

## **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 N<sub>2</sub> using flame-dried glassware. Et<sub>2</sub>O and THF were freshly distilled from sodium and benzophenone. Alkylolithiums were titrated against *N*-benzylbenzamide before use. All diamines used in lithiation reactions were distilled over CaH<sub>2</sub> 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 F<sub>254</sub> 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 CDCl<sub>3</sub>, chemical shifts are quoted in parts per million relative to CHCl<sub>3</sub> ( $\delta_{\text{H}}$  7.26) and CDCl<sub>3</sub> ( $\delta_{\text{C}}$  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 Daltronics microOTOF spectrometer. Optical rotations were recorded at room temperature on a Jasco DIP-370 polarimeter (using sodium D line, 589 nm) and  $[\alpha]_{\text{D}}$  given in units of 10<sup>-1</sup> deg cm<sup>3</sup> g<sup>-1</sup>. Chiral stationary phase HPLC was performed on an Agilent 1200 series chromatograph. *In situ* ReactIR<sup>™</sup> 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**,<sup>1</sup> (+)-sparteine surrogate<sup>2</sup> and *tert*-butyl piperazine-1-carboxylate.<sup>1</sup>

## 1.2 General Procedures

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

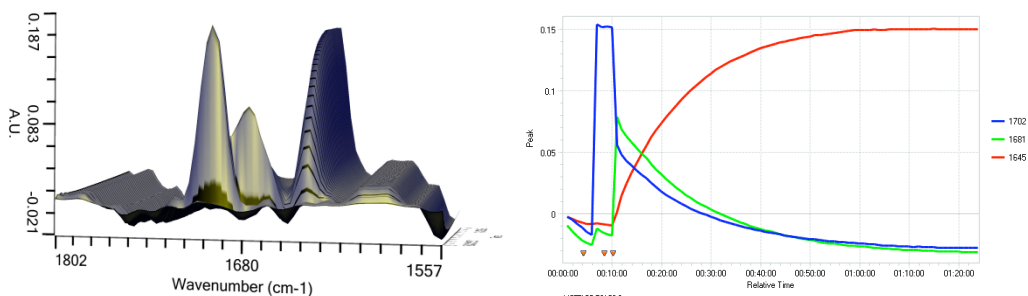
*s*-BuLi (1.3 M solution in hexanes, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc piperazine (1.0 eq.) and diamine (1.3 eq.) in Et<sub>2</sub>O (4-7 mL) at -78 °C under Ar. The resulting solution was stirred at -78 °C for 10 min to 6 h. Then, the electrophile (1.3-2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated NH<sub>4</sub>Cl<sub>(aq)</sub> (10 mL) (and saturated NaHCO<sub>3(aq)</sub> (10 mL) or 20% NaOH<sub>(aq)</sub> (10 mL) where used) was added and the two layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) 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 NH<sub>4</sub>Cl<sub>(aq)</sub> (10 mL) (and saturated NaHCO<sub>3(aq)</sub> (10 mL) or 20% NaOH<sub>(aq)</sub> (10 mL) where used) was added and the two layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) 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)

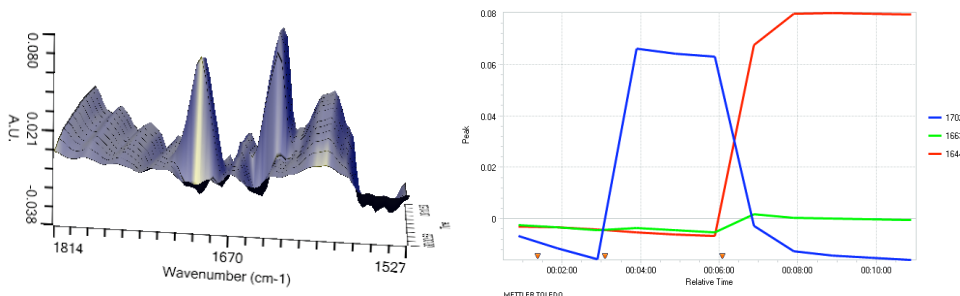


(Scheme 2)

Et<sub>2</sub>O (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<sub>2</sub>O (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<sup>-1</sup> was observed and assigned to ν<sub>C=O</sub>. After addition of *s*-BuLi, a new peak at 1681 cm<sup>-1</sup> was observed which was assigned to ν<sub>C=O</sub> in the pre-lithiation complex **5**. A new peak at 1645 cm<sup>-1</sup> was observed which was assigned to ν<sub>C=O</sub> 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<sup>-1</sup>, a half-life value, t<sub>1/2</sub> 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)

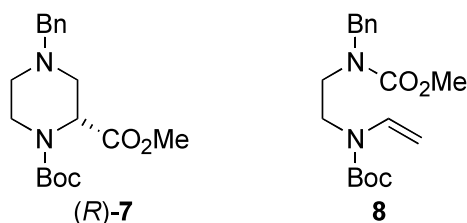
Et<sub>2</sub>O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to -78 °C, a solution of (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et<sub>2</sub>O (2 mL) was added followed by a solution of *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in Et<sub>2</sub>O (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  $-78\text{ }^{\circ}\text{C}$  for 5 min.

For *N*-Boc-*N'*-benzyl piperazine **4**, a peak at  $1702\text{ cm}^{-1}$  was observed and assigned to  $\nu_{\text{C=O}}$ . After addition of *s*-BuLi, a new peak at  $1663\text{ cm}^{-1}$  was observed which was assigned to  $\nu_{\text{C=O}}$  in the pre-lithiation complex **5**. A new peak at  $1644\text{ cm}^{-1}$  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  $1644\text{ cm}^{-1}$ , a half-life value,  $t_{1/2}$  of  $\sim 0.5$  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****



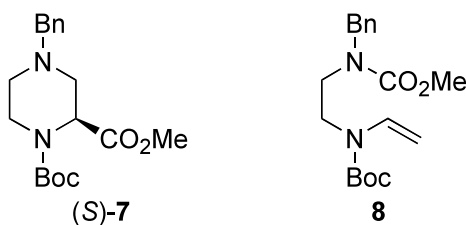
(Scheme 3)

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  $\mu\text{L}$ , 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in  $\text{Et}_2\text{O}$  (7 mL) for 90 min and methyl chloroformate (189 mg, 155  $\mu\text{L}$ , 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 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 ( $\text{CHCl}_3$ ) 2979, 1744 ( $\text{C=O}$ ,  $\text{CO}_2\text{Me}$ ), 1691 ( $\text{C=O}$ , Boc), 1408, 1366, 1301, 1169, 1119, 1046, 976, 867  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) (55:45 mixture of rotamers)  $\delta$  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,  $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$ ), 3.58 (d,  $J = 13.0$  Hz, 0.55H,  $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$ ), 3.45 (d,  $J = 13.0$  Hz, 0.55H,  $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$ ), 3.41 (d,  $J = 13.0$  Hz, 0.45H,  $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$ ), 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,  $\text{CMe}_3$ ), 1.42 (s, 4.1H,  $\text{CMe}_3$ );  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ) (mixture of rotamers)  $\delta$  171.3 ( $\text{CO}_2\text{Me}$ ), 171.1 ( $\text{CO}_2\text{Me}$ ), 155.8 ( $\text{NC=O}$ ), 155.3 ( $\text{NC=O}$ ),

137.6 (*ipso*-Ph), 128.7 (Ph), 128.1 (Ph), 127.2 (Ph), 80.2 (CMe<sub>3</sub>), 62.3 (NCH<sub>2</sub>), 55.5 (NCH), 54.3 (NCH), 53.5 (NCH<sub>2</sub>), 52.4 (NCH<sub>2</sub>), 52.3 (NCH<sub>2</sub>), 51.9 (OMe), 42.0 (NCH<sub>2</sub>), 41.0 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>); MS (ESI)  $m/z$  335 (M + H)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 335.1965, found 335.1974 (–2.7 ppm error); [α]<sub>D</sub> +27.5 (*c* 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel AD-H (95:5 hexane:*i*-PrOH, 1.0 mL min<sup>–1</sup>) (*R*)-**7** 5.4 min, (*S*)-**7** 6.3 min, and vinyl carbamate **8** (39 mg, 12%) as a colourless oil, *R*<sub>F</sub> (8:2 petrol-EtOAc) 0.4; IR (CHCl<sub>3</sub>) 2973, 2934, 1672 (C=O), 1485, 1454, 1430, 1387, 1371, 1346, 1225, 1200, 1148, 769, 725 cm<sup>–1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (50:50 mixture of rotamers) δ 7.34–7.19 (m, 5H, Ph), 7.10–6.94 (br m, 1H, CH=CH<sub>2</sub>), 4.58–4.37 (br m, 2.5H, CH=CH<sub>2</sub> + NCH<sub>2</sub>), 4.30–4.17 (m, 1.5H, NCH<sub>2</sub>), 3.77 (s, 1.5H, OMe), 3.44 (br s, 1.5H, OMe), 3.68–3.59 (br m, 2H, NCH<sub>2</sub>), 3.38 (br s, 1H, NCH<sub>2</sub>), 3.30 (br s, 1H, NCH<sub>2</sub>), 1.49 (s, 9H, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (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=CH<sub>2</sub>), 127.8 (Ph), 127.4 (Ph), 127.1 (Ph), 79.2 (CMe<sub>3</sub>), 52.8 (CO<sub>2</sub>Me), 50.9 (NCH<sub>2</sub>Ph), 50.5 (NCH<sub>2</sub>Ph), 46.4 (NCH<sub>2</sub>), 45.7 (NCH<sub>2</sub>), 39.0 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>) (CH=CH<sub>2</sub> not resolved), MS (ESI)  $m/z$  357 [(M + Na)<sup>+</sup>, 100], 335 [(M + H)<sup>+</sup>, 10], 220 [(M – Boc)<sup>+</sup>, 80], HRMS  $m/z$  calcd for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 335.1965, found 335.1972 (–2.6 ppm error). Spectroscopic data of (*R*)-**7** consistent with those reported in the literature.<sup>1</sup>

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****



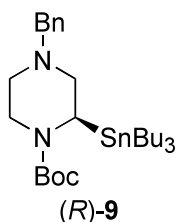
(Scheme 3)

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 Et<sub>2</sub>O (7 mL) for 1 h and methyl chloroformate (189 mg, 155 μL, 2.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (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]<sub>D</sub> –28.7 (*c* 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel

AD-H (95:5 hexane:*i*-PrOH, 1.0 mL min<sup>-1</sup>) (*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****

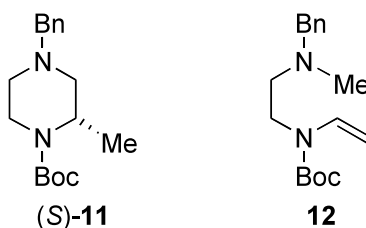


(Scheme 3)

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 Et<sub>2</sub>O (7 mL) for 10 min and Bu<sub>3</sub>SnCl (650 mg, 542 μL, 2.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (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*<sub>F</sub> (9:1 petrol-EtOAc) 0.2; IR (CHCl<sub>3</sub>) 2961, 2911, 2881, 2827, 1647 (C=O), 1433, 1395, 1395, 1344, 1278, 1231, 1151, 1088, 1055, 1007, 850, 688 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (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, CH<sub>2</sub> + CMe<sub>3</sub>), 1.35-1.23 (m, 6H, CH<sub>2</sub>), 0.99-0.78 (m, 15H, CH<sub>2</sub> + Me); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (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 (CMe<sub>3</sub>), 79.4 (CMe<sub>3</sub>), 63.3 (NCH<sub>2</sub>), 58.1 (NCH<sub>2</sub>), 53.2 (NCH<sub>2</sub>), 53.0 (NCH<sub>2</sub>), 46.5 (NCH), 45.5 (NCH), 44.8 (NCH<sub>2</sub>), 42.6 (NCH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 28.5 (CMe<sub>3</sub>), 27.9 (CH<sub>2</sub>), 27.7 (CH<sub>2</sub>), 13.8 (Me), 11.1 (CH<sub>2</sub>), 10.4 (CH<sub>2</sub>); MS (ESI) *m/z* 567 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>28</sub>H<sub>50</sub>N<sub>2</sub>O<sub>2</sub>Sn (M + H)<sup>+</sup> 567.2972, found 567.2945 (+3.9 ppm error) ; [α]<sub>D</sub> -26.0 (*c* 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min<sup>-1</sup>) (*S*)-**9** 7.2 min, (*R*)-**9** 7.8 min.

Lab Book Reference: JDF5\_468

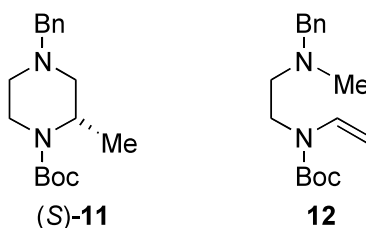
**(*S*)-tert-Butyl 4-benzyl-2-methylpiperazine-1-carboxylate (S)-11 and tert-butyl 2-(benzyl(methyl)amino)ethyl(vinyl)carbamate 12**



(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  $\mu$ L, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (138 mg, 0.5 mmol, 1.0 eq.) in Et<sub>2</sub>O (5 mL) for 90 min and methyl iodide (142 mg, 62  $\mu$ L, 1.0 mmol, 2.0 eq.), worked up with 20% NaOH<sub>(aq)</sub> (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*<sub>F</sub> (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<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>A</sub>H<sub>B</sub>Ph), 3.40 (d, *J* = 13.0 Hz, 1H, CH<sub>A</sub>H<sub>B</sub>Ph), 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, CMe<sub>3</sub>), 1.24 (d, *J* = 6.5 Hz, 3H, CHMe); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  154.8 (C=O), 138.4 (*ipso*-Ph), 128.7 (Ph), 128.2 (Ph), 127.0 (Ph), 79.3 (CMe<sub>3</sub>), 62.8 (NCH<sub>2</sub>), 57.3 (NCH<sub>2</sub>), 53.2 (NCH<sub>2</sub>), 47.0 (NCH), 39.1 (NCH<sub>2</sub>), 28.4 (CMe<sub>3</sub>), 15.9 (Me); MS (ESI) *m/z* 291 (M + H)<sup>+</sup>; CSP-HPLC: Chiralcel IC (99:1 hexane:*i*-PrOH, 1.0 mL min<sup>-1</sup>) (*R*)-**11** 12.3 min, (*S*)-**11** 14.7 min, and vinyl carbamate **12** (19 mg, 13%) as a colourless oil, *R*<sub>F</sub> (4:1 petrol-EtOAc) 0.4; IR (CHCl<sub>3</sub>) 3019, 2980, 2793, 2399, 1698 (C=O), 1627 (C=C), 1521, 1494, 1423, 1391, 1217, 1152, 1018, 928, 847, 761, 699 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.33-7.22 (m, 5H, Ph), 7.10-6.95 (br m, 1H, CH=CH<sub>2</sub>), 4.23-4.10 (m, 2H, CH=CH<sub>2</sub>), 3.68-3.51 (m, 2H, NCH<sub>2</sub>), 3.55 (s, 2H, CH<sub>2</sub>Ph), 2.53 (br s, 2H, NCH<sub>2</sub>), 2.29 (s, 3H, NMe), 1.45 (s, 9H, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  153.1 (C=O), 139.0 (*ipso*-Ph), 132.8 (CH=CH<sub>2</sub>), 128.9 (Ph), 128.2 (Ph), 127.0 (Ph), 90.5 (CH=CH<sub>2</sub>), 81.1 (CMe<sub>3</sub>), 62.7 (NCH<sub>2</sub>Ph), 62.5 (NCH<sub>2</sub>Ph), 53.3 (NCH<sub>2</sub>), 53.1 (NCH<sub>2</sub>), 42.7 (NMe), 42.5 (NMe), 41.4 (NCH<sub>2</sub>), 40.9 (NCH<sub>2</sub>), 28.2 (CMe<sub>3</sub>); MS (ESI) *m/z* 291 [(M + H)<sup>+</sup>, 100], 235 [(M – CMe<sub>3</sub>)<sup>+</sup>, 20], 191 [(M – Boc)<sup>+</sup>, 10]; HRMS *m/z* calcd for C<sub>17</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 291.2067, found 291.2072 (–1.0 ppm error). Spectroscopic data of (*S*)-**11** consistent with those reported in the literature.<sup>3</sup> 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**

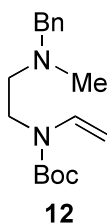


(Scheme 3)

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 Et<sub>2</sub>O (5 mL) for 90 min and dimethyl sulfate (126 mg, 97 μL, 1.0 mmol, 2.0 eq.), worked up with 20% NaOH<sub>(aq)</sub> (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<sup>–1</sup>) (*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

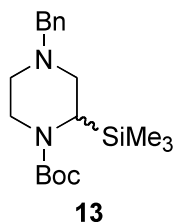
***tert*-Butyl 2-(benzyl(methyl)amino)ethyl(vinyl)carbamate 12**



(Scheme 3)

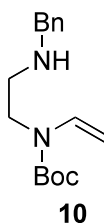
Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (276 mg, 1.0 mmol, 1.0 eq.) in Et<sub>2</sub>O (7 mL) for 10 min and dimethyl sulfate (252 mg, 189 μL, 2.0 mmol, 2.0 eq.), worked up with 20% NaOH<sub>(aq)</sub> (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 Et<sub>2</sub>O (14 mL) for 5 h and Me<sub>3</sub>SiCl (330 μL, 2.6 mmol, 2.0 eq.), worked up with saturated NH<sub>4</sub>Cl<sub>(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-Et<sub>2</sub>O as eluent gave *N*-Boc piperazine **13** (237 mg, 38%, 52:48 er by CSP-HPLC) as a yellow oil, *R*<sub>F</sub> (9:1 petrol-EtOAc) 0.4; IR (CHCl<sub>3</sub>) 2977, 2804, 1673 (C=O), 1454, 1420, 1366, 1296, 1168, 1111, 1027, 840 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (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<sub>A</sub>H<sub>B</sub>Ph), 3.40 (d, *J* = 13.0 Hz, 1H, CH<sub>A</sub>H<sub>B</sub>Ph), 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, CMe<sub>3</sub>), 0.12 (s, 9H, SiMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 154.7 (C=O), 138.3 (*ipso*-Ph), 129.1 (Ph), 128.1 (Ph), 127.0 (Ph), 79.1 (CMe<sub>3</sub>), 63.4 (NCH<sub>2</sub>), 54.3 (NCH<sub>2</sub>), 53.2 (NCH<sub>2</sub>), 45.3 (NCH), 41.4 (NCH<sub>2</sub>), 28.4 (CMe<sub>3</sub>), –0.8 (SiMe<sub>3</sub>); MS (ESI) *m/z* 349 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>19</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>Si (M + H)<sup>+</sup> 349.2306, found 349.2297 (+1.7 ppm error); CSP-HPLC: Chiralcel AD (98:2 hexane:*i*-PrOH, 0.4 mL min<sup>-1</sup>) 21.3 min (minor), 26.9 min (major). Spectroscopic data of **13** consistent with those reported in the literature.<sup>1</sup>

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

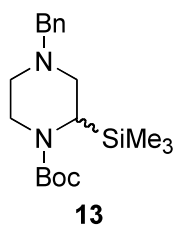
(Scheme 3)

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 μL, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine **4** (138 mg, 0.5 mmol, 1.0 eq.) in Et<sub>2</sub>O (5 mL) for 1 h and Me<sub>3</sub>SiOTf (222 mg, 181 μL, 1.0 mmol, 2.0 eq.), worked up with saturated

NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 97:3 CH<sub>2</sub>Cl<sub>2</sub>-MeOH as eluent gave alkene **10** (71 mg, 51%) as a colourless oil, *R*<sub>F</sub> (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<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35-7.29 (m, 4H, Ph), 7.29-7.21 (m, 1H, Ph), 7.04 (br s, 1H, CH=CH<sub>2</sub>), 4.33 (d, *J* = 16.0 Hz, 1H, CH=CH<sub>A</sub>H<sub>B</sub>), 4.20 (br s, 1H, CH=CH<sub>A</sub>H<sub>B</sub>), 3.82 (s, 2H, CH<sub>2</sub>Ph), 3.65 (br s, 2H, NCH<sub>2</sub>), 2.83 (t, *J* = 6.5 Hz, 2H, NCH<sub>2</sub>), 1.47 (s, 9H, CMe<sub>3</sub>) (NH not resolved); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 153.0 (C=O), 140.0 (*ipso*-Ph), 133.0 (CH=CH<sub>2</sub>), 128.3 (Ph), 128.0 (Ph), 127.0 (Ph), 90.8 (CH=CH<sub>2</sub>), 81.2 (CMe<sub>3</sub>), 53.9 (CH<sub>2</sub>Ph), 46.0 (NCH<sub>2</sub>), 42.5 (NCH<sub>2</sub>), 28.1 (CMe<sub>3</sub>); MS (ESI) *m/z* 277 [(M + H)<sup>+</sup>, 100], 221 [(M – CMe<sub>3</sub>)<sup>+</sup>, 20]; HRMS *m/z* calcd for C<sub>16</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 277.1911, found 277.1910 (+0.5 ppm error).

Lab Book Reference: JDF10\_941

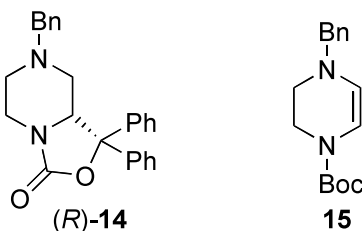
### ***tert*-Butyl 4-benzyl-2-(trimethylsilyl)piperazine-1-carboxylate **13****



(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<sub>2</sub>O (7 mL) for 1 h and Me<sub>3</sub>SiCl (217 mg, 253 μL, 2.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (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<sup>-1</sup>) 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**

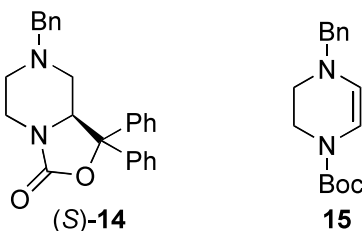
(Scheme 3)

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  $\mu$ L, 1.95 mmol, 1.3 eq.), *N*-Boc-*N'*-benzyl piperazine **4** (415 mg, 1.5 mmol, 1.0 eq.) in Et<sub>2</sub>O (10 mL) for 1 h and a solution of benzophenone (547 mg, 3.0 mmol, 2.0 eq.) in Et<sub>2</sub>O (2 mL), worked up with 20% NaOH<sub>(aq)</sub> (10 mL) gave the crude product which contained a 78:22 mixture of (R)-**14** and alkene **15** (by <sup>1</sup>H 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*<sub>F</sub> (7:3 petrol-Et<sub>2</sub>O) 0.2; IR (CHCl<sub>3</sub>) 3020, 2400, 1751 (C=O), 1422, 1215, 929, 759, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>A</sub>H<sub>B</sub>Ph), 3.31 (d, *J* = 13.0 Hz, 1H, CH<sub>A</sub>H<sub>B</sub>Ph), 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); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  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 (Ph<sub>2</sub>CO), 62.9 (NCH<sub>2</sub>), 61.1 (NCH), 55.7 (NCH<sub>2</sub>), 50.7 (NCH<sub>2</sub>), 41.5 (NCH<sub>2</sub>); MS (ESI) *m/z* 385 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>25</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 385.1911, found 385.1899 (+3.6 ppm error); [ $\alpha$ ]<sub>D</sub> +145.9 (*c* 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel OD (90:10 hexane:*i*-PrOH, 1.0 mL min<sup>-1</sup>) (S)-**14** 14.4 min, (R)-**14** 18.9 min. Spectroscopic data consistent with those reported in the literature.<sup>1</sup>

Diagnostic signals for alkene **15**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (67:33 mixture of rotamers)  $\delta$  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, CH<sub>2</sub>Ph).

Lab Book Reference: JDF1\_35

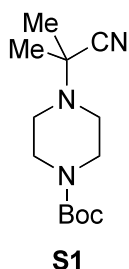


**(S)-7-Benzyl-1,1-diphenyltetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (S)-14**

(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 Et<sub>2</sub>O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et<sub>2</sub>O (1 mL), worked up with 20% NaOH<sub>(aq)</sub> (10 mL) gave the crude product which contained a 41:59 mixture of (*R*)-**14** and alkene **15** (by <sup>1</sup>H 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, [ $\alpha$ ]<sub>D</sub> −114.9 (*c* 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel OD (90:10 hexane:*i*-PrOH, 1.0 mL min<sup>−1</sup>) (*S*)-**14** 14.4 min, (*R*)-**14** 18.9 min.

Lab Book Reference: JDF1\_61

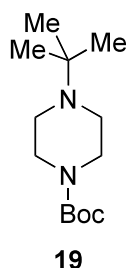
***tert*-Butyl 4-(2-cyanopropan-2-yl)piperazine-1-carboxylate S1**

HCl (40.3 mL of a 2.0 M in Et<sub>2</sub>O, 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 CH<sub>2</sub>Cl<sub>2</sub> (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 (MgSO<sub>4</sub>) and evaporated under reduced pressure to give *N*-Boc piperazine **S1** (11.0 g, 81%) as a white solid which was sufficiently pure by <sup>1</sup>H NMR spectroscopy, mp 108–110 °C; IR (CHCl<sub>3</sub>) 3018, 1686 (C=O), 1455, 1429, 1391, 1367, 1307, 1290, 1266, 1242, 1215, 1172, 1130, 750, 667 cm<sup>−1</sup>; <sup>1</sup>H NMR (400

MHz, CDCl<sub>3</sub>)  $\delta$  3.46 (t,  $J$  = 5.0 Hz, 4H, NCH<sub>2</sub>), 2.59 (t,  $J$  = 5.0 Hz, 4H, NCH<sub>2</sub>), 1.51 (s, 6H, CMe<sub>2</sub>), 1.46 (s, 9H, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  154.4 (C=O), 119.8 (CN), 79.9 (CMe<sub>3</sub>), 55.8 (CMe<sub>2</sub>), 47.3 (NCH<sub>2</sub>), 44.0 (NCH<sub>2</sub>), 28.4 (CMe<sub>3</sub>), 26.1 (CMe<sub>2</sub>); MS (ESI)  $m/z$  276 [(M + Na)<sup>+</sup>, 40], 254 [(M + H)<sup>+</sup>, 100], 198 [(M – CMe<sub>3</sub>)<sup>+</sup>, 50]; HRMS  $m/z$  calcd for C<sub>13</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub> (M + H)<sup>+</sup> 254.1863, found 254.1864 (–0.2 ppm error).

Lab Book Reference: JDF5\_447

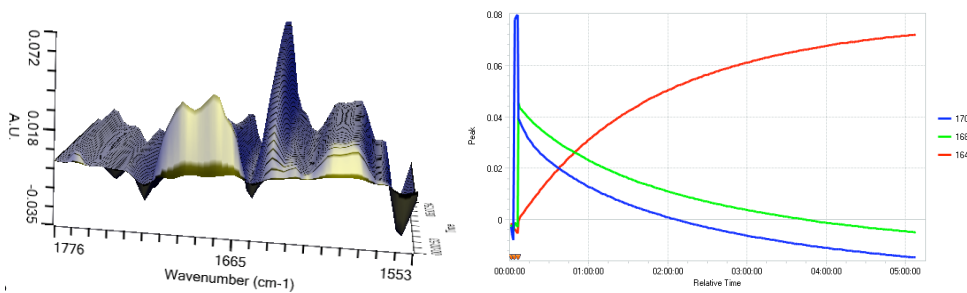
***tert*-Butyl 4-*tert*-butylpiperazine-1-carboxylate **19****



Methyl magnesium bromide (31.3 mL of a 3.0 M in Et<sub>2</sub>O, 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 (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2-94:6 CH<sub>2</sub>Cl<sub>2</sub>-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 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) 0.3; IR (CHCl<sub>3</sub>) 2977, 1682 (C=O), 1429, 1366, 1288, 1267, 1247, 1169, 1128, 953, 864, 757 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.41 (t,  $J$  = 5.0 Hz, 4H, NCH<sub>2</sub>), 2.50 (t,  $J$  = 5.0 Hz, 4H, NCH<sub>2</sub>), 1.46 (s, 9H, OCMe<sub>3</sub>), 1.06 (s, 9H, NCMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  154.6 (C=O), 79.2 (OCMe<sub>3</sub>), 53.7 (NCMe<sub>3</sub>), 45.8 (NCH<sub>2</sub>), 44.6 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>), 25.7 (CMe<sub>3</sub>); MS (ESI)  $m/z$  243 (M + H)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>13</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 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)

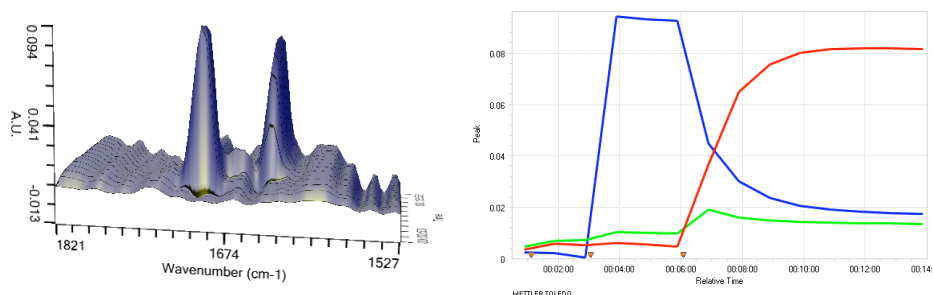


(Scheme 5)

Et<sub>2</sub>O (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<sub>2</sub>O (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<sup>-1</sup> was observed and assigned to  $\nu_{C=O}$ . After addition of *s*-BuLi, a new peak at 1680 cm<sup>-1</sup> was observed which was assigned to  $\nu_{C=O}$  in the pre-lithiation complex **23**. A new peak at 1644 cm<sup>-1</sup> was observed which was assigned to  $\nu_{C=O}$  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<sup>-1</sup>, 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)

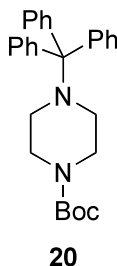
Et<sub>2</sub>O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to -78 °C, a solution of (+)-sparteine surrogate (252 mg, 1.3 mmol, 1.3 eq.) in Et<sub>2</sub>O (2 mL) was added followed by a solution *N*-Boc-*N'*-*tert*-butyl piperazine **19**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

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  $-78\text{ }^{\circ}\text{C}$  for 7 min.

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

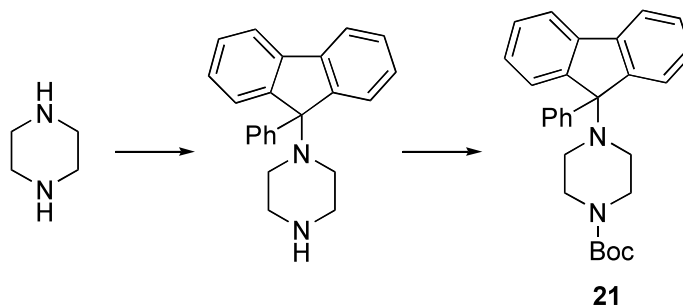
Lab Book Reference: JDF5\_427

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

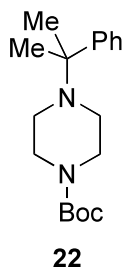


Triphenylmethyl chloride (2.06 g, 7.4 mmol 1.1 eq.) was added to a stirred solution of  $\text{Et}_3\text{N}$  (748 mg, 1.03 mL, 7.4 mmol, 1.1 eq.) and *tert*-butyl piperazine-1-carboxylate (1.25 g, 6.7 mmol, 1.0 eq.) in  $\text{CHCl}_3$  (40 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. Then, saturated  $\text{NaHCO}_{3(\text{aq})}$  (50 mL) was added and the layers were separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 30 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol- $\text{Et}_2\text{O}$  as eluent gave *N*-Boc-*N'*-trityl piperazine **20** (2.29 g, 80%) as a white solid, mp  $137\text{--}140\text{ }^{\circ}\text{C}$ ,  $R_F$  (9:1 petrol- $\text{Et}_2\text{O}$ ) 0.2; IR ( $\text{CHCl}_3$ )  $1693\text{ (C=O)}$ ,  $1410$ ,  $1364$ ,  $1169$ ,  $1115$ ,  $1003\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46 (br s, 6H, Ph), 7.37-7.21 (m, 6H, Ph), 7.15 (t,  $J = 7.5\text{ Hz}$ , 3H, Ph), 3.54 (br s, 4H,  $\text{NCH}_2$ ), 2.25 (br s, 4H,  $\text{NCH}$ ), 1.38 (s, 9H,  $\text{CMe}_3$ );  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  154.9 (C=O), 146.9 (*ipso*-Ph), 127.9 (Ph), 127.6 (Ph), 126.1 (Ph), 79.4 ( $\text{CMe}_3$ ), 76.9 ( $\text{CPh}_3$ ), 47.8 ( $\text{NCH}_2$ ), 44.4 ( $\text{NCH}_2$ ), 28.3 ( $\text{CMe}_3$ ); MS (ESI)  $m/z$  451 ( $\text{M} + \text{Na}^+$ ); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_2$  ( $\text{M} + \text{Na}^+$ ) 451.2355, found 451.2356.

Lab Book Reference: JDF5\_433

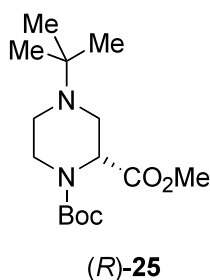
***tert*-Butyl 4-(9-phenyl-9H-fluoren-9-yl)piperazine-1-carboxylate **21****

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  $\text{K}_3\text{PO}_4$  (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<sup>®</sup> and washed with MeCN (50 mL), EtOAc (100 mL) and  $\text{CH}_2\text{Cl}_2$  (100 mL). The filtrate was evaporated under reduced pressure. Then,  $\text{CH}_2\text{Cl}_2$  (50 mL) and water (50 mL) were added and the two layers were separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  50 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to give the crude *N*-fluorophenyl piperazine (2.70 g, 83%) as a beige solid,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{NCH}_2$ ), 2.42 (br s, 4H,  $\text{NCH}_2$ ), 1.72 (br s, 1H, NH). The crude product was used in the next step without further purification ( $\geq 95\%$  purity by  $^1\text{H}$  NMR spectroscopy). Then a solution of di-*tert*-butyl dicarbonate (2.17 g, 9.93 mmol, 1.2 eq.) in  $\text{CH}_2\text{Cl}_2$  (20 mL) was added dropwise to a stirred solution of crude *N*-fluorophenyl piperazine (2.0 g, 8.27 mmol, 1.0 eq.) in  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (3  $\times$  50 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) 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 ( $\text{CHCl}_3$ ) 3008, 1681 (C=O), 1451, 1429, 1429, 1366, 1287, 1253, 1169, 1129, 1000, 756  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{NCH}_2$ ), 2.40 (br s, 4H,  $\text{NCH}_2$ ), 1.39 (s, 9H,  $\text{CMe}_3$ );  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $\text{CMe}_3$  or  $\text{NCPh}$ ), 77.9 ( $\text{CMe}_3$  or  $\text{NCPh}$ ), 47.3 ( $\text{NCH}_2$ ), 28.4 ( $\text{CMe}_3$ ) (one  $\text{NCH}_2$  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****

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<sub>4</sub>) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 Et<sub>2</sub>O-petrol and then with 98:2-94:6 CH<sub>2</sub>Cl<sub>2</sub>-MeOH as eluent gave *N*-Boc-*N'*-cumyl piperazine **22** (4.2 g, 77%) as a colourless viscous oil, *R*<sub>F</sub> (8:2 petrol-Et<sub>2</sub>O) 0.2; IR (CHCl<sub>3</sub>) 2932, 1655 (C=O), 1404, 1370, 1345, 1283, 1268, 1245, 1228, 1152, 1109, 989, 949, 850, 745, 691 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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, NCH<sub>2</sub>), 2.41 (br s, 4H, NCH<sub>2</sub>), 1.44 (s, 9H, CMe<sub>3</sub>), 1.33 (s, 6H, CMe<sub>2</sub>Ph); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 154.8 (C=O), 148.8 (*ipso*-Ph), 128.0 (Ph), 126.2 (Ph), 126.0 (Ph), 79.3 (CMe<sub>3</sub>), 59.7 (CMe<sub>2</sub>Ph), 46.0 (NCH<sub>2</sub>), 44.3 (NCH<sub>2</sub>), 28.4 (CMe<sub>3</sub>), 24.0 (CMe<sub>2</sub>Ph); MS (ESI) *m/z* 305 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 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****

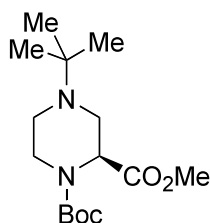
(Table 1, entry 1)

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 μL, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-*tert*-butyl piperazine **19** (121 mg, 0.5 mmol,

1.0 eq.) in Et<sub>2</sub>O (5 mL) for 6 h and methyl chloroformate (95 mg, 77  $\mu$ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (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*<sub>F</sub> (7:3 petrol-EtOAc) 0.4; IR (CHCl<sub>3</sub>) 2976, 1745 (C=O, CO<sub>2</sub>Me), 1689 (C=O, Boc), 1455, 1393, 1367, 1304, 1253, 1170, 1119, 1041, 965, 865, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (50:50 mixture of rotamers)  $\delta$  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<sub>3</sub>), 1.42 (s, 4.5H, OCMe<sub>3</sub>), 0.96 (s, 9H, NCMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  171.6 (CO<sub>2</sub>Me), 171.3 (CO<sub>2</sub>Me), 155.8 (NC=O), 155.4 (NC=O), 80.0 (OCMe<sub>3</sub>), 56.3 (NCH), 55.0 (NCH), 53.3 (NCMe<sub>3</sub>), 51.9 (OMe), 47.6 (NCH<sub>2</sub>), 45.2 (NCH<sub>2</sub>), 42.9 (NCH<sub>2</sub>), 42.0 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>), 25.8 (CMe<sub>3</sub>); MS (ESI) *m/z* 301 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>15</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 301.2122, found 301.2122 (+0.3 ppm error); [ $\alpha$ ]<sub>D</sub> +22.2 (*c* 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel AD (99:1 hexane:*i*-PrOH, 1.0 mL min<sup>-1</sup>) (*R*)-**25** 16.0 min, (*S*)-**25** 21.8 min.

Lab Book Reference: JDF2\_153

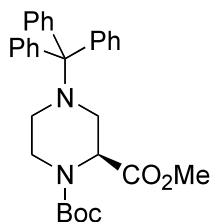
**(*S*)-1-*tert*-Butyl 2-methyl 4-*tert*-butylpiperazine-1,2-dicarboxylate (*S*)-25**



**(*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<sub>2</sub>O (7 mL) for 10 min and methyl chloroformate (190 mg, 155  $\mu$ L, 2.0 mmol, 2.0 eq.) worked up with 20% NaOH<sub>(aq)</sub> (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<sup>-1</sup>) (*R*)-**25** 14.6 min, (*S*)-**25** 23.4 min. Lab Book Reference: JDF5\_470

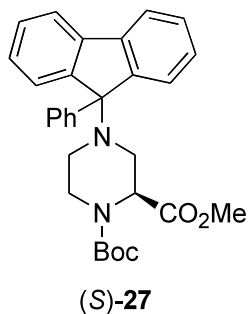
**(S)-1-*tert*-Butyl 2-methyl 4-tritylpiperazine-1,2-dicarboxylate (S)-26****(S)-26**

(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 Et<sub>2</sub>O (7 mL) for 1 h and methyl chloroformate (95 mg, 77  $\mu$ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et<sub>2</sub>O 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*<sub>F</sub> (4:1 petrol-Et<sub>2</sub>O) 0.3; IR (CHCl<sub>3</sub>) 3020, 2399, 1746 (C=O, CO<sub>2</sub>Me), 1688 (C=O, Boc), 1410, 1215, 1120, 1010, 762, 669 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (60:40 mixture of rotamers)  $\delta$  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, CMe<sub>3</sub>), 1.39 (s, 3.6H, CMe<sub>3</sub>); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  172.1 (CO<sub>2</sub>Me), 171.9 (CO<sub>2</sub>Me), 155.8 (NC=O), 155.2 (NC=O), 137.9 (*ipso*-Ph), 129.2 (Ph), 127.5 (Ph), 126.3 (Ph), 80.2 (CMe<sub>3</sub>), 76.9 (CPh<sub>3</sub>), 55.4 (NCH or OMe), 54.2 (NCH or OMe), 51.9 (NCH or OMe), 51.8 (NCH or OMe), 48.9 (NCH<sub>2</sub>), 48.8 (NCH<sub>2</sub>), 47.8 (NCH<sub>2</sub>), 47.8 (NCH<sub>2</sub>), 42.5 (NCH<sub>2</sub>), 41.5 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>); MS (ESI) *m/z* 509 (M + Na)<sup>+</sup>; MS (ESI) *m/z* 509 (M + Na)<sup>+</sup>; HRMS *m/z* calcd for C<sub>30</sub>H<sub>33</sub>N<sub>2</sub>O<sub>4</sub>Na (M + Na)<sup>+</sup> 509.2411, found 509.2417 (−0.9 ppm error); [ $\alpha$ ]<sub>D</sub> −24.0 (*c* 1.0 in CHCl<sub>3</sub>); CP-HPLC: Chiralcel AD (95:5 hexane:*i*-PrOH, 0.2 mL min<sup>-1</sup>) (*R*)-**26** 38.4 min, (*S*)-**26** 50.4 min.

Lab Book Reference: JDF5\_416

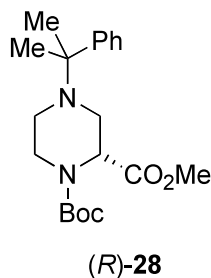


**(S)-1-tert-Butyl 2-methyl 4-(9-phenyl-9H-fluoren-9-yl)piperazine-1,2-dicarboxylate (S)-27**

(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 Et<sub>2</sub>O (7 mL) for 1 h and methyl chloroformate (74 mg, 60  $\mu$ L, 0.78 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et<sub>2</sub>O 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*<sub>F</sub> (7:3 petrol-Et<sub>2</sub>O) 0.2; IR (CHCl<sub>3</sub>) 3018, 2980, 1745 (C=O, CO<sub>2</sub>Me), 1691 (C=O, Boc), 1451, 1408, 1367, 1304, 1216, 1170, 1119, 746, 668 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (60:40 mixture of rotamers)  $\delta$  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, CMe<sub>3</sub>), 1.37 (s, 3.6H, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  171.4 (CO<sub>2</sub>Me), 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 (CMe<sub>3</sub>), 77.6 (NCPh), 55.7 (NCH or OMe), 54.6 (NCH or OMe), 51.8 (NCH or OMe), 48.6 (NCH<sub>2</sub>), 48.5 (NCH<sub>2</sub>), 47.5 (NCH<sub>2</sub>), 47.3 (NCH<sub>2</sub>), 42.7 (NCH<sub>2</sub>), 41.7 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>), 28.2 (CMe<sub>3</sub>); MS (ESI) *m/z* 485 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>30</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 485.2435, found 485.2442 (−1.4 ppm error); [ $\alpha$ ]<sub>D</sub> −100.7 (*c* 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel AD-H (99:1 hexane:*i*-PrOH, 1.0 mL min<sup>-1</sup>) (S)-**27** 25.1 min, (S)-**27** 30.4 min.

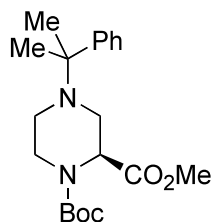
Lab Book Reference: JDF5\_417

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

(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  $\mu$ L, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-cumyl piperazine **22** (152 mg, 0.5 mmol, 1.0 eq.) in Et<sub>2</sub>O (5 mL) for 6 h and methyl chloroformate (95 mg, 77  $\mu$ L, 1.0 mmol, 2.0 eq.) worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-8:2 CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O as eluent gave *N*-Boc piperazine (R)-**28** (128 mg, 71%, 90:10 er by CSP-HPLC) as a colourless oil, *R*<sub>F</sub> (19:1 CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O) 0.2; IR (CHCl<sub>3</sub>) 2972, 2933, 1718 (C=O, CO<sub>2</sub>Me), 1662 (C=O, Boc), 1469, 1452, 1391, 1369, 1346, 1331, 1310, 1284, 1195, 1155, 1101, 1016, 951, 736, 692 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (55:45 mixture of rotamers)  $\delta$  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, CMe<sub>3</sub>), 1.41 (s, 4H, CMe<sub>3</sub>), 1.31 (s, 6H, CMe<sub>2</sub>Ph); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  171.6 (CO<sub>2</sub>Me), 171.4 (CO<sub>2</sub>Me), 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 (CMe<sub>3</sub>), 59.2 (CMe<sub>2</sub>Ph), 56.0 (NCH), 54.9 (NCH), 51.8 (OMe), 47.8 (NCH<sub>2</sub>), 45.7 (NCH<sub>2</sub>), 42.7 (NCH<sub>2</sub>), 41.7 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>), 28.2 (CMe<sub>3</sub>), 24.0 (CMe<sub>2</sub>Ph), 23.9 (CMe<sub>2</sub>Ph), 23.7 (CMe<sub>2</sub>Ph); MS (ESI) *m/z* 363 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>20</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 363.2278, found 363.2277 (0.0 ppm error); [ $\alpha$ ]<sub>D</sub> +39.0 (*c* 0.85 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min<sup>-1</sup>) (R)-**28** 11.5 min, (S)-**28** 19.5 min.

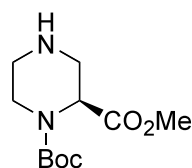
Lab Book Reference: JDF7\_603

**(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 Et<sub>2</sub>O (5 mL) for 1 h and methyl chloroformate (95 mg, 77  $\mu$ L, 1.0 mmol, 2.0 eq.) worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-8:2 CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O 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 CHCl<sub>3</sub>); CSP-HPLC: Chiralcel OD-H (95:5 hexane:*i*-PrOH, 0.5 mL min<sup>-1</sup>) (*R*)-**28** 11.5 min, (S)-**28** 19.3 min.

