Mechanistic studies on a Cu-catalyzed aerobic oxidative coupling reaction with *N*-phenyl tetrahydroisoquinolines: structure of intermediates and the role of methanol as a solvent

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Supporting Information

Experimental procedures

General methods

Unless otherwise indicated, all reagents and solvents were purchased from commercial distributors and used as received. Solvents (ethyl acetate, pentane) used for column chromatography were of technical grade and used after distillation in a rotary evaporator. TLC was used to check the reactions for full conversion and was performed on Macherey-Nagel Polygram Sil G/UV_{254} thin layer plates. TLC spots were visualized by UV-light irradiation and staining with $KMnO_4$. Flash column chromatography was carried out using Merck Silica Gel 60 (40-63 µm). Yields refer to pure isolated compounds. ^{1}H and ^{13}C NMR spectra were measured with Bruker Avance 600, AV 500 and AV 400 spectrometers. All chemical shifts are given in ppm downfield relative to TMS and were referenced to TMS or the solvent residual peaks. 1H NMR chemical shifts are designated using the following abbreviations as well as their combinations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. High resolution mass spectra were recorded with a Bruker APEX III FTICR-MS or a Finnigan SSQ 7000 quadrupole MS or a Finnigan MAT 95 double focusing sector field MS instrument.

Oxidative allylation - Optimisation study

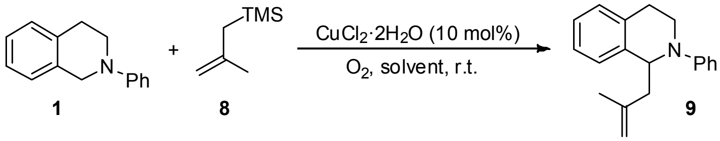


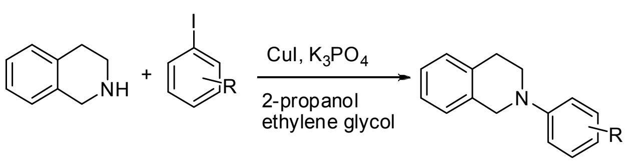
Table S1: Screening of solvents for the copper-catalyzed allylation.[a]

Entry	Solvent	Time (h)	Conversion[b]	Yield (%)[c]
1	MeOH	15	100%	89
2	Acetone	24	100%	76
3	DMF	24	100%	70
4	$CHCl_3$	24	<50%	n.d.
5	CH_2Cl_2	24	<50%	n.d.
6	Toluene	24	<50%	n.d.

[a] **1** (0.12 mmol), **8** (0.36 mmol), $CuCl_2·2H_2O$ (10 mol%), 0.5 ml solvent, O_2 (balloon), stirring at room temperature. [b] Monitored and estimated by TLC. [c] Isolated yields.

In acetone and DMF, the yields were still good but several side products were observed and the reaction time had to be increased to 24 hours to achieve full conversion (Table S1, entries 2 and 3). Performing the reaction in toluene, dichloromethane and chloroform resulted in less than 50% conversion of starting material, significant amounts of side products and only traces of product after one day (Table S1, entries 4-6). Alternative Cu and Fe salts were also tested as catalysts but without giving the same or better yield than $CuCl_2•2H_2O$. No reaction occurred if allyl-trimethylsilane was used instead of 2-methylallyl-trimethylsilane **8**.

General procedure for the preparation of starting materials



The tetrahydroisoquinolines were synthesised according to a reported method.[1] A representative procedure is given for 2-(4-tert-butylphenyl)-1,2,3,4-tetrahydroisoquinoline: copper(I)iodide (87.4 mg, 0.46 mmol) and potassium phosphate (2.0 g, 9.18 mmol) were placed into a Schlenk-tube equipped with a magnetic stirrer. The tube was evacuated and back filled with argon. 2-Propanol (4.6 mL), ethylene glycol (0.52 mL, 9.18 mmol), 1,2,3,4-tetrahydroisoquinoline (1.06 mL, 6.88 mmol) and 1-tert-Butyl-4-iodobenzene (0.81 mL, 4.59 mmol) were added successively by microsyringe at room temperature. The reaction mixture was heated at 85 °C for 24 h and then allowed to cool to room temperature. Diethyl ether (5 mL) and water (5 mL) were added to the reaction mixture and the organic layer was separated. The aqueous layer was further extracted by diethyl ether (2 x 5 mL) and the combined organic phases were dried over magnesium sulfate. The solvent was removed by rotary evaporation and the crude product was purified by column chromatography.

General procedure for the oxidative allylation

To a solution of amine (0.12 mmol) in methanol (0.5 mL), was added 2-methylallyl-trimethylsilane **8** (0.36 mmol, 3 equiv.) and $CuCl_2$·dihydrate (2 mg, 10 mol%) at room temperature. After stirring for the appropriate time under an atmosphere of oxygen, the solution was concentrated in vacuo. The crude residue was directly purified by flash column chromatography on silica gel (5-10% EtOAc/pentane) to give the corresponding allylated amine.

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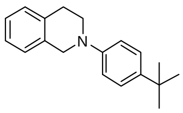
[1] Li, Z.; Li, C.-J. *J. Am. Chem. Soc*. **2005**, 127, 6968.

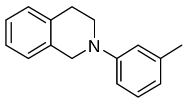
Characterisation of starting materials

2-(4-*tert*-Butylphenyl)-1,2,3,4-tetrahydroisoquinoline



Yield : 859 mg, 71%; White solid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.30 (m, 2H), 7.21-7.14 (m, 4H), 6.98-6.93 (m, 2H), 4.39 (s, 2H), 3.54 (t, J = 5.9 Hz, 2H), 2.99 (t, J = 5.9 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.47, 141.64, 134.98, 134.72, 128.69, 126.68, 126.37, 126.11, 126.08, 115.20, 51.24, 46.88, 34.05, 31.63, 29.34; HRMS-(EI) (*m/z*): M^+ calcd for $C_{19}H_{23}N_1$, 265.183051; found 265.183112.

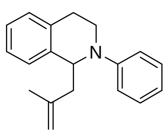
2-*m*-Tolyl-1,2,3,4-tetrahydroisoquinoline



Yield : 738 mg, 72%; Clear oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22-7.15 (m, 5H), 6.86-6.79 (m, 2H), 6.67-6.65 (m, 1H), 4.41 (s, 2H), 3.56 (t, J = 5.85 Hz, 2H), 3.0 (t, J = 5.85 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.77, 139.02, 135.02, 134.67, 129.18, 128.65, 126.67, 126.42, 126.13, 119.77, 116.10, 112.47, 50.98, 46.72, 29.33, 22.0; HRMS-(EI) (*m/z*): M^+ calcd for $C_{16}H_{17}N_1$, 223.136096; found 223.135852.

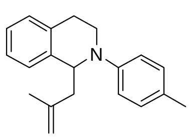
Characterisation of products

1-(2-Methylallyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (9)



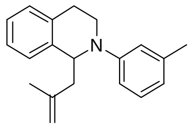
Reaction time 15h, r_f = 0.70 (EtOAc/pentane, 0.5 : 9.5); Yield : 28 mg, 89%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17-7.14 (m, 2H), 7.09-7.01 (m, 4H), 6.85 (bs, 2H), 6.67 (bs, 1H), 4.78 (t, J = 7.1 Hz, 1H), 4.73 (bs, 1H), 4.59 (bs, 1H), 3.56 (t, J = 5.6 Hz, 1H), 2.98-2.92 (m, 1H), 2.79-2.76 (m, 1H), 2.63 (dd, J = 5.5, 13.4 Hz, 1H), 2.33 (dd, J = 7.2, 13.4 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.67, 143.05, 138.62, 134.88, 129.37, 128.67, 127.58, 126.61, 125.72, 117.51, 114.36, 113.65, 58.34, 44.75, 41.82, 27.09, 23.07; HR - MS m/z: calcd for $C_{19}H_{21}N[M^+]$: 263.1674; found: 263.1671.

1-(2-Methylallyl)-2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline (10):



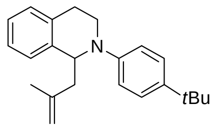
Reaction time 12h, r_f = 0.70 (EtOAc/pentane, 0.5 : 9.5); Yield : 26 mg, 78%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15-7.07 (m, 4H), 7.03 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 4.79 (t, J = 6.6 Hz, 2H), 4.66 (bs, 1H), 3.62-3.59 (m, 2H), 3.03-2.97 (m, 1H), 2.77 (td, J = 4.3, 16.2 Hz, 1H), 2.67 (dd, J = 7.2, 13.8 Hz, 1H), 2.39 (dd, J = 6.9, 13.8 Hz, 1H), 2.24 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.67, 143.22, 138.73, 134.84, 129.85, 128.76, 127.55, 127.04, 126.48, 125.64, 115.12, 113.43, 58.38, 44.69, 41.89, 26.81, 22.99, 20.43; HR - MS m/z: calcd for $C_{20}H_{23}N[M^+]$: 277.1830; found: 277.1829.

1-(2-Methylallyl)-2-(m-tolyl)-1,2,3,4-tetrahydroisoquinoline (13):



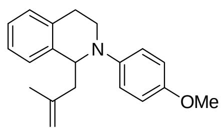
Reaction time 12h, r_f = 0.70 (EtOAc/pentane, 0.5 : 9.5); Yield : 25 mg, 75%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.14-7.06 (m, 5H), 6.73 (bs, 1H), 6.71 (d, J = 7.4 Hz, 1H), 6.56 (d, J = 7.4 Hz, 1H), 4.84 (t, J = 7.1 Hz, 1H), 4.81-4.79 (m, 1H), 4.66-4.65 (m, 1H), 3.62 (dd, J = 5.1, 7.2 Hz, 2H), 3.05-2.98 (m, 1H), 2.82 (td, J = 5.0, 16.1 Hz, 1H), 2.69 (dd, J = 6.7, 13.6 Hz, 1H), 2.39 (dd, J = 6.8, 13.6 Hz, 1H), 2.30 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.70, 143.08, 138.96, 138.67, 134.91, 129.20, 128.64, 127.57, 126.56, 125.66, 118.43, 115.11, 113.61, 111.52, 58.29, 44.75, 41.82, 27.14, 23.05, 22.10; HR - MS m/z: calcd for $C_{20}H_{23}N[M^+]$: 277.1830; found: 277.1831.

2-(4-(*tert*-Butyl)phenyl)-1-(2-methylallyl)-1,2,3,4-tetrahydroisoquinoline (11):



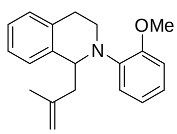
Reaction time 12h, r_f = 0.80 (EtOAc/pentane, 0.5 : 9.5); Yield : 28 mg, 73%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J = 8.9 Hz, 2H), 7.13-7.05 (m, 4H), 6.85 (d, J = 8.9 Hz, 2H), 4.81-4.79 (m, 2H), 4.66-4.65 (m, 1H), 3.63-3.59 (m, 2H), 3.06-2.98 (m, 1H), 2.80 (td, J = 3.7, 16.1 Hz, 1H), 2.69 (dd, J = 6.6, 13.3 Hz, 1H), 2.39 (dd, J = 7.1, 13.3 Hz, 1H), 1.79 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.37, 143.17, 140.11, 138.77, 134.95, 128.66, 127.58, 126.51, 126.13, 125.64, 114.02, 113.54, 58.57, 44.90, 41.80, 33.91, 31.65, 26.98, 23.12; HR - MS m/z: calcd for $C_{23}H_{29}N[M^+]$: 319.2299; found: 319.2297.

2-(4-Methoxyphenyl)-1-(2-methylallyl)-1,2,3,4-tetrahydroisoquinoline (12):



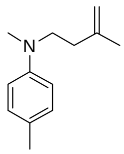
Reaction time 24h, r_f = 0.65 (EtOAc/pentane, 1 : 9); Yield : 20 mg, 56%; ^1H NMR (500 MHz, $CDCl_3$): δ 7.13-7.08 (m, 4H), 6.87 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 4.79 (bs, 1H), 4.69 (t, J = 7.0 Hz, 1H), 4.66 (bs, 1H), 3.75 (s, 3H), 3.58-3.55 (m, 2H), 3.00-2.94 (m, 1H), 2.72 (td, J = 3.8, 16.3 Hz, 1H), 2.63 (dd, J = 7.5, 13.9 Hz, 1H), 2.39 (dd, J = 6.6, 13.9 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.70, 144.56, 143.37, 138.84, 134.74, 128.92, 127.54, 126.42, 125.65, 117.74, 114.69, 113.23, 58.50, 55.77, 44.02, 42.53, 26.56, 22.88; HR - MS m/z: calcd for $C_{20}H_{23}NONa[M^++Na]$: 316.1672; found: 316.1670.

2-(2-Methoxyphenyl)-1-(2-methylallyl)-1,2,3,4-tetrahydroisoquinoline (14):



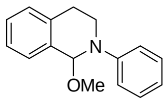
Reaction time 24h, r_f = 0.60 (EtOAc/pentane, 1 : 9); Yield : 29 mg, 82%; ^1H NMR (500 MHz, $CDCl_3$): δ 7.27-7.19 (m, 4H), 7.09-7.05 (m, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.97-6.92 (m, 2H), 4.90 (t, J = 6.6 Hz, 1H), 4.84 (bs, 1H), 4.72 (bs, 1H), 3.97 (s, 3H), 3.72-3.62 (m, 2H), 3.09-3.02 (m, 1H), 2.80 (dd, J = 2.4, 16.9 Hz, 1H), 2.68 (dd, J = 6.5, 13.9 Hz, 1H), 2.50 (dd, J = 6.7, 13.9 Hz, 1H), 1.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.84, 143.76, 140.77, 139.53, 134.38, 129.14, 127.46, 126.18, 125.43, 122.58, 121.60, 121.18, 112.87, 112.57, 57.74, 55.90, 44.12, 42.19, 27.35, 22.51,; HR - MS m/z: calcd for $C_{20}H_{23}NONa[M^++Na]$: 316.1672; found: 316.1672.

_N_,4-Dimethyl-_N_-(3-methylbut-3-en-1-yl)aniline (15):



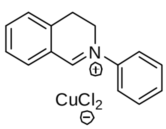
Reaction time 3 d, r_f = 0.70 (EtOAc/pentane, 0.5 : 9.5); Yield : 13 mg, 57%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (d, J = 7.5 Hz, 2H), 6.64 (d, J = 7.5 Hz, 2H), 4.78 (bs, 1H), 4.72 (bs, 1H), 3.41 (t, J = 7.8 Hz, 2H), 2.90 (s, 3H), 2.25 (s, 5H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.18, 143.96, 129.86, 125.53, 112.78, 111.38, 52.03, 38.47, 34.17, 22.95, 20.36; HR - MS m/z: calcd for $C_{13}H_{19}N[M^+]$: 189.1517; found: 189.1516.

1-Methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5):



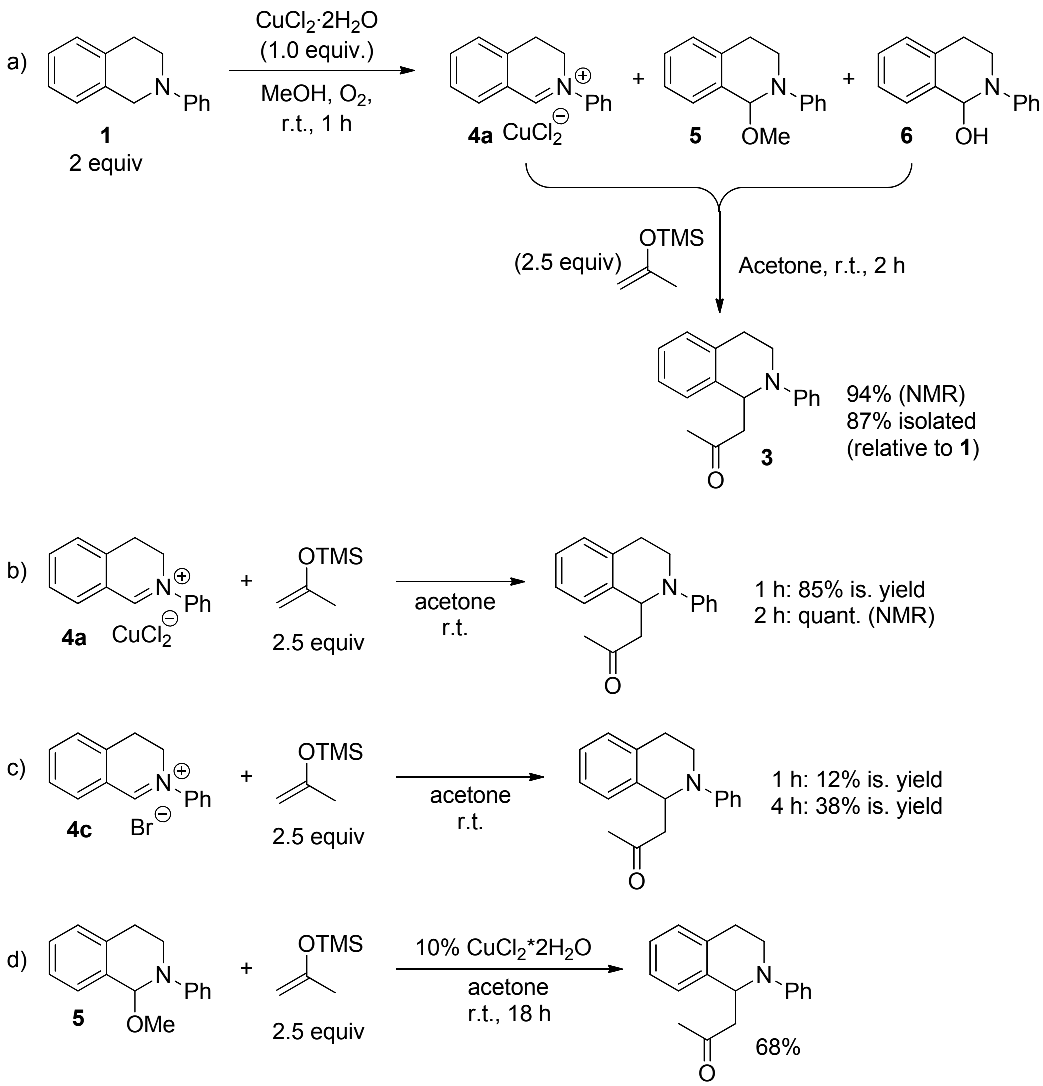
To a solution of _N_-phenyl tetrahydroisoquinoline (0.12 mmol) in methanol (0.5 mL) was added $CuCl_2{\cdot}2H_2O$ (2 mg, 10 mol%) at room temperature. The reaction was carried out under an oxygen atmosphere. After stirring for 60-72 hours, the reaction mixture was passed through a pad of celite and washed with dry MeOH. The solvent of the combined filtrates was removed in high vacuum, giving a crude product which is pure enough for characterization but decomposes when subjected to column chromatography on silica. R_f = 0.50 (EtOAc/pentane, 2 : 8); Yield : 26 mg, 91%; ^{1}H NMR (500 MHz, MeOH-D_4): δ 7.19-7.09 (m, 6H), 6.90 (d, J = 10.0 Hz, 2H), 6.69 (t, J = 5.0 Hz, 1H), 5.56 (s, 1H), 3.54-3.50 (m, 1H), 3.40-3.35 (m, 1H), 3.24 (s, 3H), 2.93-2.78 (m, 2H); ^{13}C NMR (125 MHz, MeOH-D_4): δ 150.25, 137.42, 135.35, 130.12, 129.50, 129.22, 128.99, 127.04, 120.06, 115.99, 89.57, 49.84, 43.97, 28.71; HR - MS m/z: calcd for $C_{16}H_{17}NO[M^+]$: 239.1310; found: 239.1311.

2-Phenyl-3,4-dihydroisoquinolinium dichlorocuprate (4a)



To a solution of N-phenyl tetrahydroisoquinoline (300mg, 1.43 mmol) in methanol (1.44 mL) was added $CuCl_2{\cdot}2H_2O$ (122.2 mg, 0.72 mmol) at room temperature. The reaction was carried out under an oxygen atmosphere. After stirring for 1 h, the reaction mixture was passed through a pad of cotton wool and washed with a small amount of MeOH. The crude residue was crystallized from MeOH. Yield : 63 mg, 26%; ^{1}H NMR (500 MHz, DMSO): δ 9.64 (s, 1H), 8.04-8.0 (m, 1H), 7.92-7.85 (m, 3H), 7.72-7.59 (m, 5H), 4.60 (t, J = 7.82 Hz, 2H), 3.42 (t, J = 7.82 Hz, 2H); ^{13}C NMR (125 MHz, DMSO): δ 167.19, 142.97, 138.44, 137.10, 134.82, 130.91, 130.0, 128.35, 128.33, 125.58, 122.75, 50.67, 24.88; HR-MS m/z: calculated for $C_{15}H_{14}N[M^+]$: 208.11208, found: 208.11204 (M – $CuCl_2^-$).

Reactivity studies



Scheme S1: Overview of reactivity studies between amine species and silyl enolate **2**.

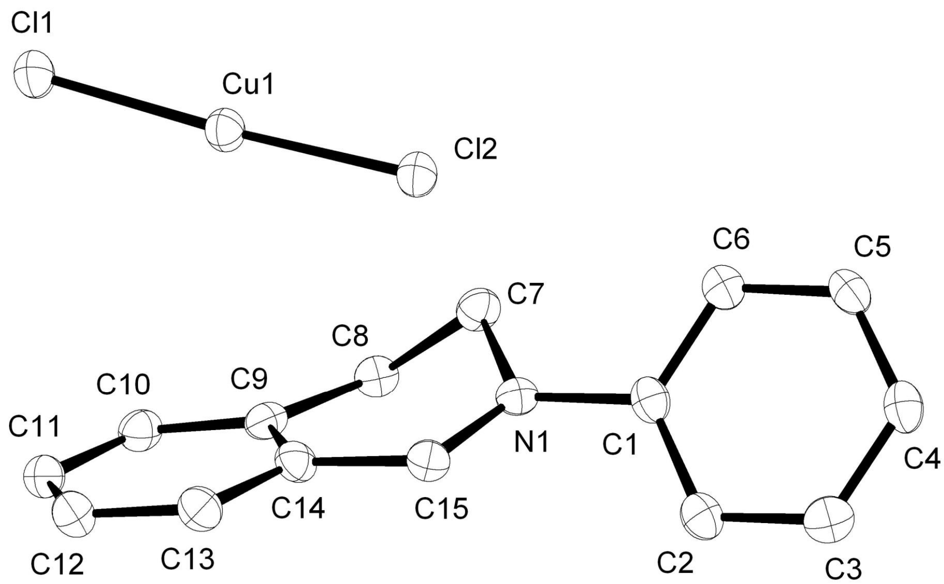
Iminium bromide **4c** was synthesized according to a literature procedure.[2]

[2] Bulman Page, P. C.; Buckley, B. R.; Appleby, L. F.; Alsters, P. A. *Synthesis* **2005**, 3405.

X-ray studies

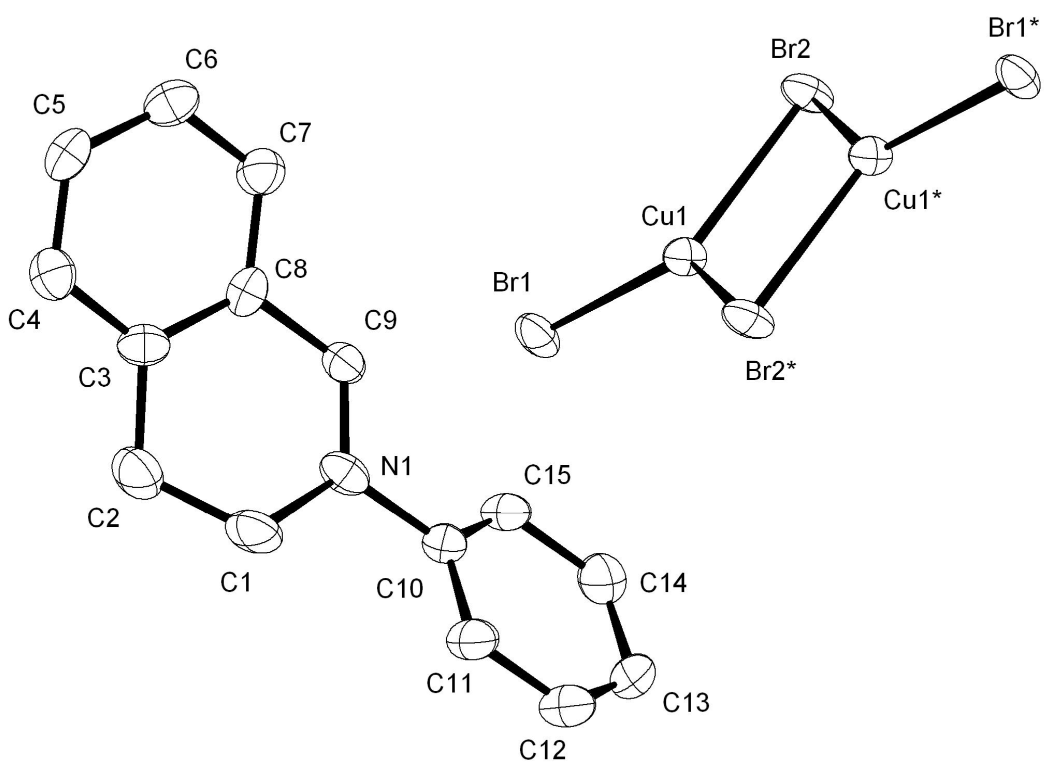
Single crystals of **4a** and **4b** were crystallised from MeOH.

