

## Supporting Information

# Continuous Flow Synthesis of *meta*-Substituted Phenol Derivatives

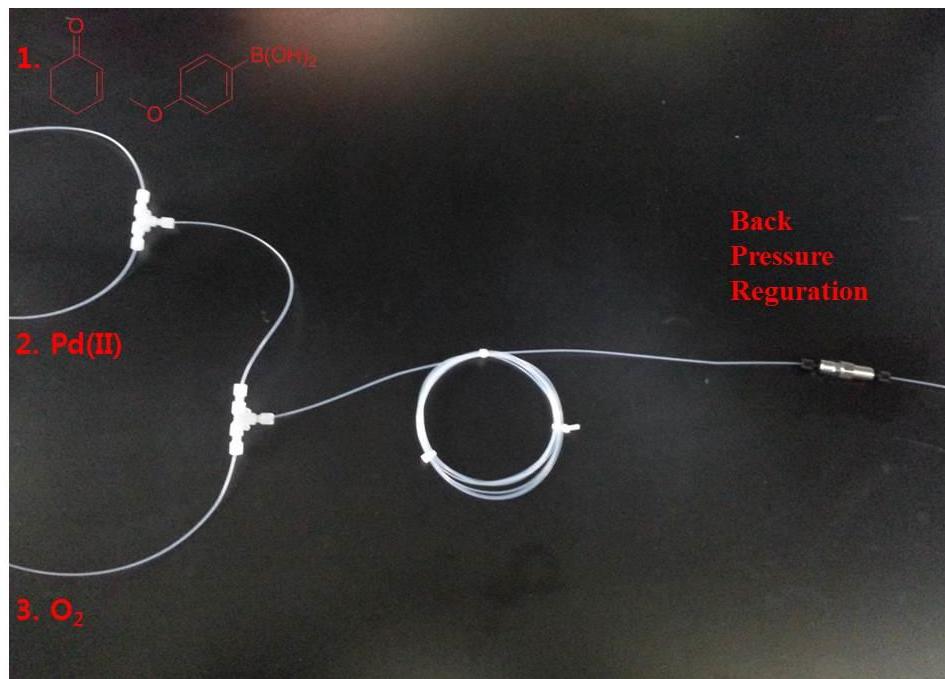
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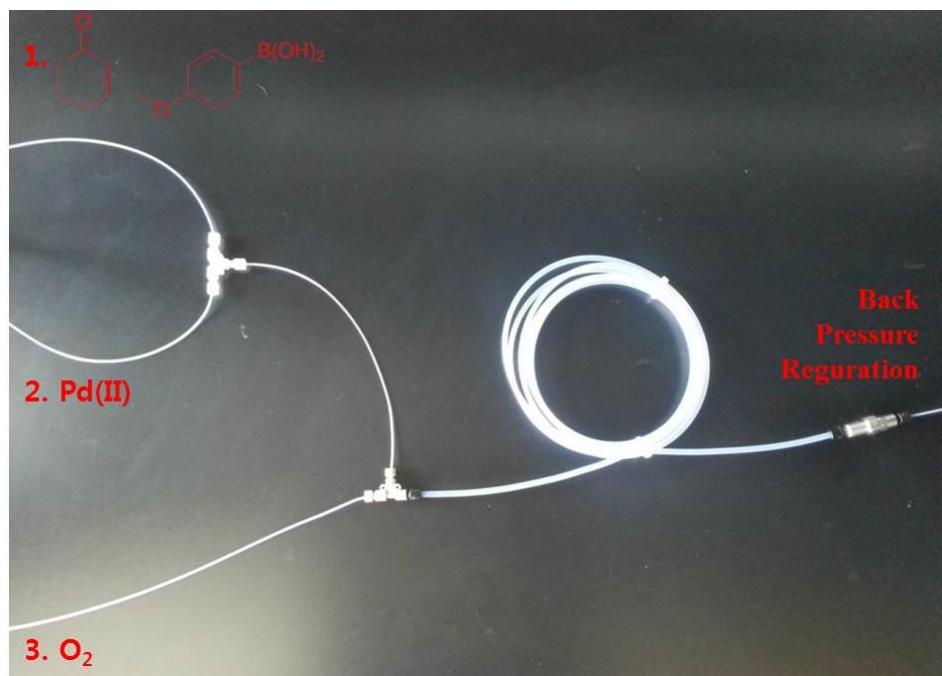
**General Prodedures:** Thin-layer chromatography (TLC) was performed using 60 mesh silica gel plates visualized with short-wavelength UV light (254 nm). Silica gel 60 (230~400 mesh) was used for column chromatography.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Bruker Advance 300 and Bruker Advance 600. Proton chemical shifts are reported in ppm ( $\delta$ ) relative to TMS with the solvent resonance employed as the internal standard ( $\text{CDCl}_3$ ,  $\delta$  = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet and doublet dt = doublet and triplet, m = multiplet), coupling constants (Hz) and integration. Carbon chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ( $\text{CDCl}_3$   $\delta$  = 77.0 ppm). PTFE tubing and static mixing tees were purchased from UPCHURCH, USA.

**General description of the microchemical oxidative Heck reaction:** NMP(*N*-methyl-2-pyrrolidone) solution(0.4 mL) of aryl boronic acid (1.0 mmol) and cyclohex-2-enone (3.0 mmol) was placed in the first inlet. NMP solution(0.4 mL) of a Pd(II) complex prepared with 0.05 mmol  $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$  and 0.05 mmol 6,6'-dimethyl-2,2'-bipyridyl was placed in the second inlet, oxygen gas was placed in the third inlet. The oxygen gas flow-rate was controlled by a MFC (TSC-200, 0.1 – 5.0 mL/min, NF System, Korea) combined with a readout box (KR04000S, NFSSystem, Korea). The reaction streams were introduced to the three-inlets of the microreactor, the injection rates of reagent and catalyst varied from 1.0 to 2.0  $\mu\text{L}/\text{min}$ , and

pressure of oxygen gas was varied from 1.3 to 1.6 atm. The reaction result was collected through a backpressure regulator, reaction yield was measured through the  $^1\text{H}$  NMR analysis using an external capillary standard ( $\text{CH}_2\text{Cl}_2$  in  $\text{CDCl}_3$ ).



**Figure 1S.** Oxidative Heck reaction in the capillary microreactor



**Figure 2S.** Oxidative Heck reaction in the tube in tube microreactor

entry 1	temp. (°C)	pressure (atm)	time (min)	yield(%)	
				capillary	Tube-in-tube
1	60	1.3	20	53	51
2	70	1.3	20	70	71
3	70	1.6	10	75	75
4	70	1.6	20	95	95

**Table 1S.** Oxidative Heck reactions of cyclohex-2-enone with 4-methoxyphenylboronic acid in the capillary microreactor and the tube-in-tube microreactor. Yields were determined by <sup>1</sup>H NMR analysis.

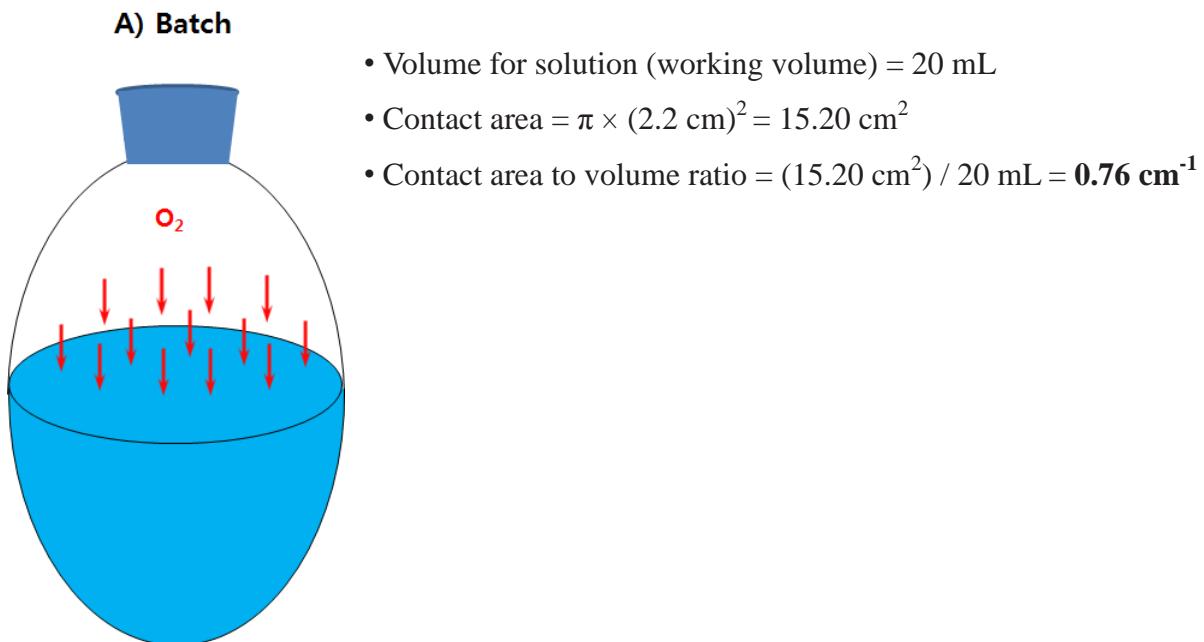
**General description of the microchemical oxidative dehydrogenation reaction:** 0.8 mL NMP solution of the oxidative Heck reaction was placed in a syringe, and 2.0 mL of a DMSO solution containing 5% CF<sub>3</sub>CO<sub>2</sub>H was placed in another syringe. Oxygen gas was placed in the third inlet. The oxygen gas flow-rate was controlled by a MFC (TSC-200, 0.1 – 5.0 mL/min, NFSSystem, Korea) combined with a readout box (KR04000S, NFSSystem, Korea). The reaction streams were introduced to the three inlets of the microreactor, the injection speeds were varied from 0.5 to 2.0  $\mu$ L/min, and the pressure of the oxygen gas was varied from 1.6 to 2.0 atm. The product was collected through a backpressure regulator, and reaction yield was measured through <sup>1</sup>H NMR analysis using an external capillary standard (CH<sub>2</sub>Cl<sub>2</sub> in CDCl<sub>3</sub>).

entry 1	temp. (°C)	pressure (atm)	time (min)	yield (%)	
				capillary	Tube-in-tube
1	100	3	120	38	36
2	120	3	120	58	57
3	120	5	120	85	87

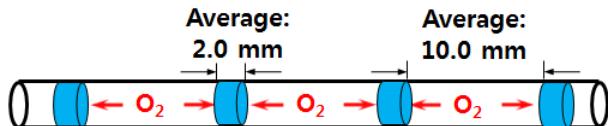
**Table 2S.** Oxidative dehydrogenations of **1a** (*3-(4-methoxyphenyl)cyclohex-2-enone*) in the capillary microreactor and the tube-in-tube microreactor. Yields were determined by <sup>1</sup>H NMR analysis.

**General description of synthesis of *meta*-substituted phenol derivatives in the tube-in-tube microreactor:** 1.6 mL NMP solution of cyclohex-2-enone (15 mmol, 1.43 g) and arylboronic acid (5 mmol) was placed in the first syringe, and 1.6 mL NMP solution of  $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$  (5 mol%) and 6,6'-dimethyl-2,2'-bipyridyl (5 mol%) was placed in the second syringe. The oxygen gas (5 atm) was injected by a MFC (TSC-200, 0.1 – 5.0 mL/min, NFSSystem, Korea) combined with a readout box (KR04000S, NFSSystem, Korea), and 5% TFA (trifluoroacetic acid) in DMSO (8 mL) was connected in the fourth syringe. The reaction streams were introduced to the inlets of the microreactor. The product was collected through a backpressure regulator, and isolated yields were obtained after column chromatography.

**The contact area to volume ratios and working volume in two microreactors and batch system :** Even though the lengths of each drops in the capillary microreactor was variable and the contact angle of solution to channel surface was not  $90^\circ$ , we simplified the average length of drops and assumed vertical contact between gas and liquid for simple calculation. For the batch system and the contact area was calculated under condition of no stirring and no bubbling.

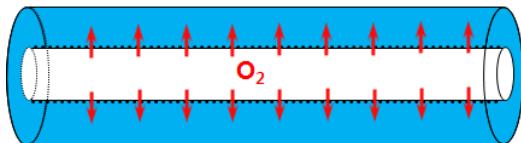


### B) Capillary microreactor



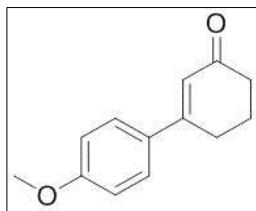
- Volume of microreactor =  $0.025\text{cm} \times 0.025\text{cm} \times \pi \times 300\text{cm} = 0.58875\text{mL}$
- Volume for solution (working volume) =  $0.58875\text{mL} \times 2/12 = \mathbf{0.098125\text{mL}}$
- Contact area =  $0.025\text{cm} \times 0.025\text{cm} \times \pi \times 2 \times (300\text{cm}/1.2\text{cm}) = 0.98125 \text{ cm}^2$
- Contact area to volume ratio =  $\mathbf{10.0\text{cm}^{-1}}$

### C) Tube-in-tube microreactor

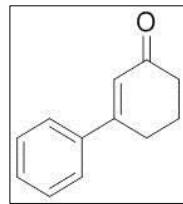


- Volume of outer tube =  $0.1\text{cm} \times 0.1\text{cm} \times \pi \times 300\text{cm} = 9.42\text{mL}$
- Volume of inner tube =  $0.04\text{cm} \times 0.04 \text{ cm} \times \pi \times 300\text{cm} = 1.70\text{mL}$
- Volume for solution (working volume) =  $9.42\text{mL} - 1.70\text{mL} = \mathbf{7.72\text{mL}}$
- Contact area =  $2 \times \pi \times 0.04\text{cm} \times 300\text{cm} = 75.36 \text{ cm}^2$
- Contact area to volume ratio =  $\mathbf{9.76\text{cm}^{-1}}$

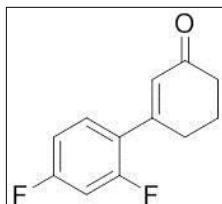
**Figure 3S.** The contact area to volume ratios and working volume in two microreactors and batch system.