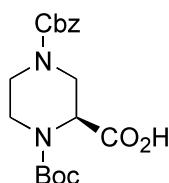
Lab Book Reference: JDF7\_646

**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)<sub>2</sub>/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<sup>®</sup> 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 CHCl<sub>3</sub>); IR (ATR) 3352 (NH), 2975, 1743 (C=O, CO<sub>2</sub>Me), 1692 (C=O), 1454, 1391, 1364, 1340, 1317, 1290, 1252, 1223, 1201, 1112, 1072, 1038, 975, 917, 862, 829, 776, 731 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (50:50 mixture of rotamers)  $\delta$  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, CO<sub>2</sub>Me), 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,

<sup>1</sup>H, NH), 1.44 (s, 4.5H, CMe<sub>3</sub>), 1.40 (s, 4.5H, CMe<sub>3</sub>) <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers) δ 171.8 (CO<sub>2</sub>Me), 171.6 (CO<sub>2</sub>Me), 155.9 (NC=O), 155.5 (NC=O), 80.4 (CMe<sub>3</sub>), 55.5 (NCH), 54.2 (NCH), 52.3 (CO<sub>2</sub>Me), 47.3 (NCH<sub>2</sub>), 47.1 (NCH<sub>2</sub>), 45.3 (NCH<sub>2</sub>), 42.7 (NCH<sub>2</sub>), 41.5 (NCH<sub>2</sub>), 28.4 (CMe<sub>3</sub>); MS (ESI) *m/z* 267 [(M + Na)<sup>+</sup>, 30], 245 [(M + H)<sup>+</sup>, 50], 189 [(M – CMe<sub>3</sub>)<sup>+</sup>, 100], 145 [(M – Boc)<sup>+</sup>, 80]; HRMS *m/z* calcd for C<sub>11</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 245.1493, found 245.1496 (+1.7 ppm error).  
Lab Book Reference: JDF10\_1053

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



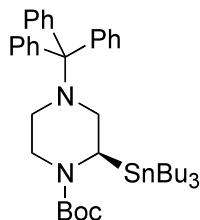
**(S)-S3**

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 Et<sub>3</sub>N (9 mg, 12 μL, 0.086 mmol, 1.5 eq.) in CH<sub>2</sub>Cl<sub>2</sub> at rt. The resulting solution was stirred for 16 h. Water (5 mL) was added and the layers separated. The aqueous was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 5 mL). The combined organic layers were dried (MgSO<sub>4</sub>) 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*<sub>F</sub> (7:3 petrol-EtOAc) 0.3; [α]<sub>D</sub> –3.4 (*c* 0.75 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2973, 1718 (C=O, CO<sub>2</sub>Me), 1672 (C=O), 1492, 1409, 1346, 1302, 1203, 1193, 1094, 1025, 914, 776, 741, 721, 659 cm<sup>–1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (45:55 mixture of rotamers) δ 7.28–7.40 (5H, m, Ph), 5.17 (br d, *J* = 12.0 Hz, 1H, CH<sub>A</sub>H<sub>B</sub>Ph), 5.08 (d, *J* = 12.0 Hz, 1H, CH<sub>A</sub>H<sub>B</sub>Ph), 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, CMe<sub>3</sub>), 1.43 (s, 4H, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers) δ 170.5 (CO<sub>2</sub>Me), 170.3 (CO<sub>2</sub>Me), 155.5 (NC=O), 155.0 (NC=O), 136.3 (*ipso*-Ph), 128.4 (Ph), 128.0 (Ph), 127.8 (Ph), 80.9 (CMe<sub>3</sub>), 67.4 (CH<sub>2</sub>Ph), 54.8 (NCH), 53.4 (CO<sub>2</sub>Me), 52.3 (CO<sub>2</sub>Me), 44.7 (NCH<sub>2</sub>), 43.2 (NCH<sub>2</sub>), 42.9 (NCH<sub>2</sub>), 40.0 (NCH<sub>2</sub>), 28.2 (CMe<sub>3</sub>); MS (ESI) *m/z* 401 [(M + Na)<sup>+</sup>, 100], 323 [(M – Boc)<sup>+</sup>, 30]; HRMS *m/z* calcd for C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>Na (M + Na)<sup>+</sup> 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<sub>2</sub>Cl<sub>2</sub> (5 mL) and the two layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 66:33:1 CH<sub>2</sub>Cl<sub>2</sub>-EtOAc-AcOH as eluent gave carboxylic acid (*S*)-**S3** (14 mg, 84%) as a pale yellow oil. *R*<sub>F</sub> (66:33:1 CH<sub>2</sub>Cl<sub>2</sub>-EtOAc-AcOH); 0.2; [α]<sub>D</sub> −14.9 (*c* 0.7 in CHCl<sub>3</sub>) (lit.,<sup>4</sup> [α]<sub>D</sub> −17.5 (*c* 1.02 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (45:55 mixture of rotamers) δ 7.27-7.40 (5H, m, Ph), 5.07-5.21 (m, 2H, CH<sub>2</sub>Ph), 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<sub>3</sub>), 1.44 (s, 4H, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (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<sub>3</sub>), 67.8 (NCH), 54.6 (CH<sub>2</sub>Ph), 53.4 (CH<sub>2</sub>Ph), 44.5 (NCH<sub>2</sub>), 44.5 (NCH<sub>2</sub>), 44.3 (NCH<sub>2</sub>), 43.2 (NCH<sub>2</sub>), 41.4 (NCH<sub>2</sub>), 40.2 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>). Spectroscopic data consistent with those reported in the literature.<sup>4</sup>

Lab Book Reference: JDF7\_682 and JDF7\_693

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



**(*R*)-29**

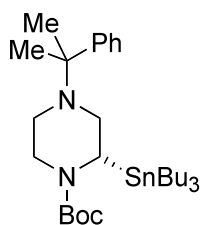
(Table 1, entry 7)

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<sub>2</sub>O (7 mL) for 1 h and Bu<sub>3</sub>SnCl (325 mg, 271 μL, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et<sub>2</sub>O as eluent gave *N*-Boc piperazine (*R*)-**29** (265 mg, 74%, 82:18 er by CSP-HPLC) as a pale yellow oil, *R*<sub>F</sub> (19:1 petrol-EtOAc) 0.4; IR (CHCl<sub>3</sub>) 2911, 2879, 1646 (C=O), 1465, 1428, 1402, 1344, 1277, 1232, 1196, 1134, 1092, 987, 744, 698 cm<sup>−1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (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, CH<sub>2</sub> + CMe<sub>3</sub>), 1.29-1.14 (m, 6H, CH<sub>2</sub>), 0.95-0.61 (m, 15H, CH<sub>2</sub> + Me); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 155.6 (C=O), 142.8 (*ipso*-Ph), 129.3 (Ph), 127.4 (Ph), 126.0 (Ph), 79.3 (CMe<sub>3</sub>), 77.1

(CPh<sub>3</sub>), 52.4 (NCH<sub>2</sub>), 48.5 (NCH<sub>2</sub>), 46.6 (NCH<sub>2</sub>), 45.4 (NCH), 29.2 (CH<sub>2</sub>), 28.2 (CMe<sub>3</sub>), 27.6 (CH<sub>2</sub>), 13.7 (Me), 11.9 (CH<sub>2</sub>); MS (ESI)  $m/z$  719 (M + H)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>40</sub>H<sub>58</sub>N<sub>2</sub>O<sub>2</sub>Sn (M + H)<sup>+</sup> 719.3601, found 719.3605 (−0.6 ppm error); [α]<sub>D</sub> −27.4 (c 1.1 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel OD-H (99:1 hexane:*i*-PrOH, 0.5 mL min<sup>−1</sup>) (*R*)-**29** 6.7 min, (*S*)-**29** 7.6 min.

Lab Book Reference: JDF6\_505

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



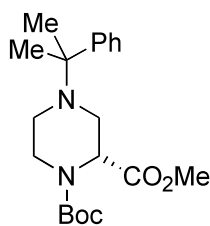
**(*S*)-30**

(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 Et<sub>2</sub>O (5 mL) for 6 h and Bu<sub>3</sub>SnCl (325 mg, 271 μL, 1.0 mmol, 2.0 eq.) worked up with saturated NaHCO<sub>3(aq)</sub> (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*<sub>F</sub> (19:1 petrol-EtOAc) 0.3; IR (CHCl<sub>3</sub>) 2971, 2913, 2881, 2827, 1645 (C=O), 1432, 1397, 1344, 1280, 1197, 1152, 1090, 1002, 947, 908, 849, 743, 691, 658 cm<sup>−1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (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, CMe<sub>3</sub> + CH<sub>2</sub>), 1.33–1.22 (m, 12H, CMe<sub>2</sub>Ph + CH<sub>2</sub>), 0.95–0.83 (m, 15H, CH<sub>2</sub> + Me); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (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 (CMe<sub>3</sub>), 79.0 (CMe<sub>3</sub>), 60.0 (CMe<sub>2</sub>Ph), 50.2 (NCH<sub>2</sub>), 46.9 (NCH<sub>2</sub>), 45.9 (NCH<sub>2</sub>), 45.6 (NCH<sub>2</sub>), 43.0 (NCH), 29.2 (CH<sub>2</sub>), 28.4 (CMe<sub>3</sub>), 27.9 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 27.6 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 22.1 (CMe<sub>2</sub>Ph), 20.7 (CMe<sub>2</sub>Ph), 13.7 (Me), 11.1 (CH<sub>2</sub>), 10.4 (CH<sub>2</sub>); MS (ESI)  $m/z$  595 (M + H)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>30</sub>H<sub>54</sub>N<sub>2</sub>O<sub>2</sub>Sn (M + H)<sup>+</sup> 595.3285, found 595.3261 (+3.6 ppm error); [α]<sub>D</sub> +32.6 (c 1.0 in CHCl<sub>3</sub>).

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****

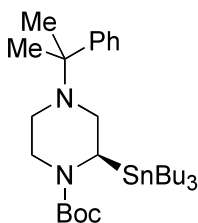


**(*R*)-**28****

*n*-BuLi (35  $\mu$ 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  $\mu$ L, 0.08 mmol, 1.3 eq.) in Et<sub>2</sub>O (3 mL) at  $-78$  °C under Ar. The resulting solution was stirred at  $-78$  °C for 10 min. Then, methyl chloroformate (11 mg, 9  $\mu$ 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 NH<sub>4</sub>Cl<sub>(aq)</sub> (5 mL) and saturated NaHCO<sub>3(aq)</sub> (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  5 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et<sub>2</sub>O 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<sup>-1</sup>) (*R*)-**28** 11.2 min, (*S*)-**28** 18.7 min.

Lab Book Reference: JDF7\_661

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



**(*R*)-**30****

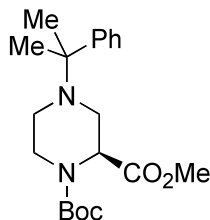
(Table 1, entry 9)

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 Et<sub>2</sub>O (5 mL) for 1 h and Bu<sub>3</sub>SnCl (325 mg, 271  $\mu$ L, 1.0 mmol, 2.0 eq.) worked up with saturated NaHCO<sub>3(aq)</sub> (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  $\text{CHCl}_3$ );

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****

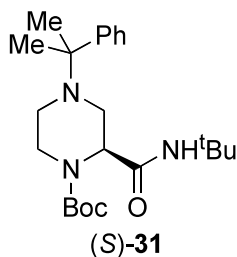


(*S*)-**28**

*n*-BuLi (35  $\mu\text{L}$  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  $\mu\text{L}$ , 0.08 mmol, 1.3 eq.) in  $\text{Et}_2\text{O}$  (3 mL) at  $-78^\circ\text{C}$  under Ar. The resulting solution was stirred at  $-78^\circ\text{C}$  for 10 min. Then, methyl chloroformate (11 mg, 9  $\mu\text{L}$ , 0.12 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at  $-78^\circ\text{C}$  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  $\text{Et}_2\text{O}$  ( $3 \times 5$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 petrol- $\text{Et}_2\text{O}$  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  $\text{min}^{-1}$ ) (*R*)-**28** 11.2 min, (*S*)-**28** 18.7 min.

Lab Book Reference: JDF7\_660

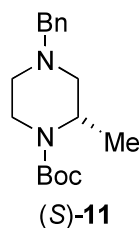


**(S)-tert-Butyl 2-(tert-butylcarbamoyl)-4-(2-phenylpropan-2-yl)piperazine-1-carboxylate (S)-31**

(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 Et<sub>2</sub>O (5 mL) for 1 h and *tert*-butyl isocyanate (64 mg, 74  $\mu$ L, 0.65 mmol, 1.3 eq.) worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 17:3-1:1 petrol-Et<sub>2</sub>O 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*<sub>F</sub> (8:2 petrol-EtOAc) 0.3; IR (CHCl<sub>3</sub>) 2933, 1651 (C=O), 1524, 1488, 1430, 1371, 1345, 1283, 1152, 1102, 951, 742 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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, CMe<sub>3</sub>), 1.41 (s, 9H, CMe<sub>3</sub>), 1.35 (s, 3H, CMe<sub>2</sub>Ph), 1.33 (s, 3H, CMe<sub>2</sub>Ph); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  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 (OCMe<sub>3</sub>), 59.7 (CMe<sub>2</sub>Ph), 57.3 (br, NCH), 51.8 (NCH<sub>2</sub>), 51.2 (NCMe<sub>3</sub>), 46.5 (NCH<sub>2</sub>), 42.1 (br, NCH<sub>2</sub>), 28.9 (OCMe<sub>3</sub>), 28.4 (OCMe<sub>3</sub>), 27.8 (NCMe<sub>3</sub>), 20.3 (CMe<sub>2</sub>Ph); MS (ESI) *m/z* 404 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>23</sub>H<sub>37</sub>N<sub>3</sub>O<sub>3</sub> (M + H)<sup>+</sup> 404.2908, found 404.2914 (+2.2 ppm error); [ $\alpha$ ]<sub>D</sub> -33.2 (*c* 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel OD-H (98:2 hexane:*i*-PrOH, 0.5 mL min<sup>-1</sup>) (*R*)-**31** 14.3 min, (S)-**31** 16.6 min.

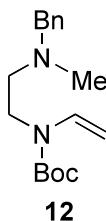
Lab Book Reference: JDF7\_651

**(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  $\mu$ L, 0.65 mmol, 1.3 eq.) in Et<sub>2</sub>O (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 Et<sub>2</sub>O (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 90 min. Then, TMEDA (280 mg, 375  $\mu$ 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  $\mu$ L, 1.0 mmol, 2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated NH<sub>4</sub>Cl<sub>(aq)</sub> (10 mL) and 20% NaOH<sub>(aq)</sub> (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) 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<sup>–1</sup>) (*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**

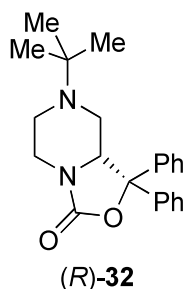
(Scheme 6)

*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 Et<sub>2</sub>O (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 Et<sub>2</sub>O (1 mL) was added dropwise. The resulting solution was stirred at –

78 °C for 10 min. Then, TMEDA (280 mg, 375  $\mu$ 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  $\mu$ 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  $\text{Et}_2\text{O}$  (3  $\times$  10 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) 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-1H-oxazolo[3,4-*a*]pyrazin-3(5H)-one (*R*)-32**



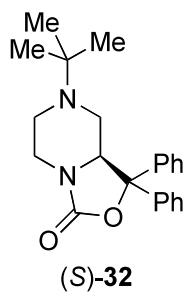
(Table 2, entry 3)

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  $\mu$ L, 1.3 mmol, 1.3 eq.), *N*-Boc-*N'*-*tert*-butyl piperazine **19** (242 mg, 1.0 mmol, 1.0 eq.) in  $\text{Et}_2\text{O}$  (7 mL) for 6 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in  $\text{Et}_2\text{O}$  (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  $\text{CH}_2\text{Cl}_2$ -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  $\text{CH}_2\text{Cl}_2$ -MeOH) 0.2; IR ( $\text{CHCl}_3$ ) 2975, 1750 (C=O), 1449, 1363, 1302, 1255, 1203, 1036, 984  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CMe}_3$ );  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  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<sub>2</sub>CO), 61.9 (NCH), 54.3 ( $\text{CMe}_3$ ), 48.8 (NCH<sub>2</sub>), 44.8 (NCH<sub>2</sub>), 42.6 (NCH<sub>2</sub>), 26.0 ( $\text{CMe}_3$ ); MS (ESI)  $m/z$  351 ( $\text{M} + \text{H}$ )<sup>+</sup>; HRMS  $m/z$  calcd for  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2$  ( $\text{M} + \text{H}$ )<sup>+</sup> 351.2067, found 351.2062 (+0.7 ppm)

error);  $[\alpha]_D +184.1$  ( $c$  1.0 in  $\text{CHCl}_3$ ); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min<sup>-1</sup>) (*S*)-**32** 13.4 min, (*R*)-**32** 16.5 min.

Lab Book Reference: JDF4\_392

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

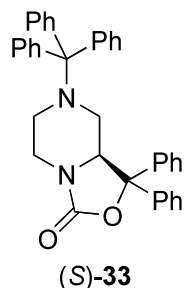


(Table 2, entry 4)

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  $\text{Et}_2\text{O}$  (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in  $\text{Et}_2\text{O}$  (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  $\text{CH}_2\text{Cl}_2$ -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  $\text{CHCl}_3$ ); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min<sup>-1</sup>) (*S*)-**32** 13.4 min, (*R*)-**32** 17.7 min.

Lab Book Reference: JDF4\_400

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



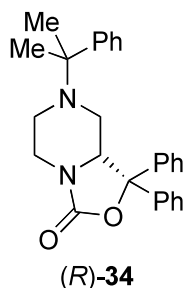
(Table 2, entry 5)

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  $\text{Et}_2\text{O}$  (7 mL) for 1 h and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in  $\text{Et}_2\text{O}$  (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- $\text{Et}_2\text{O}$  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-Et<sub>2</sub>O) 0.1; IR (CHCl<sub>3</sub>) 2964, 1743 (C=O), 1467, 1426, 1398, 1341, 1280, 1214, 1164, 1107, 1017, 973, 929, 889, 747, 700, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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, CDCl<sub>3</sub>)  $\delta$  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 (Ph<sub>2</sub>CO), 77.2 (CPh<sub>3</sub>), 62.0 (NCH), 52.0 (NCH<sub>2</sub>), 47.0 (NCH<sub>2</sub>), 42.0 (NCH<sub>2</sub>); MS (ESI)  $m/z$  559 (M + Na)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>37</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub> (M + Na)<sup>+</sup> 559.2356, found 559.2376 (-3.6 ppm error); [ $\alpha$ ]<sub>D</sub> -121.8 (c 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel AD-H (95:5 hexane:*i*-PrOH, 1.0 mL min<sup>-1</sup>) (*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-1H-oxazolo[3,4-a]pyrazin-3(5H)-one (*R*)-34**



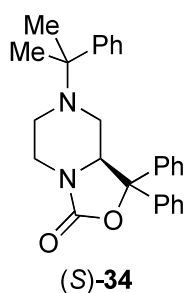
(Table 2, entry 6)

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  $\mu$ L, 0.65 mmol, 1.3 eq.), *N*-Boc-*N'*-cumyl piperazine **22** (152 mg, 0.5 mmol, 1.0 eq.) in Et<sub>2</sub>O (5 mL) for 6 h and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et<sub>2</sub>O (1 mL) worked up with saturated NaHCO<sub>3(aq)</sub> (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 (CHCl<sub>3</sub>) 2963, 2931, 1723 (C=O), 1470, 1426, 1390, 1342, 1282, 1241, 1159, 1100, 1059, 1016, 971, 895, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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, CMe<sub>2</sub>Ph), 1.18 (s, 3H, CMe<sub>2</sub>Ph); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  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 (Ph<sub>2</sub>CO), 62.4 (NCH), 60.2 (CMe<sub>2</sub>Ph), 49.3 (NCH<sub>2</sub>), 45.3 (NCH<sub>2</sub>), 42.5 (NCH<sub>2</sub>), 25.0 (CMe<sub>2</sub>Ph), 23.3 (CMe<sub>2</sub>Ph); MS (ESI)  $m/z$  413 (M + H)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 413.2224, found 413.2216 (+2.6 ppm error); [α]<sub>D</sub> +144.7 (*c* 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min<sup>-1</sup>) (*S*)-**34** 19.7 min, (*R*)-**34** 27.7 min.

Lab Book Reference: JDF7\_625

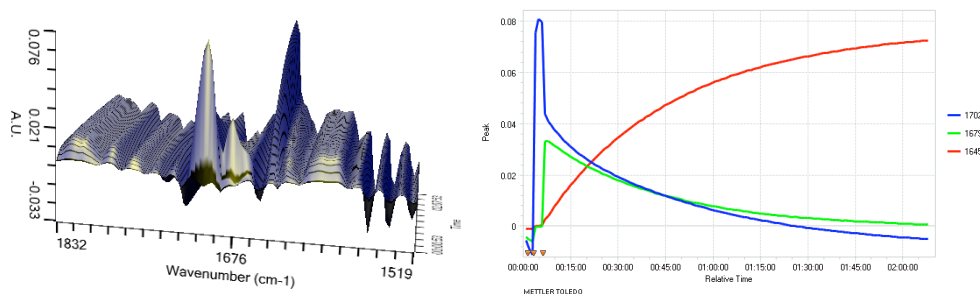
**(*S*)-1,1-Diphenyl-7-(2-phenylpropan-2-yl)tetrahydro-1H-oxazolo[3,4-*a*]pyrazin-3(5H)-one (*S*)-34**



(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 Et<sub>2</sub>O (5 mL) for 1 h and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et<sub>2</sub>O (1 mL) worked up with saturated NaHCO<sub>3(aq)</sub> (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]<sub>D</sub> −106.0 (*c* 1.0 in CHCl<sub>3</sub>); CSP-HPLC: Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min<sup>-1</sup>) (*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*)- $\alpha$ -methylbenzyl piperazine (*S*)-**36** ((-)-sparteine)**

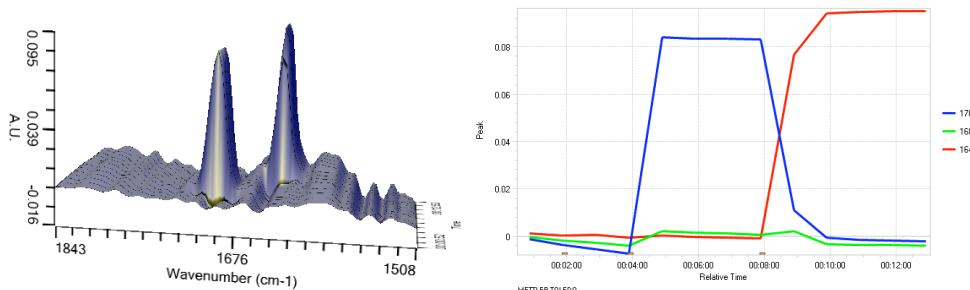
(Scheme 7)

Et<sub>2</sub>O (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  $\mu$ L, 1.3 mmol, 1.3 eq.) was added followed by a solution *N*-Boc-*N'*-(*S*)- $\alpha$ -methylbenzyl piperazine (*S*)-**36** (290 mg, 1.0 mmol, 1.0 eq.) in Et<sub>2</sub>O (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*)- $\alpha$ -methylbenzyl piperazine (*S*)-**36**, a peak at 1702 cm<sup>-1</sup> was observed and assigned to  $\nu_{\text{C=O}}$ . After addition of *s*-BuLi, a new peak at 1679 cm<sup>-1</sup> was observed which was assigned to  $\nu_{\text{C=O}}$  in the pre-lithiation complex **37**. A new peak at 1645 cm<sup>-1</sup> 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*)- $\alpha$ -methylbenzyl piperazine (*S*)-**36** to give the lithiated intermediate **38** and *N*-Boc-*N'*-(*S*)- $\alpha$ -methylbenzyl piperazine (*S*)-**36** was observed. Using the peak at 1645 cm<sup>-1</sup>, 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*)- $\alpha$ -methylbenzyl piperazine (*S*)-**36** ((+)-sparteine surrogate)**

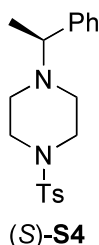


(Scheme 7)

Et<sub>2</sub>O (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<sub>2</sub>O (2 mL) was added followed by a solution *N*-Boc-*N'*-(*S*)- $\alpha$ -methylbenzyl piperazine (*S*)-**36** (290 mg, 1.0 mmol, 1.0 eq.) in Et<sub>2</sub>O (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*)- $\alpha$ -methylbenzyl piperazine (*S*)-**36**, a peak at 1701 cm<sup>−1</sup> was observed and assigned to  $\nu_{\text{C=O}}$ . After addition of *s*-BuLi, a new peak at 1681 cm<sup>−1</sup> was observed which was assigned to  $\nu_{\text{C=O}}$  in the pre-lithiation complex **37**. A new peak at 1645 cm<sup>−1</sup> 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*)- $\alpha$ -methylbenzyl piperazine (*S*)-**36** to give the lithiated intermediate **38** was observed. Using the peak at 1645 cm<sup>−1</sup>, 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****



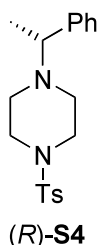
A mixture of *N,N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide (17.8 g, 60.0 mmol, 1.1 eq.), (*S*)-(−)- $\alpha$ -methylbenzylamine (6.6 g, 7.0 mL, 54.5 mmol, 1.0 eq., >99.5:0.5 er) and *i*-Pr<sub>2</sub>NEt (15.5 g, 20.9 mL, 120 mmol, 2.2 eq.) was stirred and heated at 120 °C for 16 h. After being allowed to cool to rt, 7:3 H<sub>2</sub>O-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<sub>2</sub>O-EtOH (2 × 100 mL) and then cyclohexane (3 × 50 mL)



to give *N*-tosyl piperazine (*S*)-**S4** (17.9 g, 84%) as an off white solid that was used without further purification,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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, Ar*Me*), 1.31 (d,  $J$  = 6.5 Hz, 3H, *CHMe*);  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  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 (NCH<sub>2</sub>), 46.3 (NCH<sub>2</sub>), 21.5 (Me), 19.4 (Me).

Lab Book Reference: JDF5\_422

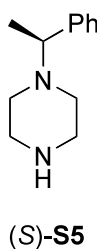
**(*R*)-1-(1-Phenylethyl)-4-methylbenzenesulfonylpiperazine (*R*)-S4**



Using the above procedure, a mixture of *N,N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide (4.0 g, 13.3 mmol, 1.1 eq.), (*R*)-(-)- $\alpha$ -methylbenzylamine (1.47 g, 1.56 mL, 12.1 mmol, 1.0 eq., >98:2 er) and *i*-Pr<sub>2</sub>NEt (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**

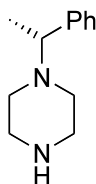


A suspension of tosyl piperazine (*S*)-**S4** (17.9 g, 52 mmol, 1.0 eq.) and 4-hydroxybenzoic acid (21.6 g, 156 mmol, 3.0 eq.) in HBr (33 wt. % in AcOH, 125 mL) was stirred for at rt for 3 d under air. Then, H<sub>2</sub>O (150 mL) was added and the mixture was stirred for 2 h. The resulting white precipitate was removed by filtration and washed with H<sub>2</sub>O (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 ( $\text{MgSO}_4$ ) 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 CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2985, 2363, 1498, 1428, 1301, 1214, 1180, 1012, 913, 801, 692, 650, 616 cm<sup>–1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 143.8 (*ipso*-Ph), 128.1 (Ph), 127.6 (Ph), 126.8 (Ph), 65.3 (NCHPh), 51.8 (NCH<sub>2</sub>), 46.3 (NCH<sub>2</sub>), 19.5 (CHMe); MS (ESI) *m/z* 191 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>12</sub>H<sub>18</sub>N<sub>2</sub> (M + H)<sup>+</sup> 191.1543, found 191.1549 (–1.9 ppm error).

Lab Book Reference: JDF5\_424

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

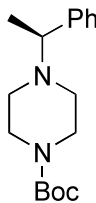


**(*R*)-S5**

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]<sub>D</sub> +32.6 (*c* 1.0 in CHCl<sub>3</sub>).

Lab Book Reference: JDF6\_537

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



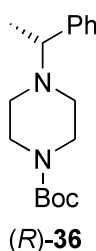
**(*S*)-36**

A solution of di-*tert*-butyl dicarbonate (14.0 g, 64.2 mmol, 1.3 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added dropwise to a stirred solution of piperazine (*S*)-S5 (9.4 g, 49.4 mmol, 1.0 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3(aq)</sub> (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>) 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*<sub>F</sub> (7:3 petrol-EtOAc) 0.2; [α]<sub>D</sub> –40.3 (*c* 1.0 in CHCl<sub>3</sub>) (lit.,<sup>5</sup> [α]<sub>D</sub> –32 (*c* 1.04 in CHCl<sub>3</sub>) for (*S*)-36 of >99:1 er);

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33-7.20 (m, 5H, Ph), 3.39 (t,  $J$  = 5.0 Hz, 4H,  $\text{NCH}_2$ ), 3.37 (q,  $J$  = 6.5 Hz, 1H,  $\text{CHMe}$ ), 2.44-2.41 (m, 2H, NCH), 2.35-2.31 (m, 2H, NCH), 1.43 (s, 9H,  $\text{CMe}_3$ ), 1.36 (d,  $J$  = 6.5 Hz, 3H,  $\text{CHMe}$ );  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  154.7 (C=O), 143.6 (*ipso*-Ph), 128.2 (Ph), 127.6 (Ph), 127.0 (Ph), 79.4 ( $\text{CMe}_3$ ), 64.7 (NCHPh), 50.2 ( $\text{NCH}_2$ ); 44.0 ( $\text{NCH}_2$ ), 28.4 ( $\text{CMe}_3$ ), 19.6 ( $\text{CHMe}$ ). Spectroscopic data consistent with those reported in the literature.<sup>5</sup>

Lab Book Reference: JDF5\_426

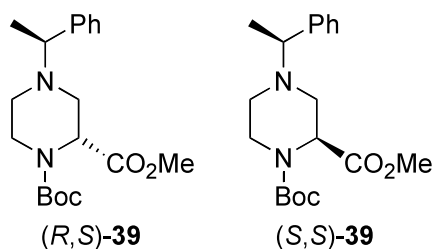
**(*R*)-*tert*-Butyl 4-(1-phenylethyl)piperazine-1-carboxylate (*R*)-36**



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  $\text{CH}_2\text{Cl}_2$  (30 mL) gave *N*-Boc piperazine (*R*)-**36** (2.2 g, 96%) as a pale yellow oil,  $[\alpha]_{\text{D}}^{25} +43.5$  ( $c$  1.0 in  $\text{CHCl}_3$ ) (lit.,<sup>5</sup>  $[\alpha]_{\text{D}}^{25} -32$  ( $c$  1.04 in  $\text{CHCl}_3$ ) for (*S*)-**36** of >99:1 er); Spectroscopic data consistent with those reported in the literature.<sup>5</sup>

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**



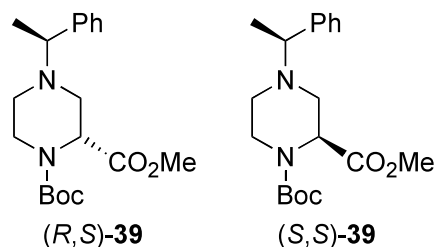
(Scheme 8)

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  $\text{Et}_2\text{O}$  (10 mL) for 10 min and methyl chloroformate (378 mg, 309  $\mu\text{L}$ , 4.0 mmol, 2.0 eq.), worked up with saturated  $\text{NaHCO}_{3(\text{aq})}$  (10 mL) gave the crude product which contained a 95:5 mixture of (*S,S*)-**39** and (*R,S*)-**39** (by  $^1\text{H}$  NMR spectroscopy). Purification by flash column chromatography on silica with 8:2-7:3 petrol- $\text{Et}_2\text{O}$  as eluent gave *N*-Boc piperazine (*R,S*)-**39** (31 mg, 4%) as a colourless oil,  $R_{\text{F}}$  (4:1

petrol-Et<sub>2</sub>O) 0.2; [ $\alpha$ ]<sub>D</sub> +23.4 (*c* 1.1 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 1717 (C=O, CO<sub>2</sub>Me), 1660 (C=O, Boc), 1498, 1453, 1398, 1346, 1199, 1101, 999, 913, 760 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (55:45 mixture of rotamers)  $\delta$  7.34-7.16 (m, 5H, Ph), 4.73 (s, 0.55H, NCH), 4.56 (s, 0.45H, NCH), 3.74 (s, 1.65H, CO<sub>2</sub>Me), 3.72 (s, 1.35H, CO<sub>2</sub>Me), 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, CMe<sub>3</sub>), 1.42 (s, 4H, CMe<sub>3</sub>), 1.31 (d, *J* = 6.5 Hz, 3H, CHMe); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  171.6 (CO<sub>2</sub>Me), 171.3 (CO<sub>2</sub>Me), 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 (CMe<sub>3</sub>), 63.5 (NCHPh), 63.3 (NCHPh), 55.7 (NCH), 54.6 (NCH), 52.0 (CO<sub>2</sub>Me), 50.4 (NCH<sub>2</sub>), 50.2 (NCH<sub>2</sub>), 50.0 (NCH<sub>2</sub>), 42.3 (NCH<sub>2</sub>), 41.3 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>), 18.7 (CHMe), 18.3 (CHMe); MS (ESI) *m/z* 349 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>19</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 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*<sub>F</sub> (4:1 petrol-Et<sub>2</sub>O) 0.15; [ $\alpha$ ]<sub>D</sub> -45.7 (*c* 1.5 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 1717 (C=O, CO<sub>2</sub>Me), 1661 (C=O, Boc), 1431, 1346, 1282, 1197, 1145, 1102, 1051, 959, 743 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (55:45 mixture of rotamers)  $\delta$  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, CO<sub>2</sub>Me), 3.69 (s, 1.65H, CO<sub>2</sub>Me), 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, CMe<sub>3</sub>), 1.40 (s, 4H, CMe<sub>3</sub>), 1.31 (d, *J* = 6.5 Hz, 3H, CHMe); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  171.2 (CO<sub>2</sub>Me), 171.0 (CO<sub>2</sub>Me), 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 (CMe<sub>3</sub>), 80.1 (CMe<sub>3</sub>), 64.1 (NCHPh), 55.6 (NCH), 54.4 (NCH), 51.8 (CO<sub>2</sub>Me), 51.7 (NCH<sub>2</sub>), 51.5 (NCH<sub>2</sub>), 49.2 (NCH<sub>2</sub>), 42.2 (NCH<sub>2</sub>), 41.2 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>), 28.2 (CMe<sub>3</sub>), 19.9 (CHMe), 19.7 (CHMe); MS (ESI) *m/z* 349 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>19</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 349.2118, found 349.2116 (+1.2 ppm error); CSP-HPLC: Chiralcel AD-H (98:2 hexane:*i*-PrOH, 1.0 mL min<sup>-1</sup>) (*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**

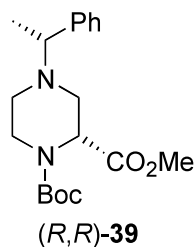


(Scheme 8)

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  $\mu$ L, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-36 (145 mg, 0.5 mmol, 1.0 eq.) in Et<sub>2</sub>O (5 mL) for 3 h and methyl chloroformate (95 mg, 77  $\mu$ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product which contained a 37:63 mixture of (*S,S*)-39 and (*R,S*)-39 (by <sup>1</sup>H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et<sub>2</sub>O 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.

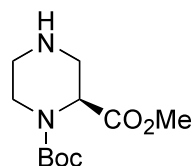
Lab Book Reference: JDF8\_710

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



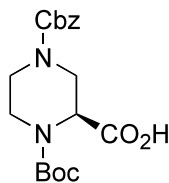
Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (–)-sparteine (152 mg, 149  $\mu$ L, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-36 (145 mg, 0.5 mmol, 1.0 eq.) in Et<sub>2</sub>O (5 mL) for 1 h and methyl chloroformate (95 mg, 77  $\mu$ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product which contained a >95:5 mixture of (*R,R*)-39 and (*S,R*)-39 (by <sup>1</sup>H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3 petrol-Et<sub>2</sub>O 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<sup>–1</sup>) (*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 H<sub>2</sub> was attached and the reaction mixture was stirred vigorously at rt under H<sub>2</sub> for 48 h. The mixture was filtered through Celite<sup>®</sup> 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

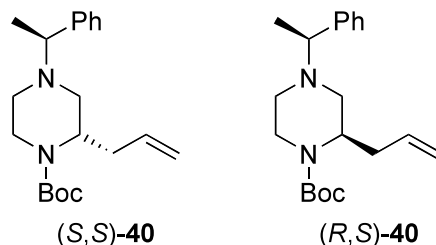
**(*S*)-4-(Benzyloxycarbonyl)-1-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (*S*)-**S3******(*S*)-**S3****

Benzyl chloroformate (15 mg, 12  $\mu$ 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 Et<sub>3</sub>N (9 mg, 12  $\mu$ L, 0.086 mmol, 1.5 eq.) in CH<sub>2</sub>Cl<sub>2</sub> at rt. The resulting solution was stirred for 16 h. Water (5 mL) was added and the layers separated. The aqueous was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 5 mL). The combined organic layers were dried (MgSO<sub>4</sub>) 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 CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the two layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 66:33:1 CH<sub>2</sub>Cl<sub>2</sub>-EtOAc-AcOH as eluent gave carboxylic acid

(*S*)-**S3** (14 mg, 84%) as a pale yellow oil,  $R_F$  (66:33:1  $\text{CH}_2\text{Cl}_2$ -EtOAc-AcOH); 0.2;  $[\alpha]_D -14.3$  ( $c$  0.7 in  $\text{CHCl}_3$ ) (lit.,<sup>4</sup>  $[\alpha]_D -17.5$  ( $c$  1.02 in  $\text{CHCl}_3$ )).

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**



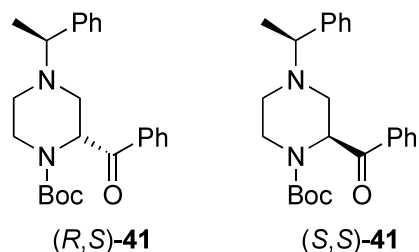
(Scheme 9)

*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  $\text{Et}_2\text{O}$  (4 mL) at  $-78^\circ\text{C}$  under Ar. The resulting solution was stirred at  $-78^\circ\text{C}$  for 15 min. Then, a solution of *N*-Boc piperazine (*S*)-**36** (145 mg, 0.5 mmol, 1.0 eq.), in  $\text{Et}_2\text{O}$  (1 mL) was added dropwise. The resulting solution was stirred at  $-78^\circ\text{C}$  for 1 h. Then a solution of  $\text{CuCN}\cdot 2\text{LiCl}$  (0.25 mmol, 0.5 eq.) in THF (1 mL) was added dropwise. The resulting solution was stirred at  $-78^\circ\text{C}$  for 1 h. Then, allyl bromide (121 mg, 87  $\mu\text{L}$ , 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 saturated  $\text{NaHCO}_{3(\text{aq})}$  (10 mL) was added and the two layers were separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) 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  $^1\text{H}$  NMR spectroscopy). Purification by flash column chromatography on silica with 9:1 petrol- $\text{Et}_2\text{O}$  as eluent gave *N*-Boc piperazine (*S,S*)-**40** (8 mg, 5%) as a colourless oil,  $R_F$  (9:1 petrol- $\text{Et}_2\text{O}$ ) 0.2;  $[\alpha]_D +7.6$  ( $c$  1.4 in  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 2960, 2770, 2323, 2304, 1654 ( $\text{C}=\text{O}$ ), 1430, 1397, 1346, 1304, 1282, 1233, 1152, 1092, 1050, 929, 904, 746  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-7.28 (m, 4H, Ph), 7.27-7.21 (m, 1H, Ph), 5.74 (td,  $J = 17.0, 7.5$  Hz, 1H,  $\text{CH}=\text{CH}_2$ ), 5.09-5.02 (m, 1H,  $\text{CH}=\text{CH}_A\text{H}_B$ ), 5.02-4.98 (m, 1H,  $\text{CH}=\text{CH}_A\text{H}_B$ ), 4.08 (s, 1H, NCH), 3.74 (s, 1H, NCH), 3.34 (q,  $J = 6.5$  Hz, 1H,  $\text{CHMe}$ ), 3.04-2.85 (m, 2H, NCH), 2.70-2.40 (m, 3H, NCH +  $\text{CH}_2$ ), 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,  $\text{CMe}_3$ ), 1.29 (d,  $J = 6.5$  Hz, 3H,  $\text{CHMe}$ );  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  154.8 ( $\text{C}=\text{O}$ ), 144.4 (*ipso*-Ph), 135.6 ( $\text{CH}=\text{CH}_2$ ), 128.2 (Ph), 127.4 (Ph), 126.8 (Ph), 117.0 ( $\text{CH}=\text{CH}_2$ ), 79.3 ( $\text{CMe}_3$ ), 64.0 ( $\text{CHMe}$ ), 51.0 ( $\text{NCH}_2$ ), 50.9 ( $\text{NCH}_2$ ), 39.7 (br,  $\text{NCH}_2$ ), 34.3 ( $\text{CH}_2$ ), 28.3 ( $\text{CMe}_3$ ), 19.0 ( $\text{CHMe}$ ); MS

(ESI)  $m/z$  331 ( $M + H$ )<sup>+</sup>; HRMS  $m/z$  calcd for  $C_{20}H_{30}N_2O_2$  ( $M + H$ )<sup>+</sup> 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-Et<sub>2</sub>O) 0.1;  $[\alpha]_D -47.3$  (c 1.0 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2931, 2323, 2304, 1653 (C=O), 1430, 1390, 1345, 1300, 1282, 1233, 1148, 1092, 1050, 935, 904, 746 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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=CH<sub>2</sub>), 5.01 (dd,  $J = 17.0, 1.5$  Hz, 1H, CH=CH<sub>A</sub>H<sub>B</sub>), 4.95-4.90 (m, 1H, CH=CH<sub>A</sub>H<sub>B</sub>), 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, CH<sub>2</sub>), 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, CMe<sub>3</sub>), 1.33 (d,  $J = 6.5$  Hz, 3H, CHMe); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  154.8 (C=O), 144.0 (*ipso*-Ph), 135.5 (CH=CH<sub>2</sub>), 128.2 (Ph), 127.5 (Ph), 126.9 (Ph), 117.0 (CH=CH<sub>2</sub>), 79.3 (CMe<sub>3</sub>), 64.5 (CHMe), 52.8 (NCH<sub>2</sub>), 49.8 (NCH<sub>2</sub>), 39.3 (br, NCH<sub>2</sub>), 34.4 (CH<sub>2</sub>), 28.4 (CMe<sub>3</sub>), 19.8 (CHMe); MS (ESI)  $m/z$  331 ( $M + H$ )<sup>+</sup>; HRMS  $m/z$  calcd for  $C_{20}H_{30}N_2O_2$  ( $M + H$ )<sup>+</sup> 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)

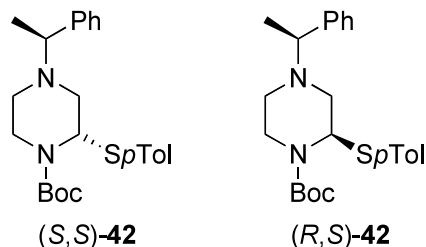
Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate (126 mg, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**36** (145 mg, 0.5 mmol, 1.0 eq.) in Et<sub>2</sub>O (5 mL) for 1 h and *N*-methoxy-*N*-methylbenzamide (107 mg, 99  $\mu$ L, 0.65 mmol, 1.3 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product which contained a 7:93 mixture of (*R,S*)-**41** and (*S,S*)-**41** (by <sup>1</sup>H NMR spectroscopy). Purification by flash column chromatography on silica with 99:1-97:3 CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O as eluent gave *N*-Boc piperazine (*R,S*)-**41** (12 mg, 6%) as a white solid, mp 104-105 °C;  $R_F$  (98:2 CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O) 0.2;  $[\alpha]_D +1.9$  (c 0.65 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2967, 2933, 2772, 1674 (C=O, PhCO), 1661 (C=O, Boc), 1429, 1385, 1345, 1283, 1234, 1144, 1102, 1051, 931, 848 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (55:45 mixture of rotamers)  $\delta$  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,



CHMe + NCH), 2.78-2.56 (m, 1H, NCH), 2.49-2.34 (m, 1H, NCH), 2.14-1.97 (m, 1H, NCH), 1.45 (s, 4.95H, CMe<sub>3</sub>), 1.37 (s, 3.05H, CMe<sub>3</sub>), 1.02 (d,  $J = 6.5$  Hz, 3H, CHMe); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  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<sub>3</sub>), 64.5 (CHMe), 59.0 (NCH), 58.0 (NCH), 52.9 (NCH<sub>2</sub>), 50.4 (NCH<sub>2</sub>), 42.5 (NCH<sub>2</sub>), 41.7 (NCH<sub>2</sub>), 28.3 (CMe<sub>3</sub>), 28.3 (CMe<sub>3</sub>), 18.4 (CHMe), 18.3 (CHMe); MS (ESI)  $m/z$  395 (M + H)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub> (M + H)<sup>+</sup> 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<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O) 0.1;  $[\alpha]_D -2.6$  ( $c$  0.8 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2967, 2933, 2772, 1674 (C=O, PhCO), 1661 (C=O, Boc), 1430, 1385, 1346, 1281, 1234, 1150, 1102, 1051, 931, 848 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (55:45 mixture of rotamers)  $\delta$  7.75-7.59 (m, 2H, Ph), 7.55-7.43 (m, 1H, Ph), 7.41-7.31 (m, 2H, Ph), 7.06-6.78 (m, 5H, Ph), 5.39 (br s, 0.55H, NCH), 5.21 (br s, 0.45H, NCH), 3.91 (br d,  $J = 12.0$  Hz, 0.45H, NCH), 3.82 (br d,  $J = 12.0$  Hz, 0.55H, NCH), 3.62-3.43 (m, 1H, CHMe), 3.24-3.02 (m, 2.45H, NCH), 2.98 (br d,  $J = 10.0$  Hz, 0.55H), 2.22 (dd,  $J = 12.0, 4.5$  Hz, 1H, NCH), 2.04 (br s, 1H, NCH), 1.47 (s, 4.95H, CMe<sub>3</sub>), 1.36 (s, 3.05H, CMe<sub>3</sub>), 1.17 (d,  $J = 6.5$  Hz, 3H, CHMe); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  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<sub>3</sub>), 64.5 (CHMe), 58.9 (NCH), 57.9 (NCH), 52.3 (NCH<sub>2</sub>), 52.3 (NCH<sub>2</sub>), 49.7 (NCH<sub>2</sub>), 42.6 (NCH<sub>2</sub>), 41.8 (NCH<sub>2</sub>), 28.5 (CMe<sub>3</sub>), 28.3 (CMe<sub>3</sub>), 20.2 (CHMe); 20.1 (CHMe); MS (ESI)  $m/z$  395 (M + H)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub> (M + H)<sup>+</sup> 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****



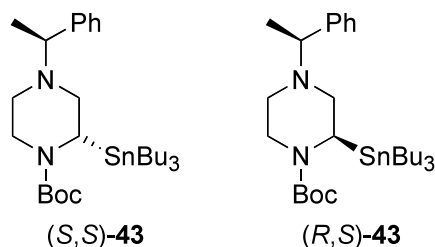
(Scheme 9)

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<sub>2</sub>O (5 mL) for 1 h and *p*-tolyl disulfide (246 mg, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product which contained a 5:95 mixture of (*S,S*)-**42** and (*R,S*)-**42** (by <sup>1</sup>H NMR spectroscopy). Purification by flash column chromatography on silica (prewashed with 99:1 CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>3</sub>N) with CH<sub>2</sub>Cl<sub>2</sub> as eluent gave *N*-Boc piperazine (*S,S*)-**42** (8 mg, 4%) as a pale yellow oil, *R*<sub>F</sub> (CH<sub>2</sub>Cl<sub>2</sub>) 0.2; [α]<sub>D</sub> -46.5 (*c* 0.4 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2931, 2881, 1661 (C=O), 1469, 1429, 1387, 1347, 1283, 1283, 1253, 1146, 1101, 1001, 930, 846, 801 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (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<sub>3</sub>), 1.10 (br s, 5.8H, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (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<sub>3</sub>), 65.0 (NCH), 63.8 (CHMe), 54.8 (NCH<sub>2</sub>), 50.5 (NCH<sub>2</sub>), 42.0 (NCH<sub>2</sub>), 38.5 (NCH<sub>2</sub>), 27.7 (CMe<sub>3</sub>), 21.1 (ArMe), 19.0 (CHMe); MS (ESI) *m/z* 413 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>S (M + H)<sup>+</sup> 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*<sub>F</sub> (CH<sub>2</sub>Cl<sub>2</sub>) 0.1; [α]<sub>D</sub> +37.9 (*c* 1.0 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2934, 2776, 1662 (C=O), 1469, 1429, 1388, 1346, 1287, 1196, 1149, 1101, 1047, 998, 921, 844, 764 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (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<sub>3</sub>), 1.08 (br s, 5.8H, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (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<sub>3</sub>), 64.6 (NCH), 64.3 (CHMe), 55.4 (NCH<sub>2</sub>), 54.5 (NCH<sub>2</sub>), 50.0 (NCH<sub>2</sub>), 39.8 (NCH<sub>2</sub>), 38.4 (NCH<sub>2</sub>), 28.1 (CMe<sub>3</sub>), 27.6 (CMe<sub>3</sub>), 21.0 (ArMe), 19.8 (CHMe); MS (ESI) *m/z* 413 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>S (M + H)<sup>+</sup> 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**



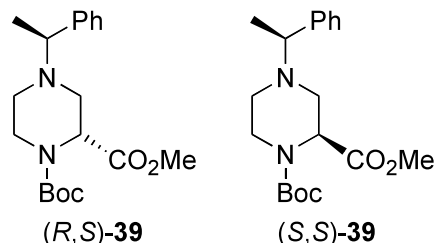
(Scheme 9)

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 Et<sub>2</sub>O (5 mL) for 1 h and Bu<sub>3</sub>SnCl (325 mg, 271  $\mu$ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (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<sub>F</sub>* (19:1 petrol-EtOAc) 0.2; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (50:50 mixture of rotamers)  $\delta$  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, CH<sub>2</sub> + CHMe + CMe<sub>3</sub>), 1.21-1.34 (m, 6H, CH<sub>2</sub>), 0.79-0.97 (m, 15H, CH<sub>2</sub> + 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**

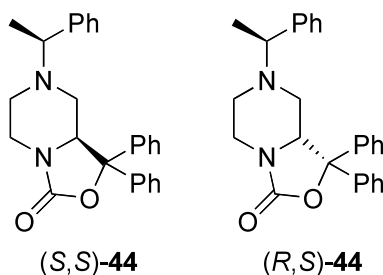


*n*-BuLi (51  $\mu$ L of a 2.2 M solution in hexanes, 0.11 mmol, 1.3 eq.) was added dropwise to a stirred solution of diastereomeric stannanes (*S,S*)-43 and (*R,S*)-43 (50 mg, 0.09 mmol, 1.0 eq.) and TMEDA (13 mg, 17  $\mu$ L, 0.11 mmol, 1.3 eq.) in Et<sub>2</sub>O (3 mL) at -78 °C under Ar. The resulting solution was

stirred at  $-78\text{ }^{\circ}\text{C}$  for 10 min. Then, methyl chloroformate (16 mg,  $13\text{ }\mu\text{L}$ , 0.17 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  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  $\text{Et}_2\text{O}$  ( $3 \times 5\text{ mL}$ ). The combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure gave the crude product which contained a 7:93 mixture of (*R,S*)-**39** and (*S,S*)-**39** (by  $^1\text{H}$  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*)-**39** and (*S,S*)-**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 (*R,S*)-44**



(Scheme 9)

