

Supporting Information

Phenol-mediated decarboxylative proton transfers of γ -methylidene- δ -valerolactone: an approach to (*E*)-2,4-pentadienoates

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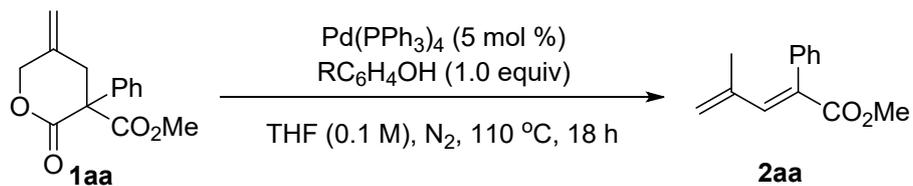
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I. General Procedure Information and Materials

All commercial reagents were used without further purification unless otherwise noted. Solvents were freshly dried according to *the purification handbook Purification of Laboratory Chemicals* before using. All of γ -methylidene- δ -valerolactones (GMDVs) **1aa-1da** were prepared according to literature procedure.¹⁻⁴ Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on a Bruker Avance 500MHz spectrometer. Tetramethylsilane (TMS) served as the internal standard for ^1H NMR, and CDCl_3 served as the internal standard for ^{13}C NMR. ^1H NMR data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, td = triplet of doublet, dt = doublet of triplet, dd = doublet of doublet), coupling constants (Hz), and integration. The X-ray single-crystal diffraction was performed on Saturn 724+ instrument. High resolution mass spectra were obtained on an Ultima Global spectrometer with an ESI source.

II. Optimization of Reaction Conditions

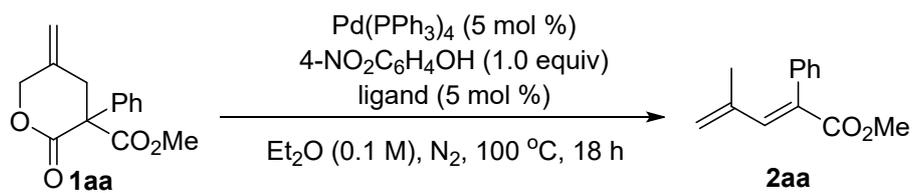
Table S1. Optimization of the Phenol Derivatives ^a



entry	R	yield (%) ^b
1	H	25
2	2-CF ₃	70
3	4-CF ₃	77
4	4-NO₂	82
5	3-OMe	39
6	4-OMe	21
7	2-Br	trace
8	3-Br	trace
9	4-Br	16
10	4-F	23
11	4-Cl	36
12	2-CH ₃	10

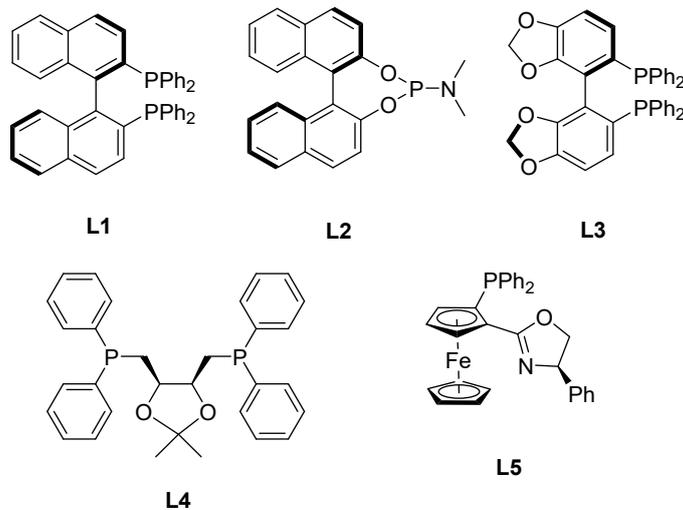
^a Reaction conditions: **1aa** (0.1 mmol), Pd(PPh₃)₄ (5 mol %) and RC₆H₄OH (1.0 equiv) in dry THF (1.0 mL) under the N₂ atmosphere at 110 °C for 18 h. ^b Isolated yield, *E/Z* = 83:17.

Table S2. Optimization of the Ligand ^a



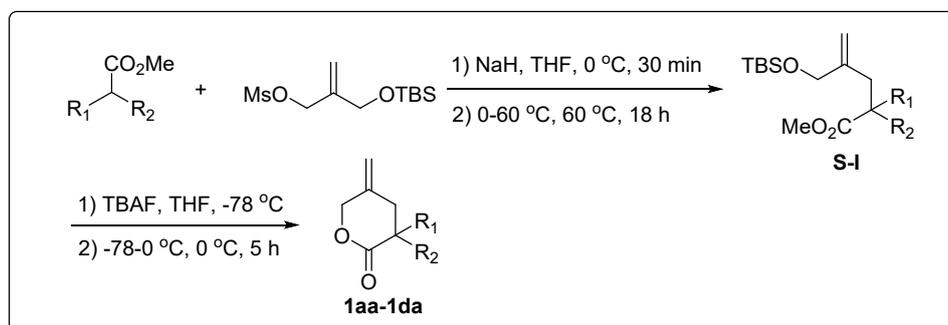
entry	ligand	yield (%) ^b	<i>E/Z</i> ^c
1	L1	92%	95:5
2	L2	92%	90:10
3	L3	trace	97:3
4	L4	96%	84:16
5	L5	90%	95:5

^a Reaction conditions: **1aa** (0.1 mmol), $\text{Pd(PPh}_3)_4$ (5 mol %), ligand (5 mol %), and $4\text{-NO}_2\text{C}_6\text{H}_4\text{OH}$ (1.0 equiv) in dry Et_2O (1 mL) under the N_2 atmosphere at 100 °C for 18 h. ^b Isolated yield. ^c Determined by $^1\text{H NMR}$.



III. Experimental Procedure and Characterization Data

A) Preparation of γ -Methylidene- δ -valerolactones¹⁻⁴

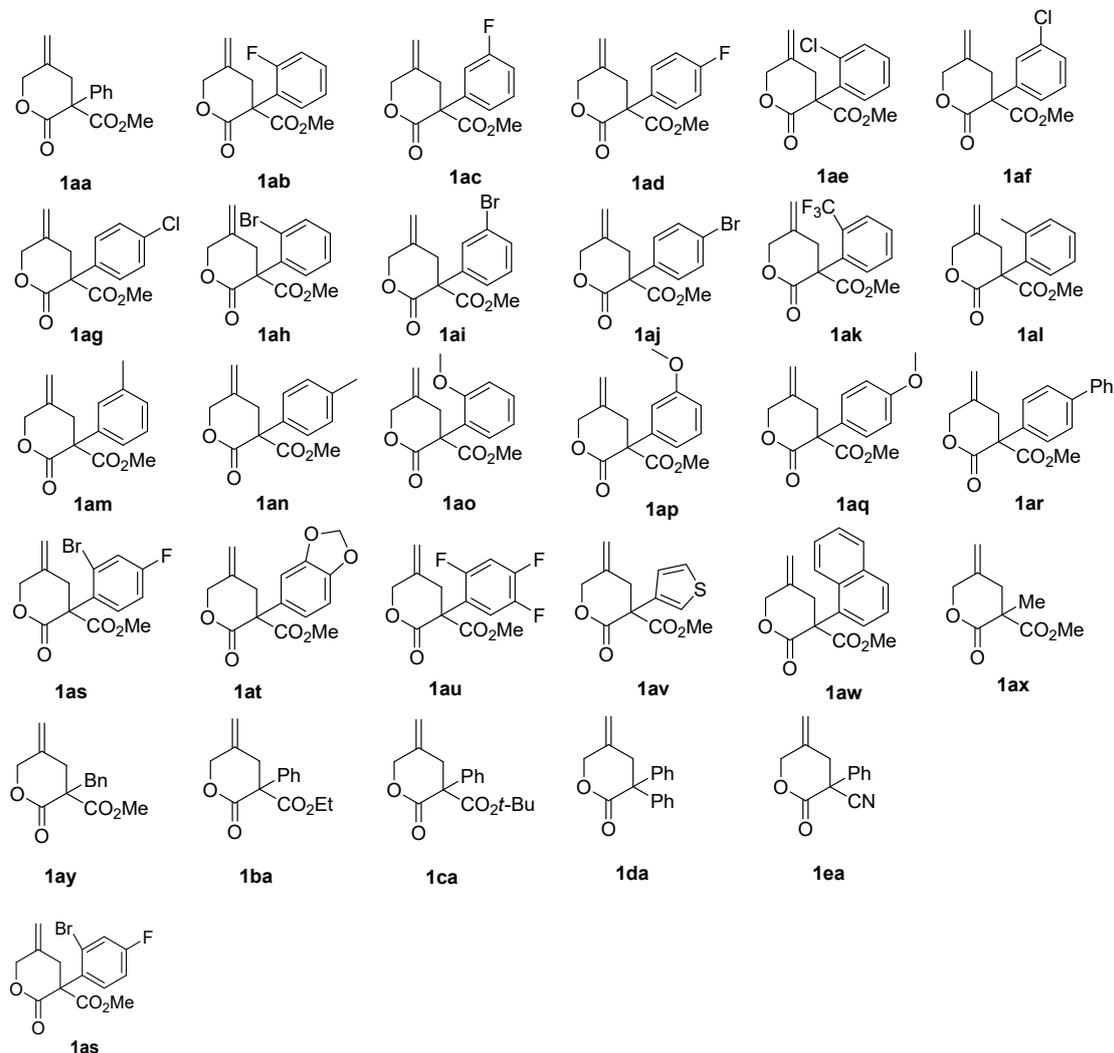


General procedure I: A solution of dimethyl phenylmalonate (2.08 g, 10.0 mmol) in THF (15 mL) was added to a suspension of NaH (420 mg, 10.5 mmol; 60 wt% in mineral oil) in THF (5 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and a solution of 2-(tert-butyl(dimethyl)silyloxy)methyl-2-propen-1-yl methanesulfonate (3.23 g, 11.5 mmol) in THF (12 mL) was then added to the reaction mixture. The resulting mixture was stirred for 18 h at 60 °C and quenched with water. After extraction with EtOAc, the combined organic layer was washed with NaCl (saturated aqueous), dried over Na_2SO_4 , filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (20:1, v/v) to afford the product **S-I**.

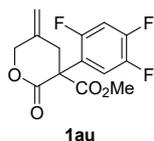
TBAF (1.1 equiv; 1.0 M solution in THF) was added to a solution of **S-I** in THF at -78 °C. The mixture was stirred for 5 h while gradually raising the temperature to 0 °C and the reaction was quenched with water. After extraction with EtOAc, the organic layer was washed with NaCl (saturated aqueous), dried over Na_2SO_4 , filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (5:1, v/v) to afford the products **1aa-1da**.

To a stirred solution of **S-I** in DCM (40 mL) was added $TsOH \cdot H_2O$ (2.0 equiv) at rt. The mixture was stirred at room temperature overnight. After filtration, the solvent was removed under reduced pressure to give the crude product. The crude product was

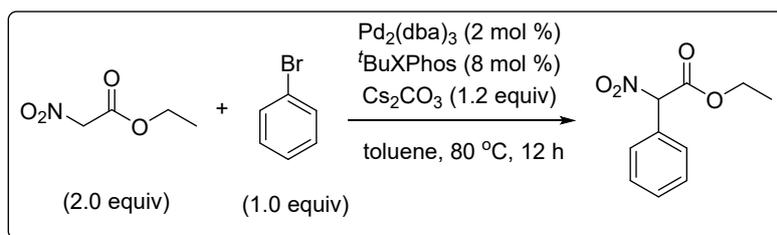
purified by column chromatography with PE/EA = 1/10 to afford the desired product **1ea** as a known compound.



1as: Prepared according to the general procedure I above, and purified by a flash chromatography column with PE/EA (5:1, v/v) as the eluent. White solid (46% yield). Melting point: 140.6-150.8 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.38 (dd, $J = 8.0, 2.5$ Hz, 1H), 7.11 (dd, $J = 9.0, 6.0$ Hz, 1H), 7.04-7.00 (m, 1H), 4.94-4.91 (m, 3H), 4.83 (d, $J = 14.0$ Hz, 1H), 3.81 (s, 3H), 3.63 (d, $J = 15.0$ Hz, 1H), 3.40 (d, $J = 15.0$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 169.1, 167.5, 161.6 (d, $^1J_{\text{C-F}} = 253.3$ Hz), 135.0, 131.9 (d, $^4J_{\text{C-F}} = 3.8$ Hz), 130.8 (d, $^3J_{\text{C-F}} = 8.8$ Hz), 123.3 (d, $^3J_{\text{C-F}} = 9.3$ Hz), 122.5 (d, $^2J_{\text{C-F}} = 23.9$ Hz), 114.7 (d, $^2J_{\text{C-F}} = 21.4$ Hz), 113.3, 72.6, 62.7, 53.6, 36.8. HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{12}\text{BrFO}_4\text{Na}$: 364.9795, found: 364.9796.

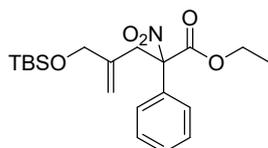


1au: Prepared according to the general procedure I above, and purified by a flash chromatography column with PE/EA (5:1, v/v) as the eluent. White solid (36% yield). Melting point: 100.3-110.5 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.06 – 6.94 (m, 2H), 5.04 (d, $J = 7.0$ Hz, 2H), 4.92 (d, $J = 14.0$ Hz, 1H), 4.86 (d, $J = 14.5$ Hz, 1H), 3.81 (s, 3H), 3.31 (d, $J = 14.5$ Hz, 1H), 3.19 (d, $J = 14.5$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 168.7, 166.7, 155.7 (ddd, $^1J_{\text{C-F}} = 247.8$ Hz, $^3J_{\text{C-F}} = 9.3$ Hz, $^4J_{\text{C-F}} = 2.8$ Hz), 149.9 (dt, $^1J_{\text{C-F}} = 254.4$ Hz, $^3J_{\text{C-F}} = 13.2$ Hz), 146.5 (ddd, $^1J_{\text{C-F}} = 245.7$ Hz, $^3J_{\text{C-F}} = 12.5$ Hz, $^4J_{\text{C-F}} = 3.3$ Hz), 134.8, 121.0 (dt, $^3J_{\text{C-F}} = 14.6$ Hz, $^4J_{\text{C-F}} = 4.9$ Hz), 116.9 (dd, $^2J_{\text{C-F}} = 21.1$ Hz, $^4J_{\text{C-F}} = 5.0$ Hz), 113.6, 106.6 (dd, $^2J_{\text{C-F}} = 28.7, 21.1$ Hz), 72.4, 58.4, 53.6, 37.1 (d, $^4J_{\text{C-F}} = 4.0$ Hz). HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{F}_3\text{O}_4\text{Na}$: 323.0502, found: 323.0508.

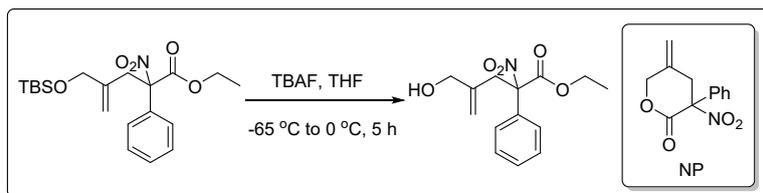


Synthesis of ethyl α -nitrobenzeneacetate: In a nitrogen atmosphere, to an oven-dried 250ml eggplant shaped bottle was added $\text{Pd}_2(\text{dba})_3$ (366 mg, 0.4 mmol), $t\text{-BuXPhos}$ (680 mg, 1.6 mmol), and Cs_2CO_3 (7.8 g, 24.0 mmol). Next, toluene (150 mL), ethyl nitroacetate (4.5 mL, 40.0 mmol), and bromobenzene (2.1 mL, 20.0 mmol) were added to give a heterogenous reaction mixture. The solution was then heated to 80 °C and stirred vigorously for 12 h. After cooling, the reaction mixture was diluted with EtOAc and acidified with HCl (1 M). The aqueous layer was extracted with additional EtOAc ($\times 3$) and washed with brine. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by a flash chromatography column with PE/EA (30:1, v/v) as the eluent. Afford the desired ethyl α -nitrobenzeneacetate as a yellow oil (3.88 g, 18.6 mmol, 86% yield). The ^1H NMR is in accordance with the literature.⁶

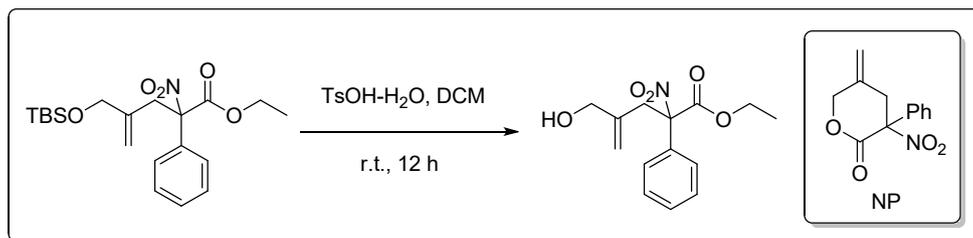
^1H NMR (500 MHz, CDCl_3) δ 7.51- 7.44 (m, 5H), 6.18 (s, 1H), 4.40 – 4.26 (m, 2H), 1.29 (t, $J = 7.0$ Hz, 3H) ppm.



Synthesis of ethyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-nitro-2-phenylpent-4-enoate: A solution of ethyl α -nitrobenzeneacetate (3.88 g, 18.6 mmol) in THF (28 mL) was added to a suspension of NaH (782 mg, 19.5 mmol; 60 wt% in mineral oil) in THF (9 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C and a solution of 2-(*tert*-butyldimethylsilyloxy)methyl-2-propen-1-yl methanesulfonate (6.01 g, 21.4 mmol) in THF (23 mL) was added to it. The resulting mixture was stirred for 36 h at 60 °C and was quenched with water. After extraction with EtOAc, the organic layer was washed with NaCl (saturated aqueous), dried over Na₂SO₄, filtered, and concentrated in vacuum. The residue was chromatographed on silica gel with PE/EA (50:1, v/v) to afford the product as a yellow oil (1.19 g, 3.1 mmol; 16% yield). The product was prepared according to the reported literature procedures.¹ ¹H NMR (500 MHz, CDCl₃) δ 7.46 – 7.38 (m, 5H), 5.23 (d, J = 1.7 Hz, 1H), 5.10 (d, J = 1.4 Hz, 1H), 4.78 (s, 2H), 4.35 (q, J = 7.2 Hz, 2H), 4.13 (s, 2H), 1.35 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 163.6, 149.6, 143.9, 129.6, 129.5, 129.1, 127.9, 113.1, 76.5, 63.8, 62.1, 25.9, 18.4, 14.2, -5.5 ppm.

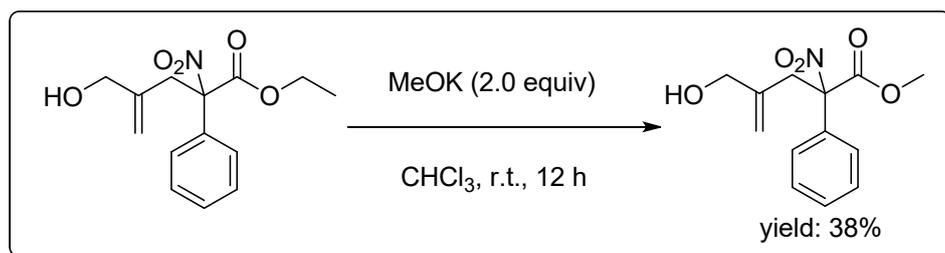


Method A: TBAF (1.1 mL, 1.1 mmol; 1.0 M solution in THF) was added to a solution of ethyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-nitro-2-phenylpent-4-enoate (393 mg, 1.0 mmol) in THF (3 mL) at $-65\text{ }^{\circ}\text{C}$. The mixture was stirred for 5 h while gradually raising the temperature to $0\text{ }^{\circ}\text{C}$ and the reaction was quenched with water. After extraction with EtOAc, the organic layer was washed with NaCl (saturated aqueous), dried over Na_2SO_4 , filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with PE/EA (2:1, v/v) to afford ethyl 4-(hydroxymethyl)-2-nitro-2-phenylpent-4-enoate as a colorless oil (165 mg, 0.59 mmol; 59% yield). No desired product was obtained.



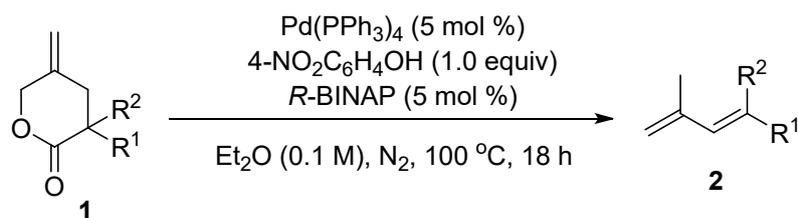
Method B: To a stirred solution of ethyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-nitro-2-phenylpent-4-enoate (393 mg, 1.0 equiv.) in DCM (8 mL) was added $\text{TsOH}\cdot\text{H}_2\text{O}$ (2.0 equiv.) at rt. The mixture was stirred at rt overnight. After filtration, the solvent was removed under reduced pressure to give the crude product. The crude product was purified by column chromatography with PE/EA (2:1, v/v) to afford ethyl 4-(hydroxymethyl)-2-nitro-2-phenylpent-4-enoate as a colorless oil (136 mg, 0.49 mmol; 49% yield). No desired product was obtained.