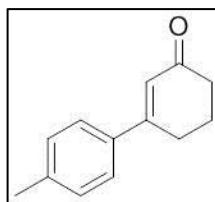
*3-(4-methoxyphenyl)cyclohex-2-enone (1a).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 4) in 92% yield (559 mg, yellow solid (m.p.: 81-83°C)). Experimental data were in accordance with those reported in the previous literature.<sup>1</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.54(d, *J* = 8.82 Hz, 2H), 6.95 (d, *J* = 8.89 Hz, 2H), 6.41 (s, 1H), 3.86 (s, 3H), 2.76 (t, *J* = 5.46 Hz, 2H), 2.48 (t, *J* = 6.97 Hz, 2H), 2.20-2.11 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 199.78, 161.26, 159.05, 130.86, 127.61, 123.74, 114.17, 55.37, 37.19, 27.89, 22.78.



*3-phenylcyclohex-2-enone (1b).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 3) in 86% yield (445 mg, colorless crystals solid (m.p.: 58-60°C)). Experimental data were in accordance with those reported in the previous literature.<sup>1</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.55-7.52 (dd, *J* = 5.44 Hz, 2.28 Hz, 2H), 7.41-7.42(m, 3H), 6.43(s, 1H), 2.78 (t, *J* = 5.7 Hz, 2H), 2.49 (t, *J* = 6.75 Hz, 2H), 2.20-2.09 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 199.82, 159.79, 138.80, 129.97, 128.75, 126.07, 125.43, 37.26, 28.11, 22.82.

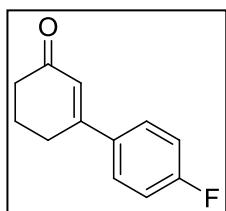


*3-(2,4-difluorophenyl)cyclohex-2-enone (1c).* The yellowish liquid was isolated after column chromatography (EtOAc : Hexane = 1 : 3) in 88% yield (549 mg, yellow oil). Experimental data were in accordance with those reported in the previous literature.<sup>1</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.39-7.22 (m, 1H ), 6.96-6.80 (m, 2H), 6.27 (s, 1H), 2.75 (t, *J* = 5.85 Hz, 2H), 2.52 (t, *J* = 6.98 Hz, 2H), 2.20-2.12 (m, *J* = 6.4, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>). δ 199.38, 163.43 (*J*<sub>CF</sub> = 251.34 Hz), 160.17 (*J*<sub>CF</sub> = 253.21 Hz), 156.00, 129.94, 129.88, 124.06 (*J*<sub>CF</sub> = 13.56 Hz), 111.83 (*J*<sub>CF</sub> = 20.8 Hz), 104.82 (*J*<sub>CF</sub> = 25.42 Hz), 37.33, 29.59, 23.08; HRMS (ESI) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>10</sub>F<sub>2</sub>ONa 231.0597; Found 231.0582.

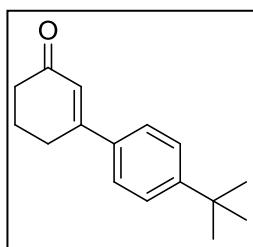


*3-p-tolylcyclohex-2-enone (1d).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 3) in 91% yield (509 mg, yellow oil). Experimental data were in accordance with those reported in the previous literature.<sup>1</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.46 (d, *J* = 8.2 Hz,

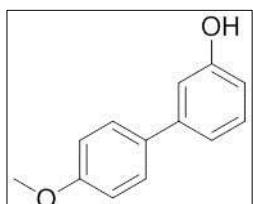
2H), 7.23 (d,  $J$  = 7.99 Hz, 2H), 6.43 (s, 1H), 2.77 (t,  $J$  = 5.41 Hz, 2H), 2.49 (t,  $J$  = 7.1 Hz, 2H), 2.39 (s, 3H), 2.20-2.11 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  200.02, 159.75, 140.42, 135.85, 129.52, 126.08, 124.71, 37.32, 28.04, 22.85, 21.35.



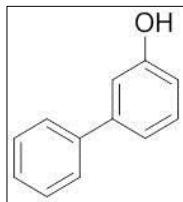
*3-(4-fluorophenyl)cyclohex-2-enone (1e).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 3) in 86% yield (491 mg, colorless oil). Experimental data were in accordance with those reported in the previous literature.<sup>2</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57-7.47 (dd,  $J$  = 5.18 Hz, 2H), 7.12 (t,  $J$  = 8.87 Hz, 2H), 6.39 (s, 1H), 2.77 (t,  $J$  = 5.54 Hz, 2H), 2.50 (t,  $J$  = 7.70 Hz, 2H), 2.17 (q,  $J$  = 6.12 Hz, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  199.68, 163.8 ( $J_{\text{CF}}$  = 250.77 Hz), 158.43, 134.88, 128.05, 128.00, 125.31, 115.91, 115.77, 37.16, 28.15, 22.76.



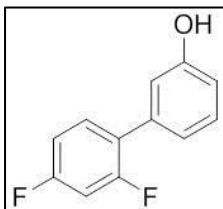
*3-(4-tert-butylphenyl)cyclohex-2-enone (1f).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 3) in 85% yield (582 mg, off-white crystalline solid (m.p.: 47.5-49.5 °C)). Experimental data were in accordance with those reported in the previous literature.<sup>2</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 (d,  $J$  = 8.70 Hz, 2H), 7.47 (d,  $J$  = 8.70 Hz, 2H), 6.46 (s, 1H), 2.80 (t,  $J$  = 5.60 Hz, 2H), 2.51 (t,  $J$  = 7.13 Hz, 2H), 2.17 (q,  $J$  = 6.37 Hz, 2H), 1.36 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  200.02, 159.60, 153.57, 136.74, 125.92, 125.76, 124.75, 37.31, 34.82, 31.19, 27.97, 22.84.



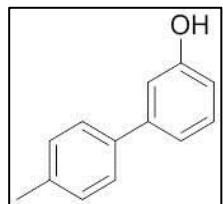
*4'-methoxybiphenyl-3-ol (2a).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 6) in 84% yield (837 mg, white powder (m.p.: 117°C)). Experimental data were in accordance with those reported in the previous literature.<sup>1</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (d,  $J$  = 8.66 Hz, 2H), 7.30 (t,  $J$  = 7.76 Hz, 1H), 7.15 (d,  $J$  = 7.53 Hz, 1H), 7.05 (s, 1H), 6.99 (d,  $J$  = 8.67 Hz, 2H), 6.80 (dd,  $J$  = 7.71 Hz, 1.94 Hz, 1H), 4.94 (bs, OH), 3.87 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  159.32, 155.87, 142.64, 133.32, 129.91, 128.11, 119.36, 114.22, 113.68, 113.60, 55.36.



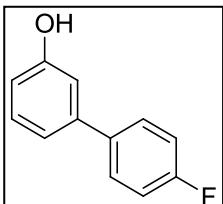
*biphenyl-3-ol (2b).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 6) in 83% yield (705 mg, white solid (m.p.: 73-74°C)). Experimental data were in accordance with those reported in the previous literature.<sup>1</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.60 (dd, *J* = 6.98 Hz, 1.52 Hz, 2H), 7.46 (t, *J* = 6.98 Hz, 2H), 7.31-7.39 (m, 2H), 7.20 (d, *J* = 7.71 Hz, 1H), 7.09 (s, 1H), 6.84 (dd, *J* = 8.18 Hz, 1.79 Hz, 1H), 4.75 (bs, OH); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 155.86, 143.04, 140.76, 130.01, 128.77, 127.52, 127.15, 119.83, 114.18, 114.12.



*2',4'-difluorobiphenyl-3-ol (2c).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 7) in 85% yield (876 mg, yellow oil). Experimental data were in accordance with those reported in the previous literature.<sup>3</sup> <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.43 (q, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.02 (s, 1H), 6.99-6.92 (m, 2H), 6.89 (dd, *J* = 7.9 Hz, 1.83 Hz), 4.78 (bs, OH); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 162.37 (*J*<sub>CF</sub> = 249.43 Hz), 159.72 (*J*<sub>CF</sub> = 250.61 Hz), 155.52, 136.57, 131.39, 129.78, 124.86 (*J*<sub>CF</sub> = 13.48 Hz), 121.53, 115.94, 114.75, 111.56 (*J*<sub>CF</sub> = 20.28 Hz), 104.40 (*J*<sub>CF</sub> = 24.75 Hz).

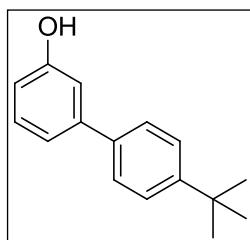


*4'-methylbiphenyl-3-ol (2d).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 4) in 87% yield (801 mg, white solid (m.p.: 75.2-75.3°C)). Experimental data were in accordance with those reported in the previous literature.<sup>1</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.53 (d, *J* = 8.09 Hz, 2H), 7.37 (t, *J* = 8.05 Hz, 1H), 7.29 (d, *J* = 7.77 Hz, 2H), 7.23 (d, *J* = 7.89, 1H), 7.10 (s, 1H), 6.83 (dd, *J* = 7.89, 1.7 Hz, 1H), 5.28 (bs, OH), 2.44 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 155.82, 143.00, 137.88, 137.32, 129.98, 129.50, 126.97, 119.66, 113.99, 113.97, 21.10.

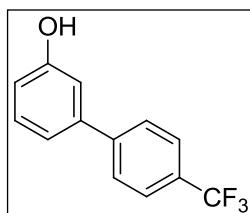


*4'-fluorobiphenyl-3-ol (2e).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 6) in 84% yield (792 mg, amorphous solid (m.p.: 78-79°C)). Experimental data were in accordance with those reported in the previous literature.<sup>3</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.57-7.52 (dd, *J* = 5.66 Hz, 8.48 Hz, 2H), 7.33 (t, *J* = 7.91 Hz, 1H), 7.17-7.11 (m, 3H), 7.04 (s, 1H), 6.86 (dd, *J* = 7.79, 2.03 Hz, 1H), 4.89 (bs, OH); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ

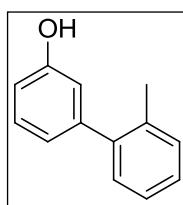
162.57 ( $J_{\text{CF}} = 246.06$  Hz), 155.95, 142.04, 136.88, 130.07, 128.70, 128.65, 119.61, 115.69, 115.56, 114.21, 114.02.



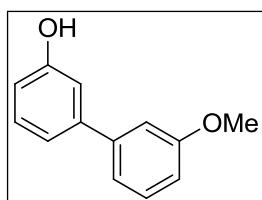
*4'-tert-butylbiphenyl-3-ol (2f).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 6) in 80% yield (906 mg, yellow solid (m.p.: 89.5°C)). Experimental data were in accordance with those reported in the previous literature.<sup>3</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (d,  $J = 8.29$  Hz, 2H), 7.47 (d,  $J = 8.11$  Hz, 2H), 7.32 (t,  $J = 7.92$  Hz, 1H), 7.20 (d,  $J = 7.91$  Hz, 1H), 7.08 (s, 1H), 6.84 (d,  $J = 7.90$ , 1H), 4.79 (bs, OH), 1.38 (s, 9H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  155.79, 150.56, 142.88, 137.80, 129.93, 126.75, 125.72, 119.68, 113.92, 113.91, 34.56, 31.37.



*4'-(trifluoromethyl)biphenyl-3-ol (2g).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 6) in 32% yield (381 mg, colorless needles (m.p.: 73-75°C)). Experimental data were in accordance with those reported in the previous literature.<sup>4</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (s, 4H), 7.37 (t,  $J = 7.79$  Hz, 1H), 7.20 (d,  $J = 7.79$  Hz, 1H), 7.09 (s, 1H), 6.90 (dd, 7.79 Hz, 1.95 Hz, 1H), 4.86 (bs, OH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.00, 144.26, 141.54, 130.24, 127.40, 125.70 ( $J_{\text{CF}} = 3.42$  Hz), 119.90, 115.11, 114.24.

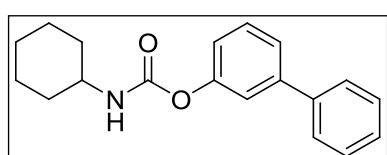


*2'-methylbiphenyl-3-ol (2h).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 4) in 54% yield (497 mg, colourless oil). Experimental data were in accordance with those reported in the previous literature.<sup>5</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33-7.25 (m, 5H), 6.92 (d,  $J = 7.15$  Hz, 1H), 6.85-6.82 (m, 2H), 4.80 (bs, OH), 2.30 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  155.19, 143.72, 141.48, 135.29, 130.29, 129.58, 129.28, 127.35, 125.71, 121.91, 116.20, 113.70, 20.38.



*3'-methoxybiphenyl-3-ol (2i).* The compound was isolated after column chromatography (EtOAc : Hexane = 1 : 4) in 59% yield (590 mg, brown oil). Experimental data were in accordance with those

reported in the previous literature.<sup>6</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.40-7.30 (m, 2H), 7.20-7.08 (m, 4H), 6.93 (dd, J = 8.41 Hz, 2.4 Hz, 1H), 6.85 (dd, J = 8 Hz, 2 Hz, 1H), 3.89 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 159.93, 155.82, 142.91, 142.29, 129.95, 129.74, 119.83, 119.65, 114.34, 114.16, 113.00, 112.85, 55.32.



