Electronic Supplementary Material (ESI) for Chemical Science.

Readily Accessible Sp^3-Rich Cyclic Hydrazine Frameworks Exploiting Nitrogen Fluxionality

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General Details

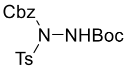
All reactions were performed under an atmosphere of nitrogen in oven-dried glassware unless otherwise stated. Anhydrous solvents were purchased from Sigma-Aldrich or Acros Organics in Sure-Seal^{TM} bottles for use as reaction solvents. All other solvents were reagent grade and used as received. Petroleum ether refers to the fraction that boils in the range 40-60 °C. Commercially available starting materials were used without purification.

Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Silicagel 60 F254), visualized by UV 254 nm then stained with phosphomolybdic acid (PMA) or potassium permanganate ($KMnO_4$) dip and heated. Flash column chromatography was performed using 40-63 µm Silica Gel.

Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX (300 or 400 MHz) or AV (500 or 600 MHz) spectrometers. Chemicals shifts (δ) are reported in parts per million (ppm) relative to the solvent residual peaks ($CDCl_3$ δ_H: 7.26 ppm, δ_C: 77.16 ppm; D6-DMSO δ_H: 2.50 ppm, δ_C: 39.52 ppm). Coupling constants (*J*) are reported in hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or some combination of these.

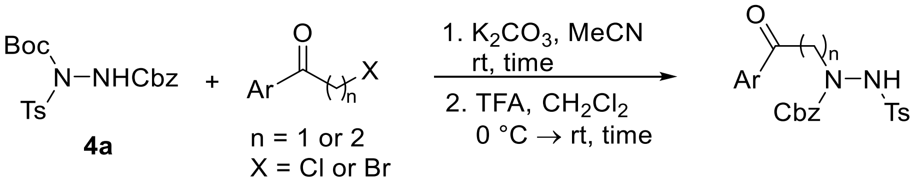
Low-resolution mass spectra were recorded on an Agilent Technologies 6130 Quadrupole LC-MS instrument. High-resolution mass spectra were recorded using a Bruker MaXis Impact. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer and are given in cm^{-1}. Melting points were recorded with a Gallenkamp MPD350 apparatus and are reported as observed. Optical rotations were measured using an AA-1000 polarimeter using a 2 dm cuvette and reported as observed.

Experimental Procedures and Characterization Data

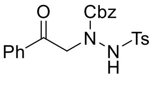


1-Benzyl 2-(*tert*-butyl) 1-tosylhydrazine-1,2-dicarboxylate (4b). *tert*-Butyl 2-tosylhydrazine-1-carboxylate[3] (3.22 g, 11.3 mmol, 1.0 equiv), triethylamine (1.65 mL, 11.8 mmol, 1.05 equiv), 4-dimethylaminopyridine (138 mg, 1.1 mmol, 0.1 equiv) and dichloromethane (20 mL) were stirred at 0 °C. Then benzyl chloroformate (1.69 mL, 11.8 mol, 1.05 equiv) in dichloromethane (20 mL) was added via syringe pump over 1 h. The reaction mixture was then quenched with sodium hydrogen carbonate (20 mL), extracted with dichloromethane (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a clear oil. The crude product was purified by column chromatography (15% EtOAc/pet ether) to give **4b** (4.35 g, 10.4 mmol, 92%) as a colourless oil. R_f = 0.12 (15% EtOAc in petroleum ether); IR (film) 3336, 2981, 1736, 1365, 1155 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.92 (2H, d, *J* 8.0, Ar-*H*), 7.36-7.25 (7H, m, Ar-*H*), 6.95 and 6.63 (minor rotamer) (1H, s, NH), 5.28-5.13 (2H, m, C*H₂*Ph), 2.44 (3H, s, C*H₃*) 1.49 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 153.5 (C=O), 151.5 (C=O), 145.3 (Ar-C), 131.7 (Ar-C), 134.2 (Ar-C), 129.6 (Ar-CH), 129.2 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 82.8 (C), 69.6 (CH_2), 28.0 (CH_3), 21.7 (CH_3); HRMS (ESI^+) calculated for $C_{20}H_{24}N_2NaO_6S$ $[M+Na]^+$ 443.1247; found 443.1245.

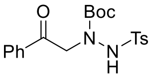
General method 1: Synthesis of keto hydrazines using triply protected hydrazines 4a-b



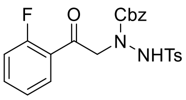
To a solution of hydrazine **4a**[1] or **4b** (1.0 equiv) in anhydrous CH_3CN (0.1 M) was added halide (1.1 equiv) followed by potassium carbonate (1.1 equiv). The reaction mixture was stirred at rt until completion of the reaction (6-24 h). Water (10 mL) was then added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (15-40% EtOAc/ pet ether) to gave the tetrasubstituted hydrazine. To this compound (1.0 equiv) in dichloromethane (0.1 M) was added trifluroacetic acid (10 equiv) at 0 °C. After 2 h, the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (15-40% EtOAc/ pet ether) to give the following compounds.



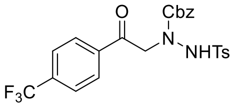
Benzyl 1-(2-oxo-2-phenylethyl)-2-tosylhydrazine-1-carboxylate (5a). Following general procdure 1, hydrazine **4a** (693 mg, 1.65 mmol, 1.0 equiv), 2-bromoacetophenone (360 mg, 1.81 mol, 1.1 equiv), potassium carbonate (250 mg 1.81 mmol, 1.1 equiv) and acetonitrile (17 mL, 0.1 M), then trifluoroacetic acid (1.27 mL, 16.5 mmol, 10 equiv) and dichloromethane (17 mL, 0.1 M) gave **5a** (582 mg, 1.33 mmol, 81%) as a white solid. R_f = 0.38 (30% EtOAc in petroleum ether); M.p. 123-124 °C; IR (film) 3220, 2924, 1724, 1340, 1184 cm^{-1}; δH (400 MHz; $CDCl_3$) 7.90-7.48 (7H, m, Ar-*H*), 7.34-7.23 (4H, m, Ar-*H*), 7.14-7.04 (3H, m, Ar-*H*), 5.07 (2H, s, CH_2Ph), 4.92 (2H, s, NCH_2), 2.43 (major) and 2.38 (minor) (3H, s, CH_3); δC (100 MHz; $CDCl_3$) 193.8 (C=O, rotamer), 193.4 (C=O, rotamer), 157.1 (C=O), 144.5 (Ar-C, rotamer), 144.3 (Ar-C, rotamer), 135.3 (Ar-C), 134.4 (Ar-C, rotamer), 134.3 (Ar-C, rotamer), 134.2 (Ar-CH), 133.9 (Ar-C), 129.5 (Ar-CH), 129.0 (Ar-CH), 128.7 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-CH), 68.8 (CH_2), 59.1 (NCH_2 rotamer), 58.2 (NCH_2 rotamer), 21.8 (CH_3 rotamer), 21.7 (CH_3 rotamer); HRMS (ESI^+) calculated for $C_{23}H_{22}N_2NaO_5S$ $[M+Na]^+$ 461.1142; found 461.1139.



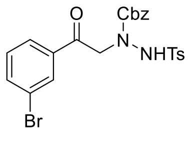
***tert*-Butyl 1-(2-oxo-2-phenylethyl)-2-tosylhydrazine-1-carboxylate (5b).** Hydrazine **4b** (310 mg, 0.74 mmol, 1.0 equiv), 2-bromoacetophenone (161 mg, 0.81 mol, 1.1 equiv), potassium carbonate (112 mg 0.81 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M) were stirred at room temperature for 24 h. The solution was then quenched with water (10 mL), extracted with dichloromethane (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a clear oil. The product was purified by column chromatography (10% EtOAc in petroleum ether) to give a white solid. This was stirred under an atmosphere of hydrogen with 3 wt% palladium on charcoal (30 mg) and ethyl acetate (3.0 mL). The reaction was carefully monitored by TLC, as over-reduction to *rac*-**6b** was seen to occur after Cbz removal. Generally the reaction was complete in approximately 2 h. The crude reaction mixture was then filtered through a plug of Celite and concentrated *in vacuo* to give a clear oil, which was purified by column chromatography (25% EtOAc in petroleum ether) to give **5b** (153 mg, 0.38 mmol, 51%) as a white solid. R_f = 0.52 (25% EtOAc in petroleum ether); M.p. 148-150 °C; IR (film) 3219, 2981, 1710, 1695, 1329, 1156 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.93 (2H, d, *J* 7.4, Ar-*H*), 7.85 (2H, d, *J* 8.2, Ar-H), 7.64 (1H, q, *J* 8.0, Ar-H), 7.55-7.49 (2H, m, Ar-H), 7.41-7.30 (2H, m, Ar-*H*), 7.21 and 7.00 (minor rotamer) (1H, s, NH), 5.01 (2H, s, CH_2N), 2.50-2.42 (3H, m, CH_3), 1.20 and 1.15 (minor rotamer) (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 193.9 (minor rotamer) and 193.6 (C=O), 155.6 and 154.7 (minor rotamer, C=O), 144.5 (minor rotamer) and 144.4 (Ar-C), 134.5 (Ar-C), 134.0 (Ar-CH), 133.6 (Ar-C), 134.2 (Ar-CH), 133.9 (Ar-C), 129.7 (minor rotamer) and 129.3 (Ar-CH), 128.9 and 128.7 (minor rotamer, Ar-CH), 128.8 and 128.6 minor rotamer, Ar-CH), 128.0 (minor rotamer) and 127.9 (Ar-CH), 83.1 (minor rotamer) and 82.8 (C), 58.9, and 58.1 (minor rotamer, CH_2), 27.6 and 27.5 (minor rotamer, CH_3), 21.6 (CH_3); HRMS (ESI^+) calculated for $C_{20}H_{24}N_2NaO_5S$ $[M+Na]^+$ 427.1298; found 427.1296.



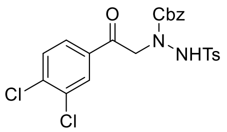
Benzyl 1-(2-(2-fluorophenyl)-2-oxoethyl)-2-tosylhydrazine-1-carboxylate (5c). Following general procdure 1, hydrazine **4a** (300 mg, 0.72 mmol, 1.0 equiv), 2-bromo-2`-fluoroacetophenone (171 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10 equiv) and dichloromethane (8.0 mL, 0.1 M) gave **5c** (204 mg, 0.45 mmol, 62%) as a white solid. R_f = 0.21 (15% EtOAc in petroleum ether); M.p. 122-123 °C; IR (film) 3211, 2966, 1721, 1693, 1609, 1499, 1255, 1200 cm^{-1}; δ*H* (600 MHz; D6-DMSO at 100 °C) 9.97 (1H, s, NH), 7.80 (1H, t, *J* 7.5 Ar-*H*), 7.73-7.67 (3H, m, Ar-*H*), 7.38-7.27 (7H, m, Ar-*H*), 7.21-7.14 (2H, m, Ar-H), 4.84 (2H, s, CH_2Ph), 4.81 (2H, s, NCH_2) 2.36 (3H, s, CH_3); δ*C* (150 MHz, D6-DMSO at 100 °C) 144.0 (Ar-C), 136.1 (d, *J* 9.0, Ar-CH) 130.6 (Ar-CH), 129.7 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 127.8 (Ar-CH), 125.4 (Ar-CH), 117.2 (d, *J* 24 Ar-CH), 68.0 (CH_2), 61.7 (CH_2), 21.4 (CH_3), 2 C=O, 4 Ar-C not seen; δ*F* (376 MHz, D6-DMSO) -108.8 (C-F); HRMS (ESI^+) calculated for $C_{23}H_{21}FN_2O_5S$ $[M+Na]^+$ 479.1047; found 479.1048.



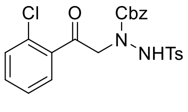
Benzyl 1-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-2-tosylhydrazine-1-carboxylate (5d). Following general procdure 1, hydrazine **4a** (300 mg, 0.72 mmol, 1.0 equiv), 2-bromo-4‘-(trifluoromethyl)acetophenone (211 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10 equiv) and dichloromethane (8.0 mL, 0.1 M) gave **5d** (204 mg, 0.40 mmol, 56%) as a white solid. R_f = 0.19 (15% EtOAc in petroleum ether); M.p. 203-205 °C. IR (film) 3263, 2925, 1710, 1687, 1324, 830, 811 cm^{-1}; δH (500 MHz; $CDCl_3$) 8.05-7.97 (2H, m, Ar-*H*), 7.81-7.68 (4H, m, Ar-*H*), 7.36-7.03 (7H, m, Ar-*H*), 5.11-4.87 (4H, m, NCH_2 and CH_2Ph), 2.43 and 2.39 (minor rotamer) (3H, s, CH_3); δC (125 MHz, $CDCl_3$) 192.4 (C=O, seen on HMBC), 144.0 (Ar-C, seen on HMBC), 136.7 (Ar-C, seen on HMBC), 135.5 (Ar-C), 129.6 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 126.0 (Ar-CH), 68.9 (CH_2), 59.1 (CH_2) and 58.3 (CH_2, minor rotamer), 21.8 (CH_3), CF_3, 2 Ar-C and C=O not seen; δ*F* (376 MHz; $CDCl_3$) -63.3 (CF_3); HRMS (ESI^+) calculated for $C_{24}H_{21}F_3N_2O_5S$ $[M+Na]^+$ 529.1015; found 529.1016.



Benzyl 1-(2-(3-bromophenyl)-2-oxoethyl)-2-tosylhydrazine-1-carboxylate (5e). Following general procdure 1, hydrazine **4a** (300 mg, 0.72 mmol, 1.0 equiv), 2,3‘-bromoacetophenone (220 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10 equiv) and dichloromethane (8.0 mL, 0.1 M) gave **5e** (201 mg, 0.39 mmol, 54%) as a white solid. R_f = 0.18 (15% EtOAc in petroleum ether); M.p. 131-133 °C. IR (film) 3230, 2964, 2919, 1719, 1682, 1494, 1343, 1215 cm^{-1}; δH (500 MHz; $CDCl_3$) 8.03 (1H, d, *J* 8.3, Ar-*H*), 7.86-7.68 (4H, m, Ar-*H*), 7.41-7.02 (8H, m, Ar-*H*), 5.09-4.85 (4H, m, NC*H₂* and C*H₂*Ph), 2.43 and 2.39 (minor rotamer) (3H, s, CH_3); δC (125 MHz, $CDCl_3$) 192.1 (C=O), 156.8 (C=O), 144.6 (Ar-C), 137.0 (Ar-CH), 131.1 (Ar-CH), 130.5 (Ar-CH), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.0 (Ar-CH), 126.5 (Ar-CH), 123.3 (Ar-C), 68.9 (CH_2), 58.9 (CH_2) and 58.1 (CH_2, minor rotamer), 21.8 (CH_3), 3 Ar-C not seen; HRMS (ESI$^+$) calculated for $C_{23}H_{21}{}^{79}BrN_2O_5S$ [M+Na]$^+$ 539.0247; found 539.0240.

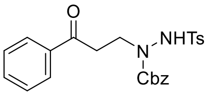


Benzyl 1-(2-(3,4-dichlorophenyl)-2-oxoethyl)-2-tosylhydrazine-1-carboxylate (5f). Following general procdure 1, hydrazine **4a** (204 mg, 0.76 mmol, 1.0 equiv), 2-bromo-3`,4`-dichloroacetophenone (212 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M), then trifluoroacetic acid (586 µL, 7.60 mmol, 10 equiv) and dichloromethane (8.0 mL, 0.1 M) gave **5f** (157 mg, 0.31 mmol, 41%) as a white solid. R_f = 0.22 (15% EtOAc in petroleum ether); M.p. 174-177 °C. IR (film) 3257, 2928, 1710, 1421, 1183 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.97 (1H, d, *J* 8.9, Ar-*H*), 7.81-7.67 (3H, m, Ar-*H*), 7.58 (1H, d, *J* 8.2, Ar-*H*) 7.37-7.01 (7H, m, Ar-*H*), 5.07-4.87 (4H, m, NC*H₂* and C*H₂*Ph), 2.43 and 2.39 (minor rotamer) (3H, s, C*H₃*); δ*C* (125 MHz, $CDCl_3$) 191.8 (C=O, major rotamer), 191.4 (C=O, minor rotamer), 156.7 (C=O), 144.7 (Ar-C), 138.9 (Ar-C) 133.8 (Ar-C), 133.7 (Ar-C), 131.1 (Ar-CH), 130.0 (Ar-CH), 129.6 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 126.9 (Ar-CH), 68.9 (CH_2), 58.8 (CH_2, major rotamer), 58.0 (CH_2, minor rotamer), 21.8 (CH_3), 2 Ar-C not seen; HRMS (ESI$^+$) calculated for $C_{23}H_{20}{}^{35}Cl_2N_2O_5S$ [M+Na]$^+$ 529.0362; found 529.0357.



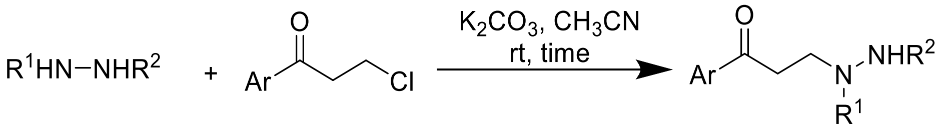
Benzyl 1-(2-(2-chlorophenyl)-2-oxoethyl)-2-tosylhydrazine-1-carboxylate (5g). Following general procdure 1, hydrazine **4a** (300 mg, 0.72 mmol, 1.0 equiv), 2-bromo-2`-chloroacetophenone (184 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (7.2 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10 equiv) and dichloromethane (7.2 mL, 0.1 M) gave **5g** (191 mg, 0.40 mmol, 56%) as a white solid. R_f = 0.42 (25% EtOAc in petroleum ether); M.p. 89-93 °C; IR (film) 3195, 2941, 1728, 1704, 1417, 1382, 1219 cm^{-1}; δ*H* (500 MHz; d6-DMSO) 10.63 and 10.52 (minor rotamer) (1H, s, NH), 7.76-7.43 (5H, m, Ar-*H*), 7.36-7.10 (8H, m, Ar-*H*), 5.15-4.35 (4H, m, NC*H₂* and C*H₂*Ph), 2.30 (3H, s, C*H₃*); δ*C* (125 MHz, d6-DMSO) 195.7 (C=O), 155.6 (C=O), 144.0 (Ar-C), 137.8 (Ar-C), 136.1 (Ar-C), 135.8 (Ar-C), 133.8 (Ar-CH), 131.2 (Ar-CH), 130.8 (Ar-C), 130.2 (Ar-CH), 129.8 (Ar-CH), 129.4 (Ar-

CH), 128.7 (Ar-CH), 128.1 (Ar-CH), 127.8 (Ar-CH), 125.8 (Ar-CH), 67.8 (CH_2), 60.8 (CH_2), 21.6 (CH_3); HRMS (ESI^+) calculated for $C_{23}H_{21}{}^{35}ClN_2O_5S$ $[M+Na]^+$ 495.0752; found 495.0737.

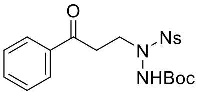


Benzyl 1-(3-oxo-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (5h). Following general procdure 1, hydrazine **4a** (300 mg, 0.72 mmol, 1.0 equiv), 3-chloropropiophenone (133 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (7.2 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10 equiv) and dichloromethane (7.2 mL, 0.1 M) gave **5h** (293 mg, 0.65 mmol, 90%) as a white solid. R_f = 0.20 (15% EtOAc in petroleum ether); M.p. 122-123 °C; IR (film) 3231, 3034, 1702, 1666, 1380, 1307, 1184 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.95 (2H, d, *J* 7.8 Ar-H), 7.75 (2H, d, *J* 8.0, Ar-H), 7.60 (1H, t, *J* 7.3, Ar-H), 7.49 (2H, t, *J* 7.6, Ar-H), 7.33 (3H, d, *J* 4.9, Ar-H), 7.22 (2H, d, *J* 8.0, Ar-H), 7.15 (2H, s, Ar-H), 4.91 (2H, br s, CO_2CH_2), 4.08 (2H, br s, NCH_2), 3.40 (2H, br s, $COCH_2$), 2.42 (3H, s, Ar-CH_3); δ*C* (125 MHz, $CDCl_3$) 198.3 (C=O, seen on HMBC), 144.5 (Ar-C), 136.4 (Ar-C), 135.2 (Ar-C), 133.5 (Ar-CH), 129.6 (Ar-CH), 128.7 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-CH), 128.1 (Ar-CH), 68.5 (CH_2), 46.8 (CH_2), 35.9 (CH_2), 21.7 (CH_3), 1 C=O, 1 Ar-H and 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{24}H_{24}N_2O_5S$ $[M+Na]^+$ 475.1298; found 475.1302.

General method 2: Synthesis of keto hydrazines using diprotected hydrazines

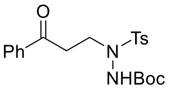


To a solution of protected hydrazine (1.0 equiv) in acetonitrile (0.1 M) was added the organic halide (1.0 equiv) followed by potassium carbonate (1.1 equiv). The reaction mixture was stirred at rt until completion of the reaction (6-24 h, monitored by TLC). Water (10 mL) was then added and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (30-40% EtOAc/ pet ether) to give the following compounds.

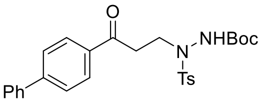


***tert*-Butyl 2-((4-nitrophenyl)sulfonyl)-2-(3-oxo-3-phenylpropyl)hydrazine-1-carboxylate (5i).** Following general method 2, *tert*-butyl 2-((4-nitrophenyl)sulfonyl)hydrazine-1-carboxylate[2] (250 mg, 0.79 mmol, 1.0 equiv), acetonitrile (7.9 mL, 0.1 M), 3-chloropropiophenone (133 mg, 0.83 mmol, 1.05 equiv) and potassium carbonate (112 mg, 0.87 mmol, 1.1 equiv) yielded **5i** as a white solid (249 mg, 0.56 mmol, 70%). R_f = 0.39 (25% EtOAc in petroleum ether); M.p; 157-159 °C; IR (film) 3316, 2984, 1735, 1679, 1526, 1317, 1208 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.80

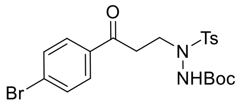
(4H, t, *J* 9.1, Ar-CH), 7.61 (2H, d, *J* 8.3, Ar-CH), 7.32 (2H, d, *J* 7.8, Ar-CH), 6.36 (1H, br s, NH), 3.88 (2H, br s, $COCH_2$), 3.34 (2H, t, *J* 6.3, CH_2NNs), 1.27 (9H, br s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 197.0 (C=O, seen on HMBC), 196.6 (C=O, seen on HMBC), 144.6 (Ar-C), 135.1 (Ar-C), 133.8 (Ar-C), 132.0 (Ar-CH), 129.7 (Ar-CH), 129.6 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH),. 81.8 (C), 46.2 (NCH_2), 37.3 (CH_2), 27.9 (CH_3), 1 C=O not seen; HRMS (ESI^+) calculated for $C_{21}H_{25}{}^{79}BrN_2O_5S$ $[M+Na]^+$ 519.0560; found 519.0564.



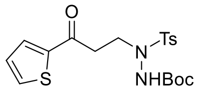
***tert*-Butyl 2-(3-oxo-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (5j).** Following general method 2, *tert*-butyl 2-tosylhydrazine-1-carboxylate[3] (100 mg, 0.35 mmol, 1.0 equiv), acetonitrile (3.5 mL, 0.1 M), 3-chloropropiophenone (59 mg, 0.35 mmol, 1.0 equiv) and potassium carbonate (48 mg, 0.35 mmol, 1.0 equiv) yielded **5j** as a white solid (139 mg, 0.33 mmol, 95%). R_f = 0.29 (30% EtOAc in petroleum ether); M.p. 136-137.5 °C; IR (film) 2986, 2900, 1451, 1250, 1066 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.95-7.78 (4H, m, Ar-*H*), 7.59-7.26 (5H, m, Ar-*H*), 6.38 (major) and 6.03 (minor) (1H, br s, N*H*), 3.89 (2H, br s, NC*H₂*), 3.38 (2H, t, *J* 6.2, C*H₂*CO), 2.42 (3H, s, CH_3), 1.26 (9H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 198.0 (C=O, seen on HMBC), 144.6 (Ar-C), 136.5 (Ar-C), 133.9 (Ar-C), 133.6 (Ar-CH), 129.8 (Ar-CH), 128.7 (Ar-CH), 128.2 (Ar-CH), 81.8 (C), 46.4 (NCH_2), 37.4 (CH_2), 28.0 (Boc-CH_3), 21.7 (CH_3), 1 Ar-CH and 1 C=O not seen; HRMS (ESI^+) calculated for $C_{21}H_{26}N_2NaO_5S$ $[M+Na]^+$ 441.1455; found 441.1459.



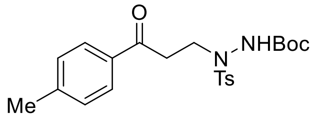
***tert*-Butyl 2-(3-([1,1'-biphenyl]-4-yl)-3-oxopropyl)-2-tosylhydrazine-1-carboxylate (5k).** Following general method 2, *tert*-butyl 2-tosylhydrazine-1-carboxylate[3] (500 mg, 1.75 mmol, 1.00 equiv), acetonitrile (17.5 mL, 0.1 M), 1-([1,1'-biphenyl]-4-yl)-3-chloropropan-1-one[4] (470 mg, 1.92 mmol, 1.1 equiv) and potassium carbonate (265 mg, 1.92 mmol, 1.1 equiv) yielded **5k** as a white solid (635 mg, 1.28 mmol, 73%). M.p. 156-157 °C; R_f = 0.34 (25% EtOAc in petroleum ether); IR (film) 3299, 2983, 2900, 1718, 1660, 1603, 1380, 1252 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.04 (2H, d, *J* 8.3, Ar-H), 7.82 (2H, d, *J* 8.2, Ar-H), 7.71 (2H, d, *J* 8.2, Ar-H), 7.65 (2H, d, *J* 7.4, Ar-H), 7.50 (2H, t, *J* 7.5, Ar-H), 7.43 (1H, t, *J* 7.3, Ar-H), 7.35 (2H, d, *J* 7.8, Ar-H), 3.93 (2H, br s, $COCH_2$), 3.43 (2H, t, *J* 6.1, CH_2NTs), 2.45 (3H, s, CH_3), 1.59 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 197.6 (C=O, seen on HMBC), 146.1 (Ar-C), 144.5 (Ar-C), 139.8 (Ar-C), 135.1 (Ar-C), 129.7 (Ar-CH), 129.6 (Ar-C, seen on HMBC) 129.0 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.3 (Ar-CH), 127.3 (Ar-CH), 127.3 (Ar-CH), 81.5 (C, seen on HMBC), 46.4 (NCH_2), 41.4 (CH_2), 27.9 (CH_3), 21.6 (CH_3), 1 C=O not seen; HRMS (ESI^+) calculated for $C_{27}H_{30}N_2O_5S$ $[M+Na]^+$ 517.1768; found 517.1771.



***tert*-Butyl 2-(3-(4-bromophenyl)-3-oxopropyl)-2-tosylhydrazine-1-carboxylate (5l).** Following general method 2, *tert*-butyl 2-tosylhydrazine-1-carboxylate[3] (150 mg, 0.52 mmol, 1.0 equiv), acetonitrile (5.2 mL, 0.1 M), 4'-bromo-3-chloropropiophenone (129 mg, 0.52 mmol, 1.0 equiv) and potassium carbonate (75 mg, 0.55 mmol, 1.05 equiv) yielded **5l** as a white solid (216 mg, 0.44 mmol, 85%). R_f = 0.29 (25% EtOAc in petroleum ether); M.p. 165-166 °C; IR (film) 3267, 2975, 2927, 1732, 1714, 1368, 1159 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.80 (4H, t, *J* 9.1, Ar-CH), 7.61 (2H, d, *J* 8.3, Ar-CH), 7.32 (2H, d, *J* 7.8, Ar-CH), 6.36 (1H, br s, NH), 3.88 (2H, br s, $COCH_2$), 3.34 (2H, t, *J* 6.3, CH_2NTs), 2.43 (3H, s, Ar-CH_3) 1.27 (9H, br s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 197.0 (C=O, seen on HMBC), 196.6 (C=O, seen on HMBC), 144.6 (Ar-C), 135.1 (Ar-C), 133.8 (Ar-C), 132.0 (Ar-CH), 129.7 (Ar-CH), 129.6 (Ar-CH), 128.7 (Ar-C), 128.6 (Ar-CH), 81.8 (C), 46.2 (NCH_2), 37.3 (CH_2), 27.9 (CH_3), 21.6 (CH_3), 1 C=O not seen; HRMS (ESI^+) calculated for $C_{21}H_{25}{}^{79}BrN_2O_5S$ $[M+Na]^+$ 519.0560; found 519.0564.

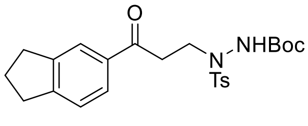


***tert*-Butyl 2-(3-oxo-3-(thiophen-2-yl)propyl)-2-tosylhydrazine-1-carboxylate (5m).** Following general method 2, *tert*-butyl 2-tosylhydrazine-1-carboxylate [3] (200 mg, 0.70 mmol, 1.0 equiv), acetonitrile (7.0 mL, 0.1 M), 3-chloro-1-(thiophen-2-yl)propan-1-one (123 mg, 0.70 mmol, 1.0 equiv) and potassium carbonate (102 mg, 0.74 mmol, 1.05 equiv) yielded **5m** as a pale yellow solid (222 mg, 0.52 mmol, 75%). R_f = 0.38 (25% EtOAc in petroleum ether); M.p. 39-40 °C; IR (film) 3320, 2978, 1718, 1654, 1347, 1237, 1152 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.80 (2H, t, *J* 8.2, Ar-H), 7.76 (2H, d, *J* 3.4, Ar-H), 7.68 (2H, d, *J* 4.8, Ar-H), 7.16 (1H, t, *J* 4.3, Ar-H), 6.35 (1H, br s, NH), 3.90 (2H, br s, $COCH_2$), 3.33 (2H, t, *J* 6.3, CH_2NTs), 2.45 (3H, s, CH_3) 1.28 (9H, br s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 190.9 (C=O, seen on HMBC), 144.5 (Ar-C), 143.7 (Ar-C), 134.2 (Ar-CH), 132.6 (Ar-CH), 129.7 (Ar-CH), 129.6 (Ar-C, seen on HMBC), 128.6 (Ar-CH), 128.3 (Ar-CH), 81.7 (C), 46.3 (NCH_2), 38.0 (CH_2), 27.8 (CH_3), 21.6 (CH_3), Ar-CH and 1 C=O not seen; HRMS (ESI^+) calculated for $C_{19}H_{24}N_2O_5S_2$ $[M+Na]^+$ 447.1018; found 447.1021.

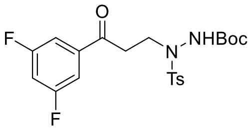


***tert*-Butyl 2-(3-oxo-3-(*p*-tolyl)propyl)-2-tosylhydrazine-1-carboxylate (5n).** Following general method 2, *tert*-butyl 2-tosylhydrazine-1-carboxylate[3] (2.59 g, 9.03 mmol, 1.0 equiv), acetonitrile (90 mL, 0.1 M), 3-chloro-1-(*p*-tolyl)propan-1-one[5] (1.65 g, 9.03 mmol, 1.0 equiv) and potassium carbonate (1.37 g, 9.93 mmol, 1.1 equiv) yielded **5n** after purification by column chromatography (33% EtOAc in petroleum ether) as a white solid (3.41 g, 7.88 mmol, 79%). M.p. 146-147 °C; R_f = 0.17 (33% EtOAc in petroleum ether); IR (neat) 3314, 1719, 1667, 1346, 1154, 1101, 1023, 973, 813, 775, 739 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.83 (2H, d, *J* 8.2, Ar-*H*), 7.78 (2H, d, *J* 8.2, Ar-*H*), 7.30 (2H, d, *J* 8.0, Ar-*H*), 7.24 (2H, d, *J* 8.0, Ar-*H*), 6.41

(0.74H, br s, NH major), 6.09 (0.26H, br s, NH minor), 3.86 (2H, br s, NCH$_2$), 3.34 (2H, t, *J* 6.8, CH$_2$CO), 2.41 (3H, s, CH$_3$), 2.40 (3H, s, CH$_3$), 1.26 (9H, s, (CH$_3$)$_3$); δ*C* (101 MHz; CDCl$_3$) 199.9 (C=O, seen on HMBC), 144.5 (Ar-C), 144.4 (Ar-C), 134.1 (Ar-C), 134.1 (Ar-C), 129.8 (Ar-CH), 129.5 (Ar-CH), 128.7 (Ar-CH), 128.3 (Ar-CH), 81.7 (C, seen on HMBC), 46.5 (NCH$_2$), 37.2 (*C*H$_2$CO), 28.0 (Boc-CH$_3$), 21.8 (CH$_3$), 21.7 (CH$_3$), Boc-C=O not observed; HRMS (ESI$^+$) calculated for C$_{22}$H$_{28}$N$_2$NaO$_5$S [M+Na]$^+$ 455.1611; found 455.1612.

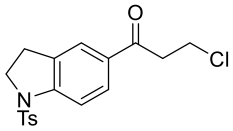


***tert*-Butyl 2-(3-(2,3-dihydro-1*H*-inden-5-yl)-3-oxopropyl)-2-tosylhydrazine-1-carboxylate (5o).** Following general method 2, *tert*-butyl 2-tosylhydrazine-1-carboxylate[3] (2.81 g, 9.82 mmol, 1.0 equiv), acetonitrile (98 mL, 0.1 M), 3-chloro-1-(2,3-dihydro-1*H*-inden-5-yl)propan-1-one[5] (2.05 g, 9.82 mmol, 1.0 equiv) and potassium carbonate (1.49 g, 10.8 mmol, 1.1 equiv) yielded **5o** after purification by column chromatography (20-33% EtOAc in petroleum ether) as a colouless gum (3.84 g, 8.37 mmol, 85%). R$_f$ = 0.31 (33% EtOAc in petroleum ether); IR (neat) 3303, 2975, 1724, 1675, 1366, 1237, 1152, 1090, 814, 753 cm^{-1}; δ*H* (400 MHz; CDCl$_3$) 7.81-7.77 (3H, m, Ar-*H*), 7.73 (1H, d, *J* 8.0, Ar-*H*), 7.31 (2H, d, *J* 8.1, Ar-*H*), 7.28 (1H, d, *J* 8.0, Ar-*H*), 6.38 (1H, br s, NH), 3.86 (2H, br m, NCH$_2$), 3.35 (2H, t, *J* 6.7, CH$_2$CO), 2.94 (4H, t, *J* 7.4, CH$_2$), 2.42 (3H, s, CH$_3$), 2.11 (2H, p, *J* 7.4, CH$_2$C*H$_2$*CH$_2$), 1.27 (9H, s, (CH$_3$)$_3$); δ*C* (101 MHz; CDCl$_3$) 198.0 (C=O, seen on HMBC), 150.8 (Ar-C), 145.0 (Ar-C), 144.5 (Ar-C), 135.1 (Ar-C), 134.0 (Ar-C), 129.8 (Ar-CH), 128.7 (Ar-CH), 126.8 (Ar-CH), 124.6 (Ar-CH), 124.2 (Ar-CH), 81.6 (C, seen on HMBC), 46.6 (NCH$_2$), 37.3 (*C*H$_2$CO), 33.2 (CH$_2$), 32.7 (CH$_2$), 28.0 (Boc-CH$_3$), 25.5 (CH$_2$*C*H$_2$CH$_2$), 21.7 (CH$_3$), Boc-C=O not observed; HRMS (ESI$^+$) calculated for C$_{24}$H$_{30}$N$_2$NaO$_5$S [M+Na]$^+$ 481.1768; found 481.1772.

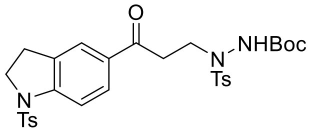


***tert*-Butyl 2-(3-(3,5-difluorophenyl)-3-oxopropyl)-2-tosylhydrazine-1-carboxylate (5p).** Following general procedure 2, *tert*-butyl 2-tosylhydrazine-1-carboxylate[3] (350 mg, 1.22 mmol, 1.0 equiv), 3-chloro-1-(3,5-difluorophenyl)propan-1-one (250 mg, 1.22 mol, 1.1 equiv), potassium carbonate (185 mg, 1.34 mmol, 1.1 equiv) and acetonitrile (12 mL, 0.1 M) gave **5p** (409 mg, 0.90 mmol, 74%) as a white solid. R$_f$ = 0.29 (15% EtOAc in petroleum ether); M.p. 158-159 °C; IR (film) 3250, 2923, 1733, 1692, 1240, 1028 cm^{-1}; δ*H* (500 MHz; CDCl$_3$) 7.81 (2H, d, *J* 8.2, Ar-H), 7.46 (2H, d, *J* 5.6, Ar-H), 7.35 (2H, d, *J* 7.8, Ar-H), 7.05 (1H, t, J 8.2, Ar-H), 6.39 and 5.96 (minor rotamer) (1H, s, NH), 3.95-3.62 (2H, br m, C*H$_2$*N), 3.34 (2H, t, *J* 6.4, COCH$_2$), 2.45 (3H, s, C*H$_3$*), 1.30 (9H, s, C(CH$_3$)$_3$); δ*C* (125 MHz; CDCl$_3$) 164.2 (C=O), 163.1 (dd, *J* 251.4, 11.7, Ar-CF), 144.7 (Ar-C), 139.3 (Ar-C), 129.7 (Ar-CH), 128.6 (Ar-CH), 111.1 (dd, *J* 18.9, 6.3, Ar-CH), 108.7 (t, *J* 25.0, Ar-CH), 81.9 (C), 50.8 (CH$_2$), 46.0 (CH$_2$), 27.9

(CH_3), 21.6 (CH_3), 1 C=O and 1 Ar-C not seen; δ*F* (376 MHz; $CDCl_3$) -107.8 (Ar-CF); HRMS (ESI$^+$) calculated for $C_{21}H_{24}N_2NaO_5SF_2$ [M+Na]$^+$ 477.1266; found 477.1264.

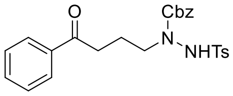


3-Chloro-1-(1-tosylindolin-5-yl)propan-1-one (12). Aluminium trichloride (733 mg, 5.50 mmol, 1.1 equiv) was slowly added to a solution of 1-tosylindoline[6] (1.37 g, 5.00 mmol, 1.0 equiv) and 3-chloropropionyl chloride (525 µL, 5.50 mmol, 1.1 equiv) in dichloromethane (5.0 mL) at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Water (10 mL) was carefully added at 0 ºC, the layers were separated and the organic layer was washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL). The resulting organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was recrystallised from EtOAc to give **12** as a tan-coloured solid (1.72 g, 4.72 mmol, 94%). M.p. 152-154 °C; IR (neat) 1676, 1602, 1486, 1350, 1247, 1159, 1099, 1038, 969, 819 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.81 (1H, d, *J* 8.4, Ar-*H*), 7.71 (2H, d, *J* 8.2, Ar-*H*), 7.70 (1H, d, *J* 8.3, Ar-*H*), 7.67 (1H, d, *J* 8.3, Ar-*H*), 7.26 (2H, d, *J* 8.2, Ar-*H*), 3.97 (2H, t, *J* 8.6, NCH_2), 3.89 (2H, t, *J* 6.8, CH_2Cl), 3.37 (2H, t, *J* 6.8, CH_2CO), 3.01 (2H, t, *J* 8.6, $NCH_2C\mathit{H_2}$), 2.38 (3H, s, CH_3); δ*C* (101 MHz; $CDCl_3$) 195.3 (C=O), 146.8 (Ar-C), 144.8 (Ar-C), 133.9 (Ar-C), 132.2 (Ar-C), 132.1 (Ar-C), 130.0 (Ar-CH), 129.3 (Ar-CH), 127.3 (Ar-CH), 125.3 (Ar-CH), 113.6 (Ar-CH), 50.3 (NCH_2), 41.1 (CH_2CO), 39.0 (CH_2Cl), 27.4 (NCH_2CH_2), 21.7 (CH_3); HRMS (ESI$^+$) calculated for $C_{18}H_{18}Cl^{35}NNaO_3S$ [M+Na]$^+$ 386.0588; found 386.0584.

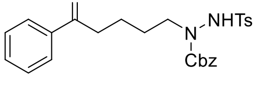


***tert*-Butyl 2-(3-oxo-3-(1-tosylindolin-5-yl)propyl)-2-tosylhydrazine-1-carboxylate (5q).** Following general method 2, *tert*-butyl 2-tosylhydrazine-1-carboxylate[3] (897 mg, 3.13 mmol, 1.0 equiv), acetonitrile (32 mL, 0.1 M), 3-chloro-1-(1-tosylindolin-5-yl)propan-1-one (**12**) (1.14 g, 3.13 mmol, 1.0 equiv) and potassium carbonate (476 mg, 3.44 mmol, 1.1 equiv) yielded **5q** after purification by column chromatography (33-50% EtOAc in petroleum ether) as a white foam (1.42 g, 2.31 mmol, 75%). M.p. 87-89 °C; R_f = 0.32 (50% EtOAc in petroleum ether); IR (neat) 3294, 2974, 1674, 1602, 1353, 1244, 1159, 1090, 1051, 973, 813 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.80 (1H, d, *J* 8.6, Ar-*H*), 7.78 (2H, d, *J* 8.3, Ar-*H*), 7.71 (2H, d, *J* 8.3, Ar-*H*), 7.68 (1H, s, Ar-*H*), 7.66 (1H, d, *J* 8.6, Ar-*H*), 7.31 (2H, d, *J* 7.9, Ar-*H*), 7.27 (2H, d, *J* 7.9, Ar-*H*), 6.33 (1H, br s, NH), 3.97 (2H, t, *J* 8.6, $N\mathit{CH_2}CH_2C$), 3.84 (2H, br m, $N\mathit{CH_2}CH_2CO$), 3.29 (2H, t, *J* 6.7, $NCH_2C\mathit{H_2}CO$), 3.00 (t, *J* 8.6, 2H $NCH_2C\mathit{H_2}C$), 2.42 (3H, s, CH_3), 2.38 (3H, s, CH_3), 1.25 (9H, s, $(CH_3)_3$); δ*C* (101 MHz; $CDCl_3$) 196.6 (C=O, seen on HMBC), 146.7 (Ar-C), 144.8 (Ar-C), 144.6 (Ar-C), 133.9 (Ar-C), 132.2 (Ar-C), 132.1 (Ar-C), 130.0 (Ar-CH), 129.8 (Ar-CH), 129.3 (Ar-CH), 128.7 (Ar-CH), 127.4 (Ar-CH), 125.4 (Ar-CH), 113.6 (Ar-CH), 81.6 (C, seen on HMBC), 50.4 (NCH_2CH_2C), 46.6 (NCH_2CH_2CO), 36.8 (NCH_2CH_2CO), 28.0 (Boc-CH_3), 27.4 (NCH_2CH_2C), 21.74 (CH_3), 21.70 (CH_3), one Ar-C and Boc-C=O not observed; HRMS (ESI$^+$) calculated for $C_{30}H_{35}N_3NaO_7S_2$ [M+Na]$^+$ 636.1809; found 636.1809.

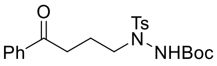
<u>Other Aryl Ketone Syntheses</u>



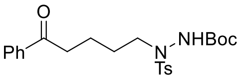
Benzyl 1-(4-oxo-4-phenylbutyl)-2-tosylhydrazine-1-carboxylate (5r). Hydrazine **4a**[1] (400 mg, 0.96 mmol, 1.0 equiv), 4-hydroxy-1-phenylbutan-1-one[10] 158 mg, 0.96 mmol, 1.0 equiv), triphenylphosphine (376 mg, 1.44 mmol, 1.5 equiv), diethyl azodicarboxylate (224 µL, 1.44 mmol, 1.5 equiv) and tetrahydrofuran (10 mL, 0.1 M) were combined and stirred at room temperature for 24 h. The reaction mixture was then concentrated *in vacuo*. The crude product was purified by column chromatography (30% EtOAc/ pet ether) to give the tetrasubstituted hydrazine. To this hydrazine was added trifluoroacetic acid (735 µL, 9.60 mmol, 10.0 equiv) and dichloromethane (9.6 mL, 0.1 M), the solution was then stirred for 2 h. The resulting yellow solution was concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography (25% EtOAc/pet ether) to yield **5r** as a white solid (215 mg, 0.46 mmol, 48%). R_f = 0.26 (25% EtOAc in petroleum ether); M.p. 136-137 °C; IR (film) 3179, 3060, 2955, 1709, 1687, 1369, 1270 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.91 (2H, d, *J* 7.6 Ar-CH), 7.72 (2H, d, *J* 7.8, Ar-CH), 7.58 (1H, t, *J* 7.3, Ar-CH), 7.46 (2H, t, *J* 7.7, Ar-CH), 7.31 (3H, t, *J* 6.9, Ar-CH), 7.19 (2H, d, *J* 7.5, Ar-CH), 7.10-7.00 (3H, m, Ar-CH and NH), 4.78 (2H, br s, $COOCH_2$), 3.79 (2H, br s, CH_2NCbz), 3.01 (2H, br s, $COCH_2$), 2.41 (3H, s, Ar-CH_3), 2.15-2.08 (2H, m, $COCH_2CH_2$); δ*C* (125 MHz, $CDCl_3$) 199.2 (C=O, seen on HMBC), 144.4 (Ar-C), 136.7 (Ar-C), 135.2 (Ar-C), 133.2 (Ar-CH), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 127.7 (Ar-C), 68.3 (CH_2), 50.6 (CH_2), 35.6 (CH_2), 22.7 (CH_2), 21.7 (Ar-CH_3), 1 C=O and 1 Ar-CH not seen; HRMS (ESI$^+$) calculated for $C_{25}H_{26}N_2O_5S$ [M+Na]$^+$ 489.1455; found 489.1455.



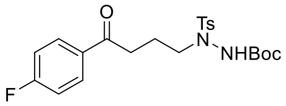
Benzyl 1-(5-oxo-5-phenylpentyl)-2-tosylhydrazine-1-carboxylate (5s). Hydrazine **4a**[1] (200 mg, 0.48 mmol, 1.0 equiv), 5-hydroxy-1-phenylpentan-1-one[10] (84 mg, 0.48 mmol, 1.0 equiv), triphenylphosphine (188 mg, 0.72 mmol, 1.5 equiv), diethyl azodicarboxylate (112 µL, 0.72 mmol, 1.5 equiv) and tetrahydrofuran (4.8 mL, 0.1 M) were combined and stirred at room temperature for 24 h. The reaction mixture was then concentrated *in vacuo*. The crude product was purified by column chromatography (30% EtOAc/ pet ether) to give the tetrasubstituted hydrazine. To this hydrazine was added trifluoroacetic acid (368 µL, 4.8 mmol, 10.0 equiv) and dichloromethane (4.8 mL, 0.1 M), the solution was then stirred for 2 h. The resulting yellow solution was concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography (25% EtOAc/pet ether) to yield **5s** as a white solid (140 mg, 0.29 mmol, 61%). R_f = 0.28 (25% EtOAc in petroleum ether); M.p. 86-88 °C; IR (film) 3214, 2957, 1699, 1671, 1364, 1181 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.96 (2H, d, *J* 7.6, Ar-H), 7.74 (2H, d, *J* 8.0, Ar-H), 7.59 (1H, t, *J* 7.3, Ar-H), 7.49 (2H, t, *J* 7.7, Ar-H), 7.38-7.30 (3H, m, Ar-H), 7.22 (2H, d, *J* 8.0, Ar-H), 7.15 (2H, s, Ar-H), 6.99 (1H, s, NH), 4.90 (2H, br s, $COOCH_2$), 3.72 (2H, br s, CH_2NCbz), 2.99 (2H, br s, $COCH_2$), 2.42 (3H, s, CH_3), 1.79-1.67 (4H, m, $COCH_2C\mathit{H_2}C\mathit{H_2}$); δC (125 MHz, $CDCl_3$) 199.8 (C=O), 144.5 (Ar-C), 136.9 (Ar-C), 135.2 (Ar-C), 133.1 (Ar-CH), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 68.4 (CH_2), 50.7 (CH_2), 37.9 (CH_2), 26.5 (CH_2), 21.7 (Ar-CH_3), 20.9 (CH_2), 1 C=O, 1 Ar-C and 1 Ar-CH not seen; HRMS (ESI$^+$) calculated for $C_{26}H_{28}N_2O_5S$ $[M+Na]^+$ 503.1611; found 503.1615.



***tert*-Butyl 2-(4-oxo-4-phenylbutyl)-2-tosylhydrazine-1-carboxylate (5t).** To a solution of *tert*-butyl 2-tosylhydrazine-1-carboxylate [3] (4.20 g, 14.7 mmol, 1.0 equiv) in dimethylformamide (146 mL) was added 4-iodo-1-phenylbutan-1-one[8] (6.04 g, 22.0 mmol, 1.5 equiv) followed by potassium carbonate (3.34 g, 24.2 mmol, 1.6 equiv). The reaction mixture was stirred at rt for 20 h. The mixture was concentrated under reduced pressure, ethyl acetate (100 mL) was added, and mixture was washed with water (5 × 80 mL), brine (80 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (20-33% EtOAc/petroleum ether) to give **5t** as a white solid (4.92 g, 11.4 mmol, 78%). R_f = 0.32 (33% EtOAc in petroleum ether); M.p. 133-135 °C; IR (neat) 3277, 2977, 2910, 1717, 1677, 1342, 1161, 994, 665 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.96 (2H, d, *J* 7.2, Ar-*H*), 7.74 (2H, d, *J* 7.5, Ar-*H*), 7.56 (1H, t, *J* 7.3, Ar-*H*), 7.45 (2H, t, *J* 7.6, Ar-*H*), 7.30-7.25 (2H, m, Ar-*H*), 6.37 (0.70H, br s, N*H* major), 5.84 (0.30H, br s, N*H* minor), 3.52 (2H, br s, $NC\mathit{H_2}$), 3.17 (2H, t, *J* 6.8, $C\mathit{H_2}CO$), 2.39 (3H, s, CH_3), 2.00 (2H, p, *J* 6.5, $C\mathit{H_2}CH_2N$), 1.33 (9H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 199.9 (C=O), 153.6 (Boc-C=O), 144.4 (Ar-C), 137.0 (Ar-C), 134.2 (Ar-C), 133.2 (Ar-CH), 129.7 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.2 (Ar-CH), 81.7 (C), 49.5 (NCH_2), 35.5 ($\mathit{C}H_2CO$), 28.1 (Boc-CH_3), 21.7 (CH_3), 21.2 ($\mathit{C}H_2CH_2N$); HRMS (ESI$^+$) calculated for $C_{22}H_{28}N_2NaO_5S$ $[M+Na]^+$ 455.1611; found 455.1612.

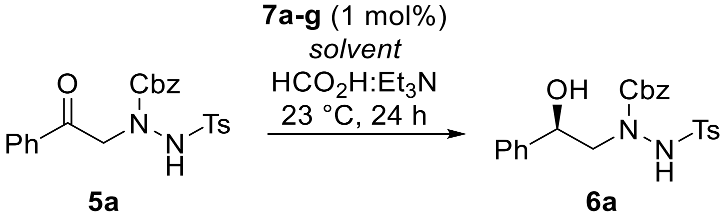


***tert*-Butyl 2-(5-oxo-5-phenylpentyl)-2-tosylhydrazine-1-carboxylate (5u).** To a solution of *tert*-butyl 2-tosylhydrazine-1-carboxylate[3] (2.58 g, 9.00 mmol, 1.0 equiv) in anhydrous dimethylformamide (90 mL) was added 5-iodo-1-phenylpentan-1-one[10] (3.92 g, 13.5 mmol, 1.5 equiv) followed by potassium carbonate (1.99 g, 14.4 mmol, 1.6 equiv). The reaction mixture was stirred at rt for 28 h. The mixture was concentrated under reduced pressure, ethyl acetate (60 mL) was added, and mixture was washed with water (5 × 50 mL), brine (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (20-33% EtOAc/petroleum ether) to give **5u** as a colourless oil, which crystallised upon standing to a white solid (2.63 g, 5.90 mmol, 65%). R_f = 0.31 (33% EtOAc in petroleum ether); M.p. 89-91 °C; IR (neat) 3226, 3141, 2958, 1697, 1680, 1315, 1117, 1041, 976, 772, 693 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.96 (2H, d, *J* 7.6, Ar-*H*), 7.77 (2H, d, *J* 8.2, Ar-*H*), 7.56 (1H, t, *J* 7.4, Ar-*H*), 7.46 (2H, t, *J* 7.6, Ar-*H*), 7.36–7.28 (2H, m, Ar-*H*), 6.40 (0.68H, br s, N*H* major), 5.84 (0.32H, br s, N*H* minor), 3.48 (2H, br s, NC*H$_2$*), 3.01 (2H, t, *J* 7.1, C*H$_2$*CO), 2.41 (3H, s, CH_3), 1.88-1.79 (2H, m, C*H$_2$*CH_2CO), 1.68 (2H, p, *J* 7.6, C*H$_2$*CH_2N), 1.31 (9H, br s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 200.1 (C=O), 153.4 (Boc-C=O), 144.4 (Ar-C), 137.0 (Ar-C), 134.4 (Ar-C), 133.2 (Ar-CH), 129.7 (Ar-CH), 128.7 (Ar-CH), 128.2 (Ar-CH), 81.6 (C), 49.5 (NCH_2), 37.8 (CH_2CO), 28.1 (Boc-CH_3), 26.7 (*C*H_2CH_2N), 21.7 (CH_3), 21.1 (*C*H_2CH_2CO), 1 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{23}H_{30}N_2NaO_5S$ $[M+Na]^+$ 469.1768; found 469.1765.

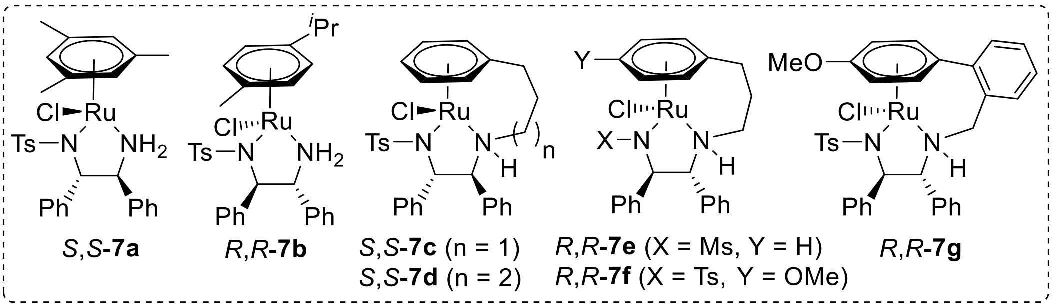


***tert*-Butyl 2-(4-(4-fluorocyclohexa-2,4-dien-1-yl)-4-oxobutyl)-2-tosylhydrazine-1-carboxylate (5v).** To a solution of *tert*-butyl 2-tosylhydrazine-1-carboxylate[3] (4.24 g, 14.8 mmol, 1.0 equiv) in dimethylformamide (150 mL) was added 1-(4-fluorophenyl)-4-iodobutan-1-one[11] (6.48 g, 22.2 mmol, 1.5 equiv) followed by potassium carbonate (3.27 g, 23.7 mmol, 1.6 equiv). The reaction mixture was stirred at rt for 26 h. The mixture was concentrated under reduced pressure, ethyl acetate (100 mL) was added, and mixture was washed with water (5 × 80 mL), brine (80 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (20-33% EtOAc/petroleum ether) to give **5v** as a white solid (5.25 g, 11.7 mmol, 79%). M.p. 135-137 °C; R_f = 0.34 (33% EtOAc in petroleum ether); IR (neat) 3254, 2980, 1738, 1670, 1596, 1508, 1366, 1242, 1159, 1048, 814, 742, 655 cm^{-1}; δ*H* (300 MHz; $CDCl_3$) 8.00 (2H, dd, *J* 8.1, 5.8, Ar-*H*), 7.74 (2H, d, *J* 8.0 Hz, Ar-*H*), 7.33-7.26 (2H, m, Ar-*H*), 7.12 (2H, t, *J* 8.4, Ar-*H*), 6.33 (0.74H, br s, N*H* major), 5.83 (0.26H, br s, N*H* minor), 3.50 (2H, br s, NC*H$_2$*), 3.16 (2H, t, *J* 6.9, C*H$_2$*CO), 2.40 (3H, s, CH_3), 2.00 (2H, p, *J* 6.5, C*H$_2$*CH_2N), 1.33 (9H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) δ 198.5 (C=O), 165.9 (d, *J* 254.5, CF), 153.6 (Boc-C=O), 144.5 (Ar-C), 134.2 (Ar-C), 133.5 (d, *J* 2.9, Ar-C), 130.9 (d, *J* 7.4, Ar-CH), 129.7 (Ar-CH), 128.6 (Ar-CH), 115.8 (d, *J* 21.7, Ar-CH), 81.8 (C), 49.6 (NCH_2), 35.4 (*C*H_2CO), 28.1 (Boc-CH_3), 21.7 (CH_3), 21.2 (*C*H_2CH_2N); δ*F* (376 MHz; $CDCl_3$) –105.5 (CF); HRMS (ESI^+) calculated for $C_{22}H_{27}FN_2NaO_5S$ $[M+Na]^+$ 473.1517; found 473.1522.

Asymmetric Transfer Hydrogenation: Optimization



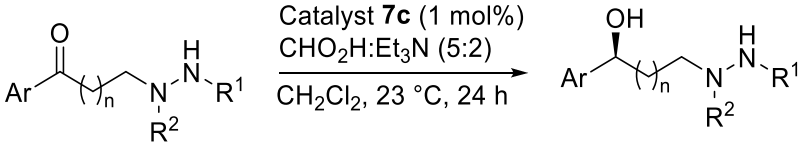
The catalyst (1 mol%) was stirred in formic acid : triethylamine (5 : 2) azeotrope (0.11 mL) for 10 min. Aryl ketone **5a** (50 mg, 0.11 mmol, 1.0 equiv) and solvent (so that [S] = 0.2-0.5 M) were added and the solution was stirred for 24-48 h at 23 °C. The solution was then concentrated *in vacuo* and the crude product was purified by column chromatography (30% ethyl acetate in petroleum ether). Enantiomeric excess (98% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak ADH column 2-propanol/hexane = 15/85; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 26.8 min; t_R 28.8 min.



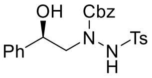
Entry	Catalyst	Solvent	Yield [%][a]	Ee [%][b]
1	*S,S*-**7a**	CH_2Cl_2	86	97 (*R*)
2	*R,R*-**7b**	CH_2Cl_2	16[c]	91 (*S*) [d]
3	*S,S*-**7c**	CH_2Cl_2	97	99 (*R*)
4	*S,S*-**7d**	CH_2Cl_2	7	97 (*R*)
5	*R,R*-**7e**	CH_2Cl_2	97	97 (*S*) [d]
6	*R,R*-**7f**	CH_2Cl_2	80	99 (*S*) [d]
7	*R,R*-**7g**	CH_2Cl_2	16	98 (*S*) [d]
8	*S,S*-**7c**	$CHCl_3$	96	99 (*R*)
9	*S,S*-**7c**	EtOAc	88	99 (*R*)
10	*S,S*-**7c**	MeCN[e]	66	98 (*R*)
11	*S,S*-**7c**	MeOH[f]	92	99 (*R*)

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis using chiralpak ADH. [c] reaction run for 48 h. [d] Opposite *S*-enantiomer produced. [e] reaction run at 0.3 M. [f] reaction run at 0.2 M.

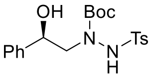
General method 3: Asymmetric Transfer Hydrogenation (ATH)



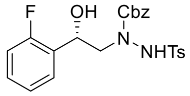
A solution of catalyst (0.5 - 1 mol%) in formic acid : triethylamine (5 : 2) azeotrope (so that [S] = 1.0 M) was stirred for 15 min. The ketone substrate (1.0 equiv) and Dichloromethane (so that [S] = 0.25 – 0.5 M) were added and stirred at 23 °C. After 24 h, the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (35-40% EtOAc/ pet ether) to give the following alcohols.



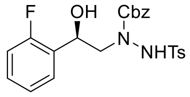
Benzyl (*R*)-1-(2-hydroxy-2-phenylethyl)-2-tosylhydrazine-1-carboxylate (6a). Following general method 3, aryl ketone **5a** (100 mg, 0.23 mmol, 1.0 equiv), catalyst **7c** (1.4 mg, 2.3 μmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.23 mL, 1.0 M) in dichloromethane (0.46 mL, 0.5 M) yielded **6a** as a white solid (97 mg, 0.22 mmol, 97%). M.p. 100-101 °C; R_f = 0.29 (40% EtOAc in petroleum ether); $[\alpha]^{31}_{D}$ –50.5 (*c* 0.30, $CHCl_3$). Enantiomeric excess (98% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak ADH column 2-propanol/hexane = 15/85; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 26.8 min; t_R 28.8 min. IR (film) 3228, 2925, 1716, 1340, 1185 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.73-7.71 (2H, m, Ar-*H*), 7.32-7.13 (12H, m, Ar-*H*), 5.13-4.85 (3H, m, C*H*OH and OCH_2Ph), 3.88-3.73 (2H, m, NCH_2), 2.79 (1H, br s, OH), 2.39 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 144.6 (Ar-C), 141.1 (Ar-C), 129.6 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 126.0 (Ar-CH), 71.0 (CH, seen on HSQC), 68.8 (CH_2), 58.4 (NCH_2), 21.8 (CH_3), C=O, 2 Ar-C and 1 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{23}H_{24}N_2NaO_5S$ $[M+Na]^+$ 463.1298; found 463.1302.



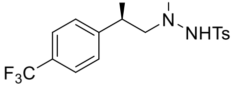
***tert*-Butyl (*R*)-1-(2-hydroxy-2-phenylethyl)-2-tosylhydrazine-1-carboxylate (6b).** Following general method 4, aryl ketone **5b** (100 mg, 0.25 mmol, 1.0 equiv), (*S*,*S*)-catalyst **7c** (1.6 mg, 2.5 μmol, 0.01 equiv), 5:2 FA:TEA complex (0.25 mL, 1 M) and CH_2Cl_2 (0.50 mL, 0.5 M) yielded **6b** as a white solid (100 mg, 0.25 mmol, 99%). R_f = 0.21 (25% EtOAc in petroleum ether); M.p. 138-139 °C; $[\alpha]_D^{28}$ = –4.8 (*c* 0.12, $CHCl_3$); Enantiomeric excess (99% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 1.5/98.5; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 37.7 min; t_R 42.4 min; IR (film) 3456, 3128, 2975, 1709, 1089; δ*H* (500 MHz, $CHCl_3$) 7.82 (2H, d, *J* 8.2, Ar-H), 7.36 (7H, m, Ar-H), 5.17 (1H, dd, *J* 9.9, 3.6, CHPh), 3.86 (1H, br m, NC*H*H), 3.74 (1H, d, *J* 9.9, NCH*H*), 2.44 (3H, s, CH_3), 1.18 (9H, br s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 144.6 (C=O), 141.4 (Ar-C), 132.2 (Ar-C), 132.1 (Ar-C) 130.0 (Ar-CH), 129.8 (Ar-CH), 128.6 (Ar-CH), 128.0 (Ar-CH), 126.0 (Ar-CH), 82.9 (C), 75.2 (CH), 58.8 (CH_2) 27.8 (CH_3), 21.6 (CH_3); HRMS (ES^+) calculated for $C_{20}H_{26}N_2O_5S$ $(M+Na)^+$ 429.1451; found 429.1455.



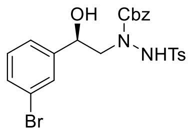
Benzyl (*S*)-1-(2-(2-fluorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (6c). Following general method 3, aryl ketone **5c** (100 mg, 0.22 mmol, 1.0 equiv), catalyst **7f** (1.5 mg, 2.2 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.22 mL, 1.0 M) and dichloromethane (0.44 mL, 0.5 M) yielded **6c** as a colourless oil (97 mg, 0.21 mmol, 97%). R_f = 0.21 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +4.0 (*c* 0.22, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 56.4 min; t_R 61.4 min. IR (film) 3503, 3237, 2926, 1713, 1305, 1128 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.73 (2H, d, *J* 7.9, Ar-CH), 7.47 (1H, t, *J* 7.3, Ar-H), 7.42 (1H, d, *J* 7.7, Ar-H), 7.38-7.26 (3H, m, Ar-H), 7.20 (2H, d, *J* 8.0, Ar-H), 7.18-7.11 (3H, m, Ar-H), 7.00 (1H, t, *J* 10.0, Ar-H), 5.44-5.34 (1H, m, C*H*OH), 4.86 (2H, br s, C*H₂*Ph), 3.99-3.89 and 2.95-2.75 (minor rotamer) (2H, m, NCH_2) 2.40 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 159.9 (d, *J* 245.0, Ar-CF), 144.6 (Ar-C), 135.0 (Ar-C), 129.6 (Ar-CH), 129.6 (Ar-CH), 128.0 (d, *J* 12.5, Ar-C), 127.7 (d, *J* 3.8, Ar-CH), 124.5 (d, *J* 3.8, Ar-CH), 115.4 (d, *J* 21.3, Ar-CH), 68.7 (CH_2), 66.3 (CH, seen on HSQC), 57.0 (CH_2), 21.7 (CH_3), 1 Ar-C, 4 Ar-CH, C=O not seen; δ*F* (376 MHz, $CDCl_3$) -118.6 (CF); HRMS (ESI^+) calculated for $C_{23}H_{23}FN_2O_5S$ $[M+Na]^+$ 481.1204; found 481.1209.



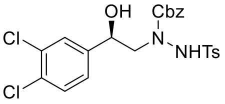
Benzyl (*R*)-1-(2-(2-fluorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (6c). Following general method 3, aryl ketone **5c** (100 mg, 0.22 mmol, 1.0 equiv), catalyst **7c** (1.5 mg, 2.2 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.22 mL, 1.0 M) and dichloromethane (0.44 mL, 0.5 M) yielded **6c** as a colourless oil (97 mg, 0.21 mmol, 97%). $[\alpha]^{32}_D$ –3.17 (*c* 0.30, $CHCl_3$). Enantiomeric excess (77% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 56.4 min; t_R 61.4 min.



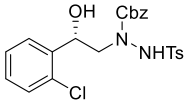
Benzyl (*R*)-1-(2-hydroxy-2-(4-(trifluoromethyl)phenyl)ethyl)-2-tosylhydrazine-1-carboxylate (6d). Following general method 3, aryl ketone **5d** (100 mg, 0.20 mmol, 1.0 equiv), catalyst **7c** (1.24 mg, 2.0 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.2 mL, 1.0 M) and dichloromethane (0.4 mL, 0.5 M) yielded **6d** as a white solid (97 mg, 0.19 mmol, 96%). R_f = 0.19 (35% EtOAc in petroleum ether); M.p. 147-148 °C; $[\alpha]^{32}_D$ –18.1 (*c* 0.06, $CHCl_3$). Enantiomeric excess (95% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 8/92; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 20.6 min; t_R 25.4 min; IR (film) 3439, 3144, 2923, 1716, 1401, 1324, 1087 cm^{-1}; δ*H* (600 MHz; d6-DMSO at 100 °C) 9.66 (1H, s, NH), 7.68 (2H, d, *J* 8.2, Ar-H), 7.61 (2H, d, *J* 8.1, Ar-H), 7.50 (2H, d, *J* 8.0, Ar-H), 7.39-7.25 (5H, m, Ar-H), 7.15 (2H, d, *J* 7.5, Ar-H), 5.31 (1H, s, OH), 4.96-4.92 (1H, t, *J* 8.2, C*H*OH), 4.75-4.63 (2H, m, C*H$_2$*Ph), 3.75-3.58 (2H, m, NC*H$_2$*), 2.38 (3H, s, CH_3); δ*C* (150 MHz; D6-DMSO at 100 °C) 155.7 (C=O), 148.1 (Ar-C), 143.9 (Ar-C), 137.3 (Ar-C), 136.3 (Ar-C), 129.8 (Ar-CH), 128.6 (q, *J* 26.3, Ar-C), 128.5 (Ar-CH), 128.2 (Ar-CH), 127.9 (Ar-CH), 127.9 (Ar-CH), 127.3 (Ar-CH), 125.3 (q, *J* 3.8, Ar-CH), 124.8 (q, *J* 225.0, CF_3), 69.5 (CH), 67.7 (CH_2), 58.0 (CH_2), 21.4 (CH_3); δ*F* (286 MHz, D6-DMSO) -61.8 (CF_3); HRMS (ESI$^+$) calculated for $C_{24}H_{23}F_3N_2O_5S$ $[M+Na]^+$ 531.1172; found 531.1173.



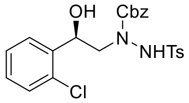
Benzyl (*R*)-1-(2-(3-bromophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (6e). Following general method 3, aryl ketone **5e** (80 mg, 0.15 mmol, 1.0 equiv), catalyst **7c** (1.0 mg, 1.5 μmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.15 mL, 1.0 M) and dichloromethane (0.3 mL, 0.5 M) yielded **6e** as a white solid (80 mg, 0.15 mmol, 99%). R_f = 0.20 (35% EtOAc in petroleum ether); M.p. 135-136 °C; $[\alpha]^{32}_D$ –16.0 (*c* 0.50, $CHCl_3$); Enantiomeric excess (97% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 9/91; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 19.6 min; t_R 25.1 min; IR (film) 3456, 3222, 2929, 1715, 1323, 1211, 1185 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.73 (2H, d, *J* 8.0, Ar-CH), 7.50 (1H, s, Ar-H), 7.42 (1H, d, *J* 7.7, Ar-H), 7.36-7.32 (3H, m, Ar-H), 7.27-7.05 (6H, m, Ar-H) 5.11 (1H, d, *J* 9.5, C*H*OH), 4.87 (2H, br s, C*H$_2$*Ph), 3.90-3.65 (2H, m, NCH_2) 2.41 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 144.8 (Ar-C), 143.4 (Ar-C), 131.1 (Ar-CH), 130.2 (Ar-CH), 129.7 (Ar-CH), 129.0 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 124.6 (Ar-CH), 122.8 (Ar-C), 70.6 (CH, seen on HSQC), 68.8 (CH_2), 58.5 (CH_2), 21.8 (CH_3), 2 Ar-C, 1 Ar-CH, C=O not seen; HRMS (ESI$^+$) calculated for $C_{23}H_{23}{}^{79}BrN_2O_5S$ $[M+Na]^+$ 541.0403; found 541.0411.



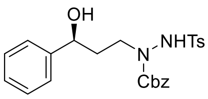
Benzyl (*R*)-1-(2-(3,4-dichlorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (6f). Following general method 3, aryl ketone **5f** (100 mg, 0.20 mmol, 1.0 equiv), catalyst **7c** (1.2 mg, 2.0 μmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.2 mL, 1 M) and dichloromethane (0.4 mL, 0.5 M) yielded **6f** as a white solid (100 mg, 0.2 mmol, 99%). M.p. 141-142 °C; R_f = 0.21 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –37.7 (*c* 0.12, $CHCl_3$). Enantiomeric excess (92% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 12/88; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 18.4 min; t_R 24.1 min; IR (film) 3424, 3118, 2968, 2891, 1715, 1466, 1394, 1203 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.73 (2H, d, *J* 8.0, Ar-H), 7.45 (1H, s, Ar-H), 7.40 (1H, d, *J* 8.2, Ar-H), 7.36-7.32 (3H, m, Ar-H), 7.22 (2H, d, *J* 8.1, Ar-H), 7.19-7.05 (4H, m, Ar-H), 5.12 (1H, dd, *J* 9.1, 2.1, C*H*OH), 4.87 (2H, br s, C*H₂*Ph), 3.81 (1H, t, *J* 8.9, NC*H*H), 3.71 (1H, d, *J* 13.8, NCH*H*) 2.42 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 144.9 (Ar-C), 141.2 (Ar-C), 132.8 (Ar-C), 131.9 (Ar-C), 130.6 (Ar-CH), 129.7 (Ar-CH), 129.7 (Ar-C, seen on HMBC), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 125.3 (Ar-CH), 70.5 (CH, seen on HSQC), 68.9 (CH_2), 58.7 (CH_2), 21.8 (CH_3), 1 Ar-C, C=O not seen; HRMS (ESI^+) calculated for $C_{23}H_{22}{}^{35}Cl_2N_2O_5S$ $[M+Na]^+$ 531.0519; found 531.0517.



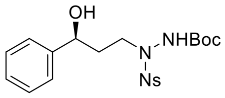
Benzyl (*S*)-1-(2-(2-chlorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (6g). Following general method 3, aryl ketone **5g** (100 mg, 0.20 mmol, 1.0 equiv), catalyst **7f** (1.3 mg, 2.0 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.2 mL, 1.0 M) and dichloromethane (0.4 mL, 0.5 M) yielded **6g** as a colourless oil (100 mg, 0.2 mmol, 99%). R_f = 0.21 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +35.8 (*c* 0.12, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 57.1 min; t_R 65.2 min; IR (film) 3443, 3115, 2896, 1717, 1457, 1432, 1250 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.74 (2H, d, *J* 7.8, Ar-H), 7.57 (1H, d, *J* 7.5, Ar-H), 7.40 (1H, d, *J* 8.2, Ar-H), 7.35-7.10 (9H, m, Ar-H), 5.48 (1H, m, C*H*OH), 4.88 (2H, br s, C*H₂*Ph), 3.87 and 2.92 (minor rotamer) (2H, br s, NCH_2), 2.40 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 144.6 (Ar-C), 138.4 (Ar-C), 131.9 (Ar-C), 129.6 (Ar-CH), 129.5 (Ar-CH), 129.1 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 127.6 (Ar-CH), 127.2 (Ar-CH), 69.0 (CH, seen on HSQC), 68.7 (CH_2), 56.6 (CH_2), 21.7 (CH_3), 2 Ar-C, 2 Ar-CH, C=O not seen; HRMS (ESI^+) calculated for $C_{23}H_{24}{}^{35}ClN_2O_5S$ $[M+Na]^+$ 497.0908; found 497.0905.



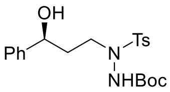
Benzyl (*R*)-1-(2-(2-chlorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (6g). Following general method 3, aryl ketone **5g** (100 mg, 0.20 mmol, 1.0 equiv), catalyst **7c** (1.3 mg, 2.0 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.2 mL, 1.0 M) and dichloromethane (0.4 mL, 0.5 M) yielded **6g** as a colourless oil (100 mg, 0.2 mmol, 99%). $[\alpha]^{32}_D$ –14.7 (*c* 0.10, $CHCl_3$). Enantiomeric excess (19% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 57.1 min; t_R 65.2 min.



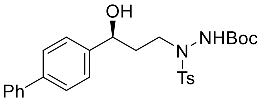
Benzyl (*S*)-1-(3-hydroxy-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (6h). Following general method 3, aryl ketone **5h** (100 mg, 0.22 mmol), catalyst **7c** (1.4 mg, 2.2 µmol), 5 : 2 formic acid : triethylamine complex (0.22 mL, 1.0 M) and dichloromethane (0.88 mL, 0.25 M) yielded **6h** as a colourless oil (100 mg, 0.22 mmol, 99%). R$_f$ = 0.23 (35% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ –4.6 (*c* 0.75, $CHCl_3$). Enantiomeric excess was determined after cyclisation to **8h**. IR (film) 3503, 3228, 2951, 1707, 1340, 1185 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.73 (2H, d, *J* 7.9, Ar-CH), 7.38-7.29 (5H, m, Ar-H) 7.47 (4H, dd, *J* 13.5 and 7.9, Ar-H), 7.21 (3H, d, *J* 7.9, Ar-H), 7.02 (1H, br s, NH), 5.01-4.59 (3H, m, C*H*OH and CH_2Ph), 3.84 (2H, br s, NCH_2), 2.42 (3H, s, CH_3) 2.09-2.03 (2H, m, C*H$_2$*CHOH); δ*C* (125 MHz; $CDCl_3$) 144.4 (Ar-C), 143.4 (Ar-C), 135.1 (Ar-C), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-CH), 127.8 (Ar-CH), 125.6 (Ar-CH), 72.3 (CH), 68.4 (CH_2), 48.7 (CH_2), 35.0 (CH_2), 21.7 (CH_3), C=O and 1 Ar-C not seen; HRMS (ESI$^+$) calculated for $C_{24}H_{26}N_2O_5S$ [M+Na]$^+$ 477.1455; found 477.1457.



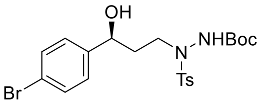
***tert*-Butyl (*S*)-2-(3-hydroxy-3-phenylpropyl)-2-((4-nitrophenyl)sulfonyl)-hydrazine-1-carboxylate (6i).** Following general method 3, aryl ketone **5i** (100 mg, 0.22 mmol, 1.0 equiv), catalyst **7c** (1.4 mg, 2.2 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.22 mL, 1.0 M) and dichloromethane (0.88 mL, 0.25 M) yielded **6i** as a white solid (86 mg, 0.19 mmol, 86%). R$_f$ = 0.18 (35% EtOAc in petroleum ether); M.p. 112-114 °C; $[\alpha]^{32}_{D}$ –5.0 (*c* 0.30, $CHCl_3$); enantiomeric excess was determined after cyclisation to **8i**. IR (film) 3512, 3287, 2951, 1712, 1620, 1350, 1158 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.28 (2H, d, *J* 8.3, Ar-H), 8.04 (2H, t, *J* 9.2, Ar-H), 7.29 (3H, d, *J* 4.3, Ar-H), 7.28-7.19 (2H, m, Ar-H), 6.62 (1H, s, NH), 4.84 (1H, t, *J* 6.1, C*H*OH), 3.84-3.45 (2H, m, NCH_2), 1.95 (2H, q, *J* 6.1, C*H$_2$*CHOH), 1.26-1.18 (9H, m, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 153.5 (C=O), 150.5 (Ar-C), 143.9 (Ar-C), 128.7 (Ar-CH), 128.6 (Ar-CH), 127.8 (Ar-CH), 125.7 (Ar-CH), 124.0 (Ar-CH), 83.3 (C) and 82.6 (minor rotamer), 71.7 (CH), 47.5 (CH_2), 36.4 (CH_2), 27.9 (CH_3) and 27.8 (minor rotamer), 1 Ar-C not seen; HRMS (ESI$^+$) calculated for $C_{20}H_{25}N_3O_7$ [M+Na]$^+$ 474.1305; found 474.1307.



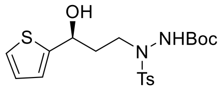
***tert*-Butyl (*S*)-2-(3-hydroxy-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (6j).** Following general method 3, aryl ketone **5j** (97 mg, 0.23 mmol, 1.0 equiv), catalyst **7c** (1.4 mg, 2.3 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.23 mL, 1.0 M) in dichloromethane (0.92 mL, 0.25 M) yielded **6j** as a colourless oil (96 mg, 0.23 mmol, 98%). R$_f$ = 0.22 (35% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ –34.4 (*c* 0.20, $CHCl_3$). Enantiomeric excess (96% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 15/85; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 15.4 min; t_R 20.1 min; IR (film) 3294, 2985, 1745, 1393, 1159, 1055 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.81-7.79 (2H, m, Ar-*H*), 7.38-7.27 (7H, m, Ar-*H*), 6.45 (major) and 6.08 (minor) (1H, br s, N*H*), 4.97 (1H, br s, C*H*OH), 3.68-3.48 (2H, m, NC*H*$_2$), 2.95 (1H, br s, O*H*), 2.42 (3H, s, Ts-C*H*$_3$), 1.97 (2H, br s, CHC*H*$_2$), 1.32 (9H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 153.9 (C=O), 144.7 (Ar-C), 144.6 (Ar-C), 133.8 (Ar-C), 129.7 (Ar-CH), 128.8 (Ar-CH), 128.6 (Ar-CH), 127.5 (Ar-CH), 125.8 (Ar-CH), 81.9 (C), 71.5 (CH), 47.8 (NCH_2), 36.6 (CH_2), 28.0 (CH_3), 21.8 (CH_3); HRMS (ESI$^+$) calculated for $C_{21}H_{28}N_2NaO_5S$ $[M+Na]^+$ 443.1611; found 443.1610.



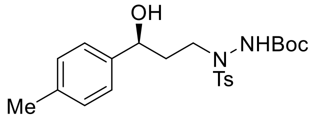
***tert*-Butyl (*S*)-2-(3-([1,1'-biphenyl]-4-yl)-3-hydroxypropyl)-2-tosylhydrazine-1-carboxylate (6k).** Following general method 3, aryl ketone **5k** (100 mg, 0.20 mmol, 1.0 equiv), catalyst **7c** (1.3 mg, 2.0 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.20 mL, 1.0 M) and Dichloromethane (0.80 mL, 0.25 M) yielded **6k** as a white solid (100 mg, 0.20 mmol, 99%). M.p. 62-63 °C; R_f = 0.19 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –17.7 (*c* 0.62, $CHCl_3$). Enantiomeric excess was determined after cyclisation to **8k**. IR (film) 3513, 3303, 2926, 1704, 1391, 1247 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.84 (2H, d, *J* 7.1, Ar-CH), 7.60 (4H, t, *J* 7.1, Ar-H) 7.47 (4H, dd, *J* 13.5, 7.9, Ar-H), 7.36 (3H, t, *J* 7.5, Ar-H), 6.40 (1H, br s, NH), 5.07 (1H, s, C*H*OH), 3.81-3.42 (2H, m, NCH_2), 2.46 (3H, s, CH_3) 2.09-1.96 (2H, m, C*H*$_2$CHOH), 1.26 (9H, s, $C(CH_3)_3$); δC (125 MHz; $CDCl_3$) 153.9 (C=O), 150.5 (Ar-C), 144.6 (Ar-C), 143.5 (Ar-C), 140.3 (Ar-C), 133.7 (Ar-C), 129.7 (Ar-CH), 128.8 (Ar-CH), 128.7 (Ar-CH), 127.2 (Ar-CH), 127.2 (Ar-CH), 127.1 (Ar-CH), 126.2 (Ar-CH), 81.9 (C), 71.2 (CH), 47.8 (CH_2), 36.5 (CH_2), 28.0 (CH_3) 21.6 (CH_3); HRMS (ESI$^+$) calculated for $C_{27}H_{32}N_2O_5S$ $[M+Na]^+$ 519.1924; found 519.1924.



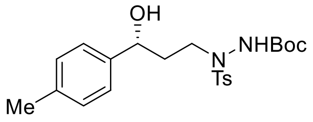
***tert*-Butyl (*S*)-2-(3-(4-bromophenyl)-3-hydroxypropyl)-2-tosylhydrazine-1-carboxylate (6l).** Following general method 3, aryl ketone **5l** (100 mg, 0.20 mmol, 1.0 equiv), catalyst **7c** (1.27 mg, 2.0 µmol), 5 : 2 formic acid : triethylamine complex (0.20 mL, 1.0 M) and dichloromethane (0.80 mL, 0.25 M) yielded **6l** as a white solid (100 mg, 0.20 mmol, 99%). M.p. 121-124 °C; R_f = 0.17 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –25.8 (*c* 0.65, $CHCl_3$). Enantiomeric excess (91% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 25.0 min; t_R 30.2 min. IR (film) 3513, 3303, 2925, 1704, 1367, 1247 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.83 (2H, d, *J* 7.1, Ar-CH), 7.48 (2H, d, *J* 7.8, Ar-H), 7.36 (2H, d, *J* 7.7, Ar-H), 7.36 (2H, d, *J* 7.6, Ar-H), 5.02 (1H, br s, C*H*OH), 3.88-3.01 (2H, m, NCH_2), 2.46 (3H, s, CH_3) 2.05-1.82 (2H, m, C*H*$_2$CHOH), 1.36 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 154.1 (C=O), 144.8 (Ar-C), 143.6 (Ar-C), 133.5 (Ar-C), 131.5 (Ar-CH), 129.7 (Ar-CH), 128.7 (Ar-CH), 127.5 (Ar-CH), 121.0 (Ar-C), 82.1 (C), 70.8 (CH), 47.8 (CH_2), 36.5 (CH_2), 27.9 (CH_3), 21.6 (CH_3); HRMS (ESI$^+$) calculated for $C_{21}H_{27}{}^{79}BrN_2O_5S$ $[M+Na]^+$ 521.0716; found 521.0716.



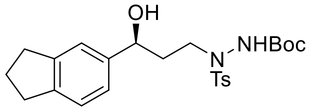
tert-Butyl (_S_)-2-(3-hydroxy-3-(thiophen-2-yl)propyl)-2-tosylhydrazine-1-carboxylate (6m). Following general method 3, aryl ketone **5m** (100 mg, 0.24 mmol, 1.0 equiv), catalyst **7c** (1.5 mg, 2.4 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.24 mL, 1.0 M) and Dichloromethane (0.48 mL, 0.25 M) yielded **6m** as a colourless oil (97 mg, 0.23 mmol, 97%). R_f = 0.21 (35% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ –6.5 (*c* 0.13, $CHCl_3$). Enantiomeric excess (98% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 22.4 min; t_R 24.5 min; IR (film) 3453, 3309, 2926, 1704, 1354, 1252 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.82 (2H, d, *J* 7.4, Ar-CH), 7.35 (2H, d, *J* 6.6, Ar-H), 7.26 (1H, d, *J* 4.0, Ar-H), 7.08-6.94 (2H, m, Ar-H), 6.43 (1H, s, NH), 5.27 (1H, br s, C*H*OH), 3.79-3.47 (2H, m, NCH_2), 2.45 (3H, s, CH_3) 2.20-2.03 (2H, m, CH_2CHOH), 1.34 (9H, s, $C(CH_3)_3$); δC (125 MHz; $CDCl_3$) 153.8 (C=O), 148.4 (Ar-C), 144.6 (Ar-C), 133.7 (Ar-C), 129.6 (Ar-CH), 128.7 (Ar-CH), 126.7 (Ar-CH), 124.4 (Ar-CH), 123.5 (Ar-CH), 82.0 (C), 67.7 (CH), 47.6 (CH_2), 36.6 (CH_2), 27.9 (CH_3), 21.6 (CH_3); HRMS (ESI$^+$) calculated for $C_{19}H_{26}N_2O_5S_2$ $[M+Na]^+$ 449.1175; found 449.1179.



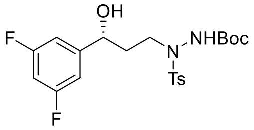
tert-Butyl (_S_)-2-(3-hydroxy-3-(_p_-tolyl)propyl)-2-tosylhydrazine-1-carboxylate ((_S_)-6n). Following general method 3, aryl ketone **5n** (433 mg, 1.00 mmol, 1.0 equiv), catalyst (*S*,*S*)-**7c** (6.2 mg, 10 µmol, 1.0 mol%), formic acid : triethylamine (5 : 2) complex (1.0 mL, 1.0 M) and dichloromethane (3.0 mL, 0.33 M) yielded (*S*)-**6n** after purification by column chromatography (33-50% EtOAc/petroleum ether) as a colourless gum (432 mg, 0.99 mmol, 99%). R_f = 0.40 (50% EtOAc in petroleum ether); $[\alpha]^{23}_{D}$ –23.4 (*c* 0.46, $CHCl_3$). Enantiomeric excess (96% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 24.3 min; t_R 27.1 min; IR (neat) 3313, 2977, 2927, 1719, 1367, 1153, 813 cm^{-1}; δH (300 MHz; $CDCl_3$) 7.82 (2H, d, *J* 7.8, Ar-*H*), 7.34 (2H, d, *J* 7.8, Ar-*H*), 7.29 (2H, d, *J* 7.8, Ar-*H*), 7.17 (2H, d, *J* 7.8, Ar-*H*), 6.40 (1H, br s, NH), 5.01-4.90 (1H, m, C*H*OH), 3.68 (1H, br m, NC*H*H), 3.50 (1H, br m, NCH*H*), 2.45 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.20 (1H, br s, OH), 1.98 (2H, dd, *J* 11.5, 6.1, CH_2CHOH), 1.35 (9H, s, $(CH_3)_3$); δC (101 MHz; $CDCl_3$) 144.6 (Ar-C), 141.6 (Ar-C), 140.2 (Ar-C, seen on HMBC), 137.1 (Ar-C, seen on HMBC), 129.7 (Ar-CH), 129.2 (Ar-CH), 128.8 (Ar-CH), 125.8 (Ar-CH), 81.5 (C, seen on HMBC), 71.4 (CHOH), 47.7 (NCH_2), 36.5 (CH_2CHOH), 28.0 (Boc-CH_3), 21.7 (CH_3), 21.2 (CH_3), Boc-C=O not observed; HRMS (ESI$^+$) calculated for $C_{22}H_{30}N_2NaO_5S$ $[M+Na]^+$ 457.1768; found 457.1765.



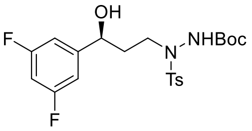
***tert*-Butyl (*R*)-2-(3-hydroxy-3-(*p*-tolyl)propyl)-2-tosylhydrazine-1-carboxylate ((*R*)-6n).** Following general method 3, aryl ketone **5n** (433 mg, 1.00 mmol, 1.0 equiv), catalyst (*R*,*R*)-**7c** (3.1 mg, 5.0 µmol, 1.0 mol%), formic acid : triethylamine (5 : 2) complex (1.0 mL, 1.0 M) and dichloromethane (3.0 mL, 0.33 M) yielded (*R*)-**6n** after purification by column chromatography (33-50% EtOAc/petroleum ether) as a colourless gum (373 mg, 0.86 mmol, 86%). $[\alpha]^{22}_{D}$ +39.6 (*c* 0.40, $CHCl_3$). Enantiomeric excess (97% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 24.6 min; t_R 30.5 min.



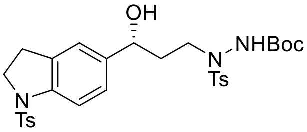
***tert*-Butyl (*S*)-2-(3-(2,3-dihydro-1*H*-inden-5-yl)-3-hydroxypropyl)-2-tosylhydrazine-1-carboxylate (6o).** Following general method 3, aryl ketone **5o** (917 mg, 2.00 mmol, 1.0 equiv), catalyst **7c** (12.4 mg, 20 µmol, 1.0 mol%), formic acid : triethylamine (5 : 2) complex (2.0 mL, 1.0 M) and dichloromethane (4.0 mL, 0.5 M) yielded **6o** after purification by column chromatography (33-50% EtOAc/petroleum ether) as a white foam (905 mg, 1.96 mmol, 98%). M.p. 41-43 °C; R_f = 0.52 (50% EtOAc in petroleum ether); $[\alpha]^{23}_{D}$ –25.9 (*c* 0.62, $CHCl_3$). Enantiomeric excess (95% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 24.3 min; t_R 34.4 min; IR (neat) 3311, 2930, 2846, 1704, 1351, 1246, 1152, 814, 715 cm^{-1}; δ*H* (300 MHz; $CDCl_3$) 7.80 (2H, d, *J* 7.7, Ar-*H*), 7.32 (2H, d, *J* 7.7, Ar-*H*), 7.24 (1H, s, Ar-*H*), 7.19 (1H, d, *J* 7.8, Ar-*H*), 7.12 (1H, d, *J* 7.8, Ar-*H*), 6.38 (1H, br s, NH), 4.92 (1H, t, *J* 4.9, C*H*OH), 3.67 (1H, br m, NC*H*H), 3.50 (1H, br m, NCH*H*), 2.89 (4H, t, *J* 7.3, CH_2), 2.67 (1H, br s, OH), 2.43 (3H, s, CH_3), 2.07 (2H, p, *J* 7.3, $CH_2CH_2CH_2$), 1.97 (2H, dd, *J* 11.8, 6.1, CH_2CHOH), 1.32 (9H, s, $(CH_3)_3$); δ*C* (101 MHz; $CDCl_3$) 144.6 (Ar-C), 144.2 (Ar-C, seen on HMBC), 143.6 (Ar-C, seen on HMBC), 133.5 (Ar-C, seen on HMBC), 129.7 (Ar-CH), 128.8 (Ar-CH), 124.4 (Ar-CH), 123.8 (Ar-CH), 121.9 (Ar-CH), 81.5 (C, seen on HMBC), 71.8 (CHOH), 47.8 (NCH_2), 36.7 (CH_2CHOH), 32.9 (CH_2), 32.7 (CH_2), 28.1 (Boc-CH_3), 25.6 ($CH_2CH_2CH_2$), 21.7 (CH_3), one Ar-C and Boc-C=O not observed; HRMS (ESI$^+$) calculated for $C_{24}H_{32}N_2NaO_5S$ $[M+Na]^+$ 483.1924; found 483.1921 .



***tert*-Butyl (*R*)-2-(3-(3,5-difluorophenyl)-3-hydroxypropyl)-2-tosylhydrazine-1-carboxylate (6p).** Following general procedure 4, aryl ketone **5p** (572 mg, 1.26 mmol, 1.0 equiv), (*R*,*R*)-catalyst **7f** (8.4 mg, 13 µmol, 0.01 equiv), 5:2 FA:TEA complex (1.26 mL, 1 M) and CH_2Cl_2 (5 mL, 0.25 M) yielded **6p** as a white solid (572 mg, 1.26 mmol, 99%). R_f = 0.46 (33% EtOAc in petroleum ether); $[\alpha]_D^{24}$ +55.3 (*c* 0.03, $CHCl_3$); Enantiomeric excess (93% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 13.5 min; t_R 16.3 min. M.p. 110-111 °C; IR (film) 3333, 3165, 2980, 1740, 1625, 1183 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.84 (2H, d, *J* 7.4, Ar-H), 7.37 (2H, d, *J* 7.8, Ar-H), 6.95 (2H, d, *J* 6.3, Ar-H), 6.70 (1H, t, *J* 7.7, Ar-H), 6.33 (1H, s, NH), 5.08 (1H, d, *J* 5.1, C*H*OH), 3.79-3.65 (1H, br m, C*H*HN), 3.48-3.37 (1H, br m, CH*H*N), 2.46 (3H, s, C*H₃*), 2.04-1.95 (1H, br m, CHOHC*H*H), 1.92-1.79 (1H, br m, CHOHCH*H*), 1.37 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 163.1 (dd, *J* 246.2, 12.5, Ar-CF), 154.3 (C=O), 149.0 (Ar-C), 144.9 (Ar-C), 133.3 (Ar-C), 129.7 (Ar-CH), 128.7 (Ar-CH), 108.5 (dd, *J* 21.3, 6.3, Ar-CH), 102.4 (t, *J* 26.3, Ar-CH), 82.3 (C), 70.4 (CH), 47.8 (CH_2), 36.4 (CH_2), 27.9 (CH_3), 21.6 (CH_3); δ*F* (376 MHz; $CDCl_3$) -109.9 (Ar-CF); HRMS (ESI$^+$) calculated for $C_{21}H_{26}N_2NaO_5SF_2$ $[M+Na]^+$ 479.1423; found 479.1421.

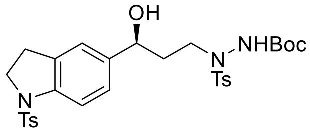


***tert*-Butyl (*S*)-2-(3-(3,5-difluorophenyl)-3-hydroxypropyl)-2-tosylhydrazine-1-carboxylate (6p).** Following general procedure 4, aryl ketone **5p** (266 mg, 0.59 mmol, 1.0 equiv), (*S*,*S*)-catalyst **7c** (3.6 mg, 6 µmol, 0.01 equiv), 5:2 FA:TEA complex (0.59 mL, 1 M) and CH_2Cl_2 (2.4 mL, 0.25 M) yielded **6p** as a white solid (266 mg, 0.59 mmol, 99%). $[\alpha]_D^{24}$ –14.2 (c 0.10, $CHCl_3$); Enantiomeric excess (80% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 13.5 min; t_R 16.3 min.

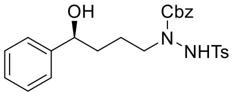


***tert*-Butyl (*R*)-2-(3-hydroxy-3-(1-tosylindolin-5-yl)propyl)-2-tosylhydrazine-1-carboxylate ((*R*)-6q).** Following general method 3, aryl ketone **5q** (1.42 g, 2.31 mmol, 1.0 equiv), catalyst (*R*,*R*)-**7c** (14.3 mg, 23 µmol, 1.0 mol%), formic acid : triethylamine (5 : 2) complex (2.3 mL, 1.0 M) and dichloromethane (6.9 mL, 0.33 M) yielded (*R*)-**6q** after purification by column chromatography (33-50% EtOAc/petroleum ether) as a white foam (1.13 g, 1.84 mmol, 92%). M.p. 65-68 °C; R_f = 0.22 (50% EtOAc in petroleum ether); $[\alpha]^{22}_D$ +20.9 (*c* 0.32, $CHCl_3$). Enantiomeric excess (88% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 20/80; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 41.3 min; t_R 46.2 min; IR (neat) 3305, 2928, 1722, 1599, 1486, 1350, 1245, 1158, 1089, 1052, 974, 813 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.79 (2H, d, *J* 8.0, Ar-*H*), 7.66 (2H, d, *J* 8.0, Ar-*H*), 7.58 (1H, d, *J* 8.4, Ar-*H*), 7.32 (2H, d, *J* 8.0, Ar-*H*), 7.22 (2H, d, *J* 8.0, Ar-*H*), 7.17 (1H, d, *J* 8.4, Ar-*H*), 7.13 (1H, s, Ar-*H*), 6.32 (1H, br s, NH), 4.91 (1H, br m, C*H*OH), 3.90 (2H, t, *J* 8.4, NC*H₂*CH₂C), 3.64 (1H, br m, NC*H*HCH₂CO), 3.44 (1H, br m, NCH*H*CH₂CO), 2.94 (1H, br s, OH), 2.87 (2H, t, *J* 8.2, NCH₂C*H₂*C), 2.43 (3H, s, CH_3), 2.37 (3H, s, CH_3), 1.98-1.83 (2H, m, NCH₂C*H₂*CO), 1.32 (9H, s, $(CH_3)_3$); δ*C* (151 MHz; $CDCl_3$) 144.8 (Ar-C), 144.2 (Ar-C), 141.4

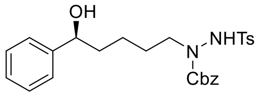
(Ar-C), 140.3 (Ar-C, seen on HMBC), 134.0 (Ar-C), 132.2 (Ar-C), 129.82 (Ar-CH), 129.80 (Ar-CH), 128.8 (Ar-CH), 127.5 (Ar-CH), 125.5 (Ar-CH), 122.8 (Ar-CH), 114.9 (Ar-CH), 81.8 (C, seen on HMBC), 71.4 (CHOH), 50.3 (N*C*$H_2$$CH_2$C), 47.9 (N*C*$H_2$$CH_2$CHOH, seen on HMBC), 36.1 (NCH_2*C*H_2CHOH, seen on HMBC), 28.1 (Boc-CH_3), 28.0 (NCH_2*C*H_2C), 21.8 (CH_3), 21.7 (CH_3), one Ar-C Boc-C=O not observed; HRMS (ESI$^+$) calculated for $C_{30}H_{37}N_3NaO_7S_2$ [M+Na]$^+$ 638.1965; found 638.1961.



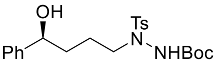
***tert*-Butyl (*S*)-2-(3-hydroxy-3-(1-tosylindolin-5-yl)propyl)-2-tosylhydrazine-1-carboxylate ((*S*)-6q).** Following general method 3, aryl ketone **5q** (505 mg, 0.82 mmol, 1.0 equiv), catalyst (*S*,*S*)-**7c** (5.1 mg, 8.2 µmol, 1.0 mol%), formic acid : triethylamine (5 : 2) complex (0.8 mL, 1.0 M) and dichloromethane (1.6 mL, 0.5 M) yielded (*S*)-**6q** after purification by column chromatography (33-50% EtOAc/petroleum ether) as a colourless gum (356 mg, 0.58 mmol, 71%). $[\alpha]^{22}_D$ –20.6 (*c* 0.38, $CHCl_3$). Enantiomeric excess (89% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 20/80; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 39.7 min; t_R 47.1 min.



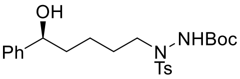
Benzyl (*S*)-1-(4-hydroxy-4-phenylbutyl)-2-tosylhydrazine-1-carboxylate (6r). Following general method 3, aryl ketone **5r** (60 mg, 0.13 mmol, 1.0 equiv), catalyst **7c** (1 mg, 1.3 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.13 mL, 1.0 M) and dichloromethane (0.26 mL, 0.5 M) yielded **6r** as a colourless oil (60 mg, 0.13 mmol, 99%). R_f = 0.20 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –13.0 (*c* 0.92, $CHCl_3$); enantiomeric excess was determined after cyclisation to **8r**; IR (film) 3510, 3285, 2946, 1717, 1375, 1184 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.72 (2H, d, *J* 8.0, Ar-H), 7.40-7.30 (8H, m, Ar-H), 7.21 (2H, d, *J* 8.1, Ar-H), 7.12 (2H, d, *J* 6.1, Ar-H), 4.88 (2H, s, CH_2Ph), 4.69 (1H, s, C*H*OH), 3.70 (2H, br s, NCH_2), 2.42 (3H, s, CH_3), 1.85-1.62 (4H, m, C*H_2*C*H_2*CHOH); δ*C* (125 MHz; $CDCl_3$) 144.5 (Ar-C), 144.4 (Ar-C), 135.2 (Ar-C), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 127.7 (Ar-CH), 125.8 (Ar-CH), 74.2 (CH), 68.4 (CH_2), 50.8 (CH_2), 35.7 (CH_2), 23.4 (CH_2), 21.7 (CH_3), C=O, 1 Ar-C and 1 Ar-CH not seen; HRMS (ESI$^+$) calculated for $C_{25}H_{26}N_2O_5S$ [M+Na]$^+$ 489.1455; found 489.1455.



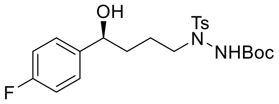
Benzyl (*S*)-1-(5-hydroxy-5-phenylpentyl)-2-tosylhydrazine-1-carboxylate (6s). Following general method3, aryl ketone **5** (80 mg, 0.17 mmol, 1.0 equiv), catalyst **7c** (1.0 mg, 1.7 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.17 mL, 1.0 M) and dichloromethane (0.34 mL, 0.5 M) yielded **6s** as a colourless oil (80 mg, 0.17 mmol, 99%). R_f = 0.20 (35% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ –8.2 (*c* 1.13, $CHCl_3$). Enantiomeric excess was determined after cyclisation to **8s**; IR (film) 3489, 3233, 2925, 1707, 1340, 1215 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.72 (2H, d, *J* 8.0, Ar-H), 7.38-7.31 (8H, m, Ar-H), 7.21 (2H, d, *J* 8.1, Ar-H), 7.14 (2H, s, Ar-H), 6.91 (1H, s, NH), 4.88 (2H, s, CH_2Ph), 4.69-4.61 (1H, m, C*H*OH), 3.65 (2H, br s, NCH_2), 2.42 (3H, s, CH_3) 1.85-1.62 (4H, m, NCH_2CH_2 and CH_2CHOH), 1.42-1.31 (2H, m, $CH_2CH_2CH_2$); δC (125 MHz; $CDCl_3$) 144.6 (Ar-C), 144.5 (Ar-C), 135.2 (Ar-C), 129.5 (Ar-CH), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 127.6 (Ar-CH), 125.8 (Ar-CH), 74.3 (CH), 68.3 (CH_2), 50.9 (CH_2), 38.5 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 21.7 (CH_3), 1 C=O, 1 Ar-C and 2 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{26}H_{30}N_2O_5S$ $[M+Na]^+$ 505.1768; found 505.1767.



***tert*-Butyl (*S*)-2-(4-hydroxy-4-phenylbutyl)-2-tosylhydrazine-1-carboxylate (6t).** Following general method 3, aryl ketone **5t** (5.21 g, 12.0 mmol, 1.0 equiv) catalyst **7c** (37 mg, 60 µmol, 0.5 mol%), formic acid : triethylamine (5 : 2) complex (12 mL, 1.0 M), dichloromethane (24 mL, 0.5 M) yielded **6t** as a white, sticky foam (5.21 g, 12.0 mmol) in quantitative yield. R_f = 0.35 (50% EtOAc in petroleum ether); $[\alpha]^{28}_{D}$ –18.0 (*c* 0.32, $CHCl_3$). Enantiomeric excess (91% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 2.5/97.5; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 87.8 min; t_R 97.6 min; IR (neat) 2979, 2930, 1703, 1351, 1151, 1088, 753, 700, 659 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.76 (2H, d, *J* 7.8, Ar-*H*), 7.35-7.33 (4H, m, Ar-*H*), 7.33-7.27 (3H, m, Ar-*H*), 6.27 (0.70H, br s, N*H* major), 5.77 (0.30H, br s, N*H* minor), 4.77 (1H, br s, C*H*OH), 3.44 (2H, br s, 2H, NCH_2), 2.45 (1H, br s, O*H*), 2.42 (3H, s, CH_3), 1.92–1.82 (2H, m, CH_2CHOH), 1.75–1.63 (2H, m, CH_2CH_2N), 1.31 (9H, br s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 153.8 (Boc-C=O), 144.8 (Ar-C), 144.6 (Ar-C), 134.0 (Ar-C), 129.7 (Ar-CH), 128.7 (Ar-CH), 128.5 (Ar-CH), 127.5 (Ar-CH), 125.9 (Ar-CH), 81.9 (C), 73.5 (CHOH), 50.0 (NCH_2), 36.3 (CH_2CHOH), 28.1 (Boc-CH_3), 23.0 (CH_2CH_2N), 21.7 (CH_3); HRMS (ESI^+) calculated for $C_{22}H_{30}N_2NaO_5S$ $[M+Na]^+$ 457.1768; found 457.1763.

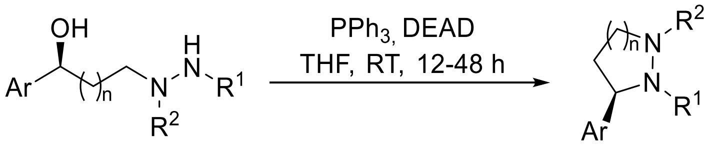


***tert*-Butyl (*S*)-2-(5-hydroxy-5-phenylpentyl)-2-tosylhydrazine-1-carboxylate (6u).** Following general method 3, aryl ketone **5u** (2.60 g, 5.82 mmol, 1.0 equiv), catalyst **7c** (18 mg, 29 µmol, 0.5 mol%), formic acid : triethylamine (5 : 2) complex (6.0 mL, 1.0 M), dichloromethane (12 mL, 0.5 M) yielded **6u** as a white solid (2.46 g, 5.48 mmol, 94%). M.p. 83.5-85 °C; R_f = 0.43 (50% EtOAc in petroleum ether); $[\alpha]^{28}_{D}$ –18.4 (*c* 0.35, $CHCl_3$). Enantiomeric excess (93% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 4/96; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 39.8 min; t_R 47.0 min; IR (neat) 3310, 2930, 1702, 1351, 1151, 756, 700, 659 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.75 (2H, d, *J* 7.0, Ar-*H*), 7.34 (4H, d, *J* 3.8, Ar-*H*), 7.32-7.27 (3H, m, Ar-*H*), 6.35 (0.80H, br s, N*H* major), 5.81 (0.20H, br s, N*H* minor), 4.66 (1H, t, *J* 6.1, C*H*OH), 3.41 (2H, br d, *J* 16.7, NC*H*$_2$), 2.41 (3H, s, CH_3), 2.21 (1H, br s, O*H*), 1.84-1.77 (1H, m, C*H*HCHOH), 1.76-1.69 (1H, m, CH*H*CHOH), 1.59 (2H, tt, *J* 10.5, 5.4, C*H*$_2$$CH_2$N), 1.55-1.49 (1H, m, C*H*HCH_2CH_2N), 1.48-1.39 (1H, m, CH*H*CH_2CH_2N), 1.31 (9H, br s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 153.5 (C=O), 144.9 (Ar-C), 144.4 (Ar-C), 134.3 (Ar-C), 129.6 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 127.6 (Ar-CH), 126.0 (Ar-CH), 81.7 (C), 74.1 (CHOH), 49.8 (NCH_2), 38.7 (*C*H_2CHOH), 28.1 (Boc-CH_3), 26.9 (*C*H_2CH_2N), 22.8 (*C*$H_2CH_2CH_2$N), 21.7 (CH_3). HRMS (ESI$^+$) calculated for $C_{23}H_{32}N_2NaO_5S$ $[M+Na]^+$ 471.1924; found 471.1921.

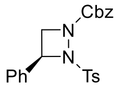


***tert*-Butyl (*S*)-2-(4-(4-fluorophenyl)-4-hydroxybutyl)-2-tosylhydrazine-1-carboxylate (6v).** Following general method 3, aryl ketone **5v** (3.25 g, 7.21 mmol, 1.0 equiv), catalyst **7c** (22 mg, 36 μmol, 0.5 mol%), formic acid : triethylamine (5 : 2) complex (7.0 mL, 1.0 M), dichloromethane (14 mL, 0.5 M) yielded **6v** as a colourless gum (3.26 g, 7.21 mmol) in quantitative yield. R_f = 0.36 (50% EtOAc in petroleum ether); $[\alpha]^{28}_D$ –13.9 (*c* 0.94, $CHCl_3$). Enantiomeric excess (87% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 4/96; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 29.9 min; t_R 34.4 min; IR (neat) 3310, 2979, 2930, 1703, 1509, 1350, 1220, 1152, 813, 658 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.76 (2H, d, *J* 7.9, Ar-*H*), 7.37-7.27 (4H, m, Ar-*H*), 7.02 (2H, t, *J* 8.6, Ar-*H*), 6.23 (0.75H, br s, N*H* major), 5.77 (0.25H, br s, N*H* minor), 4.78 (1H, br s, C*H*OH), 3.46 (1H, br s, NC*H*H), 3.41 (1H, br s, NCH*H*), 2.57 (1H, br s, O*H*), 2.42 (3H, s, CH_3), 1.94-1.78 (2H, m, C*H*$_2$CHOH), 1.71-1.61 (2H, m, C*H*$_2$$CH_2$N), 1.31 (9H, br s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 162.2 (d, *J* 244.7, CF), 154.0 (Boc-C=O), 144.7 (Ar-C), 140.6 (Ar-C), 133.8 (Ar-C), 129.8 (Ar-CH), 128.8 (Ar-CH), 127.5 (d, *J* 8.0, Ar-CH), 115.3 (d, *J* 21.1, Ar-CH), 82.0 (C), 72.7 (CHOH), 50.0 (NCH_2), 36.5 (*C*H_2CHOH), 28.1 (Boc-CH_3), 22.8 (*C*H_2CH_2N), 21.7 (CH_3); δ*F* (376 MHz; $CDCl_3$) –115.6 (CF); HRMS (ESI$^+$) calculated for $C_{22}H_{29}FN_2NaO_5S$ $[M+Na]^+$ 475.1673; found 475.1671.

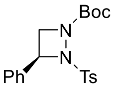
General method 4: Mitsunobu cyclisation



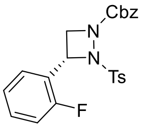
To a solution of alcohol (1.0 equiv) in tetrahydrofuran (0.01 M) was added triphenylphosphine (1.5-2.5 equiv) and diethyl azodicarboxylate (1.5-2.5 equiv). The reaction mixture was stirred at rt until completion of the reaction (12-48 h, monitored by TLC). The reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (20-30% EtOAc in petroleum ether) to give the following compounds.



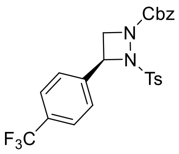
Benzyl (*S*)-3-phenyl-2-tosyl-1,2-diazetidine-1-carboxylate (8a). Following general method 4, **6a** (91 mg, 0.21 mmol, 1.0 equiv), triphenylphosphine (142 mg, 0.54 mmol, 2.5 equiv), diethyl azodicarboxylate (77 µL, 0.54 mmol, 2.5 equiv) in tetrahydrofuran (21 mL, 0.01 M) yielded **8a** as a white solid (75 mg, 0.18 mmol, 86%). R_f = 0.32 (20% EtOAc in petroleum ether); M.p. 113-114.5 °C; $[\alpha]^{32}_{D}$ +21.5 (*c* 0.50, $CHCl_3$); Enantiomeric excess (96% *ee*) was determined by HPLC analysis (25 °C). [Chiralcel ODH column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 21.7 min; t_R 27.2 min. IR (film) 3032, 1751, 1720, 1305, 1185 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.89-7.87 (2H, m, Ar-*H*), 7.34-7.31 (12H, m, Ar-*H*), 5.25-4.96 (3H, m, C*H*Ph and OC*H₂*Ph), 4.23 (1H, t, *J* 8.6, NC*H*H), 4.00 (1H, t, *J* 8.6, NCH*H*), 2.44 (3H, s, Ts-C*H₃*); δ*C* (100 MHz; $CDCl_3$) 160.3 (C=O), 145.4 (Ar-C), 137.3 (Ar-C), 135.5 (Ar-C), 130.6 (Ar-C), 130.1 (Ar-CH), 129.0 (Ar-CH), 128.8 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 126.4 (Ar-CH), 68.5 (CH_2), 61.6 (CH), 56.6 (CH_2), 21.9 (CH_3), 2 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{23}H_{22}N_2NaO_4S$ $[M+Na]^+$ 445.1192; found 445.1194.



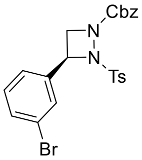
***tert*-Butyl (*S*)-3-phenyl-2-tosyl-1,2-diazetidine-1-carboxylate (8b)** Following general procedure 5, alcohol **6b** (450 mg, 1.11 mmol, 1.0 equiv), triphenylphosphine (727 mg, 2.77 mmol, 2.5 equiv), diethylazodicarboxylate (436 µL, 2.77 mmol, 2.5 equiv) and tetrahydrofuran (111 mL, 0.01 M) yielded **8b** as a white solid (328 mg, 0.84 mmol, 76%). R_f = 0.25 (15% EtOAc/petroleum ether); M.p. 166-167 °C; $[\alpha]_D^{28}$ +7.6 (*c* 0.09, $CHCl_3$); Enantiomeric excess (98% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 0.6/99.4; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 54.5 min; t_R 63.1 min. IR (film) 2980, 2932, 1733, 1395, 1358 cm^{-1}; δ*H* (500 MHz, $CDCl_3$) 7.93 (2H, d, *J* 8.2, Ar-CH), 7.37 (7H, m, Ar-CH), 5.06 (1H, dd, *J* 8.7, 5.9, CHPh), 4.21 (1H, t, *J* 8.7, NC*H*H), 3.96 (1H, dd, *J* 8.5, 5.9, NCH*H*), 2.51 (3H, s, CH_3), 1.45 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 159.3 (C=O), 145.2 (Ar-C), 137.6 (Ar-C), 130.8 (Ar-CH), 130.1 (Ar-CH), 130.0 (Ar-C), 129.6 (Ar-CH), 128.9 (Ar-CH), 126.4 (Ar-CH), 82.9 (C), 61.3 (CH), 56.3 (CH_2), 28.0 (CH_3), 21.8 (CH_3); HRMS (ES^+) calculated for $C_{20}H_{24}N_2O_4S$ $(M+Na)^+$ 411.1349; found 411.1352.



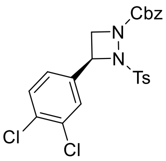
Benzyl (*R*)-3-(2-fluorophenyl)-2-tosyl-1,2-diazetidine-1-carboxylate (8c). Following general method 4, **6c** (44 mg, 0.10 mmol, 1.0 equiv), triphenylphosphine (36 mg, 0.15 mmol, 1.5 equiv), diethyl azodicarboxylate (22 µL, 0.15 mmol, 1.5 equiv) and tetrahydrofuran (10 mL, 0.01 M) yielded **8c** as a colourless oil (32 mg, 70 µmol, 75%). R_f = 0.26 (25% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ –15.6 (*c* 0.15, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 15.0 min; t_R 21.1 min; IR (film) 3034, 2924, 1720, 1236, 1162 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.83 (2H, d, *J* 8.2, Ar-H), 7.55 (1H, t, *J* 7.5, Ar-H), 7.30-7.26 (7H, m, Ar-H), 7.19 (1H, s, Ar-H), 7.10 (1H, t, *J* 7.5, Ar-H), 6.96 (1H, t, *J* 10.0, Ar-H), 5.20-5.04 (3H, m, CH_2Ph and NCHPh), 4.14 (1H, t, *J* 8.7, NC*H*H), 3.90 (1H, dd, *J* 8.4, 6.0, NCH*H*), 2.40 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 160.1 (C=O), 159.7 (d, *J* 246.3, Ar-CF), 145.5 (Ar-C), 135.4 (Ar-C), 130.4 (d, *J* 8.8, Ar-CH), 130.1 (Ar-CH), 130.0 (Ar-C), 129.7 (Ar-CH), 128.5 (Ar-CH), 128.5 (d, *J* 3.8, Ar-CH), 129.7 (Ar-CH), 128.3 (Ar-CH), 127.9 (Ar-CH), 124.7 (d, *J* 13.8, Ar-C), 124.7 (d, *J* 2.5, Ar-CH), 115.5 (d, *J* 20.0, Ar-CH), 68.4 (CH_2), 57.1 (d, *J* 3.8, CH), 56.1 (d, *J* 2.5, CH_2), 21.8 (CH_3); δ*F* (376 MHz; $CDCl_3$) -118.4 (CF); HRMS (ESI^+) calculated for $C_{23}H_{21}FN_2O_4S$ $[M+Na]^+$ 463.1098; found 463.1097.



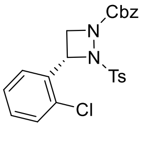
Benzyl (*S*)-2-tosyl-3-(4-(trifluoromethyl)phenyl)-1,2-diazetidine-1-carboxylate (8d). Following general method 4, **6d** (60 mg, 0.12 mmol, 1.0 equiv), triphenylphosphine (77 mg, 0.29 mmol, 2.5 equiv), diethyl azodicarboxylate (63 µL, 0.29 mmol, 2.5 equiv) and tetrahydrofuran (12 mL, 0.01 M) yielded **8d** as a white solid (48 mg, 0.10 mmol, 82%). M.p. 117-119 °C; R_f = 0.21 (25% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ +18.9 (*c* 2.86, $CHCl_3$). Enantiomeric excess (94% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 19.5 min; t_R 24.3 min; IR (film) 2925, 1750, 1693, 1360, 1151, 1087 cm^{-1}; δ*H* (500 MHz; d6-DMSO) 7.89 (2H, d, *J* 8.2, Ar-H), 7.79 (2H, d, *J* 8.2, Ar-H) 7.65 (2H, d, *J* 8.1, Ar-H), 7.54 (2H, d, *J* 8.1, Ar-H), 7.39-7.32 (5H, m, Ar-H), 5.38-5.09 (3H, m, C*H*OH and CH_2Ph), 4.09 (1H, t, *J* 8.9, NC*H*H), 3.93 (1H, dd, *J* 8.9, 5.8, NCH*H*), 2.46 (3H, s, CH_3); δ*C* (125 MHz; d6-DMSO) 159.5 (C=O) 145.6 (Ar-C), 135.6 (Ar-C), 130.1 (Ar-CH), 129.8 (Ar-CH), 129.2 (Ar-C), 129.0 (q, *J* 31.9, Ar-C), 128.4 (Ar-CH), 128.2 (Ar-CH), 127.7 (Ar-CH), 127.4 (Ar-CH), 125.6 (q, *J* 3.8, Ar-CH), 124.1 (q, *J* 272.2, CF_3), 67.8 (CH_2), 60.1 (CH), 56.1 (CH_2), 21.3 (CH_3), 1 Ar-C not seen; δ*F* (376 MHz; d6-DMSO) -61.1 (CF_3); HRMS (ESI^+) calculated for $C_{24}H_{21}F_3N_2O_4S$ $[M+Na]^+$ 513.1066; found 513.1061.



Benzyl (*S*)-3-(3-bromophenyl)-2-tosyl-1,2-diazetidine-1-carboxylate (8e). Following general method 4, **6e** (61 mg, 0.12 mmol, 1.0 equiv), triphenylphosphine (77 mg, 0.29 mmol, 2.5 equiv), diethyl azodicarboxylate (63 µL, 0.29 mmol, 2.5 equiv) and tetrahydrofuran (12 mL, 0.01 M) yielded **8e** as a colourless oil (47 mg, 90 µmol, 79%). R$_f$ = 0.25 (25% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ +34.8 (*c* 0.38, $CHCl_3$). Enantiomeric excess (97% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 9/91; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 19.6 min; t_R 25.1 min; IR (film) 2923, 1718, 1302, 1212 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.87 (2H, d, *J* 8.2, Ar-H), 7.50 (1H, s, Ar-H), 7.38-7.29 (8H, m, Ar-H), 7.23 (1H, t, *J* 7.8, Ar-H), 5.19 (1H, d, *J* 12.3 C*H*HAr), 5.11 (1H, d, *J* 12.3, CH*H*Ar), 5.07 (1H, dd, *J* 8.7, 6.0, NCHAr) 4.23 (1H, t, *J* 8.7, NC*H*H), 3.97 (1H, dd, *J* 8.7, 6.0, NCH*H*), 2.46 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 160.1 (C=O) 145.5 (Ar-C), 139.5 (Ar-C), 135.3 (Ar-C), 131.9 (Ar-CH), 130.6 (Ar-CH), 131.0 (Ar-CH), 130.3 (Ar-C) 130.0 (Ar-CH), 129.7 (Ar-CH), 129.4 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 127.9 (Ar-CH), 68.5 (CH_2), 60.5 (CH), 56.2 (CH_2), 21.8 (CH_3), 1 Ar-C and 1 Ar-CH not seen; HRMS (ESI$^+$) calculated for $C_{23}H_{21}{}^{79}BrN_2O_4S$ [M+Na]$^+$ 523.0298; found 523.0294.

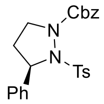


Benzyl (*S*)-3-(3,4-dichlorophenyl)-2-tosyl-1,2-diazetidine-1-carboxylate (8f). Following general method 4, **6f** (100 mg, 0.20 mmol, 1.0 equiv), triphenylphosphine (129 mg, 0.49 mmol, 2.5 equiv), diethyl azodicarboxylate (76 µL, 0.49 mmol, 2.5 equiv) and tetrahydrofuran (20 mL, 0.01 M) yielded **8f** as a white solid (75 mg, 0.15 mmol, 78%). M.p. 133-135 °C; R$_f$ = 0.23 (25% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ +33.2 (*c* 4.40, $CHCl_3$); Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 25.0 min; t_R 33.1 min; IR (film) 2983, 1711, 1337, 1313, 1212 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.86 (2H, d, *J* 7.6, Ar-H), 7.50-7.27 (8H, m, Ar-H), 7.19 (2H, d, *J* 8.5, Ar-H), 5.25-4.98 (3H, m, CHAr and CH_2Ph), 4.25 (1H, t, *J* 8.9, NC*H*H), 3.94 (1H, t, *J* 8.9, NCH*H*), 2.43 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 160.1 (C=O), 145.6 (Ar-C), 137.4 (Ar-C), 135.2 (Ar-C), 133.2 (Ar-C) 133.0 (Ar-C), 131.0 (Ar-CH), 130.2 (Ar-C) 130.0 (Ar-CH), 129.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.0 (Ar-CH), 125.6 (Ar-CH), 68.6 (CH_2), 60.0 (CH), 56.1 (CH_2), 21.8 (CH_3); HRMS (ESI$^+$) calculated for $C_{23}H_{20}{}^{35}Cl_2N_2O_5S$ [M+Na]$^+$ 513.0413; found 513.0413.

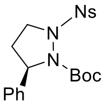


Benzyl (*R*)-3-(2-chlorophenyl)-2-tosyl-1,2-diazetidine-1-carboxylate (8g). Following general method 4, **6g** (81 mg, 0.17 mmol, 1.0 equiv), triphenylphosphine (112 mg, 0.43 mmol, 2.5 equiv), diethyl azodicarboxylate (66 µL, 0.43 mmol, 2.5 equiv) and tetrahydrofuran (17 mL, 0.01 M) yielded **8g** as a colourless oil (50 mg, 0.11 mmol, 65%). R$_f$ = 0.24 (25% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ +33.2 (*c* 0.44, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis

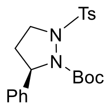
(25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 13.6 min; t_R 17.1 min. IR (film) 2924, 1749, 1271, 1186 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.92 (2H, d, *J* 8.2, Ar-H), 7.83 (1H, d, *J* 7.0, Ar-H), 7.37-7.27 (9H, m, Ar-H), 5.25 (1H, dd, *J* 8.6, 5.9, CHAr), 5.21 (1H, d, *J* 12.4, C*H*HPh), 5.11 (1H, d, *J* 12.4, CH*H*Ph), 4.25 (1H, t, *J* 8.7, NC*H*H), 3.83 (1H, dd, *J* 8.6, 5.8, NCH*H*), 2.48 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 160.2 (C=O) 145.6 (Ar-C), 135.4 (Ar-C), 135.3 (Ar-C), 131.0 (Ar-C) 130.1 (Ar-CH), 130.0 (Ar-C), 129.8 (Ar-CH), 129.6 (Ar-CH), 129.2 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 127.5 (Ar-CH), 68.4 (CH_2), 59.8 (CH), 56.5 (CH_2), 21.8 (CH_3); HRMS (ESI$^+$) calculated for $C_{23}H_{21}{}^{35}ClN_2O_4S$ [M+Na]$^+$ 479.0803; found 479.0805.



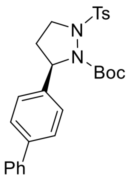
Benzyl (*R*)-3-phenyl-2-tosylpyrazolidine-1-carboxylate (8h). Following general method 4, **6h** (60 mg, 0.13 mmol, 1.0 equiv), triphenylphosphine (52 mg, 0.20 mmol, 1.5 equiv), diethylazodicarboxylate (31 µL, 0.20 mmol, 1.5 equiv) and tetrahydrofuran (13 mL, 0.01 M) yielded **8h** as a white solid (51 mg, 0.12 mmol, 90%). M.p. 105-106 °C; R$_f$ = 0.24 (25% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ +52.1 (*c* 0.02, $CHCl_3$). Enantiomeric excess (96% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 13.0 min; t_R 14.1 min. IR (film) 3034, 2959, 2925, 1702, 1344, 1216, 1181 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.84 (2H, d, *J* 8.2, Ar-CH), 7.37-7.31 (5H, m, Ar-H), 7.28-7.22 (5H, m, Ar-H), 7.21-7.18 (2H, m, Ar-H), 5.37 (1H, dd, *J* 8.0, 4.7, C*H*Ph), 5.09 (1H, d, *J* 12.2, CO_2C*H*HPh), 4.82 (1H, d, *J* 12.2, CO_2CH*H*Ph), 3.98 (1H, ddd, *J* 11.0, 8.4, 5.7, NC*H*H), 3.29 (1H, dt, *J* 10.8, 8.3, NCH*H*), 2.45-2.39 (4H, m, CH_3 and CHPhC*H*H), 2.17 (1H, dtd, *J* 12.7, 7.2, 5.1, CHPhCH*H*); δ*C* (125 MHz; $CDCl_3$) 157.3 (C=O), 144.8 (Ar-C), 139.9 (Ar-C) 135.6 (Ar-C), 133.2 (Ar-C), 129.6 (Ar-CH), 129.4 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.6 (Ar-CH), 126.2 (Ar-CH), 68.2 (CH_2), 63.4 (CH), 47.8 (CH_2), 33.8 (CH_2), 21.7 (CH_3); HRMS (ESI$^+$) calculated for $C_{24}H_{24}N_2O_4S$ [M+Na]$^+$ 459.1349; found 459.1349.



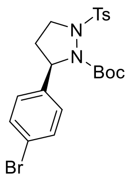
***tert*-Butyl (*R*)-5-(thiophen-2-yl)-2-tosylpyrazolidine-1-carboxylate (8i).** Following general method 4, **6i** (42 mg, 0.09 mmol, 1.0 equiv), triphenylphosphine (37 mg, 0.14 mmol, 1.5 equiv), diethylazodicarboxylate (22 µL, 0.14 mmol, 1.5 equiv) and tetrahydrofuran (9 mL, 0.01 M) yielded **8i** as a colourless oil (36 mg, 0.08 mmol, 85%). R$_f$ = 0.18 (25% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ +7.8 (*c* 0.17, $CHCl_3$). Enantiomeric excess (99% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 25.6 min; t_R 28.9 min. IR (film) 2979, 2931, 1712, 1530, 1346, 1161 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.27 (2H, d, *J* 8.6, Ar-H), 8.18 (2H, t, *J* 8.7, Ar-H) 7.43 (2H, d, *J* 6.9, Ar-H), 7.36 (2H, t, *J* 7.4, Ar-H), 7.31 (1H, d, *J* 7.1, Ar-H), 5.04 (1H, t, *J* 8.6, C*H*Ph), 4.21 (1H, br s, NC*H*H), 3.42 (1H, br s, NCH*H*), 2.59 (2H, dt, *J* 12.9, 6.5, CHPhC*H*H), 2.31 (1H, p, *J* 11.5, CHPhCH*H*), 1.27 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 155.8 (C=O seen on HMBC), 142.9 (Ar-C), 130.7 (Ar-CH), 128.4 (Ar-CH), 127.5 (Ar-CH), 126.6 (Ar-CH), 123.7 (Ar-CH), 114.1 (Ar-C), 82.7 (C), 65.4 (CH), 49.3 (CH_2), 36.1 (CH_2), 27.9 (CH_3), 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{20}H_{23}N_3O_6$ $[M+Na]^+$ 456.1200; found 456.1198.



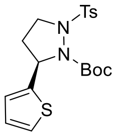
***tert*-Butyl (*R*)-5-phenyl-2-tosylpyrazolidine-1-carboxylate (8j).** Following general method 4, **6j** (72 mg, 0.17 mmol, 1.0 equiv), triphenylphosphine (112 mg, 0.43 mmol, 2.5 equiv), diethyl azodicarboxylate (74 mg, 0.43 mmol, 2.5 equiv) in tetrahydrofuran (17 mL, 0.01 M) yielded **8j** as a colourless oil (62 mg, 0.15 mmol, 90%). R_f = 0.30 (30% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ +23.5 (*c* 0.70, $CHCl_3$). Enantiomeric excess (95% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 10.9 min; t_R 17.4 min. IR (film) 2987, 2900, 1706, 1405, 1075 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.86-7.85 (2H, m, Ar-H), 7.45-7.25 (7H, m, Ar-H), 4.99 (1H, dd, *J* 8.7, 6.2, CHPh), 4.10 (1H, br s, NC*H*H), 3.29 (1H, br s, NCH*H*), 2.48-2.26 (5H, m, CH_2, CH_3), 1.25 (9H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 156.6 (C=O), 144.7 (Ar-C), 141.5 (Ar-C), 133.8 (Ar-C), 129.6 (Ar-CH), 129.5 (Ar-CH), 128.4 (Ar-CH), 127.2 (Ar-CH), 126.8 (Ar-CH), 82.0 (C), 65.6 (CH), 49.3 (CH_2), 36.1 (CH_2), 27.9 (CH_3), 21.7 (CH_3); HRMS (ESI^+) calculated for $C_{21}H_{26}N_2NaO_4S$ $[M+Na]^+$ 425.1505; found 425.1504.



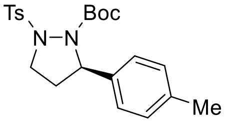
***tert*-Butyl (*R*)-5-([1,1'-biphenyl]-4-yl)-2-tosylpyrazolidine-1-carboxylate (8k).** Following general method 4, **6k** (84 mg, 0.17 mmol, 1.0 equiv), triphenylphosphine (66 mg, 0.25 mmol, 1.5 equiv), diethyl azodicarboxylate (39 µL, 0.25 mmol, 1.0 equiv) and tetrahydrofuran (17 mL, 0.01 M) yielded **8k** as a white solid (70 mg, 0.15 mmol, 86%). M.p. 109-111 °C; R_f = 0.24 (25% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ +75.0 (*c* 0.03, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 9.5 min; t_R 10.5 min. IR (film) 2980, 2924, 1701, 1393, 1357, 1255 cm^{-1} δ*H* (500 MHz; $CDCl_3$) 7.90 (2H, d, *J* 8.2, Ar-H), 7.63 (4H, t, *J* 7.5, Ar-H), 7.60 (2H, d, *J* 7.9, Ar-H), 7.56 (2H, s, Ar-H), 7.47 (2H, t, *J* 7.6, Ar-H), 7.37 (1H, t, *J* 7.4, Ar-H), 7.27 (1H, d, *J* 9.4, Ar-H), 5.07 (1H, t, *J* 8.8, C*H*Ar), 4.17 (1H, br s, NC*H*H), 3.33 (1H, br s, NCH*H*), 2.58-2.49 (1H, m, CHArC*H*H), 2.46-2.35 (4H, m, CH_3 and CHNCH*H*), 1.30 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 156.8 (C=O seen on HMBC), 150.5 (Ar-C), 144.6 (Ar-C), 140.9 (Ar-C), 140.1 (Ar-C), 133.8 (Ar-C), 129.6 (Ar-CH), 129.4 (Ar-CH), 128.8 (Ar-CH), 127.2 (Ar-CH), 127.1 (Ar-CH), 82.1 (C), 65.3 (CH), 49.3 (CH_2), 36.0 (CH_2), 27.9 (CH_3) 21.6 (CH_3), 2 Ar-CH not seen; HRMS (ESI$^+$) calculated for $C_{27}H_{30}N_2O_4S$ [M+Na]$^+$ 501.1818; found 501.1819.



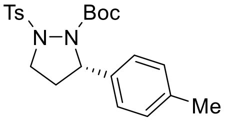
***tert*-Butyl (*R*)-5-(4-bromophenyl)-2-tosylpyrazolidine-1-carboxylate (8l).** Following general method 4, **6l** (61 mg, 0.12 mmol, 1.0 equiv), triphenylphosphine (47 mg, 0.18 mmol, 1.5 equiv), diethyl azodicarboxylate (28 µL, 0.18 mmol, 1.5 equiv) and tetrahydrofuran (12 mL, 0.01 M) yielded **8l** as a colourless oil (52 mg, 0.11 mmol, 90%). R$_f$ = 0.22 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +34.6 (*c* 0.25, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 12.5 min; t_R 15.5 min. IR (film) 2979, 2928, 1705, 1366, 1133 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.77 (2H, d, *J* 8.1, Ar-H), 7.39 (2H, d, *J* 8.4, Ar-H), 7.30 (2H, s, Ar-H), 7.19 (2H, d, *J* 7.8, Ar-H), 4.88 (1H, t, *J* 9.8 C*H*Ar), 4.07 (1H, br s, NC*H*H), 3.20 (1H, br s, NCH*H*), 2.43 (1H, sex, *J* 6.9, CHArC*H*H), 2.46 (3H, s, CH_3), 2.05-1.82 (1H, m, CHArCH*H*), 1.19 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 156.3 (C=O, seen on HMBC), 144.8 (Ar-C), 140.4 (Ar-C), 133.6 (Ar-C), 131.4 (Ar-CH), 129.6 (Ar-CH), 129.4 (Ar-CH), 128.6 (Ar-CH), 121.1 (Ar-C), 82.2 (C), 65.0 (CH), 49.3 (CH_2), 36.0 (CH_2), 27.9 (CH_3), 21.7 (CH_3); HRMS (ESI$^+$) calculated for $C_{21}H_{25}{}^{79}BrN_2O_4S$ [M+Na]$^+$ 503.0611; found 503.0612.



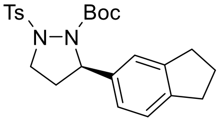
***tert*-Butyl (*R*)-5-(thiophen-2-yl)-2-tosylpyrazolidine-1-carboxylate (8m).** Following general method 4, **6m** (41 mg, 0.10 mmol, 1.0 equiv), triphenylphosphine (39 mg, 0.15 mmol, 1.5 equiv), diethylazodicarboxylate (24 µL, 0.15 mmol, 1.5 equiv) and tetrahydrofuran (10 mL, 0.01 M) yielded **8m** as a colourless oil (28 mg, 0.07 mmol, 72%). R$_f$ = 0.26 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +31.3 (*c* 0.07, $CHCl_3$). Enantiomeric excess (73% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 3/97; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 18.5 min; t_R 19.5 min. IR (film) 2978, 2925, 1704, 1256, 1133 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.79 (2H, d, *J* 7.9, Ar-H), 7.25 (1H, d, *J* 5.1, Ar-H), 7.23 (2H, d, *J* 7.9, Ar-H), 6.99 (1H, s, Ar-H), 6.94 (1H, t, *J* 3.7, Ar-H), 5.29 (1H, t, *J* 8.7, CHAr), 4.27 (1H, br s, NC*H*H), 3.32 (1H, br s, NCH*H*), 2.64-2.44 (2H, m, CHArC*H$_2$*), 2.42 (3H, s, CH_3), 1.32 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 156.3 (C=O seen on HMBC), 144.6 (Ar-C), 133.3 (Ar-C), 129.7 (Ar-CH), 129.3 (Ar-CH), 126.2 (Ar-CH), 125.1 (Ar-CH), 124.9 (Ar-CH), 82.3 (C), 60.7 (CH), 49.2 (CH_2), 35.5 (CH_2), 27.9 (CH_3), 21.6 (CH_3), 1 Ar-C not seen; HRMS (ESI$^+$) calculated for $C_{19}H_{24}N_2O_4S_2$ [M+Na]$^+$ 431.1070; found 431.1073.



***tert*-Butyl (*R*)-5-(*p*-tolyl)-2-tosylpyrazolidine-1-carboxylate ((*R*)-8n).** Following general method 4, (*S*)-**6n** (217 mg, 0.50 mmol, 1.0 equiv), triphenylphosphine (328 mg, 1.25 mmol, 2.5 equiv), diethyl azodicarboxylate (DEAD) (197 µL, 1.25 mmol, 2.5 equiv) and tetrahydrofuran (50 mL, 0.01 M) yielded (*R*)-**8n** after purification by column chromatography (20-33% EtOAc/petroleum ether) as a colourless gum (190 mg, 0.46 mmol, 91%). Alternatively replacing DEAD with diisopropyl azodicarboxylate (DIAD) in general method 4, (*R*)-**8n** was obtained as a colourless gum (249 mg, 0.60 mmol, 91%). M.p. 103-106 °C; R_f = 0.35 (33% EtOAc in petroleum ether); $[\alpha]^{23}_{D}$ –26.8 (*c* 0.59, $CHCl_3$). Enantiomeric excess for reaction with DEAD (93% *ee*) and reaction with DIAD (95% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 12.2 min; t_R 16.3 min; IR (neat) 2979, 2928, 1705, 1330, 1159, 1133, 1088, 814, 761 cm^{-1}; δ*H* (300 MHz; $CDCl_3$) 7.88 (2H, d, *J* 8.1, Ar-*H*), 7.37 (2H, d, *J* 6.5, Ar-*H*), 7.27 (2H, d, *J* 9.0, Ar-*H*), 7.16 (2H, d, *J* 7.8, Ar-*H*), 4.98 (1H, t, *J* 8.7, NCH), 4.13 (1H, br m, NC*H*H), 3.31 (1H, br m, NCH*H*), 2.53-2.44 (1H, m, C*H*HCHN), 2.42 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.35-2.26 (1H, m, CH*H*CHN), 1.27 (9H, s, $(CH_3)_3$); δ*C* (101 MHz; $CDCl_3$) 144.7 (Ar-C), 138.4 (Ar-C, seen on HMBC), 136.9 (Ar-C), 134.0 (Ar-C), 129.7 (Ar-CH), 129.5 (Ar-CH), 129.1 (Ar-CH), 126.9 (Ar-CH), 82.0 (C), 65.6 (NCH), 49.4 (NCH_2), 36.2 (CH_2CHN), 28.0 (Boc-CH_3), 21.8 (CH_3), 21.3 (CH_3), Boc-C=O not observed; HRMS (ESI^+) calculated for $C_{22}H_{28}N_2NaO_4S$ $[M+Na]^+$ 439.1662; found 439.1660.

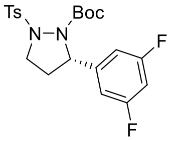


***tert*-Butyl (*S*)-5-(*p*-tolyl)-2-tosylpyrazolidine-1-carboxylate ((*S*)-8n).** Following general method 4, (*R*)-**6n** (306 mg, 0.70 mmol, 1.0 equiv), triphenylphosphine (462 mg, 1.76 mmol, 2.5 equiv), diisopropyl azodicarboxylate (DIAD) (347 µL, 1.76 mmol, 2.5 equiv) and tetrahydrofuran (70 mL, 0.01 M) yielded (*S*)-**8n** after purification by column chromatography (20-33% EtOAc/petroleum ether) as a colourless gum (236 mg, 0.57 mmol, 81%). $[\alpha]^{22}_{D}$ +26.0 (*c* 0.49, $CHCl_3$). Enantiomeric excess (95% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 12.2 min; t_R 16.3 min.

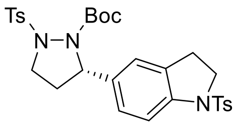


***tert*-Butyl (*R*)-5-(2,3-dihydro-1*H*-inden-5-yl)-2-tosylpyrazolidine-1-carboxylate (8o).** Following general method 4, **6o** (115 mg, 0.25 mmol, 1.0 equiv), triphenylphosphine (164 mg, 0.63 mmol, 2.5 equiv), diethyl azodicarboxylate (DEAD) (98 µL, 0.63 mmol, 2.5 equiv) and tetrahydrofuran (25 mL, 0.01 M) yielded **8o** after purification by column chromatography (10-20% EtOAc/petroleum ether) as a colourless gum (98 mg, 0.22 mmol, 89%). R_f = 0.20 (20% EtOAc in petroleum ether); $[\alpha]^{22}_{D}$

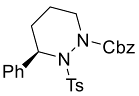
+25.1 (*c* 0.22, $CHCl_3$). Enantiomeric excess (94% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 7.9 min; t_R 11.1 min; IR (neat) 2930, 1707, 1366, 1332, 1160, 1135, 1088, 815, 750 cm^{-1}; δ*H* (600 MHz; $CDCl_3$) 7.87 (2H, d, *J* 8.1, Ar-*H*), 7.33-7.20 (4H, m, Ar-*H*), 7.17 (1H, d, *J* 7.6, Ar-*H*), 4.96 (1H, t, *J* 8.6, NCH), 4.11 (1H, br m, NC*H*H), 3.27 (1H, br m, NCH*H*), 2.90 (4H, t, *J* 7.8, CH_2), 2.47-2.42 (m, 1H, C*H*HCHN), 2.41 (3H, s, CH_3), 2.38-2.29 (1H, m, CH*H*CHN), 2.07 (2H, p, *J* 7.8, 2H, $CH_2CH_2CH_2$), 1.27 (9H, s, $(CH_3)_3$); δ*C* (151 MHz; $CDCl_3$) 144.7 (Ar-C), 144.3 (Ar-C), 143.3 (Ar-C), 138.4 (Ar-C, seen on HMBC), 134.0 (Ar-C), 129.7 (Ar-CH), 129.5 (Ar-CH), 124.9 (Ar-CH, seen on HMBC), 124.3 (Ar-CH), 123.0 (Ar-CH, seen on HMBC), 81.9 (C), 65.9 (NCH), 49.5 (NCH_2), 36.4 (CH_2CHN), 33.0 (CH_2), 32.7 (CH_2), 28.0 (Boc-CH_3), 25.7 ($CH_2CH_2CH_2$), 21.7 (CH_3), Boc-C=O not observed; HRMS (ESI^+) calculated for $C_{24}H_{30}N_2NaO_4S$ $[M+Na]^+$ 465.1818; found 465.1815.



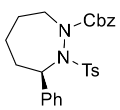
***tert*-Butyl (*S*)-5-(3,5-difluorophenyl)-2-tosylpyrazolidine-1-carboxylate (8p).** Following general procedure 5, alcohol **6p** (239 mg, 0.50 mmol, 1.0 equiv), triphenylphosphine (330 mg, 1.26 mmol, 2.5 equiv), diethylazodicarboxylate (198 µL, 1.26 mmol, 2.5 equiv) and tetrahydrofuran (50 mL, 0.01 M) yielded **8p** as a white solid (193 mg, 0.44 mmol, 88%). R_f = 0.08 (15% EtOAc in petroleum ether); $[\alpha]_D^{24}$ –16.4 (*c* 0.11, $CHCl_3$); Enantiomeric excess (93% *ee*) was determined by HPLC analysis (15 °C). [Chiralcel OD column 2-propanol/hexane = 1/99; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 34.7 min; t_R 43.2 min. M.p. 103-104 °C; IR (film) 2974, 1721, 1680, 1155, 1113 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.85 (2H, d, *J* 8.2, Ar-*H*), 7.28 (2H, d, *J* 8.1, Ar-H), 6.98 (2H, d, *J* 6.0, Ar-H), 6.70 (1H, tt, *J* 8.8, 2.2, Ar-H), 6.33 (1H, s, NH), 4.98 (1H, d, *J* 8.9, CHAr), 4.24-4.12 (1H, br m, C*H*HN), 3.33-3.21 (1H, br m, CH*H*N), 2.54-2.46 (1H, m, CHArC*H*H), 2.42 (3H, s, C*H₃*), 2.36-2.24 (1H, br m, CHArCH*H*), 1.27 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 162.9 (dd, *J* 246.3, 12.5, Ar-CF), 145.5 (Ar-C), 145.0 (Ar-C), 133.5 (Ar-C), 129.6 (Ar-CH), 129.5 (Ar-CH), 109.6 (d, *J* 25.0, Ar-CH), 102.6 (t, *J* 25.0, Ar-CH), 82.5 (C), 64.8 (CH), 49.2 (CH_2), 35.7 (CH_2), 27.8 (CH_3), 21.6 (CH_3), C=O not seen; δ*F* (376 MHz; $CDCl_3$) -109.7 (Ar-CF); HRMS (ESI^+) calculated for $C_{21}H_{24}N_2NaO_4SF_2$ $[M+Na]^+$ 461.1317; found 461.1322.



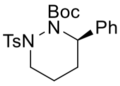
***tert*-Butyl (*S*)-2-tosyl-5-(1-tosylindolin-5-yl)pyrazolidine-1-carboxylate ((*S*)-8q).** Following general method 4, (*R*)-**6q** (308 mg, 0.50 mmol, 1.0 equiv), triphenylphosphine (328 mg, 1.25 mmol, 2.5 equiv), diethyl azodicarboxylate (DEAD) (197 µL, 1.25 mmol, 2.5 equiv) and tetrahydrofuran (50 mL, 0.01 M) yielded (*S*)-**8q** after purification by column chromatography (33-50% EtOAc/petroleum ether) as a colourless gum (244 mg, 0.41 mmol, 82%). Alternatively replacing DEAD with diisopropyl azodicarboxylate (DIAD) in general method 4, (*S*)-**8q** was obtained as a white foam (274 mg, 0.46 mmol, 92%). M.p. 148-151 °C (decomposition); R_f = 0.29 (50% EtOAc in petroleum ether); $[\alpha]^{22}_{D}$ –34.3 (*c* 0.20, CHCl$_3$). Enantiomeric excess for reaction with DEAD (85% *ee*) and reaction with DIAD (85% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 54.3 min; t_R 59.1 min; IR (neat) 2928, 1711, 1488, 1334, 1248, 1161, 1090, 1055, 976, 815 cm^{-1}; δ*H* (400 MHz; CDCl$_3$) 7.83 (2H, d, *J* 8.2, Ar-*H*), 7.69 (2H, d, *J* 8.2, Ar-*H*), 7.56 (1H, d, *J* 8.9, Ar-*H*), 7.26-7.19 (6H, m, Ar-*H*), 4.91 (1H, t, *J* 8.7, NCH), 4.07 (1H, br m, NC*H*HCH$_2$CH), 3.98-3.85 (2H, m, NC*H$_2$*CH$_2$C), 3.24 (1H, br m, NCH*H*CH$_2$CH), 2.91 (2H, t, *J* 8.4, NCH$_2$C*H$_2$*C), 2.47-2.41 (NCH$_2$C*H*HCH), 2.41 (3H, s, CH$_3$), 2.37 (3H, s, CH$_3$), 2.33-2.26 (NCH$_2$CH*H*CH), 1.26 (9H, s, (CH$_3$)$_3$); δ*C* (151 MHz; CDCl$_3$) 144.9 (Ar-C), 144.2 (Ar-C), 141.3 (Ar-C), 136.8 (Ar-C, seen on HMBC), 134.1 (Ar-C), 133.9 (Ar-C), 132.0 (Ar-C), 129.8 (Ar-CH), 129.7 (Ar-CH), 129.5 (Ar-CH), 127.5 (Ar-CH), 123.6 (Ar-CH, seen on HSQC), 114.5 (Ar-CH), 82.0 (C), 65.3 (NCH, seen on HSQC), 50.3 (N*C*H$_2$CH$_2$C), 49.3 (N*C*H$_2$CH$_2$CH, seen on HSQC), 36.2 (NCH$_2$*C*H$_2$CH), 28.1 (NCH$_2$*C*H$_2$C), 28.0 (Boc-CH$_3$), 21.8 (CH$_3$), 21.7 (CH$_3$), one Ar-CH and Boc-C=O not observed; HRMS (ESI$^+$) calculated for $C_{30}H_{35}N_3NaO_6S_2$ [M+Na]$^+$ 620.1859; found 620.1864.



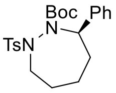
Benzyl (*R*)-3-phenyl-2-tosyltetrahydropyridazine-1(2H)-carboxylate (8r). Following general method 4, **6r** (46 mg, 0.10 mmol, 1.0 equiv), triphenylphosphine (39 mg, 0.15 mmol, 1.5 equiv), diethylazodicarboxylate (23 µL, 0.15 mmol, 1.5 equiv) and tetrahydrofuran (10 mL, 0.01 M) yielded **8r** as a colourless oil (29 mg, 0.06 mmol, 63%). R_f = 0.29 (25% EtOAc in petroleum ether); $[\alpha]^{32}_{D}$ +43.8 (*c* 0.04, CHCl$_3$). Enantiomeric excess (94% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 1.5/98.5; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 34.0 min; t_R 36.3 min. IR (film) 2953, 2925, 1706, 1353, 1260 cm^{-1}; δ*H* (500 MHz; CDCl$_3$) 7.79-7.66 (2H, m, Ar-H), 7.60-7.31 (6H, m, Ar-H) 7.22-7.06 (6H, m, Ar-H), 5.21-5.08 (1H, m, C*H*Ph), 4.85 (1H, d, *J* 11.8, CO$_2$C*H*H), 4.70 (1H, d, *J* 11.9, CO$_2$CH*H*), 4.28-4.02 (1H, m, NC*H*H), 3.71-3.44 (1H, m, NCH*H*), 2.43-2.31 (4H, m, CH$_3$ and CHPhC*H*H), 2.17-2.10 (1H, m, CHPhCH*H*), 1.97 (1H, br s, CH$_2$C*H*HCH$_2$), 1.78-1.71 (1H, m, CH$_2$CH*H*CH$_2$); δ*C* (125 MHz; CDCl$_3$) 155.9 (C=O), 144.4 (Ar-C), 138.6 (Ar-C) 135.5 (Ar-C), 134.9 (Ar-C), 132.2 (Ar-CH), 132.0 (Ar-CH), 129.4 (Ar-CH), 128.8 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.2 (Ar-CH), 127.4 (Ar-CH), 68.2 (CH$_2$), 57.4 (CH), 43.6 (CH$_2$), 29.7 (CH$_2$), 21.7 (CH$_3$), 19.1 (CH$_2$); HRMS (ESI$^+$) calculated for $C_{25}H_{26}N_2O_4S$ [M+Na]$^+$ 473.1505; found 473.1503.



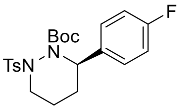
Benzyl (*R*)-3-phenyl-2-tosyl-1,2-diazepane-1-carboxylate (8s). Following general method 4, **6s** (27 mg, 56 µmol, 1.0 equiv), triphenylphosphine (22 mg, 84 µmol, 1.5 equiv), diethylazodicarboxylate (13 µL, 84 µmol, 1.5 equiv) and tetrahydrofuran (5.6 mL, 0.01 M) yielded **8s** as a colourless oil (17 mg, 38 µmol, 67%). R$_f$ = 0.31 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +22.3 (*c* 0.09, CHCl$_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 2/98; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 14.8 min; t_R16.8 min. IR (film) 2925, 2856, 1705, 1401, 1126 cm^{-1}; δ*H* (500 MHz; CDCl$_3$) 7.34-7.23 (5H, m, Ar-CH), 7.15-7.00 (6H, m, Ar-H) 6.90-6.84 (3H, m, Ar-H), 5.11-5.00 (1H, m, CHPh), 4.85 (1H, d, *J* 11.8, CO$_2$C*H*HPh), 4.70 (1H, d, *J* 11.9, CO$_2$CH*H*Ph), 4.28-4.02 (1H, m, NC*H*H), 3.71-3.44 (1H, m, NCH*H*), 2.43-2.31 (4H, m, CH$_3$ and CHPhC*H*H) 2.17-2.10 (1H, m, CHPhCH*H*), 1.99-1.72 (4H, br s, CH$_2$(C*H$_2$*)$_2$CH2),; δ*C* (125 MHz; CDCl$_3$) 156.2 (minor rotamer) and 156.1 (C=O), 143.5 (Ar-C) and 143.4 (minor rotamer), 142.6 (Ar-C) and 142.3 (minor rotamer), 136.3 (minor rotamer) and 136.2 (Ar-C), 136.1 (minor rotamer) and 135.0 (Ar-C), 129.1 (Ar-CH), 128.9 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 127.5 (Ar-CH), 127.2 (Ar-CH), 127.0 (Ar-CH), 126.9 (Ar-CH), 68.5 (minor rotamer) and 67.0 (CH$_2$), 68.4 (CH), 54.1 (minor rotamer) and 52.9 (CH$_2$), 36.2 (minor rotamer) and 36.1 (CH$_2$), 28.3 (CH$_2$) and 28.2 (minor rotamer), 27.2 (minor rotamer) and 26.3 (CH$_2$), 21.5 (CH$_3$); HRMS (ESI$^+$) calculated for $C_{26}H_{28}N_2O_4S$ [M+Na]$^+$ 487.1662; found 487.1656.



