Electronic Supplementary Information

Pd-catalyzed intermolecular C–H bond arylation reactions: effect of bulkiness of carboxylate ligands

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Contents

1. Instrumentation and Chemicals

All reactions were performed under an argon atmosphere using standard Schlenk-type glasswares on a dual-manifold Schlenk line. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECZ-400 spectrometer or a JEOL ECX-400P spectrometer. Chemical shift values (δ) are reported in ppm and calibrated to tetramethylsilane (TMS, 0.00 ppm) or residual protiated solvent (7.26 ppm in $CDCl_3$, 2.50 ppm in DMSO-d_6) for ^{1}H and to $CDCl_3$ (77.0 ppm) or DMSO-d_6 (39.5 ppm) for ^{13}C. High-resolution mass spectra were obtained with a Thermo Fischer Scientific EXACTIVE spectrometer for APCI-HRMS, a JEOL JMS-MS700 spectrometer for EI-HRMS, and a JEOL JMX-SX 102A spectrometer for ESI-HRMS. GC analysis was carried out using Shimadzu GC-17A with a capillary column (CBP-20, 0.25 mm i.d. × 25 m). TLC analysis was performed on commercial glass plates bearing a 0.25 mm layer of Merck Silica gel 60F254. Column chromatography was carried out on silica gel (Kanto, silica gel N60, spherical, neutral, 63–210 μm or Kanto silica gel 60, spherical, acidic, 63–210 μm) or alumina (Wako, alumina activated, basic, ca.75 μm).

Anhydrous THF, toluene and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. and further purified by passage through activated alumina under positive argon pressure as described by Grubbs *et al*.[1] DMA, NMP, TMU, DMI, **2a**, **2b**, **3a**, **3b**, **3c**, **3d** and **3e** were purified by distillation. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

2. Experimental Procedures

2.1. Typical procedure for the intermolecular C(sp^2)–H arylation reaction (Table 1)

To a 10-mL Schlenk flask were added Rb_2CO_3 (69 mg, 0.30 mmol), and it was dried by heating under vacuum for 15 min. The flask was backfilled with argon and $PdCl_2$ (1.8 mg, 0.010 mmol, 5.0 mol%) was added. Carboxylic acid (**1**, 0.060 mmol, 30 mol%) was added at this point if a solid. The flask was evacuated and backfilled with argon three times. Then, DMA (1.0 mL) and **3a** (1.0 mL) were added. Carboxylic acid (**1**, 0.060 mmol, 30 mol%) was added at this point if liquid. Then, **2a** (25 μL, 0.20 mmol) was added and the mixture was stirred at 70 °C for 40 h. The reaction mixture was analyzed by GC using tridecane (50 μL) as an internal standard.

2.2. General procedure for intermolecular C(sp^2)—H arylation (Table 2)

To a 10-mL Schlenk flask were added Rb_2CO_3 (69 mg, 0.30 mmol), and it was dried by heating under vacuum for 15 min. The flask was backfilled with argon and $PdCl_2$ (1.8

mg, 0.010 mmol, 5.0 mol%) and **1m** (14 mg, 0.060 mmol, 30 mol%) were added. The flask was evacuated and backfilled with argon three times. Then, DMA (1.0 mL) and **3** (1.0 mL) were added. Then substrate (**2**, 0.20 mmol) was added to the mixture. The resulting mixture was stirred for 40 h. After the reaction, 1 M HCl (5 mL) and EtOAc (5 mL) were added, and the mixture was extracted with EtOAc (5 mL × 3). The collected organic layer was combined and washed with brine (5 mL), dried over anhydrous $MgSO_4$. After removal of all volatiles, the residue was purified by flash column chromatography and alumina column chromatography using hexane/acetone as an eluent.

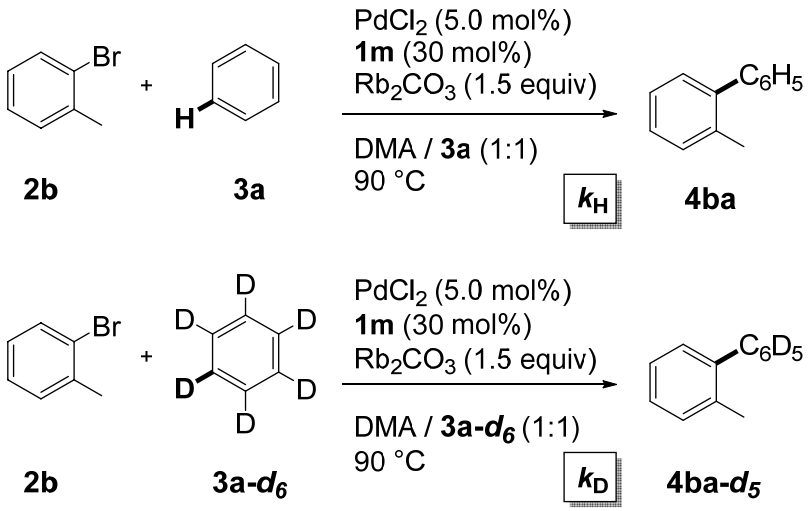
2.3. Experimental procedure for KIE (Scheme 1, Figure S1)

To a 10-mL Schlenk flask were added Rb_2CO_3 (69 mg, 0.30 mmol), and it was dried by heating under vacuum for 15 min. The flask was backfilled with argon and $PdCl_2$ (1.8 mg, 0.010 mmol, 5.0 mol%) and **1m** (14 mg, 0.060 mmol, 30 mol%) were added. The flask was evacuated and backfilled with argon three times. Then, DMA (1.0 mL) and benzene (**3a**, 1.0 mL) were added. Then tetradecane (50 μL) as an internal standard and **2b** (24 μL, 0.20 mmol) were added to the mixture. The resulting mixture was stirred at 90 °C. An aliquot of sample was taken out every 1 hour using 100 μL air-tight syringe and these samples were analysed by GC.

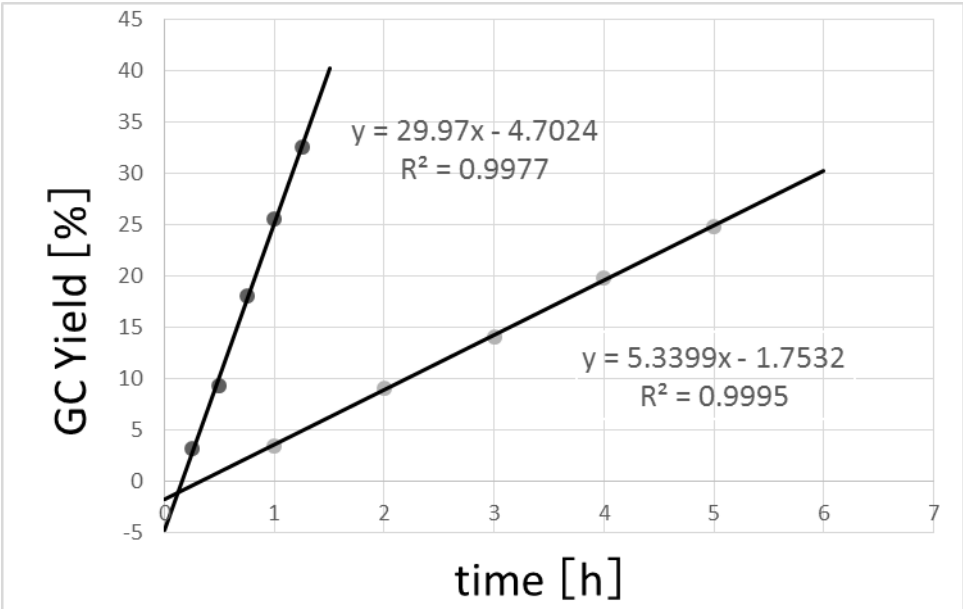
2.4. Typical procedure intramolecular C(sp^2)–H arylation reaction (Scheme 2(a))

To a 10-mL Schlenk flask was added Rb_2CO_3 (69 mg, 0.30 mmol), and it was dried by heating under vacuum for 15 min. The flask was backfilled with argon and $PdCl_2$ (1.77 mg, 0.010 mmol, 5.0 mol%) and carboxylic acid (**1**, 0.060 mmol, 30 mol%) were added. The flask was evacuated and backfilled with argon three times. Then, DMI (0.50 mL) was added and the mixture was stirred at 60 °C for 15 min. After cooling to room temperature, **5** (53mg, 0.20 mmol) was added and the mixture was stirred at 25 °C for 24 h. The reaction mixture was analysed by GC using tetradecane (50 μL) as an internal standard.

Figure S1. Kinetic Isotope Effect



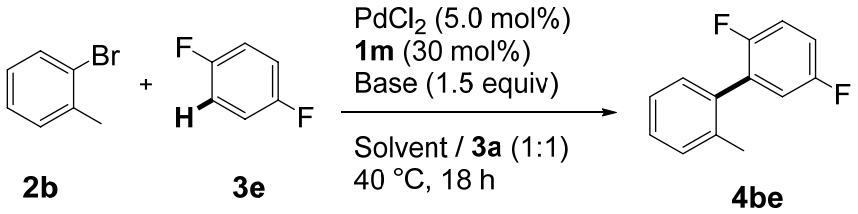
k_H / k_D = 5.61



2.5. Typical procedure for screening of solvents and bases on the intermolecular C(sp^2)–H arylation reaction (Table S1)

To a 10-mL Schlenk flask were added base (0.30 mmol), and it was dried by heating under vacuum for 15 min. The flask was backfilled with argon and $PdCl_2$ (1.8 mg, 0.010 mmol, 5.0 mol%) was added. **1m** (14 mg, 0.060 mmol, 30 mol%) was added. The flask was evacuated and backfilled with argon three times. Then, solvent (1.0 mL), **3e** (1.0 mL) and **2b** (25 μL, 0.20 mmol) were added and the mixture was stirred at 40 °C for 18 h. The reaction mixture was analysed by GC using tridecane (50 μL) as an internal standard.

Table S1. Effect of solvents and bases on the Pd-catalyzed intermolecular C(sp^2)–H arylation reaction using **2b** and **3a**[a]



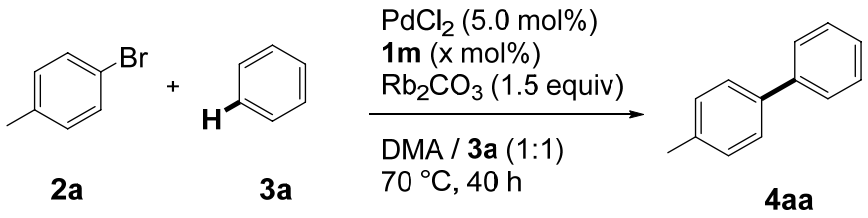
Entry	Solvent	Base	Yield of **4be** (%)[b]
1	DMA	Rb_2CO_3	92
2	DMI	Rb_2CO_3	1
3	DMF	Rb_2CO_3	81
4	NMP	Rb_2CO_3	84
5	THF	Rb_2CO_3	2
6	DMA	Li_2CO_3	0
7	DMA	Na_2CO_3	1
8	DMA	K_2CO_3	30
9	DMA	Cs_2CO_3	88
10	DMA	K_3PO_4	61

[a] Conditions: **2b** (0.20 mmol), **3e** (1.0 mL), $PdCl_2$ (0.010 mmol, 5.0 mol%), **1m** (0.060 mmol, 30 mol%), base (0.30 mmol, 1.5 equiv), solvent (1.0 mL), 40 °C, 18 h. [b] Determined by GC.

2.6. Typical procedure for screening of loading of carboxylic acid on the intermolecular C(sp^2)–H arylation reaction (Table S2)

To a 10-mL Schlenk flask were added Rb_2CO_3 (69 mg, 0.30 mmol), and it was dried by heating under vacuum for 15 min. The flask was backfilled with argon and $PdCl_2$ (1.8 mg, 0.010 mmol, 5.0 mol%) and **1m** were added. The flask was evacuated and backfilled with argon three times. Then, DMA (1.0 mL), benzene (**3a**, 1.0 mL) and **2a** (25 μL, 0.20 mmol) was added and the mixture was stirred at 70 °C for 40 h. The reaction mixture was analyzed by GC using tridecane (50 μL) as an internal standard.

Table S2. Effect of loading of carboxylic acid on the Pd-catalyzed intermolecular C(sp^2)–H arylation reaction[a]



Entry	x (mol%)	Yield of **4aa** (%)[b]
1	30	72
2	20	75
3	10	73
4	7.5	53
5	5.0	47

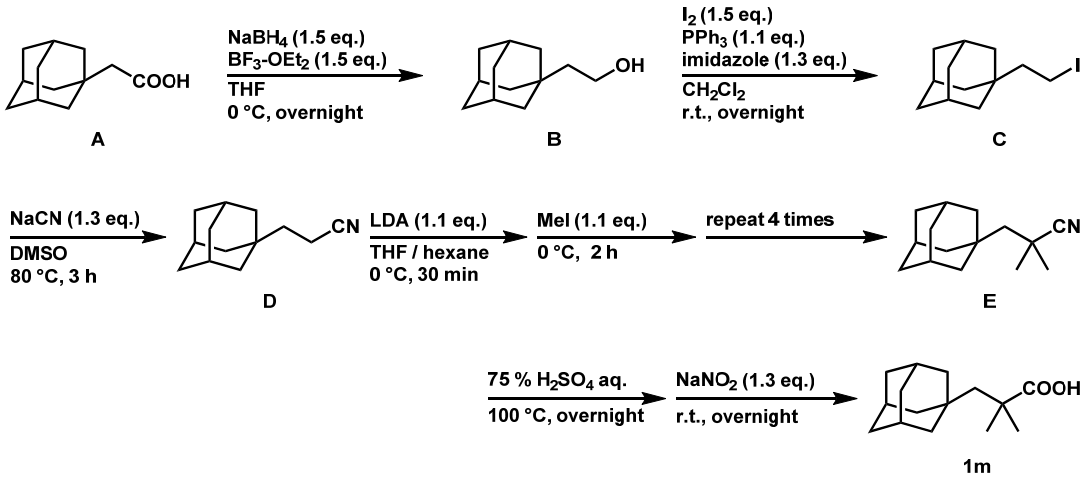
[a] Conditions: **2a** (0.20 mmol), **3a** (1.0 mL), $PdCl_2$ (0.010 mmol, 5.0 mol %), **1m** (x mol%), Rb_2CO_3 (0.30 mmol, 1.5 equiv), DMA (1.0 mL), 40 °C, 18 h. [b] Determined by GC.

3. Preparation of Carboxylic Acids

Carboxylic acids **1a**, **1c**, **1d**, **1e**, **1f** and **1g** were purchased from Wako Chemicals. Carboxylic acids **1b**[2], **1h**[3] and **1k**[3] were prepared according to modified literature methods.

3.1. Preparation of Carboxylic Acids

Preparation of 3-(1-adamantyl)-3-methylbutanoic acid (1m)



To a solution of 1-adamantaneacetic acid (**A**, 19.4 g, 100 mmol) in THF (250 mL) was added $NaBH_4$ (5.71 g, 150 mmol) on an ice-water bath. The mixture was stirred for 15 min. Then, BF_3-OEt_2 (28.5 mL, 150 mmol) was added and the resulting mixture was further stirred for 16 h at room temperature. Then, the mixture was carefully diluted with 1 M NaOH aq. (150 mL) and separated by celite filtration. Next, the filtrate was extracted with Et_2O (100 mL ×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 2-(adamant-1-yl)ethanol (**B**, 17.1 g, 95 mmol) in 95% yield, white powder. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 3.72 (2H, t, J = 53.5 Hz), 2.00-1.90 (3H, m), 1.75-1.67 (3H, m), 1.67-1.59 (3H, m), 1.55-1.50 (6H, m), 1.42-1.35 (2H, m), 1.08-1.03 (1H, m).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ 58.84, 47.24, 42.74, 37.06, 31.86, 28.61. All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[4]

To a solution of **B** (18.0 g, 100 mmol) in CH_2Cl_2 (200 mL) were added PPh_3 (39.4 g, 150 mmol) and imidazole (8.85 g, 130 mmol). The reaction mixture was stirred at 0 °C for 15 h. Then, I_2 (38.1 g, 150 mmol) was added and the mixture was further stirred for 16 h at room temperature. After being added $NaHSO_3$ (10.5 g, 100 mmol), the reaction mixture was extracted with Et_2O (100 mL × 3). The organic layer was washed with

brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel column chromatography (hexane/acetone = 50/1) to give 1-iodo-2-(adamant-1-yl)ethane (**C**, 23.5g, 81 mmol) in 81% yield as light yellow powder. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 3.21-3.14 (2H, m), 1.99-1.92 (3H, m), 1.83-1.75 (2H, m), 1.74-1.66 (3H, m), 1.66-1.57 (3H, m), 1.53-1.48 (6H, m). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 49.86, 41.79, 36.96, 35.34, 28.47, 1.18. All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[5]

To a DMSO solution of **C** (23.3g, 80 mmol in DMSO 80 mL) was added NaCN (5.10 g, 104 mmol). The reaction mixture was stirred at 80 °C for 3 h. After being quenched with 1 M NaOH aq. (300 mL), the mixture was extracted with EtOAc (100 mL ×3). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 3-(adamantan-1-yl)propanenitrile (**D**, 15.2 g, 80 mmol) quantitatively as light yellow powder. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 2.31-2.24 (2H, m), 2.02-1.95 (3H, m), 1.76-1.68 (3H, m), 1.66-1.58 (3H, m), 1.51-1.45 (8H, m). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 120.90, 41.57, 39.40, 36.75, 32.06, 28.30, 10.92.
All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[6]

To a solution of lithium diisopropyl amide (LDA, 88 mmol) in THF (150 mL) was added **D** (15.2 g, 80 mmol) using an ice-water bath. The mixture was stirred for 30 min on the ice-water bath. Then, MeI (10.7 mL, 88 mmol) was added and the resulting mixture was stirred for 2 h at room temperature. The mixture was carefully quenched by adding 1 M HCl aq. (100 mL) and extracted with Et_2O (100 mL ×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. These operations were repeated 5 times. The crude product was purified by silica gel column chromatography (hexane/acetone = 2/1) to give 1.1-dimetyl-3-(adamantan-1-yl)propanenitrile (**E**, 16.7 g, 77 mmol) in 96% yield as light yellow powder. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 1.99-1.96 (3H, m), 1.72-1.64 (12H, m), 1.40 (6H, s), 1.37 (2H, s). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 126.32, 54.46, 43.14, 36.76, 33.78, 29.93, 28.60. **EI-HRMS** (*m*/*z*): [M] calcd for $C_{15}H_{23}N$, 217.1830; found, 217.1828.