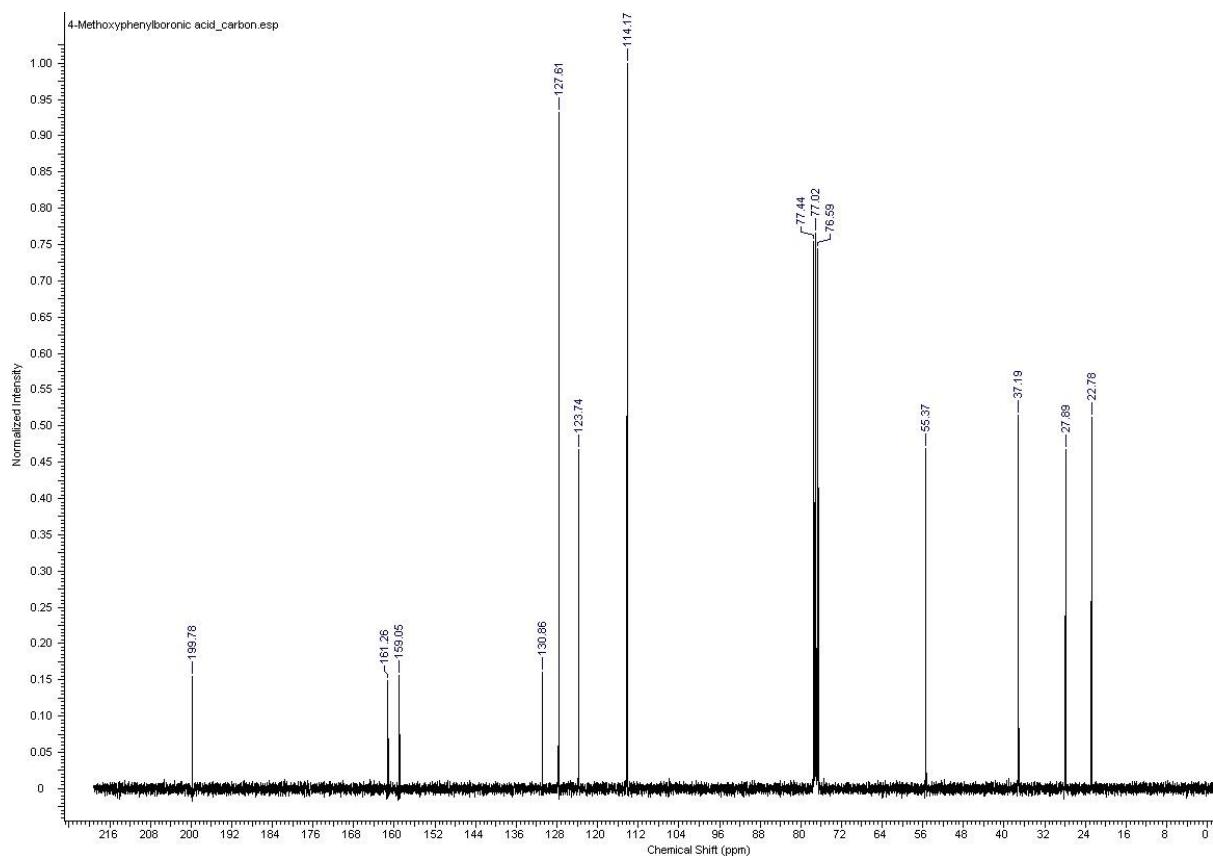
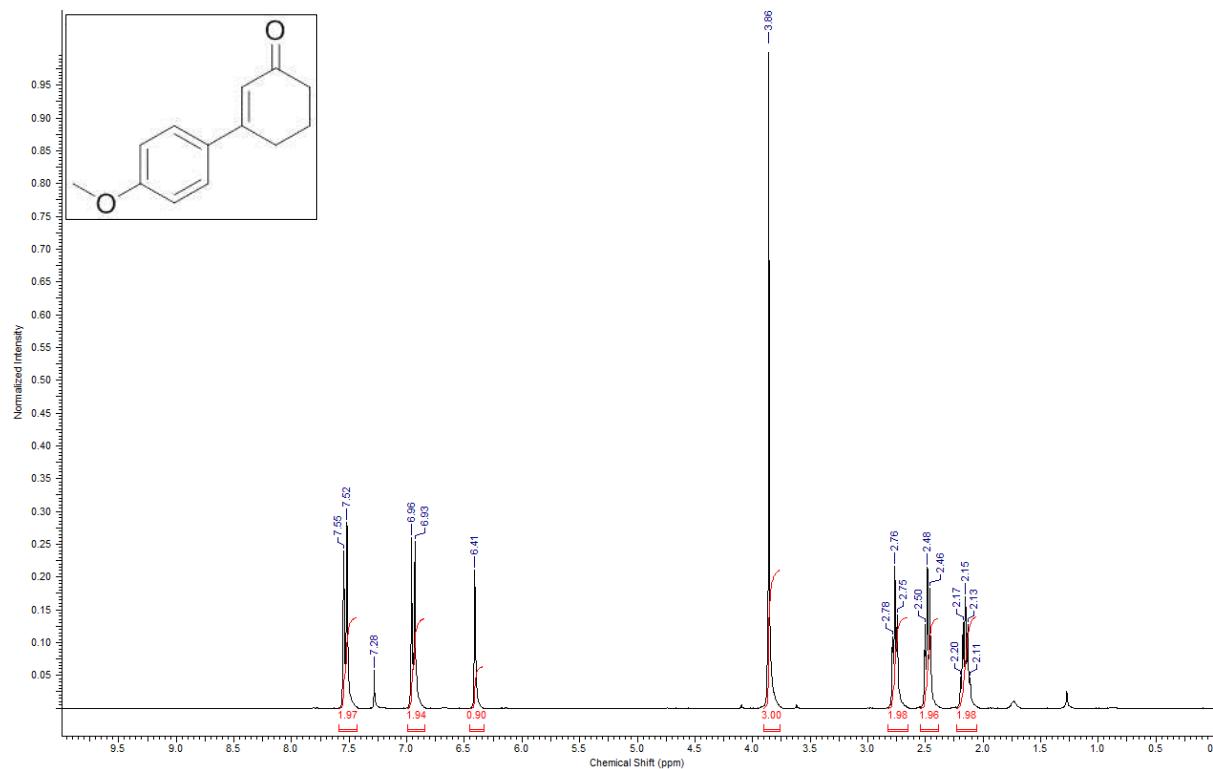
*biphenyl-3-yl cyclohexylcarbamate (3b).* The compound was isolated after column chromatography (EtOAc : hexane = 1 : 3) in 92% yield (1.12 g, white crystals (m.p.: 141-143 °C))

Experimental data were in accordance with those reported in the previous literature.<sup>7</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.51-7.04 (m, 9H), 4.86 (m, 1H), 3.52 (m, 1H), 1.97-1.13(m, 10H); <sup>13</sup>C NMR(150 MHz, CDCl<sub>3</sub>) δ 153.65, 151.48, 142.63, 140.42, 129.52, 128.75, 127.51, 127.22, 123.94, 120.41, 50.18, 33.31, 25.48, 24.78.