***tert*-Butyl (*R*)-6-phenyl-2-tosyltetrahydropyridazine-1(2*H*)-carboxylate (8t).** Following general method 4 **6t** (3.72 g, 8.56 mmol, 1.0 equiv), triphenylphosphine (5.61 g, 21.4 mmol, 2.5 equiv), diethyl azodicarboxylate (3.37 mL, 21.4 mmol, 2.5 equiv), tetrahydrofuran (860 mL, 0.01 M) yielded **8t** as a colourless oil, which crystallised upon standing to a white solid (2.16 g, 5.19 mmol, 61%). M.p. 99-102 °C; R$_f$ = 0.24 (20% EtOAc in petroleum ether); $[\alpha]^{28}_D$ –26.3 (*c* 0.31, CHCl$_3$). Enantiomeric excess (91% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 2/98; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 13.7 min; t_R 15.3 min; IR (neat) 2980, 1707, 1357, 1157, 747, 659 cm^{-1}; δ*H* (400 MHz; CDCl$_3$) 7.45 (2H d, *J* 7.6, Ar-*H*), 7.39-7.28 (5H, m, Ar-*H*), 7.05 (2H, d, *J* 8.0, Ar-*H*), 5.21 (1H, t, *J* 5.9, NCH), 3.66 (1H, dt, *J* 13.1, 6.7, NC*H*H), 3.41 (1H, dt, *J* 12.9, 6.4, NCH*H*), 2.34 (3H, s, CH$_3$), 2.01-1.95 (2H, m, C*H$_2$*CHN), 1.93-1.85 (1H, m, C*H*HCH$_2$N), 1.55-1.48 (1H, m, CH*H*CH$_2$N), 1.47 (9H, s, (CH$_3$)$_3$); δ*C* (125 MHz; CDCl$_3$) 156.9 (Boc-C=O), 143.2 (Ar-C), 140.6 (Ar-C), 136.7 (Ar-C), 129.3 (Ar-CH), 128.3 (Ar-CH), 128.1 (Ar-CH), 127.5 (Ar-CH), 127.2 (Ar-CH), 82.5 (C), 58.9 (NCH), 44.9 (NCH$_2$), 28.2 (Boc-CH$_3$), 24.9 (*C*H$_2$CHN), 21.6 (CH$_3$), 19.5 (*C*H$_2$CH$_2$N); HRMS (ESI$^+$) calculated for $C_{22}H_{28}N_2NaO_4S$ [M+Na]$^+$ 439.1662; found 439.1657.

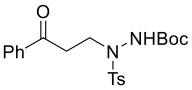


***tert*-Butyl (*R*)-7-phenyl-2-tosyl-1,2-diazepane-1-carboxylate (8u).** Following general method 4, **6u** (2.44 g, 5.67 mmol, 1.0 equiv), triphenylphosphine (3.72 g, 14.2 mmol, 2.5 equiv), diethyl azodicarboxylate (2.24 mL, 14.2 mmol, 2.5 equiv) and tetrahydrofuran (570 mL, 0.01 M) yielded **8u** as a colourless, highly viscous oil (969 mg, 2.25 mmol, 40%). R_f = 0.29 (20% EtOAc in petroleum ether); IR (neat) 2932, 1714, 1320, 1157, 1089, 957, 753, 698, 665 cm^{-1}; $[\alpha]^{28}_D$ +1.4 (*c* 0.22, $CHCl_3$). Enantiomeric excess (93% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 2/98; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 11.5 min; t_R 13.5 min; δ*H* (400 MHz; $CDCl_3$) 7.68-7.56 (4H, m, Ar-*H*), 7.36 (2H, t, *J* 7.5, Ar-*H*), 7.31-7.28 (1H, m, Ar-*H*), 7.21 (2H, d, *J* 8.0, Ar-*H*), 4.92 (1H, br s, NCH), 4.17 (1H, dt, *J* 14.0, 4.1, NC*H*H), 3.13 (1H, ddd, *J* 14.2, 10.7, 3.6, 1H, NCH*H*), 2.40 (3H, s, CH_3), 2.24-2.15 (1H, m, *CH*HCHN), 2.09-2.03 (2H, m, C*H*HCHN, C*H*HCH$_2$CH$_2$N), 1.81-1.67 (2H, m, C*H$_2$*CH$_2$N), 1.55-1.45 (1H, m, CH*H*CH$_2$CH$_2$N), 1.26 (9H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 155.7 (Boc-C=O), 143.3 (Ar-C), 142.6 (Ar-C), 137.2 (Ar-C), 129.3 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 127.6 (Ar-CH), 127.1 (Ar-CH), 82.2 (C), 66.4 (NCH), 51.7 (NCH_2), 31.8 (*C*H$_2$CHN), 28.5 (*C*H$_2$CH$_2$N), 28.0 (Boc-CH_3), 27.0 (*C*H$_2$CH$_2$CH$_2$N), 21.6 (CH_3); HRMS (ESI^+) calculated for $C_{23}H_{30}N_2NaO_4S$ $[M+Na]^+$ 453.1818; found 453.1816.

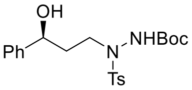


***tert*-Butyl (*R*)-6-(4-fluorophenyl)-2-tosyltetrahydropyridazine-1(2*H*)-carboxylate (8v).** Following general method 4, **6v** (805 mg, 1.78 mmol, 1.0 equiv), triphenylphosphine (1.17 g, 4.45 mmol, 2.5 equiv), diethyl azodicarboxylate (701 µL, 4.45 mmol, 2.5 equiv) and tetrahydrofuran (178 mL, 0.01 M) yielded **8v** as a colourless oil (466 mg, 1.07 mmol, 60%). R_f = 0.21 (20% EtOAc in petroleum ether); $[\alpha]^{28}_D$ –9.8 (*c* 0.52, $CHCl_3$). Enantiomeric excess (82% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 0.8/99.2; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 23.4 min; t_R 25.8 min; IR (neat) 2977, 1707, 1510, 1351, 1222, 1154, 835, 652 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.45 (2H, d, *J* 7.8, Ar-*H*), 7.42 (2H, dd, *J* 8.3, 5.7, Ar-*H*), 7.10 (2H, d, *J* 8.0, Ar-*H*), 7.00 (2H, t, *J* 8.7, Ar-*H*), 5.15 (1H, t, *J* 6.1, NCH), 3.71 (1H, dt, *J* 13.0, 6.6, NC*H*H), 3.40 (1H, dt, *J* 12.6, 6.2, NCH*H*), 2.36 (3H, s, CH_3), 1.99-1.92 (3H, m, C*H$_2$*CHN, C*H*HCH$_2$N), 1.55-1.49 (1H, m, CH*H*CH$_2$N), 1.45 (9H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 162.2 (d, *J* 245.6, CF), 156.8 (Boc-C=O), 143.5 (Ar-C), 136.7 (Ar-C), 136.5 (d, *J* 2.8, Ar-C), 129.3 (Ar-CH), 129.2 (d, *J* 8.0, Ar-CH), 128.1 (Ar-CH), 115.0 (d, *J* 21.4, Ar-CH), 82.6 (C), 58.5 (NCH), 44.9 (NCH_2), 28.2 (Boc-CH_3), 25.1 (*C*H$_2$CHN), 21.6 (CH_3), 19.4 (*C*H$_2$CH$_2$N); δ*F* (282 MHz; $CDCl_3$) –115.9 (CF); HRMS (ESI^+) calculated for $C_{22}H_{27}FN_2NaO_4S$ $[M+Na]^+$ 457.1568; found 457.1564.

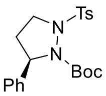
Large Scale Synthesis



***tert*-Butyl 2-(3-oxo-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (5j).** *tert*-Butyl carbazate (10.0 g, 75.7 mmol, 1.0 equiv), *para*-toluenesulphonyl chloride (15.1 g, 79.4 mmol, 1.05 equiv) and tetrahydrofuran (250 mL) were cooled to 0 °C. Pyridine (30 mL, 379 mmol, 5.0 equiv) was added dropwise over 30 min, then the reaction was allowed to warm to rt and stirred for 2 h. The reaction was quenched with 2 M HCl (50 mL) mixed with ice cold water (50 mL), which was added portionwise over 10 min. This was exracted with dichloromethane (3 × 50 mL) and the combined organic extracts were dried over magnesium sulphate and concentrated *in vacuo* to give a pale yellow solid. This crude material was dissolved in acetonitrile (400 mL), then 3-chloropropiophenone (12.8 g, 75.7 mmol, 1.0 equiv) and potassium carbonate (11.0 g, 79.4 mmol, 1.05 equiv) were added. This was stirred for 18 h and then quenched with water (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried over magnesium sulphate and concentrated *in vacuo* to give a pale yellow solid. This was purified by recrystallisation from an 8:1 mixture of ethyl actate : dichloromethane (900 mL) to give **5j** as a white solid (20.7 g, 49.5 mmol, 65%). [Data on page **S8**].



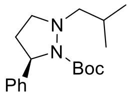
***tert*-Butyl (*S*)-2-(3-hydroxy-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (6j)** **5j** (5.00 g, 12.0 mmol, 1.0 equiv), catalyst **7c** (37 mg, 0.06 mmol, 0.5 mol%) and formic acid : triethylamine (5 : 2) azeotrope (12.0 mL, 1M) were combined and stirred in dichloromethane (47.8 mL, 0.25 M) for 72 h. The solution was then concentrated *in vacuo* to give a red oil. This was purified by column chromatography (33% ethyl acetate in petroleum ether) to give **6j** as a white solid (5.00 g, 11.9 mmol, 99%). [Data on page **S20**].



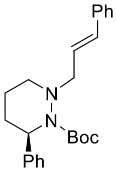
***tert*-Butyl (*R*)-5-phenyl-2-tosylpyrazolidine-1-carboxylate (8j)** **6j** (6.00 g, 14.3 mmol, 1.0 equiv), triphenylphosphine (6.74 g, 25.7 mmol, 1.8 equiv), diethylazodicarboxylate (4.05 mL, 25.7 mmol, 1.8 equiv) and tetrahydrofuran (143 mL, 0.1 M) were combined and stirred at rt for 24 h. The solution was then concentrated *in vacuo* to give a yellow oil. This was purified by column chromatography (20% ethyl acetate in petroleum ether) to give **8j** as a white solid (5.57 g, 13.8 mmol, 97%). [Data on page **S32**].

Nitrogen Functionalisation: Reductive Amination

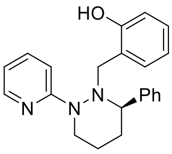
N.B. Magnesium turnings were activated by washing them with 1.0 M hydrochloric acid solution (2 × 20 mL), water (20 mL) and methanol (20 mL).



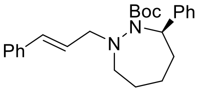
***tert*-Butyl (*R*)-2-isobutyl-5-phenylpyrazolidine-1-carboxylate (9b).** Cyclic hydrazine **8i** (84 mg, 0.20 mmol, 1.0 equiv), activated magnesium turnings (24 mg, 1.0 mmol, 5.0 equiv) and methanol (2.0 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a clear oil. To this was added sodium triacetoxyborohydride (212 mg, 1.00 mmol, 5.0 equiv), isobutyraldehyde (91 µL, 1.0 mmol, 5.0 equiv) and tetrahydrofuran (2 mL, 0.1 M). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with 1 M NaOH (5 mL), extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (5-10% ethyl acetate in petroleum ether) to give **9b** as a colourless oil (39 mg, 0.13 mmol, 63%). R_f = 0.38 (15% ethyl acetate in heptane). $[\alpha]^{32}_D$ +35.8 (*c* 0.30, dichloromethane). IR (film) 2955, 2878, 1690, 1366, 1173 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.39-7.15 (5H, m, Ar-*H*), 4.97 (1H, t, *J* 8.4, C*H*Ph), 3.15 (1H, td, *J* 11.3, 5.9, NC*H*HCH_2), 3.03 (1H, ddd, *J* 11.6, 6.6, 2.3, NCH*H*CH_2), 2.71 (1H, dd, *J* 11.5, 7.1, NC*H*HCH$(CH_3)_2$), 2.56-2.43 (2H, m, NCH*H*CH$(CH_3)_2$ and C*H*HCHPh), 2.23-2.10 (1H, m, CH*H*CHPh), 1.80 (1H, nonet, *J* 7.0, C*H*$(CH_3)_2$), 1.36 (9H, s, $C(CH_3)_3$), 1.05 (3H, d, *J* 6.6, CHC*H₃*), 1.02 (3H, d, *J* 6.6, CHC*H₃*); δ*C* (100 MHz; $CDCl_3$) 143.8 (Ar-C), 128.3 (Ar-CH), 126.6 (Ar-CH), 125.7 (Ar-CH), 80.1 (C), 66.8 (CH_2), 63.1 (CH), 53.3 (CH_2), 34.9 (CH_2), 28.3 (CH_3), 27.5 (CH), 21.3 (CH_3), 20.9 (CH_3), C=O not seen; HRMS (ESI$^+$) calculated for $C_{18}H_{28}N_2O_2$ $[M+Na]^+$ 327.2048; found 327.2052.



***tert*-Butyl (*R*)-2-cinnamyl-6-phenyltetrahydropyridazine-1(*2H*)-carboxylate (9k).** Cyclic hydrazine **8o** (134 mg, 0.31 mmol, 1.0 equiv), activated magnesium turnings (38 mg, 1.55 mmol, 5.0 equiv) and methanol (3.1 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 h. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a clear oil. To this was added sodium triacetoxyborohydride (323 mg, 1.52 mmol, 5.0 equiv), *E*-cinnamaldehyde (193 µL, 1.52 mmol, 5.0 equiv) and tetrahydrofuran (3.1 mL, 0.1 M). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with 1 M NaOH (5 mL), extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (5-10% ethyl acetate in petroleum ether) to give **9k** as a colourless oil (105 mg, 0.28 mmol, 91%). R_f = 0.16 (10% ethyl acetate in heptane); $[\alpha]^{32}_{D}$ +24.0 (*c* 0.35, $CHCl_3$). IR (film) 3007, 2866, 1681, 1390, 1069 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.48-7.43 (2H, m, Ar-*H*), 7.35 (2H, t, *J* 7.5, Ar-H), 7.32-7.27 (5H, m, Ar-H), 7.25-7.20 (1H, m, Ar-H), 6.22 (1H, d, *J* 15.9, C=CH), 6.09 (1H, dt, *J* 15.8, 6.3, C=CH), 5.37 (1H, s, C*H*Ph), 3.58 (2H, d, *J* 7.0, NC*H*$_2$CH=C), 3.22-3.07 (1H, m, NC*H*HCH$_2$), 2.99-2.92 (1H, m, NCH*H*CH$_2$), 2.42-2.21 (1H, m, C*H*HCHPh), 2.09-1.95 (2H, m, CH*H*CHPh and NCH$_2$C*H*H), 1.53 (10H, s, NCH$_2$CH*H* and C(CH$_3$)$_3$); δ*C* (125 MHz; $CDCl_3$) 142.0 (Ar-C), 137.2 (Ar-C), 131.7 (C=CH) 128.5 (Ar-CH), 128.2 (Ar-CH), 127.4 (C=CH), 127.2 (Ar-CH), 127.1 (Ar-CH), 126.6 (Ar-CH), 126.3 (Ar-CH), 80.5 (C), 57.9 (CH$_2$), 55.2 (CH, seen on HSQC), 49.0 (CH$_2$), 29.7 (CH$_2$), 28.5 (CH$_3$), 25.6 (CH$_2$), 17.9 (CH$_3$), C=O not seen; HRMS (ESI$^+$) calculated for $C_{24}H_{30}N_2O_2$ [M+Na]$^+$ 401.2199; found 401.2197.

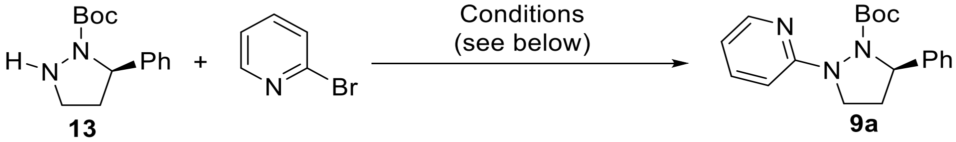


(*R*)-2-((6-Phenyl-2-(pyridin-2-yl)tetrahydropyridazin-1(2*H*)-yl)methyl)phenol (10j). Cyclic hydrazine **9j** (53 mg, 155 μmol, 1.0 equiv) in HCl/1,4-dioxane (4M, 2.5 mL) was stirred for 2 h at rt. The solvent was removed *in vacuo* and dichloromethane (15 mL) and saturated $NaHCO_3$ solution (15 mL) were added. The layers were separated and the aqueous one was extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was dissolved anhydrous THF (2.0 mL) and salicylaldehyde (83 μL, 0.78 mmol, 5.0 equiv) and sodium triacetoxyborohydride (164 mg, 0.78 mmol, 5.0 equiv) were added. The reaction mixture was stirred for 24 h at rt, quenched with aqueous NaOH (1M, 4.0 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The redidue was purified by column chromatography (20-33% EtOAc/petroleum ether) to give **10j** as a colourless, viscous oil (33 mg, 96 μmol, 62%). R_f = 0.17 (33% EtOAc in petroleum ether); $[\alpha]^{29}_{D}$ +61.4 (*c* 0.02, $CHCl_3$); IR (neat) 2926, 1591, 1466, 1437, 1348, 1258, 1159, 957, 770, 753, 693 cm^{-1} δ*H* (600 MHz; $CDCl_3$; 233 K) Two confomers in a ratio of 66:34 are observed at 233 K: 8.36 (1H, d, *J* 4.4, Ar-*H*), 8.16 (2H, d, *J* 4.1, Ar-*H*), 7.54-7.50 (2H, m, Ar-*H*), 7.50-7.47 (6H, m, Ar-*H*), 7.42 (4H, t, *J* 7.5, Ar-*H*), 7.37-7.33 (4H, m, Ar-*H*), 7.23 (2H, t, *J* 7.6, Ar-*H*), 7.19 (1H, t, *J* 7.7, Ar-*H*), 7.16-7.10 (2H, m, Ar-*H*), 6.92 (1H, d, *J* 8.0, Ar-*H*), 6.75 (1H, t, *J* 7.1, Ar-*H*), 6.70 (1H, dd, *J* 6.6, 5.5, Ar-*H*), 6.63 (2H, dd, *J* 6.3, 5.5, Ar-*H*), 6.57 (1H, d, *J* 8.7 , Ar-*H*), 4.73 (2H, d, *J* 10.8, NC*H*HCH$_2$), 4.34 (1H, d, *J* 12.4, NC*H*H), 4.16 (1H, br d, *J* 2.4, NC*H*), 4.12 (1H, d, *J* 12.3, NCH*H*), 3.89 (2H d, *J* 10.4, NC*H*), 3.65 (3H, br d, *J* 10.6, NC*H*HCH$_2$, O*H*), 3.49 (1H, m, NCH*H*CH$_2$), 2.96 (2H, t, *J* 11.2, NCH*H*CH$_2$), 2.45 (1H, ddd, *J* 17.6, 9.2, 4.3, C*H*$_2$), 2.24-2.08 (3H, m, C*H*$_2$, C*H*$_2$), 1.98-1.94 (2H, m, C*H*$_2$), 1.94-1.68 (6H, m, C*H*$_2$). *N.B.* Compound decomposes in $CDCl_3$ within several hours. δ*C* (150 MHz; $CDCl_3$; 233 K) Chemical shifts for the major confomer at 233 K: 159.7 (Ar-C), 158.2 (Ar-C), 147.2 (Ar-CH), 141.2 (Ar-C), 137.8 (Ar-CH), 128.6 (Ar-CH), 128.2 (Ar-CH), 127.7 (Ar-CH), 127.0 (Ar-CH), 126.8 (Ar-CH), 121.8 (Ar-C), 118.3 (Ar-CH), 116.9 (Ar-CH), 113.2 (Ar-CH), 108.5 (Ar-CH), 59.0 (NCH_2), 50.8 (NCH), 45.1 (N*C*H_2CH_2), 31.1 ($NCHCH_2$), 23.6 (NCH_2*C*H_2); HRMS (ESI^+) calculated for $C_{22}H_{24}N_3O$ $[M+H]^+$ 346.1914; found 346.1917.



***tert*-Butyl (*R*)-2-cinnamyl-7-phenyl-1,2-diazepane-1-carboxylate (9o).** To a solution of cyclic hydrazine **8p** (160 mg, 0.37 mmol, 1.0 equiv) in methanol (10 mL) was added activated magnesium turnings (5.0 equiv), and the mixture was stirred vigorously for 4 h at rt. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with dichloromethane (4 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The residue was dissolved anhydrous THF (6.0 mL) and cinnmaldehyde (233 µL, 1.85 mmol, 5.0 equiv) and sodium triacetoxyborohydride (392 mg, 1.85 mmol, 5.0 equiv) were added. The reaction mixture was stirred for 20 h at rt, quenched with aqueous NaOH (1M, 4.0 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (10-20% EtOAc/petroleum ether) to give **9o** as a colourless oil (131 mg, 0.33 mmol, 90%). R_f = 0.62 (20% EtOAc in petroleum ether); $[\alpha]^{27}_D$ –9.0 (*c* 0.20, $CHCl_3$); IR (neat) 2939, 2873, 1702, 1456, 1326, 985, 781, 706 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) Two confomers in a 50:50 ratio are observed: 7.46 (1H, d, *J* 7.5, Ar-*H*), 7.42 (1H, d, *J* 7.1, Ar-*H*), 7.30-7.20 (8H, m, Ar-*H*), 6.43 (1H, d, *J* 15.9, C=CH), 6.02-5.88 (1H, m, C=CH), 5.12 (0.5H, dd, *J* 9.5, 6.4, NC*H*), 4.85 (0.5H, dd, *J* 10.5, 5.3, NC*H*), 4.01 (0.5H, dd, *J* 14.1, 7.5, C*H*HCH), 3.76 (0.5H, dd, *J* 14.2, 7.5, C*H*HCH), 3.58 (0.5H, dd, *J* 14.0, 4.7, CH*H*CH), 3.46 (0.5H, dd, *J* 14.0, 4.3, CH*H*CH), 3.29-3.20 (0.5H, m, NC*H*H), 3.08-2.99 (0.5H, m, NC*H*H), 2.86-2.81 (1H, m, NCH*H*), 2.29-2.19 (1H, m, C*H*HCHN), 2.06-1.88 (2H, m, CH*H*CHN, C*H*HCH_2CHN), 1.69-1.61 (2H, m, C*H₂*CH_2N), 1.57-1.52 (1H, m, CH*H*CH_2CHN), 1.53 (4.5H, s, $(CH_3)_3$), 1.47 (4.5H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) Two confomers are observed: 156.8 (Boc-C=O), 154.7 (Boc-C=O), 143.31 (Ar-C), 143.27 (Ar-C), 137.5 (Ar-C), 137.3 (Ar-C), 131.6 (alk-CH), 131.4 (alk-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 127.7 (alk-CH), 127.5 (alk-CH), 127.4 (Ar-CH), 127.3 (Ar-CH), 127.1 (Ar-CH), 127.0 (Ar-CH), 126.5 (Ar-CH), 80.5 (C), 80.4 (C), 62.2 (NCH), 60.9 (*C*H_2CH), 60.5 (NCH), 59.7 (*C*H_2CH), 52.2 (NCH_2), 51.6 (NCH_2), 33.8 (*C*H_2CHN), 33.3 (*C*H_2CHN), 30.7 (*C*H_2CH_2N), 30.3 (*C*H_2CH_2N), 29.0 (Boc-CH_3), 28.8 (Boc-CH_3), 25.6 (*C*H_2CH_2CHN), 25.2 (*C*H_2CH_2CHN); HRMS (ESI^+) calculated for $C_{25}H_{32}N_2NaO_2$ $[M+Na]^+$ 415.2356; found 415.2359.

Buchwald-Hartwig Amination Screen 1 – 96 Well Screen



The reactions were performed in an aluminium heating block with 96 x 750 µL vials, each with a teflon coated magnetic stirrer bar. These vials were arranged in 12 columns (labelled 1-12) and 8 rows (labelled A-H). The following powders were weighed into the vials using a Mettler Toledo QX96 powder dispenser inside a glovebox.

All vials in rows A, E: Sodium *tert*-butoxide (4.3 mg, 44 µmol, 2.0 equiv).

All vials in rows B, F: Caesium carbonate (14.4 mg, 44 µmol, 2.0 equiv).

All vials in rows C, G: Potassium carbonate (6.1 mg, 44 µmol, 2.0 equiv).

All vials in rows D, H: Potassium phosphate tribasic (9.4 mg, 44 µmol, 2.0 equiv).

All vials in column 1: [XantPhos Pd(allyl)]Cl (1.7 mg, 2.2 µmol, 0.1 equiv).

All vials in column 2: [(*R*)-BINAP Pd(allyl)]Cl (1.9 mg, 2.2 µmol, 0.1 equiv).

All vials in column 3: Pd(dppf)Cl_2 · dichloromethane (1.8 mg, 2.2 µmol, 0.1 equiv).

All vials in column 4: [P(*t*Bu)$_3$] Pd(crotyl) Cl (0.9 mg, 2.2 µmol, 0.1 equiv).

All vials in column 5: JohnPhos (0.8 mg, 2.2 µmol, 0.1 equiv) and palladium (II) acetate (0.5 mg, 2.2 µmol, 1.0 equiv).

All vials in column 6: AdBrettPhos (1.7 mg, 2.7 µmol, 0.12 equiv) and palladium (II) acetate (0.5 mg, 2.2 µmol, 0.1 equiv).

All vials in column 7: [*t*BuBrettPhos Pd(allyl)]OTf (1.7 mg, 2.2 µmol, 0.1 equiv).

All vials in column 8: MorDalPhos (1.2 mg, 2.6 µmol, 0.12 equiv) and palladium (II) acetate (0.5 mg, 2.2 µmol, 0.1 equiv).

All vials in column 9: [BrettPhos Pd(crotyl)]OTf (1.9 mg, 2.2 µmol, 0.1 equiv).

All vials in column 10: [*t*BuXPhos Pd(allyl)]OTf (1.6 mg, 2.2 µmol, 0.1 equiv).

All vials in column 11: XPhos Pd(crotyl)Cl (1.5 mg, 2.2 µmol, 0.1 equiv).

All vials in column 12: RuPhos Pd(crotyl)Cl (1.5 mg, 2.2 µmol, 0.1 equiv).

The following stock solutions were then made:

Stock Solution 1: *tert*-butyl (*R*)-5-phenylpyrazolidine-1-carboxylate (**13**) (286 mg, 1.15 mmol) and 2-bromopyridine (333 mg, 2.10 mmol) in toluene (4.42 mL).

Stock Solution 2: *tert*-butyl (*R*)-5-phenylpyrazolidine-1-carboxylate (**13**) (286 mg, 1.15 mmol) and 2-bromopyridine (333 mg, 2.10 mmol) in dioxane (4.42 mL).

All vials in rows A-D were dosed with 85 µL of Stock Solution 1 which contained *tert*-butyl (*R*)-5-phenylpyrazolidine-1-carboxylate (**13**) (5.5 mg, 22 µmol, 1.0 equiv, obtained by deprotection of **8j** using procedure in gerneal method 5) and 2-bromopyridine (6.4 mg, 41 µmol, 1.8 equiv).

All vials in rows E-H were dosed with 85 µL of Stock Solution 2 which contained *tert*-butyl (*R*)-5-phenylpyrazolidine-1-carboxylate (**13**) (5.5 mg, 2.2 µmol, 1.0 equiv) and 2-bromopyridine (6.4 mg, 41 µmol, 1.8 equiv).

The plate was sealed with a silicone and PFA mat and placed on an HEL polyblock. The plate was then heated at 90 °C for 16 h. The vials were then cooled to rt and DMSO (300 µL) was added to each using a multichannel pipette. A 5 µL aliquot was extracted from each then added to a 96-well analytical plate and diluted with DMSO (50 µL). The plate was analyzed by reverse phase LCMS (XBridge C_{18} 3.5-µm 2.1 × 35 mm Column, 1.6 mL min^{-1}, 50 °C; gradient 5:95 to 99:1 (pH 9 H_2O + 10 mM NH_4HCO_2) / MeCN over 0.7 min + 0.3 min hold). The LCMS traces were processed using in-house software and the results visualized using Spotfire software to give **Figure S1**.

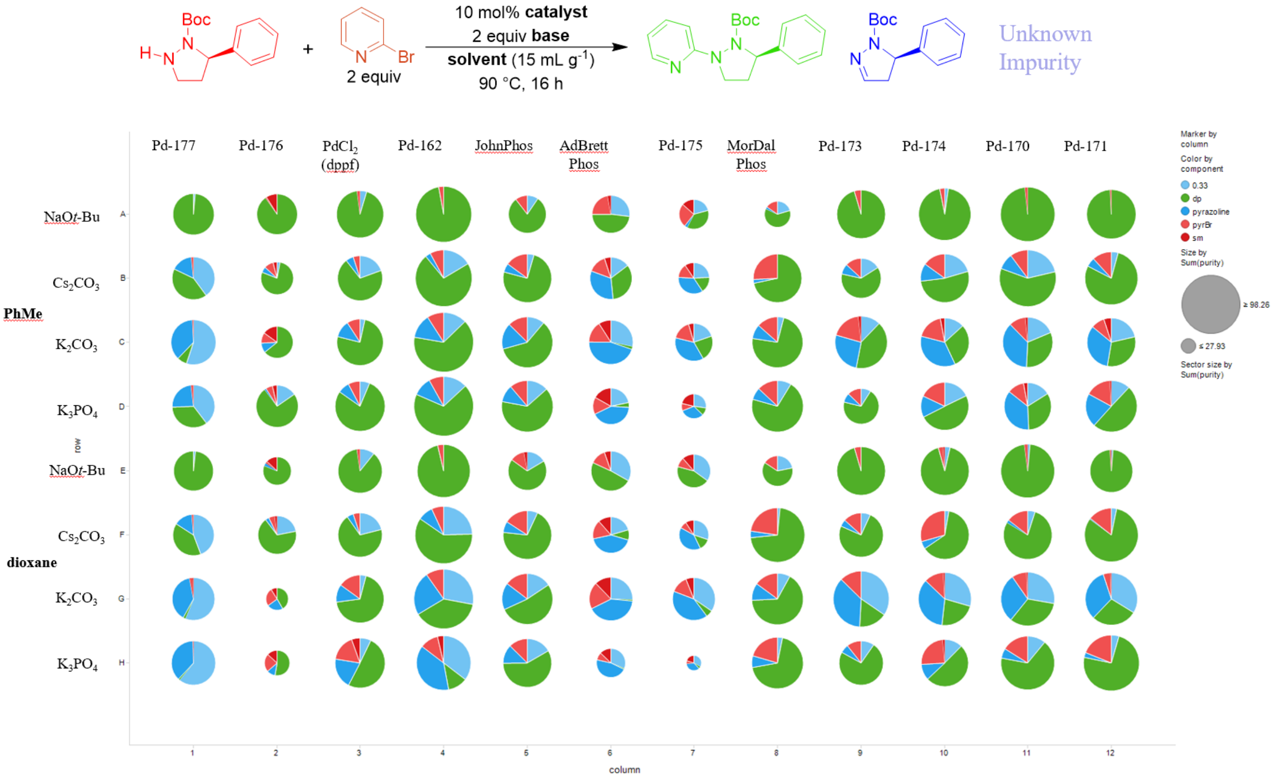
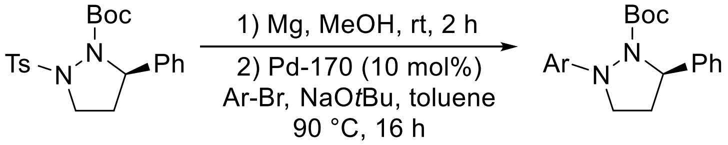


*Figure **S1** High throughput screening of the Buchwald-Hartwig coupling using **13***

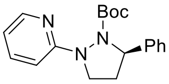
From this reaction screen conditions used in vial A11 were chosen for subsequent Buchwald-Hartwig aminations (see general method 5).

General method 5: Buchwald-Hartwig Amination

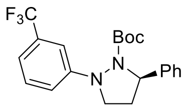


N.B. Magnesium turnings were activated by washing them with 1 M hydrochloric acid solution (2 × 20 mL), water (20 mL) and methanol (20 mL).

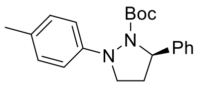
tert-Butyl-(*R*)-5-phenyl-2-tosylpyrazolidine-1-carboxylate (**8j**) (1.0 equiv), activated magnesium turnings (5.0 equiv) and MeOH (0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extrcts were dried over $MgSO_4$ and concentrated in vacuo to give a clear oil. To this was added toluene (1.0 M) was added XPhos Pd(crotyl)Cl (0.1 equiv), sodium *tert*-butoxide (2.0 equiv) and aryl halide (2.0 equiv). The reaction mixture was stirred at 90 °C for 16 h. The mixture was cooled to rt then quenched with saturated ammonium chloride solution (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography (30% ethyl acetate in petroleum ether) to give the following compounds.



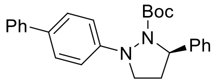
***tert*-Butyl (*R*)-5-phenyl-2-(pyridin-2-yl)pyrazolidine-1-carboxylate (9a).** Following general method 5, **8j** (72 mg, 0.18 mmol, 1.0 equiv), magnesium turnings (22 mg, 0.90 mmol, 5.0 equiv) and methanol (1.8 mL, 0.1 M), then XPhos Pd(crotyl)Cl (12 mg, 18 µmol, 0.1 equiv), sodium *tert*-butoxide (35 mg, 0.36 mmol, 2.0 equiv) and 2-bromopyridine (34 µL, 0.36 mmol, 2.0 equiv) in toluene (0.18 mL, 1.0 M) yielded **9a** as a white solid (50 mg, 0.16 mmol, 85%). M.p. 98-99 °C; R_f = 0.34 (30% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ –91.3 (*c* 0.04, $CHCl_3$); IR (film) 2989, 1698, 1588, 1388, 1161 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.25 (1H, d, *J* 4.8, Ar-H), 7.59 (1H, td, *J* 7.8, 1.8, Ar-H), 7.30-7.18 (5H, m, Ar-*H*), 6.95 (1H, d, *J* 8.4, Ar-H), 6.82 (1H, dd, *J* 6.7, 5.3, Ar-H), 5.19 (1H, t, *J* 8.1, C*H*Ph), 4.89 (1H, t, *J* 10.3, NC*H*H), 3.49-3.41 (1H, m, NCH*H*), 2.58-2.51 (1H, m, CHPhC*H*H), 2.09-1.98 (1H, m, CHPhCH*H*), 1.43 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 160.9 (Ar-C), 156.8 (C=O), 147.3 (Ar-CH), 142.1 (Ar-C), 137.5 (Ar-CH), 128.4 (Ar-CH), 127.2 (Ar-CH), 126.6 (Ar-CH), 115.8 (Ar-CH), 110.4 (Ar-CH), 81.5 (C), 65.5 (CH), 48.2 (CH_2), 36.2 (CH_2), 28.2 (CH_3); HRMS (ESI$^+$) calculated for $C_{19}H_{24}N_3O_2$ $[M+Na]^+$ 326.1863; found 326.1867.



***tert*-Butyl (*R*)-5-phenyl-2-(3-(trifluoromethyl)phenyl)pyrazolidine-1-carboxylate (9c).** Following general method 5, **8j** (85 mg, 0.21 mmol, 1.0 equiv), magnesium turnings (26 mg, 1.05 mmol, 5.0 equiv) and methanol (2.1 mL, 0.1 M), then XPhos Pd(crotyl)Cl (7 mg, 10 µmol, 0.05 equiv), sodium *tert*-butoxide (40 mg, 0.42 mmol, 2.0 equiv) and 3-bromobenzotrifluoride (55 µL, 0.42 mmol, 2.0 equiv) in toluene (0.21 mL, 1.0 M) yielded **9c** as a clear oil (69 mg, 0.18 mmol, 85%). R_f = 0.28 (20% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ –9.8 (*c* 0.25, dichloromethane). IR (film) 2978, 2930, 1704, 1451, 1367, 1164 cm^{-1}; δH (500 MHz; $CDCl_3$7.37 (1H, t, *J* 8.0, Ar-CH), 7.30-7.21 (5H, m, Ar-H), 7.19 (1H, s, Ar-H), 7.15 (1H, d, *J* 7.6, Ar-H), 7.11 (1H, dd, *J* 8.3, 1.6, Ar-CH), 5.20 (1H, t, *J* 7.5, C*H*Ph), 3.85 (1H, ddd, *J* 11.0, 6.5, 4.5, NC*H*H), 3.69 (1H, ddd, *J* 11.0, 8.9, 6.3, NCH*H*), 2.54 (1H, qd, *J* 6.3, 4.5, CHPhC*H*H), 2.13 (1H, dt, *J* 15.7, 7.2, CHPhCH*H*), 1.39 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 156.1 (C=O), 150.7 (Ar-C), 141.4 (Ar-C), 131.1 (q, *J* 32.5, Ar-C), 129.3 (Ar-CH), 128.5 (Ar-CH), 127.4 (Ar-CH), 126.7 (Ar-CH), 124.3 (q, *J* 271.3, CF_3), 118.2 (Ar-CH), 117.9 (q, *J* 3.8, Ar-CH), 111.9 (q, *J* 3.8, Ar-CH), 81.7 (C), 63.3 (CH), 52.3 (CH_2), 35.4 (CH_2), 28.1 (CH_3); δ*F* (282 MHz; $CDCl_3$) -62.8 (CF_3); HRMS (ESI$^+$) calculated for $F_3C_{21}H_{23}N_2O_2$ $[M+Na]^+$ 415.1604; found 415.1597.



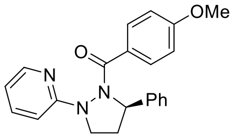
***tert*-Butyl (*R*)-5-phenyl-2-(*p*-tolyl)pyrazolidine-1-carboxylate (9e).** Following general method 5, **8j** (105 mg, 0.26 mmol, 1.0 equiv), magnesium turnings (32 mg, 1.30 mmol, 5.0 equiv) and methanol (2.6 mL, 0.1 M), then XPhos Pd(crotyl)Cl (18 mg, 26 µmol, 0.1 equiv), sodium *tert*-butoxide (50 mg, 0.52 mmol, 2.0 equiv) and 4-chlorotoluene (63 µL, 0.52 mmol, 2.0 equiv) in toluene (0.26 mL, 1.0 M) yielded **9e** as an orange oil (73 mg, 0.22 mmol, 82%). R_f = 0.30 (30% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ –27.5 (*c* 0.26, dichloromethane); IR (film) 2978, 2924, 1697, 1512, 1366, 1134 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.30-7.23 (5H, m, Ar-*H*), 7.08 (2H, d, *J* 8.4, Ar-H), 6.91 (2H, d, *J* 8.5, Ar-H) 5.09 (1H, t, *J* 7.8, CHPh), 3.95-3.80 (1H, m, NC*H*H), 3.62-3.54 (1H, m, NCH*H*), 2.54-2.42 (1H, m, CHPhC*H*H), 2.29 (3H, s, Ar-CH_3), 2.09-1.99 (1H, m, CHPhCH*H*), 1.35 (9H, s, $C(CH_3)_3$); δ*C* (100 MHz; $CDCl_3$) 148.3 (Ar-C) 142.2 (Ar-C), 130.3 (Ar-C), 129.4 (Ar-CH), 128.3 (Ar-CH), 127.1 (Ar-CH), 126.9 (Ar-CH), 115.8 (Ar-CH), 81.0 (C), 63.6 (CH), 53.0 (CH_2), 35.7 (CH_2), 28.2 (CH_3), 20.5 (CH_3), C=O not seen; HRMS (ESI$^+$) calculated for $C_{21}H_{26}N_2O_2$ $[M+Na]^+$ 361.1892; found 361.1896.



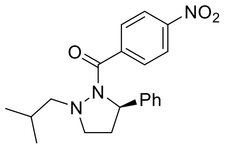
***tert*-Butyl (*R*)-2-([1,1'-biphenyl]-4-yl)-5-phenylpyrazolidine-1-carboxylate (9f).** Following general method 5, **8j** (101 mg, 0.25 mmol, 1.0 equiv), magnesium turnings (30 mg, 1.25 mmol, 5.0 equiv) and methanol (2.5 mL, 0.1 M), then XPhos Pd(crotyl)Cl (8 mg, 12 µmol, 0.05 equiv), sodium *tert*-butoxide (48 mg, 0.50 mmol, 2.0 equiv) and 4-bromobiphenyl (116 mg, 0.50 mmol, 2.0 equiv) in toluene (0.25 mL, 1.0 M) yielded **9f** as a clear oil (73 mg, 0.18 mmol, 73%). R*f* = 0.17 (15% ethyl acetate in petroleum ether); $[\alpha]^{32}_{D}$ –28.2 (*c* 0.19, $CHCl_3$); IR (film) 3030, 2977, 1700, 1608, 1366, 1132 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.61 (2H, d, *J* 7.4, Ar-H), 7.56 (2H, d, *J* 8.7, Ar-CH), 7.44 (2H, t, *J* 7.7, Ar-CH), 7.31-7.27 (6H, m, Ar-H), 7.10 (2H, d, *J* 8.6, Ar-H), 5.18 (1H, t, *J* 7.6, C*H*Ph), 3.96 (1H, ddd, *J* 10.7, 6.2, 4.2, NC*H*H), 3.74-3.64 (1H, m, NCH*H*), 2.61-2.53 (1H, m, CHPhC*H*H), 2.20-2.10 (1H, m, CHPhCH*H*), 1.41 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 155.9 (C=O), 149.7 (Ar-C), 141.9 (Ar-C), 140.9 (Ar-C), 133.8 (Ar-C), 128.7 (Ar-CH), 128.4 (Ar-CH), 127.5 (Ar-CH), 127.3 (Ar-CH), 126.9 (Ar-CH), 126.6 (Ar-CH), 126.6 (Ar-CH), 115.9 (Ar-CH), 81.4 (C), 63.6 (CH), 52.8 (CH_2), 35.7 (CH_2), 28.2 (CH_3); HRMS (ESI$^+$) calculated for $C_{26}H_{28}N_2O_2$ $[M+Na]^+$ 423.2043; found 423.2037.

Nitrogen Functionalisation: Acylation

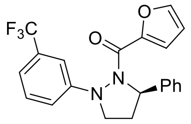
N.B. Magnesium turnings were activated by washing them with 1.0 M hydrochloric acid solution (2 × 20 mL), water (20 mL) and methanol (20 mL).



(*R*)-(4-Methoxyphenyl)(5-phenyl-2-(pyridin-2-yl)pyrazolidin-1-yl)methanone (10a). Cyclic hydrazine **9a** (29 mg, 90 µmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2 mL) and stirred for 2 h. It was then concentrated *in vacuo* and 4-methoxybenzoyl chloride (38 mg, 0.23 mmol, 2.5 equiv) in dichloromethane (90 µL, 0.1 M) was added. The reaction mixture was cooled over an ice bath then *N*,*N*-diisopropylethylamine (31 µL, 0.18 mmol, 2.0 equiv) in dichloromethane (2 mL) was added dropwise over 30 min. The reaction mixture was allowed to warm to rt then stirred for 18 h. The mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over $MgSO_4$. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **10a** as a white solid (26 mg, 70 µmol, 82%). R*f* = 0.21 (25% ethyl acetate in petroleum ether); M.p. 131-132 °C; $[\alpha]^{32}_{D}$ –26.7 (*c* 0.06, CH_2Cl_2). IR (film) 2924, 1643, 1597, 1466, 1258 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 8.25 (1H, d, *J* 4.0, Ar-H), 7.78 (2H, d, *J* 8.4, Ar-H), 7.45 (1H, t, *J* 7.6, Ar-H), 7.26-7.19 (5H, m, Ar-*H*), 6.88-6.74 (4H, m, Ar-H), 5.60 (1H, s, C*H*Ph), 4.65 (1H, br s, NC*H*H), 3.78 (3H, s, OCH_3), 3.60 (1H, s, NCH*H*), 2.63 (1H, dt, *J* 12.4, 6.1, CHPhC*H*H), 2.22 (1H, td, *J* 13.4, 7.2, CHPhCH*H*); δ*C* (100 MHz; $CDCl_3$) 161.9 (C=O), 147.8 (Ar-CH), 141.0 (Ar-C), 137.5 (Ar-CH), 130.7 (Ar-C), 128.5 (Ar-CH), 127.3 (Ar-CH), 126.9 (Ar-CH), 126.4 (Ar-C), 116.4 (Ar-CH), 113.3 (Ar-CH), 110.6 (Ar-CH), 69.6 (CH), 55.3 (CH_3), 34.0 (CH_2), 1 Ar-CH, 1 CH_2 and 1 Ar-C not seen; HRMS (ESI$^+$) calculated for $C_{22}H_{21}N_3O_2$ $[M+H]^+$ 360.1712; found 360.1712.

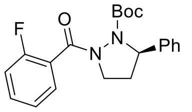


(*R*)-(2-Isobutyl-5-phenylpyrazolidin-1-yl)(4-nitrophenyl)methanone (10b). Cyclic hydrazine **9b** (43 mg, 0.14 mmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2 mL) and stirred for 2 h. It was then concentrated *in vacuo* and a solution of 4-nitrobenzoyl chloride (63 mg, 0.34 mmol, 2.5 equiv) in dichloromethane (135 µL, 0.1 M) were added. The mixture was cooled over an ice bath then *N*,*N*-diisopropylethylamine (47 µL, 0.27 mmol, 2.0 equiv) in dichloromethane (2.0 mL) was added dropwise over 30 minutes. The reaction mixture was allowed to warm to rt then stirred for 18 h. The reaction mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 × 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (20% ethyl acetate in petroleum ether) to give **10b** as a white solid (37 mg, 0.1 mmol, 77%). R_f = 0.18 (20% ethyl acetate in petroleum ether); $[\alpha]^{32}_{D}$ +5.2 (*c* 0.17, $CHCl_3$); Enantiomeric excess (95% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 17.4 min; t_R 36.3 min; IR (film) 2923, 2851, 1635, 1521, 1346 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.24 (2H, d, *J* 8.6, Ar-H), 7.84-7.74 (2H, br m, Ar-H), 7.33 (5H, br m, Ar-H), 5.48 (1H, br s, C*H*Ph), 3.24-3.09 (1H, br m, NCH_2CH_2), 2.83-2.74 (1H, br m, CHPhC*H*H), 2.49-2.29 (3H, br m, CHPhCH*H* and $CH_2CH(CH_3)_2$) 1.45 (1H, br s, $CH(CH_3)_2$), 0.55 (6H, s, $CH(CH_3)_2$); δ*C* (125 MHz; $CDCl_3$) 166.6 (C=O), 148.2 (Ar-C), 142.8 (Ar-C), 142.1 (Ar-C), 129.0 (Ar-CH), 128.6 (Ar-CH), 125.7 (Ar-CH), 123.6 (Ar-CH), 122.9 (Ar-CH), 65.8 (CH_2), 61.8 (CH), 33.2 (CH_2), 27.2 (CH), 20.5 (CH_3), 20.2 (CH_3), 1 CH_2 not seen; HRMS (ESI$^+$) calculated for $C_{20}H_{23}N_3O_3$ $[M+Na]^+$ 376.1632; found 376.1632.

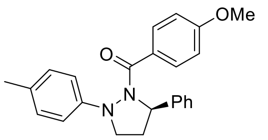


(*R*)-Furan-2-yl(5-phenyl-2-(3-(trifluoromethyl)phenyl)pyrazolidin-1-yl)methanone (10c). Cyclic hydrazine **9c** (41 mg, 0.10 mmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2 mL) and stirred for 2 h. It was then concentrated *in vacuo* then 2-furoyl chloride (26 µL, 0.26 mmol, 2.5 equiv) and dichloromethane (100 µL, 0.1 M) were added. The reaction mixture was cooled over an ice bath then a solution of *N*,*N*-diisopropylethylamine (37 µL, 0.21 mmol, 2.0 equiv) in dichloromethane (2 mL) was added dropwise over 30 minutes. The mixture was allowed to warm to rt then stirred for 18 h. The mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 × 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **10c** as a yellow solid (28 mg, 71 µmol, 69%). R_f = 0.18 (25% ethyl acetate in petroleum ether); $[\alpha]^{32}_{D}$ +0.9 (*c* 0.33, $CHCl_3$). IR (film) 2927, 1649, 1470, 1337, 1124 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.55 (1H, s, Ar-H), 7.40-7.21 (9H, m, Ar-H), 6.95 (1H, d, *J* 3.0, Ar-*H*), 6.38 (1H, dd, *J* 3.5 and 1.6, Ar-H), 5.75 (1H, t, *J*

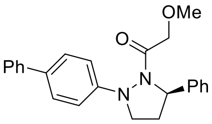
8.2, C*H*Ph), 4.12-4.07 (1H, br m, NC*H*H), 3.62-3.48 (1H, br m, NCH*H*), 2.68-2.62 (1H, m, CHPhC*H*H), 2.37-2.28 (1H, m, CHPhCH*H*); δ*C* (125 MHz; $CDCl_3$) 162.5 (C=O, seen on HMBC), 150.3 (Ar-C), 145.7 (Ar-CH), 139.8 (Ar-C), 131.6 (q, *J* 31.3, Ar-C), 129.7 (Ar-CH), 128.4 (Ar-CH), 127.6 (Ar-CH), 123.9 (q, *J* 270, Ar-C), 119.5 (Ar-CH), 118.7 (Ar-CH), 118.2 (Ar-CH), 112.9 (Ar-CH), 111.7 (Ar-CH), 62.5 (CH), 54.3 (CH_2), 32.6 (CH_2), 1 Ar-C and 1 Ar-CH not seen; δ*F* (282 MHz; $CDCl_3$) -62.8 (CF_3); HRMS (ESI^+) calculated for $F_3C_{21}H_{17}N_2O_2$ $[M+Na]^+$ 409.1134; found 409.1131.



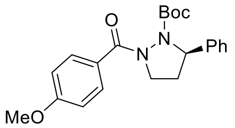
***tert*-Butyl (*R*)-2-(2-fluorobenzoyl)-5-phenylpyrazolidine-1-carboxylate (9d).** Cyclic hydrazine **8j** (64 mg, 0.16 mmol, 1.0 equiv), magnesium turnings (19 mg, 0.80 mmol, 5.0 equiv) and methanol (1.6 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extrcts were dried over $MgSO_4$ and concentrated *in vacuo* to give a clear oil. To this was added then 2-fluorobenzoyl chloride (48 µL, 0.40 mmol, 2.5 equiv) in dichloromethane (1.6 mL). The reaction mixture was stirred at rt for 18 h. The mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **9d** as a clear oil (46 mg, 0.12 mmol, 77%). R_f = 0.21 (25% ethyl acetate in petroleum ether). $[\alpha]^{32}_D$ +7.1 (*c* 0.12, $CHCl_3$). IR (film) 2978, 1725, 1714, 1368, 1154 cm^{-1}; δ*H* (500 MHz; d6-DMSO at 373 K) 7.47 (1H, d, *J* 5.3, Ar-H), 7.39-7.25 (5H, m, Ar-H), 7.25-7.13 (3H, m, Ar-H), 5.27 (1H, t, *J* 6.6, C*H*Ph), 4.05-3.91 (1H, br m, NC*H*H), 3.47 (1H, dd, *J* 17.9 and 8.5, NCH*H*), 2.69-2.60 (1H, m, CHPhC*H*H), 2.23-2.16 (1H, br m, CHPhCH*H*), 1.38 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; d6-DMSO at 373 K) 159.9 (C=O), 157.9 (C=O), 143.7 (Ar-C, seen on HMBC), 141.7 (Ar-C, seen on HMBC), 141.3 (Ar-C, seen on HMBC), 132.5 (d, *J* 7.5, Ar-CH), 129.2 (d, *J* 2.5, Ar-CH), 129.1 (Ar-CH), 128.7 (Ar-CH), 127.6 (Ar-CH), 127.0 (Ar-CH), 126.7 (Ar-CH), 116.2 (d, *J* 21.3, 82.1 Ar-C), 63.5 (CH), 28.0 (CH_3), 2 x CH_2, 2 x C=O and 1 x Ar-C not seen; δ*F* (282 MHz; $CDCl_3$) -112.3 (CF); HRMS (ESI^+) calculated for $C_{21}H_{23}N_2O_3F$ $[M+Na]^+$ 393.1585; found 393.1587.



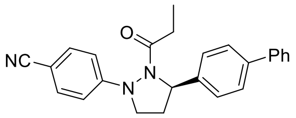
(*R*)-(4-Methoxyphenyl)(5-phenyl-2-(*p*-tolyl)pyrazolidin-1-yl)methanone (10e). Cyclic hydrazine **9e** (34 mg, 0.1 mmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2 mL) and stirred for 2 h. It was then concentrated *in vacuo* and 4-methoxybenzoyl chloride (34 µL, 0.25 mmol, 2.5 equiv) and dichloromethane (100 µL, 0.1 M) were added. The reaction mixture was cooled over an ice bath then a solution of *N*,*N*-diisopropylethylamine (36 µL, 0.21 mmol, 2.0 equiv) in dichloromethane (2.0 mL) was added dropwise over 30 minutes. The mixture was allowed to warm to rt then stirred for 18 h. The mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo*. The crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **10e** as a white solid (32 mg, 86 µmol, 84%). R_f = 0.18 (25% ethyl acetate in petroleum ether); M.p. 165-166 °C; $[\alpha]^{32}_{D}$ –3.8 (*c* 0.17, $CHCl_3$); IR (film) 2923, 1635, 1509, 1254, 1175 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.81-7.73 (2H, br m, Ar-H), 7.78 (2H, d, *J* 8.4, Ar-CH), 7.32 (2H, t, *J* 7.4, Ar-*H*), 7.26 (1H, t, *J* 7.2, Ar-H), 7.05 (2H, d, *J* 8.2, Ar-H), 6.91 (2H, d, *J* 8.1, Ar-H), 6.78 (2H, d, *J* 8.8, Ar-H), 5.72-5.64 (1H, br m, C*H*Ph), 3.92-3.79 (1H, br m, NC*H*H), 3.80 (3H, s, OCH_3), 3.60-3.39 (1H, br m, NCH*H*), 2.58 (1H, sextet, *J* 12.0, CHPhC*H*H), 2.32-2.18 (4H, br m, CHPhCH*H* and CH_3Ar); δ*C* (100 MHz; $CDCl_3$) 161.7 (Ar-C), 132.3 (Ar-CH), 130.9 (Ar-CH), 129.5 (Ar-CH), 128.4 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-C), 113.8 (Ar-CH), 113.0 (Ar-CH), 62.8 (CH, seen on HSQC), 55.2 (OCH_3), 29.7 (CH_2), 20.5 (CH_3), 3 Ar-C, 1 CH_2 and 1 C=O not seen; HRMS (ESI$^+$) calculated for $C_{24}H_{24}N_2O_2$ $[M+Na]^+$ 395.1730; found 395.1727.



(*R*)-1-(2-([1,1'-Biphenyl]-4-yl)-5-phenylpyrazolidin-1-yl)-2-methoxyethan-1-one (10f). Cyclic hydrazine **9f** (45 mg, 0.11 mmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2.0 mL) and stirred for 2 h. It was then concentrated *in vacuo* and methoxyacetyl chloride (26 µL, 0.28 mmol, 2.5 equiv) and dichloromethane (110 µL, 0.1 M) were added. The reaction mixture was cooled over an ice bath then a solution of *N*,*N*-diisopropylethylamine (39 µL, 0.22 mmol, 2.0 equiv) in dichloromethane (2.0 mL) was added dropwise over 30 minutes. The reaction mixture was allowed to warm to rt then stirred for 18 h. The reaction mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 × 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **10f** as a white solid (28 mg, 74 µmol, 66%). R_f = 0.16 (50% ethyl acetate in petroleum ether); $[\alpha]^{32}_{D}$ –17.5 (*c* 0.35, $CHCl_3$). IR (film) 2926, 1686, 1485, 1197, 1128 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.57 (2H, d, *J* 7.3, Ar-H), 7.51 (2H, d, *J* 8.4, Ar-CH), 7.46-7.38 (4H, m, Ar-H), 7.37-7.23 (4H, m, Ar-*H*), 7.06 (2H, d, *J* 8.5, Ar-H), 5.46 (1H, t, *J* 8.5, C*H*Ph), 4.48 (1H, d, J 15.5, NC*H*H), 4.06 (2H, d, *J* 15.6, CH_2OMe) 3.49-3.43 (4H, m, NCH*H* and OCH_3), 2.63-2.56 (1H, m, CHPhC*H*H), 2.35-2.25 (1H, br m, CHPhCH*H*); δ*C* (125 MHz; $CDCl_3$) 174.5 (C=O), 148.9 (Ar-C), 140.3 (Ar-C), 140.1 (Ar-C), 135.0 (Ar-C), 128.8 (Ar-CH), 128.4 (Ar-CH), 127.8 (Ar-CH), 127.5 (Ar-CH), 127.0 (Ar-CH), 126.7 (Ar-CH), 116.3 (Ar-CH), 70.5 (CH_2), 61.8 (CH), 59.4 (OCH_3), 54.4 (CH_2), 32.0 (CH_2), 1 Ar-CH not seen; HRMS (ESI$^+$) calculated for $C_{24}H_{24}N_2O_2$ $[M+Na]^+$ 395.1730; found 395.1721.

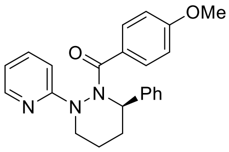


***tert*-Butyl (*R*)-2-(4-methoxybenzoyl)-5-phenylpyrazolidine-1-carboxylate (9g).** Cyclic hydrazine **8j** (36 mg, 90 µmol, 1.0 equiv), magnesium turnings (11 mg, 0.45 mmol, 5.0 equiv) and methanol (0.9 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over magnesium sulphate and concentrated *in vacuo* to give a clear oil. Then a solution of 4-methoxybenzoyl chloride (30 µL, 0.23 mmol, 2.5 equiv) in dichloromethane (0.9 mL) were added. The reaction mixture was stirred at rt for 18 h. The mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **9g** as a clear oil (27 mg, 70 µmol, 80%). R_f = 0.21 (25% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ +19.6 (*c* 0.18, dichloromethane); IR (film) 2989, 2924, 1712, 1611, 1388, 1161 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.58-7.49 (2H, m, Ar-H), 7.36-7.23 (5H, m, Ar-*H*), 6.79 (2H, d, *J* 8.4, Ar-H), 5.32 (1H, br s, C*H*Ph), 4.34-4.17 (1H, m, NC*H*H), 3.81 (3H, s, OCH_3), 3.54 (1H, d, *J* 8.6, NCH*H*), 2.55 (1H, dtd, *J* 12.5, 8.3, 4.2, CHPhC*H*H), 2.27 (1H, br s, CHPhCH*H*), 1.35 (9H, s, $C(CH_3)_3$); δ*C* (100 MHz; $CDCl_3$) 161.6 (C=O), 140.6 (Ar-C), 132.2 (Ar-C), 130.2 (Ar-CH), 128.6 (Ar-CH), 127.5 (Ar-CH), 126.5 (Ar-CH), 113.1 (Ar-CH), 82.3 (C), 62.9 (CH), 55.3 (CH_3), 36.2 (CH_2), 28.0 (CH_3), C=O, Ar-C and CH_2 not seen; HRMS (ESI$^+$) calculated for $C_{22}H_{26}N_2O_4$ $[M+Na]^+$ 405.1790; found 405.1793.

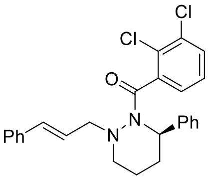


(*R*)-4-(3-([1,1'-Biphenyl]-4-yl)-2-propionylpyrazolidin-1-yl)benzonitrile (10h). Cyclic hydrazine **9h** (20 mg, 47 µmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2.0 mL) and stirred for 2 h. It was then concentrated *in vacuo* then propionyl chloride (12 µL, 0.14 mmol, 2.5 equiv) and dichloromethane (47 µL, 0.1 M) were added. The reaction mixture was cooled over an ice bath then a solution of *N*,*N*-diisopropylethylamine (16 µL, 94 µmol, 2.0 equiv) in dichloromethane (2 mL) was added dropwise over 30 minutes. The mixture was allowed to warm to rt then stirred for 18 h. The mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 × 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **10h** as a yellow oil (12 mg, 31 µmol, 66%). R_f = 0.16 (50% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ –22.2 (*c* 0.12, $CHCl_3$). IR (film) 2925, 2220, 1675, 1603, 1504, 1175 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.56 (4H, t, *J* 7.7, Ar-H), 7.53 (2H, d, *J* 8.3, Ar-H), 7.45 (2H, t, *J* 7.6, Ar-H), 7.40-7.34 (3H, m, Ar-*H*), 7.03 (2H, d, *J* 8.4, Ar-H), 5.51 (1H, t, *J* 7.3, C*H*Ph), 4.12-4.04 (1H, br m, NC*H*H), 3.60-3.52 (1H, m, NCH*H*), 2.67-2.52 (2H, m, CHPhC*H*H and CO_2C*H*H), 2.35-2.20 (2H, m, CHPhCH*H* and CO_2CH*H*), 1.12 (3H, t, *J* 7.4, CH_3); δ*C* (125 MHz; $CDCl_3$) 153.5 (C=O), 140.7 (Ar-C), 140.5

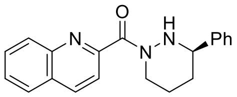
(Ar-C), 139.1 (Ar-C), 133.5 (Ar-CH), 128.8 (Ar-CH), 128.1 (Ar-CH), 127.4 (Ar-CH), 127.3 (Ar-CH), 127.1 (Ar-CH), 119.2 (Ar-C), 115.3 (Ar-CH), 114.1 (Ar-CH), 104.0 (CN), 61.2 (CH), 53.1 (CH_2), 33.7 (CH_2), 26.4 (CH_2), 8.6 (CH_3); HRMS (ESI$^+$) calculated for $C_{25}H_{23}N_3O$ $[M+Na]^+$ 404.1733; found 404.1732.



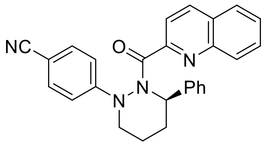
(*R*)-(4-Methoxyphenyl)(6-phenyl-2-(pyridin-2-yl)tetrahydropyridazin-1(2*H*)-yl)methanone (10i). A solution of cyclic hydrazine **9i** (53 mg, 155 μmol, 1.0 equiv) in 4M HCl/dioxane (2.5 mL) was stirred for 2 h at rt. The solution was concentrated *in vacuo* and dichloromethane (15 mL) and saturated $NaHCO_3$ solution (15 mL) were added. The layers were separated and the aqueous one was extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was dissolved anhydrous dichloromethane (2.0 mL), cooled to 0 ºC, and a solution of 4-methoxybenzoyl chloride (79 mg, 0.47 mmol, 3.0 equiv) and *N*,*N*-diisopropylethylamine (54 μL, 0.31 mmol, 2.0 equiv) in anhydrous dichloromethane (1.0 mL) was added slowly. The reaction mixture was allowed to warm to rt then stirred for 26 h. The reaction mixture was quenched with saturated Ammonium chloride solution (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20-33% EtOAc/petroleum ether) to give **10i** as a colourless gum (49 mg, 131 μmol, 85%). R_f = 0.22 (33% EtOAc in petroleum ether); $[\alpha]^{29}_D$ +72.8 (*c* 0.70, $CHCl_3$). Enantiomeric excess (91% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 96/4; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 21.2 min; t_R 32.2 min; IR (neat) 2932, 1660, 1590, 1470, 1434, 1301, 1248, 1171, 1027, 840, 756, 697 cm^{-1}; δ*H* (600 MHz; $CDCl_3$; 233 K) Three confomers in a ratio of 66:27:7 are observed at 233 K: 8.31 (0.14H, d, *J* 4.3, Ar-*H*), 8.26 (0.47H, d, *J* 4.5, Ar-*H*), 8.00 (0.39H, d, *J* 4.5, Ar-*H*), 7.83 (0.14H, t, *J* 7.6, Ar-*H*), 7.58 (1.90H, t, *J* 7.3, Ar-*H*), 7.54-7.46 (0.88H, m, Ar-*H*), 7.45-7.41 (0.78, m, Ar-*H*), 7.41-7.29 (2.66H, m, Ar-*H*), 7.19-7.15 (1.12H, m, Ar-*H*), 6.98 (0.39H, t, *J* 7.6, Ar-*H*), 6.88 (1.07H, d, *J* 8.4, Ar-*H*), 6.83 (0.47H, d, *J* 8.5, Ar-*H*), 6.77-6.70 (1.29H, m, Ar-*H*), 6.46 (0.39H, dd, *J* 6.3, 5.7, Ar-*H*), 6.19 (0.39H, d, *J* 8.6, Ar-*H*), 6.04 (0.39H, t, *J* 5.6, NC*H*), 5.22 (0.47H, t, *J* 5.5, NC*H*), 4.80-4.73 (0.39H, m, NC*H*H), 4.70 (0.14H, br d, *J* 12.7, NC*H*H), 4.53 (0.47H, br s, NC*H*H), 4.46 (0.14H, d, *J* 10.9, NC*H*), 3.83 (1.41H, s, OC*H₃*), 3.73 (1.18H, s, OC*H₃*), 3.72 (0.42H, s, OC*H₃*), 3.66 (0.47H, br s, NCH*H*), 3.32-3.25 (0.39H, m, NCH*H*), 3.04 (0.14H, t, *J* 10.7, NCH*H*), 2.63-2.56 (0.14H, m, C*H₂*), 2.36-2.23 (0.82H, m, C*H₂*), 2.24-2.11 (0.61H, m, C*H₂*), 2.11-1.76 (2.30H, m, C*H₂*), 1.69-1.63 (0.47H, m, C*H₂*); δ*C* (150 MHz; $CDCl_3$; 233 K) Three confomers are observed at 233 K: 173.8 (C=O), 173.0 (C=O), 172.9 (C=O), 162.1 (Ar-C), 161.7 (Ar-C), 160.9 (Ar-C), 158.3 (Ar-C), 157.9 (Ar-C), 148.5 (Ar-CH), 146.6 (Ar-CH), 140.8 (Ar-C), 140.2 (Ar-C), 139.8 (Ar-C), 139.0 (Ar-CH), 136.6 (Ar-CH), 130.4 (Ar-CH), 130.1 (Ar-CH), 129.4 (Ar-CH), 128.9 (Ar-CH), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 127.5 (Ar-CH), 127.4 (Ar-CH), 126.9 (Ar-CH), 126.2 (Ar-CH), 126.0 (Ar-C), 125.6 (Ar-C), 115.5 (Ar-CH), 114.2 (Ar-CH), 114.1 (Ar-CH), 113.7 (Ar-CH), 112.9 (Ar-CH), 112.8 (Ar-CH), 109.0 (Ar-CH), 108.1 (Ar-CH), 107.0 (Ar-CH), 63.2 (NCH), 60.4 (NCH), 55.6 (OCH_3), 55.4 (OCH_3), 55.3 (OCH_3), 55.0 (NCH), 46.3 (NCH_2), 45.8 (NCH_2), 44.2 (NCH_2), 30.7 (CH_2), 25.2 (CH_2), 24.8 (CH_2), 21.8 (CH_2), 19.3 (CH_2), 19.1 (CH_2); HRMS (ESI^+) calculated for $C_{23}H_{24}N_3O_2$ $[M+H]^+$ 374.1863; found 374.1858.



(*R*)-(2-Cinnamyl-6-phenyltetrahydropyridazin-1(2*H*)-yl)(2,3-dichlorophenyl)methanone (10k). Cyclic hydrazine **9k** (100 mg, 0.26 mmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2.0 mL) and stirred for 2 h. It was then concentrated *in vacuo* and 2,3-dichlorobenzoyl chloride (139 mg, 0.66 mmol, 2.5 equiv) and dichloromethane (100 µL and 2 mL) were added. The reaction mixture was cooled over an ice bath then a solution of *N*,*N*-diisopropylethylamine (93 µL, 0.53 mmol, 2.0 equiv) in dichloromethane (2 mL) was added dropwise over 30 min. The mixture was allowed to warm to rt then stirred for 18 h. The mixture was then quenched with 1.0 M hydrochloric acid (5.0 mL), extracted with dichloromethane (3 × 5.0 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo*. and the crude product was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **10k** as a clear oil (95 mg, 0.21 mmol, 80%). R_f = 0.10 (10% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ +2.1 (*c* 0.61, $CHCl_3$). IR (film) 2934, 2866, 1642, 1414, 970 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.63 (2H, d, *J* 7.4, Ar-H), 7.47 (1H, d, *J* 7.2, Ar-H), 7.44 (2H, t, *J* 7.6, Ar-H), 7.35 (1H, t, *J* 7.3, Ar-H), 7.27-7.18 (5H, m, Ar-H), 7.09 (2H, d, *J* 7.3, Ar-H), 6.09 (1H, d, *J* 3.5, C=CH), 5.76 (1H, d, *J* 15.9, C=CH), 5.43-5.33 (1H, br m, C*H*Ph), 3.14 (1H, dd, *J* 12.9, 7.6, NC*H*H), 2.90 (1H, d, *J* 11.5, NC*H*HCH=CH), 2.69 (1H, d, *J* 11.3, NCH*H*), 2.27-2.15 (2H, m, CHPhC*H*H and NCH*H*CH=CH), 1.69-1.50 (2H, m, CHPhCH*H* and CH_2C*H*HCH_2), 1.52-1.46 (1H, m, CH_2CH*H*CH_2); δC (125 MHz; $CDCl_3$) 169.9 (C=O), 140.8 (Ar-C), 136.5 (Ar-C), 133.1 (Ar-C), 131.9 (C=CH) 129.6 (Ar-CH), 128.7 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-C), 127.5 (Ar-CH), 127.4 (Ar-CH), 127.3 (Ar-CH), 127.3 (Ar-CH), 126.1 (Ar-CH), 125.5 (Ar-CH), 57.8 (CH_2), 48.4 (CH), 40.8 (CH_2), 24.4 (CH_2), 14.0 (CH_2), 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{26}H_{24}N_2O^{35}Cl_2$ $[M+Na]^+$ 473.1158; found 473.1151.

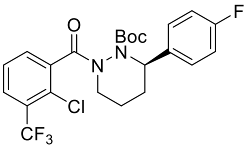


(*R*)-(3-Phenyltetrahydropyridazin-1(2*H*)-yl)(quinolin-2-yl)methanone (10l). To a solution of cyclic hydrazine **8t** (167 mg, 0.40 mmol, 1.0 equiv) in methanol (16 mL) was added activated magnesium turnings (5.0 equiv), and the mixture was stirred (800 rpm) for 2 h at rt. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in dichloromethane (12 mL), quinaldoyl chloride (192 mg, 1.0 mmol, 2.5 equiv) was added, and the mixture was stirred at rt for 18 h. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were wahed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (25-33% ethyl acetate in petroleum ether) to give a white solid. The product was dissolved in 4 M HCl/dioxane solution (4.0 mL) and stirred at rt for 2 h. The solvent was removed *in vacuo* and dichloromethane (15 mL) and saturated $NaHCO_3$ solution (15 mL) were added. The layers were separated and the aqueous one was extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (33-50% EtOAc/petroleum ether) to give **10l** as a white solid (91 mg, 0.29 mmol, 73% over three steps). M.p. 154-156 °C; R_f = 0.49 (50% EtOAc in petroleum ether); $[\alpha]^{29}_D$ +22.0 (*c* 0.52, $CHCl_3$); IR (neat) 2937, 1714, 1347, 1158, 1090, 750, 698, 665 cm^{-1}; δ*H* (600 MHz; $CDCl_3$; 233 K) Three confomers in a ratio of 66:27:7 are observed at 233 K. Only chemical shifts for the major confomer are reported: 8.32 (1H, d, *J* 8.4, Ar-*H*), 8.13 (1H, d, *J* 8.4, Ar-*H*), 7.90 (1H, d, *J* 8.1, Ar-*H*), 7.80 (1H, d, *J* 8.8, Ar-*H*), 7.78 (1H, d, *J* 8.5, Ar-*H*), 7.65 (1H, t, *J* 7.4, Ar-*H*), 7.46 (2H, d, *J* 7.4, Ar-*H*), 7.40 (2H, t, *J* 7.4, Ar-*H*), 7.35 (1H, t, *J* 7.2, Ar-*H*), 6.77 (1H, s, N*H*), 4.39 (1H, d, *J* 13.0, NC*H*H), 4.02 (1H, d, *J* 10.4, NC*H*), 3.53-3.47 (1H, m, NCH*H*), 2.04-1.94 (2H, m, CH_2CHN), 1.92-1.84 (2H, m, CH_2CH_2N); δ*C* (150 MHz; $CDCl_3$; 233 K) Chemical shifts for the major confomer at 233 K: 163.1 (C=O), 152.4 (Ar-C), 146.5 (Ar-C), 141.2 (Ar-C), 137.5 (Ar-CH), 130.4 (Ar-CH), 129.7 (Ar-CH), 128.6 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-C), 127.8 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-CH), 120.8 (Ar-CH), 62.3 (NCH), 47.0 (NCH_2), 32.8 (CH_2CHN), 25.2 (CH_2CH_2N); HRMS (ESI^+) calculated for $C_{20}H_{19}N_3NaO$ $[M+Na]^+$ 340.1420; found 340.1417.

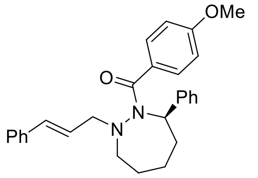


(*R*)-4-(3-Phenyl-2-(quinoline-2-carbonyl)tetrahydropyridazin-1(2*H*)-yl)benzonitrile (10m). A solution of cyclic hydrazine **9m** (92 mg, 0.25 mmol, 1.0 equiv) in HCl/1,4-dioxane (4M, 5.0 mL) was stirred for 2 h at rt. The solvent was removed *in vacuo* and dichloromethane (15 mL) and saturated

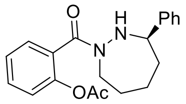
$NaHCO_3$ solution (15 mL) were added. The layers were separated and the aqueous one was extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was dissolved anhydrous dichloromethane (6.0 mL), cooled to 0 ºC, and a solution of quinaldoyl chloride (144 mg, 0.75 mmol, 3.0 equiv) and *N*,*N*-diisopropylethylamine (88 µL, 0.50 mmol, 2.0 equiv) in anhydrous dichloromethane (2.0 mL) was added slowly. The reaction mixture was allowed to warm to rt then stirred for 16 h. The mixture was quenched with saturated Ammonium chloride solution (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20-50% EtOAc/petroleum ether) to give **10m** as a pale-yellow oil (77 mg, 0.18 mmol, 73%). R_f = 0.32 (50% EtOAc in petroleum ether); $[\alpha]^{25}_{D}$ –108.2 (*c* 0.43, $CHCl_3$); IR (neat) 2930, 2865, 2233, 1666, 1598, 1508, 1371, 1178, 837, 734, 703 cm^{-1}; δ*H* (600 MHz; $CDCl_3$; 273 K) Two main confomers in a ratio of 67:33 are observed at 273 K. Chemical shifts of the major confomer: 8.02 (1H, d, *J* 8.5, Ar-*H*), 7.96 (1H, d, *J* 8.5, Ar-*H*), 7.79-7.74 (1H, m, Ar-*H*), 7.72 (1H, d, *J* 8.1, Ar-*H*), 7.69 (1H, t, *J* 7.7, Ar-*H*), 7.55-7.50 (4H, m, Ar-*H*), 7.39 (1H, t, *J* 7.5, Ar-*H*), 7.31-7.28 (3H, m, Ar-*H*), 7.05 (2H, d, *J* 8.9, Ar-*H*), 6.32 (2H, d, *J* 8.9, Ar-*H*), 5.91 (1H, t, *J* 7.9, NC*H*), 4.10 (1H, dt, *J* 9.7, 4.9, NC*H*H), 3.70 (1H, td, *J* 9.4, 6.7, NCH*H*), 2.41-2.35 (1H, m, NCHC*H*H), 2.28-2.23 (1H, m, NCH_2C*H*H), 2.16-2.10 (2H, m, NCHC*H*H, NCH_2C*H*H); δ*C* (150 MHz; $CDCl_3$; 273 K) Chemical shifts of the major confomer at 273 K: 171.6 (C=O), 152.8 (Ar-C), 150.9 (Ar-C), 146.5 (Ar-C), 139.7 (Ar-C), 136.8 (Ar-CH), 132.9 (Ar-CH), 130.1 (Ar-CH), 129.6 (Ar-CH), 128.7 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 128.1 (Ar-C), 127.8 (Ar-CH), 127.6 (Ar-CH), 127.4 (Ar-CH), 120.1 (Ar-C), 119.3 (Ar-CH), 99.8 (CN), 58.5 (NCH), 48.9 (NCH_2), 26.2 (NCHCH_2), 19.8 (NCH_2CH_2); HRMS (ESI^+) calculated for $C_{27}H_{22}N_4NaO$ $[M+Na]^+$ 441.1686; found 441.1680.



***tert*-Butyl (*R*)-2-(2-chloro-3-(trifluoromethyl)benzoyl)-6-(4-fluorophenyl)tetrahydropyridazine-1(2*H*)-carboxylate (9n).** To a solution of cyclic hydrazine **8v** (217 mg, 0.50 mmol, 1.0 equiv) in methanol (20 mL) was added activated magnesium turnings (5.0 equiv), and the mixture was stirred (800 rpm) for 2 h at rt. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in dichloromethane (15 mL), 2-chloro-3-(trifluoromethyl)benzoyl chloride (304 mg, 1.25 mmol, 2.5 equiv) was added, and the mixture was stirred for 18 h at rt. The reaction mixture was quenched with saturated Ammonium chloride solution (20 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (20-33% ethyl acetate in petroleum ether) to give **9n** as a colourless, viscous oil (174 mg, 0.36 mmol, 71%). R_f = 0.29 (33% EtOAc in petroleum ether); $[\alpha]^{29}_{D}$ –8.8 (*c* 0.31, $CHCl_3$); IR (neat) 2976, 1714, 1667, 1511, 1315, 1133, 836, 734 cm^{-1}; δ*H* (600 MHz; d6-DMSO at 373 K) Two main confomers in a ratio of 56:44 are observed at 373 K: 7.90 (0.44H, d, *J* 7.9, Ar-*H*), 7.78 (0.56H, d, *J* 7.6, Ar-*H*), 7.69-7.59 (1.50H, m, Ar-*H*), 7.53-7.44 (1.32 H, m, Ar-*H*), 7.13 (1.0H, t, *J* 8.6, Ar-*H*), 6.88-6.77 (2.52H, m, Ar-*H*), 5.40 (0.44H, br. s, 2H, NC*H*), 5.13-5.09 (0.56H, m, NC*H*), 4.26-4.20 (0,56H, m, NCH_2), 3.44-3.31 (1.24H, m, NCH_2), 3.25 (0.48H, br s, NCH_2), 2.29-2.19 (0.8H, m, CH_2), 2.16-2.01 (1.9H, m, CH_2), 1.94-1.86 (0.74H, m, CH_2), 1.79 (0.53 H, br s, CH_2), 1.52 (9H, s, $(CH_3)_3$); δ*C* (150 MHz; d6-DMSO at 373 K) Only chemical shifts for the major confomer are reported: 161.7 (C=O), 156.0 (Boc-C=O), 137.3 (Ar-C), 135.3 (Ar-C), 129.7 (Ar-CH), 128.3 (d, *J* 7.8, Ar-CH), 127.4 (d, *J* 8.3, Ar-CH), 126.1 (Ar-CH), 122.9 (Ar-C), 113.9 (d, *J* 21.4, Ar-CH), 82.5 (C), 59.3 (NCH), 41.2 (NCH_2), 27.3 (CH_3), 23.1 (CH_2CHN), 18.3 (CH_2CH_2N); CF and CF_3 are not observed; δ*F* (376 MHz; d6-DMSO) -61.2 (CF_3), -116.3 (CF); HRMS (ESI^+) calculated for $C_{23}H_{23}ClF_4N_2NaO_3$ $[M+Na]^+$ 509.1226; found 509.1229.



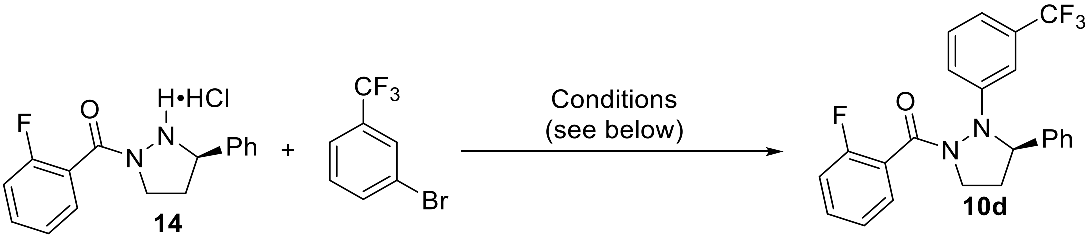
(*R*)-(2-Cinnamyl-7-phenyl-1,2-diazepan-1-yl)(4-methoxyphenyl)methanone (10o). A solution of cyclic hydrazine **9o** (140 mg, 0.36 mmol, 1.0 equiv) in HCl/dioxane (4M, 5.0 mL) was stirred for 2 h at rt. The solvent was removed *in vacuo* and dichloromethane (15 mL) and saturated $NaHCO_3$ solution (15 mL) were added. The layers were separated and the aqueous one was extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with brine, dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The crude product was dissolved anhydrous dichloromethane (4.0 mL), cooled to 0 ºC, and a solution of 4-methoxybenzoyl chloride (182 mg, 1.07 mmol, 3.0 equiv) and *N*,*N*-diisopropylethylamine (125 μL, 0.72 mmol, 2.0 equiv) in dichloromethane (2.0 mL) was added slowly. The reaction mixture was allowed to warm to rt then stirred for 18 h. The reaction mixture was quenched with saturated Ammonium chloride solution (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried over magnesium $sulphate_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5-10% EtOAc/toluene) to give **10o** as a colourless gum (50 mg, 0.12 mmol, 33%). R_f = 0.40 (10% EtOAc in toluene); $[\alpha]^{27}_{D}$ –2.0 (*c* 0.55, $CHCl_3$); Enantiomeric excess (93% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 2/98; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 55.2 min; t_R 66.8 min; IR (neat) 2918, 2848, 1635, 1605, 1327, 1252, 1171, 1032, 961, 831, 763, 699 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) Chemical shifts for the major confomer: 7.61-7.41 (1H, m, Ar-H), 7.36-7.27 (8H, m, Ar-H), 7.25-7.10 (3H, m, Ar-H), 6.86 (2H, d, *J* 8.3, Ar-H), 6.57 (1H, d, *J* 15.8, C=CH), 6.12 (1H, dt, *J* 12.2, 6.3, C=CH), 4.56 (1H, dd, *J* 8.5, 6.0, NC*H*), 4.38 (1H, dd, *J* 14.0, 7.4, C*H*HCH), 3.90-3.84 (1H, m, CH*H*CH), 3.83 (3H, s, OCH_3), 3.76-3.55 (1H, m, NC*H*H), 2.98 (1H, br d, *J* 12.1, NCH*H*), 2.23-2.10 (1H, m, C*H*HCHN), 2.03-1.82 (2H, m, CH*H*CHN, C*H*HCH_2CHN), 1.81-1.67 (2H, m, CH*H*CH_2N), 1.57-1.45 (1H, m, CH*H*CH_2CHN); δ*C* (125 MHz; $CDCl_3$) Chemical shifts for the major confomer: 172.2 (C=O), 160.5 (Ar-C), 143.3 (Ar-C), 137.4 (Ar-C), 132.0 (alk-CH), 130.2 (Ar-C), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.41 (Ar-CH), 128.37 (Ar-CH), 127.8 (128.41 (Ar-CH), 127.4 (128.41 (Ar-CH), 127.3 (alk-CH), 126.5 (Ar-CH), 113.7 (Ar-CH), 64.7 (NCH), 59.6 (*C*H_2CH), 55.4 (OCH_3), 51.2 (NCH_2), 36.4 (NCH*C*H_2), 30.8 (NCH_2*C*H_2), 25.3 (NCHCH_2*C*H_2); HRMS (ESI$^+$) calculated for $C_{28}H_{30}N_2NaO_2$ $[M+H]^+$ 449.2199; found 449.2201.



(*R*)-2-(3-Phenyl-1,2-diazepane-1-carbonyl)phenyl acetate (10p). To a solution of cyclic hydrazine **8u** (200 mg, 0.46 mmol, 1.0 equiv) in methanol (20 mL) was added activated magnesium turnings (5.0 equiv), and the mixture was stirred vigorously for 4 h at rt. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried over magnesium sulphate, filtered, and concentrated *in vacuo*. The residue was dissolved in dichloromethane (15 mL), *O*-acetylsalicyloyl chloride (231 mg, 1.16 mmol, 2.5 equiv) was added, and the mixture was stirred at rt for 20 h. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (20-50% ethyl acetate in petroleum ether) to give a colourless oil. The oil was dissolved in HCl/1,4-dioxane solution (4M, 5.0 mL) and stirred at rt for 2 h. The solvent was removed *in vacuo* and dichloromethane (15 mL) and saturated $NaHCO_3$ solution (15 mL) were added. The layers were separated and the aqueous one was extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (33-50% EtOAc/petroleum ether) to give **10p** as a colourless, viscous oil (84 mg, 0.25 mmol, 53% over three steps). R_f = 0.39 (50% EtOAc in petroleum ether); $[\alpha]^{29}_D$ +10.5 (*c* 0.41, $CHCl_3$); IR (film) 2933, 1766, 1626, 1403, 1198, 908, 732 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) Two confomers in a ratio of 85:15 are observed, only chemical shifts for the major confomer are reported: 7.49 (2H, d, *J* 7.3, Ar-*H*), 7.44 (1H, d, *J* 8.2, Ar-*H*), 7.38-7.33 (3H, m, Ar-*H*), 7.29 (2H, t, *J* 7.6, Ar-

H), 7.20 (1H, d, *J* 8.2, Ar-*H*), 5.61 (1H, br s, N*H*), 4.03 (1H, dd, *J* 10.2, 2.8, NC*H*), 3.48 (2H, dd, *J* 7.7, 5.4, NC*H₂*), 2.28 (3H, s, CH_3), 2.01-1.80 (5H m, C*H₂*CHN, C*H₂*CH_2N, C*H*HCH_2CH_2N), 1.63-1.51 (1H, m, CH*H*CH_2CH_2N); δ*C* (125 MHz; $CDCl_3$) Chemical shifts for the major confomer: 169.1 (COO), 166.9 (CON), 147.2 (Ar-C), 141.9 (Ar-C), 130.5 (Ar-CH), 129.4 (Ar-C), 128.7 (Ar-CH), 127.9 (Ar-CH), 127.6 (Ar-CH), 127.4 (Ar-CH), 126.1 (Ar-CH), 123.3 (Ar-CH), 65.9 (NCH), 50.6 (NCH_2), 37.8 (*C*H_2CHN), 27.4 (*C*H_2CH_2N), 24.2 (*C*$H_2CH_2CH_2$N), 21.1 (CH_3); HRMS (ESI$^+$) calculated for $C_{20}H_{22}N_2NaO_3$ $[M+Na]^+$ 361.1523; found 361.1518.

Buchwald-Hartwig Amination Screen 2 – 48 Well Screen



The reactions were performed in an aluminium heating block with 48 x 750 µL vials, each with a teflon coated magnetic stirrer bar. These vials were arranged in 12 columns (labelled 1-12) and 4 rows (labelled A-D). The following powders were weighed into the vials using a Mettler Toledo QX96 powder dispenser inside a glovebox.

All vials in row A: Sodium *tert*-butoxide (4.7 mg, 49 µmol, 3.0 equiv).
All vials in rows B, F: Caesium carbonate (15.9 mg, 49 µmol, 3.0 equiv).
All vials in rows C, G: Potassium carbonate (6.8 mg, 49 µmol, 3.0 equiv).
All vials in rows D, H: Potassium phosphate tribasic (10.4 mg, 49 µmol, 3.0 equiv).
All vials in column 1: [XantPhos Pd(allyl)]Cl (1.2 mg, 1.6 µmol, 0.1 equiv).
All vials in column 2: [(*R*)-BINAP Pd(allyl)]Cl (1.4 mg, 1.6 µmol, 0.1 equiv).
All vials in column 3: Pd(dppf)Cl_2 · Dichloromethane (1.3 mg, 1.6 µmol, 0.1 equiv).
All vials in column 4: [P(*t*Bu)$_3$] Pd(crotyl) Cl (0.7 mg, 2.0 µmol, 0.12 equiv).
All vials in column 5: [BippyPhos Pd(allyl)]OTf (1.3 mg, 1.6 µmol, 0.1 equiv)
All vials in column 6: AdBettPhos (1.3 mg, 2.0 µmol, 0.12 equiv) and palladium (II) acetate (0.5 mg, 2.2 µmol, 0.1 equiv).
All vials in column 7: [*t*BuBrettPhos Pd(allyl)]OTf (1.3 mg, 1.7 µmol, 0.1 equiv).
All vials in column 8: MorDalPhos (0.9 mg, 2.0 µmol, 0.12 equiv) and palladium (II) acetate (0.5 mg, 2.2 µmol, 0.1 equiv).
All vials in column 9: [BrettPhos Pd(crotyl)]OTf (1.4 mg, 1.7 µmol, 0.1 equiv).
All vials in column 10: [*t*BuXPhos Pd(allyl)]OTf (1.2 mg, 1.7 µmol, 0.1 equiv).
All vials in column 11: XPhos Pd(crotyl)Cl (1.1 mg, 1.6 µmol, 0.1 equiv).
All vials in column 12: RuPhos Pd(crotyl)Cl (1.1 mg, 1.7 µmol, 0.1 equiv).

Stock Solution: (2-Fluorophenyl)-[(3*R*)-3-phenylpyrazolidin-1-yl]methanone hydrochloride (**14**) (258 mg, 0.78 mmol) and 3-bromobenzotrifluoride (265 mg, 164 µL, 1.18 mmol) in toluene (3.60 mL).

All vials were dosed with 75 µL of Stock Solution which contained (2-fluorophenyl)-[(3*R*)-3-phenylpyrazolidin-1-yl]methanone hydrochloride (**14**) (5.4 mg, 16 µmol, 1.0 equiv) and 3-bromobenzotrifluoride (5.5 mg, 34 µL, 25 µmol, 1.5 equiv).

N.B. **14** was obtained by stirring **9d** (1 g) in HCl/dioxane solution (10 mL) for 2 h. This solution was then concentrated in vacuo to give **14** as a pale yellow solid which was used in the screen without further purification.

The plate was sealed with a silicone and PFA mat and placed on an HEL polyblock. The plate was then heated at 90 °C for 16 h. The vials were the cooled to rt and DMSO (300 µL) was added to each using a multichannel pipette. A 5 µL aliquot was extracted from each then added to a 96-well analyical plate and diluted with DMSO (50 µL). The plate was analyzed by reverse phase LCMS (XBridge C_{18} 3.5-µm 2.1 × 35 mm Column, 1.6 mL min^{-1}, 50 °C; gradient 5:95 to 99:1 (pH 9 H_2O + 10 mM NH_4HCO_2) / MeCN over 0.7 min + 0.3 min hold). The LCMS traces were processed using in-house software and the results visualized using Spotfire software to give Figure **S2:**

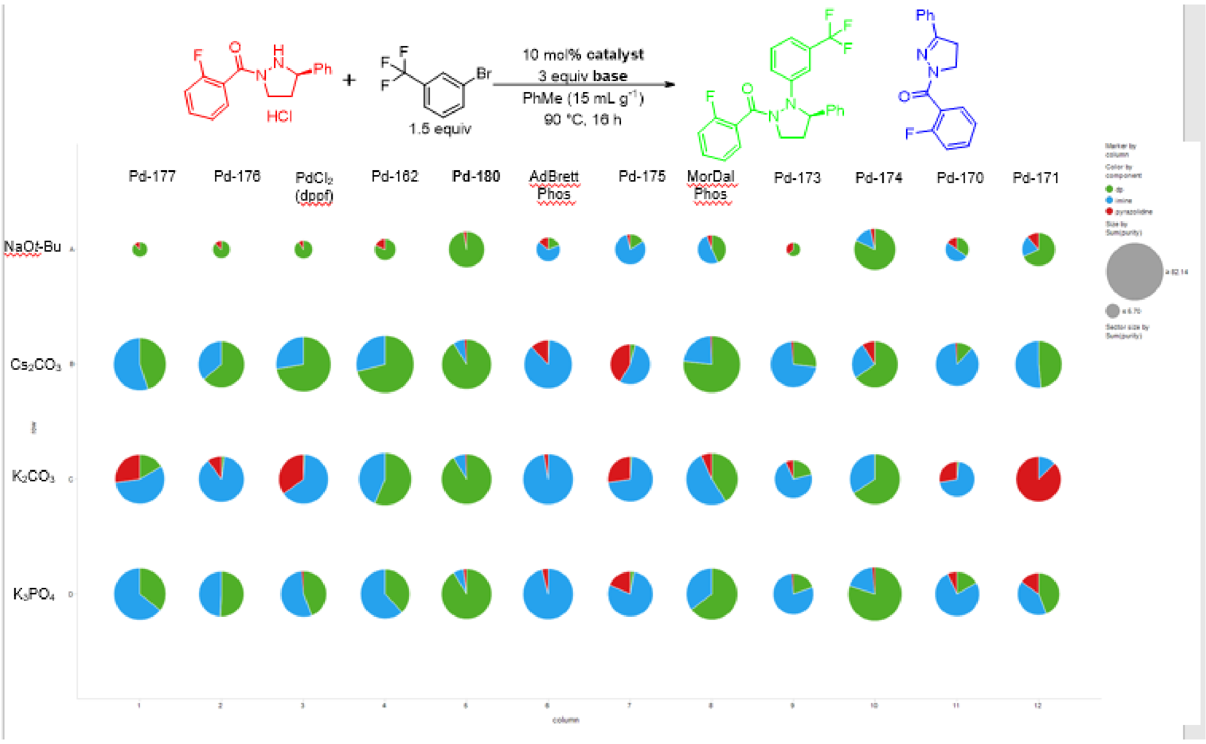
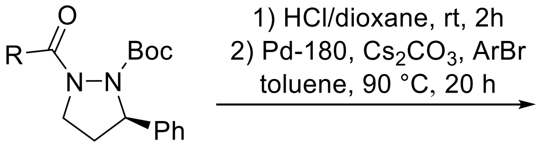
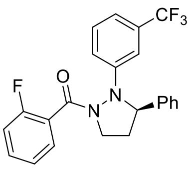


*Figure **S2** High throughput screening of the Buchwald-Hartwig coupling of **14***

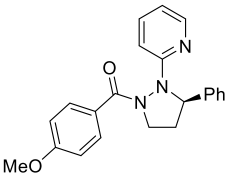
General method 6: Buchwald-Hartwig Amination with Pd-180



The cyclic hydrazine was dissolved in HCl/dioxane solution (4M, 2.0 mL) and stirred for 2 h at rt. It was then concentrated *in vacuo*. To this was added Pd-180 (0.05 equiv), caesium carbonate (3.0 equiv), aryl bromide (1.5 equiv) and toluene (1.0 M), and the solution was stirred at 90 °C for 20 h. The reaction mixture was then quenched with saturated ammonium chloride solution (5.0 mL), extracted with dichloromethane (3 x 5.0 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (15-25% ethyl acetate in petroleum ether) to give the following compounds.



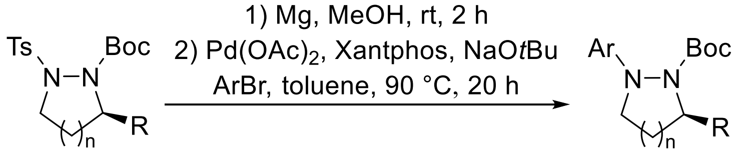
(*R*)-(2-Fluorophenyl)(3-phenyl-2-(3-(trifluoromethyl)phenyl)pyrazolidin-1-yl)methanone (10d). Following general method 6, cyclic hydrazine **9d** (26 mg, 70 µmol, 1.0 equiv), with Pd-180 (3 mg, 4 µmol, 0.05 equiv), caesium carbonate (68 mg, 0.21 mmol, 3.0 equiv), 3-bromobenzotrifluoride (15 µL, 0.11 mmol, 1.5 equiv) and toluene (70 µL) gave **10d** as a clear oil (21 mg, 54 µmol, 77%). R$_f$ = 0.15 (15% ethyl acetate in petroleum ether); $[\alpha]^{32}_{D}$ –8.5 (*c* 0.14, $CHCl_3$); Enantiomeric excess (94% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 1/99; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 33.9 min; t_R 37.8 min; IR (film) 2925, 1659, 1491, 1382, 1211 cm^{-1}; δ*H* (500 MHz; d6-DMSO at 373 K) 7.60-7.03 (13H, m, Ar-H), 5.04 (1H, t, *J* 5.5, C*H*Ph), 4.09-3.87 (1H, br m, NC*H*H), 3.65 (1H, dd, *J* 17.3, 8.9, NCH*H*), 2.68-2.58 (1H, br m, CHPhC*H*H), 2.34-2.22 (1H, br m, CHPhCH*H*); δ*C* (125 MHz, d6-DMSO at 373 K) 159.7 (C=O), 157.8 (Ar-C), 145.7 (Ar-CH), 132.2 (Ar-CH), 130.5 (q, *J* 31.3, Ar-C), 130.5 (Ar-CH), 129.0 (Ar-CH), 127.9 (Ar-CH), 126.8 (Ar-CH), 124.6 (q, *J* 271, CF_3), 124.5 (d, *J* 15, Ar-C), 116.2 (d, *J* 23, Ar-CH), 2 CH_2, 1 CH and 4 Ar-CH not seen; δ*F* (276 MHz; d6-DMSO) -61.1 (minor), -61.4 (CF_3), -114.7 (minor), -115.1 (Ar-CF); HRMS (ESI$^+$) calculated for $F_4C_{23}H_{18}N_2O$ [M+Na]$^+$ 437.1247; found 437.1248.



(*R*)-(4-Methoxyphenyl)(3-phenyl-2-(pyridin-2-yl)pyrazolidin-1-yl)methanone (10g). Following general method 6, cyclic hydrazine **9g** (25 mg, 65 µmol, 1.0 equiv), with Pd-180 (3 mg, 3 µmol, 0.05 equiv), caesium carbonate (64 mg, 0.20 mmol, 3.0 equiv), 2-bromopyridine (9 µL, 0.10 mmol, 1.5 equiv) and toluene (65 µL) gave **10g** as a clear oil (19 mg, 52 µmol, 80%). R$_f$ = 0.13 (33% ethyl acetate in petroleum ether); $[\alpha]^{32}_{D}$ +9.2 (*c* 0.23, dichloromethane).

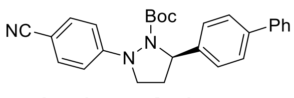
IR (film) 2932, 1651, 1597, 1461, 1432, 1258, 1173 cm^{-1}; δ*H* (400 MHz; CDCl$_3$) 8.32 (1H, s, Ar-CH), 7.60 (1H, t, *J* 7.3, Ar-H), 7.53-6.87 (9H, m, Ar-H), 6.69 (1H, s, Ar-H), 5.88 (1H, t, *J* 7.5, C*H*Ph), 4.70-3.39 (1H, br m, NC*H*H), 3.76 (3H, s, CH$_3$), 3.52-3.49 (1H, br m, NCH*H*), 2.53-2.31 (2H, br m, CHPhCH$_2$); δ*C* (100 MHz; CDCl$_3$) 161.5 (C=O), 148.4 (Ar-C), 138.2 (Ar-C), 130.3 (Ar-CH), 128.4 (Ar-CH), 127.2 (Ar-CH), 126.7 (Ar-CH), 117.5 (Ar-CH), 113.0 (Ar-CH), 109.1 (Ar-CH), 66.1 (CH), 55.2 (CH$_3$), 44.7 (CH$_2$), 2 Ar-C, 2 Ar-CH and 1 CH$_2$ not seen; HRMS (ESI$^+$) calculated for $C_{22}H_{21}N_3O_2$ [M+H]$^+$ 360.1712; found 360.1712.

General method 7: Buchwald-Hartwig Amination with Pd(OAc)$_2$ and Xantphos



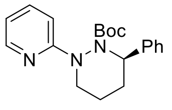
N.B. Magnesium turnings were activated by washing them with 1.0 M hydrochloric acid solution (2 × 20 mL), water (20 mL) and methanol (20 mL).

To a solution of cyclic hydrazine in methanol (0.1 M) was added activated magnesium turnings (5.0 equiv), and the mixture was stirred vigorously (800 rpm) for 2 h at rt. The reaction mixture was quenched with saturated ammonium chloride solution (10 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (30 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in toluene (1.0 M), and palladium acetate (5-10 mol%), Xantphos (10-20 mol%), sodium *tert*-butoxide (2.0 equiv) and aryl bromide (1.5 equiv) were added and the solution was stirred at 90 °C for 20 h. The reaction mixture was then quenched with saturated ammonium chloride solution (5 mL), extracted with dichloromethane (3 × 5 mL), dried over magnesium sulphate and then concentrated *in vacuo*. The crude product was purified by column chromatography (15-25% ethyl acetate in petroleum ether) to give the following compounds.

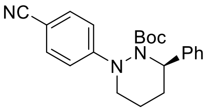


***tert*-Butyl (*R*)-5-([1,1'-biphenyl]-4-yl)-2-(4-cyanophenyl)pyrazolidine-1-carboxylate (9h).** Following general method 7, **8k** (40 mg, 0.12 mmol, 1.0 equiv), magnesium turnings (15 mg, 0.60 mmol, 5.0 equiv) and methanol (1.2 mL, 0.1 M), then palladium acetate (3 mg, 12 µmol, 0.1 equiv), Xantphos (14 mg, 25 µmol, 0.2 equiv), sodium *tert*-butoxide (24 mg, 0.25 mmol, 2.0 equiv) and 4-bromobenzonitrile (45 mg, 0.25 mmol, 2.0 equiv) in toluene (0.12 mL, 1.0 M) yielded **9h** as a clear oil (45 mg, 0.11 mmol, 86%). R$_f$ = 0.23 (25% ethyl acetate in petroleum ether); $[\alpha]^{32}_{D}$ –10.7 (*c* 0.42, CHCl$_3$); IR (film) 2977, 2928, 2218, 1705, 1603, 1509, 1338, 1142 cm^{-1};

δH (500 MHz; $CDCl_3$) 7.48 (4H, dd, *J* 8.0, 4.8, Ar-H), 7.44 (2H, d, *J* 8.2, Ar-H), 7.35 (2H, t, *J* 7.6, Ar-H), 7.27 (1H, t, *J* 7.4, Ar-H), 7.21 (2H, d, *J* 8.2, Ar-H), 6.86 (2H, d, *J* 8.8, Ar-H), 5.26 (1H, t, *J* 6.9, CHPh), 3.77-3.70 (1H, m, NC*H*H), 3.66 (1H, dt, *J* 10.5, 7.4, NCH*H*), 2.53 (1H, td, *J* 12.5, 7.1, CHPhC*H*H), 2.23-2.12 (1H, m, CHPhCH*H*), 1.36 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 152.8 (C=O), 140.5 (Ar-C), 139.8 (Ar-C), 133.2 (Ar-C), 128.8 (Ar-CH), 127.4 (Ar-CH), 127.3 (Ar-CH), 127.0 (Ar-CH), 127.0 (Ar-CH), 126.6 (Ar-C), 126.6 (Ar-CH), 119.9 (Ar-C) 114.2 (Ar-CH), 102.1 (CN), 82.3 (C), 62.8 (CH), 50.6 (CH_2), 35.1 (CH_2), 28.2 (CH_3); HRMS (ESI$^+$) calculated for $C_{27}H_{27}N_3O_2$ $[M+Na]^+$ 448.1995; found 448.1999.

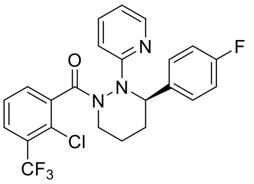


***tert*-Butyl (*R*)-6-phenyl-2-(pyridin-2-yl)tetrahydropyridazine-1(2*H*)-carboxylatemethanone (9i).** Following general method 7, **8t** (208 mg, 0.50 mmol, 1.0 equiv), methanol (20 mL, 0.1 M), activated magnesium turnings (61 mg, 2.50 mmol, 5.0 equiv), then toluene (1.0 mL, 0.5 M), palladium acetate (5.6 mg, 25 μmol, 5 mol%), Xantphos (29 mg, 50 μmol, 10 mol%), sodium *tert*-butoxide (96 mg, 1.0 mmol, 2.0 equiv), and 2-bromopyridine (95 μL, 1.0 mmol, 2.0 equiv) yielded **9i** as an off-white solid (113 mg, 0,33 mmol, 67%). M.p. 72-74 °C; R_f = 0.23 (20% EtOAc in petroleum ether); $[\alpha]^{29}_D$ +68.8 (*c* 0.53, $CHCl_3$). Enantiomeric excess (91% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 0.8/99.2; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 6.7 min; t_R 7.3 min; IR (neat) 2967, 2876, 1591, 1476, 1439, 1299, 1153, 1075, 1044, 877, 766, 701 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.11 (1H, d, *J* 4.4, Ar-*H*), 7.40 (2H, d, *J* 7.4, Ar-*H*), 7.34 (1H, ddd, *J* 8.5, 7.0, 1.3, Ar-*H*), 7.28 (2H, d, *J* 7.2, Ar-*H*), 7.22 (1H, t, *J* 7.2, Ar-*H*), 6.57 (2H, dd, *J* 6.9, 5.3, Ar-*H*), 5.40 (1H, br s, NC*H*), 4.42 (1H, br s, NC*H*H), 3.33 (1H, br s, NCH*H*), 2.10-2.00 (3H, m, C*H₂*CHN, C*H*HCH₂N), 1.67-1.60 (1H, m, CH*H*CH₂N), 1.31 (9H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 159.5 (Ar-C), 147.0 (Ar-CH), 141.3 (Ar-C), 136.9 (Ar-CH), 128.5 (Ar-CH), 127.4 (Ar-CH), 127.3 (Ar-CH), 113.5 (Ar-CH), 107.8 (Ar-CH), 81.6 (C), 59.1 (NCH), 43.5 (NCH_2), 28.2 (Boc-CH_3), 27.3 (*C*H_2CHN), 20.0 (*C*H_2CH_2N), Boc C=O not observed; HRMS (ESI$^+$) calculated for $C_{20}H_{26}N_3O_2$ $[M+H]^+$ 340.2020; found 340.2023.

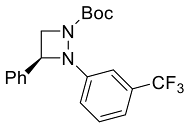


***tert*-Butyl (*R*)-2-(4-cyanophenyl)-6-phenyltetrahydropyridazine-1(2*H*)-carboxylate (9m).** Following general method 7, **8t** (208 mg, 0.50 mmol, 1.0 equiv), methanol (20 mL, 0.1 M), activated magnesium turnings (61 mg, 2.50 mmol, 5.0 equiv), then toluene (1.0 mL, 0.5 M), palladium acetate (5.6 mg, 25 μmol, 5 mol%), Xantphos (29 mg, 50 μmol, 10 mol%), sodium *tert*-butoxide (96 mg, 1.0 mmol, 2.0 equiv), and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.0 equiv) gave **9m** as a colourless oil that crystallised upon standing to an off-white solid (104 mg, 0.29 mmol, 57%). M.p. 124-125 °C; R_f = 0.19 (20% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +123.5 (*c* 0.08, $CHCl_3$); IR (neat)

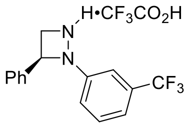
2977, 2860, 2227, 1704, 1606, 1297, 1168, 835, 714 cm^{-1}; δ*H* (400 MHz; CDCl$_3$) 7.40 (2H, d, *J* 8.9, Ar-*H*), 7.38-7.34 (2H, m, Ar-*H*), 7.33-7.27 (3H, m, Ar-*H*), 6.64 (2H, d, *J* 8.8, Ar-*H*), 5.35 (1H, br s, NC*H*), 3.67 (1H, dd, *J* 16.6, 9.1, NC*H*H), 3.49 (1H, br s, NCH*H*), 2.17-2.05 (2H, m, C*H*HCHN, C*H*HCH$_2$N), 1.93 (1H, dd, *J* 21.6, 10.8, CH*H*CHN), 1.70-1.63 (1H, m, CH*H*CH$_2$N), 1.26 (9H, br s, (CH$_3$)$_3$); δ*C* (125 MHz; CDCl$_3$) 155.6 (Boc C=O),152.3 (Ar-C), 141.2 (Ar-C), 133.3 (Ar-CH), 128.7 (Ar-CH), 127.8 (Ar-CH), 127.21 (Ar-CH), 120.4 (Ar-C), 111.5 (Ar-CH), 100.1 (CN), 82.1 (C), 60.1 (NCH), 45.8 (NCH$_2$), 28.2 (Boc-CH$_3$), 27.0 (*C*H$_2$CHN), 20.1 (*C*H$_2$CH$_2$N); HRMS (ESI$^+$) calculated for C$_{22}$H$_{25}$N$_3$NaO$_2$ [M+Na]$^+$ 386.1839; found 386.1837.



(*R*)-(2-Chloro-3-(trifluoromethyl)phenyl)(3-(4-fluorophenyl)-2-(pyridin-2-yl)tetrahydropyridazin-1(2*H*)-yl)methanone (10n). A solution of cyclic hydrazine **9n** (80 mg, 165 μmol, 1.0 equiv) in 4 M HCl/dioxane (2.5 mL) was stirred for 2 h at rt. The solvent was removed *in vacuo* and dichloromethane (15 mL) and saturated NaHCO$_3$ solution (15 mL) were added. The layers were separated and the aqueous one was extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The crude product was dissolved anhydrous toluene (1.0 mL), Pd(OAc)$_2$ (3.7 mg, 16.5 μmol, 10 mol%), Xantphos (19 mg, 33 μmol, 20 mol%), sodium *tert*-butoxide (32 mg, 0.33 mmol, 2.0 equiv), and 2-bromopyridine (31 μL, 0.33 mmol, 2.0 equiv) were added and the reaction mixture was stirred at 90 °C for 18 h. The mixture was cooled to rt, then quenched with saturated Ammonium chloride solution (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (33-50% ethyl acetate in petroleum ether) to give **10n** as a pale-yellow oil (38 mg, 82 μmol, 50%). R$_f$ = 0.42 (50% EtOAc in petroleum ether); $[\alpha]^{29}_{D}$ –57.9 (*c* 0.12, CHCl$_3$); IR (neat) 2916, 1659, 1588, 1510, 1467, 1432, 1316, 1222, 1132, 1090, 808, 765, 730, 673 cm^{-1}; δ*H* (600 MHz; CDCl$_3$) Only chemical shifts for the major confomer are reported: 8.33 (1H, d, *J* 4.5, Ar-*H*), 7.72-7.69 (2H, m, Ar-*H*), 7.55 (1H, d, *J* 7.8, Ar-*H*), 7.12 (1H, br s, Ar-*H*), 6.96-6.90 (2H, m, Ar-*H*), 6.82-6.78 (2H, m, Ar-*H*), 6.69 (2H, t, *J* 8.4, Ar-*H*), 5.62 (1H, s, NC*H*), 4.60 (1H, dt, *J* 13.0, 7.8, NC*H*H), 3.59-3.50 (1H, m, NCH*H*), 2.27-2.22 (1H, m, C*H*H), 2.20-2.14 (1H, m, C*H*H), 2.13-2.07 (1H, m, CH*H*), 1.63-1.56 (1H, m, CH*H*); δ*C* (125 MHz; CDCl$_3$) 169.5 (C=O), 162.1 (d, *J* 246.0, CF), 160.3 (Ar-C), 148.9 (Ar-CH), 138.5 (d, *J* 9.0, Ar-CH), 138.0 (Ar-C), 136.1 (Ar-C), 128.1 (d, *J* 8.0, Ar-CH), 125.7 (Ar-CH), 123.9 (Ar-CH), 122.5 (q, *J* 273.5, CF$_3$), 121.3 (Ar-CH), 117.0 (Ar-CH), 115.0 (d, *J* 21.5, Ar-CH), 108.1 (Ar-CH), 60.6 (NCH), 40.4 (NCH$_2$), 23.7 (CH$_2$NCH), 19.5 (CH$_2$NCH$_2$), 2 Ar-C not seen; δ*F* (282 MHz; CDCl$_3$) –61.5 (CF$_3$), –116.1 (CF); HRMS (ESI$^+$) calculated for C$_{23}$H$_{18}$ClF$_4$N$_3$NaO [M+Na]$^+$ 486.0967; found 486.0963.



***tert*-Butyl (*S*)-3-phenyl-2-(3-(trifluoromethyl)phenyl)-1,2-diazetidine-1-carboxylate (9q).** Following general method 7, cyclic hydrazine **8b** (100 mg, 0.26 mmol, 1.0 equiv), magnesium turnings (31 mg, 1.29 mmol, 5.0 equiv) and methanol (5.0 mL) then palladium acetate (6.0 mg, 26 µmol, 0.1 equiv), Xantphos (30 mg, 51 µmol, 0.2 equiv), sodium *tert*-butoxide (49 mg, 0.51 mmol, 2.0 equiv), 3-trifluoromethyl-bromobenzene (71 µL, 0.51 mmol, 2.0 equiv) and toluene (5.0 mL) yielded **9q** as an orange oil (35 mg, 90 µmol, 35%). R_f = 0.78 (25% EtOAc/petroleum ether); $[\alpha]^{24}_{D}$ +4.6 (*c* 0.23, $CHCl_3$); IR (film) 2978, 1715, 1327, 1120, 1028 cm^{-1}; δ*H* (500 MHz; $CDCl_3$); 7.56 (2H, d, *J* 7.3, Ar-H), 7.48 (2H, t, *J* 7.5, Ar-H), 7.42 (1H, d, *J* 7.2, Ar-H), 7.33 (1H, t, *J* 7.9, Ar-H), 7.22 (1H, d, *J* 7.7, Ar-H), 7.15 (1H, s, Ar-H), 6.94 (1H, d, *J* 8.6, Ar-H), 4.94 (1H, t, *J* 8.4, CHPh), 4.58 (1H, t, *J* 8.5, NC*H*H) 4.10 (1H, t, *J* 7.6, NCH*H*), 1.56 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 161.1 (C=O), 153.6 (Ar-C), 139.1 (Ar-C), 130.9 (q, *J* 31.3, Ar-C), 129.1 (Ar-CH), 129.0 (Ar-CH), 128.7 (Ar-CH), 126.7 (Ar-CH), 124.1 (q, *J* 271.3, CF_3), 118.4 (q, *J* 3.8, Ar-CH), 117.4 (Ar-CH), 111.3 (q, *J* 5.0, Ar-CH), 82.5 (C), 67.7 (CH), 56.8 (CH_2), 28.2 (CH_3); δ*F* (376 MHz; $CDCl_3$) -62.8 (CF_3); HRMS (ESI^+) calculated for $C_{20}H_{21}N_2O_2F_3$ $[M+Na]^+$ 401.1447; found 401.1450.



(*S*)-4-Phenyl-1-(3-trifluoromethyl)phenyl-1,2-diazetidine trifluoroacetic acid (10q). Cyclic hydrazine **9q** (14 mg, 38 µmol, 1.0 equiv), trifluoroacetic acid (30 µL, 0.38 mmol, 10.0 equiv) and dichloromethane (1.0 mL) were stirred at rt for 2 h then concentrated *in vacuo* to yield **10q** as an orange oil (13 mg, 33 µmol, 88%). $[\alpha]^{24}_{D}$ –4.8 (*c* 0.36, $CHCl_3$); IR (film) 2920, 2852 1759, 1460, 1232, 1032 cm^{-1}; δ*H* (500 MHz; $CDCl_3$); 7.46-7.37 (6H, m, Ar-H), 7.20 (1H, d, *J* 7.6, Ar-H), 7.05 (1H, s, Ar-H), 6.99 (1H, d, *J* 8.1, Ar-H), 5.69 (1H, t, *J* 8.0, CHPh), 4.20 (1H, t, *J* 8.3, NC*H*H), 3.73 (1H, t, *J* 8.3, NCH*H*), δ*C* (125 MHz; $CDCl_3$) 146.4 (Ar-C), 137.1 (Ar-C), 130.0 (Ar-CH), 129.4 (Ar-CH), 129.1 (Ar-CH), 125.7 (Ar-CH), 118.2 (q, *J* 3.8, Ar-CH), 116.4 (Ar-CH), 109.7 (q, *J* 2.5, Ar-CH), 74.5 (CH), 53.9 (CH_2), 28.2 (CH_3), 1 C=O, 2 CF_3 and 1 Ar-C not seen; δ*F* (376 MHz; $CDCl_3$) –62.9 (CF_3), –70.8 and –70.9 (1:1 rotamer, CF_3CO_2H); HRMS (ESI^+) calculated for $C_{15}H_{13}N_2F_3$ $[M+Na]^+$ 301.0929; found 301.0930.

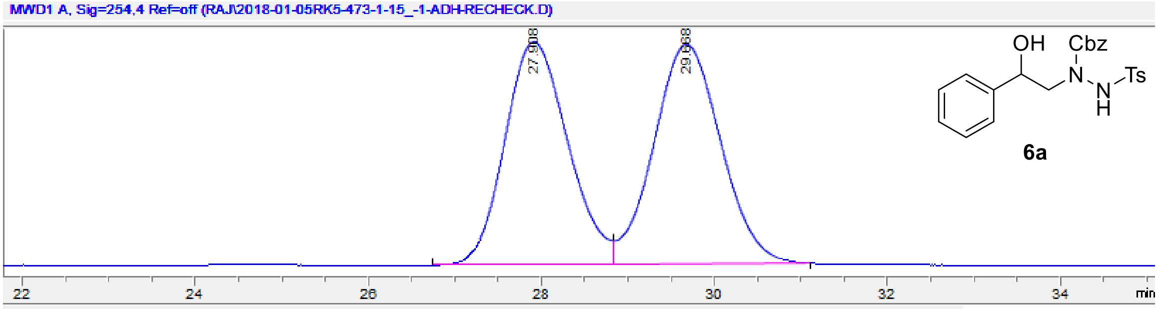
HPLC Profiles of 6a-v, 8a-v, 10b, 10d, 10i and 10o

HPLC analysis was conducted on an Agilent Technologies 1200 Series HPLC, using a ratio of HPLC grade hexane and propan-2-ol as the eluent, and detection by UV at 254 nm. *Racemic* traces were produced by $NaBH_4$-mediated reduction of the corresponding ketone or mixing of equal quantities of the *R* and *S* enantiomers.

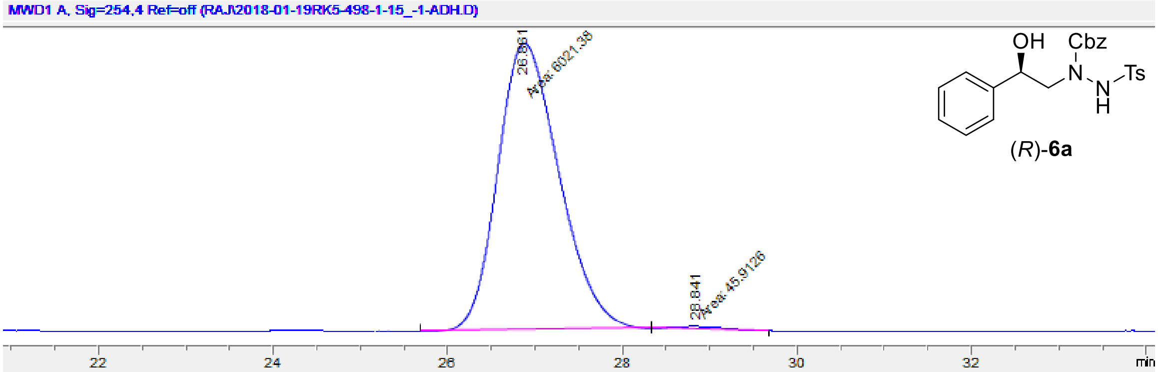
The HPLC profiles of **6h**, **6i**, **6k**, **6r**, and **6s** were not determined, the data for the corresponding hydrazines (**8h**, **8i**, **8k**, **8r**, and **8s**) were used to determine the expected enantiomeric excesses of these compounds.

HPLC profile of **6a**

Chiralpak AD-H column (0.46 cm ø x 25 cm), 85:15 hexane:propan-2-ol, T = 25°C, flow rate = 1.0 mL/min.



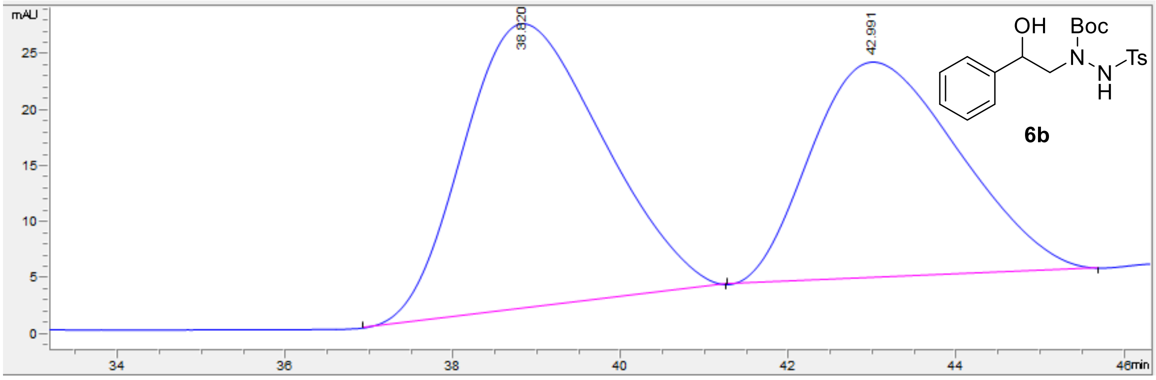
#	Time	Area	Height	Width	Area%	Symmetry
1	27.908	2116.4	41.8	0.6019	48.693	0.835
2	29.668	2230	41.2	0.6369	51.307	0.904



#	Time	Area	Height	Width	Area%	Symmetry
1	26.861	6021.4	123.4	0.8134	99.243	0.745
2	28.841	45.9	1.2	0.6466	0.757	0.741

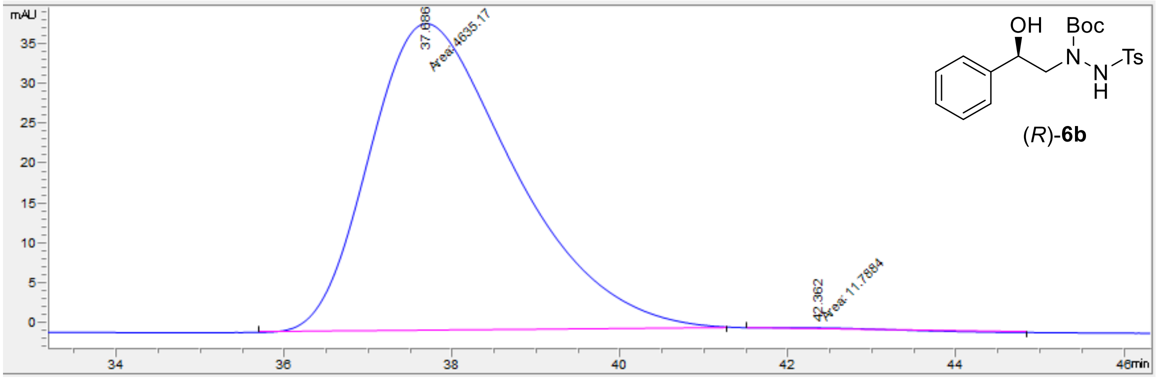
HPLC Trace of **6b**

Chiralpak IA column (0.46 cm ø x 25 cm) 98.5:1.5 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



6b

#	Time	Area	Height	Width	Area%	Symmetry
1	38.82	2943.5	25.5	1.5475	55.505	0.71
2	42.991	2359.6	19.3	1.4556	44.495	0.708

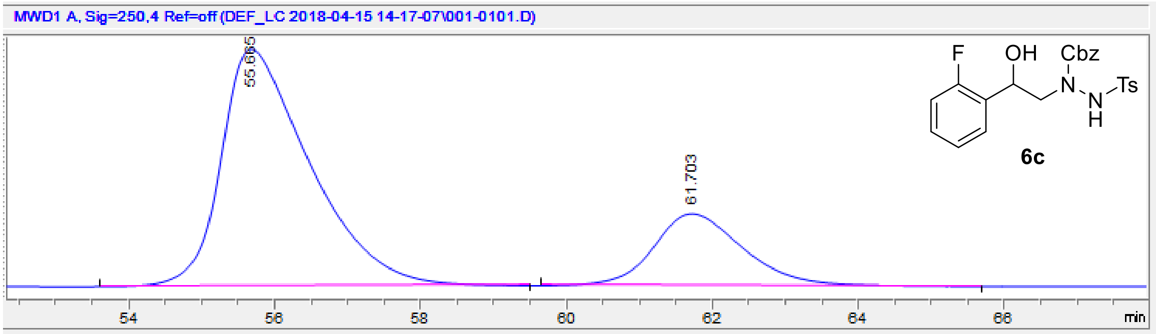


(*R*)-**6b**

#	Time	Area	Height	Width	Area%	Symmetry
1	37.686	4635.2	38.7	1.9974	99.746	0.632
2	42.362	11.8	1.5E-1	1.3107	0.254	0.45

HPLC profile of **6c**

Chiralpak IA column (0.46 cm ø x 25 cm) 95:5 hexane:propan-2-ol, T = 25 °C, flow rate 1.0 mL/min.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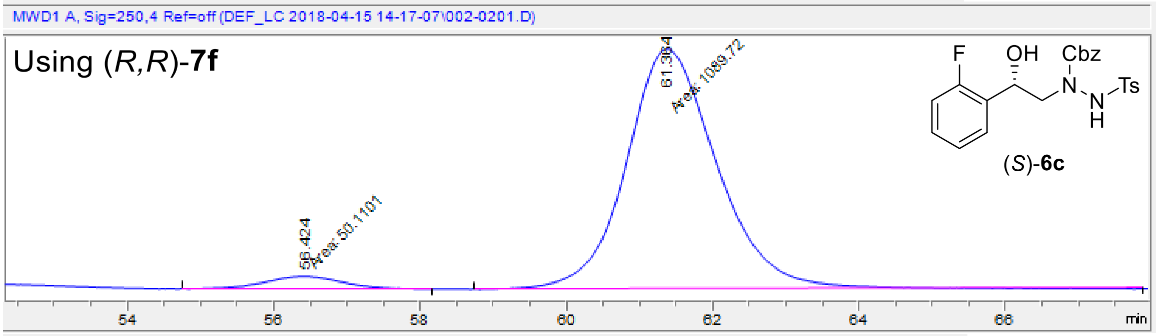
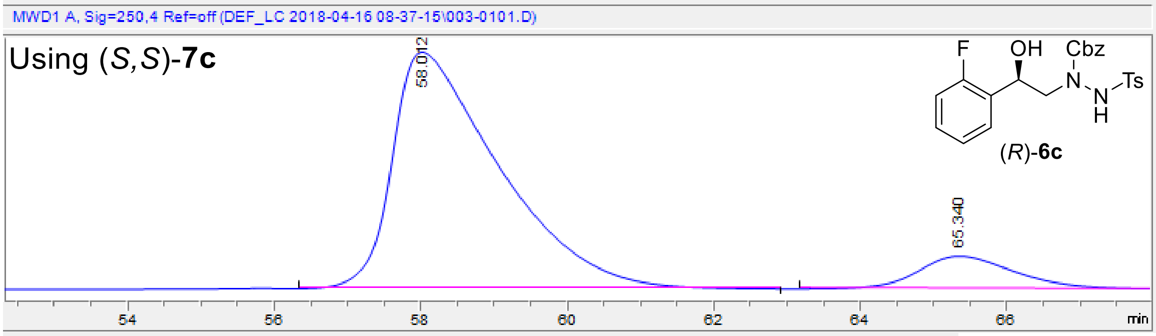
#	Time	Area	Height	Width	Area%	Symmetry
1	55.665	7250.3	85.4	1.2364	76.463	0.496
2	61.703	2231.9	26	1.2444	23.537	0.723


MWD1 A, Sig=250,4 Ref=off (DEF_LC 2018-04-15 14-17-07\002-0201.D)

Using (*R*,*R*)-**7f**

#	Time	Area	Height	Width	Area%	Symmetry
1	56.424	50.1	6.6E-1	1.2728	4.396	1.055
2	61.364	1089.7	12.5	1.4486	95.604	0.806

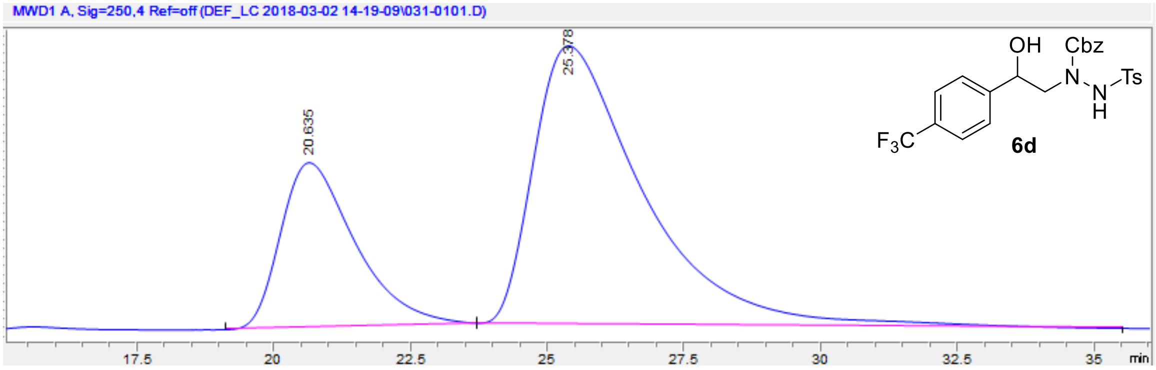

MWD1 A, Sig=250,4 Ref=off (DEF_LC 2018-04-16 08-37-15\003-0101.D)

Using (*S*,*S*)-**7c**

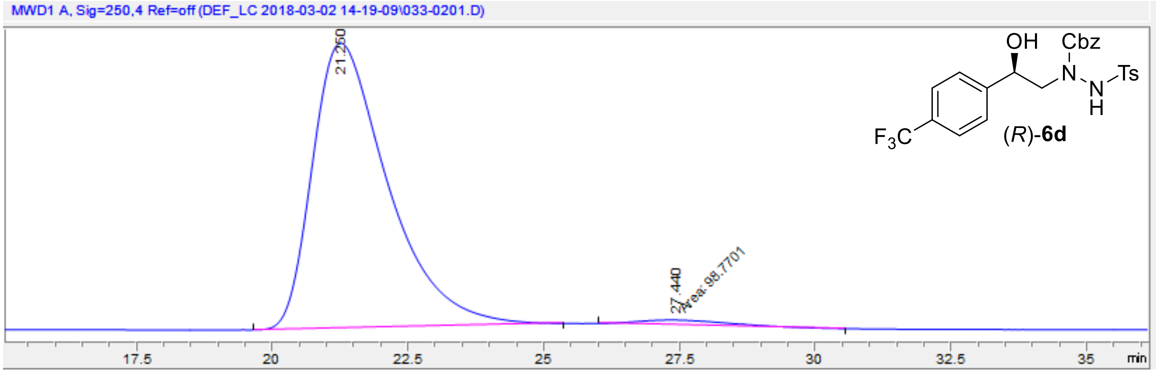
#	Time	Area	Height	Width	Area%	Symmetry
1	58.012	15828	155.7	1.4539	88.651	0.372
2	65.34	2026.2	21.7	1.3387	11.349	0.716

HPLC profile of **6d**

Chiralpak OD-H column (0.46 cm ø x 25 cm) 92:8 hexane:propan-2-ol, T = 25 °C, flow rate 1.0 mL/min.



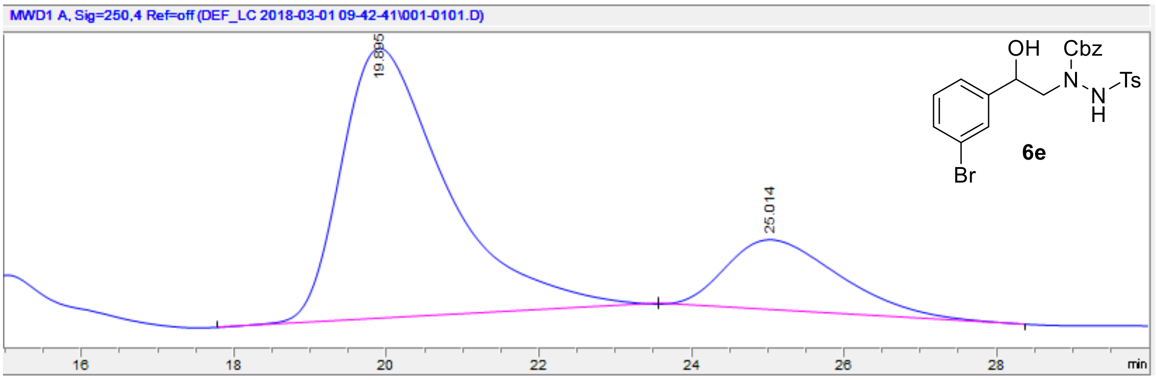
#	Time	Area	Height	Width	Area%	Symmetry
1	20.635	3538.6	37.4	1.3676	28.519	0.594
2	25.378	8869.5	63.1	1.9315	71.481	0.434



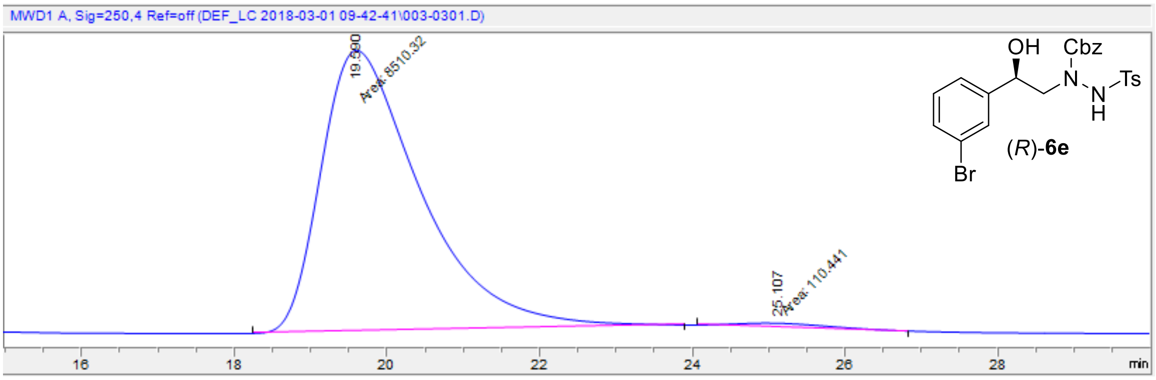
#	Time	Area	Height	Width	Area%	Symmetry
1	21.25	4579.6	47.3	1.406	97.889	0.559
2	27.44	98.8	8.4E-1	1.9503	2.111	0.592

HPLC profile of **6e**

Chiralpak OD-H column (0.46 cm ø x 25 cm) 91:9 hexane:propan-2-ol, T = 25 °C, flow rate 1.0 mL/min.



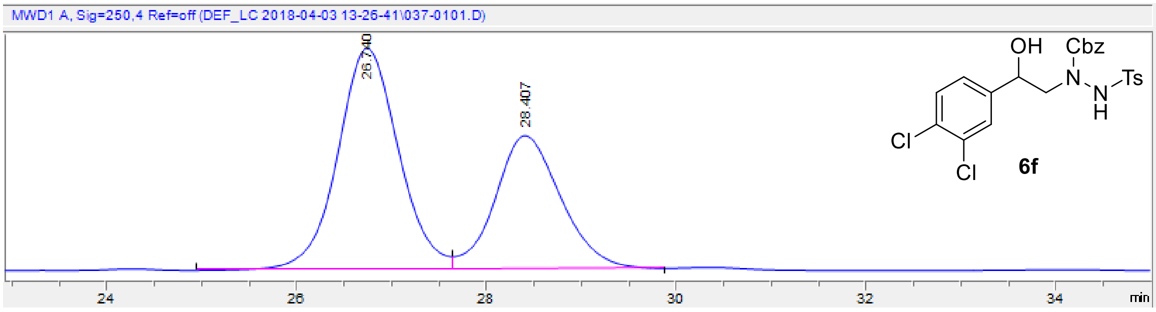
#	Time	Area	Height	Width	Area%	Symmetry
1	19.895	5848	60.5	1.4069	77.980	0.535
2	25.014	1651.3	15.8	1.27	22.020	0.628



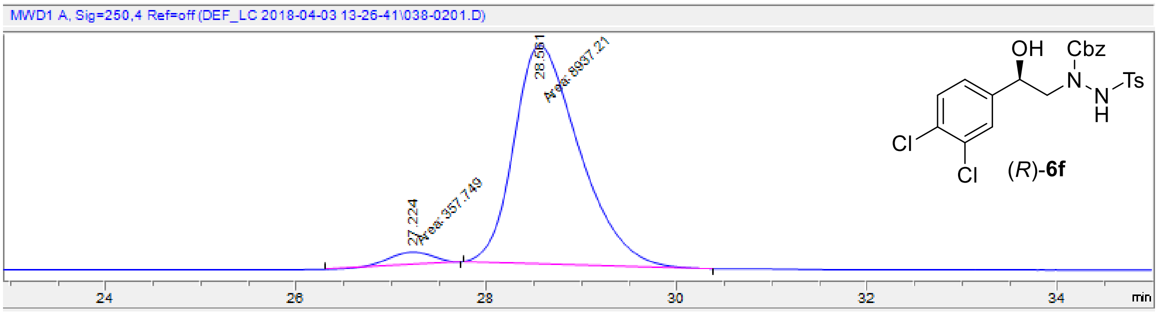
#	Time	Area	Height	Width	Area%	Symmetry
1	19.59	8510.3	93.2	1.522	98.719	0.534
2	25.107	110.4	1.3	1.3682	1.281	0.458

HPLC profile of **6f**

Chiralpak IA column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



#	Time	Area	Height	Width	Area%	Symmetry
1	26.74	3715.8	83.2	0.6833	60.641	0.92
2	28.407	2411.8	50.1	0.7339	39.359	0.812

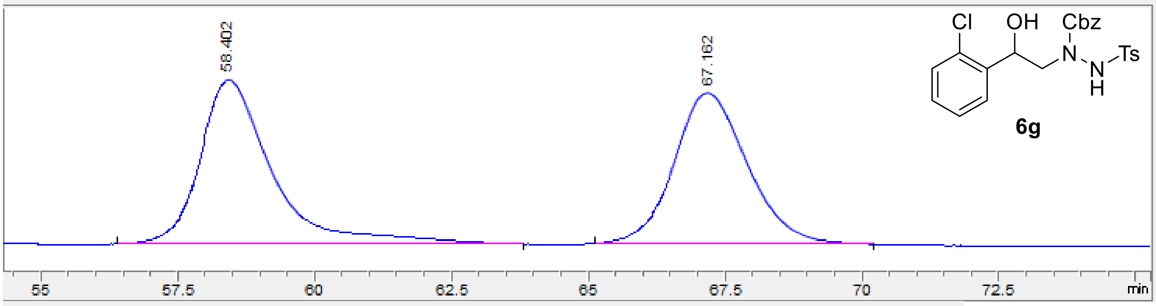


#	Time	Area	Height	Width	Area%	Symmetry
1	27.224	357.7	10.7	0.555	3.849	1.281
2	28.561	8937.2	186.6	0.7984	96.151	0.636

HPLC profile of **6g**

Chiralpak IA column (0.46 cm ø x 25 cm) 95:5 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.

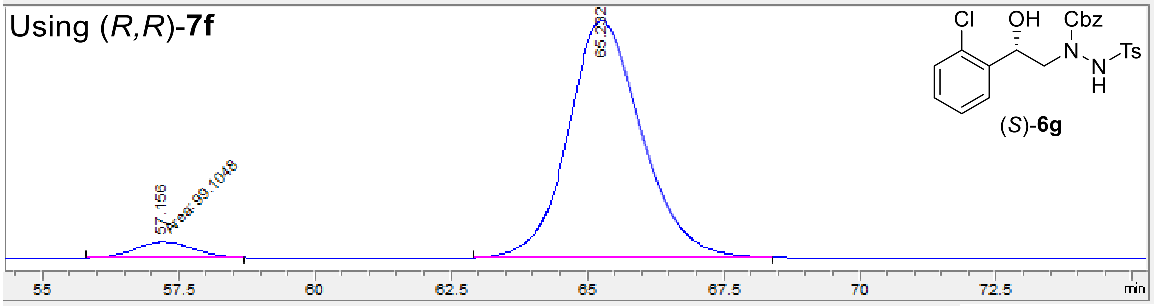
MWD1 A, Sig=250,4 Ref=off (DEF_LC 2018-04-16 12-14-29\004-0101.D)



#	Time	Area	Height	Width	Area%	Symmetry
1	58.402	1011.5	11	1.1557	51.695	0.604
2	67.162	945.1	10.1	1.1159	48.305	0.821

MWD1 A, Sig=250,4 Ref=off (DEF_LC 2018-04-16 12-14-29\005-0201.D)

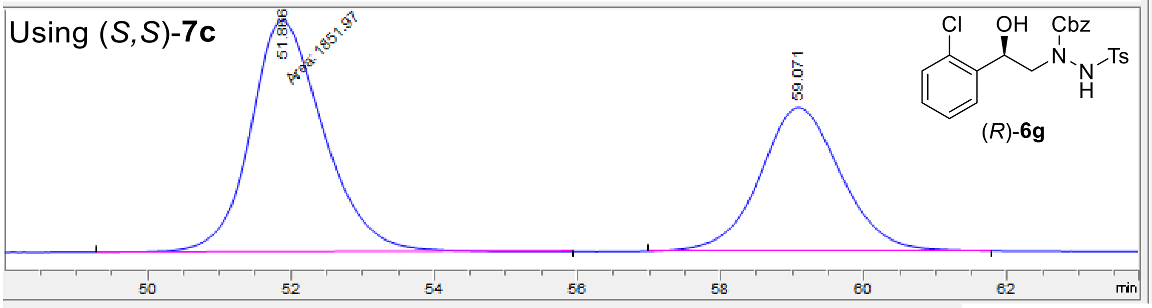
Using (*R*,*R*)-**7f**



#	Time	Area	Height	Width	Area%	Symmetry
1	57.156	99.1	1.3	1.2536	5.085	0.836
2	65.232	1850	19.7	1.2242	94.915	0.819

MWD1 A, Sig=250,4 Ref=off (DEF_LC 2018-04-19 14-20-41\009-0101.D)

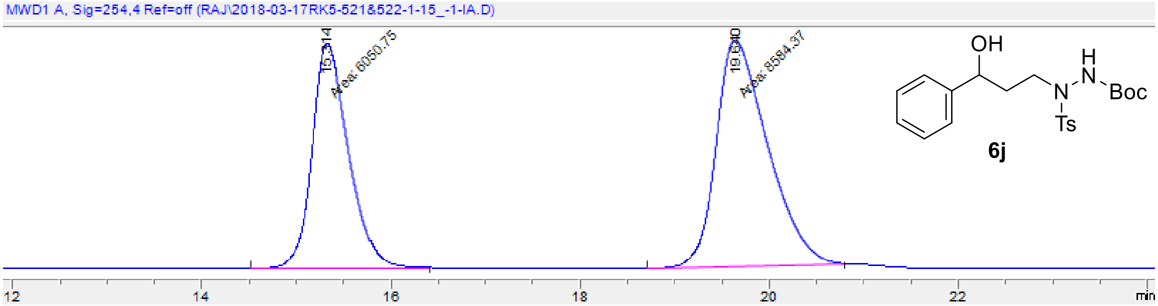
Using (*S*,*S*)-**7c**



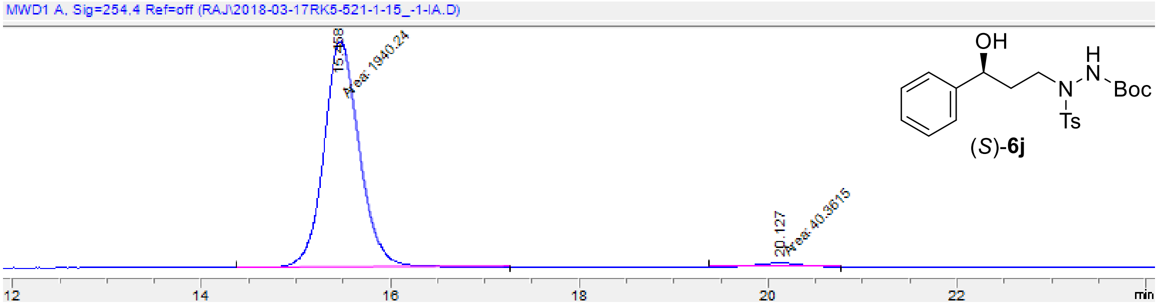
#	Time	Area	Height	Width	Area%	Symmetry
1	51.866	1852	25.8	1.1948	59.537	0.749
2	59.071	1258.6	16	1.1093	40.463	0.89

HPLC profile of **6j**

Chiralpak IA column (0.46 cm ø x 25 cm), 85:15 hexane:propan-2-ol, T = 25°C, flow rate = 1.0 mL/min.



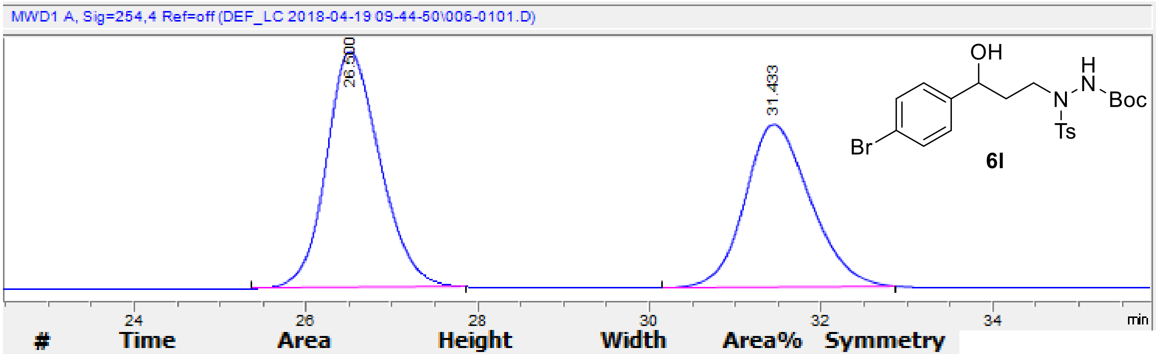
#	Time	Area	Height	Width	Area%	Symmetry
1	15.314	6050.7	224.1	0.45	41.344	0.681
2	19.64	8584.4	225.3	0.6351	58.656	0.582



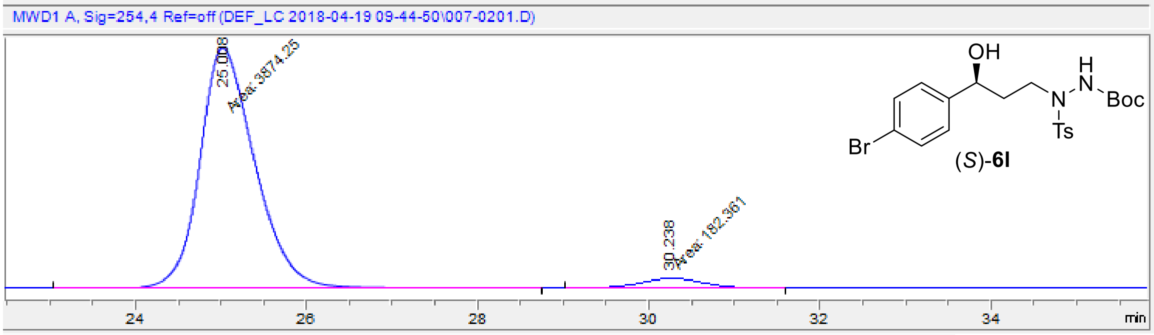
#	Time	Area	Height	Width	Area%	Symmetry
1	15.458	1940.2	73.5	0.4397	97.962	0.835
2	20.127	40.4	1.2	0.5577	2.038	1.232

HPLC profile of **6l**

Chiralpak OD-H column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



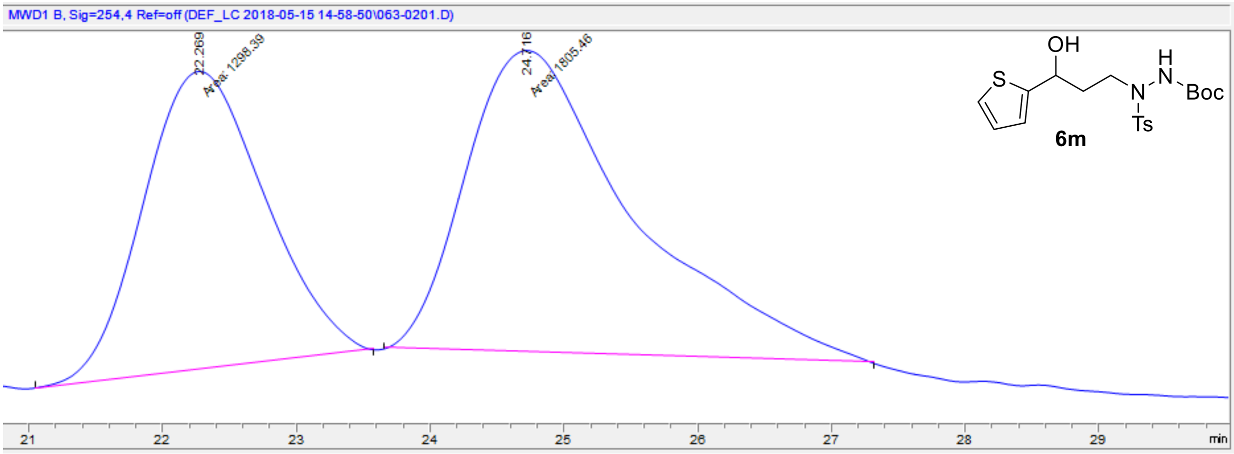
#	Time	Area	Height	Width	Area%	Symmetry
1	26.5	2336.9	53.3	0.5448	54.447	0.754
2	31.433	1955.1	36.7	0.6275	45.553	0.793



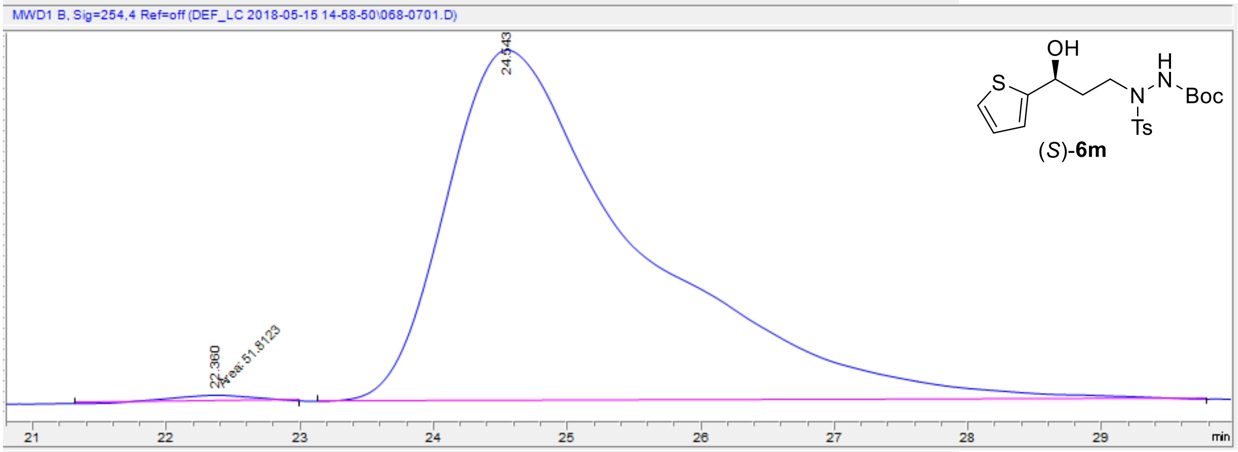
#	Time	Area	Height	Width	Area%	Symmetry
1	25.008	3874.2	86.4	0.7477	95.505	0.697
2	30.238	182.4	3.5	0.8652	4.495	0.909

HPLC profile of **6m**

Chiralpak IA column (0.46 cm ø x 25 cm) 95:5 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



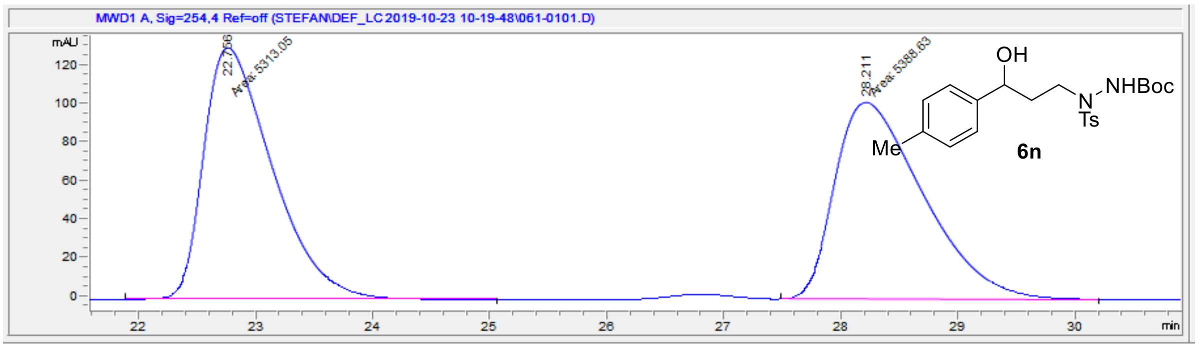
#	Time	Area	Height	Width	Area%	Symmetry
1	22.269	1298.4	20.5	1.0559	41.832	0.859
2	24.716	1805.5	20.7	1.4522	58.168	0.554

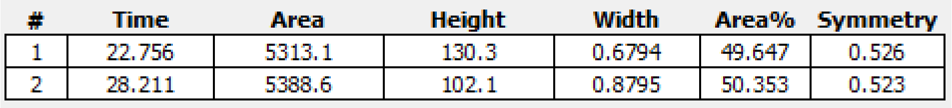


#	Time	Area	Height	Width	Area%	Symmetry
1	22.36	51.8	1.2	0.7206	0.757	1.233
2	24.543	6790.3	67.1	1.44	99.243	0.42

HPLC profile of **6n**

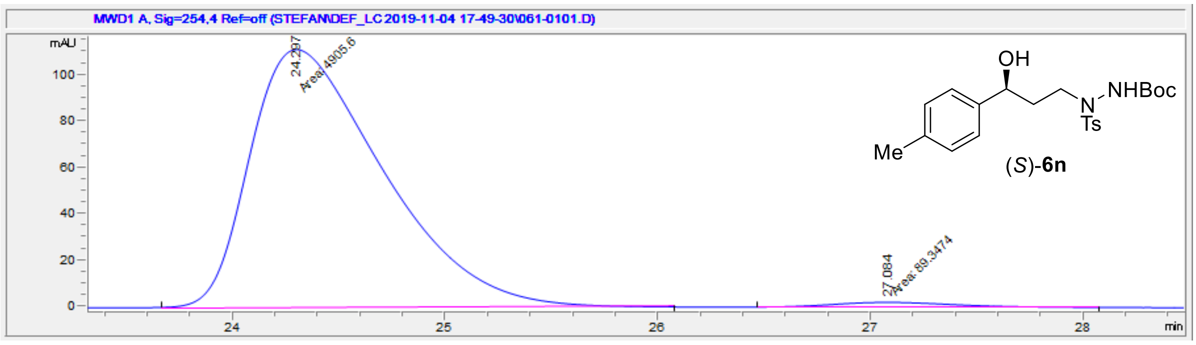
Chiralpak IA column (0.46 cm ø x 25 cm), 90:10 hexane:propan-2-ol, T = 25°C, flow rate = 1.0 mL/min.

