Supporting Information

For

Amine Protection/α-Activation with the *tert*-Butoxythiocarbonyl Group: Application to Azetidine Lithiation–Electrophilic Substitution

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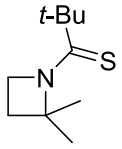
1. General Details

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of nitrogen or argon. CH_2Cl_2, toluene, pentane, THF and Et_2O were degassed and dried over activated alumina under nitrogen.[1] TMEDA was distilled over CaH_2; MeI and BuI were passed through basic alumina immediately before use; TMSCl was distilled and passed through basic alumina; benzaldehyde, *p*-anisaldehyde and allyl bromide were distilled; 4-chlorobenzaldehyde was recrystallised from Et_2O; acetone was refluxed over CaO and distilled; all other reagents were used as received. *s*-BuLi was titrated on arrival, and periodically thereafter, using 2-propanol solution in toluene with 0.2% 1,10-phenanthroline indicator titration solution for quantitative analysis of BuLi.

Thin layer chromatography (TLC) was carried out on aluminium-backed plates pre-coated with silica (0.2 mm, 60 F254 nm), which were visualized UV light (λmax = 254 nm) and/or developed with basic potassium permanganate solution with heating. Flash column chromatography was carried out on Si-gel (43–63 μm) in the solvents systems indicated, applying head pressure by means of a low pressure nitrogen line (0.1–0.3 atm). Petroleum ether refers to the fraction boiling between 30 °C – 40 °C. Melting points are uncorrected. Infra-red spectra were recorded neat and the intensity of the peaks are reported as s, m, w, br, denoting strong, medium, weak and broad, respectively. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 25 °C in $CDCl_3$ or D_2O. ^{13}C DEPT, COSY and HSQC spectra were used to aid structure assignments. Data are expressed as chemical shifts (δ) in parts per million (ppm) relative to $CDCl_3$ (^{1}H δ 7.27 ppm, ^{13}C δ 77.0 ppm, respectively) or D_2O (^{1}H δ 4.75 ppm) as the internal standard on the δ scale. TMS (^{13}C δ 0.00 ppm) or $CFCl_3$ (^{19}F δ 0.00 ppm) were employed as external references. The multiplicity of each signal is reported as s, d, t, q, quin, br, m, denoting singlet, doublet, triplet, quartet, quintet, broad, and multiplet, respectively. Proton coupling constants *J* are reported to the nearest 0.1 Hz. Discernible NMR signals for minor rotamers or diastereomers are indicated in parentheses. High resolution mass spectra were obtained by field ionization (FI), or by electrospray ionization (ESI) using tetraoctylammonium bromide or sodium dodecyl sulfate as the lock mass; values are quotes as ratio of mass to charge (m/z) in Daltons, and relative intensities of assignable peaks observed are quoted as a percentage value of the base peak.

2. Experimental Conditions

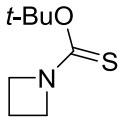
1-(2,2-Dimethylazetidin-1-yl)-2,2-dimethylpropane-1-thione (3)



A solution of 2,2-dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (**2**)[2] (E = Me) (59 mg, 0.34 mmol) in THF (2 mL) was cooled to −78 °C (acetone / dry-ice) before the addition of TMEDA (124 µL, 0.83 mmol). *s*-BuLi (1.3 M in cyclohexane / hexane, 317 µL, 0.41 mmol) was then added quickly in one portion. The reaction mixture was stirred for 30 min at −78 °C before addition of MeI (64 µL, 1.0 mmol). The reaction mixture was stirred for a further 15 min at −78 °C, warmed to rt over 10 min, stirred at rt for 20 min, then quenched with sat. aq NH_4Cl (5 mL), and extracted with Et_2O (4 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the pale yellow solid (SiO_2, 3–5% Et_2O / petroleum ether) gave a white solid, 2,2-disubstituted azetidine **3** (32 mg, 50%).

R_f 0.52 (30% Et_2O / petroleum ether); mp 65–67 °C; IR (neat / cm^{-1}) 2992 w, 2960 m, 2923 w, 1468 m, 1458 m, 1429 s, 1362 s, 1270 w, 1252 w, 1231 w, 1154 w, 1113 s; δ_H (400 MHz, $CDCl_3$) 4.51–4.46 (2H, m, NCH_2), 2.10–2.06 (2H, m, $NCH_2C\mathit{H}_2$), 1.79 (6H, s, $C(CH_3)_2$), 1.30 (9H, s, $(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 208.7 (C=S), 74.4 (NC_qCH_3), 54.3 (NCH_2), 43.6 ($\mathit{C}(CH_3)_3$), 31.1 (CH_2), 29.3 ($(CH_3)_3$), 24.7 ($C_q(\mathit{C}H_3)_2$); HRMS (ESI^+) calcd for $C_{10}H_{19}NNaS$: 208.1130, found 208.1124.

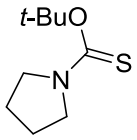
***O-tert*-Butyl azetidine-1-carbothioate (5)**



To a solution of *O-tert*-butyl *S*-methyl carbonodithioate (**4**)[3] (300 mg, 1.83 mmol) in pentane (0.5 mL) at 0 °C (ice-bath) was added azetidine (112 µL, 1.66 mmol). The reaction mixture was stirred at 0 °C for 1.5 h, then stirred at rt for 1 h, then concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 5–20% Et_2O / petroleum ether) gave a colorless oil, azetidine thiocarbamate **5** (254 mg, 88%).

R_f 0.44 (5% EtOAc / petroleum ether); IR (neat / cm^{-1}) 2975 s, 2882 w, 1488 br, 1438 s, 1391 m, 1365 m, 1741 br, 1245 s, 1228 m, 1139 br, 1024 m, 944 w, 818 w; δ_H (400 MHz, $CDCl_3$) 4.13 (2H, t, J = 7.5 Hz, NCH_2), 4.01 (2H, t, J = 7.5 Hz, NCH_2), 2.21–2.14 (2H, m, $NCH_2C\mathit{H}_2$), 1.64 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 184.9 (C=S), 84.6 ($\mathit{C}(CH_3)_3$), 51.7 (NCH_2), 50.6 (NCH_2), 28.4 ($C(\mathit{C}H_3)_3$), 13.9 ($NCH_2\mathit{C}H_2$); HRMS (FI^+) calcd for $C_8H_{15}NOS$: 173.0874, found 173.0869.

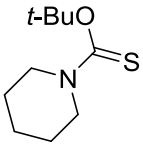
_O_-_tert_-Butyl pyrrolidine-1-carbothioate (SI-1)



To a solution of *O-tert*-butyl *S*-methyl carbonodithioate (**4**)[3] (300 mg, 1.83 mmol) in pentane (0.5 mL) at 0 °C (ice-bath) was added pyrrolidine (141 µL, 1.66 mmol). The reaction mixture was stirred at 0 °C for 1 h, then stirred at rt for 1 h, then concentrated under reduced pressure. Purification of the resulting yellow oil (SiO_2, 5–10% Et_2O / petroleum ether) gave a colorless oil, pyrrolidine thiocarbamate **SI-1** (277 mg, 89%).

R_f 0.66 (5% EtOAc / petroleum ether); IR (neat / cm^{-1}) 2973 s, 2928 m, 2876 s, 1468 m, 1437 b, 1390 m, 1364 m, 1333 m, 1267 s, 1232 w, 1143 br, 997 w, 858 m; δ_H (400 MHz, $CDCl_3$) 3.70–3.66 (2H, m, NCH_2), 3.48–3.45 (2H, m, NCH_2), 1.94–1.88 (4H, m, $NCH_2CH_2 \times 2$), 1.67 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 183.2 (C=S), 84.7 ($C(CH_3)_3$), 51.1 (NCH_2), 48.3 (NCH_2), 28.5 ($C(CH_3)_3$), 25.6 (CH_2CH_2), 24.6 (CH_2CH_2); HRMS (FI^+) calcd for $C_9H_{17}NOS$: 187.1031, found 187.1025.

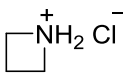
_O_-(_tert_-Butyl) piperidine-1-carbothioate (SI-2)



To a solution of *O-tert*-butyl *S*-methyl carbonodithioate (**4**)[3] (300 mg, 1.83 mmol) in pentane (0.5 mL) at 0 °C (ice-bath) was added piperidine (164 µL, 1.66 mmol). The reaction mixture was stirred at 0 °C for 30 min, and then stirred at rt for 30 min. The reaction mixture was concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 1% EtOAc / petroleum ether) gave a colorless oil, piperidine thiocarbamate **SI-2** (300 mg, 90%).

R_f 0.76 (5% EtOAc / petroleum ether); IR (neat / cm^{-1}) 2975 w, 2935 m, 2857 w, 1479 s, 1428 s, 1391 w, 1365 w, 1289 s, 1271 w, 1236 s, 1205 w, 1139 s, 1010 m, 954 w, 852 w; δ_H (400 MHz, $CDCl_3$) 4.02 (2H, br s, NCH_2), 3.64–3.61 (2H, m, NCH_2), 1.66 (9H, s, $C(CH_3)_3$), 1.63 (4H, br s, $NCH_2CH_2 \times 2$), 1.53 (2H, br s, $N(CH_2)_2CH_2$); δ_C (100 MHz, $CDCl_3$) 184.8 (C=S), 85.2 ($C(CH_3)_3$), 49.7 (NCH_2), 46.9 (NCH_2), 28.6 ($C(CH_3)_3$), 26.0 (NCH_2CH_2), 25.2 (NCH_2CH_2), 24.4 ($N(CH_2)_2CH_2$); HRMS (ESI^+) calcd for $C_{10}H_{19}NNaOS$: 224.1080, found 224.1078.

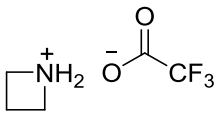
Azetidinium chloride (6a)



HCl (2 M in Et_2O, 577 µL, 1.15 mmol) was added to *O-tert*-butyl azetidine-1-carbothioate (**5**) (50 mg, 0.29 mmol) at rt. The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a white solid, azetidine salt **6a**[4] (27 mg, quant.).

IR (neat / cm^{-1}) 3386 br, 2928 s, 2644 m, 2394 w, 1639 w, 1449 m, 1317 s, 1254 m, 952 w, 909 m; δ_H (400 MHz, D_2O) 4.08 (4H, t, J = 8.4 Hz, NCH_2), 2.50 (2H, quin, J = 8.3 Hz, NCH_2CH_2); δ_C (100 MHz, D_2O) 46.8 (NCH_2), 18.4 (NCH_2CH_2).

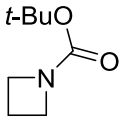
Azetidinium trifluoroacetate (6b)



To a solution of *O-tert*-butyl azetidine-1-carbothioate (**5**) (45 mg, 0.26 mmol) in CH_2Cl_2 (0.5 ml) at rt was added TFA (50 µl, 1.07 mmol). The reaction mixture was stirred for 30 min at rt, then concentrated under reduced pressure to give a grey liquid, azetidine salt **6b** (44 mg, quant.).

IR (neat / cm^{-1}) 2993 br, 2682 w, 2361 w, 1672 s, 1178 s, 1127 s, 836 w, 799 w, 721 w; δ_H (500 MHz, $CDCl_3$) 9.49 (2H, br s, NH_2), 4.13–4.08 (4H, m, NCH_2 × 2), 2.56 (2H, quin, J = 8.4 Hz, NCH_2CH_2); δ_C (125 MHz, $CDCl_3$) 162.1 (q, J = 35 Hz, C=O), 116.5 (Q, J = 292 Hz, CF_3), 46.2 (NCH_2 × 2), 18.7 (NCH_2CH_2); δ_F (470 MHz, $CDCl_3$) −75.9.

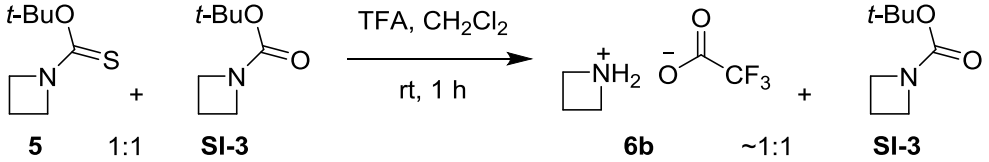
***tert*-Butyl azetidine-1-carboxylate (SI-3)**



Prepared by analogy to a lit.[5] procedure for *N*-Boc-pyrrolidine. Boc_2O (0.57 mL, 2.5 mmol) was added dropwise to an ice-cold, stirred solution of azetidine (0.17 mL, 2.5 mmol) and Et_3N (0.70 mL, 5 mmol) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred overnight, warming to rt. After quenching with aq HCl (1 M, 5 mL) and partitioning, the aq layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the pale yellow oil (SiO_2, 50% Et_2O / petroleum ether) gave a colorless oil, *N*-Boc-azetidine **SI-3**[6] (376 mg, 96%).

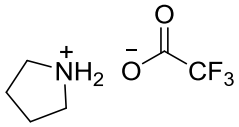
R_f 0.3 (20% Et_2O / petroleum ether); IR (neat / cm-1) 2975 m, 2888 w, 1698 br, 1479 w, 1455 w, 1390 s, 1365 s, 1304 w, 1180 m, 1132 s, 966 w; δ_H (400 MHz, $CDCl_3$) 3.94 (4H, t, J = 7.6 Hz, NCH_2), 2.17 (2H, quin, J = 7.6 Hz, NCH_2CH_2), 1.43 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 156.3 (C=O), 79.1 $C(CH_3)_3$), 49.2 (br, NCH_2), 28.4 ($C(CH_3)_3$), 15.3 (CH_2); LRMS (ESI^+) 180.1 ($[M+Na]^+$, 100%).

Selective deprotection of *N*-Botc-azetidine 5 in the presence of *N*-Boc-azetidine SI-3



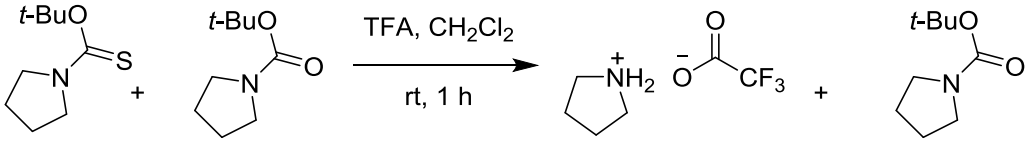
To a solution of *O-tert*-butyl azetidine-1-carbothioate (**5**) (22 mg, 0.13 mmol) and *tert*-butyl azetidine-1-carboxylate (**SI-3**) (20 mg, 0.13 mmol) in CH_2Cl_2 (0.5 ml) at rt was added TFA (29 µl, 0.38 mmol). The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a colorless oil (43 mg). ^{1}H NMR analysis (400 MHz, $CDCl_3$, p S32) indicated a 1.02:0.98 ratio of azetidine salt **6b** and *N*-Boc-azetidine **SI-3**.

Pyrrolidinium trifluoroacetate (SI-4)



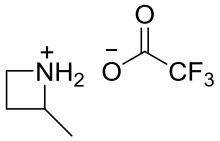
To a solution of *O-tert*-butyl pyrrolidine-1-carbothioate (**SI-2**) (50 mg, 0.27 mmol) in CH_2Cl_2 (1 ml) at rt was added TFA (82 µl, 1.07 mmol). The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a colorless liquid, pyrrolidine salt **SI-4**[7] (49 mg, quant.). IR (neat / cm^{-1}) 2986 br, 2850 w, 2486 w, 1670 s, 1462 w, 1426 w, 1198 s, 1173 s, 1125 s, 833 m, 797 m; δ_H (300 MHz, $CDCl_3$) 9.43 (1H, br s, NH_2), 4.66 (1H, br s, NH_2), 3.27–3.23 (4H, m, NCH_2 × 2), 2.02–1.97 (4H, m, NCH_2CH_2 × 2); δ_C (125 MHz, $CDCl_3$) 162.1 (q, *J* = 36 Hz, C=O), 116 (Q, *J* = 292 Hz, CF_3), 45.1 (NCH_2 × 2), 24.2 ($(CH_2)_2$); δ_F (470 MHz, $CDCl_3$) −75.8.

Selective deprotection of *N*-Botc-pyrrolidine SI-1 in the presence of *N*-Boc-pyrrolidine SI-5



To a solution of *O-tert*-butyl pyrrolidine-1-carbothioate (**SI-1**) (50 mg, 0.27 mmol) and *tert*-butyl pyrrolidine-1-carboxylate (**SI-5**)[5] (46 mg, 0.27 mmol) in CH_2Cl_2 (1 ml) at rt was added TFA (41 µl, 0.53 mmol). The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a colorless oil (93 mg). ^{1}H NMR analysis (400 MHz, $CDCl_3$, p S34) indicated a 1.2:0.8 ratio of pyrrolidine salt **SI-4** and *N*-Boc-pyrrolidine **SI-5**.

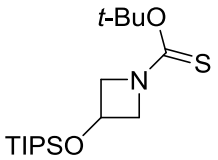
2-Methylazetidinium trifluoroacetate (SI-6)



To a solution of *O*-*tert*-butyl 2-methylazetidine-1-carbothioate (**10h**) (60 mg, 0.32 mmol) in CH_2Cl_2 (1 ml) at rt was added TFA (61 µl, 0.80 mmol). The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a colorless liquid, 2-methylazetidine salt **SI-6** (59 mg, quant.).

IR (neat / cm^{-1}); 3434 br, 2987 br, 2680 br, 2494 br, 1671 s, 1452 w, 1428 w, 1395 w, 1339 w, 1173 s, 1129 s, 1045 w, 925 w, 835 m, 798 m, 721 m, 706 m; δ_H (400 MHz, $CDCl_3$) 9.26 (1H, br s, N*H*H′), 9.06 (1H, br s, NH*H*′), 4.60–4.58 (1H, m, NCH), 4.01–3.91 (2H, m, NCH_2), 2.63–2.55 (1H, m, C*H*H′), 2.35–2.26 (1H, m, CH*H*′), 1.54 (3H, d, J = 6.8 Hz, CH_3); δ_C (125 MHz, $CDCl_3$) 161.7 (q, J = 36 Hz, C=O), 116.2 (Q, J = 300 Hz, CF_3), 57.4 (NCH), 42.1 (NCH_2), 26.3 ($NCH_2C\mathit{H}_2$), 19.5 (CH_3); δ_F (377 MHz, $CDCl_3$) −75.9.

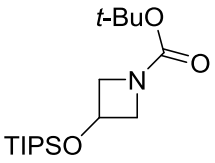
***O*-(*tert*-Butyl) 3-((triisopropylsilyl)oxy)azetidine-1-carbothioate (7)**



To a solution of *O*-*tert*-butyl *S*-methyl carbonodithioate (**4**)[3] (215 mg, 1.31 mmol) in pentane (1 mL) at 0 °C (ice-bath) was added 3-((triisopropylsilyl)oxy)azetidine (**9**) (200 mg, 0.87 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 1–1.5% Et_2O / petroleum ether) gave a colorless oil, azetidine thiocarbamate **7** (196 mg, 65%).

R_f 0.32 (2% Et_2O / petroleum ether); IR (neat / cm^{-1}) 2943 w, 2867 w, 1482 s, 1444 s, 1391 w, 1366 w, 1275 m, 1228 w, 1133 s, 1009 s, 882 s, 683 m; δ_H (400 MHz, $CDCl_3$) 4.58 (1H, tt, J = 6.5, 4.3 Hz, OCH), 4.31 (1H, ddd, J = 10.7, 6.6, 1.5 Hz, NC*H*H′), 4.19 (1H, ddd, J = 10.5, 6.6, 1.5 Hz, NC*H*H′), 3.99–3.95 (1H, m, NCH*H*′), 3.84–3.80 (1H, m, NCH*H*′), 1.63 (9H, s, $C(CH_3)_3$), 1.10–1.00 (21 H, m, SiCH × 3, CH_3 × 6); δ_C (100 MHz, $CDCl_3$) 185.2 (C=S), 84.9 ($\mathit{C}(CH_3)_3$), 62.1 (NCH_2), 60.7 (NCH_2), 60.3 (OCH), 28.3 ($C(\mathit{C}H_3)_3$), 17.7 ($CH\mathit{C}H_3$), 11.7 (SiCH); HRMS (ESI^+) calcd for $C_{17}H_{35}NNaO_2SSi$: 368.2050, found 368.2043.

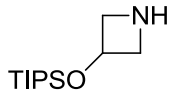
tert-Butyl 3-((triisopropylsilyl)oxy)azetidine-1-carboxylate (8)



To a solution of di-*tert*-butyl dicarbonate (327 µL, 1.43 mmol) in EtOH (4 mL) at rt was added a solution of 3-((triisopropylsilyl)oxy)azetidine (**9**) (218 mg, 0.95 mmol) in EtOH (4 mL). After 10 min, imidazole (65 mg, 0.95 mmol) was added and after a further 5 min the reaction mixture was concentrated under reduced pressure. $CHCl_3$ (8 mL) was added and the mixture was washed with 1% aq HCl (2 × 8 mL, 0 °C) with cooling (ice-bath). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 5–10% Et_2O / petroleum ether) gave a colorless oil, Boc-protected-azetidine **8** (290 mg, 93%).

R_f 0.24 (5% Et_2O / petroleum ether); IR (neat / cm^{-1}) 2944 m, 2867 m, 1707 s, 1463 m, 1402 s, 1366 m, 1251 w, 1123 m, 1064 s, 1014 s, 948 w, 883 s, 773 w, 680 m; δ_H (400 MHz, $CDCl_3$) 4.60 (1H, tt, *J* = 6.6, 4.7 Hz, OCH), 4.11–4.07 (2H, m, NC*H*H′), 3.79 (2H, dd, *J* = 9.5, 4.6 Hz, NCH*H*′), 1.43 (9H, s, $C(CH_3)_3$), 1.07–1.00 (21 H, m, SiCH × 3, CH_3 × 6); δ_C (125 MHz, $CDCl_3$) 156.4 (C=O), 79.3 (*C*$(CH_3)_3$), 61.6 (OCH), 59.5 (NCH_2), 28.4 (C(*C*$H_3)_3$), 17.7 (CH*C*H_3), 11.8 (SiCH); HRMS (ESI^+) calcd for $C_{17}H_{35}NNaO_3Si$: 352.2278, found 352.2268.

3-((Triisopropylsilyl)oxy)azetidine (9)

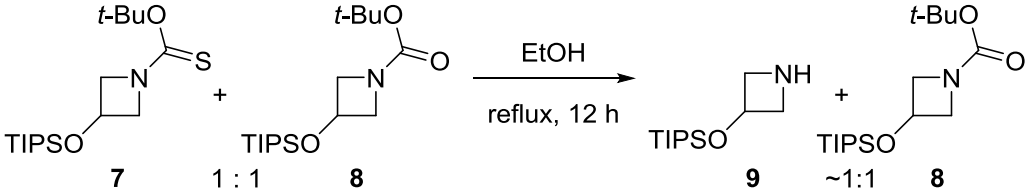


A suspension of 3-hydroxyazetidine hydrochloride (250 mg, 2.28 mmol) and imidazole (932 mg, 13.7 mmol) in CH_2Cl_2 (3 mL) was stirred at rt for 10 min before the addition of TIPSCl (1.1 mL, 5.1 mmol). The reaction was stirred at rt for a further 48 h before addition of H_2O (6 mL), followed by aq NaOH (6 M, 2 mL). The mixture was partitioned and the organic layer was washed with H_2O (2 × 6 mL) and brine (6 mL). The aqueous extracts were then re-extracted with CH_2Cl_2 (2 × 6 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. HCl (2 M in Et_2O, 3 mL) was added to the resulting pale yellow liquid and the mixture was stirred at rt for 1 h before addition of H_2O (6 mL). The mixture was partitioned and the organic layer was extracted with H_2O (2 × 6 mL). The combined aqueous extracts were basified by addition of aq NaOH (6 M) until pH paper indicated ~pH 10, then extracted with Et_2O (3 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a colorless oil, TIPS-protected 3-hydroxyazetidine **9** (425 mg, 81%).

R_f 0.49 (1% Et_3N / 20% MeOH / petroleum ether); IR (neat / cm^{-1}) 2943 m, 2866 m, 1739 w, 1542 w, 1463 m, 1383 s, 1169 s, 1126 m, 1013 w, 994 w, 863 s, 682 m; δ_H (400 MHz, $CDCl_3$) 4.66 (1H, quin, *J* = 6.5 Hz, OCH), 3.66–3.56 (4H, m, NCH_2), 2.06 (1H, br s, NH), 1.05–1.00 (21 H, m, SiCH × 3,

CH_3 × 6); δ_C (100 MHz, $CDCl_3$) 66.3 (OCH), 58.0 (NCH_2), 17.8 (CH_3), 11.8 (SiCH); HRMS (ESI^+) calcd for $C_{12}H_{28}NOSi$: 230.1935, found 230.1931.

Selective thermal deprotection of *O*-(*tert*-Butyl) 3-((triisopropylsilyl)oxy)azetidine-1-carbothioate (7) in the presence of *tert*-Butyl 3-((triisopropylsilyl)oxy)azetidine-1-carboxylate (8)

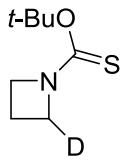


A solution of *O*-(*tert*-butyl) 3-((triisopropylsilyl)oxy)azetidine-1-carbothioate (**7**) (30 mg, 0.087 mmol) and *tert*-butyl 3-((triisopropylsilyl)oxy)azetidine-1-carboxylate (**8**) (29 mg, 0.088 mmol) in EtOH (4 mL) was heated at reflux for 12 h. The reaction mixture was concentrated under reduced pressure to give a colorless oil (48 mg). ^{1}H NMR analysis (400 MHz, $CDCl_3$, p S40) indicated a ~1:1 mixture of azetidine salt **9** and *N*-Boc-azetidine **8**.

General Procedure A: α-deprotonation-electrophile trapping of *O-tert*-butyl azetidine-1-carbothioate (5)

A solution of *O-tert*-butyl azetidine-1-carbothioate (**5**) (1 equiv) in THF (5 mL/ mmol **5**) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (2.4 equiv). *s*-BuLi [1.3 M in cyclohexane / hexane, 1.3 equiv (1 equiv for reactions with aromatic aldehydes)] was then added dropwise over 3 min. The reaction mixture was stirred for 30 min at −78 °C before the addition of the electrophile (3 equiv). The reaction mixture was stirred for the time and at the temp described below, then quenched with sat. aq NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

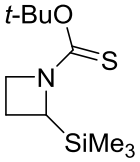
***O-tert*-Butyl (2-$^2H_1$)azetidine-1-carbothioate (10a)**



O-tert-Butyl azetidine-1-carbothioate (**5**) (40 mg, 0.23 mmol) and CD_3OD (28 µL, 0.69 mmol) were used following General Procedure A, with stirring following electrophile addition for 60 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 5 min. Purification of the resulting pale yellow oil (SiO_2, 10% Et_2O / petroleum ether) gave a colorless oil, deuterated azetidine **10a** (36 mg, 90% mass recovery, 95% D by HRMS analysis).

R_f 0.33 (5% EtOAc / petroleum ether); IR (neat / cm^{-1}) 2974 w, 2929 w, 1481 s, 1442 s, 1391 w, 1365 m, 1267 s, 1226 w, 1142 s, 1022 w, 898 w, 736 w; δ_H (500 MHz, $CDCl_3$) 4.12–3.96 (3H, m, NCHD and NCH_2), 2.17–2.13 (2H, m, NCHCH_2), 1.62 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.0 (C=S), 84.6 ($C(CH_3)_3$), 51.7 (50.6) (NCH_2), 51.4 (50.3) (T, J = 22.9 Hz, NCHD), 28.4 ($C(CH_3)_3$), 13.8 (13.9) (NCHCH_2); HRMS (FI^+) calcd for C_8H_{14}DNOS: 174.0937, found 174.0930.

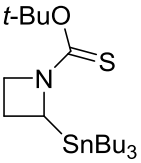
O-tert-Butyl 2-(trimethylsilyl)azetidine-1-carbothioate (10b)



O-tert-Butyl azetidine-1-carbothioate (**5**) (147 mg, 0.85 mmol) and TMSCl (323 µL, 2.54 mmol) were used following General Procedure A, with stirring following electrophile addition for 30 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min. Purification of the resulting pale yellow oil (SiO_2, 2–5% Et_2O / petroleum ether) gave a colorless oil, silane **10b** (158 mg, 76%).

R_f 0.59 (5% EtOAc / petroleum ether); IR (neat / cm^{-1}) 2961 w, 2882 w, 1483 s, 1445 s, 1390 m, 1365 m, 1267 s, 1248 s, 1227 m, 1022 w, 992 w, 937 w, 754 w, 737 w, 695 w; δ_H (400 MHz, $CDCl_3$) (3.5:1 rotamer mixture by analysis of $C(CH_3)_3$ signals at 1.66 and 1.61) 4.26–3.89 (3H, m, NCH and NCH_2), 2.43–2.25 (1H, m, NCHC*H*H′), 1.99–1.89 (1H, m, NCHCH*H*′), 1.66 (1.61) (9H, s, $C(CH_3)_3$), 0.11 (0.18) (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 183.8 (C=S), 85.0 ($C(CH_3)_3$), 57.3 (NCH), 52.7 (51.1) (NCH_2), 28.7 (28.5) ($C(CH_3)_3$), 16.6 (NCHCH_2), −3.2 (−2.2) ($Si(CH_3)_3$); HRMS (ESI^+) calcd for $C_{11}H_{23}$NNaOSSi: 268.1162, found 268.1158.

O-tert-Butyl 2-(tributylstannyl)azetidine-1-carbothioate (10c)

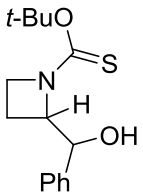


O-tert-Butyl azetidine-1-carbothioate (**5**) (150 mg, 0.87 mmol) and Bu_3SnCl (704 µL, 2.60 mmol) were used following General Procedure A, with stirring following electrophile addition for 30 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min. Purification of the resulting colorless liquid (SiO_2, 1–3% Et_2O / petroleum ether) gave a colorless oil, stannane **10c** (300 mg, 75%).

R_f 0.65 (10% Et_2O / petroleum ether); IR (neat / cm^{-1}) 2956 w, 2923 m, 1490 s, 1446 m, 1390 w, 1365 w, 1265 s, 1225 w, 1138 s, 1073 w, 1023 w, 875 w, 823 w; δ_H (400 MHz, $CDCl_3$) (2:1 rotamer mixture by analysis of $C(CH_3)_3$ signals at 1.66 and 1.60) 4.48–4.45 (1H, m NCH), 4.15–4.09 (4.28–4.21) (1H, td, J = 10.0, 5.0 Hz, NC*H*H′), 4.05–3.99 (4.15–4.09) (1H, m, NCH*H*′), 2.56–2.39

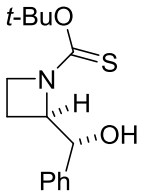
(1H, m, NCH_2CHH'), 2.17–2.06 (1H, m, NCH_2CHH'), 1.60 (1.66) (9H, s, $C(CH_3)_3$), 1.64–1.43 (6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$), 1.36–1.26 (6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$), 0.97 (1.03) (9H, t, J = 8.0 Hz, $Sn(CH_2CH_2CH_2CH_3)_3$), 0.92−0.88 (6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 181.2 (181.7) (C=S), 83.5 (84.6) ($C(CH_3)_3$), 55.1 (54.4) ($J_{119Sn-C}$ = 325 Hz, $J_{117Sn-C}$ = 302 Hz ($J_{119Sn-C}$ = 294 Hz, $J_{117Sn-C}$ = 280 Hz), NCH), 50.8 (52.7) (NCH_2), 29.1 (29.0) ($SnCH_2CH_2$), 28.5 (28.7) ($C(CH_3)_3$), 27.5 (27.4) (CH_3CH_2), 18.2 (18.7) ($NCHCH_2$), 13.69 (13.65) (CH_3CH_2), 11.0 (9.5) ($J_{119Sn-C}$ = 322 Hz, $J_{117Sn-C}$ = 308 Hz ($J_{119Sn-C}$ = 318 Hz, $J_{117Sn-C}$ = 302 Hz), $SnCH_2$); HRMS (FI^+) calcd for $C_{20}H_{41}NOS^{120}Sn$: 463.1931, found 463.1928.

_O_-_tert_-Butyl 2-(hydroxy(phenyl)methyl)azetidine-1-carbothioate (10d)



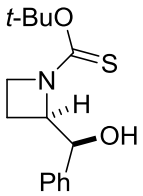
O-*tert*-Butyl azetidine-1-carbothioate (**5**) (150 mg, 0.87 mmol) and benzaldehyde (264 µL, 2.60 mmol) were used following General Procedure A for an aromatic aldehyde, with stirring following electrophile addition for 2 h at −78 °C. Purification of the resulting pale brown oil (SiO_2, 5–30% Et_2O / petroleum ether) gave first a colorless oil, the minor diastereomer (*R**,*R**)-**10d-minor** (53 mg, 22%), followed by a colorless oil, the major diastereomer (*R**,*S**)-**10d-major** (127 mg, 52%); stereochemistry was assigned by analogy to **10e**.

_O_-(_tert_-Butyl) (*R)-2-((*R**)-hydroxy(phenyl)methyl)azetidine-1-carbothioate ((*R**,*R**)-10d-minor)**



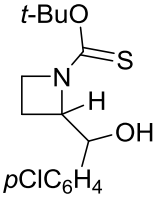
R_f 0.43 (20% EtOAc / petroleum ether); IR (neat / cm^{-1}) 3397 br, 2974 w, 2927 w, 2360 w, 1481 s, 1450 m, 1436 s, 1391 w, 1366 w, 1281 s, 1143 s, 1069 w, 1015 w, 977 w, 927 w, 701 w; δ_H (500 MHz, $CDCl_3$) (1.4:1 rotamer mixture by analysis of NCH signals in the region 4.92–4.50) 7.44–7.28 (5H, m, Ar), 5.33 (5.29) (1H, br s, C*H*OH), 4.92–4.89 (4.52–4.50) (1H, m, NCH), 4.32 (2.56) (1H, br s, OH), 4.00–3.39 (2H, m, NCH_2), 2.36–1.87 (2H, m, NCH_2CH_2), 1.65 (1.72) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 186.3 (186.4) (C=S), 139.5 (139.1) (Ar), 128.5 (Ar), 128.1 (Ar), 127.5 (127.8) (Ar), 126.9 (Ar) 125.8 (Ar), 85.6 (85.7) ($C(CH_3)_3$), 73.5 (71.8) (*C*HOH), 69.8 (68.9) (NCH), 49.1 (50.0) (NCH_2), 28.4 (28.5) ($C(CH_3)_3$), 16.1 (14.3) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{15}H_{21}NNaO_2S$: 302.1185, found 302.1183.

***O*-(*tert*-Butyl) (*R**)-2-((*S**)-hydroxy(phenyl)methyl)azetidine-1-carbothioate ((*R*,S**)-10d-major)**



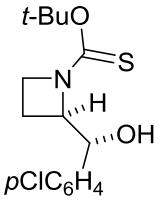
R_f 0.31 (20% EtOAc petroleum ether); IR (neat / cm^{-1}) 3295 br, 2975 w, 2928 w, 1476 s, 1462 s, 1452 s, 1437 s, 1392 m, 1366 m, 1278 s, 1198 m, 1086 s, 1061 w, 1039 w, 1027 w, 865 w, 823 w; δ_H (400 MHz, $CDCl_3$) (3:1 rotamer mixture by analysis of C*H*OH signals in the region 4.98–4.89) 7.43–7.29 (5H, m, Ar), 5.90 (1H, br s, OH), 4.97 (4.90) (1H, d, *J* = 8.6 Hz (*J* = 7.8 Hz), C*H*OH), 4.78–4.72 (4.57–4.44) (1H, m, NCH), 4.03–3.81 (2H, m, NCH_2), 2.05–1.78 (2H, m, NCH_2CH_2), 1.67 (1.74) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 187.3 (C=S), 139.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 127.4 (Ar), 127.0 (Ar), 86.2 ($C(CH_3)_3$), 79.2 (*C*HOH), 70.8 (69.7) (NCH), 48.8 (49.6) (NCH_2), 28.4 (28.5) ($C(CH_3)_3$), 18.2 (17.3) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{15}H_{21}NNaO_2S$: 302.1185, found 302.1179.

***O-tert*-Butyl 2-((4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate (10e)**



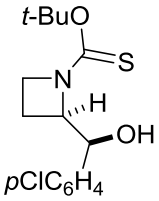
O-tert-Butyl azetidine-1-carbothioate (**5**) (150 mg, 0.87 mmol) and a solution of 4-chlorobenzaldehyde (365 mg, 2.60 mmol) in THF (0.5 mL) were used following General Procedure A for an aromatic aldehyde, with stirring following electrophile addition for 2 h at −78 °C. Purification of the resulting pale brown oil (SiO_2, 5–20% Et_2O/ petroleum ether) gave first a colorless oil, the minor diastereomer (*R**,*R**)-**10e-minor** (57 mg, 21%), followed by a white solid, the major diastereomer (*R**,*S**)-**10e-major** (131 mg, 48%); stereochemistry was determined by conversion to the corresponding *N*-piv azetidines (*R**,*R**)-**SI-8** and (*R**,*S**)-**SI-8** and comparing characterization data to that of an authentic sample of (*R**,*R**)-**SI-8**, see below.

***O-tert*-Butyl (*R**)-2-((*R**)-(4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate ((*R**,*R**)-10e-minor)**



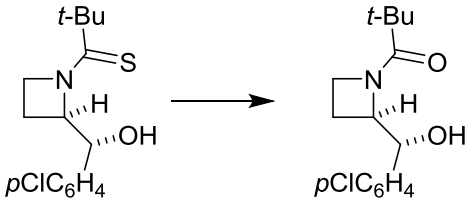
R_f 0.43 (20% EtOAc / petroleum ether); IR (neat / cm^{-1}) 3396 br, 2975 m, 2928 w, 1480 s, 1436 s, 1391 m, 1366 m, 1281 s, 1142 s, 1090 m, 1013 m, 977 w, 912 w, 837 w, 823 w, 781 w; δ_H (400 MHz, $CDCl_3$) (1.9:1 rotamer mixture by analysis of NCH signals at 4.88 and 4.46) 7.38–7.25 (4H, m, Ar), 5.25 (1H, d, J = 4.0 Hz, C*H*OH), 4.88 (4.46) (1H, t, J = 7.1 Hz (J = 6.3 Hz), NCH), 4.56 (2.74) (1H, d, J = 6.8 Hz (J = 3.0 Hz), OH), 3.76 (4.00–3.88) (1H, td (m), J = 9.6, 6.1 Hz, NC*H*H′), 3.40 (4.00–3.88) (1H, td (m), J = 9.3, 6.7 Hz, NCH*H*′), 2.14–2.05 (2.30–2.22) (1H, m, NCH_2C*H*H′), 2.00–1.84 (1H, m, NCH_2CH*H*′), 1.64 (1.71) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 186.5 (C=S), 138.1 (137.6) (Ar), 133.3 (133.5) (Ar), 128.3 (128.6) (Ar), 128.2 (127.2) (Ar), 85.8 (*C*$(CH_3)_3$), 73.2 (71.2) (*C*HOH), 69.6 (68.7) (NCH), 49.0 (50.0) (NCH_2), 28.3 (28.5) (C(*C*$H_3)_3$), 16.1 (14.2) (NCH_2*C*H_2); HRMS (FI^+) calcd for $C_{15}H_{20}NO_2SCl$: 313.0903, found 313.0905.