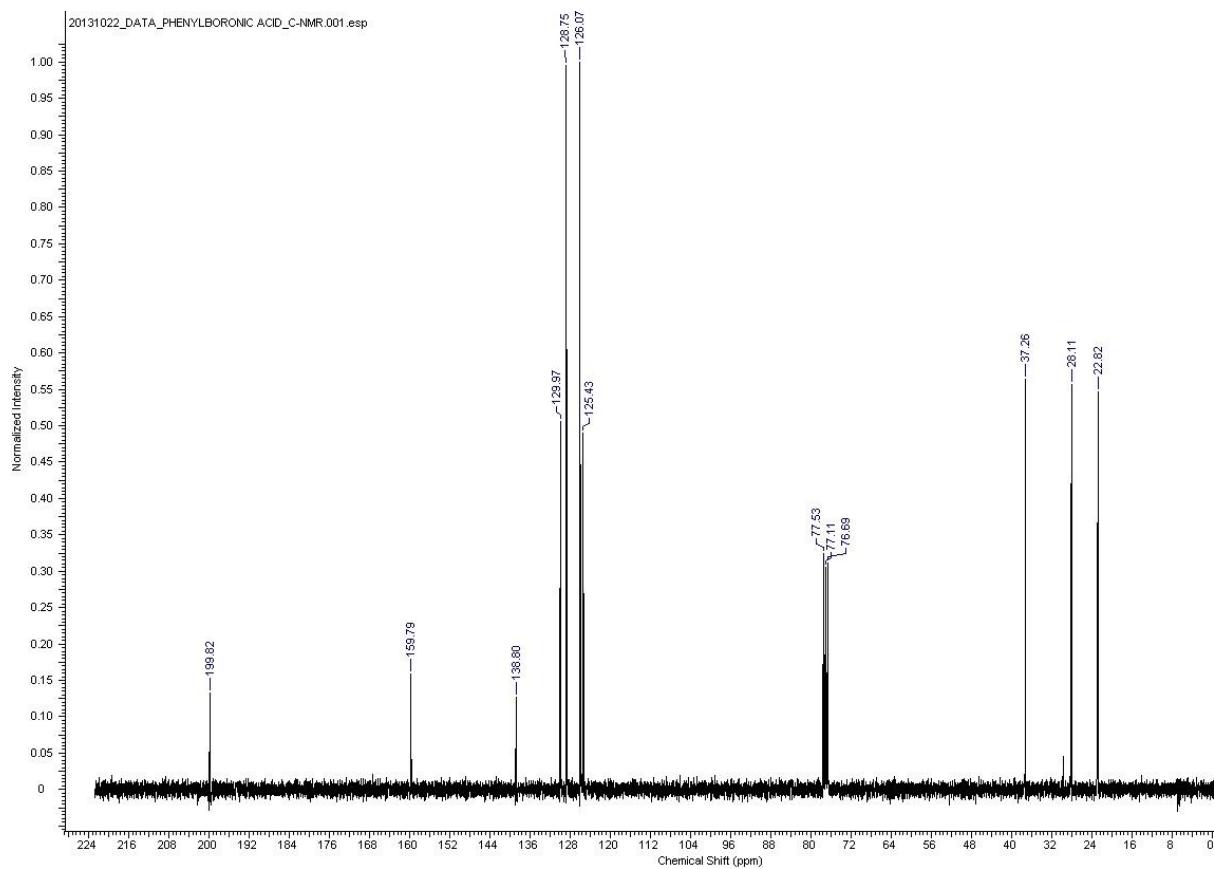
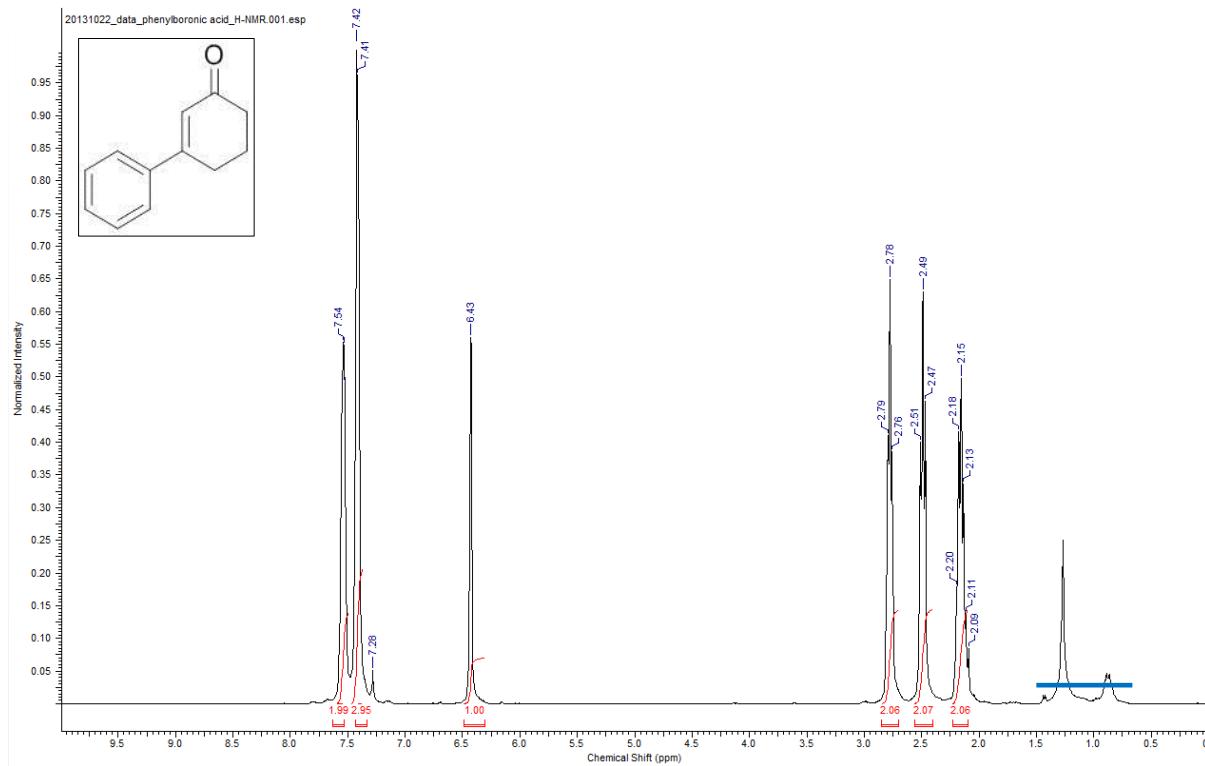
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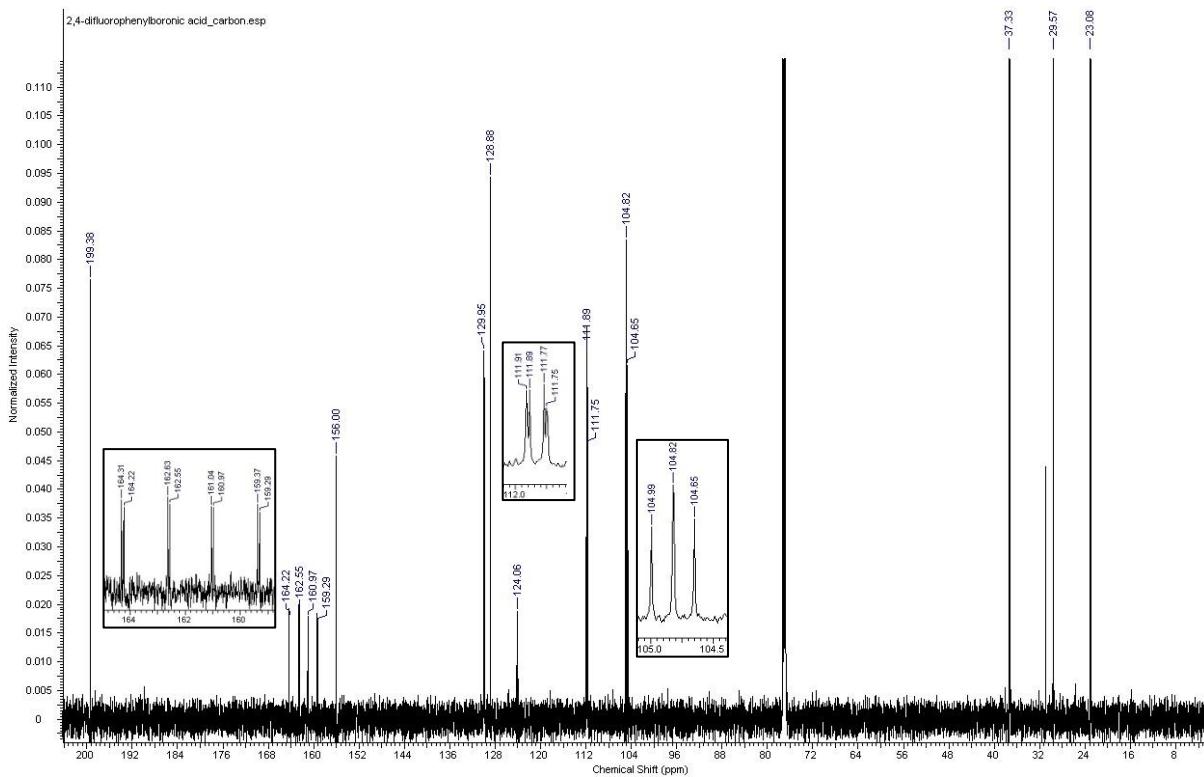
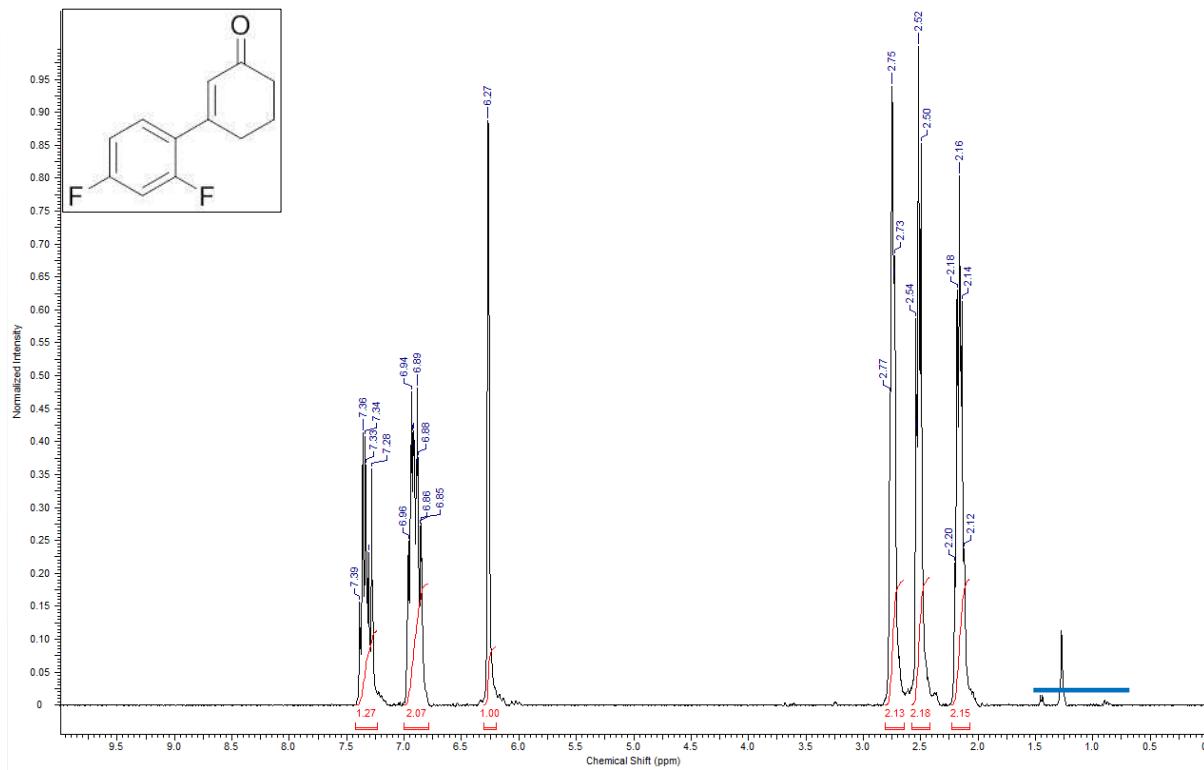
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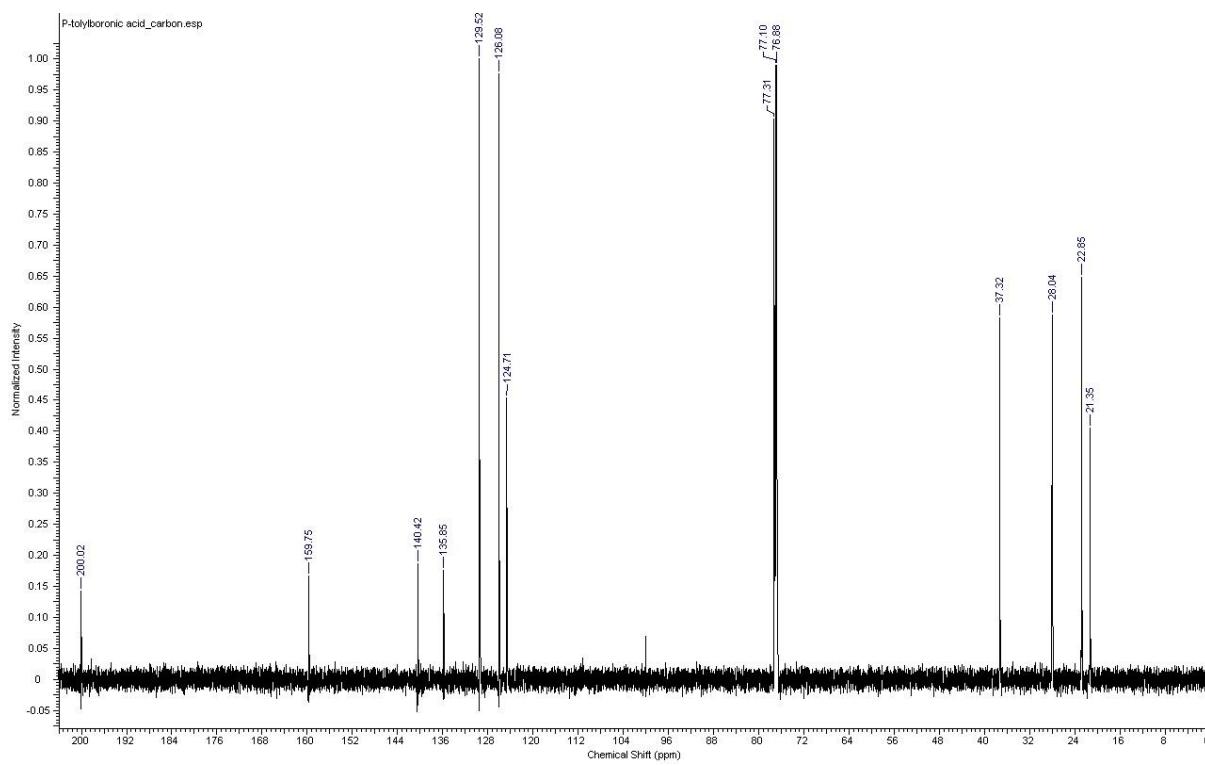
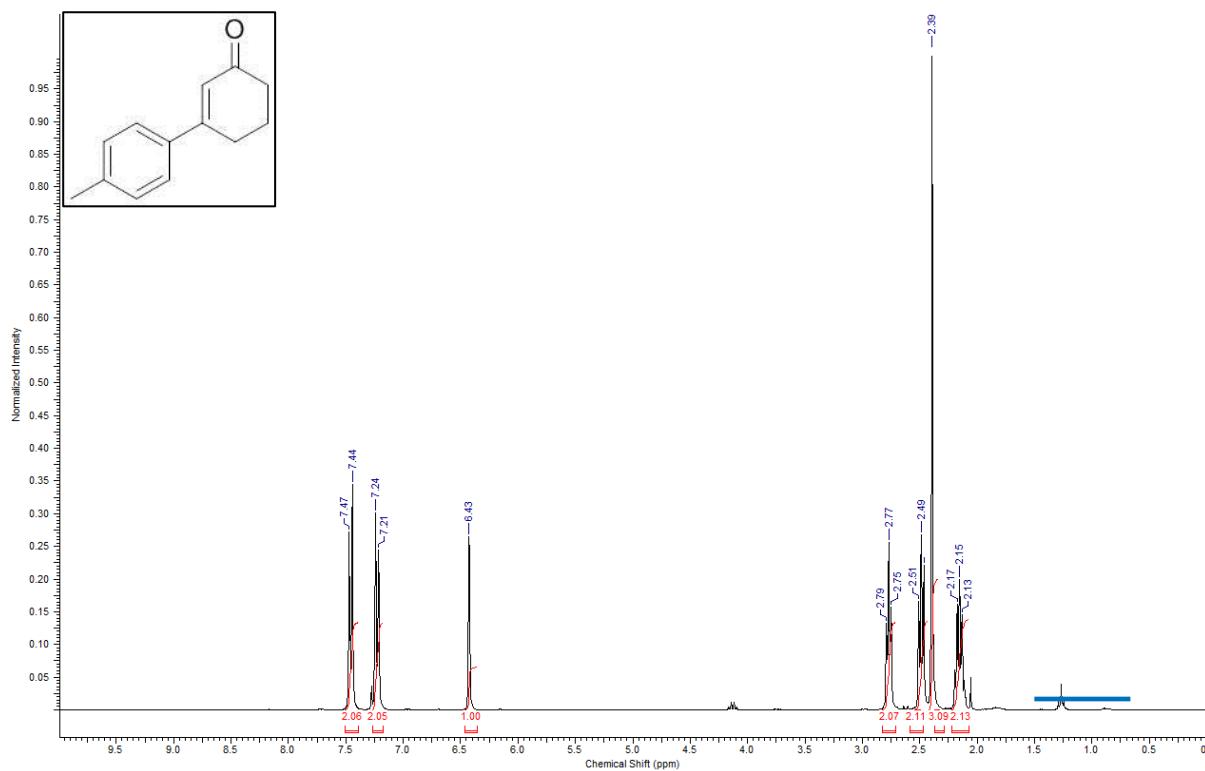
