A SYNTHETIC AND SPECTROSCOPIC INVESTIGATION OF THE ASYMMETRIC α-LITHIATION-TRAPPING OF SIX-MEMEBERED *N*-BOC HETEROCYCLES USING ALEXAKIS DIAMINES

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1. Experimental Details

1.1. General

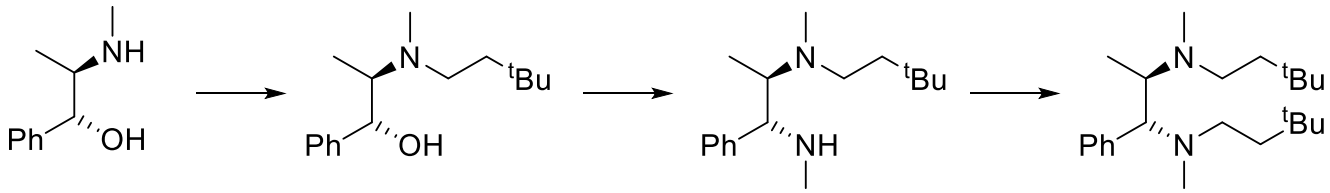
All-non aqueous reactions were carried out under oxygen free Ar or N_2 using flame-dried glassware. Et_2O and THF were freshly distilled from sodium and benzophenone. Alkyllithiums were titrated against *N*-benzylbenzamide before use. Petrol refers to the fraction of petroleum ether boiling in the range 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_{254} 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 $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Boiling points give for compounds purified by Kügelrohr distillation correspond to the oven temperature during distillation. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer or a Perkin Elmer UATR Two FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer. Optical rotations were recorded at room temperature on a Jasco DIP-370 polarimeter (using sodium D line, 589 nm) and $[\alpha]_D$ given in units of 10^{-1} deg cm^3 g^{-1}. Chiral stationary phase HPLC was performed on an Agilent 1200 series chromatograph. *In situ* ReactIR™ infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR iC10 spectrometer with a silicon-tipped (SiComp) probe.

1.2 Synthesis of Diamines and Lithiation Substrates

The following diamines and substrates were synthesised according to the reported procedures: (+)-sparteine surrogate (+)-**1**,[1] (*S*,*S*)-**2** and (*R*,*R*)-**2**,[2] *N*-Boc-*N*'-benzyl piperazine **8**,[3] *N*-Boc-*N*'-methyl piperazine **13**,[4] *N*-Boc-*N*'-*tert*-butyl piperazine **18**[5] and *N*-Boc-4-chloro piperidine **7**.[6]

(3,3-Dimethylbutyl)[(1*R*,2*R*)-1-[(3,3-dimethylbutyl)(methyl)amino]-1-phenylpropan-2-yl]methylamine (*R*,*R*)-3



(*R*,*R*)-**S1** (*R*,*R*)-**S2** (*R*,*R*)-**3**

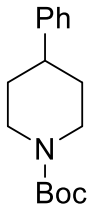
A solution of *tert*-butylacetyl chloride (4.24 mL, 30.3 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of (1*R*,2*R*)-(–)-pseudoephedrine (5.00 g, 30.3 mmol, 1.0 eq.) and Et_3N (3.06 g, 4.22 mL, 30.3 mmol, 1.0 eq.) in CH_2Cl_2 at 0 °C under Ar. The resulting mixture was allowed to warm to rt and stirred at rt for 16 h. Water (100 mL) was added and the layers separated. The aqueous was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amide (7.94 g) as a pale yellow oil. A solution of crude amide (max. 30.3 mmol, 1.0 eq.) in THF (40 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (3.45 g, 90.8 mmol, 3.0 eq.) in THF (60 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_2O (100 mL). Water (3.5 mL), 20% $NaOH_{(aq)}$ (7.0 mL) and water (3.5 mL) were sequentially added dropwise and the mixture stirred for 15 min. Then, anhydrous $MgSO_4$ was added and the mixture stirred for 1 h. The solids were removed by filtration through Celite and washed with Et_2O (150 mL). The filtrate was concentrated under reduced pressure to give the crude amine (*R*,*R*)-**S1** (7.65 g, quant.) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H, Ph), 5.24 (br s, 1H, OH), 4.20 (d, *J* = 9.5 Hz, 1H, C*H*OH), 2.63 (dq, *J* = 9.5, 7.0 Hz, 1H, C*H*N), 2.54 (ddd, *J* = 11.0, 5.5, 5.5 Hz, 1H, NCH_2), 2.36 (ddd, *J* = 11.0, 5.5, 5.5 Hz, 1H, NCH_2), 2.25 (s, 3H, NMe), 1.45 (qdd, *J* = 13.0, 11.0, 5.5 Hz, 2H, CH_2), 0.93 (s, 9H, CMe_3), 0.74 (d, *J* = 7.0 Hz, 3H, CH*Me*). Spectroscopic data consistent with those reported in the literature.[7] The crude product was used in the next step without further purification.

Methanesulfonyl chloride (4.16 g, 2.81 mL, 36.3 mmol, 1.2 eq.) was added dropwise to a solution of crude amine (*R*,*R*)-**S1** (max. 30.3 mmol, 1.0 eq.) and Et_3N (5.21 g, 7.17 mL, 51.4 mmol, 1.7 eq.) in Et_2O (150 mL) at 0 °C under Ar. The resulting solution was stirred for 30 min at 0 °C then Et_3N (6.12 g, 8.44 mL, 60.5 mmol, 2.0 eq.) was added. The resulting solution was allowed to warm to rt then dimethylamine (64.3 mL of a 8 M solution in EtOH, 514 mmol, 17.0 eq.) was added. The resulting solution was stirred at rt for 40 h. Then, the volatiles were removed under reduced pressure and water (200 mL) was added to the residue. 20% $NaOH_{(aq)}$ (50 mL) was added and the aqueous layer extracted with Et_2O (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude diamine (*R*,*R*)-**S2** (7.4 g, 93%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H, Ph), 3.18 (d, *J* = 10.0 Hz, 1H, CHPh), 2.94 (br s, 1H, NH), 2.73 (dq, *J* = 10.0, 6.5 Hz, 1H, C*H*Me), 2.46 (ddd, *J* = 11.5, 5.0, 5.0 Hz, 1H, NCH_2), 2.30 (ddd, *J* = 11.5, 5.0, 5.0 Hz, 1H, NCH_2), 2.20 (s, 3H, NMe), 2.19 (s, 3H, NMe), 1.48 (ddd, *J* = 13.0, 11.5, 5.0 Hz, 1H, CH_2), 1.35 (ddd, *J* = 13.0, 11.5, 5.0 Hz, 1H, CH_2), 0.92 (s, 9H, CMe_3), 0.59 (d, *J* = 6.5 Hz, 3H, CH*Me*). Spectroscopic data consistent with those reported in the literature.[7] The crude product was used in the next step without further purification.

A solution of *tert*-butylacetyl chloride (2.56 g, 2.67 mL, 19.1 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of crude amine (*R*,*R*)-**S2** (max. 19.1 mmol, 1.0 eq) and Et_3N (1.93 g, 2.66 mL, 19.1 mmol, 1.0 eq.) in CH_2Cl_2 at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Water (50 mL) and 20% $NaOH_{(aq)}$ (50 mL) were added and the layers separated. The aqueous was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amide (6.36 g, 93%) as a white solid. A solution of crude amide (max. 17.6 mmol, 1.0 eq.) in THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (2.01 g, 52.9 mmol, 3.0 eq.) in THF (80 mL) at 0 °C under Ar. The resulting suspension 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_2O (100 mL). Water (2 mL), 20% $NaOH_{(aq)}$ (4 mL) and water (2 mL) were sequentially added dropwise and the mixture stirred for 15 min. Then, anhydrous $MgSO_4$ was added and the mixture stirred for 1 h. The solids were removed by filtration through Celite and washed with Et_2O (150 mL). The filtrate was concentrated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diamine (*R*,*R*)-**3** (5.94 g, 97%) as a colourless oil that solidified upon standing, mp 42-44 °C (lit.,[7] 35 °C); bp 142 °C at 1.0 mmHg (lit.,[7] 155 °C at 0.4 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H, Ph), 7.27-7.22 (m, 1H, Ph), 7.16-7.14 (m, 2H, Ph), 3.60 (d, *J* = 10.0 Hz, 1H, CHPh), 3.36 (dq, *J* = 10.0, 6.5 Hz, 1H, C*H*Me), 2.57-2.41 (m, 2H, NCH_2), 2.31 (ddd, *J* = 12.0, 4.5, 4.5 Hz, 1H, NCH_2), 2.28 (s, 3H, NMe), 2.16 (s, 3H, NMe), 2.11 (ddd,

J = 12.0, 4.5, 4.5 Hz, 1H, NCH_2), 1.57-1.35 (m, 4H, CH_2), 0.92 (s, 9H, CMe_3), 0.85 (s, 9H, CMe_3), 0.64 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.2 (*ipso*-Ph), 129.4 (Ph), 127.6 (Ph), 126.7 (Ph), 69.5 (Ph*C*H), 56.0 (Me*C*H), 50.1 (NCH_2), 50.0 (NCH_2), 41.9 (NCH_2), 41.1 (NCH_2), 37.9 (NMe), 36.6 (NMe), 29.8 (*C*Me_3), 29.7 (C*Me*$_3$), 29.6 (C*Me*$_3$), 10.2 (*Me*CH) (one *C*Me3 not resolved); $[\alpha]_D$ − 39.4 (*c* 1.0 in $CHCl_3$) (lit.,[7] $[\alpha]_D$ +36.2 (*c* 0.97 in $CHCl_3$) for (*S*,*S*)-**3** of >99:1 er). Spectroscopic data consistent with those reported in the literature.[7]

***tert*-Butyl 4-phenylpiperidine-1-carboxylate 6**



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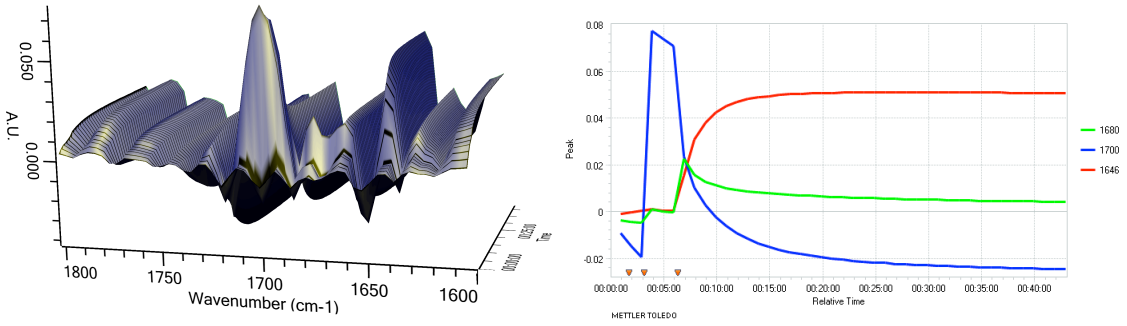
A solution of di-*tert*-butyl dicarbonate (3.0 g, 13.6 mmol, 1.1 eq.) in CH_2Cl_2 (20 mL) was added dropwise a stirred solution of 4-phenyl piperidine (2.0 g, 12.4 mmol, 1.0 eq.) in CH_2Cl_2 (80 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (100 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1-4:1 petrol-EtOAc as eluent gave *N*-Boc piperidine **6** (3.2 g, 99%) as a pale yellow oil, R_F (9:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 2H, Ph), 7.23-7.19 (m, 3H, Ph), 4.29-4.20 (m, 2H, NCH), 2.80 (td, *J* = 13.0, 2.5 Hz, 2H, NCH), 2.64 (tt, *J* = 12.0, 3.5 Hz, 1H, C*H*Ph), 1.88-1.77 (m, 2H, CH), 1.64 (td, *J* = 12.5, 4.0 Hz, 2H, CH), 1.49 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.9 (C=O), 145.8 (*ipso*-Ph), 128.5 (Ph), 126.8 (Ph), 126.3 (Ph), 79.4 (*C*Me_3), 44.5 (NCH_2), 42.8 (*C*HPh), 33.3 (NCH_2CH_2), 28.6 (C*Me*$_3$). Spectroscopic data consistent with those reported in the literature.[8]

1.3 ReactIR™ monitoring

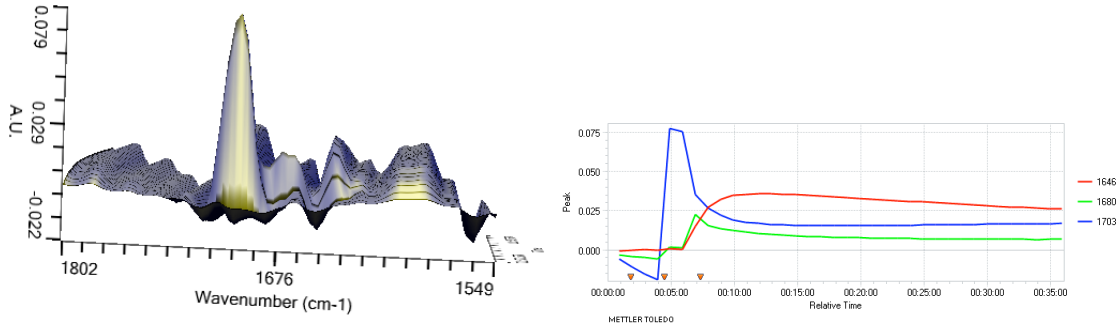
ReactIR™ monitoring of the (*S*,*S*)-2 mediated lithiation of *N*-Boc-*N′* -benzyl piperazine 8



Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of (*S*,*S*)-**2** (403 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc-*N′* -benzyl piperazine **8** (276 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 35 min.

For *N*-Boc-*N′* -benzyl piperazine **8**, a peak at 1700 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **9**. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **10**. After a lithiation time of 30 min, complete lithiation of *N*-Boc-*N′* -benzyl piperazine **8** to give the lithiated intermediate **10** was observed.

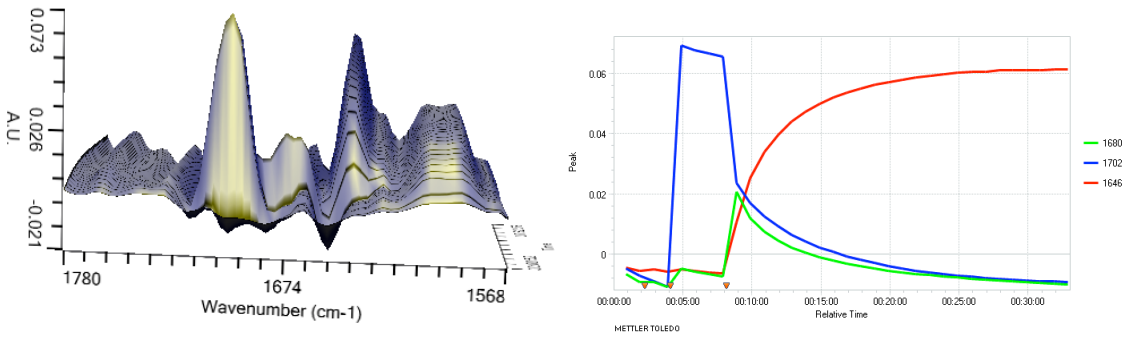
ReactIR™ monitoring of the (*S*,*S*)-2 mediated lithiation of *N*-Boc-*N′* -methyl piperazine 13



Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of (*S*,*S*)-**2** (403 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc-*N′* -methyl piperazine **13** (200 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 30 min.

For *N*-Boc-*N′* -methyl piperazine **13**, a peak at 1703 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **14**. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **15**. After a lithiation time of 10 min, incomplete lithiation of *N*-Boc-*N′* -methyl piperazine **13** to give the lithiated intermediate **15** was observed.

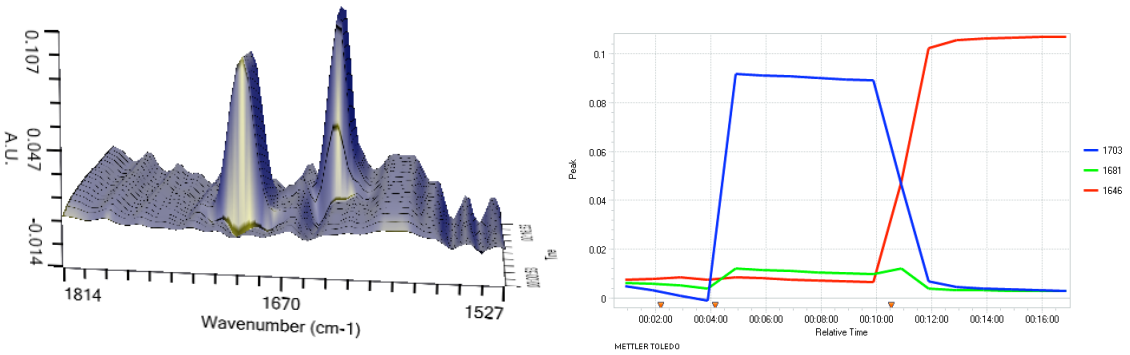
ReactIR™ monitoring of the (*R*,*R*)-3 mediated lithiation of *N*-Boc-*N′* -methyl piperazine 13



Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of (*R*,*R*)-**3** (450 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc-*N′* -methyl piperazine **13** (200 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 30 min.

For *N*-Boc-*N′* -methyl piperazine **13**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **14**. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **15**. After a lithiation time of 30 min, complete lithiation of *N*-Boc-*N′* -methyl piperazine **13** to give the lithiated intermediate **15** was observed.

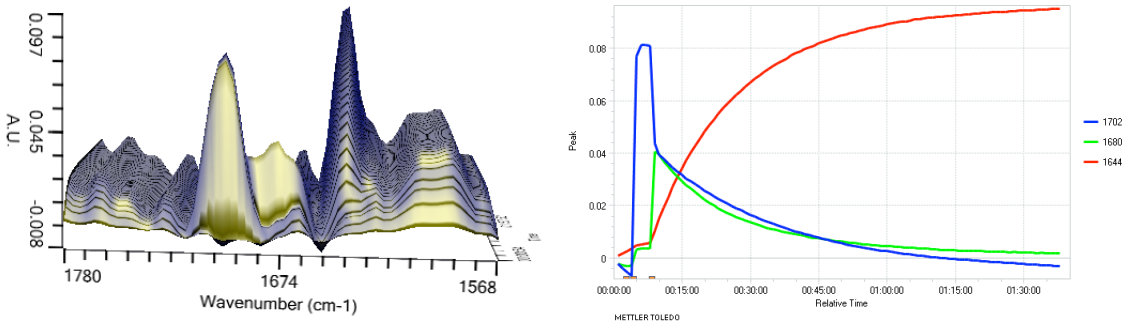
ReactIR™ monitoring of the (+)-1 mediated lithiation of *N*-Boc-*N′* -methyl piperazine 13



Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of (+)-sparteine surrogate (+)-**1** (252 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc-*N′* -methyl piperazine **13** (200 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 7 min.

