Thia-, Aza-, and Selena[3.3.1]Bicyclononane Dichlorides: Rates vs. Internal Nucleophile in Anchimeric Assistance

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1. Syntheses of WCL Electrophiles

2,6-Dichloro-9-selenabicyclo[3.3.1]nonane (**2**). A solution of sulfuryl chloride (1.35 g, 0.01 mol) in $CHCl_3$ (40 mL) was added dropwise to a mixture of selenium (0.8 g, 0.01 mol) and $CHCl_3$ (20 mL) and the mixture was stirred overnight at room temperature. The resulting solution of selenium dichloride was added dropwise over 90 min to a stirred solution of 1,5-COD (1.08 g, 0.01 mol) in $CHCl_3$ (30 mL) cooled in an ice bath. The mixture was stirred for 4 h with cooling and allowed to warm to room temperature overnight. Insoluble byproducts were removed by filtration. The filtrate was evaporated and the residue recrystallized from CCl_4 to give **2** (2.5 g, 96% yield). Mp 95-98 °C. ^{1}H NMR (500 MHz, CD_3CN) δ 2.25-2.45 (m, 6H), 2.82 (m, 2H), 3.11 (m, 2H), 5.00 (m, 2H). ^{13}C NMR (125 MHz, CD_3CN) δ 30.9, 33.0, 34.4, 65.5. ^{77}Se NMR (75 MHz, $CDCl_3$) δ 379.2. Anal. Calcd for $C_8H_{12}Cl_2Se$: C, 37.24; H, 4.69; Cl, 27.48; Se, 30.60. Found: C, 37.66; H, 4.73; Cl, 27.59; Se, 30.83.

2,6-Dichloro-9-phenylaminobicyclo[3.3.1]nonane hydrochloride (**3a**). To a 25 mL round-bottomed flask was added *cis*-1,5-cyclooctadiene diepoxide **4**[1] (1.00 g, 7.14 mmol), aniline (975 µL, 10.7 mmol), and 10 mL of water. The mixture was stirred at 60 °C under nitrogen for 14 h. The solution was cooled to room temperature and the pH was adjusted to approximately 11 by the addition of 1 mL of 10% NaOH. The crude product was extracted into EtOAc (3 x 10 mL). Excess aniline was removed by flash

1. Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189-6190.

column chromatography (1:1 hexanes:ethyl acetate) to yield intermediate diol **5a** as a mixture of [3.3.1] and [4.2.1] isomers (84%). This material (50 mg, 0.214 mmol) was dissolved in THF (1 mL) and treated with methanesulfonyl chloride (39.8 μL, 0.513 mmol) and 4-dimethylaminopyridine (26.1 mg, 0.214 mmol). The mixture was heated at 40°C for 24 hours, after which the solvent and excess reagents were removed under vacuum to give a blue oil, which was further purified by flash column chromatography using 95:5 hexanes:ethyl acetate to give the final product **3a** as a pale blue oil (50%). This compound was found to exist as a 91:9 mixture of [3.3.1] and [4.2.1] isomers respectively, as shown by 1D and 2D NMR analysis (see supporting information). Major product: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.92 (m, 2H), 2.18 (m, 6H), 4.04 (m, 2H), 4.34 (m, 2H), 6.69 (t, J = 5Hz, 1H), 6.91 (d, J = 5Hz, 2H), 7.19 (t, J = 7.5Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.5, 32.0, 52.8, 59.9, 115.1, 118.9, 130.4, 147.9. Minor product: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.79 (m, 2H), 1.90* (m, 2H) (as established by 2D experiments), 2.02 (m, 2H), 2.11 (dd, J_1 = 6Hz, J_2 = 12Hz, 2H), 4.50 (m, 2H), 4.56 (m, 2H), 6.62 (t, J = 5Hz, 1H), 6.75 (d, J = 5Hz, 2H), 7.16 (t, J = 10Hz, 2H).

2,6-Dichloro-9-heptylaminobicyclo[3.3.1]nonane hydrochloride (**3b**). The above procedure was used with heptylamine (1.59 mL, 10.7 mmol) and 1,5-cycloctadiene diepoxide **4** (1.00 g, 7.14 mmol). The resultant intermediate diol mixture **5b** (0.50 g, 1.95 mmol) was treated with freshly distilled thionyl chloride (1.5 mL, 10 equiv) and warmed to 50 °C for three hours under a nitrogen atmosphere. The reaction was monitored by diluting aliquots into 9:1 acetonitrile:water and analyzing by LC-MS. Excess thionyl chloride was removed under vacuum and the brown residue was triturated with diethyl ether to give an off-white precipitate, which was dissolved in minimal CH_2Cl_2 and re-precipitated by dropwise addition into cold ether. This procedure was repeated a second time; the product was washed with additional portions of cold ether and dried under vacuum to give **3b** (20%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 5 Hz, 3H), 1.30 (m, 8H), 1.42 (m, 2H), 1.95 (m, 2H), 2.15 (m, 4H), 2.25 (m, 2H), 2.76 (m, 2H), 2.90 (t, J = 5 Hz, 2H), 4.41 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 14.5, 22.8, 23.0, 27.4, 29.1, 29.5, 32.20, 32.24, 52.8, 55.8, 59.3. Anal. (HCl salt) Calcd for $C_{15}H_{28}Cl_3N$: C, 54.80; H, 8.58; N, 4.26. Found: C, 53.77; H, 7.85; N, 3.72.

2,6-Dihydroxy-9-propargylaminobicyclo[3.3.1]nonane and 2,5-Dihydroxy-9-propargylaminobicyclo[4.2.1]-nonane. A 250 mL round-bottomed flask was charged with *cis*-1,5-cyclooctadiene diepoxide **4**[1] (5.01 g, 35.7 mmol), propargylamine (0.238 mL, 29.8 mmol), and water (50 mL) under N_2. The slurry was vigorously stirred at 70 °C for 12 h during which its color changed

to brown. The reaction progress was monitored by GC-MS. Upon completion, the mixture was cooled to room temperature and CH_2Cl_2 (50 mL) and 1 N NaOH (50 mL) solution were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and EtOAc (1 x 50 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the crude product as a brown solid. This material was dissolved in minimal CH_2Cl_2 (20 mL) and then precipitated by addition to hexane (60 mL). The pale yellow precipitate was collected and allowed to dry in air to give the desired diols (1.3 g, 22%). GC-MS (0.25 μm HP-5MS capillary column, 30 m x 0.25 mm; He flow rate 0.5 mL/min; temperature program from 100 to 200 °C at 10 deg/min, followed by increase to 275 °C at 15 deg/min) 14.08 min, 14.52 min (both showing m/z of parent $[M+H]^+$ ion = 195, intensity ratio 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35-1.80 (m, 6H), 1.90~2.10 (m, 2H), 2.18 (t, J_1=2.4 Hz, 1H), 2.82~3.00 (br, 2H), 3.38 (d, J_1=2.4, 2H), 3.42 (m, 2H), 3.95 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 23.4, 29.2, 46.2, 68.2, 71.2, 72.5, 82.1.

2,6-Dichloro-9-propargylaminobicyclo[3.3.1]nonane (**3c**). A 50-mL round-bottomed flask was charged with the mixture of 9-propargylaminobicyclononane diols (1.2 g, 6.0 mmol) and freshly distilled thionyl chloride (25 mL). The mixture was stirred at 50 °C and the reaction was found by GC-MS to reach completion in less than one hour. The solvent was then reduced to 1 mL under reduced pressure and diethylether (50 mL) was added to precipitate the product. The solid was filtered and dried in air to give **3c** as a brown solid of >95% purity by NMR and GC-MS, used without further purification (yield = 0.68 g, 49%). GC-MS as above showed a single peak at 14.28 min (m/z of parent ion = 231, 233). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.99 (m, 2H), 2.16 (m, 4H), 2.28 (m, 1H), 2.31 (m, 2H), 3.14 (t, J = 5Hz, 2H), 3.65 (s, 2H), 4.42 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 32.0, 42.4, 55.3, 58.2, 73.4, 80.5. Anal. (HCl salt) Calcd for $C_{11}H_{16}Cl_3N$: C, 49.19; H, 6.00; N, 5.21. Found: C, 48.43; H, 5.83; N, 5.49.

2,6-Dichloro-9-benzylaminobicyclo[3.3.1]nonane hydrochloride (**3d**). The epoxide ring opening procedure described for **3a** was used with benzylamine (1.17 mL, 10.7 mmol) and 1,5-cycloctadiene diepoxide **4** (1.00 g, 7.14 mmol). The resulting intermediate diol mixture **5d** (0.50 g, 2.02 mmol) was treated with freshly distilled thionyl chloride (1.5 mL, 10 equiv) and warmed to 50 °C for three hours under a nitrogen atmosphere. The reaction was monitored by diluting aliquots into 9:1 acetonitrile:water and analyzing by LC-MS. Excess thionyl chloride was removed under vacuum and the brown residue was triturated with diethyl ether to give an off-white precipitate, which was dissolved in minimal CH_2Cl_2 and precipitated by dropwise addition into cold ether. This procedure

was repeated a second time; the product was washed with additional portions of cold ether and dried under vacuum to give hydrochloride salt **3d** (80%). For NMR analysis the dichloro product was dissolved in water, extracted into ethyl acetate three times, and the organic layer was dried with magnesium sulfate. After the solvent was removed *in vacuo* the resultant yellow oil was soluble in chloroform. GC-MS single peak at 17.84 min (m/z of parent ion = 283.1) ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.99-2.10 (m, 2H), 2.11-2.24 (m, 6H), 2.86 (t, J = 5Hz, 2H), 4.06 (dd, J_1 = 15Hz, J_2 = 25Hz, 2H), 4.63 (m, 2H), 7.31 (m, 1H), 7.40 (m, 4H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 23.0, 32.2, 55.0, 56.2, 60.0, 127.9, 128.9, 129.2, 140.0. Anal. (HCl salt) Calcd for $C_{15}H_{20}Cl_3N$: C, 56.18; H, 6.29; N, 4.37. Found: C, 55.39; H, 6.14; N, 4.46.

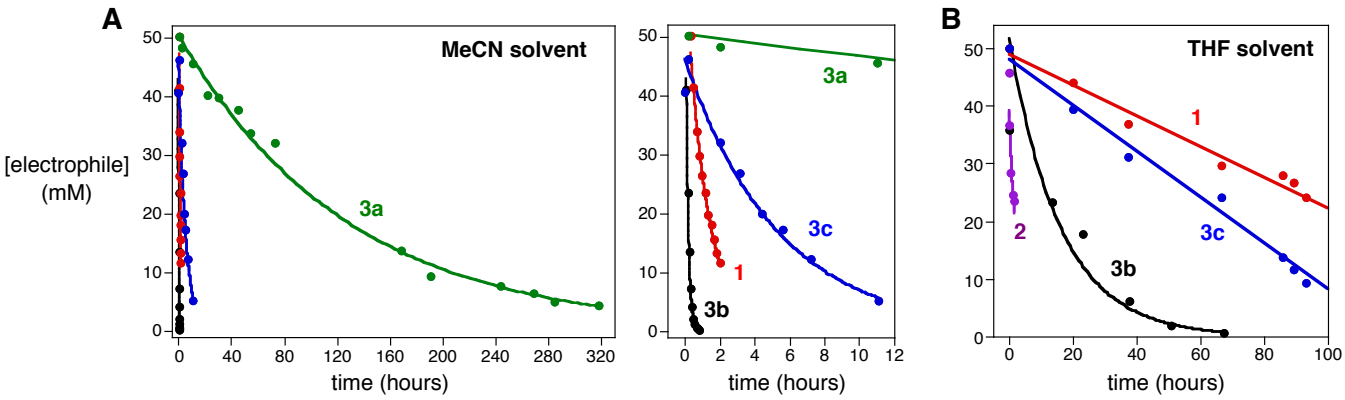
2. Kinetics

General. Kinetics experiments as a function of electrophile (Table 1, entries 1-10) were performed at room temperature on 50 mM solutions of each dichloride in dry THF or acetonitrile containing acetanilide (50 mM) as an internal standard. The reaction was initiated by the addition of 15 equiv of freshly distilled neat benzylamine to the rapidly stirred solution. Reaction progress was followed by removing 10 μL aliquots at intervals and diluting each immediately into 990 μL of THF for GC-MS analysis. Control experiments showed that the reactions proceeded no further after such dilution. Concentrations of WCL starting materials were calculated based on the observed intensity ratios vs. internal standard, and rate constants were obtained from linear fits ($R^2 > 0.99$, except where noted) of first-order ln(starting material) *vs.* time plots.

Similar kinetics measurements were performed at room temperature as a function of nucleophile (Table 1, entries 11-15) on solutions of **3d** (5 mM) in 2:1 THF:water containing caffeine (0.3 mM) as an internal standard and 25 mM (5.0 equiv.) of NEt_3 to neutralize any dissolved HCl. It was previously reported that NEt_3 does not add to WCL electrophiles,[6a] and determined here that varying amounts of NEt_3 did not affect the reaction rate (data not shown). Each reaction was initiated by addition of nucleophile to a concentration of 75 mM. Ionic strength was made equivalent for all cases by adding 75 mM of $NaPF_6$ to the *n*-propylamine and pyridine cases (Table 1, entries 11 and 14) or 75 mM NaOH to the phenol case (Table 1, entry 15). At each time point, an aliquot was removed and transferred to a solution containing a large excess of benzylamine in water. The concentration of dibenzylamine adduct, representing the concentration of dichloride starting material at each time point, was determined by HPLC against the internal standard.