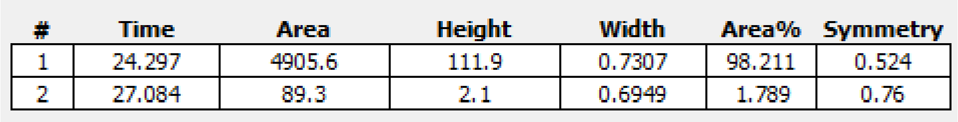




#	Time	Area	Height	Width	Area%	Symmetry
1	22.756	5313.1	130.3	0.6794	49.647	0.526
2	28.211	5388.6	102.1	0.8795	50.353	0.523

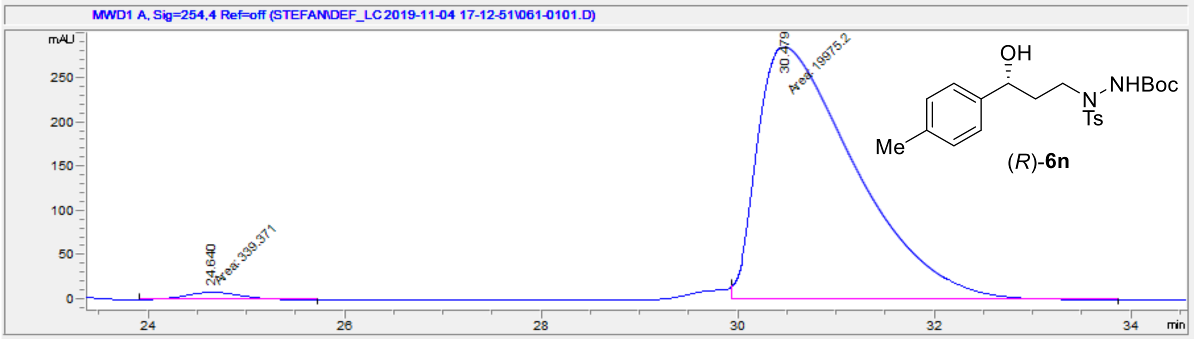
Using (*S*,*S*)-**7c**

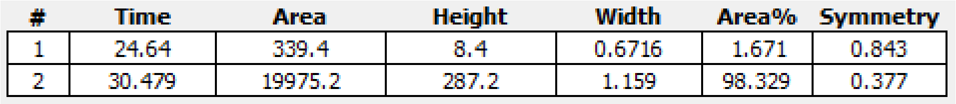




#	Time	Area	Height	Width	Area%	Symmetry
1	24.297	4905.6	111.9	0.7307	98.211	0.524
2	27.084	89.3	2.1	0.6949	1.789	0.76

Using (*R*,*R*)-**7c**

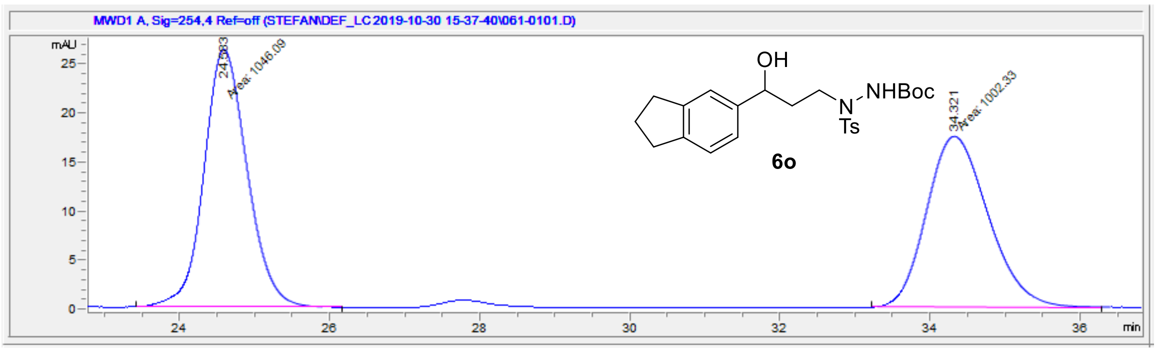


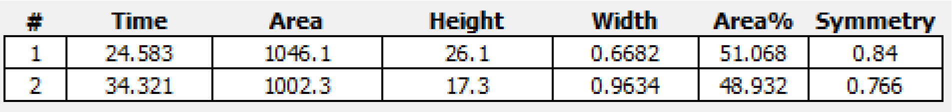


#	Time	Area	Height	Width	Area%	Symmetry
1	24.64	339.4	8.4	0.6716	1.671	0.843
2	30.479	19975.2	287.2	1.159	98.329	0.377

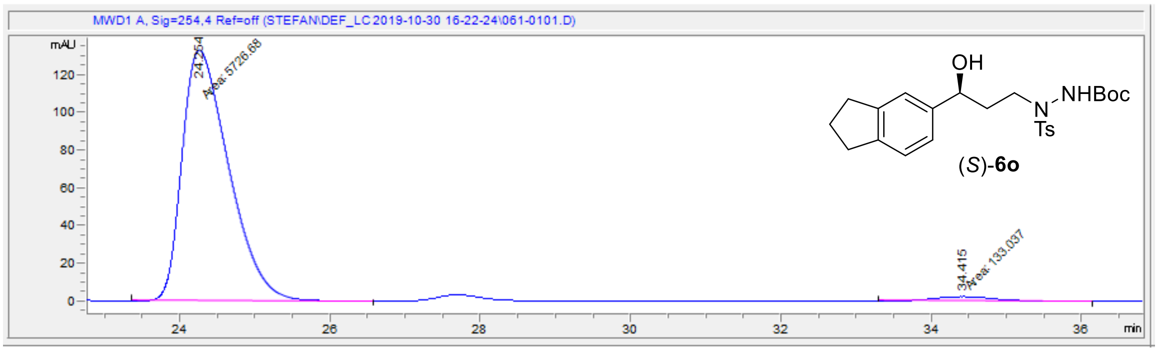
HPLC profile of **6o**

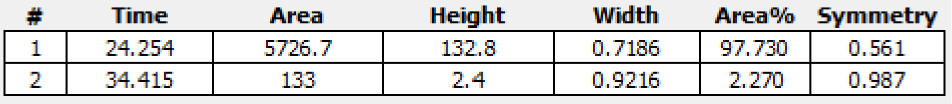
Chiralpak IA column (0.46 cm ø x 25 cm), 90:10 hexane:propan-2-ol, T = 25°C, flow rate = 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	24.583	1046.1	26.1	0.6682	51.068	0.84
2	34.321	1002.3	17.3	0.9634	48.932	0.766

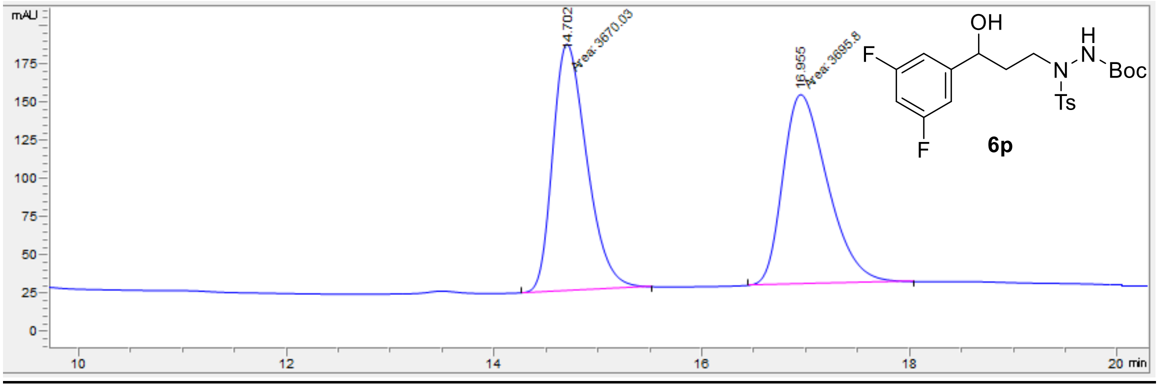




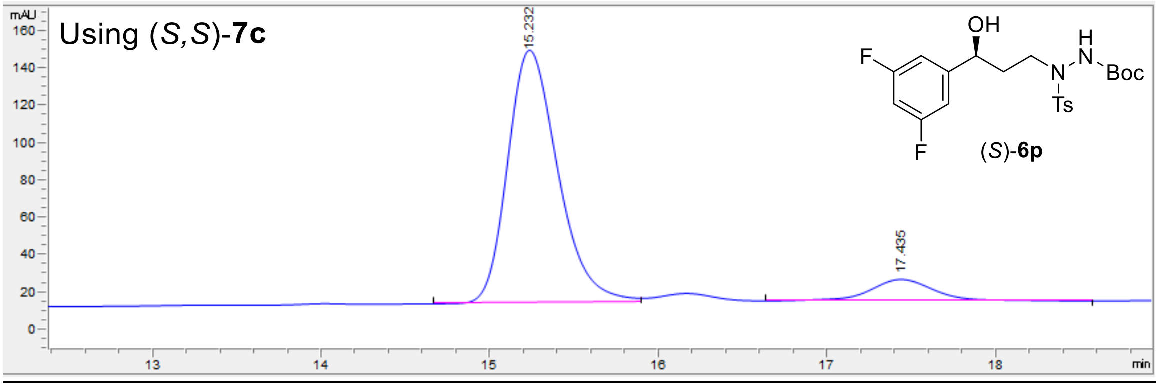
#	Time	Area	Height	Width	Area%	Symmetry
1	24.254	5726.7	132.8	0.7186	97.730	0.561
2	34.415	133	2.4	0.9216	2.270	0.987

HPLC Trace of **6p**

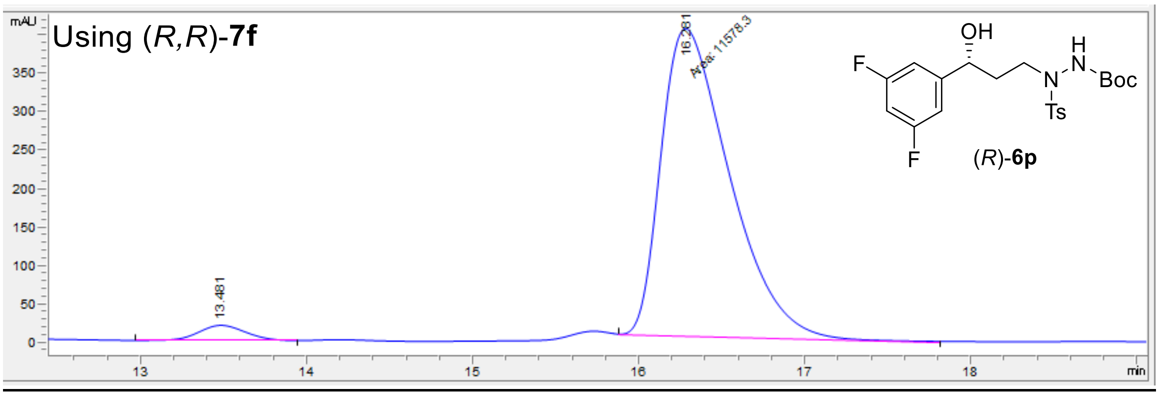
Chiralpak IA column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



#	Time	Area	Height	Width	Area%	Symmetry
1	14.702	3670	160.5	0.381	49.825	0.691
2	16.955	3695.8	123.4	0.4992	50.175	0.652



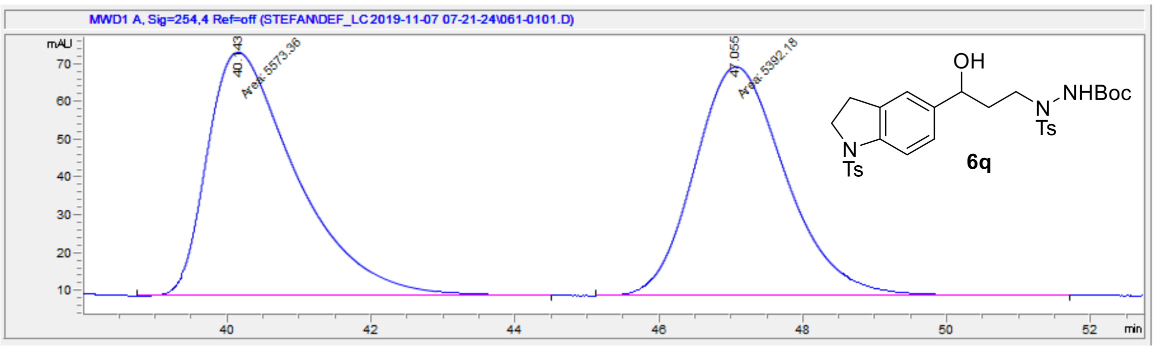
#	Time	Area	Height	Width	Area%	Symmetry
1	15.232	2820	135.9	0.32	90.121	0.728
2	17.435	309.1	11.5	0.4044	9.879	0.915



#	Time	Area	Height	Width	Area%	Symmetry
1	13.481	401.3	19.9	0.3136	3.350	0.86
2	16.281	11578.3	399.8	0.4827	96.650	0.538

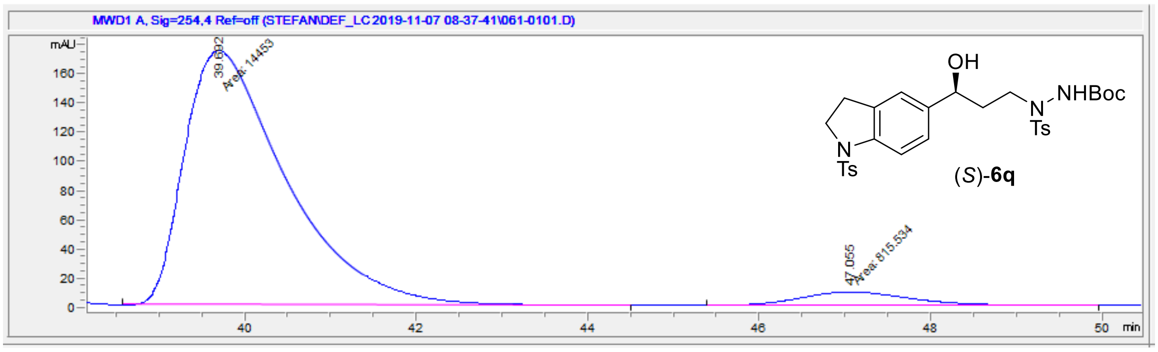
HPLC profile of **6q**

Chiralpak IA column (0.46 cm ø x 25 cm), 80:20 hexane:propan-2-ol, T = 25°C, flow rate = 1.0 mL/min.



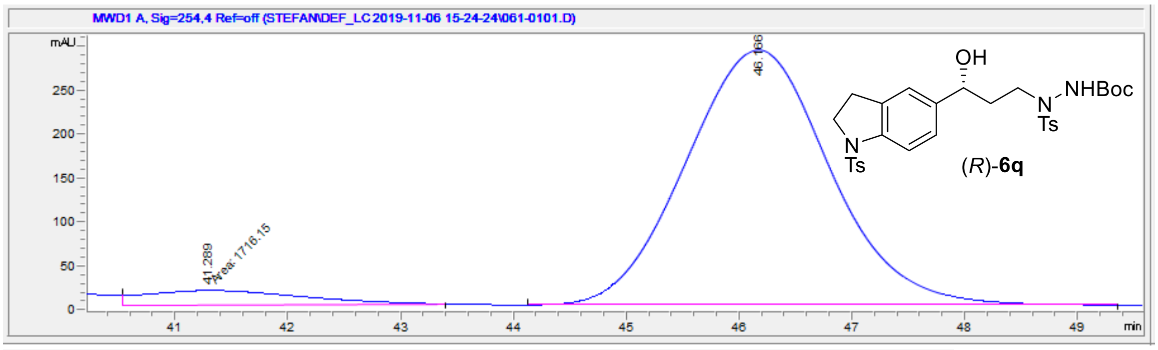
#	Time	Area	Height	Width	Area%	Symmetry
1	40.143	5573.4	64.8	1.4331	50.826	0.507
2	47.055	5392.2	61	1.4743	49.174	0.797

Using (*S*,*S*)-**7c**



#	Time	Area	Height	Width	Area%	Symmetry
1	39.692	14453	174.6	1.3794	94.659	0.491
2	47.055	815.5	9.2	1.4793	5.341	0.785

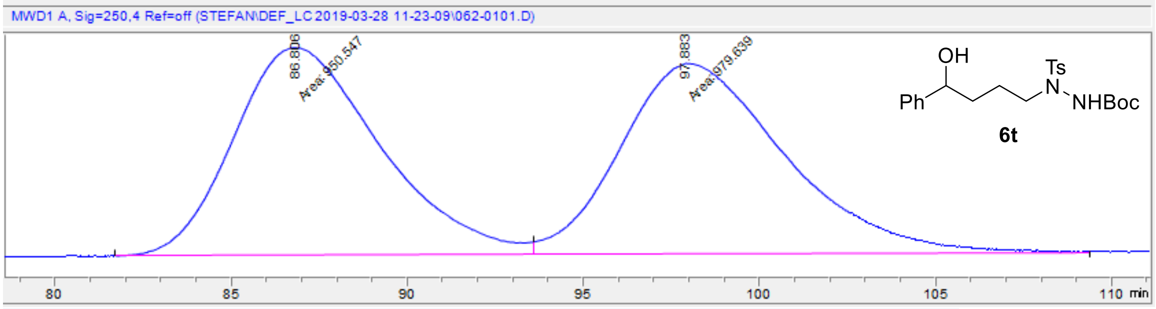
Using (*R*,*R*)-**7c**

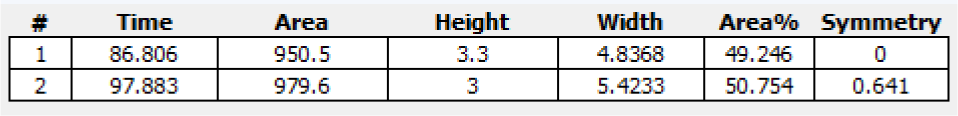


#	Time	Area	Height	Width	Area%	Symmetry
1	41.289	1716.1	17.3	1.6486	6.208	0.646
2	46.166	25927.2	291.5	1.1131	93.792	0.951

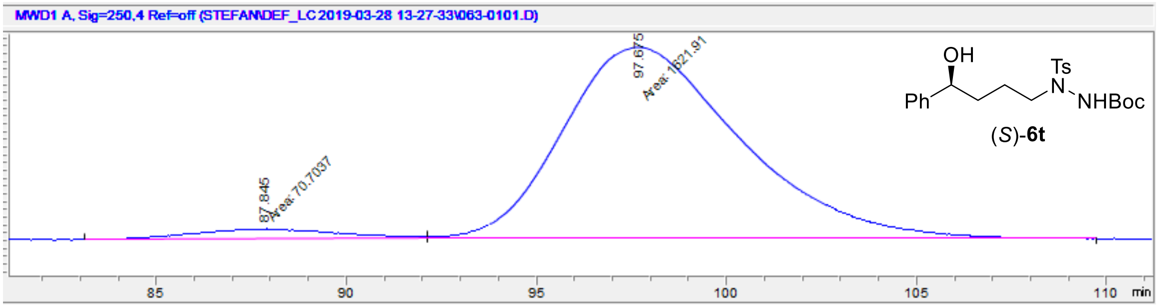
HPLC profile of **6t**

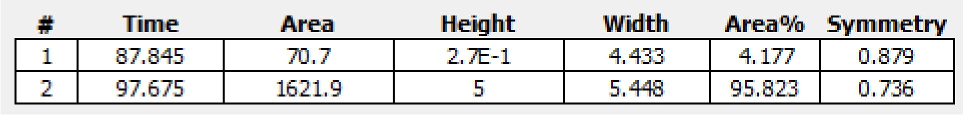
Chiralpak OD-H column (0.46 cm ø x 25 cm), 97.5:2.5 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	86.806	950.5	3.3	4.8368	49.246	0
2	97.883	979.6	3	5.4233	50.754	0.641

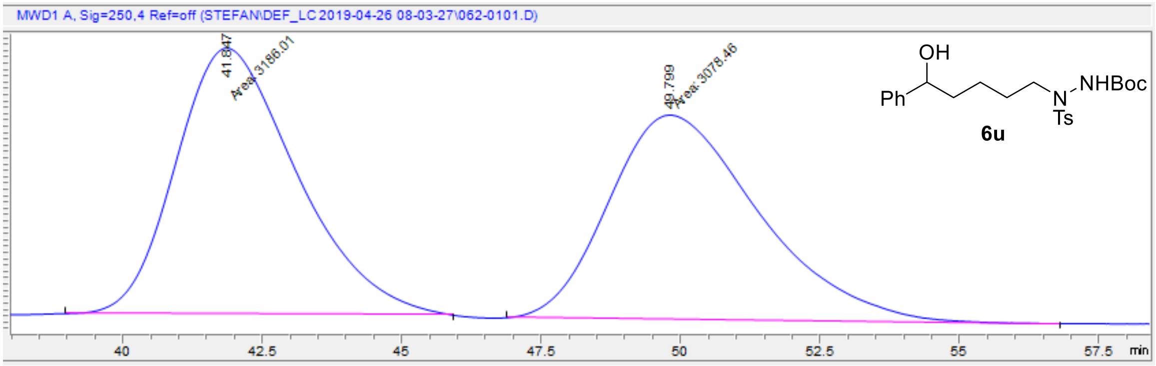


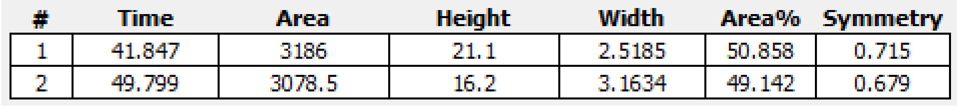


#	Time	Area	Height	Width	Area%	Symmetry
1	87.845	70.7	2.7E-1	4.433	4.177	0.879
2	97.675	1621.9	5	5.448	95.823	0.736

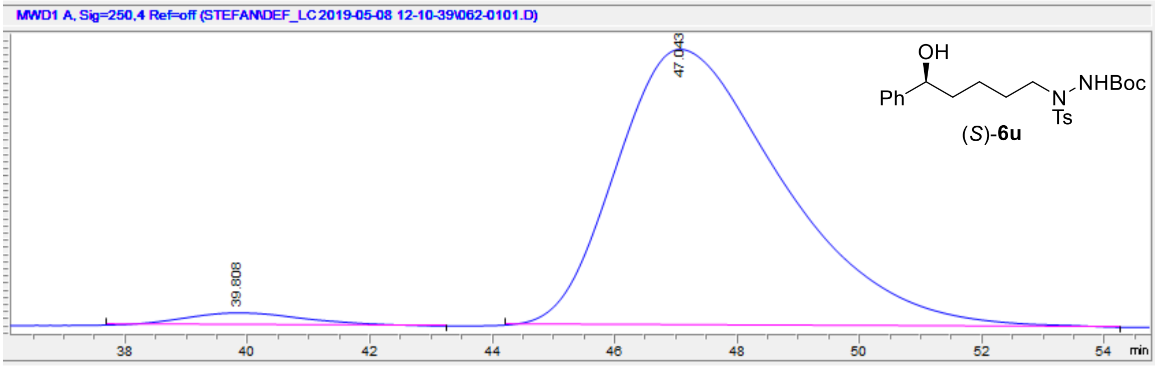
HPLC profile of **6u**

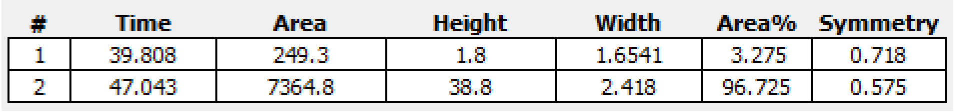
Chiralpak OD-H column (0.46 cm ø x 25 cm), 96:4 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	41.847	3186	21.1	2.5185	50.858	0.715
2	49.799	3078.5	16.2	3.1634	49.142	0.679

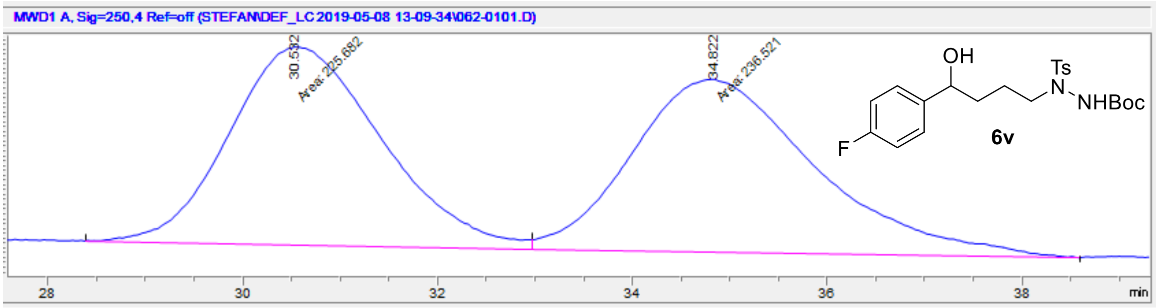


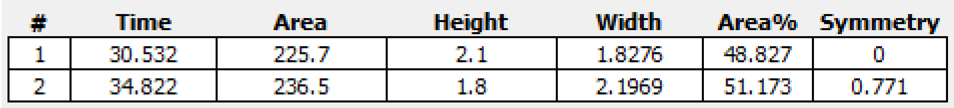


#	Time	Area	Height	Width	Area%	Symmetry
1	39.808	249.3	1.8	1.6541	3.275	0.718
2	47.043	7364.8	38.8	2.418	96.725	0.575

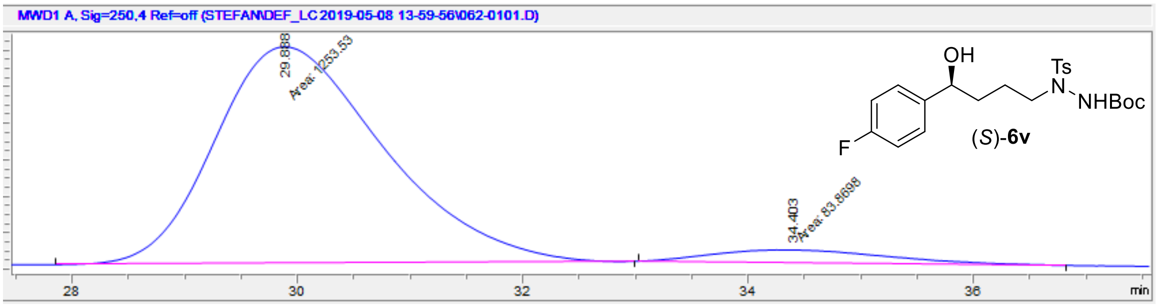
HPLC profile of **6v**

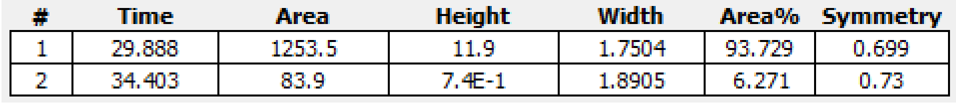
Chiralpak OD-H column (0.46 cm ø x 25 cm), 96:4 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	30.532	225.7	2.1	1.8276	48.827	0
2	34.822	236.5	1.8	2.1969	51.173	0.771

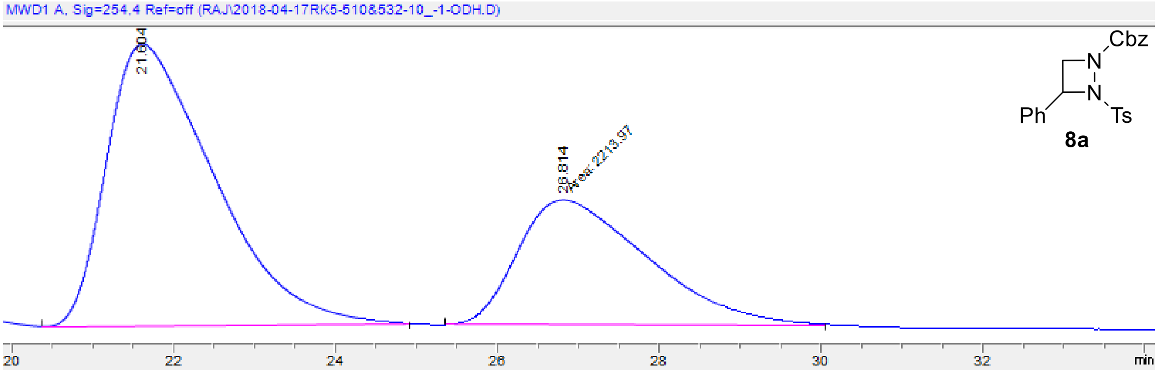




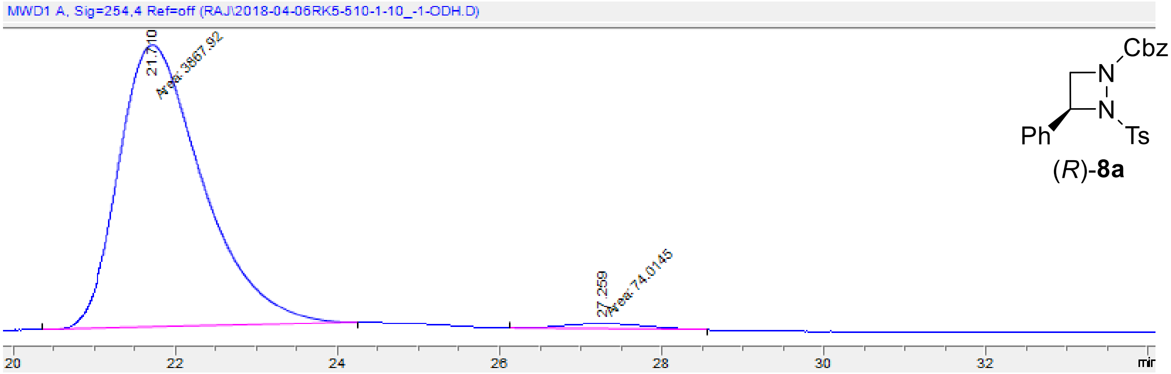
#	Time	Area	Height	Width	Area%	Symmetry
1	29.888	1253.5	11.9	1.7504	93.729	0.699
2	34.403	83.9	7.4E-1	1.8905	6.271	0.73

HPLC profile of **8a**

Chiralcel OD-H column (0.46 cm ø x 25 cm), 90:10 hexane:propan-2-ol, T = 25°C, flow rate = 1.0 mL/min.



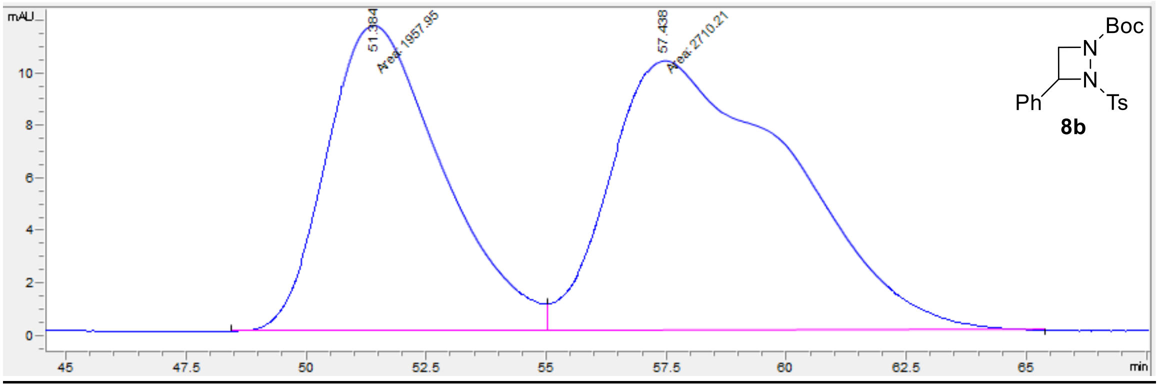
#	Time	Area	Height	Width	Area%	Symmetry
1	21.604	4125.4	44.5	1.085	65.076	0.487
2	26.814	2214	19.7	1.8684	34.924	0.531

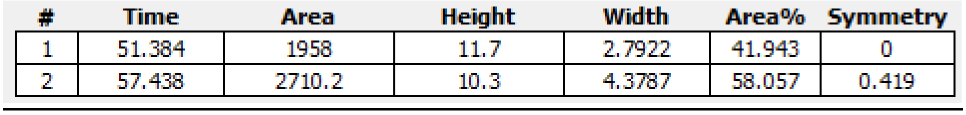


#	Time	Area	Height	Width	Area%	Symmetry
1	21.71	3867.9	53.5	1.2048	98.122	0.651
2	27.259	74	1	1.2028	1.878	0.794

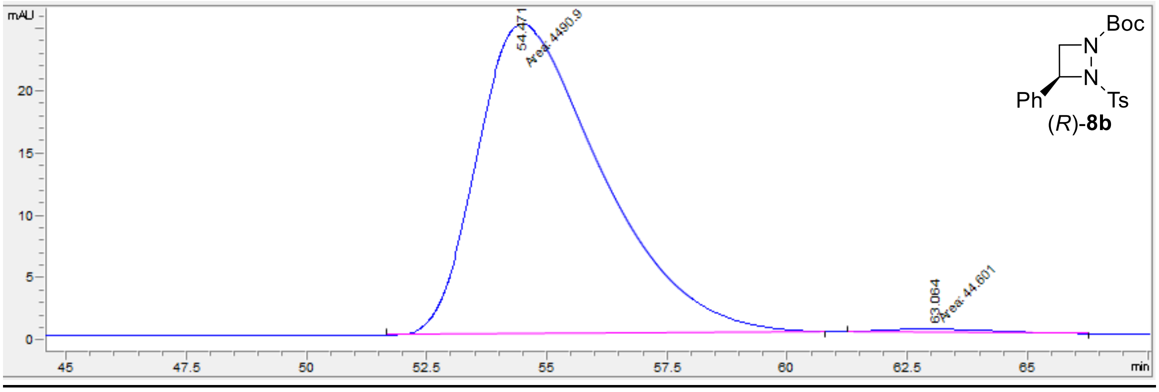
HPLC Trace of **8b**

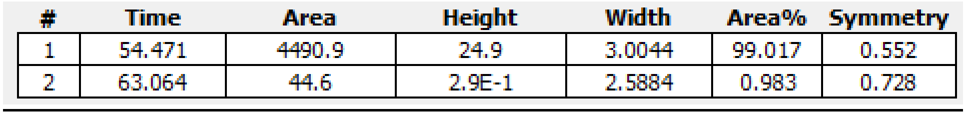
Chiralpak IA column (0.46 cm ø x 25 cm) 99.4:0.6 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	51.384	1958	11.7	2.7922	41.943	0
2	57.438	2710.2	10.3	4.3787	58.057	0.419

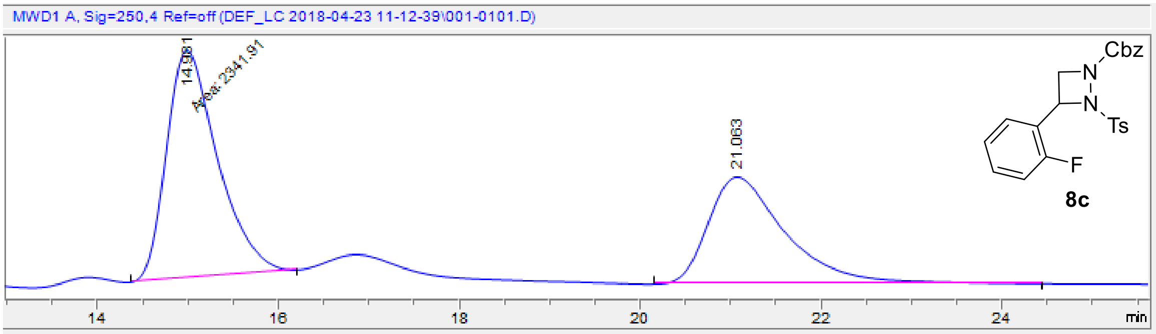




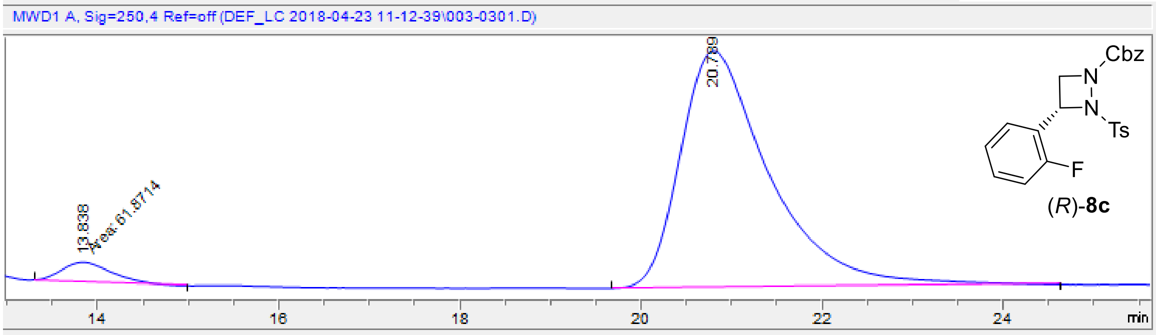
#	Time	Area	Height	Width	Area%	Symmetry
1	54.471	4490.9	24.9	3.0044	99.017	0.552
2	63.064	44.6	2.9E-1	2.5884	0.983	0.728

HPLC profile of **8c**

Chiralpak OD-H column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate 1.0 mL/min.



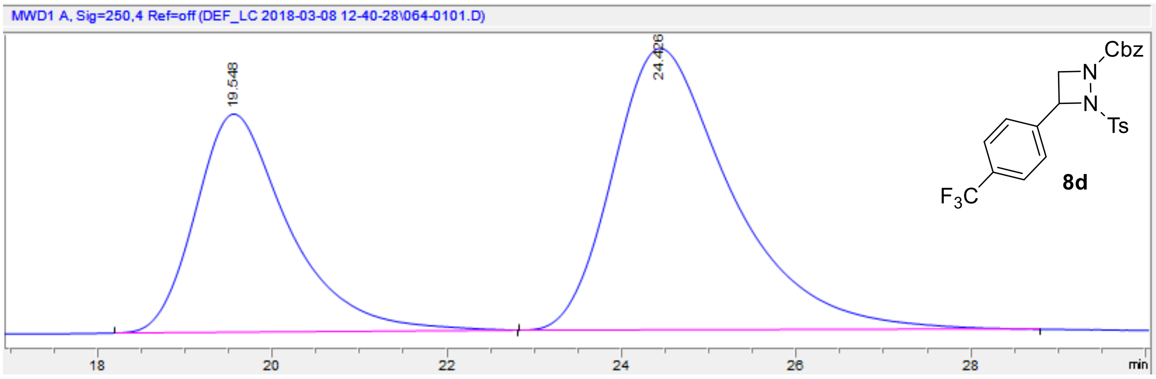
#	Time	Area	Height	Width	Area%	Symmetry
1	14.981	2341.9	59.8	0.6528	58.244	0.65
2	21.063	1678.9	28.1	0.8697	41.756	0.551

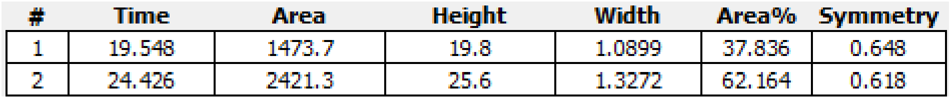


#	Time	Area	Height	Width	Area%	Symmetry
1	13.838	61.9	1.6	0.6588	4.615	0.708
2	20.789	1278.7	18.6	0.9917	95.385	0.552

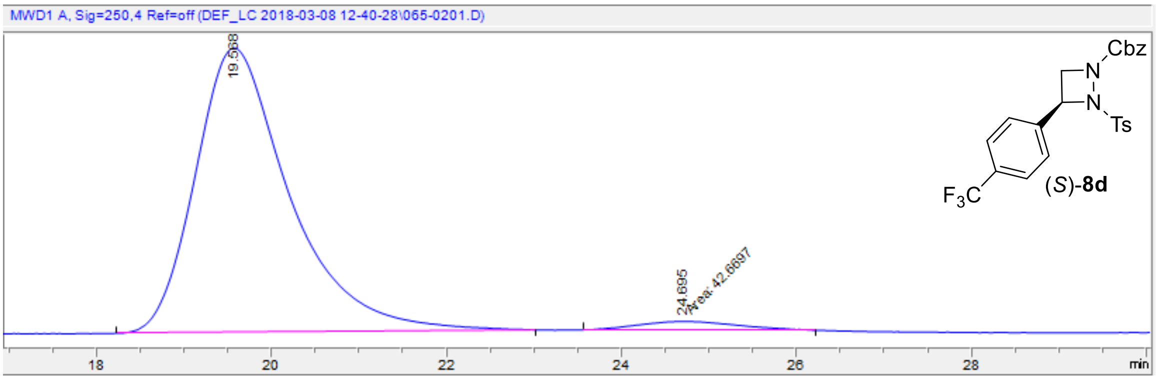
HPLC profile of **8d**

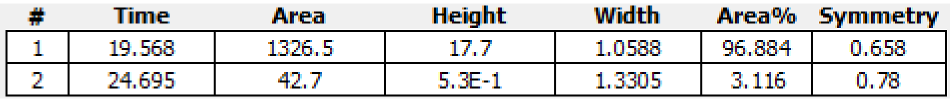
Chiralpak OD-H column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	19.548	1473.7	19.8	1.0899	37.836	0.648
2	24.426	2421.3	25.6	1.3272	62.164	0.618



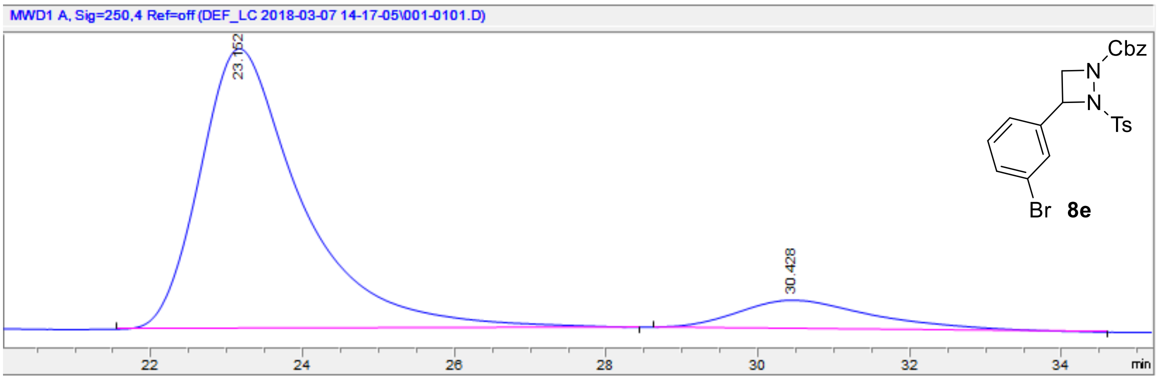


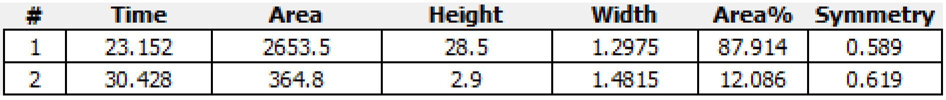
#	Time	Area	Height	Width	Area%	Symmetry
1	19.568	1326.5	17.7	1.0588	96.884	0.658
2	24.695	42.7	5.3E-1	1.3305	3.116	0.78

HPLC profile of **8e**

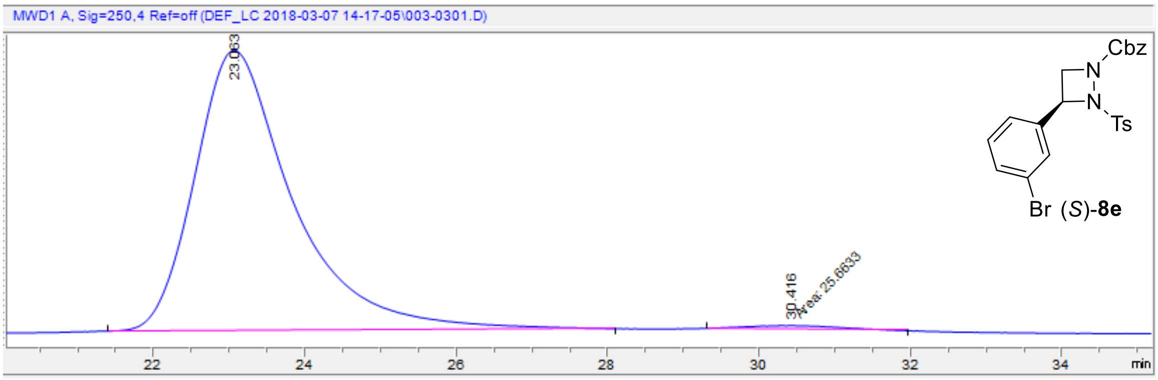
Chiralpak OD-H column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate 1.0 mL/min.

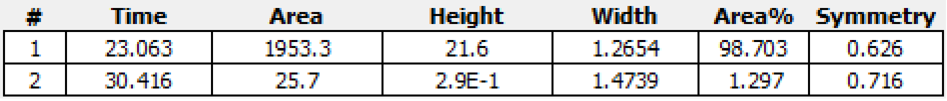
N.B. The racemic HPLC trace was generated by mixing the (*R*) and (*S*) enantiomers.





#	Time	Area	Height	Width	Area%	Symmetry
1	23.152	2653.5	28.5	1.2975	87.914	0.589
2	30.428	364.8	2.9	1.4815	12.086	0.619



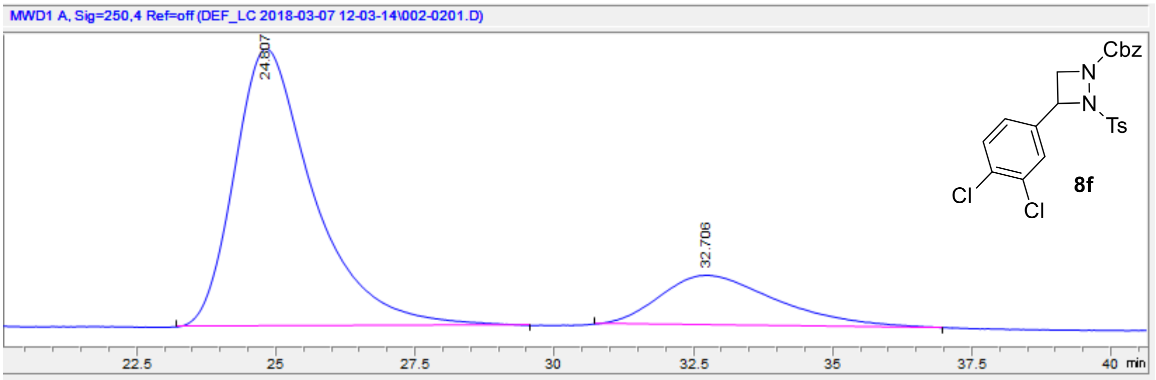


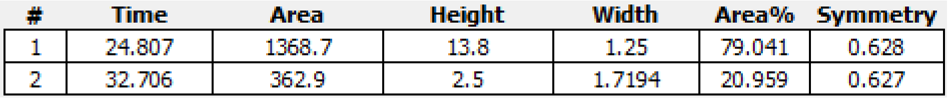
#	Time	Area	Height	Width	Area%	Symmetry
1	23.063	1953.3	21.6	1.2654	98.703	0.626
2	30.416	25.7	2.9E-1	1.4739	1.297	0.716

HPLC profile of **8f**

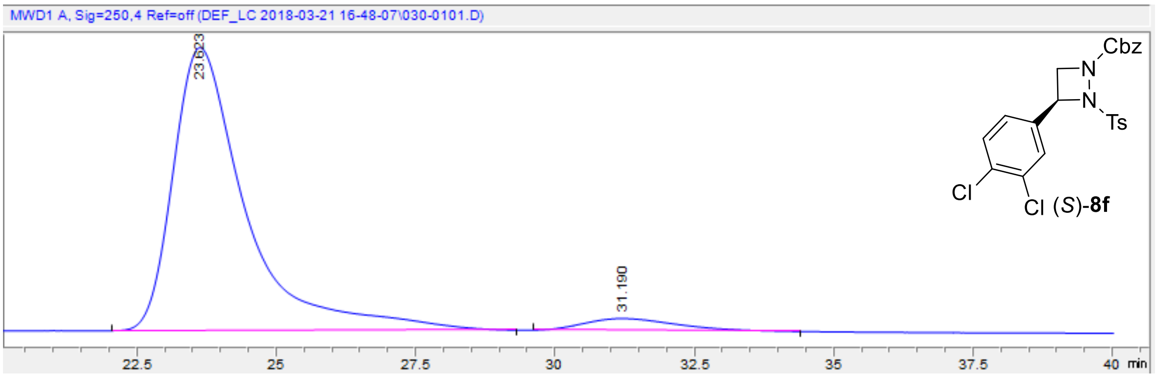
Chiralpak OD-H column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.

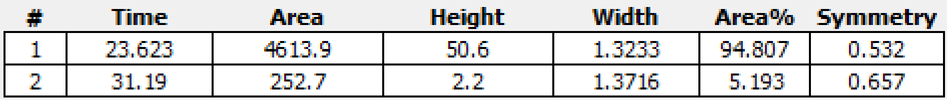
N.B. The racemic HPLC trace was generated by mixing the (*R*) and (*S*) enantiomers.





#	Time	Area	Height	Width	Area%	Symmetry
1	24.807	1368.7	13.8	1.25	79.041	0.628
2	32.706	362.9	2.5	1.7194	20.959	0.627

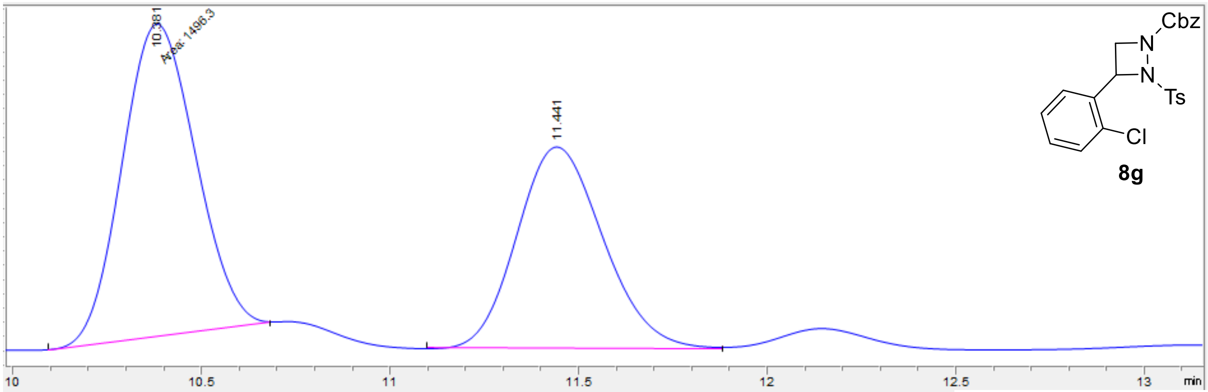




#	Time	Area	Height	Width	Area%	Symmetry
1	23.623	4613.9	50.6	1.3233	94.807	0.532
2	31.19	252.7	2.2	1.3716	5.193	0.657

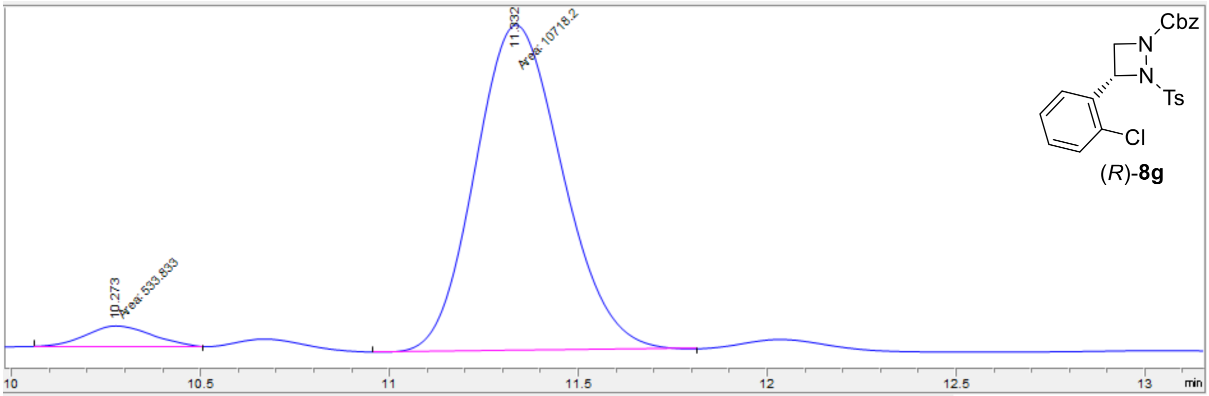
HPLC profile of **8g**

Chiralpak IA column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



8g

#	Time	Area	Height	Width	Area%	Symmetry
1	10.381	1496.3	110.2	0.2264	56.881	0.893
2	11.441	1134.3	70.9	0.2486	43.119	0.822



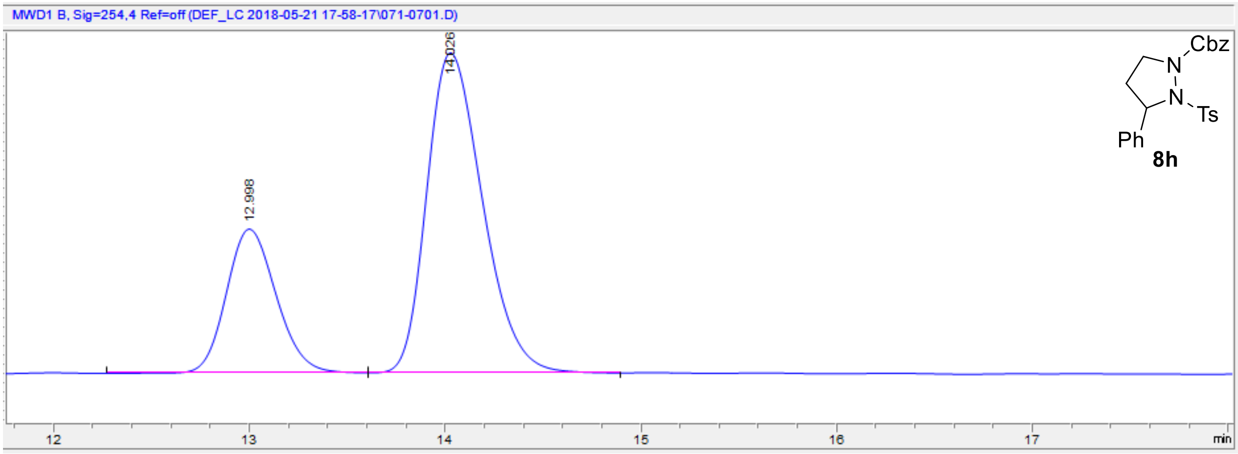
(*R*)-**8g**

#	Time	Area	Height	Width	Area%	Symmetry
1	10.273	533.8	42.9	0.2075	4.744	0.824
2	11.332	10718.2	665	0.2686	95.256	0.853

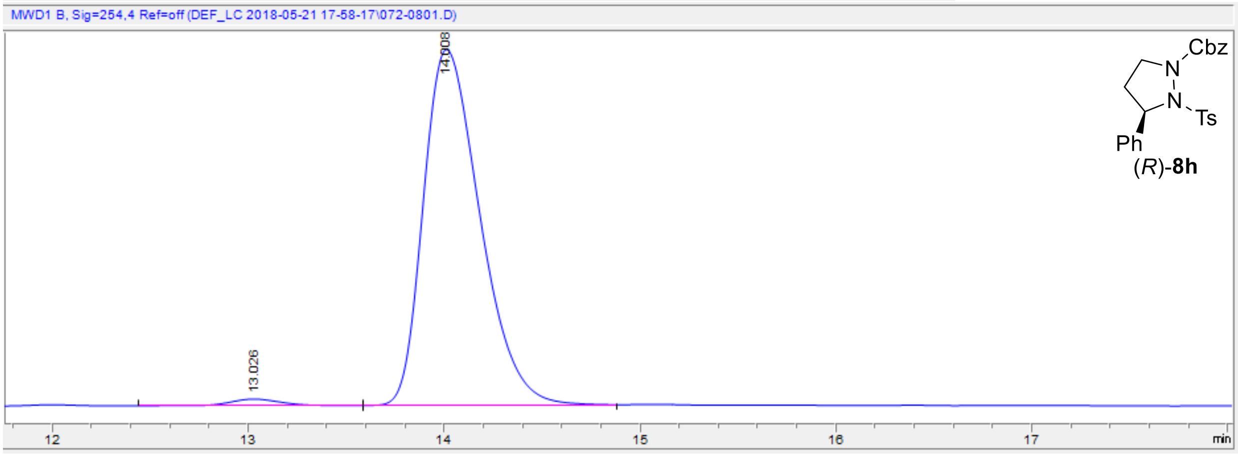
HPLC profile of **8h**

Chiralpak IA column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.

N.B. The racemic HPLC trace was generated by mixing the (*R*) and (*S*) enantiomers.



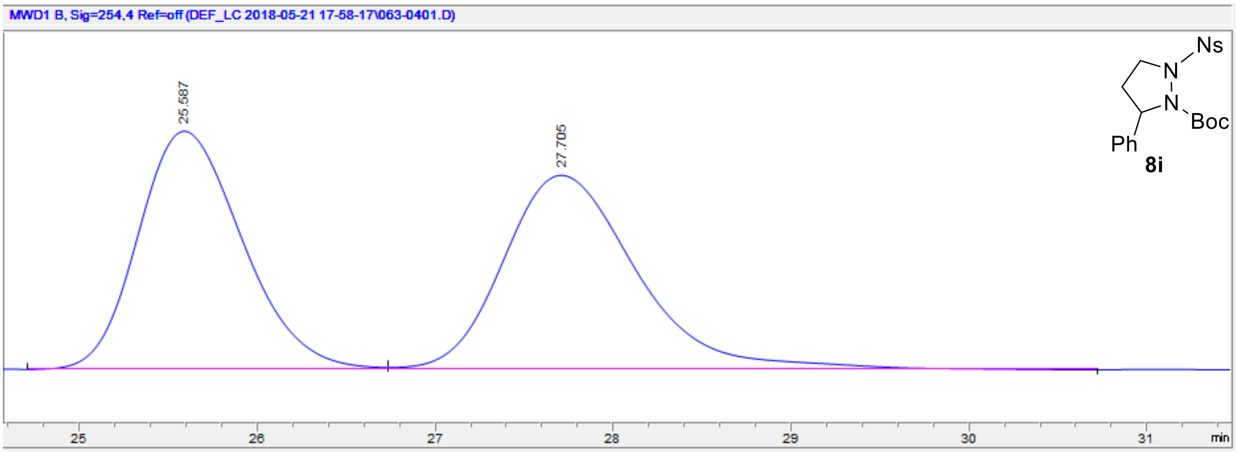
#	Time	Area	Height	Width	Area%	Symmetry
1	12.998	1395	78.3	0.2758	28.780	0.819
2	14.026	3452.2	173.9	0.3096	71.220	0.699



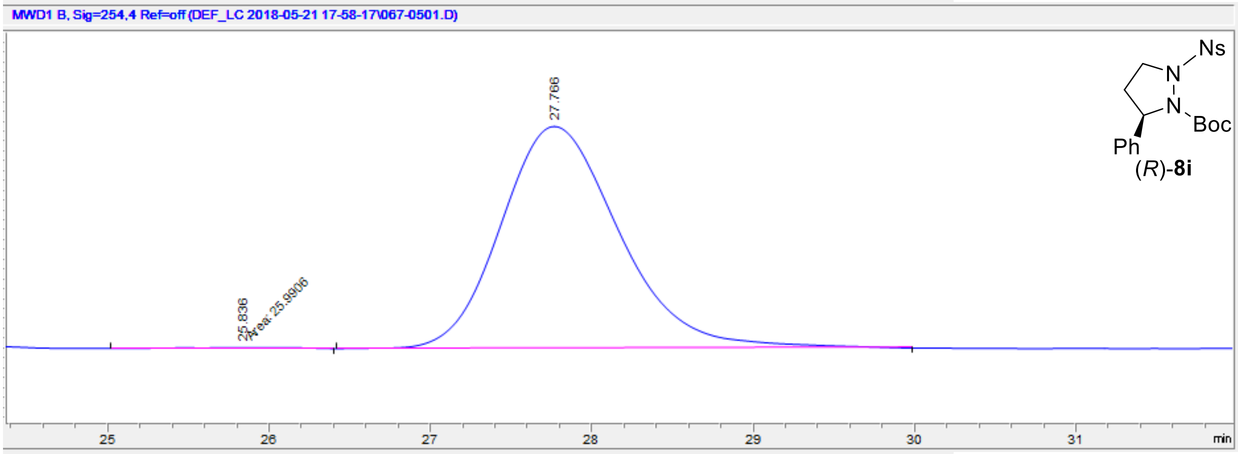
#	Time	Area	Height	Width	Area%	Symmetry
1	13.026	117.8	6.3	0.2853	1.699	0.869
2	14.008	6813.6	339.6	0.3121	98.301	0.652

HPLC profile of **8i**

Chiralpak IA column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



#	Time	Area	Height	Width	Area%	Symmetry
1	25.587	10377.4	254	0.6387	48.791	0.761
2	27.705	10891.7	207	0.8079	51.209	0.723

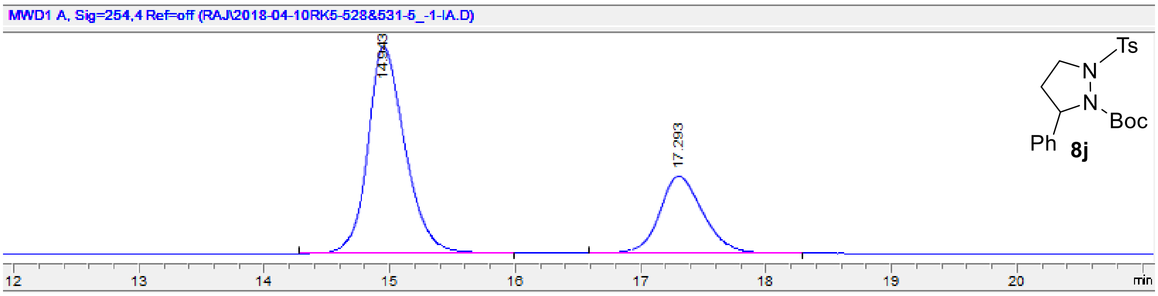


#	Time	Area	Height	Width	Area%	Symmetry
1	25.836	26	5E-1	0.8658	0.448	1.199
2	27.766	5774	112.7	0.7918	99.552	0.776

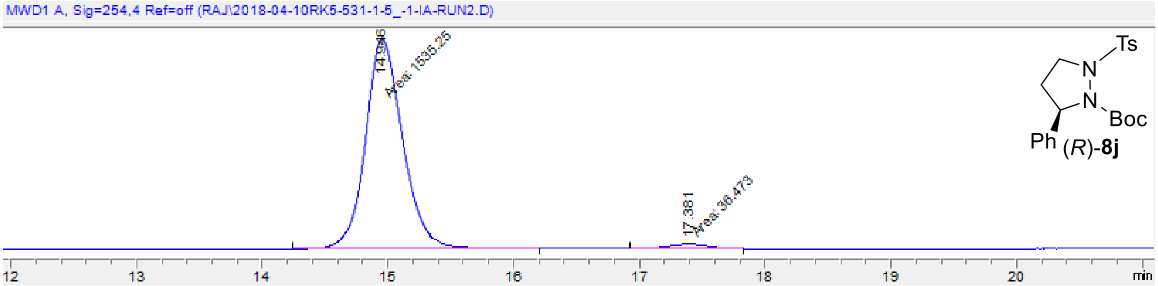
HPLC profile of **8j**

Chiralpak IA column (4.6 cm ø x 250 cm), 95:5 hexane:propan-2-ol, T = 25°C, flow rate = 1.0 mL/min.

N.B. The racemic HPLC trace was generated by mixing the (*R*) and (*S*) enantiomers.



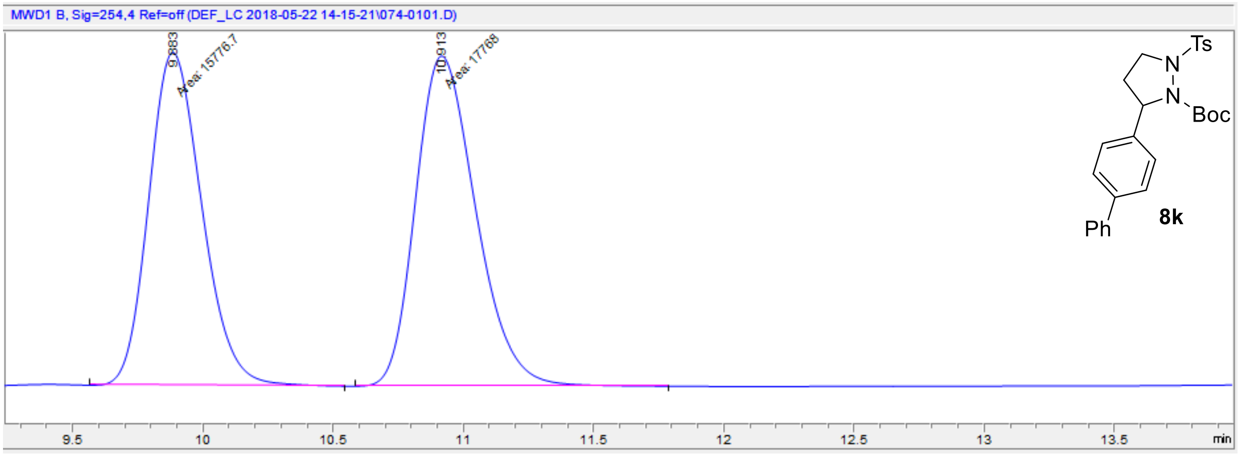
#	Time	Area	Height	Width	Area%	Symmetry
1	14.943	2899.7	140.8	0.3088	69.625	0.719
2	17.293	1265.1	52.5	0.3521	30.375	0.77



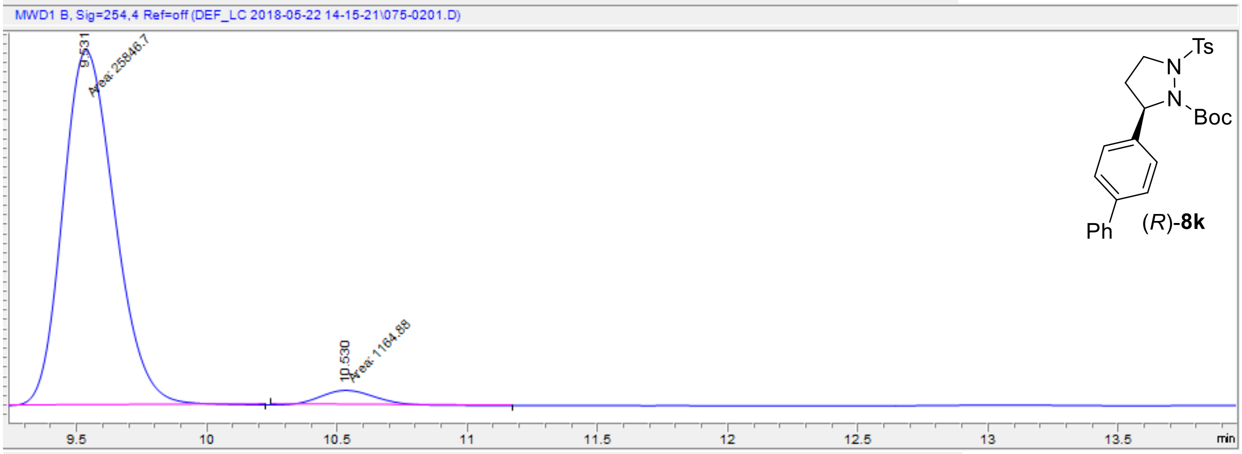
#	Time	Area	Height	Width	Area%	Symmetry
1	14.946	1535.2	74.7	0.3426	97.679	0.798
2	17.381	36.5	1.6	0.3732	2.321	1.044

HPLC profile of **8k**

Chiralpak IA column (0.46 cm ø x 25 cm) 90:10 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



#	Time	Area	Height	Width	Area%	Symmetry
1	9.883	15776.7	1114.6	0.2359	47.032	0.8
2	10.913	17768	1104.8	0.268	52.968	0.736

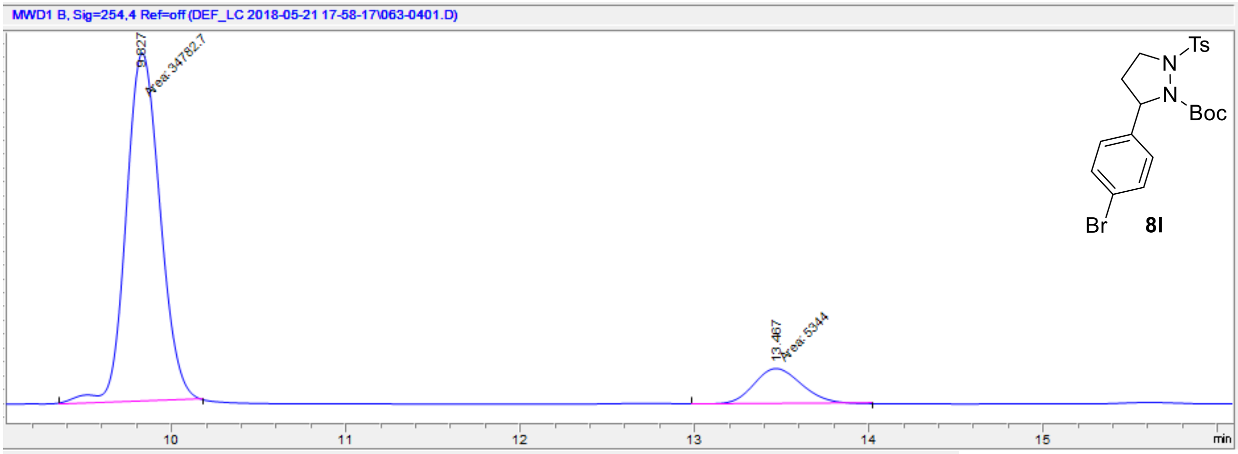


#	Time	Area	Height	Width	Area%	Symmetry
1	9.531	25846.7	1863.5	0.2312	95.687	0.783
2	10.53	1164.9	77.5	0.2504	4.313	0.833

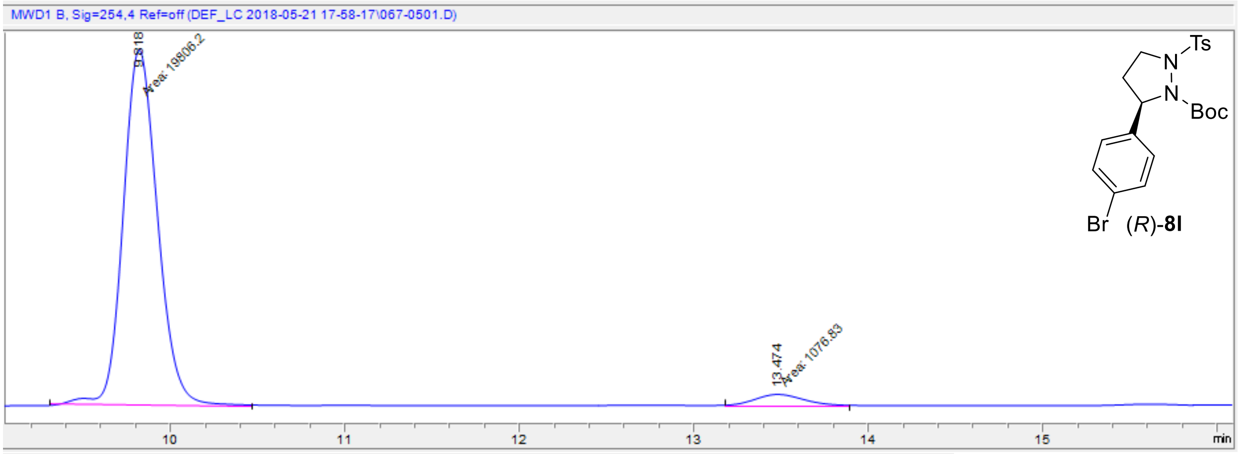
HPLC profile of **8l**

Chiralpak OD-H column (0.46 cm ø x 25 cm) 95:5 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.

N.B. The racemic HPLC trace was generated by mixing the (*R*) and (*S*) enantiomers.



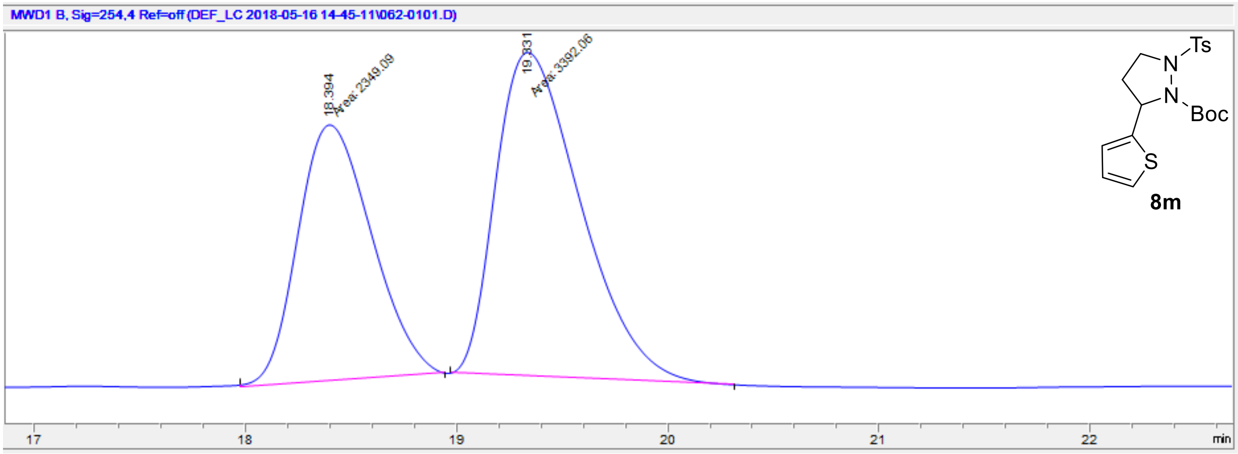
#	Time	Area	Height	Width	Area%	Symmetry
1	9.827	34782.7	2538.7	0.2284	86.682	0.895
2	13.467	5344	263.2	0.3384	13.318	0.867



#	Time	Area	Height	Width	Area%	Symmetry
1	9.818	19806.2	1444.3	0.2286	94.844	0.84
2	13.474	1076.8	50.1	0.3582	5.156	0.817

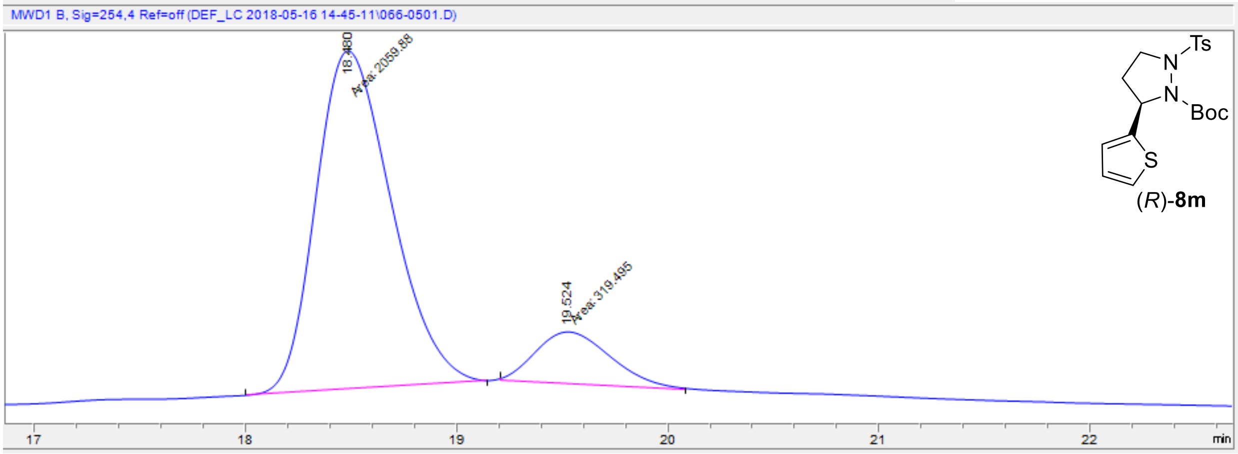
HPLC profile of **8m**

Chiralpak IA column (0.46 cm ø x 25 cm) 97:3 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



8m

#	Time	Area	Height	Width	Area%	Symmetry
1	18.394	2349.1	96.3	0.4065	40.917	0.751
2	19.331	3392.1	121.2	0.4664	59.083	0.584

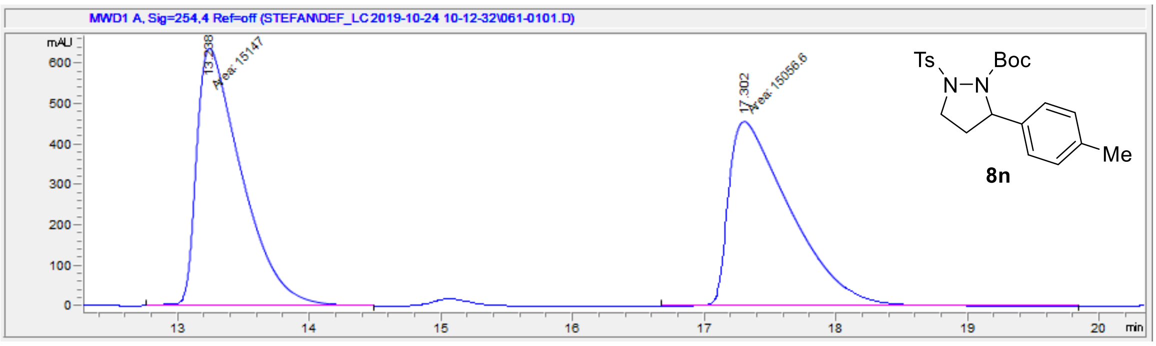


(*R*)-**8m**

#	Time	Area	Height	Width	Area%	Symmetry
1	18.48	2059.9	83.2	0.4124	86.572	0.73
2	19.524	319.5	12.8	0.4159	13.428	0.715

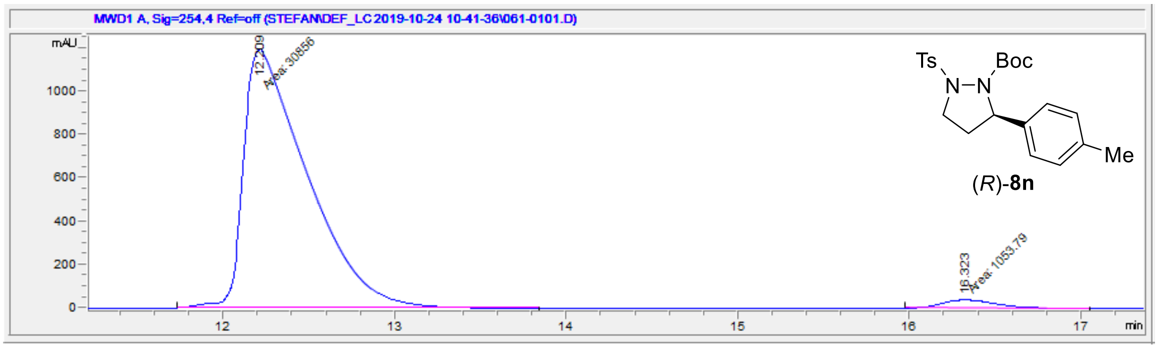
HPLC profile of **8n**

Chiralpak IA column (0.46 cm ø x 25 cm), 95:5 hexane:propan-2-ol, T = 25°C, flow rate = 1.0 mL/min.



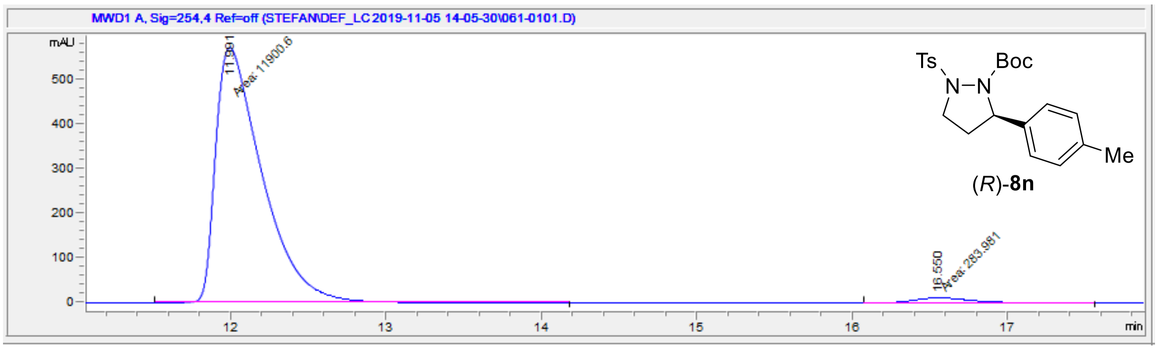
#	Time	Area	Height	Width	Area%	Symmetry
1	13.238	15147	637.9	0.3958	50.150	0.393
2	17.302	15056.6	458.1	0.5478	49.850	0.332

Cyclisation with DEAD



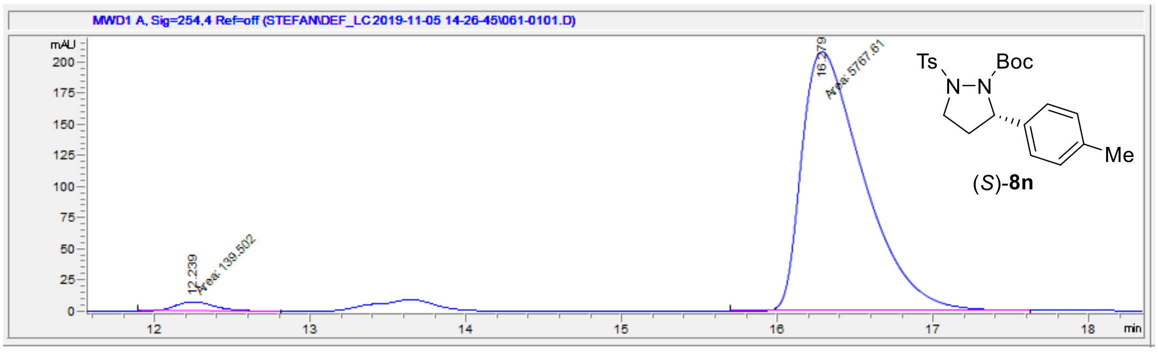
#	Time	Area	Height	Width	Area%	Symmetry
1	12.209	30856	1193.5	0.4309	96.698	0.331
2	16.323	1053.8	40.7	0.4312	3.302	0.597

Cyclisation with DIAD



#	Time	Area	Height	Width	Area%	Symmetry
1	11.991	11900.6	570.7	0.3476	97.669	0.419
2	16.55	284	11.2	0.4219	2.331	0.714

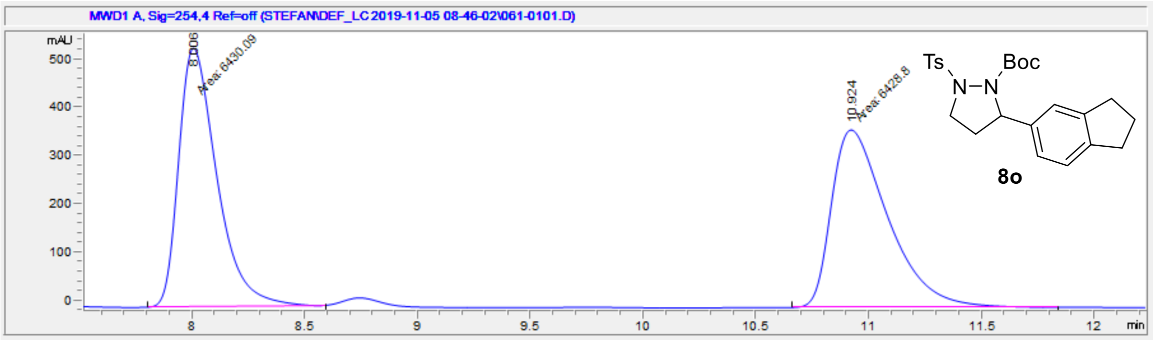
Cyclisation with DIAD

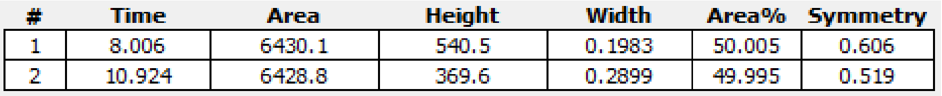


#	Time	Area	Height	Width	Area%	Symmetry
1	12.239	139.5	7.6	0.3069	2.362	0.736
2	16.279	5767.6	208.8	0.4603	97.638	0.475

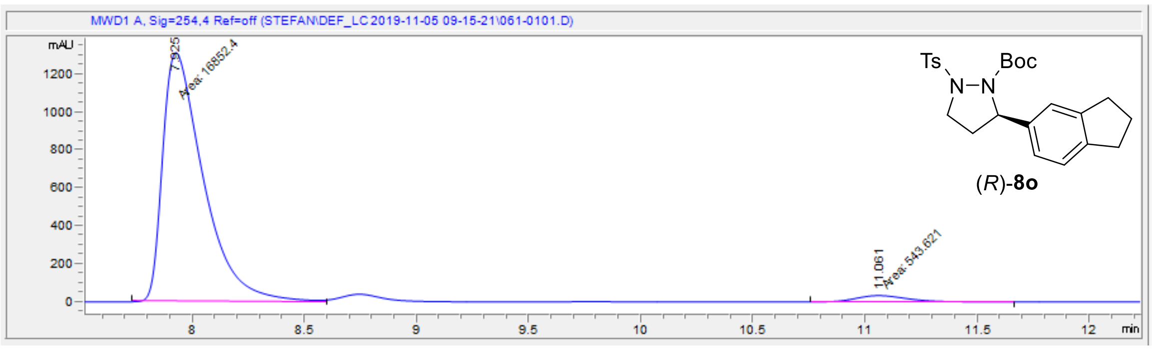
HPLC profile of **8o**

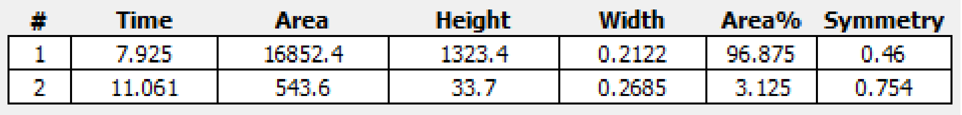
Chiralpak IA column (0.46 cm ø x 25 cm), 90:10 hexane:propan-2-ol, T = 25°C, flow rate = 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	8.006	6430.1	540.5	0.1983	50.005	0.606
2	10.924	6428.8	369.6	0.2899	49.995	0.519

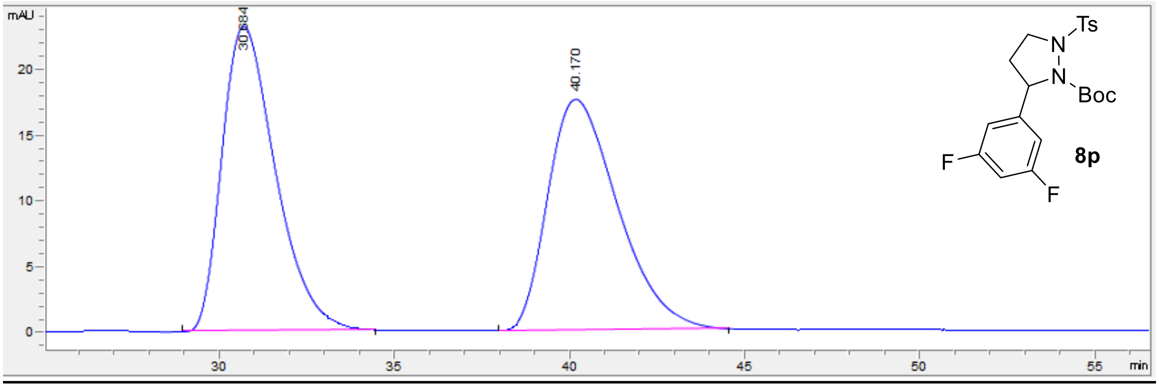




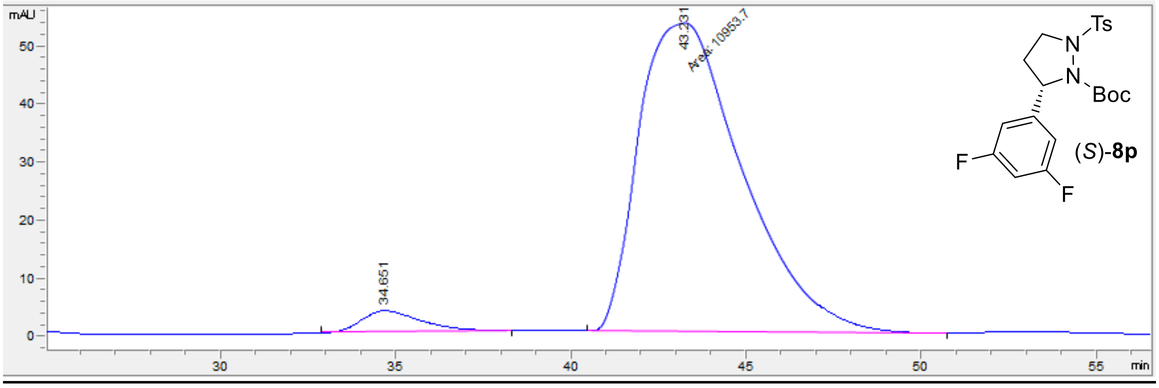
#	Time	Area	Height	Width	Area%	Symmetry
1	7.925	16852.4	1323.4	0.2122	96.875	0.46
2	11.061	543.6	33.7	0.2685	3.125	0.754

HPLC traces of **8p**

Chiralpak OD-H column (0.46 cm ø x 25 cm) 99:1 hexane:propan-2-ol, T = 15 °C, flow rate = 1.0 mL/min.



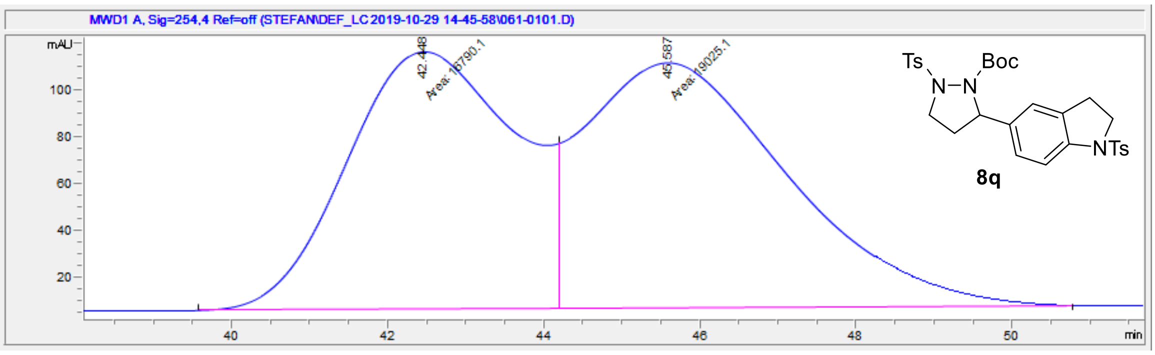
#	Time	Area	Height	Width	Area%	Symmetry
1	30.684	2487.5	23.4	1.5484	50.222	0.651
2	40.17	2465.5	17.7	1.6708	49.778	0.63



#	Time	Area	Height	Width	Area%	Symmetry
1	34.651	437.3	3.7	1.4013	3.839	0.613
2	43.231	10953.7	53.1	3.4409	96.161	0.733

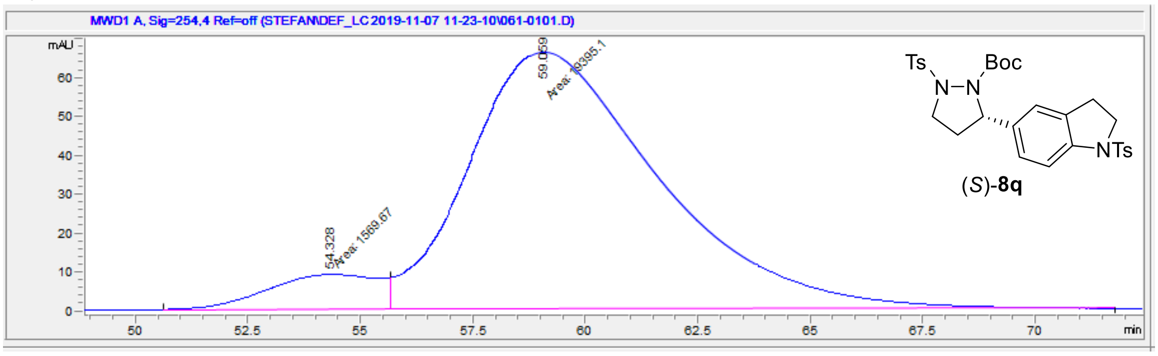
HPLC profile of **8q**

Chiralpak OD-H column (0.46 cm ø x 25 cm), 90:10 hexane:propan-2-ol, T = 25°C, flow rate = 1.0 mL/min.



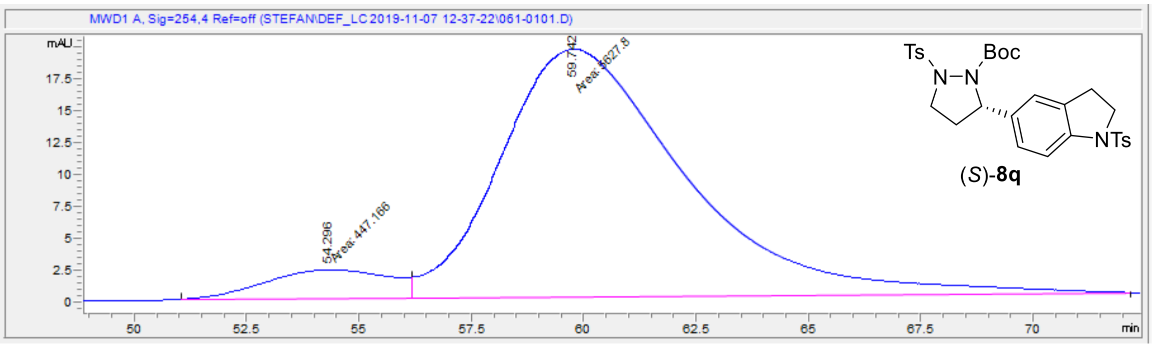
#	Time	Area	Height	Width	Area%	Symmetry
1	42.448	16790.1	110.7	2.5269	46.880	0
2	45.587	19025.1	105.6	3.0041	53.120	0.648

Cyclisation with DEAD



#	Time	Area	Height	Width	Area%	Symmetry
1	54.328	1569.7	9	2.8925	7.487	0
2	59.059	19395.1	66.3	4.8778	92.513	0.632

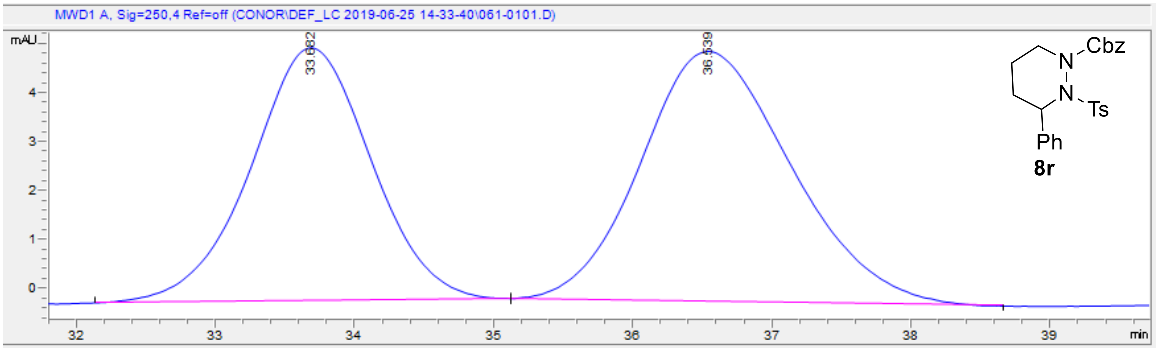
Cyclisation with DIAD

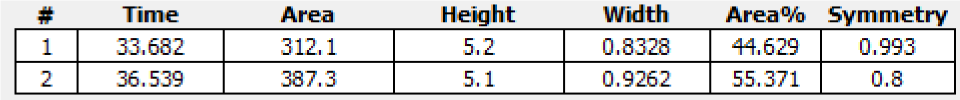


#	Time	Area	Height	Width	Area%	Symmetry
1	54.296	447.2	2.3	3.2436	7.361	1.02
2	59.742	5627.8	19.5	4.8176	92.639	0.617

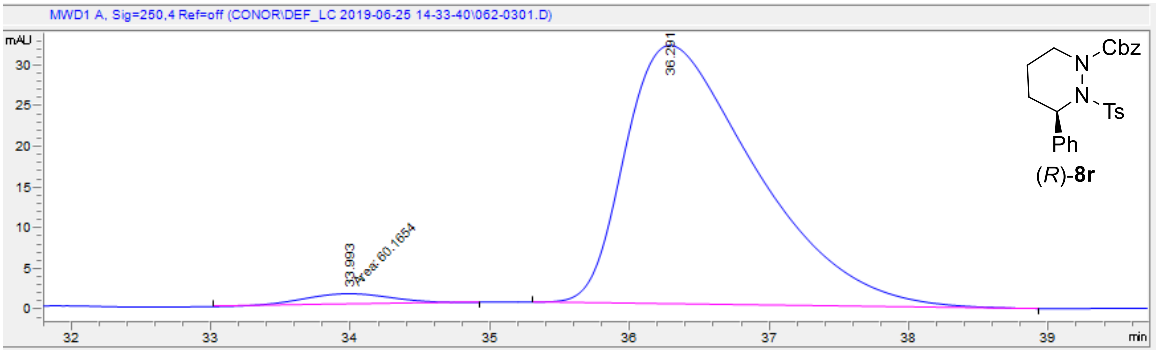
HPLC profile of compound **8r**

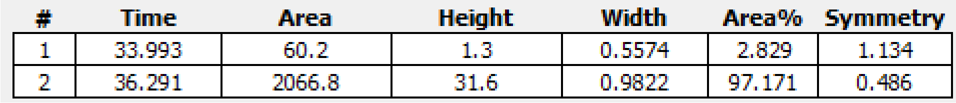
Chiralpak IA column (0.46 cm ø x 25 cm) 98.5:1.5 hexane:propan-2-ol, T = 25 °C, flow rate 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	33.682	312.1	5.2	0.8328	44.629	0.993
2	36.539	387.3	5.1	0.9262	55.371	0.8

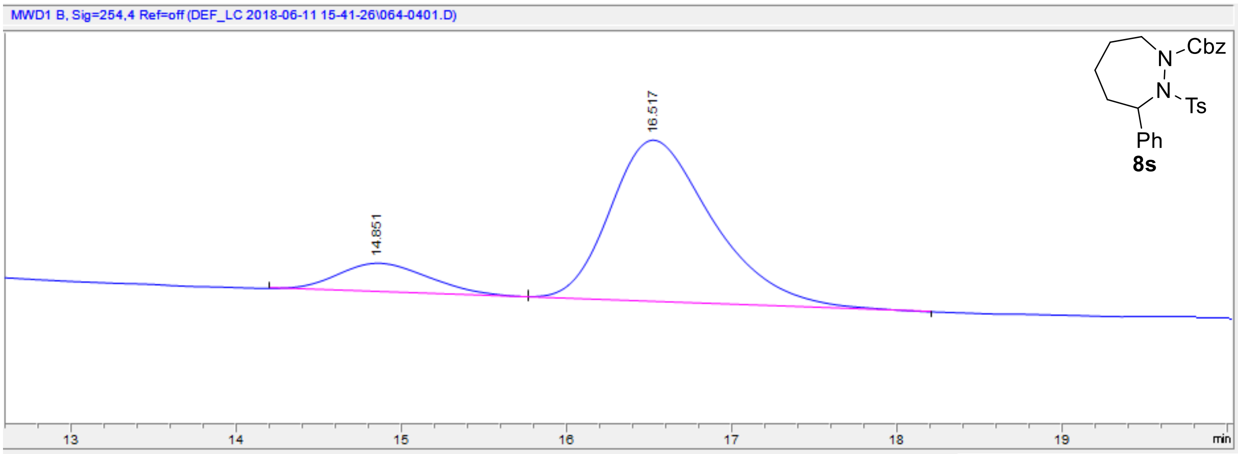




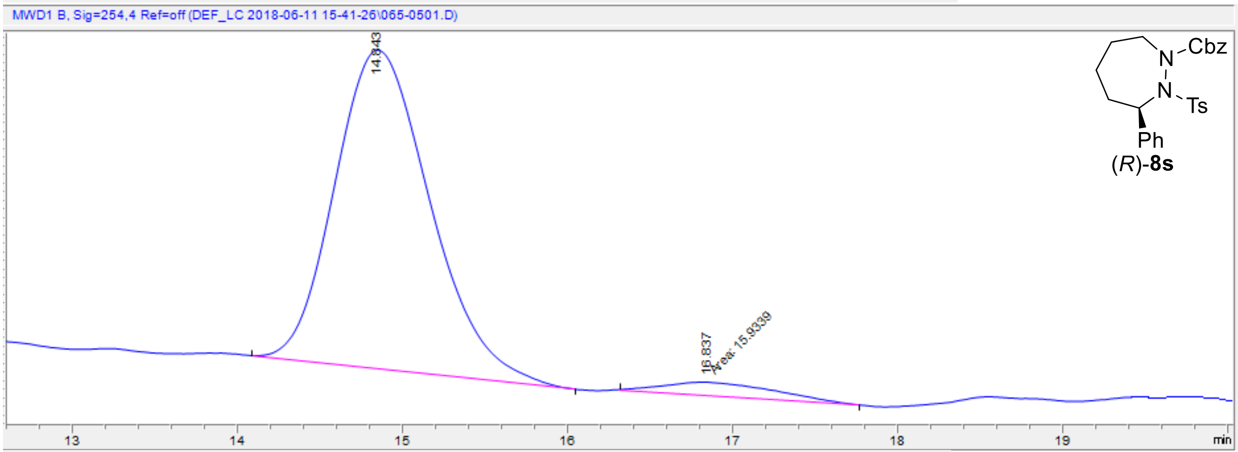
#	Time	Area	Height	Width	Area%	Symmetry
1	33.993	60.2	1.3	0.5574	2.829	1.134
2	36.291	2066.8	31.6	0.9822	97.171	0.486

HPLC profile of compound **8s**

Chiralpak OD-H column (0.46 cm ø x 25 cm) 98:2 hexane:propan-2-ol, T = 25 °C, flow rate 1.0 mL/min.



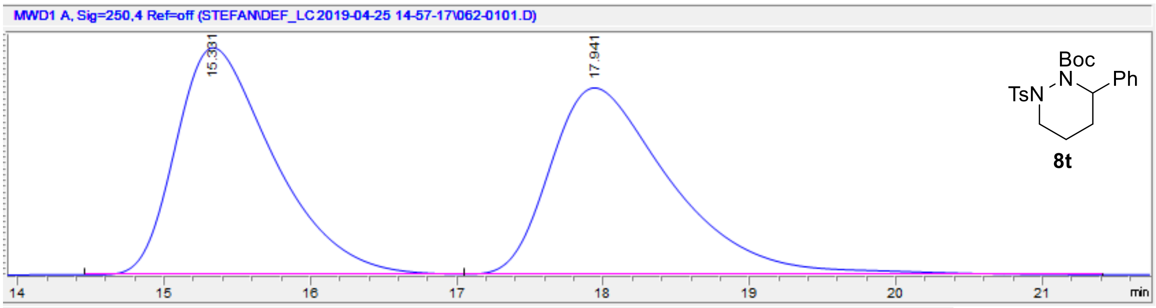
#	Time	Area	Height	Width	Area%	Symmetry
1	14.851	179	4.5	0.5799	13.977	0.734
2	16.517	1101.5	25.3	0.6579	86.023	0.681



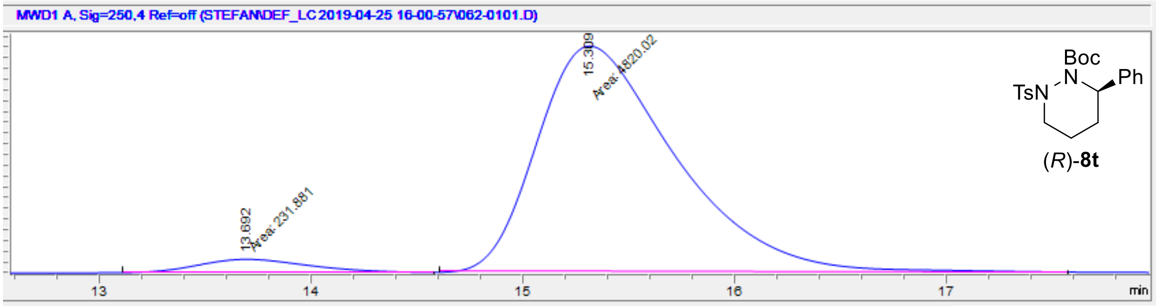
#	Time	Area	Height	Width	Area%	Symmetry
1	14.843	296.8	7.4	0.6006	94.905	0.778
2	16.837	15.9	3.2E-1	0.8188	5.095	0.543

HPLC profile of **8t**

Chiralpak OD-H column (0.46 cm ø x 25 cm), 98:2 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



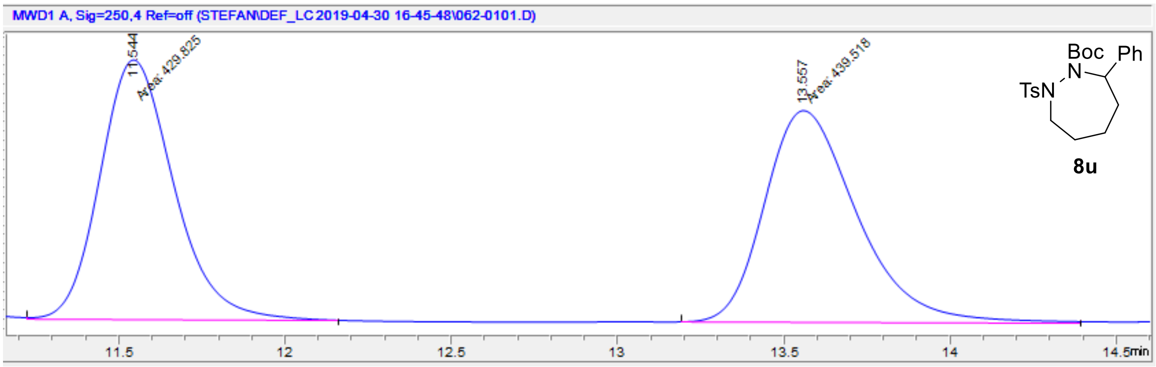
#	Time	Area	Height	Width	Area%	Symmetry
1	15.331	3650	78.2	0.7048	49.564	0.581
2	17.941	3714.2	64.3	0.8636	50.436	0.543



#	Time	Area	Height	Width	Area%	Symmetry
1	13.692	231.9	6.2	0.6204	4.590	0.708
2	15.309	4820	105.4	0.7621	95.410	0.588

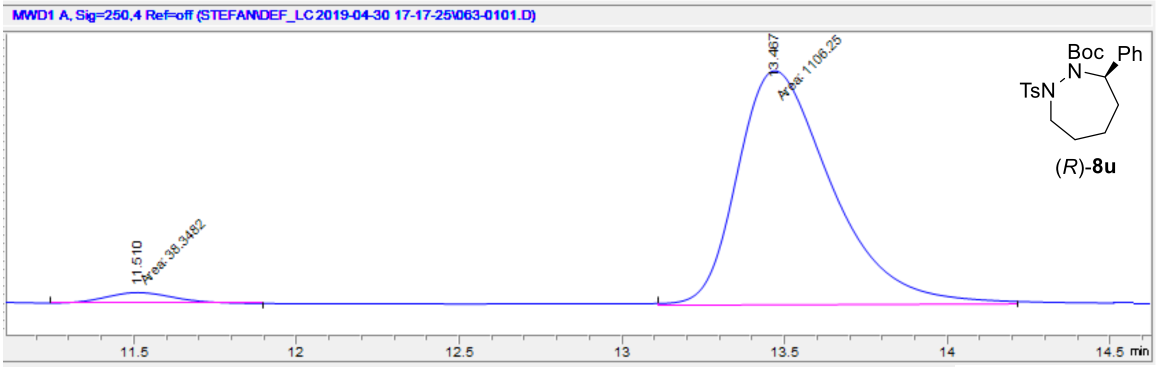
HPLC profile of **8u**

Chiralpak IA column (0.46 cm ø x 25 cm), 98:2 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.



8u

#	Time	Area	Height	Width	Area%	Symmetry
1	11.544	429.8	27.7	0.259	49.442	0.803
2	13.557	439.5	22.5	0.3251	50.558	0.698

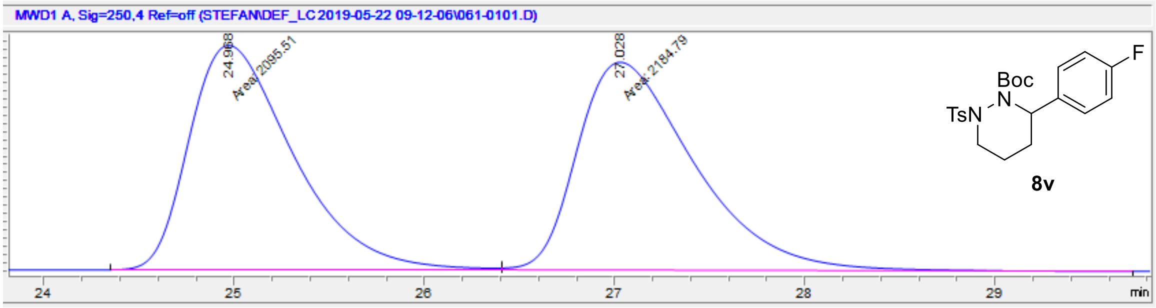


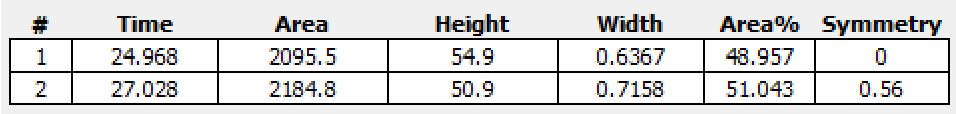
(*R*)-**8u**

#	Time	Area	Height	Width	Area%	Symmetry
1	11.51	38.3	2.5	0.2524	3.350	0.825
2	13.467	1106.3	54.8	0.3362	96.650	0.633

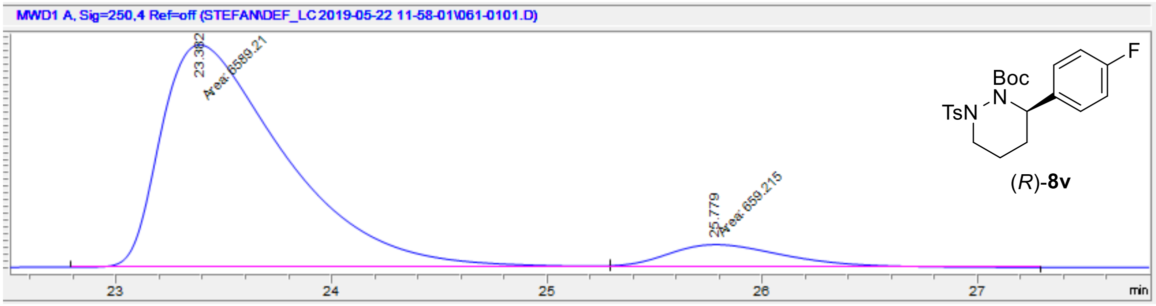
HPLC profile of **8v**

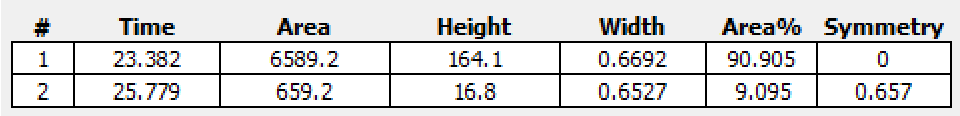
Chiralpak IA column (0.46 cm ø x 25 cm), 99.2:0.8 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	24.968	2095.5	54.9	0.6367	48.957	0
2	27.028	2184.8	50.9	0.7158	51.043	0.56



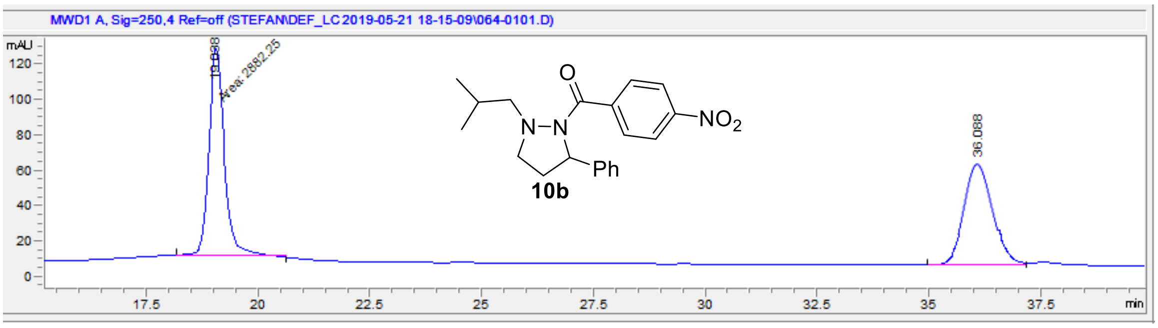


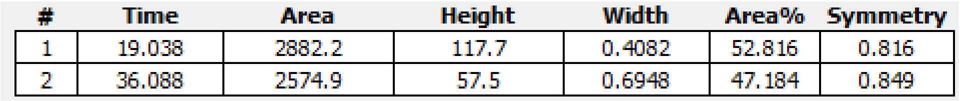
#	Time	Area	Height	Width	Area%	Symmetry
1	23.382	6589.2	164.1	0.6692	90.905	0
2	25.779	659.2	16.8	0.6527	9.095	0.657

HPLC profiles of functionalised hydrazines **10b**, **10d** and **10i and 10o**

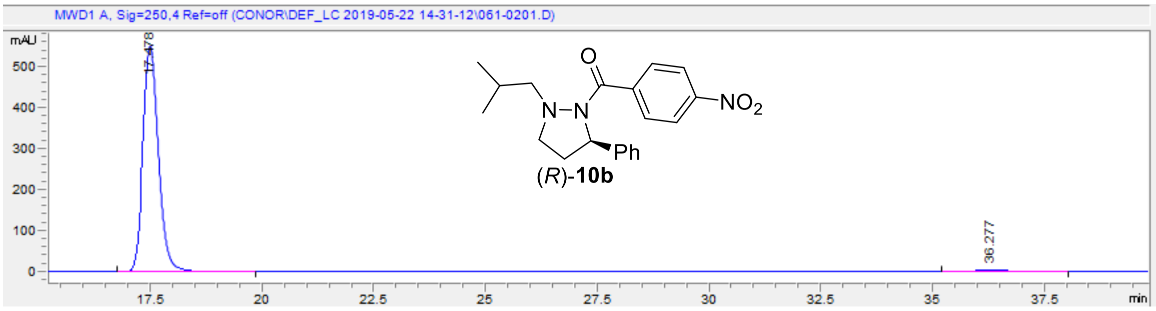
HPLC profile of compound **10b**

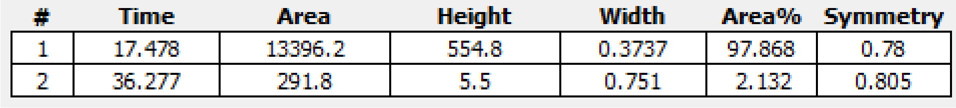
Chiralpak IA (0.46 cm ø x 25 cm) column, 90:10 Hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	19.038	2882.2	117.7	0.4082	52.816	0.816
2	36.088	2574.9	57.5	0.6948	47.184	0.849

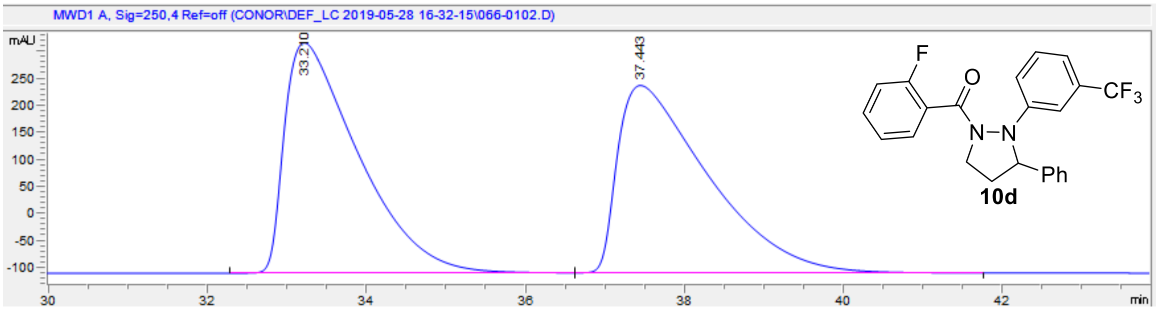


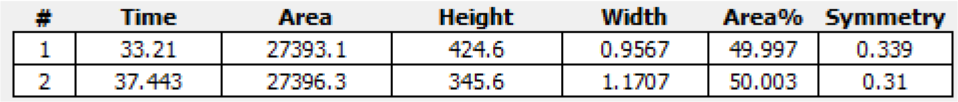


#	Time	Area	Height	Width	Area%	Symmetry
1	17.478	13396.2	554.8	0.3737	97.868	0.78
2	36.277	291.8	5.5	0.751	2.132	0.805

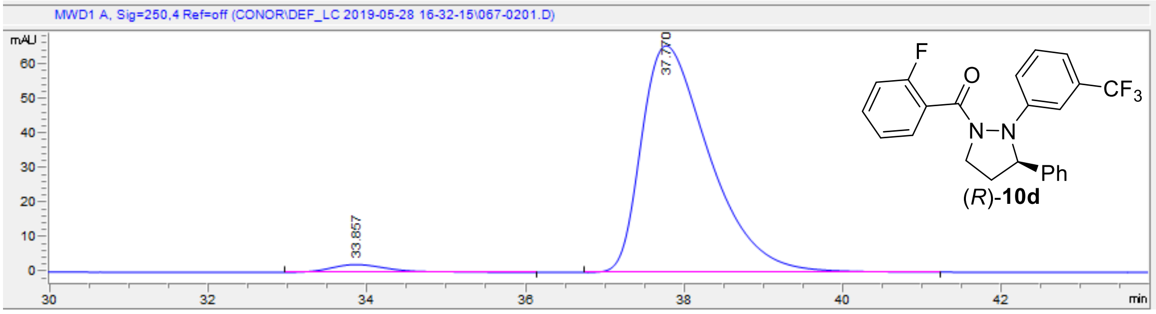
HPLC profile of compound **10d**

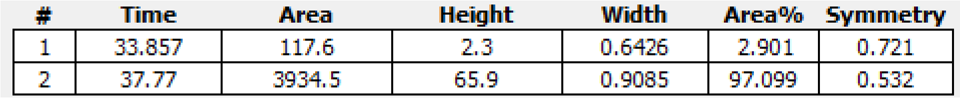
Chiralpak IA column (0.46 cm ø x 25 cm), 99:1 hexane:propan-2-ol, T = 25 °C, flow rate 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	33.21	27393.1	424.6	0.9567	49.997	0.339
2	37.443	27396.3	345.6	1.1707	50.003	0.31

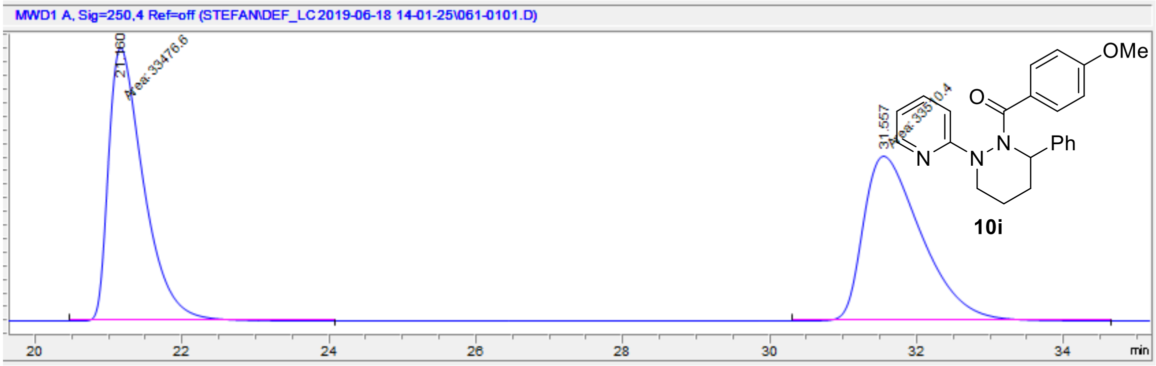


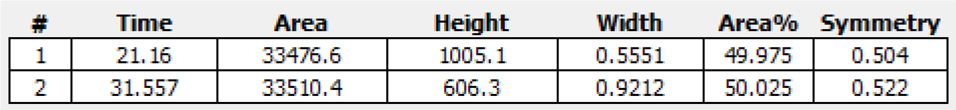


#	Time	Area	Height	Width	Area%	Symmetry
1	33.857	117.6	2.3	0.6426	2.901	0.721
2	37.77	3934.5	65.9	0.9085	97.099	0.532

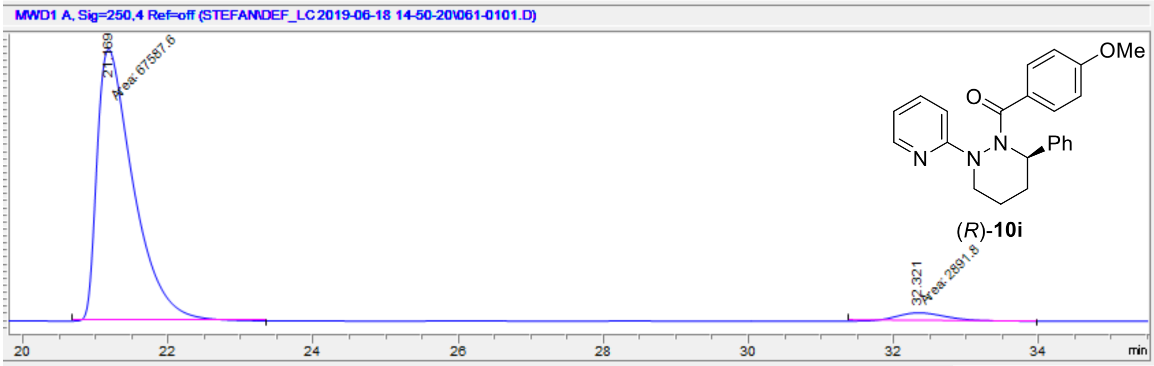
HPLC profile of **10i**

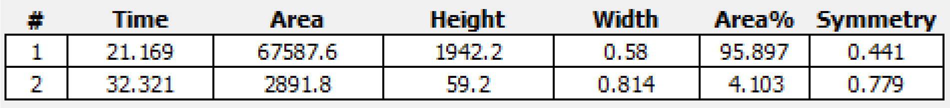
Chiralpak IA column (0.46 cm ø x 25 cm), 96:4 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.





#	Time	Area	Height	Width	Area%	Symmetry
1	21.16	33476.6	1005.1	0.5551	49.975	0.504
2	31.557	33510.4	606.3	0.9212	50.025	0.522

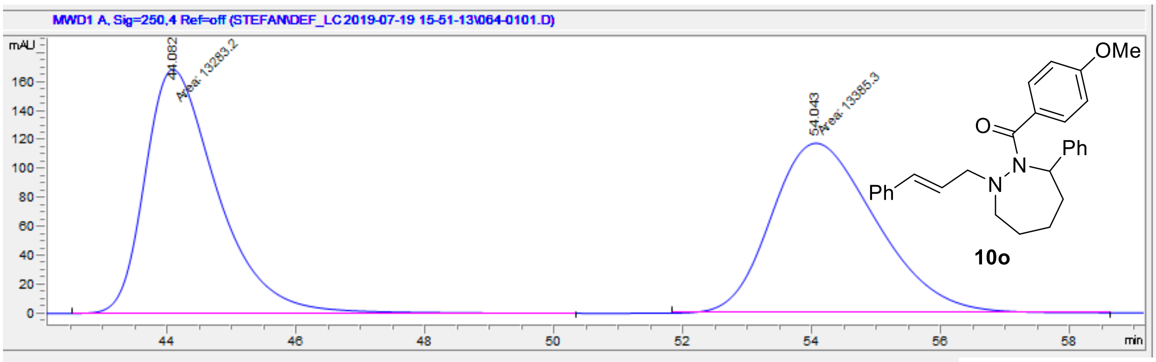




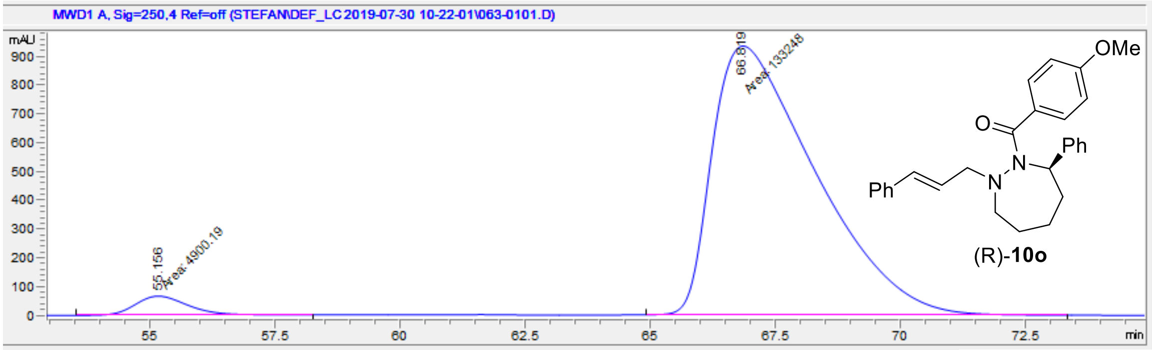
#	Time	Area	Height	Width	Area%	Symmetry
1	21.169	67587.6	1942.2	0.58	95.897	0.441
2	32.321	2891.8	59.2	0.814	4.103	0.779

HPLC profile of **10o**

Chiralpak OD-H column (0.46 cm ø x 25 cm), 98:2 hexane:propan-2-ol, T = 25 °C, flow rate = 1.0 mL/min.