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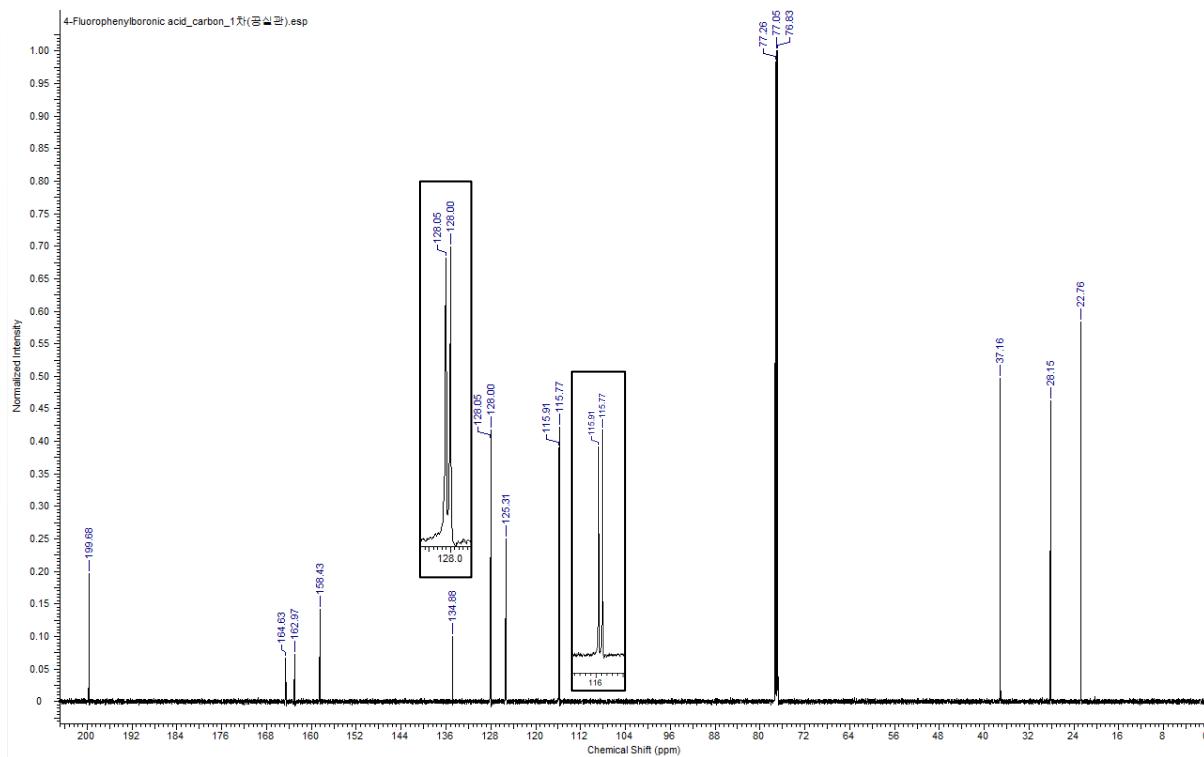
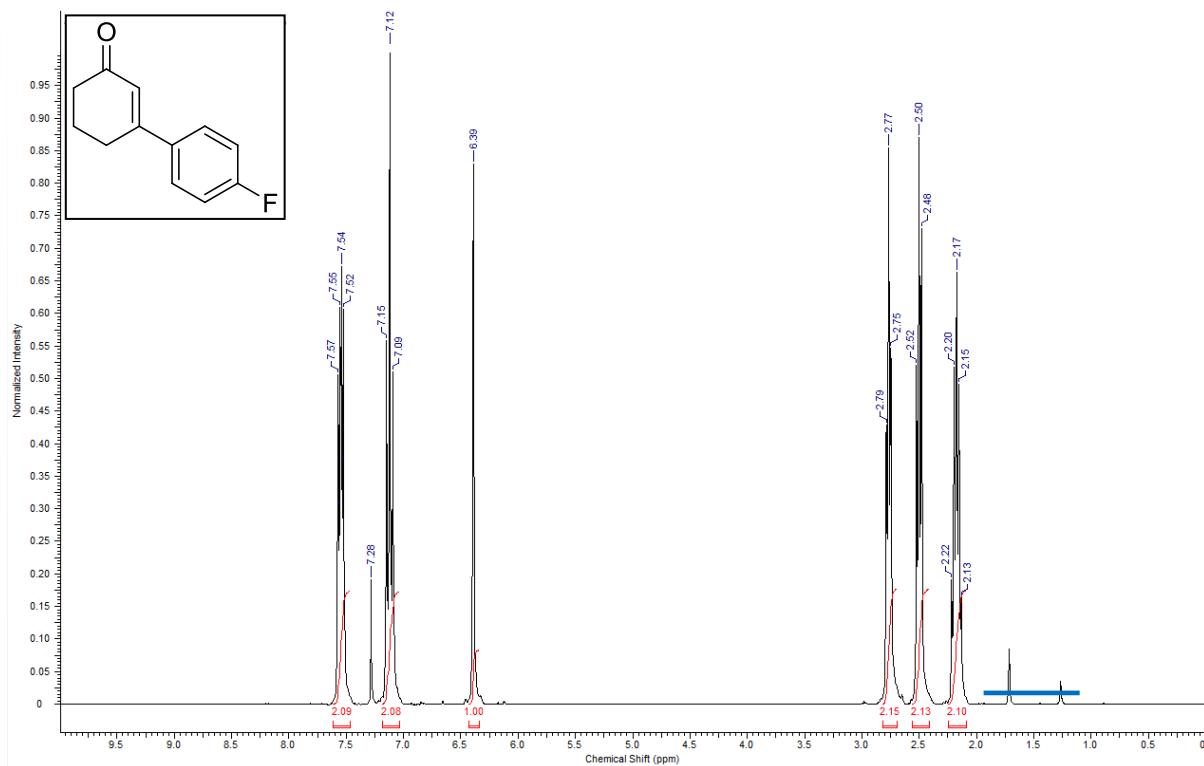
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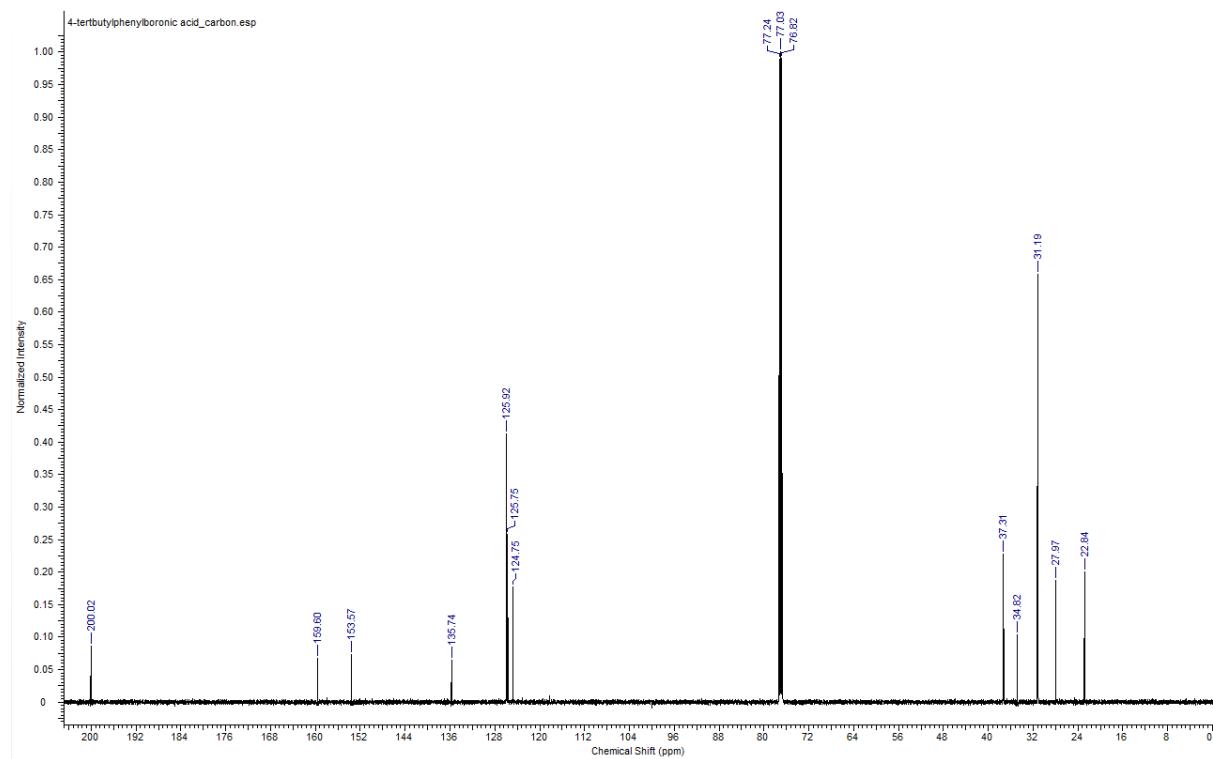
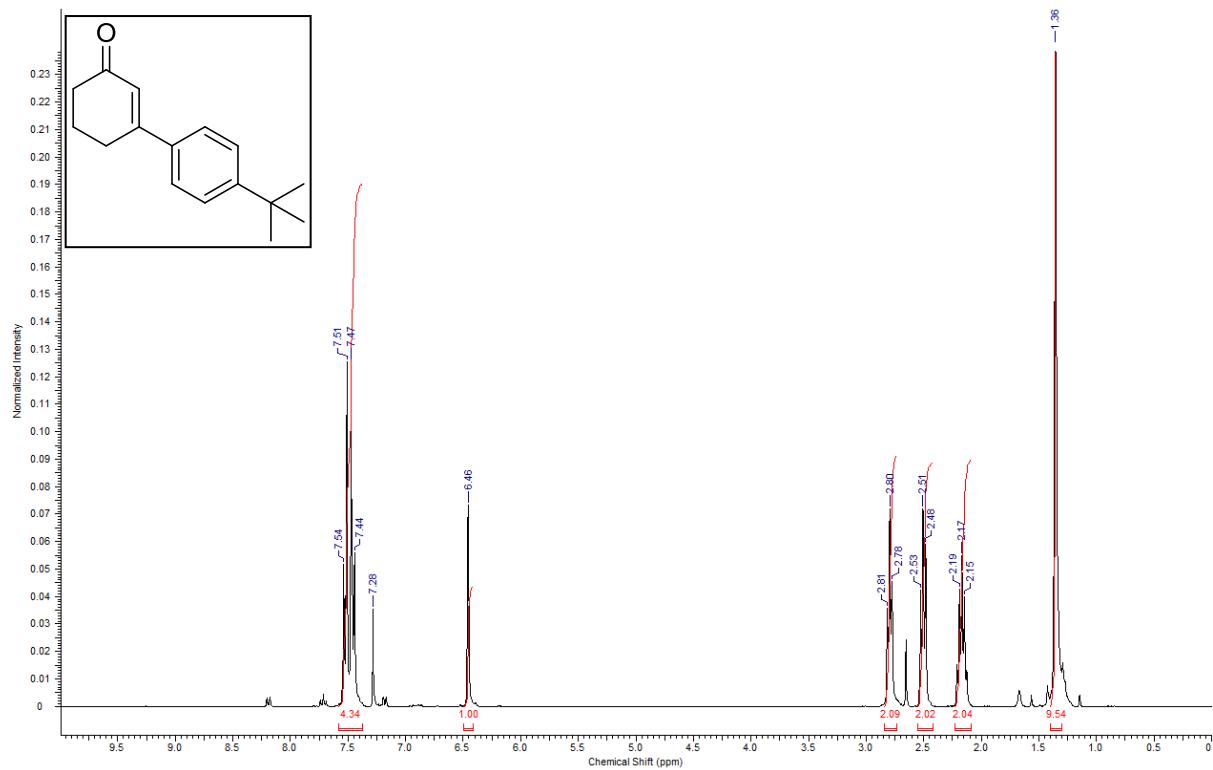
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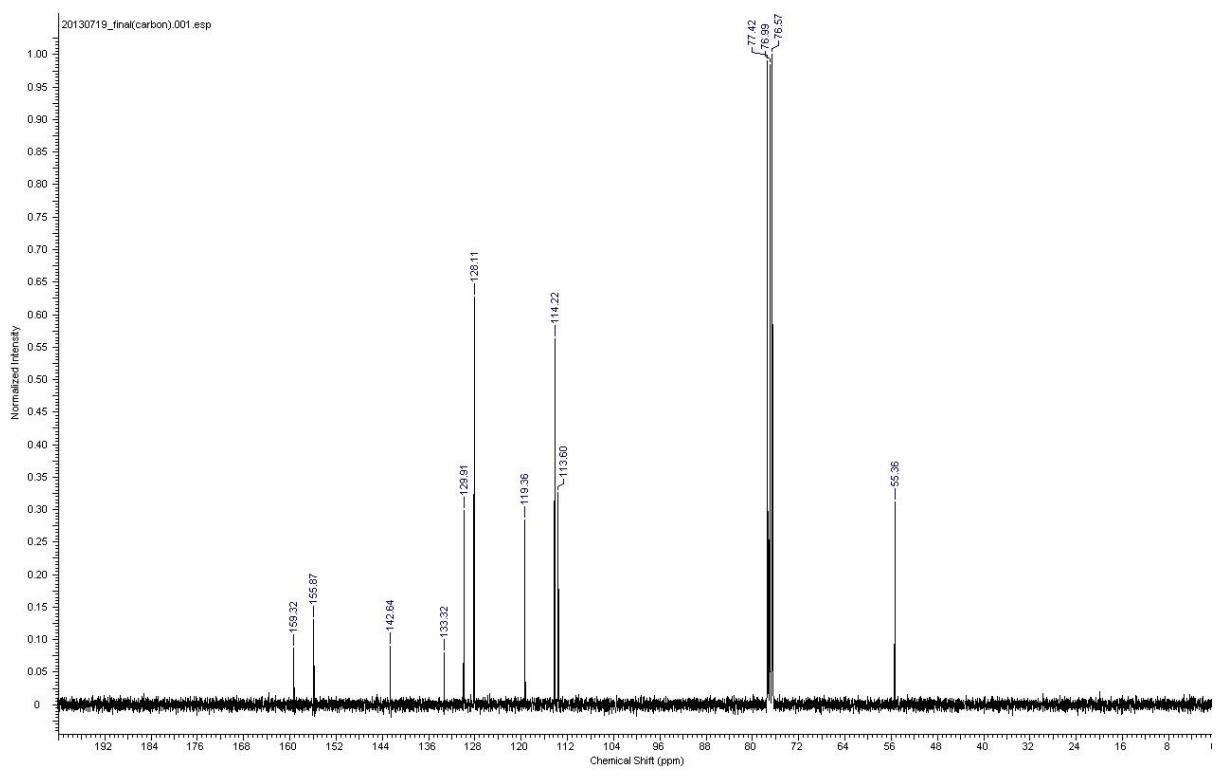
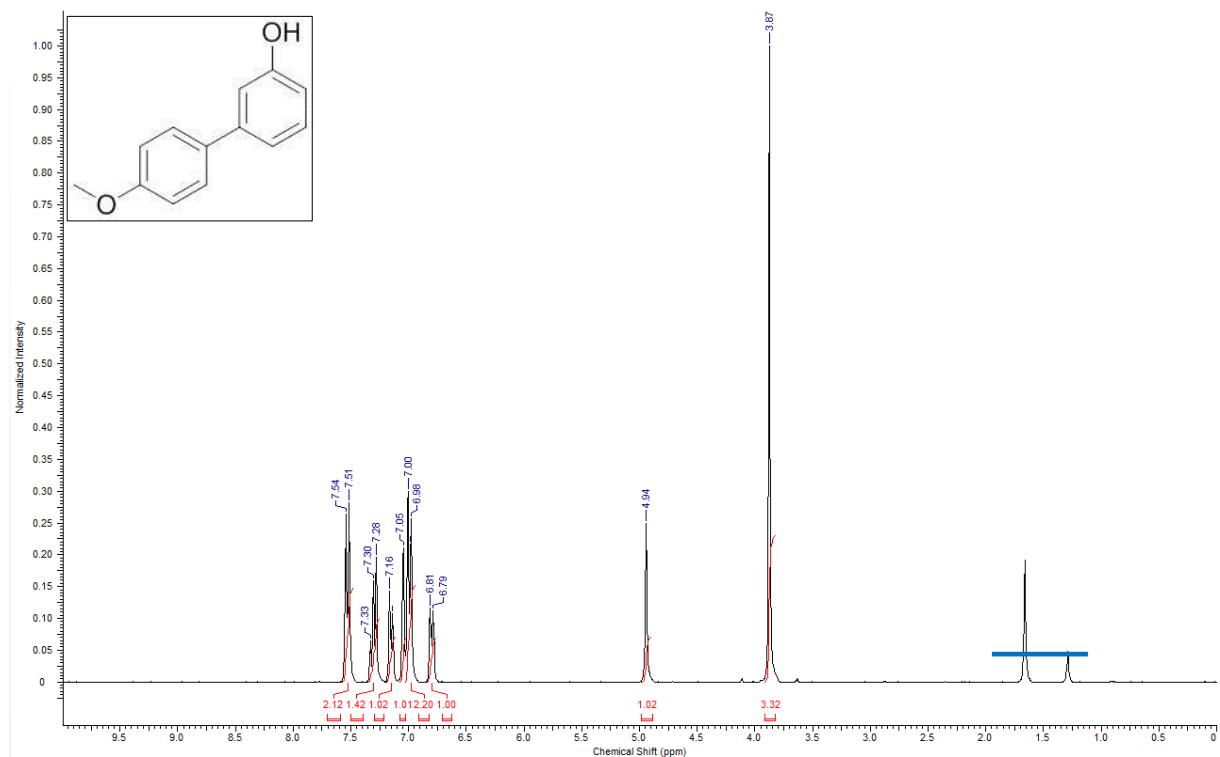
