

Intramolecular addition of diarylmethanols to imines promoted by KO^t-Bu/DMF: a new synthetic approach to indole derivatives

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Supporting Information

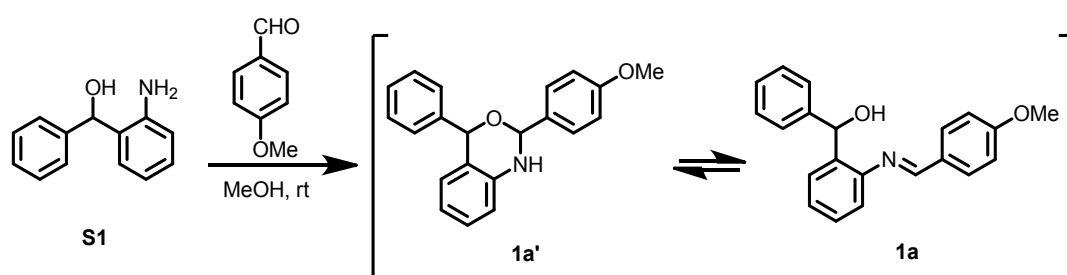
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1. General Information

^1H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 400 spectrometer. Chemical shifts of protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CDCl_3 : δ 7.26; DMSO: δ 2.50). Chemical shifts of carbon are referenced to the carbon resonances of the solvent (CDCl_3 : δ 77.0; DMSO: δ 39.5). Peaks are labeled as singlet (s), broad singlet (br), doublet (d), triplet (t), double doublet (dd), multiplet (m). All products were further characterized by HRMS (high resolution mass spectra). Copies of their ^1H NMR and ^{13}C NMR spectra were provided. GC spectra were taken on an Agilent-6890A instrument. The normal and 99.99% purity of KO t -Bu were purchased from J&K chemical company and Sigma-Aldrich chemical company respectively and used without further purification. DMF (*N,N*-Dimethylformamide) and THF (tetrahydrofuran) were dried and redistilled according to standard methods. DMSO (dimethyl sulfoxide), DMEU (1,3-dimethyl-2-imidazolidinone), and 2-MeTHF (2-methyltetrahydrofuran) were dried over 4Å molecular sieves.

2. General procedures

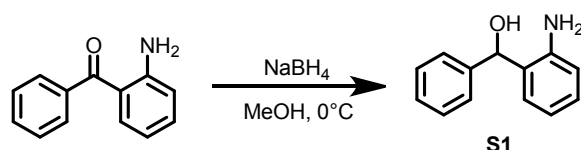
(1) General procedure for the preparation of substrates **1a/1a'**:



To a mixture of (2-aminophenyl)(phenyl)methanol **S1** (199.3 mg, 1 mmol) and 4-methoxybenzaldehyde (136.2 mg, 1 mmol) was added dry methanol (2 mL). The mixture was stirred at room temperature for 24 hours. The formed precipitate was filtered and washed with isopropyl ether (10 mL) and dry pentane (10 mL). The solid was dried under vacuum and was proved to be the inseparable mixture of 3 isomers: imine **1a** (13.5 %) and oxazine *cis*-**1a'** (54.1%), *trans*-**1a'** (32.4%). The mixture was then used for the next step directly without further purification (282 mg, 88% yield).

The intermediate **S1** was synthesized according to the followed **methods A-C**:

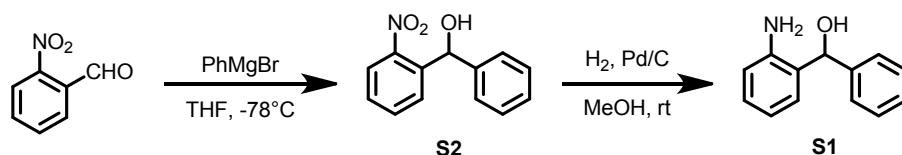
Method A:^[1]



To the solution of 2-aminobenzophenone (987 mg, 5 mmol) in methanol (15 mL) was added sodium borohydride (947 mg, 25 mmol) in 3 portions at an interval of 15 min at 0°C. After the completion of the

reaction (by TLC), saturated NH_4Cl (5 mL) was slowly added to quench the reaction. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (20 mL \times 3). The combined organic layers was then washed with brine (20 mL) and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/EtOAc = 10:1) to give **S1** (956.2 mg, 96% yield).

Method B: ^[2]



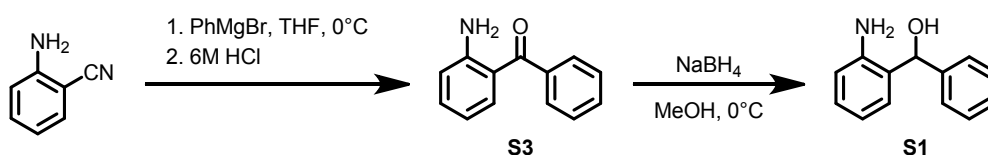
Step 1:

To a solution of 2-nitrobenzaldehyde (1.51 g, 10 mmol) in anhydrous THF (20 mL) was added phenylmagnesium bromide (10 mL, 1.0 M solution in THF) dropwise at -78°C . The mixture was then stirred at -78°C for 1 hour under an argon atmosphere. After being warmed to room temperature, saturated NH_4Cl solution (5 mL) was added dropwise to quench the reaction. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (20 mL \times 3). The combined organic layers was then washed with brine (20 mL) and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/EtOAc = 5:1) to give **S2** (2.45 g, 84% yield).

Step 2:

To a solution of **S2** (2.05 g, 7 mmol) in methanol (20 mL) was added Pd/C (500 mg) and two drops of acetic acid. Then the mixture was stirred at room temperature under hydrogen (1 atm) atmosphere for 5 hours. Then the solid was filtered off and the solution was concentrated in *vacuo*. The residue was purified by column chromatography (petroleum ether/EtOAc = 10:1) to give **S1** (1.54g, 95% yield).

Method C: ^[3]



Step 1:

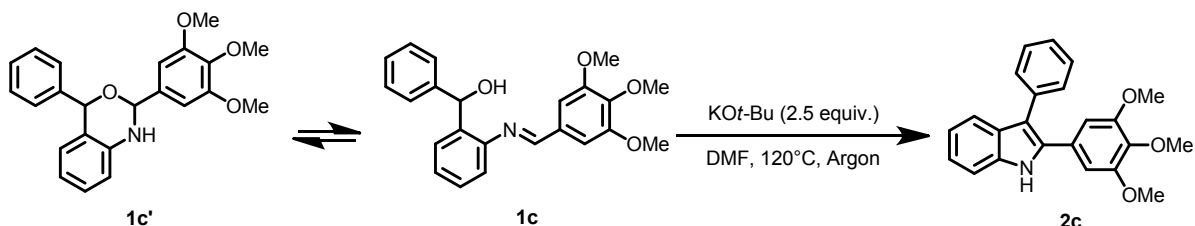
To a solution of 2-aminobenzonitrile (1.18 g, 10 mmol) in anhydrous THF (20 mL) was added the phenylmagnesium bromide (30 mL, 1.0 M solution in THF) dropwise at 0°C under an Argon atmosphere. The mixture was stirred for 1 hour at 0°C and 12 hours at room temperature. After cooled down to 0°C , HCl solution (10 mL, 6 M) was added dropwise and the mixture was stirred at room temperature for another 12

hours. Then the mixture was basified to pH = 9 with 10% NaOH solution. THF was removed under reduced pressure and the residue was extracted with ethyl acetate (20 mL × 3). The combined organic layers was then washed with brine (20 mL) and dried over anhydrous Na₂SO₄. The residue was purified by column chromatography (petroleum ether/EtOAc = 20:1) to give **S3** (1.50 g, 75% yield).

Step 2:

To the solution of **S3** (1.38 g, 7 mmol) in methanol (20 mL) was added sodium borohydride (1.33 g, 35 mmol) in 3 portions at an interval of 15 min at 0°C. After the completion of the reaction (by TLC), saturated NH₄Cl solution (5 mL) was slowly added to quench the reaction. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (20 mL × 3). The combined organic layers was then washed with brine (20 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/EtOAc = 10:1) to give **S1** (1.35 g, 97% yield).

(2) General procedure for the gram-scale experiment

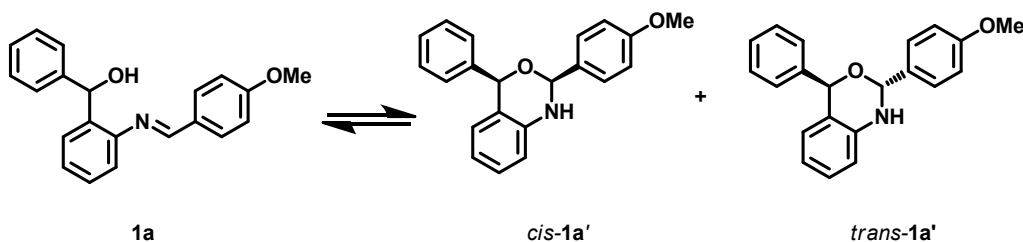


To a 100 mL dried flask was added the mixture of **1c/1c'** (1.51 g, 4.0 mol), KO^t-Bu (1.12 g, 10.0 mmol) and dry DMF (40.0 mL). The mixture was stirred at 120°C for 2 hours under argon atmosphere. After cooled to room temperature, the mixture was poured into 200 mL iced water and stirred for 5 minutes. The precipitated solid was collected by filtration and further purified by recrystallization (petroleum ether/EtOAc) to afford **2c** as a white solid (1.08 g, 75% yield).

3. Characterization data of the starting materials

Representative full data of **1a/1a'** is shown below:

(2-((4-methoxybenzylidene) amino) phenyl)(phenyl)methanol (**1a**) and 2-(4-methoxyphenyl)-4-phenyl-1,4-dihydro-2H-benzo[d][1,3]oxazine (**1a'**).



Selected signals: ¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H, NCHAr, imine), 6.14 (s, 1H, NHCHO, cis), 6.10 (s,

1H, ArCH₂OH, imine), 6.02 (s, 1H, NHCHO, trans), 5.85 (d, J = 3.5 Hz, 1H, ArCHAr, cis), 5.48 (d, J = 4.1 Hz, 1H, ArCHAr, trans), 4.29 (s, 1H, ArNH, cis), 4.21 (s, 1H, ArNH, trans), 3.91 (s, 3H, OCH₃, imine), 3.84 (s, 3H, OCH₃, cis), 3.83 (s, 3H, OCH₃, trans). ¹³C NMR (100 MHz, CDCl₃): δ 158.8 (imine), 85.3 (cis), 81.1 (cis), 78.7 (trans), 77.2 (trans), 55.8 (imine), 55.4 (cis and trans, one carbon was missing due to overlapping). HRMS (ESI) calculated for C₂₁H₂₀NO₂ [M+H]⁺: 318.1494, found: 318.1487.

Because of the complex overlapping signals and the differences in the concentration of the 3 isomers, the NMR data of the **1a/1a'-1t/1t'** was not given here. The properties, the HRMS data, the yields and the proton signals of N=CH are summarised in Table 1.

Table 1 Selected data for **1a/1a'-1t/1t'**

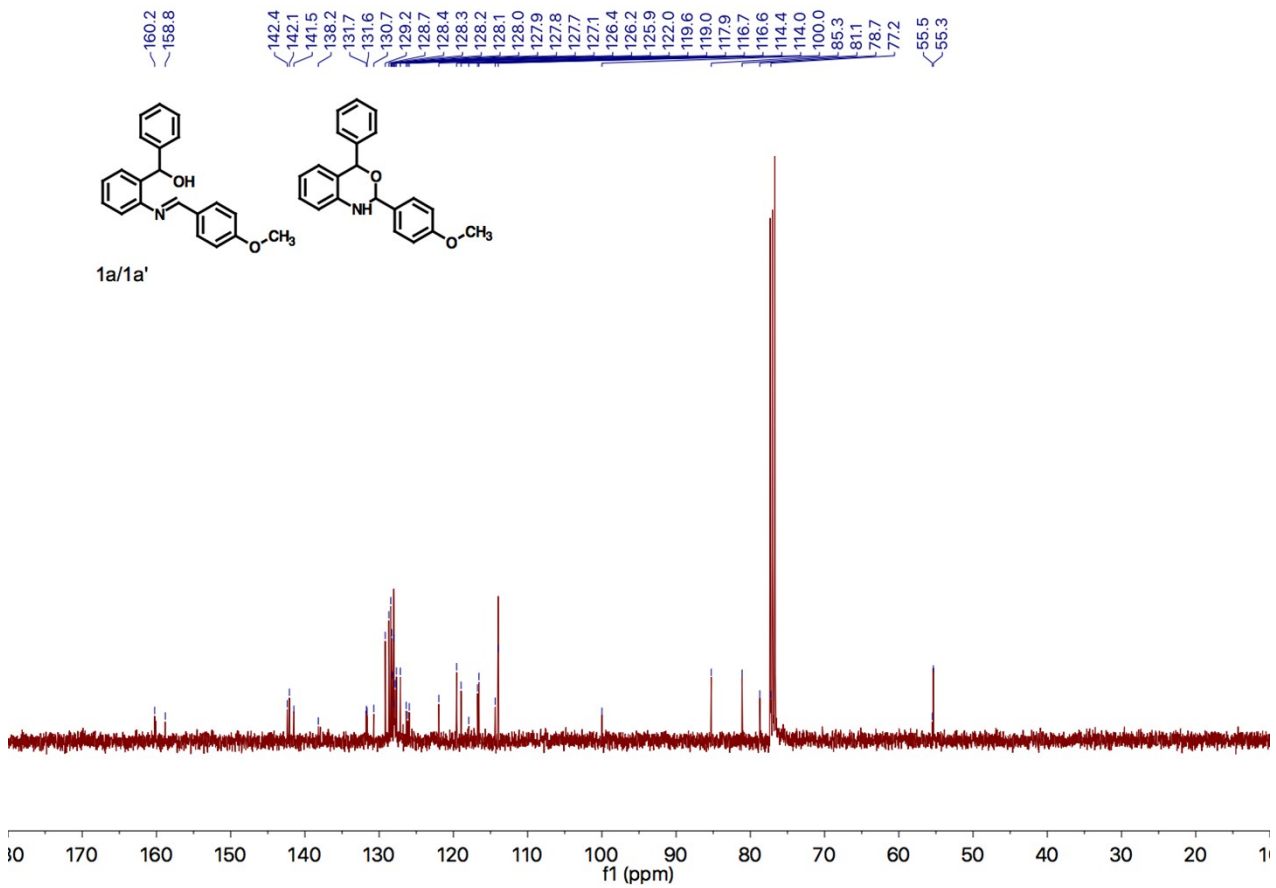
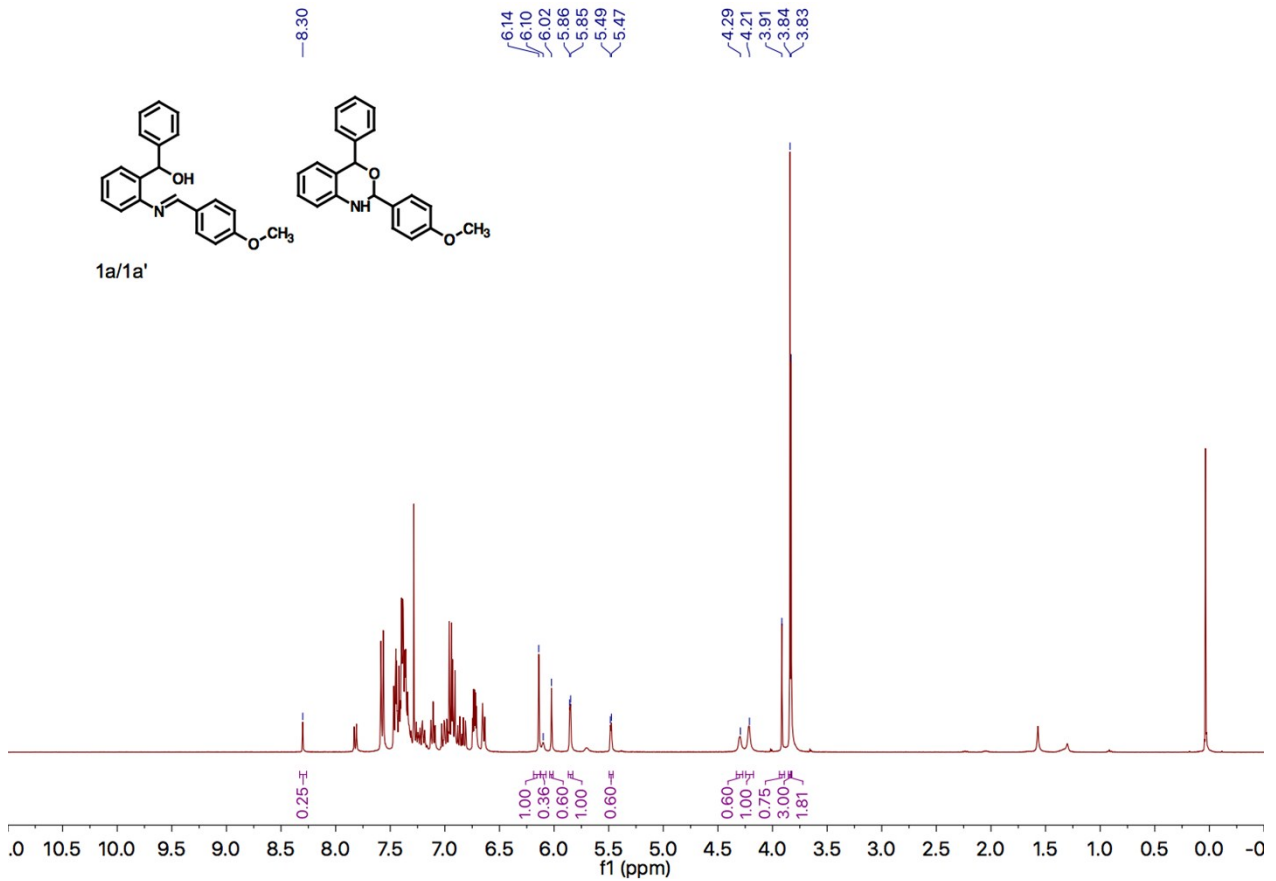
Compd.	Status	Yield (%)	Formula	HRMS found (calc.)	δ [ppm] N=CH
1a/1a'	white solid	88	C ₂₁ H ₁₉ NO ₂	318.1487 (318.1494)	8.30
1b/1b'	white solid	81	C ₂₂ H ₂₁ NO ₃	348.1583 (348.1594)	8.85
1c/1c'	white solid	78	C ₂₃ H ₂₃ NO ₄	378.1682 (378.1700)	8.79
1d/1d'	white solid	72	C ₂₄ H ₂₄ N ₂ O ₂	373.1902 (373.1911)	8.29
1e/1e'	white solid	74	C ₂₁ H ₁₆ N ₂ O	313.1325 (313.1335)	8.33
1f/1f'	yellow solid	90	C ₂₄ H ₁₈ N ₂ O ₃	383.1378 (383.1390)	-
1g/1g'	white solid	86	C ₂₅ H ₂₄ N ₂ O ₂	385.1895 (385.1911)	8.33
1h/1h'	white solid	79	C ₂₄ H ₁₉ NO	337.1459 (337.1467)	8.53
1i/1i'	white solid	82	C ₂₅ H ₂₁ NO ₂	368.1636 (368.1645)	8.48
1j/1j'	pale solid	81	C ₂₆ H ₂₁ NO	364.1683 (364.1696)	8.44
1k/1k'	yellow solid	88	C ₃₀ H ₂₃ NO	413.1728 (413.1774)	9.40
1l/1l'	white solid	79	C ₁₈ H ₁₅ NOS	294.0938 (294.0947)	8.47
1m/1m'	white solid	86	C ₂₃ H ₁₈ N ₂ O	339.1476 (339.1492)	-
1n/1n'	white solid	84	C ₂₅ H ₂₁ NO	352.1681 (352.1696)	8.54
1o/1o'	white solid	86	C ₂₅ H ₂₁ NO	352.1684 (352.1696)	8.51
1p/1p'	white solid	85	C ₂₄ H ₁₈ FNO	356.1432 (356.1445)	8.45
1q/1q'	white solid	82	C ₂₄ H ₂₅ NO	344.1993 (344.2009)	8.61
1r/1r'	white solid	88	C ₂₅ H ₂₁ NO	352.1681 (352.1696)	8.47
1s/1s'	white solid	87	C ₂₅ H ₂₁ NO	352.1689 (352.1696)	8.44
1t/1t'	white solid	78	C ₂₄ H ₁₈ FNO	356.1435 (356.1445)	8.53

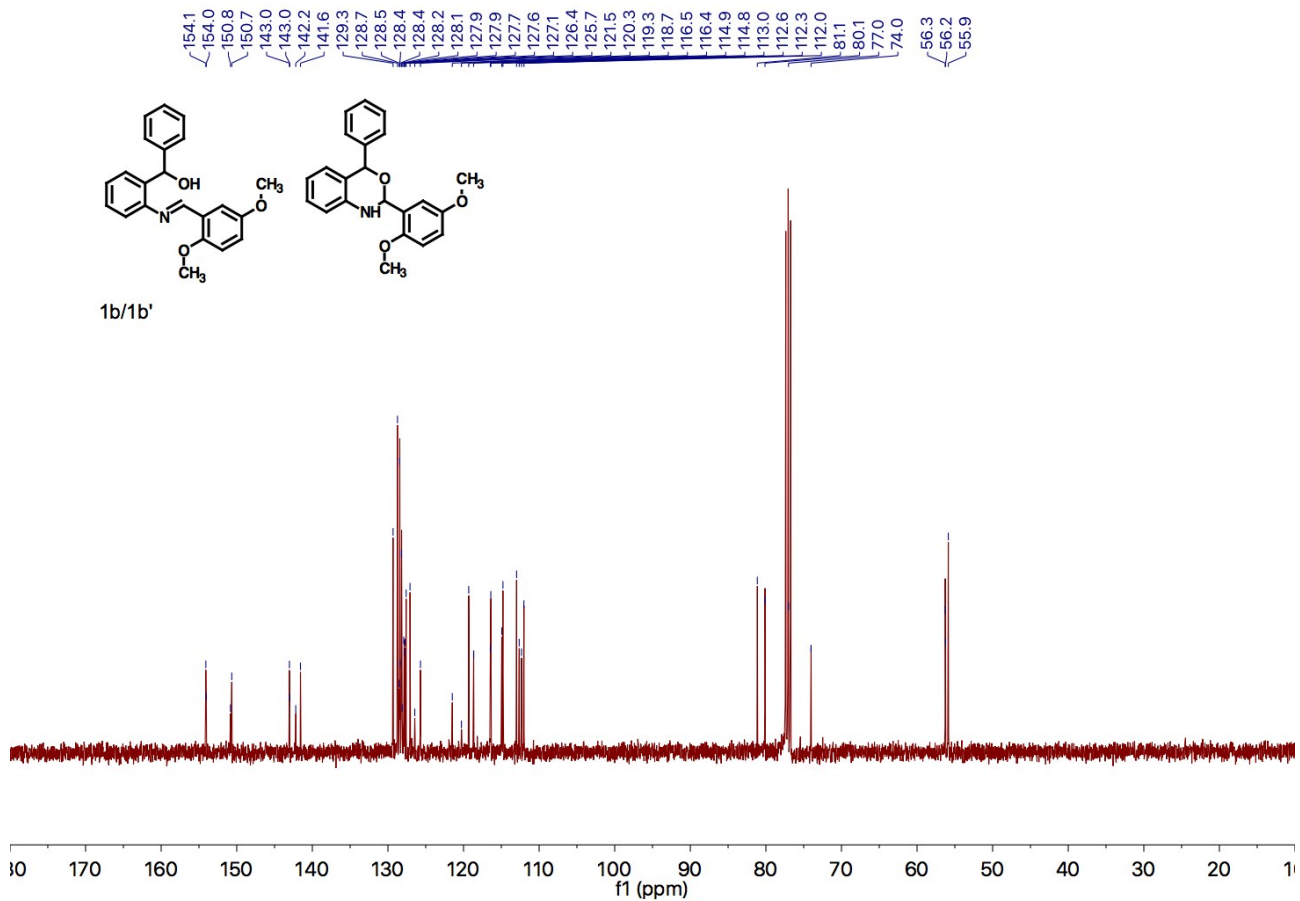
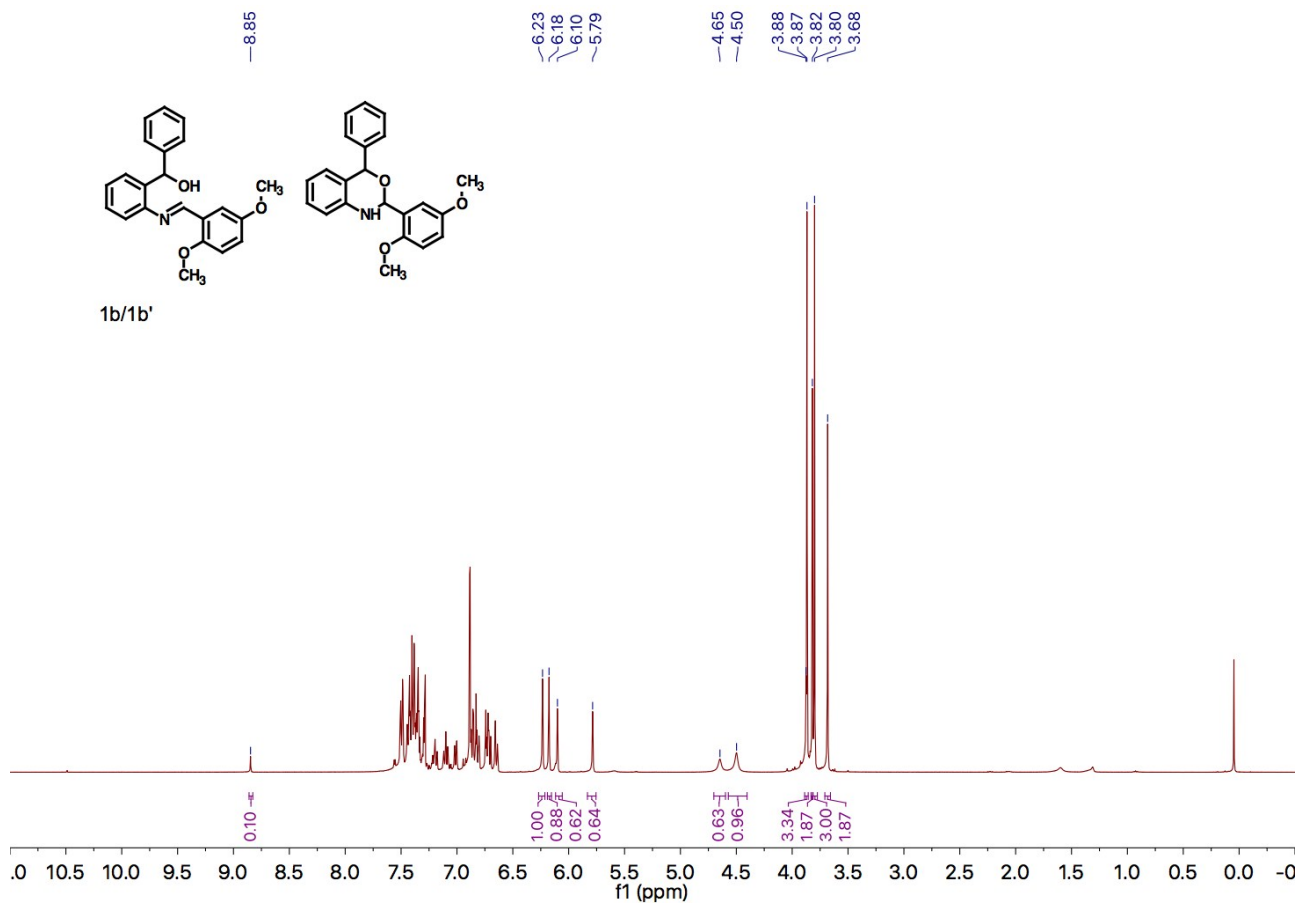
^aThe imine was not detected due to the low concentration.

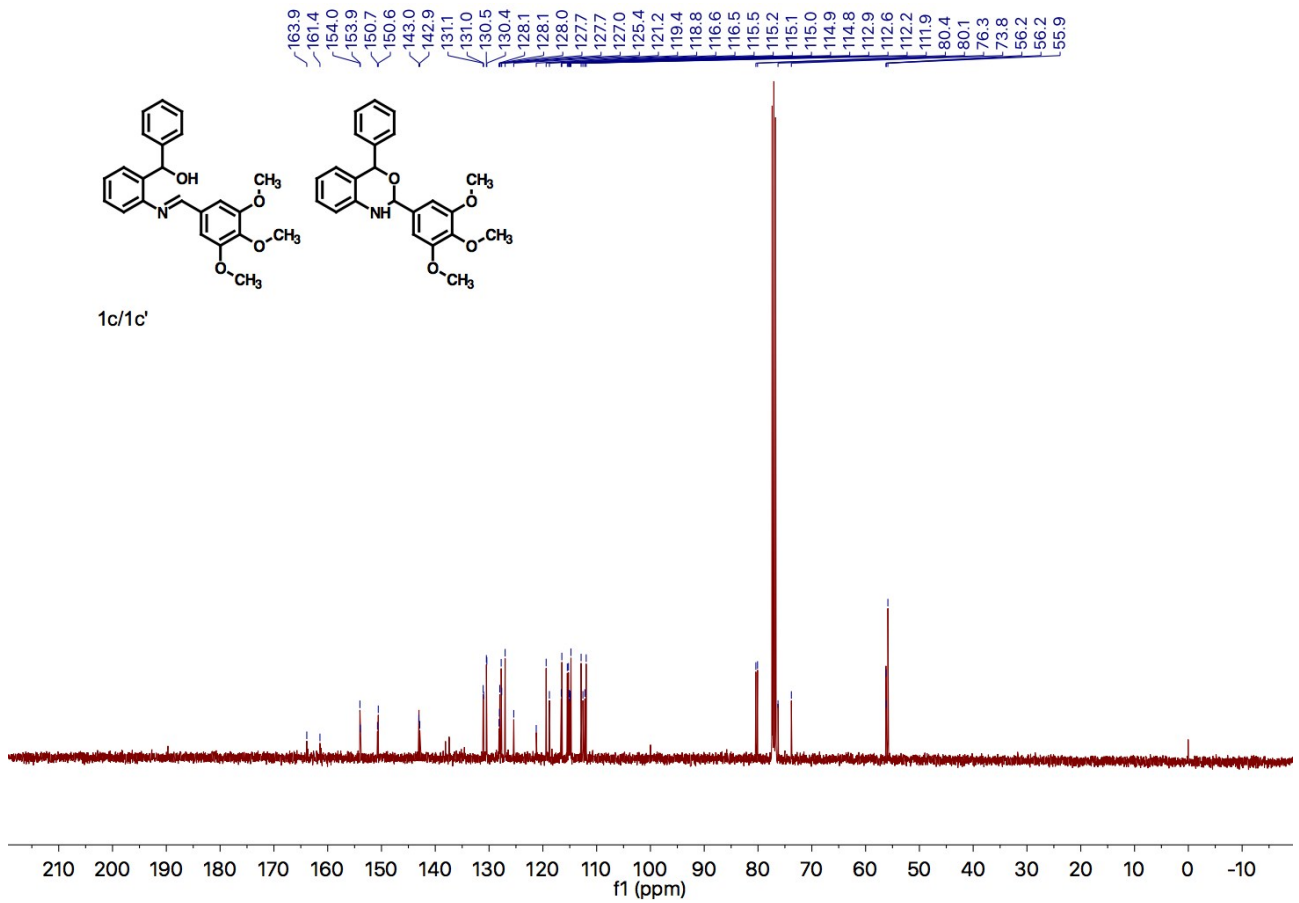
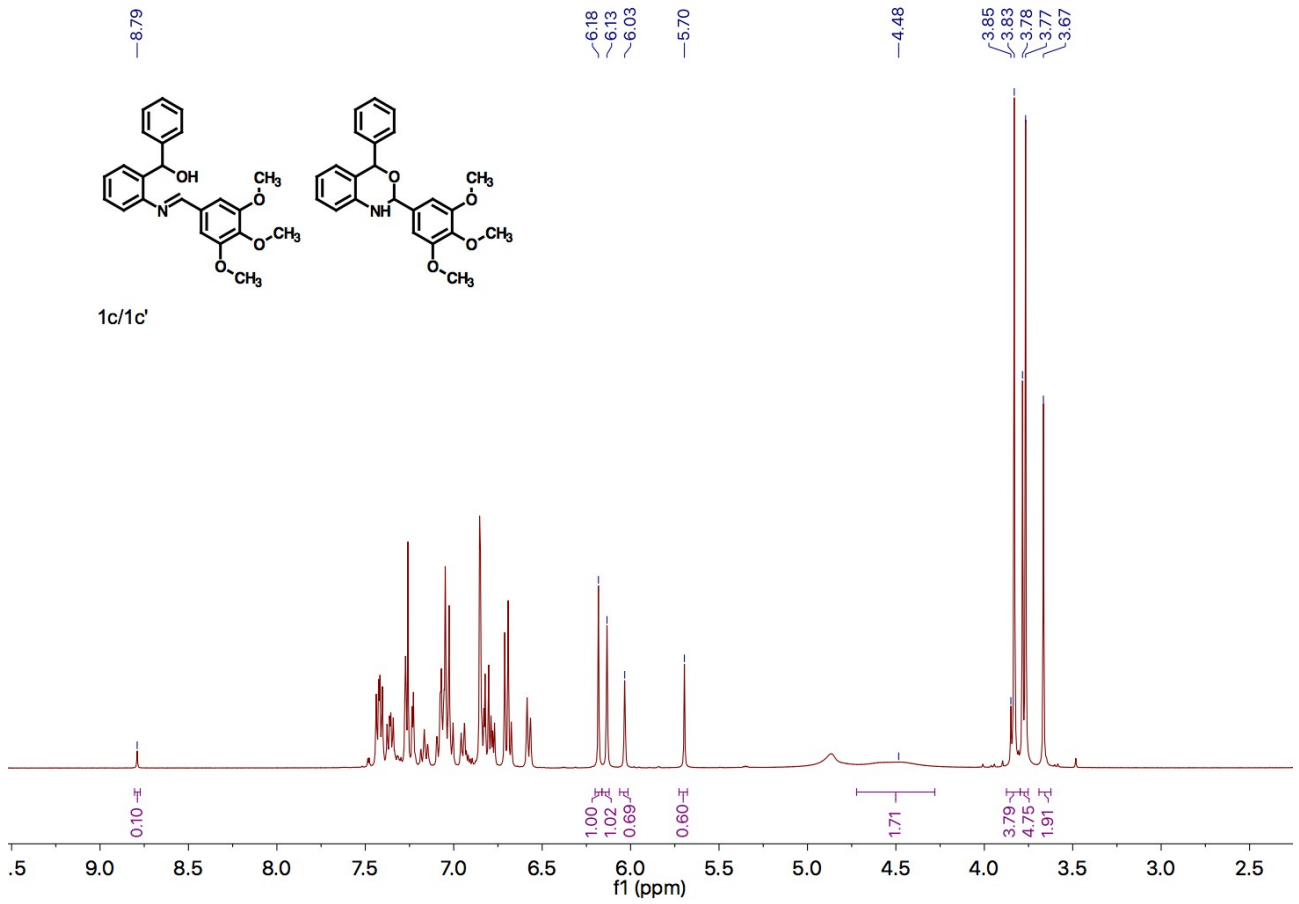
4. References