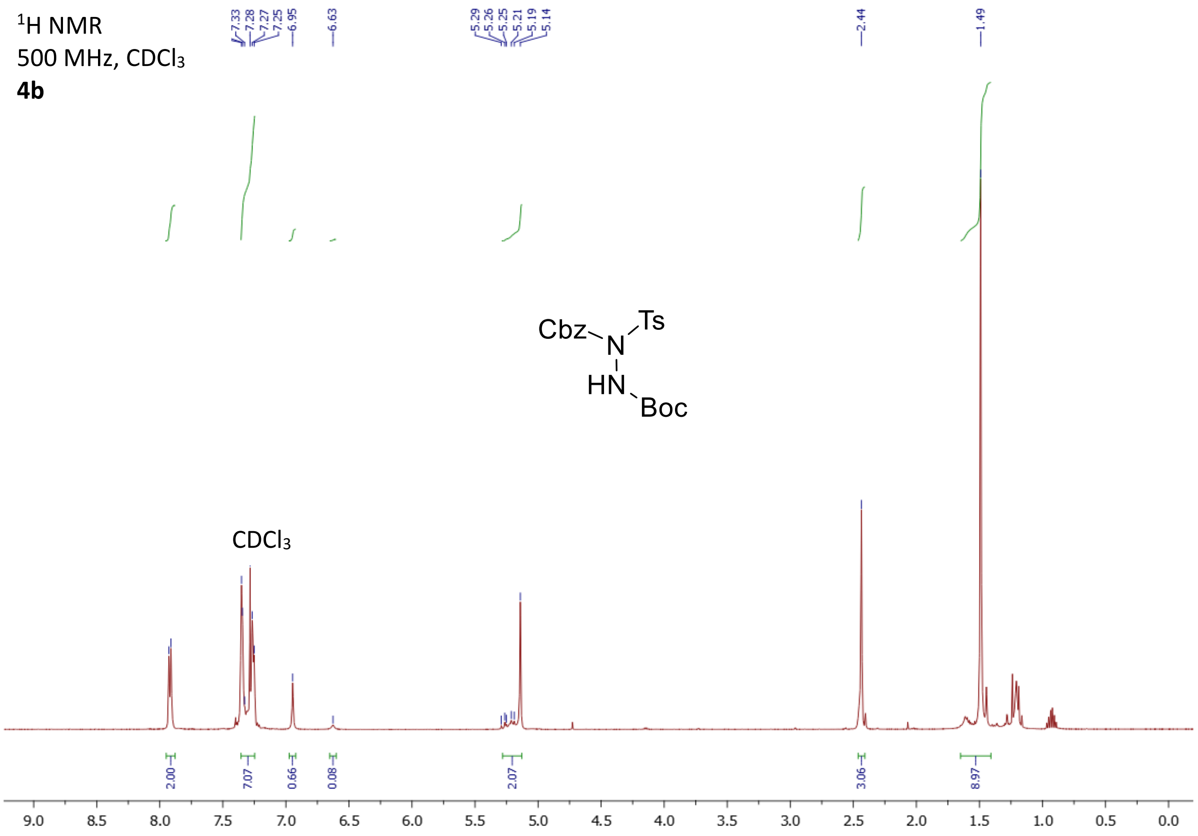


#	Time	Area	Height	Width	Area%	Symmetry
1	44.082	13283.2	169.6	1.305	49.808	0.601
2	54.043	13385.3	118.1	1.8895	50.192	0.722

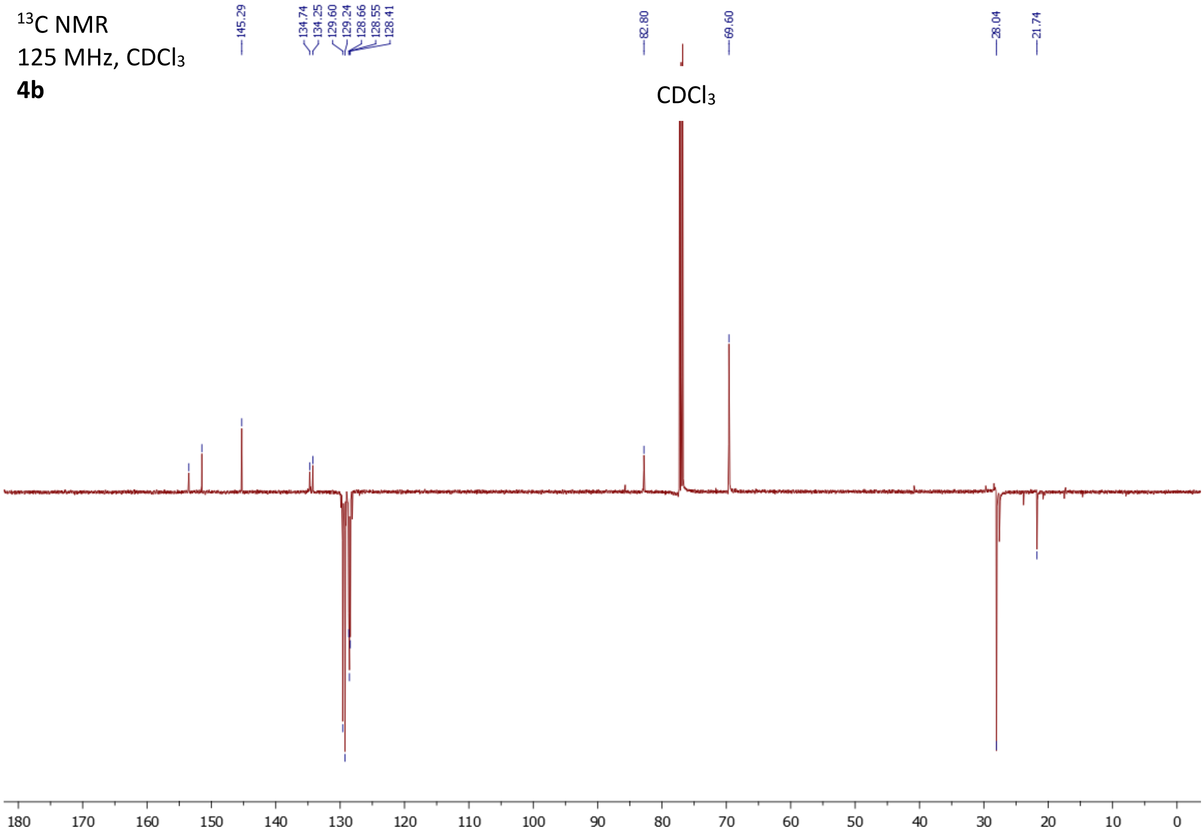


#	Time	Area	Height	Width	Area%	Symmetry
1	55.156	4900.2	66.1	1.2349	3.547	0.744
2	66.819	133248	932.6	2.3814	96.453	0.415

^{1}H and ^{13}C NMR Spectra of 4b, 5a-v, 6a-v, 8a-v, 10a-q and 12

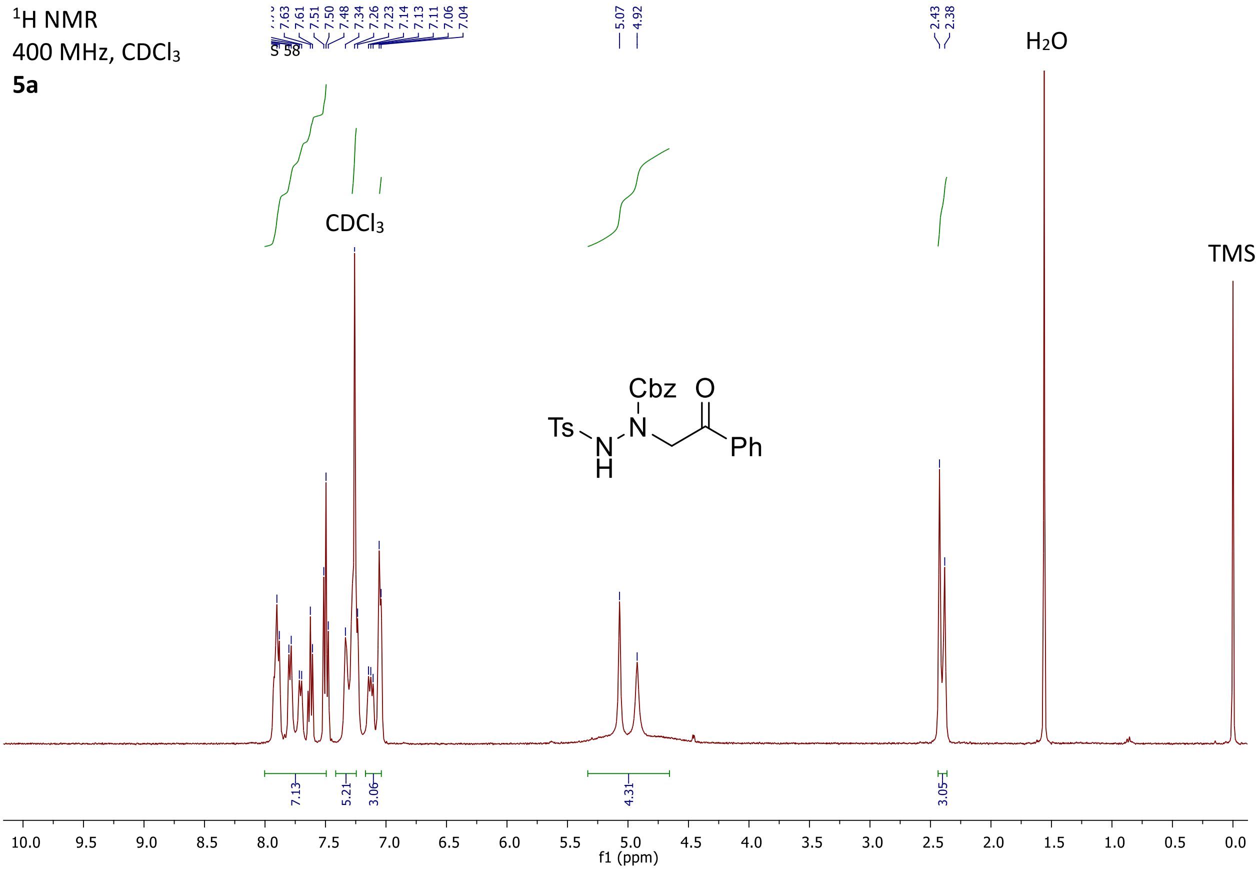


^{1}H NMR
500 MHz, $CDCl_3$
4b

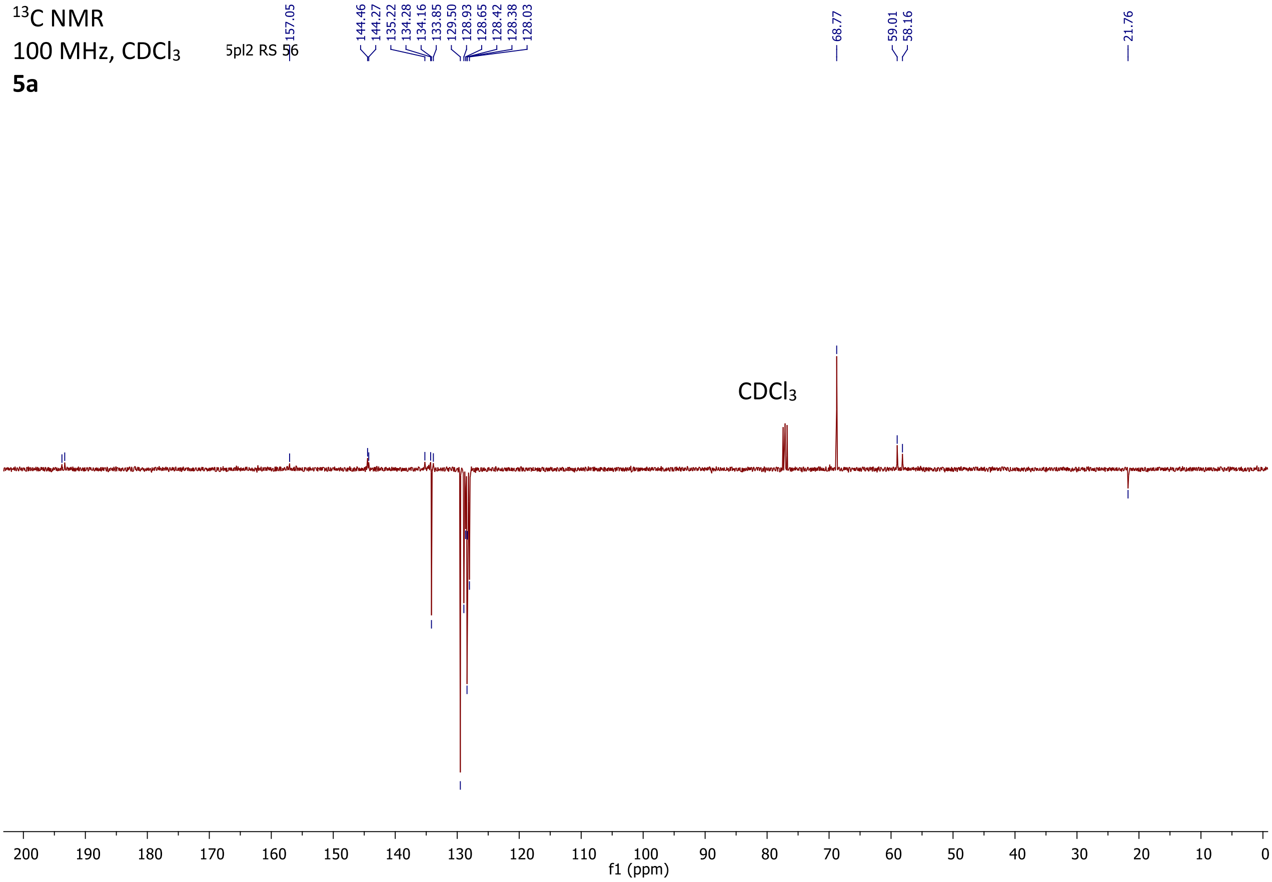


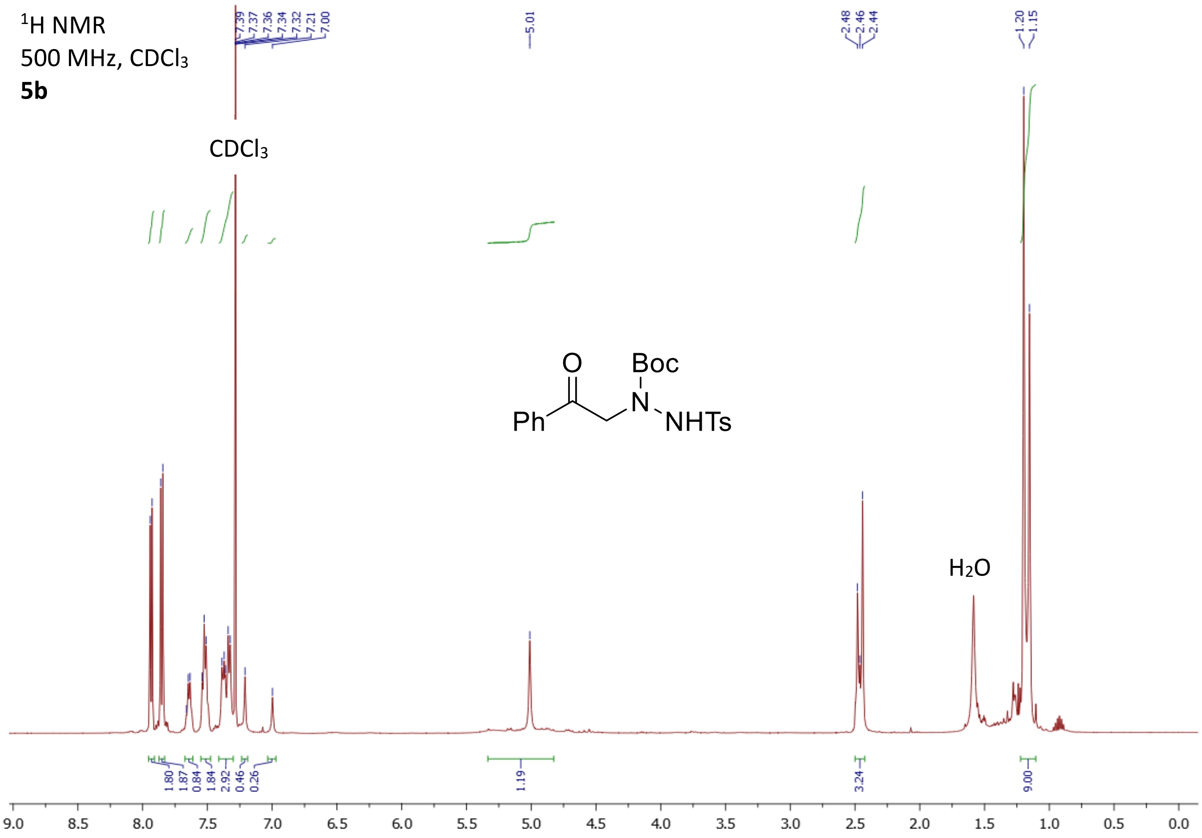
^{13}C NMR
125 MHz, $CDCl_3$
4b

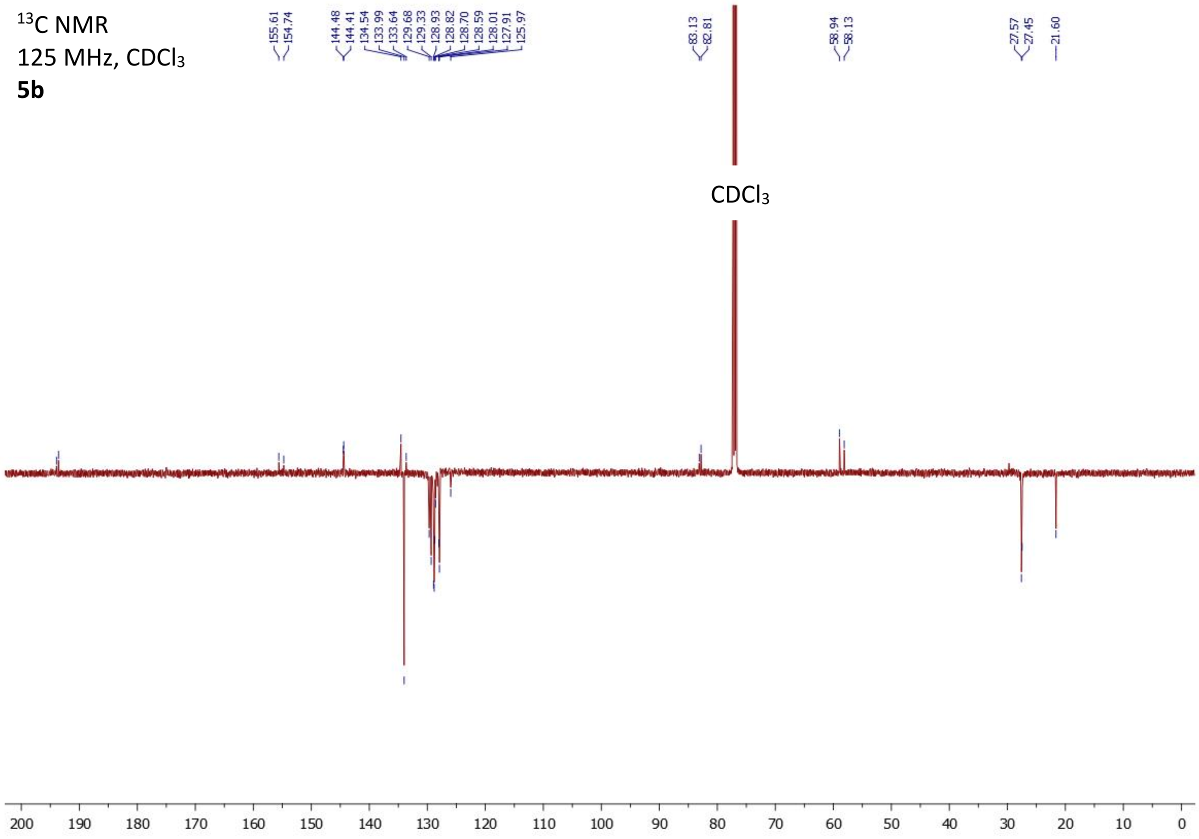
^{1}H NMR
400 MHz, $CDCl_3$
5a



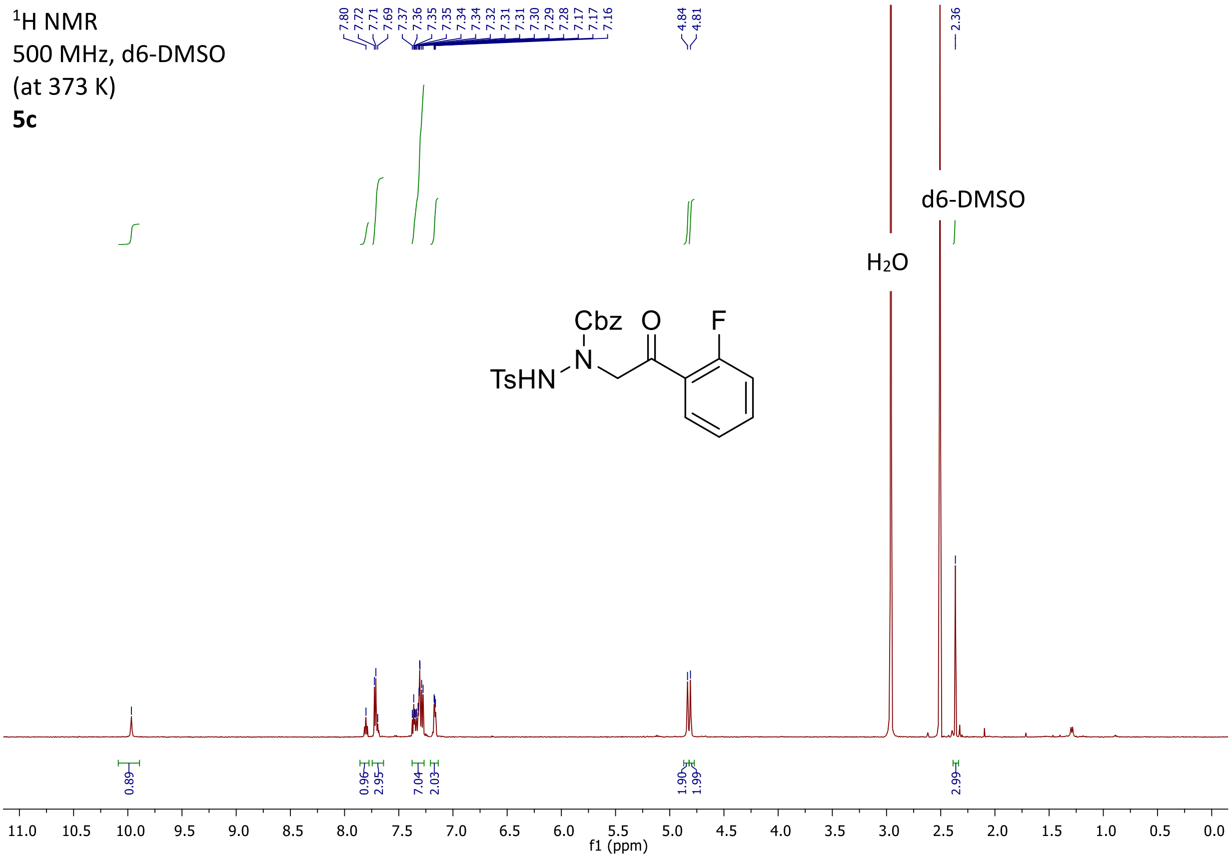
^{13}C NMR
100 MHz, $CDCl_3$
5a



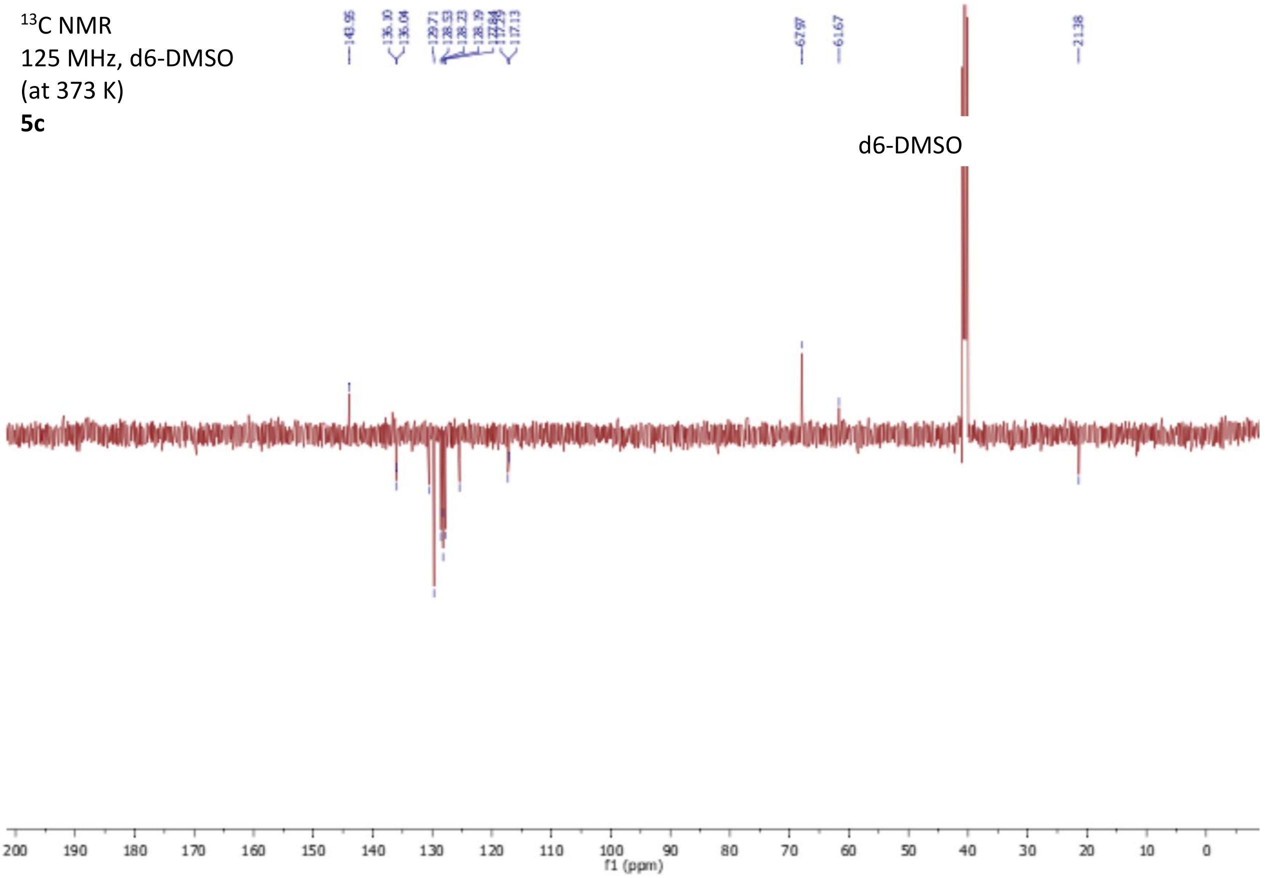

^{1}H NMR
500 MHz, CDCl$_3$
5b
7.39
7.37
7.36
7.34
7.32
7.21
7.00
5.01
2.48
2.46
2.44
1.20
1.15
CDCl$_3$
O
Boc
N
Ph
NHTs
H$_2$O
1.80
1.87
0.84
1.84
2.92
0.46
0.26
1.19
3.24
9.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

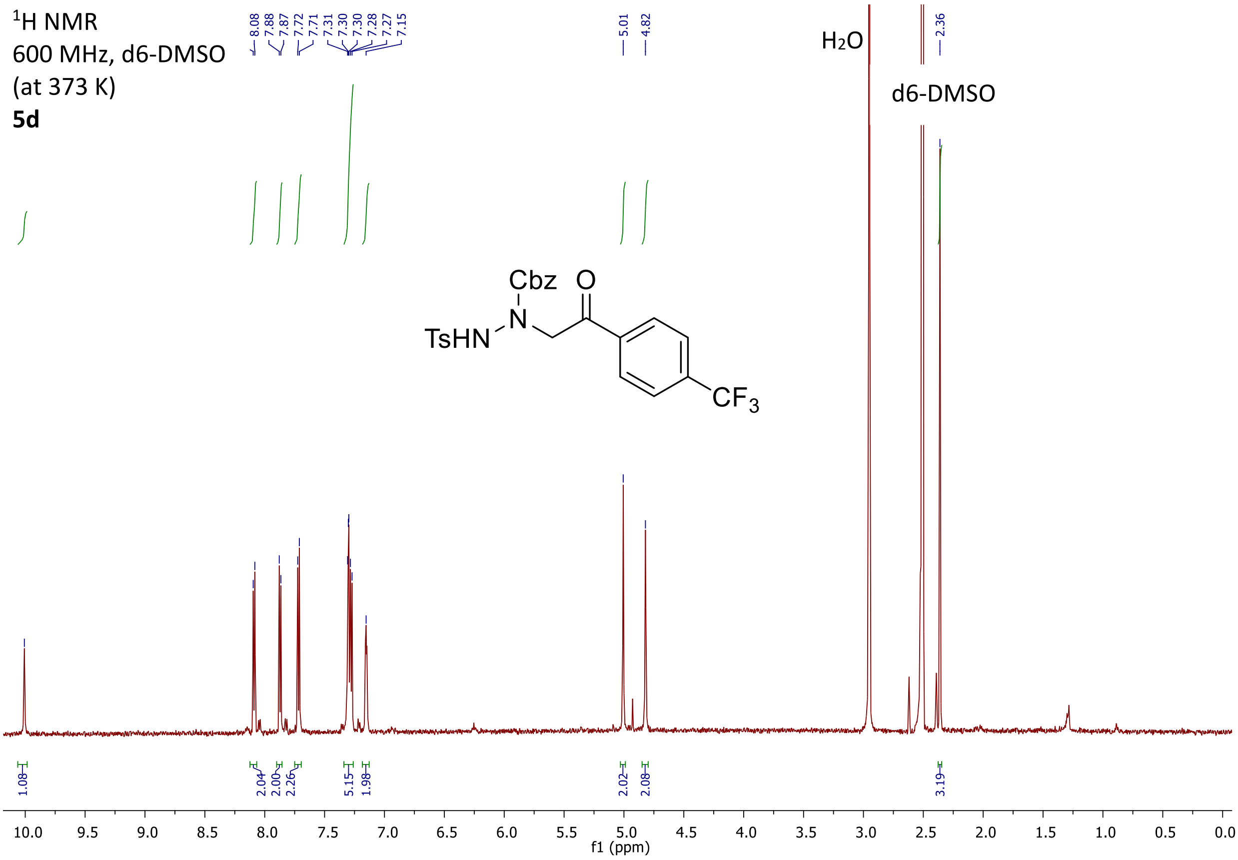

^{13}C NMR
125 MHz, CDCl$_3$
5b
155.61
154.74
144.48
144.41
134.54
133.99
133.64
129.68
129.33
128.93
128.82
128.70
128.59
128.01
127.91
125.97
83.13
82.81
58.94
58.13
27.57
27.45
21.60
CDCl$_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

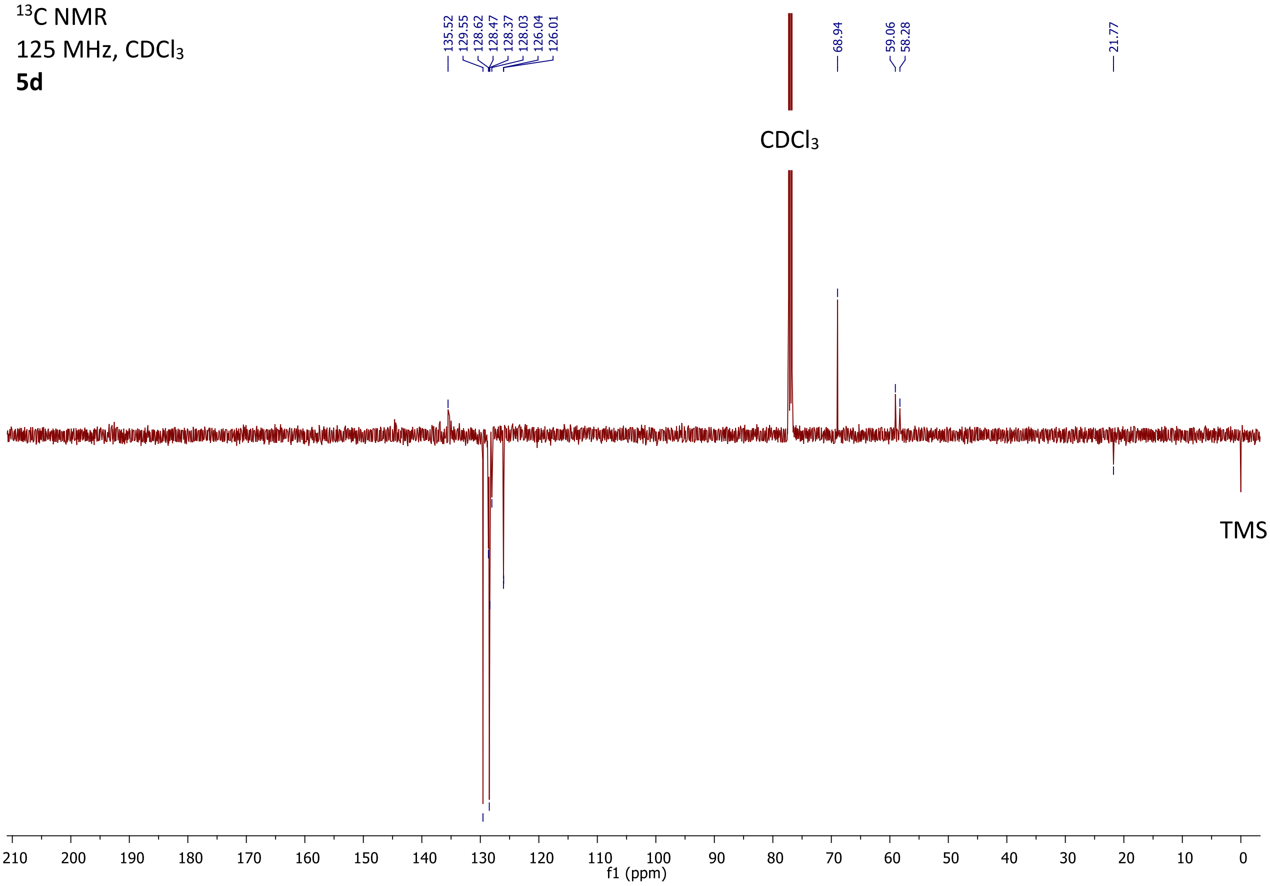
^{1}H NMR
500 MHz, d6-DMSO
(at 373 K)
5c

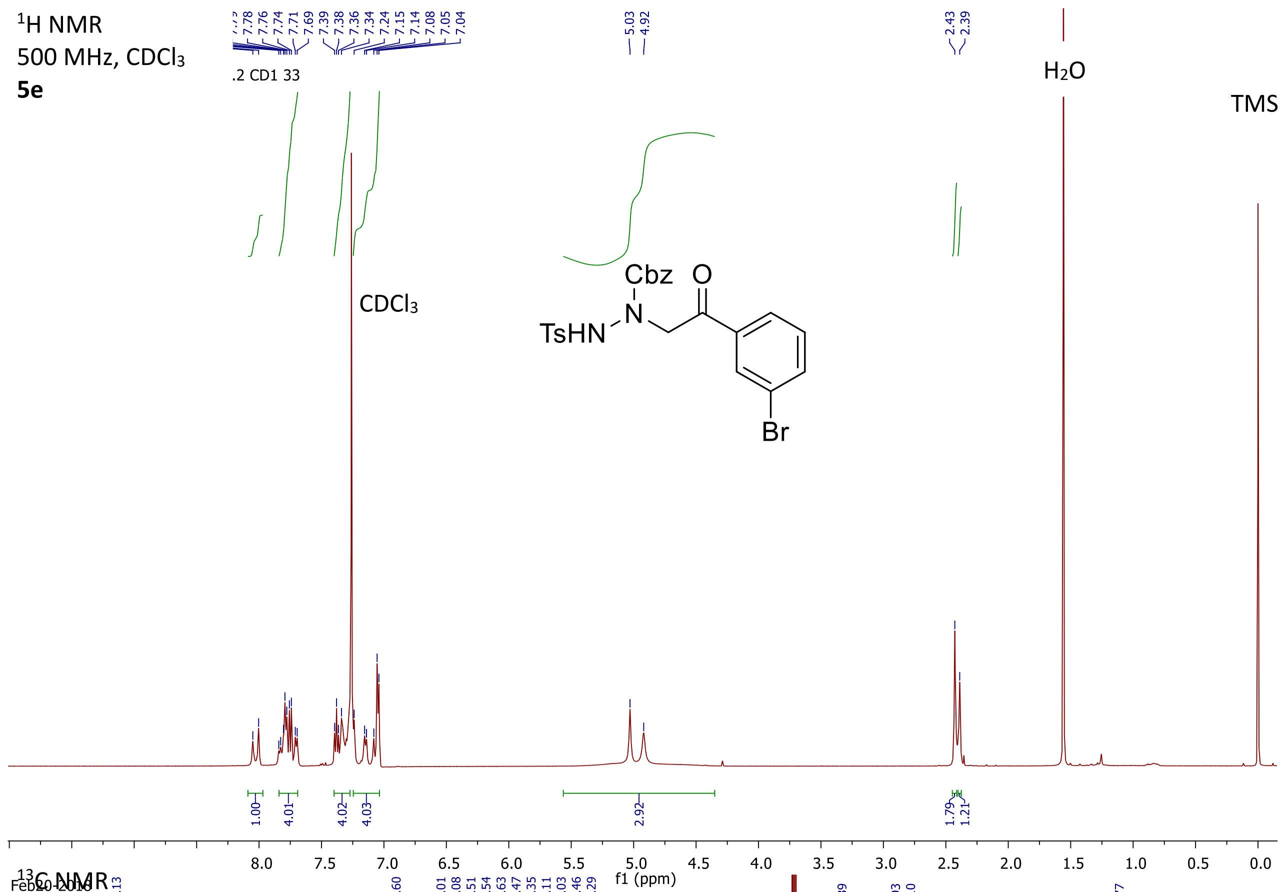


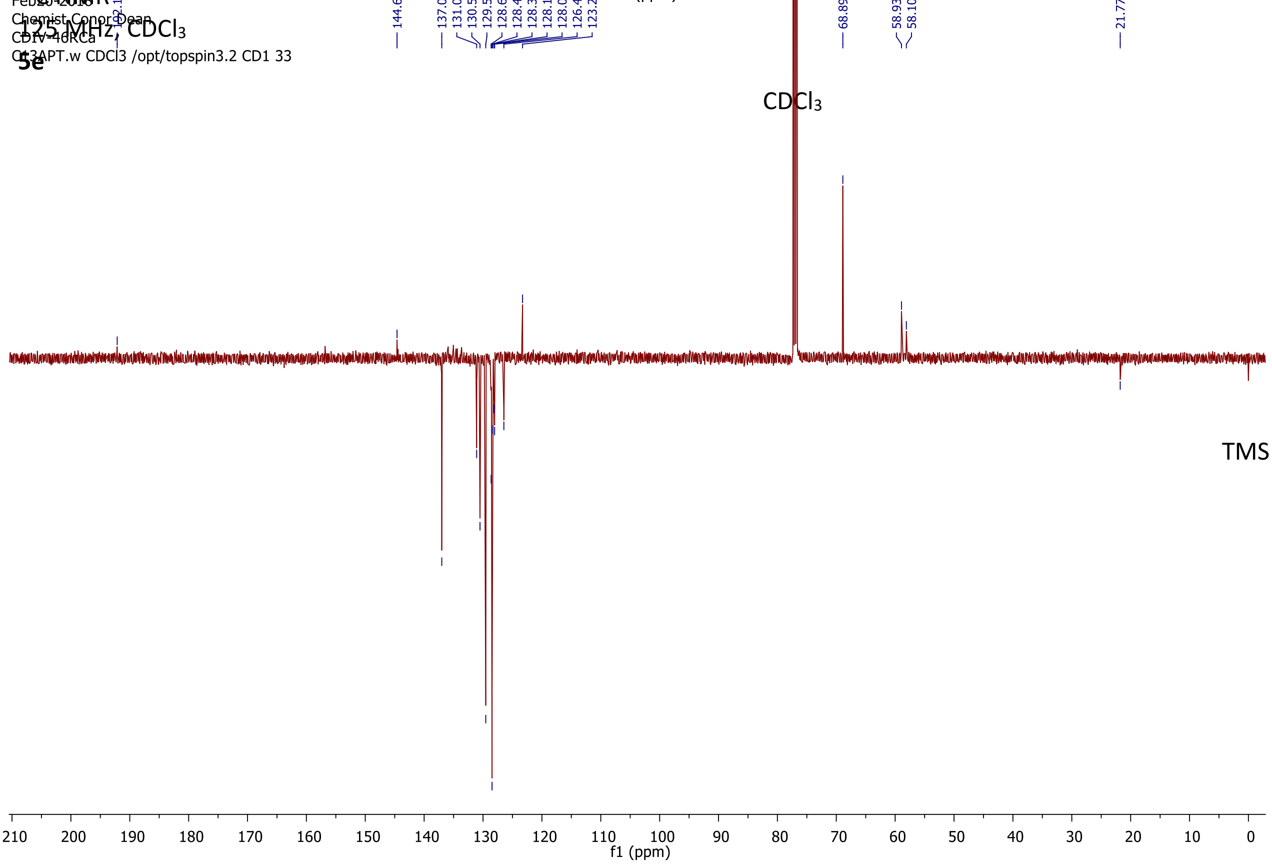
^{13}C NMR
125 MHz, d6-DMSO
(at 373 K)
5c



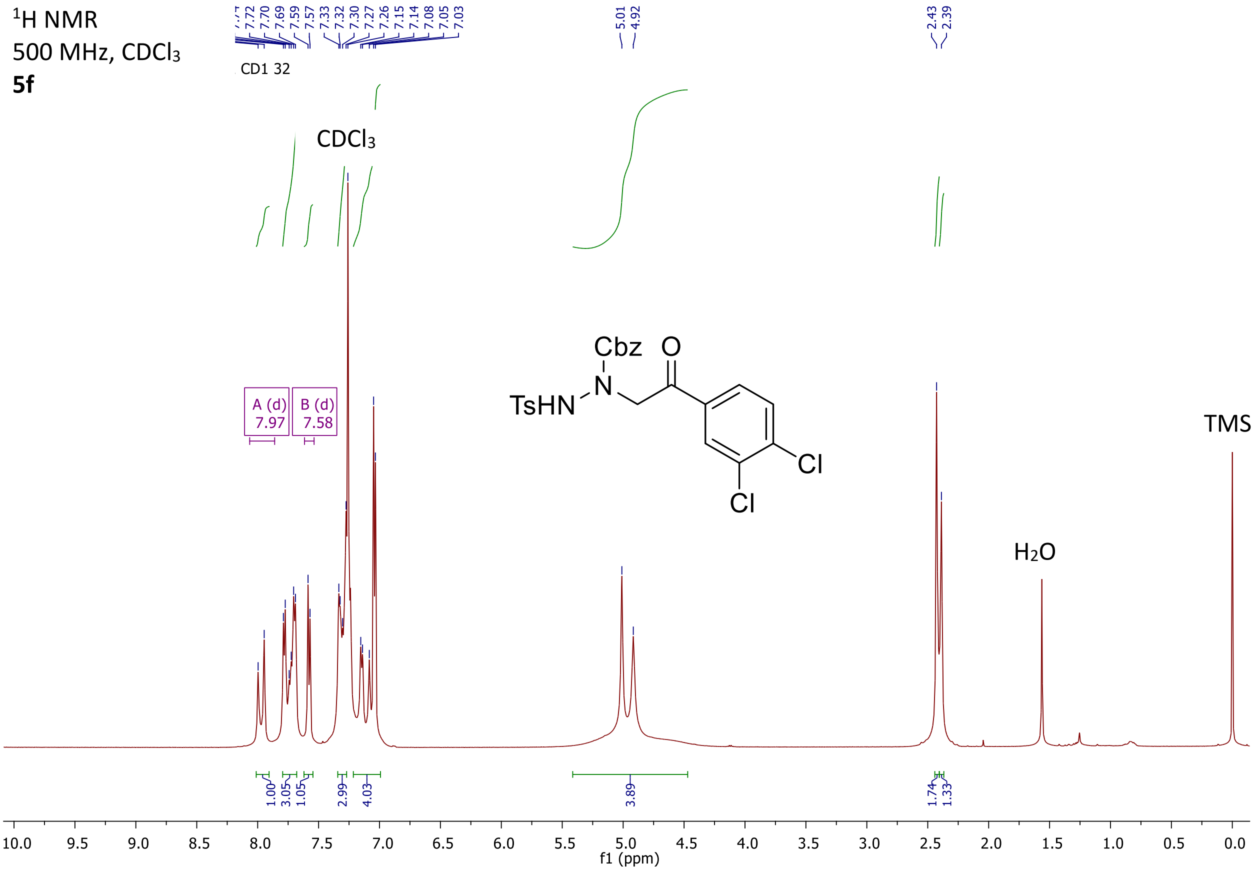

^{1}H NMR
600 MHz, d6-DMSO
(at 373 K)
5d
8.08
7.88
7.87
7.72
7.71
7.31
7.30
7.28
7.27
7.15
5.01
4.82
2.36
H₂O
d6-DMSO
Cbz
O
N
TsHN
CF₃
1.08
2.04
2.00
2.26
5.15
1.98
2.02
2.08
3.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


^{13}C NMR
125 MHz, CDCl₃
5d
135.52
129.55
128.62
128.47
128.37
128.03
126.04
126.01
68.94
59.06
58.28
21.77
CDCl₃
TMS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

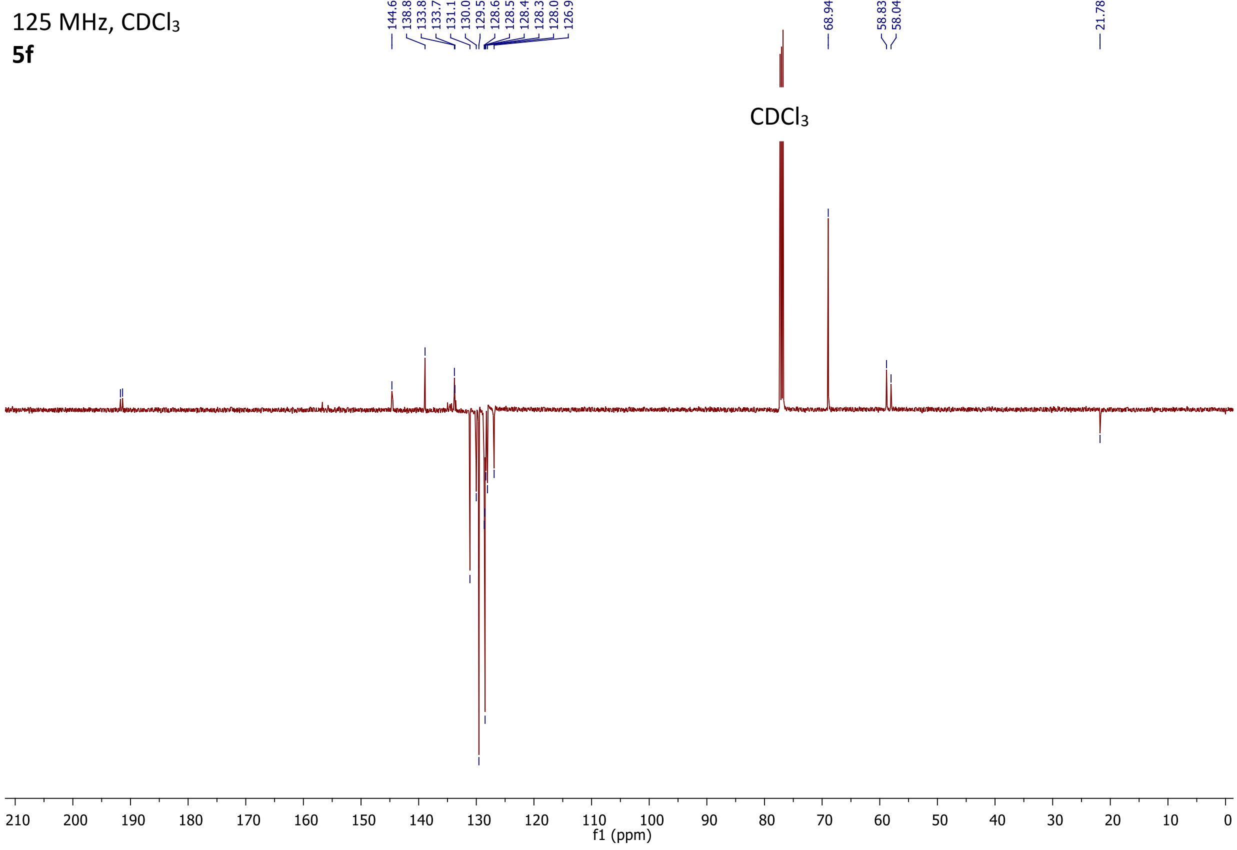

^{1}H NMR
500 MHz, CDCl$_3$
5e
.2 CD1 33
7.78
7.76
7.74
7.71
7.69
7.39
7.38
7.36
7.34
7.24
7.15
7.14
7.08
7.05
7.04
5.03
4.92
2.43
2.39
H$_2$O
TMS
CDCl$_3$
Cbz
O
N
TsHN
Br
1.00
4.01
4.02
4.03
2.92
1.79
1.21
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

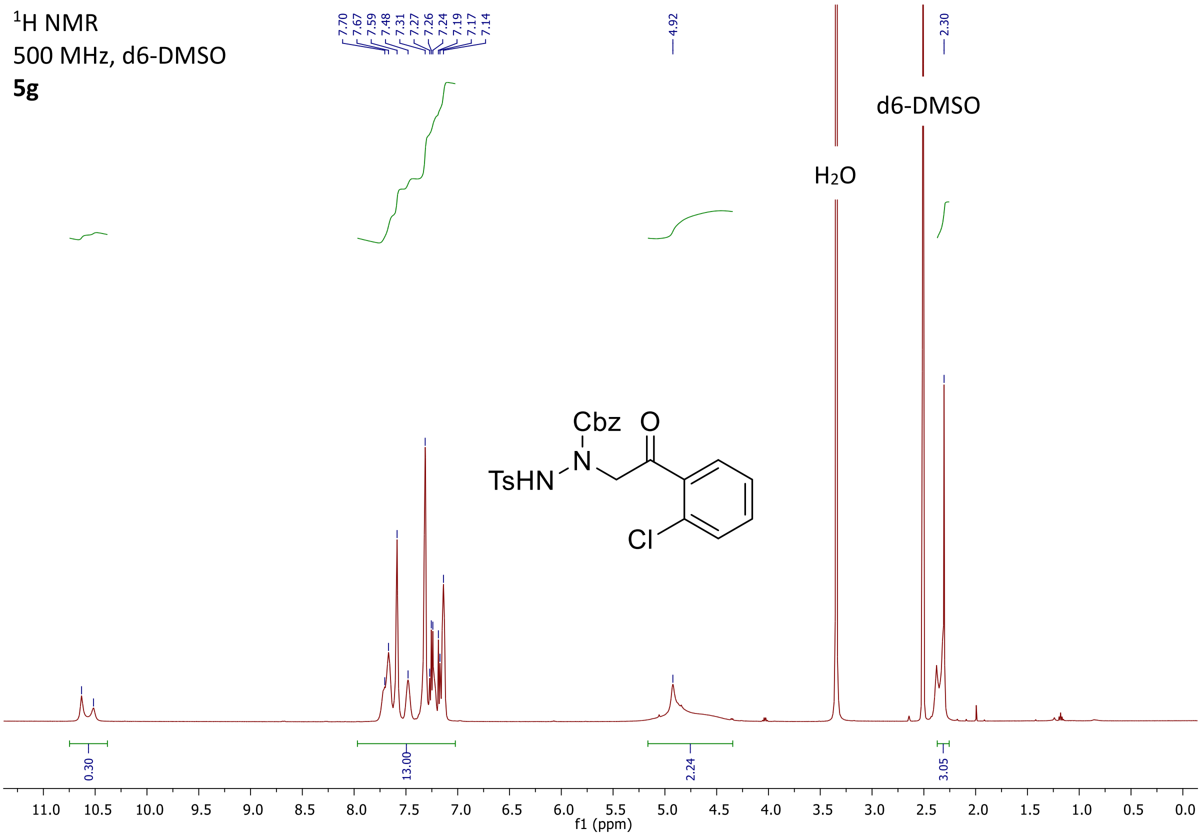

^{13}C NMR
125 MHz, CDCl$_3$
5e
Feb20-2016
Chemist Conor Dean
CD1V-46RCa
C13APT.w CDCl3 /opt/topspin3.2 CD1 33
192.13
144.60
137.01
131.08
130.51
129.54
128.63
128.47
128.35
128.11
128.03
126.46
123.29
68.89
58.93
58.10
21.77
CDCl$_3$
TMS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

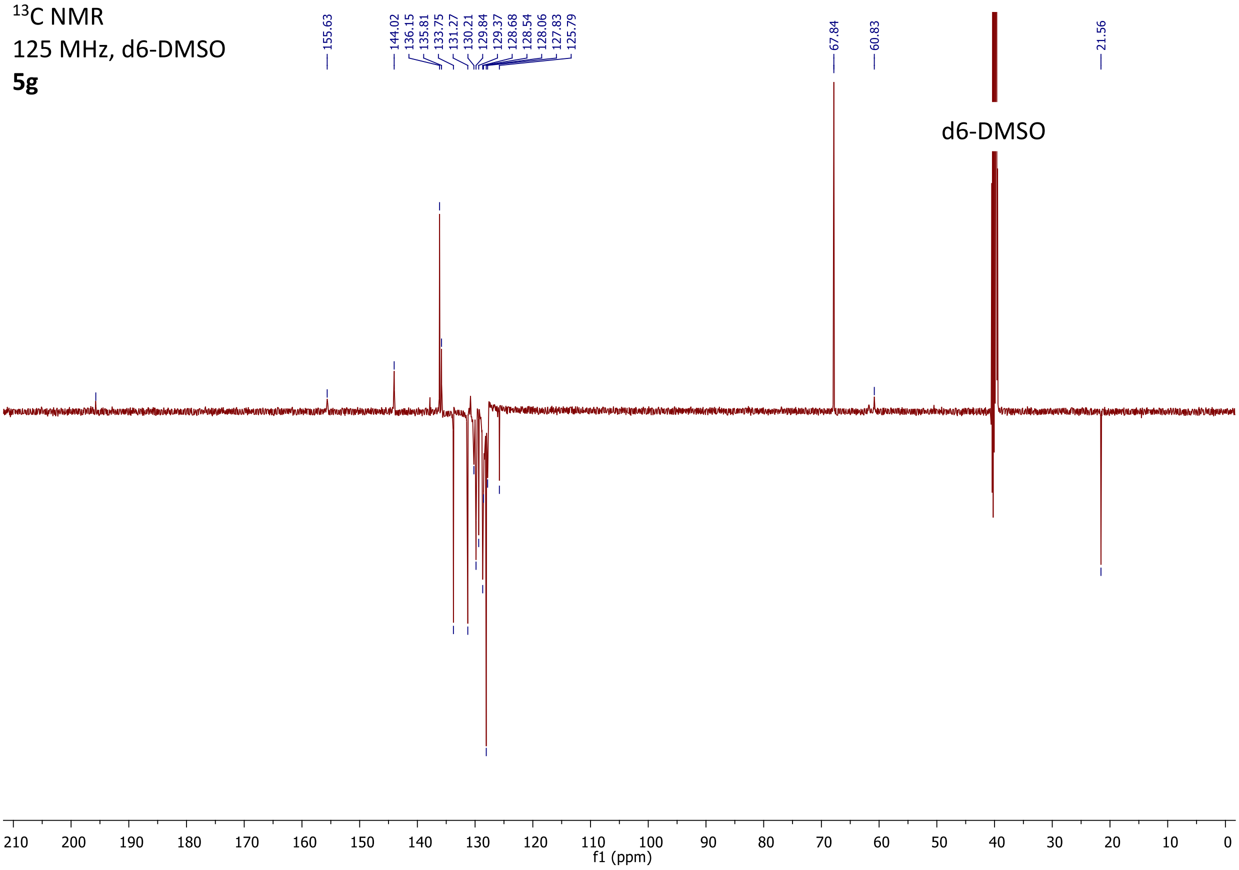
^{1}H NMR
500 MHz, $CDCl_3$
5f



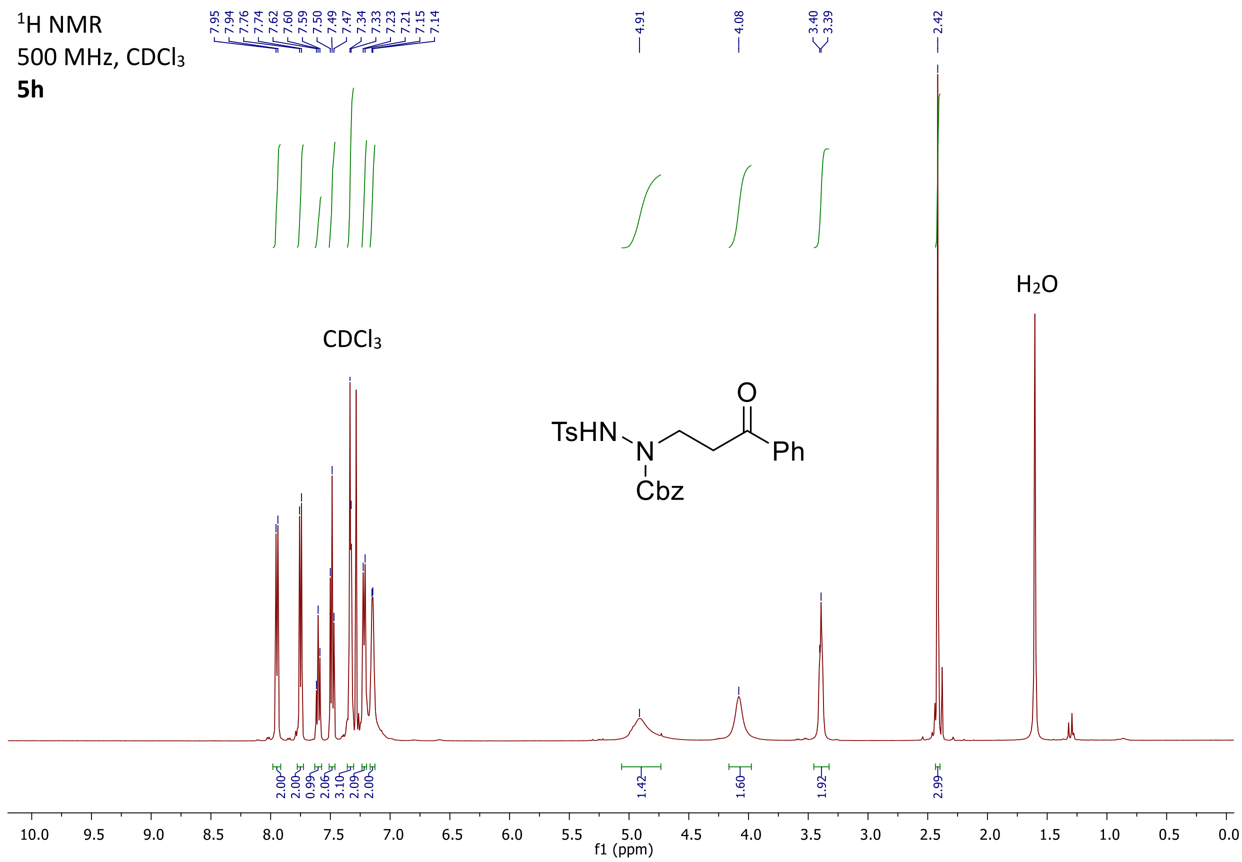
^{13}C NMR
125 MHz, $CDCl_3$
5f



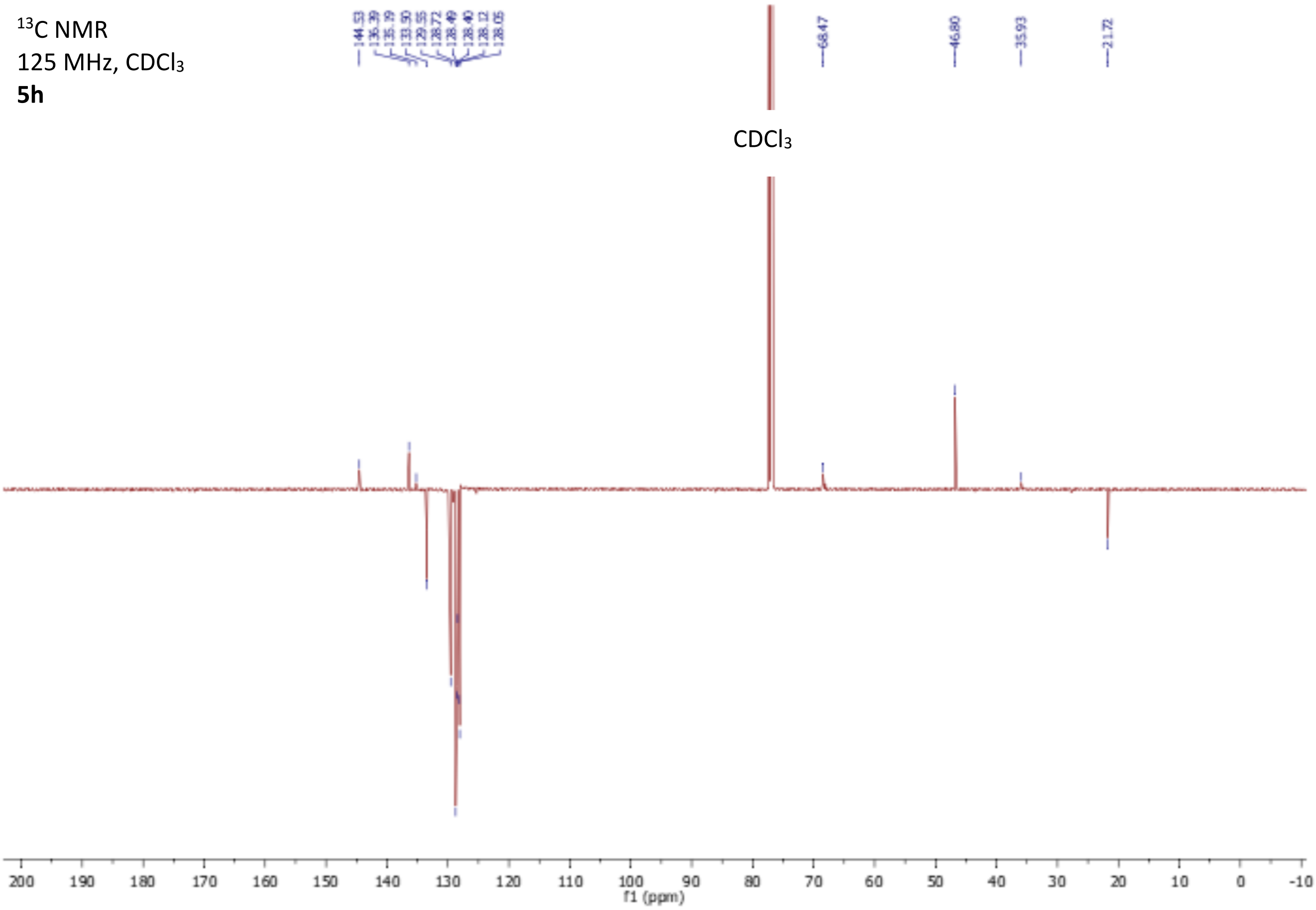

^{1}H NMR
500 MHz, d6-DMSO
5g


^{13}C NMR
125 MHz, d6-DMSO
5g

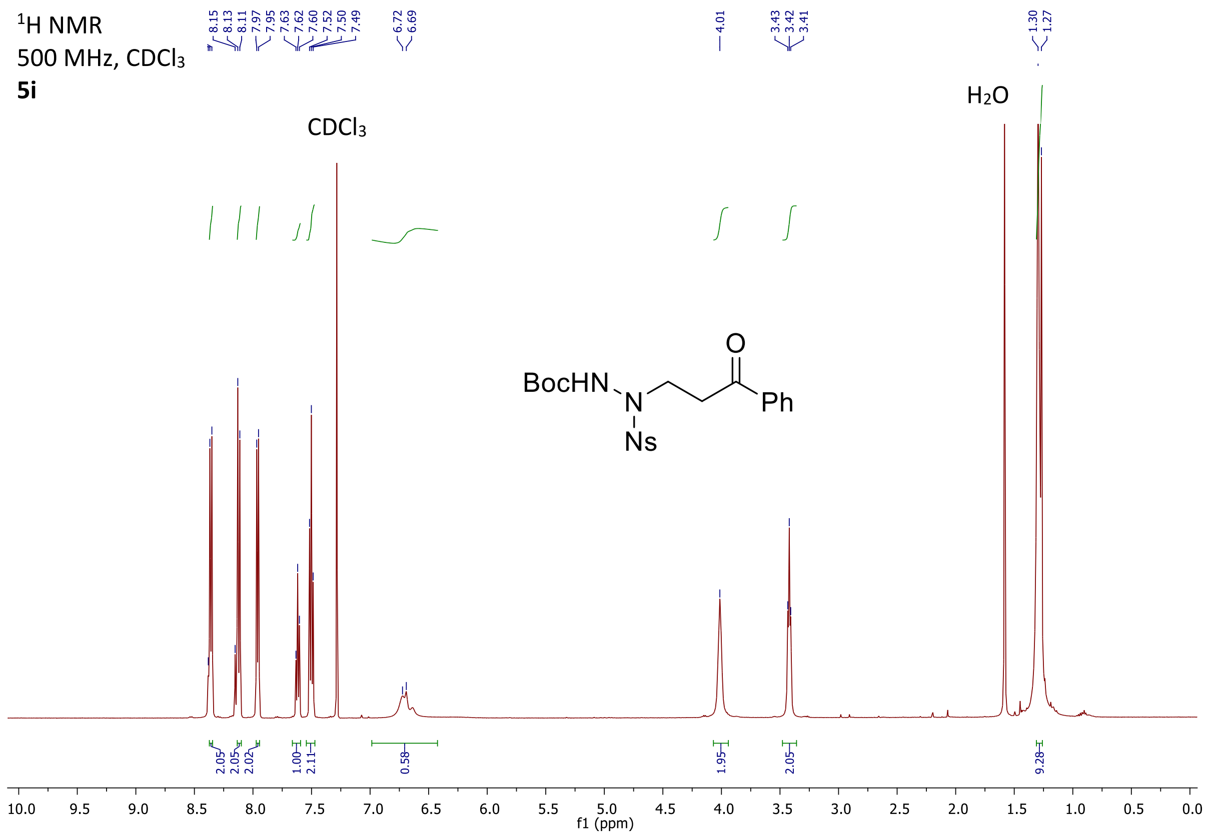
^{1}H NMR
500 MHz, $CDCl_3$
5h



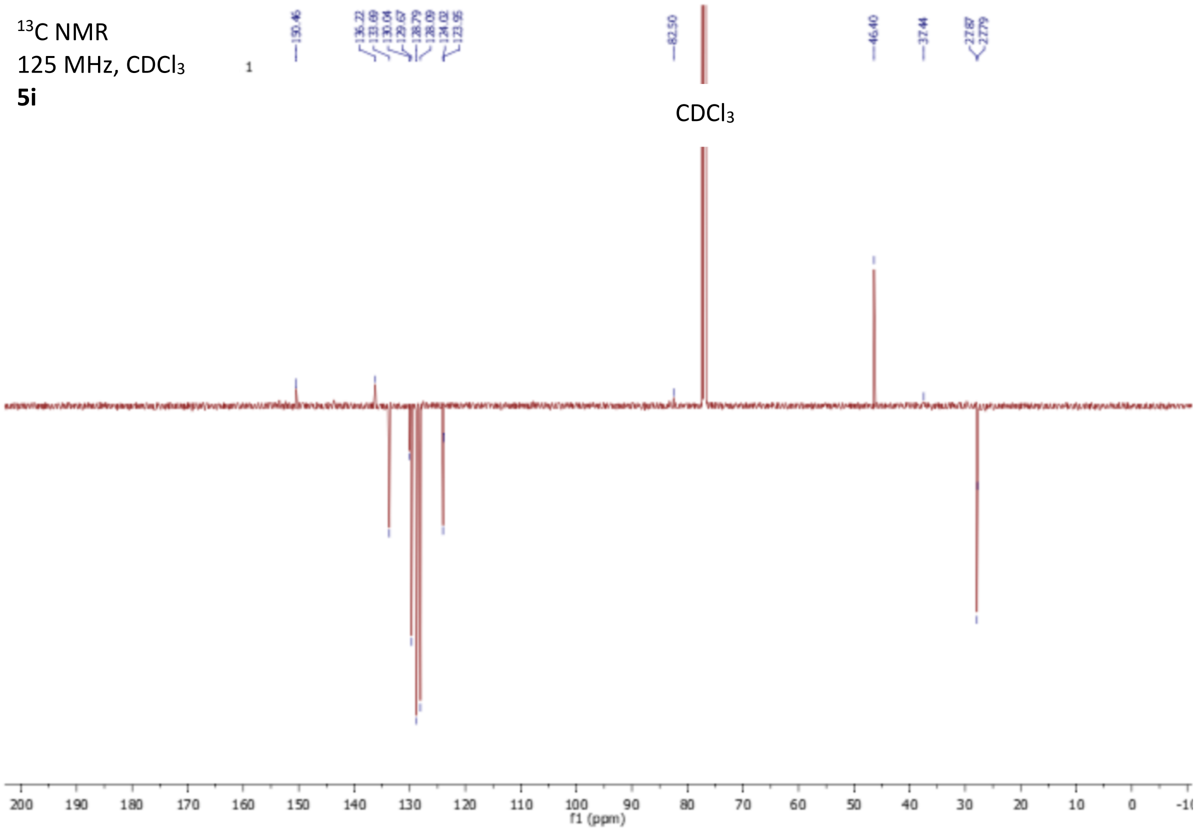
^{13}C NMR
125 MHz, $CDCl_3$
5h



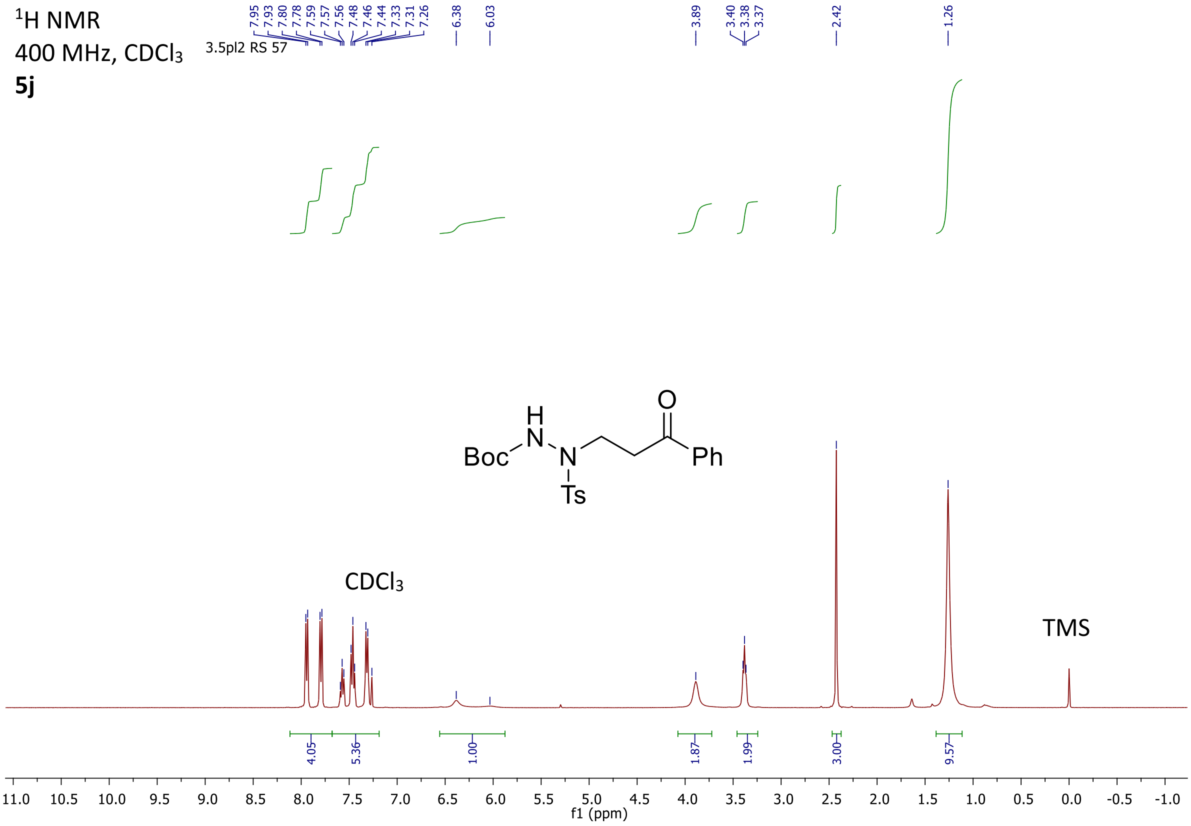
^{1}H NMR
500 MHz, $CDCl_3$
5i



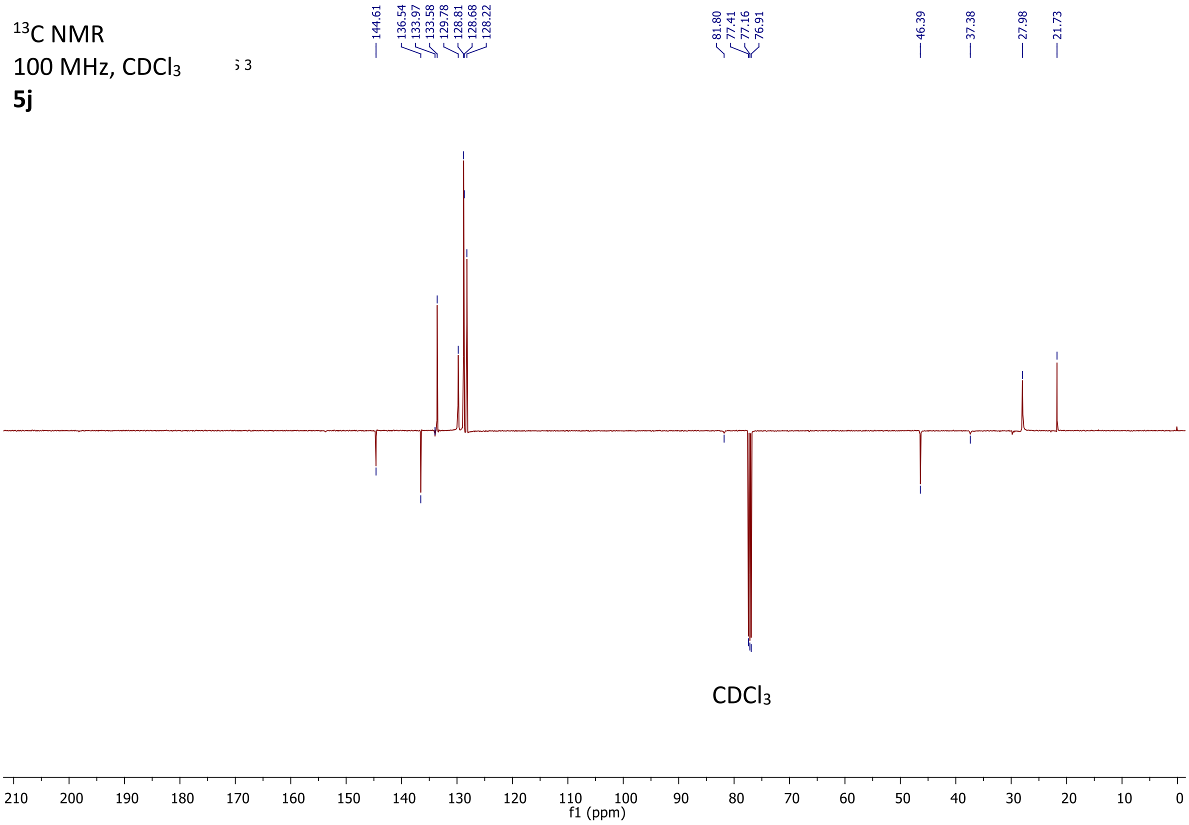
^{13}C NMR
125 MHz, $CDCl_3$
5i



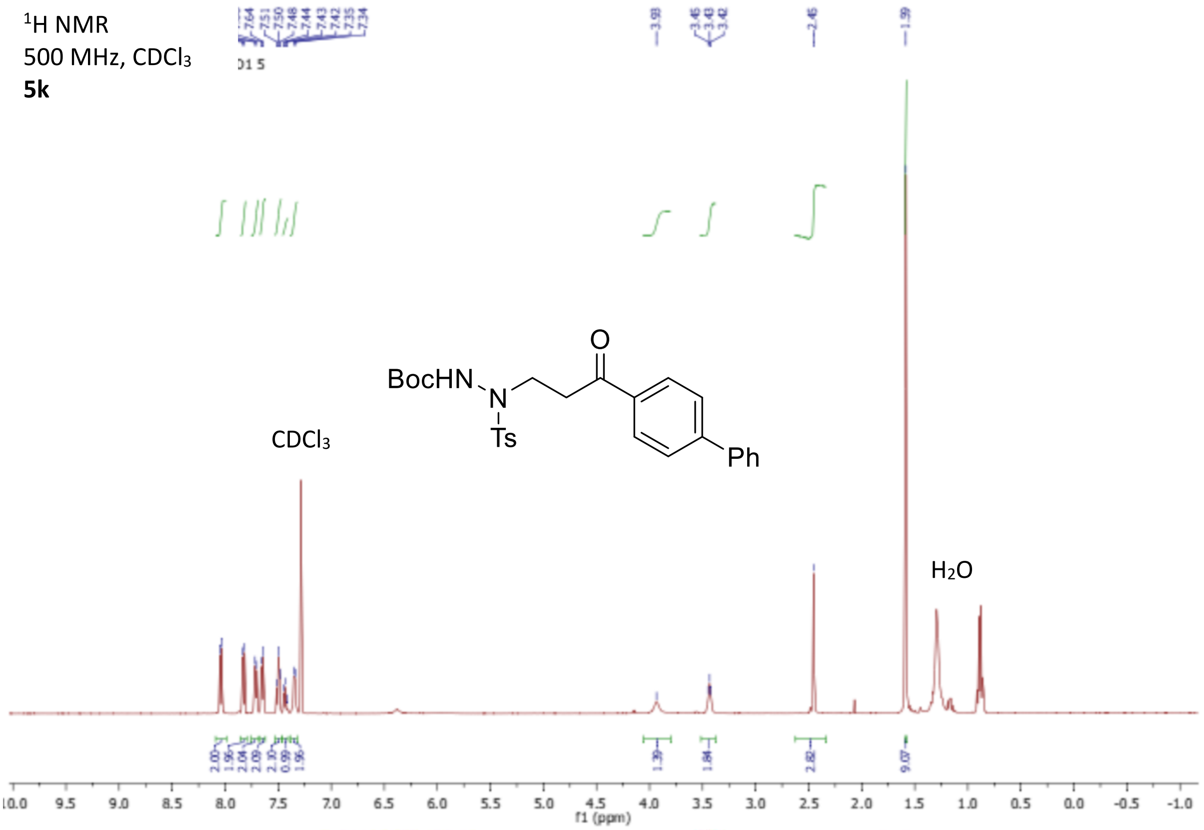
^{1}H NMR
400 MHz, $CDCl_3$
5j



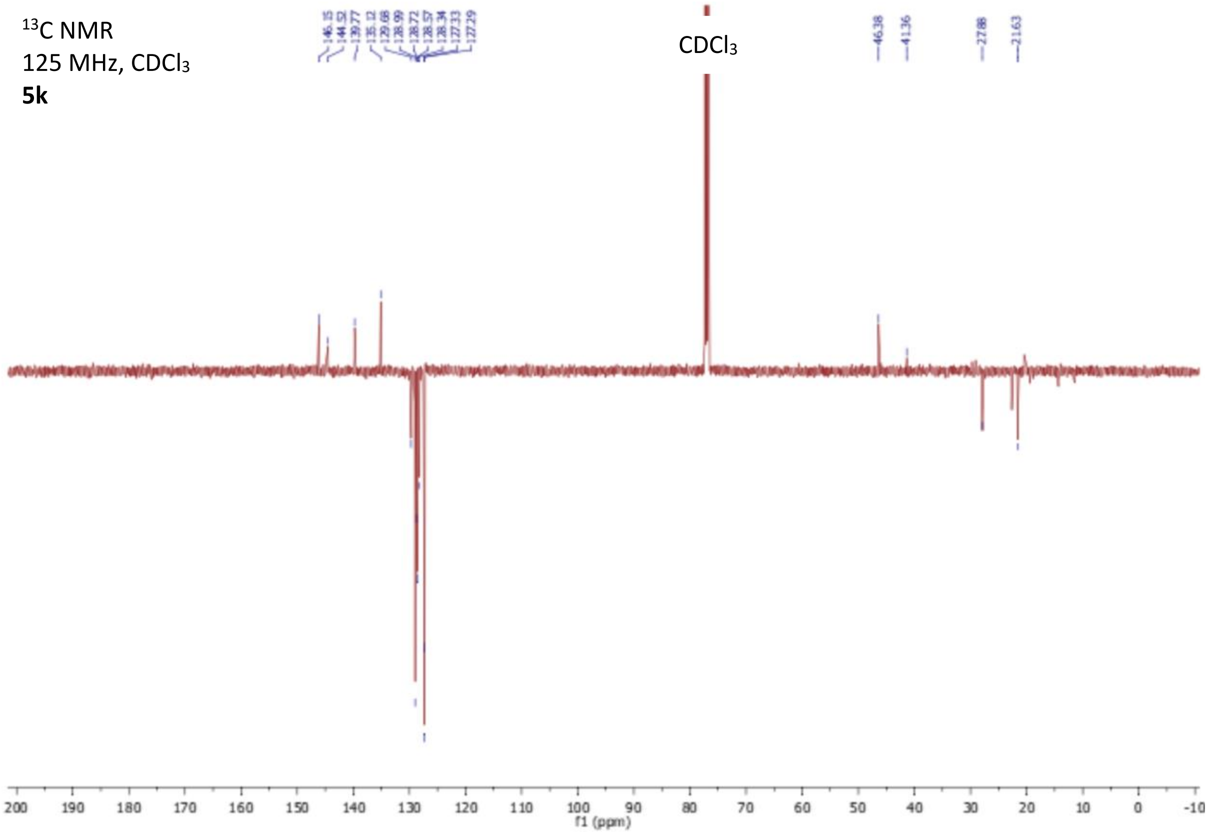
^{13}C NMR
100 MHz, $CDCl_3$
5j



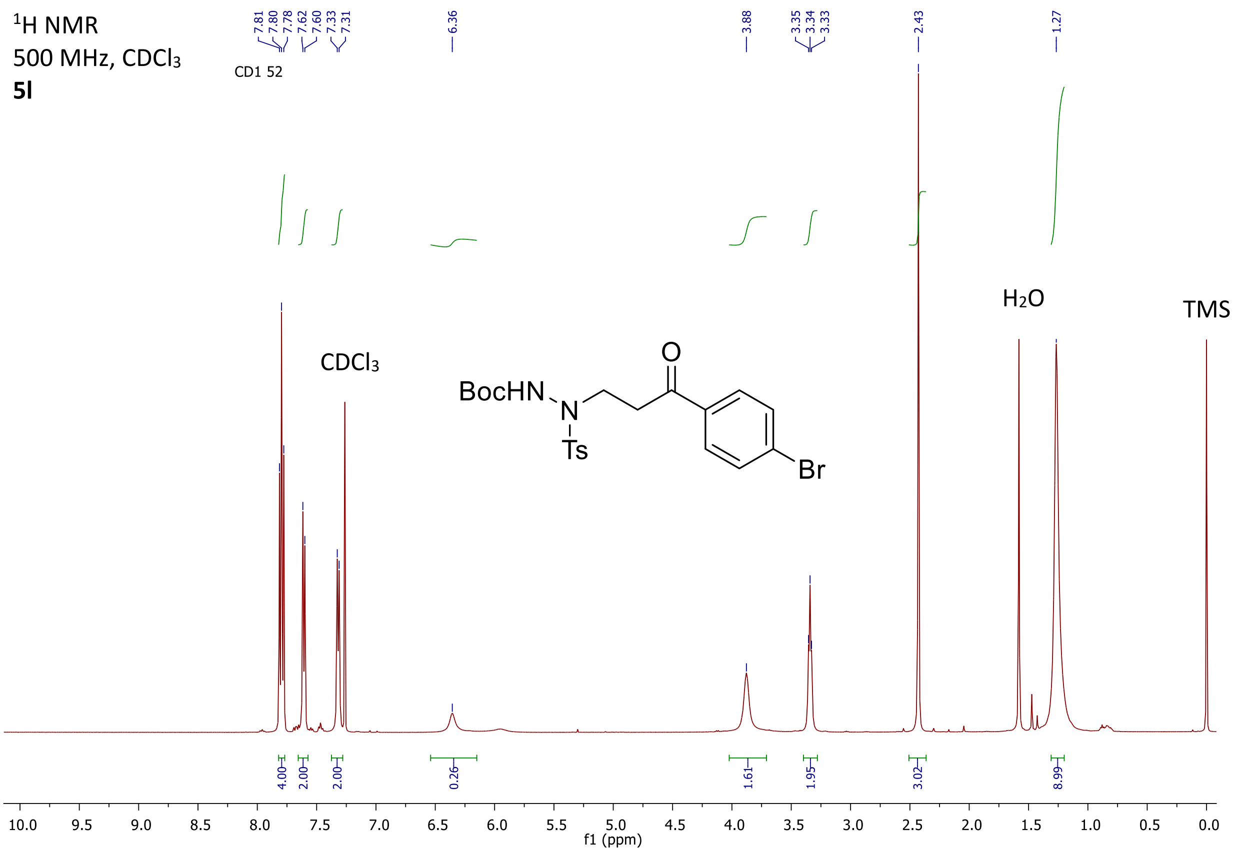
^{1}H NMR
500 MHz, $CDCl_3$
5k



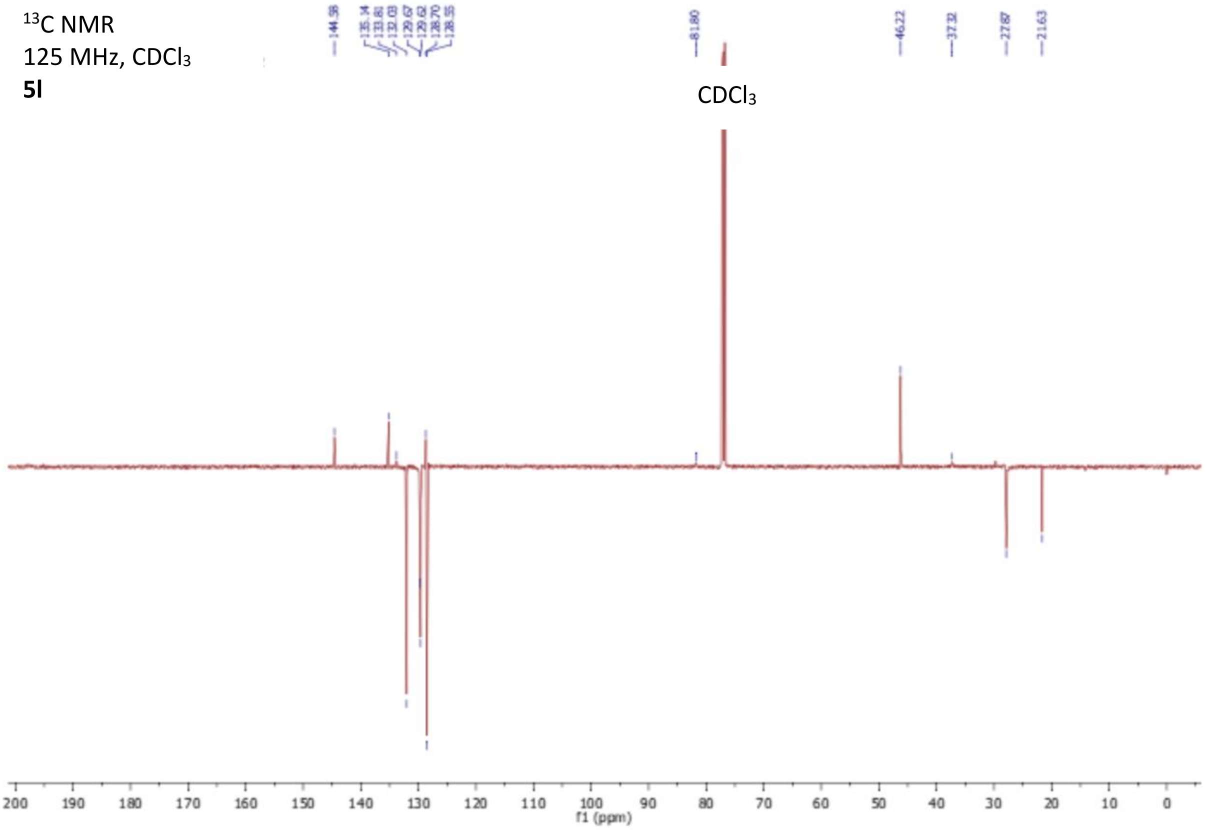
^{13}C NMR
125 MHz, $CDCl_3$
5k



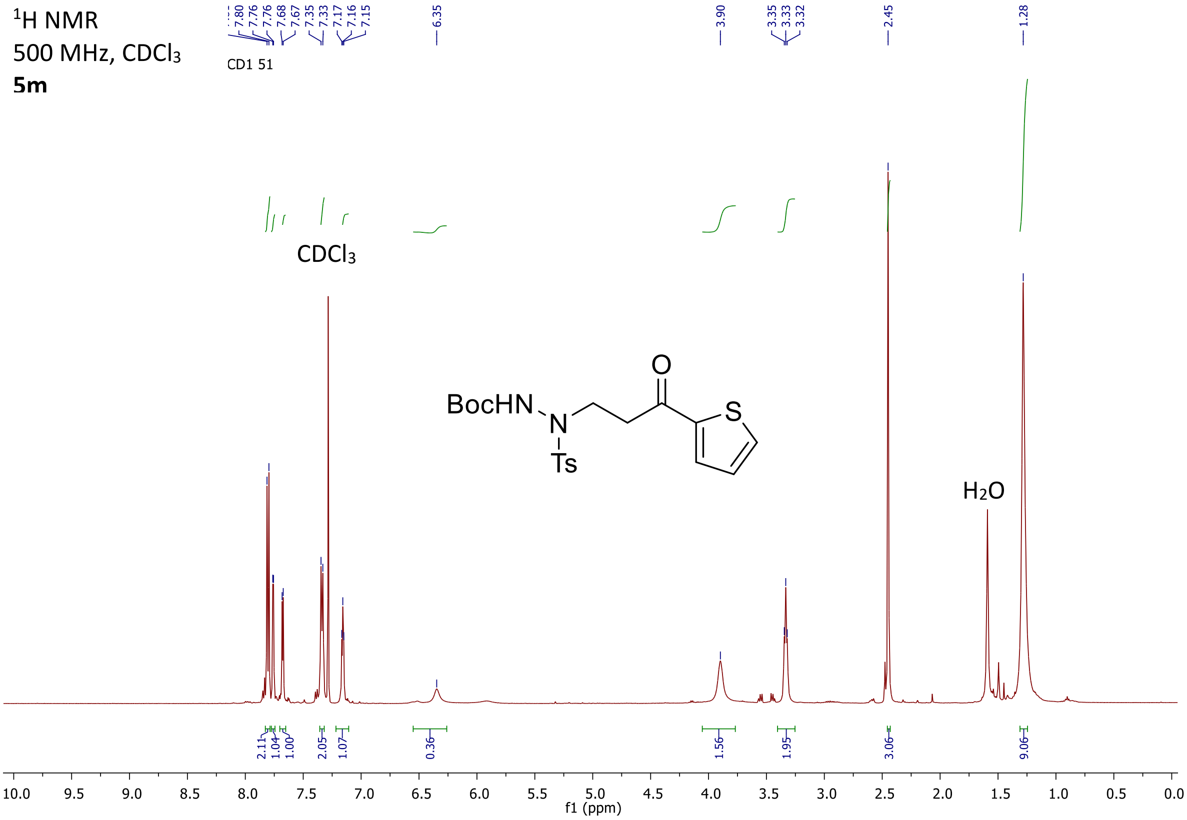
^{1}H NMR
500 MHz, $CDCl_3$
5l



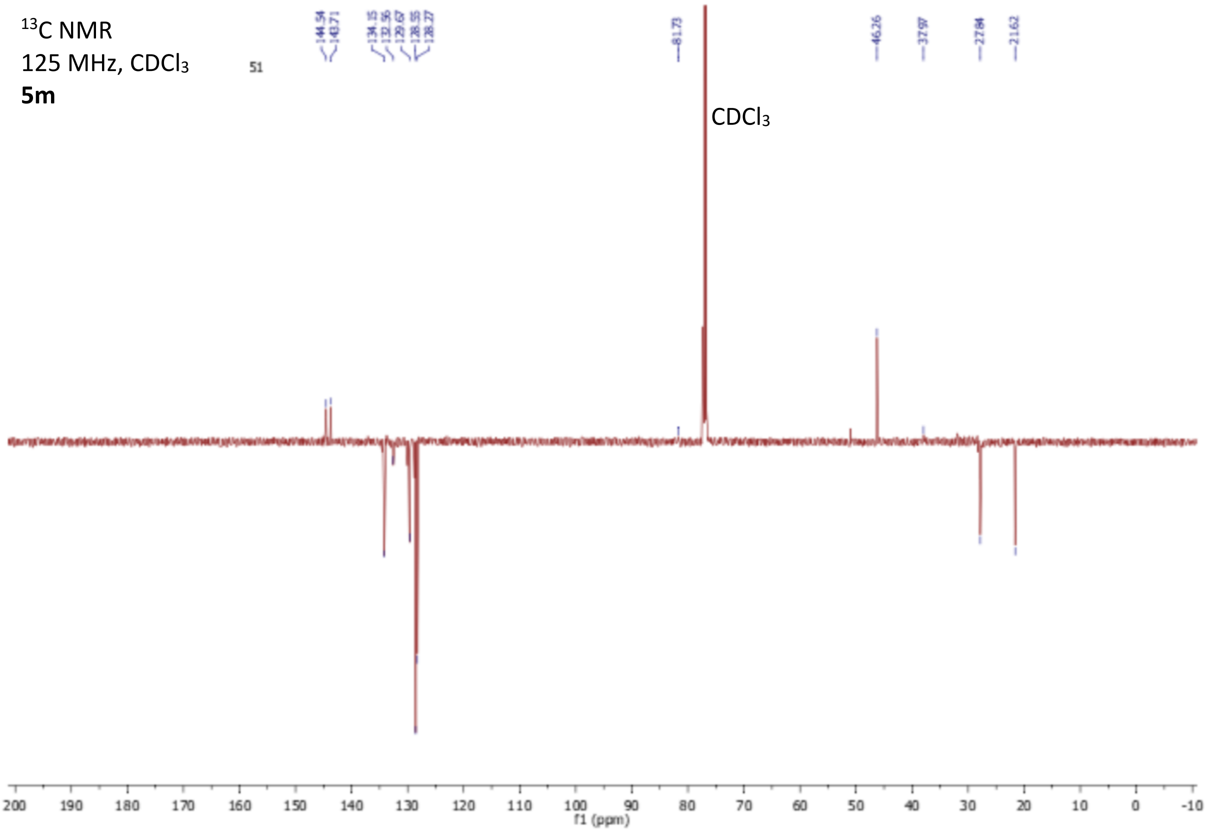
^{13}C NMR
125 MHz, $CDCl_3$
5l



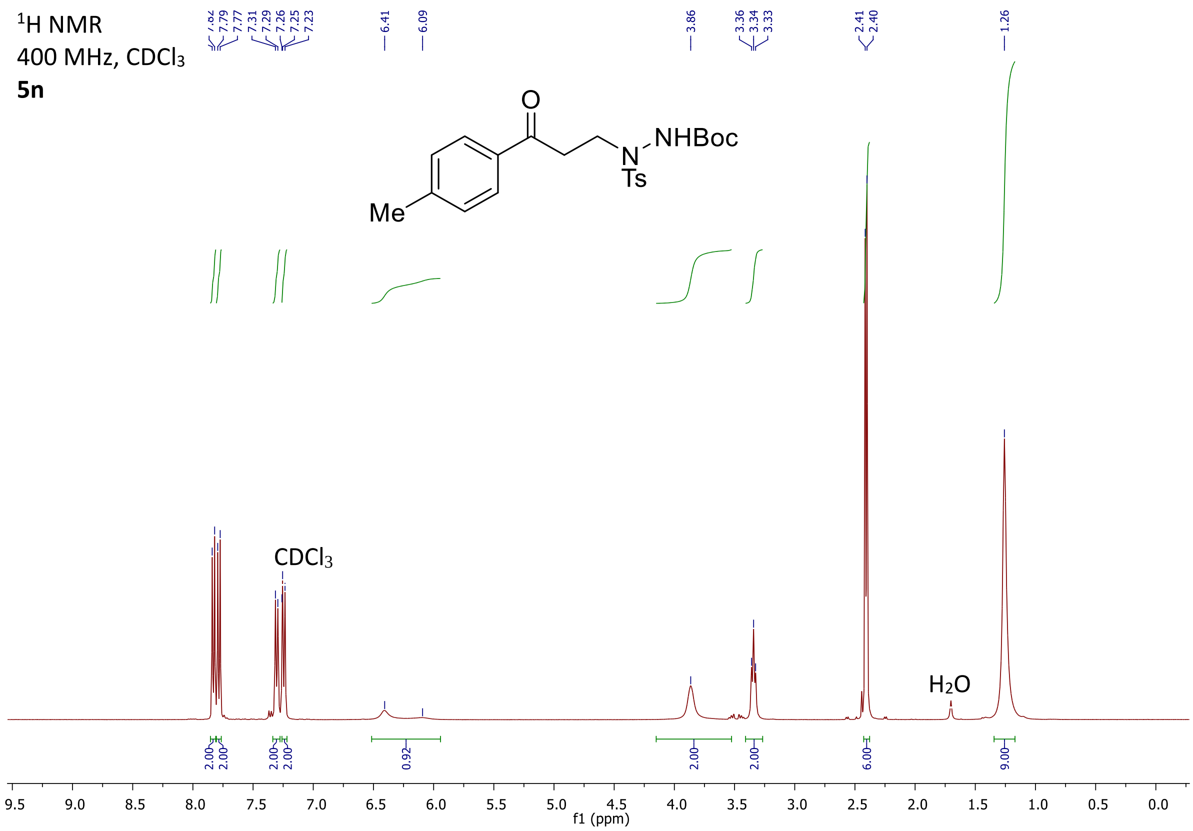
^{1}H NMR
500 MHz, $CDCl_3$
5m



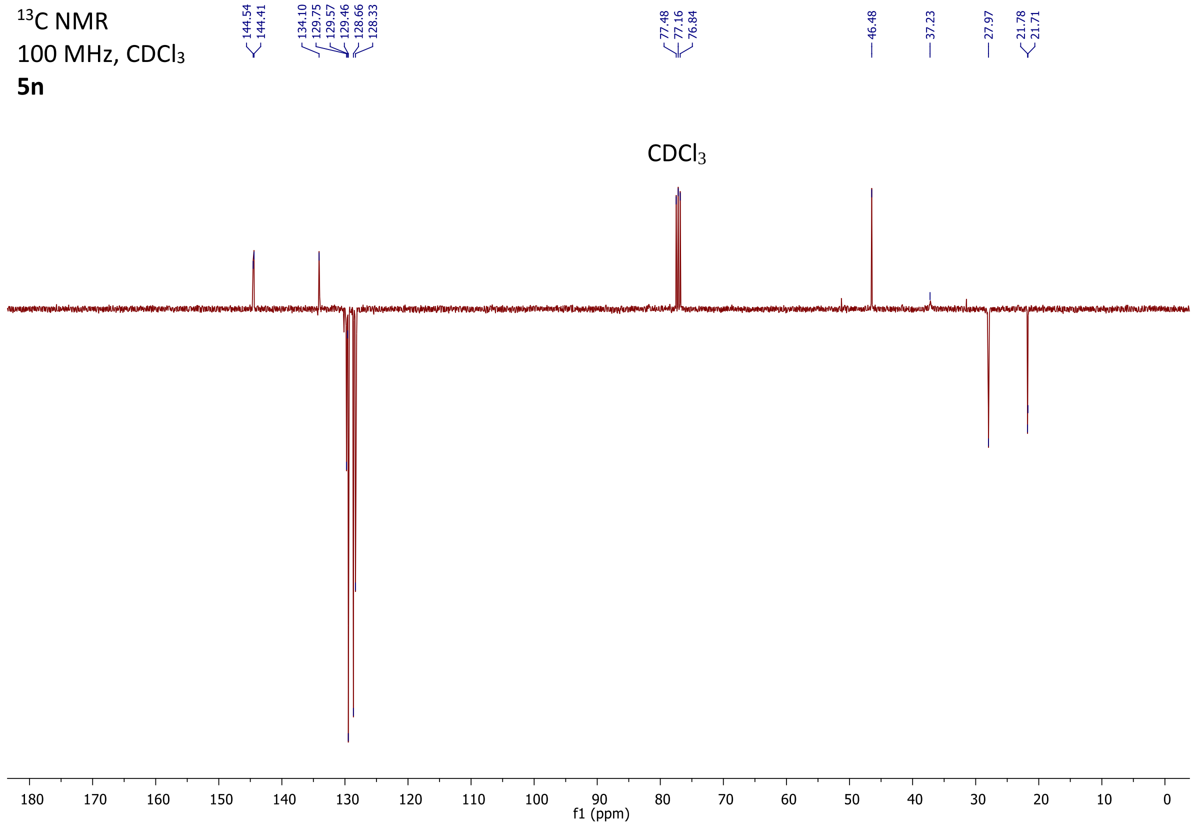
^{13}C NMR
125 MHz, $CDCl_3$
5m



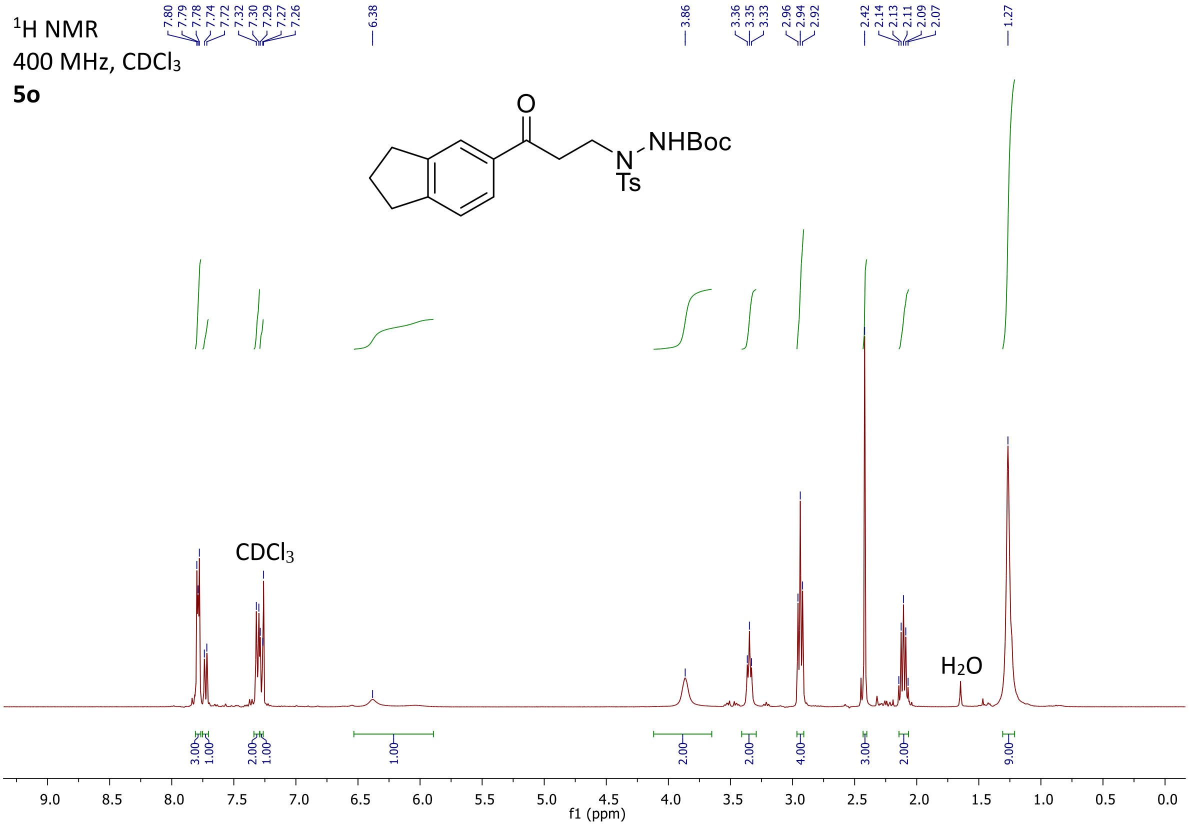
^{1}H NMR
400 MHz, CDCl$_3$
5n



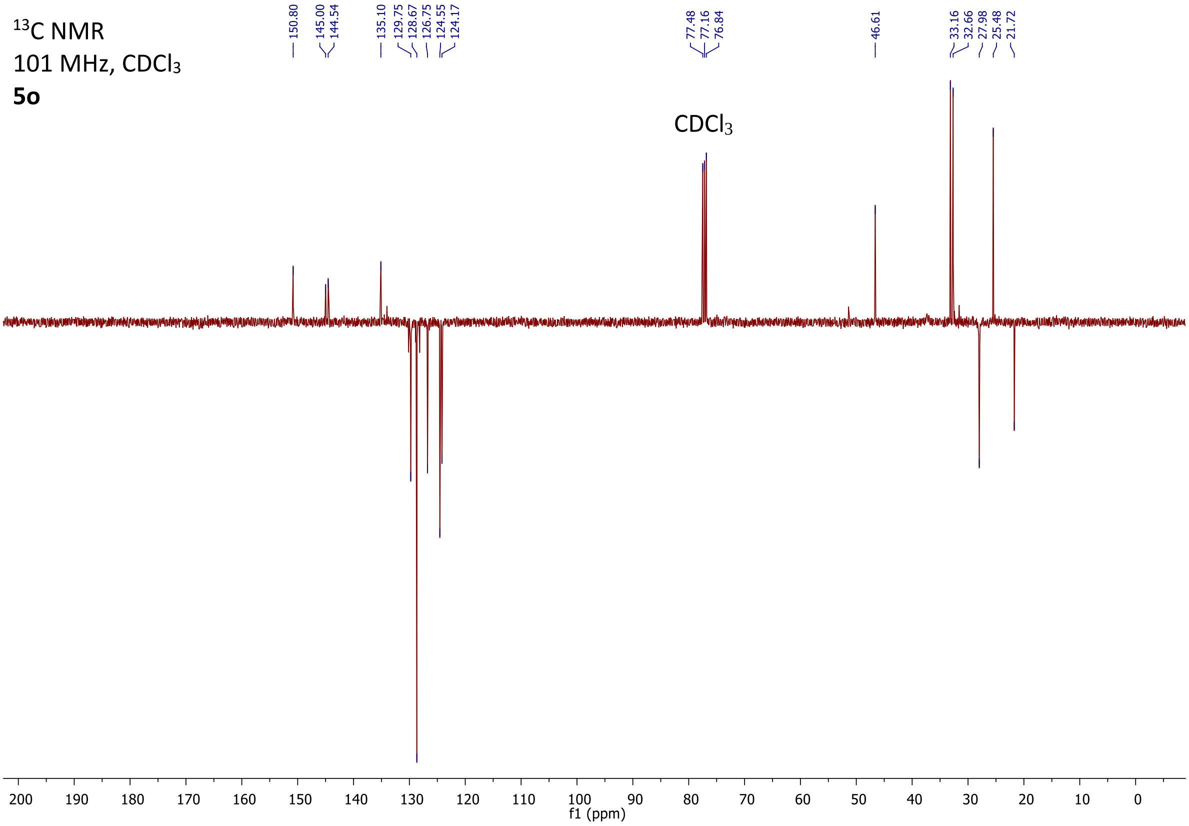
^{13}C NMR
100 MHz, CDCl$_3$
5n

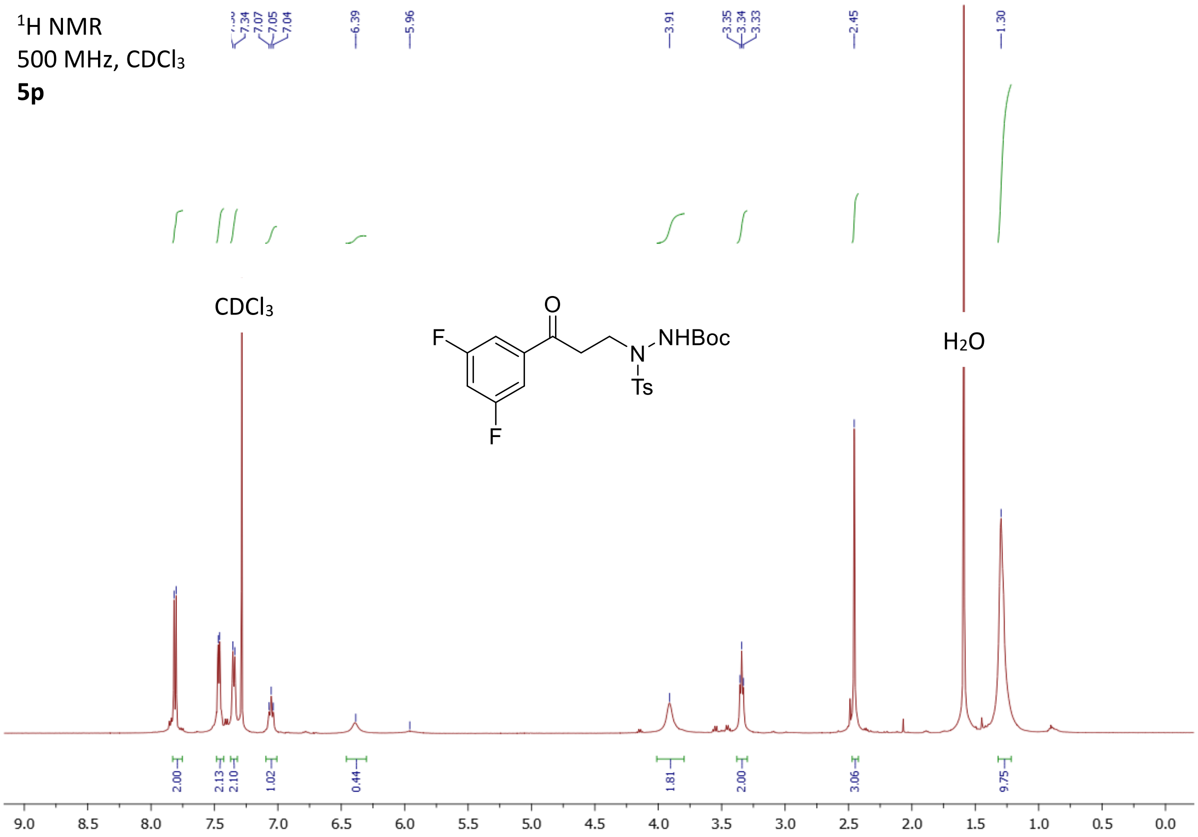


^{1}H NMR
400 MHz, $CDCl_3$
5o

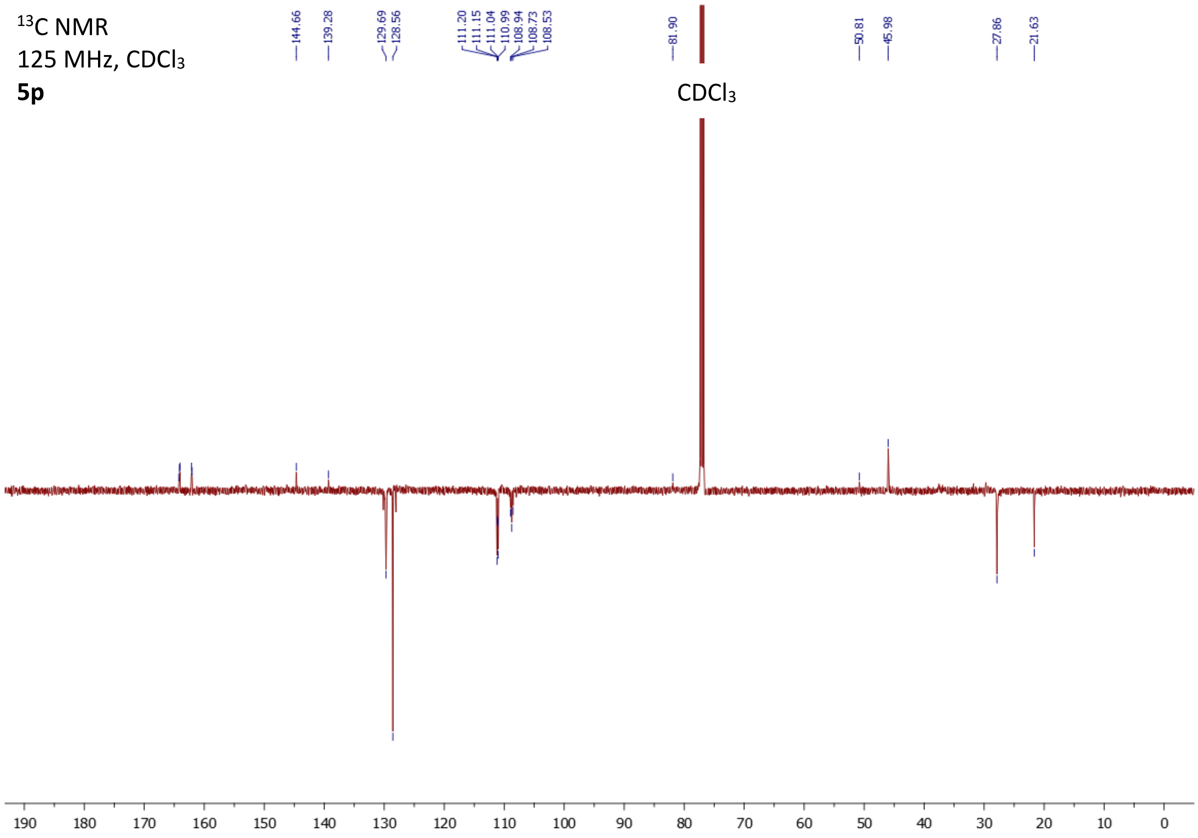


^{13}C NMR
101 MHz, $CDCl_3$
5o



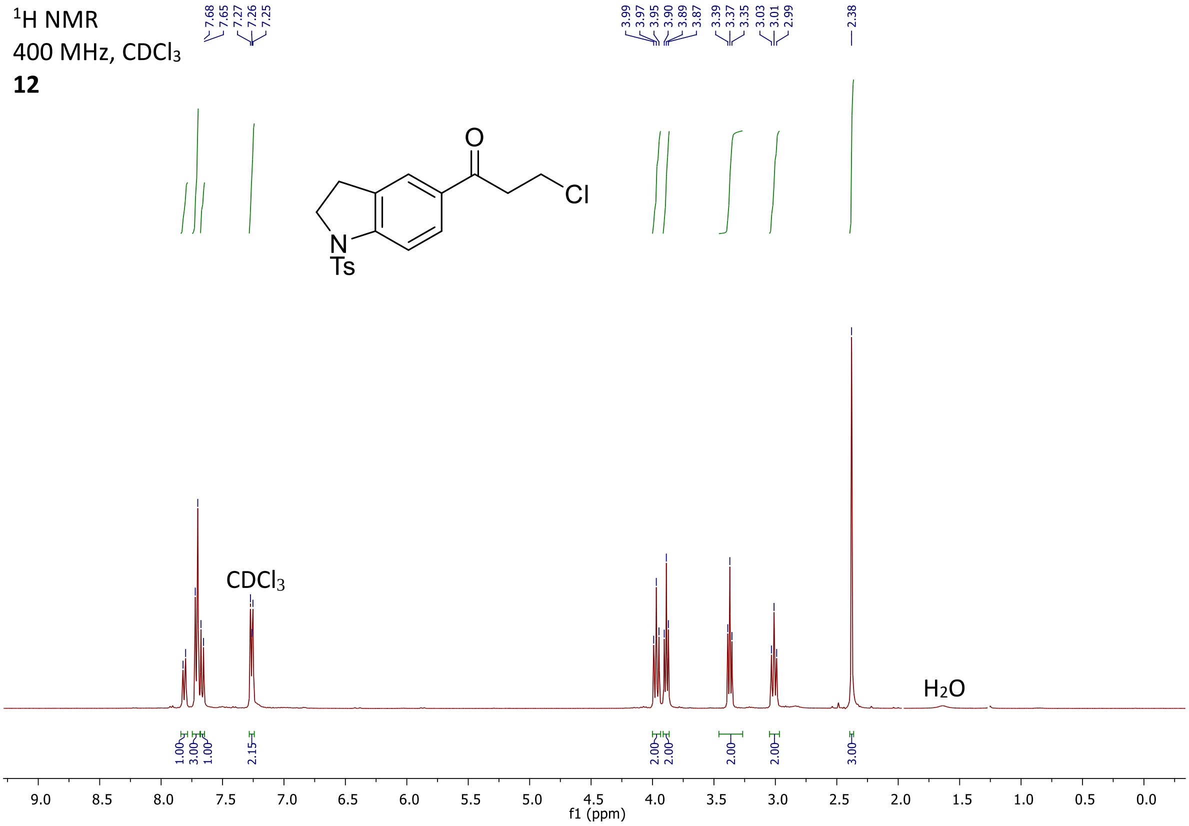


^{1}H NMR
500 MHz, $CDCl_3$
5p

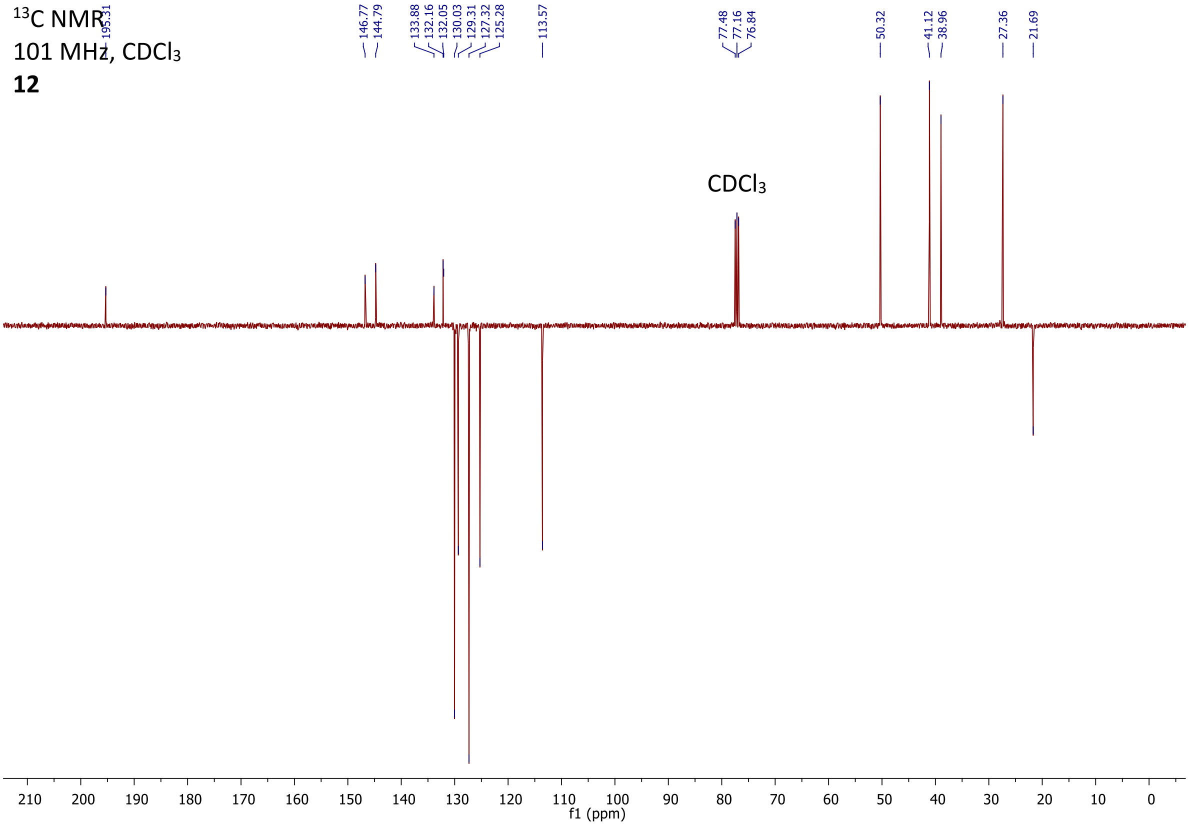


^{13}C NMR
125 MHz, $CDCl_3$
5p

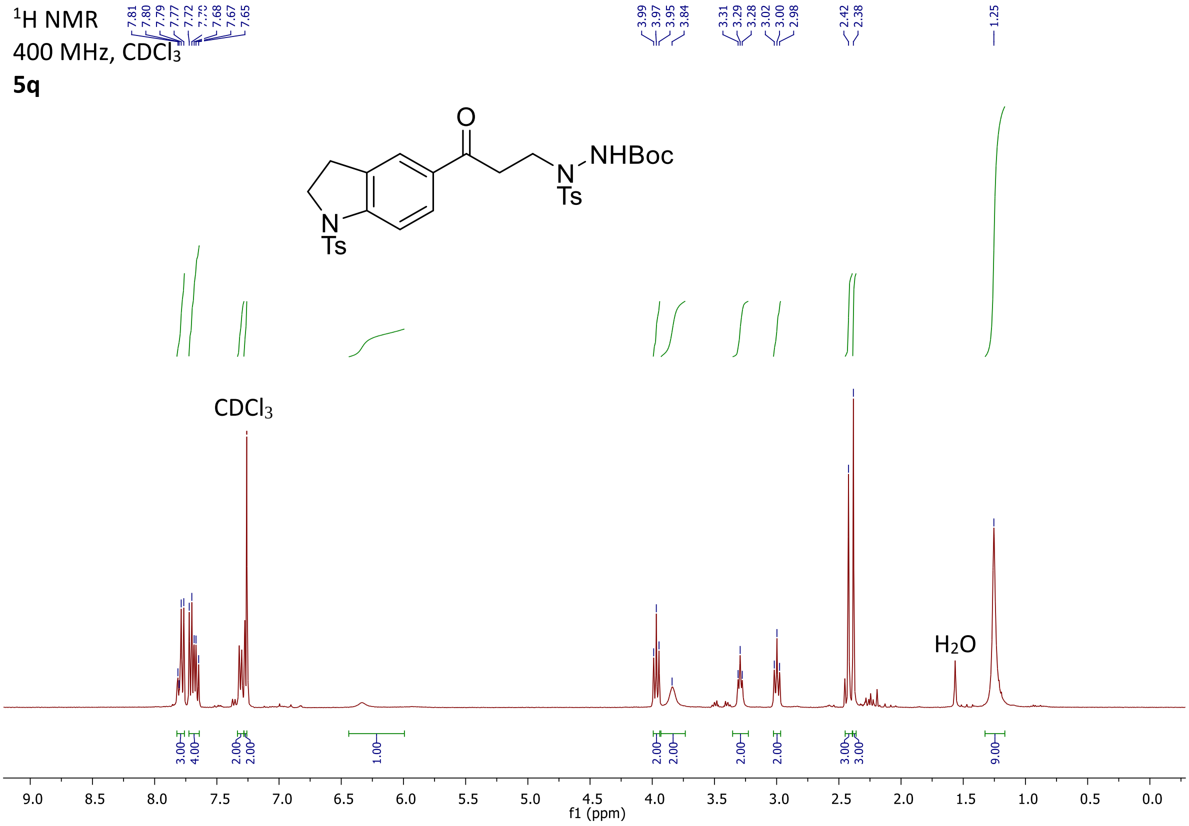
^{1}H NMR
400 MHz, $CDCl_3$
12



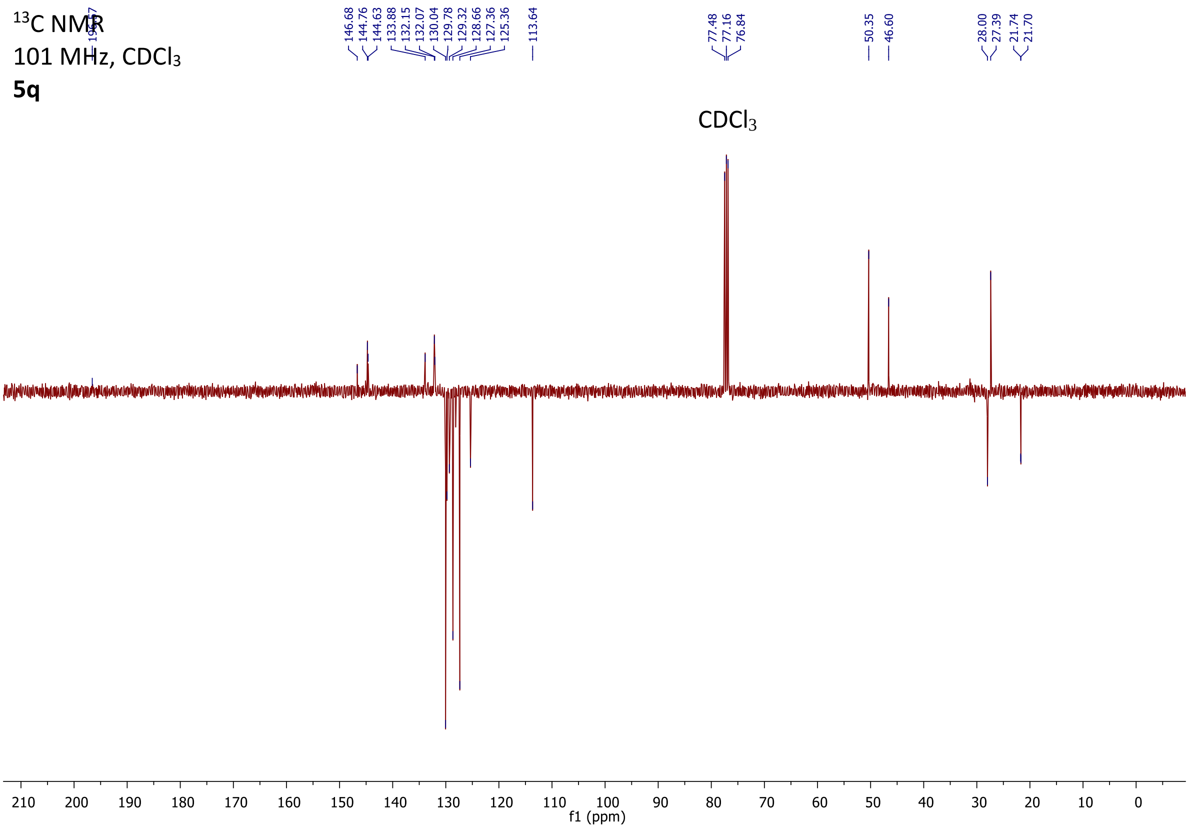
^{13}C NMR
101 MHz, $CDCl_3$
12



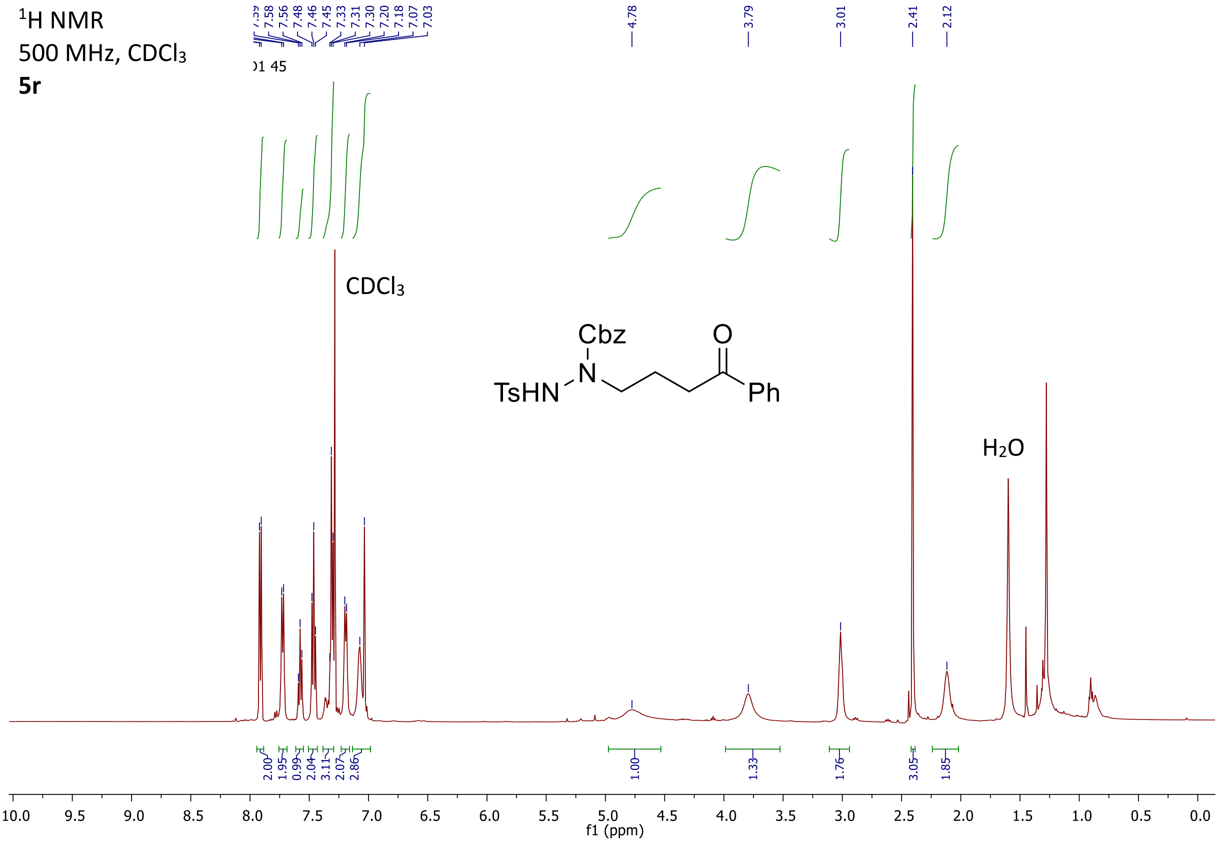
^{1}H NMR
400 MHz, $CDCl_3$
5q



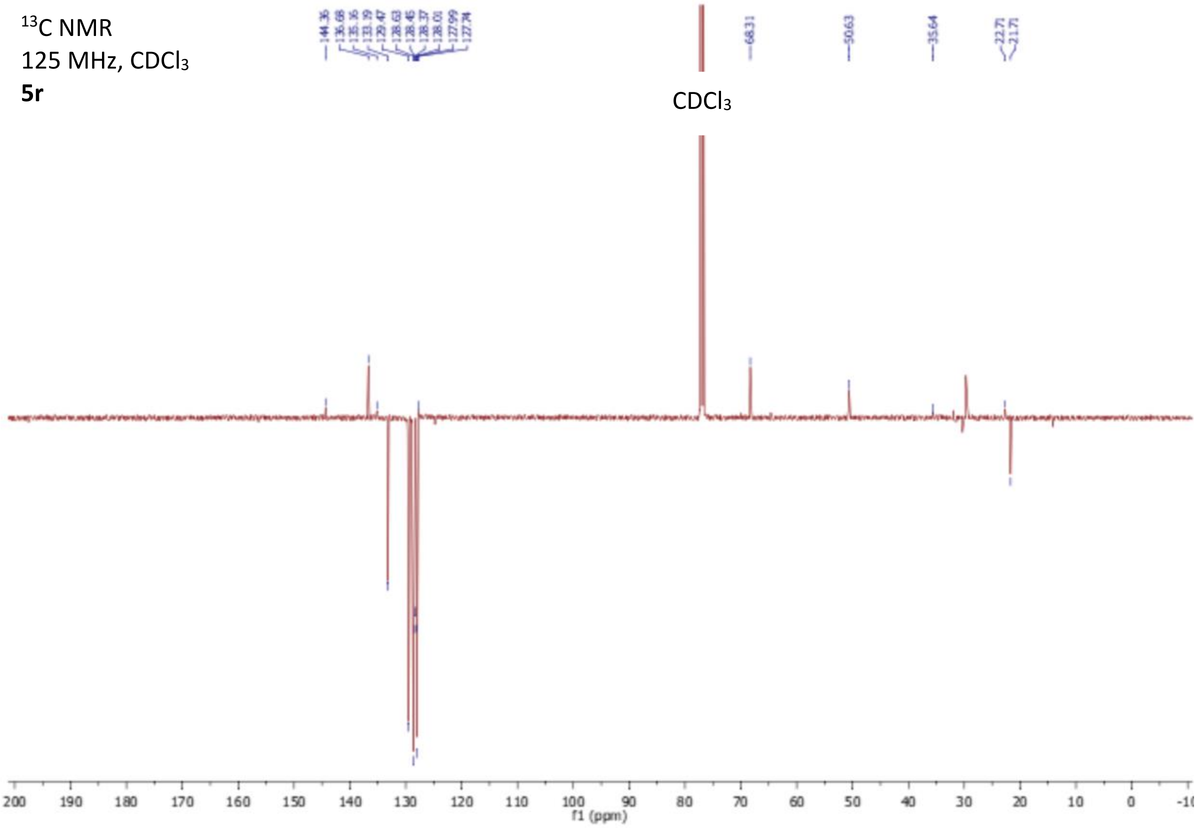
^{13}C NMR
101 MHz, $CDCl_3$
5q



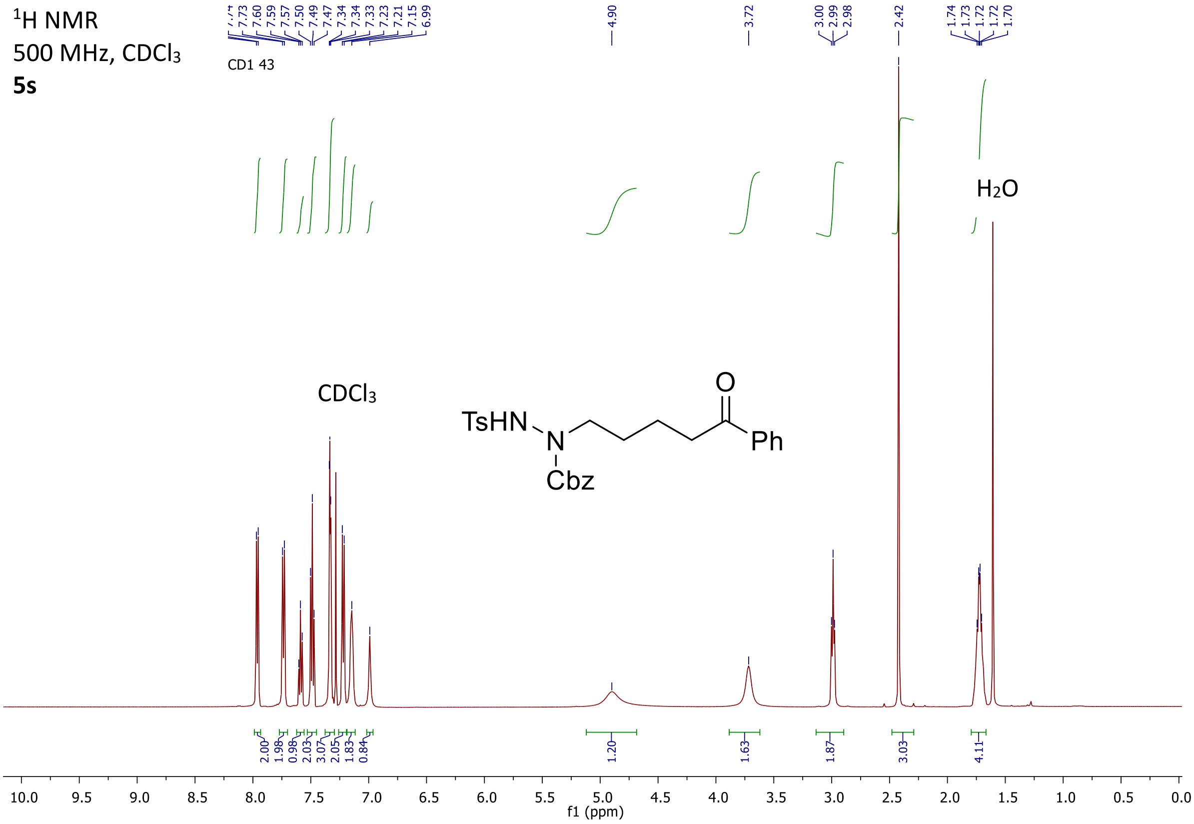
^{1}H NMR
500 MHz, $CDCl_3$
5r



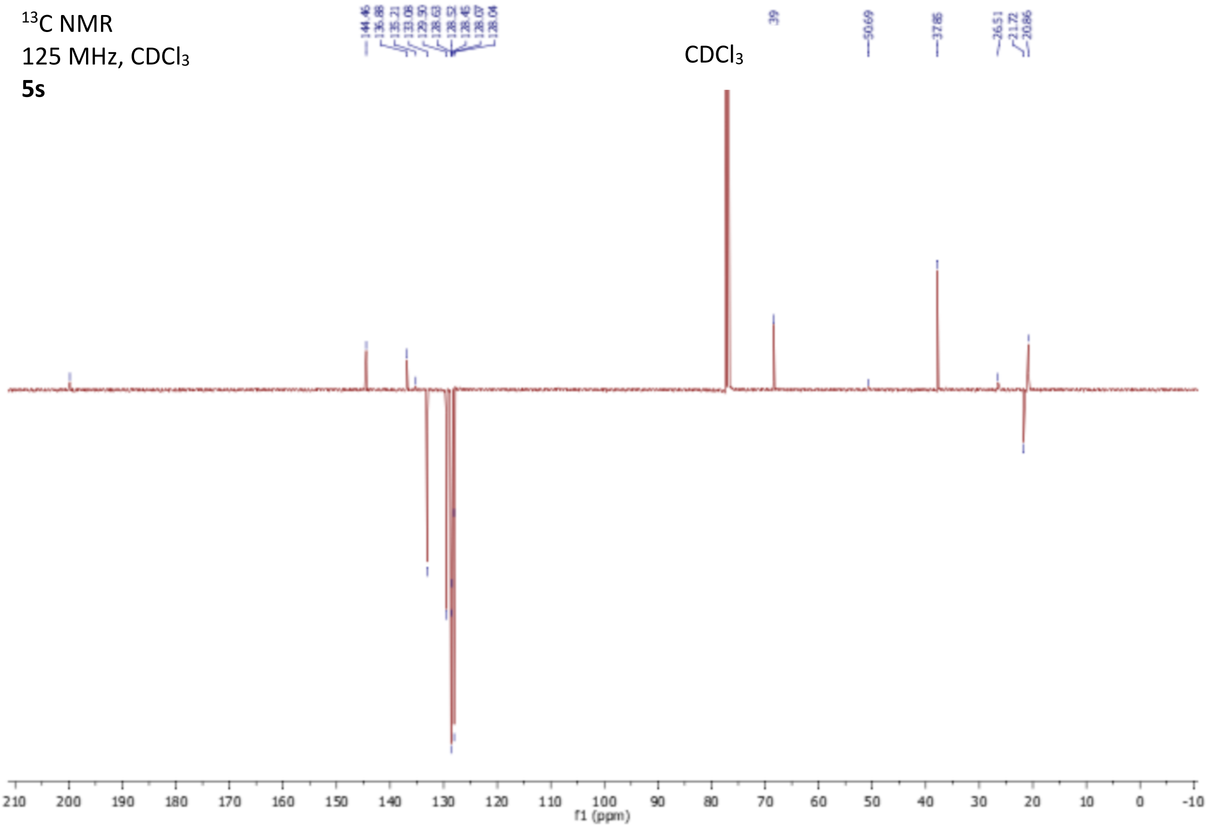
^{13}C NMR
125 MHz, $CDCl_3$
5r

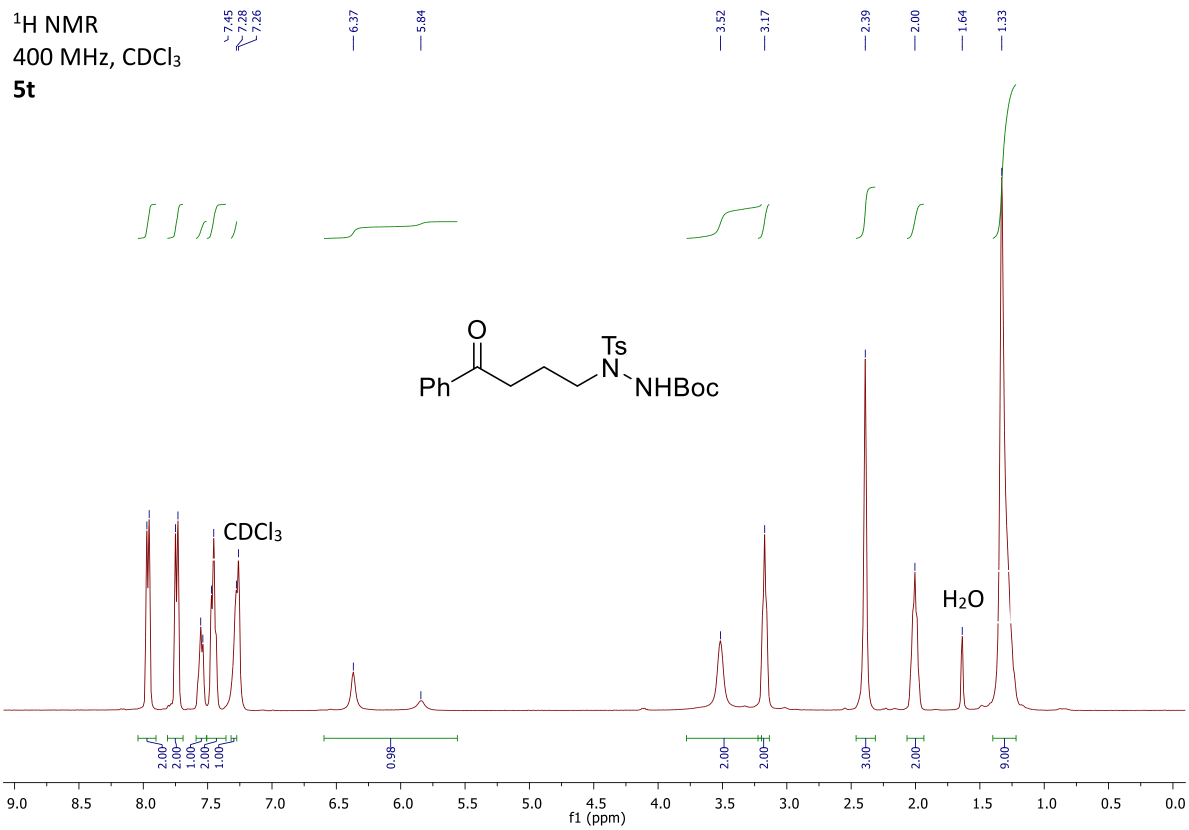


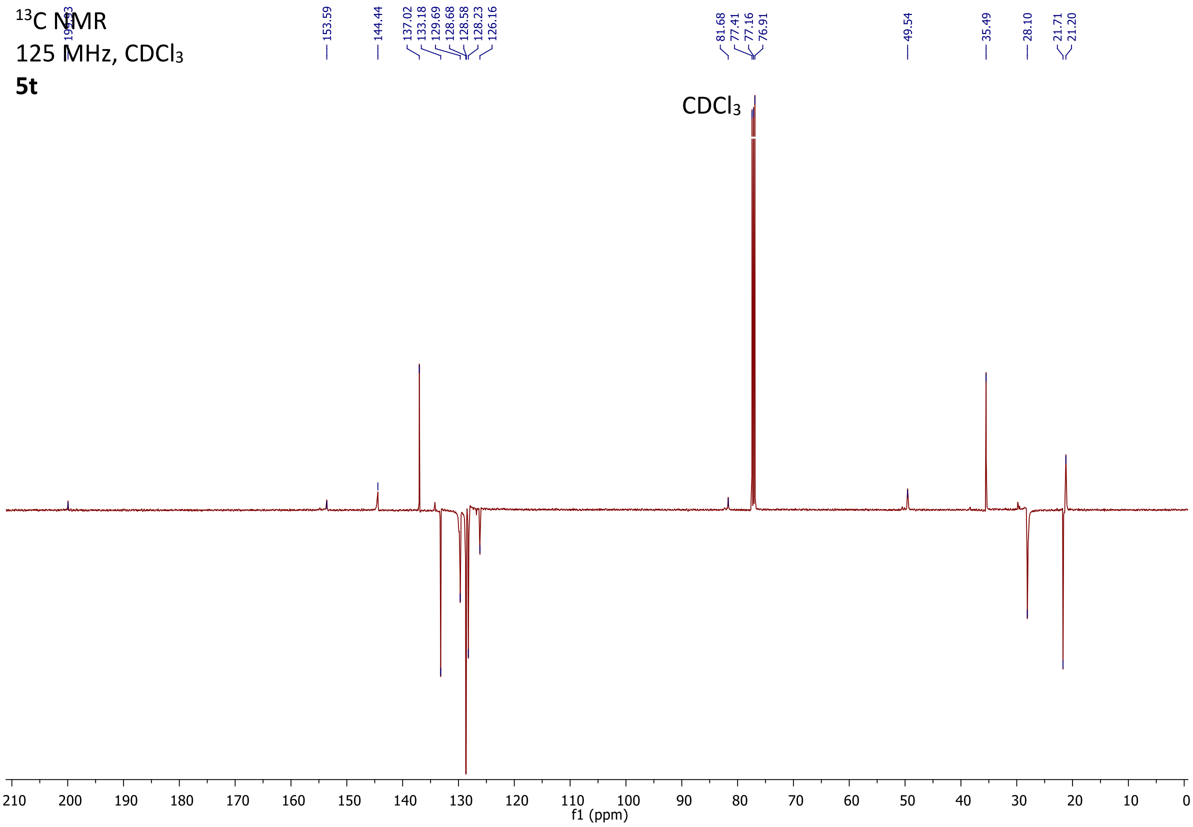
^{1}H NMR
500 MHz, $CDCl_3$
5s



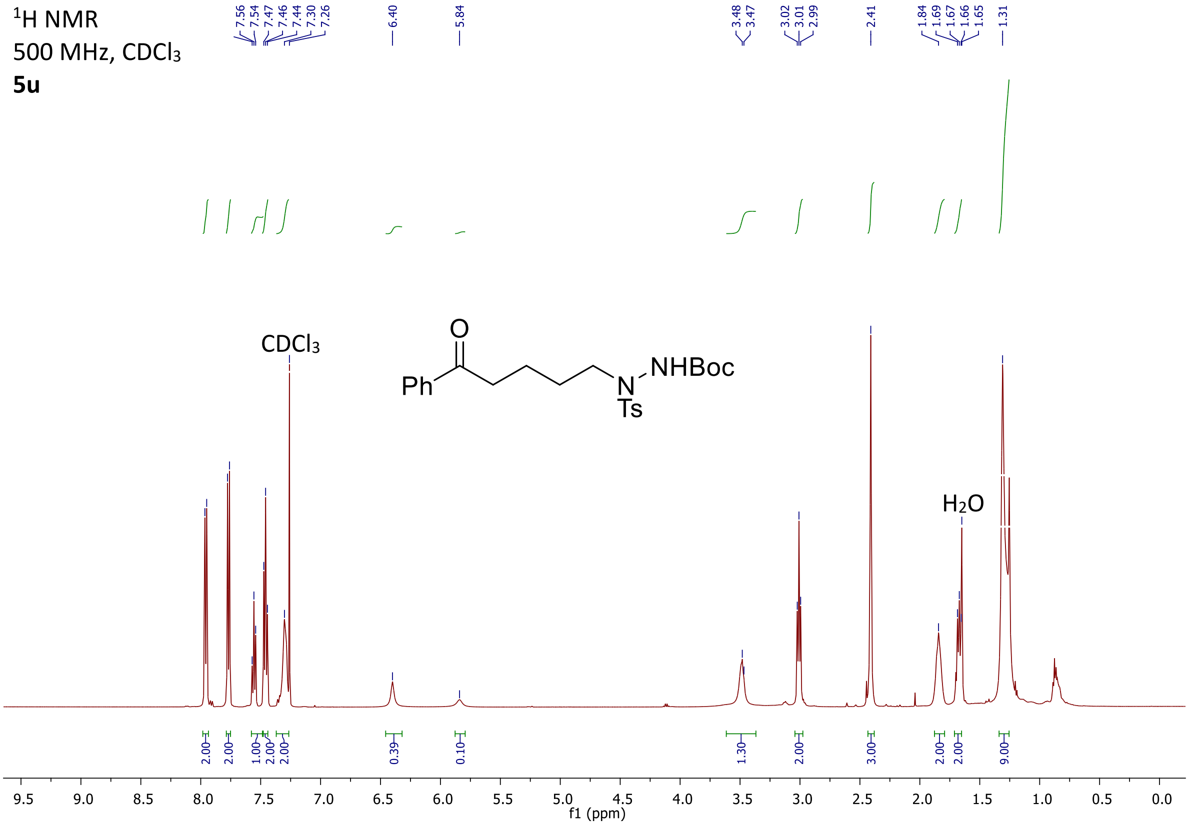
^{13}C NMR
125 MHz, $CDCl_3$
5s



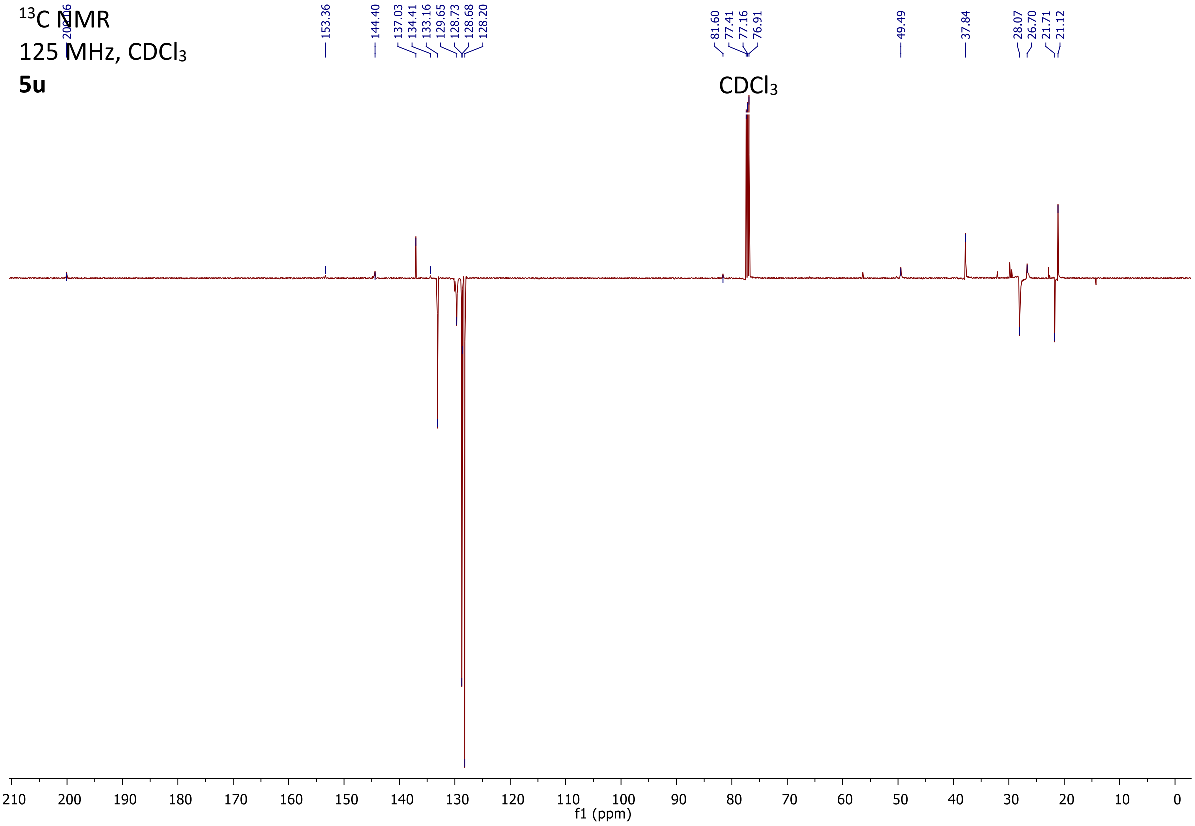

^{1}H NMR
400 MHz, CDCl$_3$
5t
7.45
7.28
7.26
6.37
5.84
3.52
3.17
2.39
2.00
1.64
1.33
O
Ph
Ts
N
NHBoc
CDCl$_3$
H$_2$O
2.00
2.00
1.00
2.00
1.00
0.98
2.00
2.00
3.00
2.00
9.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

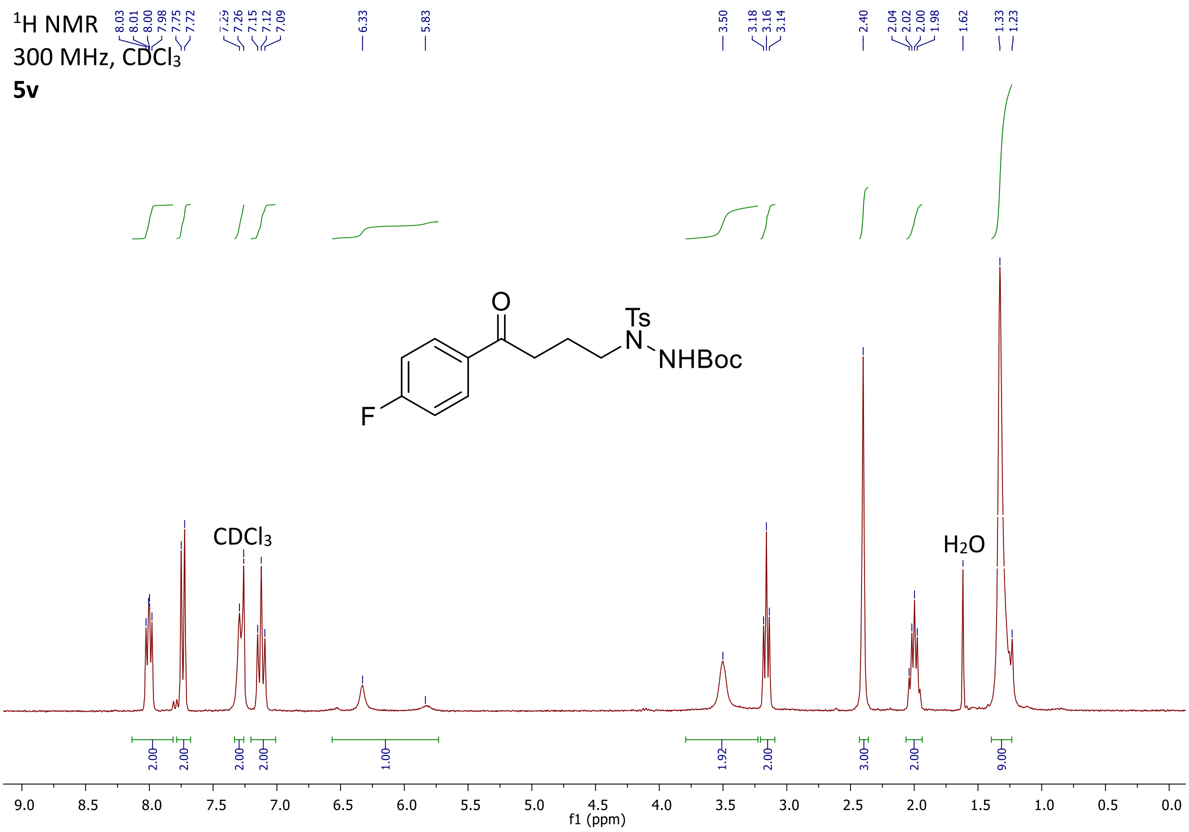

^{13}C NMR
125 MHz, CDCl$_3$
5t
199.93
153.59
144.44
137.02
133.18
129.69
128.68
128.58
128.23
126.16
81.68
77.41
77.16
76.91
49.54
35.49
28.10
21.71
21.20
CDCl$_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

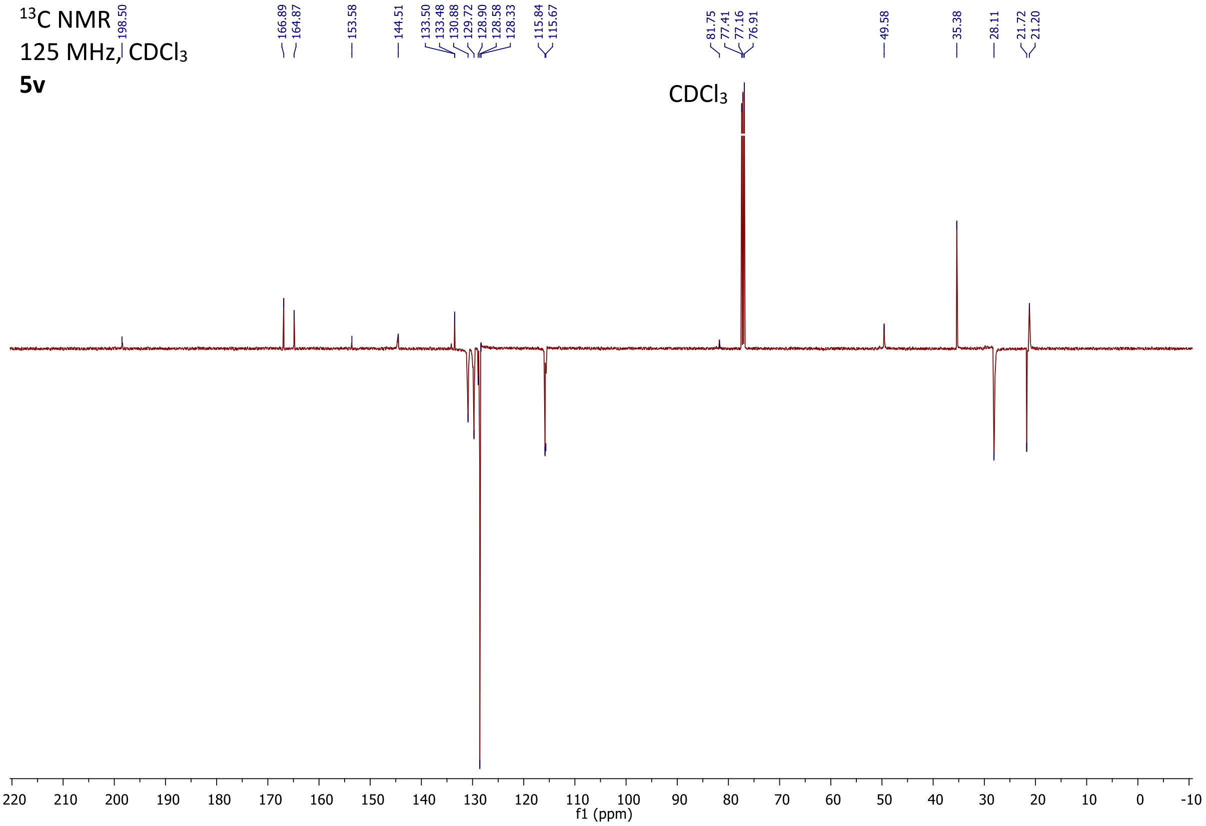
^{1}H NMR
500 MHz, $CDCl_3$
5u



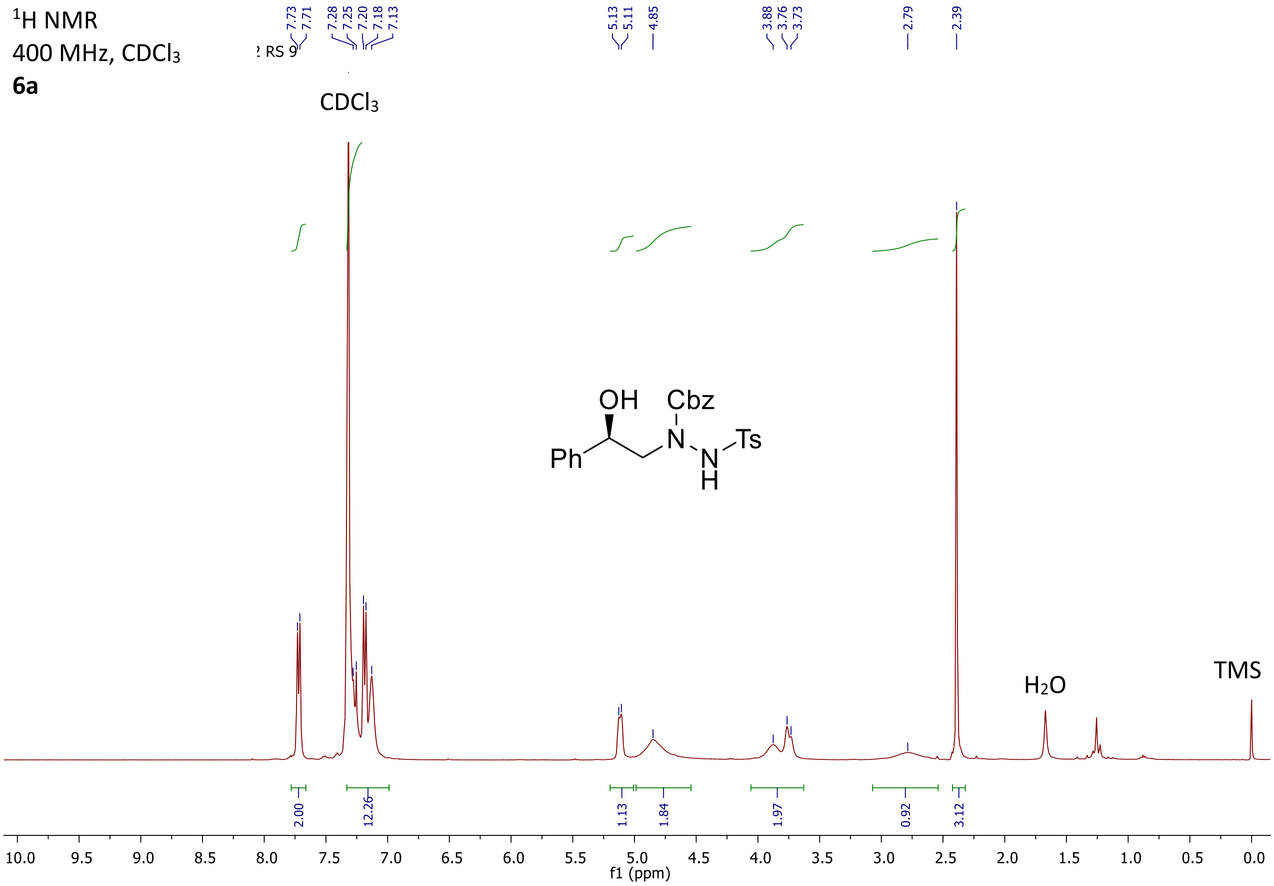
^{13}C NMR
125 MHz, $CDCl_3$
5u



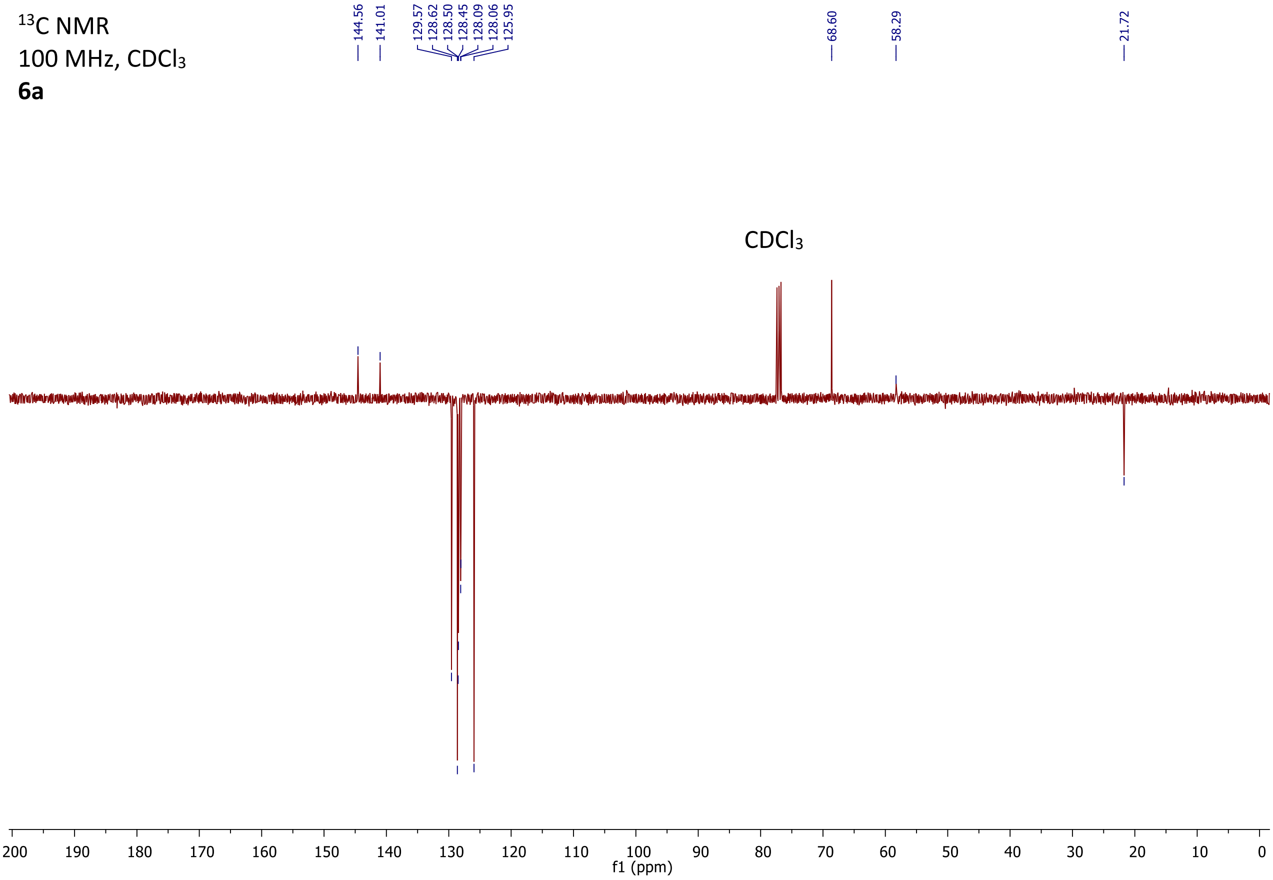

1H NMR
300 MHz, CDCl3
5v
8.03
8.01
8.00
7.98
7.75
7.72
7.29
7.26
7.15
7.12
7.09
6.33
5.83
3.50
3.18
3.16
3.14
2.40
2.04
2.02
2.00
1.98
1.62
1.33
1.23
O
Ts
N
NHBoc
F
CDCl3
H2O
2.00
2.00
2.00
2.00
1.00
1.92
2.00
3.00
2.00
9.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

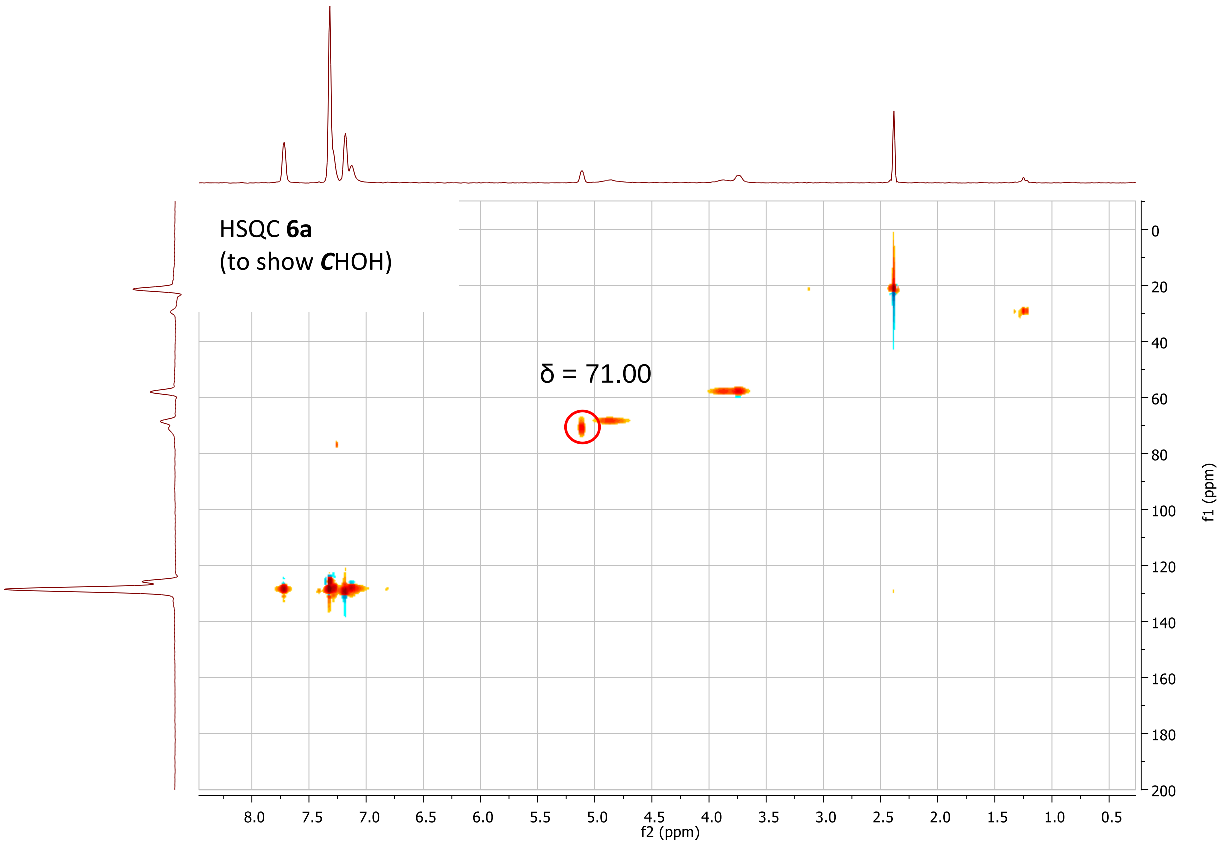

13C NMR
125 MHz, CDCl3
5v
198.50
166.89
164.87
153.58
144.51
133.50
133.48
130.88
129.72
128.90
128.58
128.33
115.84
115.67
81.75
77.41
77.16
76.91
49.58
35.38
28.11
21.72
21.20
CDCl3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

^1H NMR
400 MHz, $CDCl_3$
6a

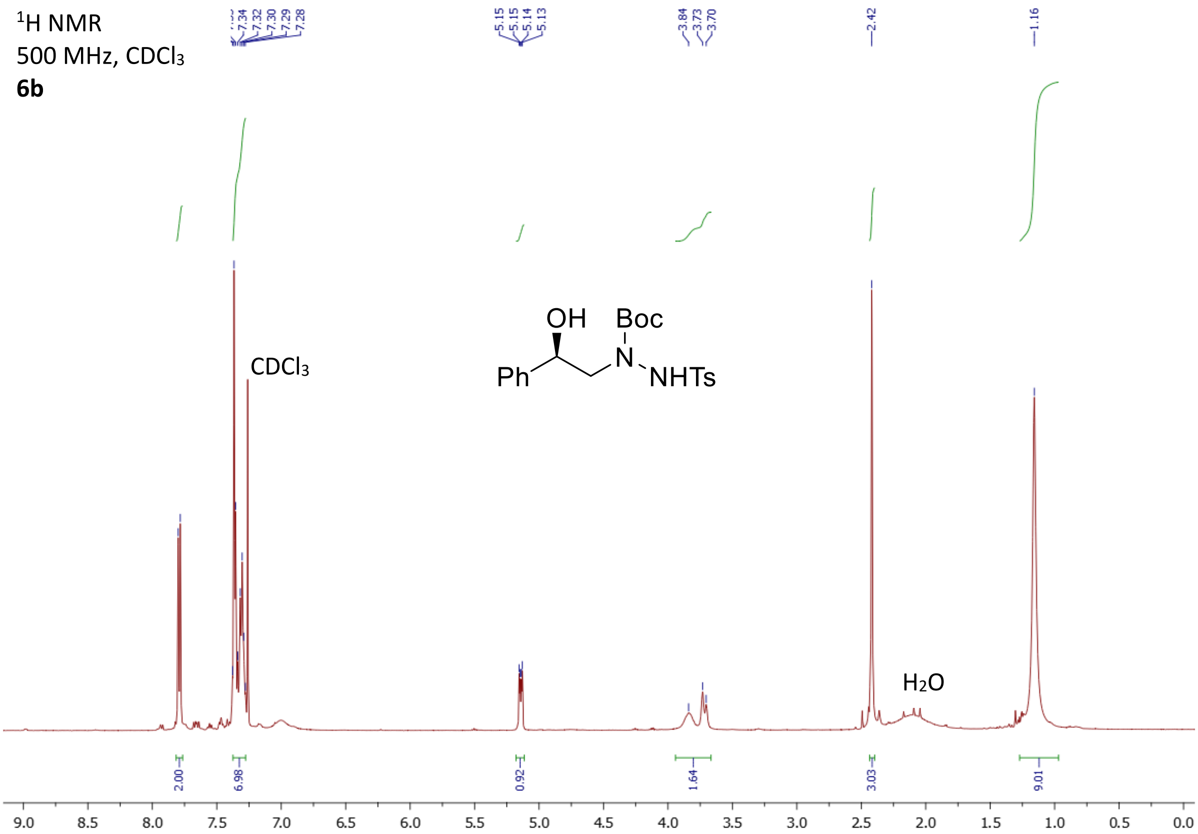


^{13}C NMR
100 MHz, $CDCl_3$
6a

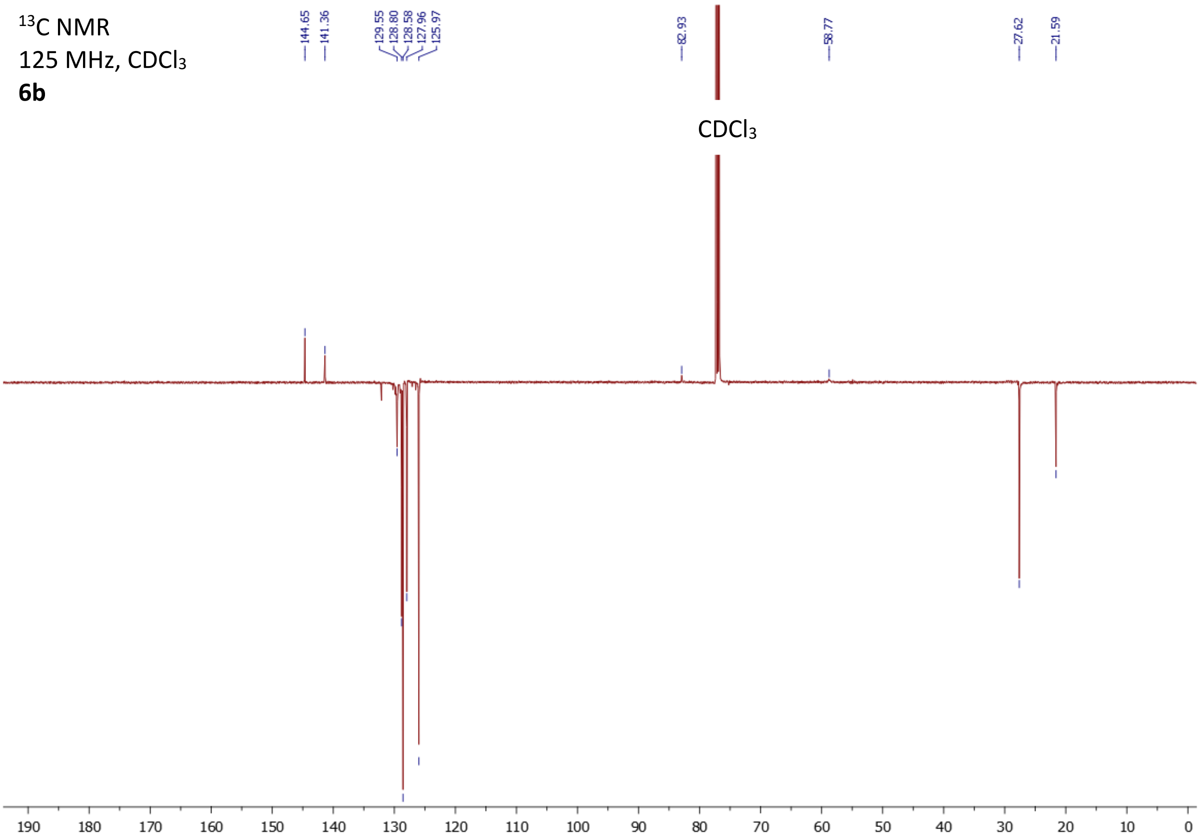


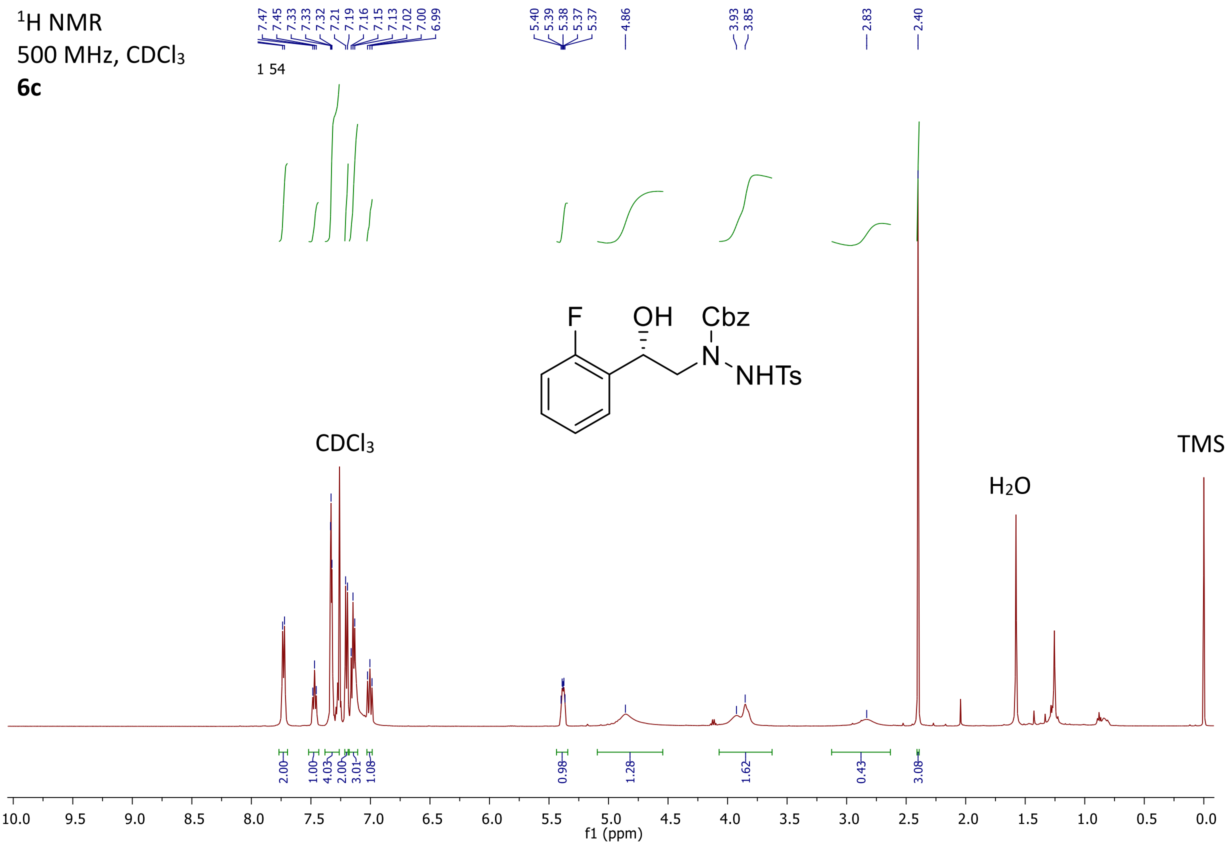

HSQC **6a**
(to show ***C***HOH)
δ = 71.00
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
20
40
60
80
100
120
140
160
180
200