Ethyl 4-(hydroxymethyl)-2-nitro-2-phenylpent-4-enoate: ^1H NMR (500 MHz, CDCl_3) δ 7.45 – 7.39 (m, 5H), 5.21 (d, $J = 1.5\text{ Hz}$, 1H), 5.13 (d, $J = 1.0\text{ Hz}$, 1H), 4.80 (s, 2H), 4.33 (q, $J = 7.0\text{ Hz}$, 2H), 4.12 (s, 2H), 1.33 (t, $J = 7.0\text{ Hz}$, 3H) ppm. ^{13}C NMR (126 MHz, CDCl_3) δ 163.4, 149.5, 144.3, 129.7, 129.2, 129.1, 128.0, 115.0, 77.4, 63.9, 62.2, 14.1 ppm.



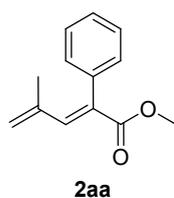
Colorless oil, 38 % yield. ¹H NMR (500 MHz, CDCl₃) δ 7.42 (s, 5H), 5.23 (s, 1H), 5.15 (s, 1H), 4.82 (s, 2H), 4.14 (s, 2H), 3.88 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 163.7, 149.4, 144.9, 129.8, 129.1, 129.1, 128.1, 115.1, 76.8, 64.0, 53.0.

B) Synthesis of 1,3-diene products 2

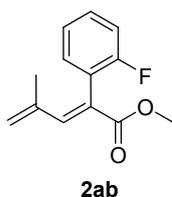


General Procedure II: Under a nitrogen atmosphere, to an oven dried 10 mL Schlenk flask equipped with a stirring bar was added GMDVs **1** (0.1 mmol), 4-NO₂C₆H₄OH (0.1 mmol), Pd(PPh₃)₄ (5 mol %), *R*-BINAP (5 mol %) and dry Et₂O (1.0 mL). The resultant mixture was degassed three times by freeze-pump-thaw cycles, and then stirred at 100 °C for 18 h. The reaction mixture was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate, giving the corresponding product **2**.

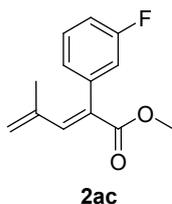
Large-scale Reaction: Under a nitrogen atmosphere, to an oven dried 100 mL Schlenk flask equipped with a stirring bar was added GMDVs **1aa** (1.48g, 6.0 mmol), 4-NO₂C₆H₄OH (6.0 mmol), Pd(PPh₃)₄ (5 mol %), *R*-BINAP (5 mol %) and dry Et₂O (60.0 mL). The resultant mixture was degassed three times by freeze-pump-thaw cycles, and then stirred at 100 °C for 18 h. The reaction mixture was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate, giving the corresponding product **2aa** (1.13g, 93%, *E/Z* = 90:10).



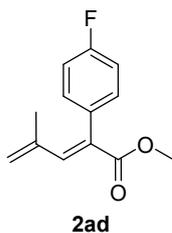
2aa: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (18.6 mg, 92% yield, *E/Z* = 95:5). ¹H NMR (500 MHz, CDCl₃ for major isomer **E-2aa**) δ 7.48 (s, 1H), 7.35 – 7.28 (m, 3H), 7.19-7.18 (m, 2H), 5.24 (s, 1H), 5.18 (s, 1H), 3.72 (s, 3H), 1.37 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer **E-2aa**) δ 168.5, 142.8, 141.0, 136.0, 131.9, 130.1, 127.7, 127.6, 124.97, 52.25, 21.18 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₃H₁₄O₂Na: 225.0886, found: 225.0890.



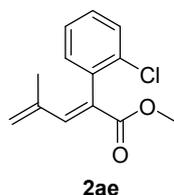
2ab: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (13.9 mg, 63% yield, *E/Z* = 96:4). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2ab**) δ 7.59 (s, 1H), 7.35 – 7.29 (m, 1H), 7.17 – 7.11 (m, 2H), 7.06 (t, *J* = 9.0 Hz, 1H), 5.28 (s, 1H), 5.23 (s, 1H), 3.74 (s, 3H), 1.95 (s, 0.12H), 1.44 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃ major isomer **E-2ab**) δ 167.6, 160.2 (d, ¹*J*_{C-F} = 245.8 Hz), 144.8, 140.6, 132.1, 129.8 (d, ³*J*_{C-F} = 7.8 Hz), 125.5, 125.4, 123.8 (d, ²*J*_{C-F} = 17.2 Hz), 123.5 (d, ⁴*J*_{C-F} = 2.5 Hz), 115.2 (d, ²*J*_{C-F} = 22.0 Hz), 52.3, 20.6 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₃H₁₃FO₂Na: 243.0792, found: 243.0794.



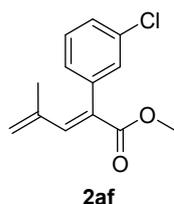
2ac: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (10.1 mg, 46% yield, *E/Z* = 83:17). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2ac**) δ 7.49 (s, 1H), 7.29 (dd, *J* = 14.0, 7.8 Hz, 1H), 7.02 (td, *J* = 8.5, 2.0 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 9.5 Hz, 1H), 5.27 (s, 1H), 5.22 (s, 1H), 3.74 (s, 3H), 1.41 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer **E-2ac**) δ 168.0, 162.2 (d, ¹*J*_{C-F} = 246.2 Hz), 143.4, 140.5, 138.1 (d, ³*J*_{C-F} = 8.0 Hz), 134.0, 130.5, 129.2 (d, ³*J*_{C-F} = 8.3 Hz), 125.9 (d, ⁴*J*_{C-F} = 2.1 Hz), 125.5, 117.2 (d, ²*J*_{C-F} = 21.5 Hz), 114.6 (d, *J* = 21.0 Hz), 113.16 (d, *J* = 22.9 Hz), 52.32, 21.12 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₃H₁₃FO₂Na: 243.0792, found: 243.0787.



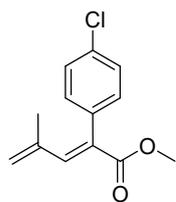
2ad: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v, for major isomer **E-2ad**) as the eluent. Colorless oil (8.4 mg, 38% yield, *E/Z* = 86:14). ¹H NMR (500 MHz, CDCl₃) δ 7.49 (s, 1H), 7.18 – 7.13 (m, 2H), 7.05 – 7.00 (m, 2H), 5.26 (s, 1H), 5.21 (s, 1H), 3.74 (s, 3H), 1.39 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 168.3, 162.4 (d, ¹J_{C-F} = 246.7 Hz), 143.3, 140.7, 133.2, 131.8 (d, ⁴J_{C-F} = 3.5 Hz), 131.72 (d, ³J_{C-F} = 8.0 Hz), 130.8, 125.3, 114.75 (d, ²J_{C-F} = 21.5 Hz), 52.3, 21.3 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₃H₁₃FO₂Na: 243.0792, found: 243.0795.



2ae: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (21.7 mg, 92% yield, *E/Z* = 99:1). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2ae**) δ 7.55 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.26 (dt, *J* = 14.5, 7.5 Hz, 2H), 7.17 (d, *J* = 7.5 Hz, 1H), 5.28 (s, 1H), 5.23 (s, 1H), 3.73 (s, 3H), 1.38 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 167.6, 144.0, 140.7, 135.3, 134.4, 131.8, 129.3, 129.0, 126.2, 125.8, 52.4, 20.5 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₃H₁₃ClO₂Na: 259.0496, found: 259.0492.

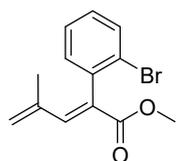


2af: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (17.9 mg, 76% yield, *E/Z* = 88:12). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2af**) δ 7.49 (s, 1H), 7.31 – 7.25 (m, 2H), 7.19 (s, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 5.27 (s, 1H), 5.23 (s, 1H), 3.74 (s, 3H), 1.40 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 167.0, 142.5, 139.5, 136.8, 132.6, 129.4, 129.1, 127.9, 127.3, 126.8, 124.7, 51.4, 20.3 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₃H₁₃ClO₂Na: 259.0496, found: 259.0496.



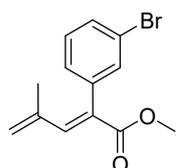
2ag

2ag: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (30.7 mg, 45% yield, *E/Z* = 83:17). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2ag**) δ 7.49 (s, 1H), 7.17 – 7.12 (m, 2H), 7.05 – 7.01 (m, 2H), 5.26 (s, 1H), 5.21 (s, 1H), 3.74 (s, 3H), 1.39 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 167.32, 162.37, 160.41, 142.27, 139.72, 132.17, 130.86, 130.83, 130.75, 130.69, 130.44, 129.76, 127.03, 126.96, 124.25, 119.41, 114.70, 114.53, 113.84, 113.67, 51.30, 51.14, 30.43, 29.21, 20.27, 19.04 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₃H₁₃ClO₂Na: 259.0496, found: 259.0497.



2ah

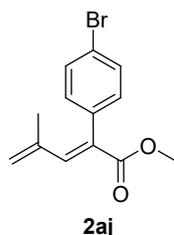
2ah: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (27.2 mg, 97% yield, *E/Z* = 99:1). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2ah**) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.53 (s, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.19 (dd, *J* = 13.0, 7.5 Hz, 2H), 5.29 (s, 1H), 5.23 (s, 1H), 3.73 (s, 3H), 1.38 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer **E-2ah**) δ 166.4, 142.7, 139.7, 136.4, 131.2, 130.7, 129.8, 128.3, 125.8, 124.7, 123.7, 51.4, 19.6 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₃H₁₃BrO₂Na: 302.9991, found: 302.9987.



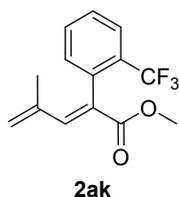
2ai

2ai: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (6.2 mg,

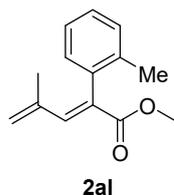
22% yield, *E/Z* = 95:5). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2ai**) δ 7.49 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 5.28 (s, 1H), 5.24 (s, 1H), 3.74 (s, 3H), 1.41 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer **E-2ai**) δ 168.0, 143.6, 140.5, 138.1, 133.0, 130.7, 130.3, 129.2, 128.8, 125.8, 121.7, 52.4, 21.3 ppm. HRMS (ESI) [M+H]⁺ calcd for C₁₃H₁₄BrO₂: 281.0172, found: 281.0178.



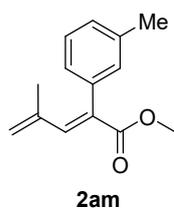
2aj: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (6.2 mg, 22% yield, *E/Z* = 95:5). ¹H NMR (400 MHz, CDCl₃, for major isomer **E-2aj**) δ 7.49 (s, 1H), 7.47 (d, *J* = 9.5 Hz, 2H), 7.07 (d, *J* = 10.5 Hz, 2H), 5.26 (s, 1H), 5.22 (s, 1H), 3.74 (s, 3H), 1.41 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 168.1, 143.4, 140.6, 135.0, 131.8, 131.0, 130.5, 125.6, 121.9, 52.4, 21.4 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₃H₁₃BrO₂Na: 302.9991, found: 302.9981.



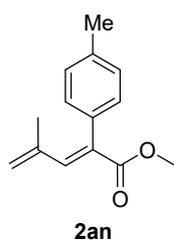
2ak: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (22.9 mg, 85% yield, *E/Z* = 99:1). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2ak**) δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 6.5 Hz, 1H), 5.29 (s, 1H), 5.23 (s, 1H), 3.70 (s, 3H), 1.29 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer **E-2ak**) δ 167.7, 143.7, 140.5, 134.9, 132.3, 131.1, 129.37 (q, ²*J*_{C-F} = 30.2 Hz), 128.4, 128.1, 126.4, 125.99 (q, ³*J*_{C-F} = 5.0 Hz), 124.01 (q, ¹*J*_{C-F} = 274.7 Hz) 52.3, 20.5 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₄H₁₃F₃O₂Na: 293.0760, found: 293.0761.



2al: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (19.5 mg, 90% yield, *E/Z* = 98:2). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2al**) δ 7.51 (s, 1H), 7.19 (d, *J* = 16.5 Hz, 1H), 7.17 – 7.13 (m, 2H), 7.05 (d, *J* = 7.0 Hz, 1H), 5.25 (s, 1H), 5.18 (s, 1H), 3.71 (s, 3H), 2.16 (s, 3H), 1.31 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer **E-2al**) δ 168.4, 143.0, 141.1, 136.9, 135.7, 131.0, 130.1, 129.5, 128.0, 125.2, 125.2, 52.3, 20.6, 19.8 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₄H₁₆O₂Na: 239.1043, found: 239.1044.

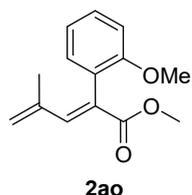


2am: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (16.4 mg, 76% yield, *E/Z* = 80:20). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2am**) δ 7.47 (s, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 5.26 (s, 1H), 5.19 (s, 1H), 3.74 (s, 3H), 2.35 (s, 3H), 1.39 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer **E-2am**) δ 168.7, 142.6, 141.1, 137.2, 135.9, 131.9, 130.7, 128.4, 127.6, 127.1, 125.0, 52.3, 21.4, 21.2 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₄H₁₆O₂Na: 239.1043, found: 239.1048.

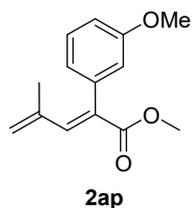


2an: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (21.2 mg,

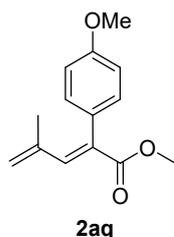
98% yield, *E/Z* = 80:20). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2an**) δ 7.46 (s, 1H), 7.16 – 7.11 (m, 2H), 7.07 (d, *J* = 7.5 Hz, 2H), 5.24 (s, 1H), 5.17 (s, 1H), 3.72 (s, 3H), 2.36 (s, 3H), 1.39 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer **E-2an**) δ 167.7, 141.6, 140.1, 136.3, 132.0, 128.90, 128.4, 127.4, 125.0, 123.6, 51.2, 51.0, 20.3, 20.2, ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₄H₁₆O₂Na: 239.1043, found: 239.1043.



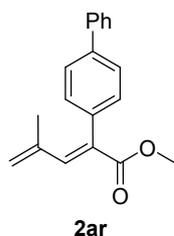
2ao: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (22.9 mg, 99% yield, *E/Z* = 96:4). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2ao**) δ 7.48 (s, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 5.24 (s, 1H), 5.17 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 1.41 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer **E-2ao**) δ 167.5, 156.5, 141.9, 140.1, 130.4, 128.4, 127.7, 124.4, 123.4, 119.1, 109.5, 54.6, 51.1, 19.7 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₄H₁₆O₃Na: 255.0992, found: 255.1000.



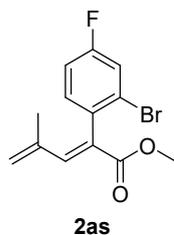
2ap: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (30.7 mg, 46% yield, *E/Z* = 97:3). ¹H NMR (500 MHz, CDCl₃, for major isomer **E-2ap**) δ 7.47 (s, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.74 (s, 1H), 5.27 (s, 1H), 5.20 (s, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 1.42 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer **E-2ap**) δ 167.4, 158.0, 141.8, 140.0, 136.3, 130.6, 127.7, 124.0, 121.6, 114.8, 112.1, 54.2, 51.3, 20.0 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₄H₁₆O₃Na: 255.0992, found: 255.0985.



2aq: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (22.7 mg, 98% yield, *E/Z* = 80:20). ^1H NMR (500 MHz, CDCl_3 , for major isomer **E-2aq**) δ 7.46 (s, 1H), 7.11 (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.25 (s, 1H), 5.19 (s, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 1.41 (s, 3H) ppm. ^{13}C NMR (126 MHz, CDCl_3 , for major isomer **E-2aq**) δ 167.8, 158.1, 141.7, 140.1, 130.2, 127.1, 126.4, 123.6, 112.2, 54.2, 51.2, 20.2 ppm. HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3\text{Na}$: 255.0992, found: 255.0998.

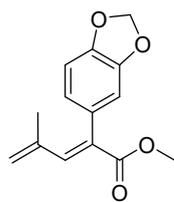


2ar: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (19.5 mg, 70% yield, *E/Z* = 91:9). ^1H NMR (500 MHz, CDCl_3 , for major isomer **E-2ar**) δ 7.56 (d, $J = 7.5$ Hz, 2H), 7.50 (d, $J = 8.5$ Hz, 2H), 7.44 (s, 1H), 7.37 (t, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 7.5$ Hz, 1H), 7.19 (d, $J = 8.0$ Hz, 2H), 5.21 (s, 1H), 5.14 (s, 1H), 3.69 (s, 3H), 1.37 (s, 3H) ppm. ^{13}C NMR (126 MHz, CDCl_3 , for major isomer **E-2ar**) δ 168.5, 143.0, 141.0, 140.7, 140.4, 135.0, 131.5, 130.5, 128.8, 127.4, 127.1, 126.4, 125.0, 52.3, 21.3 ppm. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{O}_2$: 279.1380, found: 279.1385.



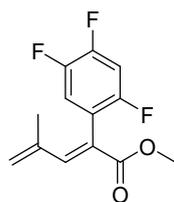
2as: Prepared according to the general procedure II above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (19.4 mg, 65% yield, *E/Z* > 99:1). ^1H NMR (500 MHz, CDCl_3 , for major isomer **E-2as**) δ 7.54 (s, 1H),

7.33 (dd, $J = 8.0, 2.5$ Hz, 1H), 7.16 – 7.13 (m, 1H), 7.04 – 7.00 (m, 1H), 5.30 (s, 1H), 5.25 (s, 1H), 3.73 (s, 3H), 1.39 (s, 3H) ppm. ^{13}C NMR (126 MHz, CDCl_3 , for major isomer **E-2as**) δ 167.3, 162.0 (d, $^1J_{\text{C-H}} = 252.0$ Hz), 144.3, 140.4, 133.4 (d, $^4J_{\text{C-H}} = 2.5$ Hz), 132.5 (d, $^3J_{\text{C-H}} = 8.8$ Hz), 129.8, 126.2, 124.9 (d, $^3J_{\text{C-H}} = 10.1$ Hz), 119.6 (d, $^2J_{\text{C-H}} = 23.9$ Hz), 114.2 (d, $^2J_{\text{C-H}} = 21.4$ Hz), 52.4, 20.7 ppm. HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{12}\text{BrFO}_2\text{Na}$: 320.9897, found: 320.9897.



2at

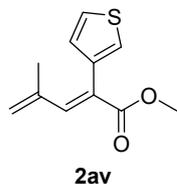
2at: Prepared according to the general procedure above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (20.9 mg, 85% yield, $E/Z = 83:17$). ^1H NMR (500 MHz, CDCl_3 , for major isomer **E-2at**) δ 7.44 (s, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.68 (s, 1H), 6.63 (dd, $J = 8.0, 1.5$ Hz, 1H), 5.97 (s, 2H), 5.26 (s, 1H), 5.20 (s, 1H), 3.74 (s, 3H), 1.46 (s, 3H) ppm. ^{13}C NMR (126 MHz, CDCl_3 , for major isomer **E-2at**) δ 168.5, 147.2, 147.1, 143.0, 141.0, 131.3, 129.5, 124.9, 123.7, 110.6, 107.7, 101.1, 52.3, 21.1 ppm. HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{14}\text{O}_4\text{Na}$: 269.0784, found: 269.0791.



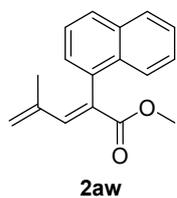
2au

2au: Prepared according to the general procedure above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (20.7 mg, 81% yield, $E/Z = 96:4$). ^1H NMR (500 MHz, CDCl_3 , for major isomer **E-2au**) δ 7.58 (s, 1H), 7.03 – 6.88 (m, 2H), 5.28 (s, 2H), 3.74 (s, 3H), 1.50 (s, 3H) ppm. ^{13}C NMR (126 MHz, CDCl_3 , for major isomer **E-2au**) δ 166.9, 155.7 (ddd, $^1J_{\text{C-F}} = 245.7$ Hz, $^3J_{\text{C-F}} = 8.8$ Hz, $^4J_{\text{C-F}} = 2.5$ Hz), 149.9 (ddd, $^1J_{\text{C-F}} = 253.3$ Hz, $^2J_{\text{C-F}} = 13.9, 12.6$ Hz), 146.5 (ddd, $^1J_{\text{C-F}} = 245.7$ Hz, $^2J_{\text{C-F}} = 12.6$ Hz, $^4J_{\text{C-F}} = 3.8$ Hz), 145.8, 140.0, 126.2, 123.4, 120.0 (ddd, $^2J_{\text{C-F}} = 20.2$ Hz, $^3J_{\text{C-F}} = 6.3$ Hz, $^4J_{\text{C-F}} = 5.0$ Hz), 119.7 (dd, $^2J_{\text{C-F}} = 18.9$ Hz, $^4J_{\text{C-F}} = 3.8$ Hz), 105.3 (dd, $^2J_{\text{C-F}} = 29.0$,

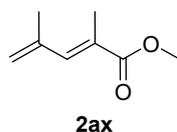
21.4 Hz), 52.4, 20.6 ppm. HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_{13}F_3O_2$: 257.0784, found: 257.0782.