X-ray structure of 4a



Sum formula: C_{15} H_{14} Cl_2 Cu N. CCDC reference number: 807625

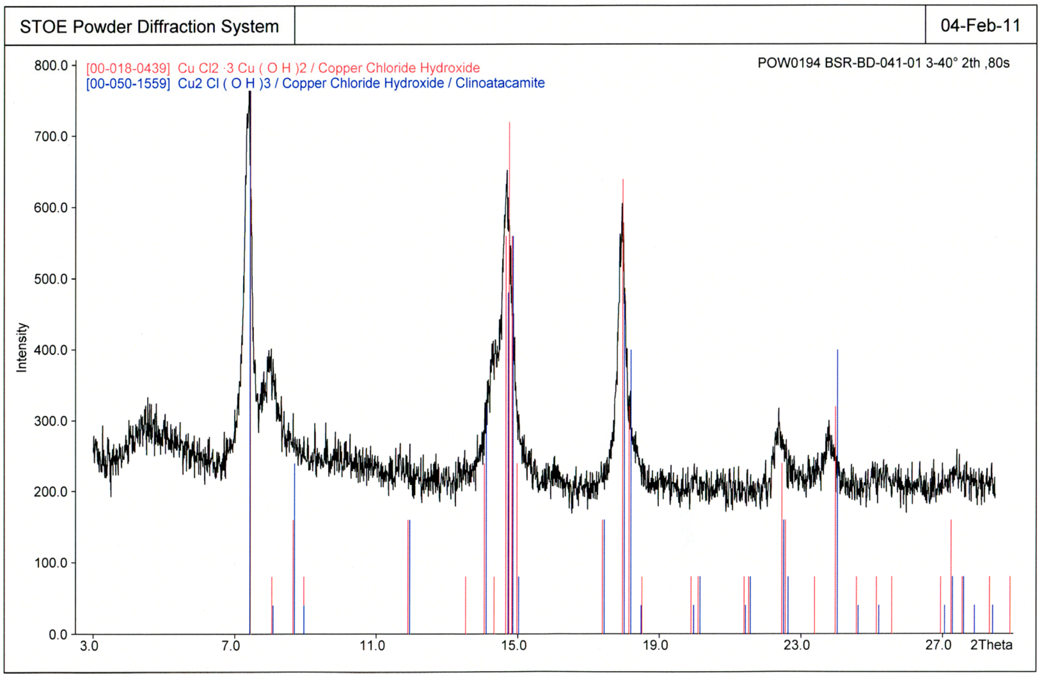
X-ray structure of 4b



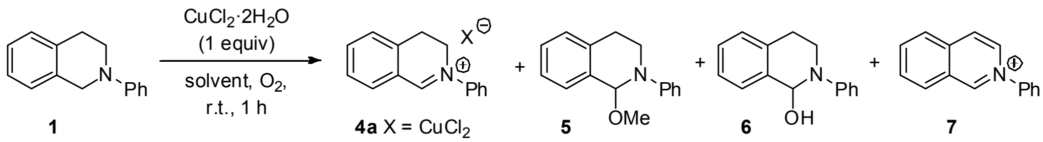
Sum formula: C_{15} H_{14} Br_2 Cu N. CCDC reference number: 813339

Powder-X-ray of the CuCl(OH)-precipitate

Shown is the powder X-ray of the precipitate collected from the reaction mixture of Scheme 3, in comparison with two calculated X-ray patterns of $CuCl_2$•$3Cu(OH)_2$ and $Cu_2Cl(OH)_3$.



NMR studies



Reactions between amine 1 and $CuCl_2$ dihydrate in CD_3OD and in acetone-d_6, direct analysis

Typical procedure: to a solution of N-phenyl tetrahydroisoquinoline (300mg, 1.43 mmol) in CD_3OD or acetone-d_6 (1.44 mL) was added $CuCl_2{\cdot}2H_2O$ (122.2 mg, 0.72 mmol) at room temperature. The reaction was carried out under an oxygen atmosphere. After stirring for 1 h, the reaction mixture was filtered over cotton and the filtrate was directly analyzed by NMR (Figure S1).

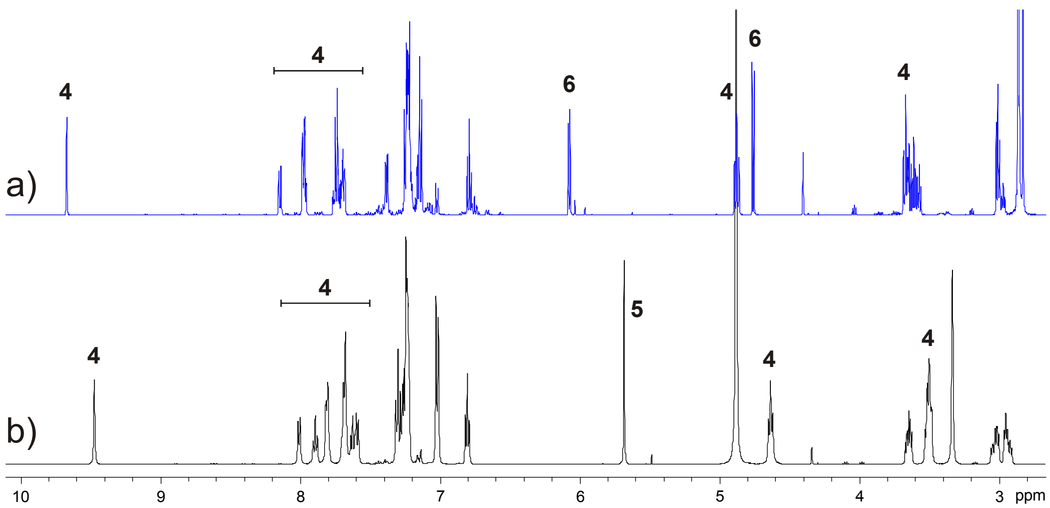


Figure S1: NMR analysis of the compound mixtures resulting from reactions of amine **1** with $CuCl_2$ dihydrate, indicated are characteristic peaks of compounds **4**, **5** and **6**; a) reaction performed and analyzed in acetone-d_6, b) reaction performed and analyzed in CD_3OD.

In MeOD, compounds **4** and **5** were formed in a ratio of ca. 40:60. In acetone-d_6, compounds **4** and **6** were formed in a ratio of ca. 40:60.

Further experiments have been performed in MeOH and analyzed in DMSO-d_6 which gives a better resolution, less overlapping of peaks and allowed the full characterization of compounds **4**-**7**.

Compound mixtures from reactions between amine 1 and $CuCl_2$ dihydrate in different ratios, analysis in DMSO-d_6

Typical procedure: to a solution of N-phenyl tetrahydroisoquinoline (300mg, 1.43 mmol) in methanol (1.44 mL) was added $CuCl_2{\cdot}2H_2O$ (122.2 mg, 0.72 mmol) at room temperature. The reaction was carried out under an oxygen atmosphere. After stirring for 1 h, the reaction mixture was filtered over cotton or a fritted glass funnel. The green precipitate was washed with methanol and analyzed by powder X-ray diffraction (see below). The solvent of the filtrate was removed in vacuo and the residue analyzed by NMR in DMSO-d_6 (Table S2, Figure S2).

Table S2: Ratio of products formed in the mixture as observed by 1H-NMR in DMSO-d6 (Figure S3).

#	eq. amine	4	5	6	7
1	1	1.0	1.6	0.2	0.0
2	2	1.0	0.7	0.7	0.0
3	3	1.0	1.0	1.0	0.1
4	4	1.0	1.0	0.3	0.1

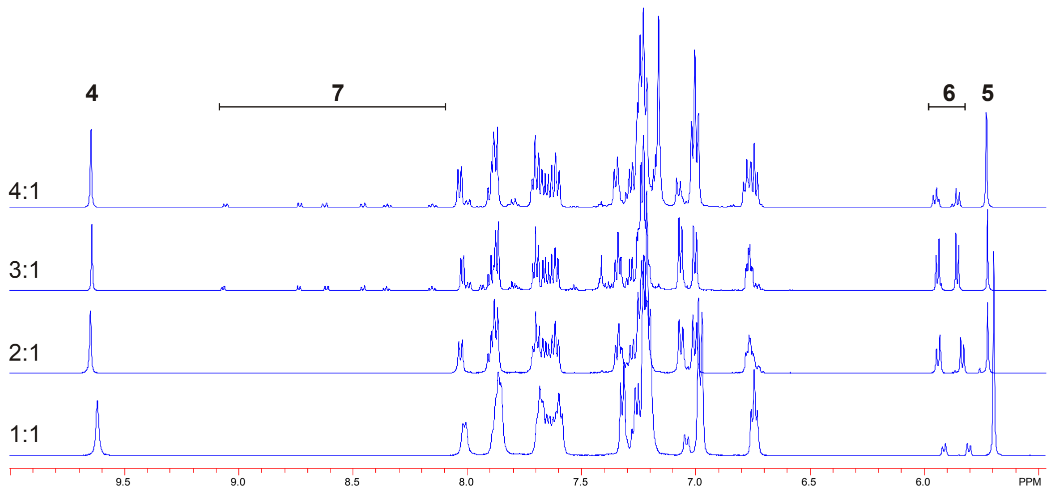


Figure S2: ^{1}H-NMR spectra of mixtures resulting from reacting amine **1** and $CuCl_2$ dihydrate in MeOH at various ratios (NMR's measured in DMSO-d_6).

Characterization of compounds 4-7 in DMSO, results and discussion

NMR spectra were recorded at 291 K on a Bruker Avance 600 (600.22 MHz) spectrometer. For the characterization of the components, 1D ^{1}H, 1D ^{13}C, 1D ^{13}C-dept135, ^{1}H,^{1}H-COSY, ^{1}H,^{1}H-NOESY/EXSY, ^{1}H,^{13}C-HSQC, ^{1}H,^{13}C-HMBC and ^{1}H,^{15}N-HMBC were measured. For the NOESY/EXSY spectrum a mixing time of 700 ms was used. NMR data were processed and evaluated with Bruker´s TOPSPIN 2.1.

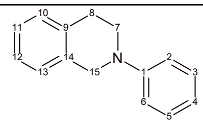
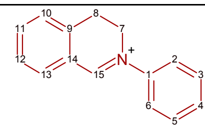
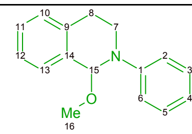
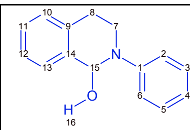
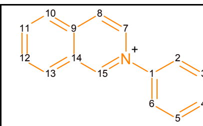
a) The ^{1}H, ^{13}C and ^{15}N chemical shift assignments (see Table S3) of the 4 product species (**4, 5, 6**, and **7**) of **Scheme 3** were completed on the reaction mixture after solvent replacement with DMSO-d_6. The relative concentration of **4**, **5** and **6** close to 1:1:1 initially complicated their identification as three distinct components as shown in the ^{1}H spectrum in Figure S3, top trace. Individual components can however be identified by comparing the ^{1}H spectra measured on a pure iminium salt **4a** sample (Figure S3, bottom trace) and on a mixture of the salt **4** with hemiaminal **6** in DMSO-d_6 (Figure S3, middle trace).

b) Trace amounts (4% relative to **4**) of the fully aromatic isoquinolinium salt (**7**) was also identified in the mixture sample and ^{1}H and ^{13}C assignment could be completed due to low field shift of a number of its protons and carbons. The assignment is also given in Table S3.

c) No trace of amine **1** was observed in the mixture. Full assignment of **1** (Table S3) was obtained on a separate sample prepared in DMSO-d_6.

d) The NOESY/EXSY experiment conducted on the mixture revealed exchange cross-peaks between corresponding ^{1}H from the iminium salt **4** and the hemiaminal **6** (see Figure S4). Cross-peak integration reveals that the exchange occurs at an estimated rate of approx. 0.07 s^{-1}. Exchange cross-peaks are also visible between corresponding ^{1}H from the iminium salt **4** and the methanol adduct **5,** albeit in a much weaker regime. Cross-peak integration at position H15 reveals exchanges occurring between **4a-5** and **4a-6** at estimated rates of 0.002s-1 and 0.042s^{-1}, respectively, using a simple 3-site exchange model and first order approximations. No such exchange cross-peaks are observed from the isoquinolinium salt (**7**) or between **5** and **6**, indicating very slow or absence of exchange.

Table S3: ^{1}H, ^{13}C and ^{15}N chemical shift assignments (solvent: DMSO-d_6).

Atom No.	 1		 4		 5		 6		 7	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	150.11		142.93		148.46		149.02		142.99	
2	114.70	6.98	122.71	7.86	114.17	6.99	115.5	7.05	124.97	7.98
3	129.04	7.19-7.24	129.96	7.69	129.04	7.18-7.26	128.84	7.18-7.26	130.24	7.79
4	117.95	6.73	131.09	7.58-7.67	118.2	6.76	118.28	6.75	131.09	7.77
5	129.04	7.19-7.24	129.96	7.69	129.04	7.18-7.26	128.84	7.18-7.26	130.24	7.79
6	114.70	6.98	122.71	7.86	114.17	6.99	115.5	7.05	124.97	7.98
7	45.67	3.51	50.63	4.59	42.01	3.48, 3.54	40.77	3.52	134.98	9.06
8	28.09	2.88	24.84	3.41	26.99	2.86-2.99	28.78	2.86-2.99	125.69	8.73
9	134.61		137.05		135.7		134.82		137.23	
10	128.38	7.15	128.3*	7.58-7.67	127.84	7.18-7.26	127.85	7.18-7.26	127.28	8.45
11			138.39	7.89	128.18	7.28	127.43	7.18-7.26	137.68	8.34
12	125.85	7.16	128.28*	7.58-7.67	125.69	7.18-7.26	125.9	7.18-7.26	131.48	8.14
13	126.61	7.19-7.24	134.78	8.01	128.03	7.34	128.1	7.32	131.23	8.61
14	134.48		125.54		134.24		137.83		127.33	
15	49.78	4.36	167.14	9.63	86.72	5.71	78.68	5.93	150.57	10.39
16					53.15 (OMe)	3.16 (OMe)		5.84 (OH)		
	^{15}N		^{15}N		^{15}N		^{15}N		^{15}N	
	-319.2		-171.3		-306.0		-301.2		-184.9	

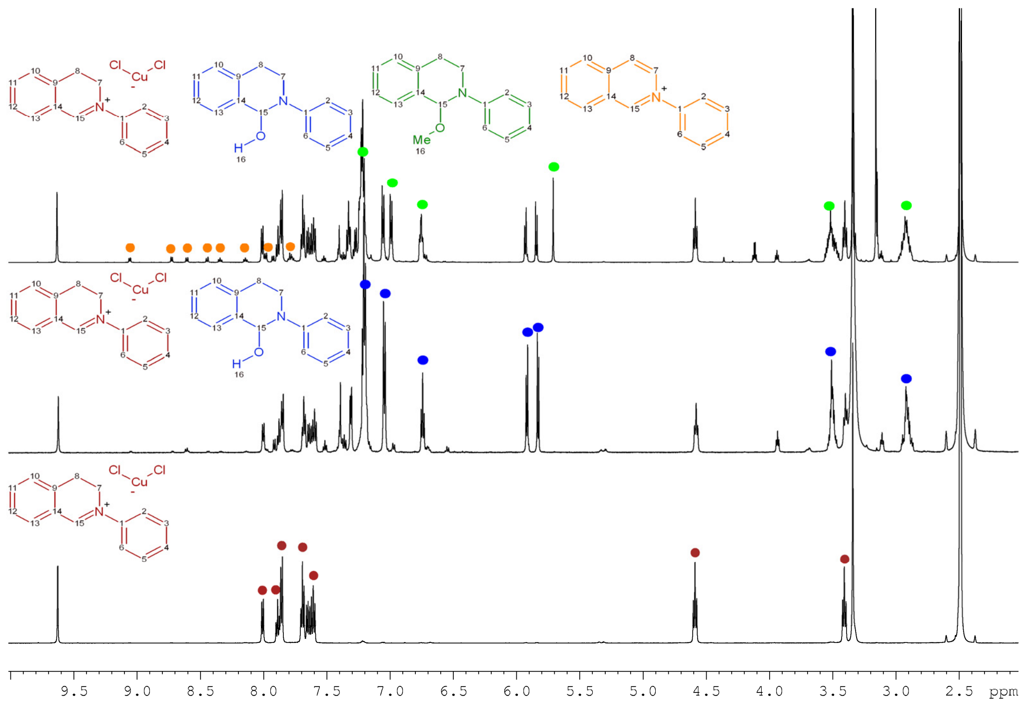


Figure S3: 1H spectra of 4 (bottom), mixture of 4 and 6 (middle) and mixture of 4, 5, 6 and 7 (with peak labels: red, green, blue and orange, respectively). Spectra were recorded in DMSO-d_6 at 291 K on a Bruker Avance 600 (600.22 MHz) spectrometer, equipped with a TCI cryoprobe with z-gradient.

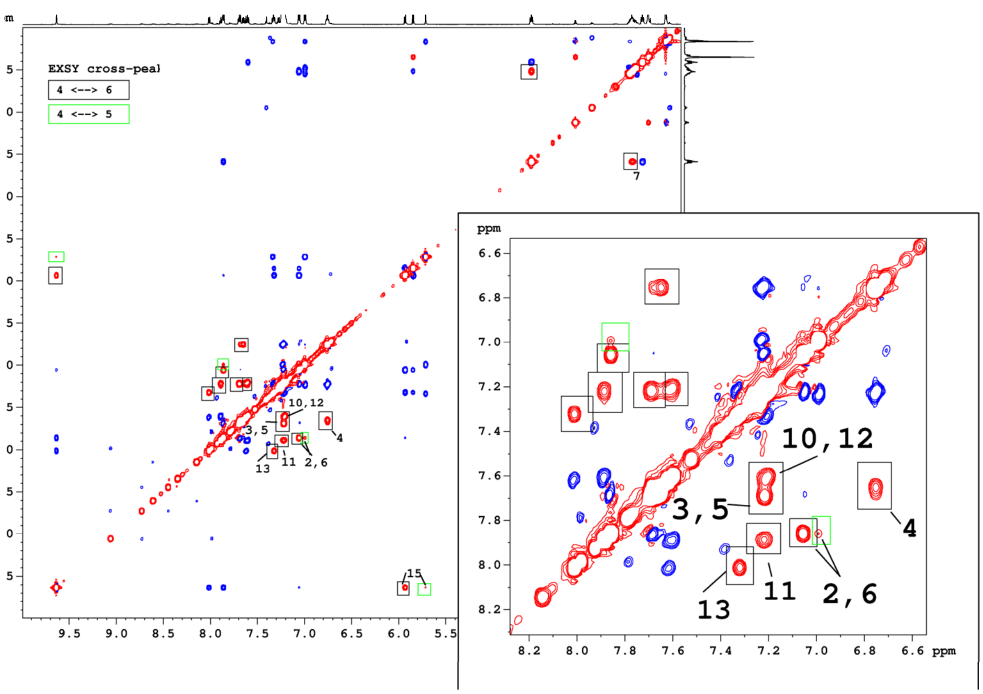


Figure S4: Two-dimensional 1H,1H NOESY/EXSY in DMSO-d_6 (tm=700ms) spectrum of 4/5/6/7 mixture showing exchange cross-peaks between species 4 and 6 (black boxes) and between 4 and 5 (green boxes).

NMR-studies of the oxidative coupling reaction

The reactions were performed according to the general procedures given for the oxidative coupling with enolat **2**[3] or with allyl silane **8** (see above) in methanol-d_4 and acetone-d_6, respectively. Samples were taken at intervals and diluted with the same solvent prior to NMR-spectroscopic analysis. During the coupling with **2**, the intermediates **4**, **5** and **6** were not clearly visible by NMR.

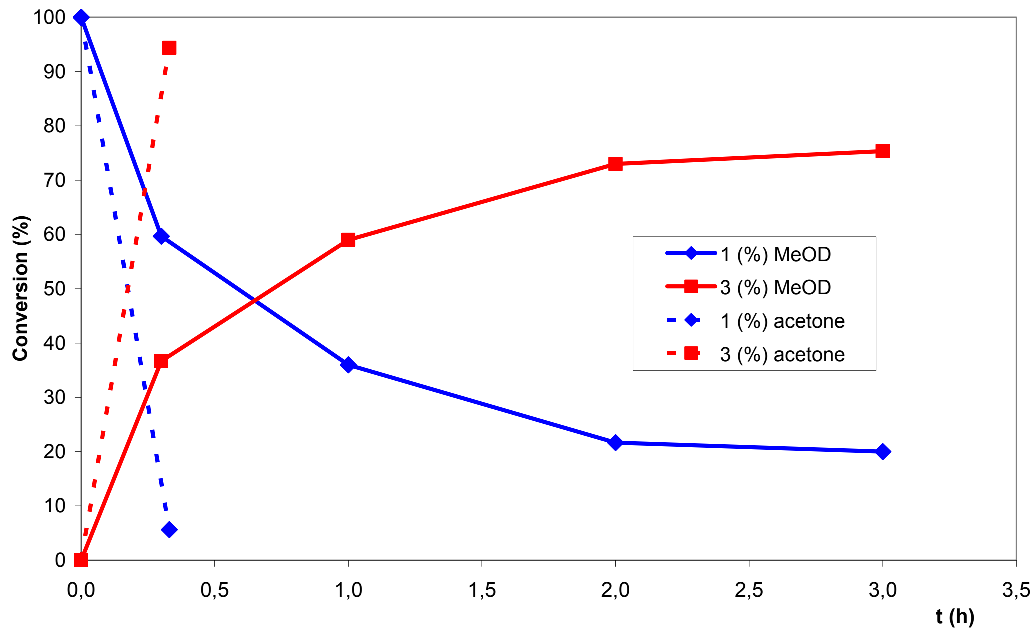


Figure S5: Oxidative coupling of amine **1** with enolate **2** to product **3** in methanol-d_4 and acetone-d_6.

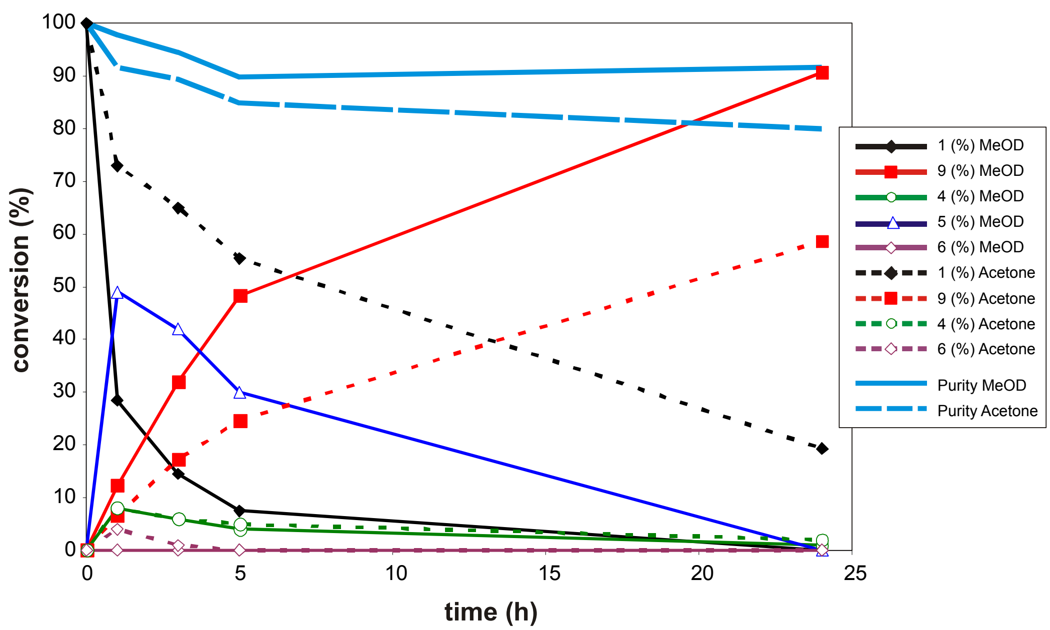


Figure S6: Oxidative coupling of **1** with allyl silane **8** to product **9**, comparison of solvents methanol-d_4 and acetone-d_6. Purity: Percentage of identified species **1**, **4**, **5**, **6**, **8** and **9** in the reaction mixture.

[3] Sureshkumar, D.; Sud, A.; Klussmann, M. *Synlett* **2009**, 1558-1561.

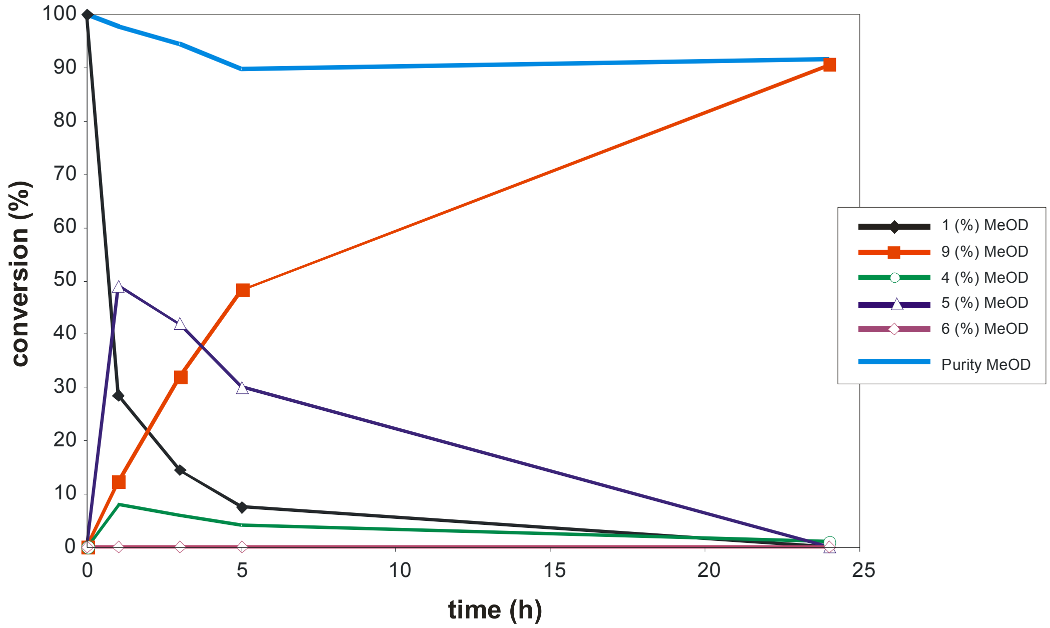


Figure S7: Oxidative coupling of amine **1** with allyl silane **8** to product **9** in methanol-d_4. Purity: Percentage of identified species **1**, **4**, **5**, **6**, **8** and **9** in the reaction mixture.