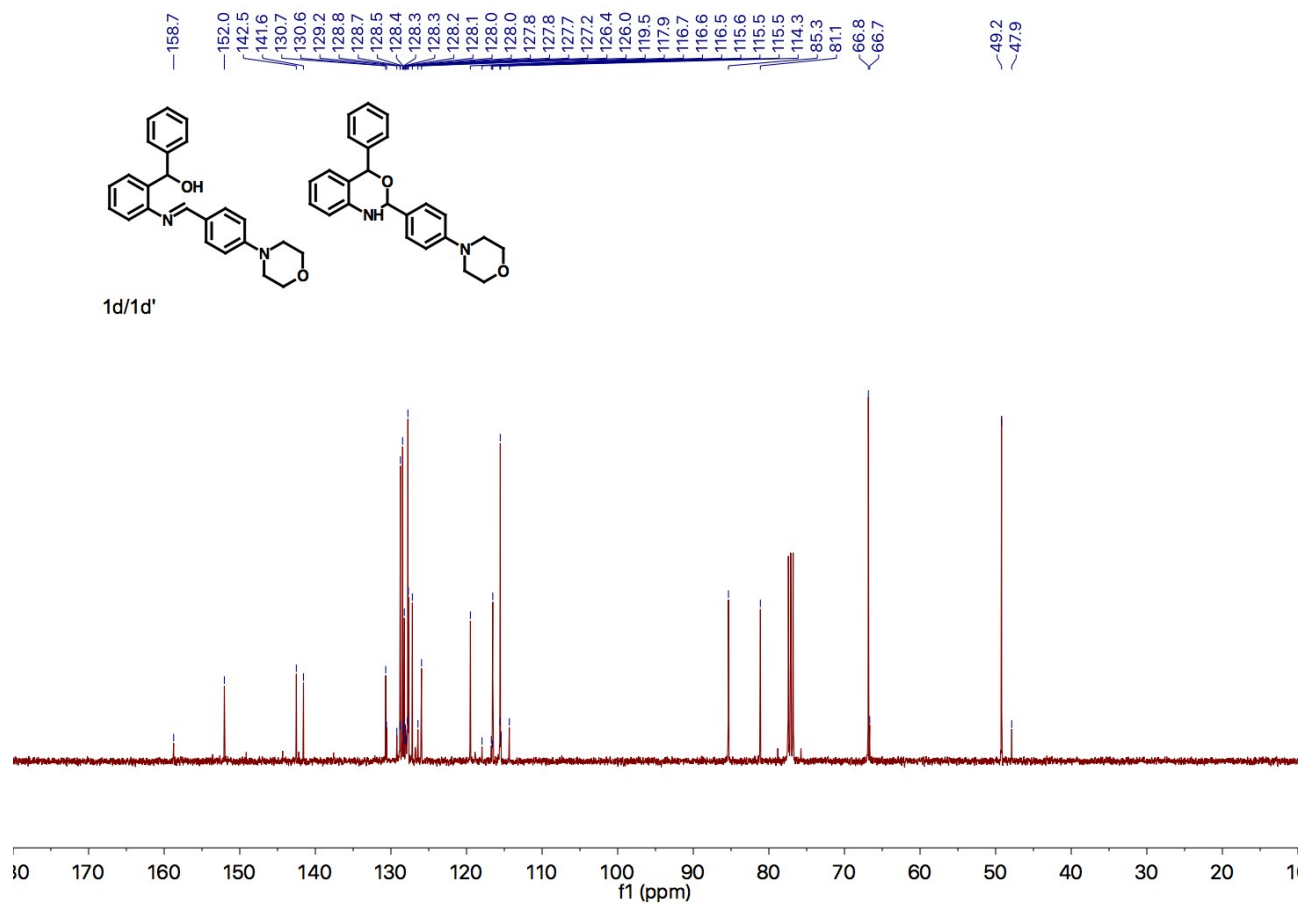
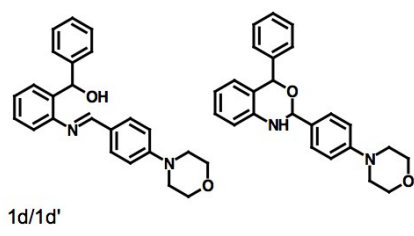
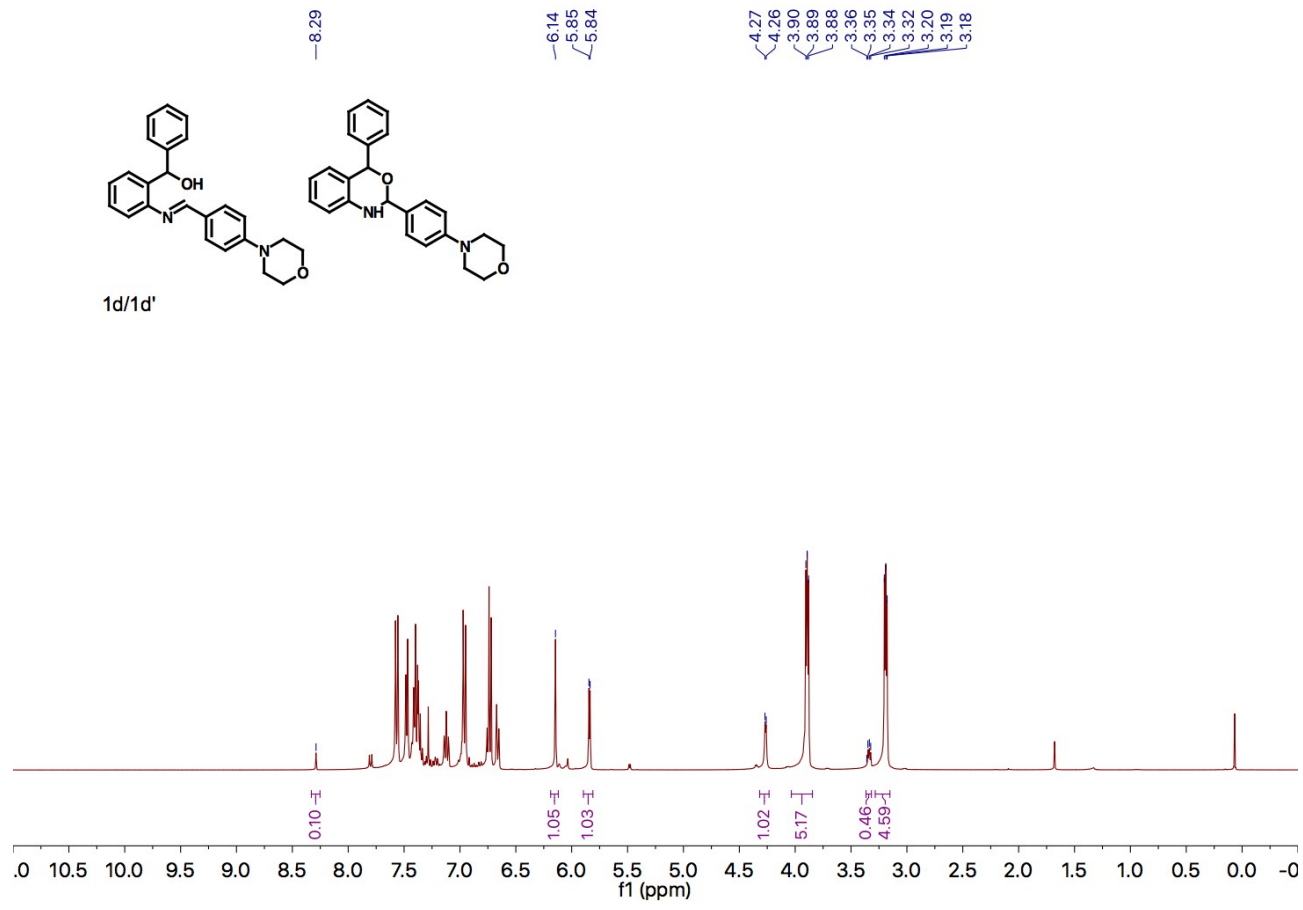
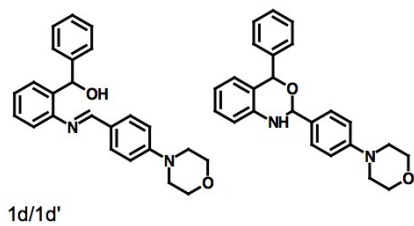
- [1] R. Martínez, D.J. Ramón, M. Yus, *J. Org. Chem.* 2008, **73**, 9778.
- [2] J. Fan, C. Wan, G. Sun, Z. Wang, *J. Org. Chem.*, 2008, **73**, 8608.
- [3] J. Zhang, C. Yu, S. Wang, C. Wan, Z. Wang, *Chem. Commun.*, 2010, **46**, 5244.

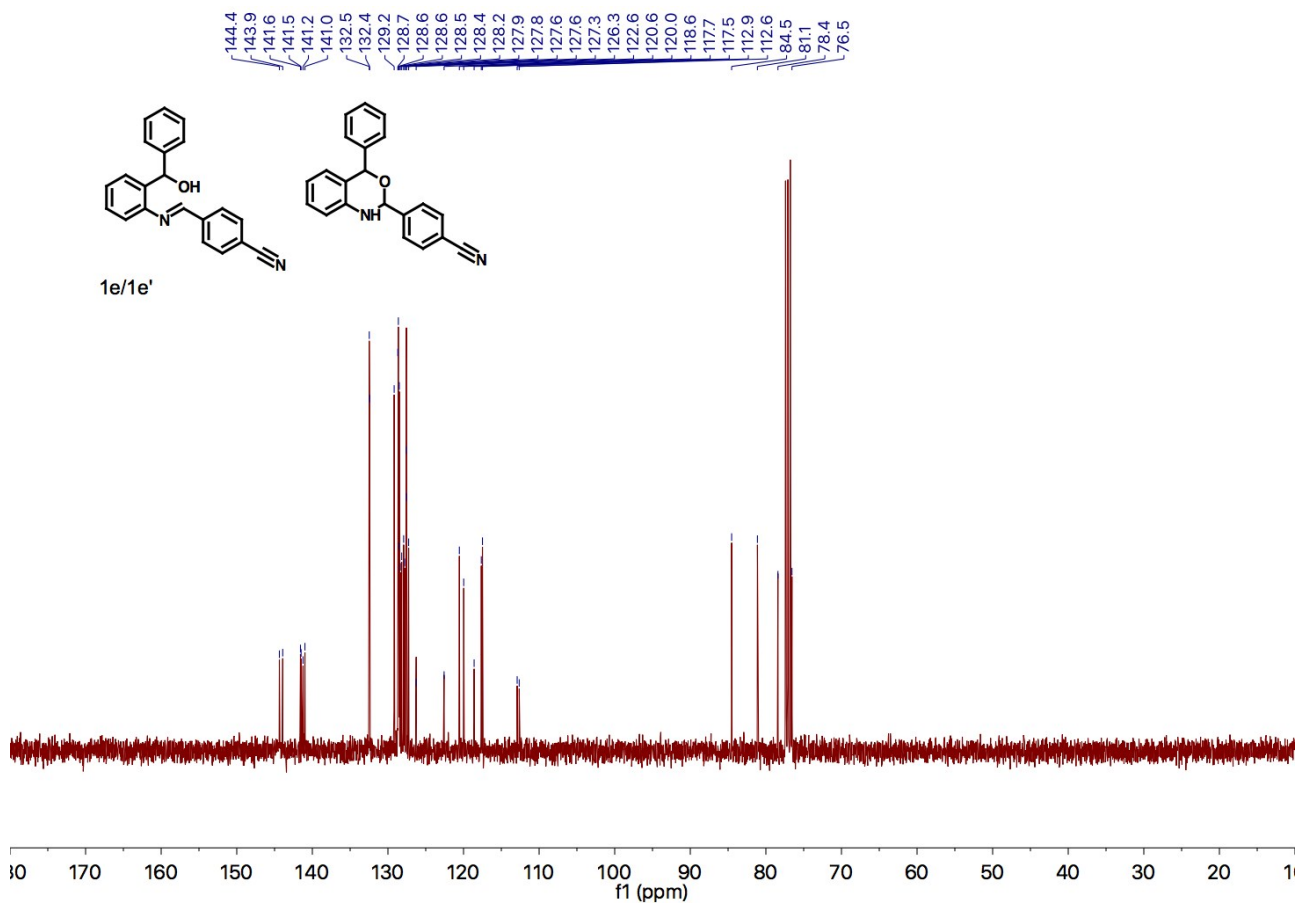
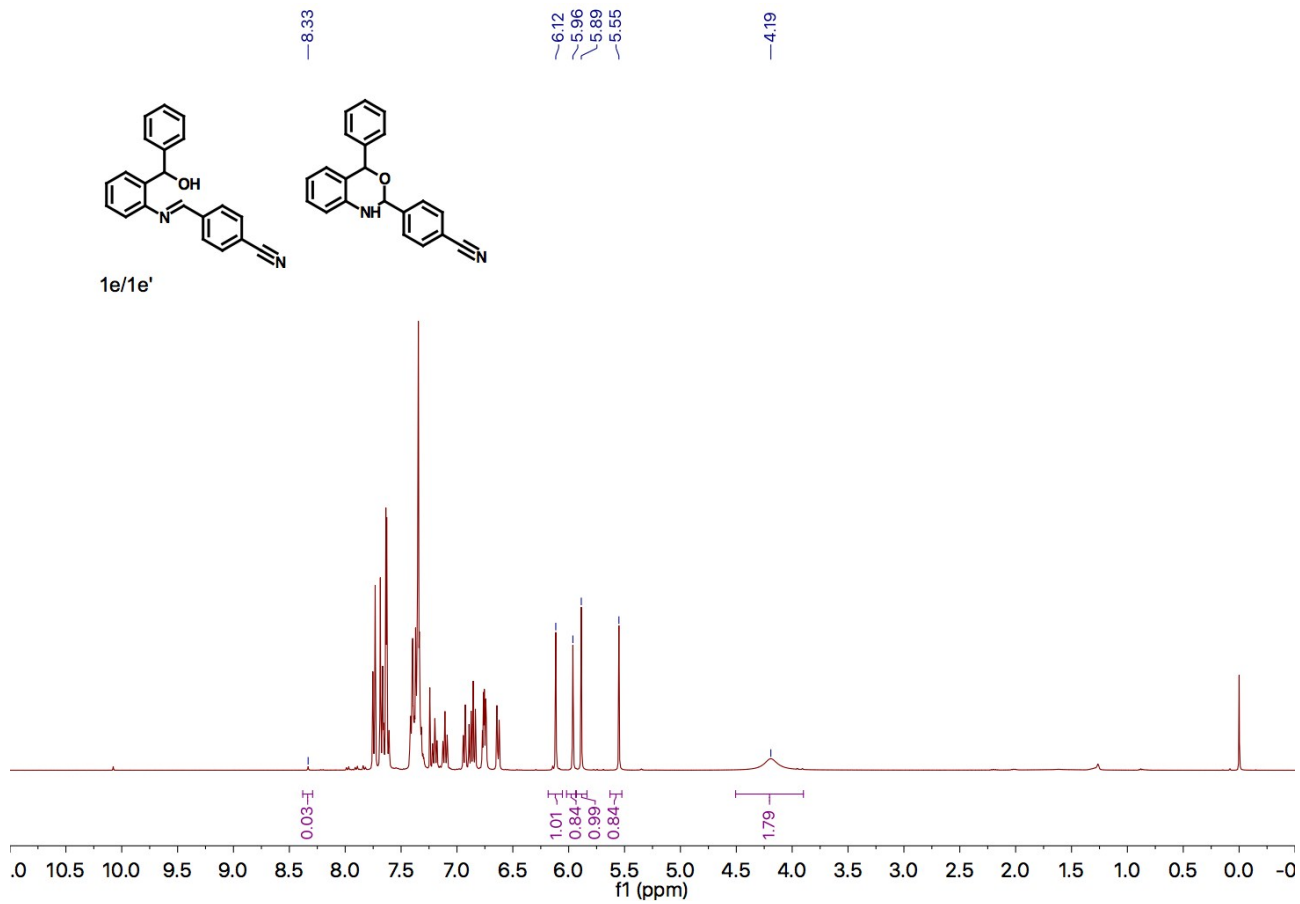
5. NMR Spectra

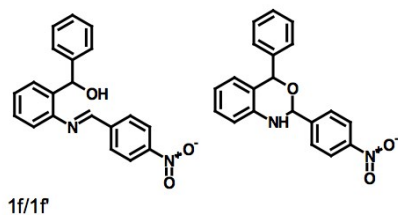




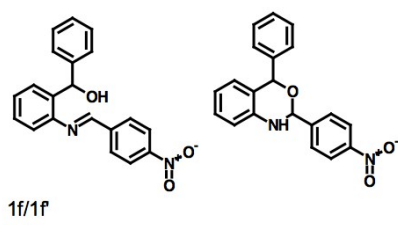
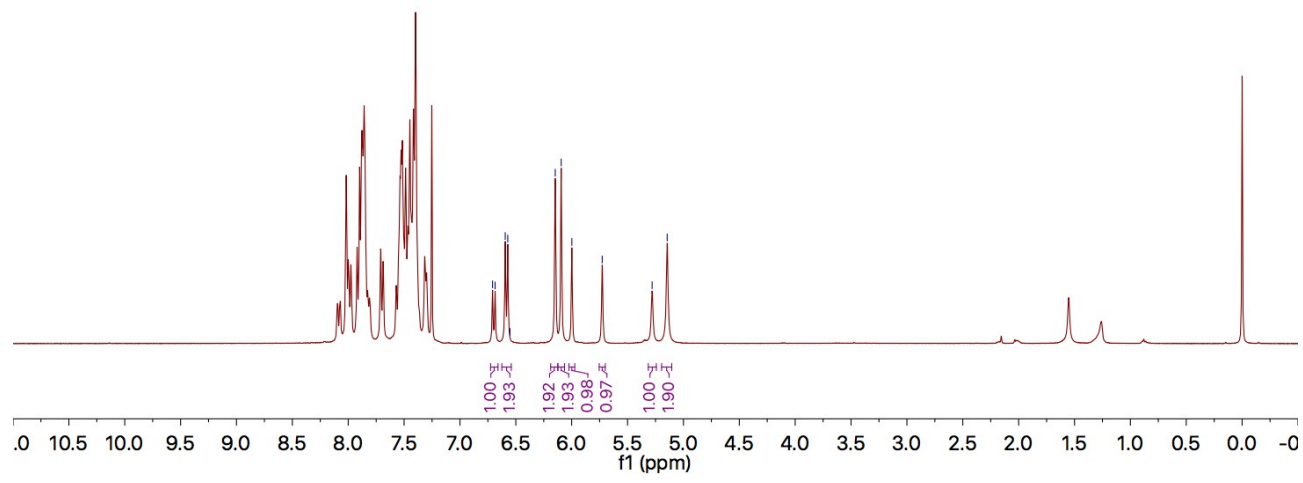




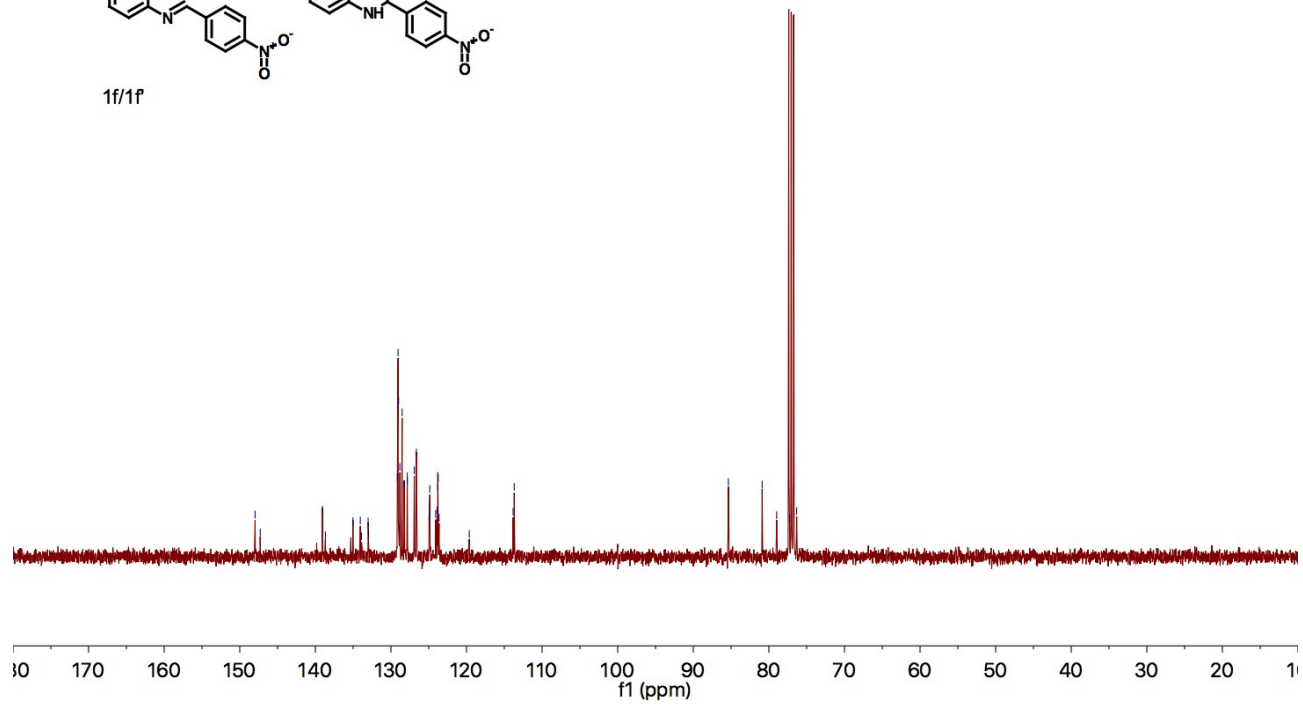


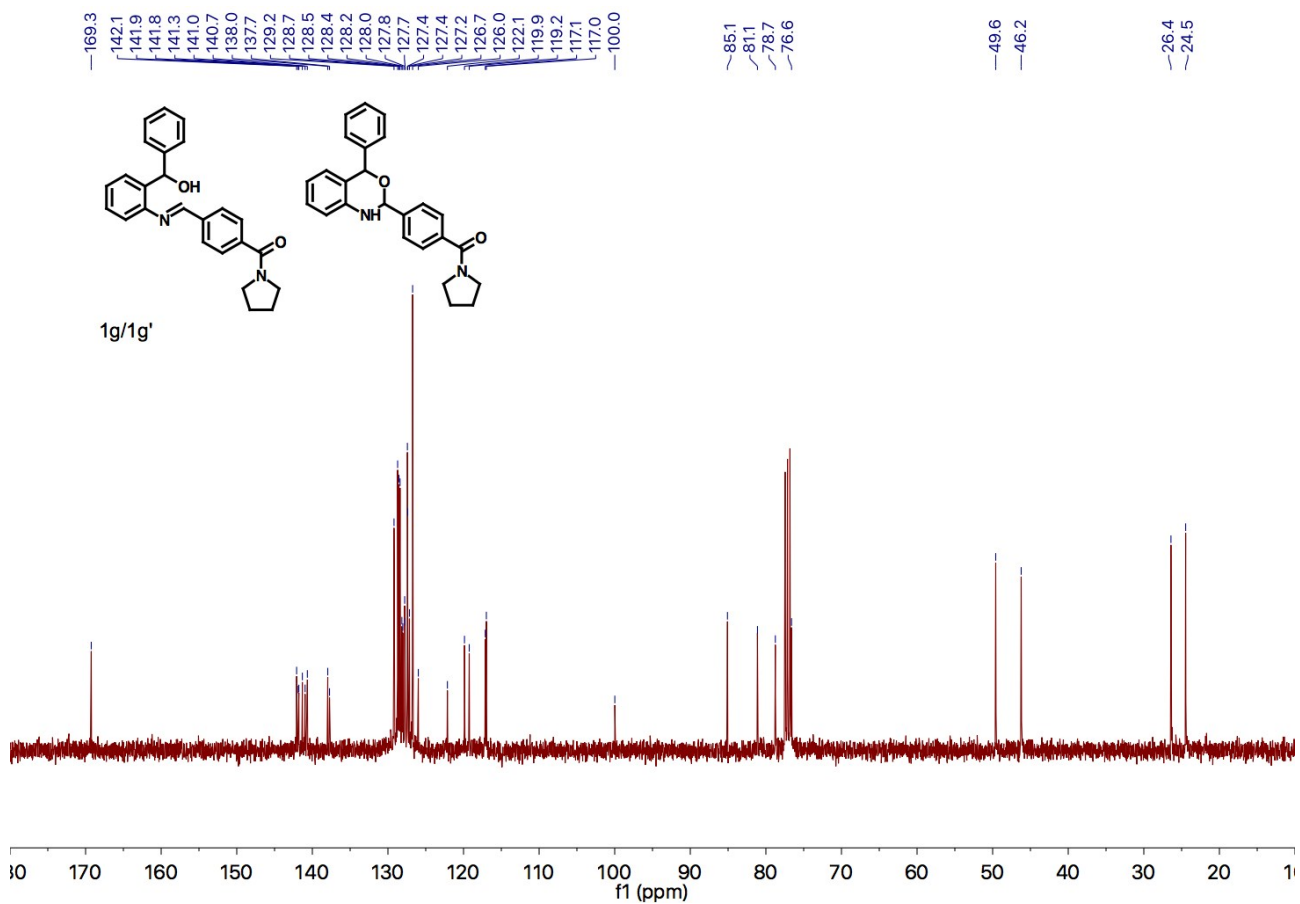
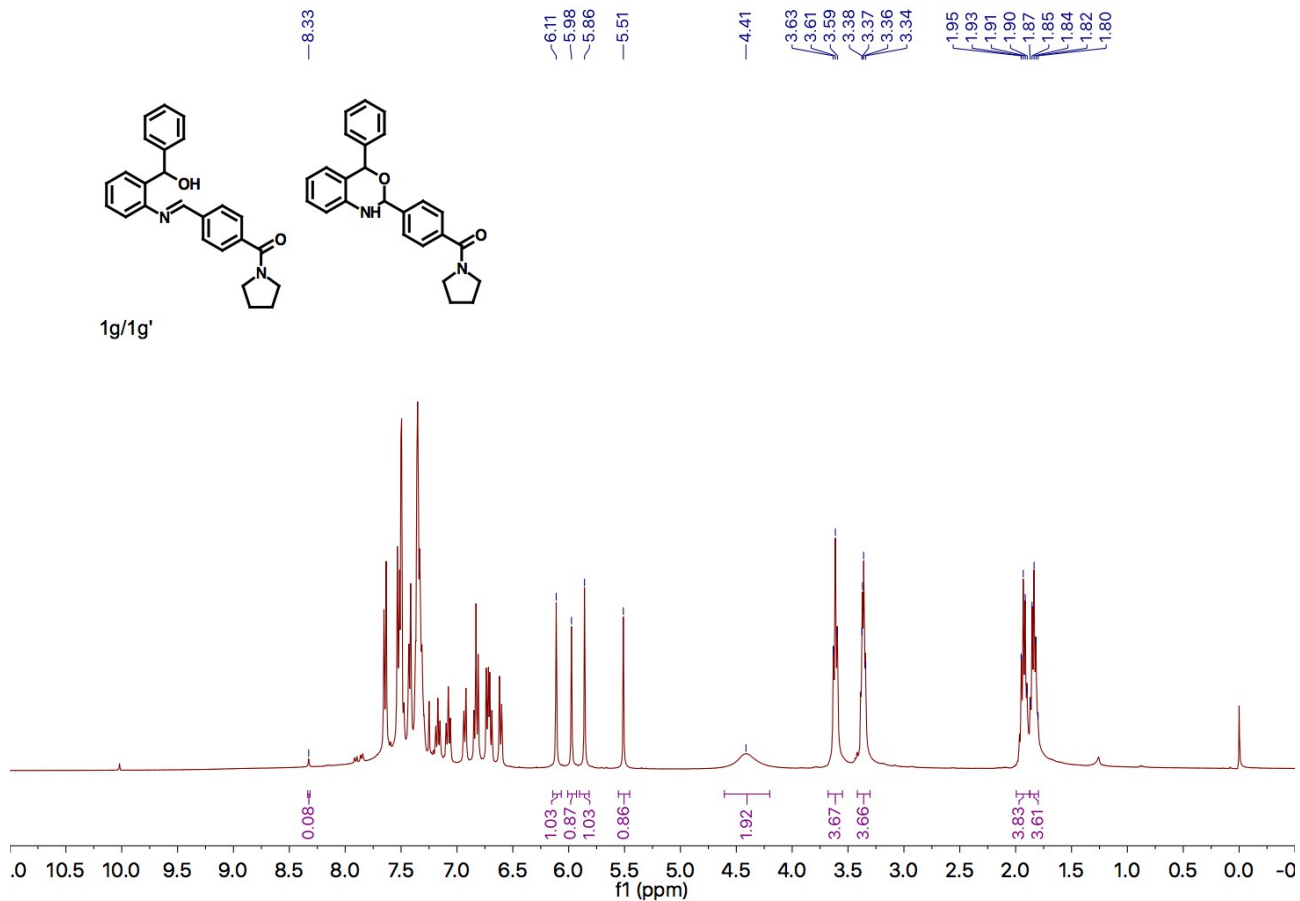