For *N*-Boc-*N′* -methyl piperazine **13**, a peak at 1703 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **14**. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **15**. After a lithiation time of 4 min, complete lithiation of *N*-Boc-*N′* -methyl piperazine **13** to give the lithiated intermediate **15** was observed.

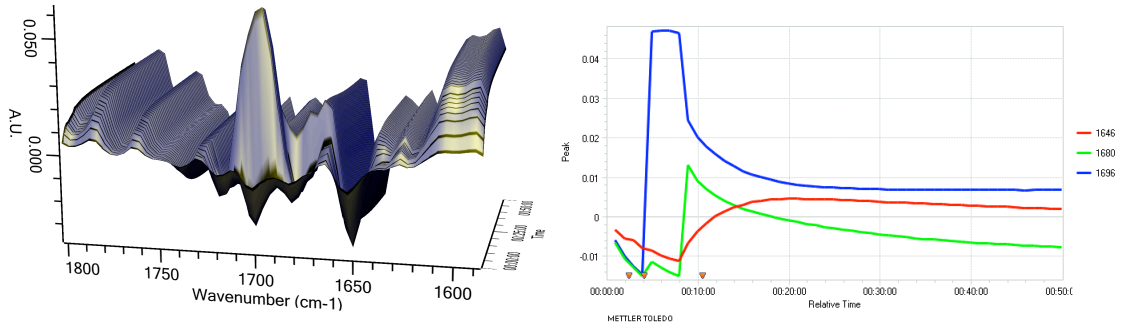
ReactIR™ monitoring of the (–)-sparteine mediated lithiation of *N*-Boc-*N′* -methyl piperazine 13



Et_2O (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, (–)-sparteine (299 μL, 1.3 mmol, 1.3 eq.) was added followed by a solution of *N*-Boc-*N′* -methyl piperazine **13** (200 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 90 min.

For *N*-Boc-*N′* -methyl piperazine **13**, a peak at 1702 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex **14**. A new peak at 1644 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate **15**. After a lithiation time of 90 min, complete lithiation of *N*-Boc-*N′* -methyl piperazine **13** to give the lithiated intermediate **15** was observed.

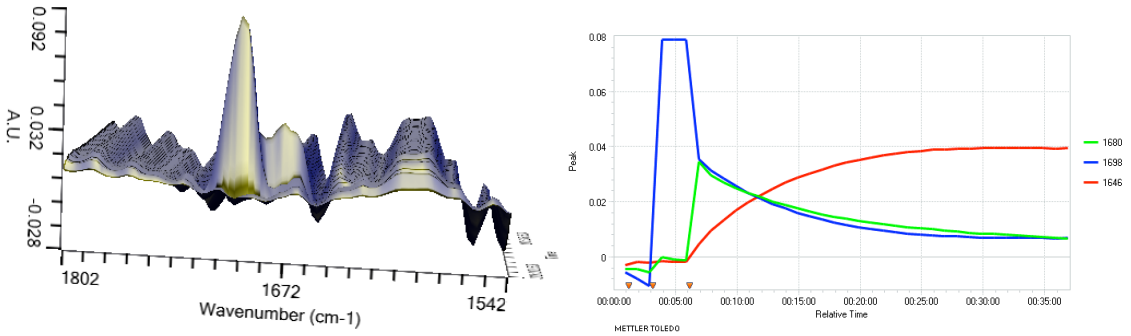
ReactIR™ monitoring of the (*S*,*S*)-2 mediated lithiation of *N*-Boc-*N′* -*tert*-butyl piperazine 18



Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of (*S*,*S*)-**2** (403 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc-*N′* -*tert*-butyl piperazine **18** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 45 min.

For *N*-Boc-*N′* -*tert*-butyl piperazine **18**, a peak at 1696 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 15 min, incomplete lithiation of *N*-Boc-*N′* -*tert*-butyl piperazine **18** to give the lithiated intermediate was observed.

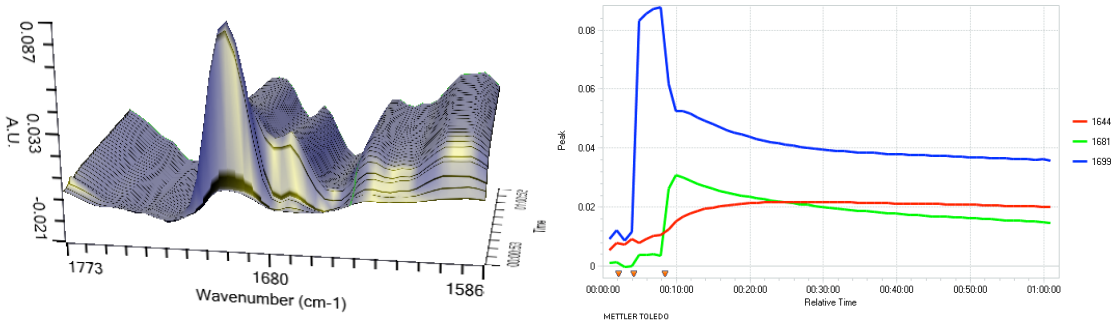
ReactIR™ monitoring of the (*R*,*R*)-3 mediated lithiation of *N*-Boc-*N′* -*tert*-butyl piperazine 18



Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of (*R*,*R*)-**3** (450 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc-*N′* -*tert*-butyl piperazine **18** (242 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 30 min.

For *N*-Boc-*N′* -*tert*-butyl piperazine **18**, a peak at 1698 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1680 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1646 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 30 min, complete lithiation of *N*-Boc-*N′* -*tert*-butyl piperazine **18** to give the lithiated intermediate was observed.

ReactIR™ monitoring of the (*S*,*S*)-2 mediated lithiation of *N*-Boc-4-phenyl piperidine 6

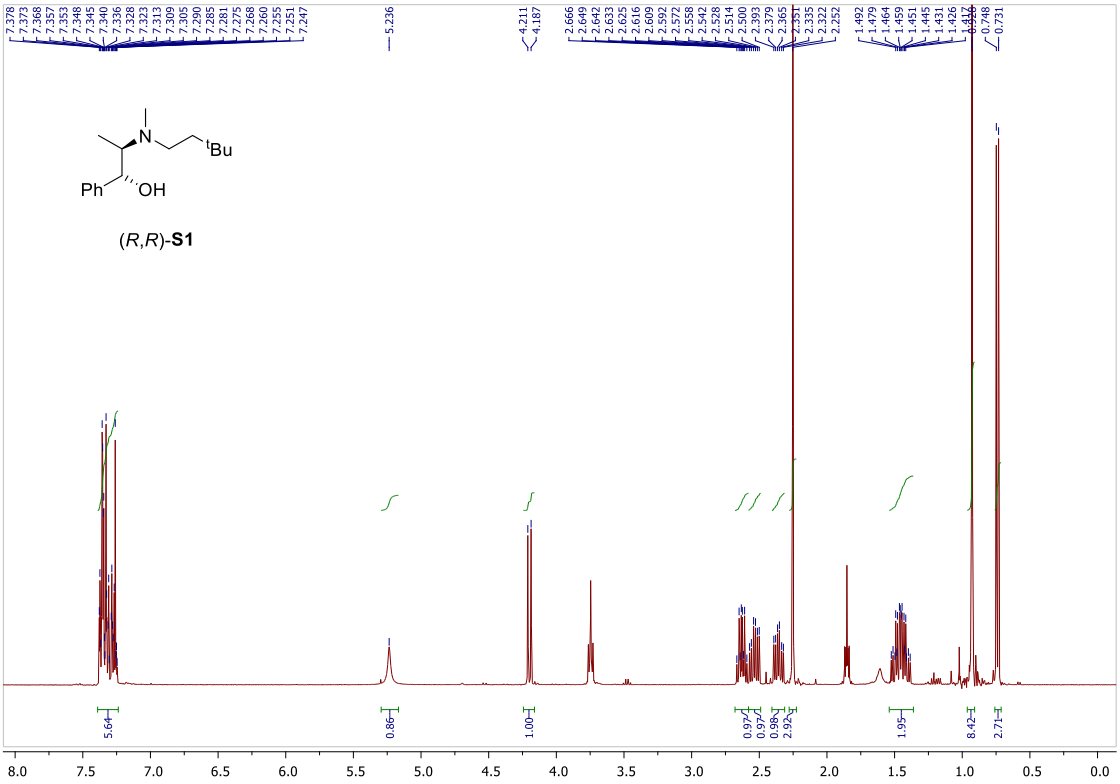


Et_2O (10 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at rt under Ar. After cooling to –78 °C, a solution of (*S*,*S*)-**2** (403 mg, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) was added followed by a solution of *N*-Boc-4-phenyl piperidine **6** (261 mg, 1.0 mmol, 1.0 eq.) in Et_2O (2 mL). The solution was stirred for 5 min (to verify the stability of readout on ReactIR™). Then, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise. The solution was stirred at –78 °C for 55 min.

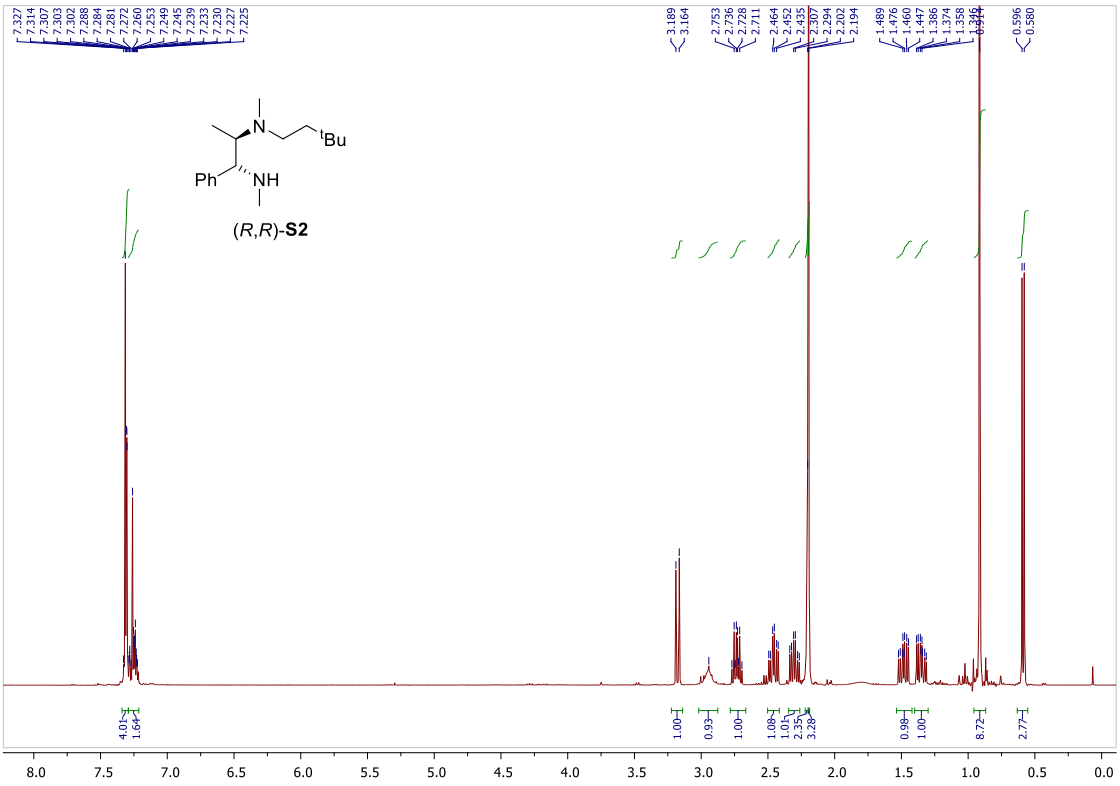
For *N*-Boc-*N′ -tert*-butyl piperazine **6**, a peak at 1699 cm^{-1} was observed and assigned to $\nu_{C=O}$. After addition of *s*-BuLi, a new peak at 1681 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the pre-lithiation complex. A new peak at 1644 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate. After a lithiation time of 20 min, incomplete lithiation of *N*-Boc-4-phenyl piperidine **6** to give the lithiated intermediate was observed.

