

Supporting Information

***Para*-Selective Halogenation of Nitrosoarenes with Copper(II) Halides**

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1. General Information

All reactions were carried out under air unless otherwise stated. Nitrosobenzene derivatives **1c-1o** were prepared according to literature procedures using commercial reagents (Section 2). All other starting materials and solvents were purchased from commercial suppliers. NCS and NBS were recrystallized from water. All other reagents were used as received (CuCl₂ (98%), CuBr₂, (99%)).

¹H NMR and ¹³C NMR spectra were recorded at room temperature in CDCl₃ on a Bruker 400 or a 500 MHz spectrometer. Chemical shifts (δ) are reported in ppm with the following abbreviations used for the observed multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet for unresolved lines). ¹H NMR chemical shifts were referenced to the residual solvent signal for CHCl₃ (7.26 ppm) or MeCN-*d*₃ (1.94 ppm), and ¹³C NMR chemical shifts were referenced to the solvent signal of CDCl₃ (77.16 ppm). Analytical TLC was performed on pre-coated silica gel plates. After elution, the plates were visualized by UV illumination at 254–360 nm and by staining with ethanolic KMnO₄ or ethanolic phosphomolybdic acid. Column chromatography was performed using Davisil 60Å silica gel (35–70 μ m). HRMS data were recorded on a micrOTOF instrument using ESI and APCI techniques. LRMS data were recorded on a GCQ-plus instrument using EI technique. HPLC samples were analyzed by UV-detection (at 270 nm) using a Waters 2695 HPLC (column: Chiracel OB, mobile phase: iso-hexane:2-propanol 95:5, 0.5 mL/h).

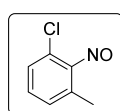
The regiochemistry of the products was established by analysis of the typical chemical shifts,¹ 1D differential NOE experiments and DEPT experiments for compounds **2b**, **3b**, **2m** and **3m**, all other products were assigned by analogy.

2. Experimental Procedures and Spectral Data

2.1. Preparation of starting materials

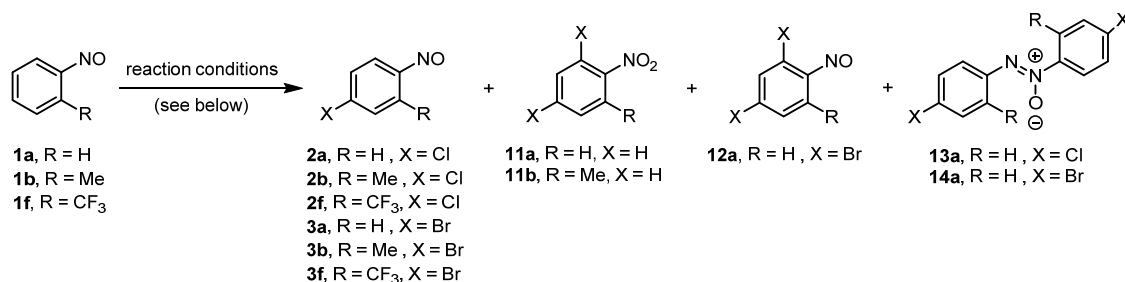
Nitrosobenzene derivatives **1c–1o** were synthesized from the corresponding aniline derivatives according to an adapted version of a literature procedure.² Spectral data for the compounds above can be found in the following references: **1c**,³ **1d**,⁴ **1e**,⁵ **1f**,⁶ **1g**,⁷ **1h**,⁸ **1i**,⁹ **1j**,¹⁰ **1k,l**,¹¹ **1m**,¹² and **1n**.¹³ NCS and NBS were obtained from commercial sources and recrystallized from water. All other compounds were used as received from commercial sources.

1-Chloro-3-methyl-2-nitrosobenzene (**1o**)



1o: as a mixture of its *cis*- and *trans*-dimer (ratio 4.8:1.0). ¹H NMR (400 MHz, CDCl₃): δ ppm 7.41-7.33 (m, 2H), 7.28-7.24 (m, 1H), 2.56 and 2.47 (s, 3H in total); ¹³C NMR (100 MHz, CDCl₃): δ 139.43, 139.31, 136.35, 135.38, 131.50, 131.47, 130.15, 129.81, 129.19, 128.62, 128.43, 128.18, 19.89, 18.80 ppm; HRMS (ESI): *m/z* calcd for C₇H₆ClNNaO [M+Na]⁺, 178.0030 found 178.0037

2.2. Screening of reaction conditions and comparison with literature procedures



Scheme S-1: The reactions were performed in a screw-cap vial equipped with a magnetic stirring bar on a 0.025-0.50 mmol scale with the indicated reagents under the conditions shown below. Reactions executed according to adapted literature procedures are given with the appropriate references. ¹H NMR yields were determined by analyzing the crude reaction mixture, using diiodomethane as an internal standard. For a comparison with classical halogenation employing Br₂ or Cl₂, see Scheme 1.

Table S-1: Relevant findings in the reaction development

Entry	1x	Reaction scale (mmol)	Reagents (equiv)	Reaction conditions (°C/h)	Solvent (mL)	¹ H NMR yield (%) (Isolated yield (%))	¹ H NMR yield starting material and by-products (%)
Chlorination							
1	1a	0.10	CuCl ₂ (1.0)	40/18	MeCN (0.4 mL)	2a : 24	1a : 19, 13a : 5
2	1a	0.10	CuCl ₂ (2.0)	40/8	MeCN (0.4 mL)	2a : 49	1a : 11, 13a : 7
3	1a	0.10	CuCl ₂ (2.0)	40/7	MeCN (0.4 mL)	2a : 0	1a intact

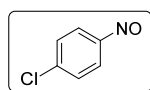
4	1a	0.30	CuCl ₂ (2.0)	rt/24	MeCN (1.2 mL)	2a : 0	1a intact
5	1a	0.10	CuCl ₂ (2.2), BHT (0.01)	rt/2	MeCN (0.4 mL)	2a : 47	1a : 10, 13a : 15
6	1a	0.30	CuCl ₂ (2.2), BHT (0.01)	rt/2	MeCN (1.2 mL)	2a : (43)	
7	1a	0.10	CuCl ₂ (2.2), BHT (0.1)	rt/2	MeCN (0.4 mL)	2a : 42	1a : 10, 13a : 16
8	1a	0.10	CuCl ₂ (2.2), BHT (1.0)	rt/2	MeCN (0.4 mL)	2a : 34	1a : 21, 13a : 15
9	1a	0.10	CuCl ₂ (1.0 or 2.0)	40-70/18	CH ₂ Cl ₂ , THF, DMSO, AcOH or PhMe (0.4 mL)	2a : 0	1a intact
10	1a	0.30	CuCl ₂ (2.0)	40/22 (under argon)	MeCN (1.2 mL)	2a : 0	1a intact
11	1a	0.10	CuCl ₂ (2.2), BHT (0.01)	rt/2 (under argon)	MeCN (0.4 mL)	2a : 40	1a : 16, 13a : 13
12	1a	0.10	CuCl ₂ (1.0), TEMPO (1.0)	40/18	MeCN (0.4 mL)	2a : 0	1a intact
13	1a	0.10	CuCl ₂ (1.0), CuCl (0.1)	40/18	MeCN (0.4 mL)	2a : 0	1a intact
14	1b	0.30	CuCl ₂ (2.2)	rt/48	MeCN (1.2 mL)	2b : 0	1b intact
15	1b	0.10	CuCl ₂ (2.2), BHT (0.01)	0/48	MeCN (0.4 mL)	2b : 0	1b intact
16	1b	0.30	CuCl ₂ (2.2), BHT (0.01)	rt/7 (slow addition)	MeCN (1.2 mL)	2b : 27	1b : 35
17	1b	0.05 (0.13 M)	CuCl ₂ (2.2), BHT (0.01)	rt/2	MeCN (0.4 mL)	2b : 55	1b : 21
18	1b	0.025 (0.06 M)	CuCl ₂ (2.2), BHT (0.01)	rt/4.5	MeCN (0.4 mL)	2b : 45	1b : 28
19	1b	0.10	NCS (1.0)	rt/16	MeCN, CH ₂ Cl ₂ , MeOH, CDCl ₃ or H ₂ O (0.4 mL)	2b : 0	1b : intact
20	1b	0.10	NCS (1.5)	50/24	MeCN (0.4 mL)	2b : 17	1b : 51, 11b : 33
21	1b	0.10	CuCl ₂ (0.1), NCS (1.5)	50/24	MeCN (0.4 mL)	2b : 19	1b : 30, 11b : 33
22	1b	0.10	CuCl ₂ (0.1), aq. NaOCl (70%) (1.5)	50/24	MeCN (0.4 mL)	2b : 0	1b : 61, 11b : 23
23	1b	0.10	CuCl ₂ (0.1), TCICA (1.5)	50/24	MeCN (0.4 mL)	2b : 0	Complex mixture
24	1a	0.10	CuCl ₂ (0.1), NCS (1.5)	50/24	MeCN (0.4 mL)	2a : 19	1a : 30, 11a : 17
25	1f	0.10	CuCl ₂ (0.1), NCS (1.5)	50/24	MeCN (0.4 mL)	2f : 0	1f intact
26 ¹⁴	1b	0.10	NCS (1.0)	rt/5 min	BF ₃ ·H ₂ O (0.1 mL)	2b : 0	Complex mixture
27 ¹⁵	1b	0.10	NCS (1.0), ZrCl ₄ (0.05)	rt/24	CH ₂ Cl ₂ (0.8 mL)	2b : 0	1b intact
28 ¹⁶	1b	0.10	KCl (1.1), Oxone (1.1)	rt/8	MeCN (0.5 mL)	2b : 0	Only 11b observed
Bromination							
29	1b	0.50	CuBr ₂ (2.2) BHT (0.01)	rt/2	MeCN (2 mL)	3b : 63 (54)	1b : 13
30 ¹⁷	1b	0.10	NBS (1.0)	rt/24	DMF or MeCN (1 mL)	3b : 0	1b intact
31	1b	0.10	NBS (1.5)	50/24	MeCN (0.4 mL)	3b : 0	1b intact

32	1b	0.10	CuBr ₂ (0.1), NBS (1.0)	rt/29	MeCN (0.4 mL)	3b : 48	1b : 36
33	1b	0.10	CuBr ₂ (0.1), NBS (1.5)	50/24	MeCN (0.4 mL)	3b : 68	1b : 25
34	1b	0.30	CuBr ₂ (0.1), NBS (1.5)	50/24	MeCN (0.4 mL)	3b : (55)	
35	1a	0.30	CuBr ₂ (0.1), NBS (1.5)	50/24	MeCN (0.4 mL)	3a : 49 (47)	1a : 29, 12a : 5
36	1f	0.30	CuBr ₂ (0.1), NBS (1.5)	50/24	MeCN (0.4 mL)	3f : 5	1f : 74
37 ¹⁵	1b	0.10	NBS (1.0) ZrCl ₄ (0.05)	rt/24	CH ₂ Cl ₂ (0.8 mL)	3b : 0	1b intact
38 ¹⁸	1b	0.10	HBr (1.1), DMSO (1.1)	60/1	EtOAc (0.4 mL)	3b : 8	Complex mixture
39	1b	0.10	Br ₂ (1.0)	rt/2	MeCN (0.4 mL)	3b : 0	Complex mixture
40 ¹⁹	1b	0.50	Br ₂ (1.02)	rt/4 (2h slow addition)	DCE (0.14 mL)	3b : 21	Complex mixture
41 ²⁰	1a	0.30	LiBr (1.0), CuBr ₂ (0.25), O ₂	60/24	AcOH (1.0 mL)	3a : 11	1a : 82, 14a : 4

2.3. General procedure for the halogenation of aryl-nitroso derivatives 1a-1m

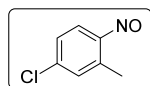
To a screw-cap vial equipped with a magnetic stirring bar were added **1** (0.30 mmol, 1.0 equiv), CuX₂ (0.66 mmol, 2.2 equiv), MeCN (0.87 mL) and a solution of 4-(*tert*-butyl)-2,6-dimethylphenol in MeCN (0.33 mL, 0.009 M, 1 mol %). The reaction mixture was stirred until crude ¹H NMR showed no further conversion of **1** (normally after 2 hours) at room temperature (unless otherwise stated). For the chlorination of **1** a distinct color change from yellow/green to brown was usually observed. The crude product was purified by absorption on silica gel followed by column chromatography with indicated eluent system to obtain aryl-nitroso derivatives **2a-2m** and **3a-3m**.

1-Chloro-4-nitrosobenzene (**2a**)



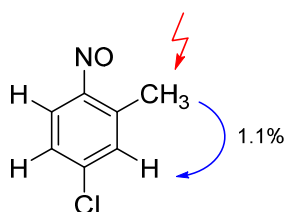
2a: (scale: 0.50 mmol, eluent: pentane, white solid, 43% yield, 30.4 mg); NMR data are in accordance with literature¹¹ values: ¹H NMR (400 MHz, CDCl₃): δ ppm 7.85 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 163.85, 142.61, 129.80, 122.30; LRMS (EI): *m/z* 141.13 [M]⁺.

4-Chloro-2-methyl-1-nitrosobenzene (**2b**)²¹

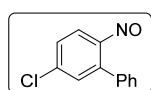


2b: (scale: 0.50/11.0 mmol, eluent: pentane, white solid, 74% (0.50 mmol, 57.6 mg) and 69% (11.0 mmol, 1.18 g) yield); ¹H NMR (400 MHz, CDCl₃): δ ppm 7.54 (d, *J* = 2.0 Hz, 1H), 7.12 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.23 (d, *J* = 8.7 Hz, 1H), 3.33 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 163.07, 144.14, 142.98, 132.74, 126.33, 108.98, 17.20; HRMS (APCI): *m/z* calcd for C₇H₇ClNO [M+H]⁺, 156.0211 found 156.0216.

The regiochemistry of **2b** was confirmed by 1D differential NOE experiments:

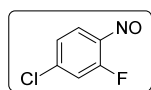


4-Chloro-2-phenyl-1-nitrosobenzene (**2c**)



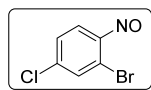
2c: (reaction time: 4 h, eluent: petroleum ether:ethyl acetate 1:0 to 50:1, light brown solid, 60% yield, 39.2 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.80 (d, $J = 2.2$ Hz, 1H), 7.69-7.66 (m, 2H), 7.54-7.51 (m, 3H), 7.29 (dd, $J = 8.7, 2.2$ Hz, 1H), 6.22 (d, $J = 8.7$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 161.52, 147.65, 142.56, 136.05, 132.15, 131.55, 129.07, 128.44, 127.62, 108.04; **HRMS** (ESI): m/z calcd for $\text{C}_{12}\text{H}_8\text{ClNO}$ $[\text{M}+\text{Na}]^+$ 240.0187, found 240.0186.

4-Chloro-2-fluoro-1-nitrosobenzene (**2d**)



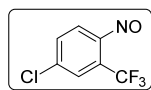
2d: (reaction time: 5 h, eluent: pentane, 42% yield, 20.2 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.55 (dd, $J = 9.7, 2.0$ Hz, 1H), 7.13 (d, $J = 8.7$ Hz, 1H), 6.47 (dd, $J = 8.5, 7.6$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 164.49 (d, $J_{\text{C-F}} = 270.5$ Hz), 153.29 (d, $J_{\text{C-F}} = 7.2$ Hz), 144.22 (d, $J_{\text{C-F}} = 10.2$ Hz), 124.59 (d, $J_{\text{C-F}} = 3.5$ Hz), 119.30 (d, $J_{\text{C-F}} = 22.5$ Hz), 111.05; **HRMS** (APCI): m/z calcd for $\text{C}_6\text{H}_4\text{ClFNO}$ $[\text{M}+\text{H}]^+$ 159.9960, found 159.9963.

2-Bromo-4-chloro-1-nitrosobenzene (**2e**)

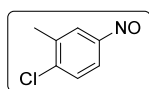


2e: (eluent: pentane, 37% yield, 24.5 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 8.00 (d, $J = 2.0$ Hz, 1H), 7.26 (dd, $J = 8.6, 2.0$ Hz, 1H), 6.18 (d, $J = 8.6$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 159.59, 143.27, 134.82, 133.81, 127.95, 110.19; **HRMS** (APCI): m/z calcd for $\text{C}_6\text{H}_4\text{BrClNO}$ $[\text{M}+\text{H}]^+$ 219.9159, found 219.9165.

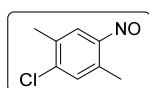
4-Chloro-1-nitroso-2-(trifluoromethyl)benzene (**2f**)



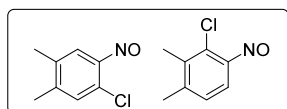
2f: (reaction temperature: 50 °C, reaction time: 7 h, eluent: pentane, blue liquid, 49% yield, 30.8 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 8.04 (d, $J = 2.1$ Hz, 1H), 7.56 (dd, $J = 8.6, 2.1$ Hz, 1H), 6.24 (d, $J = 8.6$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 157.09, 142.34, 133.87 (q, $J_{\text{C-F}} = 33.9$ Hz), 132.53, 127.66 (q, $J_{\text{C-F}} = 5.7$ Hz), 123.81 (q, $J_{\text{C-F}} = 275.3$ Hz), 108.03; **HRMS** (APCI): m/z calcd for $\text{C}_7\text{H}_4\text{ClF}_3\text{NO}$ $[\text{M}+\text{H}]^+$ 209.9928, found 209.9929.

1-Chloro-2-methyl-4-nitrosobenzene (2h)

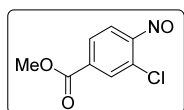
2h: (eluent: pentane, yellow solid, 40% yield, 18.7 mg); NMR data are in accordance with literature²² values: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.78 (d, $J = 1.7$ Hz, 1H), 7.66 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.57 (d, $J = 8.4$ Hz, 1H), 2.52 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 164.30, 142.75, 137.83, 130.17, 123.51, 119.46, 20.29; **HRMS** (APCI): m/z calcd for $\text{C}_7\text{H}_7\text{ClNO}$ $[\text{M}+\text{H}]^+$ 156.0211, found 156.0206.

1-Chloro-2,5-dimethyl-4-nitrosobenzene (2i)

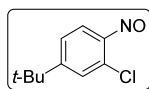
2i: (eluent: pentane, pale yellow solid, 66% yield, 33.6 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.53 (s, 1H), 6.16 (s, 1H), 3.27 (s, 3H), 2.31 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 163.24, 143.25, 141.13, 134.03, 133.08, 109.73, 19.70, 16.66; **HRMS** (APCI): m/z calcd for $\text{C}_8\text{H}_9\text{ClNO}$ $[\text{M}+\text{H}]^+$ 170.0367, found 170.0360.

1-Chloro-4,5-dimethyl-2-nitrosobenzene (2j) and 2-chloro-3,4-dimethyl-1-nitrosobenzene (2j')

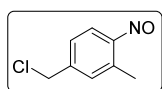
2j and **2j'** (Compounds were not separable): (eluent: pentane:dichloromethane 100:1, green solid, 53% yield in total, 27.0 mg, ratio 4:1); **1-chloro-4,5-dimethyl-2-nitrosobenzene (2j):** $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.53 (s, 1H), 6.08 (s, 1H), 2.32 (s, 3H), 2.21 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 160.80, 147.78, 140.54, 135.65, 132.43, 109.64, 20.57, 19.36. **2-chloro-3,4-dimethyl-1-nitrosobenzene (2j'):** $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 6.99 (d, $J = 8.2$ Hz, 1H), 6.02 (d, $J = 8.2$ Hz, 1H), 2.58 (s, 3H), 2.38 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 161.65, 147.27, 143.99, 137.56, 127.53, 105.70, 21.79, 16.23; **2j** and **2j'**: **HRMS** (APCI): m/z calcd for $\text{C}_8\text{H}_9\text{ClNO}$ $[\text{M}+\text{H}]^+$ 170.0367, found 170.0363.

Methyl 3-chloro-4-nitrosobenzoate (2k)

2k: (reaction temperature: 50 °C, reaction time: 24 h, eluent: pentane:diethyl ether 100:1, 26% yield, 15.7 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 8.47 (d, $J = 1.6$ Hz, 1H), 7.88 (dd, $J = 8.4, 1.6$ Hz, 1H), 6.21 (d, $J = 8.4$ Hz, 1H), 3.98 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 164.81, 159.60, 142.14, 136.57, 134.04, 128.22, 108.65, 53.19; **HRMS** (APCI): m/z calcd for $\text{C}_8\text{H}_7\text{ClNO}_3$ $[\text{M}+\text{H}]^+$ 200.0109, found 200.0104.

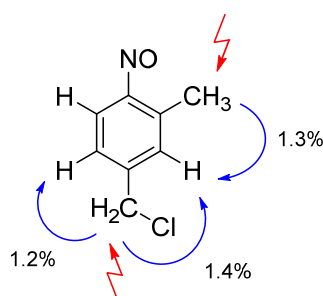
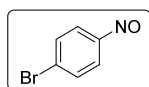
4-(tert-Butyl)-2-chloro-1-nitrosobenzene (2l)

2l: (reaction time: 7 h, eluent: pentane:diethyl ether 100:1, green liquid, 50% yield, 29.7 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.75 (d, $J = 1.9$ Hz, 1H), 7.24 (dd, $J = 8.6, 1.9$ Hz, 1H), 6.24 (d, $J = 8.6$ Hz, 1H), 1.36 (s, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 161.58, 160.33, 142.99, 128.87, 123.92, 108.68, 35.91, 30.91; **HRMS** (ESI): m/z calcd for $\text{C}_{10}\text{H}_{12}\text{ClNNaO}$ $[\text{M}+\text{Na}]^+$ 220.0500, found 220.0505.

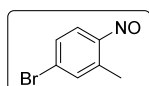
4-(Chloromethyl)-2-methyl-1-nitrosobenzene (2m)

2m: (reaction time: 7 h, eluent: pentane:ethyl acetate 50:1, pale yellow solid. 57% yield, 29.0 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.57 (s, 1H), 7.18 (dd, $J = 8.3, 1.5$ Hz, 1H), 6.28 (d, $J = 8.3$ Hz, 1H), 4.57 (s, 2H), 3.36 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 164.06, 145.38, 142.93, 133.04, 126.03, 108.05, 45.18 (CH_2), 17.40; **HRMS** (APCI): m/z calcd for $\text{C}_8\text{H}_9\text{ClNO}$ $[\text{M}+\text{H}]^+$ 170.0367, found 170.0363.

The regiochemistry of **2m** was confirmed by 1D differential NOE experiments:

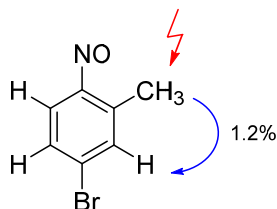
**1-Bromo-4-nitrosobenzene (3a)**

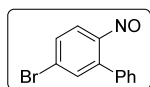
3a: (eluent: pentane, white solid, 48% yield, 29.5 mg, with traces (ratio 1:0.07) of **3e**); NMR data are in accordance with literature¹¹ values: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.78 (s, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 163.95, 132.83, 131.82, 122.25; **HRMS** (APCI): m/z calcd for $\text{C}_6\text{H}_5\text{BrNO}$ $[\text{M}+\text{H}]^+$ 185.9549, found 185.9557.

4-Bromo-2-methyl-1-nitrosobenzene (3b)²³

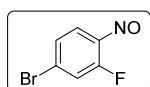
3b: (scale: 0.50/11.0 mmol, eluent: pentane, white solid, 54% (0.50 mmol, 53.9 mg) and 57% (11.0 mmol, 1.25 g) yield); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.75 (d, $J = 2.0$ Hz, 1H); 7.31 (dd, $J = 8.6, 2.0$ Hz, 1H), 6.14 (d, $J = 8.6$ Hz, 1H), 3.34 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 163.21, 144.09, 135.83, 132.32, 129.34, 108.91, 17.11; **HRMS** (ESI): m/z calcd for $\text{C}_7\text{H}_7\text{BrNO}$ $[\text{M}+\text{H}]^+$ 199.9706, found 199.9697.

The regiochemistry of **3b** was confirmed by 1D differential NOE experiments:

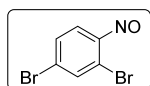


4-Bromo-2-phenyl-nitrosobenzene (3c)

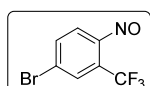
3c: (eluent: petroleum ether:ethyl acetate 50:1, white solid, 59% yield, 51.6 mg, with traces of its' dimer (ratio 1:0.09) and **1c** (ratio 1:0.16)); **¹H NMR** (400 MHz, CDCl₃): δ ppm 7.99 (d, *J* = 2.0 Hz, 1H); 7.69-7.65 (m, 2H), 7.54-7.51 (m, 3H), 7.47 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.13 (d, *J* = 8.7 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 161.50, 147.61, 135.77, 135.14, 131.69, 131.58, 130.56, 129.09, 128.42, 107.82; **HRMS** (ESI): *m/z* calcd for C₁₂H₈BrNNO [M+Na]⁺ 283.9681, found 283.9672.

4-Bromo-2-fluoro-1-nitrosobenzene (3d)

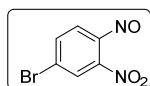
3d: (eluent: pentane, 29% yield, 17.8 mg); **¹H NMR** (400 MHz, CDCl₃): δ ppm 7.74 (dd, *J* = 9.5, 1.8 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 6.37 (dd, *J* = 8.5, 7.5 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 164.18 (d, *J*_{C-F} = 271.5 Hz), 153.40, 132.84 (d, *J*_{C-F} = 9.4 Hz), 127.53, (d, *J*_{C-F} = 3.7 Hz), 122.28 (d, *J*_{C-F} = 22.2 Hz), 110.97; **HRMS** (ESI): *m/z* calcd for C₆H₄BrFNO [M+H]⁺ 203.9455, found 203.9455.

2,4-Dibromo-1-nitrosobenzene (3e)

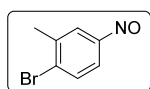
3e: (eluent: pentane, pale-green solid, 50% yield, 41.7 mg, with traces (ratio 1:0.04) of 2,4,6-tribromoaniline²⁴); NMR data are in accordance with literature²⁵ values: **¹H NMR** (400 MHz, CDCl₃): δ ppm 8.18 (d, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.09 (d, *J* = 8.6 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 159.67, 137.63, 133.83, 132.27, 130.91, 110.15; **LRMS** (EI): *m/z* 262.90 [M]⁺.

4-Bromo-1-nitroso-2-(trifluoromethyl)benzene (3f)

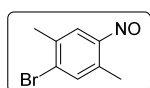
3f: (eluent: pentane, blue liquid, 49% yield, 42.0 mg, with traces (ratio 1:0.10) of 2,4-dibromo-6-(trifluoromethyl)aniline); **¹H NMR** (400 MHz, CDCl₃): δ ppm 8.21 (d, *J* = 1.9 Hz, 1H), 7.74 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.14 (d, *J* = 8.6 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 157.48, 135.66, 133.65 (q, *J*_{C-F} = 33.9 Hz), 131.11, 130.56 (q, *J*_{C-F} = 5.9 Hz), 123.76 (q, *J*_{C-F} = 275.5 Hz), 108.05; **HRMS** (APCI): *m/z* calcd for C₇H₄BrF₃NO [M+H]⁺ 253.9423, found 253.9415.

4-Bromo-2-nitro-1-nitrosobenzene (3g)

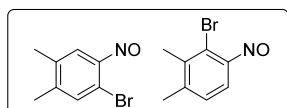
3g: (eluent: pentane, recrystallized from chloroform, yellow solid, 40% yield, 30.1 mg, not separable from **1g** (ratio 1:0.13)); **¹H NMR** data are in accordance with literature²⁶ values: **¹H NMR** (400 MHz, CDCl₃): δ ppm 8.24 (d, *J* = 1.9 Hz, 1H), 7.81 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.37 (d, *J* = 8.5 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 153.19, 136.39, 130.49, 127.39, 111.45 (signal for C-2 was not observed).

1-Bromo-2-methyl-4-nitrosobenzene (3h)²⁷

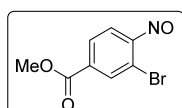
3h: (eluent: pentane:ethyl acetate 50:1, yellow solid, 54% yield, 36.3 mg, with traces (ratio 1:0.07) of 2,4,6-tribromo-3-methylaniline²⁸); **¹H NMR** (400 MHz, CDCl₃): δ ppm 7.80-7.77 (m, 2H), 7.54 (dd, $J = 8.4, 2.3$ Hz, 1H), 2.55 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 164.60, 139.77, 134.16, 133.52, 123.23, 119.08, 23.16; **HRMS** (ESI): m/z calcd for C₁₄H₁₁Br₂N₂O₂ [2M-H]⁻ 396.9193, found 396.9212.

1-Bromo-2,5-dimethyl-4-nitrosobenzene (3i)

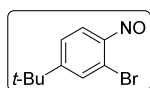
3i: (reaction time: 1 h, eluent: pentane, white solid, 57% yield, 36.6 mg); **¹H NMR** (400 MHz, CDCl₃): δ ppm 7.75 (s, 1H), 6.12 (s, 1H), 3.26 (s, 3H), 2.33 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 163.49, 140.85, 136.47, 135.90, 134.71, 109.18, 22.53, 16.51; **HRMS** (APCI): m/z calcd for C₈H₉BrNO [M+H]⁺ 213.9862, found 213.9869.

1-Bromo-4,5-dimethyl-2-nitrosobenzene (3j) and 2-bromo-3,4-dimethyl-1-nitrosobenzene (3j')

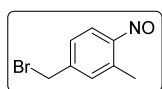
3j and **3j'**: (reaction time: 5 min, 53% yield in total, ratio 3:1, as determined from crude ¹H NMR with diiodomethane as an internal standard). The product decomposed upon attempted purification (SiO₂). Thus, the identity of the products including the regiochemistry was determined by analysis of the products of the subsequent reduction (see **5j** and **5j'**, section 2.4).

Methyl 3-bromo-4-nitrosobenzoate (3k)

3k: (eluent: pentane:diethyl ether 100:1, 34% yield, 24.8 mg); **¹H NMR** (400 MHz, CDCl₃): δ ppm 8.66 (d, $J = 1.6$ Hz, 1H), 7.92 (dd, $J = 8.3, 1.6$ Hz, 1H), 6.18 (d, $J = 8.3$ Hz, 1H), 3.98 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 164.72, 160.09, 137.04, 136.53, 132.20, 128.97, 108.90, 53.20; **HRMS** (ESI): m/z calcd for C₁₆H₁₂Br₂N₂NaO₆ [2M+Na]⁺ 508.8954, found 508.8967.

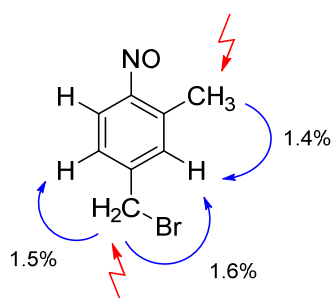
2-Bromo-4-(tert-butyl)-1-nitrosobenzene (3l)

3l: (eluent: pentane:diethyl ether, 110:1, green liquid, 52% yield, 42.1 mg, not separable from 2,6-dibromo-4-(tert-butyl)aniline²⁹ (ratio 1:0.09)); **¹H NMR** (400 MHz, CDCl₃): δ ppm 7.95 (d, $J = 1.9$ Hz, 1H), 7.28 (dd, $J = 8.5, 1.9$ Hz, 1H), 6.22 (d, $J = 8.5$ Hz, 1H), 1.36 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 161.52, 160.76, 133.88, 131.98, 124.61, 108.98, 35.84, 30.95; **HRMS** (ESI): m/z calcd for C₁₀H₁₂BrNNaO [M+Na]⁺ 263.9994, found 263.9995.

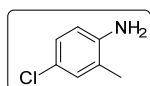
4-(Bromomethyl)-2-methyl-1-nitrosobenzene (3m)

3m: (reaction time: 1 h, eluent: pentane:ethyl acetate 100:1, white solid, 43% yield, 27.6 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.57 (d, $J = 1.7$ Hz, 1H), 7.17 (dd, $J = 8.3, 1.7$ Hz, 1H), 6.26 (d, $J = 8.3$ Hz, 1H), 4.45 (s, 2H), 3.34 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 163.84, 145.90, 142.99, 133.62, 126.69, 108.10, 31.84 (CH_2), 17.39; **HRMS** (APCI): m/z calcd for $\text{C}_8\text{H}_9\text{BrNO}$ $[\text{M}+\text{H}]^+$ 213.9862, found 213.9862.

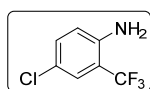
The regiochemistry of **3m** was confirmed by 1D differential NOE experiments:

**2.4. General procedure for the halogenation and subsequent reduction of aryl-nitroso derivatives 1b, 1f and 1j**

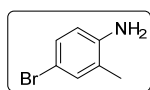
The reaction was performed as described in section 2.3 with the following changes: After the required stirring time (see section 2.3) NaBH_4 (0.60 mmol, 2.0 equiv for **4b**, **4f** and **5j**, or 0.30 mmol, 1.0 equiv for **5b**, and **5f**) was added. The reaction mixture was stirred at room temperature for the specified reaction time (2-4 h) after which the reaction was quenched with dropwise addition of water. The mixture was diluted with CH_2Cl_2 and water, and the layers were subsequently separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phases were dried (MgSO_4) and concentrated in vacuo. The crude product was purified by column chromatography with the indicated eluent system to obtain aniline derivatives **4b**, **4f**, **5b**, **5f** and **5j**.

4-Chloro-2-methylaniline (4b)

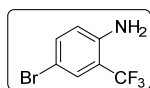
4b: (scale: 0.50 mmol, reaction time second step: 2 h, eluent: petroleum ether:ethyl acetate 10:1, 57% yield, 40.4 mg); NMR data are in accordance with literature³⁰ values: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ ppm 7.03 (d, $J = 2.2$ Hz, 1H), 6.99 (dd, $J = 8.4, 2.2$ Hz, 1H), 6.58 (d, $J = 8.4$ Hz, 1H), 3.55 (br, 2H), 2.14 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ ppm 143.24, 130.15, 126.77, 124.09, 123.08, 116.03, 17.42.

4-Chloro-2-(trifluoromethyl)aniline (4f)

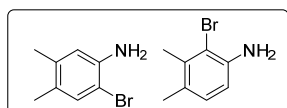
4f: (reaction time first step: 13 h, second step: 4 h, eluent: pentane:ethyl acetate 10:1, brown solid, 14% yield, 8.2 mg); NMR data are in accordance with literature³⁰ values: **¹H NMR** (400 MHz, CDCl₃): δ ppm 7.40 (d, $J = 2.5$ Hz, 1H), 7.24 (dd, $J = 8.7, 2.5$ Hz, 1H), 6.68 (d, $J = 8.7$ Hz, 1H) 4.17 (br, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 143.21, 132.93, 126.51 (q, $J_{C-F} = 5.3$ Hz), 124.26 (q, $J_{C-F} = 272.3$ Hz), 122.51, 118.59, 114.96 (q, $J_{C-F} = 30.8$ Hz).

4-Bromo-2-methylaniline (5b)

5b: (scale: 0.50 mmol, reaction time second step: 3 h, eluent: pentane:ethyl acetate 10:1, brown solid, 66% yield, 61.4 mg); NMR data are in accordance with literature³⁰ values: **¹H NMR** (400 MHz, CDCl₃): δ ppm 7.16 (d, $J = 1.9$ Hz, 1H), 7.12 (dd, $J = 8.4, 1.9$ Hz, 1H), 6.54 (d, $J = 8.4$ Hz, 1H), 3.58 (br, 2H), 2.13 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 143.74, 132.94, 129.67, 124.54, 116.45, 110.18, 17.32.

4-Bromo-2-(trifluoromethyl)aniline (5f)

5f: (reaction time second step: 2 h, eluent: petroleum ether:ethyl acetate 10:1, yellow solid, 65% yield, 46.8 mg); NMR data are in accordance with literature³⁰ values: **¹H NMR** (400 MHz, CDCl₃): δ ppm 7.53 (d, $J = 2.3$ Hz, 1H), 7.37 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.63 (d, $J = 8.7$ Hz, 1H), 4.16 (br, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 143.62, 135.77, 129.35 (q, $J_{C-F} = 5.4$ Hz), 124.15 (q, $J_{C-F} = 272.5$ Hz), 118.92, 115.30 (q, $J_{C-F} = 30.7$ Hz), 109.11.

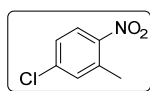
2-Bromo-4,5-dimethylaniline (5j) and 2-bromo-3,4-dimethylaniline (5j')

5j and **5j'** (compounds were not separable): (reaction time second step: 1 h, eluent: pentane:ethyl acetate 20:1, 39% yield in total, ratio 6.3:1.0, 23.3 mg); **2-bromo-4,5-dimethylaniline (5j)**: **¹H NMR** are in accordance with literature³¹ values: **¹H NMR** (400 MHz, CDCl₃): δ ppm 7.17 (s, 1H), 6.59 (s, 1H), 3.88 (br, 2H), 2.14 (s, 3H), 2.14 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm; 141.80, 136.94, 132.99, 128.07, 117.40, 106.27, 19.55, 18.61. **2-bromo-3,4-dimethylaniline (5j')**: **¹H NMR** (400 MHz, CDCl₃): δ ppm 6.90 (d, $J = 8.0$ Hz, 1H), 6.57 (d, $J = 8.0$ Hz, 1H), 3.99 (br, 2H), 2.35 (s, 3H), 2.24 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ ppm 142.39, 136.69, 129.09, 127.33, 113.44, 112.91, 20.57, 20.04. **5j** and **5j'**: **HRMS** (ESI): m/z calcd for C₈H₁₁BrN [M+H]⁺ 200.0069, found 200.0079.

2.5. General procedure for the halogenation and subsequent oxidation of aryl-nitroso derivatives 1b and 1f

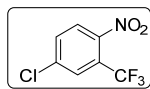
The reaction was performed as described in section 2.3 with the following changes: A round-bottom flask was used. After the required stirring time (see section 2.3) Oxone (2KHSO₅·KHSO₄·K₂SO₄, 0.90 mmol, 3.0 equiv) in water (3.0 mL) was added and the resulting mixture was stirred at room temperature for 24 hours. The mixture was then diluted with CH₂Cl₂ and water to dissolve all solids and the resulting phases were separated. The aqueous phase was extracted twice with CH₂Cl₂ and the combined organic phases were dried (MgSO₄) and concentrated in vacuo. The crude product was purified by column chromatography with the indicated eluent system to obtain aryl-nitro derivatives **6b**, **6f**, **7b**, and **7f**.