***O-tert*-Butyl (*R**)-2-((*S**)-(4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate ((*R**,*S**)-10e-major)**



R_f 0.28 (20% EtOAc petroleum ether); mp 100–102 °C (decomposes); IR (neat/cm^{-1}) 3276 br, 2976 w, 2927 w, 1477 s, 1462 s, 1436 s, 1392 m, 1366 m, 1276 s, 1142 s, 1090 w, 1069 w, 1039 w, 1014 m, 910 w, 822 m, 732 m; δ_H (400 MHz, $CDCl_3$) (3.4:1 rotamer mixture by analysis of C*H*OH signals at 4.95 and 4.87) 7.37–2.28 (4H, m, Ar), 5.94 (1H, br s, OH), 4.95 (4.87) (1H, d, J = 8.6 (7.8) Hz, C*H*OH), 4.71–4.65 (4.51–4.45) (1H, m, NCH), 4.01–3.78 (2H, m, NCH_2), 2.02–1.91 (1.81–1.69) (2H, m, NCH_2C*H*$_2$), 1.65 (1.73) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 187.4 (C=S), 138.2 (137.2) (Ar), 133.8 (Ar), 128.7 (128.6) (Ar), 128.55 (128.3) (Ar), 86.3 (87.3) (*C*$(CH_3)_3$), 78.3 (76.2) (*C*HOH), 70.5 (69.3) (NCH), 48.8 (49.5) (NCH_2), 28.3 (28.4) (C(*C*$H_3)_3$), 18.0 (17.1) (NCH_2*C*H_2); HRMS (FI^+) calcd for $C_{15}H_{20}NO_2SCl$: 313.0903, found 313.0908.

Synthesis of an authentic sample of 1-((*R)-2-((*R**)-(4-chlorophenyl)(hydroxy)methyl)azetidin-1-yl)-2,2-dimethylpropan-1-one ((*R**,*R**)-SI-8)**

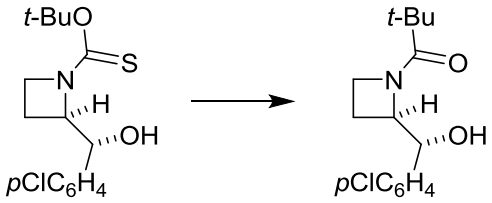


SI-7 (*R**,*R**)-**SI-8**

Aq H_2O_2 (35%, 1.7 mL) was added to an ice-cold, stirred solution of AcOH (1.3 mL). A solution of 1-((*R**)-2-((*R**)-(4-chlorophenyl)(hydroxy)methyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**SI-7**)[2] (30 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) was added slowly and the reaction mixture was stirred at 0 °C for 4 h, then poured onto sat. aq $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed successively with sat. aq $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 20–40% EtOAc/ petroleum ether) gave a white solid, *N*-piv-azetidine (*R**,*R**)-**SI-8** (18 mg, 64%).

R_f 0.24 (40% EtOAc/ petroleum ether); mp 107–110 °C; IR (neat/cm^{-1}) 3364 br, 2968 m, 1593 s, 1484 s, 1426 s, 1365 m, 1238 w, 1149 w, 1090 m, 1013 m, 978 w, 836 w, 755w; δ_H (400 MHz, $CDCl_3$) 7.37–7.24 (4H, m, Ar), 6.21 (1H, br d, *J* = 7.2 Hz, OH), 4.96 (1H, ddd, *J* = 9.0, 6.5, 1.9 Hz, NCH), 4.72 (1H, br d, *J* = 3.2 Hz, C*H*OH), 4.12 (1H, td, *J* = 8.9, 6.0 Hz, NC*H*H′), 3.60–3.55 (1H, m, NCH*H*′), 2.34–2.25 (1H, m, NCH_2CHH'), 1.94–1.85 (1H, m, NCH_2CHH'), 1.18 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 179.8 (C=O), 138.3 (Ar), 133.4 (Ar), 128.7 (Ar), 128.0 (Ar), 75.0 (CHOH), 67.7 (NCH), 50.7 (NCH_2), 38.4 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 18.0 (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{15}H_{21}NO_2Cl$: 282.1255, found 282.1251.

Synthesis of 1-((*R)-2-((*R**)-(4-chlorophenyl)(hydroxy)methyl)azetidin-1-yl)-2,2-dimethylpropan-1-one ((*R**,*R**)-SI-8) from 10e-minor**

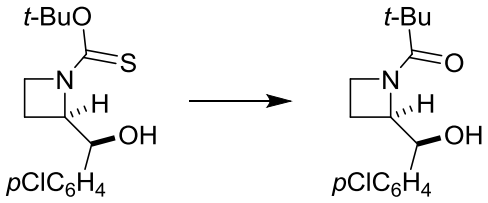


10e-minor (*R**,*R**)-**SI-8**

HCl (2 M in Et_2O, 1 mL, 2.00 mmol) was added to *O*-*tert*-butyl 2-((4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate (**10e-minor**) (22 mg, 0.07 mmol). The reaction mixture was stirred at rt for 1 h, then concentrated under reduced pressure. Py (1 mL) and DMAP (2 mg, 0.016 mmol) were added to the resulting white solid and the reaction mixture was

heated to 70 °C for 10 min, then cooled to 0 °C. PivCl (9 µL, 0.073 mmol) was added and the reaction mixture was stirred at rt for 12 h. HCl (2 M, aq, 10 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting dark brown oil (SiO_2, 20–40% EtOAc/ petroleum ether) gave *N*-piv azetidine (*R**,*R**)-**SI-8** as a white solid (11 mg, 56%). Data as above.

Synthesis of 1-((*R)-2-((*S**)-(4-chlorophenyl)(hydroxy)methyl)azetidin-1-yl)-2,2-dimethylpropan-1-one ((*R**,*S**)-SI-8) from 10e-major**

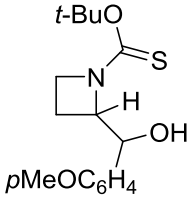


10e-major (*R**,*S**)-**SI-8**

A solution of HCl (2 M in Et_2O, 2.5 mL, 5.00 mmol) was added to *O*-*tert*-butyl 2-((4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate (**10e-major**) (66 mg, 0.21 mmol) at rt. The reaction mixture was stirred at rt for 1 h, then concentrated under reduced pressure. Py (1.5 mL) and DMAP (5 mg, 0.04 mmol) were added to the resulting white solid and the reaction mixture was heated to 70 °C for 10 min, then cooled to 0 °C. PivCl (28 µL, 0.23 mmol) was added and the reaction mixture was stirred at rt for 12 h. HCl (2 M, aq, 15 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting pale brown oil (SiO_2, 20% EtOAc/ petroleum ether) gave a white solid, *N*-piv-azetidine (*R**,*S**)-**SI-8** (22 mg, 37%).

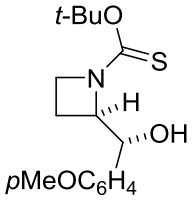
R_f 0.46 (40% EtOAc petroleum ether); mp 140–142 °C; IR (neat/cm^{-1}) 3188 br, 2965 m, 1578 s, 1483 m, 1427 s, 1365 w, 1353 w, 1220 w, 1086 w, 1073 w, 835 m, 756 w; δ_H (400 MHz, $CDCl_3$) 7.36–7.30 (4H, m, Ar), 6.72 (1H, s, OH), 4.73 (1H, d, *J* = 8.7 Hz, C*H*OH), 4.56 (1H, q, *J* = 15.9, 8.5 Hz, NCH), 4.28 (2H, t, *J* = 7.8 Hz, NCH_2), 1.96–1.82 (2H, m, NCH_2CH_2), 1.24 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 180.6 (C=O), 138.0 (Ar), 133.8 (Ar), 128.7 (Ar), 128.6 (Ar), 78.5 (CHOH), 69.6 (NCH), 50.6 (NCH_2), 38.6 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 19.2 (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{15}H_{21}NO_2Cl$: 282.1255, found 282.1254. Data differs from that of an authentic sample of (*R**,*R**)-**SI-8**, see above.

***O*-*tert*-Butyl 2-(hydroxy(4-methoxyphenyl)methyl)azetidine-1-carbothioate (10f)**



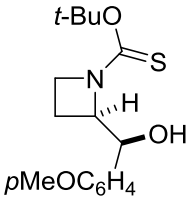
O-*tert*-Butyl azetidine-1-carbothioate (**5**) (150 mg, 0.87 mmol) and *p*-anisaldehyde (316 µL, 2.60 mmol) were used following General Procedure A for an aromatic aldehyde, with stirring following electrophile addition for 2 h at −78 °C. Purification of the resulting pale brown oil (SiO_2, 5–30% Et_2O / petroleum ether) gave first a colorless oil, the minor diastereomer (*R**,*R**)-**10f-minor** (45 mg, 17%), followed by a white solid, the major diastereomer (*R**,*S**)-**10f-major** (108 mg, 40%); stereochemistry was assigned by analogy to **10e**.

***O*-(*tert*-Butyl) (*R**)-2-((*R**)-hydroxy(4-methoxyphenyl)methyl)azetidine-1-carbothioate ((*R**,*R**)-10f-minor)**



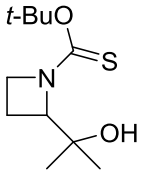
R_f 0.32 (20% EtOAc / petroleum ether); IR (neat / cm^{-1}) 3424 br, 2973 m, 2931 w, 2836 w, 1612 w, 1585 w, 1512 m, 1482 s, 1464 s, 1437 s, 1391 m, 1366 m, 1280 s, 1248 s, 1172 m, 1144 s, 1034 m, 976 w, 911 w, 847 w, 832 w, 734 w; δ_H (500 MHz, $CDCl_3$) (1.4:1 rotamer mixture by analysis of NCH signals at 4.89 and 4.48) 7.37–7.34 (7.26–7.24) (2H, m, Ar), 6.91–6.88 (2H, m, Ar), 5.22 (1H, br s, C*H*OH), 4.89 (4.48) (1H, t, *J* = 6.0 (7.0) Hz, NCH), 4.41 (2.48) (1H, d (br s), *J* = 6.5 Hz, OH), 4.00–3.90 (1H, m, NC*H*H′), 3.82 (3.81) (3H, s, OCH_3), 3.75 (3.40) (1H, td, *J* = 10.0, 6.0 (9.5, 7.0) Hz, NCH*H*′), 2.14–2.07 (2.35–2.27) (1H, m, NCH_2CHH'), 2.03–1.89 (1H, m, NCH_2CHH'), 1.65 (1.72) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 186.3 (186.4) (C=S), 159.0 (159.2) (Ar), 131.6 (131.2) (Ar), 128.1 (127.0) (Ar), 113.5 (113.9) (Ar), 85.6 (85.7) (*C*$(CH_3)_3$), 73.5 (71.6) (*C*HOH), 69.9 (69.0) (NCH), 55.2 (55.3) (OCH_3), 49.0 (50.0) (NCH_2), 28.4 (28.5) (C(*C*$H_3)_3$), 16.3 (14.4) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{16}H_{23}NO_3S$: 309.1399, found 309.1400.

***O*-(*tert*-Butyl) (*R**)-2-((*S**)-hydroxy(4-methoxyphenyl)methyl)azetidine-1-carbothioate ((*R**,*S**)-10f-major)**



R_f 0.28 (20% EtOAc petroleum ether); mp 96–98 °C (dec); IR (neat / cm^{-1}) 3300 br, 2974 m, 2929 w, 2836 w, 1613 w, 1513 m, 1477 s, 1464 s, 1438 s, 1392 w, 1367 w, 1277 s, 1250 s, 1145 s, 1067 w, 1033 m, 912 w, 829 w, 733 w; δ_H (400 MHz, $CDCl_3$) (2.7:1 rotamer mixture by analysis of C*H*OH signals at 4.92 and 4.84) 7.35–7.27 (2H, m, Ar), 6.89–6.87 (2H, m, Ar), 5.86 (1H, br s, OH), 4.92 (4.84) (1H, d, *J* = 9.0 (8.0) Hz, C*H*OH), 4.74–68 (4.54–4.48) (1H, m, NCH), 3.88 (4.01–3.93) (2H, t (m), *J* = 7.8 Hz, NCH_2), 3.80 (3H, s, OCH_3), 2.03–1.91 (1.82–1.63) (2H, m, NCH_2CH_2), 1.66 (1.74) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 187.2 (C=S), 159.4 (Ar), 131.8 (Ar), 128.5 (128.2) (Ar), 113.8 (113.9) (Ar), 86.1 (87.2) ($C(CH_3)_3$), 78.7 (76.8) (*C*HOH), 70.9 (69.8) (NCH), 55.2 (OCH_3), 48.8 (49.5) (NCH_2), 28.4 (28.5) ($C(CH_3)_3$), 18.3 (17.3) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{16}H_{23}NO_3S$: 309.1399, found 309.1404.

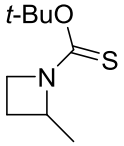
***O*-*tert*-Butyl 2-(2-hydroxypropan-2-yl)azetidine-1-carbothioate (10g)**



O-*tert*-Butyl azetidine-1-carbothioate (**5**) (70 mg, 0.40 mmol) and acetone (90 µL, 1.23 mmol) were used following General Procedure A, with stirring following electrophile addition for 3 h at −78 °C. Purification of the resulting pale yellow oil (SiO_2, 5–20% Et_2O / petroleum ether) gave a colorless oil, alcohol **10g** (60 mg, 65%).

R_f 0.22 (20% EtOAc / petroleum ether); IR (neat / cm^{-1}) 3335 br, 2975 w, 2930 w, 1474 w, 1437 s, 1391 m, 1366 m, 1271 s, 1248 m, 1225 m, 1142 s, 983 w, 911 w, 859 w; δ_H (400 MHz, $CDCl_3$) (1.7:1 rotamer mixture by analysis of NCH signals in the 4.57–4.31 region) 5.52 (1H, br s, OH), 4.57–4.53 (4.35–4.31) (1H, m, NCH), 4.10–3.82 (2H, m, NCH_2), 2.32–1.77 (2H, m, NCH_2CH_2), 1.63 (1.69) (9H, s, $C(CH_3)_3$), 1.30 (1.23) (3H, s, CH_3COH), 1.10 (1.15) (3H, s, CH_3COH); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 186.7 (C=S), 85.7 (87.0) ($C(CH_3)_3$), 74.6 (73.8) (NCH), 72.4 (72.3) (COH), 49.1 (50.4) (NCH_2), 28.3 ($C(CH_3)_3$), 24.8 (25.2) (CH_3COH), 22.9 (23.5) (CH_3COH), 18.6 (17.9) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{11}H_{21}NNaO_2S$: 254.1185, found 254.1189.

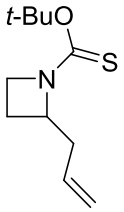
***O-tert*-Butyl 2-methylazetidine-1-carbothioate (10h)**



O-tert-Butyl azetidine-1-carbothioate (**5**) (50 mg, 0.29 mmol) and MeI (54 μL, 0.87 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C and then warmed to rt over 10 min. Purification of the resulting bright yellow oil (SiO_2, 0–5% EtOAc / *n*-hexane) gave a colorless oil, methylated azetidine **10h** (43 mg, 79%).

R_f 0.60 (5% EtOAc / petroleum ether); IR (neat / cm^{-1}) 2968 w, 1739 w, 1479 m, 1436 s, 1391 w, 1366 w, 1274 s, 1142 s; δ_H (500 MHz, $CDCl_3$) (2.5:1 rotamer mixture by analysis of NCH signals in the 4.56–4.34 region) 4.40–4.34 (4.56–4.50) (1H, m, NCH), 4.08–3.90 (2H, m, NCH_2), 2.39–2.28 (1H, m, NCHC*H*H′), 1.79–1.73 (1H, m, NCHCH*H*′), 1.64 (1.63) (9H, s, $C(CH_3)_3$), 1.42 (1.57) (3H, d, J = 6.3 Hz, NCHCH_3); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.3 (185.2) (C=S), 84.7 (84.5) ($C(CH_3)_3$), 59.9 (61.0) (NCH), 48.96 (49.04) (NCH_2), 28.48 (28.50) ($C(CH_3)_3$), 22.4 (22.8) (NCHCH_2), 20.6 (19.7) (NCHCH_3); HRMS (FI^+) calcd for $C_9H_{17}NOS$: 187.1031, found 187.1026.

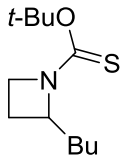
***O-tert*-Butyl 2-allylazetidine-1-carbothioate (10i)**



O-tert-Butyl azetidine-1-carbothioate (**5**) (151 mg, 0.87 mmol) and allyl bromide (226 μL, 2.61 mmol) were used following General Procedure A, with stirring following electrophile addition for 30 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min. Purification of the resulting yellow liquid (SiO_2, 5–50% Et_2O / petroleum ether) gave a colorless oil, allylated azetidine **10i** (99 mg, 53%).

R_f 0.59 (30% Et_2O / petroleum ether); IR (neat / cm^{-1}) 2975 m, 2926 w, 1641 w, 1477 s, 1435 s, 1390 m, 1365 m, 1348 w, 1138 s, 998 w, 917 m, 836 w, 733 w; δ_H (500 MHz, $CDCl_3$) (2.6:1 rotamer mixture by analysis of NCH signals in the 4.54–4.33 region) 5.82–5.70 (1H, m, CH_2=C*H*), 5.16–5.09 (2H, m, CH_2=CH), 4.38–4.33 (4.54–4.49) (1H, m NCH), 4.02–3.87 (2H, m, NCH_2), 2.60–2.55 (2.92–2.87) (1H, m, C*H*H′CH=CH_2), 2.53–2.47 (2.70–2.64) (1H, m, CH*H*′CH=CH_2), 2.30–2.16 (1H, m, NCH_2C*H*H′), 1.93–1.85 (1H, m, NCH_2CH*H*′), 1.64 (1.62) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.3 (185.2) (C=S), 132.4 (132.6) (CH_2=*C*H), 118.4 (118.2) (*C*H_2=CH), 84.9 (84.5) ($C(CH_3)_3$), 62.7 (63.6) (NCH), 49.22 (49.17) (NCH_2), 37.8 (36.3) (*C*H_2CH=CH_2), 28.5 ($C(CH_3)_3$), 19.4 (19.8) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{11}H_{19}NOS$: 213.1187, found 213.1178.

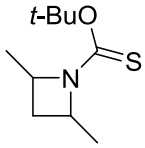
O-tert-Butyl 2-butylazetidine-1-carbothioate (10j)



O-tert-Butyl azetidine-1-carbothioate (**5**) (117 mg, 0.68 mmol) and *n*-BuI (308 µL, 2.71 mmol) were used following General Procedure A, with stirring following electrophile addition for 30 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min. Purification of the resulting yellow oil (SiO_2, 2–5% Et_2O / petroleum ether) gave a colorless oil, butylated azetidine **10j** (120 mg, 77%).

R_f 0.34 (5% EtOAc / petroleum ether); IR (neat / cm^{-1}) 2959 br, 2928 br, 1478 s, 1465 s, 1435 s, 1390 m, 1365 m, 1274 s, 1244 w, 1140 s, 1013 w, 993 w, 841 w, 735 w; δ_H (500 MHz, $CDCl_3$) (2.6:1 rotamer mixture by analysis of NCH signals in the region 4.45–4.26) 4.32–4.26 (4.45–4.40) (1H, m, NCH), 4.02–3.88 (2H, m, NCH_2), 2.38–2.22 (1H, m, NCH_2CHH'), 1.85–1.79 (1H, m, NCH_2CHH'), 1.72–1.64 (1.95–1.89) (2H, m, $CH_3(CH_2)_2CH_2$), 1.64 (1.63) (9H, s, $C(CH_3)_3$), 1.40–1.24 (4H, m, $CH_3CH_2CH_2$), 0.92 (3H, t, J = 7.0 Hz, CH_3CH_2); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.3 (185.2) (C=S), 84.7 (84.4) ($C(CH_3)_3$), 64.0 (65.1) (NCH), 49.4 (49.2) (NCH_2), 33.4 (32.2) ($NCHCH_2$), 28.5 ($C(CH_3)_3$), 26.3 (26.1) ($CH_3CH_2CH_2$), 22.5 (22.6) (CH_3CH_2), 20.4 (21.0) (NCH_2CH_2), 14.0 (14.1) (CH_3CH_2); HRMS (FI^+) calcd for $C_{12}H_{23}NOS$: 229.1500, found 229.1507.

O-tert-Butyl 2,4-dimethylazetidine-1-carbothioate (11)



A solution of *O-tert*-butyl 2-methylazetidine-1-carbothioate (**10h**) (62 mg, 0.33 mmol) in THF (2 mL) was cooled to −78 °C (acetone / dry-ice) before the addition of TMEDA (119 µL, 0.79 mmol). *s*-BuLi (1.3 M in cyclohexane/ hexane, 331 µL, 0.43 mmol) was then added dropwise over 3 min. The reaction mixture was stirred for 30 min at −78 °C before the addition of the MeI (62 µL, 1.00 mmol). The reaction mixture was stirred for a further 30 min at −78 °C, warmed to rt over 10 min, stirred at rt for 10 min, quenched with sat. aq NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting very pale yellow oil (SiO_2, 0–2% Et_2O / petroleum ether) gave a colorless oil, *N*-Botc-2,4-dimethylazetidine **11** (37 mg, 55%, 93% brsm), as a ~1:1 mixture of inseparable diastereomers.

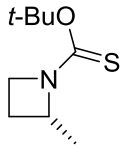
R_f 0.38 (10% Et_2O/ petroleum ether); IR (neat / cm^{-1}) 2965 w, 2927 w, 1465 m, 1430 s, 1390 w, 1365 w, 1347 w, 1268 s, 1225 w, 1138 s, 1003 m, 938 w, 835 m, 752 w; δ_H (400 MHz, $CDCl_3$) (1:1

diastereomer mixture) 4.54–4.19 (2H, m, NCH), 2.53 (1.98–1.87) (2H, dt (m), J = 11.1, 8.6 Hz, NCHCH_2), 1.64 (1.63) (9H, s, C(CH_3)$_3$), 1.56 (1.55) (3H, d, J = 6.0 Hz, NCHCH_3), 1.41 (1.39) (3H, d, J = 6.0 Hz, NCHCH_3); δ_C (100 MHz, $CDCl_3$) (diastereomer mixture) 186.4 (184.2) (C=S), 84.4 (C(CH_3)$_3$), 58.57 (58.54) (NCH), 58.1 (57.5) (NCH), 31.2 (31.1) (NCHCH_2), 28.6 (28.5) (C(CH_3)$_3$), 22.0 (21.3) (CHCH_3), 20.3 (19.0) (CHCH_3); HRMS (FI^+) calcd for $C_{10}H_{19}NOS$: 201.1187, found 201.1182.

General Procedure B: Asymmetric α-deprotonation–electrophile trapping of *O*-*tert*-butyl azetidine-1-carbothioate (5) with chiral DIANANE ligand 14

A solution of (1*S*,2*S*,4*S*,5*S*)-N^2,N^2,N^5,N^5-tetramethylbicyclo[2.2.1]heptane-2,5-diamine (**14**)[8] (1.3 equiv) in pentane (3.3 mL/ mmol **14**) was cooled to −78 °C and *s*-BuLi (1.3 M in cyclohexane / hexane, 1.3 equiv) was added dropwise. The reaction mixture was stirred for 10 min, and then transferred dropwise via cannula to a precooled solution of *O*-*tert*-butyl azetidine-1-carbothioate (**5**) (1 equiv) in pentane (4.3 mL/ mmol **5**) at the appropriate lithiation temp (−78 °C or −98 °C). The reaction mixture was stirred at this temp for the appropriate lithiation time (1 h or 3 h) before the addition of the electrophile (3 equiv). The reaction mixture was stirred at the same temp for a further 1 h, quenched with sat. aq HCl (1 M, 10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

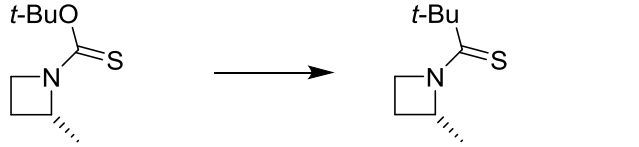
***O*-(*tert*-Butyl) (*R*)-2-methylazetidine-1-carbothioate ((*R*)-10h) (from reaction in Et_2O)**



O-*tert*-Butyl azetidine-1-carbothioate (**5**) (80 mg, 0.46 mmol) and MeI (87 μL, 1.39 mmol) were used following a modified General Procedure B (using Et_2O as solvent instead of pentane), with a lithiation temp of −78 °C and lithiation time of 1 h. Purification of the resulting colorless oil (SiO_2, 0–5% EtOAc / hexane) gave methylated azetidine (*R*)-**10h** as a colorless oil (55 mg, 64%) in 56:44 er (chiral SFC analysis, p S61, τ_R (major) = 4.50 min, τ_R (minor) = 3.75 min). Absolute configuration was assigned by conversion to the corresponding *N*-thiopivaloyl azetidine (*R*)-**2** (E = Me), see below, and comparing chiral GC data with those for enantiomerically pure (*R*)-**2** (E = Me).[2]

$[\alpha]_D^{25}$ −4.1 (*c* 1.18, $CHCl_3$); all other data as described for **10h**.

(*R*)-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (*R*)-2 (E = Me)



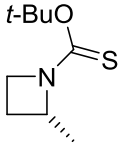
(*R*)-**10h**
(56:44 er
by chiral SFC analysis)

(*R*)-**2** (E = Me)
(56:44 er
by chiral GC analysis)

A solution of HCl in Et_2O (2 M, 3 mL, 6.0 mmol) was added to a sample *O*-(*tert*-butyl) (*R*)-2-methylazetidine-1-carbothioate ((*R*)-**10h**) (44 mg, 0.24 mmol, 56:44 er)**.** The reaction mixture was stirred at rt for 5 h, then concentrated under reduced pressure. Py (1 mL) and DMAP (6 mg, 0.05 mmol) were added to the resulting white solid and the reaction mixture heated to 70 °C for 10 min, then cooled to 0 °C. PivCl (43 µL, 0.35 mmol) was added and the reaction mixture stirred at rt for 12 h. P_2S_5 (209 mg, 0.94 mmol) and py (0.5 mL) was added and the reaction mixture stirred at 75 °C for 6 h, then aq HCl (3 M, 20 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with aq HCl (1 M, 10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting dark red oil (SiO_2, 10% Et_2O/ petroleum ether) gave a colorless oil, *N*-thiopivaloyl azetidine (*R*)-**2** (E = Me)[2] (28 mg, 70%), in 56:44 (*R*:*S*) er (by chiral GC analysis, p S63, τ_R (major) = 36.1 min, τ_R (minor) = 36.5 min; lit.[2] τ_R (*R*) = 29.6 min, τ_R (*S*) = 30.0 min).

$[\alpha]_D^{25}$ −0.1 (*c* 1.27, $CHCl_3$); lit.[2] enantiomerically pure (*R*)-**2** (E = Me) $[\alpha]_D^{25}$ −21.3 (*c* 1.15, $CHCl_3$); R_f 0.38 (30% Et_2O / petroleum ether); IR (neat/ cm^{-1}) 2963 w, 2926 w, 1456 s, 1426 s, 1394 w, 1363 m, 1331 w, 1291 w, 1255 m, 1237 w, 1139 m, 994 w, 931 w; δ_H (400 MHz, $CDCl_3$) (6.8:1 rotamer mixture by analysis of NCHCH_3 signals at 1.64 and 1.60) 4.88–4.81 (1H, m, NC*H*), 4.59–4.52 (1H, m, NC*H*H′), 4.44–4.38 (1H, m, NCH*H*′), 2.57–2.48 (1H, m, NCH_2CHH′), 1.87–1.80 (1H, m, NCH_2CH*H*′), 1.60 (1.64) (3H, d, *J* = 6.3 Hz, CH_3), 1.31 (1.39) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 209.6 (C=S), 64.7 (65.7) (NCH), 55.6 (53.6) (NCH_2), 43.2 ($C(CH_3)_3$), 29.6 (30.8) ($C(CH_3)_3$), 23.1 (22.9) (NCH_2CH_2), 18.4 ($CHCH_3$); LRMS (ESI^+) 172.1 ($[M+H]^+$, 15%), 194.1 ($[M+Na]^+$, 10%), 409.1 (100%).

***O*-(*tert*-Butyl) (*R*)-2-methylazetidine-1-carbothioate ((*R*)-10h) (from reaction in pentane)**

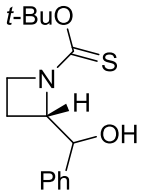


O-*tert*-Butyl azetidine-1-carbothioate (**5**) (160 mg, 0.92 mmol) and MeI (172 µL, 2.77 mmol) were used following General Procedure B, with a lithiation temp of −98 °C and lithiation time of 1 h. Purification of the resulting colorless oil (SiO_2, 3–5% Et_2O / petroleum ether) gave a colorless oil,

methylated azetidine (*R*)-**10h** (78 mg, 45%, 83% brsm) in 91:9 er (chiral SFC analysis, p S62, τ_R (*R*) = 8.39 min, τ_R (*S*) = 7.15 min).

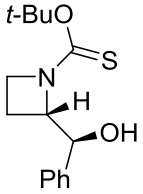
$[\alpha]_D^{25}$ −32.6 (*c* 1.12, $CHCl_3$); all other data as described for **10h**.

***O*-(*tert*-Butyl) (2*S*)-2-(hydroxy(phenyl)methyl)azetidine-1-carbothioate ((2*S*)-10d)**



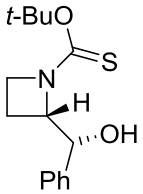
O-*tert*-Butyl azetidine-1-carbothioate (**5**) (60 mg, 0.35 mmol) and benzaldehyde (106 µL, 1.04 mmol) were used following General Procedure B, with a lithiation temp of −78 °C and lithiation time of 1 h. Purification of the resulting pale yellow oil (SiO_2, 5–30% Et_2O/ petroleum ether) gave first a colorless oil, the minor diastereomer (*S*,*S*)-**10d-minor** (34 mg, 35%) in 85:15 er (chiral HPLC analysis, p S65–S66, τ_R (major) = 11.57 min, τ_R (minor) = 12.66 min), followed by a colorless oil, the major diastereomer (*S*,*R*)-**10d-major** (51 mg, 53%) in 86:14 er (chiral HPLC analysis, p 67–68, τ_R (major) = 26.02 min, τ_R (minor) = 36.09 min); stereochemistry was assigned by analogy to (*R*)-**10h**.

***O*-(*tert*-Butyl) (*S*)-2-((*S*)-hydroxy(phenyl)methyl)azetidine-1-carbothioate ((*S*,*S*)-10d-minor)**



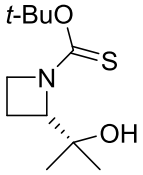
$[\alpha]_D^{25}$ +91.6 (*c* 0.98, $CHCl_3$); all other data as described for (*R**,*R**)-**10d-minor**.

***O*-(*tert*-Butyl) (*S*)-2-((*R*)-hydroxy(phenyl)methyl)azetidine-1-carbothioate ((*S*,*R*)-10d-major)**



$[\alpha]_D^{25}$ +22.7 (*c* 1.03, $CHCl_3$); all other data as described for (*R**,*S**)-**10d-major**.

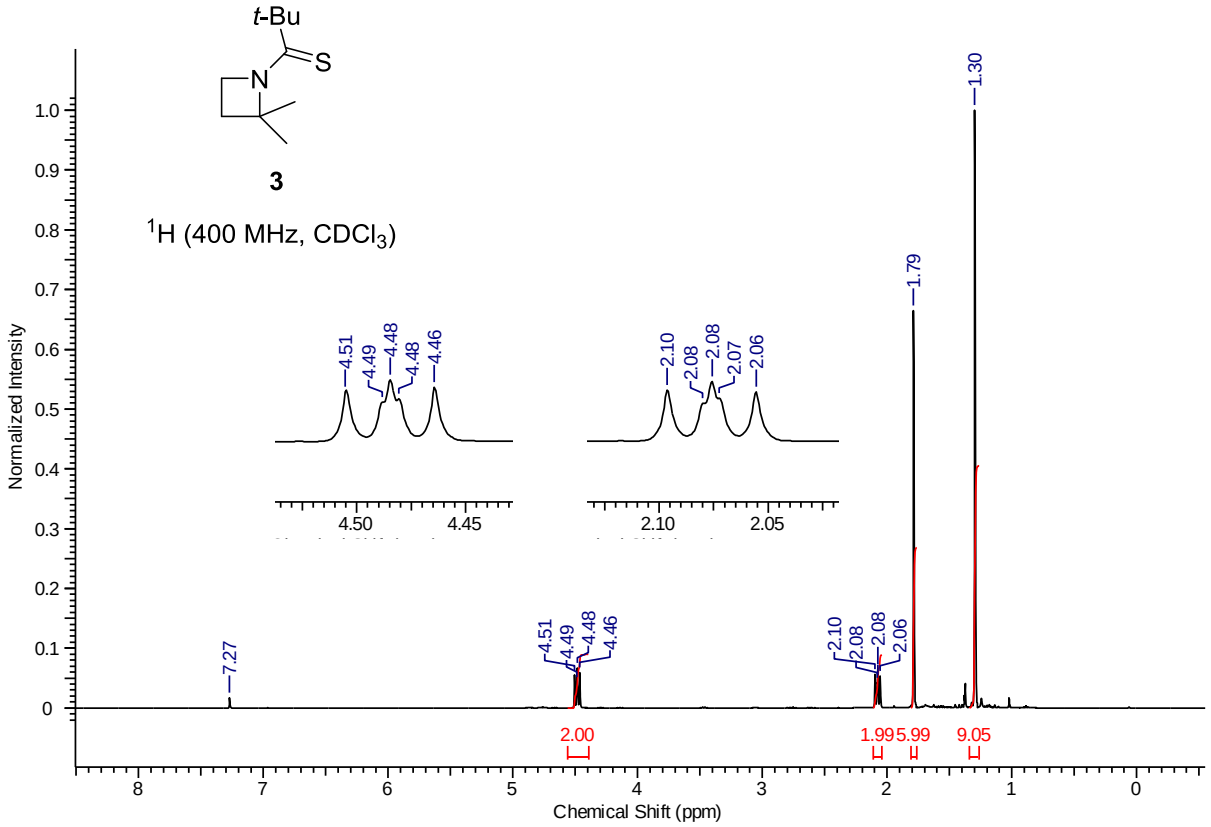
_O_-(_tert_-Butyl) (_S_)-2-(2-hydroxypropan-2-yl)azetidine-1-carbothioate ((_S_)-10g)

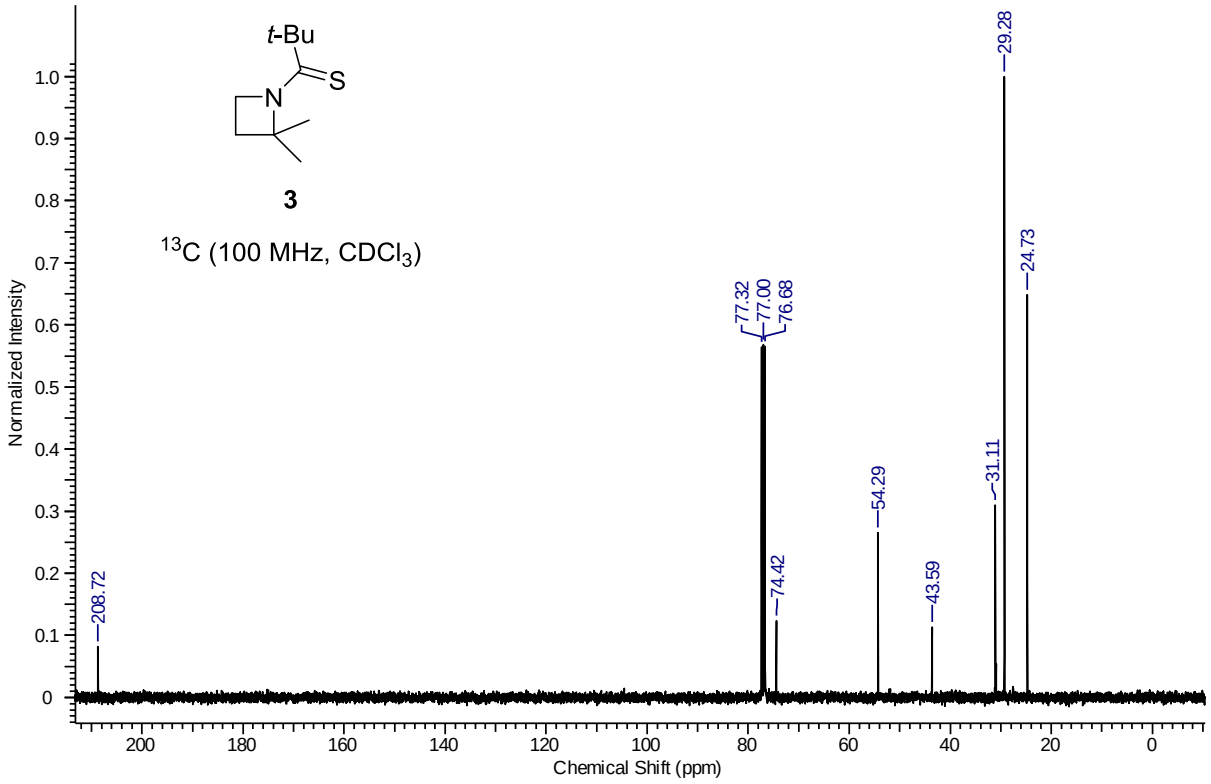


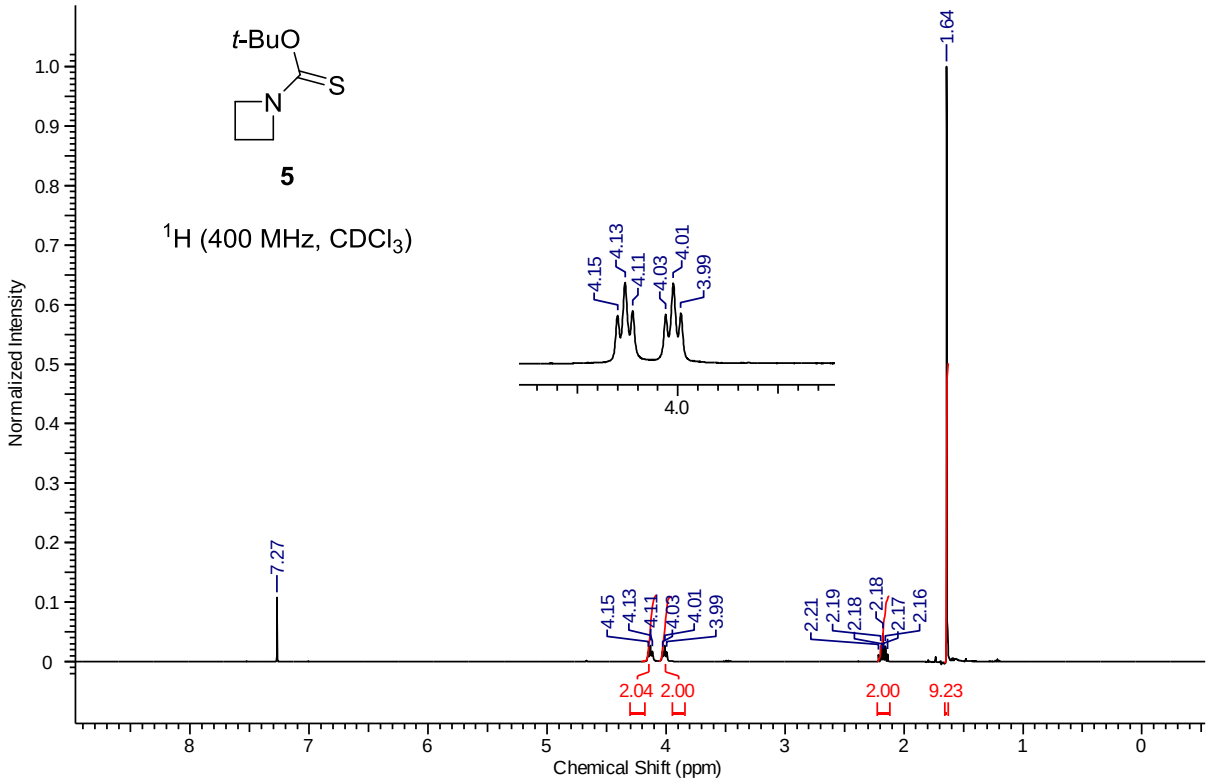
O-tert-Butyl azetidine-1-carbothioate (**5**) (60 mg, 0.35 mmol) and acetone (76 μL, 1.04 mmol) were used following General Procedure B, with a lithiation temp of −78 °C and lithiation time of 3 h. Purification of the resulting yellow oil (SiO_2, 10–40% Et_2O / petroleum ether) gave a colorless oil, alcohol (*S*)-**10g** (51 mg, 64%) in 92:8 er (chiral HPLC analysis, p S69–S70, τ_R (major) = 12.18 min, τ_R (minor) = 14.17 min); stereochemistry was assigned by analogy to (*R*)-**10h**.