2. ^{1}H and ^{13}C NMR Spectra

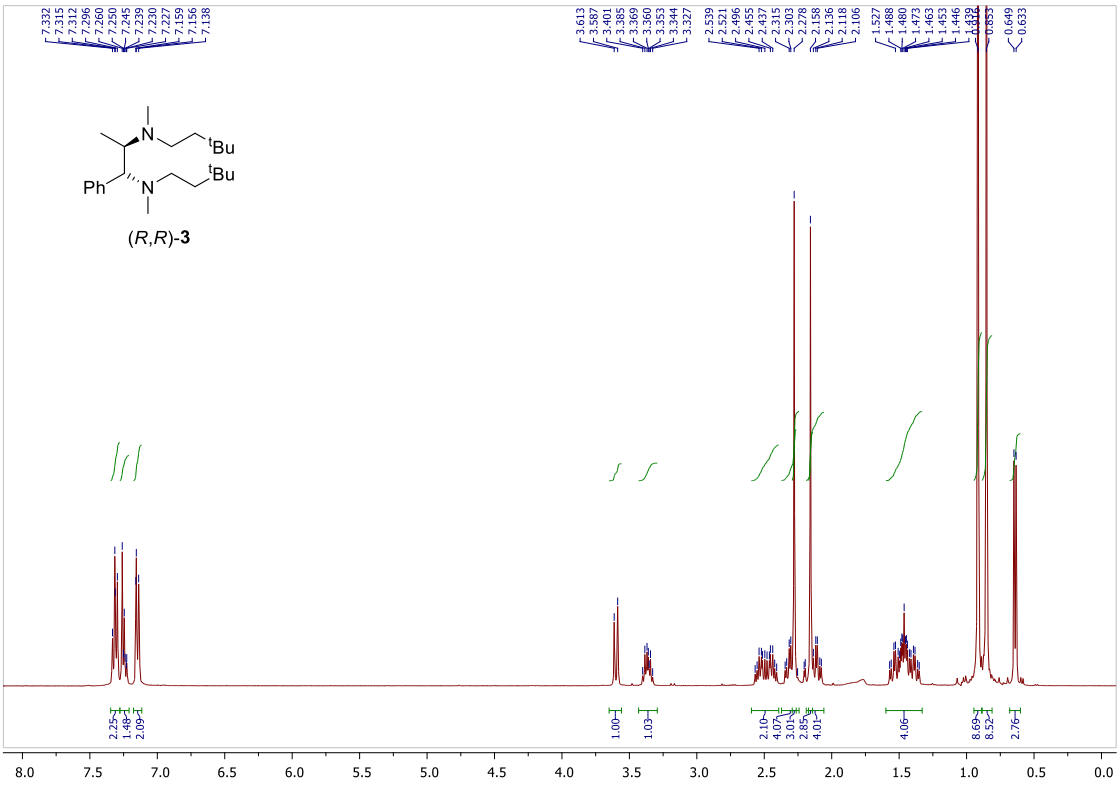
400 MHz ^{1}H NMR spectrum; $CDCl_3$

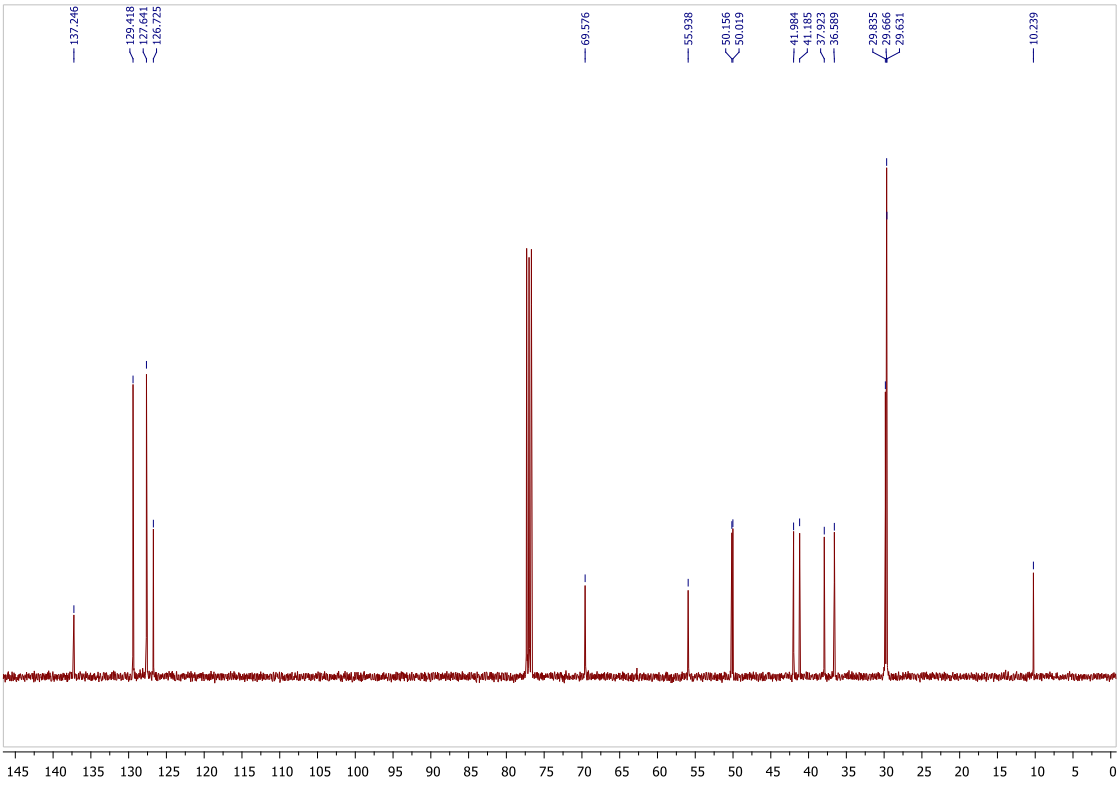


400 MHz ^{1}H NMR spectrum; $CDCl_3$

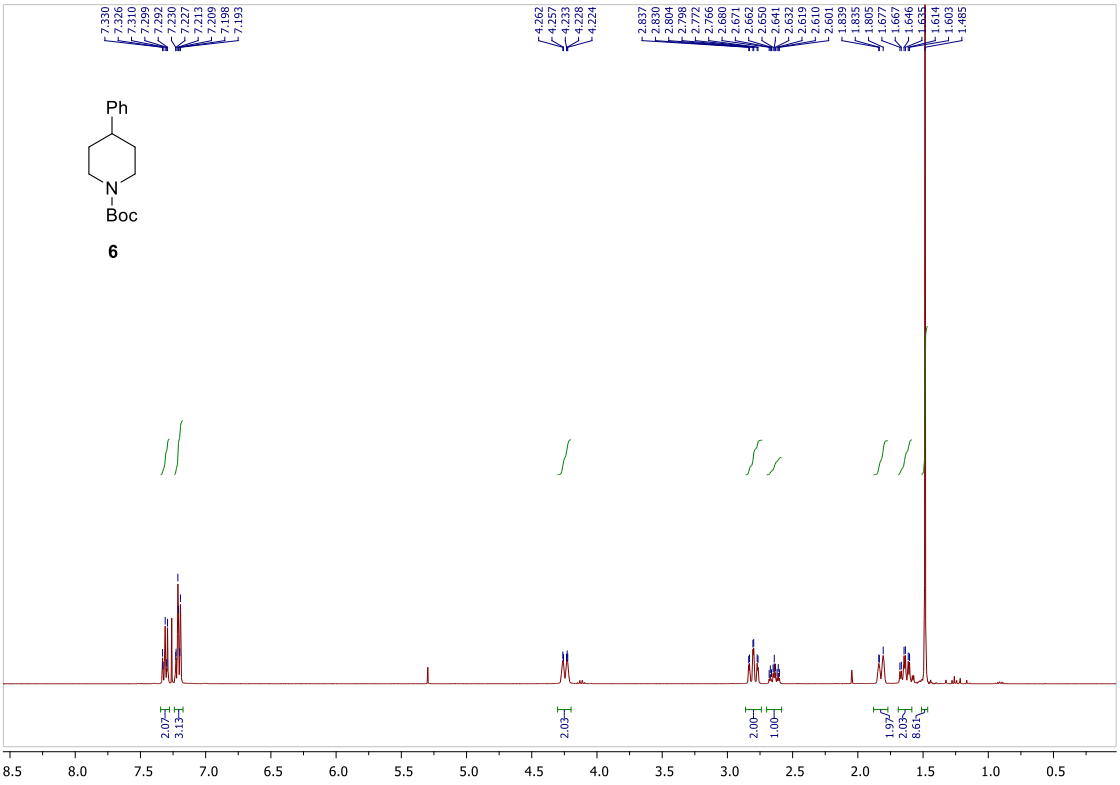


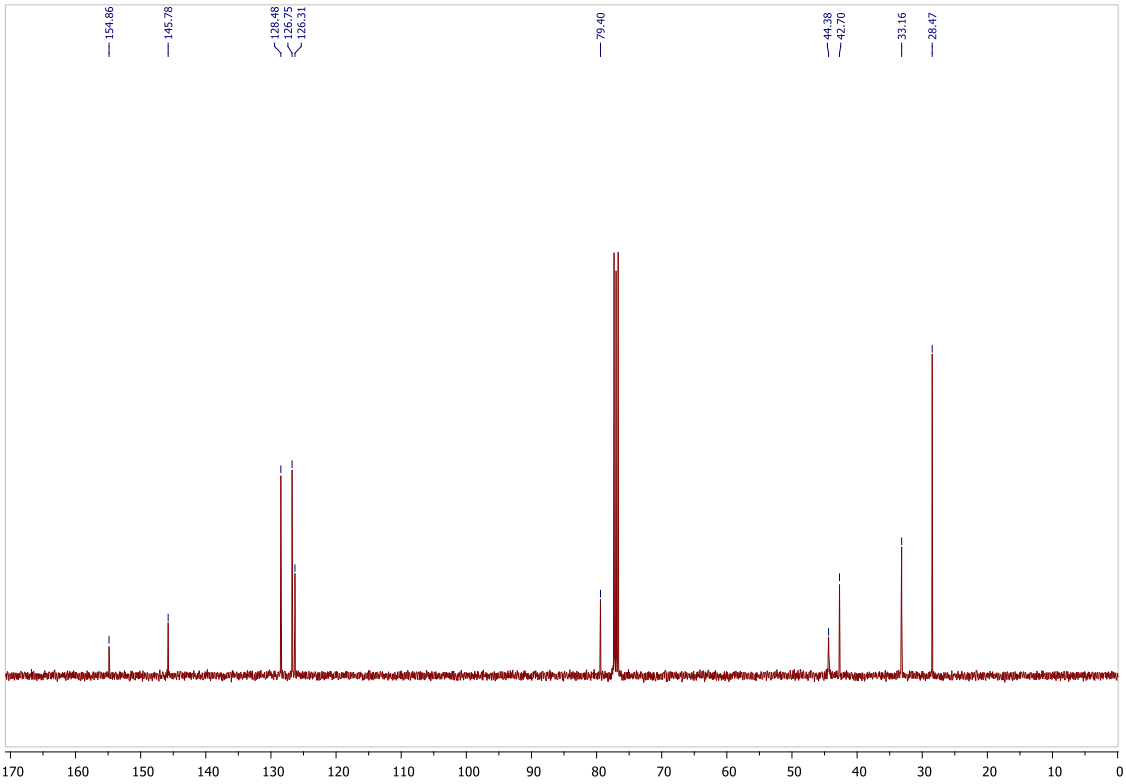
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



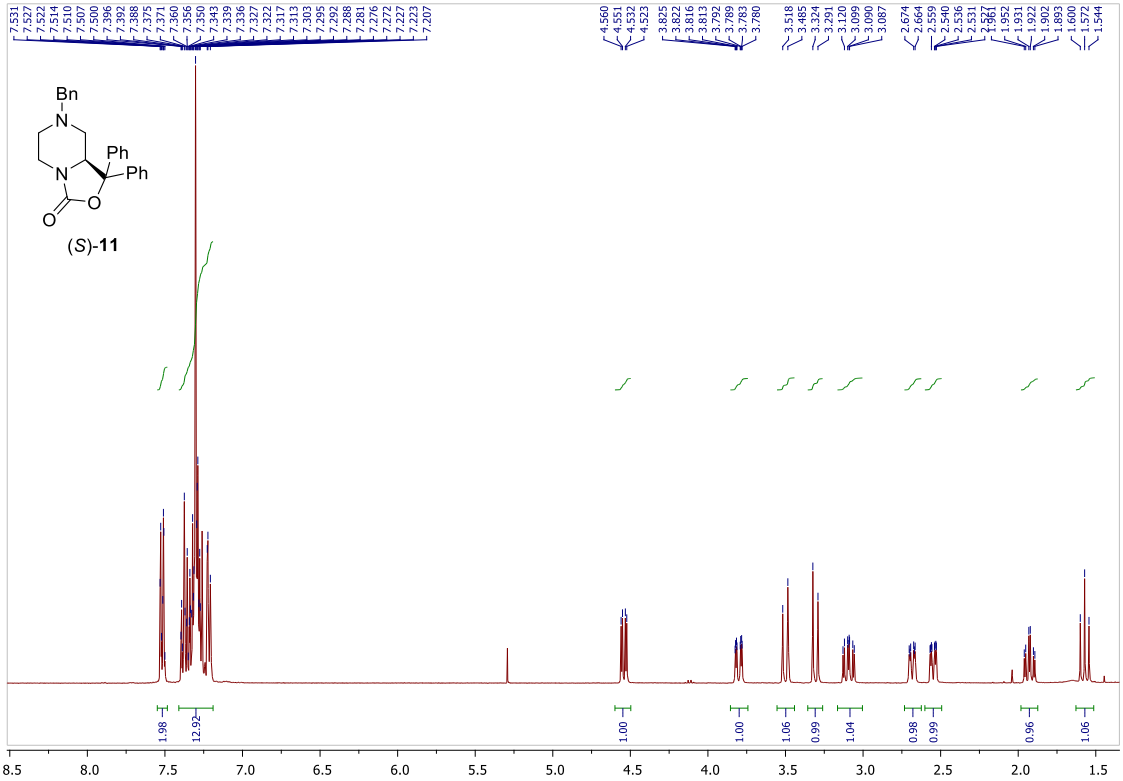


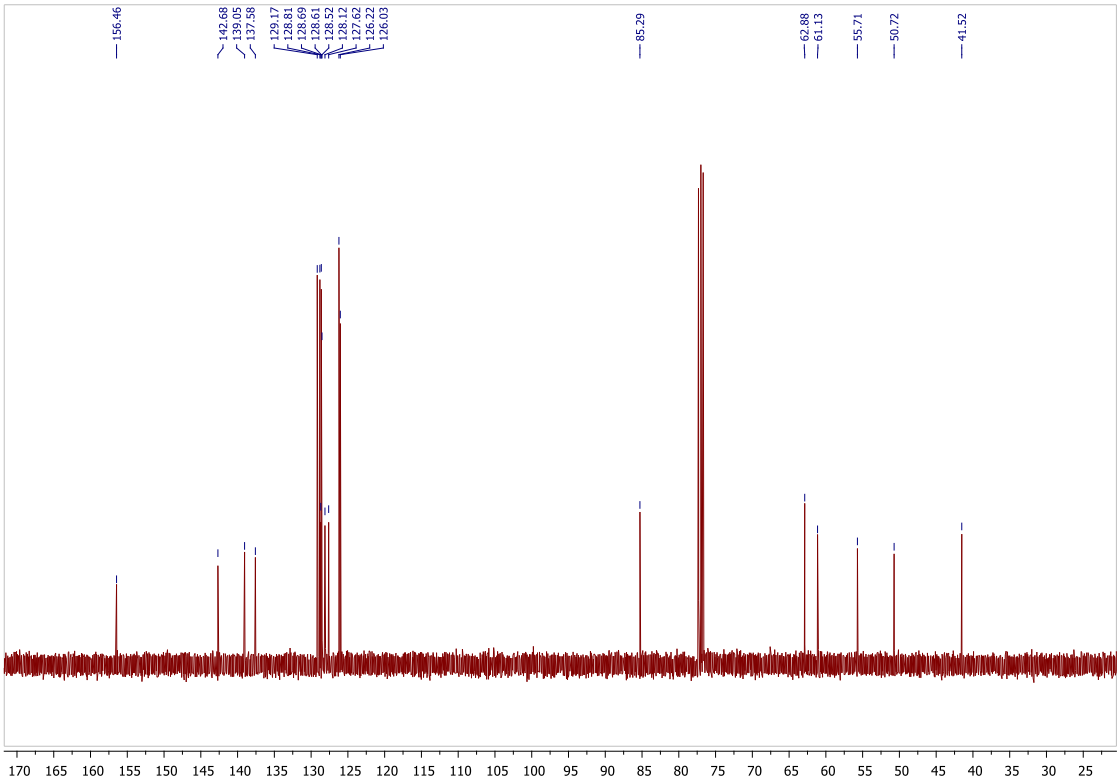
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



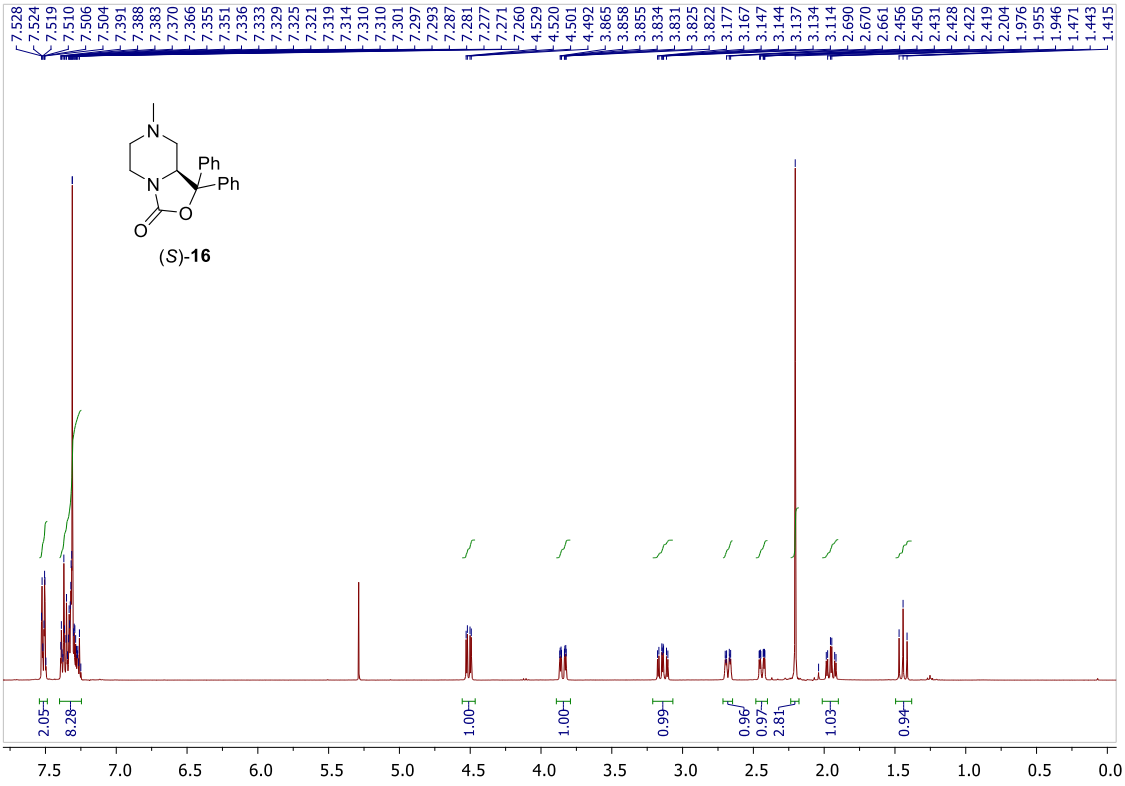


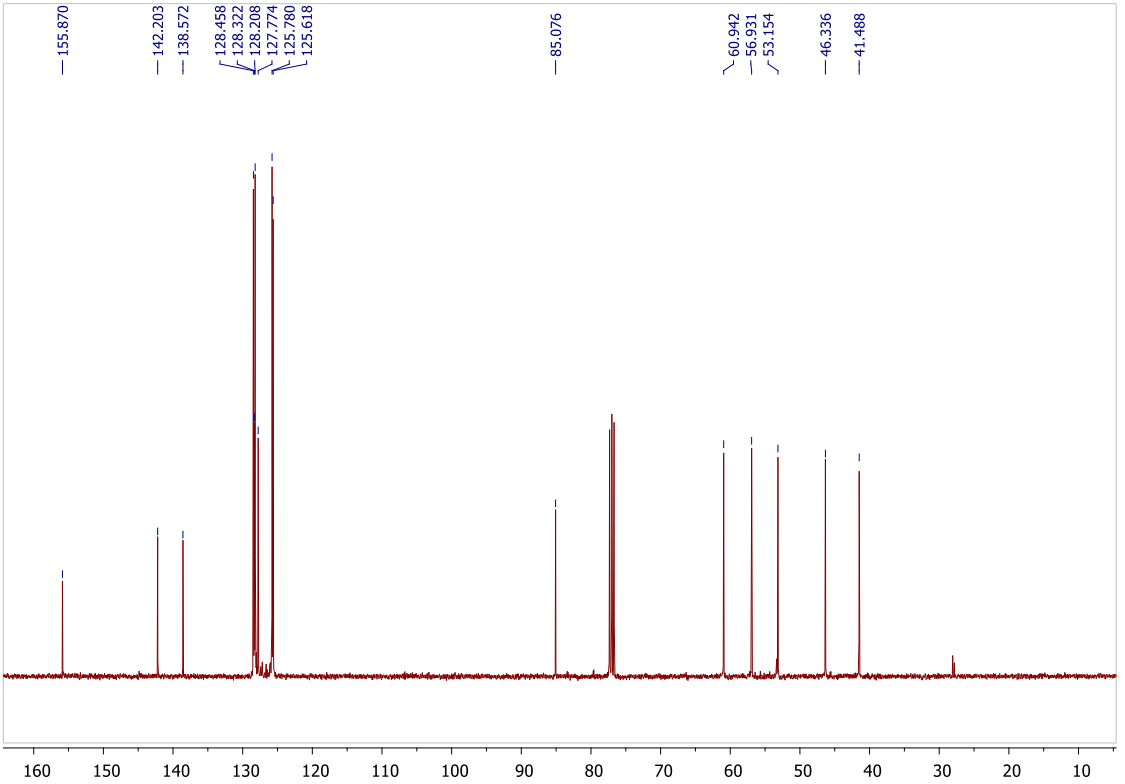
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