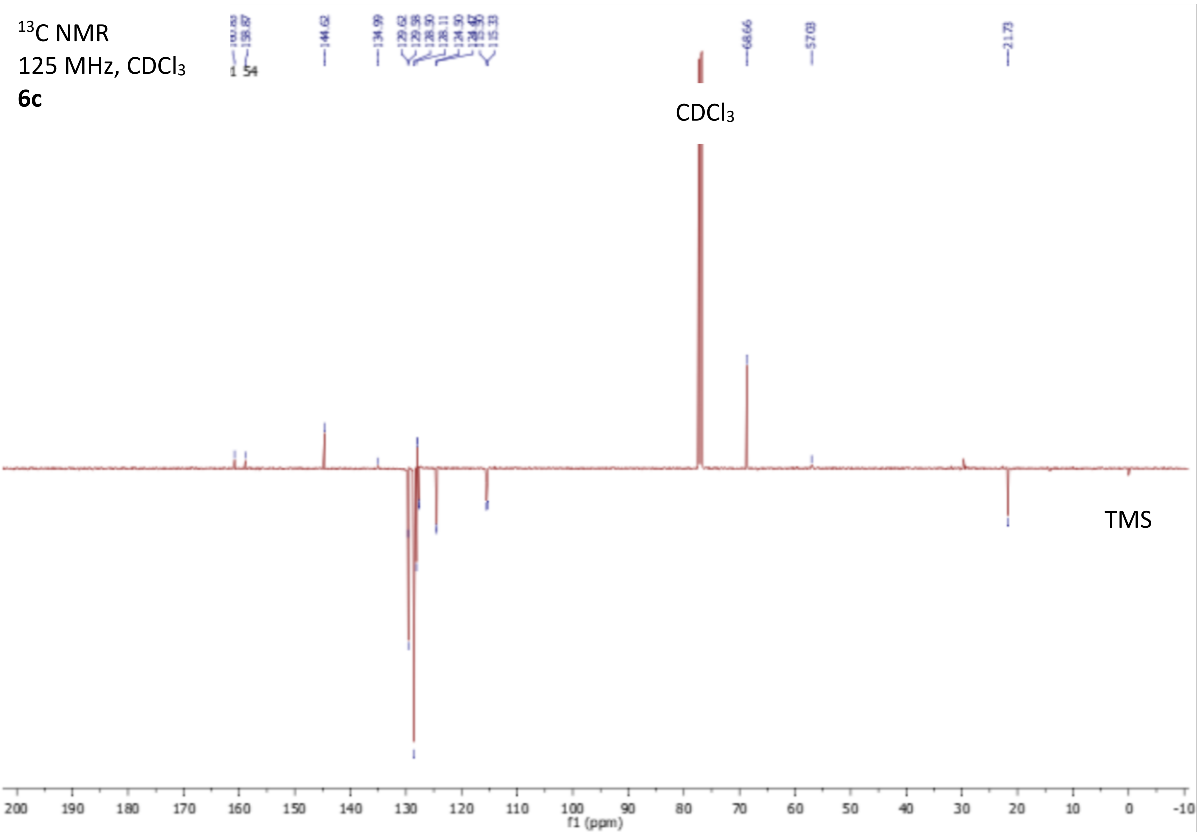
^{1}H NMR
500 MHz, $CDCl_3$
6b

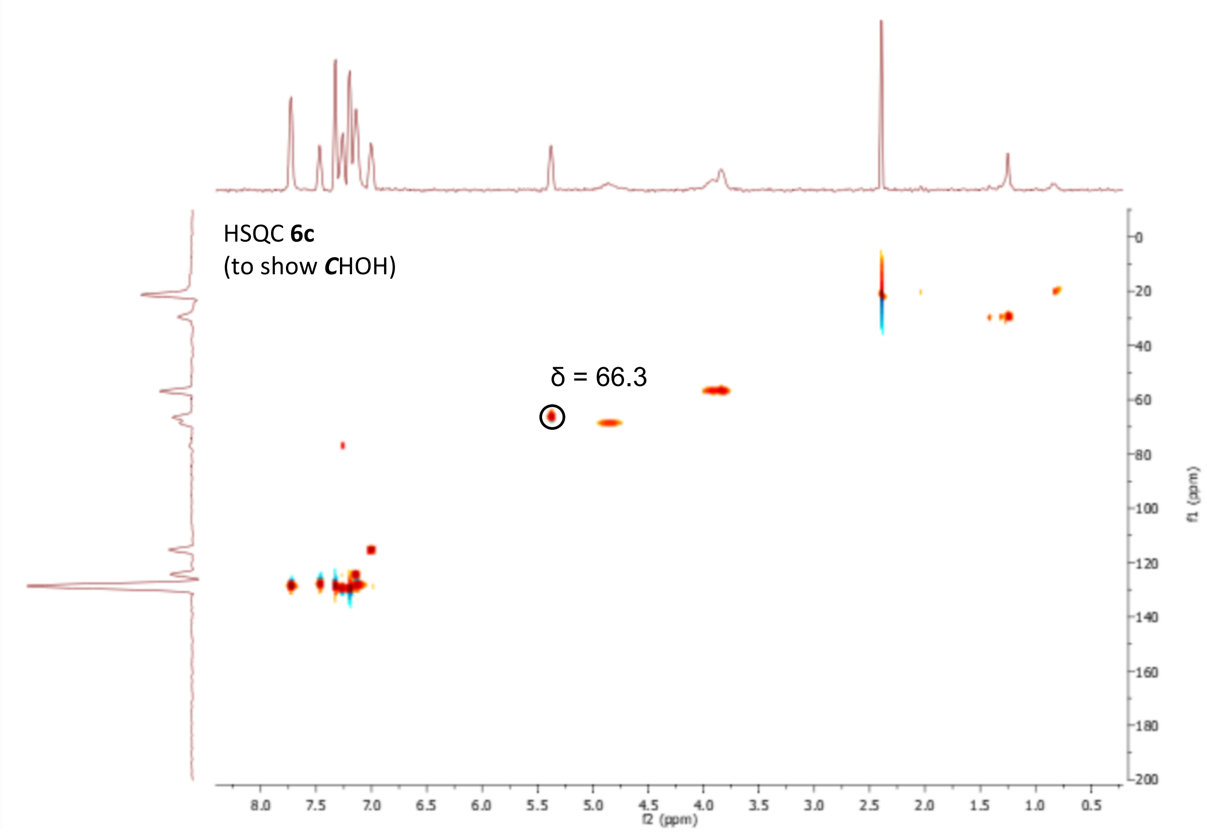


^{13}C NMR
125 MHz, $CDCl_3$
6b

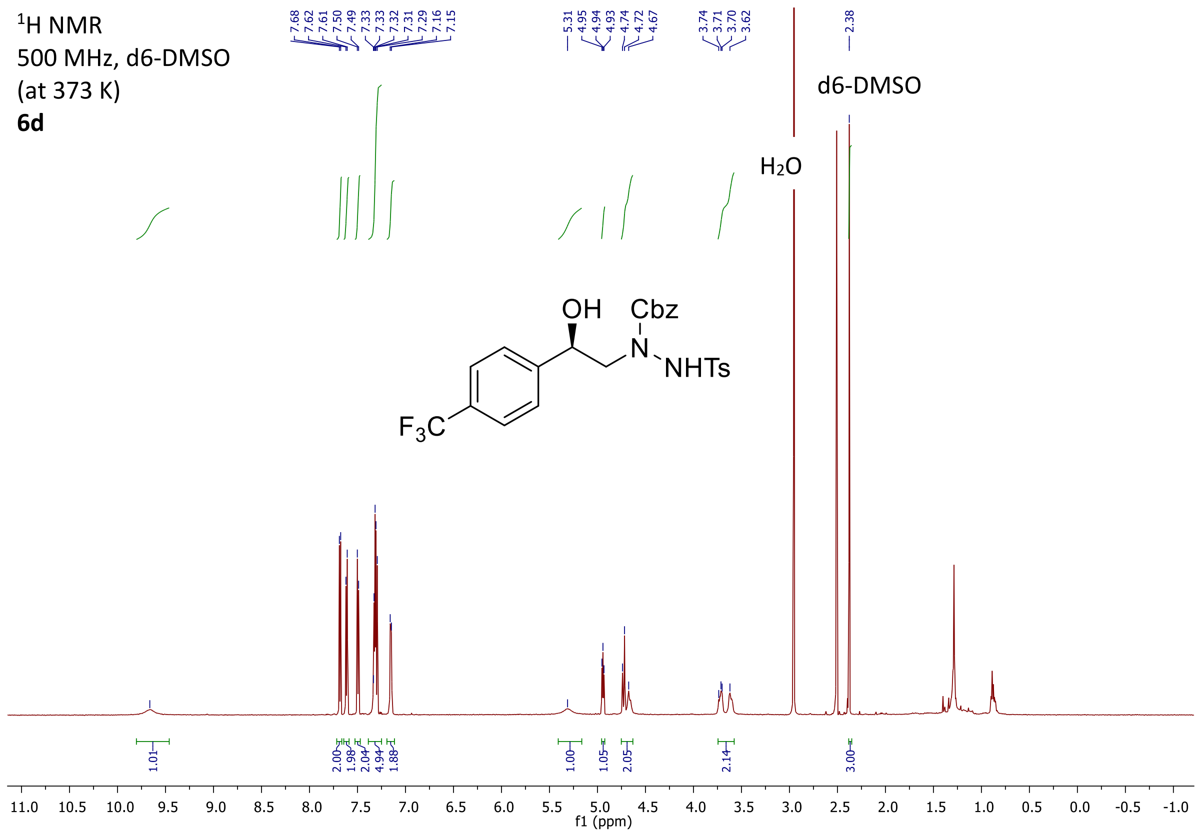



^{1}H NMR
500 MHz, CDCl$_3$
6c
7.47
7.45
7.33
7.33
7.32
7.21
7.19
7.16
7.15
7.13
7.02
7.00
6.99
5.40
5.39
5.38
5.37
5.37
4.86
3.93
3.85
2.83
2.40
F
OH
Cbz
N
NHTs
CDCl3
H2O
TMS
2.00
1.00
4.03
2.00
3.01
1.08
0.98
1.28
1.62
0.43
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

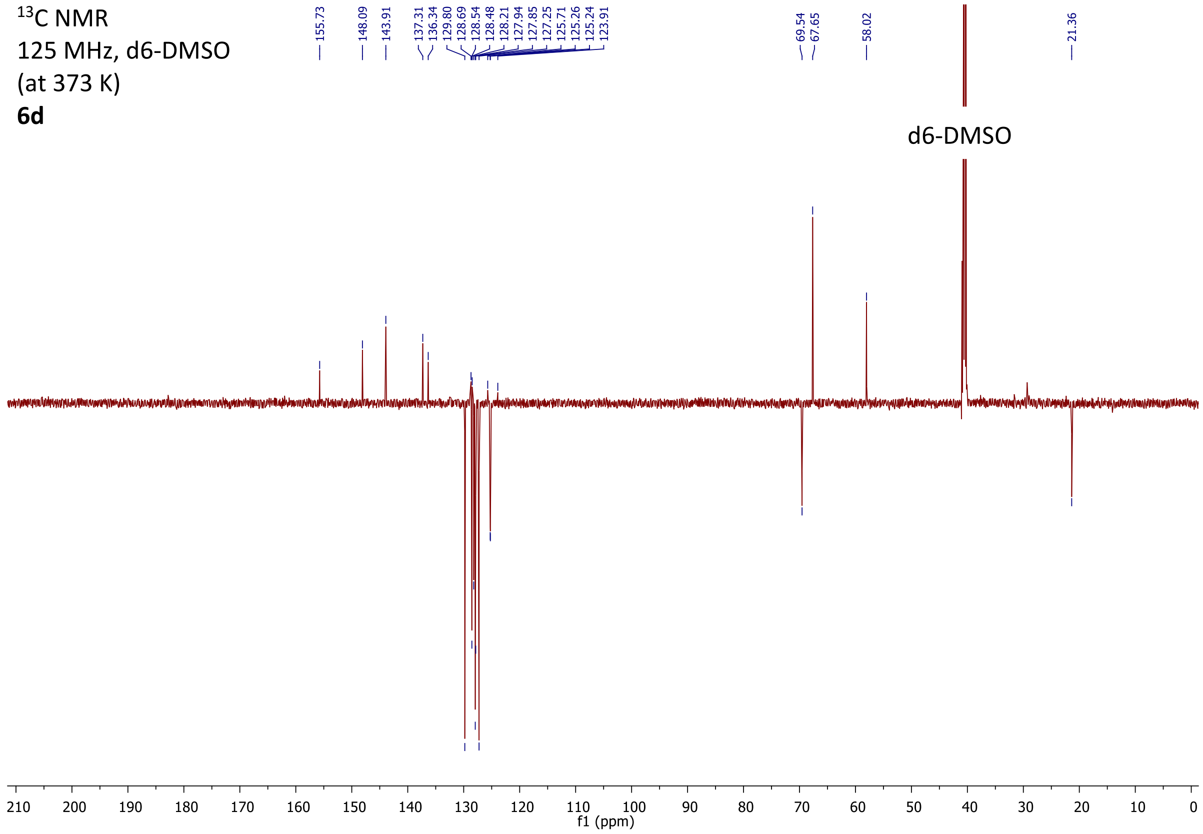

^{13}C NMR
125 MHz, CDCl$_3$
6c
158.87
144.62
134.99
129.62
129.58
128.90
128.11
124.50
124.47
115.50
115.33
68.66
57.03
21.73
CDCl3
TMS
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


HSQC **6c**
(to show ***C***HOH)
δ = 66.3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)

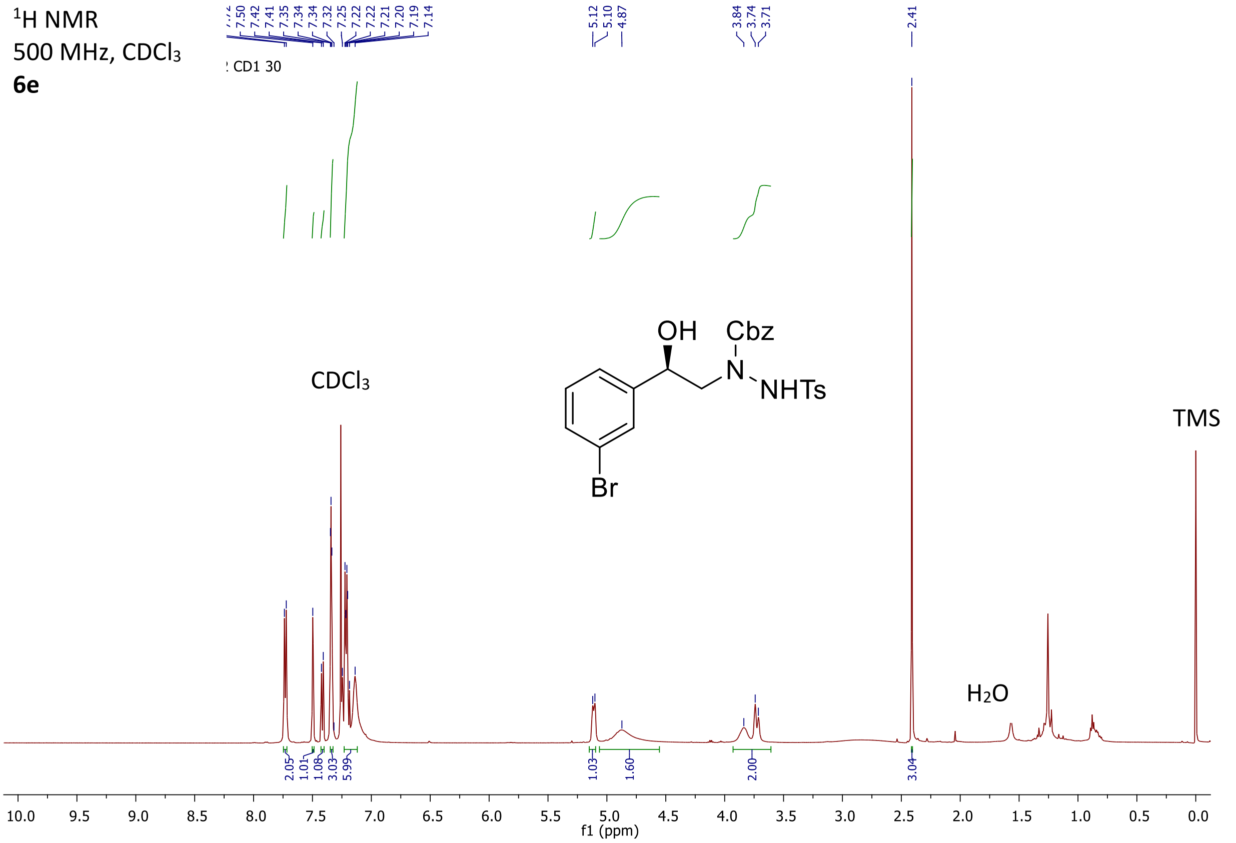
^{1}H NMR
500 MHz, d6-DMSO
(at 373 K)
6d



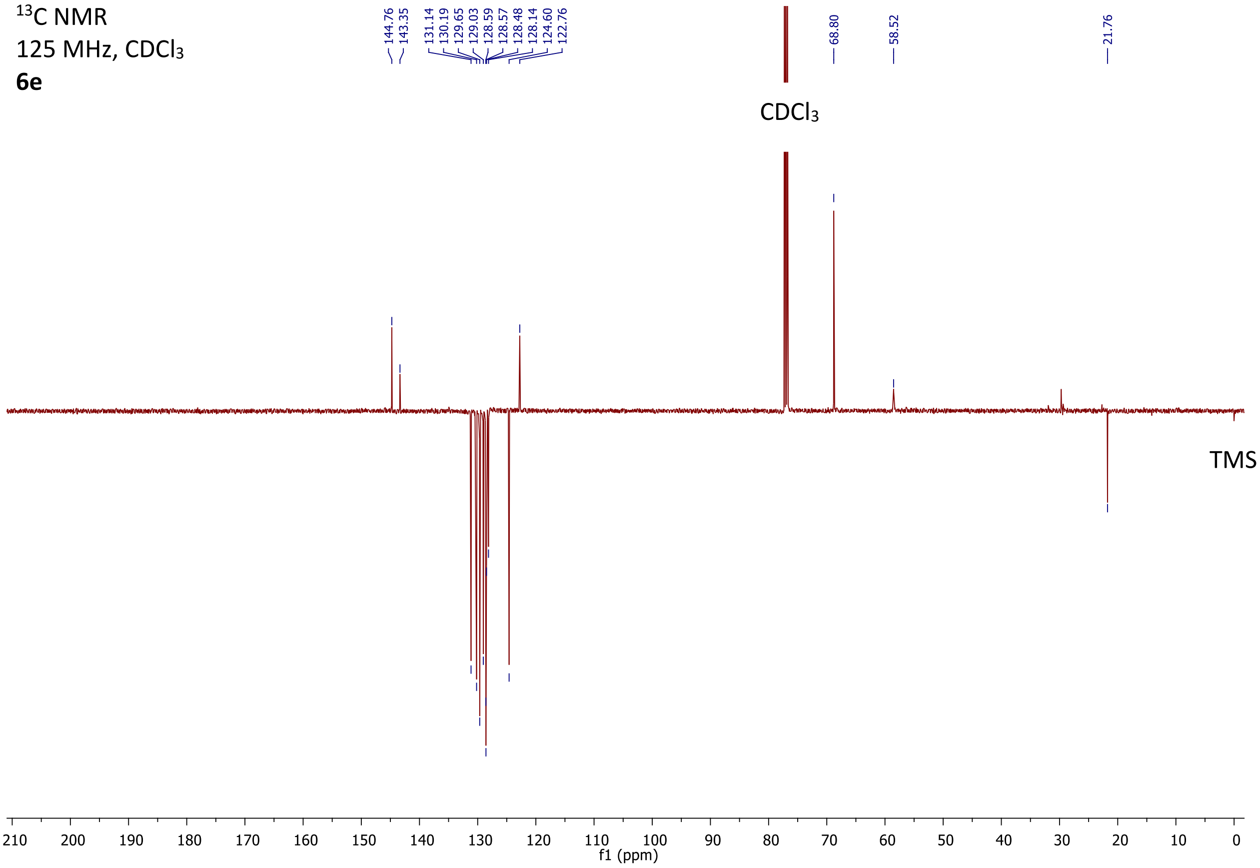
^{13}C NMR
125 MHz, d6-DMSO
(at 373 K)
6d

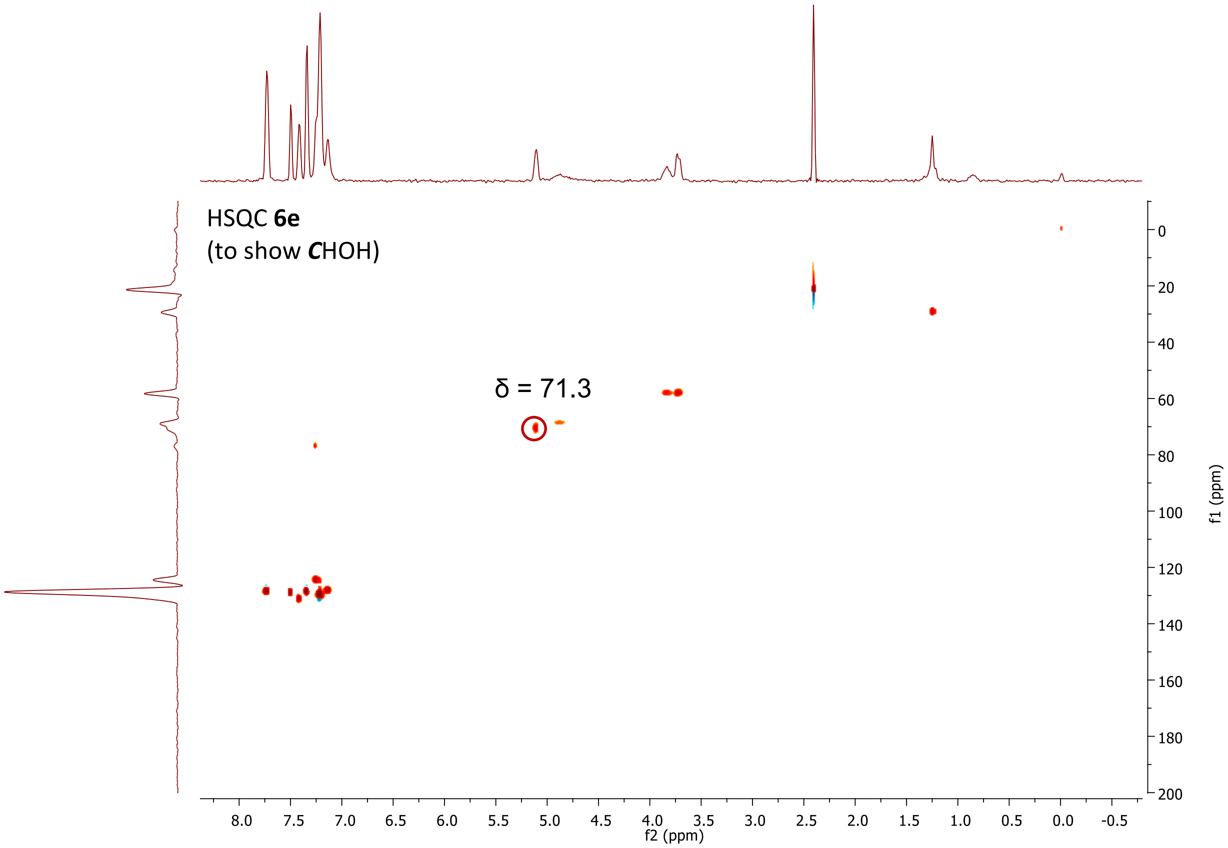


^{1}H NMR
500 MHz, $CDCl_3$
6e

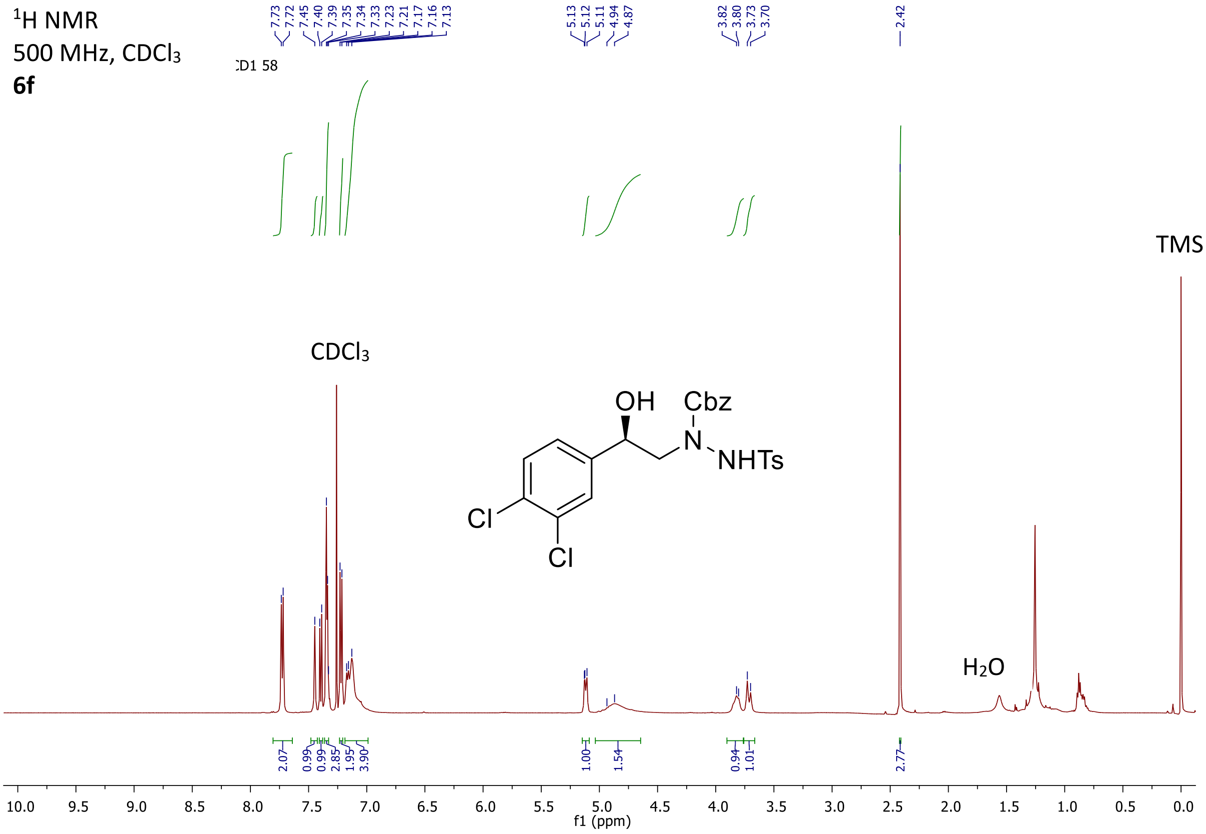


^{13}C NMR
125 MHz, $CDCl_3$
6e

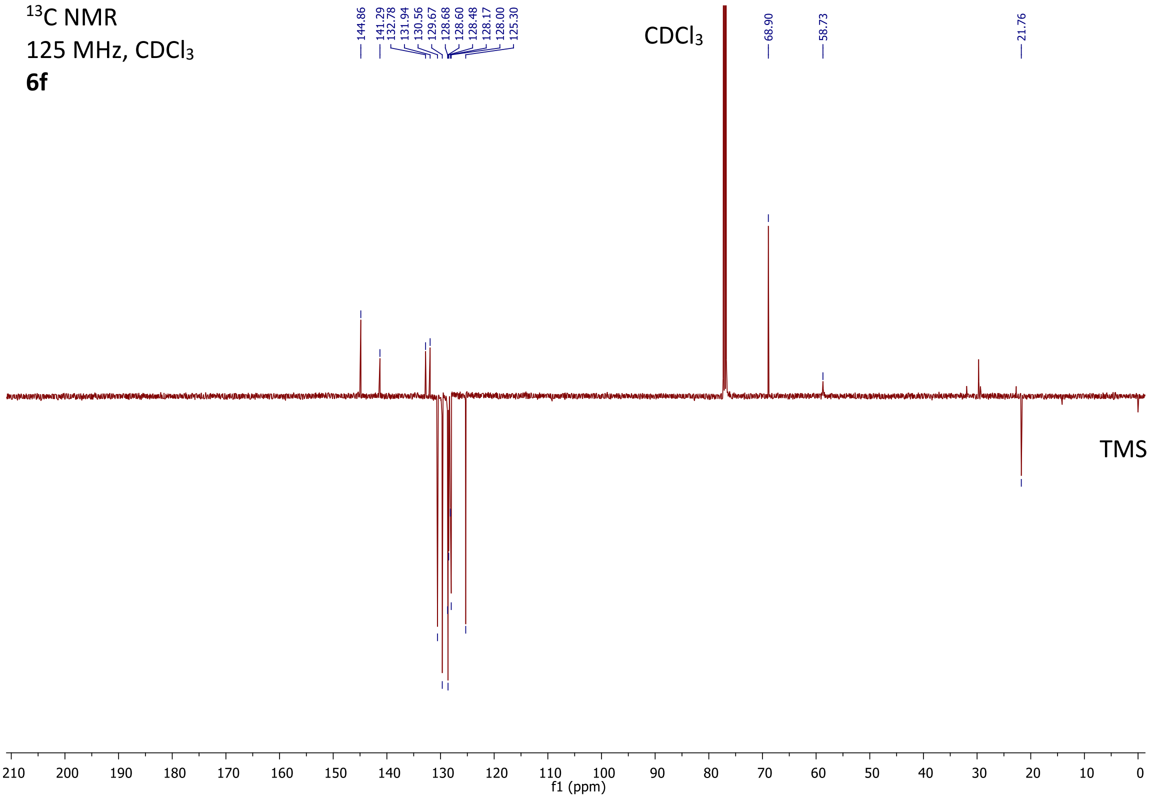


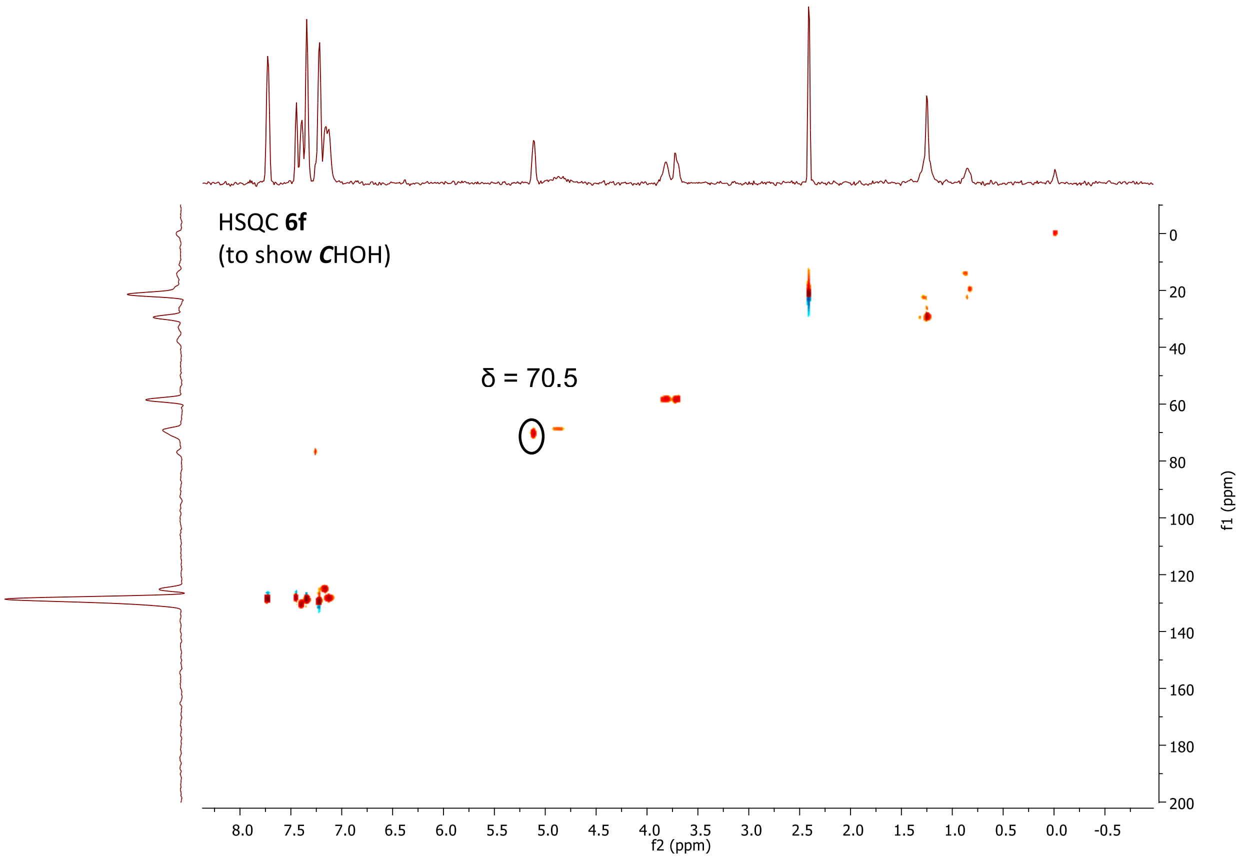

HSQC **6e**
(to show ***C***HOH)
δ = 71.3
f1 (ppm)
f2 (ppm)
0
20
40
60
80
100
120
140
160
180
200
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

^{1}H NMR
500 MHz, $CDCl_3$
6f

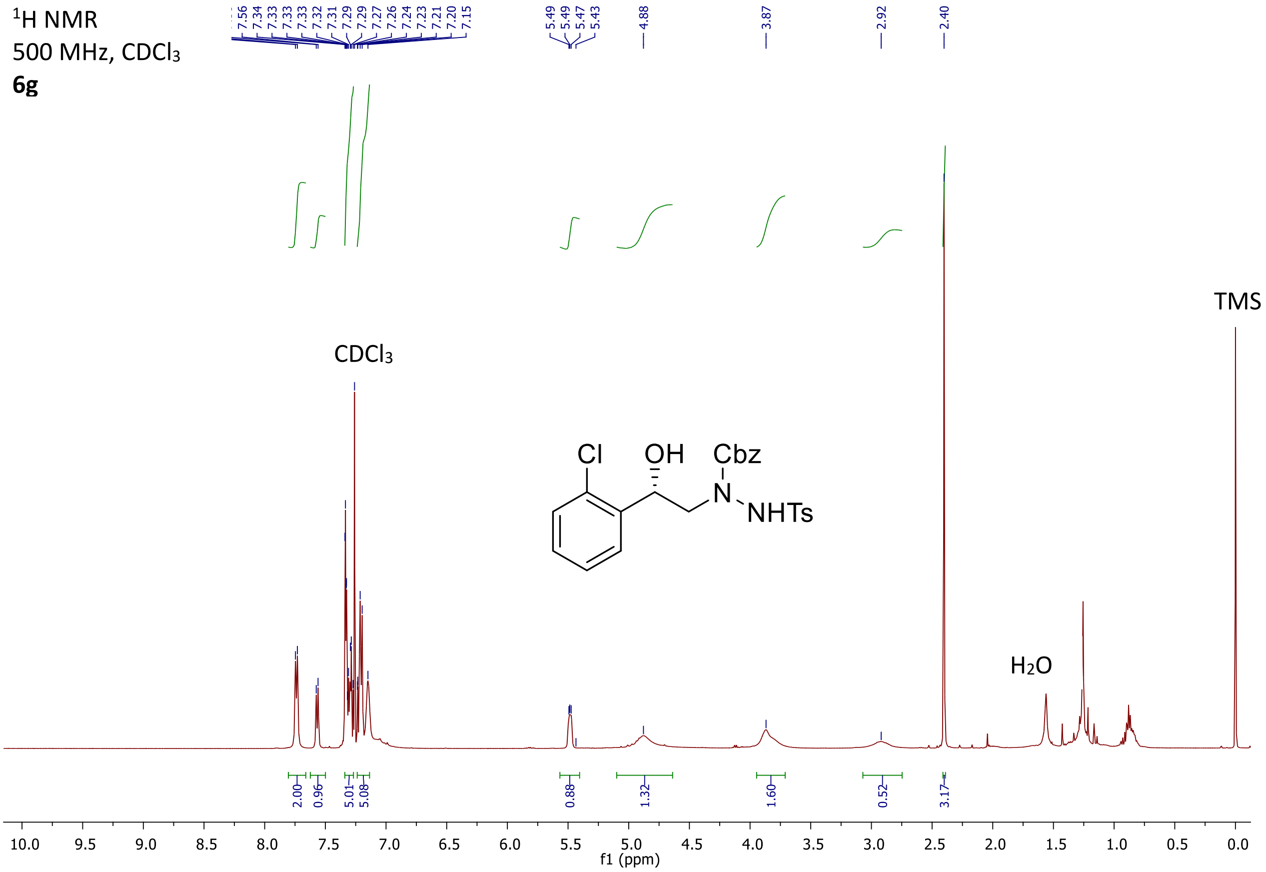


^{13}C NMR
125 MHz, $CDCl_3$
6f

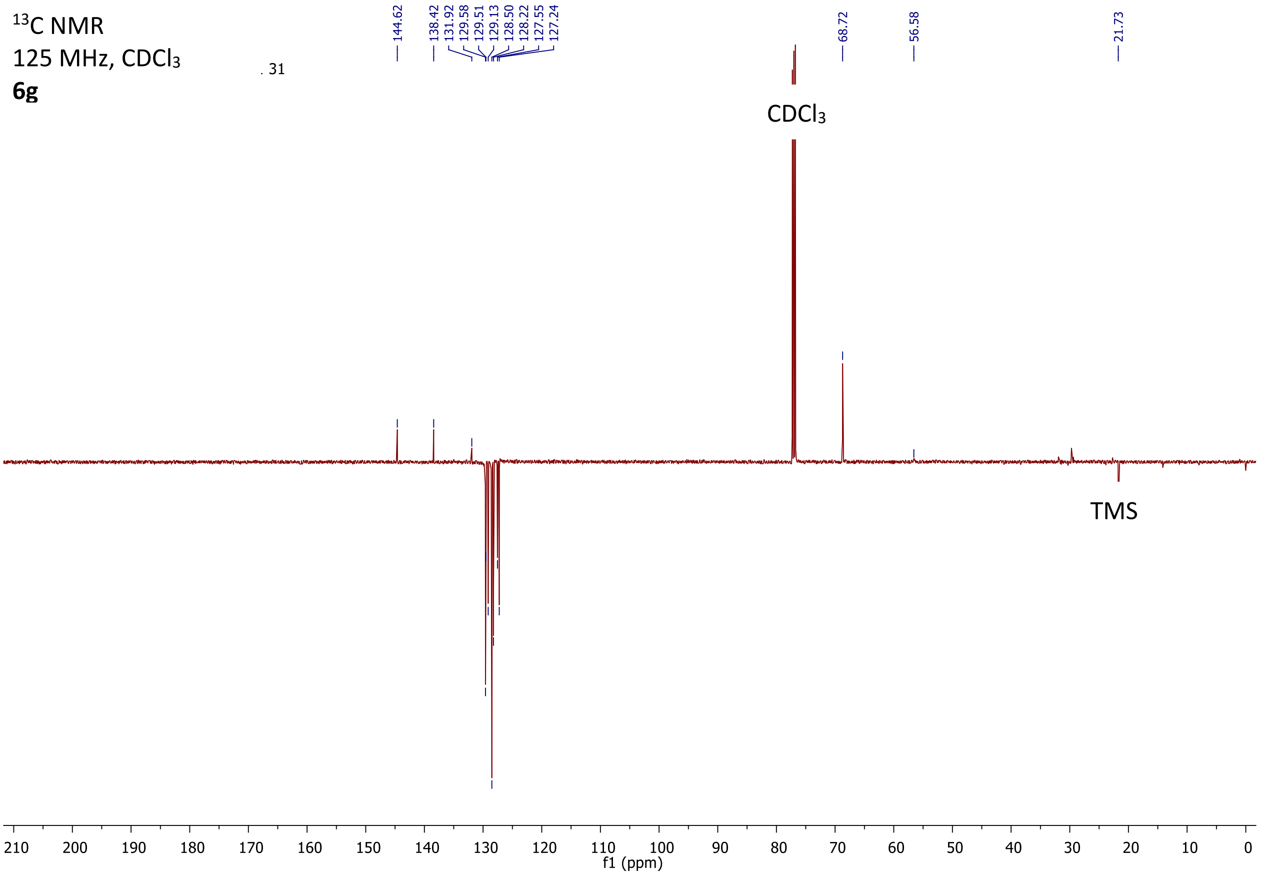


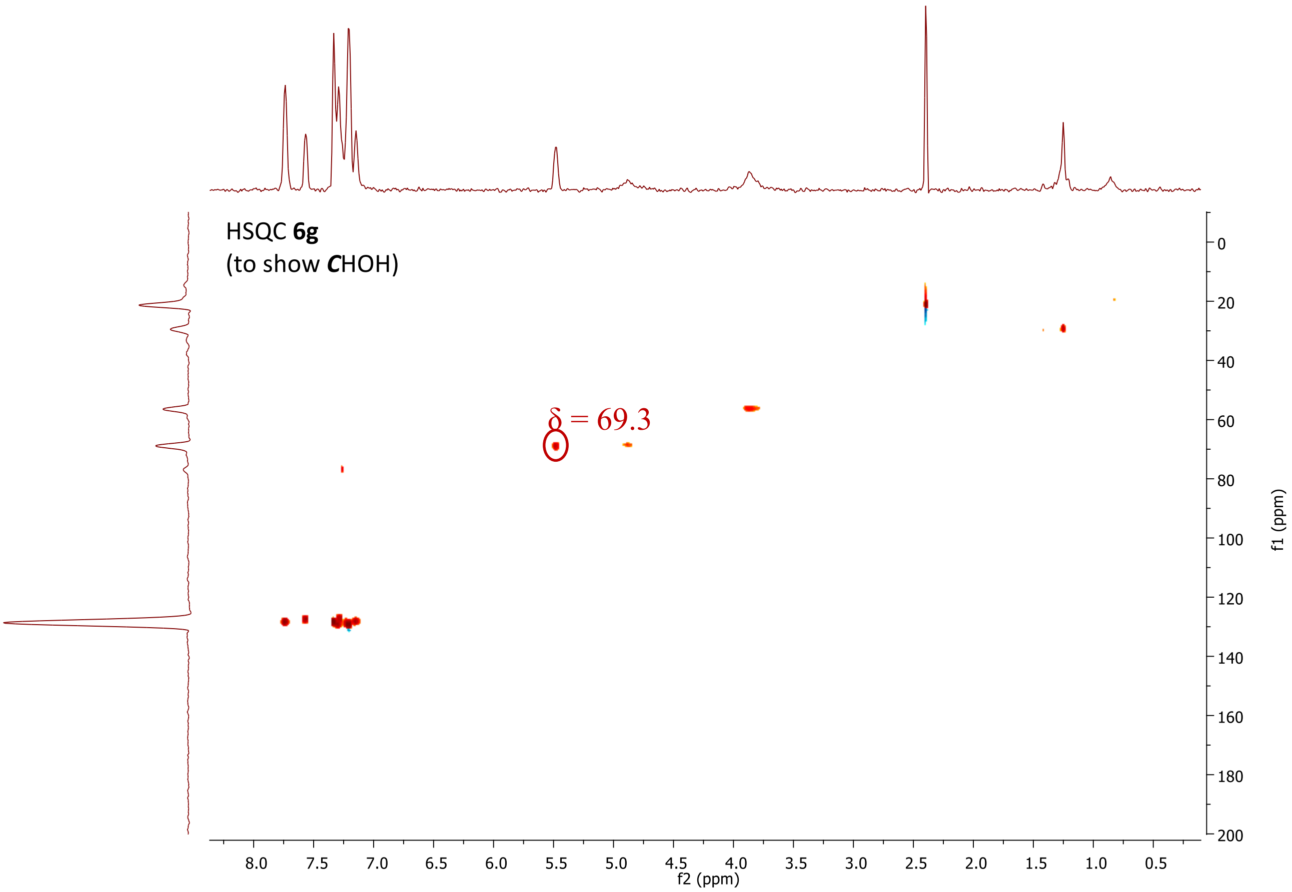

HSQC **6f**
(to show ***C***HOH)
δ = 70.5
0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)

^{1}H NMR
500 MHz, $CDCl_3$
6g

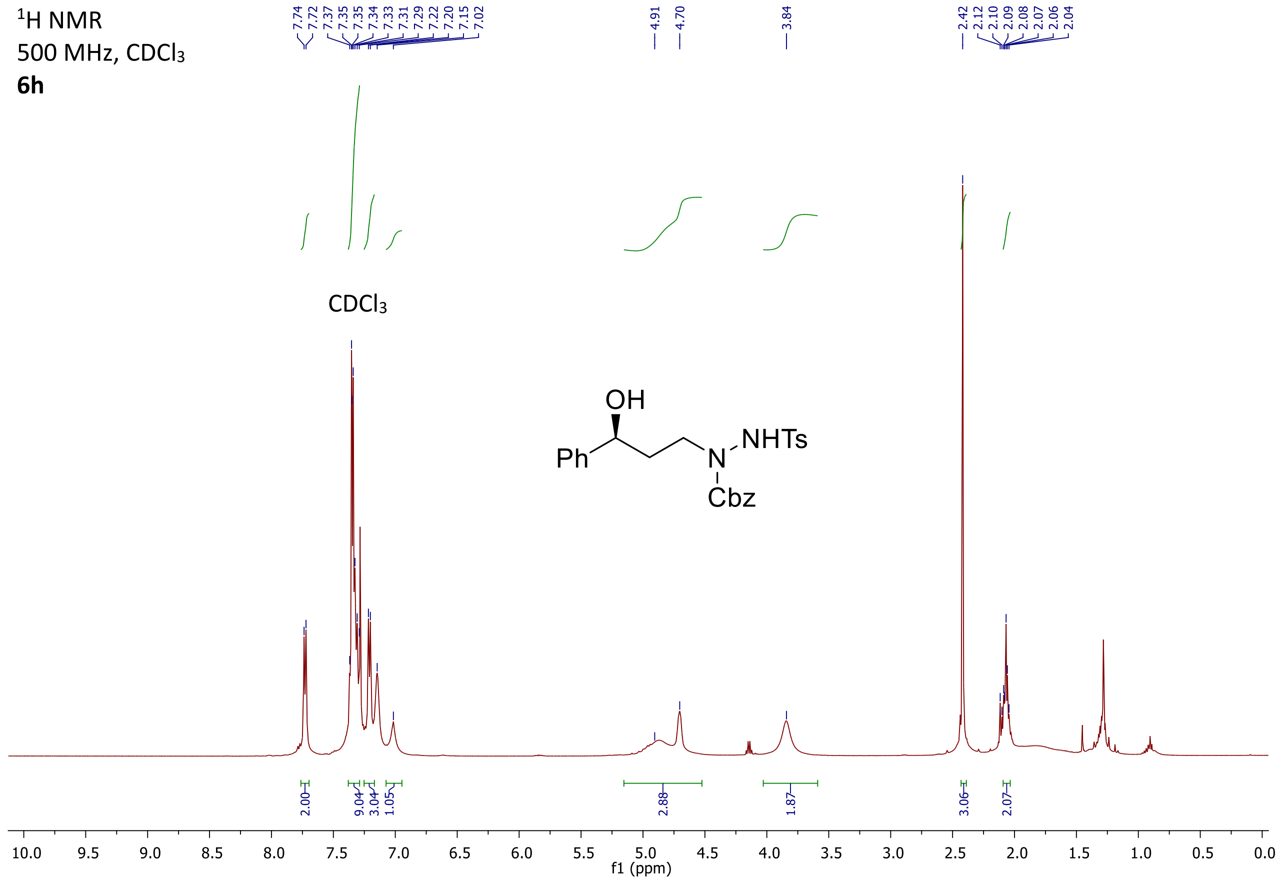


^{13}C NMR
125 MHz, $CDCl_3$
6g

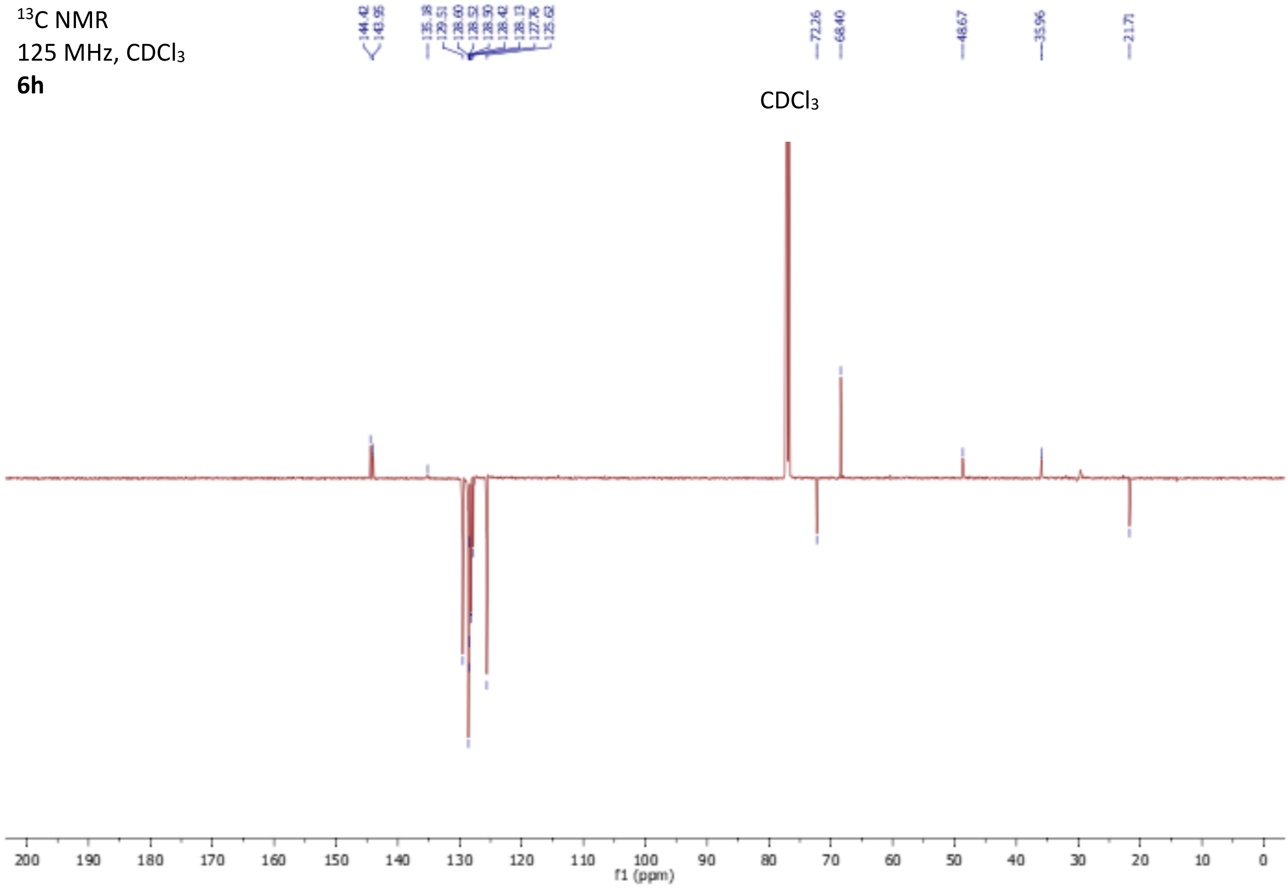


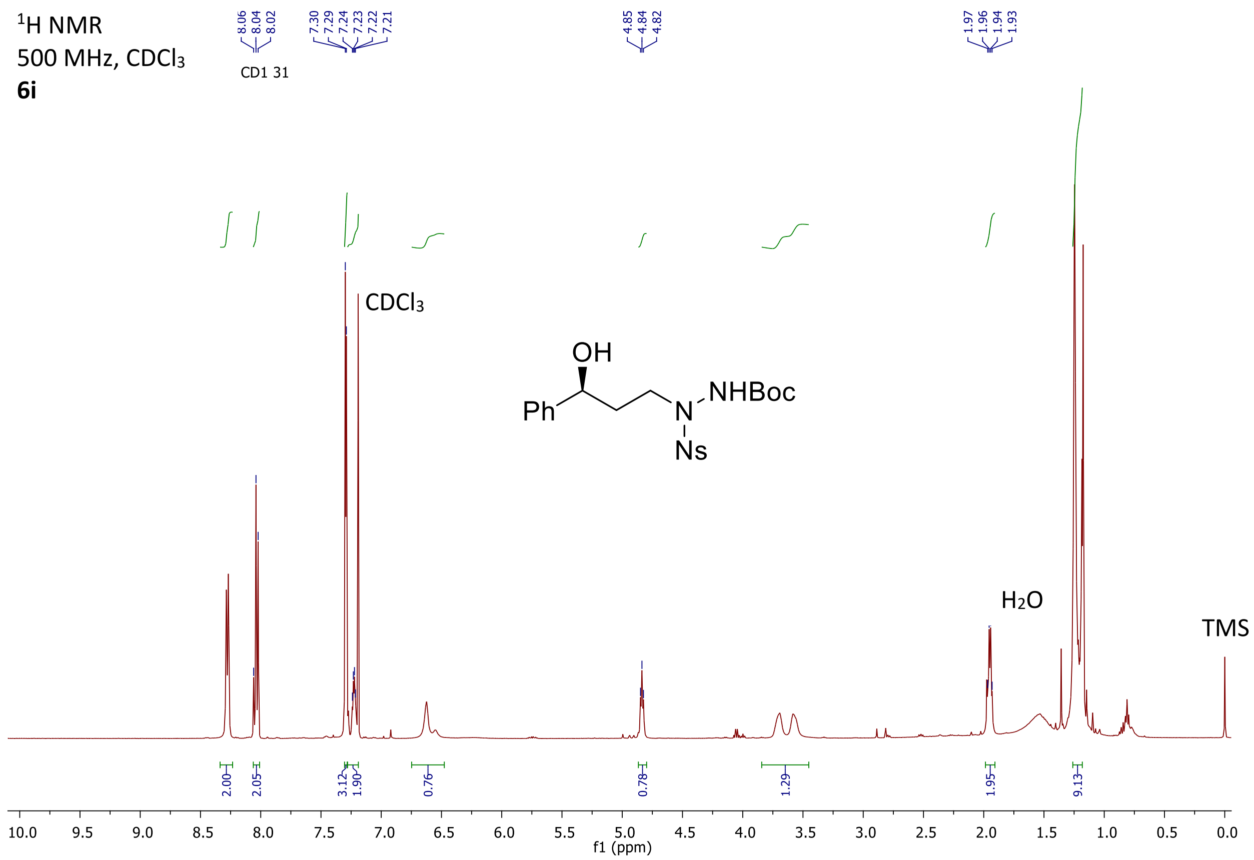

HSQC **6g**
(to show ***C*HOH)**
δ = 69.3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)

^{1}H NMR
500 MHz, $CDCl_3$
6h

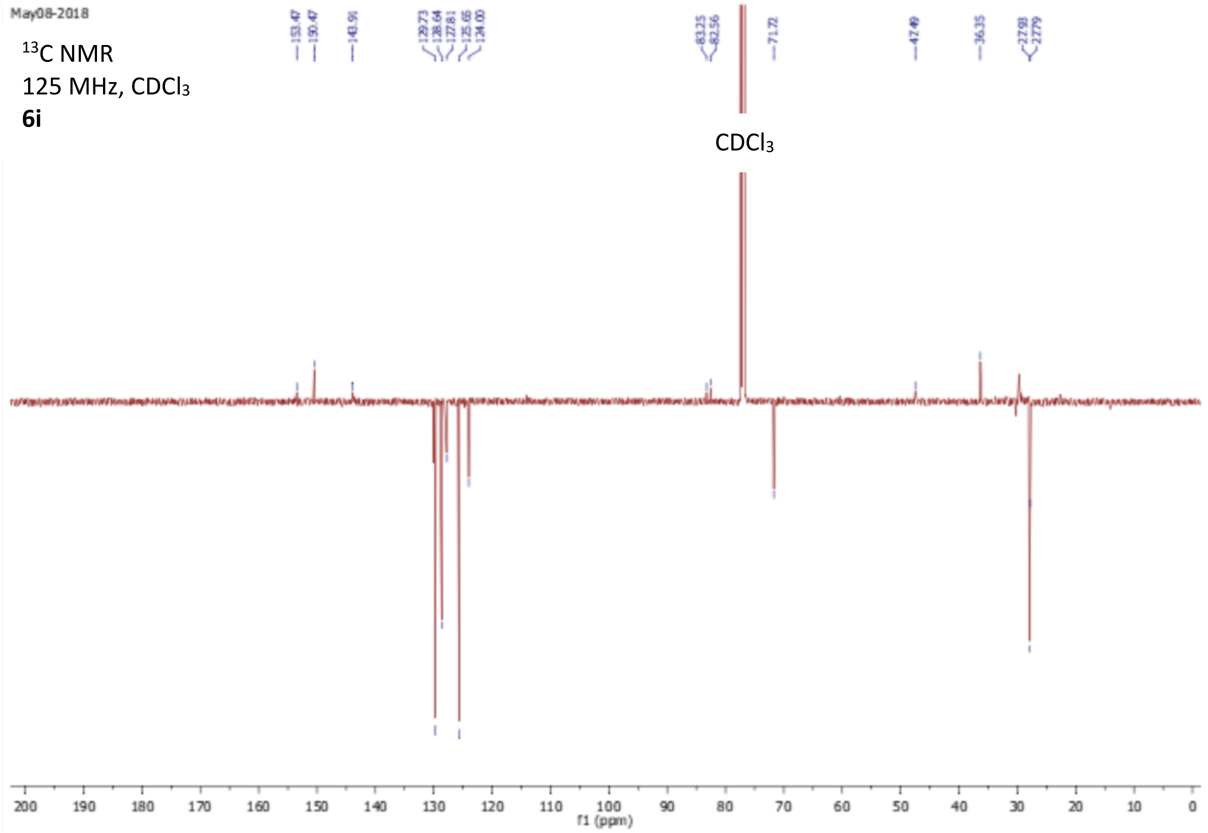


^{13}C NMR
125 MHz, $CDCl_3$
6h



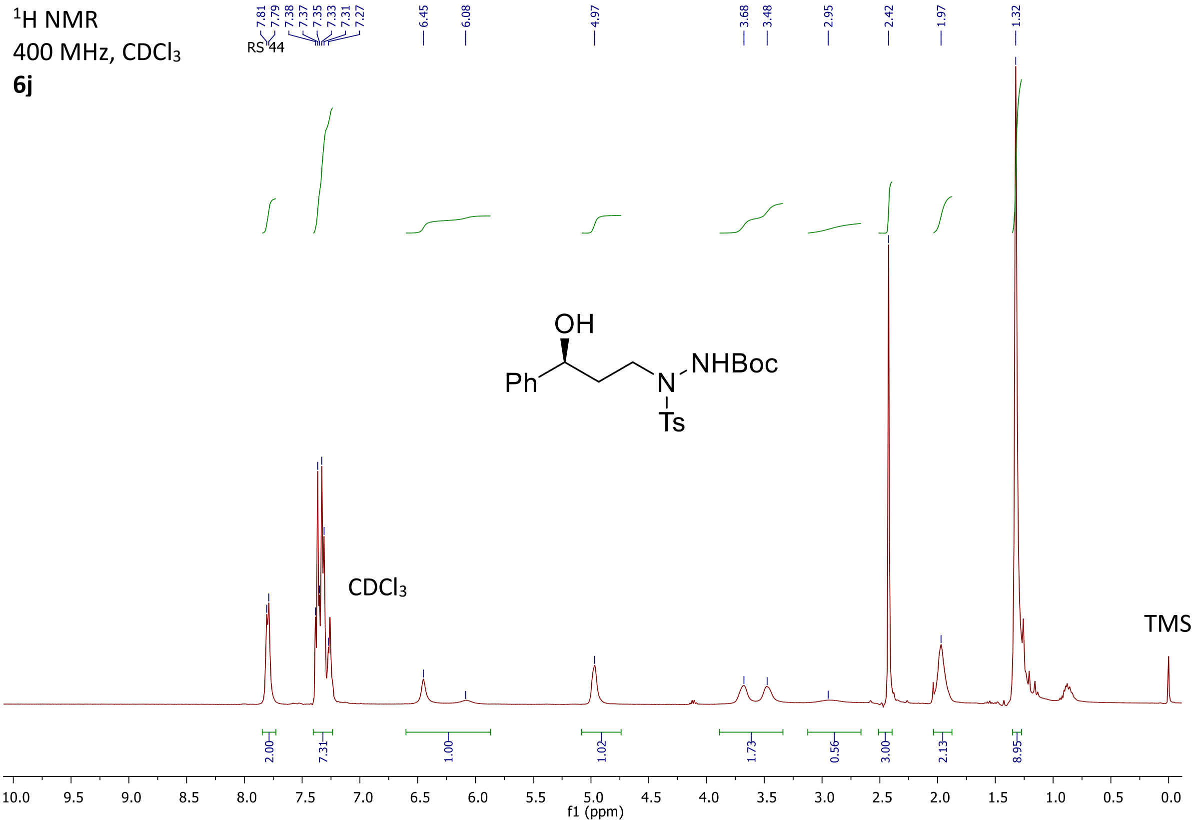


^{1}H NMR
500 MHz, $CDCl_3$
6i
8.06
8.04
8.02
CD1 31
7.30
7.29
7.24
7.23
7.22
7.21
4.85
4.84
4.82
1.97
1.96
1.94
1.93
$CDCl_3$
OH
Ph
NHBoc
N
Ns
H_2O
TMS
2.00
2.05
3.12
1.90
0.76
0.78
1.29
1.95
9.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

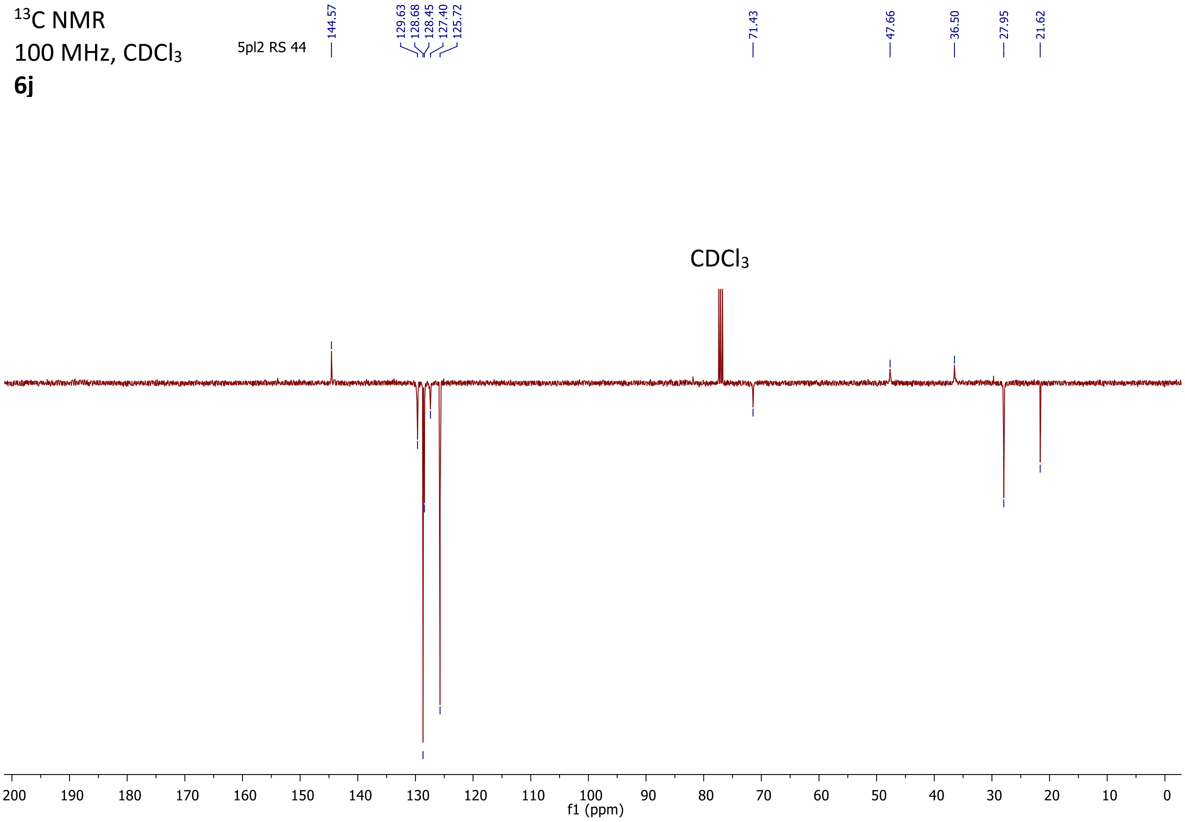


May08-2018
^{13}C NMR
125 MHz, $CDCl_3$
6i
153.47
150.47
143.91
129.73
128.64
127.81
125.65
124.00
83.25
82.56
71.72
47.49
36.35
27.93
27.79
$CDCl_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

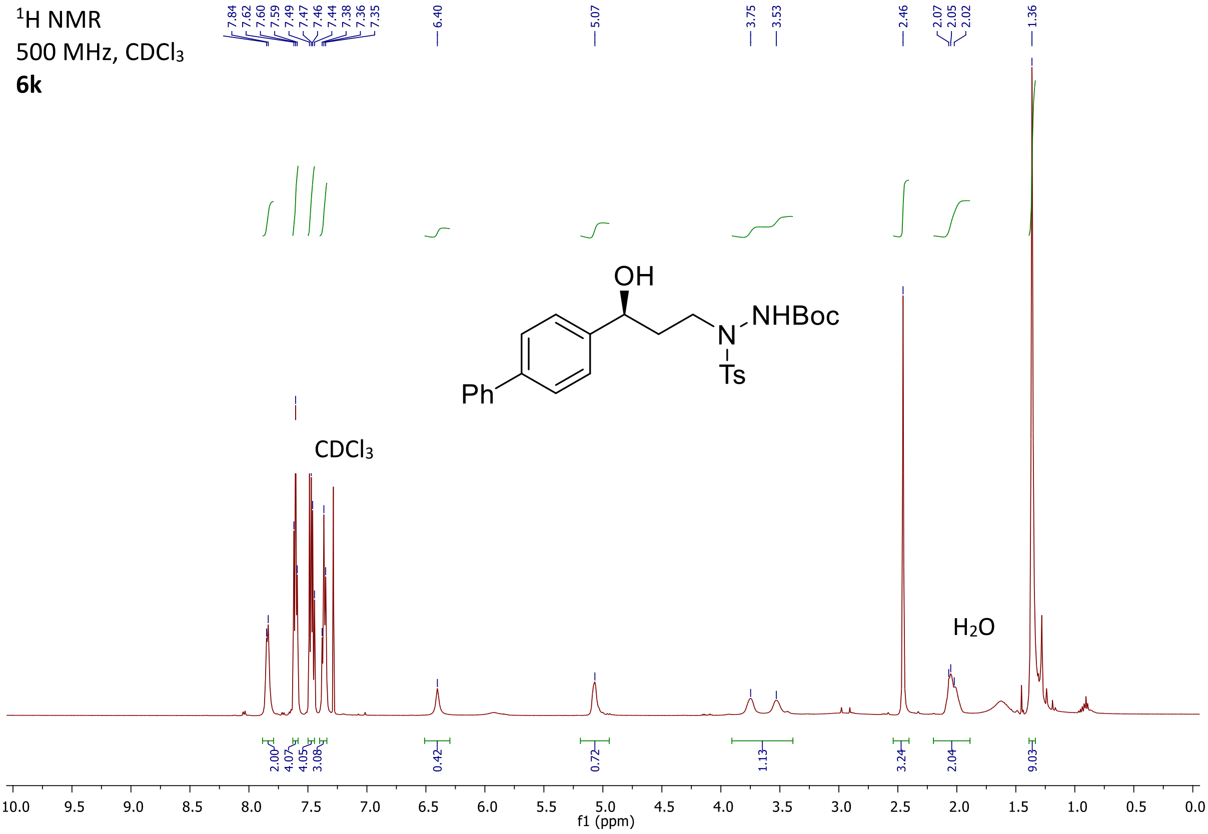
^{1}H NMR
400 MHz, $CDCl_3$
6j



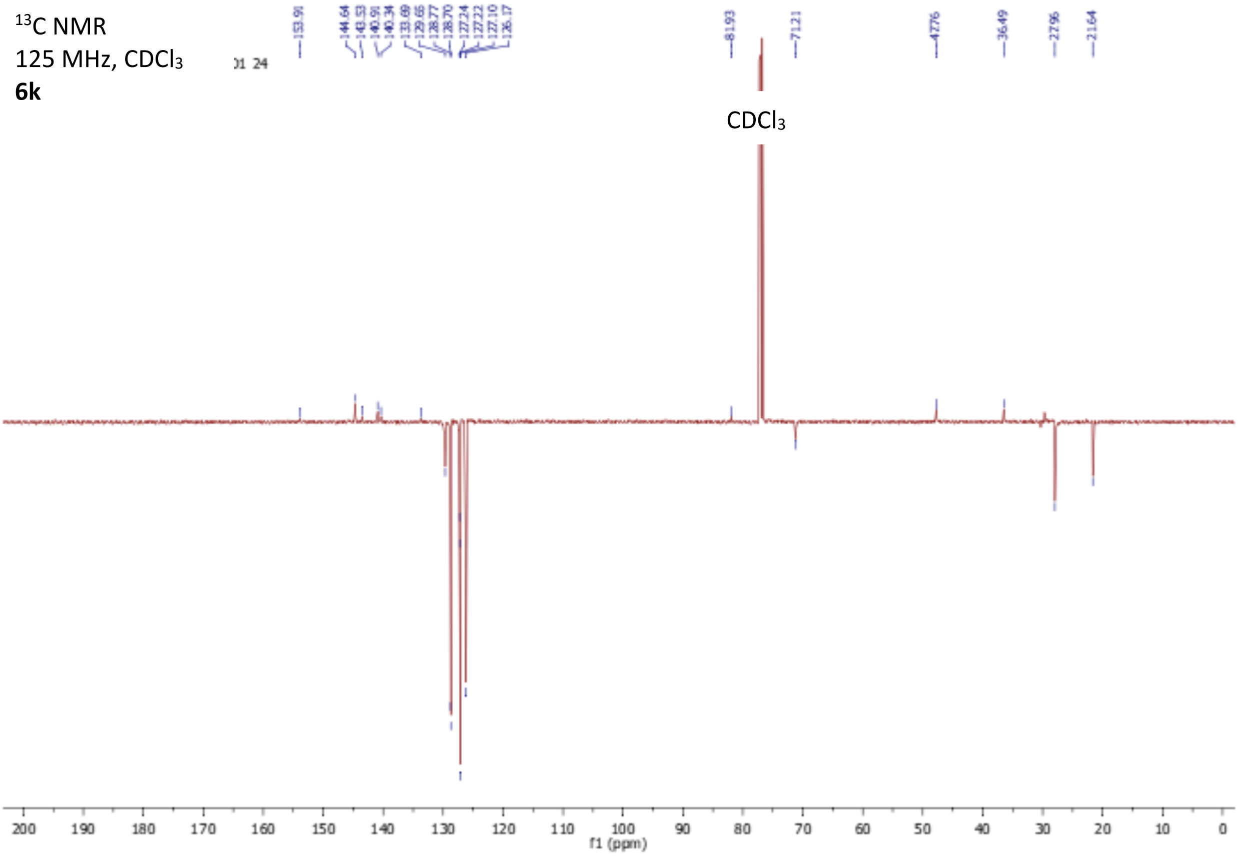
^{13}C NMR
100 MHz, $CDCl_3$
6j

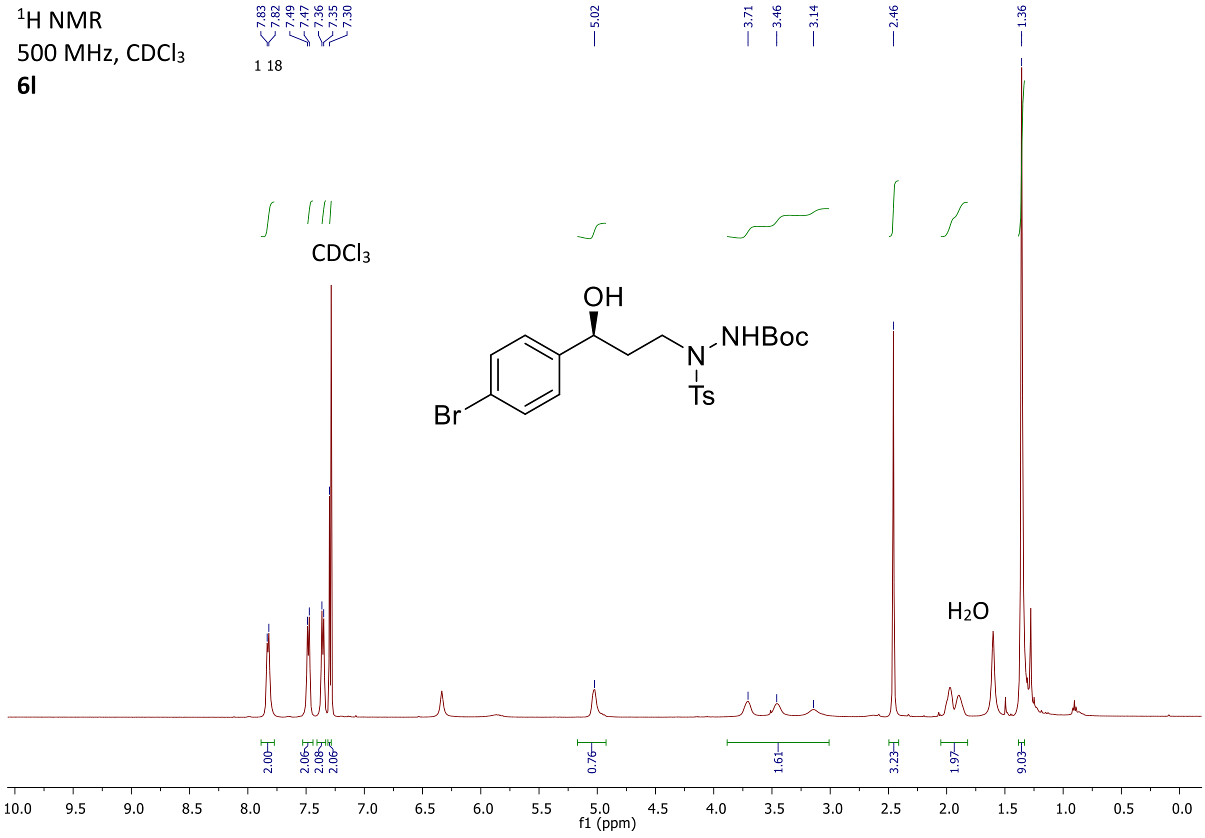


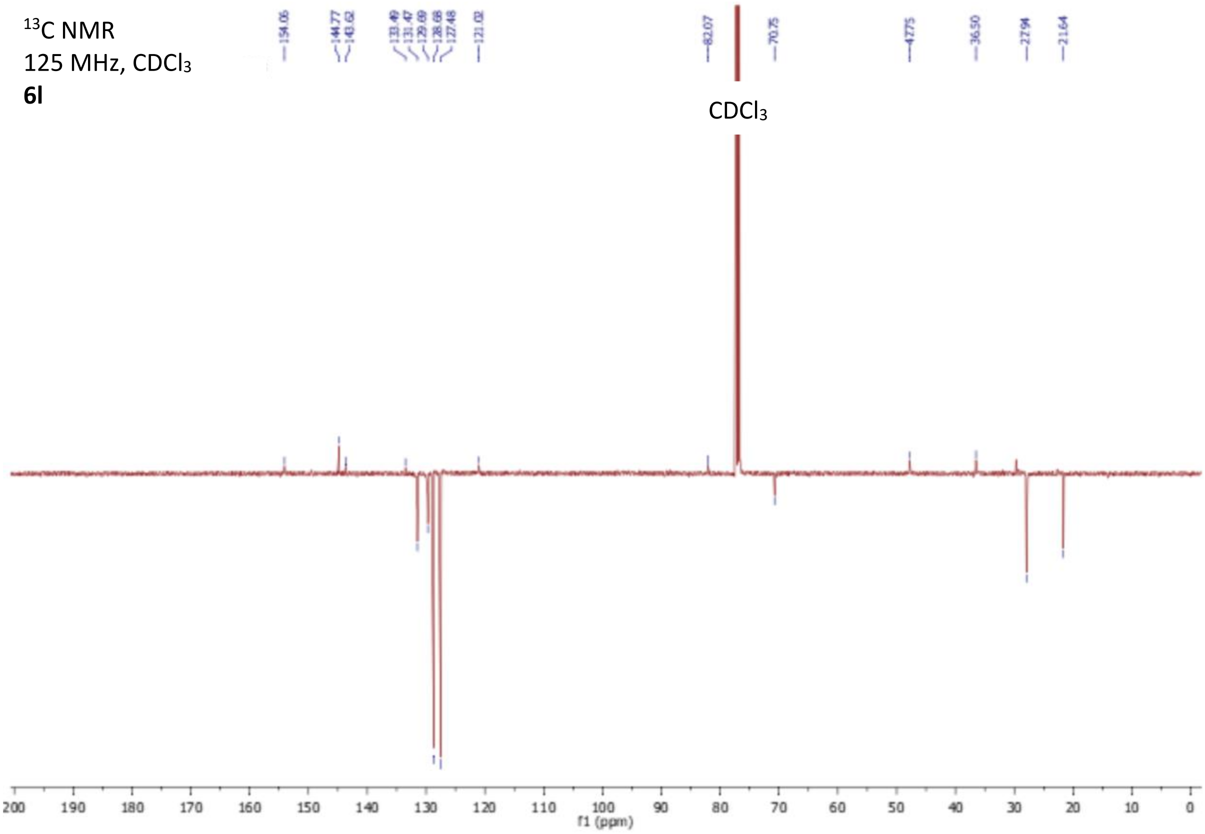
^{1}H NMR
500 MHz, $CDCl_3$
6k



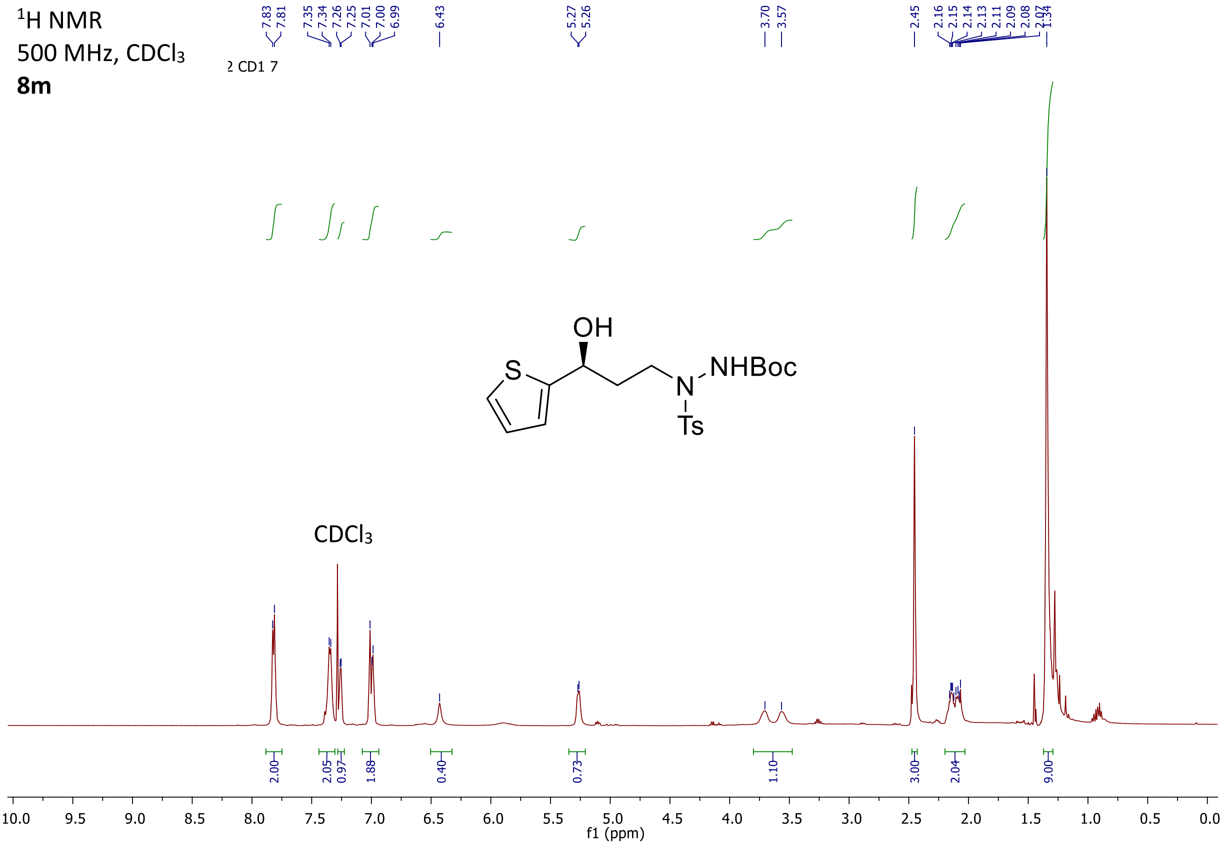
^{13}C NMR
125 MHz, $CDCl_3$
6k



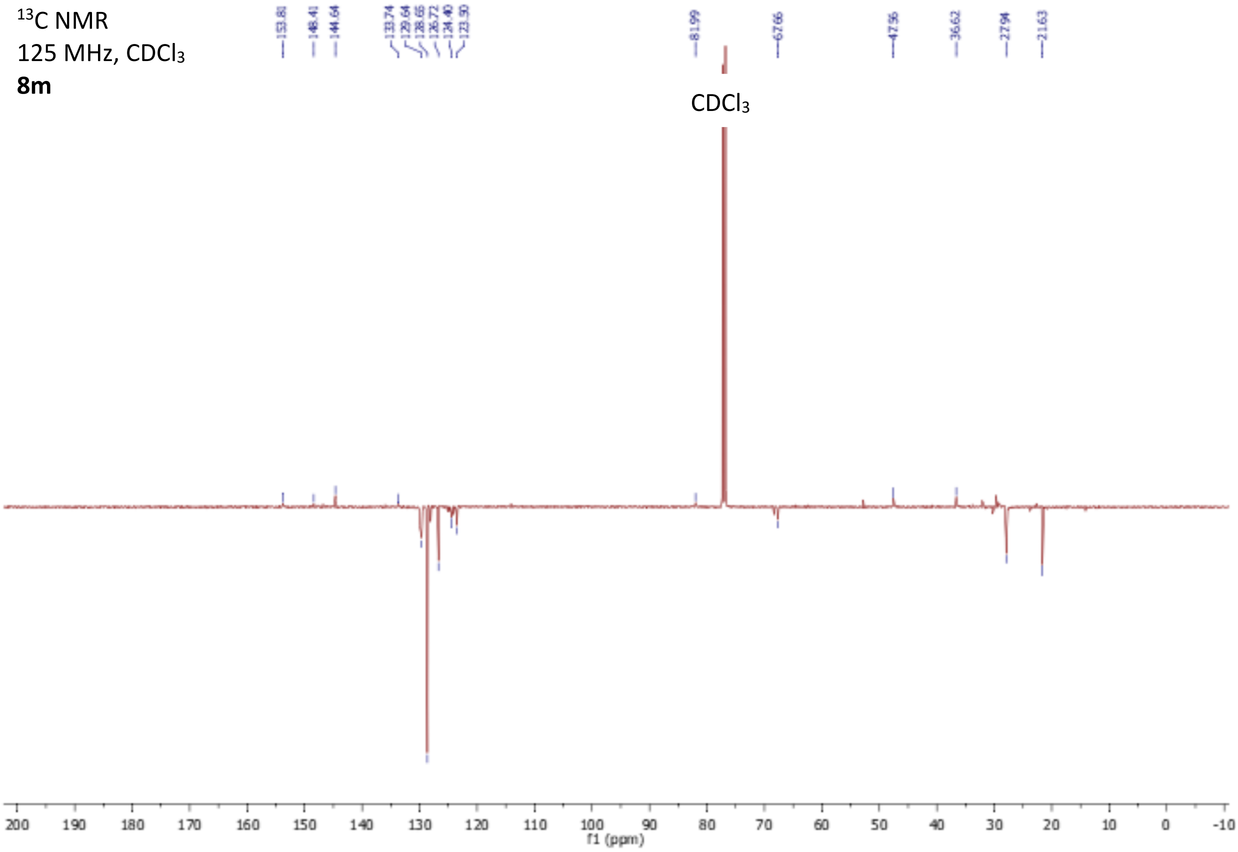

^1H NMR
500 MHz, $CDCl_3$
6l


^{13}C NMR
125 MHz, $CDCl_3$
6l

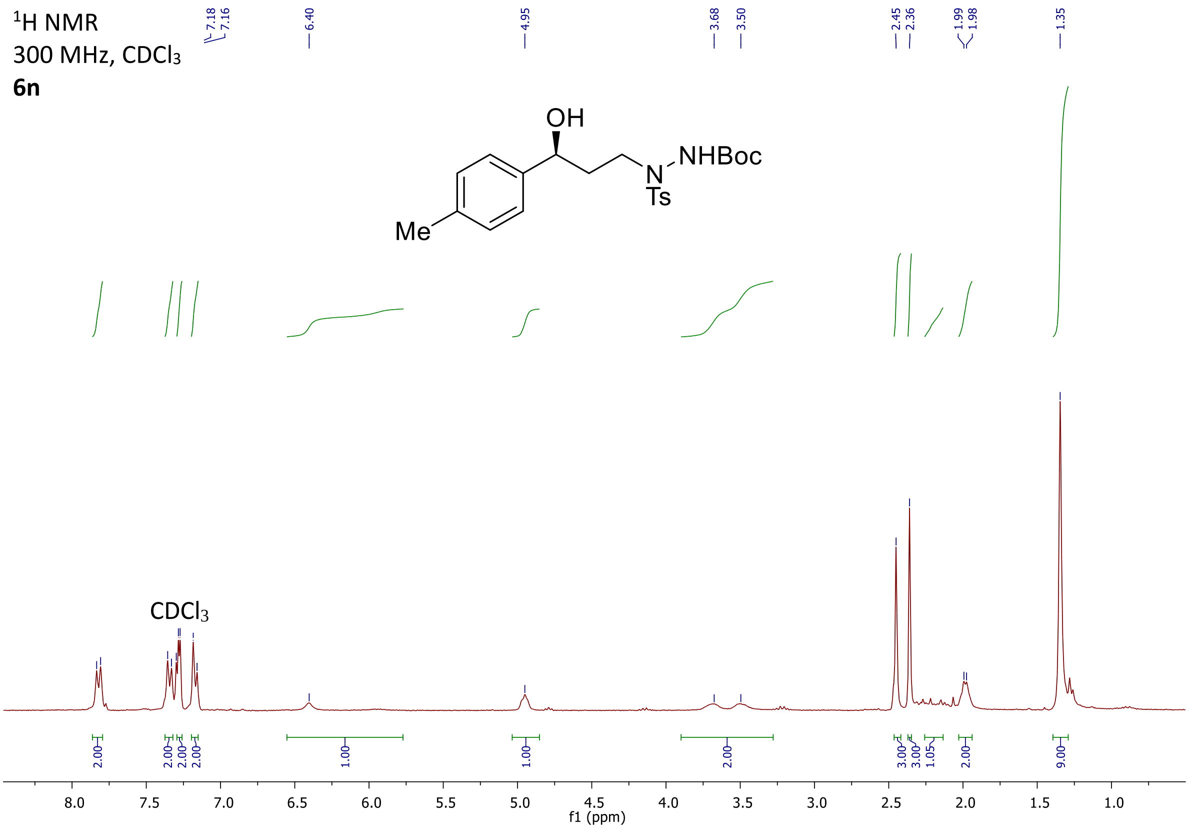
^{1}H NMR
500 MHz, $CDCl_3$
8m



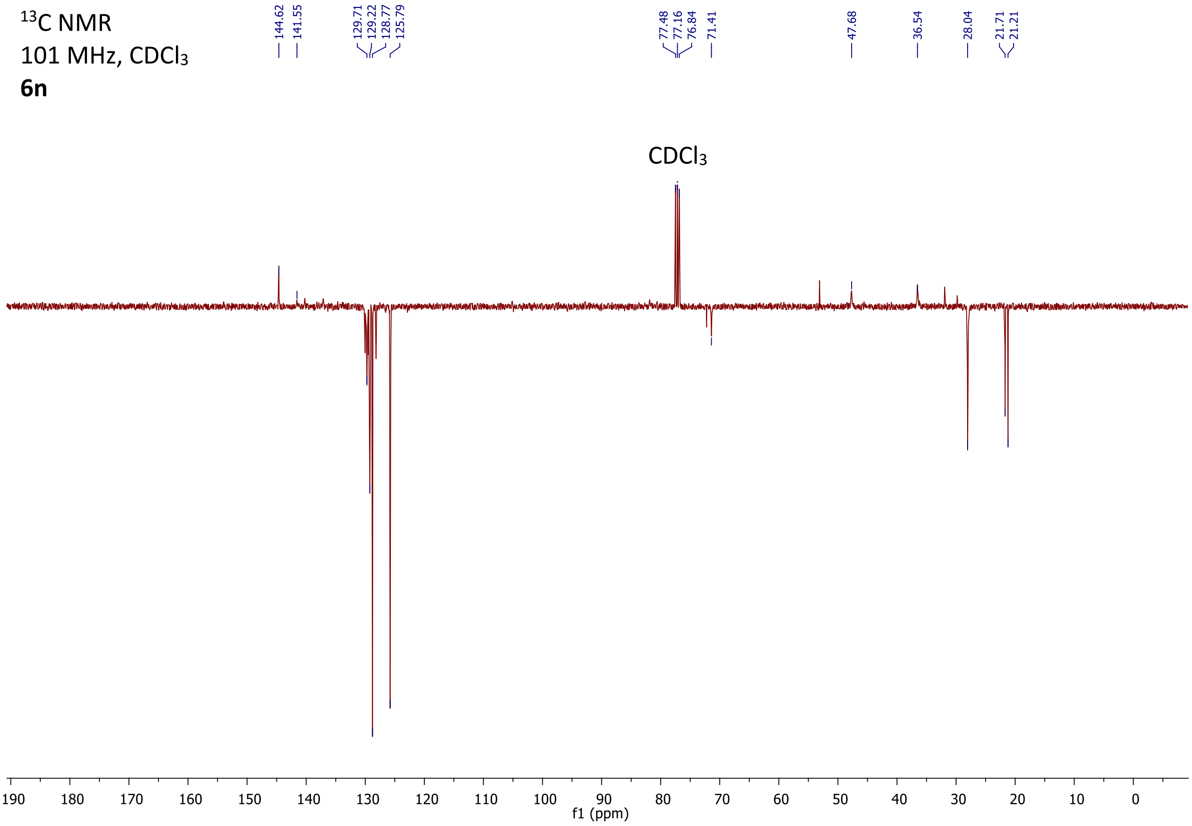
^{13}C NMR
125 MHz, $CDCl_3$
8m



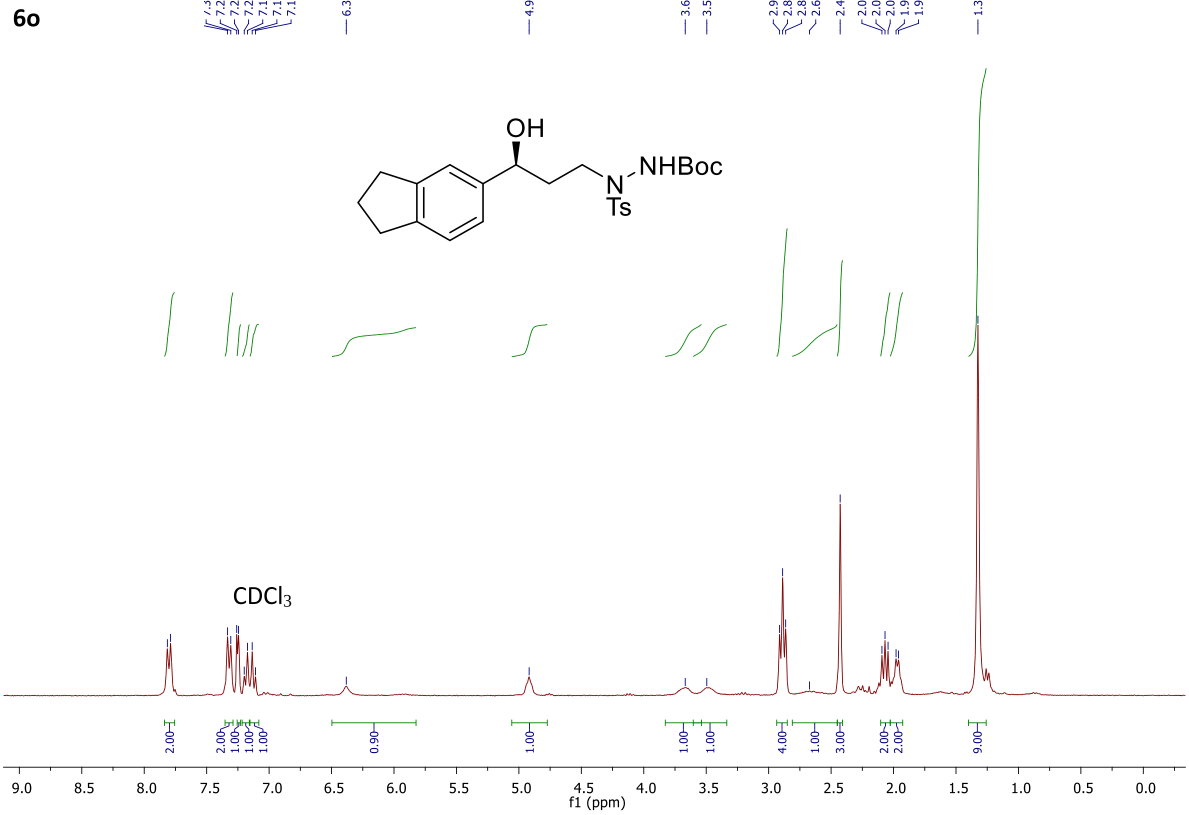
^{1}H NMR
300 MHz, CDCl$_3$
6n



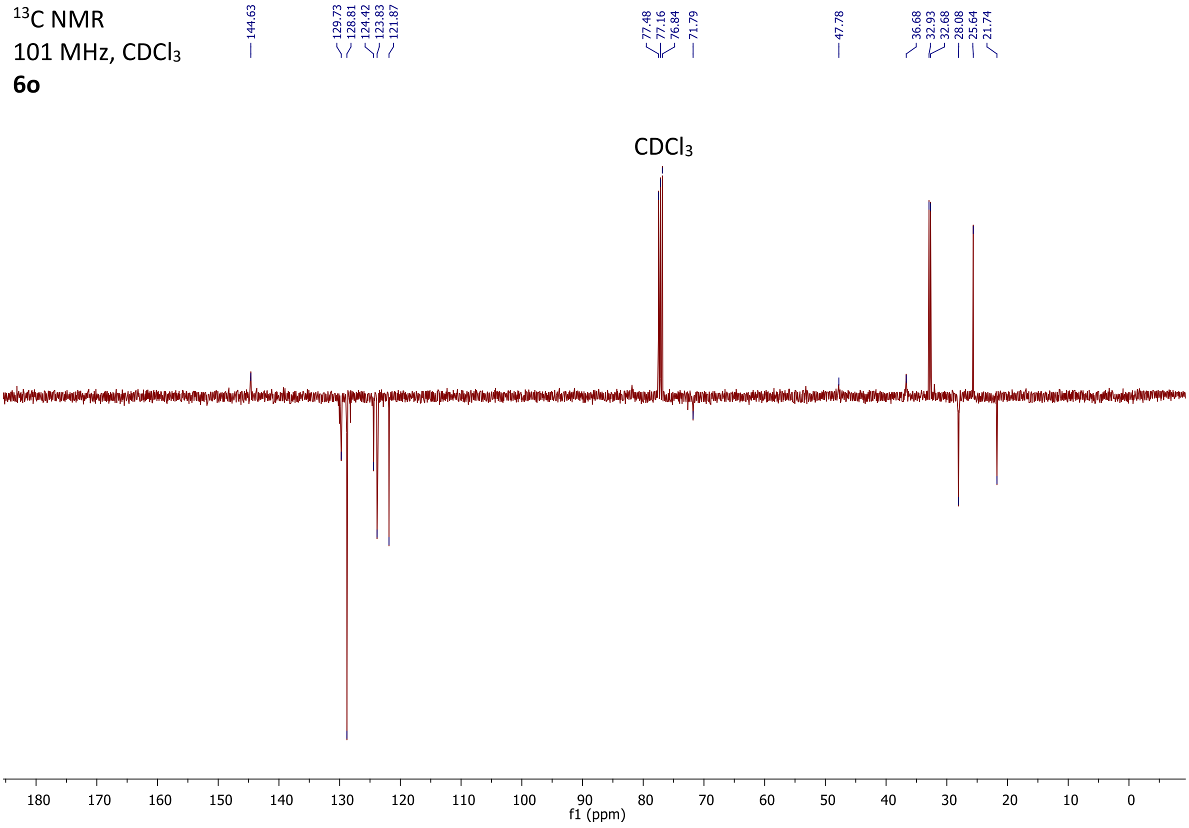
^{13}C NMR
101 MHz, CDCl$_3$
6n

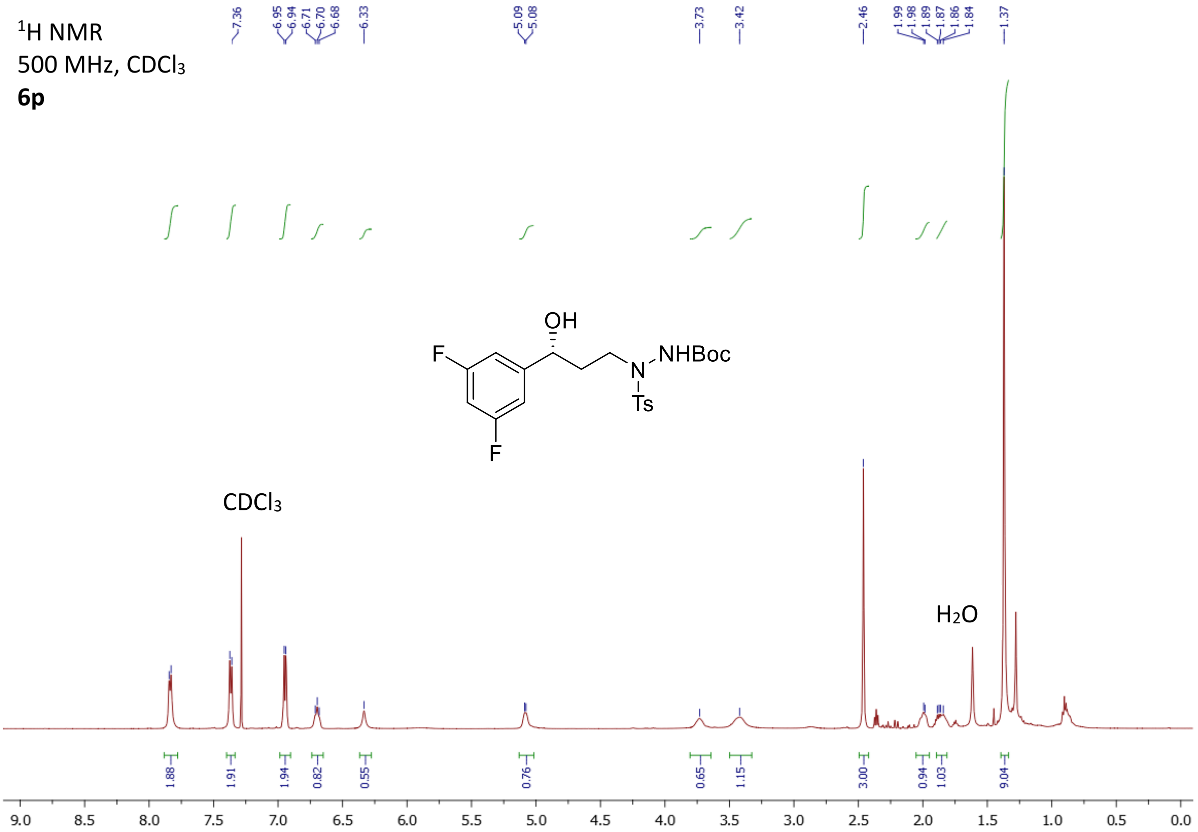


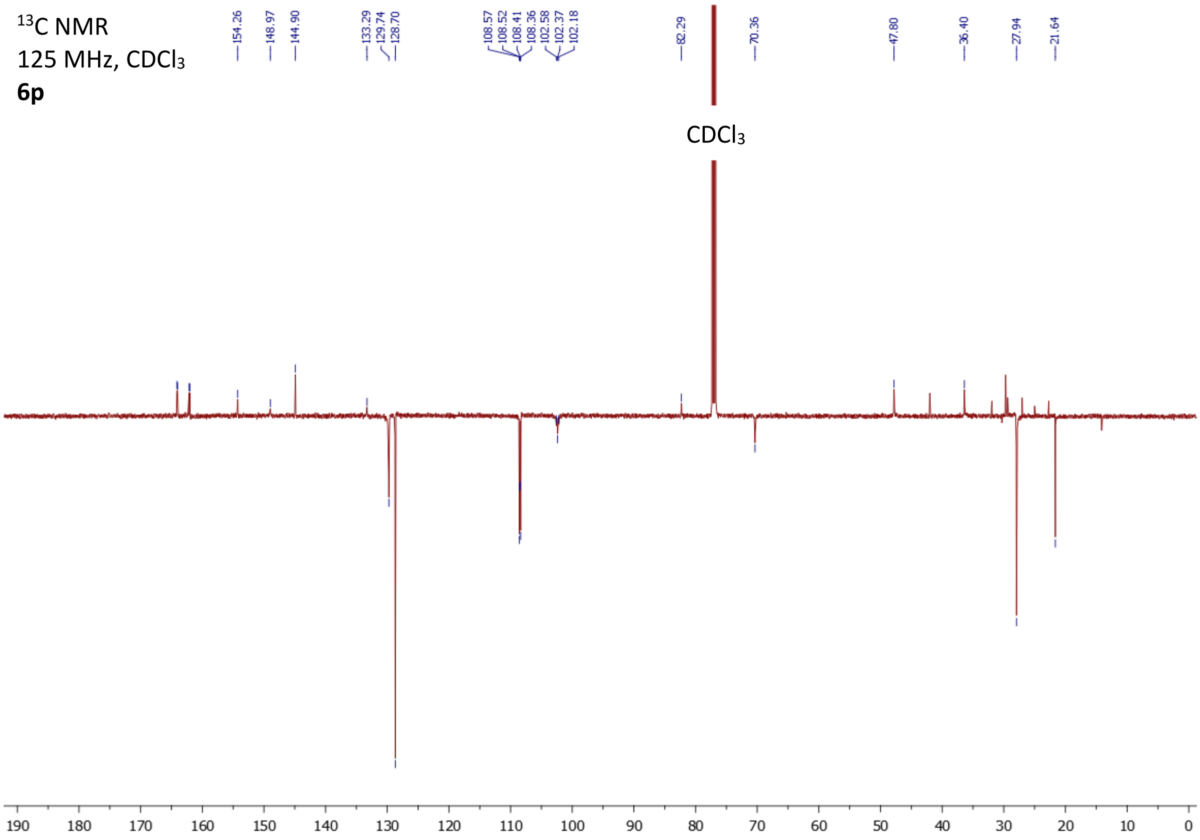
^{1}H NMR
300 MHz, CDCl$_3$
6o



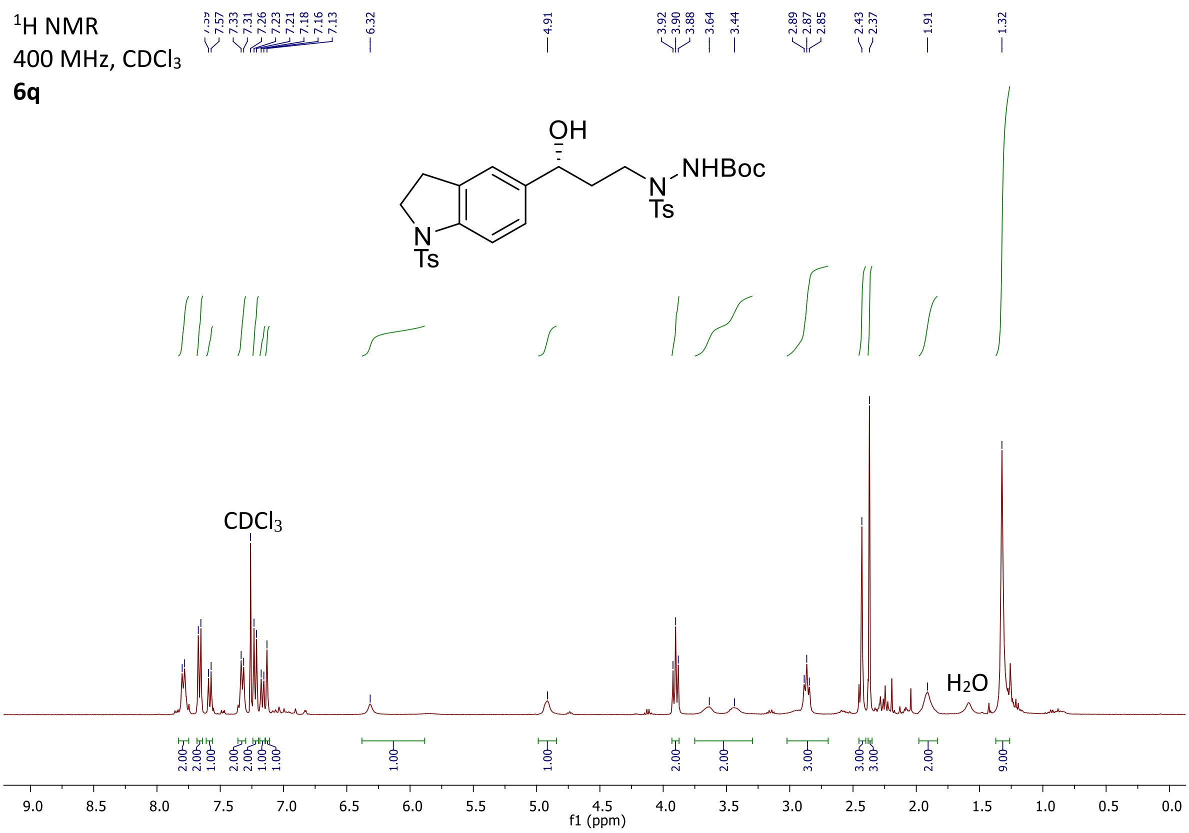
^{13}C NMR
101 MHz, CDCl$_3$
6o



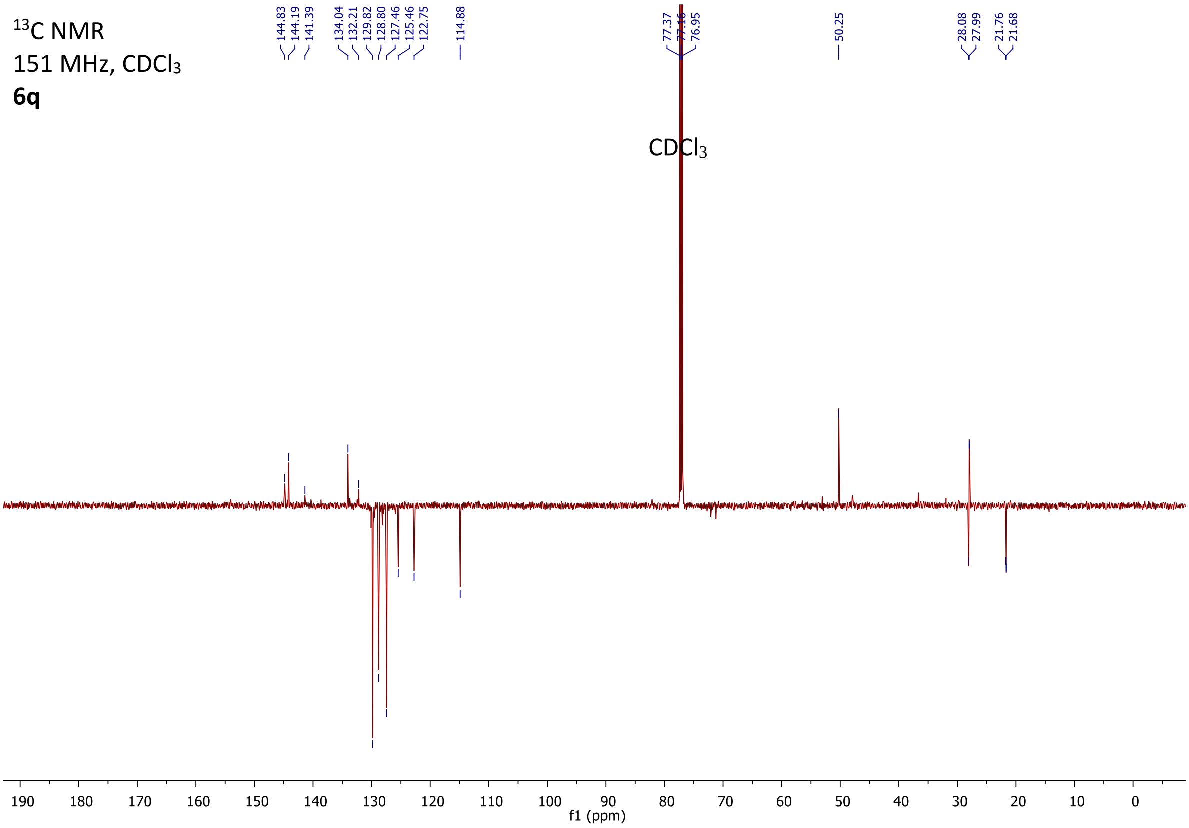

^{1}H NMR
500 MHz, CDCl$_3$
6p
7.36
6.95
6.94
6.71
6.70
6.68
6.33
5.09
5.08
3.73
3.42
2.46
1.99
1.98
1.89
1.87
1.86
1.84
1.37
OH
F
NHBoc
N
Ts
F
CDCl$_3$
H$_2$O
1.88
1.91
1.94
0.82
0.55
0.76
0.65
1.15
3.00
0.94
1.03
9.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

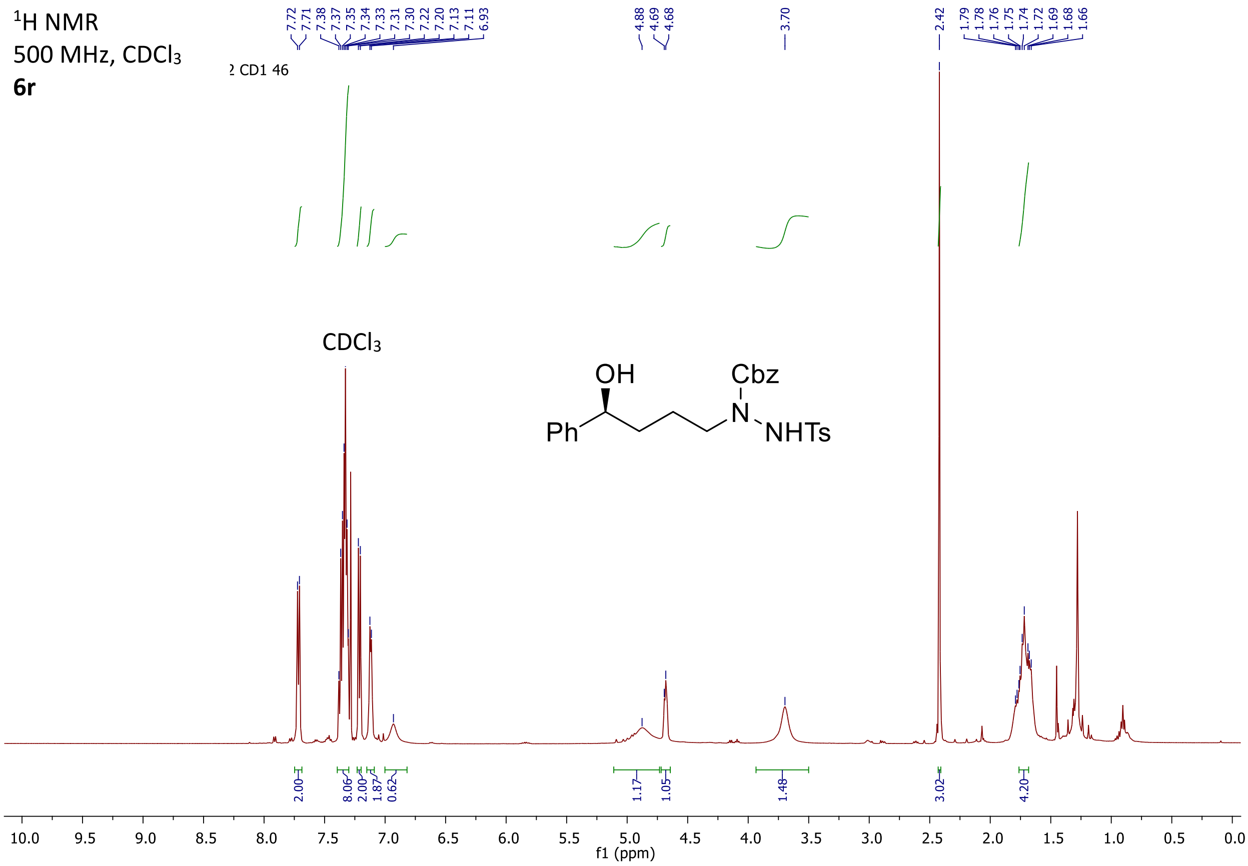

^{13}C NMR
125 MHz, CDCl$_3$
6p
154.26
148.97
144.90
133.29
129.74
128.70
108.57
108.52
108.41
108.36
102.58
102.37
102.18
82.29
70.36
47.80
36.40
27.94
21.64
CDCl$_3$
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

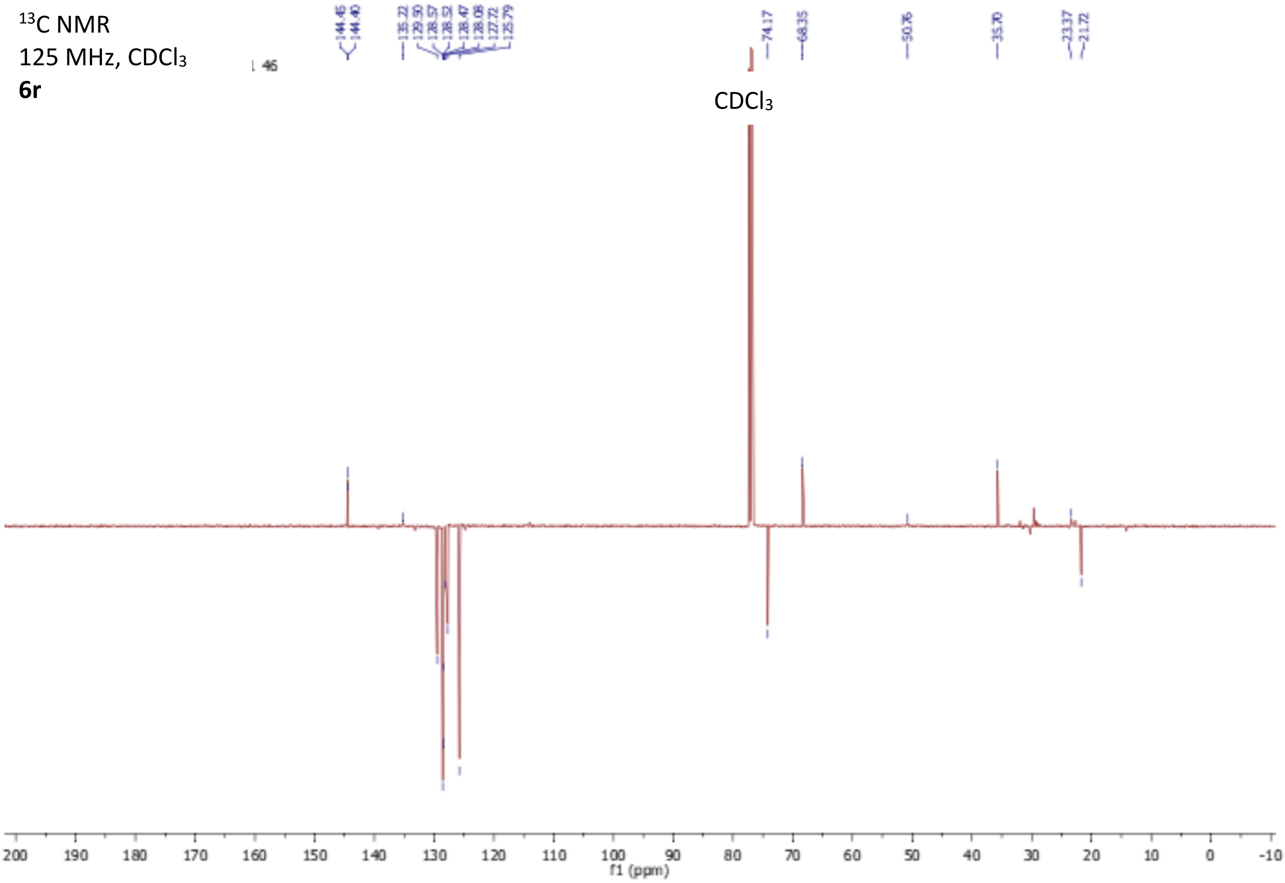
^1H NMR
400 MHz, $CDCl_3$
6q



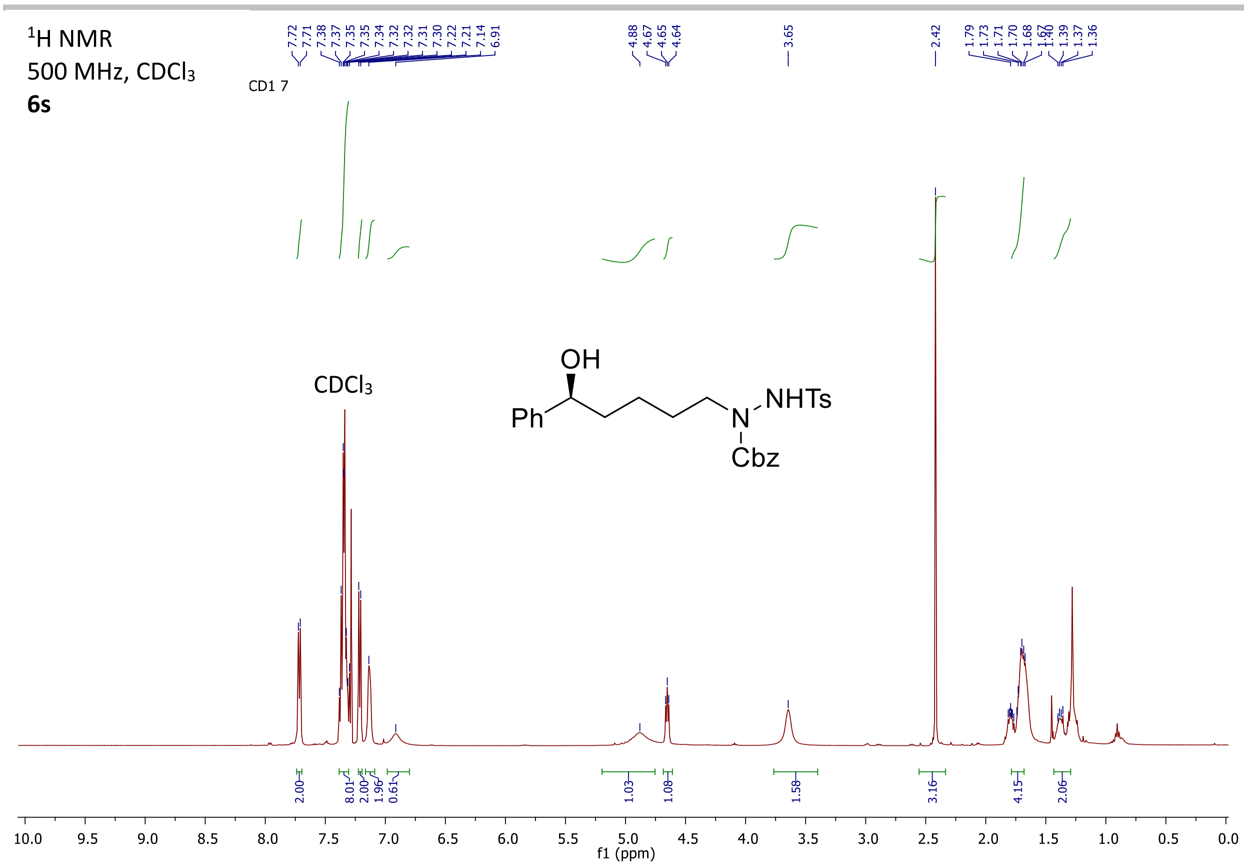
^{13}C NMR
151 MHz, $CDCl_3$
6q



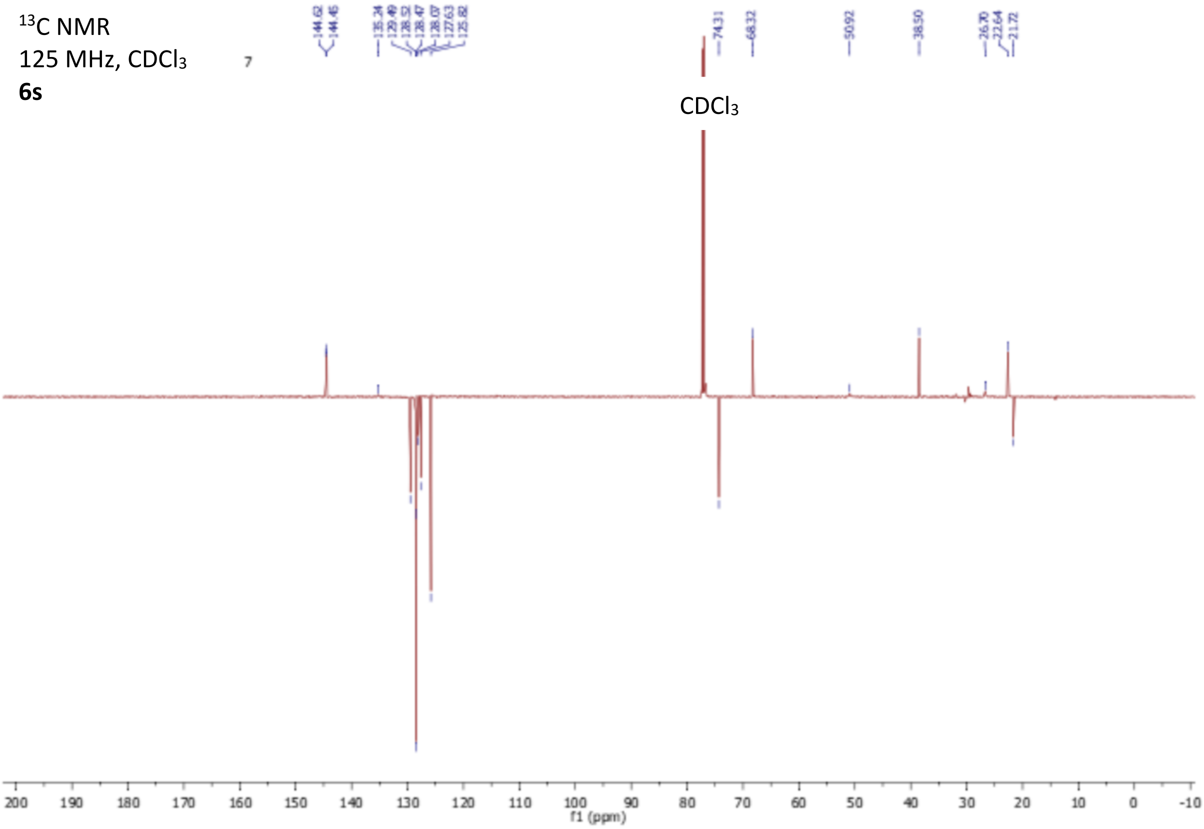

^{1}H NMR
500 MHz, CDCl$_3$
6r
2 CD1 46
7.72
7.71
7.38
7.37
7.35
7.34
7.33
7.31
7.30
7.22
7.20
7.13
7.11
6.93
4.88
4.69
4.68
3.70
2.42
1.79
1.78
1.76
1.75
1.74
1.72
1.69
1.68
1.66
CDCl$_3$
OH
Cbz
N
Ph
NHTs
2.00
8.06
2.00
1.87
0.62
1.17
1.05
1.48
3.02
4.20
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

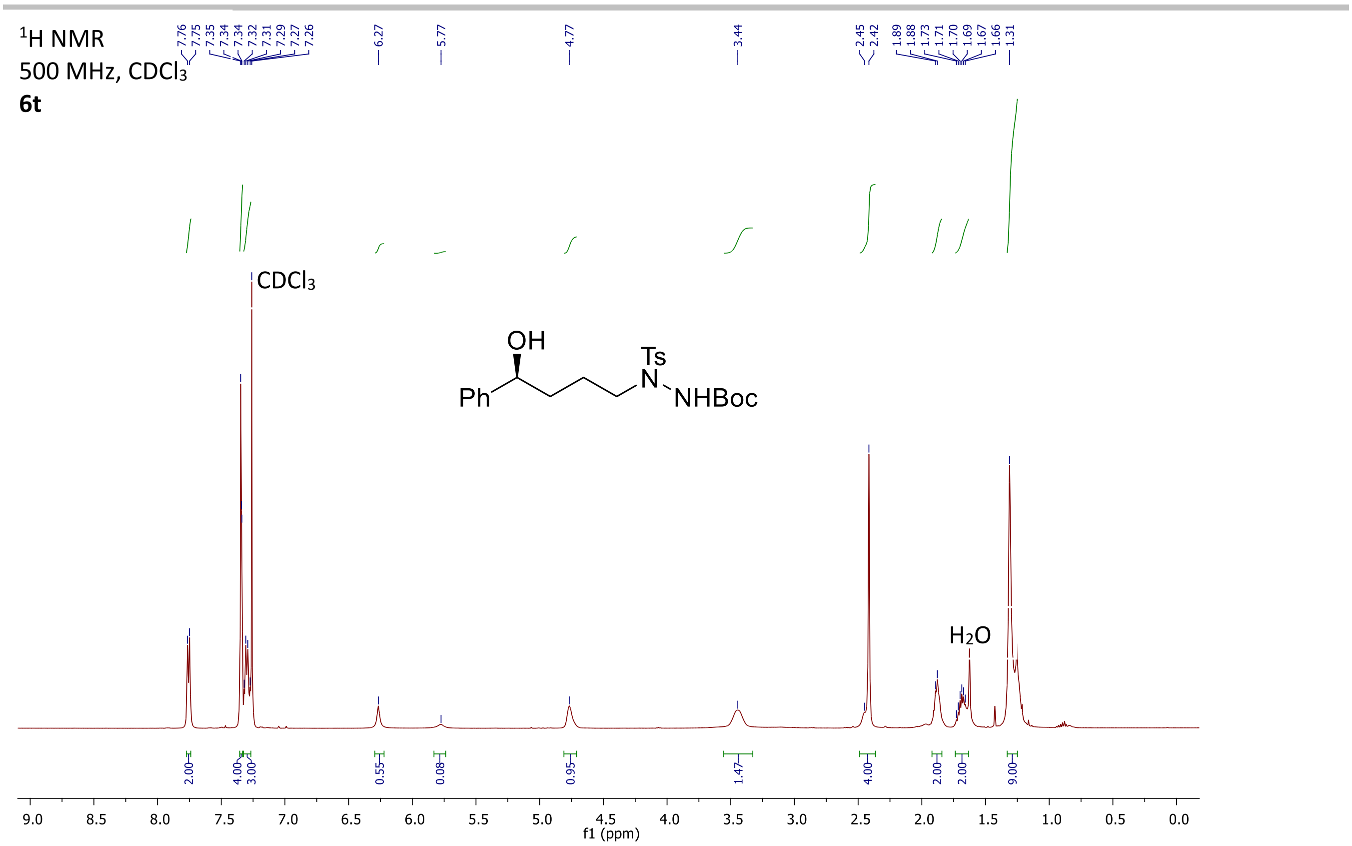

^{13}C NMR
125 MHz, CDCl$_3$
6r
l 46
144.46
144.40
135.22
129.90
128.57
128.52
128.47
128.08
127.72
125.79
74.17
68.35
50.76
35.70
23.37
21.72
CDCl$_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

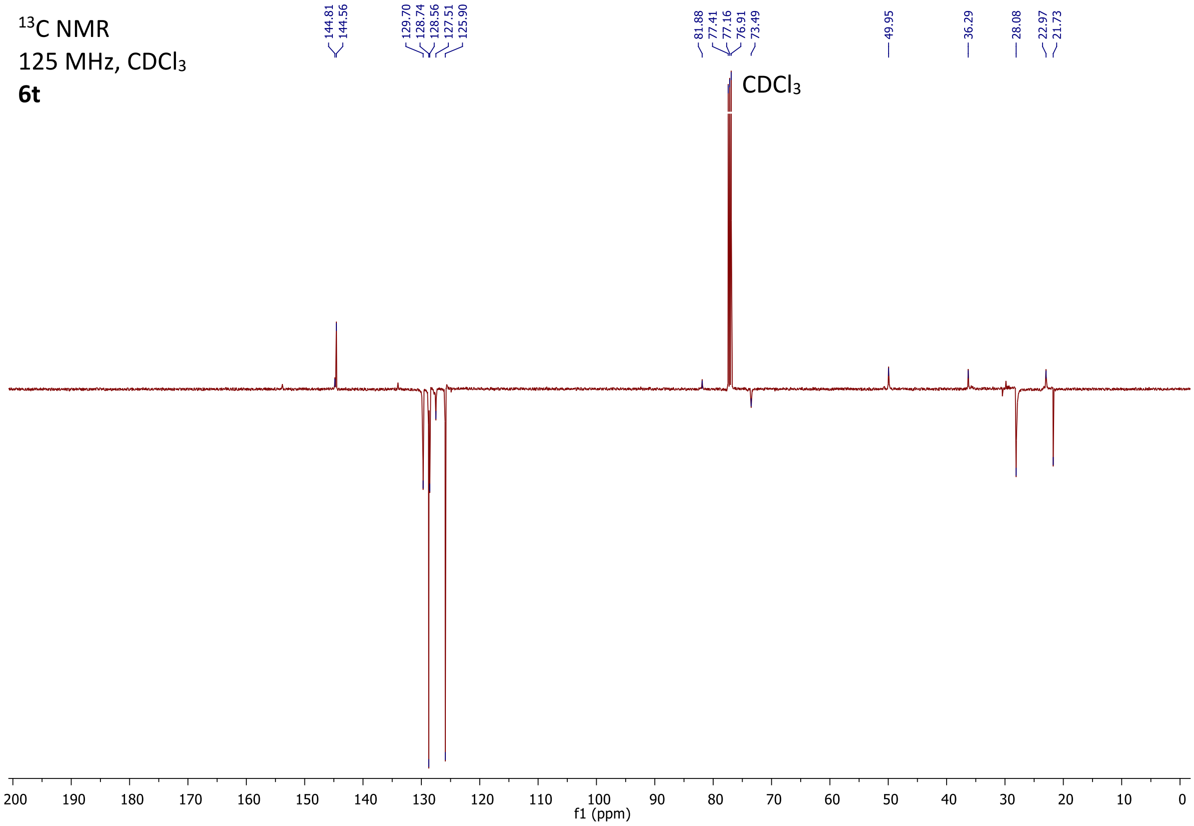
^{1}H NMR
500 MHz, $CDCl_3$
6s



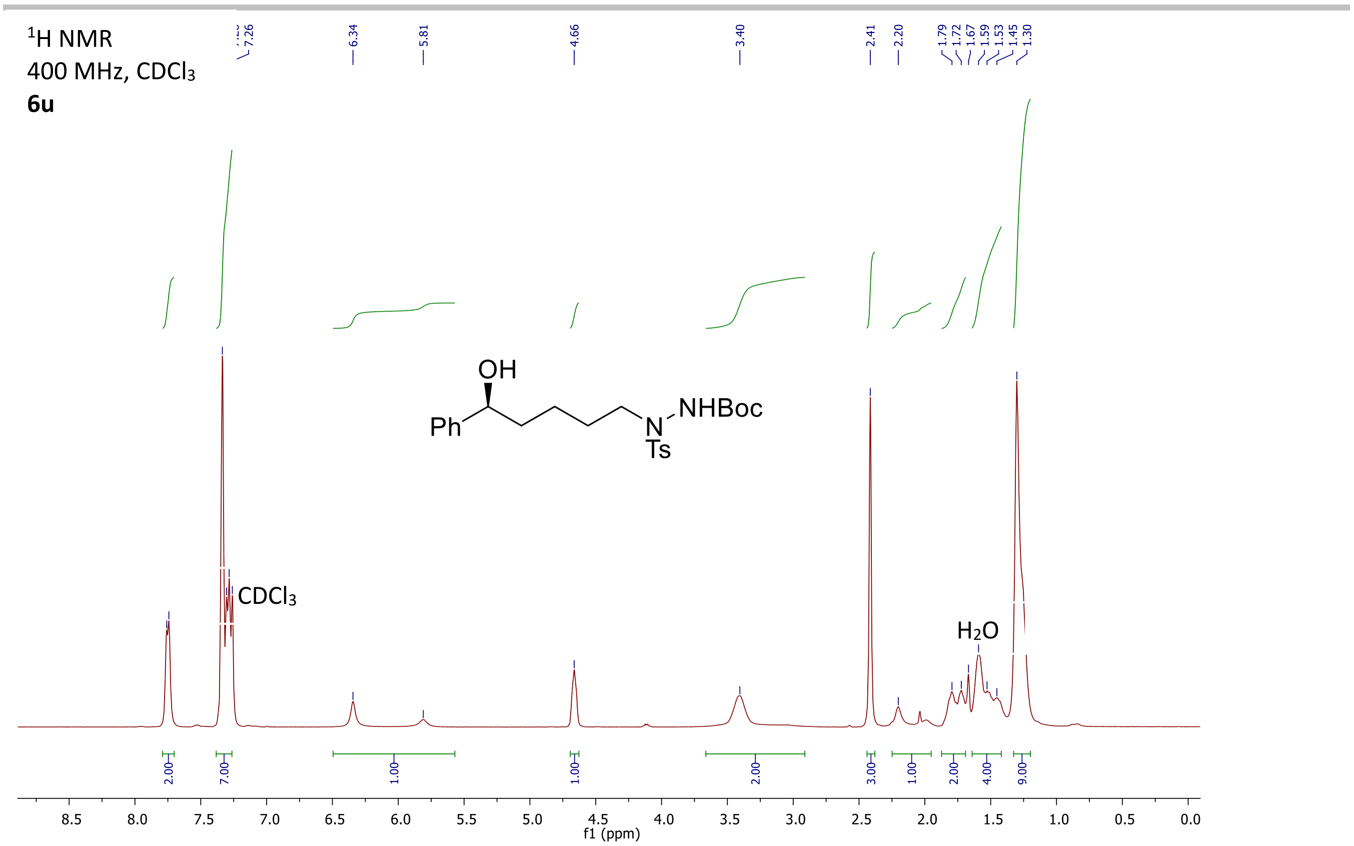
^{13}C NMR
125 MHz, $CDCl_3$
6s



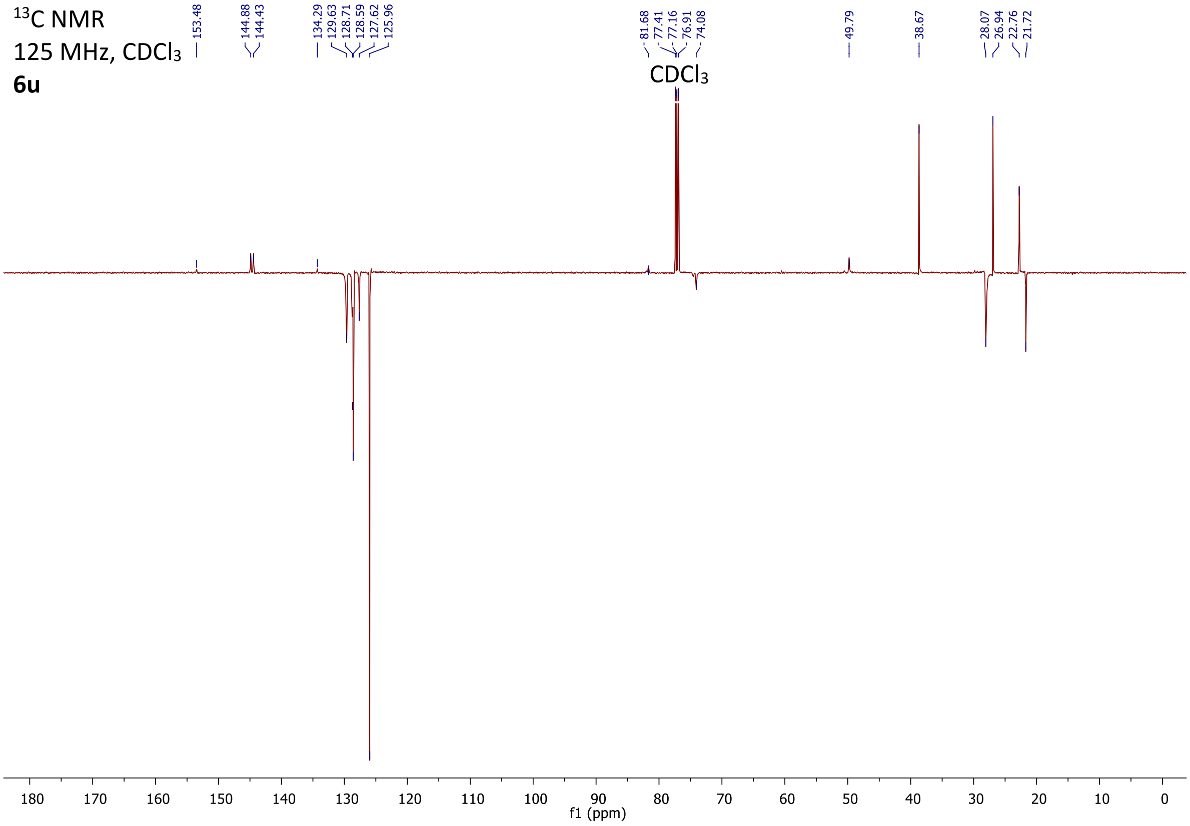

^{1}H NMR
500 MHz, CDCl$_3$
6t
7.76
7.75
7.35
7.34
7.32
7.31
7.29
7.27
7.26
6.27
5.77
4.77
3.44
2.45
2.42
1.89
1.88
1.73
1.71
1.70
1.69
1.67
1.66
1.31
CDCl3
OH
Ts
N
Ph
NHBoc
H2O
2.00
4.00
3.00
0.55
0.08
0.95
1.47
4.00
2.00
2.00
9.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


^{13}C NMR
125 MHz, CDCl$_3$
6t
144.81
144.56
129.70
128.74
128.56
127.51
125.90
81.88
77.41
77.16
76.91
73.49
49.95
36.29
28.08
22.97
21.73
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