4-Chloro-2-methyl-1-nitrobenzene (6b)



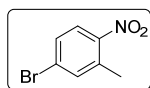
6b: (scale: 0.50 mmol, eluent: pentane:ethyl acetate 100:1, 48% yield, 41.2 mg); ¹H NMR data are in accordance with literature³² values: ¹H NMR (400 MHz, CDCl₃): δ ppm 7.95 (d, *J* = 8.6 Hz, 1H), 7.34-7.30 (m, 2H), 2.60 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 147.60, 139.36, 135.83, 132.72, 127.21, 126.34, 20.67.

4-Chloro-1-nitro-2-(trifluoromethyl)benzene (6f)



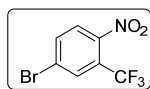
6f: (eluent: pentane:ethyl acetate 50:1, yellow liquid, 49% yield, 33.2 mg); ¹³C NMR data are in accordance with literature³³ values: ¹H NMR (400 MHz, CDCl₃): δ ppm 7.90 (d, *J* = 8.6 Hz, 1H), 7.82, (d, *J* = 2.2 Hz, 1H), 7.71, (dd, *J* = 8.6, 2.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 146.51, 139.47, 133.20, 128.53 (q, *J*_{C-F} = 5.6 Hz), 126.82, 125.63 (q, *J*_{C-F} = 35.0 Hz), 121.36 (q, *J*_{C-F} = 274.3 Hz).

4-Bromo-2-methyl-1-nitrobenzene (7b)



7b: (scale: 0.50 mmol, eluent: pentane:ethyl acetate 10:1, 68% yield, 73.4 mg); ¹H NMR data are in accordance with literature³⁴ values: ¹H NMR (400 MHz, CDCl₃): δ ppm 7.87 (d, *J* = 8.7 Hz, 1H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.48 (dd, *J* = 8.7, 2.1 Hz, 1H), 2.60 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 148.13, 135.88, 135.73, 130.26, 127.92, 126.36, 20.59.

4-Bromo-1-nitro-2-(trifluoromethyl)benzene (7f)³⁵

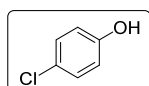


7f: (eluent: pentane:ethyl acetate 50:1, 40% yield, 32.4 mg); ¹H NMR (400 MHz, CDCl₃): δ ppm 7.98 (d, *J* = 2.0 Hz, 1H), 7.88 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 147.03, 136.31, 131.38 (q, *J*_{C-F} = 5.6 Hz), 127.42, 126.76, 125.51 (q, *J*_{C-F} = 34.7 Hz), 121.24 (q, *J*_{C-F} = 273.2 Hz); LRMS (EI): *m/z* 269.07 [M]⁺.

2.6. General procedure for the halogenation of aryl derivatives 8a-8c

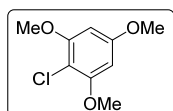
To a screw-cap vial equipped with a magnetic stirring bar were added **8** (0.30 mmol, 1.0 equiv), CuX₂ (0.66 mmol, 2.2 equiv) and MeCN (1.20 mL). The reaction mixture was stirred for the specified reaction time at room temperature (unless otherwise stated) and the crude product was subsequently purified by absorption on silica gel followed by column chromatography with indicated eluent system to obtain aryl derivatives **9a**, **9c** and **10a-10c**.

4-Chlorophenol (**9a**)



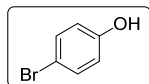
9a: (reaction temperature: 70 °C, reaction time: 6 days, eluent: petroleum ether:ethyl acetate 20:1, colorless liquid, 63% yield, 24.3 mg); NMR data are in accordance with literature³⁶ values: ¹H NMR (400 MHz, CDCl₃): δ ppm 7.21-7.17 (m, 2H), 6.79-6.75 (m, 2H), 4.74 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 154.25, 129.67, 125.83, 116.79.

2-Chloro-1,3,5-trimethoxybenzene (**9c**)



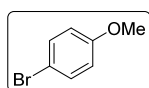
9c: (reaction temperature: 50 °C, reaction time: 24 h, eluent: petroleum ether:ethyl acetate 10:1, white solid, 78% yield, 47.4 mg); NMR data are in accordance with literature³⁷ values: ¹H NMR (400 MHz, CDCl₃): δ ppm 6.16 (s, 2H), 3.85 (s, 6H), 3.78 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 159.48, 156.57, 102.63, 91.62, 56.33, 55.57.

4-Bromophenol (**10a**)



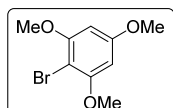
10a: (reaction time: 24 h, eluent: petroleum ether:ethyl acetate 20:1, pale yellow liquid, 84% yield, 43.6 mg); NMR data are in accordance with literature³⁶ values: ¹H NMR (400 MHz, CDCl₃): δ ppm 7.35-7.31 (m, 2H), 6.74-6.71 (m, 2H), 5.24 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 154.54, 132.62, 117.33, 113.12.

1-Bromo-4-methoxybenzene (**10b**)



10b: (reaction time: 24 h, eluent: petroleum ether:ethyl acetate 100:1, 89% yield, 50.0 mg); NMR data are in accordance with literature²⁰ values: ¹H NMR (400 MHz, CDCl₃): δ ppm 7.41-7.37 (m, 2H), 6.81-6.77 (m, 2H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 158.83, 132.37, 115.87, 112.96, 55.58.

2-Bromo-1,3,5-trimethoxybenzene (**10c**)



10c: (2.0 equiv of CuBr₂, reaction time: 45 min, eluent: petroleum ether:ethyl acetate 5:1, colorless liquid, 85% yield, 69.6 mg, with traces of 2,4-dibromo-1,3,5-trimethoxybenzene (ratio 1:0.08)); NMR data are in accordance with literature²⁰ values: ¹H NMR (400 MHz, CDCl₃): δ ppm 6.16 (s, 2H), 3.86 (s, 6H), 3.80 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 160.57, 157.55, 92.07, 91.73, 56.45, 55.62.

2.7. Procedure for the ^1H NMR traces of the chlorination of **1b** (Figure 1)

To a screw-cap vial equipped with a magnetic stirring bar were added **1b** (0.30 mmol, 1.0 equiv), CuCl_2 (0.66 mmol, 2.2 equiv), $\text{MeCN-}d_3$ (0.87 mL) and a solution of 4-(*tert*-butyl)-2,6-dimethylphenol in $\text{MeCN-}d_3$ (0.33 mL, 0.009 M, 1 mol %). To a 50 μL sample, at the time intervals shown below, were added 20 μL of a solution of the internal standard in $\text{MeCN-}d_3$ (diiodomethane, 0.62 M) and $\text{MeCN-}d_3$ (0.30 mL). The samples were subsequently analyzed by ^1H NMR.

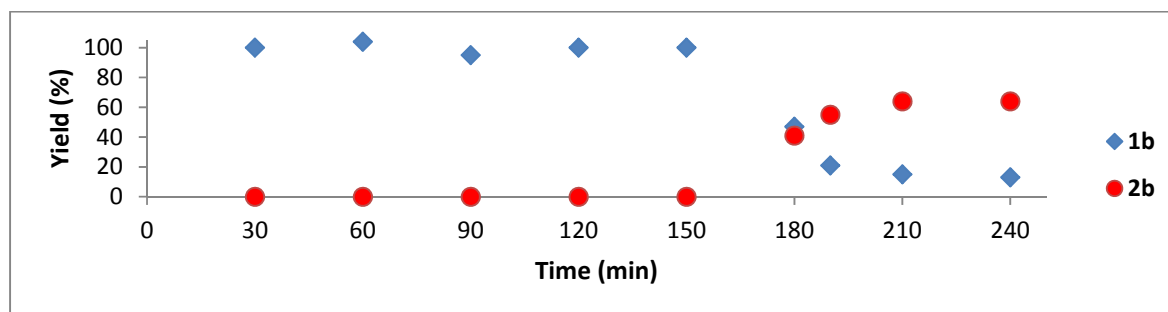


Figure S-1: ^1H NMR yields of **1b** and **2b** during the chlorination of **1b**

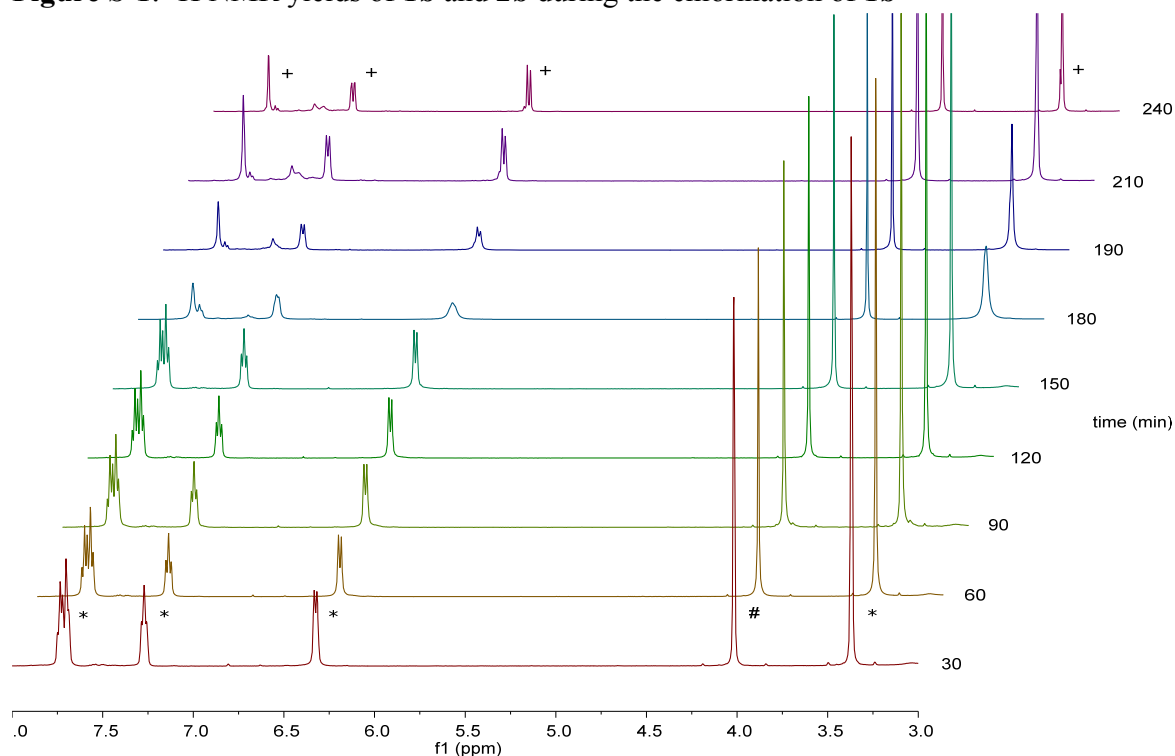


Figure S-2: ^1H NMR spectra of the chlorination of **1b** acquired at different times (*: **1b**, +: **2b**, #: diiodomethane)

Even though broad, undefined peaks were observed in the aromatic region, the formation of the *o*-chlorinated product **1o** was excluded based on comparison with an authentic sample and HPLC traces (see section 2.8). We speculate that these signals arise from dimerized, polymerized or decomposed **1b** and/or **2b** or from complexation of **1b** and/or **2b** to copper species. Similar peaks were observed when a mixture of **1b** and **2b** in MeCN-*d*₃ was treated with aqueous HCl. HCl is likely to be released during the course of the reaction and possibly causes **1b** and/or **2b** to dimerize, polymerize and/or decompose. For comparison ¹H NMR spectra of: a mixture of **1b** and **2b**, a mixture of **1b** and **2b** with aqueous HCl, and the crude reaction in MeCN-*d*₃ after 4 hours of stirring are presented in Figure S-3.

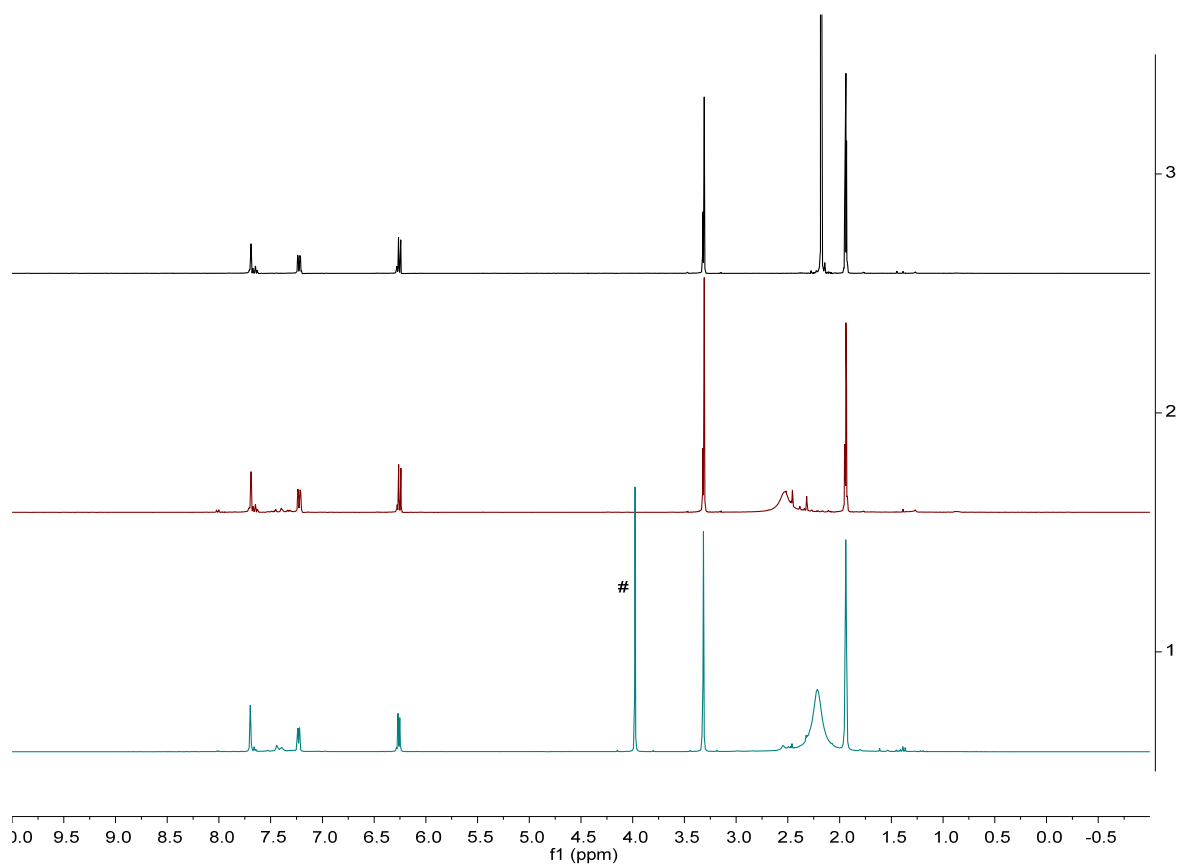


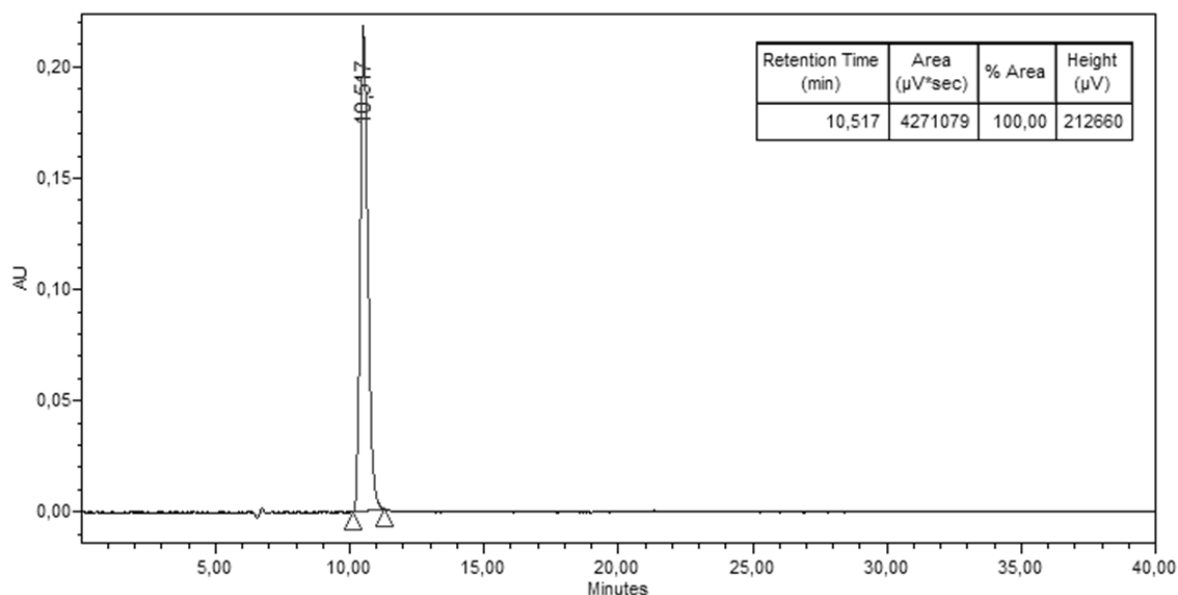
Figure S-3: ¹H NMR spectra of the chlorination of **1b** after 4 hours (1), a mixture containing **1b**, **2b** (1:2 ratio) and aqueous HCl (1 equiv, 37%) (2), and a mixture containing **1b** and **2b** (1:2 ratio) (3) (#: diiodomethane)

2.8. Procedure for the HPLC traces of the chlorination of **1b**

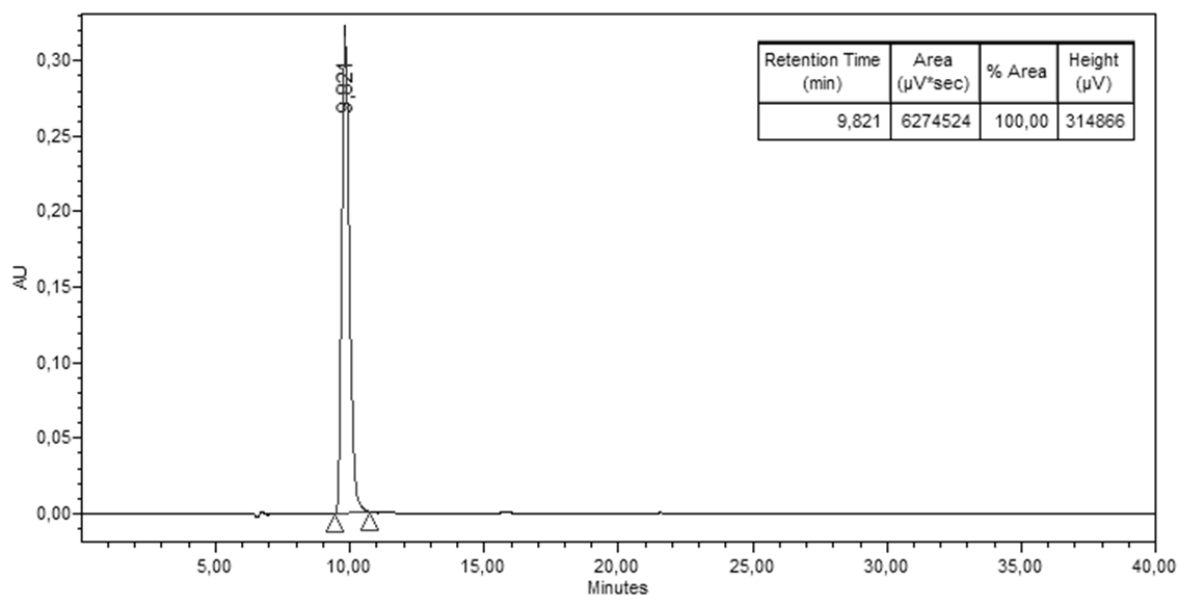
To a screw-cap vial equipped with a magnetic stirring bar were added **1b** (0.30 mmol, 1.0 equiv), CuCl₂ (0.66 mmol, 2.2 equiv), MeCN (0.87 mL) and a solution of 4-(*tert*-butyl)-2,6-dimethylphenol in MeCN (0.33 mL, 0.009 M, 1 mol %).

After completion of the reaction (150 min), to a 20 μ L sample, was added 400 μ L of a solution of the internal standard in a n-hexane:2-propanol (95:5) solution (phenol, 0.017 M) and a n-hexane:2-propanol (95:5) mixture (800 μ L). The sample was subsequently sonicated, filtered through a plug of cotton and analyzed by HPLC. (column: Chiralcel OB, eluent: iso-hexane:2-propanol 95:5, flowrate: 0.50 mL/h, wavelength: 270 nm, temperature: 23 °C). Yields were determined with the aid of calibration curves. The formation of the *o*-chlorinated product **1o** was excluded based on comparison with an authentic sample.

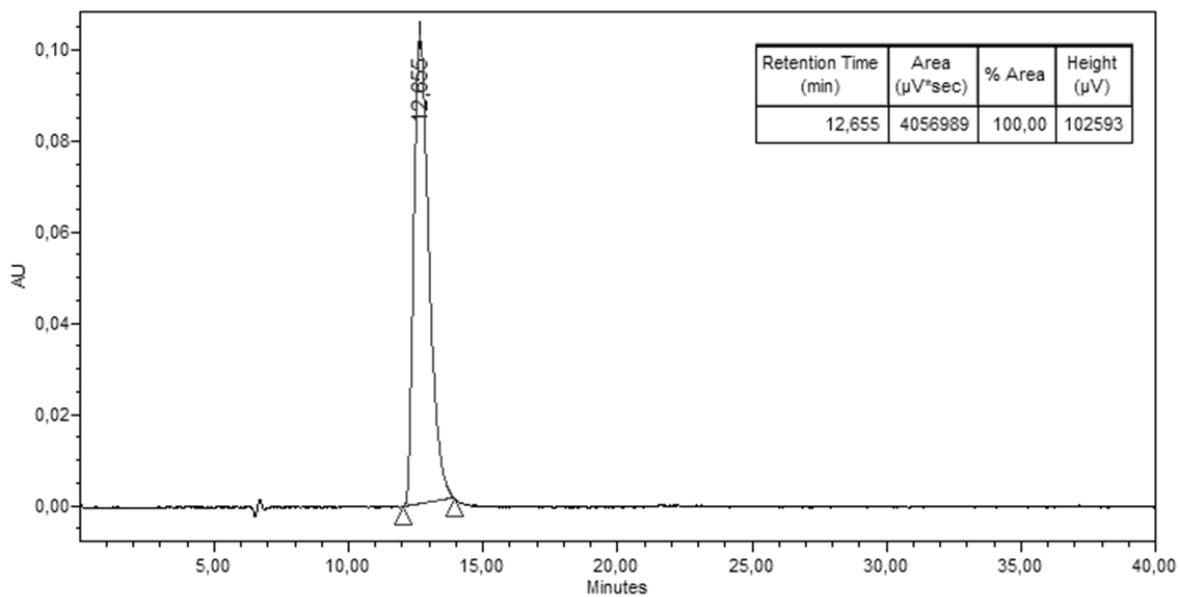
HPLC traces of **1b**:



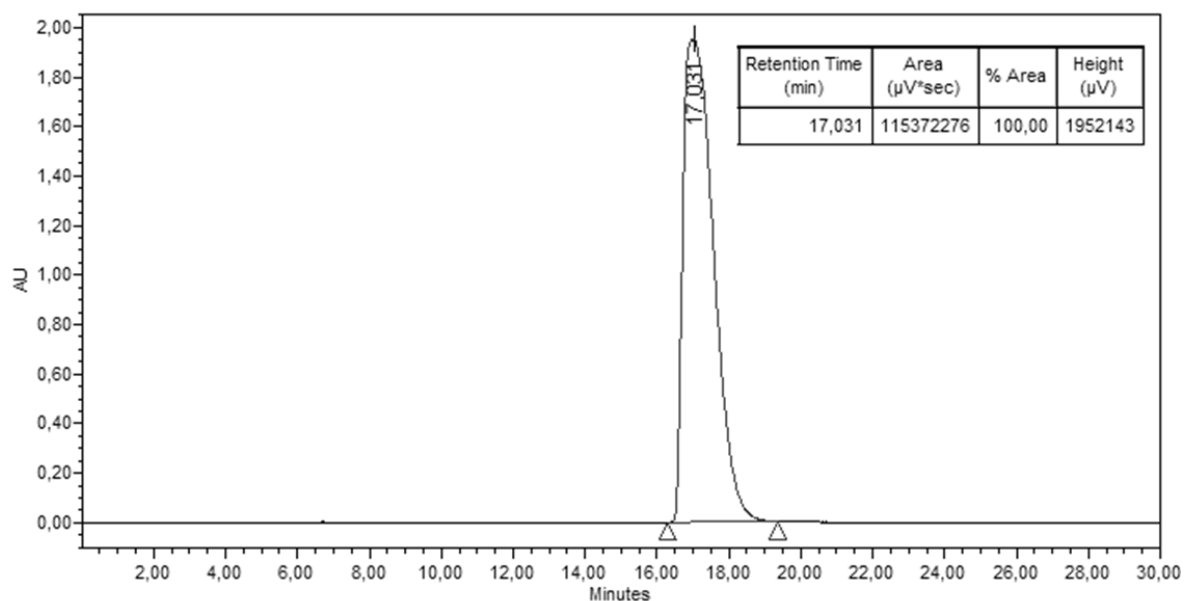
HPLC traces of **2b**:



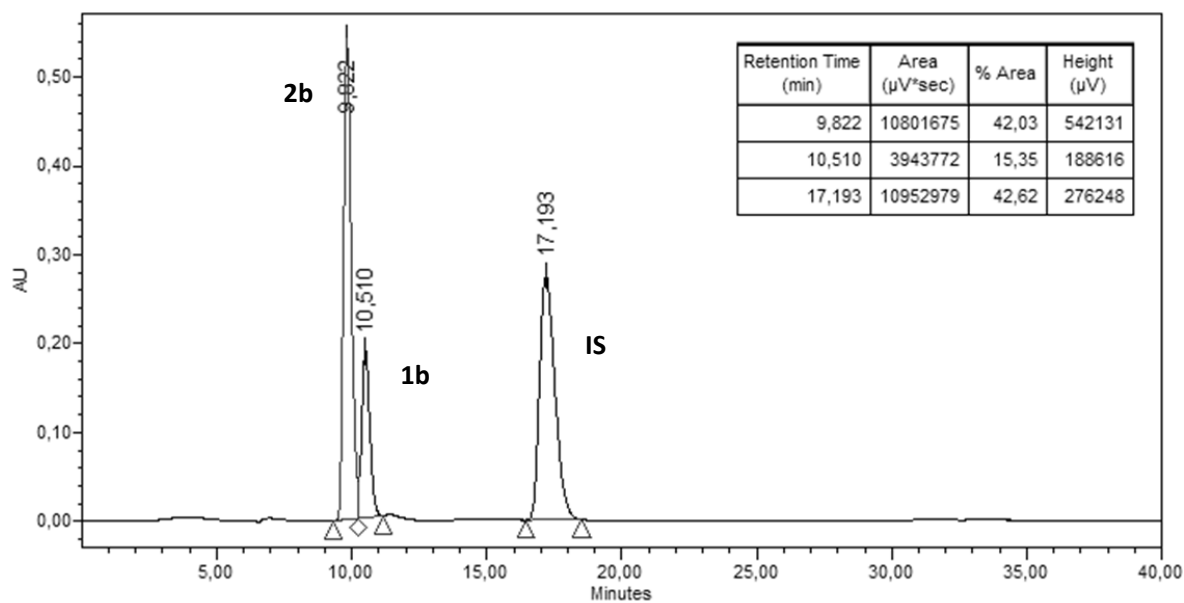
HPLC traces of **1o**:



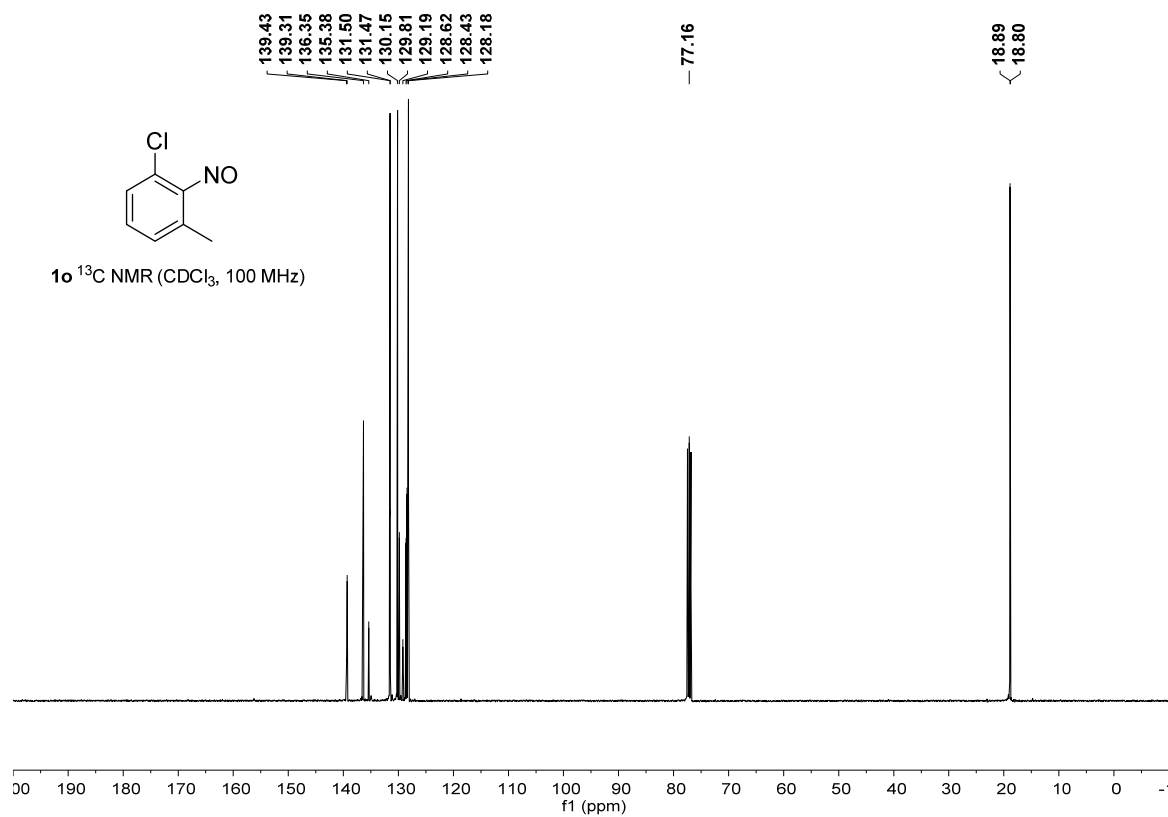
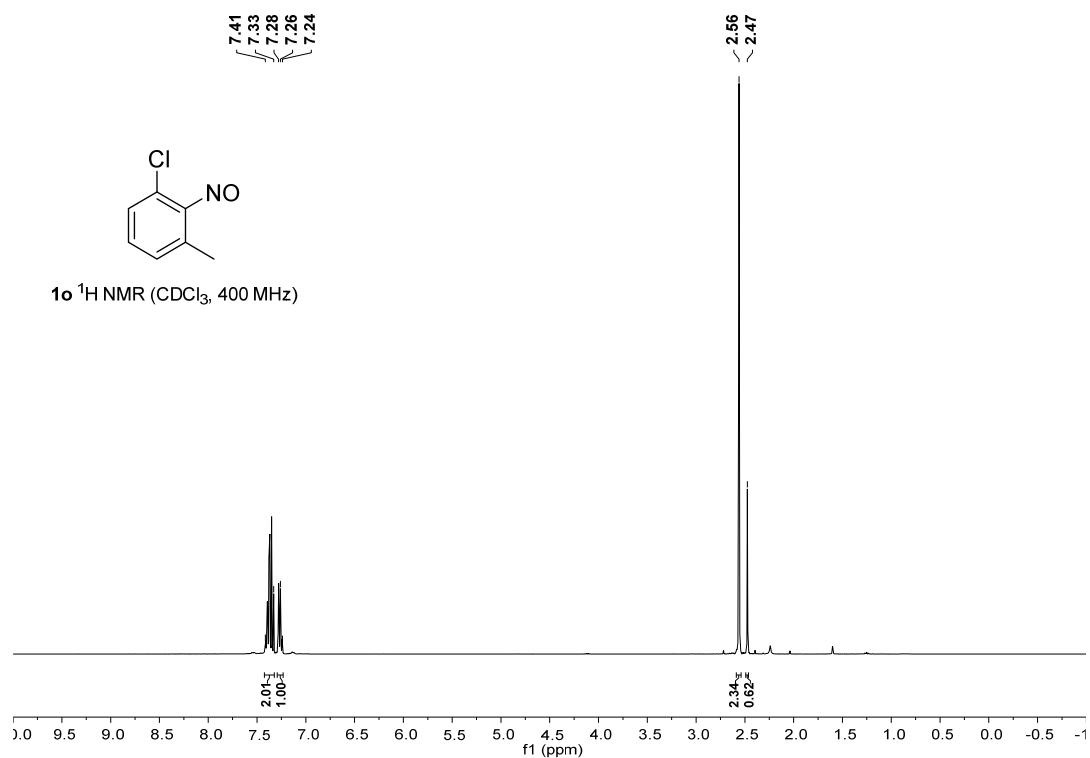
HPLC traces of Phenol (IS):

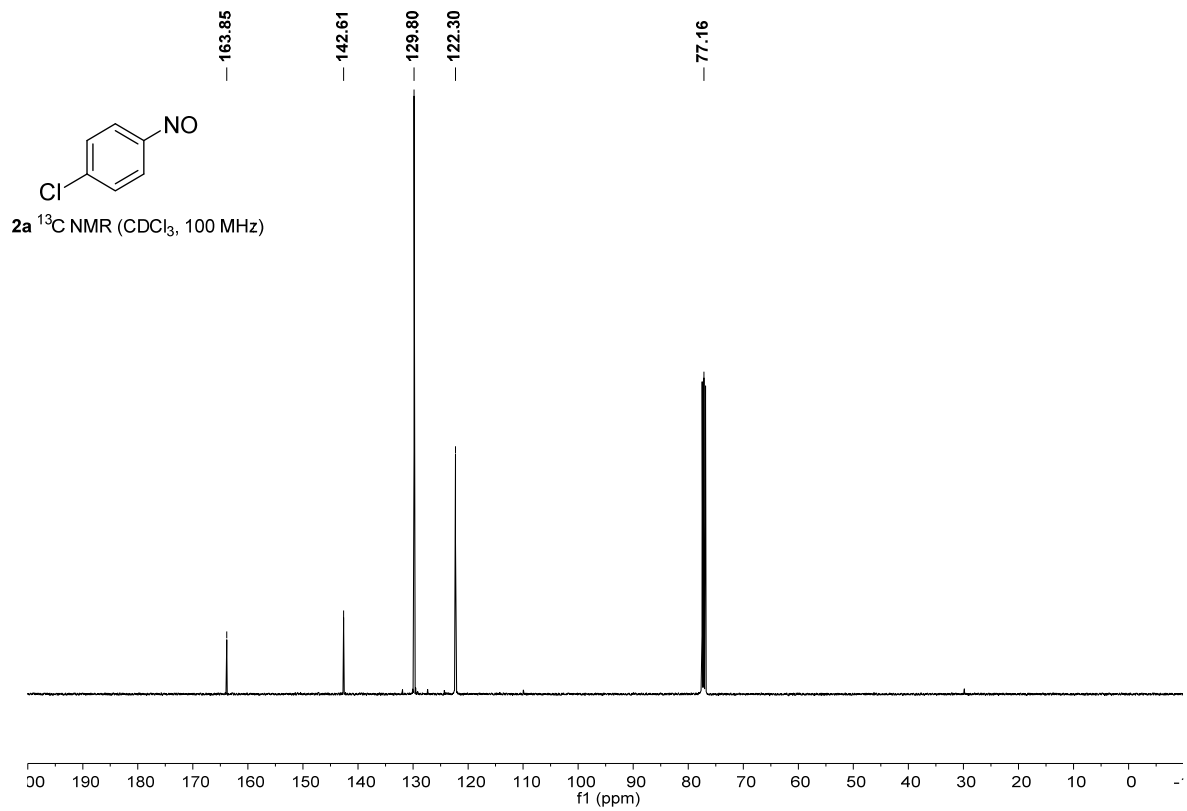
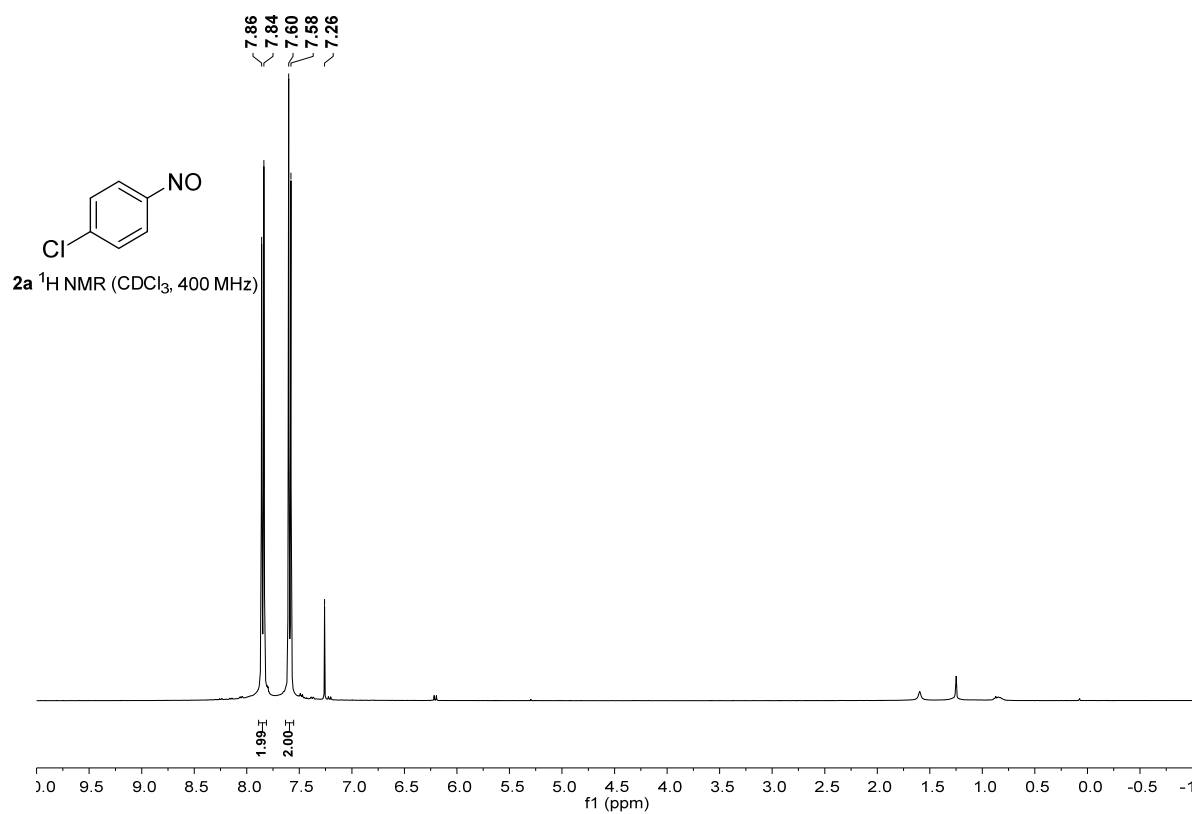