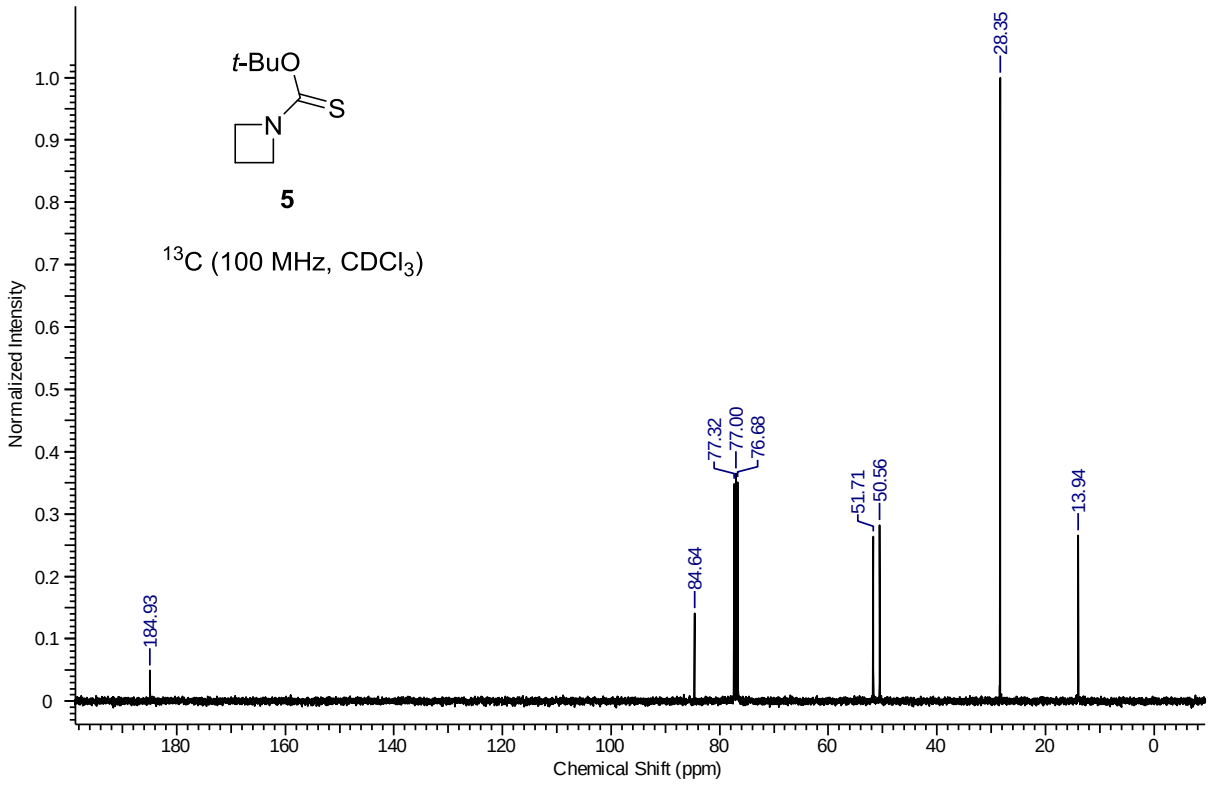
$[\alpha]_D^{25}$ +87.8 (*c* 1.02, $CHCl_3$); all other data as described for **10g**.

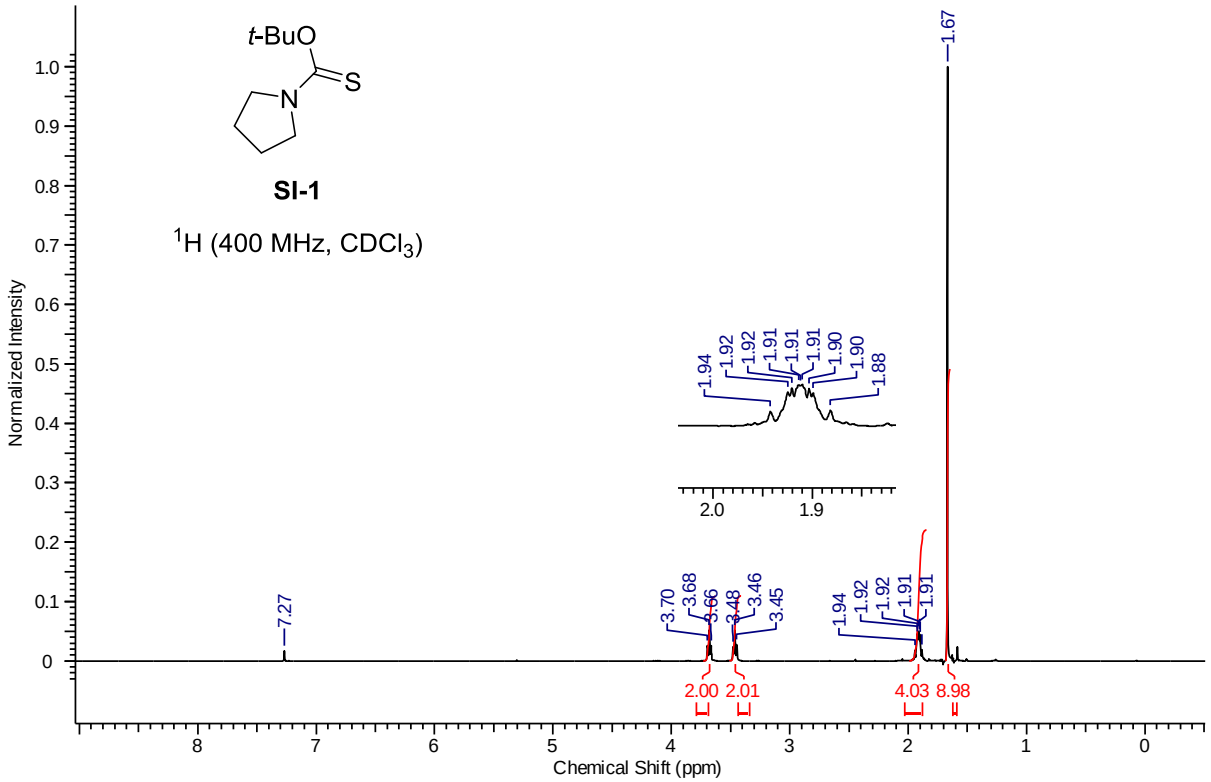
3. ^{1}H, ^{13}C and ^{19}F NMR spectra

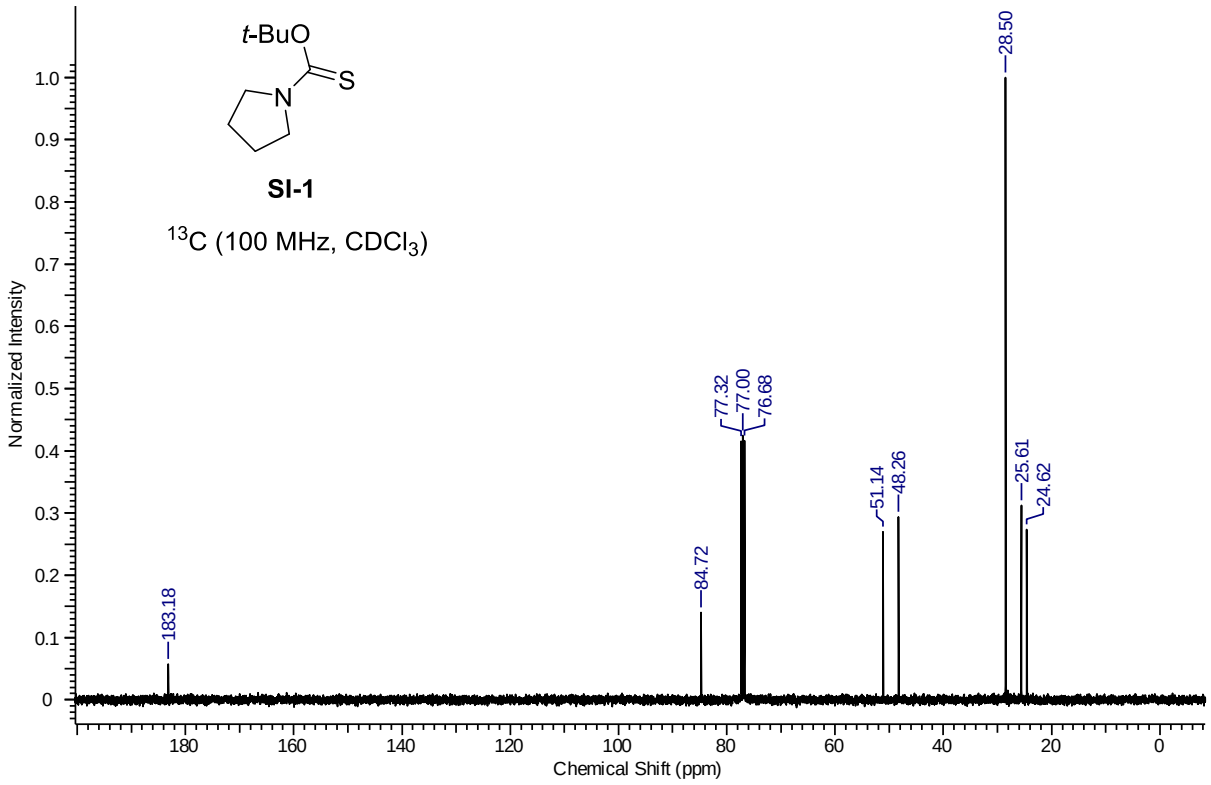


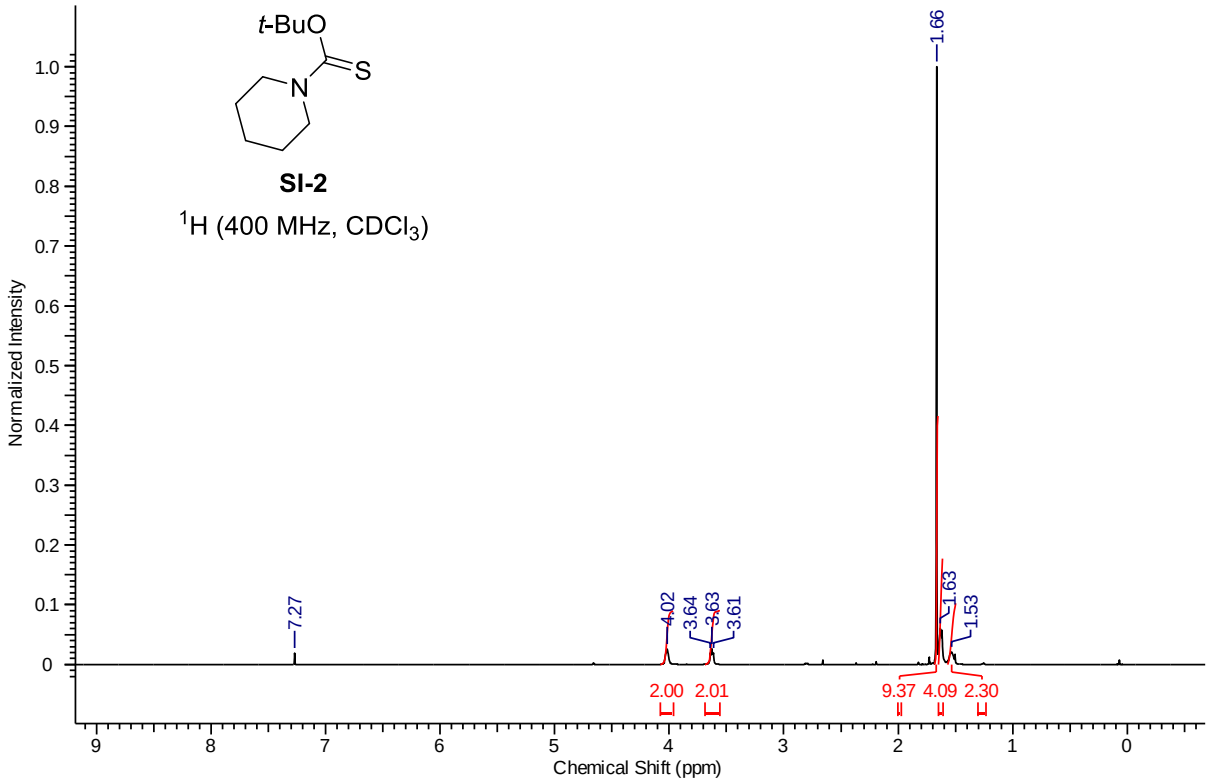


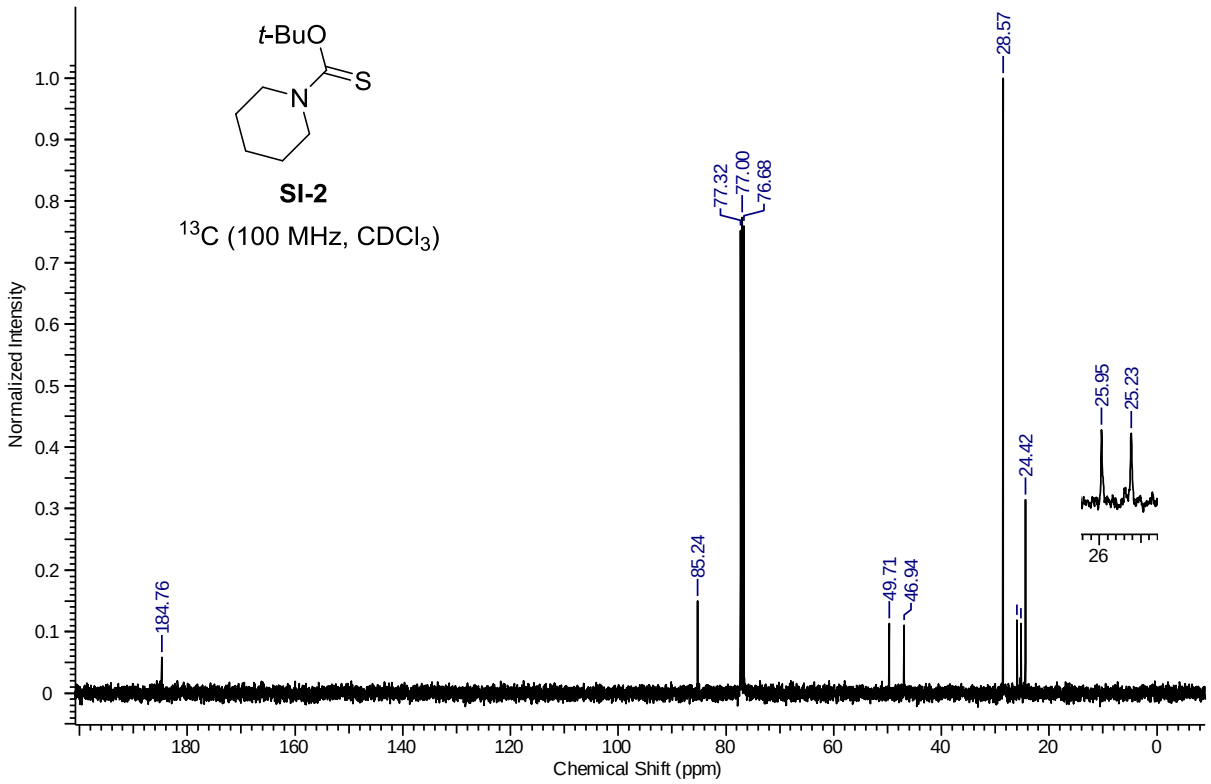

t-BuO
S
N
5
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
4.15
4.13
4.11
4.03
4.01
3.99
2.21
2.19
2.18
2.17
2.16
1.64
2.04
2.00
2.00
9.23

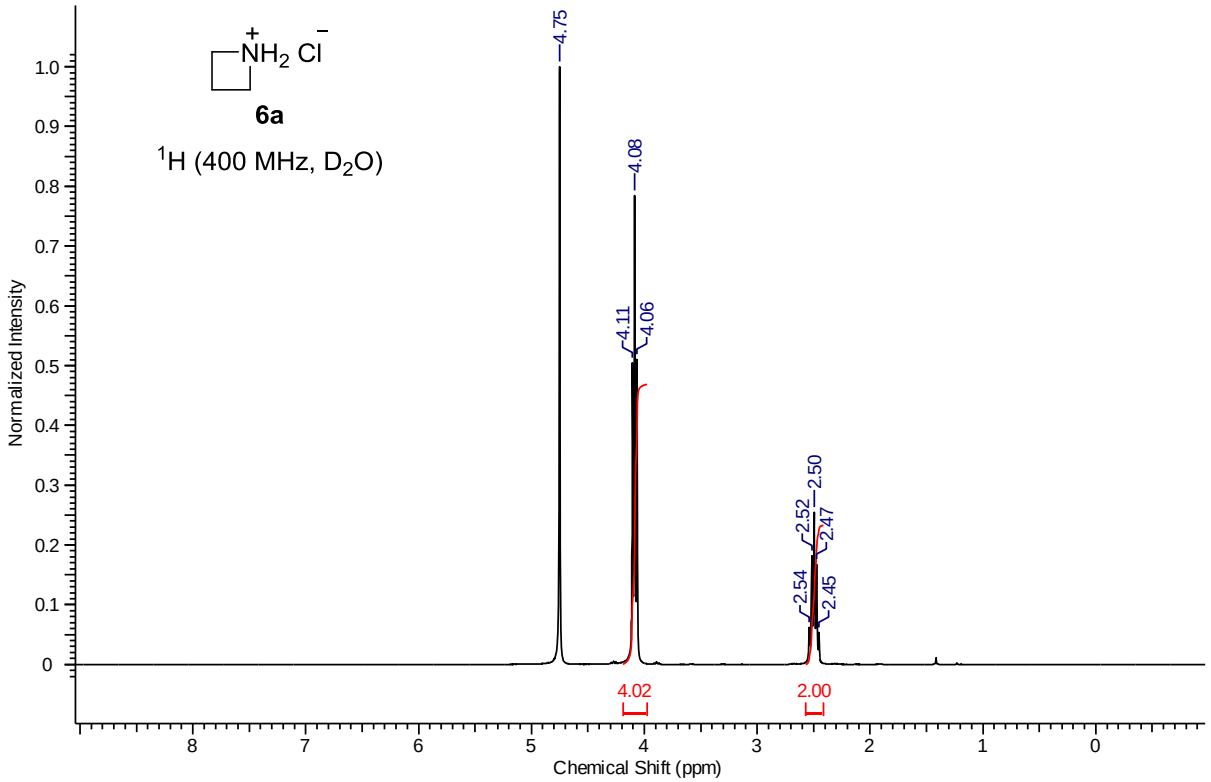

t-BuO
S
N
5
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
184.93
84.64
77.32
77.00
76.68
51.71
50.56
28.35
13.94

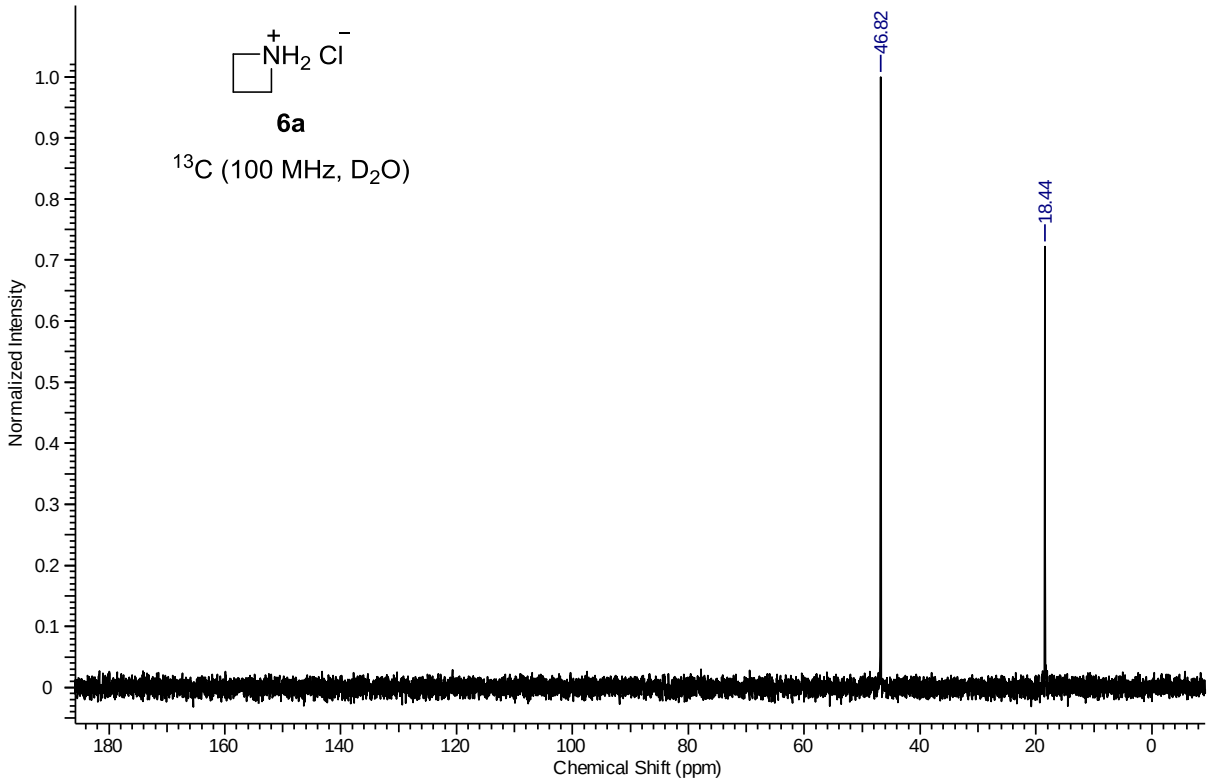

t-BuO
S
N
SI-1
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
1.67
7.27
3.70
3.68
3.66
3.48
3.46
3.45
1.94
1.92
1.92
1.91
1.91
1.91
1.90
1.90
1.88
2.00
2.01
4.03
8.98

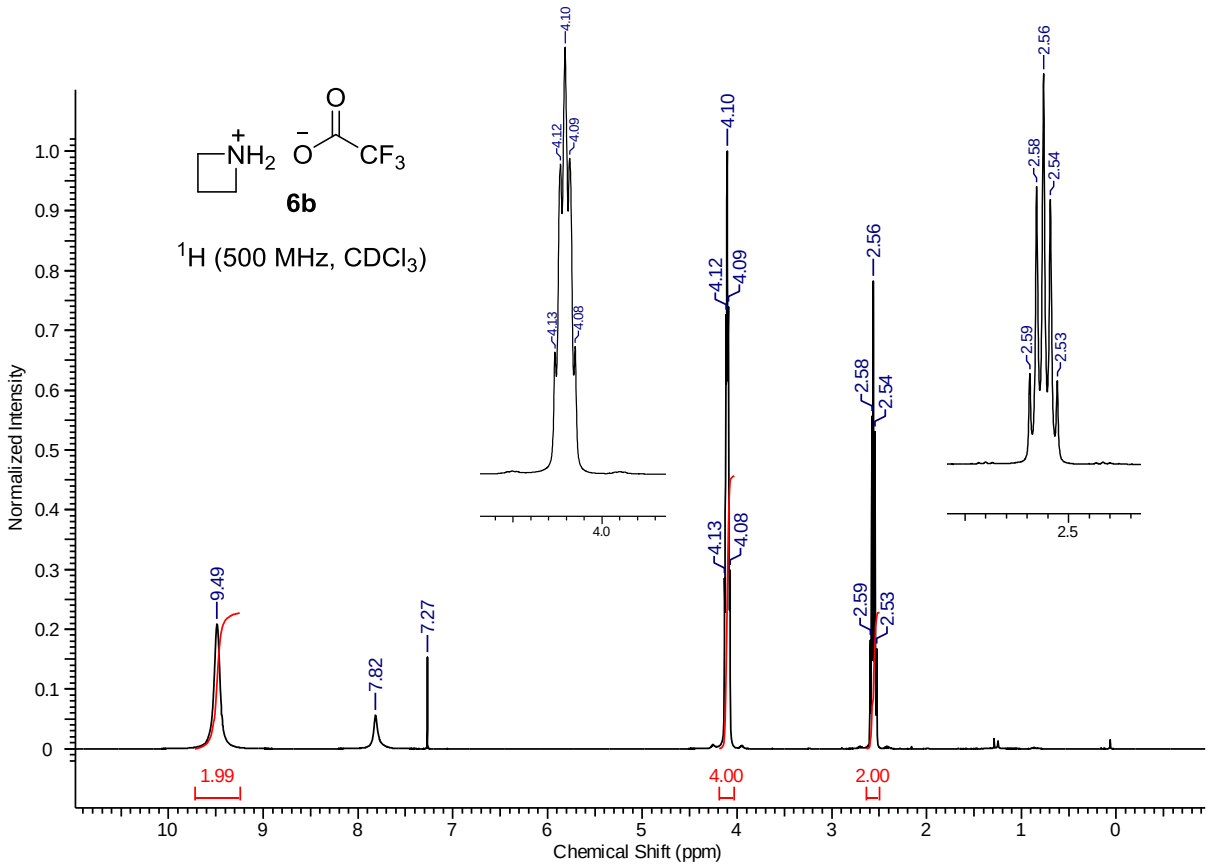

t-BuO
S
N
SI-1
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
28.50
77.32
77.00
76.68
51.14
48.26
25.61
24.62
84.72
183.18

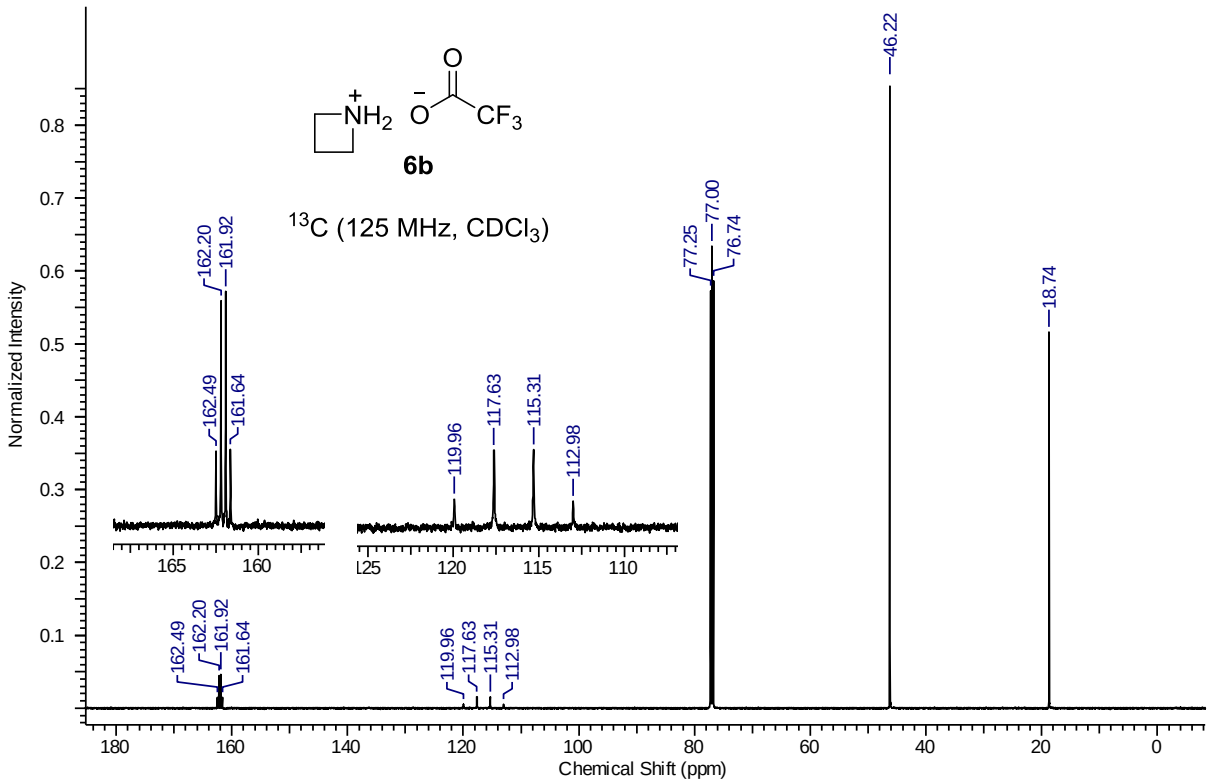

t-BuO
N
S
SI-2
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
4.02
3.64
3.63
3.61
1.66
1.63
1.53
2.00
2.01
9.37
4.09
2.30

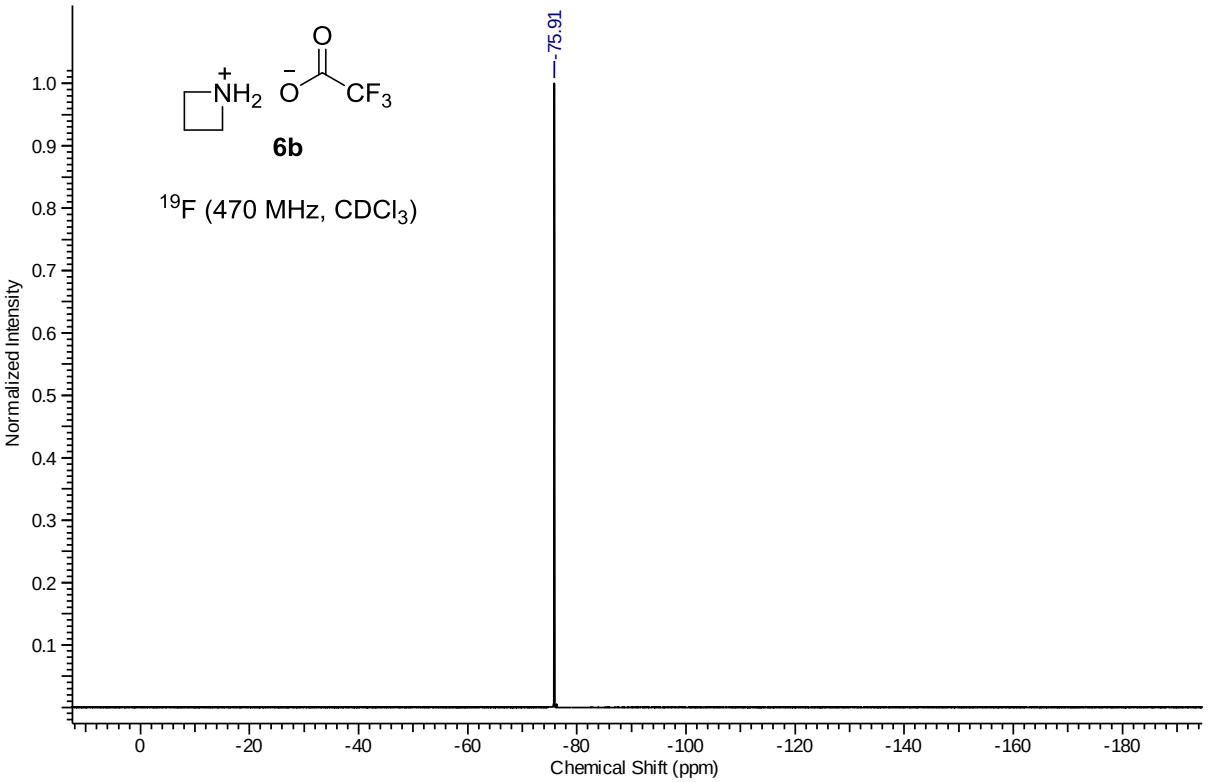

t-BuO
N
S
SI-2
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
184.76
85.24
77.32
77.00
76.68
49.71
46.94
28.57
24.42
25.95
25.23
26

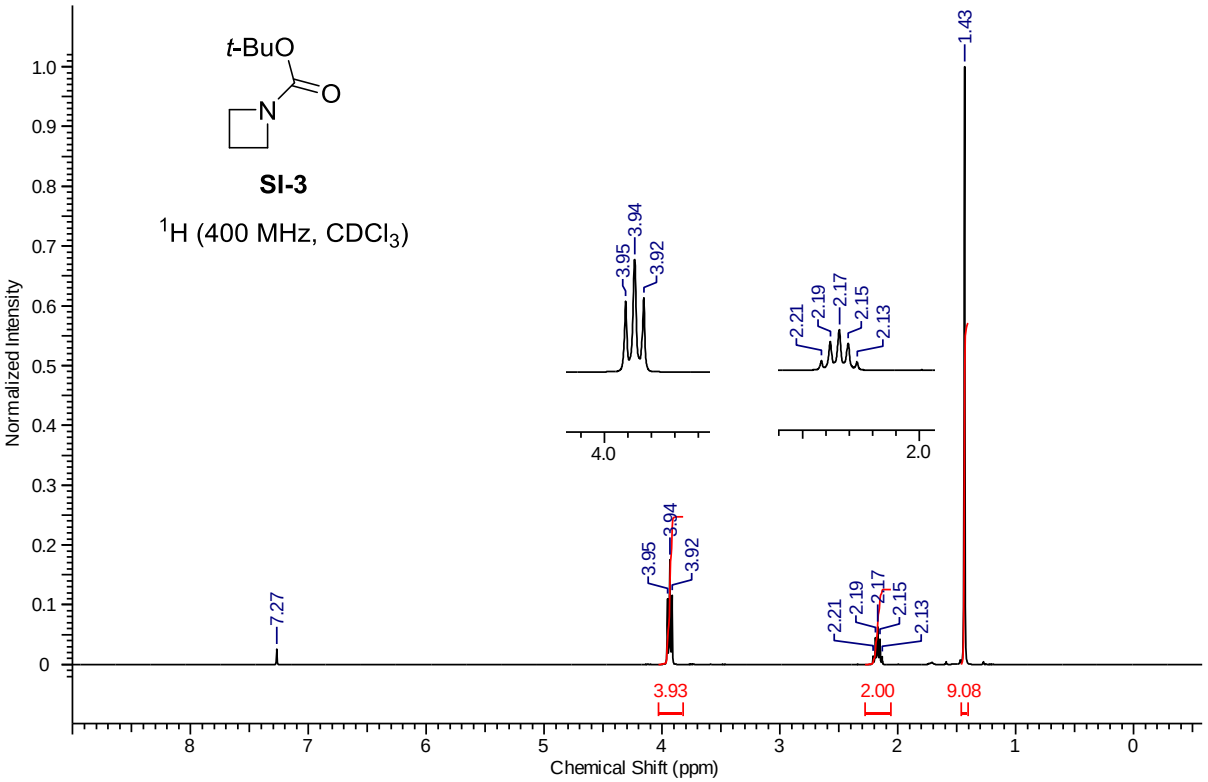

NH2 Cl
6a
1H (400 MHz, D2O)
4.75
4.08
4.11
4.06
2.52
2.50
2.47
2.54
2.45
4.02
2.00
Normalized Intensity
Chemical Shift (ppm)