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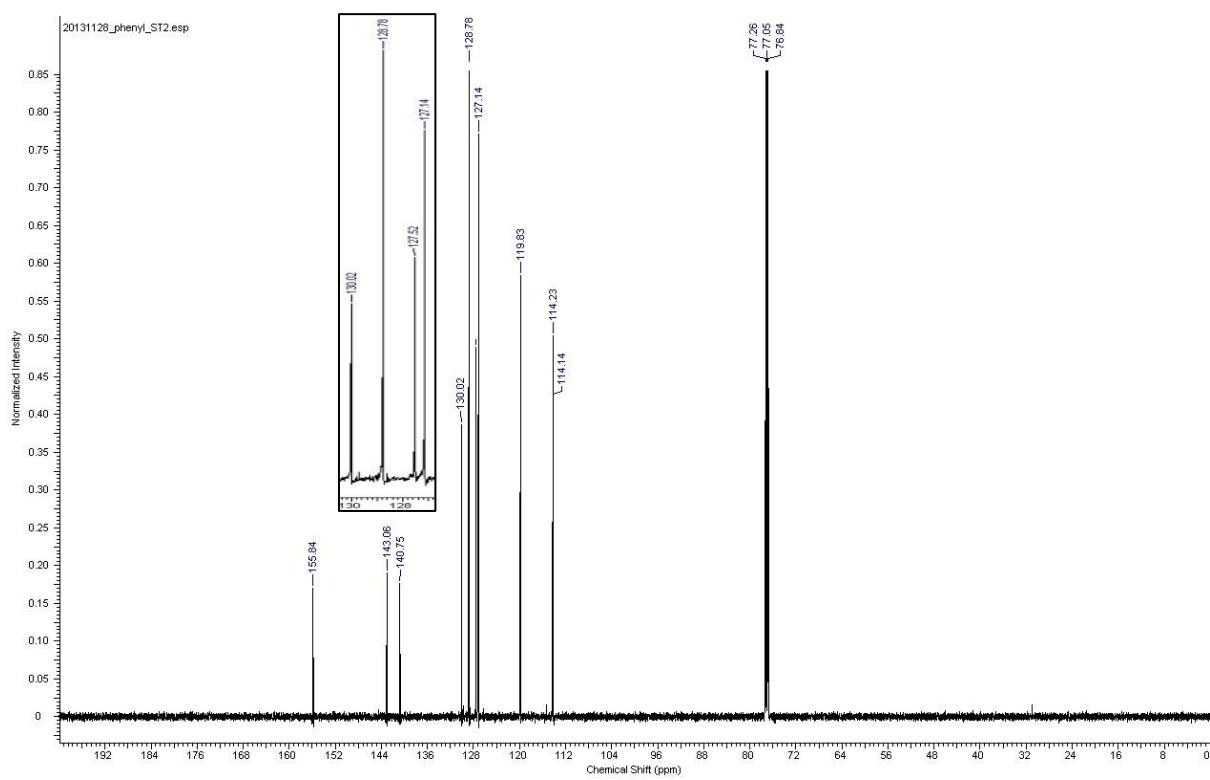
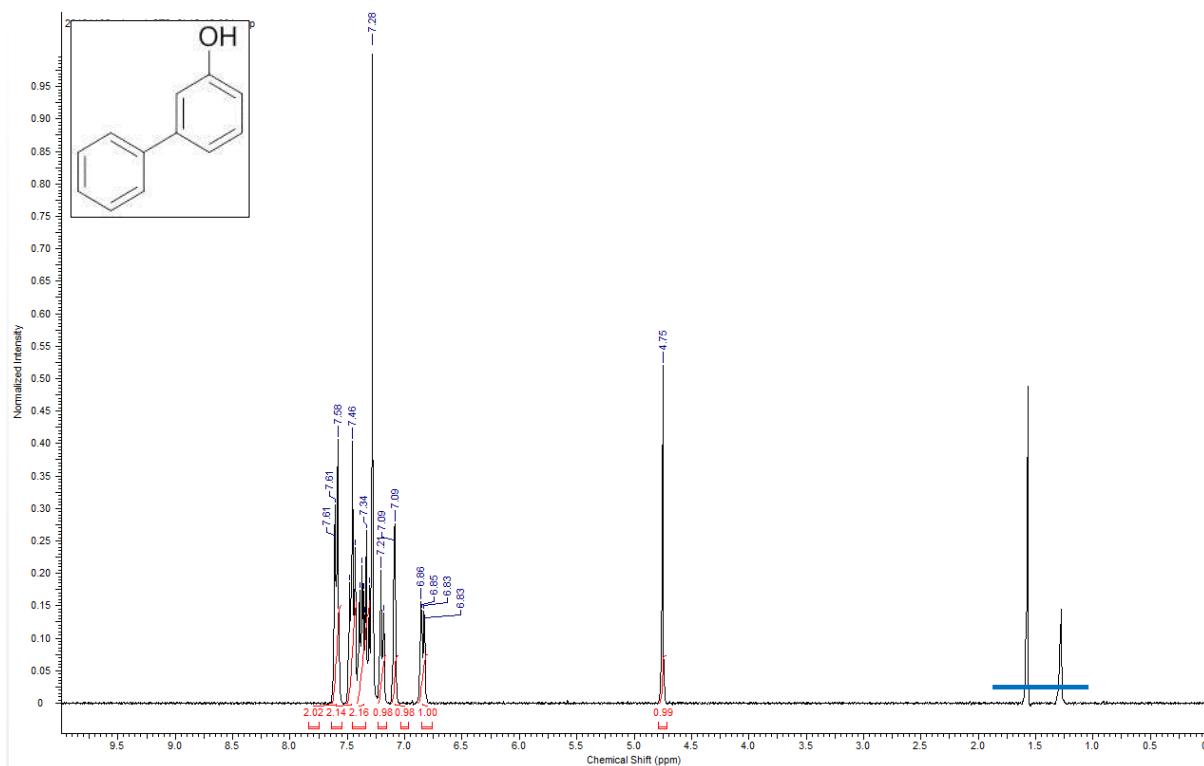
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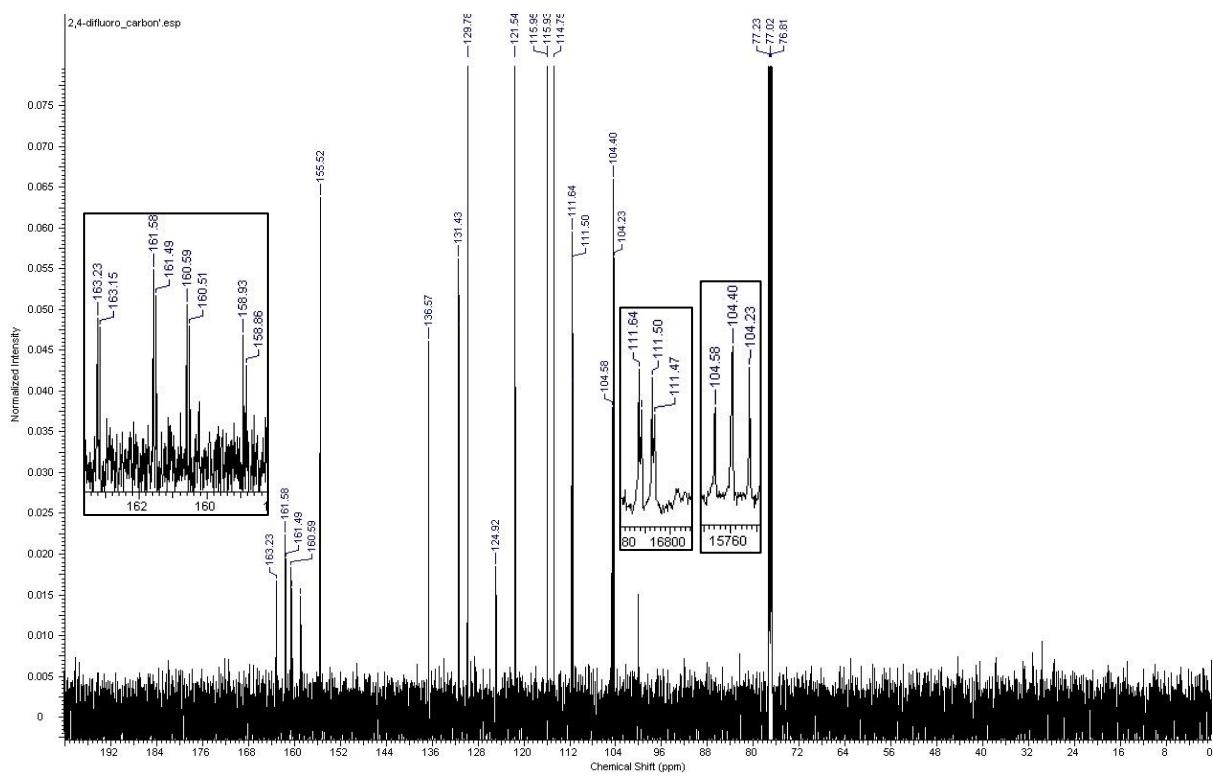
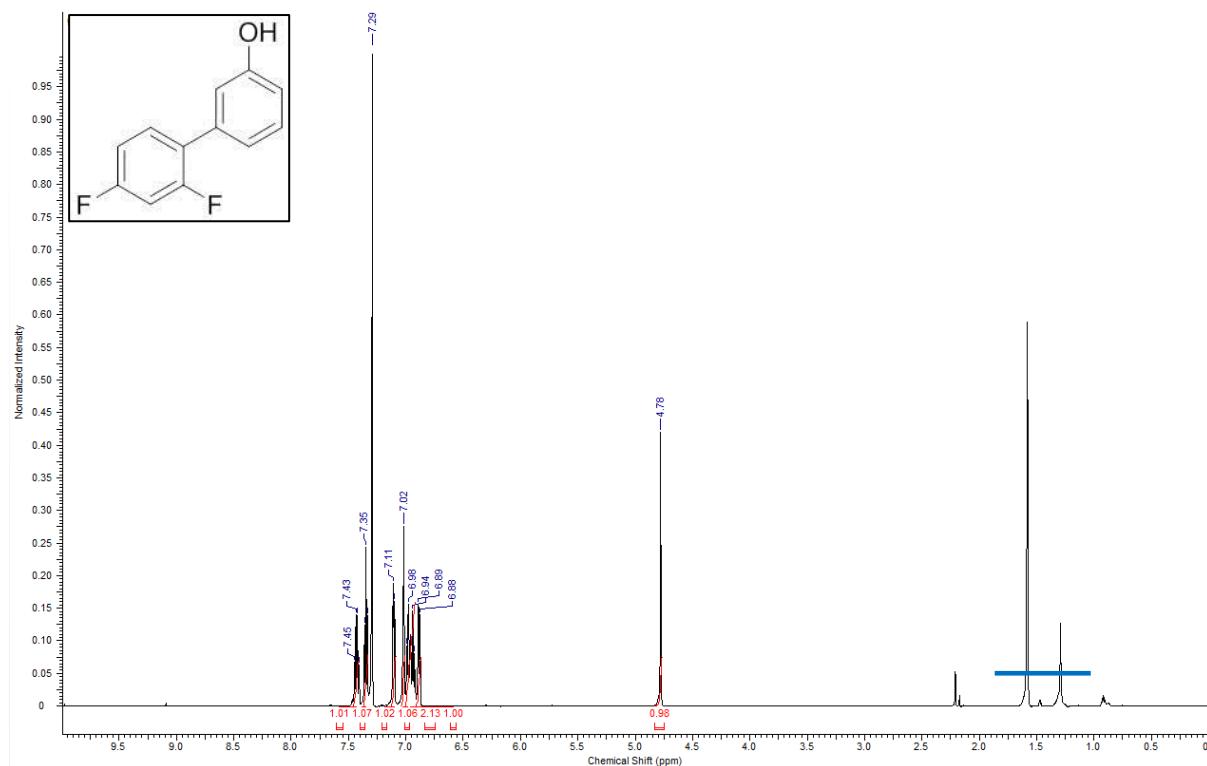
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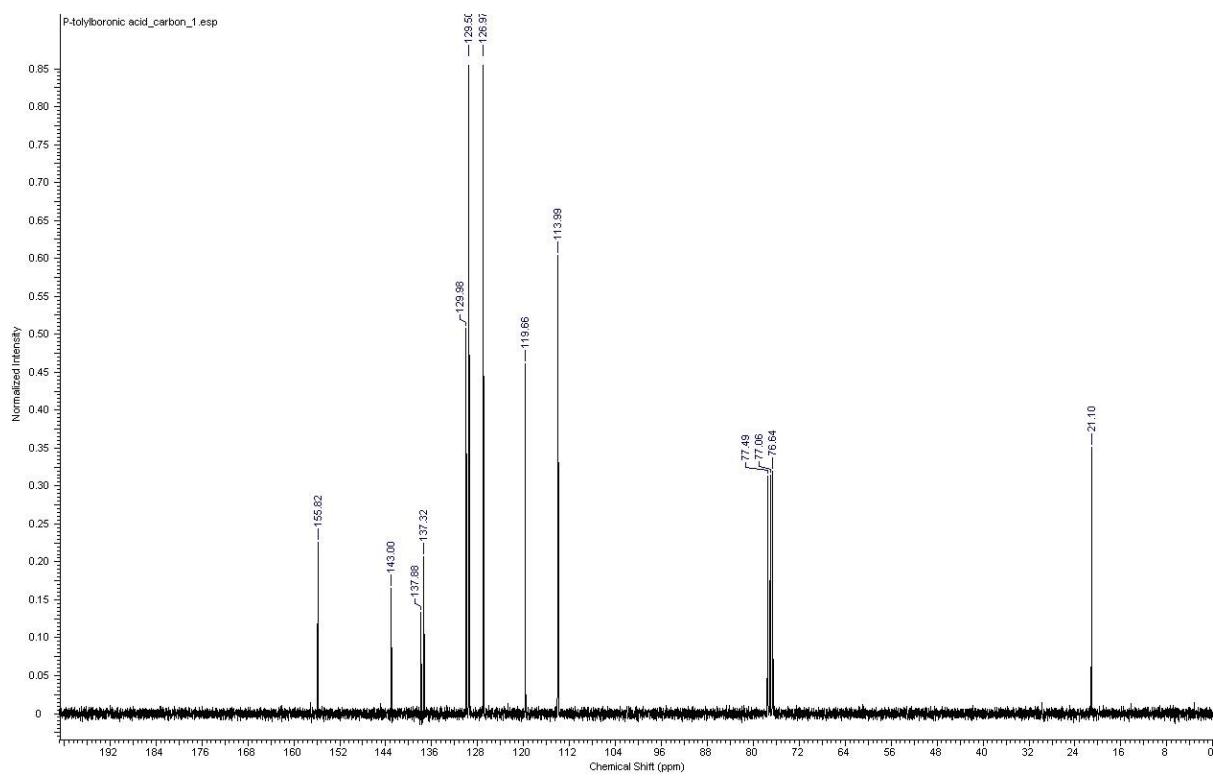
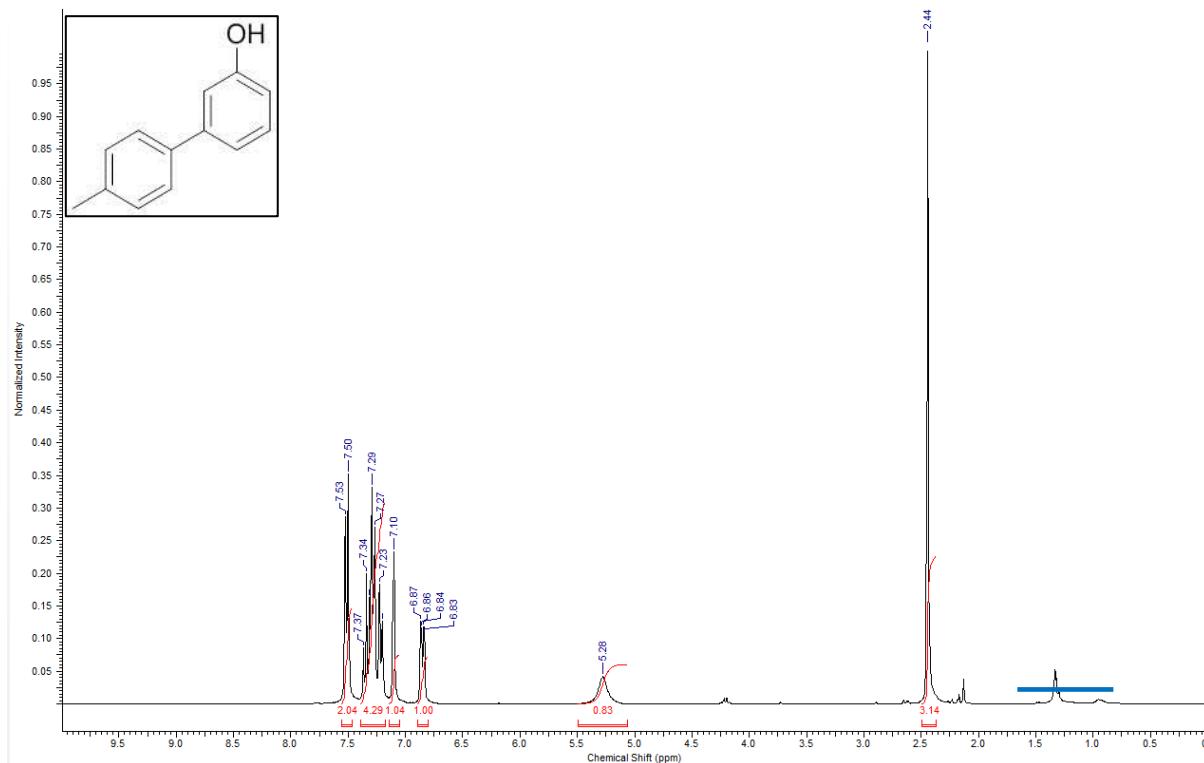
