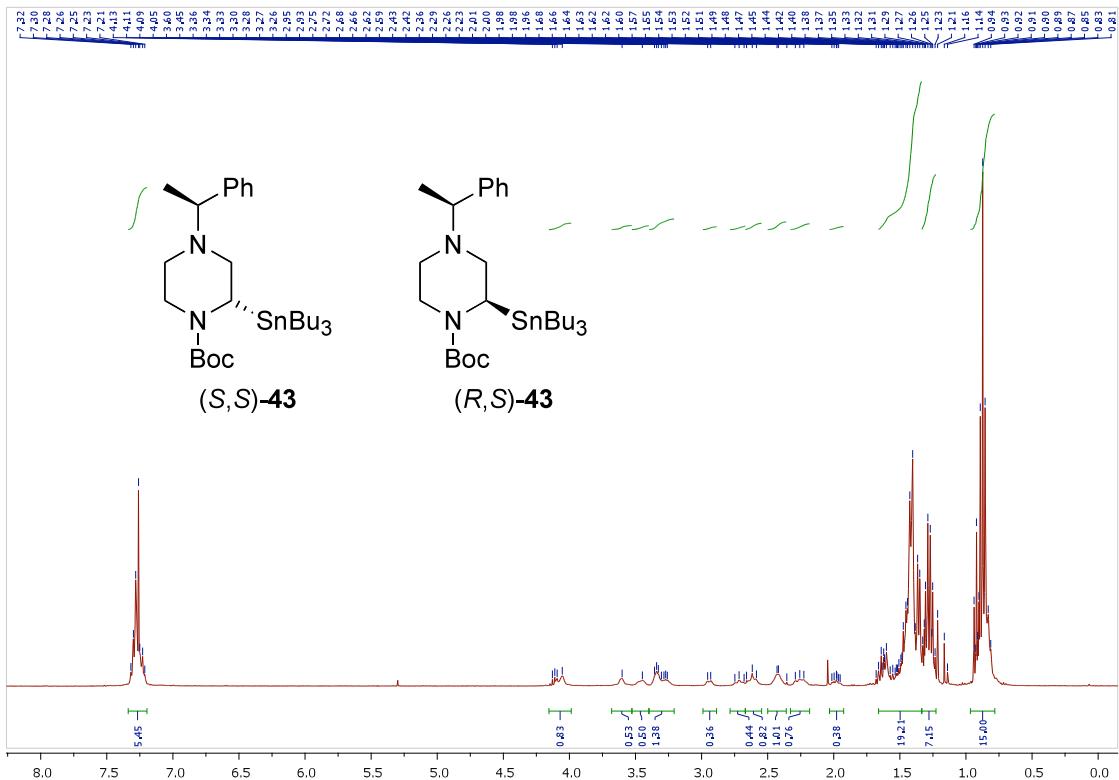
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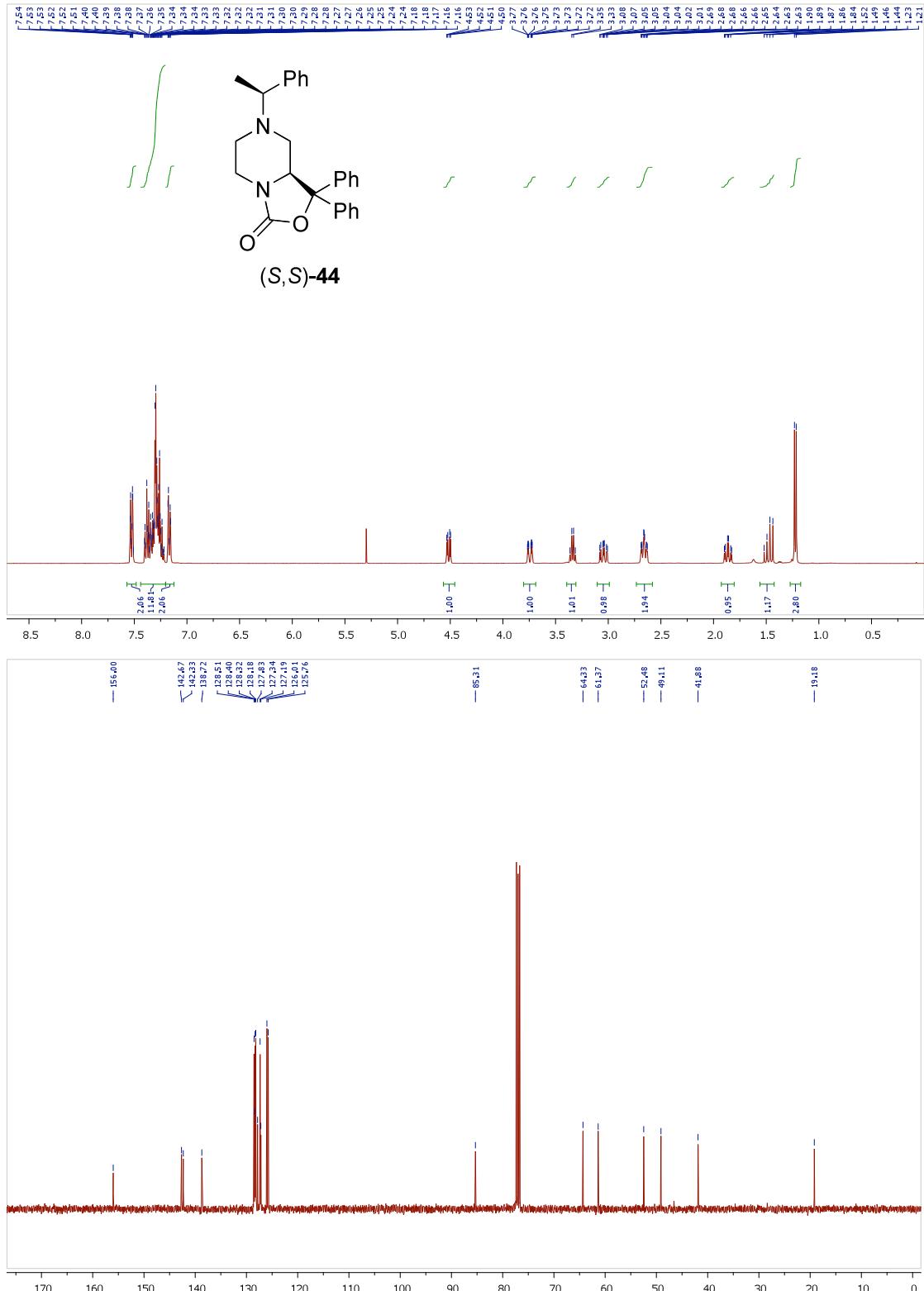
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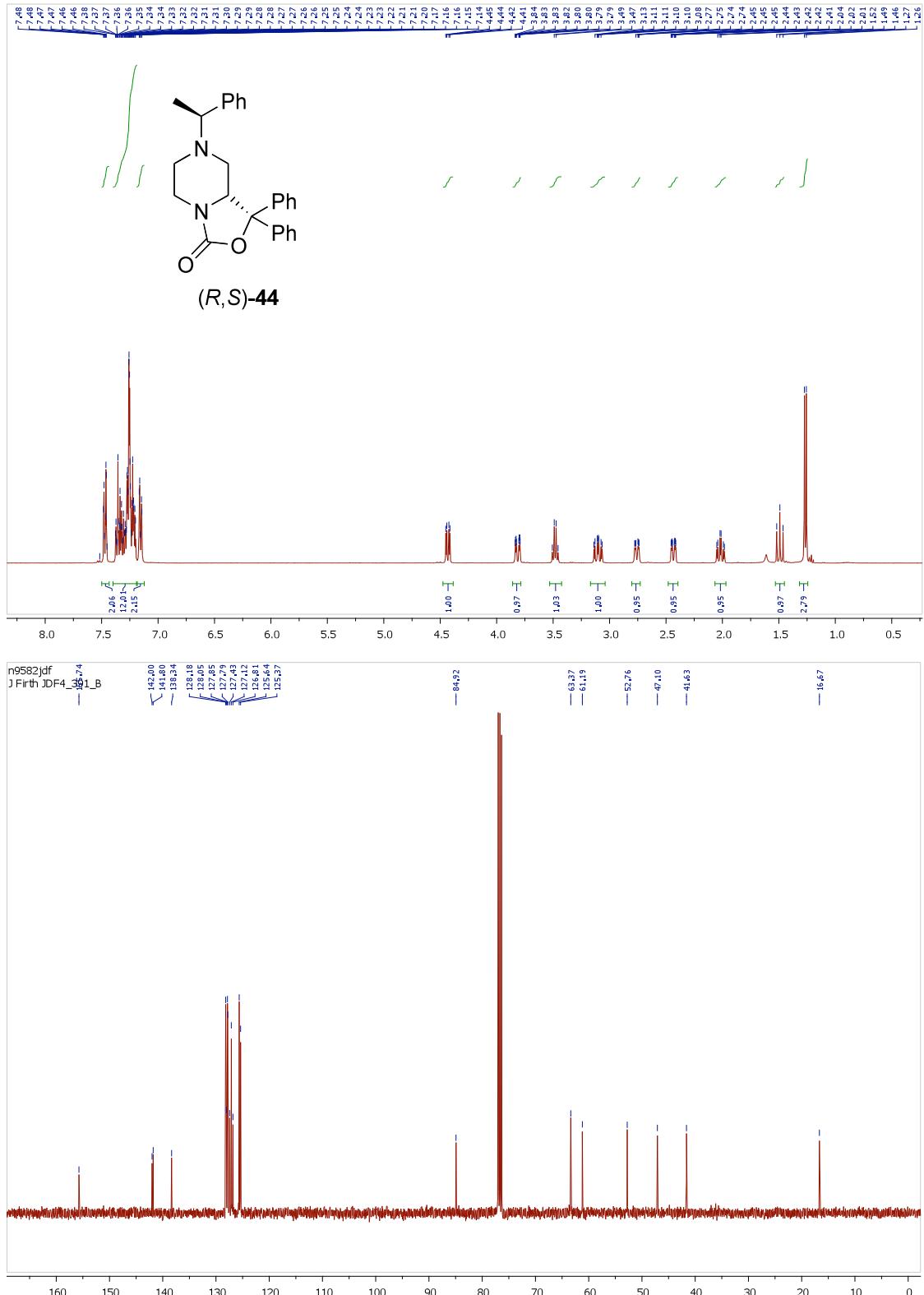
400 MHz ^1H NMR spectrum; CDCl_3