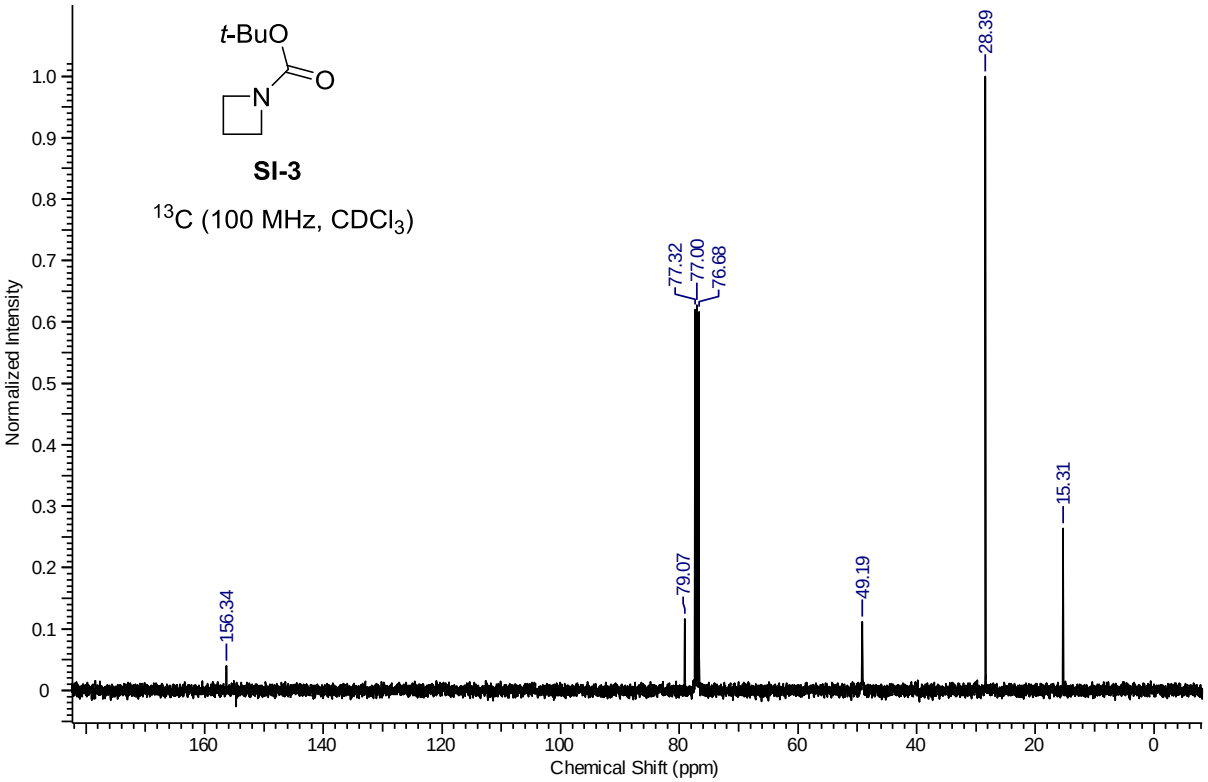

NH2 Cl
6a
13C (100 MHz, D2O)
46.82
18.44
Normalized Intensity
Chemical Shift (ppm)

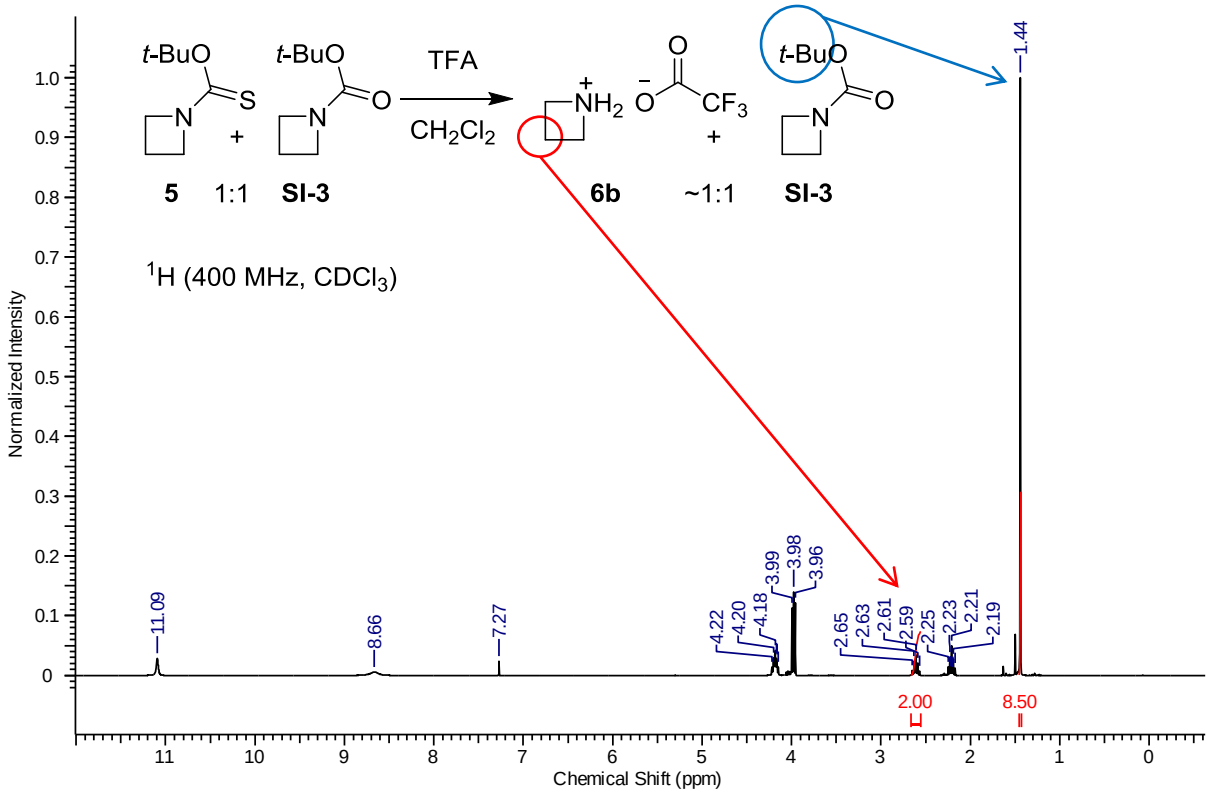

6b
^{1}H (500 MHz, $CDCl_3$)
Normalized Intensity
Chemical Shift (ppm)
9.49
7.82
7.27
4.13
4.12
4.10
4.09
4.08
2.59
2.58
2.56
2.54
2.53
1.99
4.00
2.00

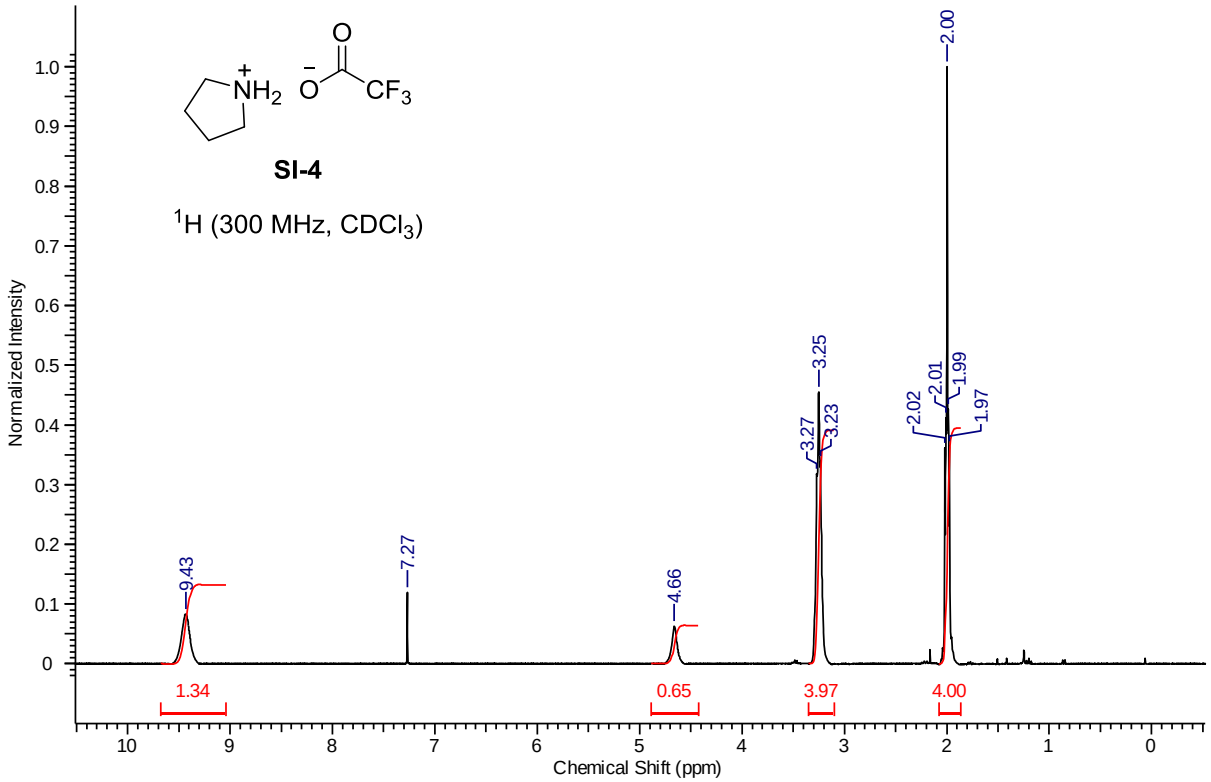

6b
^{13}C (125 MHz, $CDCl_3$)
Normalized Intensity
Chemical Shift (ppm)
162.49
162.20
161.92
161.64
119.96
117.63
115.31
112.98
77.25
77.00
76.74
46.22
18.74

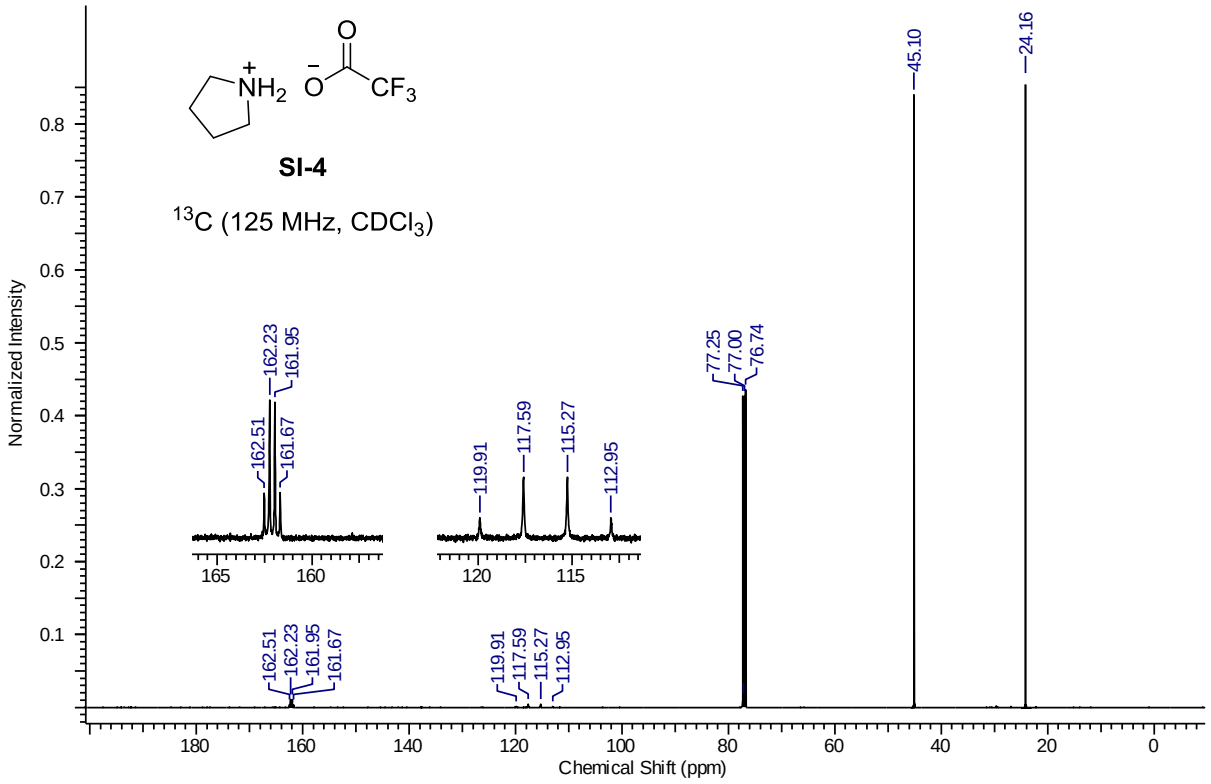

6b
^{19}F (470 MHz, $CDCl_3$)
-75.91
Normalized Intensity
Chemical Shift (ppm)

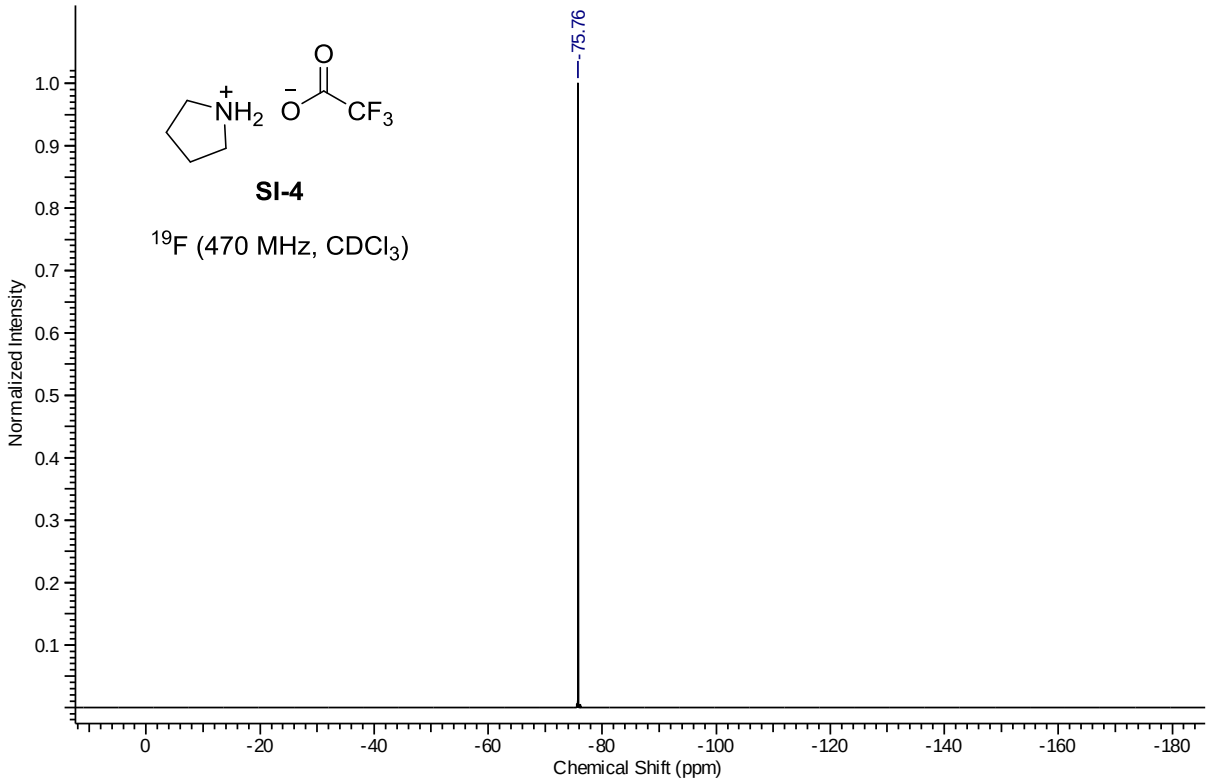

t-BuO
O
N
SI-3
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
3.95
3.94
3.92
2.21
2.19
2.17
2.15
2.13
1.43
3.93
2.00
9.08

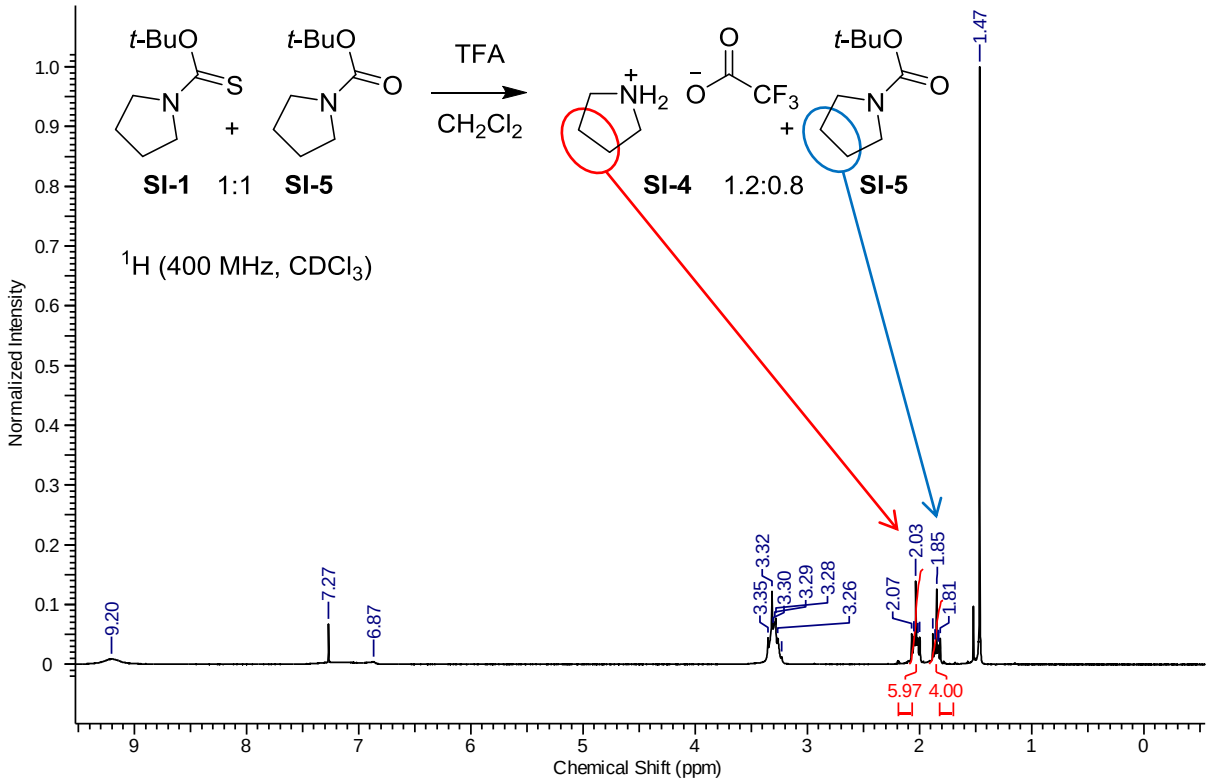

t-BuO
O
N
SI-3
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
156.34
79.07
77.32
77.00
76.68
49.19
28.39
15.31

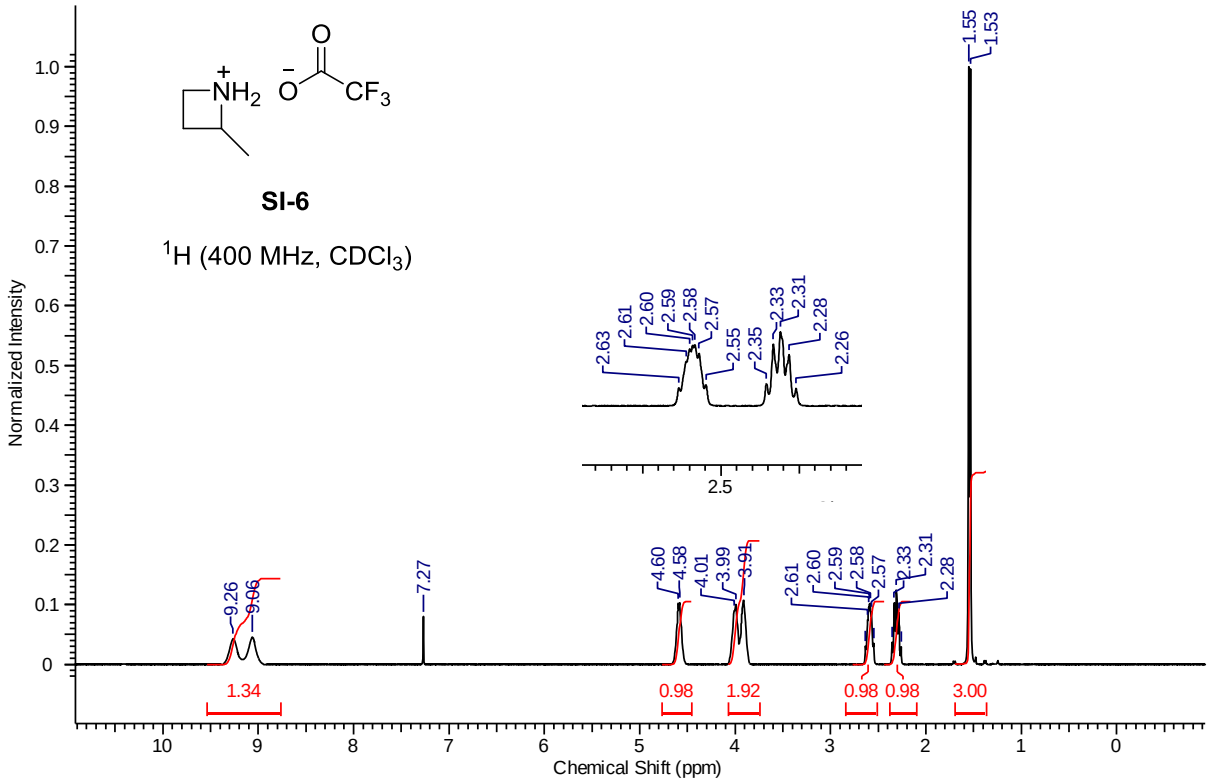

t-BuO
N
S
+
t-BuO
N
O
TFA
CH2Cl2
+NH2
O
O
CF3
+
t-BuO
N
O
5
1:1
SI-3
6b
~1:1
SI-3
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
11.09
8.66
7.27
4.22
4.20
4.18
3.99
3.98
3.96
2.65
2.63
2.61
2.59
2.25
2.23
2.21
2.19
1.44
2.00
8.50

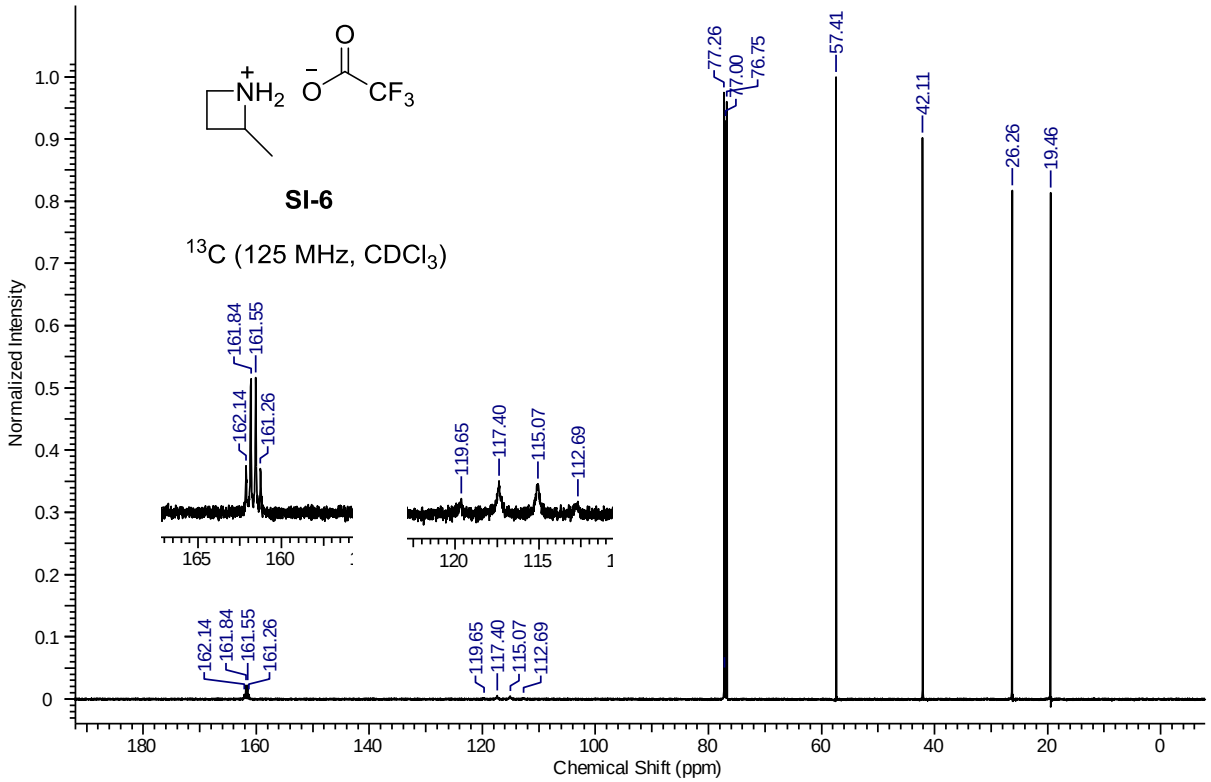

SI-4
1H (300 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
9.43
7.27
4.66
3.25
3.27
3.23
2.00
2.02
2.01
1.99
1.97
1.34
0.65
3.97
4.00

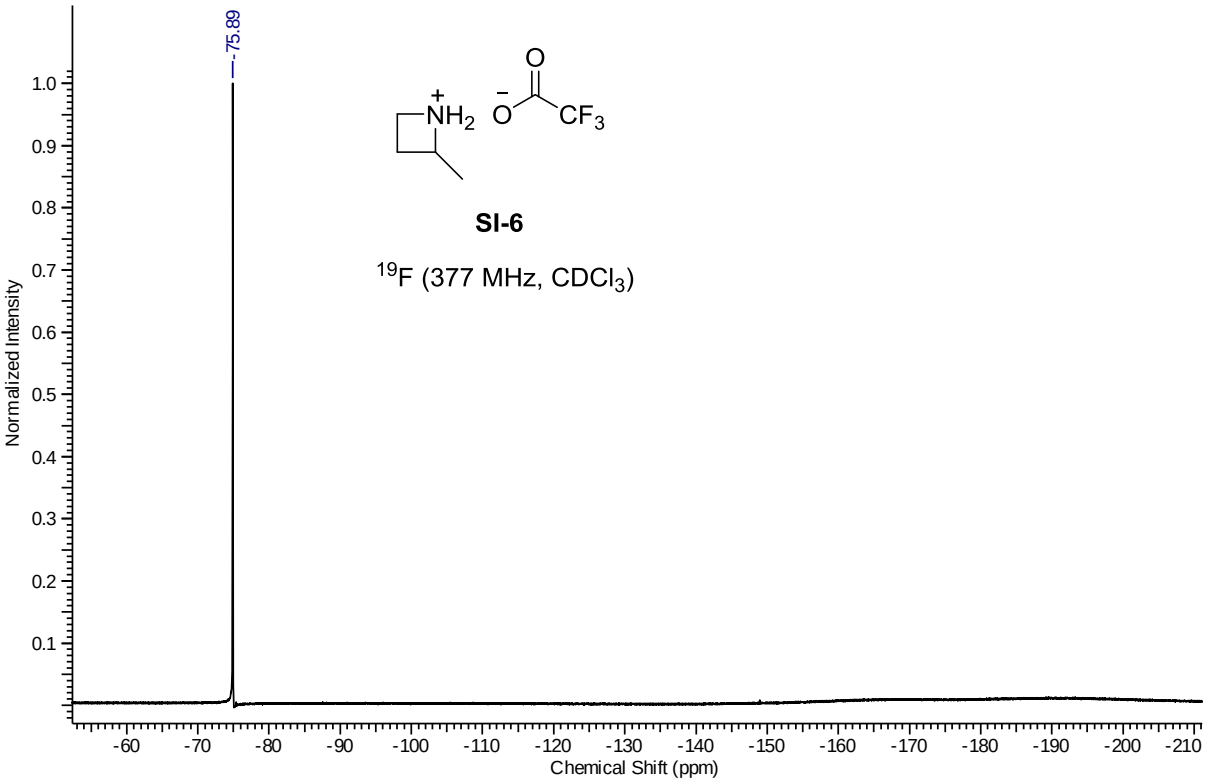

SI-4
13C (125 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
45.10
24.16
77.25
77.00
76.74
162.23
161.95
162.51
161.67
119.91
117.59
115.27
112.95


SI-4
19F (470 MHz, CDCl3)
-75.76
Normalized Intensity
Chemical Shift (ppm)


t-BuO
t-BuO
TFA
CH2Cl2
SI-1 1:1 SI-5
SI-4 1.2:0.8 SI-5
1H (400 MHz, CDCl3)
9.20
7.27
6.87
3.35
3.32
3.30
3.29
3.28
3.26
2.07
2.03
1.85
1.81
1.47
5.97
4.00
Normalized Intensity
Chemical Shift (ppm)

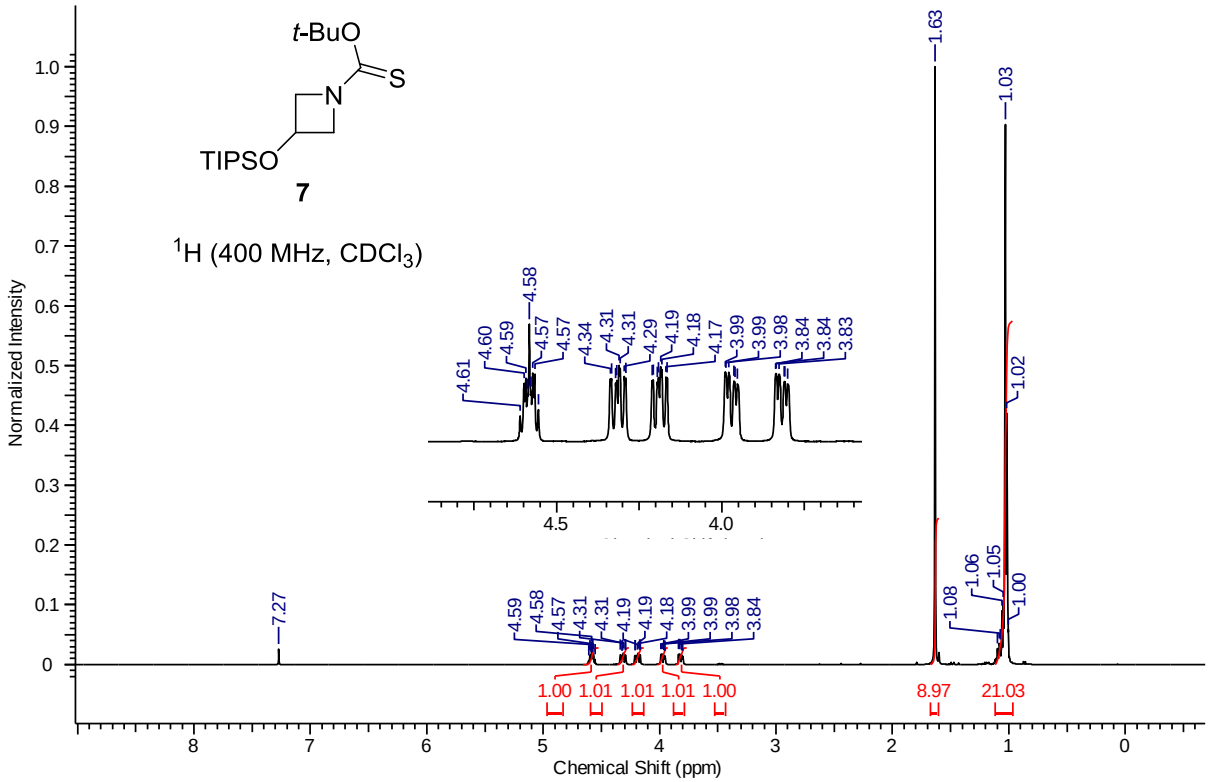

SI-6
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
9.26
9.06
7.27
4.60
4.58
4.01
3.99
3.91
2.63
2.61
2.60
2.59
2.58
2.57
2.55
2.35
2.33
2.31
2.28
2.26
1.55
1.53
1.34
0.98
1.92
0.98
0.98
3.00

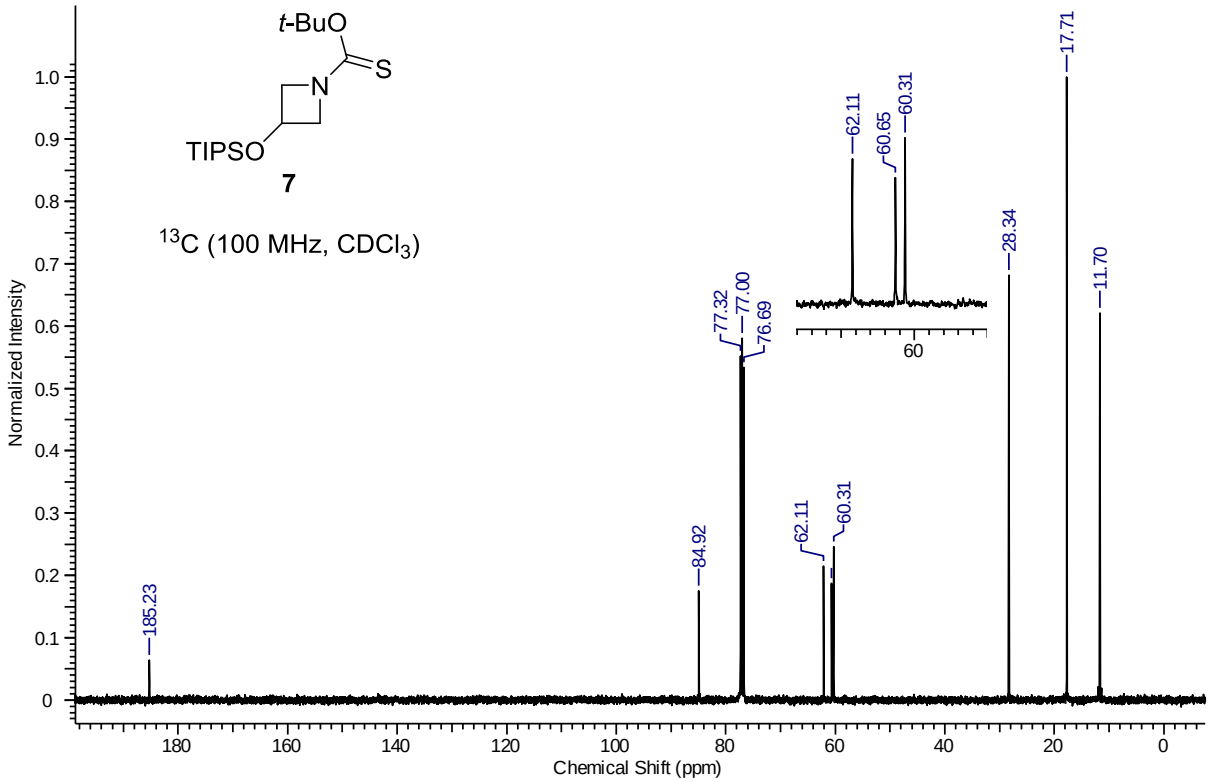

SI-6
13C (125 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
161.84
161.55
162.14
161.26
119.65
117.40
115.07
112.69
77.26
77.00
76.75
57.41
42.11
26.26
19.46

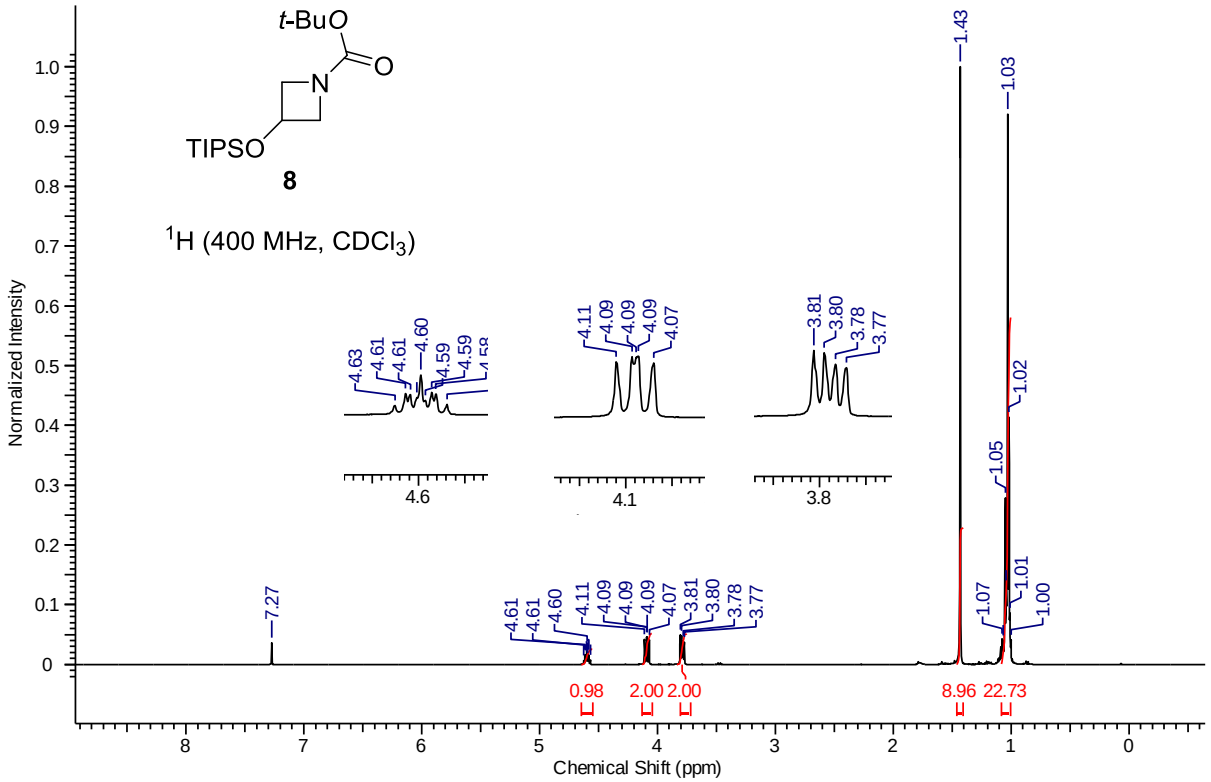


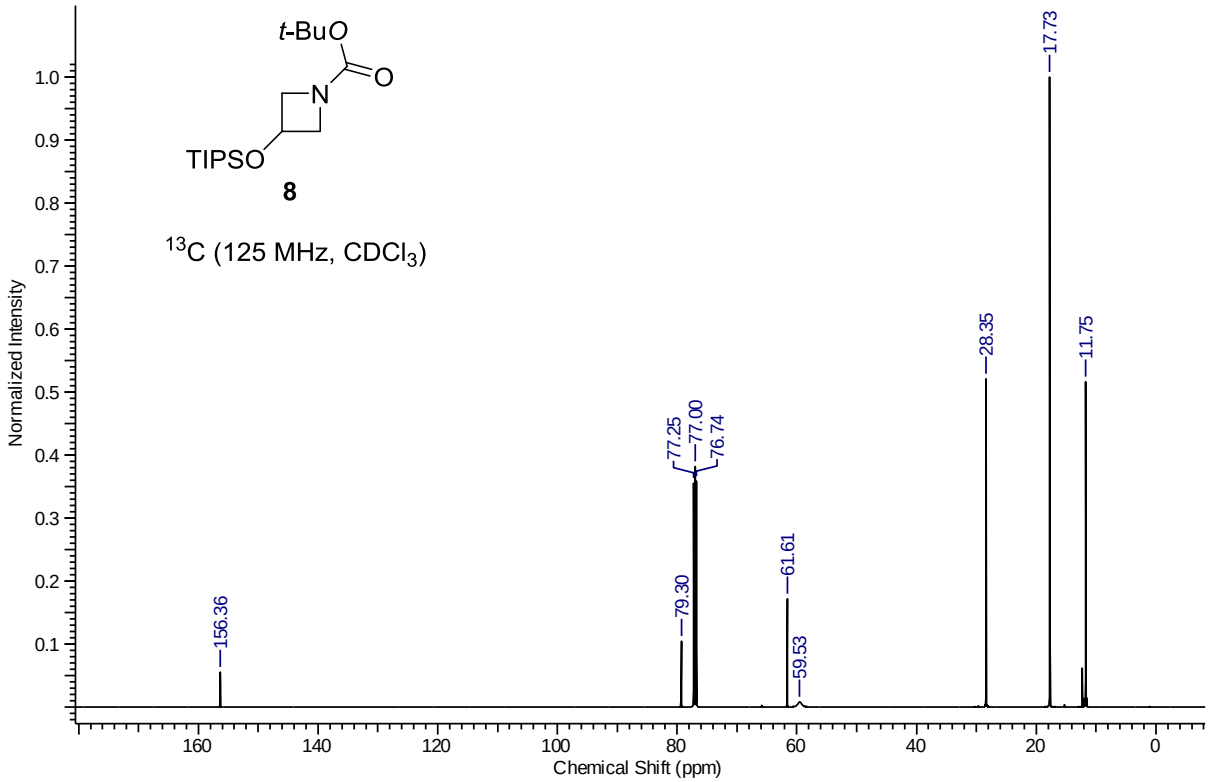
SI-6

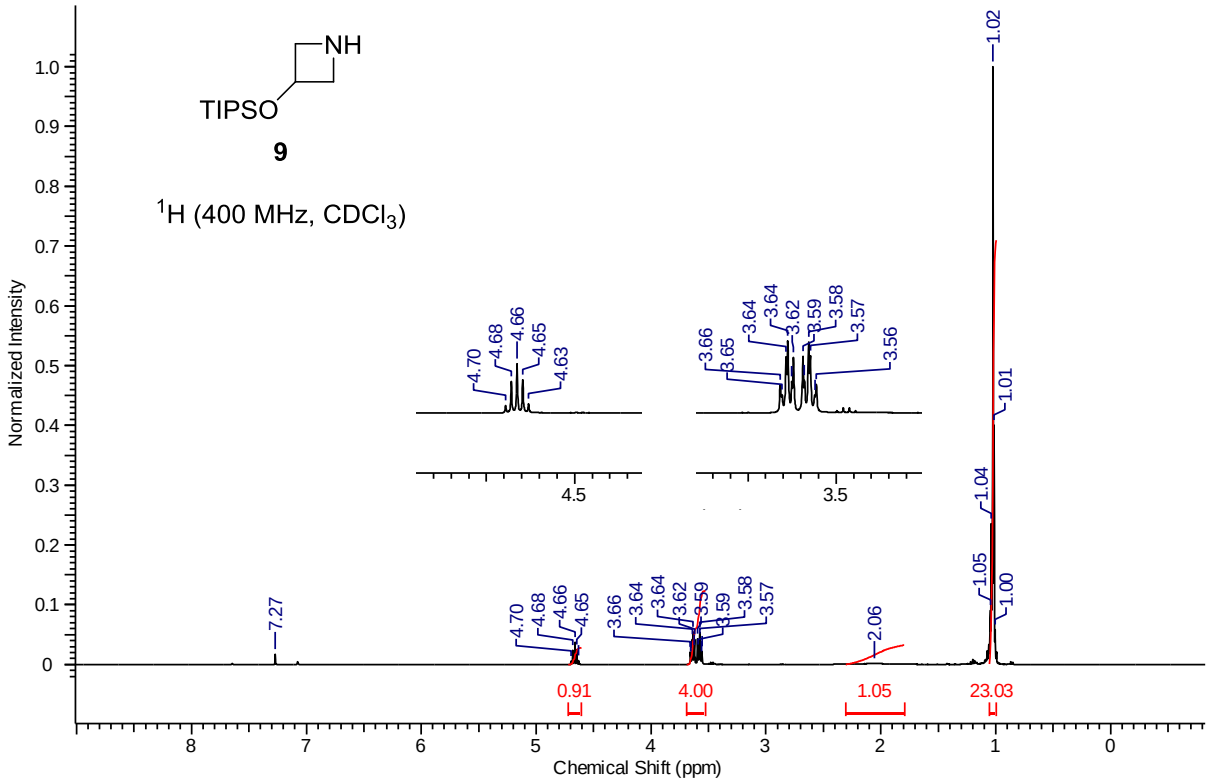
^{19}F (377 MHz, $CDCl_3$)