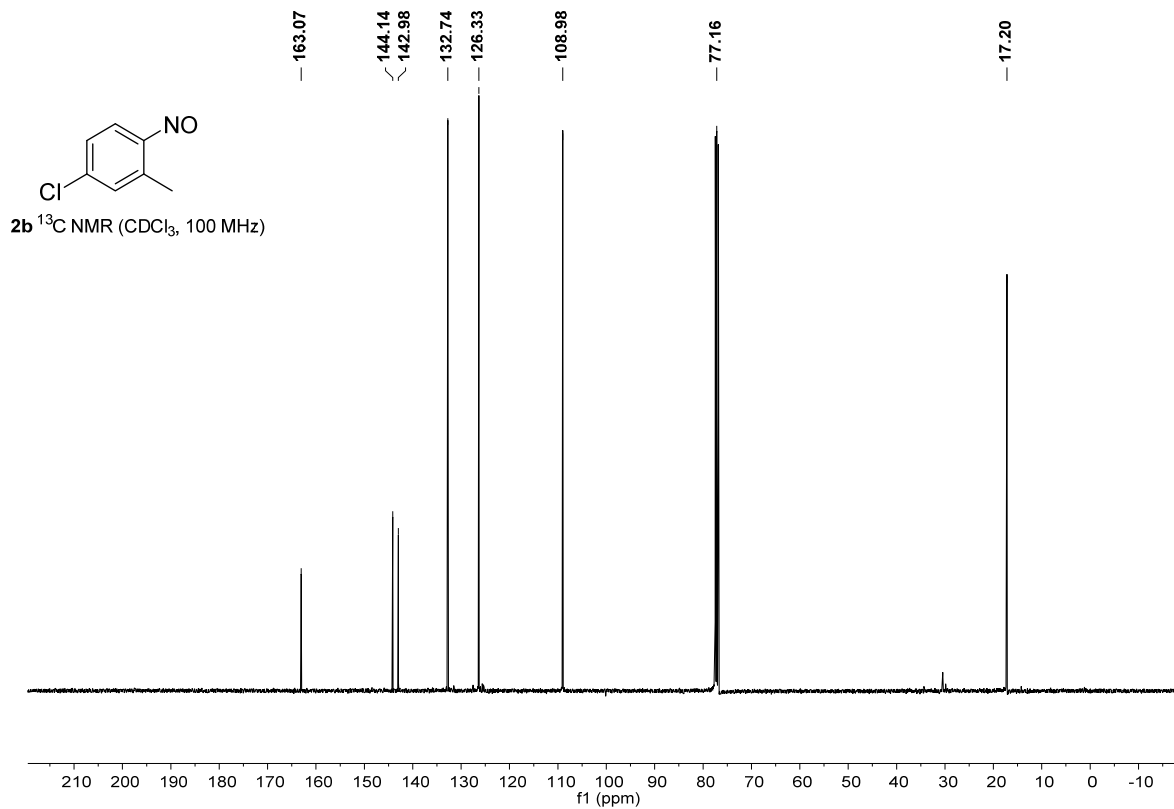
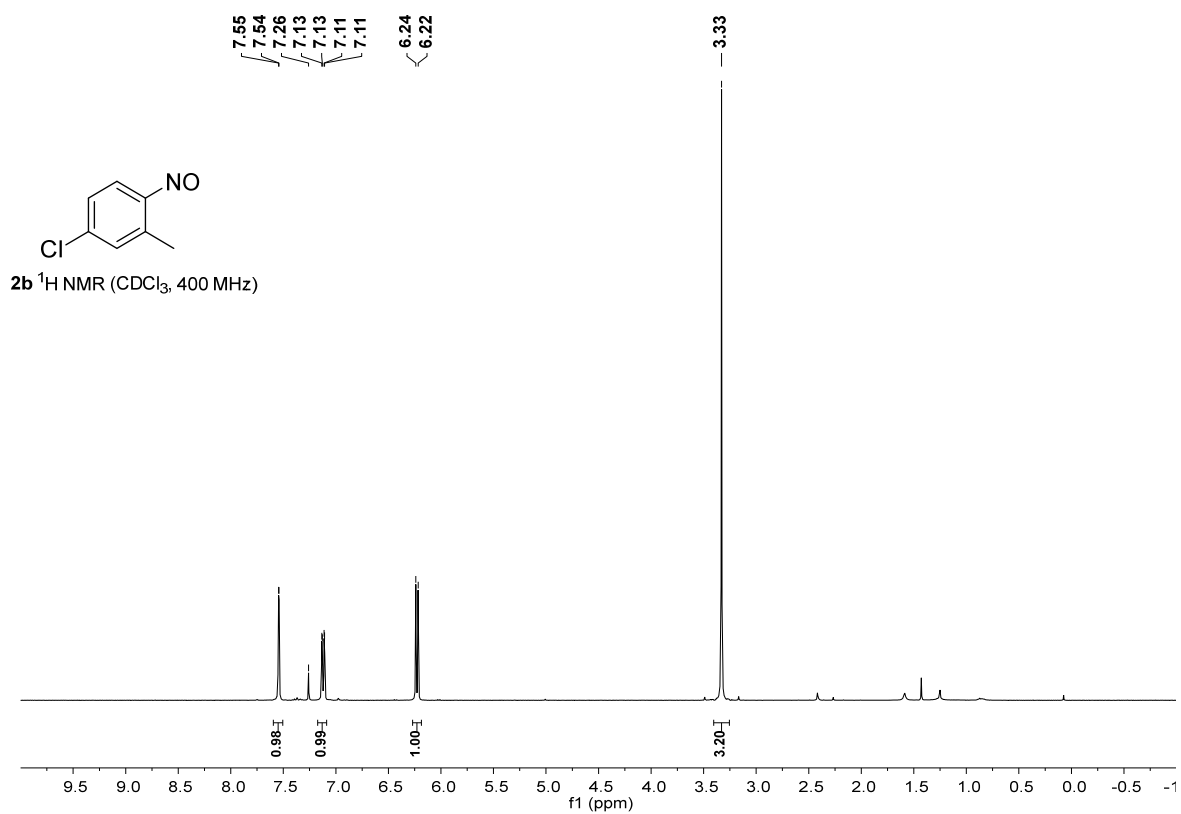
HPLC traces of the reaction after 150 min: **2b**: 62% yield, **1b**: 13% yield. Yields were calculated with the aid of calibration curves.

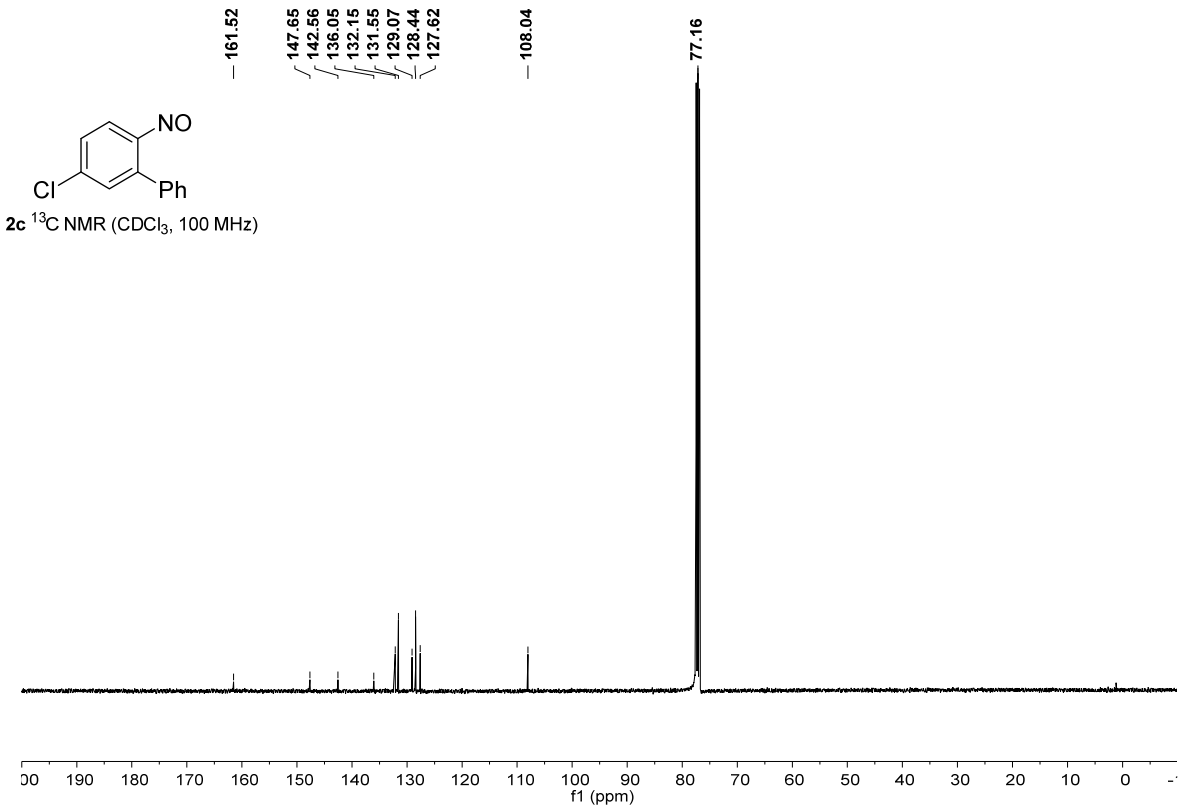
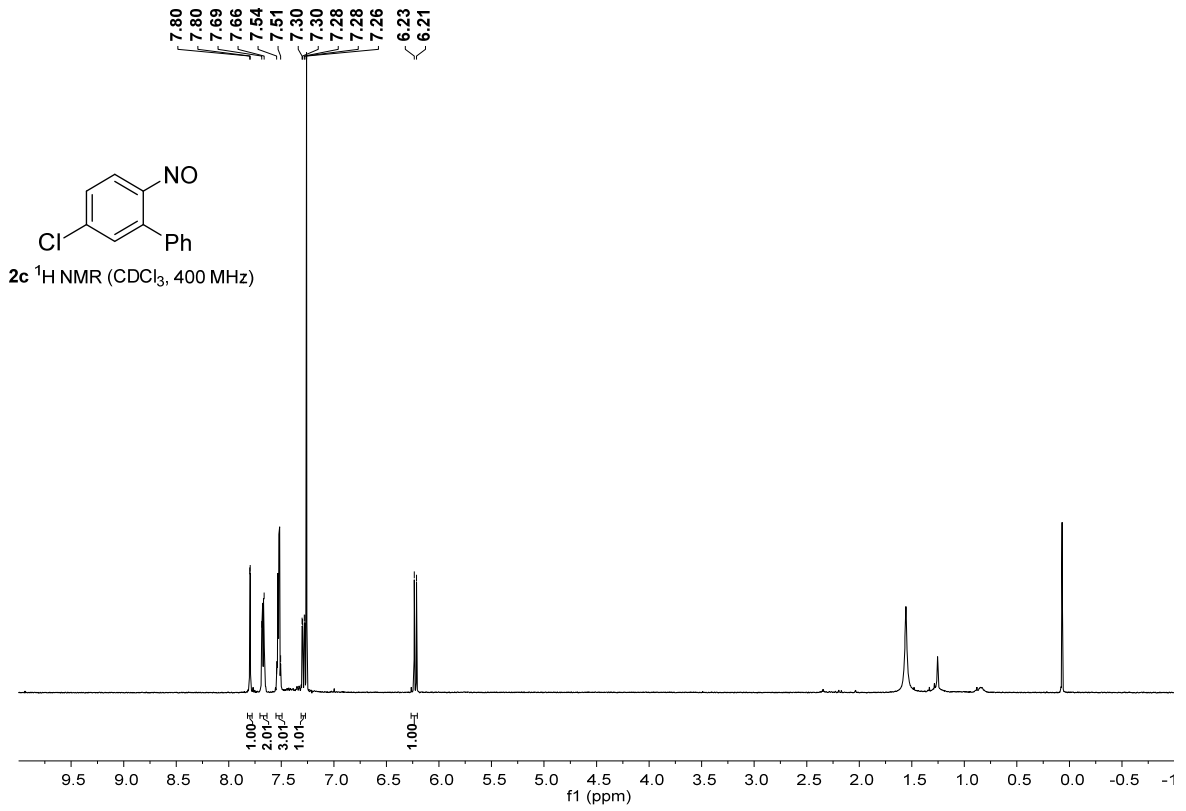


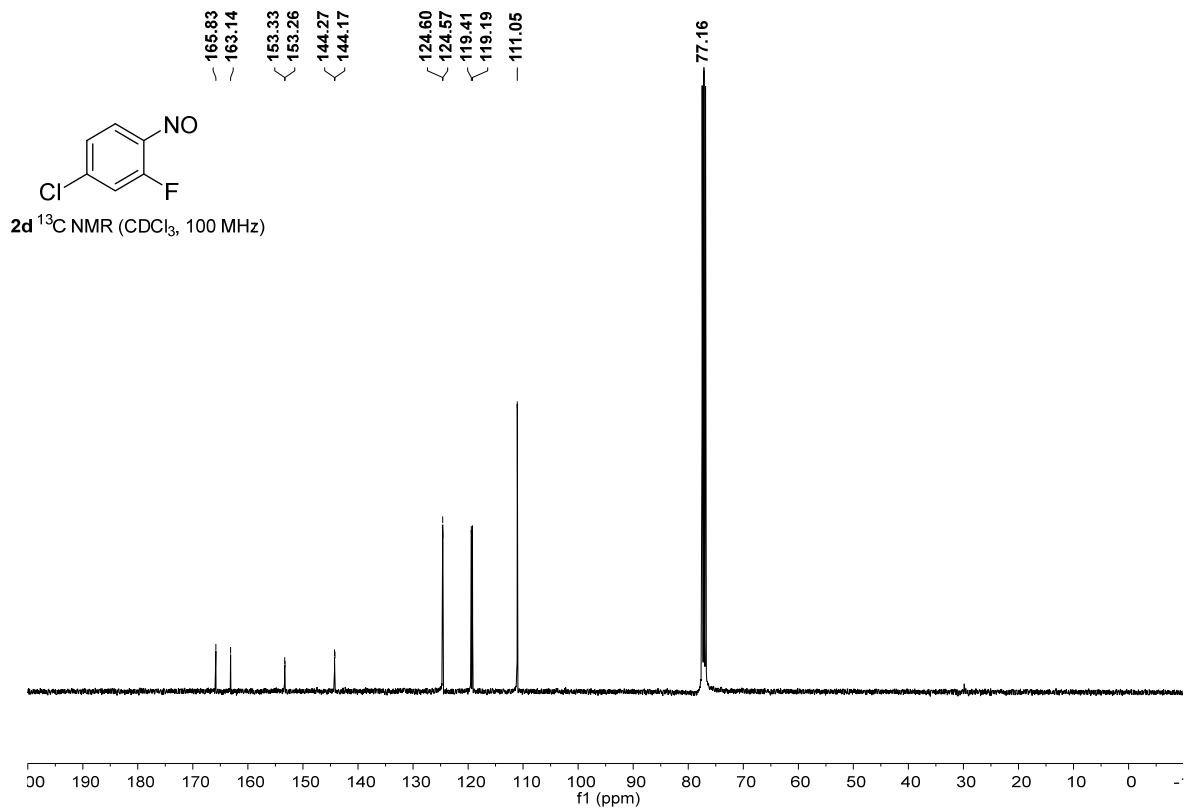
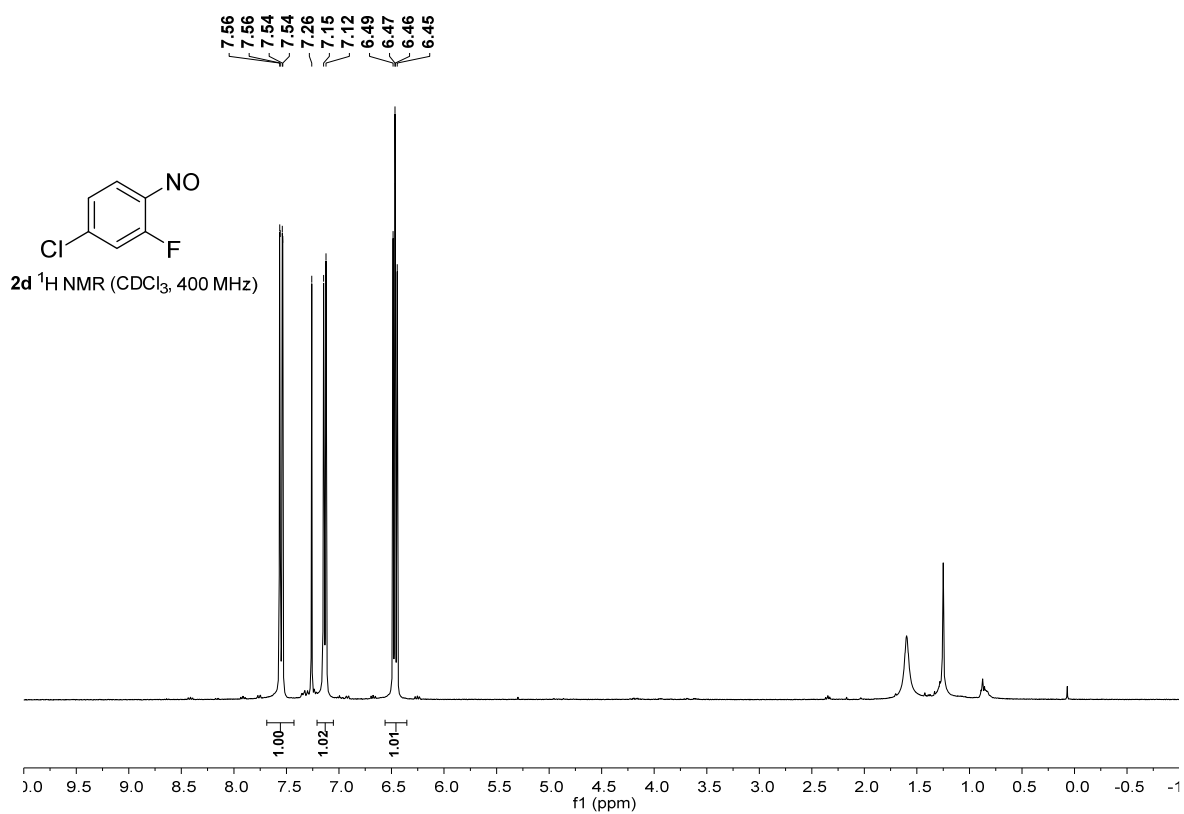
3. ^1H and ^{13}C NMR Spectra

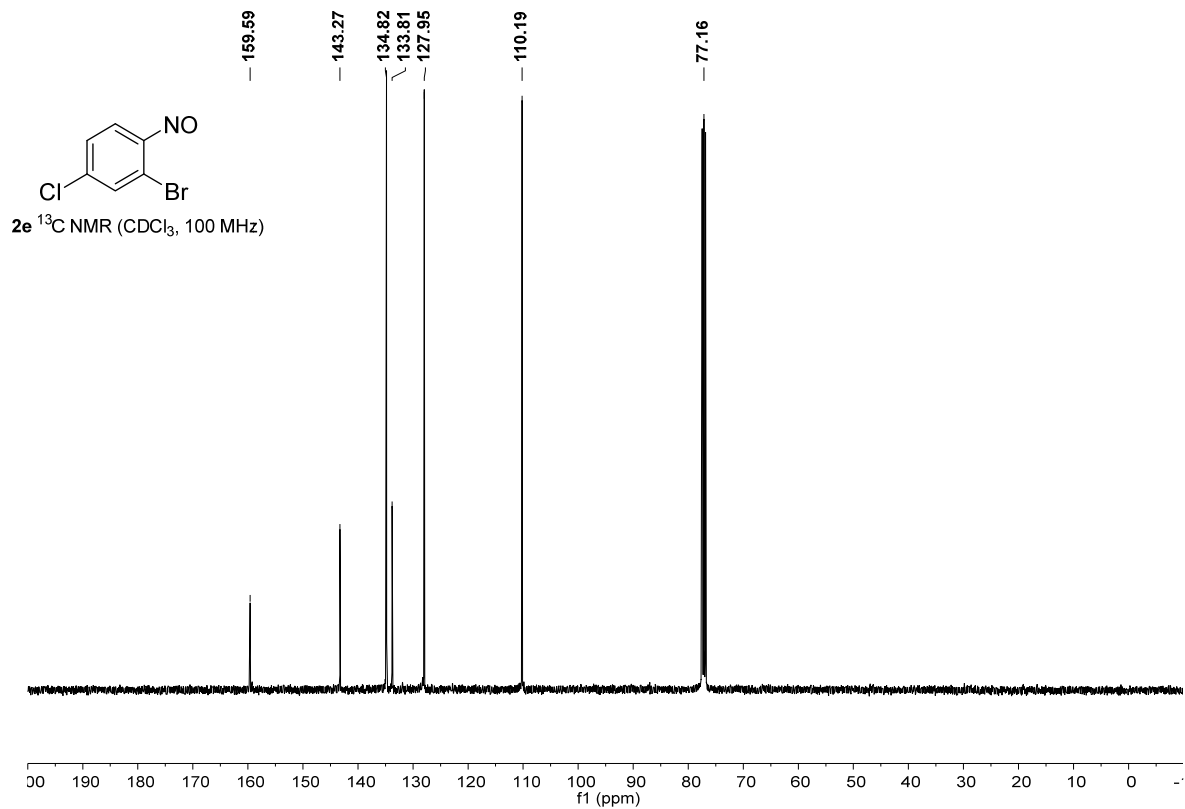
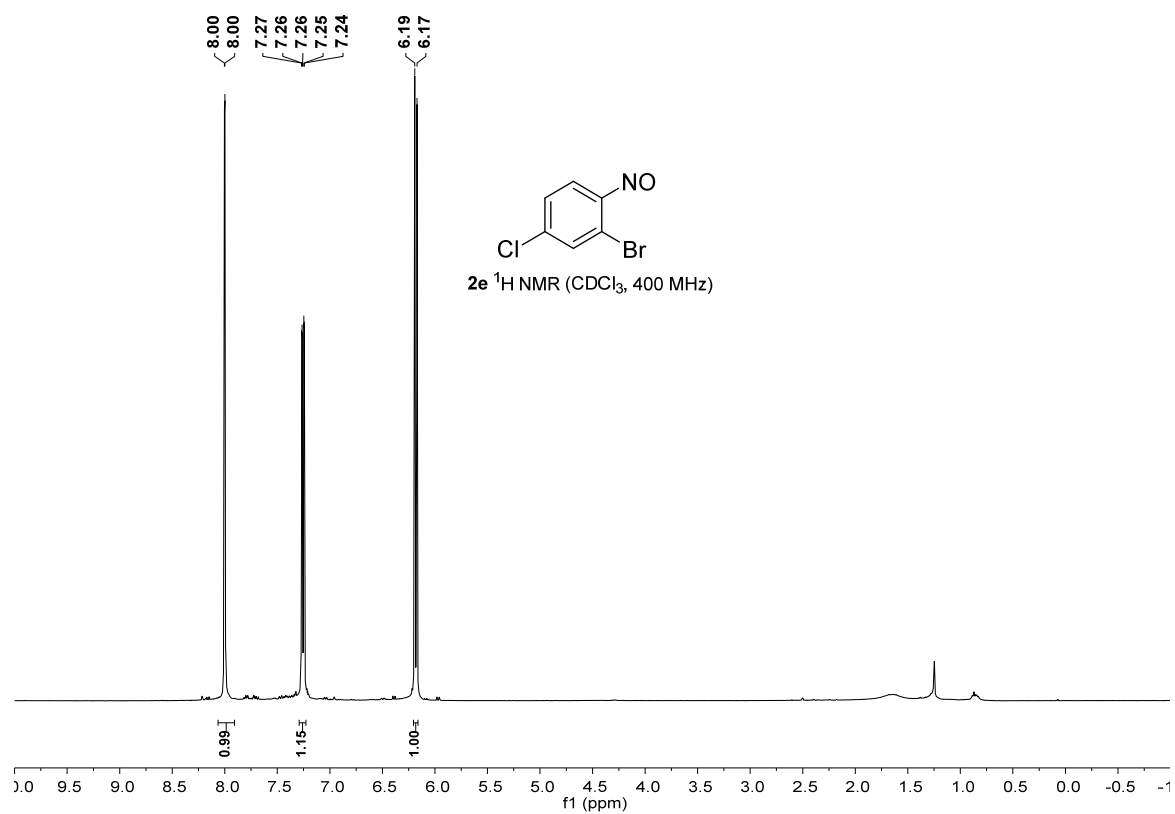


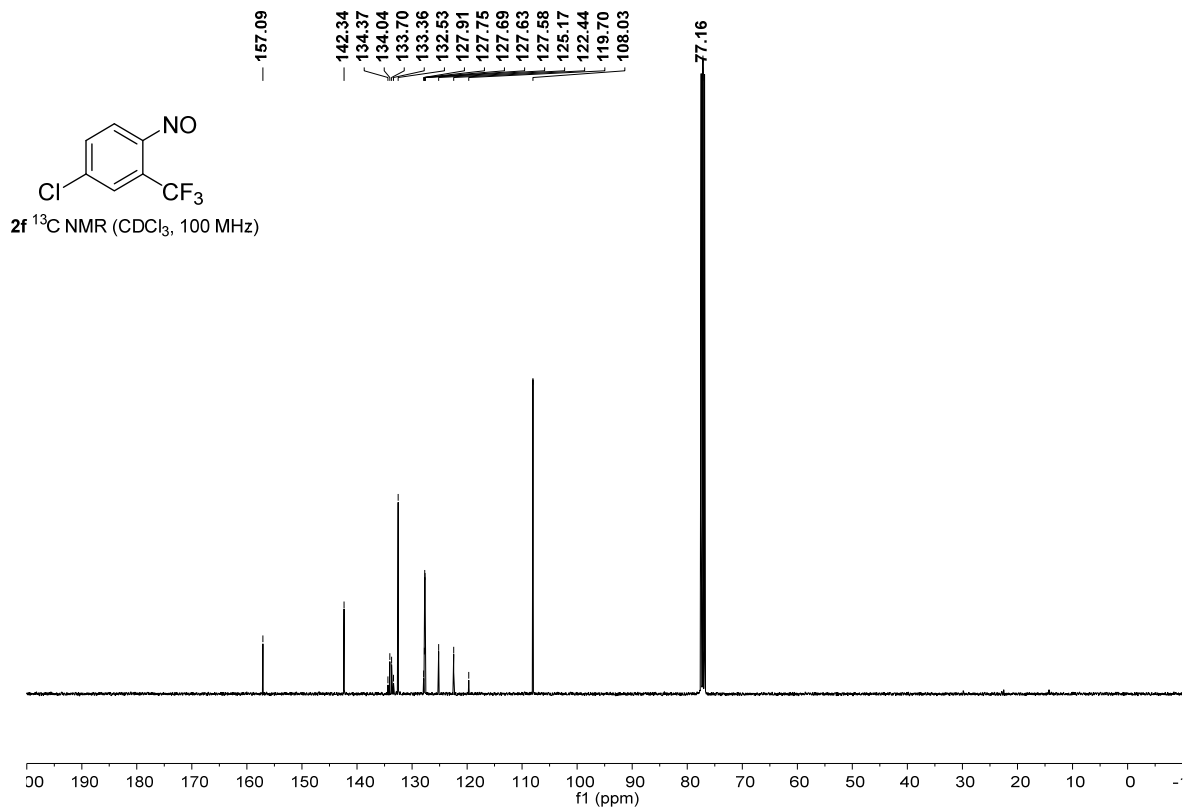
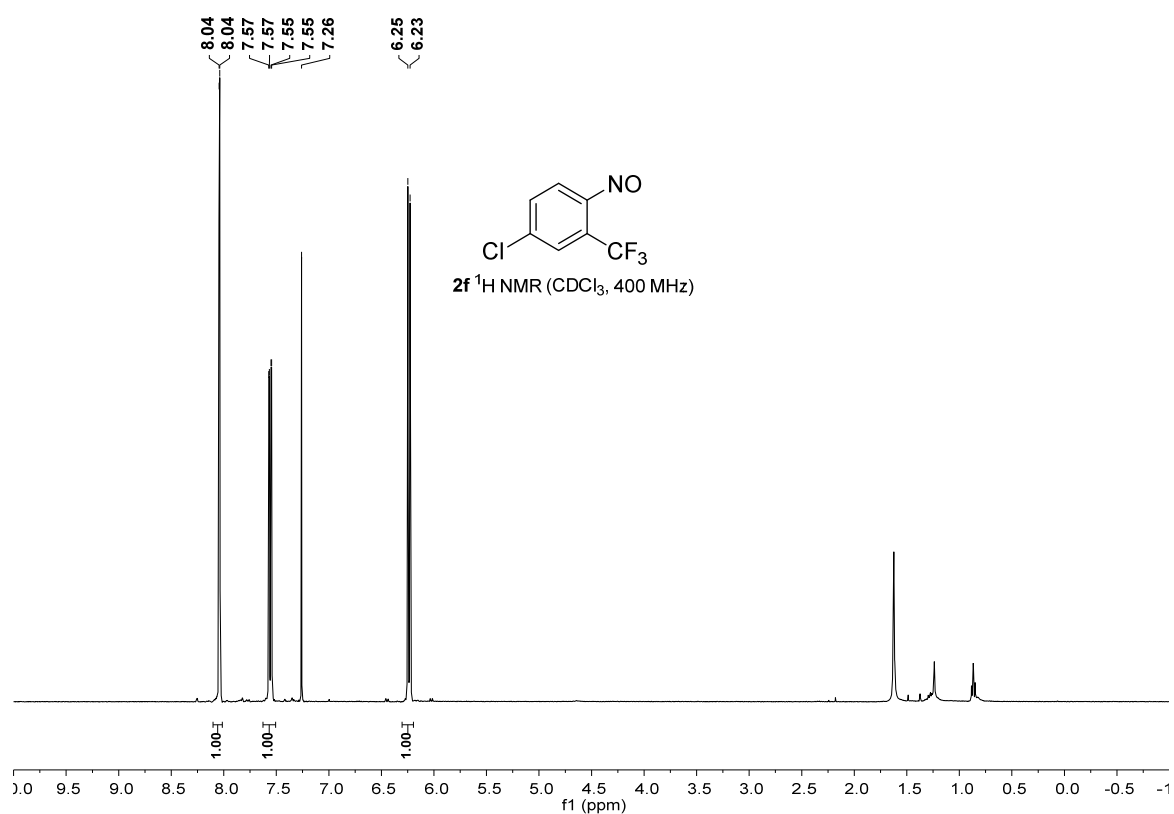


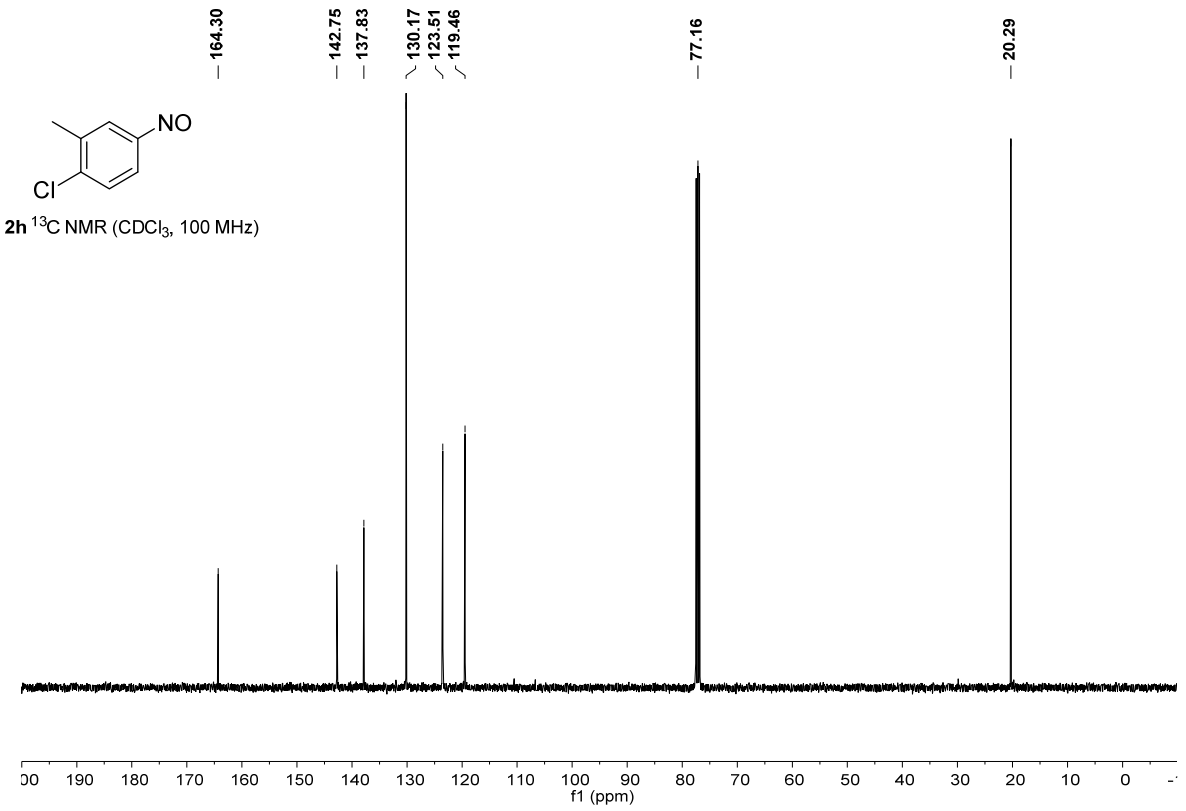
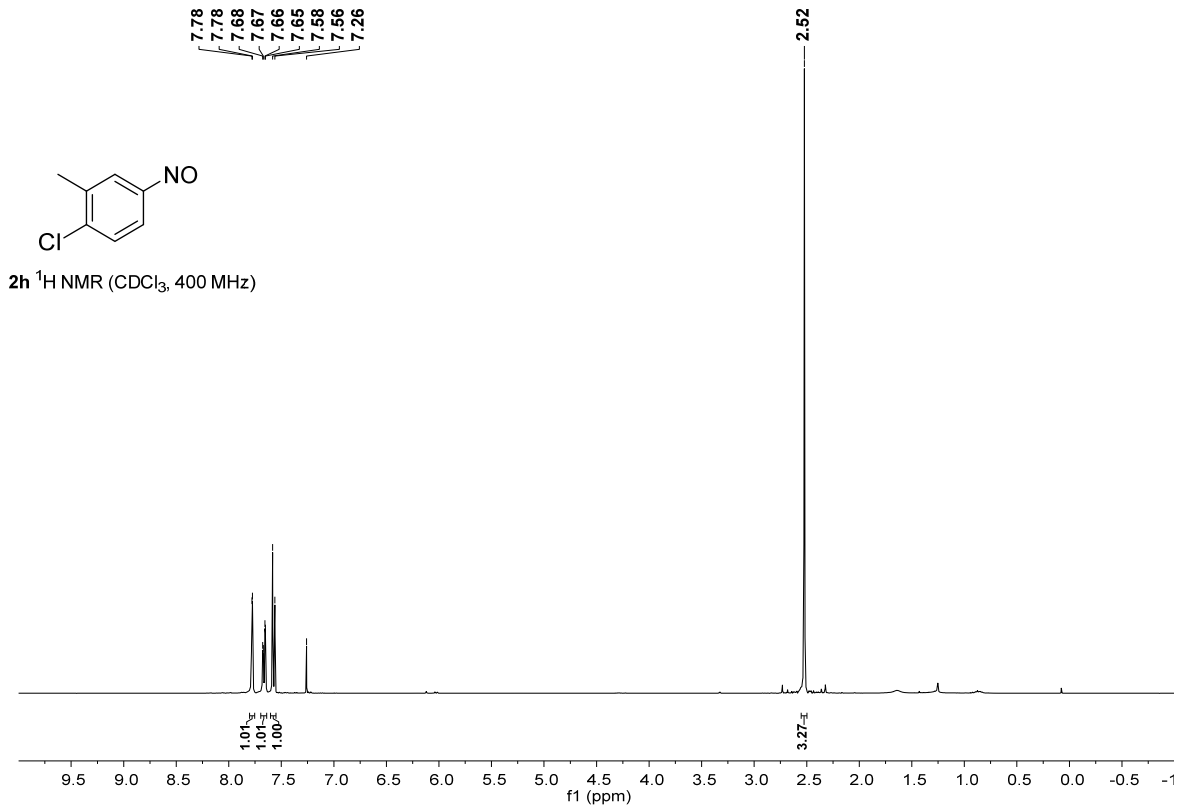