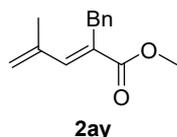
2av: Prepared according to the general procedure above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Yellow oil (19.5 mg, 99% yield, $E/Z = 75:25$). 1H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.31 – 7.27 (m, 1.33H), 7.19 (dd, $J = 9.0, 3.0$ Hz, 0.66H), 7.11 (d, $J = 1.5$ Hz, 1H), 6.98 (d, $J = 5.0$ Hz, 1H), 6.57 (s, 0.33H), 5.27 (s, 1H), 5.22 (s, 1H), 5.16 (s, 0.33H), 5.12 (s, 0.33H), 3.84 (s, 1H), 3.75 (s, 3H), 1.91 (s, 1H), 1.48 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 167.2, 142.7, 140.0, 139.6, 137.0, 134.3, 130.6, 128.6, 127.5, 125.7, 125.2, 124.1, 123.9, 123.7, 123.4, 120.9, 119.1, 51.3, 51.1, 19.6, 19.0 ppm. HRMS (ESI) $[M+Na]^+$ calcd for $C_{11}H_{12}O_2SNa$: 231.0450, found: 231.0458.



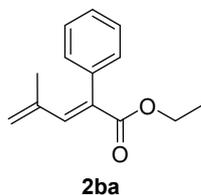
2aw: Prepared according to the general procedure above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (19.2 mg, 76% yield, $E/Z = 98:2$). 1H NMR (500 MHz, $CDCl_3$, for major isomer **E-2aw**) δ 7.86 (dd, $J = 12.5, 5.0$ Hz, 2H), 7.76 (s, 1H), 7.72 (d, $J = 8.5$ Hz, 1H), 7.50 – 7.43 (m, 3H), 7.30 (d, $J = 7.0$ Hz, 1H), 5.31 (s, 1H), 5.16 (s, 1H), 3.66 (s, 3H), 1.13 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, for major isomer **E-2aw**) δ 167.7, 143.5, 140.1, 132.8, 132.2, 131.7, 128.7, 127.3, 127.2, 126.7, 125.3, 124.8, 124.5, 123.9, 51.3, 19.4 ppm. HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{16}O_2Na$: 275.1043, found: 275.1033.



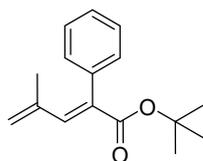
2ax: Prepared according to the general procedure above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (8.4 mg, 60% yield, *E/Z* = 99:1). ¹H NMR (500 MHz, CDCl₃) δ 7.10 (s, 1H), 5.21 (s, 1H), 5.06 (s, 1H), 3.75 (s, 3H), 2.01 (s, 3H), 1.93 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 168.3, 139.7, 139.7, 126.3, 118.7, 50.9, 21.8, 12.8 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₈H₁₂O₂Na: 163.0730, found: 163.0735.



2ay: Prepared according to the general procedure above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (20.7 mg, 96% yield, *E/Z* = 97:3). ¹H NMR (500 MHz, CDCl₃, for major isomer *E-2ay*) δ 7.34 (s, 1H), 7.29 – 7.24 (m, 2H), 7.16 (dd, *J* = 13.5, 7.5 Hz, 3H), 5.19 – 5.16 (m, 1H), 5.12 (s, 1H), 3.90 (s, 2H), 3.70 – 3.67 (m, 3H), 1.95 (s, 3H), ppm. ¹³C NMR (126 MHz, CDCl₃, for major isomer *E-2ay*) δ 165.3, 139.3, 139.2, 134.6, 131.8, 125.5, 125.4, 124.2, 122.1, 78.91, 26.1, 19.4, 18.9 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₄H₁₆O₂Na: 239.1043, found: 239.1040.

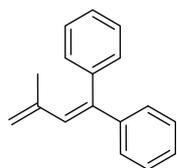


2ba: Prepared according to the general procedure above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (17.1 mg, 79% yield, *E/Z* = 80:20). ¹H NMR (500 MHz, CDCl₃) δ 7.47 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 0.5H), 7.35 (d, *J* = 7.5 Hz, 0.5H), 7.32 (d, *J* = 6.0 Hz, 3H), 7.29 (s, 0.25H), 7.20 (d, *J* = 6.5 Hz, 2H), 6.54 (s, 0.25H), 5.25 (s, 1H), 5.19 (s, 1.25H), 5.13 (s, 0.25H), 4.32 (q, *J* = 7.0 Hz, 0.5H), 4.21 (q, *J* = 7.0 Hz, 2H), 1.96 (s, 0.75H), 1.39 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 0.75H), 1.25 (t, *J* = 7.0 Hz, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 169.6, 168.0, 142.4, 141.0, 140.9, 137.0, 136.1, 133.8, 132.6, 132.3, 130.1, 128.6, 128.1, 127.6, 127.5, 126.1, 124.7, 120.2, 61.2, 61.0, 21.2, 20.2, 14.2, 14.0 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₄H₁₆O₂Na: 239.1043, found: 239.1039.



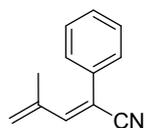
2ca

2ca: Prepared according to the general procedure above, and purified by a flash chromatography column with PE (50:1, v/v) as the eluent. Colorless oil (19.5 mg, 89% yield, *E/Z* = 80:20). ^1H NMR (500 MHz, CDCl_3) δ 7.40 (d, J = 7.5 Hz, 0.6H), 7.36 (s, 1H), 7.33 (d, J = 8.0 Hz, 0.8H), 7.30 (d, J = 7.0 Hz, 3H), 7.18 (dd, J = 7.5, 1.5 Hz, 2H), 6.43 (s, 0.28H), 5.21 (s, 1H), 5.17 (s, 1H), 5.15 (s, 0.28H), 5.10 (s, 0.28H), 2.00 (s, 0.84H), 1.54 (s, 2.52H), 1.46 (s, 9H), 1.38 (s, 3H) ppm. ^{13}C NMR (126 MHz, CDCl_3) δ 167.7, 141.5, 139.4, 138.9, 128.8, 127.4, 126.9, 124.9, 118.95, 51.0, 31.9, 21.5 ppm. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{O}_2$: 245.1536, found: 245.1532.



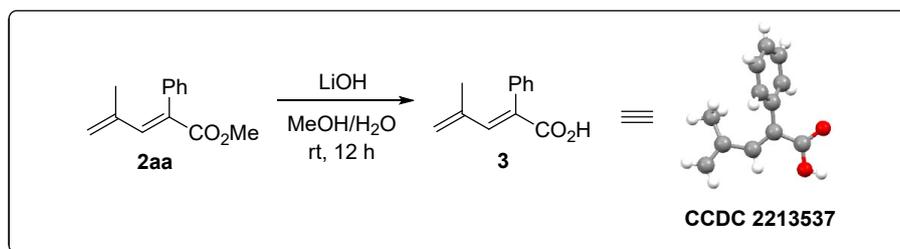
2da

2da: Prepared according to the general procedure above, and purified by a flash chromatography column with PE as the eluent. White solid (7.9 mg, 36% yield). Melting point: 35.1-38.6 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.34 – 7.32 (m, 3H), 7.26 – 7.20 (m, 7H), 6.66 (s, 1H), 5.00 (s, 1H), 4.96 (s, 1H), 1.48 (s, 3H) ppm. ^{13}C NMR (126 MHz, CDCl_3) δ 143.3, 142.4, 141.5, 140.7, 130.7, 130.3, 128.1, 127.9, 127.5, 127.2, 119.1, 22.1 ppm. HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{Na}$: 243.1144, found: 243.1145.

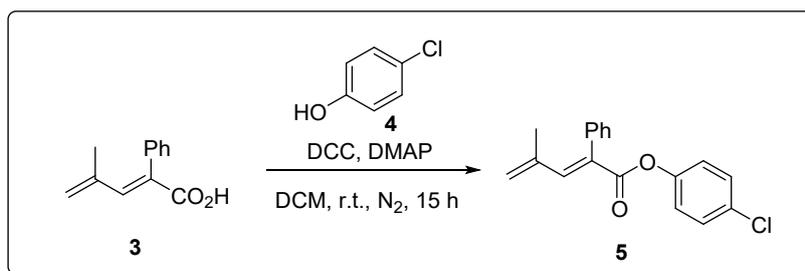


2ea

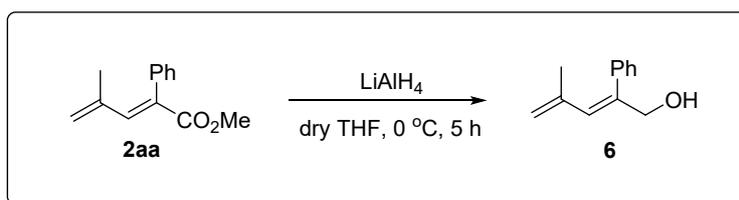
2ea: Prepared according to the general procedure above, and purified by a flash chromatography column with PE/EA (50:1, v/v) as the eluent. Colorless oil (6.2 mg, 37% yield, *E/Z* 99:1). ^1H NMR (500 MHz, d^6 -DMSO) δ 7.65 – 7.60 (m, 2H), 7.53 (s, 1H), 7.46 – 7.38 (m, 3H), 5.65 (s, 1H), 5.50 (s, 1H), 2.17 (s, 3H) ppm. ^{13}C NMR (126 MHz, d^6 -DMSO) δ 145.7, 140.5, 134.4, 129.6, 127.8, 126.3, 118.1, 110.1, 20.4 ppm. HRMS (ESI) $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{12}\text{N}$: 170.0964, found: 170.0965.



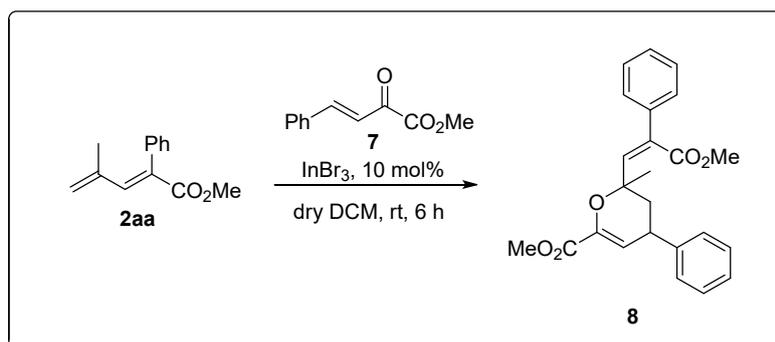
C) Synthesis of hydrolysis product 3 (CCDC 2213537): To a flame dried round bottom flask was added compound **2aa** (0.1 mmol) and LiOH (0.2 mmol). Then 1.1ml MeOH-H₂O (0.09M, 10:1) was added at room temperature and the reaction mixture was then stirred overnight. The mixture was acidified with hydrochloric acid after the completion of the reaction. Then the reaction mixture was extracted with EtOAc, dried over anhydrous sodium sulfate, concentrated under vacuum and purified by flash column chromatography with PE/EtOAc (2:1, v/v) to afford the corresponding product **3** in 92% yield as a white solid. Melting point: 91.2-105.3 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.57 (s, 1H), 7.33 – 7.32 (m, 3H), 7.20 – 7.19 (m, 2H), 5.30 (s, 1H), 5.25 (s, 1H), 1.38 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 144.7, 141.0, 135.4, 132.5, 131.1, 130.1, 127.8, 127.7, 126.1, 21.1 ppm. HRMS (ESI) [M+H]⁺ calcd for C₁₂H₁₃O₂: 189.0910, found: 189.0910.



D) Synthesis of esterification product 5: Under nitrogen atmosphere, to an oven-dried round-bottom flask was added compound **3** (1 equiv), 4-ClC₆H₄OH **4** (0.8 equiv.), 4-dimethylaminopyridine (0.1 equiv.) and dichloromethane (0.5 mmol/ml). Then the reaction mixture was cooled to 0 °C and N,N-dicyclohexylcarbodiimide (0.8 equiv) was added. The reaction mixture was allowed to stir at ambient temperature overnight. After that, the reaction mixture was quenched with aqueous NaHCO₃, extracted with EtOAc, dried over anhydrous sodium sulfate, concentrated the mixture under vacuum and then purified by flash column chromatography with PE/EA (50:1, v/v) to afford a white solid **5** in 86% yield. Melting point: 65.5-75.4 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.67 (s, 1H), 7.38 – 7.36 (m, 3H), 7.34 – 7.29 (m, 4H), 7.05 (d, *J* = 8.5 Hz, 2H), 5.36 (s, 1H), 5.29 (s, 1H), 1.44 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 165.2, 148.6, 143.6, 139.9, 134.4, 130.0, 130.0, 129.1, 128.3, 126.9, 126.8, 125.2, 121.9, 20.1 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₈H₁₅ClO₂Na: 321.0653, found: 321.0651.

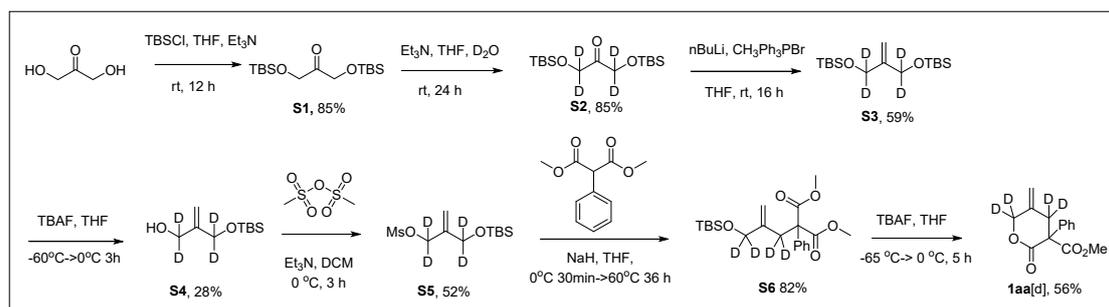


E) Synthesis of reduction product 6: Compound **2aa** was dissolved in THF (0.25 M), and the resulting solution was cooled to 0 °C. LiAlH₄ (1.5 equiv) was added portion wise, and the resulting mixture was allowed to stir for 5h. The reaction mixture was quenched by Fieser method, filtered through celite, and concentrated in vacuo. The residue was purified by column chromatography with PE/EA (3:1, v/v) to afford the colorless oil **6** in 52% yield. ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.30 (m, 3H), 7.24 (d, *J* = 7.0 Hz, 2H), 6.34 (s, 1H), 4.94 (s, 1H), 4.92 (s, 1H), 4.34 (s, 2H), 1.46 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 140.5, 139.7, 138.1, 128.0, 127.9, 127.1, 126.3, 117.2, 67.9, 21.1 ppm. HRMS (ESI) [M+Na]⁺ calcd for C₁₂H₁₄Na: 197.0937, found: 197.0939.



F) Synthesis of product 8: Under a nitrogen atmosphere, to an oven-dried 10 mL Schlenk flask equipped with a stirring bar was added **2aa** (0.1 mmol), **7** (0.1 mmol), InBr_3 (10 mol%) and dry DCM (1.0 mL). The resultant mixture was degassed three times by freeze-pump-thaw cycles. The reaction mixture was stirred at room temperature for 6 hours, then purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (10:1, v:v), giving the colorless oil **8** in 58% yield (*d.r.* = 2:1). ^1H NMR (500 MHz, CDCl_3) δ 7.34 – 7.28 (m, 5H), 7.26 – 7.19 (m, 2H), 7.15 (s, 0.7H), 7.13 – 7.08 (m, 3H), 7.07 (s, 0.3H), 6.07 (d, J = 1.5 Hz, 1H), 3.72 (s, 3H), 3.65 (d, J = 12.0 Hz, 3H), 3.55 – 3.48 (m, 0.3H), 3.46 – 3.42 (m, 0.7H), 1.98 (dd, J = 13.5, 6.0 Hz, 0.3H), 2.00 – 1.81 (m, 1.7H), 1.55 (s, 1H), 1.28 (s, 2H) ppm. ^{13}C NMR (126 MHz, CDCl_3) δ 167.7, 163.2, 162.9, 146.7, 145.7, 143.1, 142.9, 142.7, 142.3, 134.9, 134.4, 134.2, 133.3, 129.6, 129.4, 128.8, 128.7, 128.6, 127.7, 127.7, 127.7, 127.6, 127.2, 126.9, 126.2, 114.1, 112.2, 78.8, 78.2, 52.5, 52.3, 52.1, 52.0, 41.3, 40.2, 36.7, 35.6, 28.3, 23.4 ppm. HRMS (ESI) $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{24}\text{O}_5\text{Na}$: 415.1516, found: 415.1511.

G) Synthesis 1aa[d]



a) Synthesis of S1: Triethylamine (32 mL, 230 mmol) was added to a solution of 1,3-Dihydroxyacetone (10.0 g, 110 mmol) in THF (250 mL) at 0 °C. TBSCl (34.5 g, 230 mmol) was slowly added to the mixture and this was stirred for 12 h at room temperature. After dilution with water, this was extracted with EtOAc (5 times). The organic layer was washed with saturated NaCl aq, dried over Na₂SO₄ and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/PE (1:200, v/v) to afford **S1** as a colorless oil (30.0 g, 94.3 mmol; 85% yield).

b) Synthesis of S2: Add D₂O (10 mL, 0.5 mol) and Et₃N (60 mL, 432.5 mmol) to a solution of **S1** (30.0 g, 94.3 mmol) in THF (250 mL). Stir the solution at room temperature for 24 hours and subsequently reduced to a minimum volume. Treat the residue two more times (3 times in total) under the same conditions with the same reagents to obtain the residue. After dilution with water, this was extracted with EtOAc (5 times). The organic layer was washed with saturated NaCl aq, dried over Na₂SO₄ and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/PE (1:200, v/v) to afford **S2** as a colorless oil (25.6 g, 80.2 mmol; 85% yield, >85% D).

c) Synthesis of S3: To a flask charged with methyltriphenylphosphonium bromide (57 g, 160 mmol) in 250 mL of anhydrous THF at 0 °C was added *n*-butyllithium (64 mL, 2.5 M in hexanes, 160 mmol). The reaction was allowed to warm to room temperature spontaneously and then stirred for 1 h. **S2** (25.6 g, 80.2 mmol) in anhydrous THF (50 mL) was added dropwise at room temperature. After stirring for 9 h, the reaction mixture was quenched with saturated aqueous NH₄Cl, and then extracted with EtOAc for (3 times). The combined organic layer was washed with brine and dried over

anhydrous Na₂SO₄. After filtration, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel with EtOAc/PE (1:400, v/v) to afford **S3** as a colorless oil (15.2 g, 47.5 mmol; 59% yield).

d) Synthesis of S4: TBAF (47.5 mL, 47.5 mmol; 1.0 M solution in THF) was slowly added to a solution of **S3** (15.2 g, 47.5 mmol) in THF (110 mL) at -78 °C. The mixture was stirred for 3 h while gradually raising the temperature to 0 °C, and the reaction was quenched with water. After extraction with EtOAc, the organic layer was washed with saturated NaCl aq, dried over Na₂SO₄ and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/PE (1:8, v/v) to afford **S4** as a colorless oil (2.52 g, 13.3 mmol; 28% yield).