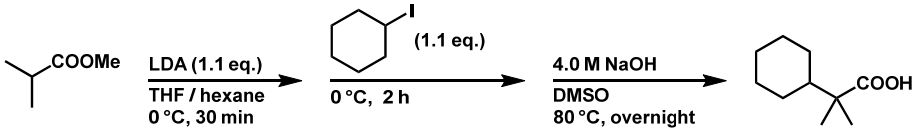
A mixture of **E** (8.69 g, 40 mmol) in 75% H_2SO_4 aq. (125 ml) was stirred for 16 h at 100 °C. After being cooled to room temperature, to the mixture were added $NaNO_2$ (11.0 g, 160 mmol) and H_2O (10 mL). The mixture was stirred for 16 h at room temperature. The mixture was extracted with Et_2O (100 mL ×3). The organic layer was

washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/acetone = 3/1) to give 2,2-dimetyl-3-(adamantan-1-yl)propanoic acid (**1m**, 5.77 g, 24 mmol) in 60% yield as white powder.**^{1}H NMR (400 MHz, $CDCl_3$)**: δ 1.91-1.88 (3H, m), 1.67-1.58 (12H, m), 1.51 (2H, s), 1.25 (6H, s). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 185.78, 54.52, 43.00, 41.57, 36.90, 33.88, 28.76, 28.03. **ESI-HRMS** (*m*/*z*): [M-H] calcd for $C_{15}H_{24}O_2$, 236.3550; found, 235.1702.

Preparation of 2,2,4,4-tetramethylpentanoic acid (1l)

The compound **1l** was synthesized by the method similar to that used for **1m** using *tert*-butylacetic acid in place of 1-adamantaneacetic acid. White powder was obtained in 30 mmol scale (0.90 g, 5.7 mmol, 10.9%). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 1.66 (2H, s), 1.25 (6H, s), 0.95 (9H, s). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 185.37, 53.24, 42.04, 31.72, 30.73, 27.53. **ESI-HRMS** (*m*/*z*): [M-H] calcd for $C_9H_{18}O_2$, 158.2410; found, 157.1234.

Preparation of 2-cyclohexyl-2-methylpropanoic acid (1i)



F 1i

To a solution of diisopropylamine (1.5 mL, 11 mmol) in THF (30 mL) was added *n*-BuLi (2.6 M solution in hexane; 11 mmol) at 0 °C, which was stirred for 30 min. To this solution was added methyl isobutyrate (**F**, 1.1 mL, 10 mmol). The reaction mixture was stirred for 30 min. Then, iodocyclohexane (1.4 mL, 11 mmol) was added and the resulting solution was stirred at room temperature overnight. After being quenched by the addition of 1 M HCl aq., the mixture was extracted with Et_2O (three times). The organic layer was washed with brine (three times), dried over $MgSO_4$ and concentrated under reduced pressure. To the mixture were added aqueous NaOH (3.2 g, 0.080 mol) solution (20 mL) and DMSO (20 mL). The reaction mixture was stirred at 80 °C overnight. After being quenched by adding 1 M HCl aq., the mixture was extracted with EtOAc (three times). The organic layer was washed with brine (three times), dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by recrystallization from acetonitrile to give 2-cyclohexyl-2-methylpropanoic acid (**1i**, 1.1 g, 6.3 mmol) in 63% yield as white powder. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 1.79-1.75 (2H, m), 1.64-1.59 (4H, m), 1.27-1.21 (2H, m), 1.12 (6H, s), 1.04-1.00 (2H, m). **^{13}C**

NMR (100 MHz, $CDCl_3$): δ 184.77, 45.58, 45.19, 27.69, 26.77, 26.50, 21.74. **ESI-HRMS** (*m*/*z*): [M-H] calcd for $C_{10}H_{18}O_2$, 170.1307; found, 169.1234.

Preparation of 4-cyclohexyl-2,2-dimethylbutanoic acid (1j)

The compound **1j** was synthesized by the method similar to that used for **1i** using cyclohexylethyl iodide in place of iodocyclohexane. White powder was obtained in 10 mmol scale (1.02 g, 5.12 mmol, 51%). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.68-1.64 (5H, m), 1.57-1.52 (2H, m), 1.26-1.22 (1H, m), 1.18 (6H, s), 1.15-1.12 (4H, m), 0.91-0.82 (2H, m). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 184.69, 42.09, 38.14, 37.90, 33.29, 32.33, 26.68, 26.37, 24.90. **ESI-HRMS** (*m*/*z*): [M-H] calcd for $C_{12}H_{22}O_2$, 198.1620; found, 197.1546.

4. DFT Calculation

4.1. Estimation of p*K*a values of carboxylic acids

DFT calculations were performed with the Gaussian 16 program.[7] Each structure of carboxylic acids was optimized by DFT calculation (B3LYP/6-311G++(2d,p)). The p*K*a values were estimated by the maximum values of their molecular electronic potential (max MEP) and listed in **Table S3**.

Table S2. Caliblation of p*K*a calues of carboxylic acids

Carboxylic Acid	max ESP*e2	p*K*a
AcOH	5.518	4.76
PivOH	5.375	5.03
$ClCH_2COOH$	6.526	2.85
$Cl_2CHCOOH$	7.133	1.48
Cl_3CCOOH	7.441	0.70

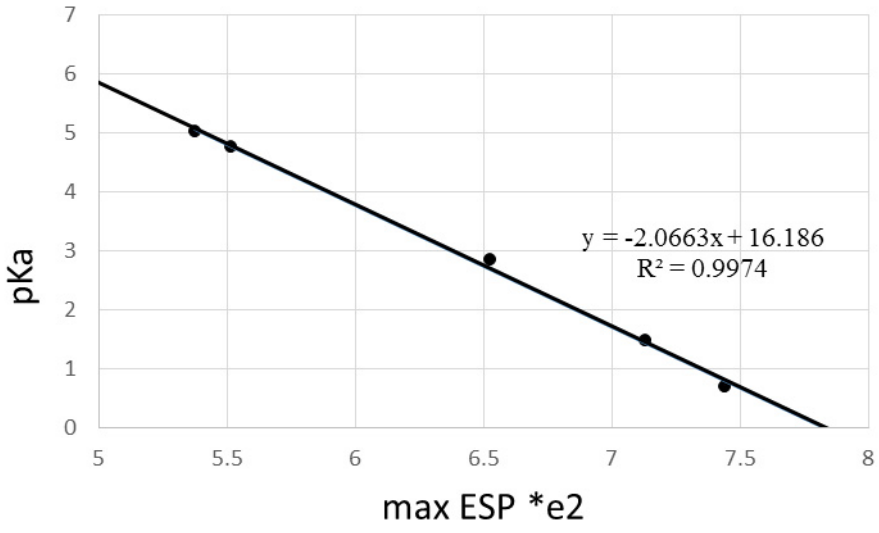


Figure S2. Caliblation of p*K*a values of carboxylic acids

Table S3. Calculated p*K*a values of carboxylic acids

Carboxylic Acid	max ESP*e2[a]	p*K*a[b]
1b	5.233	5.37
1g	5.172	5.50
1h	5.244	5.35
1i	5.286	5.26
1j	5.245	5.35
1k	5.226	5.39
1l	5.359	5.11
1m	5.219	5.40

[a] Calculated for DFT-optimized structure (B3LYP/6-311G++(2d,p)). [b] Estimated by using the following equation: p*K*a = -2.0663*(max ESP*e2) + 16.186

4.2. Calculation of energy change in the intermolecular C(sp^2)–H arylation reaction (Figure S3)

All structures of [PdPh(**1m'**)(DMA)], (**1m'** is a carboxylate ligand derived from **1m**) including two transition states were optimized by DFT calculation (B3PW91/SDD for Pd, others for 6-31G(d) level). DFT calculations were performed with the Gaussian 16 program.[7]

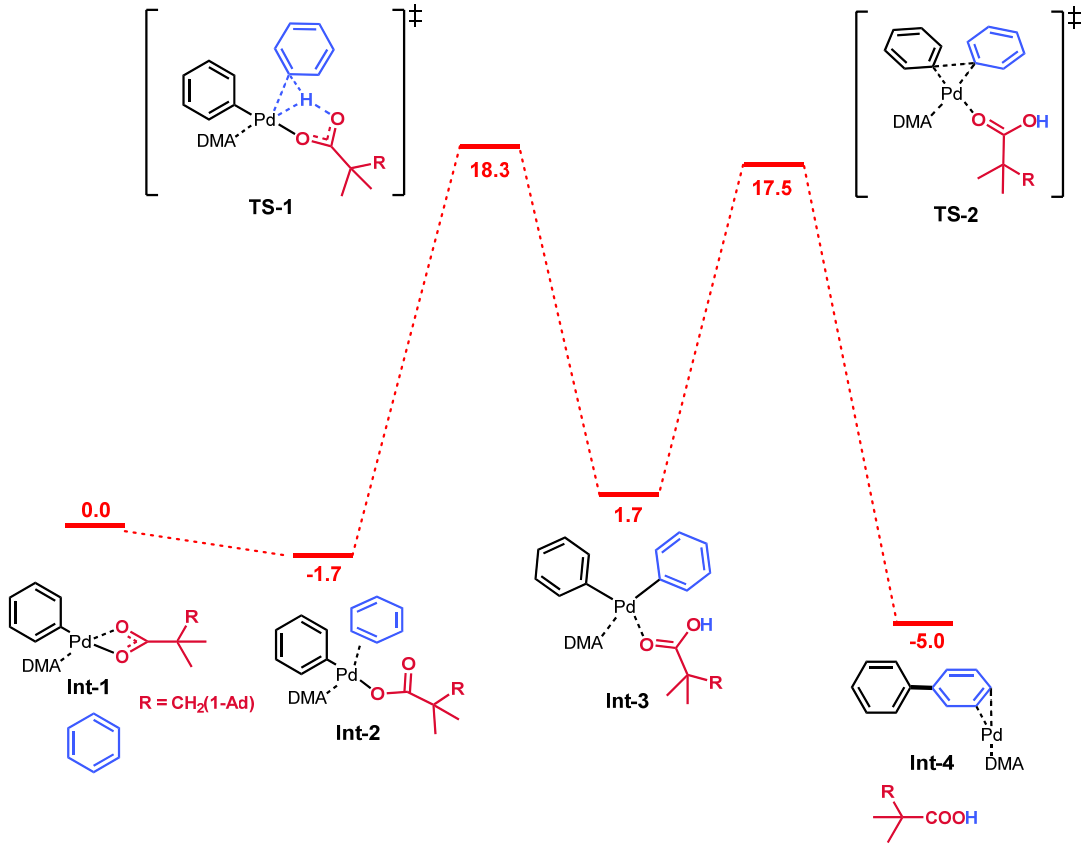
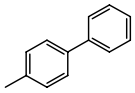


Figure S3. Gibbs energy change (ΔG, kcal/mol) in the reaction of [PdPh(**1m'**)(DMA)] with benzene.

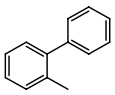
5. Characterization of the Products of C–H Arylation Reactions

Compound 4aa



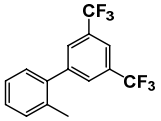
Colorless oil (20.8 mg, 62%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.58 (2H, d, J = 7.7 Hz), 7.50 (2H, d, J = 8.2 Hz), 7.44-7.42 (2H, m), 7.33-7.32 (1H, m), 7.26-7.23 (2H, m), 2.40 (3H, s). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 141.14, 138.33, 137.01, 129.46, 128.70, 127.15, 126.98, 126.96, 21.09. All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[8]

Compound 4ba



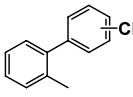
Colorless oil (20.1 mg, 60%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.44-7.41 (3H, m), 7.36-7.31 (3H, m), 7.24-7.22 (3H, m), 2.27 (3H, s). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 141.93, 135.33, 130.28, 129.77, 129.18, 128.74, 128.04, 127.22, 126.73, 125.74, 20.45. All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[9]

Compound 4bb



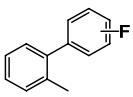
Colorless oil (52.1 mg, 86%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.87 (1H, s), 7.79 (2H, s), 7.32 (3H, tdd, J = 14.0, 6.2, 2.3 Hz), 7.22 (1H, d, J = 7.2 Hz), 2.26 (3H, s).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ 43.94, 138.81, 135.16, 131.50 (q, J = 33.1 Hz), 130.79, 129.61, 129.36 (q, J = 4.1 Hz), 128.66, 126.29, 123.39 (q, J = 272.8 Hz), 120.76 (sep, J = 3.8 Hz). **EI-HRMS** (m/z): [M] calcd for $C_{13}H_{10}F_2$, 204.0751; found, 204.0754.

Compound 4bc



Colorless oil (29.2 mg, 72%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.47-7.18 (8H, m), 2.26 for major isomer and 2.26, 2.12 for minor one (3H, s, 33 : 18 : 49). **^{13}C NMR (100 MHz, $CDCl_3$)**: (for *o*) δ: 140.61, 139.38, 136.24, 133.40, 131.02, 139.79, 129.38, 129.36, 128.54, 127.90, 126.58, 125.51, 19.78. (for *m*) δ: 143.74, 140.49, 133.91, 129.98, 129.65, 129.27, 128.89, 127.73, 127.41, 127.11, 126.91, 125.29, 20.36. (for *p*) δ: 140.66, 140.34, 135.25, 132.83, 130.52, 130.41, 129.79, 128.26, 127.57, 125.87, 20.40. All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[10]

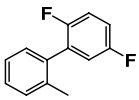
Compound 4bd



Colorless oil (27.2 mg, 73%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.35-7.10

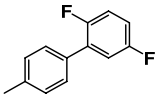
(8H, m), 2.20 for major isomer and 2.27 for minor one (3H, s, 10:1) **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 160.86, 136.65, 135.74, 131.55 (d, J = 3.9 Hz), 130.06, 129.93, 129.23 (d, J = 17.3 Hz), 129.02 (d, J = 7.7 Hz), 127.95, 125.62, 123.95 (d, J = 3.9 Hz), 115.50 (d, J = 22.2 Hz), 19.92 (d, J = 2.9 Hz). All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[11,12]

Compound 4be



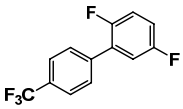
Colorless oil (31.1 mg, 76%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.35-7.23 (3H, m), 7.21-7.19 (1H, m), 7.11-6.99 (2H, m), 6.98-6.95 (1H, m), 2.21 (3H, s). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 158.40 (dd, J = 242.8, 1.9 Hz), 155.63 (dd, J = 241.3, 2.4 Hz), 136.48, 134.66, 130.60 (dd, J = 19.7, 8.2 Hz), 130.07, 129.83, 128.34, 125.73, 117.81 (dd, J = 23.6, 4.3 Hz), 116.46 (dd, J = 26.0, 8.7 Hz), 115.29 (dd, J = 24.1, 8.7 Hz), 19.82 (d, J = 2.9 Hz). **EI-HRMS** (*m*/*z*): [M] calcd for $C_{13}H_{10}F_2$, 204.0751; found, 204.0754.

Compound 4ce



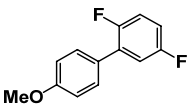
Colorless oil (28.7 mg, 70%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.44-7.41 (2H, m), 7.26-7.25 (2H, m), 7.12-7.07 (2H, m), 6.99-6.91 (1H, m), 2.40 (3H, s). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 158.74 (dd, J = 241.8, 2.4 Hz), 155.73 (dd, J = 243.2, 2.9 Hz), 138.09, 131.85, 130.34 (dd, J = 16.7, 7.2 Hz), 129.28, 128.71 (d, J = 2.9 Hz), 117.04 (dd, J = 25.7, 8.6 Hz), 116.72 (dd, J = 24.3, 4.3 Hz), 114.79 (dd, J = 23.8, 8.6 Hz), 21.19. All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[13]

Compound 4de



White powder (46.0 mg, 89%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.72-7.70 (2H, m), 7.65-7.63 (2H, m), 7.17-7.10 (2H, m), 7.09-7.02 (1H, m). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 158.80 (dd, J = 242.7, 2.4 Hz), 155.67 (dd, J = 244.1, 2.9 Hz), 138.30, 130.26 (q, J = 32.4 Hz), 129.22, 128.88 (dd, J = 16.2, 7.6 Hz), 125.52 (q, J = 3.8 Hz), 124.04 (q, J = 271.8 Hz), 117.44 (dd, J = 25.7, 8.6 Hz), 116.83 (dd, J = 24.8, 2.9 Hz), 116.19 (dd, J = 23.8, 8.6 Hz). **EI-HRMS** (m/z): [M] calcd for $C_{13}H_7F_5$, 258.0468; found, 258.0467.

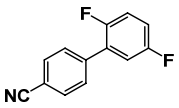
Compound 4ee



White powder (38.6 mg, 80%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.49-7.47 (2H, m), 7.14-7.05 (2H, m), 7.00-6.92 (3H, m), 3.86 (3H, s).

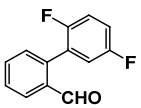
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.99 (d, J = 2.9 Hz), 159.58, 157.26 (dd, J = 66.5, 2.9 Hz), 154.51 (d, J = 2.9 Hz), 130.06 (d, J = 3.9 Hz), 127.15 (d, J = 1.9 Hz), 117.05 (dd, J = 26.0, 8.7 Hz), 116.55 (dd, J = 24.6, 4.3 Hz), 114.52 (dd, J = 23.6, 8.2 Hz), 114.04, 55.34. All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[13]

Compound 4fe



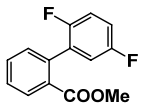
White powder (38.5 mg, 89%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.76-7.75 (2H, m), 7.66-7.64 (2H, m), 7.16-7.09 (3H, m). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 158.80 (dd, J = 244.1, 2.9 Hz), 155.57 (dd, J = 245.1, 2.9 Hz), 139.27, 132.35, 129.57 (d, J = 2.9 Hz), 128.31 (d, J = 7.6 Hz), 118.55, 117.61 (dd, J = 25.3, 9.1 Hz), 116.82 (dd, J = 5.7, 2.9 Hz), 116.58 (dd, J = 5.7, 2.9 Hz), 111.97. **EI-HRMS** (m/z): [M] calcd for $C_{13}H_7NF_2$, 215.0547; found, 215.0545.