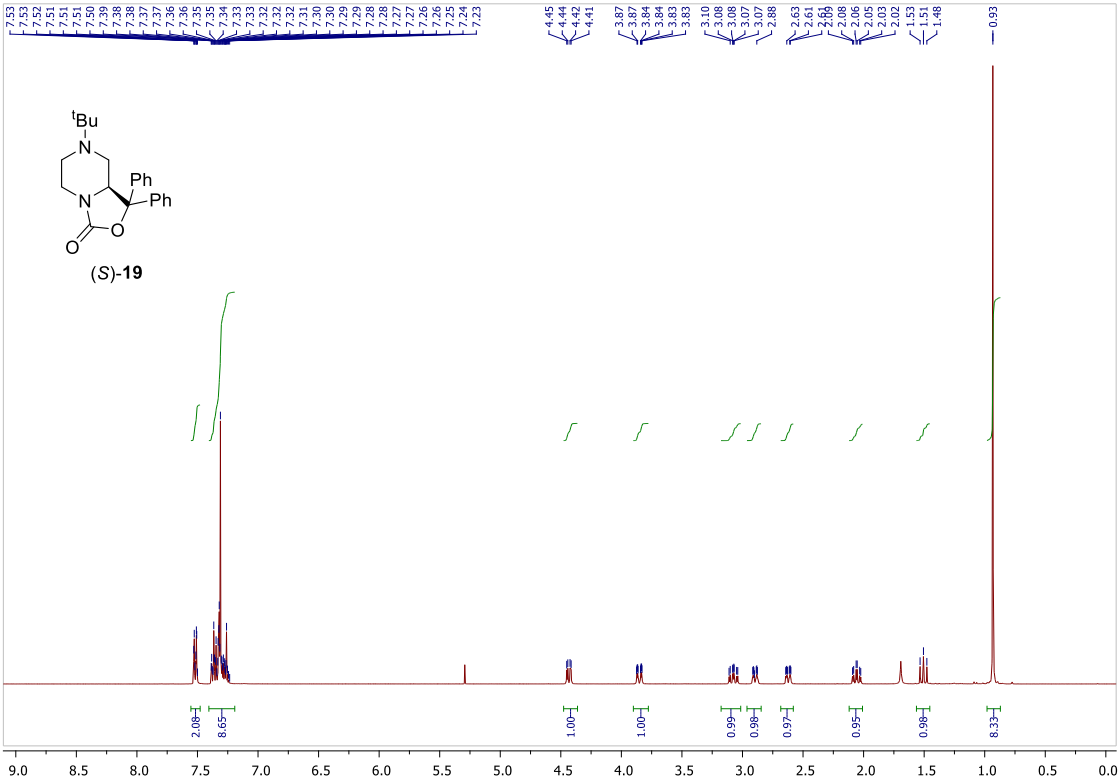


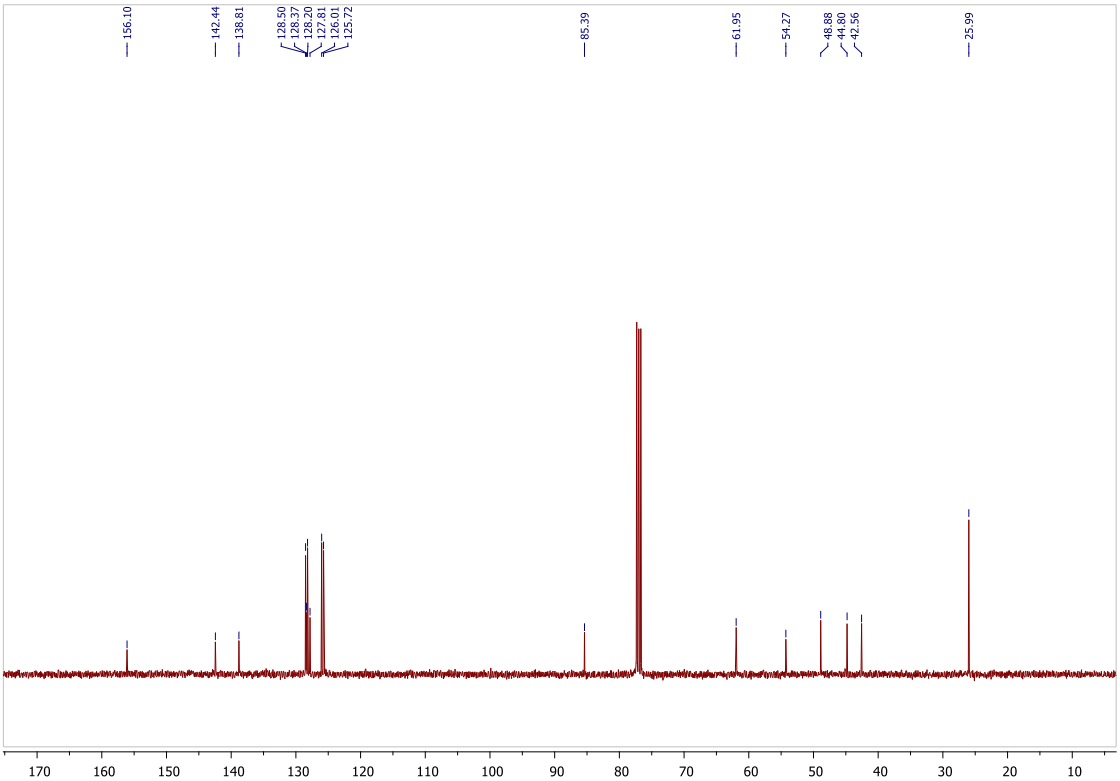
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



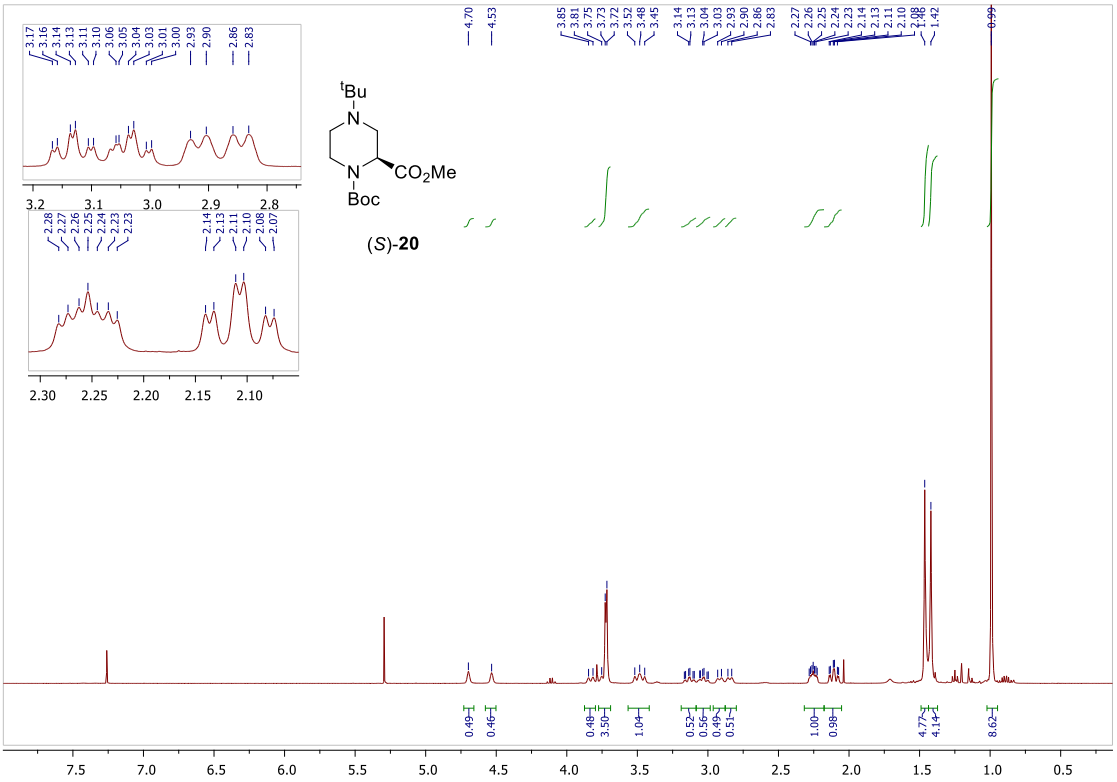


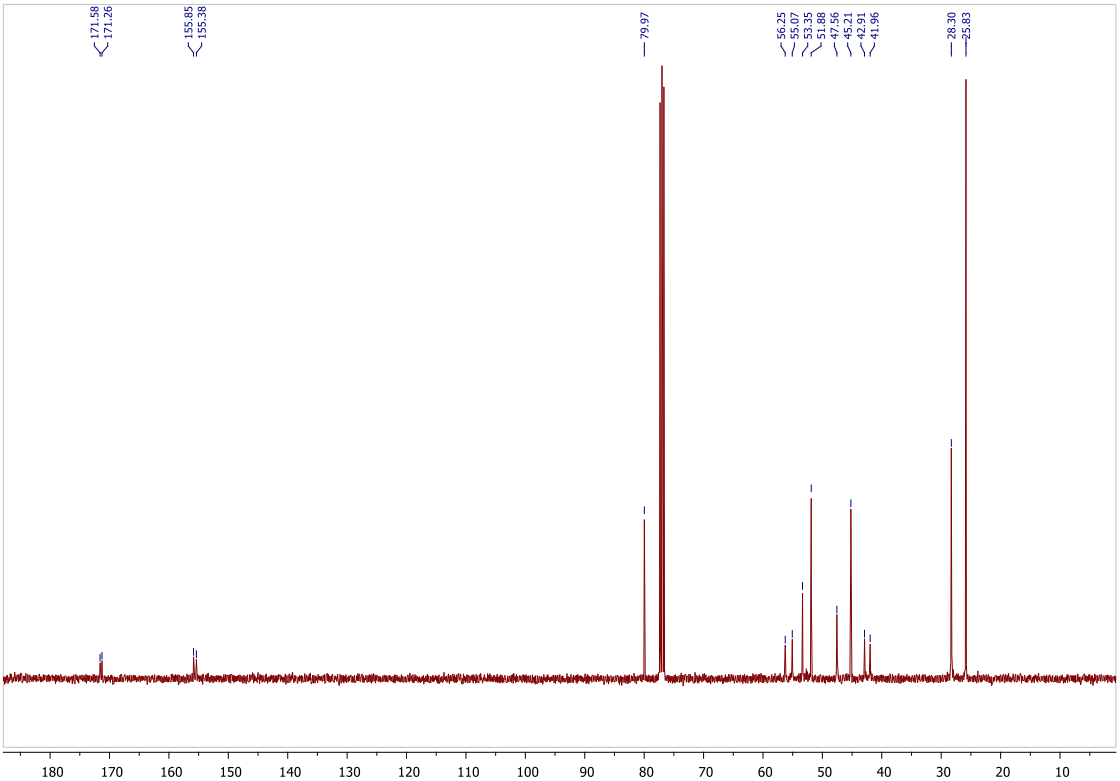
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



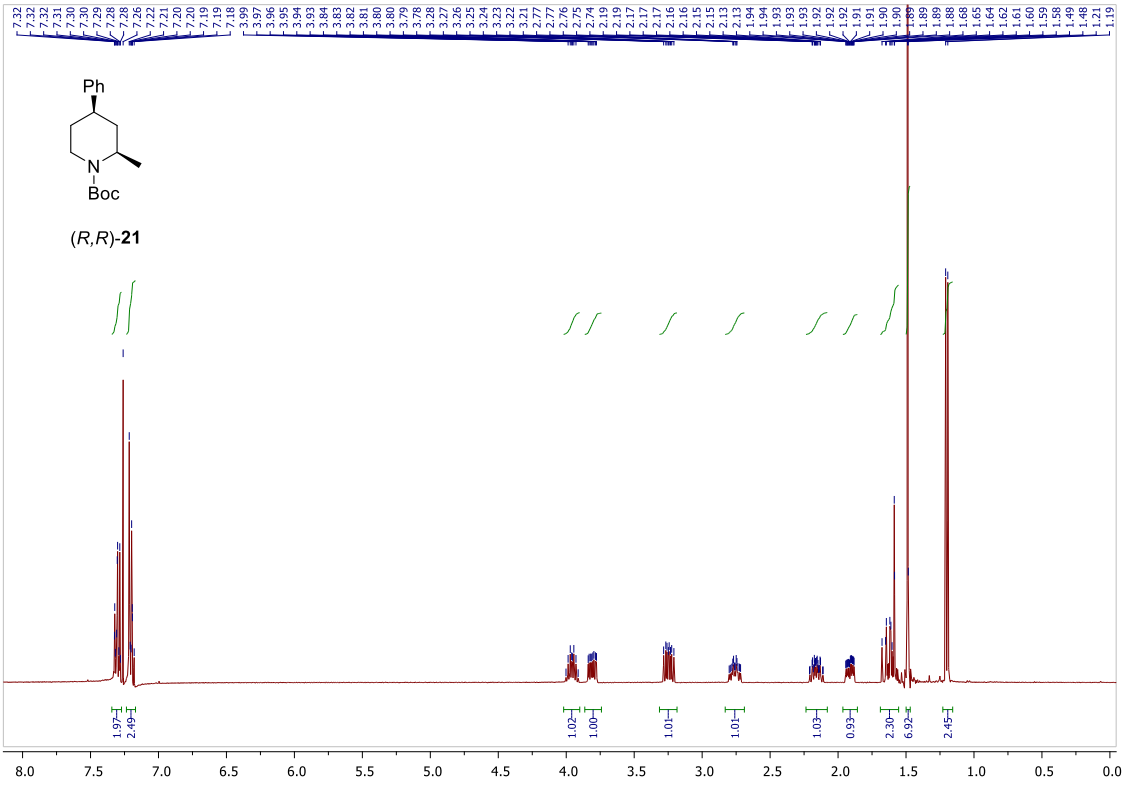


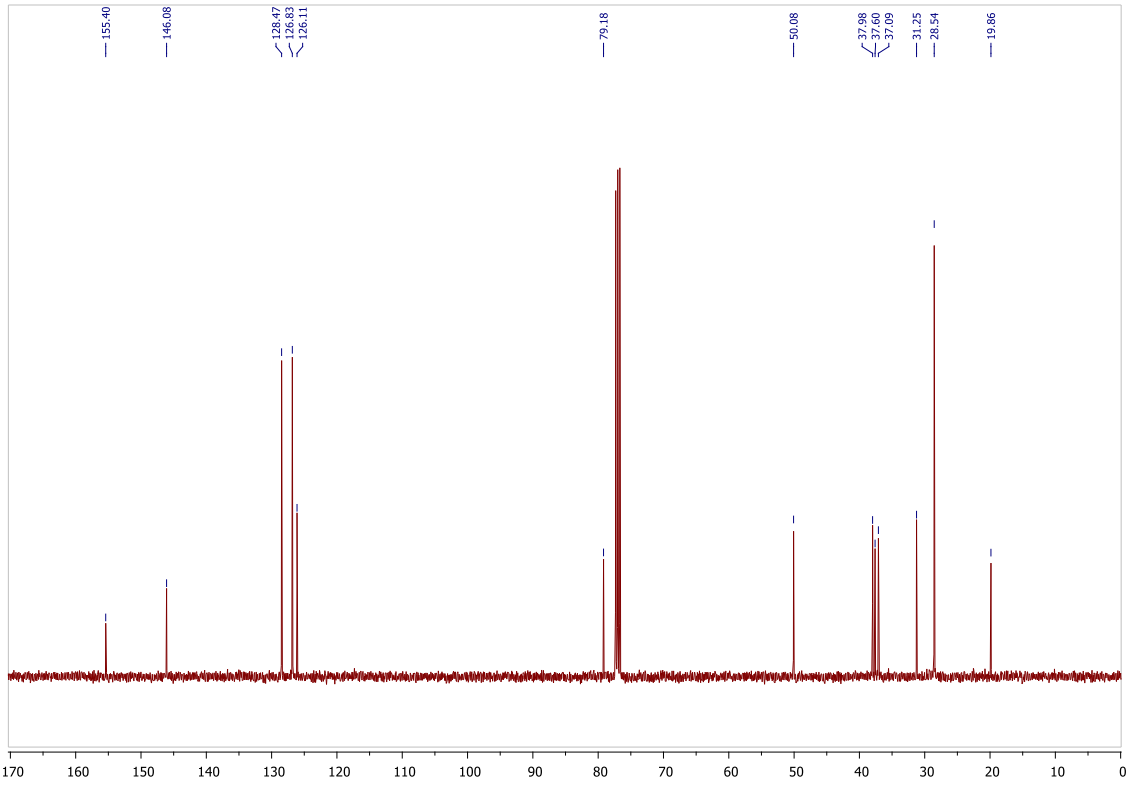
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



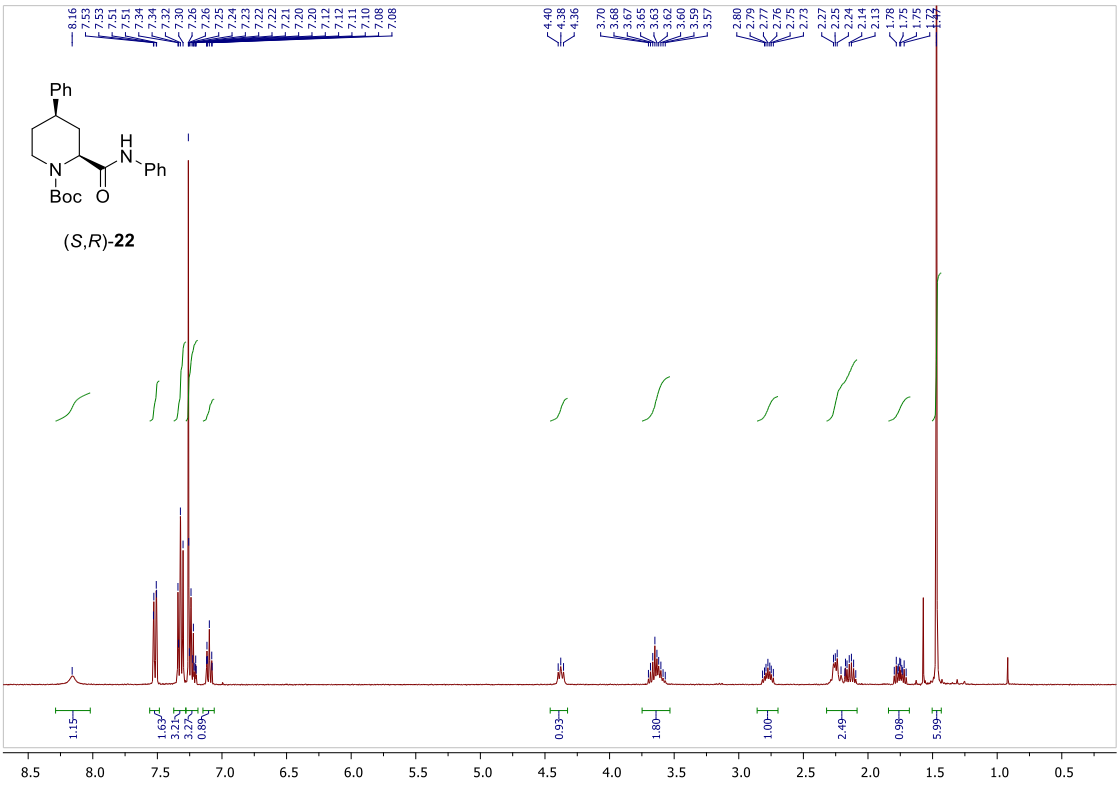


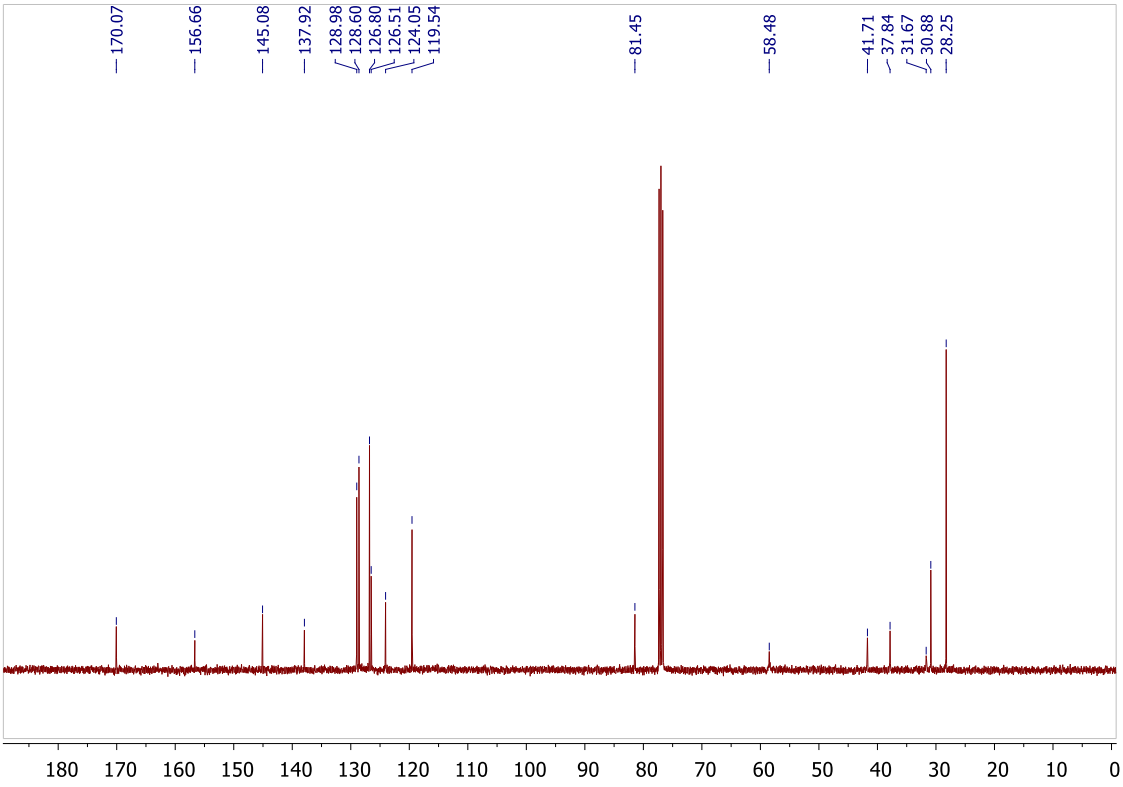
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