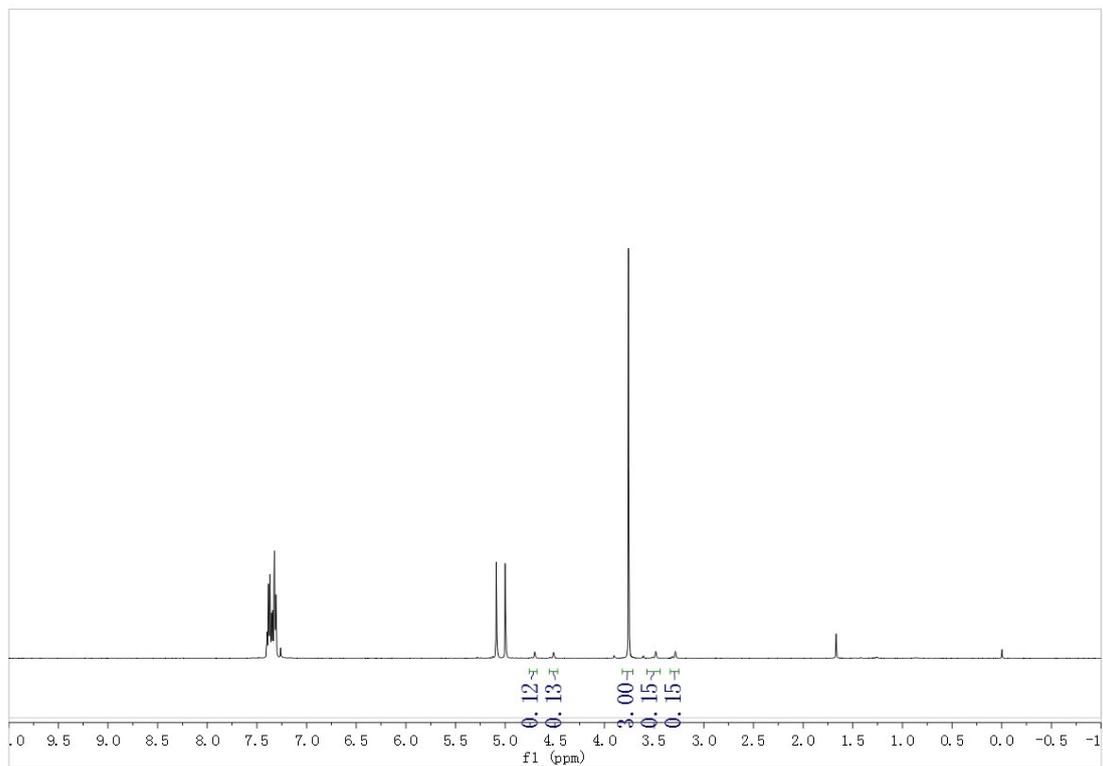
e) Synthesis of S5: Triethylamine (2.42 mL, 17.5 mmol) was added to a solution of **S4** (2.52 g, 13.3 mmol) in CH₂Cl₂ (10 mL) at 0 °C. Methanesulfonic anhydride (2.63 g, 15.1 mmol) was slowly added to the mixture and this was stirred for 1 h at 0 °C. Add another part of methanesulfonic anhydride (0.1 equiv) and triethylamine (0.2 equiv). The reaction was quenched with saturated NaHCO₃ aq and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/PE (1/8, v/v) to afford **S5** as a colorless oil (1.95 g, 6.92 mmol; 52% yield).

f) Synthesis of S6: A solution of dimethyl phenylmalonate (1.26 g, 6.0 mmol) in THF (9 mL) was added to a suspension of NaH (252 mg, 6.3 mmol; 60 wt% in mineral oil) in THF (3 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C and a solution of **S5** (1.95 g, 6.92 mmol) in THF (12 mL) was added to it. The resulting mixture was stirred for 36 h at 60 °C and was quenched with water. After extraction with EtOAc, the organic layer was washed with NaCl (saturated aqueous), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/PE (1/15, v/v) to afford **S6** as a colorless oil (2.25 g, 5.67 mmol; 82% yield).

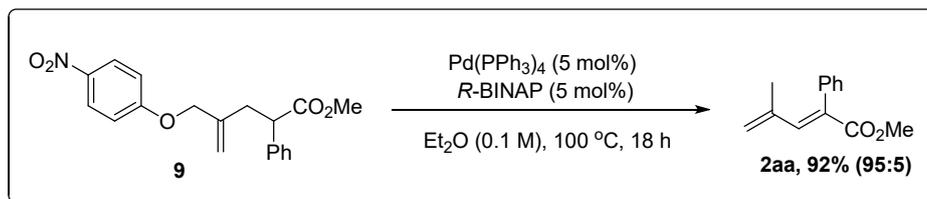
g) Synthesis of 1aa[d]: TBAF (6.26 mL, 6.26 mmol; 1.0 M solution in THF) was added to a solution of **S6** (2.25 g, 5.67 mmol) in THF (14.5 mL) at -65 °C. The mixture was stirred for 4.5 h while gradually raising the temperature to 0 °C and the reaction was

quenched with water. After extraction with EtOAc, the organic layer was washed with NaCl (saturated aqueous), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/PE (1:5 to 1:3) to afford **1aa[d]** as a white solid (790 mg, 3.16 mmol; 56% yield, >85% D).

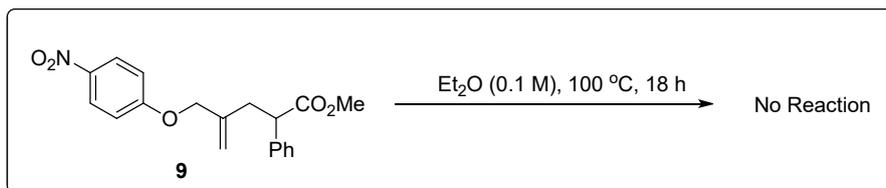
¹H NMR of 1aa[d]:



IV. Control Experiments

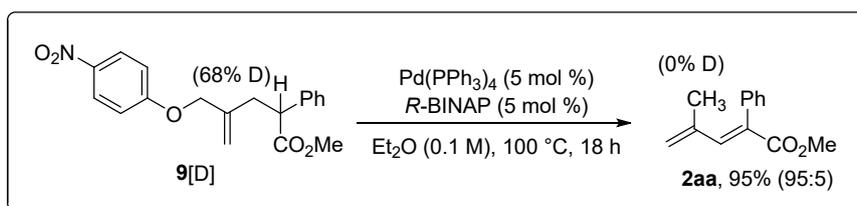


A) $\text{Pd}(\text{PPh}_3)_4$ catalyzed reaction of compound **9 as starting material:** Under a nitrogen atmosphere, to an oven dried 10 mL Schlenk flask equipped with a stirring bar was added compound **9** (0.1 mmol), $\text{Pd}(\text{PPh}_3)_4$ (5 mol %), $R\text{-BINAP}$ (5 mol %) and dry Et_2O (1.0 mL). The resultant mixture was degassed three times by freeze-pump-thaw cycles, and then stirred at $100\text{ }^\circ\text{C}$ for 18 h. The reaction mixture was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate, giving the corresponding product **2aa** (92% yield, 95:5 *E/Z*).

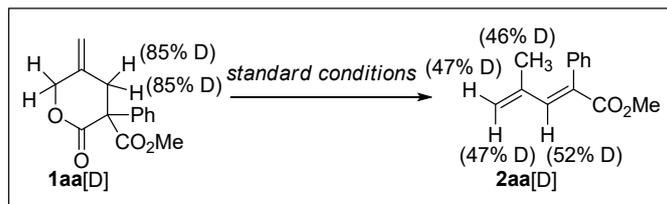


B) Reaction of 9 in the absence of $\text{Pd}(\text{PPh}_3)_4$ and *R*-BINAPL Under a nitrogen atmosphere, to an oven dried 10 mL Schlenck flask equipped with a stirring bar was added compound **9** (0.1 mmol) and dry Et_2O (1.0 mL). The resultant mixture was degassed three times by freeze-pump-thaw cycles, and then stirred at $100\text{ }^\circ\text{C}$ for 18 h, and no reaction was observed.

C) Deuterium-labeling experiment

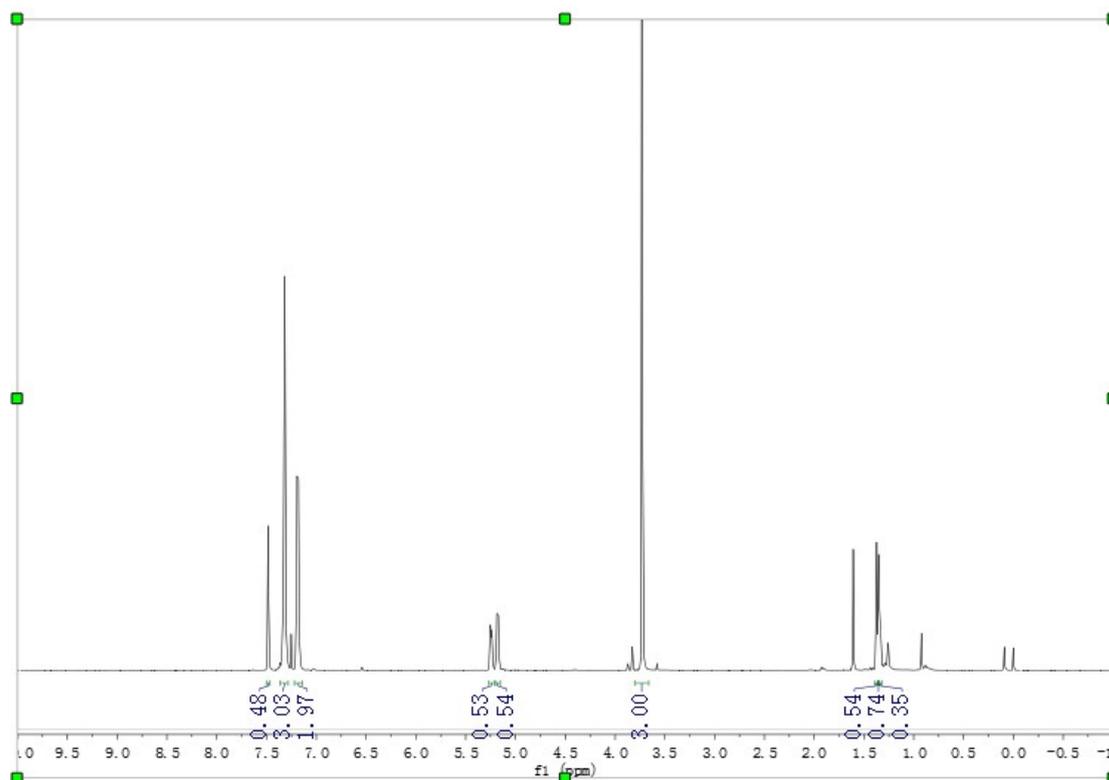


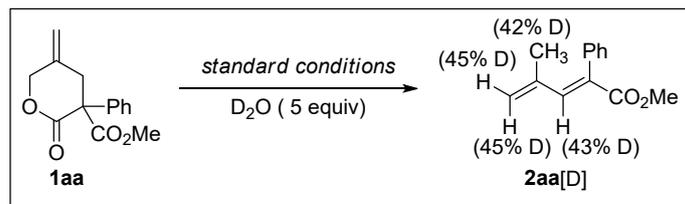
a) With allyl phenyl ether 9[D]: Under a nitrogen atmosphere, to an oven dried 10 mL Schlenck flask equipped with a stirring bar was added compound **9[D]** (0.1 mmol), $\text{Pd}(\text{PPh}_3)_4$ (5 mol %), *R*-BINAP (5 mol %) and dry Et_2O (1.0 mL). The resultant mixture was degassed three times by freeze-pump-thaw cycles, and then stirred at 100 °C for 18 h. The reaction mixture was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate, giving the corresponding product **2aa** (95% yield, 95:5 *E/Z*).



b) With γ -methylidene- δ -valerolactone **1aa[D]:** Under a nitrogen atmosphere, to an oven dried 10 mL Schlenk flask equipped with a stirring bar was added compound **1aa[D]** (0.1 mmol), Pd(PPh₃)₄ (5 mol %), *R*-BINAP (5 mol %) and dry Et₂O (1.0 mL). The resultant mixture was degassed three times by freeze-pump-thaw cycles, and then stirred at 100 °C for 18 h. The reaction mixture was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (50:1, v/v), giving the corresponding product **2aa[D]** in 92% yield.

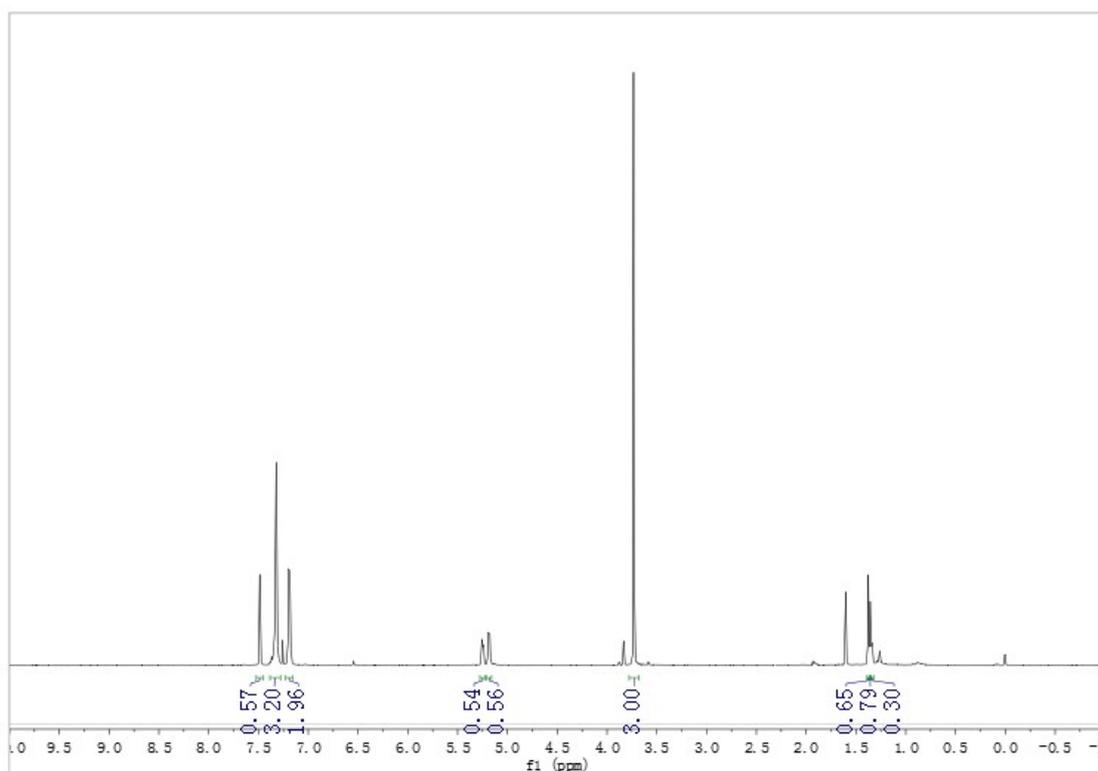
¹H NMR of **2aa[D]:**

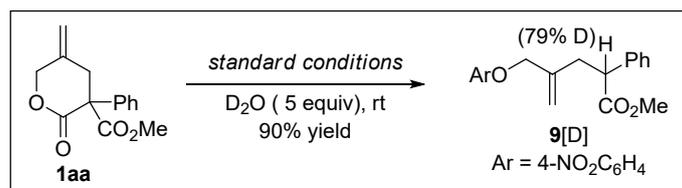




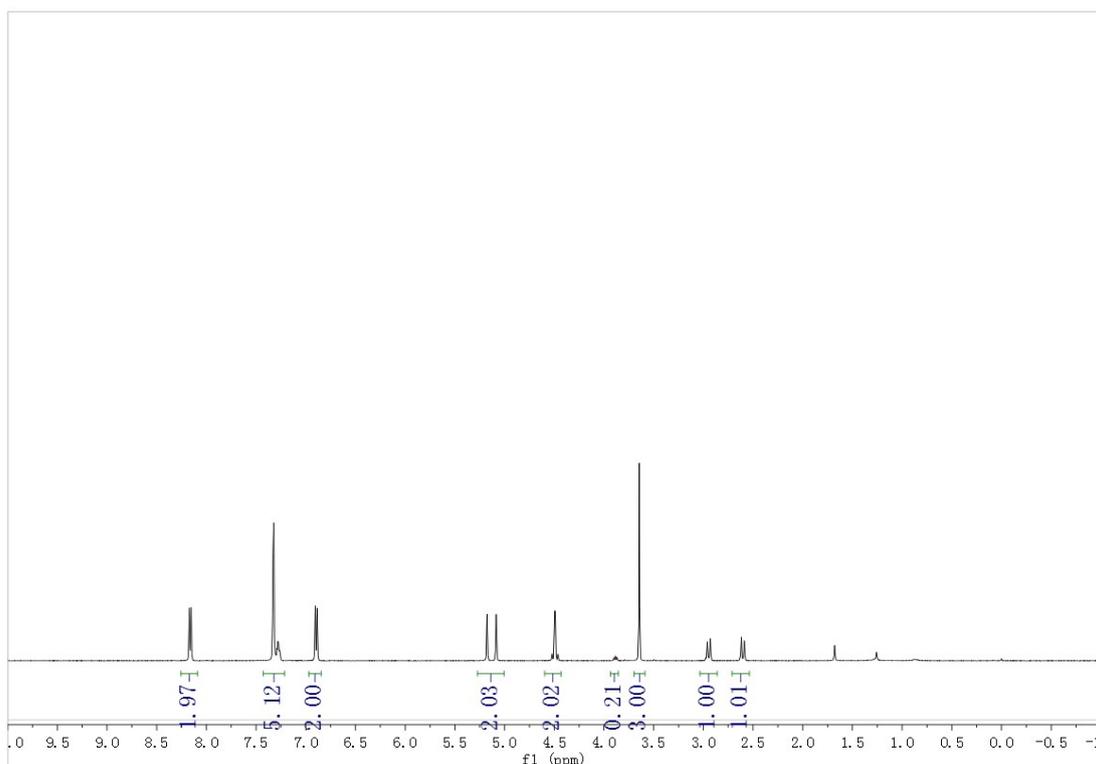
c) With D₂O under the standard condition: Under a nitrogen atmosphere, to an oven dried 10 mL Schlenk flask equipped with a stirring bar was added compound **1aa** (0.1 mmol), Pd(PPh₃)₄ (5 mol %), *R*-BINAP (5 mol %), D₂O (0.5 mmol) and dry Et₂O (1.0 mL). The resultant mixture was degassed three times by freeze-pump-thaw cycles, and then stirred at 100 °C for 18 h. The reaction mixture was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (50:1, v/v), giving the corresponding product **2aa**[D] in 85% yield.

¹H NMR of 2aa[D]:





d) With D₂O at room temperature under the standard condition: Under a nitrogen atmosphere, to an oven dried 10 mL Schlenk flask equipped with a stirring bar was added compound **1aa** (0.1 mmol), Pd(PPh₃)₄ (5 mol %), *R*-BINAP (5 mol %), D₂O (0.5 mmol) and dry Et₂O (1.0 mL). The resultant mixture was degassed three times by freeze-pump-thaw cycles, and then stirred at room temperature for 12 h. The reaction mixture was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (50:1, v/v), giving the corresponding product **9[D]** in 90% yield.