Compound 4ge



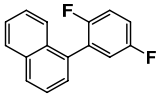
Pale-yellow oil (37.3 mg, 89%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 9.94 (1H, d, J = 3.2 Hz), 8.04 (1H, dd, J = 7.7, 1.4 Hz), 7.69 (1H, td, J = 7.6, 1.2 Hz), 7.59-7.57 (1H, m), 7.41-7.39 (1H, m), 7.14-7.13 (2H, m), 7.09-7.06 (1H, m). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 191.18, 158.56 (dd, J = 244.2, 2.4 Hz), 155.58 (dd, J = 242.8, 2.9 Hz), 137.52, 133.90, 133.77, 131.13 (d, J = 1.0 Hz), 129.13, 128.98, 128.18, 118.13 (dd, J = 24.1, 3.9 Hz), 116.87 (dd, J = 8.7, 6.7 Hz), 116.63 (dd, J = 8.2, 5.3 Hz). All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[14]

Compound 4he



White powder (47.6 mg, 96%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.01-7.99 (1H, m), 7.60-7.58 (1H, m), 7.49-7.47 (1H, m), 7.34-7.32 (1H, m), 7.09-6.99 (3H, m), 3.73 (3H, s). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 167.46, 158.47 (dd, J = 242.3, 2.4 Hz), 155.51 (dd, J = 241.3, 2.4 Hz), 135.53, 132.01, 131.25, 130.58 (dd, J = 18.3, 8.7 Hz), 130.55, 130.33, 128.37, 116.95 (dd, J = 25.0, 3.9 Hz), 115.86 (dd, J = 25.5, 9.2 Hz), 115.33 (dd, J = 24.1, 8.7 Hz), 52.08. **EI-HRMS** (m/z): [M] calcd for $C_{16}H_{10}O_2F_2$, 248.0649; found, 248.0644.

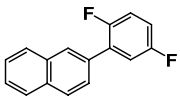
Compound 4ie



White powder (45.4 mg, 95%) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.92-7.90 (2H, m), 7.66-7.65 (1H, m), 7.51-7.46 (4H, m), 7.19-7.08 (3H, m). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 158.50 (dd, J = 240.8, 1.9 Hz),

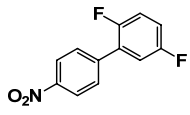
156.10 (dd, J = 242.8, 1.9 Hz), 133.52, 132.74, 131.44, 129.39 (dd, J = 19.3, 7.7 Hz), 128.83, 128.35, 127.63, 126.45, 126.03, 125.46, 125.22, 118.65 (dd, J = 24.1, 3.9 Hz), 116.70 (dd, J = 25.0, 8.7 Hz), 115.74 (dd, J = 23.6, 8.2 Hz). All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[13]

Compound 4je



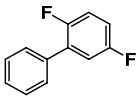
White powder (47.2 mg, 98%) **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 8.02-8.00 (1H, m), 7.91-7.88 (3H, m), 7.67-7.64 (1H, m), 7.53-7.52 (2H, m), 7.27-7.25 (1H, m), 7.16-7.14 (1H, m), 7.06-6.99 (1H, m). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 158.82 (dd, J = 242.3, 2.4 Hz), 155.92 (dd, J = 243.7, 2.9 Hz), 133.25, 132.84, 132.19 (d, J = 1.9 Hz), 130.34 (dd, J = 15.9, 8.2 Hz), 130.89, 128.80, 128.28, 128.17 (d, J = 3.9 Hz), 127.65, 126.55 (d, J = 3.9 Hz), 126.41, 117.29 (dd, J = 10.1, 6.3 Hz), 117.04 (dd, J = 9.2, 6.3 Hz), 115.23 (dd, J = 24.1, 8.7 Hz). **EI-HRMS** (m/z): [M] calcd for $C_{16}H_{10}F_2$, 240.0751; found, 240.0748.

Compound 4ke



White powder (32.3 mg, 69%) **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 8.33-8.31 (2H, m), 7.73-7.70 (2H, m), 7.21-7.08 (3H, m). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 158.80 (dd, J = 243.7, 2.4 Hz), 155.60 (dd, J = 246.0, 2.9 Hz), 147.49, 141.16 (d, J = 1.9 Hz), 129.79 (d, J = 3.8 Hz), 127.95 (dd, J = 15.3, 7.6 Hz), 123.80, 117.69 (dd, J = 25.7, 8.6 Hz), 116.99 (dd, J = 17.6, 6.2 Hz), 116.75 (dd, J = 18.1, 5.7 Hz). **EI-HRMS** (m/z): [M] calcd for $C_{12}H_7O_2NF_2$, 235.0545; found, 235.0442.

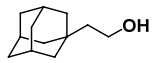
Compound 4le

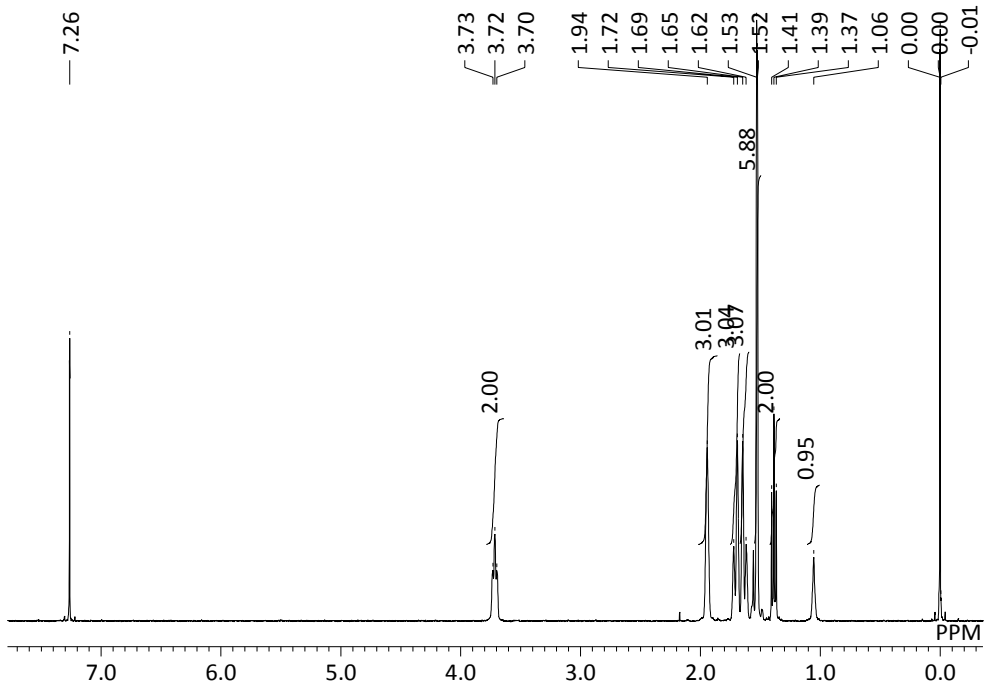


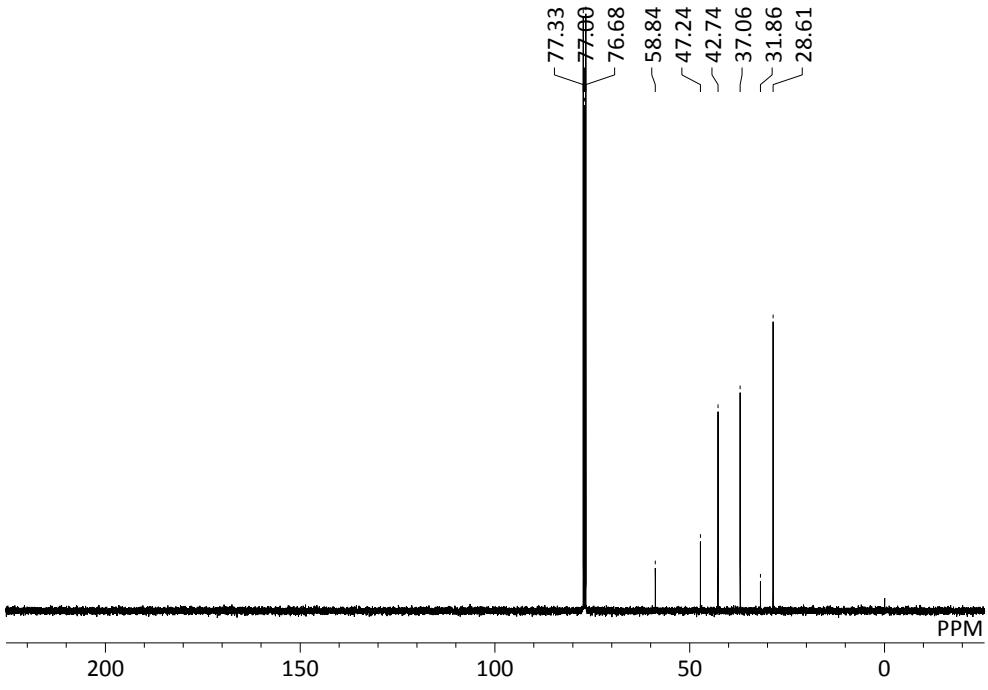
Colorless oil (28.8 mg, 76%) **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 7.56-7.51 (2H, m), 7.48-7.43 (2H, m), 7.42-7.37 (1H, m), 7.17-7.07 (2H, m), 7.03-6.96 (1H, m). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 158.78 (dd, J = 242.3, 2.4 Hz), 155.73 (dd, J = 243.7, 2.9 Hz), 134.80, 130.43 (dd, J = 10.6, 6.7 Hz), 128.89 (d, J = 2.9 Hz), 128.58, 128.19, 117.15 (dd, J = 23.6, 6.3 Hz), 116.89 (dd, J = 19.7, 4.3 Hz), 115.16 (dd, J = 24.1, 8.7 Hz). All the resonances in ^{1}H and ^{13}C spectra were consistent with reported values.[15]

6. NMR Charts

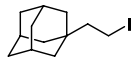
Compound B

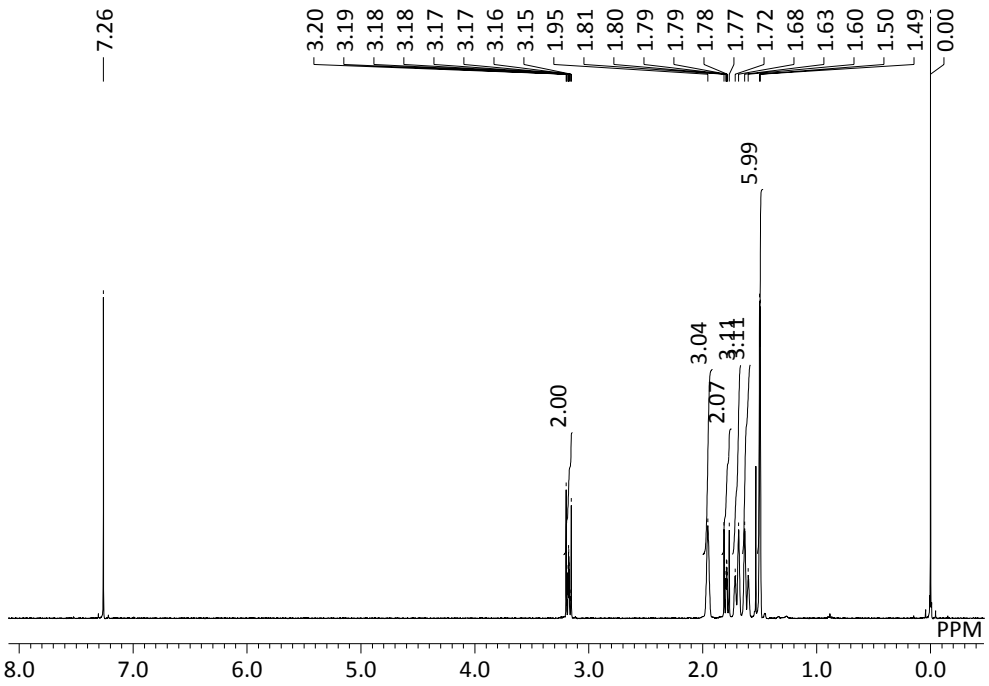


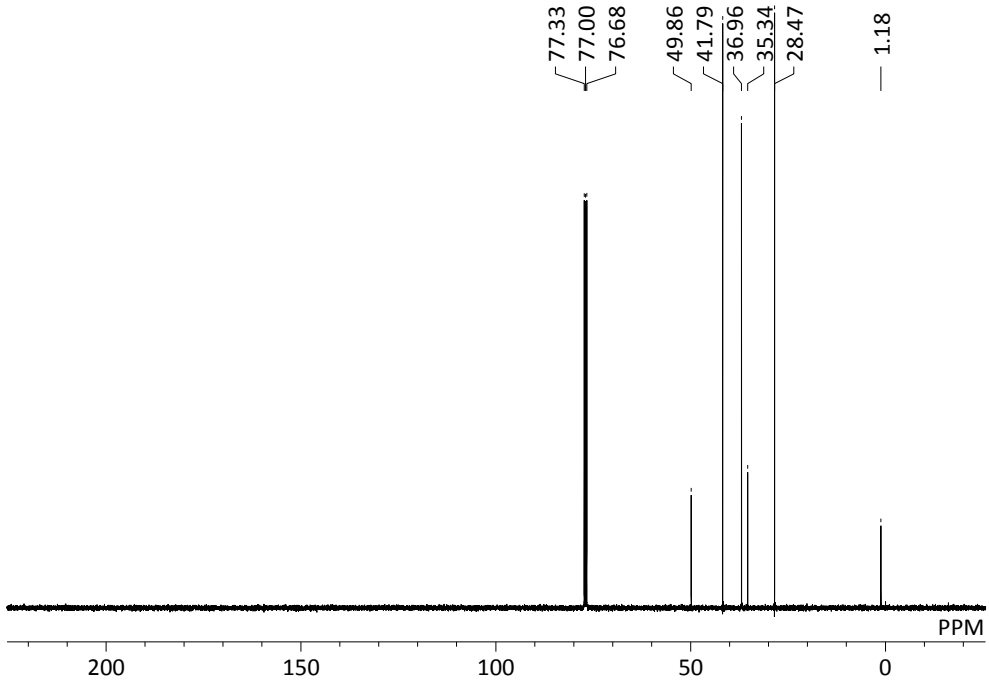




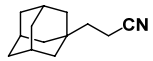
Compound C

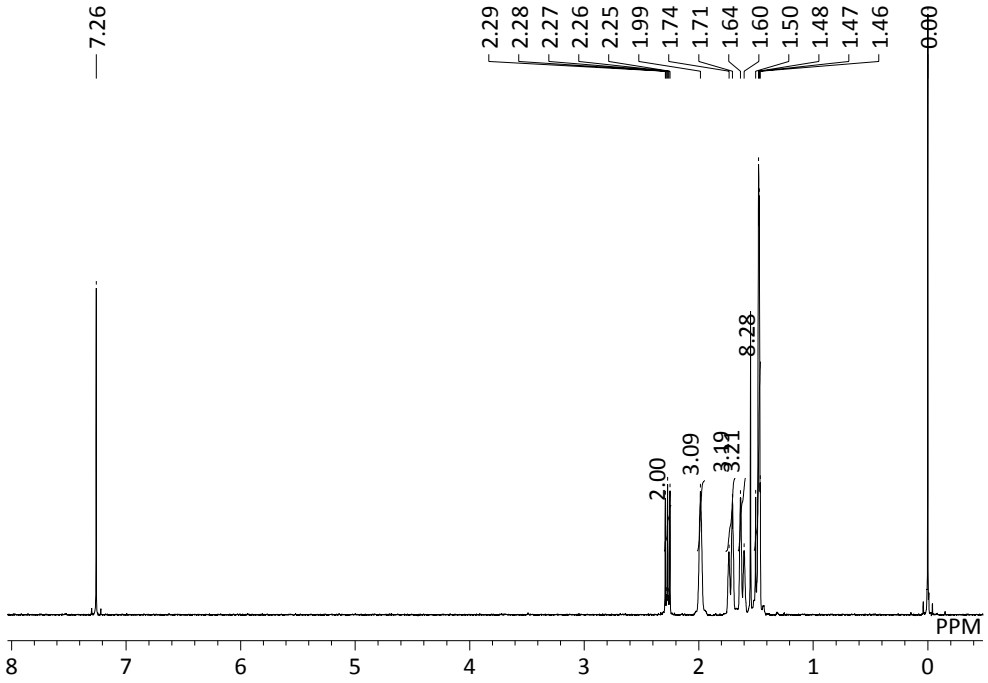


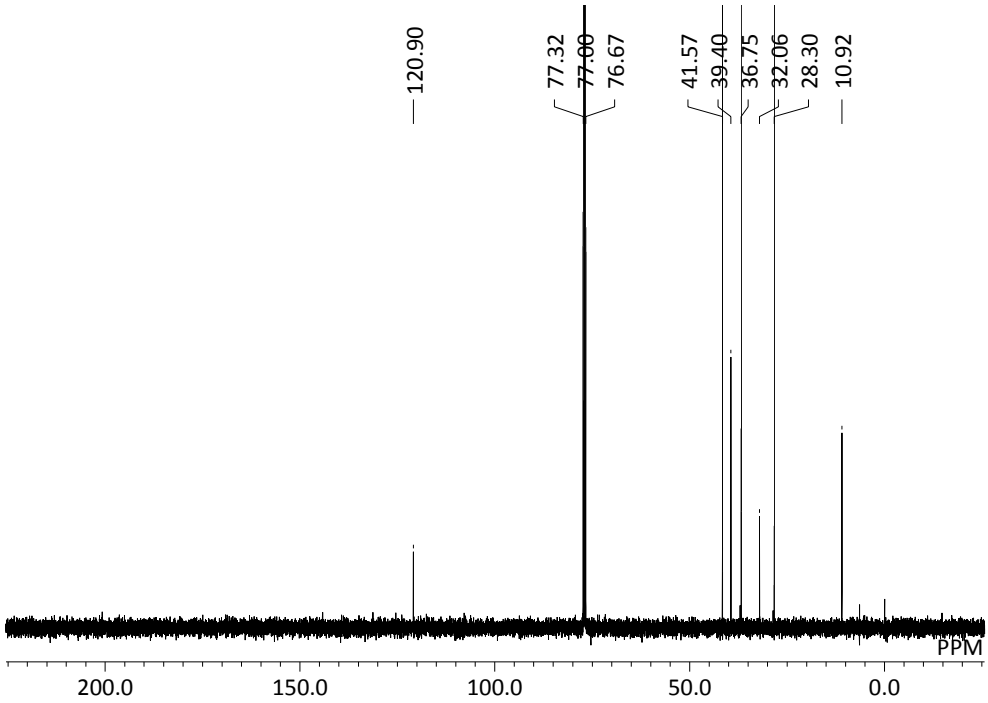

7.26
3.20
3.19
3.18
3.18
3.17
3.17
3.16
3.15
1.95
1.81
1.80
1.79
1.79
1.78
1.77
1.72
1.68
1.63
1.60
1.50
1.49
0.00
5.99
3.04
3.11
2.07
2.00
PPM
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