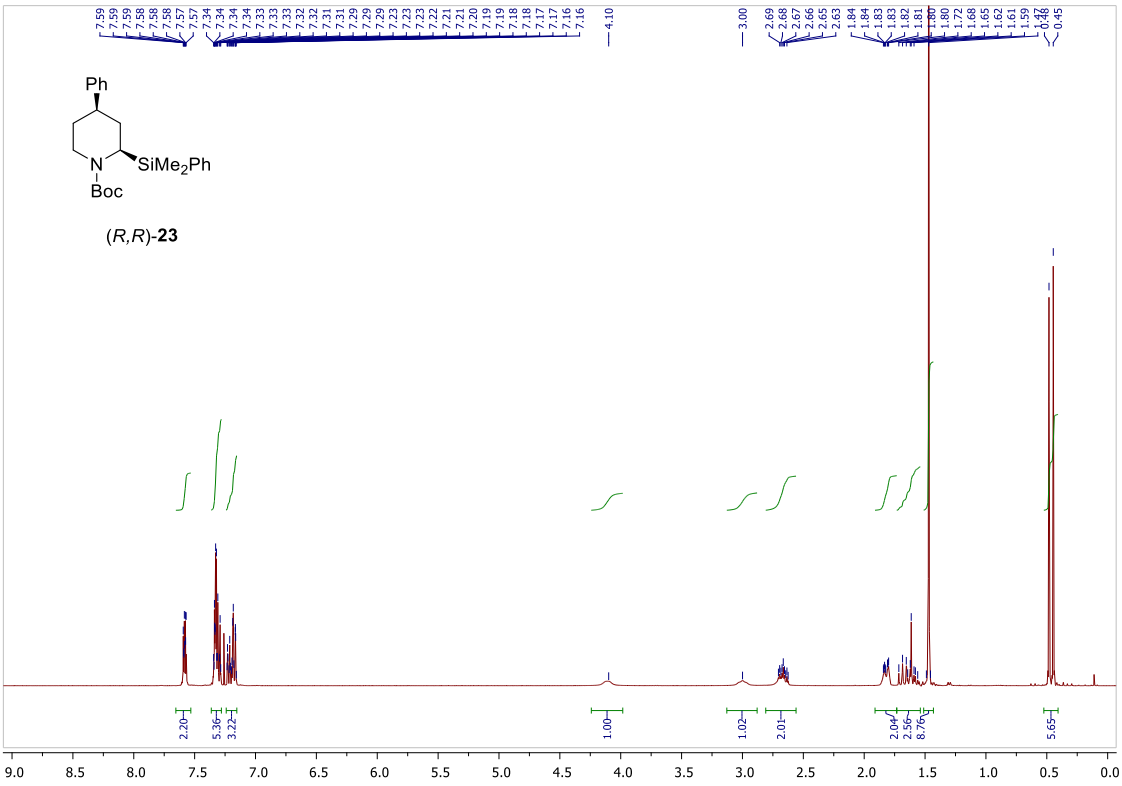


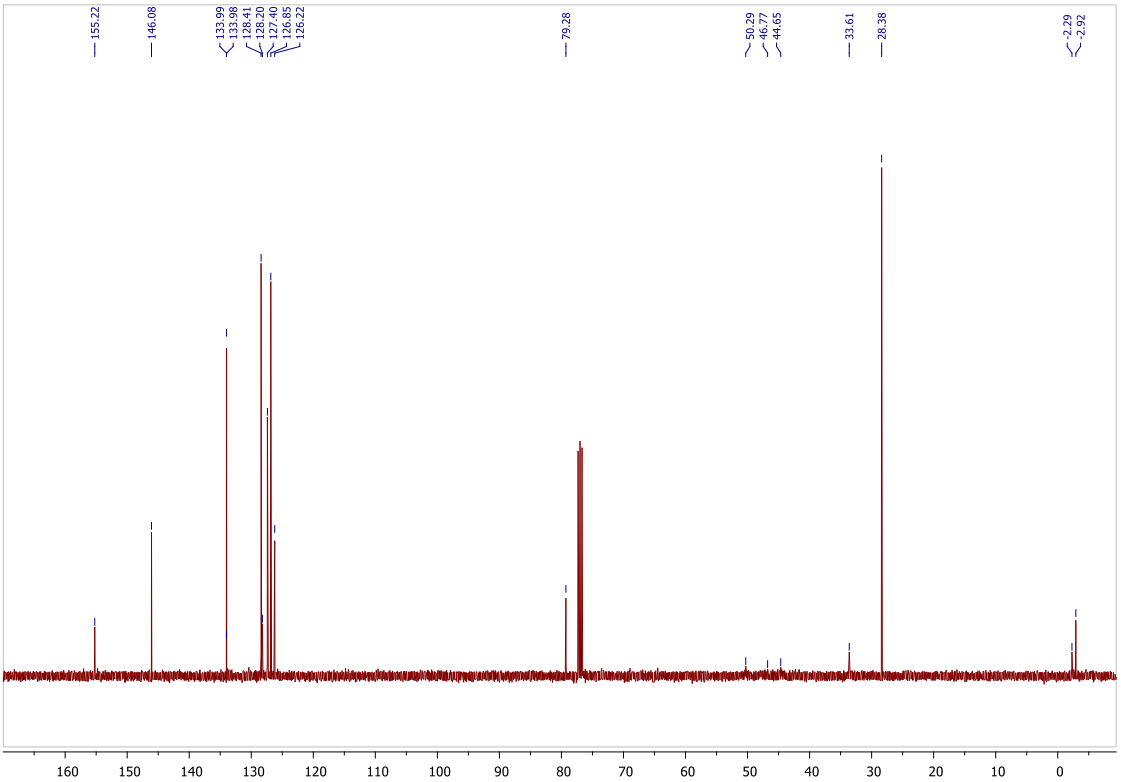
400 MHz ^{1}H NMR spectrum; $CDCl_3$



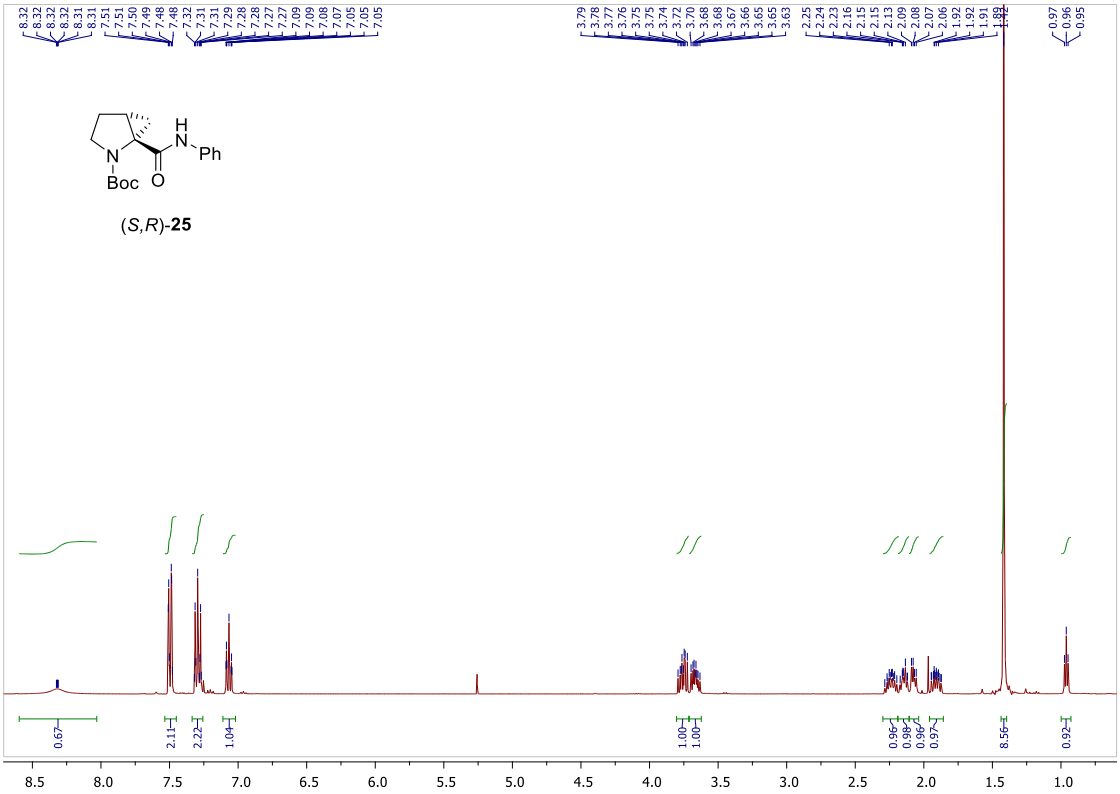


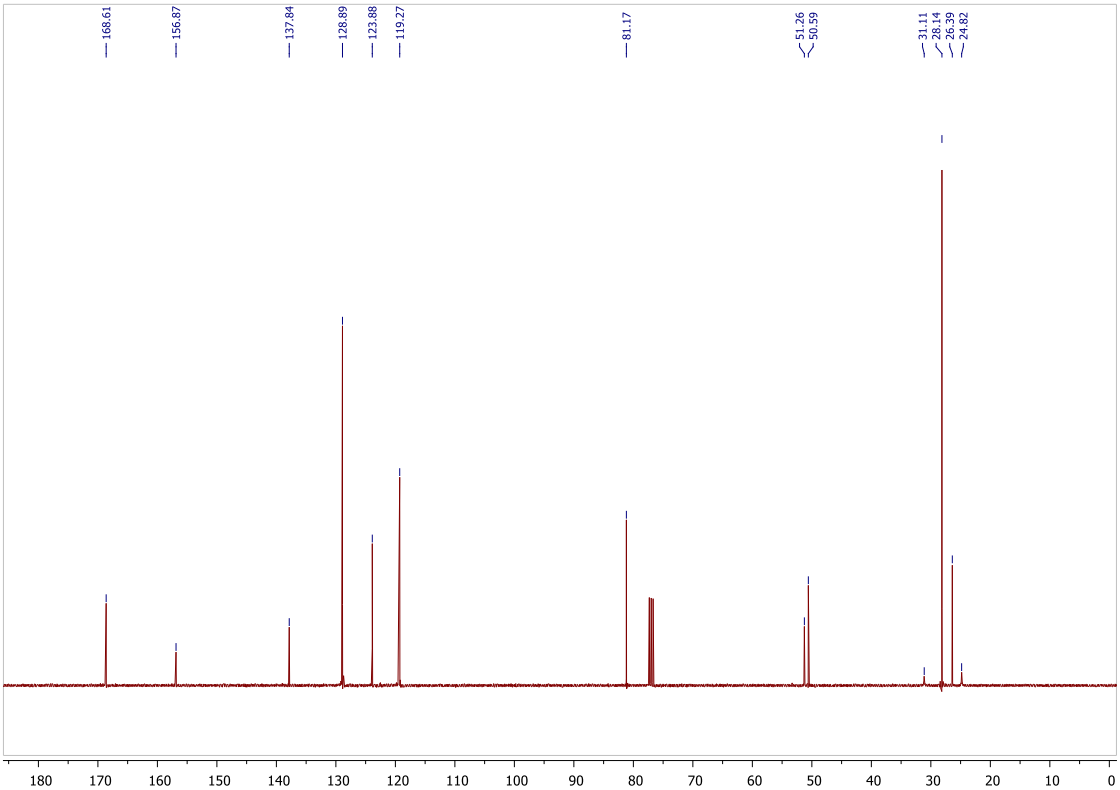
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$





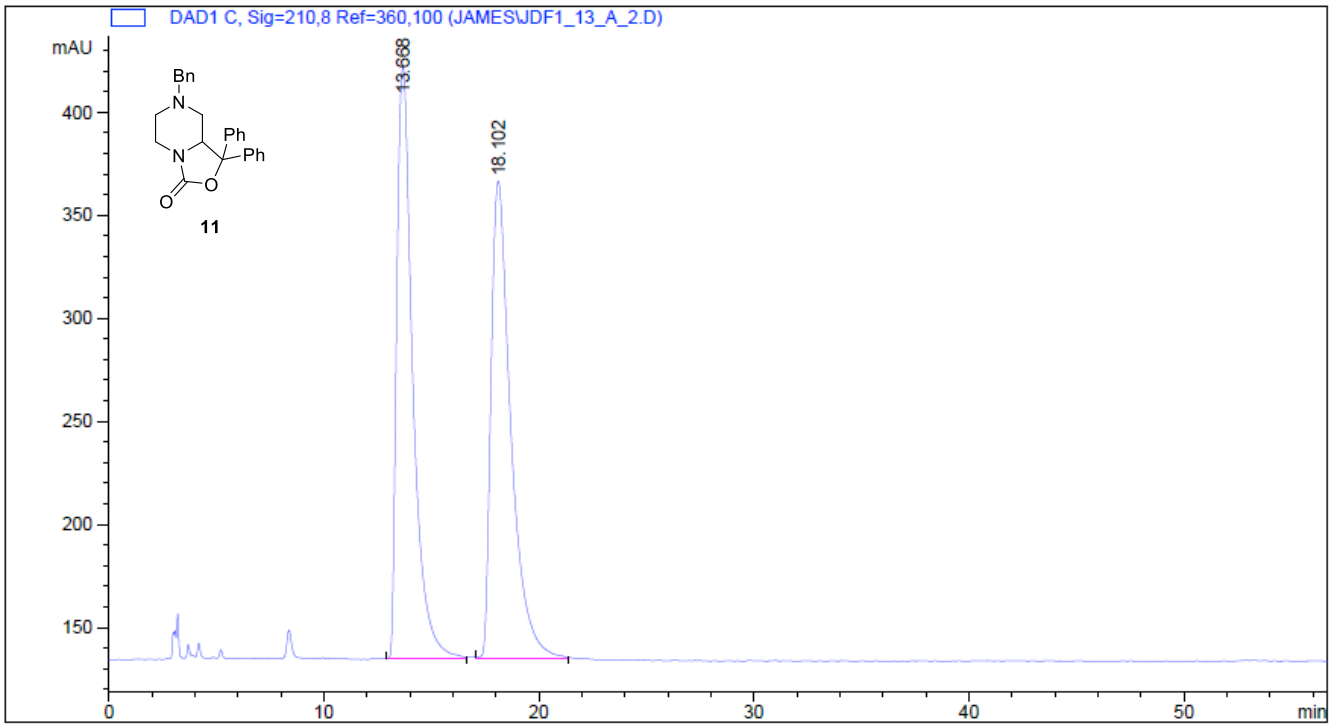
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$