V. X-ray Crystal Data

A) X-Ray Structure of product 3 (CCDC 2213537)

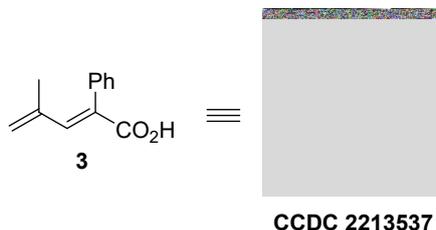


Table S3 Crystal data and structure refinement for **3**

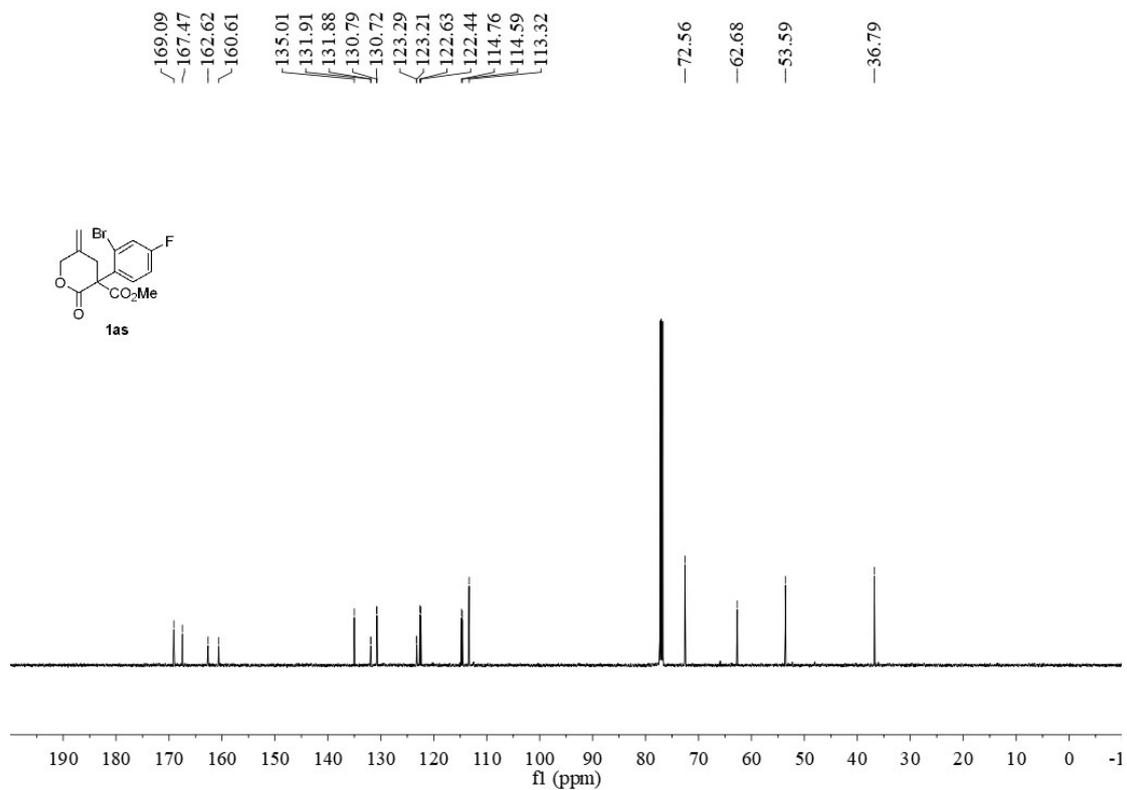
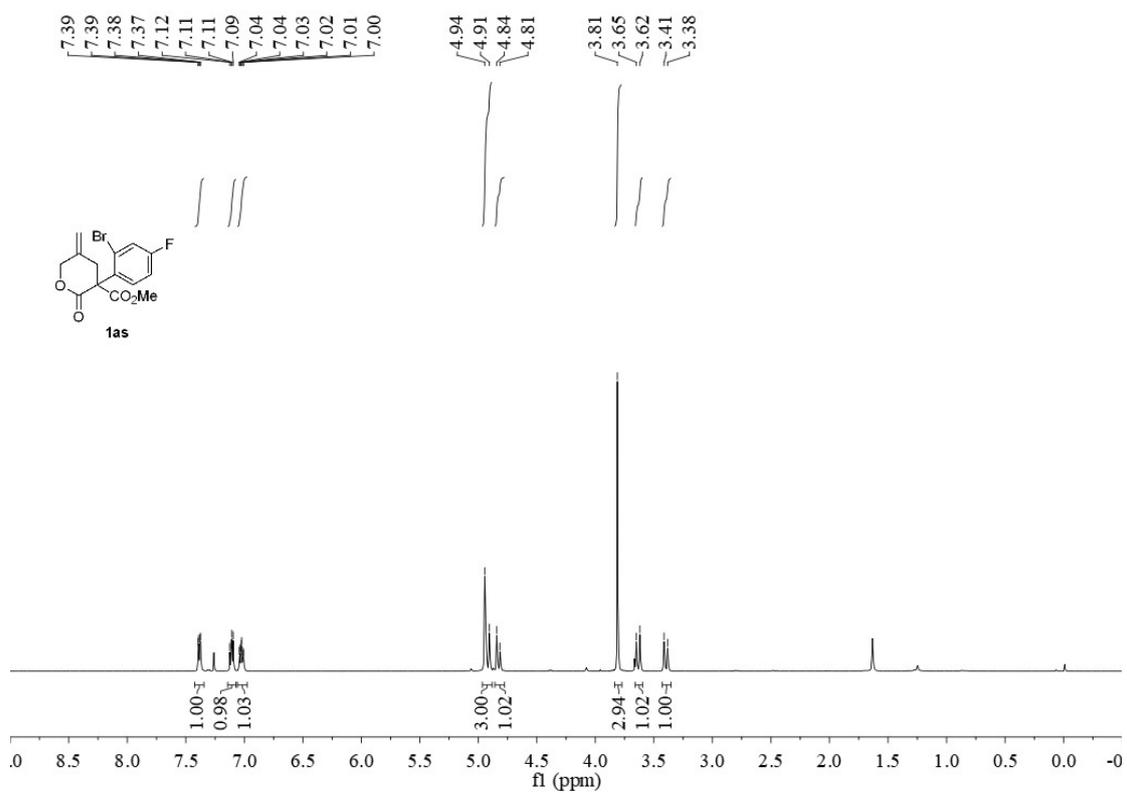
Empirical formula	C ₁₂ H ₁₂ O ₂
Formula weight	188.22
Temperature/K	298(2)
Crystal system	Monoclinic
Space group	P2(1)/c
a/Å	8.8302(8)
b/Å	5.8264(6)
c/Å	20.742(2)
α/°	90.00
β/°	98.926(2)
γ/°	90.00
Volume/Å ³	1054.24(18)
Z	4
ρ _{calc} /cm ³	1.186 Mg/m ³
μ/mm ⁻¹	0.080 mm ⁻¹
F(000)	400
Crystal size/mm ³	0.30 x 0.15 x 0.04 mm
Radiation	MoKα(λ = 0.71073)
2θ range for data collection/°	1.99 to 25.01
Index ranges	-10 ≤ h ≤ 10, -6 ≤ k ≤ 6, -19 ≤ l ≤ 24
Reflections collected	4869
Independent reflections	1852 [R(int) = 0.1283]
Data/restraints/parameters	1852 / 0 / 129
Goodness-of-fit on F ²	0.985
Final R indexes [I ≥ 2σ(I)]	R1 = 0.0702, wR2 = 0.1352
Final R indexes [all data]	R1 = 0.1774, wR2 = 0.1669
Largest diff. peak/hole / e Å ⁻³	0.176 and -0.162 e.Å ⁻³
Flack parameter	0.054(6)

VI. Reference

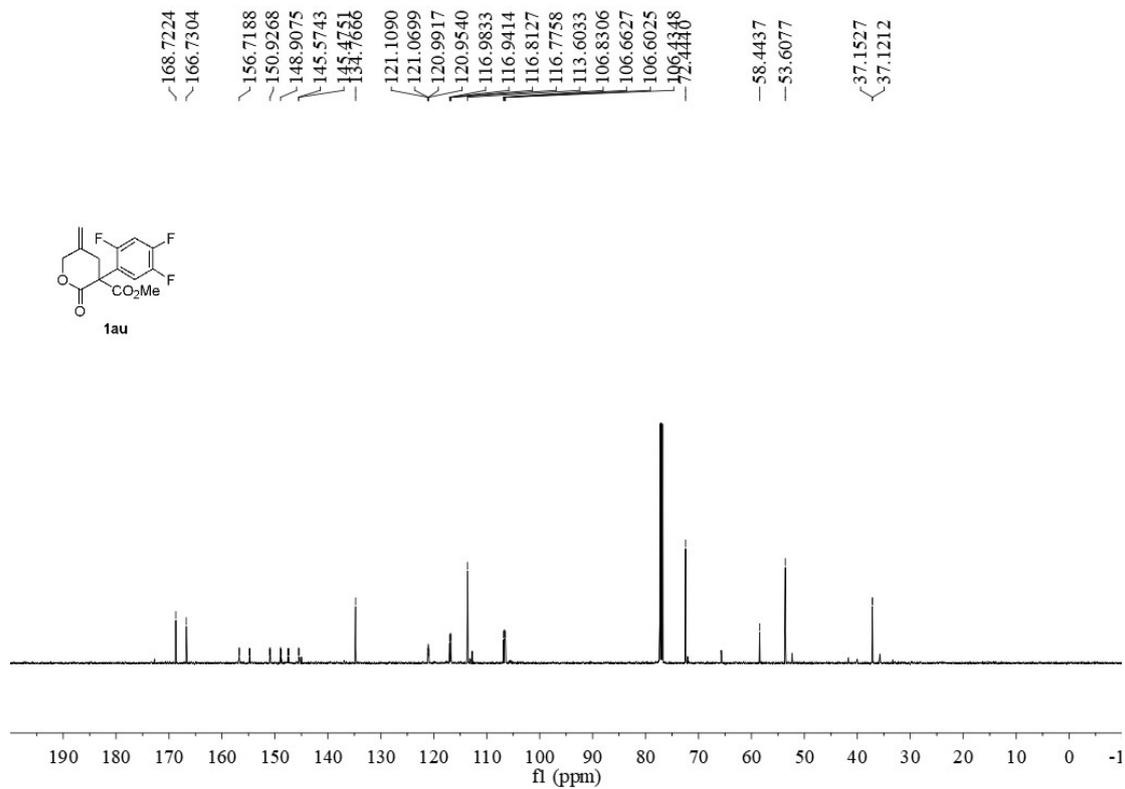
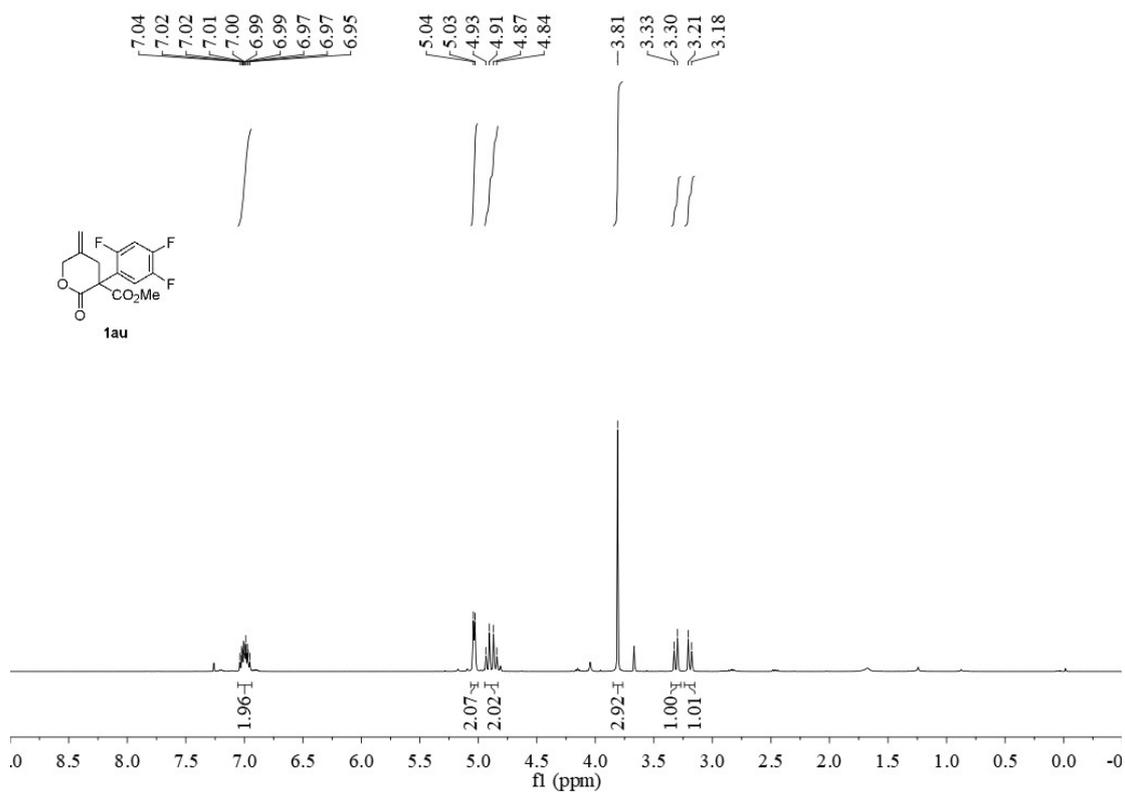
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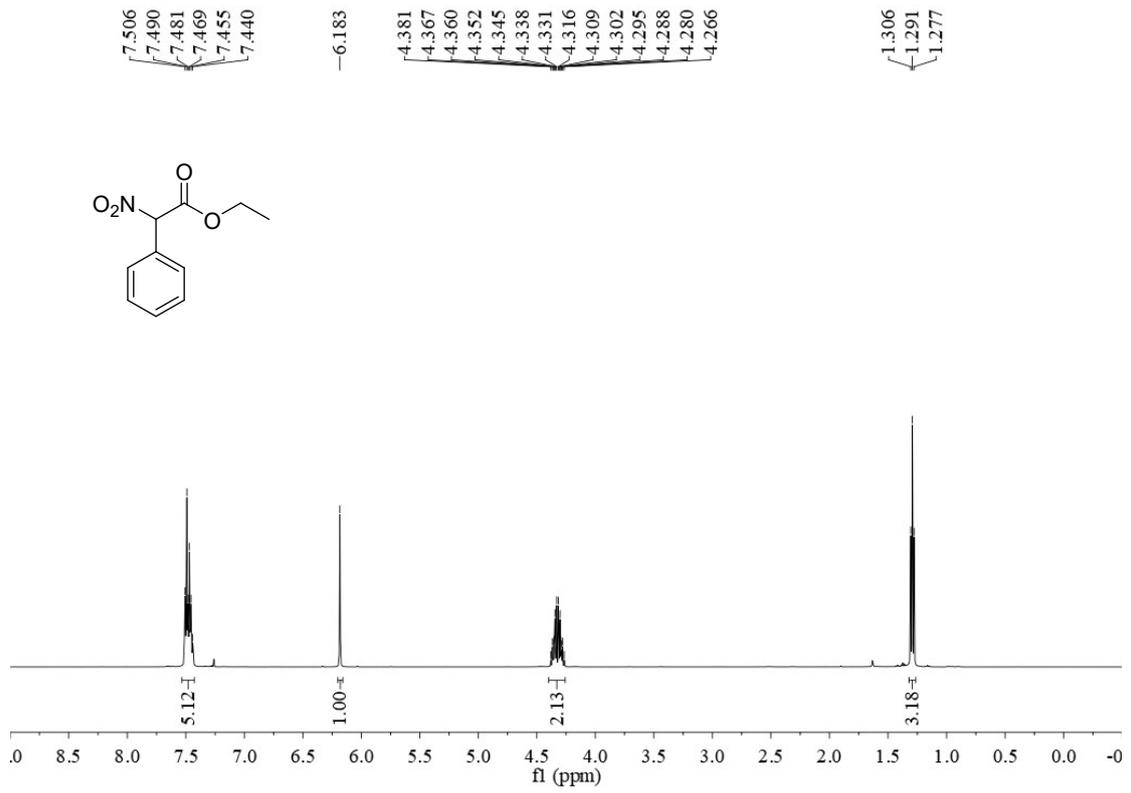
VII. NMR Spectrum

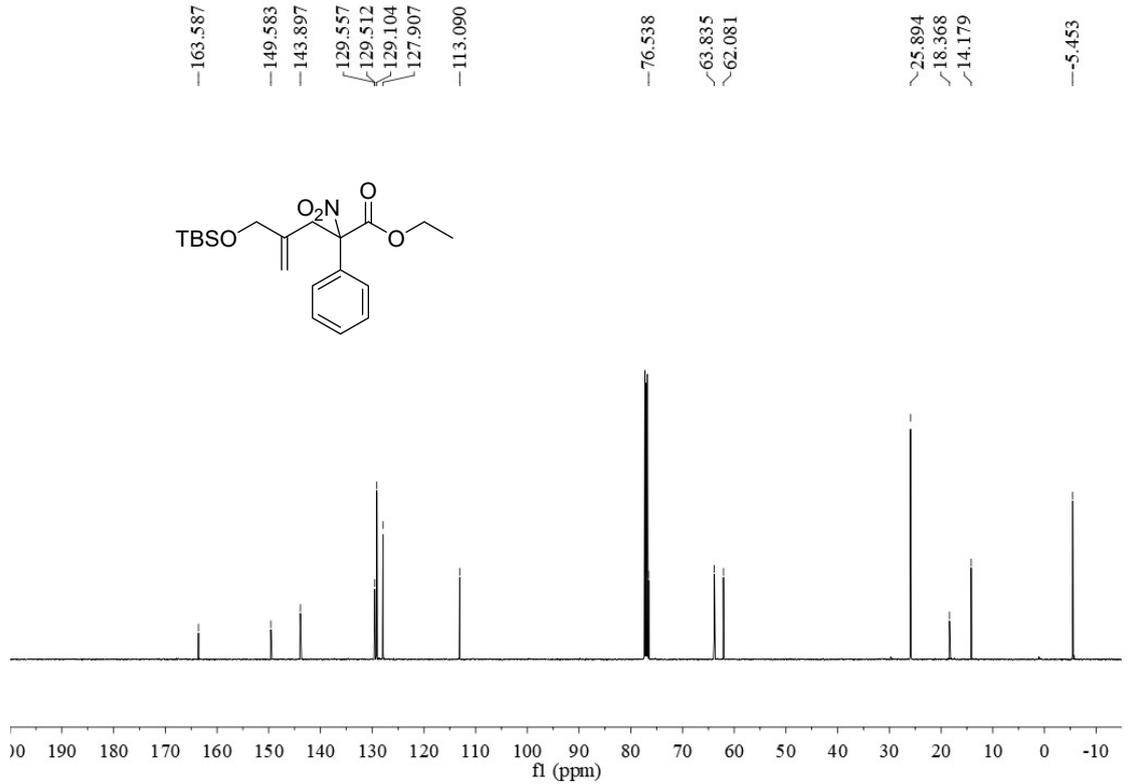
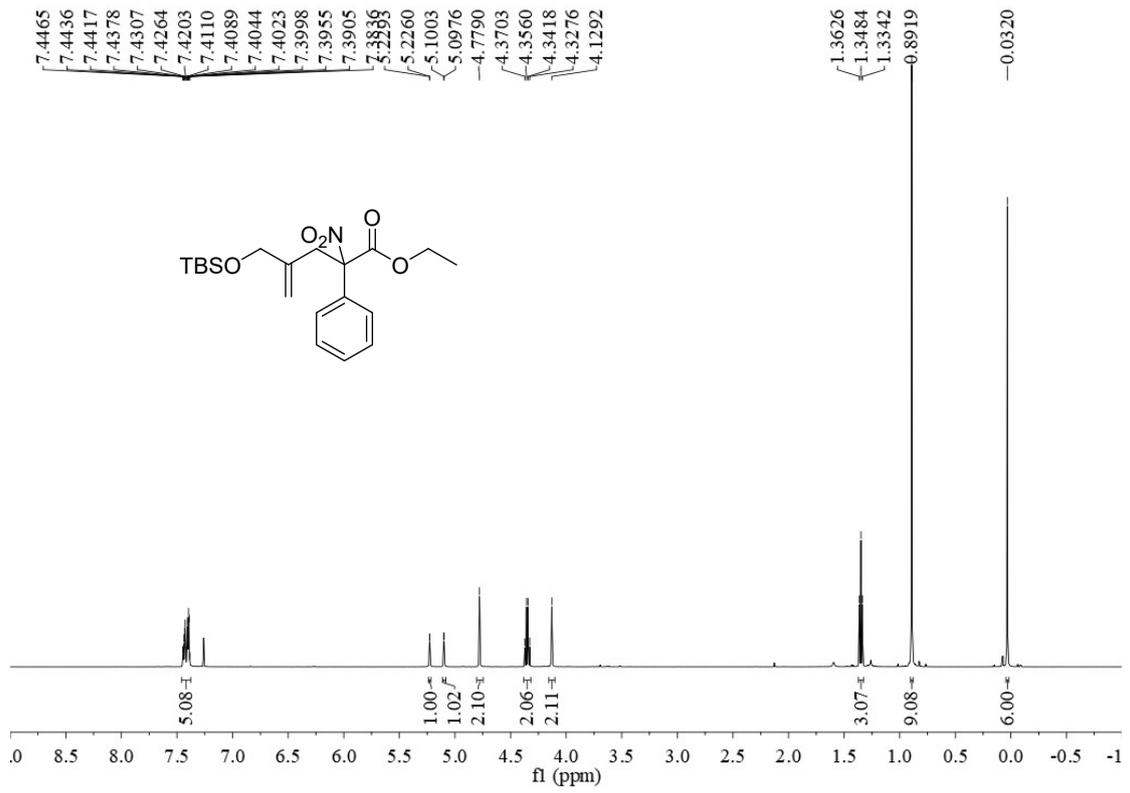
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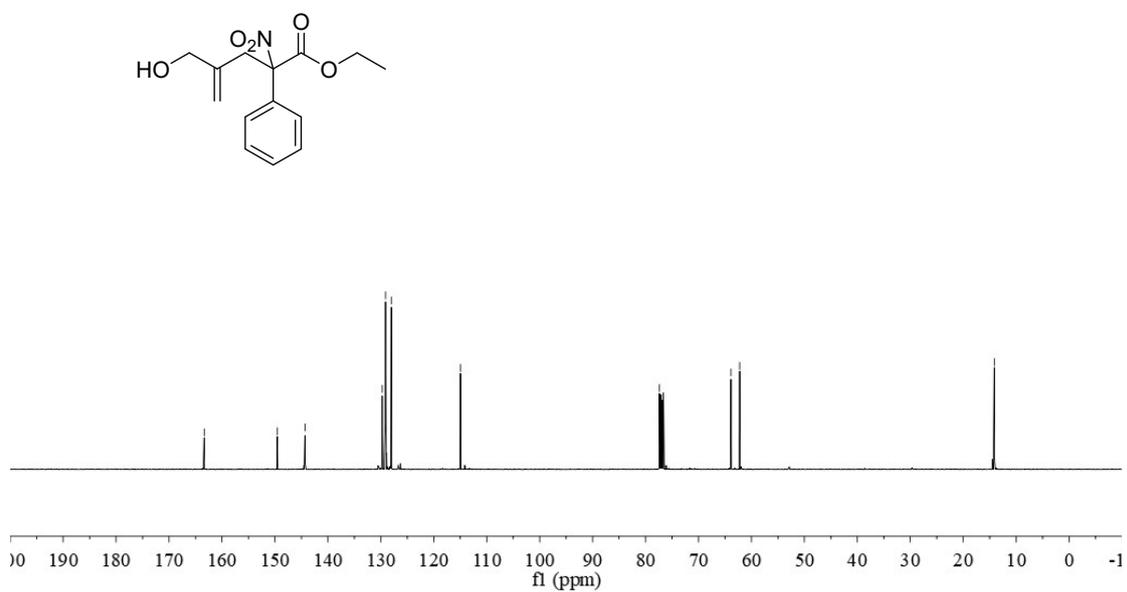
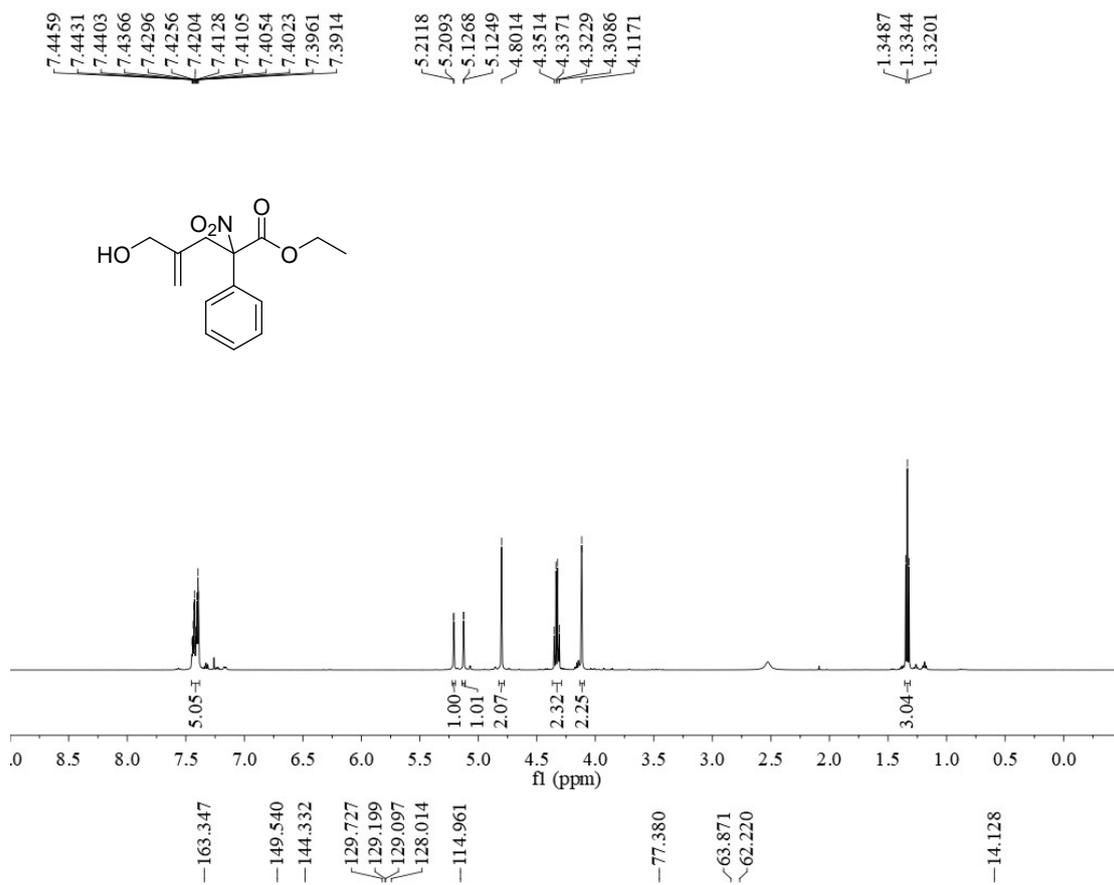