77.33
77.00
76.68
49.86
41.79
36.96
35.34
28.47
1.18
PPM
200
150
100
50
0

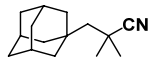
Compound D

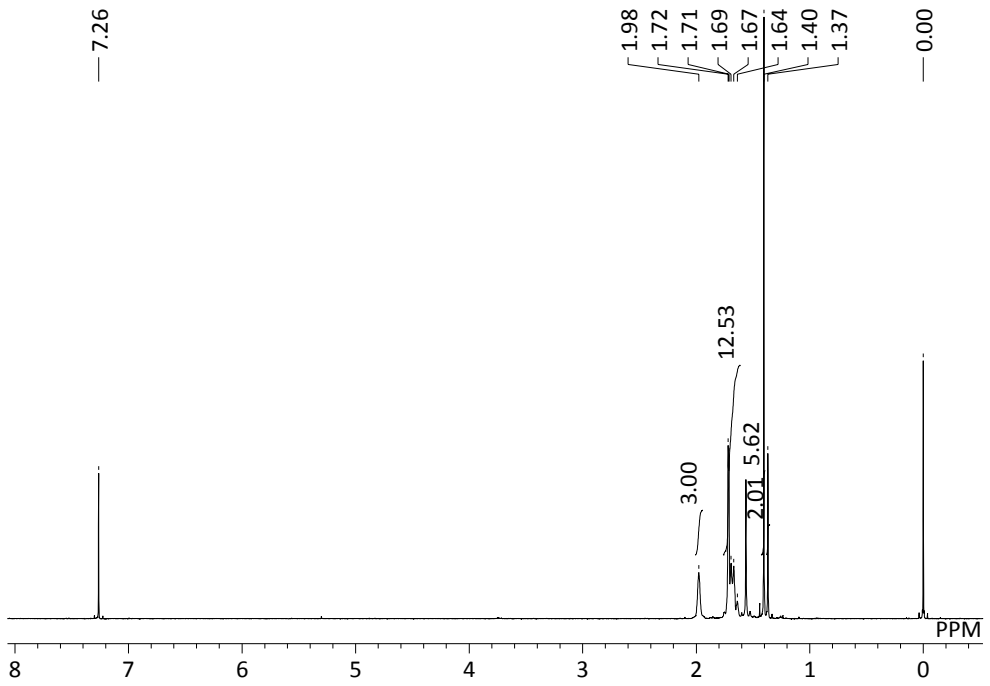

CN

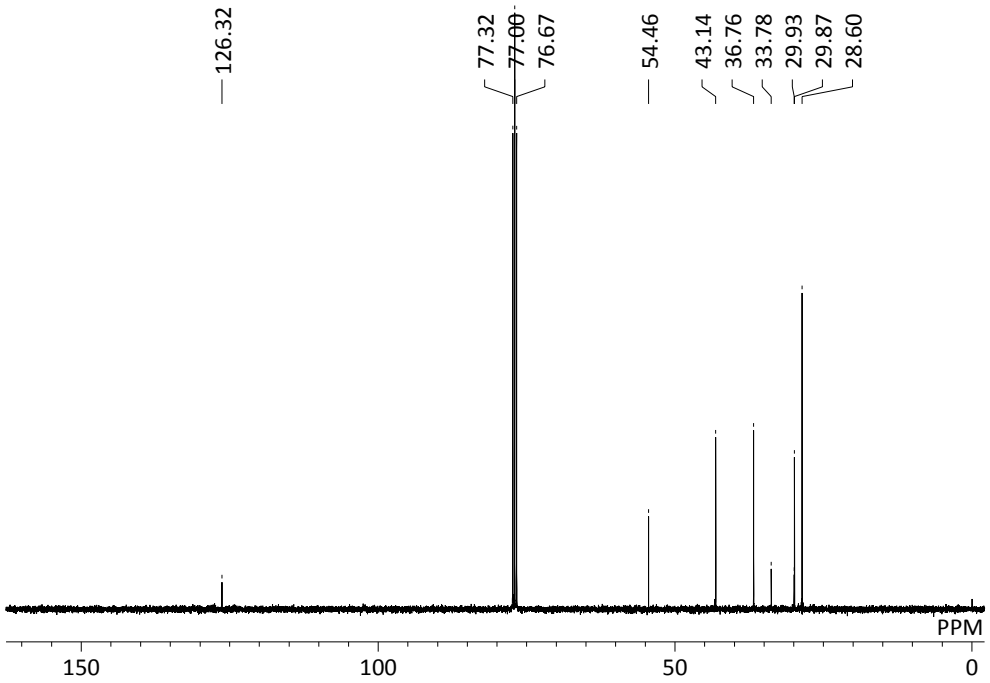

7.26
2.29
2.28
2.27
2.26
2.25
1.99
1.74
1.71
1.64
1.60
1.50
1.48
1.47
1.46
0.00
2.00
3.09
3.19
3.21
8.28
PPM
8
7
6
5
4
3
2
1
0


120.90
77.32
77.00
76.67
41.57
39.40
36.75
32.06
28.30
10.92
PPM
200.0
150.0
100.0
50.0
0.0

Compound E


CN


7.26
1.98
1.72
1.71
1.69
1.67
1.64
1.40
1.37
0.00
12.53
5.62
3.00
2.01
PPM
8
7
6
5
4
3
2
1
0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77.32
77.00
76.67
54.46
43.14
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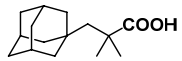
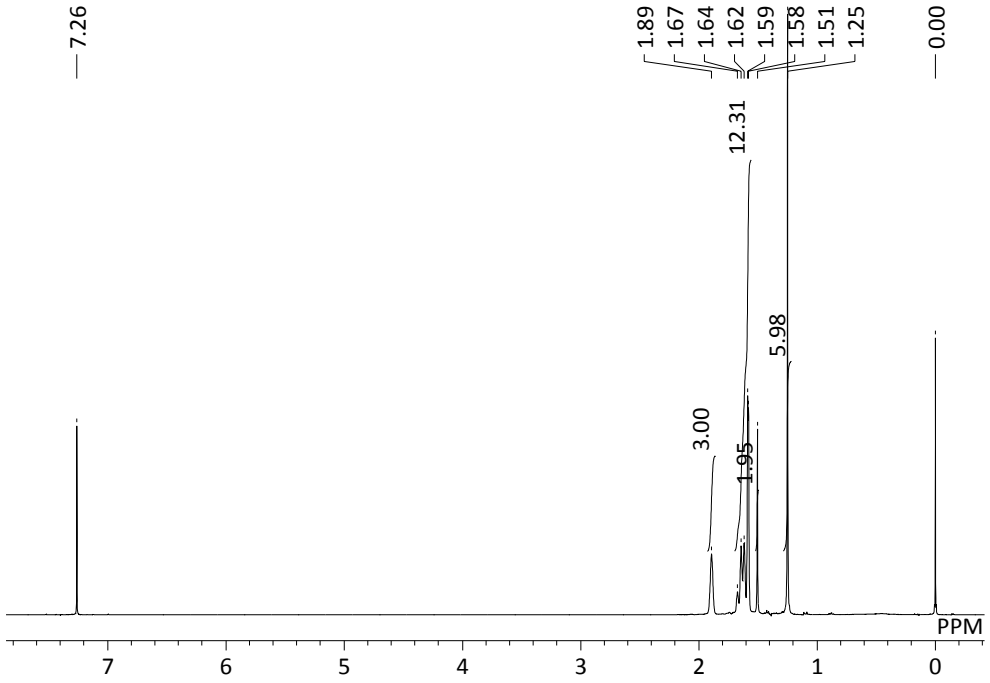
33.78
29.93
29.87
28.60
PPM
150
100
50
0

Compound 1m


COOH


7.26
1.89
1.67
1.64
1.62
1.59
1.58
1.51
1.25
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12.31
5.98
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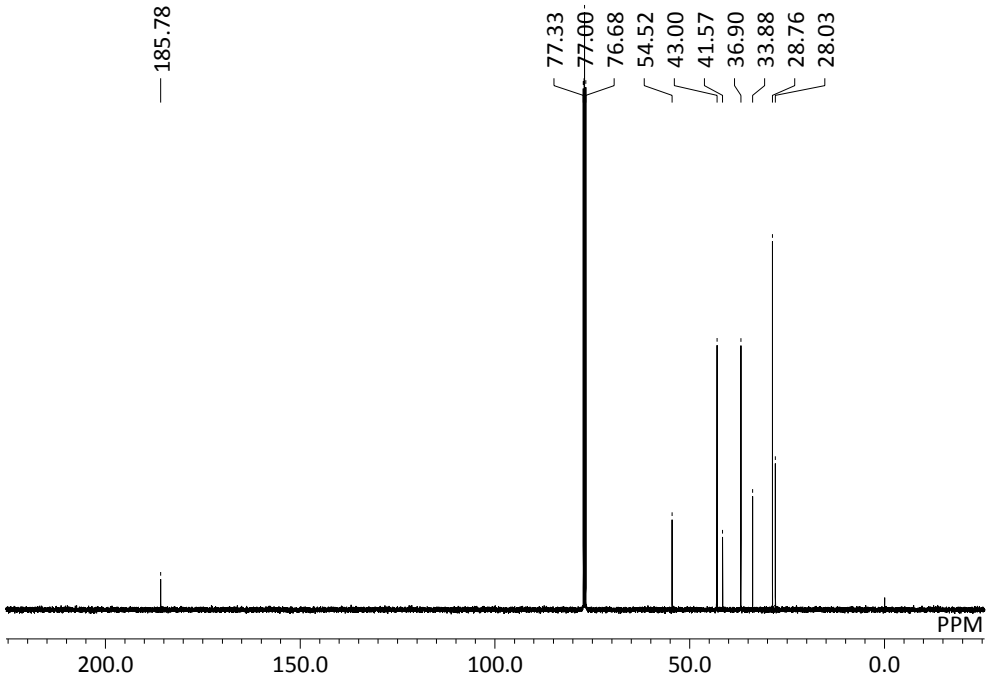
PPM
7
6
5
4
3
2
1
0


185.78
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77.00
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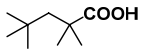
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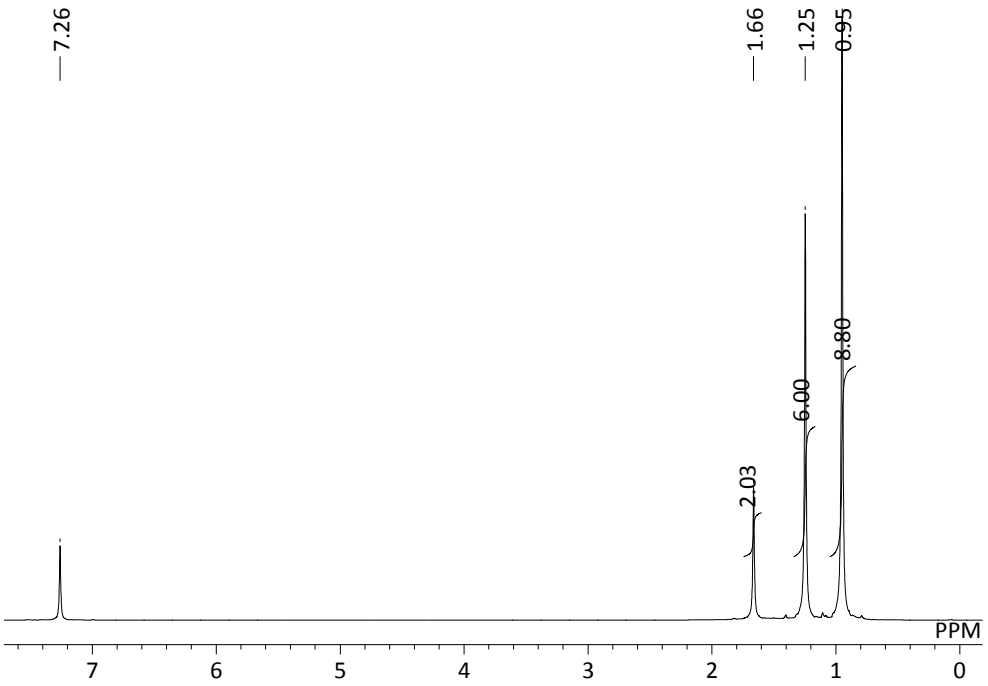
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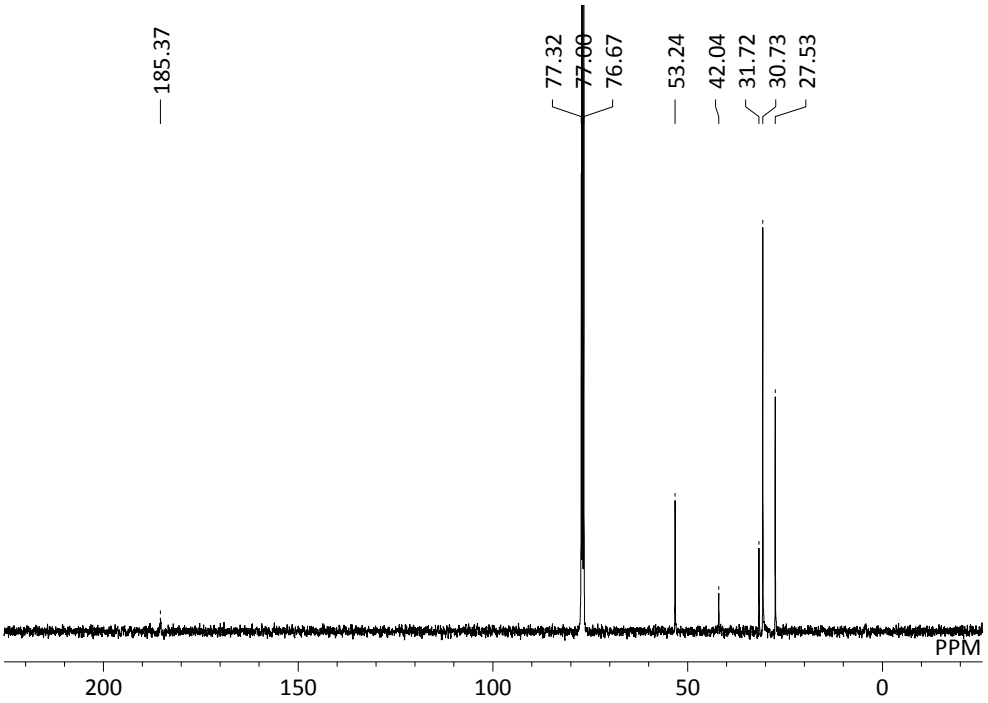
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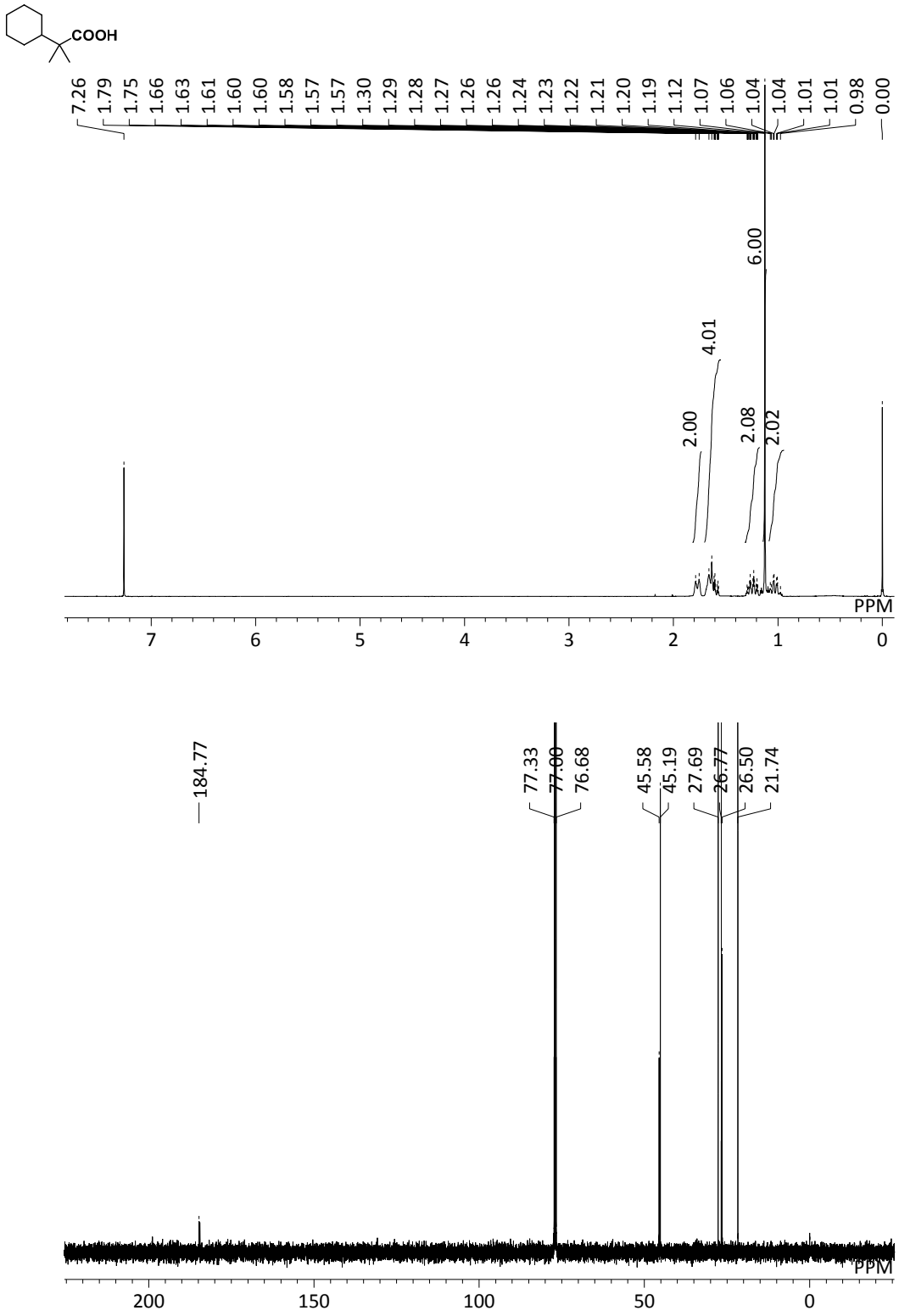
Compound 1i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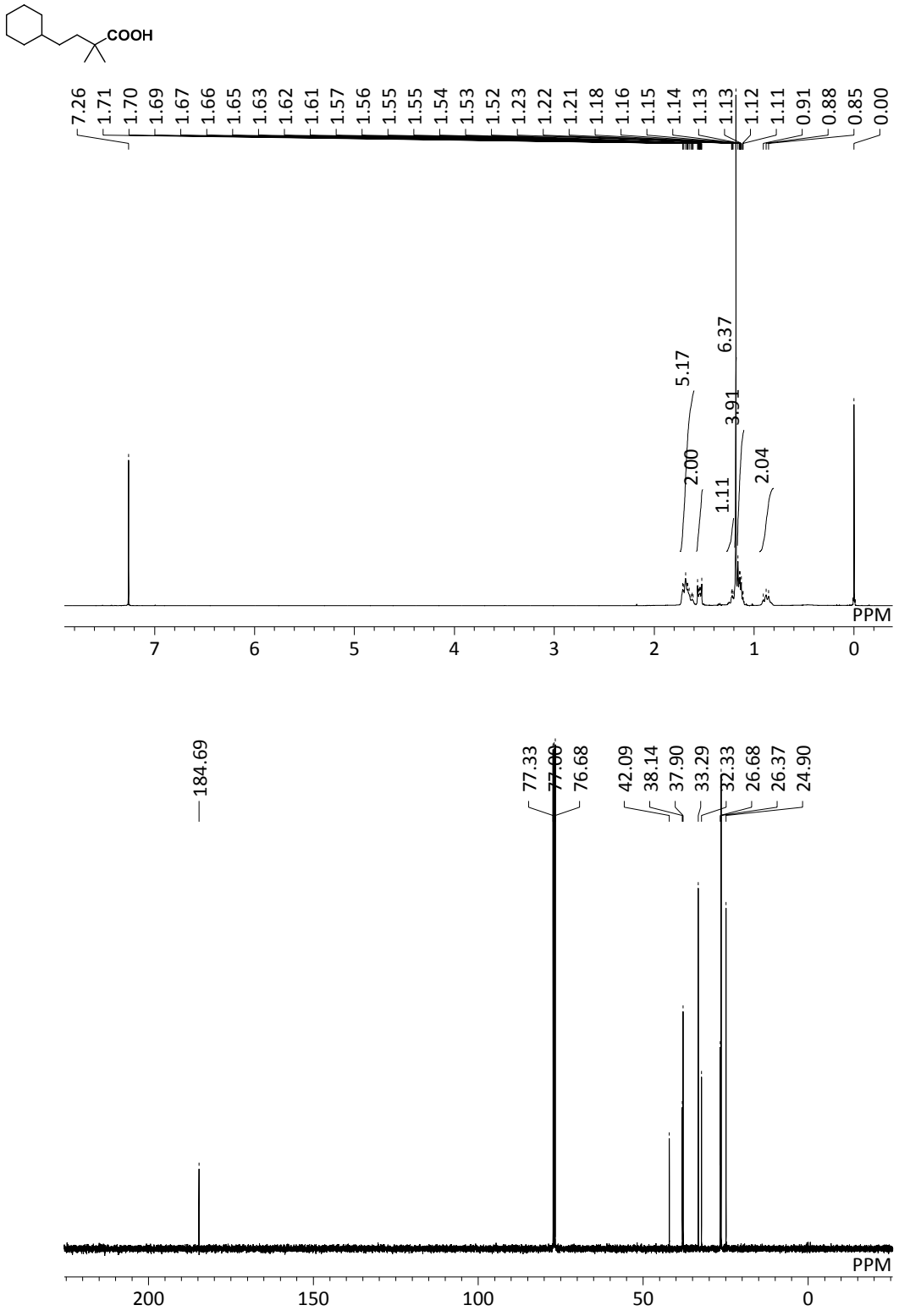
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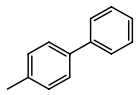
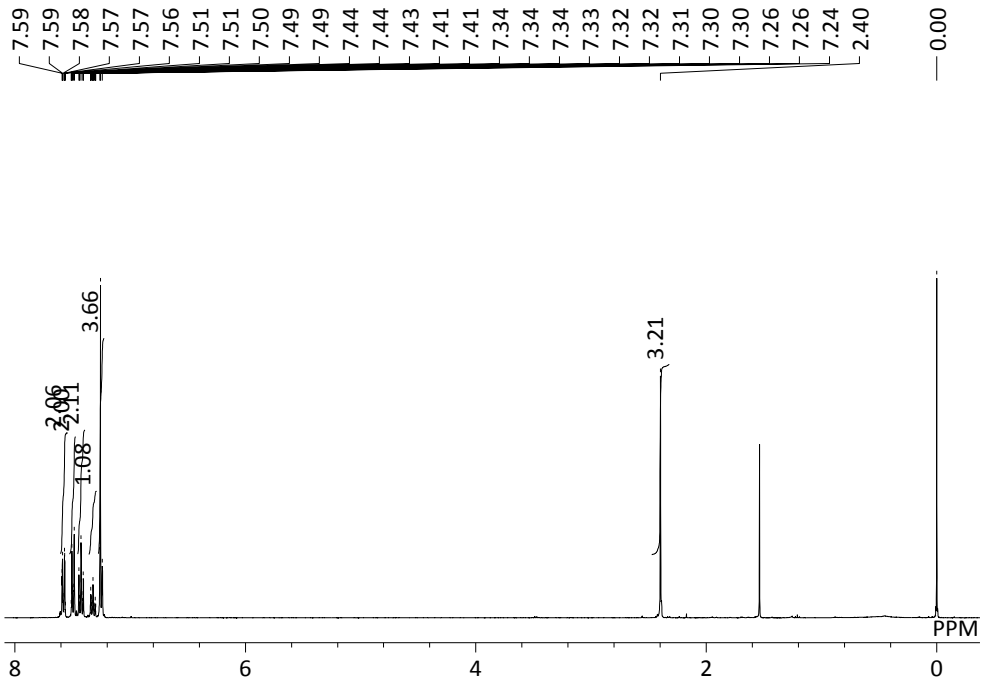
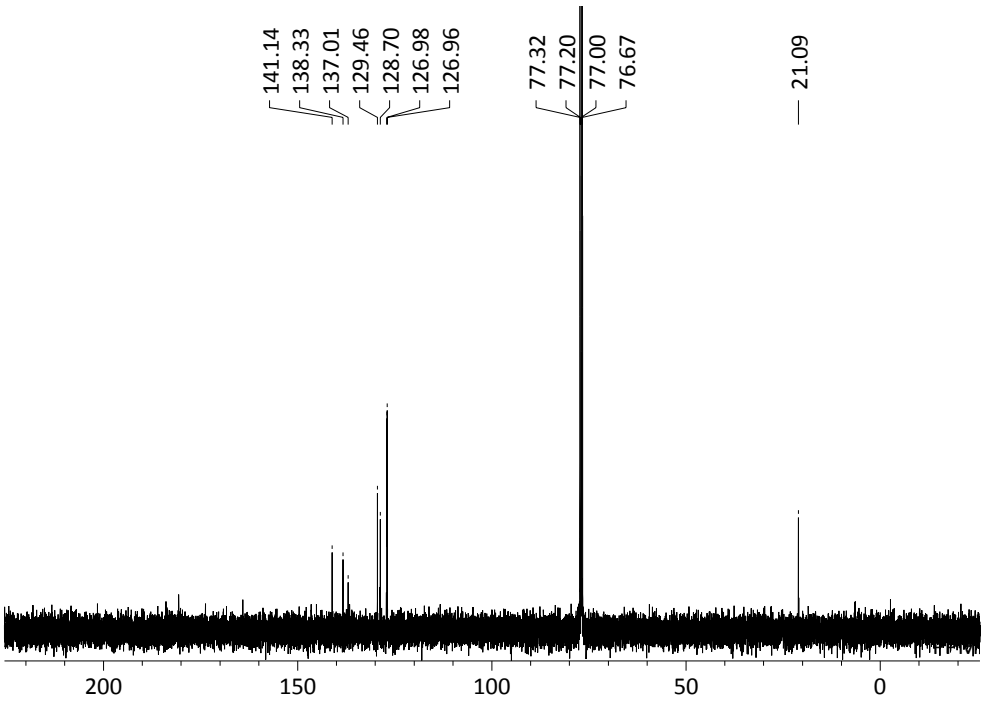
Compound 4aa