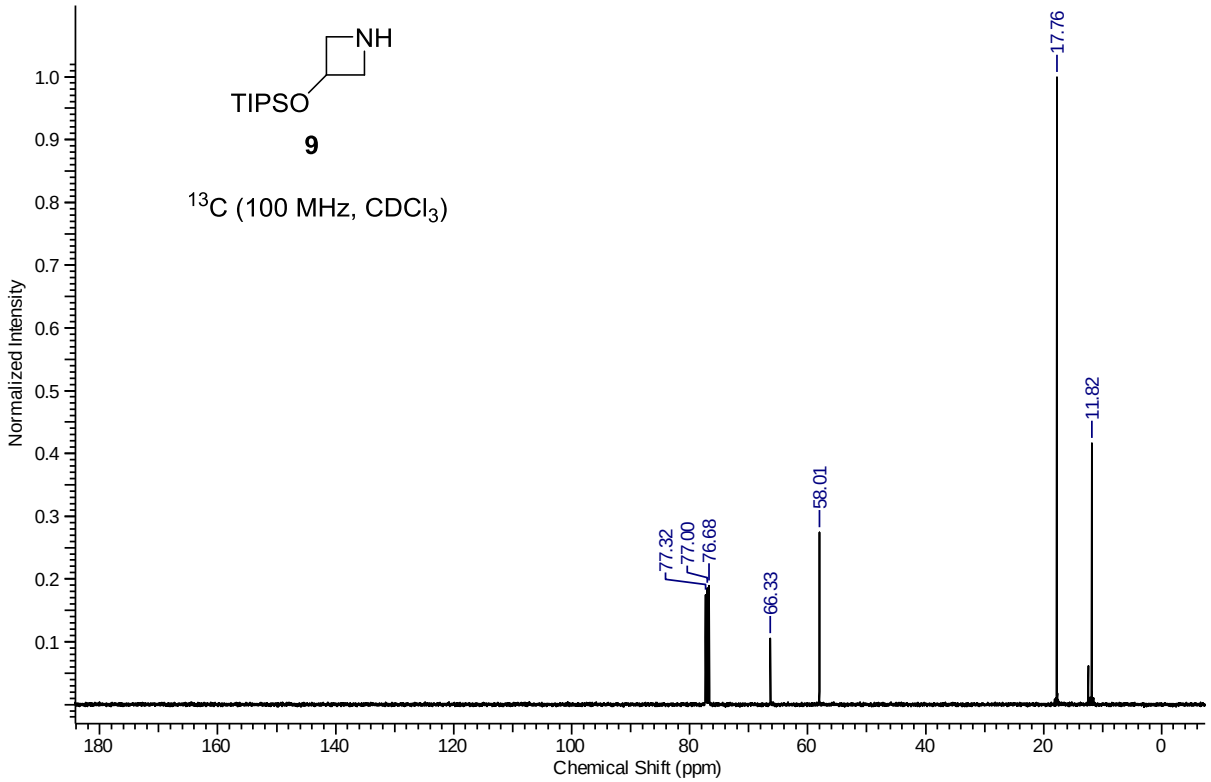

t-BuO
S
N
TIPSO
7
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
4.61
4.60
4.59
4.58
4.57
4.57
4.34
4.31
4.31
4.29
4.19
4.18
4.17
3.99
3.99
3.98
3.84
3.84
3.83
1.63
1.03
1.02
1.08
1.06
1.05
1.00
1.00 1.01 1.01 1.01 1.00
8.97
21.03

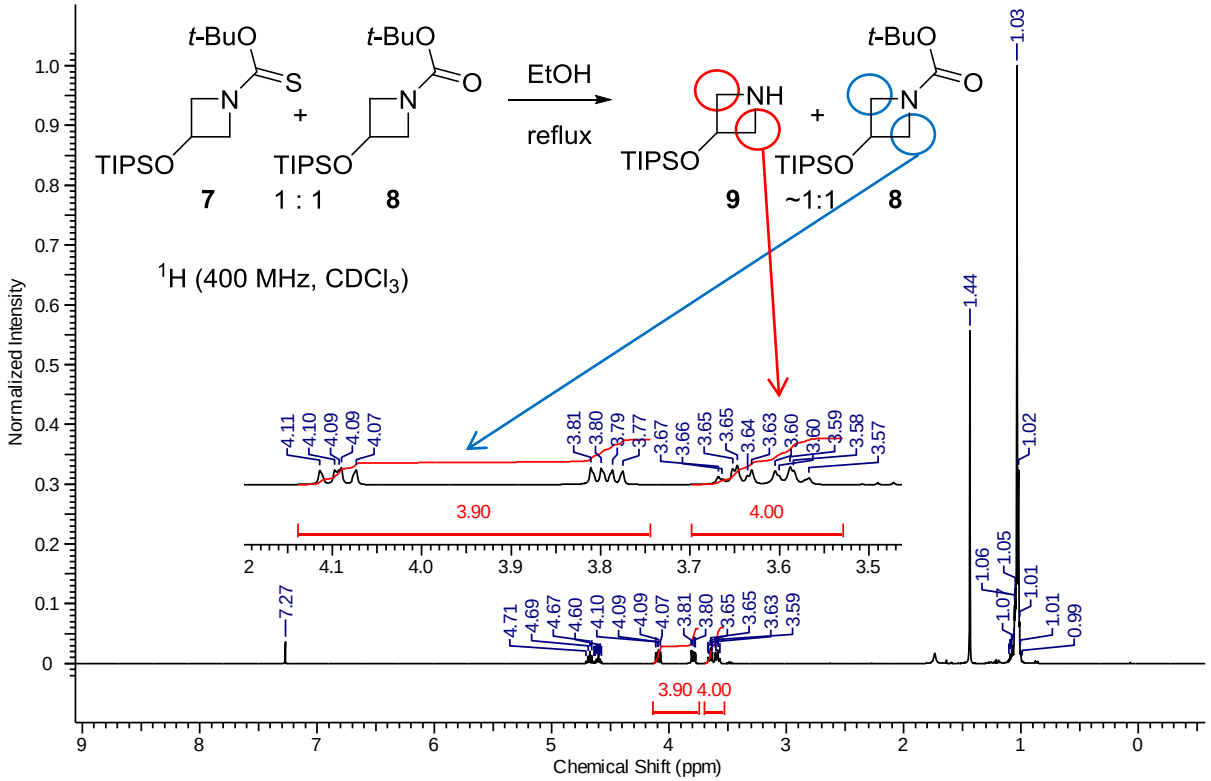

t-BuO
S
N
TIPSO
7
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
185.23
84.92
77.32
77.00
76.69
62.11
60.31
62.11
60.65
60.31
28.34
17.71
11.70

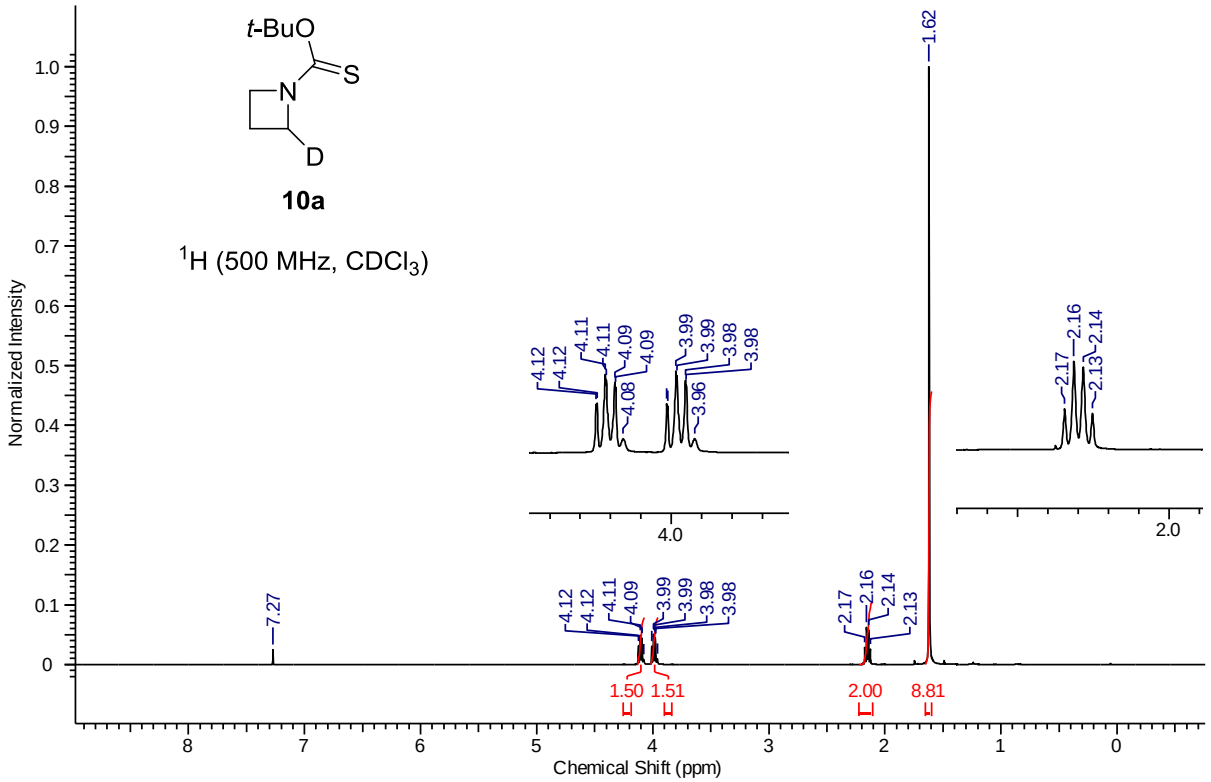

t-BuO
N
O
TIPSO
8
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
4.61
4.61
4.60
4.11
4.09
4.09
4.09
4.07
3.81
3.80
3.78
3.77
1.43
1.03
1.02
1.05
1.01
1.00
1.07
0.98
2.00
2.00
8.96
22.73

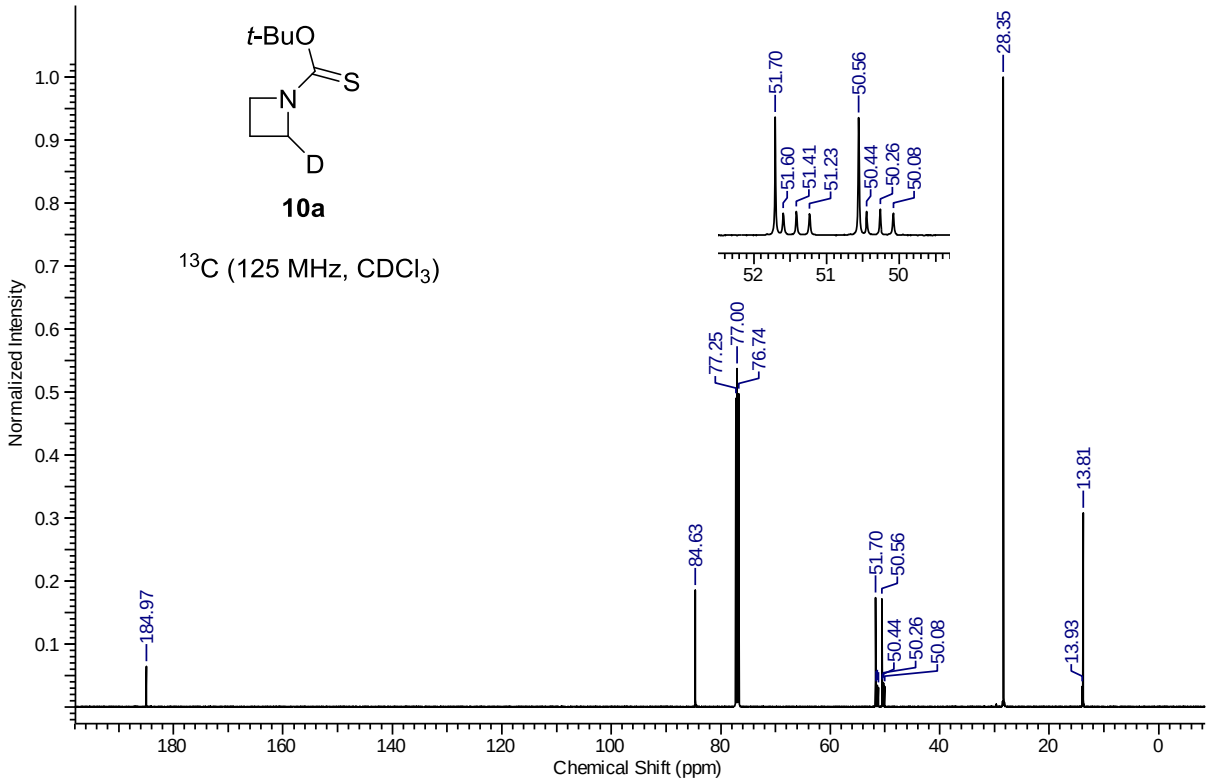

t-BuO
N
O
TIPSO
8
13C (125 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
156.36
79.30
77.25
77.00
76.74
61.61
59.53
28.35
17.73
11.75

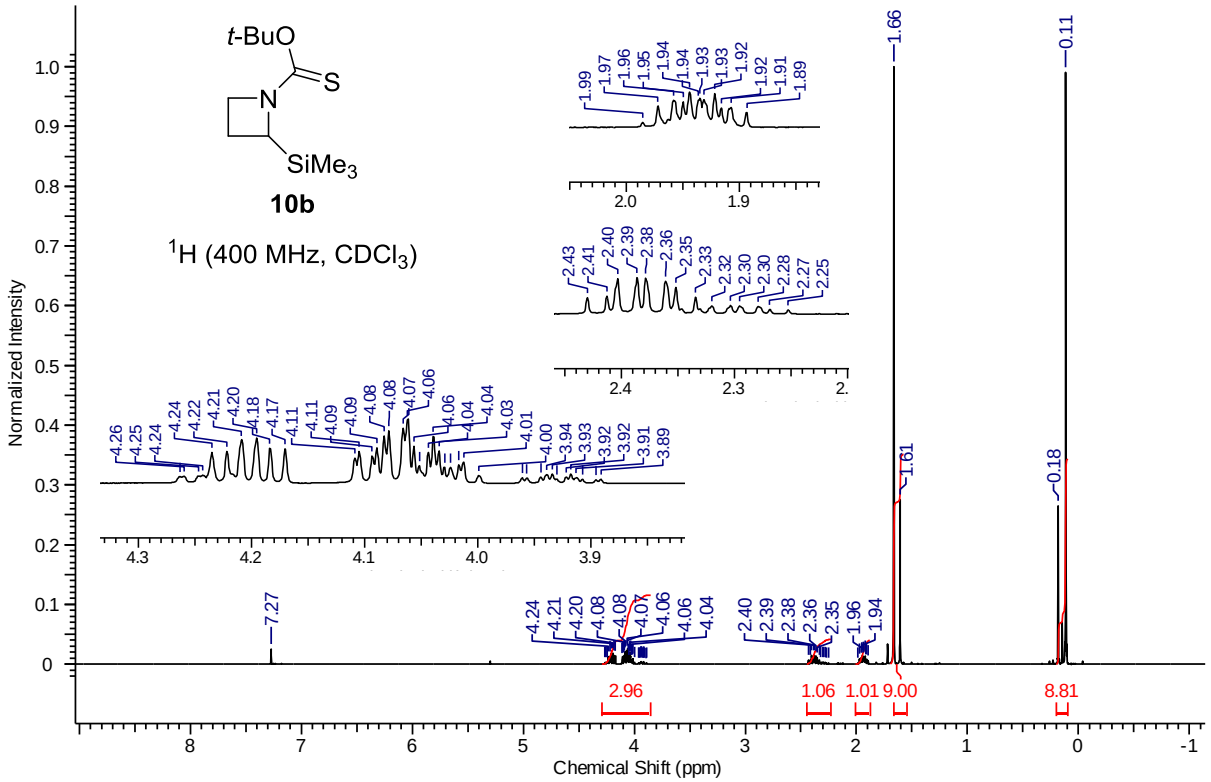

NH
TIPSO
9
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
4.70
4.68
4.66
4.65
4.63
3.66
3.65
3.64
3.62
3.59
3.58
3.57
3.56
2.06
1.02
1.01
1.04
1.05
1.00
0.91
4.00
1.05
23.03

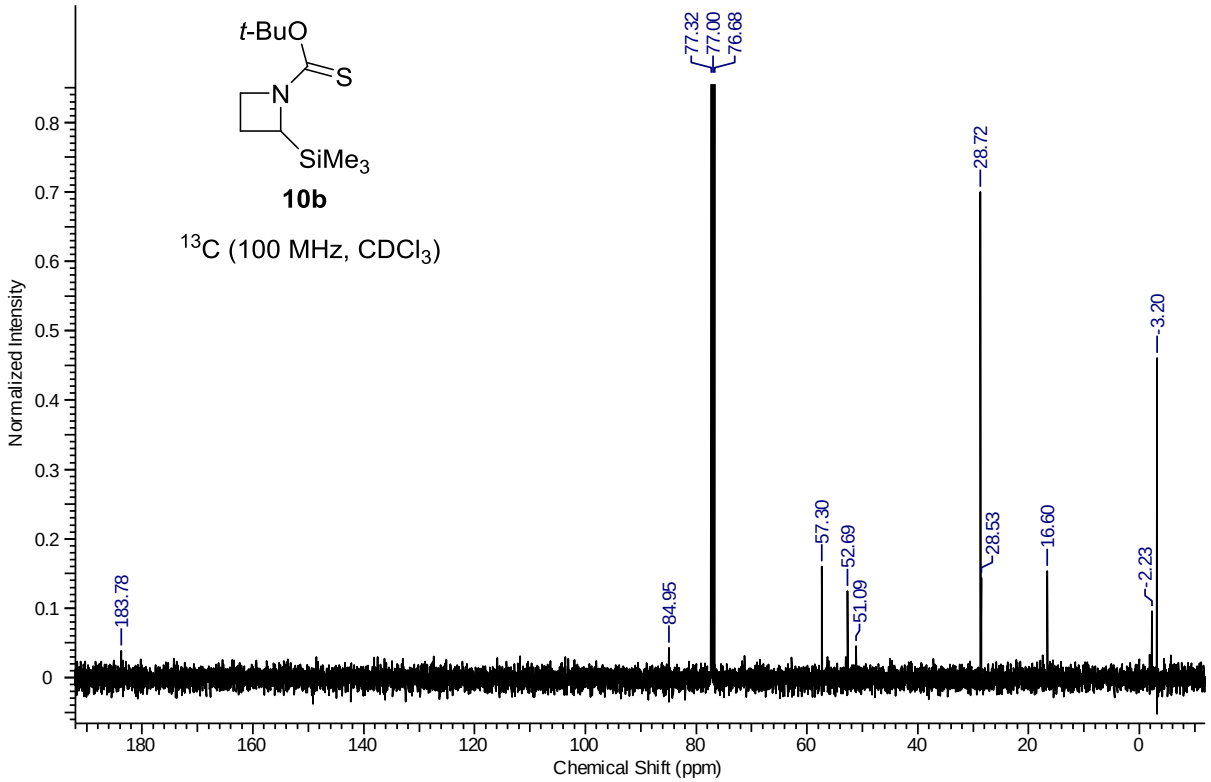

NH
TIPSO
9
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
17.76
11.82
77.32
77.00
76.68
66.33
58.01

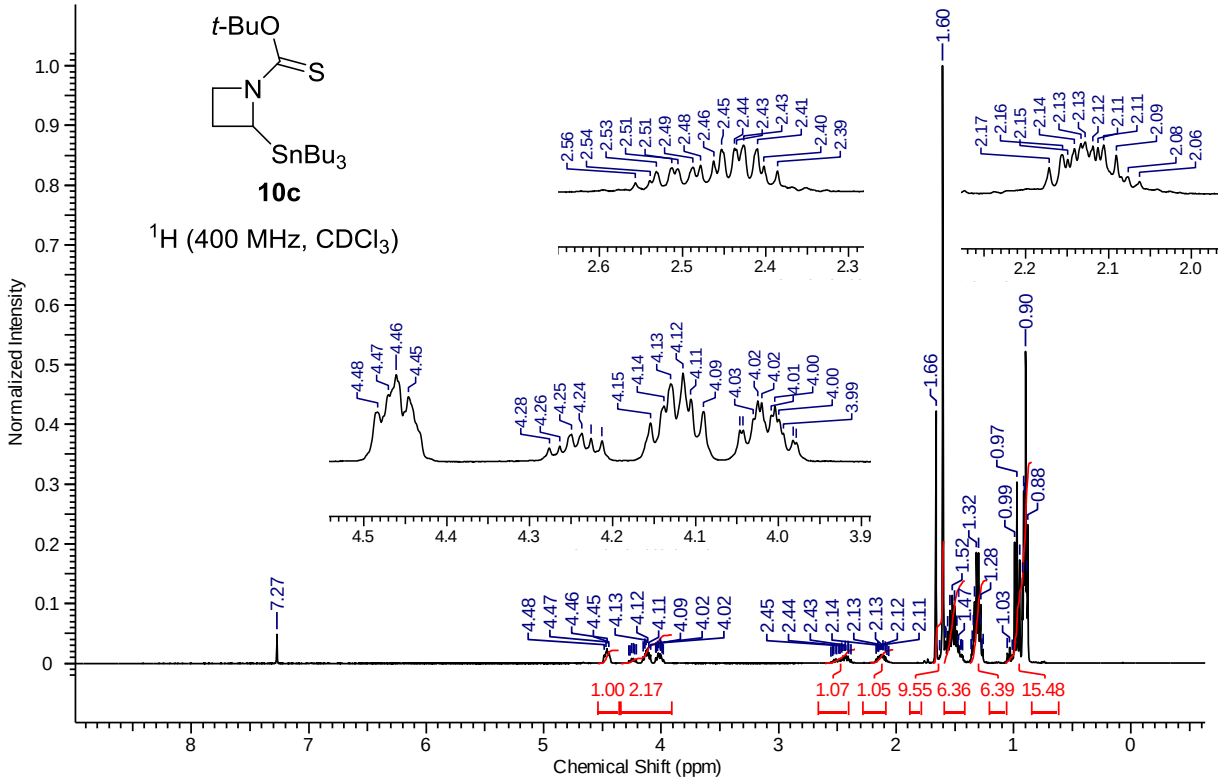

t-BuO
S
N
TIPSO
7
1 : 1
8
EtOH
reflux
NH
9
~1:1
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
3.90
4.00

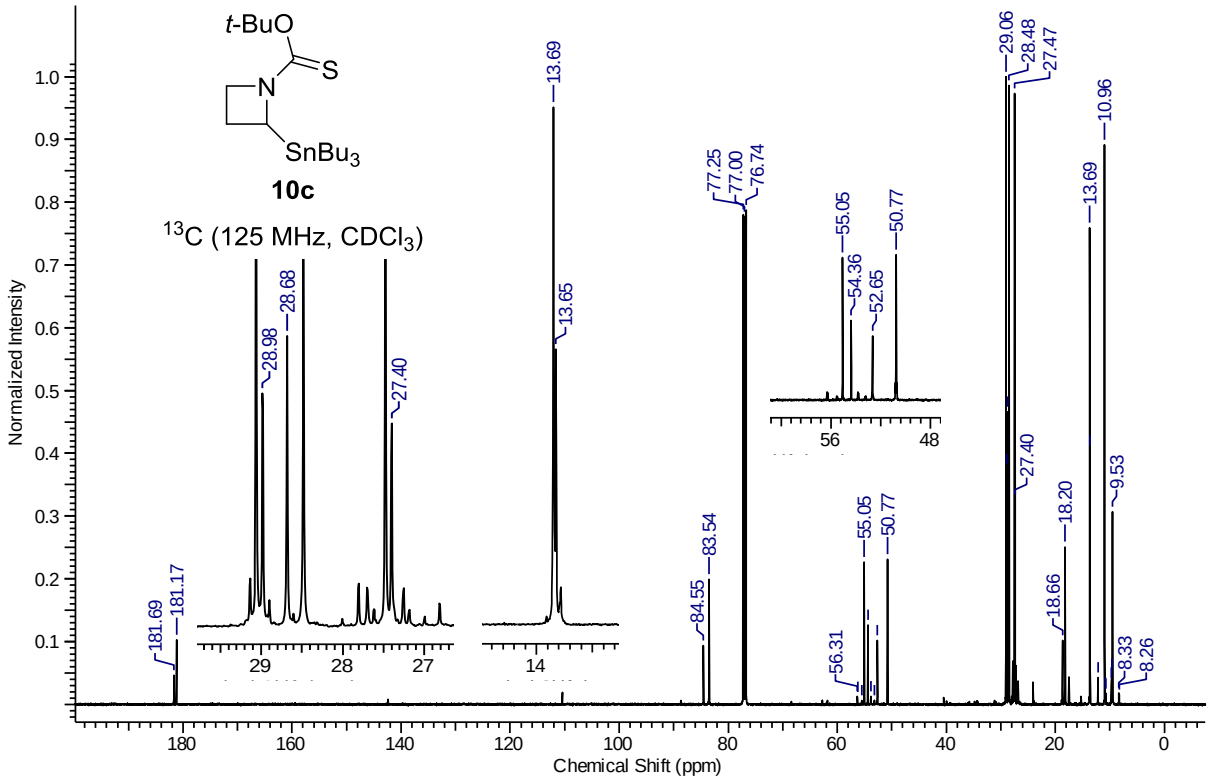

t-BuO
S
N
D
10a
1H (500 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
1.62
4.12
4.11
4.09
3.99
3.98
3.96
2.17
2.16
2.14
2.13
1.50
1.51
2.00
8.81


t-BuO
S
N
D
10a
13C (125 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
184.97
84.63
77.25
77.00
76.74
51.70
51.60
51.41
51.23
50.56
50.44
50.26
50.08
28.35
13.81
13.93

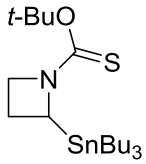

t-BuO
S
N
SiMe3
10b
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
1.66
0.11
1.61
0.18
2.96
1.06
1.01
9.00
8.81


t-BuO
S
N
SiMe3
10b
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
77.32
77.00
76.68
28.72
3.20
57.30
52.69
51.09
28.53
16.60
2.23
183.78
84.95



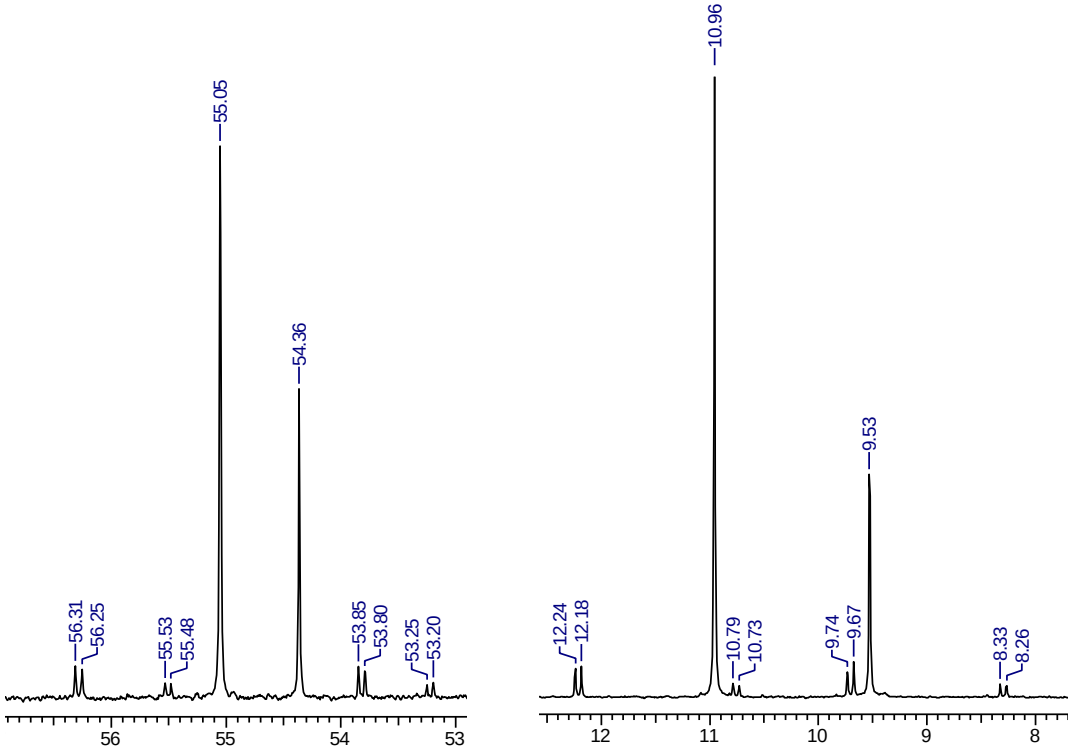


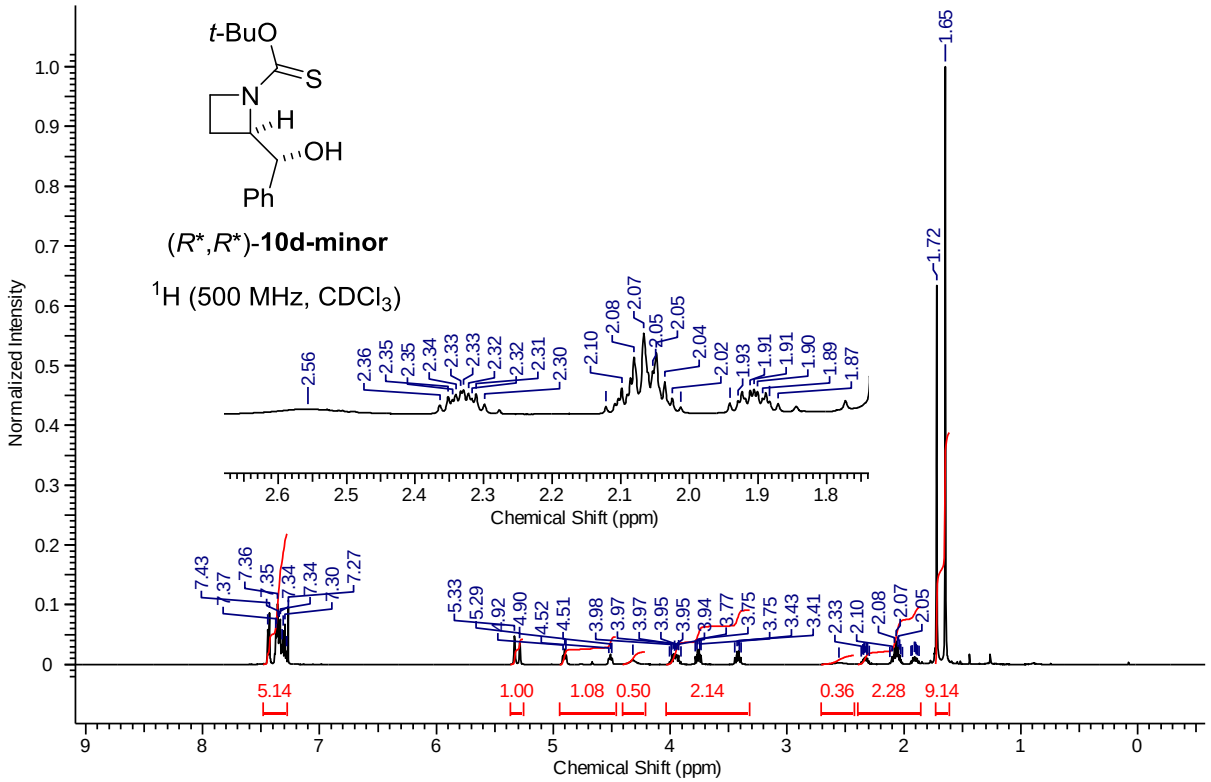
See below for ^{13}C NMR expansions showing $J_{Sn\text{-}C}$ coupling.