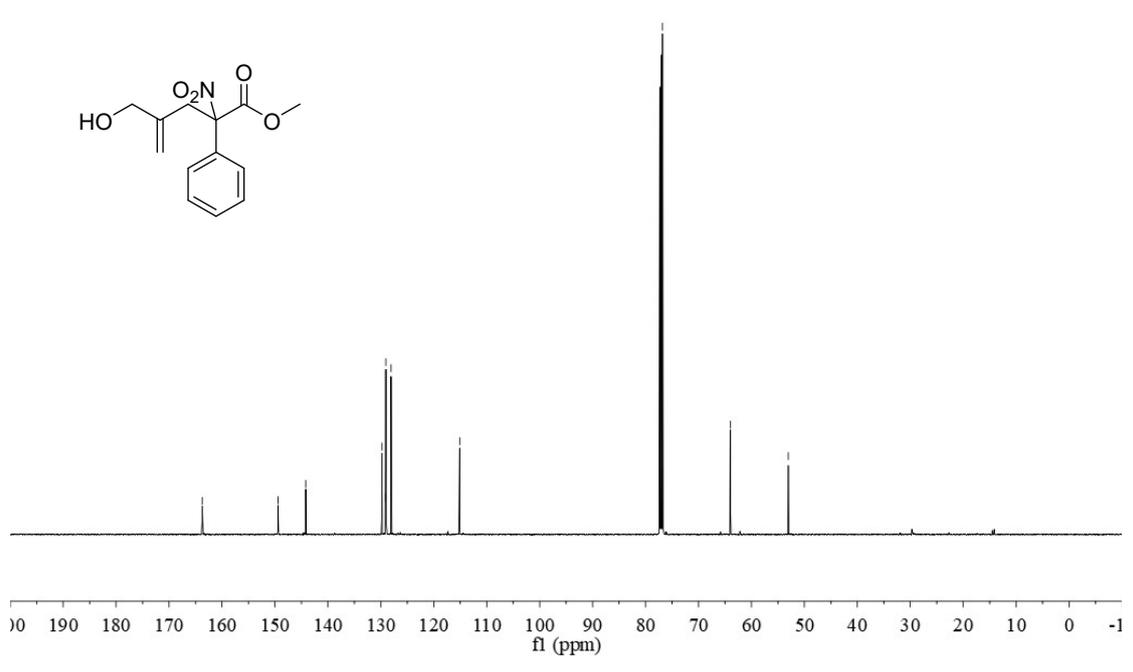
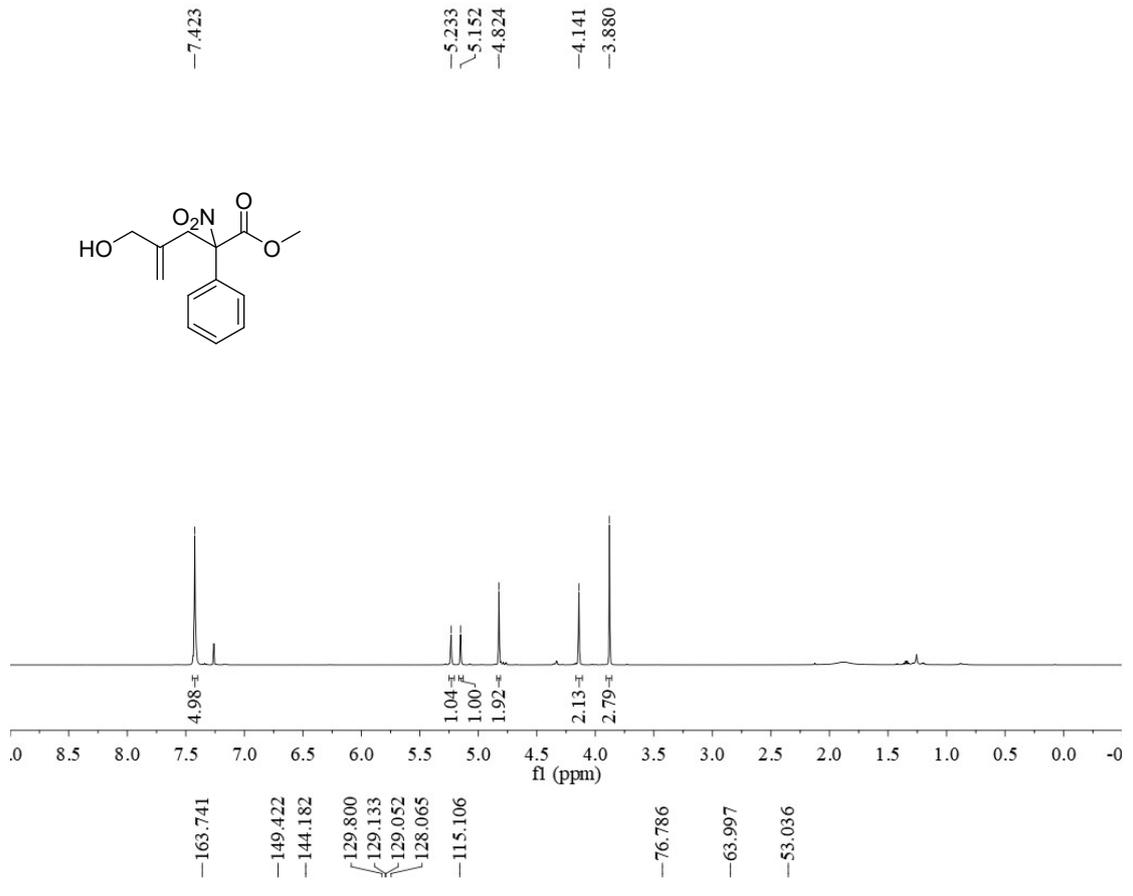
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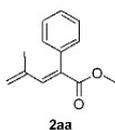
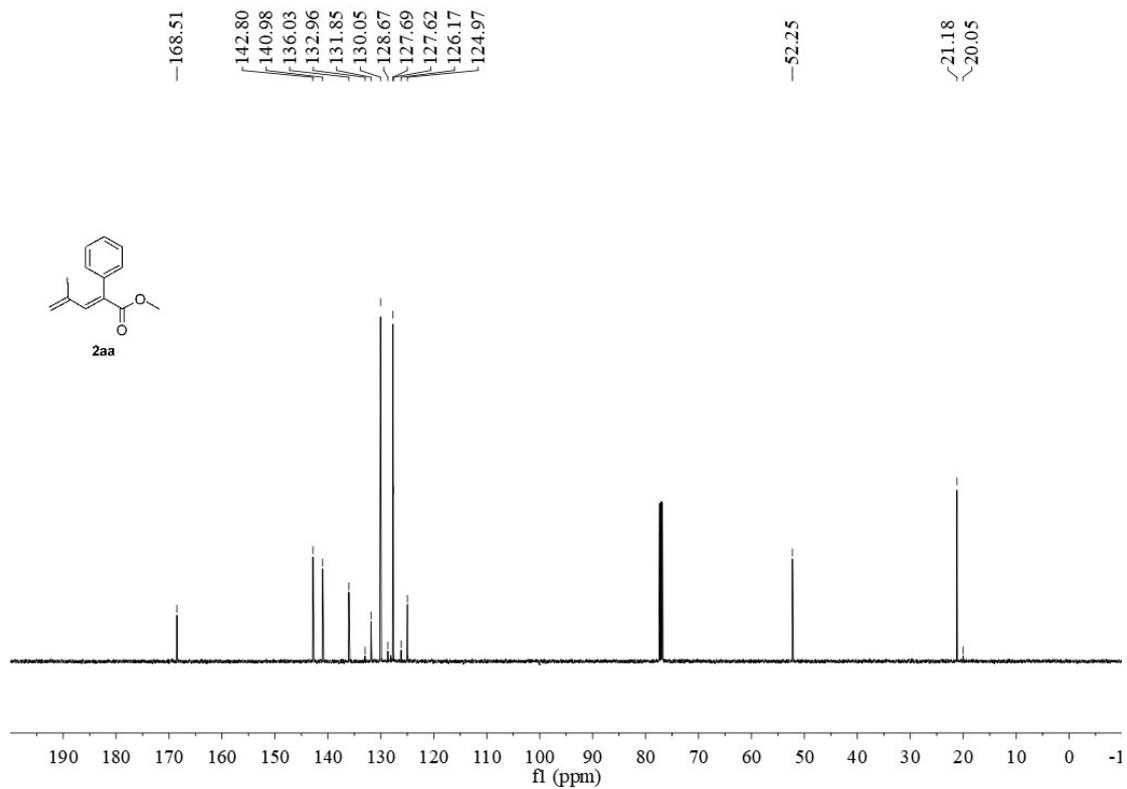
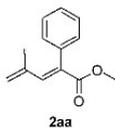
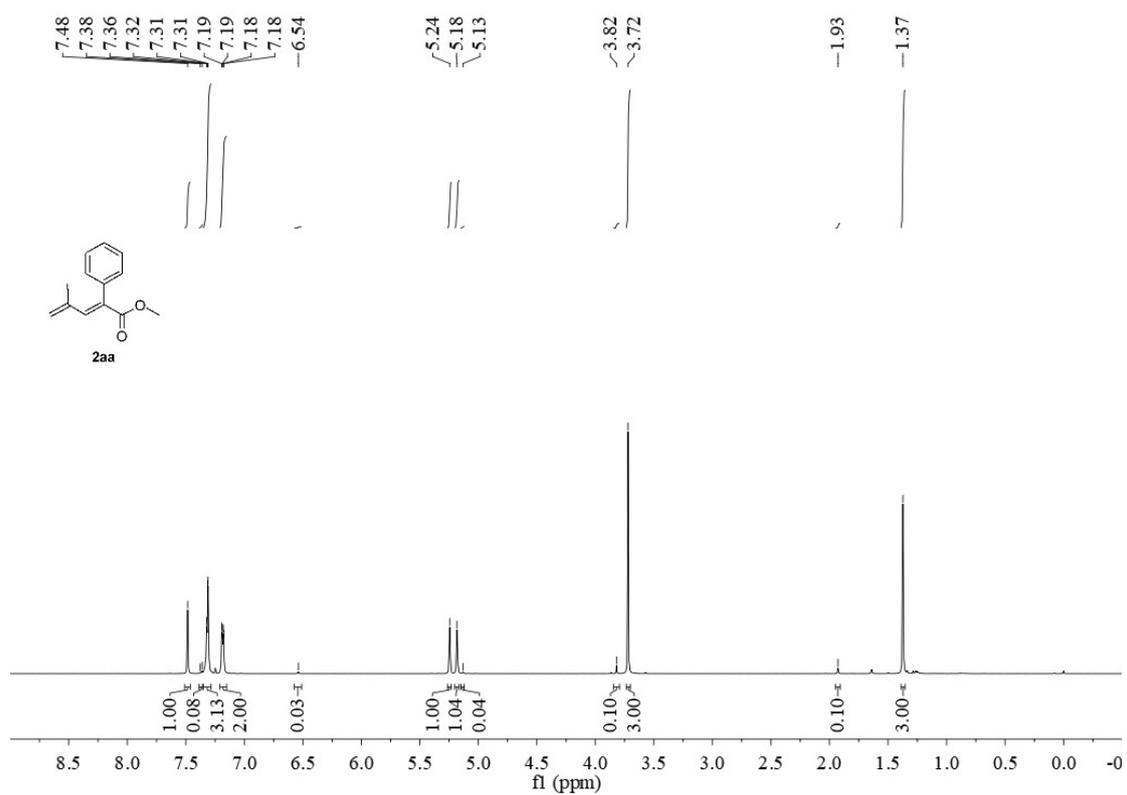




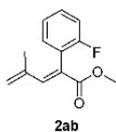
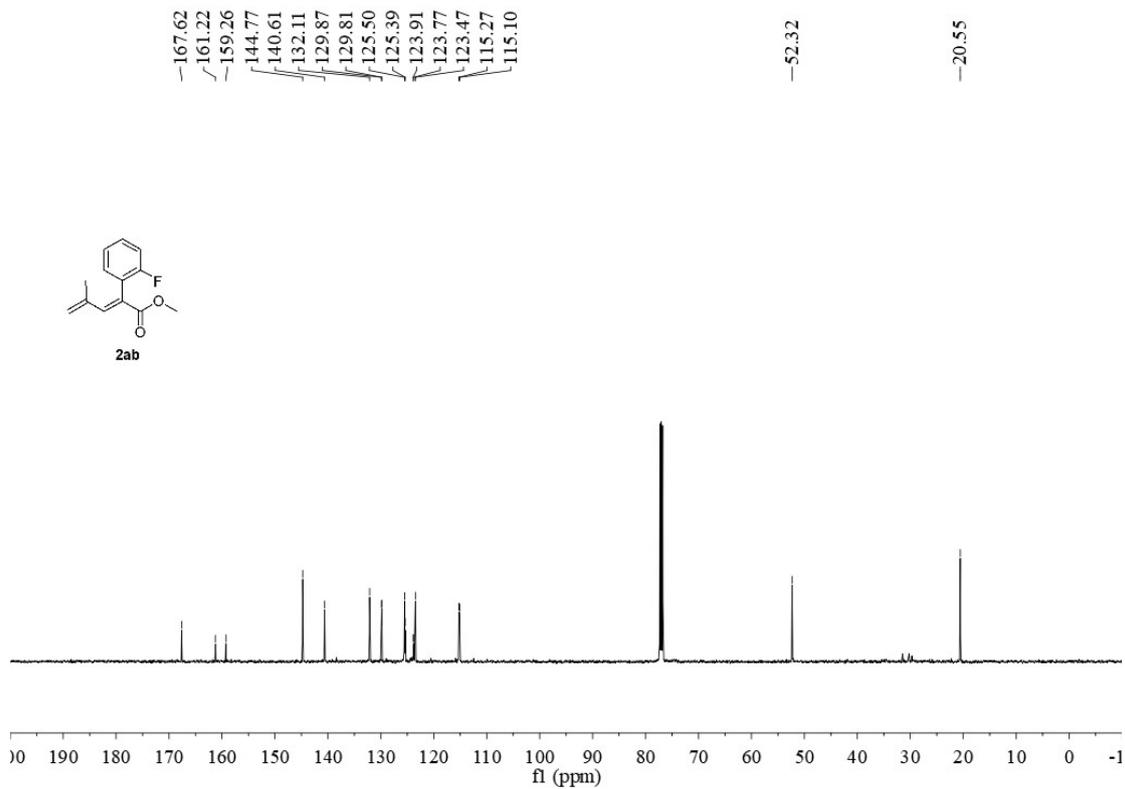
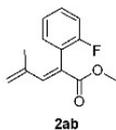
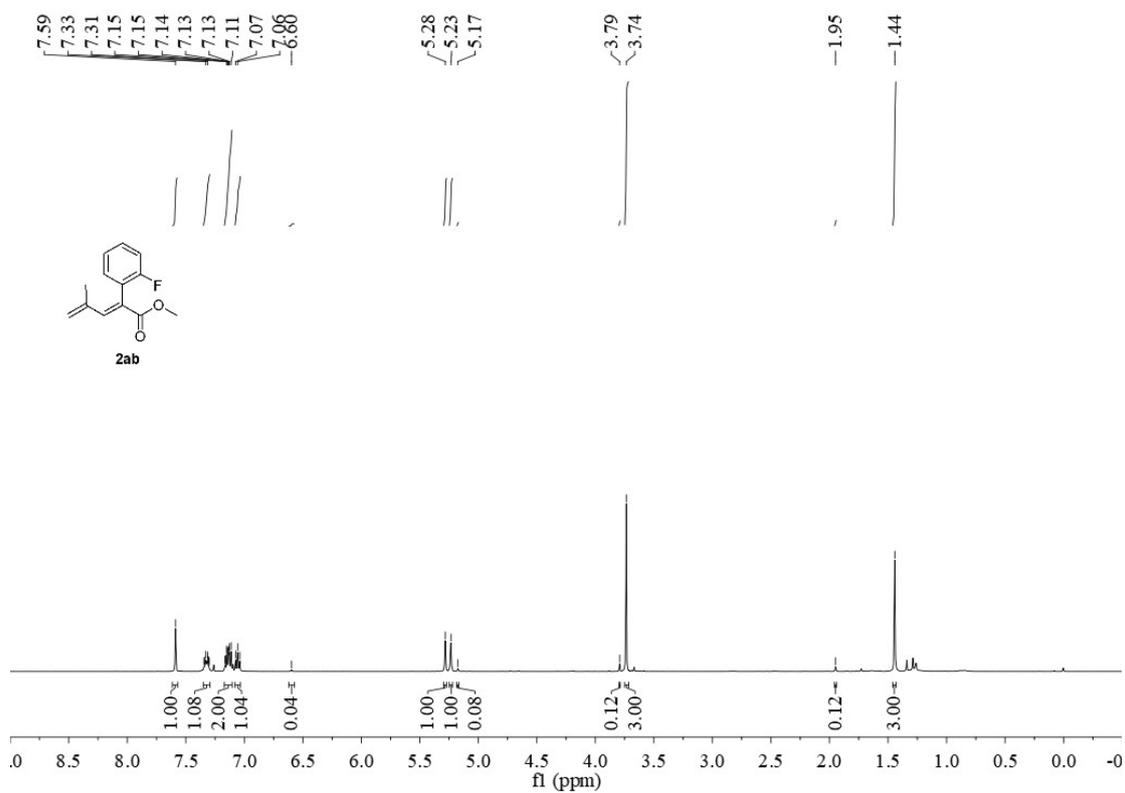