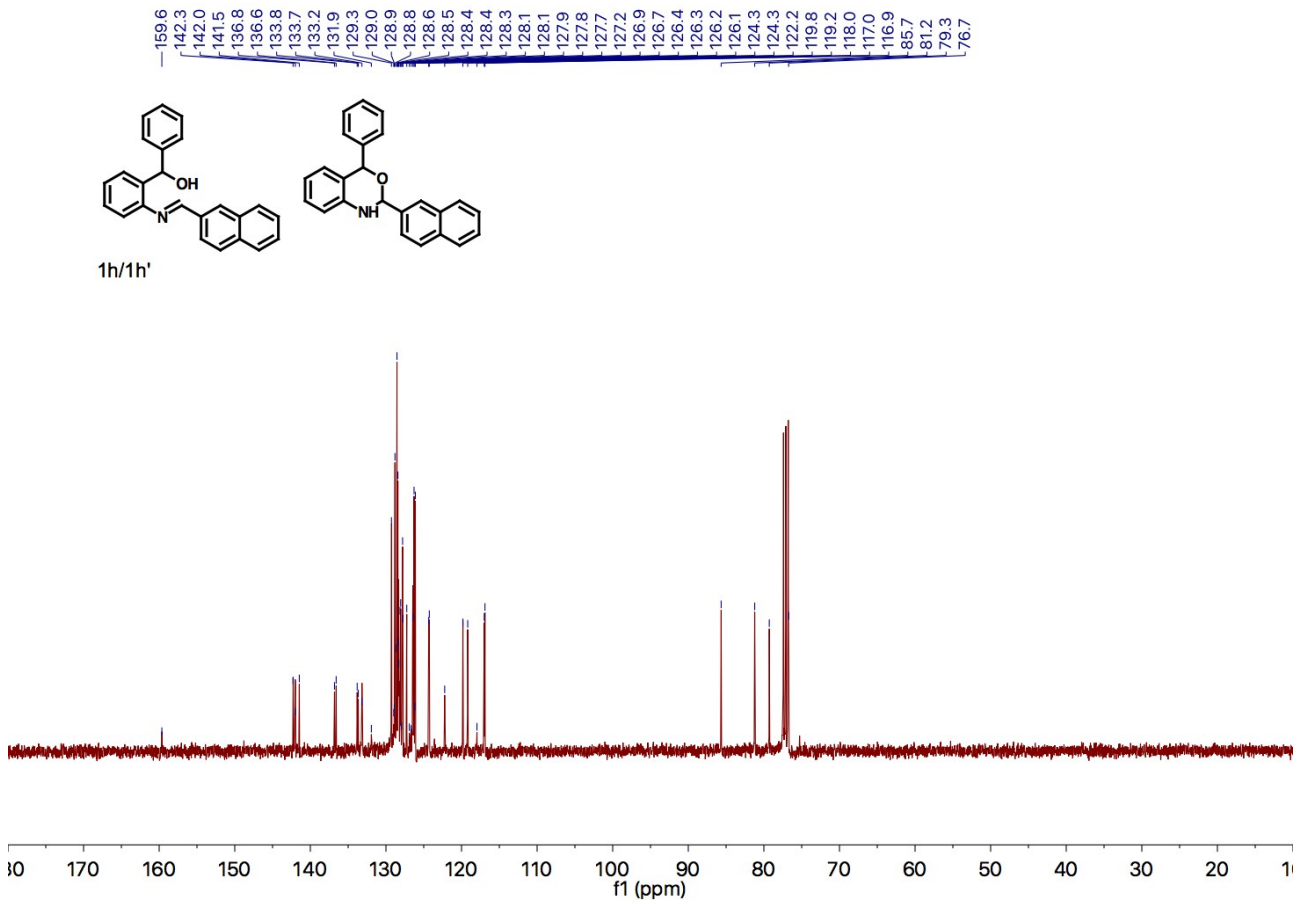
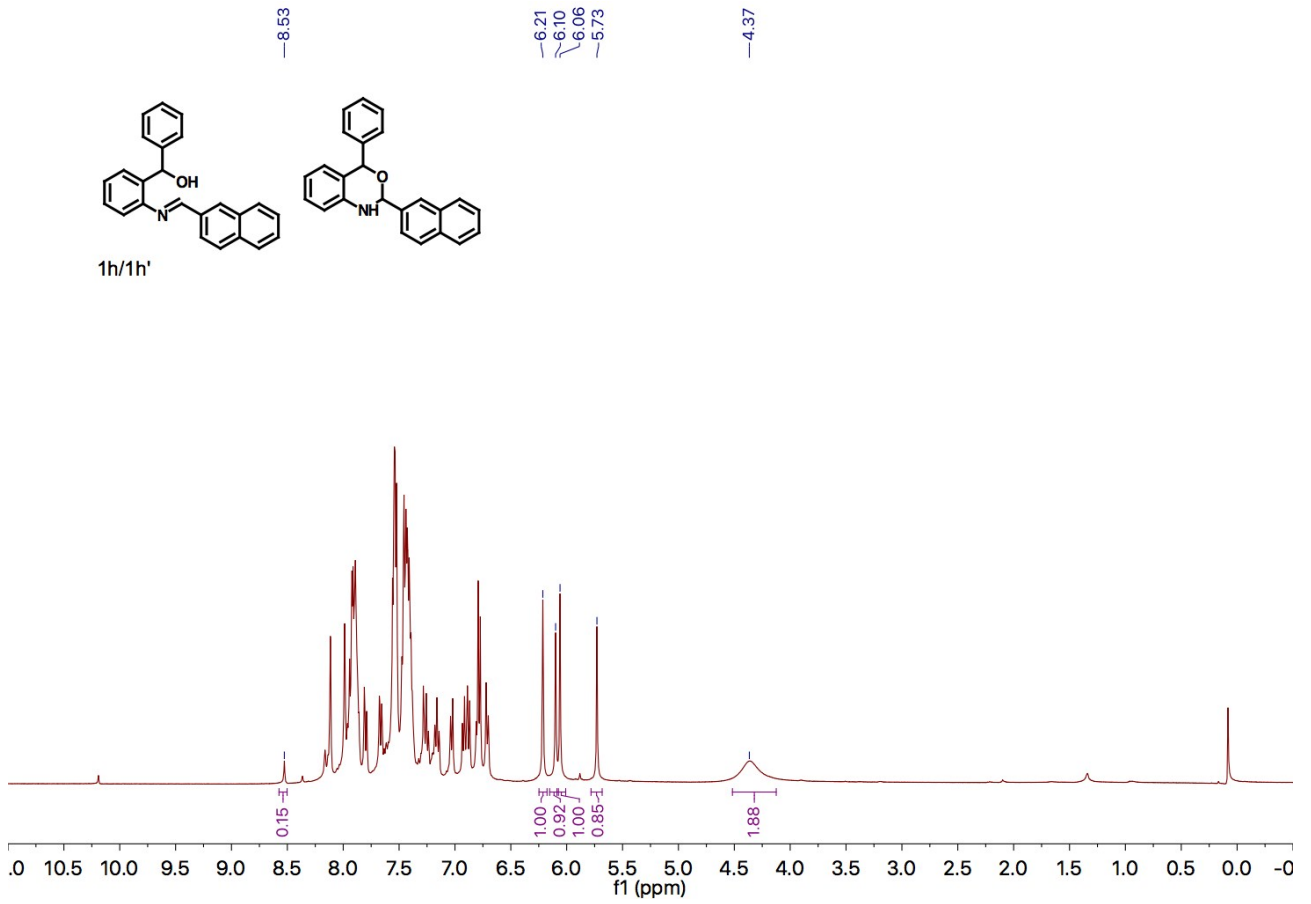
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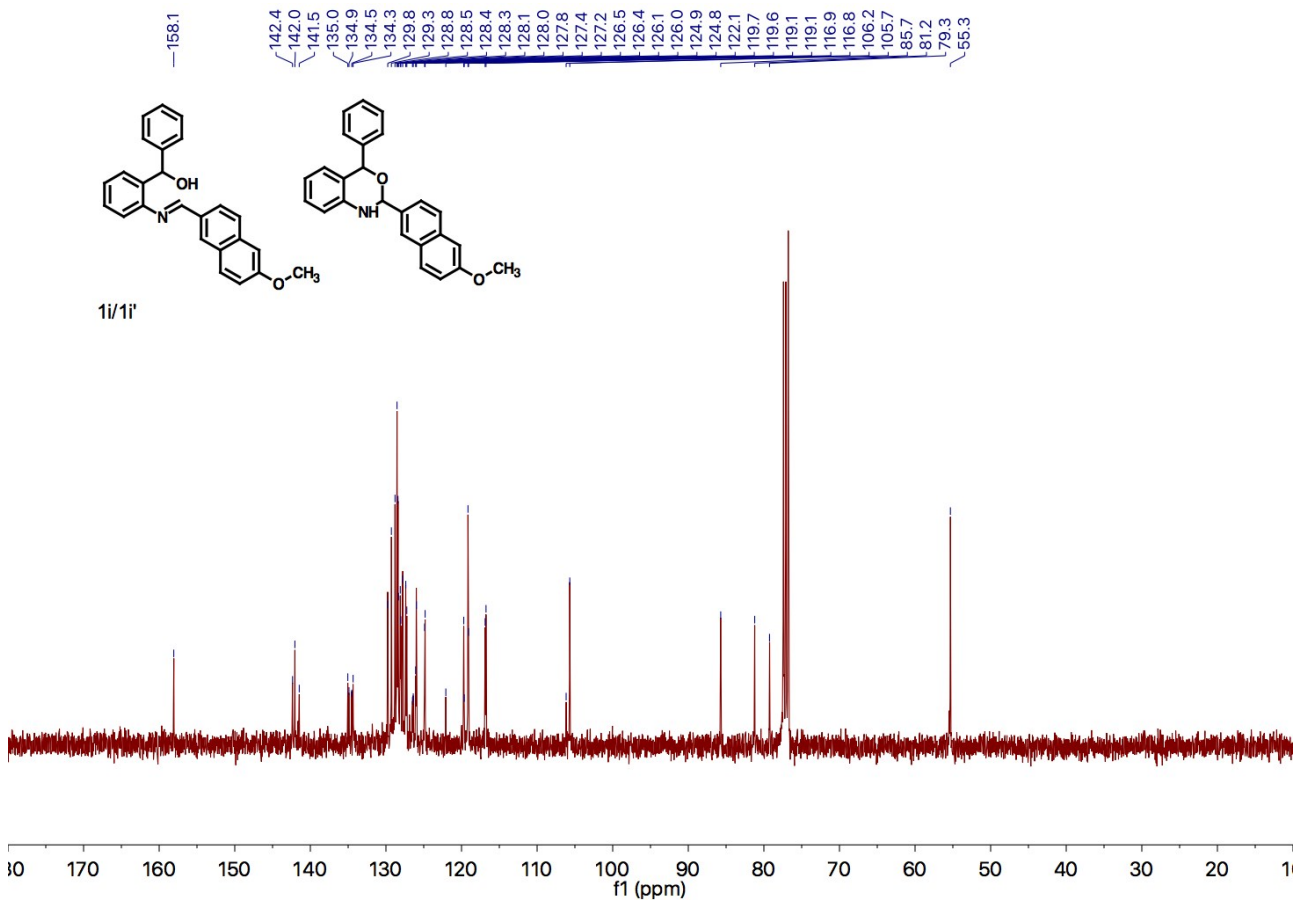
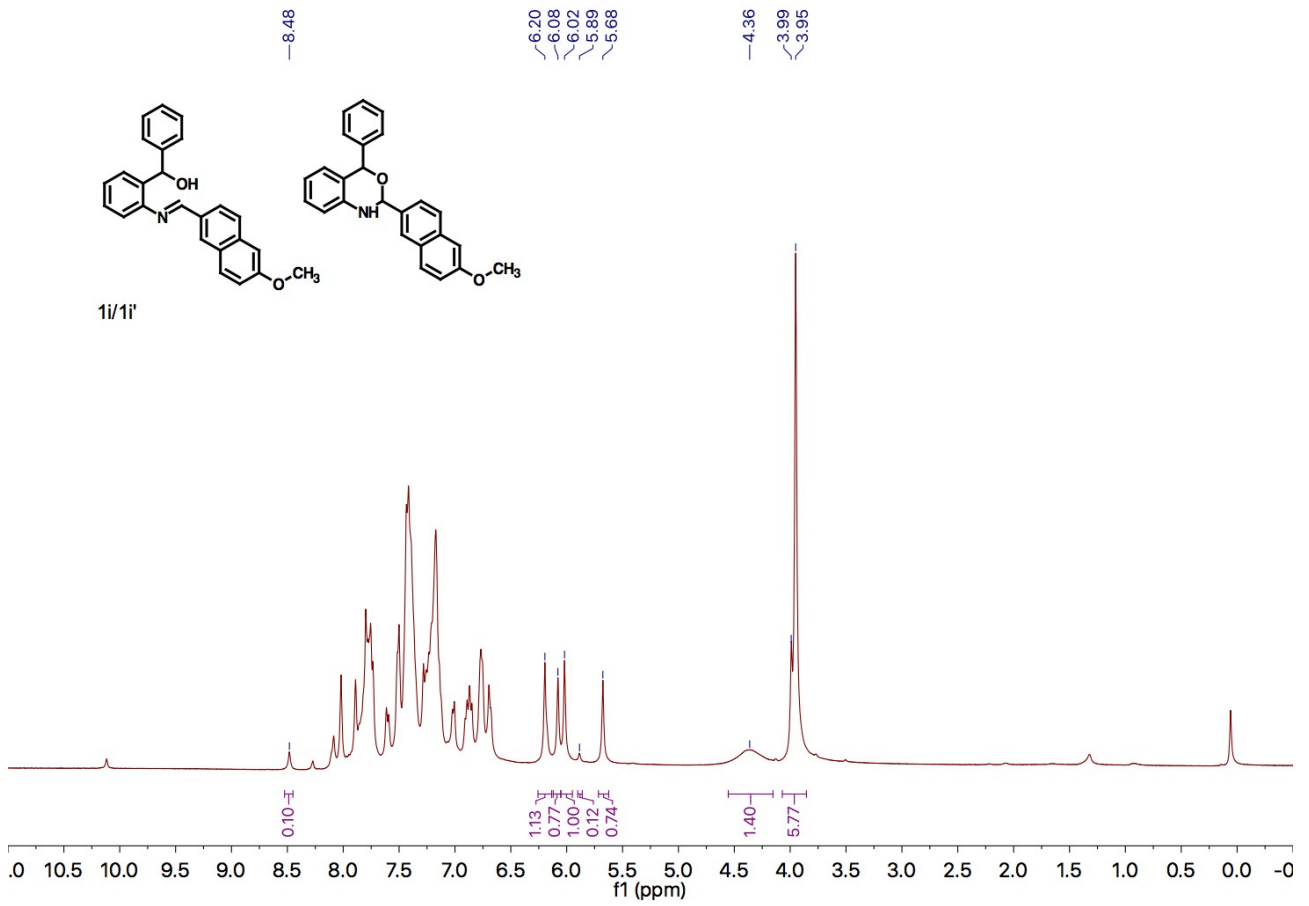


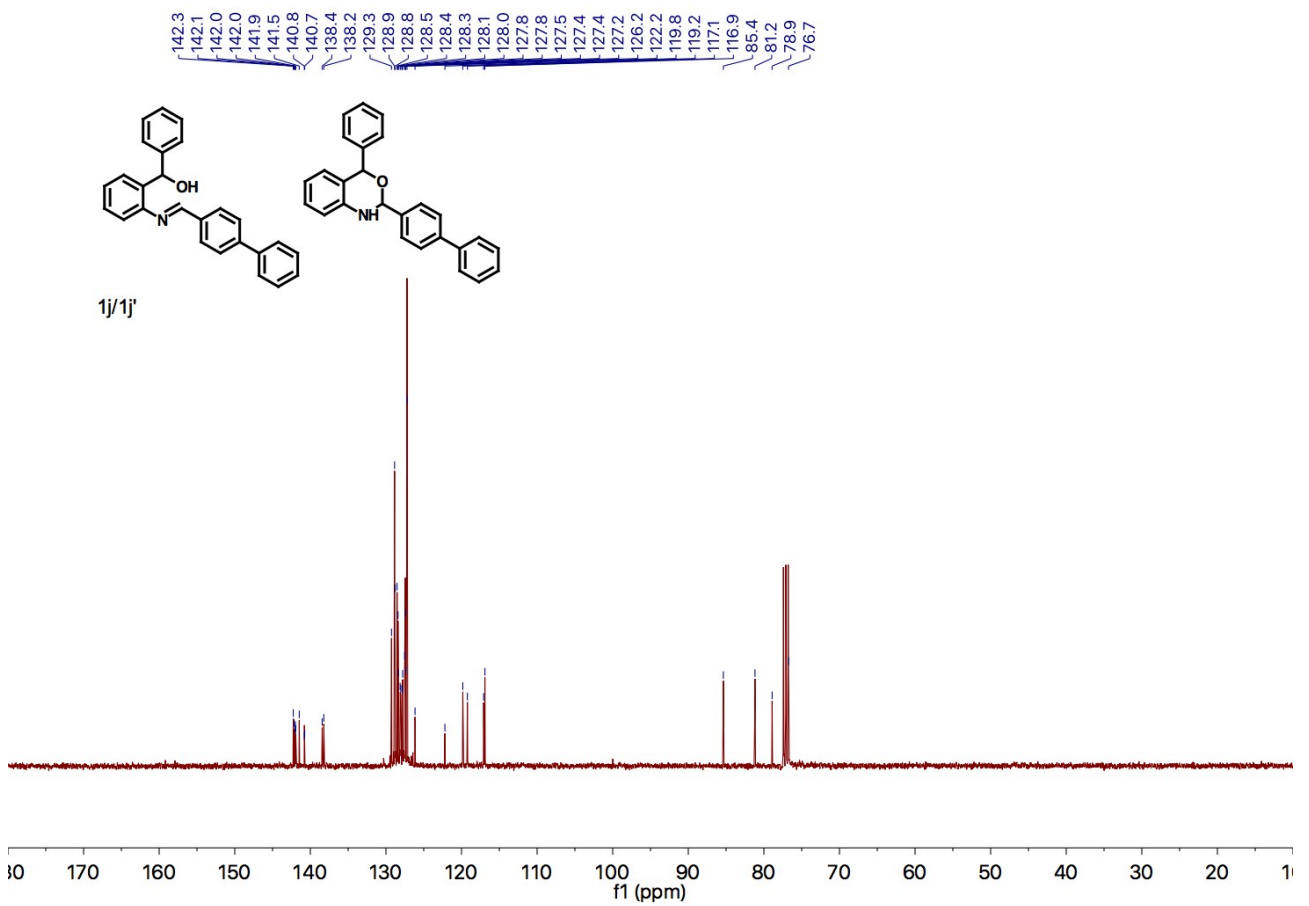
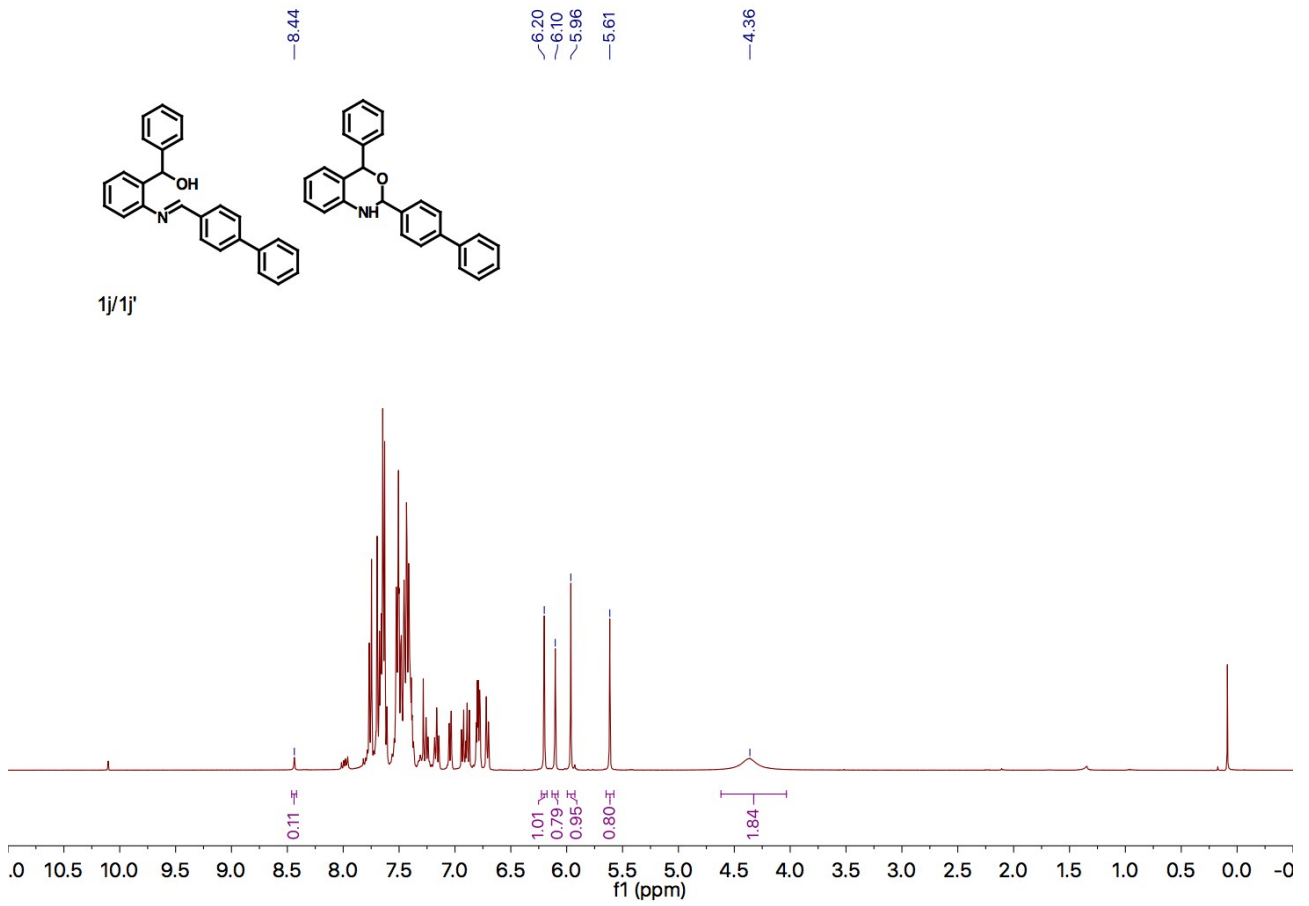
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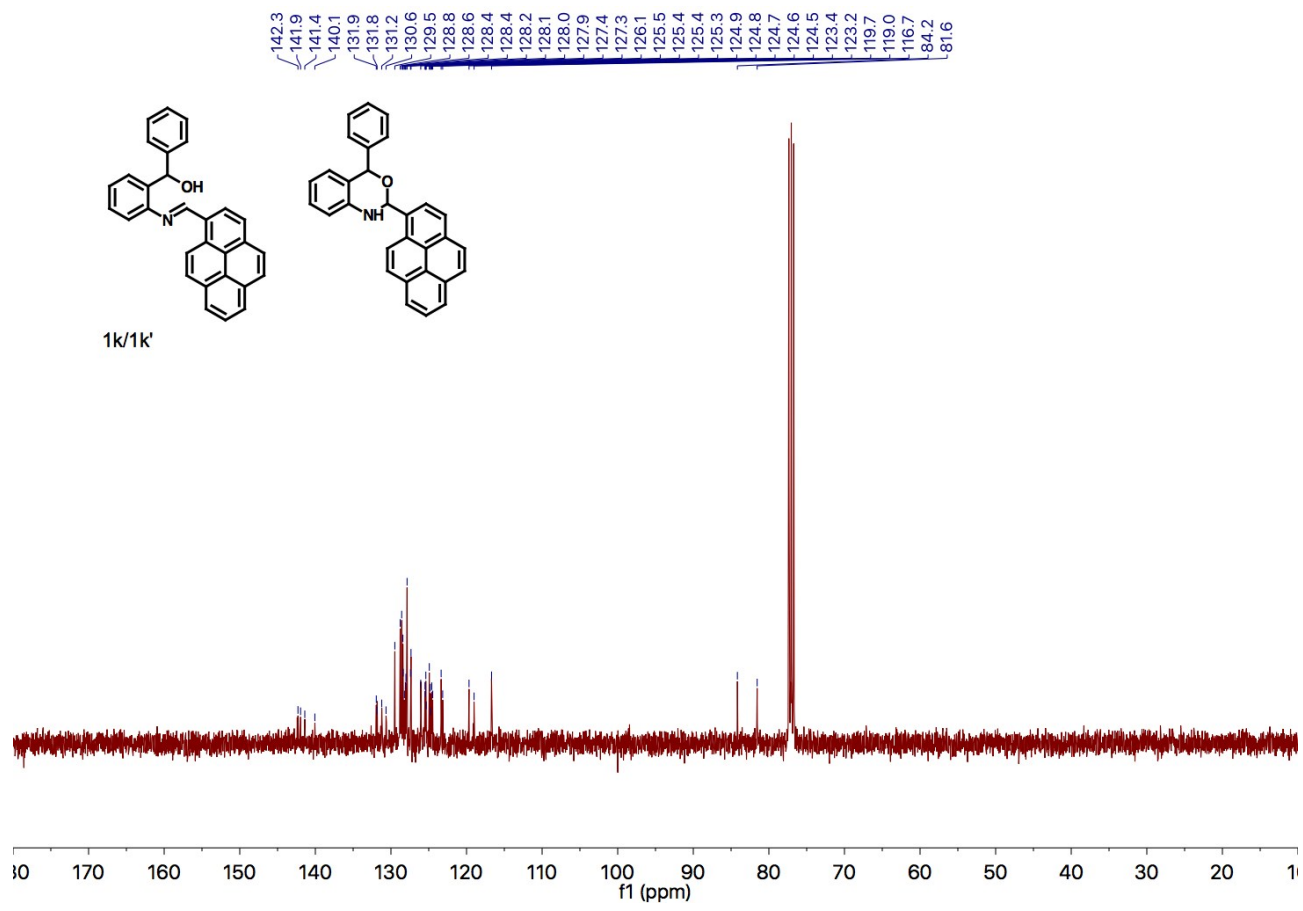
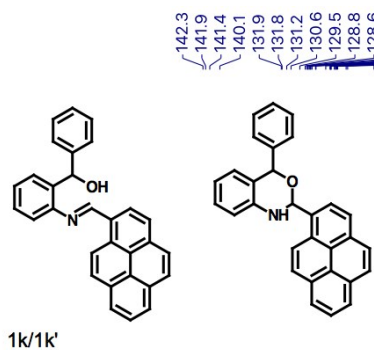
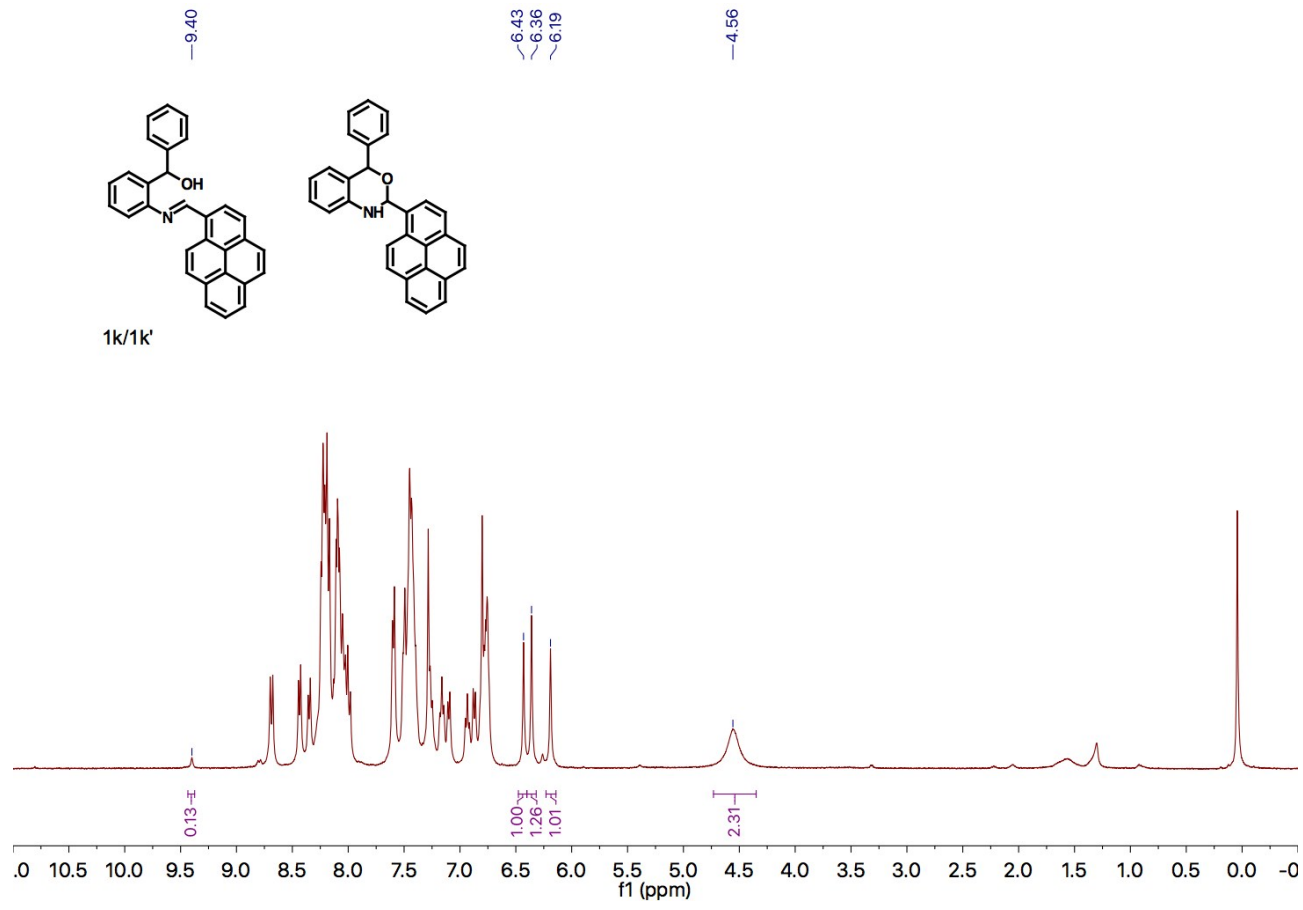
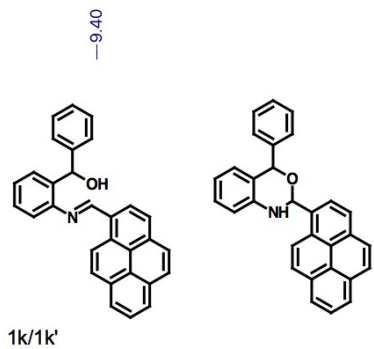


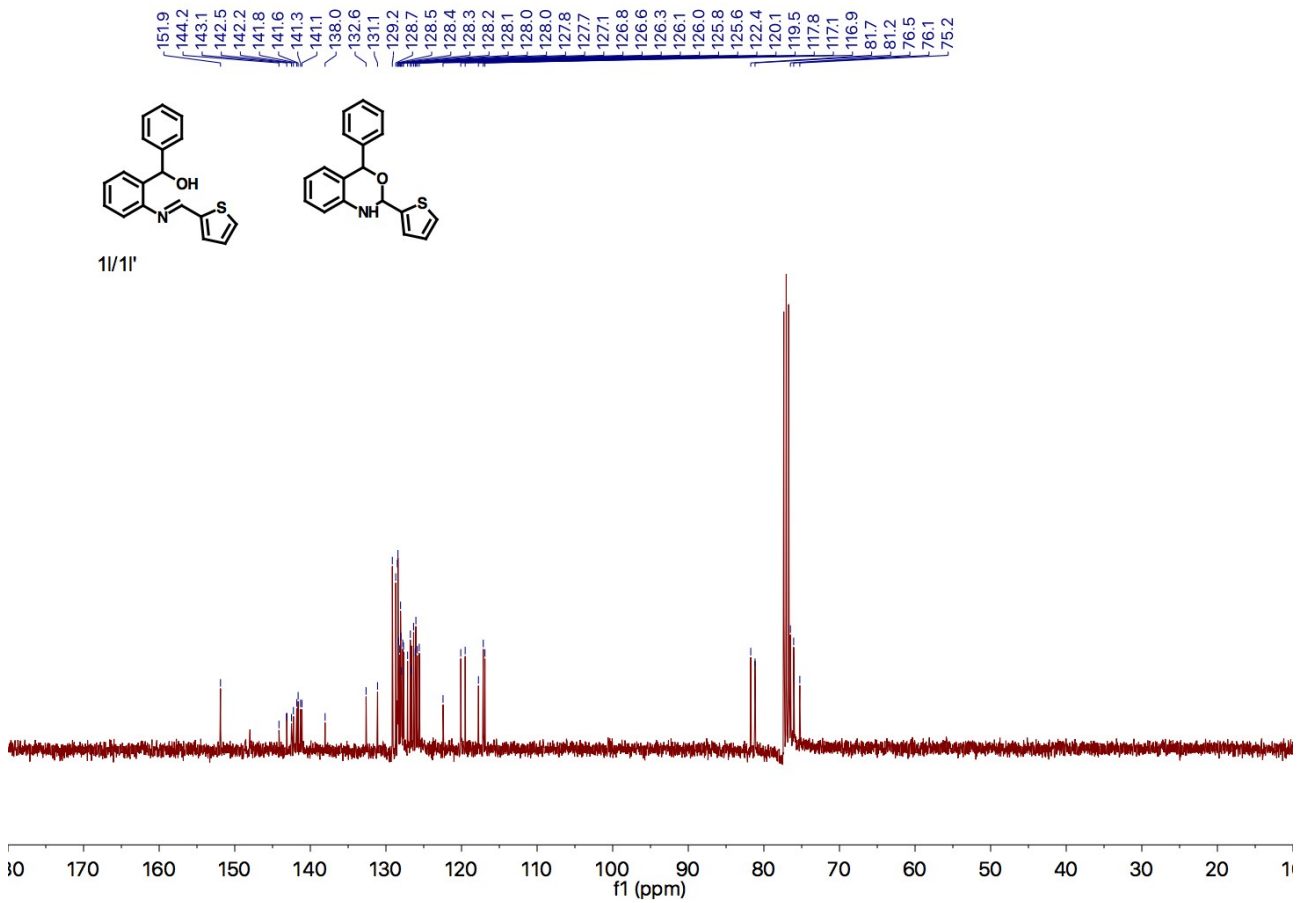
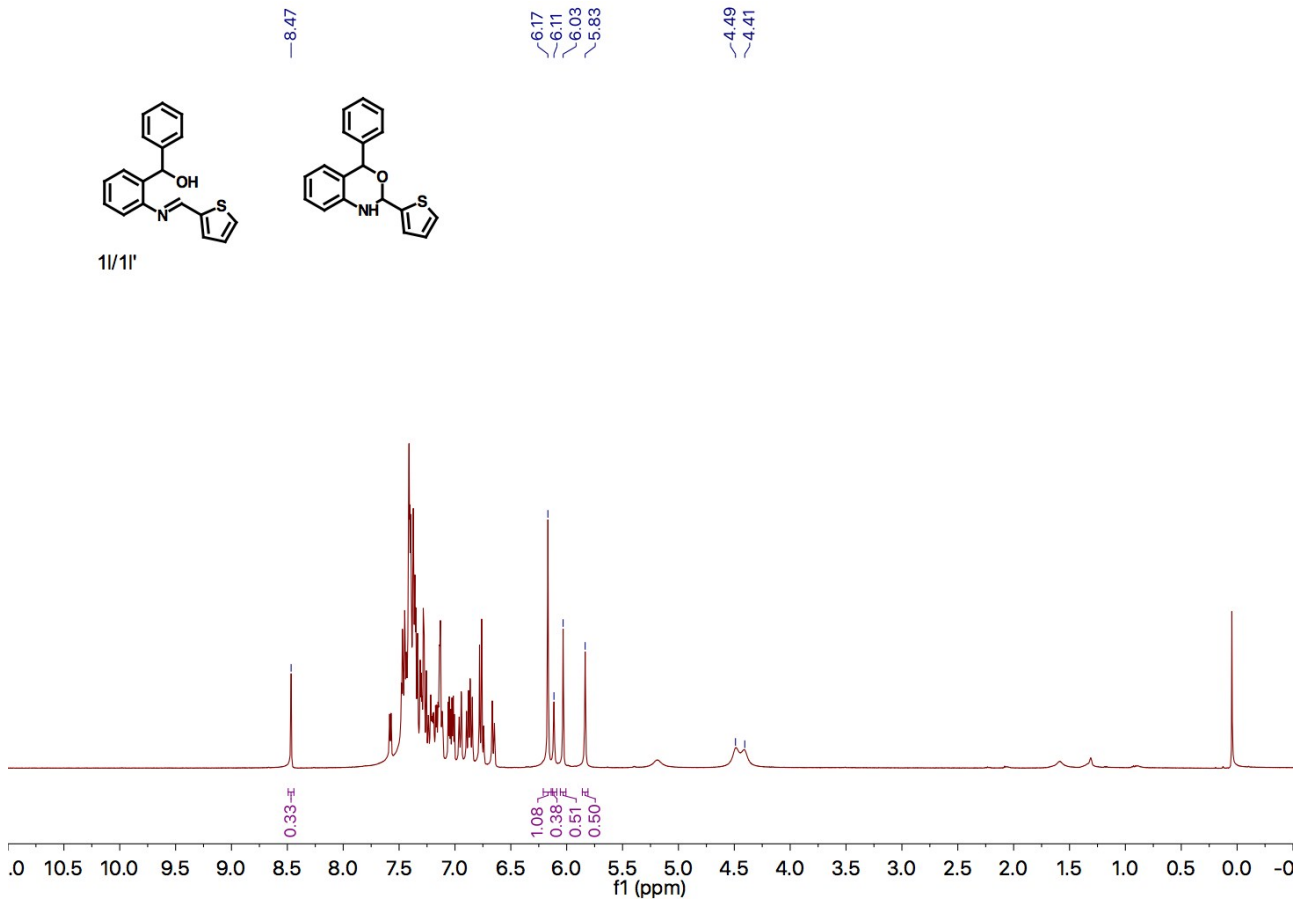