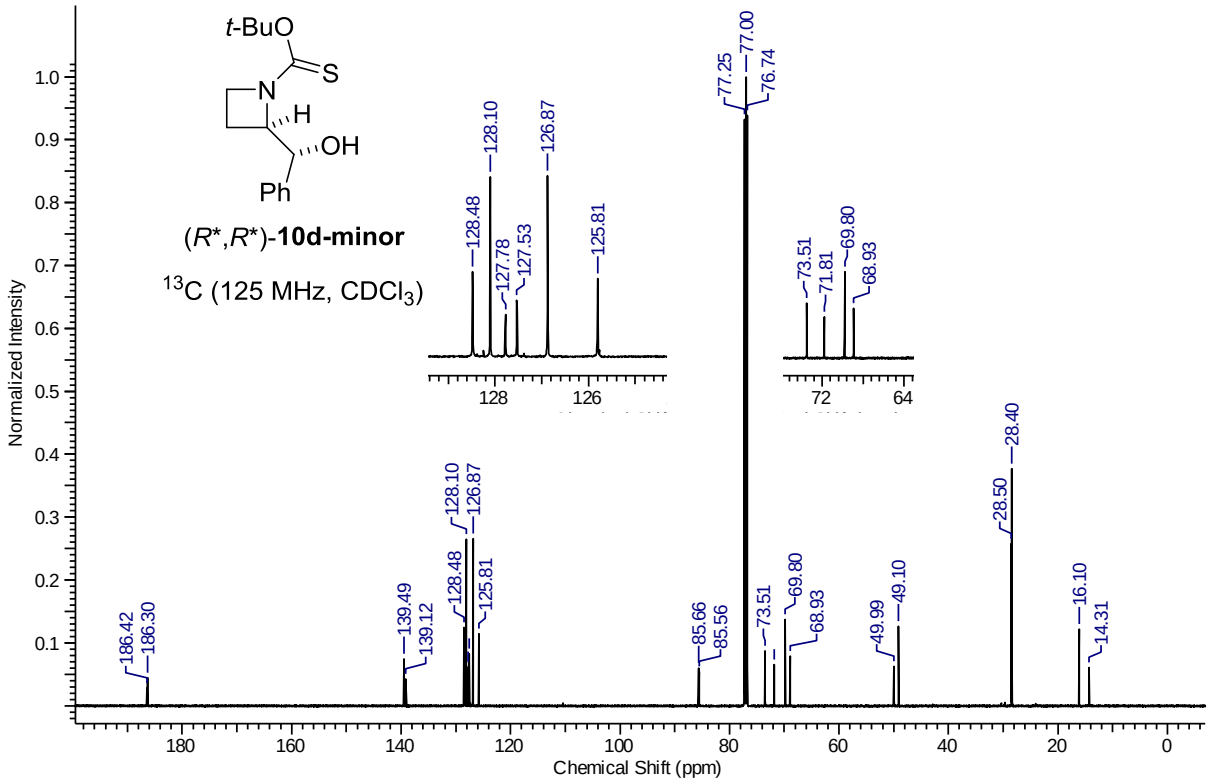


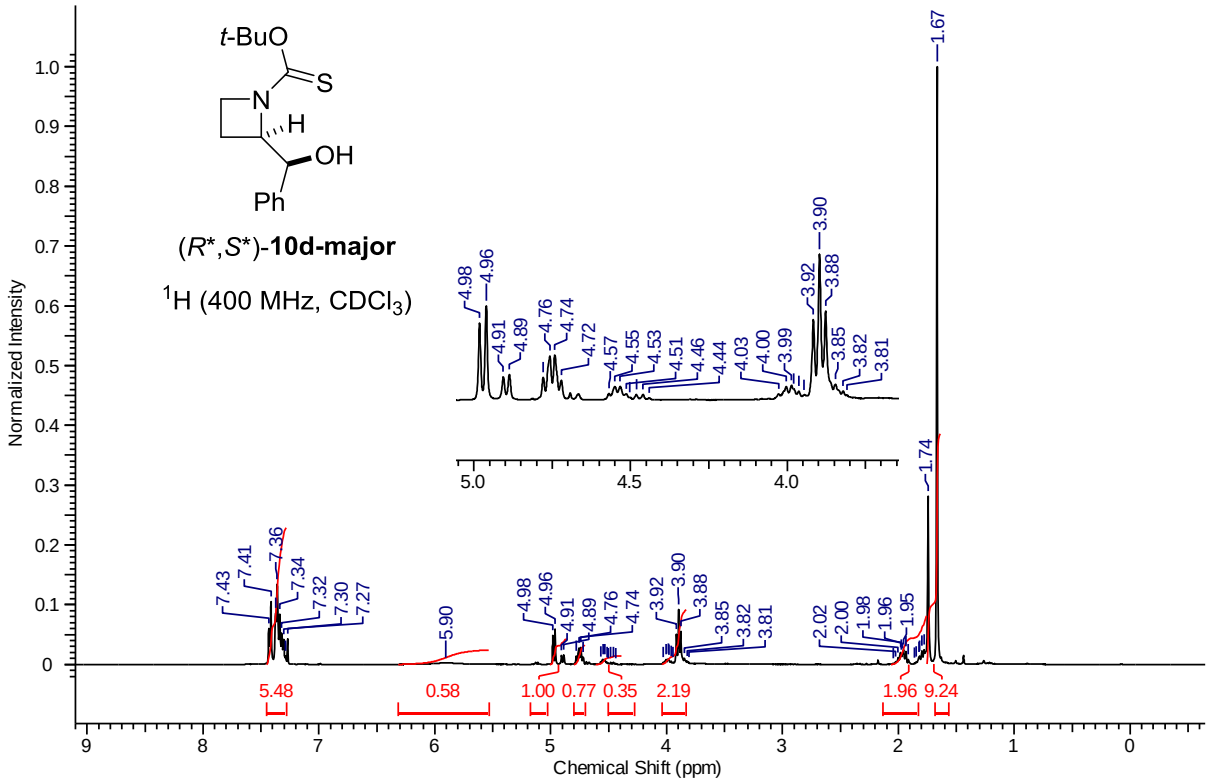
10c

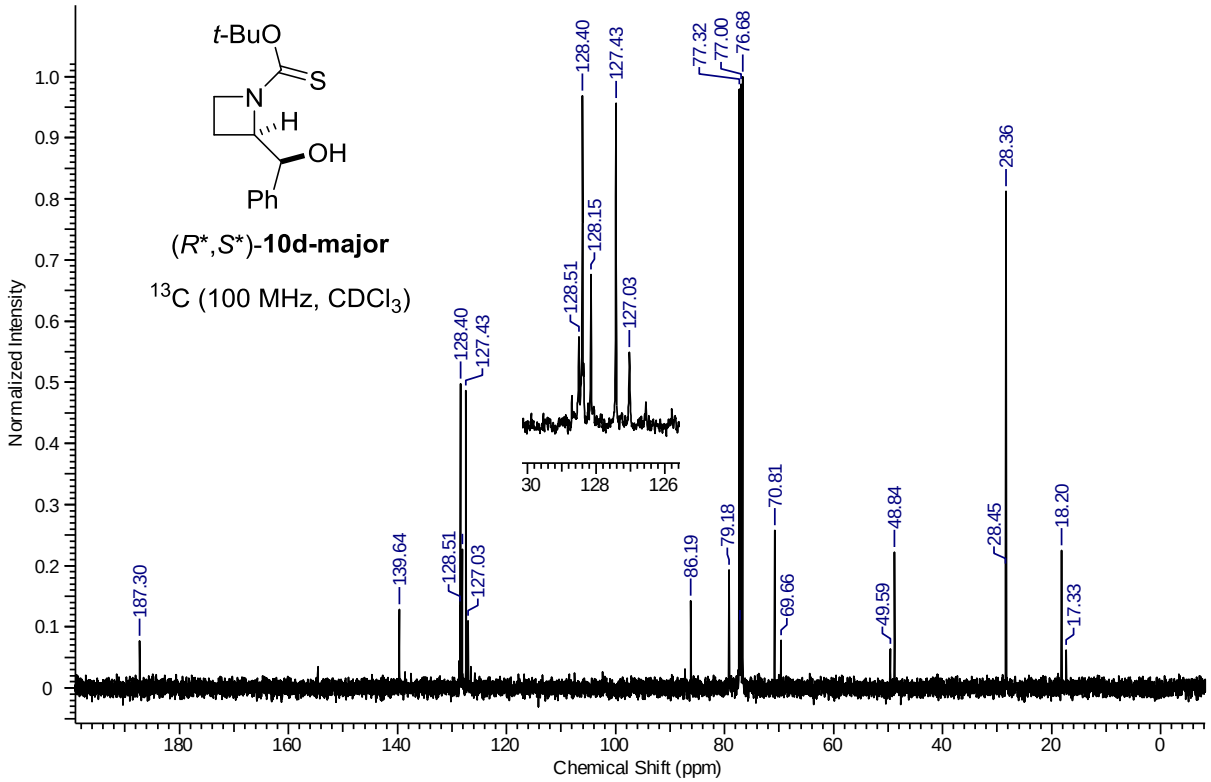
^{13}C (125 MHz, $CDCl_3$)

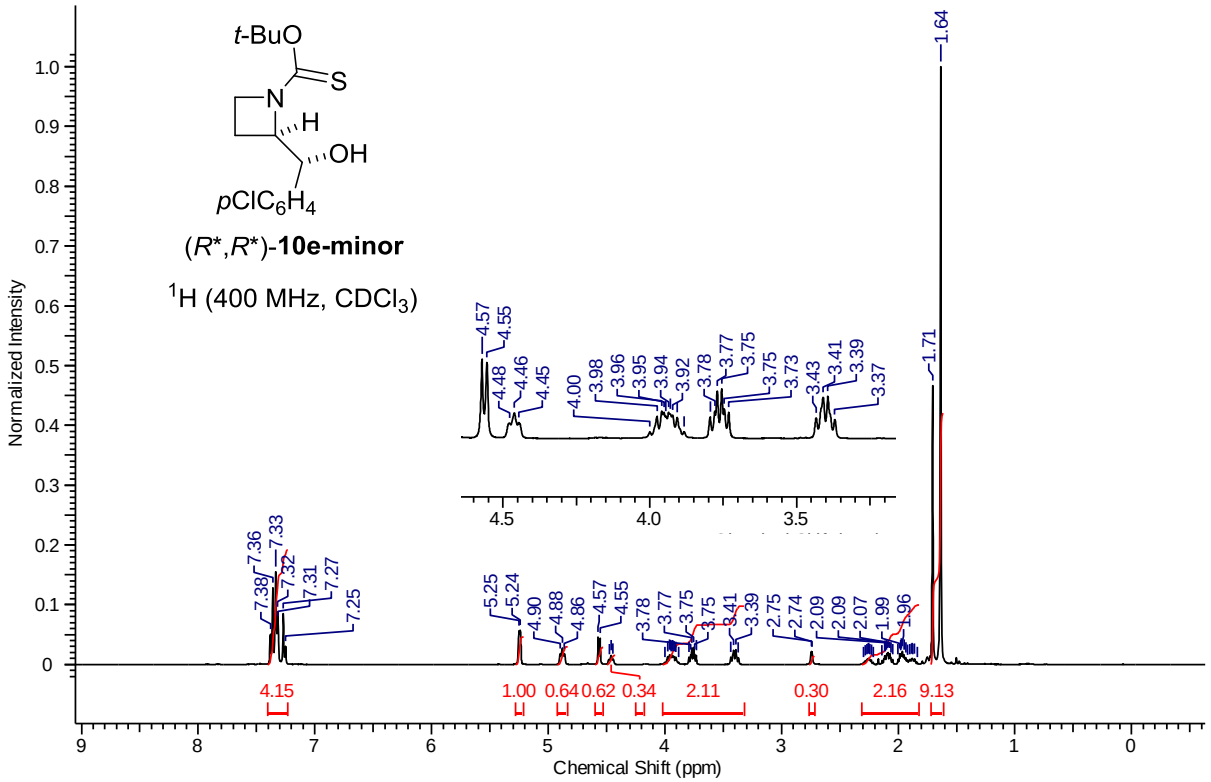


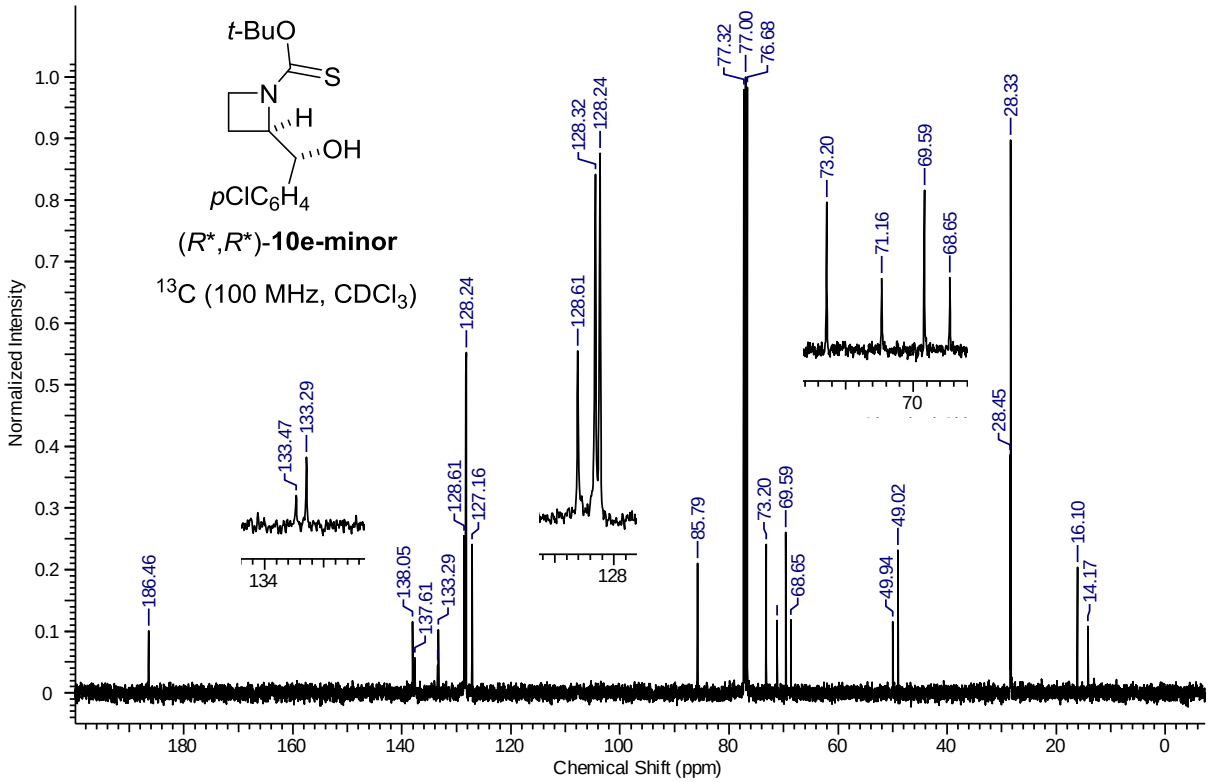

t-BuO
S
N
H
OH
Ph
(R*,R*)-10d-minor
1H (500 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
1.65
1.72
2.56
2.36
2.35
2.35
2.34
2.33
2.33
2.32
2.32
2.31
2.30
2.10
2.08
2.07
2.05
2.05
2.04
2.02
1.93
1.91
1.91
1.90
1.89
1.87
7.43
7.37
7.36
7.35
7.34
7.34
7.30
7.27
5.33
5.29
4.92
4.90
4.52
4.51
3.98
3.97
3.97
3.95
3.95
3.94
3.77
3.75
3.75
3.43
3.41
2.33
2.10
2.08
2.07
2.05
5.14
1.00
1.08
0.50
2.14
0.36
2.28
9.14

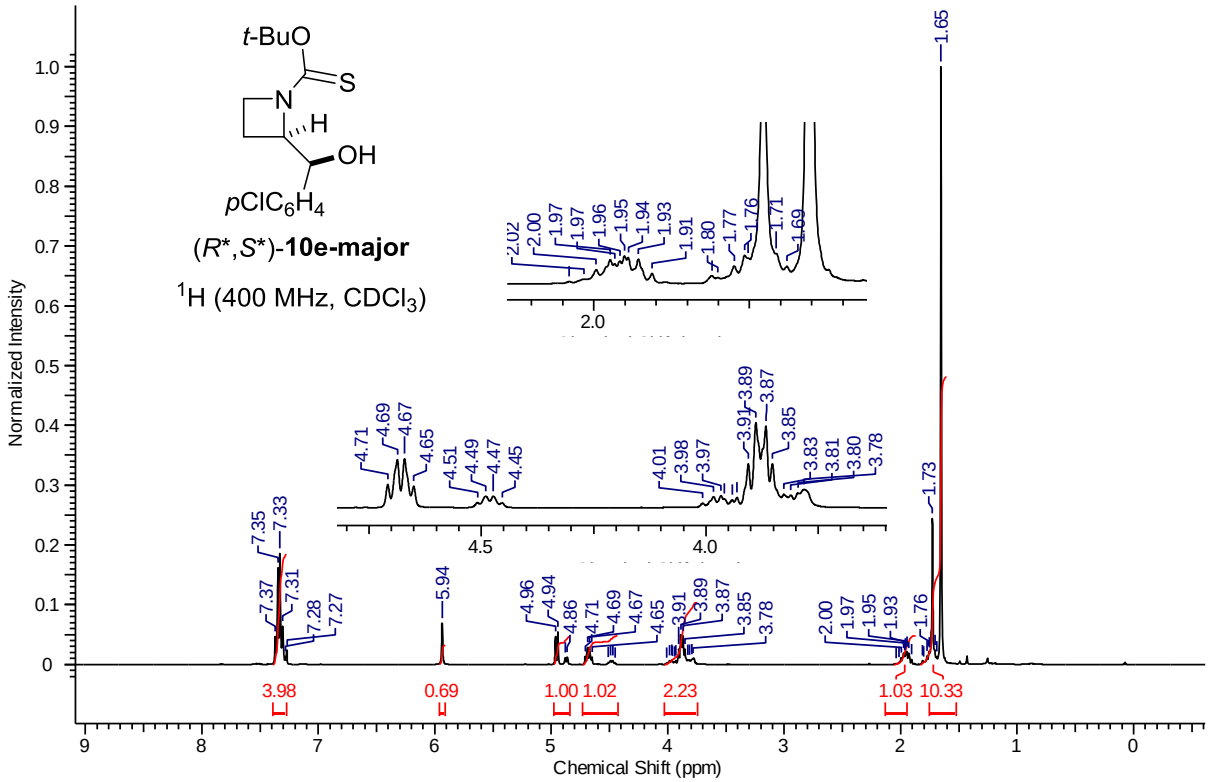

t-BuO
S
N
H
OH
Ph
(R*,R*)-10d-minor
13C (125 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
128.10
126.87
128.48
127.78
127.53
125.81
77.25
77.00
76.74
73.51
71.81
69.80
68.93
186.42
186.30
139.49
139.12
128.10
126.87
128.48
125.81
85.66
85.56
73.51
69.80
68.93
49.99
49.10
28.50
28.40
16.10
14.31

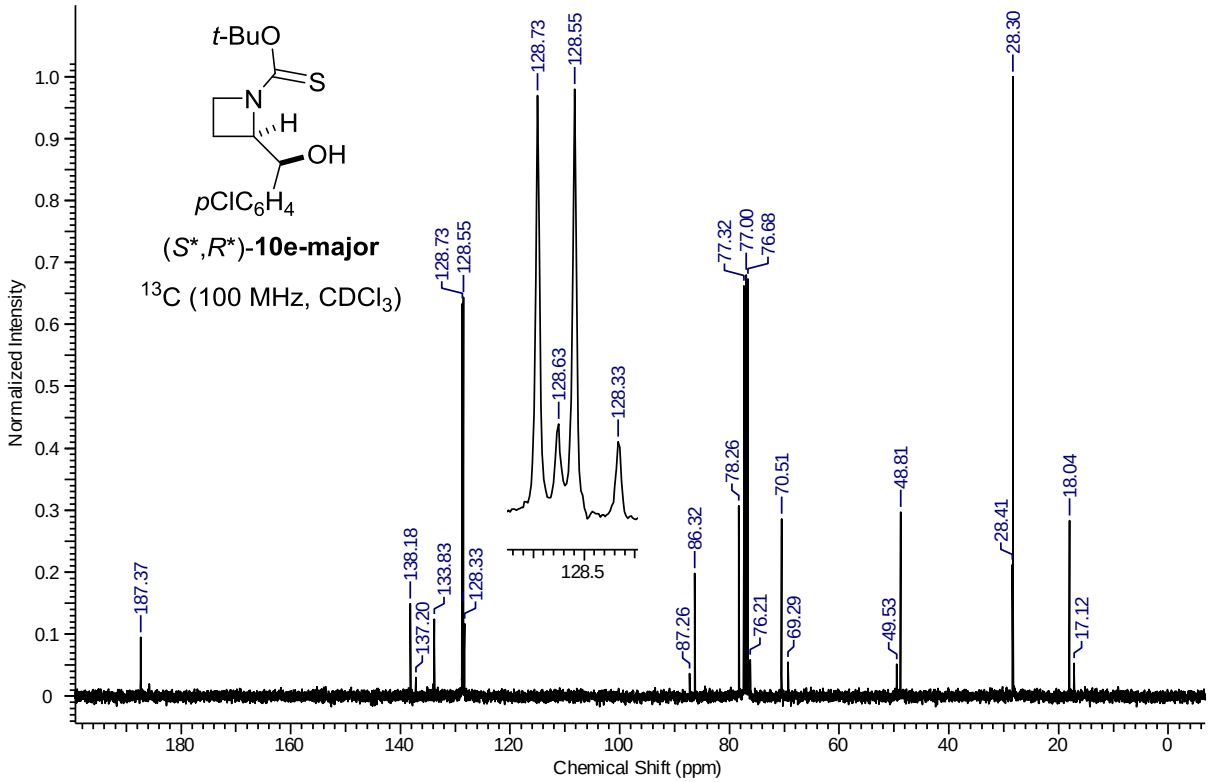

t-BuO
S
N
H
OH
Ph
(R*,S*)-10d-major
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
5.48
0.58
1.00
0.77
0.35
2.19
1.96
9.24

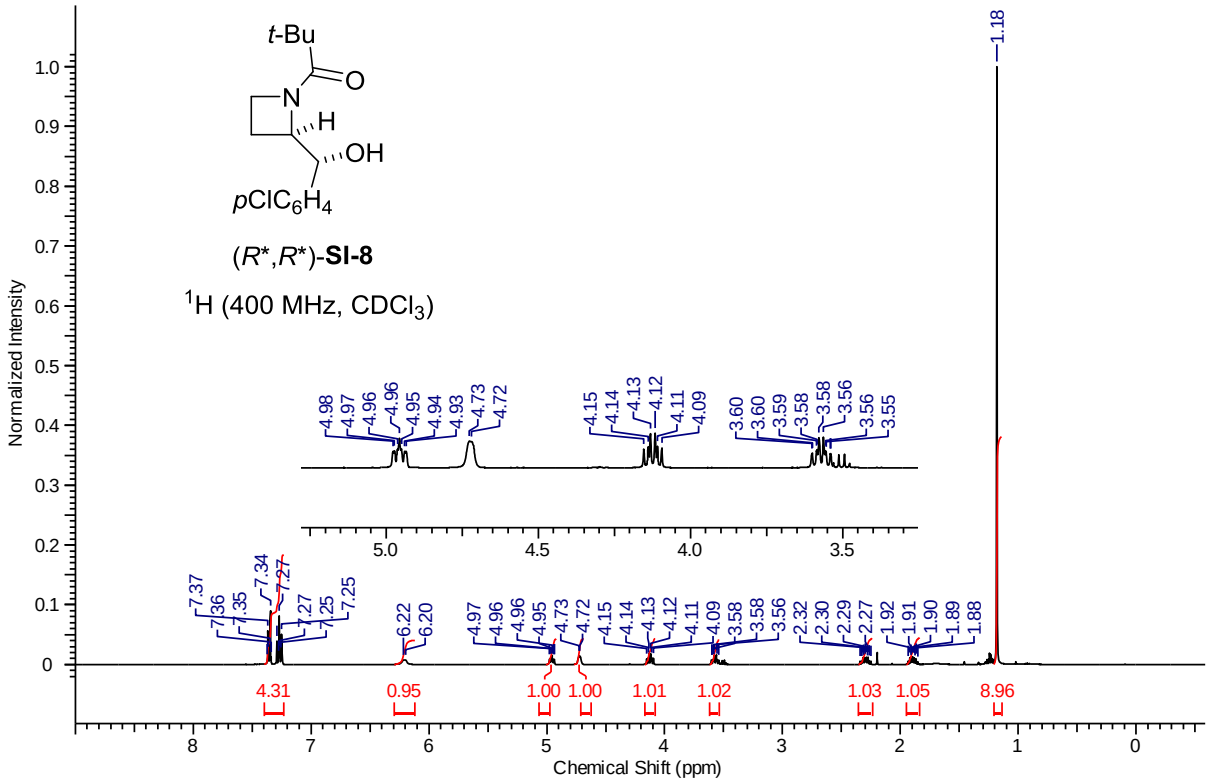

t-BuO
S
N
H
OH
Ph
(R*,S*)-10d-major
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)

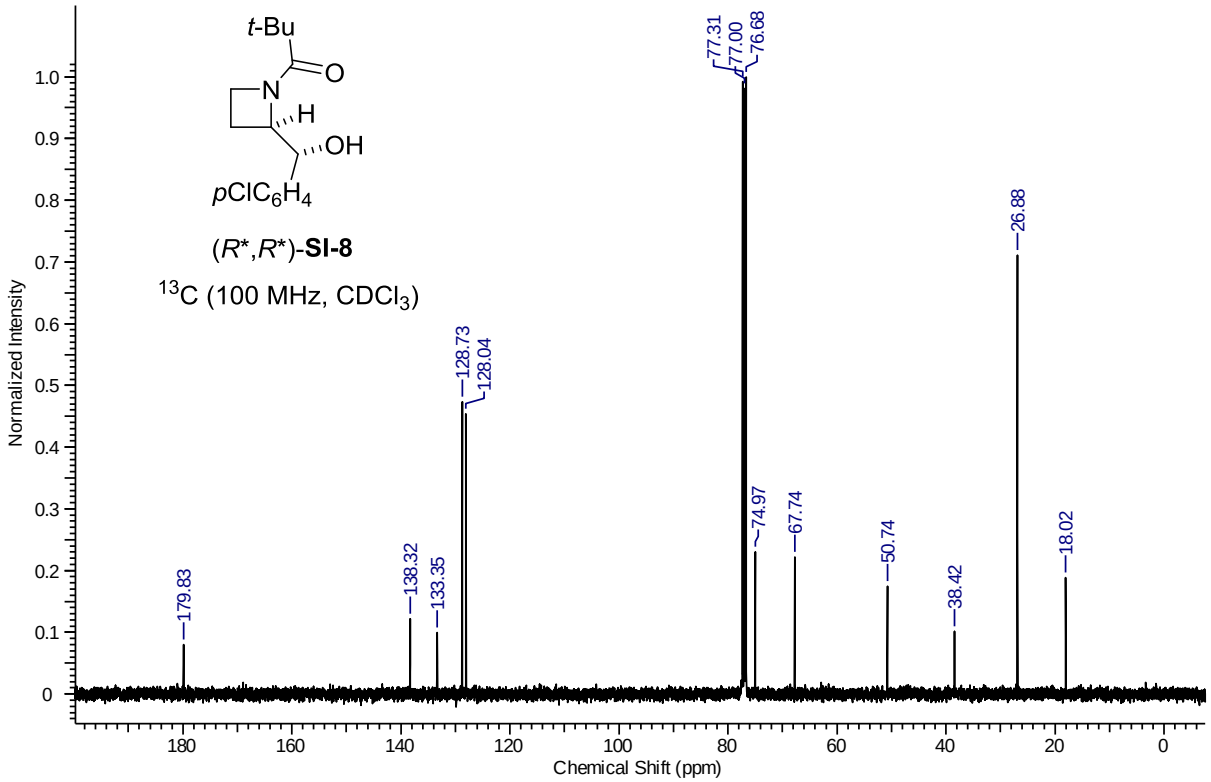

t-BuO
S
N
H
OH
pClC6H4
(R*,R*)-10e-minor
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
4.15
1.00
0.64
0.62
0.34
2.11
0.30
2.16
9.13

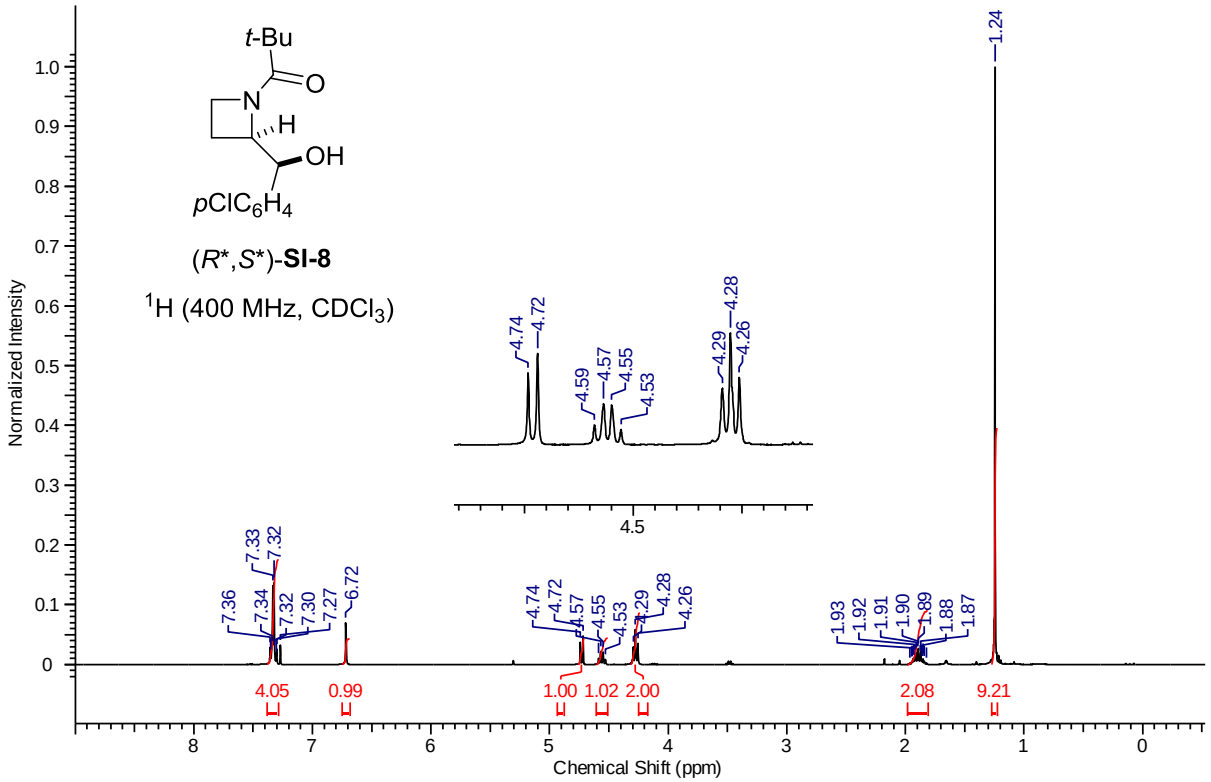

t-BuO
S
N
H
OH
pClC6H4
(R*,R*)-10e-minor
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)

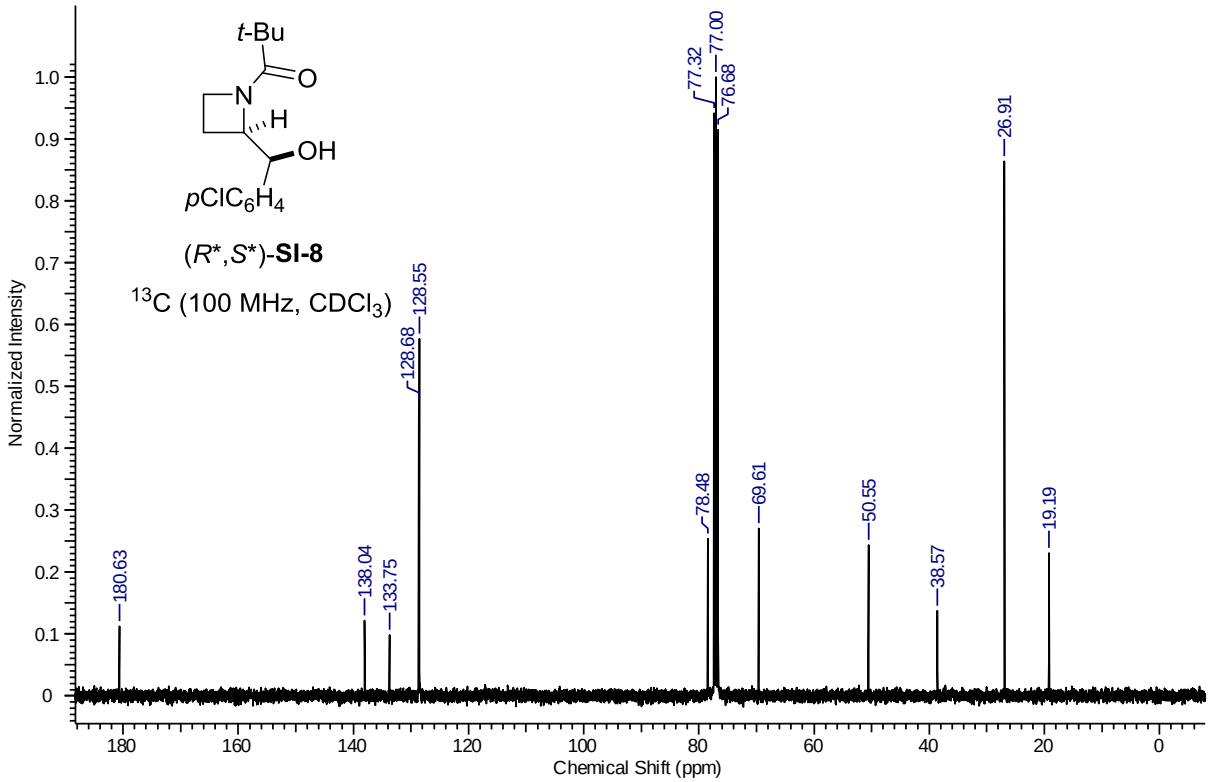

t-BuO
S
N
H
OH
pClC6H4
(R*,S*)-10e-major
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
3.98
0.69
1.00
1.02
2.23
1.03
10.33

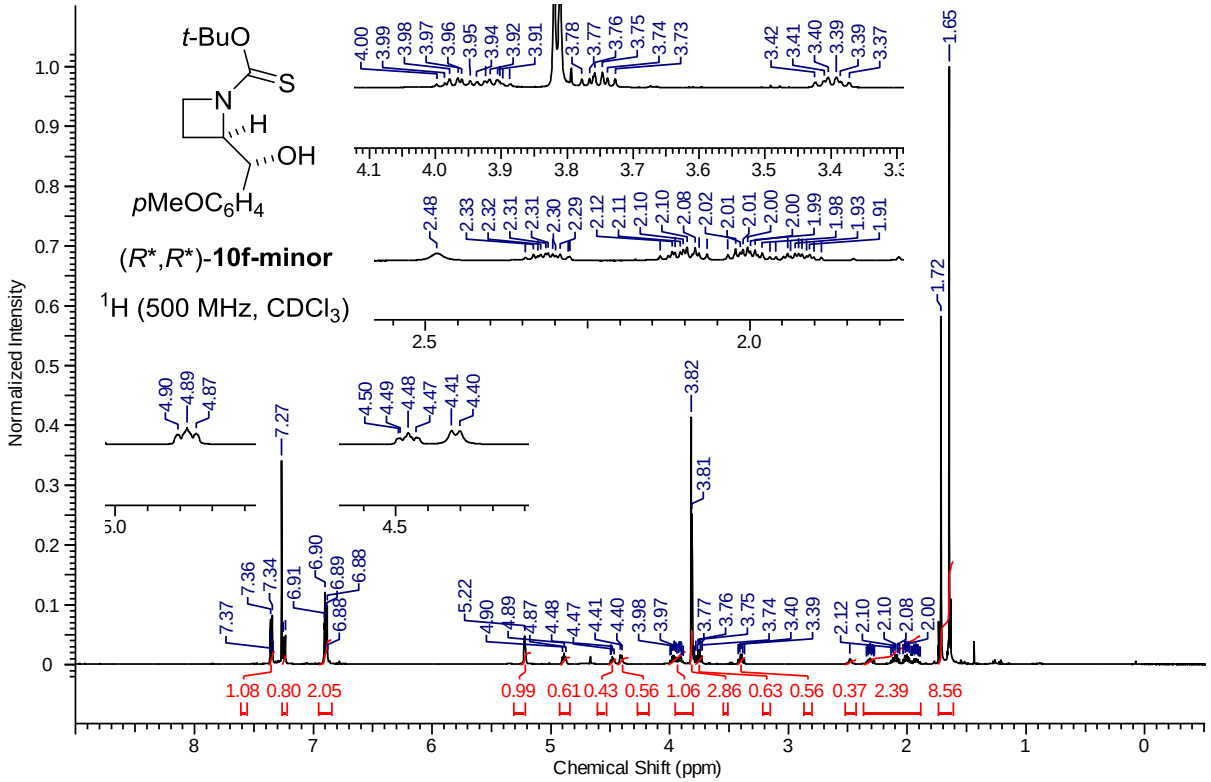

t-BuO
S
N
H
OH
pClC6H4
(S*,R*)-10e-major
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)

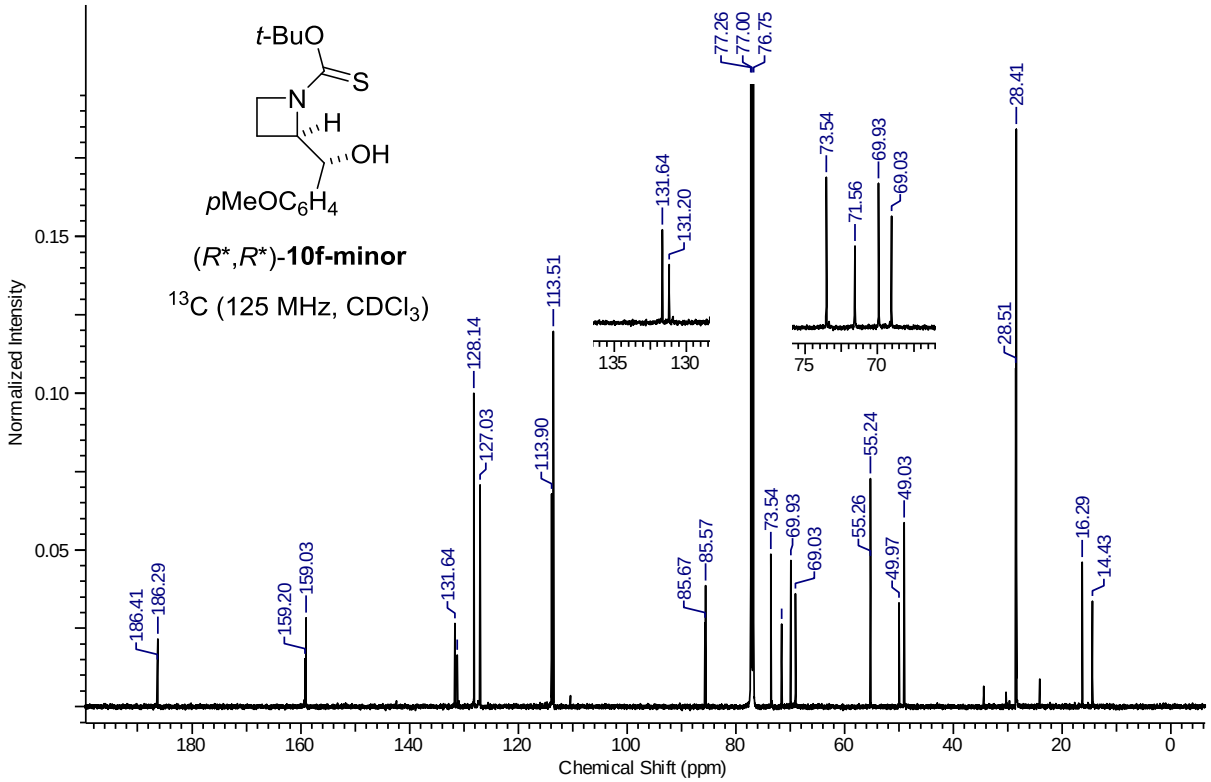

t-Bu
O
N
H
OH
pClC6H4
(R*,R*)-SI-8
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
4.31
0.95
1.00
1.00
1.01
1.02
1.03
1.05
8.96