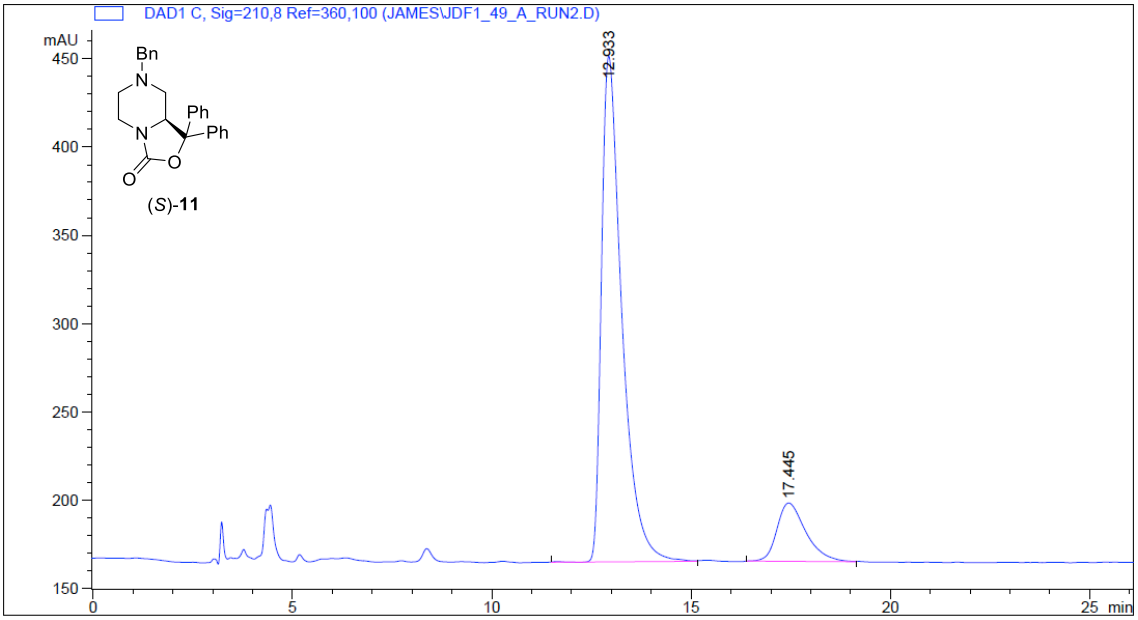
3. CSP-HPLC Traces

Racemic **11.** Chiralcel OD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1})



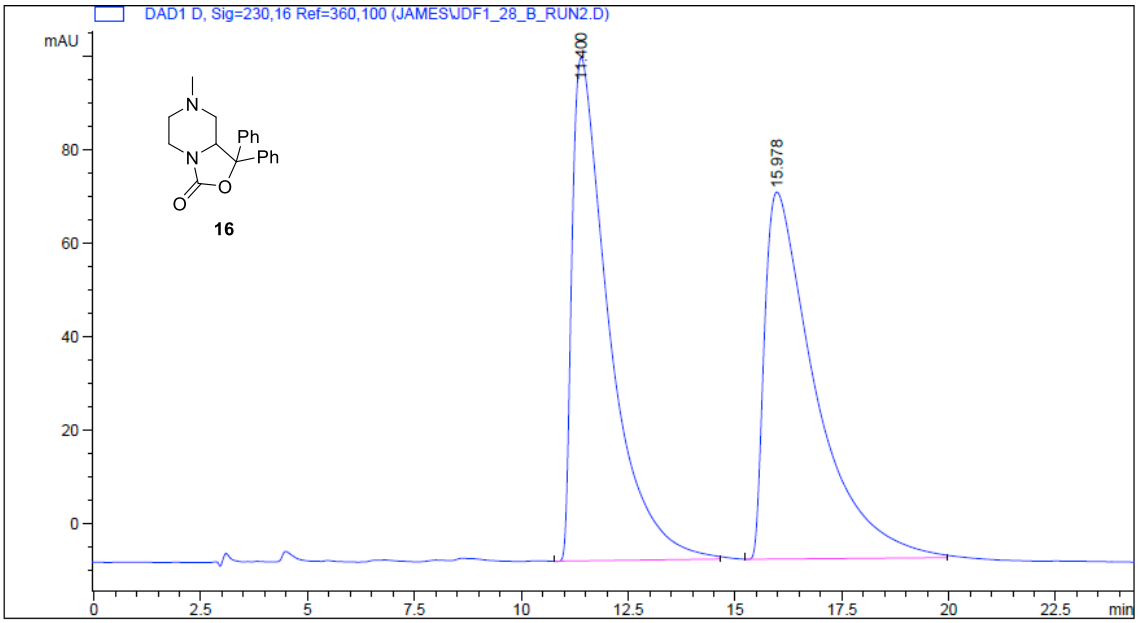
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.668	BB	0.7894	1.49061e4	287.26361	50.0736
2	18.102	BB	0.9558	1.48623e4	231.87677	49.9264

Enantioenriched (*S*)-**11**, using diamine (*S*,*S*)-**2**. Chiralcel OD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1})



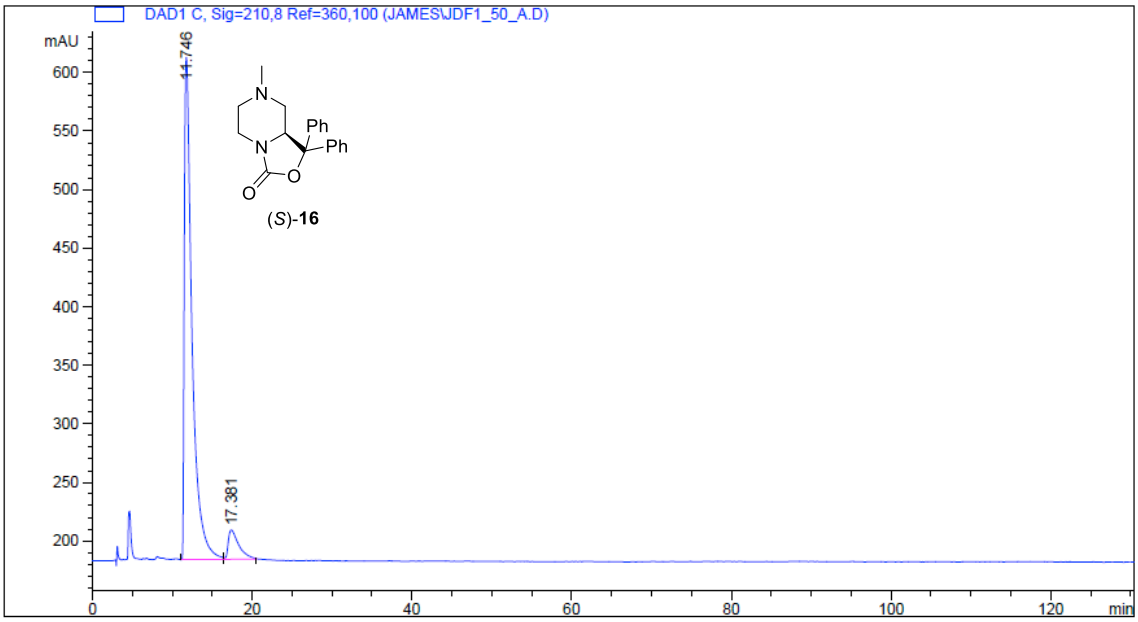
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.933	BB	0.5365	1.02219e4	286.29453	85.8871
2	17.445	BB	0.7682	1679.65283	33.08756	14.1129
Totals :				1.19015e4	319.38209	

Racemic **16.** Chiralcel AD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1})



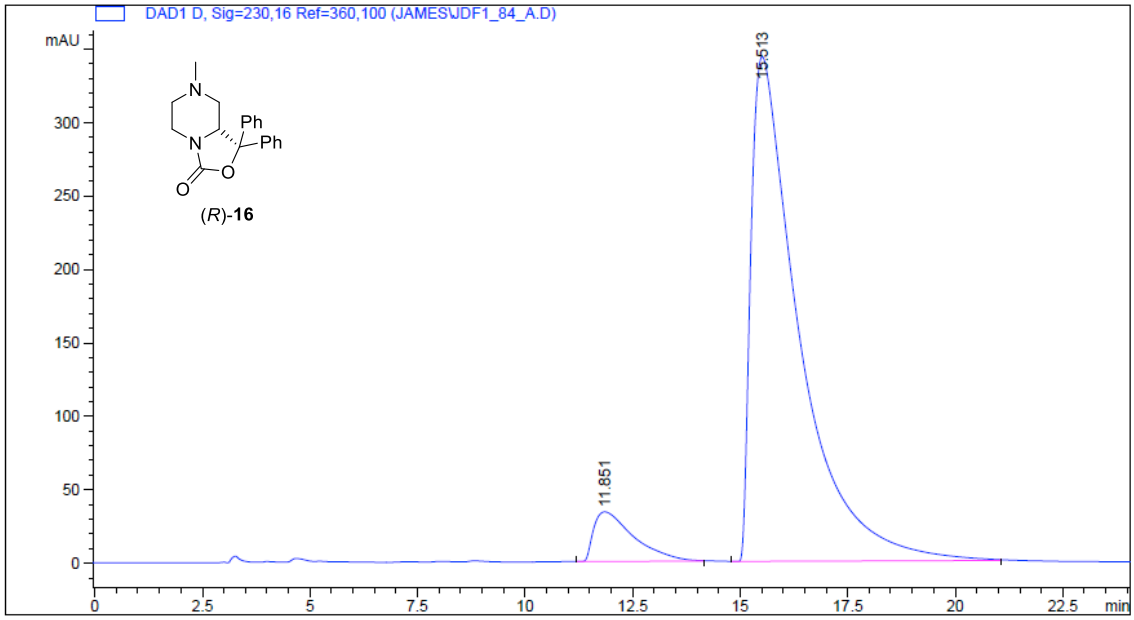
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.400	BB	0.8865	6493.20264	107.82948	50.1384
2	15.978	BB	1.2305	6457.36572	78.59532	49.8616
Totals :				1.29506e4	186.42480	

Enantioenriched (*S*)-**16**, using diamine (*S*,*S*)-**2**. Chiralcel AD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1})



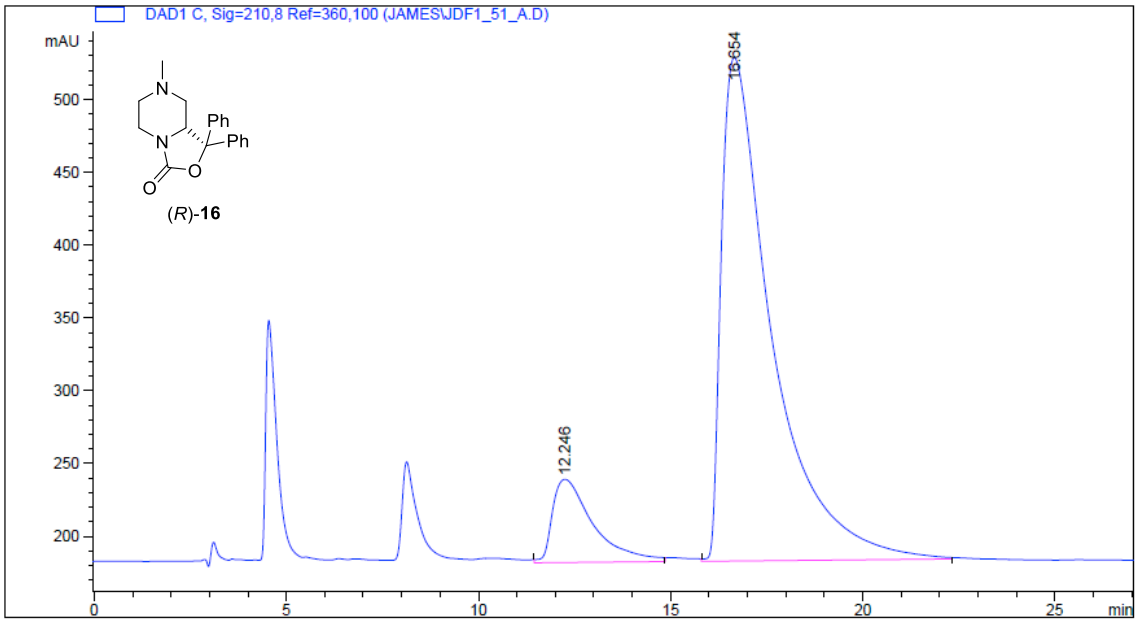
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.746	BB	0.9935	2.88723e4	428.80032	92.4943
2	17.381	BB	1.3353	2342.91553	25.13926	7.5057
Totals :				3.12152e4	453.93958	

Enantioenriched (*R*)-**16**, using diamine (*R*,*R*)-**3.** Chiralcel AD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1})



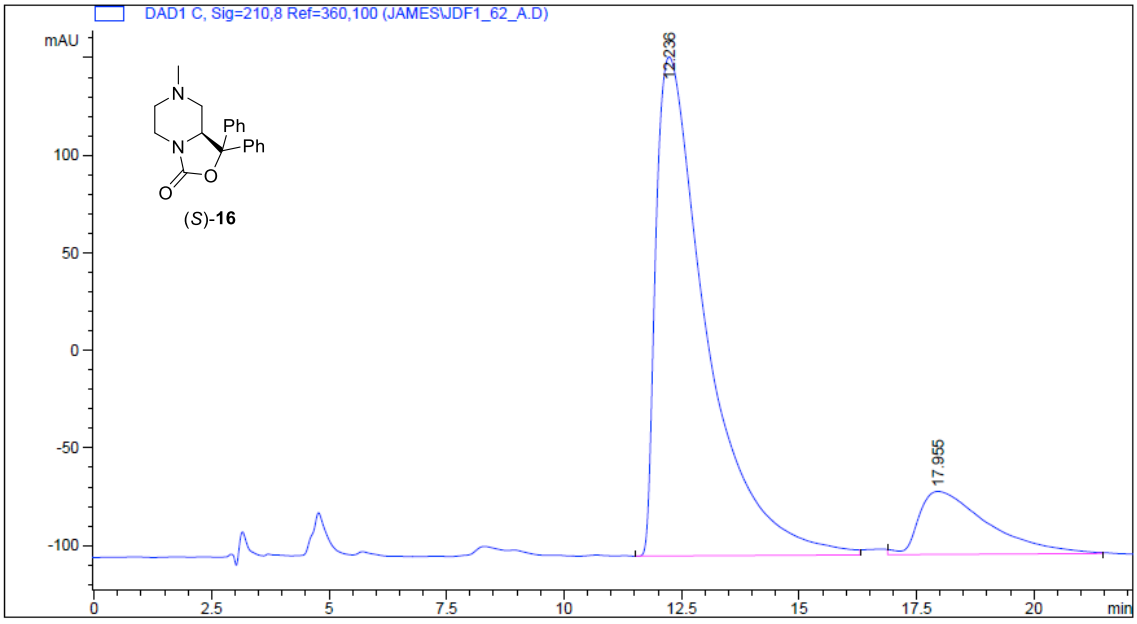
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.851	BB	0.9792	2200.14844	33.81132	7.6135
2	15.513	BB	1.1066	2.66980e4	343.58023	92.3865
Totals :				2.88982e4	377.39155	

Enantioenriched (*R*)-**16**, using (–)-sparteine**.** Chiralcel AD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1})



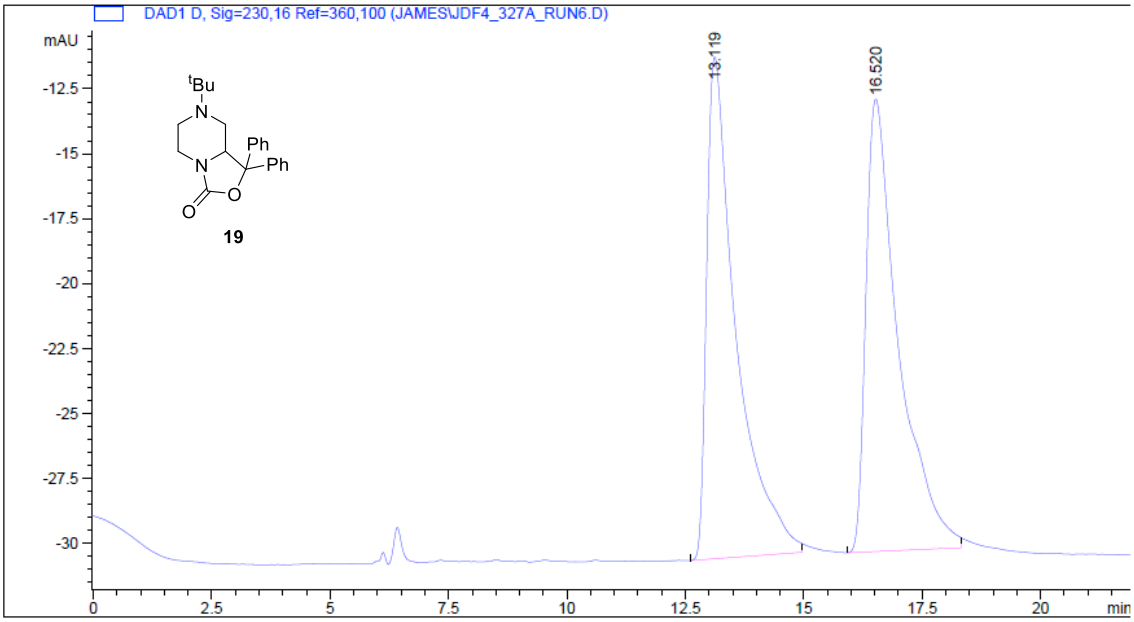
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.246	BB	1.1036	4238.22070	57.25439	11.8106
2	16.654	BB	1.3397	3.16466e4	345.79584	88.1894
Totals :				3.58848e4	403.05022	

Enantioenriched (*S*)-**16**, using diamine (+)-**1.** Chiralcel AD-H (90:10 hexane:*i*-PrOH, 1.0 mL min^{-1})