Rate as a Function of the Electrophile (Table 1, entries 1-10). Using non-reactive acetanilide as an internal standard, the rate of consumption of dichloride starting material was measured by GC-MS. Compounds and acetanilide internal standard were made 0.05 M in the reaction solvent (ACN or THF). Excess benzylamine (15 eq) was added at time zero. Time points were quenched for subsequent GC injection by diluting 100 fold into THF at time t. GC-MS experiments were conducted on a 0.25 µm HP-5MS capillary column, 30 m x 0.25 mm, Agilent Technologies; He flow rate 0.5 mL/min; temperature program from 140 to 200 °C at 10 deg/min, followed by increase to 300 °C at 15 deg/min. All kinetics runs in Figures S1 and S2 were reproduced at least three times. Standard deviations are reported in Table 1.'

Figure S1. Representative pseudo-first order kinetics experiments for reactions of WCL electrophiles with benzylamine in the indicated solvent. (A) Reactions in acetonitrile; the plot at the right shows an expansion of the first 12 hours. (B) Reactions in THF.

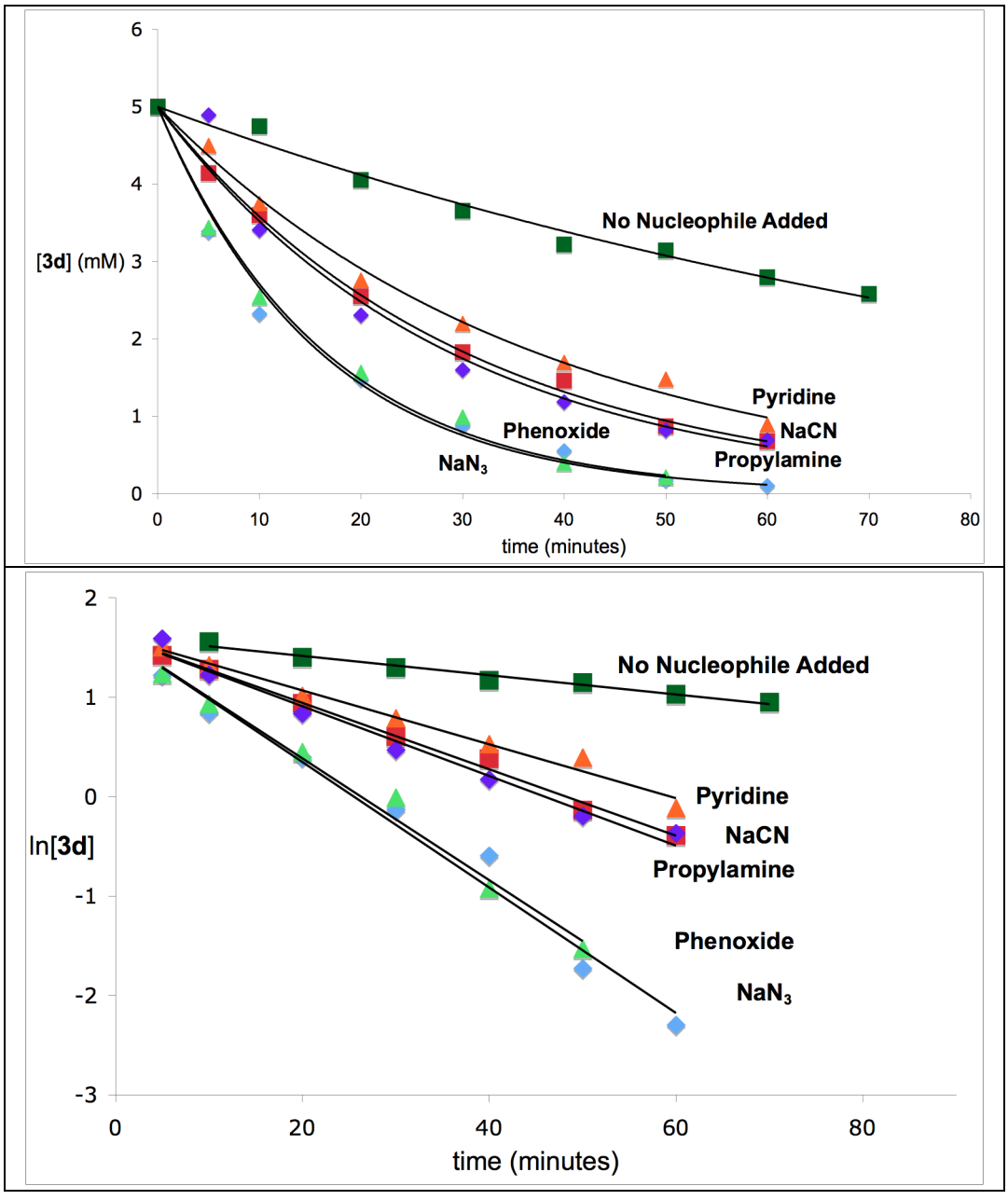


Rate as a Function of Nucleophile (Table 1, entries 11-15). The use of 2:1 THF:water gave rise to much faster reaction rates, so the concentration of electrophile was reduced to one-tenth (5 mM) of that used in the analysis in Figure S1. Each reaction was initiated by addition of 15 equiv (75 mM) of nucleophile to a stirred solution of **3d** (5mM) and caffeine (0.3 mM) at time t=0, to give the final concentrations indicated. Aliquots could not be analyzed directly for **3d** because of its slow hydrolysis in the presence of water, and so each aliquot was quenched by addition to 10 times the volume of a 75 mM benzylamine solution in 80:20 water:acetonitrile.

Control reactions established that: (a) benzylamine reactions with **3d** are irreversible, so the quenching reactions report on the amount of **3d** remaining; (b) caffeine does not react with **3d** under these conditions. Analytical HPLC was performed with a Zorbax 300SB-C18 column, 150 mm x 4.6 mm, 5 µm; flow = 1 mL/min; eluents H_2O (A) (0.1% TFA), MeCN (B) (0.1% TFA). A gradient

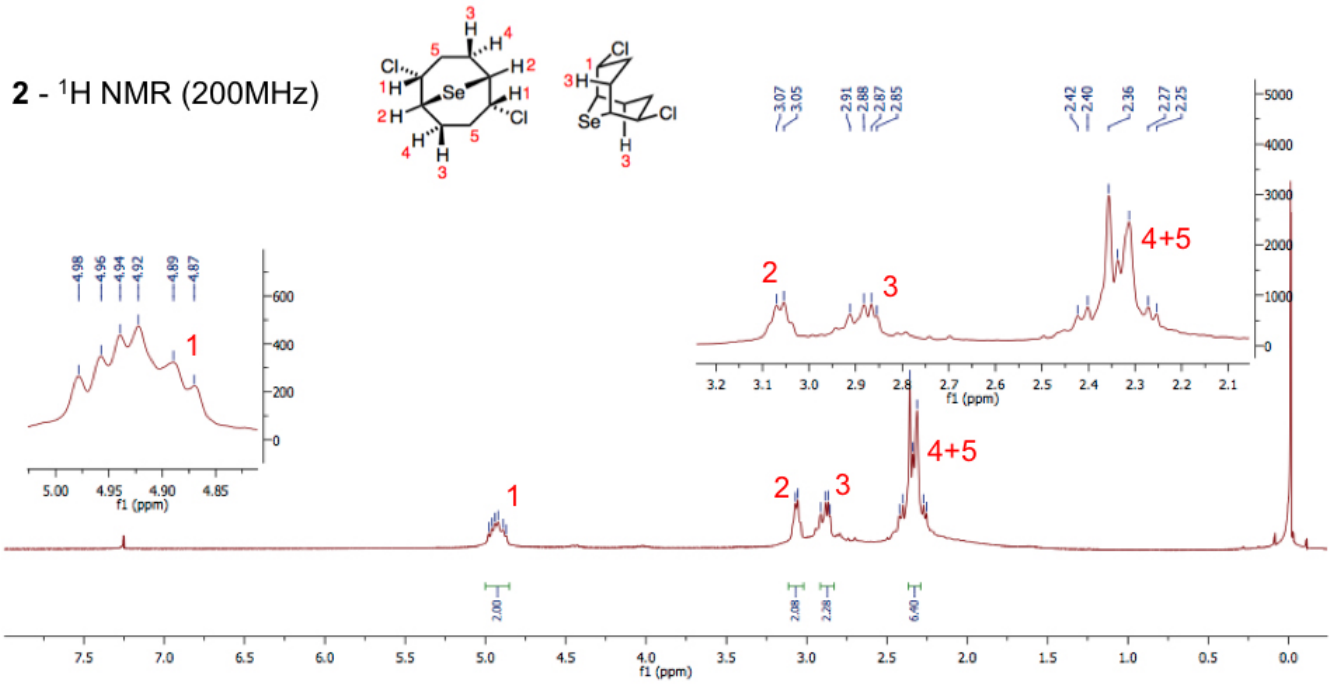
method was used in which the percentage of B was allowed to increase from 0% to 95% over 30 minutes. The column was washed thoroughly between sample injections.

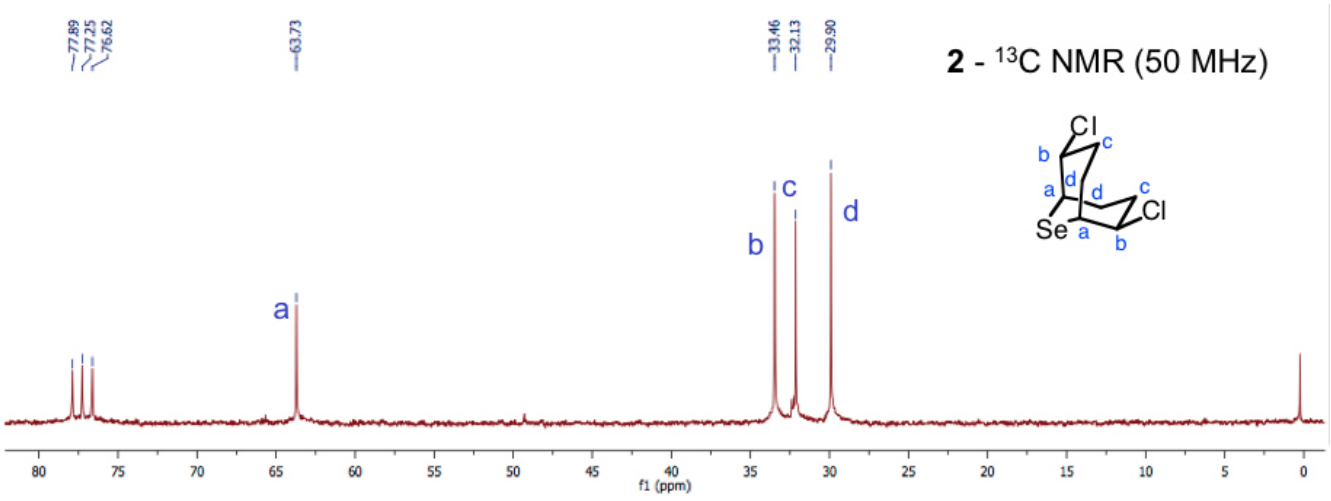
Figure S2. Representative kinetics data (top) and pseudo-first order plot (bottom) for variation in nucleophile in reactions with **3d**, in 2:1 THF:H_2O solvent.



3. NMR Spectra of Electrophiles

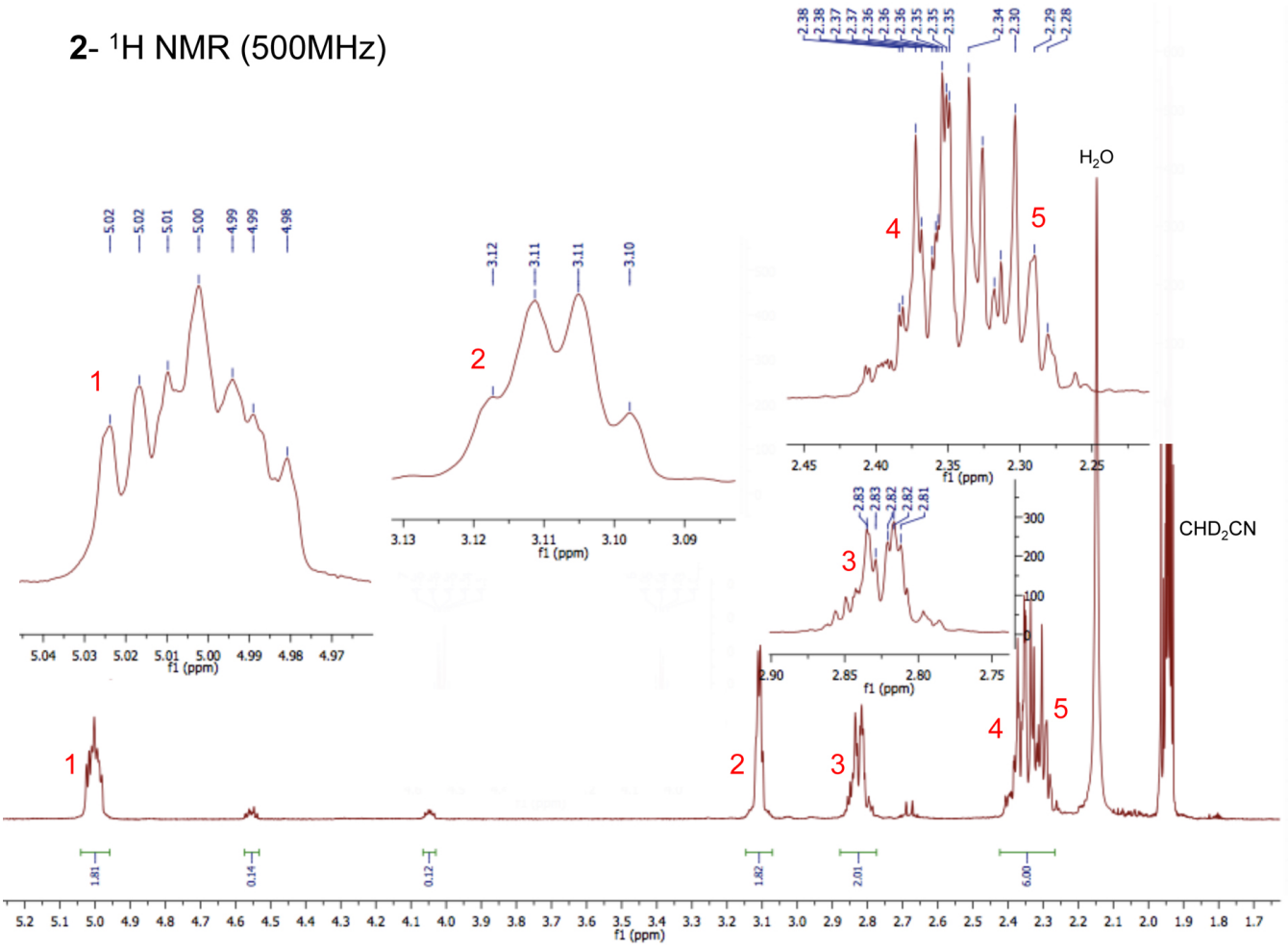
Compound **2** ($CDCl_3$)