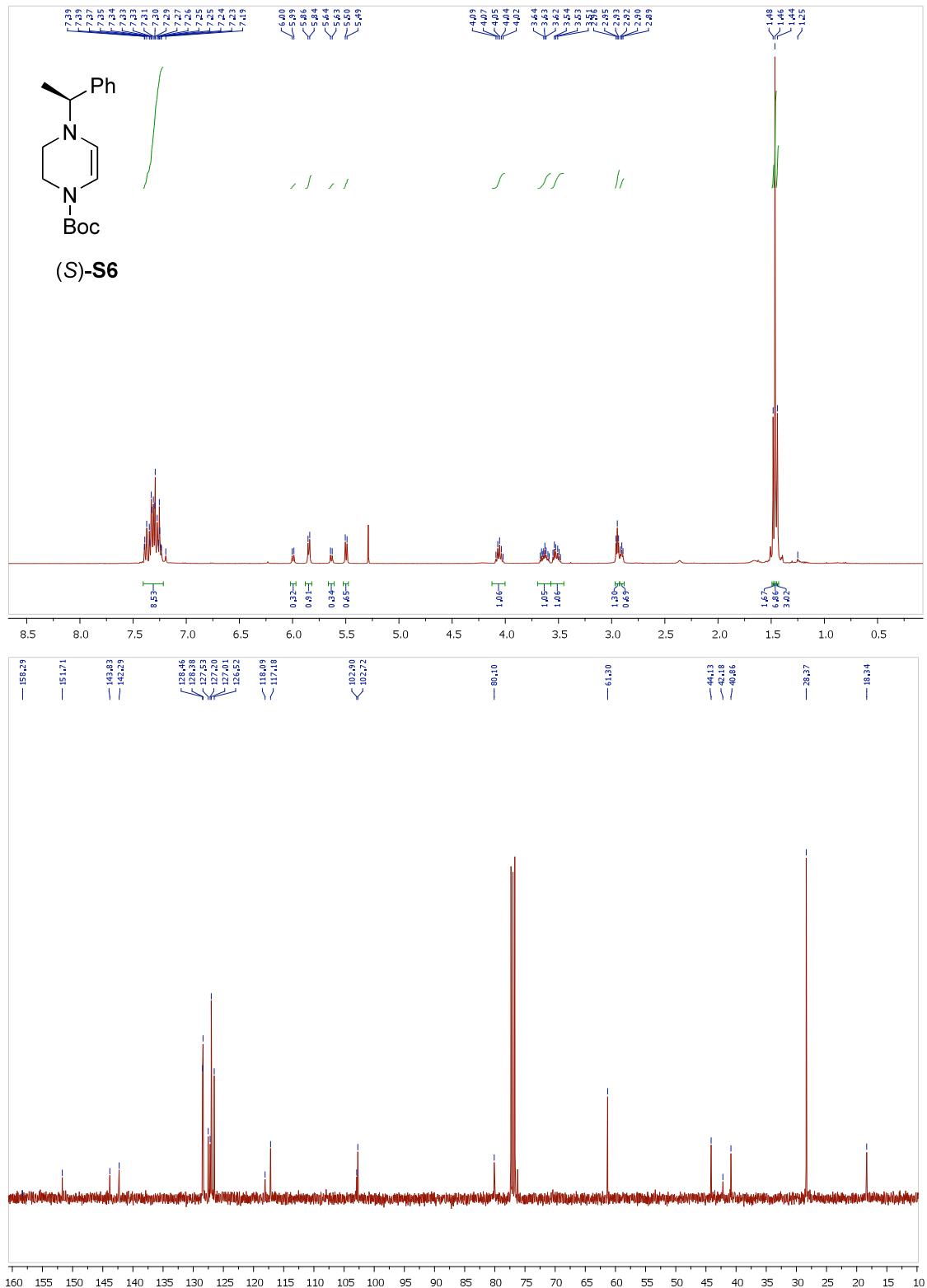
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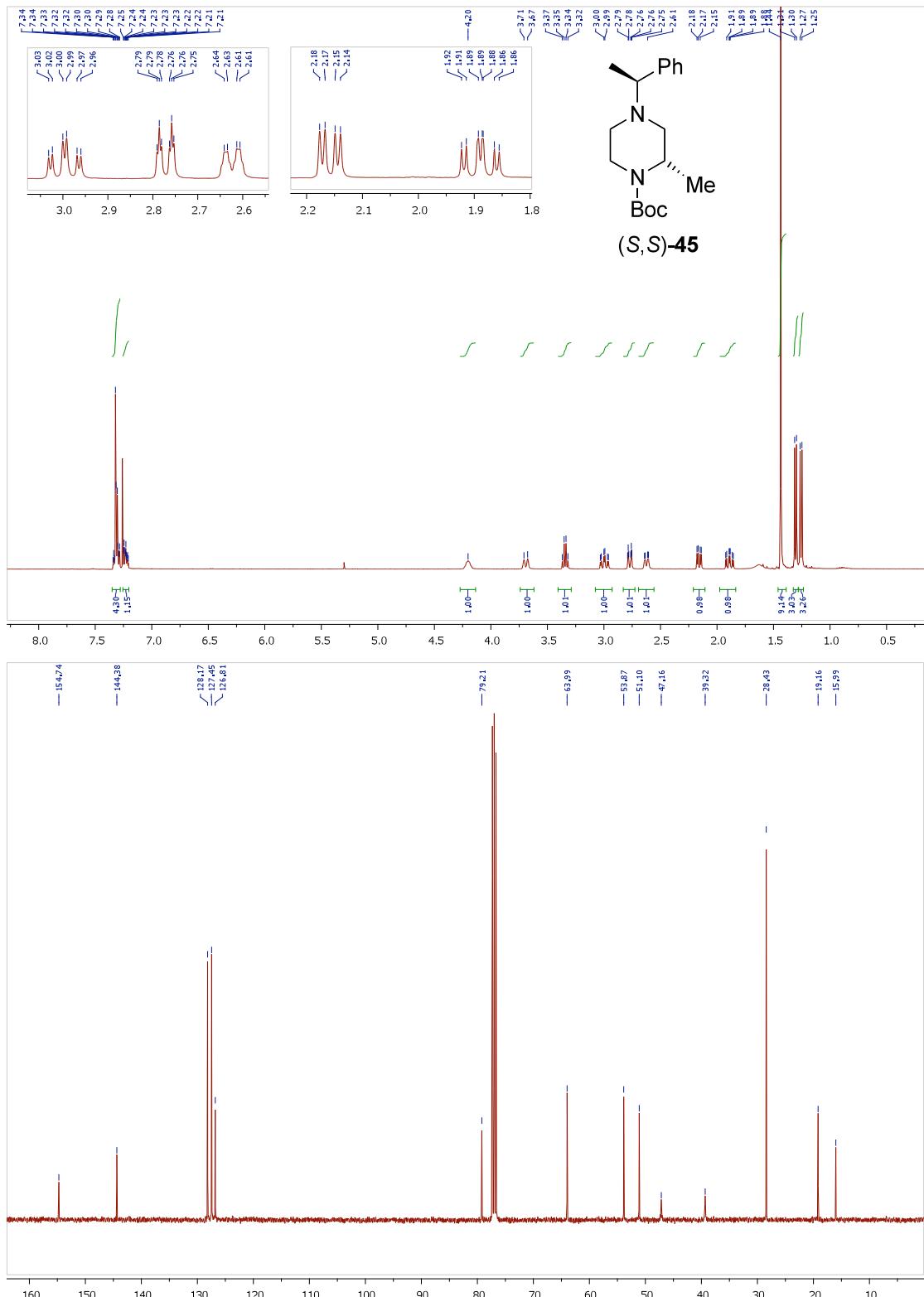
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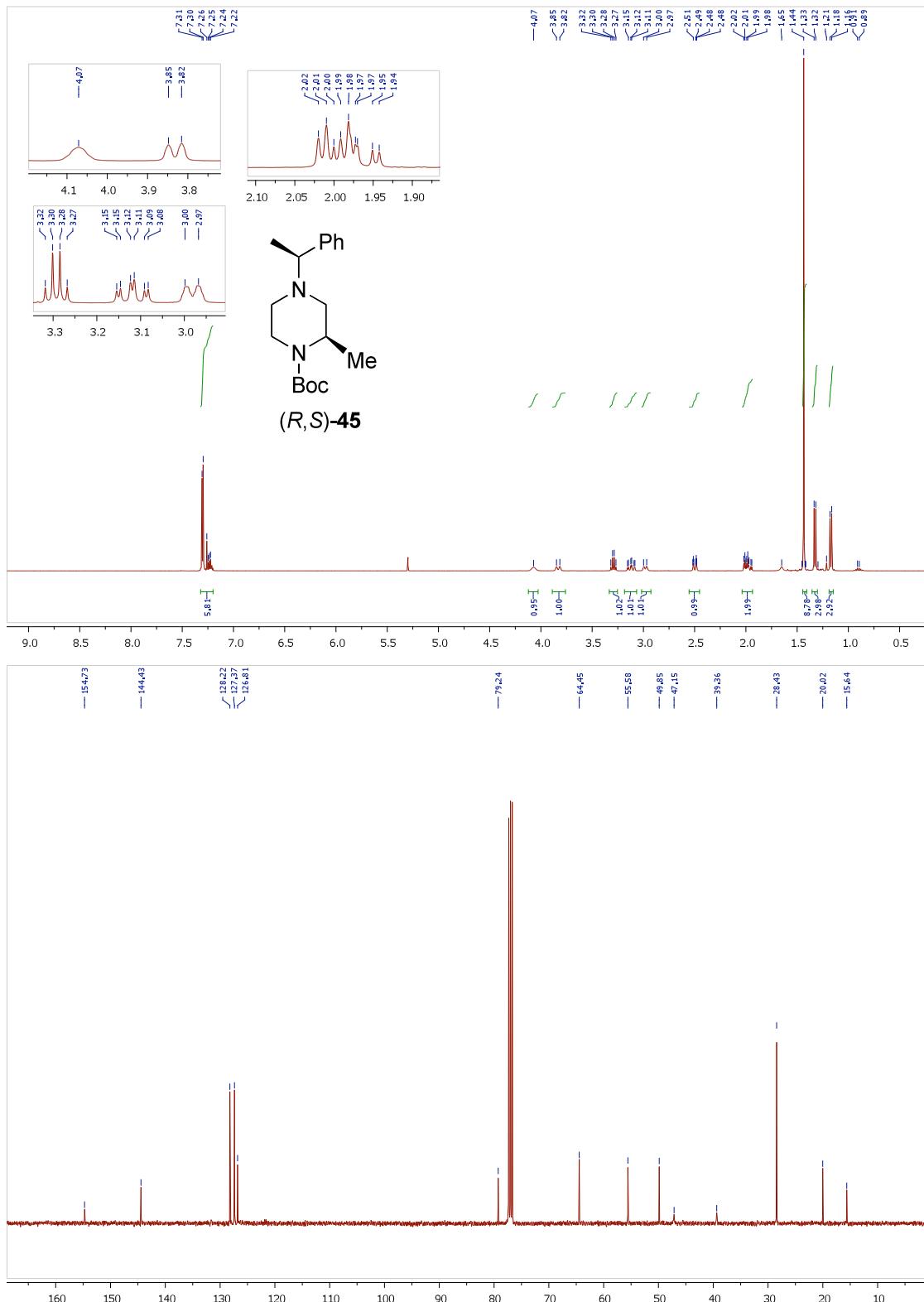
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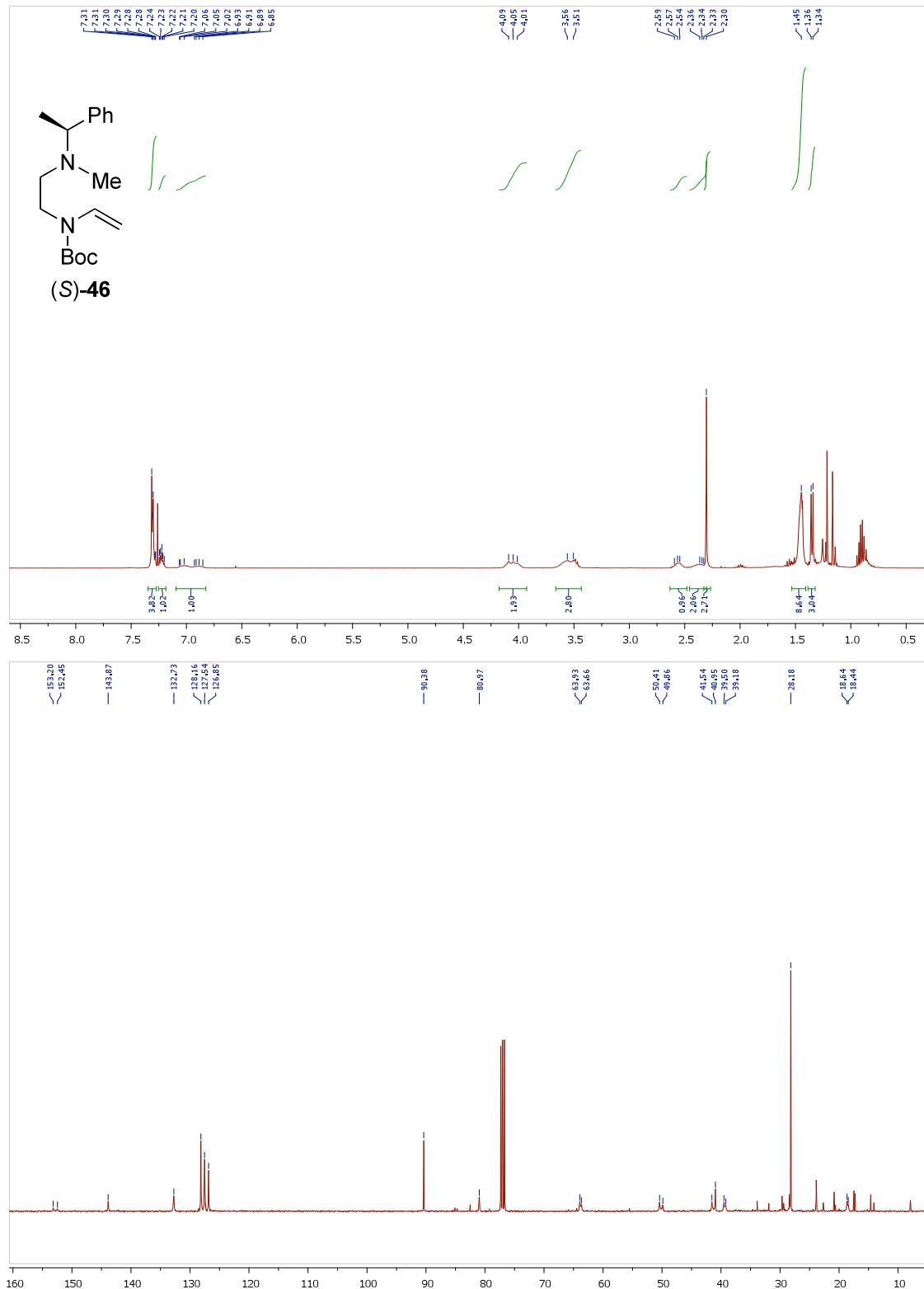
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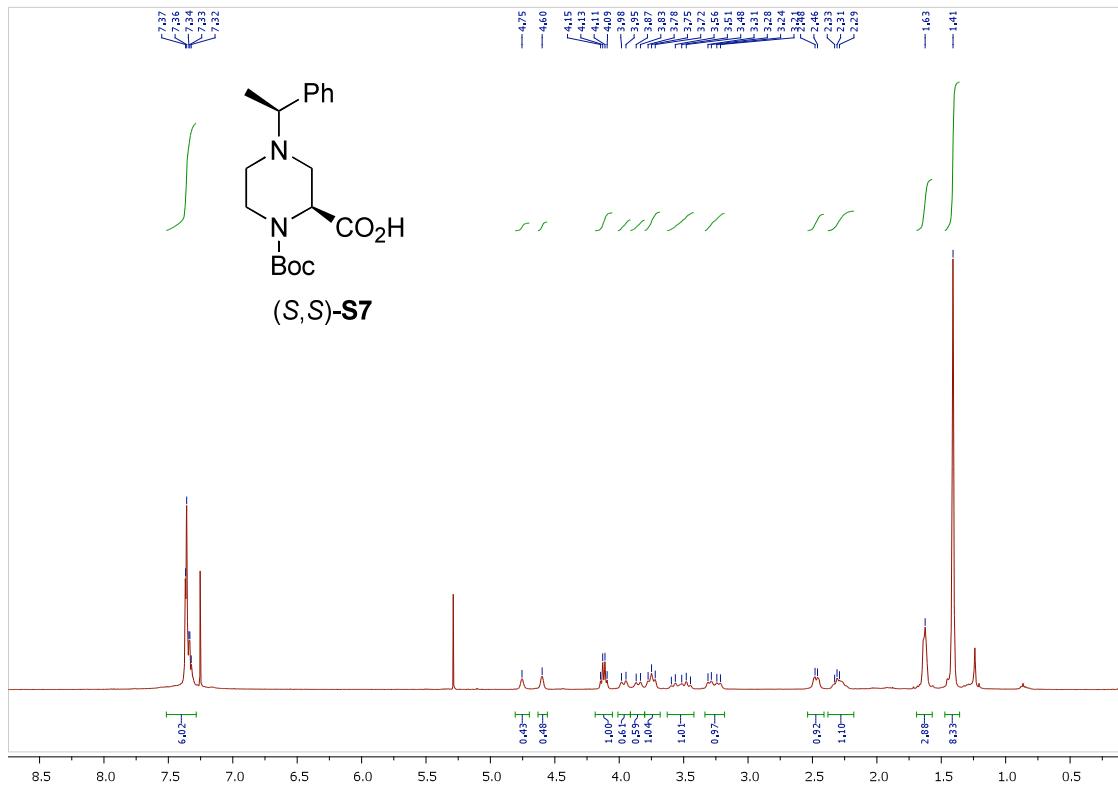


400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

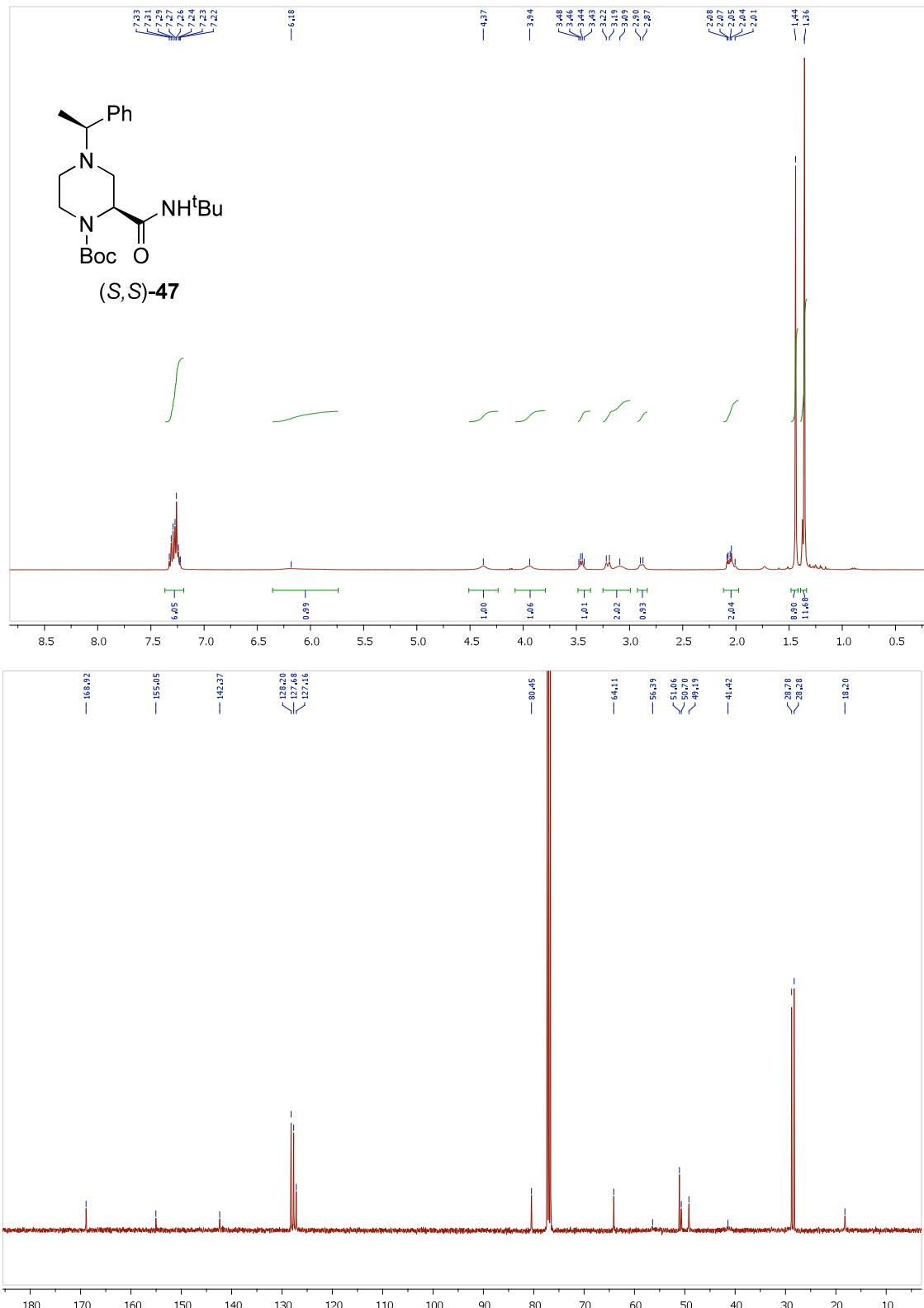


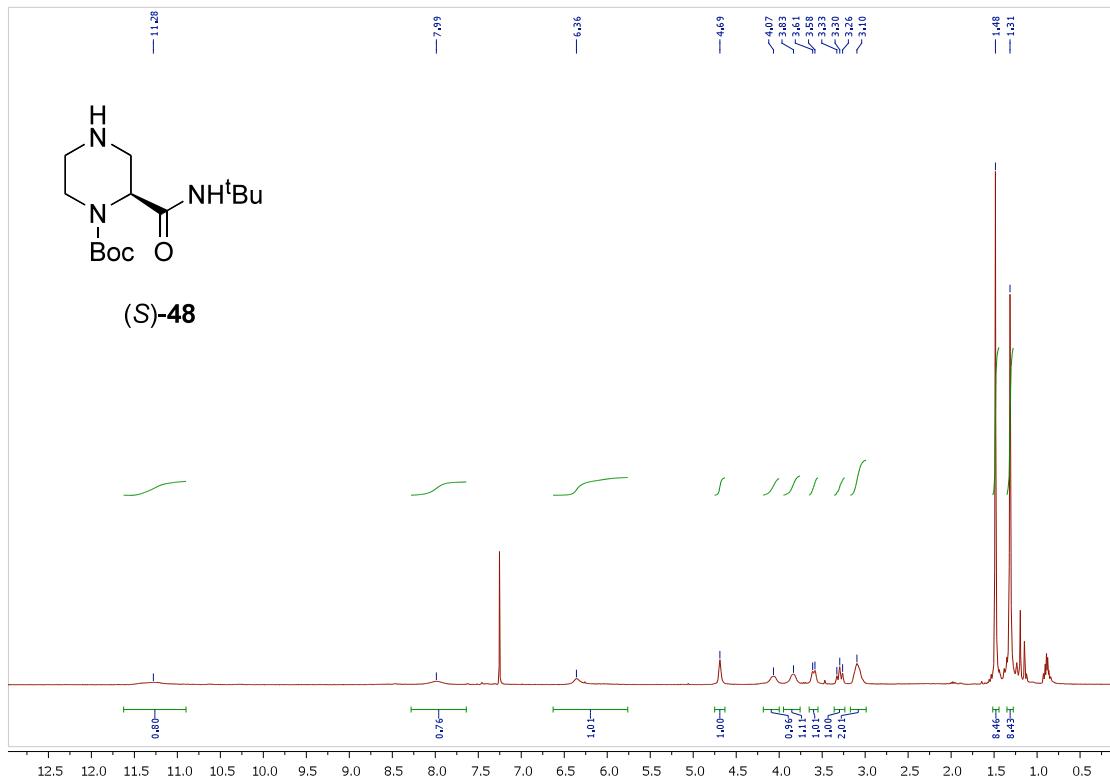
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