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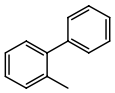

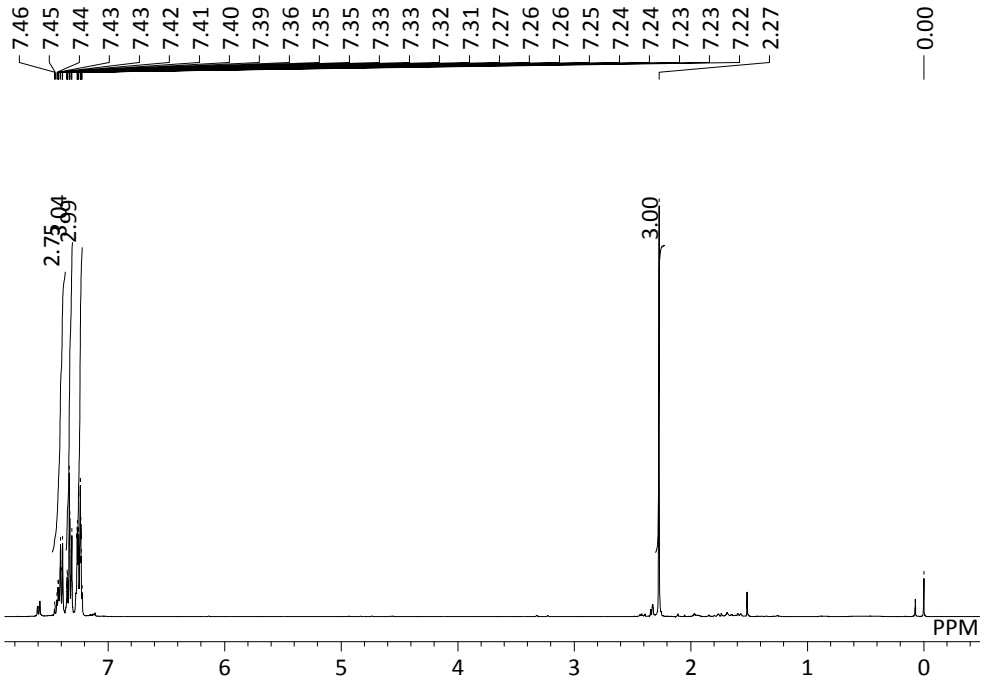

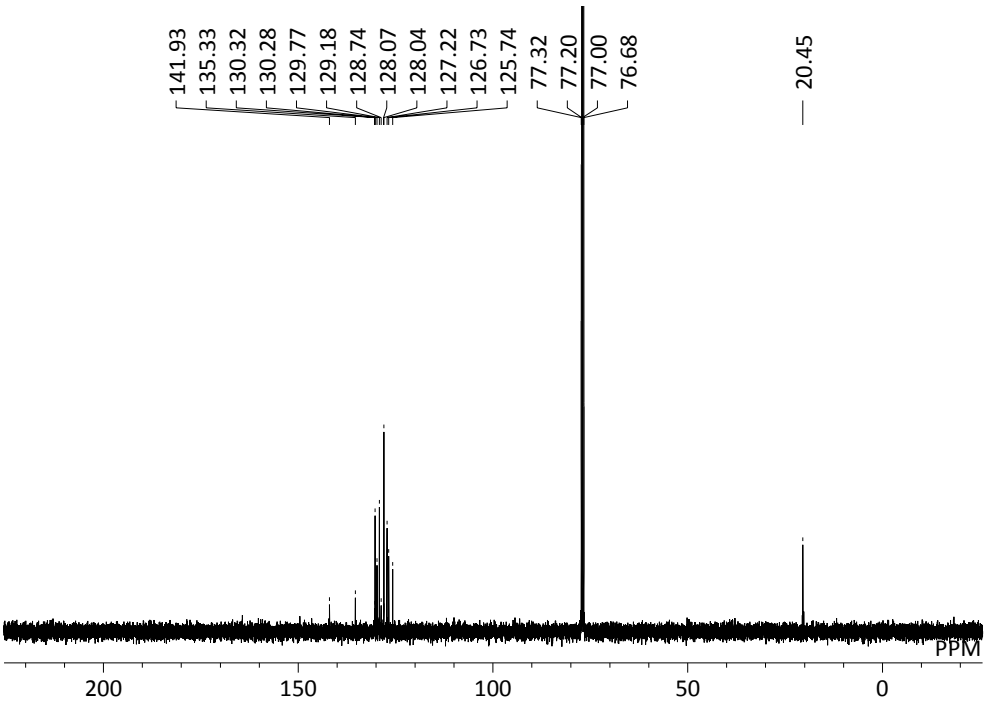

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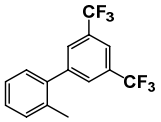

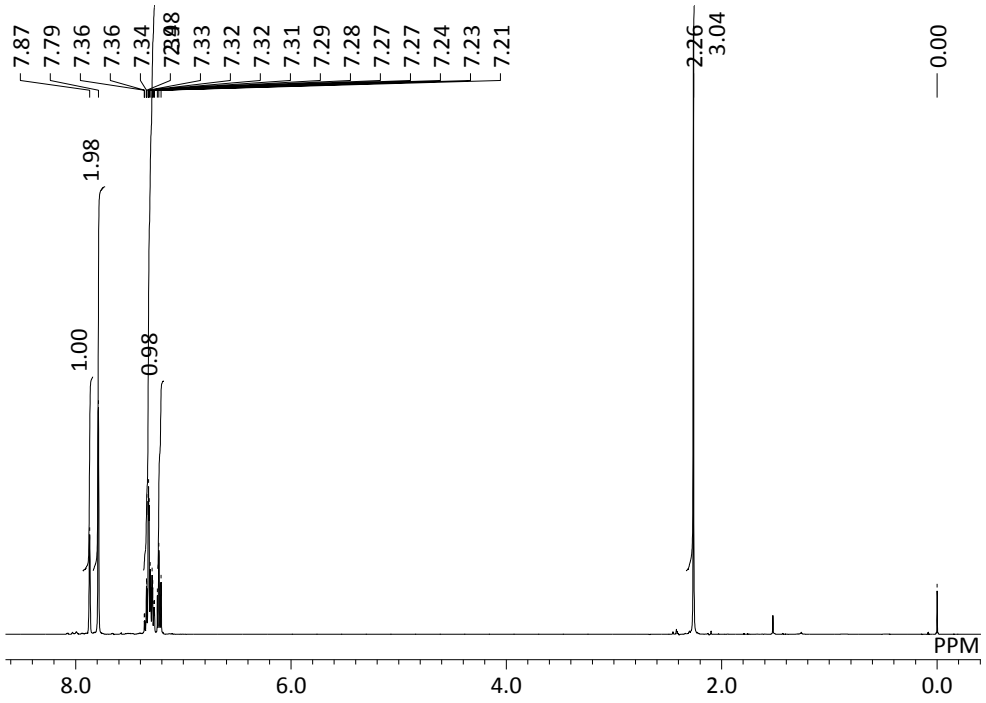

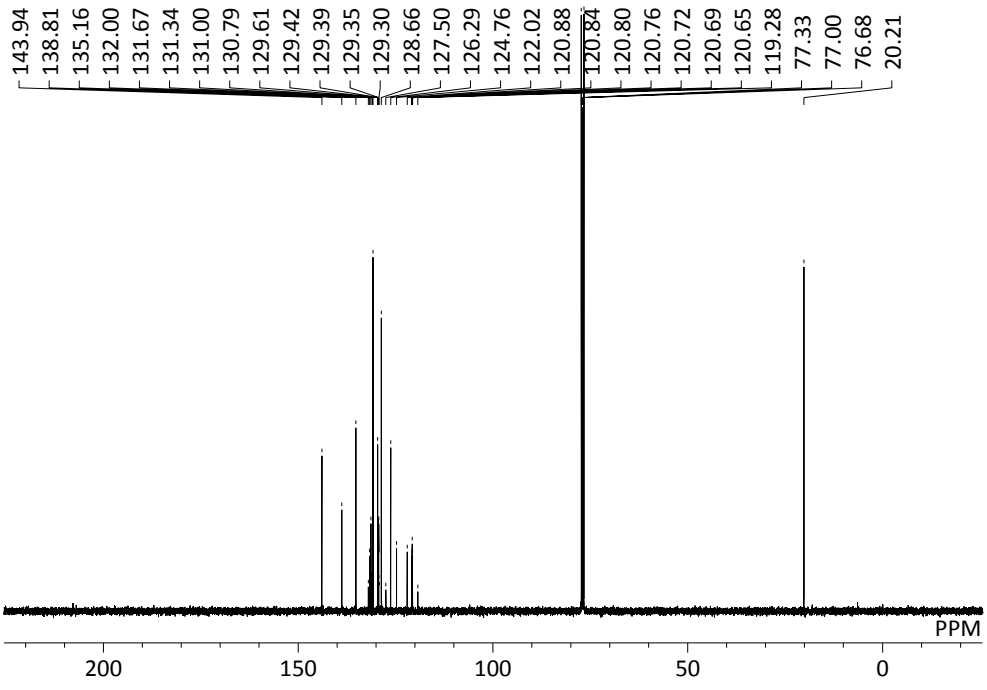

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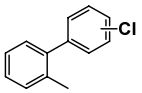