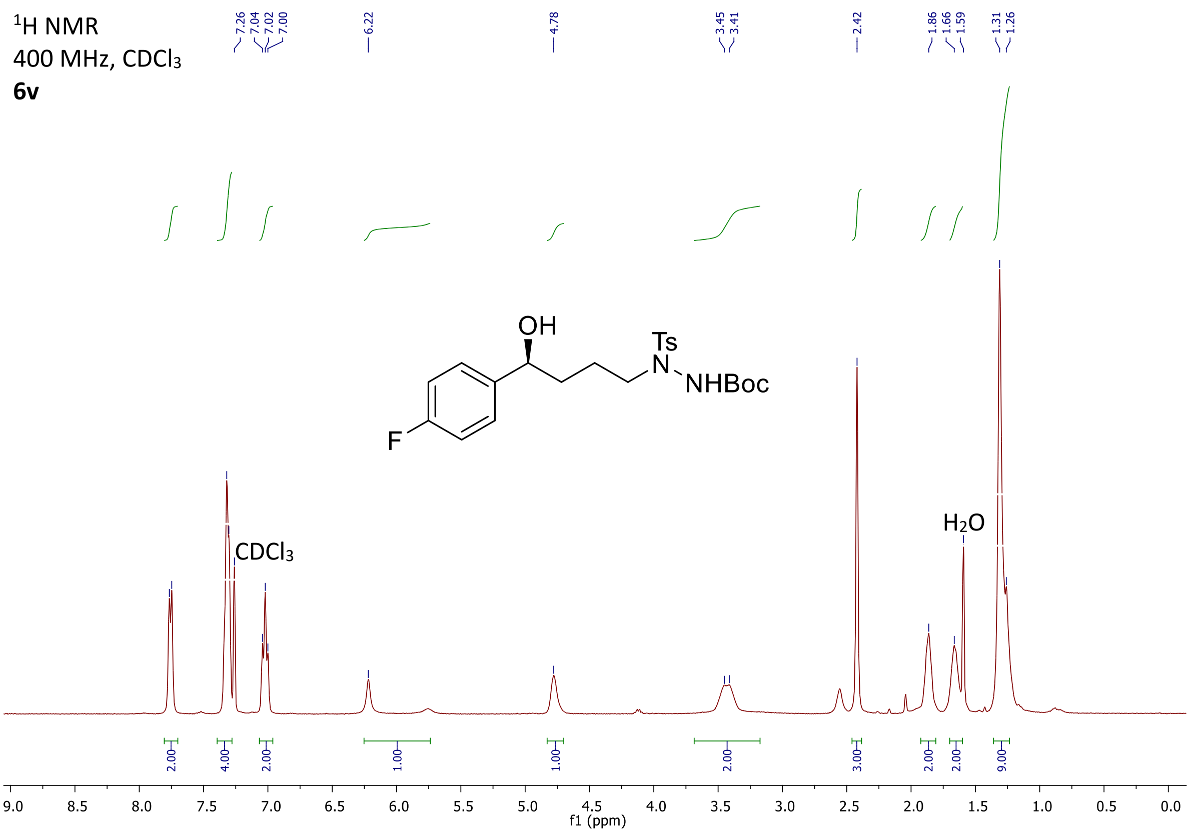
^{1}H NMR
400 MHz, $CDCl_3$
6u



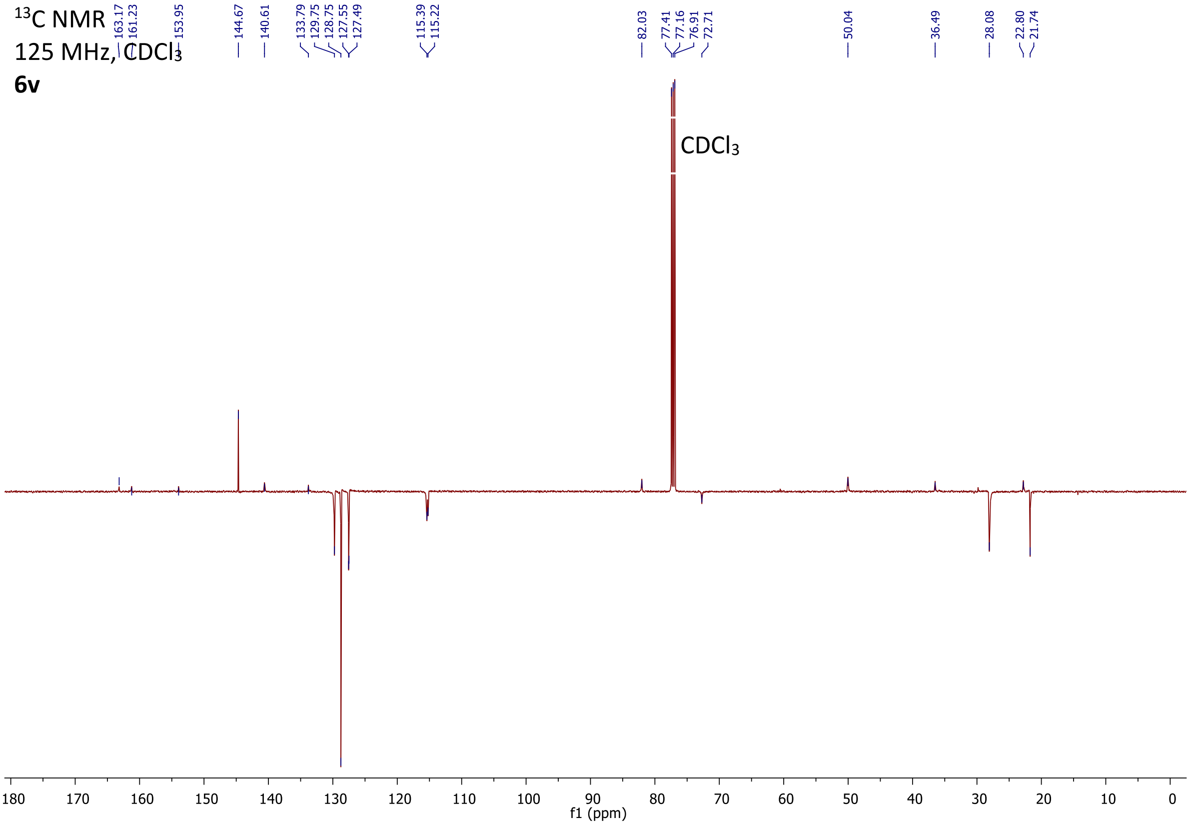
^{13}C NMR
125 MHz, $CDCl_3$
6u



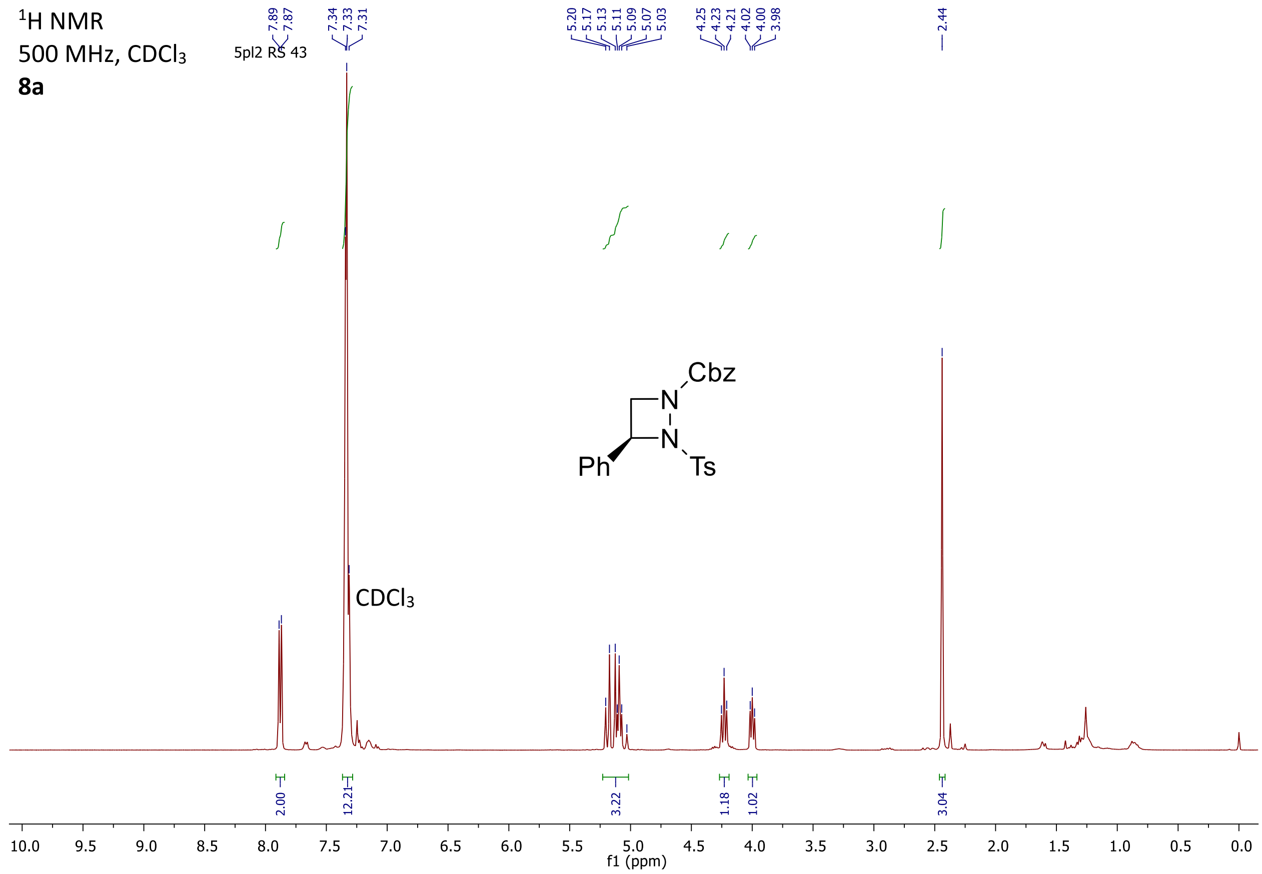
^{1}H NMR
400 MHz, $CDCl_3$
6v



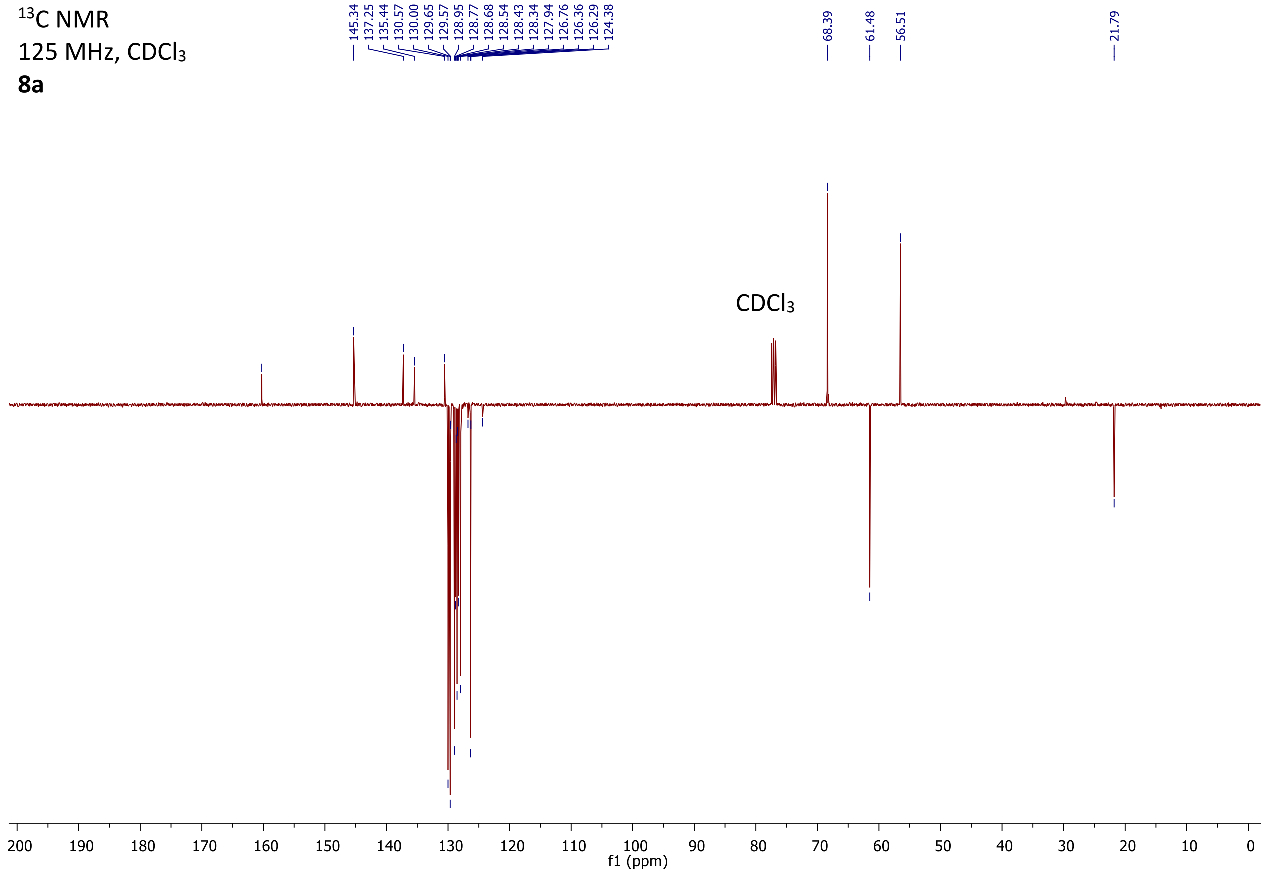
^{13}C NMR
125 MHz, $CDCl_3$
6v

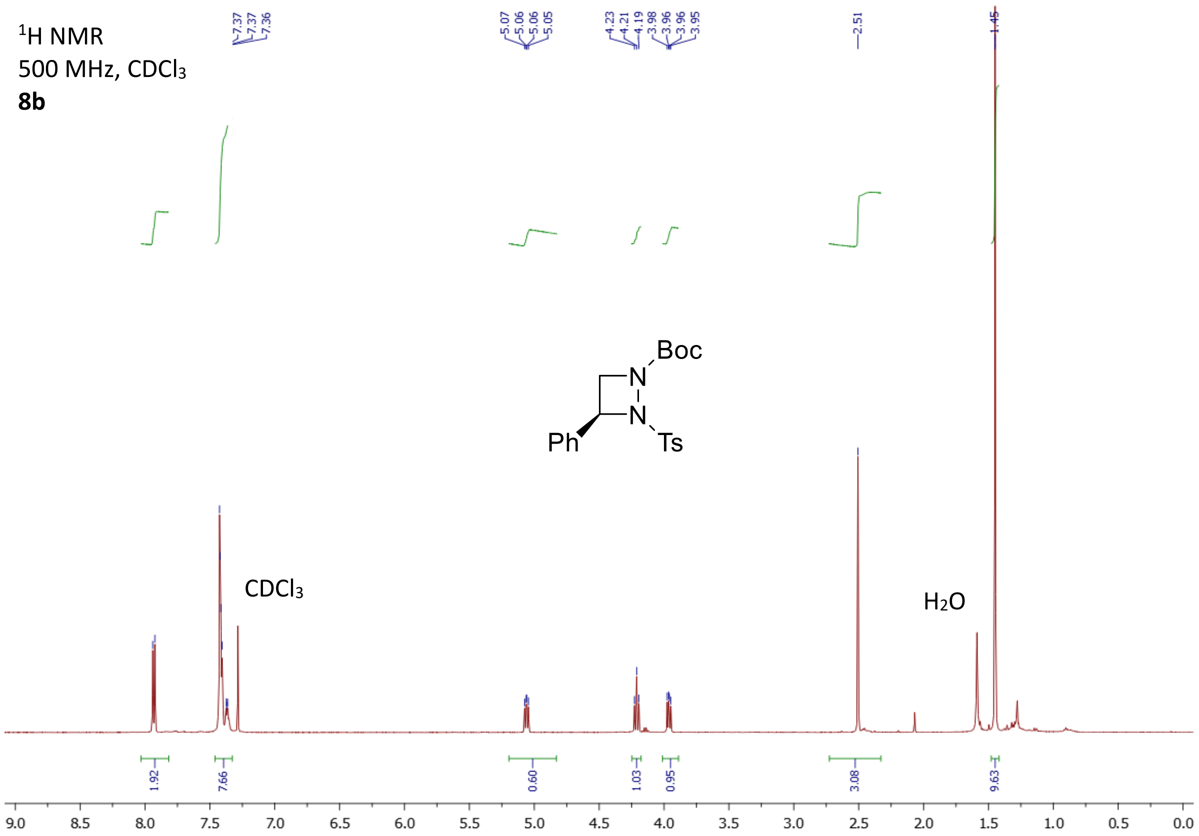


^{1}H NMR
500 MHz, $CDCl_3$
8a

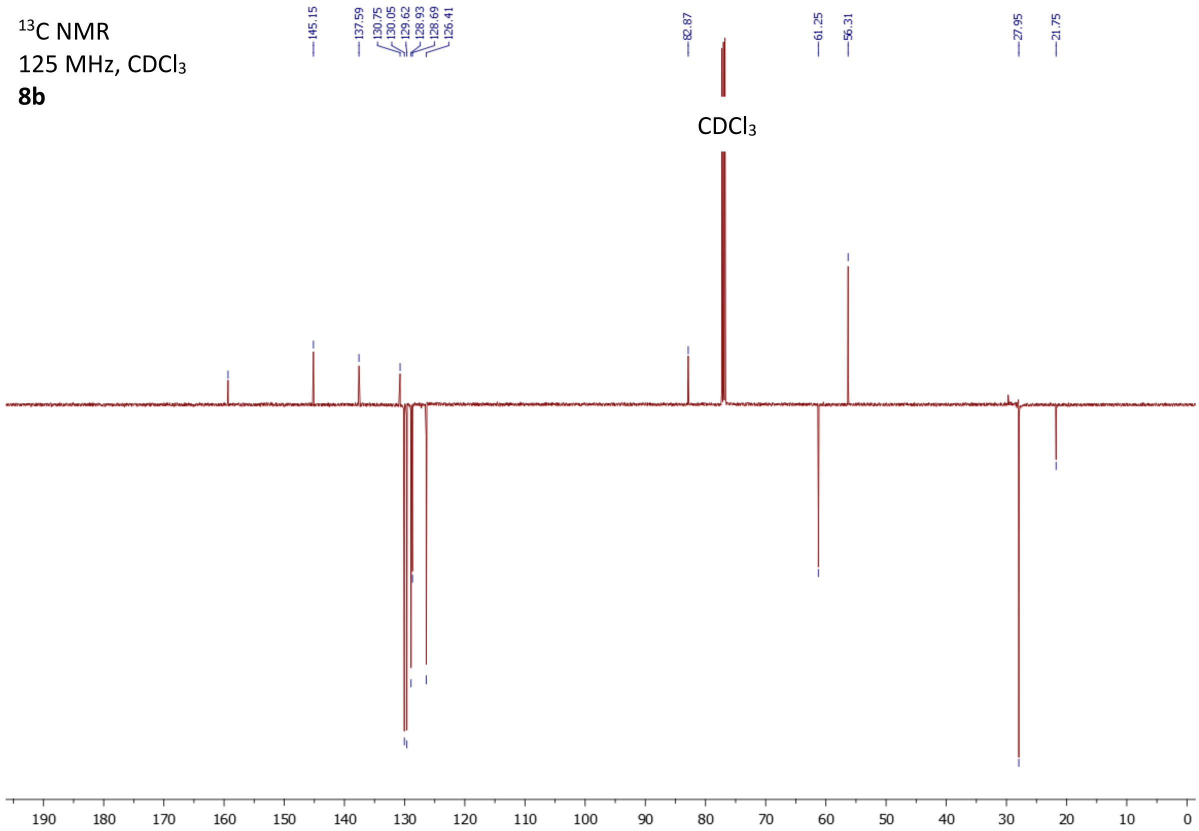


^{13}C NMR
125 MHz, $CDCl_3$
8a



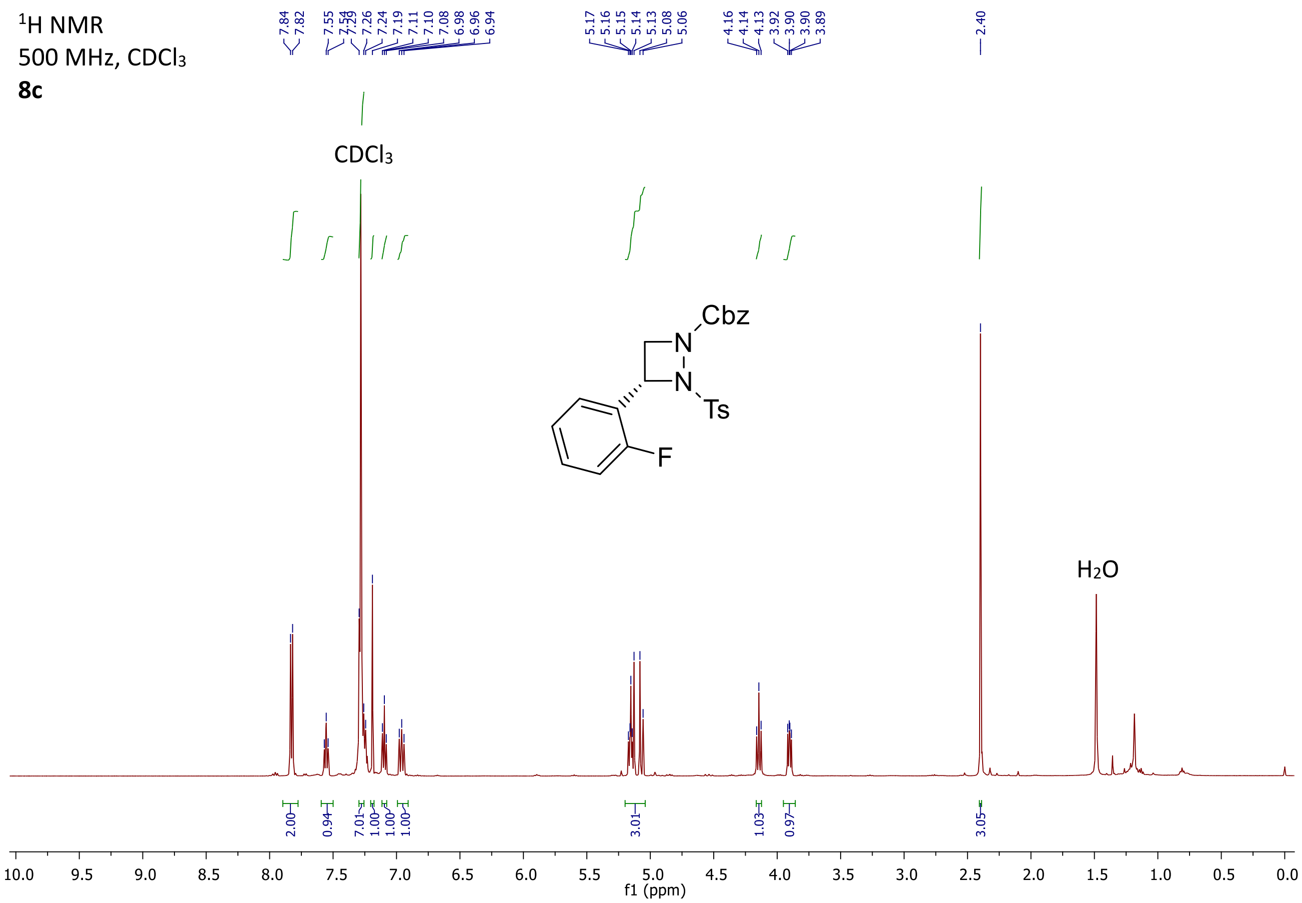


^{1}H NMR
500 MHz, $CDCl_3$
8b

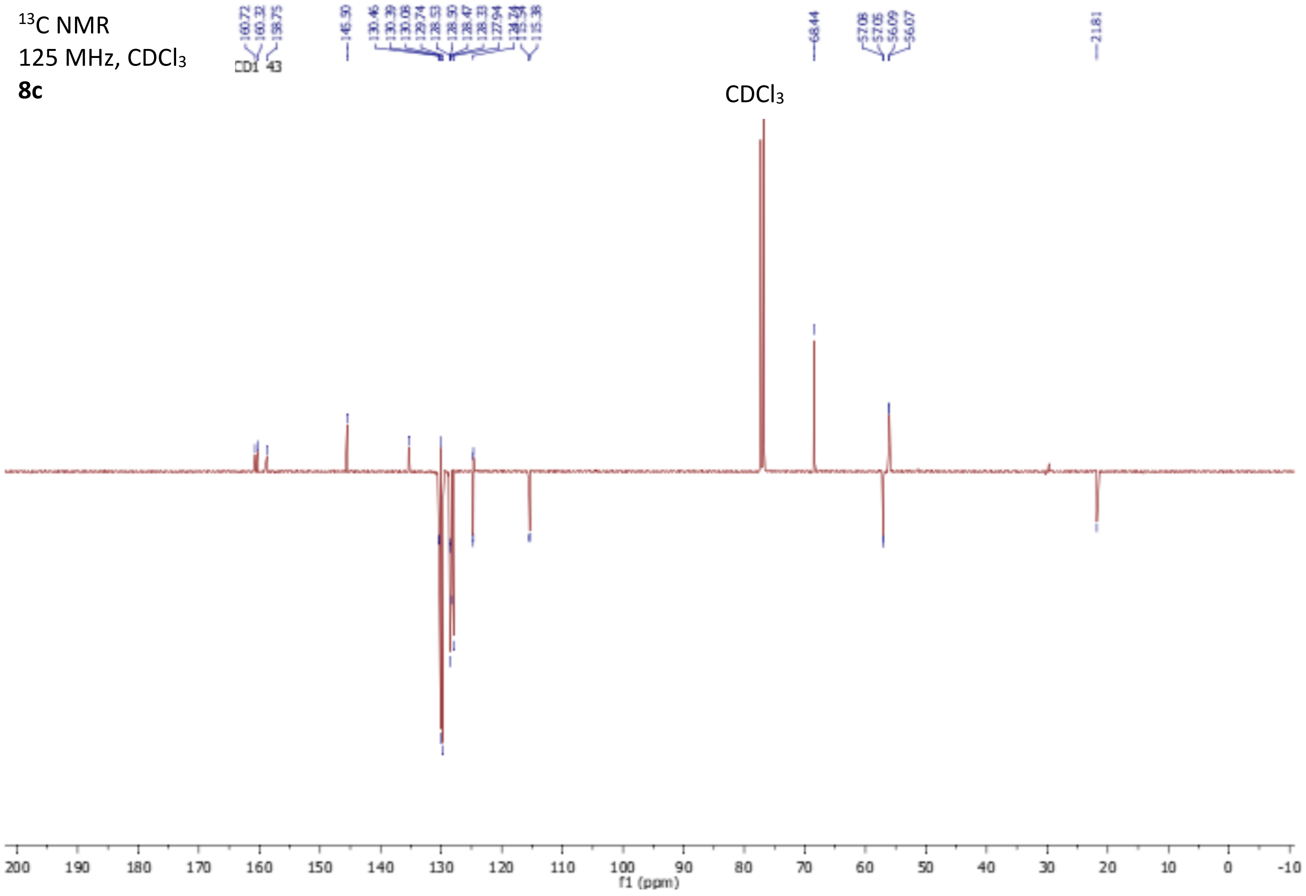


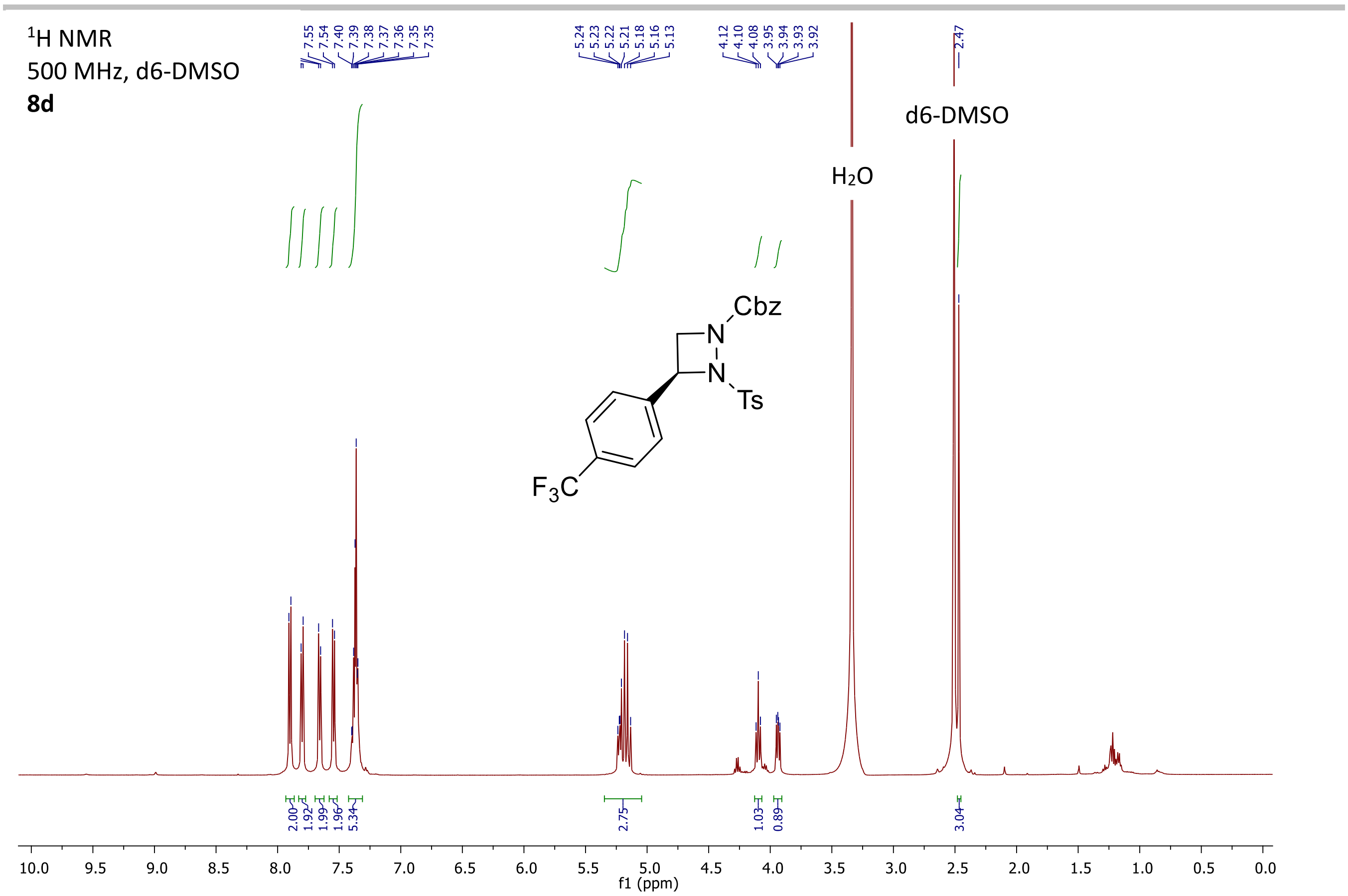
^{13}C NMR
125 MHz, $CDCl_3$
8b

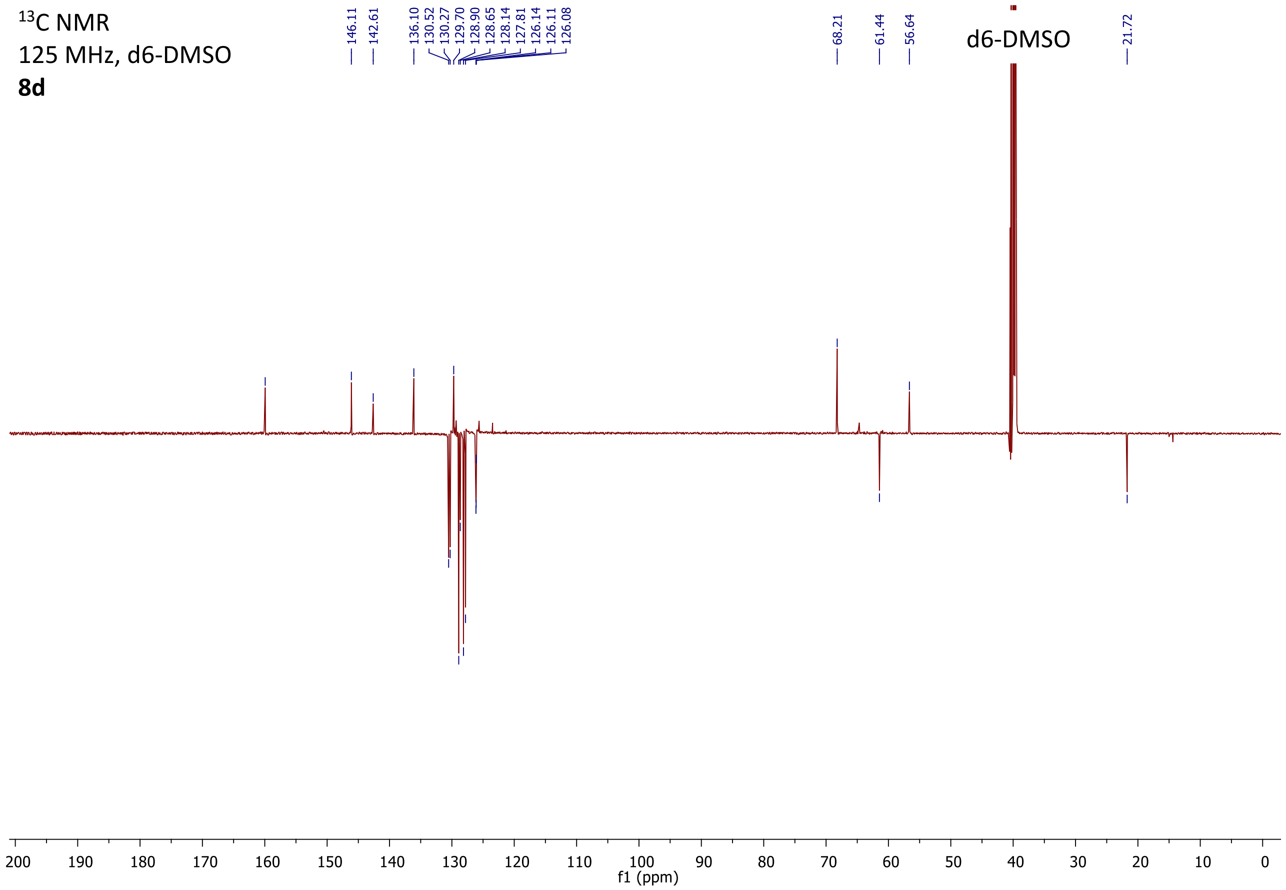
^{1}H NMR
500 MHz, $CDCl_3$
8c

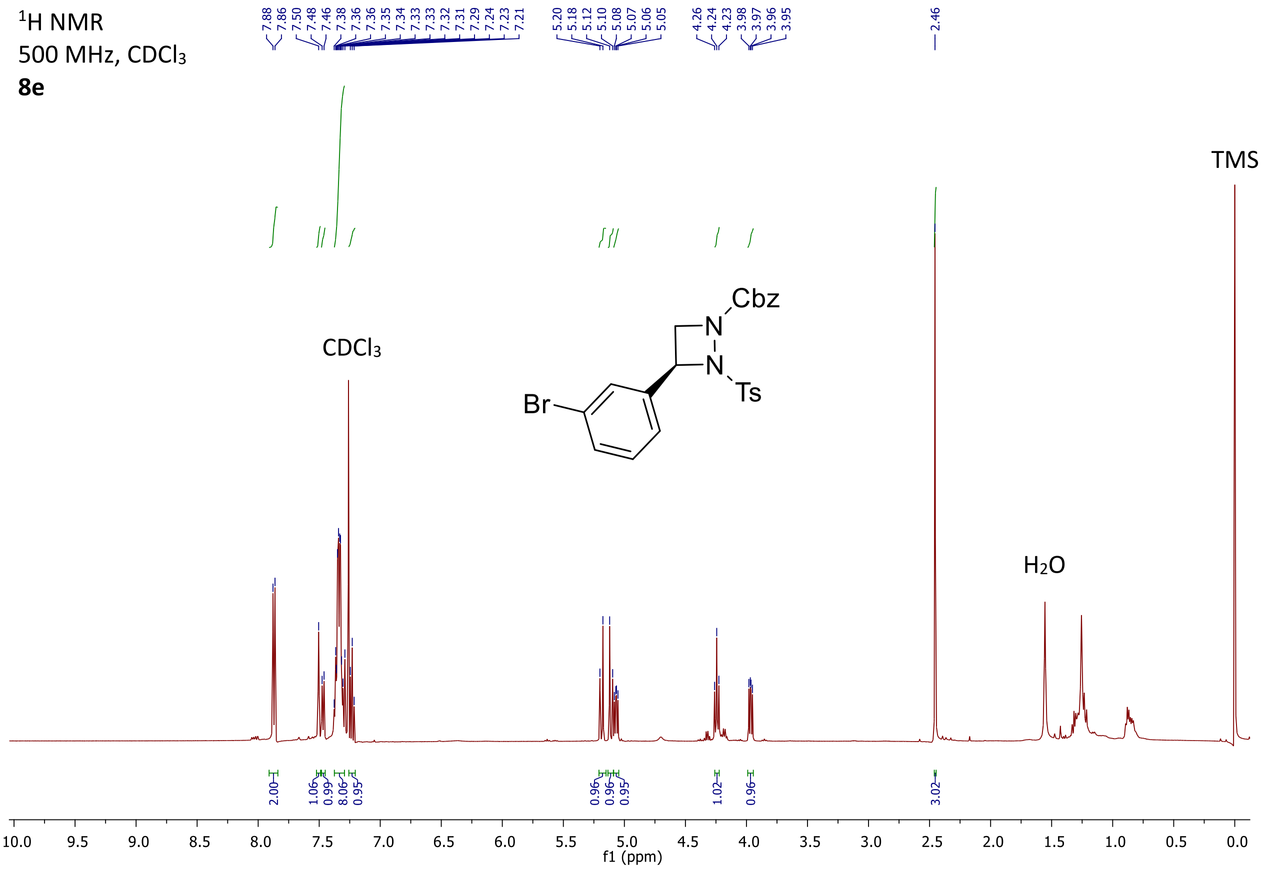


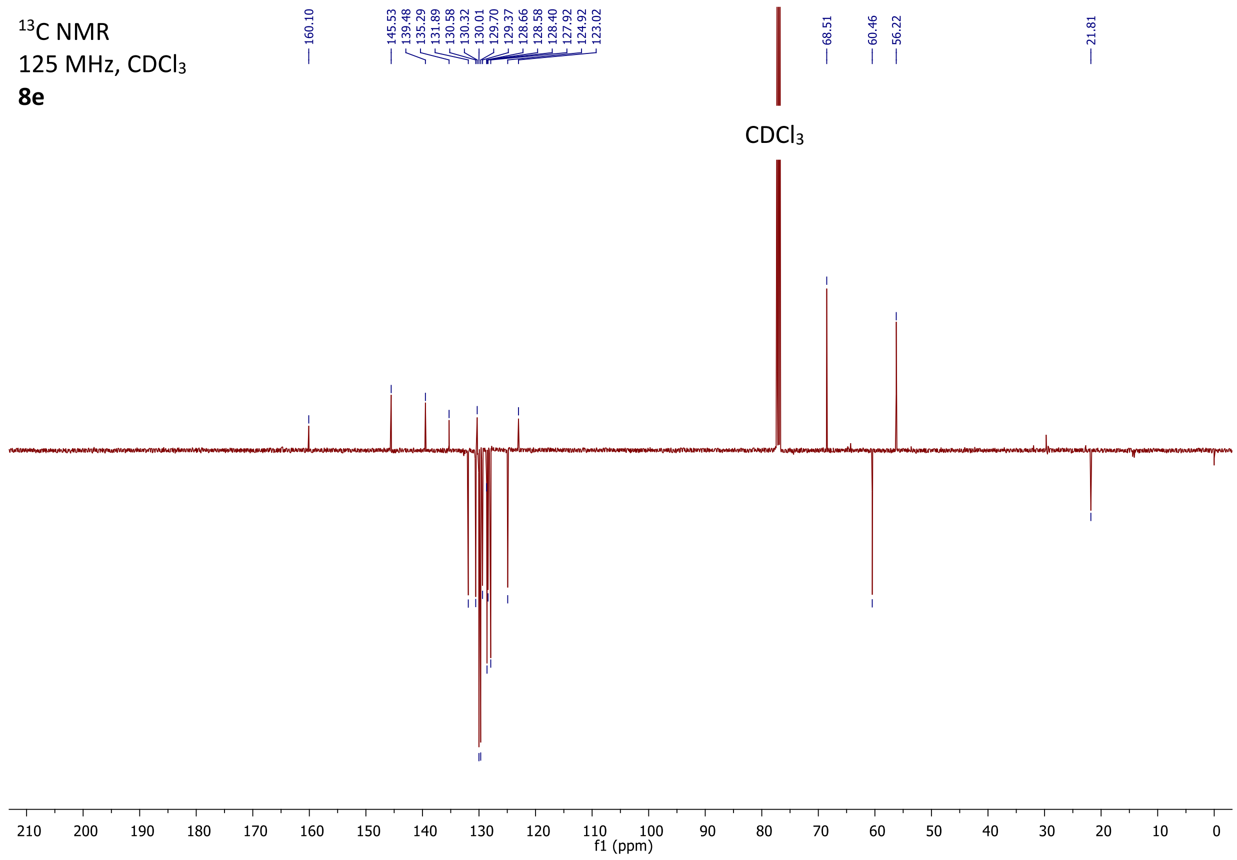
^{13}C NMR
125 MHz, $CDCl_3$
8c

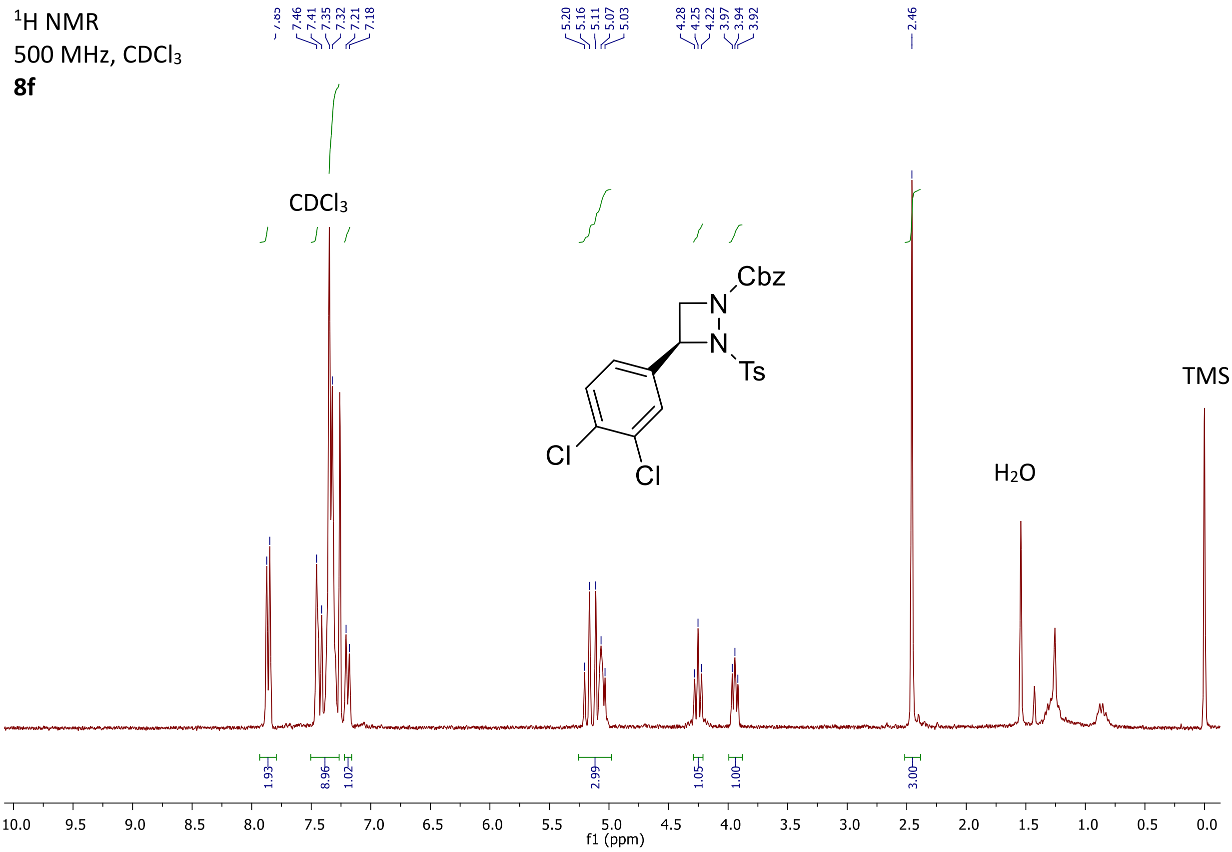


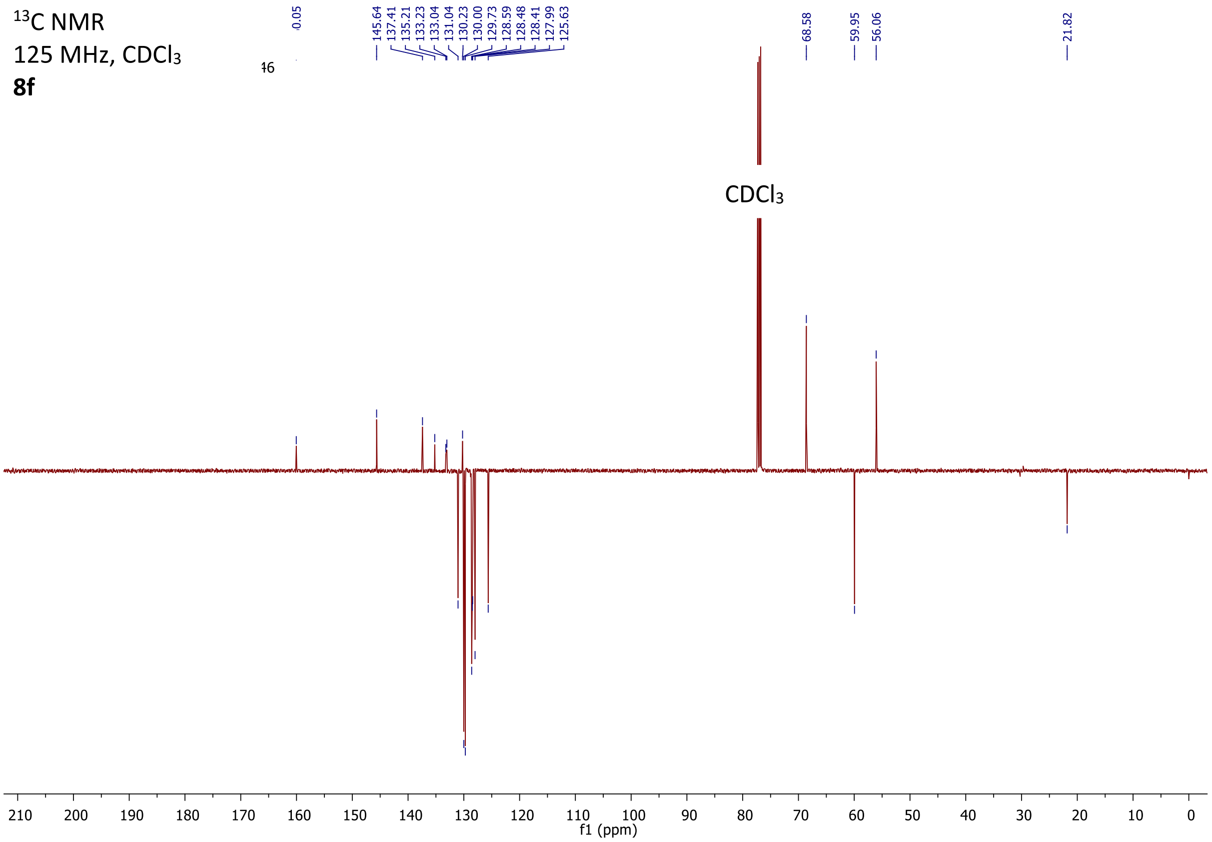

^{1}H NMR
500 MHz, d6-DMSO
8d
7.55
7.54
7.40
7.39
7.38
7.37
7.36
7.35
7.35
5.24
5.23
5.22
5.21
5.18
5.16
5.13
4.12
4.10
4.08
3.95
3.94
3.93
3.92
2.47
H$_2$O
d6-DMSO
Cbz
N
N
Ts
F$_3$C
2.00
1.92
1.99
1.96
5.34
2.75
1.03
0.89
3.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


^{13}C NMR
125 MHz, d6-DMSO
8d
146.11
142.61
136.10
130.52
130.27
129.70
128.90
128.65
128.14
127.81
126.14
126.11
126.08
68.21
61.44
56.64
d6-DMSO
21.72
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

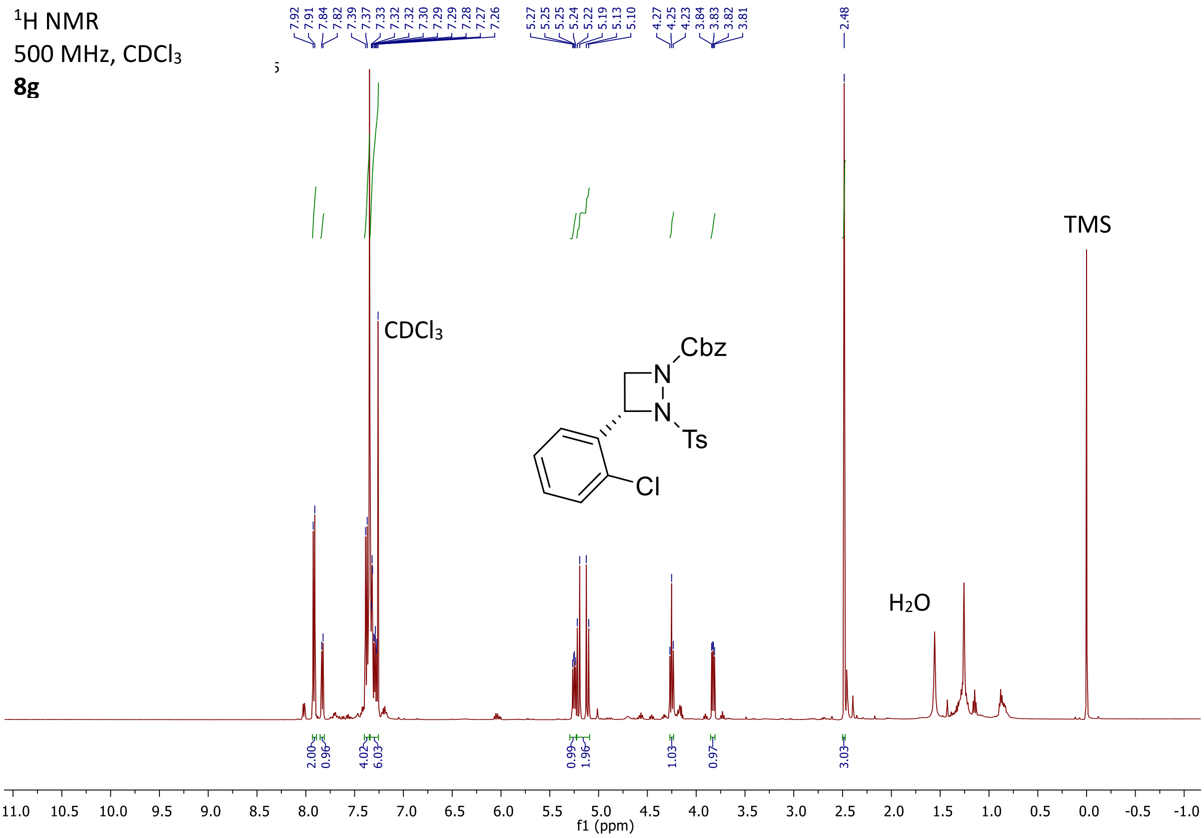

^{1}H NMR
500 MHz, $CDCl_3$
8e
7.88
7.86
7.50
7.48
7.46
7.38
7.36
7.36
7.35
7.34
7.33
7.33
7.32
7.31
7.29
7.24
7.23
7.21
5.20
5.18
5.12
5.10
5.08
5.07
5.06
5.05
4.26
4.24
4.23
3.98
3.97
3.96
3.95
2.46
TMS
Cbz
N
N
Ts
Br
$CDCl_3$
H_2O
2.00
1.06
0.99
8.06
0.95
0.96
0.96
0.95
1.02
0.96
3.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


^{13}C NMR
125 MHz, $CDCl_3$
8e
160.10
145.53
139.48
135.29
131.89
130.58
130.32
130.01
129.70
129.37
128.66
128.58
128.40
127.92
124.92
123.02
68.51
60.46
56.22
21.81
$CDCl_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

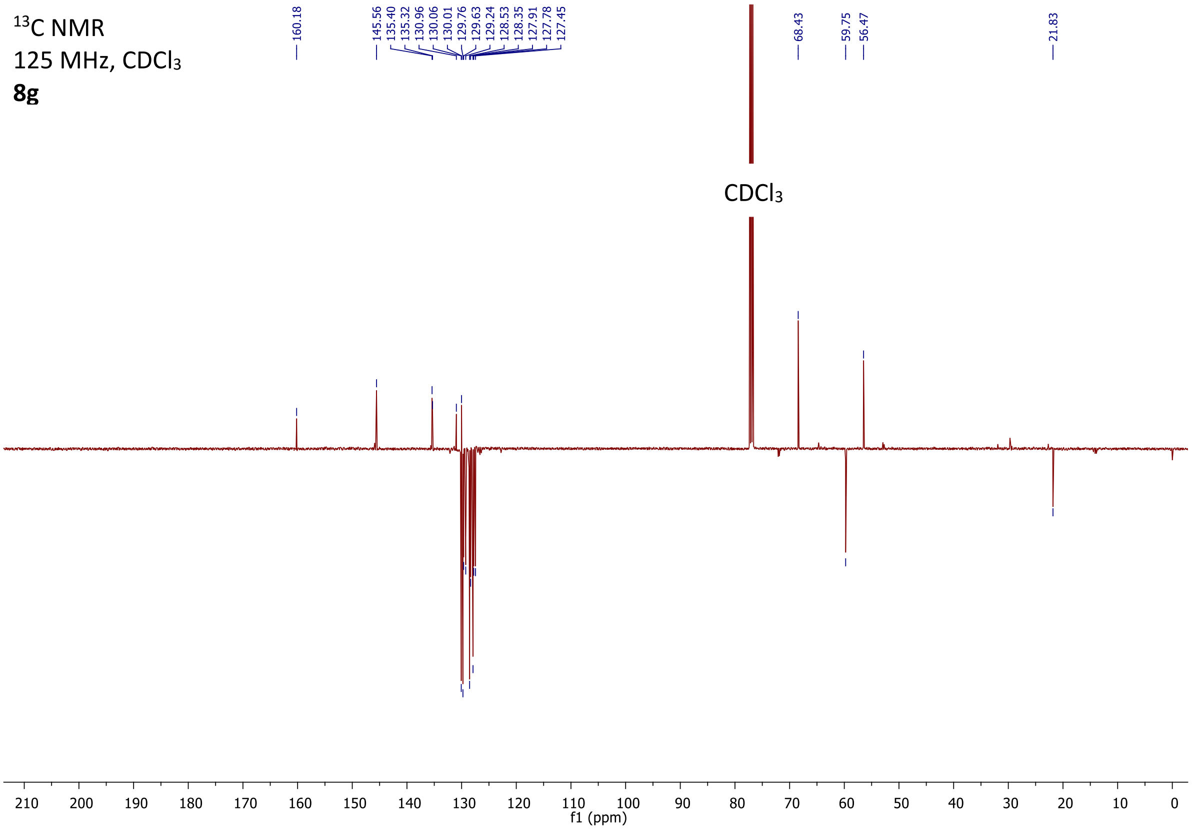

^{1}H NMR
500 MHz, $CDCl_3$
8f
7.85
7.46
7.41
7.35
7.32
7.21
7.18
5.20
5.16
5.11
5.07
5.03
4.28
4.25
4.22
3.97
3.94
3.92
2.46
$CDCl_3$
Cbz
N
N
Ts
Cl
Cl
TMS
H_2O
1.93
8.96
1.02
2.99
1.05
1.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

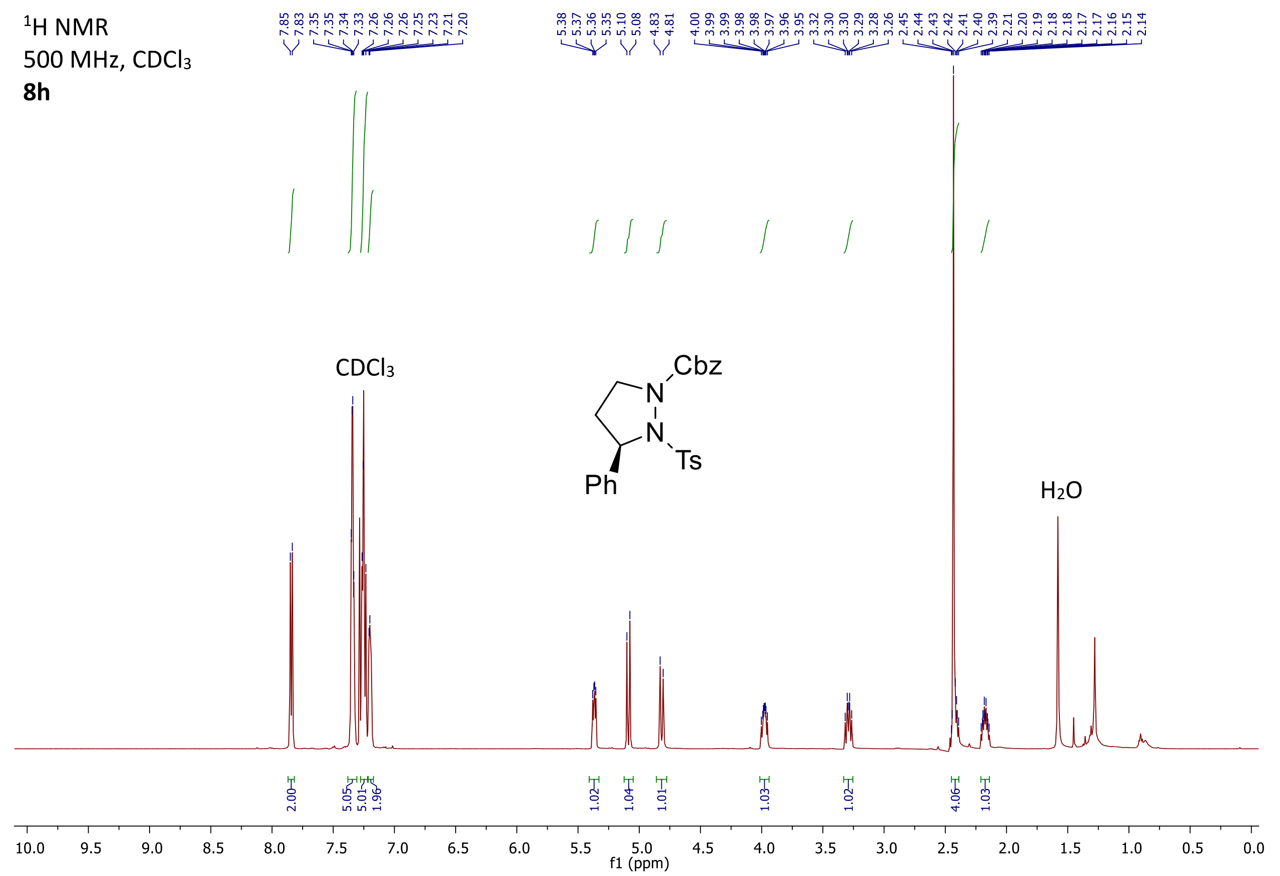

^{13}C NMR
125 MHz, $CDCl_3$
8f
0.05
46
145.64
137.41
135.21
133.23
133.04
131.04
130.23
130.00
129.73
128.59
128.48
128.41
127.99
125.63
68.58
59.95
56.06
21.82
$CDCl_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

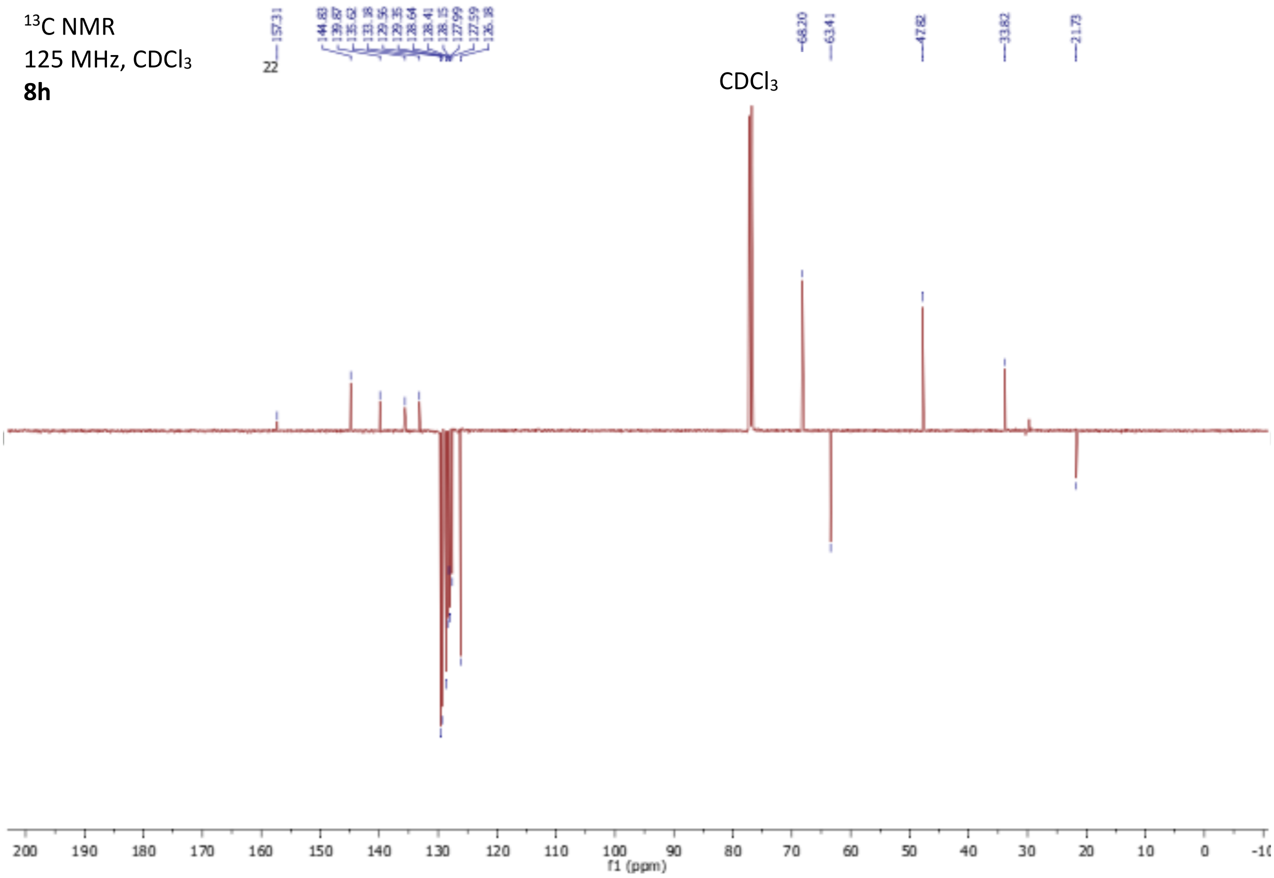
^1H NMR
500 MHz, $CDCl_3$
8g



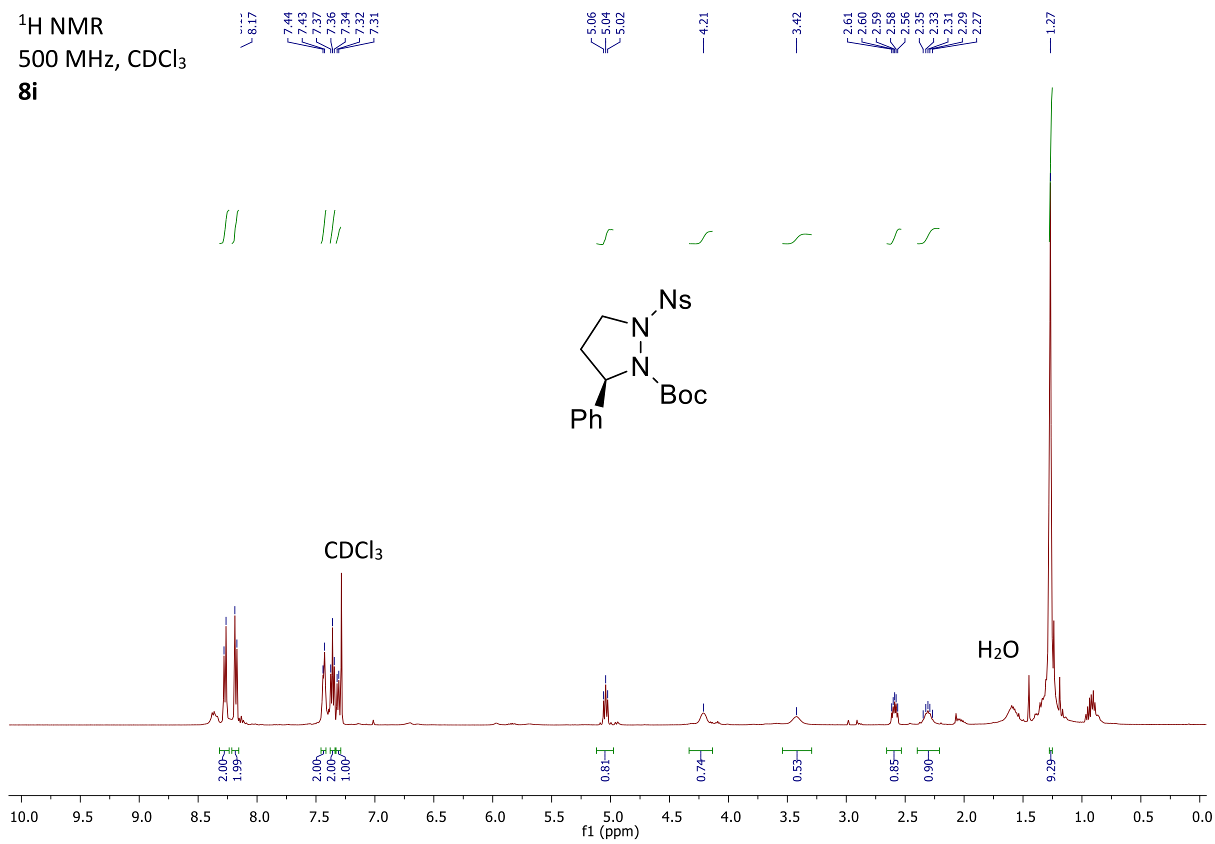
^{13}C NMR
125 MHz, $CDCl_3$
8g



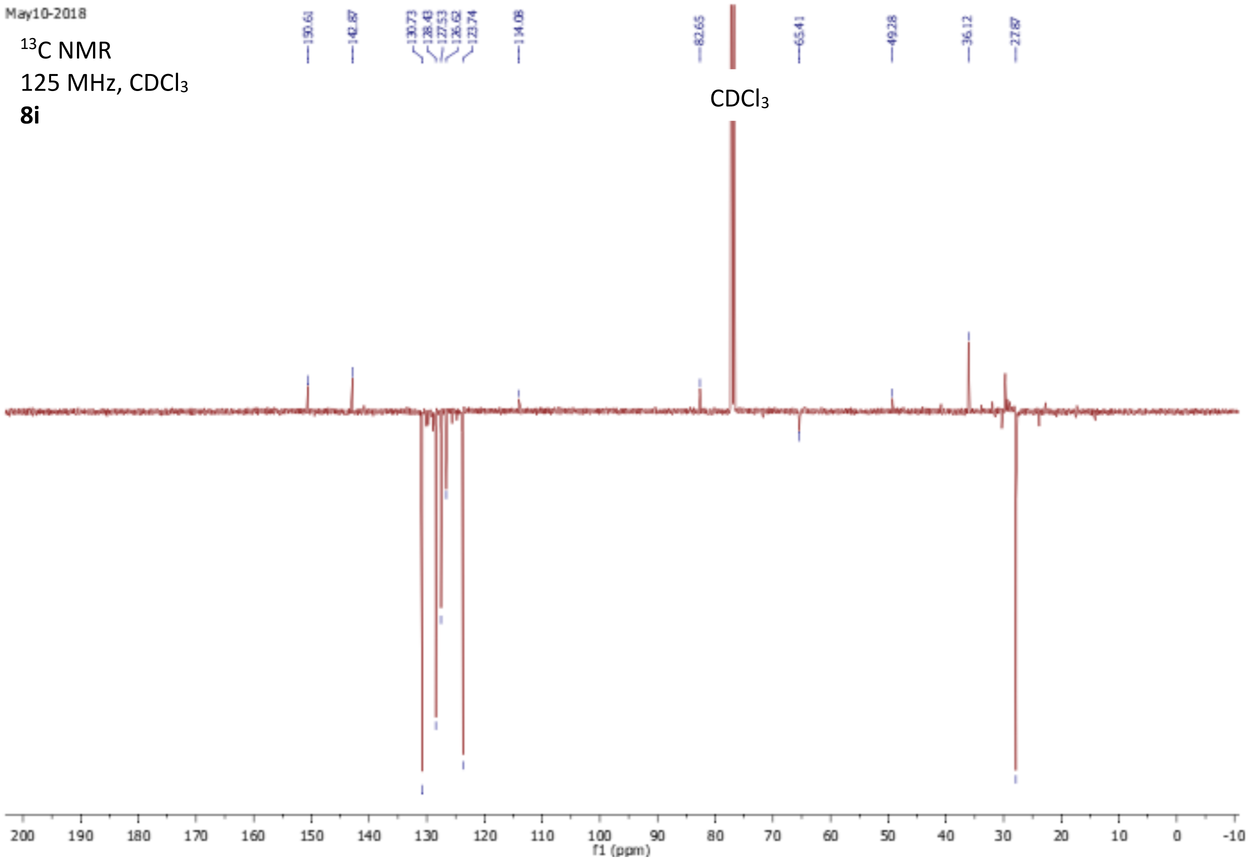

^{1}H NMR
500 MHz, CDCl$_3$
8h
7.85 7.83 7.35 7.35 7.34 7.33 7.26 7.26 7.26 7.25 7.23 7.21 7.20
5.38 5.37 5.36 5.35 5.10 5.08 4.83 4.81 4.00 3.99 3.99 3.98 3.98 3.97 3.96 3.95 3.32 3.30 3.30 3.29 3.28 3.26 2.45 2.44 2.43 2.42 2.41 2.40 2.39 2.21 2.20 2.19 2.18 2.18 2.17 2.17 2.16 2.15 2.14
CDCl3
Cbz
N
N
Ts
Ph
H2O
2.00 5.05 5.01 1.96 1.02 1.04 1.01 1.03 1.02 4.06 1.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


^{13}C NMR
125 MHz, CDCl$_3$
8h
157.31 144.83 139.87 135.62 133.38 129.56 129.35 128.64 128.41 128.15 127.99 127.59 126.38 68.20 63.41 47.82 33.82 21.73
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

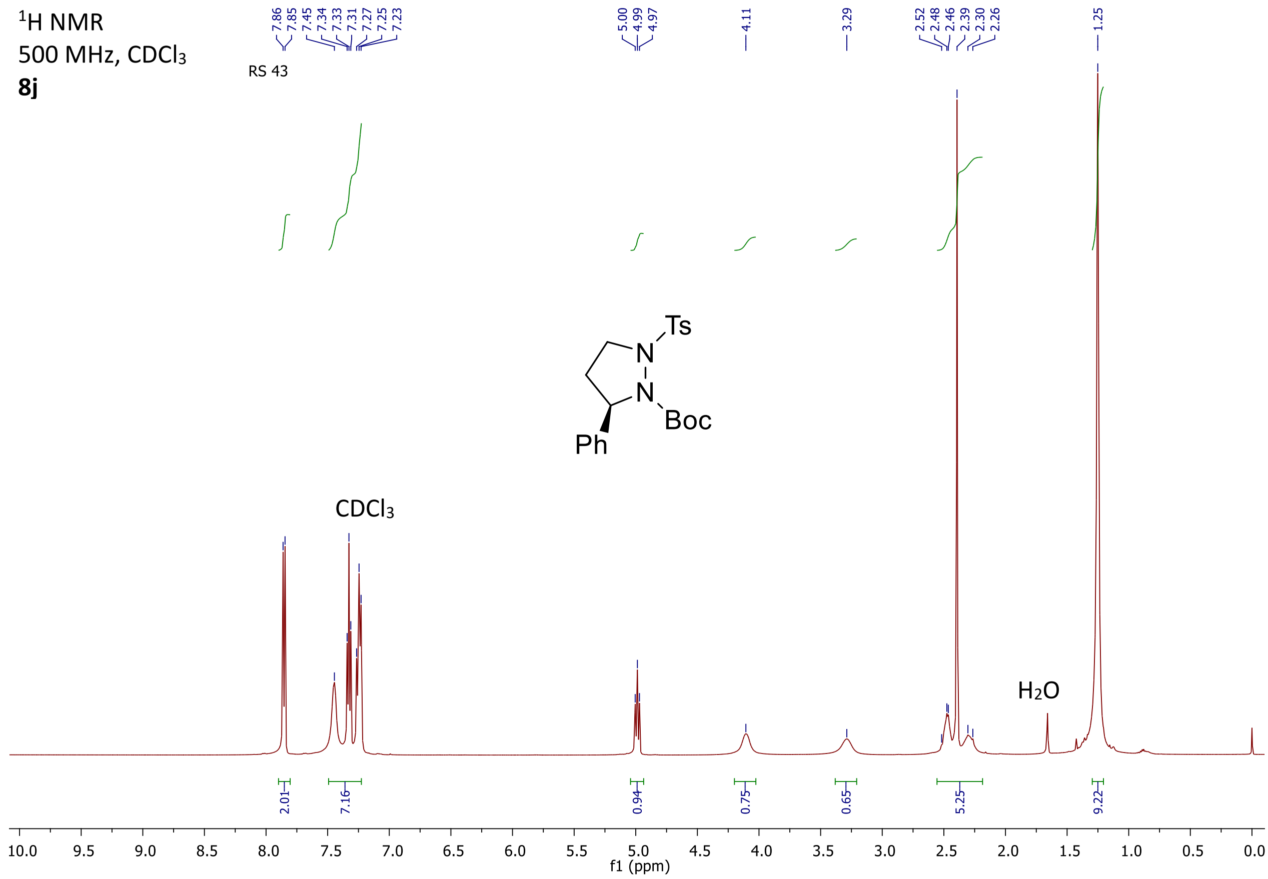
^{1}H NMR
500 MHz, $CDCl_3$
8i



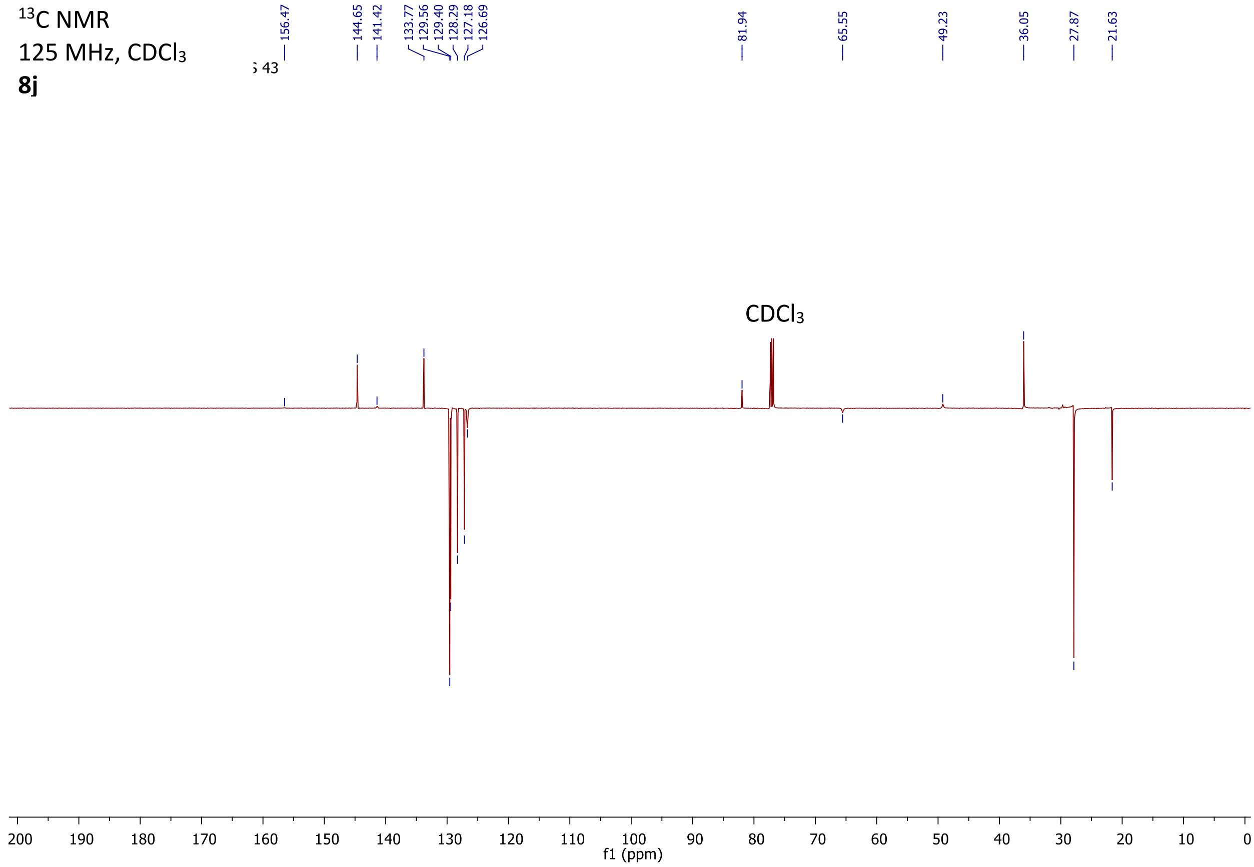
^{13}C NMR
125 MHz, $CDCl_3$
8i

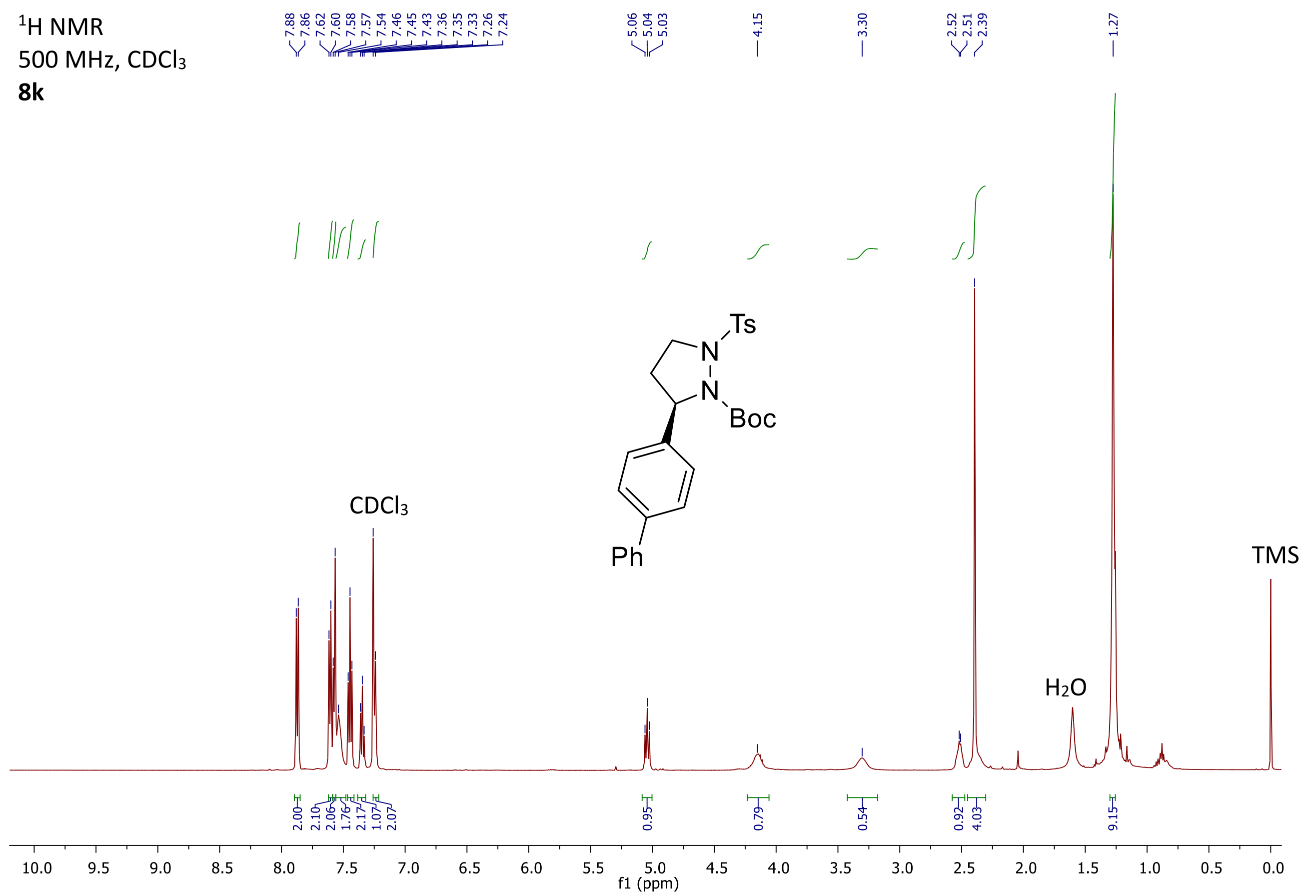


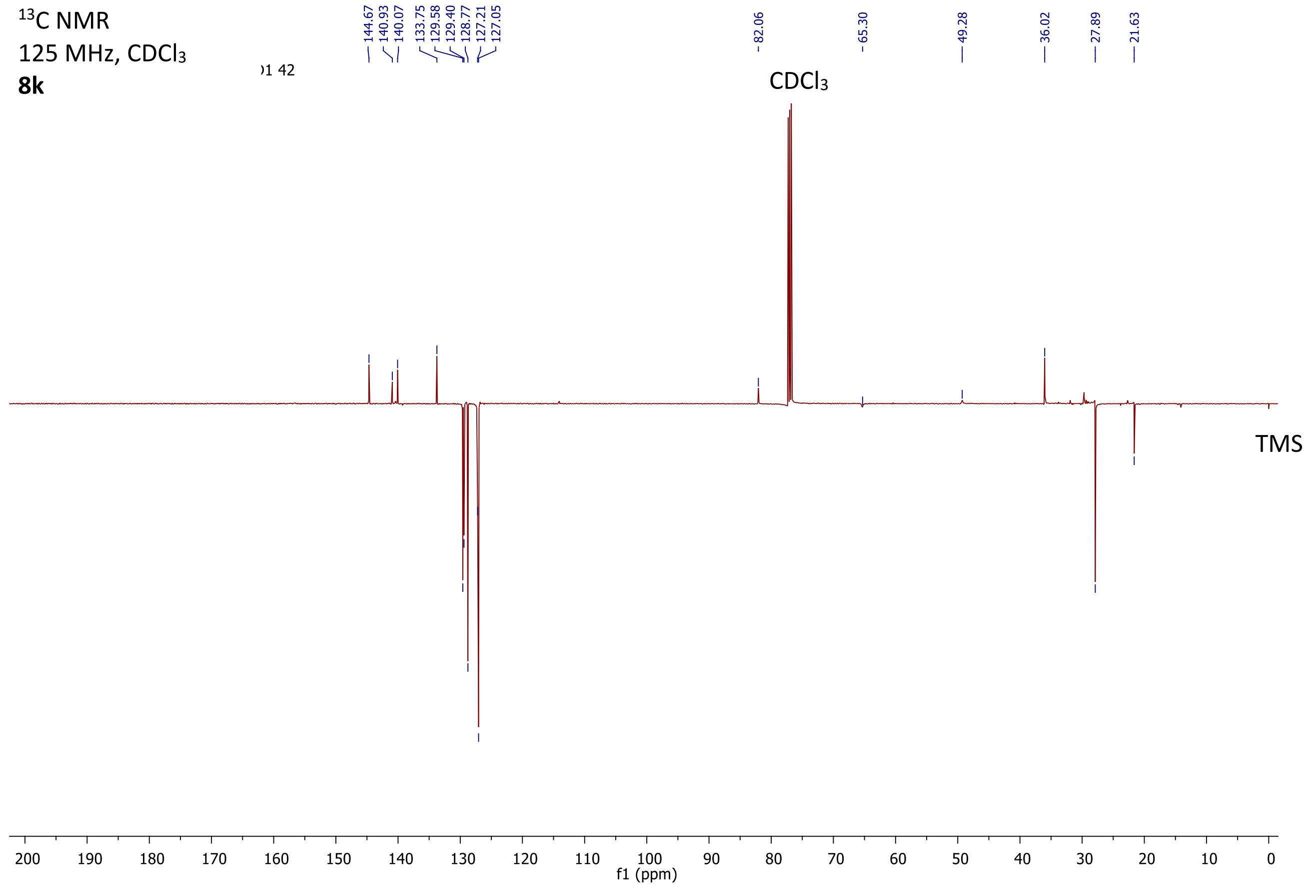
^{1}H NMR
500 MHz, $CDCl_3$
8j



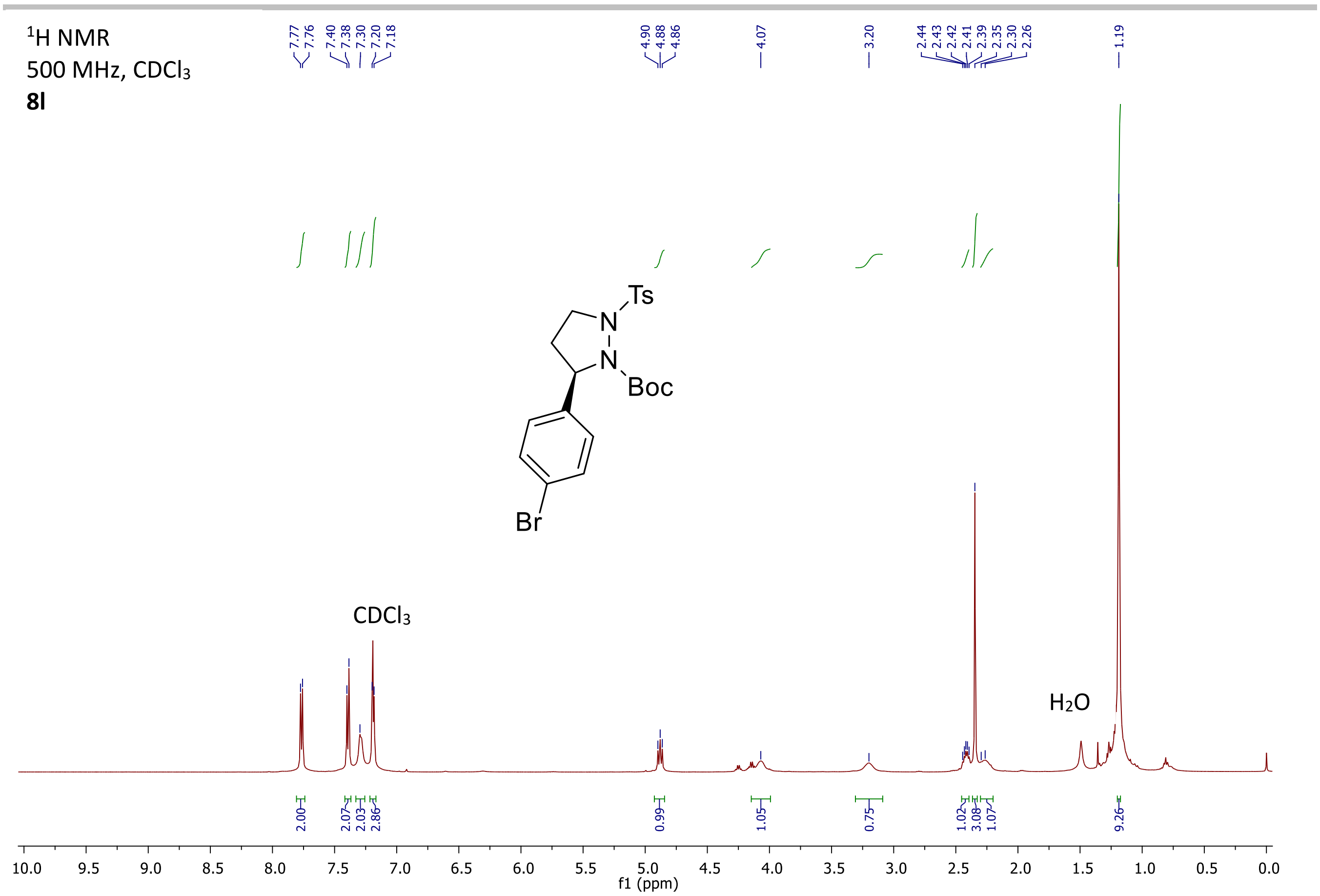
^{13}C NMR
125 MHz, $CDCl_3$
8j



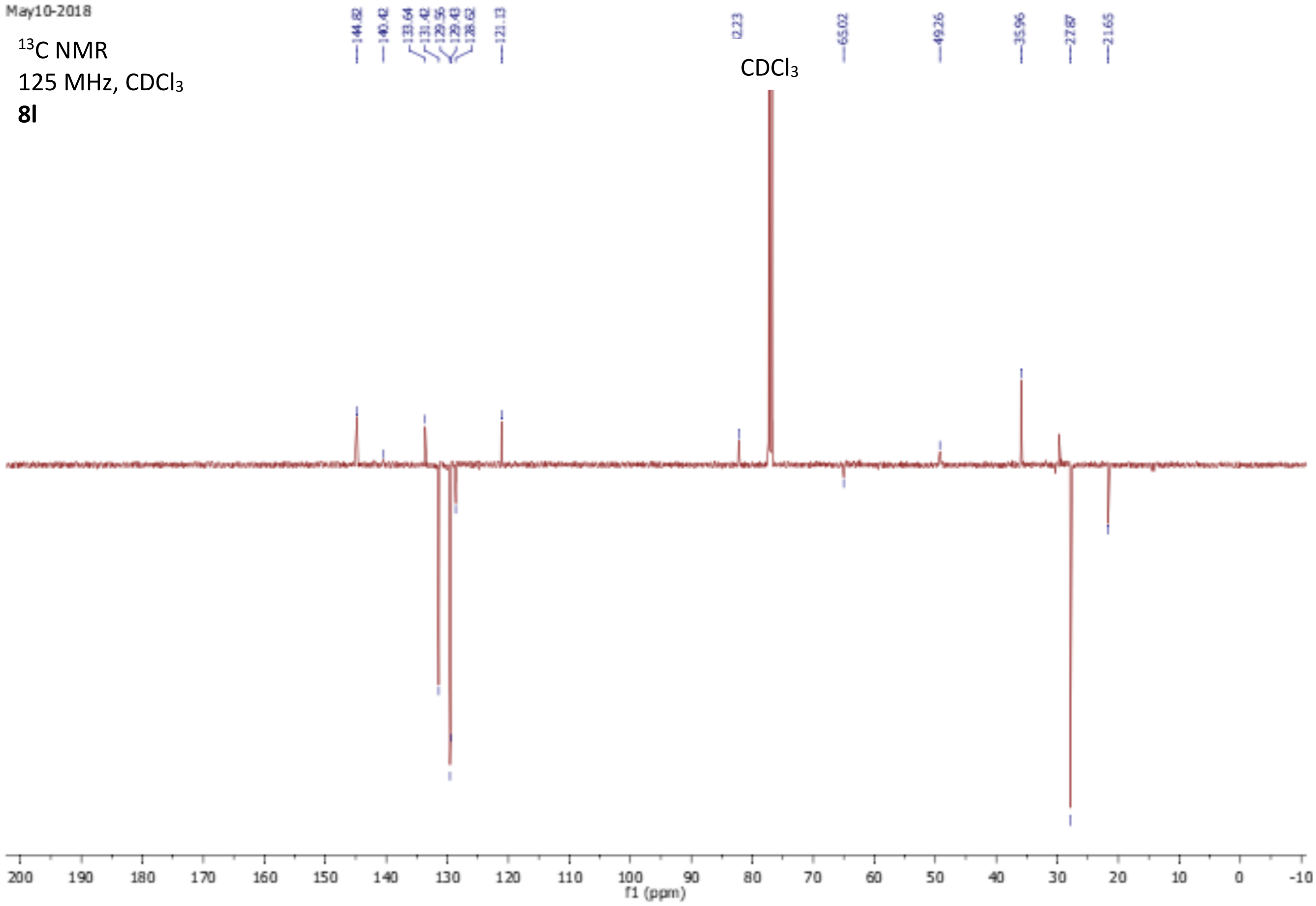

1H NMR
500 MHz, CDCl3
8k
7.88
7.86
7.62
7.60
7.58
7.57
7.54
7.46
7.45
7.43
7.36
7.35
7.33
7.26
7.24
5.06
5.04
5.03
4.15
3.30
2.52
2.51
2.39
1.27
Ts
N
N
Boc
Ph
CDCl3
H2O
TMS
2.00
2.10
2.06
1.76
2.17
1.07
2.07
0.95
0.79
0.54
0.92
4.03
9.15
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


13C NMR
125 MHz, CDCl3
8k
144.67
140.93
140.07
133.75
129.58
129.40
128.77
127.21
127.05
82.06
65.30
49.28
36.02
27.89
21.63
CDCl3
TMS
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

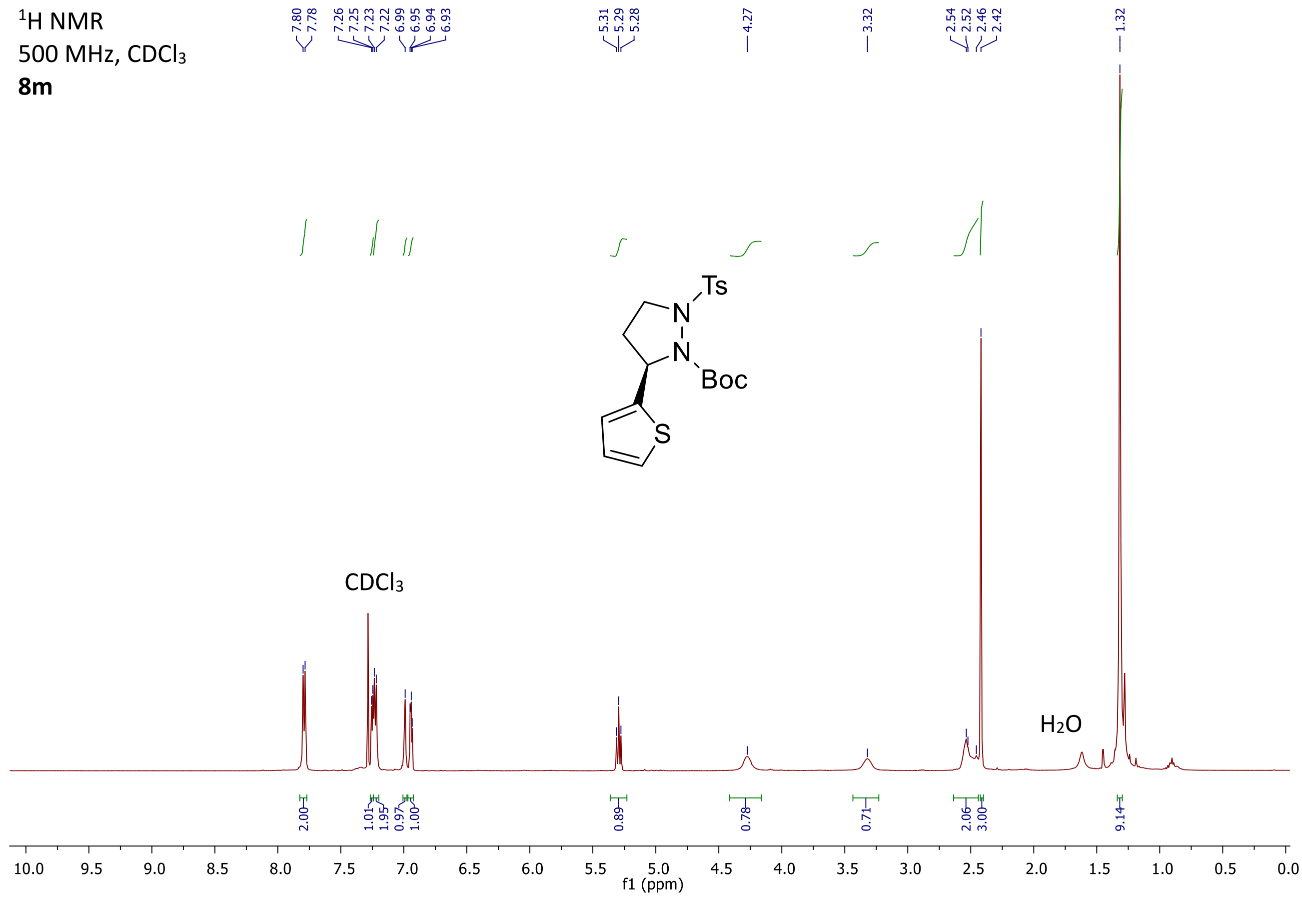
^{1}H NMR
500 MHz, $CDCl_3$
8l



^{13}C NMR
125 MHz, $CDCl_3$
8l

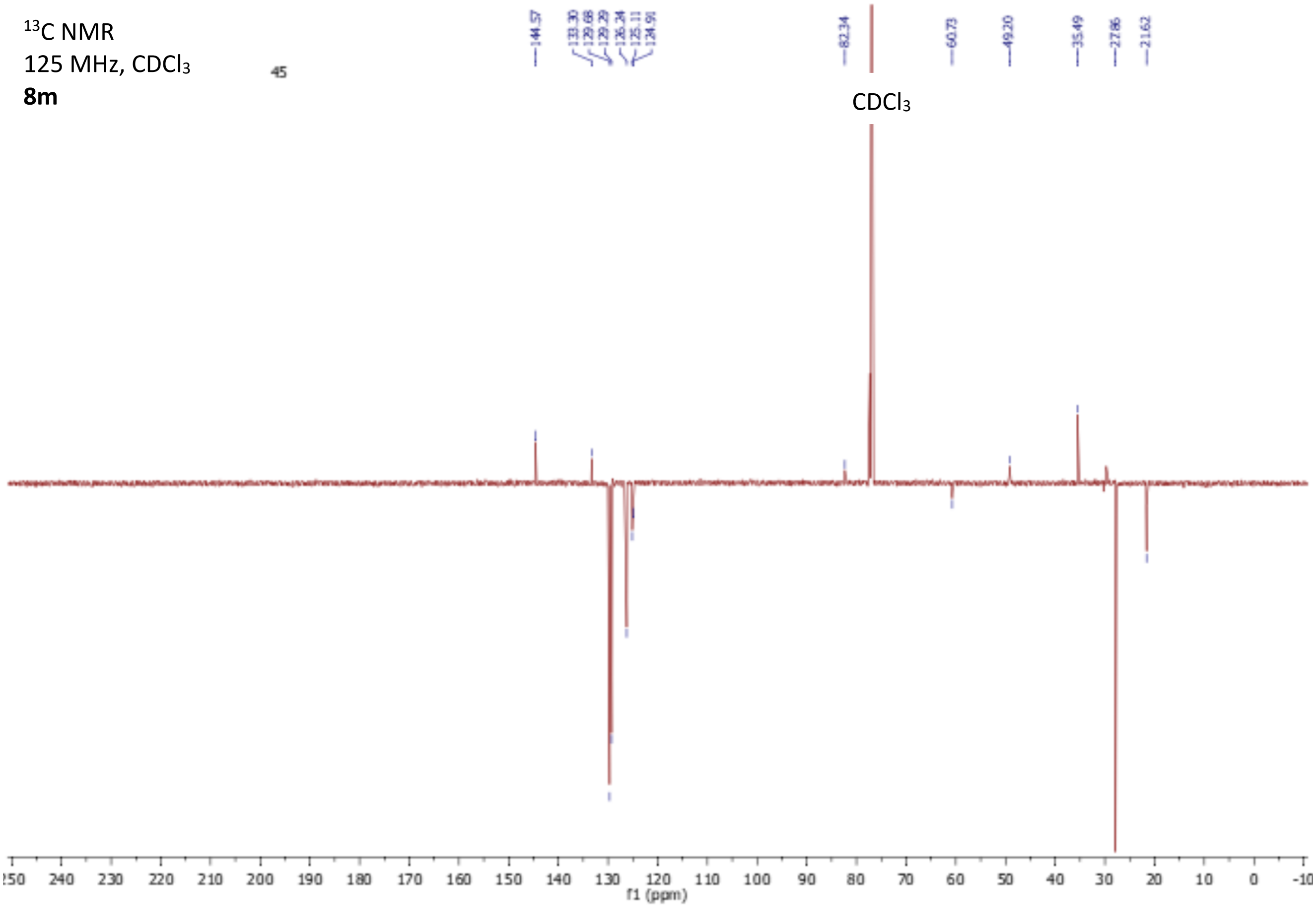


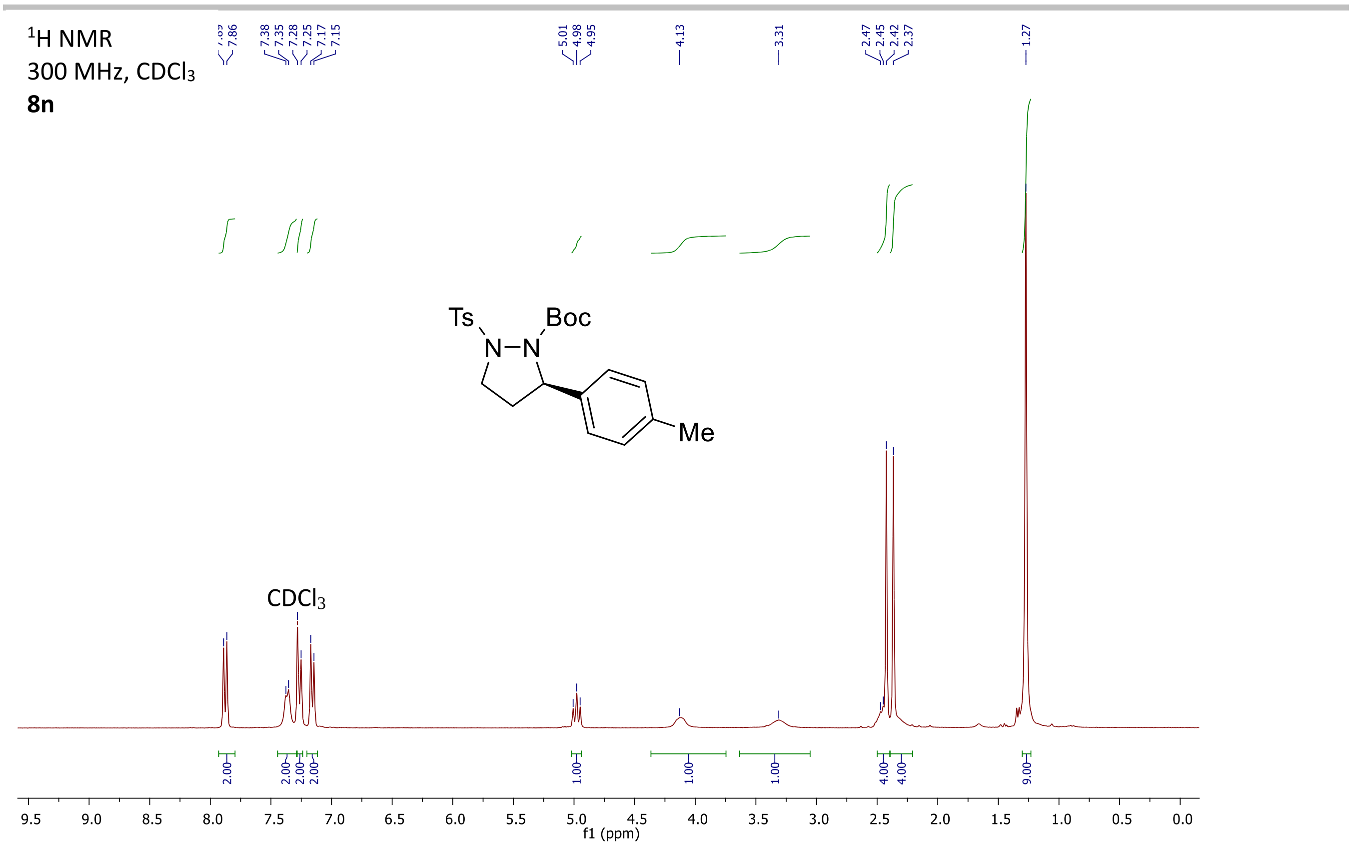
^{1}H NMR
500 MHz, $CDCl_3$
8m

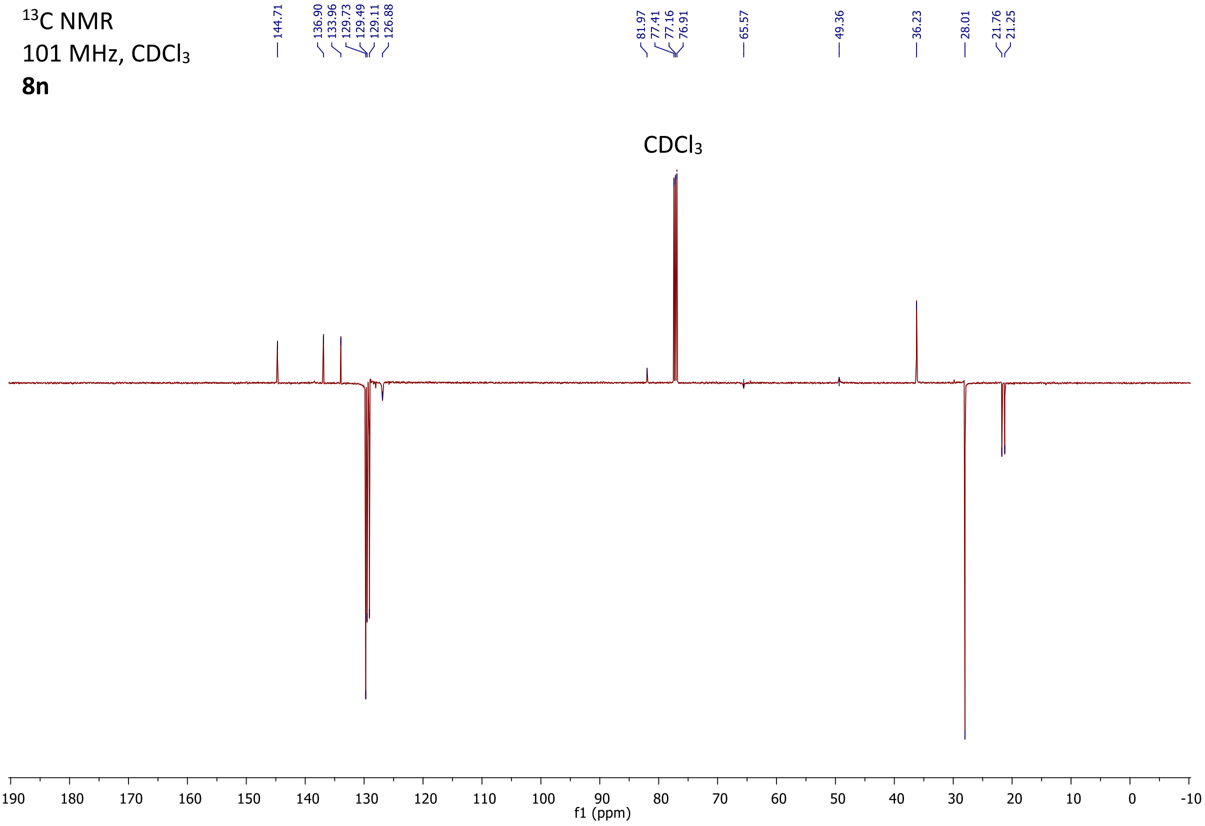


^{13}C NMR
125 MHz, $CDCl_3$
8m

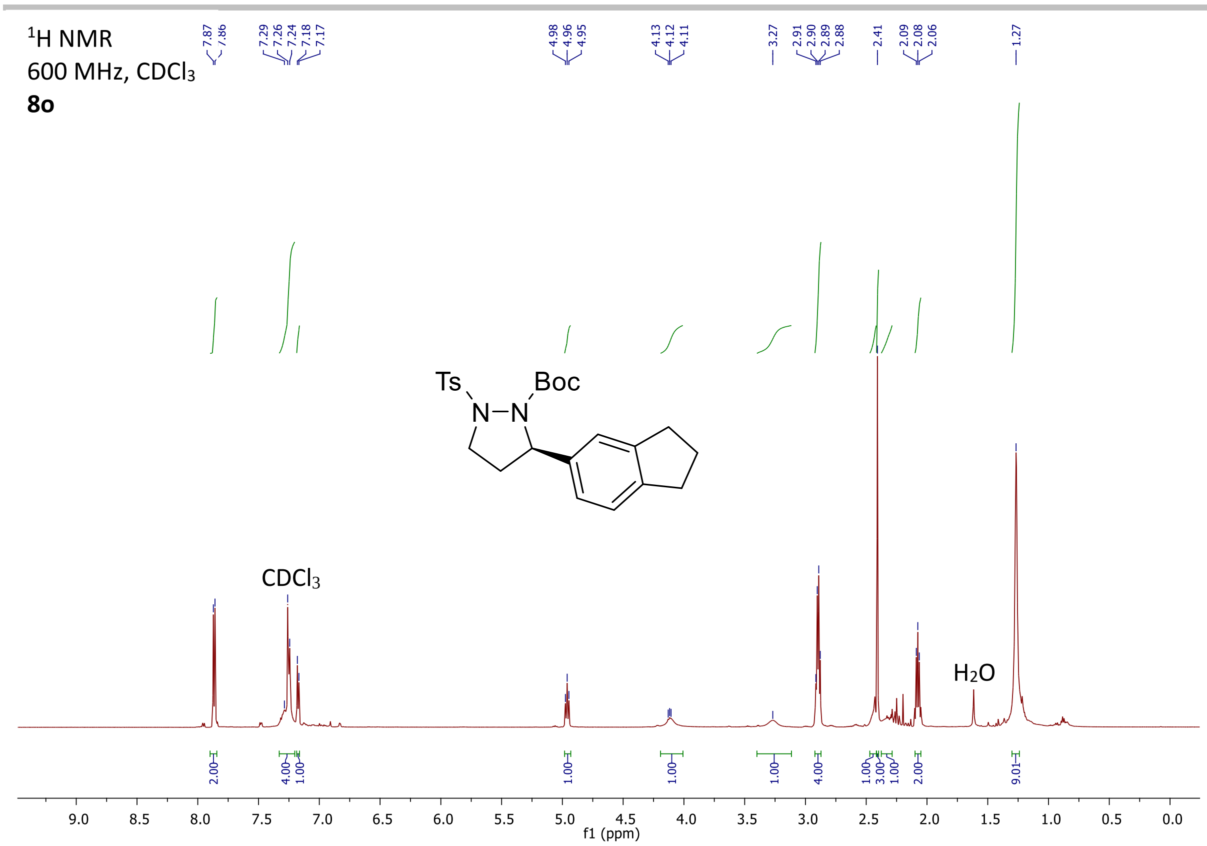
45



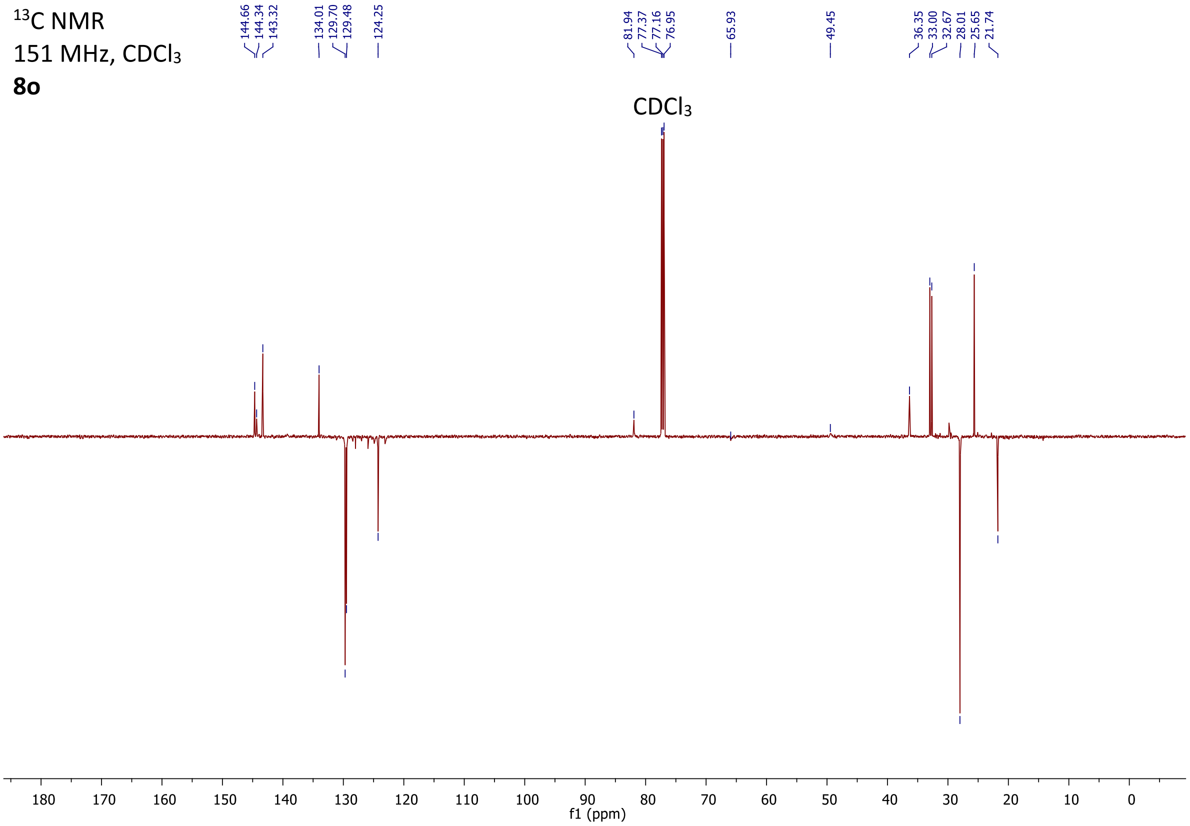

^{1}H NMR
300 MHz, $CDCl_3$
8n
7.86
7.38
7.35
7.28
7.25
7.17
7.15
5.01
4.98
4.95
4.13
3.31
2.47
2.45
2.42
2.37
1.27
Ts
Boc
N
N
Me
$CDCl_3$
2.00
2.00
2.00
2.00
1.00
1.00
1.00
4.00
4.00
9.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


^{13}C NMR
101 MHz, $CDCl_3$
8n
144.71
136.90
133.96
129.73
129.49
129.11
126.88
81.97
77.41
77.16
76.91
65.57
49.36
36.23
28.01
21.76
21.25
$CDCl_3$
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

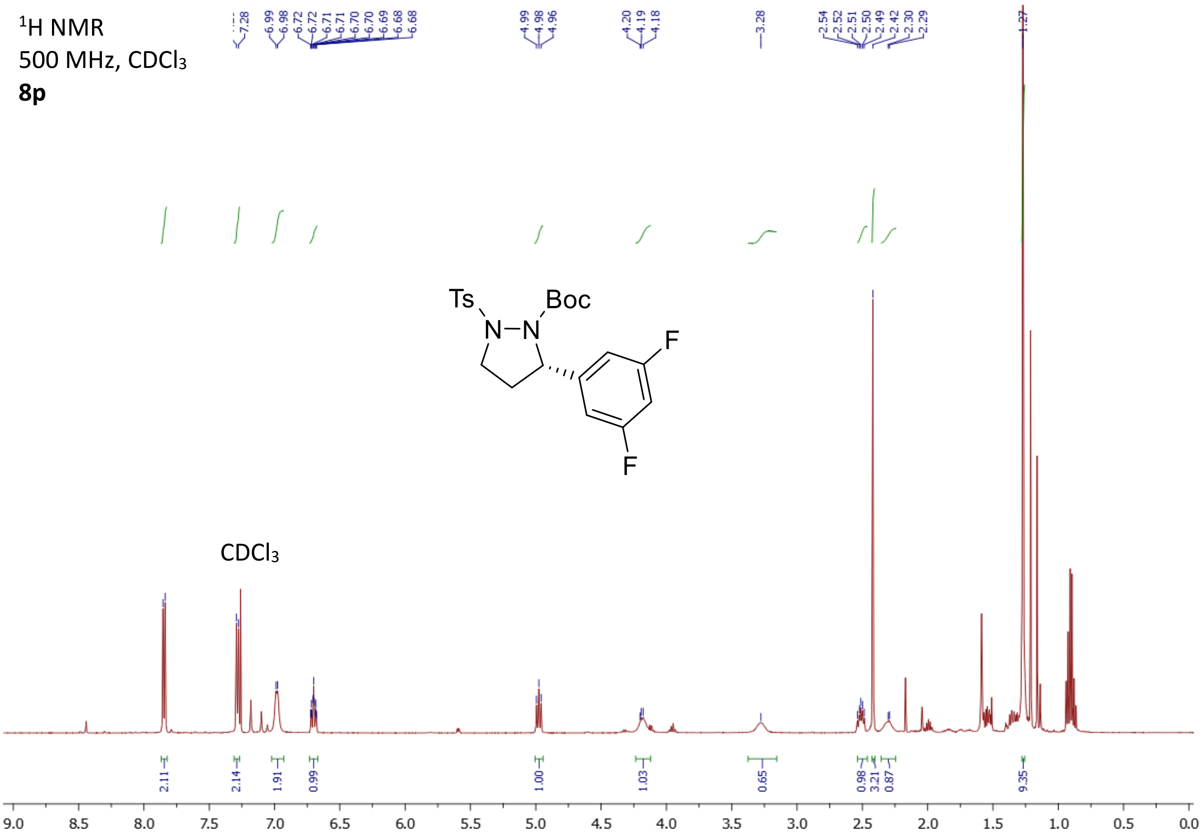
^{1}H NMR
600 MHz, $CDCl_3$
8o



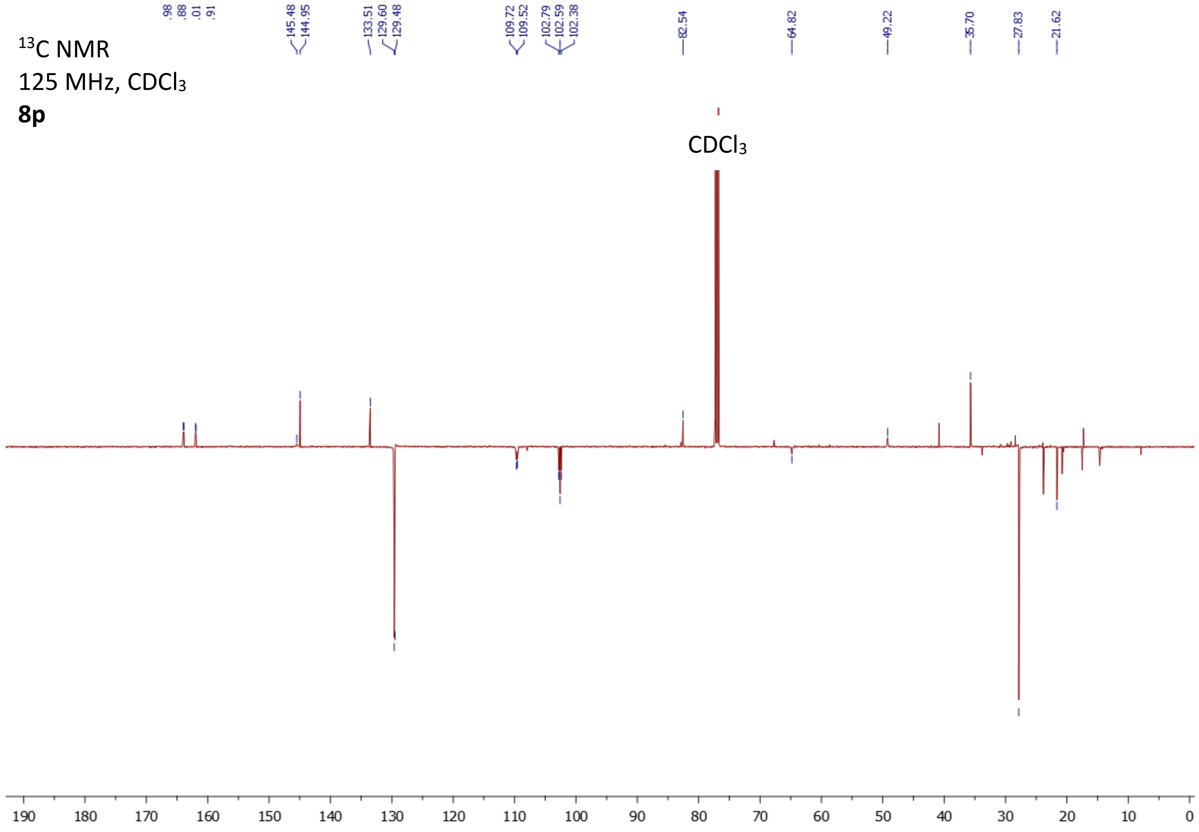
^{13}C NMR
151 MHz, $CDCl_3$
8o



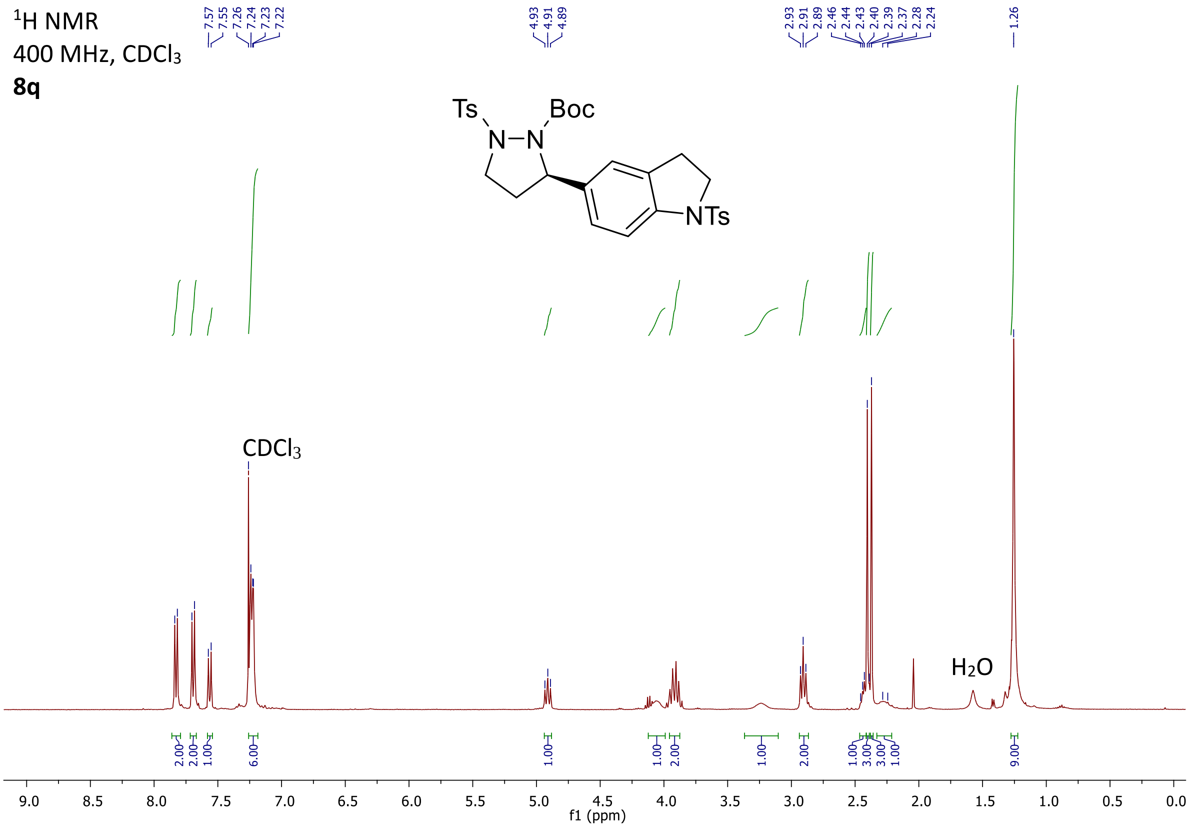
^{1}H NMR
500 MHz, $CDCl_3$
8p



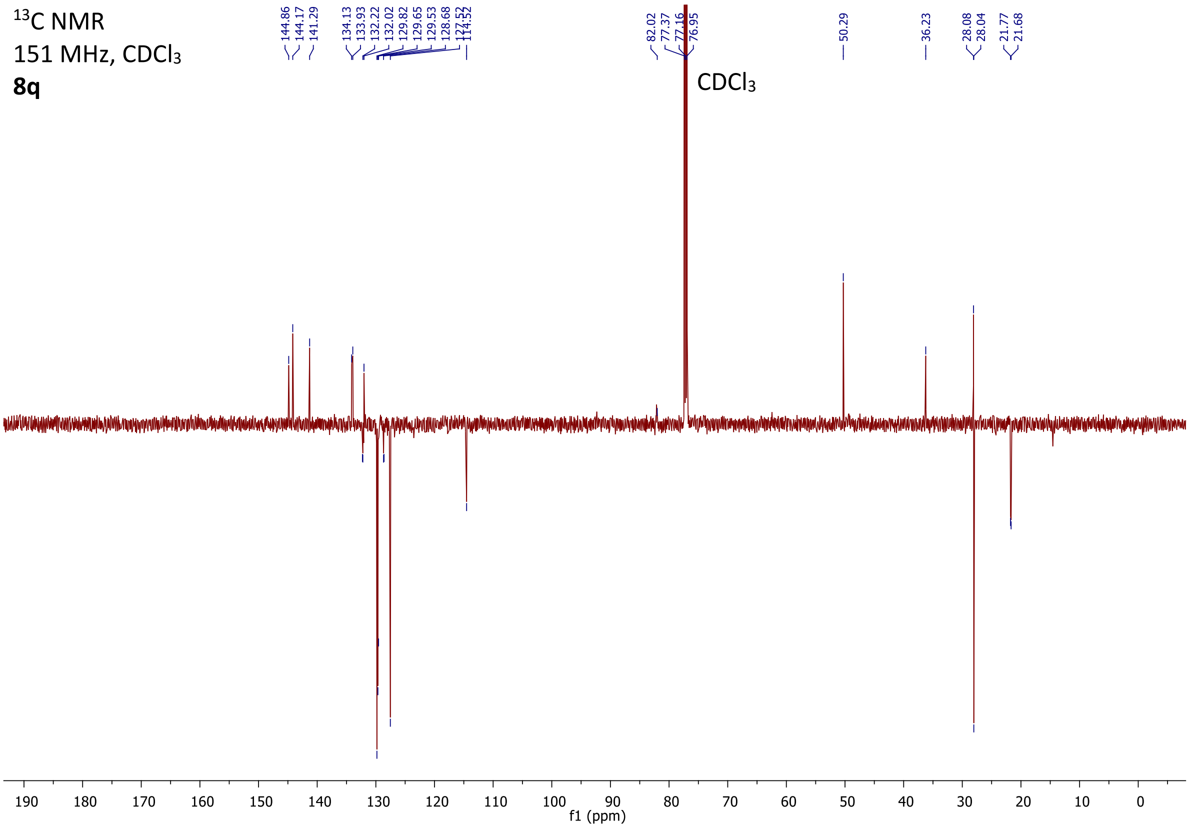
^{13}C NMR
125 MHz, $CDCl_3$
8p



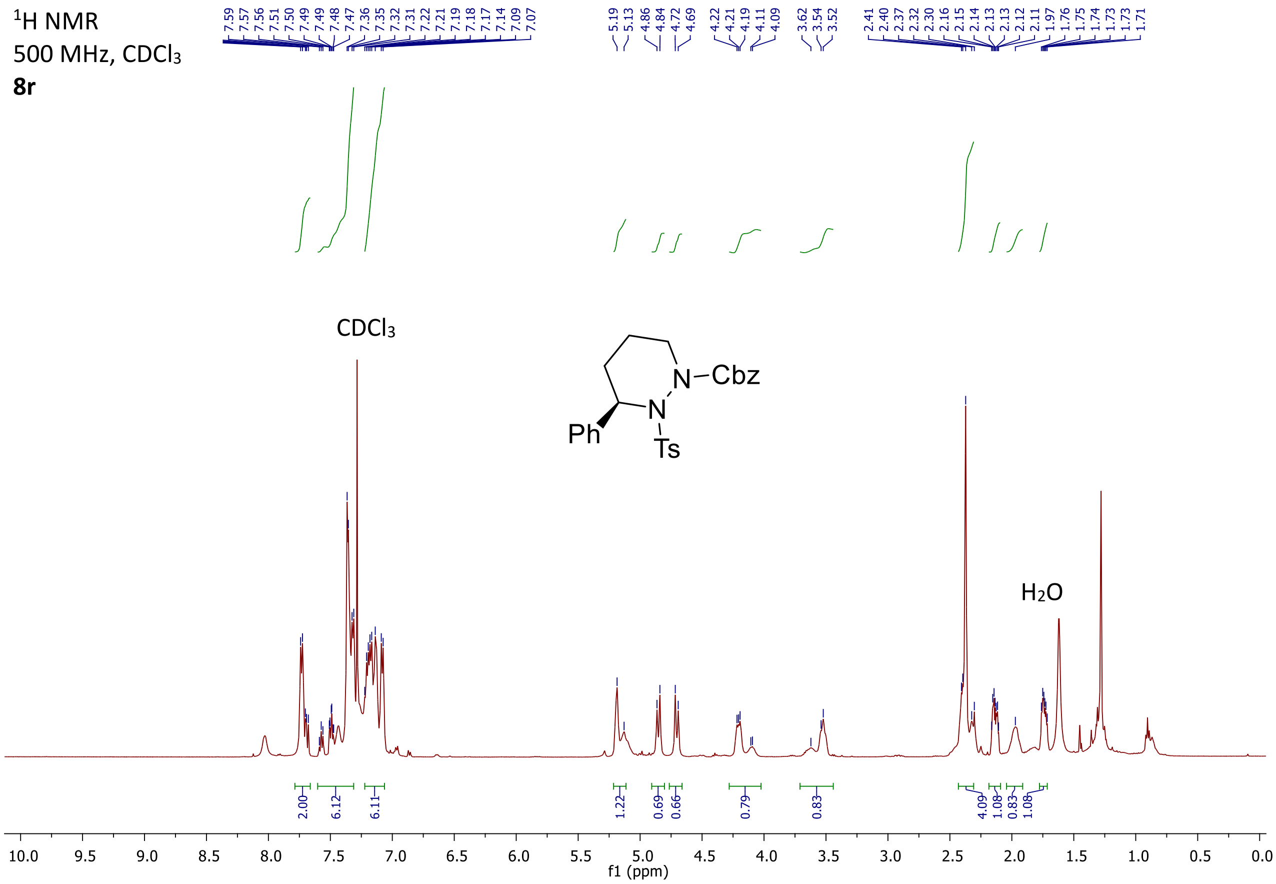
^1H NMR
400 MHz, $CDCl_3$
8q



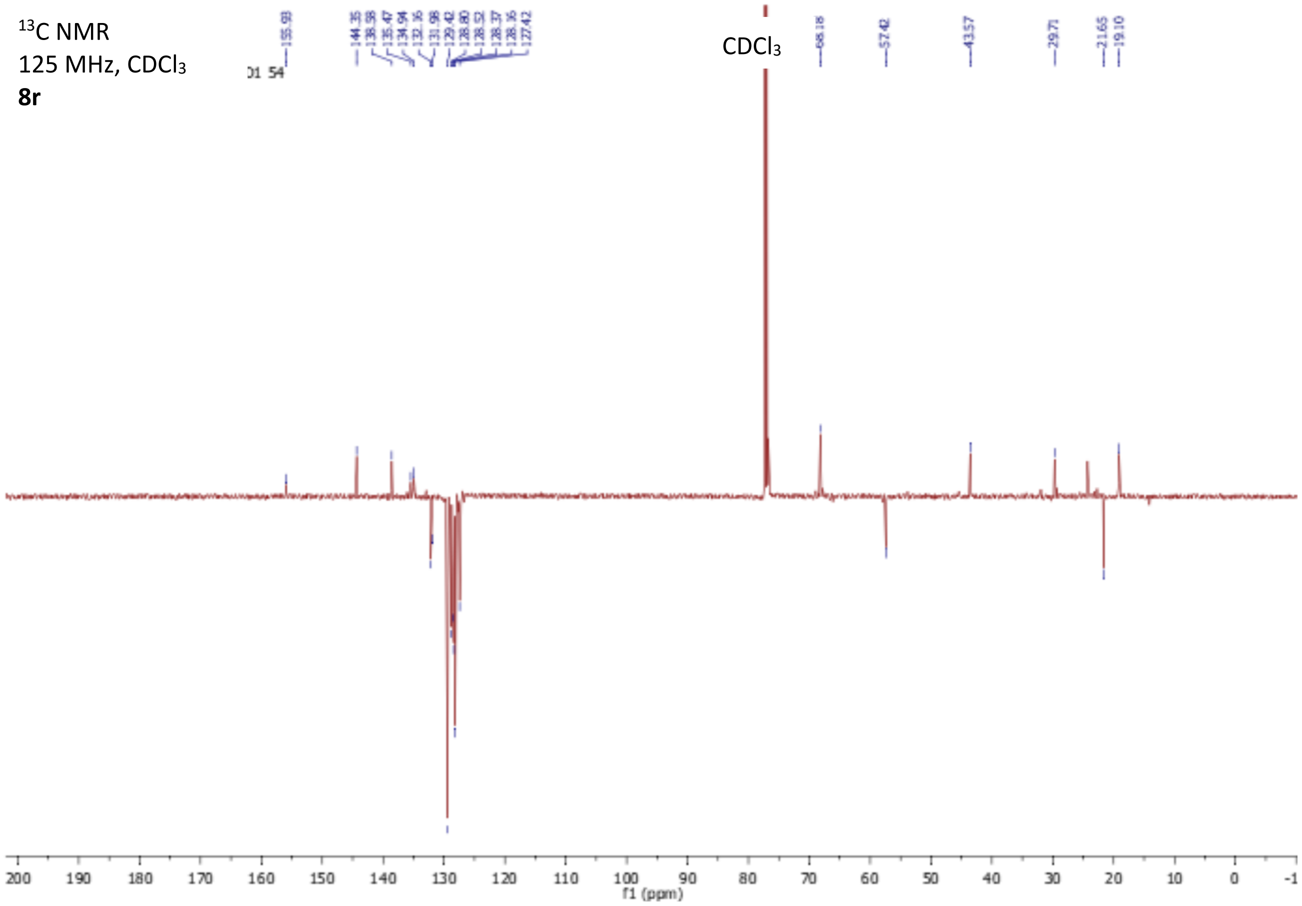
^{13}C NMR
151 MHz, $CDCl_3$
8q



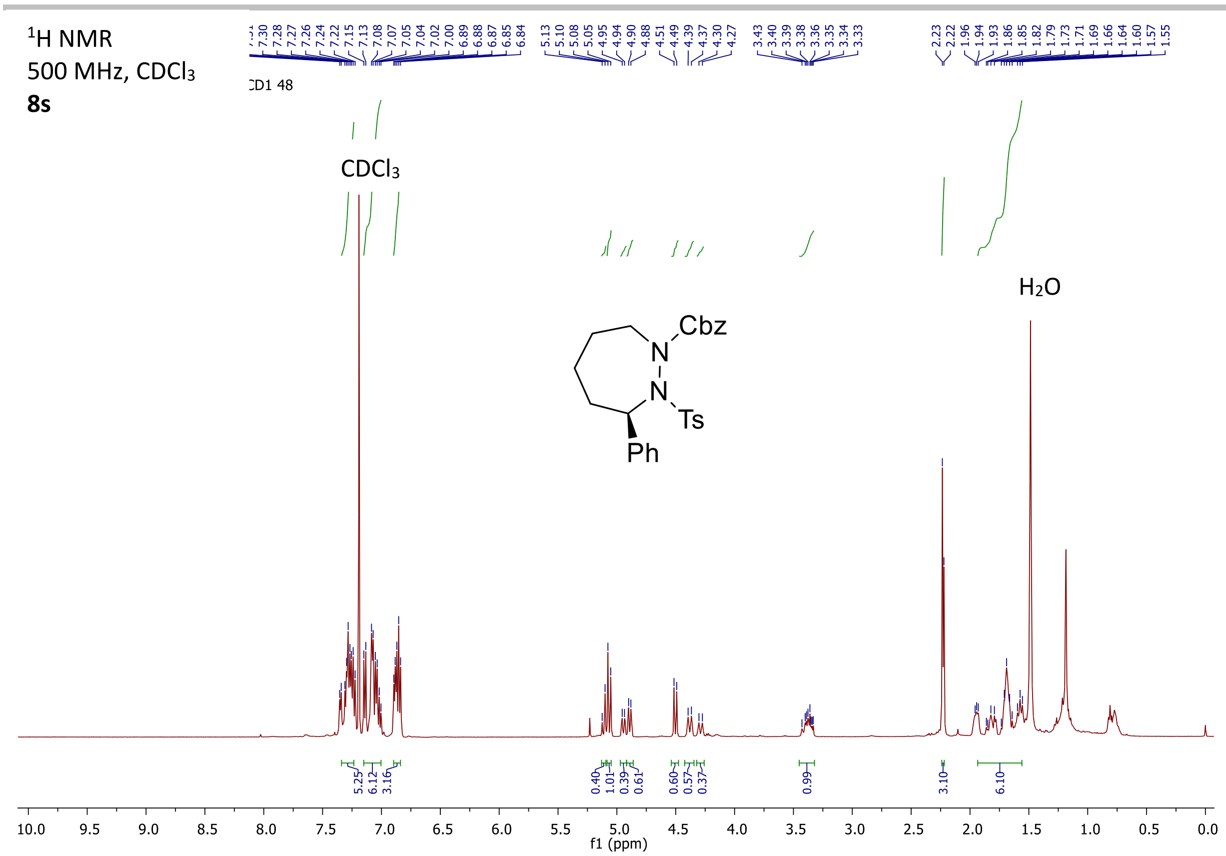
^{1}H NMR
500 MHz, CDCl$_3$
8r



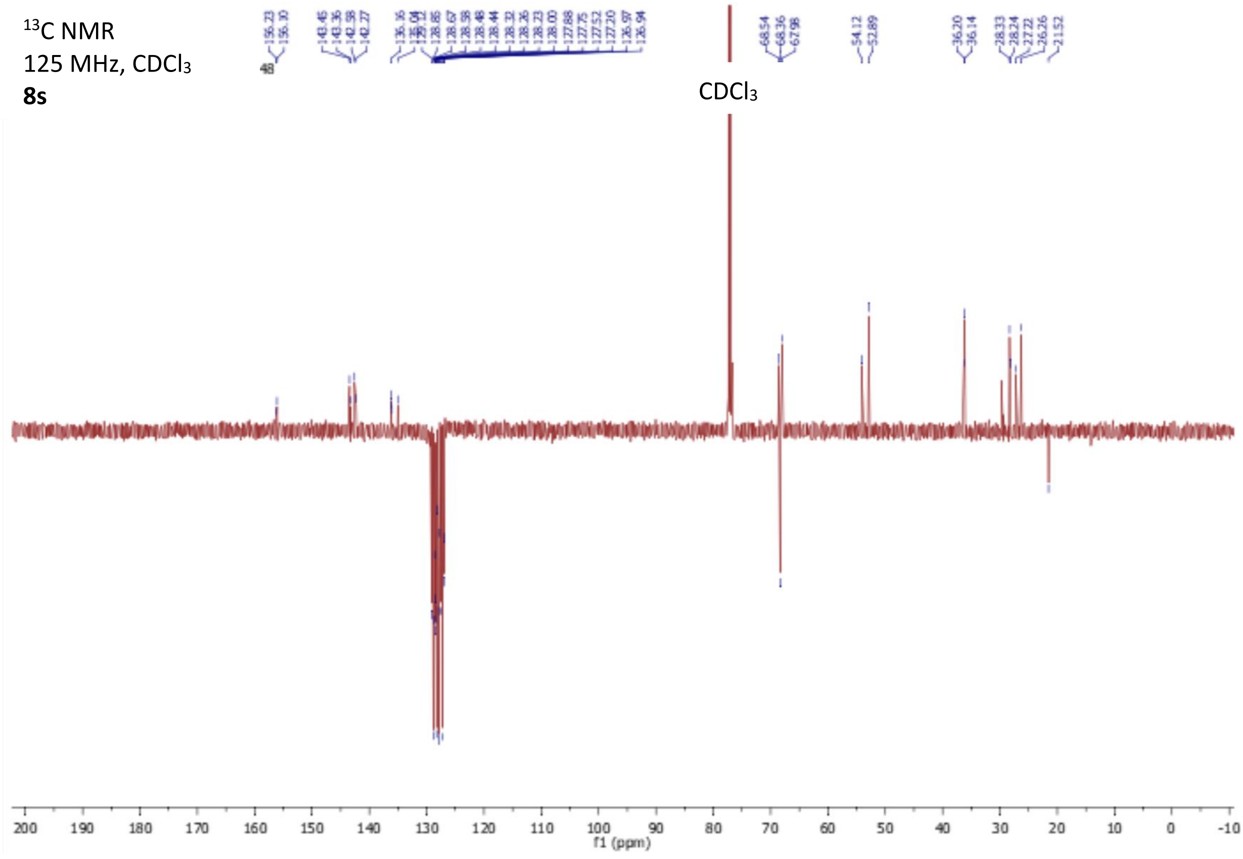
^{13}C NMR
125 MHz, CDCl$_3$
8r

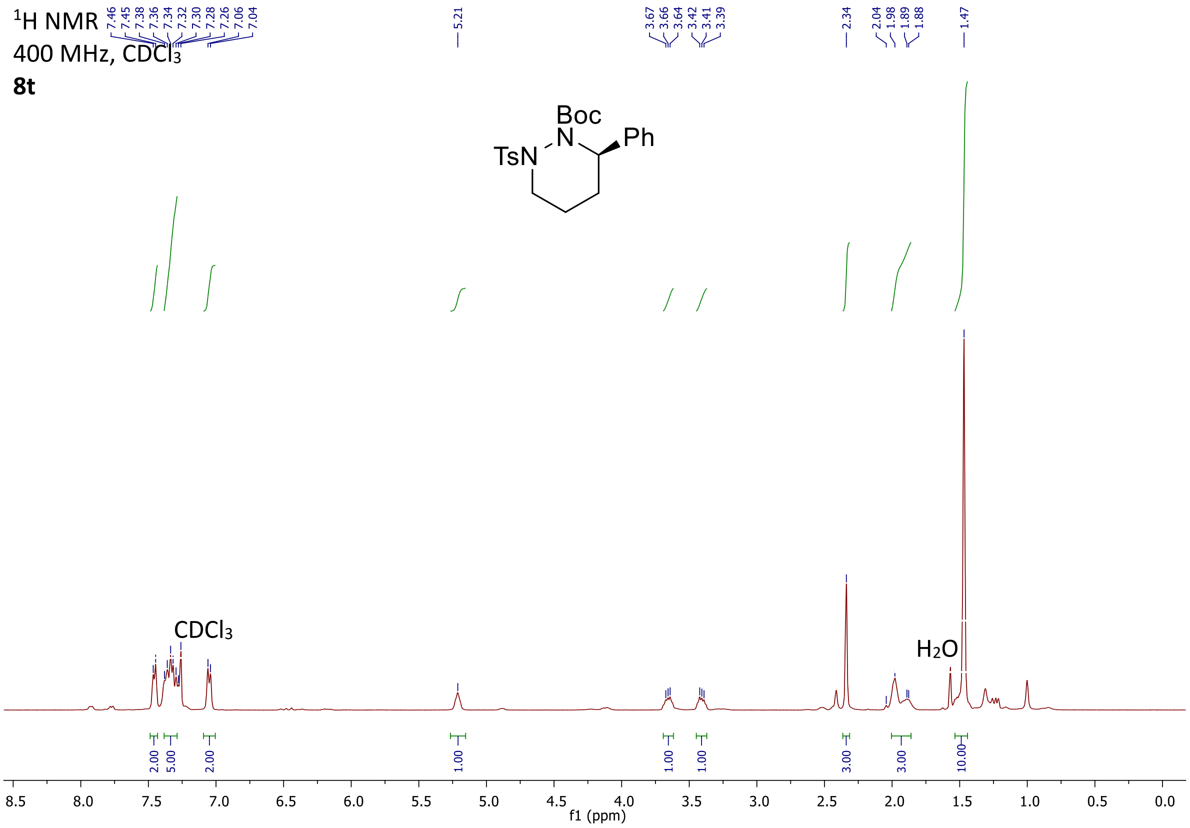


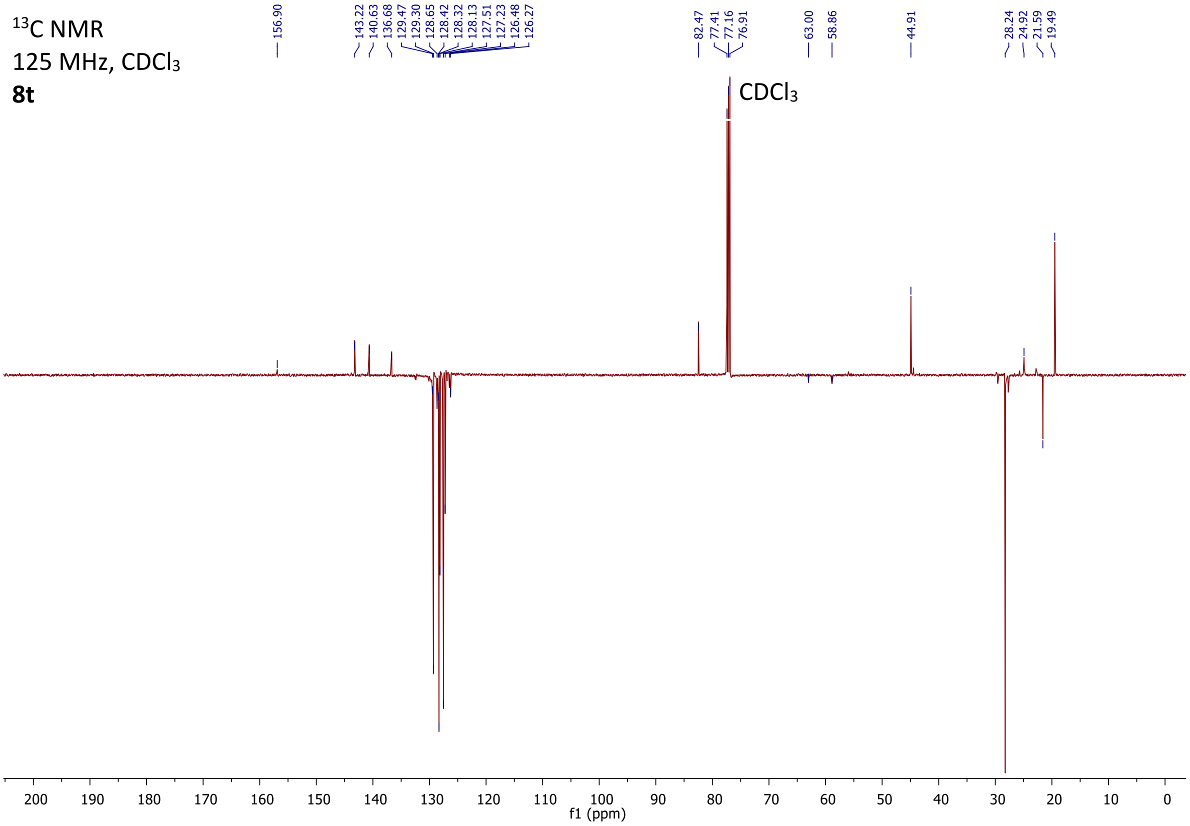
^{1}H NMR
500 MHz, $CDCl_3$
8s

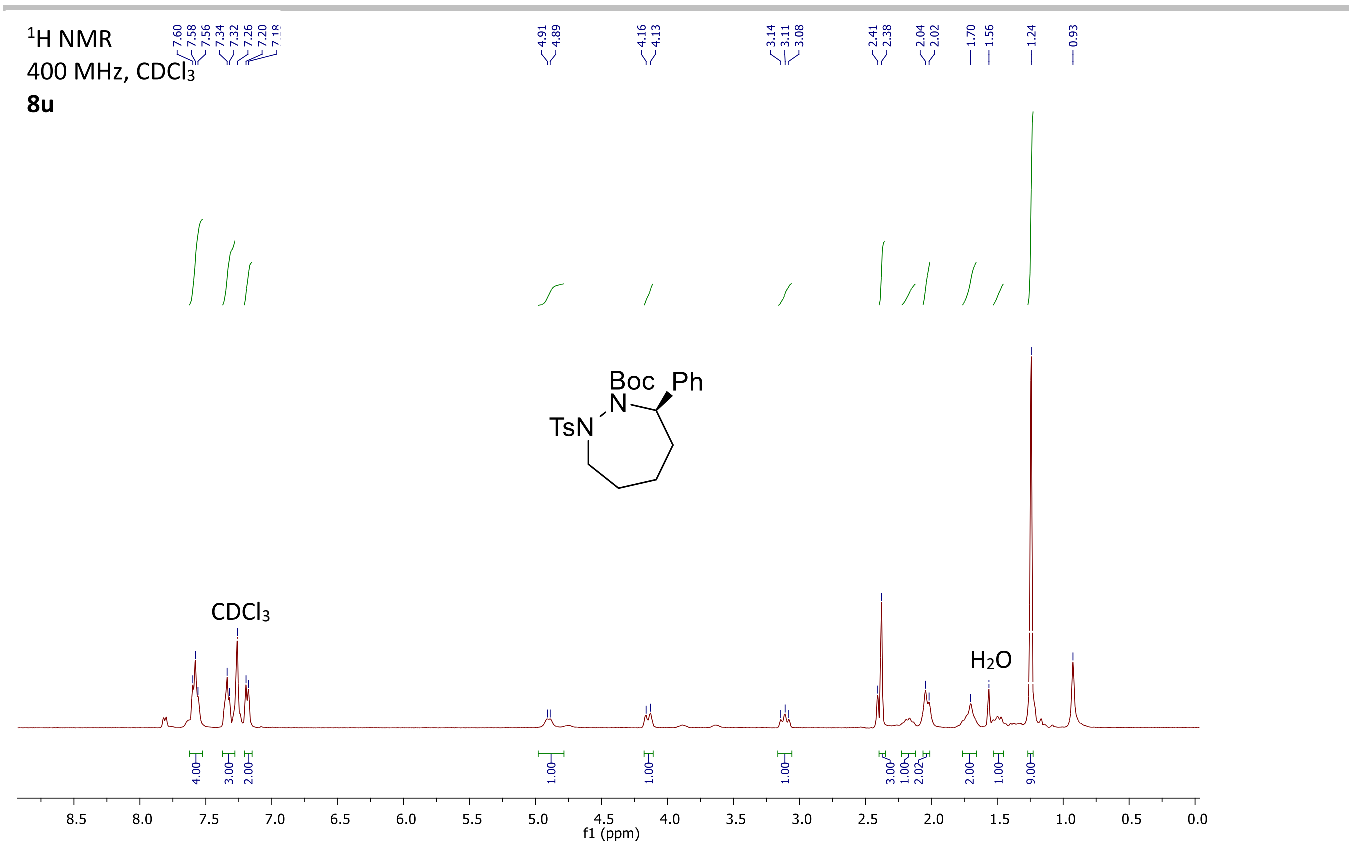


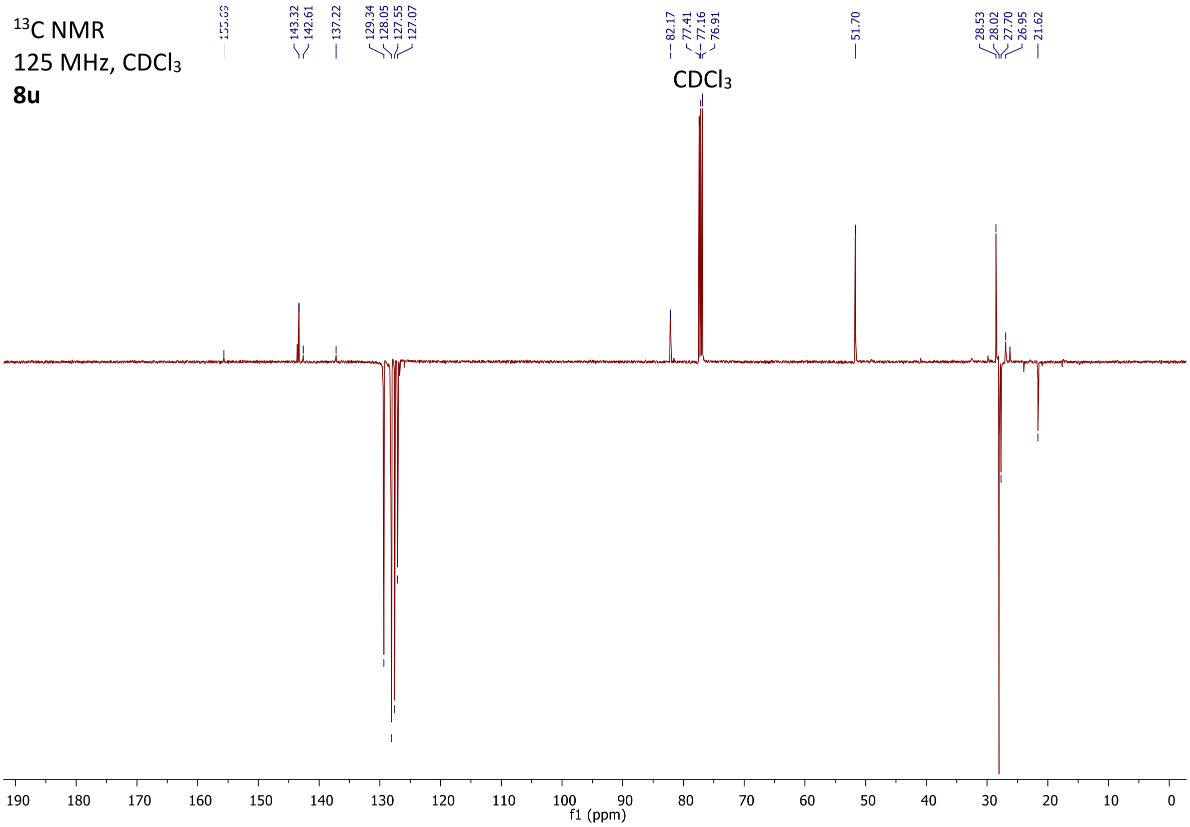
^{13}C NMR
125 MHz, $CDCl_3$
8s

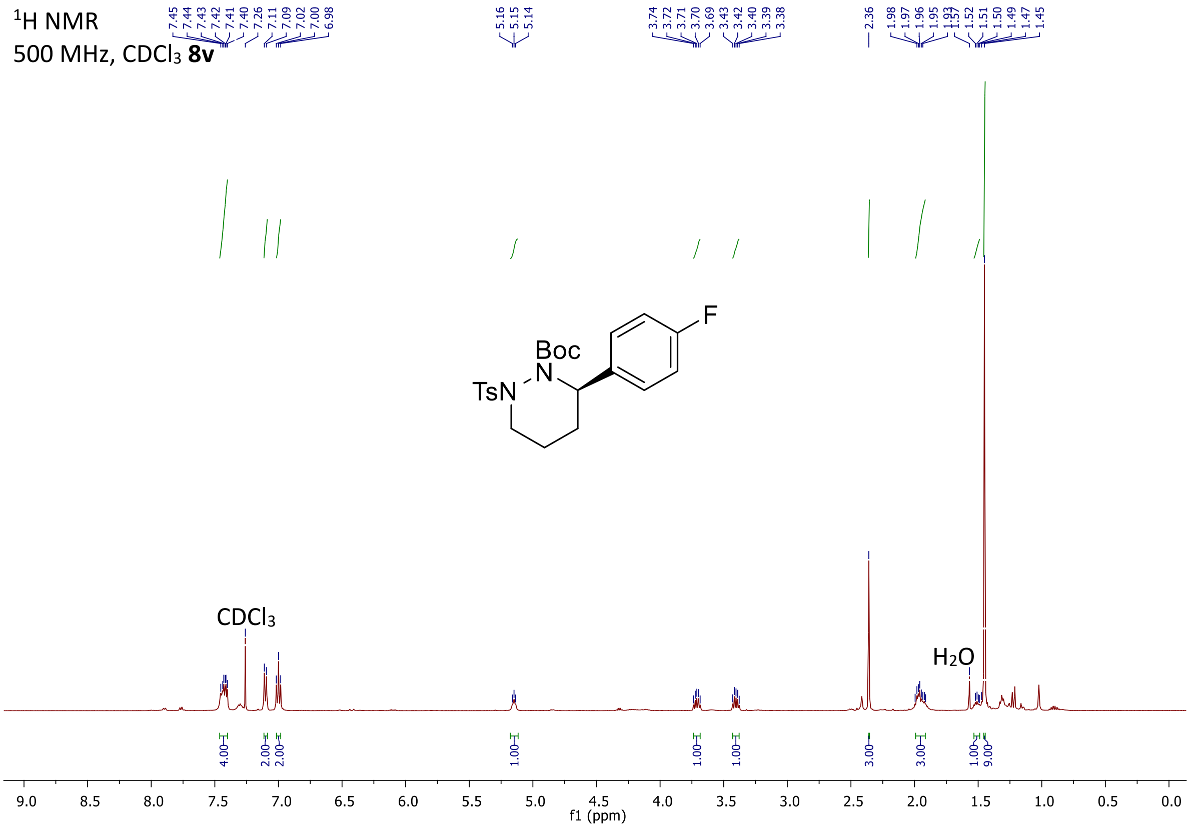



^{1}H NMR
400 MHz, CDCl$_3$
8t
7.46
7.45
7.38
7.36
7.34
7.32
7.30
7.28
7.26
7.06
7.04
5.21
3.67
3.66
3.64
3.42
3.41
3.39
2.34
2.04
1.98
1.89
1.88
1.47
Boc
N
Ph
TsN
CDCl$_3$
H$_2$O
2.00
5.00
2.00
1.00
1.00
1.00
3.00
3.00
10.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

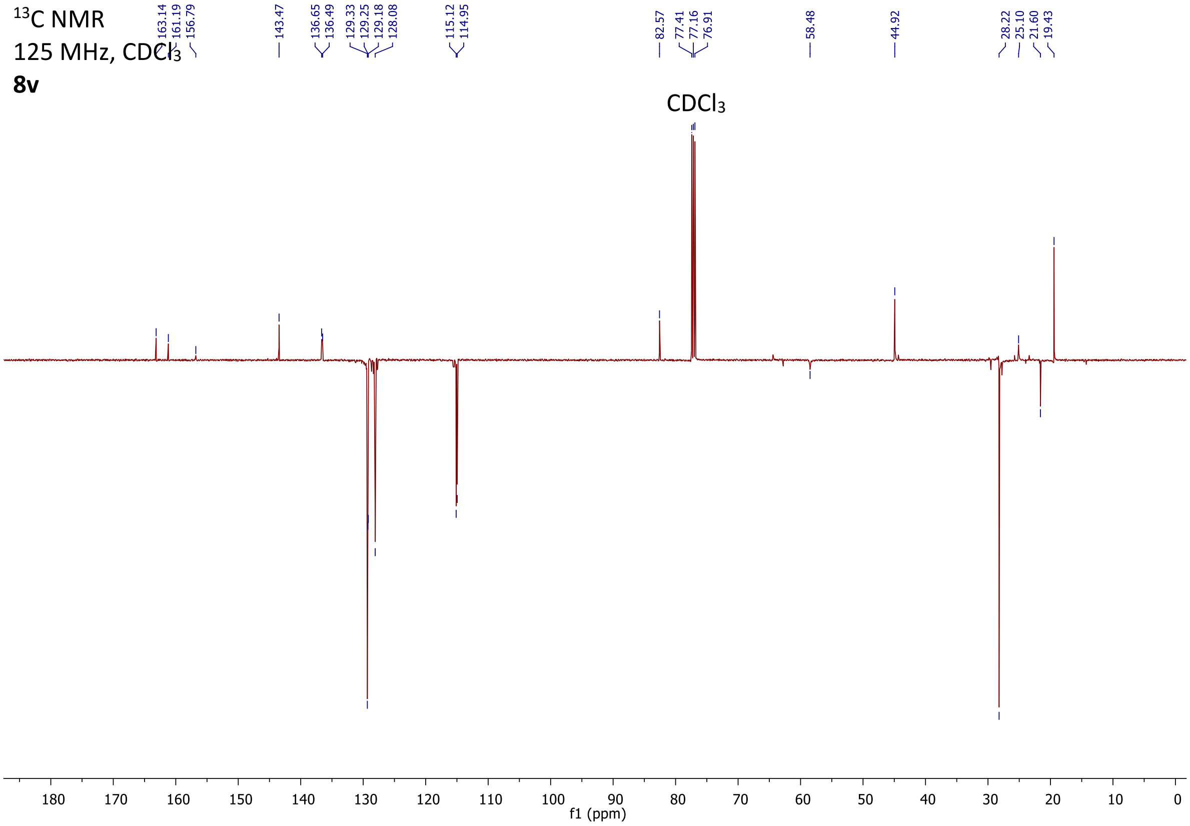

^{13}C NMR
125 MHz, CDCl$_3$
8t
156.90
143.22
140.63
136.68
129.47
129.30
128.65
128.42
128.32
128.13
127.51
127.23
126.48
126.27
82.47
77.41
77.16
76.91
63.00
58.86
44.91
28.24
24.92
21.59
19.49
CDCl$_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{1}H NMR
400 MHz, $CDCl_3$
8u
7.60
7.58
7.56
7.34
7.32
7.26
7.20
7.18
4.91
4.89
4.16
4.13
3.14
3.11
3.08
2.41
2.38
2.04
2.02
1.70
1.56
1.24
0.93
Boc
Ph
N
TsN
$CDCl_3$
H_2O
4.00
3.00
2.00
1.00
1.00
1.00
3.00
1.00
2.02
2.00
1.00
9.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


^{13}C NMR
125 MHz, $CDCl_3$
8u
155.63
143.32
142.61
137.22
129.34
128.05
127.55
127.07
82.17
77.41
77.16
76.91
51.70
28.53
28.02
27.70
26.95
21.62
$CDCl_3$
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