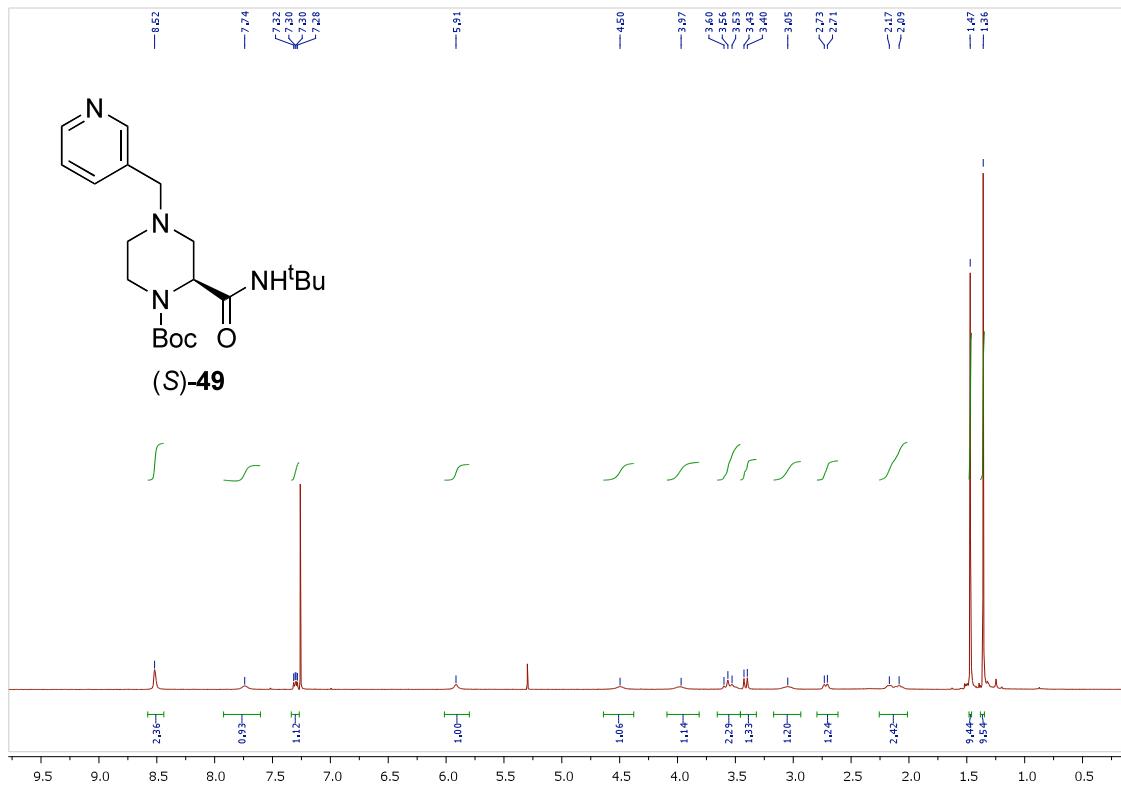


400 MHz ^1H NMR spectrum; CDCl_3 

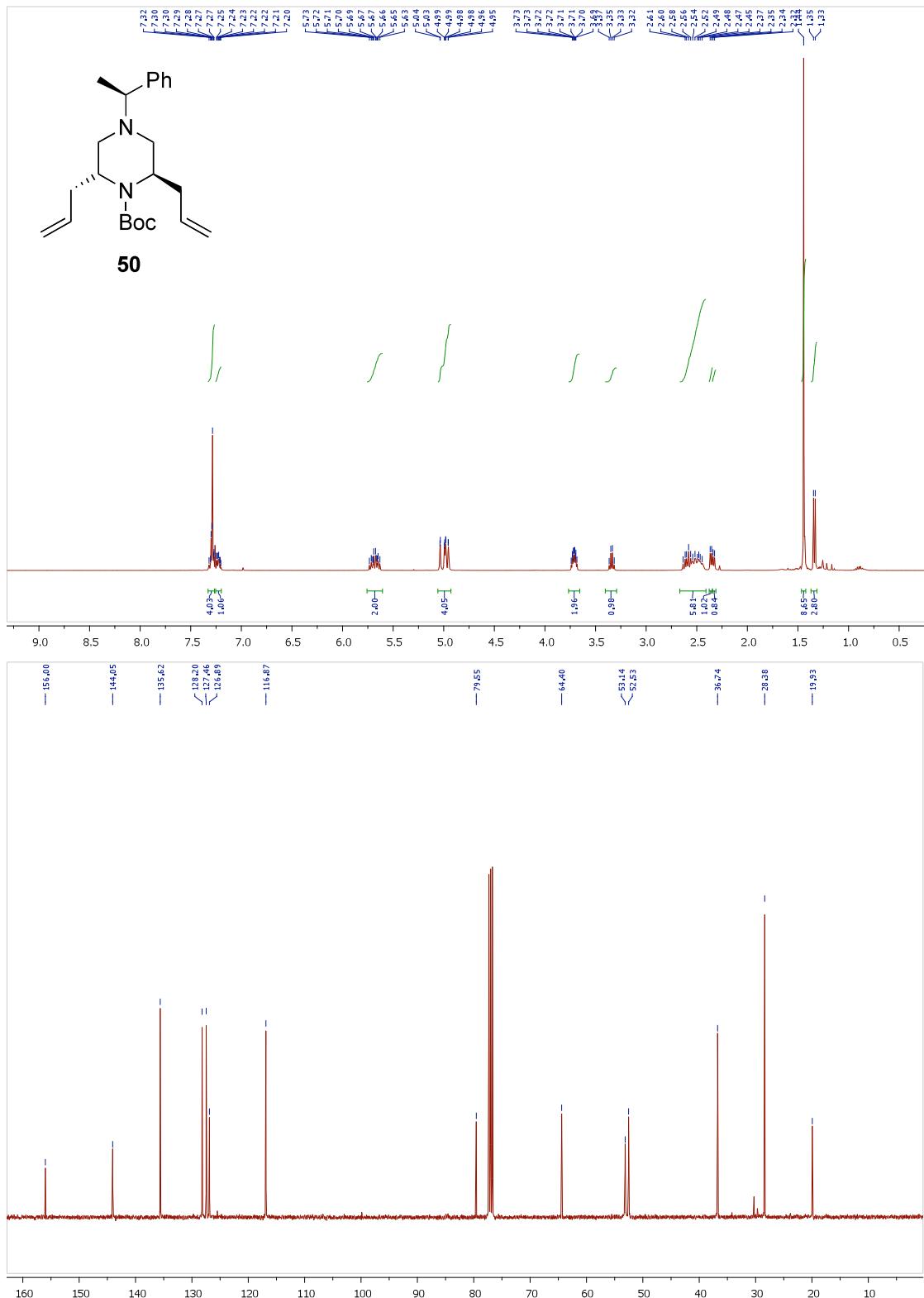
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

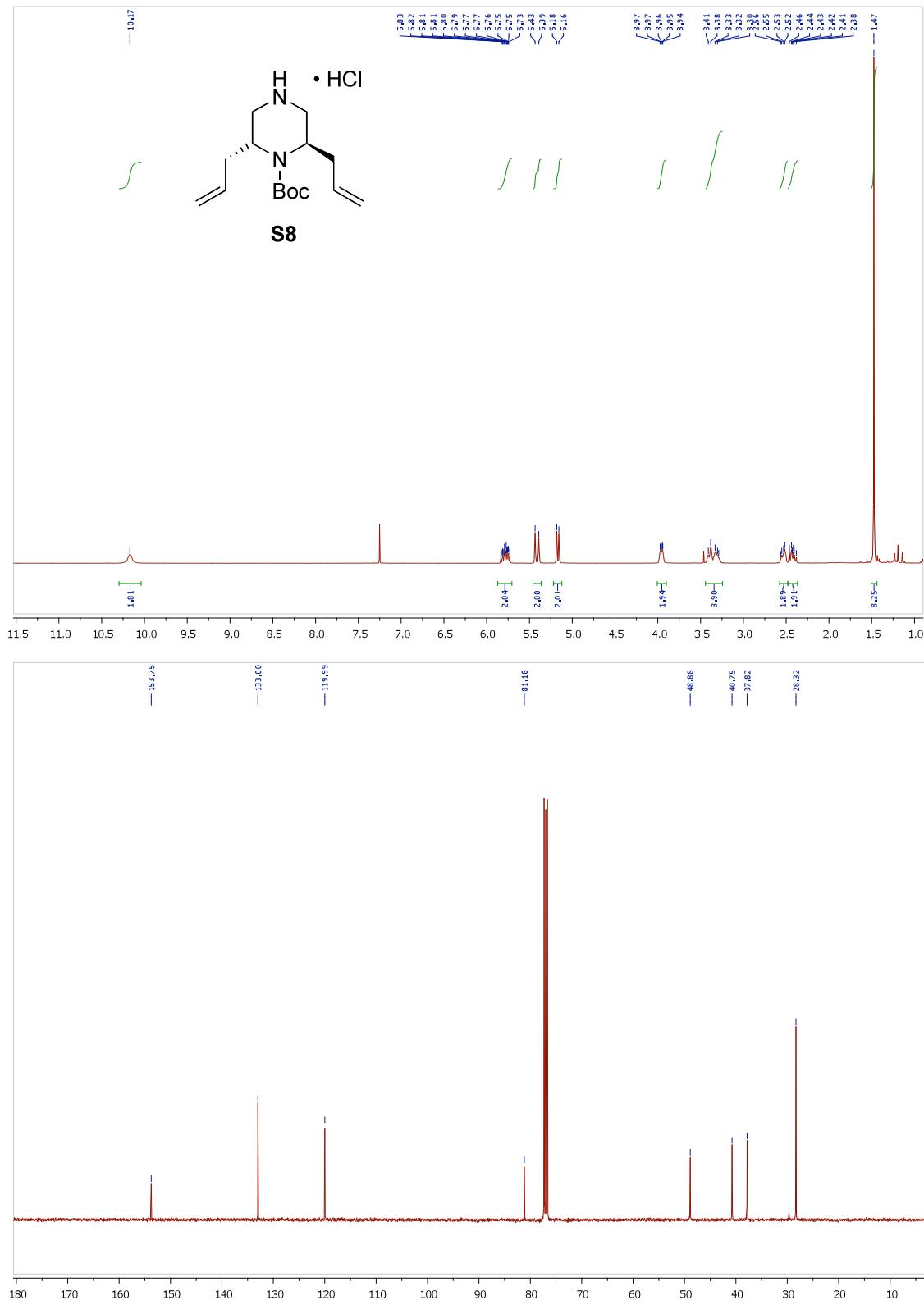


400 MHz ^1H NMR spectrum; CDCl_3 

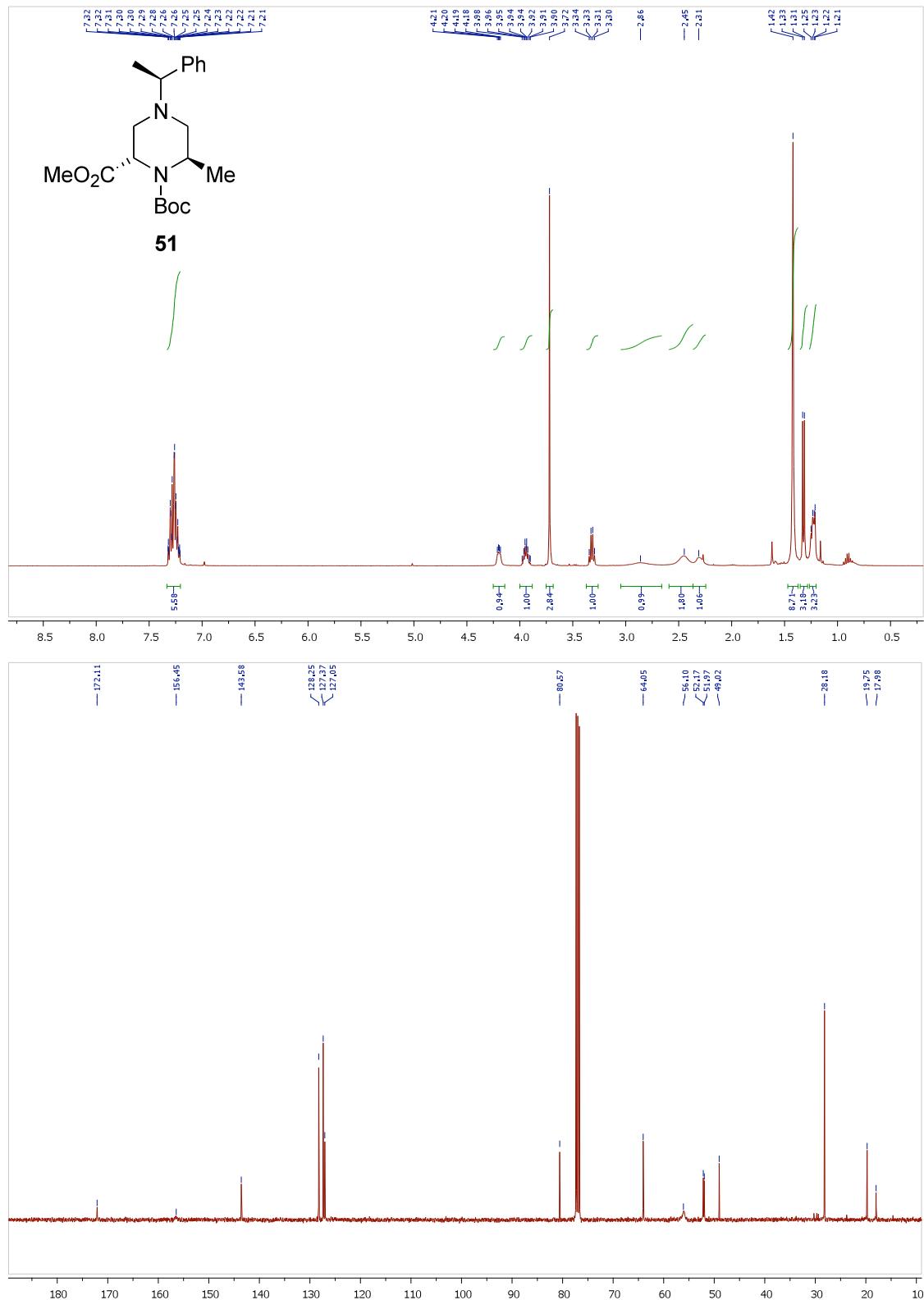
400 MHz ^1H NMR spectrum; CDCl_3 

400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

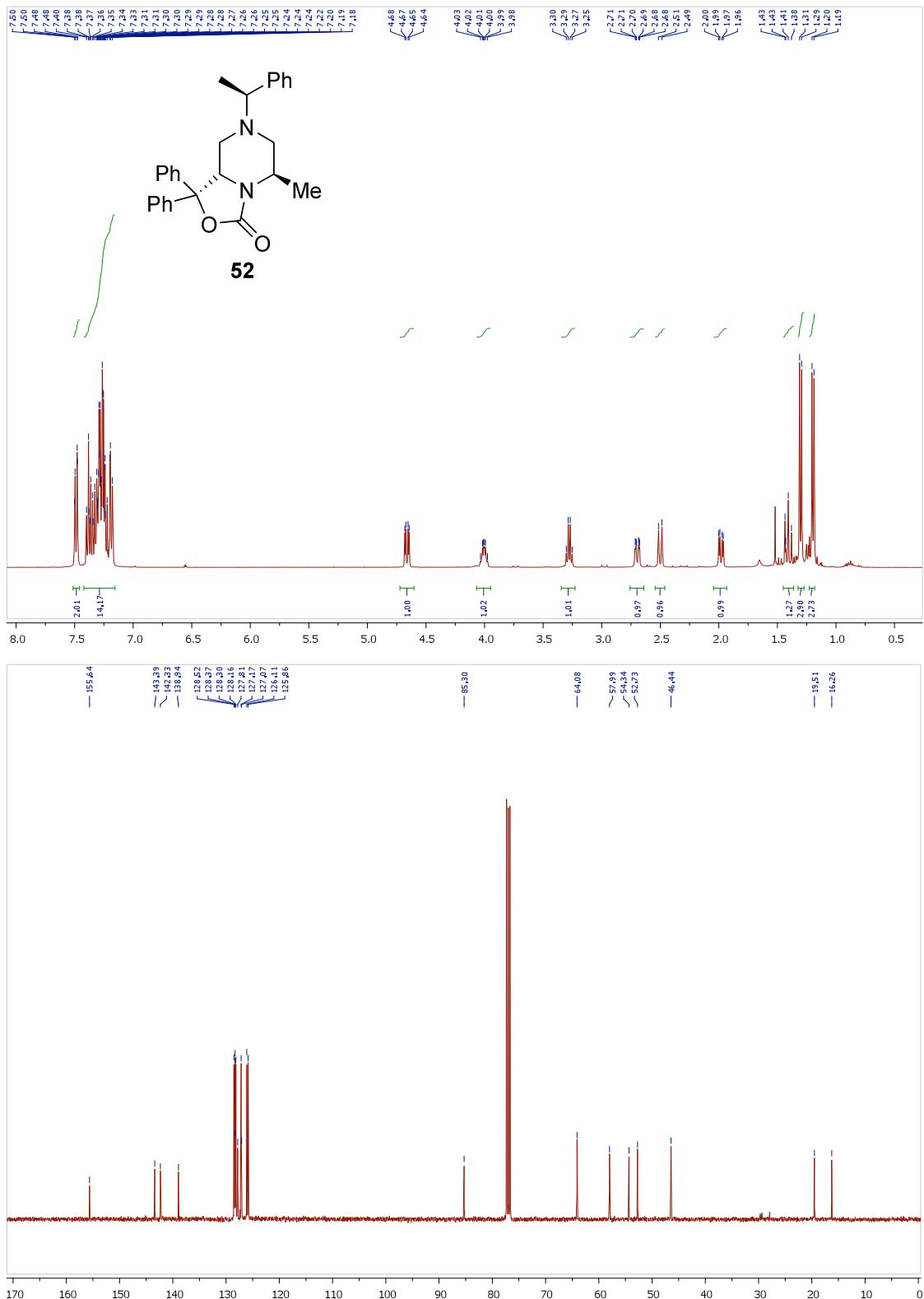


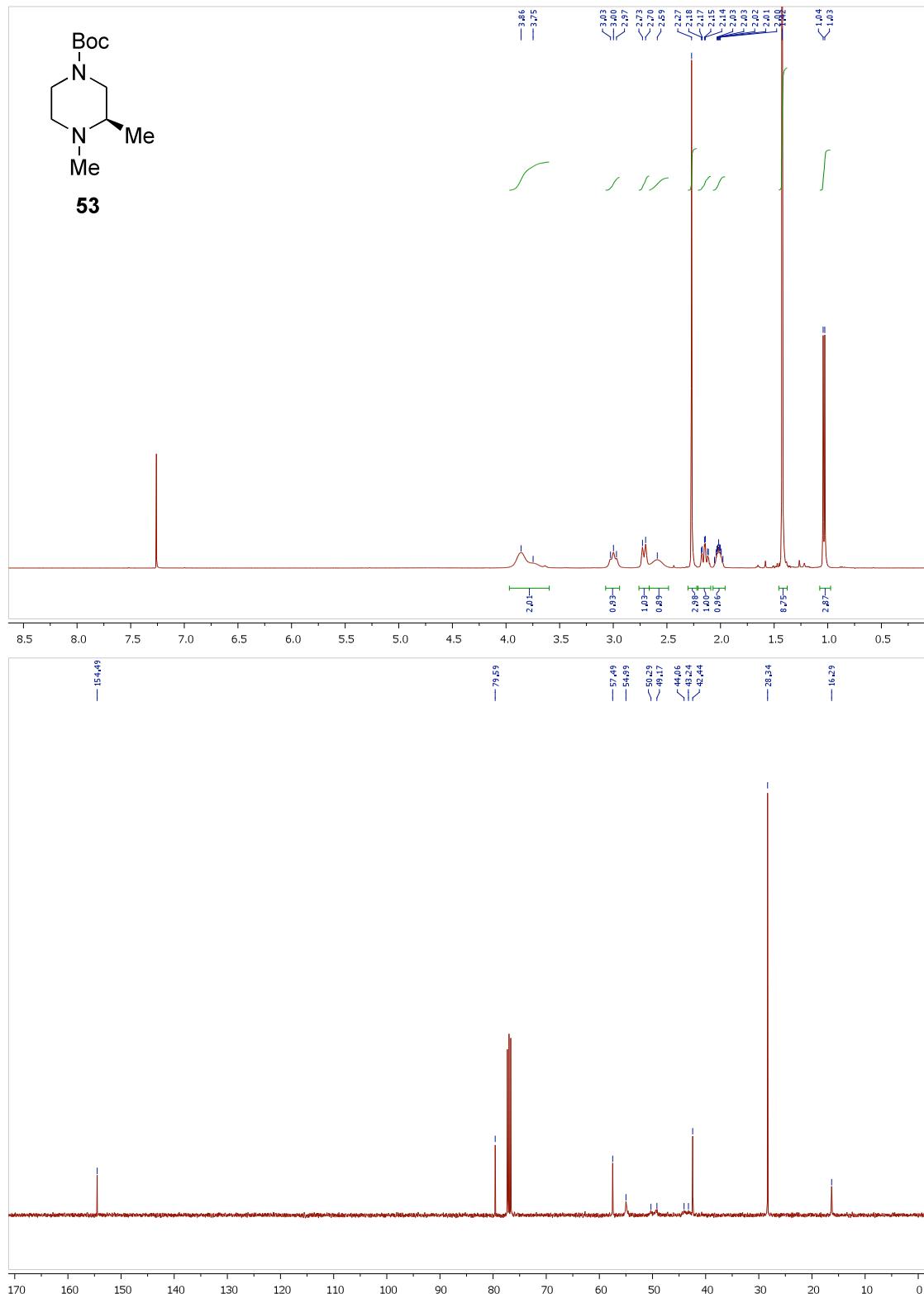
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