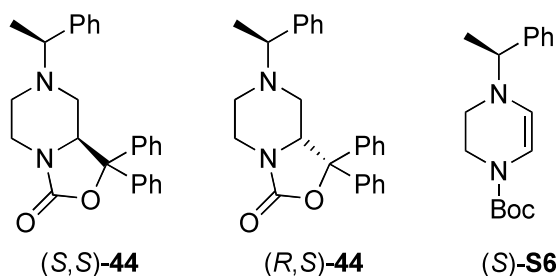
Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (+)-sparteine surrogate (152 mg, 1.3 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**36** (290 mg, 1.0 mmol, 1.0 eq.) in  $\text{Et}_2\text{O}$  (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in  $\text{Et}_2\text{O}$  (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*)-**44** and (*R,S*)-**44** (by  $^1\text{H}$  NMR spectroscopy). Purification by flash column chromatography on silica with 7:3-1:1 petrol- $\text{Et}_2\text{O}$  as eluent gave *N*-Boc piperazine (*S,S*)-**44** (122 mg, 31%) as a white solid, mp  $139\text{--}140\text{ }^{\circ}\text{C}$ ;  $R_F$  (7:3 petrol-EtOAc) 0.2;  $[\alpha]_D -244.9$  (*c* 1.0 in  $\text{CHCl}_3$ ) (lit.,<sup>5</sup>  $[\alpha]_D +213$  (*c* 0.108 in  $\text{CHCl}_3$ ) for (*S,S*)-**44** of >99:1 er);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54-7.51 (m, 2H, Ph), 7.40-7.22 (m, 11H, Ph), 7.18-7.16 (m, 2H, Ph), 4.51 (dd,  $J = 11.0, 3.5\text{ Hz}$ , 1H, NCH), 3.74 (ddd,  $J = 13.0, 3.5, 1.0\text{ Hz}$ , 1H, NCH), 3.34 (q,  $J = 7.0\text{ Hz}$ , 1H, CHMe), 3.04 (ddd,  $J = 13.0, 12.0, 3.5\text{ Hz}$ , 1H, NCH), 2.72-2.60 (m, 2H, NCH), 1.86 (td,  $J = 12.0, 3.5\text{ Hz}$ , 1H, NCH), 1.46 (t,  $J = 11.0\text{ Hz}$ , 1H, NCH), 1.22 (d,  $J = 7.0\text{ Hz}$ , 3H, CHMe);  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  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 (Ph<sub>2</sub>CO), 64.3 (CH), 61.4 (CH), 52.5 (NCH<sub>2</sub>), 49.1 (NCH<sub>2</sub>), 41.9 (NCH<sub>2</sub>), 19.2 (CHMe) and *N*-Boc piperazine (*R,S*)-**44** (15 mg, 4%) as a white solid, mp 127-129 °C; *R<sub>F</sub>* (7:3 petrol-EtOAc) 0.1; [ $\alpha$ ]<sub>D</sub> +187.7 (*c* 1.0 in CHCl<sub>3</sub>) (lit.,<sup>5</sup> [ $\alpha$ ]<sub>D</sub> -132 (*c* 0.11 in CHCl<sub>3</sub>) for (*R,S*)-**44** of >99:1 er); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  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 (Ph<sub>2</sub>CO), 63.3 (CH), 61.2 (CH), 52.8 (NCH<sub>2</sub>), 47.1 (NCH<sub>2</sub>), 41.6 (NCH<sub>2</sub>), 16.7 (CHMe); Spectroscopic data for (*S,S*)-**44** and (*R,S*)-**44** consistent with those reported in the literature.<sup>5</sup>

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**

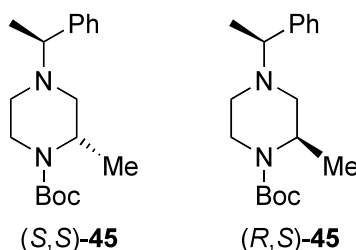


Using general procedure A, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), (–)-sparteine (305 mg, 299  $\mu$ L, 1.3 mmol, 1.3 eq.), *N*-Boc piperazine (*S*)-**36** (290 mg, 1.0 mmol, 1.0 eq.) in Et<sub>2</sub>O (7 mL) for 1 h and a solution of benzophenone (364 mg, 2.0 mmol, 2.0 eq.) in Et<sub>2</sub>O (1 mL), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product which contained a 40:60 mixture of (*S,S*)-**44** and (*R,S*)-**44** (by <sup>1</sup>H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2-1:1 petrol-Et<sub>2</sub>O 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*)-**S6** as a clear oil (29 mg, 10%), *R<sub>F</sub>* (8:2 petrol-Et<sub>2</sub>O) 0.2; IR (CHCl<sub>3</sub>) 2971, 1664 (C=O), 1505, 1471, 1430, 1371, 1347, 1203, 1189, 1147, 914, 774, 722, 691 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (70:30 mixture of rotamers)  $\delta$  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)  $\delta$  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 ( $NCH_2$ ), 42.1 ( $NCH_2$ ), 40.8 ( $NCH_2$ ), 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**

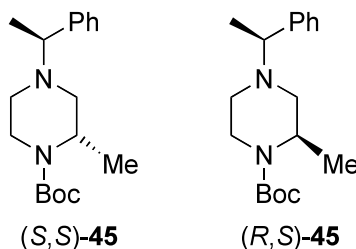


(Scheme 9)

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  $Et_2O$  (7 mL) for 1 h and methyl iodide (284 mg, 125  $\mu$ L, 2.0 mmol, 2.0 eq.), worked up with saturated  $NaHCO_{3(aq)}$  (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 petrol- $Et_2O$  as eluent gave *N*-Boc piperazine (*S,S*)-**45** (46 mg, 15%) as a colourless oil,  $R_F$  (4:1 petrol- $Et_2O$ ) 0.2;  $[\alpha]_D +24.2$  ( $c$  1.0 in  $CHCl_3$ ); IR ( $CHCl_3$ ) 2961, 2889, 2769, 1654 (C=O), 1430, 1394, 1346, 1301, 1258, 1212, 1196, 1147, 1112, 1068, 1015, 744  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  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,  $CMe_3$ ), 1.31 (d,  $J = 6.5$  Hz, 3H,  $CHMe$ ), 1.26 (d,  $J = 6.5$  Hz, 3H,  $CHMe$ );  $^{13}C$  NMR (100.6 MHz,  $CDCl_3$ )  $\delta$  154.7 (C=O), 144.4 (*ipso*-Ph), 128.8 (Ph), 127.5 (Ph), 126.8 (Ph), 79.2 ( $CMe_3$ ), 64.0 (NCHPh), 53.9 ( $NCH_2$ ), 51.1 ( $NCH_2$ ), 47.2 (NCH), 39.3 ( $NCH_2$ ), 28.4 ( $CMe_3$ ), 19.2 ( $CHMe$ ), 16.0

(CHMe); MS (ESI)  $m/z$  305 ( $M + H$ )<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub> ( $M + H$ )<sup>+</sup> 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-Et<sub>2</sub>O) 0.1;  $[\alpha]_D$  −92.8 ( $c$  1.0 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2933, 2770, 1645 (C=O), 1430, 1394, 1346, 1297, 1268, 1196, 1149, 1114, 1067, 1014, 743 cm<sup>−1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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, CMe<sub>3</sub>), 1.33 (d,  $J$  = 6.5 Hz, CHMe), 1.17 (d,  $J$  = 6.5 Hz, CHMe); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  154.7 (C=O), 144.4 (*ipso*-Ph), 128.2 (Ph), 127.3 (Ph), 126.8 (Ph), 79.2 (CMe<sub>3</sub>), 64.5 (NCHPh), 55.6 (NCH<sub>2</sub>), 49.9 (NCH<sub>2</sub>), 47.1 (NCH), 39.4 (NCH<sub>2</sub>), 28.4 (CMe<sub>3</sub>), 20.0 (CHMe), 15.6 (CHMe); MS (ESI)  $m/z$  305 ( $M + H$ )<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub> ( $M + H$ )<sup>+</sup> 305.2224, found 305.2223 (+0.6 ppm error). Lab Book Reference: JDF5\_420

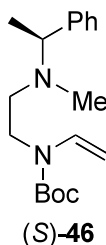
**(*S*)-tert-Butyl 2-methyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*S,S*)-**45** and (*R*)-tert-butyl 2-methyl-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*R,S*)-**45****



(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  $\mu$ L, 0.65 mmol, 1.3 eq.) in Et<sub>2</sub>O (5 mL) for 1 h and methyl trifluoromethanesulfonate (164 mg, 113  $\mu$ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product which contained a 28:72 mixture of (*S,S*)-**45** and (*R,S*)-**45** (by <sup>1</sup>H NMR spectroscopy). Purification by flash column chromatography on silica with 17:3-7:3 petrol-Et<sub>2</sub>O 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**

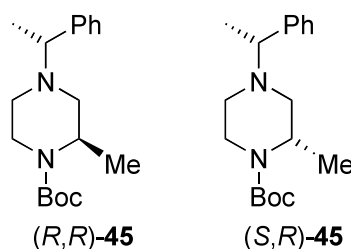
(Scheme 10)

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 Et<sub>2</sub>O (5 mL) for 1 h and methyl trifluoromethanesulfonate (164 mg, 113  $\mu$ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1-1:1 petrol-Et<sub>2</sub>O as eluent gave alkene (S)-**46** (71 mg, 46%) as a colourless oil, *R*<sub>F</sub> (4:1 petrol-Et<sub>2</sub>O) 0.2; [ $\alpha$ ]<sub>D</sub> -21.0 (*c* 1.1 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2973, 2930, 2851, 2779, 1707 (C=O), 1623 (C=C), 1453, 1419, 1360, 1324, 1247, 1205, 1150, 1060, 863, 832, 769 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.36-7.27 (m, 4H, Ph), 7.25-7.18 (m, 1H, Ph), 7.08-6.82 (br m, 1H, CH=CH<sub>2</sub>), 4.17-3.92 (m, 2H, CH=CH<sub>2</sub>), 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, CMe<sub>3</sub>), 1.35 (d, *J* = 6.5 Hz, 3H, CHMe); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  153.2 (C=O), 152.4 (C=O), 143.9 (*ipso*-Ph), 132.7 (CH=CH<sub>2</sub>), 128.2 (Ph), 127.5 (Ph), 126.8 (Ph), 90.3 (CH=CH<sub>2</sub>), 81.0 (CMe<sub>3</sub>), 63.9 (CHMe), 63.7 (CHMe), 50.4 (NCH<sub>2</sub>), 49.9 (NCH<sub>2</sub>), 41.5 (NCH<sub>2</sub>), 41.0 (NCH<sub>2</sub>), 28.1 (CMe<sub>3</sub>), 18.6 (CHMe), 18.4 (CHMe); MS (ESI) *m/z* 305 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 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**

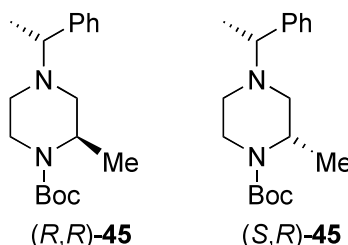


(Scheme 10)

*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  $\mu$ L, 0.65 mmol, 1.3 eq.) in Et<sub>2</sub>O (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 Et<sub>2</sub>O (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 3 h. Then, TMEDA (240 mg, 375  $\mu$ 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  $\mu$ L, 1.0 mmol, 2.0 eq.) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h. Then, saturated NH<sub>4</sub>Cl<sub>(aq)</sub> (10 mL) and saturated NaHCO<sub>3(aq)</sub> (10 mL) were added and the two layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) 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 <sup>1</sup>H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1-7:3 petrol-Et<sub>2</sub>O 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**

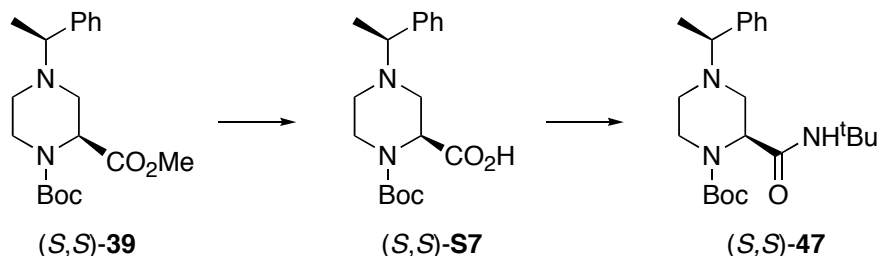


(Scheme 10)

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  $\mu$ L, 0.65 mmol, 1.3 eq.), *N*-Boc piperazine (*R*)-36 (145 mg, 0.5 mmol, 1.0 eq.), in Et<sub>2</sub>O (5 mL) for 3 h and methyl iodide (142 mg, 62  $\mu$ L, 1.0 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product which contained a 45:55 mixture of (*R,R*)-45 and (*S,R*)-45 (by <sup>1</sup>H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1-1:1 petrol-Et<sub>2</sub>O as eluent gave *N*-Boc piperazine (*R,R*)-45 (41 mg, 27%) as a colourless oil, [ $\alpha$ ]<sub>D</sub> –7.8 (*c* 1.6 in CHCl<sub>3</sub>) and *N*-Boc piperazine (*S,R*)-45 (48 mg, 32%) as a colourless oil, [ $\alpha$ ]<sub>D</sub> +80.2 (*c* 1.0 in CHCl<sub>3</sub>).

Lab Book Reference: JDF6\_577

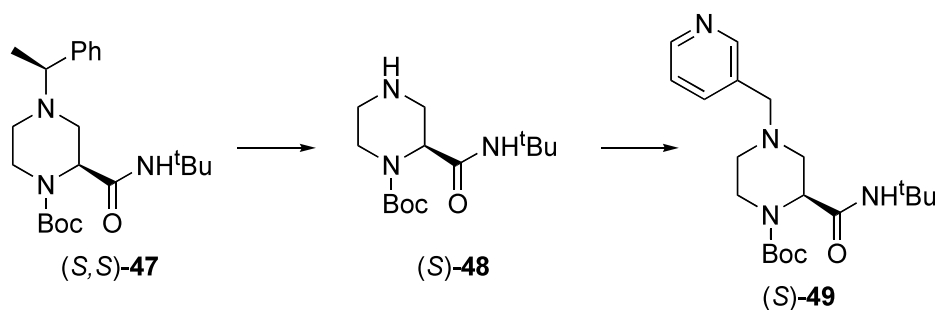
**(*S*)-*tert*-Butyl 2-(*tert*-butylcarbamoyl)-4-((*S*)-1-phenylethyl)piperazine-1-carboxylate (*S,S*)-47**



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<sub>(aq)</sub>. The aqueous was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  5 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give *N*-Boc piperazine (*S,S*)-S7 (21 mg, 99%) as a white gum, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (55:45 mixture of rotamers)  $\delta$  7.29-7.60 (m, 6H, Ph + CO<sub>2</sub>H), 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, CMe<sub>3</sub>). The crude product was used in the next step without further purification ( $\geq 90\%$  purity by <sup>1</sup>H 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  $\mu$ L, 0.094 mmol, 1.5 eq.) and DIPEA (16 mg, 22  $\mu$ 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<sub>3(aq)</sub> (5 mL) was added and the aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  5 mL). The combined organic layers were washed with brine (3  $\times$  5 mL), dried (MgSO<sub>4</sub>) 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 CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2974, 2932, 1653 (C=O), 1490, 1431, 1394, 1346, 1194, 1148, 1101, 1015, 914, 769, 731, 658 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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, CMe<sub>3</sub>), 1.36 (s, 9H, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  168.9 (Me<sub>3</sub>CNC=O), 155.0 (OC=O), 142.4 (*ipso*-Ph), 128.2 (Ph), 127.7 (Ph), 127.2 (Ph), 80.5 (OCMe<sub>3</sub>), 64.1 (CHMe), 56.4 (NCH), 51.0 (NCMe<sub>3</sub>), 50.7 (NCH<sub>2</sub>), 49.2 (NCH<sub>2</sub>), 41.4 (NCH<sub>2</sub>), 28.7 (CMe<sub>3</sub>), 28.3 (CMe<sub>3</sub>), 18.2 (CHMe); MS (ESI)  $m/z$  390 (M + H)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>22</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub> (M + H)<sup>+</sup> 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**



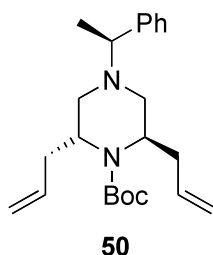
(Scheme 11)

1-Chloroethylchloroformate (27 mg, 20  $\mu$ 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%),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.28 (br s, 1H,  $\text{NH}_2^+$ ), 7.99 (br s, 1H,  $\text{NH}_2^+$ ), 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,  $\text{CMe}_3$ ), 1.31 (s, 9H,  $\text{CMe}_3$ ). The crude product was used in the next step without further purification ( $\geq 90\%$  purity by  $^1\text{H}$  NMR spectroscopy). Then, 3-(chloromethyl)pyridine hydrochloride (13mg, 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  $\text{Et}_3\text{N}$  (16 mg, 22  $\mu\text{L}$ , 0.155 mmol, 5.0 eq.) in  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1  $\text{CH}_2\text{Cl}_2$ :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  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 2924, 2883, 1652 (C=O), 1487, 1432, 1372, 1346, 1283, 1145, 1102, 961  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$ ), 3.49 (d,  $J = 13.5$  Hz, 1H,  $\text{CH}_\text{A}\text{H}_\text{B}\text{Ar}$ ), 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,  $\text{CMe}_3$ ), 1.36 (s, 9H,  $\text{CMe}_3$ ); 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**



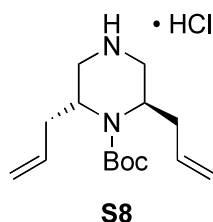
(Scheme 12)

*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  $\mu\text{L}$ , 0.20 mmol, 1.3 eq.) in  $\text{Et}_2\text{O}$  (3 mL) at  $-78$   $^\circ\text{C}$  under Ar. The resulting solution was stirred at  $-78$   $^\circ\text{C}$  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  $-78\text{ }^{\circ}\text{C}$  for 1 h. Then, allyl bromide (37 mg,  $26\text{ }\mu\text{L}$ , 0.3 mmol, 2.0 eq.) was added dropwise. The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  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  $\text{Et}_2\text{O}$  ( $3 \times 10\text{ mL}$ ). The combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1 petrol- $\text{Et}_2\text{O}$  as eluent gave *N*-Boc piperazine (*R,R,S*)-**50** (32 mg, 57%) as a colourless oil,  $R_F$  (9:1 petrol- $\text{Et}_2\text{O}$ ) 0.2;  $[\alpha]_D -35.9$  ( $c\ 1.5$  in  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 2972, 2932, 2886, 2774, 1665 (C=O), 1430, 1370, 1346, 1301, 1196, 1151, 980, 906, 840, 747, 692, 658  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $J = 6.5\text{ Hz}$ , 1H,  $\text{CHMe}$ ), 2.66-2.42 (m, 6H,  $\text{CH}_2 + \text{NCH}$ ), 2.36 (br d,  $J = 6.0\text{ Hz}$ , 1H,  $\text{CH}_2$  or NCH), 2.33 (br d,  $J = 6.0\text{ Hz}$ , 1H,  $\text{CH}_2$  or NCH), 1.44 (s, 9H,  $\text{CMe}_3$ ), 1.34 (d,  $J = 6.5\text{ Hz}$ , 3H,  $\text{CHMe}$ );  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $\text{CMe}_3$ ), 64.4 ( $\text{CHMe}$ ), 53.1 (NCH), 52.5 ( $\text{NCH}_2$ ), 36.7 ( $\text{CH}_2$ ), 28.4 ( $\text{CMe}_3$ ), 19.9 ( $\text{CHMe}$ ); 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**

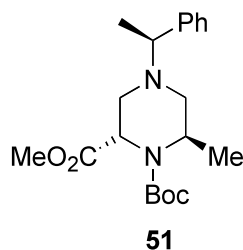


1-Chloroethylchloroformate (36 mg,  $27\text{ }\mu\text{L}$ , 0.25 mmol, 3.0 eq.) was added to a stirred solution of *N*-Boc piperazine (*R,R,S*)-**50** (31 mg, 0.08 mmol, 1.0 eq.) in 1,2-dichloroethane (3 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 3 h. After cooling 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- $\text{EtOAc}$  as eluent,  $R_F$  (9:1 petrol- $\text{EtOAc}$ ) 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 hygroscopic solid (14 mg, 55%),  $[\alpha]_D -34.9$  ( $c\ 0.7$  in  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 2933, 2666 ( $\text{NH}_2^+$ ), 1664 (C=O), 1564, 1438, 1366, 1347, 1313, 1240, 1196, 1150, 1103, 1047, 894, 741  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400

MHz, CDCl<sub>3</sub>)  $\delta$  10.17 (s, 2H, NH<sub>2</sub><sup>+</sup>), 5.84-5.72 (m, 2H, CH=CH<sub>2</sub>), 5.41 (d,  $J$  = 17.0 Hz, 2H, CH=CH<sub>A</sub>CH<sub>B</sub>), 5.17 (d,  $J$  = 10.0 Hz, 2H, CH=CH<sub>A</sub>CH<sub>B</sub>), 4.01-3.90 (m, 2H, NCH), 3.45-3.23 (m, 4H, NCH), 2.59-2.48 (m, 2H, CH<sub>2</sub>), 2.48-2.38 (m, 2H, CH<sub>2</sub>), 1.47 (s, 9H, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  153.8 (C=O), 133.0 (CH=CH<sub>2</sub>), 120.0 (CH=CH<sub>2</sub>), 81.1 (CMe<sub>3</sub>), 48.9 (NCH), 40.7 (NCH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 28.3 (CMe<sub>3</sub>); MS (ESI)  $m/z$  267 (M + H)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>15</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 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****

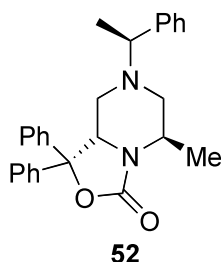


(Scheme 12)

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  $\mu$ L, 0.21 mmol, 1.3 eq.) in Et<sub>2</sub>O (3 mL) for 1 h and a methyl chloroformate (31 mg, 25  $\mu$ L 0.33 mmol, 2.0 eq.), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1-7:3 petrol-Et<sub>2</sub>O as eluent gave *N*-Boc piperazine (*R,R,S*)-**51** (46 mg, 77%) as pale yellow oil,  $R_F$  (8:2 petrol-Et<sub>2</sub>O) 0.2; [ $\alpha$ ]<sub>D</sub> -45.2 ( $c$  1.1 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2932, 2777, 1716 (C=O, ester), 1665 (C=O, Boc), 1468, 1431, 1347, 1298, 1235, 1151, 1068, 1011, 895, 847 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>Me), 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<sub>3</sub>), 1.32 (d,  $J$  = 6.5 Hz, 3H, CHMe), 1.26-1.20 (m, 3H, CHMe); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  172.1 (CO<sub>2</sub>Me), 155.6 (NC=O), 143.5 (*ipso*-Ph), 128.2 (Ph), 127.4 (Ph), 127.0 (Ph), 80.6 (CMe<sub>3</sub>), 64.1 (CHMe), 56.1 (br, NCH<sub>2</sub>), 52.2 (NCH<sub>2</sub>), 52.0 (CO<sub>2</sub>Me), 49.0 (NCH), 28.1 (CMe<sub>3</sub>), 19.7 (CHMe), 17.9 (CHMe) (NCH not resolved); MS (ESI)  $m/z$  363 (M + H)<sup>+</sup>; HRMS  $m/z$  calcd for C<sub>20</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 363.2278, found 363.2272 (+1.2 ppm error).

Lab Book Reference: JDF8\_749

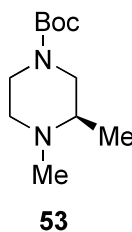
**(5*R*,8*aS*)-5-Methyl-1,1-diphenyl-7-((*S*)-1-phenylethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(*5H*)-one (*R,S,S*)-**52****



(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  $\mu$ L, 0.21 mmol, 1.3 eq.) in Et<sub>2</sub>O (3 mL), with a solution of benzophenone (60 mg, 0.33 mmol, 2.0 eq.) in Et<sub>2</sub>O (0.5 mL), worked up with saturated NaHCO<sub>3(aq)</sub> (10 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 petrol-Et<sub>2</sub>O as eluent gave oxazolidinone (*R,S,S*)-**52** (33 mg, 49%) as a white solid, mp 116-119 °C; *R*<sub>F</sub> (8:2 petrol-Et<sub>2</sub>O) 0.2; [ $\alpha$ ]<sub>D</sub> -177.1 (*c* 1.6 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2983, 2963, 1718 (C=O), 1469, 1428, 1397, 1298, 1216, 1184, 1054, 1017, 986, 691, 654 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  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 (CMe<sub>3</sub>), 64.1 (CHMe), 58.0 (NCH), 54.3 (NCH<sub>2</sub>), 52.8 (NCH<sub>2</sub>), 46.4 (NCH), 19.5 (CHMe), 16.3 (CHMe); MS (ESI) *m/z* 413 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 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)

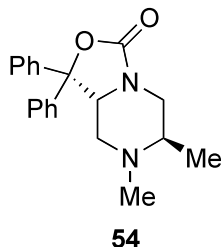
A solution of *N*-Boc piperazine (*R,S*)-**45** (244 mg, 0.80 mmol, 1.0 eq.) in THF (5 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (122 mg, 3.2 mmol, 4.0 eq.) in THF (5 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and then stirred at reflux for 16 h. After cooling to 0 °C, the mixture was diluted with Et<sub>2</sub>O (10 mL). Water (122 μL), 20% NaOH<sub>(aq)</sub> (244 μL) and water (122 μL) were sequentially added dropwise and the mixture stirred for 15 min. Then, anhydrous MgSO<sub>4</sub> was added and the mixture stirred for 30 min. The solids were removed by filtration through Celite® and washed with Et<sub>2</sub>O (10 mL). The filtrate was concentrated under reduced pressure to give the crude amine (153 mg, 88%) as a pale yellow oil, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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 <sup>1</sup>H 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 H<sub>2</sub> was attached and the reaction mixture was stirred vigorously at rt under H<sub>2</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added dropwise a stirred solution of secondary amine hydrochloride (max. 0.7 mmol, 1.0 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and Et<sub>3</sub>N (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<sub>(aq)</sub> (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH as eluent gave *N*-Boc piperazine (*R*)-**53** (130 mg, 87%) as a pale yellow oil, *R*<sub>F</sub> (19:1



CH<sub>2</sub>Cl<sub>2</sub>-MeOH) 0.1; [ $\alpha$ ]<sub>D</sub> -0.3 (*c* 0.9 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2934, 2889, 2809, 2755, 1659 (C=O), 1435, 1406, 1370, 1345, 1319, 1270, 1252, 1227, 1135, 1093, 1070, 1049, 1024, 964, 868 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>3</sub>), 1.04 (d, *J* = 6.0 Hz, 3H, CHMe); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) (mixture of rotamers)  $\delta$  154.5 (C=O), 79.6 (CMe<sub>3</sub>), 57.5 (NCH), 54.9 (NCH<sub>2</sub>), 50.2 (NCH<sub>2</sub>), 49.2 (NCH<sub>2</sub>), 44.0 (NCH<sub>2</sub>), 43.2 (NCH<sub>2</sub>), 42.4 (NMe), 28.2 (CMe<sub>3</sub>), 16.3 (CHMe); MS (ESI) *m/z* 215 [(M + H)<sup>+</sup>, 100], 159 [(M - CMe<sub>3</sub>)<sup>+</sup>, 20]; HRMS *m/z* calcd for C<sub>11</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 215.1754, found 215.1746 (+3.9 ppm error).

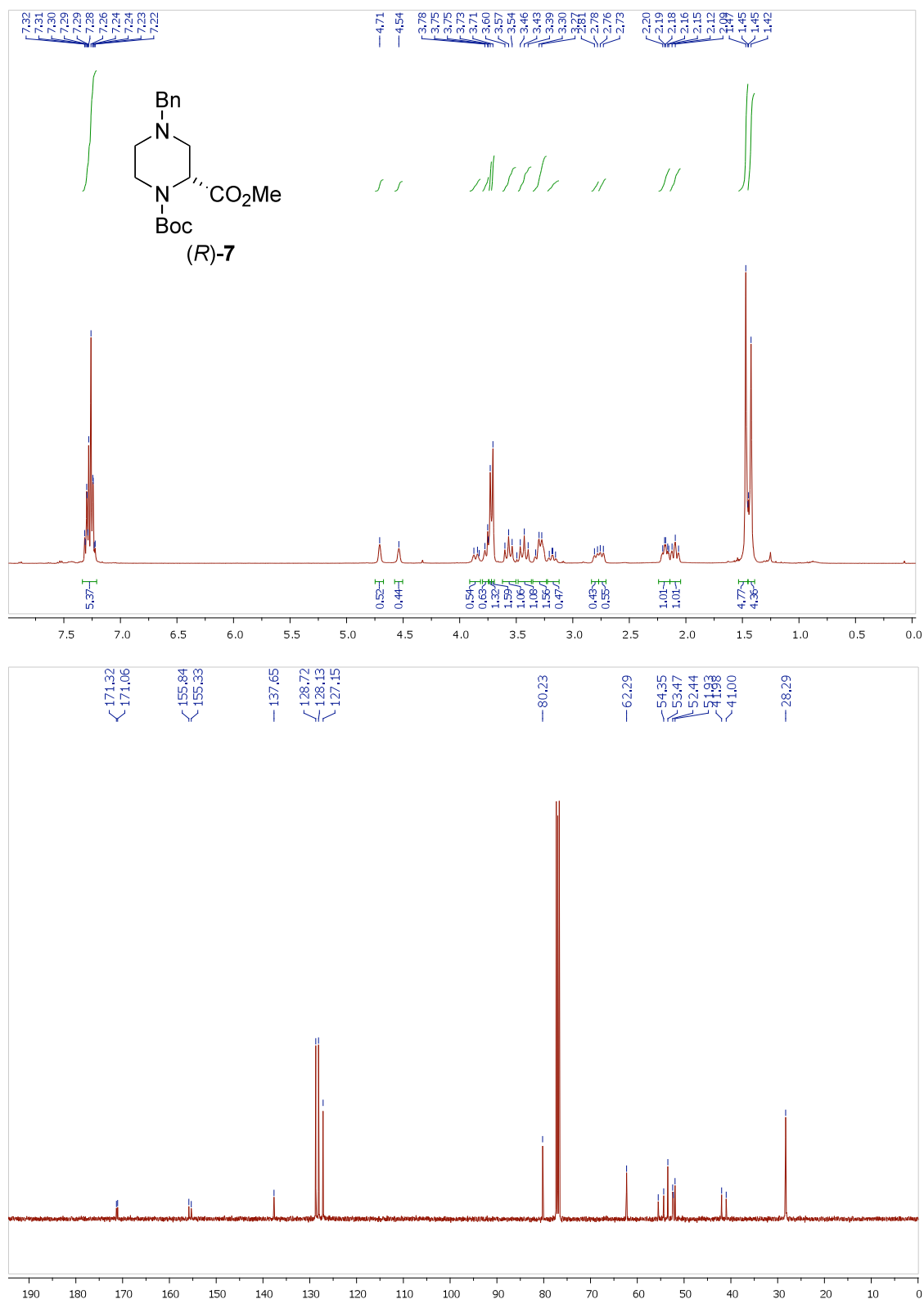
Lab Book Reference: JDF9\_810 and JDF9\_812

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

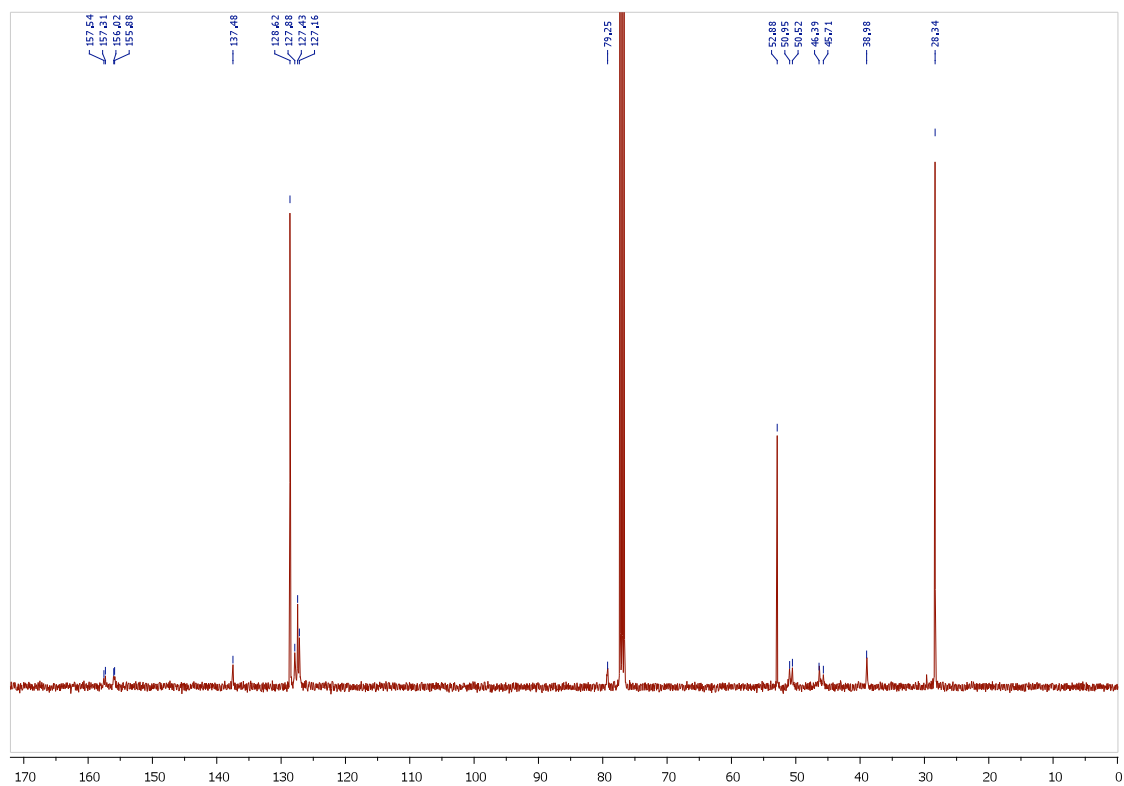
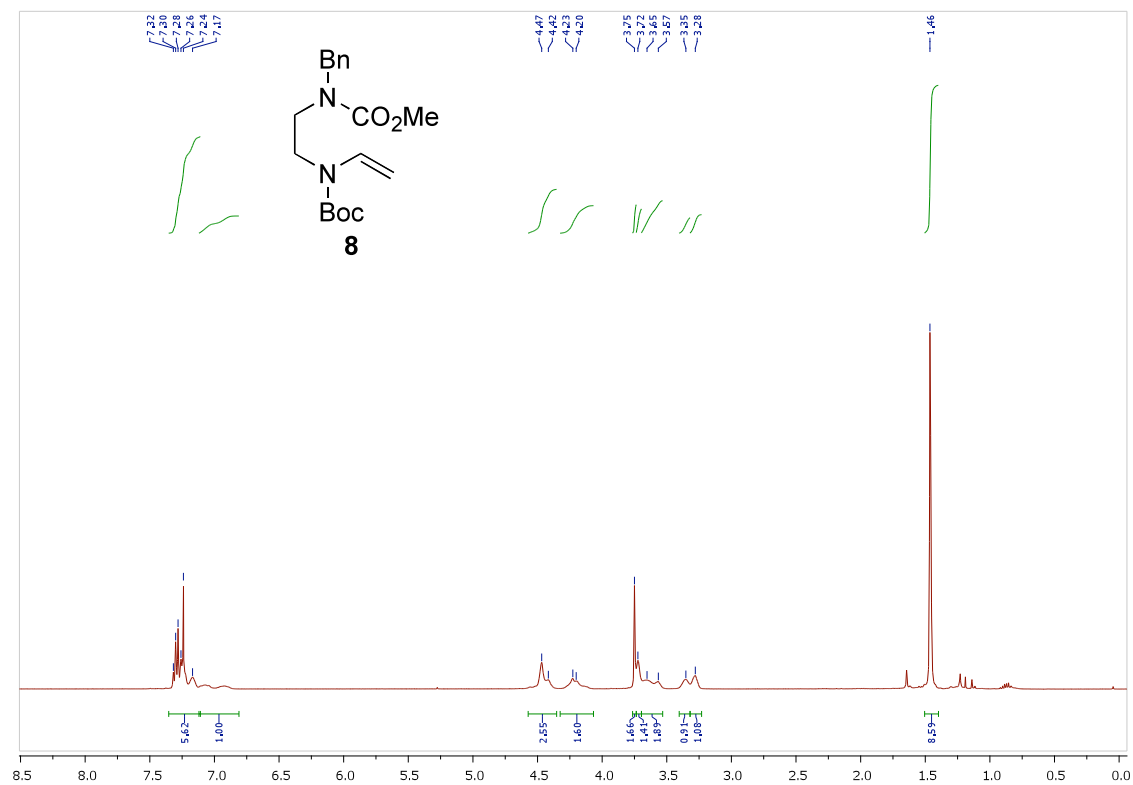


(Scheme 12)

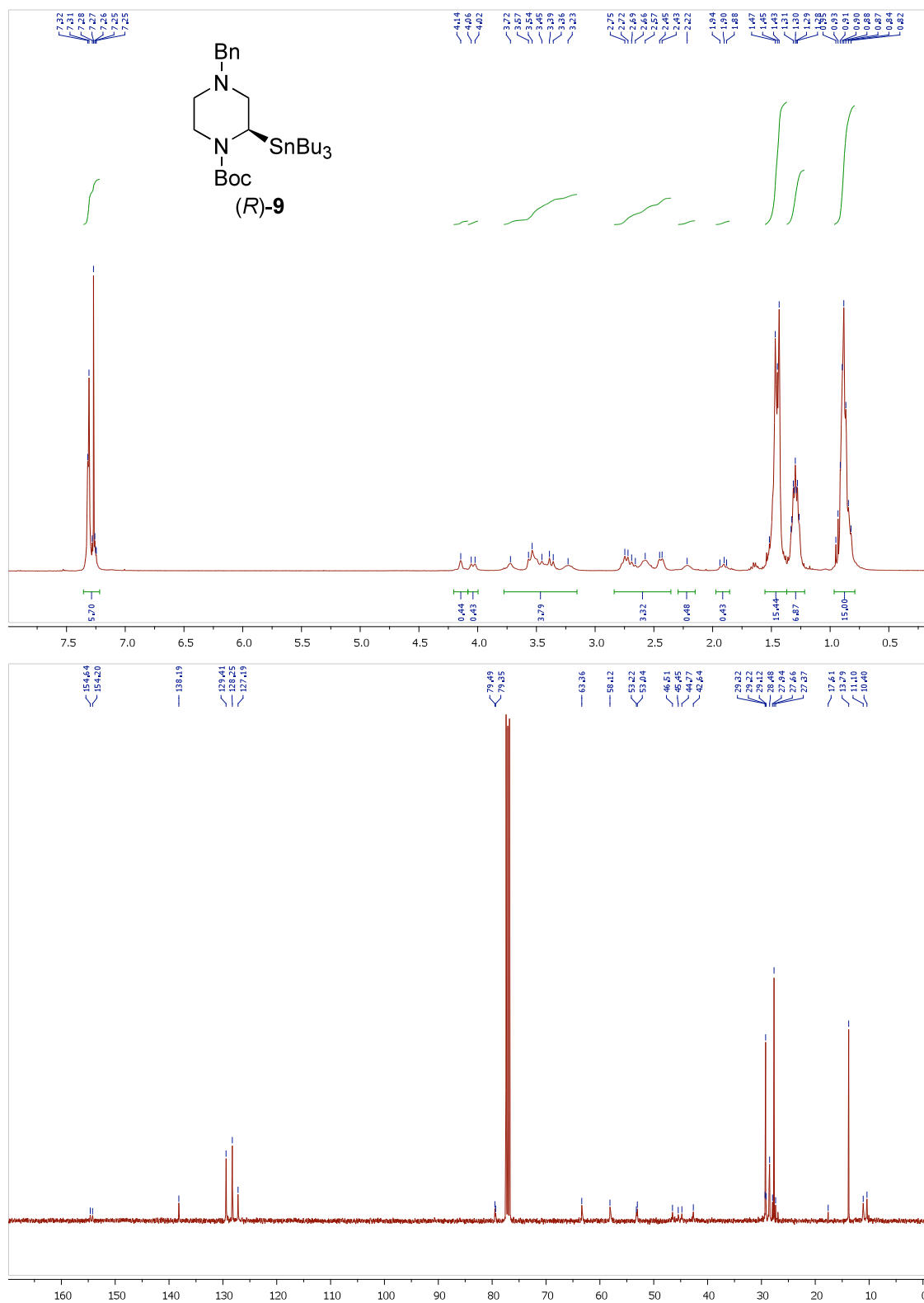
Using general procedure B, *s*-BuLi (0.14 mL of a 1.3 M solution in hexanes, 0.18 mmol, 1.3 eq.), *N*-Boc piperazine (*R*)-**53** (30 mg, 0.14 mmol, 1.0 eq.), TMEDA (21 mg, 27  $\mu$ L, 0.18 mmol, 1.3 eq.) in Et<sub>2</sub>O (3 mL) for 1 h and a solution of benzophenone (51 mg, 0.28 mmol, 2.0 eq.) in Et<sub>2</sub>O (1 mL), worked up with saturated NaHCO<sub>3(aq)</sub> (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 °C; *R*<sub>F</sub> (EtOAc) 0.2; [ $\alpha$ ]<sub>D</sub> +151.4 (*c* 1.2 in CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2972, 2885, 2813, 1724 (C=O), 1471, 1427, 1322, 1196, 1069, 996, 949, 915, 746 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>CO), 60.8 (NCH), 57.6 (NCH<sub>2</sub>), 56.9 (NCH), 47.8 (NCH<sub>2</sub>), 42.7 (NMe), 16.5 (CHMe); MS (ESI) *m/z* 323 (M + H)<sup>+</sup>; HRMS *m/z* calcd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 323.1754, found 323.1741 (+3.7 ppm error). Lab Book Reference: JDF9\_817

**$^2\text{H}/^{13}\text{C}$  NMR Spectra and CSP-GC/HPLC Data**400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

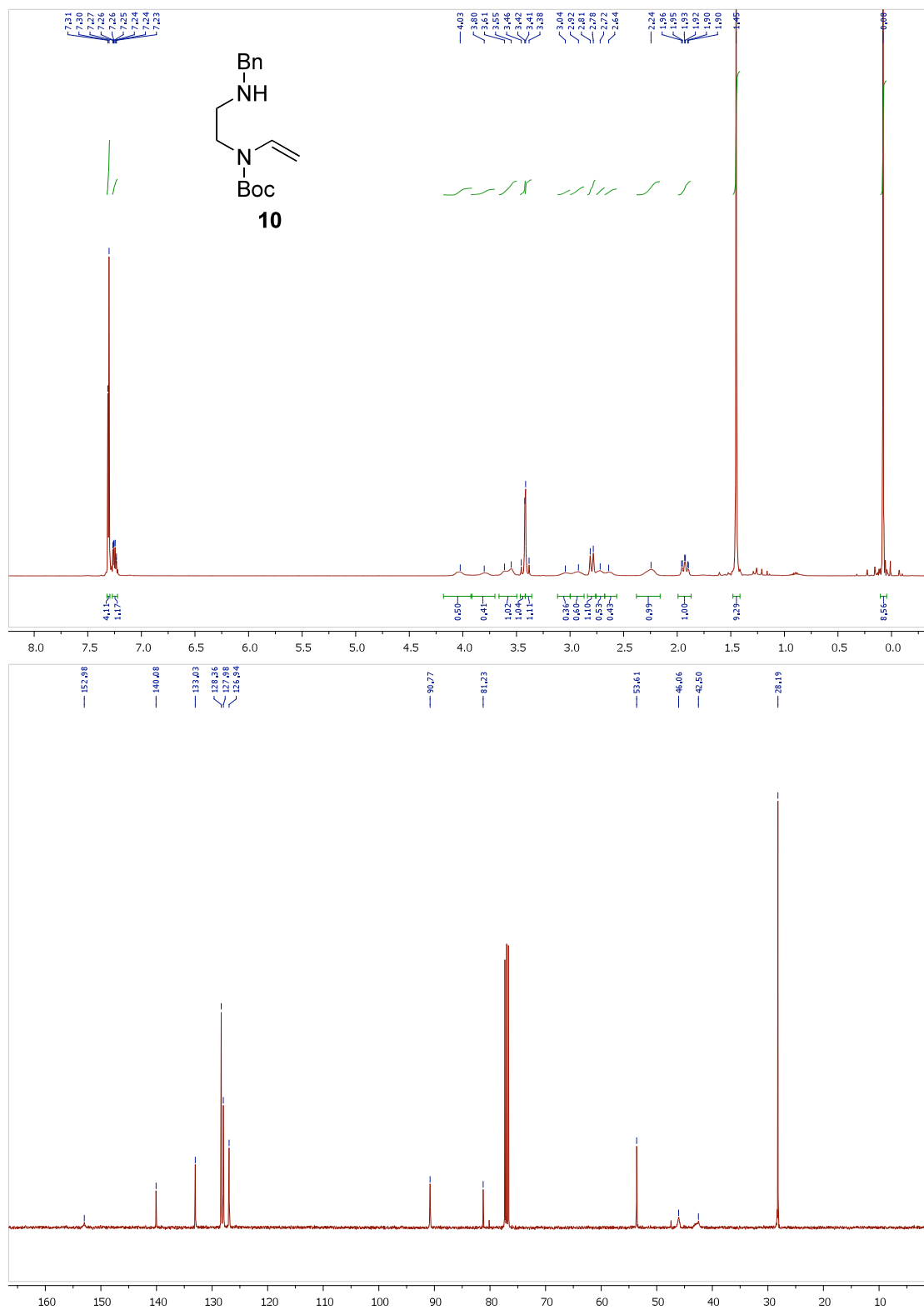
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$