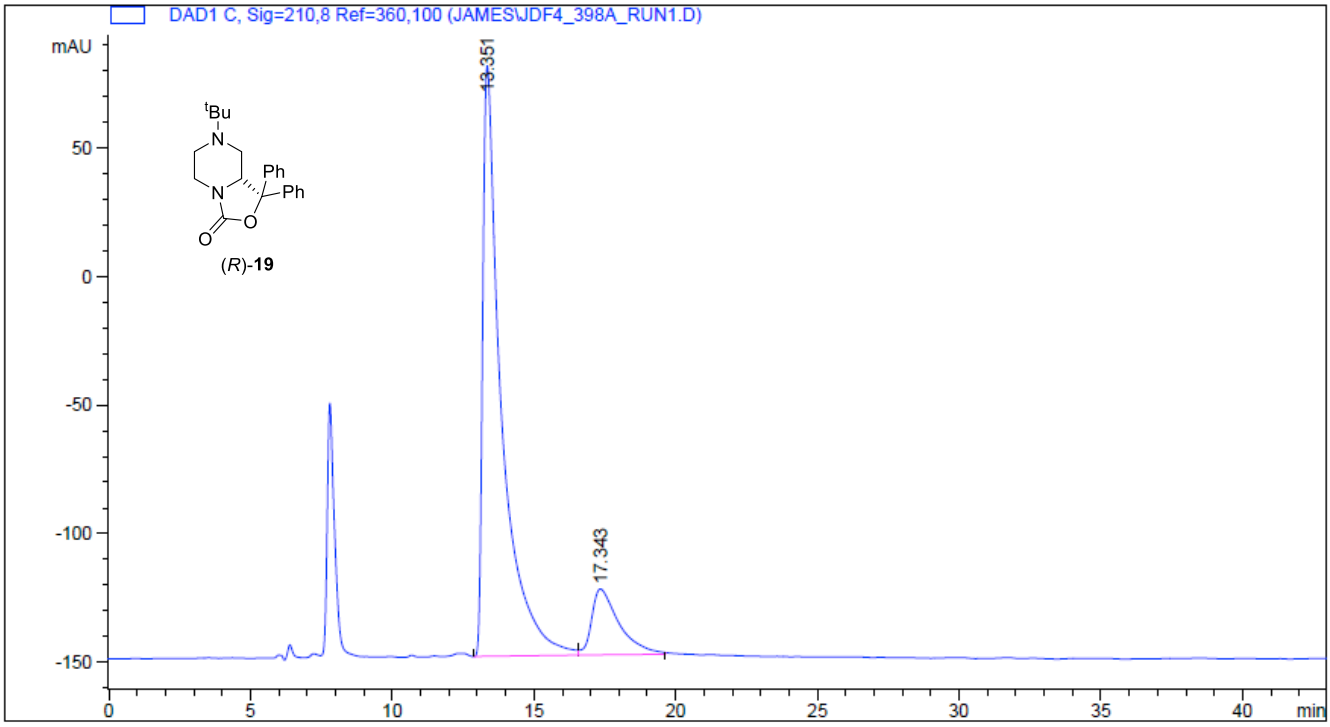
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.236	BB	1.1043	1.91344e4	255.91879	85.2483
2	17.955	BB	1.5216	3311.09180	32.36372	14.7517
Totals :				2.24455e4	288.28252	

Racemic **19**. Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min^{-1})



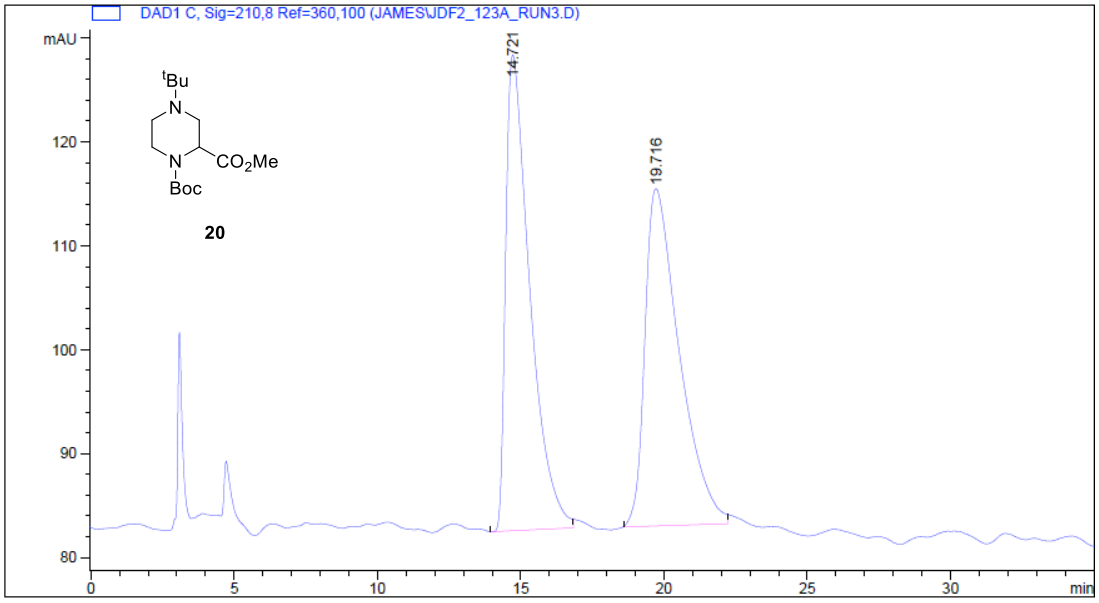
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.119	BB	0.6112	833.30585	19.31993	50.0240
2	16.520	BB	0.6896	832.50720	17.41784	49.9760
Totals :				1665.81305	36.73777	

Enantioenriched (*R*)-**19**. Chiralcel OD-H (90:10 hexane:*i*-PrOH, 0.5 mL min^{-1})



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.351	VB	0.6400	1.05605e4	229.87900	85.8656
2	17.343	BB	0.9972	1738.36218	25.69930	14.1344
Totals :				1.22988e4	255.57830	

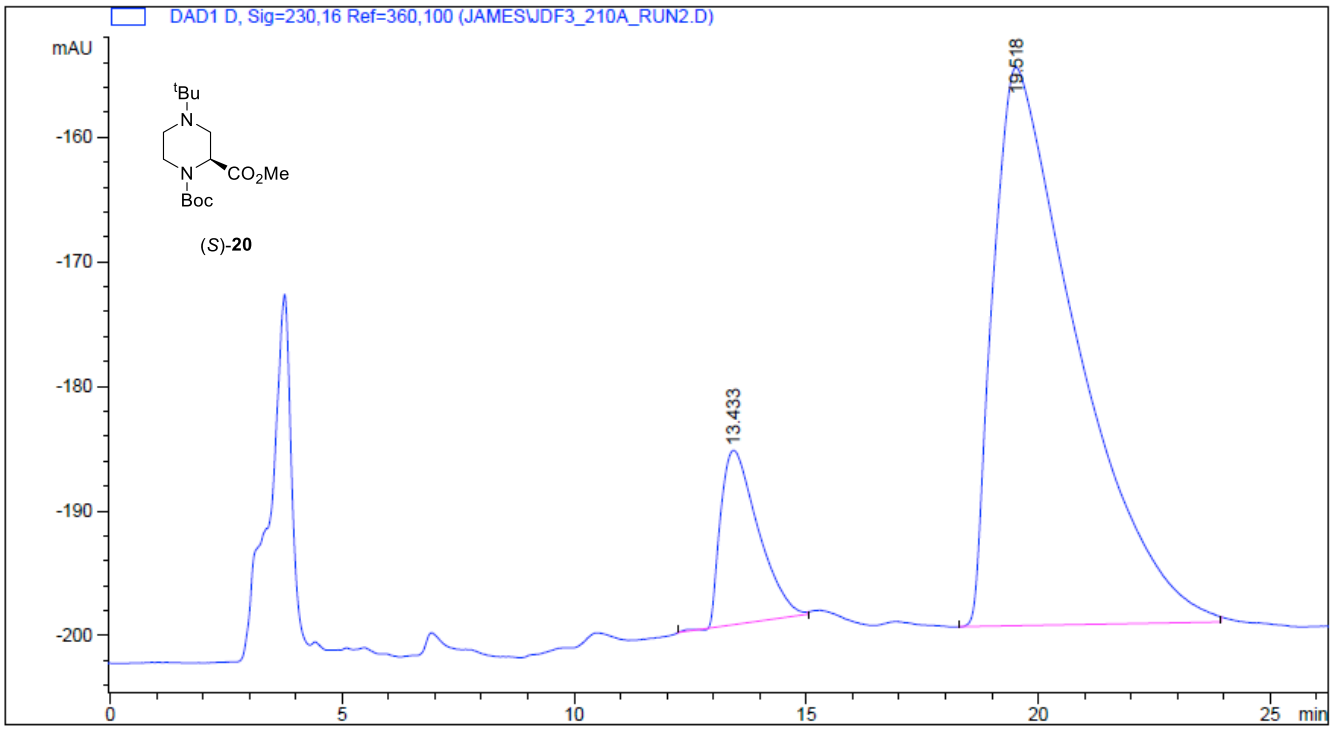
Racemic **20.** Chiralcel AD (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1})



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

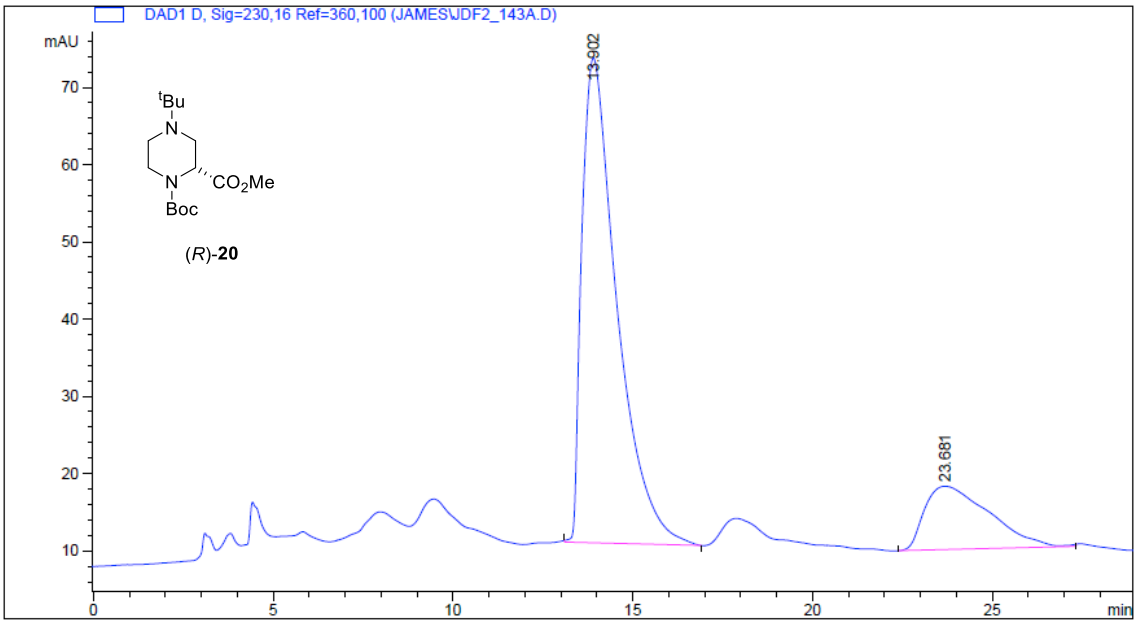
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.721	BB	0.8582	2674.99536	45.74356	49.7279
2	19.716	BB	1.2205	2704.26514	32.44119	50.2721

Enantioenriched (*S*)-**20**, using diamine (*S*,*S*)-**2.** Chiralcel AD (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1})



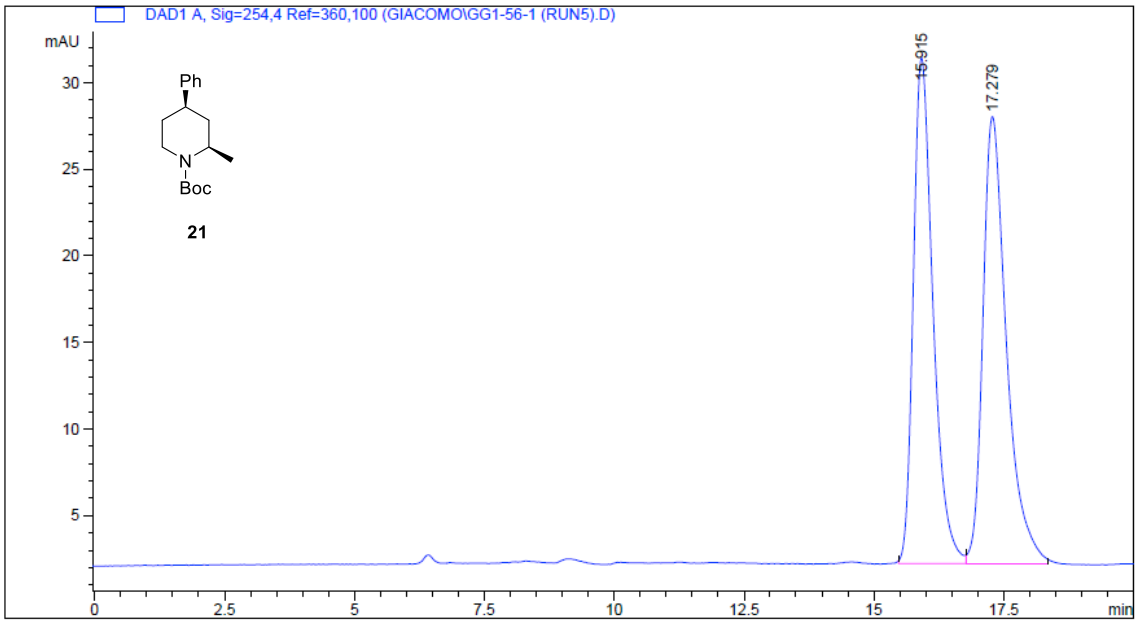
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.433	BB	0.8657	790.09064	14.01417	12.2742
2	19.518	BB	1.8740	5646.88770	44.81558	87.7258

Enantioenriched (*R*)-**20**, using diamine (*R*,*R*)-**3.** Chiralcel AD (99:1 hexane:*i*-PrOH, 1.0 mL min^{-1})



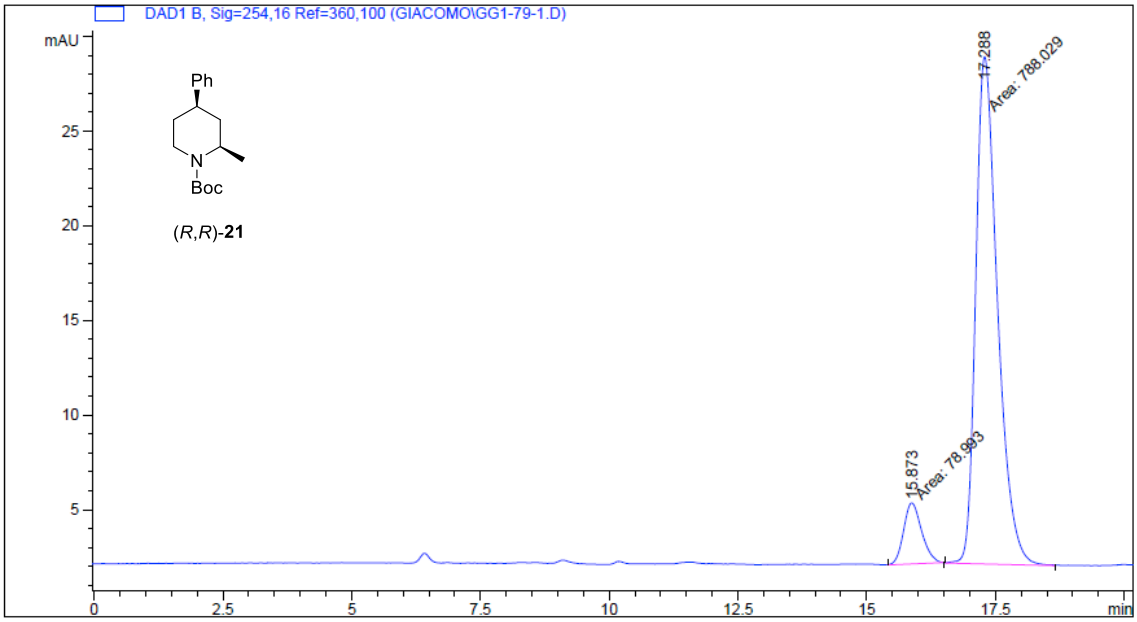
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.902	BB	1.0303	4252.83105	62.78119	80.5260
2	23.681	BB	1.8075	1028.48523	8.19907	19.4740

Racemic **21.** Chiralcel OD (99:1 hexane-*i*-PrOH, 0.5 mL min^{-1})



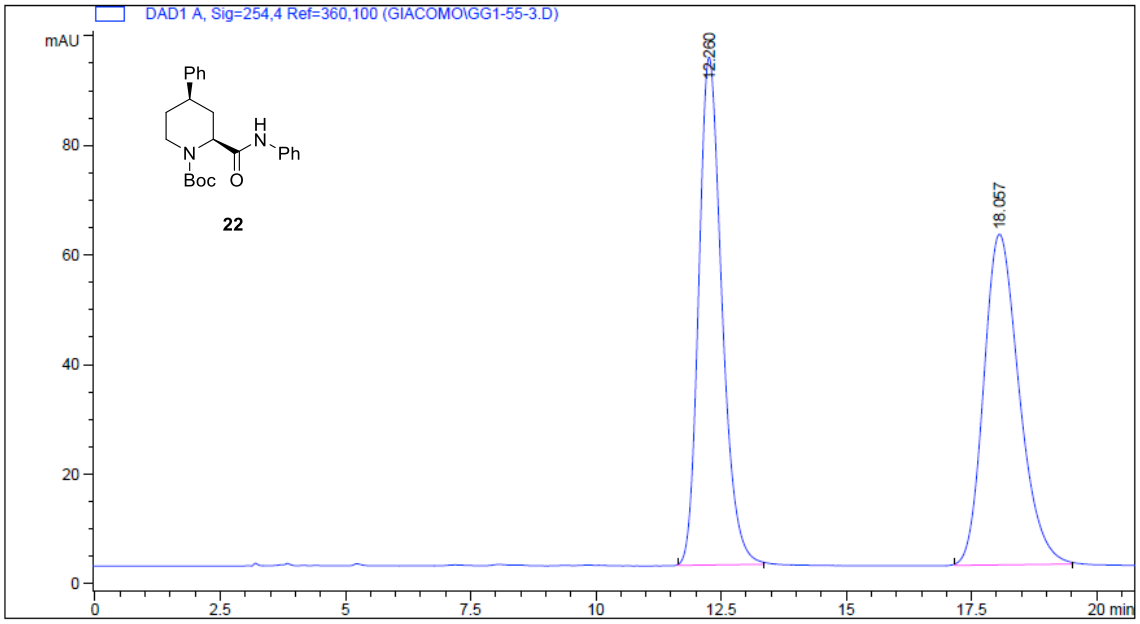
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.915	BB	0.3972	768.88562	29.19871	48.6083
2	17.279	BB	0.4793	812.91193	25.81821	51.3917

Enantioenriched (*R*,*R*)-**21.** Chiralcel OD (99:1 hexane-*i*-PrOH, 0.5 mL min^{-1})