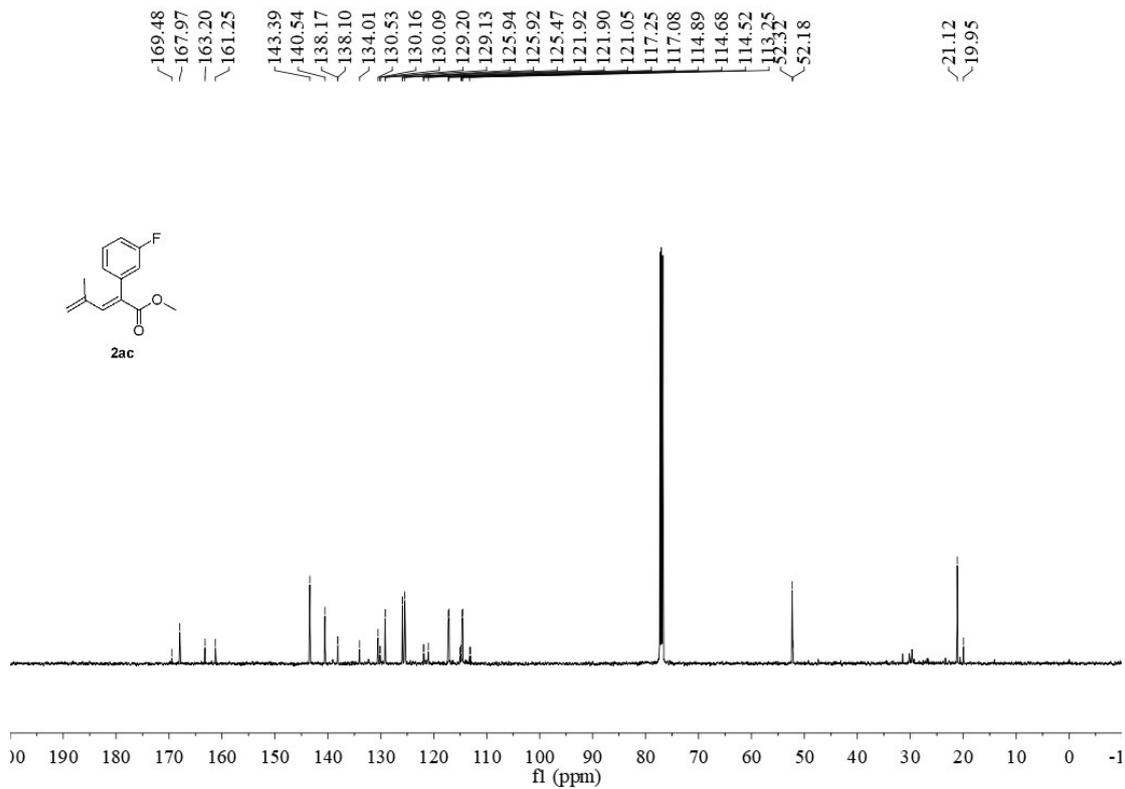
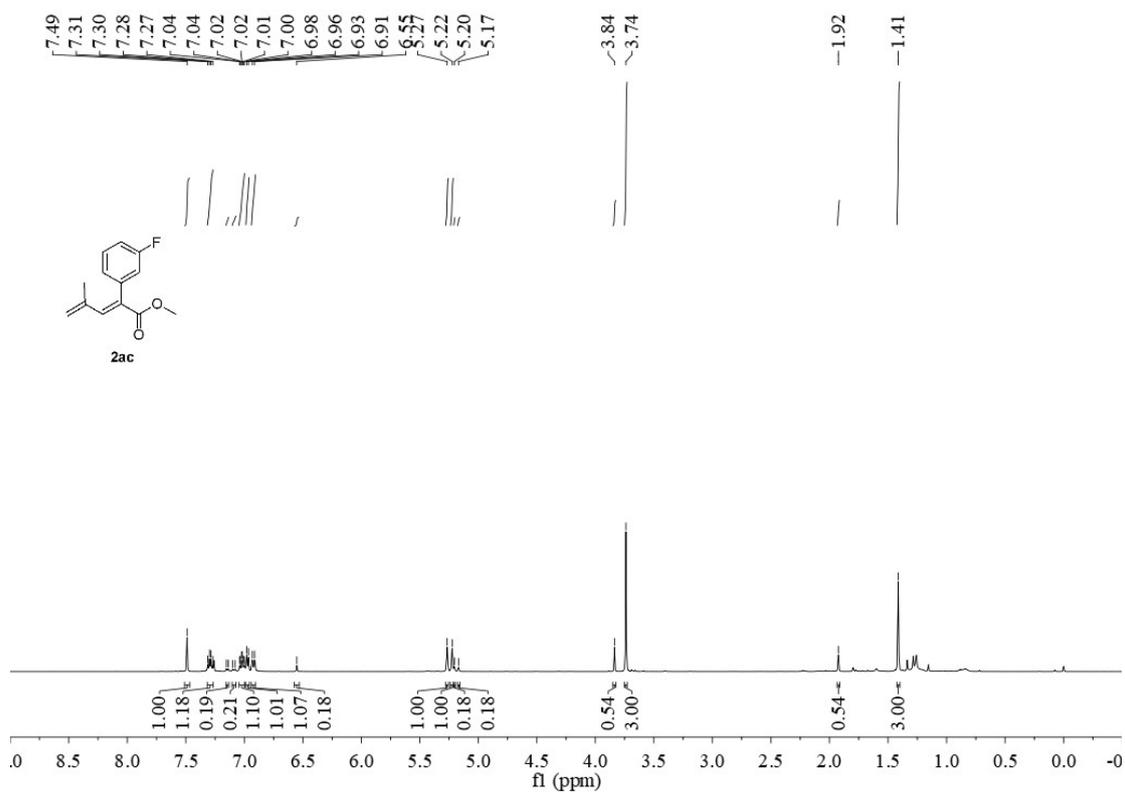
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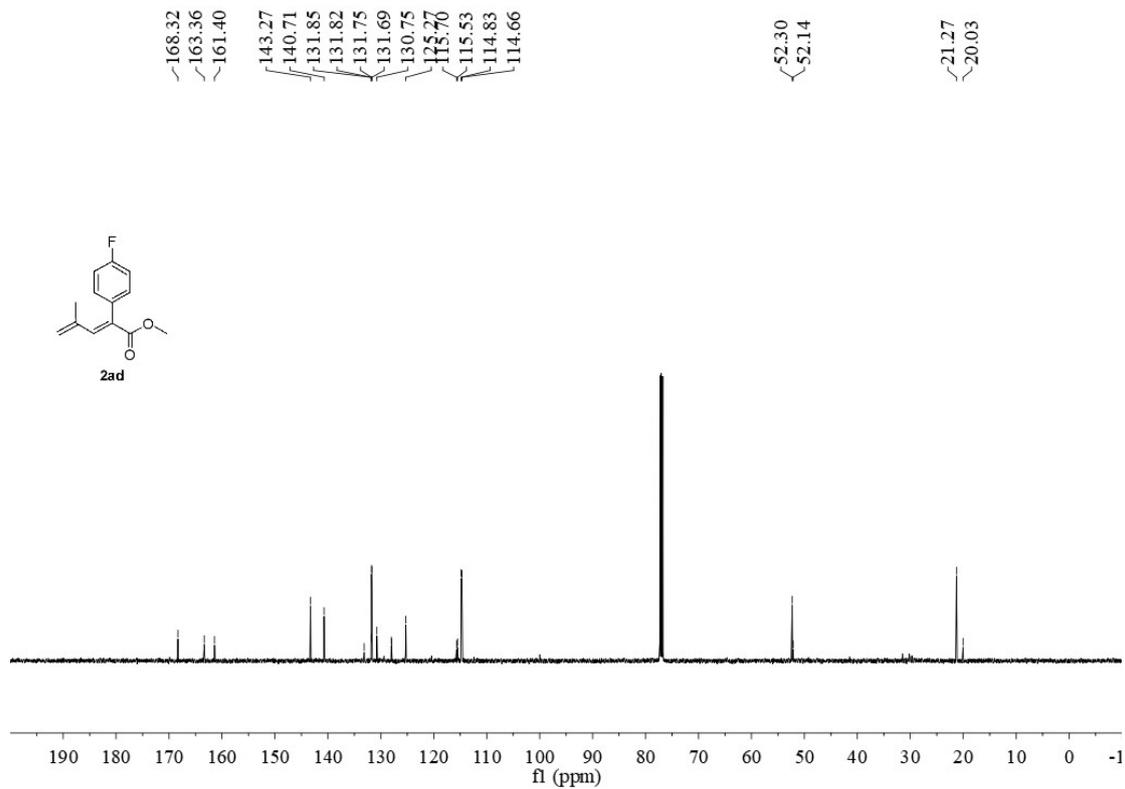
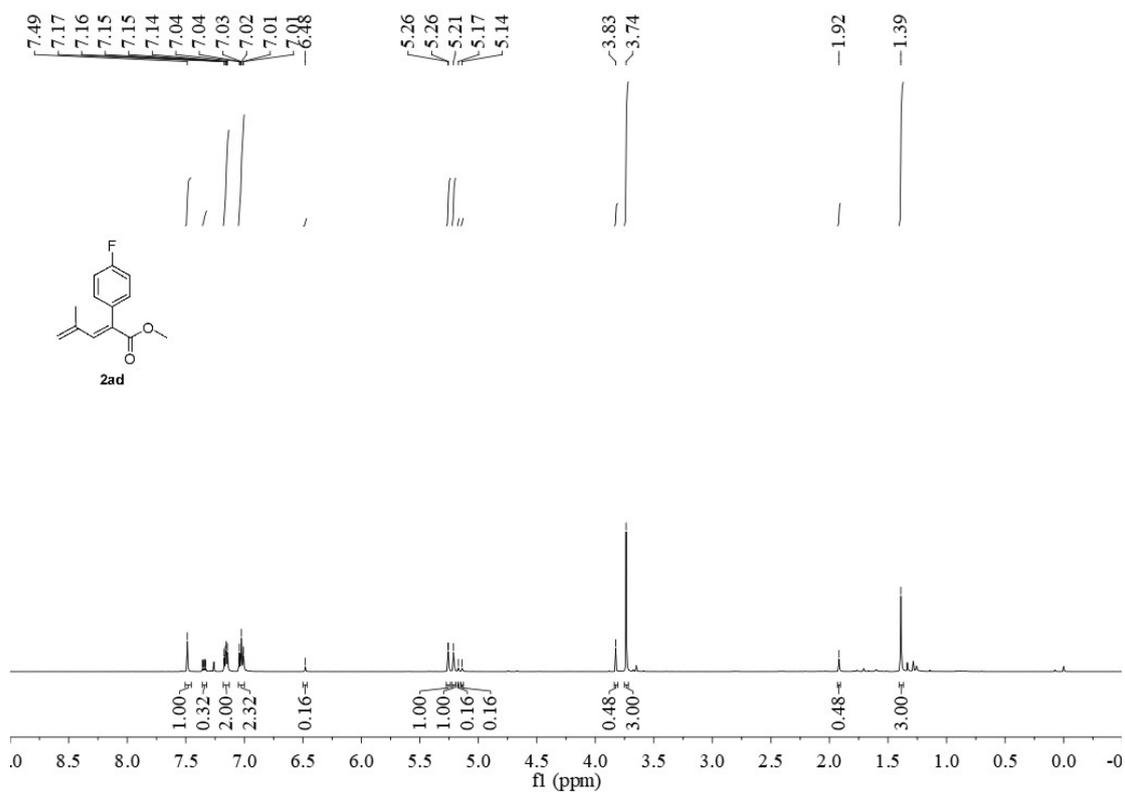
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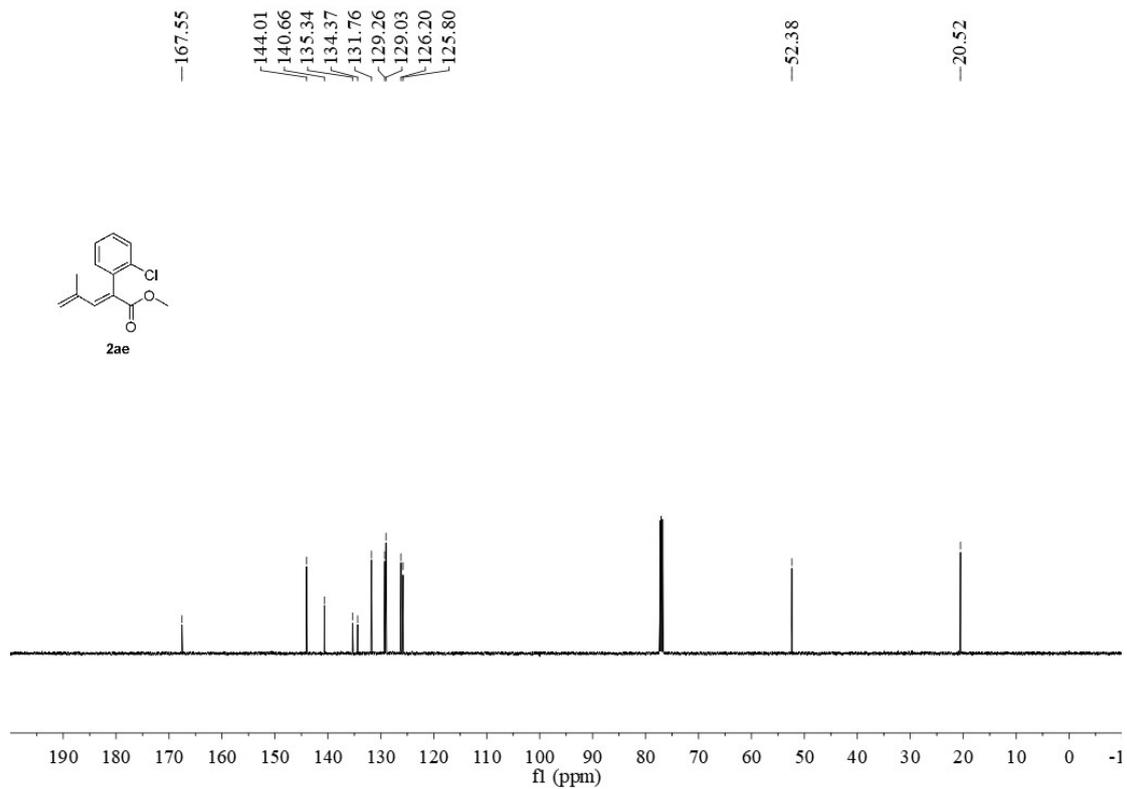
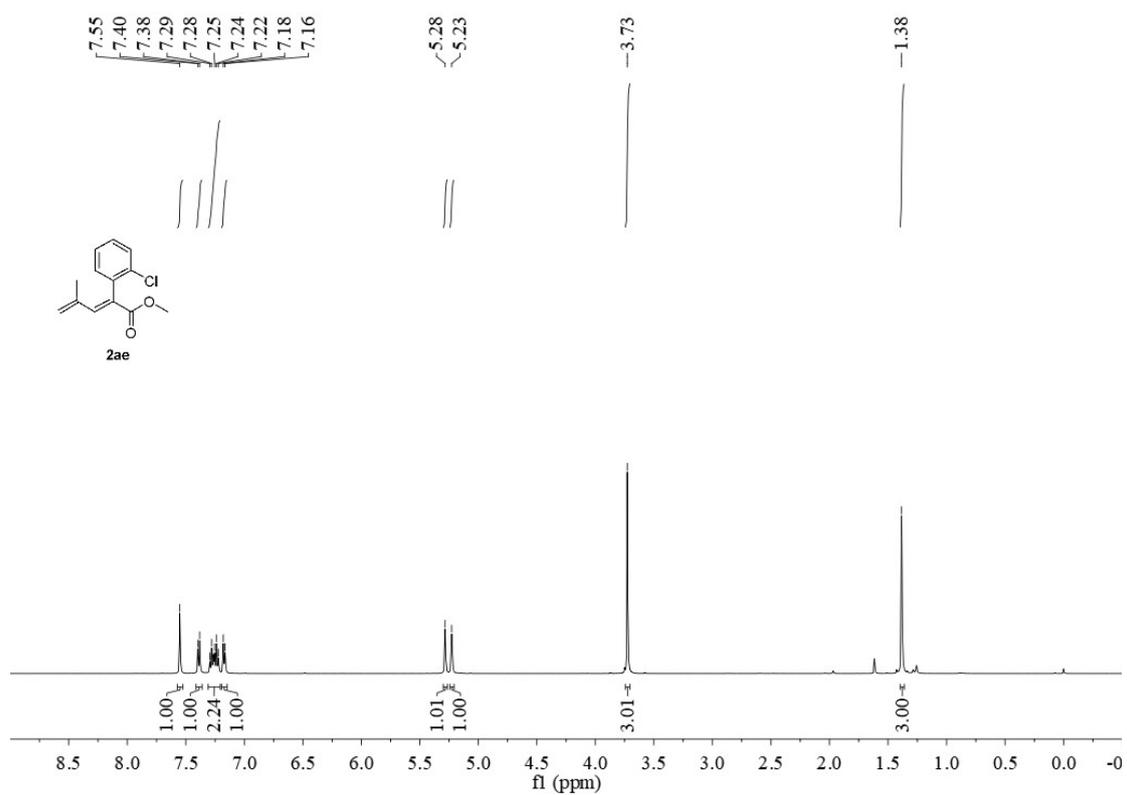
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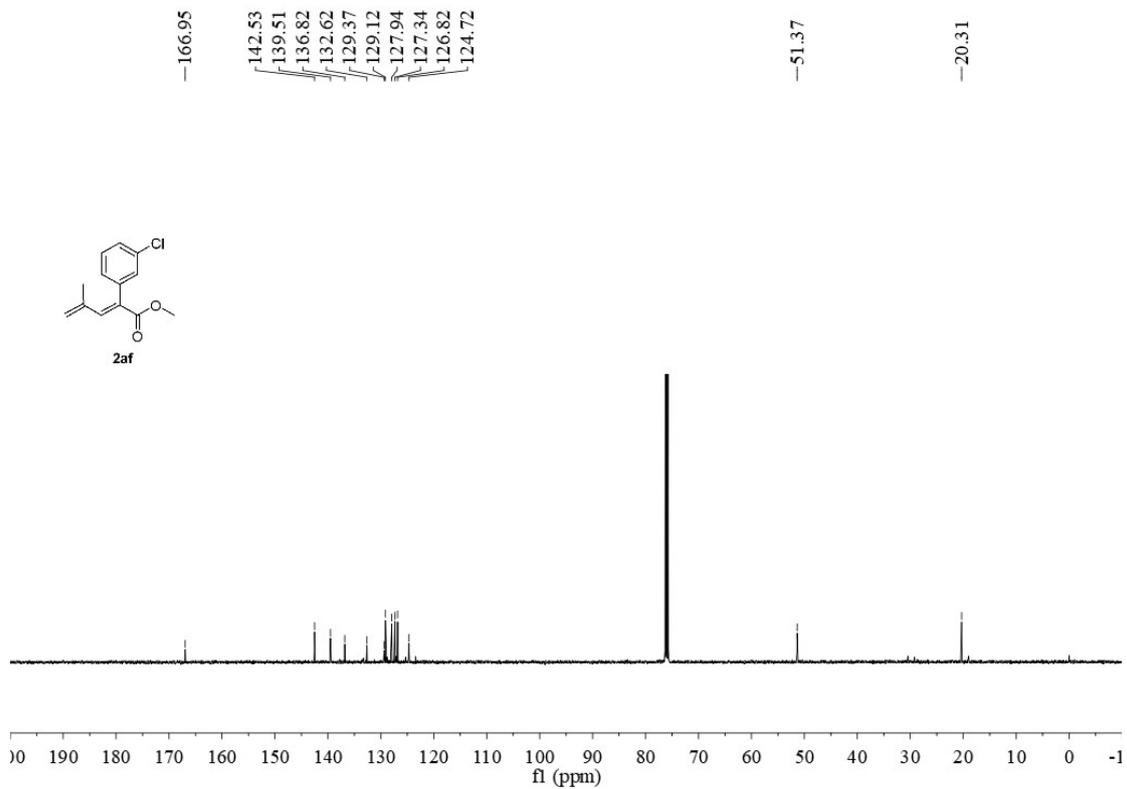
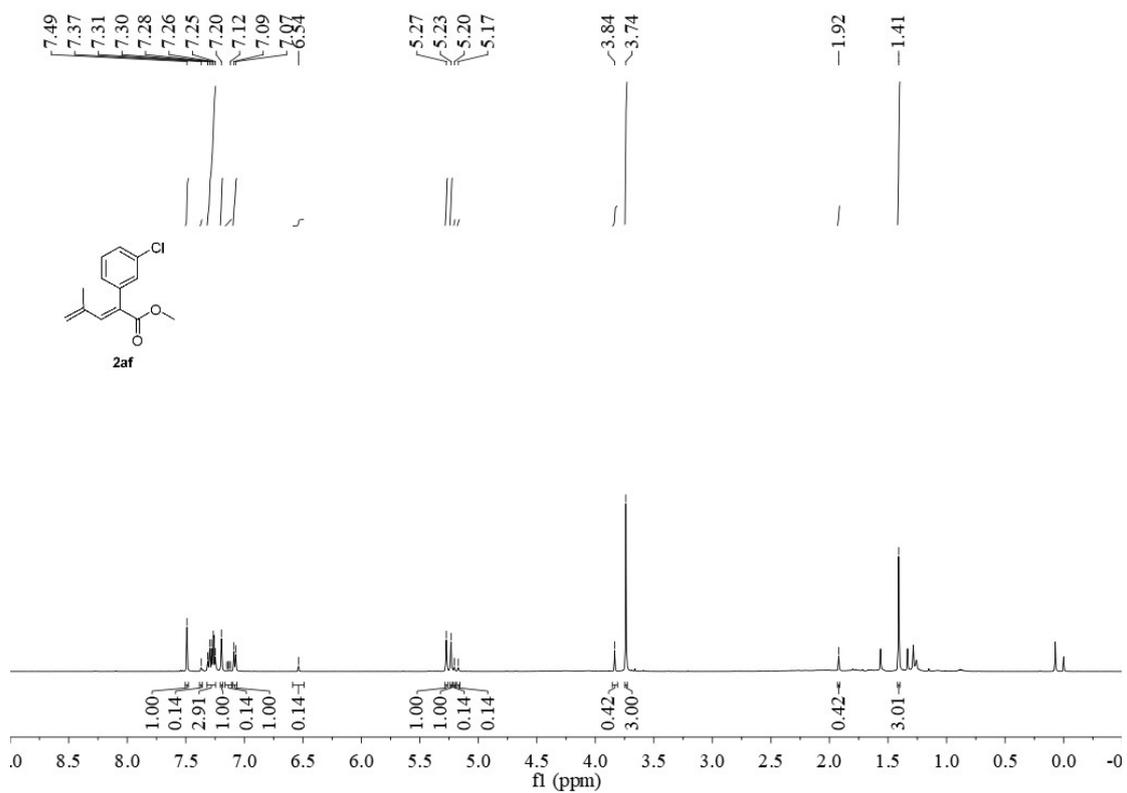