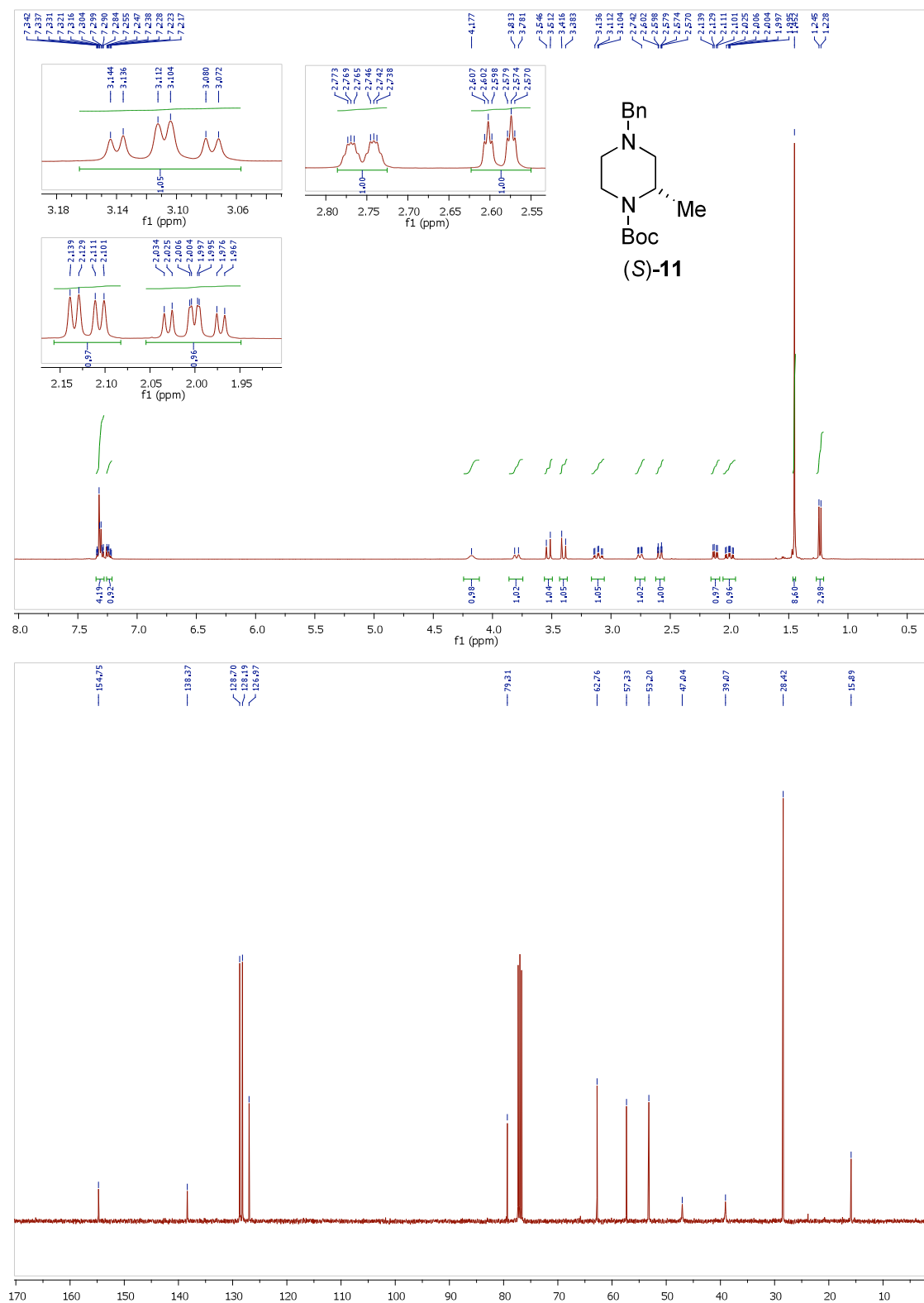


400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$

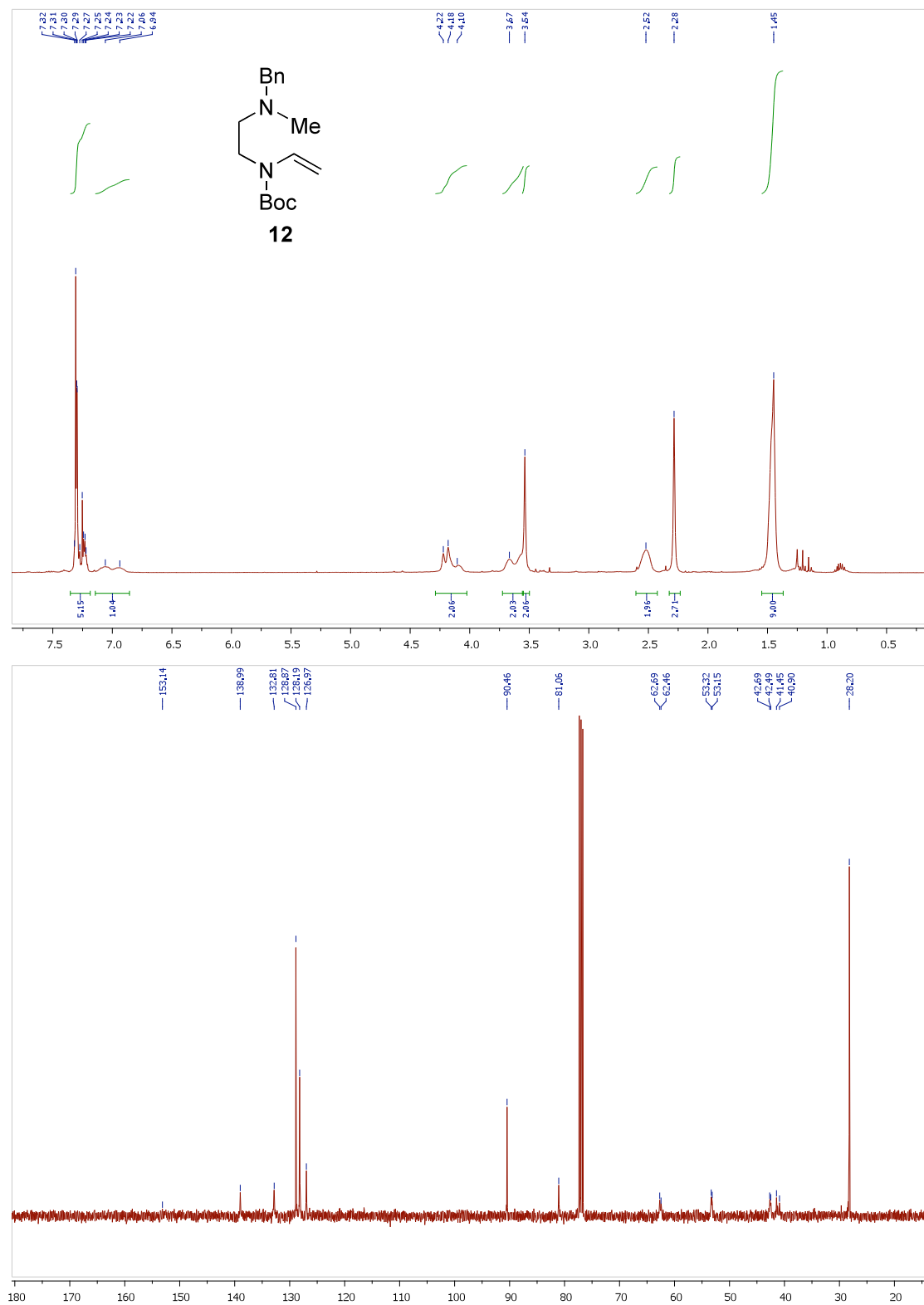


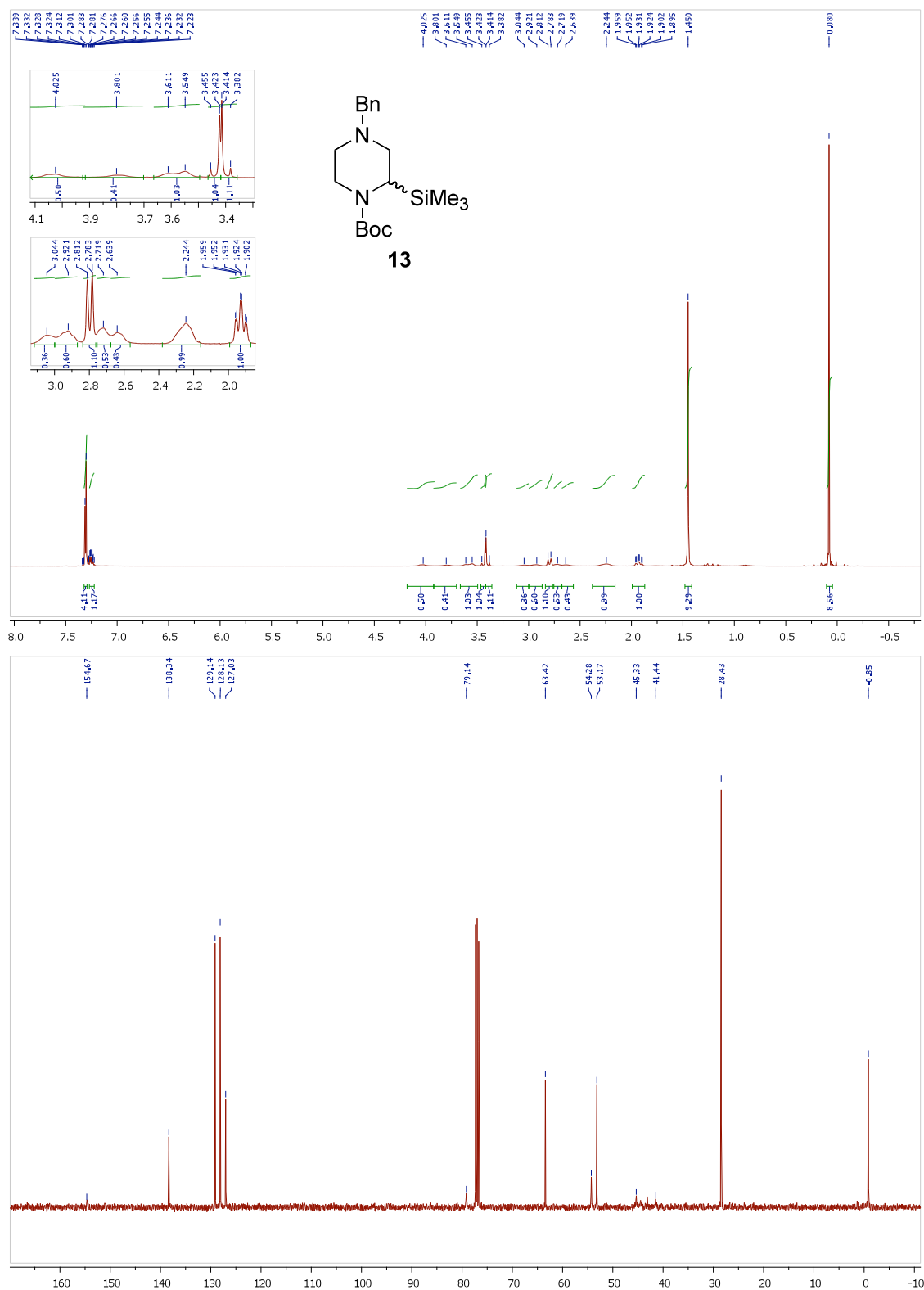
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

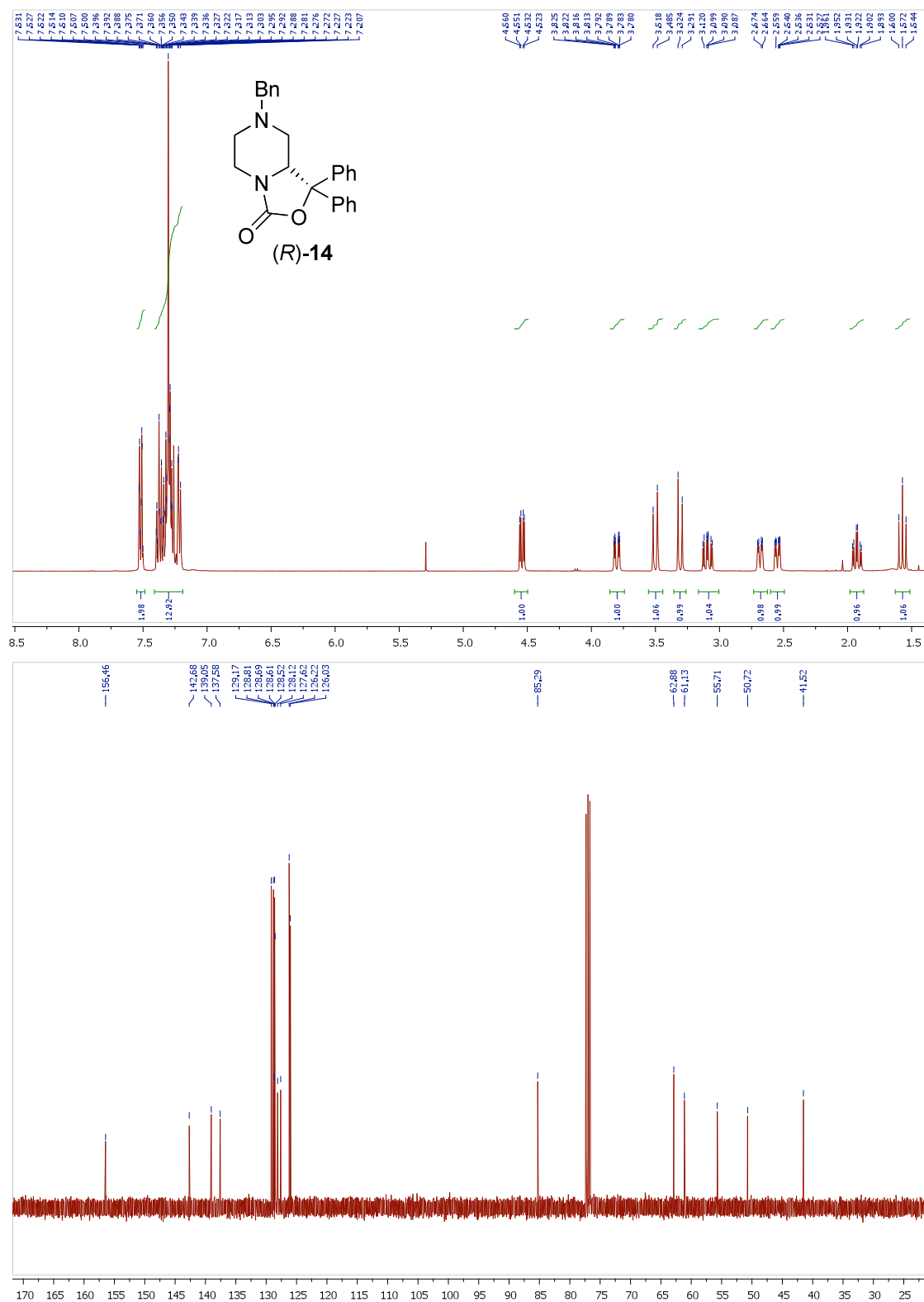
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



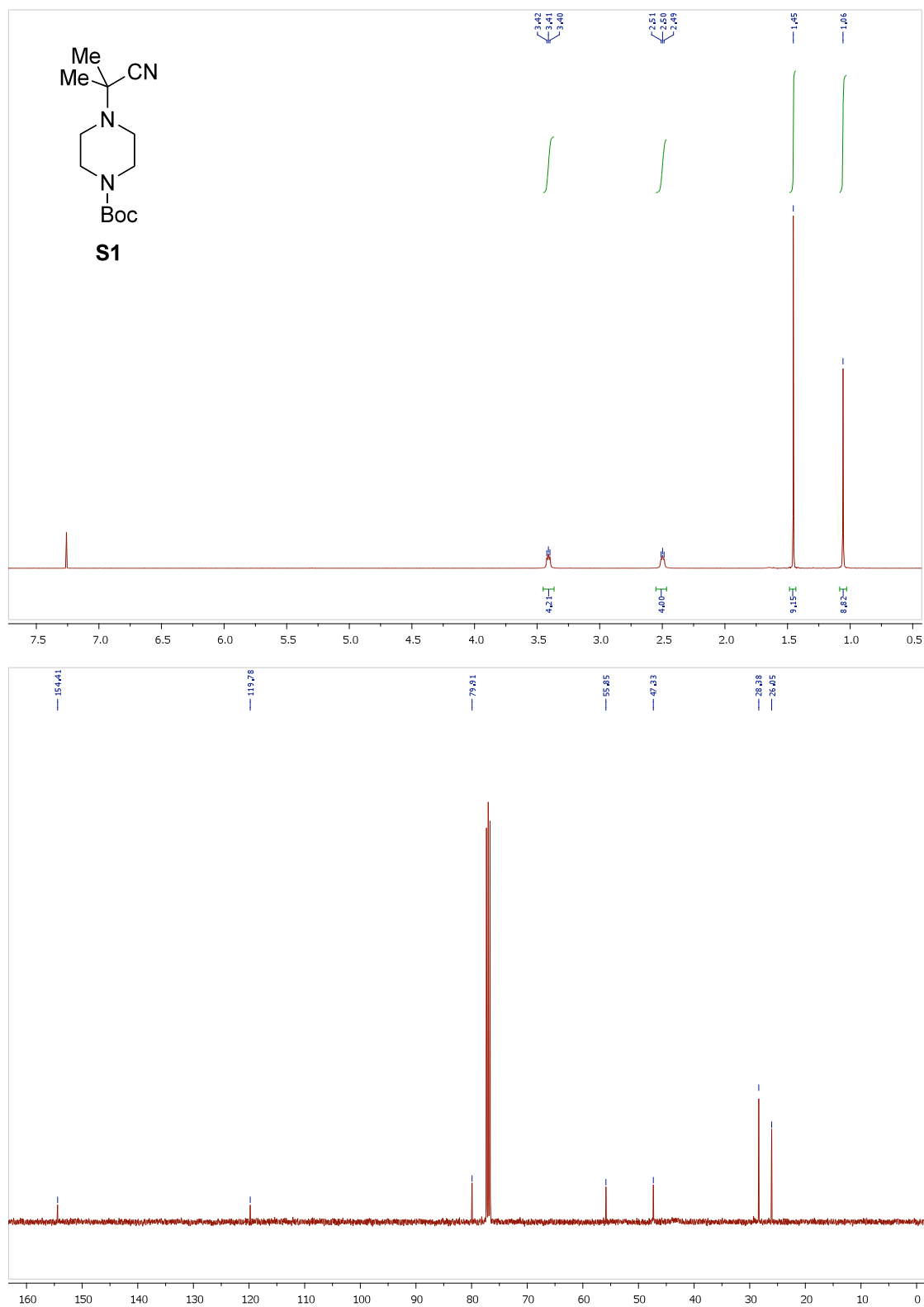
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 



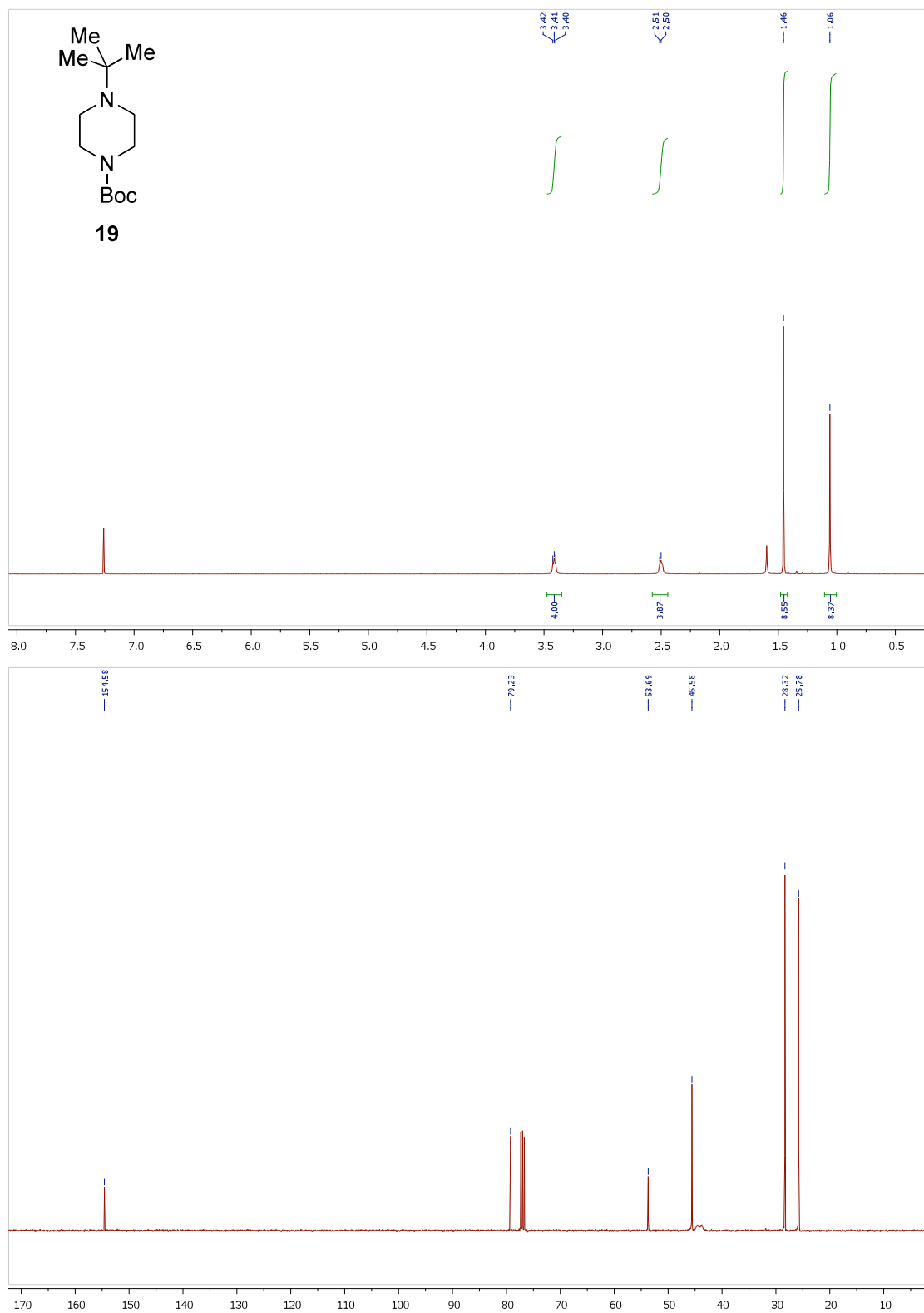
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



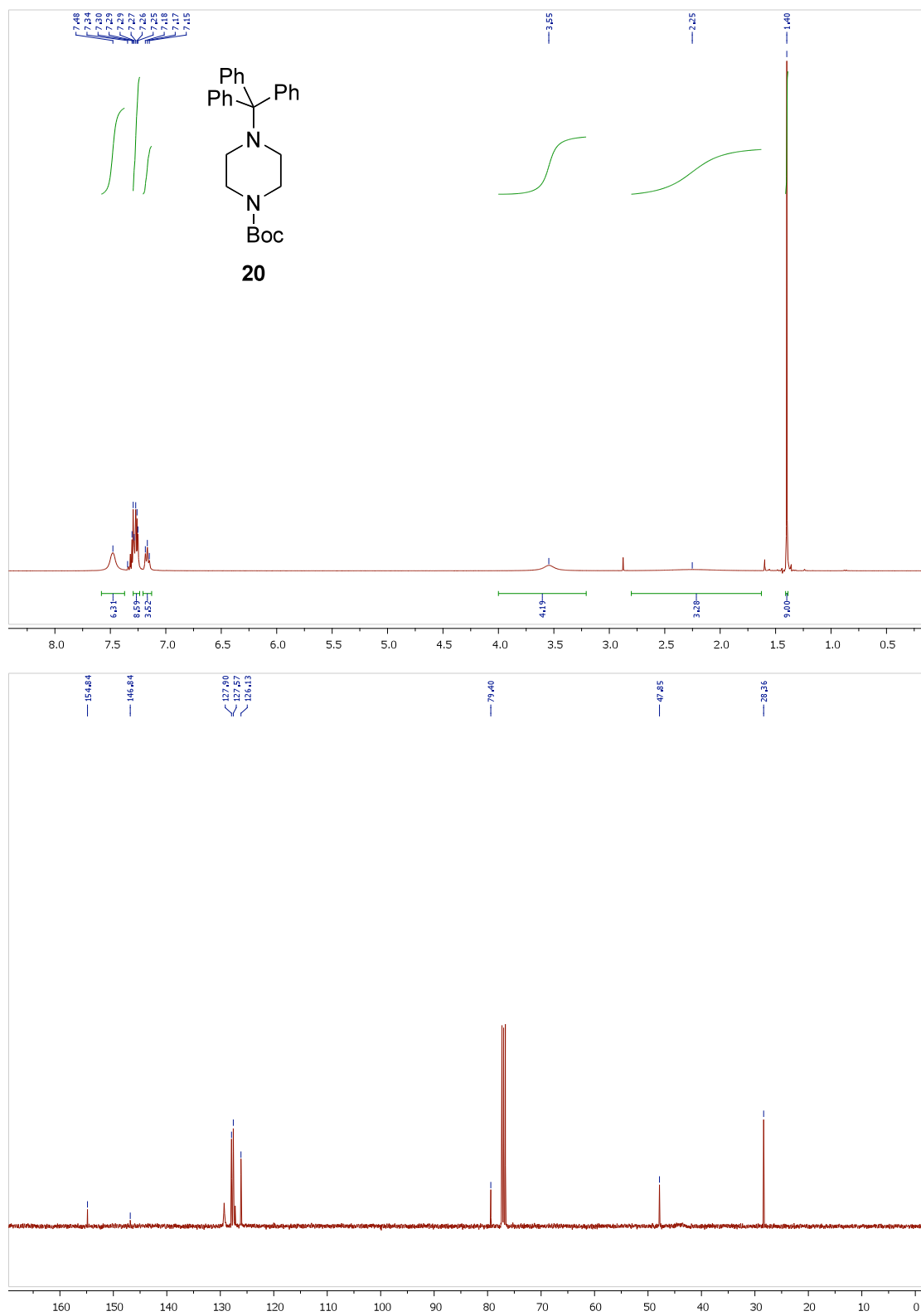
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



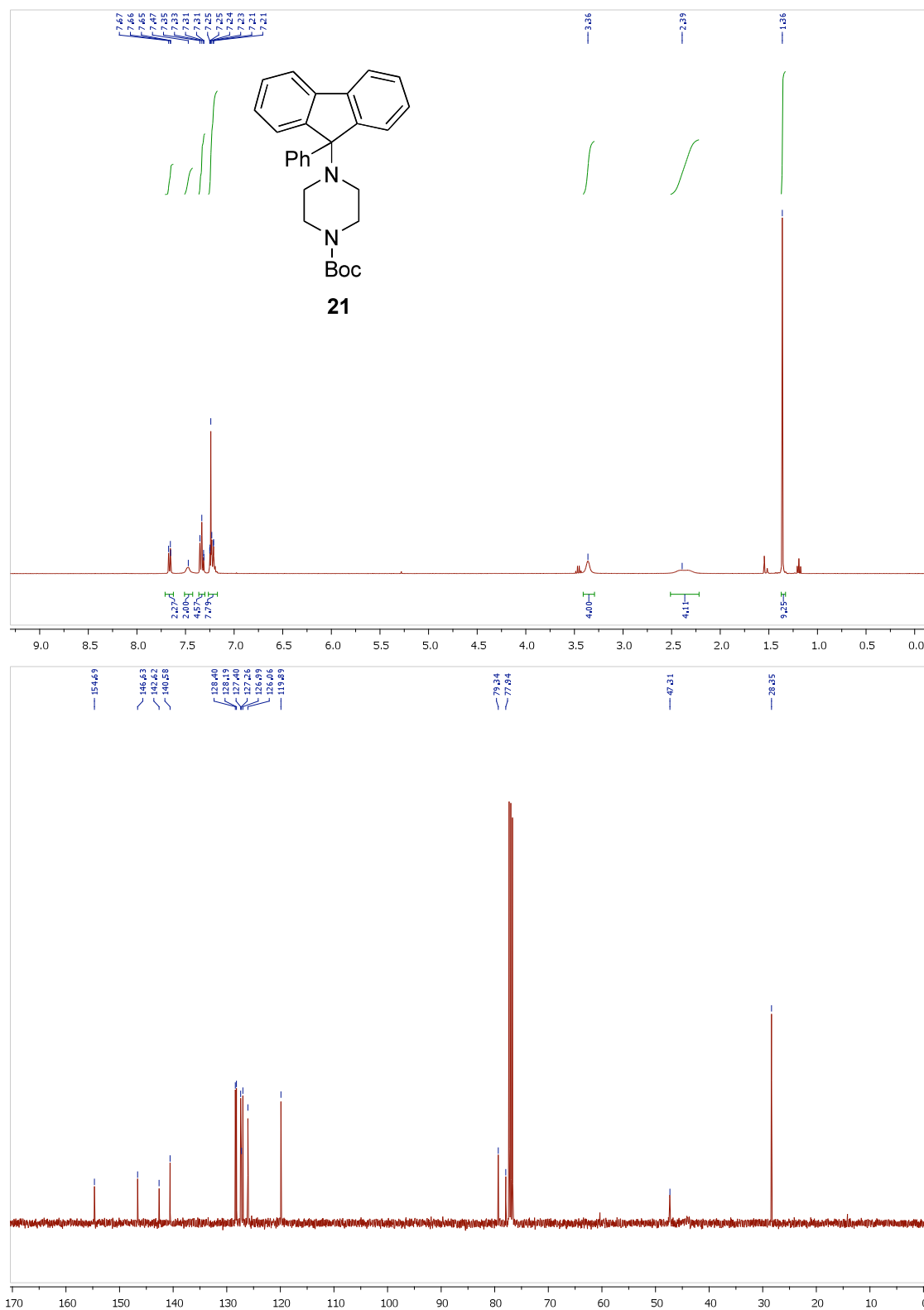
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



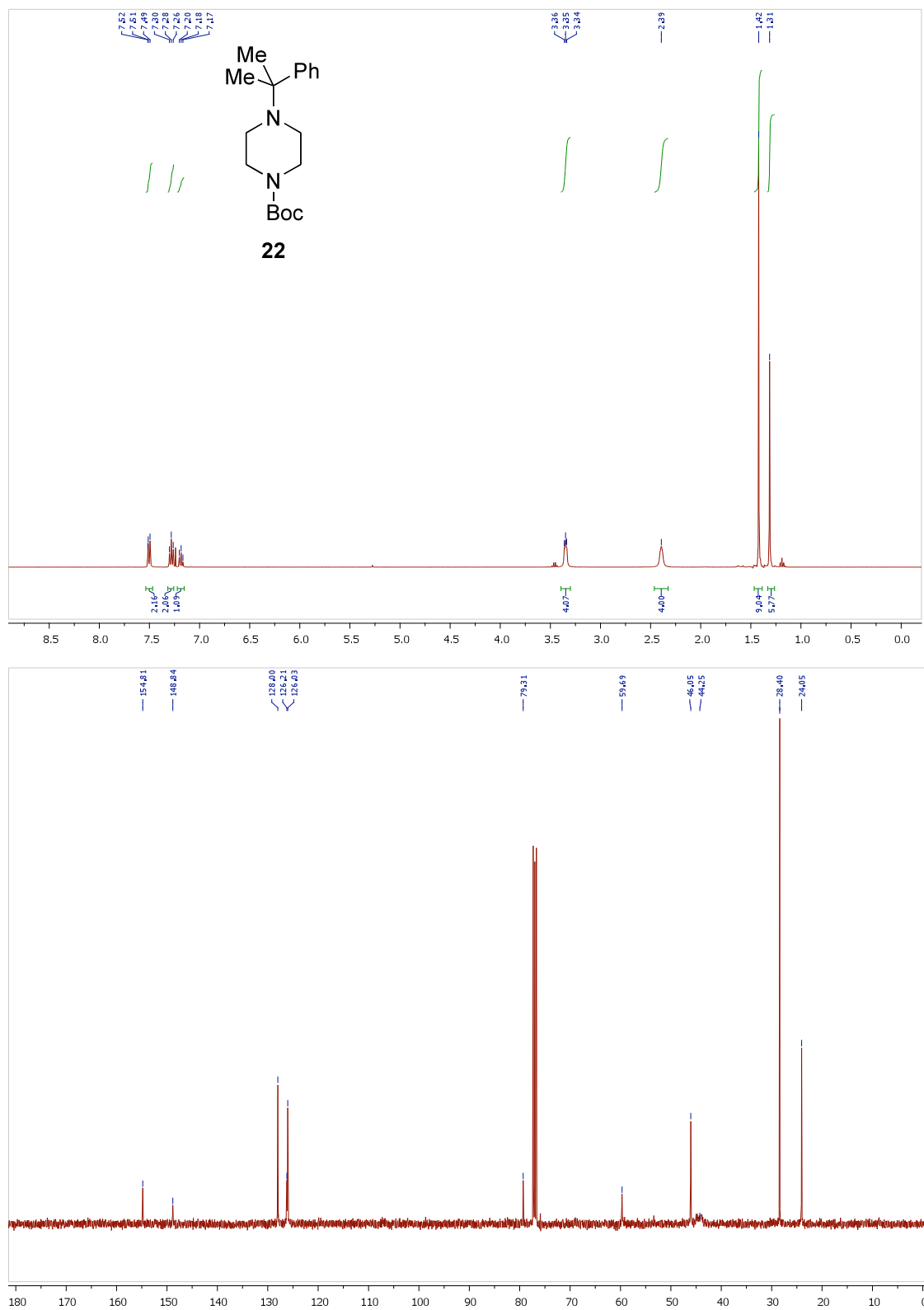
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



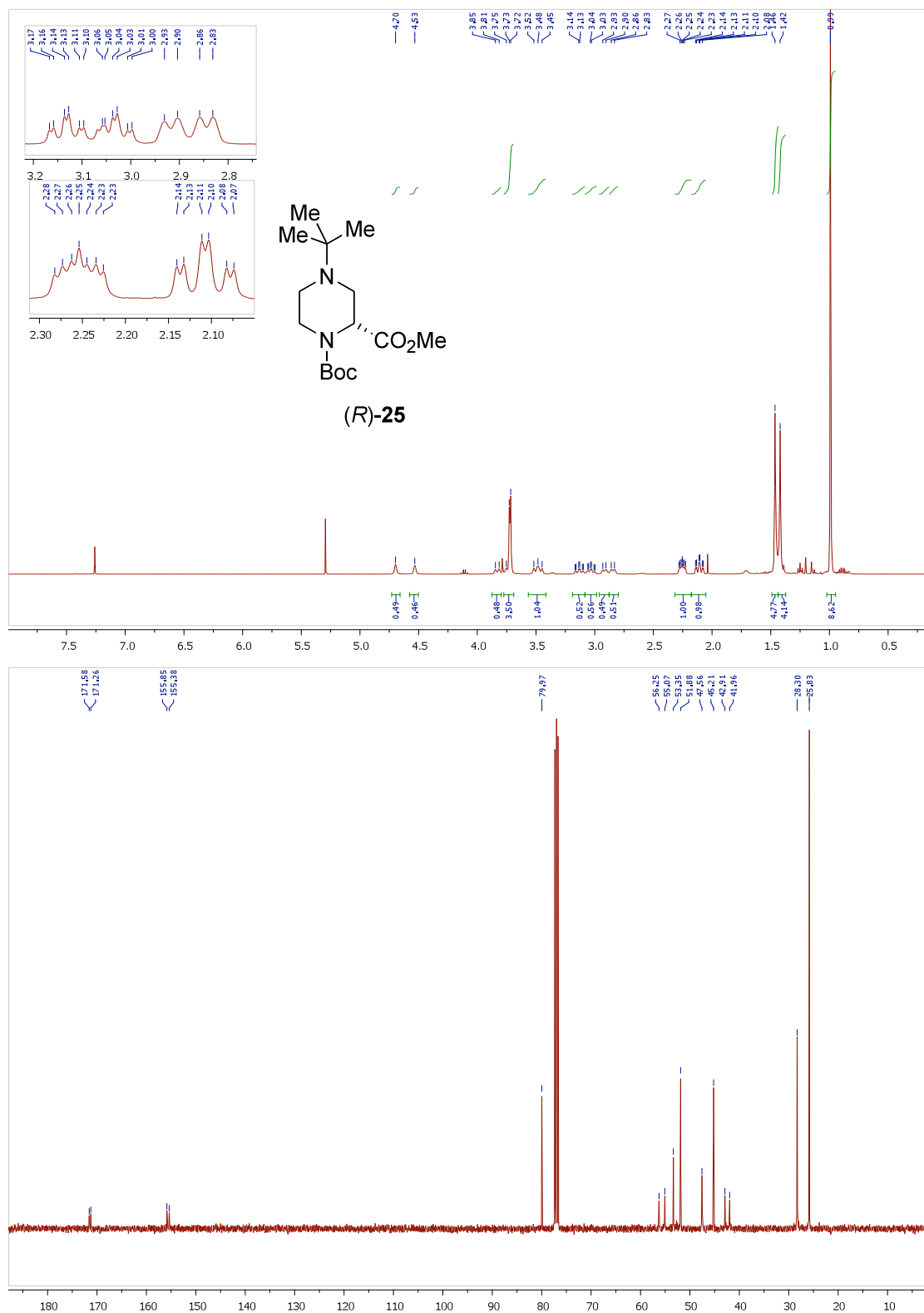
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$

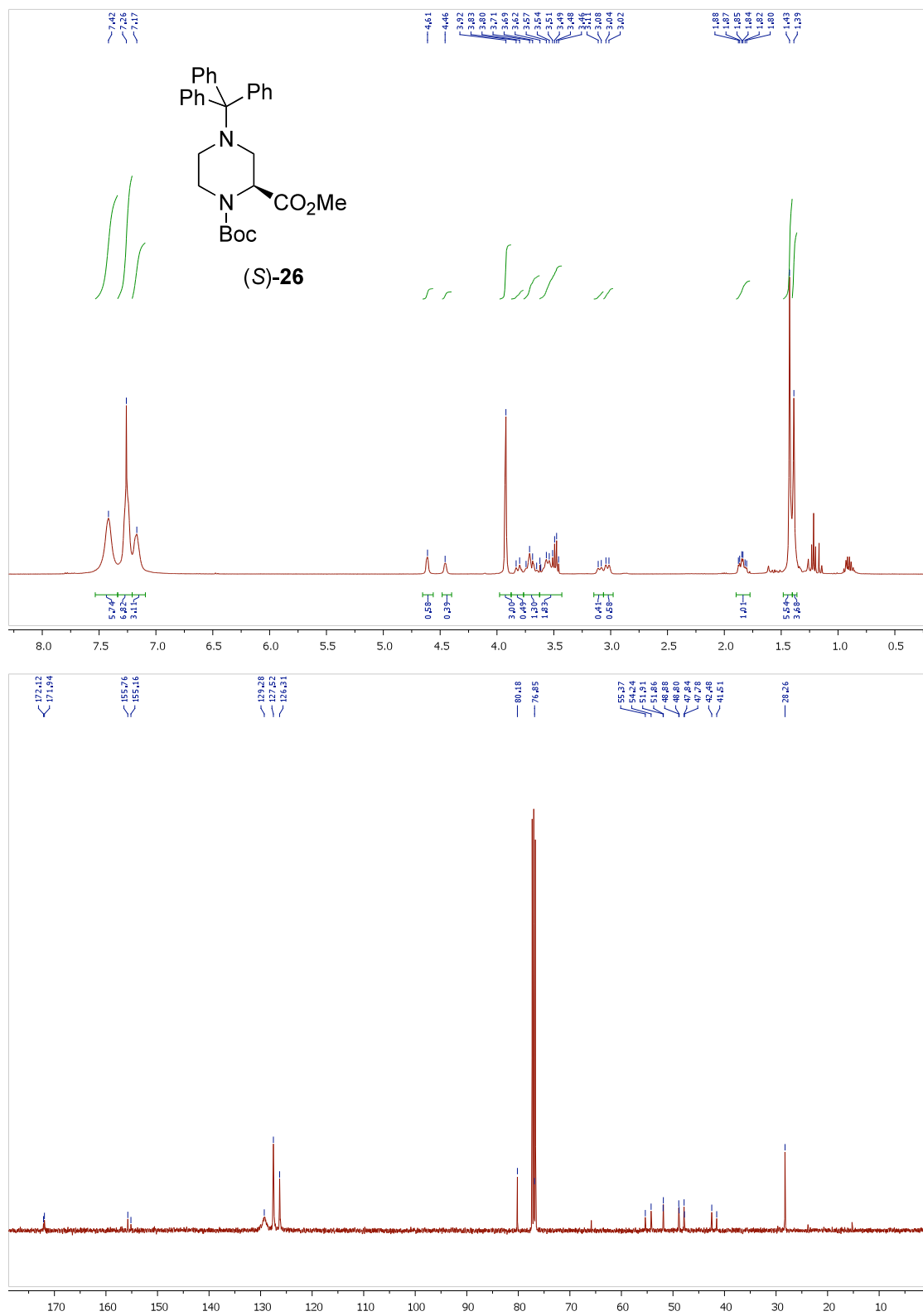


400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



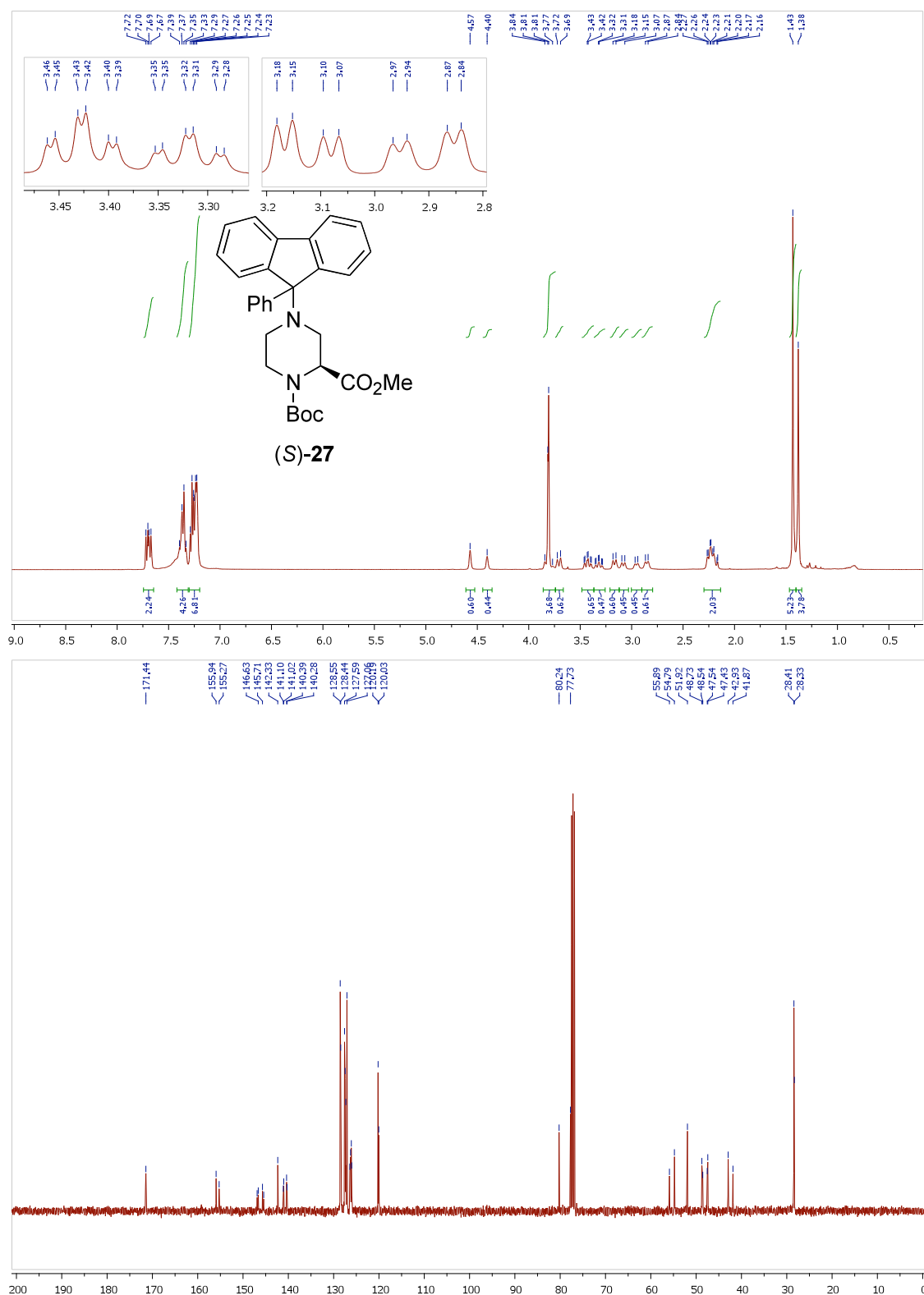
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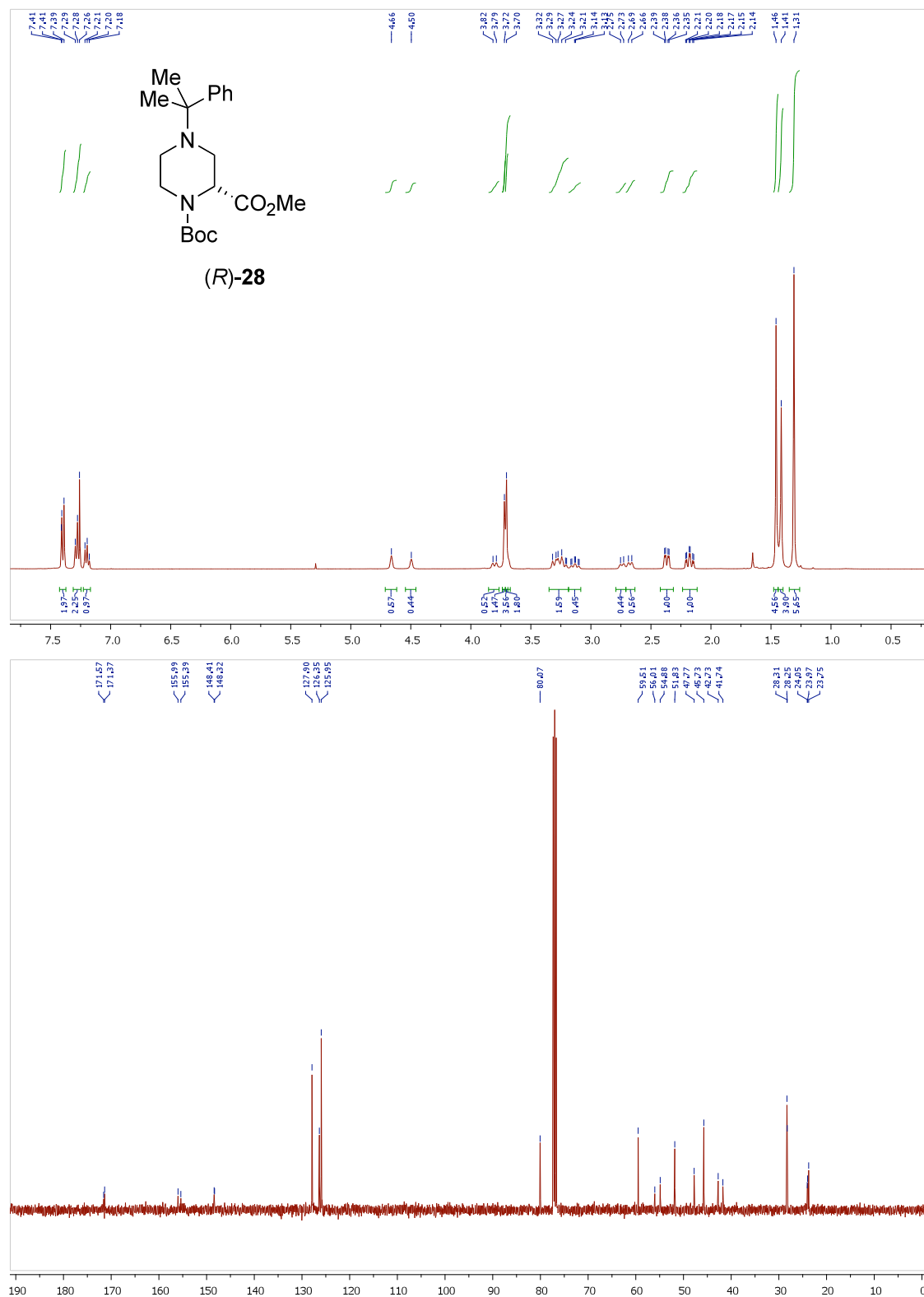


400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

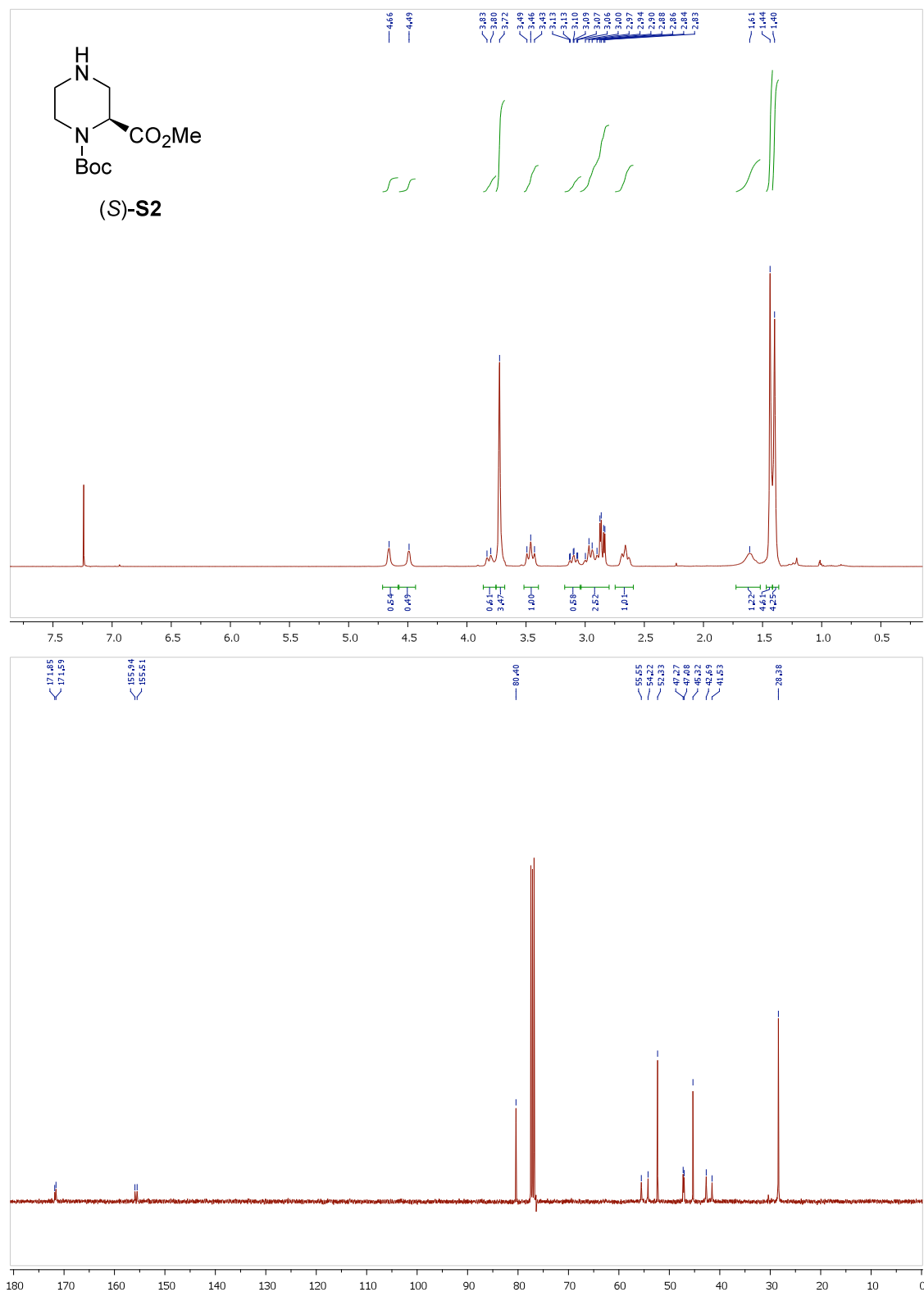


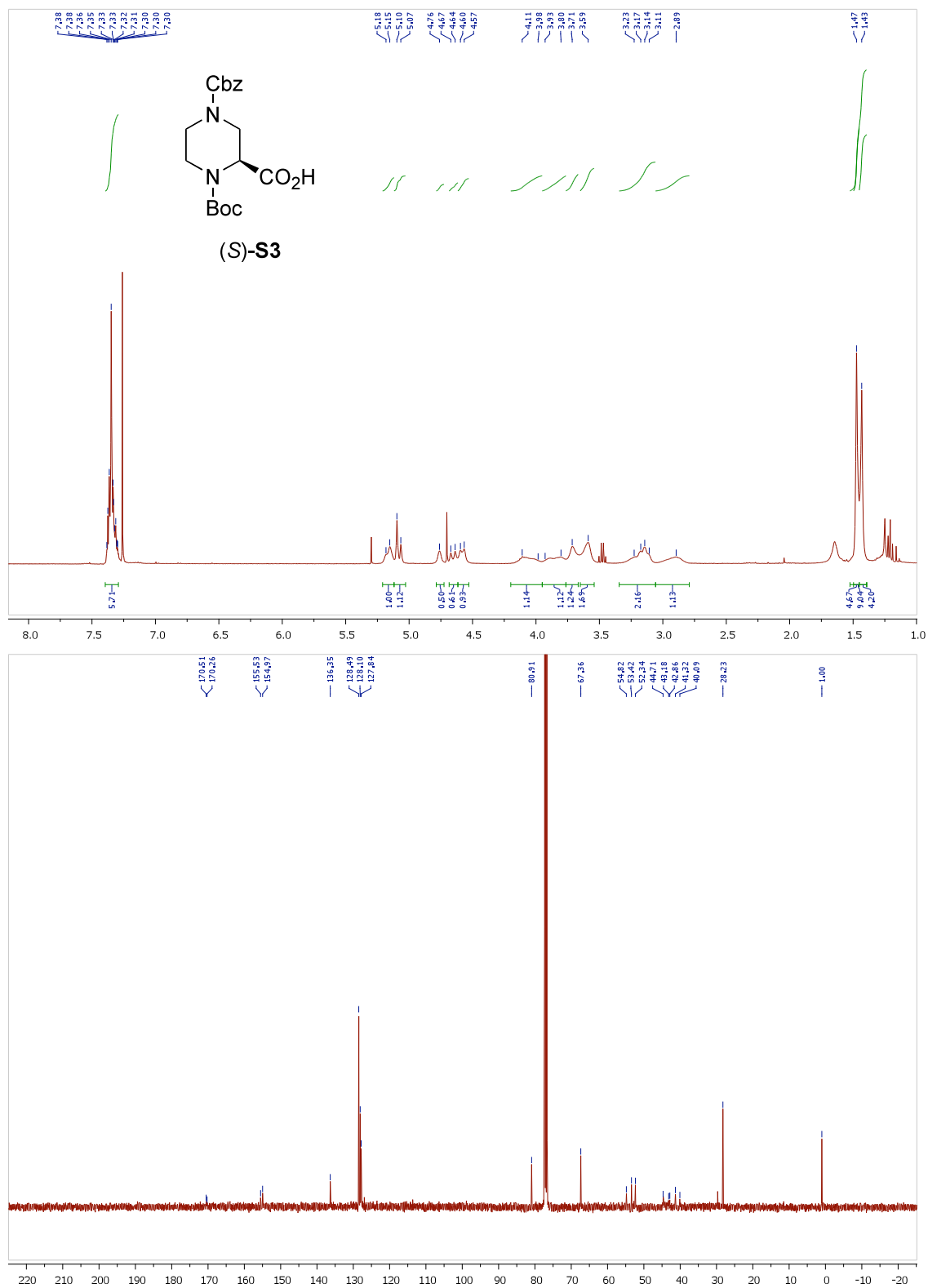
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