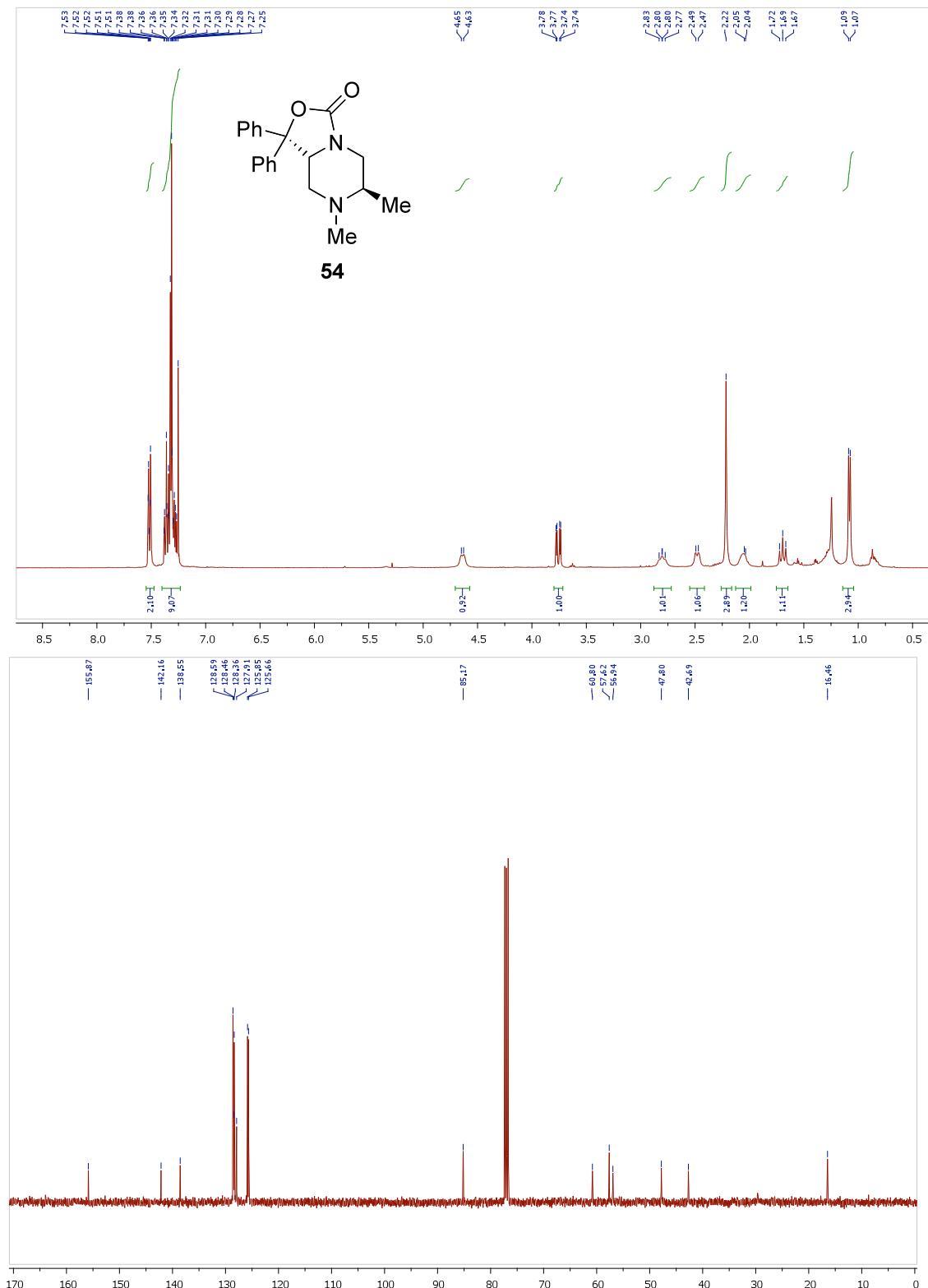


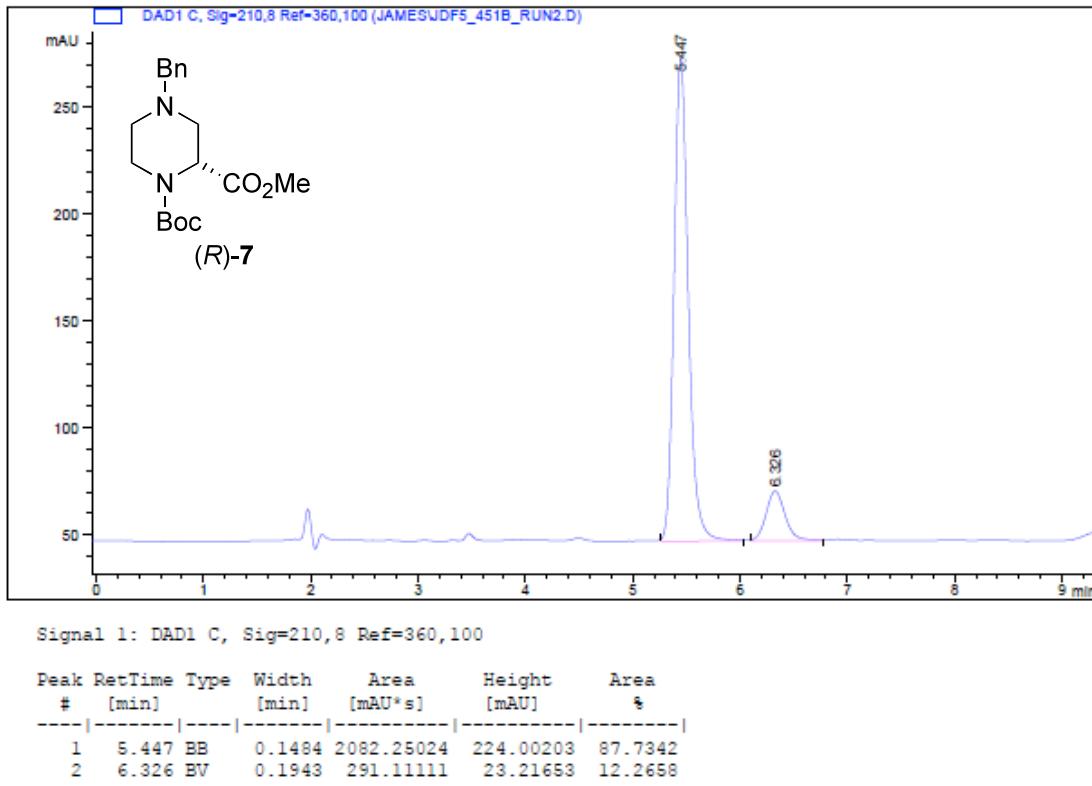
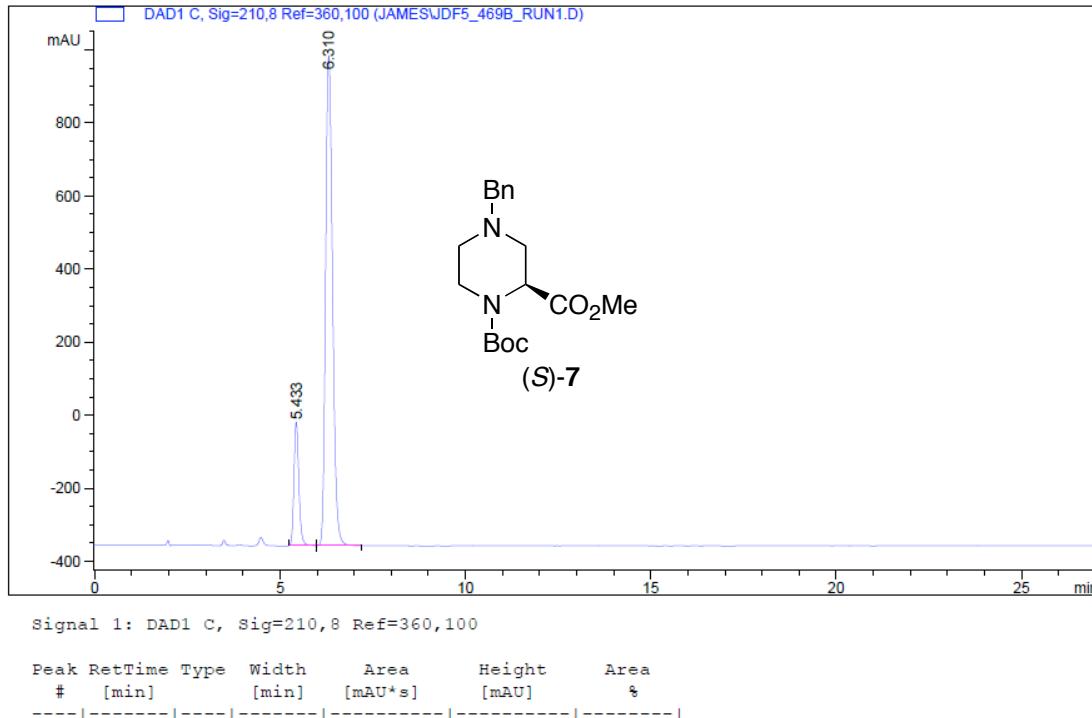
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

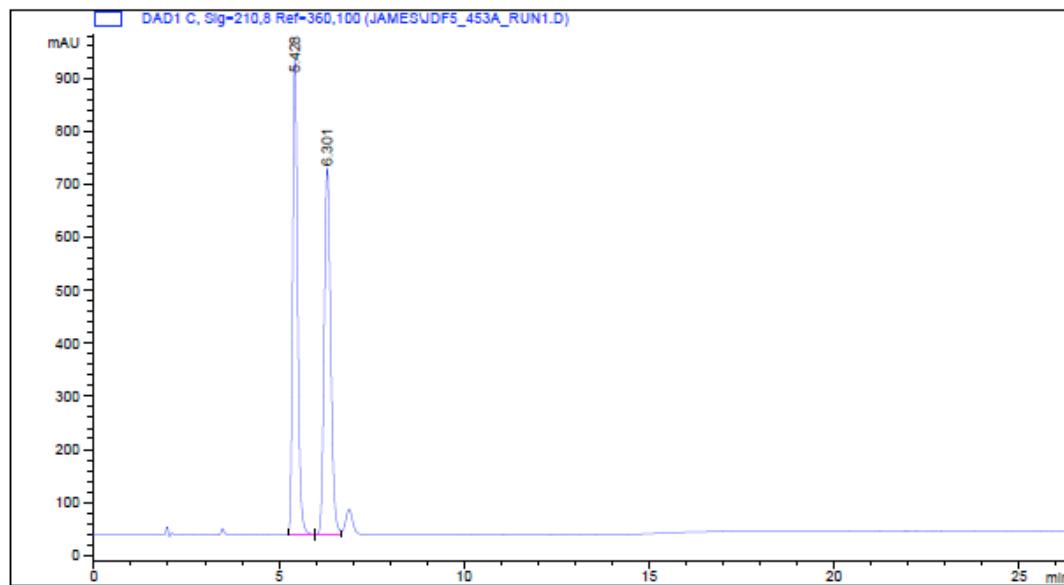


400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

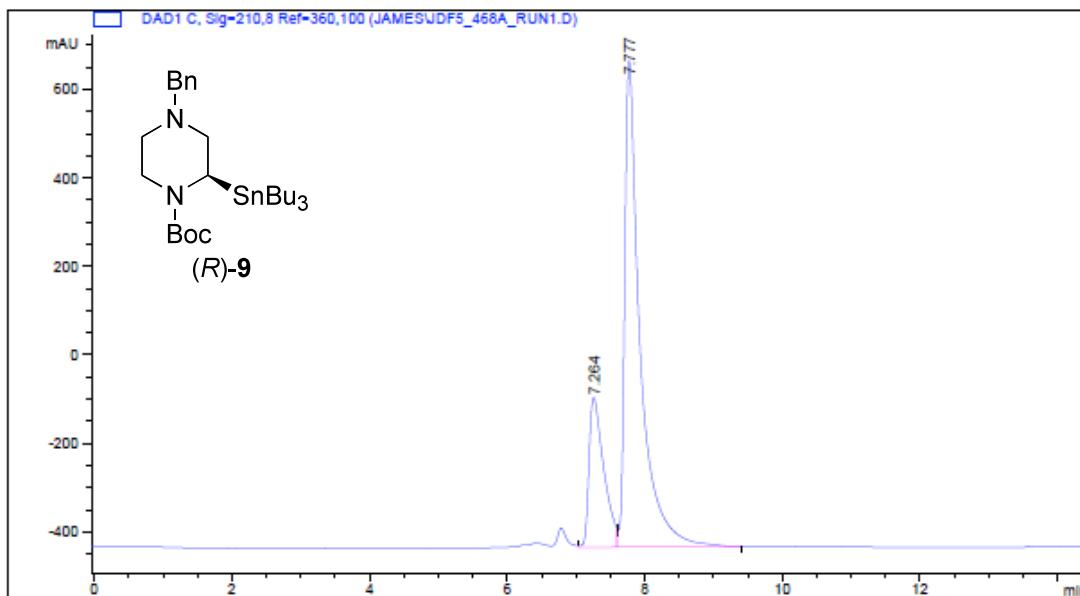


CSP-HPLC of *(R)*-7 of 88:12 erCSP-HPLC of *(S)*-7 of 85:15 er

CSP-HPLC of *rac-7*

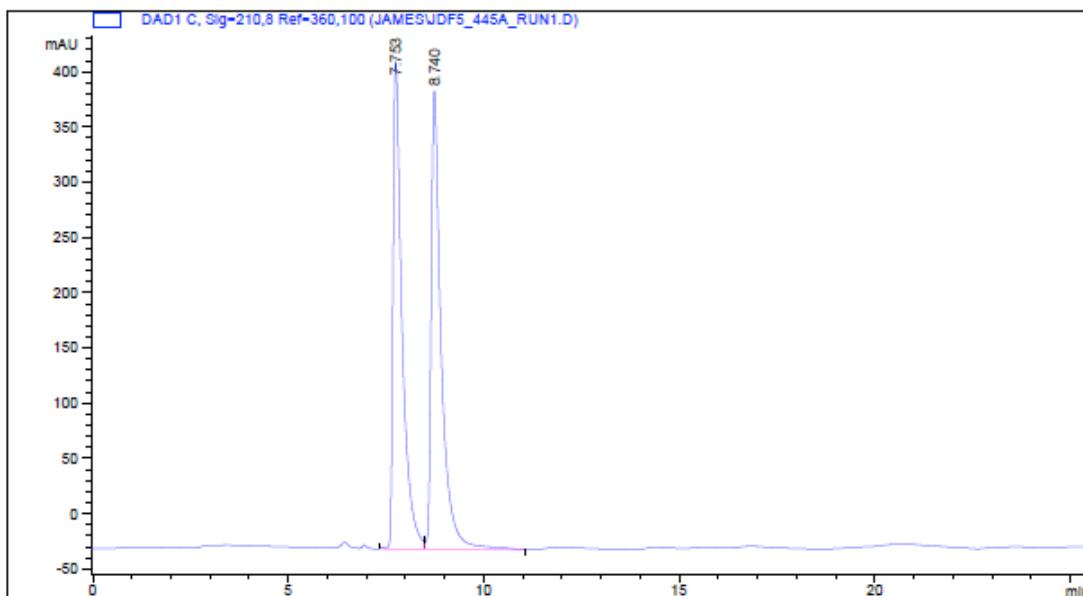
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 5.428 | BV | 0.1498 | 8386.26953 | 890.79370 | 49.7295 |
| 2 | 6.301 | VV | 0.1998 | 8477.49512 | 687.99646 | 50.2705 |

CSP-HPLC of *(R)*-9 of 77:23 er

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

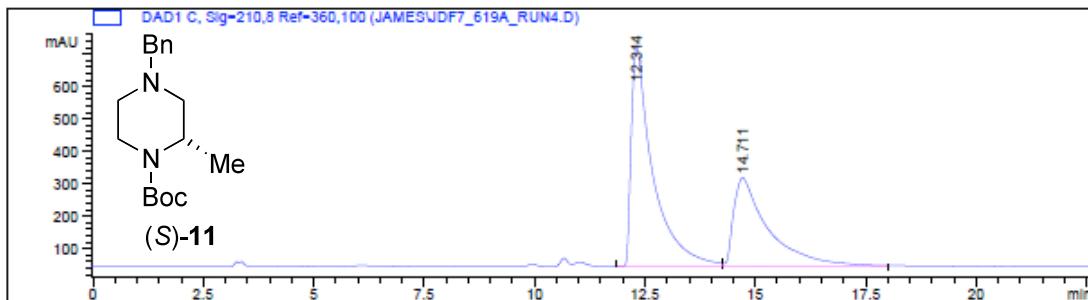
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 7.264 | VV | 0.2228 | 5053.29785 | 337.36194 | 22.7772 |
| 2 | 7.777 | VB | 0.2216 | 1.71325e4 | 1100.77344 | 77.2228 |