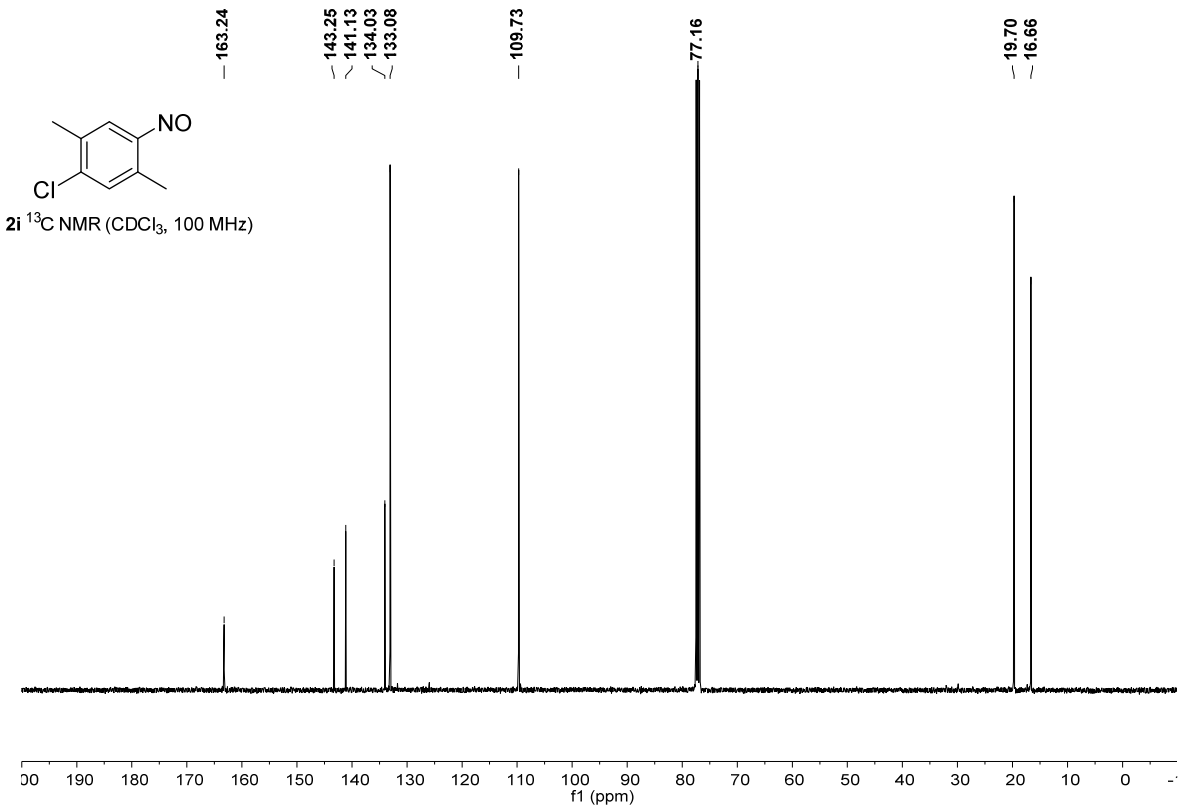
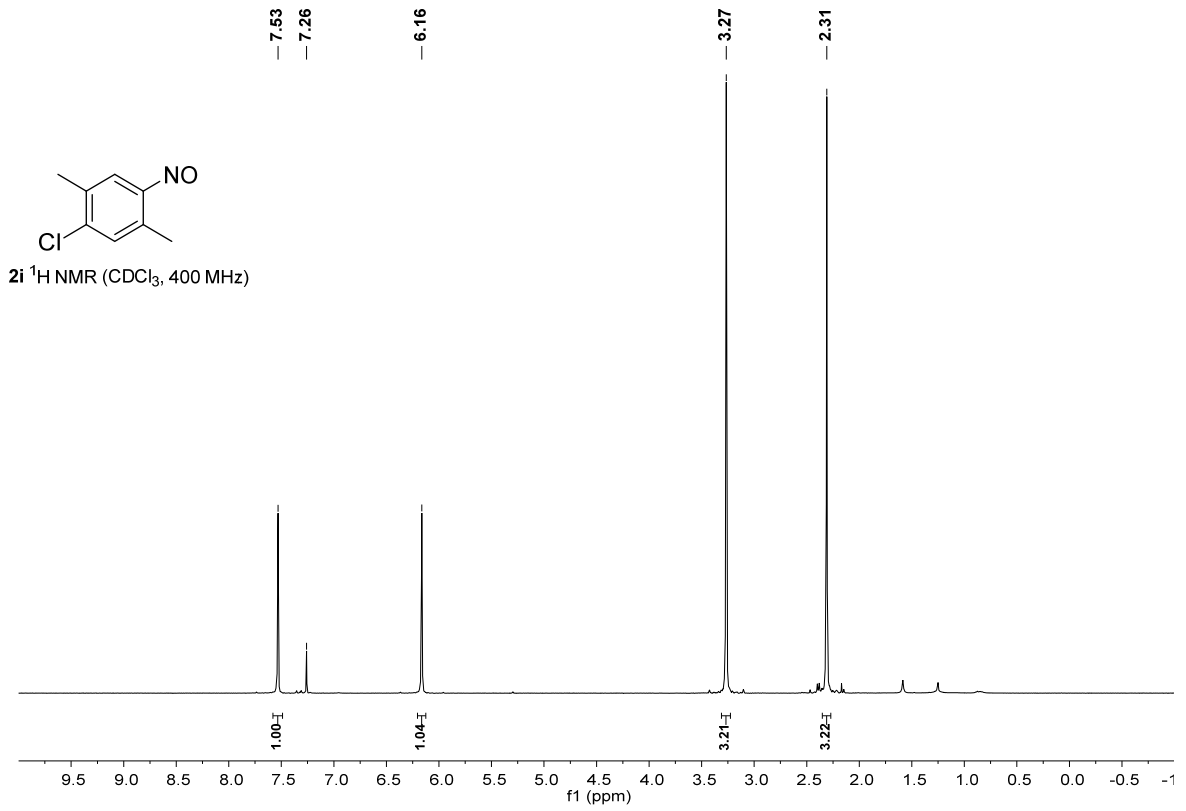


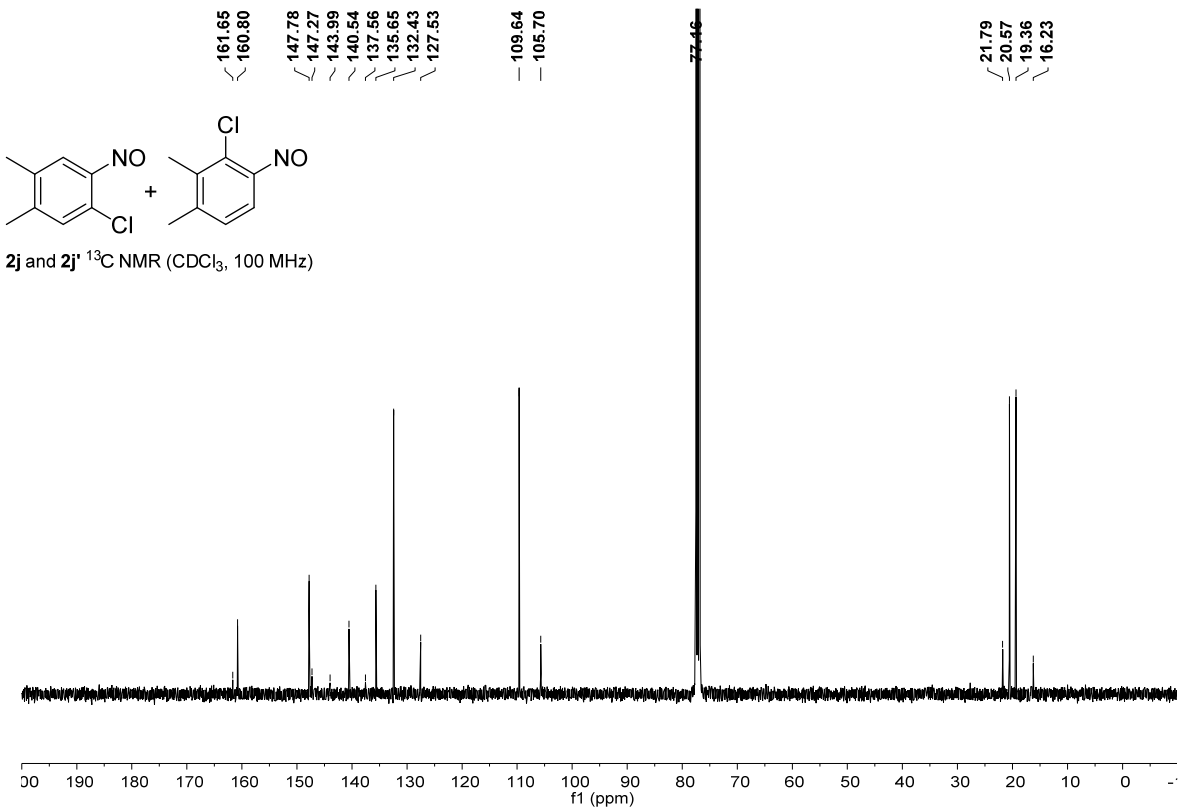
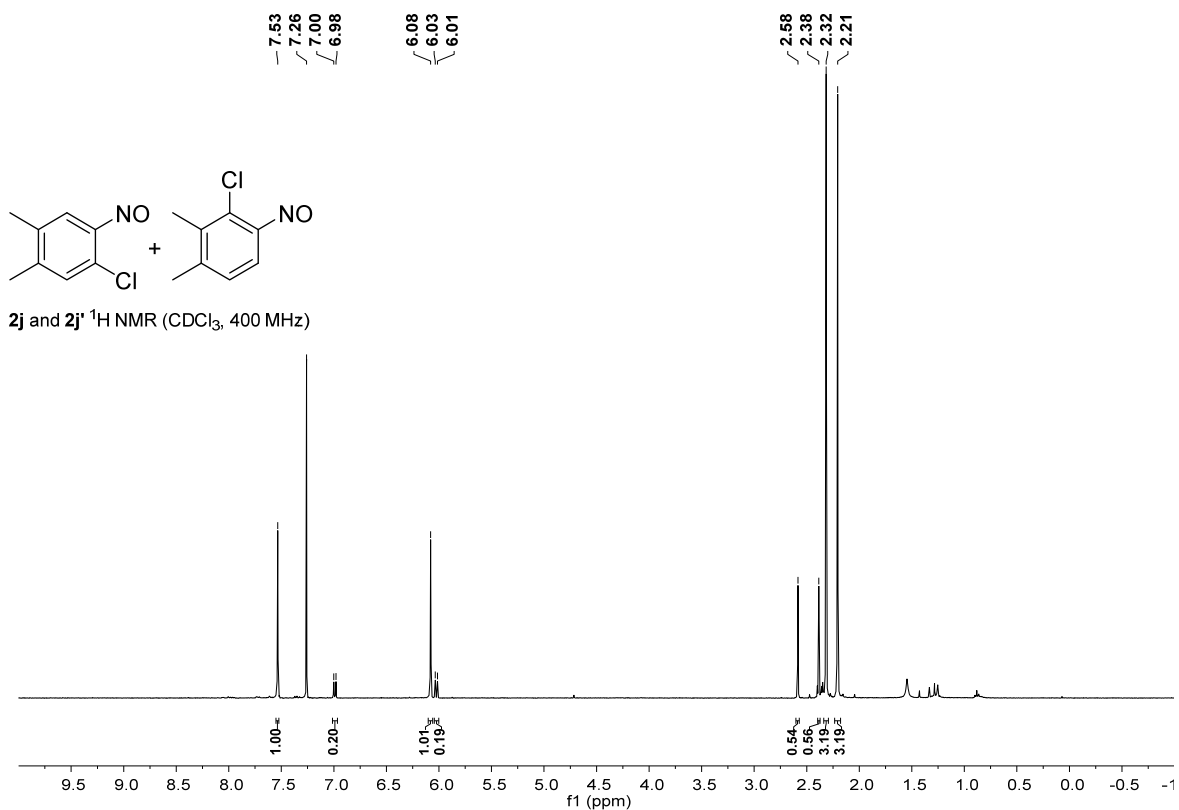


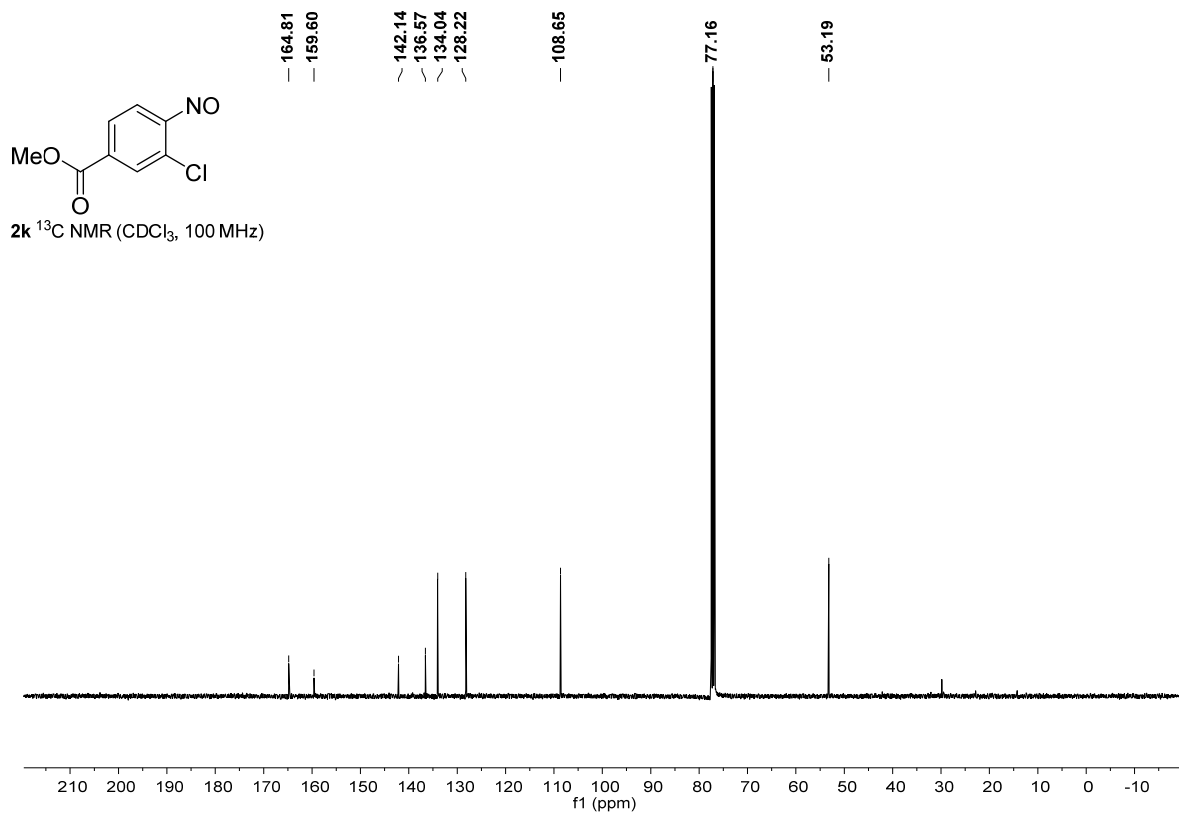
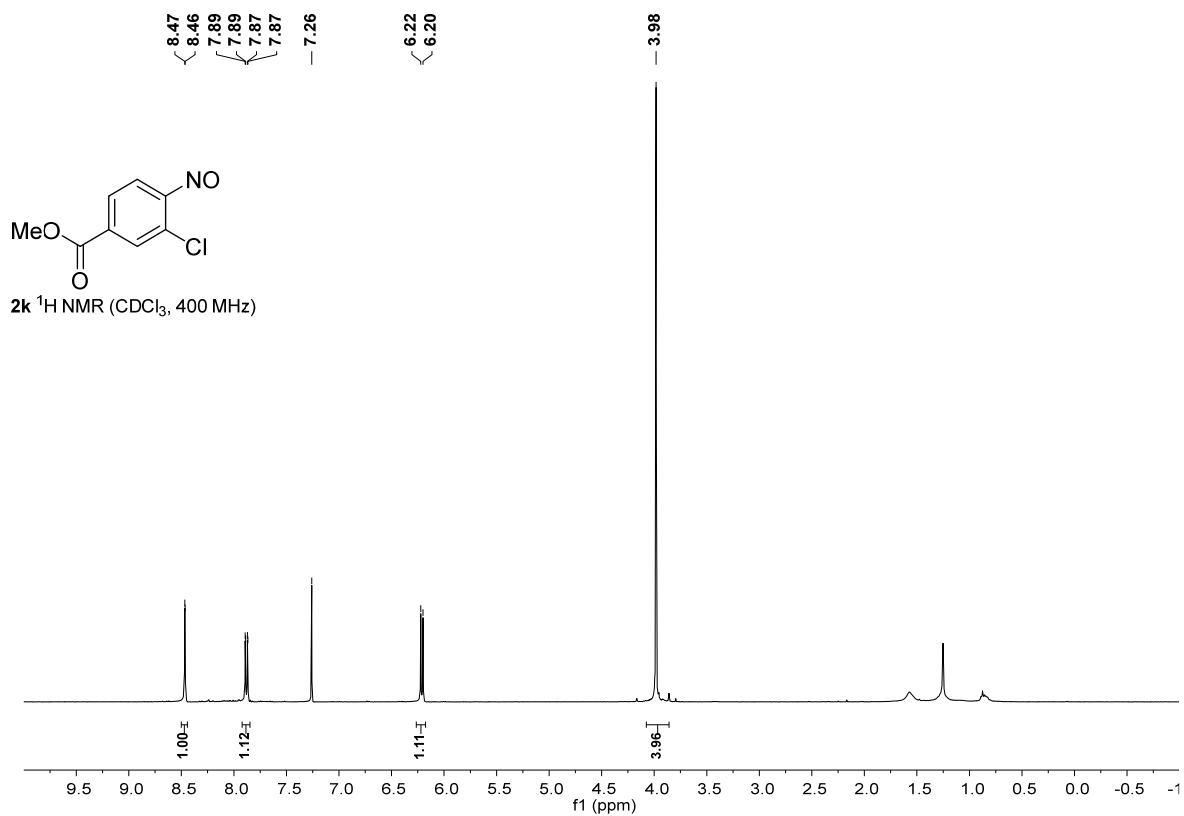


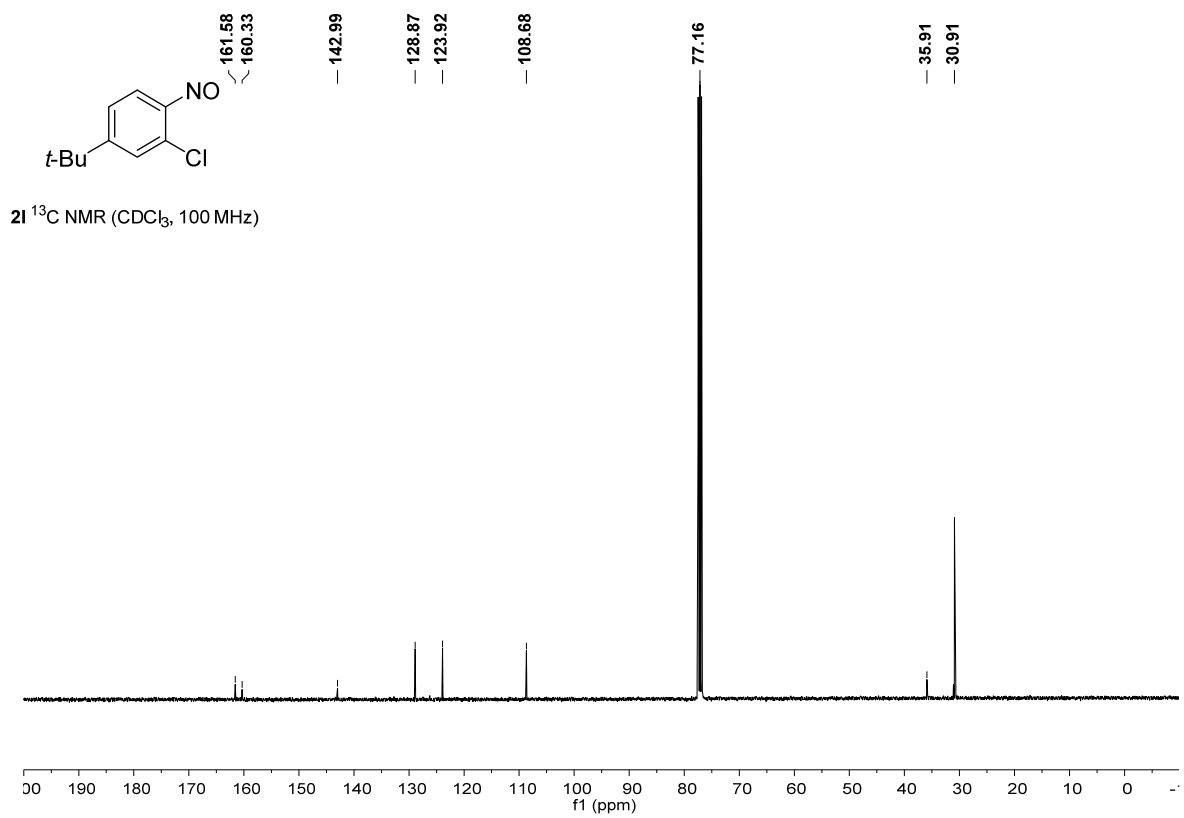
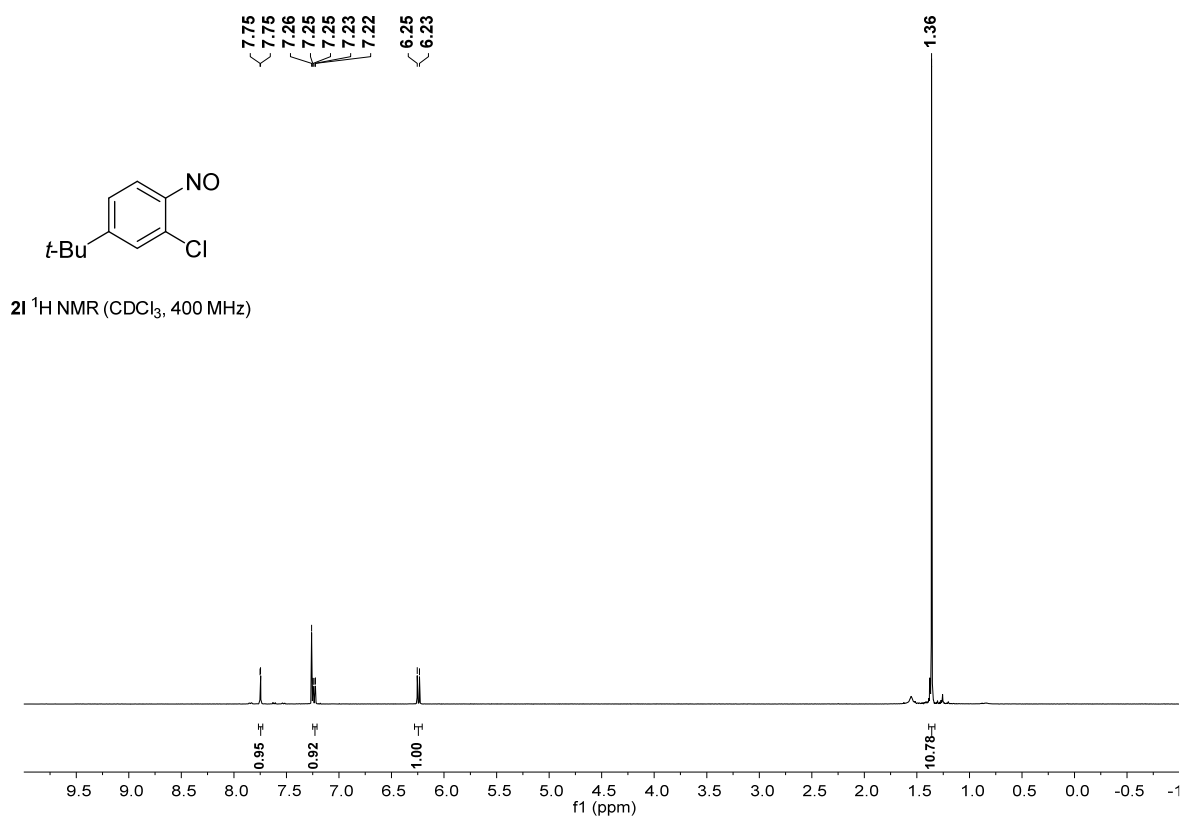


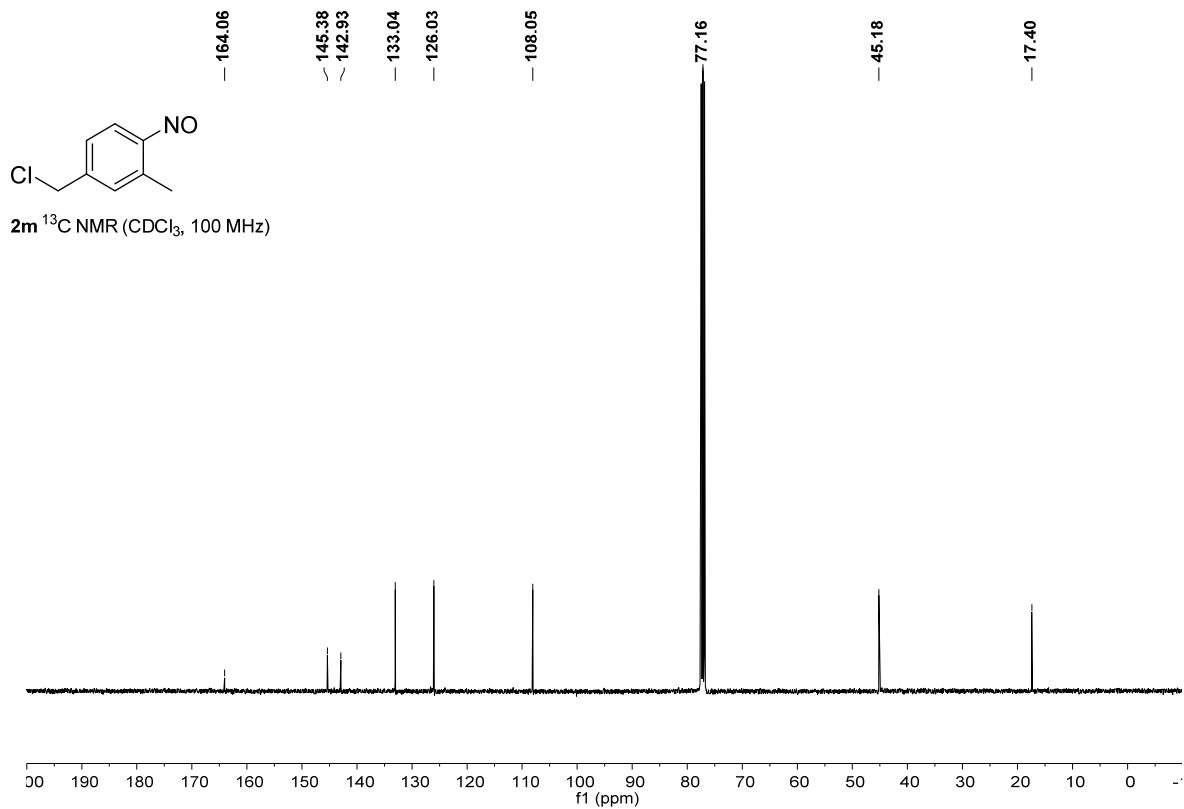
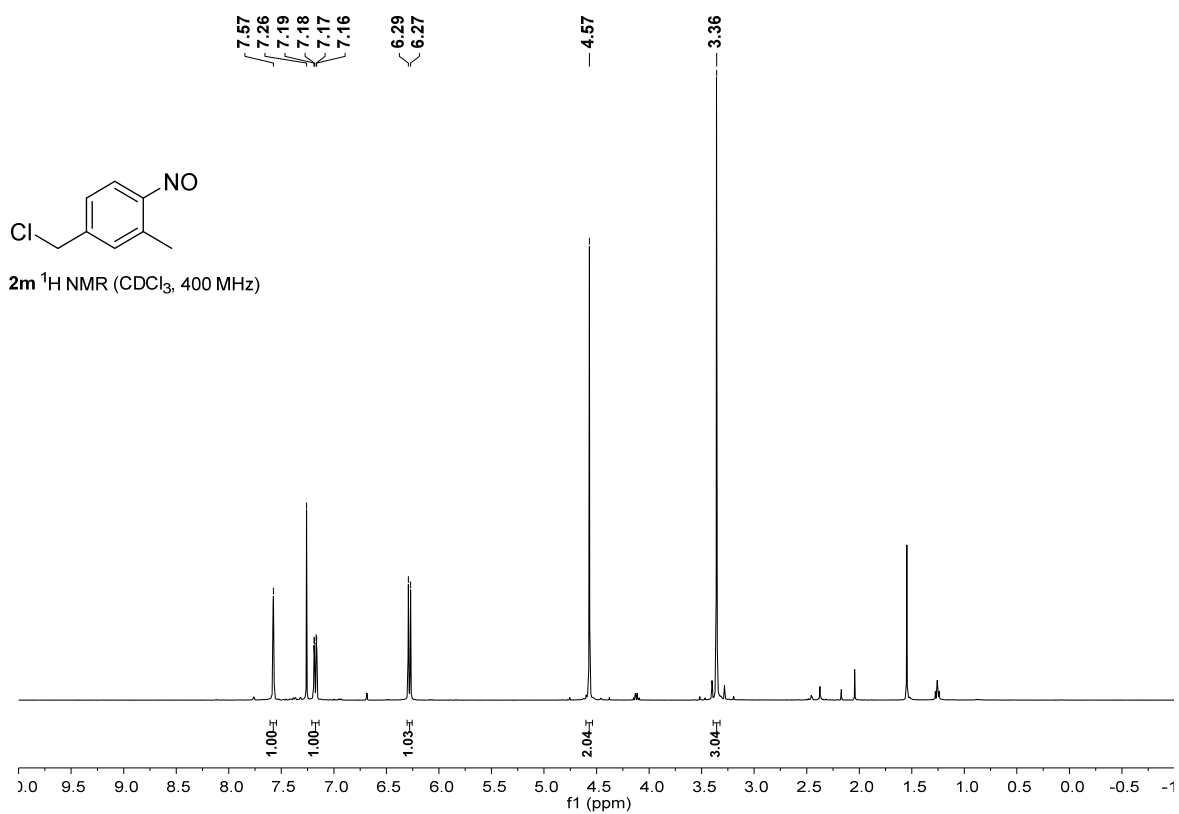


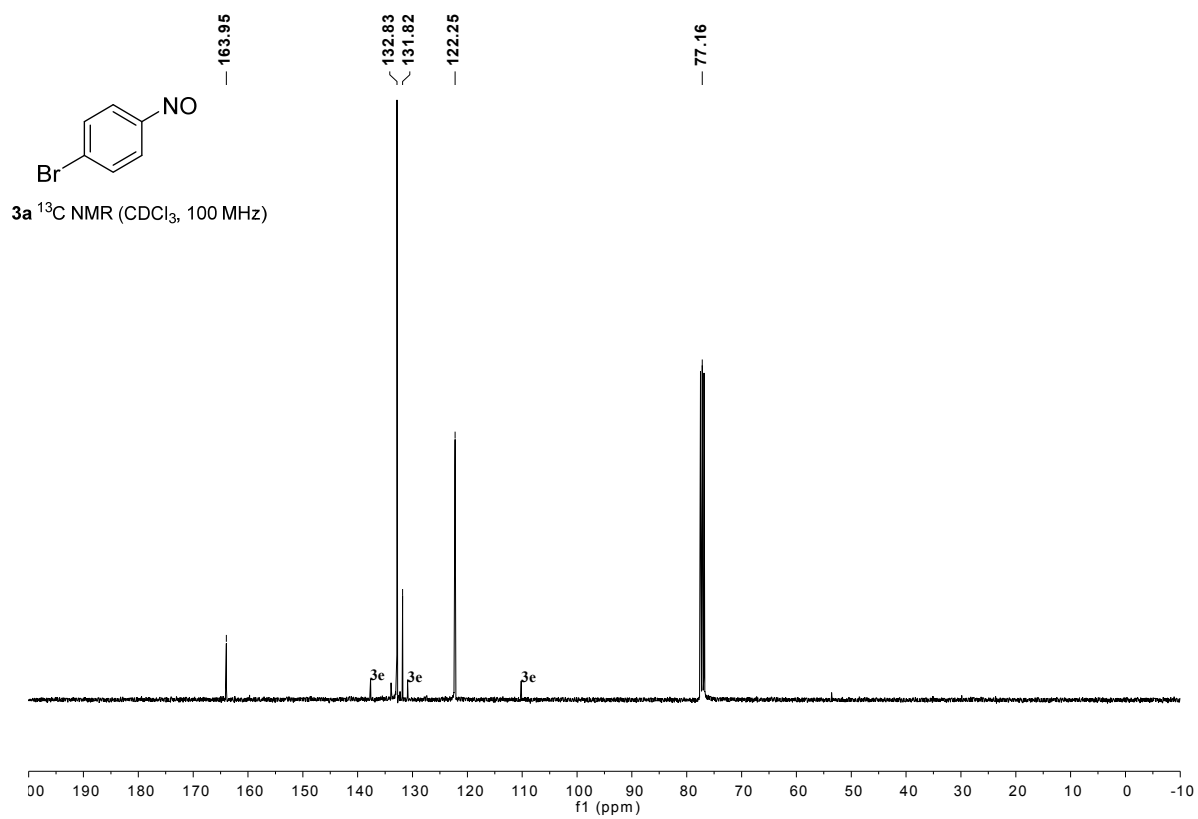
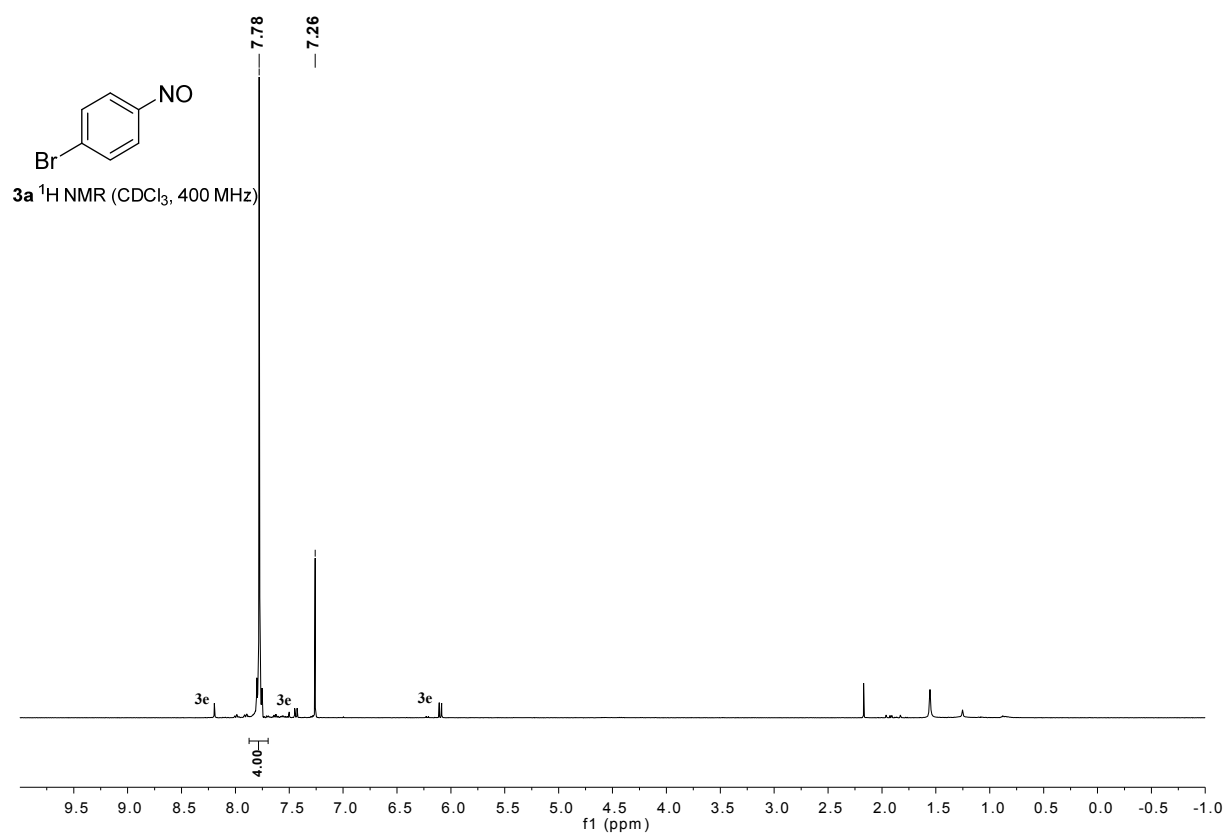