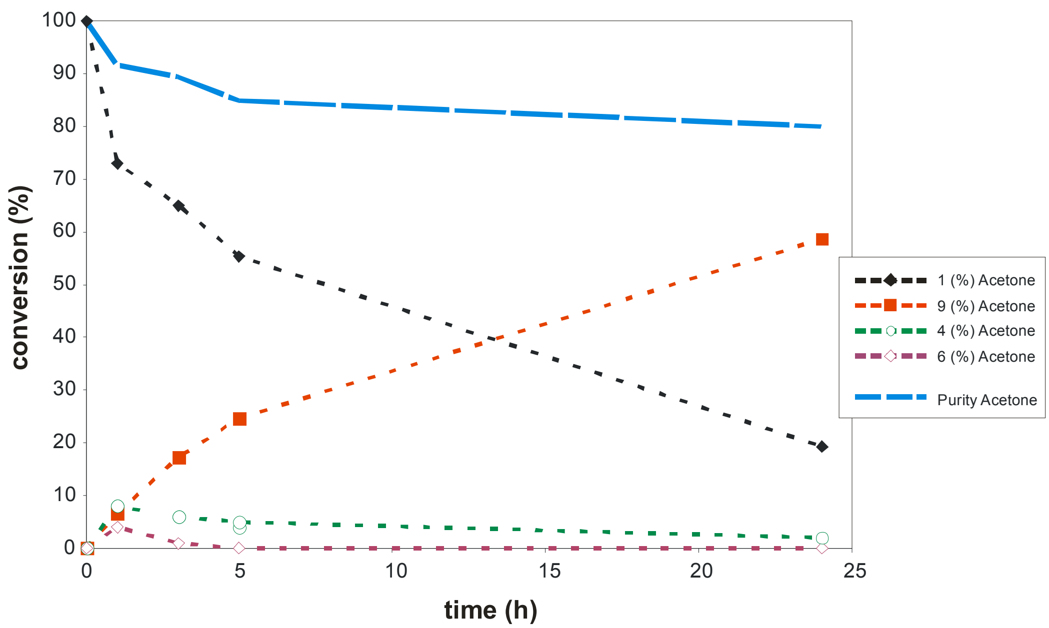


Figure S8: Oxidative coupling of amine **1** with allyl silane **8** to product **9** in acetone-d_6. Purity: Percentage of identified species **1**, **4**, **5**, **6**, **8** and **9** in the reaction mixture.

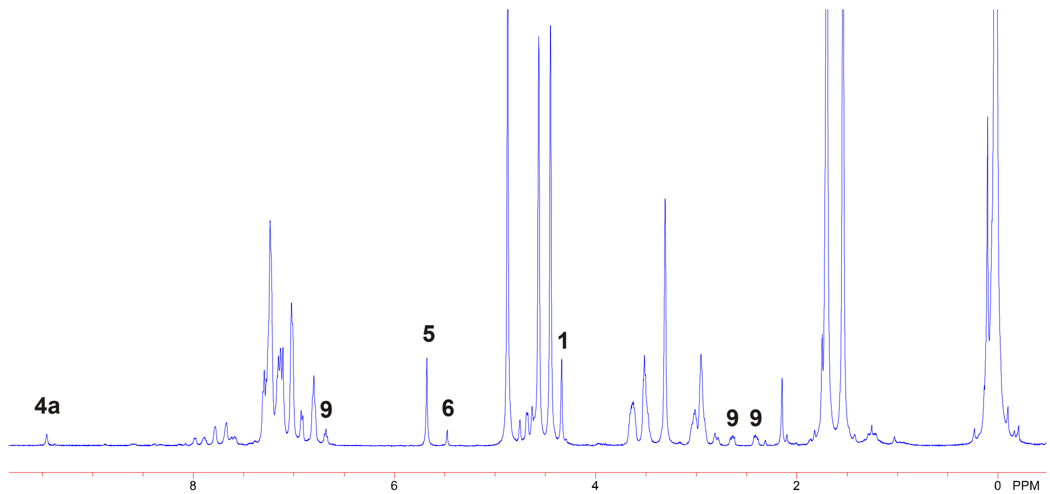


Figure S9: ^{1}H-NMR spectrum of the reaction mixture of the allylation of **1** with **8** in methanol-d_4, taken after one hour; assignment of characteristic peaks of compounds **1**, **4a**, **5**, **6** and **9**.

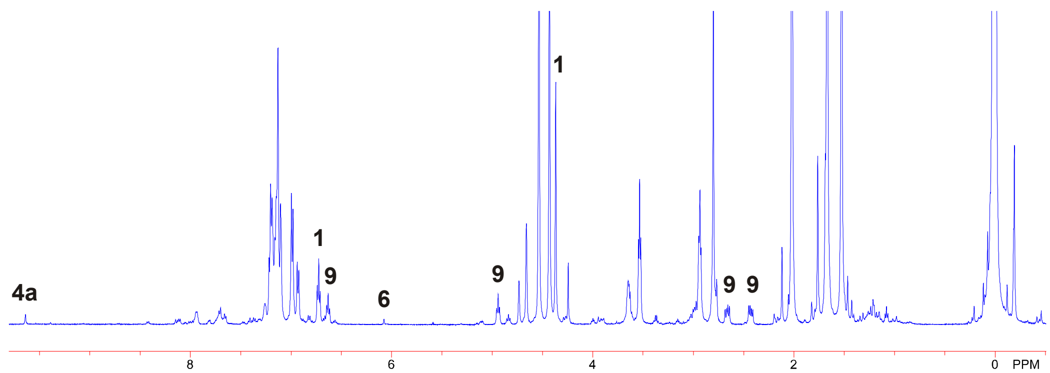


Figure S10: ^{1}H-NMR spectrum of the reaction mixture of the allylation of **1** with **8** in acetone-d_6, taken after five hours; assignment of characteristic peaks of compounds **1**, **4a**, **5**, **6** and **9**.