CSP-HPLC of *rac*-9

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

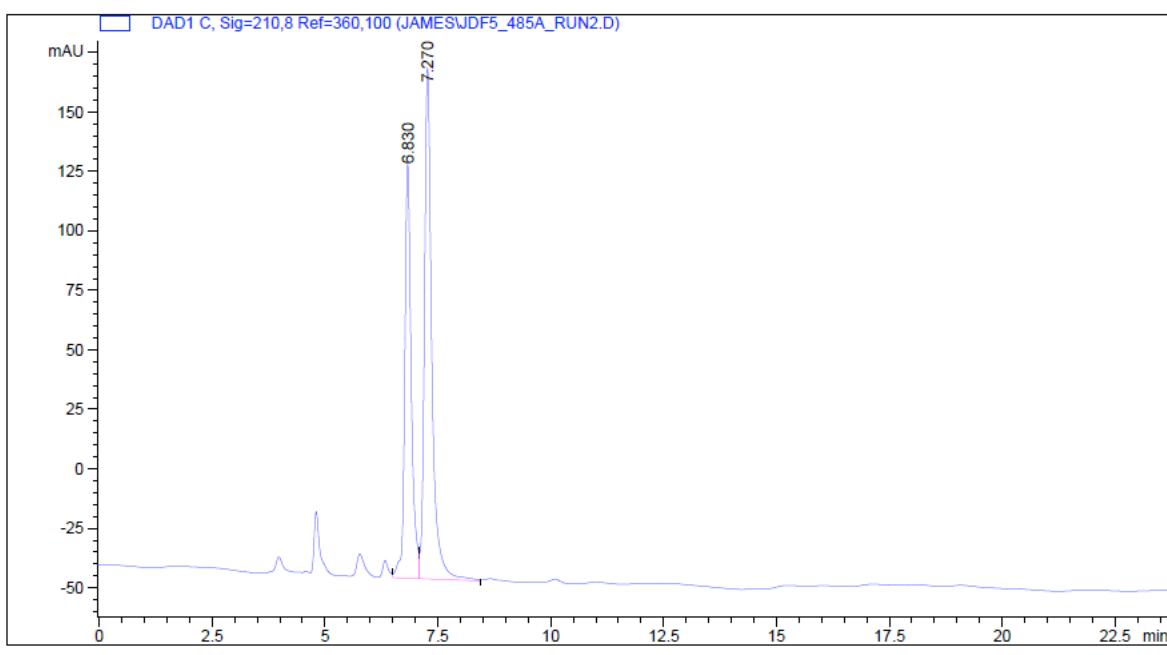
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 7.753 | BV | 0.2347 | 7080.19141 | 442.42441 | 49.0265 |
| 2 | 8.740 | VB | 0.2549 | 7361.38330 | 415.02277 | 50.9735 |

CSP-HPLC of (S)-11 of 61:39 er

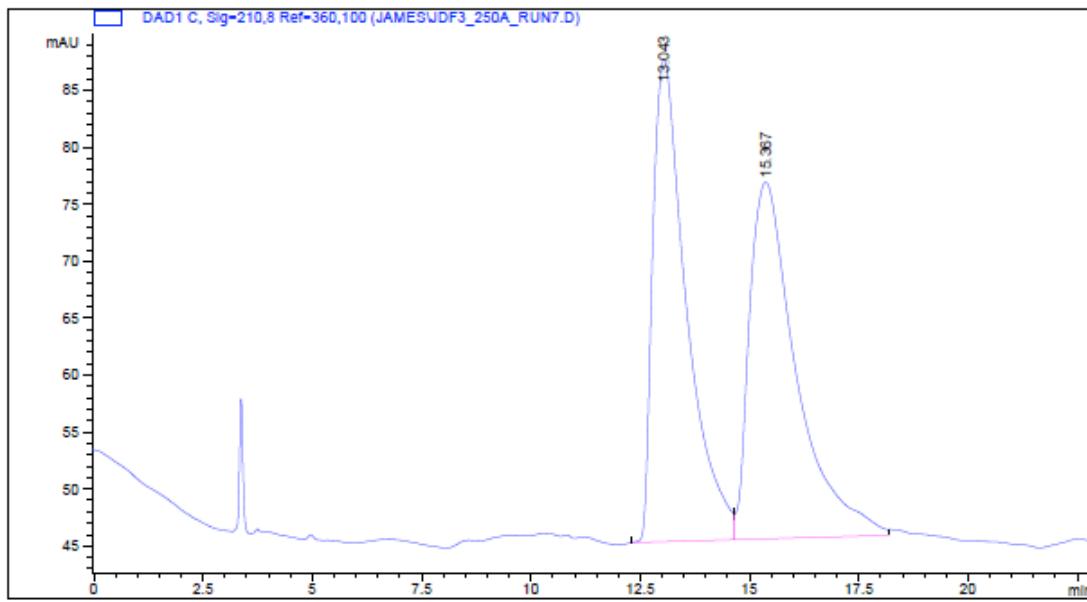


| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 12.314 | BV | 0.4764 | 2.30430e4 | 678.16760 | 60.9576 |
| 2 | 14.711 | VB | 0.7592 | 1.47587e4 | 272.79419 | 39.0424 |

CSP-HPLC of (S)-11 of 58:42 er

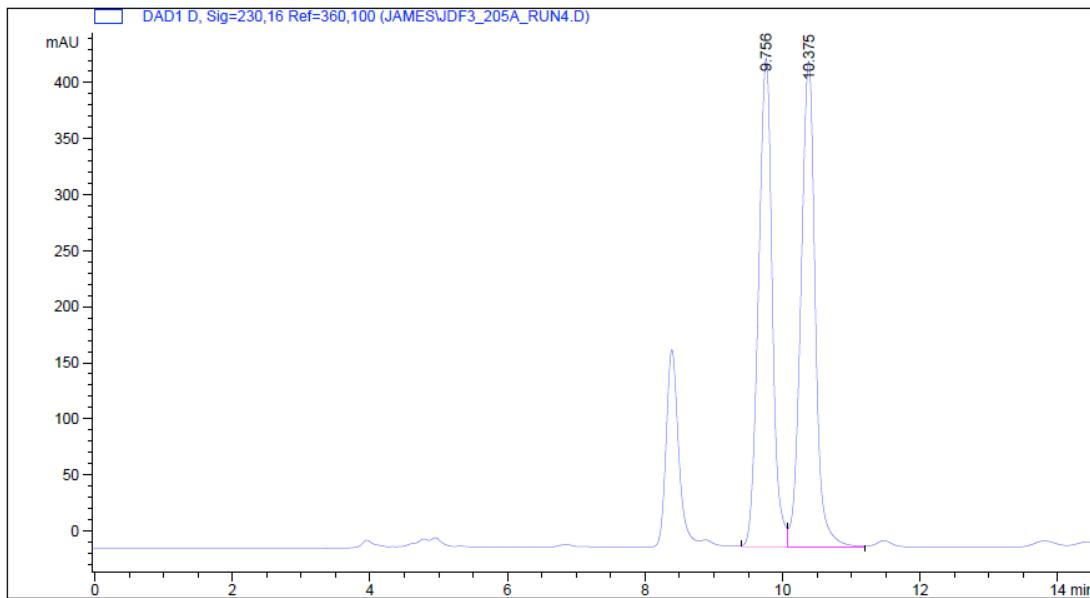


| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 6.830 | VV | 0.1587 | 1754.10193 | 172.33325 | 41.6165 |
| 2 | 7.270 | VB | 0.1744 | 2460.82202 | 213.59125 | 58.3835 |

CSP-HPLC of *rac*-11 (Chiralcel IC 99:1 hexane:*i*-PrOH, 1.0 mL min⁻¹)

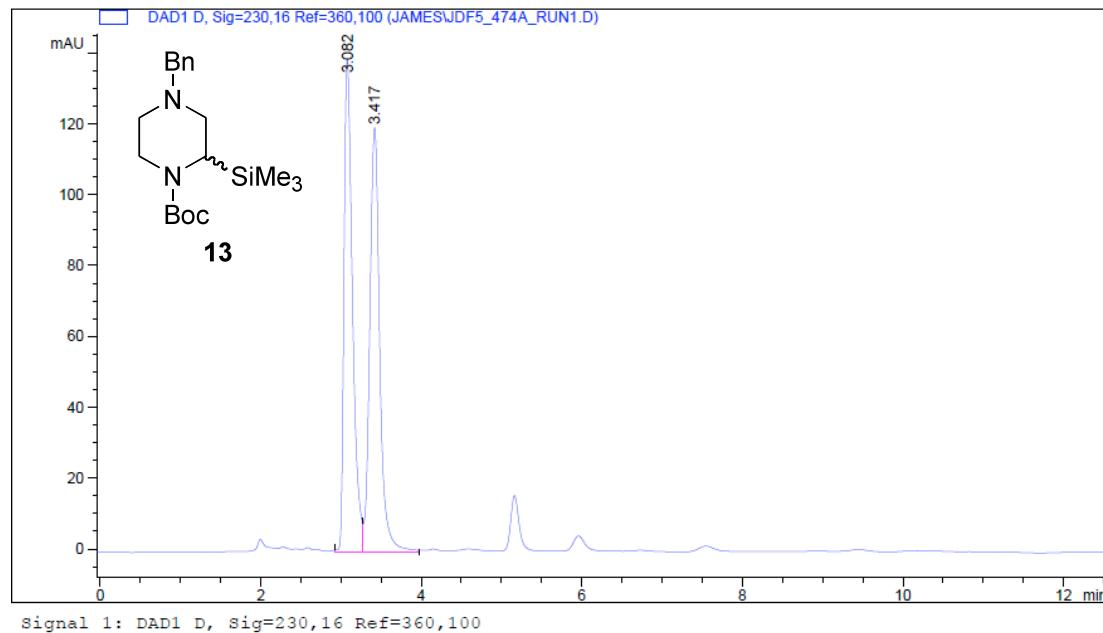
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 13.043 | BV | 0.8018 | 2270.42139 | 42.32731 | 49.2593 |
| 2 | 15.367 | VB | 1.1353 | 2338.70410 | 31.31486 | 50.7407 |

CSP-HPLC of *rac*-11 (CSP-HPLC: Chiralcel AD-H 99:1 hexane:*i*-PrOH, 0.5 mL min⁻¹)

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

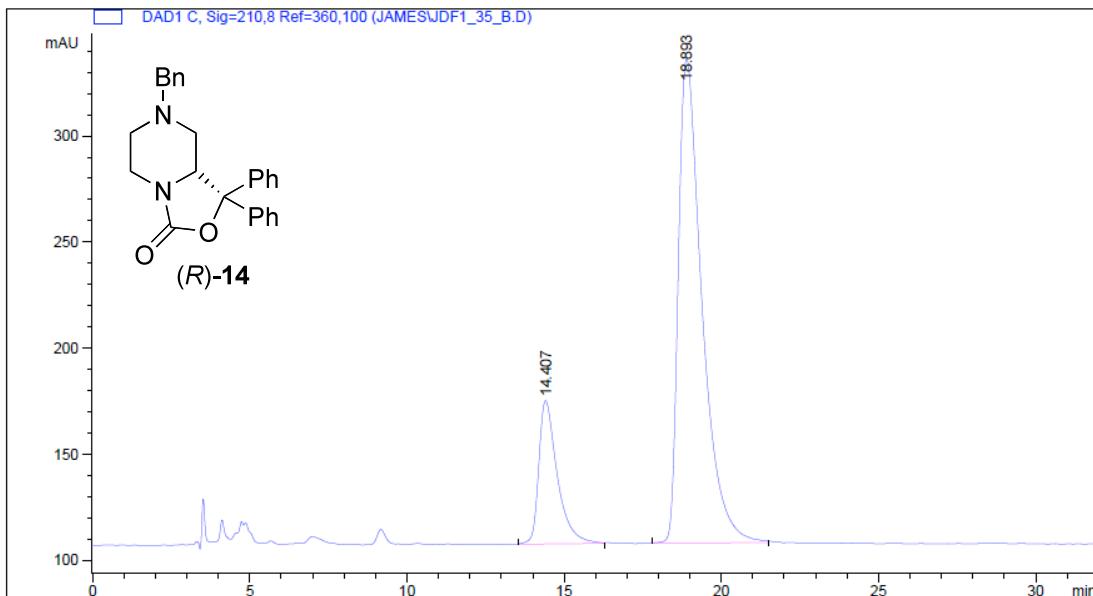
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 9.756 | BV | 0.2142 | 6070.11914 | 436.66479 | 49.1120 |
| 2 | 10.375 | VB | 0.2252 | 6289.63867 | 433.73816 | 50.8880 |

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

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 3.082 | BV | 0.1145 | 1022.69489 | 137.90204 | 49.6731 |
| 2 | 3.417 | VB | 0.1372 | 1036.15613 | 119.44853 | 50.3269 |

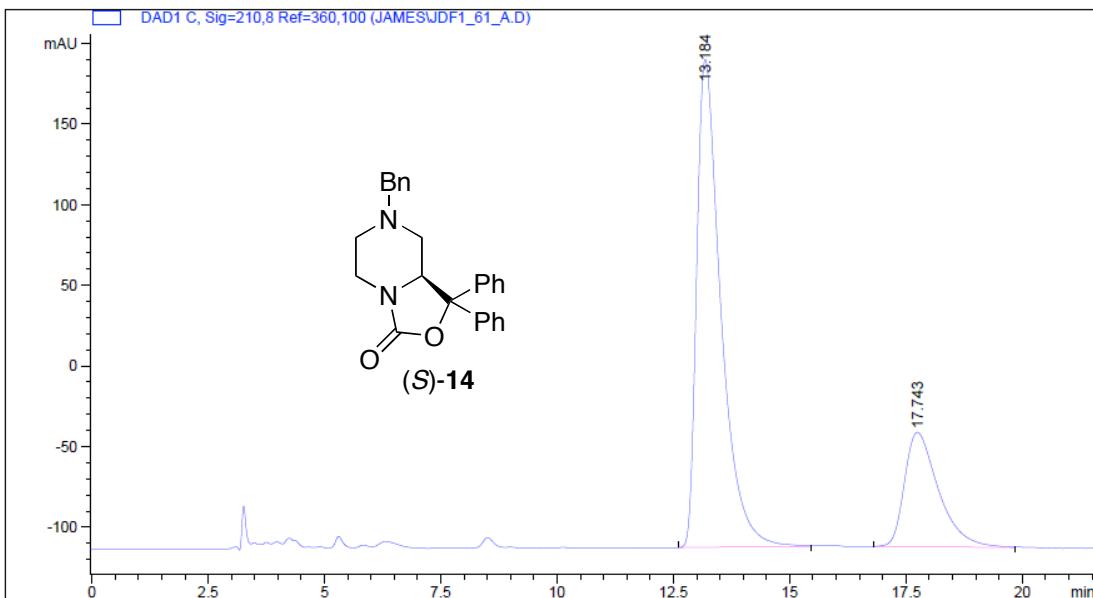
CSP-HPLC of *(R)*-14 of 81:19 er



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

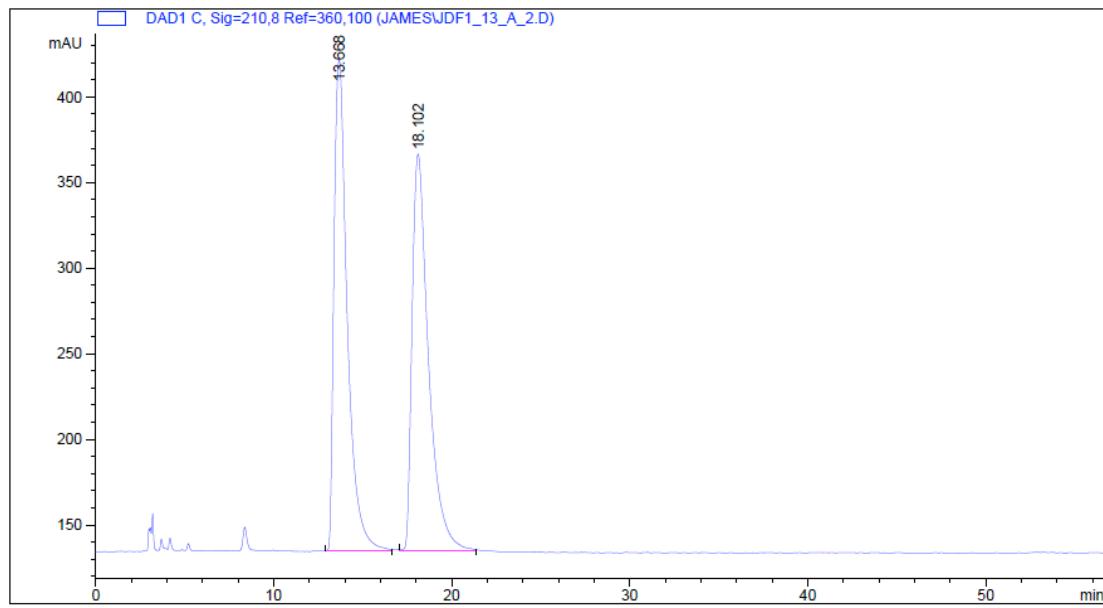
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 14.407 | BB | 0.6137 | 2765.11133 | 67.53465 | 18.8136 |
| 2 | 18.893 | BB | 0.7939 | 1.19323e4 | 228.24980 | 81.1864 |