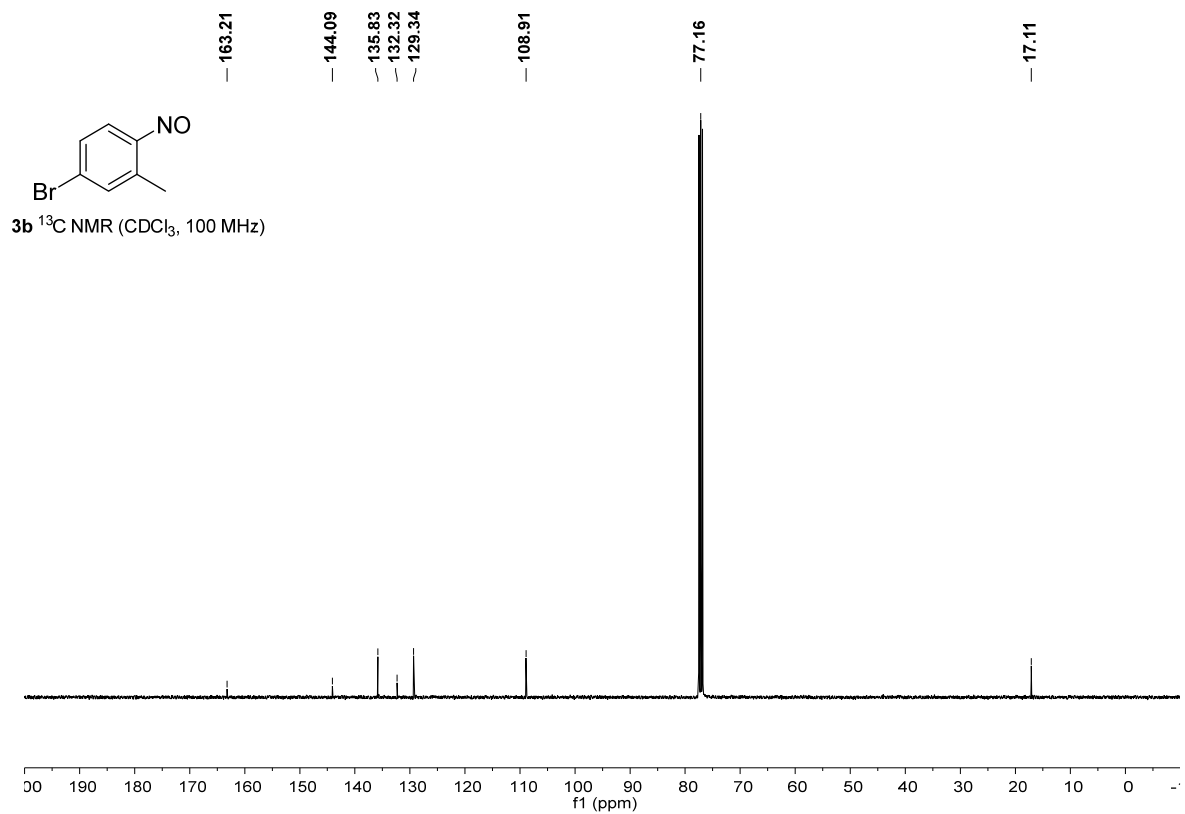
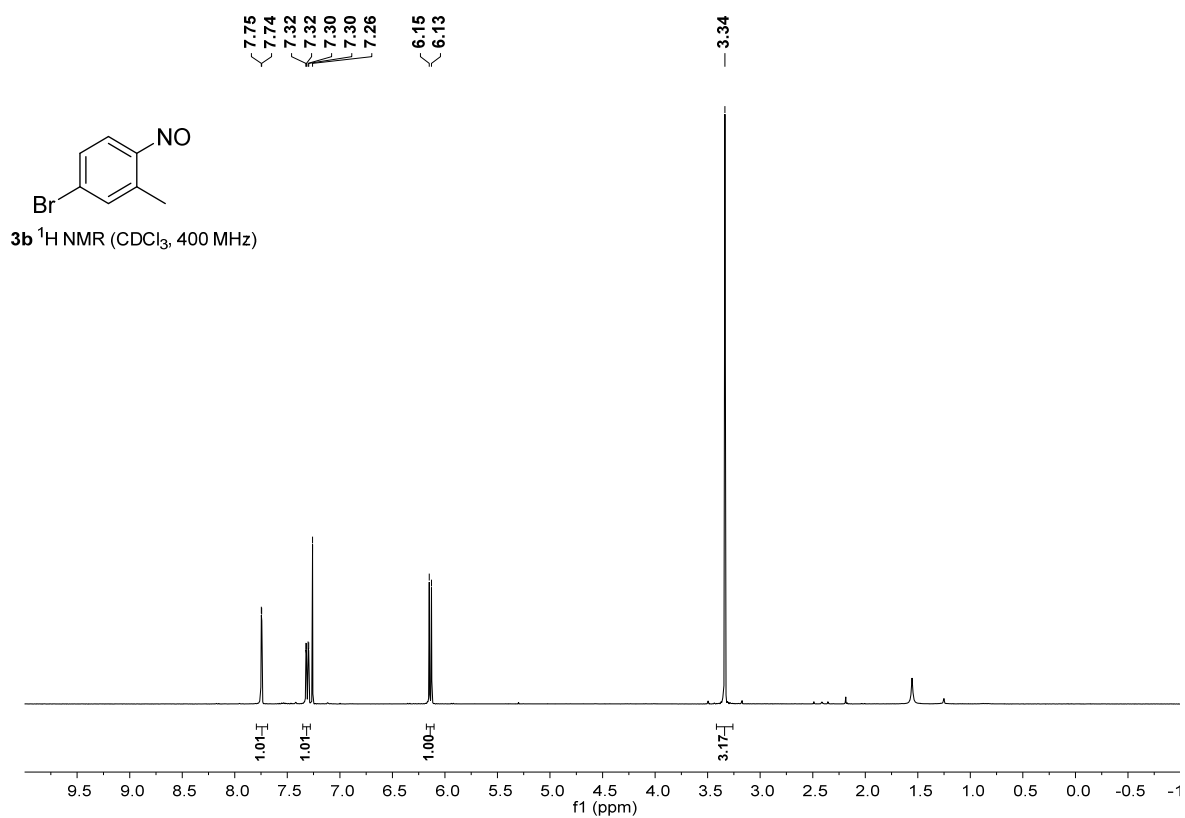


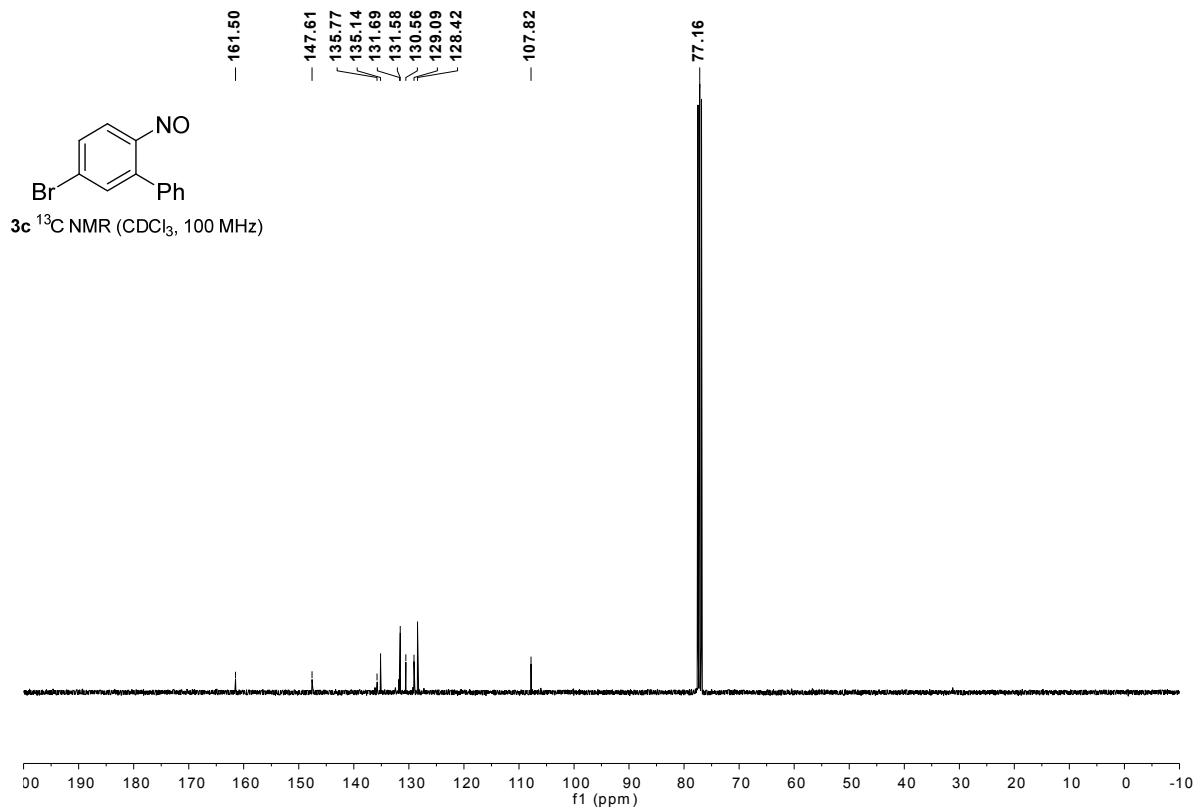
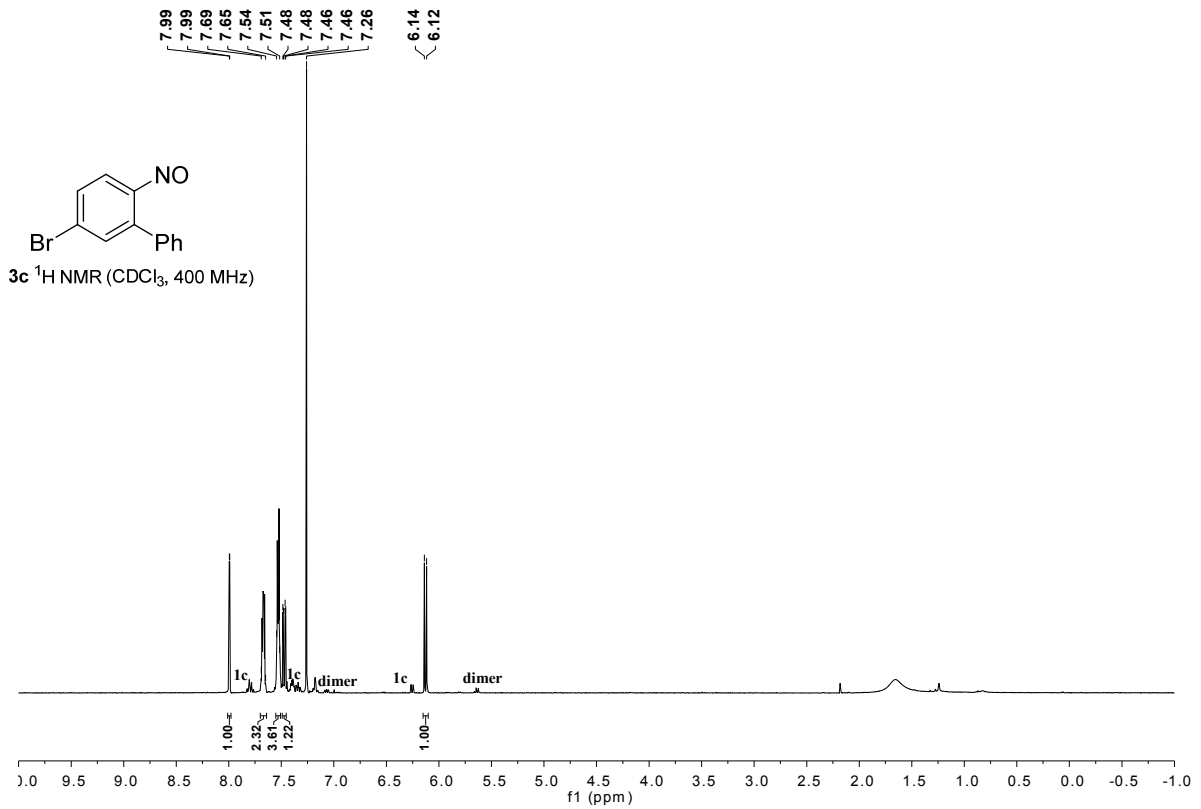


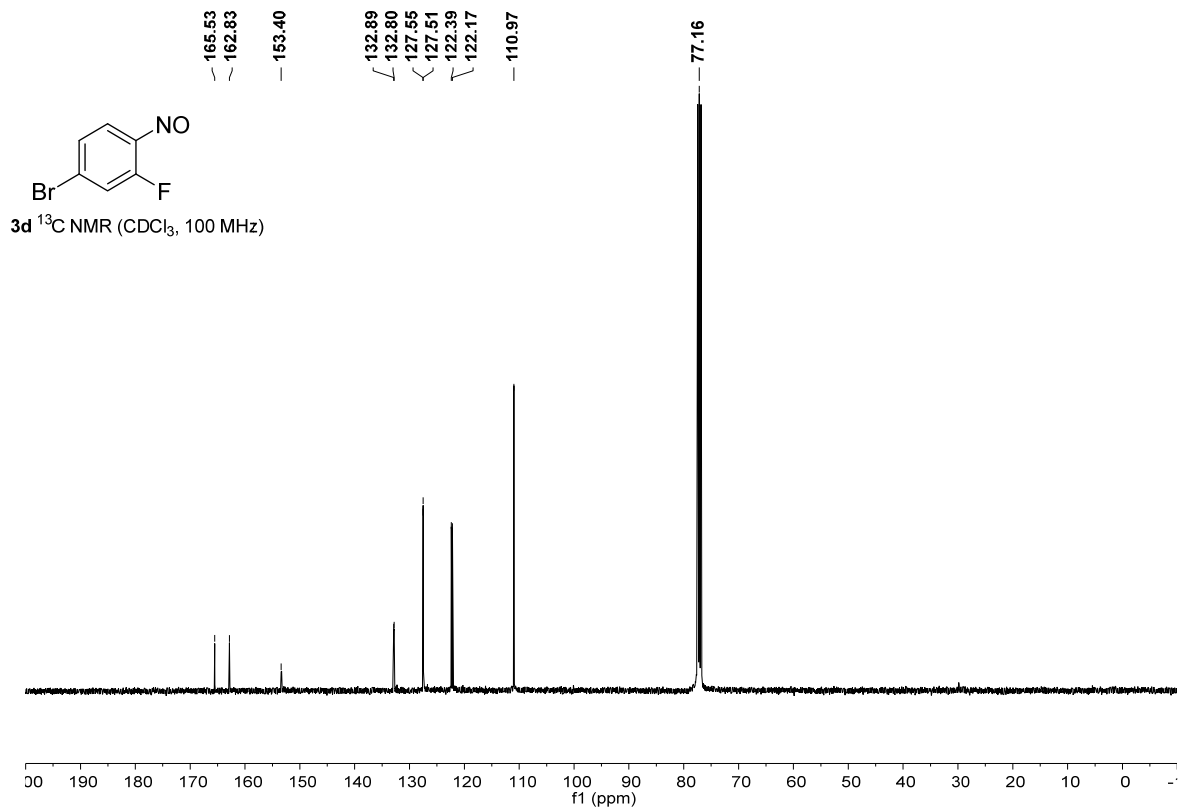
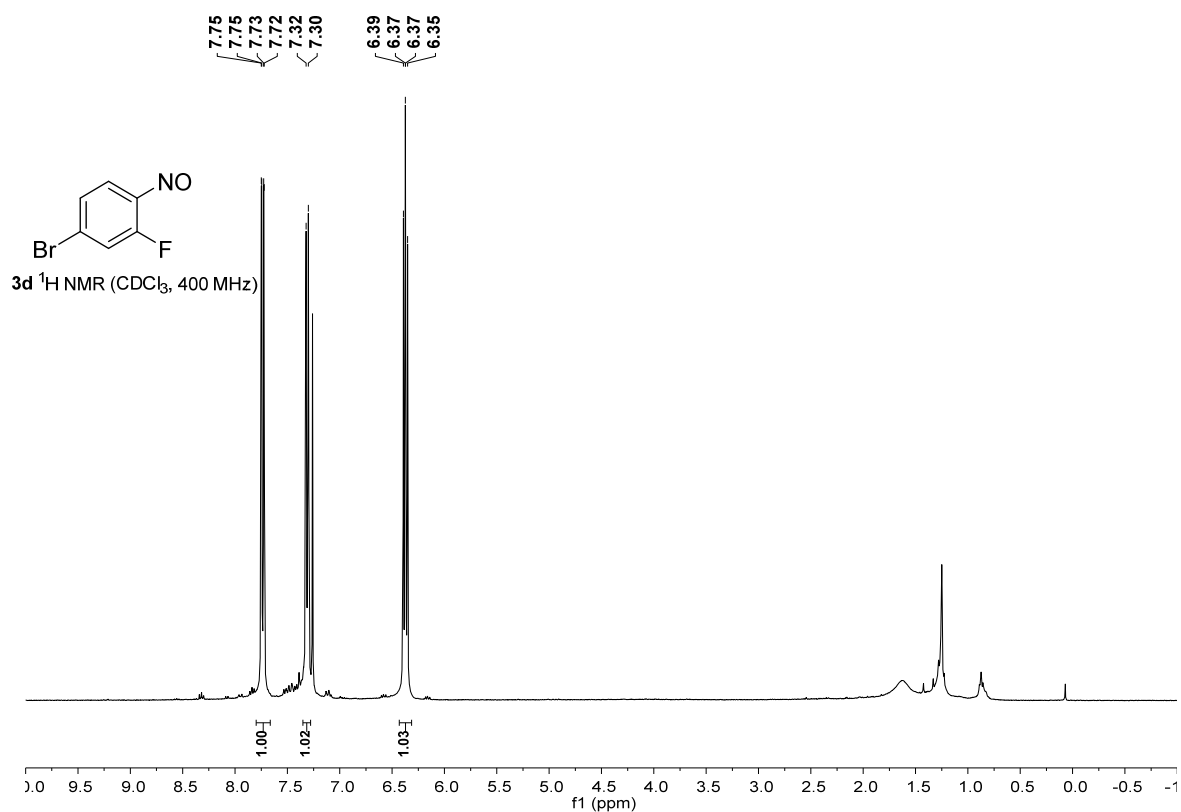


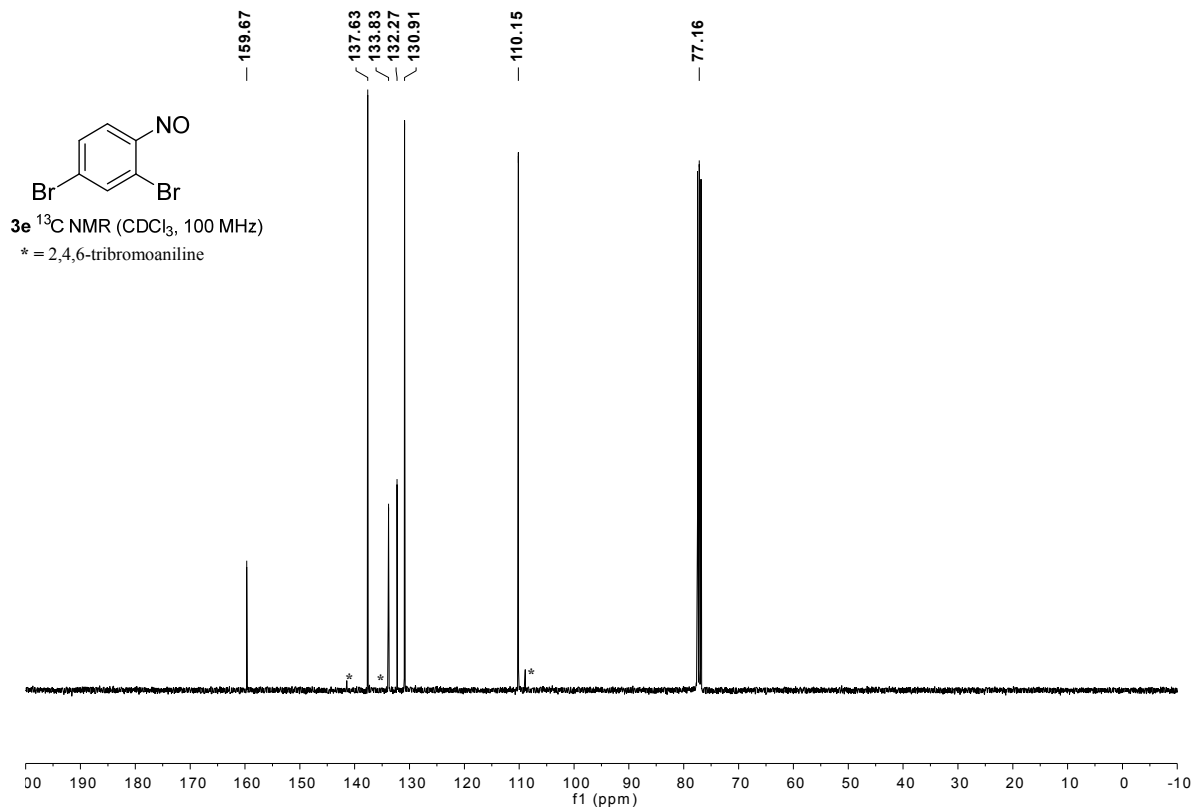
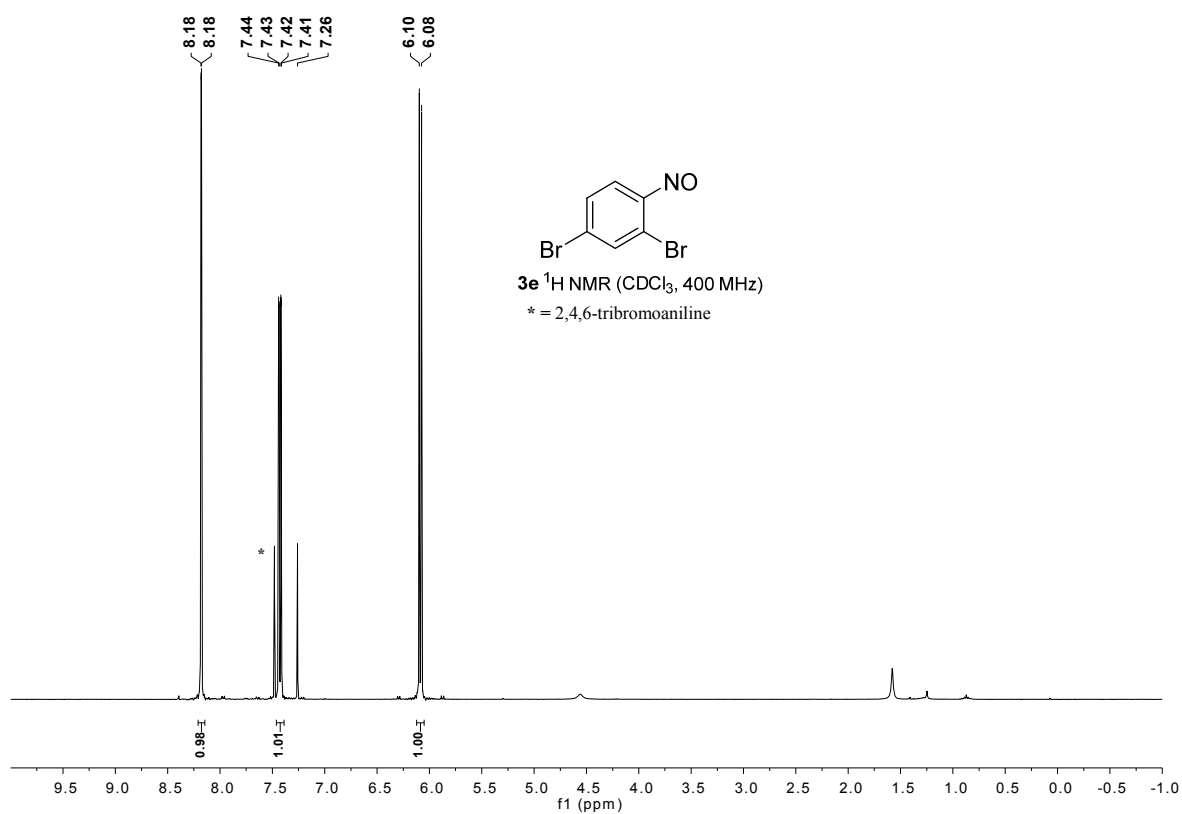


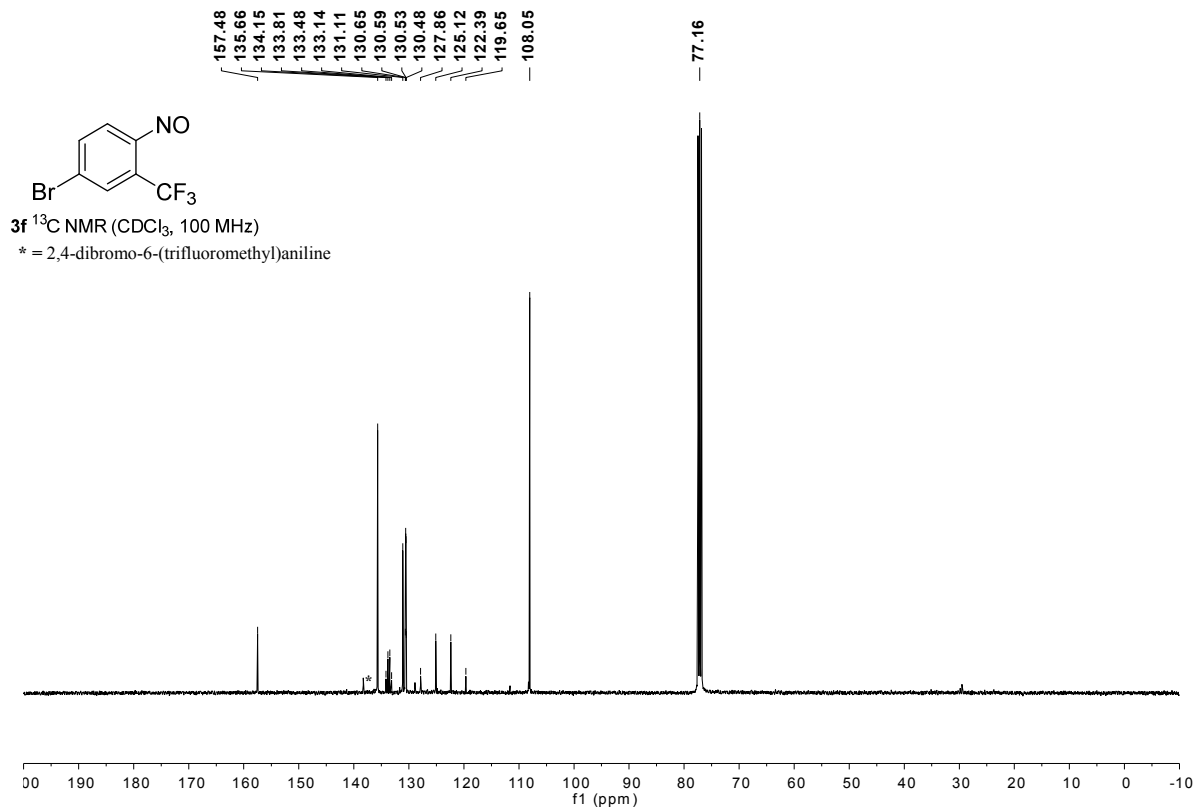
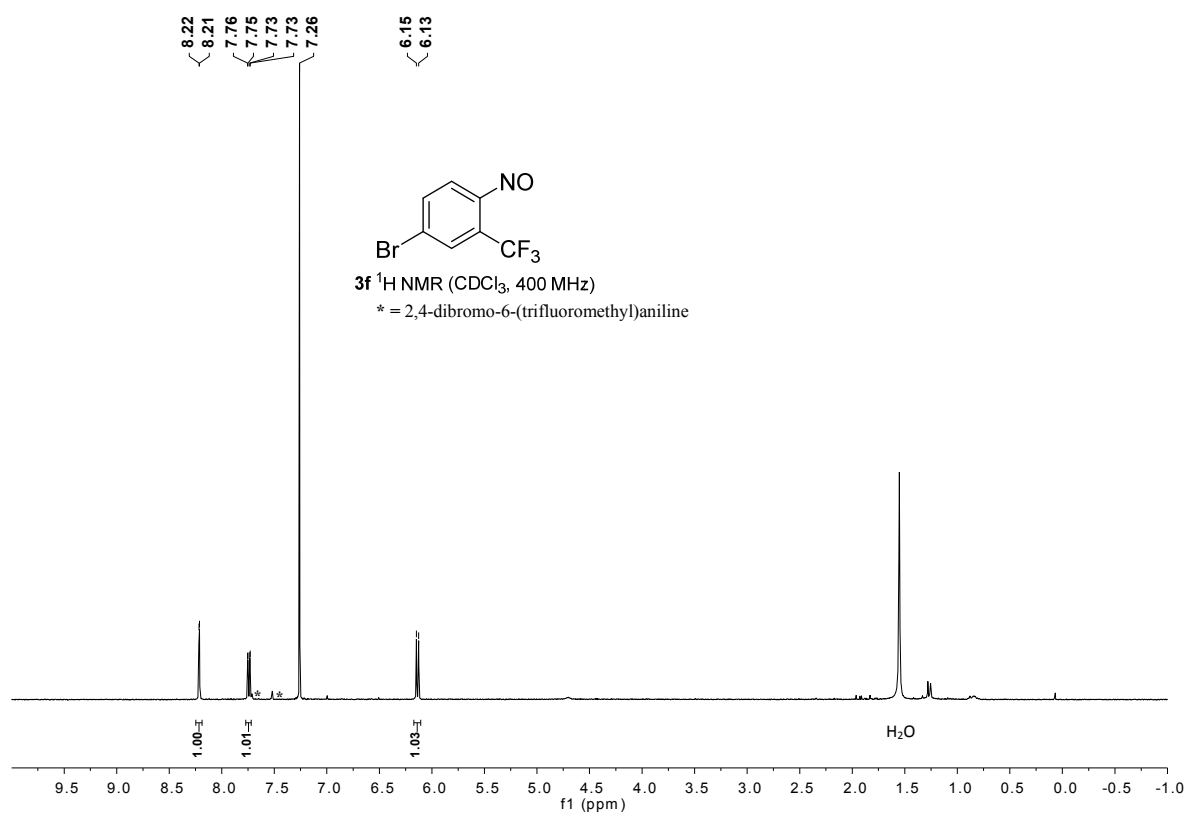


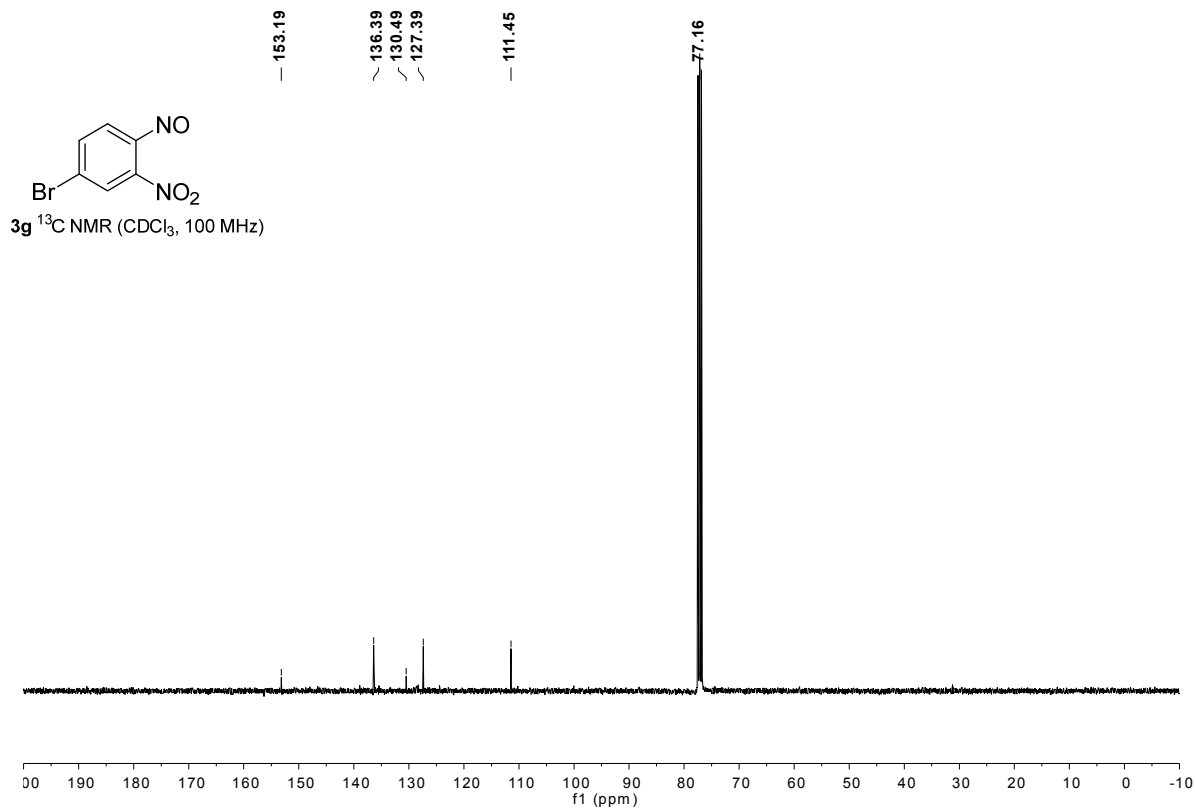
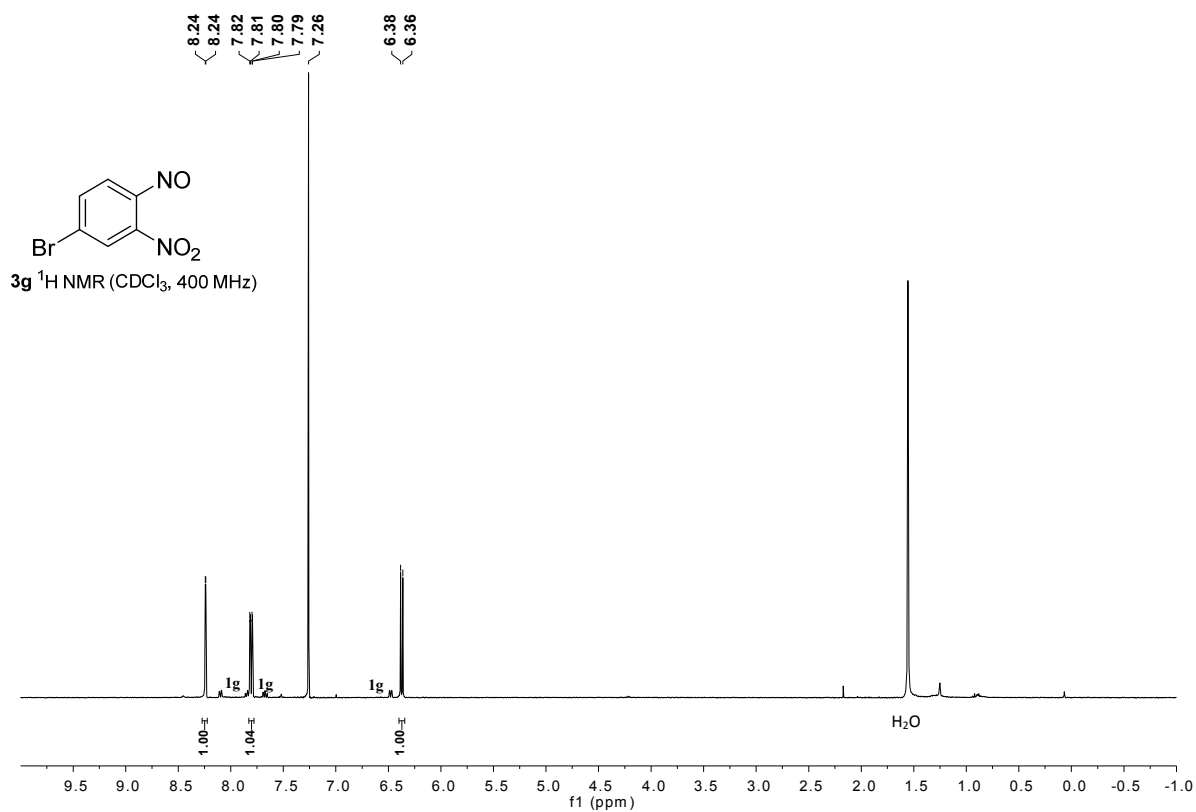


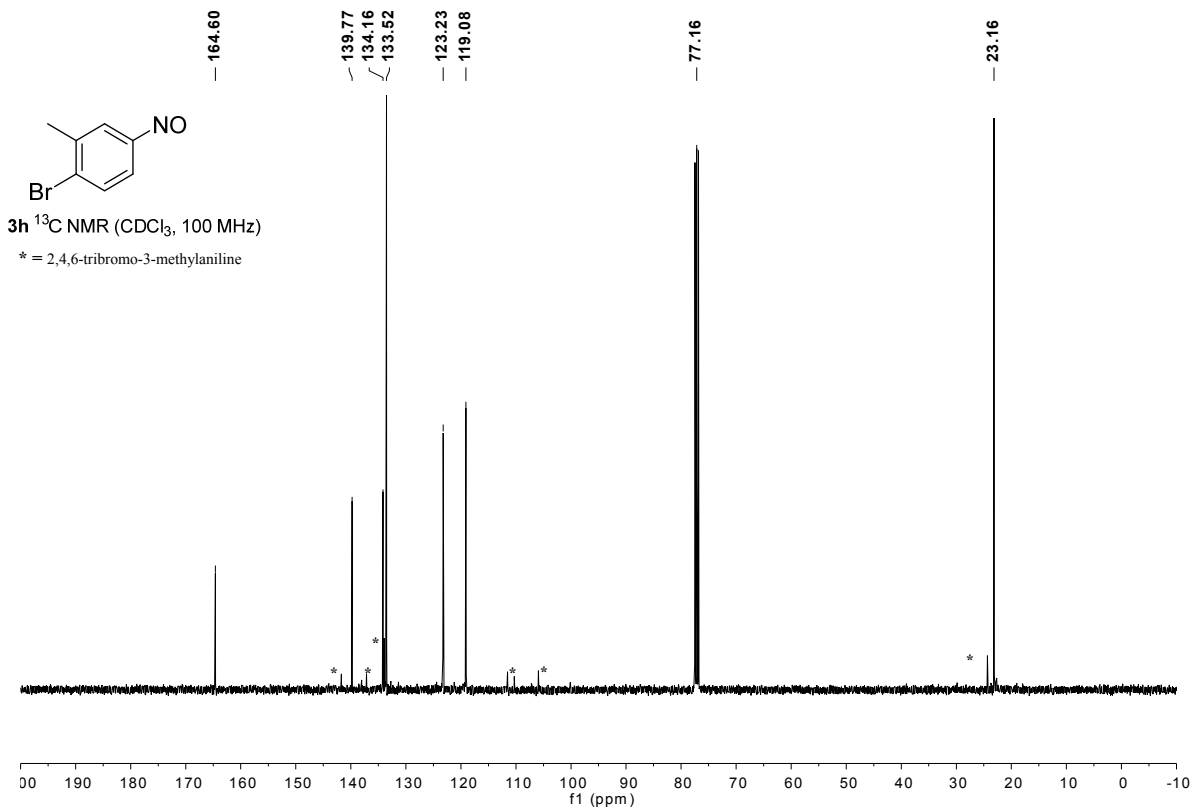
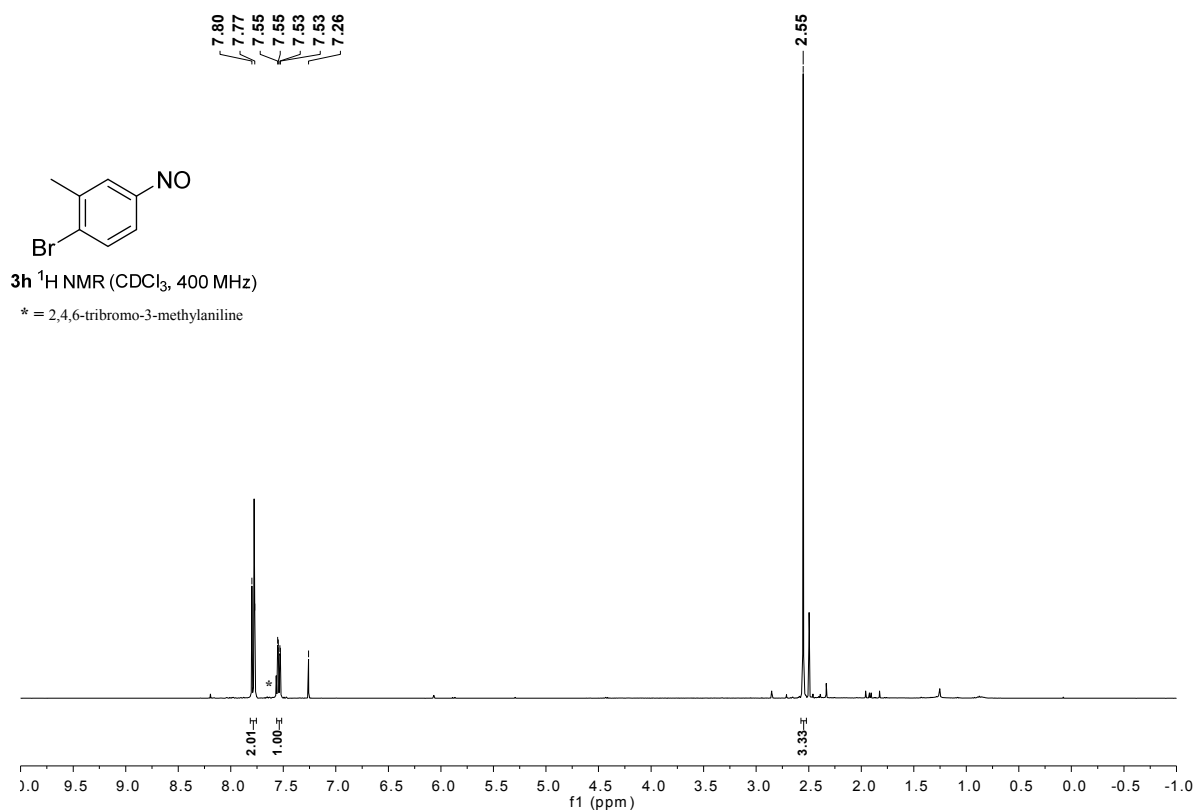