NMR-spectra of starting materials and products

Starting materials

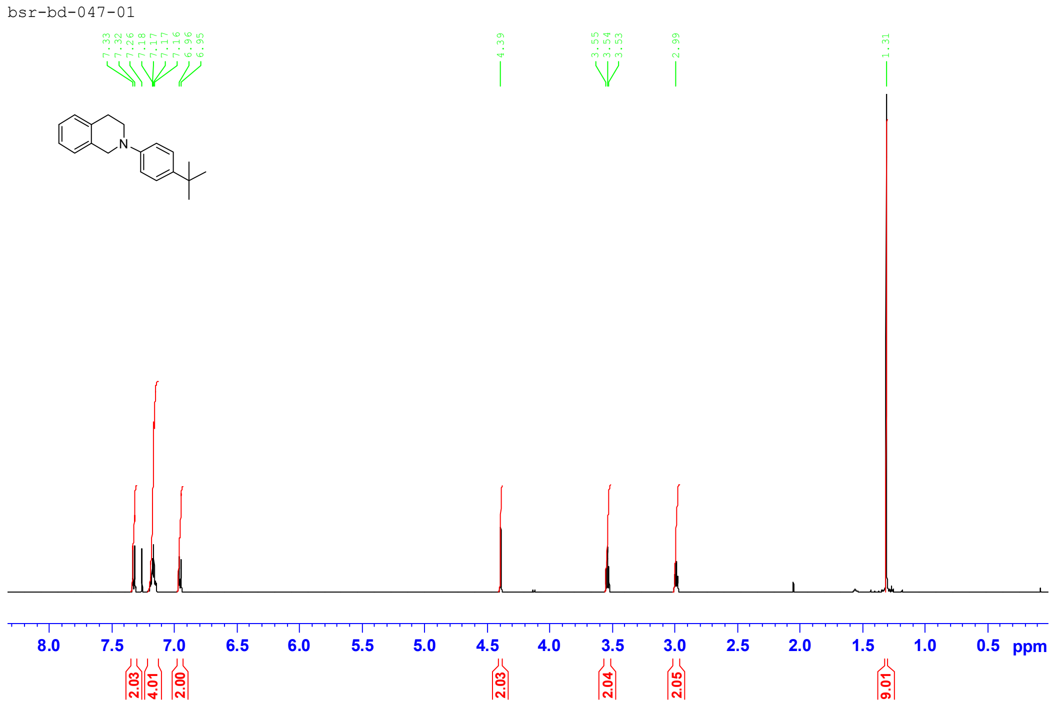


Figure S11: ^{1}H NMR in $CDCl_3$

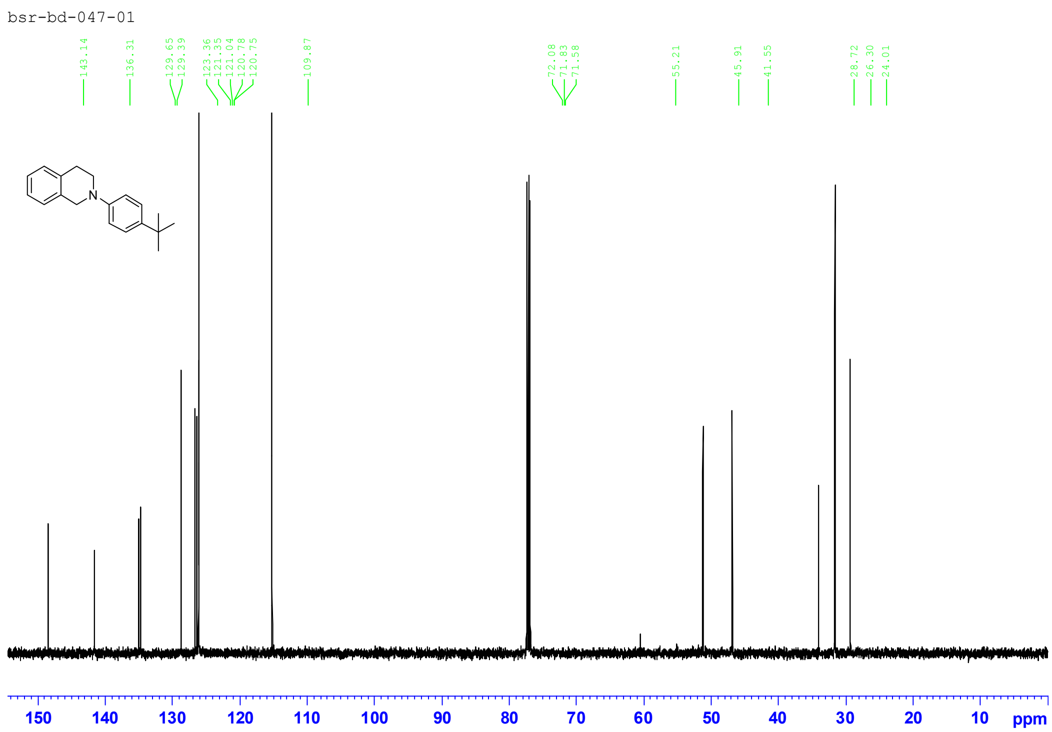


Figure S12: ^{13}C NMR in $CDCl_3$

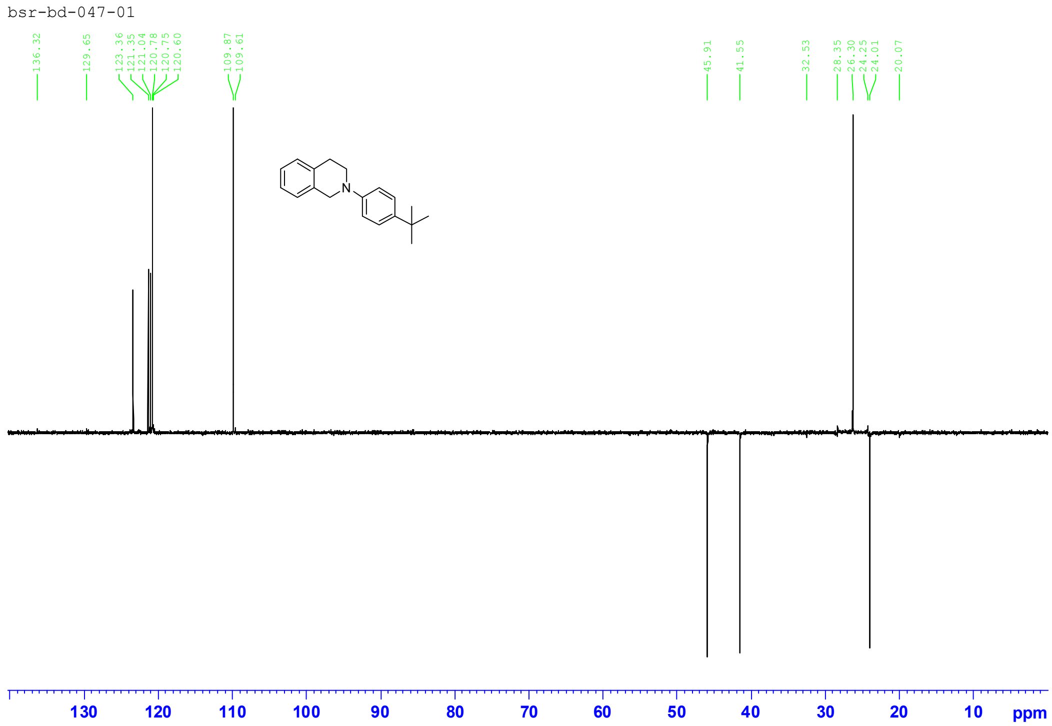


Figure S13: dept135 NMR in $CDCl_3$

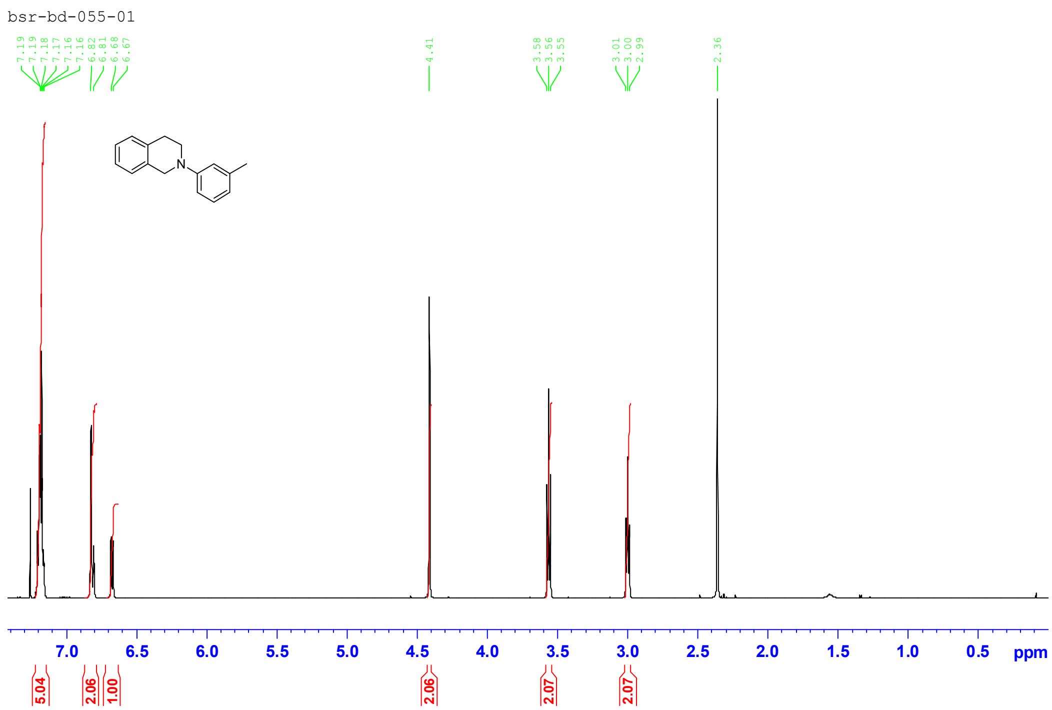


Figure S14: ^1H NMR in $CDCl_3$

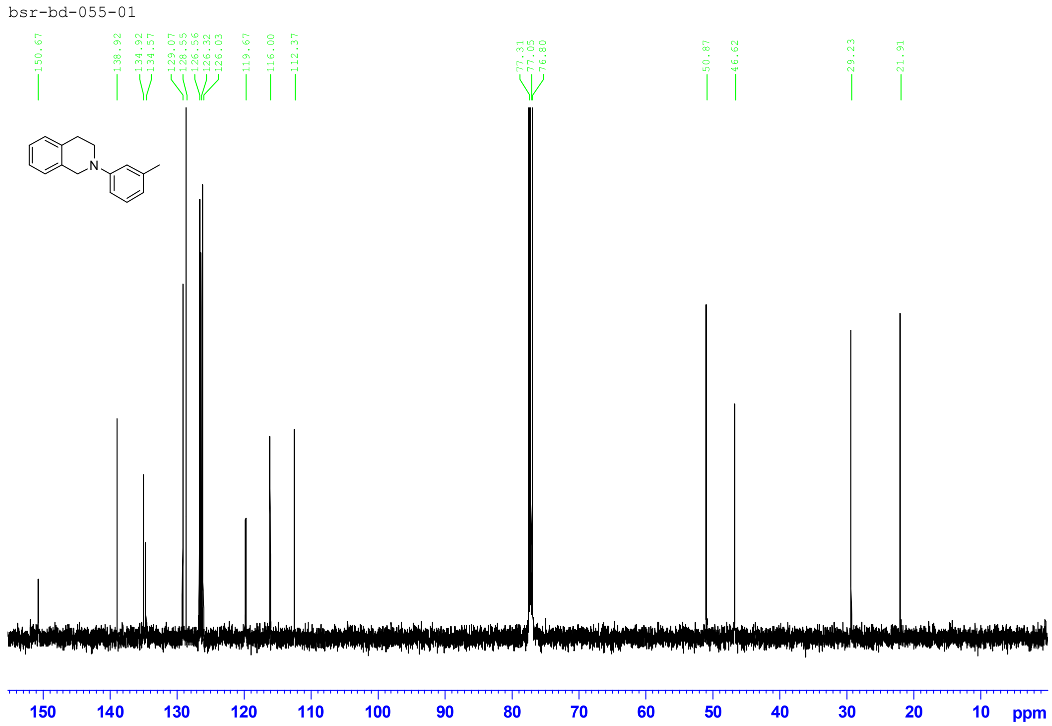


Figure S15: ^{13}C NMR in $CDCl_3$

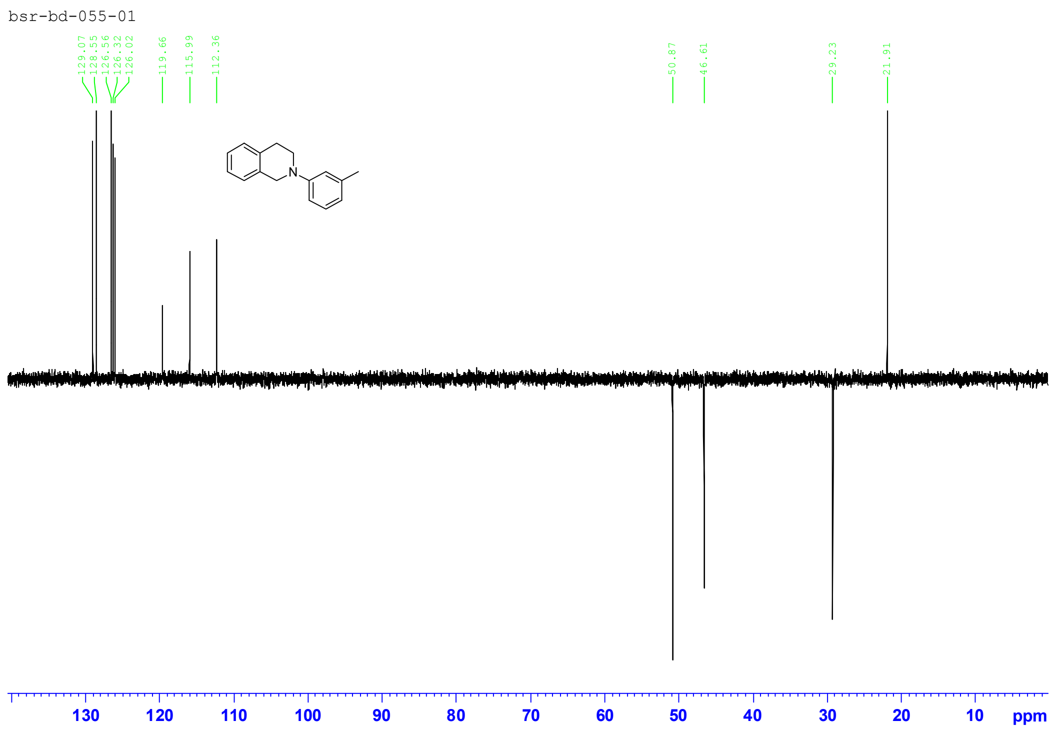


Figure S16: dept135 NMR in $CDCl_3$

Products

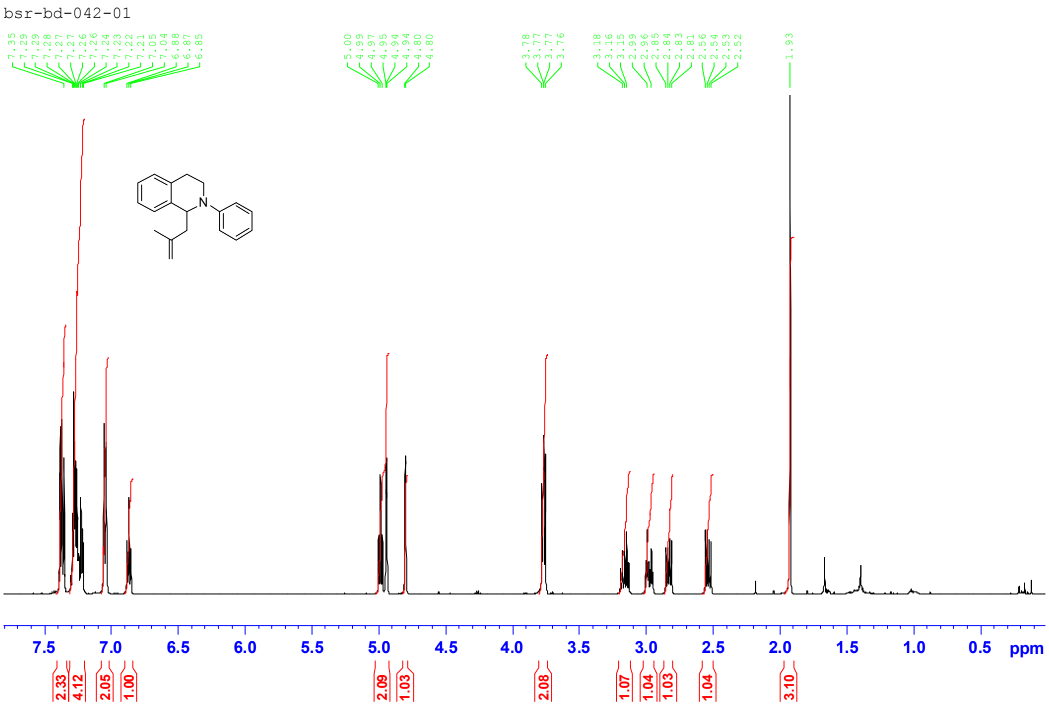


Figure S17: ^{1}H NMR in $CDCl_3$

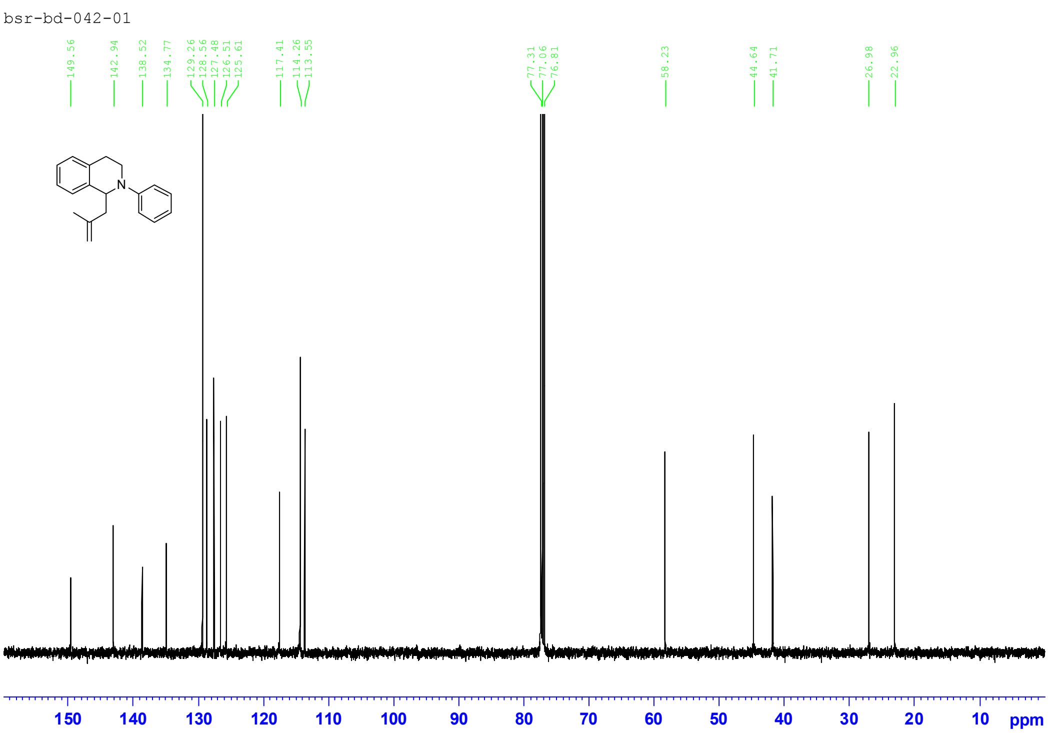


Figure S18: ^{13}C NMR in $CDCl_3$

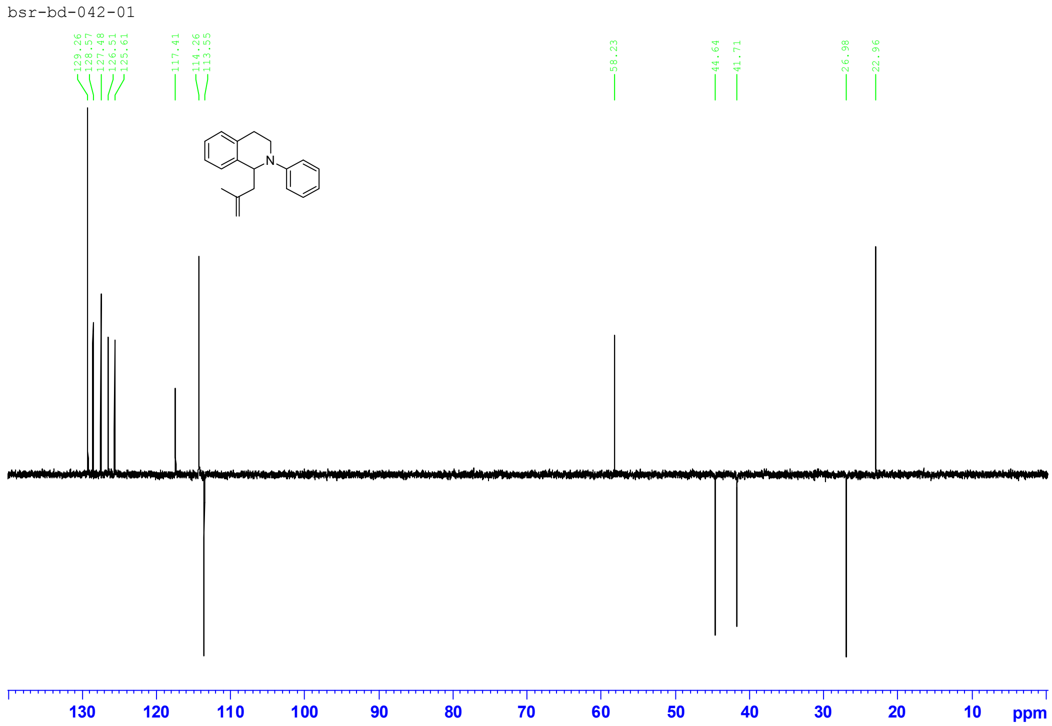


Figure S19: dept135 NMR in $CDCl_3$

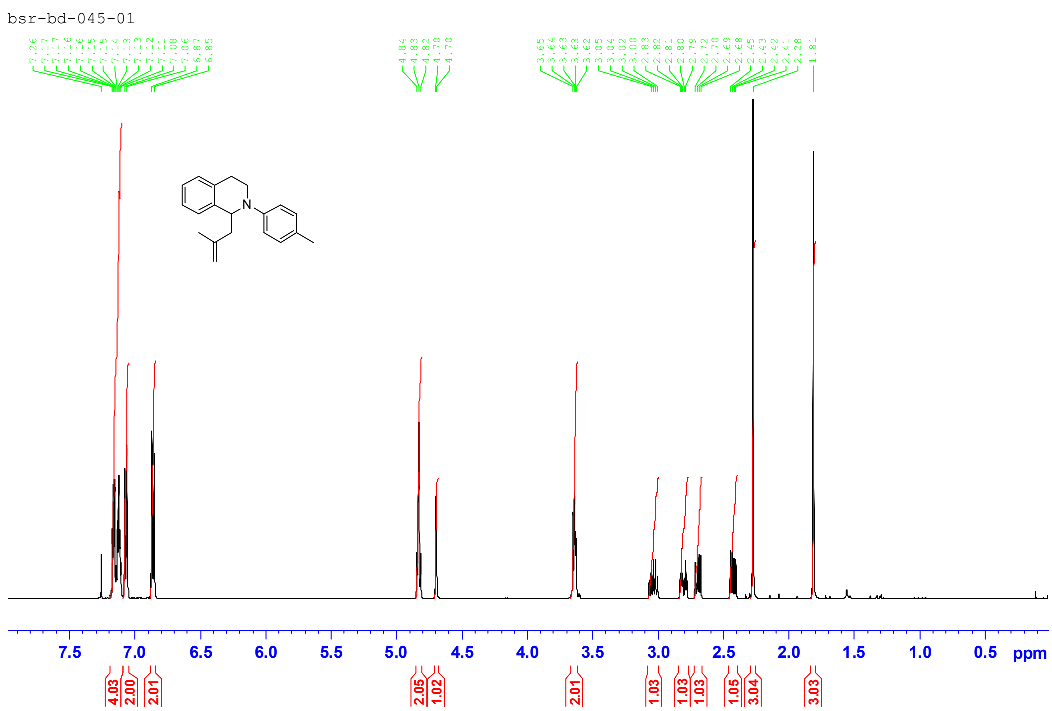


Figure S20: ^{1}H NMR in $CDCl_3$

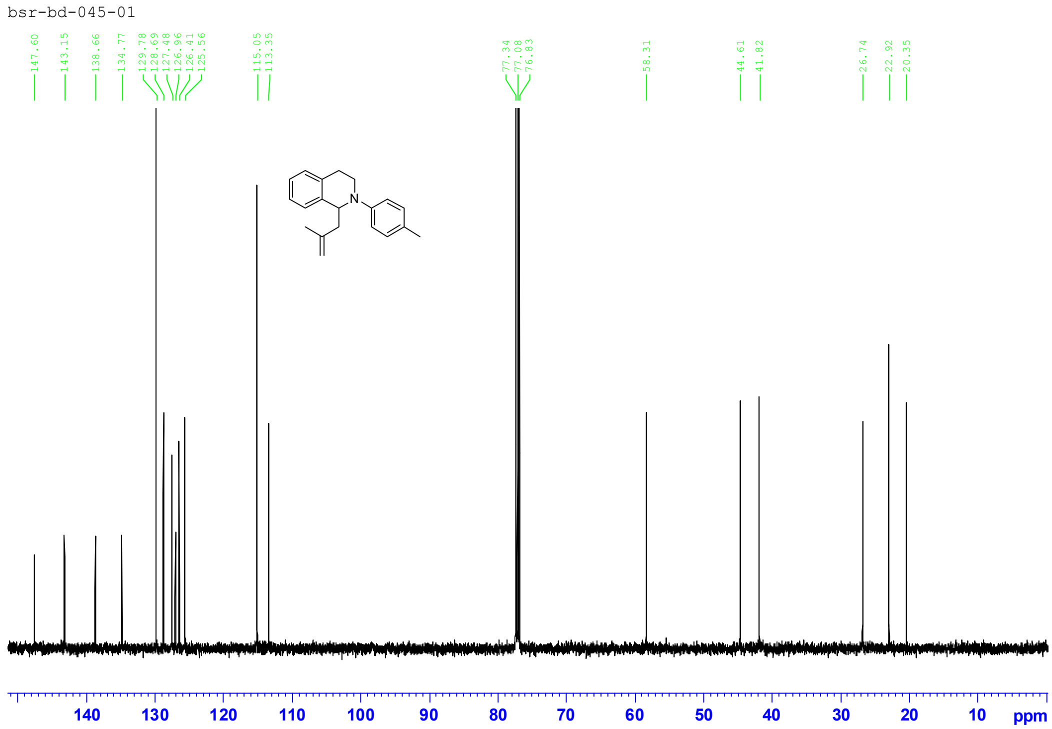


Figure S21: ^{13}C NMR in $CDCl_3$

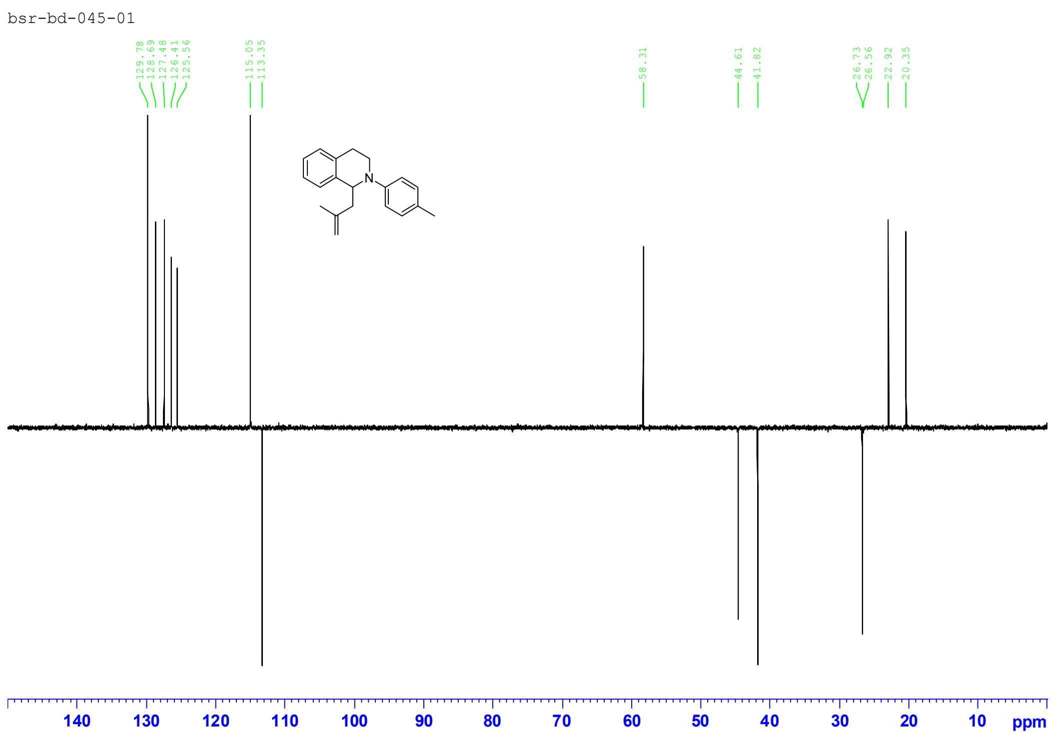


Figure S22: dept135 NMR in $CDCl_3$

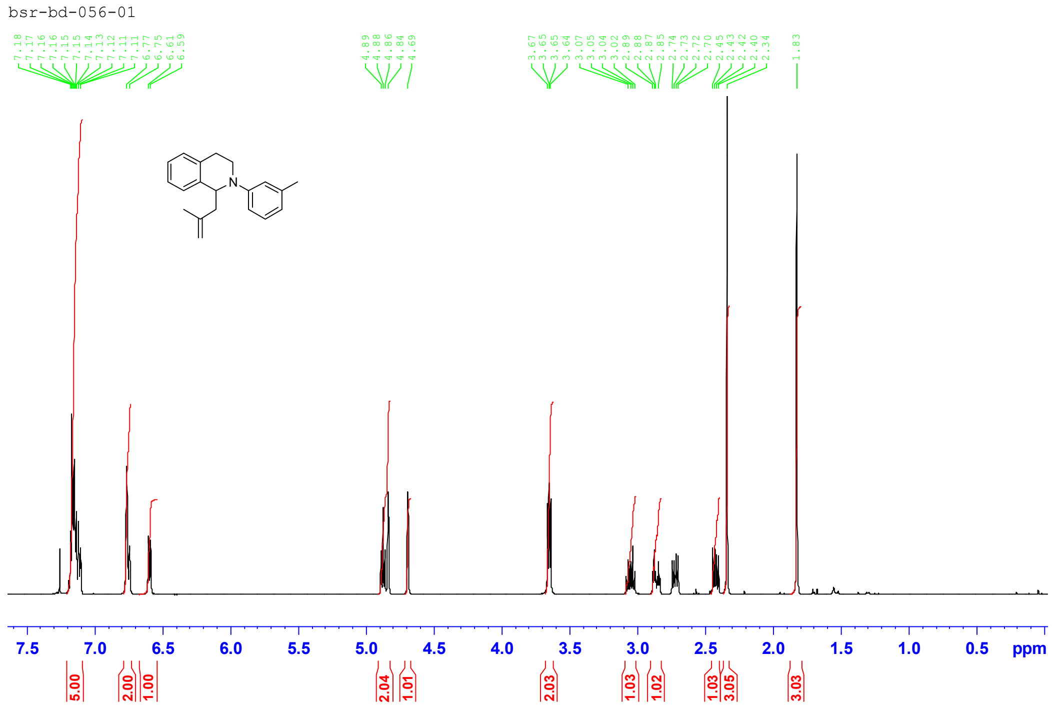


Figure S23: ^{1}H NMR in $CDCl_3$

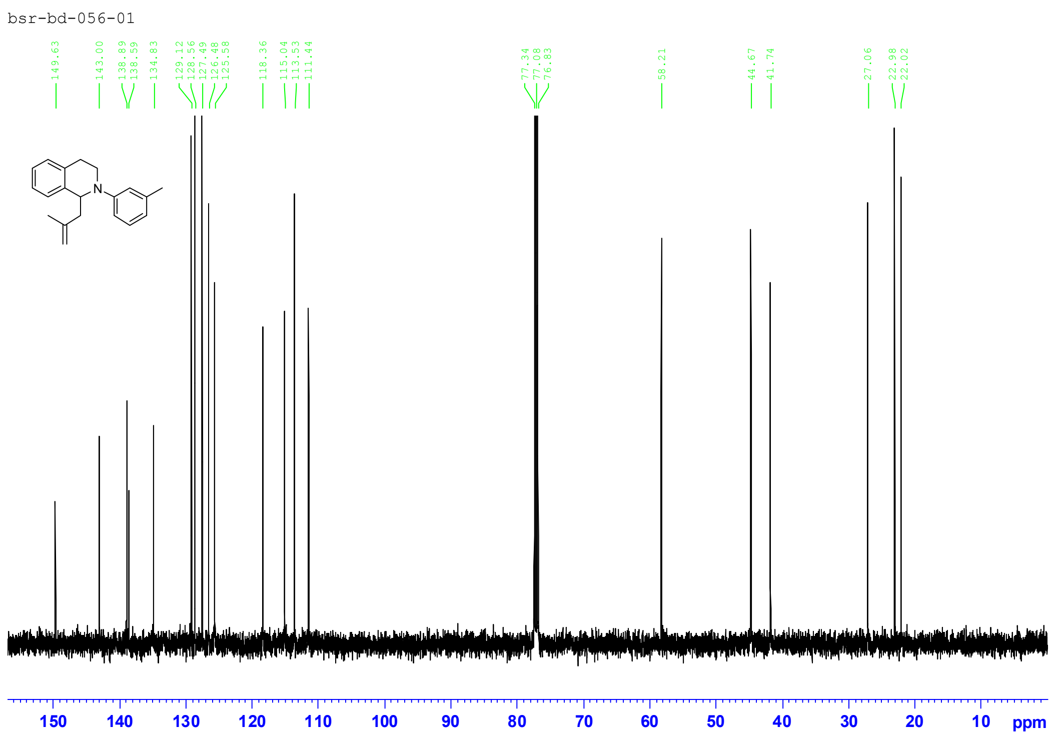


Figure S24: ^{13}C NMR in $CDCl_3$