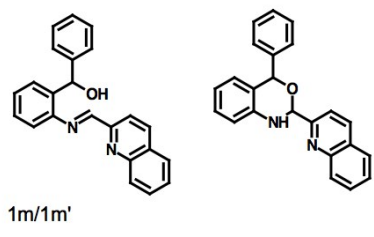




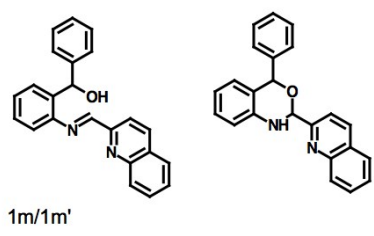
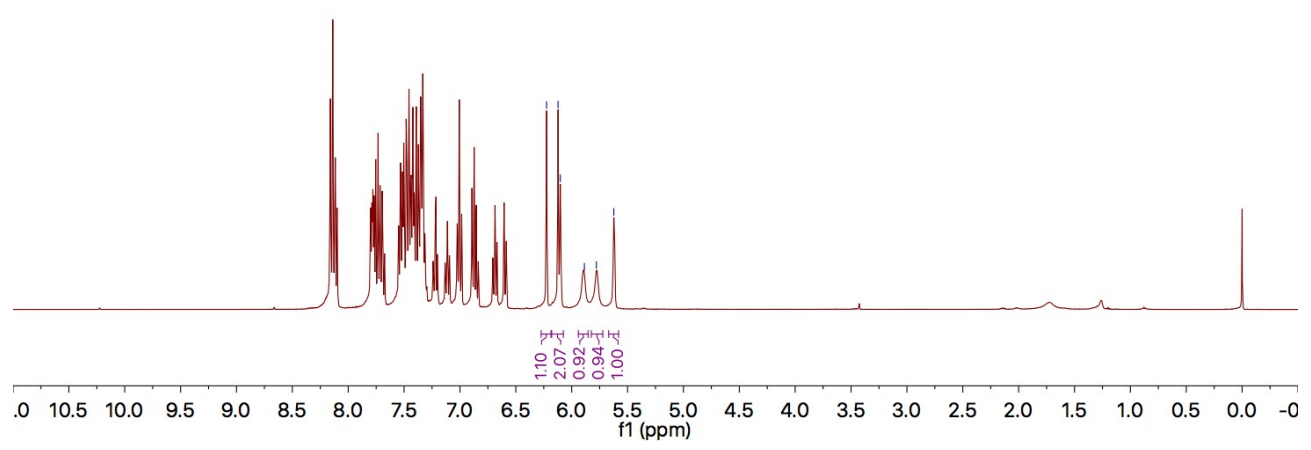




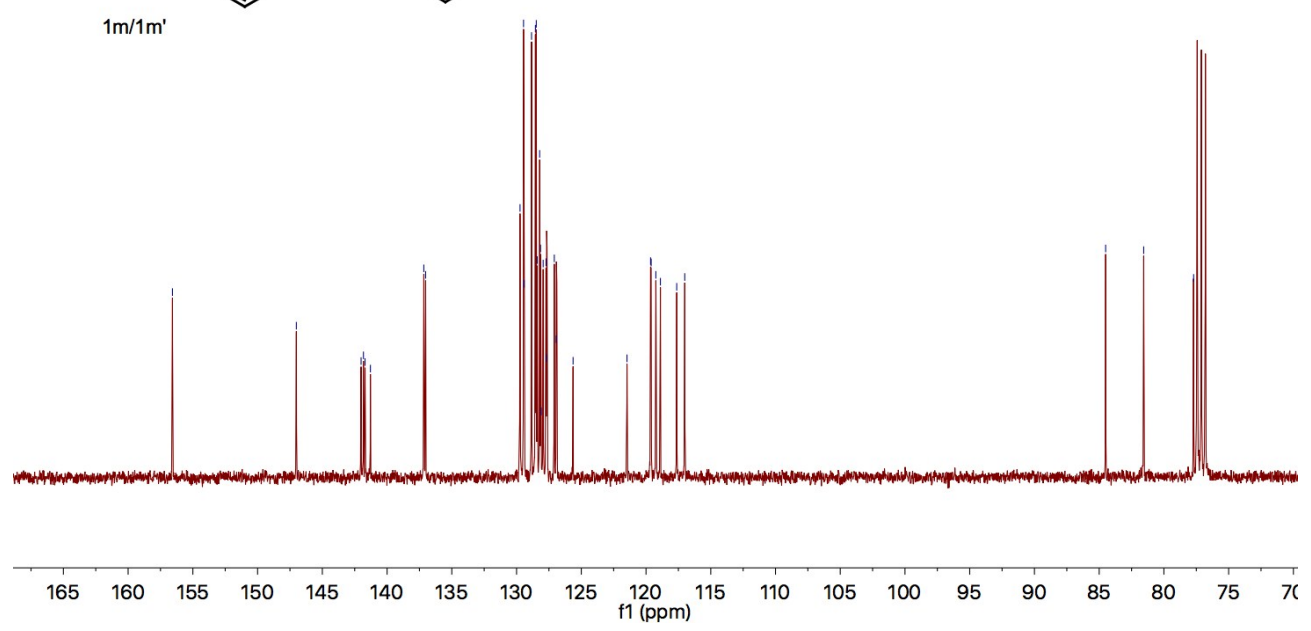


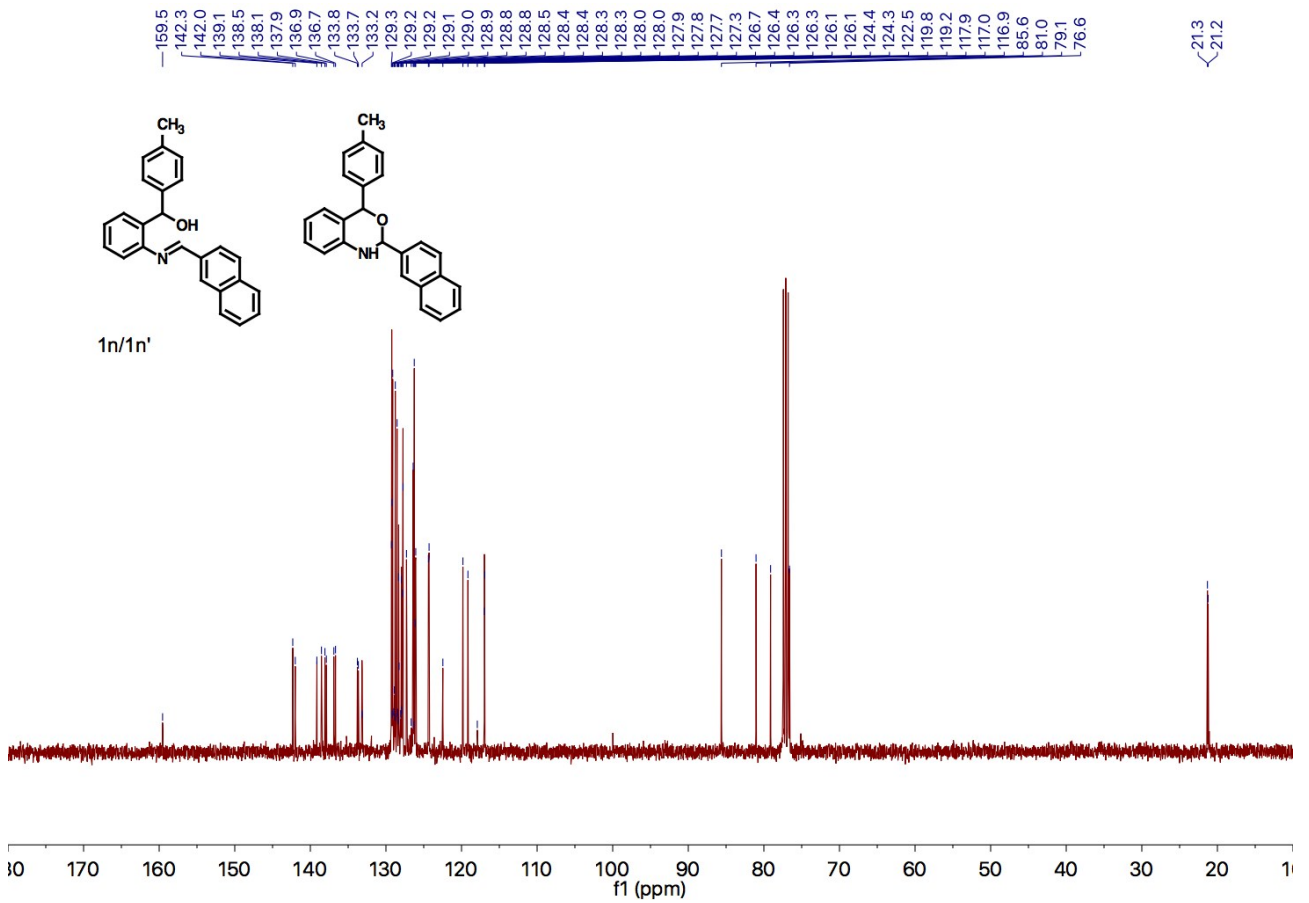
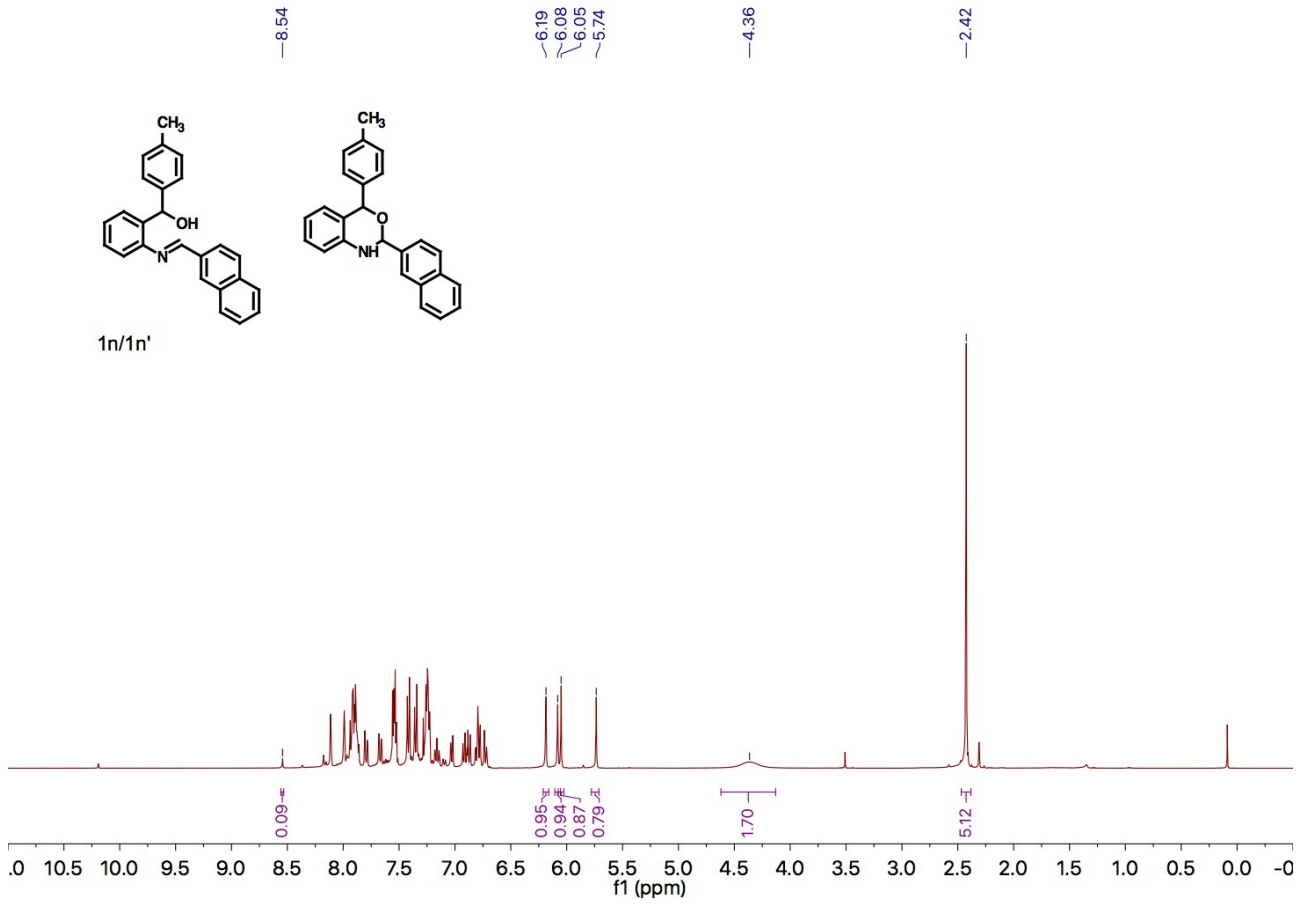


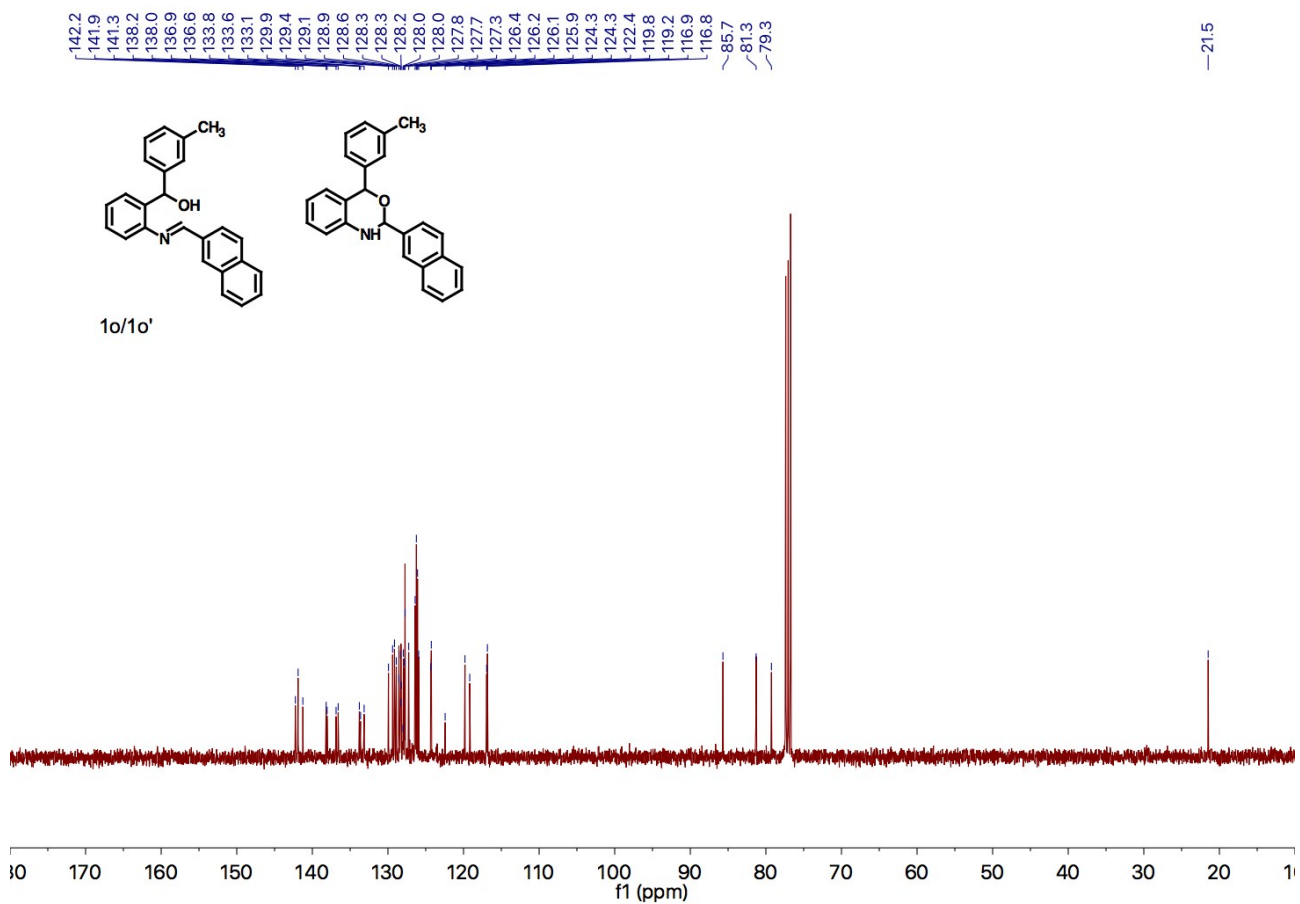
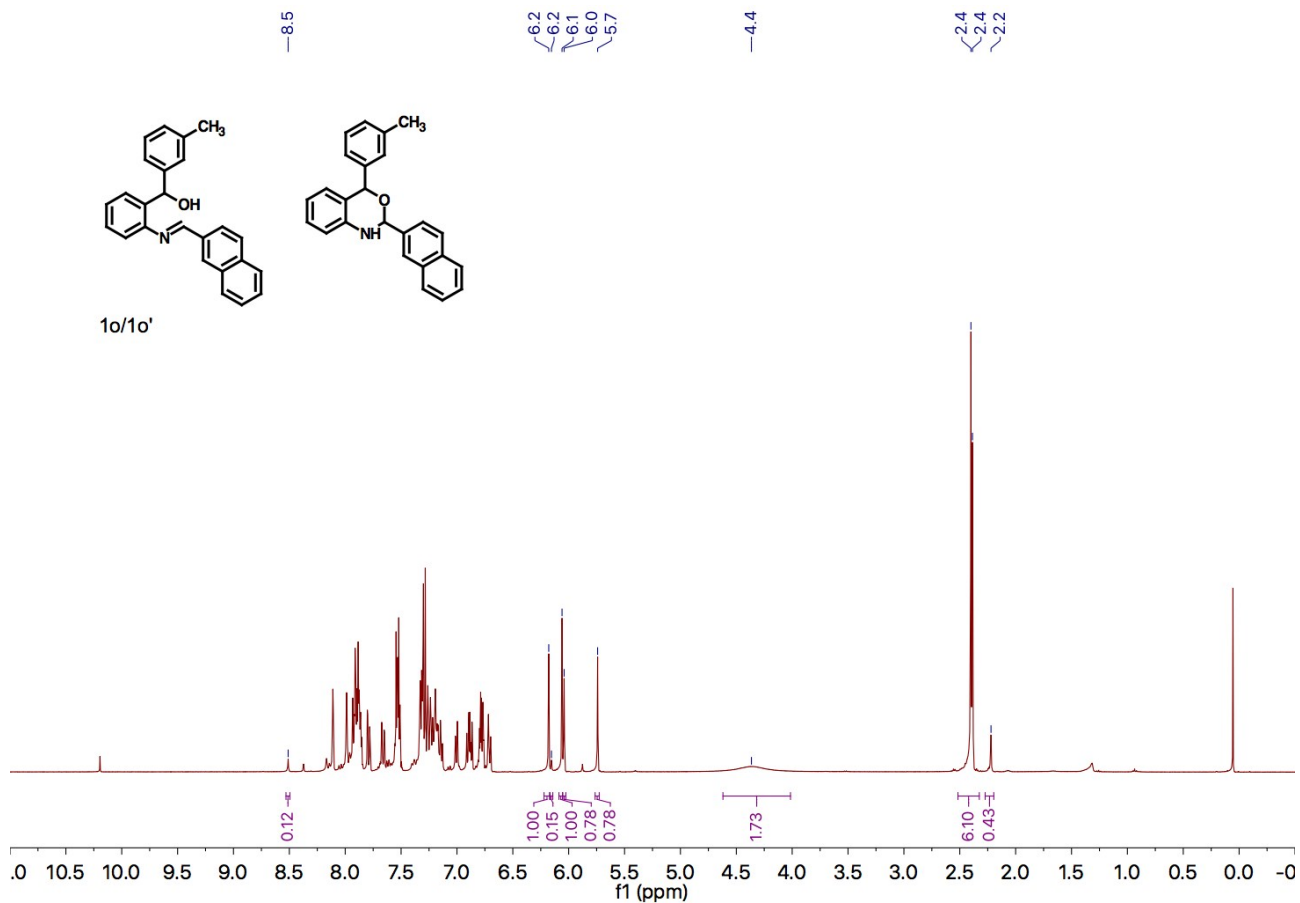
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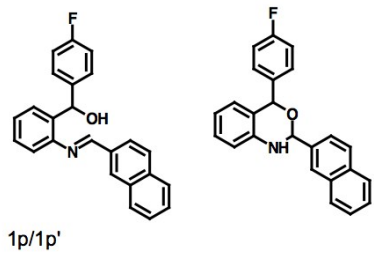


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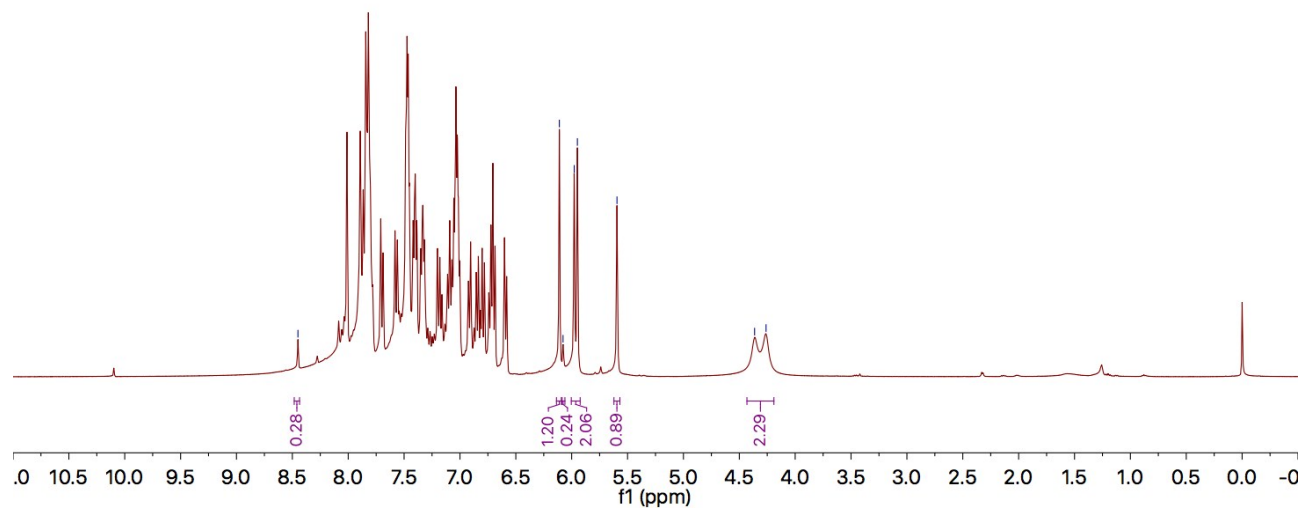




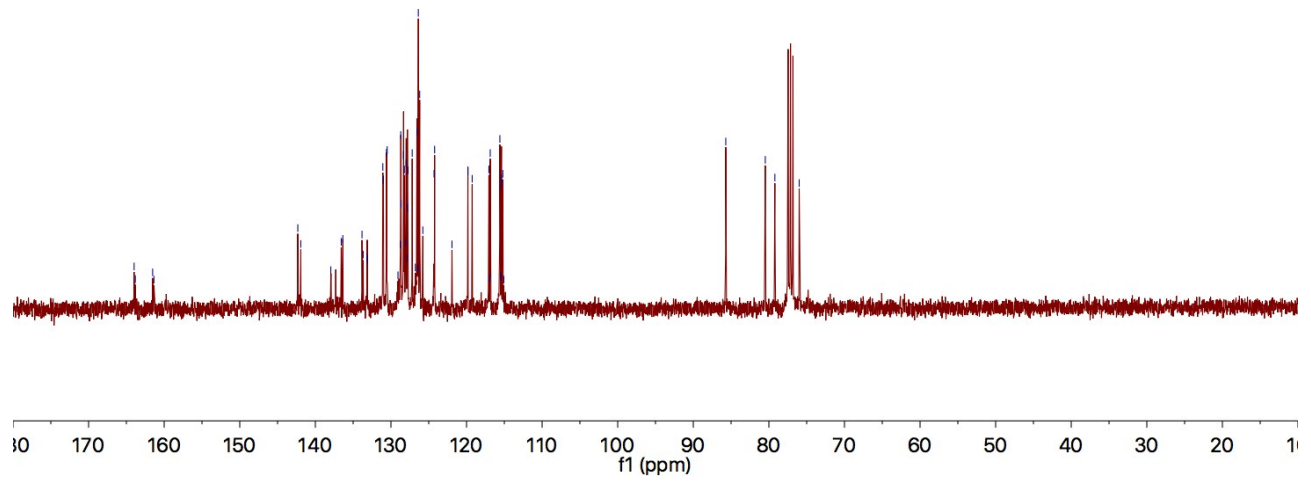
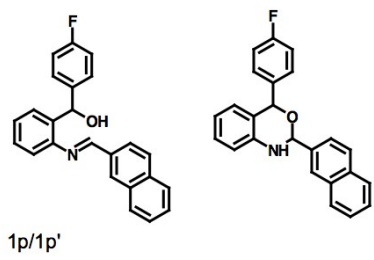


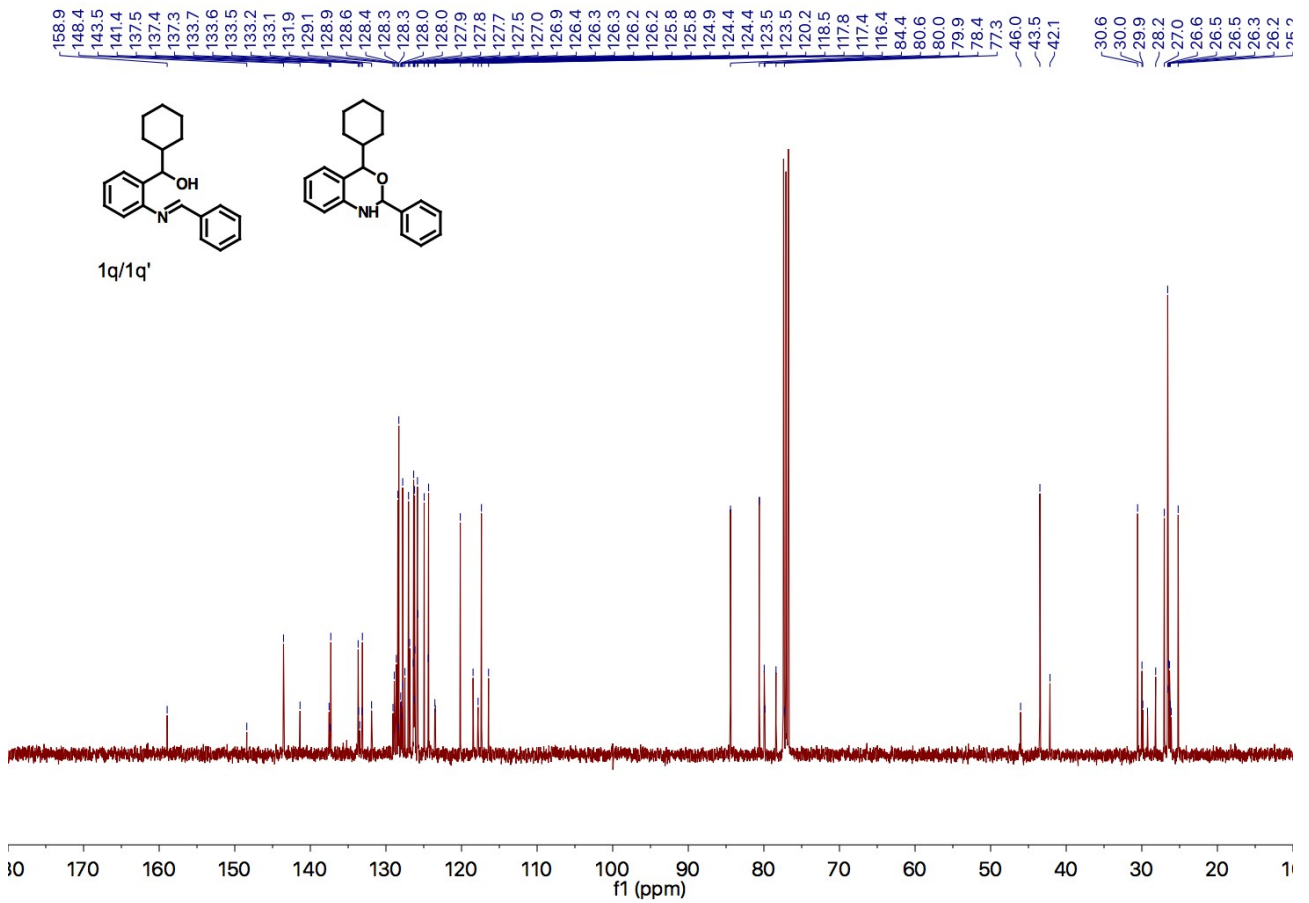
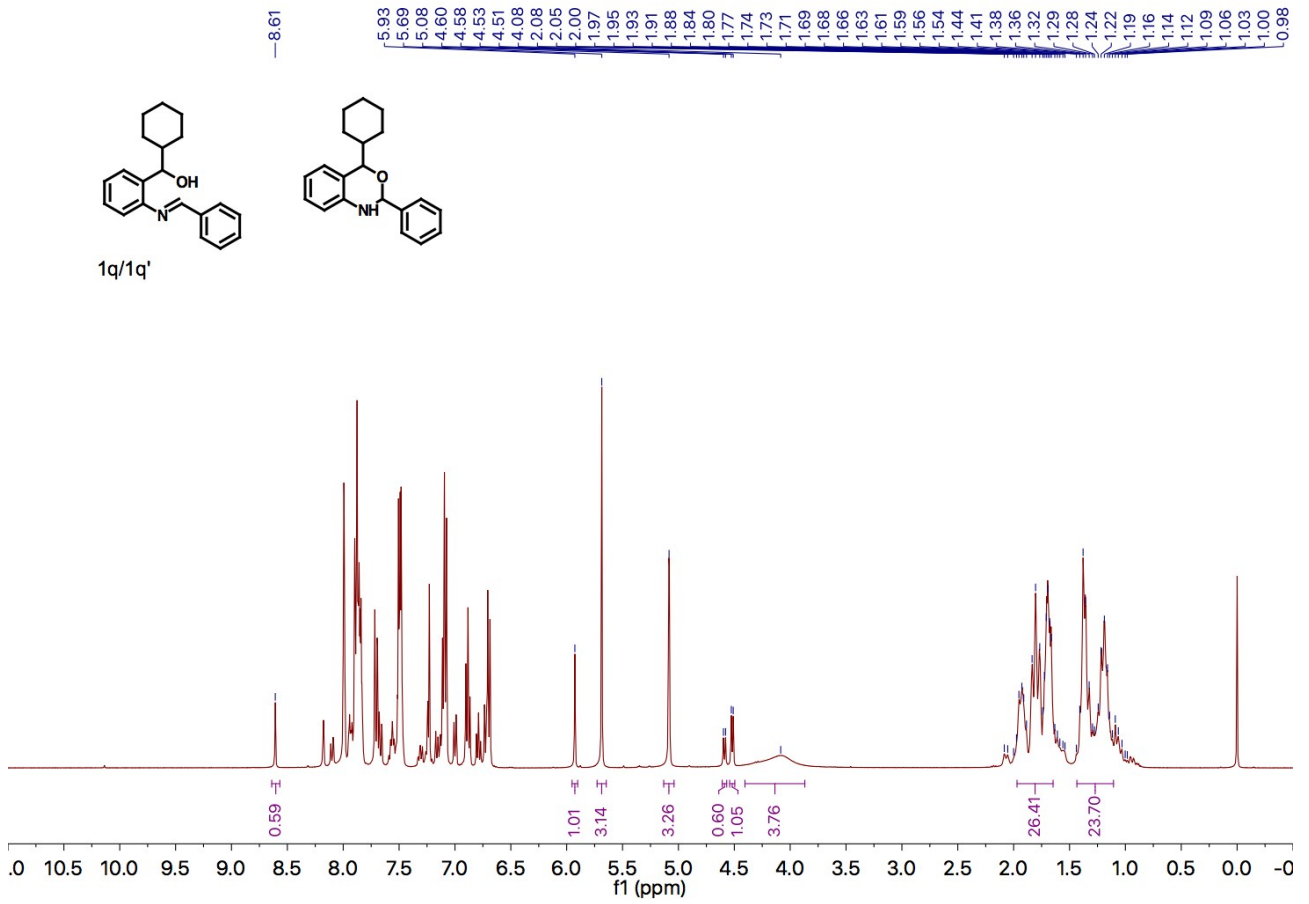