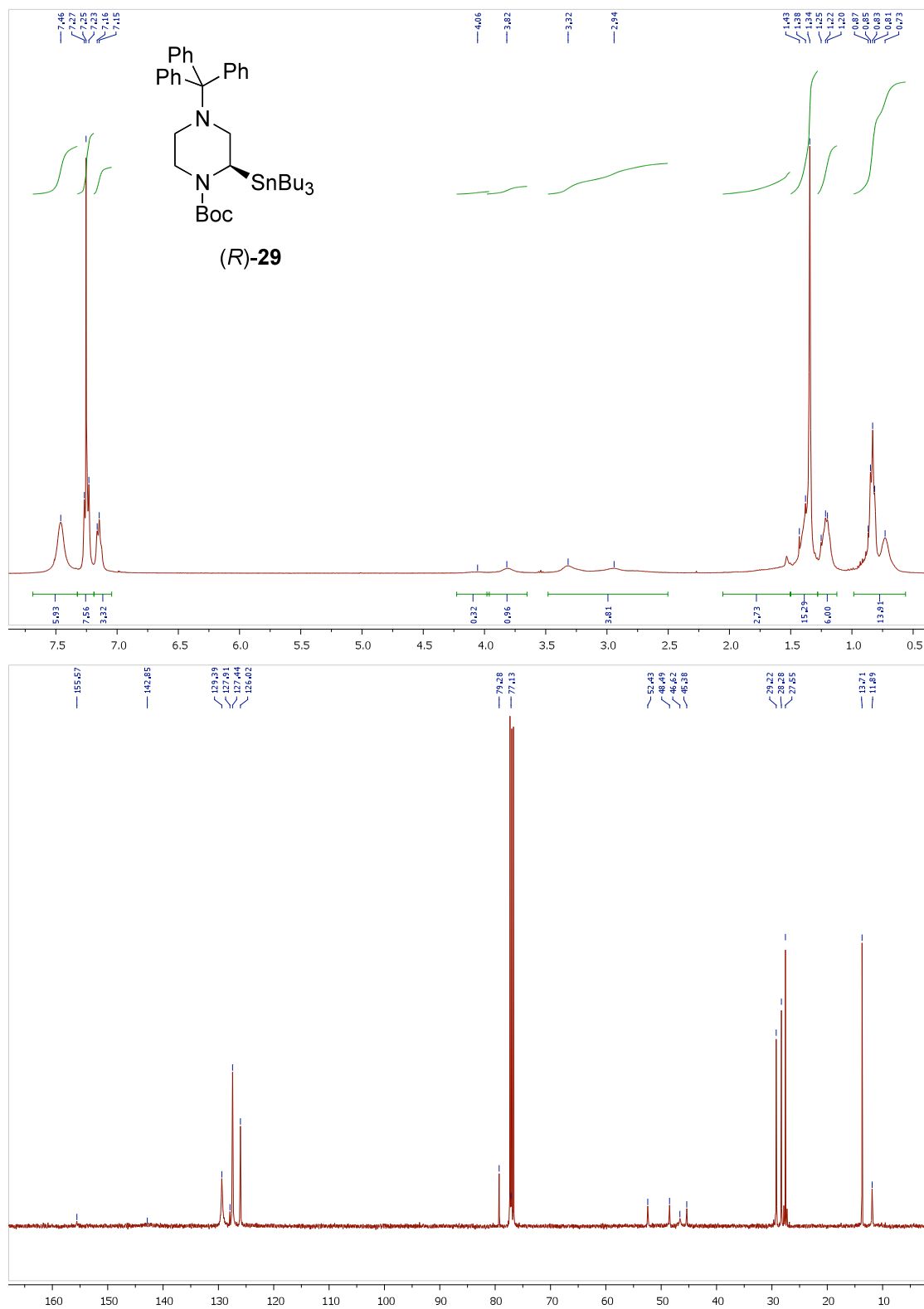
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

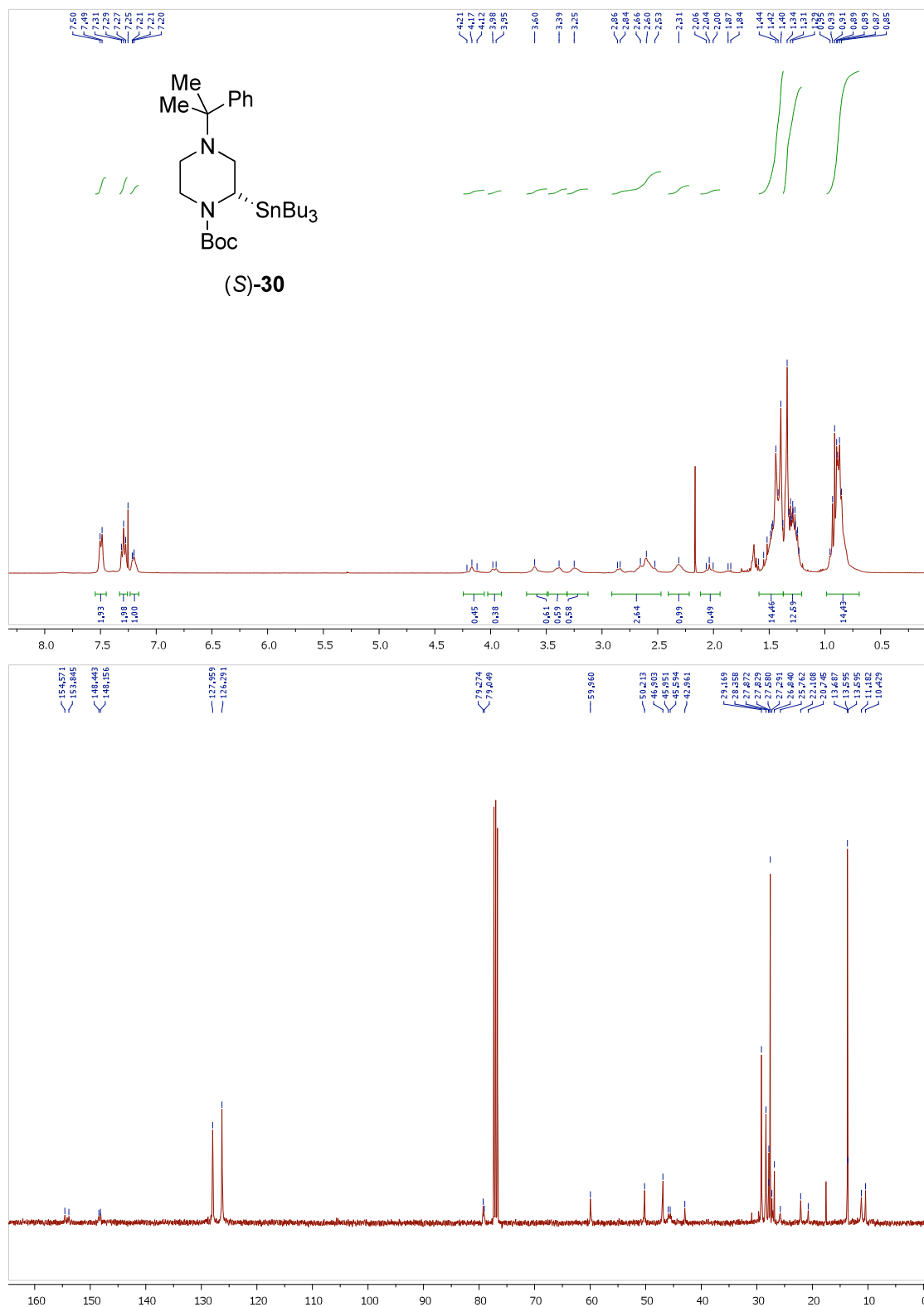
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$

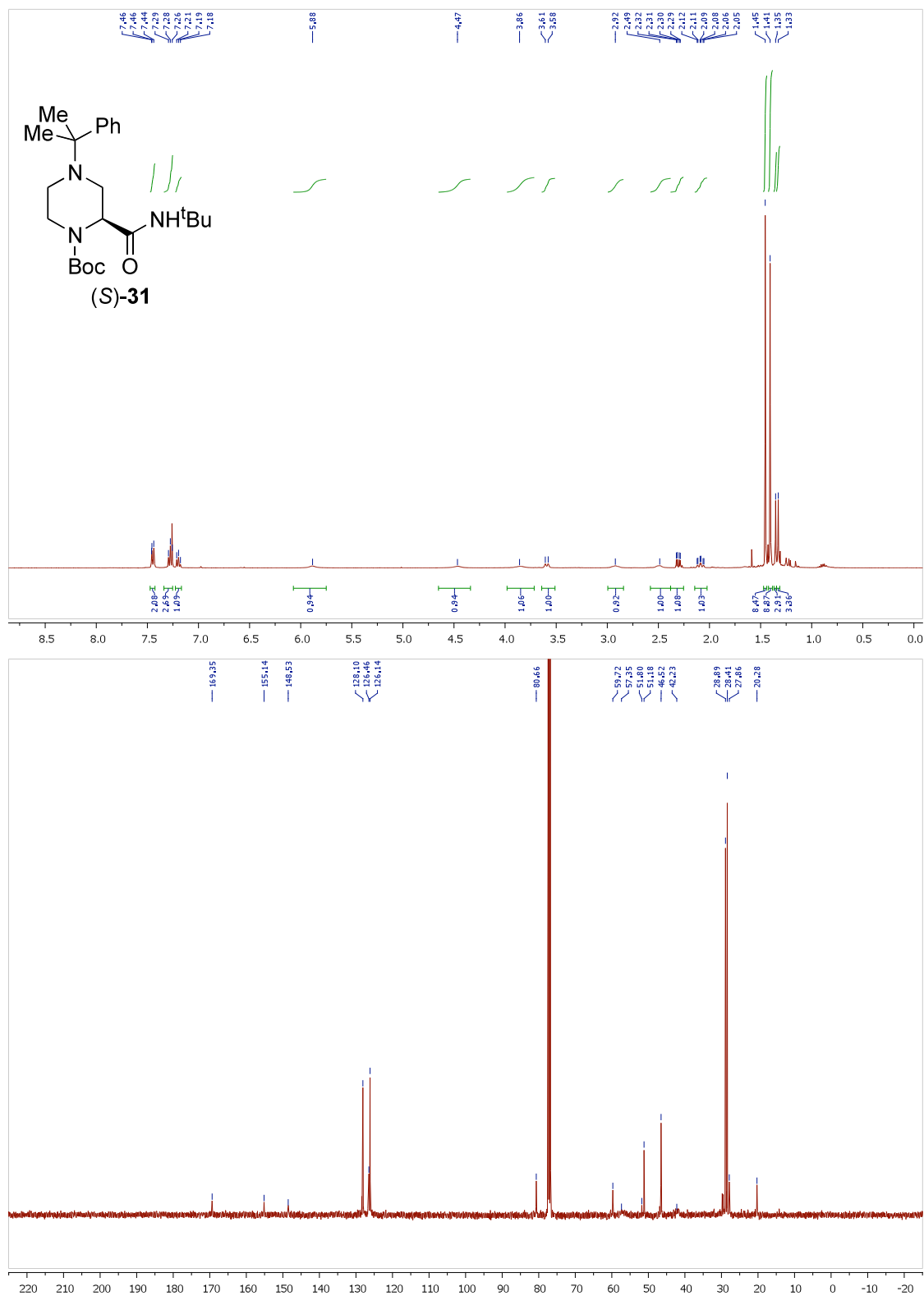


400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

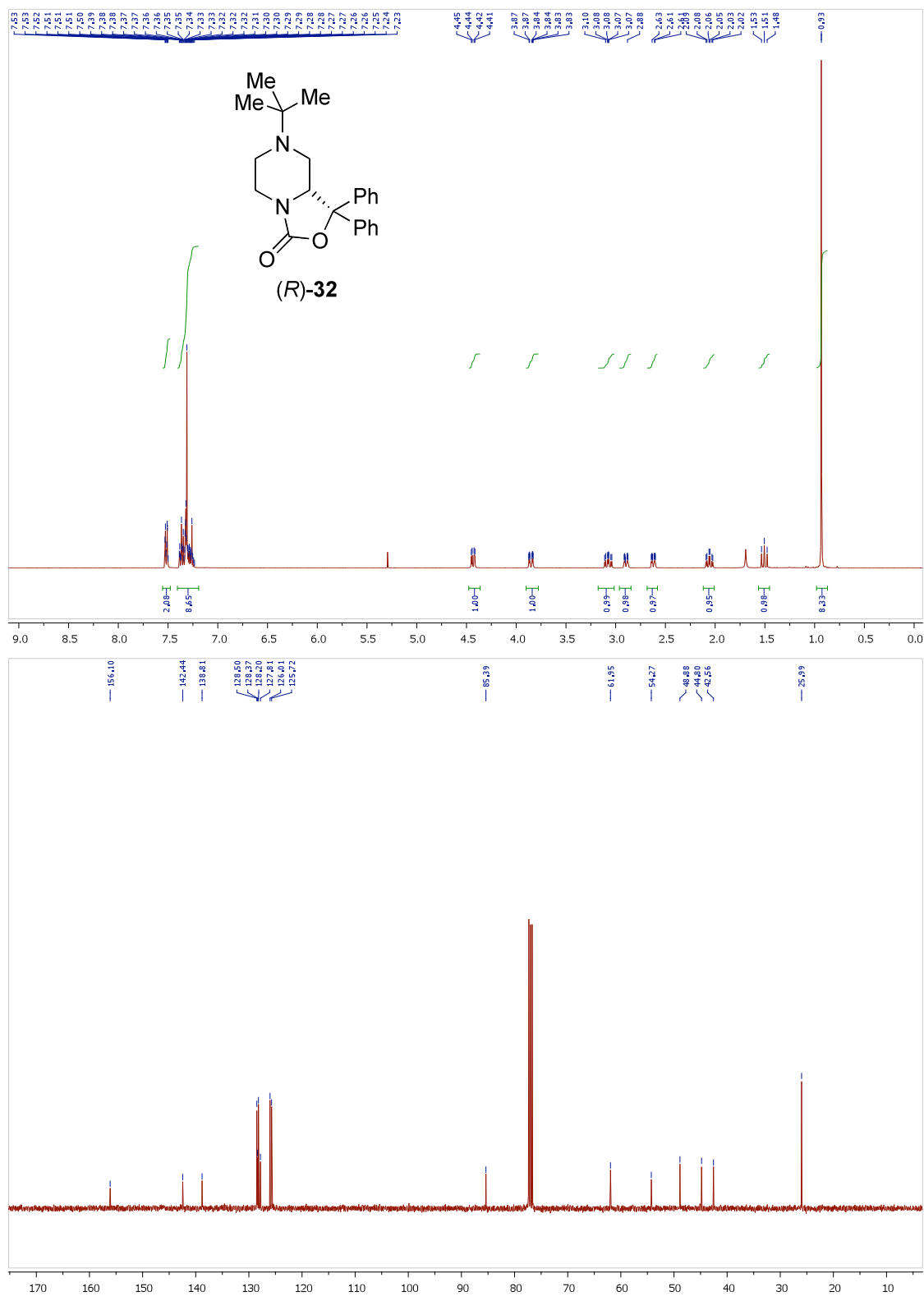
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

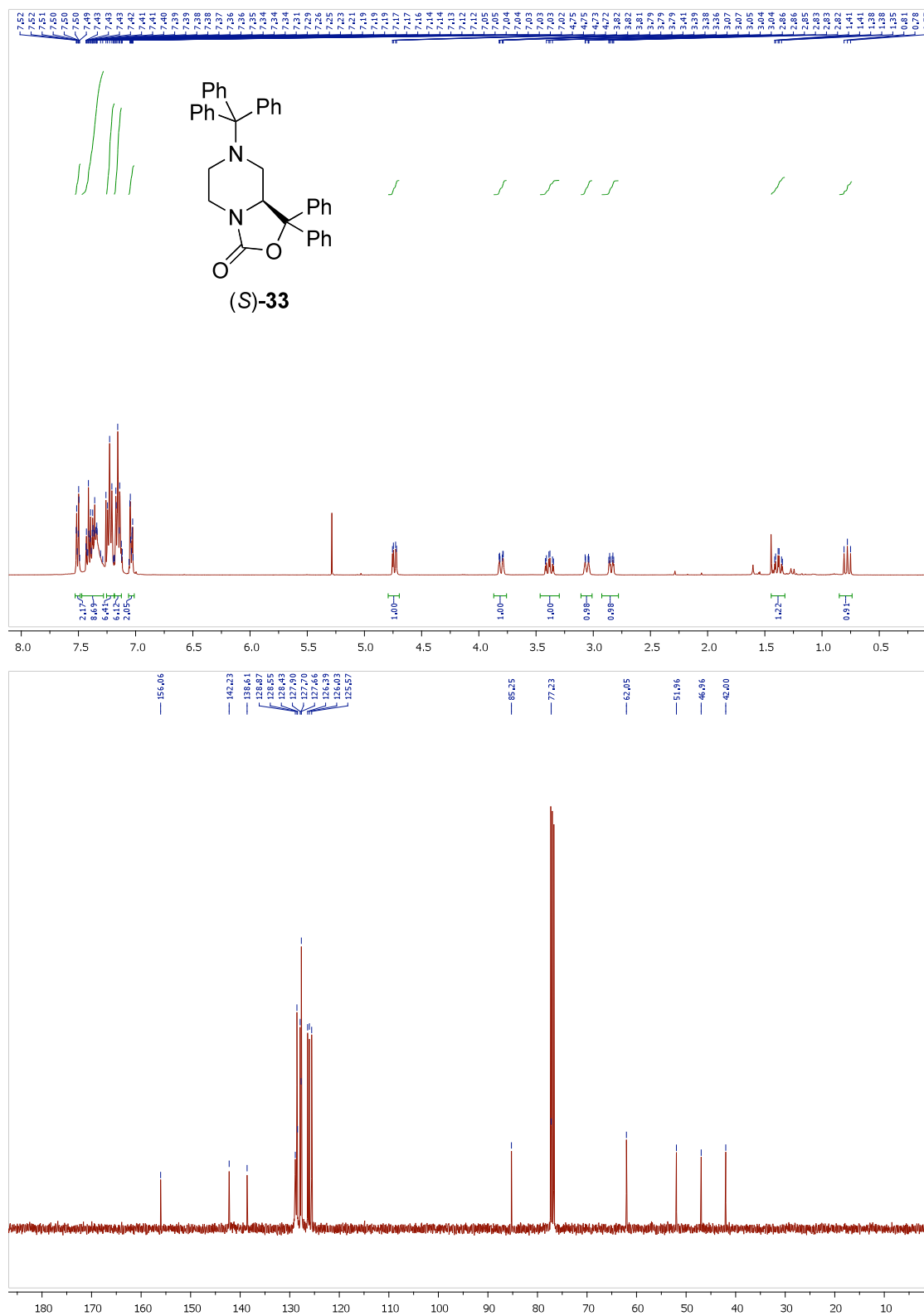
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$

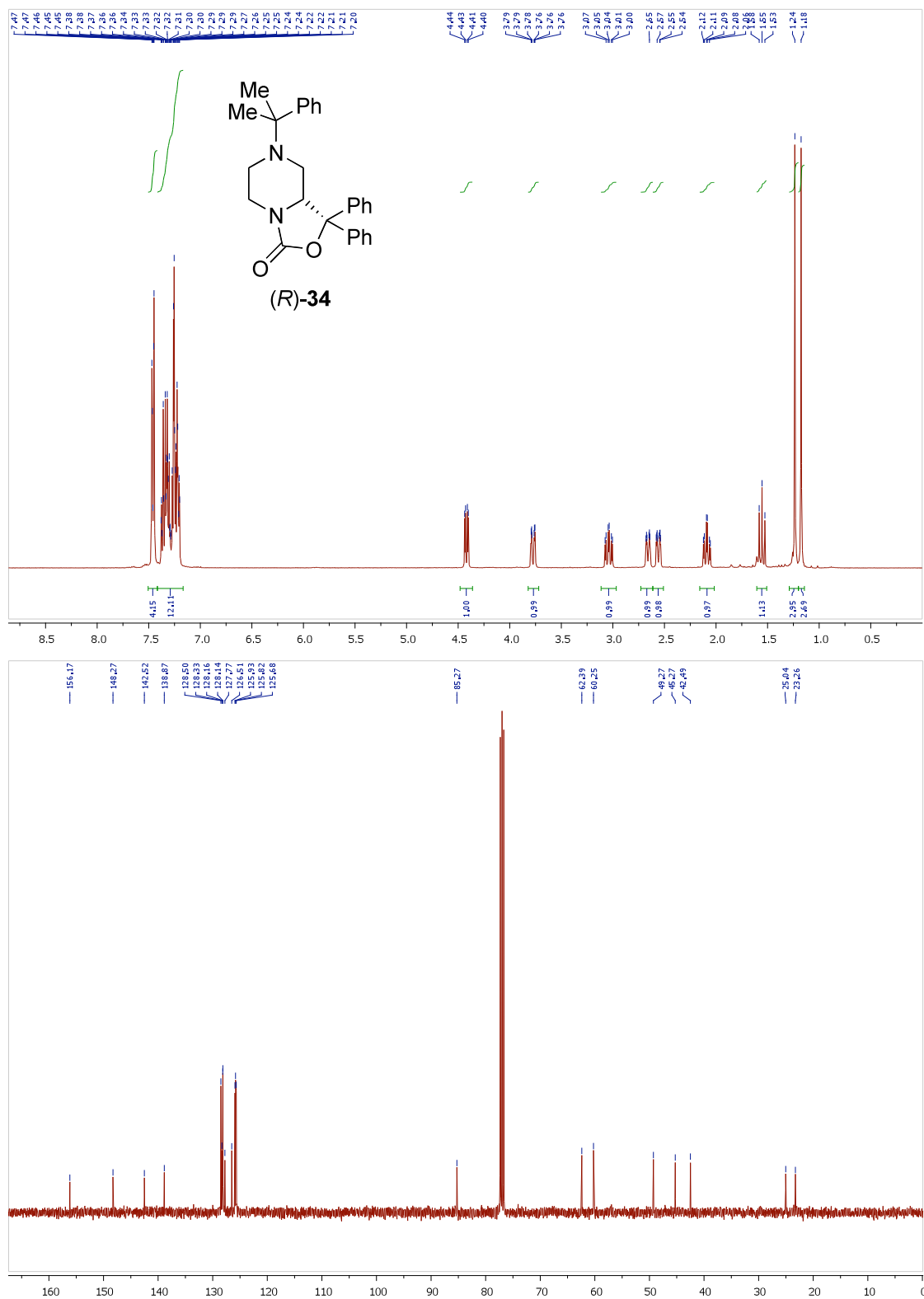




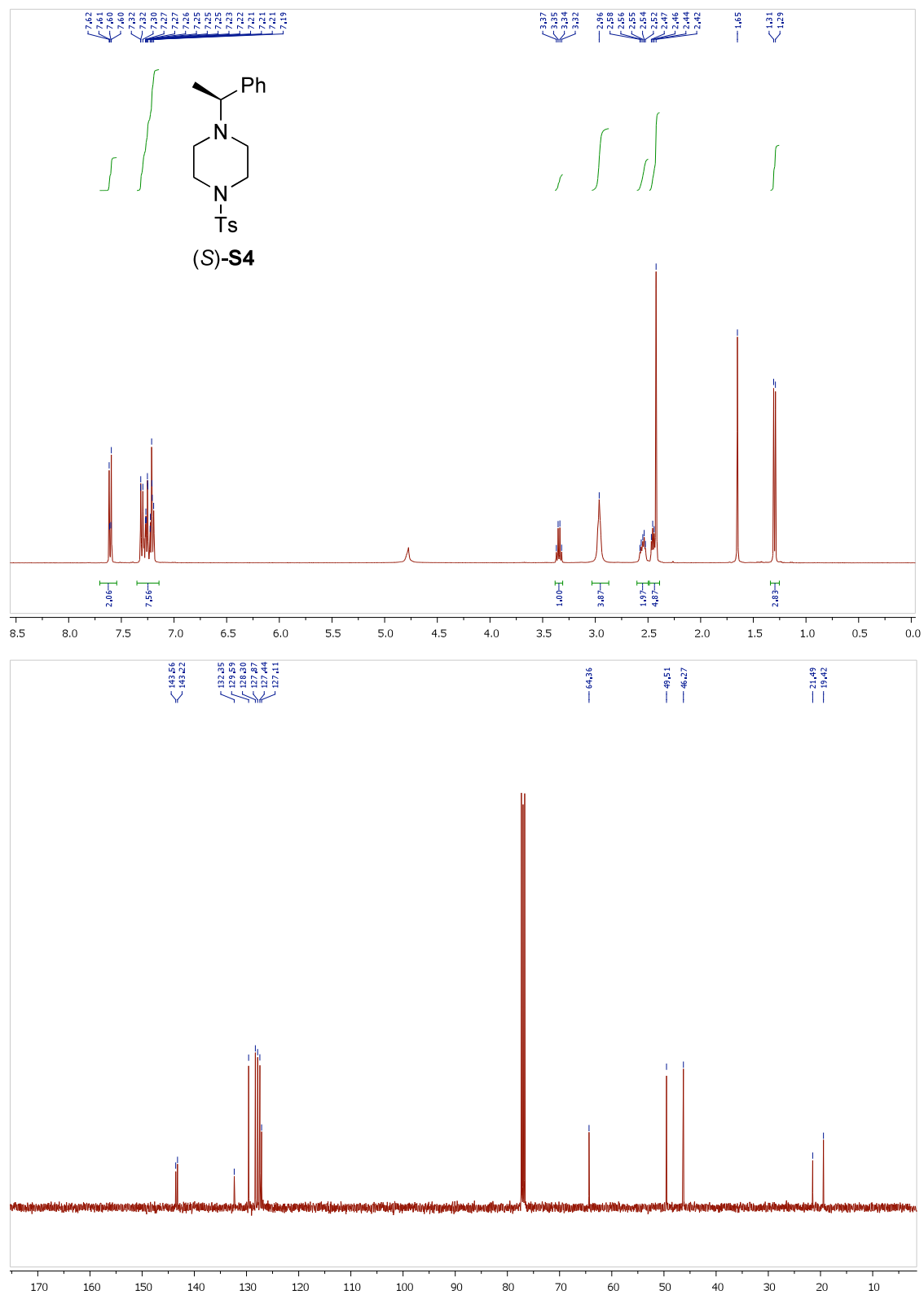
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



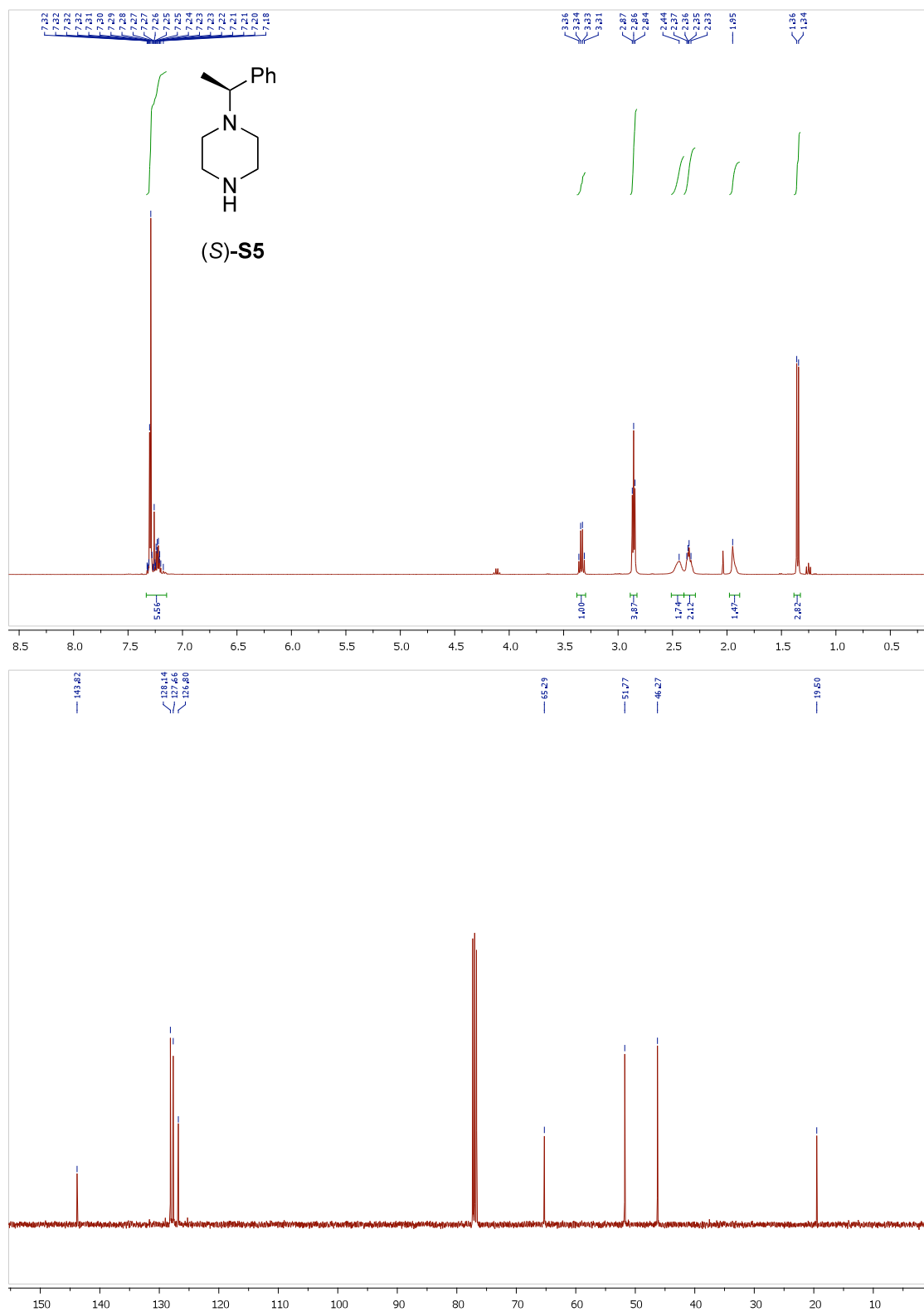
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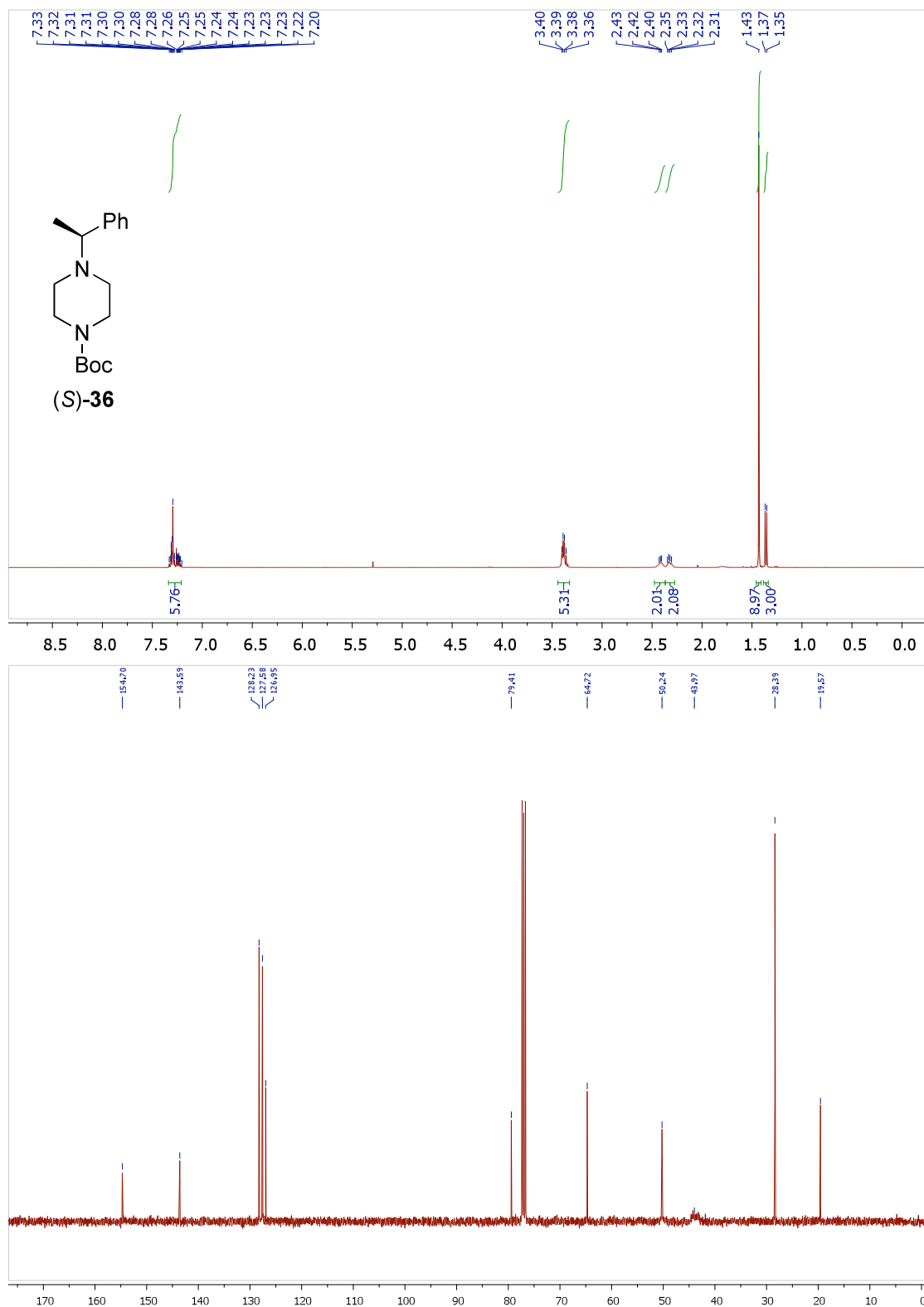


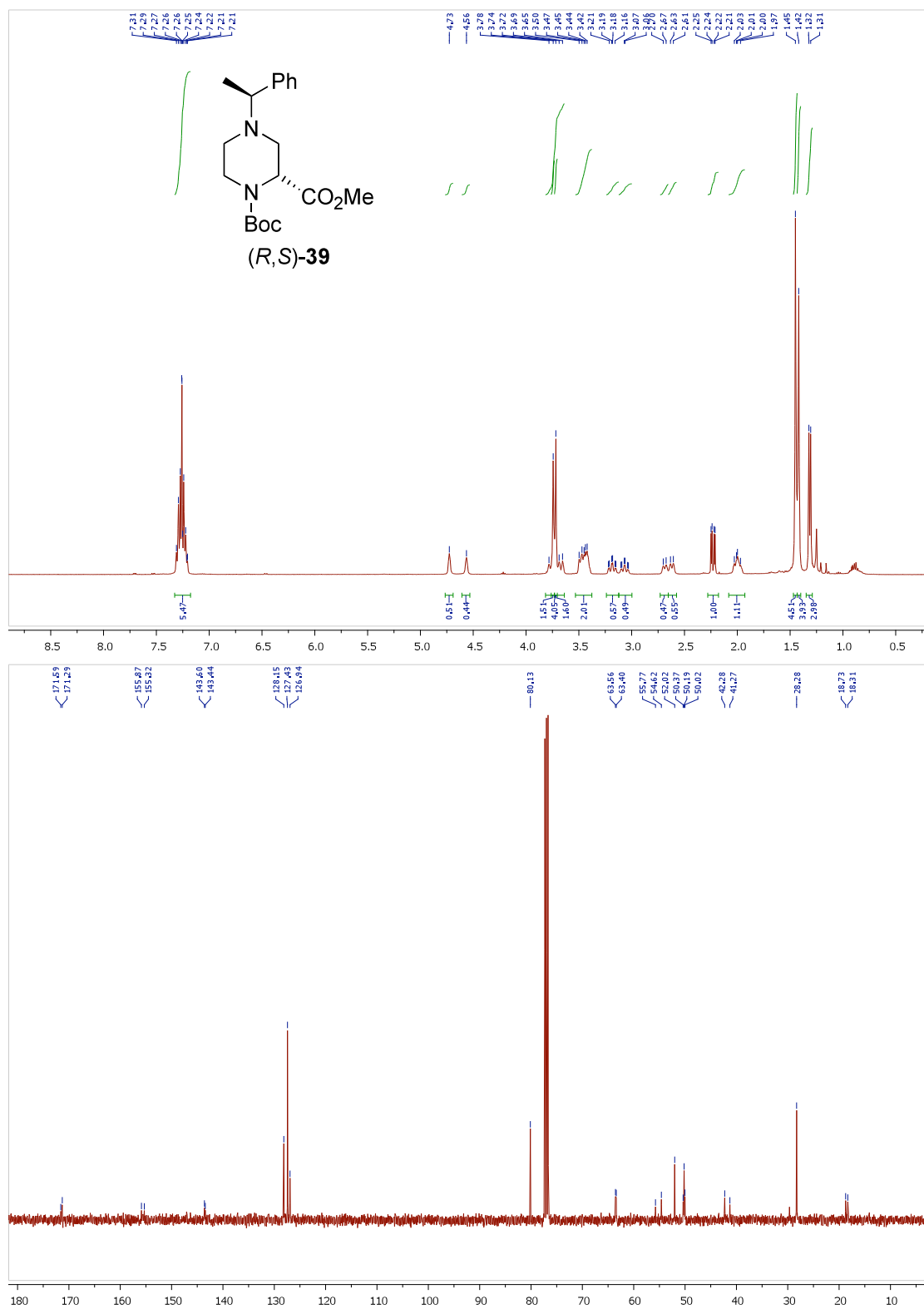
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

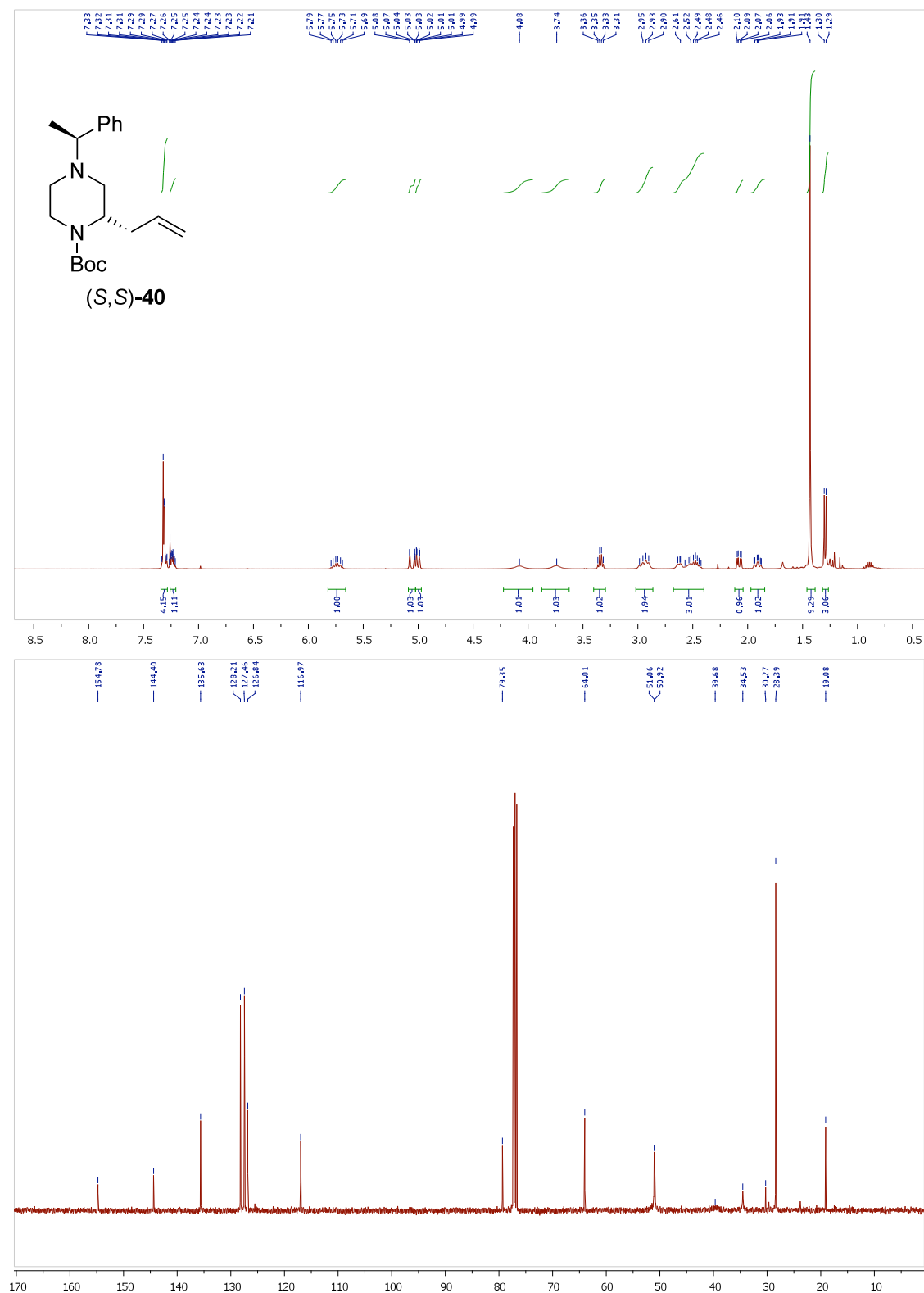
**(S,S)-39**

CC(C1CCN(C1C(=O)OC)C2=CC=CC=C2)C3=CC=CC=C3

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of (S,S)-39. The spectrum shows peaks in the aromatic region (7.1-7.4 ppm), a methoxy singlet (3.7 ppm), and aliphatic signals (1.2-1.6 ppm). Integration values are provided below the baseline.

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) spectrum of (S,S)-39. The spectrum shows carbonyl peaks at 155.2 and 155.3 ppm, aromatic carbons between 127 and 144 ppm, and aliphatic carbons between 19 and 52 ppm.