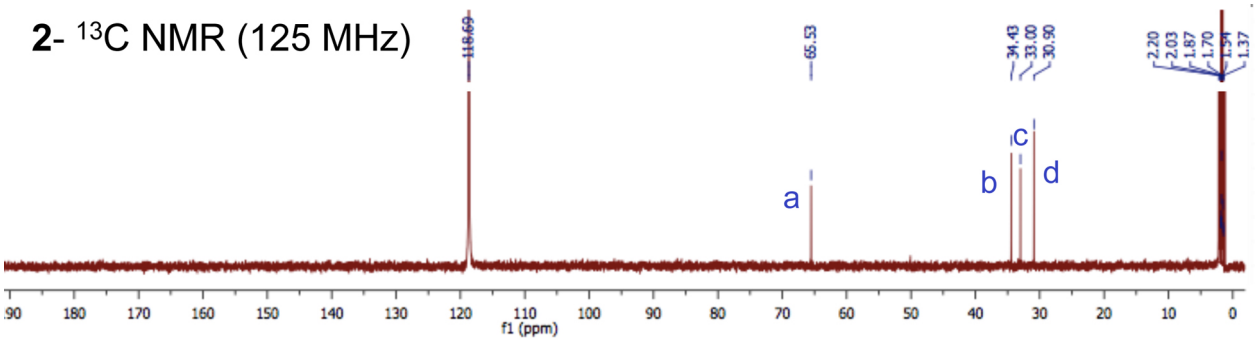


Compound **2** (CD_3CN) Impurity peaks at 4.55 and 4.05 ppm are probably due to substitution by water.

2- ^{1}H NMR (500MHz)

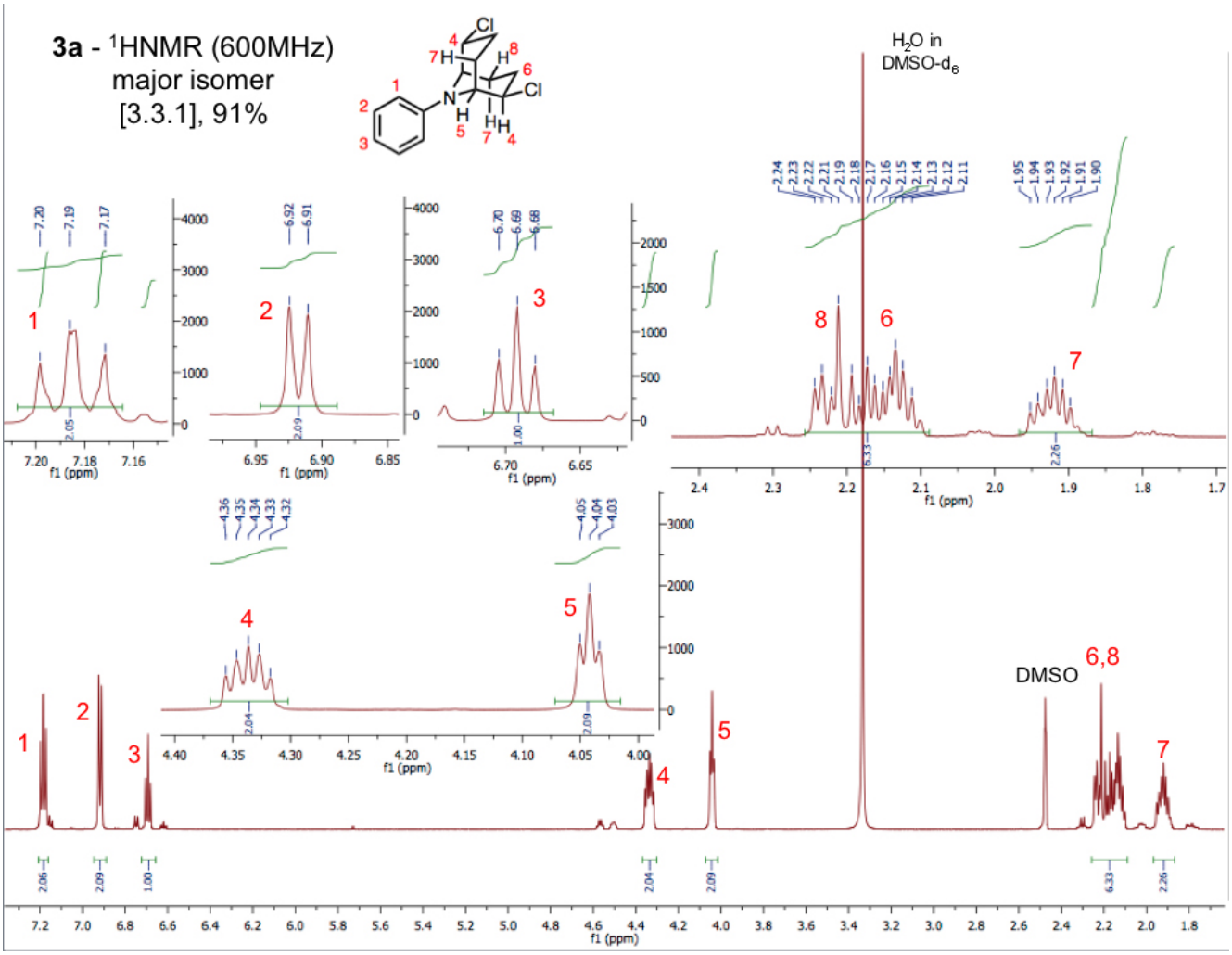


2- ^{13}C NMR (125 MHz)

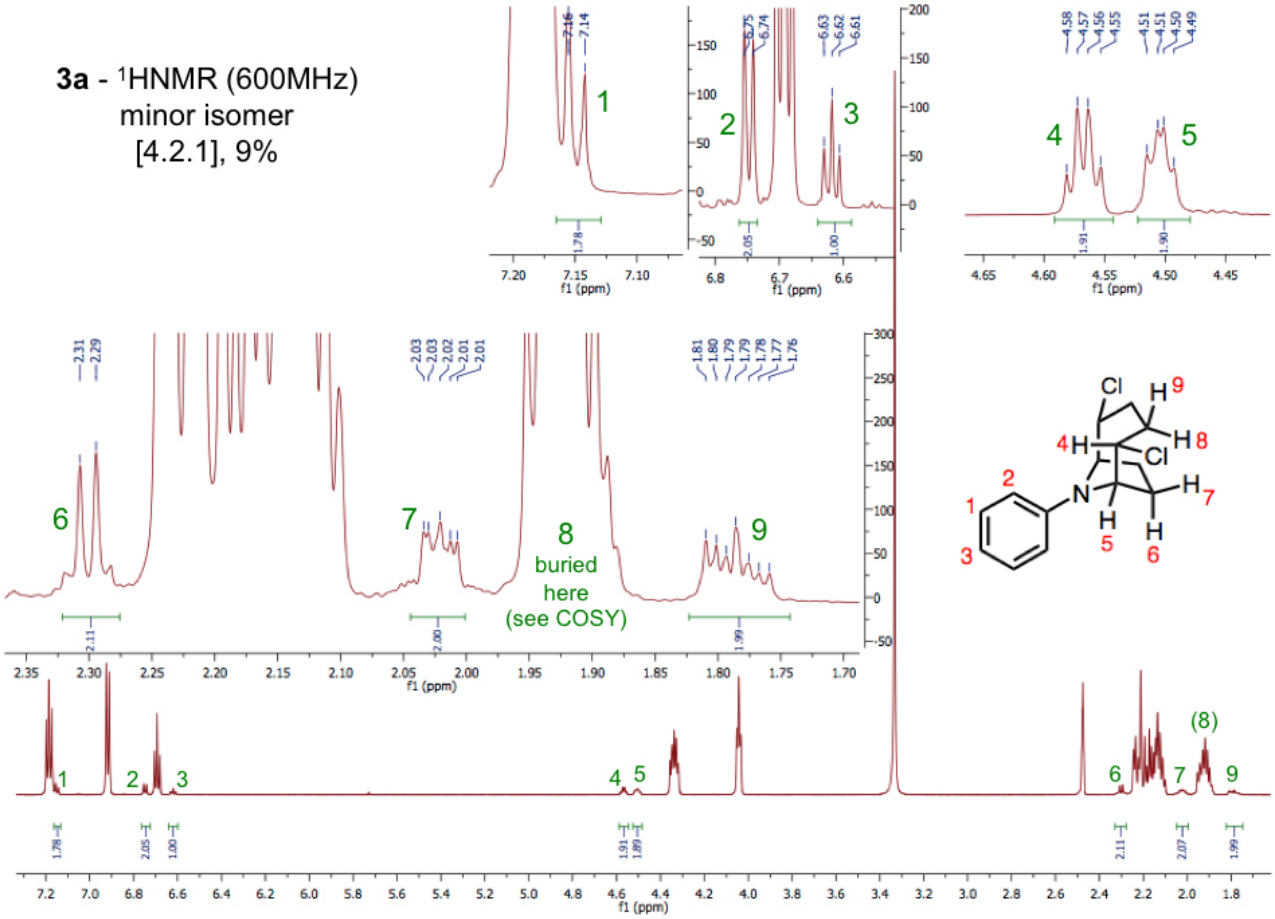


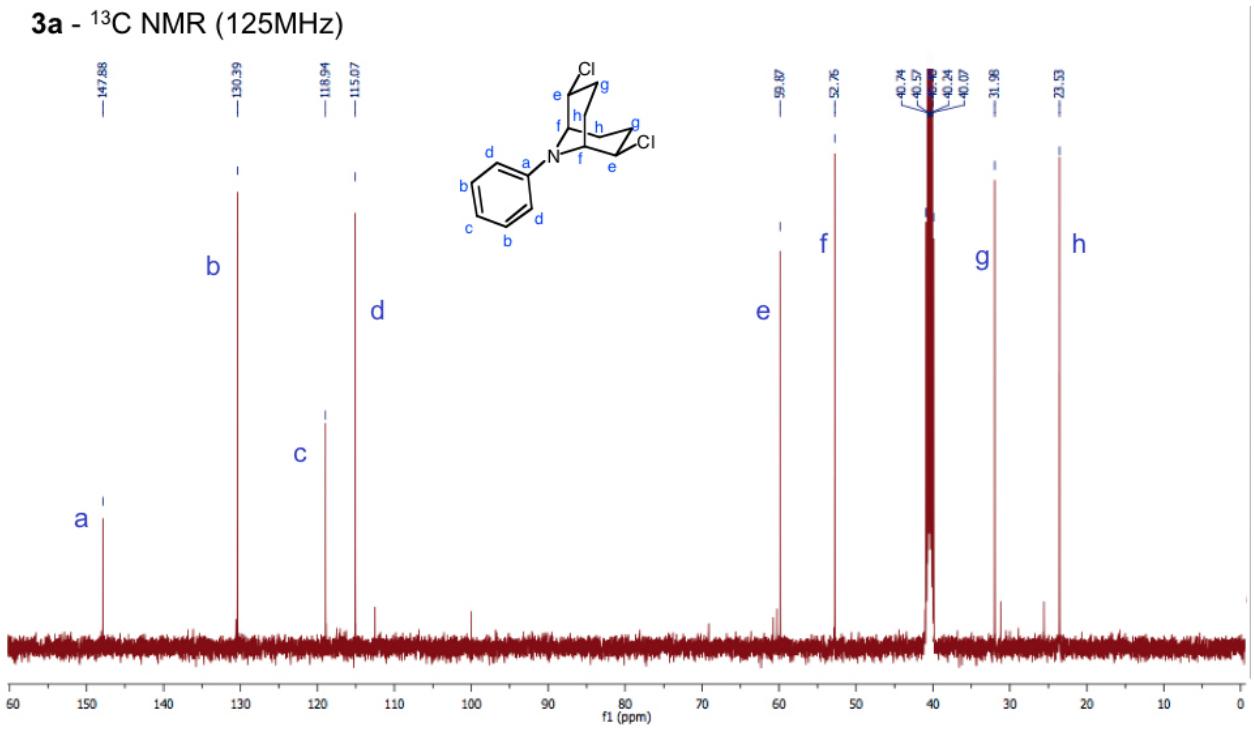
Compound **3a** (DMSO-d_6) is present as a mixture of [3.3.1] and [4.2.1] isomers, as shown on the following two sets of spectra.