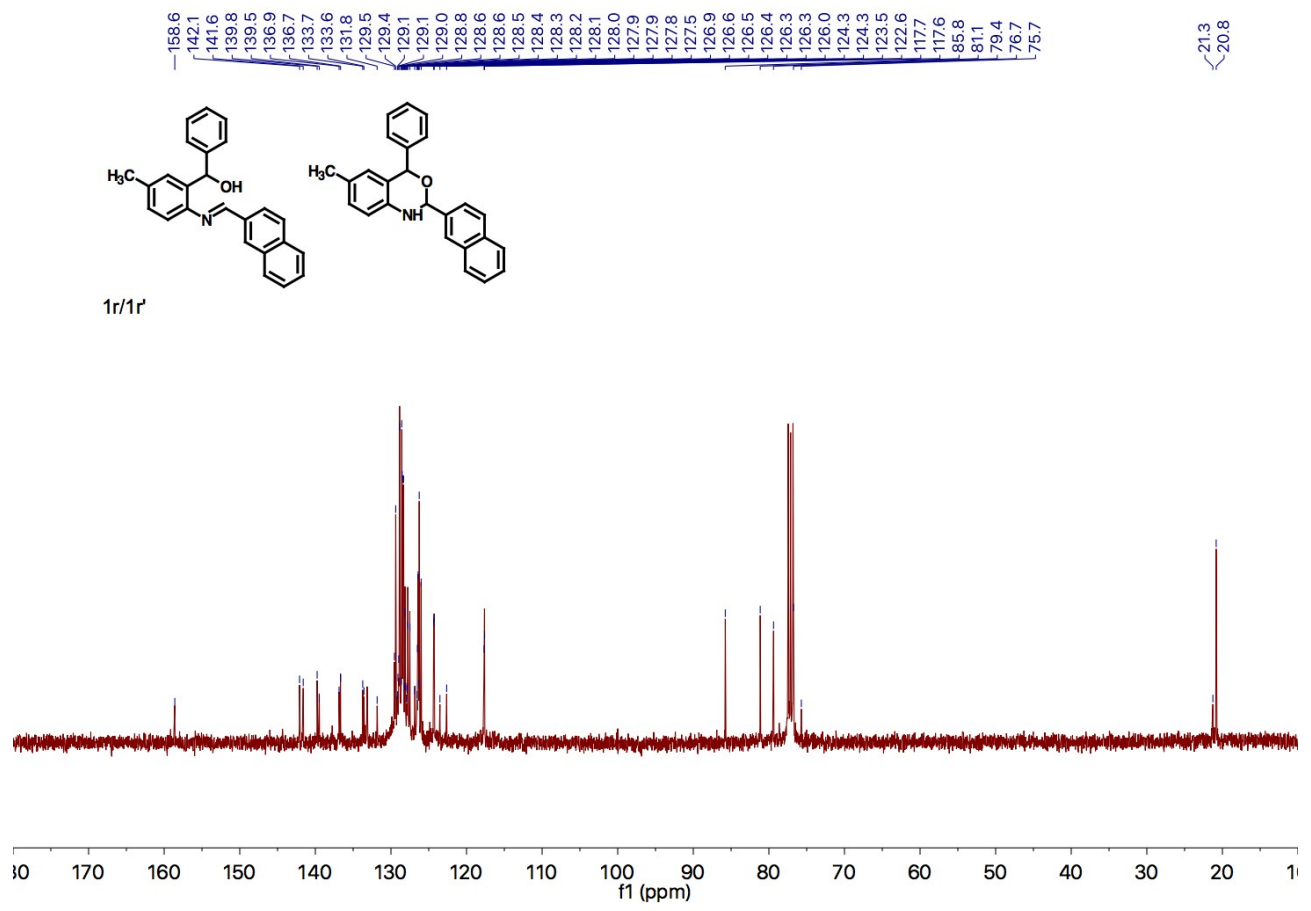
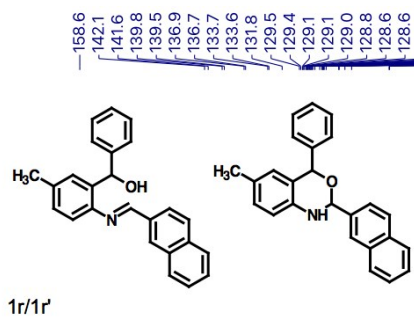
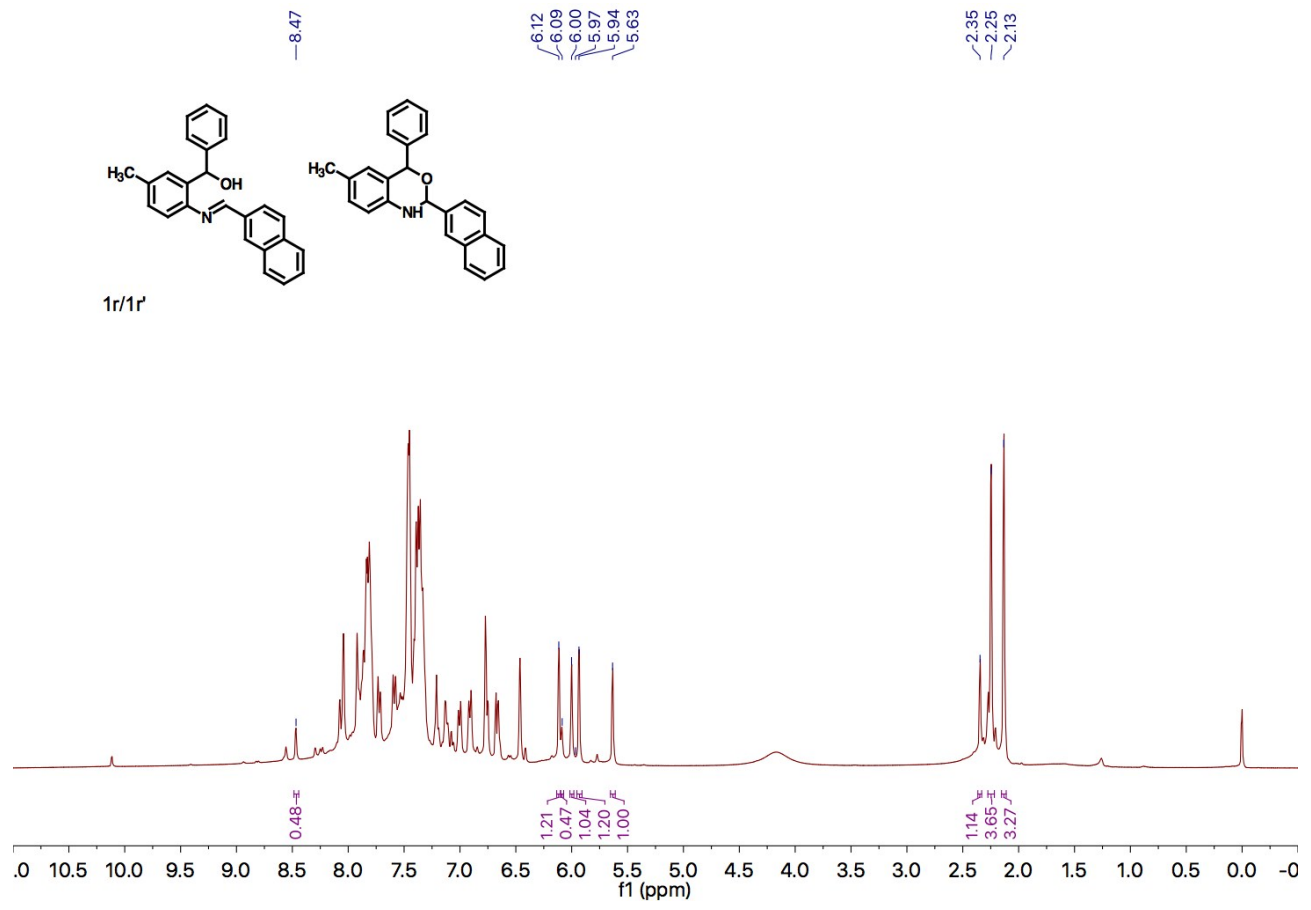
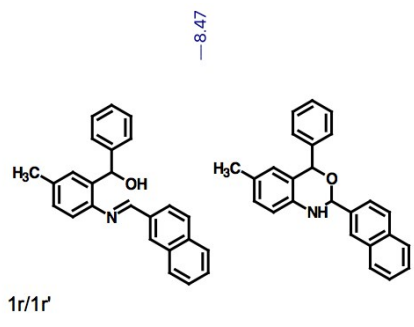
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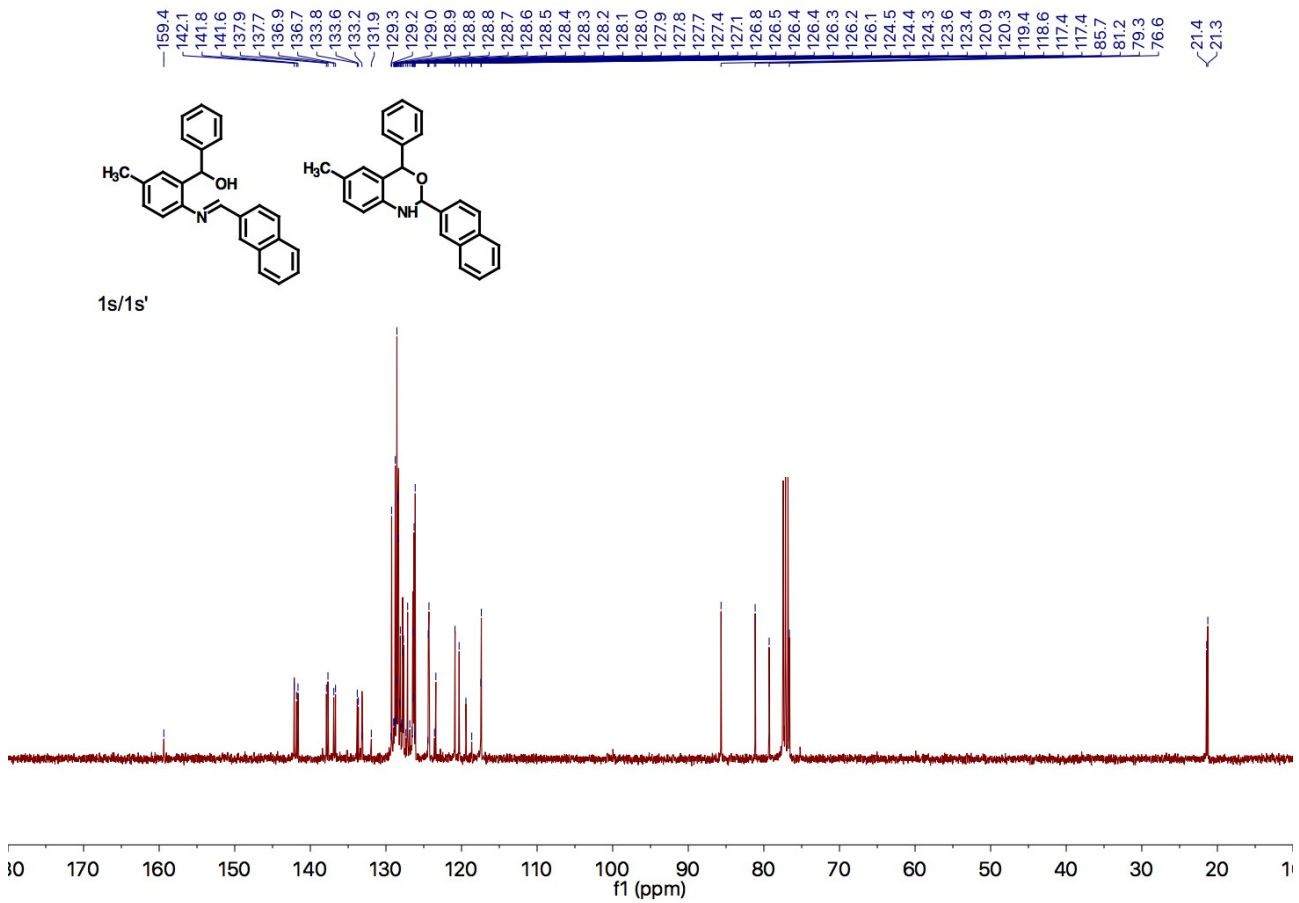
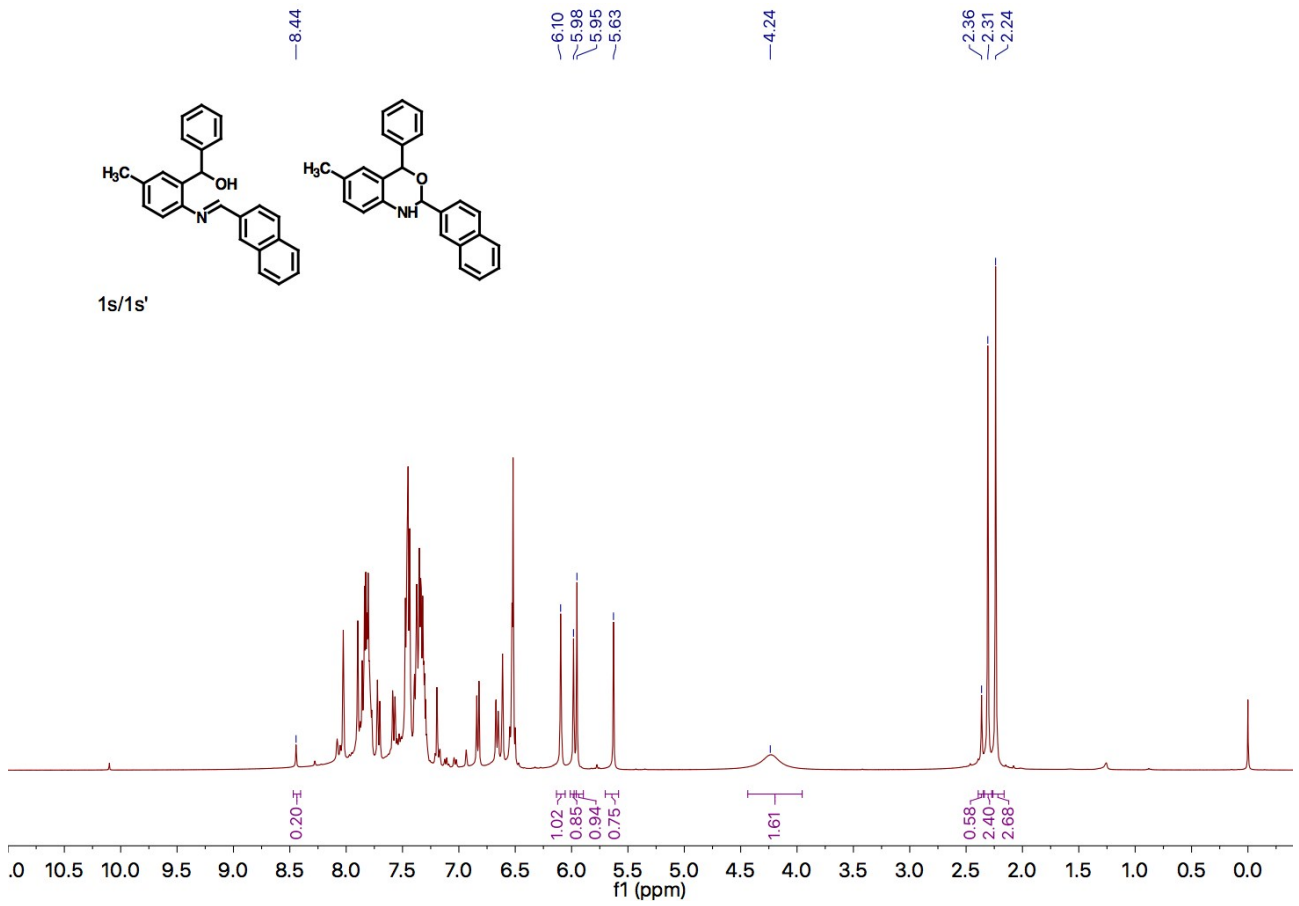


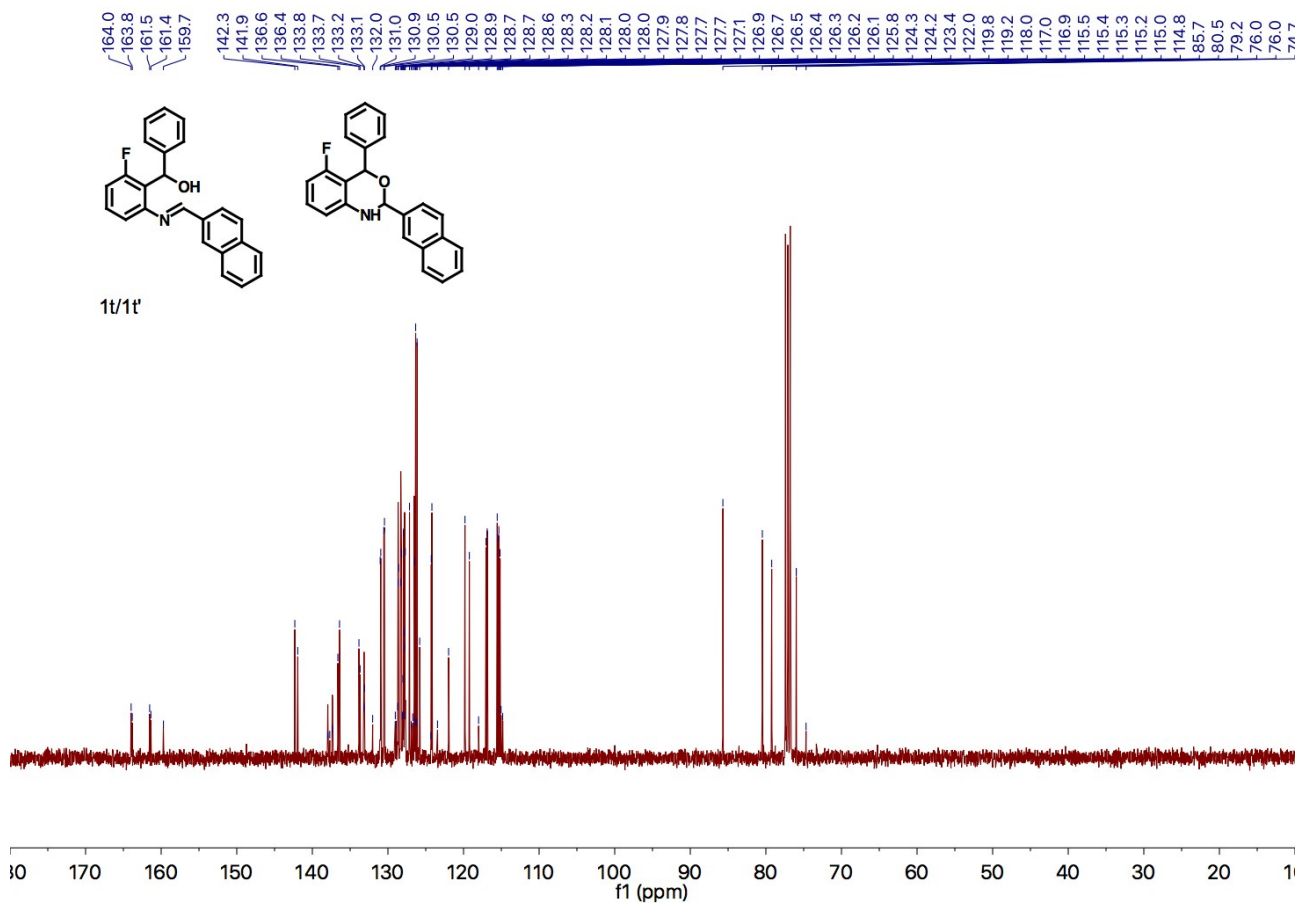
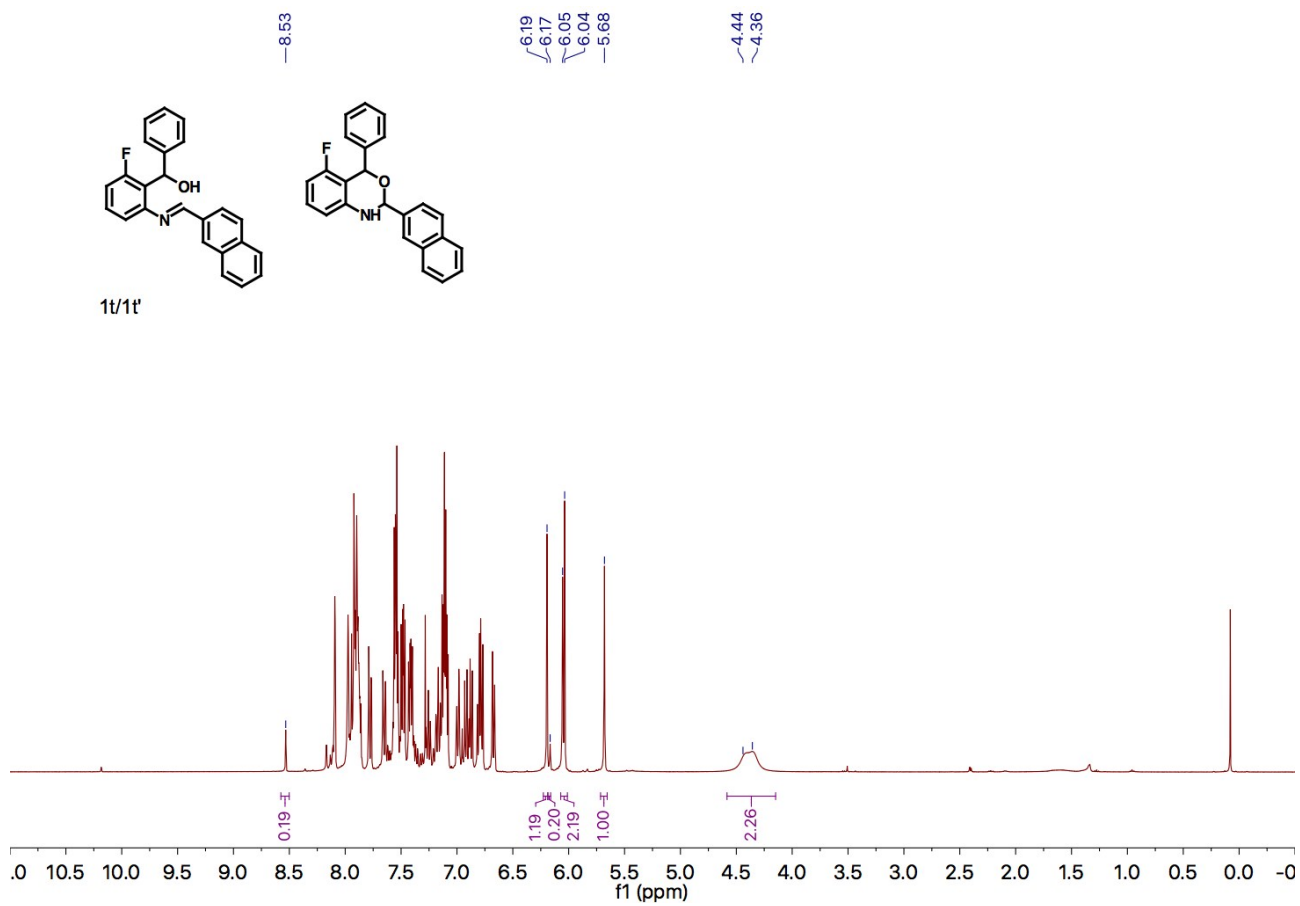
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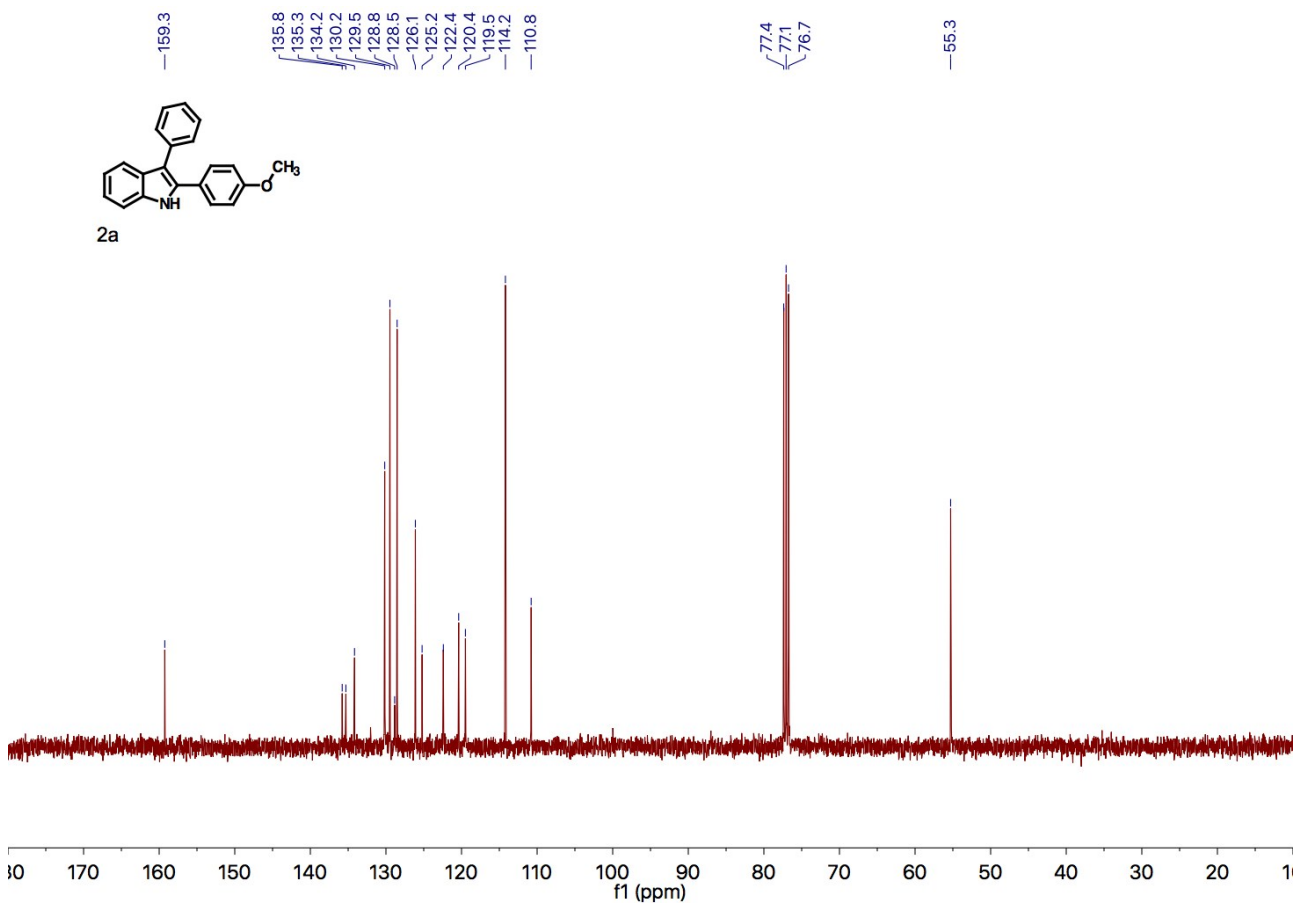
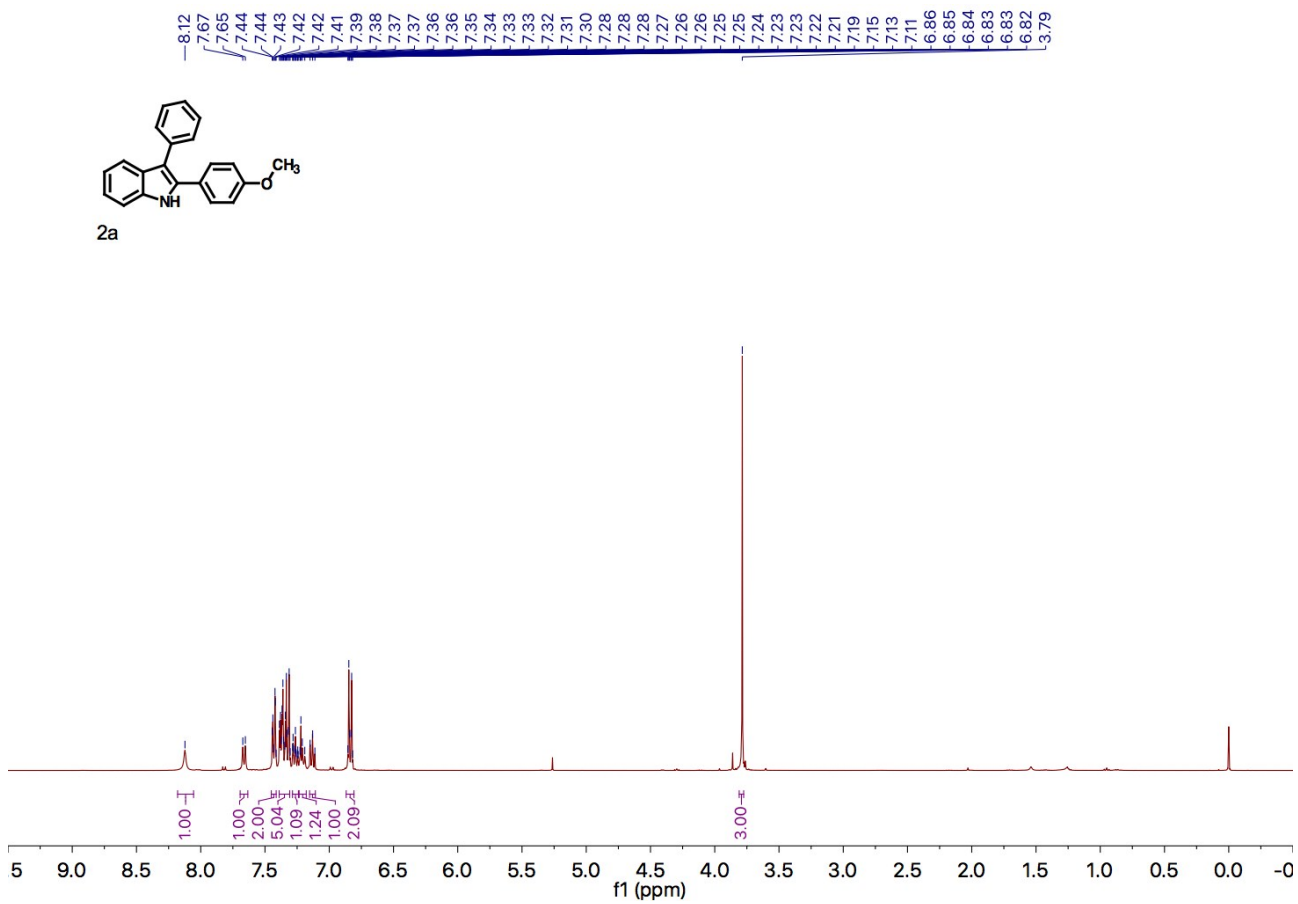


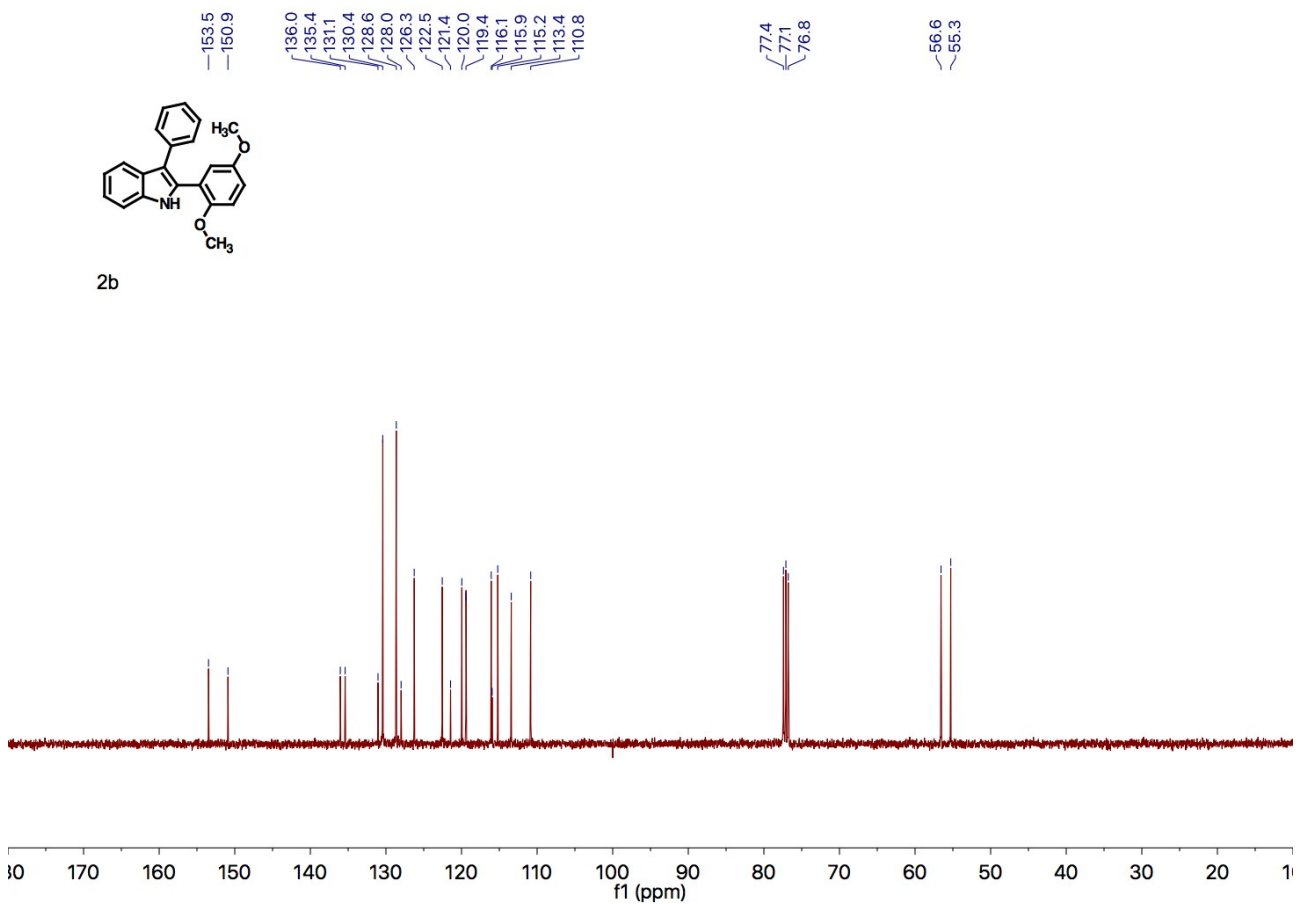
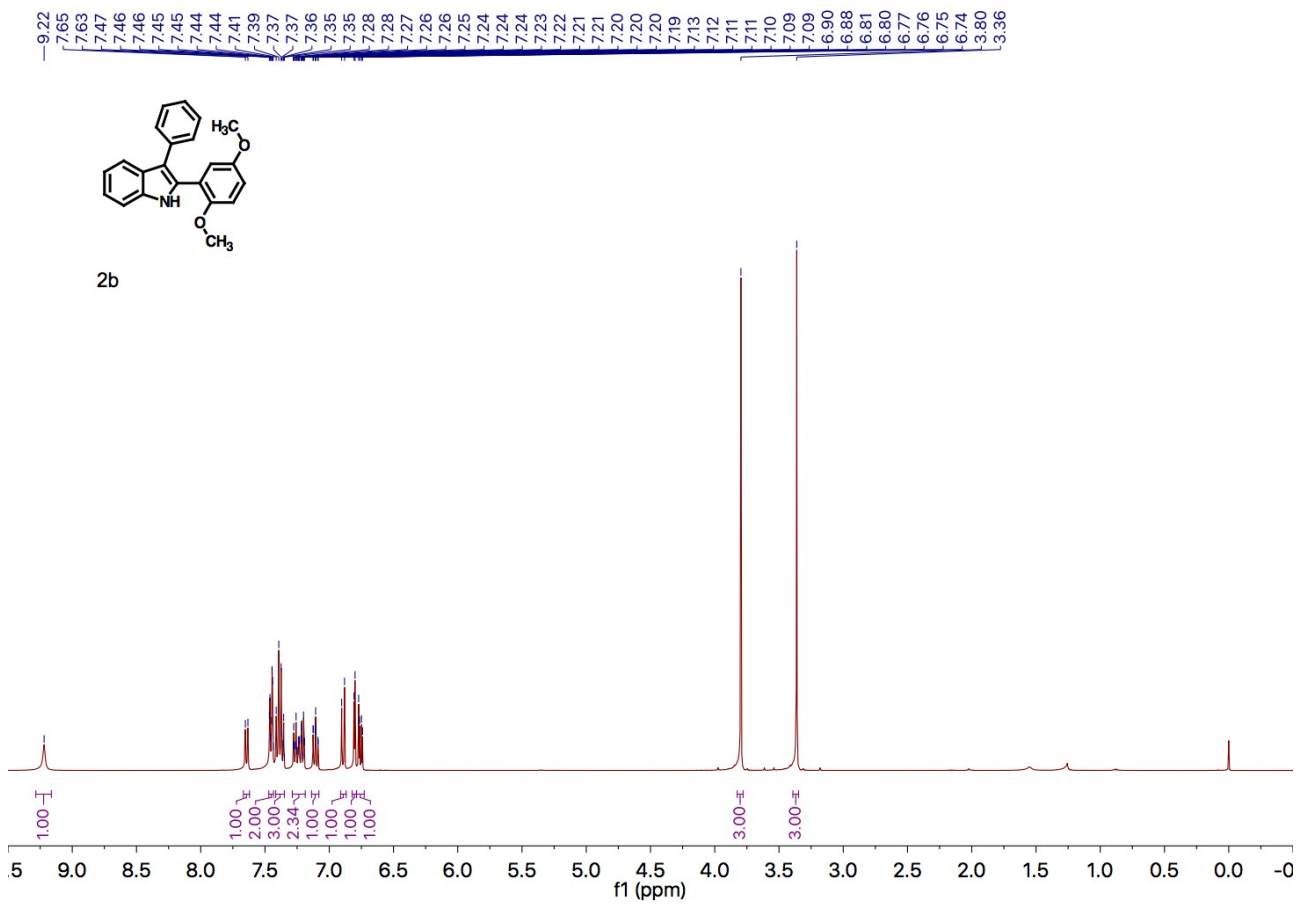