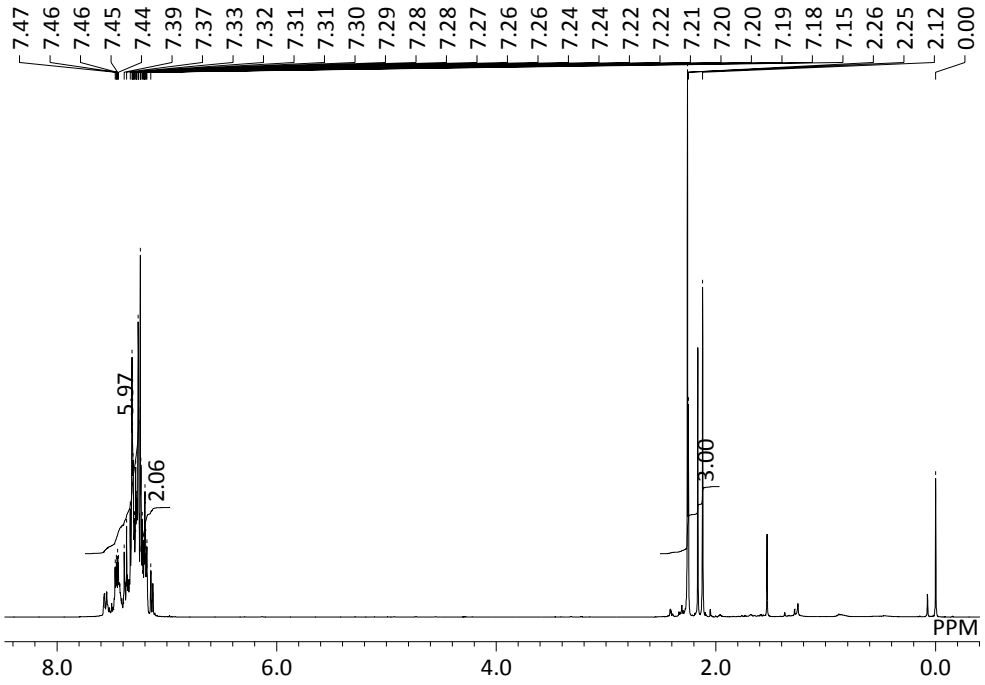

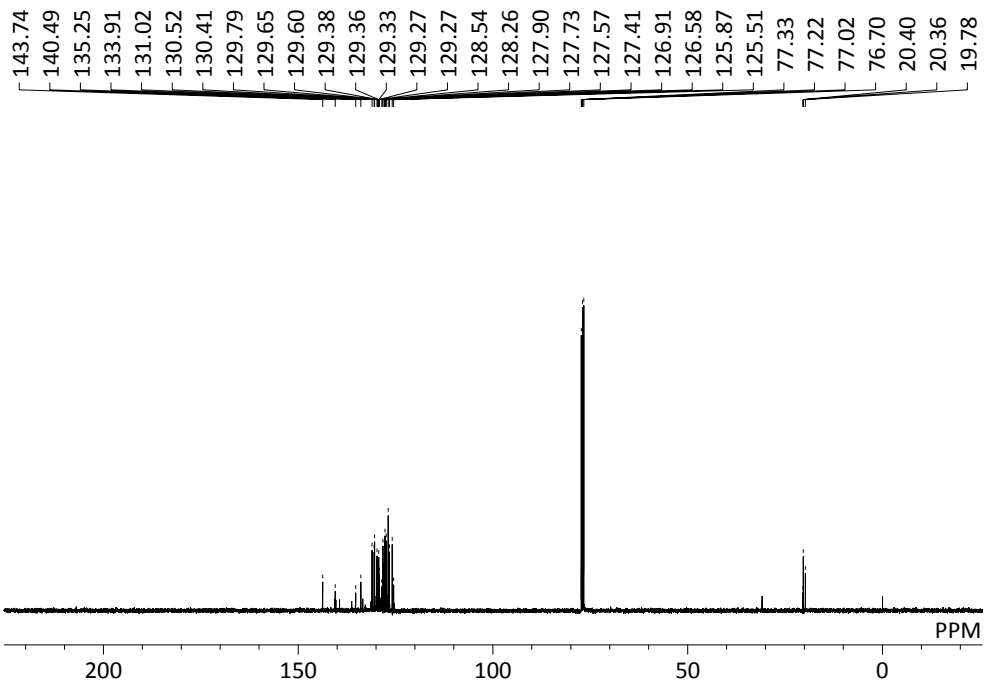

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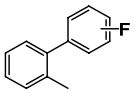

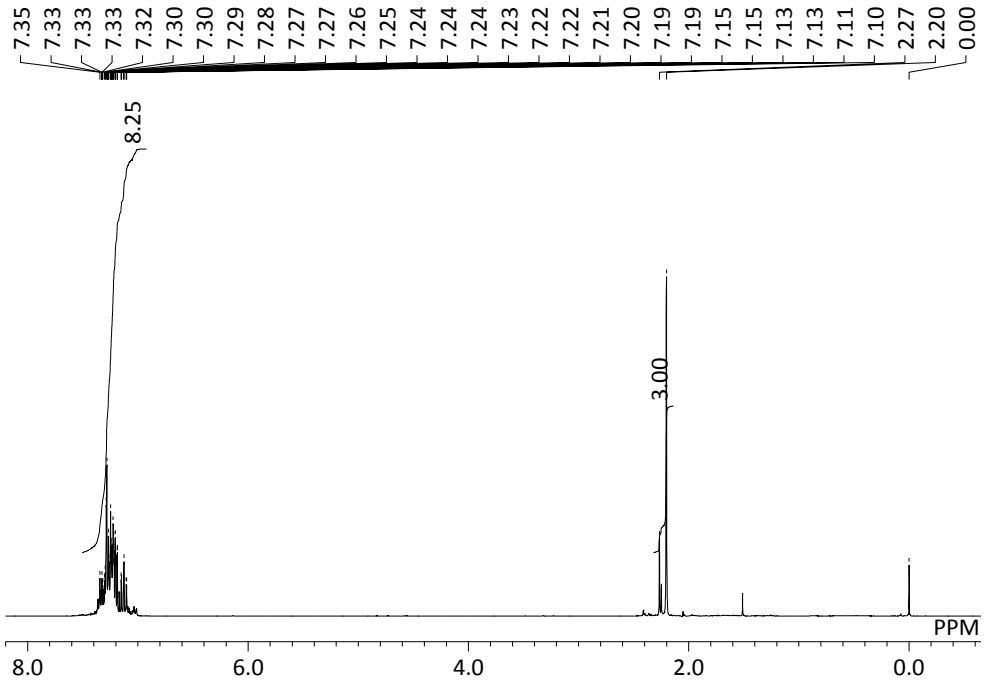

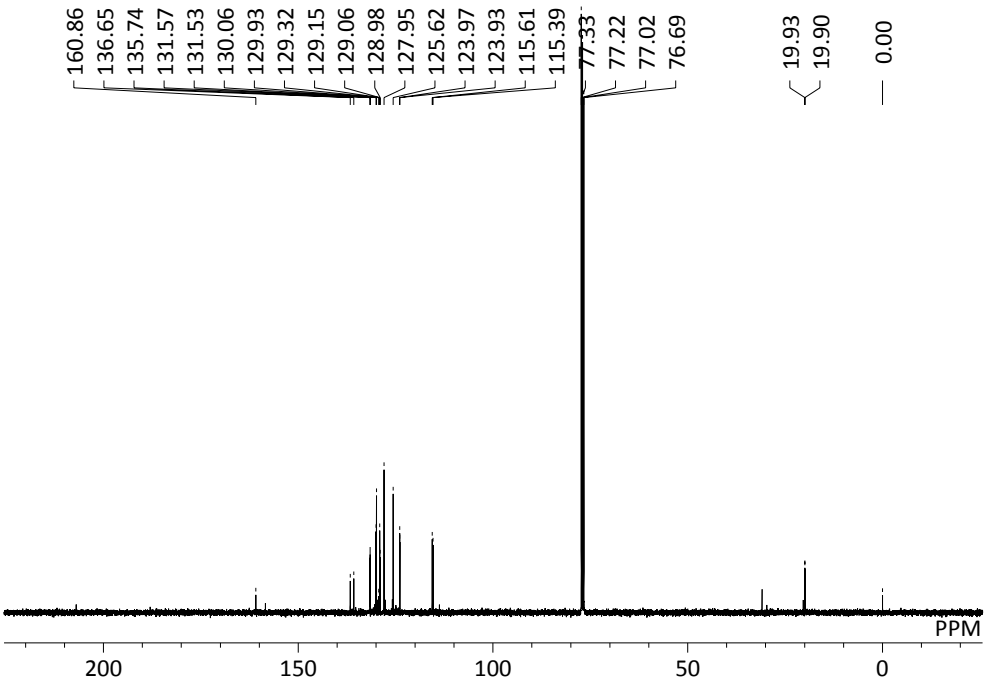

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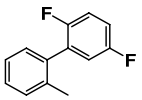

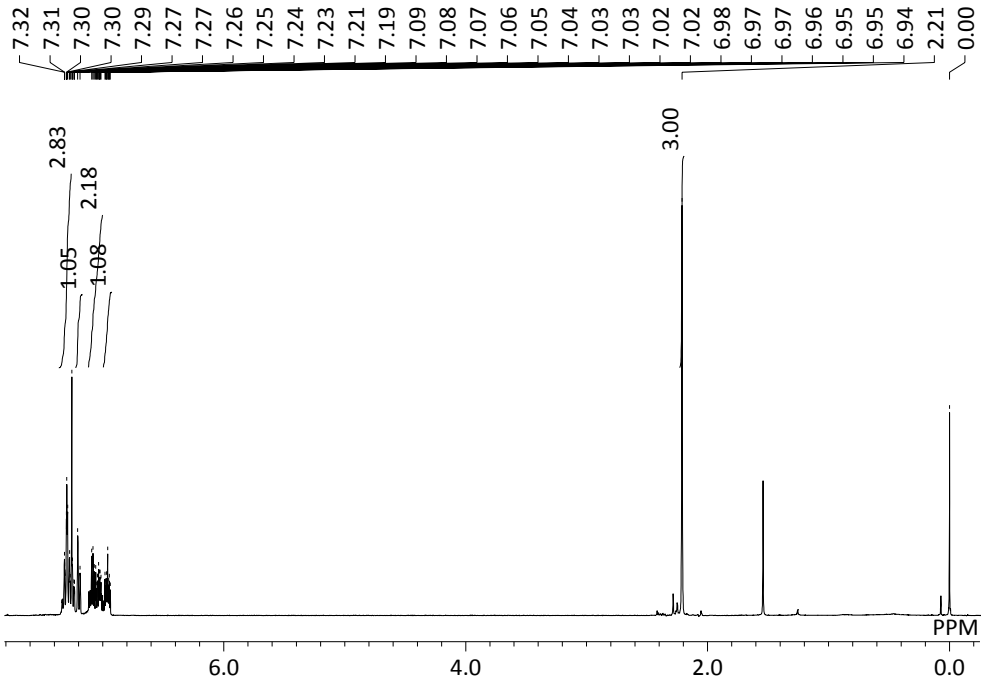

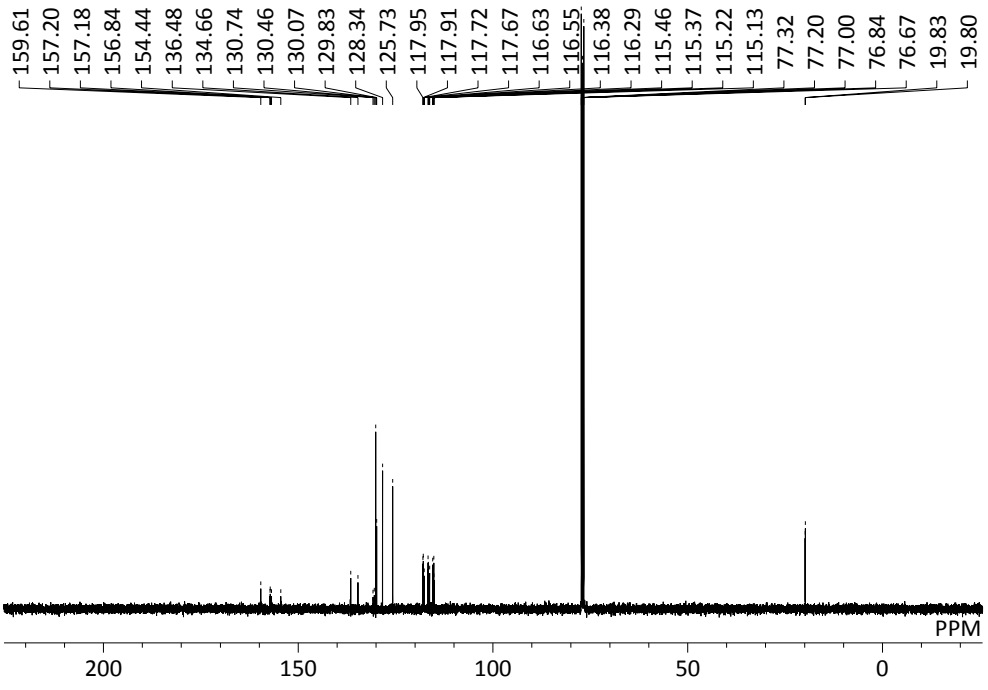

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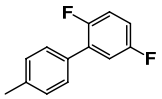

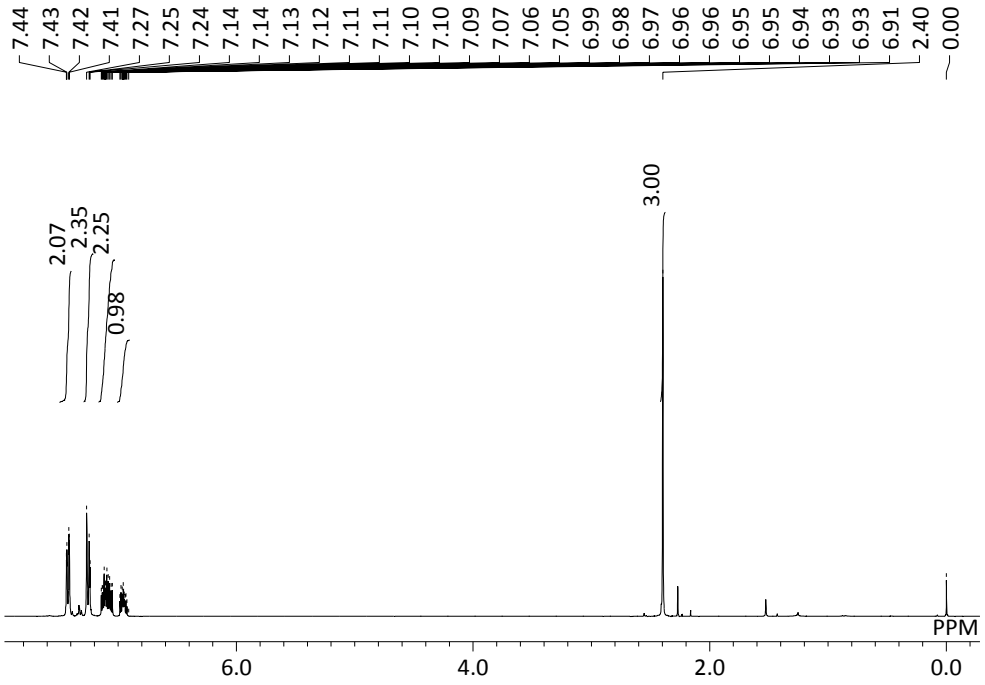

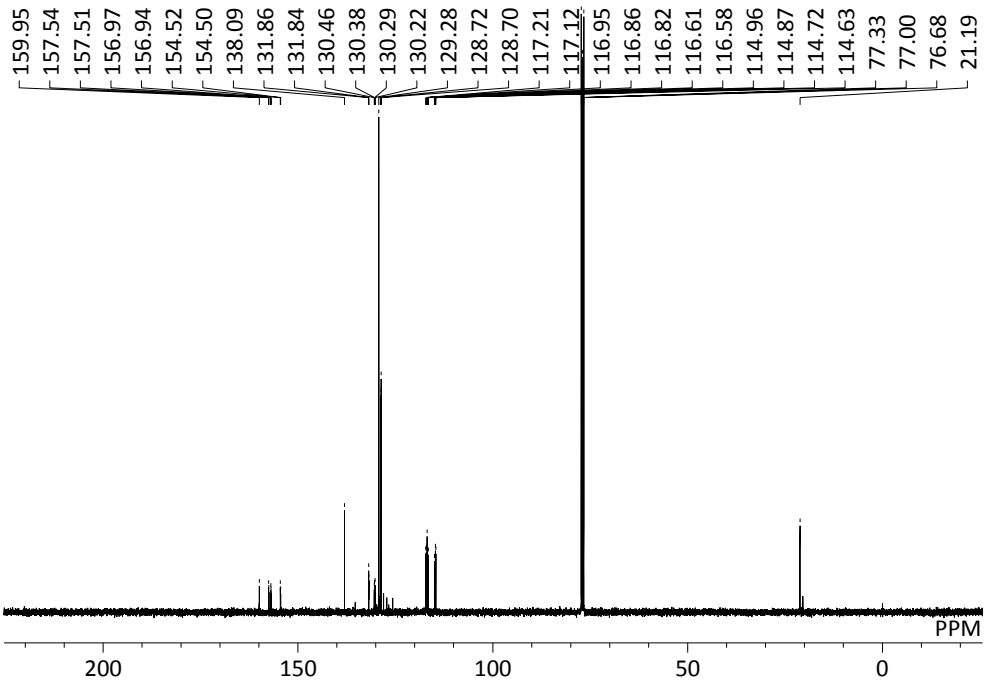

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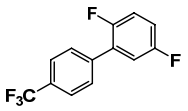

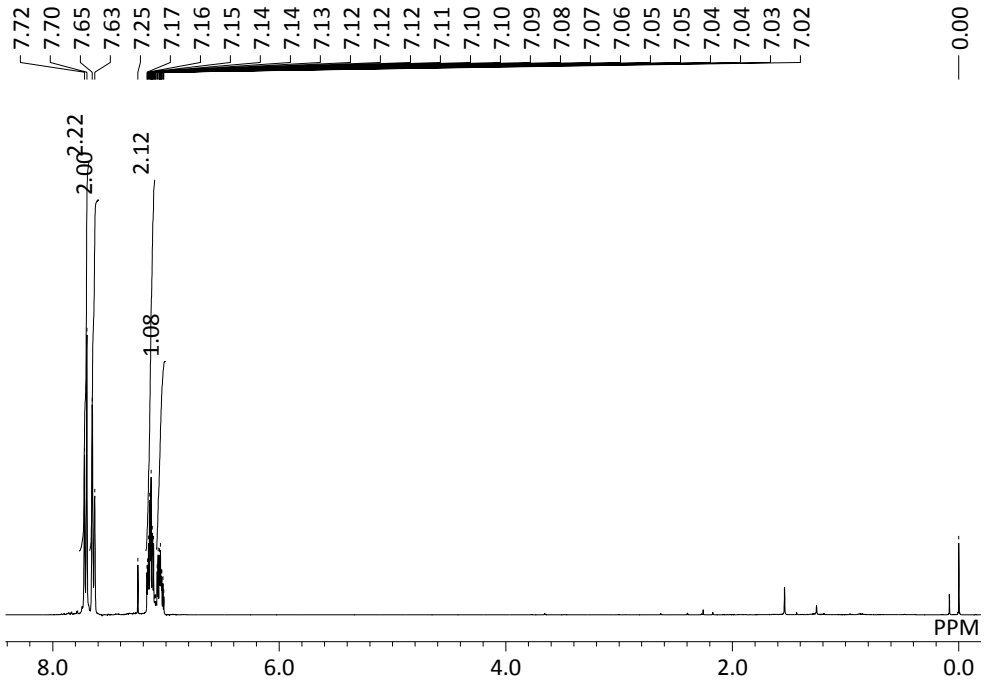

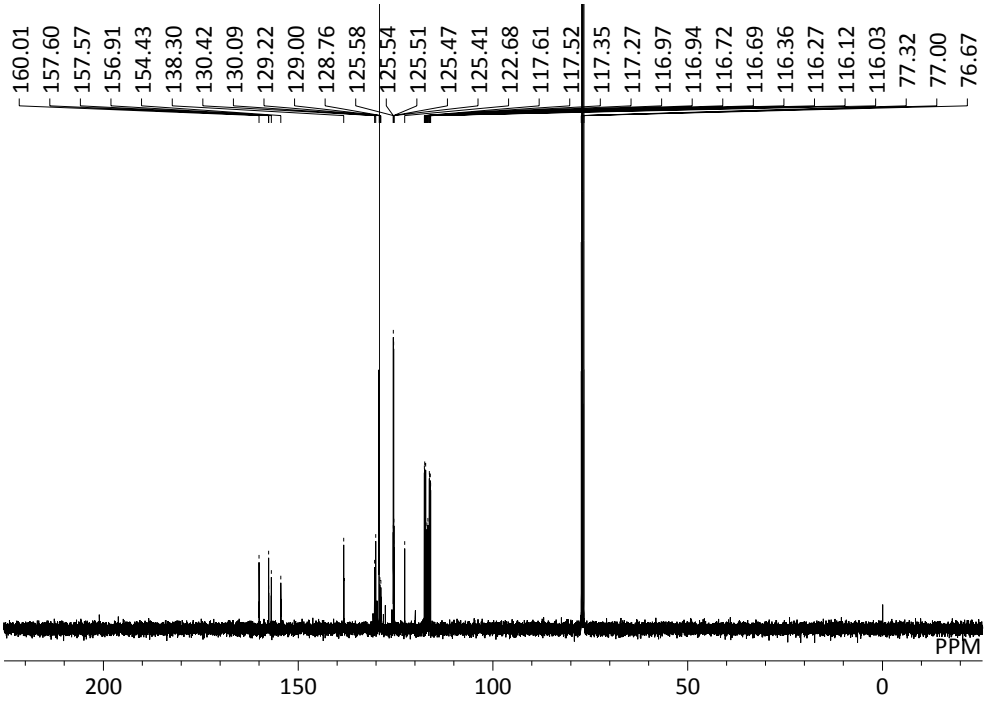

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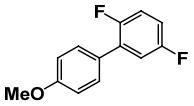