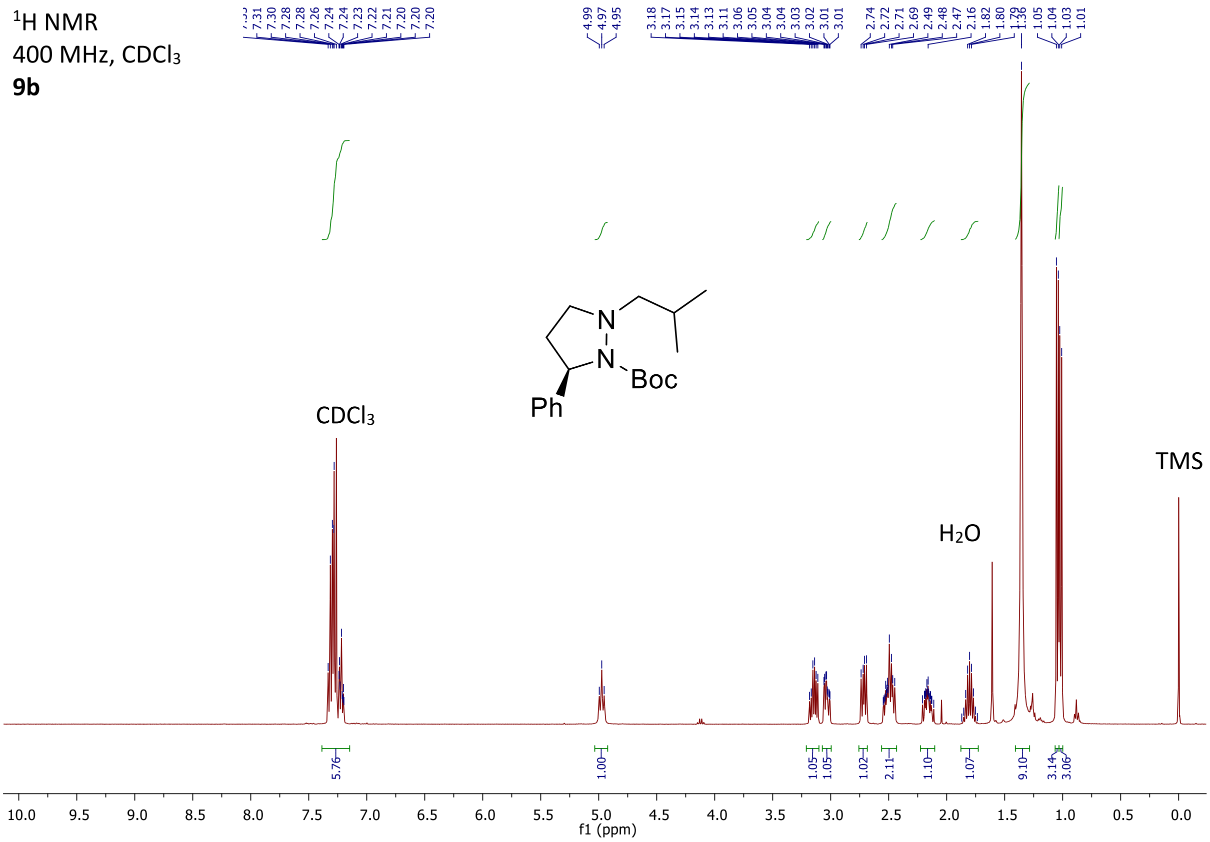


^{1}H NMR
500 MHz, $CDCl_3$ **8v**

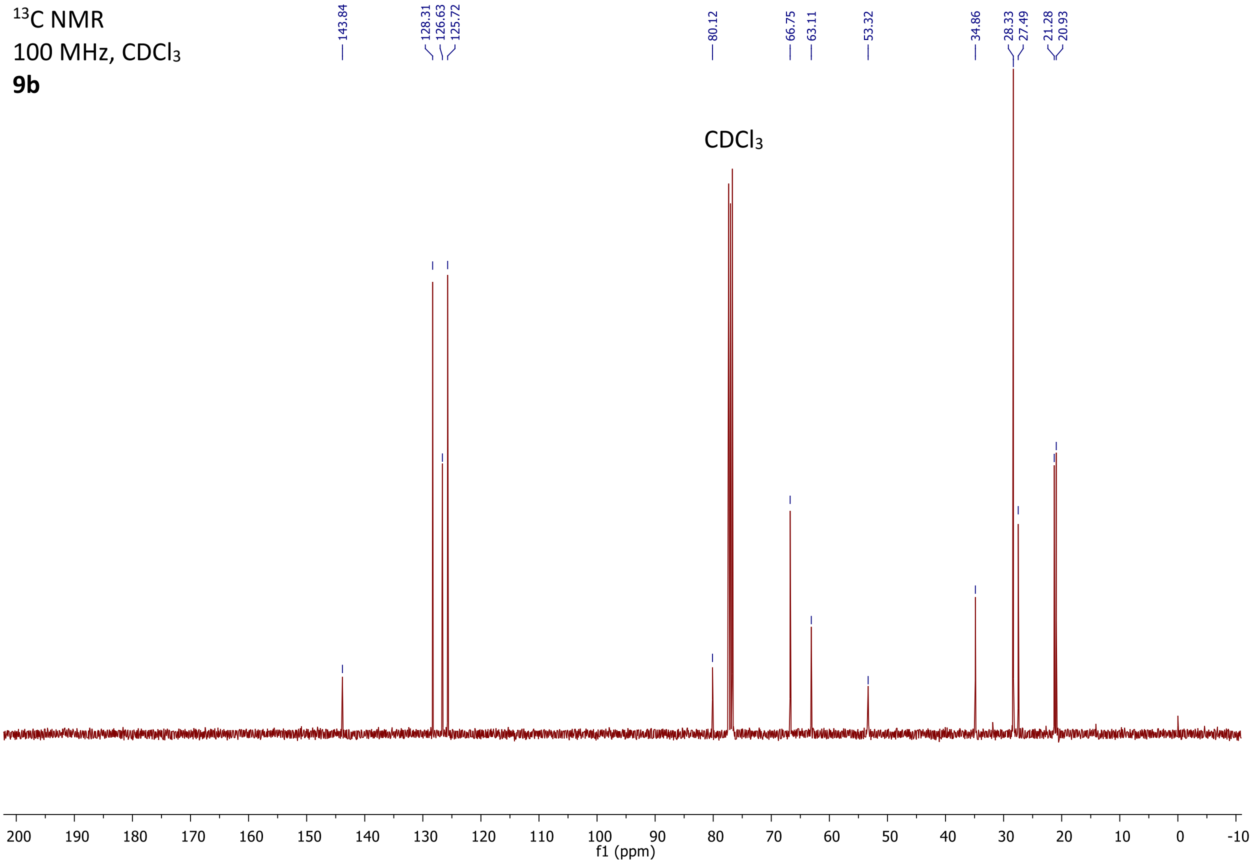


^{13}C NMR
125 MHz, $CDCl_3$
8v

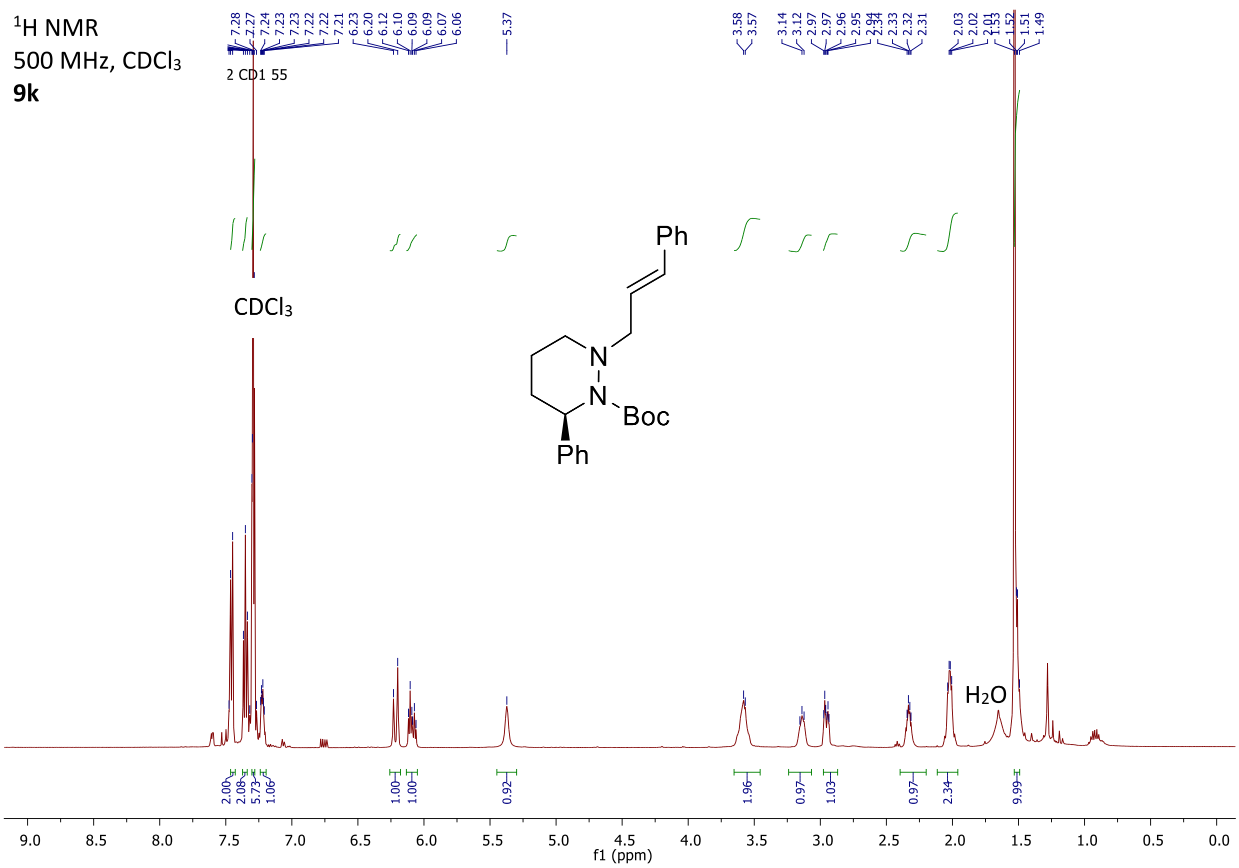
^{1}H NMR
400 MHz, $CDCl_3$
9b



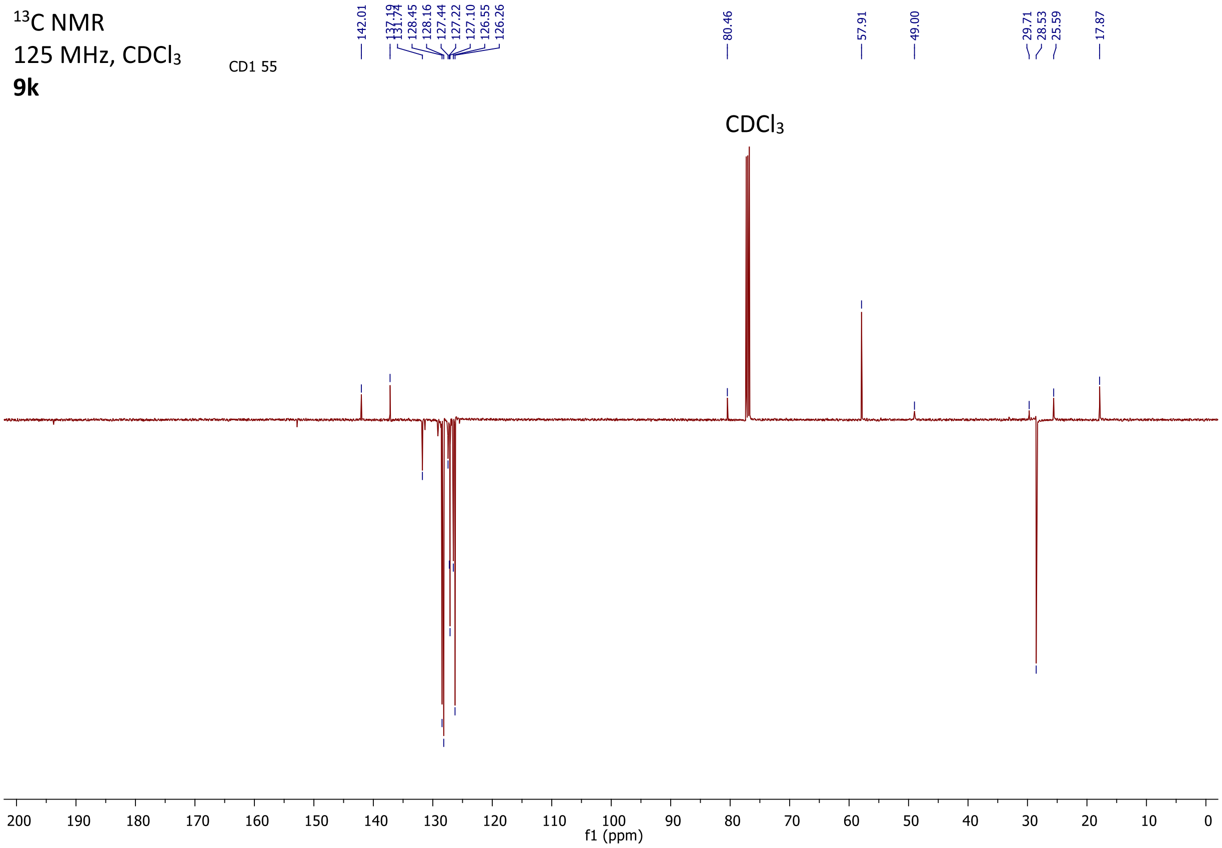
^{13}C NMR
100 MHz, $CDCl_3$
9b

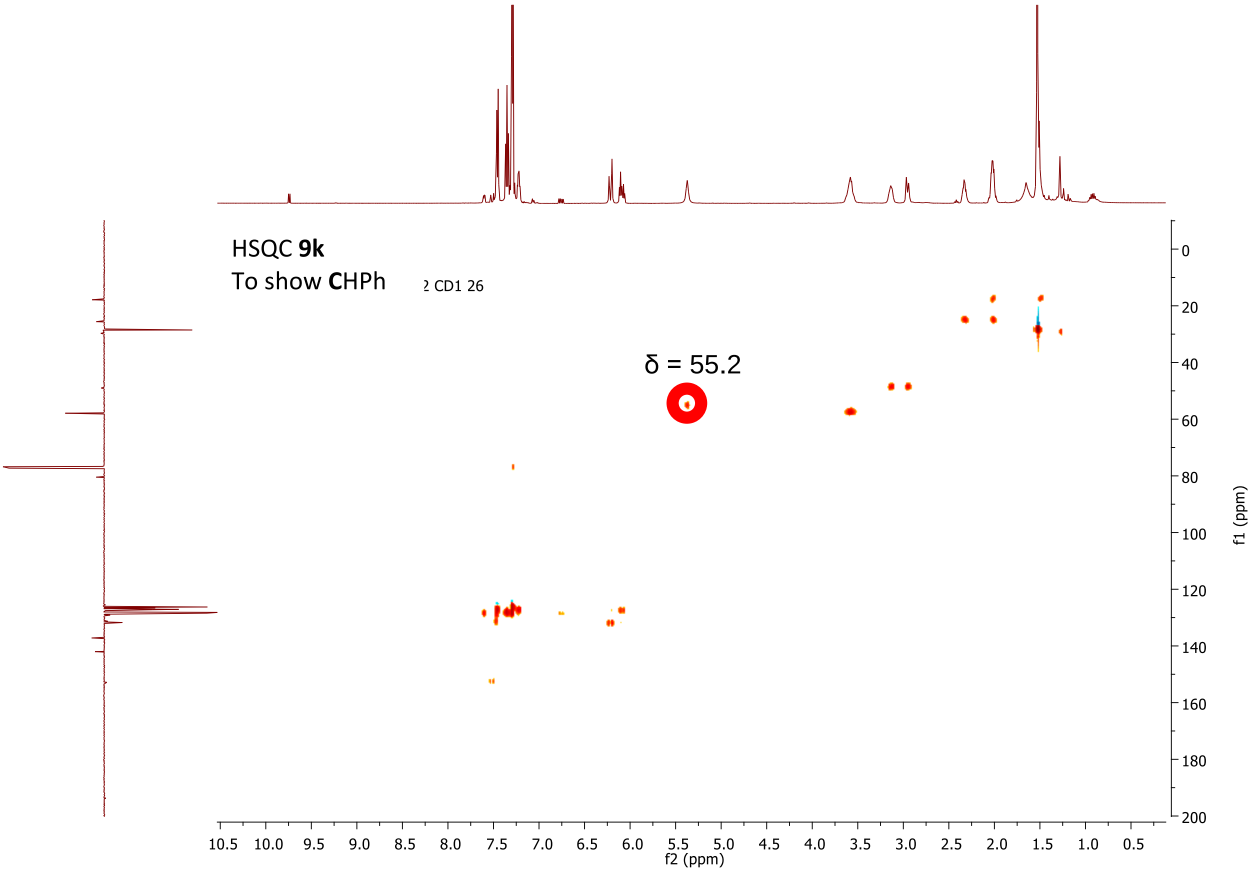


^{1}H NMR
500 MHz, CDCl$_3$
9k

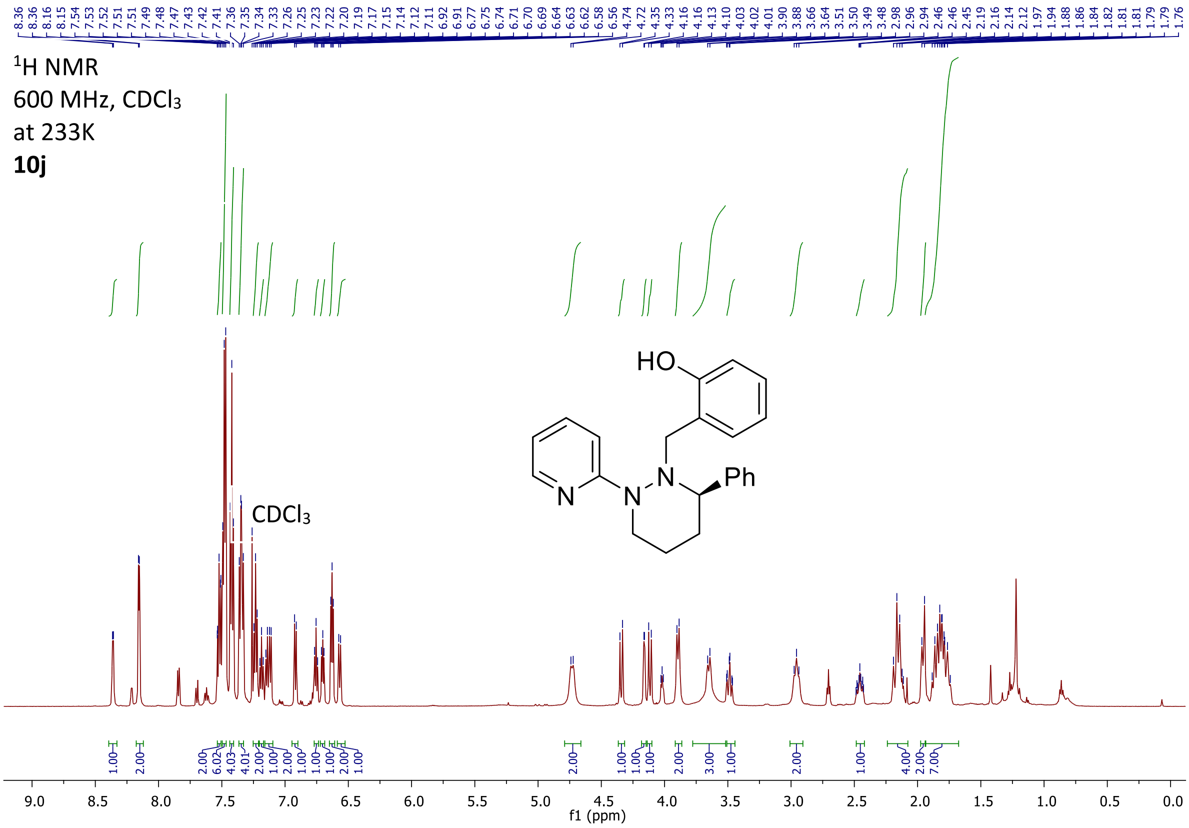


^{13}C NMR
125 MHz, CDCl$_3$
9k

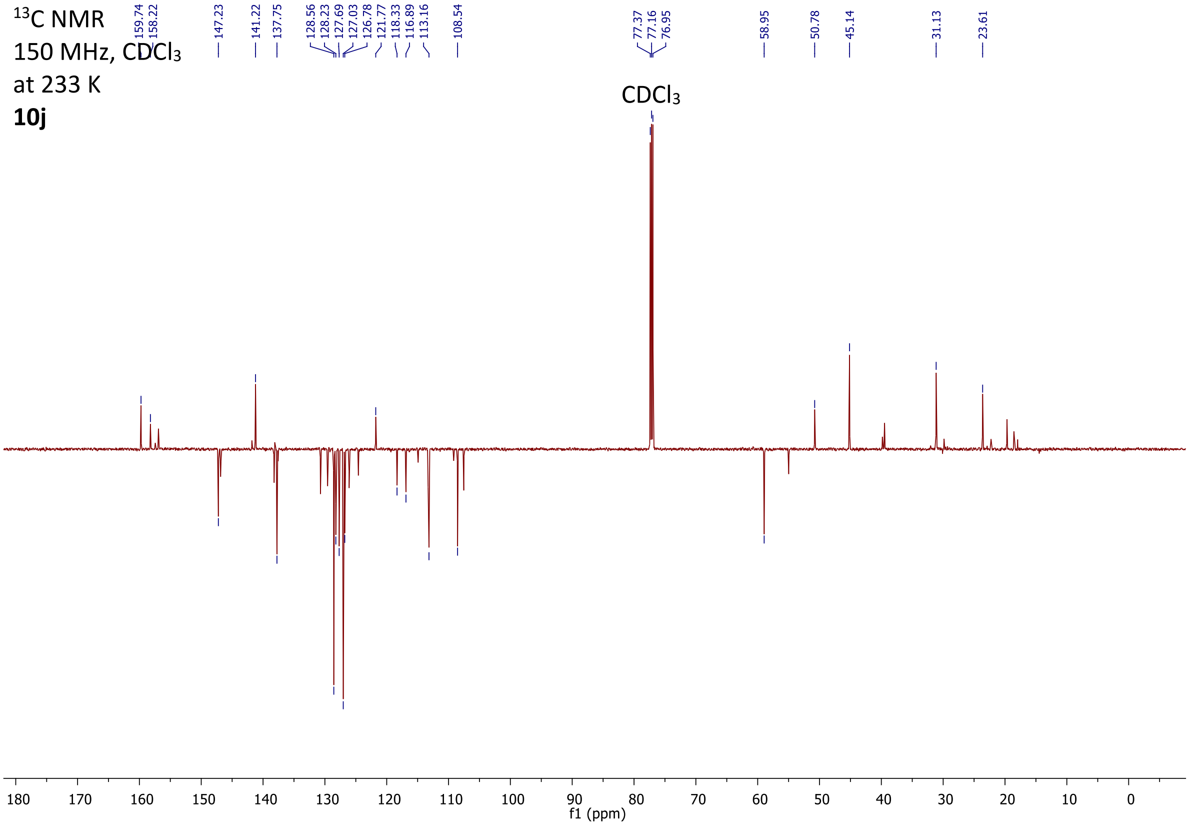



HSQC **9k**
To show **C**HPh
2 CD1 26
δ = 55.2
f1 (ppm)
0
20
40
60
80
100
120
140
160
180
200
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

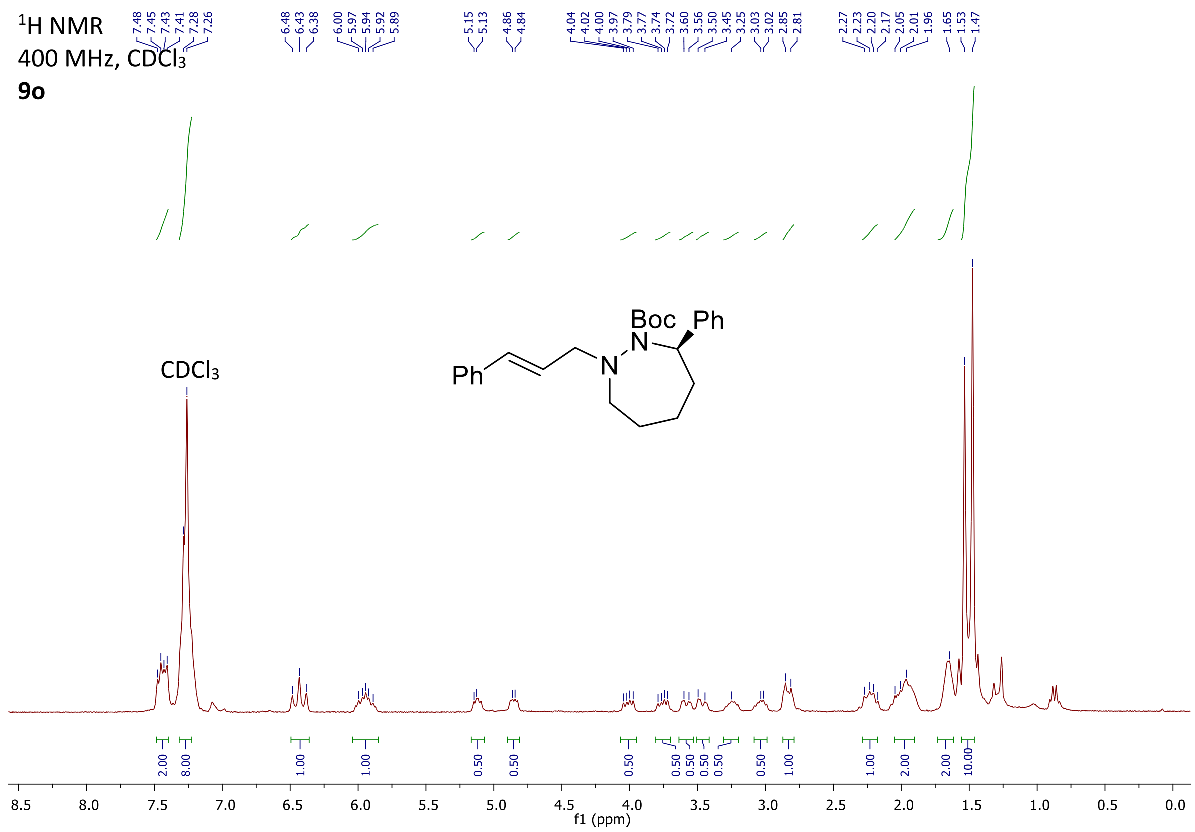
^{1}H NMR
600 MHz, $CDCl_3$
at 233K
10j



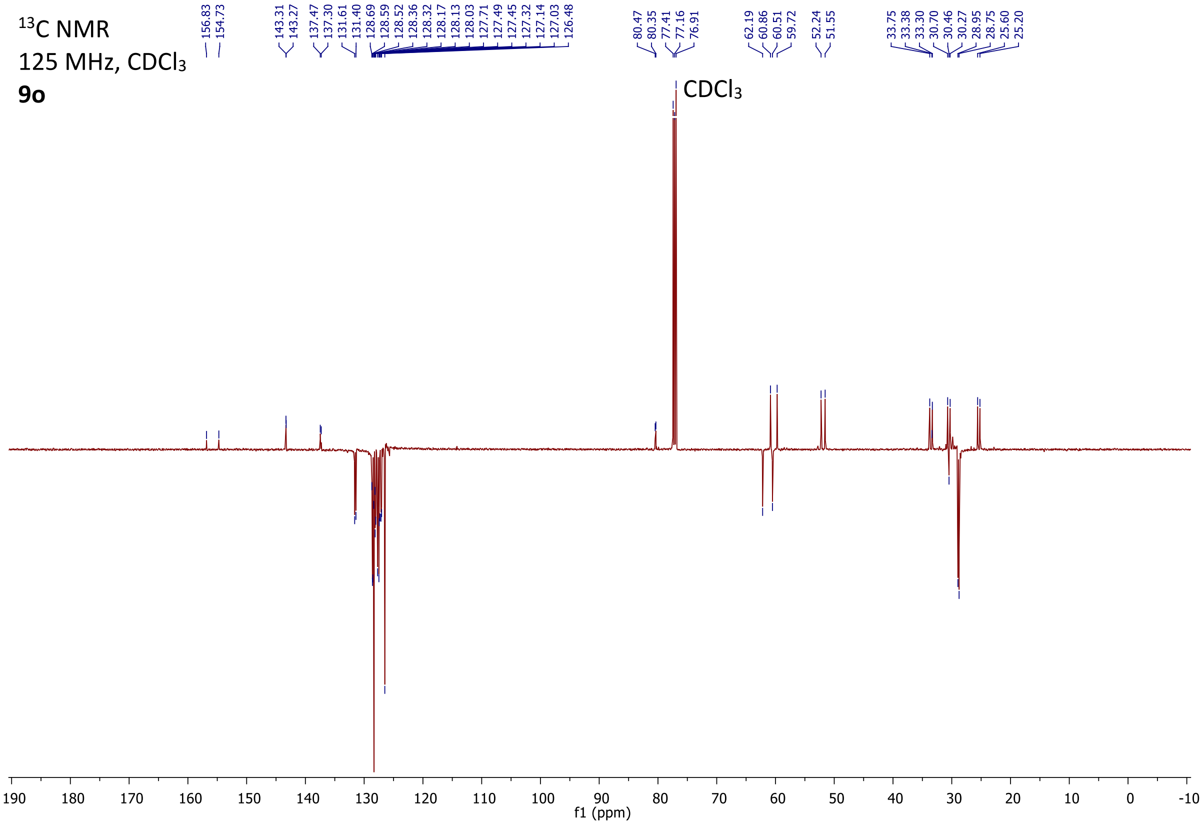
^{13}C NMR
150 MHz, $CDCl_3$
at 233 K
10j



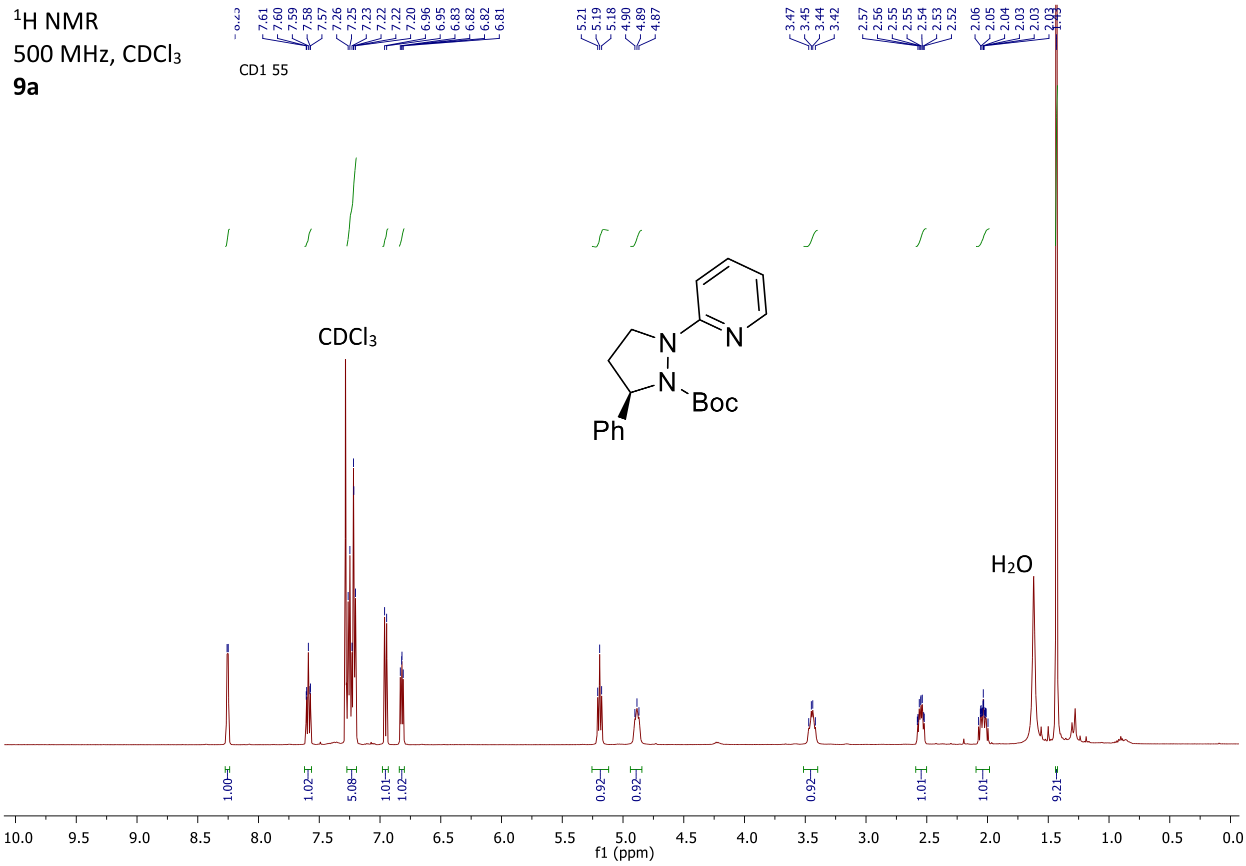
^{1}H NMR
400 MHz, $CDCl_3$
9o



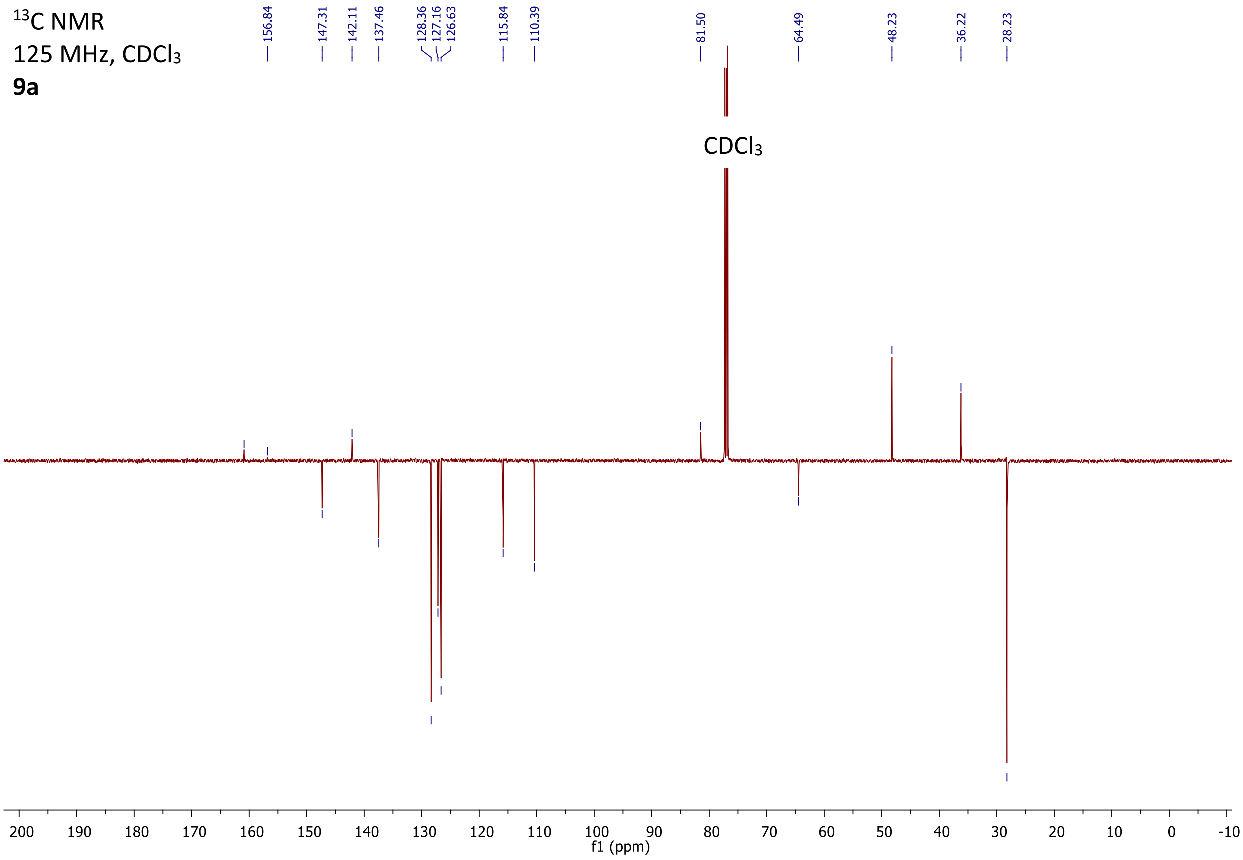
^{13}C NMR
125 MHz, $CDCl_3$
9o

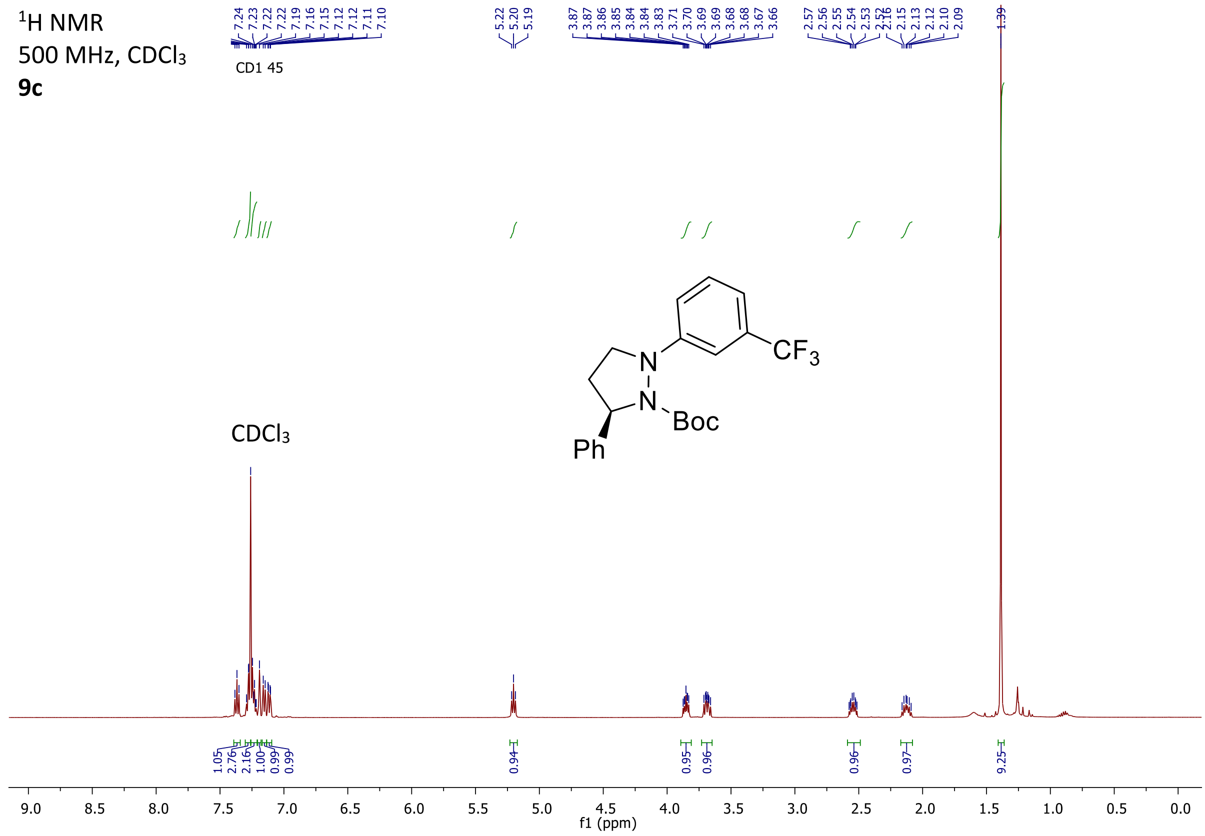


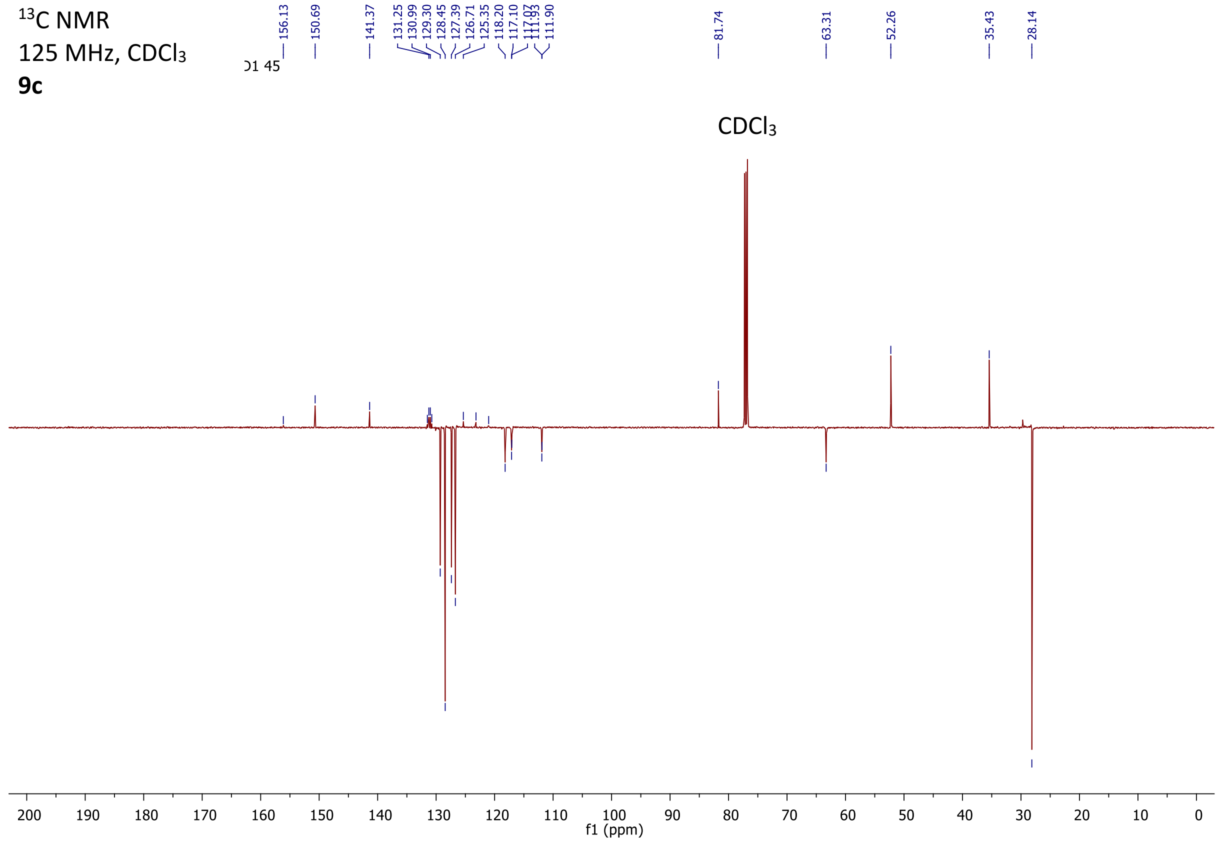
^1H NMR
500 MHz, $CDCl_3$
9a

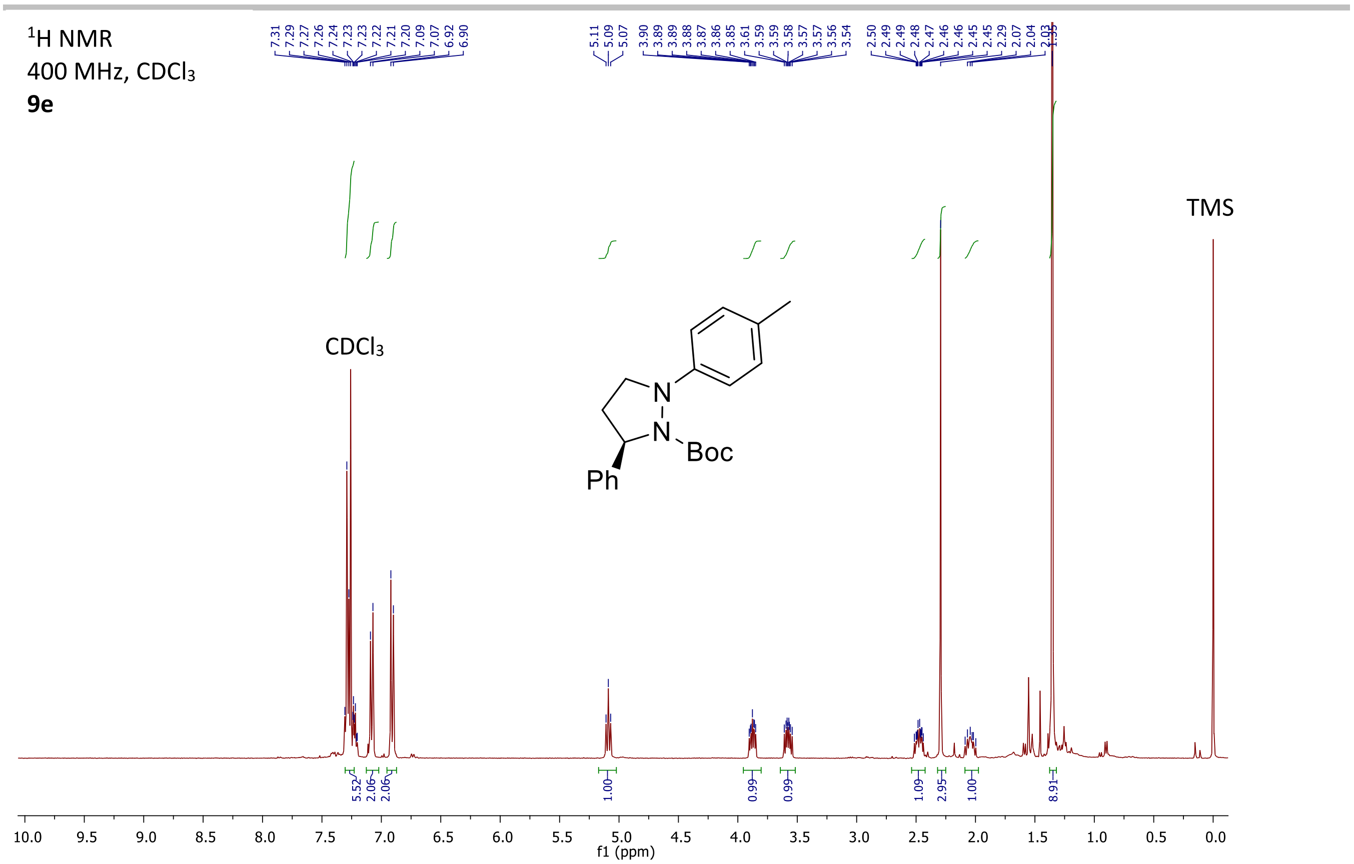


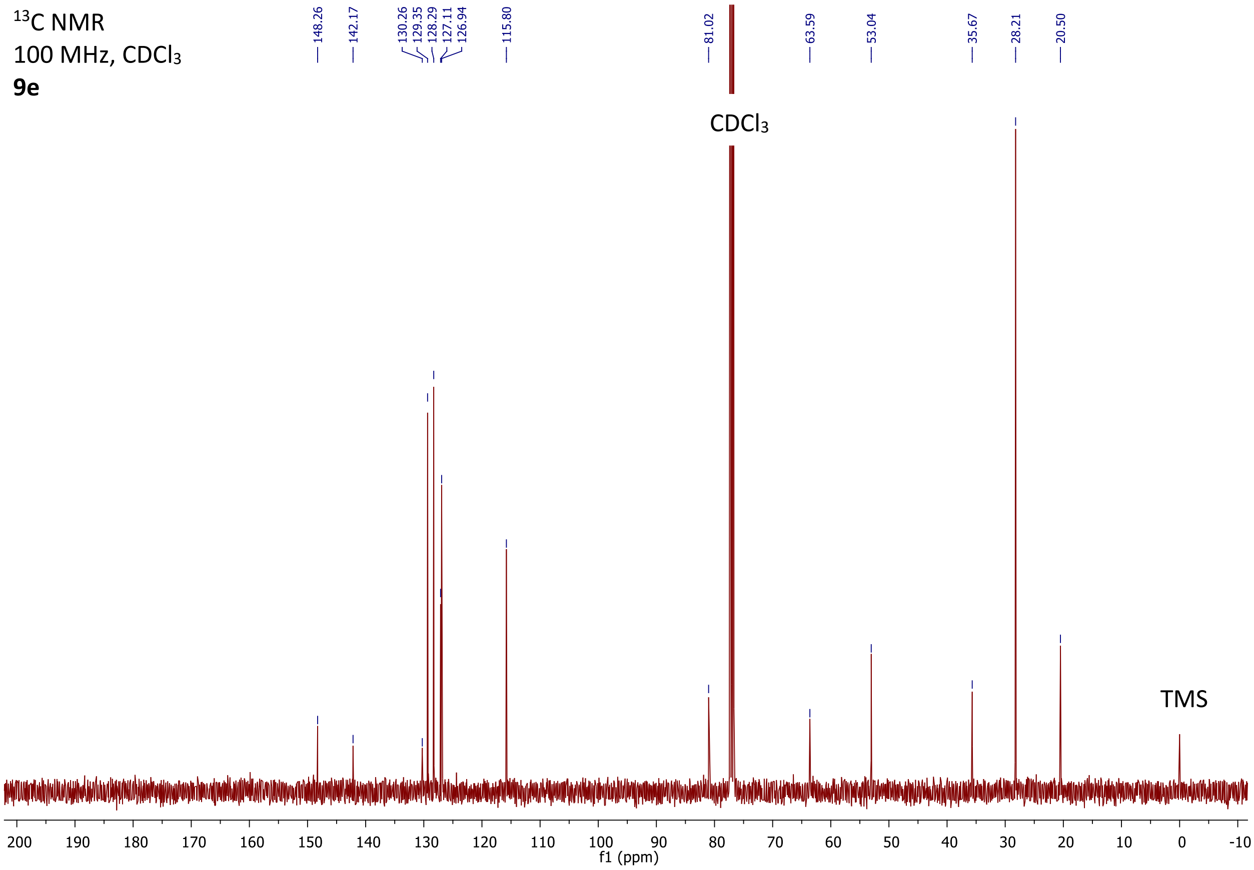
^{13}C NMR
125 MHz, $CDCl_3$
9a



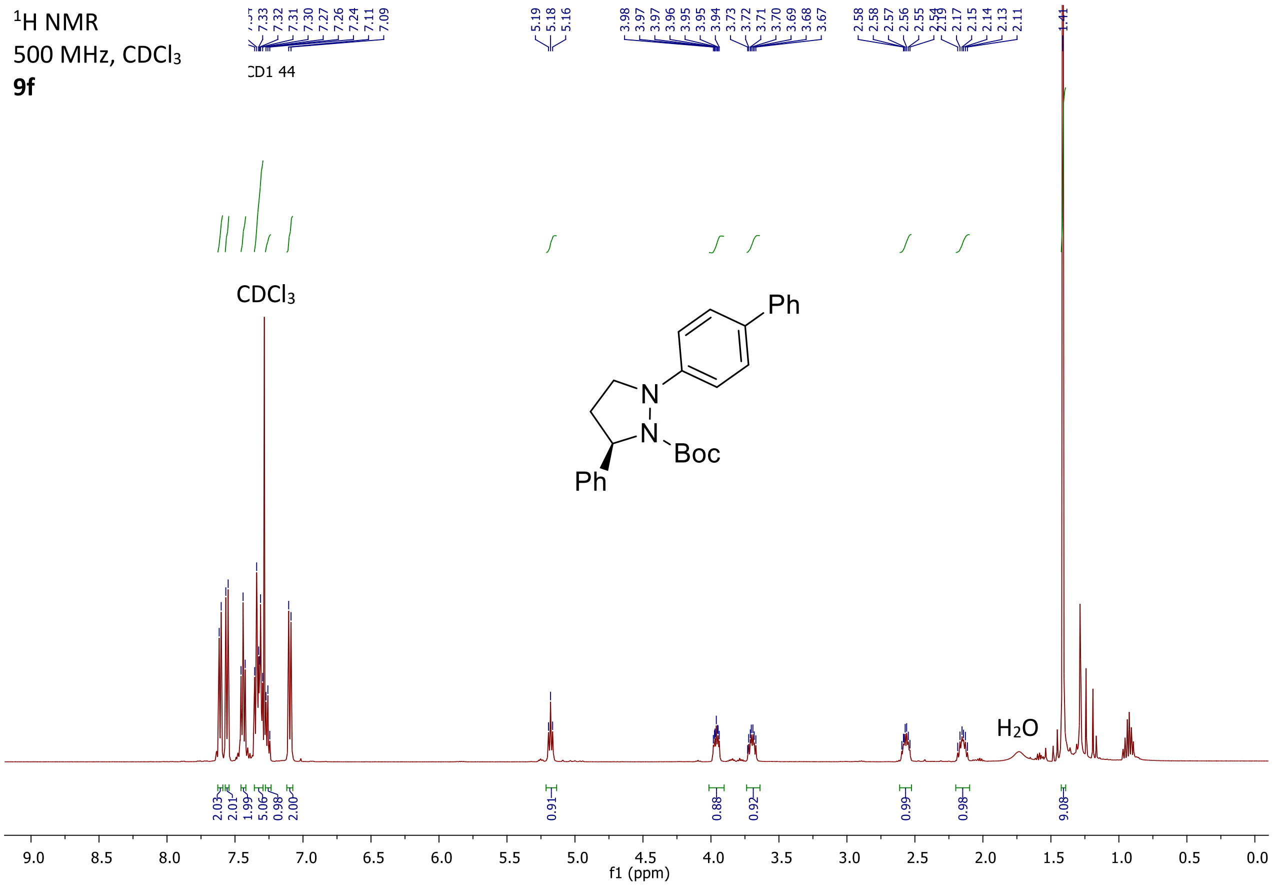

^{1}H NMR
500 MHz, CDCl$_3$
9c
CD1 45
7.24 7.23 7.22 7.22 7.19 7.16 7.15 7.12 7.12 7.11 7.10
5.22 5.20 5.19
3.87 3.87 3.86 3.85 3.84 3.84 3.83 3.71 3.70 3.69 3.69 3.68 3.67 3.66
2.57 2.56 2.55 2.54 2.53 2.52 2.16 2.15 2.13 2.12 2.10 2.09
1.39
CDCl3
N
N
Boc
Ph
CF3
1.05 2.76 2.16 1.00 0.99 0.99
0.94
0.95 0.96
0.96
0.97
9.25
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


^{13}C NMR
125 MHz, CDCl$_3$
9c
D1 45
156.13
150.69
141.37
131.25 130.99 129.30 128.45 127.39 126.71 125.35 118.20 117.10 117.07 111.93 111.90
81.74
63.31
52.26
35.43
28.14
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

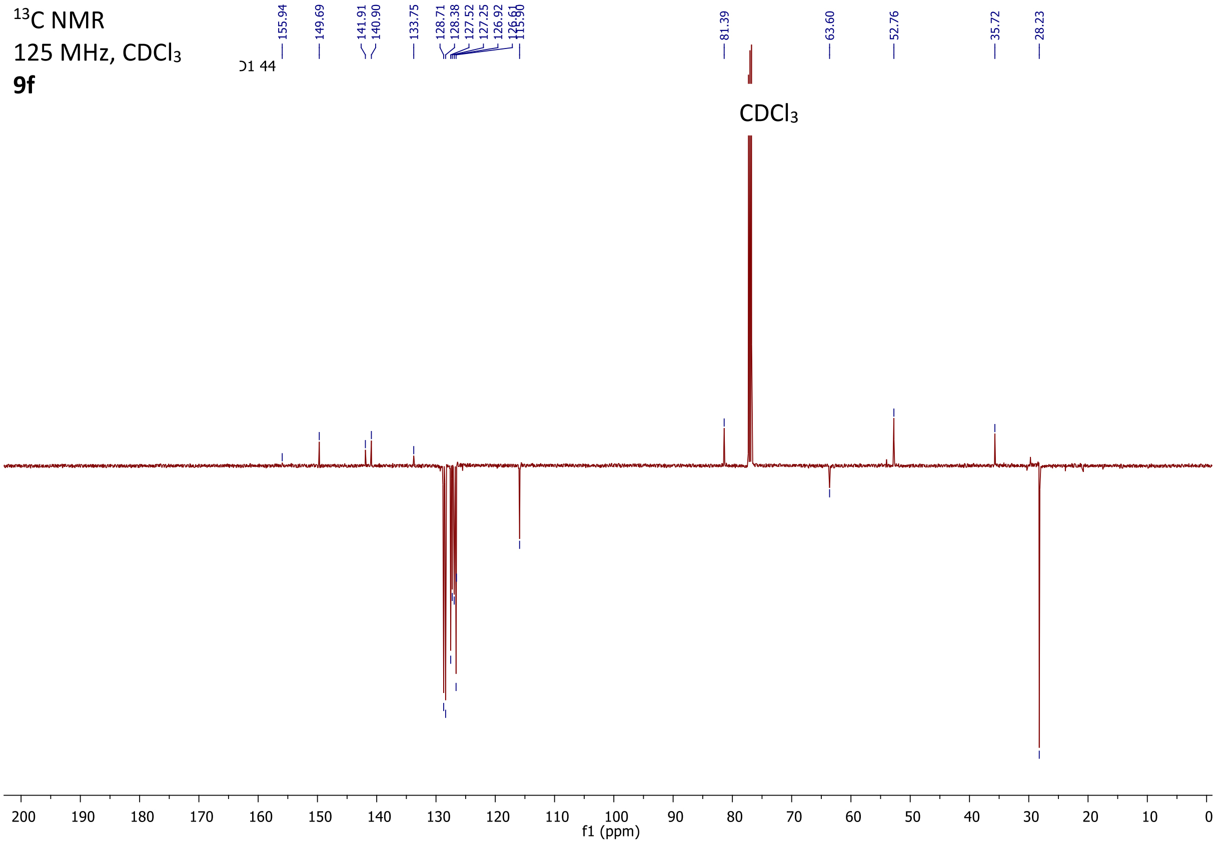

¹H NMR
400 MHz, CDCl₃
9e
7.31
7.29
7.27
7.26
7.24
7.23
7.23
7.22
7.21
7.20
7.09
7.07
6.92
6.90
5.11
5.09
5.07
3.90
3.89
3.89
3.88
3.87
3.86
3.85
3.61
3.59
3.59
3.58
3.57
3.57
3.56
3.54
2.50
2.49
2.49
2.48
2.47
2.46
2.46
2.45
2.45
2.29
2.07
2.04
2.03
1.35
CDCl₃
TMS
N
N
Boc
Ph
5.52
2.06
2.06
1.00
0.99
0.99
1.09
2.95
1.00
8.91
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


¹³C NMR
100 MHz, CDCl₃
9e
148.26
142.17
130.26
129.35
128.29
127.11
126.94
115.80
81.02
63.59
53.04
35.67
28.21
20.50
CDCl₃
TMS
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

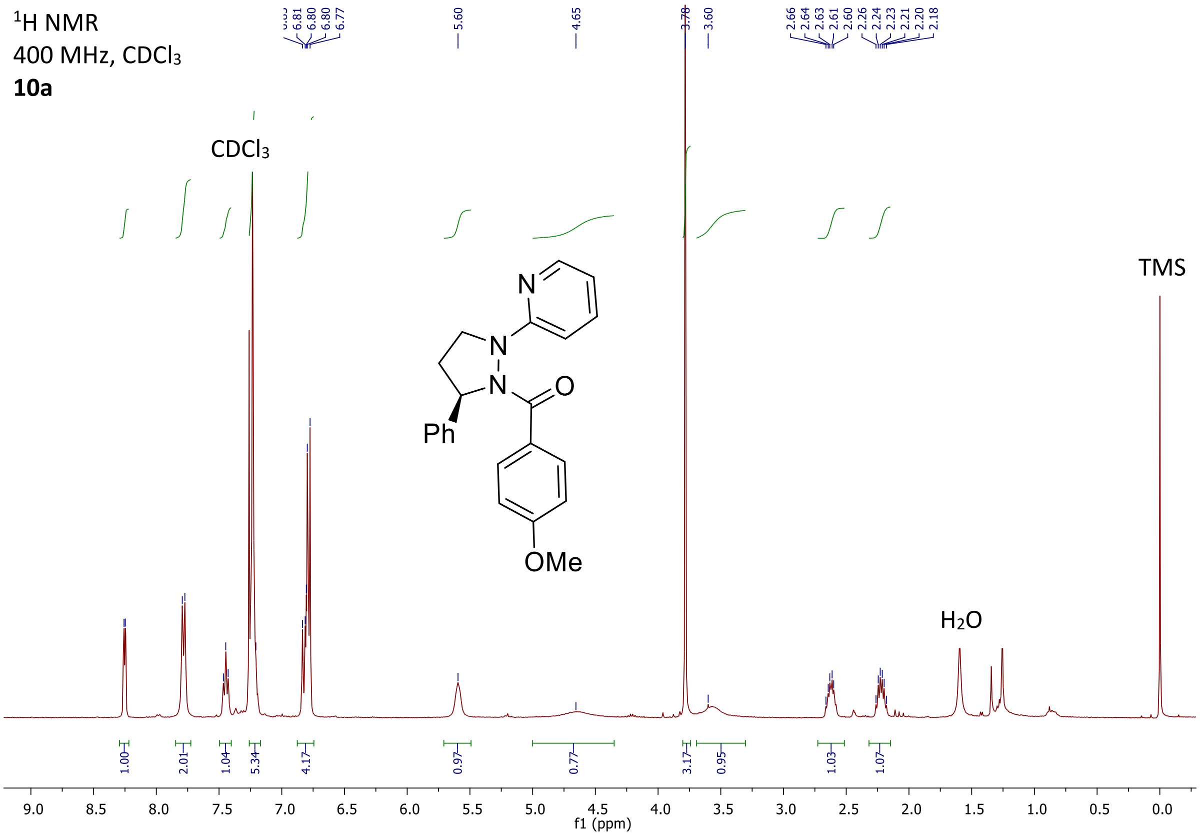
^{1}H NMR
500 MHz, $CDCl_3$
9f



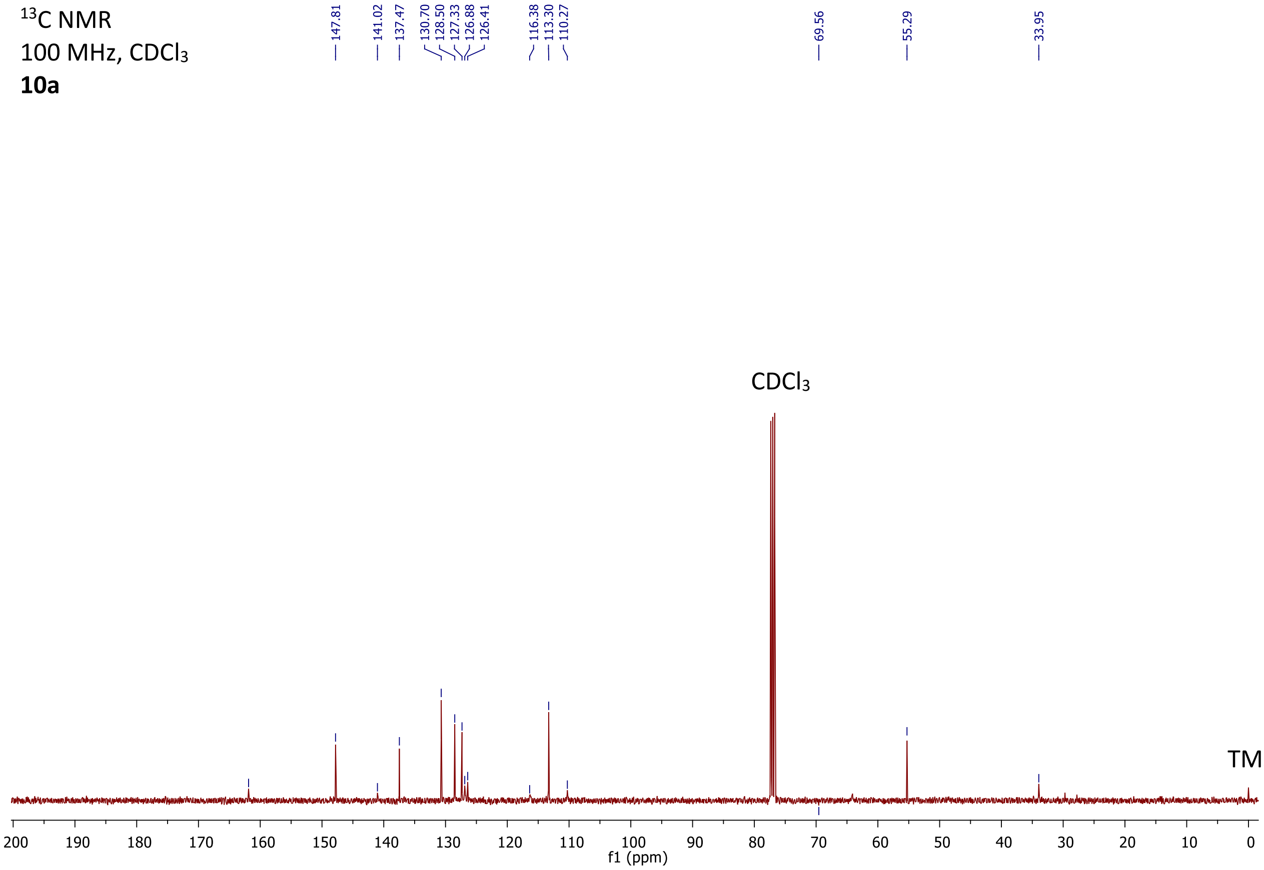
^{13}C NMR
125 MHz, $CDCl_3$
9f



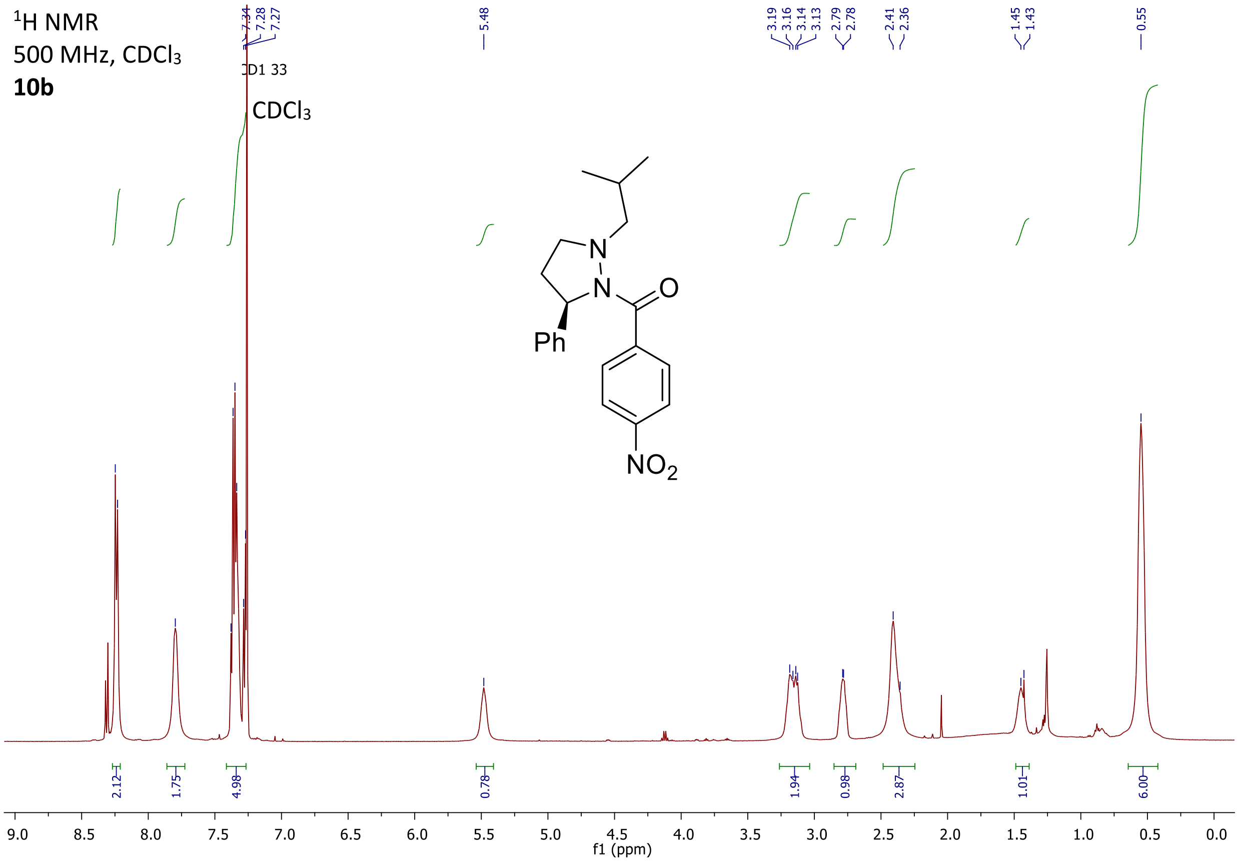
^{1}H NMR
400 MHz, $CDCl_3$
10a



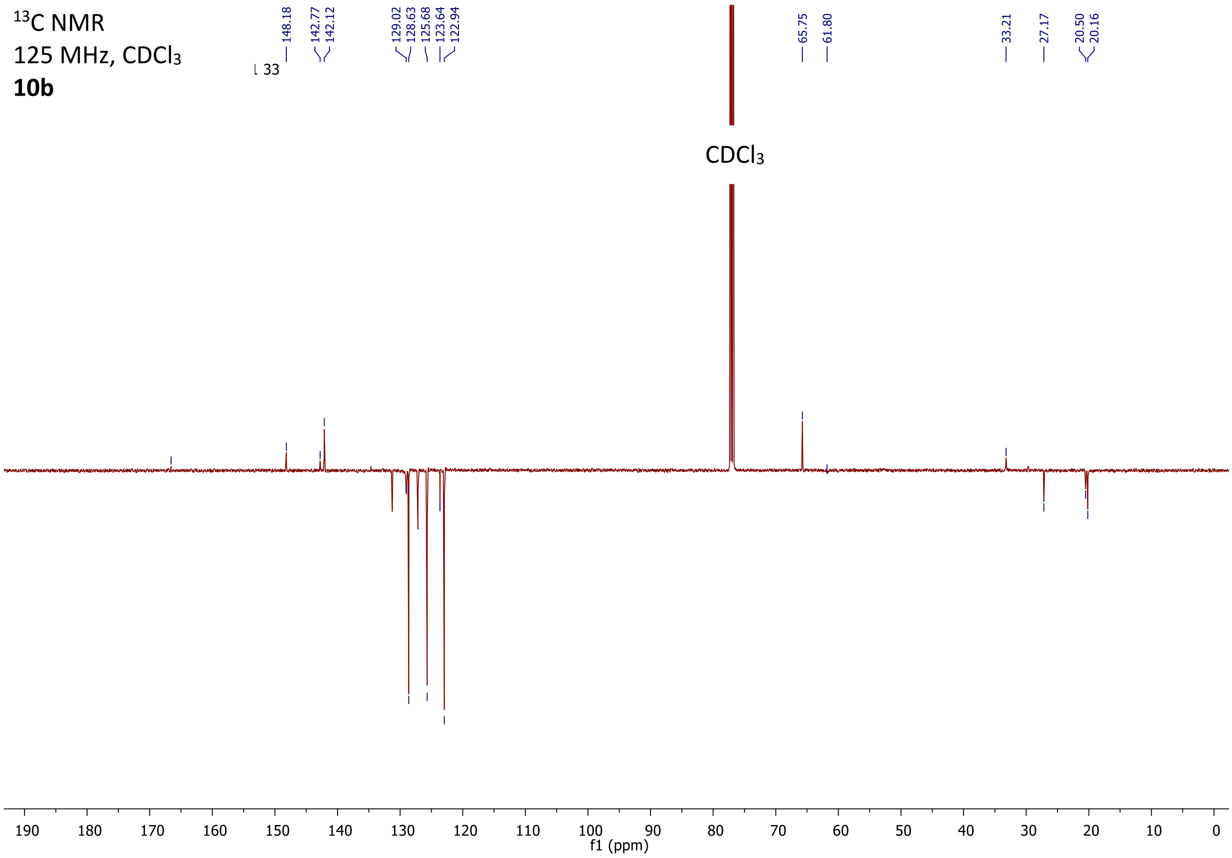
^{13}C NMR
100 MHz, $CDCl_3$
10a



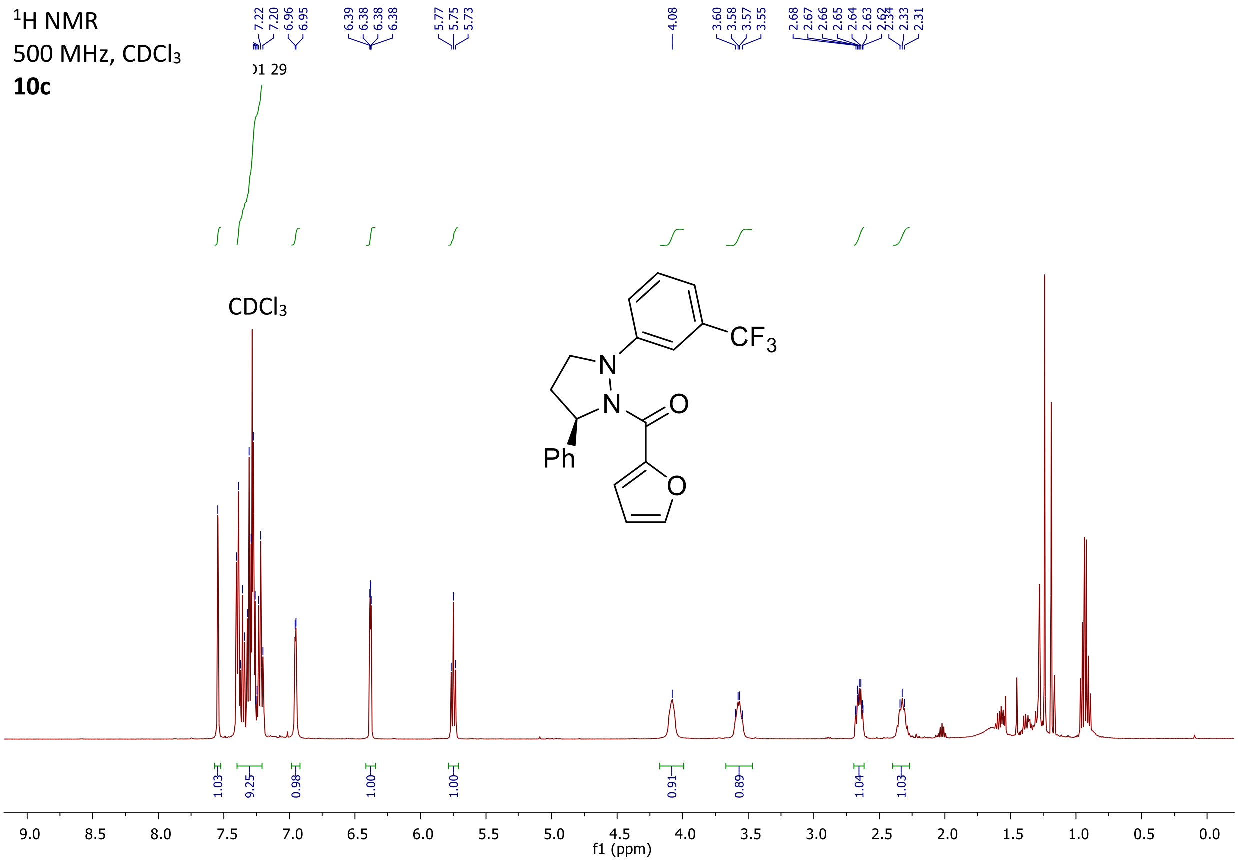
^{1}H NMR
500 MHz, $CDCl_3$
10b



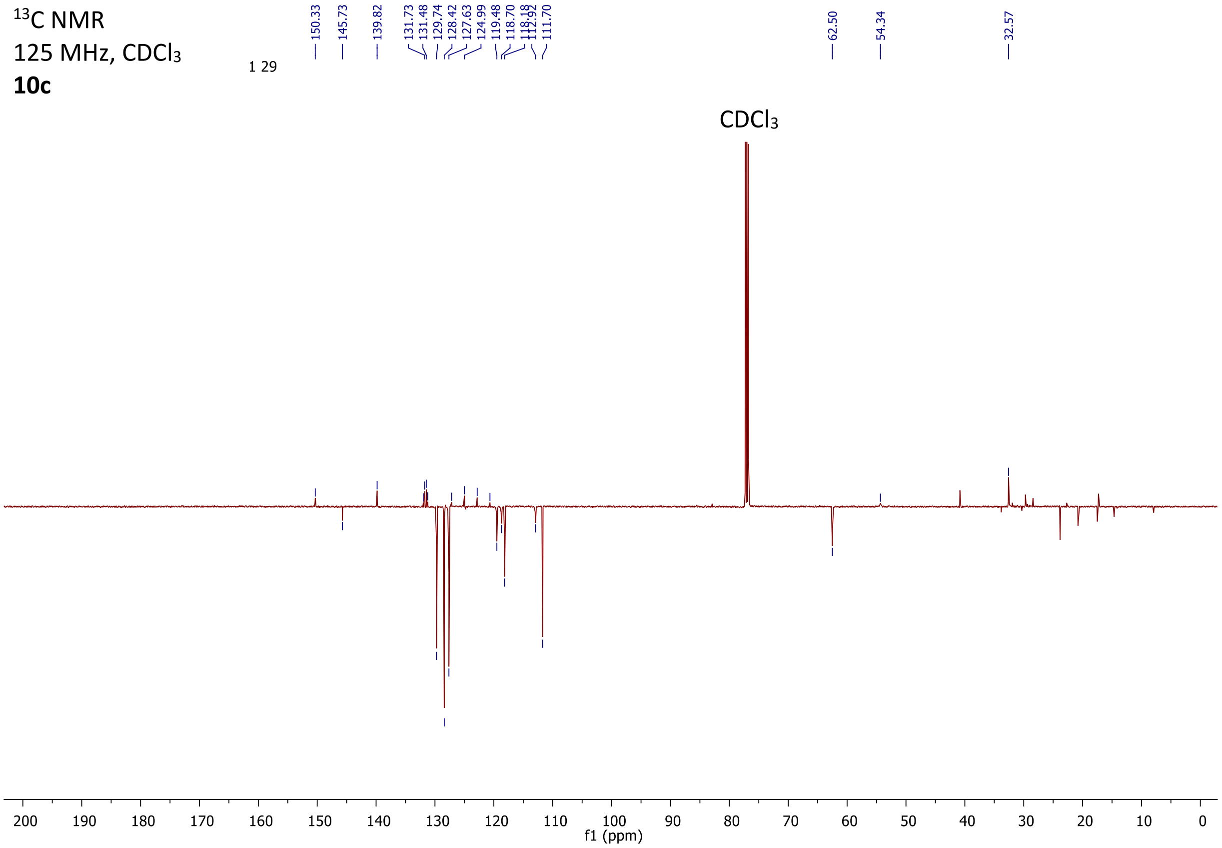
^{13}C NMR
125 MHz, $CDCl_3$
10b

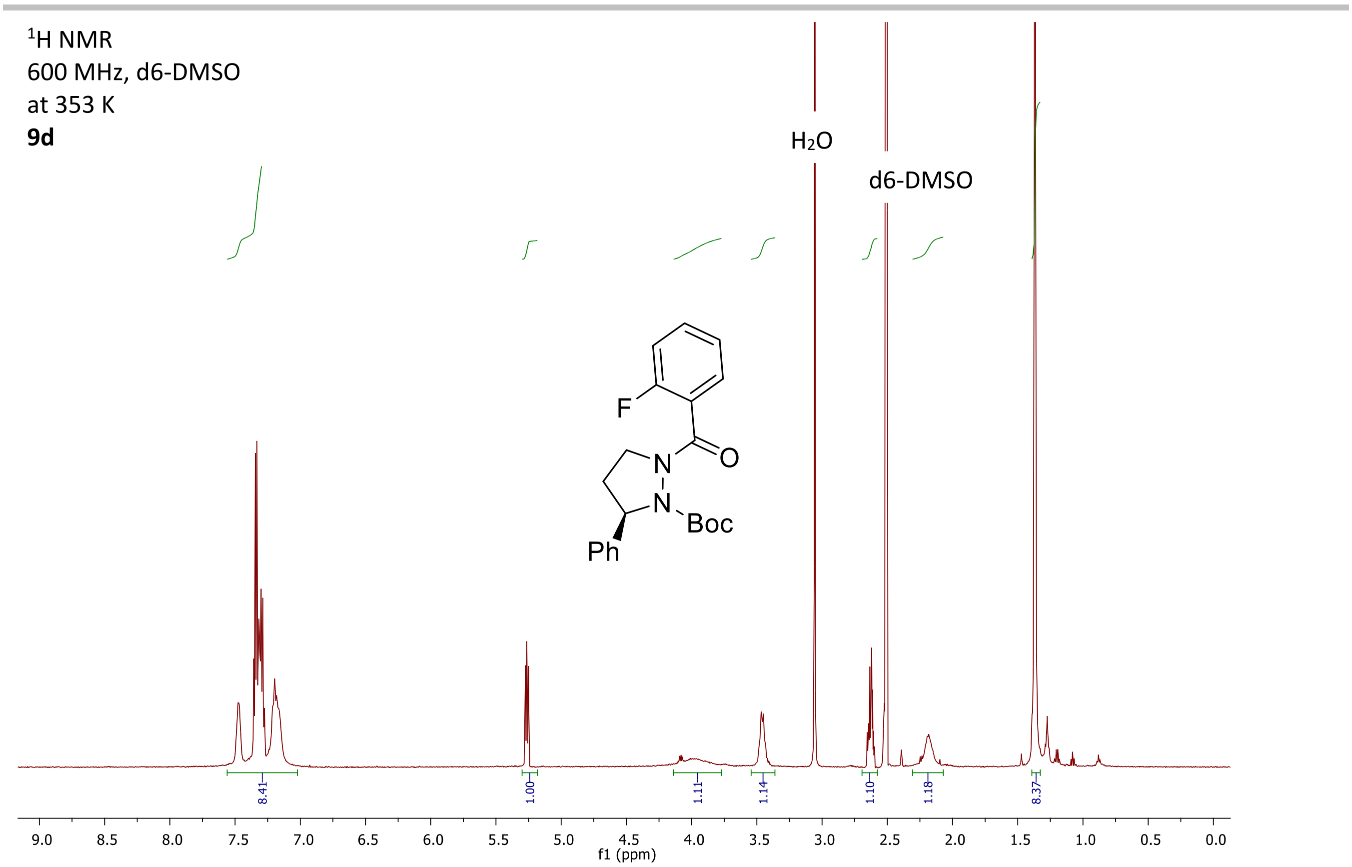


^{1}H NMR
500 MHz, $CDCl_3$
10c

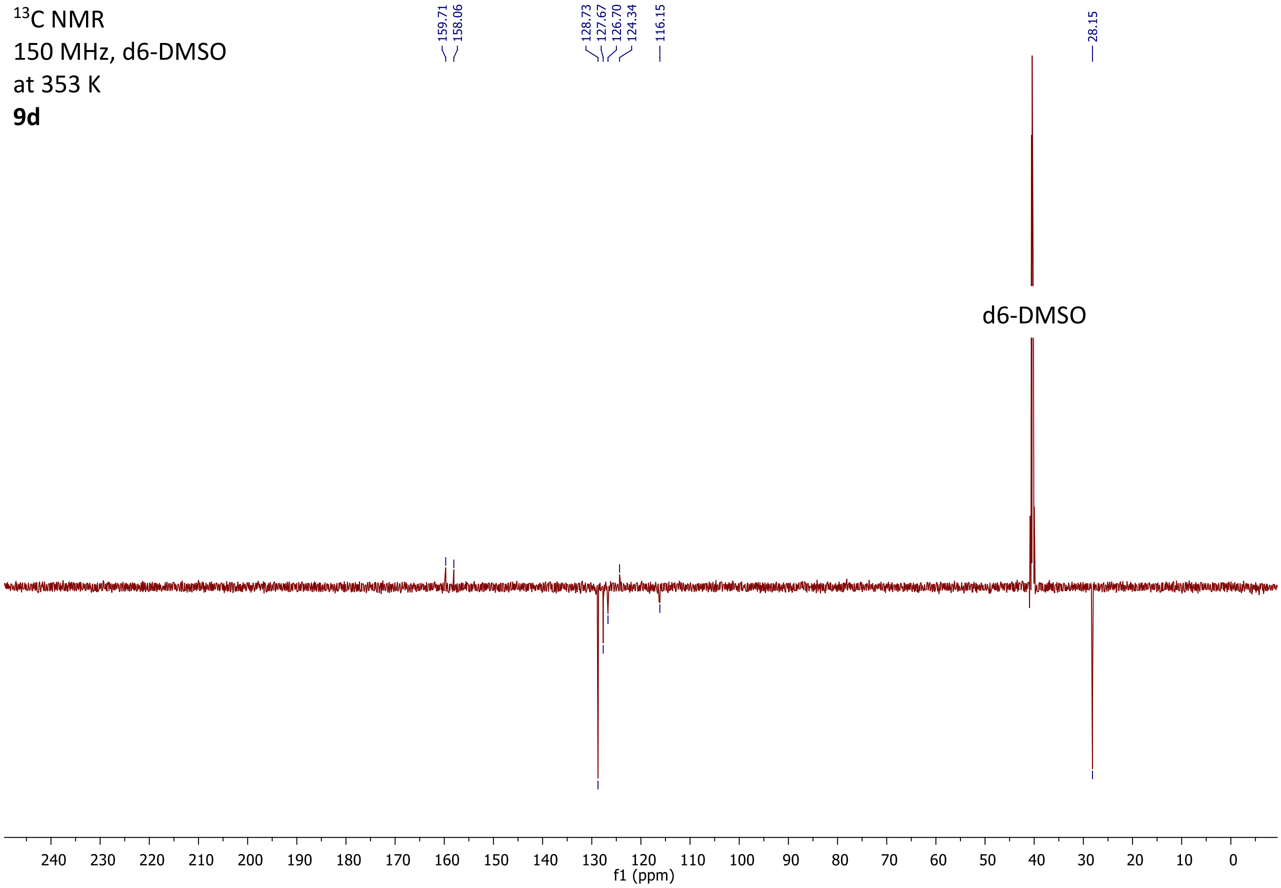


^{13}C NMR
125 MHz, $CDCl_3$
10c

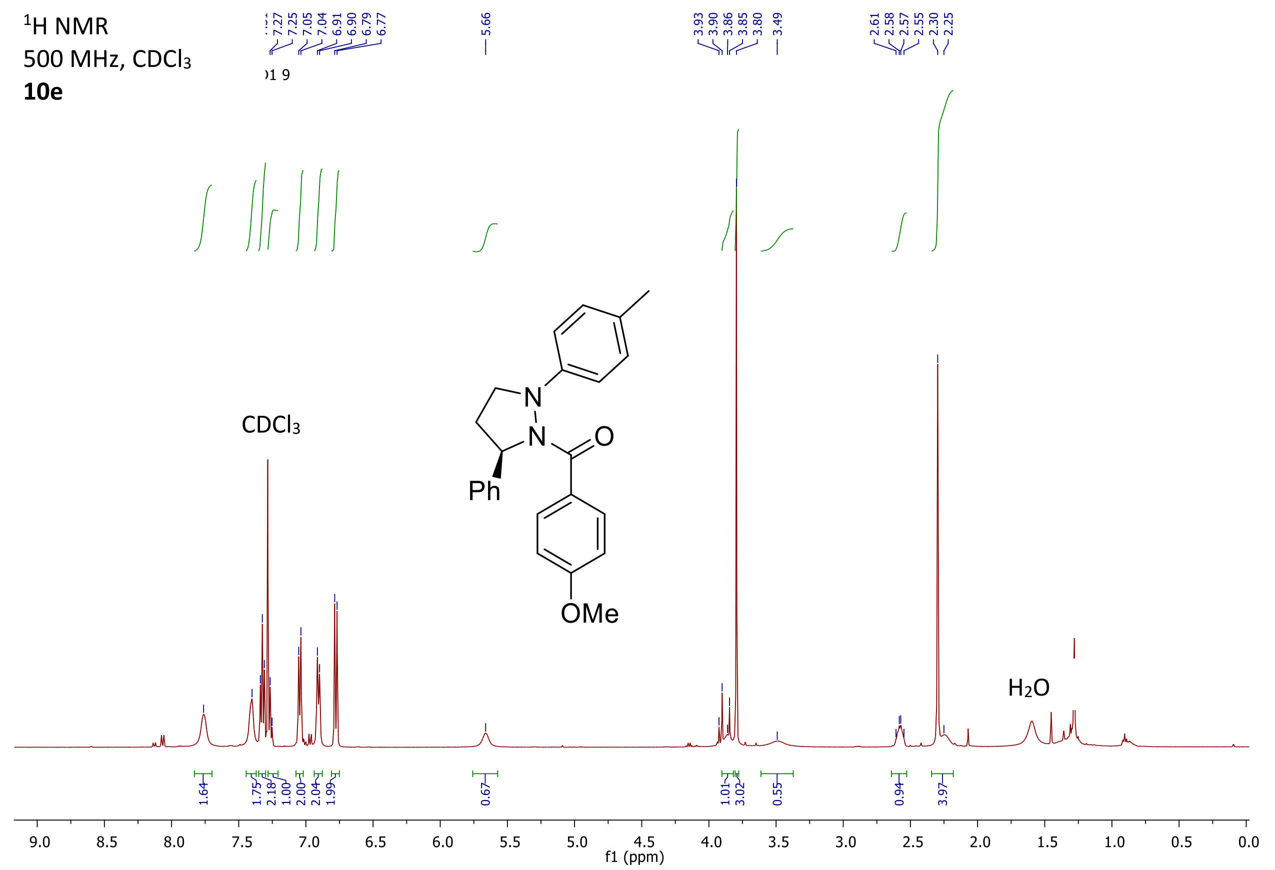




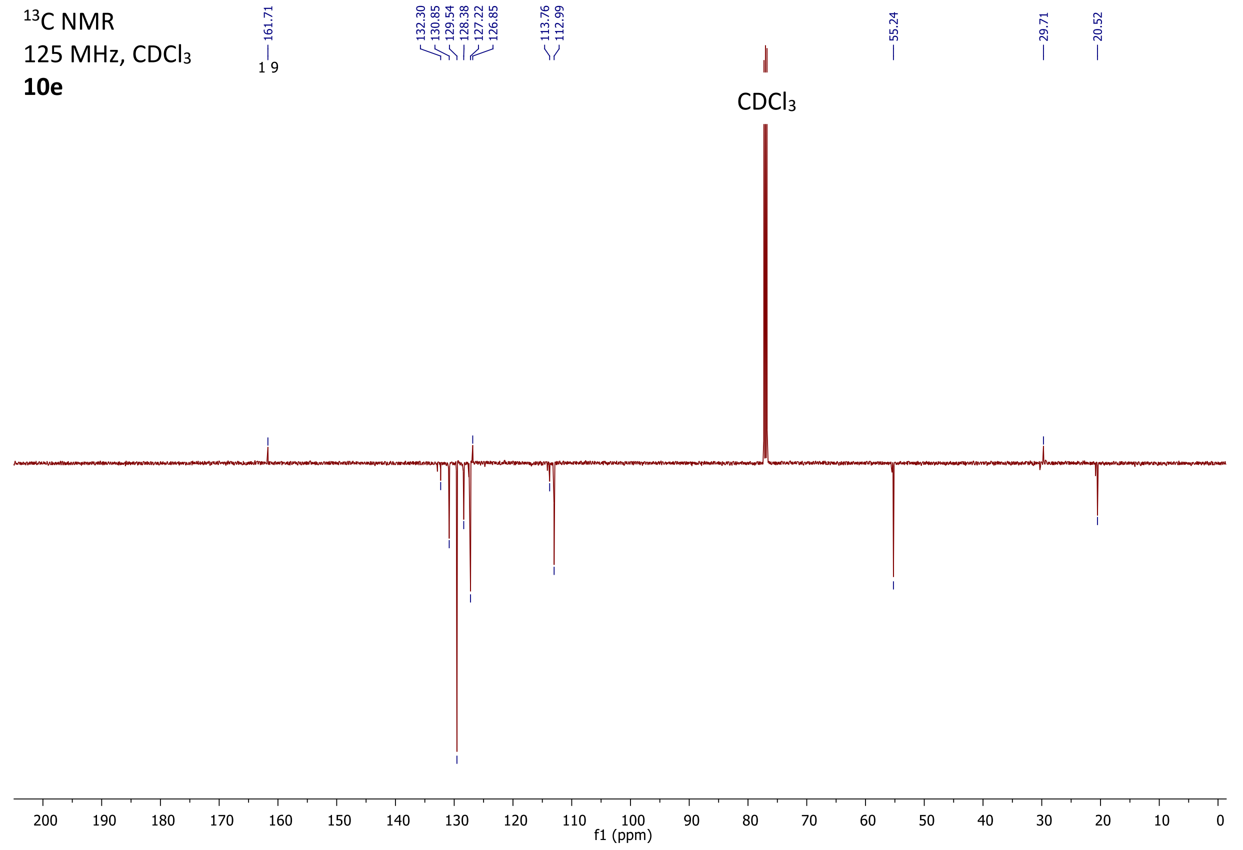
^{1}H NMR
600 MHz, d6-DMSO
at 353 K
9d
H$_2$O
d6-DMSO
F
N
N
O
Boc
Ph
8.41
1.00
1.11
1.14
1.10
1.18
8.37
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



^{13}C NMR
150 MHz, d6-DMSO
at 353 K
9d
159.71
158.06
128.73
127.67
126.70
124.34
116.15
28.15
d6-DMSO
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

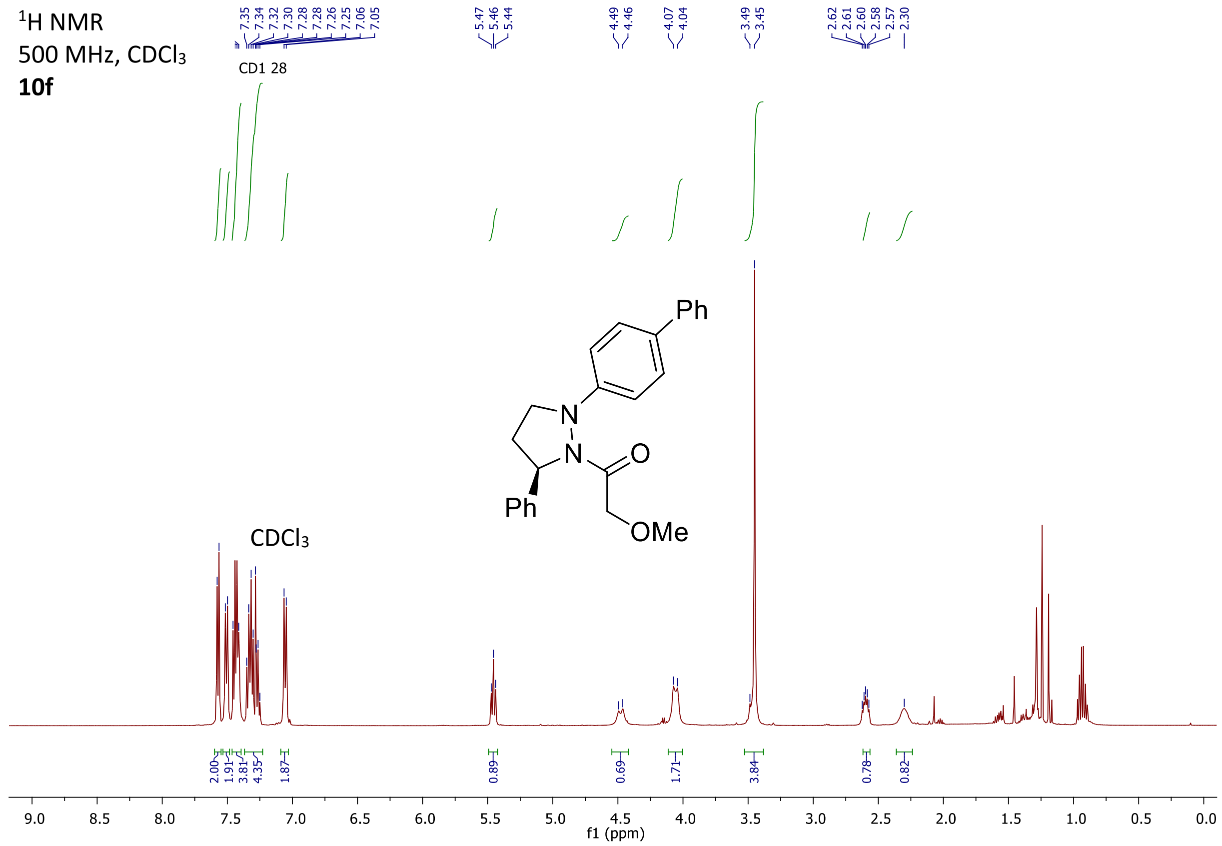


^1H NMR
500 MHz, $CDCl_3$
10e
7.27
7.25
7.05
7.04
6.91
6.90
6.79
6.77
5.66
3.93
3.90
3.86
3.85
3.80
3.49
2.61
2.58
2.57
2.55
2.30
2.25
CDCl3
N
N
O
Ph
OMe
H2O
1.64
1.75
2.18
1.00
2.00
2.04
1.99
0.67
1.01
3.02
0.55
0.94
3.97
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

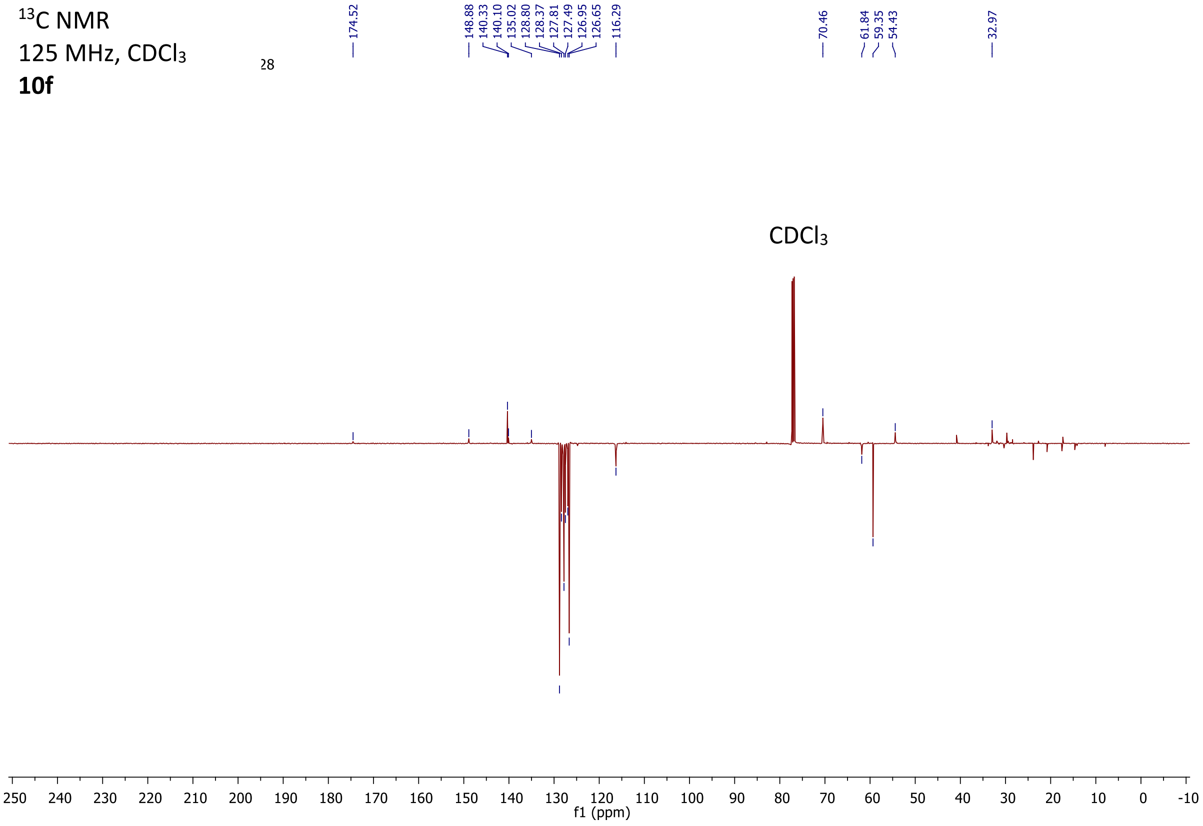


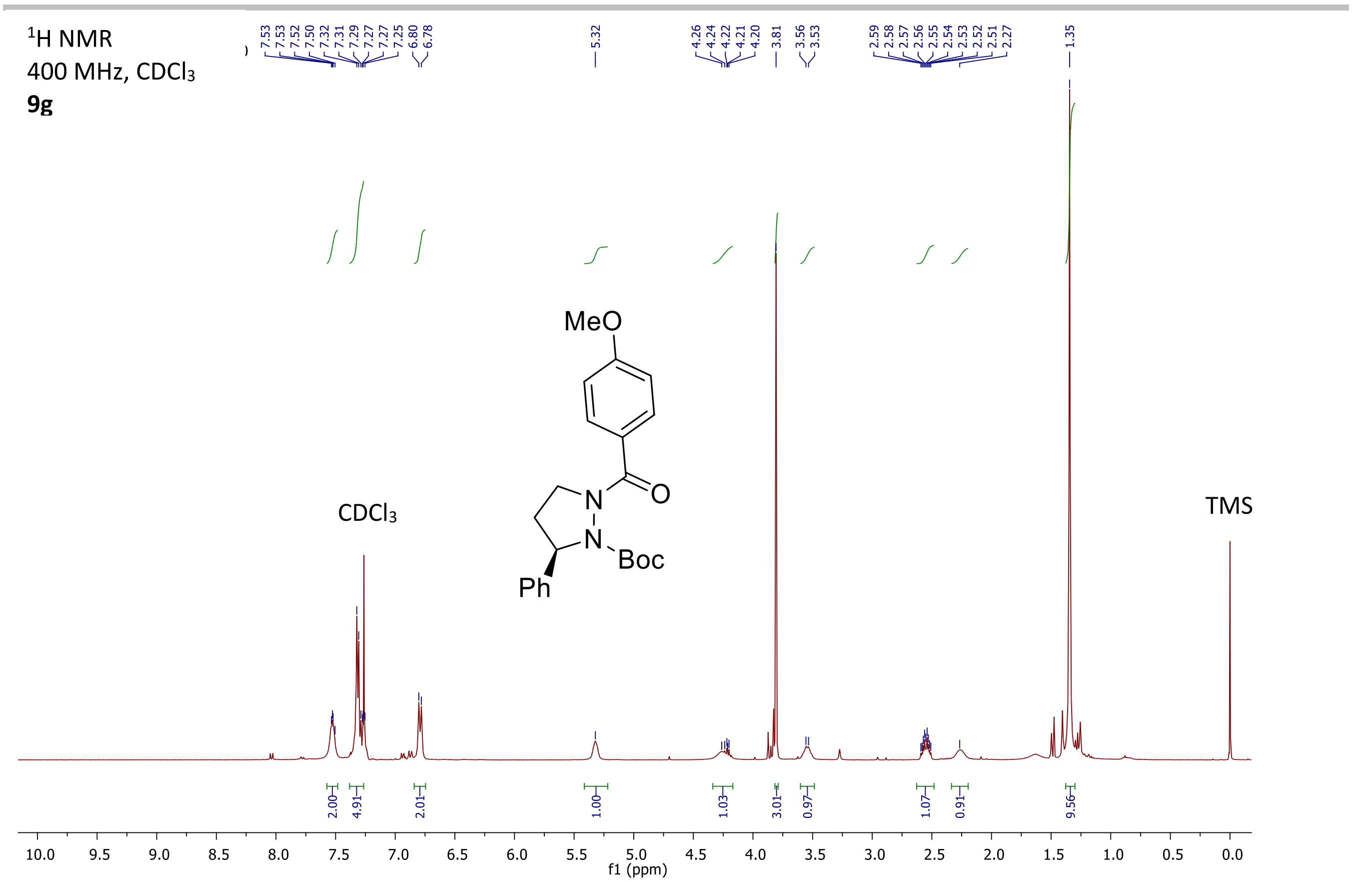
^{13}C NMR
125 MHz, $CDCl_3$
10e
161.71
132.30
130.85
129.54
128.38
127.22
126.85
113.76
112.99
55.24
29.71
20.52
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

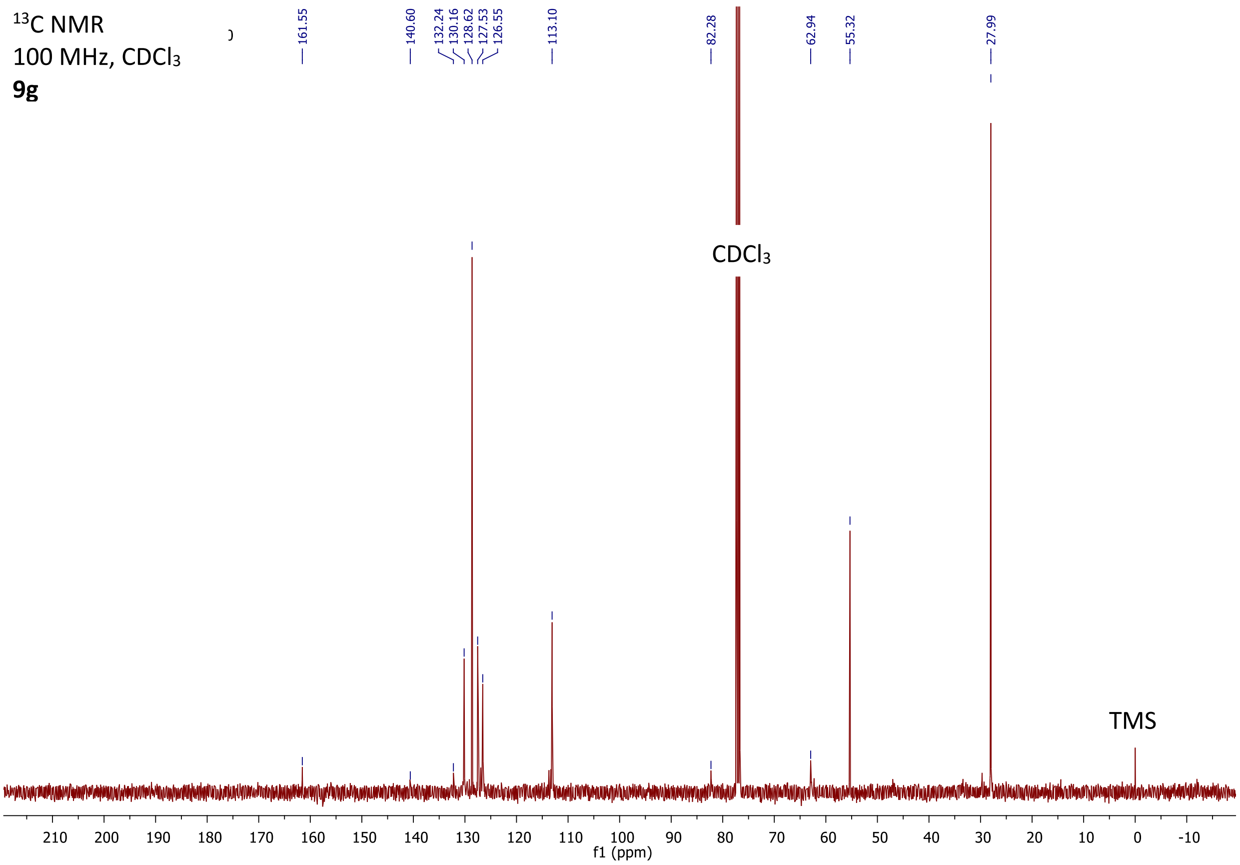
^{1}H NMR
500 MHz, $CDCl_3$
10f



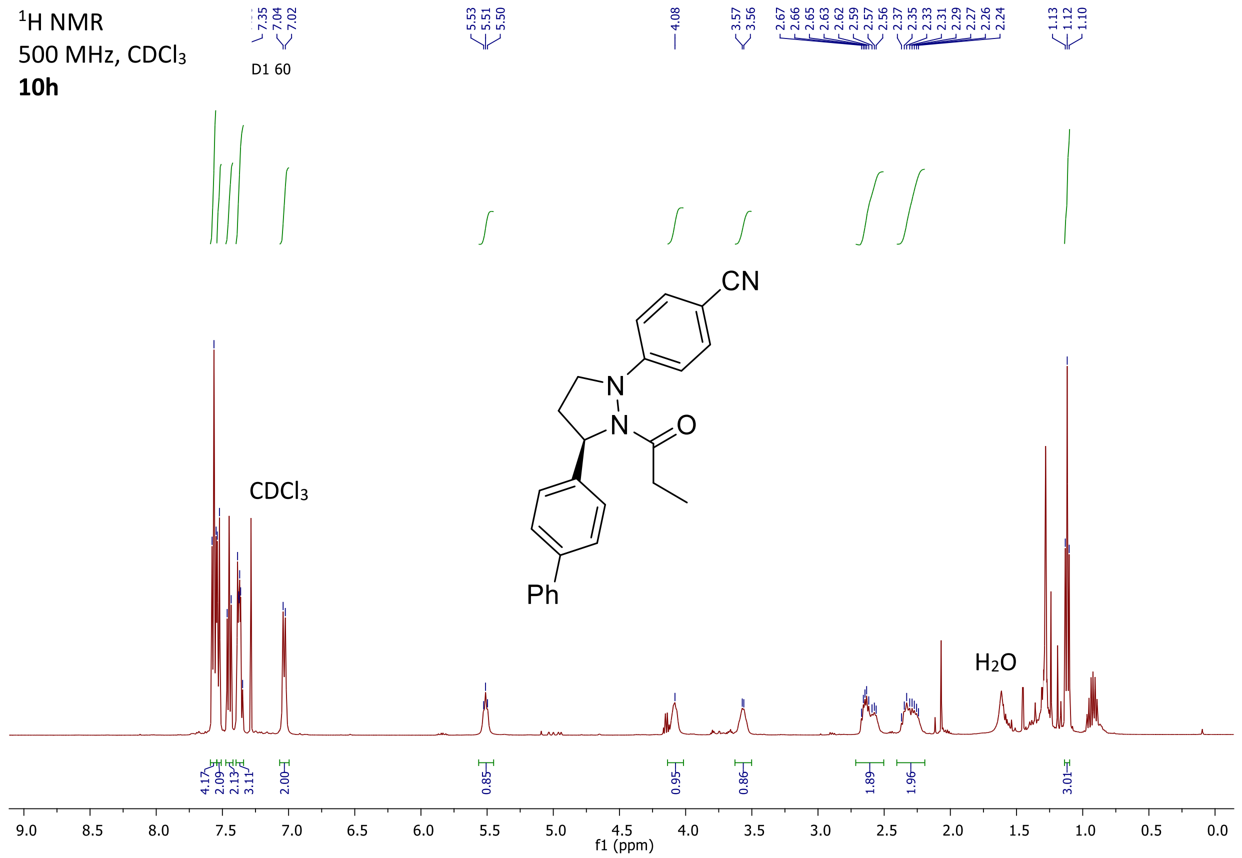
^{13}C NMR
125 MHz, $CDCl_3$
10f



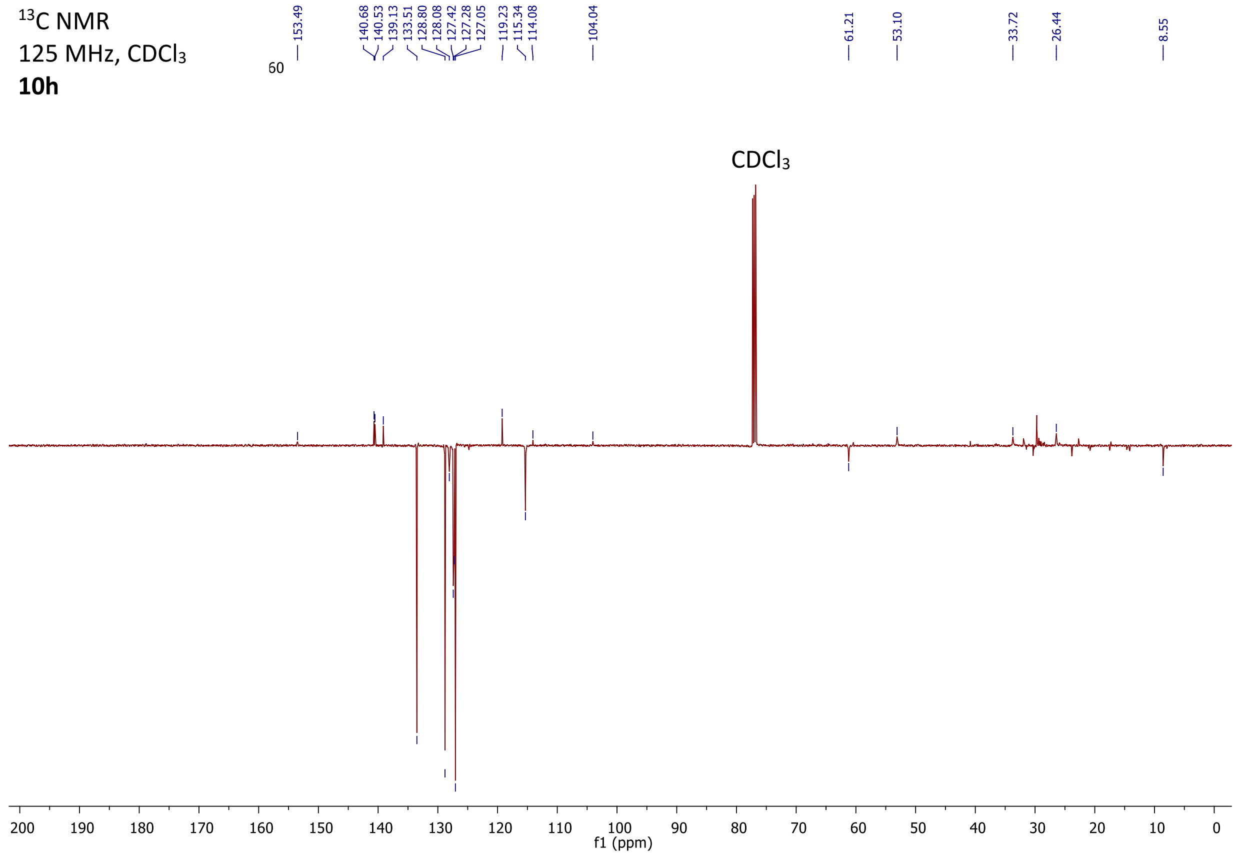

1H NMR
400 MHz, CDCl3
9g
7.53
7.53
7.52
7.50
7.32
7.31
7.29
7.27
7.27
7.25
6.80
6.78
5.32
4.26
4.24
4.22
4.21
4.20
3.81
3.56
3.53
2.59
2.58
2.57
2.56
2.55
2.54
2.53
2.52
2.51
2.27
1.35
MeO
N
N
O
Boc
Ph
CDCl3
TMS
2.00
4.91
2.01
1.00
1.03
3.01
0.97
1.07
0.91
9.56
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

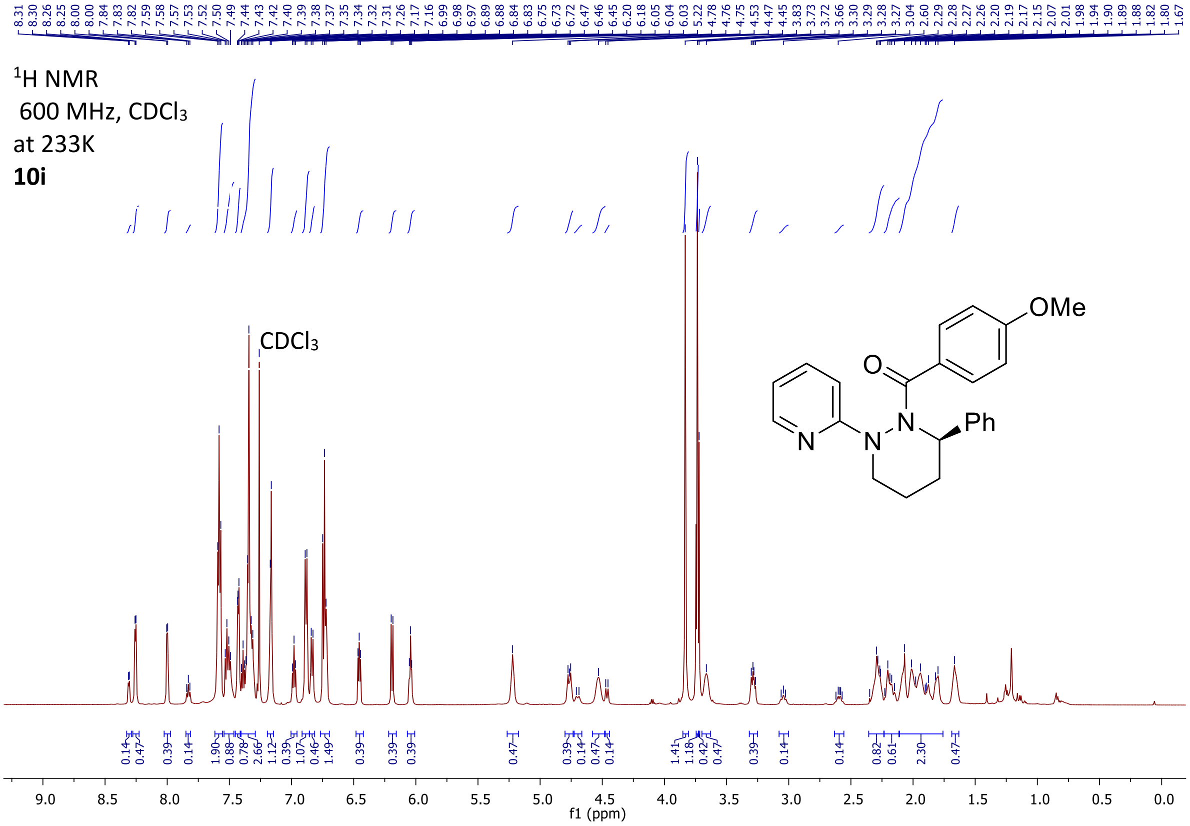

13C NMR
100 MHz, CDCl3
9g
161.55
140.60
132.24
130.16
128.62
127.53
126.55
113.10
82.28
62.94
55.32
27.99
CDCl3
TMS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

^{1}H NMR
500 MHz, $CDCl_3$
10h

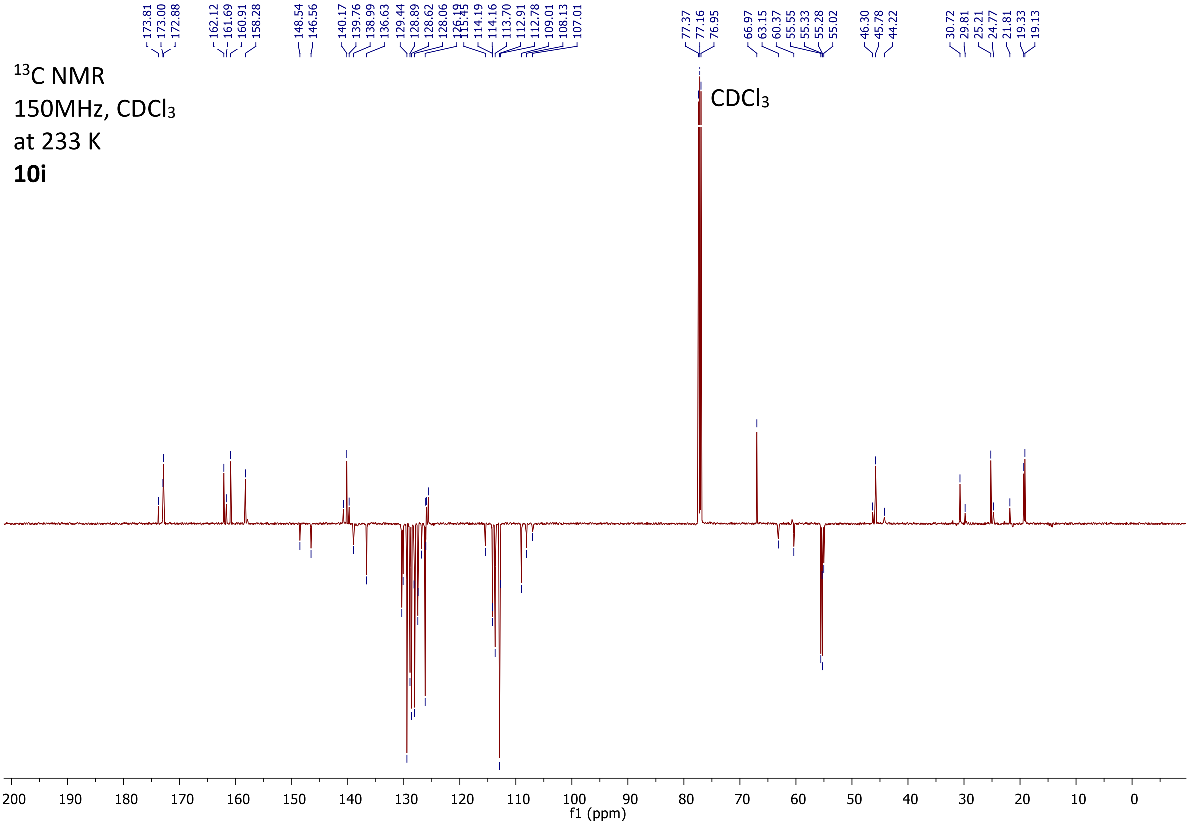


^{13}C NMR
125 MHz, $CDCl_3$
10h



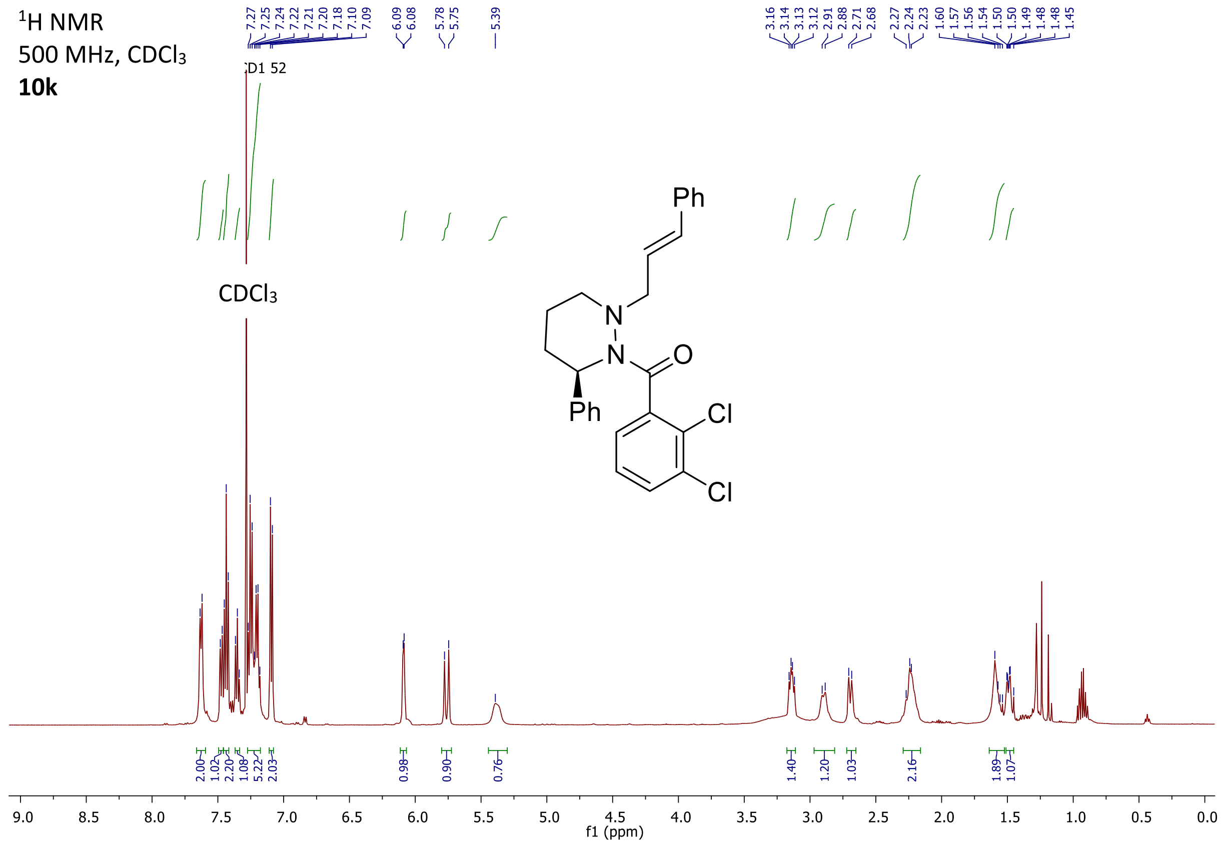


^{1}H NMR
600 MHz, CDCl$_3$
at 233K
10i

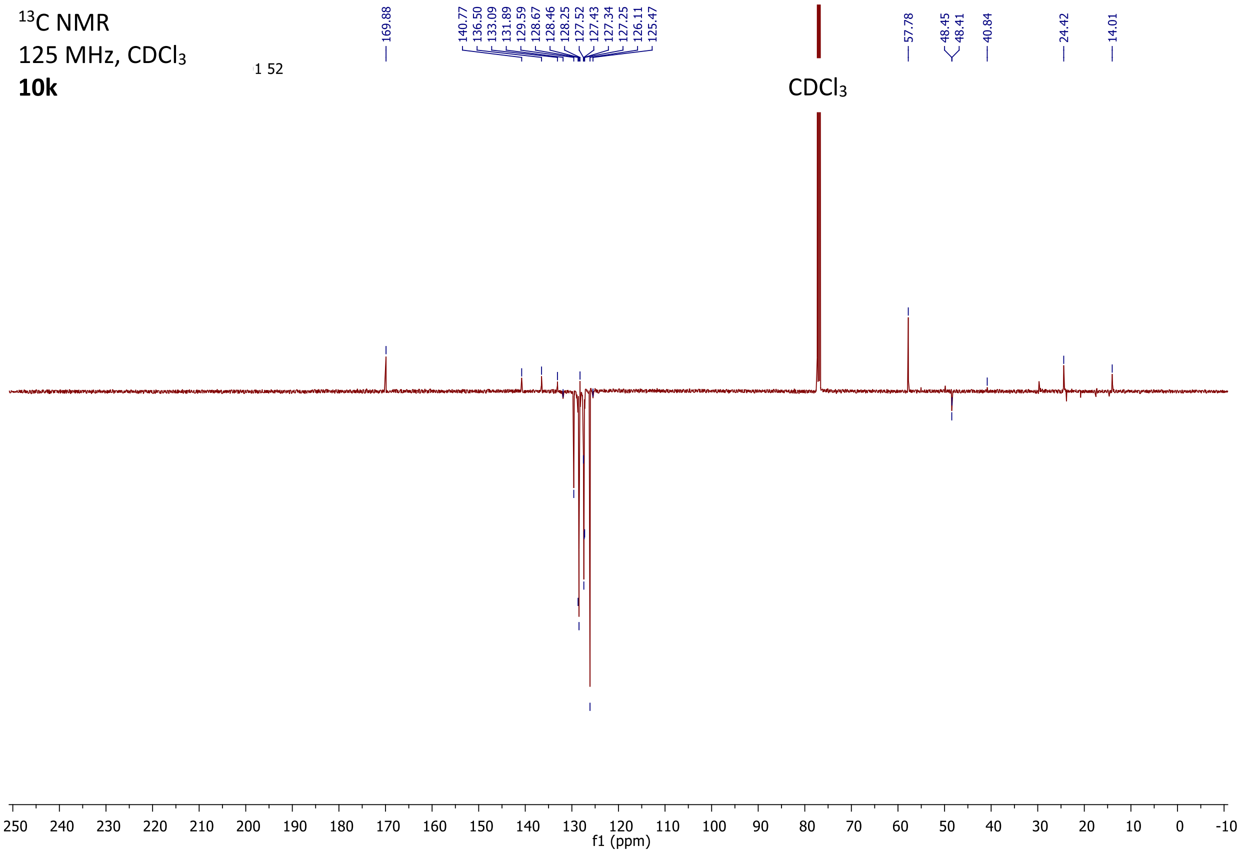


^{13}C NMR
150MHz, CDCl$_3$
at 233 K
10i

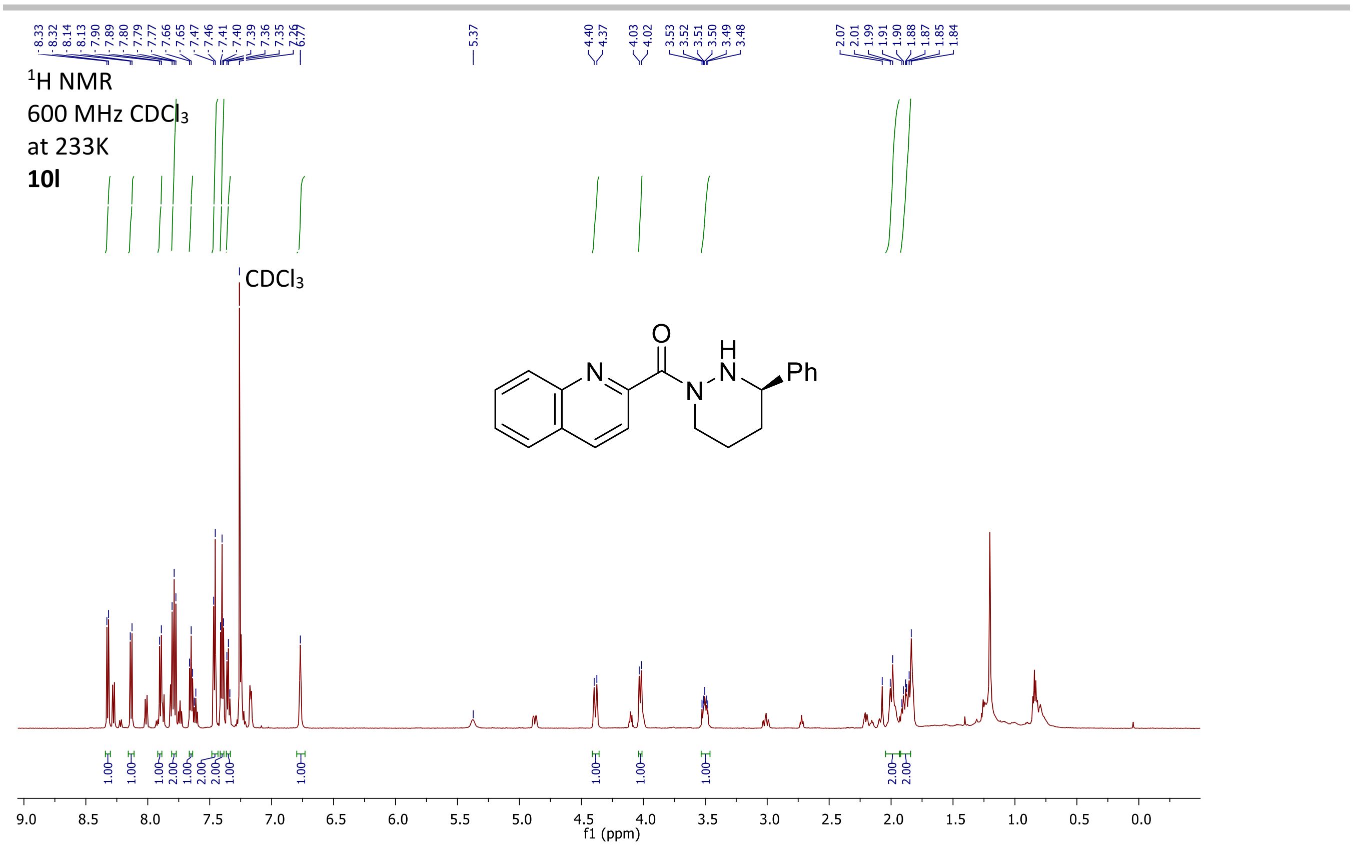
^{1}H NMR
500 MHz, CDCl$_3$
10k



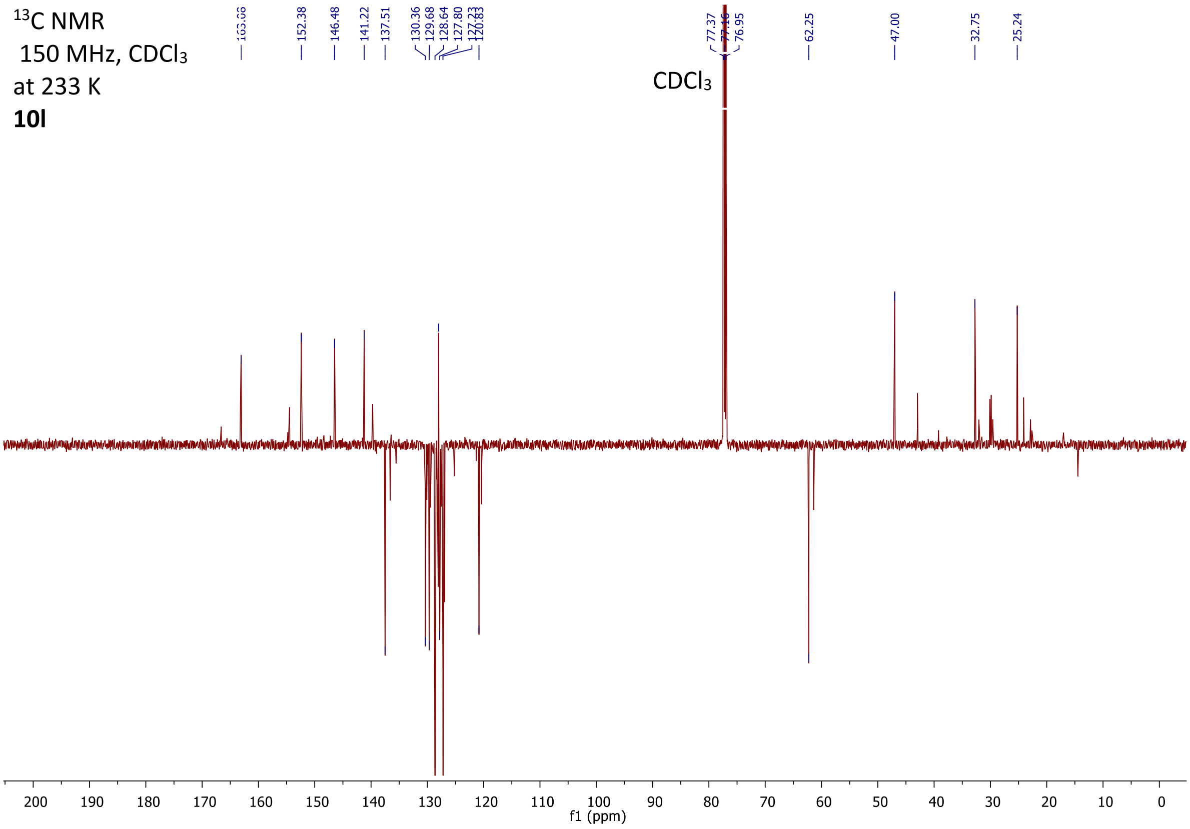
^{13}C NMR
125 MHz, CDCl$_3$
10k



^1H NMR
600 MHz $CDCl_3$
at 233K
10l



^{13}C NMR
150 MHz, $CDCl_3$
at 233 K
10l

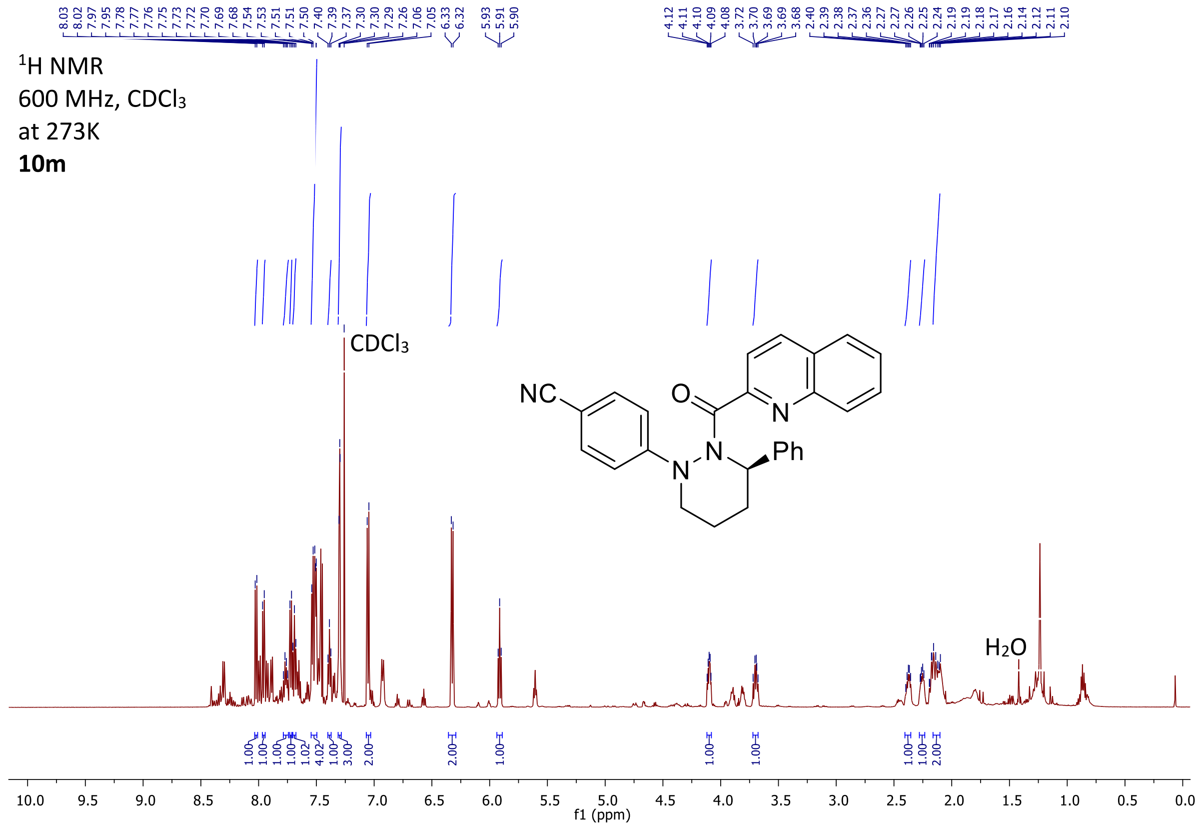


^1H NMR

600 MHz, $CDCl_3$

at 273K

10m

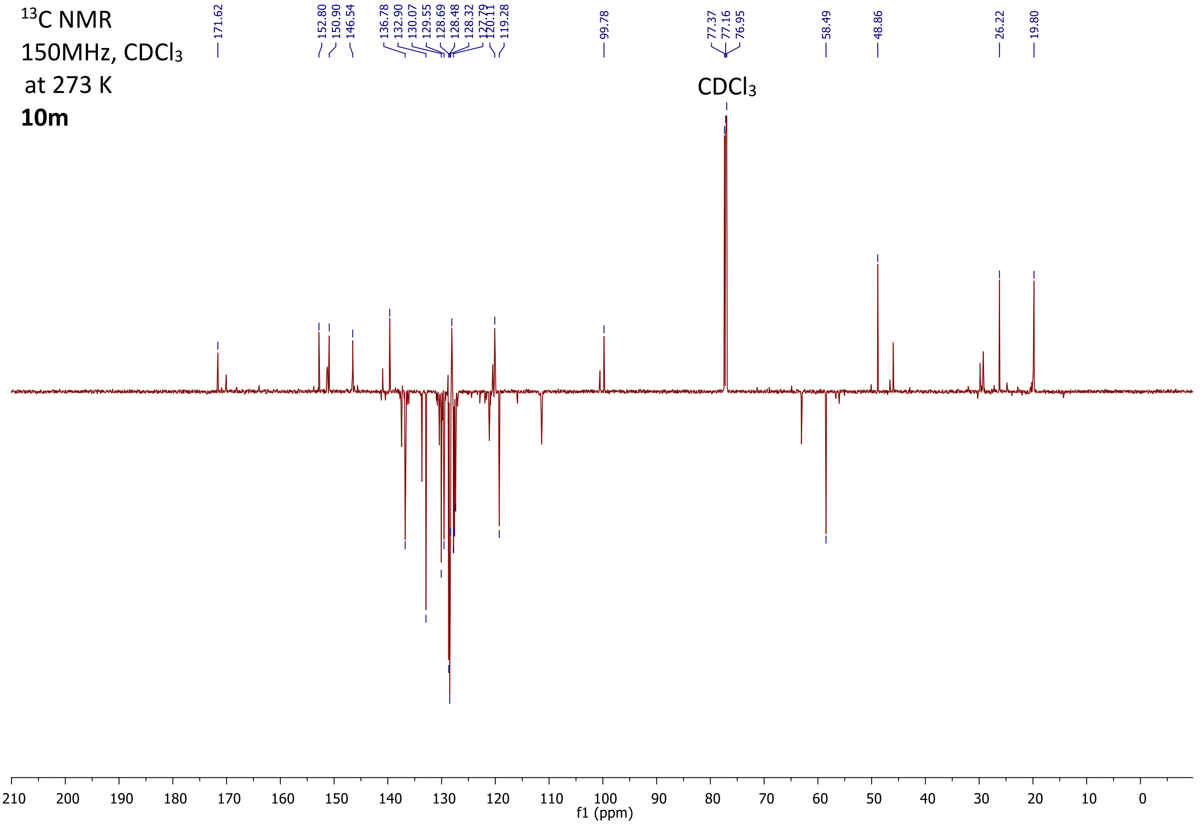


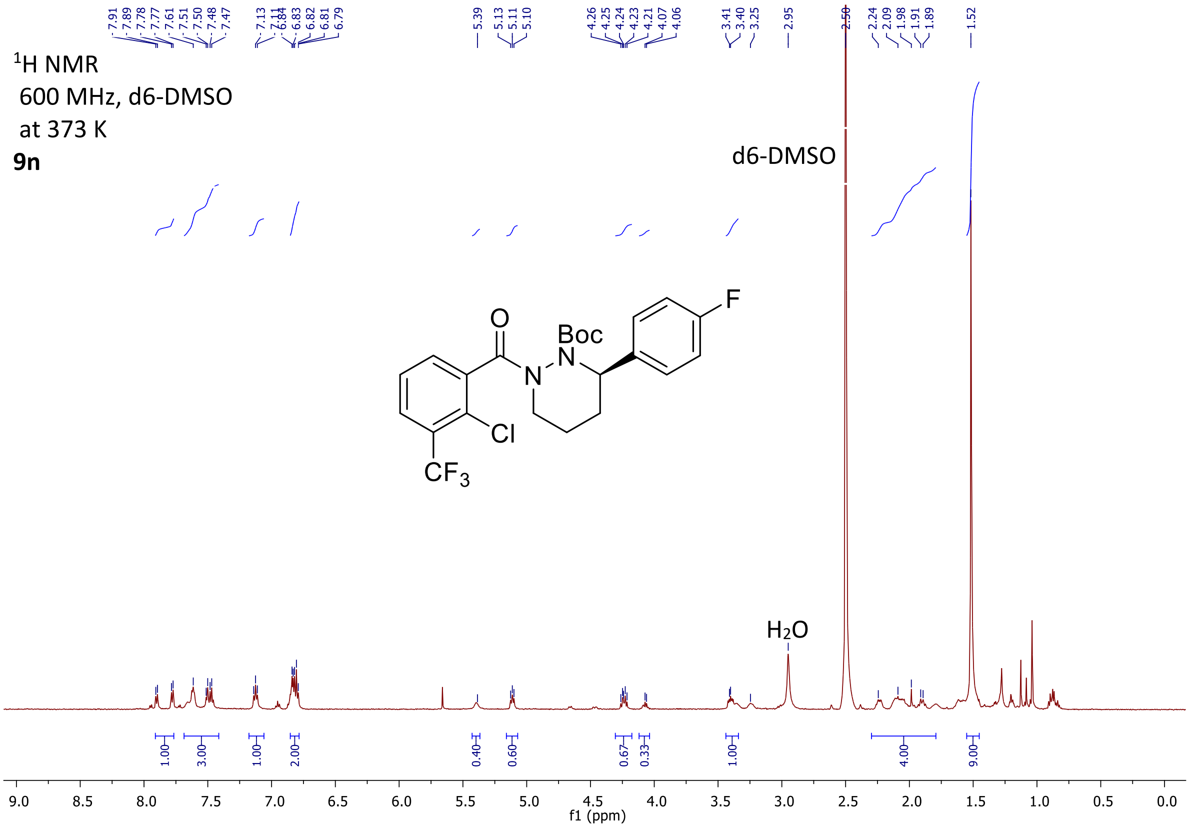
^{13}C NMR

150MHz, $CDCl_3$

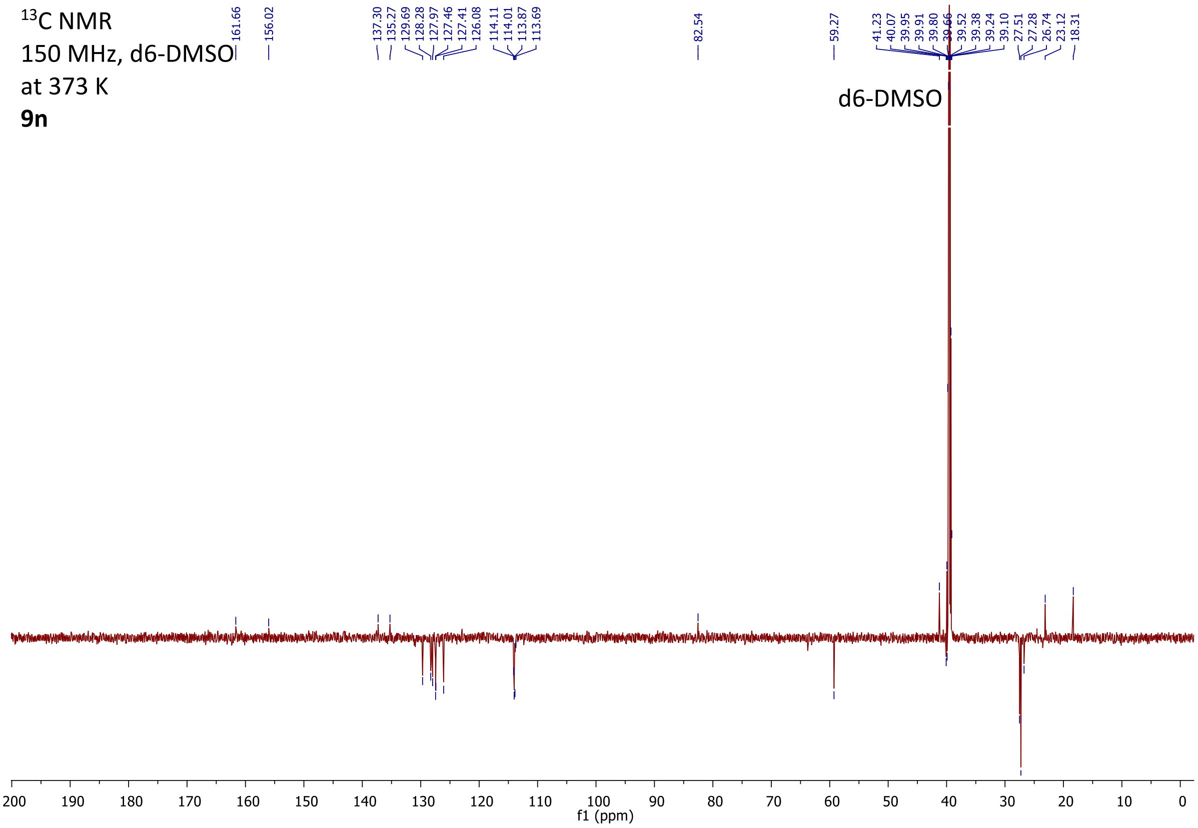
at 273 K

10m

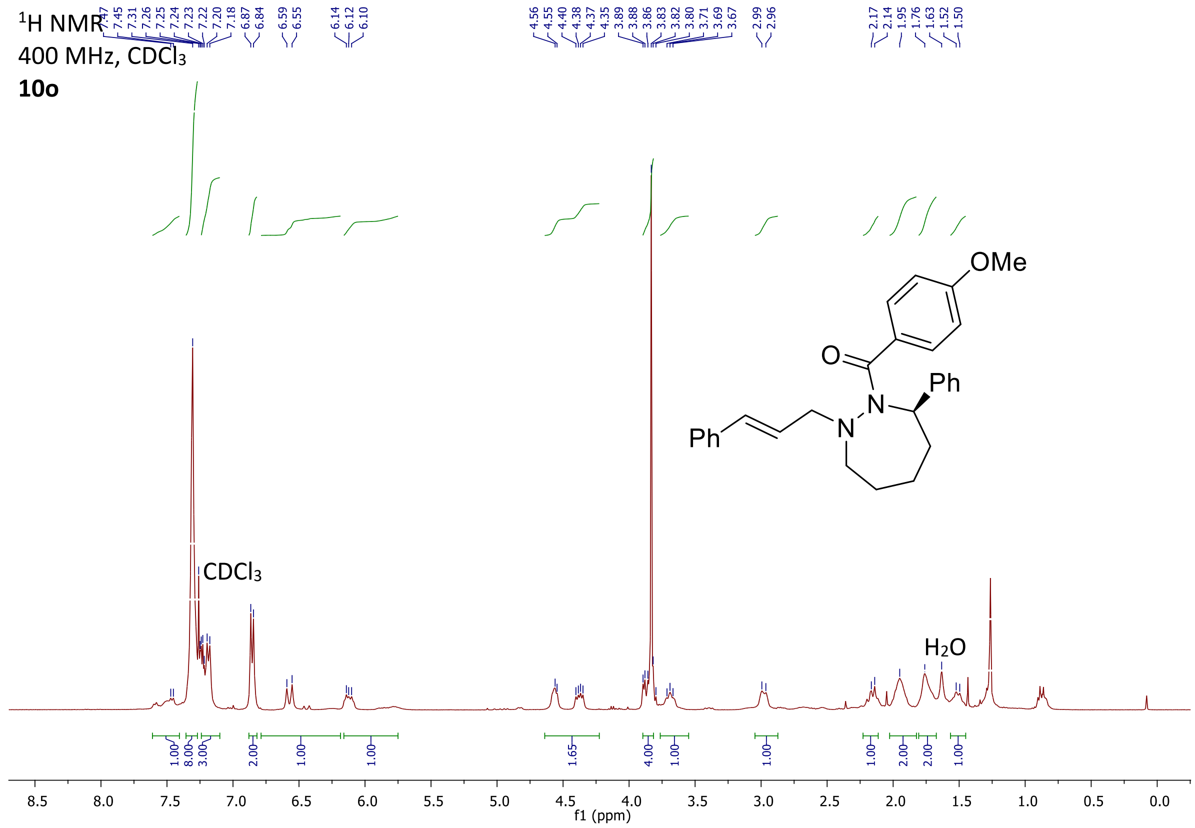




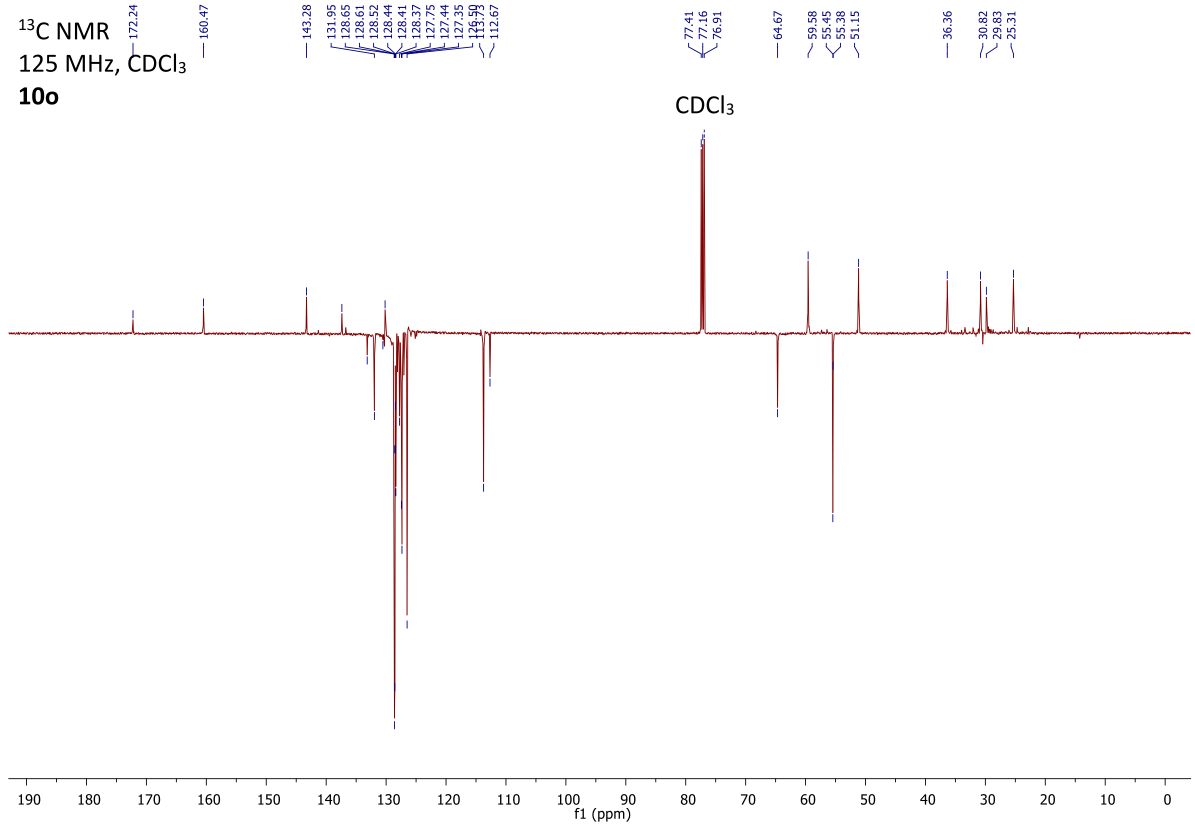
^{1}H NMR
600 MHz, d6-DMSO
at 373 K
9n
7.91
7.89
7.78
7.77
7.61
7.51
7.50
7.48
7.47
7.13
7.11
6.84
6.83
6.82
6.81
6.79
5.39
5.13
5.11
5.10
4.26
4.25
4.24
4.23
4.21
4.07
4.06
3.41
3.40
3.25
2.95
2.50
2.24
2.09
1.98
1.91
1.89
1.52
d6-DMSO
H$_2$O
O
Boc
N
N
F
Cl
CF$_3$
1.00
3.00
1.00
2.00
0.40
0.60
0.67
0.33
1.00
4.00
9.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