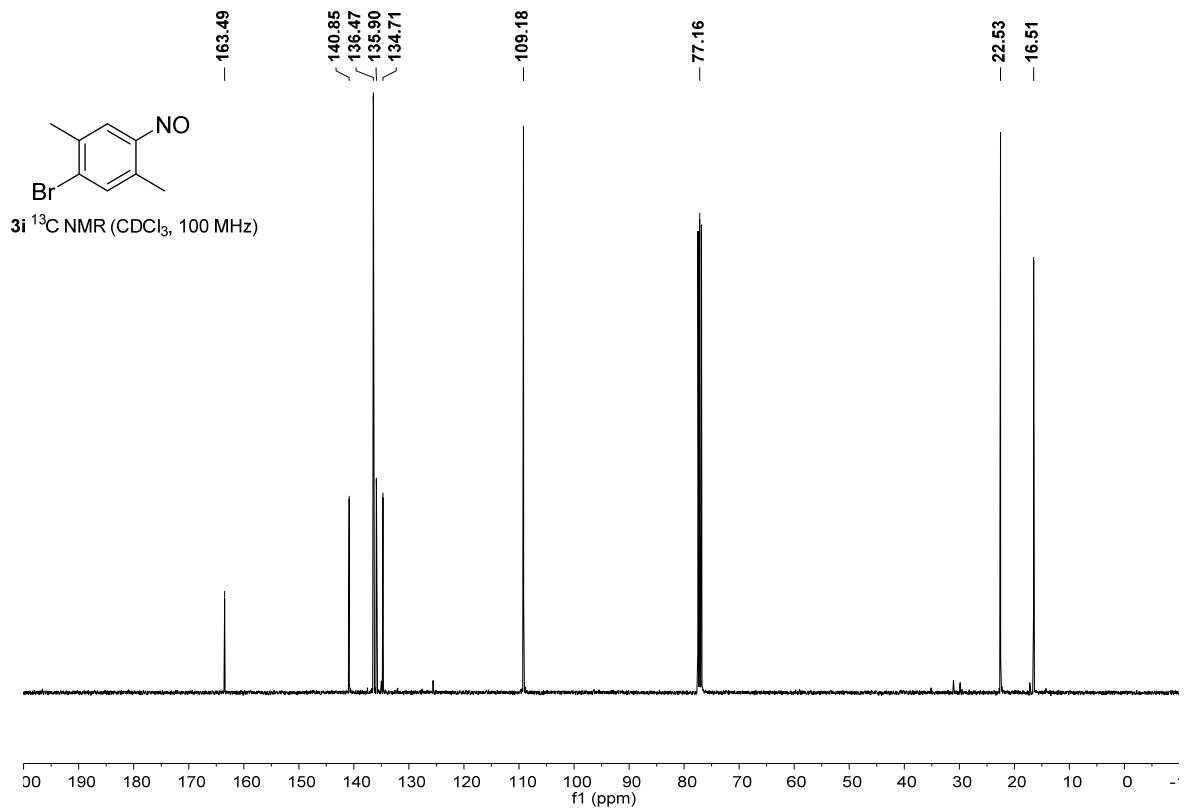
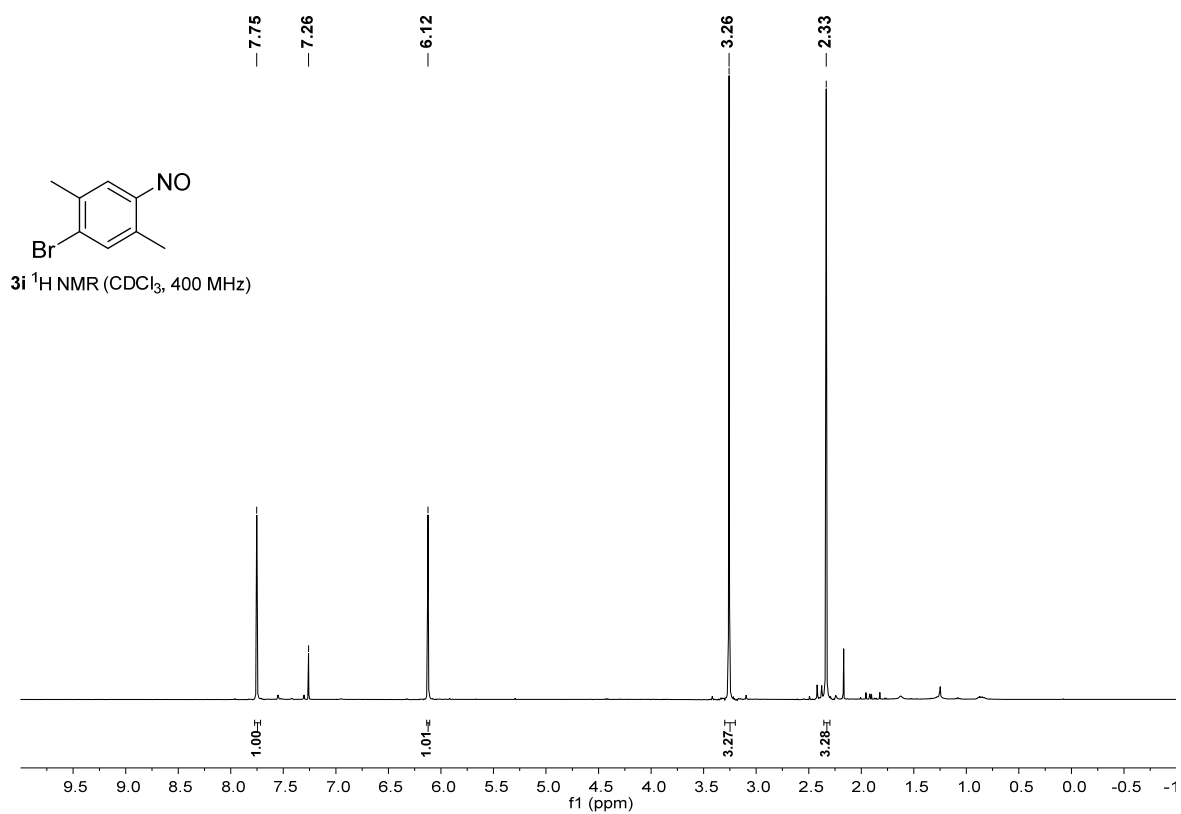


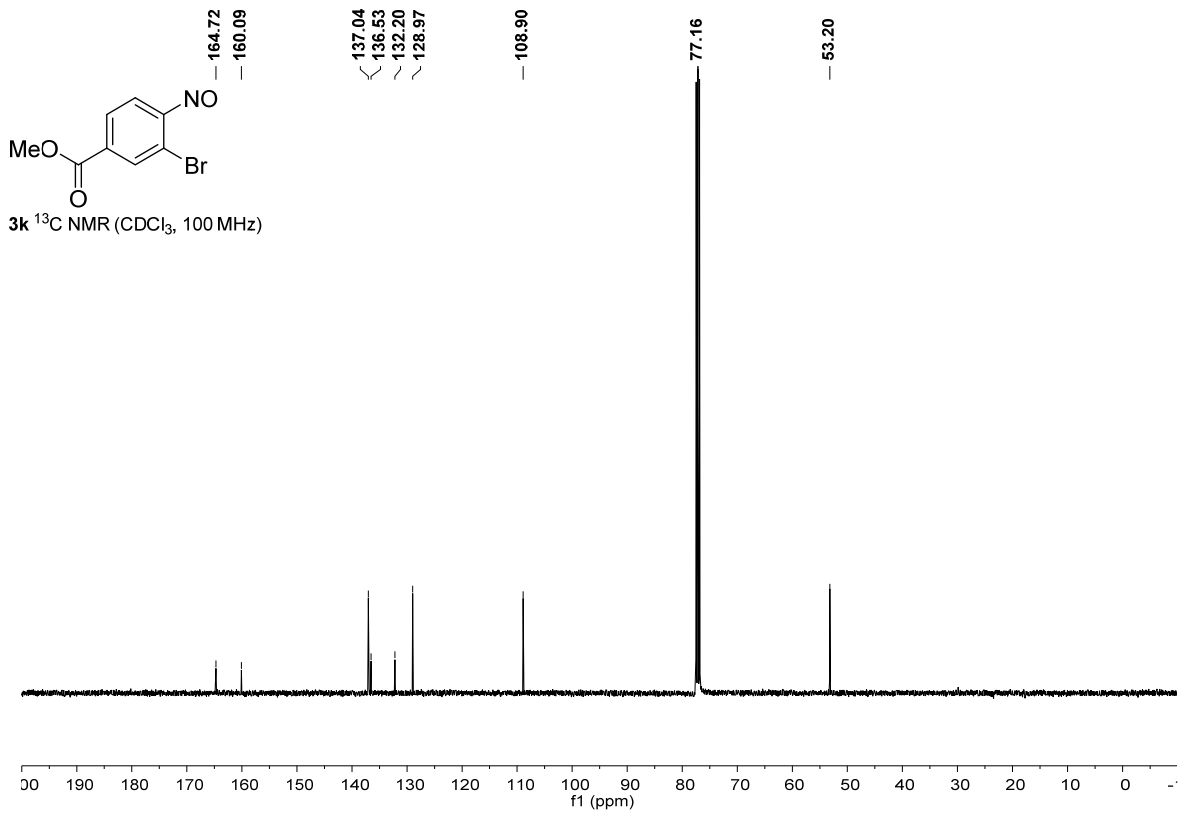
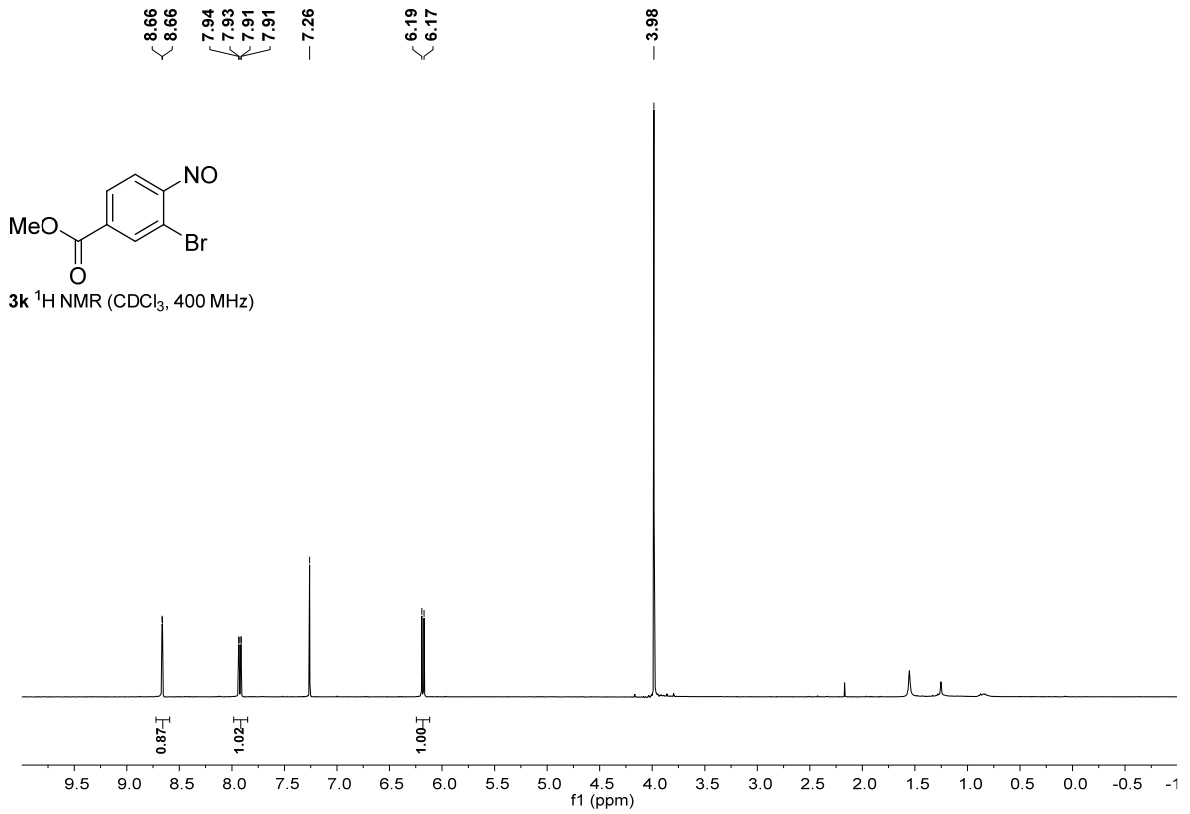


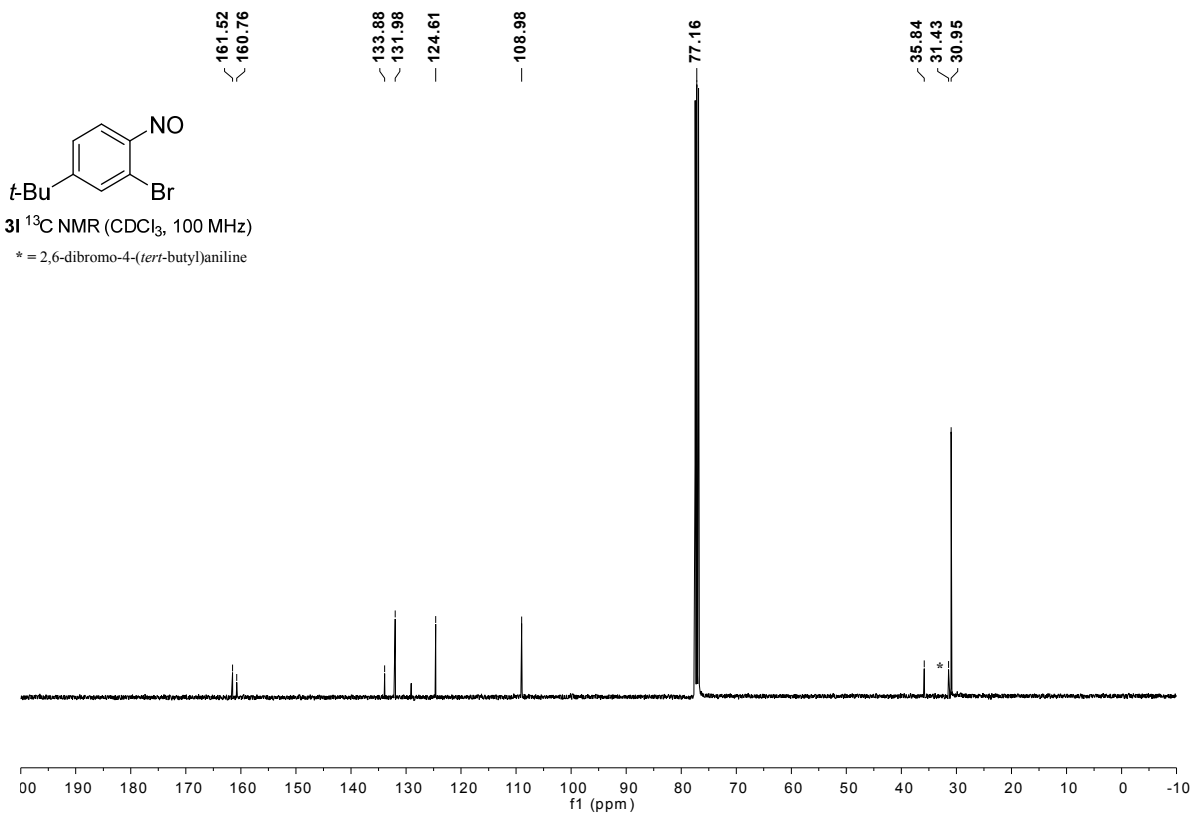
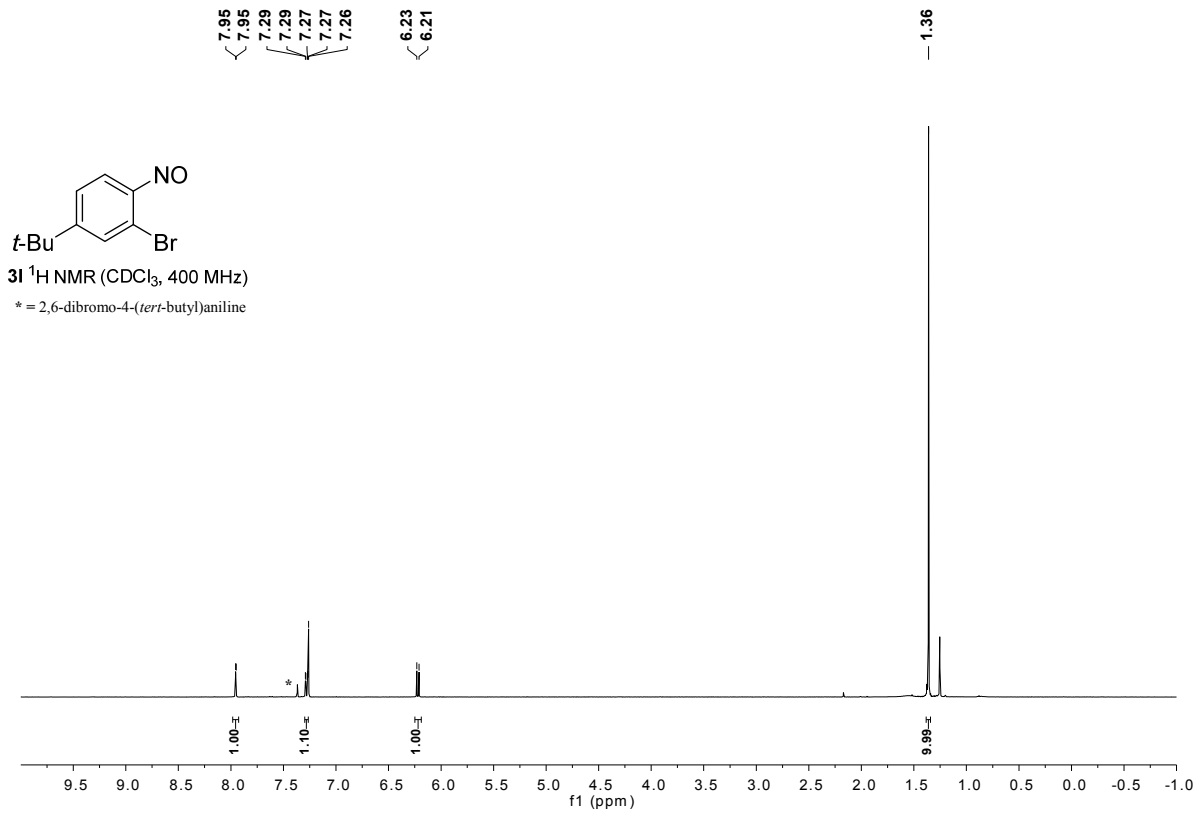


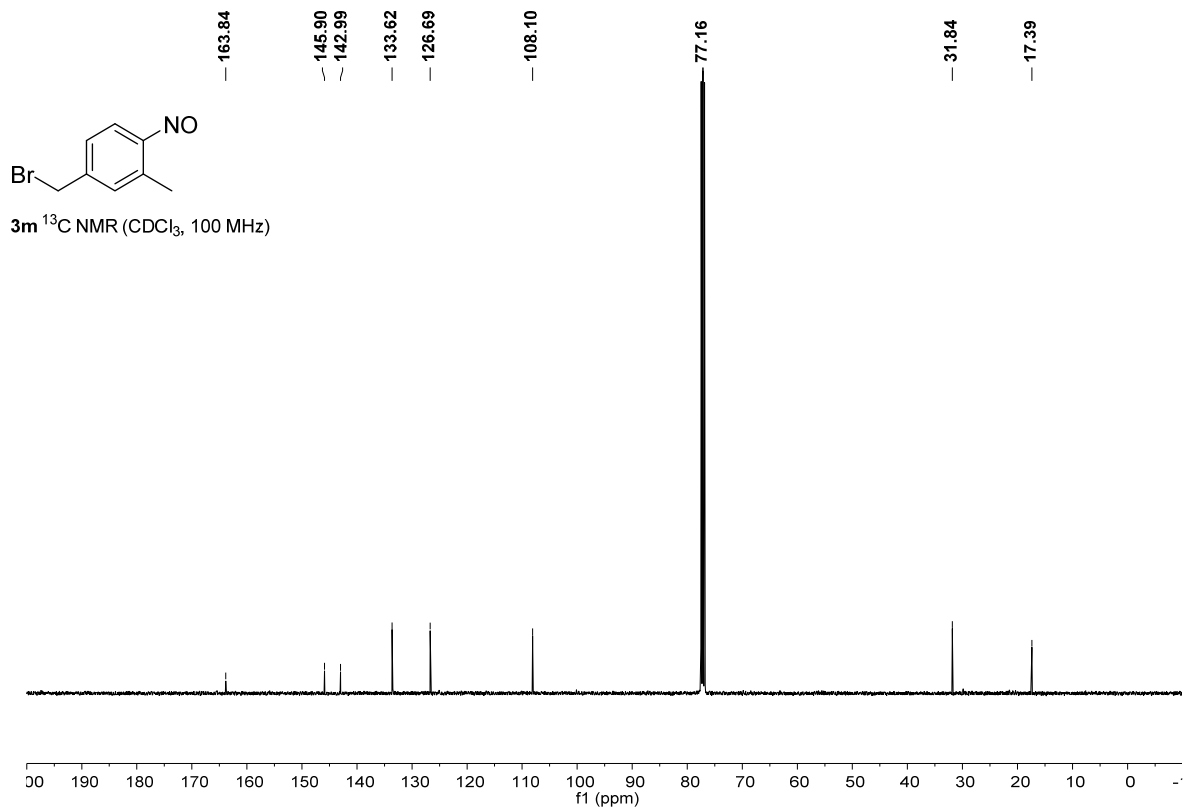
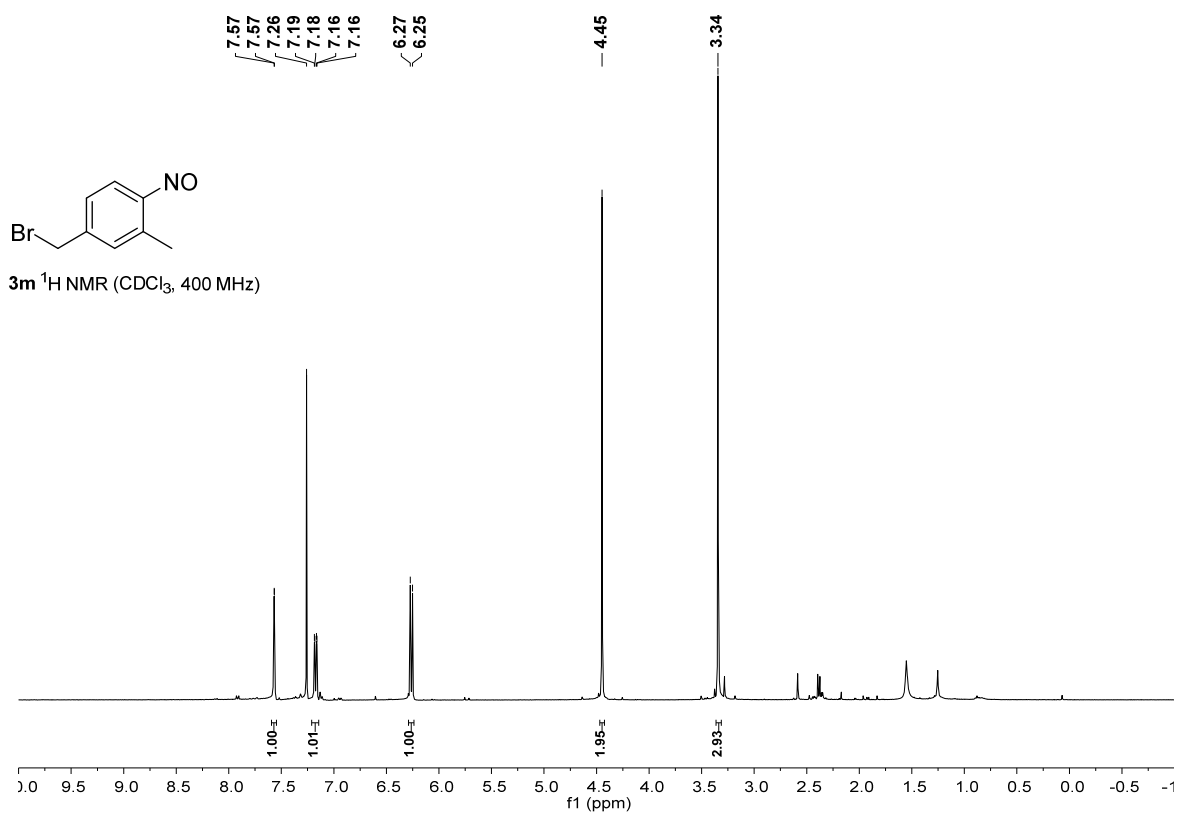


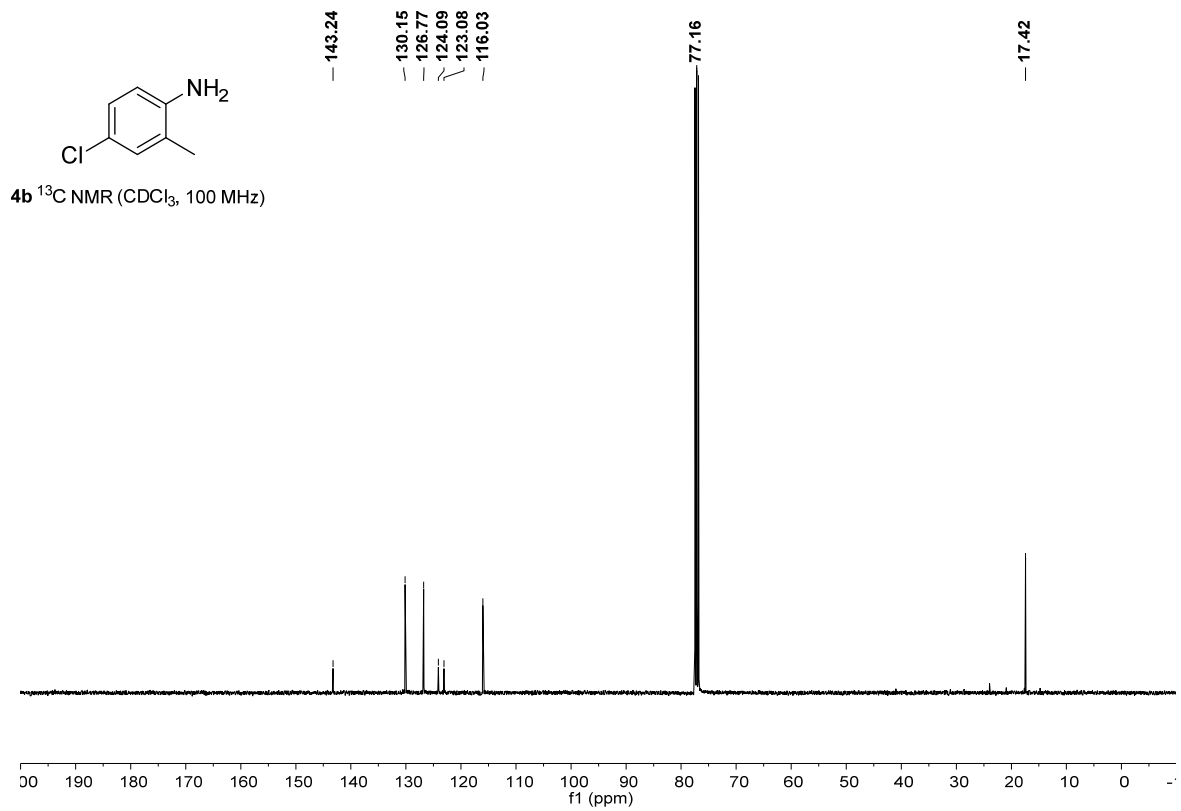
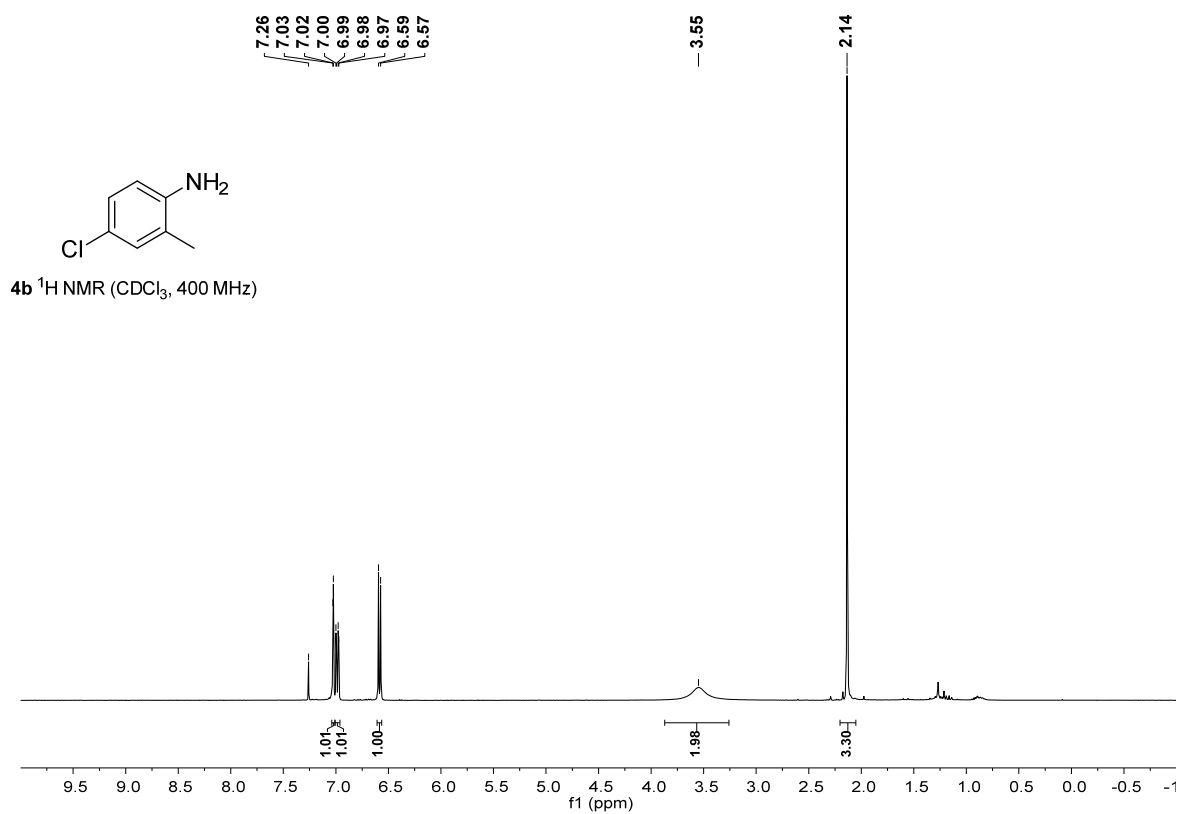


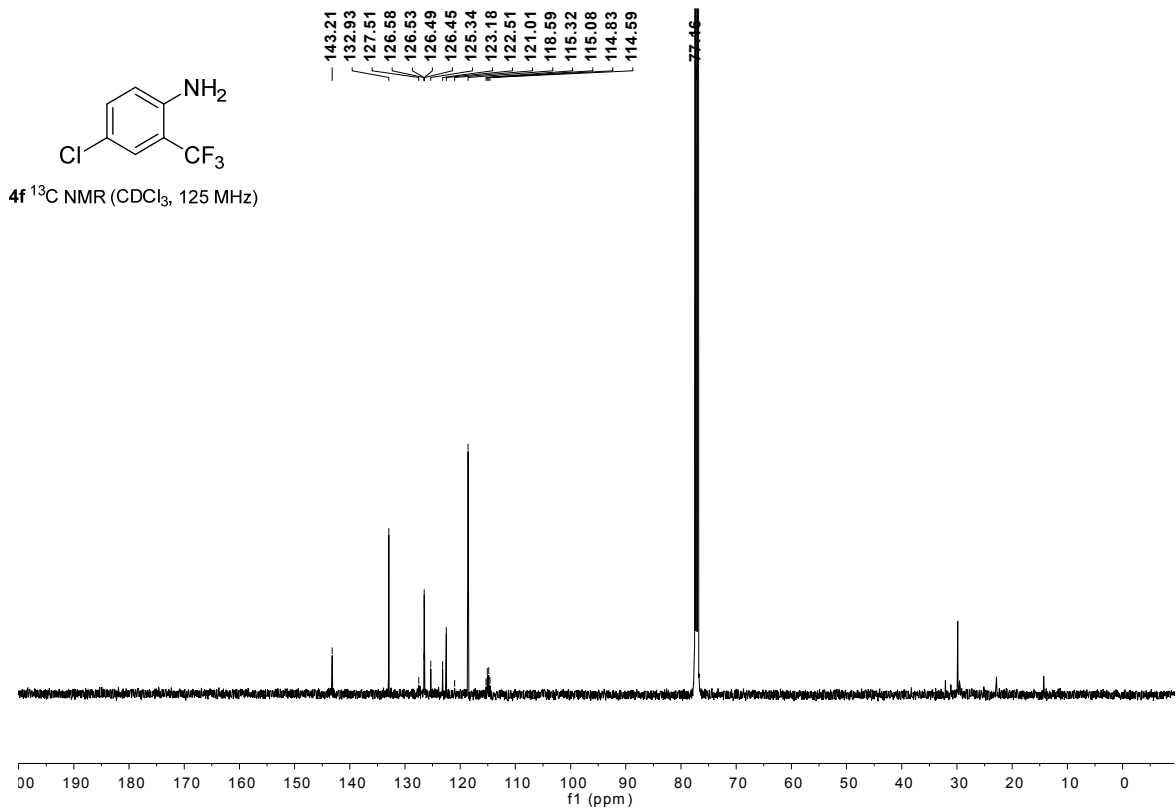
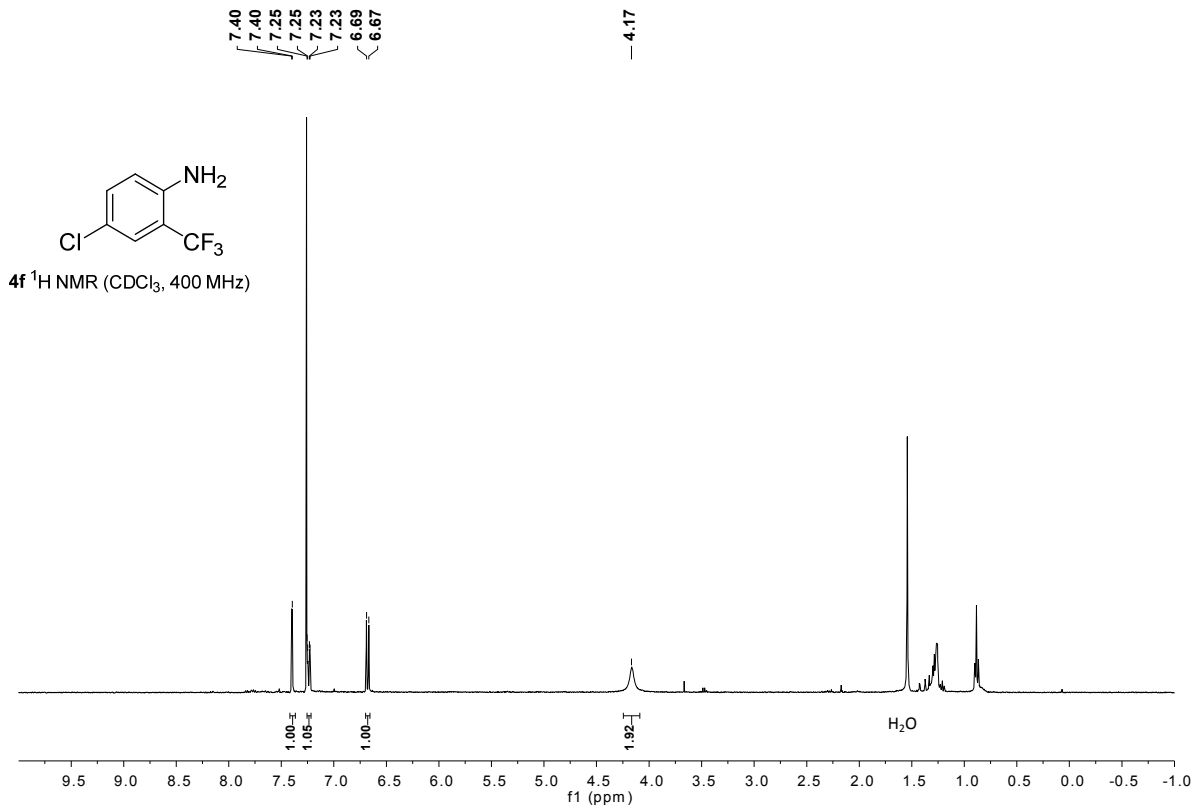