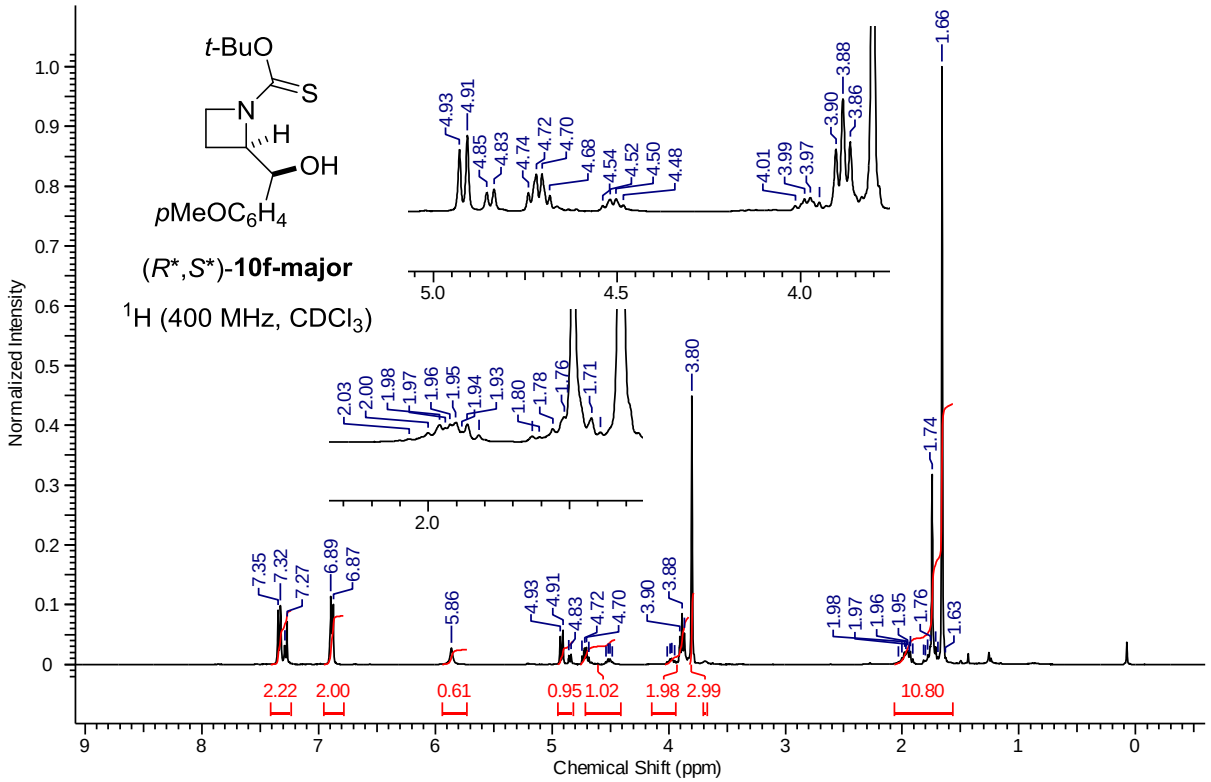

t-Bu
O
N
H
OH
pClC6H4
(R*,R*)-SI-8
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)

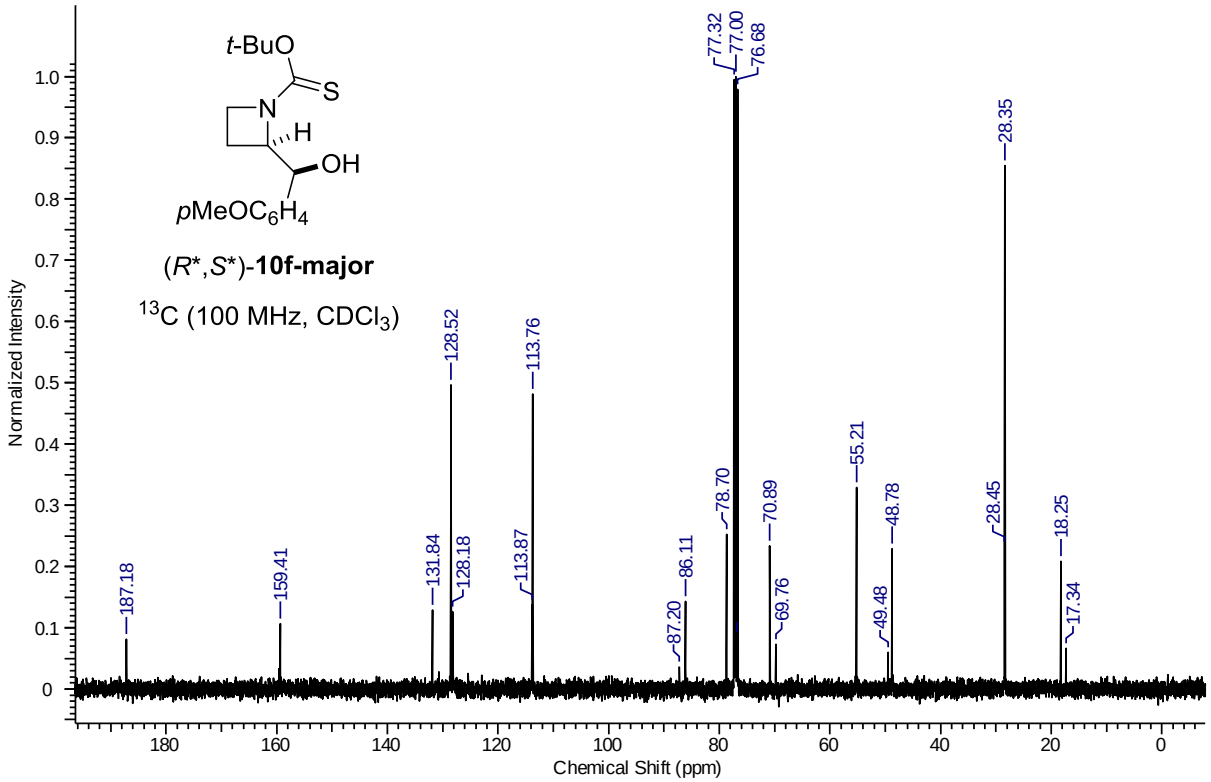

t-Bu
O
N
H
OH
pClC6H4
(R*,S*)-SI-8
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
1.24
7.33
7.32
7.36
7.34
7.32
7.30
7.27
6.72
4.74
4.72
4.57
4.55
4.53
4.29
4.28
4.26
1.93
1.92
1.91
1.90
1.89
1.88
1.87
4.05
0.99
1.00
1.02
2.00
2.08
9.21

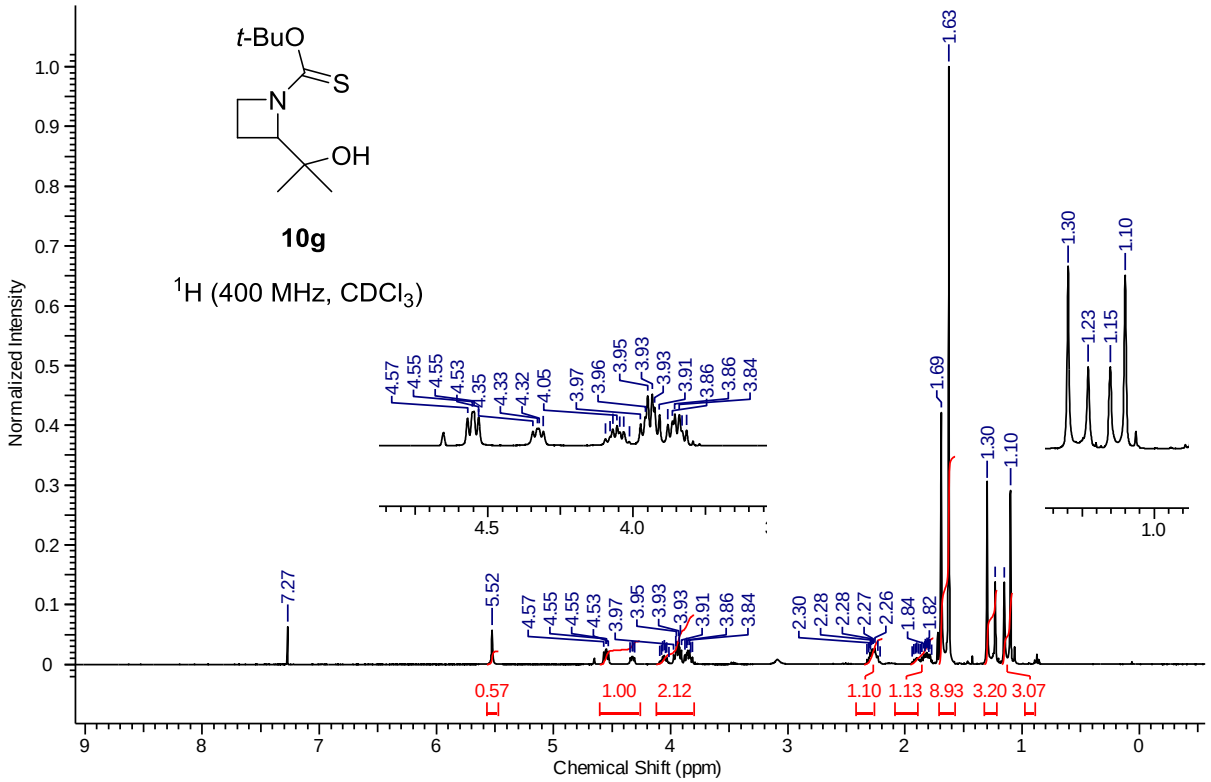

t-Bu
O
N
H
OH
pClC6H4
(R*,S*)-SI-8
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
180.63
138.04
133.75
128.68
128.55
77.32
77.00
76.68
78.48
69.61
50.55
38.57
26.91
19.19

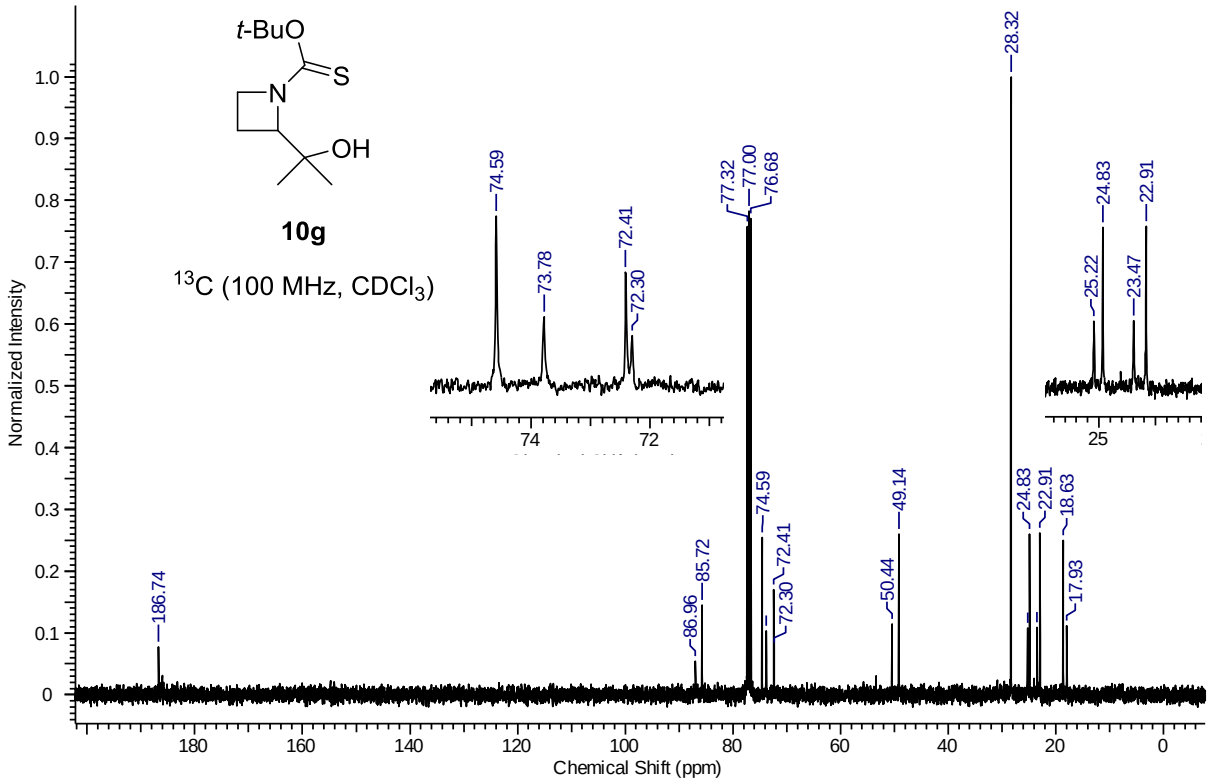

t-BuO
S
N
H
OH
pMeOC6H4
(R*,R*)-10f-minor
1H (500 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)

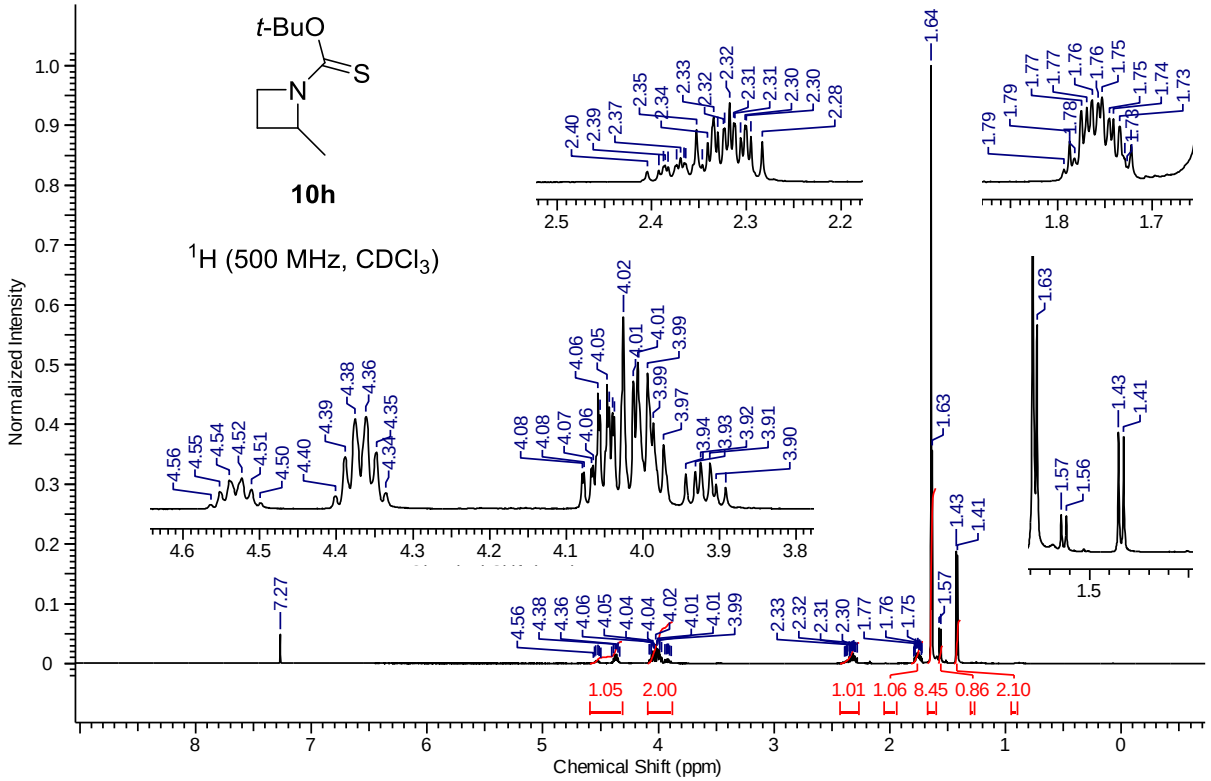

t-BuO
S
N
H
OH
pMeOC6H4
(R*,R*)-10f-minor
13C (125 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)

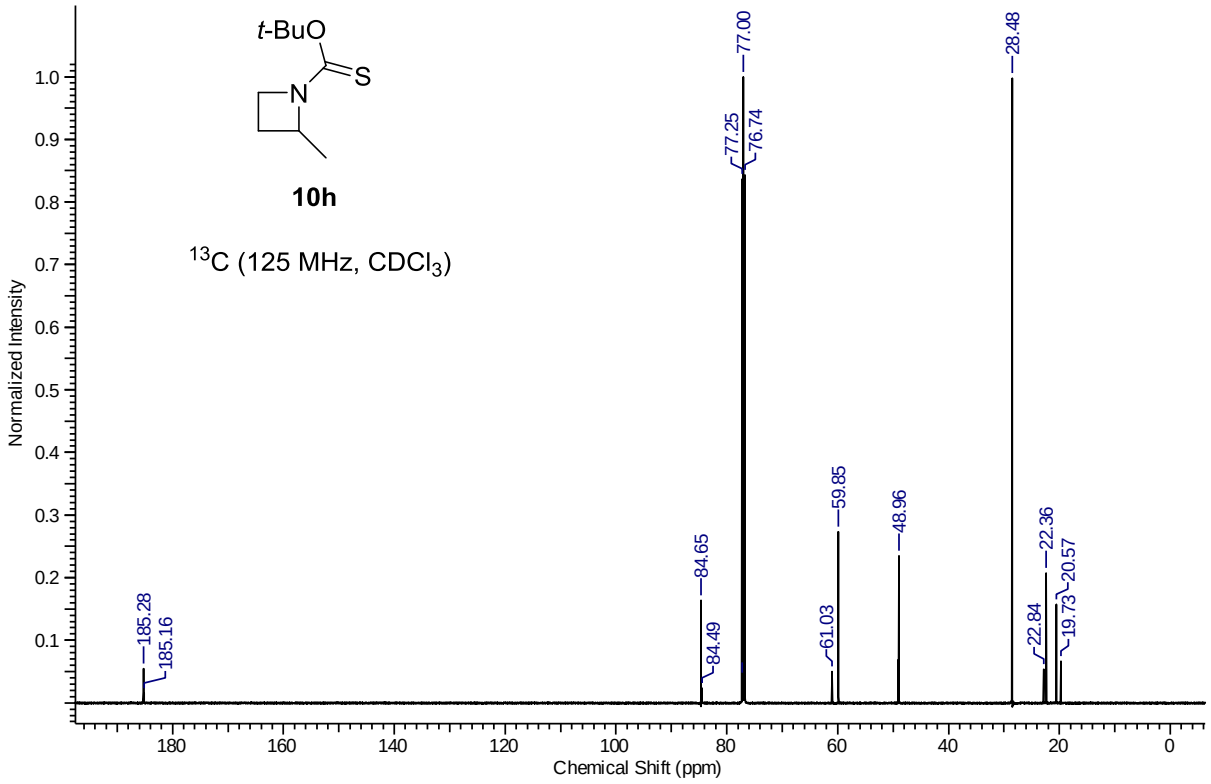

t-BuO
S
N
H
OH
pMeOC6H4
(R*,S*)-10f-major
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
4.93
4.91
4.85
4.83
4.74
4.72
4.70
4.68
4.54
4.52
4.50
4.48
4.01
3.99
3.97
3.90
3.88
3.86
1.66
2.03
2.00
1.98
1.97
1.96
1.95
1.94
1.93
1.80
1.78
1.76
1.71
3.80
1.74
7.35
7.32
7.27
6.89
6.87
5.86
3.88
1.98
1.97
1.96
1.95
1.76
1.63
2.22
2.00
0.61
0.95
1.02
1.98
2.99
10.80

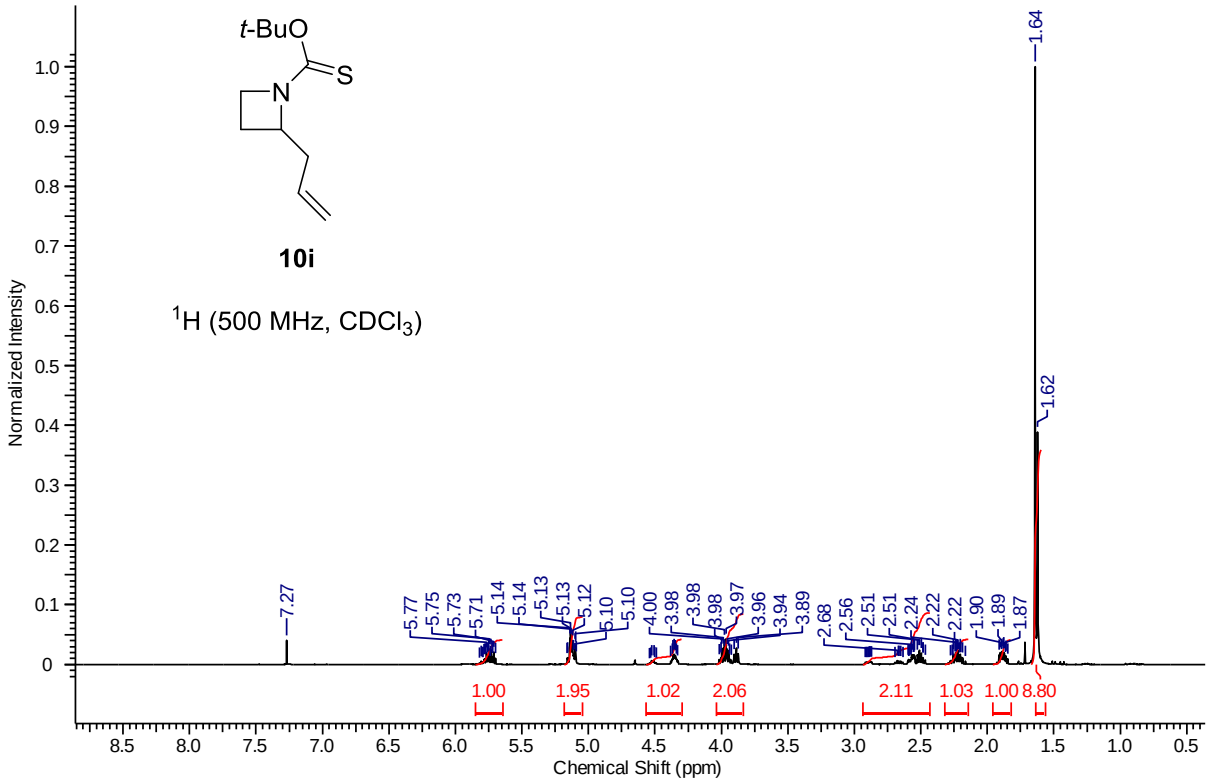

t-BuO
S
N
H
OH
pMeOC6H4
(R*,S*)-10f-major
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
77.32
77.00
76.68
28.35
128.52
113.76
55.21
78.70
70.89
48.78
28.45
18.25
187.18
159.41
131.84
128.18
113.87
86.11
87.20
69.76
49.48
17.34

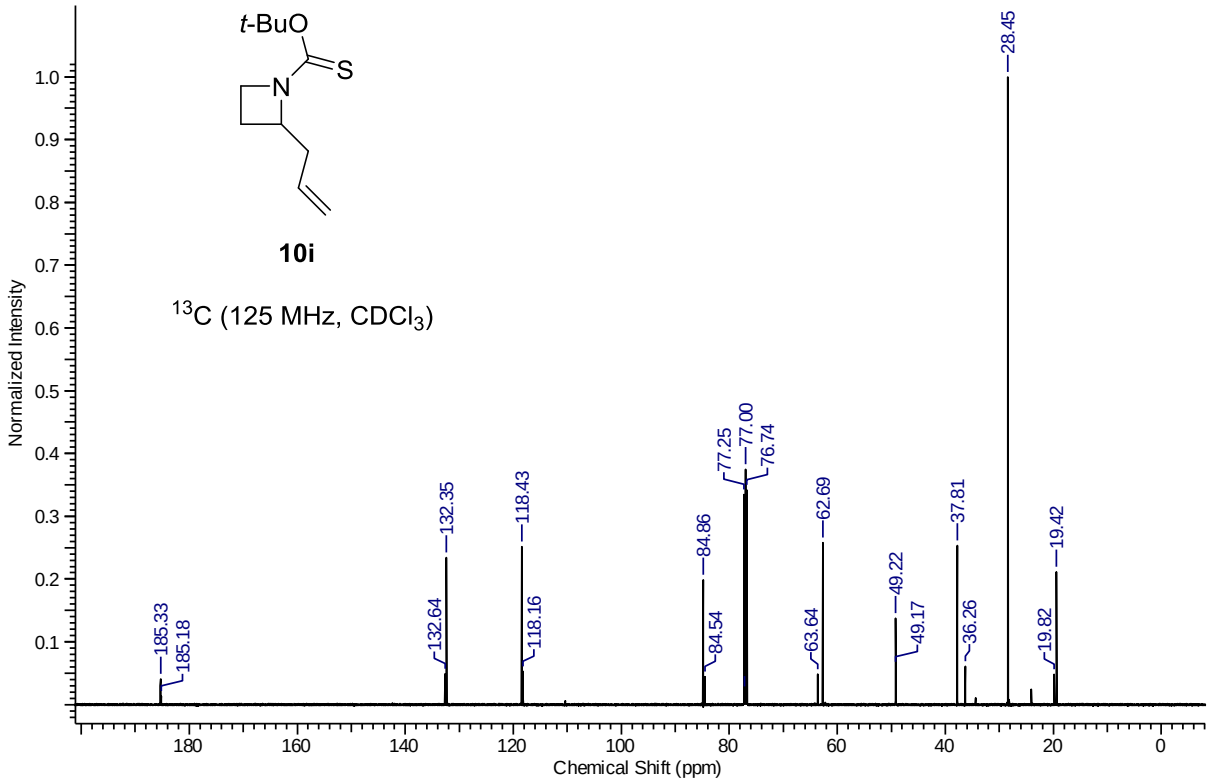

t-BuO
S
N
OH
10g
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
5.52
4.57
4.55
4.55
4.53
4.35
4.33
4.32
4.05
3.97
3.96
3.95
3.93
3.93
3.91
3.86
3.86
3.84
2.30
2.28
2.28
2.27
2.26
1.84
1.82
1.69
1.63
1.30
1.10
1.30
1.23
1.15
1.10
0.57
1.00
2.12
1.10
1.13
8.93
3.20
3.07

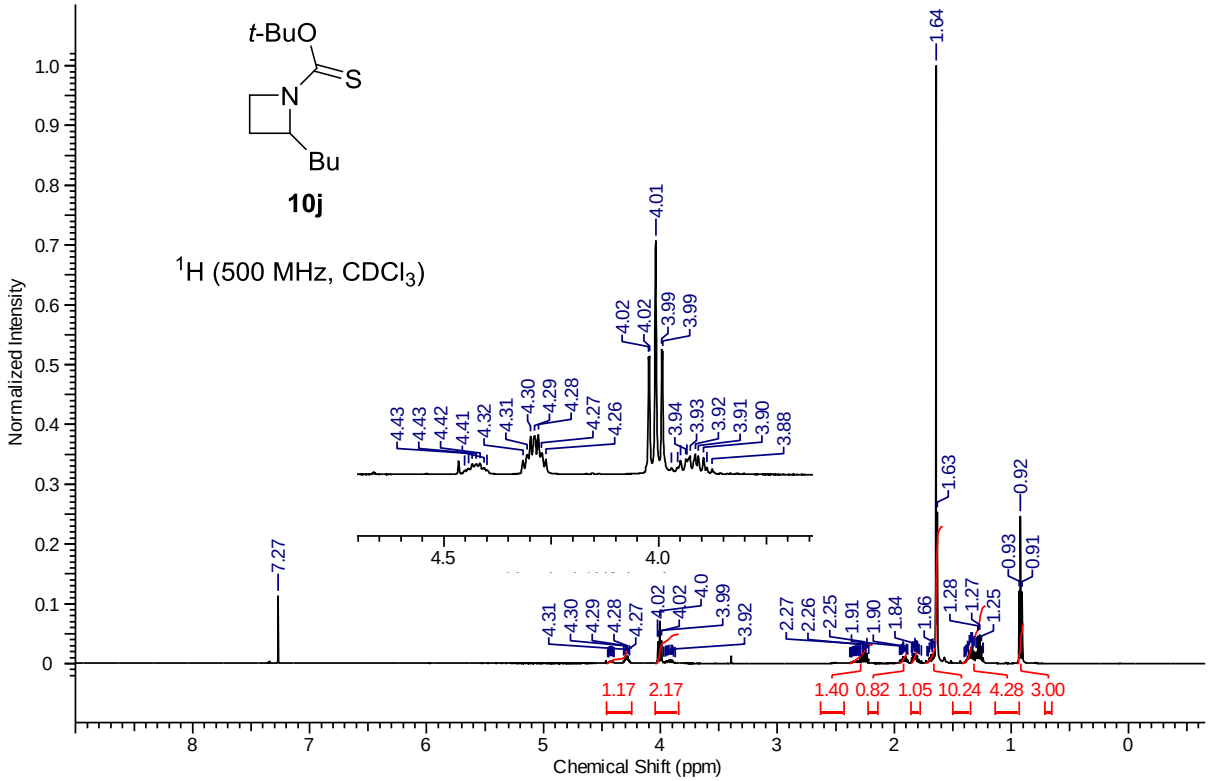

t-BuO
S
N
OH
10g
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
186.74
86.96
85.72
77.32
77.00
76.68
74.59
73.78
72.41
72.30
74.59
72.41
72.30
50.44
49.14
28.32
24.83
22.91
18.63
17.93
25.22
24.83
23.47
22.91

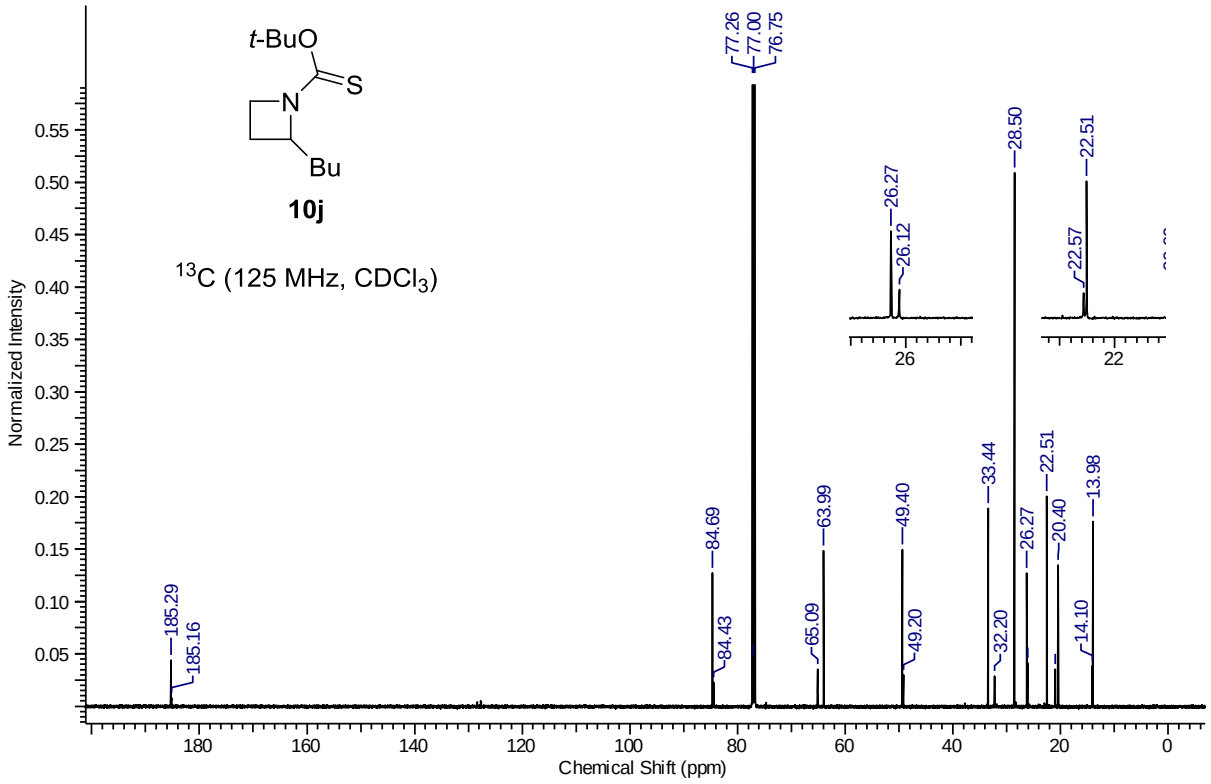

t-BuO
N
S
10h
1H (500 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
1.05 2.00 1.01 1.06 8.45 0.86 2.10

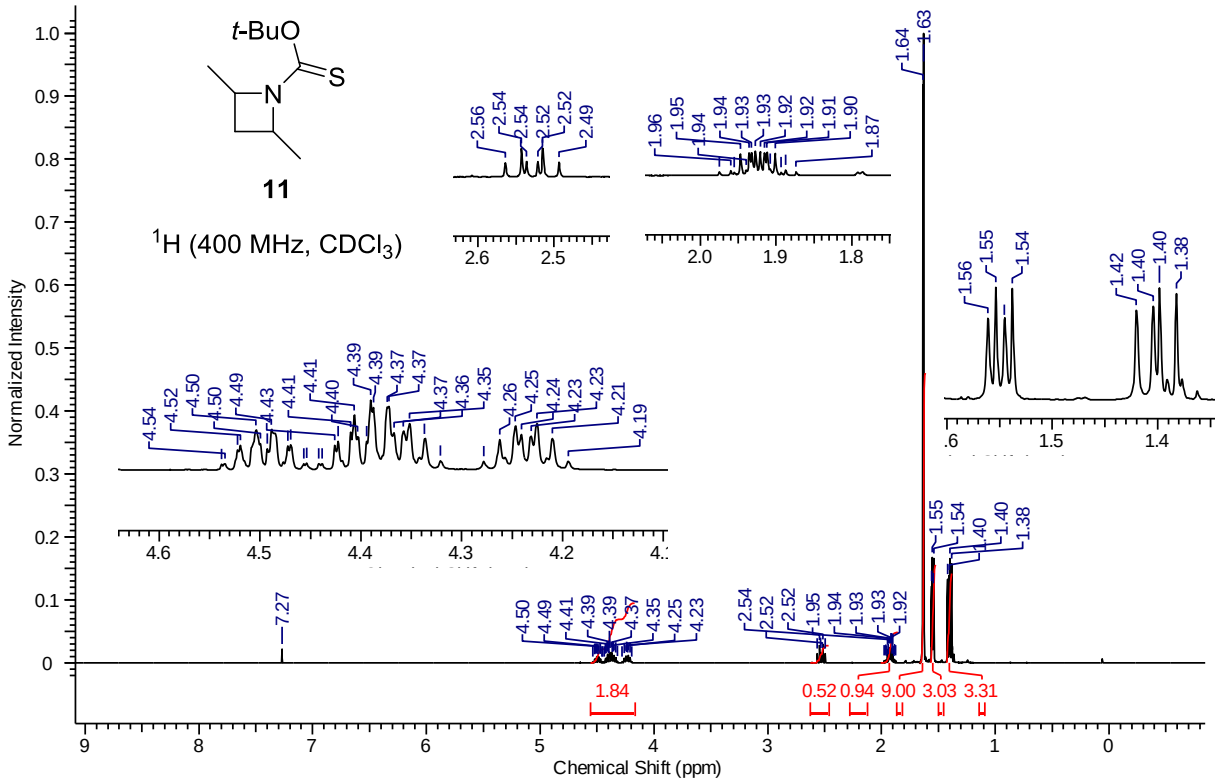

t-BuO
N
S
10h
13C (125 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)

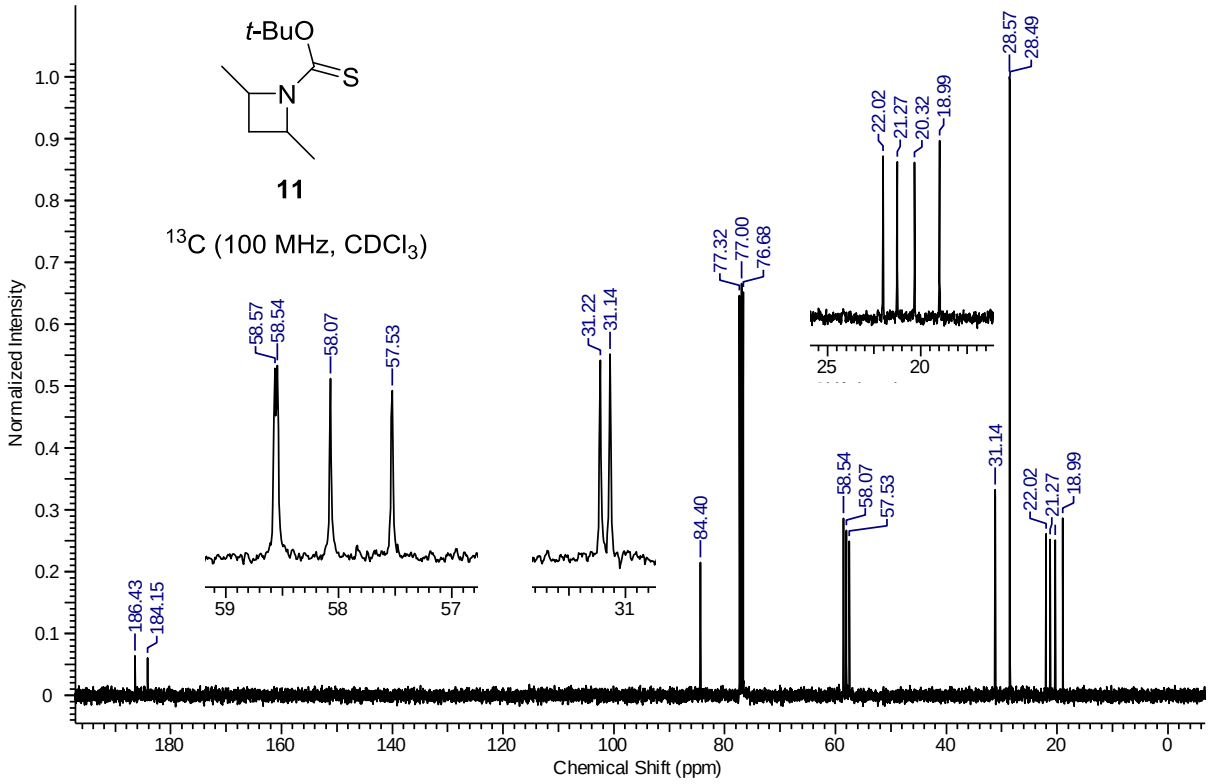

t-BuO
S
N
10i
1H (500 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
1.64
1.62
7.27
5.77
5.75
5.73
5.71
5.14
5.14
5.13
5.13
5.12
5.10
5.10
4.00
3.98
3.98
3.98
3.97
3.96
3.94
3.89
2.68
2.56
2.51
2.51
2.24
2.22
2.22
1.90
1.89
1.87
1.00
1.95
1.02
2.06
2.11
1.03
1.00
8.80