400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$





**(R,S)-40**

C[C@H](C1CCN(C1)C(=O)OC(C)(C)C)CC=C

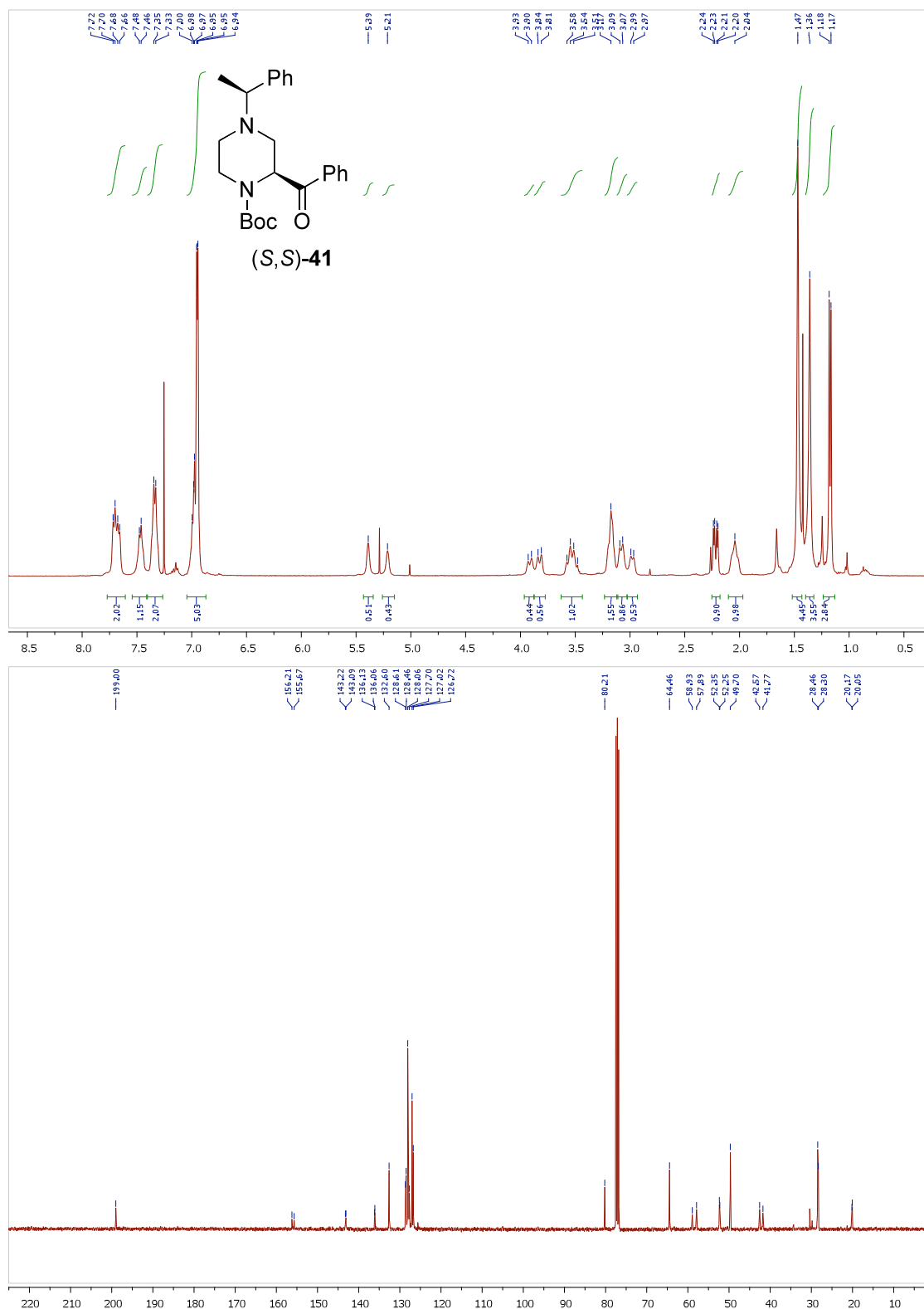
**1H NMR (400 MHz, CDCl<sub>3</sub>)**

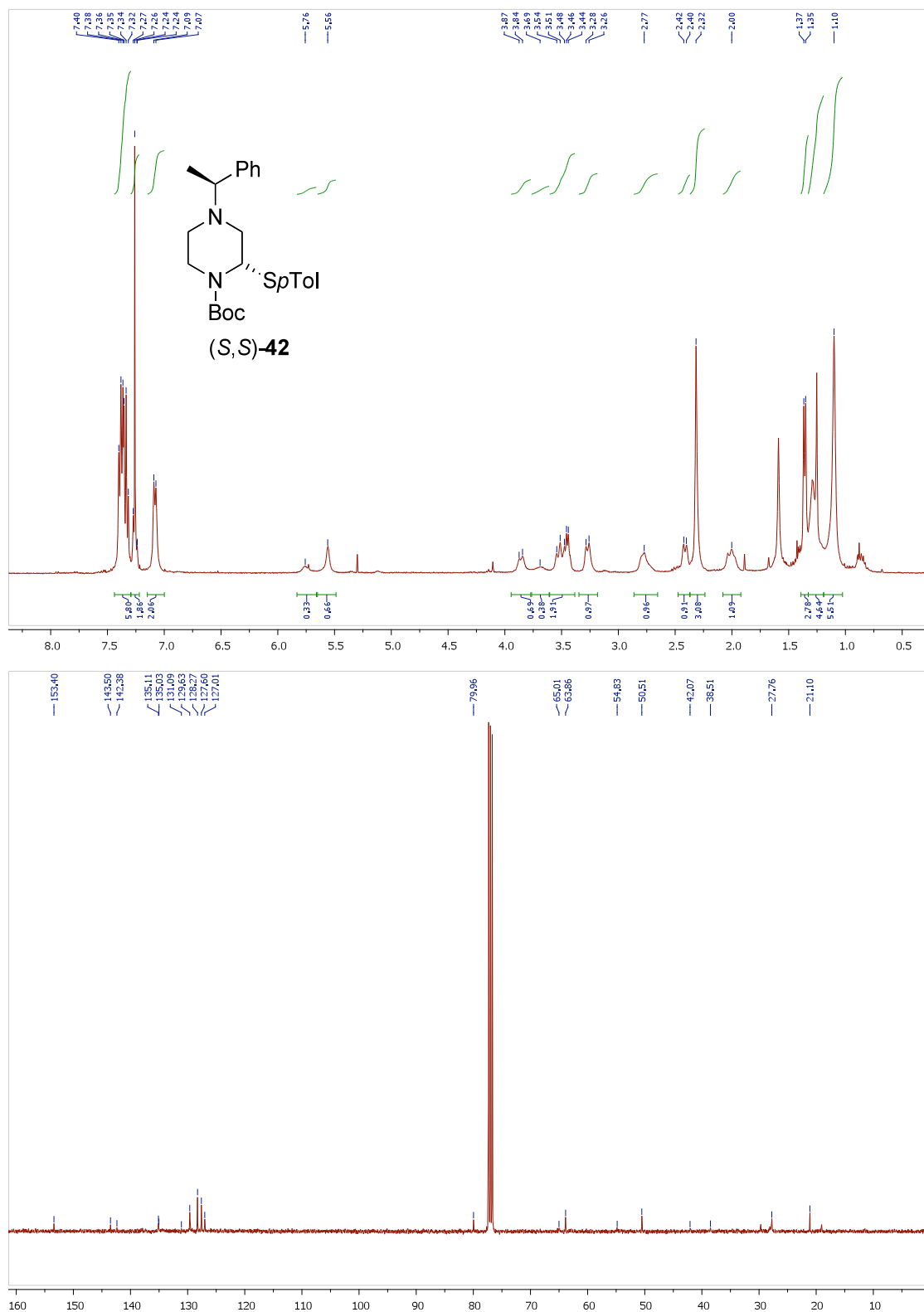
7.32, 7.30, 7.28, 7.27, 7.26, 7.25, 7.24, 7.23, 7.22, 7.21, 7.20 (m, 5H, ArH)  
5.68, 5.66, 5.64, 5.62, 5.60, 5.58, 5.03, 5.02, 4.99, 4.98, 4.94, 4.93, 4.91, 4.91 (m, 4H, =CH-)  
3.90 (s, 2H, -CH<sub>2</sub>-)  
3.33, 3.31, 3.30, 3.28, 3.00, 3.00, 3.04, 2.99, 2.97 (m, 4H, -CH<sub>2</sub>-)  
2.60, 2.46, 2.44, 2.43, 2.40, 2.40 (m, 4H, -CH<sub>2</sub>-)  
1.99, 1.98, 1.95, 1.94, 1.92, 1.91, 1.91, 1.91, 1.91 (m, 4H, -CH<sub>2</sub>-)  
1.34, 1.34, 1.32 (m, 3H, -CH<sub>3</sub>)

**13C NMR (100 MHz, CDCl<sub>3</sub>)**

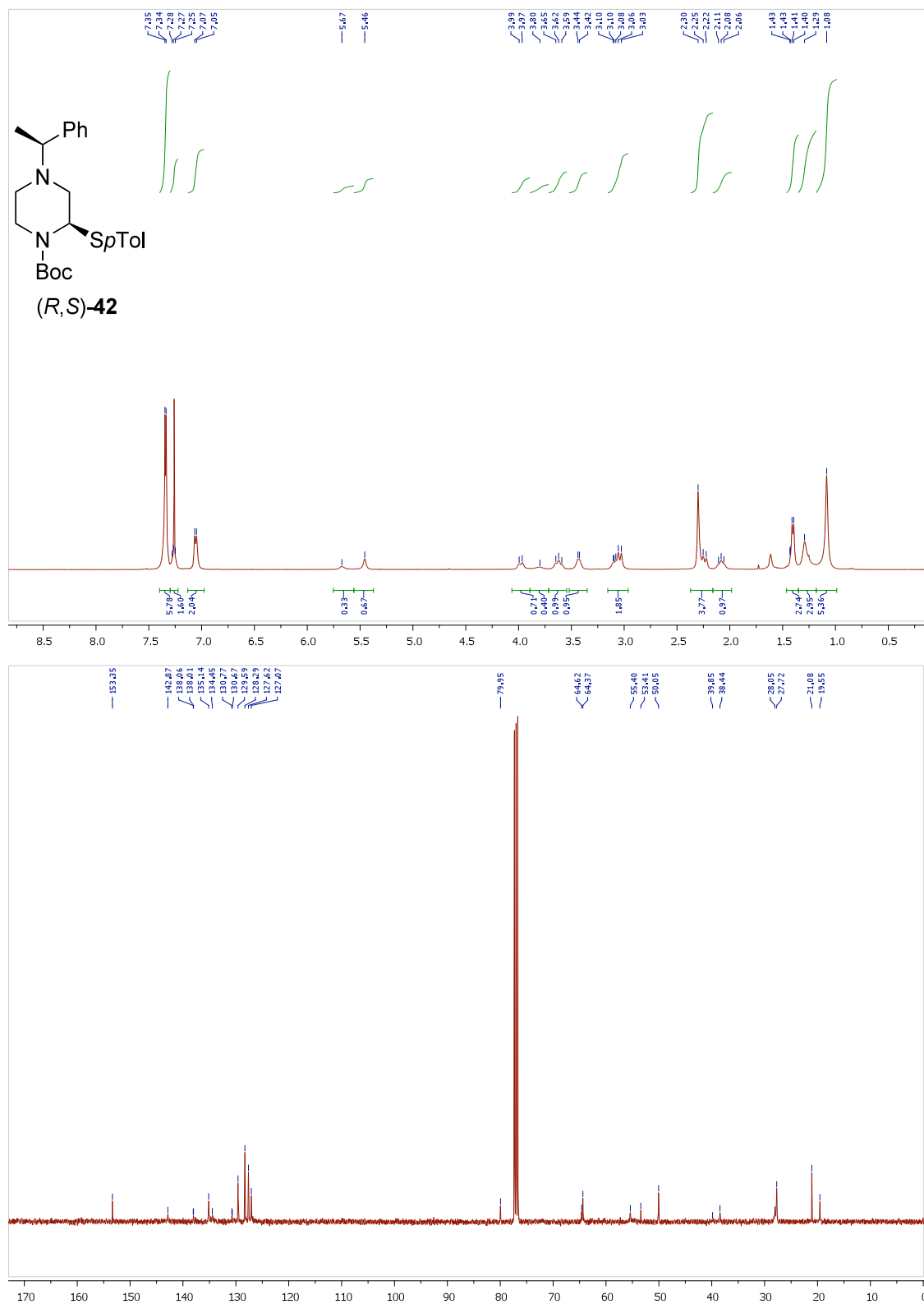
154.74, 143.68, 135.50, 128.19, 127.45, 127.45, 126.27, 116.90, 79.25, 64.49, 52.80, 49.83, 39.33, 34.43, 28.27, 19.82

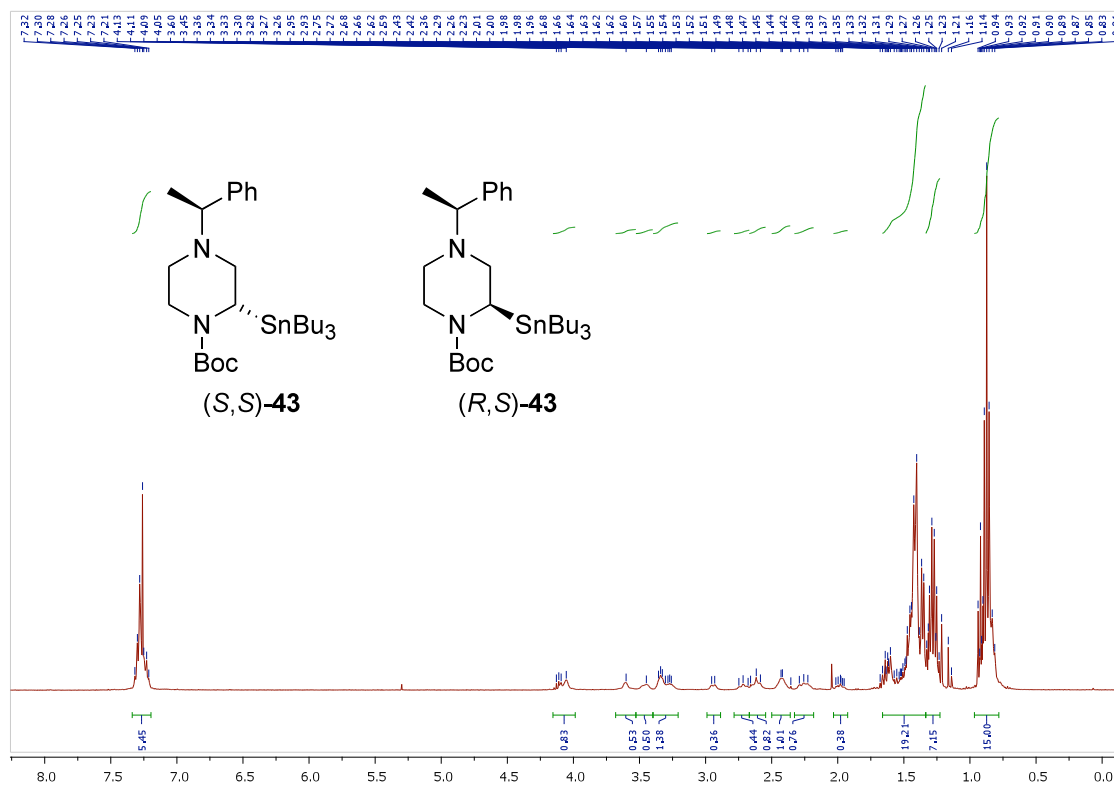
[illegible]

400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

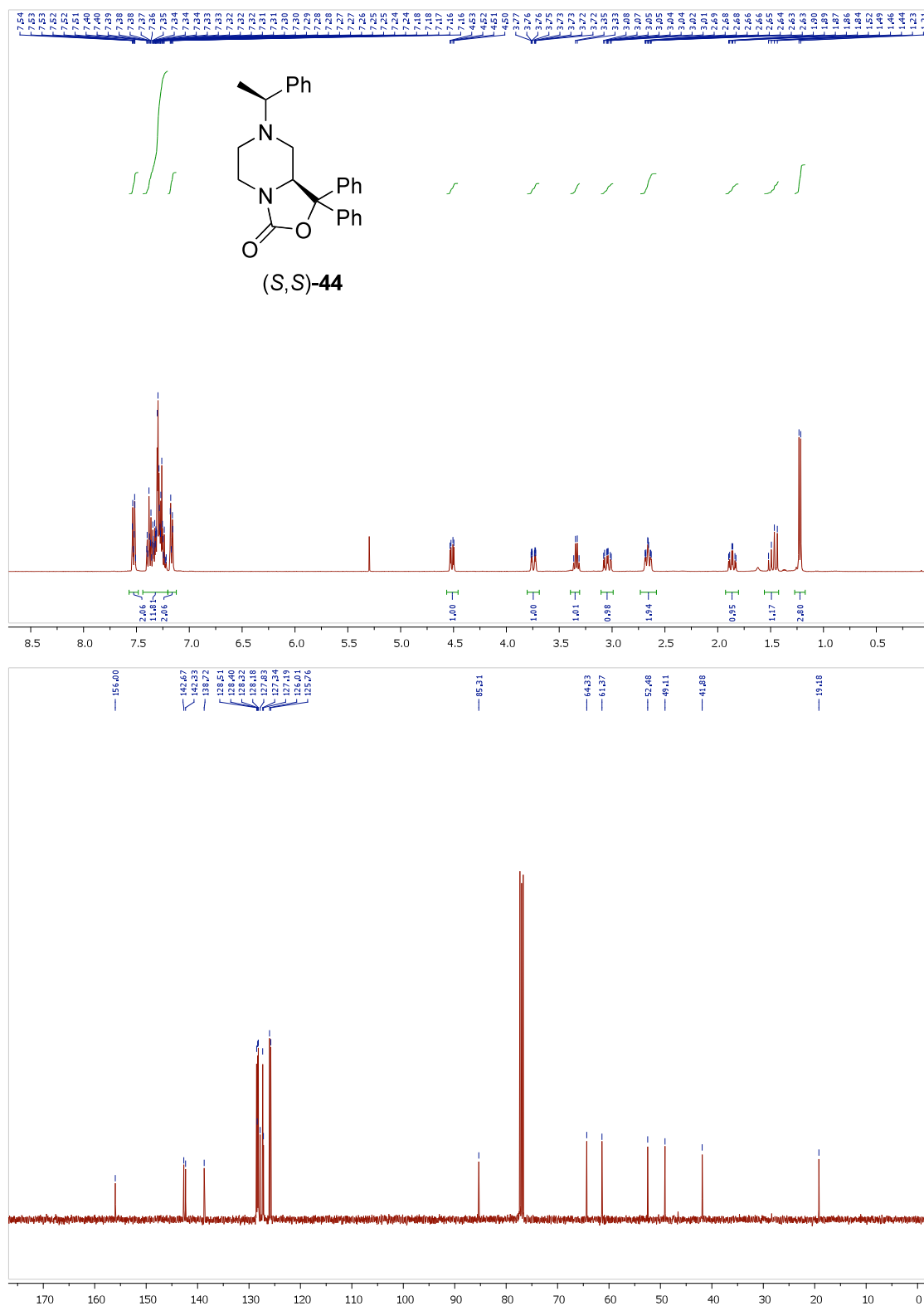
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

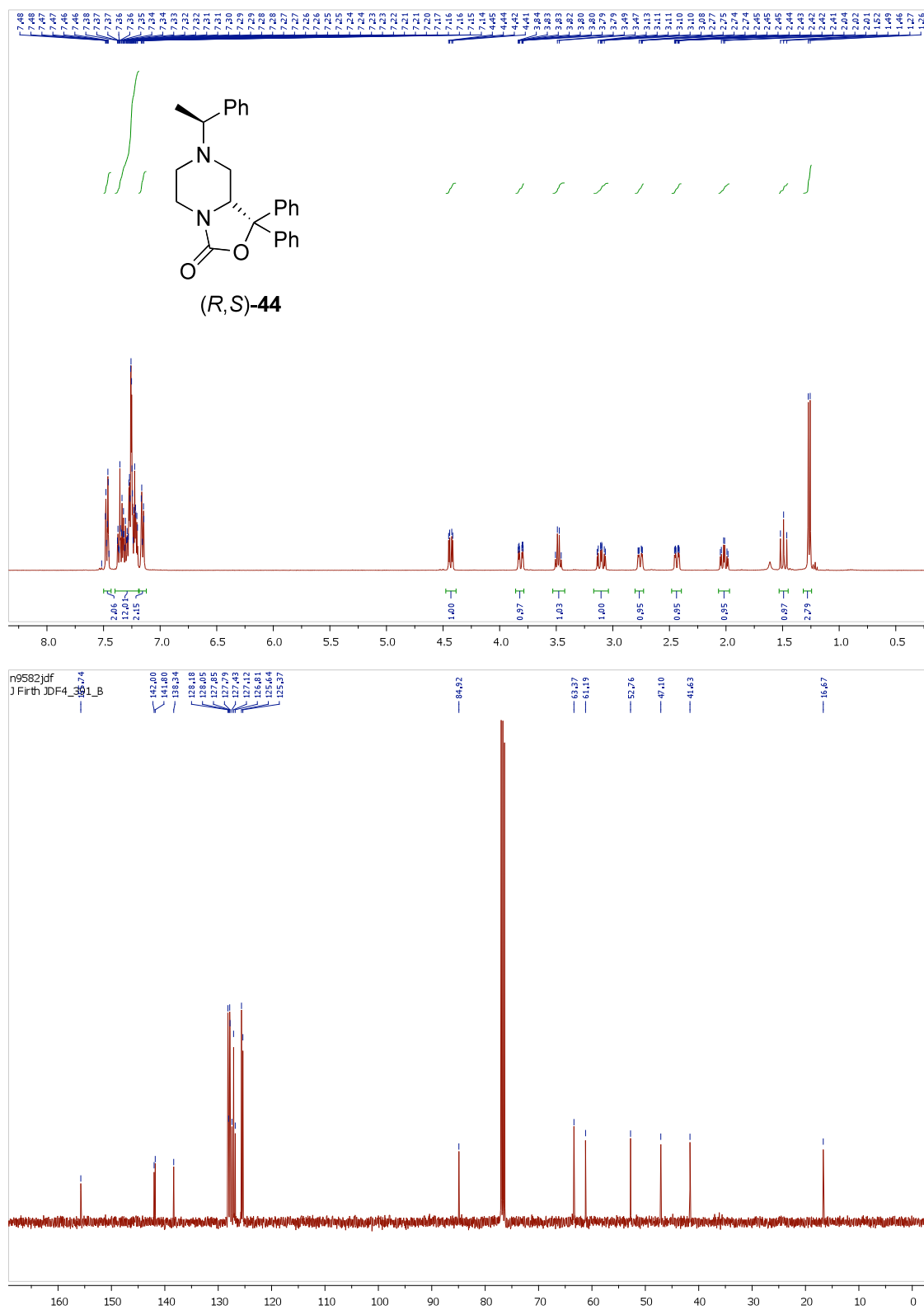
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



400 MHz  $^1\text{H}$  NMR spectrum;  $\text{CDCl}_3$ 

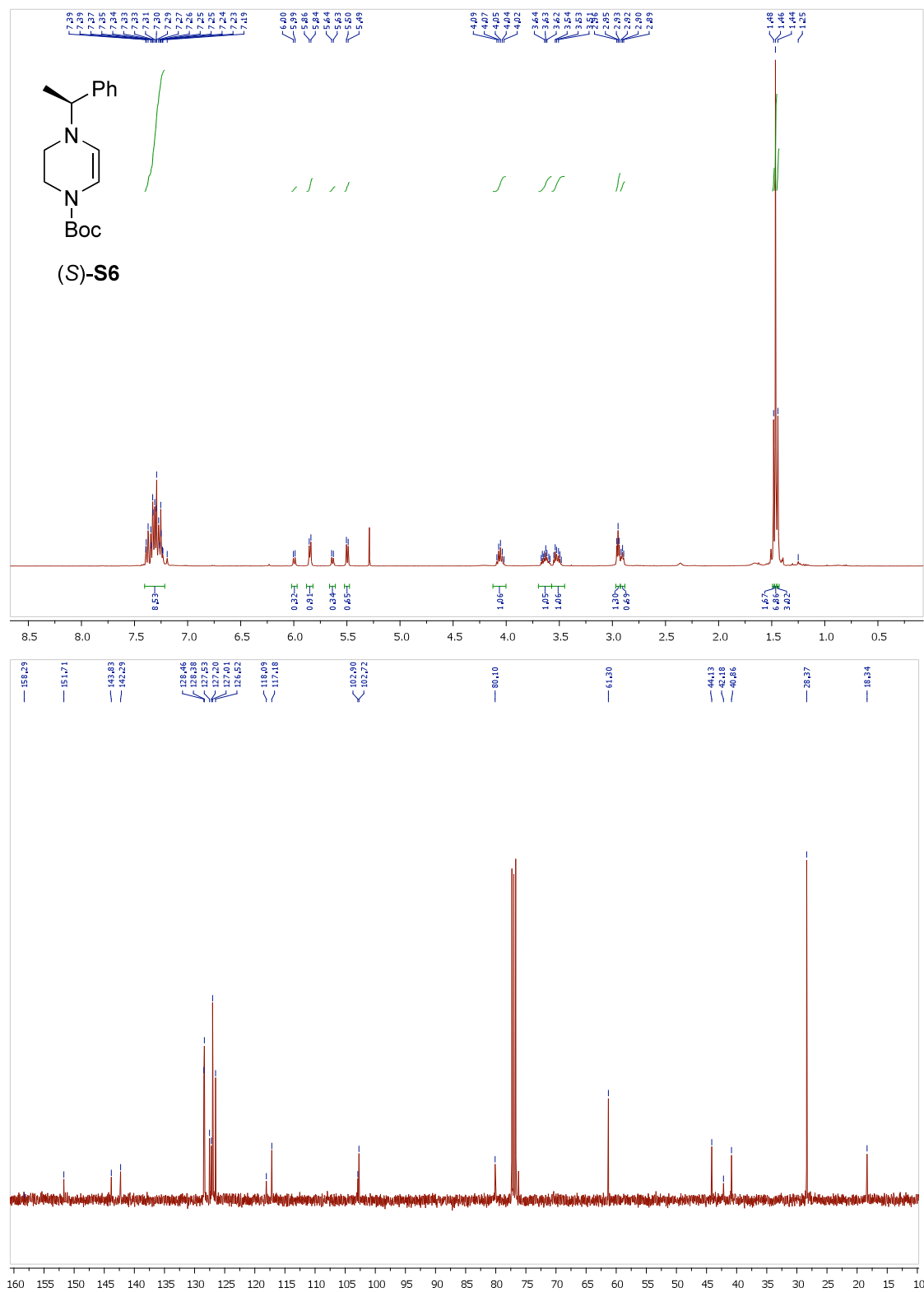
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



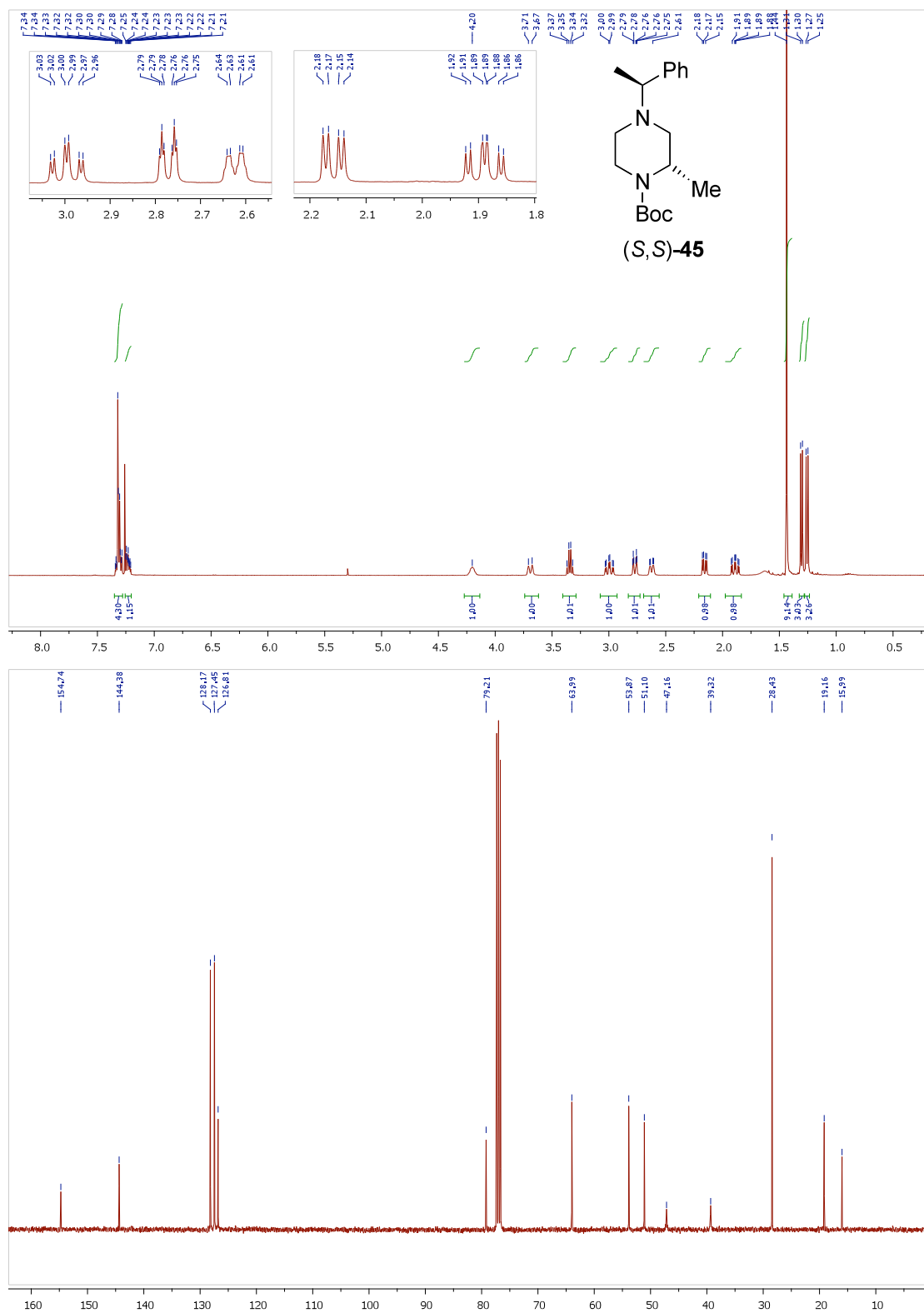
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

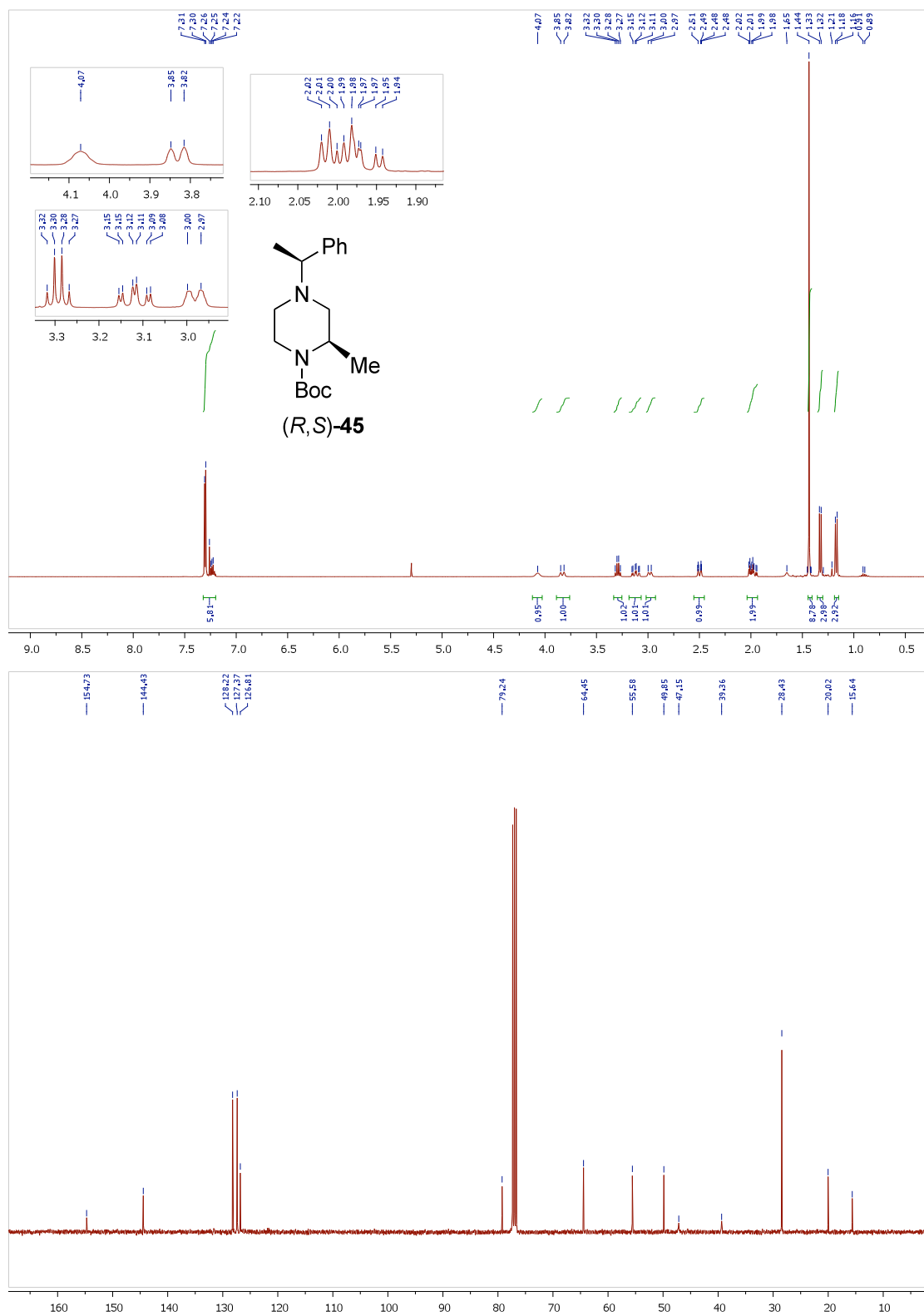


400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$

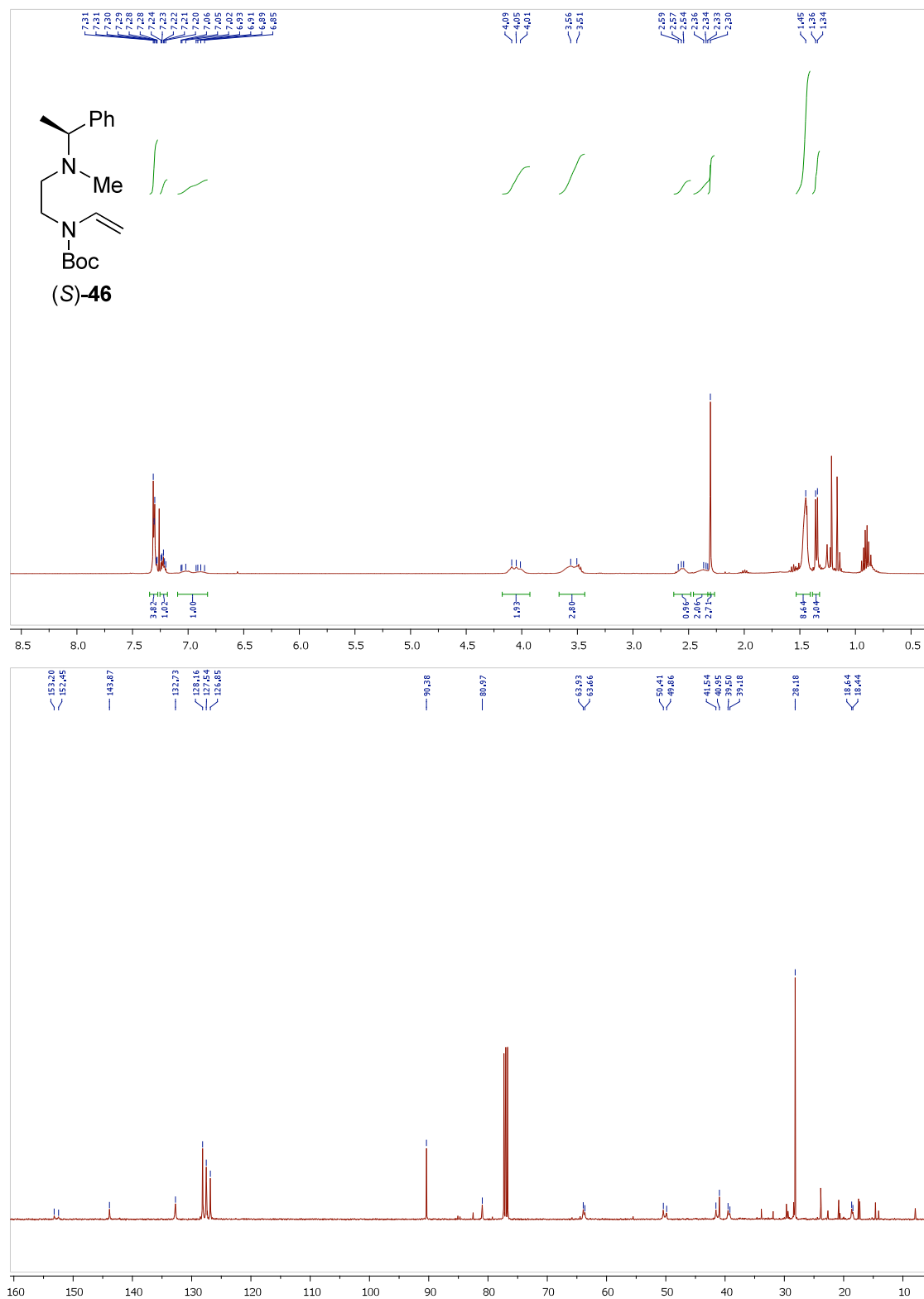


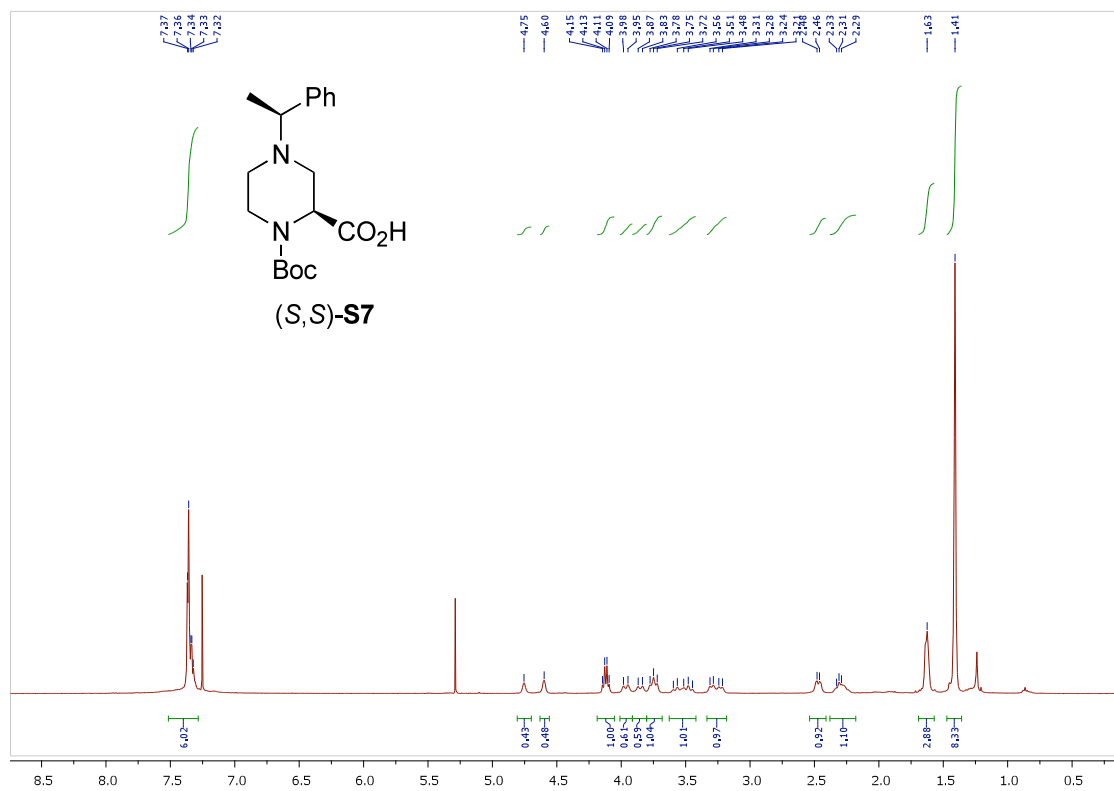
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



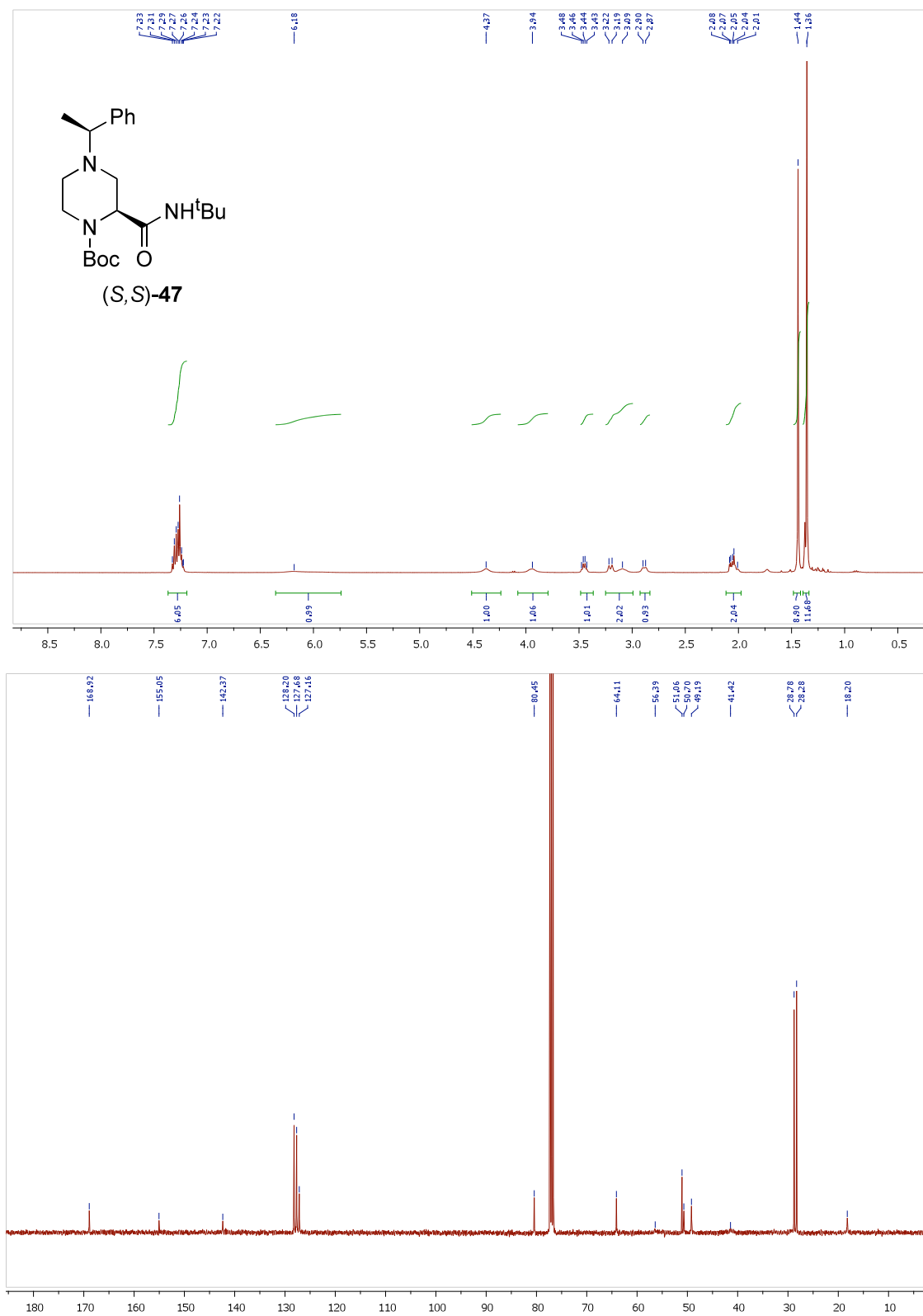
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$ 

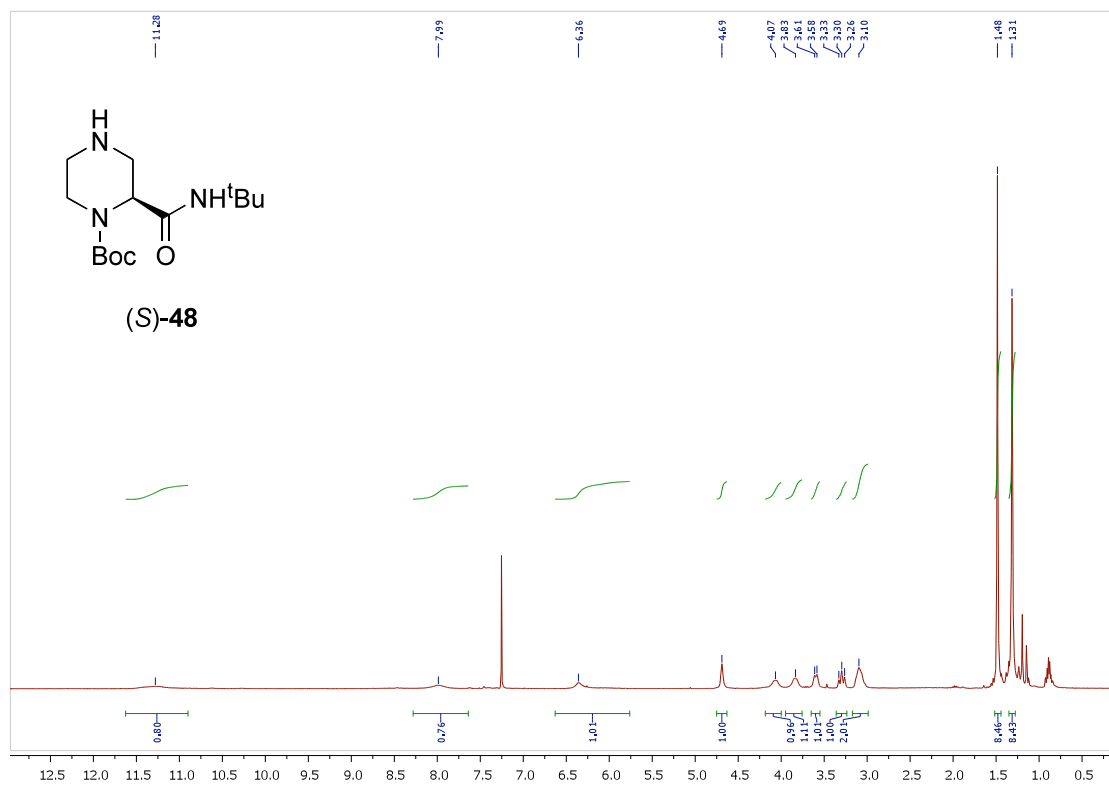
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$

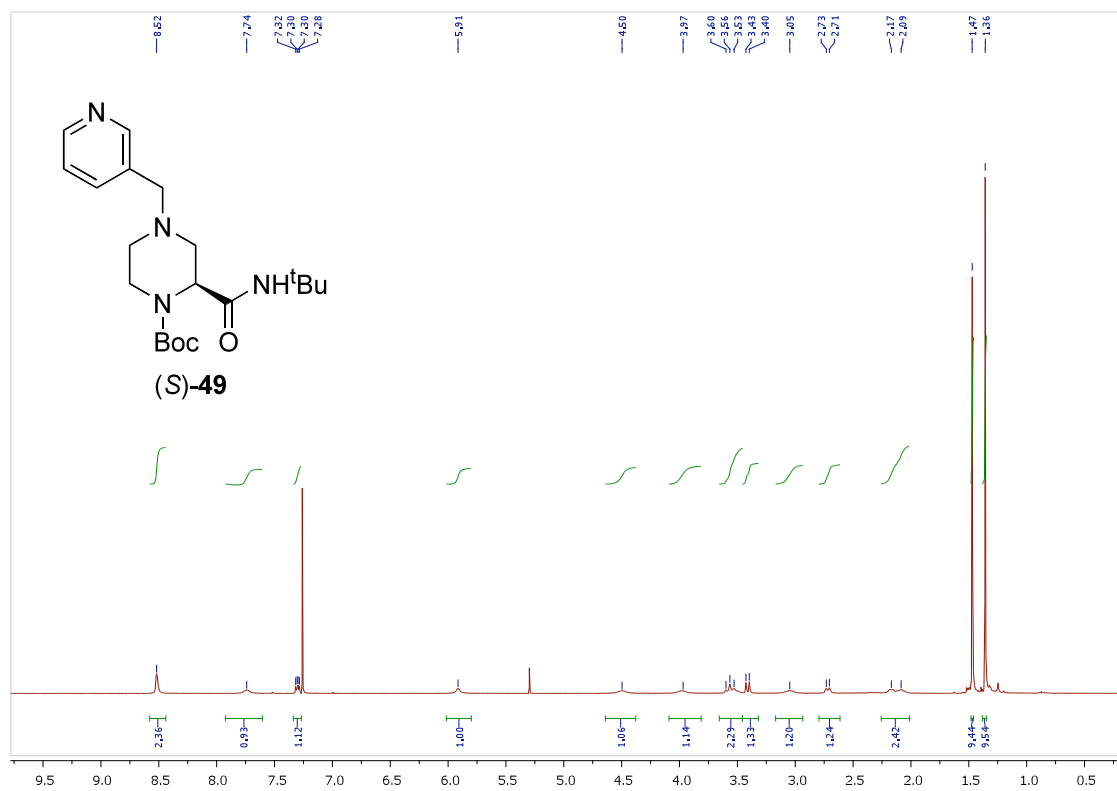


400 MHz  $^1\text{H}$  NMR spectrum;  $\text{CDCl}_3$ 

400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$

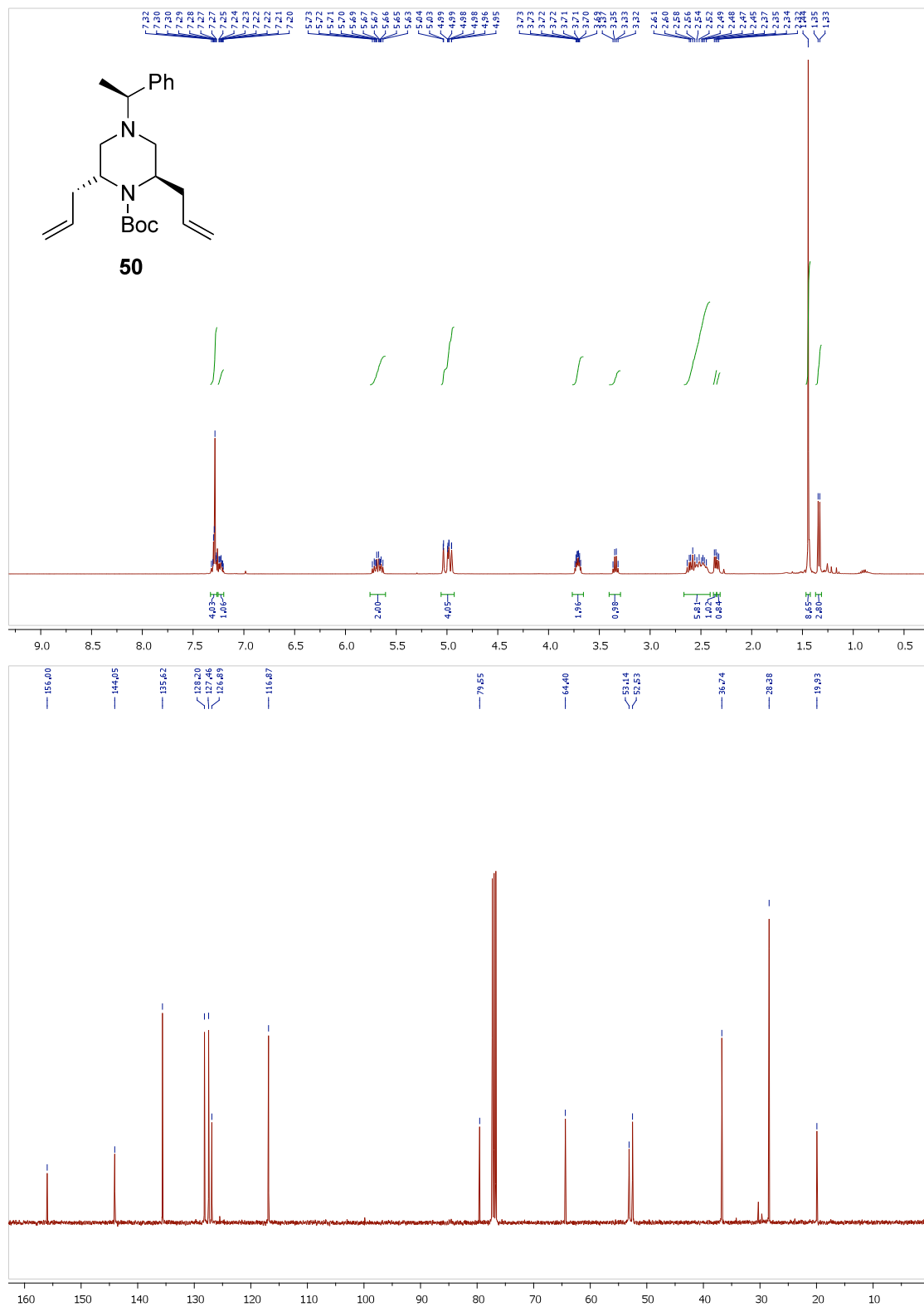


400 MHz  $^1\text{H}$  NMR spectrum;  $\text{CDCl}_3$ 

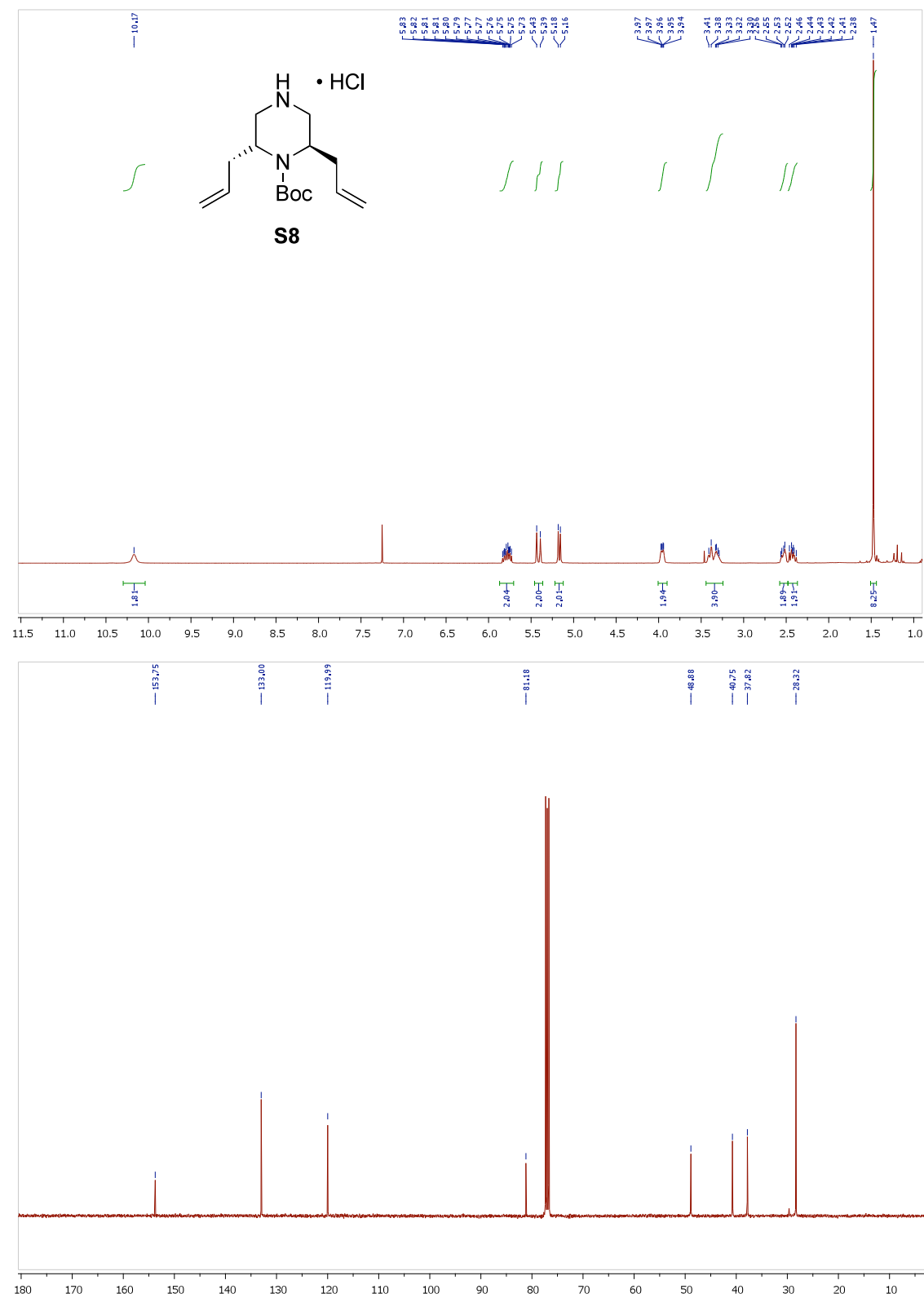
400 MHz  $^1\text{H}$  NMR spectrum;  $\text{CDCl}_3$ 