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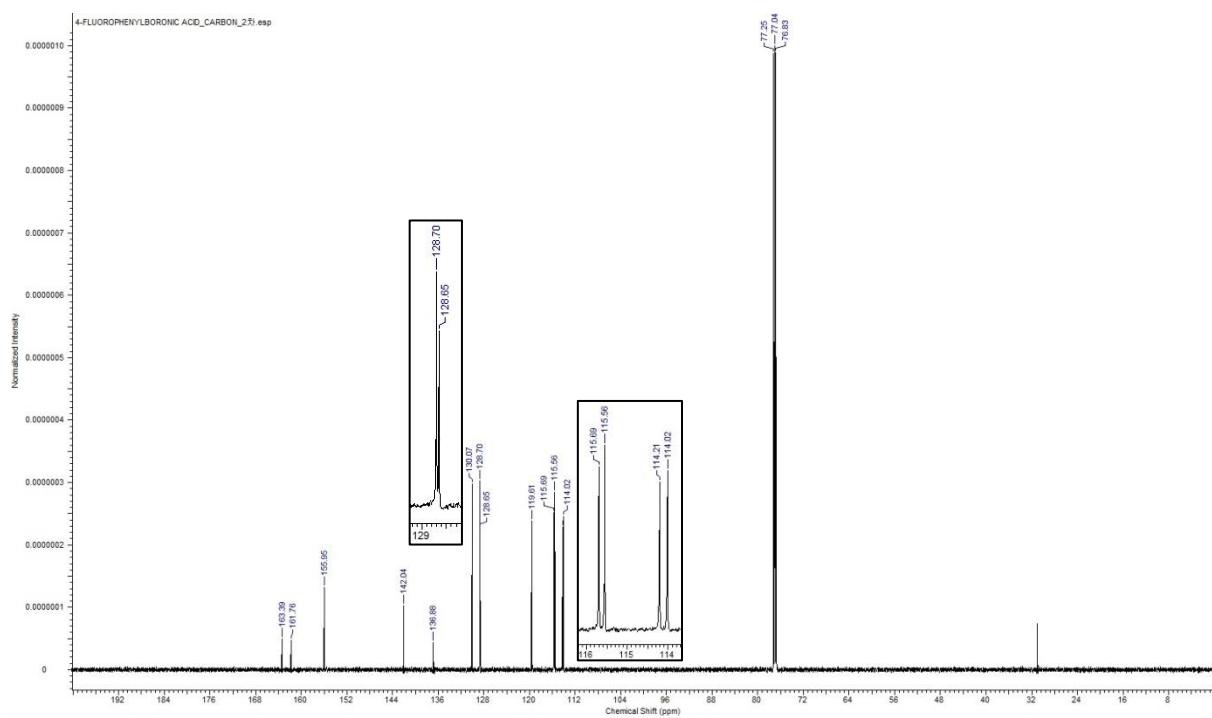
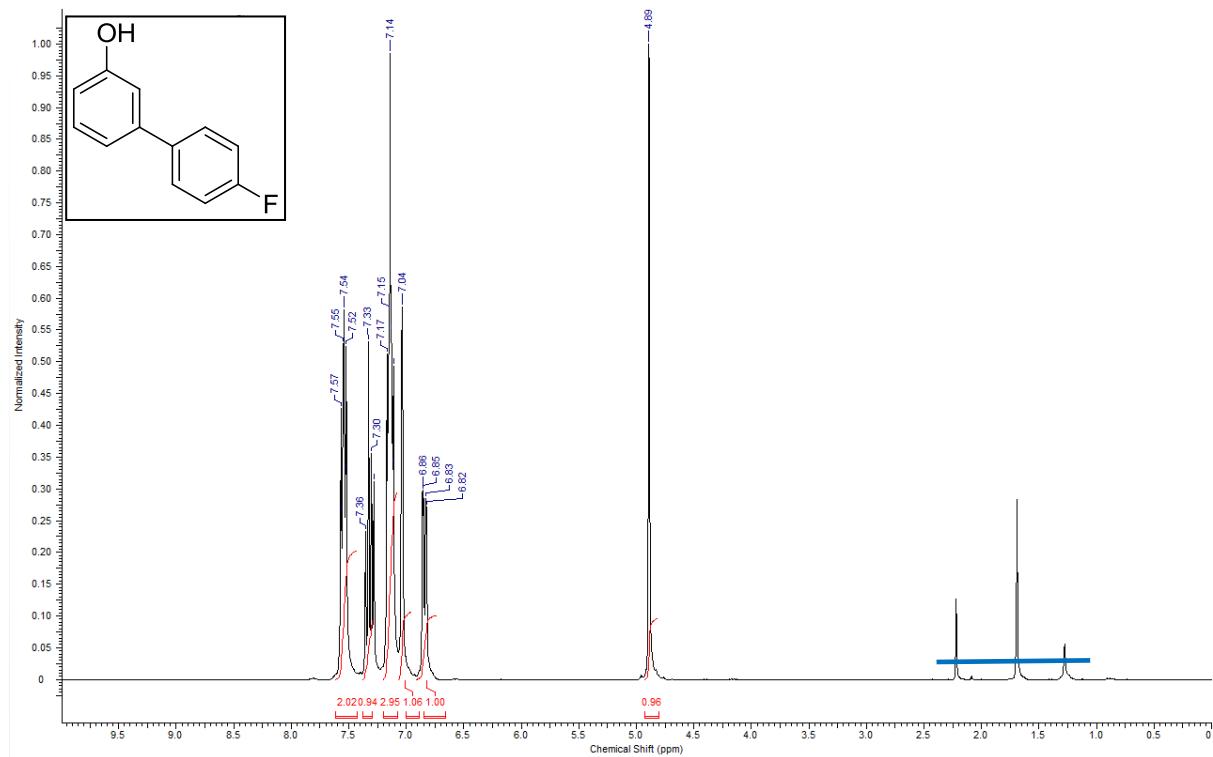
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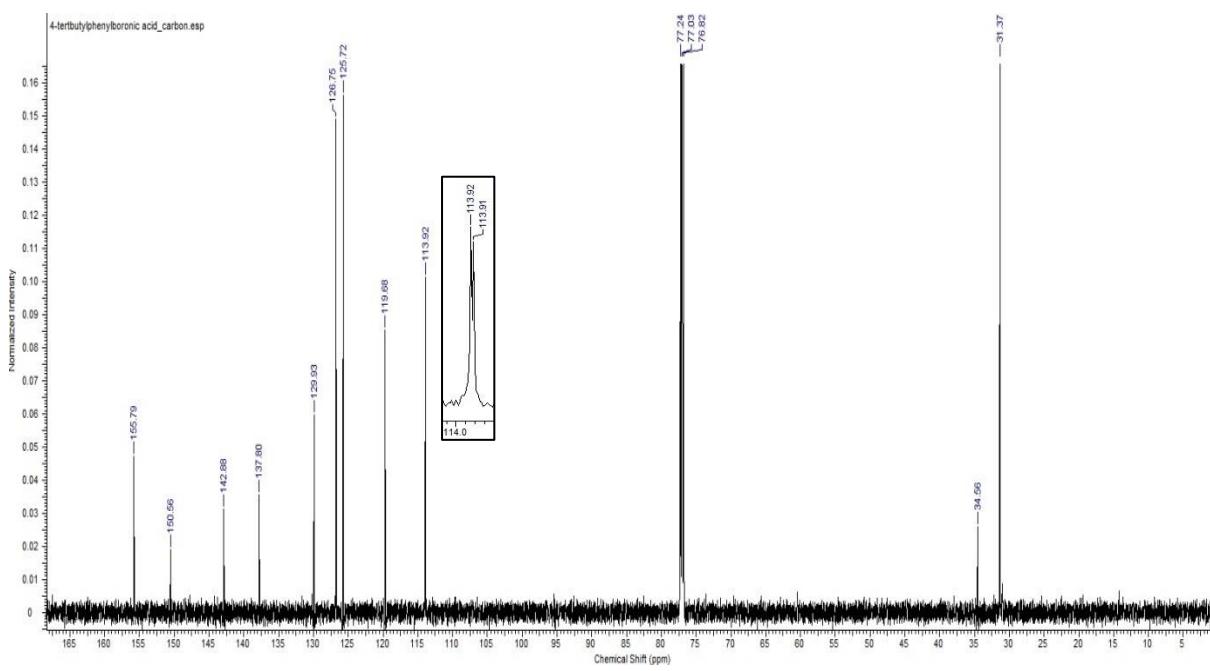
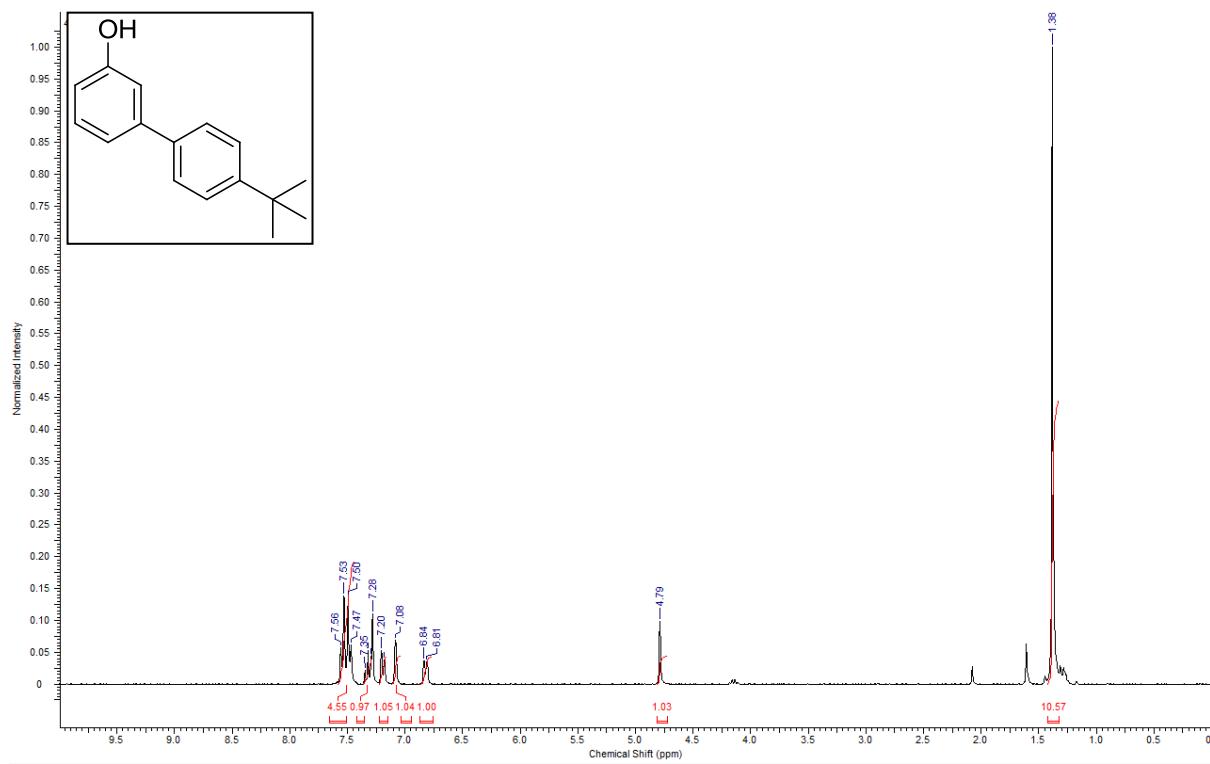
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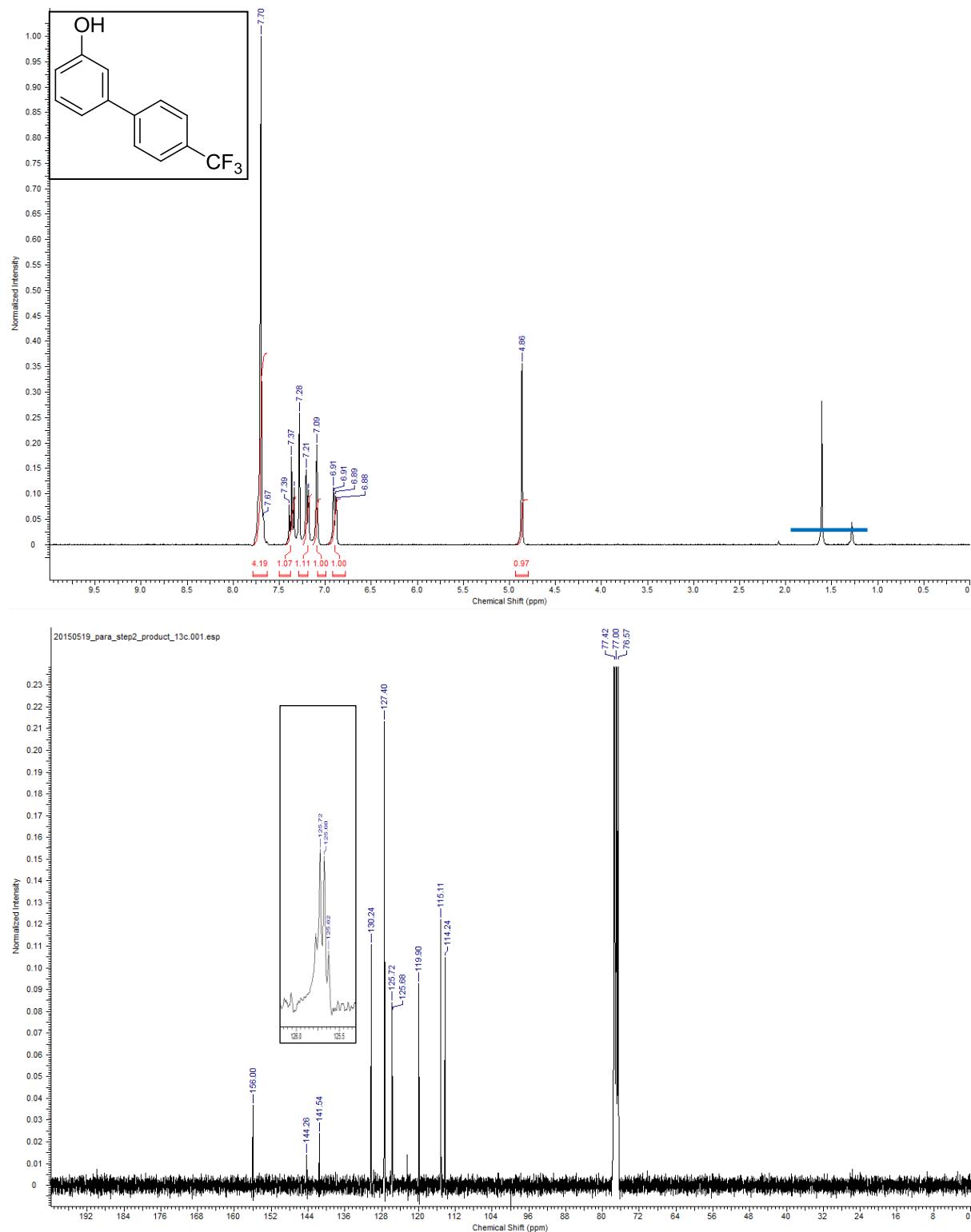
**Compound 2e**