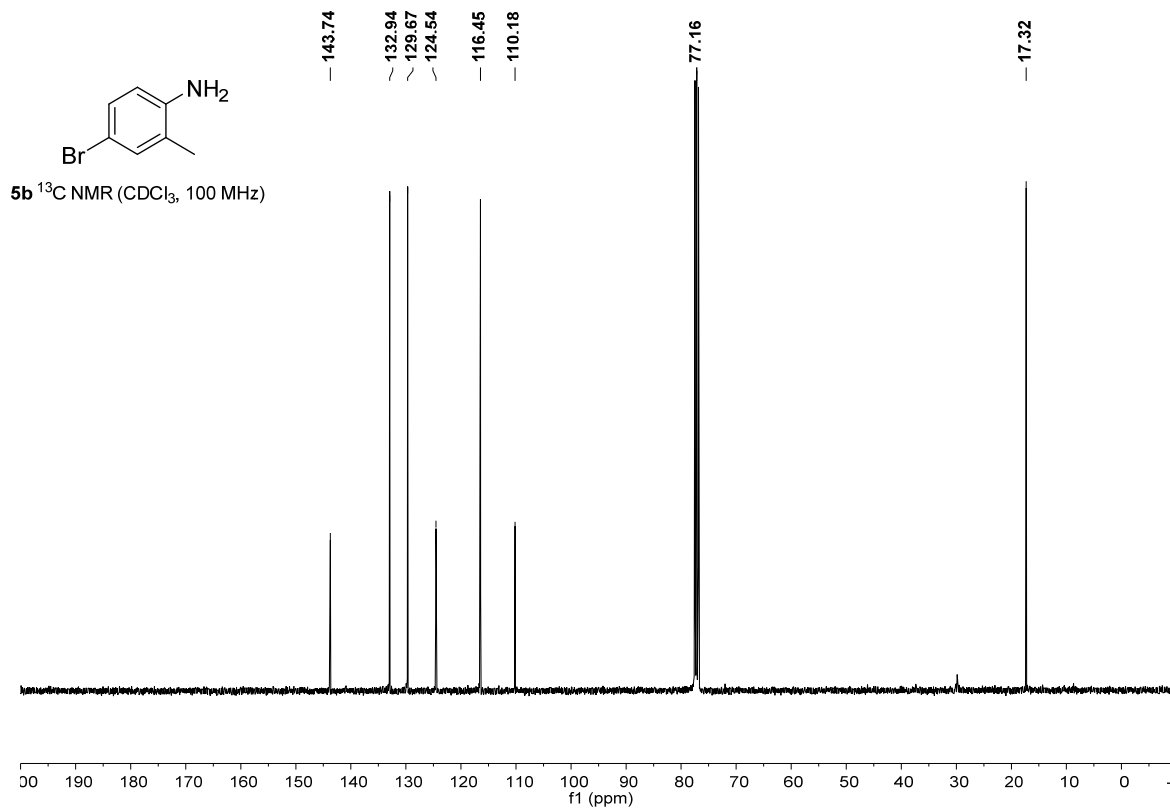
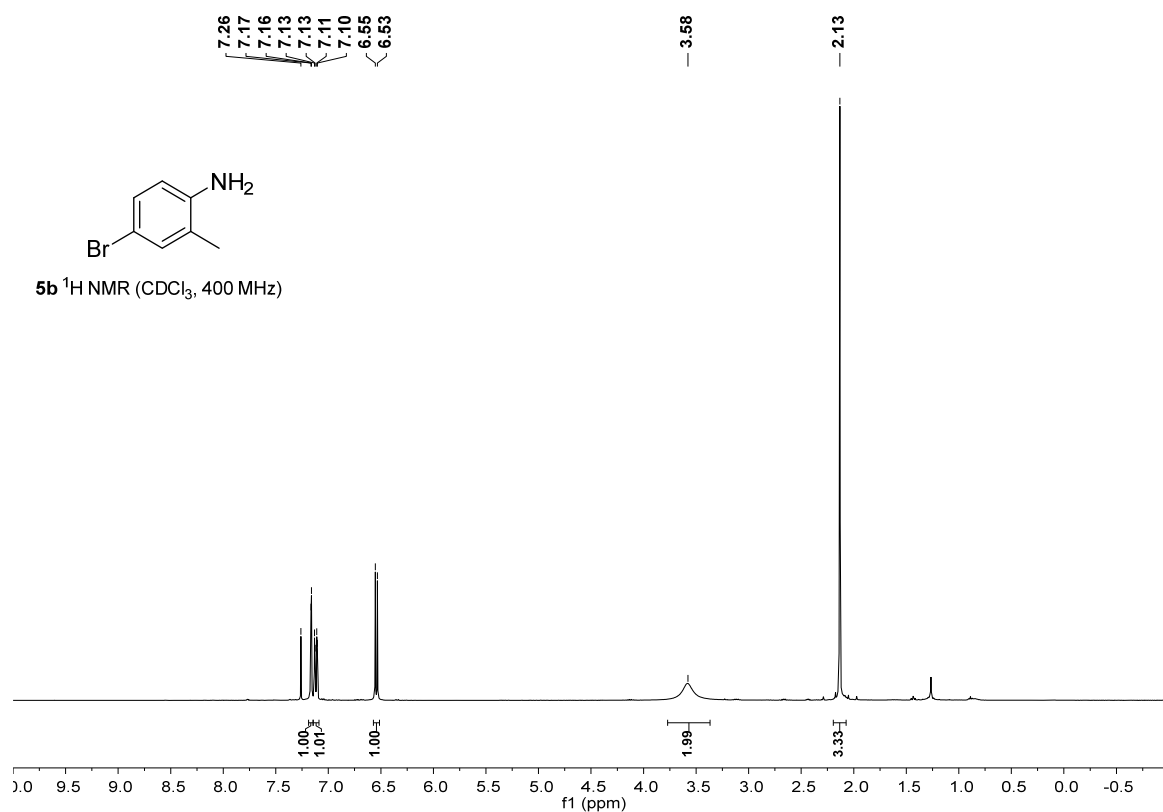


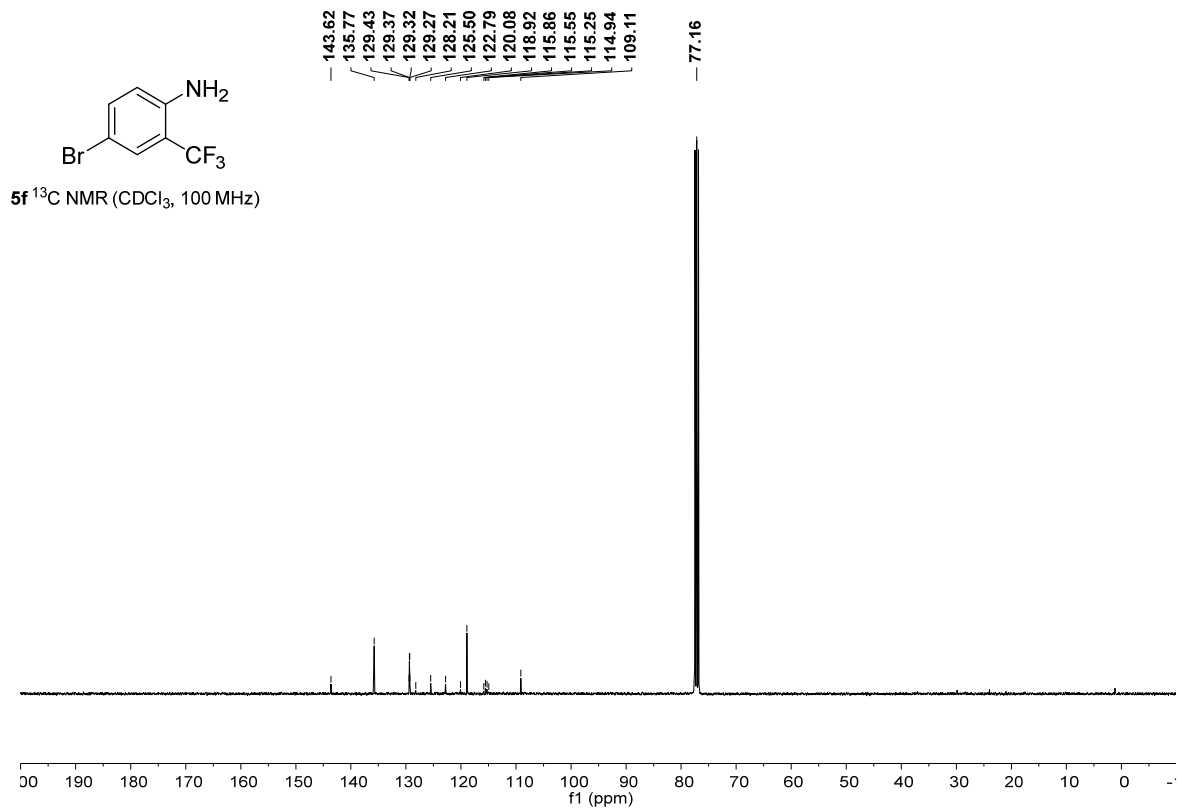
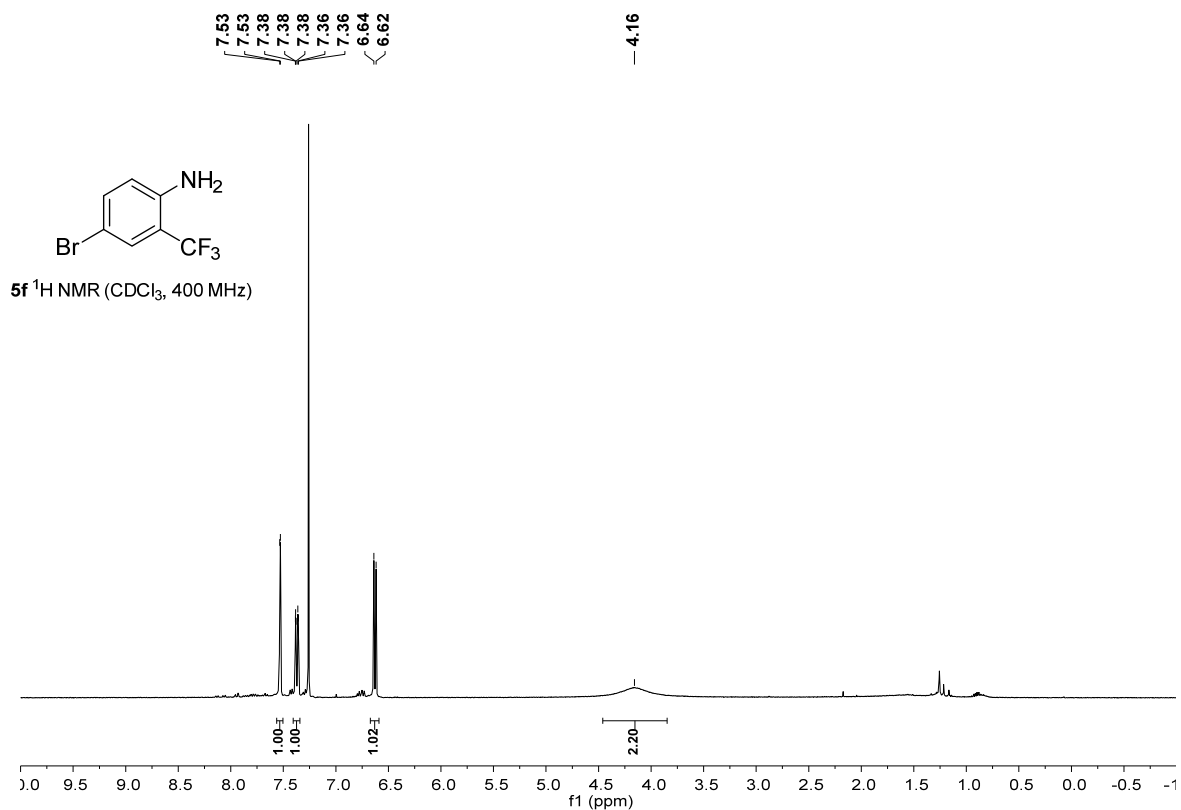


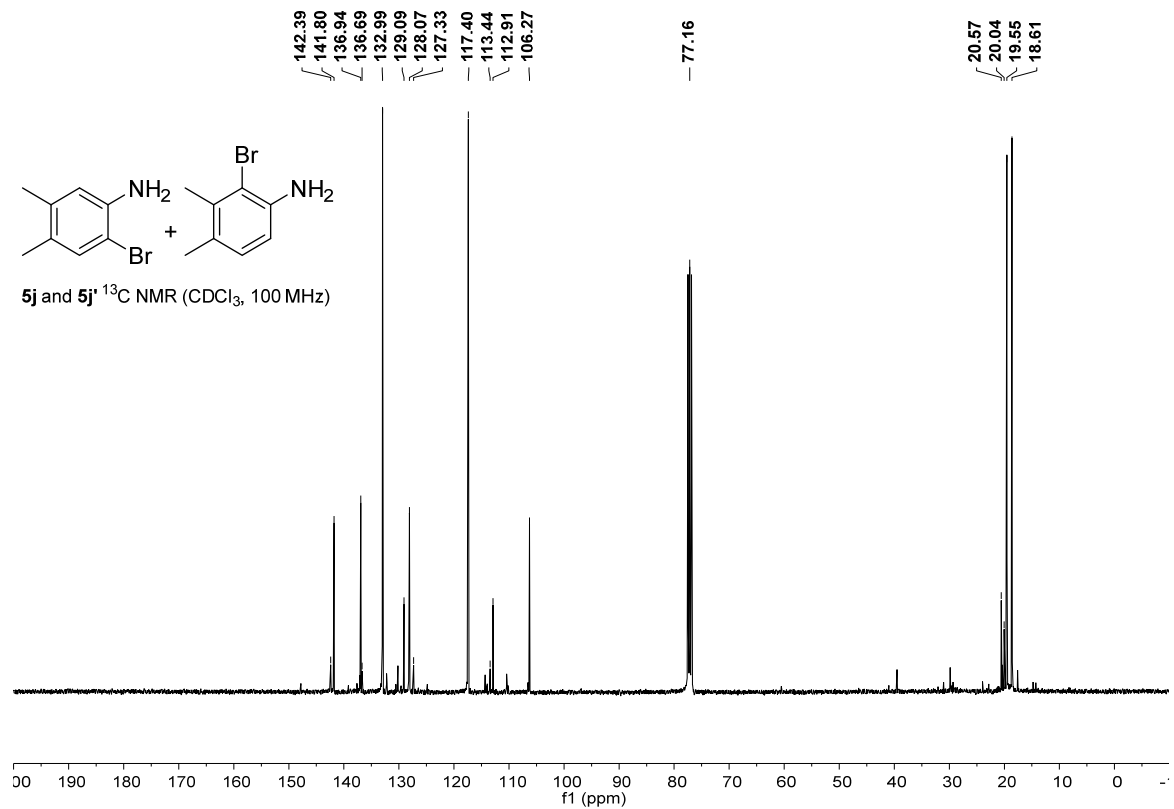
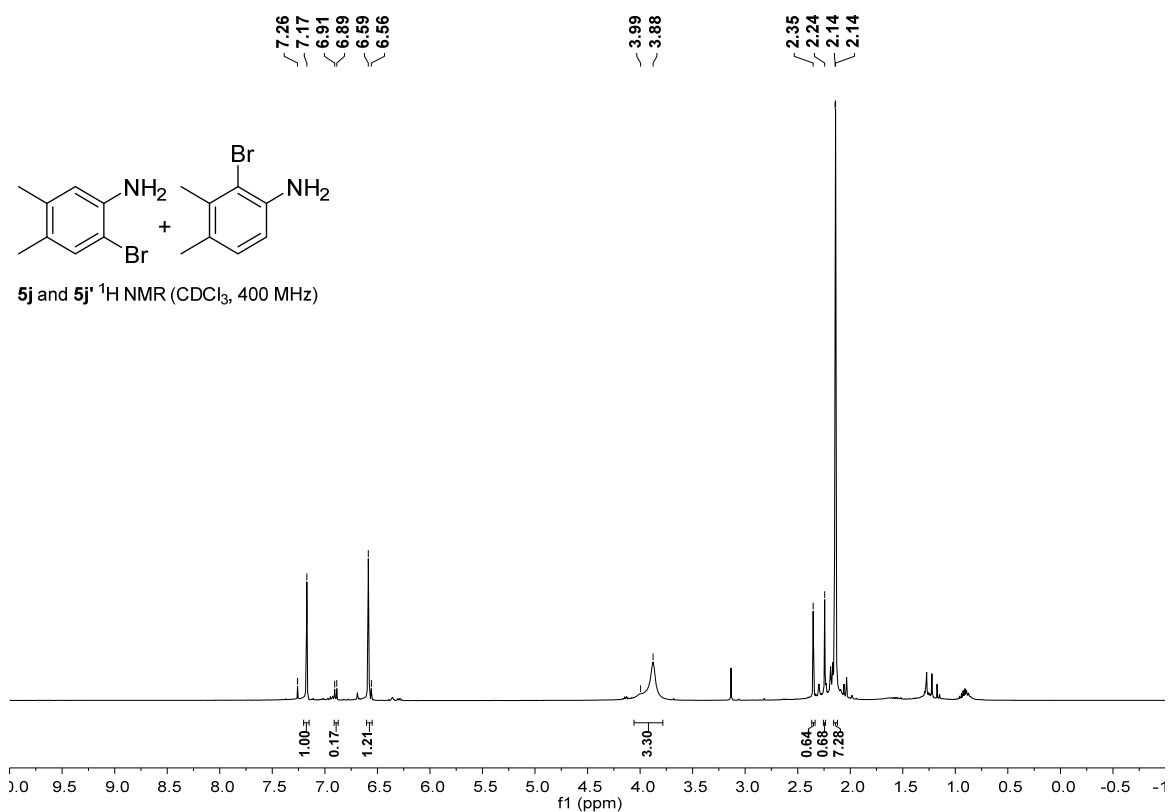


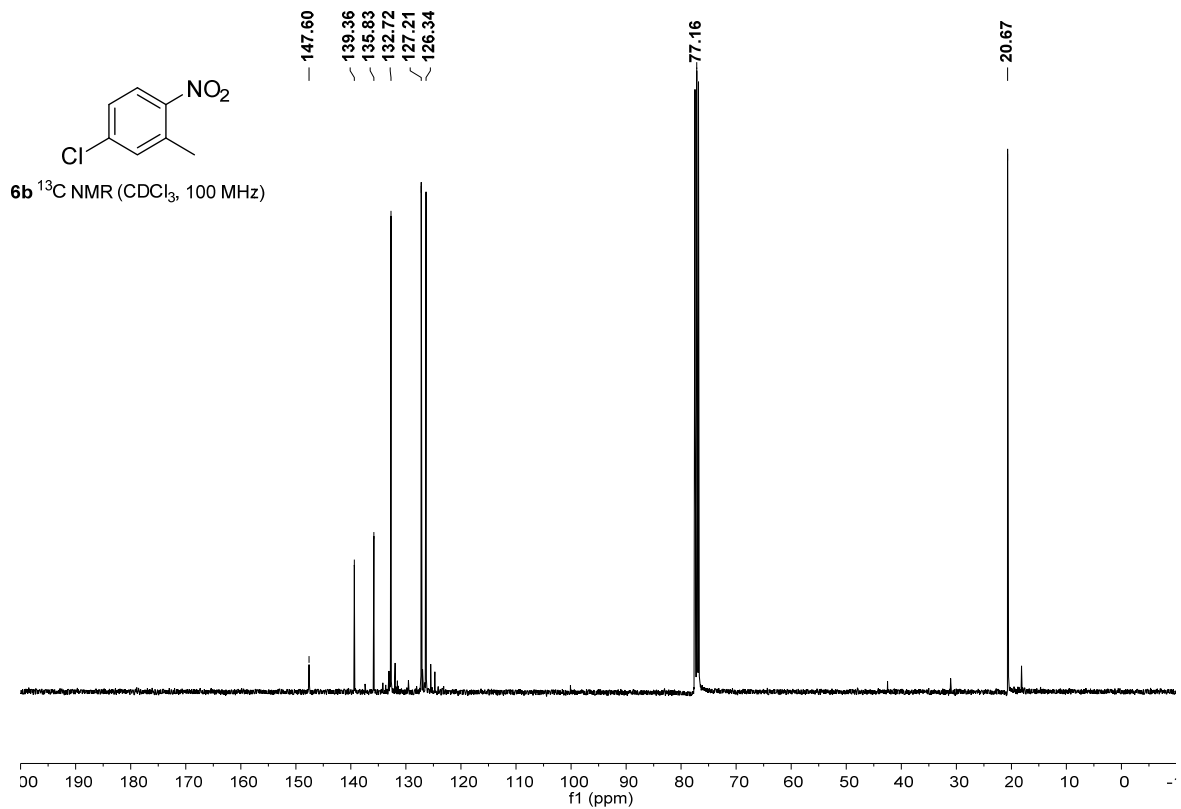
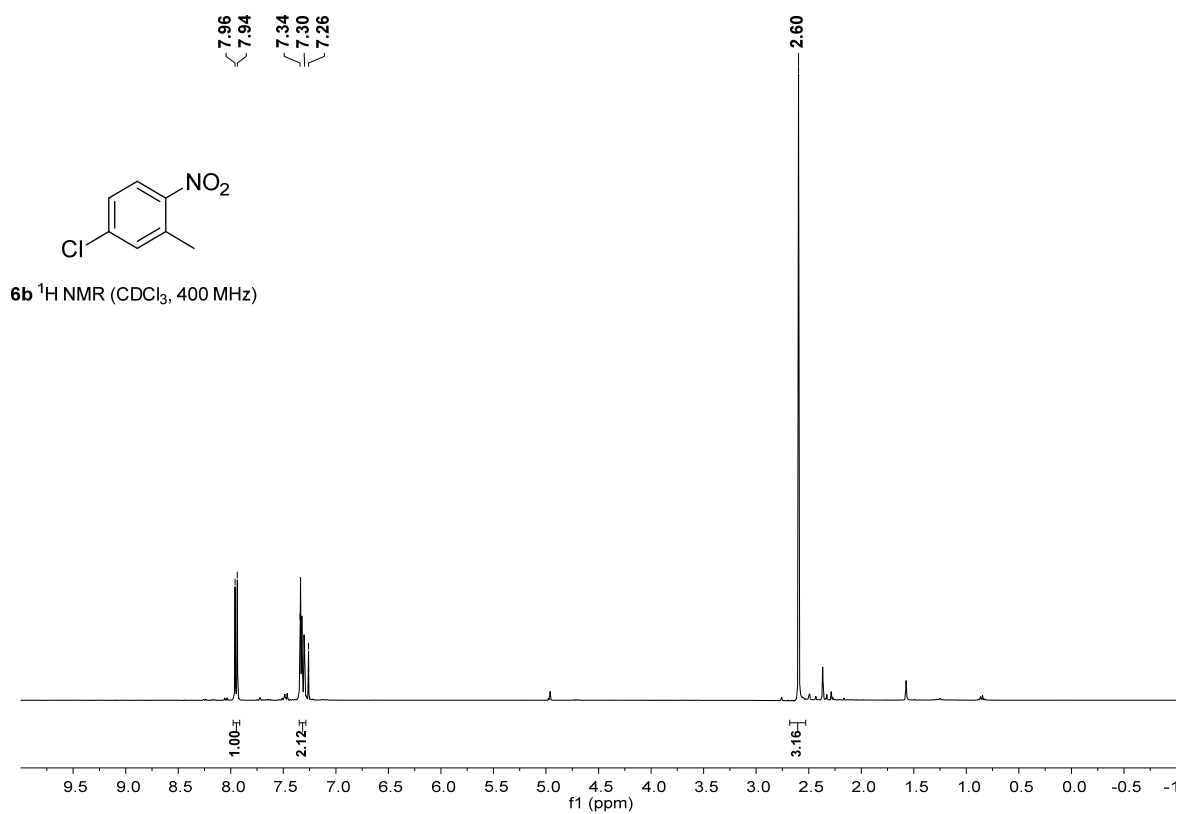


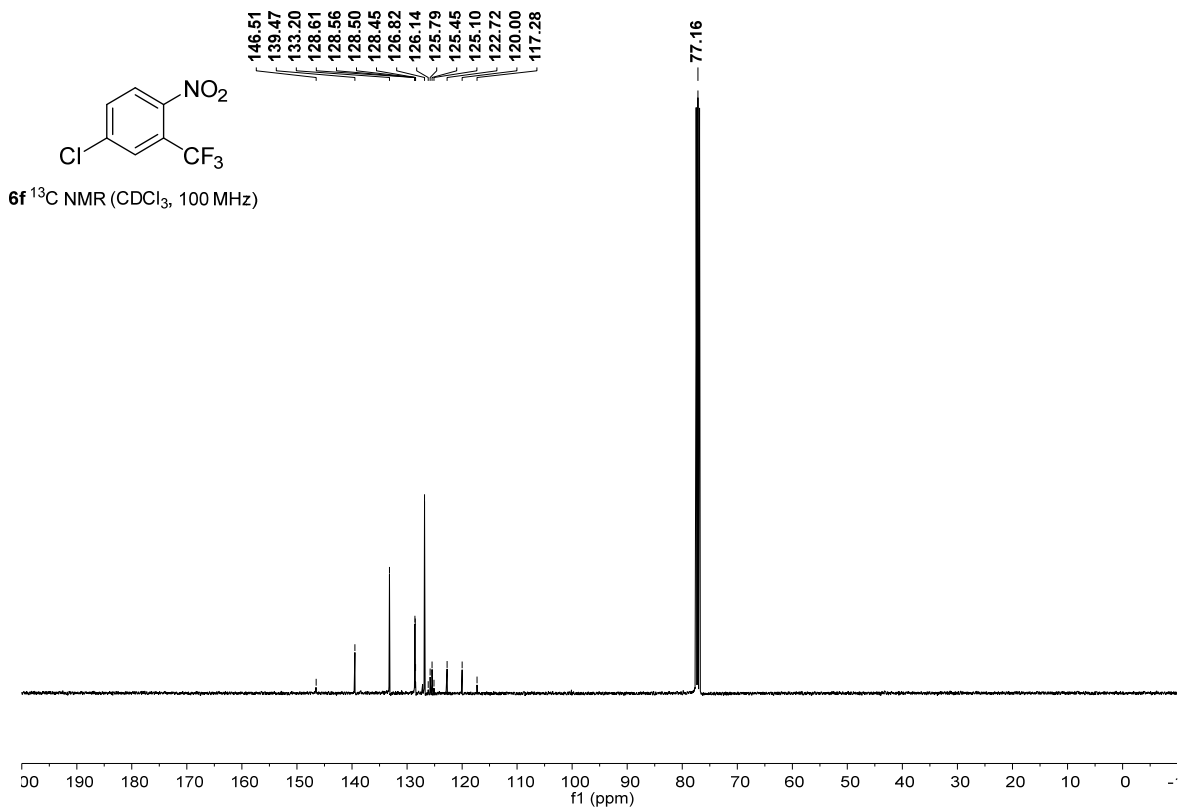
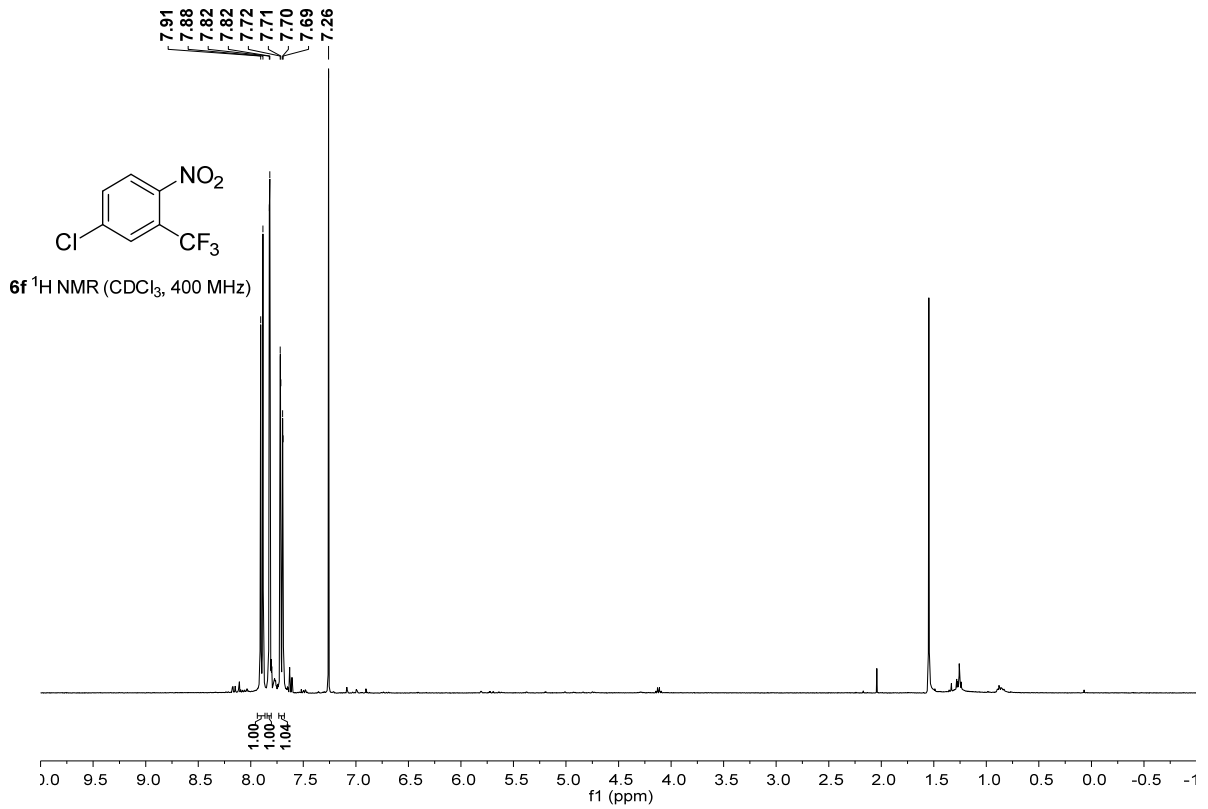


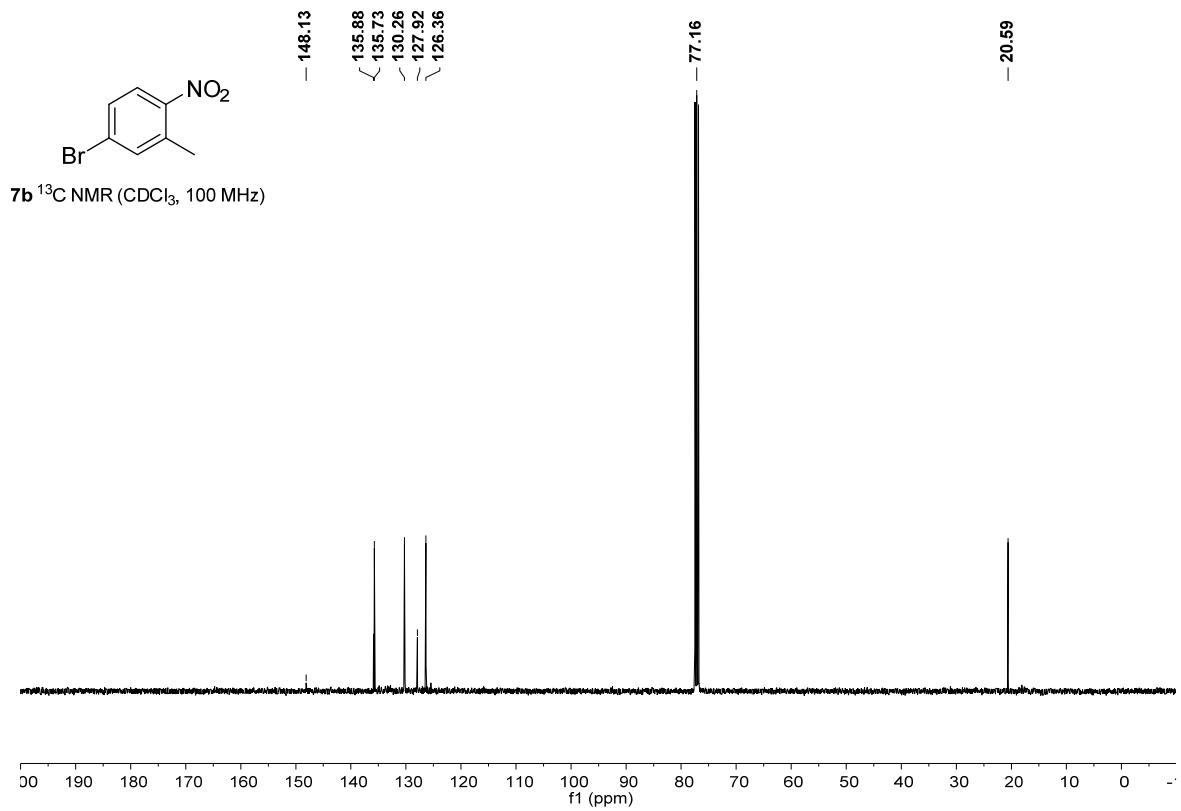
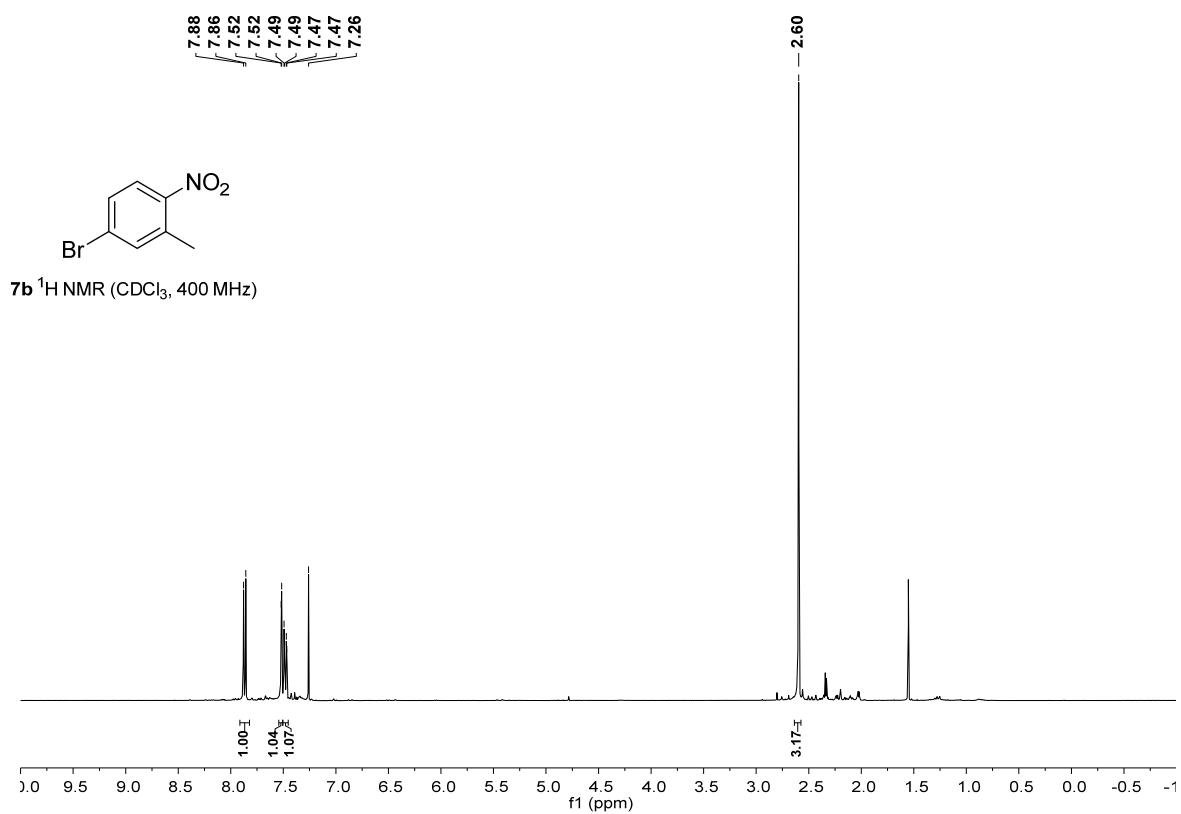