major isomer peaks expanded and labeled

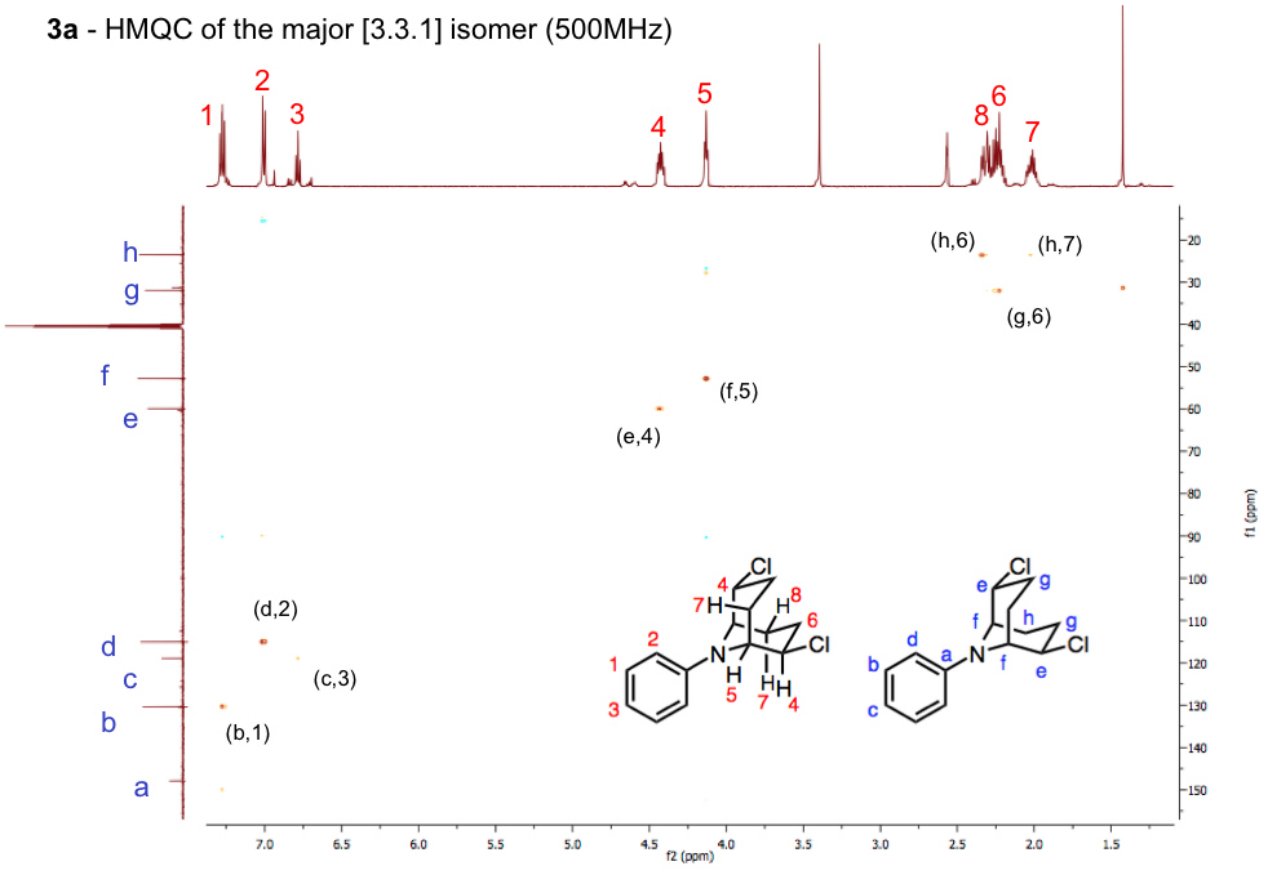


minor isomer peaks expanded and labeled

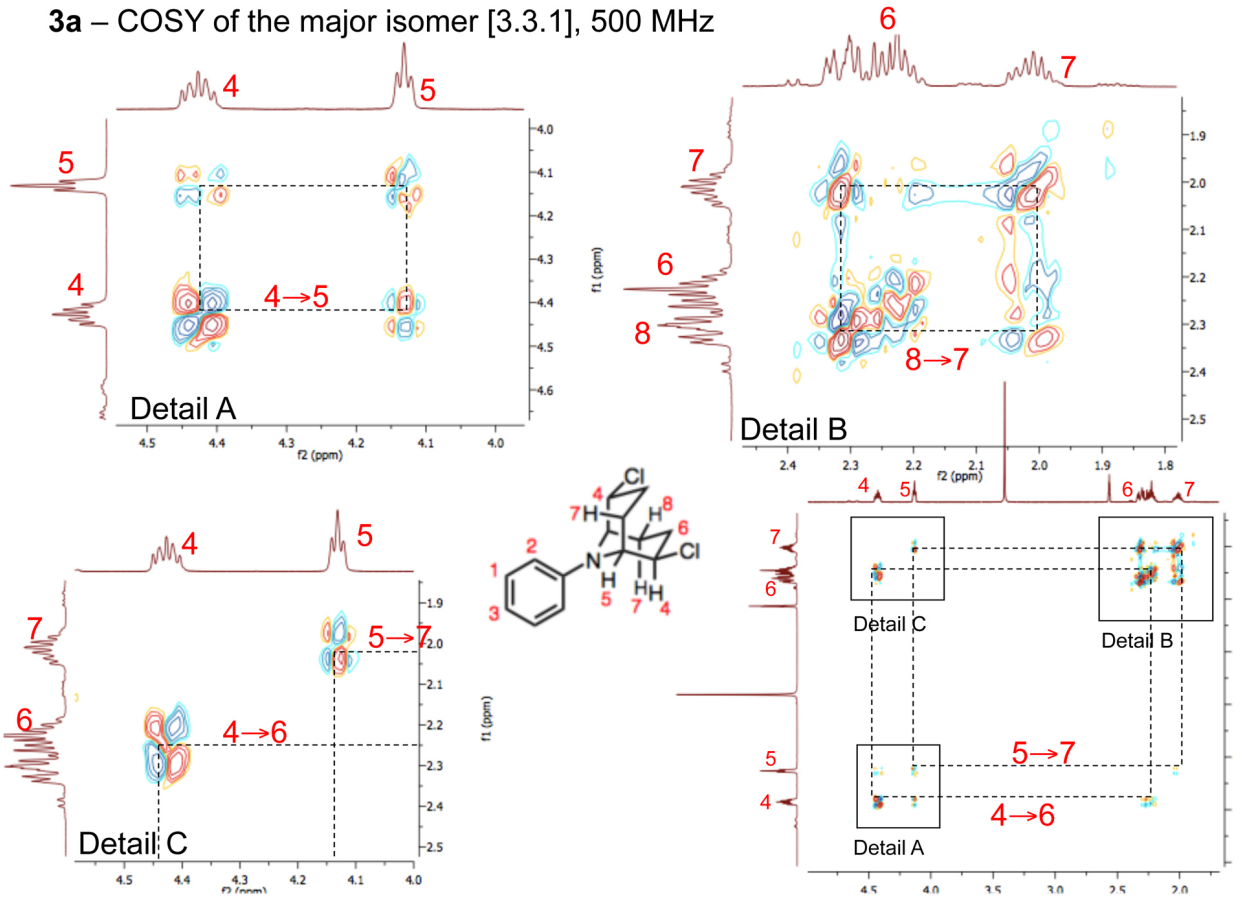




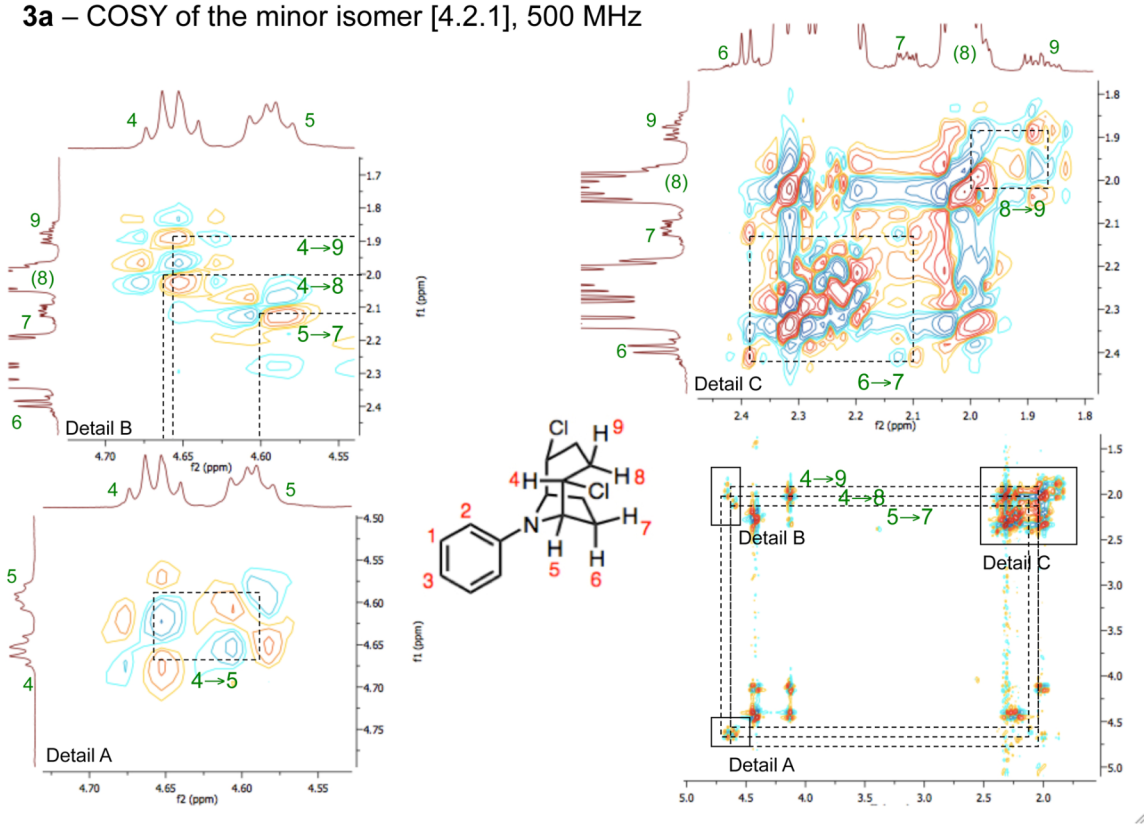
3a - HMQC of the major [3.3.1] isomer (500MHz)



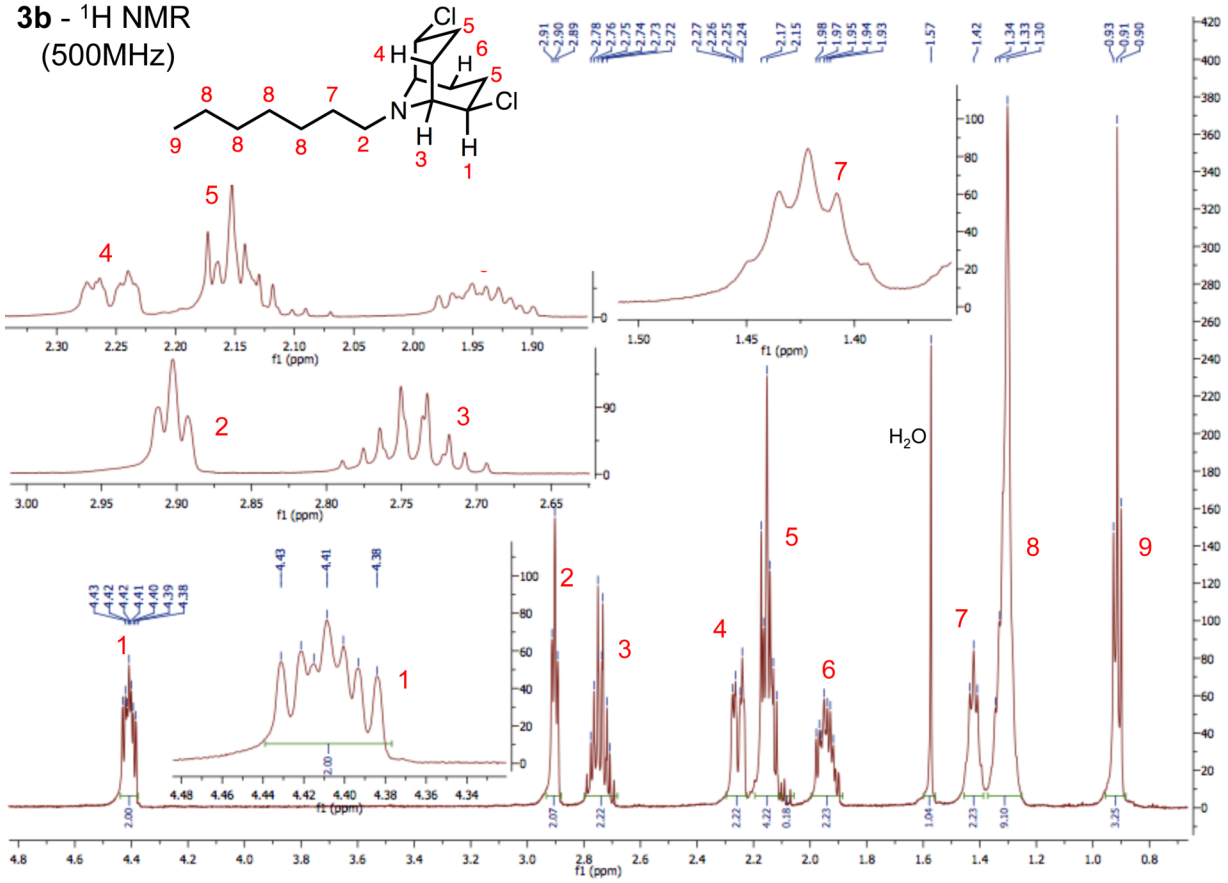
3a – COSY of the major isomer [3.3.1], 500 MHz