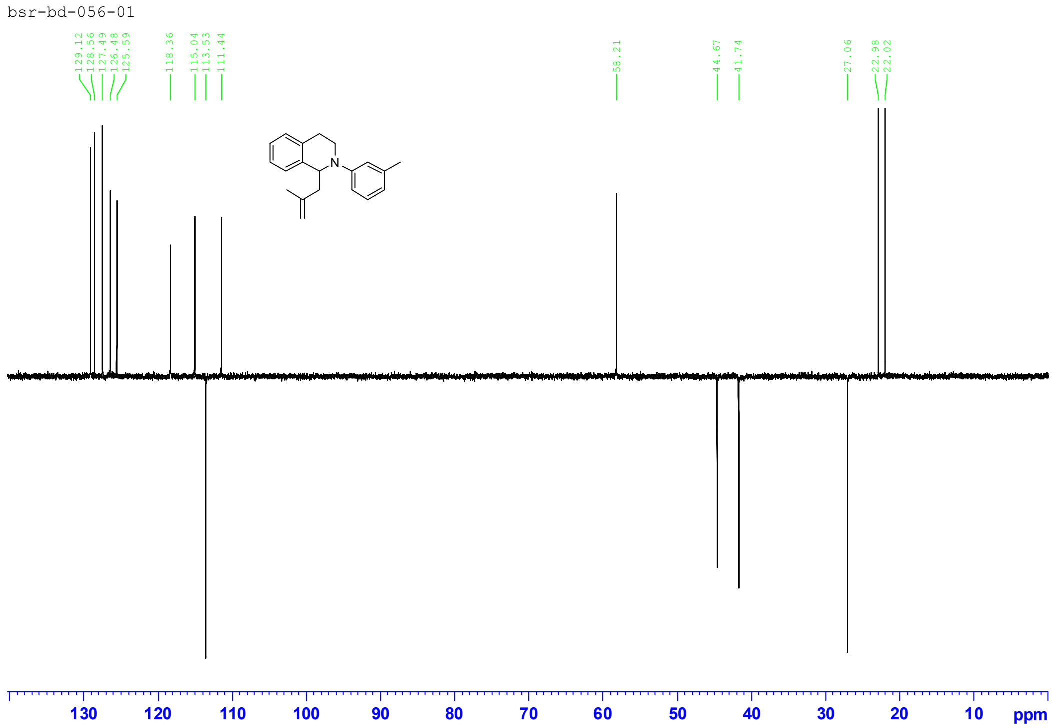


Figure S25: dept135 NMR in $CDCl_3$

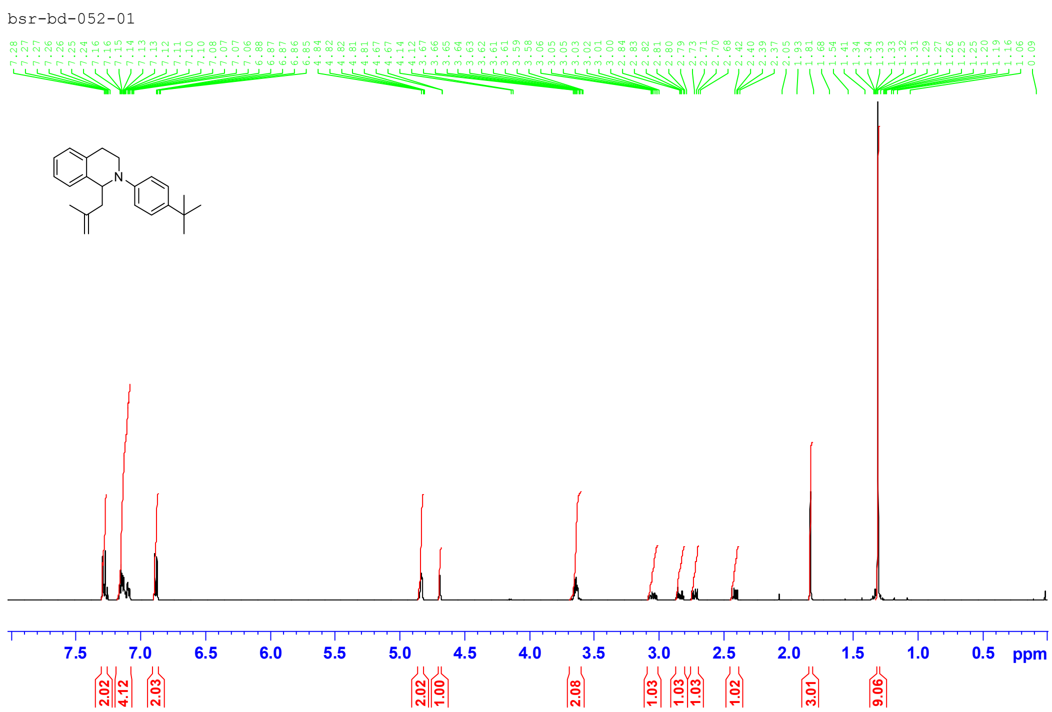


Figure S26: ^{1}H NMR in $CDCl_3$

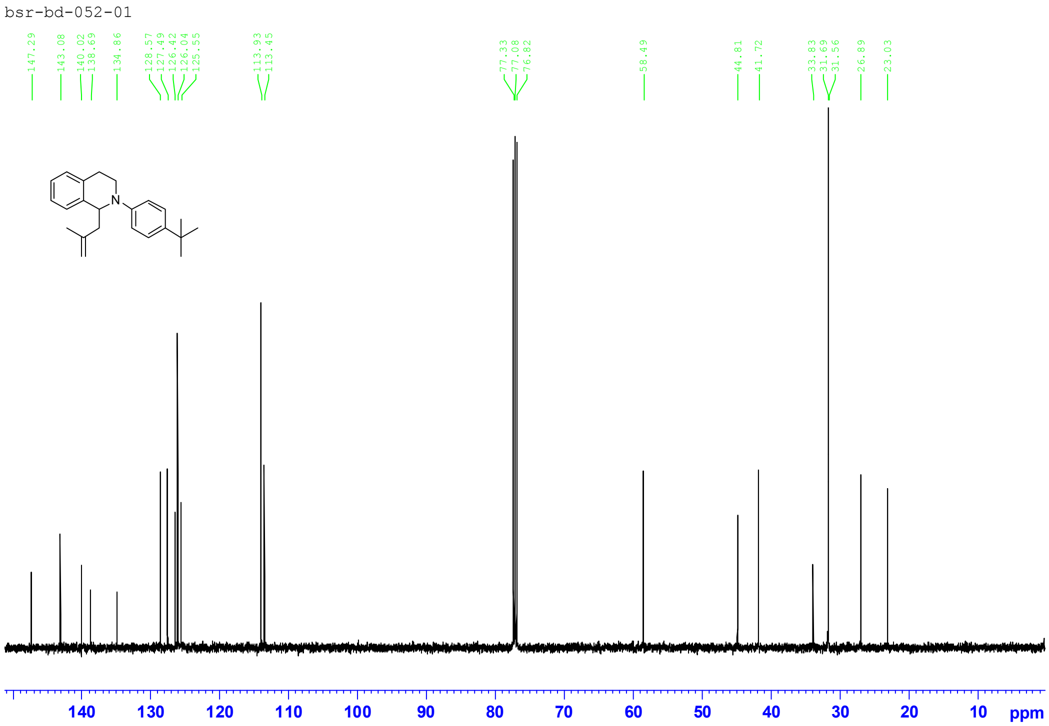


Figure S27: ^{13}C NMR in $CDCl_3$

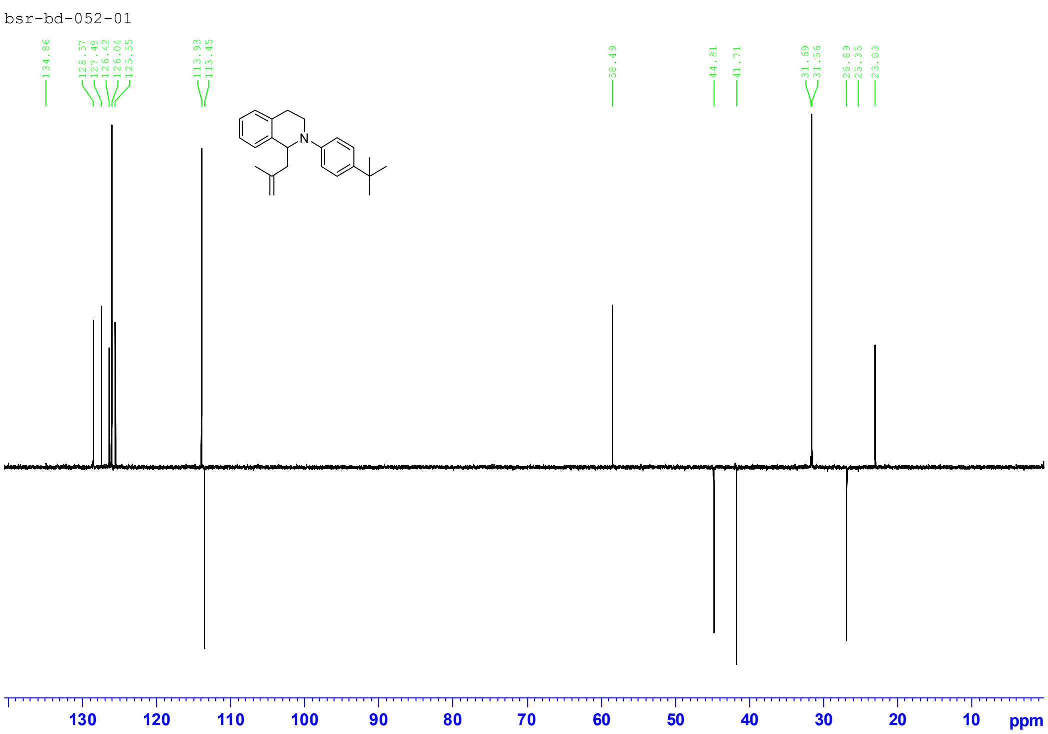


Figure S28: dept135 NMR in $CDCl_3$

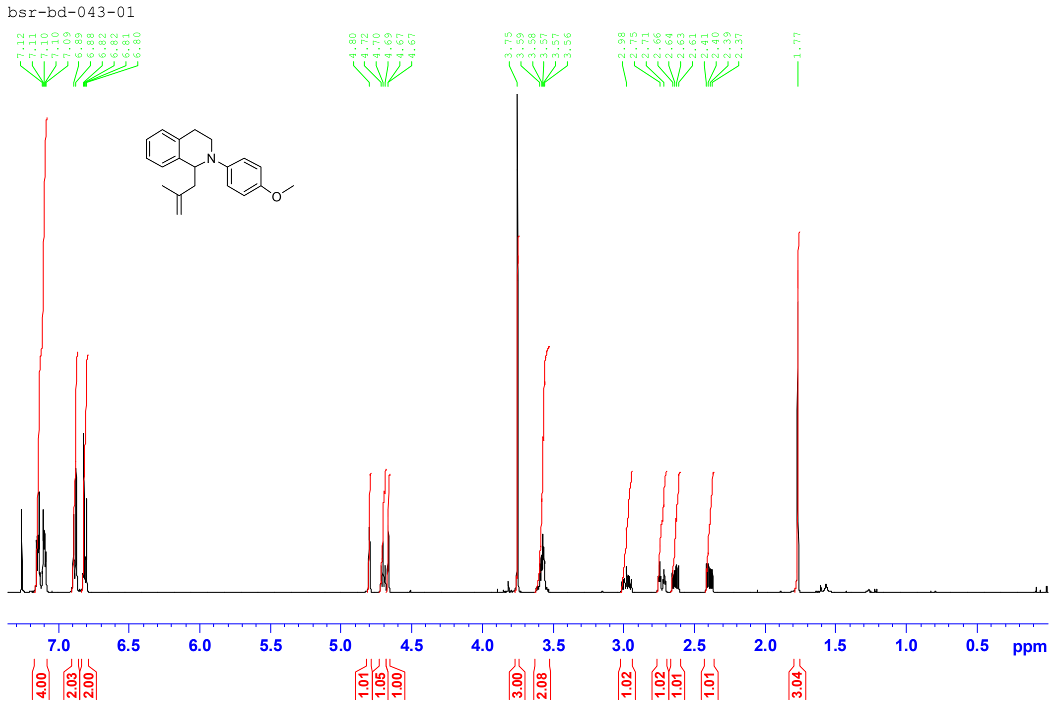


Figure S29: ^{1}H NMR in $CDCl_3$

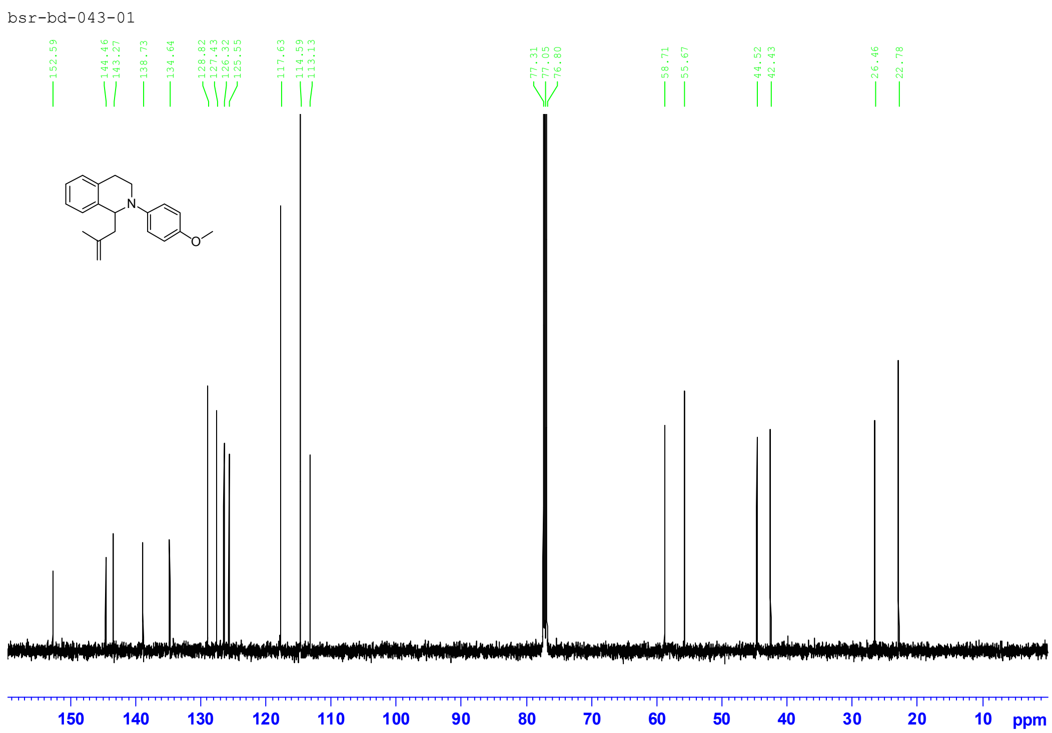


Figure S30: ^{13}C NMR in $CDCl_3$

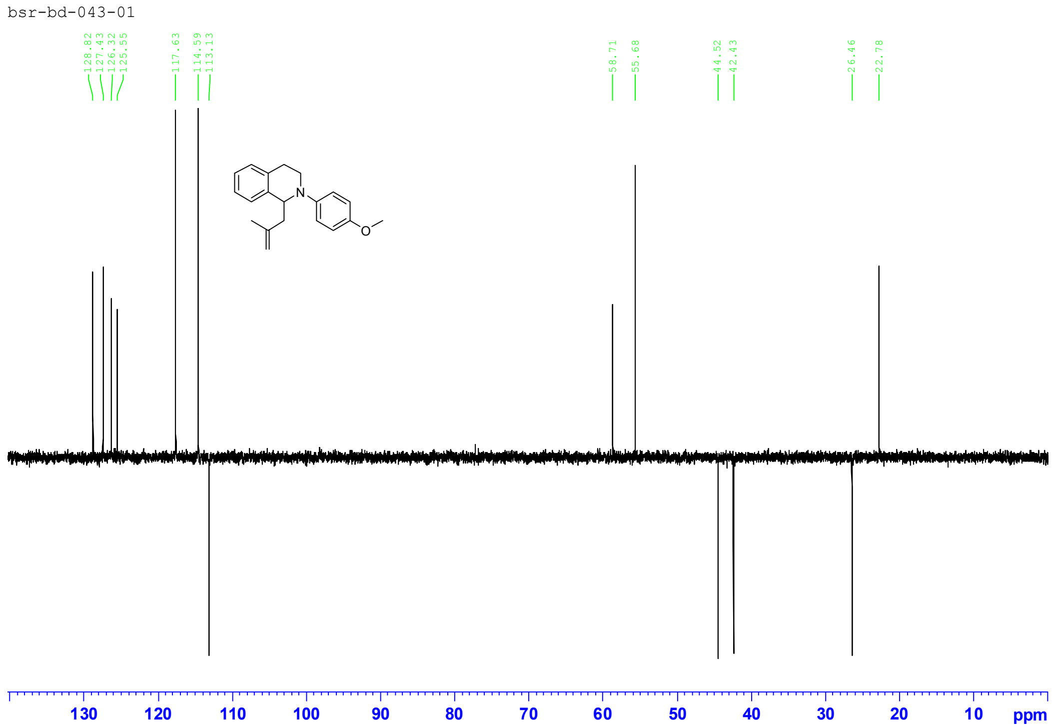


Figure S31: dept135 NMR in $CDCl_3$

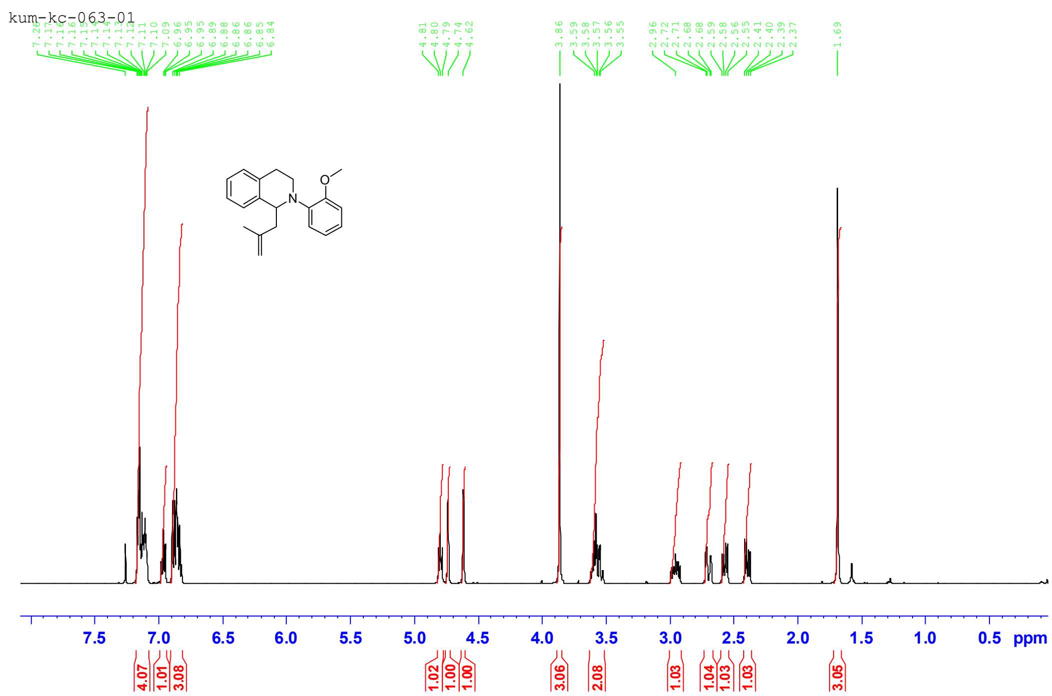


Figure S32: ^{1}H NMR in $CDCl_3$

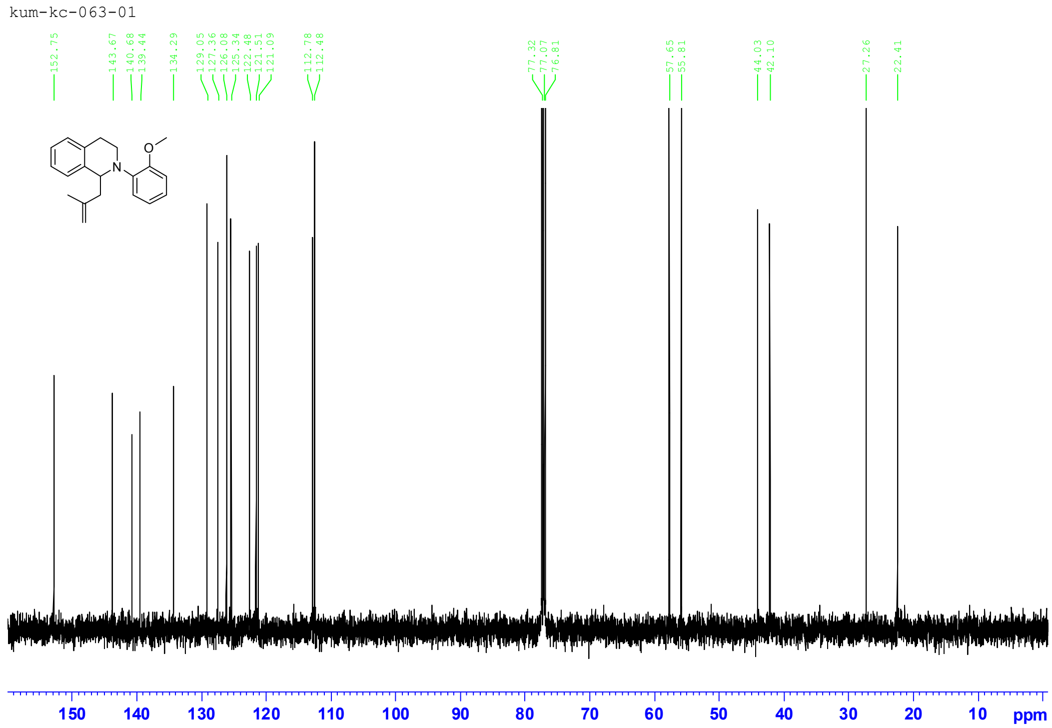


Figure S33: ^{13}C NMR in $CDCl_3$

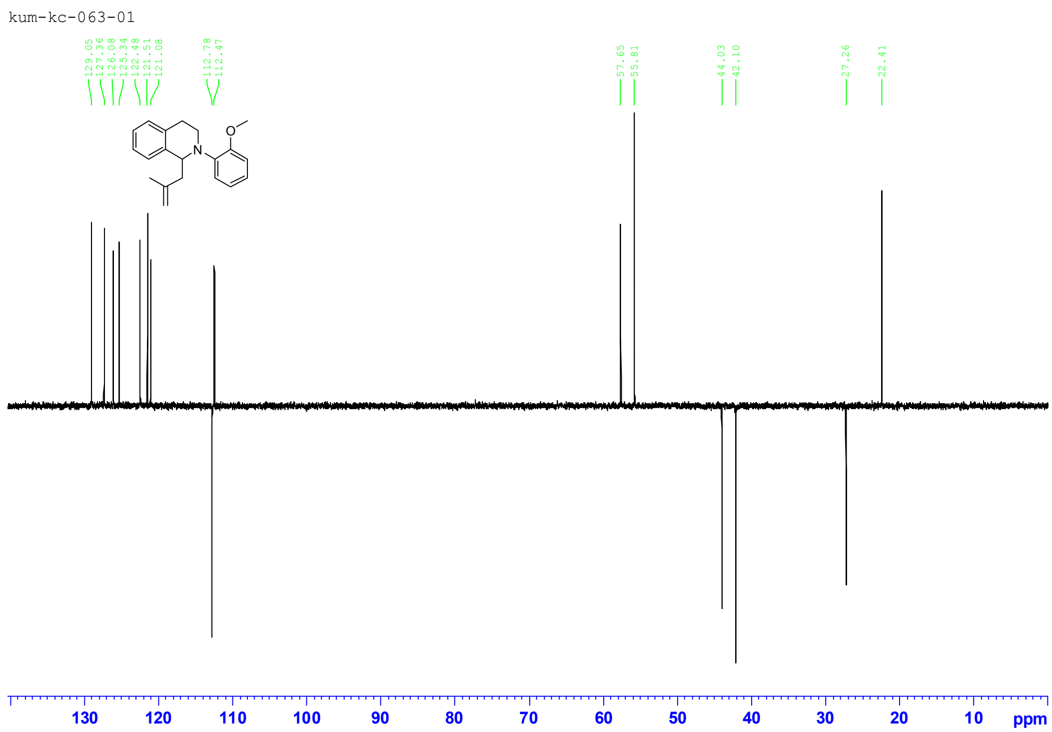


Figure S34: dept135 NMR in $CDCl_3$

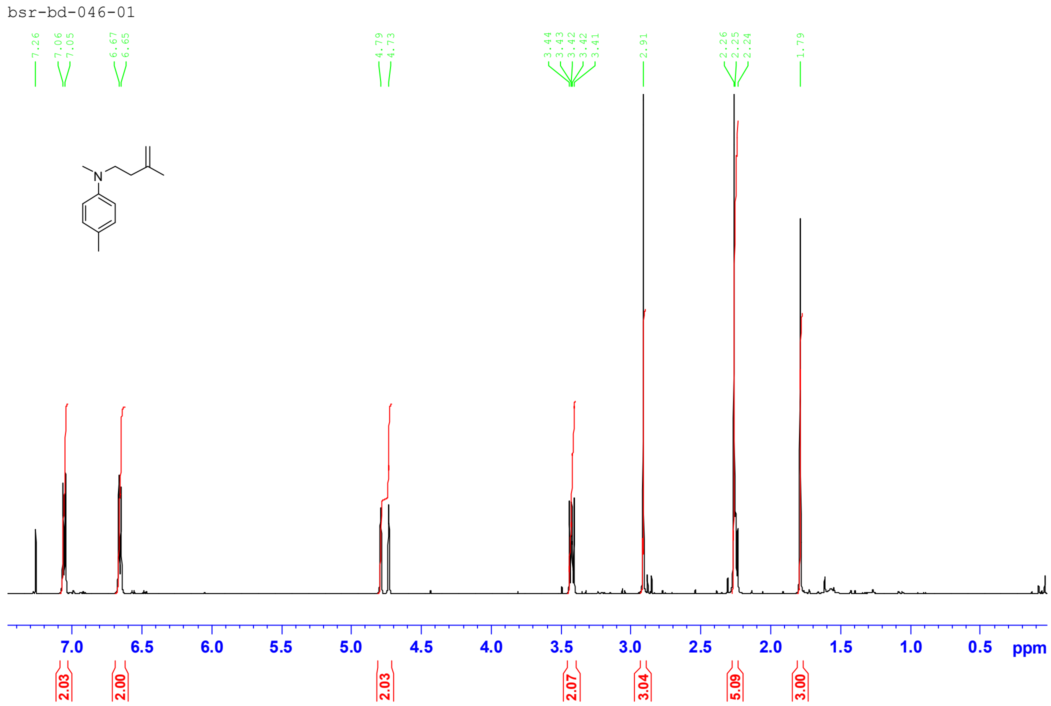


Figure S35: ^{1}H NMR in $CDCl_3$

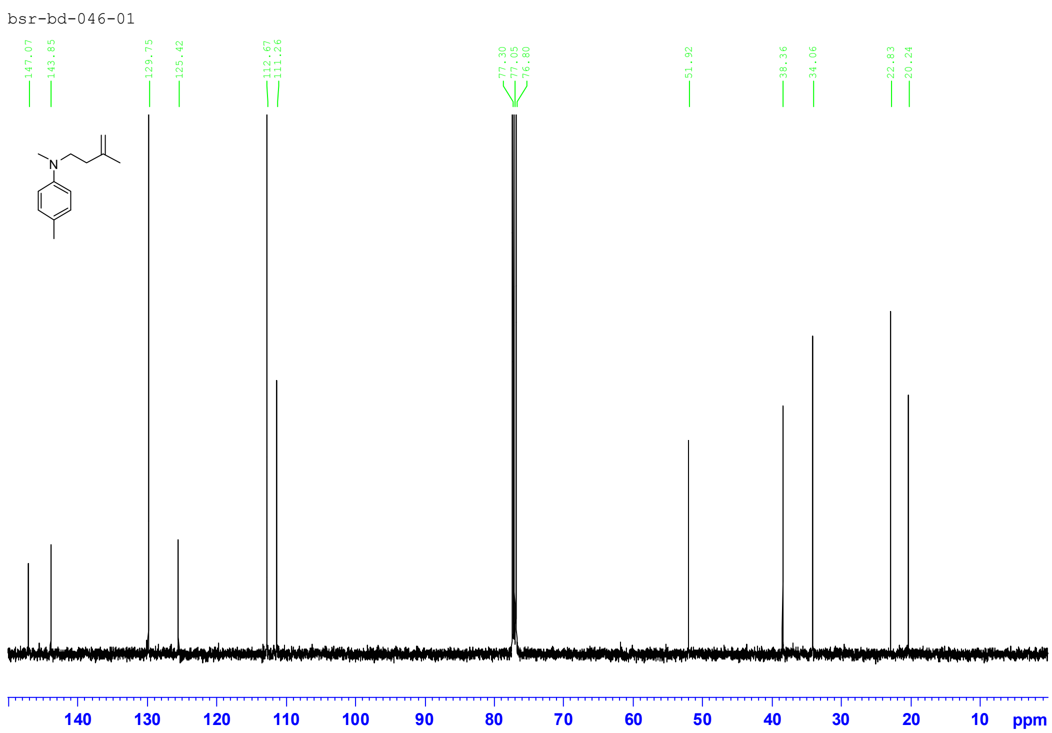


Figure S36: ^{13}C NMR in $CDCl_3$

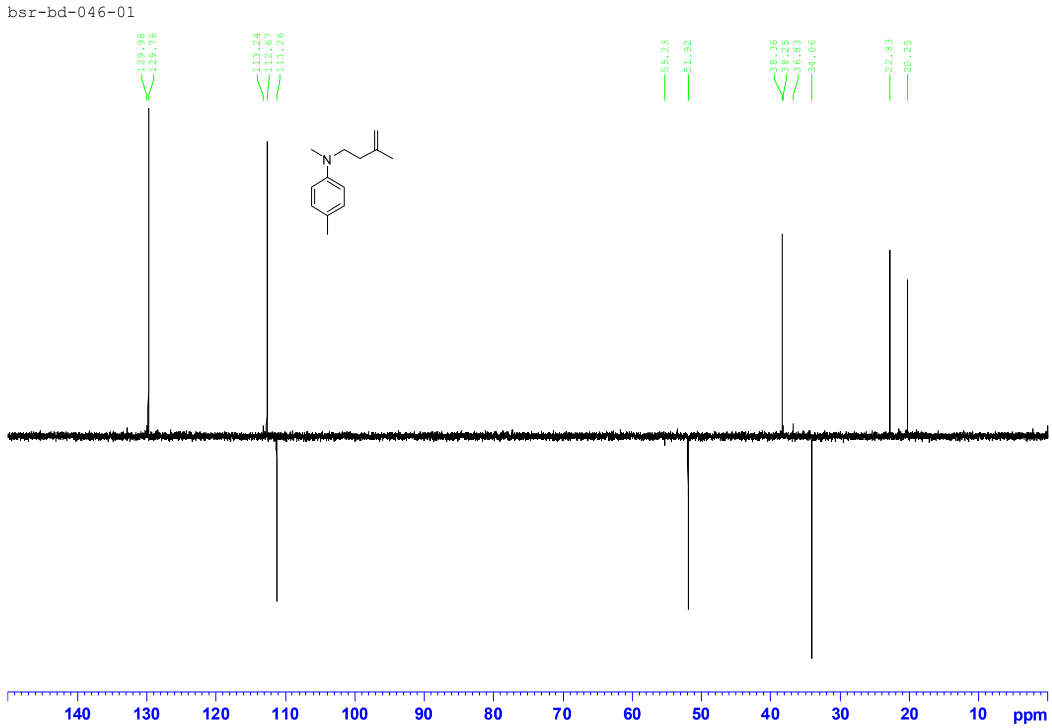


Figure S37: dept135 NMR in $CDCl_3$

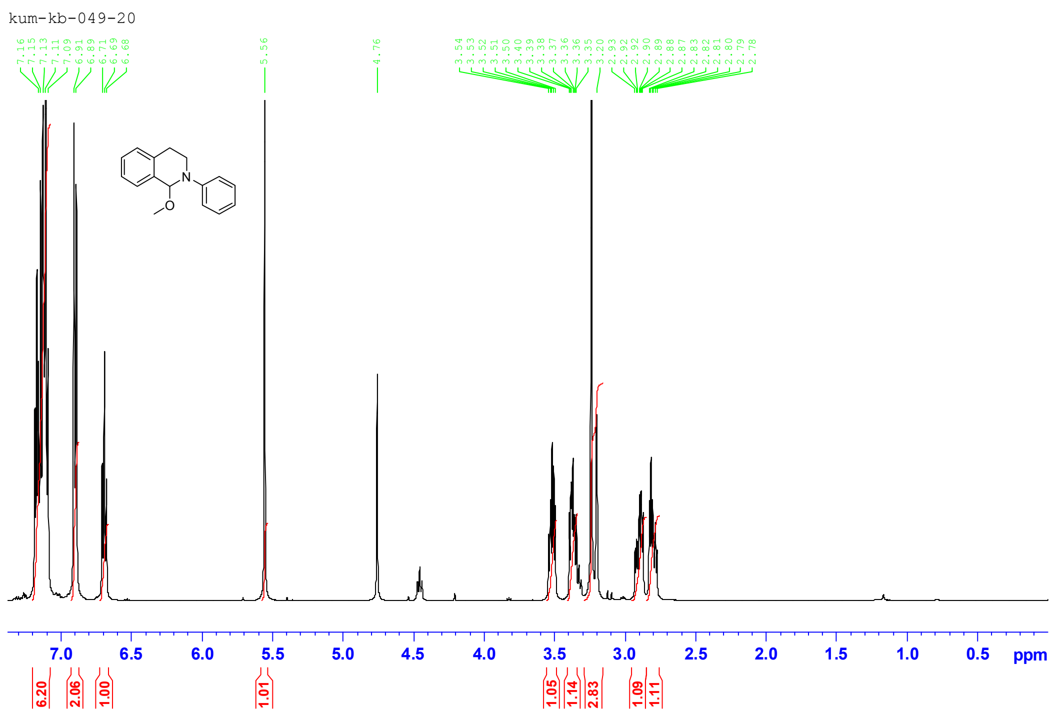


Figure S38: ^{1}H NMR in CD_3OD (crude product)

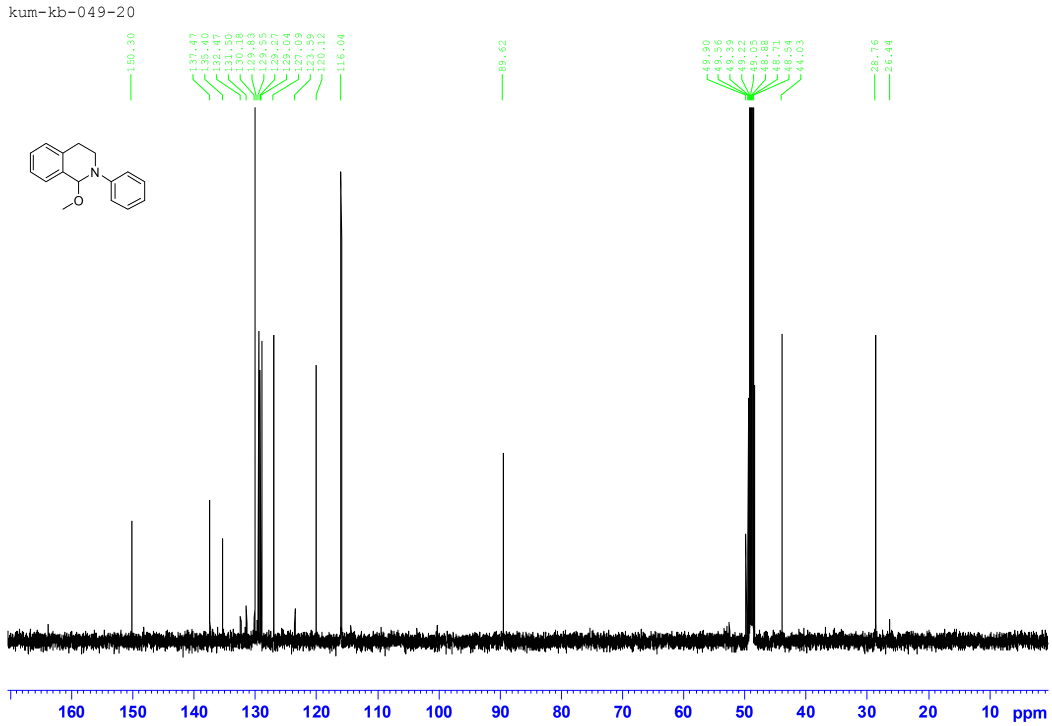


Figure S39: ^{13}C NMR in CD_3OD (crude product)