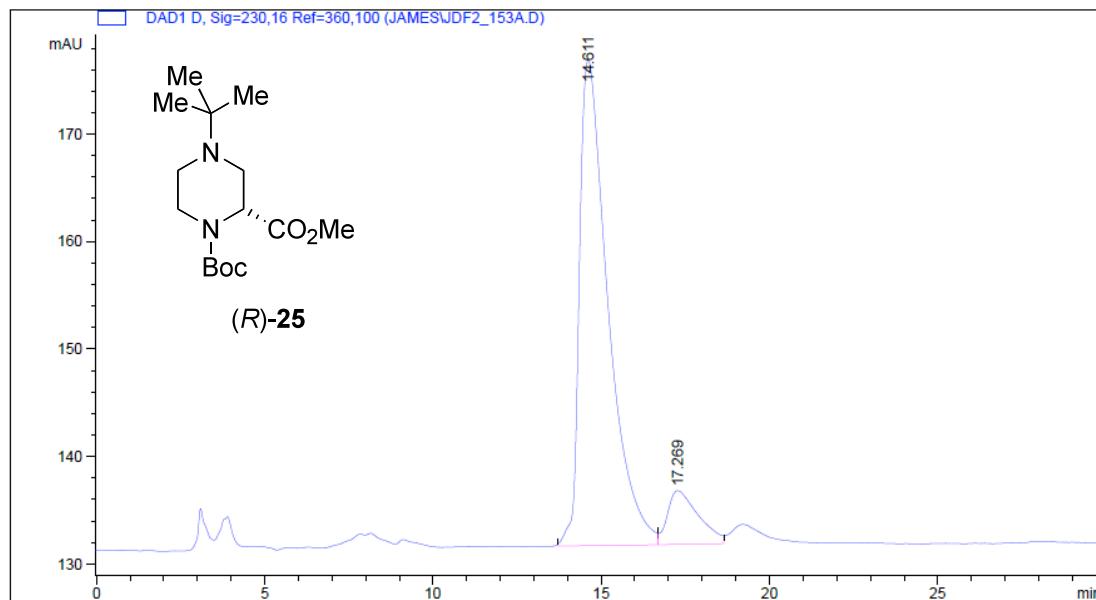
CSP-HPLC of (*S*)-14 of 75:15 er



Signal 1: DAD1 C, sig=210,8 Ref=360,100

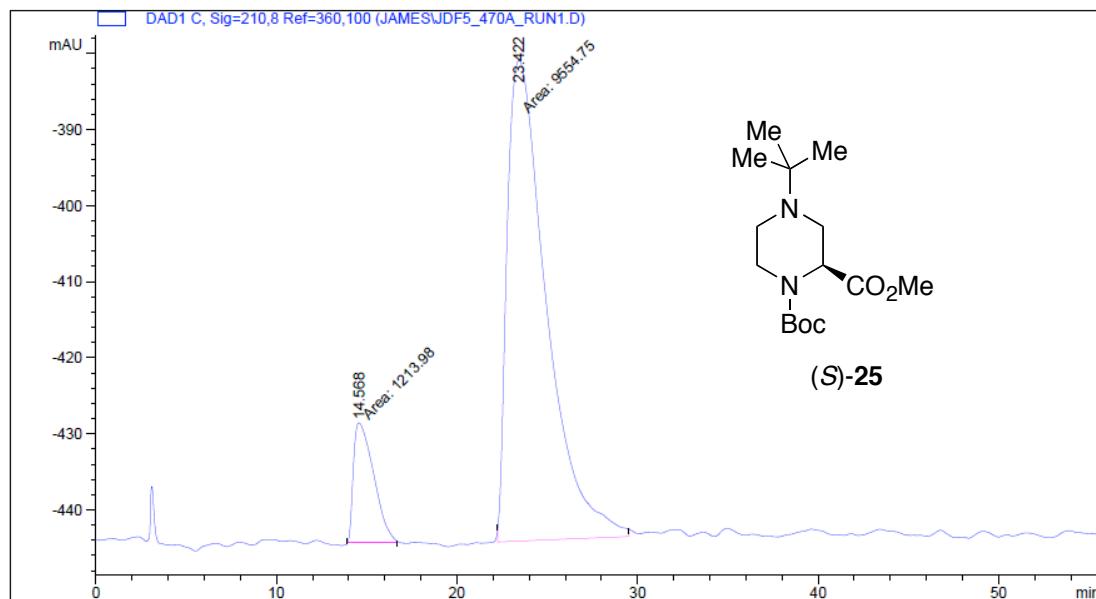
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 13.184 | BB | 0.5422 | 1.09546e4 | 302.67612 | 75.1418 |
| 2 | 17.743 | BB | 0.7709 | 3623.98145 | 71.06499 | 24.8582 |

CSP-HPLC of *rac-14*

CSP-HPLC of *(R)*-25 of 89:11 er

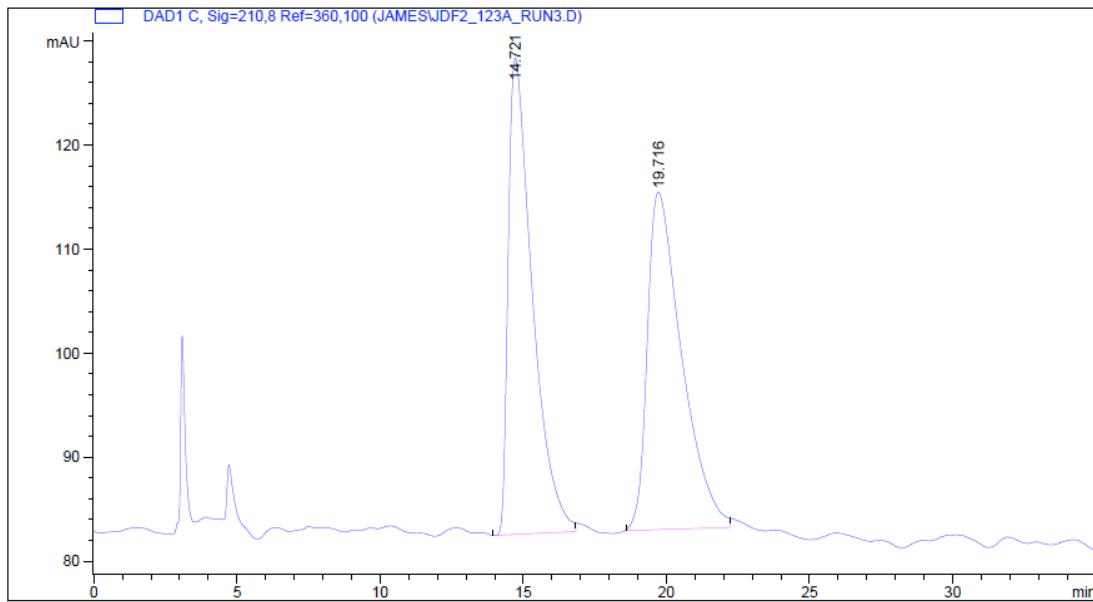
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

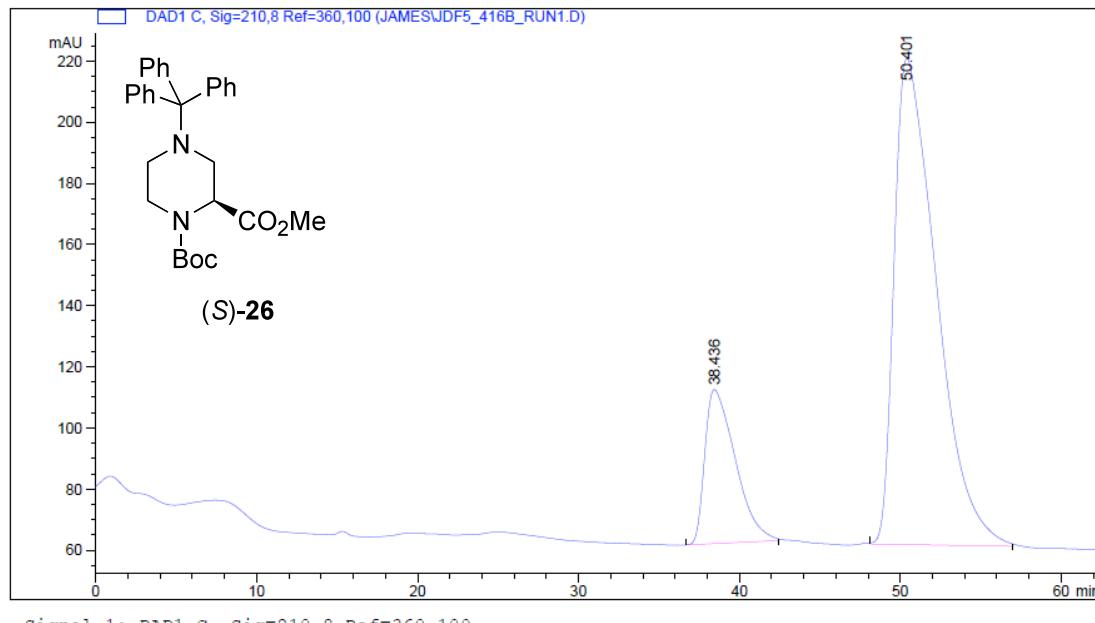
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 14.611 | BV | 0.8931 | 2670.76611 | 45.21516 | 89.2847 |
| 2 | 17.269 | VV | 0.9025 | 320.52551 | 5.00935 | 10.7153 |

CSP-HPLC of *(S)*-25 of 89:11 er)

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

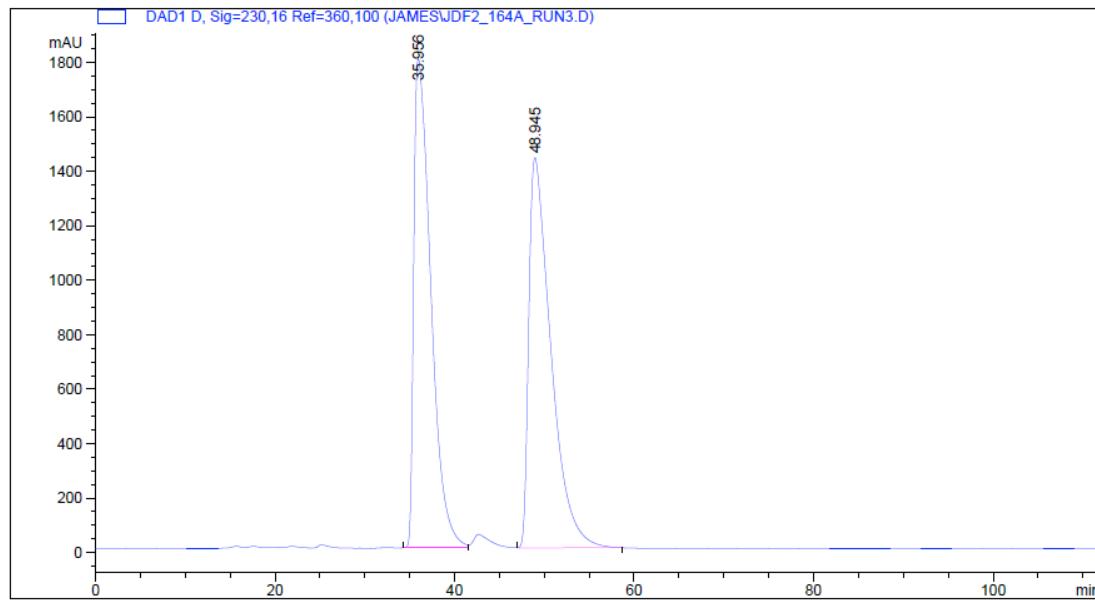
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 14.568 | MM | 1.2911 | 1213.98022 | 15.67170 | 11.2732 |
| 2 | 23.422 | MM | 2.5192 | 9554.74902 | 63.21385 | 88.7268 |

CSP-HPLC of *rac-25*

CSP-HPLC of *(S)*-26 of 81:19 er

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

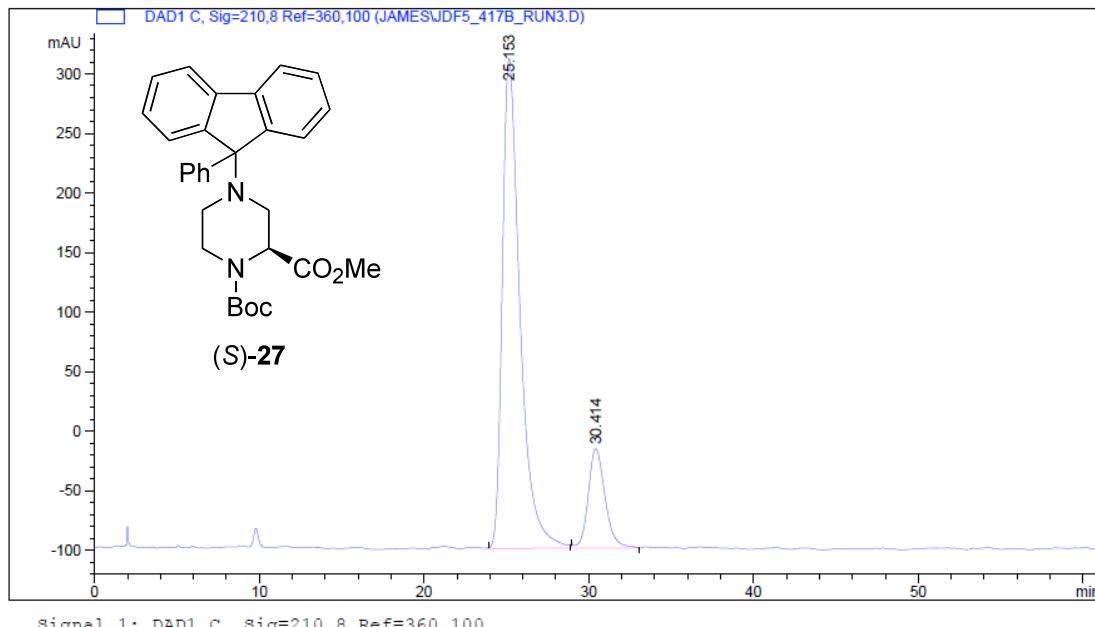
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 38.436 | BB | 1.9268 | 6627.72949 | 50.37872 | 18.6203 |
| 2 | 50.401 | BB | 2.5579 | 2.89664e4 | 158.96136 | 81.3797 |

CSP-HPLC of *rac*-26

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

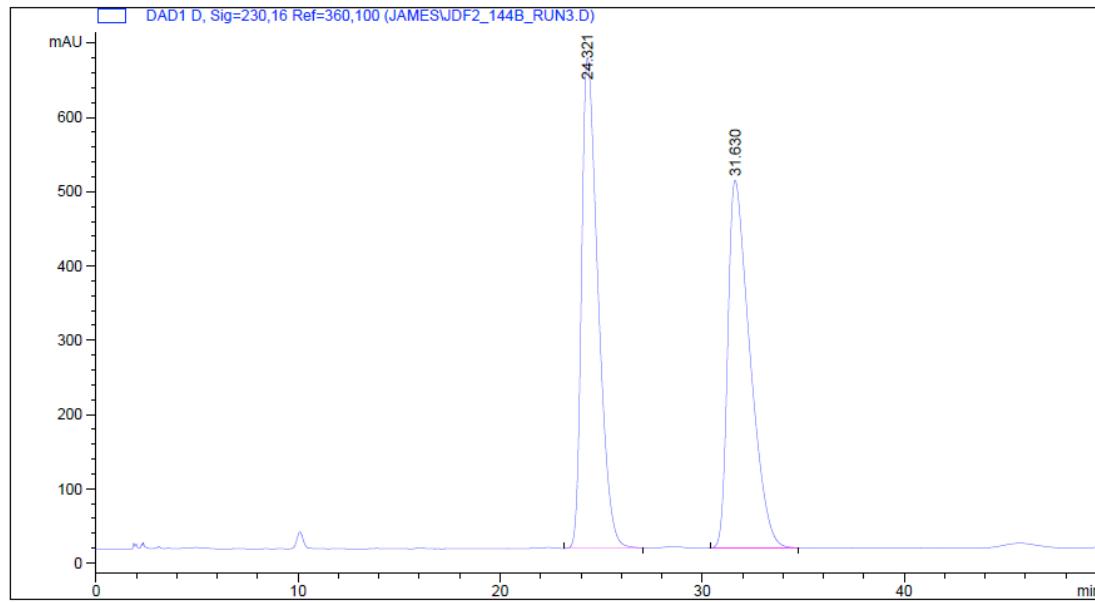
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 35.956 | BV | 2.0567 | 2.37487e5 | 1798.30664 | 49.1960 |
| 2 | 48.945 | BB | 2.4763 | 2.45249e5 | 1433.28308 | 50.8040 |

CSP-HPLC of (S)-27 of 84:16 er



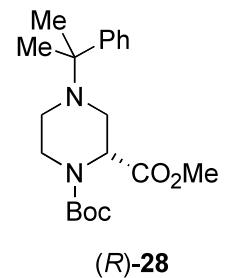
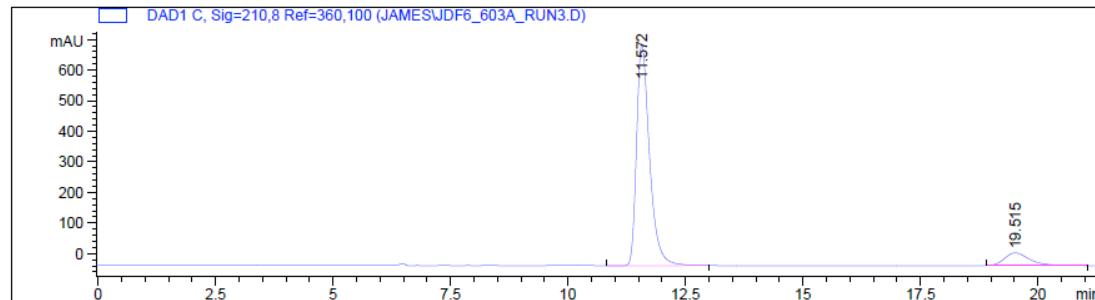
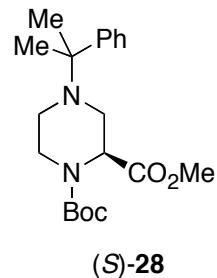
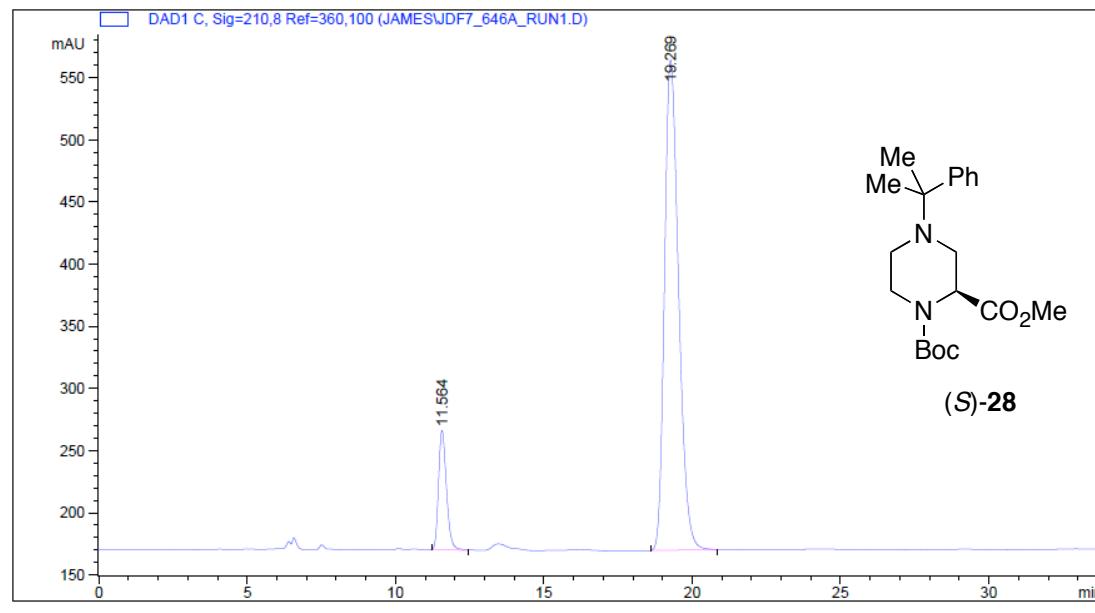
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