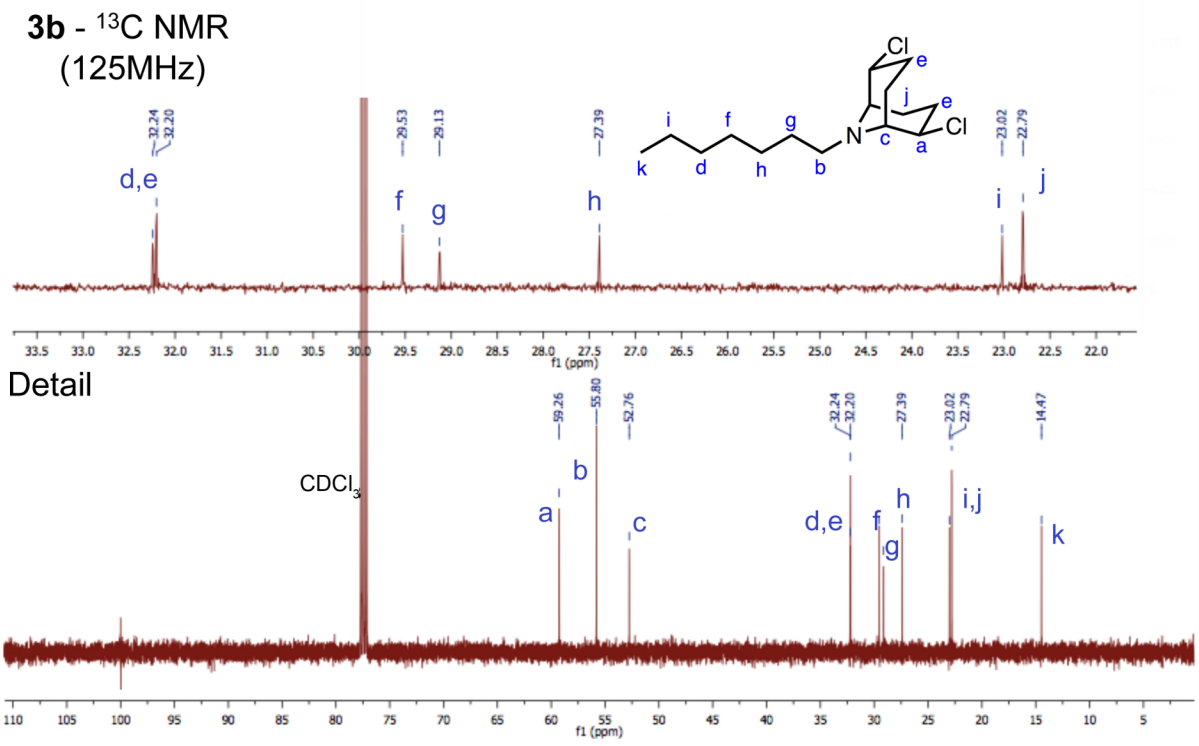


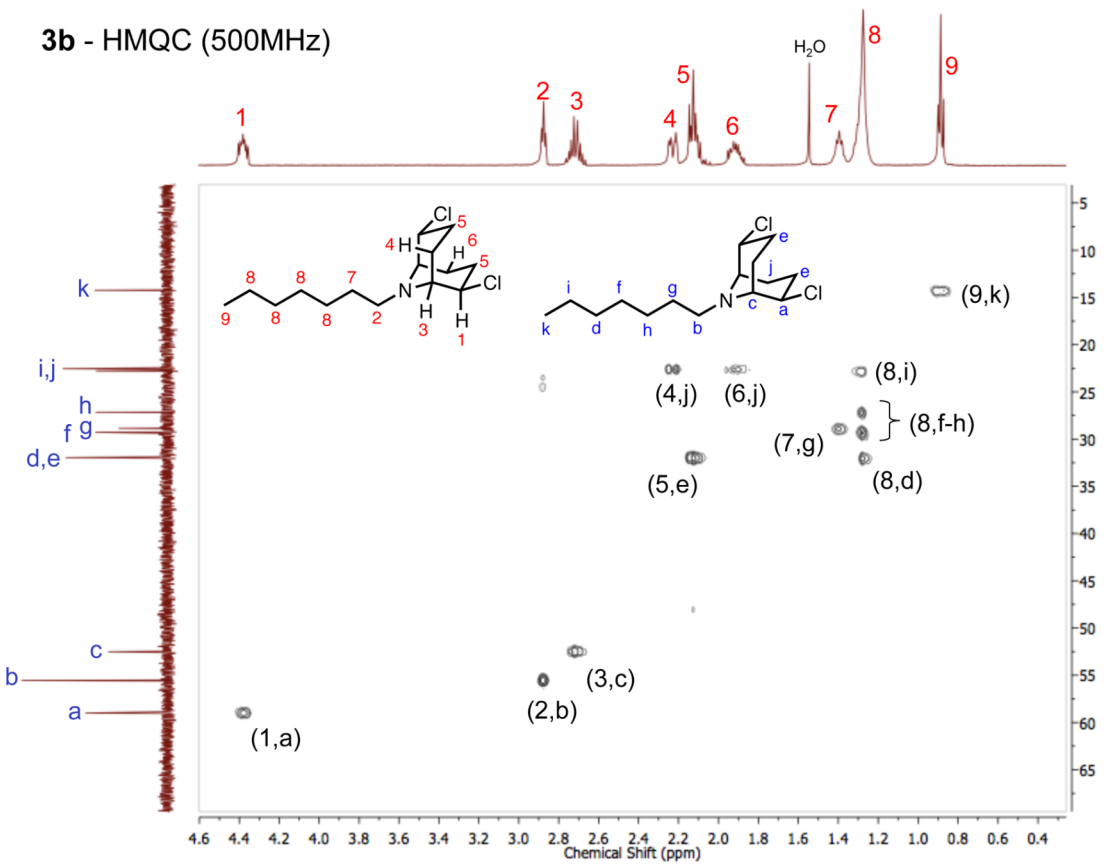
3a – COSY of the minor isomer [4.2.1], 500 MHz



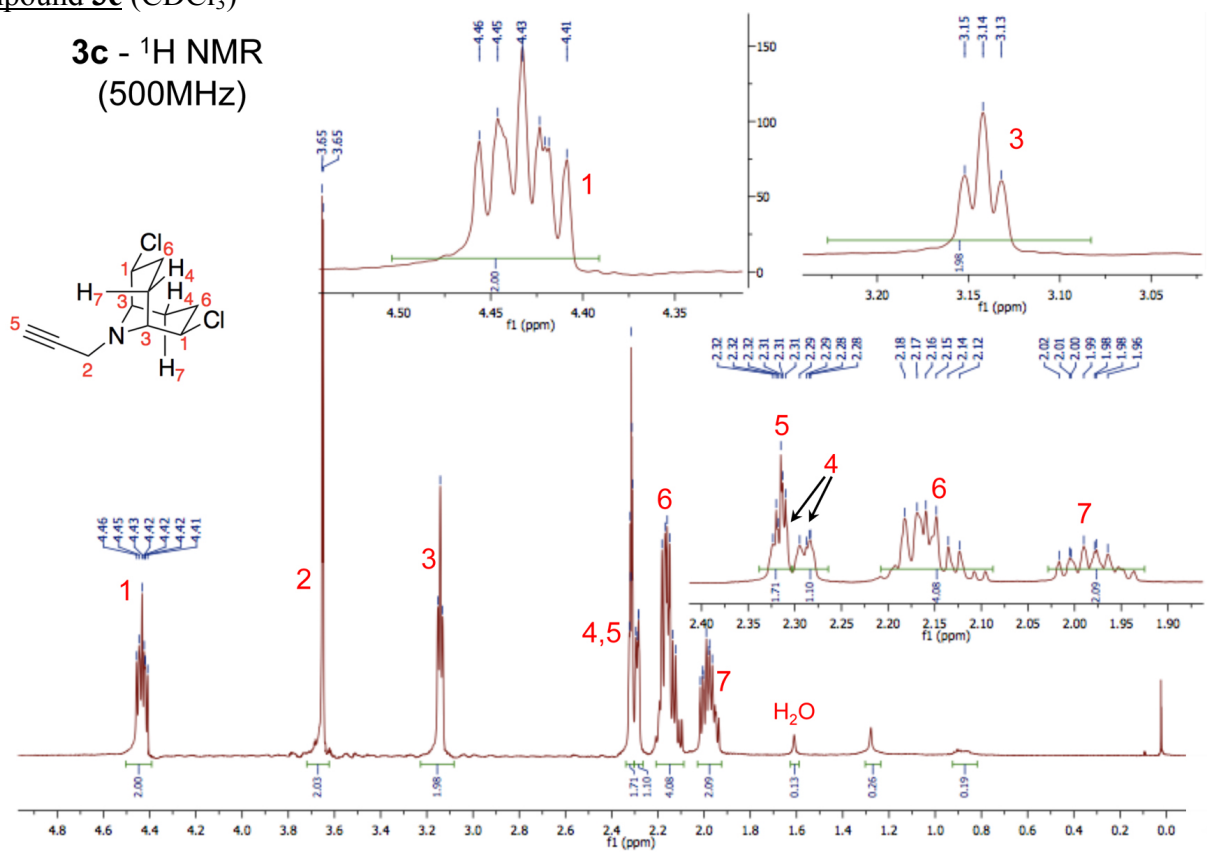
Compound **3b** ($CDCl_3$)

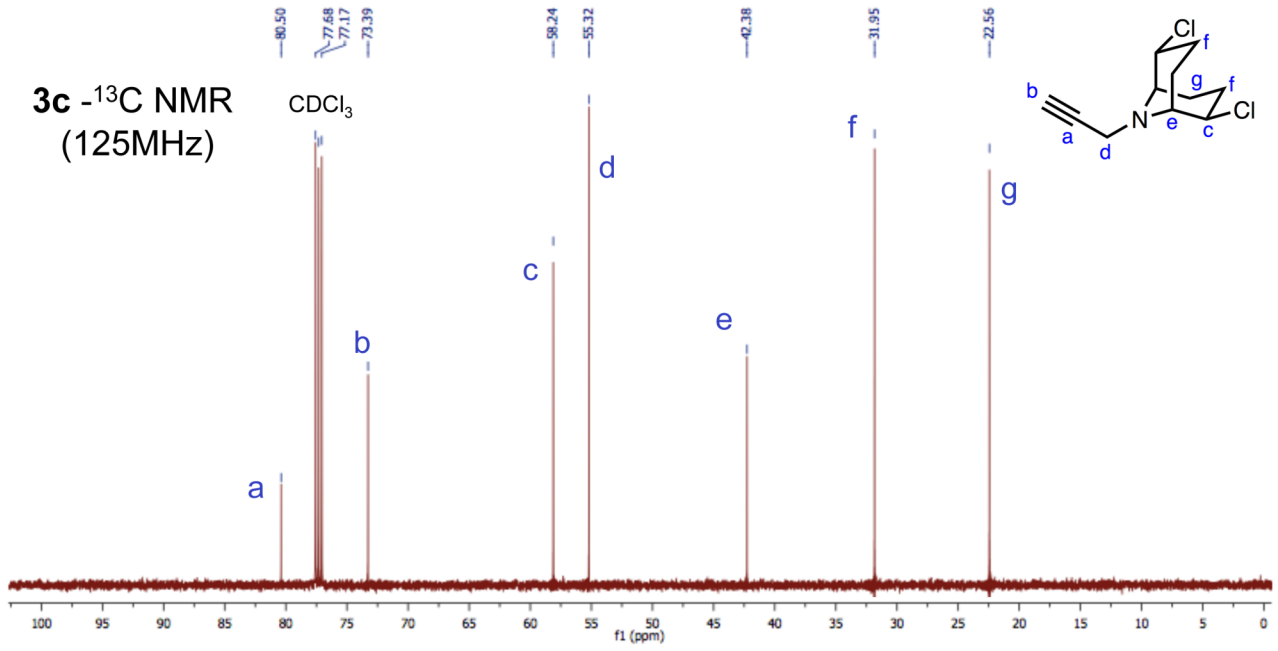


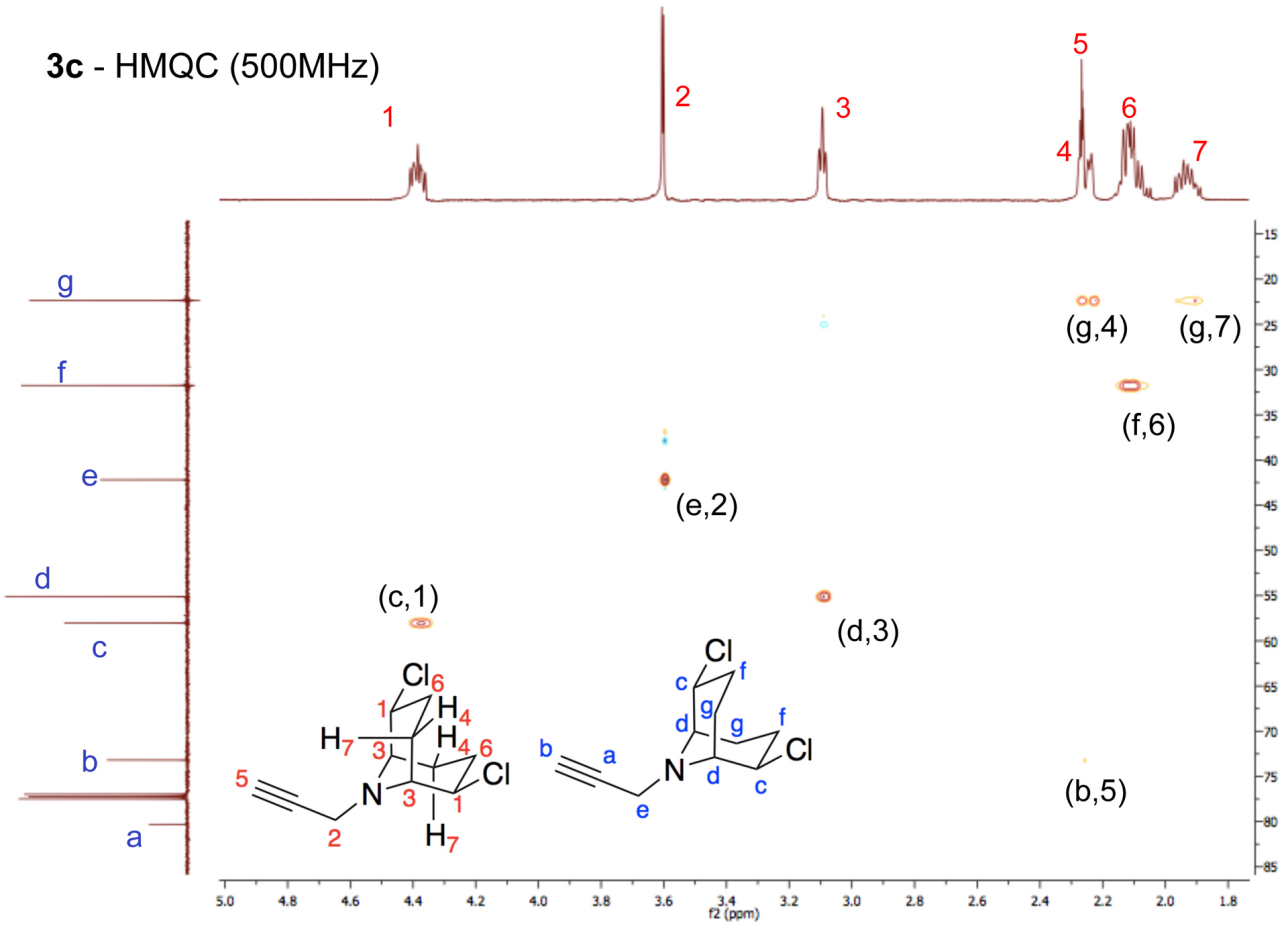




Compound **3c** ($CDCl_3$)