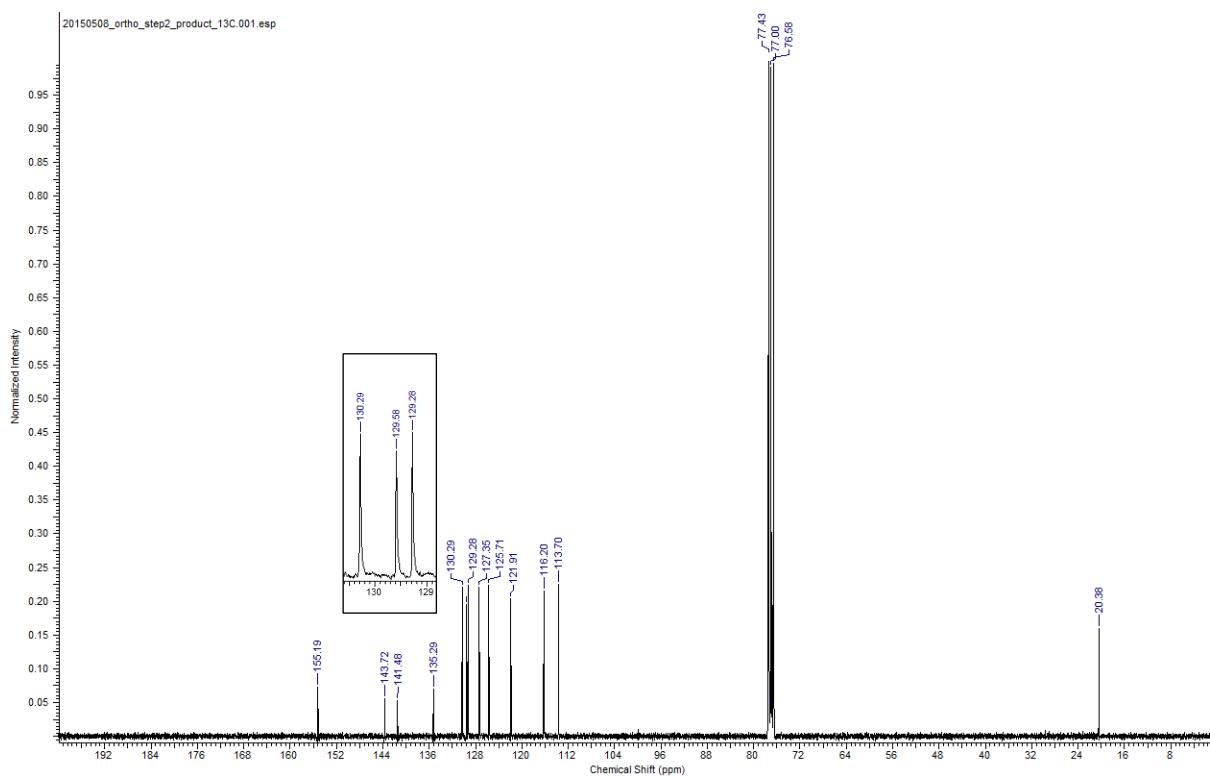
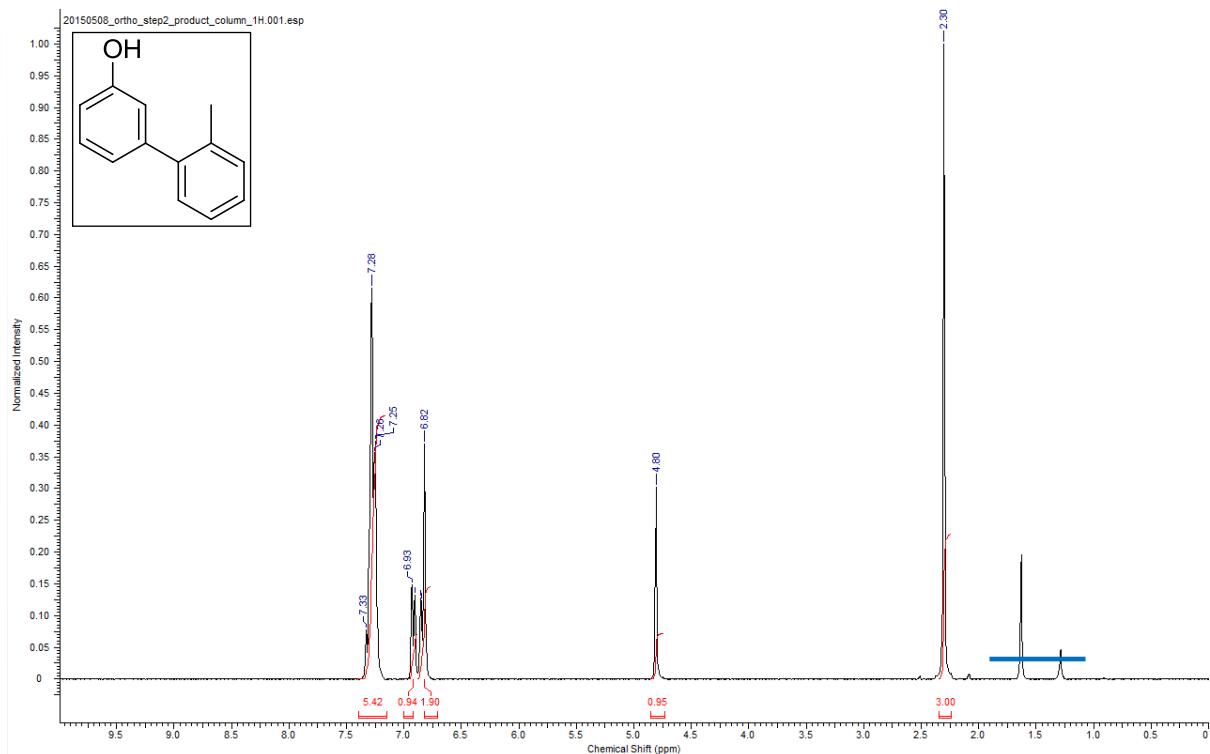
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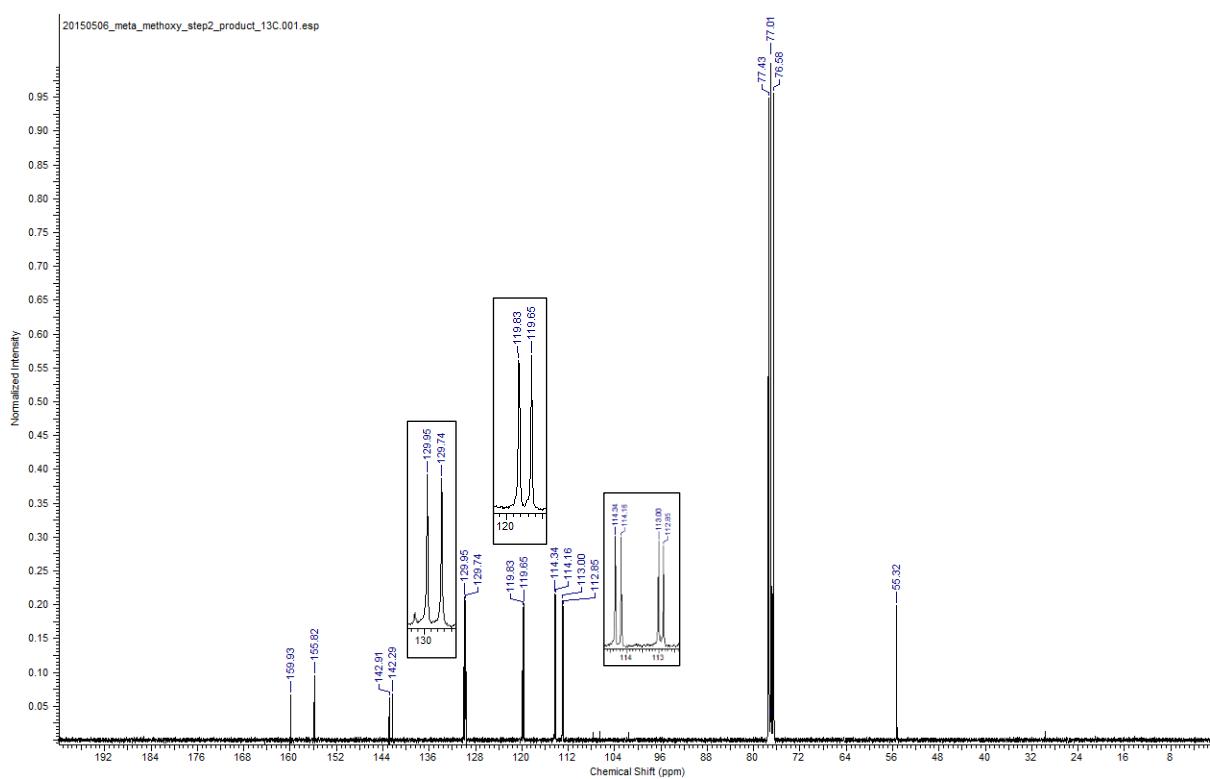
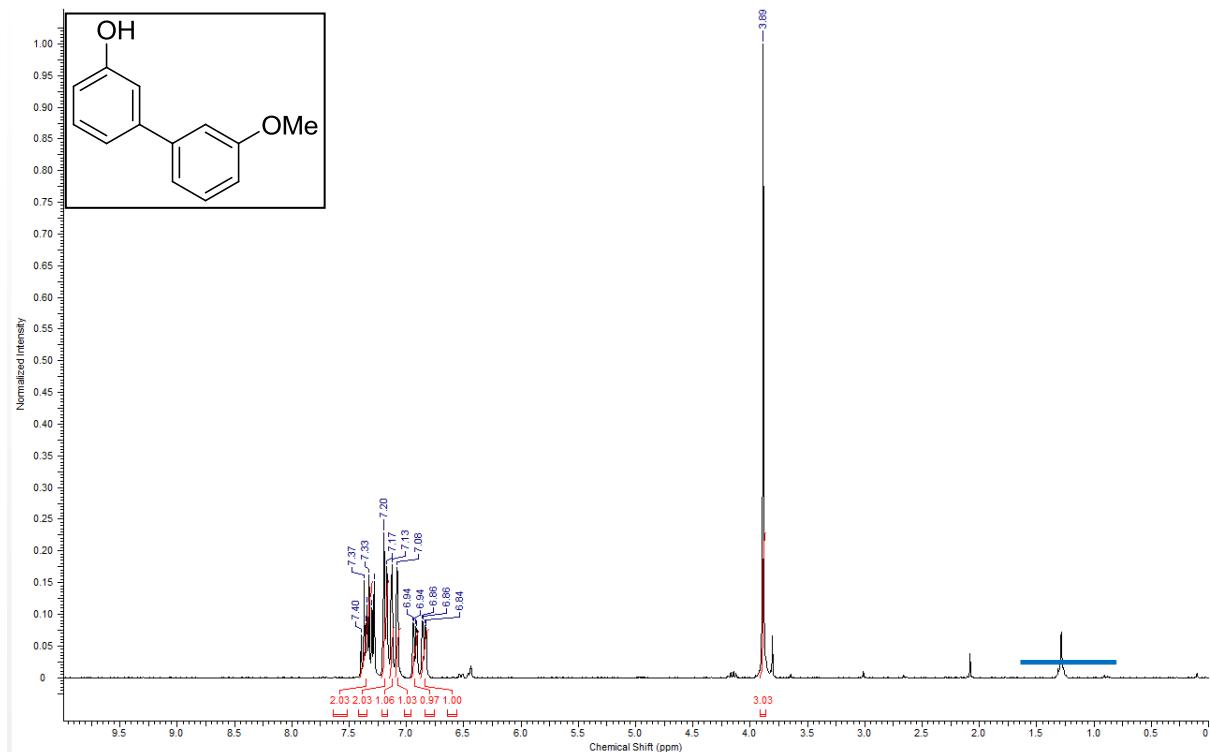
## Compound 2g.



## Compound 2h.



## Compound 2i.



## Compound 3b.