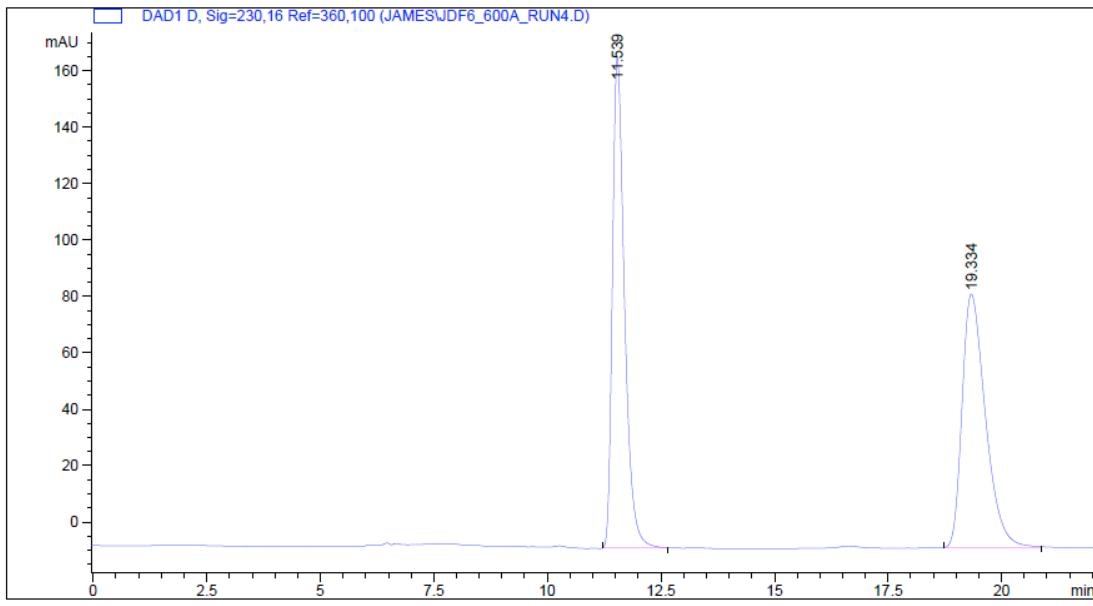
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 25.153 | BB | 1.1246 | 3.06213e4 | 411.28030 | 83.6868 |
| 2 | 30.414 | BV | 1.0814 | 5969.06836 | 83.55579 | 16.3132 |

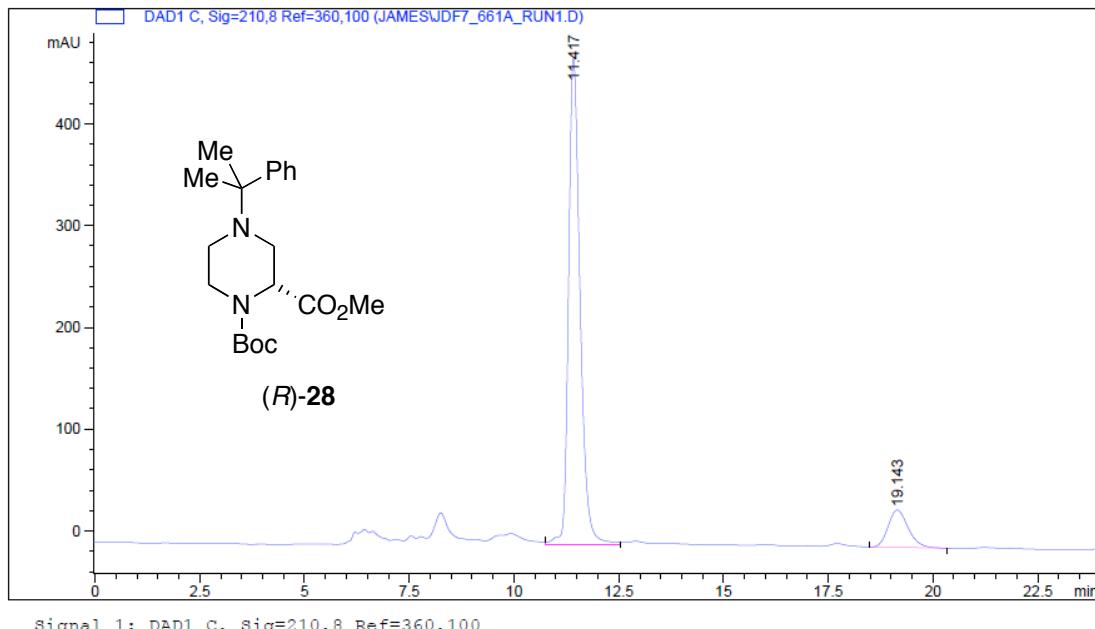
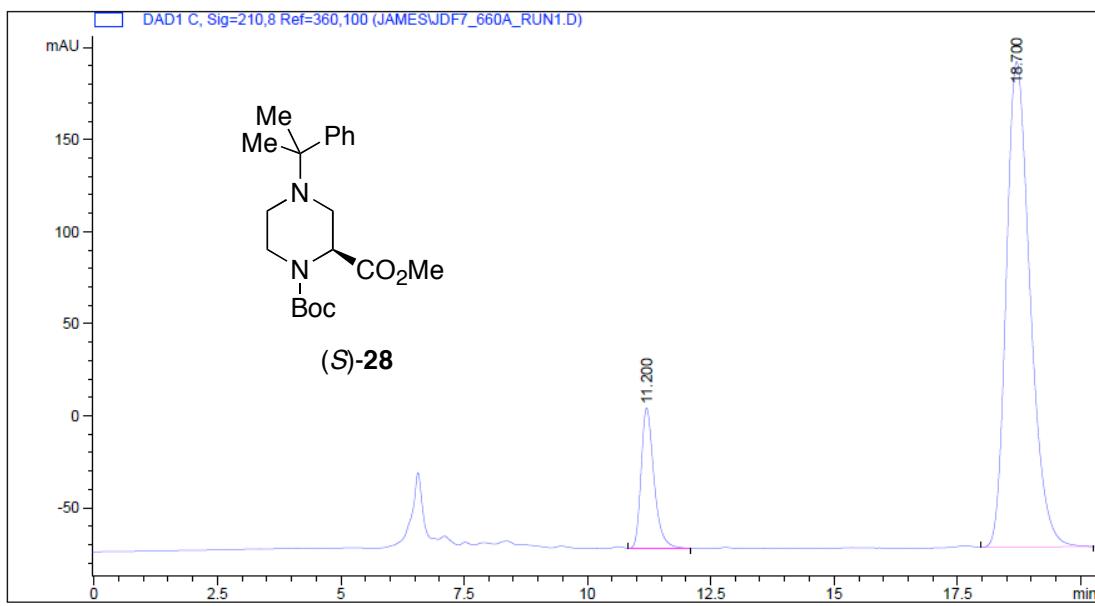
CSP-HPLC of *rac*-27

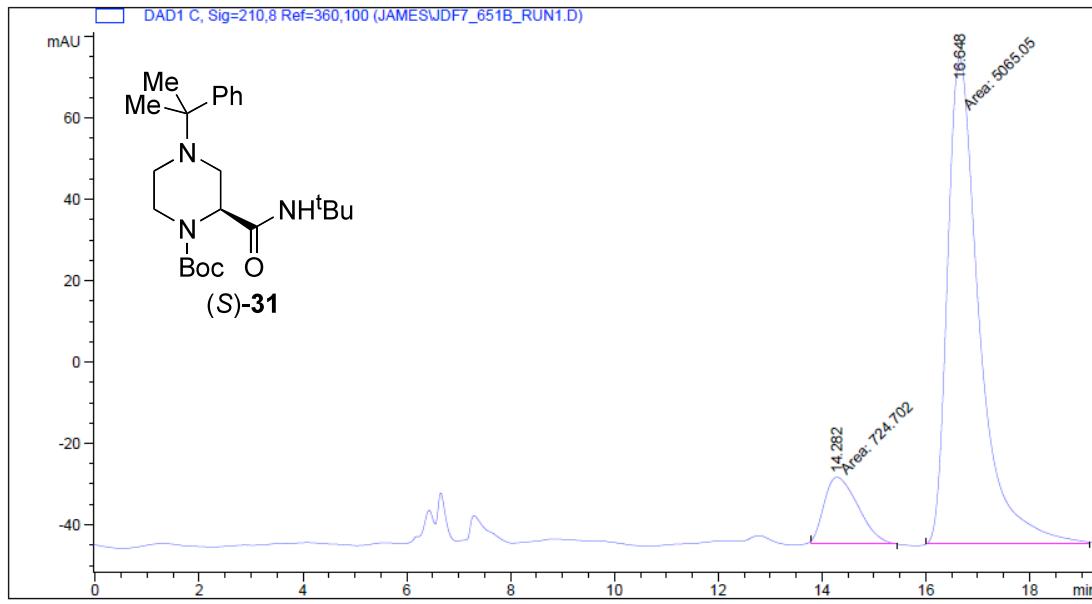
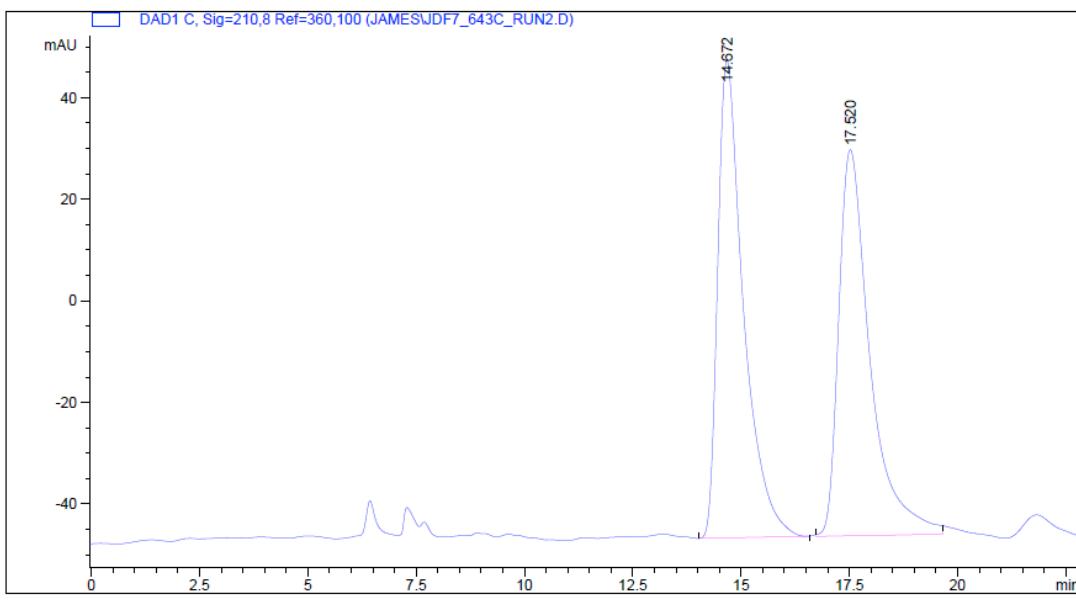
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

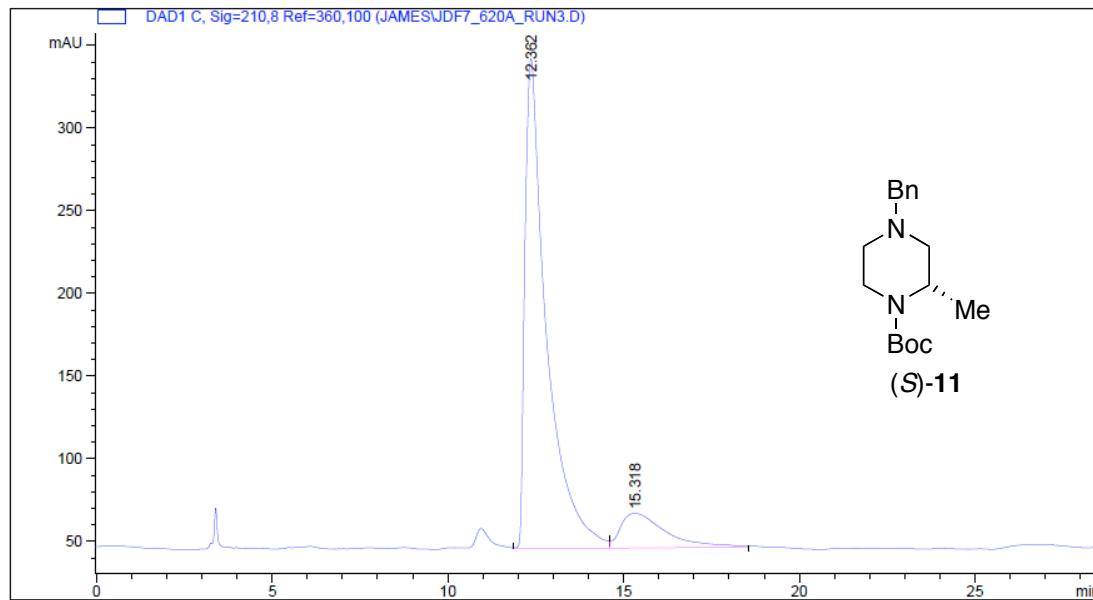
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 24.321 | VB | 0.8606 | 3.74121e4 | 660.68658 | 49.8483 |
| 2 | 31.630 | BB | 1.1305 | 3.76397e4 | 495.36377 | 50.1517 |

CSP-HPLC of *(R)*-28 of 90:10 erCSP-HPLC of *(S)*-28 of 88:12 er

CSP-HPLC of *rac-28*

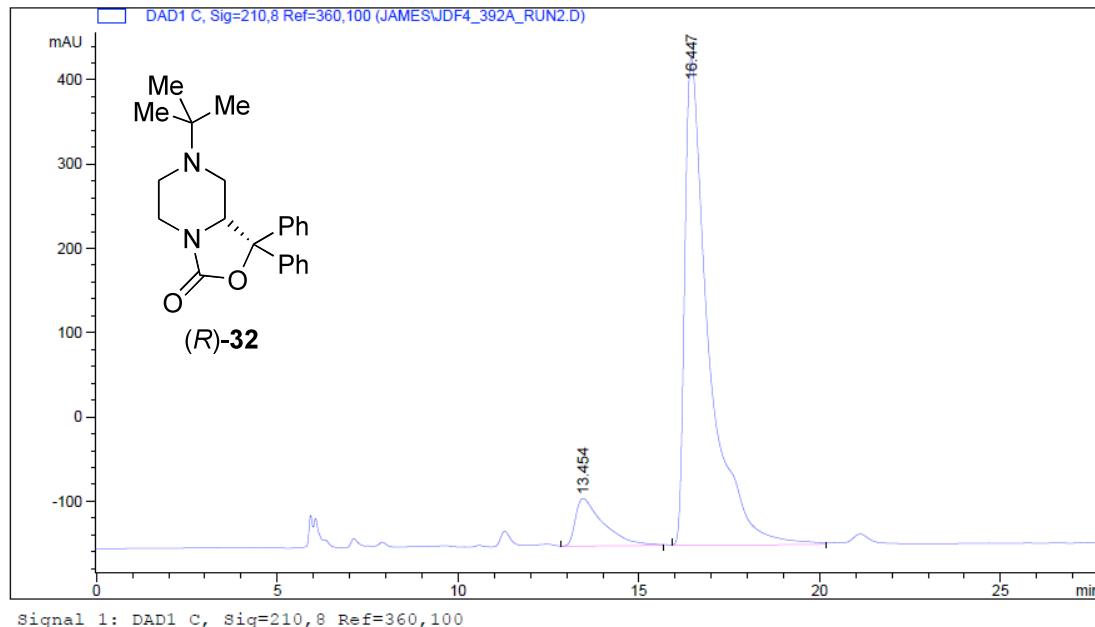
CSP-HPLC of (*R*)-**28** of 88:12 er, derived from (*S*)-**30** (Table 1, entry 8)CSP-HPLC of (*S*)-**28** of 86:14 er, derived from (*R*)-**30** (Table 1, entry 9)

CSP-HPLC of *(S)*-31 of 87:13 erCSP-HPLC of *rac*-31

CSP-HPLC of (*S*)-**11** of 87:13 er (Scheme 6)

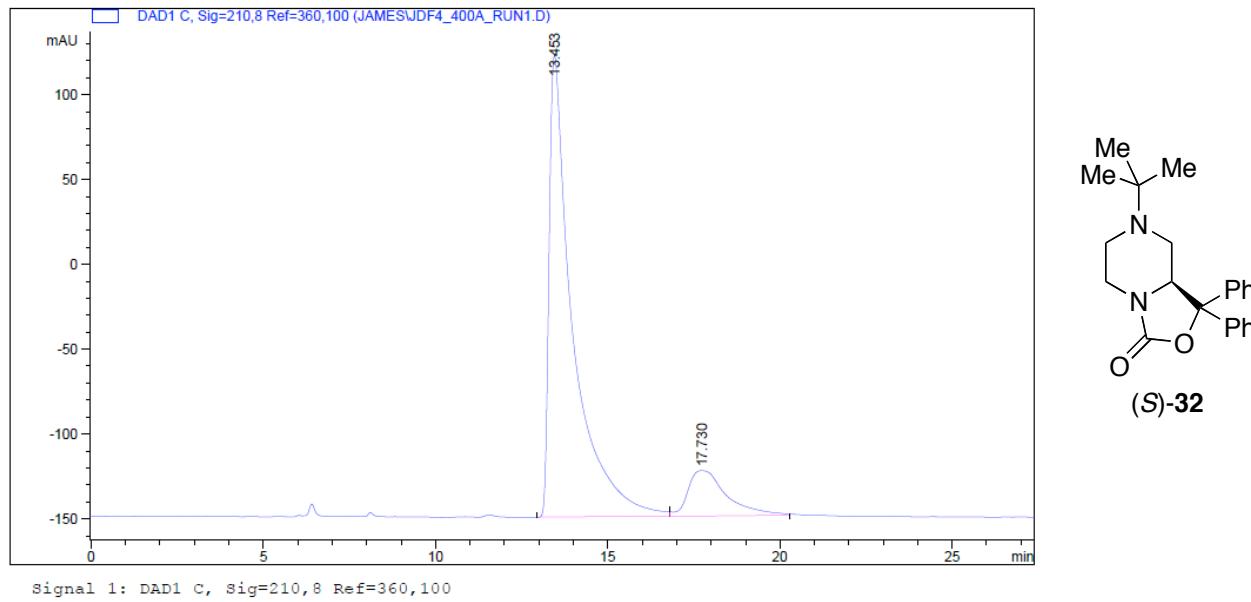
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 12.362 | VV | 0.6026 | 1.26696e4 | 296.45364 | 86.9217 |
| 2 | 15.318 | VB | 1.3314 | 1906.27734 | 20.99359 | 13.0783 |