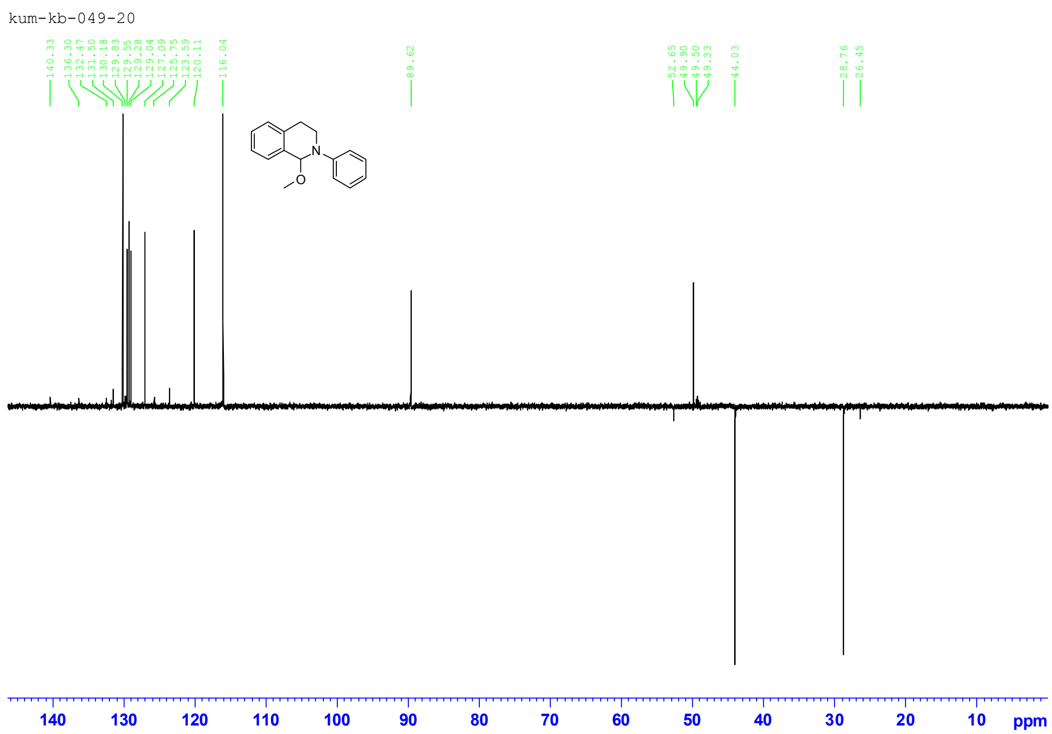


Figure S40: dept135 NMR in CD_3OD (crude product)

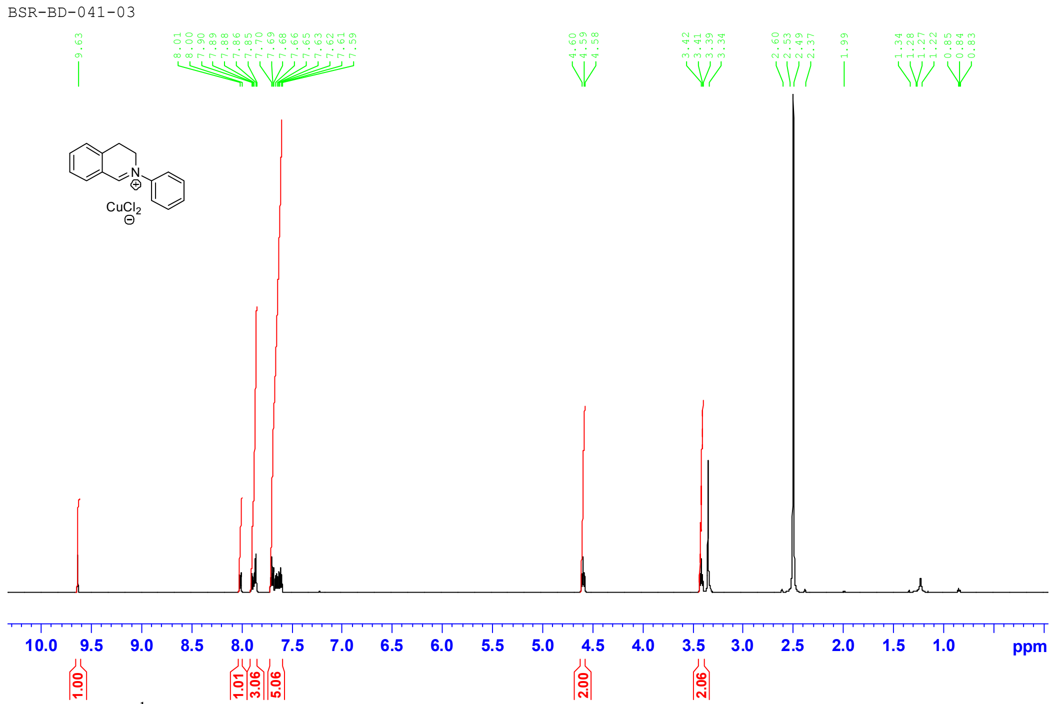


Figure S41: ^{1}H NMR in DMSO

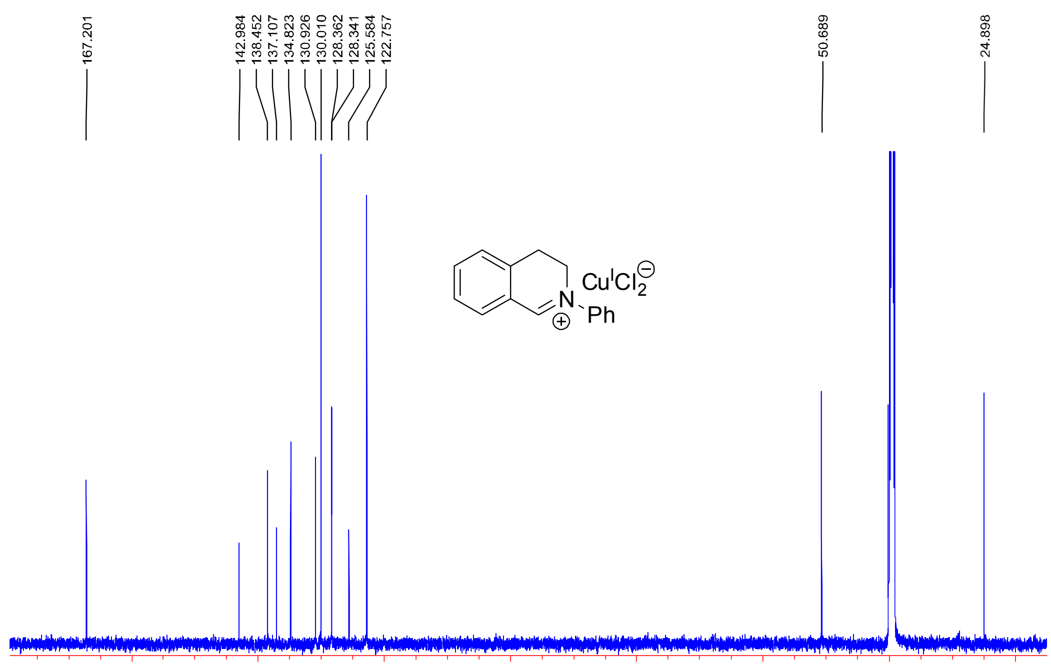


Figure S42: ^{13}C NMR in DMSO

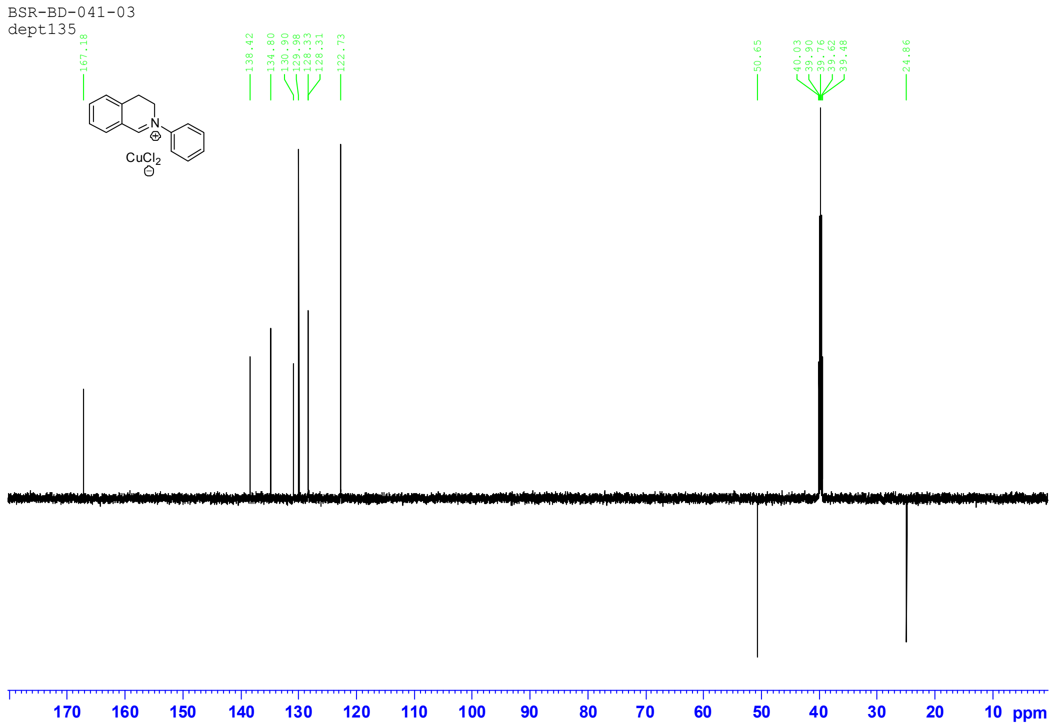


Figure S43: dept135 NMR in DMSO

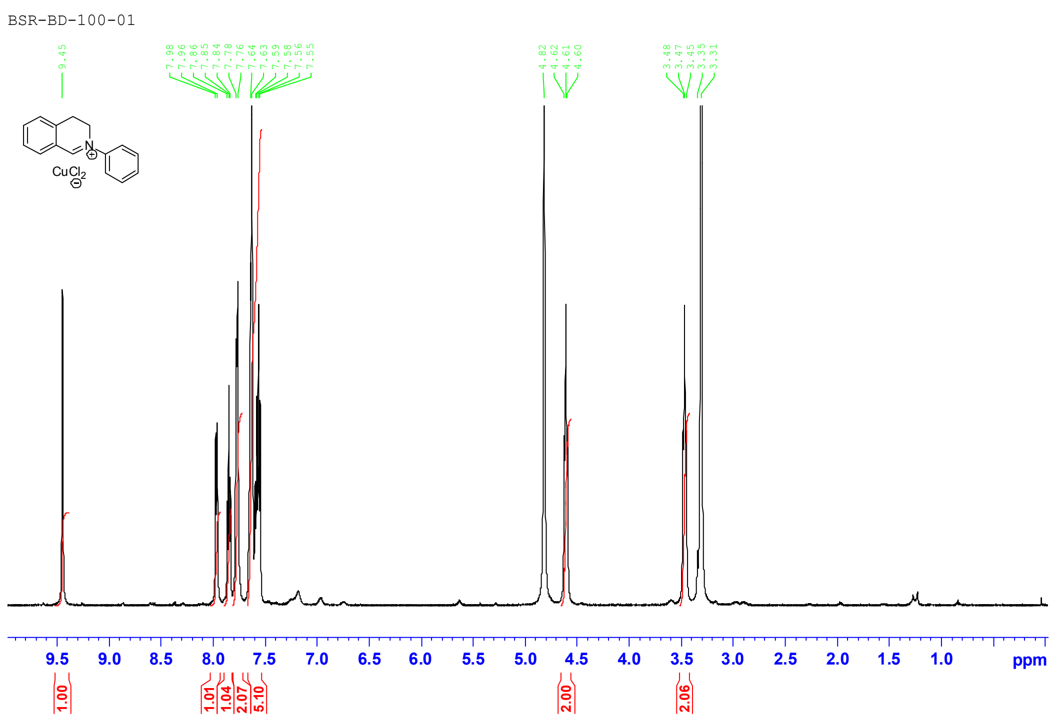


Figure 44: ^1H NMR in MeOH-d_4

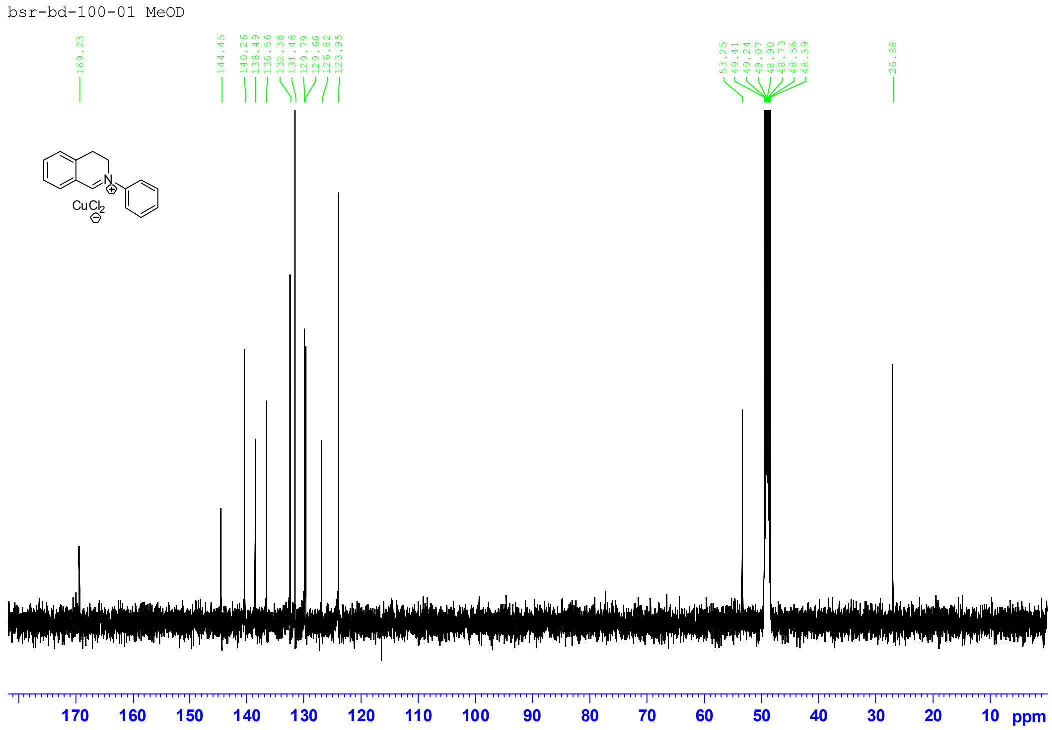


Figure 45: ^{13}C NMR in MeOH-d_4

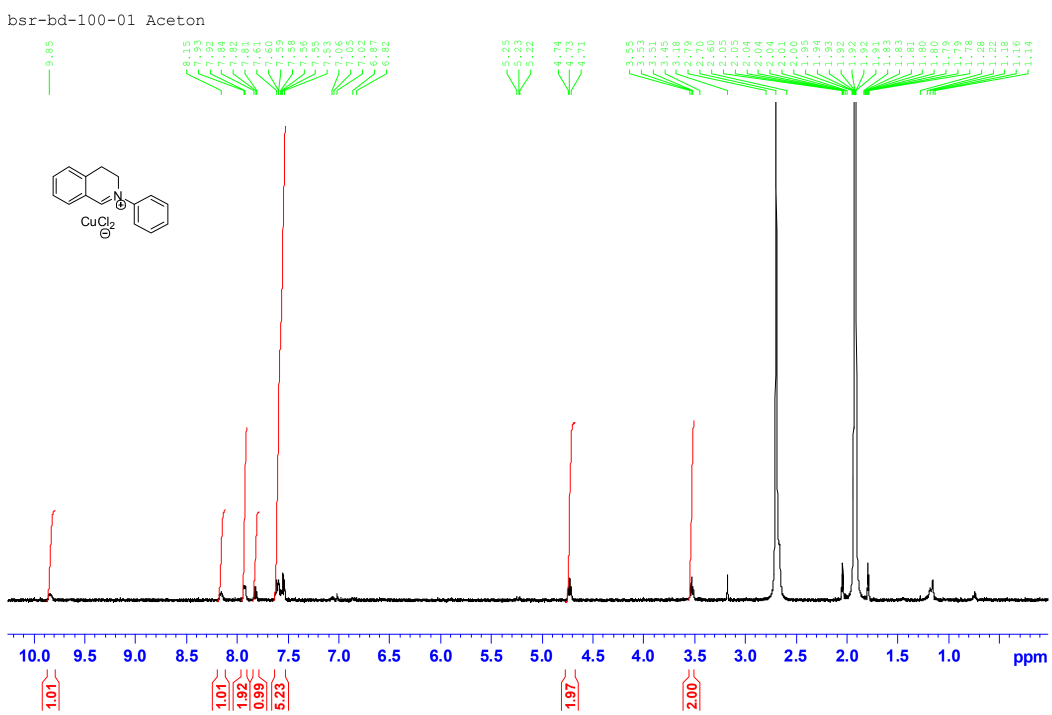
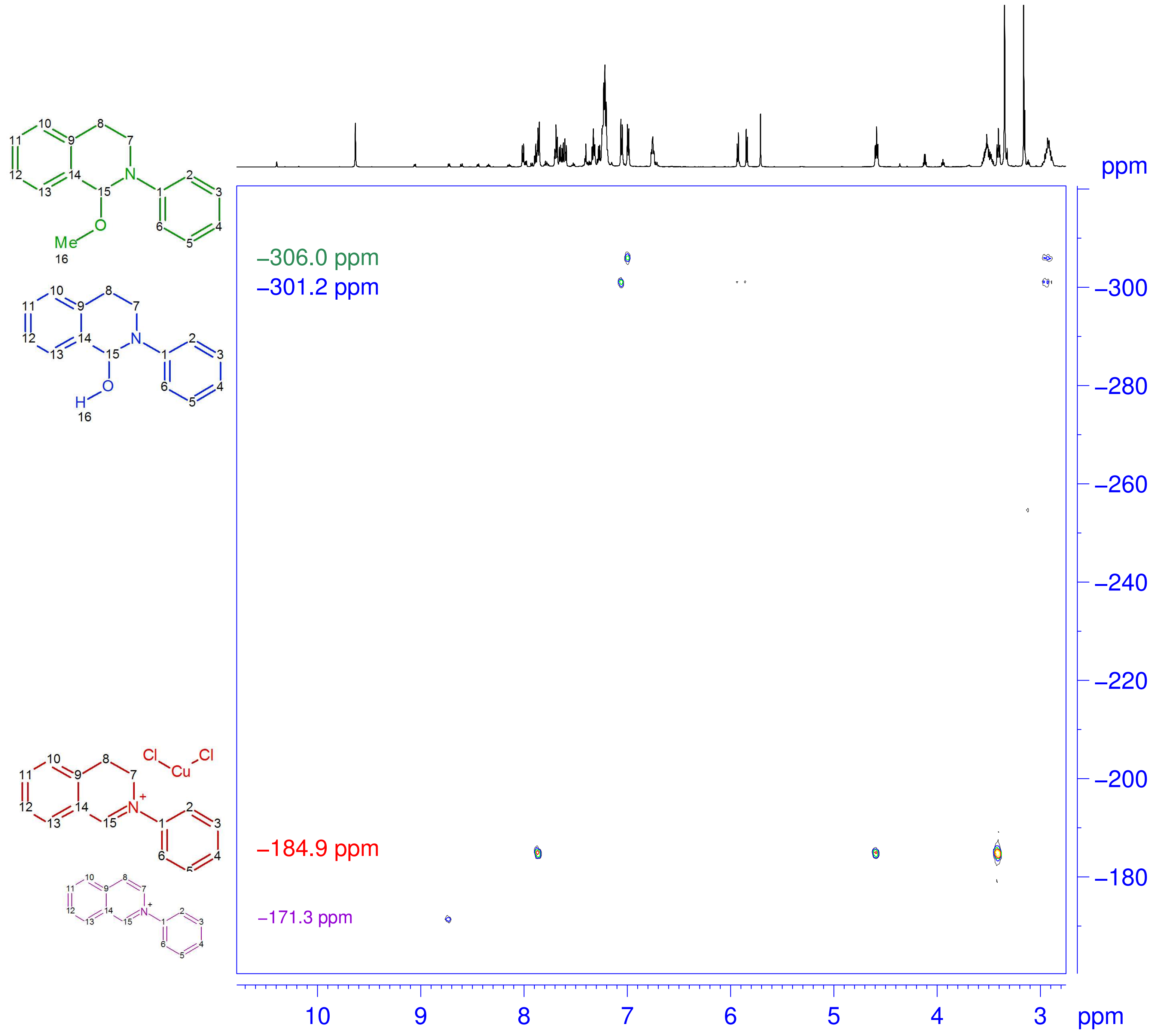


Figure 46: ^{1}H NMR in Aceton-d_6 (saturated solution).

Appendix: assignment of NMR peaks

- ^{15}N via ^{1}H HMBC of the 3:1 reaction mixture.
- Full assignment of ^{1}H- and ^{13}C-NMR peaks of components **4**-**7** in the 3:1 reaction mixture.

N614837



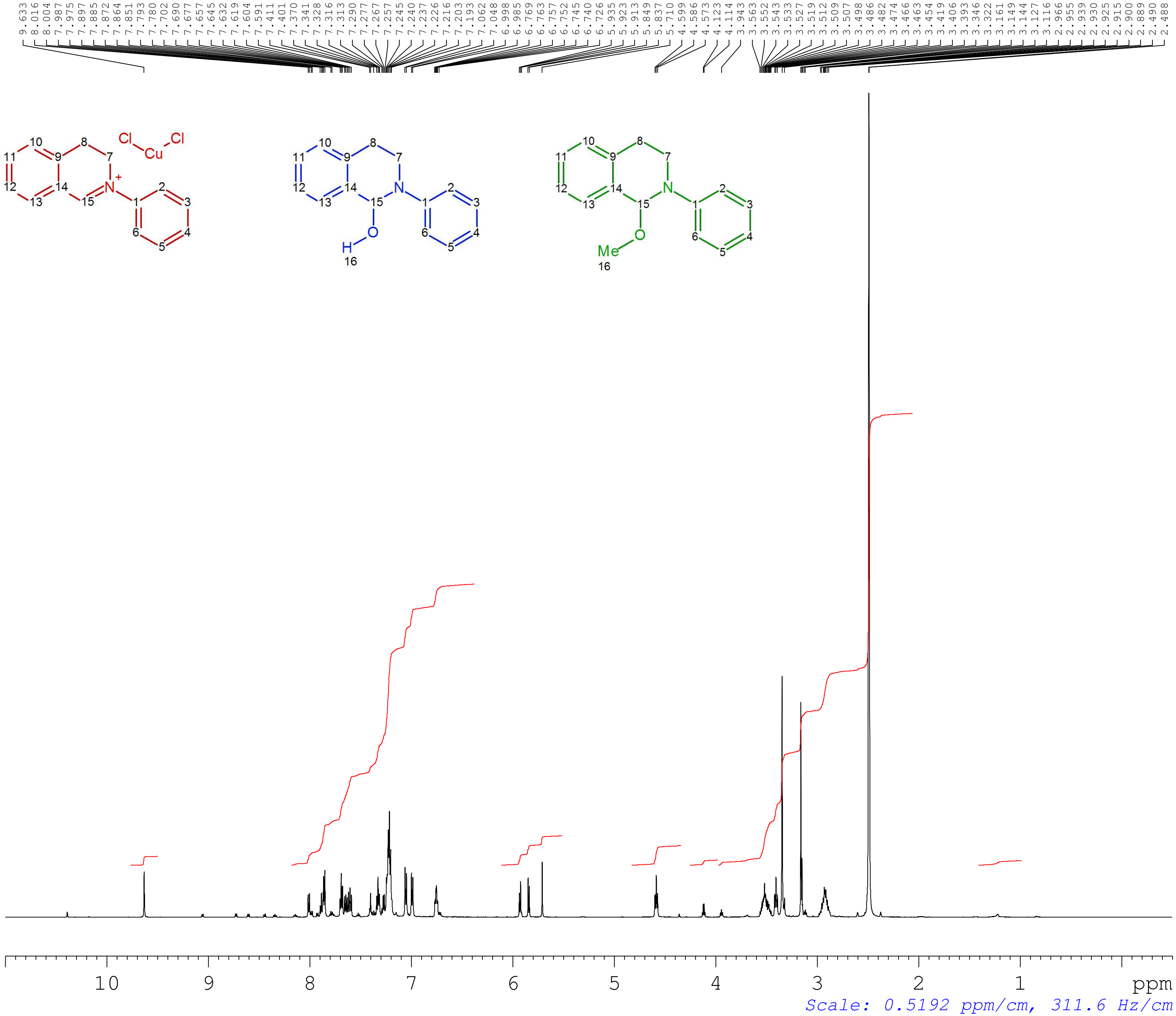

```
NAME        bsrbd04901
EXPNO              152
PROCNO               1
Date_         20110121
Time             11.43
INSTRUM          av600
PROBHD   5 mm CPTCI 1H–
PULPROG  hmbcf3gpndqf_wz
TD                1024
SOLVENT           DMSO
NS                  64
DS                  16
SWH         5281.690 Hz
FIDRES      5.157900 Hz
AQ         0.0969887 sec
RG                 512
DW          94.667 usec
DE            6.50 usec
TE             290.5 K
CNST13      10.0000000
D0      0.00000300 sec
D1      3.59999990 sec
D6      0.05000000 sec
D16     0.00020000 sec
IN0     0.00001175 sec

======== CHANNEL f1 ========
NUC1                1H
P1           8.50 usec
P2          17.00 usec
PL1            4.20 dB
PL1W      5.30020905 W
SFO1    600.2238570 MHz

======== CHANNEL f3 ========
NUC3               15N
P21         34.00 usec
PL3           -3.00 dB
PL3W    121.78849792 W
SFO3     60.8337636 MHz

====== GRADIENT CHANNEL =====
GPNAM1        SINE.100
GPNAM2        SINE.100
GPNAM3        SINE.100
GPZ1           70.00 %
GPZ2           30.00 %
GPZ3           50.10 %
P16       1000.00 usec
ND0                  2
TD                1024
SFO1      60.83376 MHz
FIDRES    41.585579 Hz
SW         700.000 ppm
FnMODE              QF
SI                1024
SF     600.2200028 MHz
WDW              QSINE
SSB                  2
LB             0.00 Hz
GB                   0
PC                1.40
SI                1024
MC2                 QF
SF      60.8428780 MHz
WDW              QSINE
SSB                  2
LB             0.00 Hz
GB                   0
```

ext. Standard
90 % CH3NO2 in CDCl3 = 0 ppm

BSR–BD–049–01
15N via 1H
HMBC nJ(NH)=10 Hz

DMX–600

H614831



NAME	bsrbd04901
EXPNO	10
PROCNO	1
Date_	20110117
Time	16.20
INSTRUM	av600
PROBHD	5 mm CPTCI 1H-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	32
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	8
DW	41.600 usec
DE	10.00 usec
TE	290.5 K
D1	1.00000000 sec
TD0	1