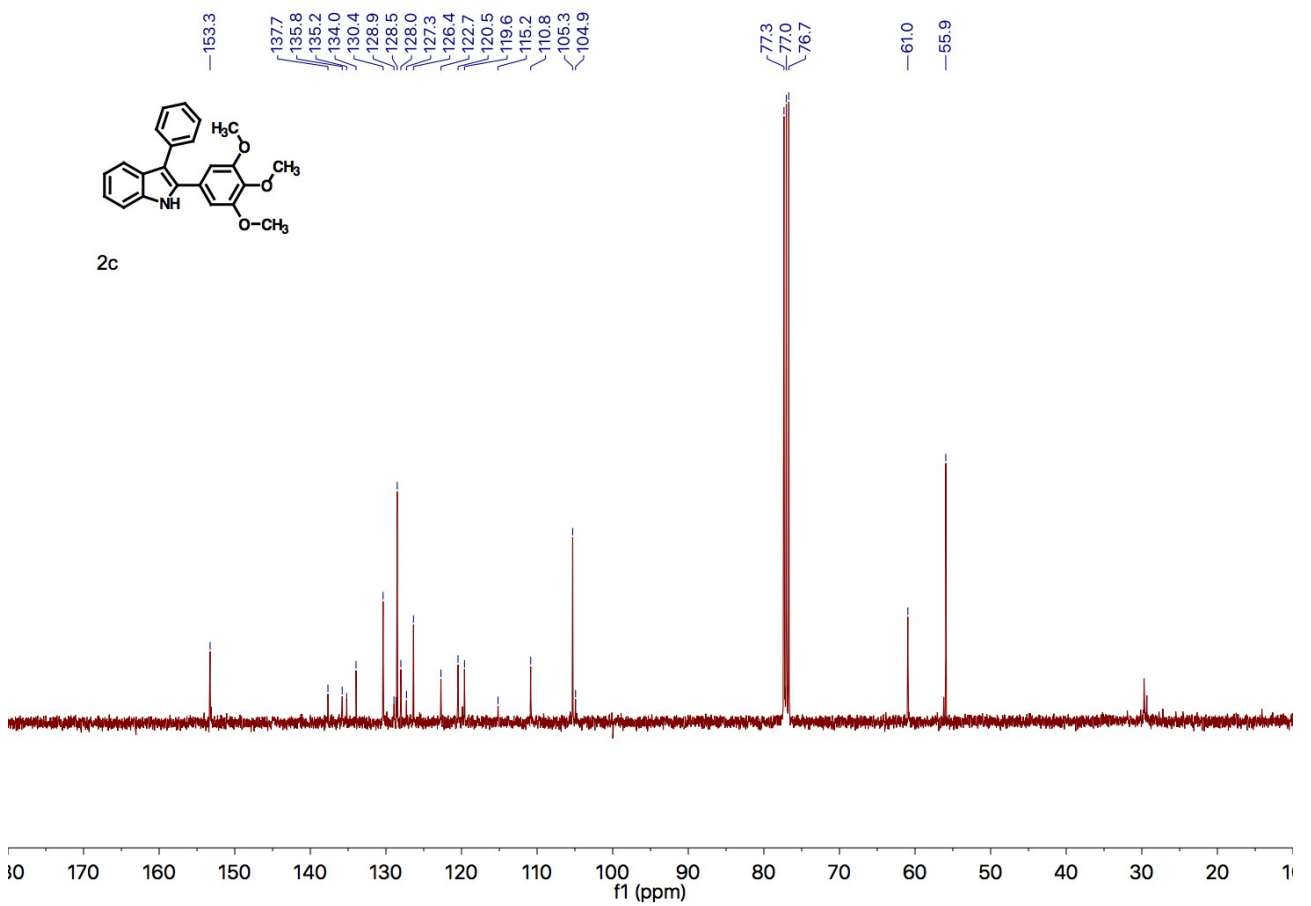
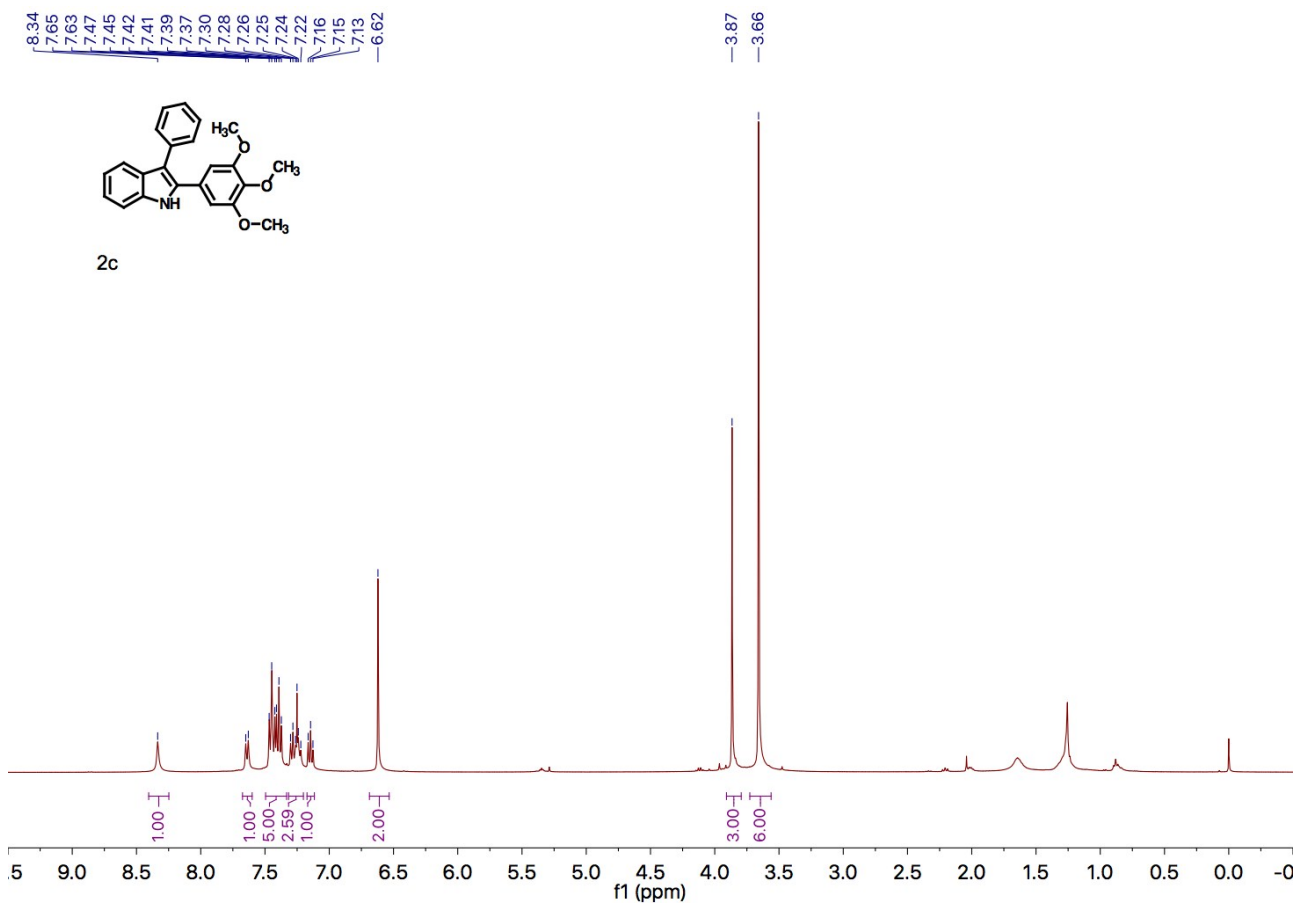


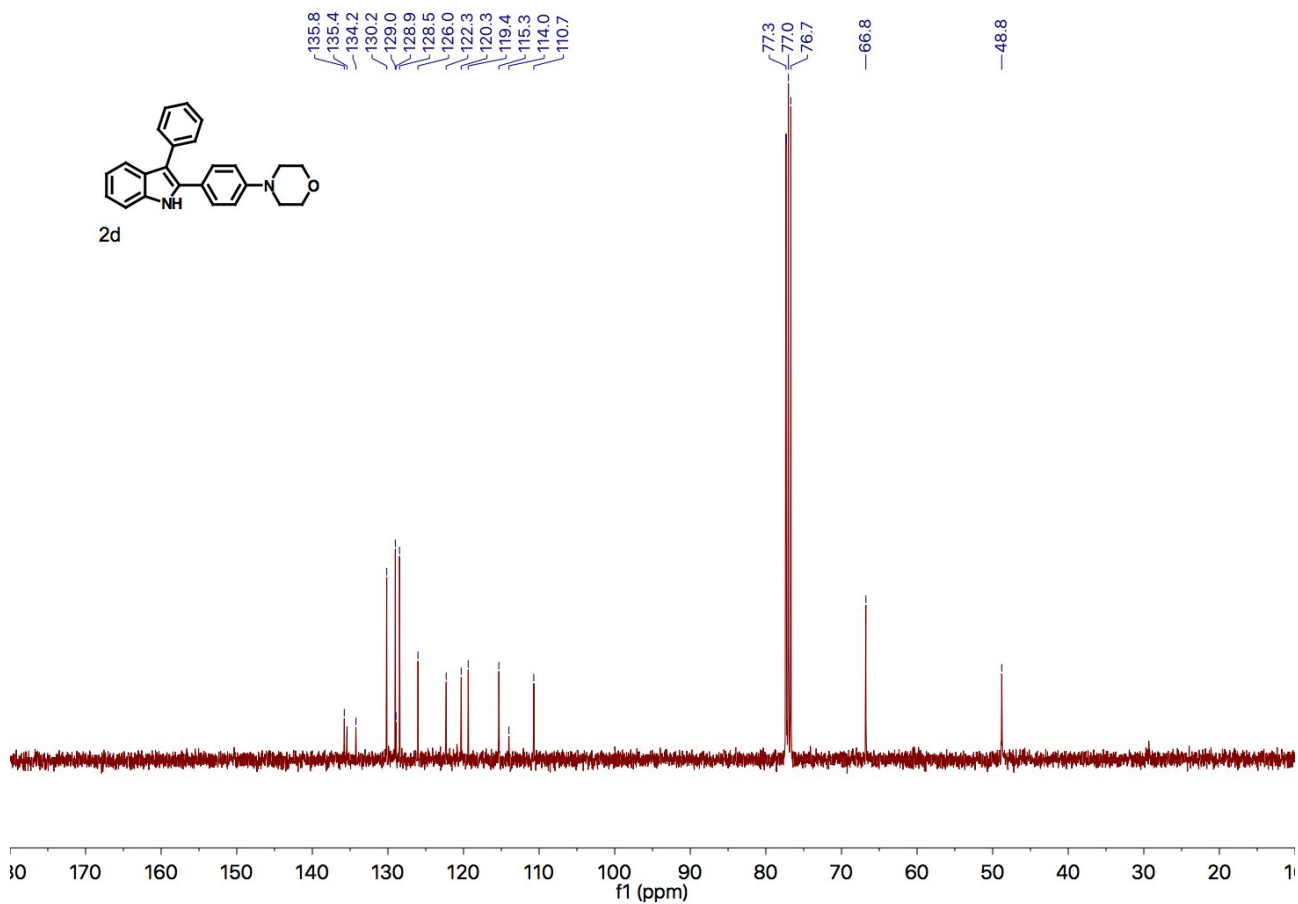
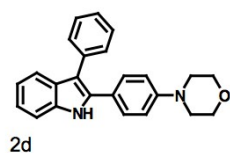
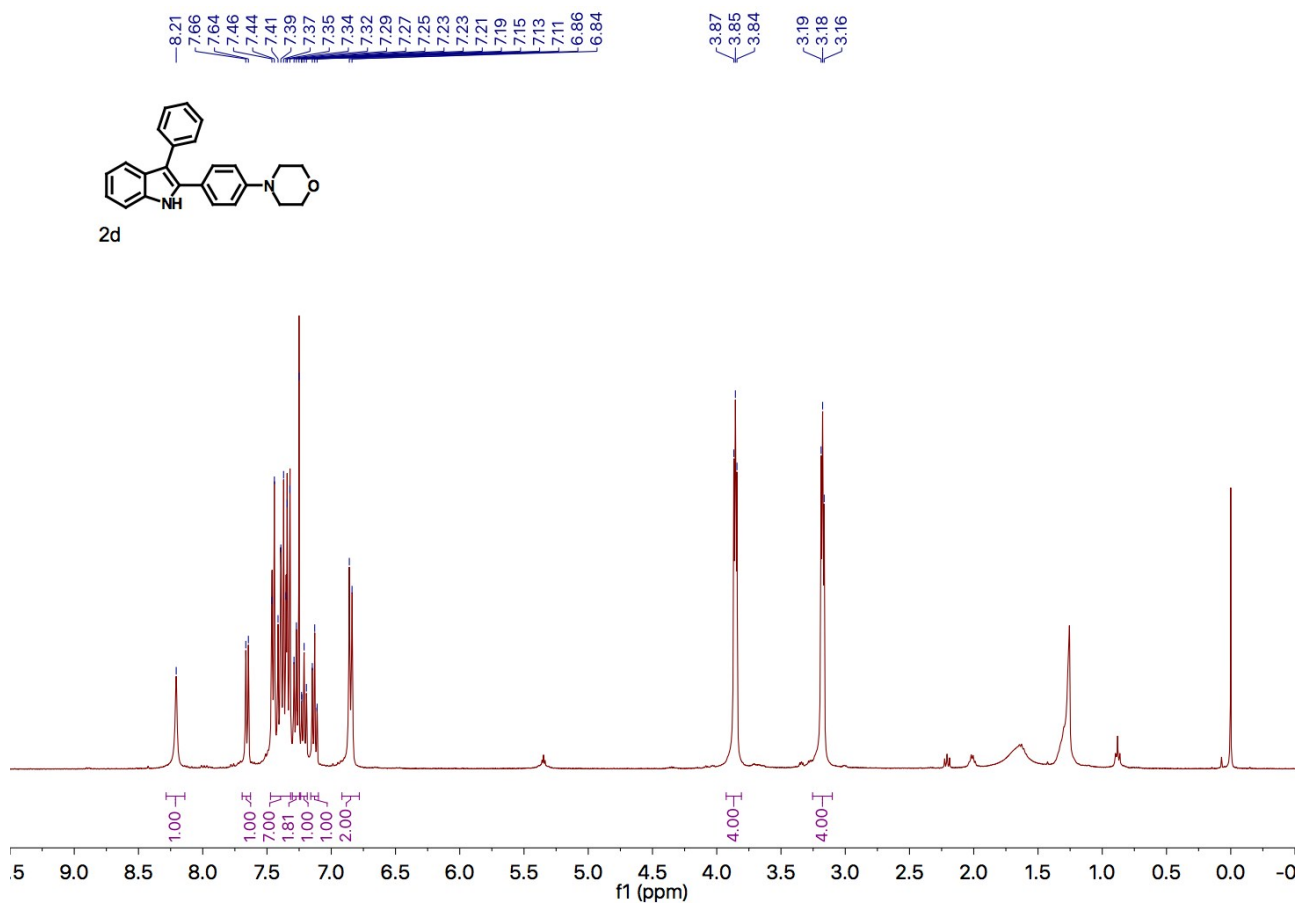
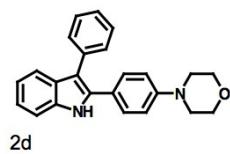


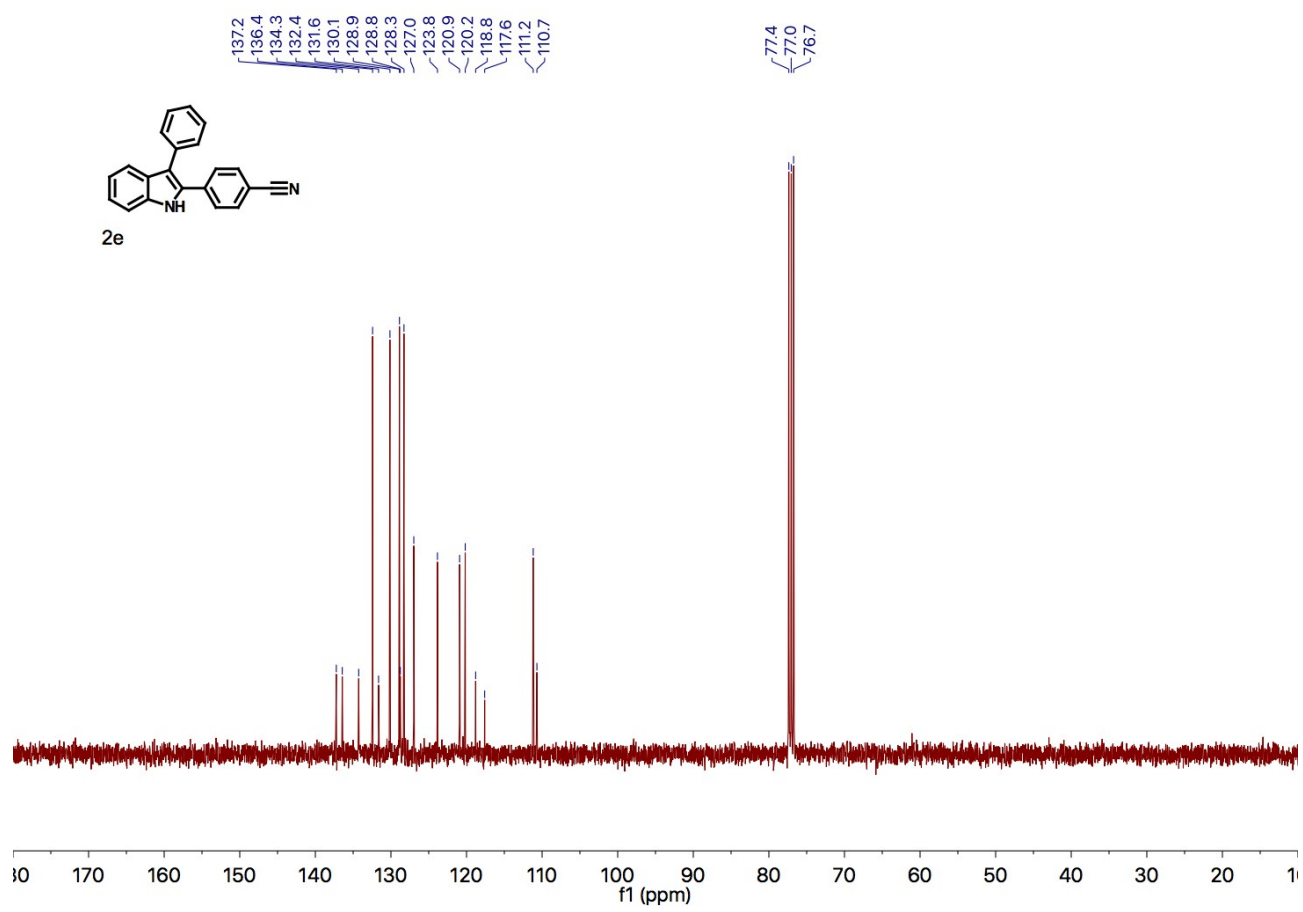
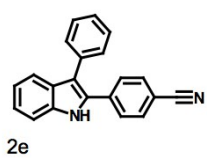
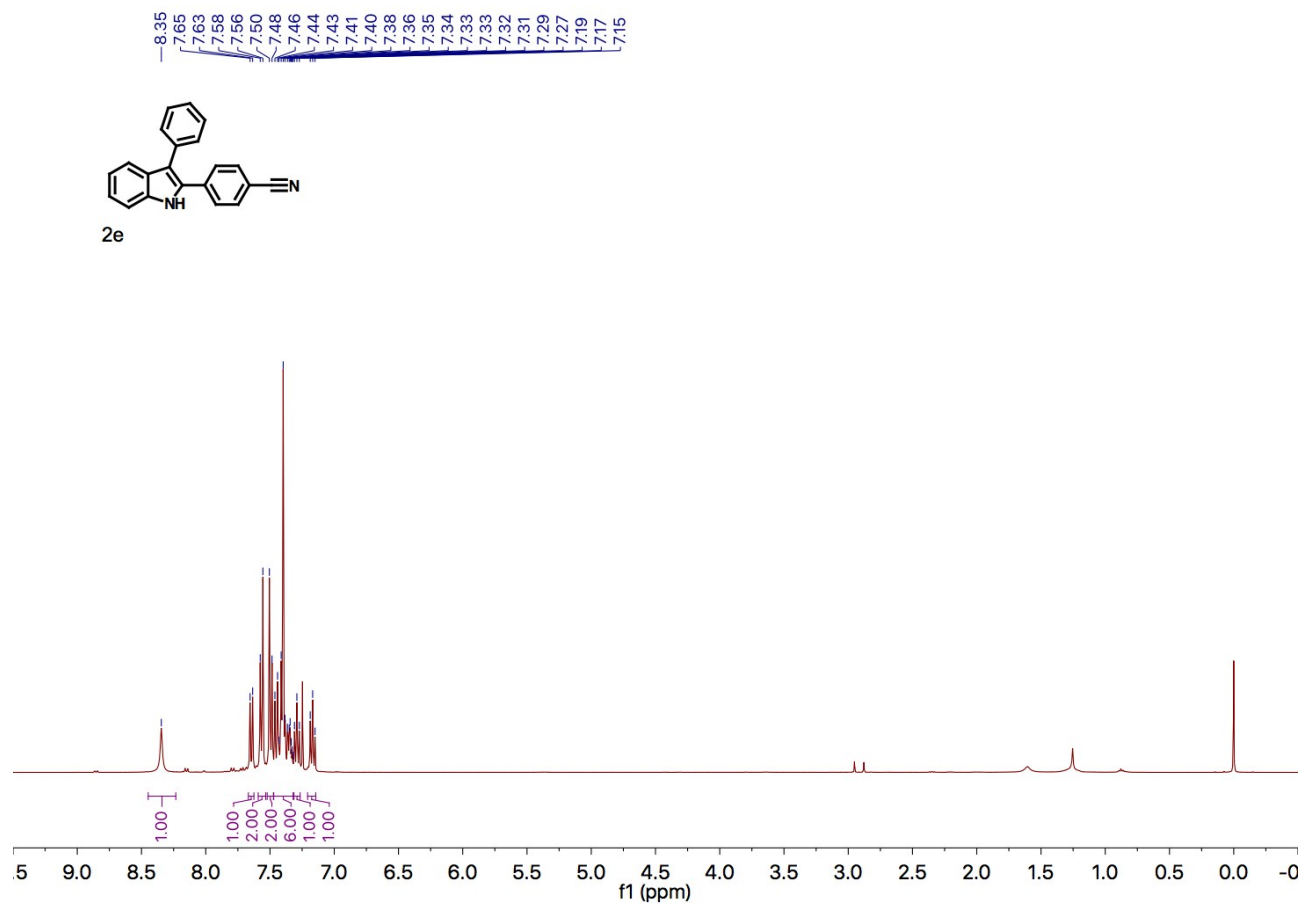
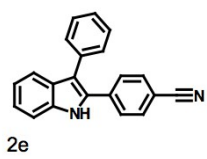


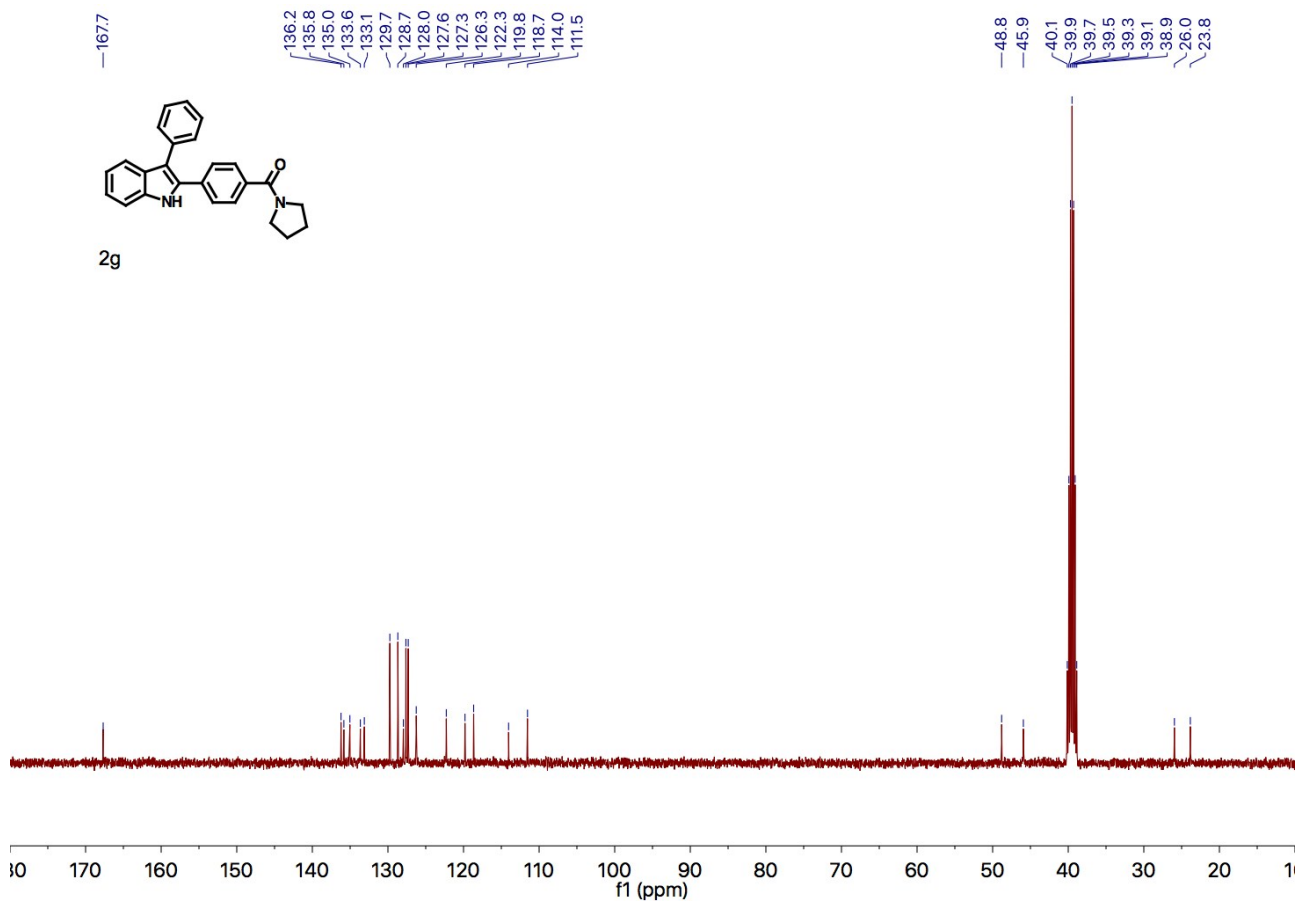
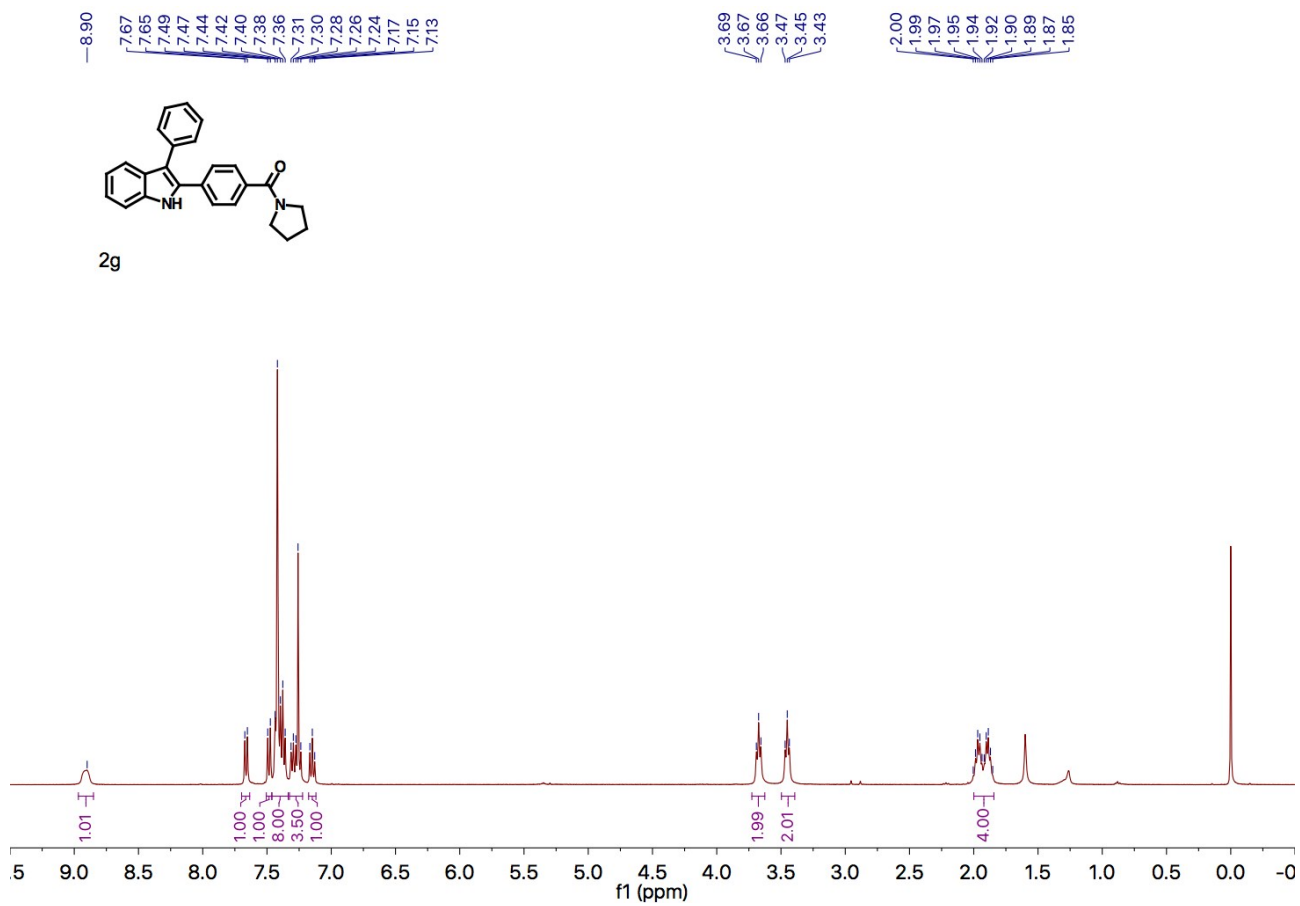


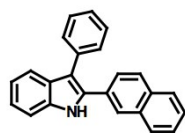




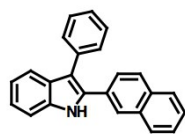
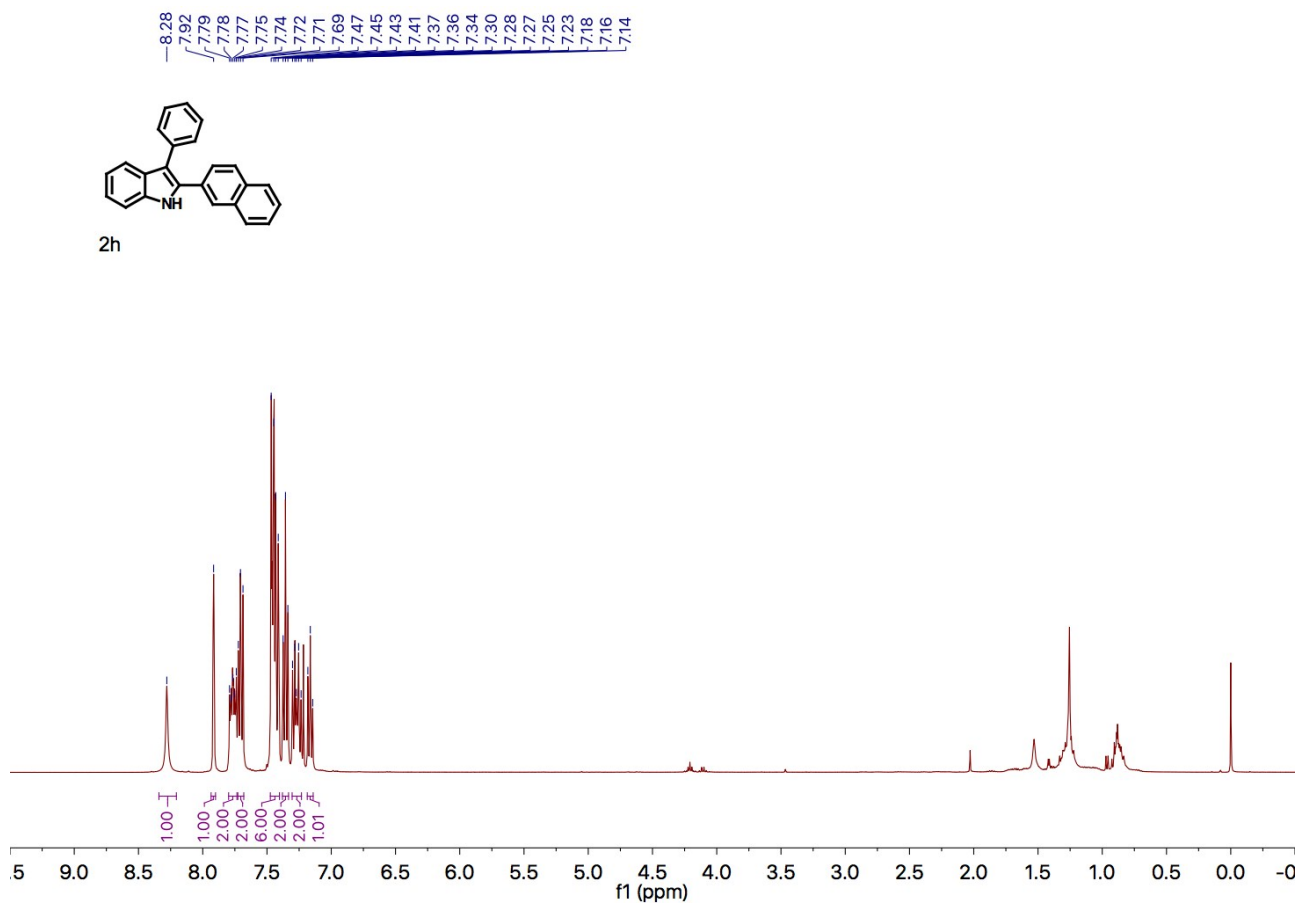