CSP-HPLC of *(R)*-32 of 90:10 er

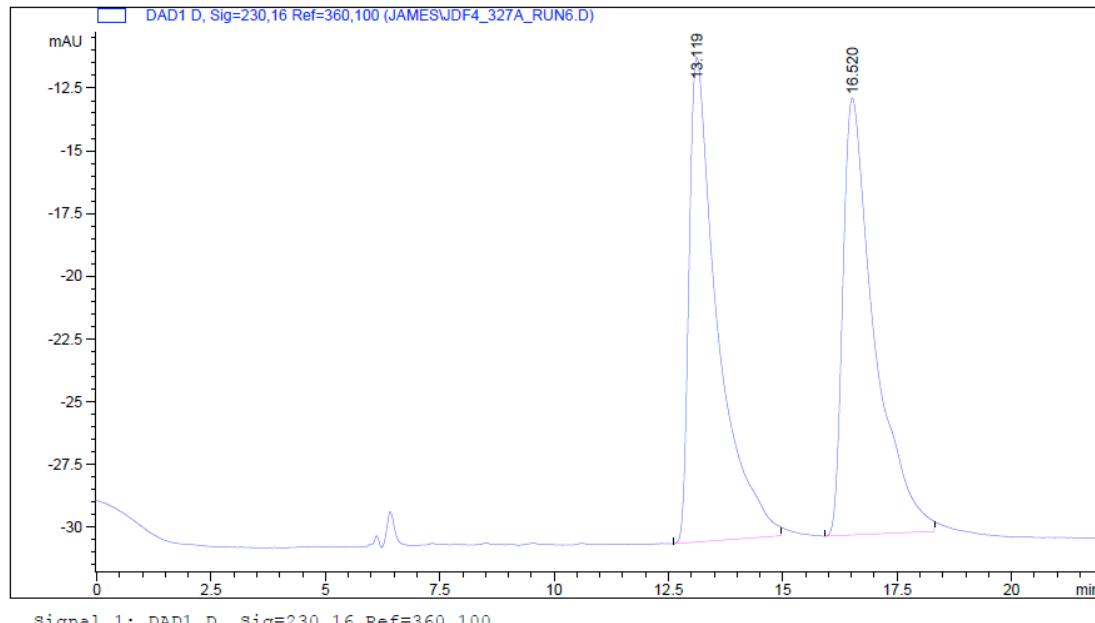
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 13.454 | VB | 0.7696 | 3078.76196 | 56.69077 | 10.3497 |
| 2 | 16.447 | BB | 0.6582 | 2.66685e4 | 578.10492 | 89.6503 |

CSP-HPLC of *(S)*-32 of 86:14 er

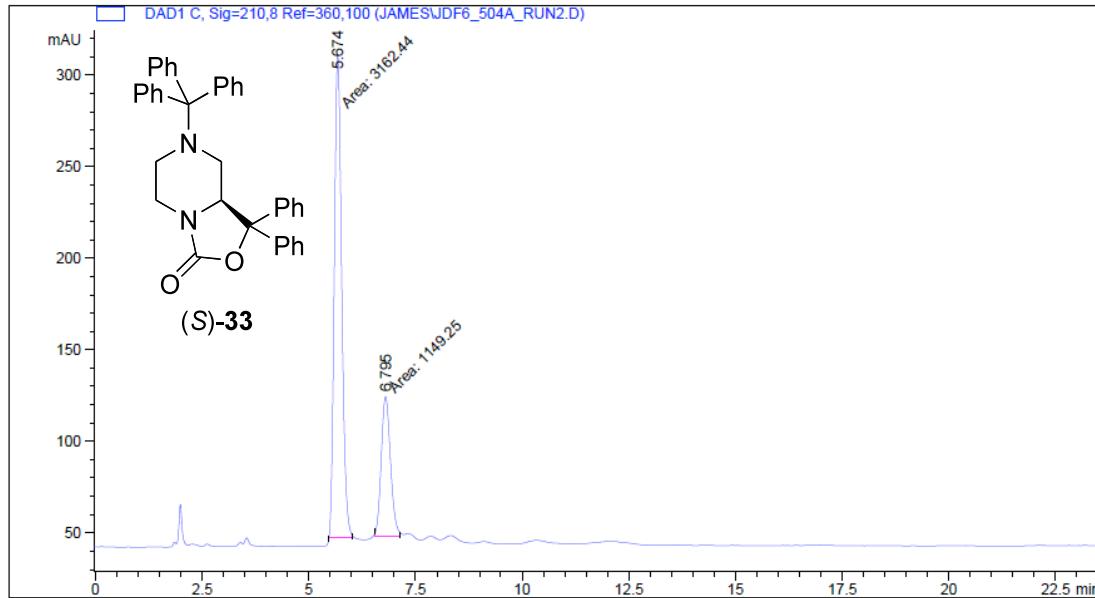
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 13.453 | BB | 0.6589 | 1.29442e4 | 272.16504 | 86.0116 |
| 2 | 17.730 | BB | 1.1744 | 2105.17236 | 26.74297 | 13.9884 |

CSP-HPLC of *rac-32*

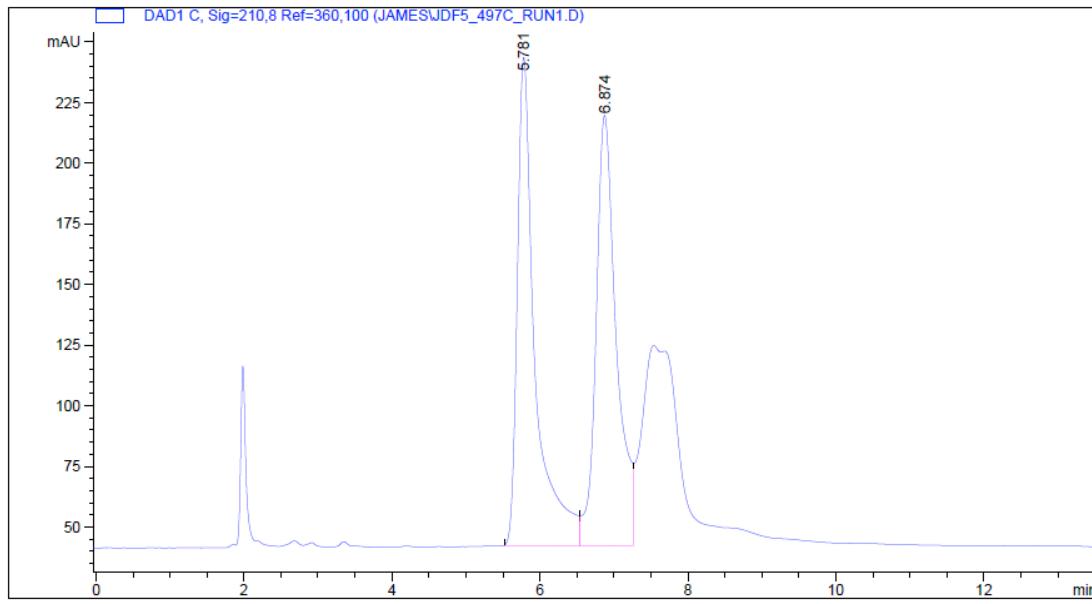
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 13.119 | BB | 0.6112 | 833.30585 | 19.31993 | 50.0240 |
| 2 | 16.520 | BB | 0.6896 | 832.50720 | 17.41784 | 49.9760 |

CSP-HPLC of *(S)*-33 of 73:27 er

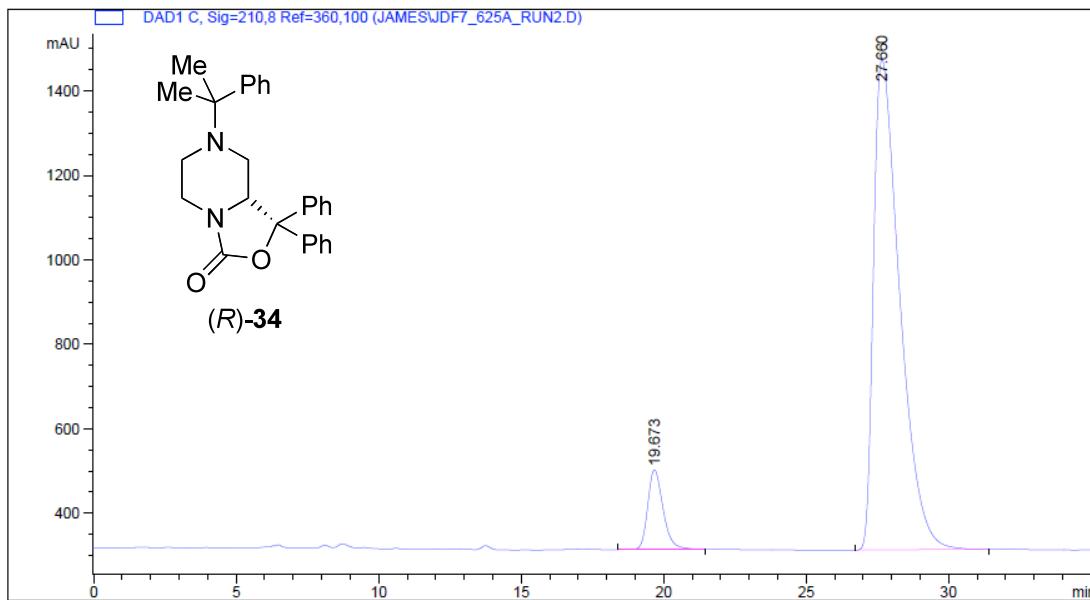
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 5.674 | MM | 0.1994 | 3162.44238 | 264.38614 | 73.3458 |
| 2 | 6.795 | MM | 0.2504 | 1149.24768 | 76.48548 | 26.6542 |

CSP-HPLC of *rac*-33

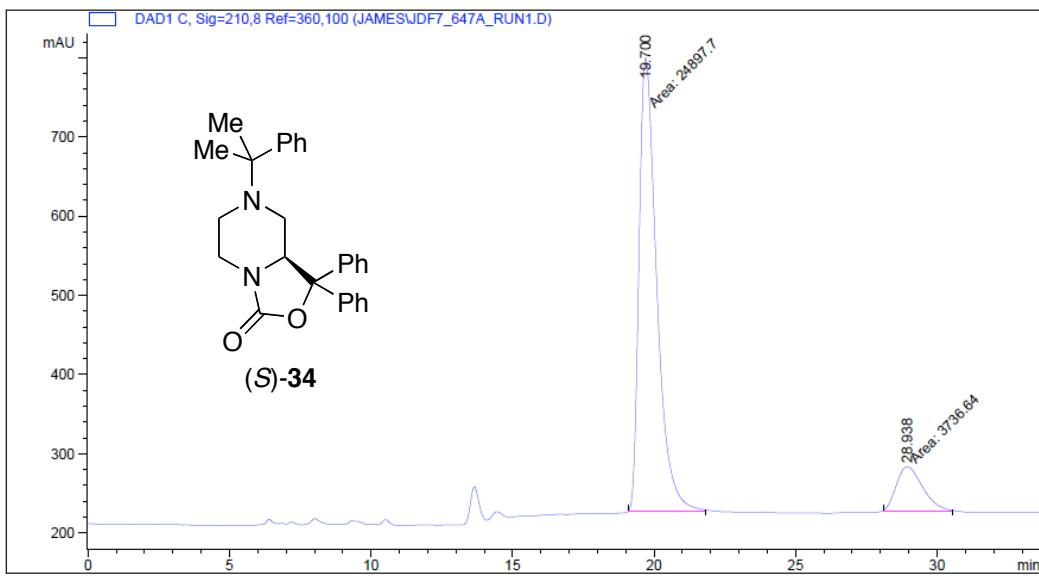
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 5.781 | BV | 0.2441 | 3360.23438 | 199.90845 | 49.8165 |
| 2 | 6.874 | VV | 0.2876 | 3384.98364 | 176.63727 | 50.1835 |

CSP-HPLC of *(R)*-34 of 91:9 er

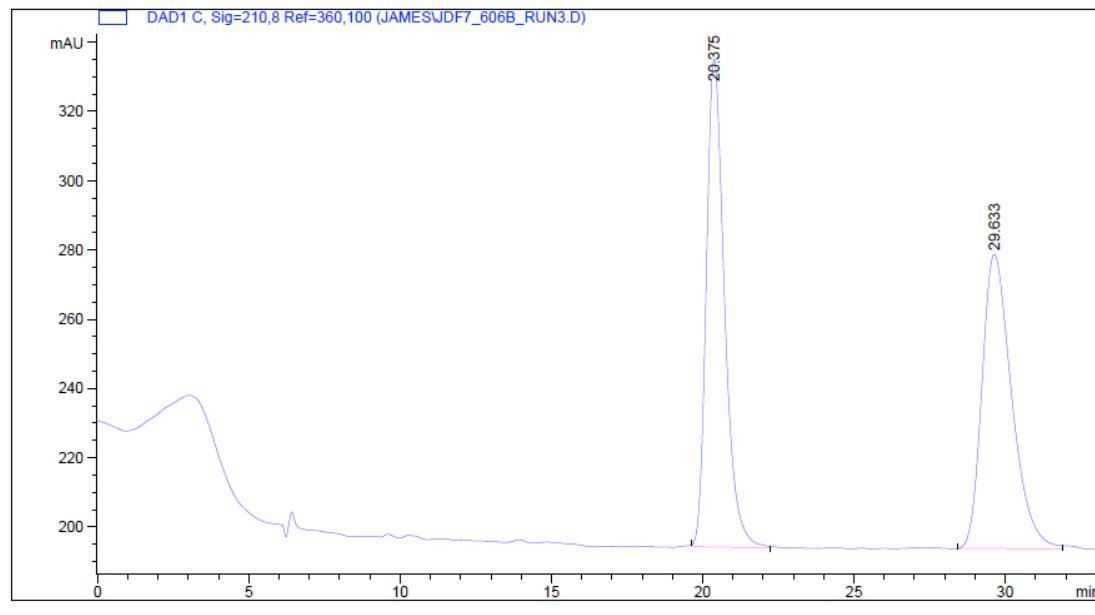
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 19.673 | BB | 0.5852 | 7146.47021 | 188.98573 | 8.7794 |
| 2 | 27.660 | BB | 0.9695 | 7.42536e4 | 1161.98181 | 91.2206 |

CSP-HPLC of *(S)*-34 of 87:13 er

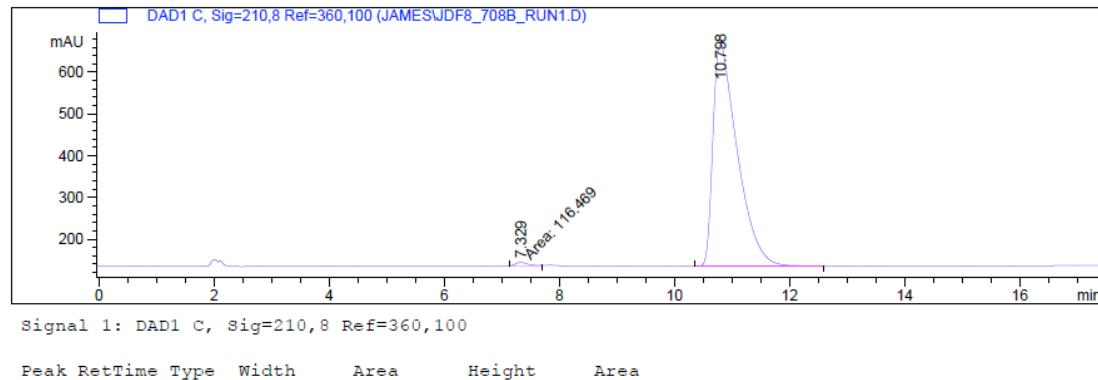
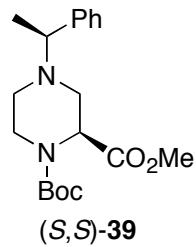
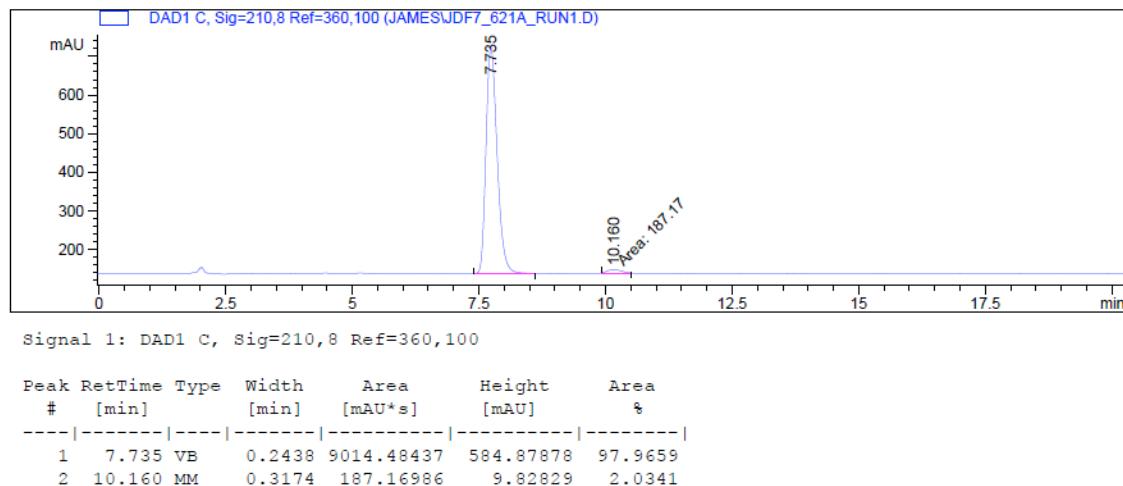
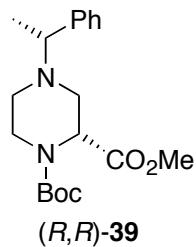
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 19.700 | MM | 0.7241 | 2.48977e4 | 573.09137 | 86.9505 |
| 2 | 28.938 | MM | 1.0947 | 3736.64233 | 56.89201 | 13.0495 |

CSP-HPLC of *rac-34*

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1 | 20.375 | BB | 0.6388 | 5876.84814 | 140.83409 | 50.3605 |
| 2 | 29.633 | BB | 1.0515 | 5792.71924 | 84.95527 | 49.6395 |

CSP-HPLC of *(S,S)*-39 of >99:1 erCSP-HPLC of *(R,R)*-39 of 98:2 er

4 References for Supporting Information

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