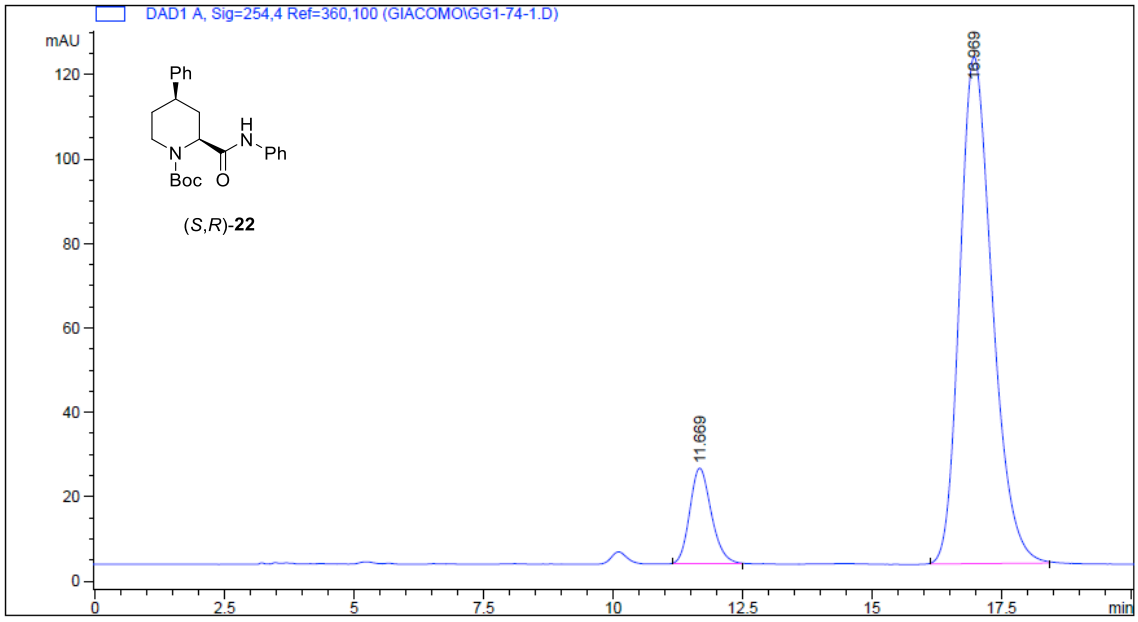
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.873	MM	0.4074	78.99297	3.23150	9.1108
2	17.288	MM	0.4900	788.02917	26.80587	90.8892

Racemic **22.** Chiralcel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1})



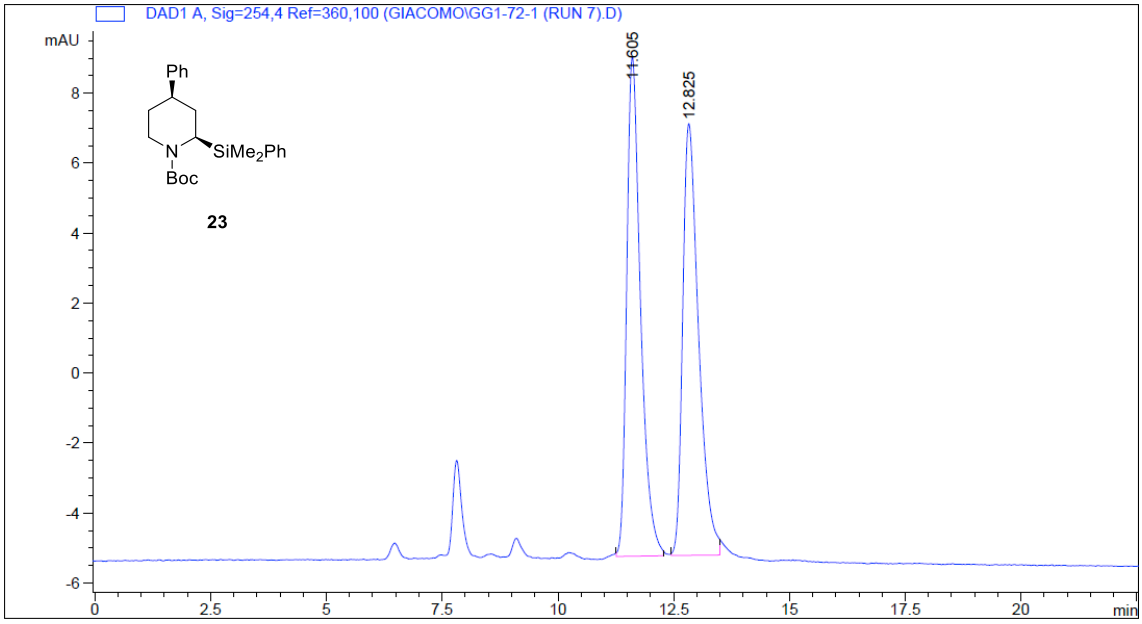
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.260	BB	0.4934	2982.11548	92.68917	50.1147
2	18.057	BB	0.7537	2968.47046	60.36130	49.8853

Enantioenriched (*S*,*R*)-**22.** Chiralcel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1})



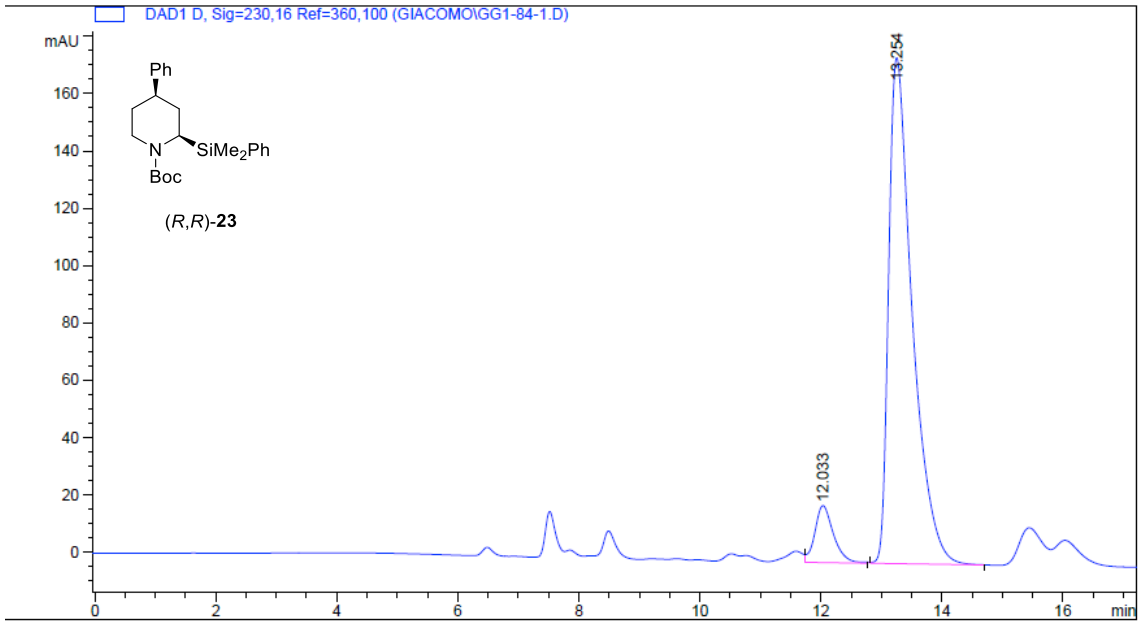
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.669	BB	0.4472	659.23657	22.67232	11.1210
2	16.969	BB	0.6716	5268.60107	120.14144	88.8790

Racemic **23.** Chiralcel OD (99.9:0.1 hexane-*i*-PrOH, 0.5 mL min^{-1})



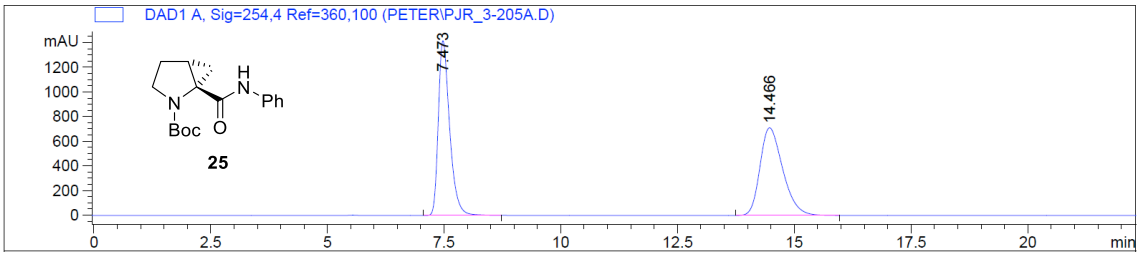
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.605	BB	0.3118	295.98273	14.27992	50.0904
2	12.825	BB	0.3566	294.91473	12.34877	49.9096

Enantioenriched (*R*,*R*)-**23.** Chiralcel OD (99.9:0.1 hexane-*i*-PrOH, 0.5 mL min^{-1})



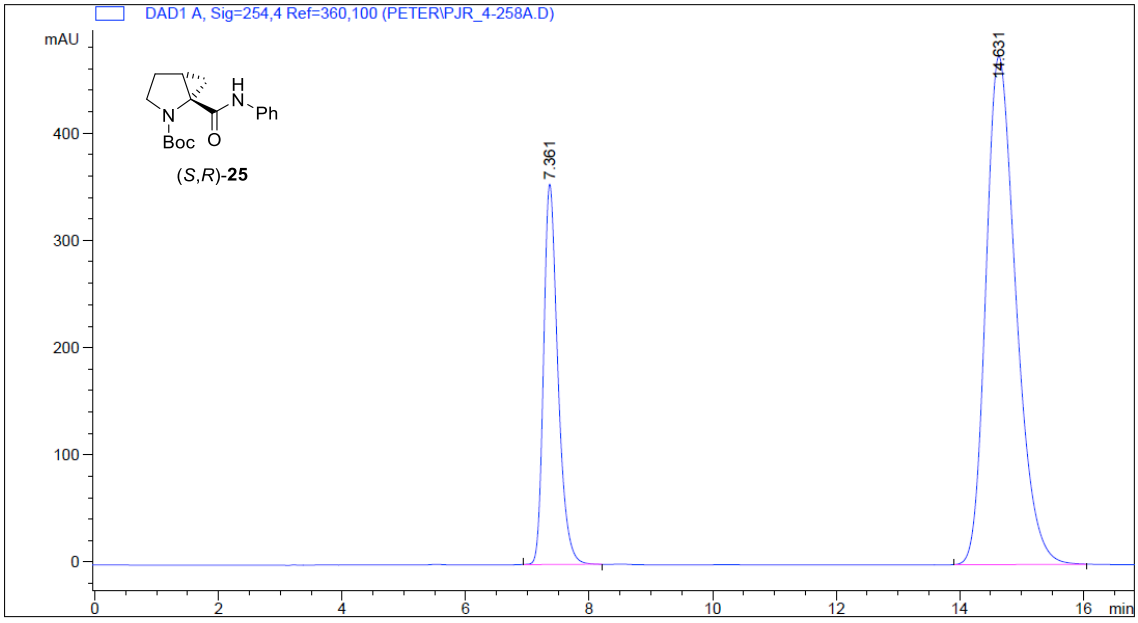
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.033	VB	0.3223	427.42438	19.92277	8.2092
2	13.254	BB	0.4078	4779.24219	176.54240	91.7908

Racemic **25.** Chiracel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1})



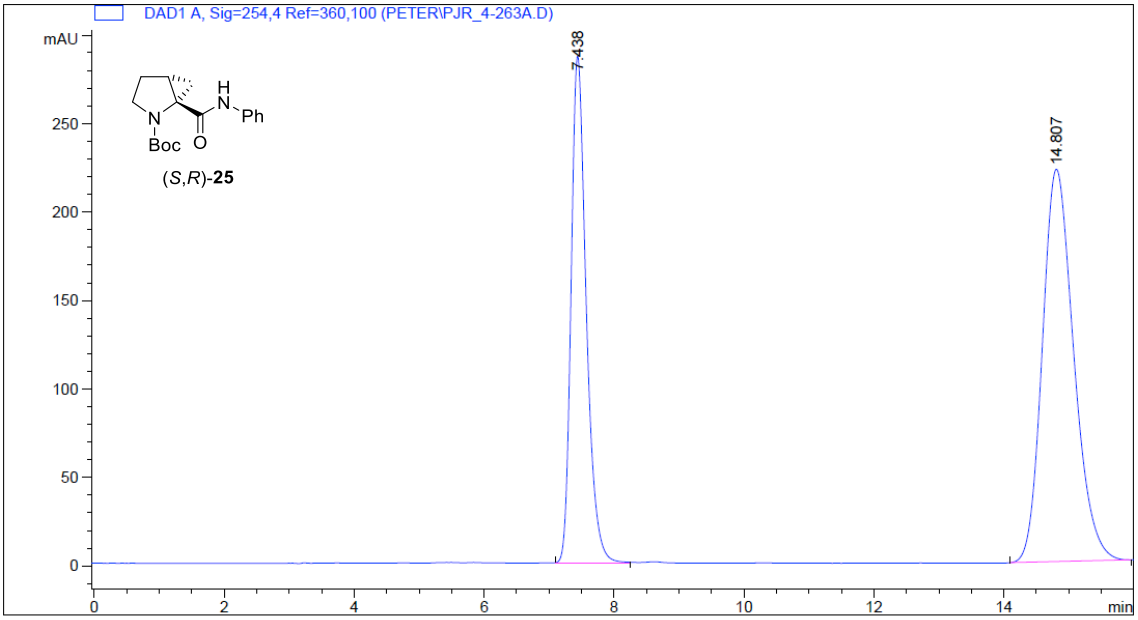
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.473	VB	0.2564	2.38878e4	1419.06726	49.7196
2	14.466	BB	0.5220	2.41572e4	711.78931	50.2804

Enantioenriched (*S*,*R*)-**25,** using diamine (*R*,*R*)-**2.** Chiracel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1})



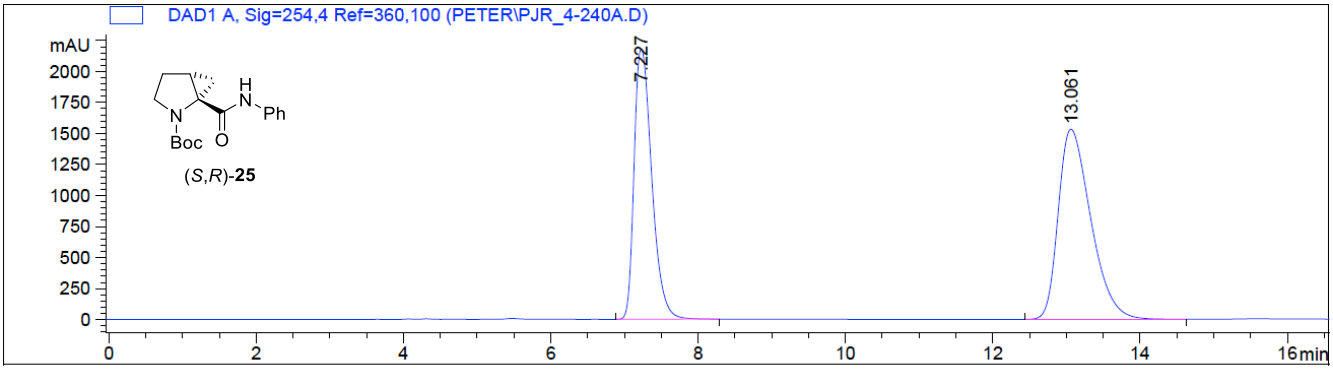
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.361	BB	0.2455	5703.33643	354.93036	26.2159
2	14.631	BB	0.5209	1.60519e4	474.20560	73.7841

Enantioenriched (*S*,*R*)-**25**, using diamine (*R*,*R*)-**3.** Chiracel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1})



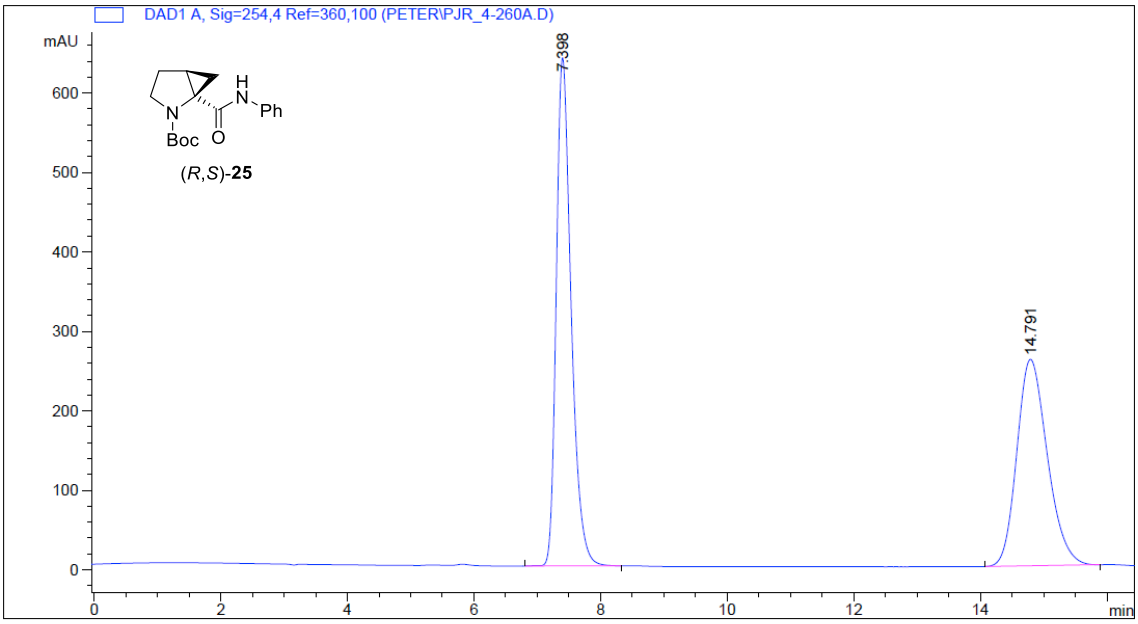
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.438	BB	0.2467	4636.60254	286.66415	38.4410
2	14.807	BB	0.5166	7424.99414	221.79704	61.5590

Enantioenriched (*S*,*R*)-**25**, using diamine (–)-sparteine. Chiracel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1})



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.227	BB	0.2604	3.63426e4	2180.89941	43.5710
2	13.061	BB	0.4740	4.70674e4	1533.75488	56.4290

Enantioenriched (*R*,*S*)-**25**, using diamine (+)-**1.** Chiracel OD (90:10 hexane-*i*-PrOH, 1.0 mL min^{-1})



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.398	BB	0.2482	1.04285e4	639.75220	54.5247
2	14.791	BB	0.5165	8697.69922	259.87189	45.4753

4. References

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