400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



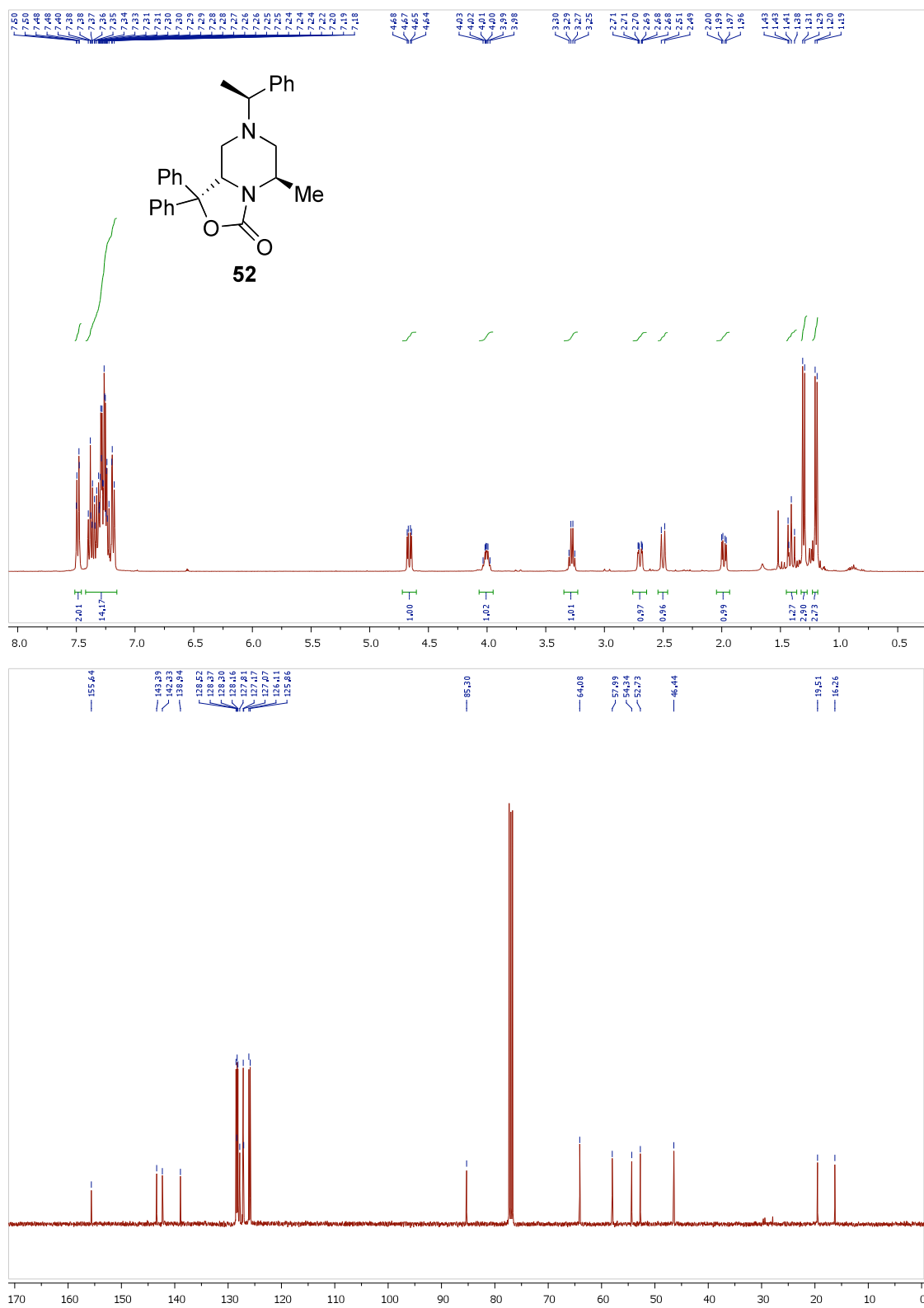
Chemical structure of compound **51** is shown above the <sup>1</sup>H NMR spectrum. The structure is a 1,3-dimethyl-4-phenyl-2-(methoxycarbonyl)-5-(tert-butoxycarbonyl)piperazine derivative. The <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) displays peaks corresponding to the structure, with chemical shifts and integrations provided.

<sup>1</sup>H NMR peaks (ppm): 7.21-7.32 (m, 5H, aromatic), 3.94-4.21 (m, 4H, CH<sub>2</sub>), 3.72 (s, 3H, Me), 3.33-3.38 (m, 2H, CH<sub>2</sub>), 2.86 (s, 3H, Me), 2.45 (s, 3H, Me), 2.31 (s, 3H, Me), 1.42-1.45 (m, 9H, t-Bu), 1.22-1.25 (m, 9H, t-Bu).

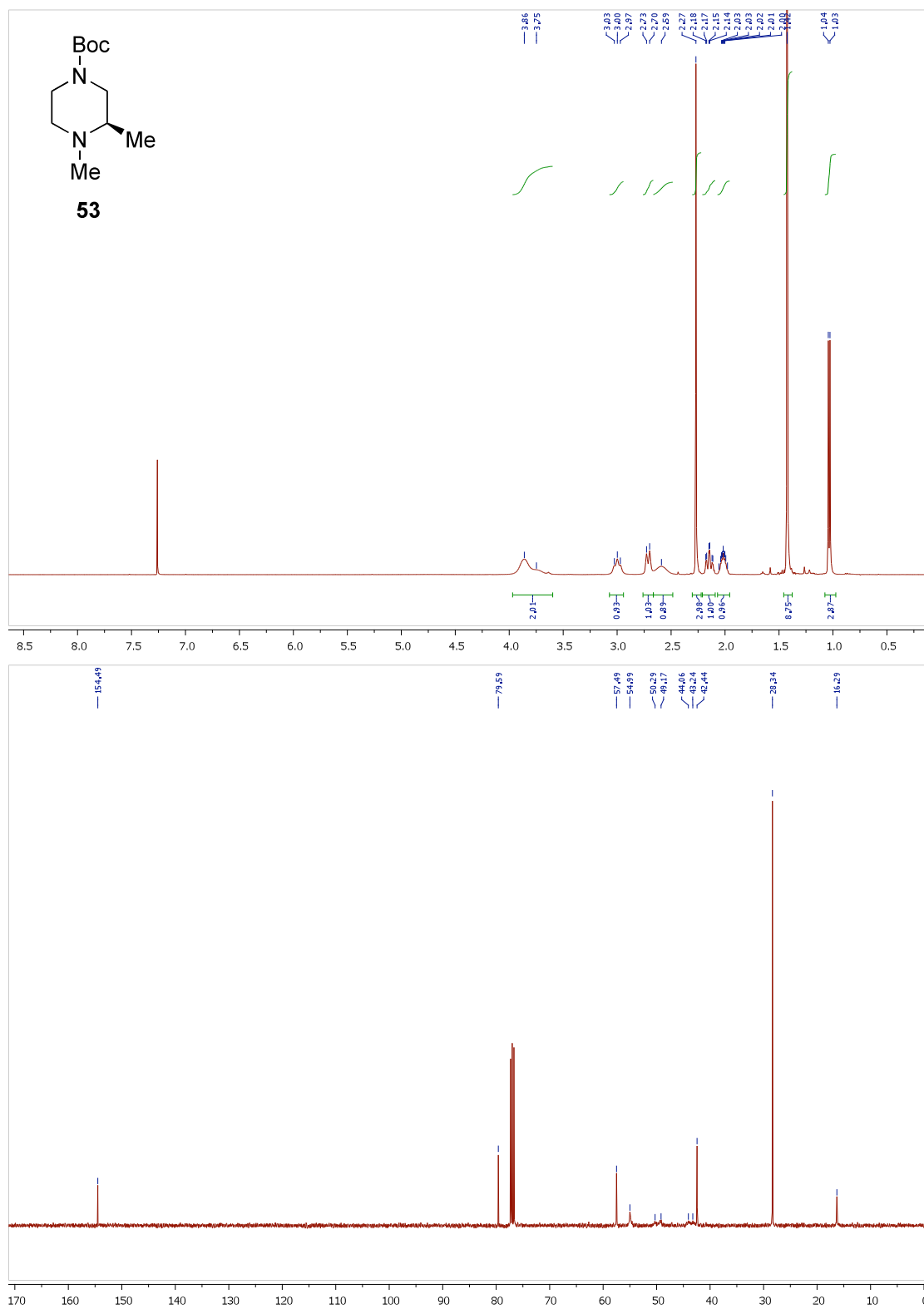
Integration values: 5.58, 0.94, 1.00, 2.84, 1.00, 0.99, 1.80, 1.06, 8.71, 3.16, 3.23.

<sup>13</sup>C NMR peaks (ppm): 172.11, 156.45, 143.58, 128.25, 127.97, 127.05, 80.57, 64.05, 56.10, 52.17, 51.97, 49.02, 38.18, 19.75, 17.98.

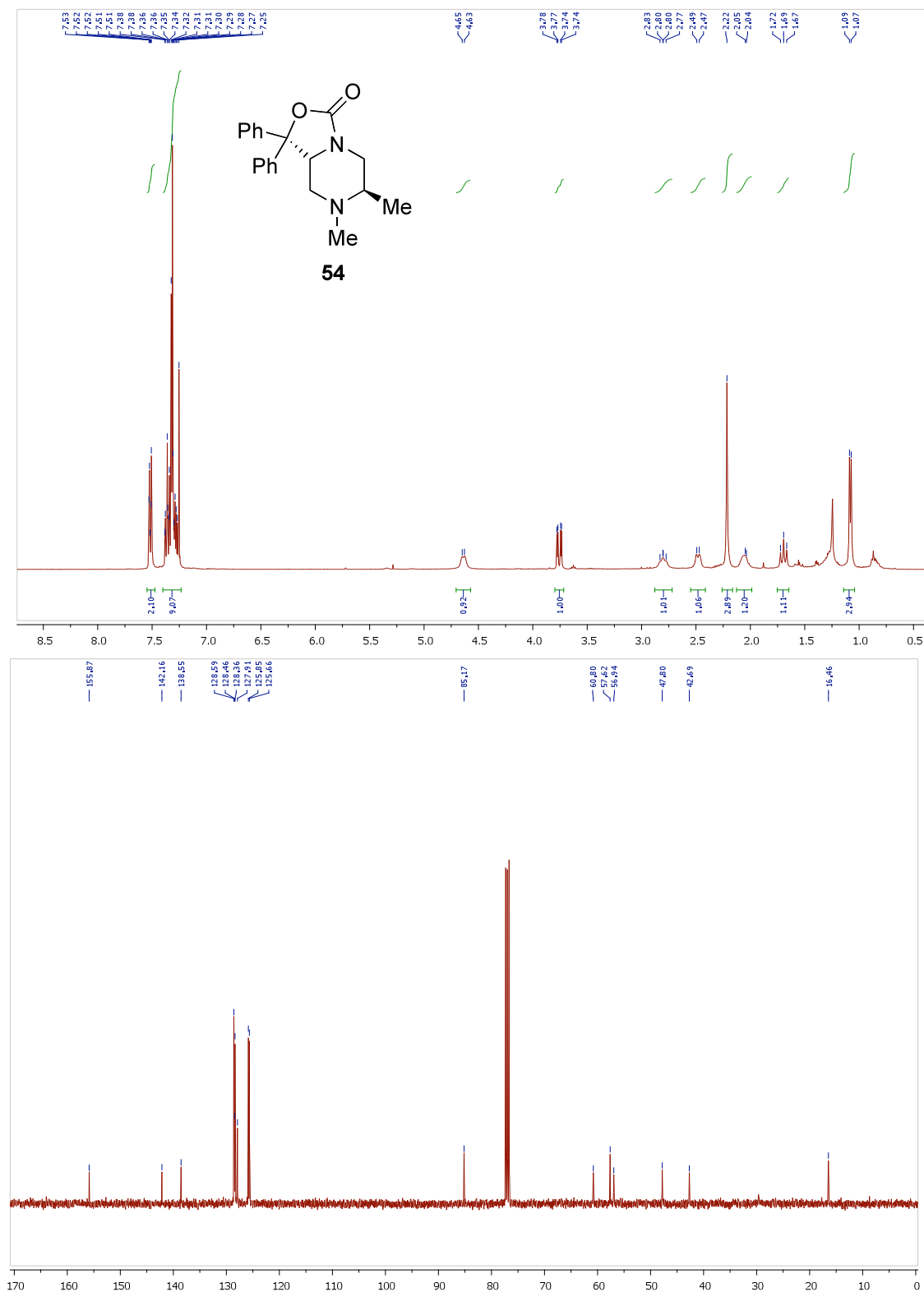
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$

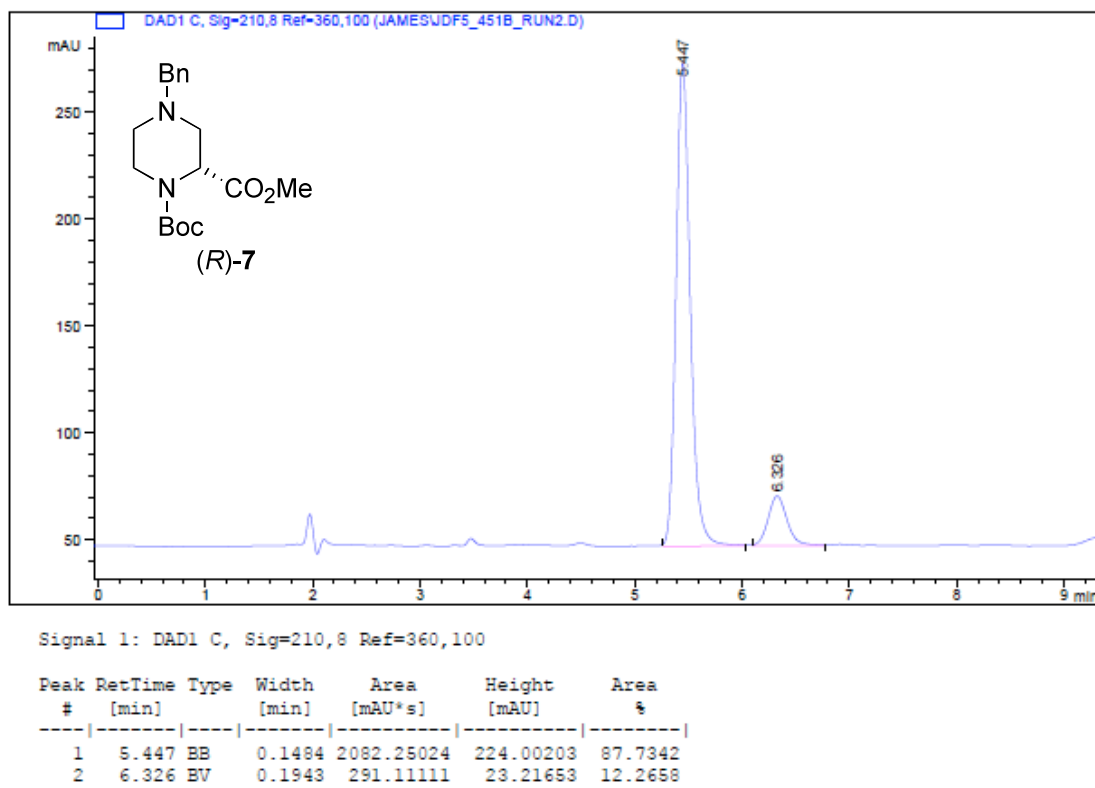
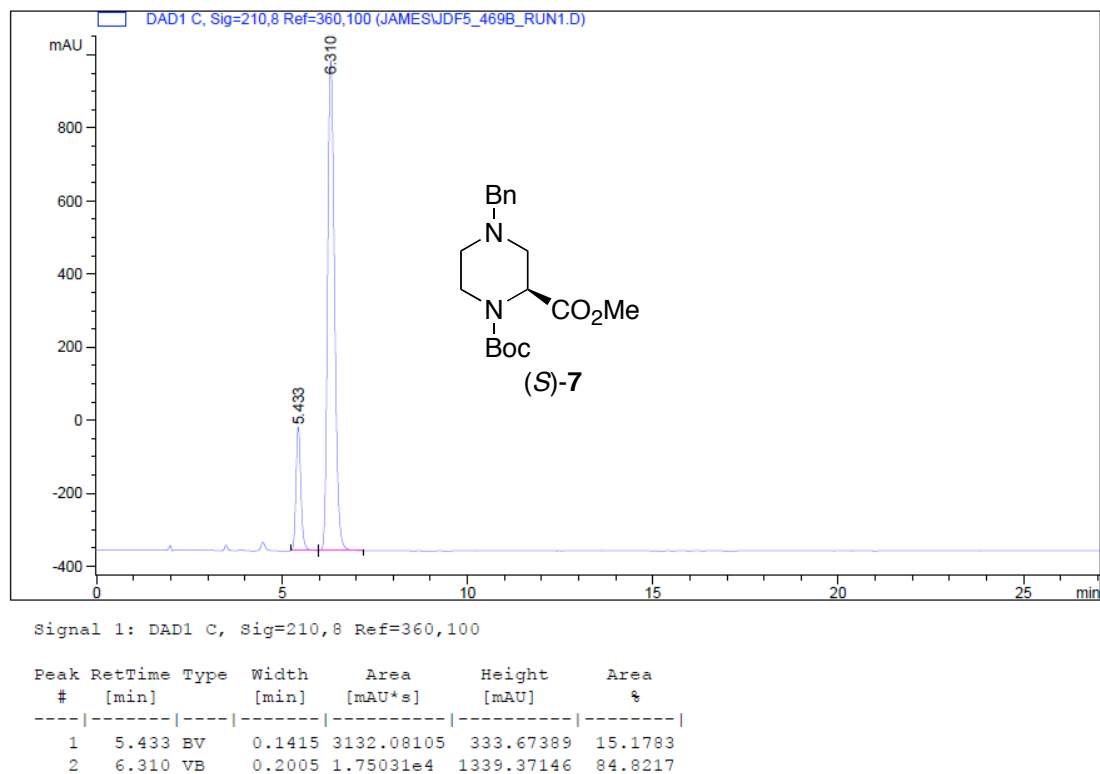


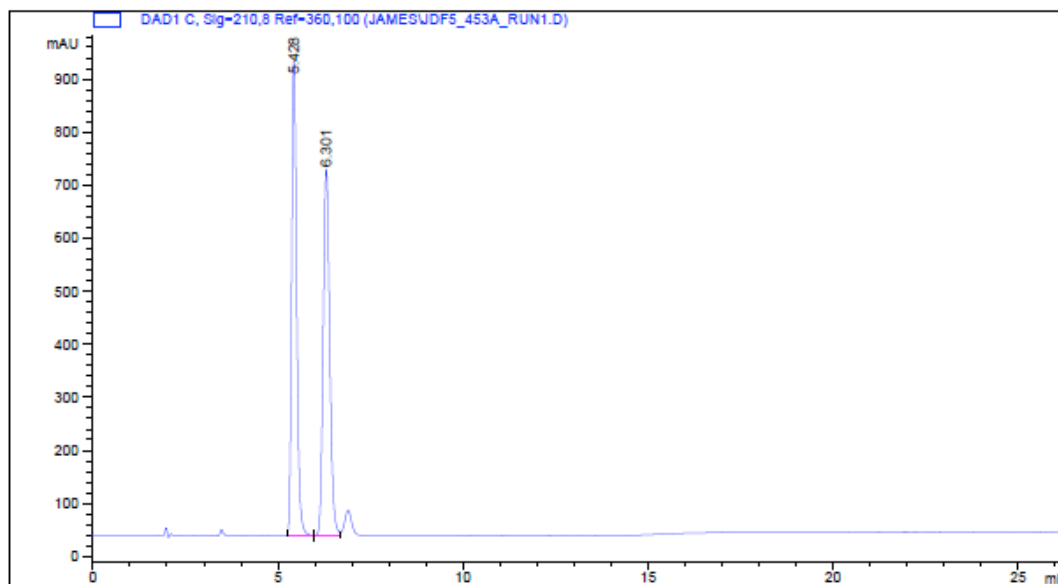
400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



400 MHz  $^1\text{H}$  NMR spectrum; 100.6 MHz  $^{13}\text{C}$  NMR spectrum;  $\text{CDCl}_3$



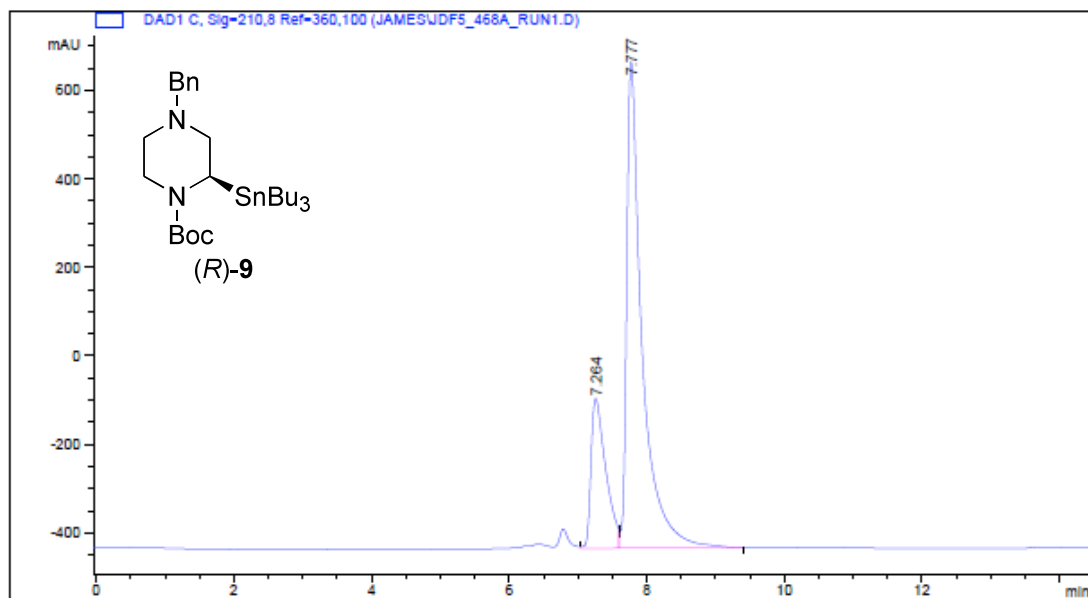
CSP-HPLC of (*R*)-7 of 88:12 erCSP-HPLC of (*S*)-7 of 85:15 er

CSP-HPLC of *rac-7*

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

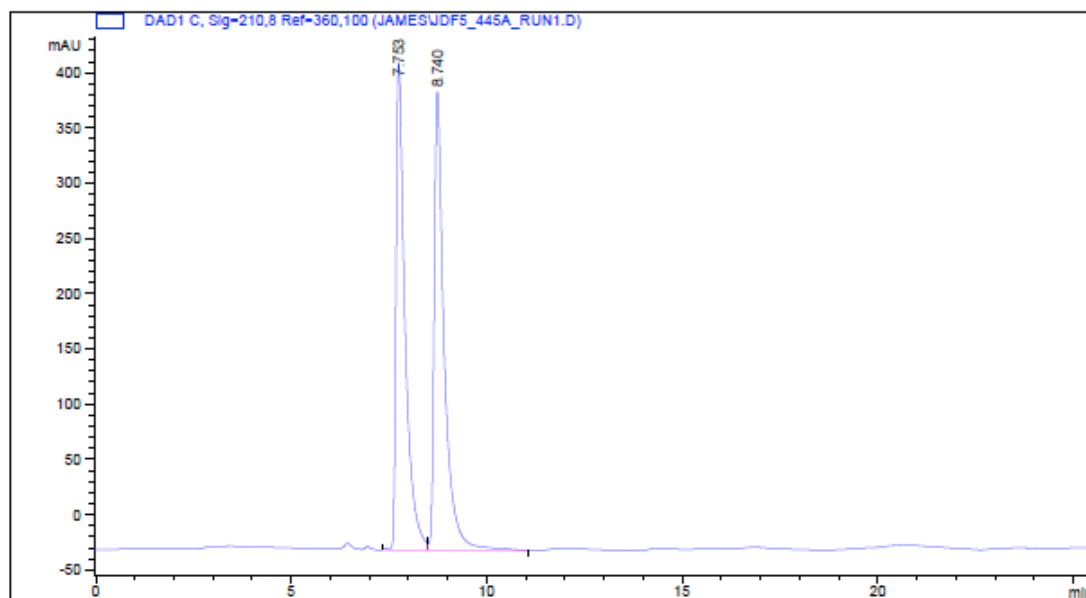
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.428	BV	0.1498	8386.26953	890.79370	49.7295
2	6.301	VV	0.1998	8477.49512	687.99646	50.2705



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

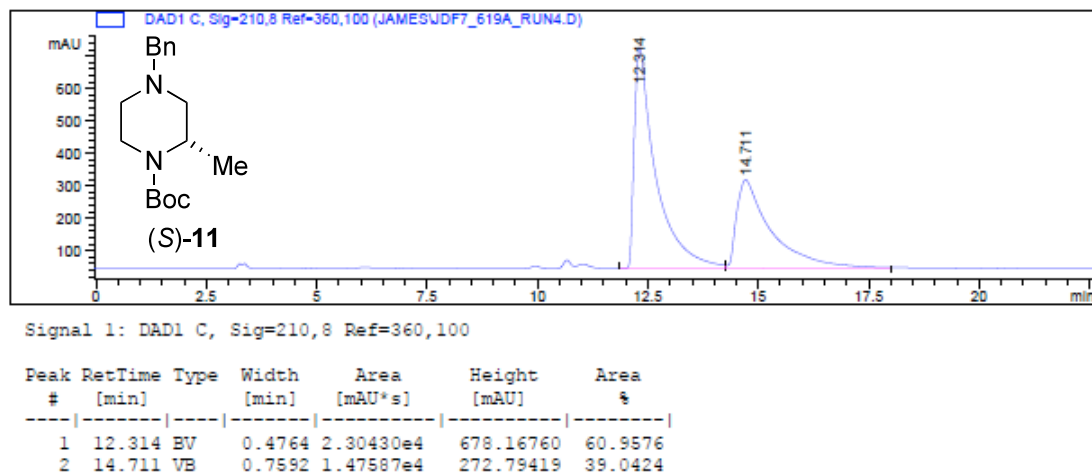
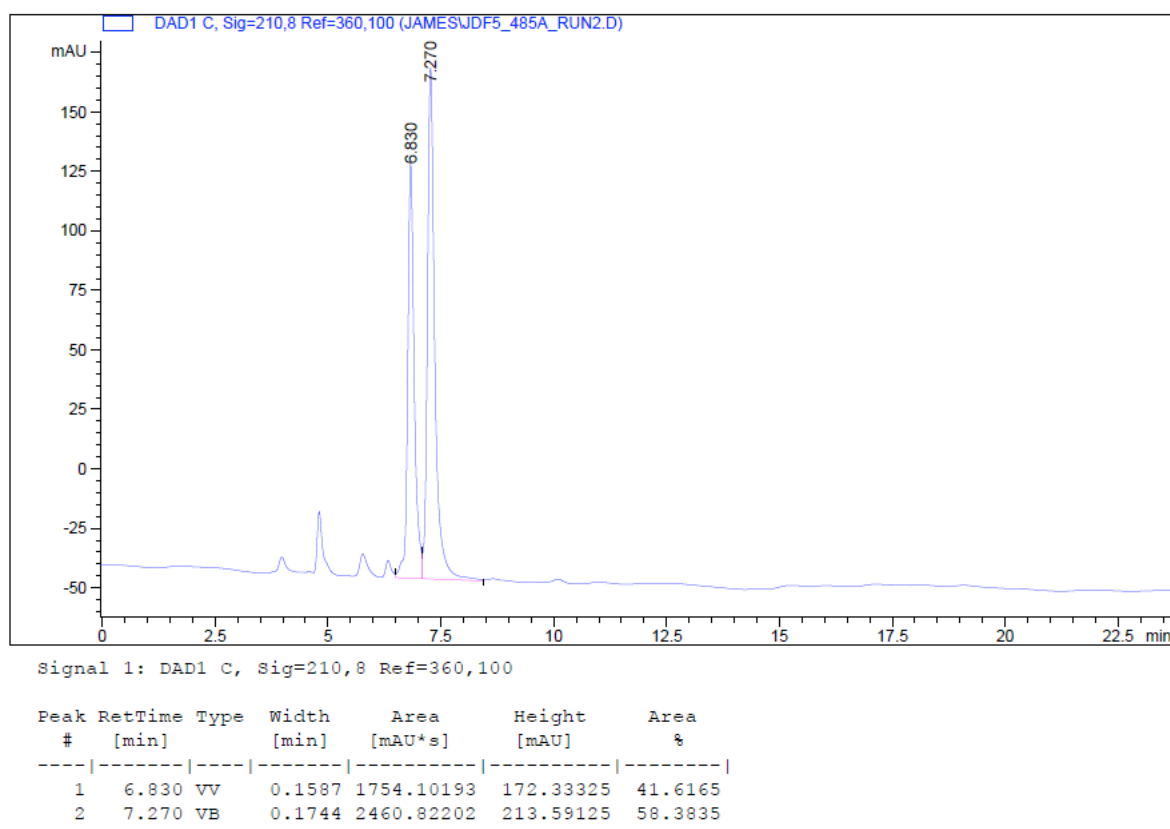
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

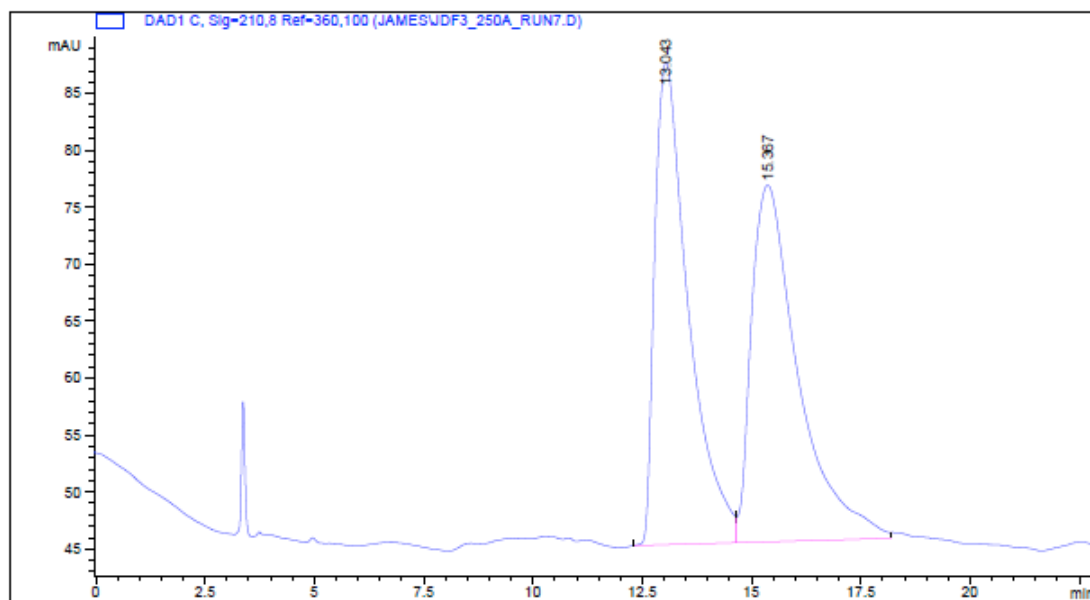
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.264	VV	0.2228	5053.29785	337.36194	22.7772
2	7.777	VB	0.2216	1.71325e4	1100.77344	77.2228

CSP-HPLC of *rac*-**9**

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

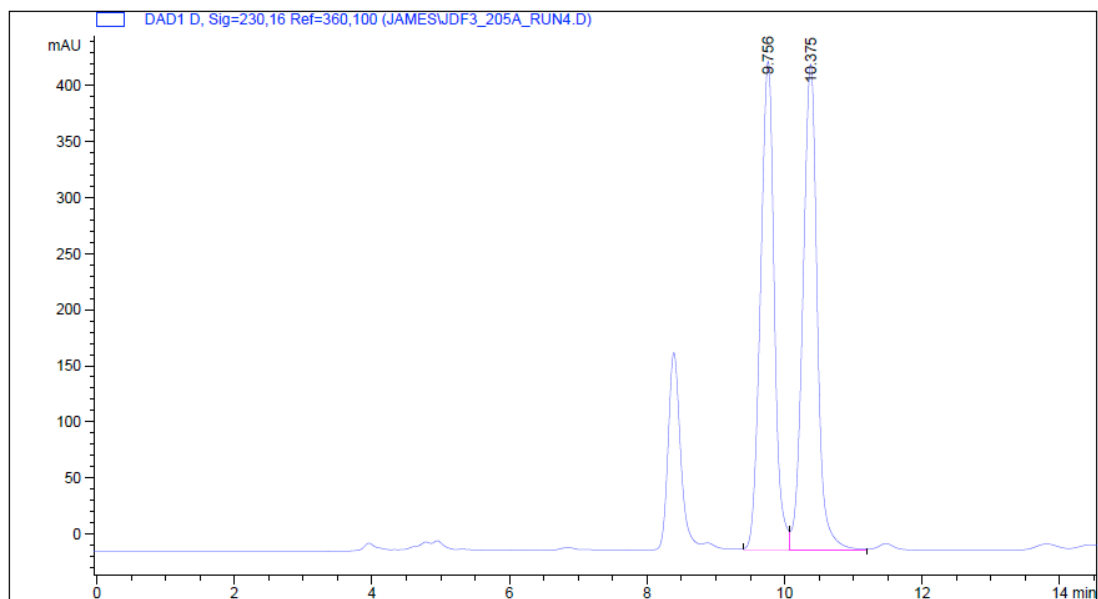
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.753	BV	0.2347	7080.19141	442.42441	49.0265
2	8.740	VB	0.2549	7361.38330	415.02277	50.9735

CSP-HPLC of (S)-**11** of 61:39 erCSP-HPLC of (S)-**11** of 58:42 er

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

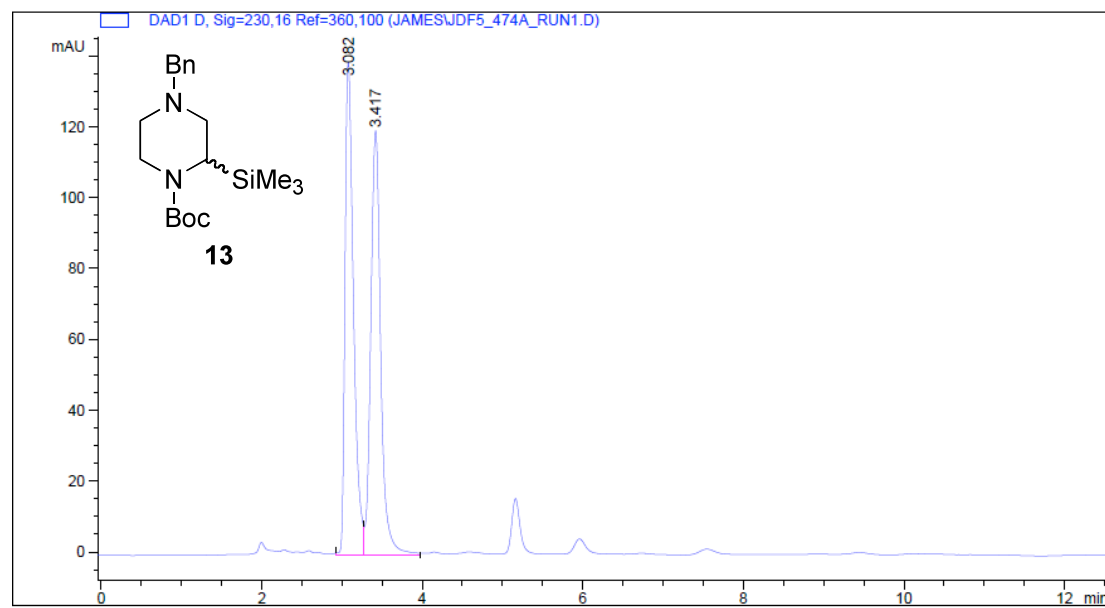
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

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<sup>-1</sup>)

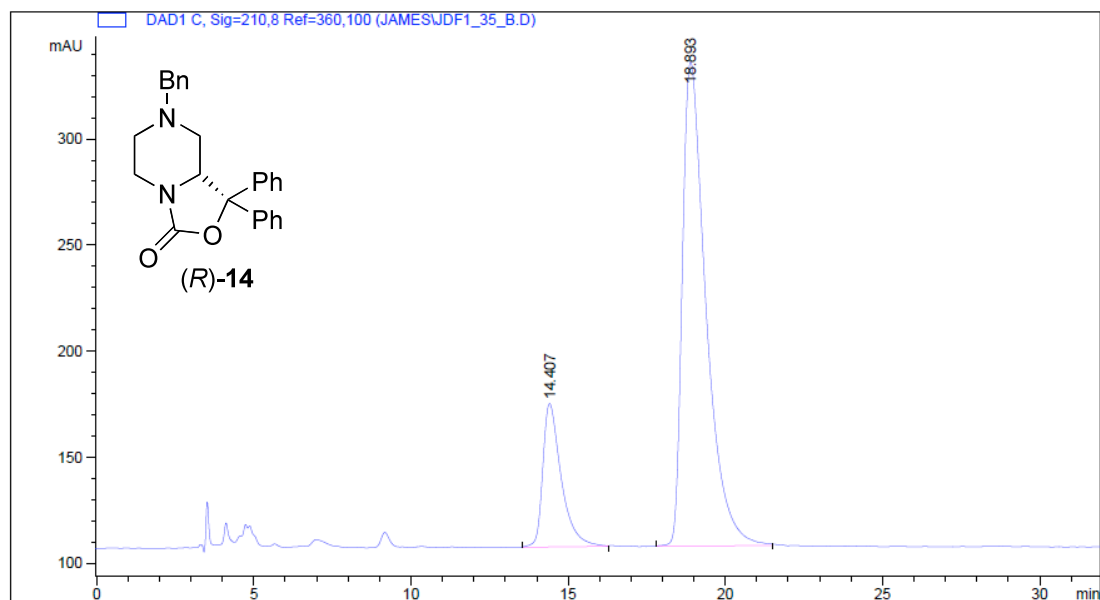
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

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

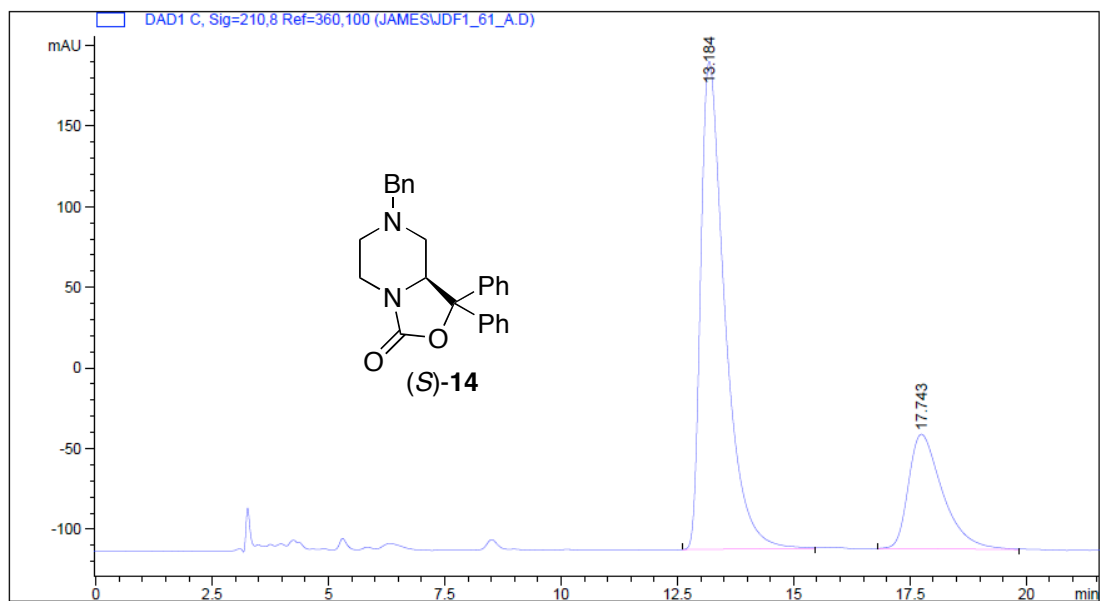
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

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

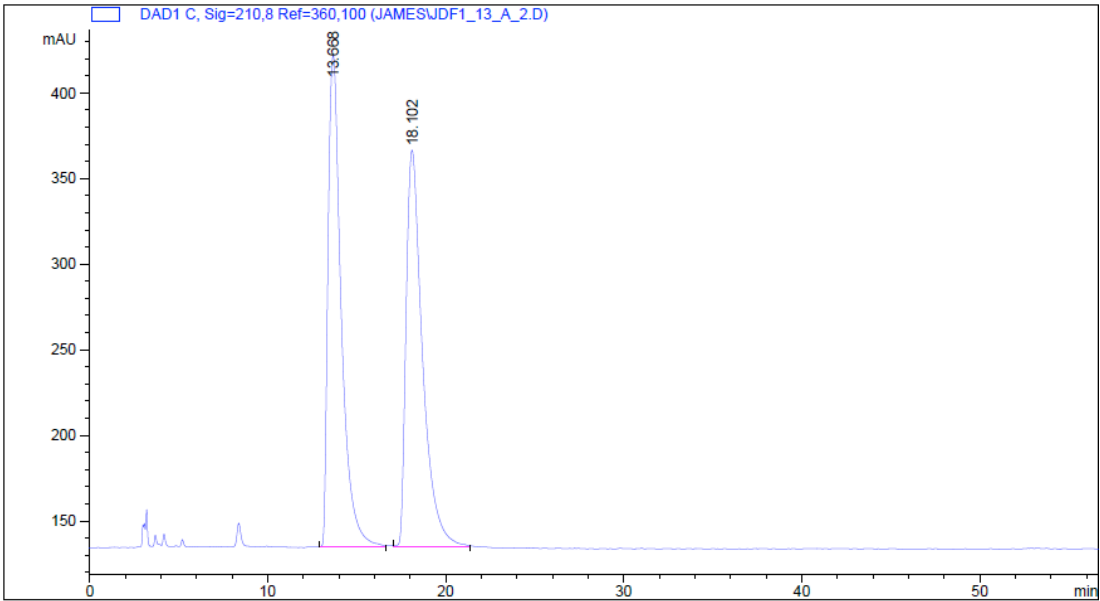
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.407	BB	0.6137	2765.11133	67.53465	18.8136
2	18.893	BB	0.7939	1.19323e4	228.24980	81.1864

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

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

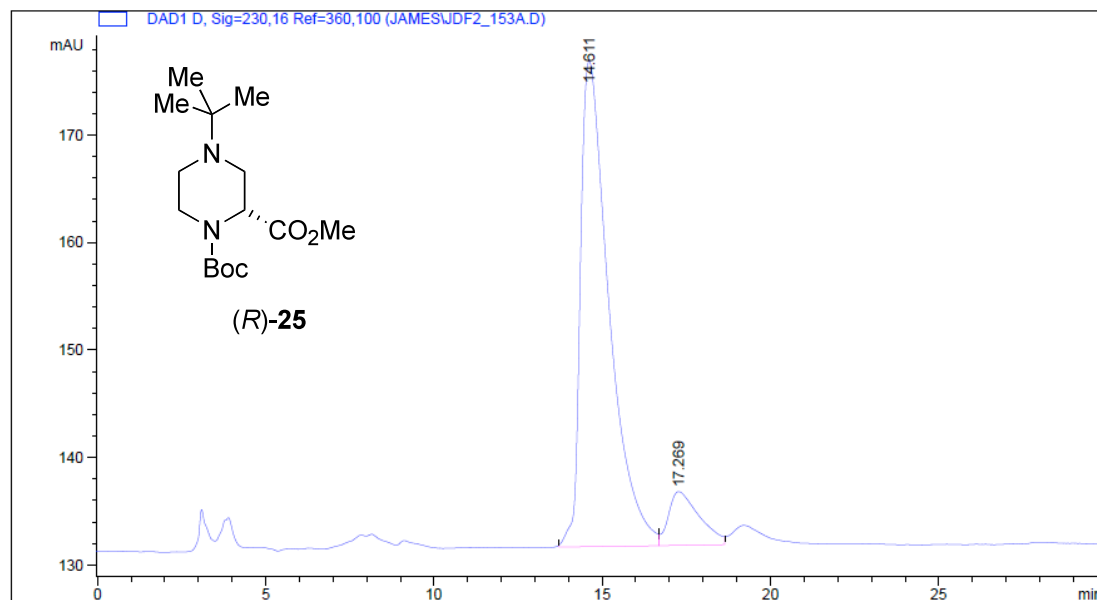
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.184	BB	0.5422	1.09546e4	302.67612	75.1418
2	17.743	BB	0.7709	3623.98145	71.06499	24.8582