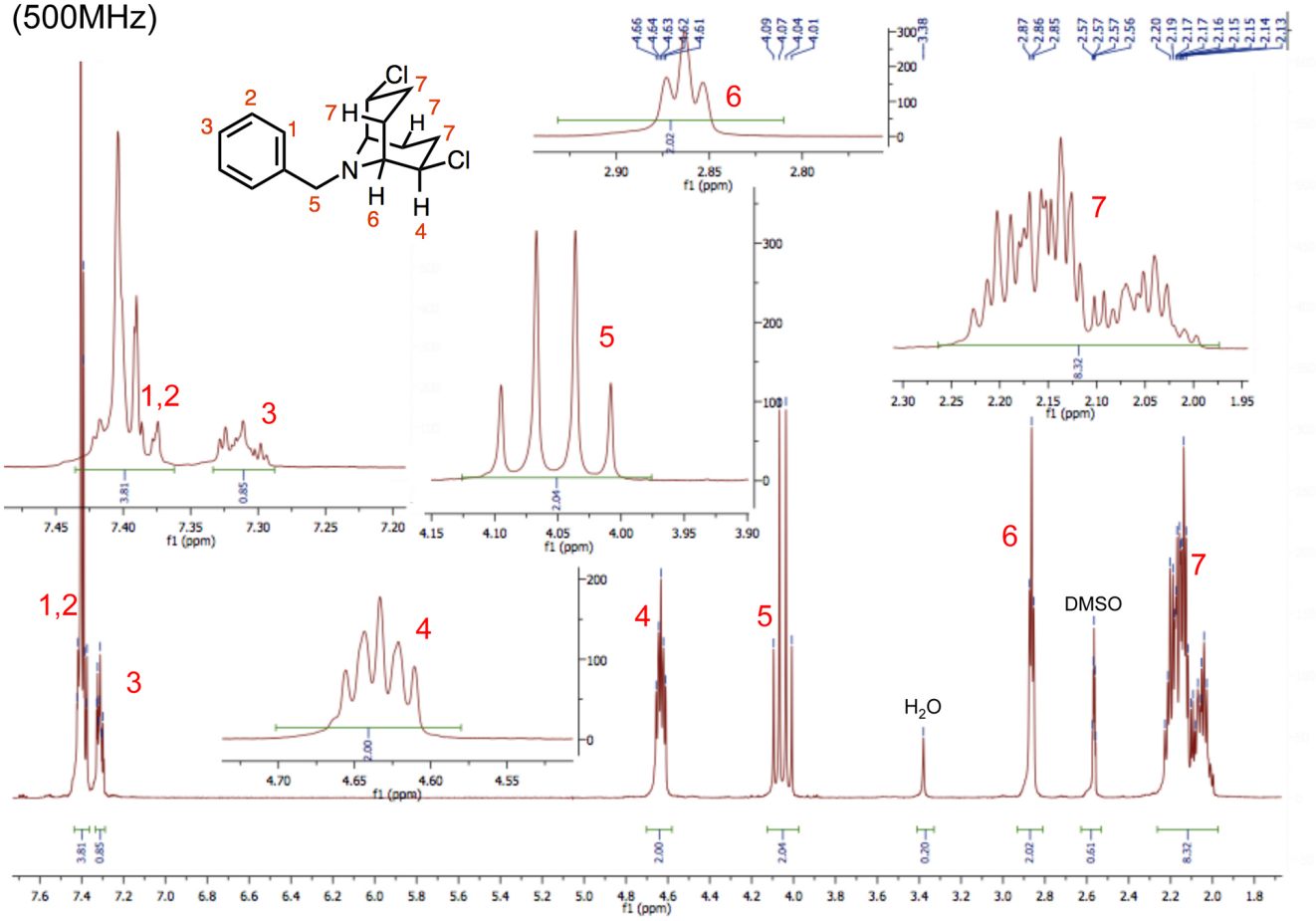



3c -13C NMR
(125MHz)
CDCl3
80.50
77.68
77.17
73.39
58.24
55.32
42.38
31.95
22.56
a
b
c
d
e
f
g
f1 (ppm)

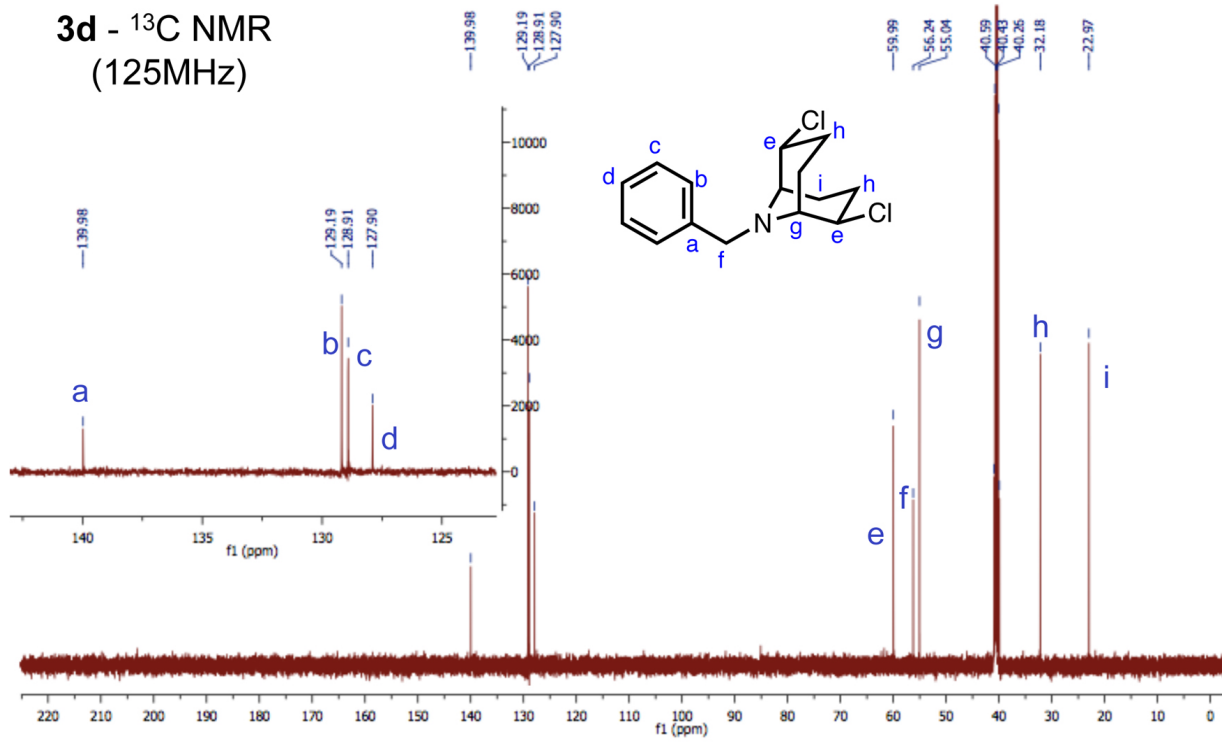

3c - HMQC (500MHz)
1
2
3
4
5
6
7
(g,4)
(g,7)
(f,6)
(e,2)
(c,1)
(d,3)
(b,5)
f2 (ppm)

Compound **3d** (DMSO-d_6)

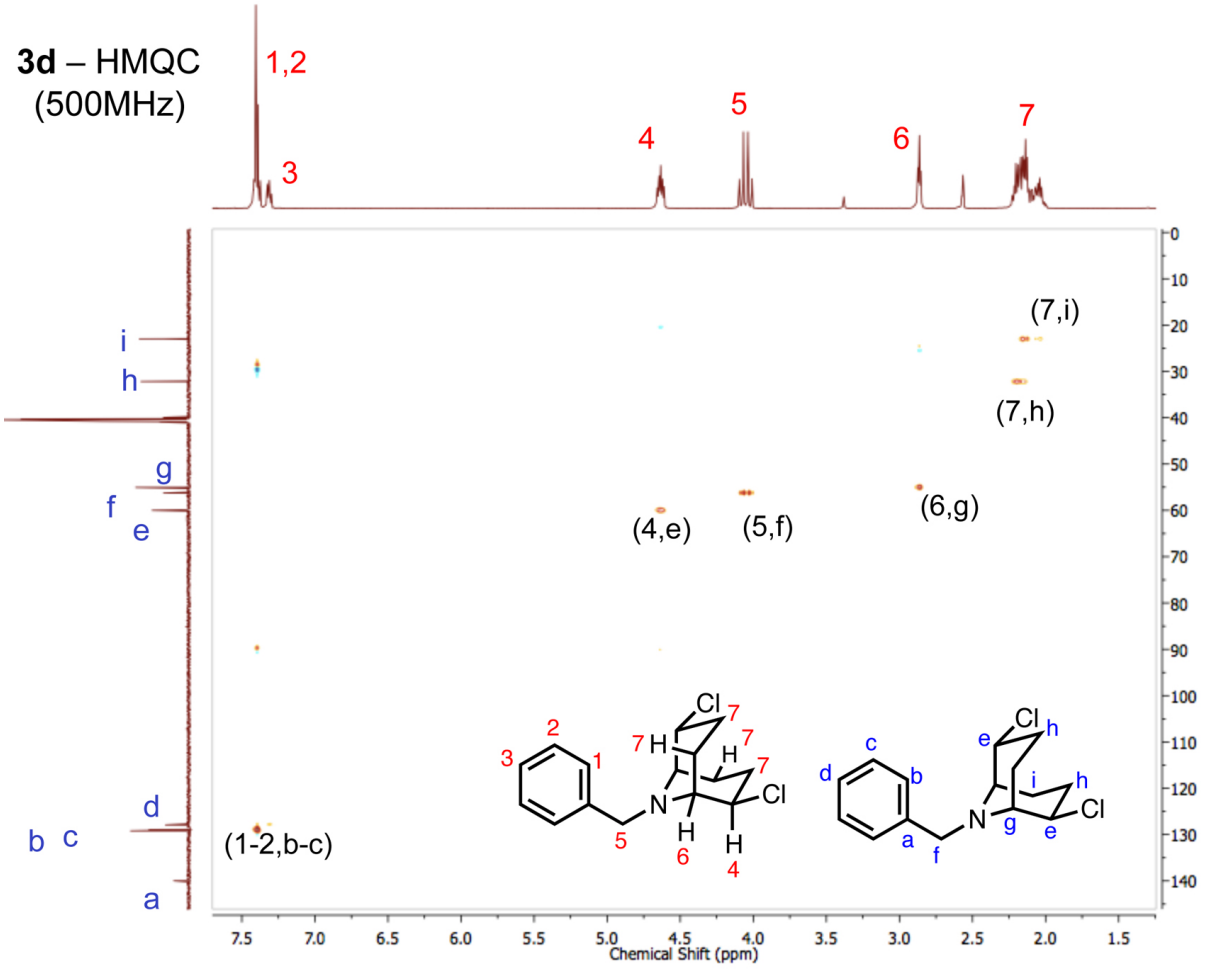
3d - ^{1}HNMR
(500MHz)



3d - ^{13}C NMR
(125MHz)