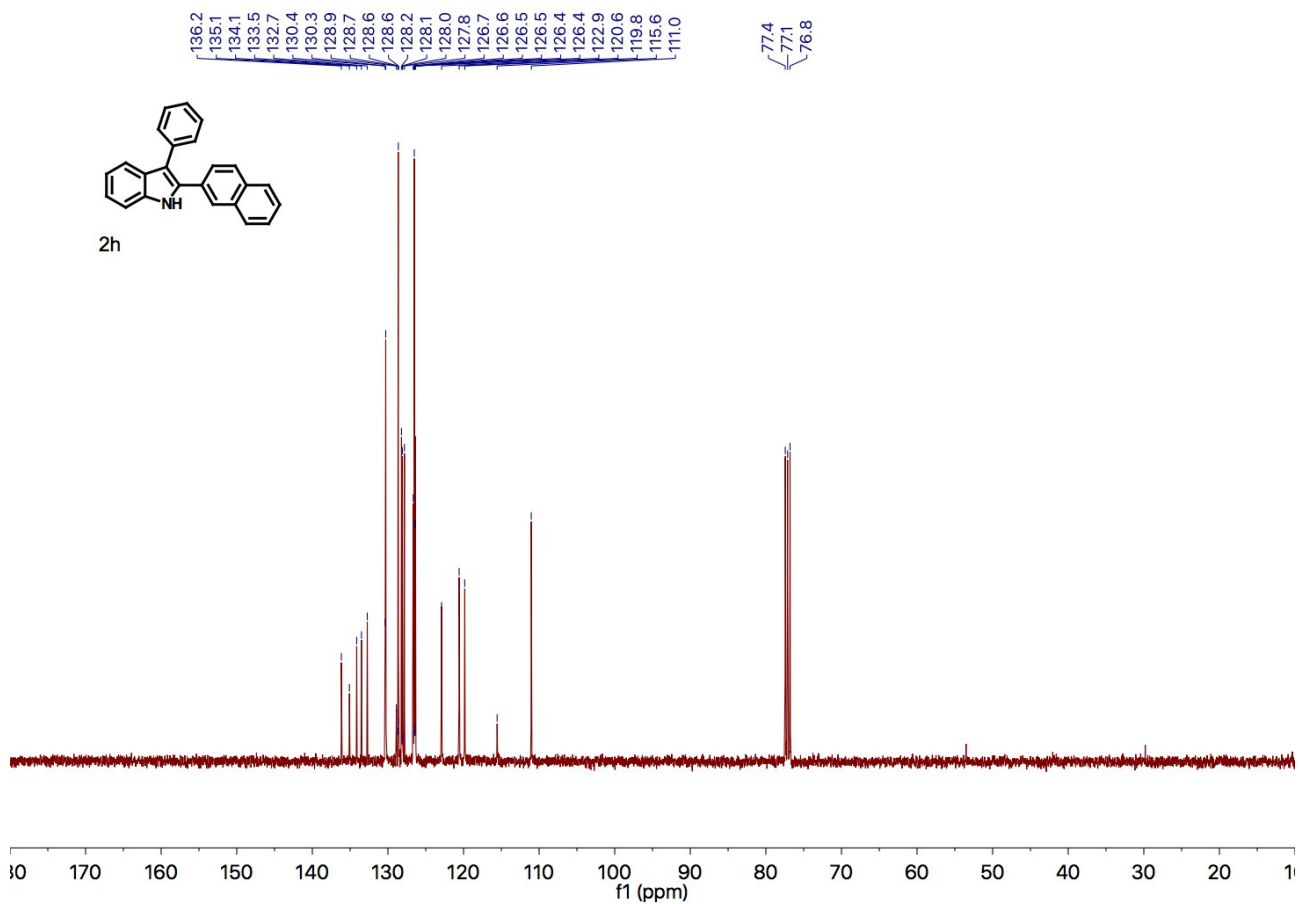


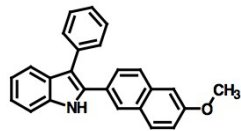


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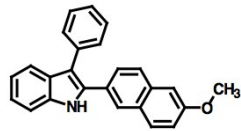
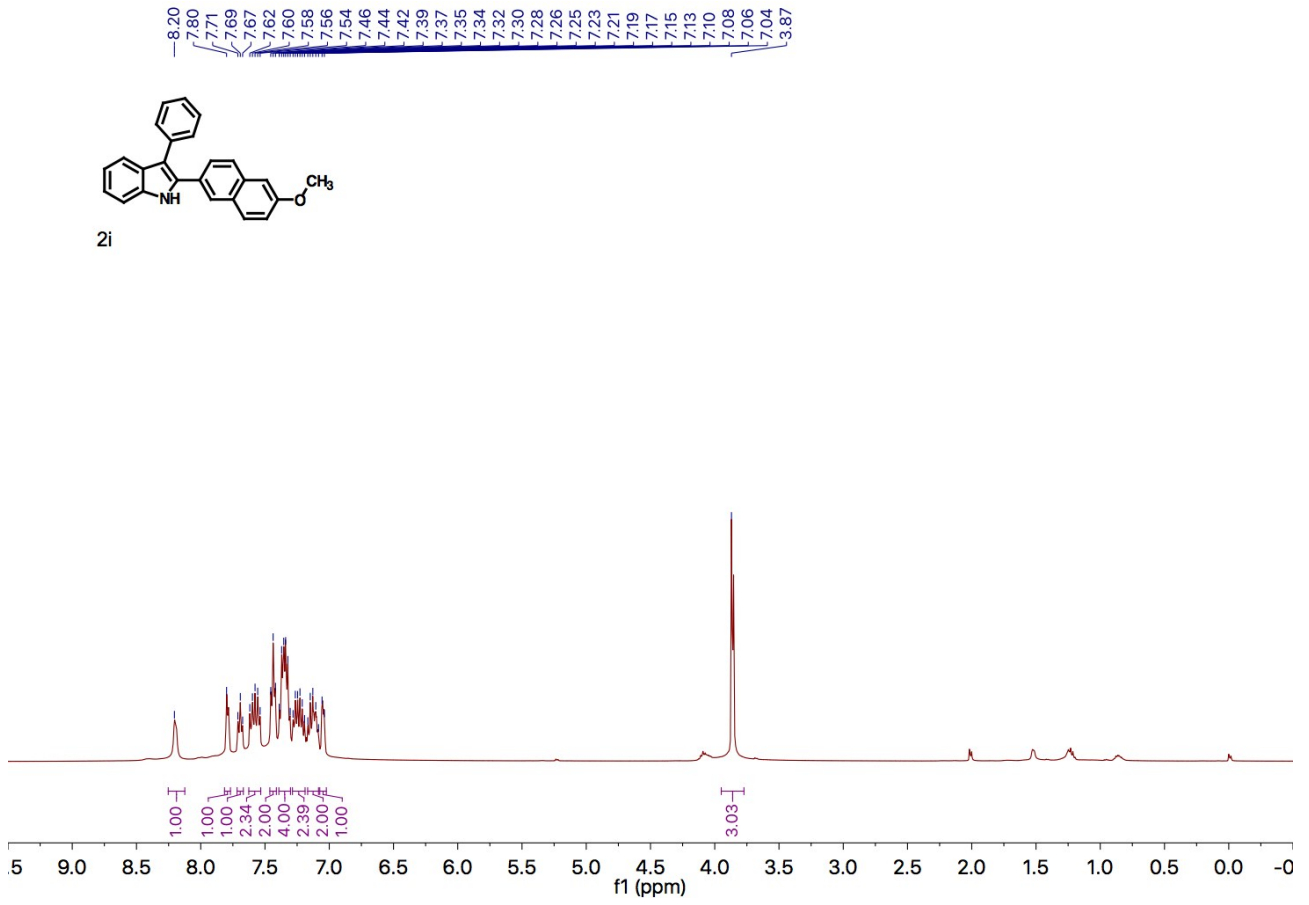


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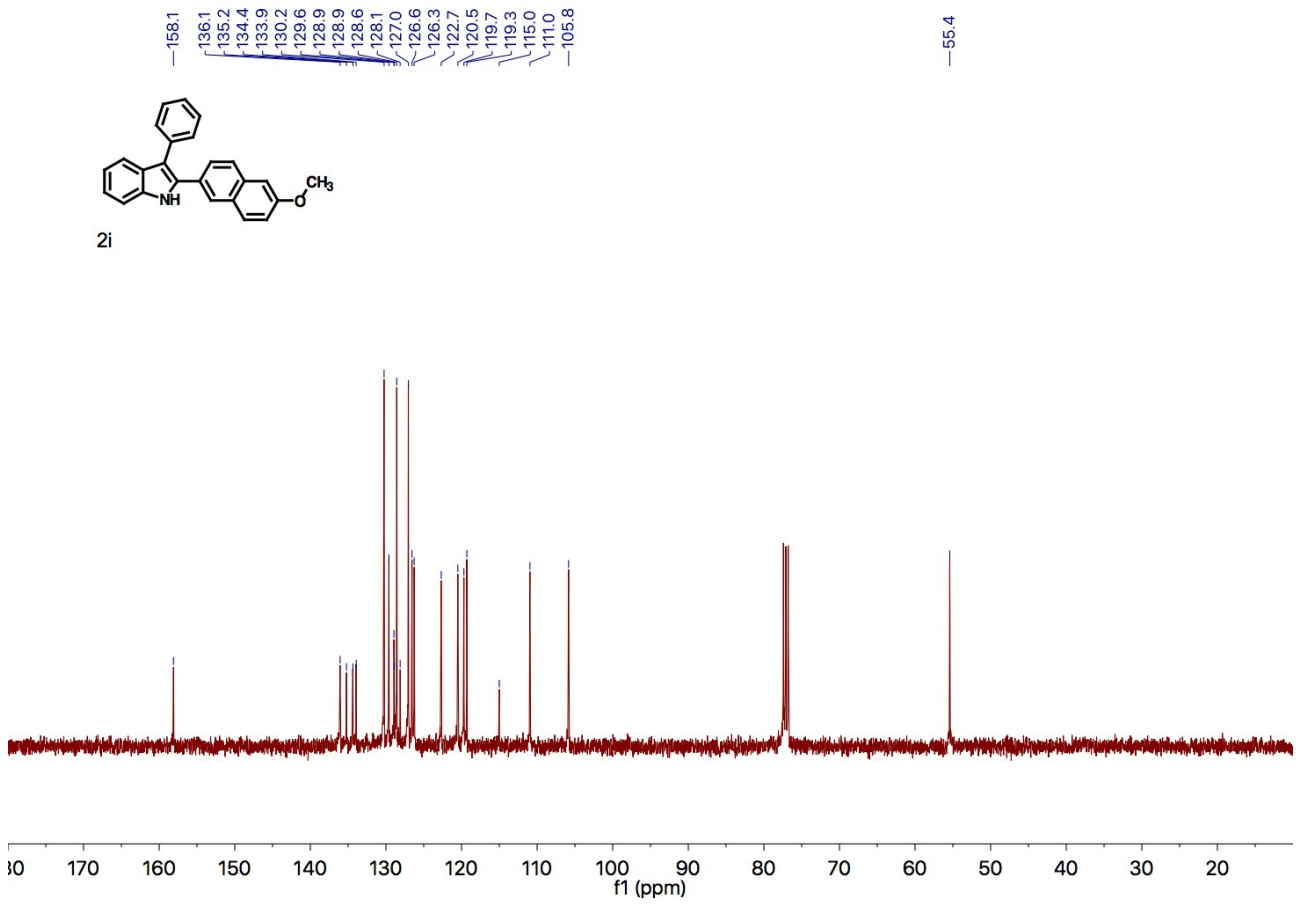


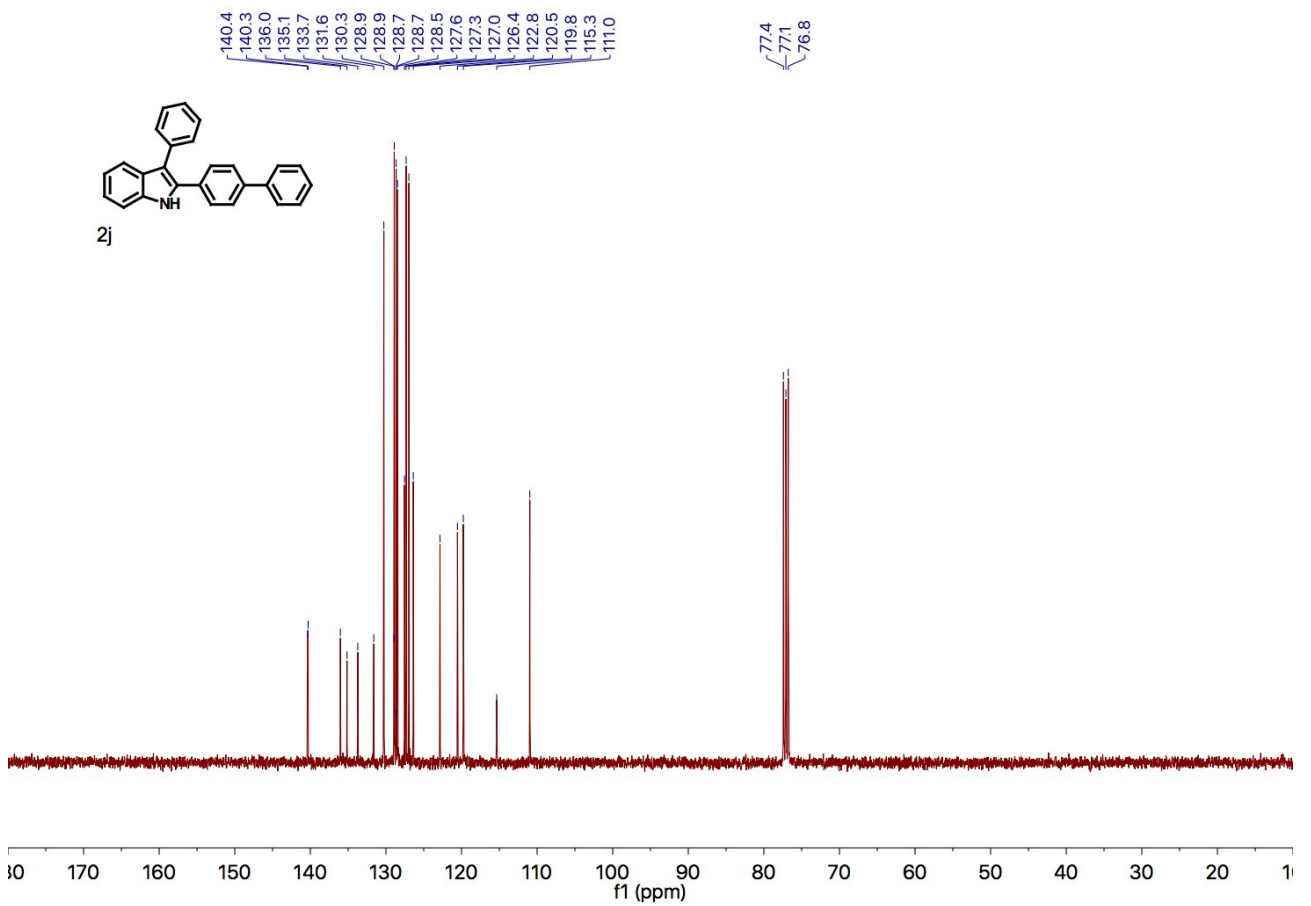
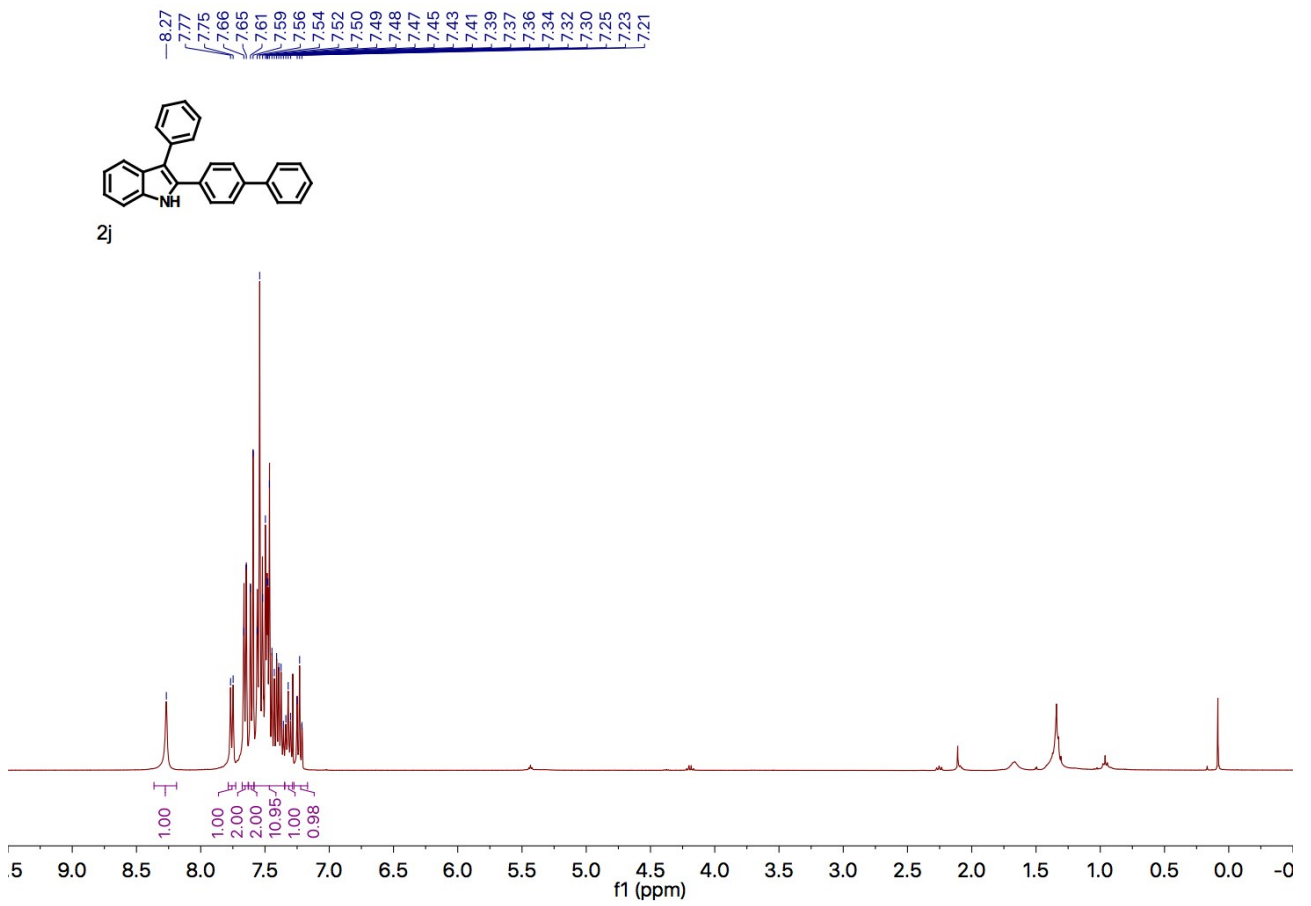


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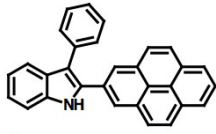


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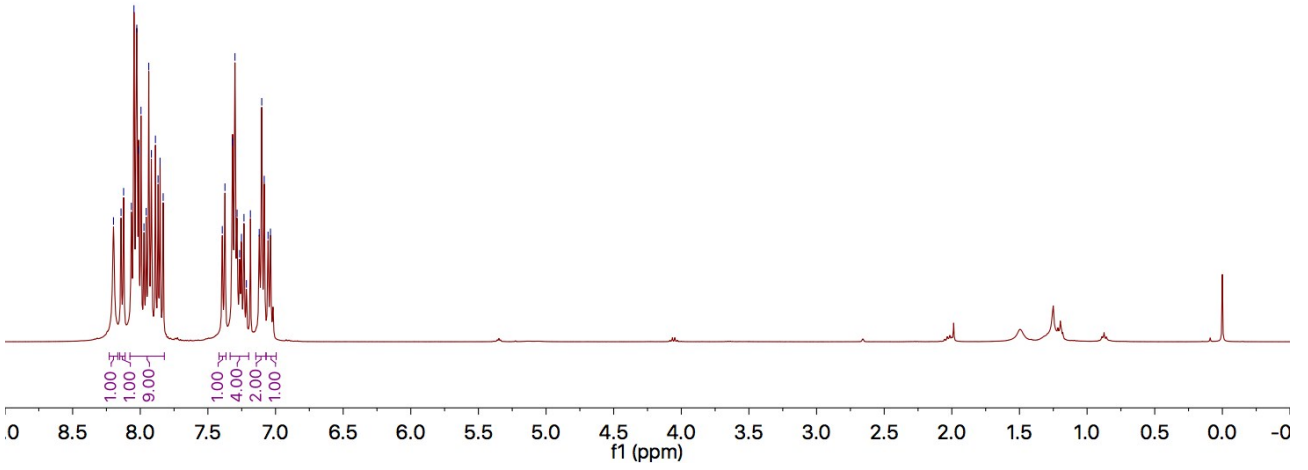




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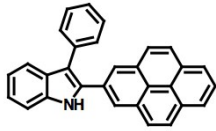


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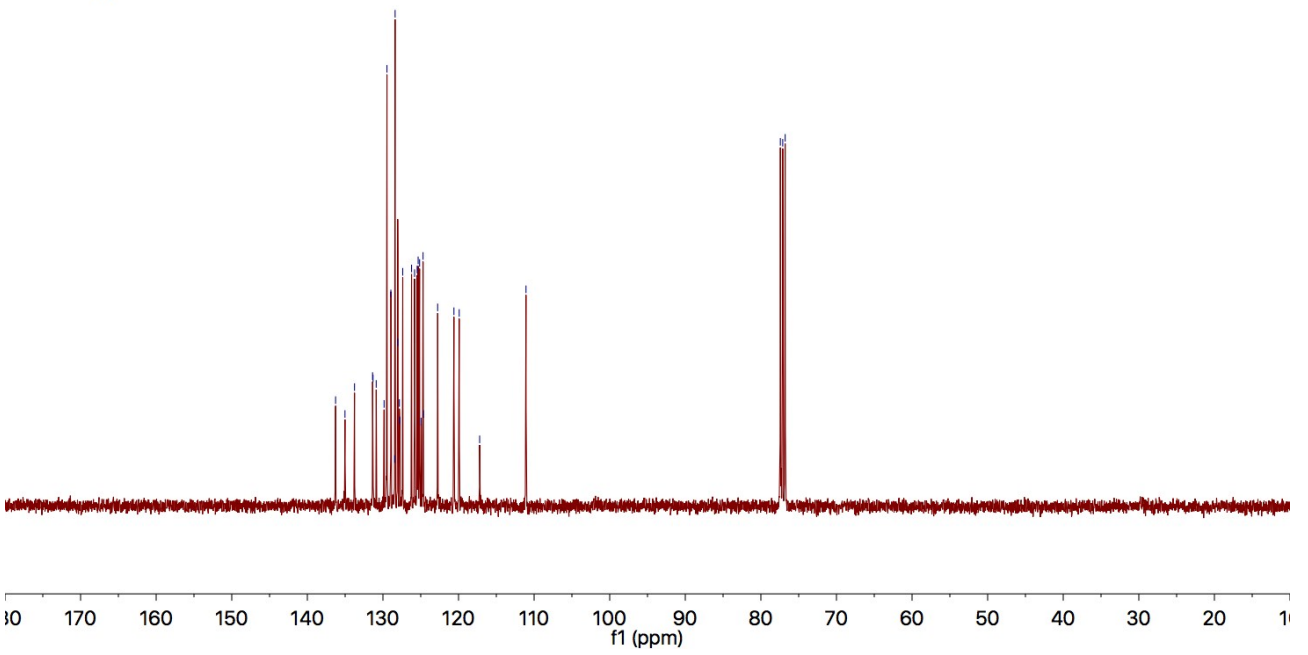


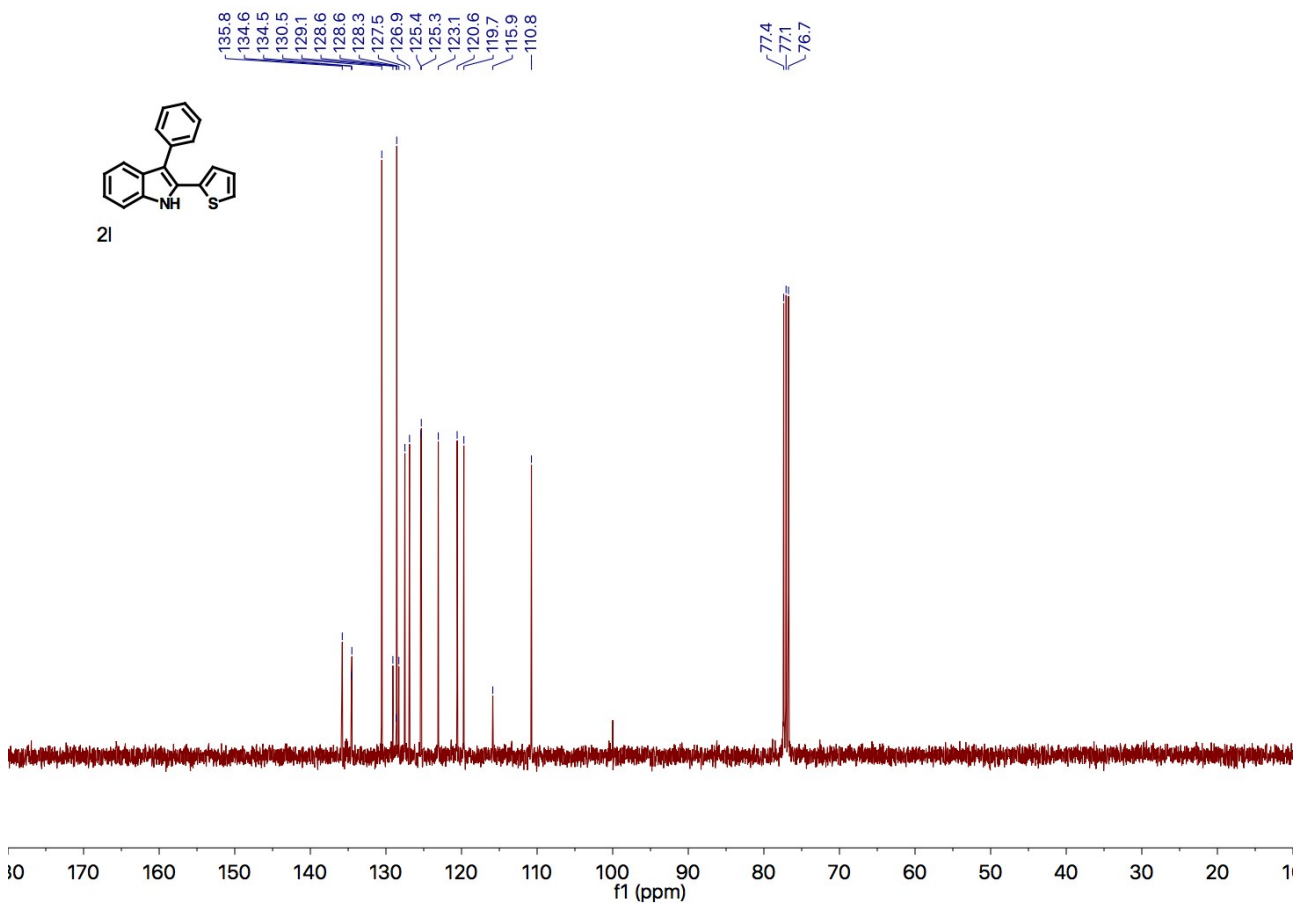
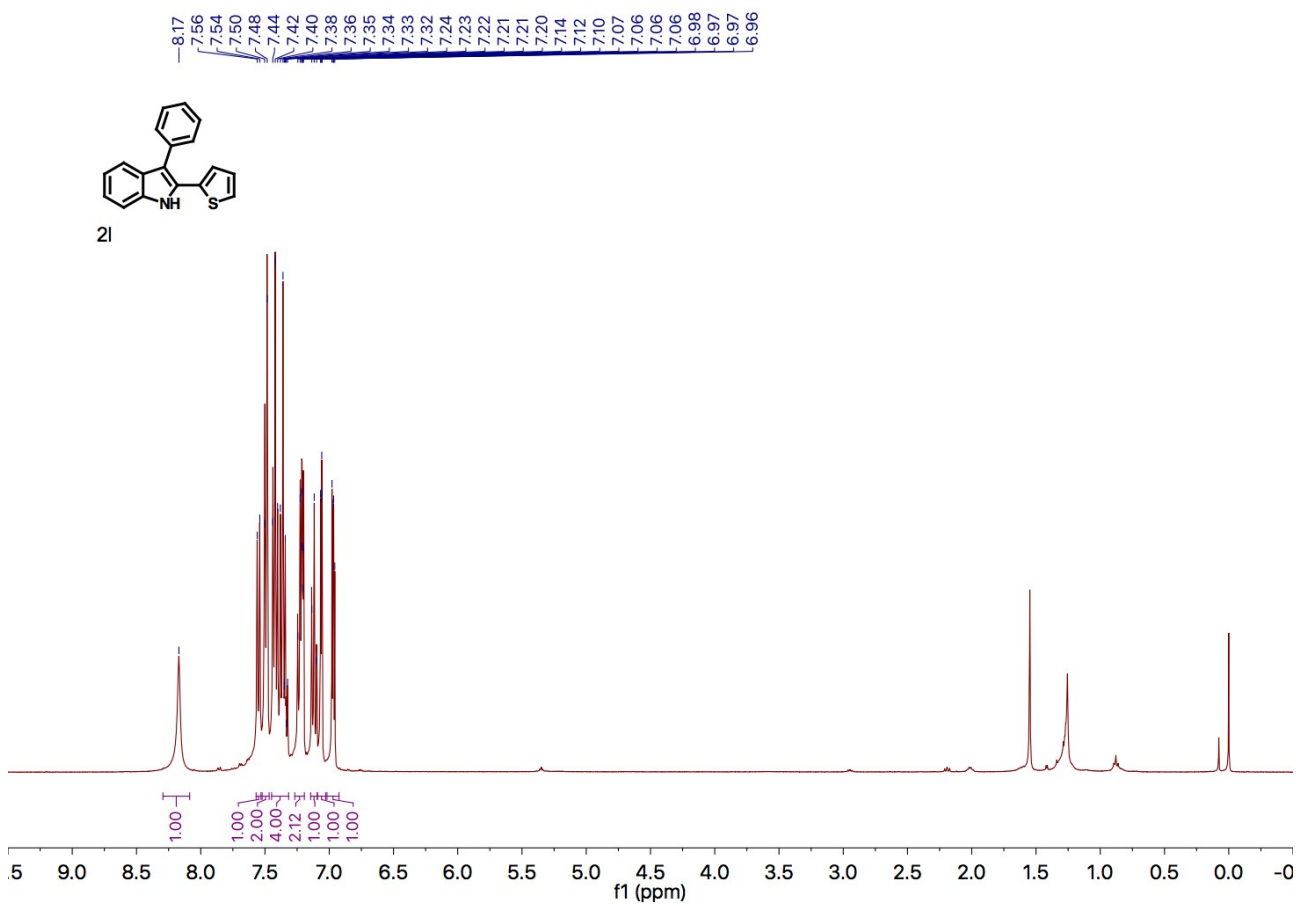
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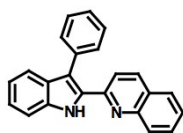


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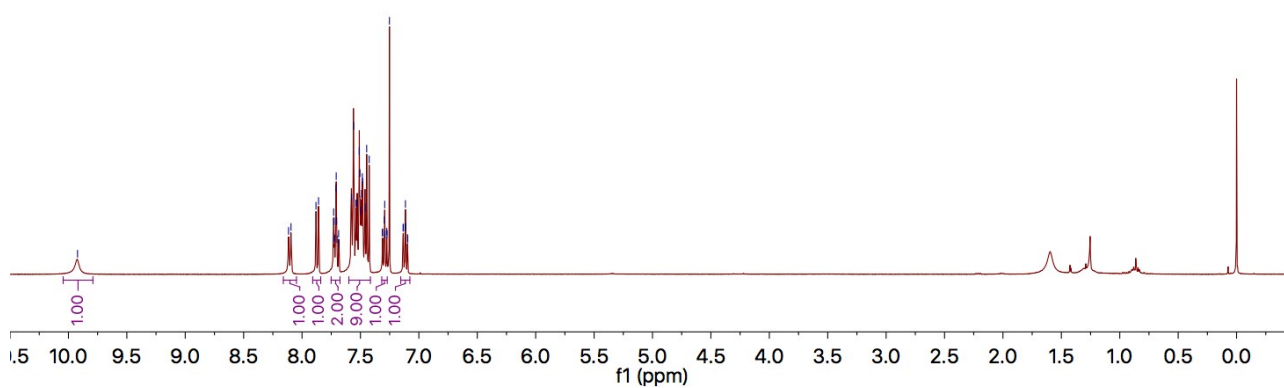




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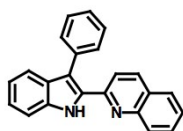


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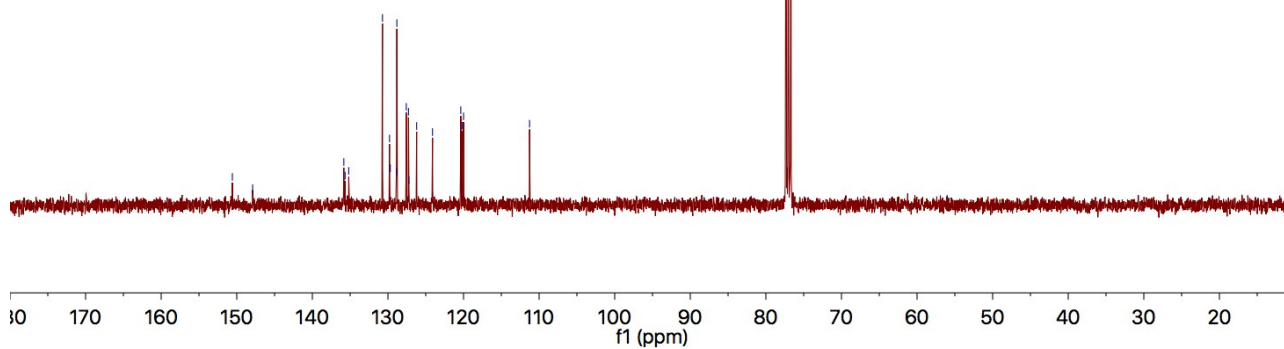