^{13}C NMR
150 MHz, d6-DMSO
at 373 K
9n
161.66
156.02
137.30
135.27
129.69
128.28
127.97
127.46
127.41
126.08
114.11
114.01
113.87
113.69
82.54
59.27
41.23
40.07
39.95
39.91
39.80
39.66
39.52
39.38
39.24
39.10
27.51
27.28
26.74
23.12
18.31
d6-DMSO
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

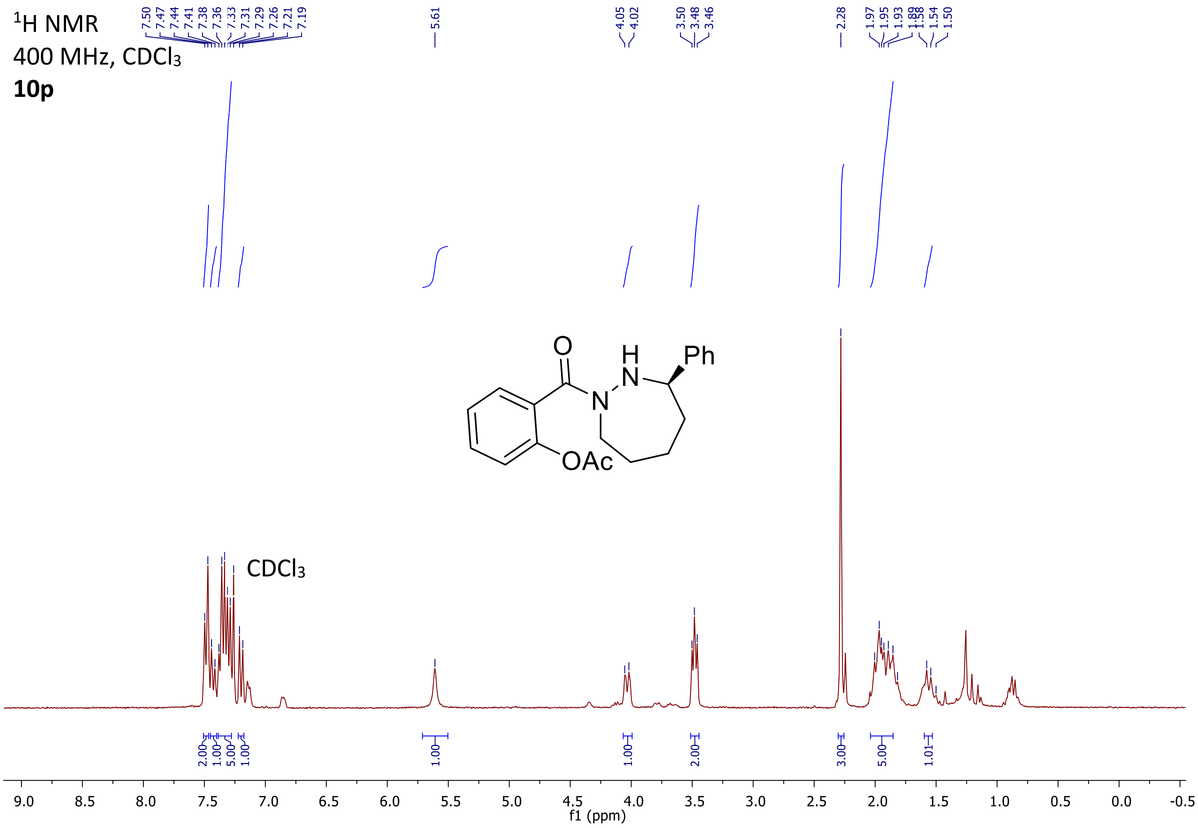


^{1}H NMR
400 MHz, $CDCl_3$
10o

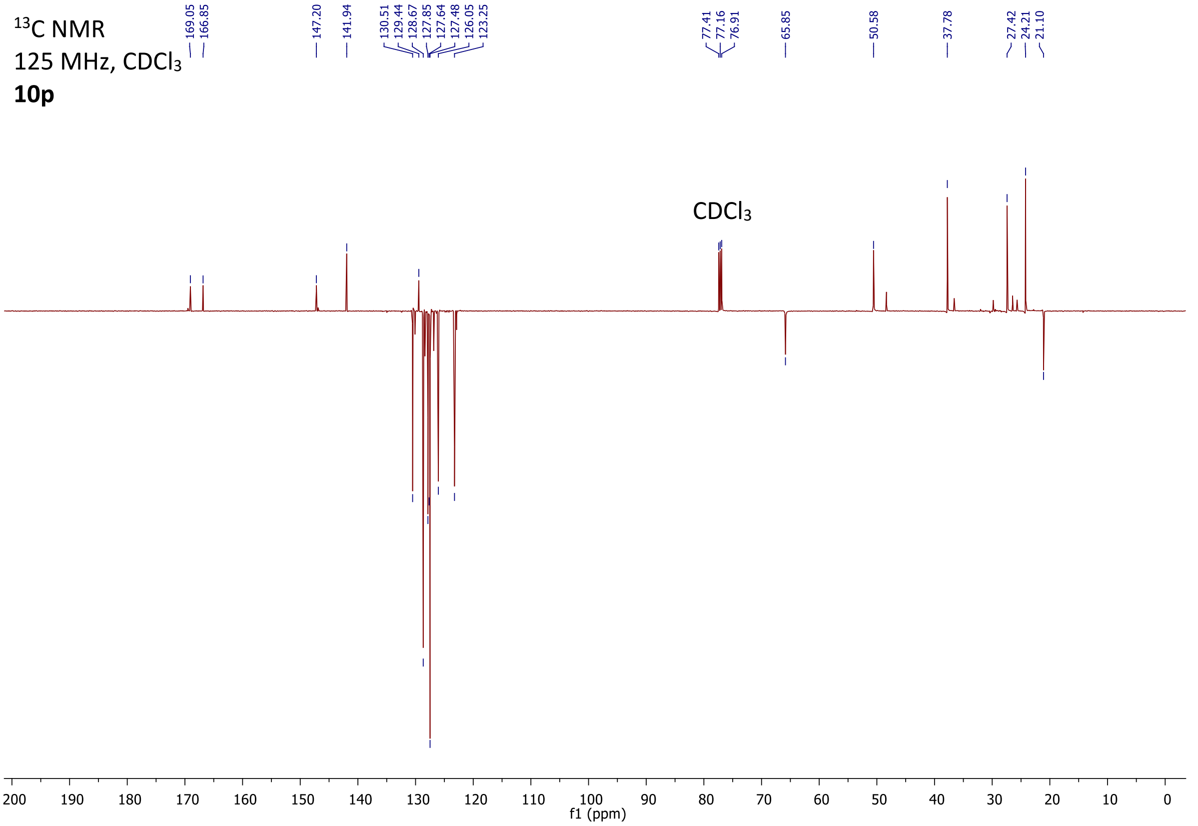


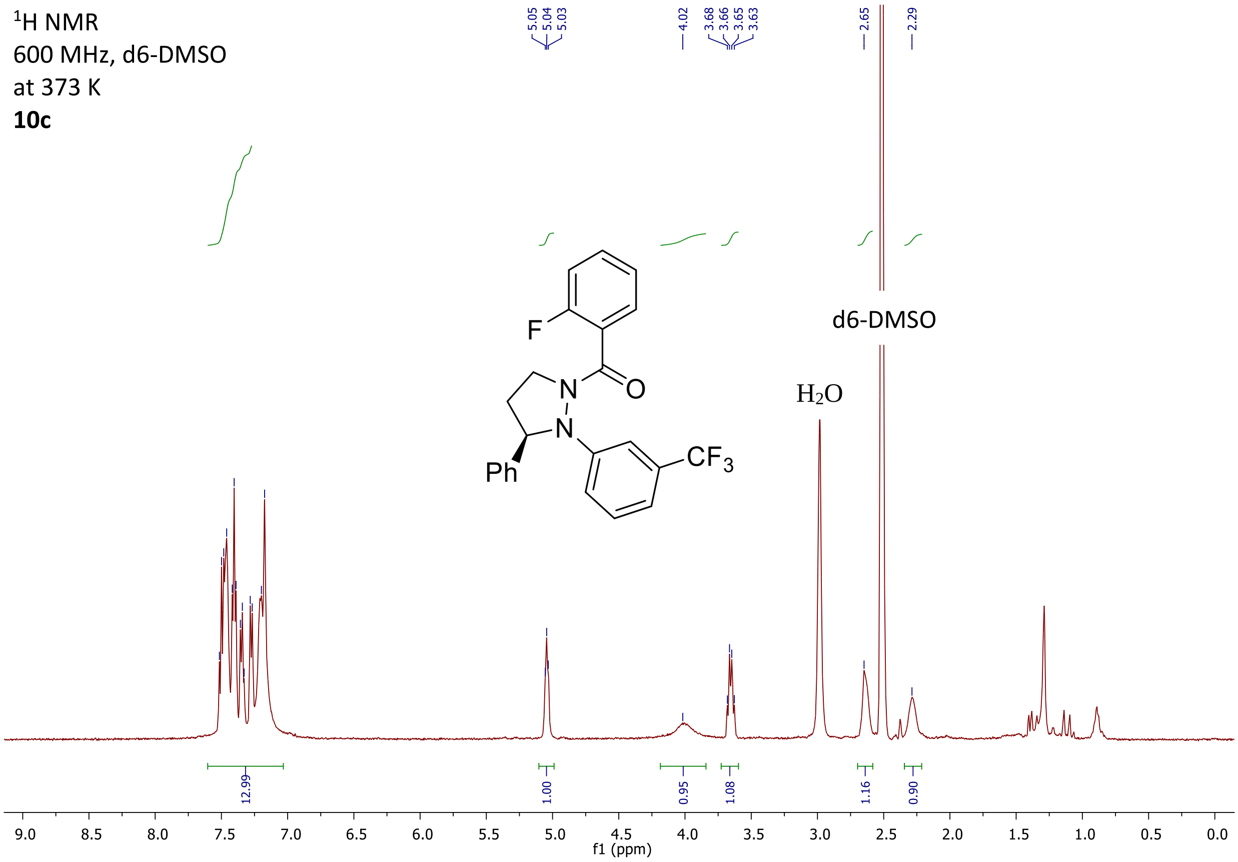
^{13}C NMR
125 MHz, $CDCl_3$
10o

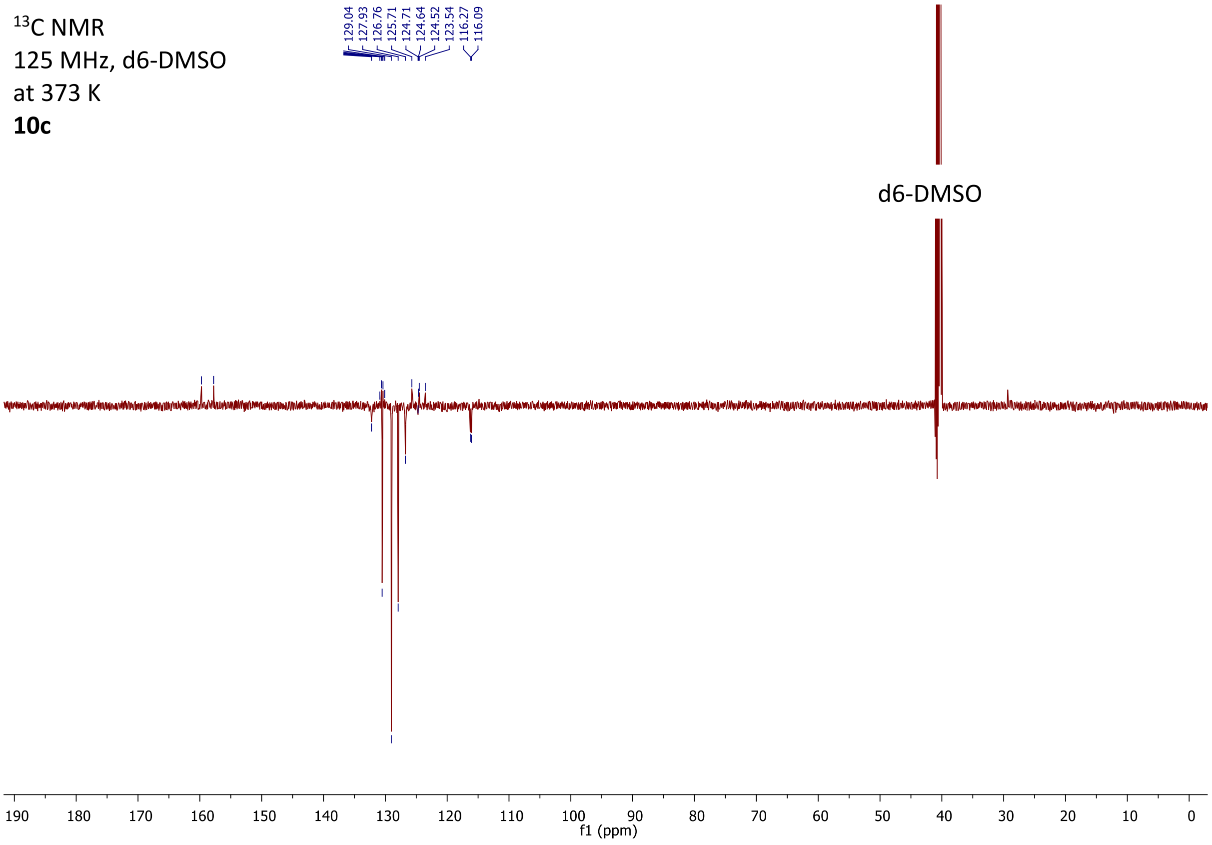
^{1}H NMR
400 MHz, $CDCl_3$
10p

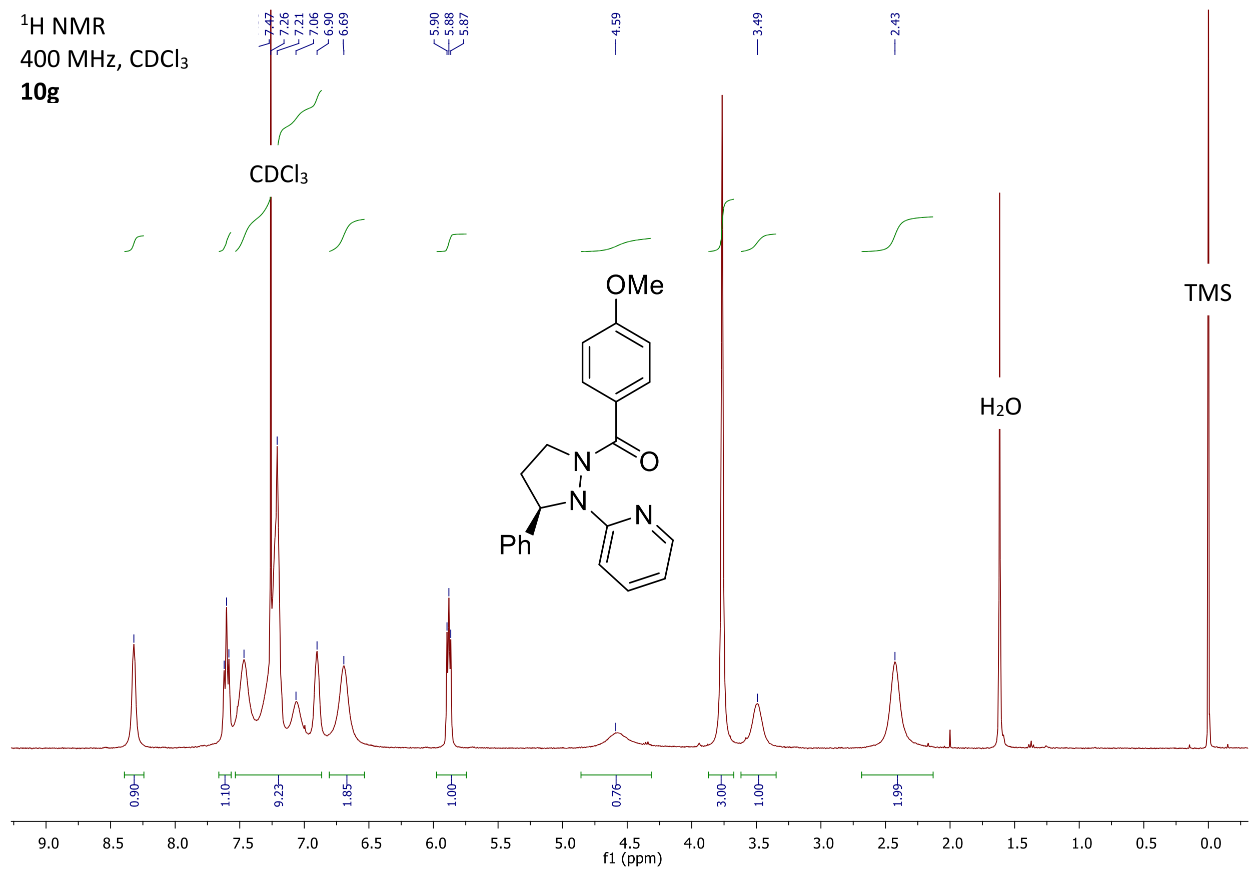


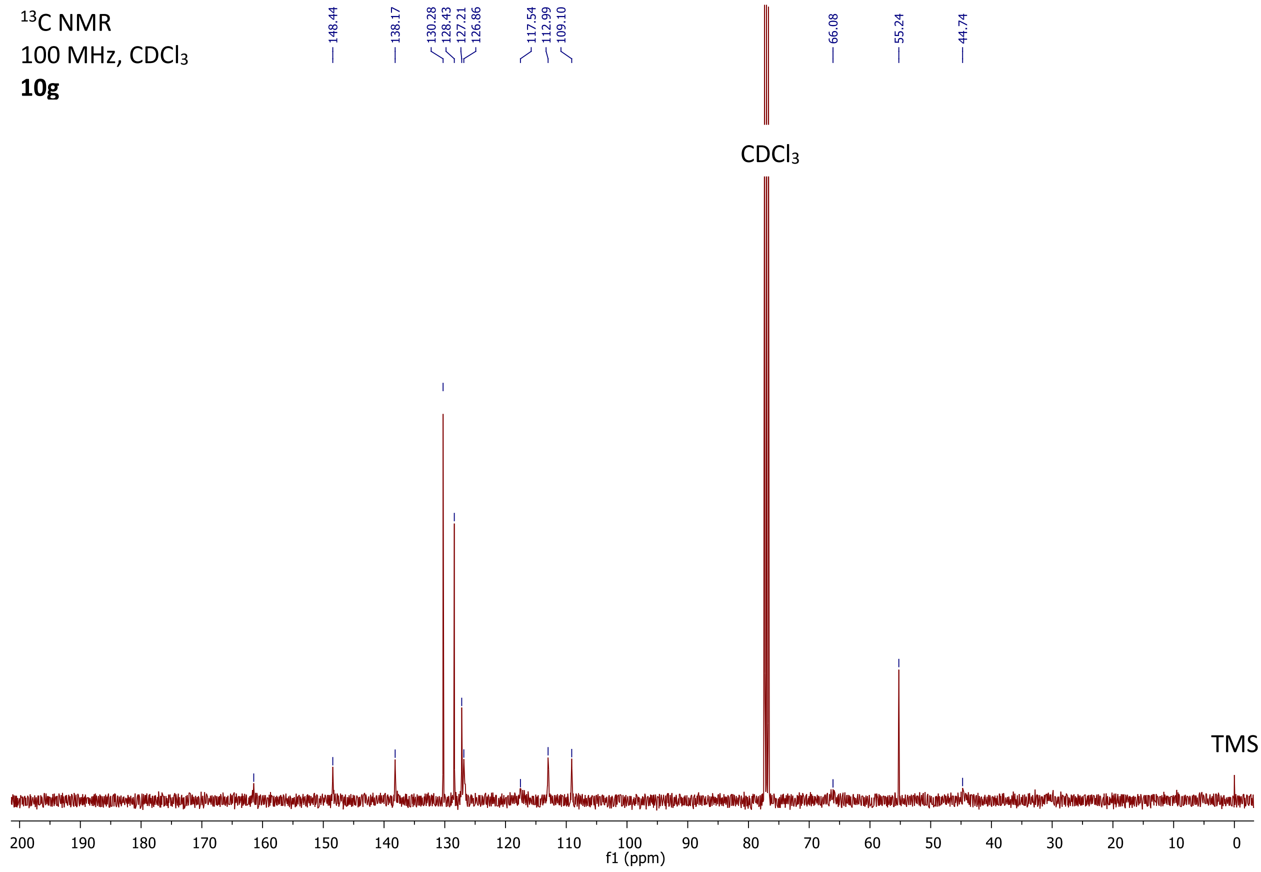
^{13}C NMR
125 MHz, $CDCl_3$
10p

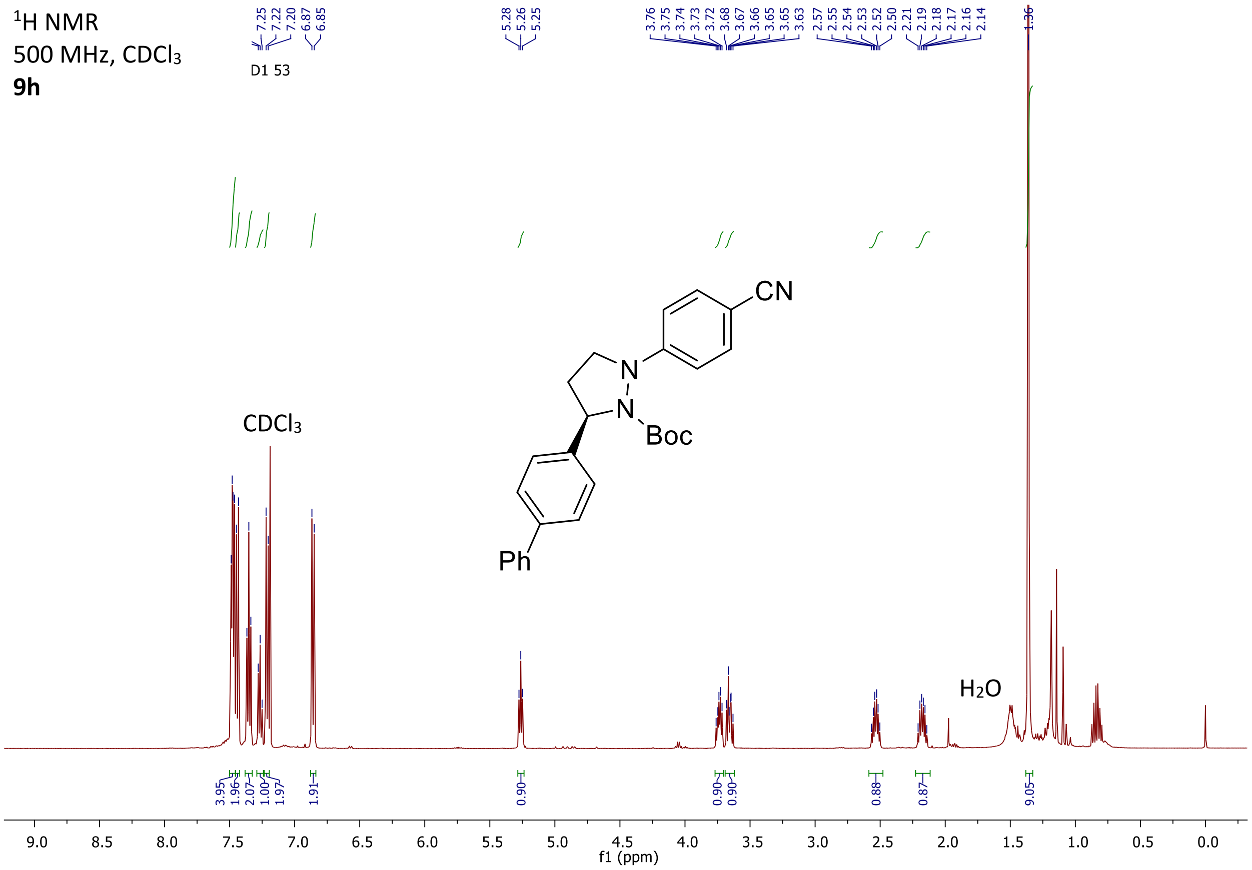



^{1}H NMR
600 MHz, d6-DMSO
at 373 K
10c
5.05
5.04
5.03
4.02
3.68
3.66
3.65
3.63
2.65
2.29
d6-DMSO
H_2O
F
N
N
O
Ph
CF_3
12.99
1.00
0.95
1.08
1.16
0.90
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

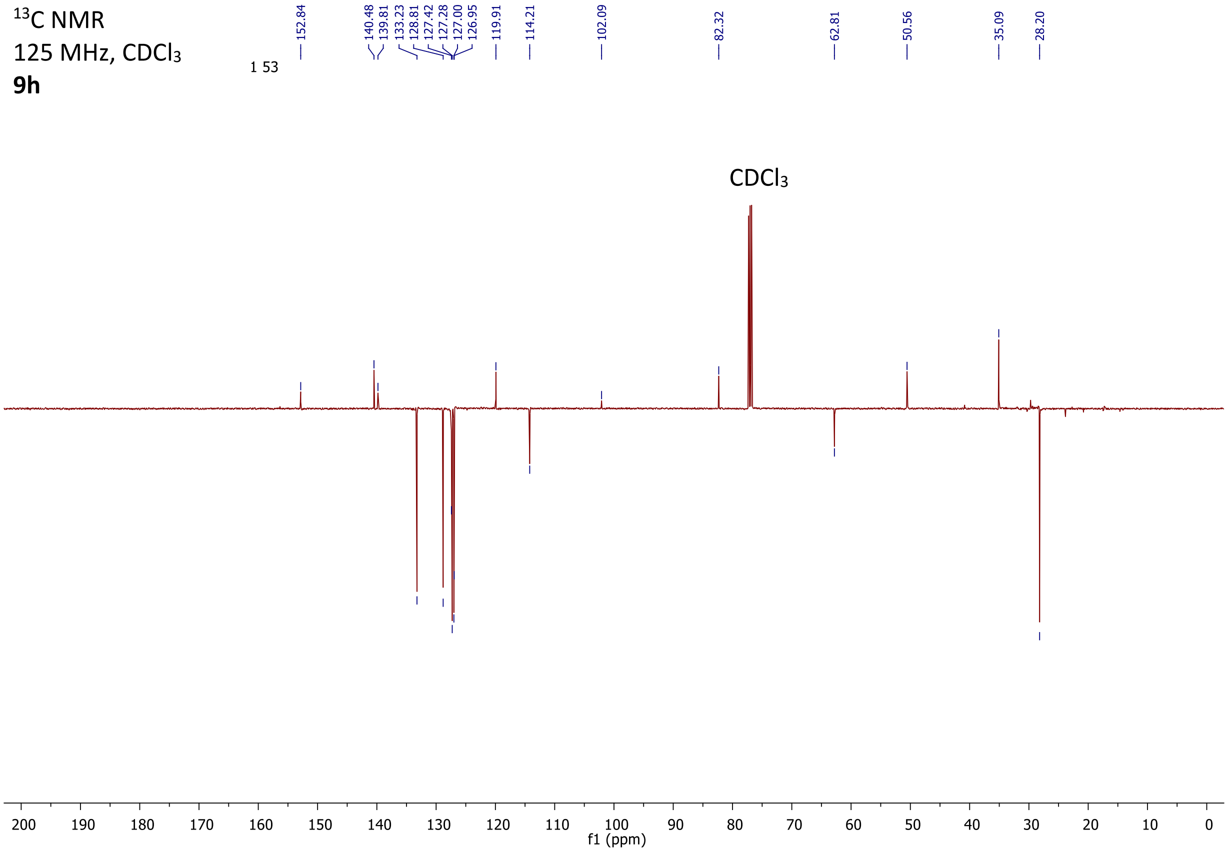

^{13}C NMR
125 MHz, d6-DMSO
at 373 K
10c
129.04
127.93
126.76
125.71
124.71
124.64
124.52
123.54
116.27
116.09
d6-DMSO
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


1H NMR
400 MHz, CDCl3
10g
7.47
7.26
7.21
7.06
6.90
6.69
5.90
5.88
5.87
4.59
3.49
2.43
CDCl3
OMe
N
O
N
N
Ph
H2O
TMS
0.90
1.10
9.23
1.85
1.00
0.76
3.00
1.00
1.99
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

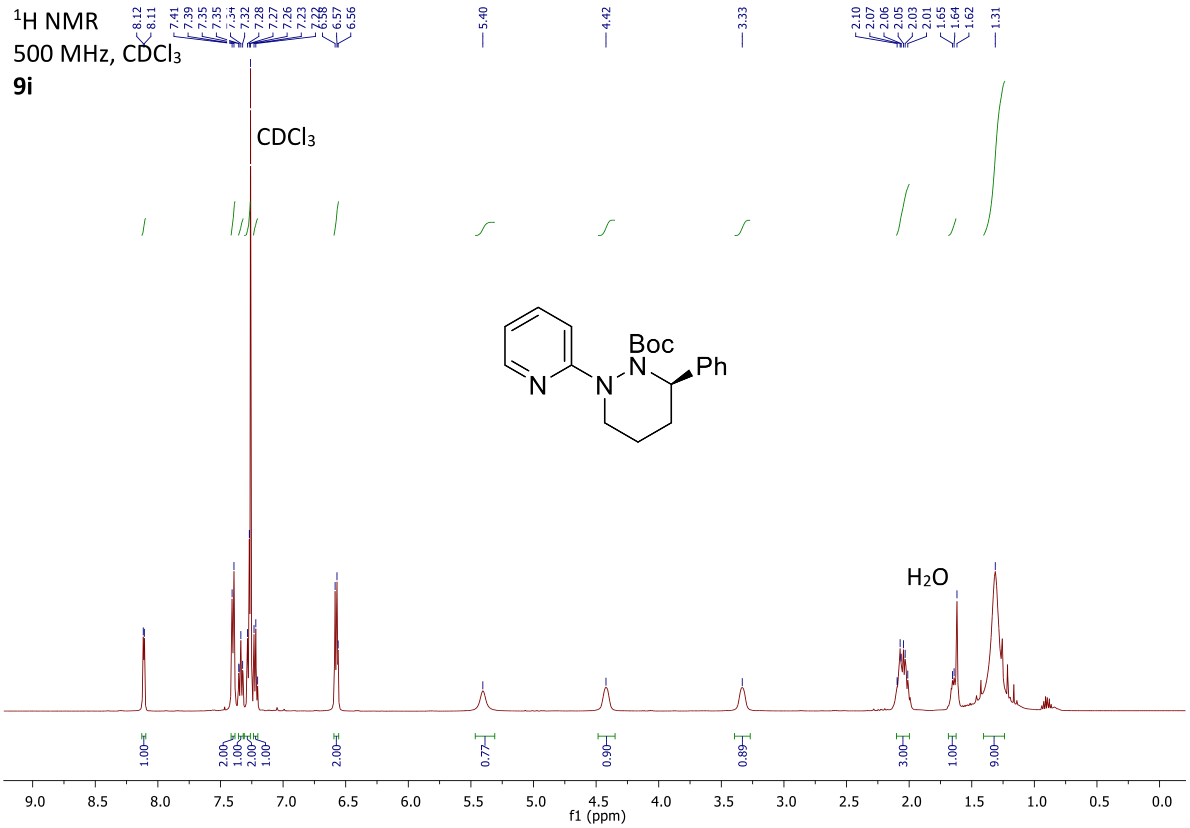

13C NMR
100 MHz, CDCl3
10g
148.44
138.17
130.28
128.43
127.21
126.86
117.54
112.99
109.10
66.08
55.24
44.74
CDCl3
TMS
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



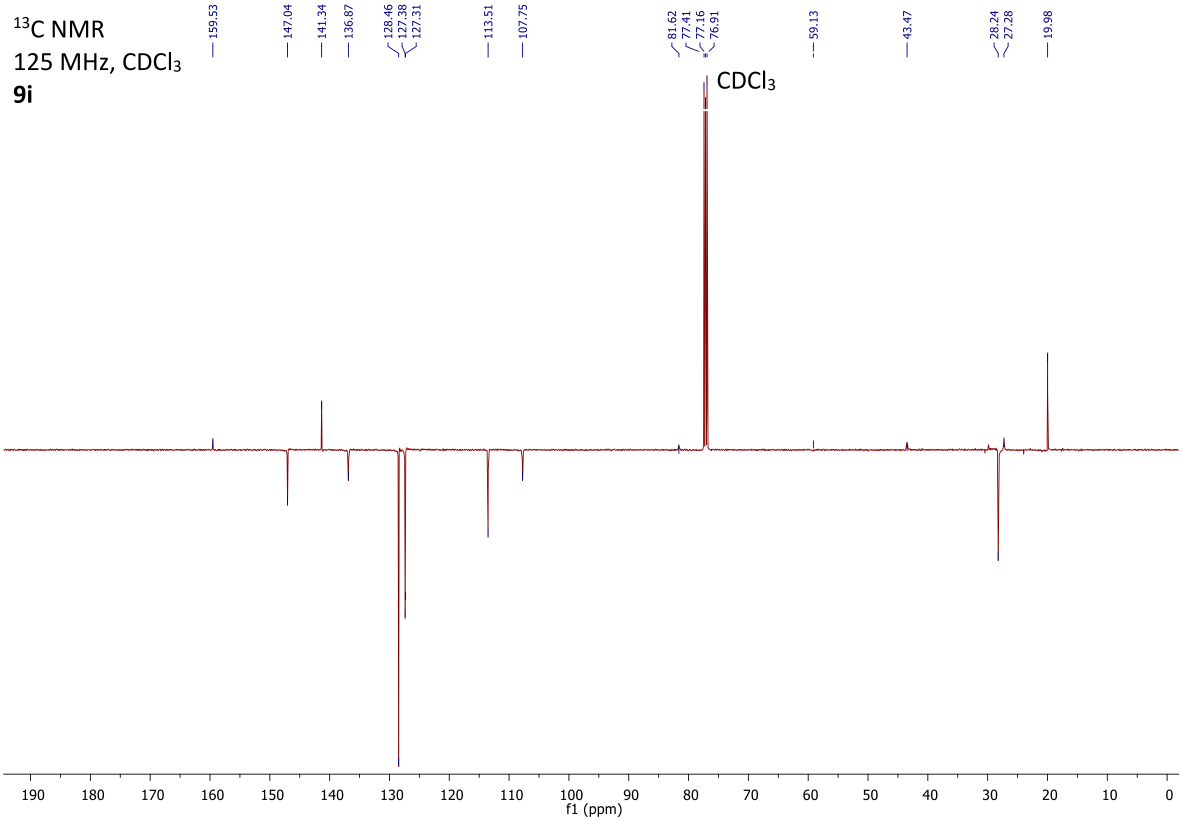
^{1}H NMR
500 MHz, CDCl$_3$
9h
D1 53
7.25 7.22 7.20 6.87 6.85
5.28 5.26 5.25
3.76 3.75 3.74 3.73 3.72 3.68 3.67 3.66 3.65 3.65 3.63
2.57 2.55 2.54 2.53 2.52 2.50 2.21 2.19 2.18 2.17 2.16 2.14
1.36
CN
N
N
Boc
Ph
CDCl$_3$
H$_2$O
3.95 1.96 2.07 1.00 1.97 1.91 0.90 0.90 0.90 0.88 0.87 9.05
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



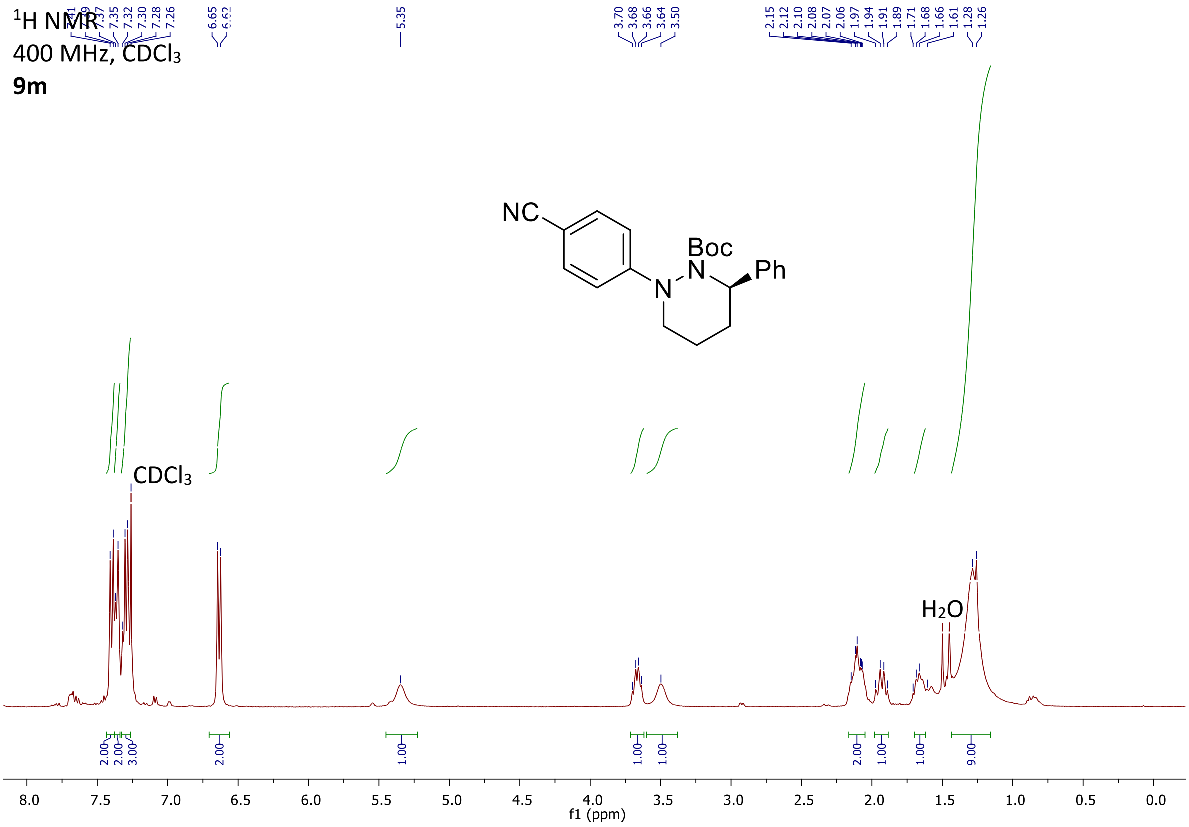
^{13}C NMR
125 MHz, CDCl$_3$
9h
1 53
152.84
140.48 139.81 133.23 128.81 127.42 127.28 127.00 126.95
119.91
114.21
102.09
82.32
62.81
50.56
35.09
28.20
CDCl$_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



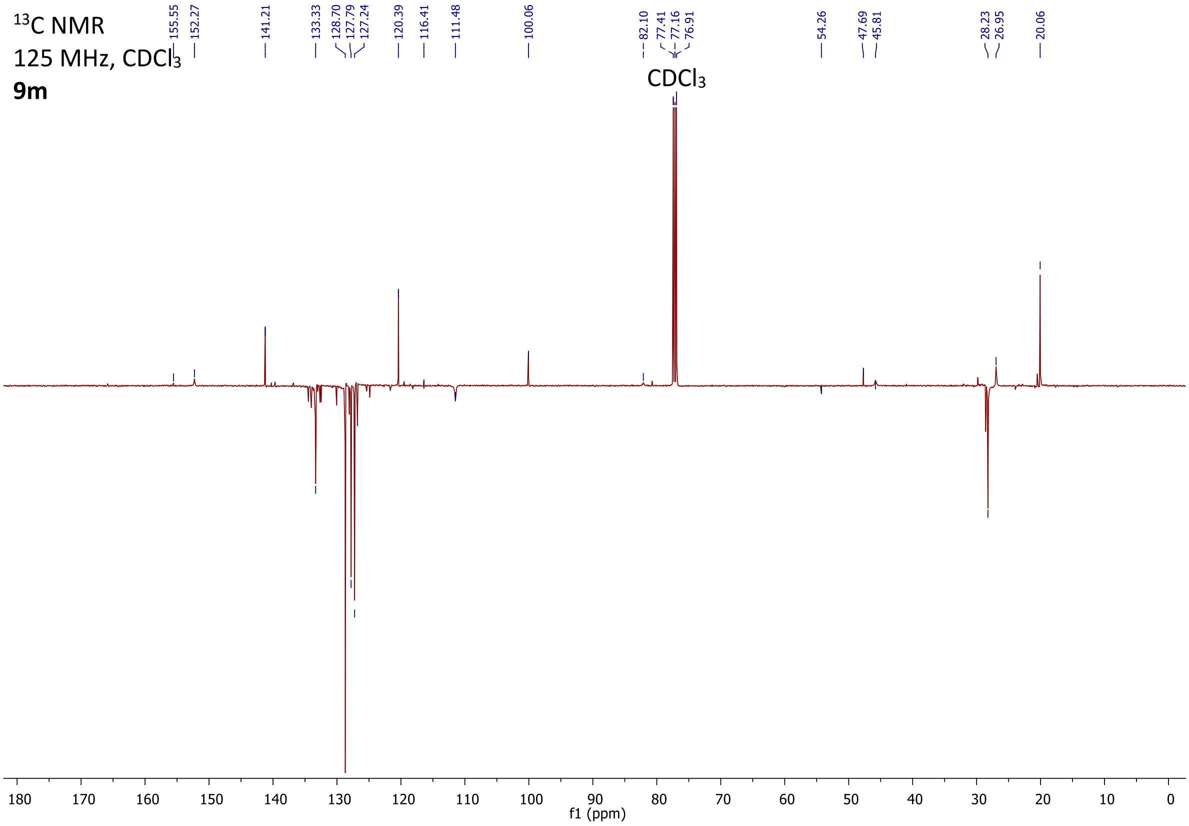
^{1}H NMR
500 MHz, CDCl$_3$
9i
8.12 8.11 7.41 7.39 7.35 7.35 7.34 7.32 7.28 7.27 7.26 7.23 7.22 6.58 6.57 6.56
5.40
4.42
3.33
2.10 2.07 2.06 2.05 2.03 2.01 1.65 1.64 1.62
1.31
CDCl$_3$
H$_2$O
Boc
N
N
N
Ph
1.00 2.00 1.00 2.00 1.00 2.00 0.77 0.90 0.89 3.00 1.00 9.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



^{13}C NMR
125 MHz, CDCl$_3$
9i
159.53
147.04
141.34
136.87
128.46 127.38 127.31
113.51
107.75
81.62 77.41 77.16 76.91
59.13
43.47
28.24 27.28
19.98
CDCl$_3$
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

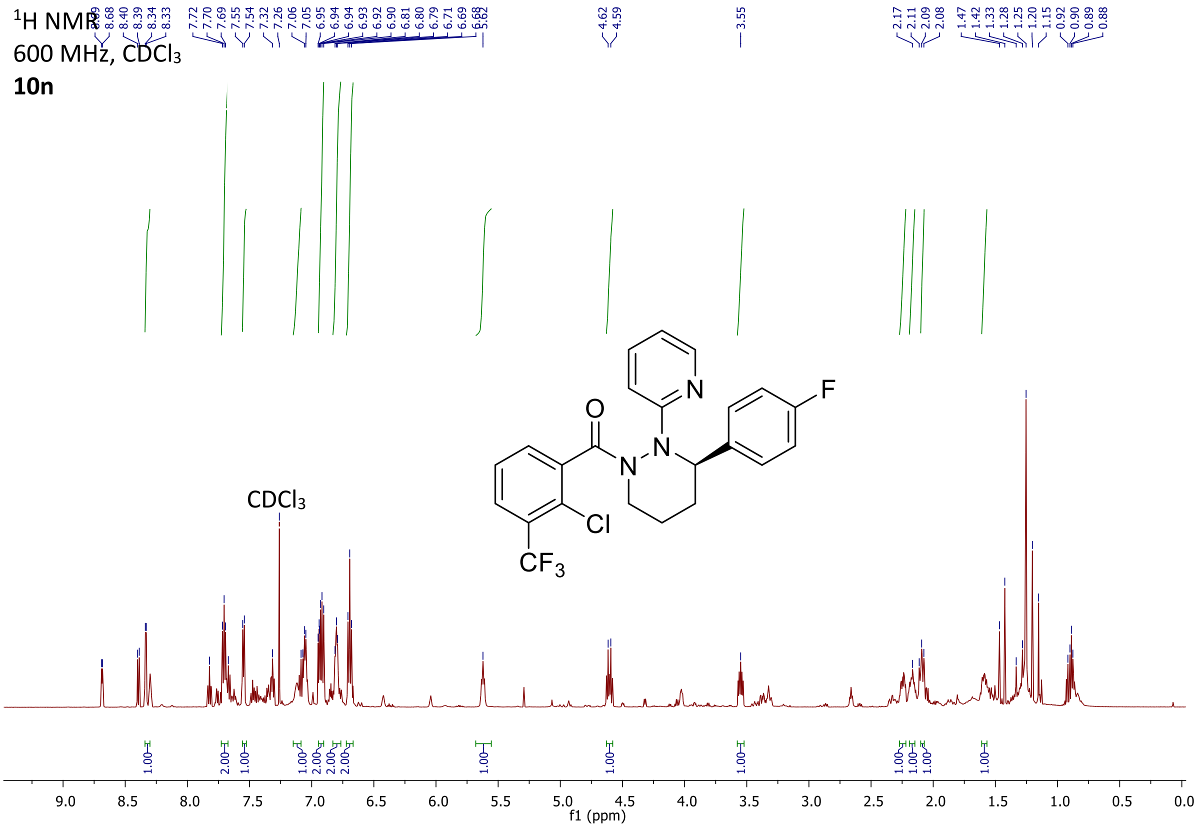


^{1}H NMR
400 MHz, $CDCl_3$
9m
7.41
7.39
7.37
7.35
7.32
7.30
7.28
7.26
6.65
6.62
5.35
3.70
3.68
3.66
3.64
3.50
2.15
2.12
2.10
2.08
2.07
2.06
1.97
1.94
1.91
1.89
1.71
1.68
1.66
1.61
1.28
1.26
NC
Boc
N
N
Ph
$CDCl_3$
H_2O
2.00
2.00
3.00
2.00
1.00
1.00
1.00
2.00
1.00
1.00
9.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

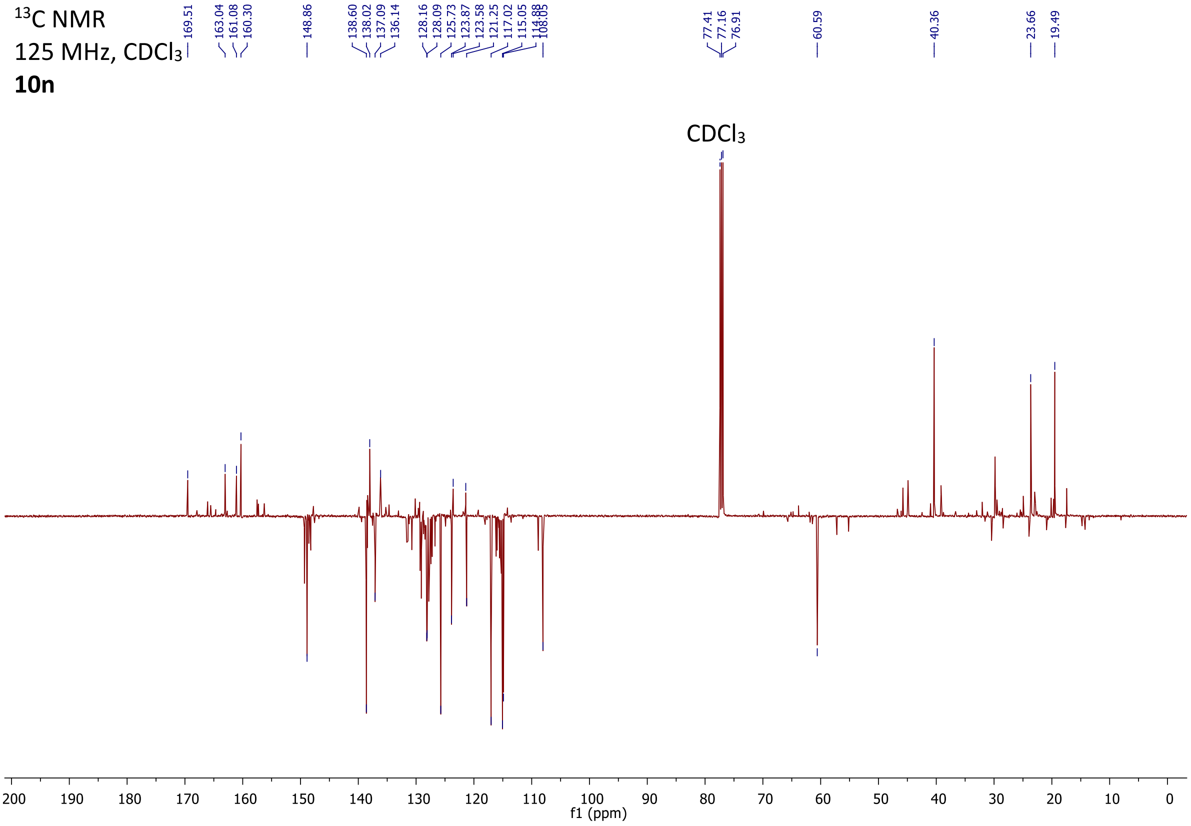


^{13}C NMR
125 MHz, $CDCl_3$
9m
155.55
152.27
141.21
133.33
128.70
127.79
127.24
120.39
116.41
111.48
100.06
82.10
77.41
77.16
76.91
54.26
47.69
45.81
28.23
26.95
20.06
$CDCl_3$
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

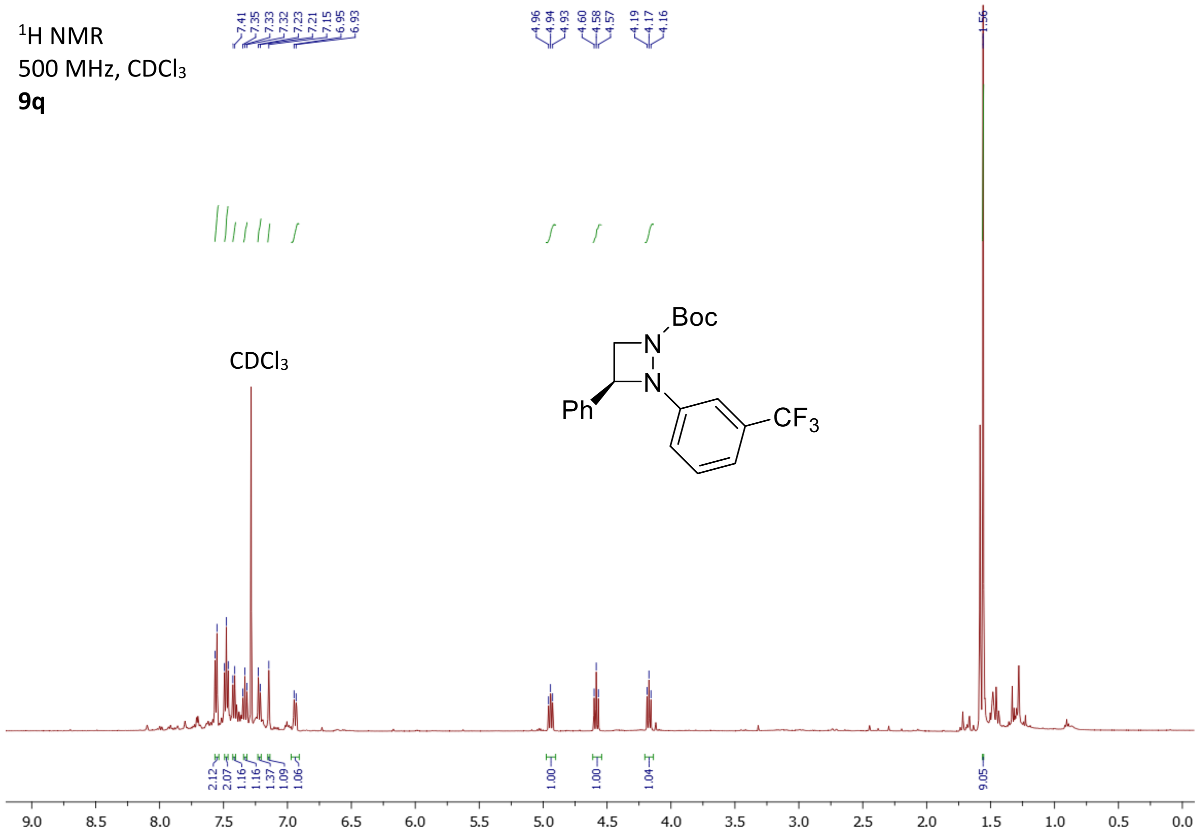
^{1}H NMR
600 MHz, $CDCl_3$
10n



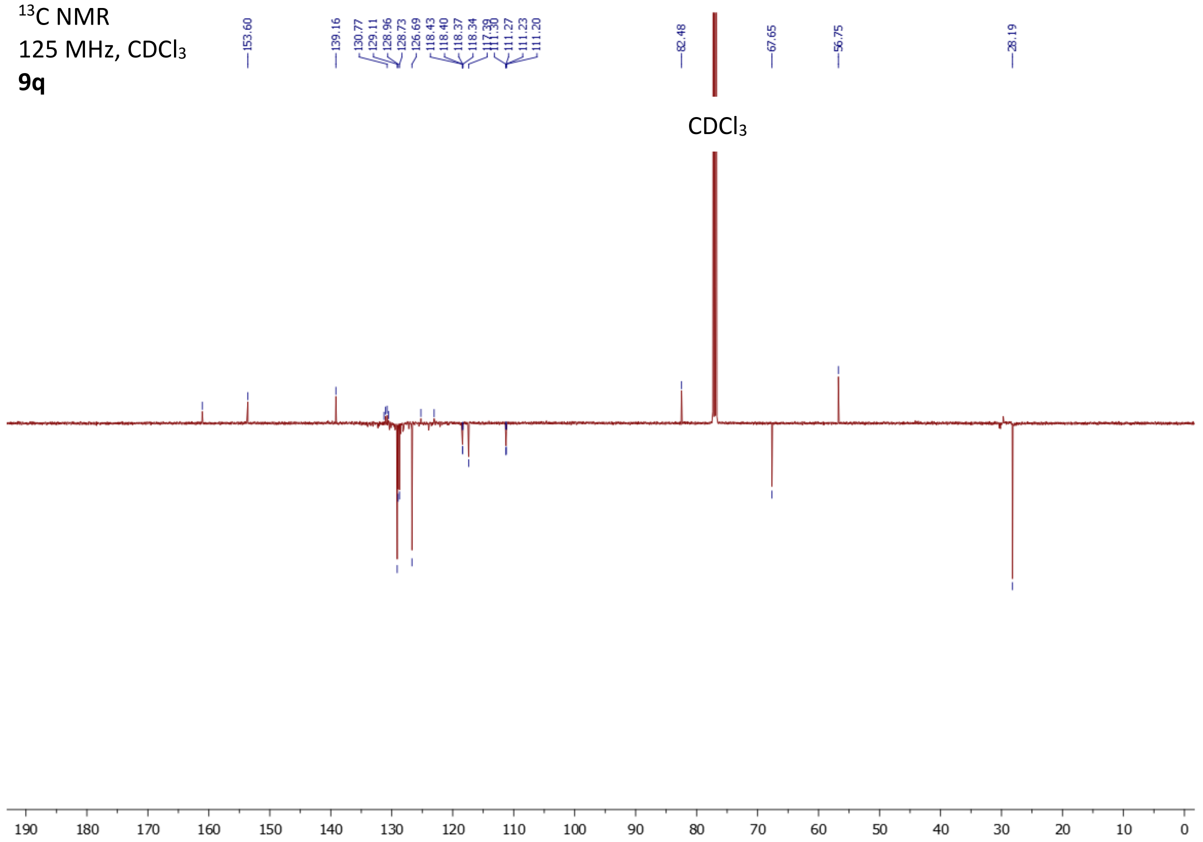
^{13}C NMR
125 MHz, $CDCl_3$
10n



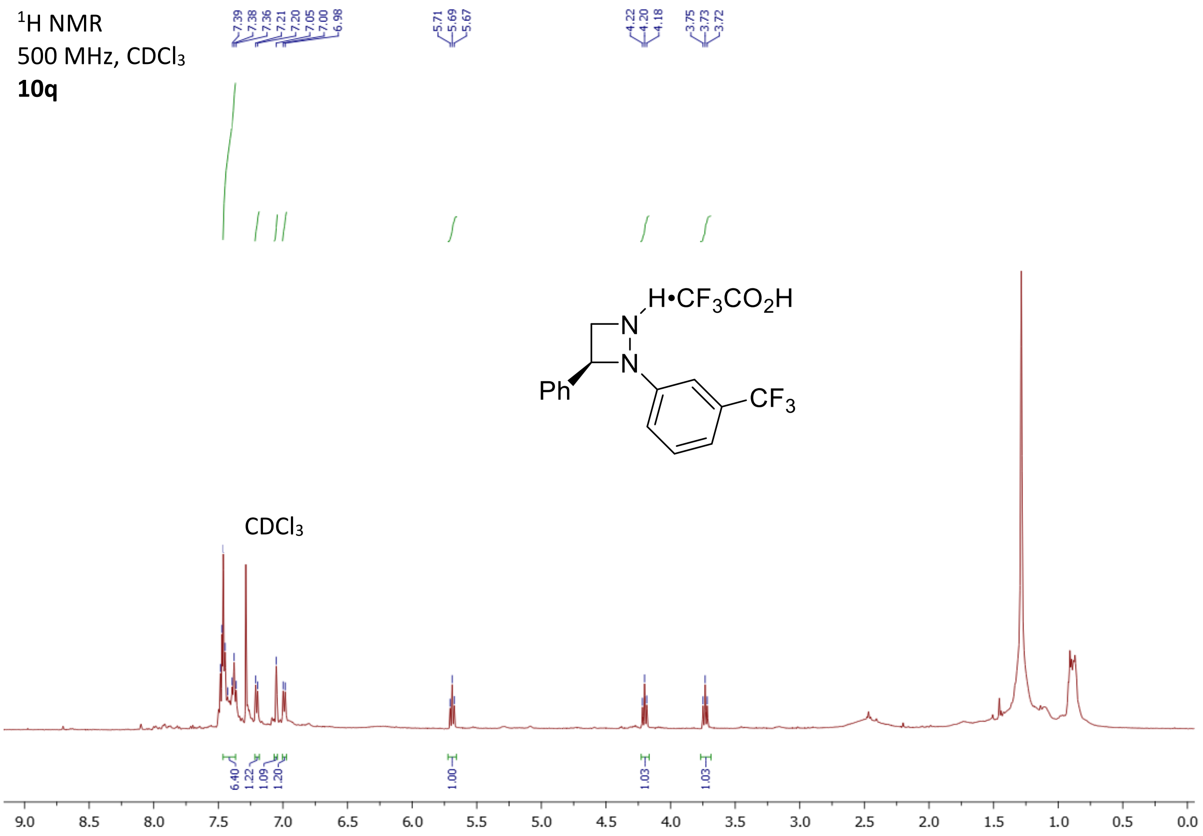
^{1}H NMR
500 MHz, $CDCl_3$
9q



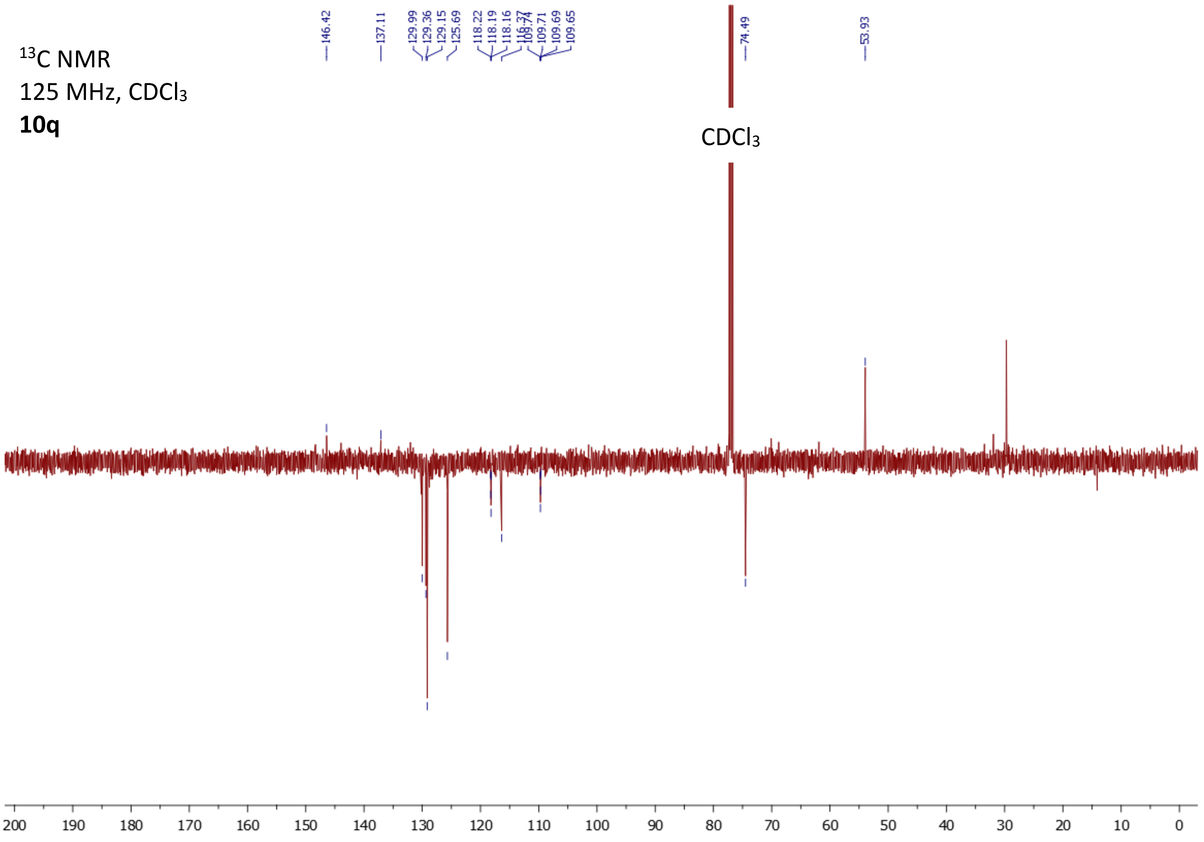
^{13}C NMR
125 MHz, $CDCl_3$
9q



^{1}H NMR
500 MHz, $CDCl_3$
10q



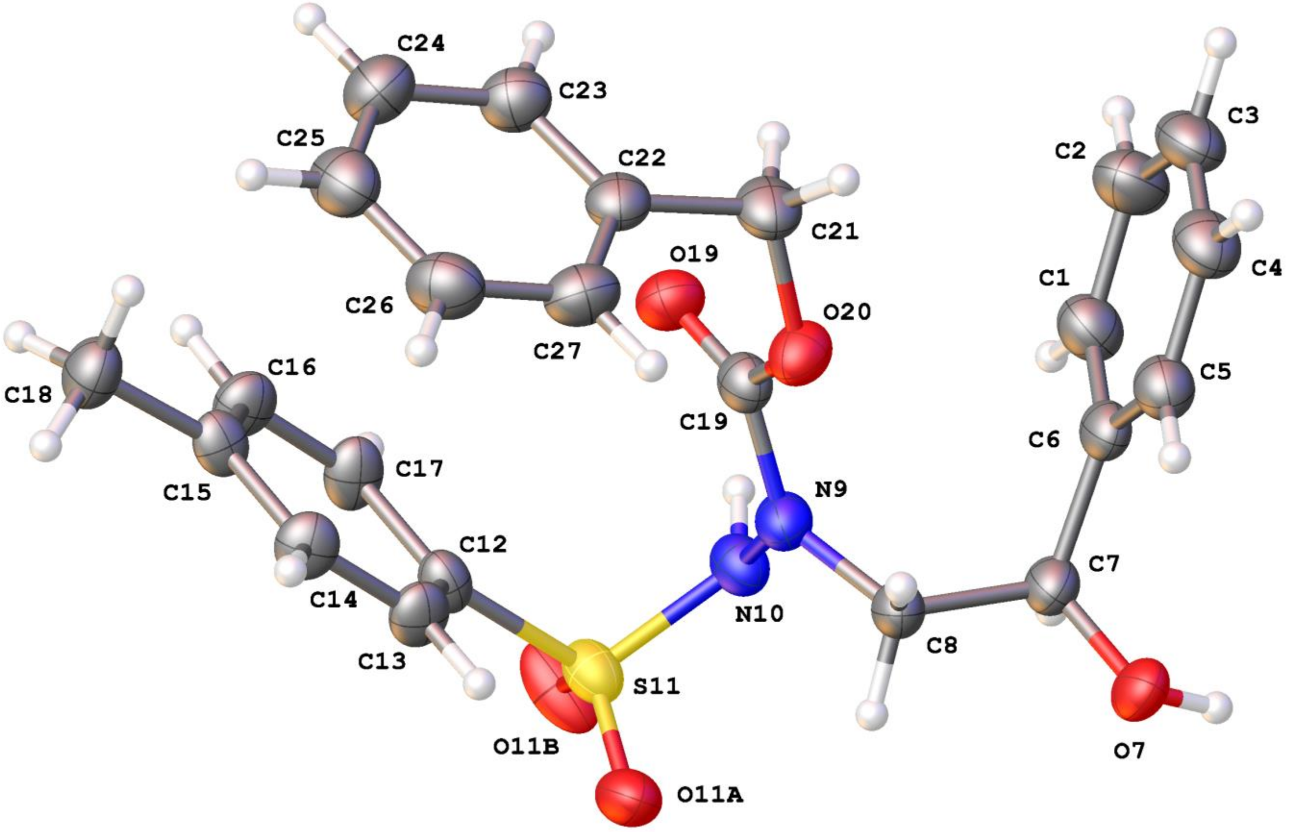
^{13}C NMR
125 MHz, $CDCl_3$
10q



Depiction of Single Crystal X-ray structures of 6a, 8d, 8h, 9i, 9m, 10a, 10b, 10l and 10o

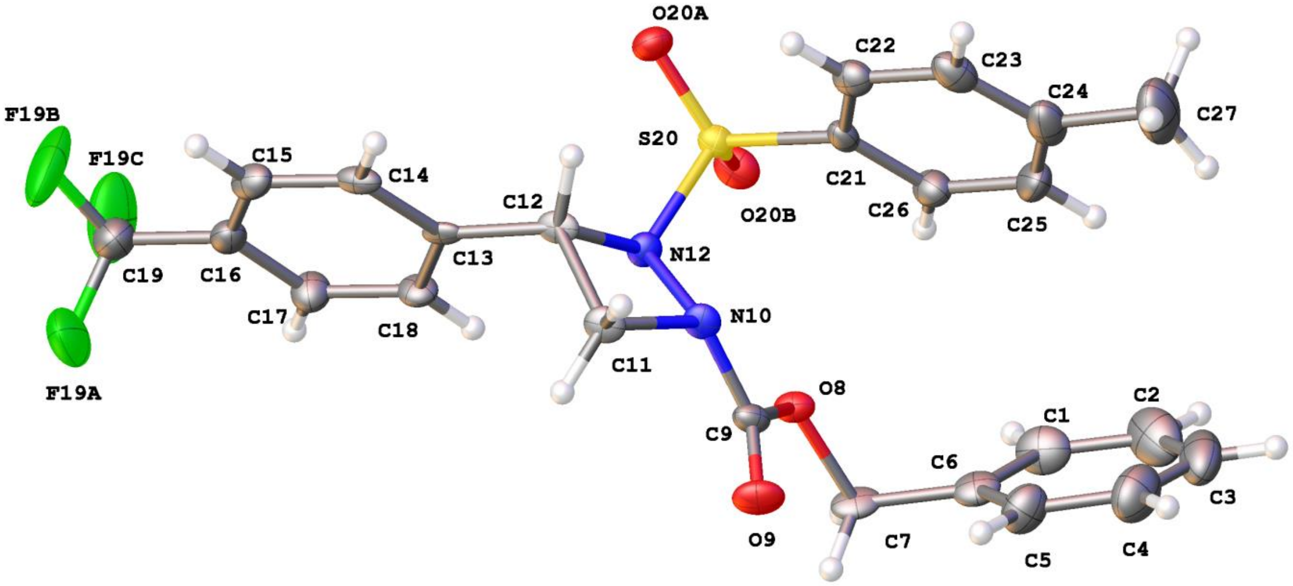
Single Crystal X-Ray Structure of 6a. Single crystals of $C_{23}H_{24}N_2O_5S$ were grown from a 9:1 mixture of hexane and isopropyl alcohol. A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Crystal Data for $C_{23}H_{24}N_2O_5S$ (M = 440.50 g/mol): orthorhombic, space group $P2_12_12$ (no. 18), a = 30.4605(6) Å, b = 11.6596(2) Å, c = 6.11590(10) Å, V = 2172.11(7) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 1.643 mm^{-1}, *Dcalc* = 1.347 g/cm^3, 21406 reflections measured (5.802° ≤ 2Θ ≤ 146.864°), 4351 unique (R_{int} = 0.0524, R_{sigma} = 0.0377) which were used in all calculations. The final R_1 was 0.0362 ($I > 2\sigma(I)$) and wR_2 was 0.0904 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944266.

Flack x: 0.004(13) Shelx2018, Hooft y: 0.005(10) Olex2. Both the Flack parameter and associated Hooft y parameter are small, so confidence in the handedness of the chiral centre is high.



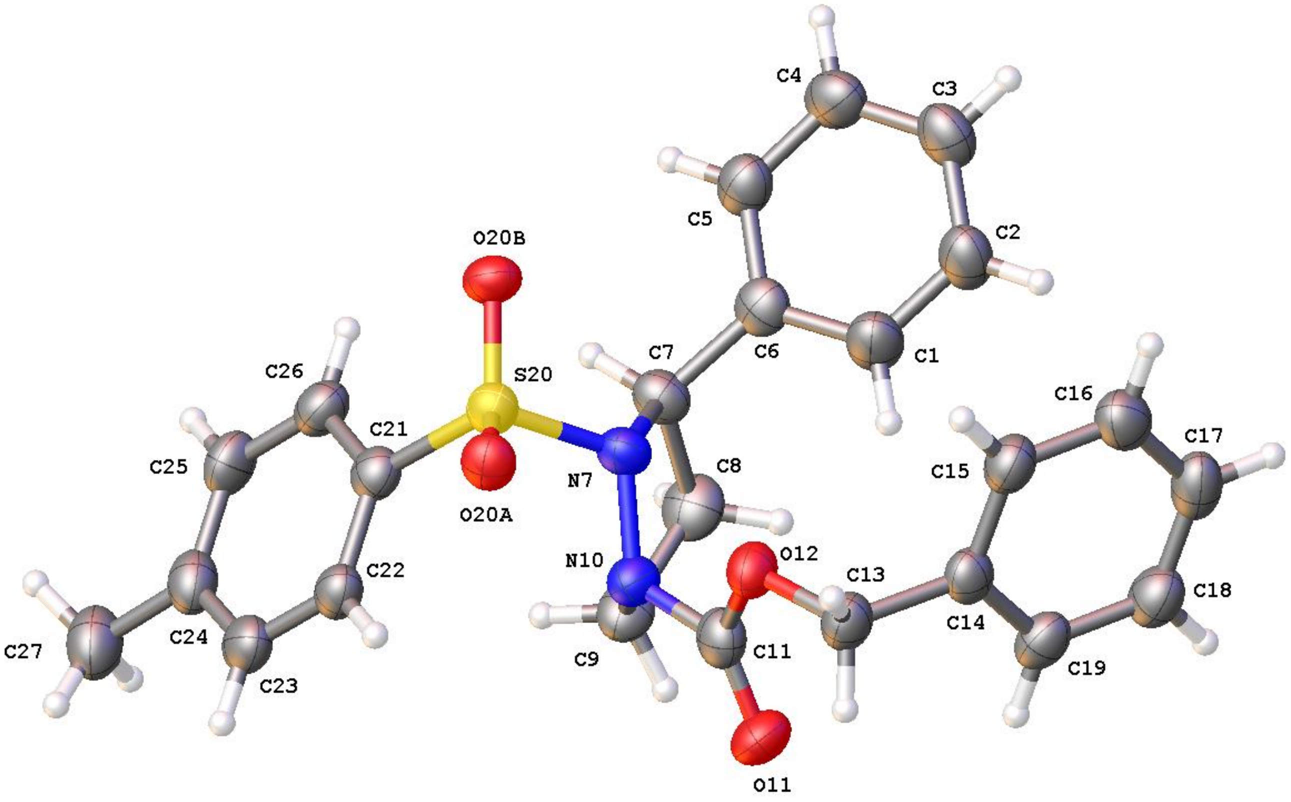
Single Crystal X-Ray Structure of 8d. Single crystals of $C_{24}H_{21}F_3N_2O_4S$ were grown from a 9:1 ratio of hexane and isopropyl alcohol. A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Crystal Data for $C_{24}H_{21}F_3N_2O_4S$ (M = 490.49 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 32.8358(3) Å, b = 11.60538(10) Å, c = 5.85758(7) Å, V = 2232.16(4) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 1.827 mm^{-1}, *Dcalc* = 1.460 g/cm^3, 72297 reflections measured (8.08° ≤ 2Θ ≤ 147.05°), 4499 unique (R_{int} = 0.0917, R_{sigma} = 0.0256) which were used in all calculations. The final R_1 was 0.0616 (I > 2σ(I)) and wR_2 was 0.1478 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944267.

Flack x: 0.015(9) Shelx2018, Hooft y: 0.009(5) Olex2. Both the Flack parameter and associated Hooft y parameter are small, so confidence in the handedness of the chiral centre is high.



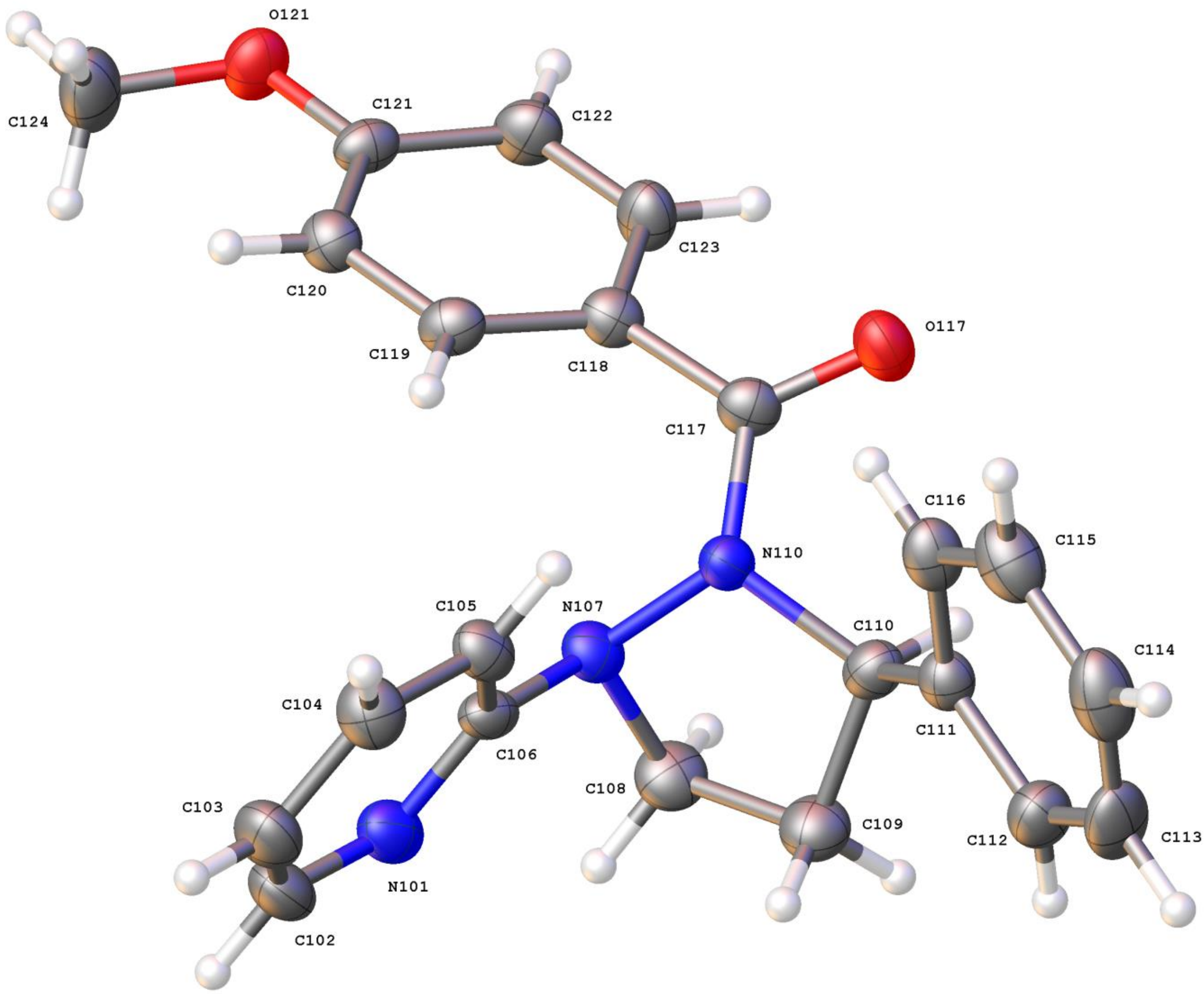
Single Crystal X-Ray Structure of 8h. Single crystals of $C_{24}H_{24}N_2O_4S$ were grown from a 9:1 mix of hexane and isopropyl alcohol. A suitable crystal was selected and mounted on a Mitegen loop with Fomblin oil and placed on a Rigaku 007HF equipped with Varimax confocal mirrors and an AFC11 goniometer and HyPix 6000 detector. The crystal was kept at 100(2) K during data collection. Crystal Data for $C_{24}H_{24}N_2O_4S$ (M = 436.51 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 6.0985(4) Å, b = 11.5023(5) Å, c = 30.8387(15) Å, V = 2163.2(2) Å3, Z = 4, T = 100(2) K, μ(CuKα) = 1.610 mm^{-1}, *Dcalc* = 1.340 g/cm^3, 17168 reflections measured (5.732° ≤ 2Θ ≤ 136.448°), 3915 unique (R_{int} = 0.1033, R_{sigma} = 0.0835) which were used in all calculations. The final R_1 was 0.0624 (I > 2σ(I)) and wR_2 was 0.1773 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944268.

Flack x: -0.03(3) Shelx2018, Hooft y: -0.05(2) Olex2. Both the Flack parameter and associated Hooft y parameter are small, so confidence in the handedness of the chiral centre is high.



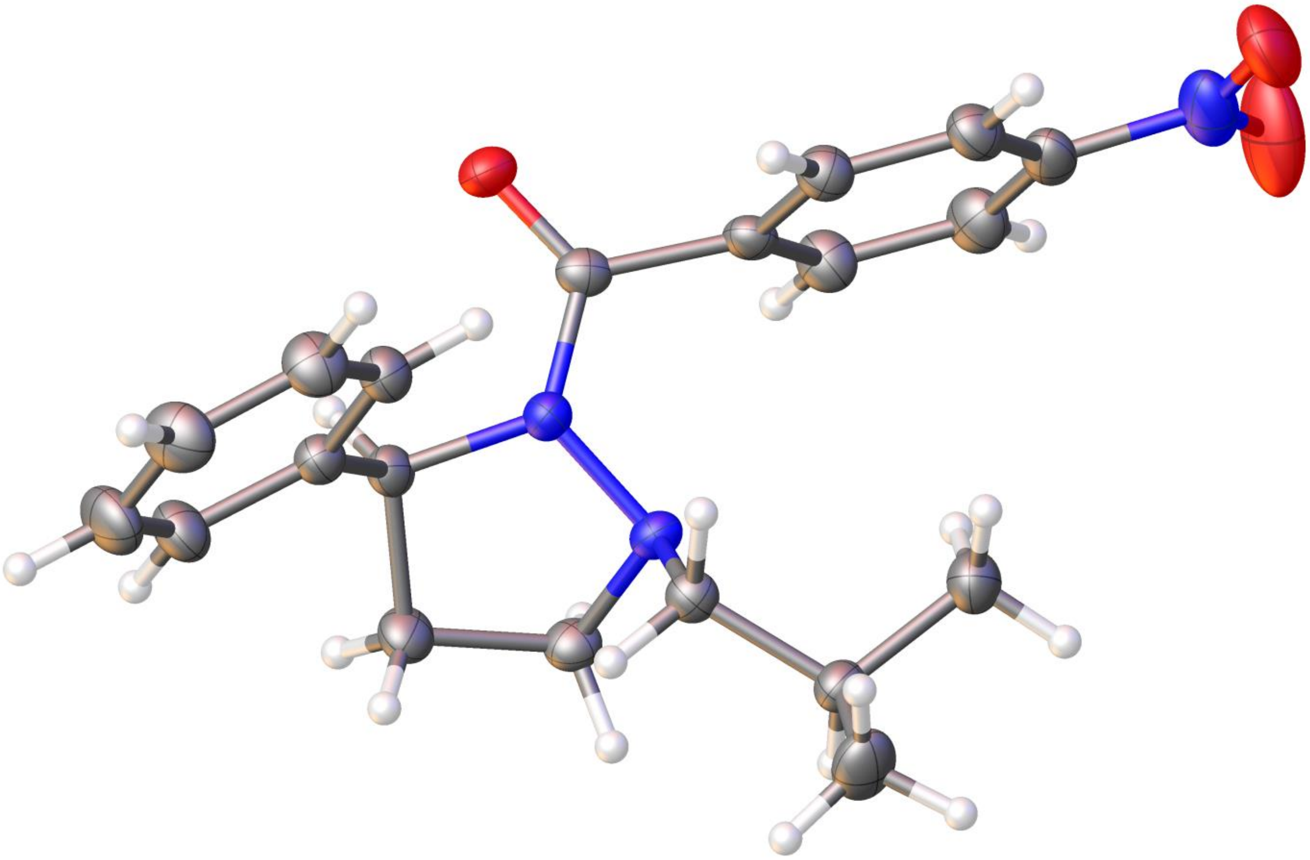
Single Crystal X-Ray Structure of 10a. Single crystals of $C_{44}H_{42.5}N_6O_{4.25}$ were grown from a 9:1 mix of hexane and isopropanol. A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Crystal Data for $C_{44}H_{42.5}N_6O_{4.25}$ (M =723.34 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 10.18405(5) Å, b = 9.71457(5) Å, c = 18.82762(9) Å, β = 93.0169(4)°, V = 1860.102(16) Å3, Z = 2, T = 150(2) K, μ(CuKα) = 0.679 mm^{-1}, *Dcalc* = 1.291 g/cm^3, 35330 reflections measured (8.694° ≤ 2Θ ≤ 147.052°), 7385 unique (R_{int} = 0.0176, R_{sigma} = 0.0104) which were used in all calculations. The final R_1 was 0.0257 (I > 2σ(I)) and wR_2 was 0.0682 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944269.

Flack x: -0.05(3) Shelx2018, Hooft y: -0.045(2) Olex2. Both the Flack parameter and associated Hooft y parameter are realtively small for a structure with no heavy atoms, so confidence in the handedness of the chiral centre is high.



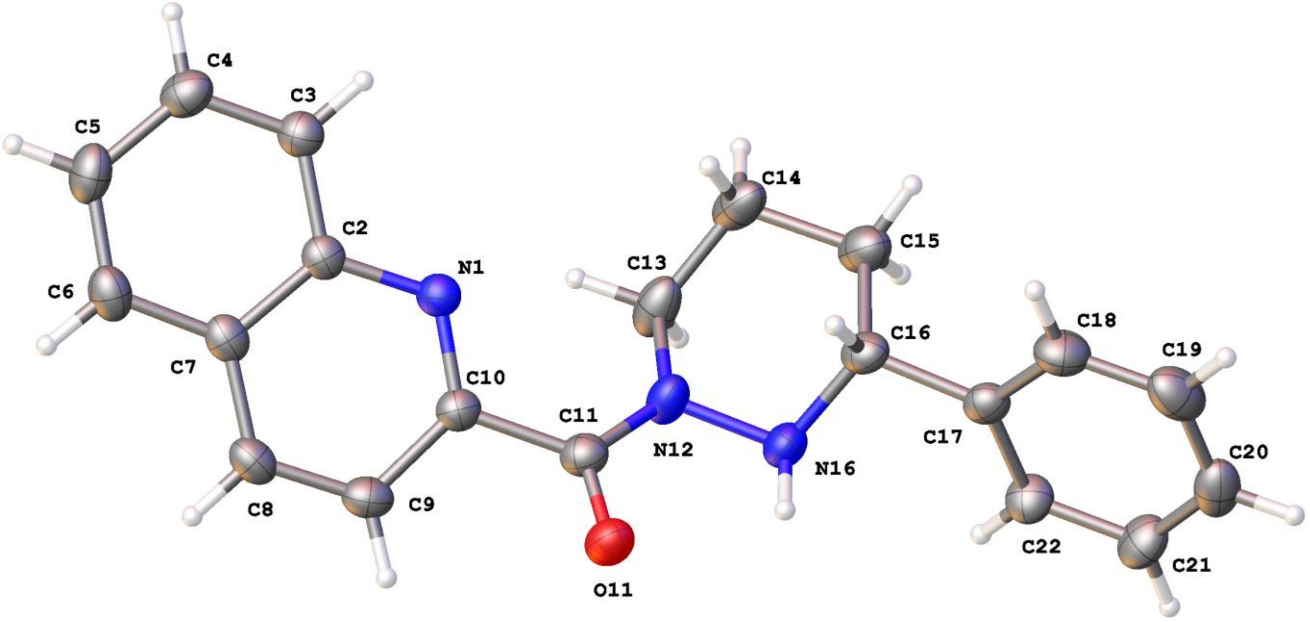
Single Crystal X-Ray Structure of rac-10b. Single crystals of $C_{20}H_{23}N_3O_3$ were grown from 9:1 hexane and isopropanol. A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation. Crystal Data for $C_{20}H_{23}N_3O_3$ (M =353.41 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.19100(10) Å, b = 13.50450(10) Å, c = 18.6644(2) Å, V = 1812.52(3) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 0.716 mm^{-1}, $Dcalc$ = 1.295 g/cm^3, 10496 reflections measured ($8.082° \leq 2\Theta \leq 147.174°$), 3514 unique ($R_{int}$ = 0.0227, R_{sigma} = 0.0229) which were used in all calculations. The final R_1 was 0.0325 ($I > 2\sigma(I)$) and wR_2 was 0.1083 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944270.

As the crystal was grown from a racemate the Flack parameter was not determined.



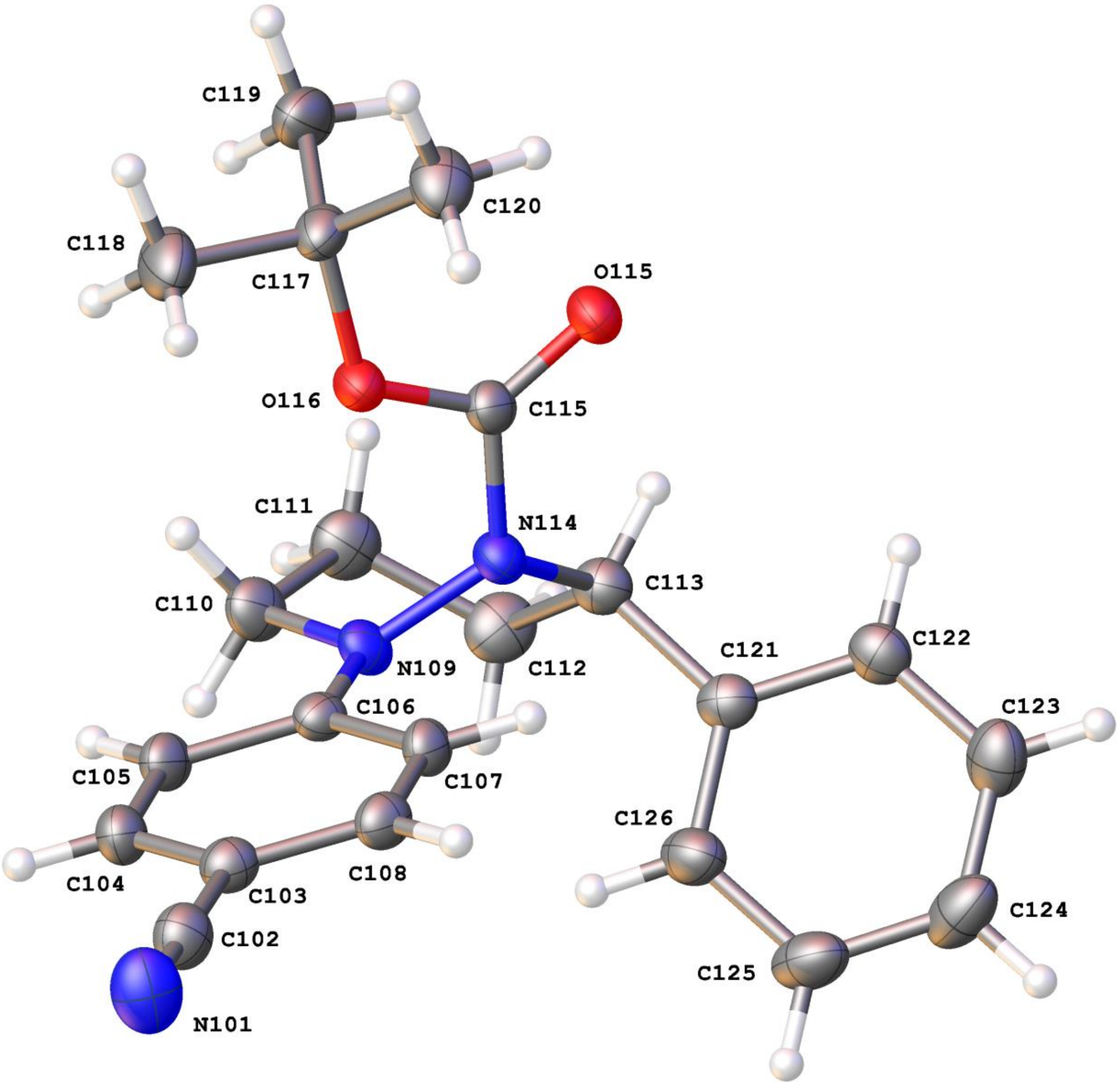
Single crystal X-Ray structure of 10l. Single crystals of $C_{20}H_{19}N_3O$ were grown from ethyl acetate. A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Crystal Data for $C_{20}H_{19}N_3O$ (M =317.38 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 10.10659(11) Å, b = 5.94958(5) Å, c = 13.62038(10) Å, β = 99.5974(8)°, V = 807.530(13) Å^3, Z = 2, T = 150.00(10) K, μ(CuKα) = 0.652 mm^{-1}, $Dcalc$ = 1.305 g/cm^3, 15974 reflections measured (6.582° ≤ 2Θ ≤ 147.044°), 3240 unique (R_{int} = 0.0310, R_{sigma} = 0.0200) which were used in all calculations. The final R_1 was 0.0274 (I > 2σ(I)) and wR_2 was 0.0705 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944272.

Flack x: -0.00(8) Shelx2018, Hooft y: -0.04(8) Olex2. Both the Flack parameter and associated Hooft y parameter are small, so confidence in the handedness of the chiral centre is high.



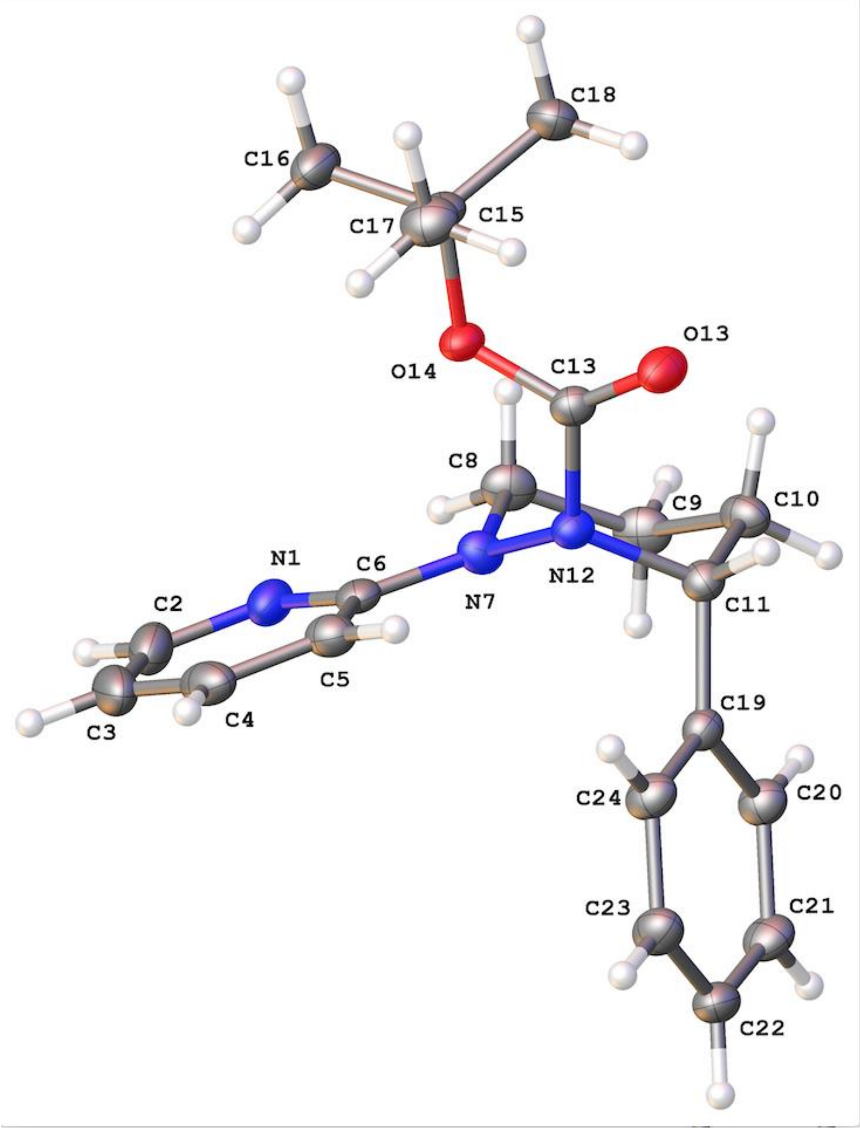
Single crystal X-Ray structure of 9m. Single crystals of $C_{22}H_{25}N_3O_2$ were grown from chloroform. A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation. Crystal data for $C_{22}H_{25}N_3O_2$ (M =363.45 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 12.47130(5) Å, b = 9.02632(4) Å, c = 17.84198(7) Å, β = 92.8702(4)°, V = 2005.951(14) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 0.622 mm^{-1}, $Dcalc$ = 1.203 g/cm^3, 60499 reflections measured (7.096° ≤ 2Θ ≤ 147.262°), 8067 unique (R_{int} = 0.0352, R_{sigma} = 0.0200) which were used in all calculations. The final R_1 was 0.0280 (I > 2σ(I)) and wR_2 was 0.0743 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944271.

Flack x: -0.01(6) Shelx2018, Hooft y: -0.01(3) Olex2. Both the Flack parameter and associated Hooft y parameter are small, so confidence in the handedness of the chiral centre is high.



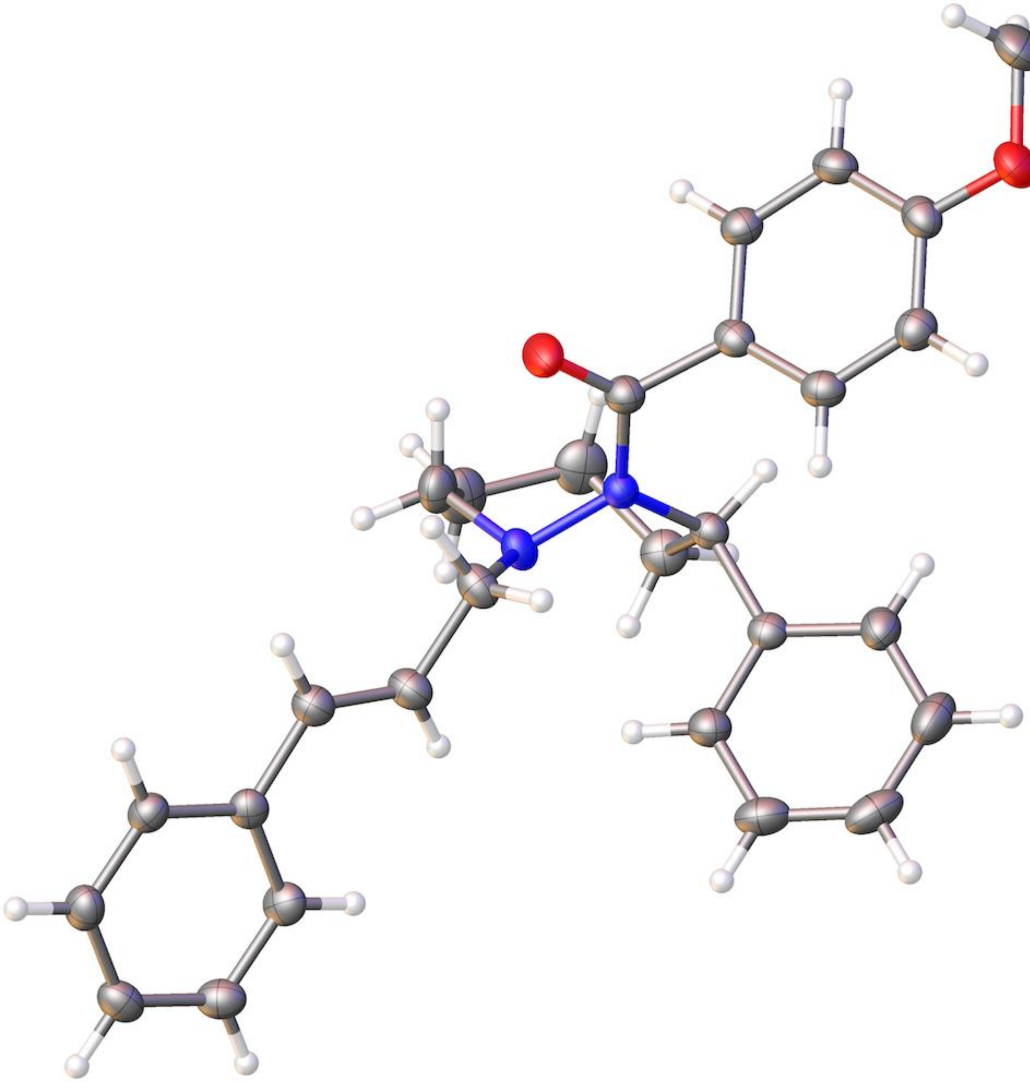
Single crystal X-Ray structure of rac-9i. Single crystals of $C_{20}H_{25}N_3O_2$ were grown from chloroform. A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation. Crystal data for $C_{20}H_{25}N_3O_2$ (M =339.43 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 6.81180(10) Å, b = 17.54950(10) Å, c = 15.11130(10) Å, β = 91.4270(10)°, V = 1805.90(3) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 0.652 mm^{-1}, $Dcalc$ = 1.248 g/cm^3, 15714 reflections measured (7.722° ≤ 2Θ ≤ 147.218°), 3594 unique (R_{int} = 0.0208, R_{sigma} = 0.0152) which were used in all calculations. The final R_1 was 0.0330 ($I > 2\sigma(I)$) and wR_2 was 0.0846 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944273.

As the crystal was grown from a racemate the Flack parameter was not determined.



Single crystal X-Ray structure of 10o. Single crystals of $C_{28}H_{30}N_2O_2$ were grown from MeOH. A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL [3] refinement package using Least Squares minimisation. Crystal Data for $C_{28}H_{30}N_2O_2$ (M =426.54 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 8.33247(2) Å, b = 15.71709(6) Å, c = 17.93381(5) Å, V = 2348.651(13) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 0.595 mm^{-1}, $Dcalc$ = 1.206 g/cm^3, 70707 reflections measured (7.48° ≤ 2Θ ≤ 147.328°), 4736 unique (R_{int} = 0.0275, R_{sigma} = 0.0106) which were used in all calculations. The final R_1 was 0.0277 (I > 2σ(I)) and wR_2 was 0.0705 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1955341.

Flack x: 0.01(3) Shelx2018, Hooft y: 0.02(3) Olex2. Both the Flack parameter and associated Hooft y parameter are small, so confidence in the handedness of the chiral centre is high.



LLAMA, NOESY and VT NMR Data

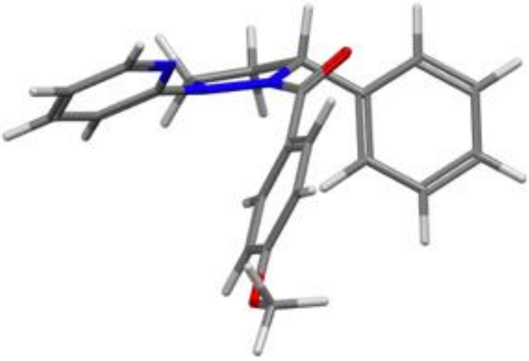
LLAMA Data – for PMI Plot

LLAMA (Lead Likeness And Molecular Analysis – see https://llama.leeds.ac.uk/ for more information[12]) was used to generate the PMI plot. The structures **10a-q** were uploaded to a new database, which then automatically analysed their molecular shape. This tool randomly selects a number of 3D-conformers for each molecule, minimises their energy and selects the lowest-energy one (see page **S224-S226**). LLAMA then calculates the moments of inertia in the x, y and z axes. The PMI I1 coordinates are calculated by dividing inertia(x) by inertia(z). The I2 coordinates are calculated by dividing inertia(y) by inertia(z). The raw data was exported as a csv file and then processed using Microsoft Excel to give the following data table:

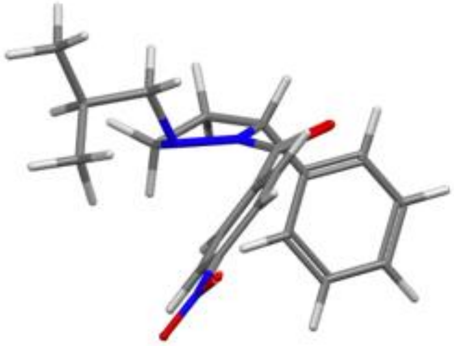
Compound	**PMI x (I1)**	**PMI y (I2)**
10a	0.44197	0.71524
10b	0.38056	0.78138
10c	0.51087	0.93768
10d	0.51368	0.78822
10e	0.40762	0.76545
10f	0.14534	0.94549
10g	0.27492	0.87452
10h	0.14647	0.98991
10i	0.46902	0.83825
10j	0.34134	0.94557
10k	0.42656	0.79292
10l	0.16026	0.95099
10m	0.29528	0.87679
10n	0.3883	0.87605
10o	0.25736	0.8502
10p	0.64152	0.74401
10q	0.35298	0.776
Average	0.363	0.855

This raw data was then used to generate a scatter plot (**Figure 5** in main paper).

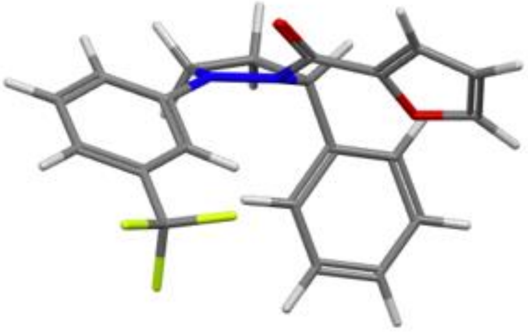
LLAMA Structures for 10a-q



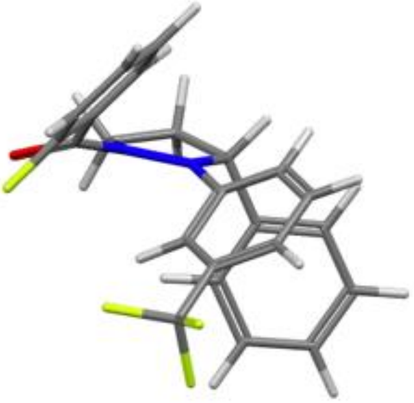
10a



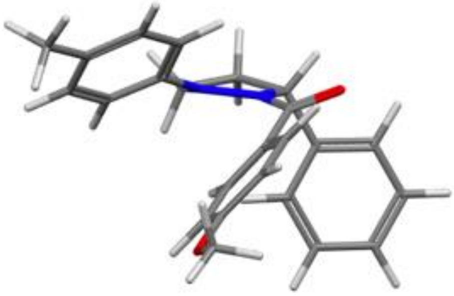
10b



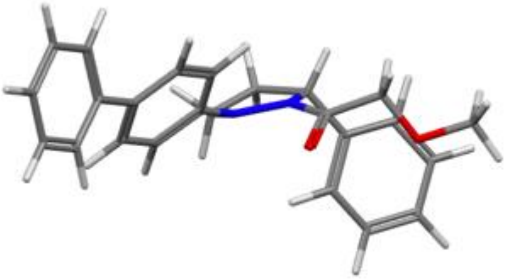
10c



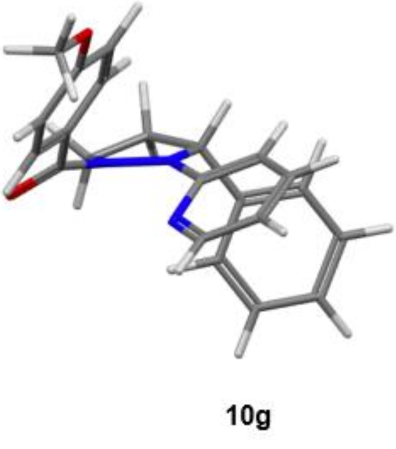
10d



10e



10f



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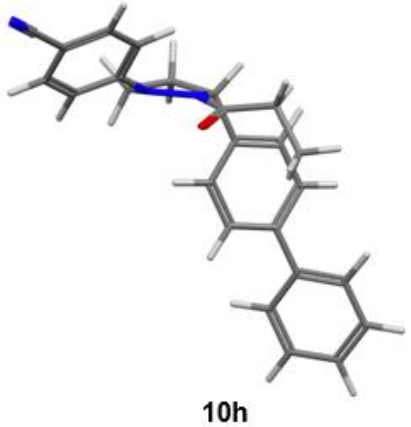

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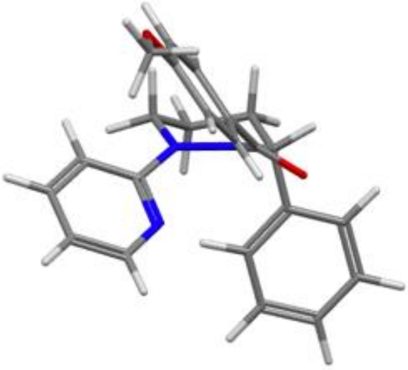

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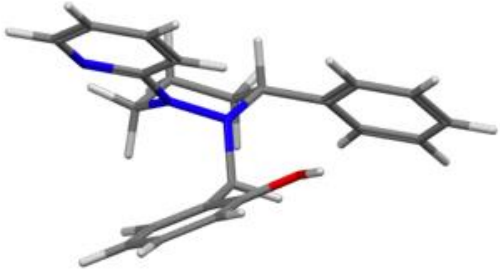
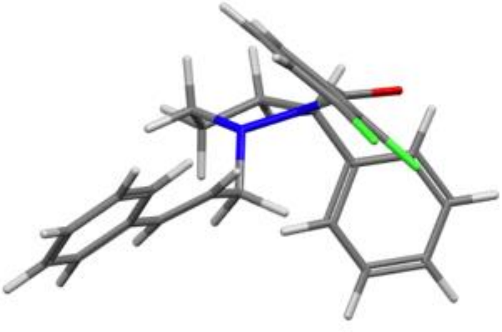
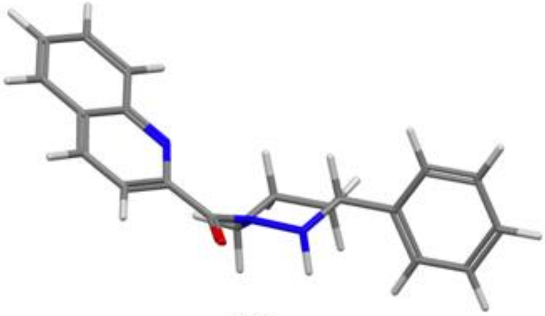


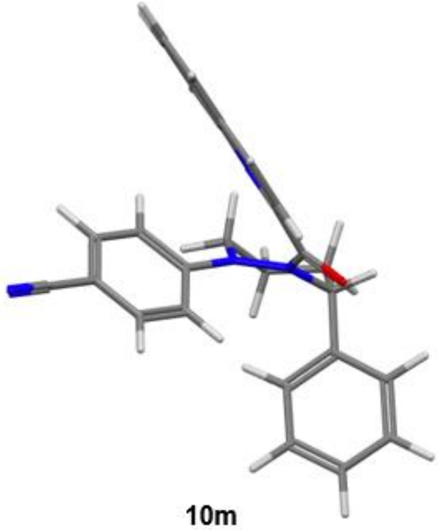
10j



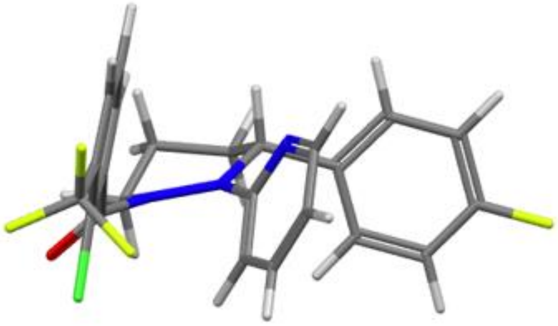
10k



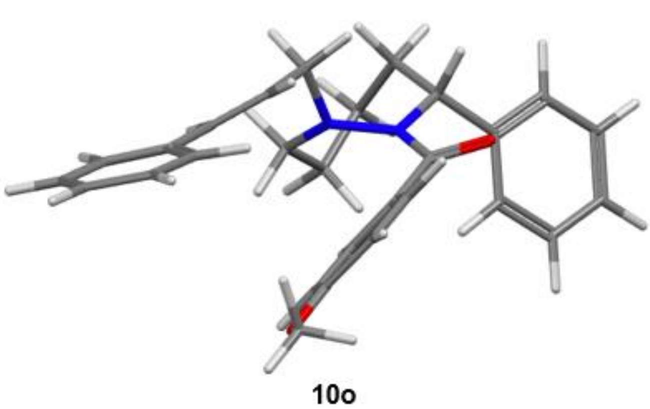
10l



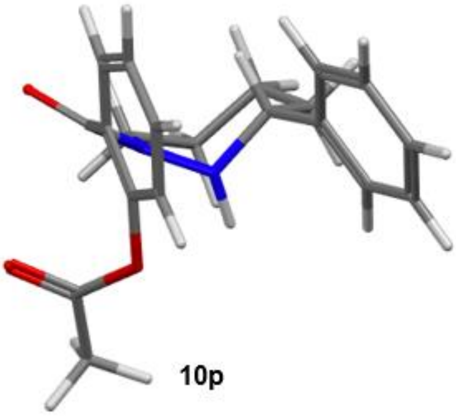
10m



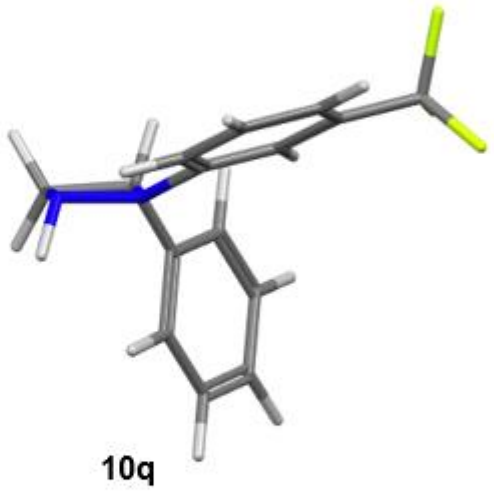
10n



10o



10p



10q

Analysis of 10b by NOESY to Determine Solution State Configuration

10b was chosen for analysis by NOESY as a solid-state structure had already been obtained by X-ray diffraction (see page **S218**). In order to get a suitable NOESY spectrum the compound was first analysed by ^{1}H NMR in order to find a suitable solvent that would resolve the numerous diastereotopic CH_2 protons (labelled as H^{7}, H^{8}, H^{9}, H^{10}, H^{11} and H^{12} – see below). d6-Benzene heated to 343 K on a 600 MHz spectrometer gave a suitable spectrum, which was assigned using a COSY. *N.B.* Complete assignment of diastereotopic protons was done in conjunction with NOESY data.

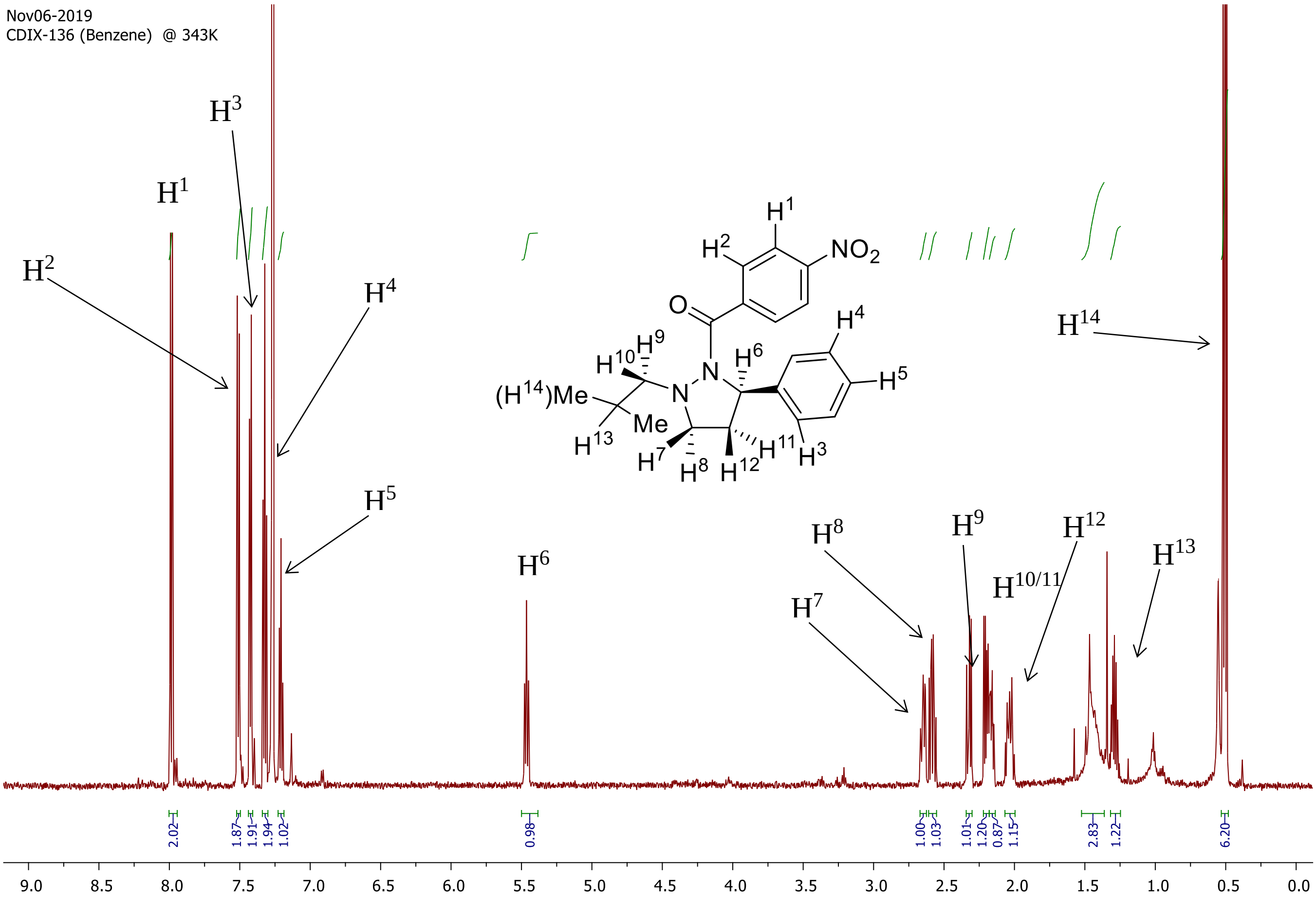


*Figure **S3** 1H NMR spectrum of **10b** in d6-benzene at 343 K*

δ*H* (600 MHz, C_6D_6 at 343 K) 7.99 (2H, d, *J* 8.5, H^{1}), 7.51 (2H, d, *J* 8.4, H^{2}), 7.42 (2H, d, *J* 7.7, H^{3}), 7.32 (2H, t, *J* 7.6, H^{4}), 7.21 (1H, t, *J* 7.3, H^{5}), 5.46 (1H, t, *J* 8.4, H^{6}), 2.67-2.63 (1H, m, H^{7}), 2.58 (1H, td, *J* 11.1, 6.7, H^{8}), 2.32 (1H, dd, *J* 11.8, 7.7, H^{9}), 2.23-2.17 (2H, m, H^{10}, H^{11}), 2.03-1.99 (1H, m, H^{12}), 1.29 (1H, septet, *J* 7.2, H^{13}), 0.51 (6H, dd, *J* 9.0, 6.9, H^{14}).

Analysis of the compound by NOESY showed several important NOE's which would be expected if the compound was in the *anti,anti*-configuration. An NOE between H^{6} and H^{8} confirmed that they are on the same face of the molecule (Figure **S4**, see also Figure **7**). An NOE is also observed between H^{8} and H^{2}, which shows that they are also on the same face. Taken together this gives evidence that H^{6} and H^{8} are on the opposite face of the molecule to the phenyl group, along with the *p*-methoxybenzoyl substituent.

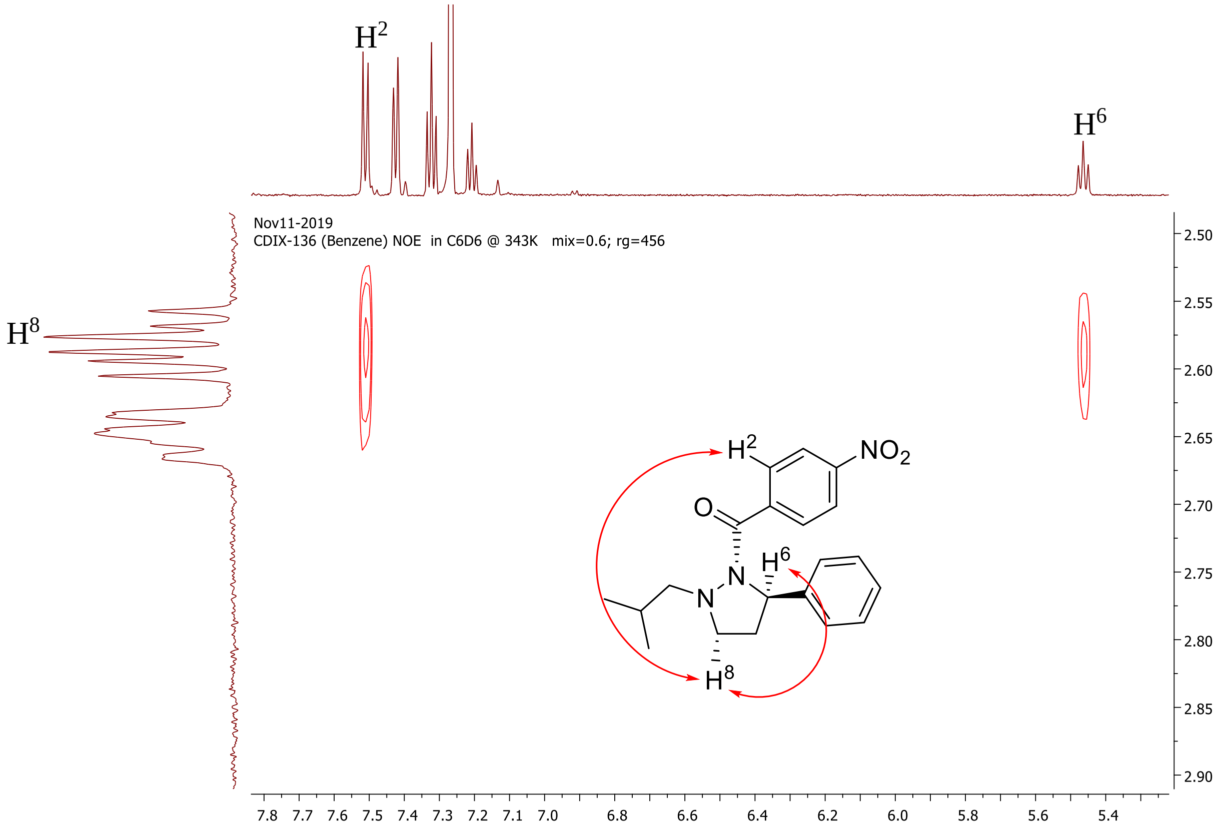


*Figure **S4** NOESY spectrum showing NOE's between H^6 to H^8 and H^8 to H^2*

Evidence for the position of the isobutyl group can also be seen (Figure **S5**, see also Figure **7**). H^3 (of the phenyl group) shows an NOE to H^9 and possibly H^{10}.

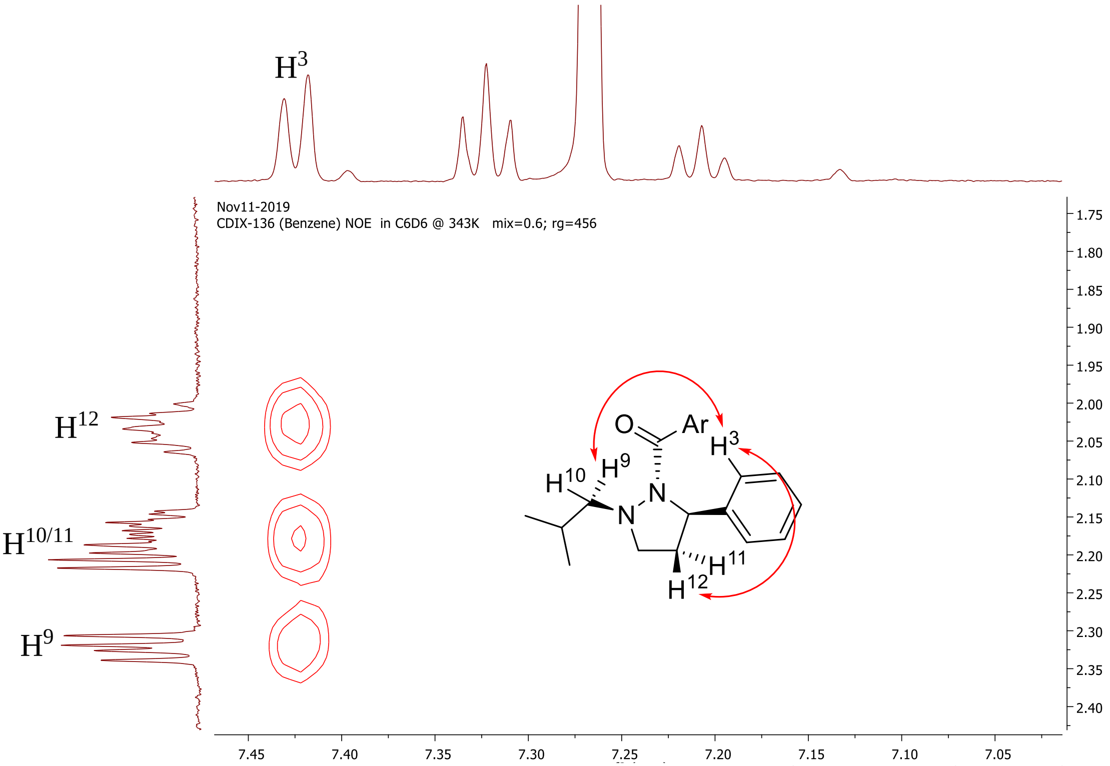


*Figure **S5** NOESY spectrum showing NOE's between H^3 and both H^9 and H^{12}*

H^{13} also shows an NOE to H^7, H^7 also NOE's to H^{12} and H^{10} (Figure **S6**). These are consistent with the assigned configuration

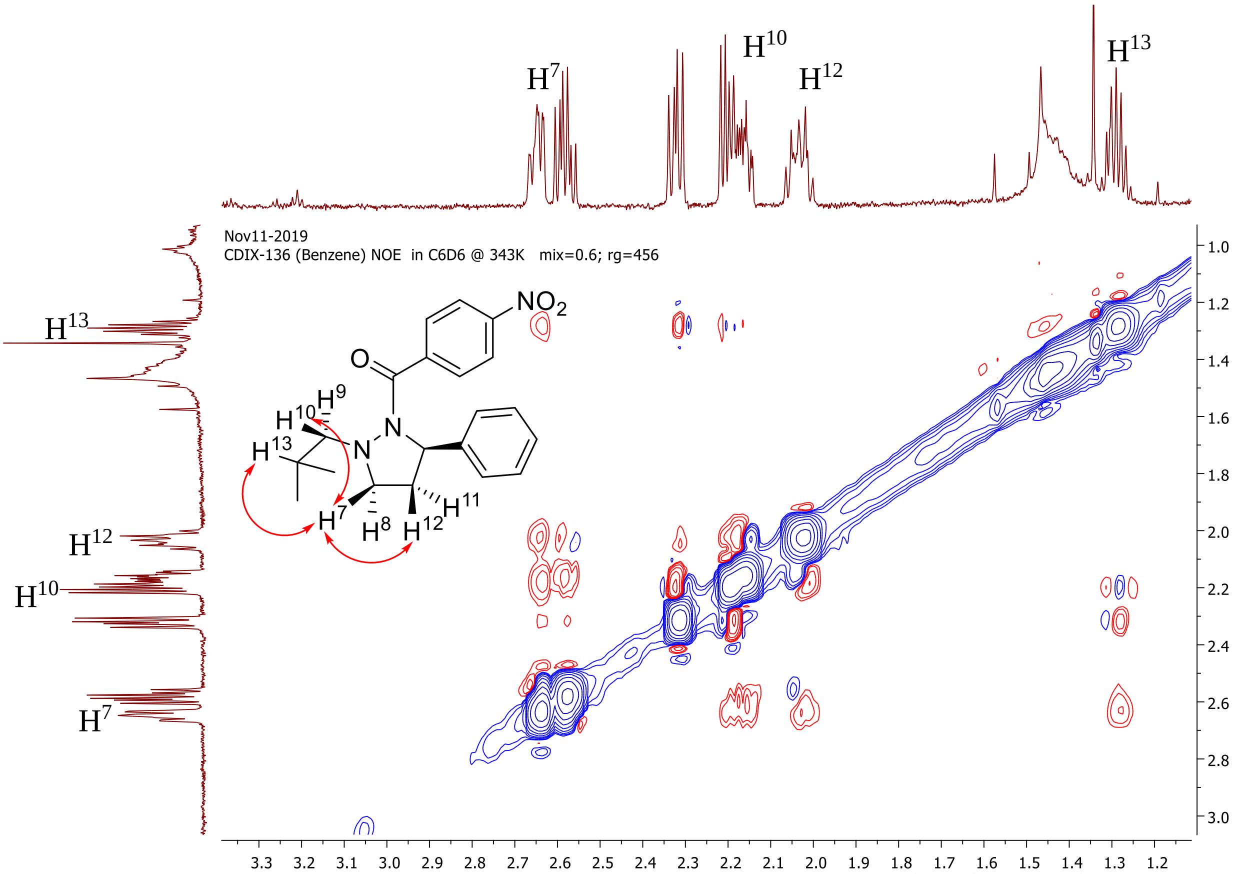


*Figure **S6** NOESY spectrum showing NOE's from H^7 to H^{12}, H^{13} and H^{10}*

Low Temperature Analysis of 10b

Cooling sample to 233 K in both $CDCl_3$ (Figure **S7**) and d6-acetone gave a complex spectrum, which appeared to have one major isomer and two minor isomers in an approximately 84:11:5 ratio.

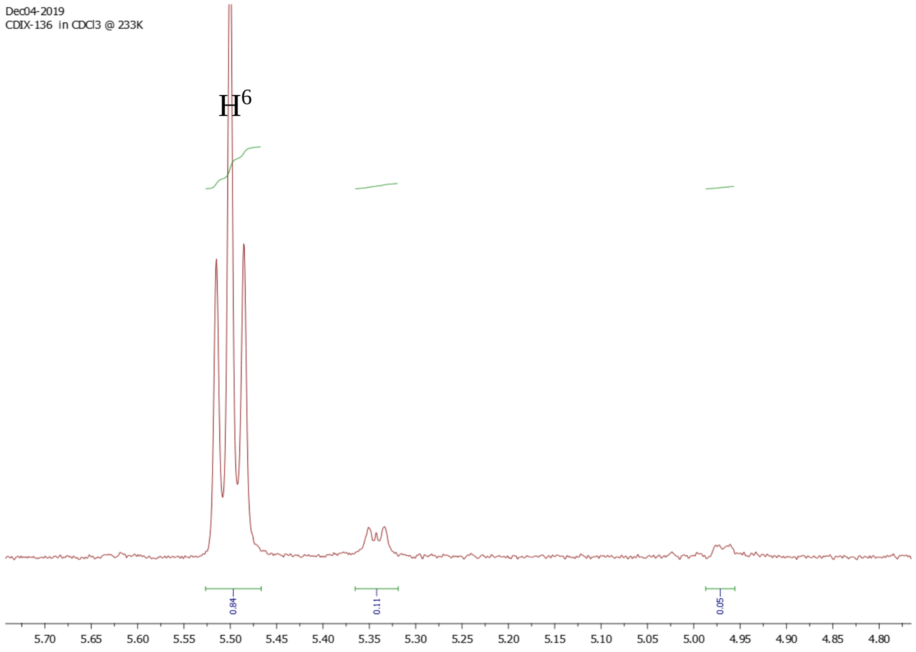


*Figure **S7** ^1H NMR spectrum of **10b** showing the complex mixture of isomers obtained at 233 K (H^6)*

Analysis of 10a by NOESY to Determine Solution State Configuration

10a was chosen for analysis by NOESY as a solid-state structure had already been obtained by X-ray diffraction (see page **S217**). Upon cooling to 233 K in $CDCl_3$ two isomers were observed in an a 56:44 ratio (see figure **S9**). Using the COSY and NOESY spectra, complete assignment of both isomers was completed (Figure **S8** and **S9**).

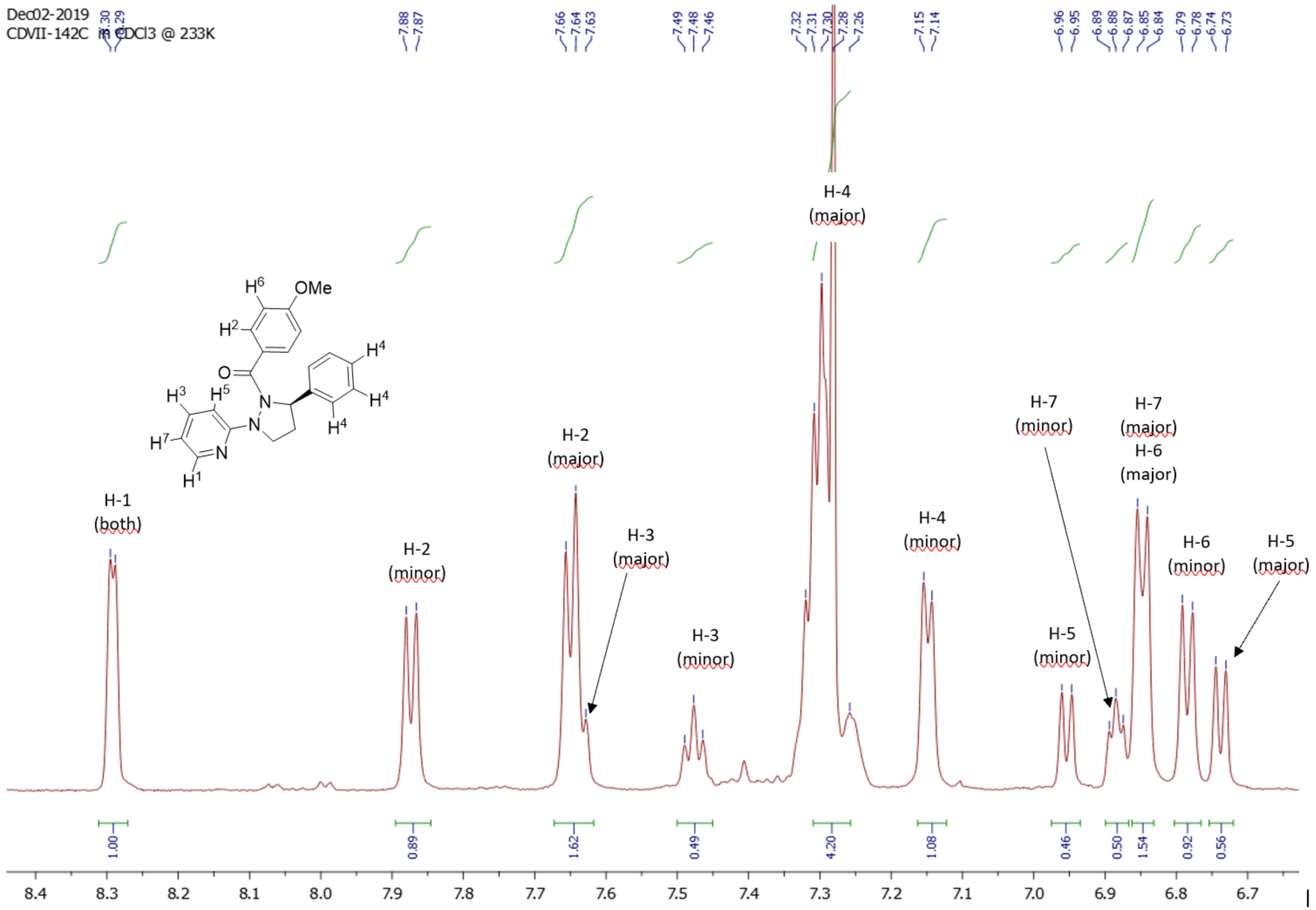


*Figure **S8** ^{1}H NMR spectrum of **10a** in $CDCl_3$ at 233 K (aromatic protons)*

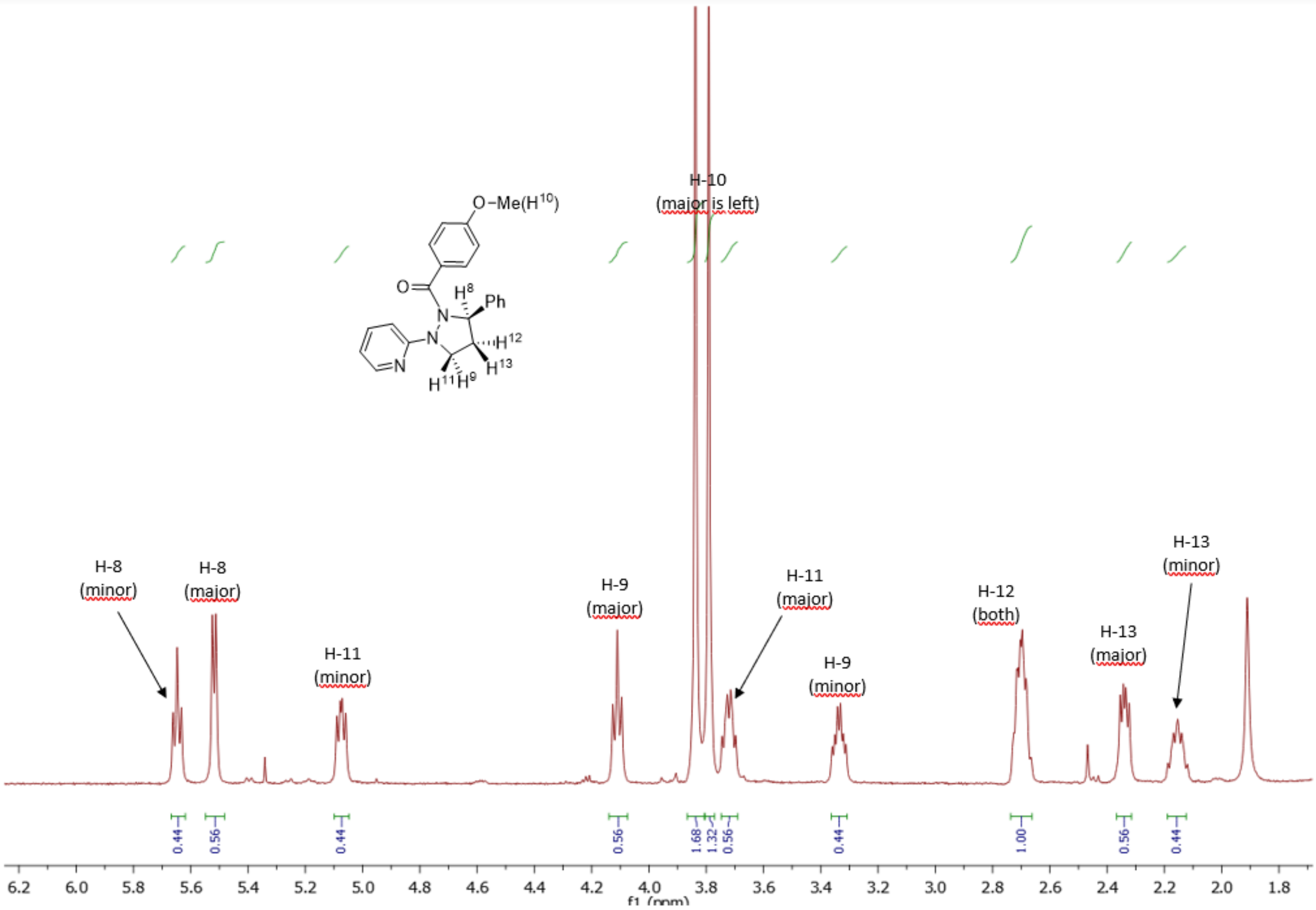


*Figure **S9** ^{1}H NMR of **10a** in CDCl$_3$ at 233 K (aliphatic protons)*

δ*H* (600 MHz, CDCl$_3$ at 233 K) 8.29 (1Hx2, d, *J* 4.0, H^1 both), 7.87 (2H, d, *J* 8.5, H^2 minor), 7.66-7.61 (3H, m, H^2 major and H^3 major), 7.48 (1H, t, *J* 7.7, H^3 minor), 7.31-7.26 (5H, m, H^4 major), 7.15 (5H, d, *J* 6.8, H^4 minor), 6.95 (1H, d, *J* 8.3, H^5 minor), 6.88 (1H, t, J 4.0, H^7 minor), 6.85 (3H, d, *J* 8.4, H^6 major, H^7 major), 6.78 (2H, d, *J* 8.5, H^6 minor), 6.74 (1H, *J* 8.4, H^5 major), 5.64 (1H, t, *J* 8.6, H^8 minor), 5.52 (1H, d, *J* 7.0, H^8 major), 5.07 (1H, dd, *J* 11.1, 7.3, H^{11} minor), 4.11 (1H, t, *J* 9.1, H^9 major), 3.84 (3H, s, H^{10} major), 3.79 (1H, s, H^{10} minor), 3.72 (1H, dd, *J* 17.6, 10.4, H^{11} major), 3.33 (1H, td, *J* 11.5, 5.7, H^9 minor), 2.74-2.65 (1Hx2, m, H^{12} both), 2.34 (1H, dd, *J* 11.9, 6.7, H^{13} major), 2.16 (1H, dd, *J* 18.8, 10.7, H^{13} minor).

Analysis by NOESY was done in CDCl$_3$ at 233 K. Initially a mixing time of 0.6 s was used and this gave a clear NOESY spectrum with a number of cross peaks. However, due to the long mixing time cross peaks were seen between major and minor isomers, suggesting that interconversion between isomers was occuring on this timescale. Reducing the mixing time to 0.3 s showed a clear NOE from H^2 to H^8 in the major isomer (**A**), which was not seen in the corresponding minor isomer (**B**) (Figure **S10**, see also Scheme **2**).

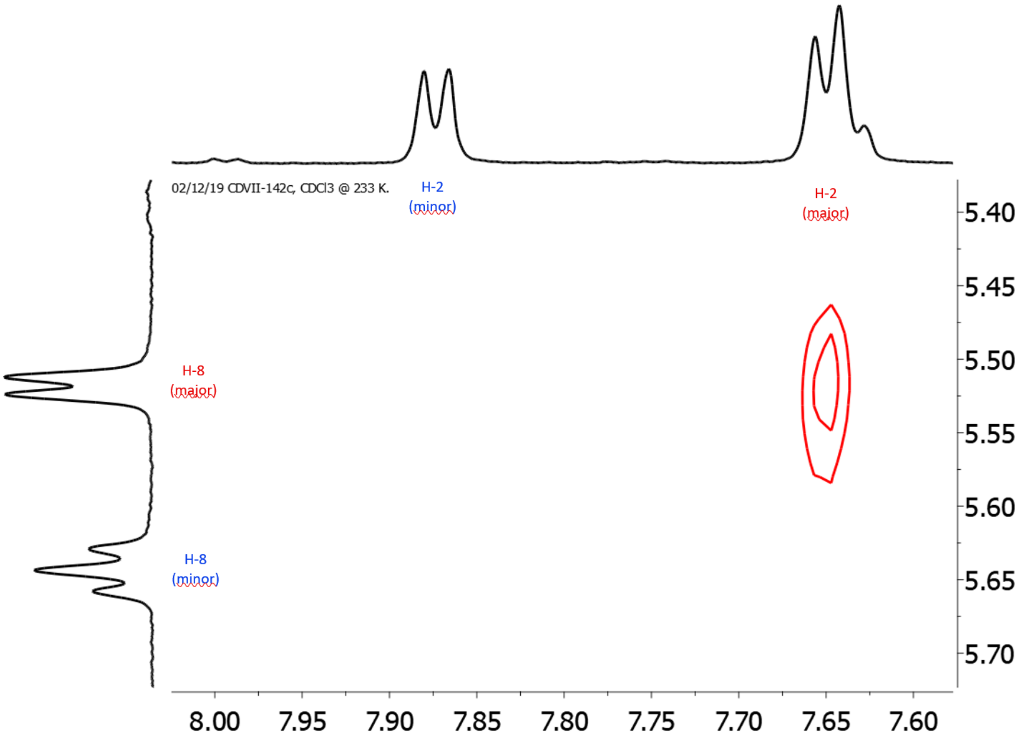


Figure ***S10*** *NOESY (0.3 s mix) of* ***10a*** *showing an NOE between* H^8 *and* H^2 *in the major isomer only*

At the 0.3 s mixing time, no NOE's are seen from the pyridyl substituent and the rest of the molecule. At 0.6 s mixing time there is a weak NOE between H^4 and H^5 suggesting they are on the same face of the molecule (Figure **S11**). However, some caution needs to be applied as the two isomers **A** and **B** are interconverting under the experimental conditions.

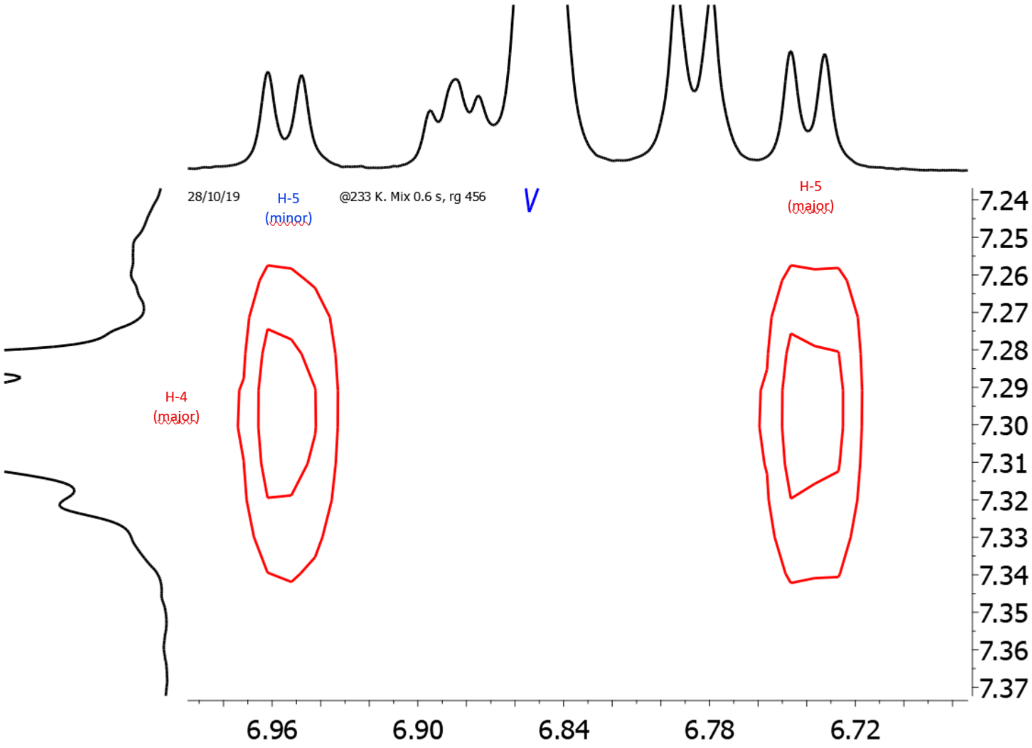


Figure ***S11*** *NOESY (0.6 s mix) spectrum of* ***10a*** *showing an NOE between* H^4 *and both isomers of* H^5

Calculation of Barrier to Inversion for 10a Using VT NMR

The barrier of inversion for **10a** was calculated using H^9. In order to calculate the coalescence temperature (T_c) **10a** was analysed by VT NMR in $CDCl_3$. Spectra were collected from 223 K to 293 K in 10 K increments (Figure **S12**).

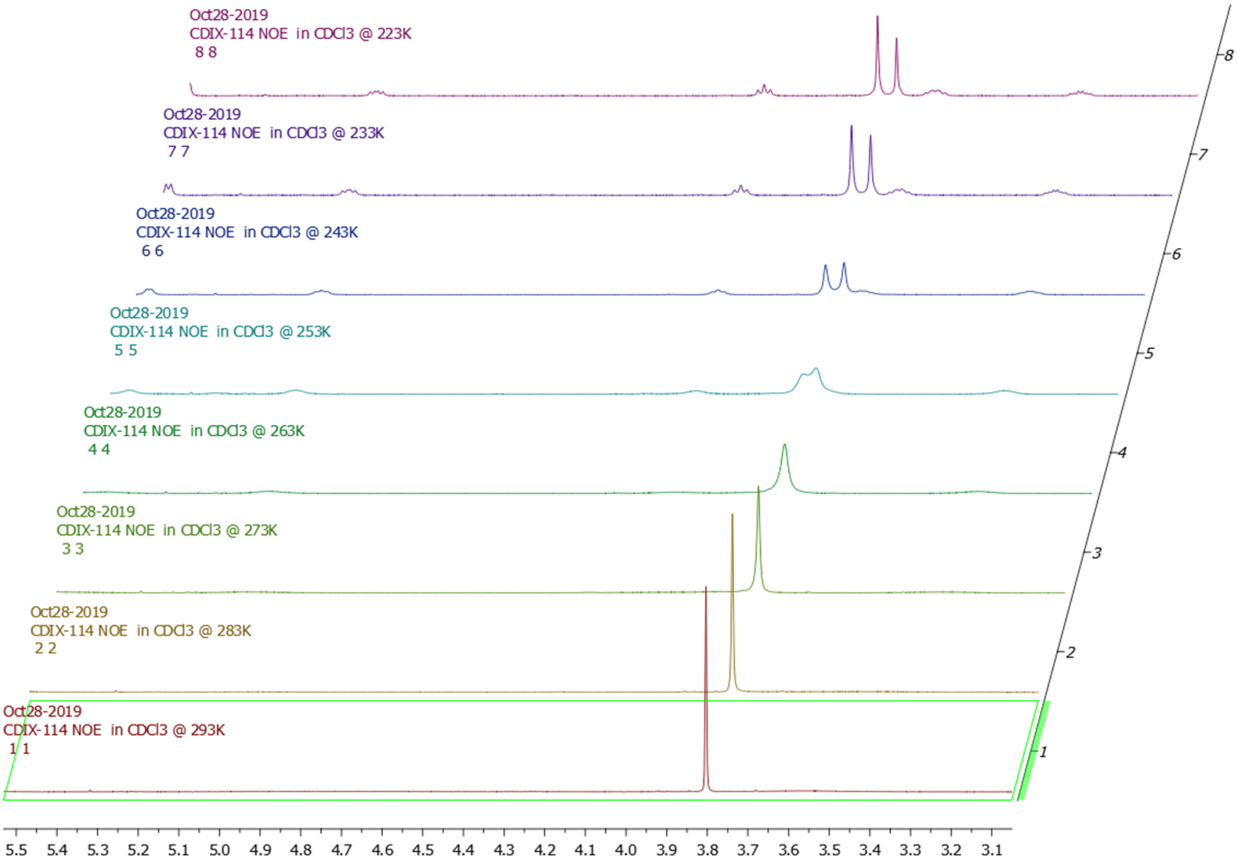


*Figure **S12** VT ^1H NMR analysis of **10a** to show the coalescence of H^9*

From this Tc was estimated to be 258 K, which was used to calulate $\Delta G_A^{\ddagger}$:

The barrier to inversion was calculated using Eyring's equations, modified by Shanan Atidi and Bar-Eli to account for unequal populations of isomers.[13]

$$\Delta G_A^{\ddagger} = RT_C\left[10.62 + \log\frac{X}{2\pi(1-\Delta P)} + \log\frac{T_C}{\Delta\upsilon}\right]$$

R = 4.57 cal mol^{-1} K^{-1}, T_C = 258 K, Δu = 30 Hz (peak difference is 0.05 ppm on a 600 MHz spectrometer), $\log\frac{X}{2\pi(1-\Delta P)} = -0.567$

$$\Delta G_A^{\ddagger} = 12.9\ kcal\ mol^{-1} = 54.1\ kJ\ mol^{-1}$$

References

[1] L. Grehn, B. Nyasse, U. Ragnarsson, *Synthesis* **1997**, 1429–1432.

[2] F. J.-J. Bihel, M. Hellal, J.-J. Bourgignon, *Synthesis* **2007**, 3791–3796.

[3] L. Grehn, T. Pehk, U. Ragnarsson, *Tetrahedron Lett.* **2014**, *55*, 7019–7022.

[4] F. Yu, J.-N. Zhou, X.-C. Zhang, Y.-Z.Sui, F.-F. Wu, L.-J. Xie, A. S. C. Chan, J. Wu, *Chem. Eur. J.* **2011**, *17*, 14234–14240.

[5] M. Salla, M. S. Butler, R. Pelingon, G. Kaeslin, D. E. Croker, J. C. Reid, J. M. Baek, P. V. Bernhardt, E. M. J. Gillam, M. A. Cooper, A. A. B. Robertson, *ACS Med. Chem. Lett.* **2016**, *7*, 1034–1038.

[6] S. Ortgies, A. Breder, *Org. Lett.* **2015**, *17*, 2748–2751.

[7] C. Gronnier, S. Kramer, Y. Odabachian, F. Gagosz, *J. Am. Chem. Soc.* **2012**, *134*, 828–831.

[8] S. K. Murphy, V. M. Dong, *J. Am. Chem. Soc.* **2013**, *135*, 5553–5556.

[9] J. S. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.

[10] F. S. Davis, L. Huang, L. Bauer, *J. Heterocyclic Chem.* **1995**, *32*, 915–920.

[11] D. Wang, J. Mao, C. Zhu, *Chem. Sci.* **2018**, *9*, 5205–5809.

[12] I. Colomer, C. J. Empson, P. Craven, Z. Owen, R. G. Doveston, I. Churcher, S. P. Marsden, A. Nelson, *Chem. Commun.*, **2016**, *52*, 7209-7212.

[13] H. Shanan-Atidi, K. H. Bar-Eli, *J. Phys. Chem.* **1970**, *74*, 961-963.