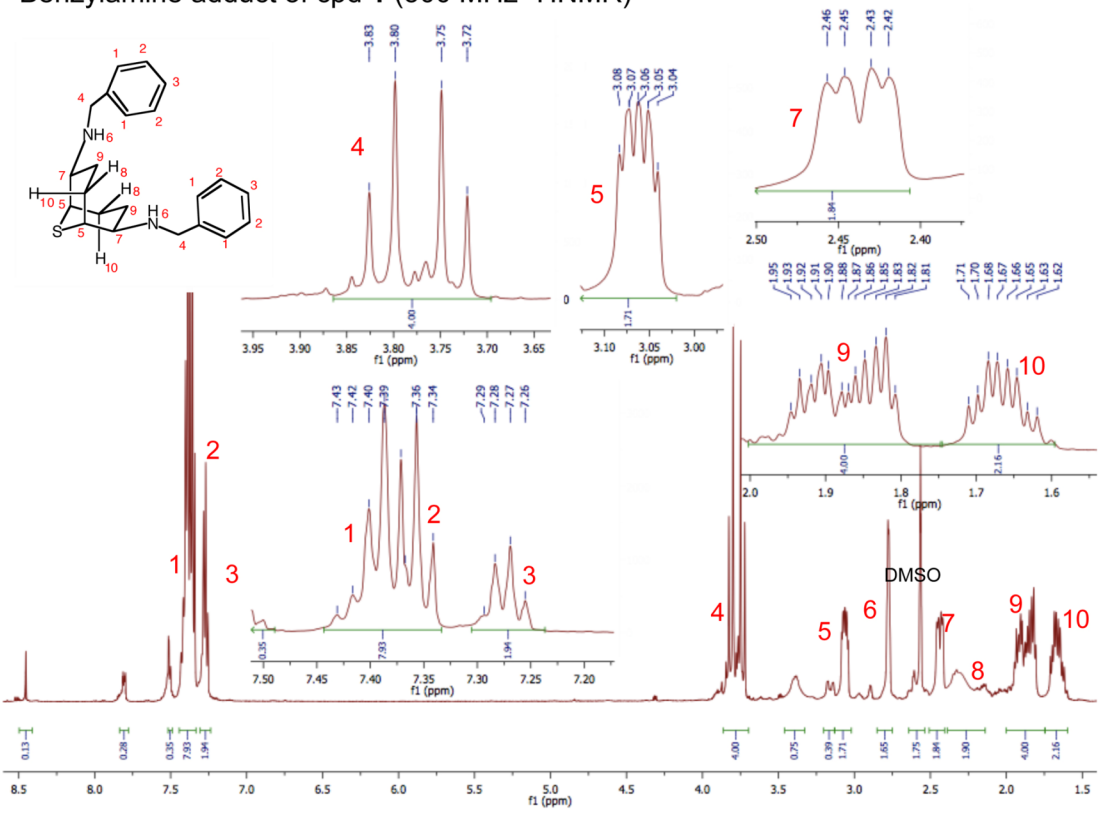
3d – HMQC
(500MHz)



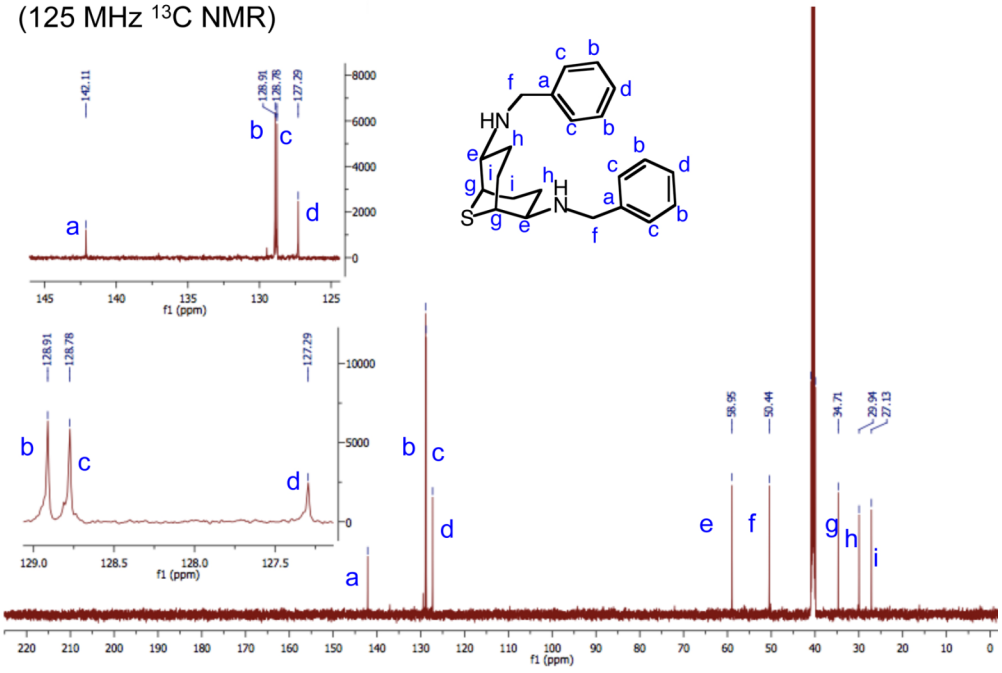
4. NMR Spectra of Representative Adducts (without purification)

Adducts of compound **1** (DMSO-d_6)

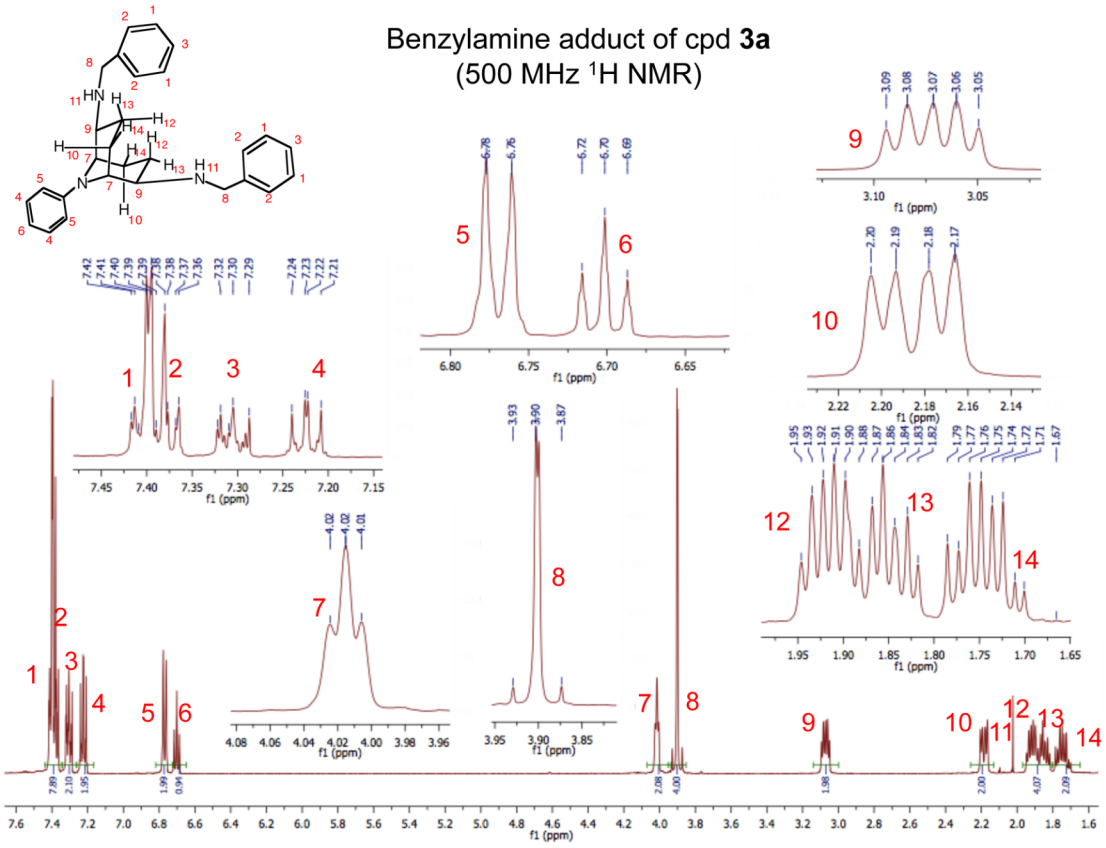
Benzylamine adduct of cpd **1** (500 MHz ^{1}HNMR)



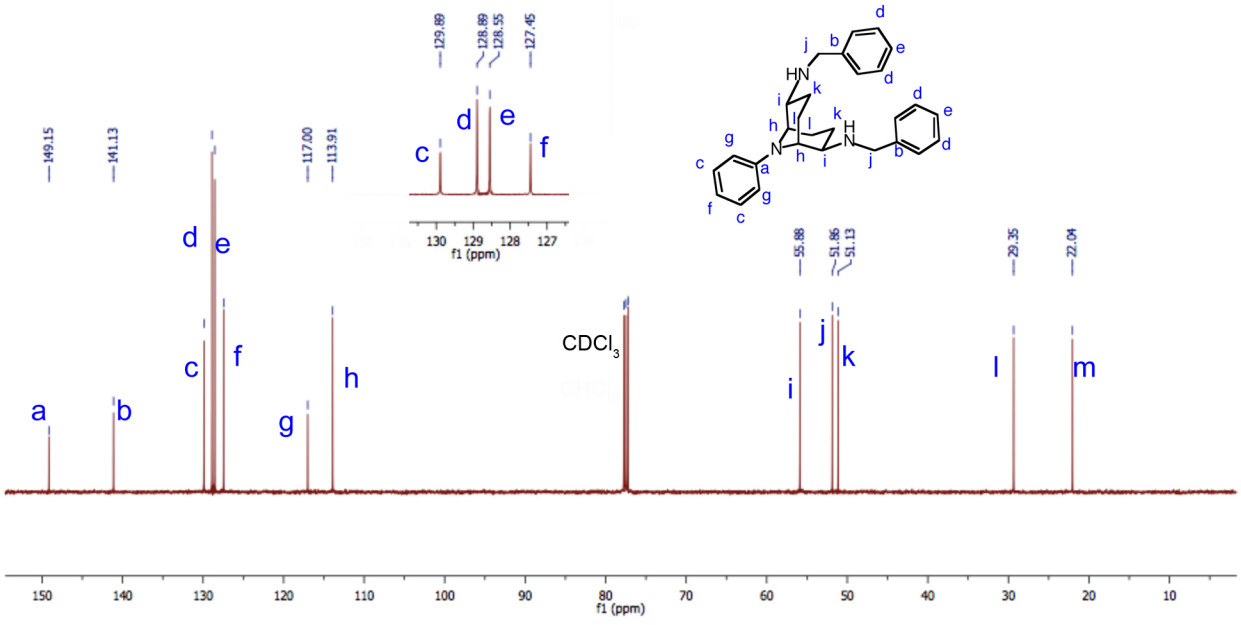
Benzylamine adduct of cpd **1**
(125 MHz ^{13}C NMR)



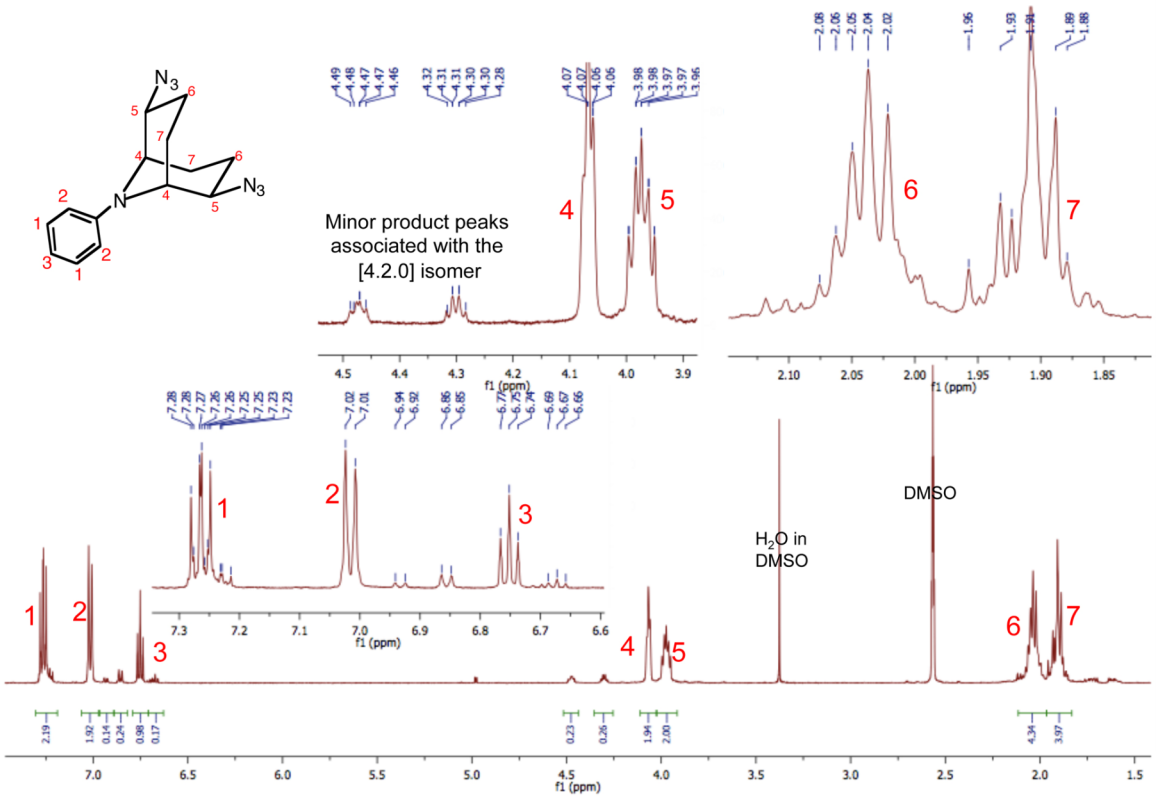
Adducts of compound **3a** (DMSO-d_6)



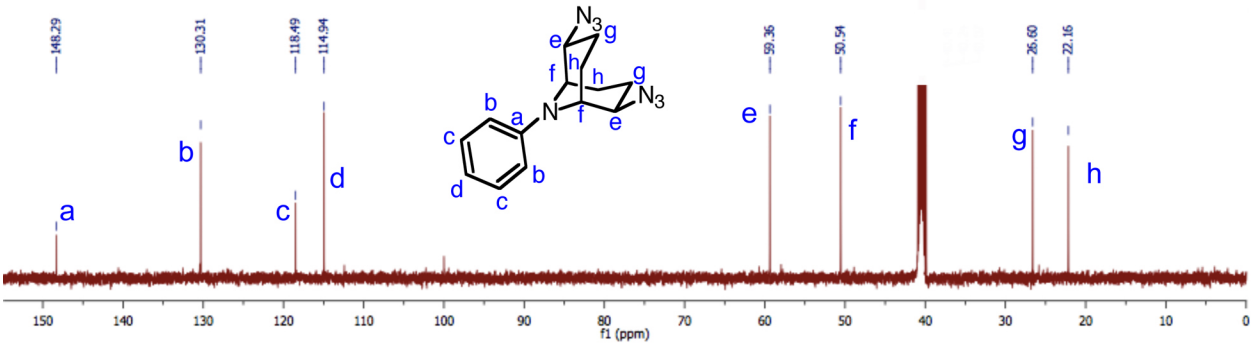
Benzylamine adduct of cpd **3a** (125 MHz ^{13}C NMR)