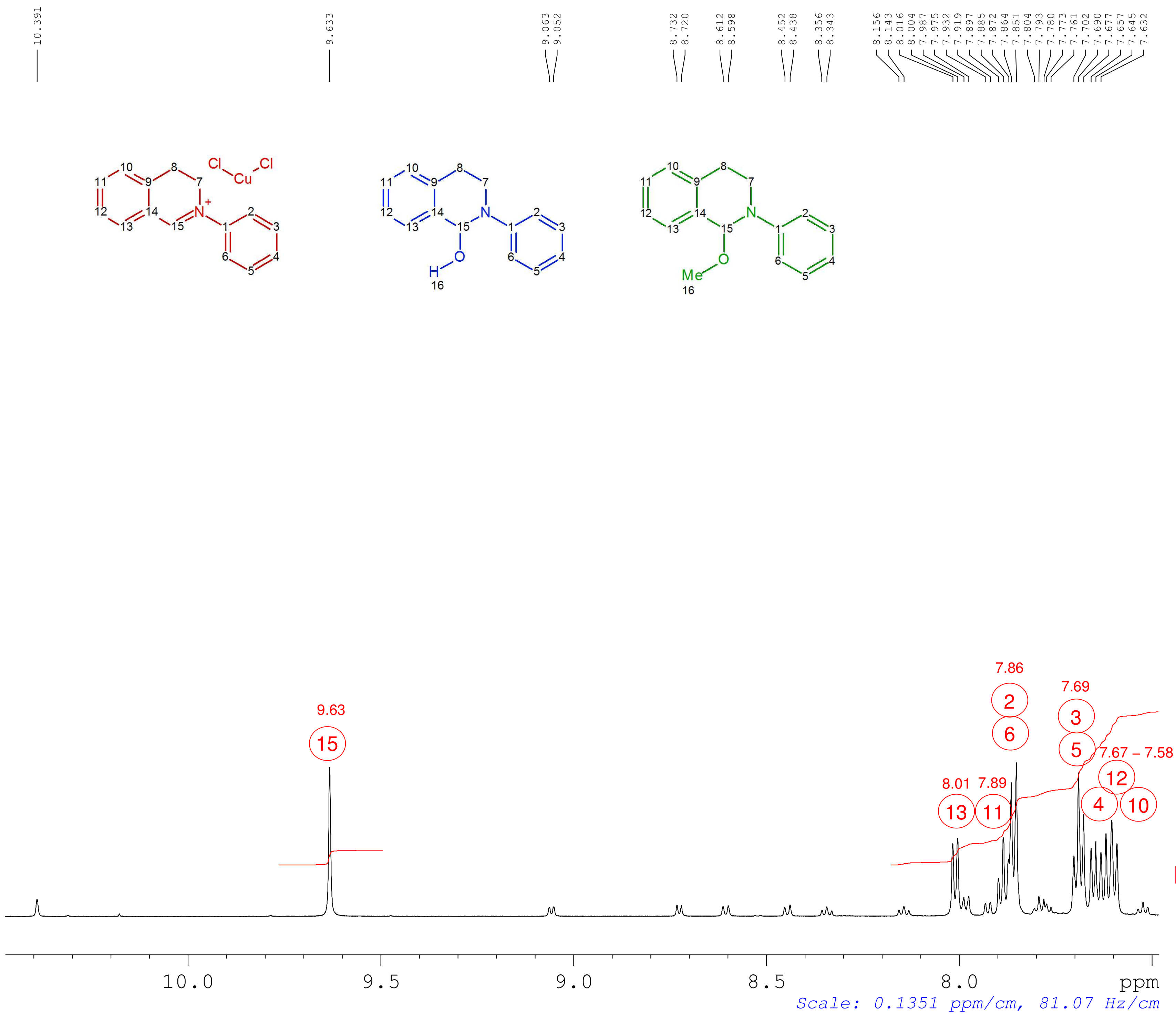
======== CHANNEL f1 ========

NUC1	1H
P1	8.50 usec
PL1	4.20 dB
PL1W	5.30020905 W
SFO1	600.2234813 MHz
SI	65536
SF	600.2200069 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

BSR–BD–049–01

av600

H614831



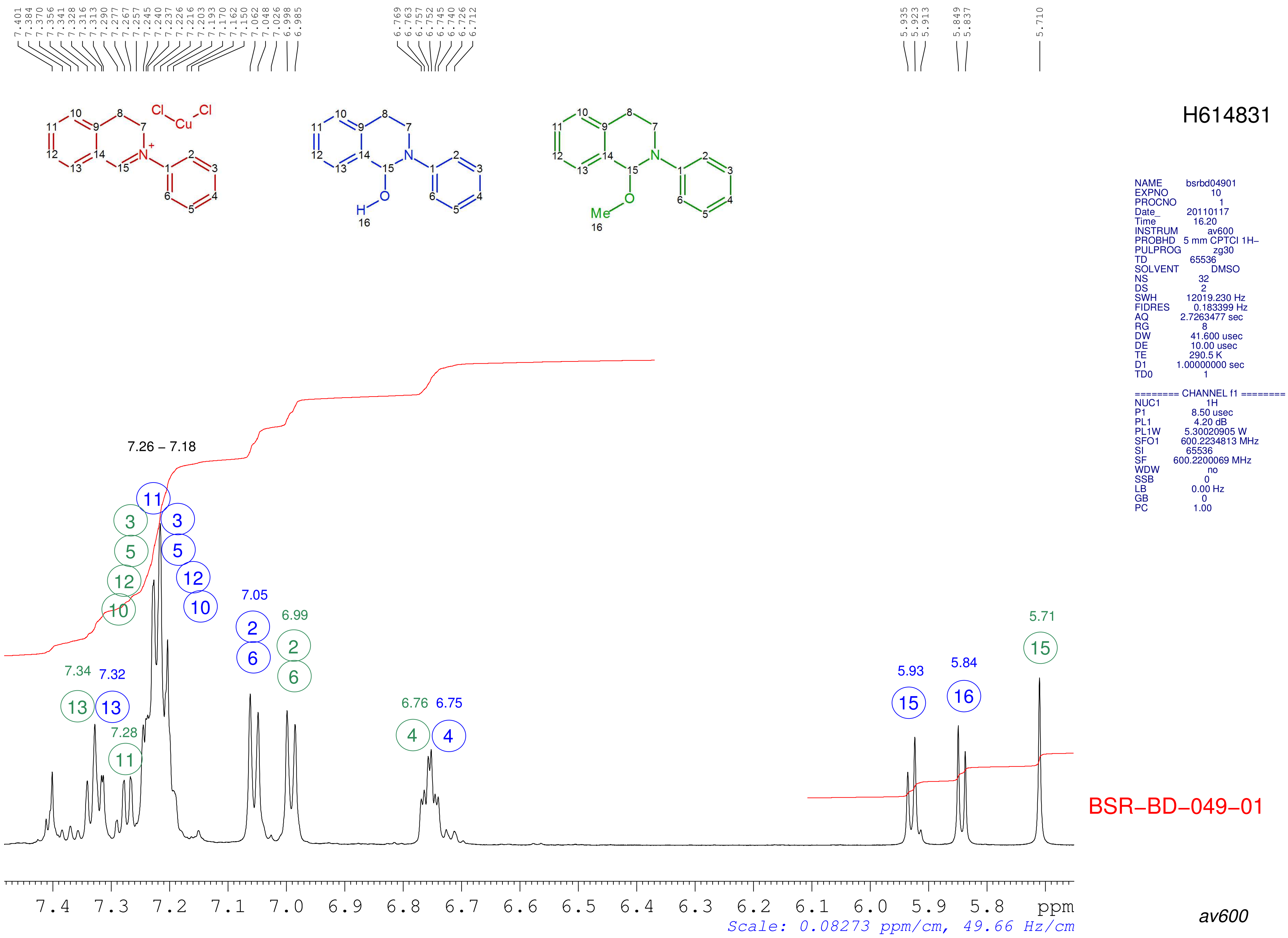
BSR–BD–049–01

NAME	bsrbd04901
EXPNO	10
PROCNO	1
Date_	20110117
Time	16.20
INSTRUM	av600
PROBHD	5 mm CPTCI 1H-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	32
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	8
DW	41.600 usec
DE	10.00 usec
TE	290.5 K
D1	1.00000000 sec
TD0	1

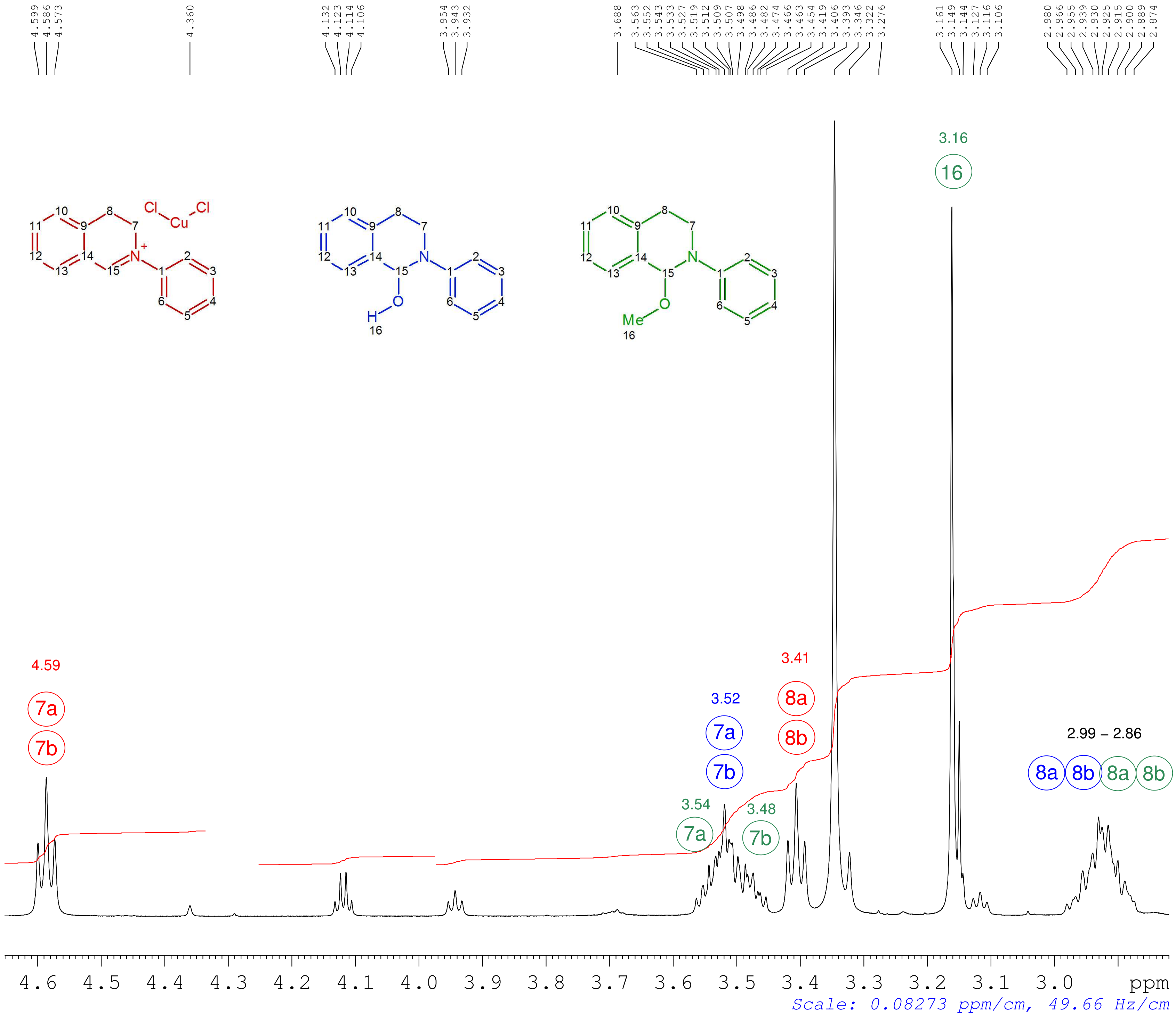
======== CHANNEL f1 ========

NUC1	1H
P1	8.50 usec
PL1	4.20 dB
PL1W	5.30020905 W
SFO1	600.2234813 MHz
SI	65536
SF	600.2200069 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

av600


7.401 7.384 7.370 7.356 7.341 7.328 7.316 7.313 7.290 7.277 7.267 7.257 7.245 7.240 7.237 7.226 7.216 7.203 7.193 7.170 7.162 7.150 7.062 7.048 7.026 6.998 6.985
6.769 6.763 6.757 6.752 6.745 6.740 6.726 6.712
5.935 5.923 5.913 5.849 5.837 5.710
H614831
NAME bsrbd04901
EXPNO 10
PROCNO 1
Date_ 20110117
Time 16.20
INSTRUM av600
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 8
DW 41.600 usec
DE 10.00 usec
TE 290.5 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.50 usec
PL1 4.20 dB
PL1W 5.30020905 W
SFO1 600.2234813 MHz
SI 65536
SF 600.2200069 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
7.26 – 7.18
7.05
6.99
7.34
7.32
7.28
6.76
6.75
5.93
5.84
5.71
BSR–BD–049–01
7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 ppm
Scale: 0.08273 ppm/cm, 49.66 Hz/cm
av600

H614831



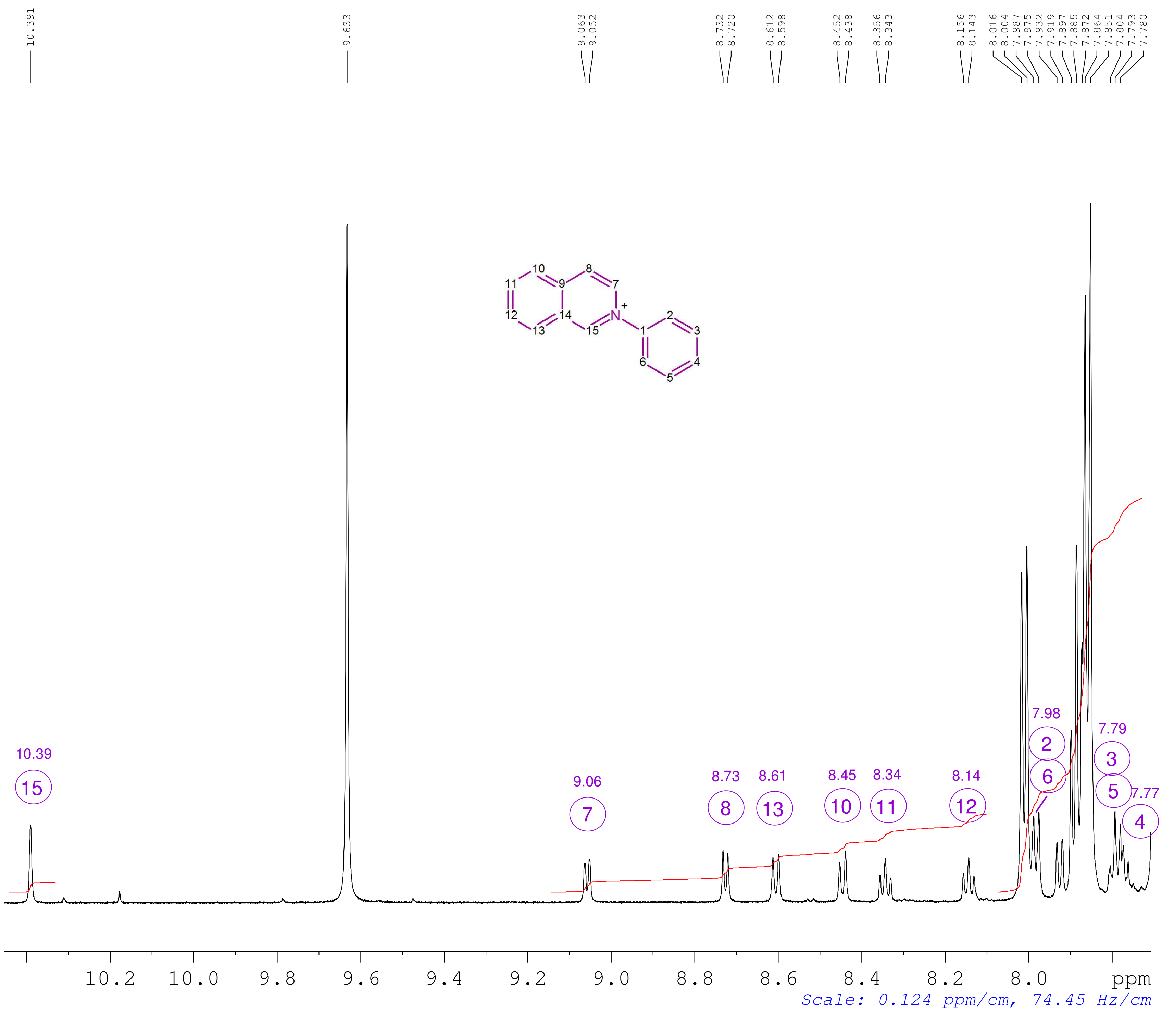
NAME bsrbd04901
EXPNO 10
PROCNO 1
Date_ 20110117
Time 16.20
INSTRUM av600
PROBHD 5 mm CPTCI 1H–
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 8
DW 41.600 usec
DE 10.00 usec
TE 290.5 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 8.50 usec
PL1 4.20 dB
PL1W 5.30020905 W
SFO1 600.2234813 MHz
SI 65536
SF 600.2200069 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

BSR–BD–049–01

av600

H614831



NAME	bsrbd04901
EXPNO	10
PROCNO	1
Date_	20110117
Time	16.20
INSTRUM	av600
PROBHD	5 mm CPTCI 1H-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	32
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	8
DW	41.600 usec
DE	10.00 usec
TE	290.5 K
D1	1.00000000 sec
TD0	1

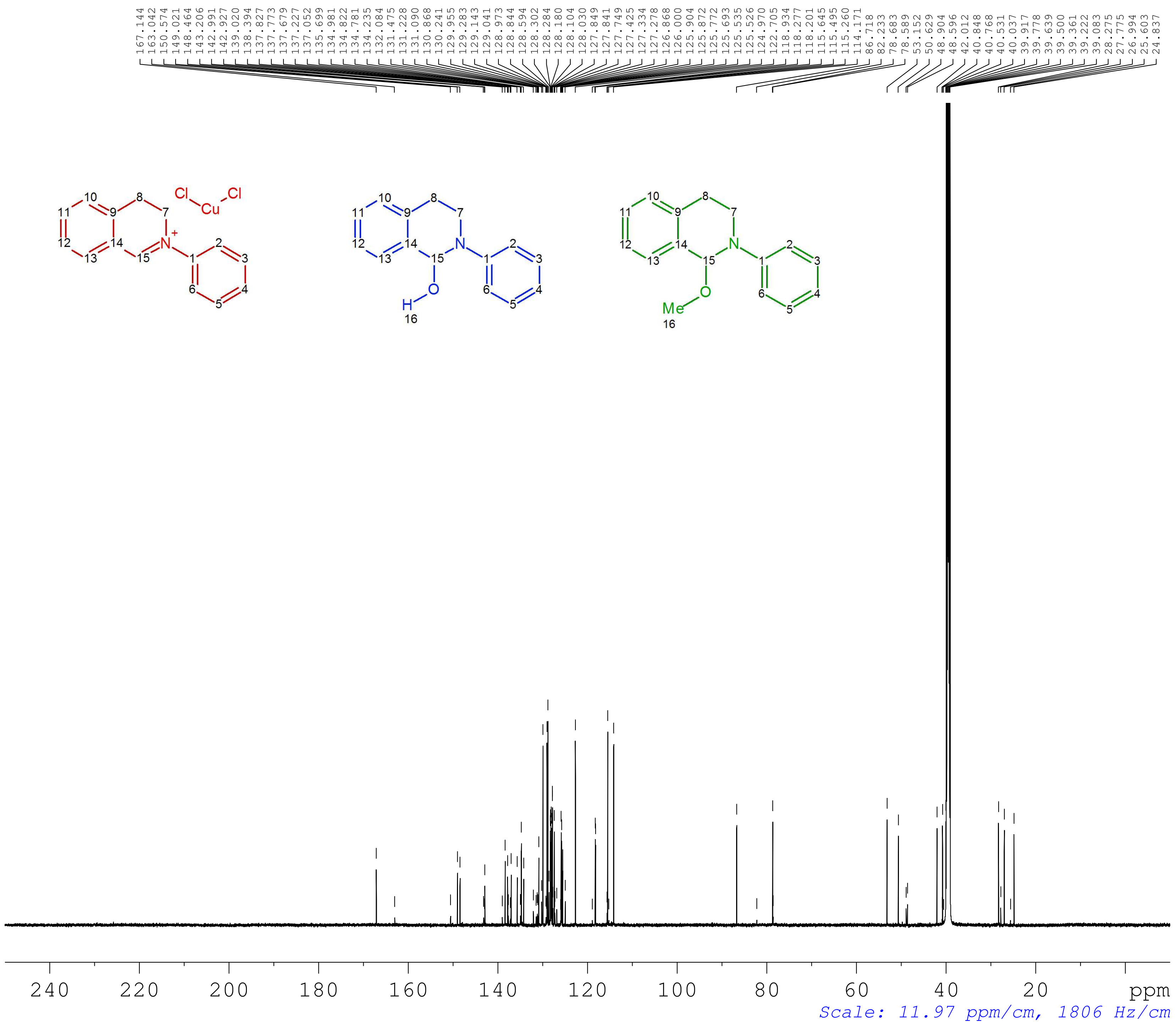
======== CHANNEL f1 ========

NUC1	1H
P1	8.50 usec
PL1	4.20 dB
PL1W	5.30020905 W
SFO1	600.2234813 MHz
SI	65536
SF	600.2200069 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

BSR-BD-049-01

av600

C614832



NAME bsrbd04901
EXPNO 11
PROCNO 1
Date_ 20110118
Time 12.12
INSTRUM av600
PROBHD 5 mm CPTCI 1H–
PULPROG zgdc30
TD 90904
SOLVENT DMSO
NS 4000
DS 128
SWH 45454.547 Hz
FIDRES 0.500028 Hz
AQ 0.9999940 sec
RG 512
DW 11.000 usec
DE 50.78 usec
TE 290.5 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 1

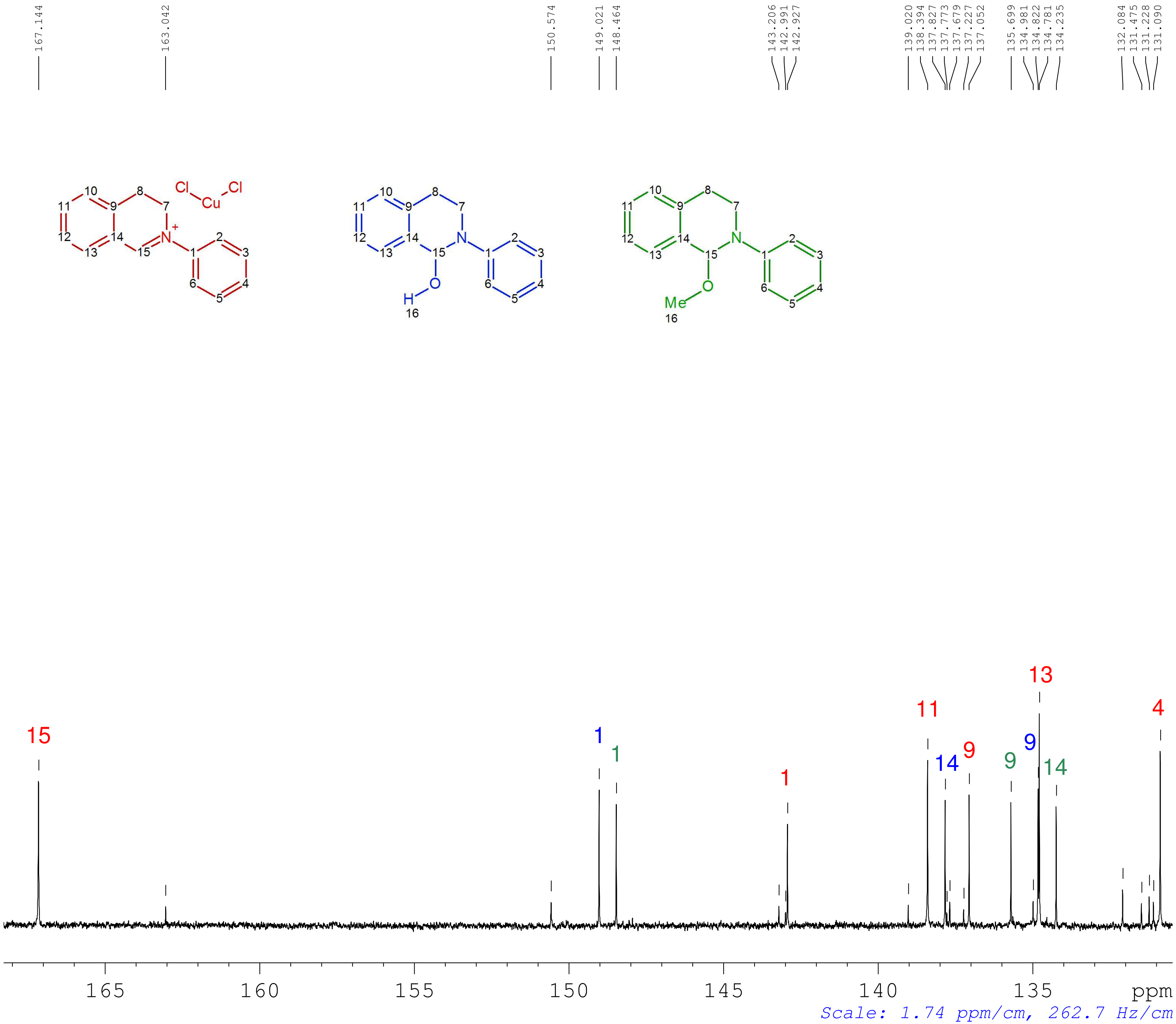
======== CHANNEL f1 ========
NUC1 13C
P1 11.00 usec
PL1 −1.00 dB
PL1W 109.73103333 W
SFO1 150.9405316 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz65
NUC2 1H
PCPD2 70.00 usec
PL2 4.20 dB
PL12 22.51 dB
PL2W 5.30020905 W
PL12W 0.07821552 W
SFO2 600.2224009 MHz
SI 131072
SF 150.9255099 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