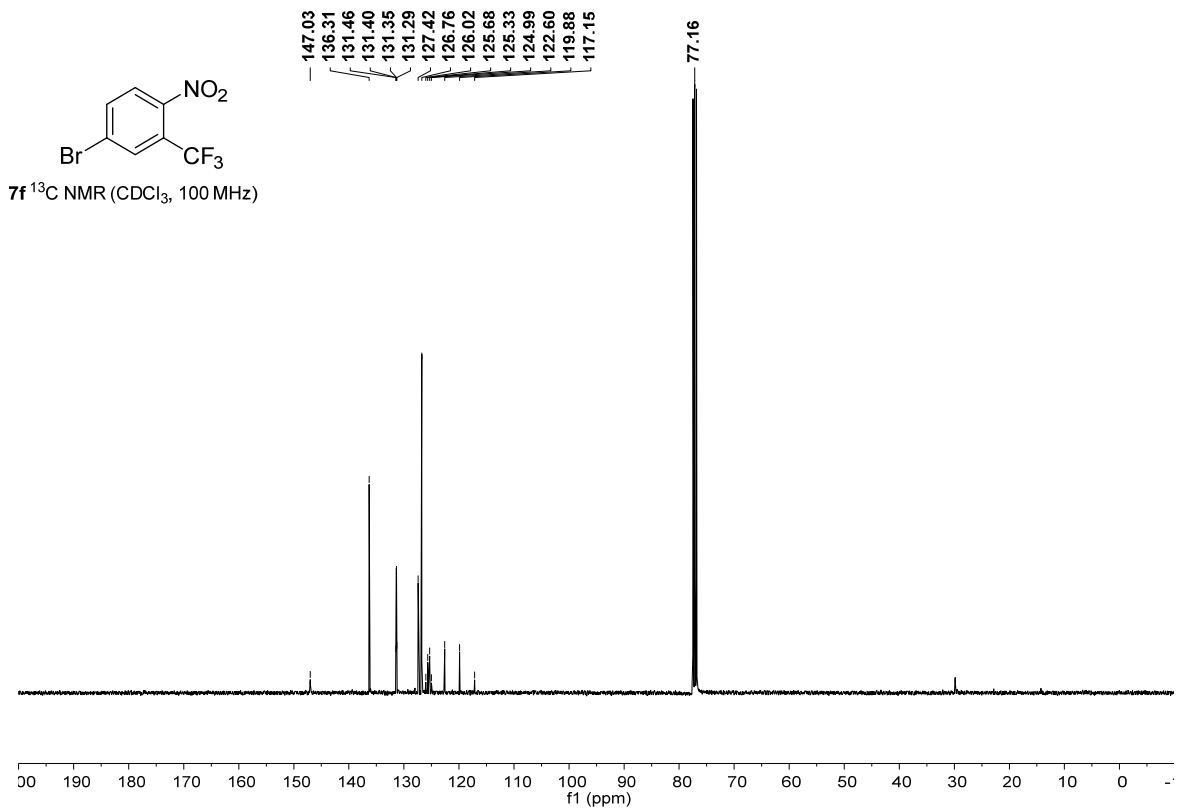
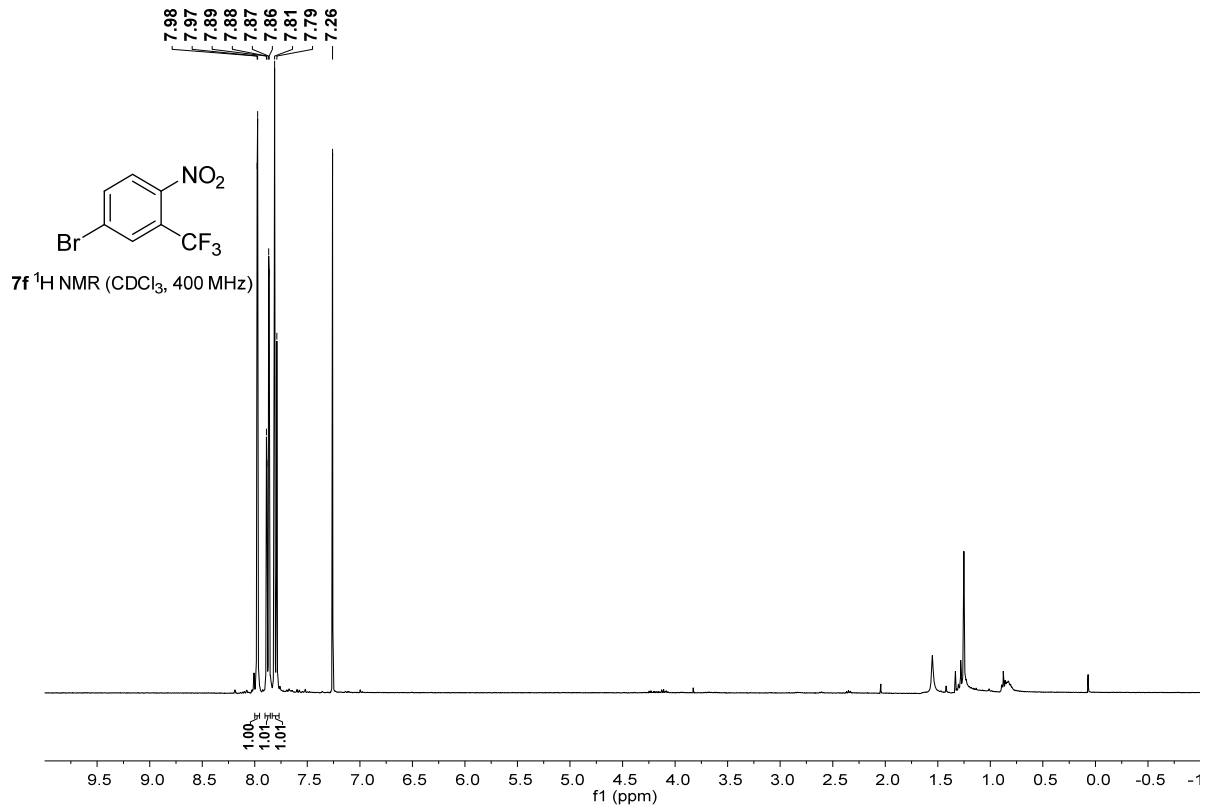


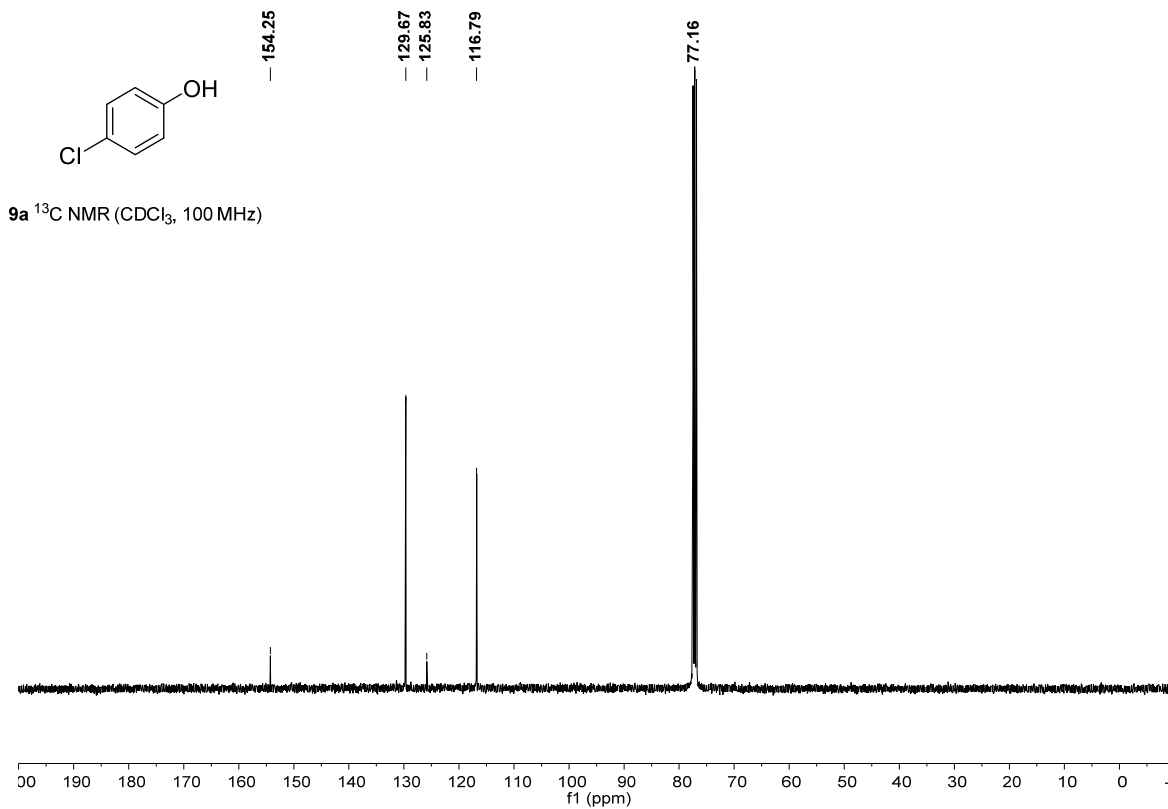
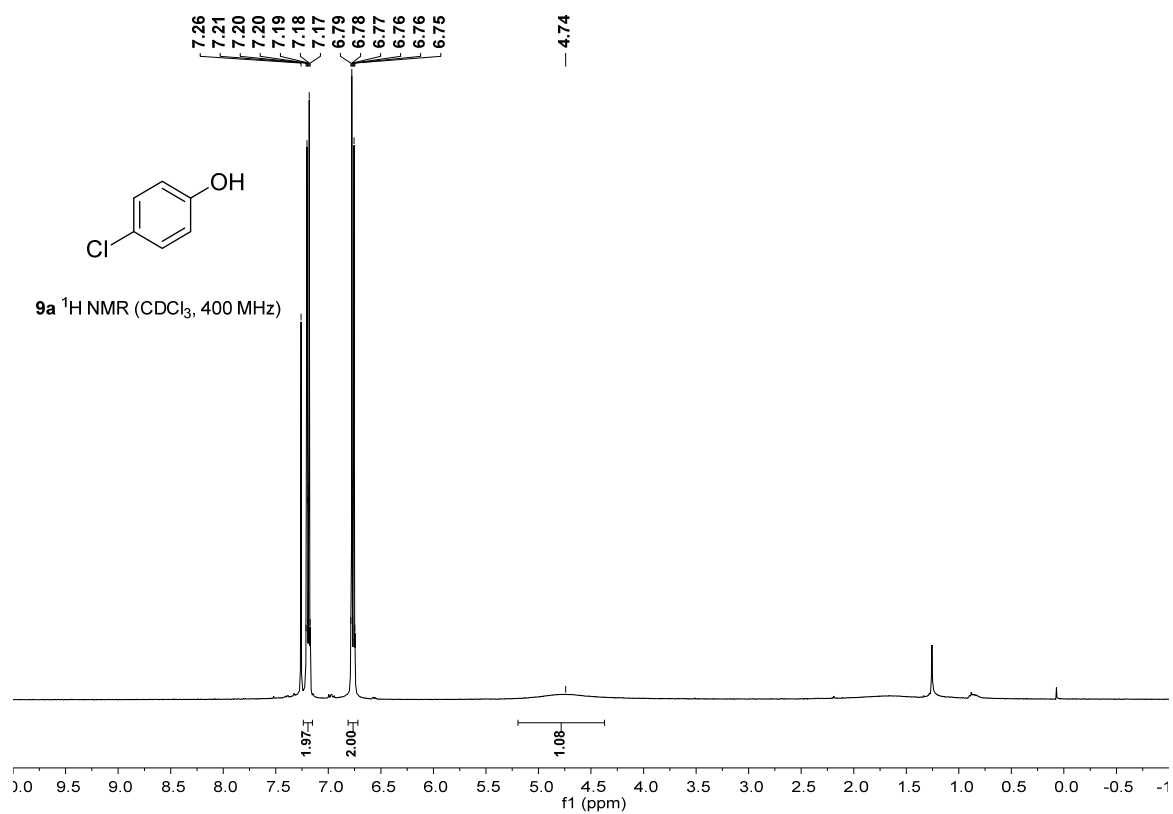


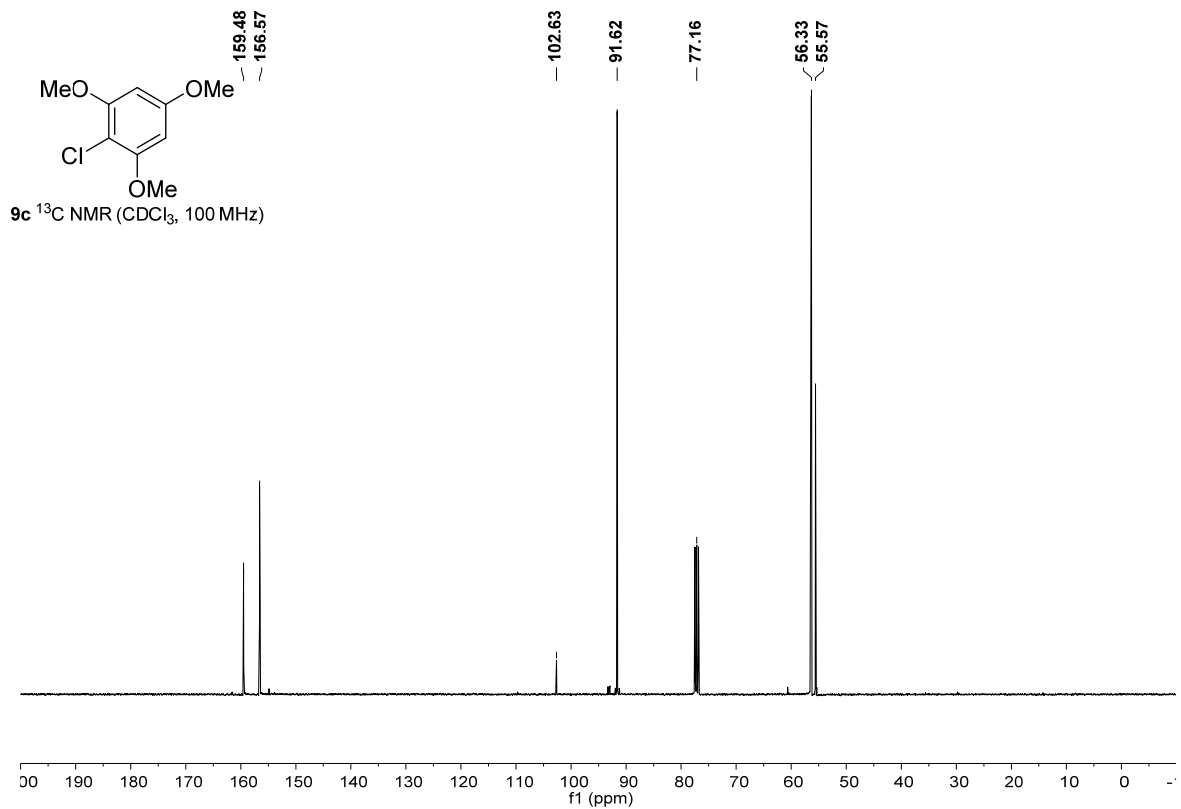
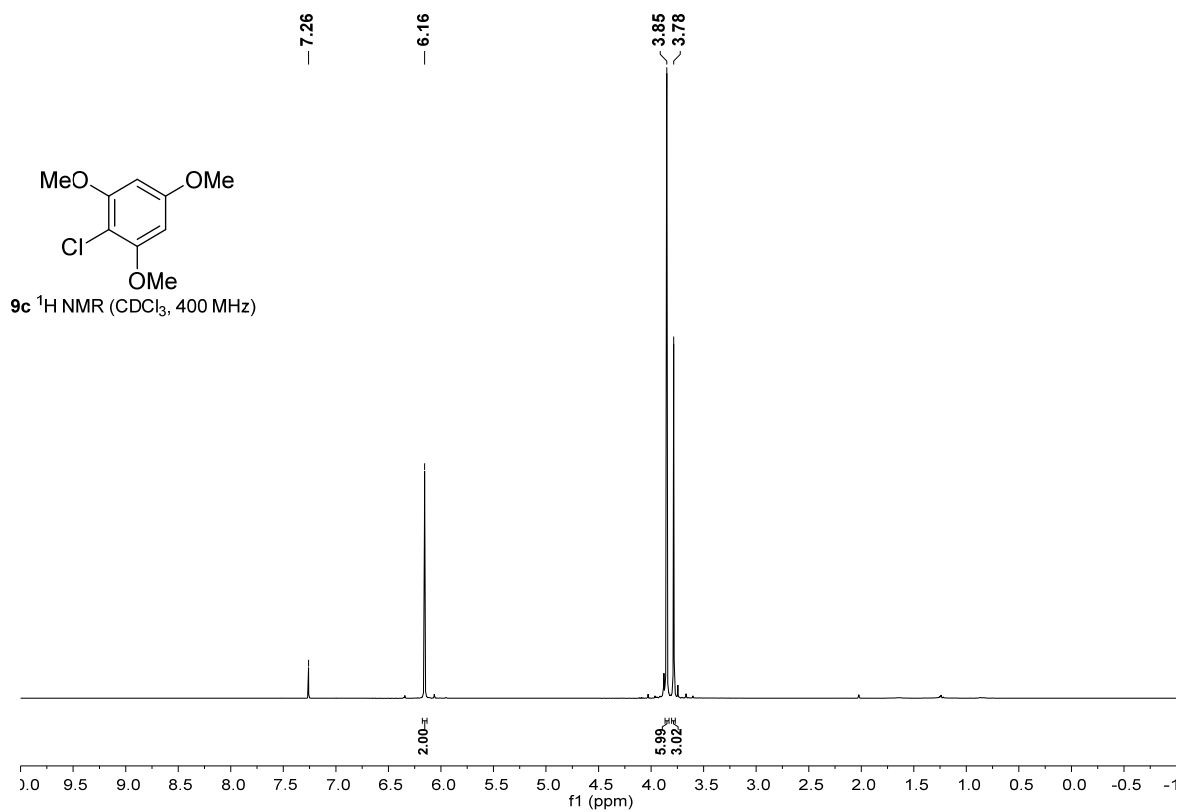


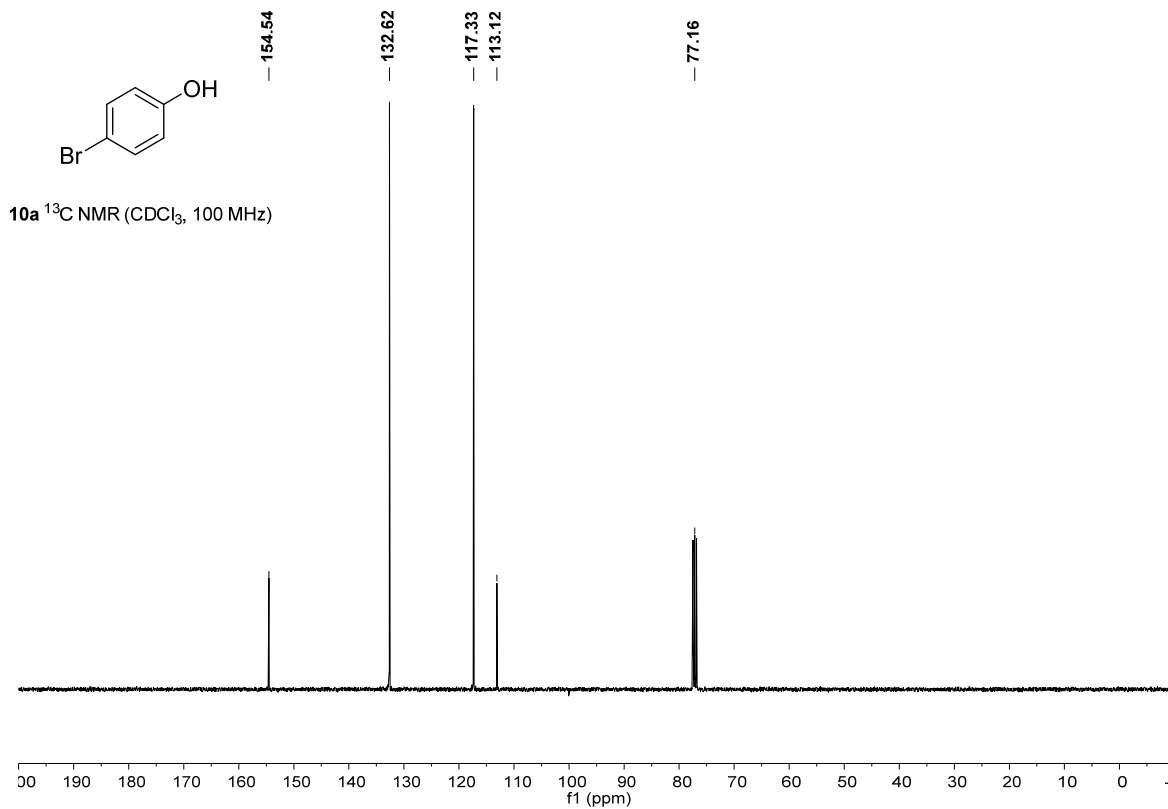
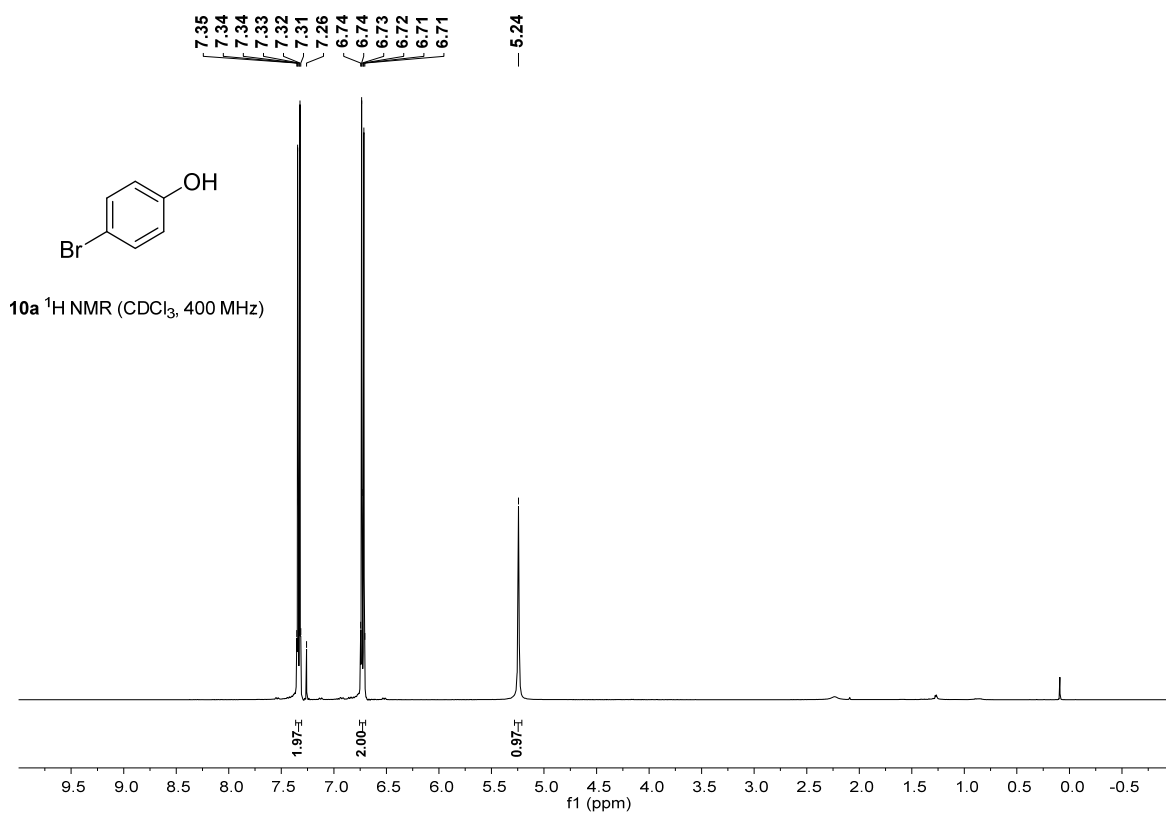


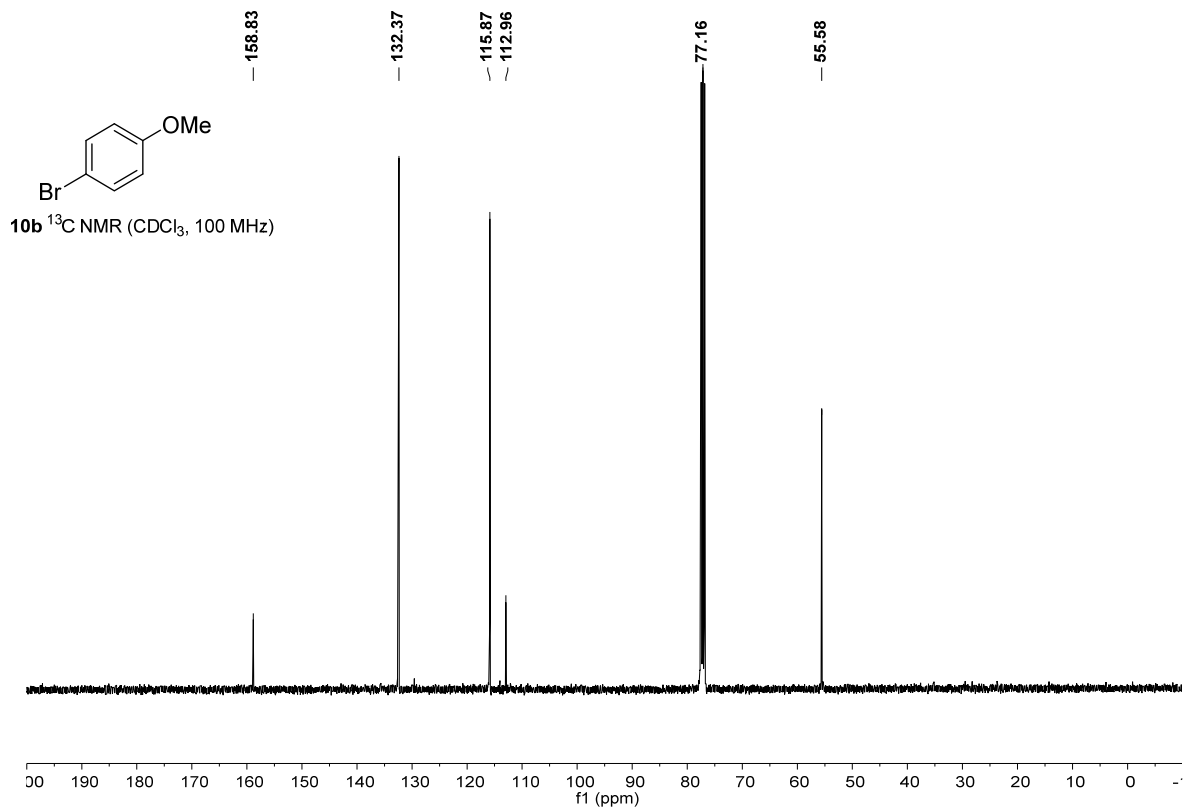
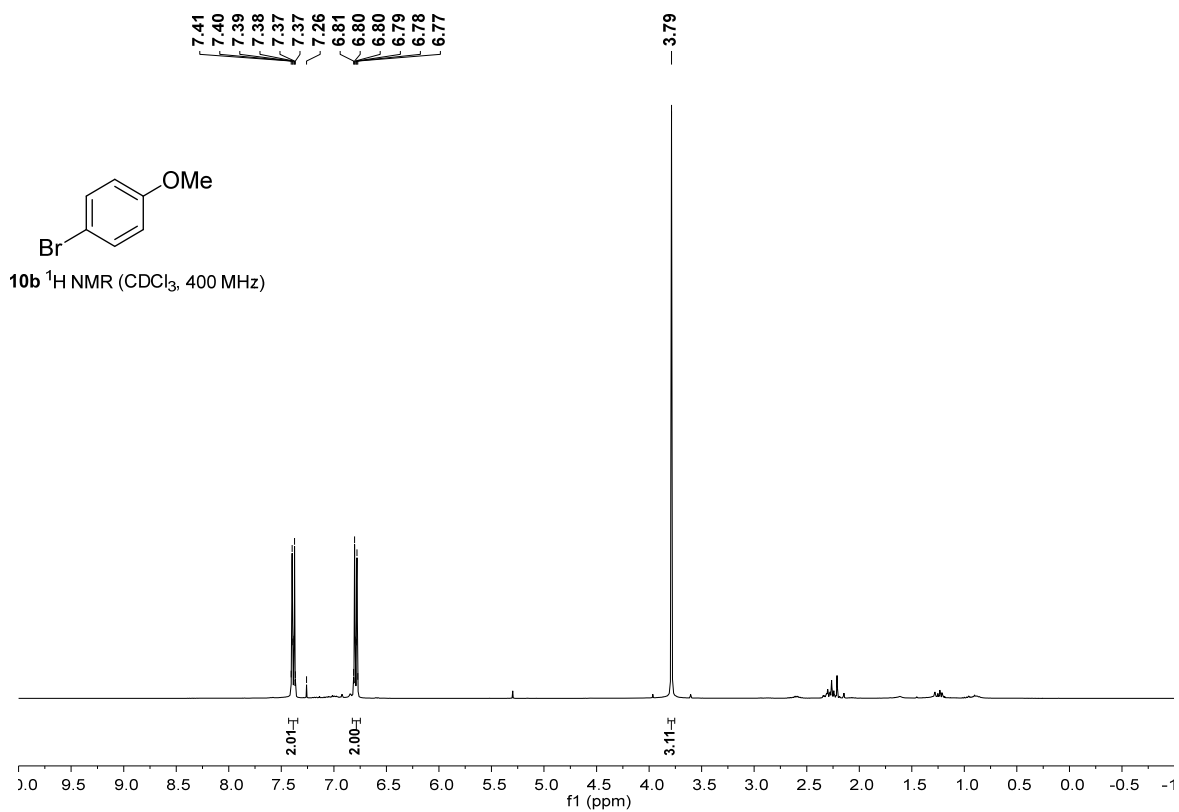


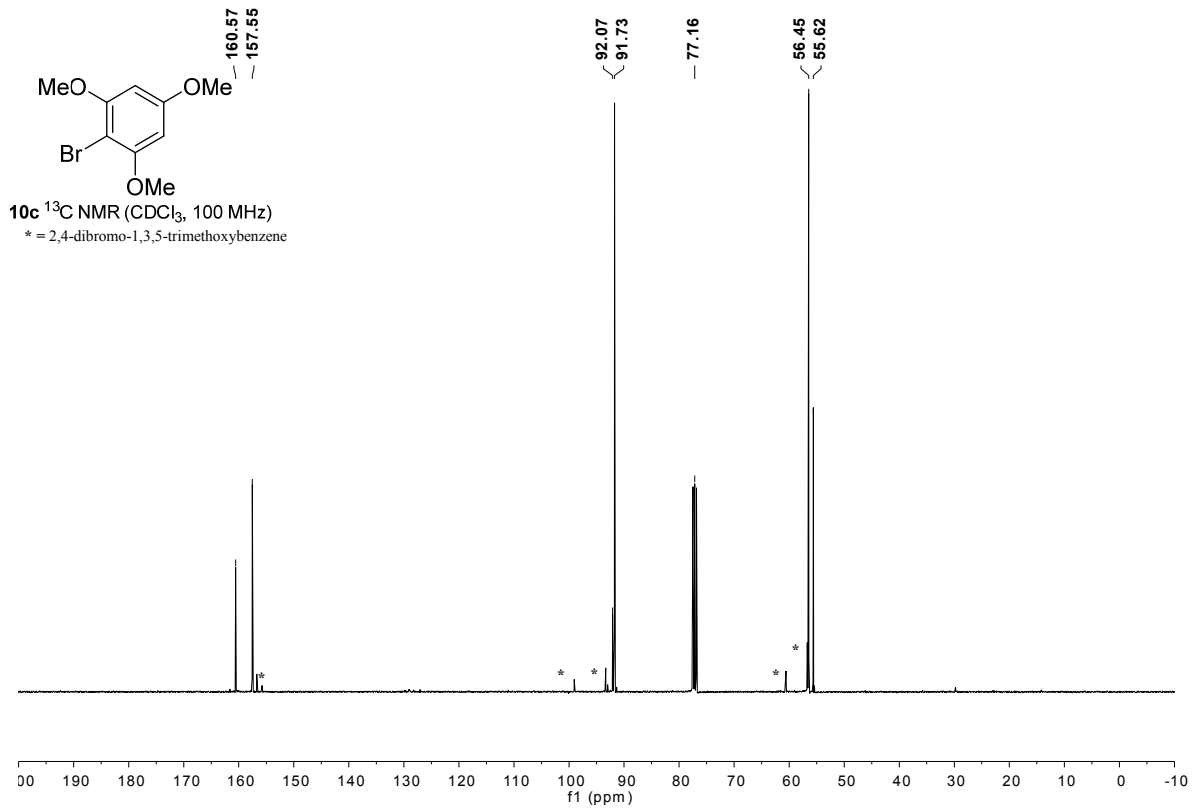
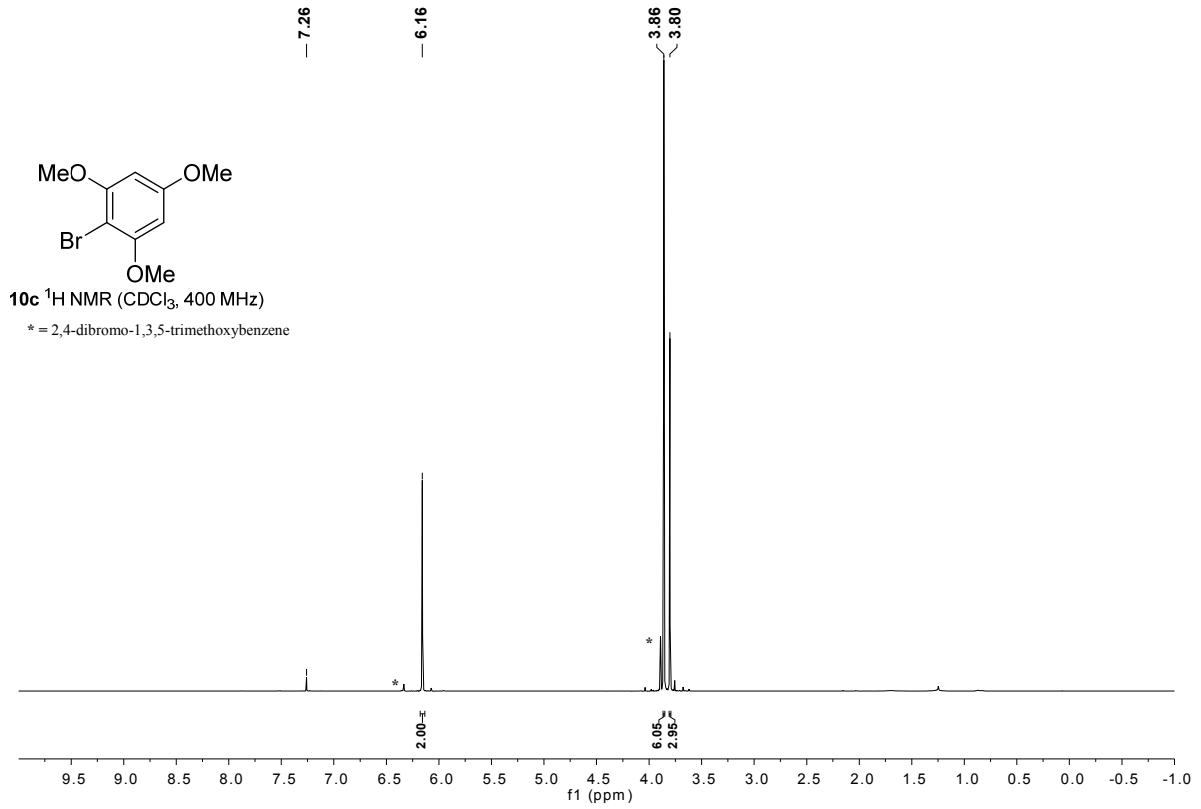












4. References

- Okazaki, R.; Inamoto, N. *J. Chem. Soc. B* **1970**, 1583.
- Priewisch, B.; Ruck-Braun, K. *J. Org. Chem.* **2005**, *70*, 2350.
- Sundberg, R. J.; Heintzelman, R. W. *J. Org. Chem.* **1974**, *39*, 2546.
- Jankowiak, A.; Obijalska, E.; Kaszynski, P.; Pieczonka, A.; Young, V. G. *Tetrahedron* **2011**, *67*, 3317.
- Chavannavar, A. P.; Oliver, A. G.; Ashfeld, B. L. *Chem. Commun.* **2014**, *50*, 10853.
- Dochnahl, M.; Fu, G. C., *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 2391.
- Apasov, E. T.; Churakov, A. M.; Strelenko, Y. A.; Ioffe, S. L.; Djetigenov, B. A.; Tartakovsky, V. A. *Tetrahedron* **1995**, *51*, 6775.
- Zhu, D.; Lu, M.; Chua, P. J.; Tan, B.; Wang, F.; Yang, X.; Zhong, G. *Org. Lett.* **2008**, *10*, 4585.
- Ran, R. Q.; Xiu, S. D.; Li, C. Y. *Org. Lett.* **2014**, *16*, 6394.
- Fletcher, D. A.; Gowenlock, B. G.; Orrell, K. G., *J. Chem. Soc. Perkin Trans. 2* **1997**, 2201.
- Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2012**, *77*, 4402.
- Bosch, E.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 5573.
- Orrell, K. G.; Stephenson, D.; Rault, T. *Magn. Reson. Chem.* **1989**, *27*, 368.
- Prakash, G. K.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770.
- Yamamoto, H.; Zhang, Y.; Shibatomi, K. *Synlett* **2005**, 2837.
- Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Commun.* **2006**, *32*, 279.
- Mitchell, R. H.; Y-H., L.; Williams, R. V. *J. Org. Chem.* **1979**, *44*, 4733.
- Song, S.; Sun, X.; Li, X.; Yuan, Y.; Jiao, N. *Org. Lett.* **2015**, *17*, 2886.
- Sankaranarayanan, A.; Chandalia, S. B. *Org. Process Res. Dev.* **2006**, *10*, 487.
- Yang, L.; Lu, Z.; Stahl, S. S. *Chem. Commun.* **2009**, 6460.
- Kimmel, E. C.; Casida, J. E.; Ruzo, L. O. *J. Agri. Food Chem.* **1986**, *34*, 157.
- Defoin, A. *Synthesis* **2004**, *2004*, 706.
- Mijs, W. J.; Hoekstra, S. E.; Ulmann, R. M.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **2010**, *77*, 746.
- Jana, N. K.; Verkade, J. G., *Org. Lett.* **2003**, *5*, 3787.
- Vemula, N.; Stevens, A. C.; Schon, T. B.; Pagenkopf, B. L. *Chem. Commun.* **2014**, *50*, 1668.
- Lipilin, D. L.; Churakov, A. M.; Strelenko, Y. A.; Tartakovsky, V. A. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 311.
- Bleger, D.; Liebig, T.; Thiermann, R.; Maskos, M.; Rabe, J. P.; Hecht, S. *Angew. Chem, Int. Ed. Engl.* **2011**, *50*, 12559.
- Fang, L.; Zhang, H.; Fang, X. B.; Gou, S. H.; Cheng, L., *Indian J. Chem. Sec B* **2014**, *53*, 635.
- Osako, T.; Uozumi, Y., *Org. Lett.* **2014**, *16*, 5866.
- Wang, H.; Wen, K.; Nurahmat, N.; Shao, Y.; Zhang, H.; Wei, C.; Li, Y.; Shen, Y.; Sun, Z. *Beilstein J. Org. Chem.* **2012**, *8*, 744.
- Matsumoto, Y.; Imai, M.; Sawai, Y.; Takeuchi, S.; Nakanishi, A.; Minamizono, K.; Yokoyama, T. Piperidine derivatives having CCR3 antagonism. EP1502916 (A1), 2005-02-02.
- Mąkosza, M.; Surowiec, M. *J. Organomet. Chem.* **2001**, *624*, 167.
- Newmark, R. A.; Hill, J. R. *Org. Magn. Reson.* **1977**, *9*, 589.
- Scmitz, U.; Roberts, C. D.; Griffith, R. C.; Botyanszki, J.; Pham, S. M. Antiviral Agents WO2008008912 (A1), 2008-01-17.
- McBee, E. T.; Pierce, O. R.; Lowery, R. D.; Rapkin, E. *J. Am. Chem. Soc.* **1951**, *73*, 3932.
- Inamoto, K.; Nozawa, K.; Yonemoto, M.; Kondo, Y. *Chem. Commun.* **2011**, *47*, 11775.
- Rana, S.; Bag, S.; Patra, T.; Maiti, D., *Adv. Synth. Catal.* **2014**, *356*, 2453.