CSP-HPLC of *rac*-14



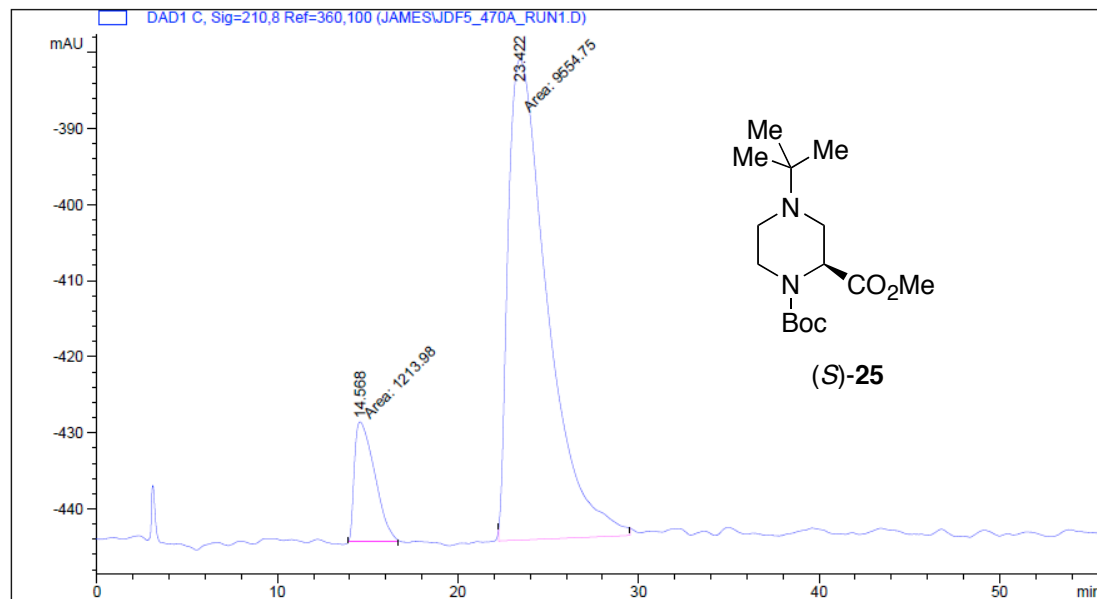
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.668	BB	0.7894	1.49061e4	287.26361	50.0736
2	18.102	BB	0.9558	1.48623e4	231.87677	49.9264

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

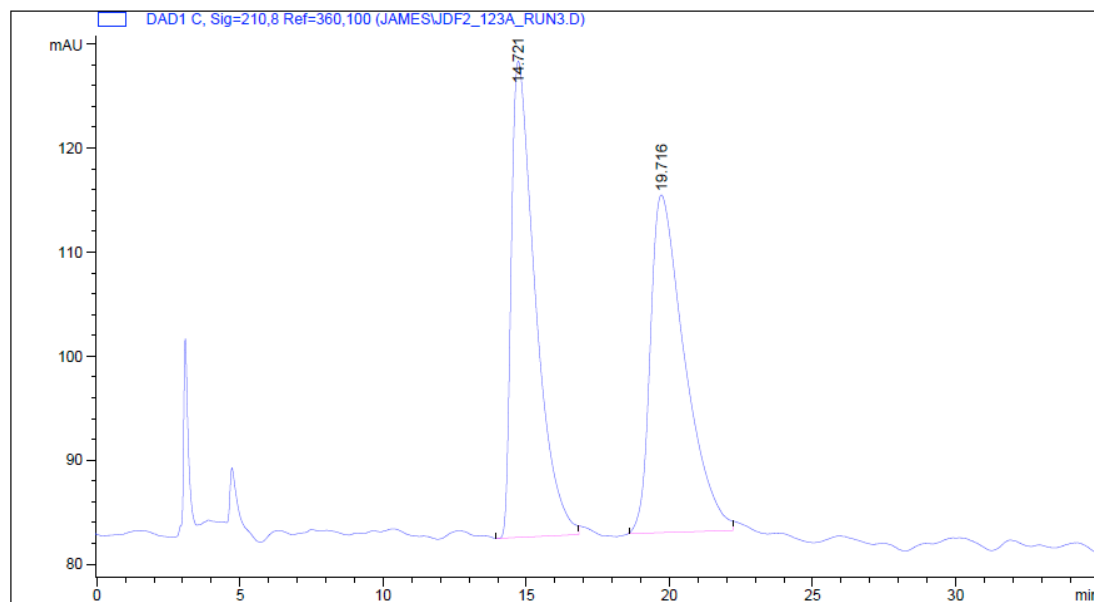
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

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

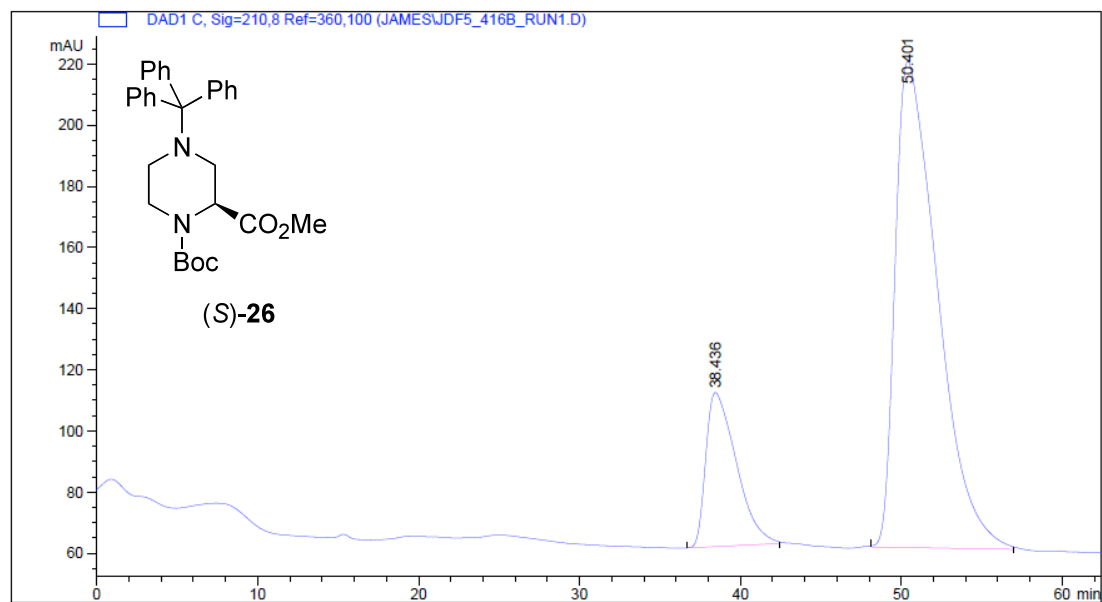
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.568	MM	1.2911	1213.98022	15.67170	11.2732
2	23.422	MM	2.5192	9554.74902	63.21385	88.7268

CSP-HPLC of *rac*-**25**

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

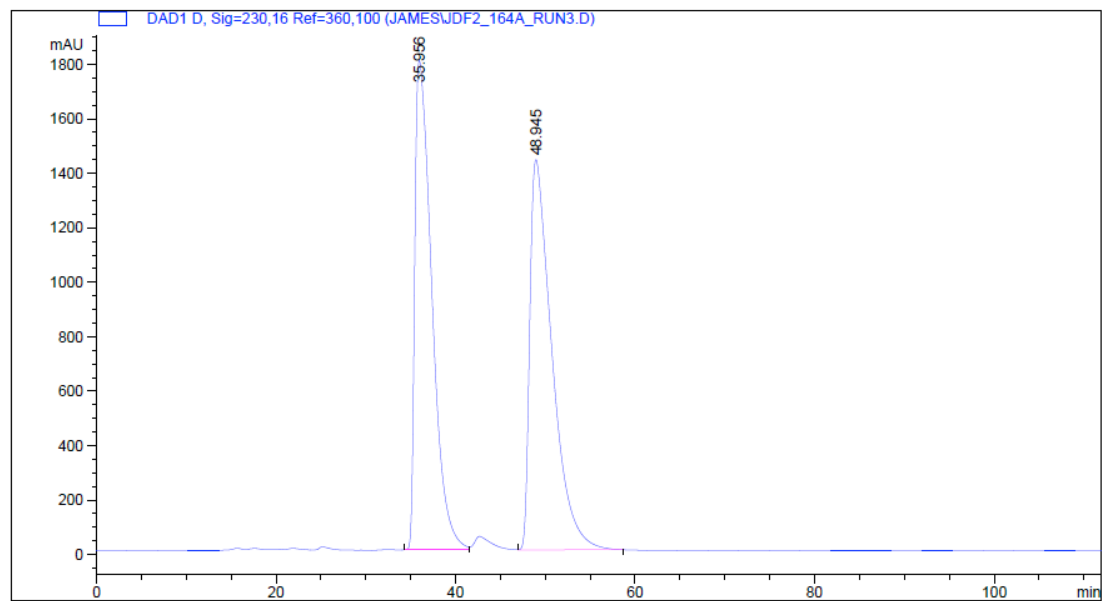
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.721	BB	0.8582	2674.99536	45.74356	49.7279
2	19.716	BB	1.2205	2704.26514	32.44119	50.2721



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

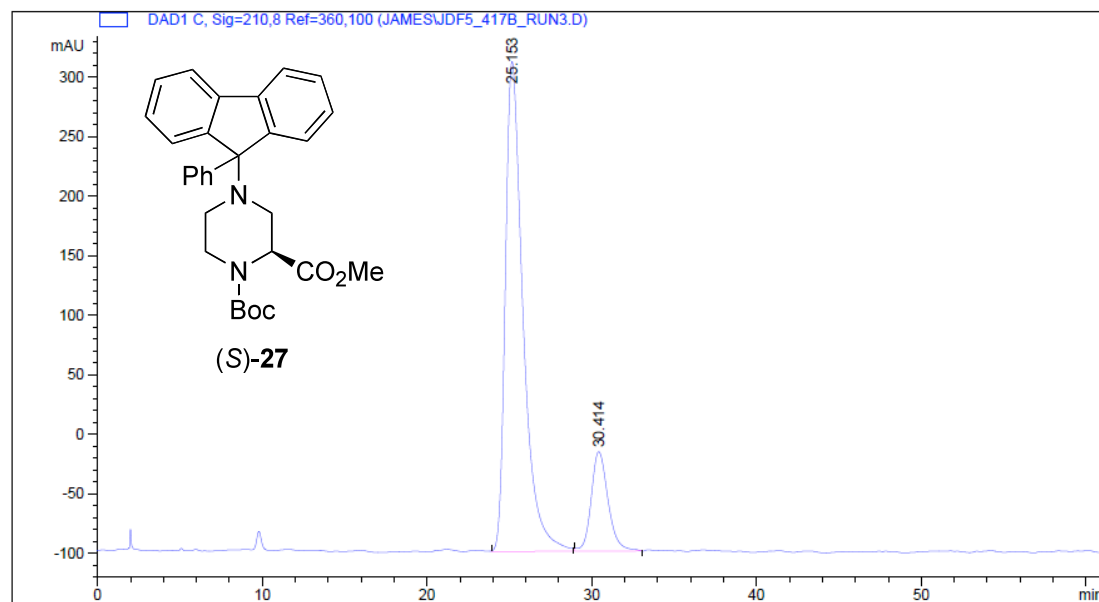
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

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**

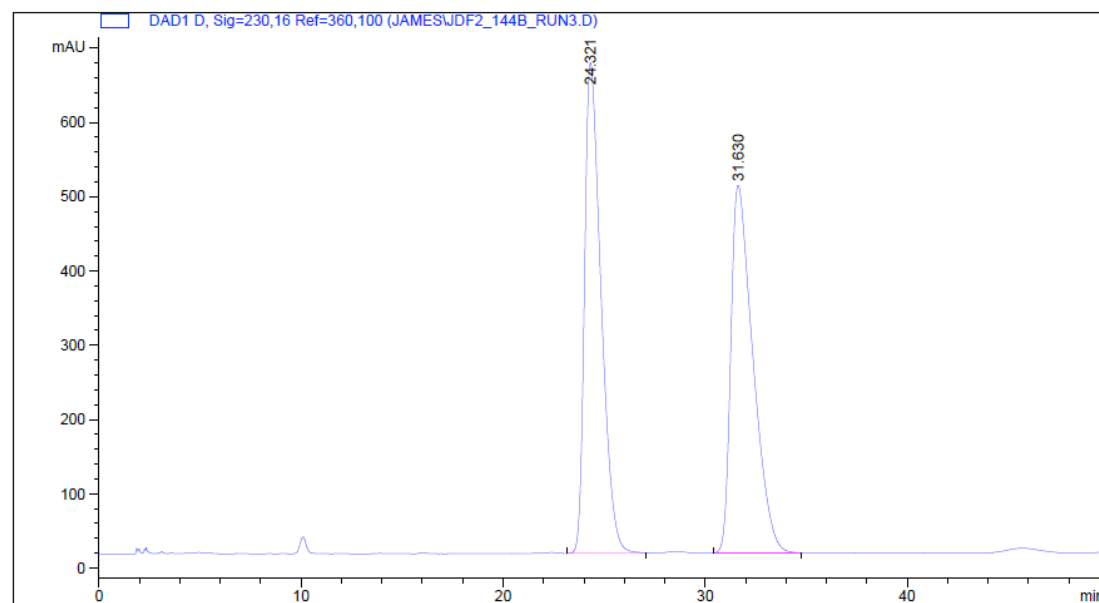
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

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

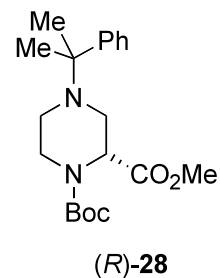
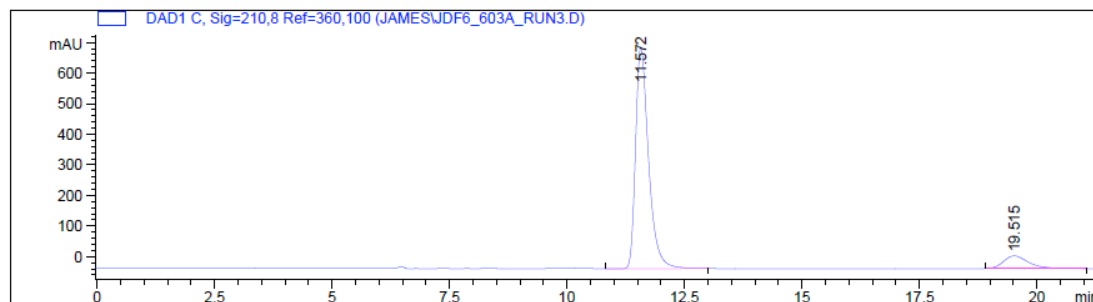
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

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**

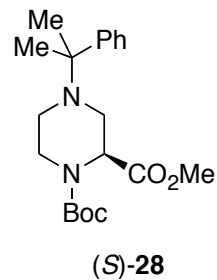
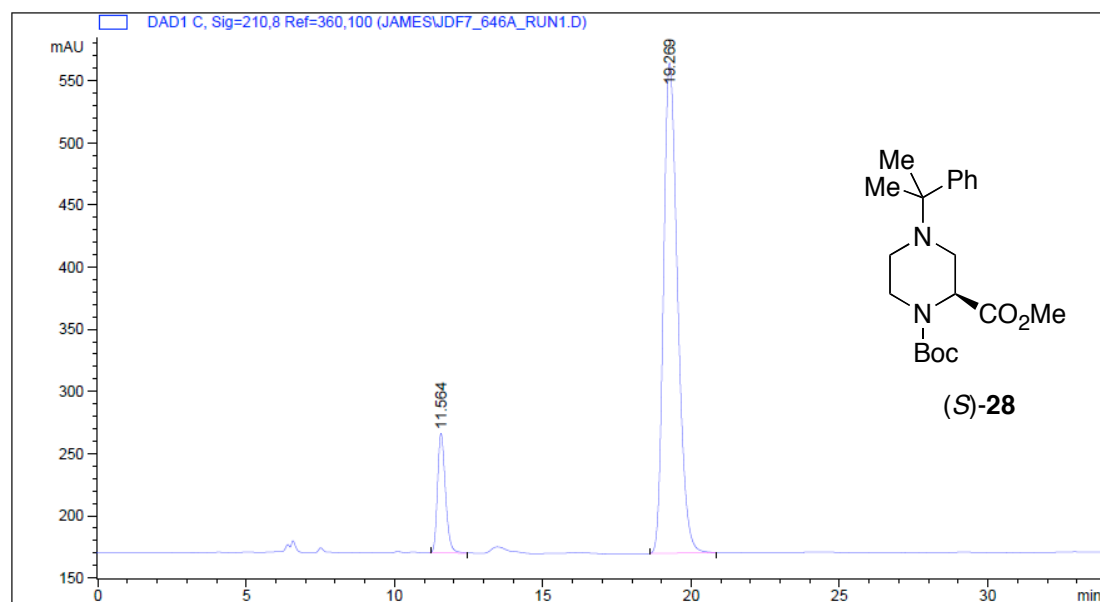
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

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 er

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

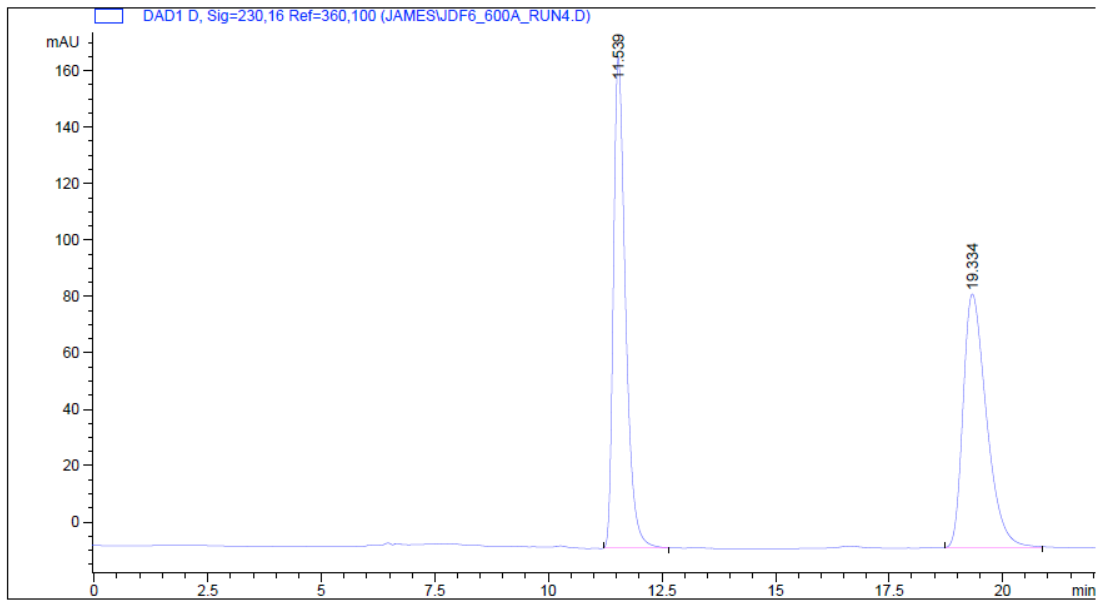
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.572	VB	0.2971	1.39530e4	723.26862	89.7759
2	19.515	BB	0.5713	1589.03577	41.82326	10.2241

CSP-HPLC of (*S*)-**28** of 88:12 er

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

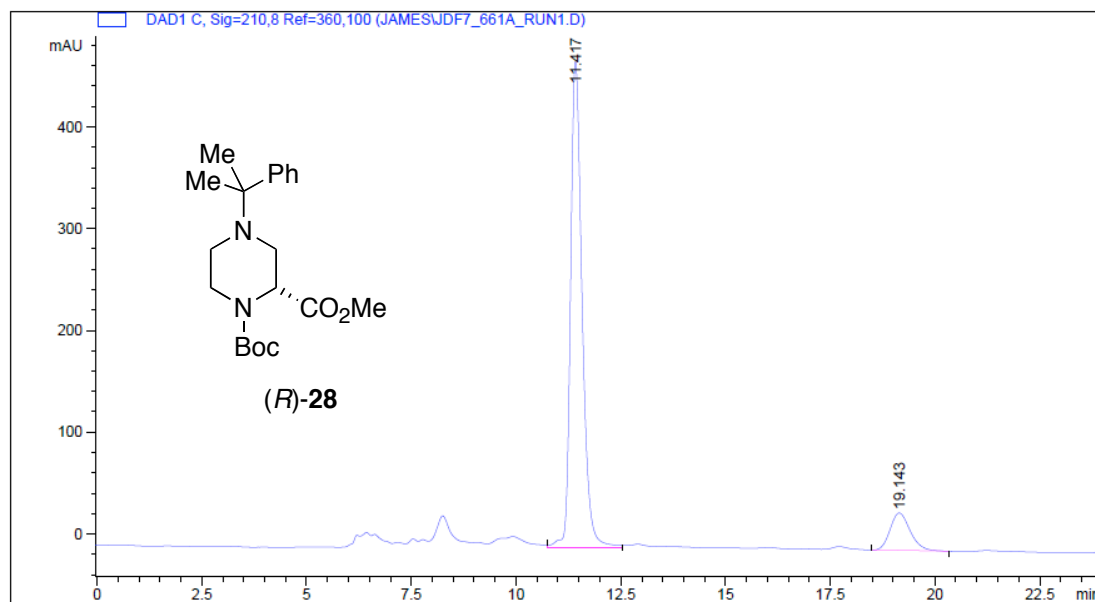
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.564	BB	0.2906	1804.91223	96.30682	12.1578
2	19.269	BB	0.5139	1.30408e4	394.27853	87.8422

CSP-HPLC of *rac*-**28**



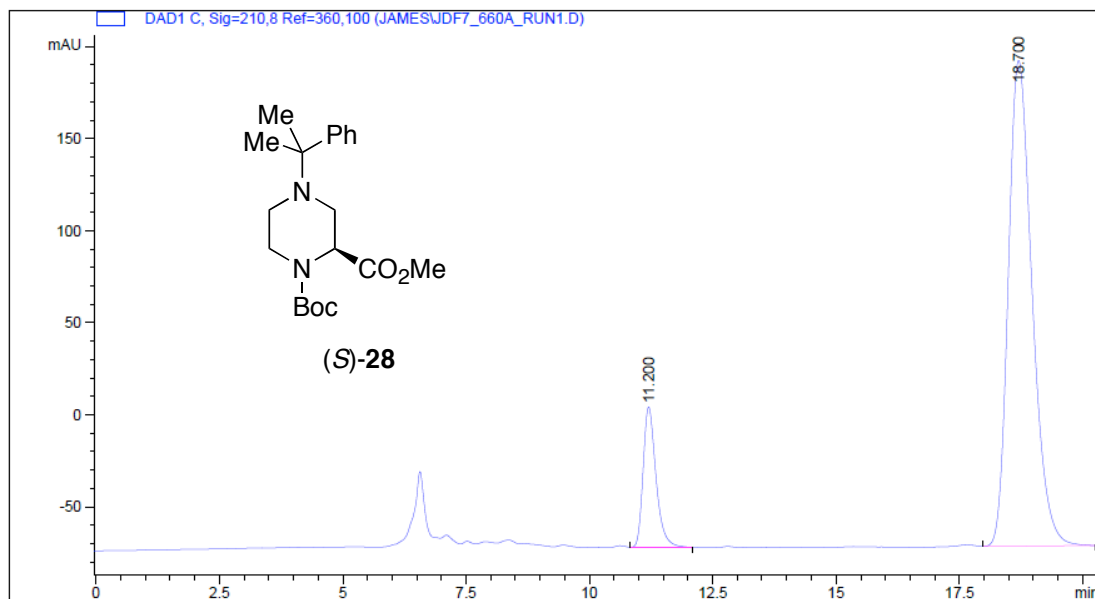
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.539	BB	0.2800	3217.17065	173.80305	49.9464
2	19.334	BB	0.5501	3224.07495	89.96127	50.0536

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

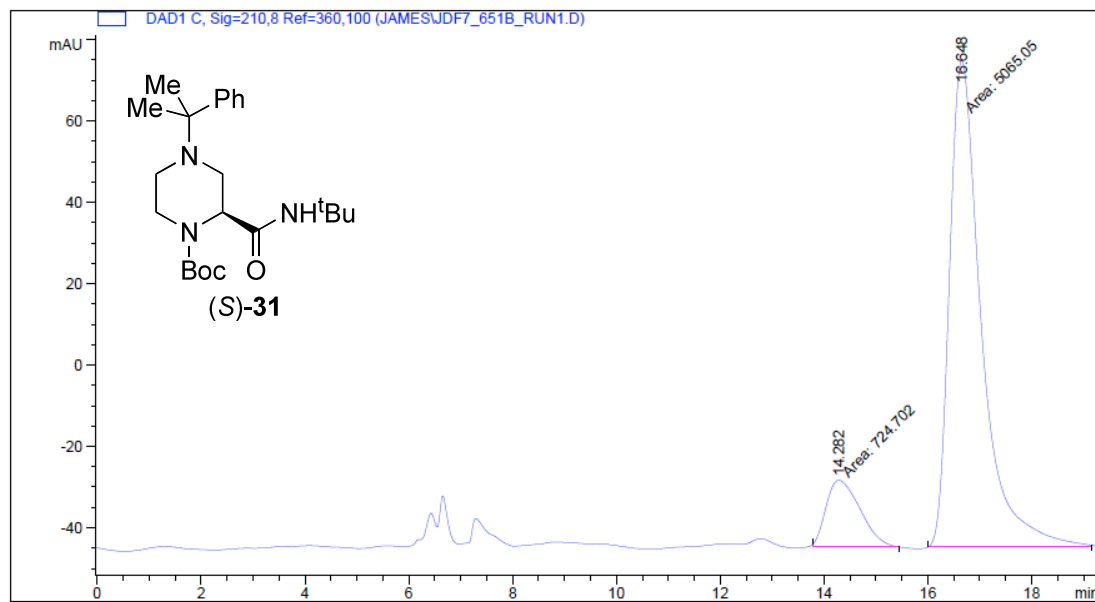
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.417	VB	0.2956	9123.80957	476.02069	88.0429
2	19.143	VB	0.5198	1239.10498	36.89610	11.9571

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

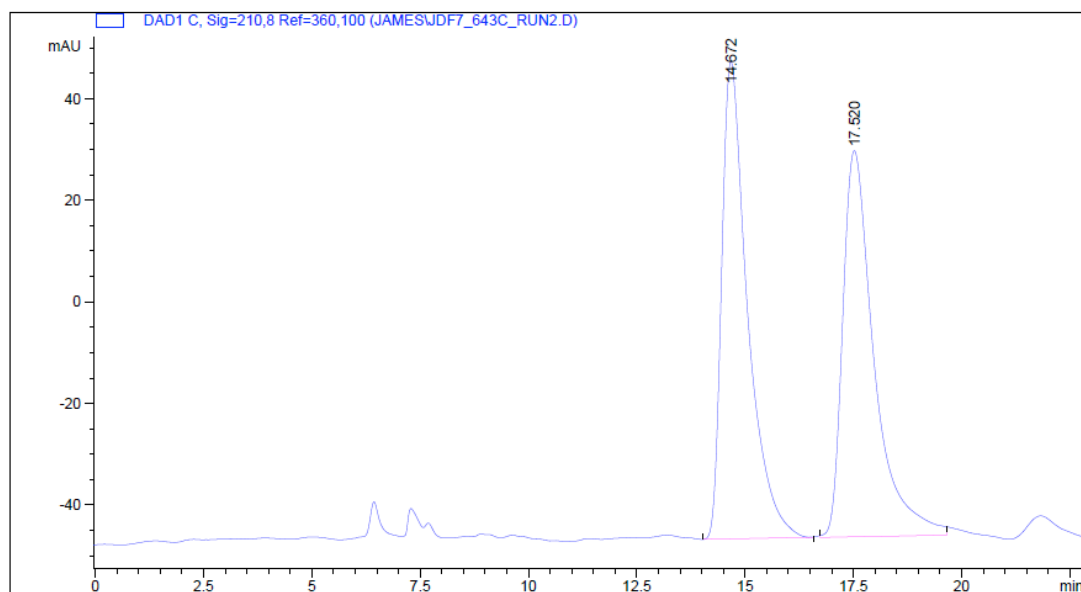
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.200	VB	0.2780	1395.74194	76.08701	13.6291
2	18.700	VB	0.5114	8845.16016	263.65994	86.3709

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

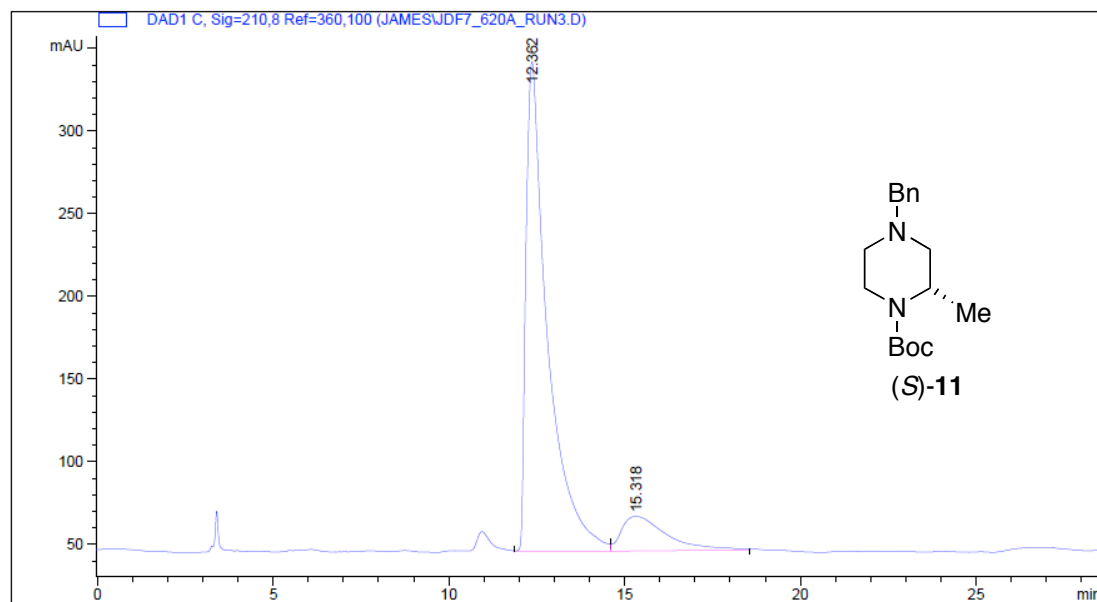
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.282	MM	0.7449	724.70245	16.21585	12.5170
2	16.648	MM	0.7067	5065.04736	119.44557	87.4830

CSP-HPLC of *rac*-**31**

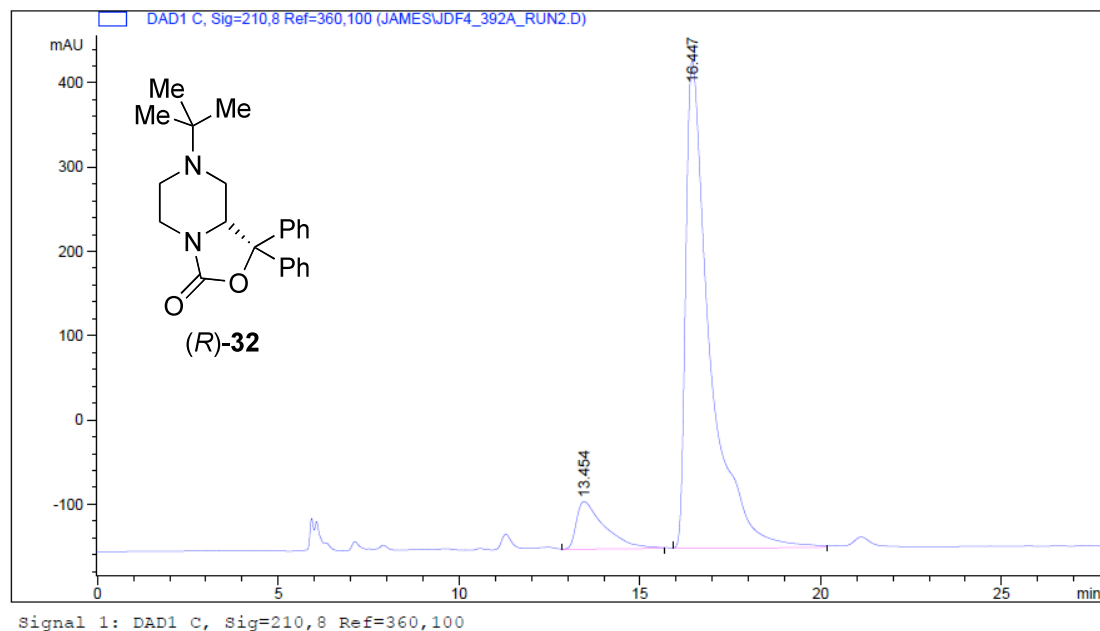
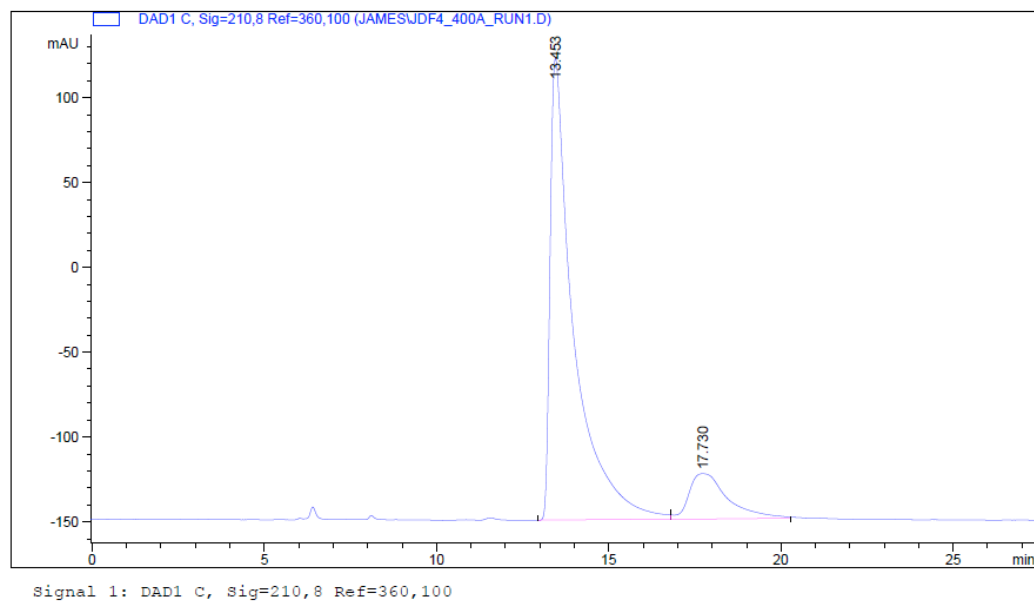
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.672	BB	0.6200	3898.10571	93.96950	50.4748
2	17.520	BB	0.7549	3824.76538	76.02827	49.5252

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

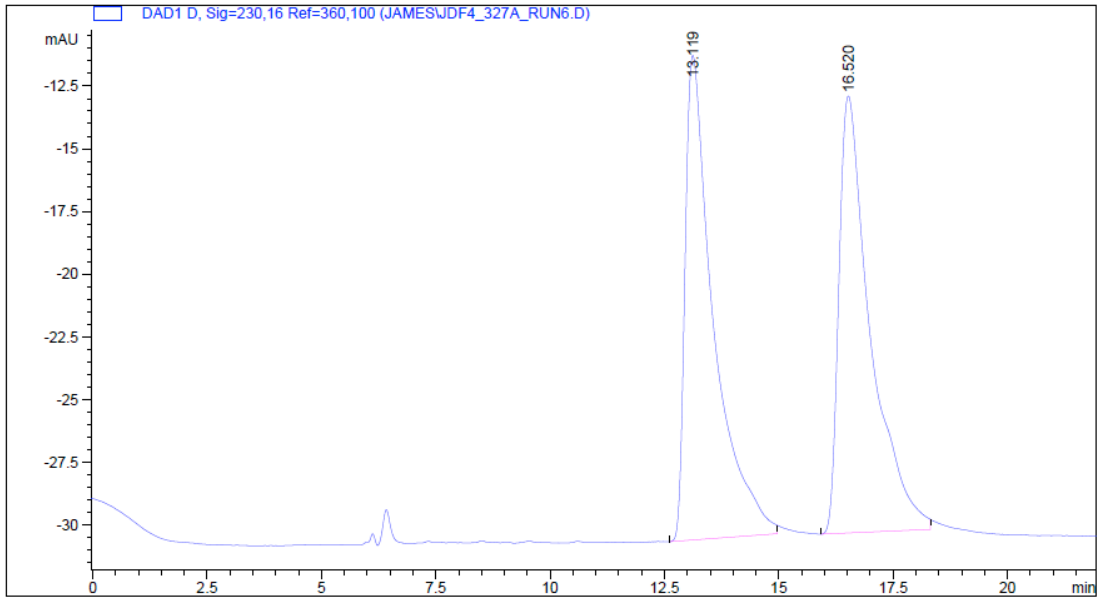
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

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

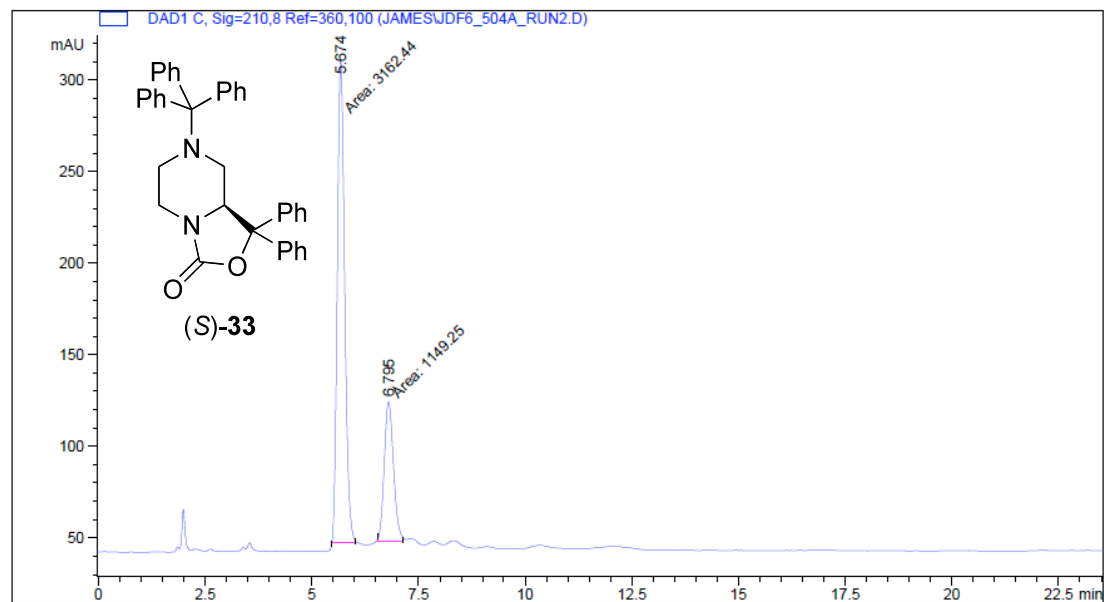


CSP-HPLC of *rac*-**32**



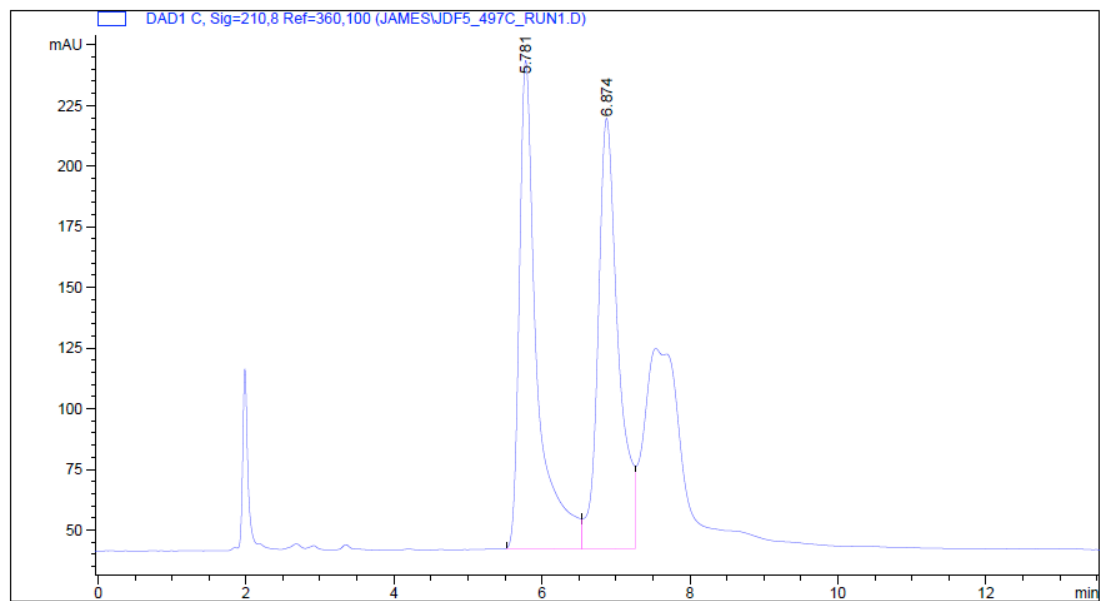
Signal 1: DAD1 D, Sig=230,16 Ref=360,100

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

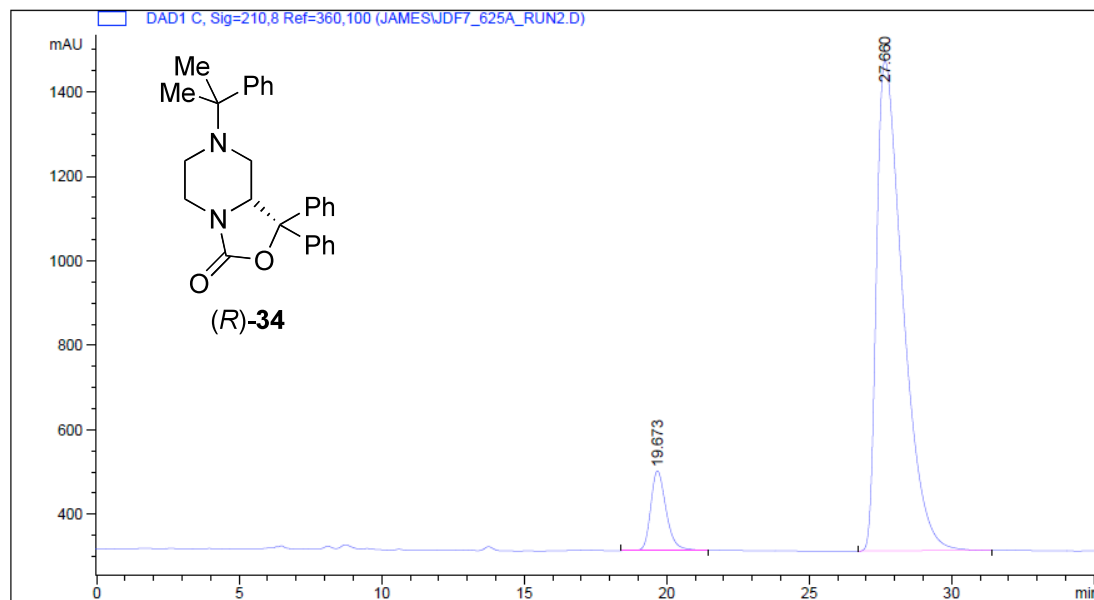
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

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**

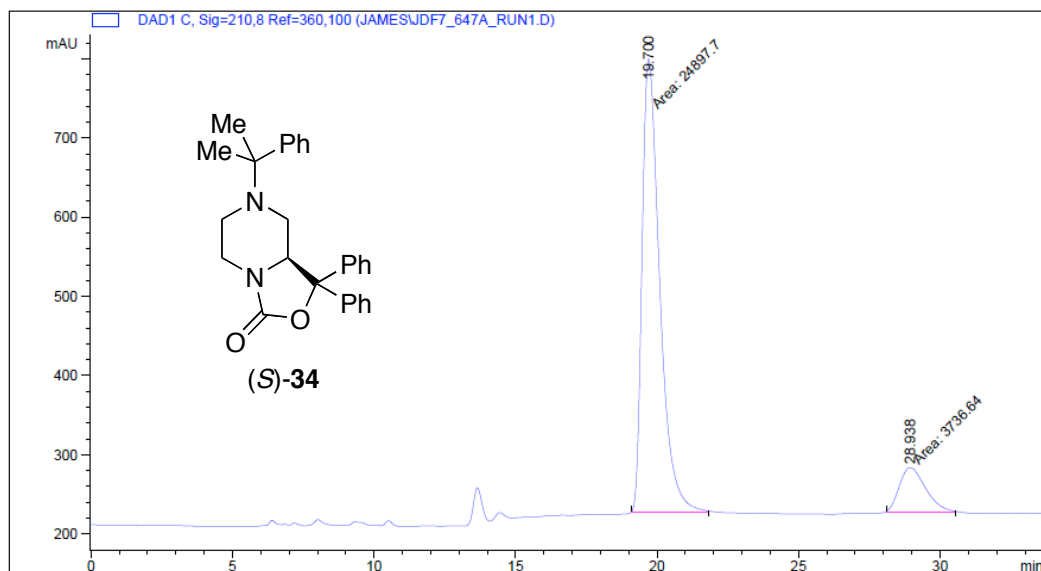
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

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

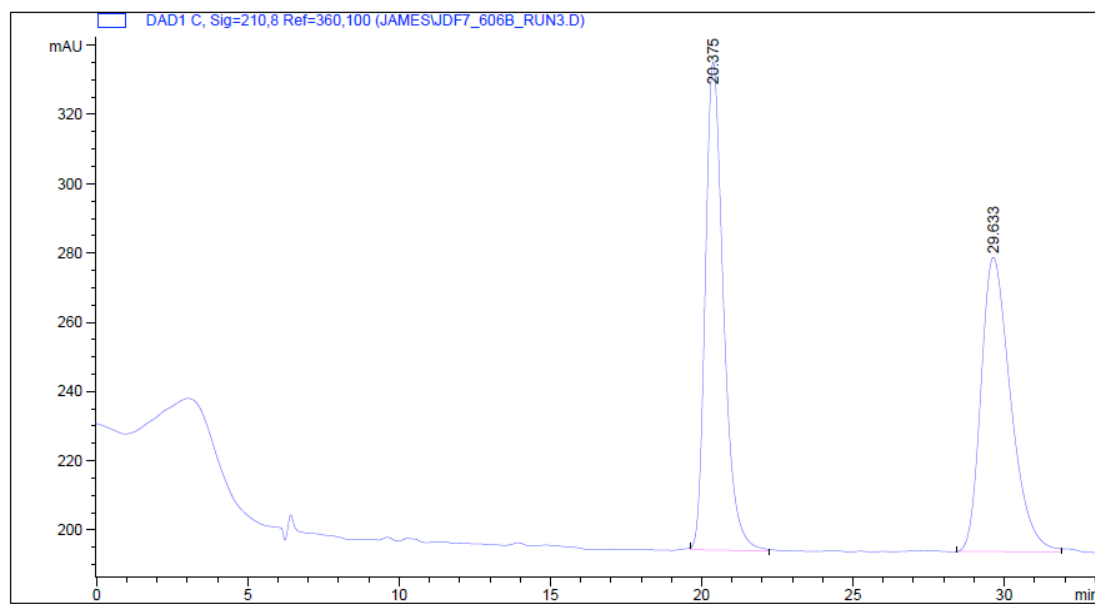
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

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

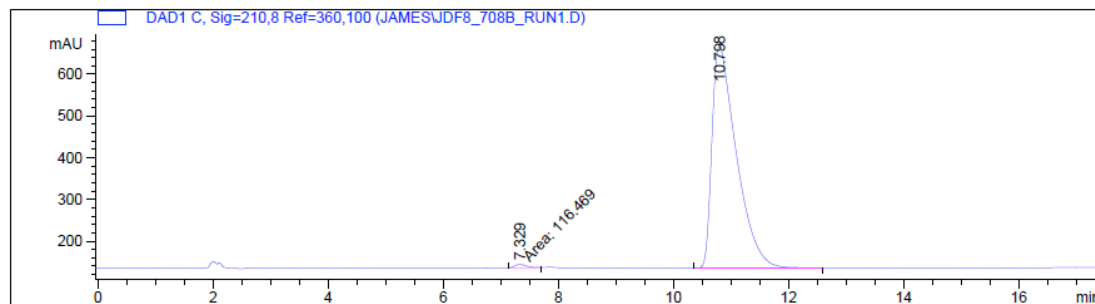
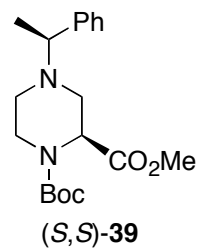
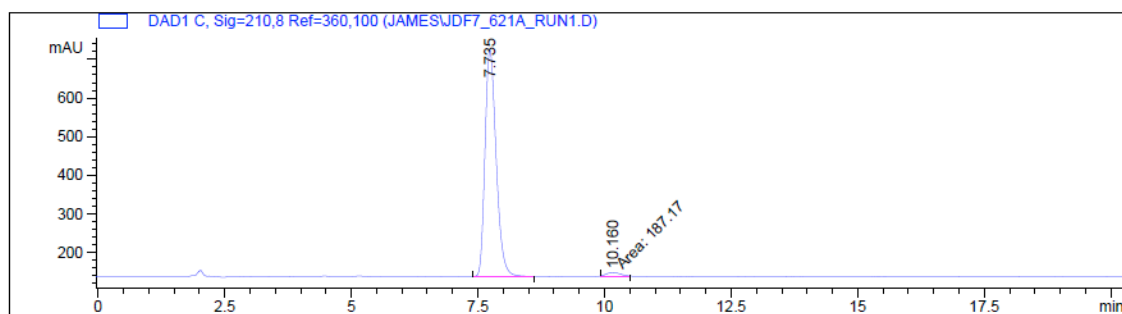
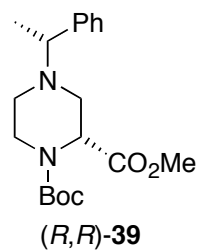
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

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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3. Mickelson, J. W.; Belonga, K. L.; Jacobsen, E. J. *J. Org. Chem.* **1995**, *60*, 4177.
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