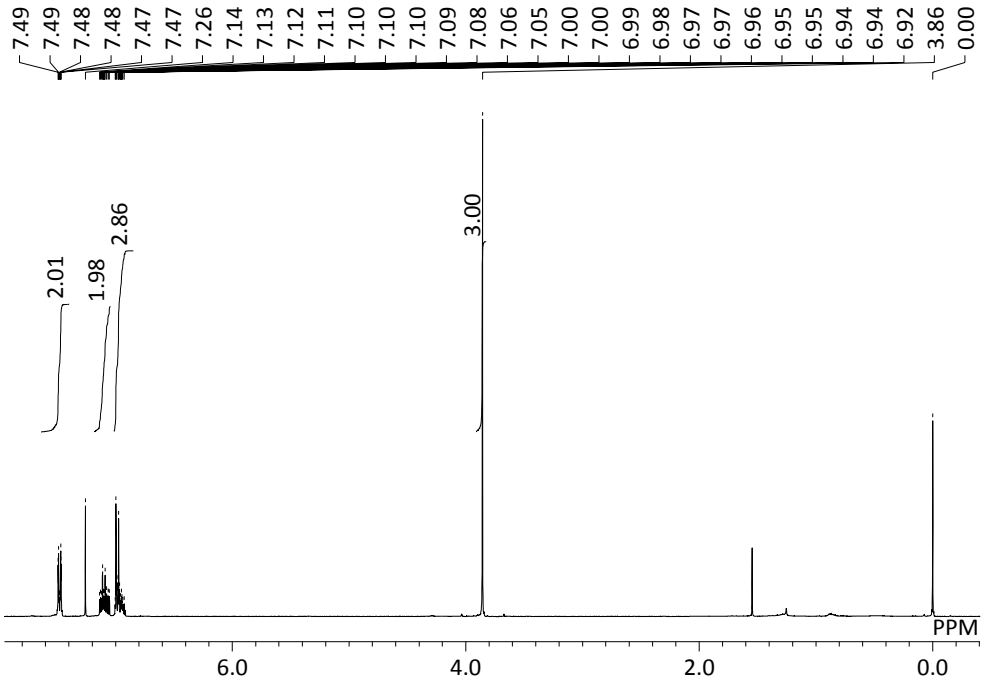

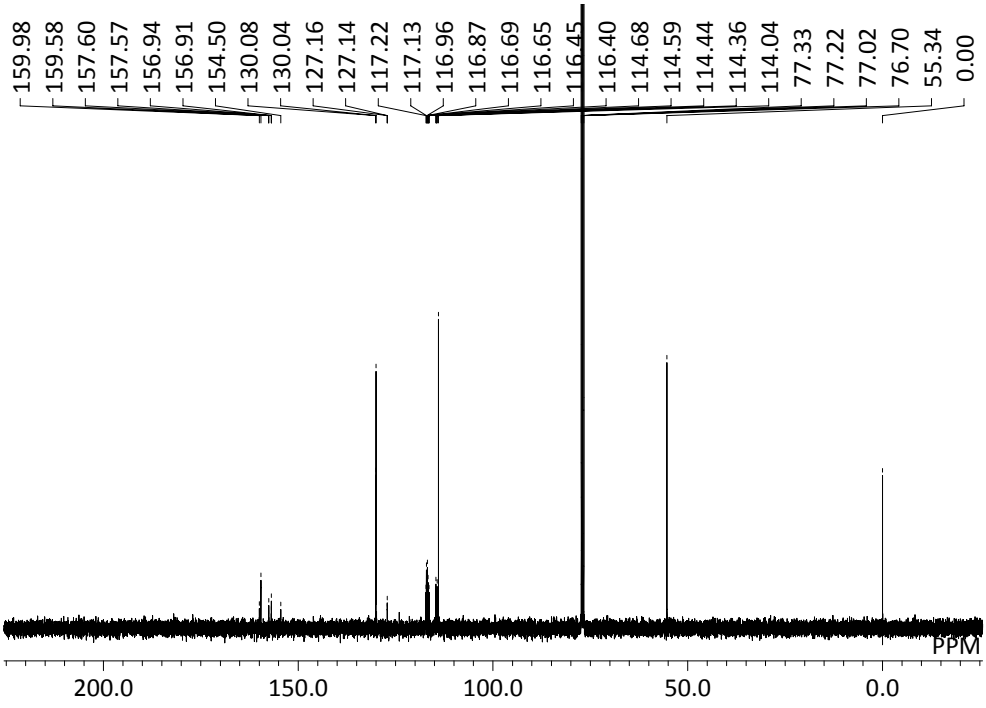

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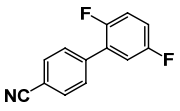

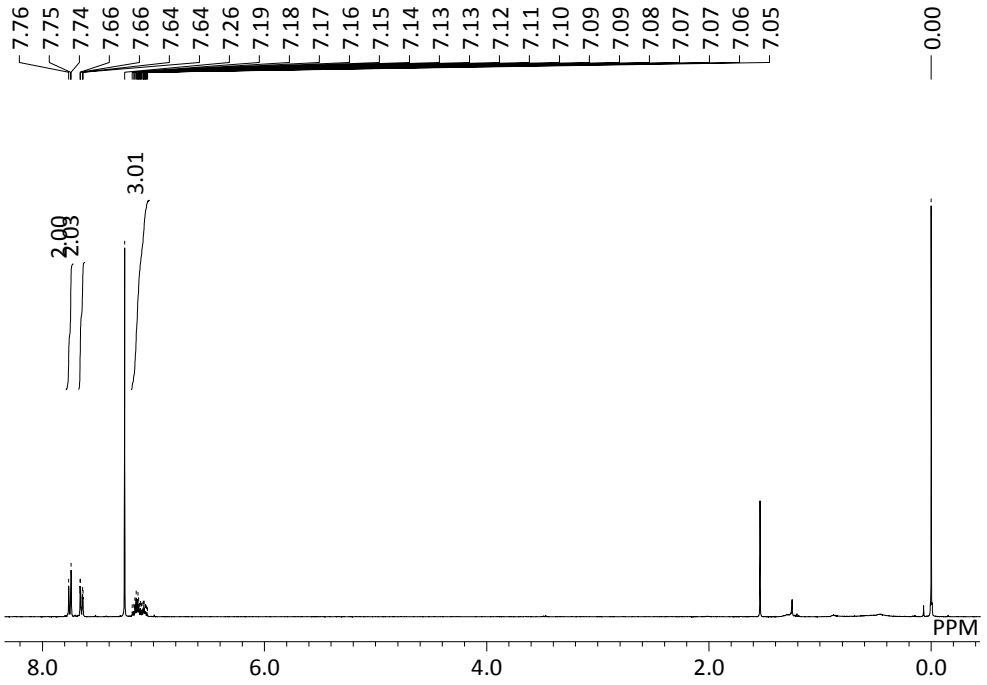

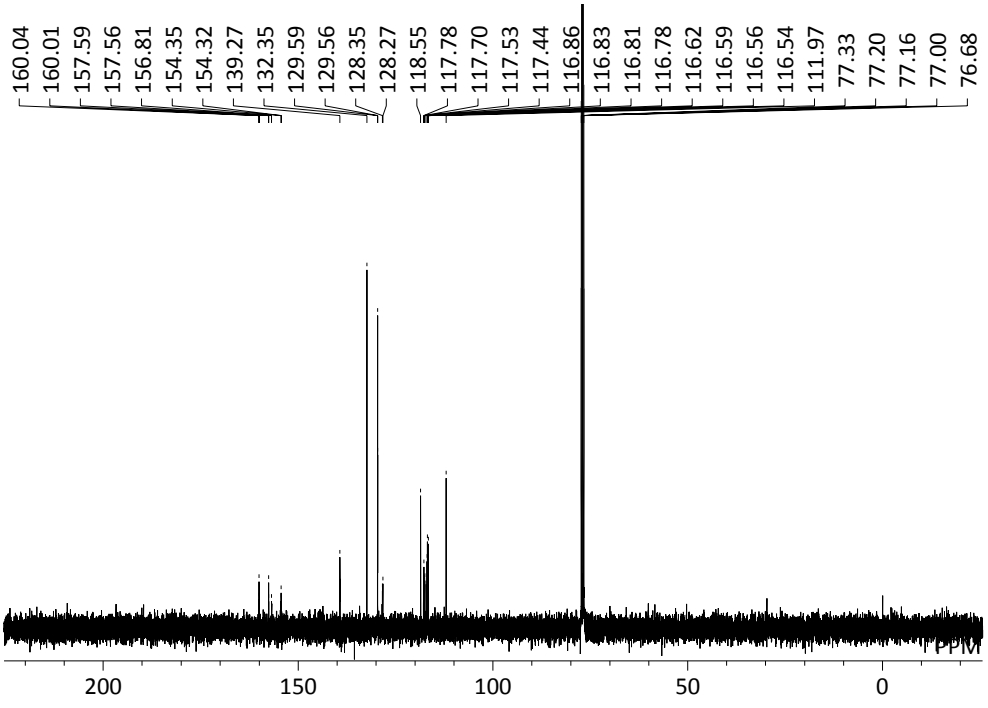

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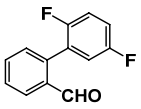

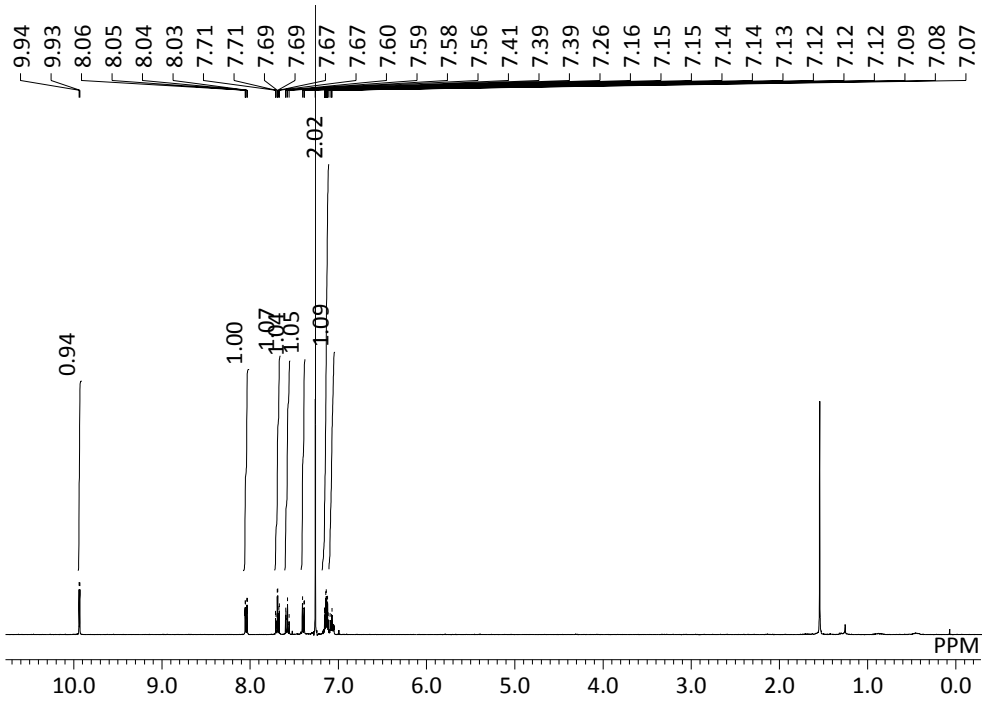

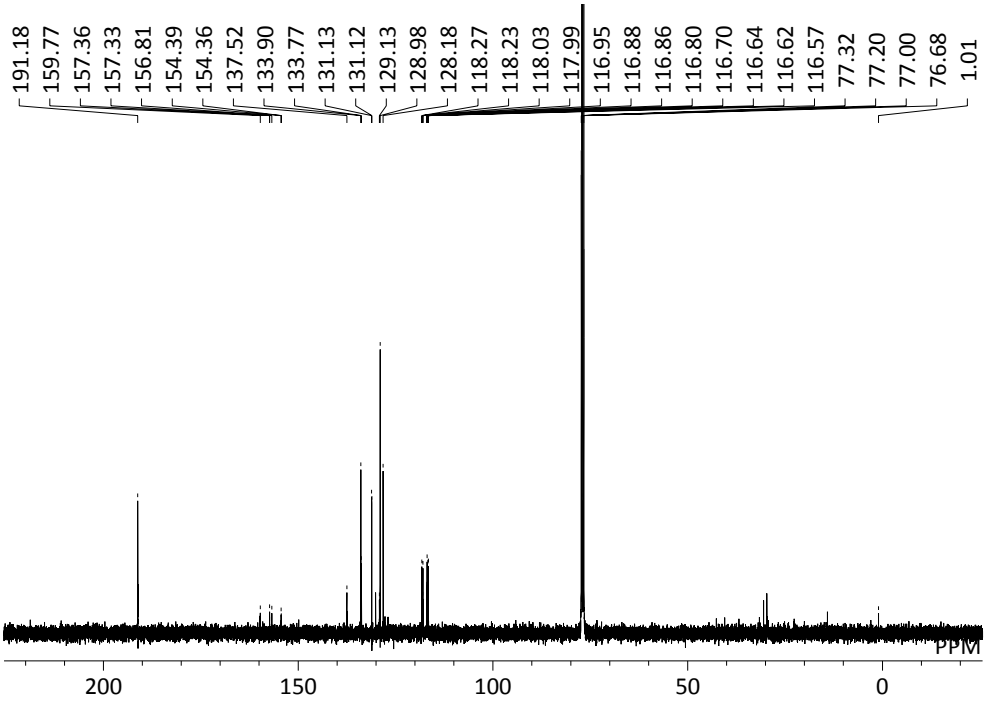

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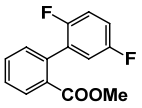

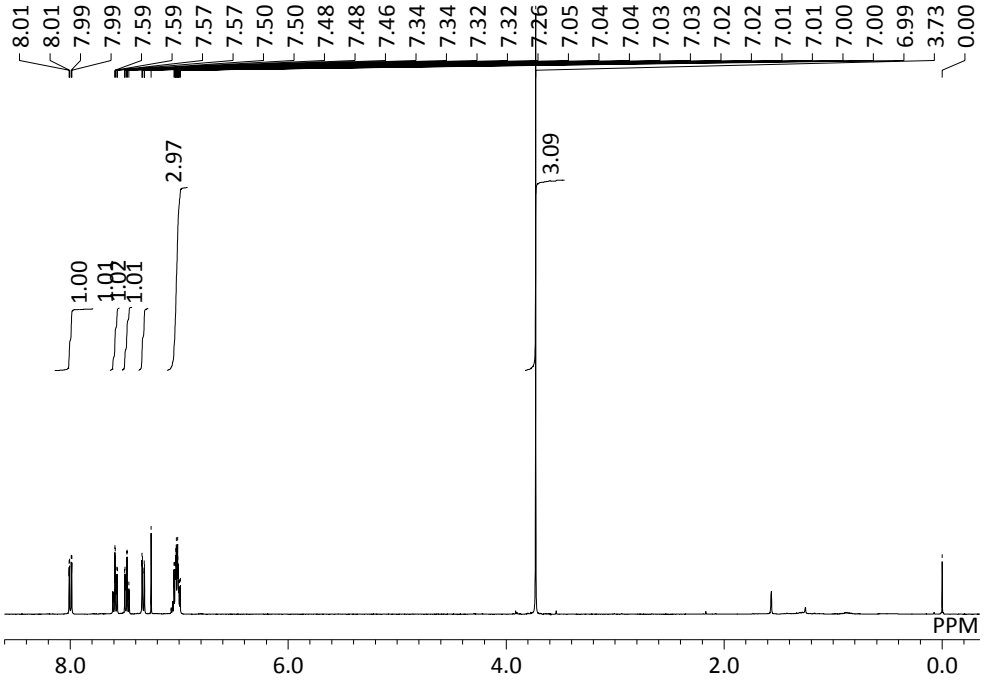

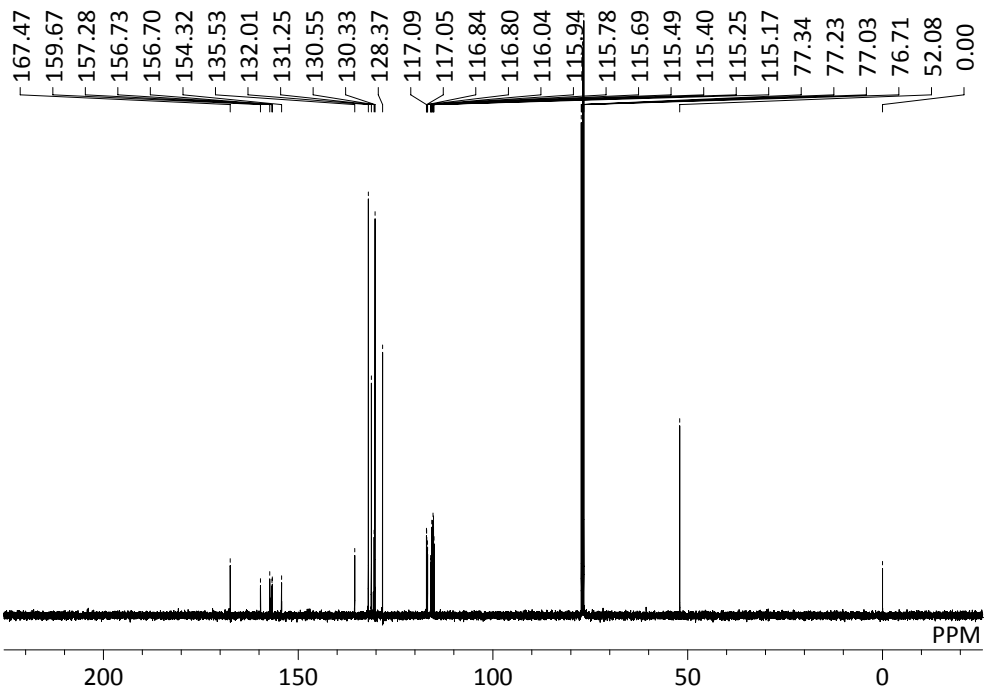

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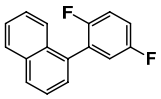