BSR–BD–049–01

av600

C614832



NAME bsrbd04901
EXPNO 11
PROCNO 1
Date_ 20110118
Time 12.12
INSTRUM av600
PROBHD 5 mm CPTCI 1H-
PULPROG zgdc30
TD 90904
SOLVENT DMSO
NS 4000
DS 128
SWH 45454.547 Hz
FIDRES 0.500028 Hz
AQ 0.9999940 sec
RG 512
DW 11.000 usec
DE 50.78 usec
TE 290.5 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 1

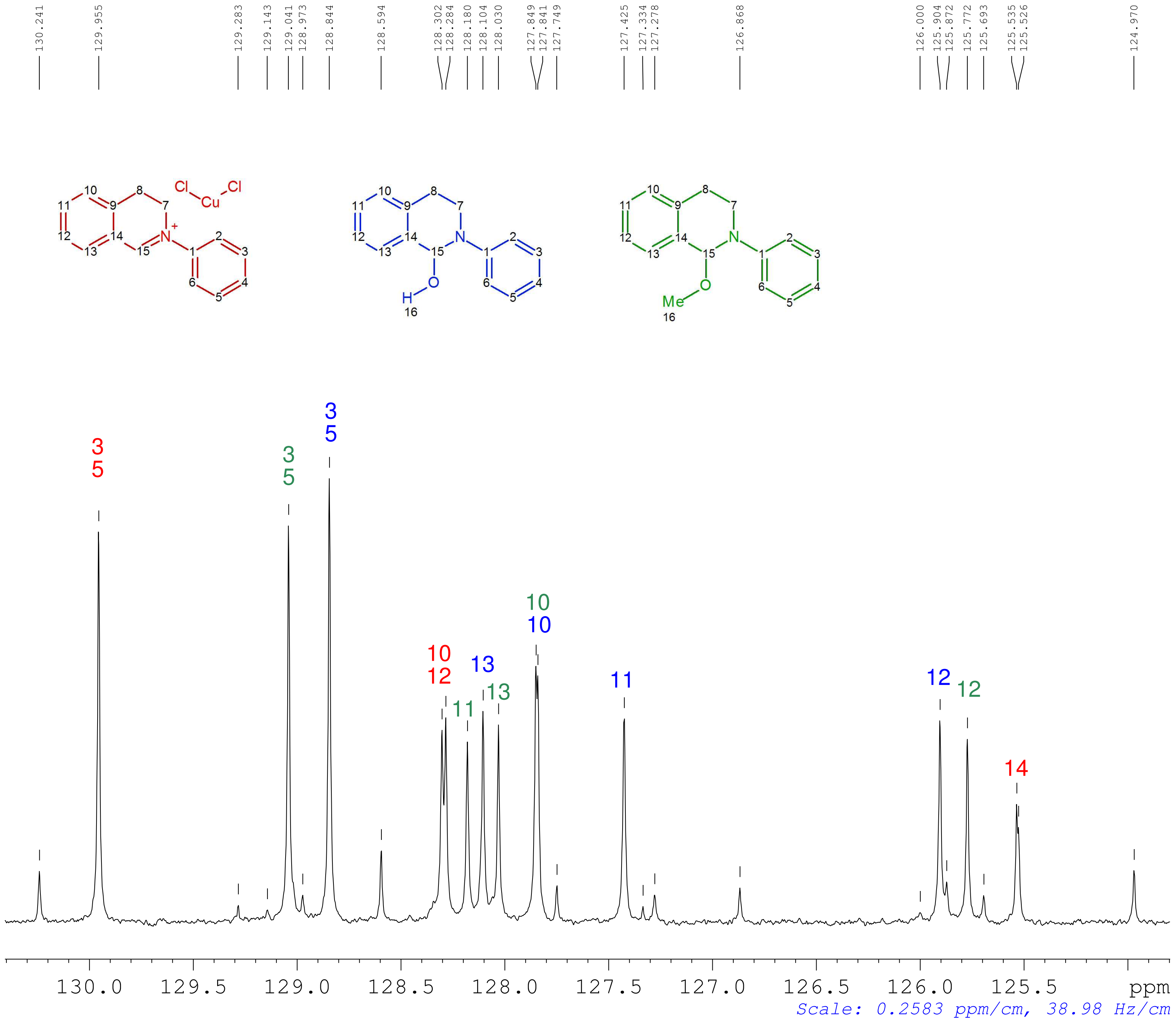
======== CHANNEL f1 ========
NUC1 13C
P1 11.00 usec
PL1 -1.00 dB
PL1W 109.73103333 W
SFO1 150.9405316 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz65
NUC2 1H
PCPD2 70.00 usec
PL2 4.20 dB
PL12 22.51 dB
PL2W 5.30020905 W
PL12W 0.07821552 W
SFO2 600.2224009 MHz
SI 131072
SF 150.9255099 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

BSR-BD-049-01

av600

C614832



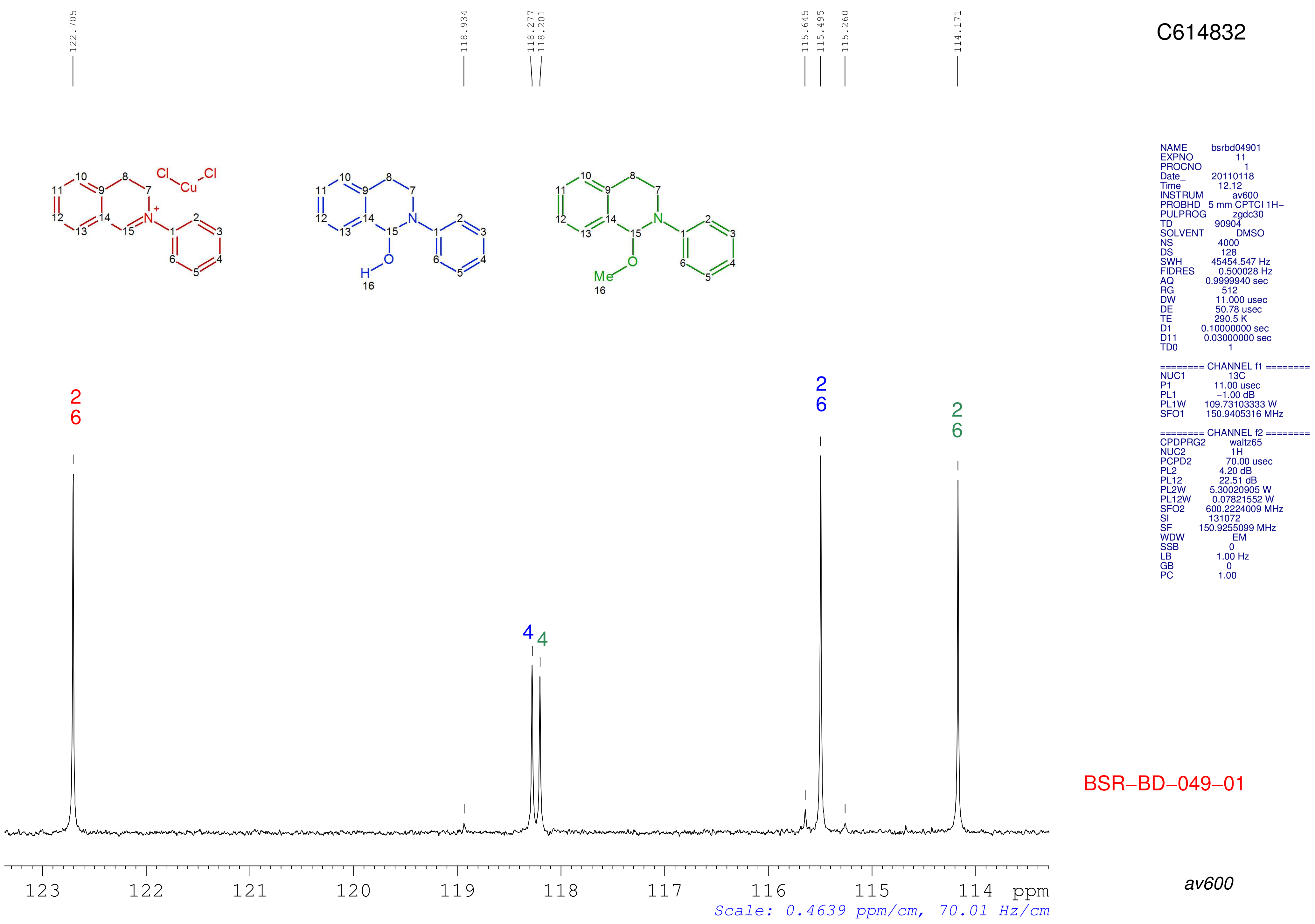
NAME bsrbd04901
EXPNO 11
PROCNO 1
Date_ 20110118
Time 12.12
INSTRUM av600
PROBHD 5 mm CPTCI 1H–
PULPROG zgdc30
TD 90904
SOLVENT DMSO
NS 4000
DS 128
SWH 45454.547 Hz
FIDRES 0.500028 Hz
AQ 0.9999940 sec
RG 512
DW 11.000 usec
DE 50.78 usec
TE 290.5 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 11.00 usec
PL1 –1.00 dB
PL1W 109.73103333 W
SFO1 150.9405316 MHz

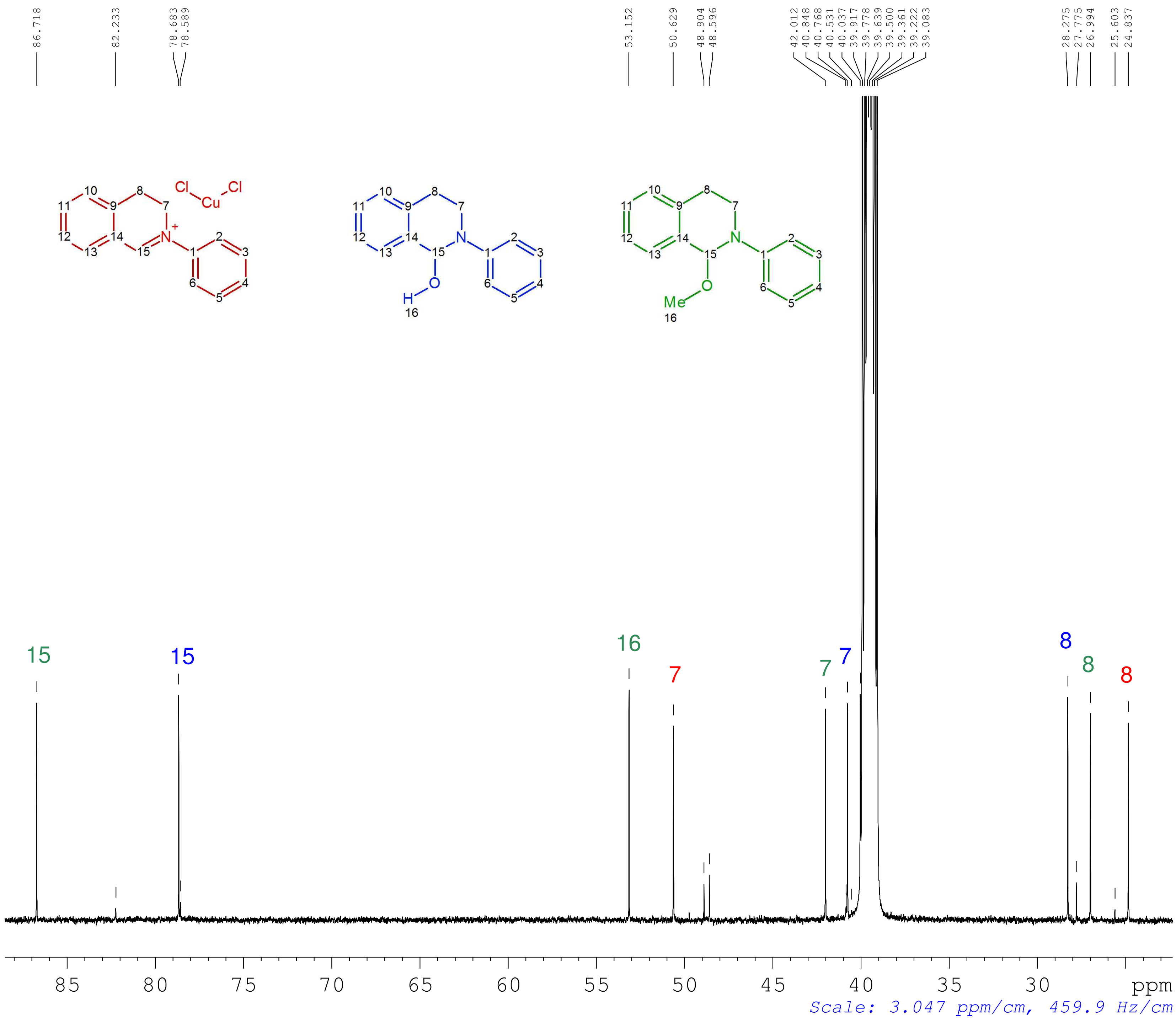
======== CHANNEL f2 ========
CPDPRG2 waltz65
NUC2 1H
PCPD2 70.00 usec
PL2 4.20 dB
PL12 22.51 dB
PL2W 5.30020905 W
PL12W 0.07821552 W
SFO2 600.2224009 MHz
SI 131072
SF 150.9255099 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

BSR–BD–049–01

av600


C614832
122.705
118.934
118.277
118.201
115.645
115.495
115.260
114.171
Cl
Cu
Cl
N+
OH
16
N
O
Me
16
N
2
6
4
4
2
6
2
6
NAME bsrbd04901
EXPNO 11
PROCNO 1
Date_ 20110118
Time 12.12
INSTRUM av600
PROBHD 5 mm CPTCI 1H–
PULPROG zgdc30
TD 90904
SOLVENT DMSO
NS 4000
DS 128
SWH 45454.547 Hz
FIDRES 0.500028 Hz
AQ 0.9999940 sec
RG 512
DW 11.000 usec
DE 50.78 usec
TE 290.5 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 11.00 usec
PL1 –1.00 dB
PL1W 109.73103333 W
SFO1 150.9405316 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz65
NUC2 1H
PCPD2 70.00 usec
PL2 4.20 dB
PL12 22.51 dB
PL2W 5.30020905 W
PL12W 0.07821552 W
SFO2 600.2224009 MHz
SI 131072
SF 150.9255099 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
BSR–BD–049–01
123 122 121 120 119 118 117 116 115 114 ppm
Scale: 0.4639 ppm/cm, 70.01 Hz/cm
av600

C614832



NAME bsrbd04901
EXPNO 11
PROCNO 1
Date_ 20110118
Time 12.12
INSTRUM av600
PROBHD 5 mm CPTCI 1H–
PULPROG zgdc30
TD 90904
SOLVENT DMSO
NS 4000
DS 128
SWH 45454.547 Hz
FIDRES 0.500028 Hz
AQ 0.9999940 sec
RG 512
DW 11.000 usec
DE 50.78 usec
TE 290.5 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 1

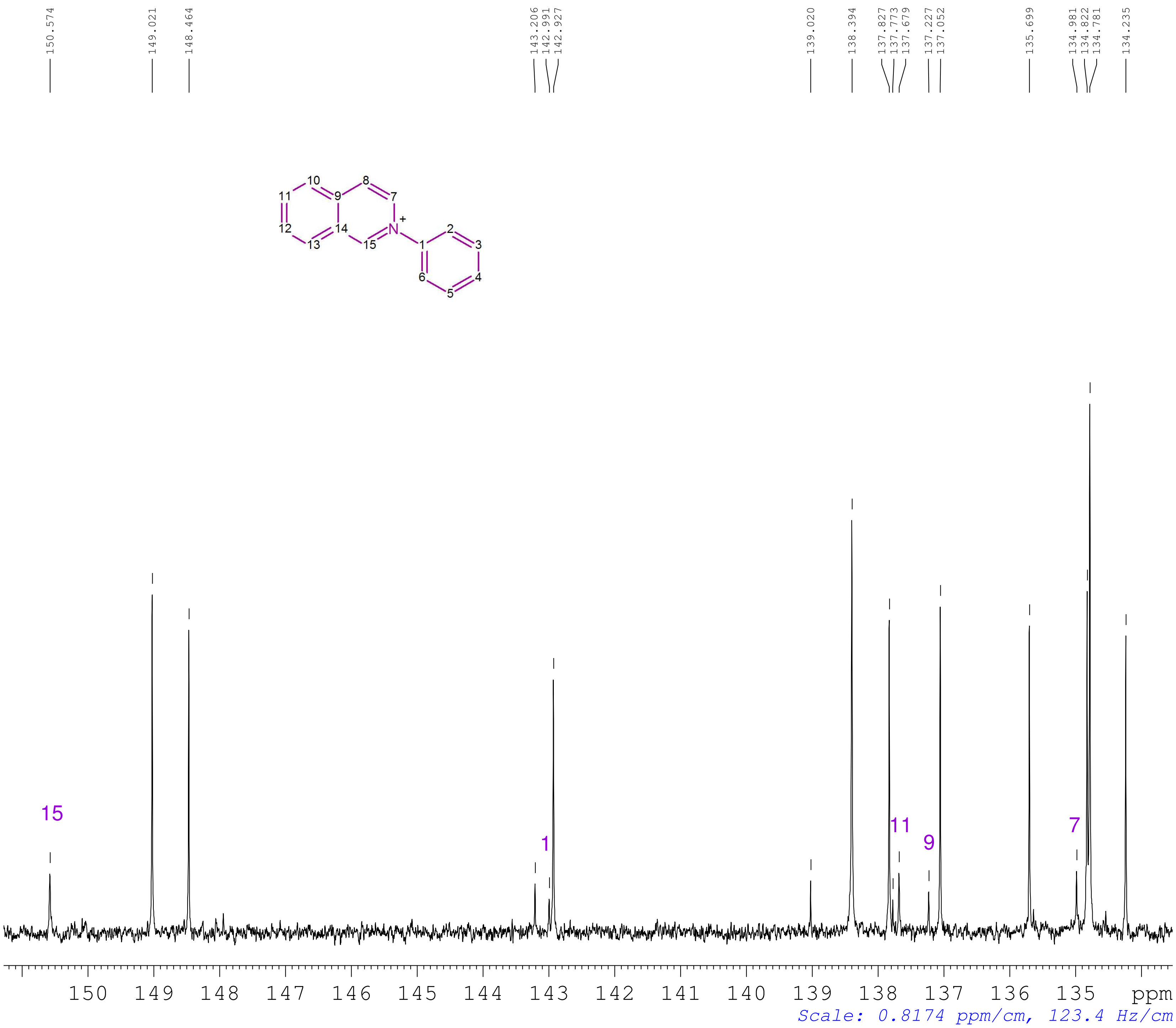
======== CHANNEL f1 ========
NUC1 13C
P1 11.00 usec
PL1 −1.00 dB
PL1W 109.73103333 W
SFO1 150.9405316 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz65
NUC2 1H
PCPD2 70.00 usec
PL2 4.20 dB
PL12 22.51 dB
PL2W 5.30020905 W
PL12W 0.07821552 W
SFO2 600.2224009 MHz
SI 131072
SF 150.9255099 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

BSR–BD–049–01

av600

C614832



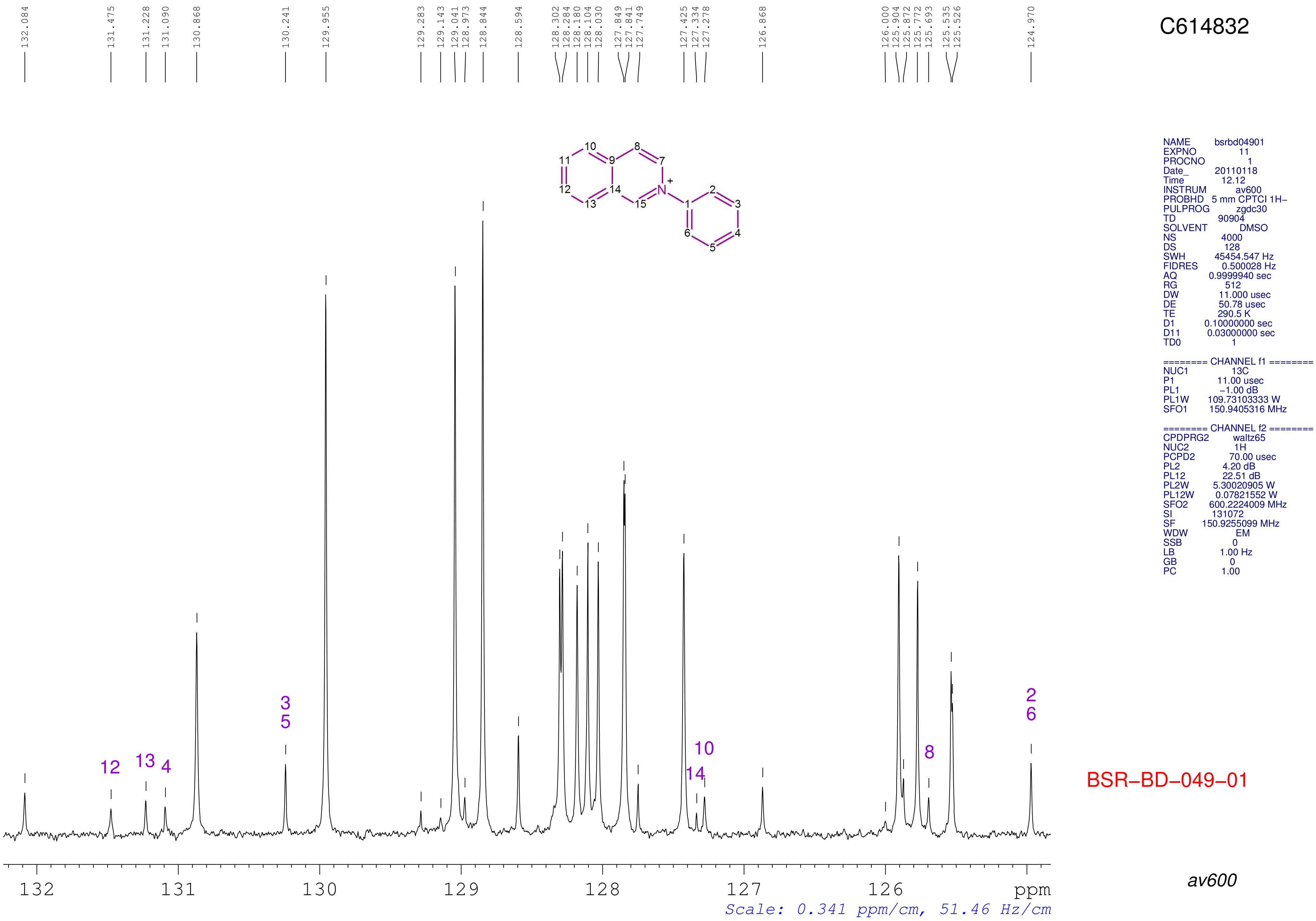
NAME bsrbd04901
EXPNO 11
PROCNO 1
Date_ 20110118
Time 12.12
INSTRUM av600
PROBHD 5 mm CPTCI 1H–
PULPROG zgdc30
TD 90904
SOLVENT DMSO
NS 4000
DS 128
SWH 45454.547 Hz
FIDRES 0.500028 Hz
AQ 0.9999940 sec
RG 512
DW 11.000 usec
DE 50.78 usec
TE 290.5 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 11.00 usec
PL1 –1.00 dB
PL1W 109.73103333 W
SFO1 150.9405316 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz65
NUC2 1H
PCPD2 70.00 usec
PL2 4.20 dB
PL12 22.51 dB
PL2W 5.30020905 W
PL12W 0.07821552 W
SFO2 600.2224009 MHz
SI 131072
SF 150.9255099 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00

BSR–BD–049–01

av600


C614832
132.084
131.475
131.228
131.090
130.868
130.241
129.955
129.283
129.143
129.041
128.973
128.844
128.594
128.302
128.284
128.180
128.104
128.030
127.849
127.841
127.749
127.425
127.334
127.278
126.868
126.000
125.904
125.872
125.772
125.693
125.535
125.526
124.970
NAME bsrbd04901
EXPNO 11
PROCNO 1
Date_ 20110118
Time 12.12
INSTRUM av600
PROBHD 5 mm CPTCI 1H–
PULPROG zgdc30
TD 90904
SOLVENT DMSO
NS 4000
DS 128
SWH 45454.547 Hz
FIDRES 0.500028 Hz
AQ 0.9999940 sec
RG 512
DW 11.000 usec
DE 50.78 usec
TE 290.5 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 11.00 usec
PL1 –1.00 dB
PL1W 109.73103333 W
SFO1 150.9405316 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz65
NUC2 1H
PCPD2 70.00 usec
PL2 4.20 dB
PL12 22.51 dB
PL2W 5.30020905 W
PL12W 0.07821552 W
SFO2 600.2224009 MHz
SI 131072
SF 150.9255099 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
12
13
4
3
5
10
14
8
2
6
BSR–BD–049–01
av600
132
131
130
129
128
127
126
ppm
Scale: 0.341 ppm/cm, 51.46 Hz/cm