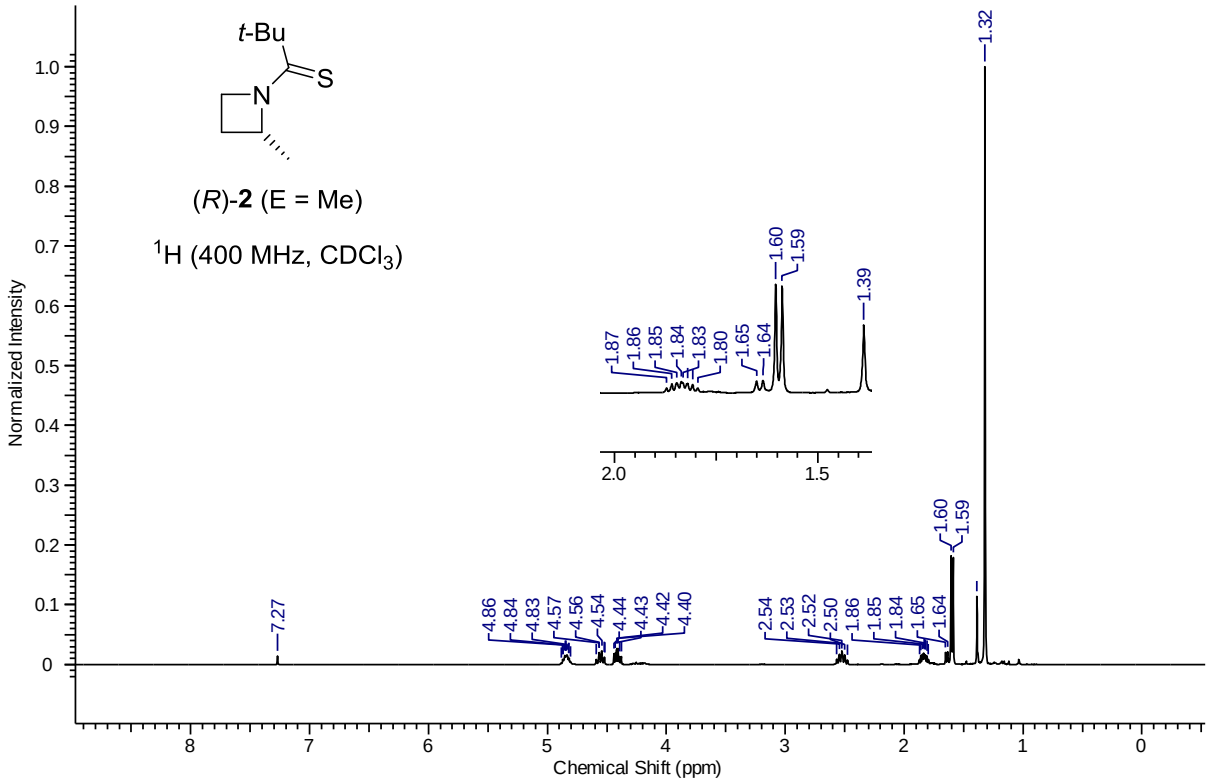

t-BuO
S
N
10i
13C (125 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
28.45
185.33
185.18
132.35
132.64
118.43
118.16
84.86
84.54
77.25
77.00
76.74
62.69
63.64
49.22
49.17
37.81
36.26
19.42
19.82

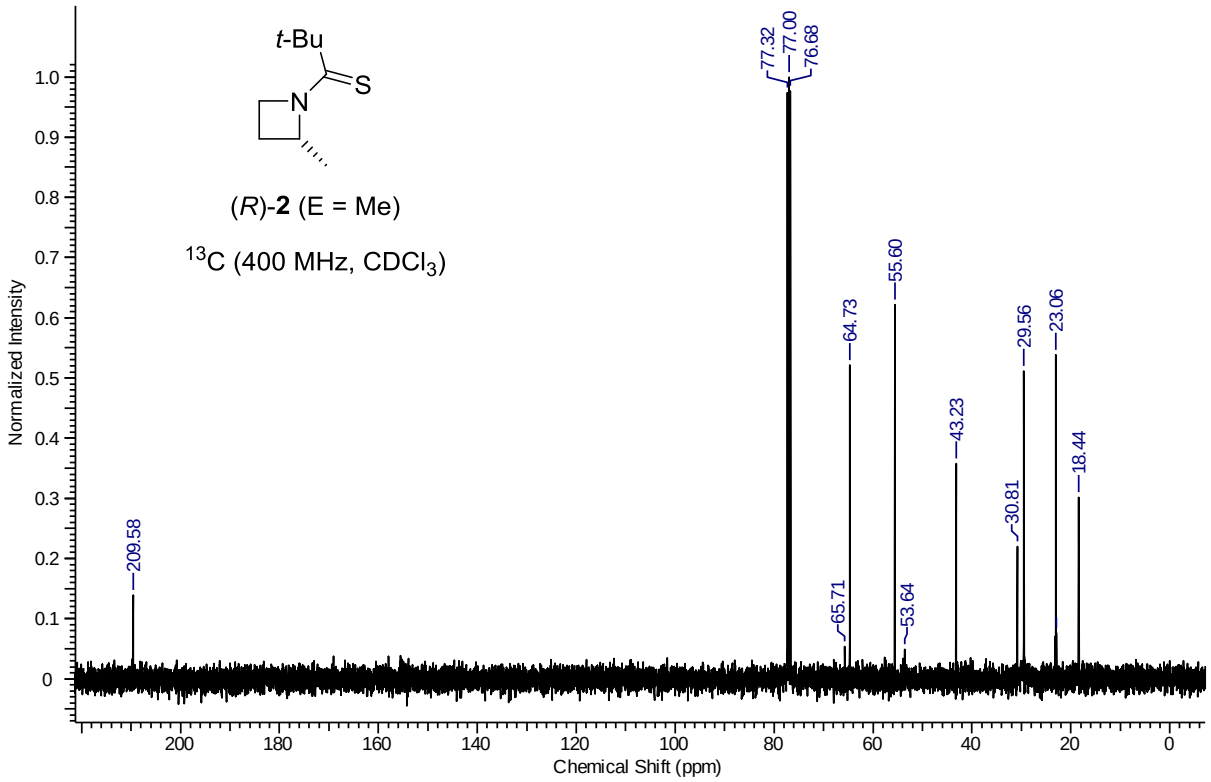

t-BuO
S
N
Bu
10j
1H (500 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
4.43
4.43
4.42
4.41
4.32
4.31
4.30
4.29
4.28
4.27
4.26
4.01
4.02
4.02
3.99
3.99
3.94
3.93
3.92
3.91
3.90
3.88
1.64
1.63
0.92
0.93
0.91
1.28
1.27
1.25
1.17
2.17
1.40
0.82
1.05
10.24
4.28
3.00


t-BuO
S
N
Bu
10j
13C (125 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
77.26
77.00
76.75
185.29
185.16
84.69
84.43
65.09
63.99
49.40
49.20
33.44
32.20
28.50
26.27
26.12
22.51
22.57
20.40
14.10
13.98


t-BuO
S
N
11
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
1.84
0.52
0.94
9.00
3.03
3.31

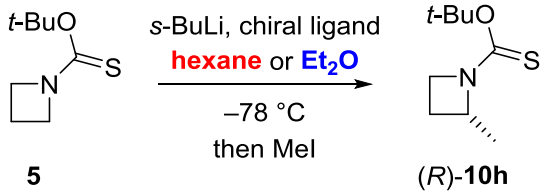

t-BuO
S
N
11
13C (100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)


t-Bu
S
N
(R)-2 (E = Me)
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
1.32
1.60
1.59
1.39
1.87
1.86
1.85
1.84
1.83
1.80
1.65
1.64
7.27
4.86
4.84
4.83
4.57
4.56
4.54
4.44
4.43
4.42
4.40
2.54
2.53
2.52
2.50
1.86
1.85
1.84
1.65
1.64


t-Bu
S
N
(R)-2 (E = Me)
13C (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
77.32
77.00
76.68
209.58
64.73
65.71
55.60
53.64
43.23
30.81
29.56
23.06
18.44

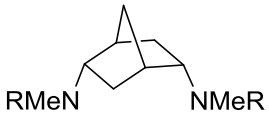
4. Chiral Ligand Screen

The following chiral ligands were tested for use in asymmetric methylation of Botc-protected azetidine **5**:

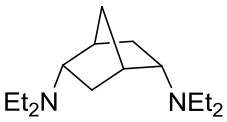


5 (*R*)-**10h**

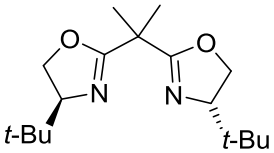
Unsuccessful ligands (0% yield, starting material recovered)**:**



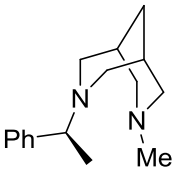
SI-9a[8] (R = CH_2CH_2t-Bu)
SI-9b[8] (R = CH_2CH_2OMe)



SI-10[8]

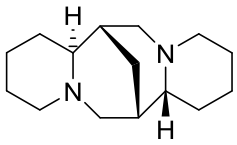


SI-11

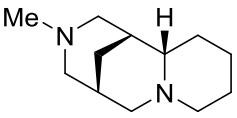


SI-12[9]

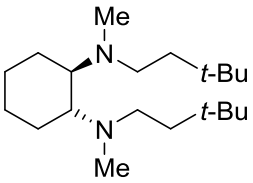
Ligands giving good yields:



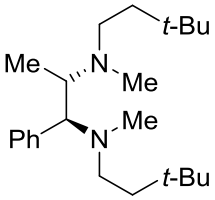
13 (hexane: 70%, 56:44 *R*:*S*
Et_2O: 78%, 52:48 *R*:*S*)



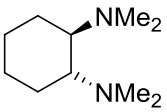
SI-13[10] (hexane : 60%, 51:49 *R*:*S*
Et_2O: 48%, 48:52 *R*:*S*)



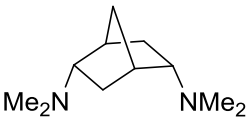
12[11] (hexane: 79%, 53:47 *R*:*S*
Et_2O: 75%, 59:41 *R*:*S*)



SI-14[12]
(hexane: 73%, 58:42 *R*:*S*
Et_2O: 58%, 47:53 *R*:*S*)



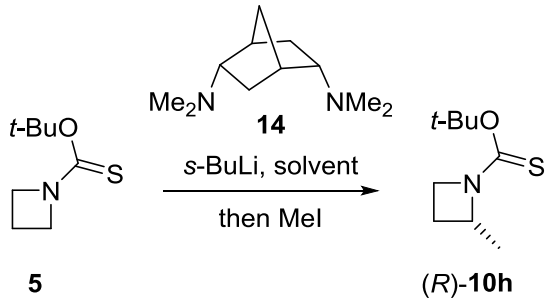
SI-15[13]
(hexane: 53%, 46:54 *R*:*S*
Et_2O: 35%, 43:57 *R*:*S*)



14[8]
(hexane: 73%, 69:31 *R*:*S*
Et_2O: 64%, 56:44 *R*:*S*)

5. Conditions for Asymmetric Methylation with DIANANE 14

The enantioselectivity of the asymmetric methylation of Botc-protected azetidine **5** with tetramethyl DIANANE **14**[8] was dependent on the durations of lithiation and methylation and the temps at which both of these steps were carried out (Table SI-1).



entry	solvent	lithiation time (temp)	methylation time (temp)	% yield	er (*R*:*S*)
1	hexane	4 h (−78 °C)	30 min (−78 °C) then 30 min (rt)	55	59:41
2		1 h (−78 °C)		73	69:31
3		5 min (−78 °C)		71	74:26
4		1 h (−78 °C)	4 h (−78 °C)	55	66:34
5	pentane	1 h (−98 °C)	30 min (−98 °C) then 30 min (rt)	54	75:25
6			1 h (−98 °C)	45	**91:9**
7		3 h (−98 °C)	1 h (−98 °C) then 30 min (rt)	60	67:33
8			1 h (−98 °C)	67	70:30
9			3 h (−98 °C)	68	66:34

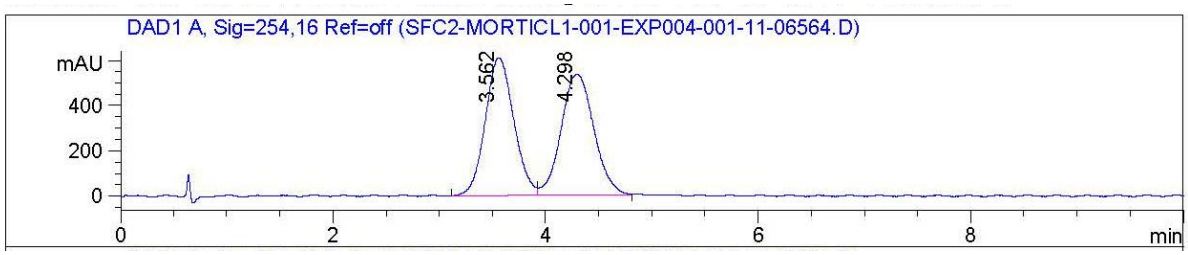
Table SI-1. Conditions for Asymmetric Methylation

6. Chiral SFC Traces

Chiral SFC traces for (*R*)-10h (initial conditions)

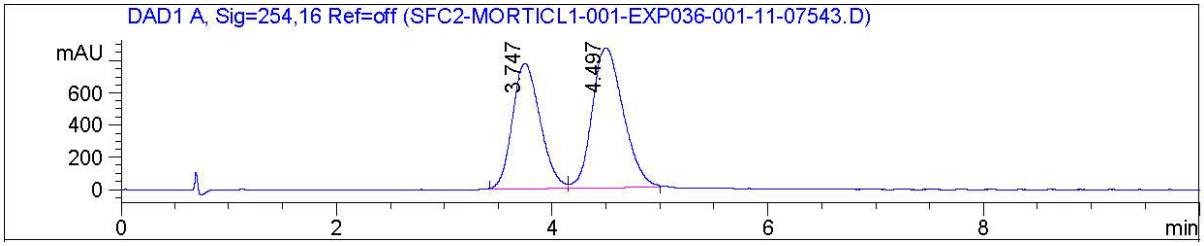
Column: CHIRALPAK IC, 150 × 2.1 mm, 3 µm, 40 °C, 0.7 mL / min, UV-vis (λ = 220 nm and 254 nm), eluent = isocratic at 5% *i*-PrOH in CO_2.

Racemic **10h**; er 50:50



Peak #	RT [min]	Type	Width [min]	Area	Area %	Symmetry
1	3.562	MF	0.31211394.0430	49.94		0.896
2	4.298	FM	0.35611421.5410	50.06		0.935

(*R*)-**10h**; from reaction in Et_2O; er 56:44 (*R*:*S*)

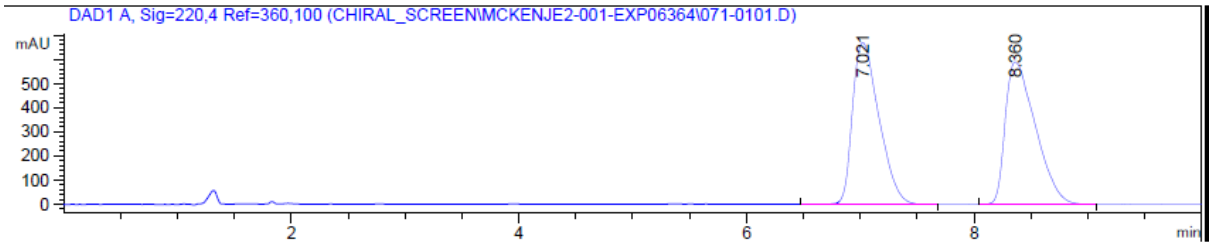


Peak #	RT [min]	Type	Width [min]	Area	Area %	Symmetry
1	3.747	BV	0.27713849.4268	44.23		0.781
2	4.497	VB	0.30617459.4141	55.77		0.736

Chiral SFC traces for (*R*)-10h

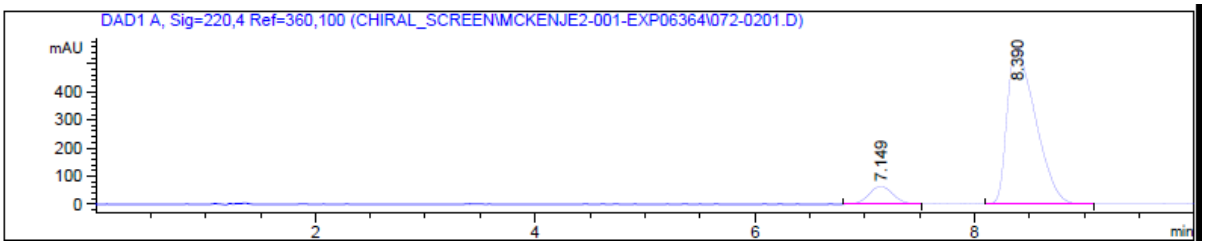
Column: CHIRALPAK IC, 250 × 4.6 mm, 5 µm, 40 °C, 3 mL/ min, UV-vis (λ = 220 nm and 254 nm), eluent = isocratic at 5% *i*-PrOH in CO_2.

Racemic **10h**; er 50:50



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.021	VB	0.2445	1.08327e4	670.59546	49.9184
2	8.360	VB	0.2687	1.08682e4	590.68292	50.0816

(*R*)-**10h**; from reaction in pentane; er 91:9 (*R*:*S*)



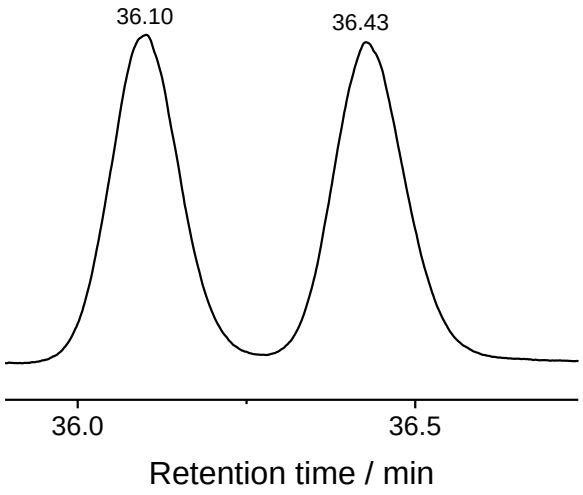
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.149	BV	0.2404	975.52692	63.09827	8.8898
2	8.390	VB	0.2538	9998.04297	561.40704	91.1102

7. Chiral GC Traces

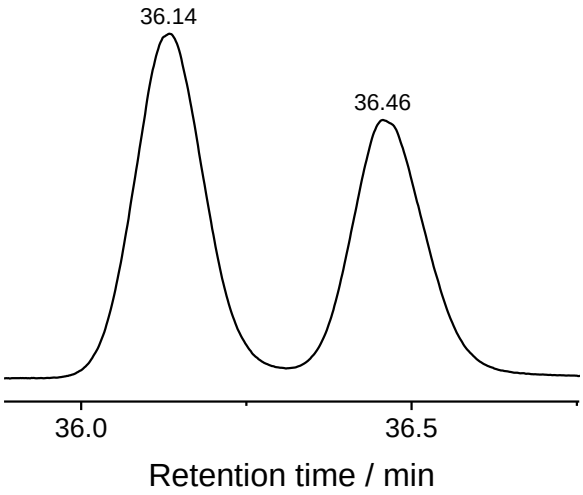
Chiral GC traces for 2 (E = Me)

Column: β-cyclodextrin, 0.22 mm × 30 m, thickness 0.25 µm, flow rate = 1 mL/ min, carrier gas = He, T injector 220 °C, T detector (FID) 250 °C, T initial 40 °C, 5 min then 5 °C/min to 140 °C.

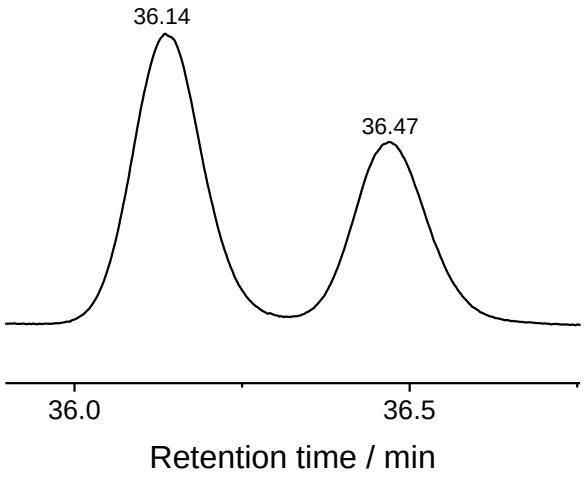
Racemic **2** (E = Me); er 50:50



(*R*)-**2** (E= Me); from reaction in Et_2O; er 56:44 (*R*:*S*)



Spiking experiment: enantiomerically pure (*R*)-**2** (E = Me)[2] added to racemic **2** (E = Me)

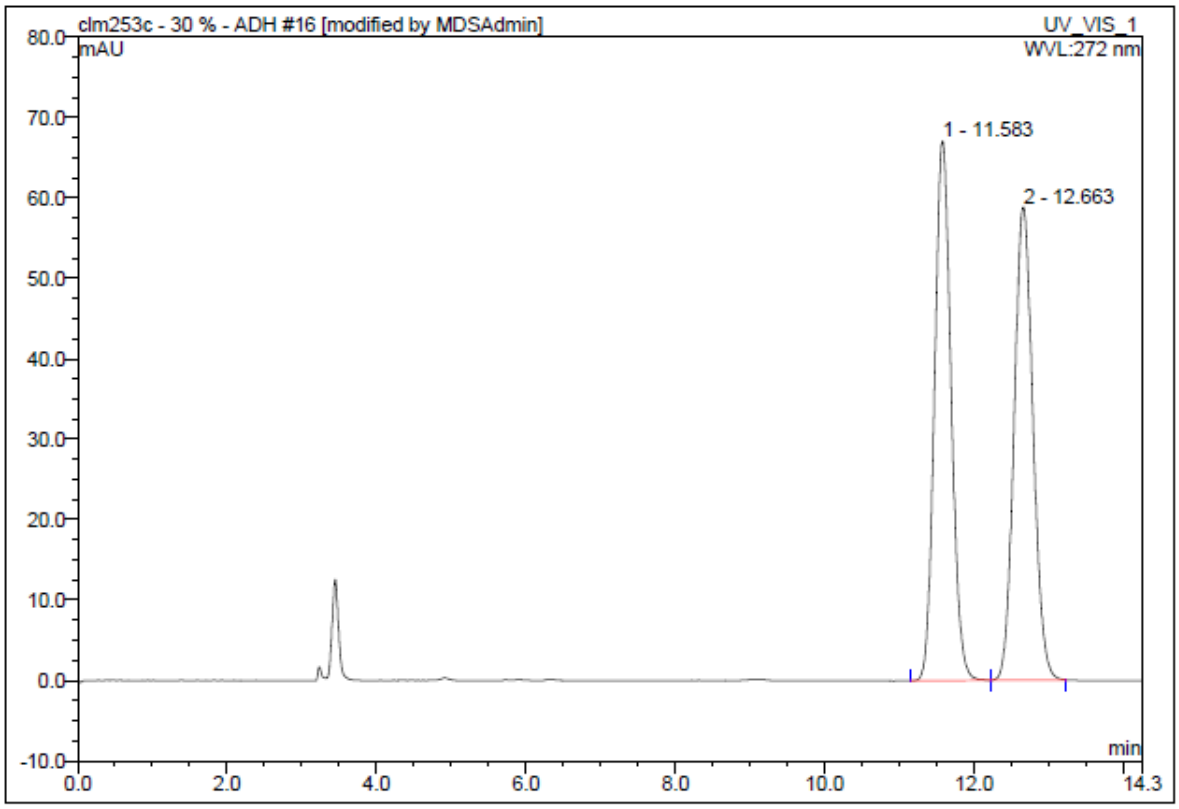


9. Chiral HPLC Traces

Chiral HPLC traces for 10d

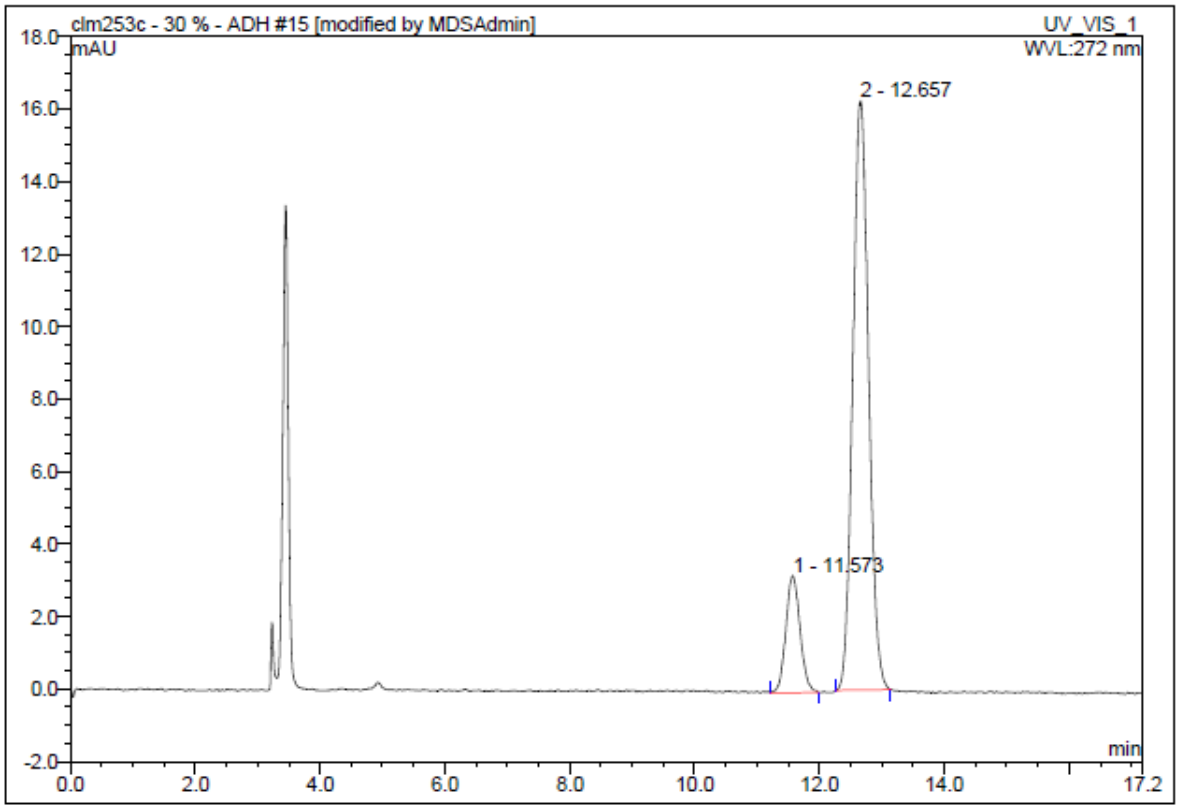
Column: CHIRALPAK AD-H, 250 × 4.6 mm, 5µm, 25 °C, 1 mL/ min, UV-vis (λ = 272 nm), eluent = isocratic at 4% *i*-PrOH in hexane.

Racemic (*R**,*R**)-**10d-minor**; er 50:50



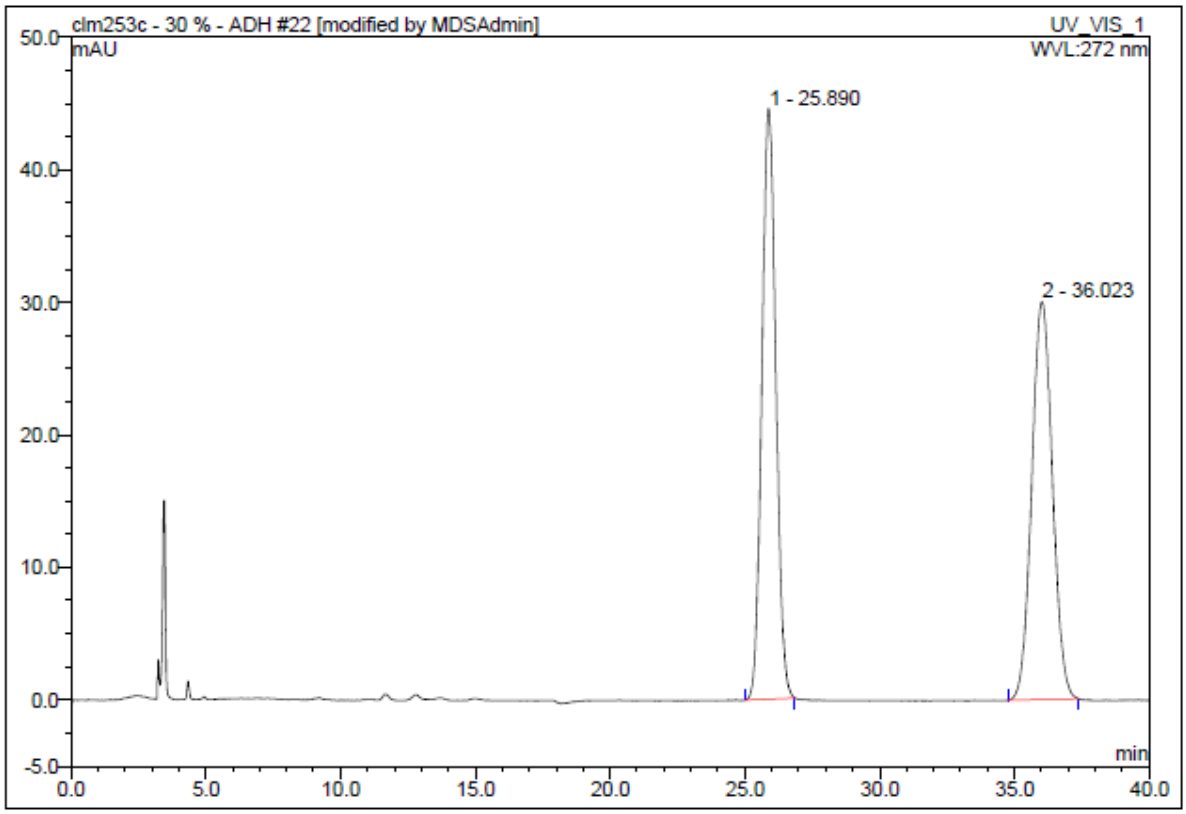
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.58	n.a.	67.093	17.305	50.06	n.a.	BM
2	12.66	n.a.	58.827	17.265	49.94	n.a.	MB
Total:			125.920	34.569	100.00	0.000	

(*S*,*S*)-**10d-minor**; er 85:15 (*S*,*S*:*R*,*R*)



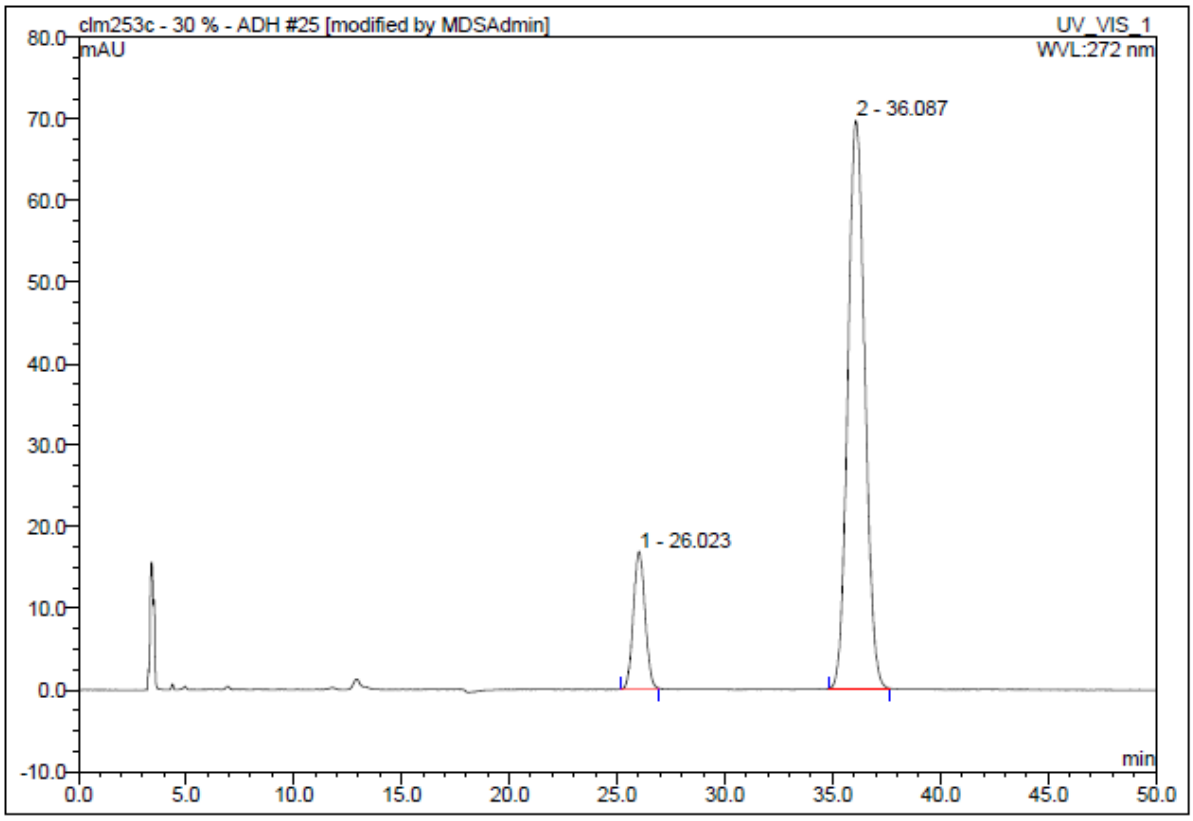
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.57	n.a.	3.214	0.848	15.12	n.a.	BMB
2	12.66	n.a.	16.251	4.758	84.88	n.a.	BMB
Total:			19.465	5.605	100.00	0.000	

Racemic (*R**,*S**)-**10d-major**; er 50:50



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.89	n.a.	44.569	26.750	50.08	n.a.	BMB
2	36.02	n.a.	29.998	26.667	49.92	n.a.	BMB
Total:			74.567	53.417	100.00	0.000	

(*S*,*R*)-**10d-major**; er 86:14 (*S*,*R*:*R*,*S*)

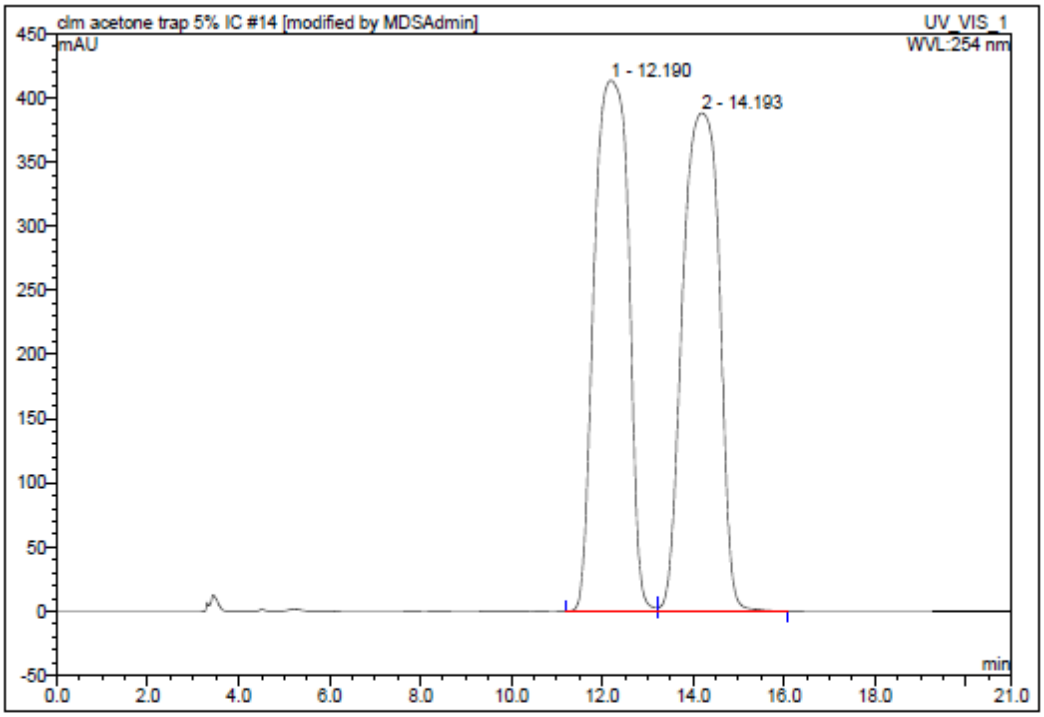


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26.02	n.a.	16.829	10.550	14.20	n.a.	BMB
2	36.09	n.a.	69.655	63.726	85.80	n.a.	BMB
Total:			86.484	74.276	100.00	0.000	

Chiral HPLC traces for 10g

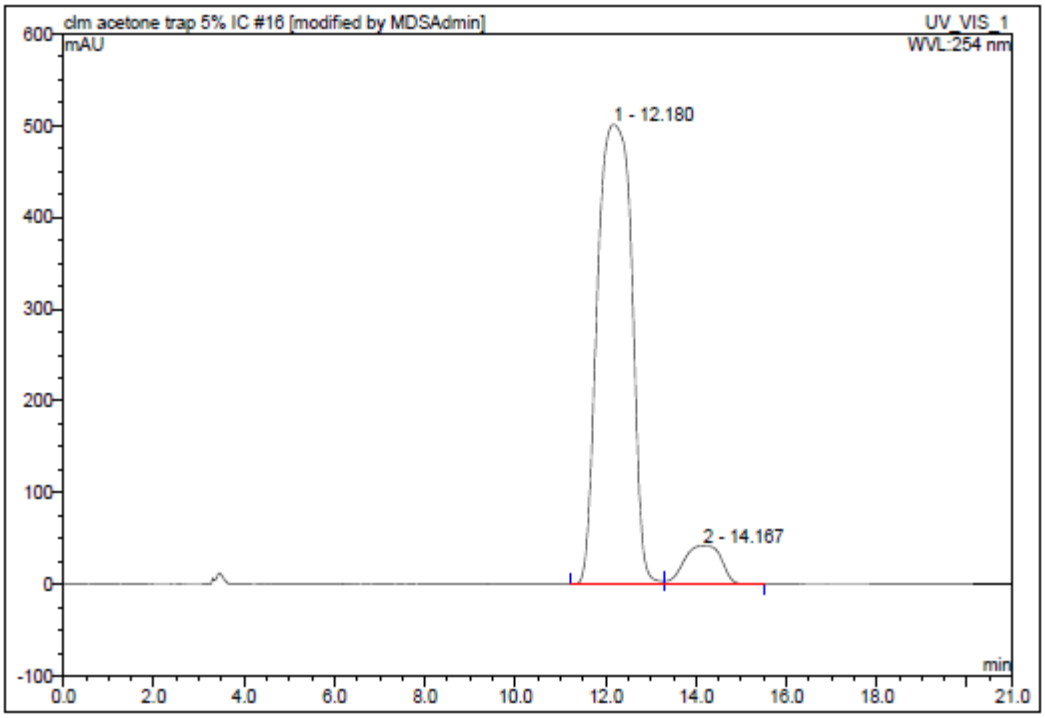
Column: CHIRALPAK AD-H, 250 × 4.6 mm, , 5µm, 25 °C, 1 mL/ min, UV-vis (λ = 254 nm), eluent = isocratic at 2% *i*-PrOH in hexane.

Racemic **10g**; er 50:50



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.19	n.a.	413.181	361.894	49.88	n.a.	BM
2	14.19	n.a.	387.866	363.671	50.12	n.a.	MB
Total:			801.047	725.565	100.00	0.000	

(*S*)-**10g**; er 92:8 (*S*:*R*)



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.18	n.a.	500.984	438.346	91.64	n.a.	BM
2	14.17	n.a.	41.863	40.007	8.36	n.a.	MB
Total:			542.847	478.353	100.00	0.000	

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