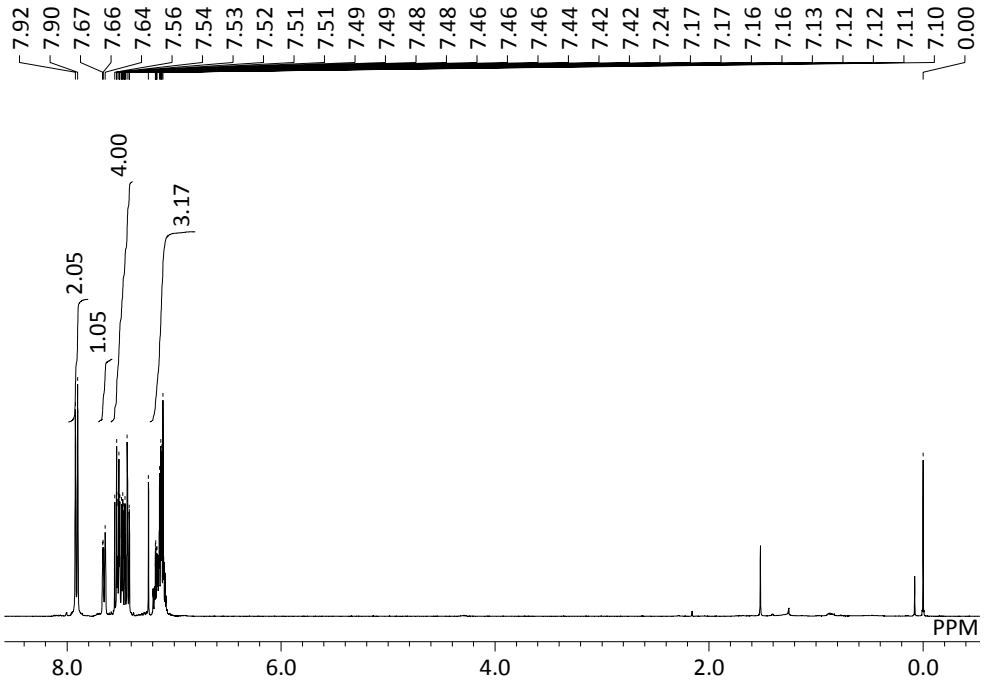

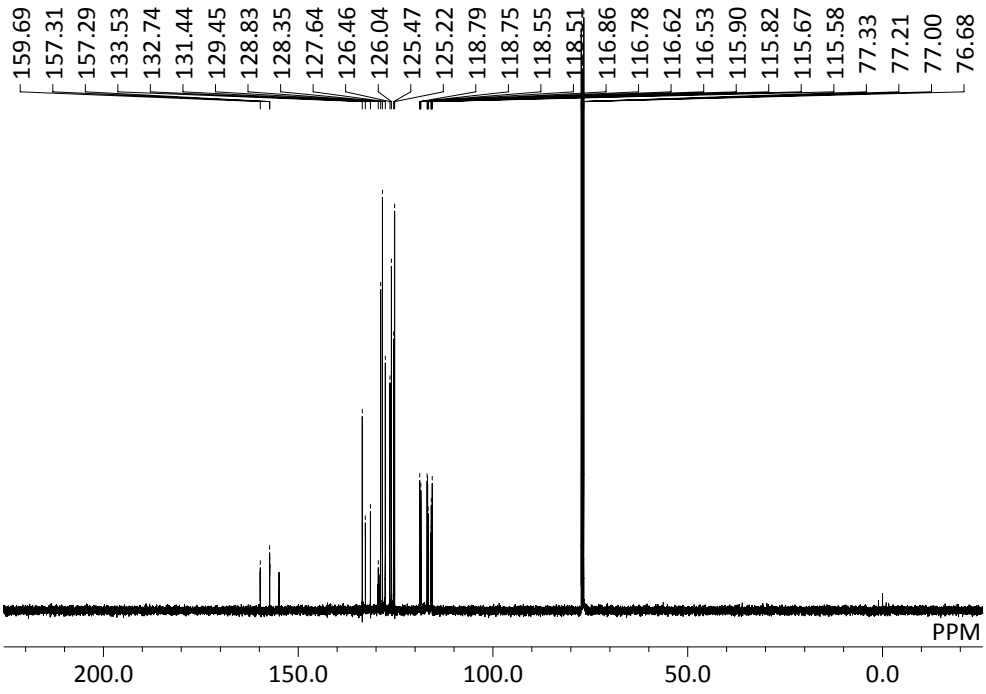

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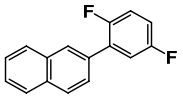

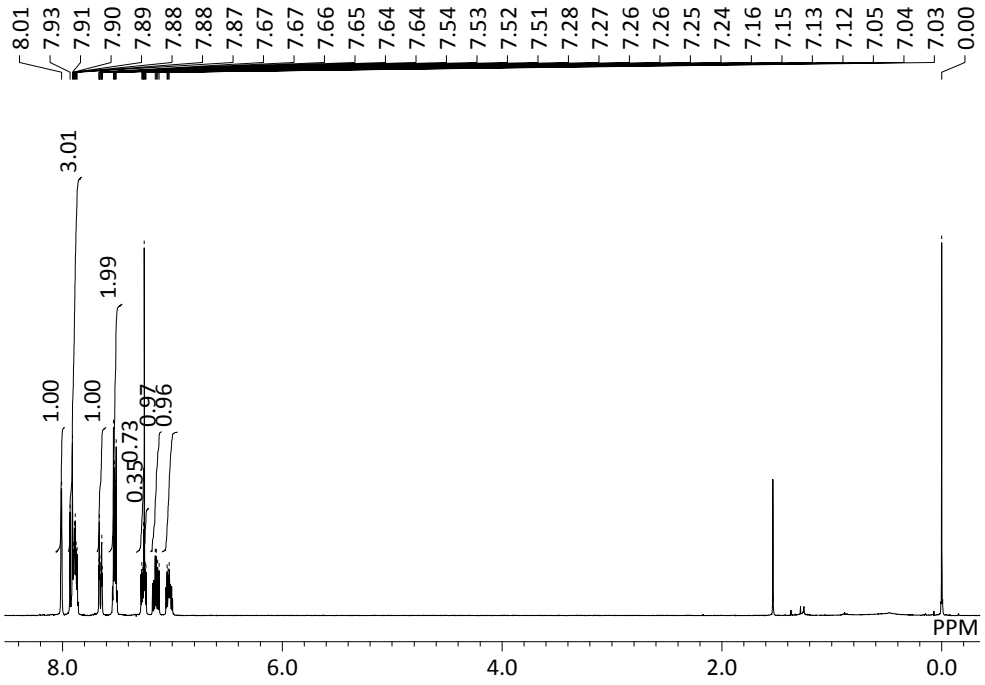

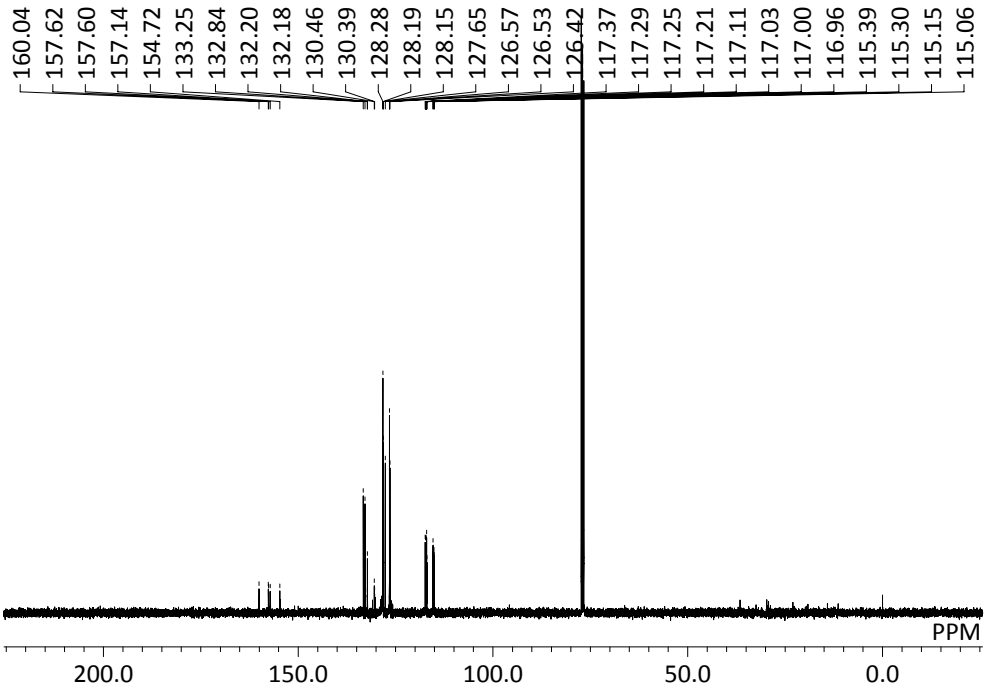

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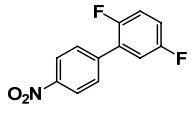

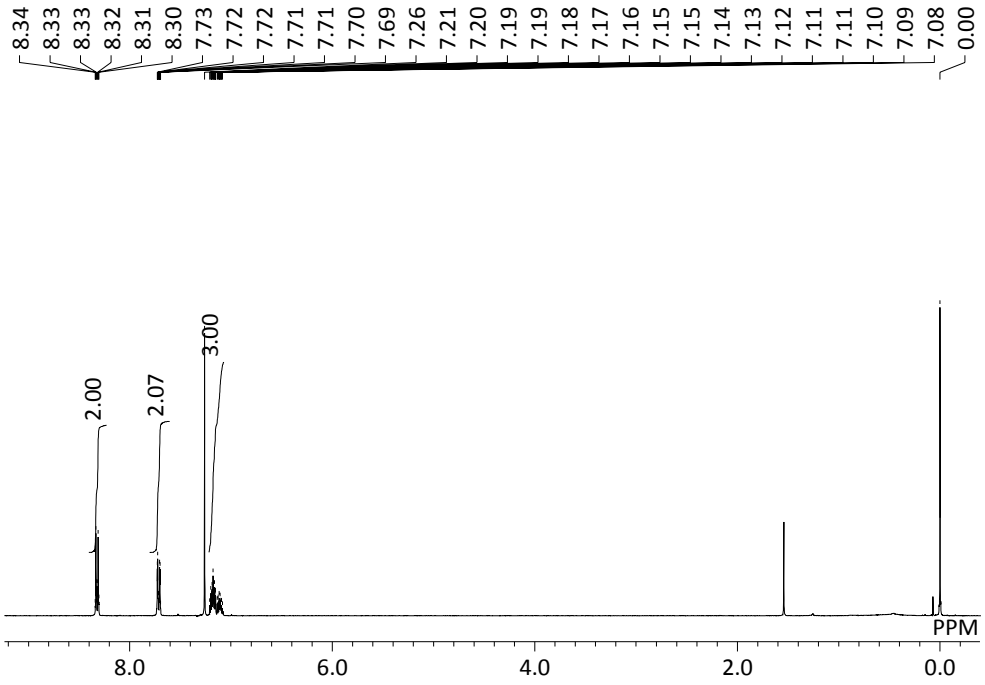

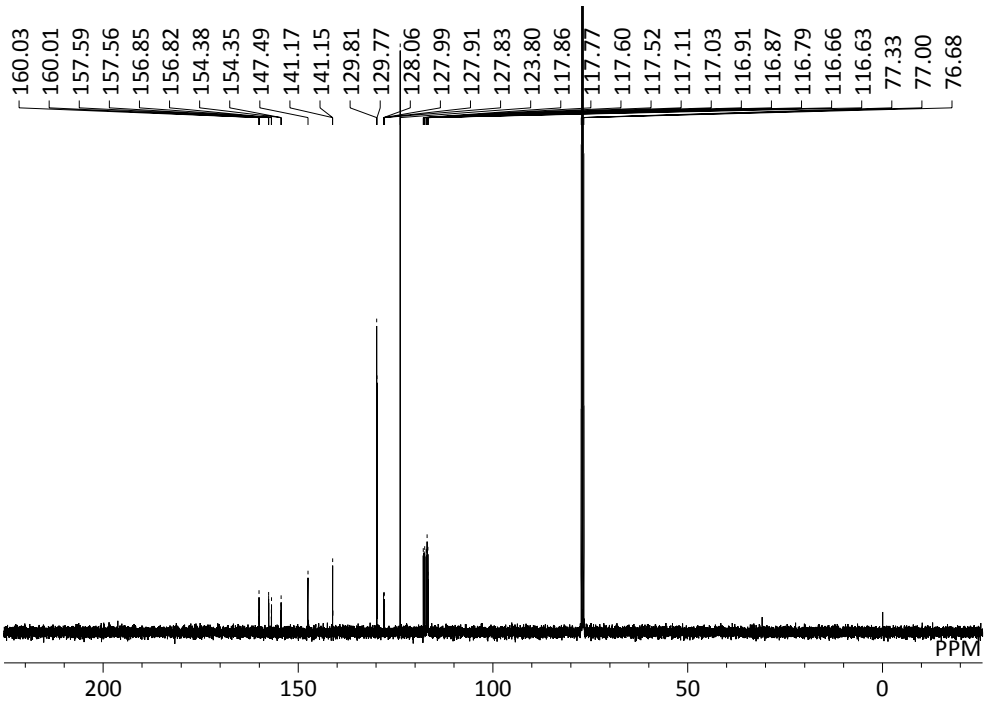

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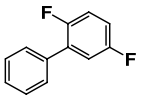

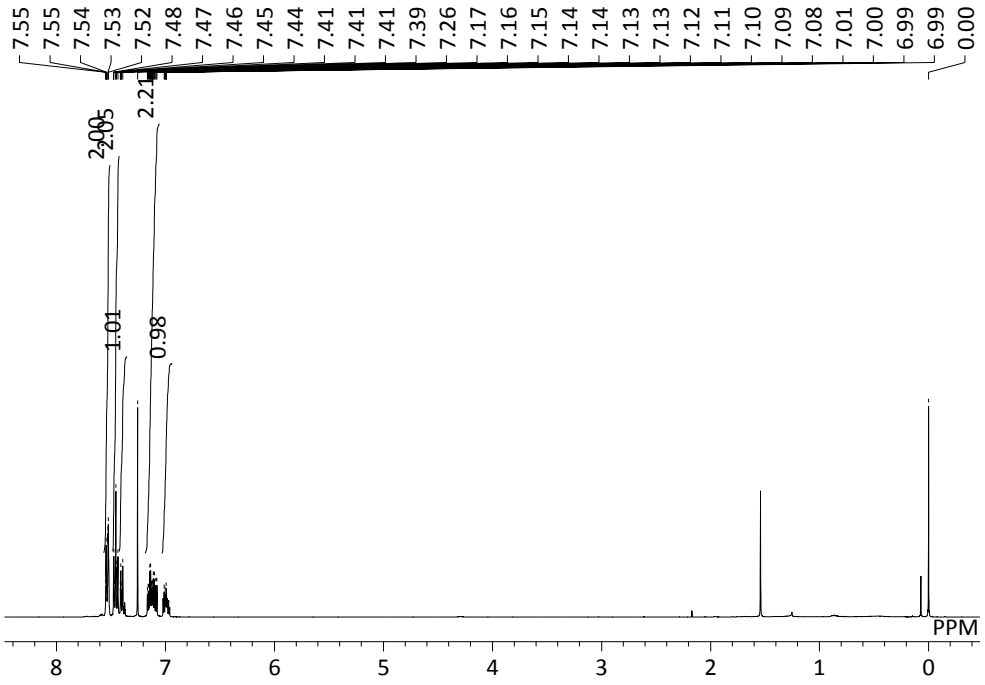

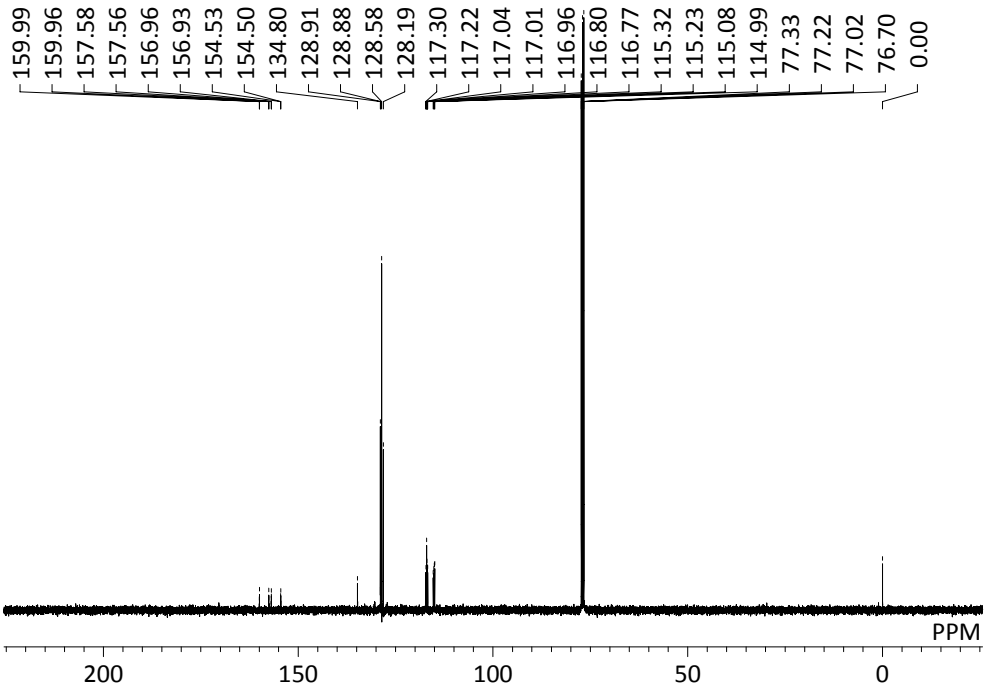

7. References

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