Azide adduct of cpd **3a** (500 MHz ^{1}H NMR)

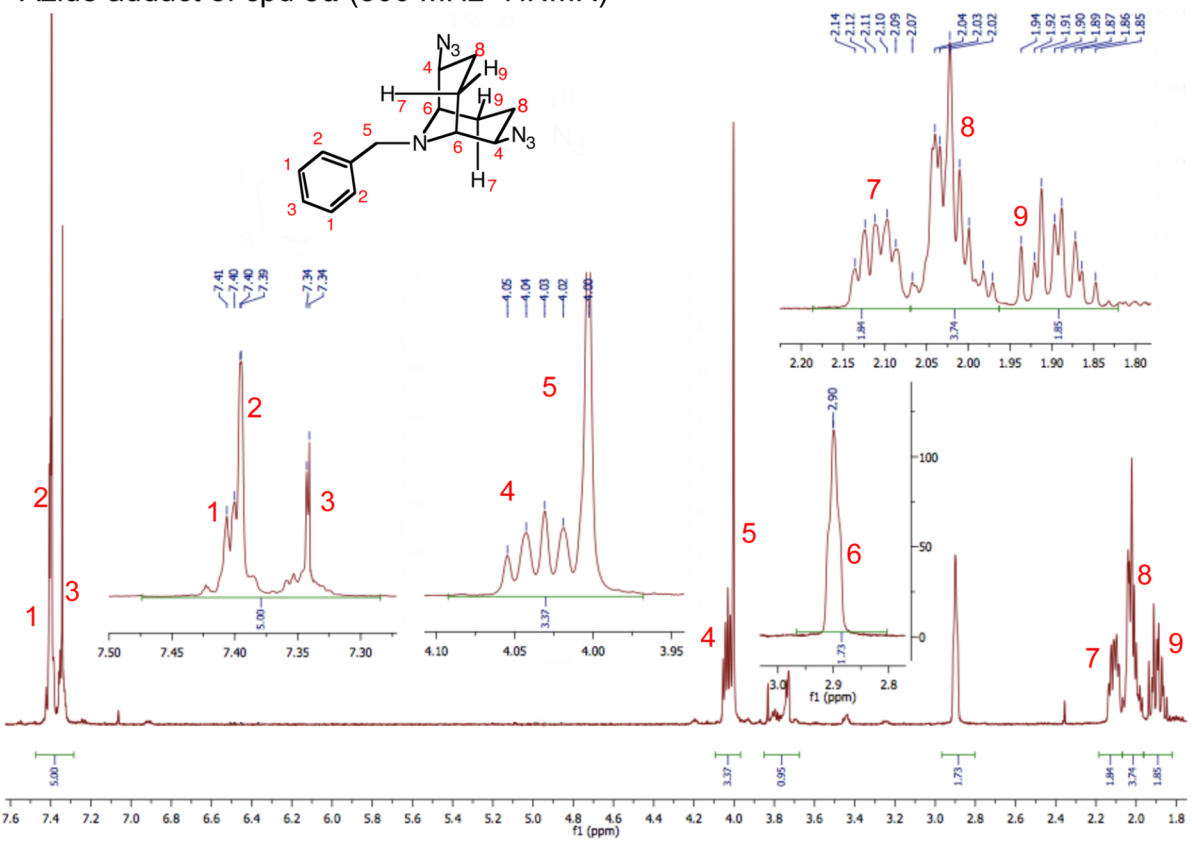


Azide adduct of cpd **3a** (125 MHz ^{13}C NMR)

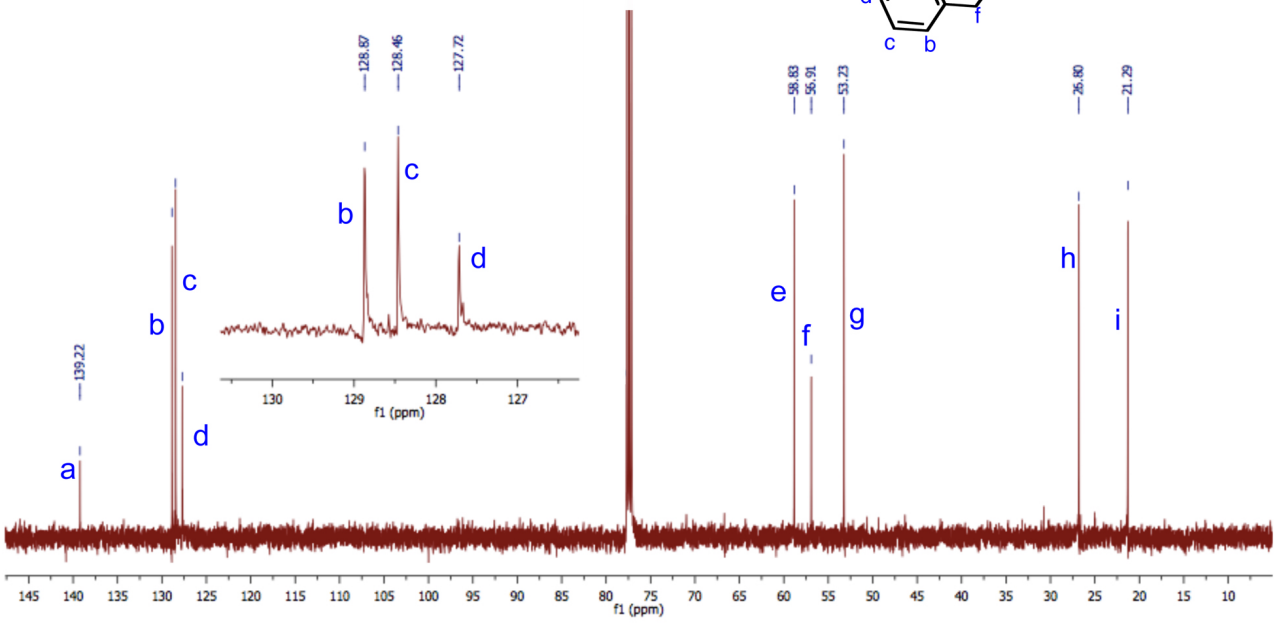


Adducts of compound **3d** ($CDCl_3$)

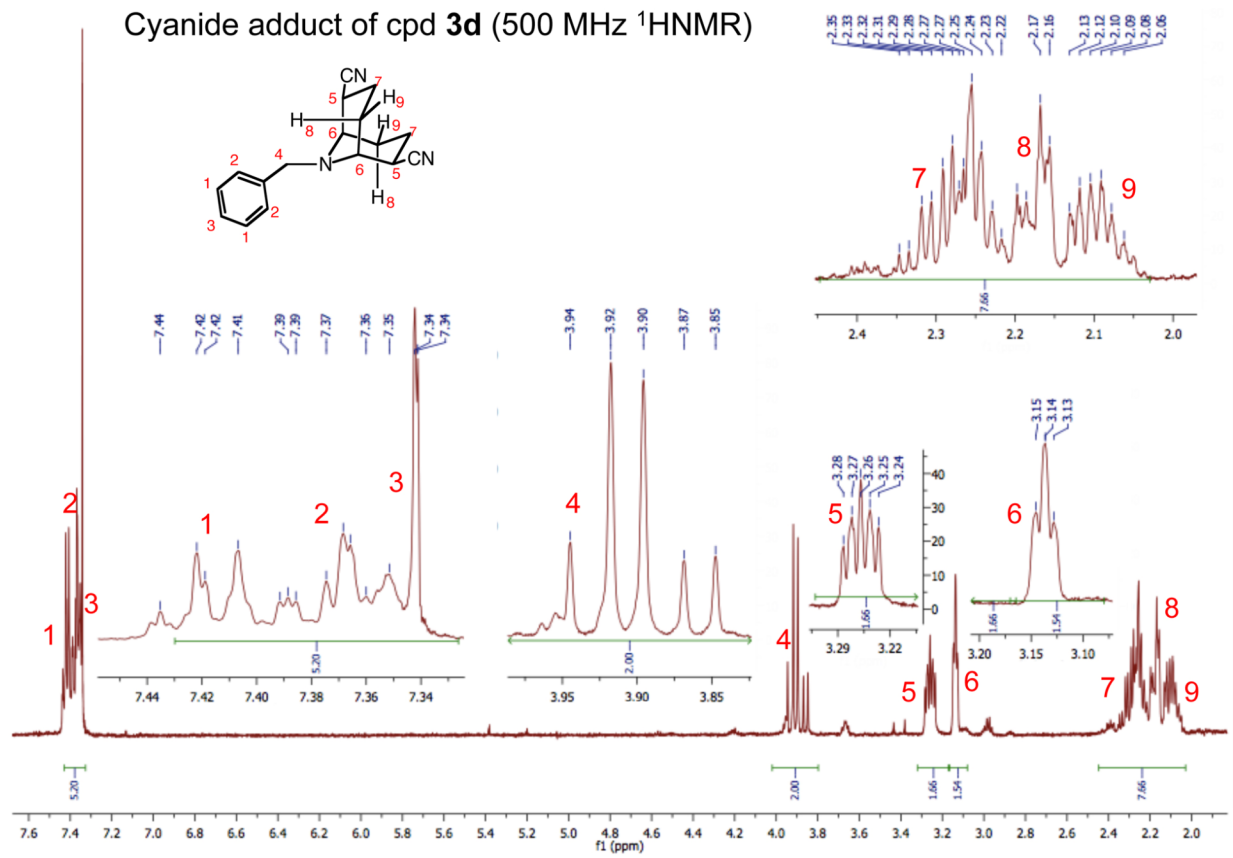
Azide adduct of cpd **3d** (500 MHz ^{1}HNMR)



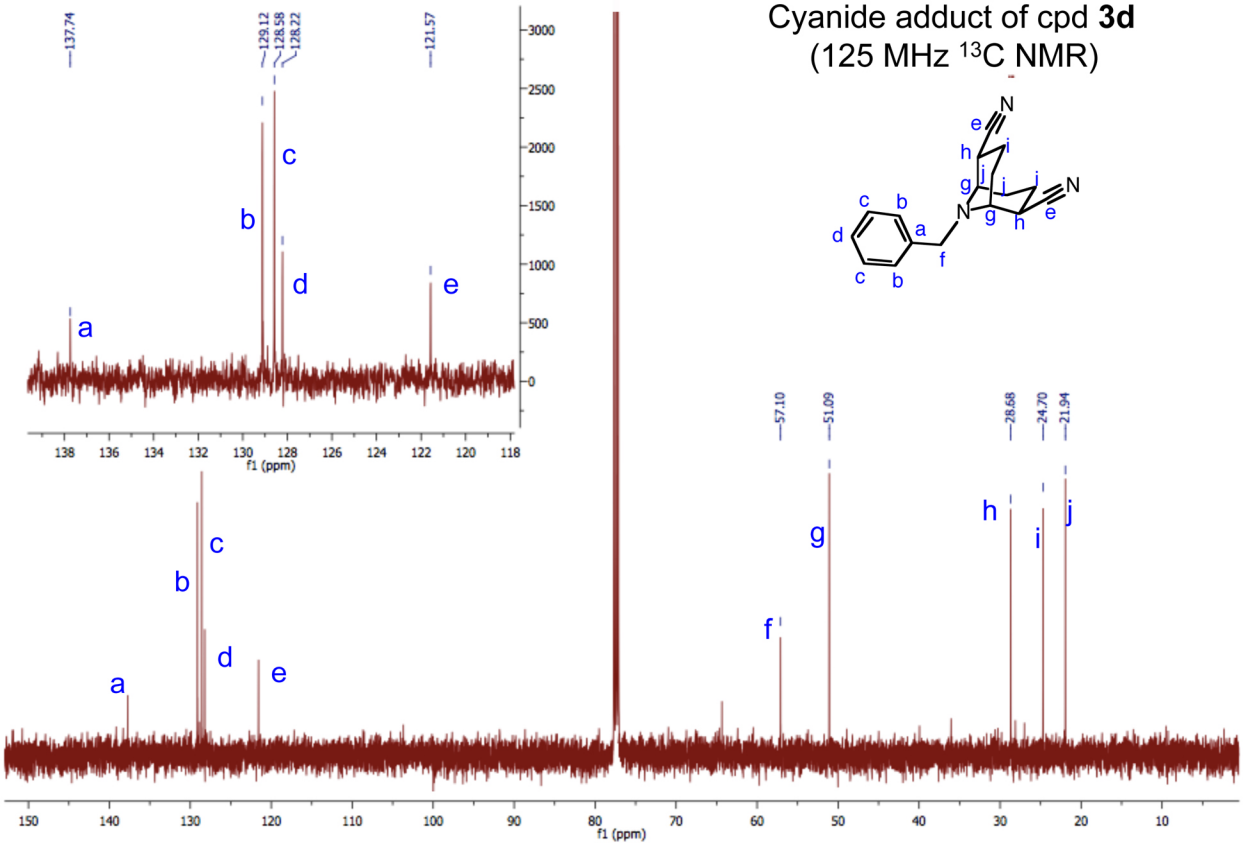
Azide adduct of cpd **3d** (125 MHz ^{13}CNMR)



Cyanide adduct of cpd **3d** (500 MHz ^{1}HNMR)



Cyanide adduct of cpd **3d**
(125 MHz ^{13}C NMR)



1. Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189-6190.