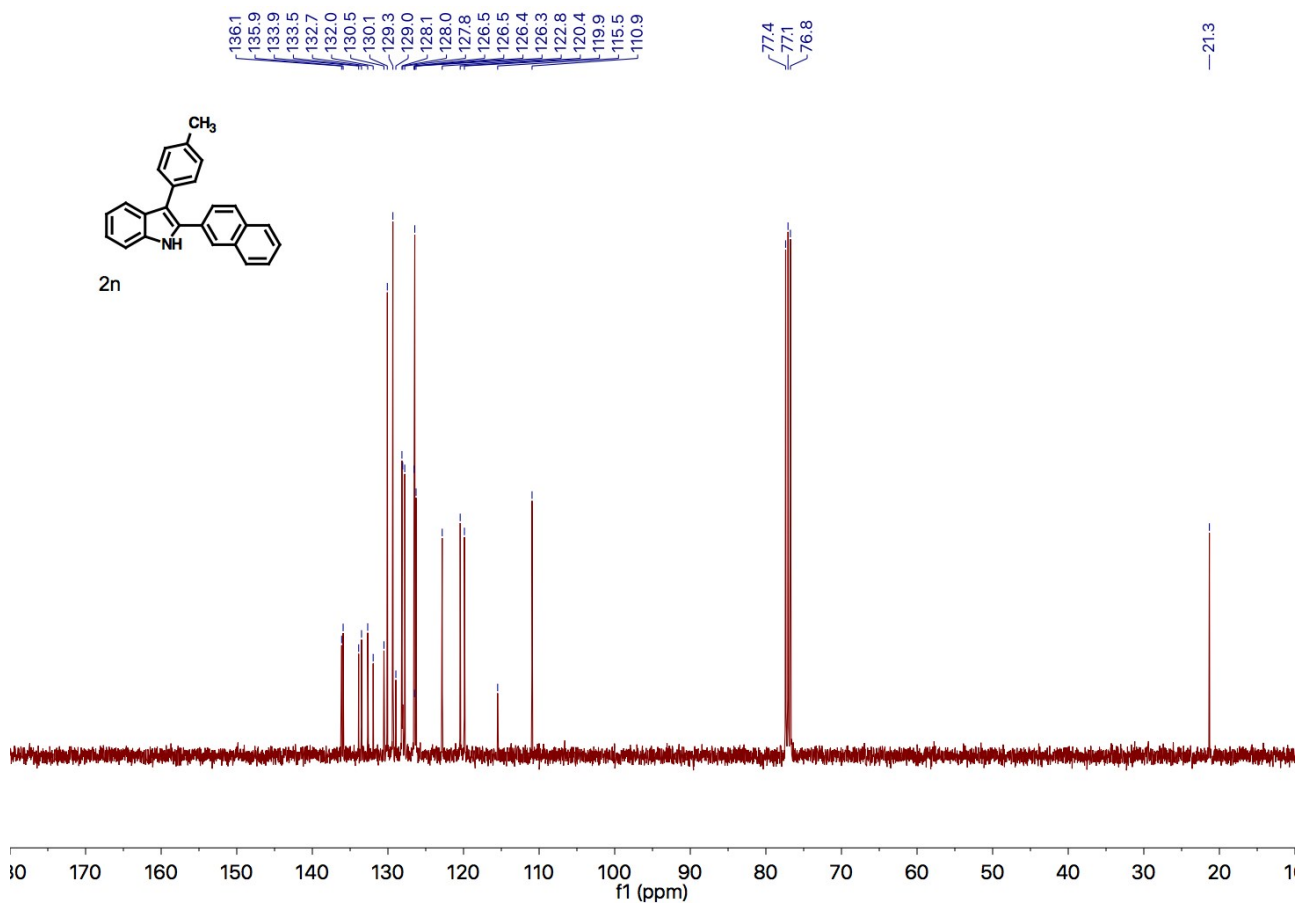
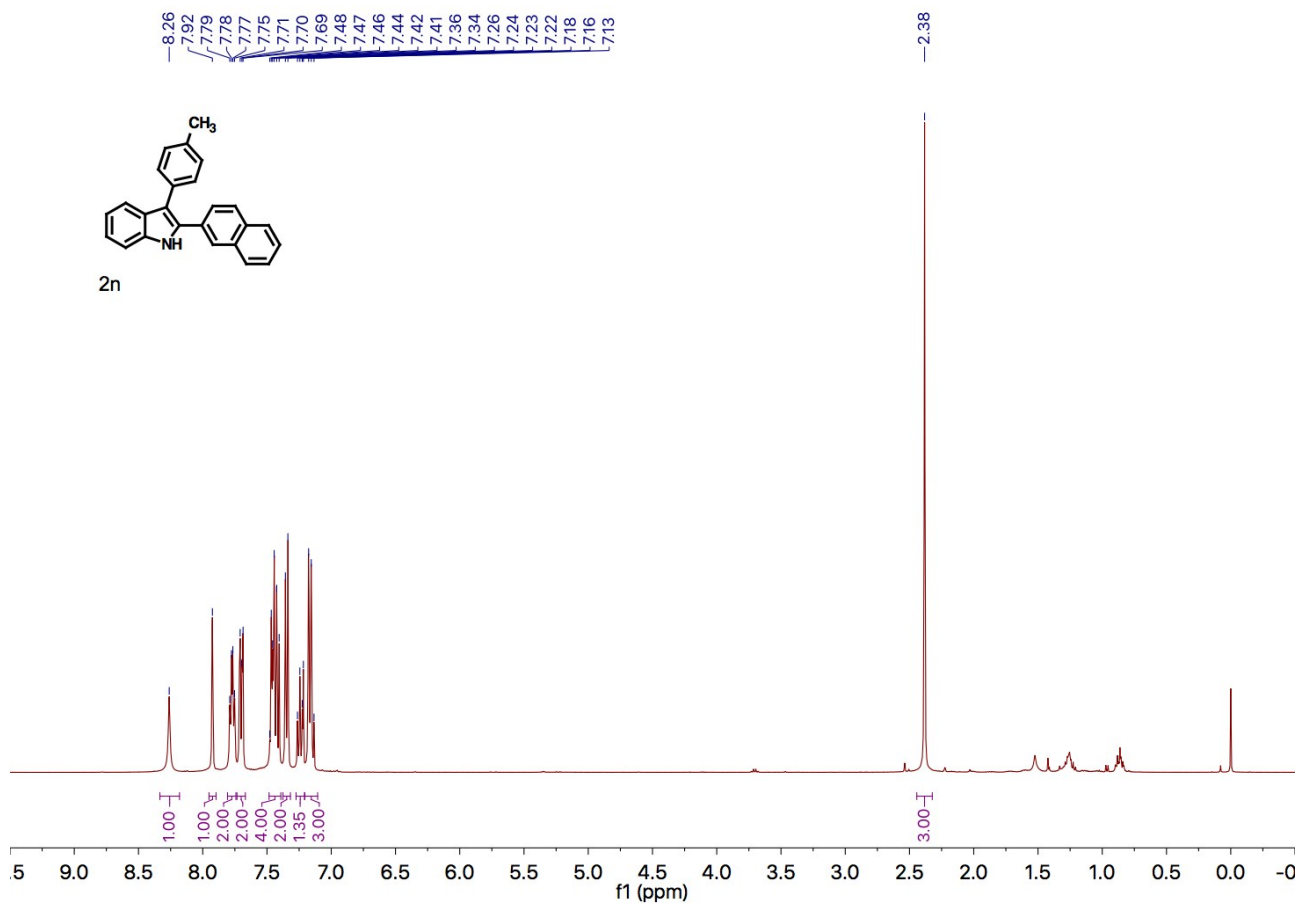
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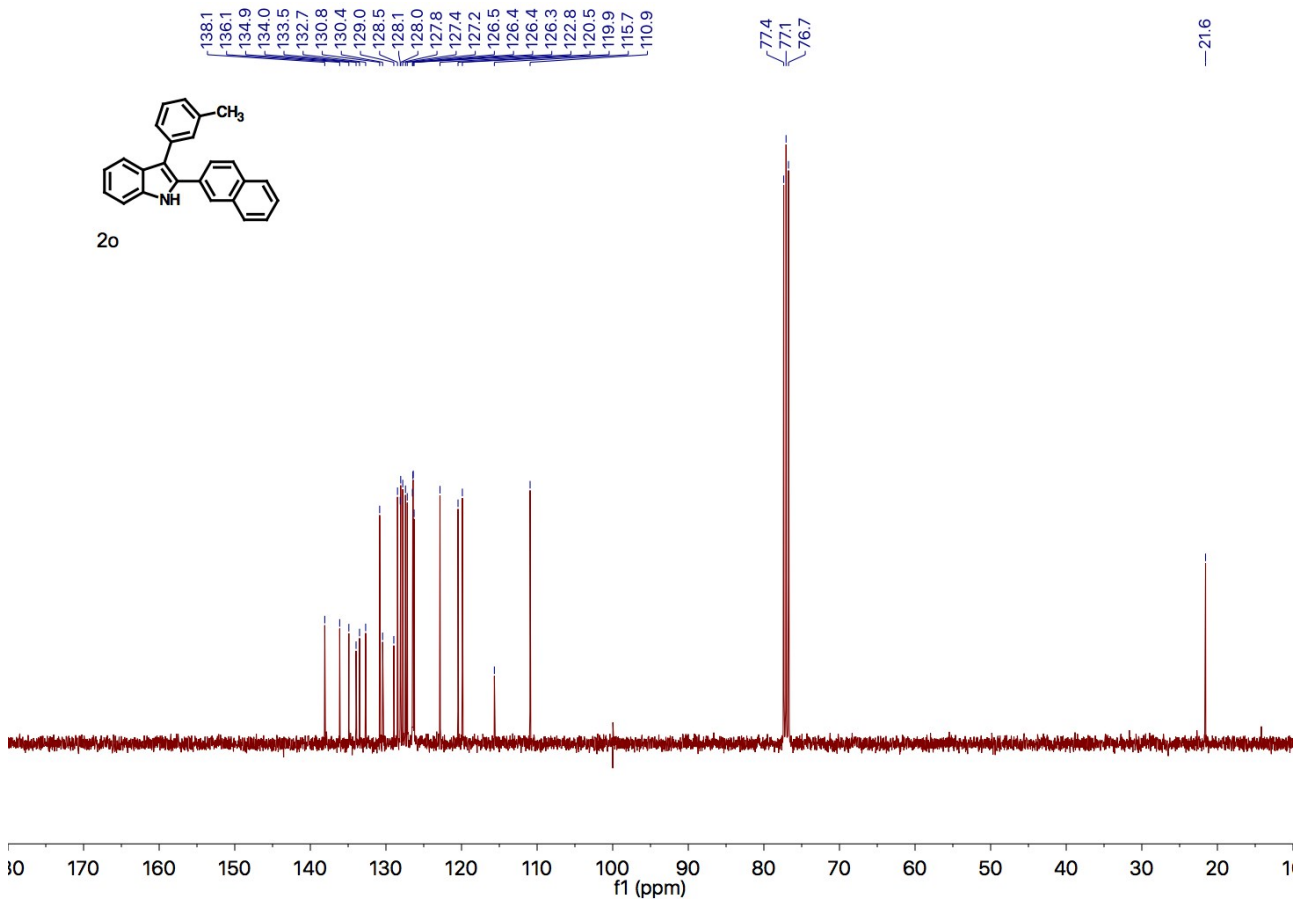
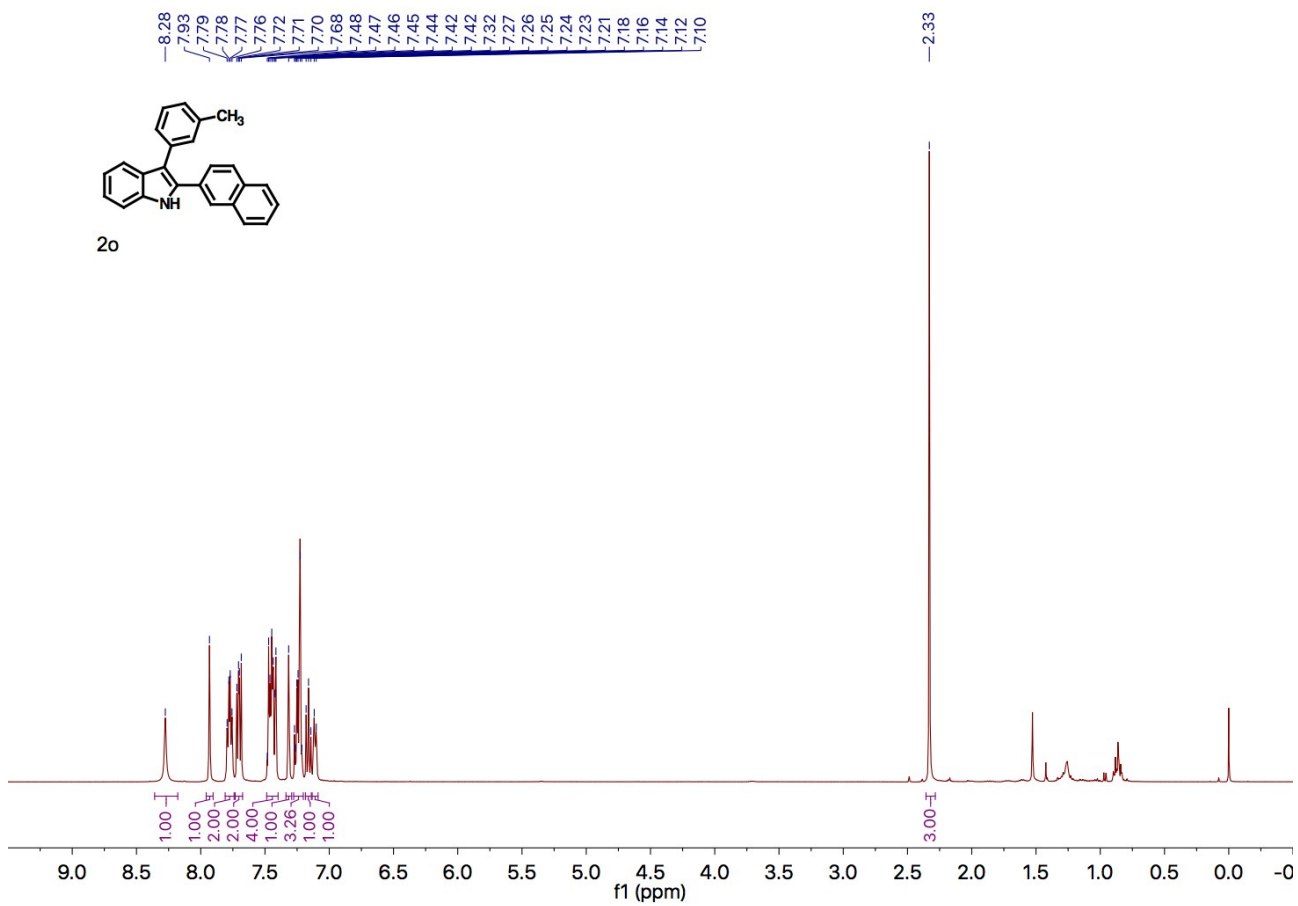
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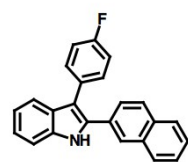


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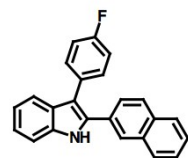
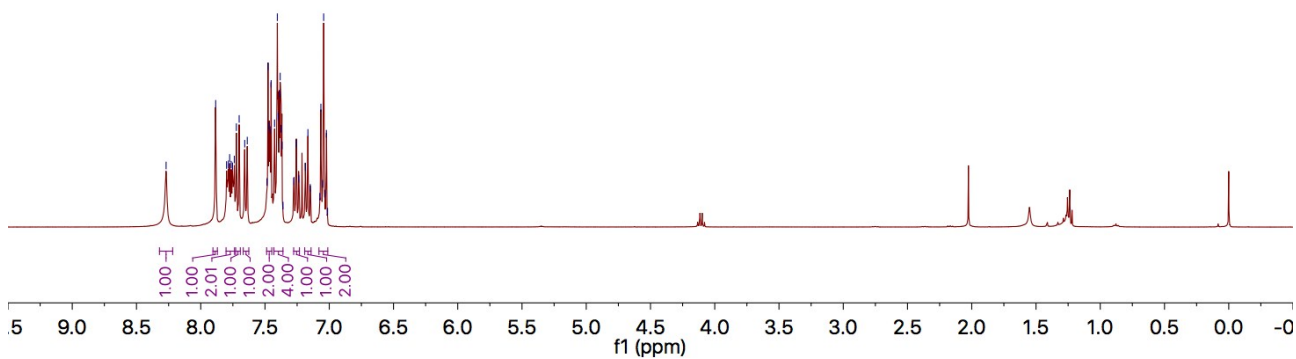






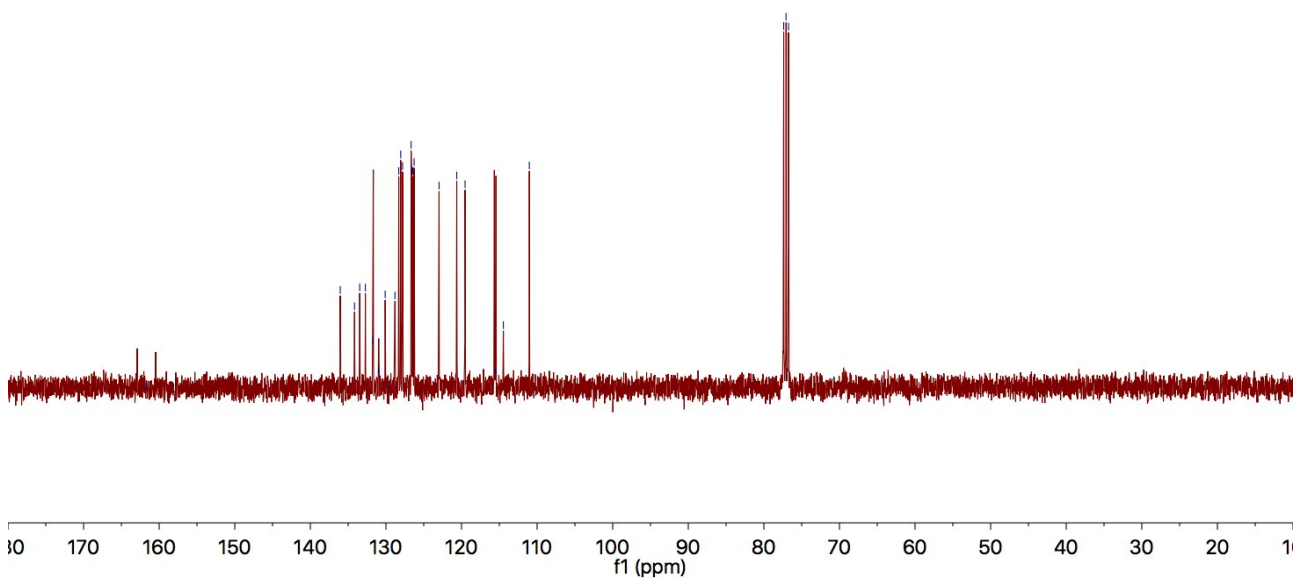
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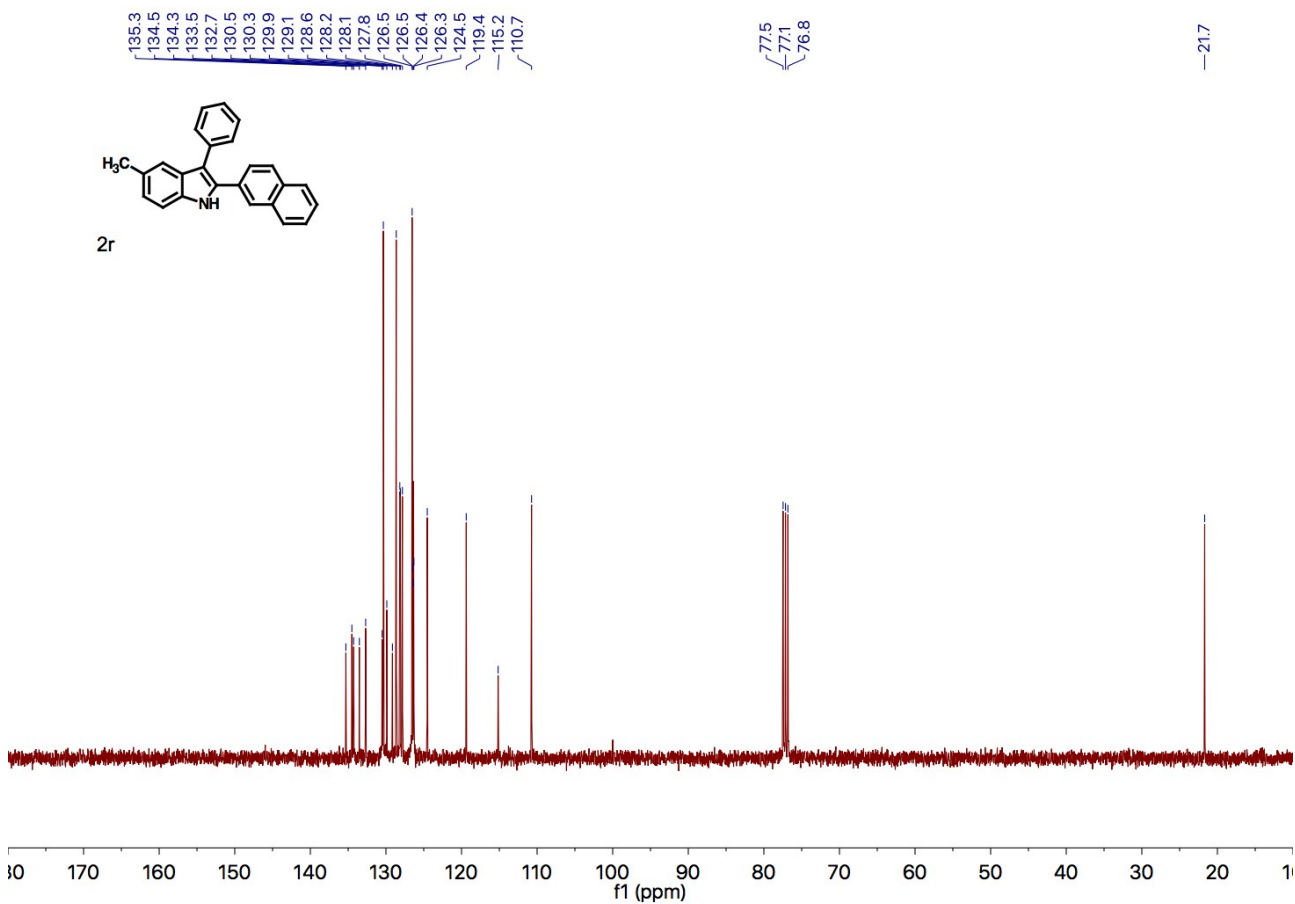
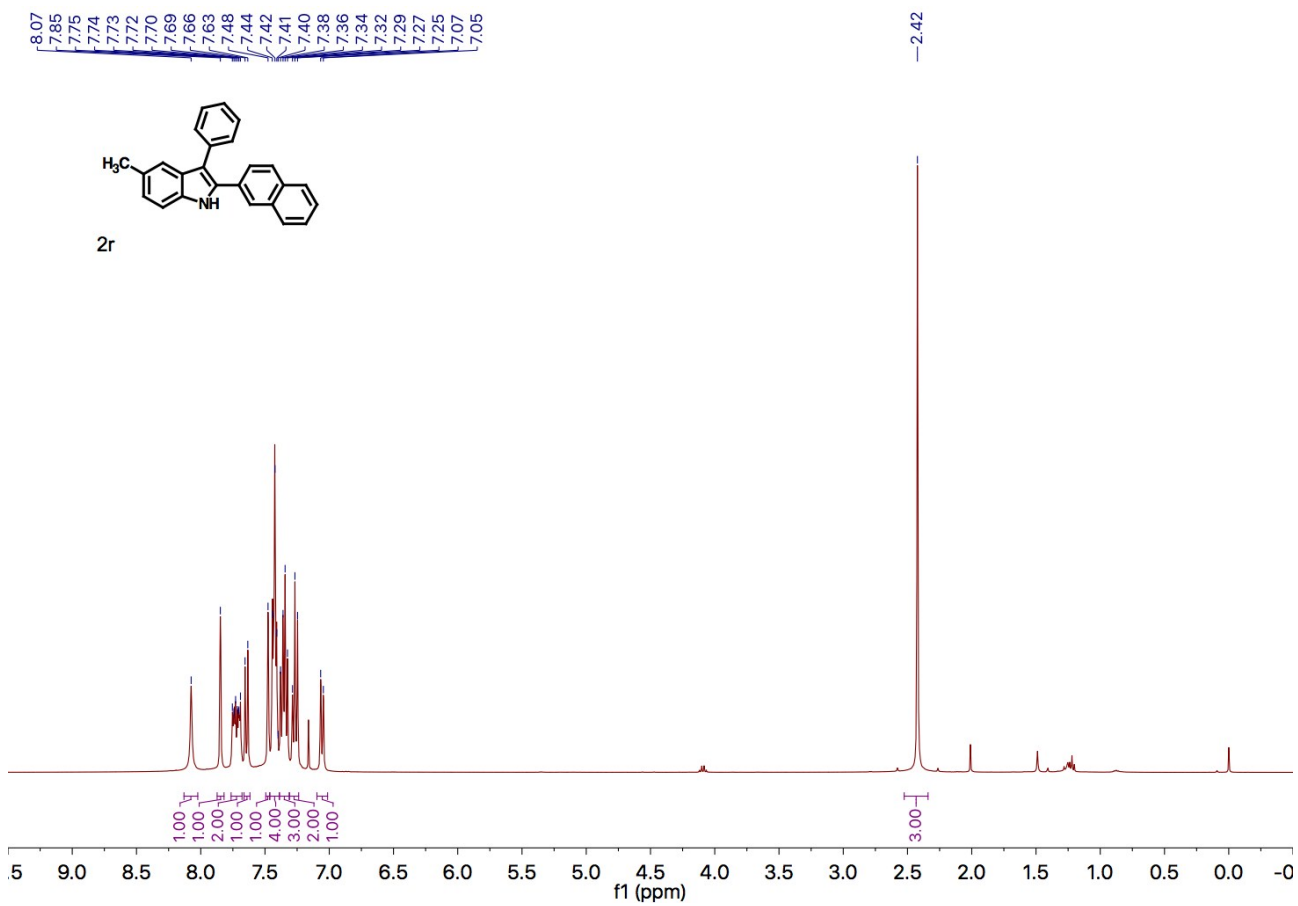
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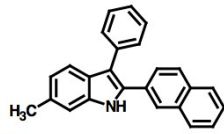
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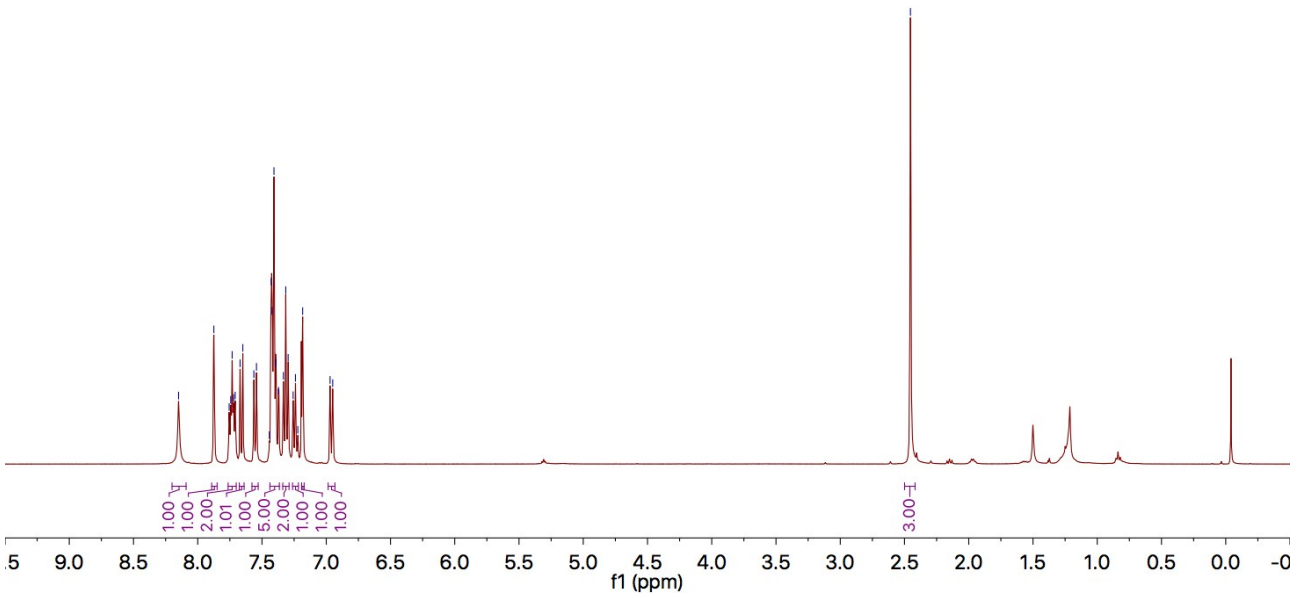


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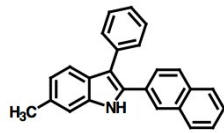


2s

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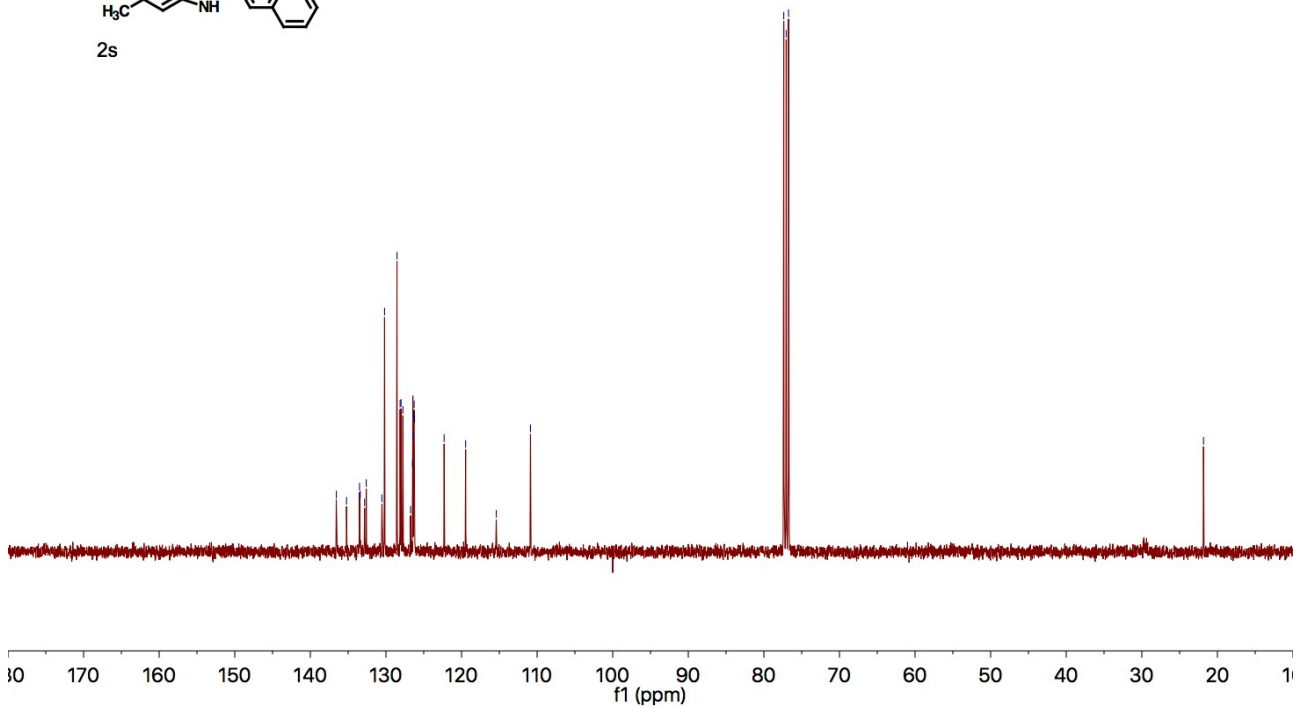
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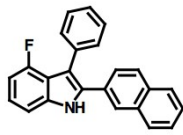


2s

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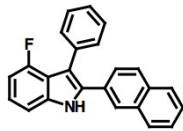
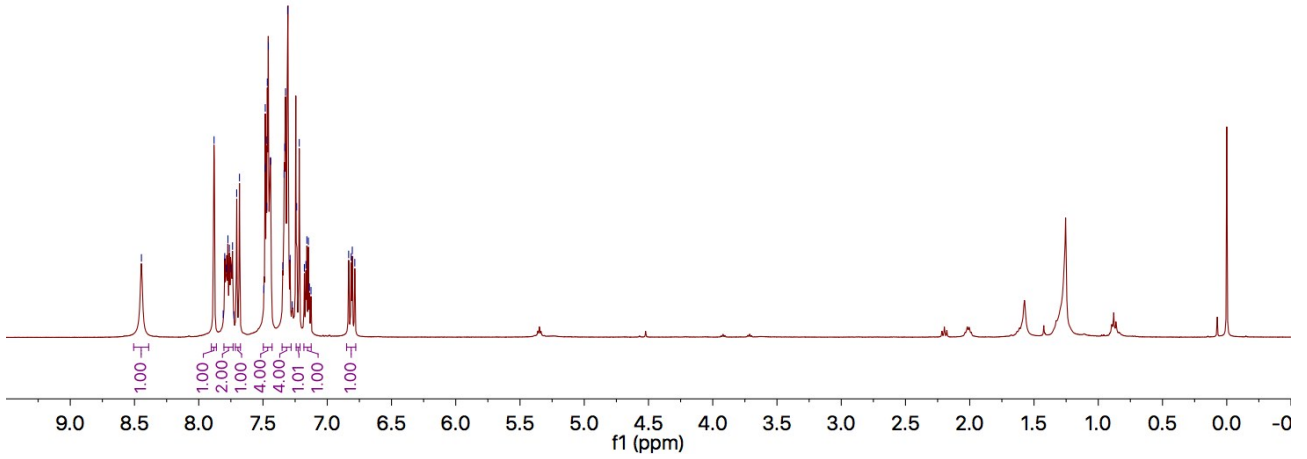
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2t

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2t

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