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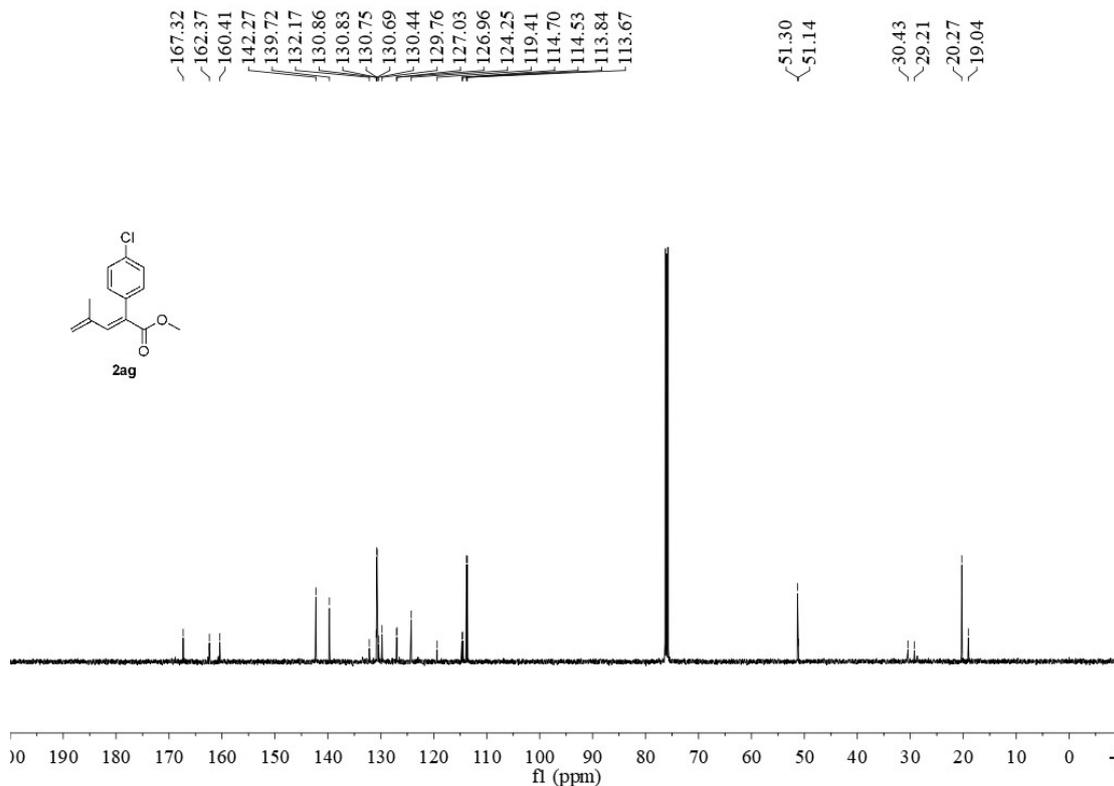
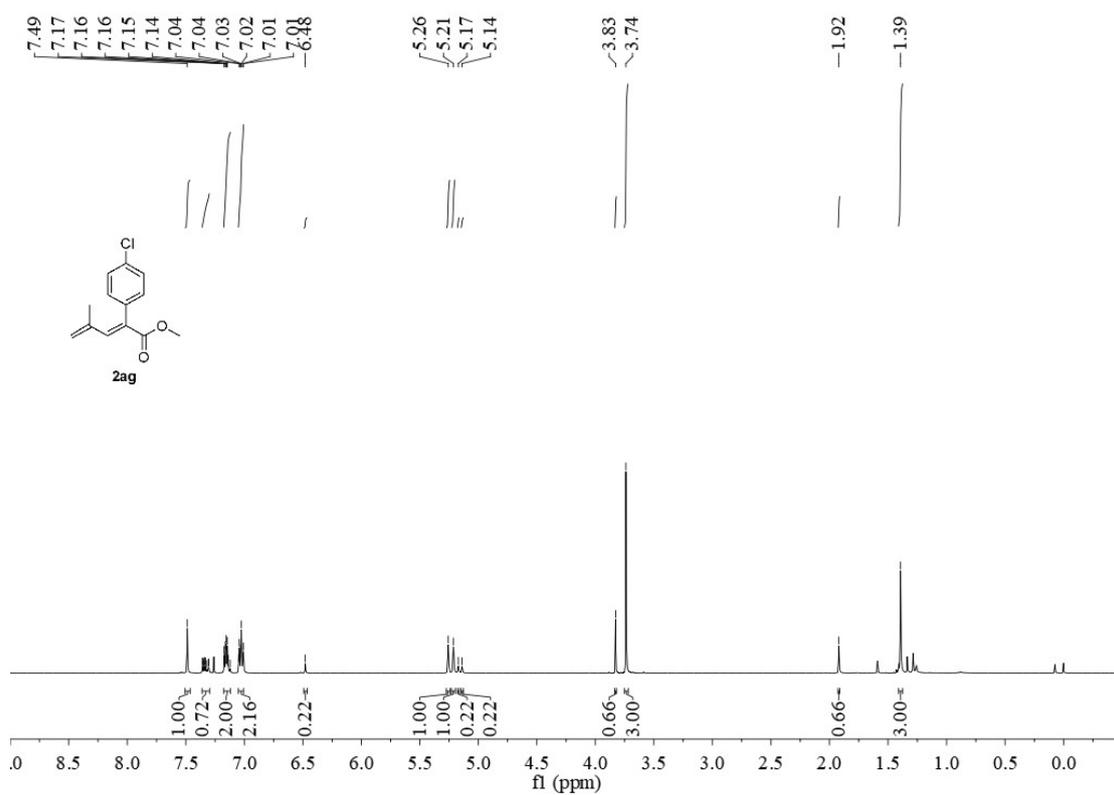
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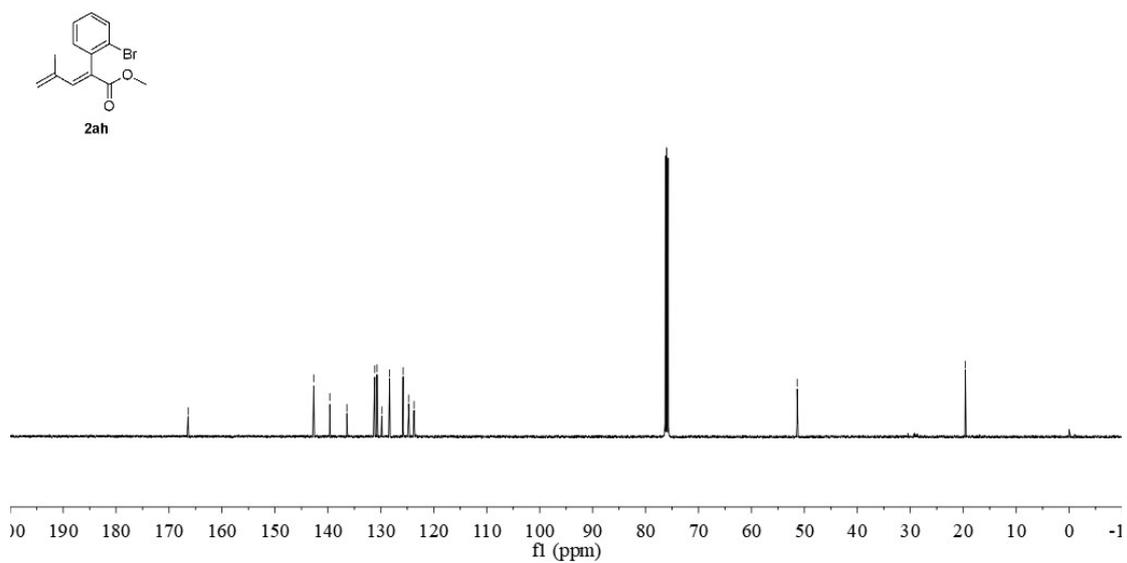
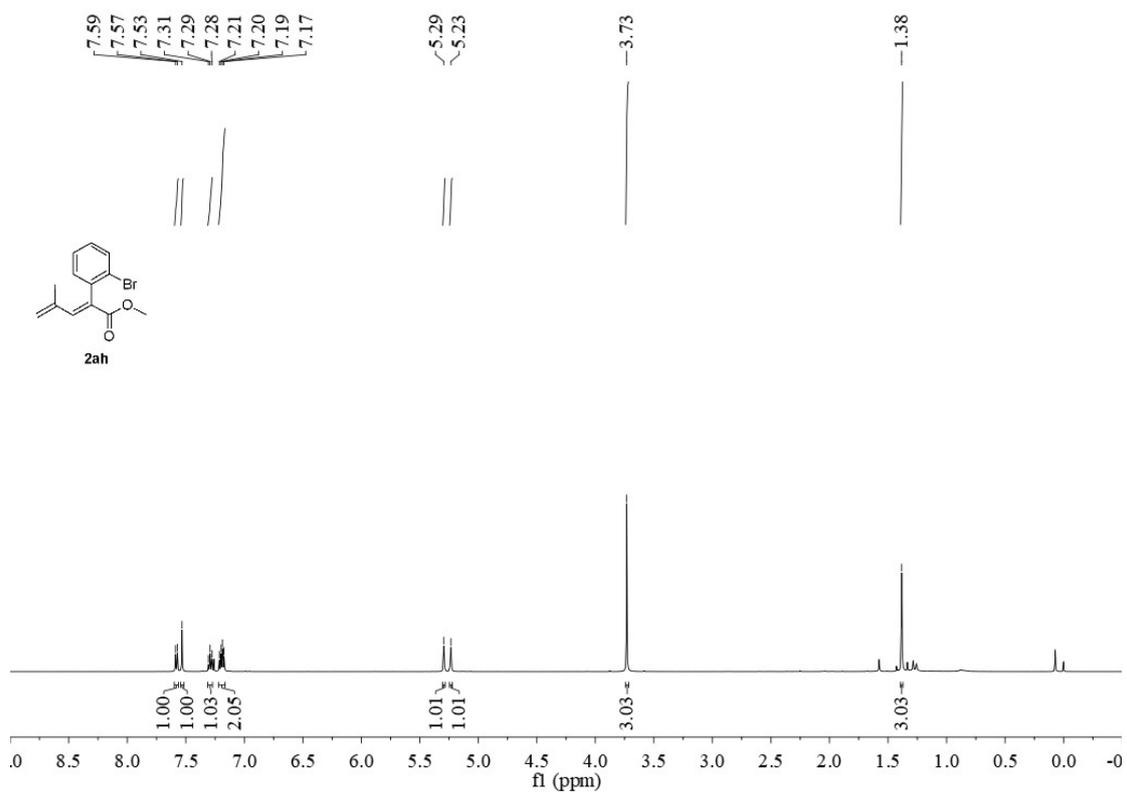
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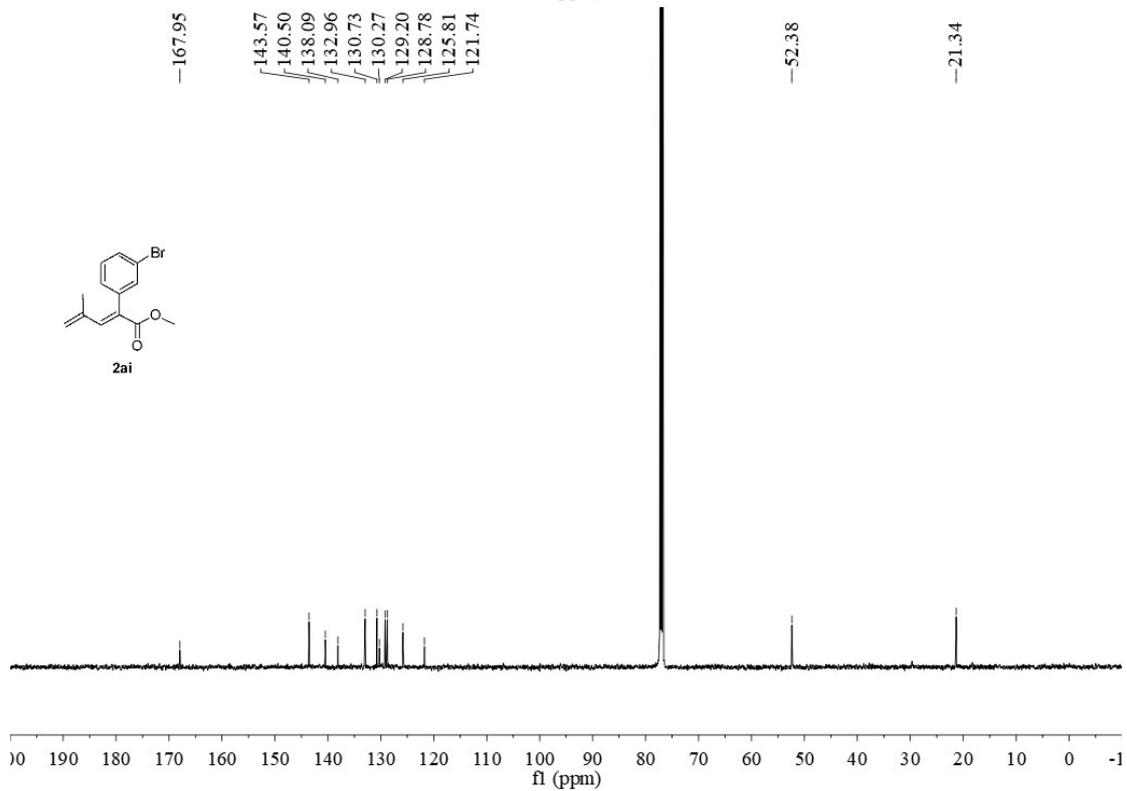
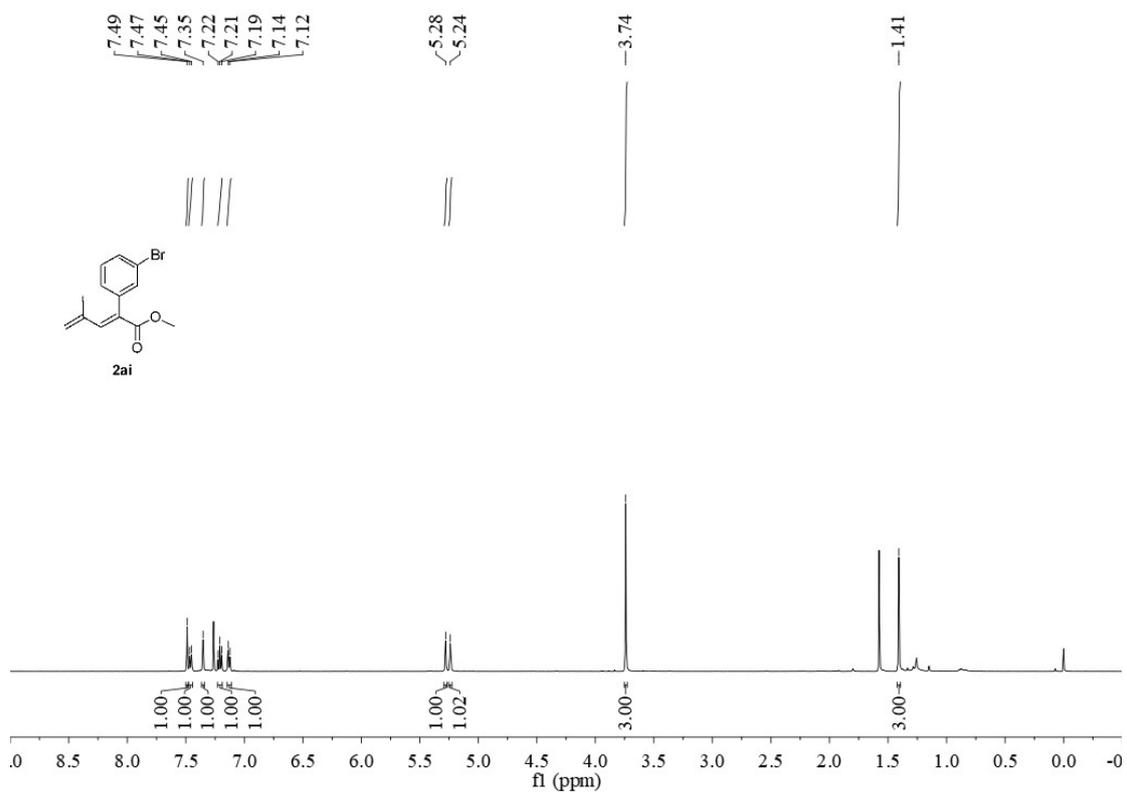
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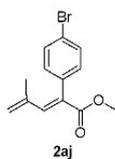
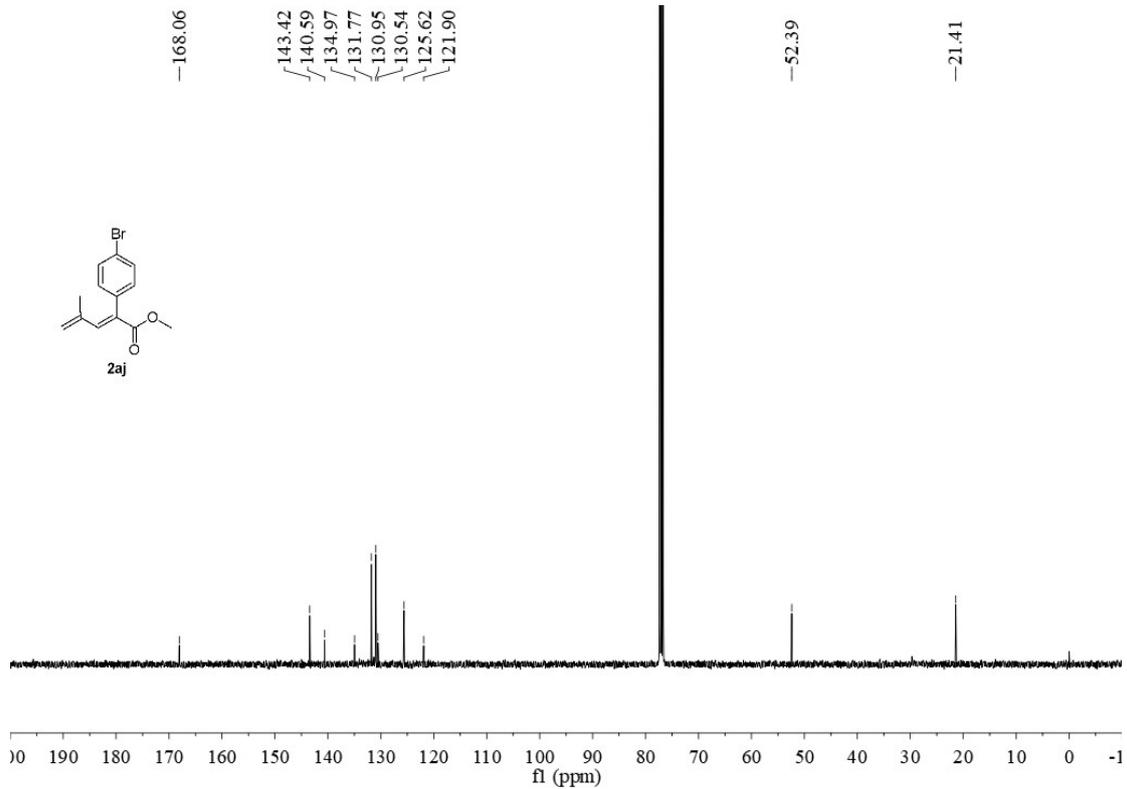
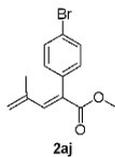
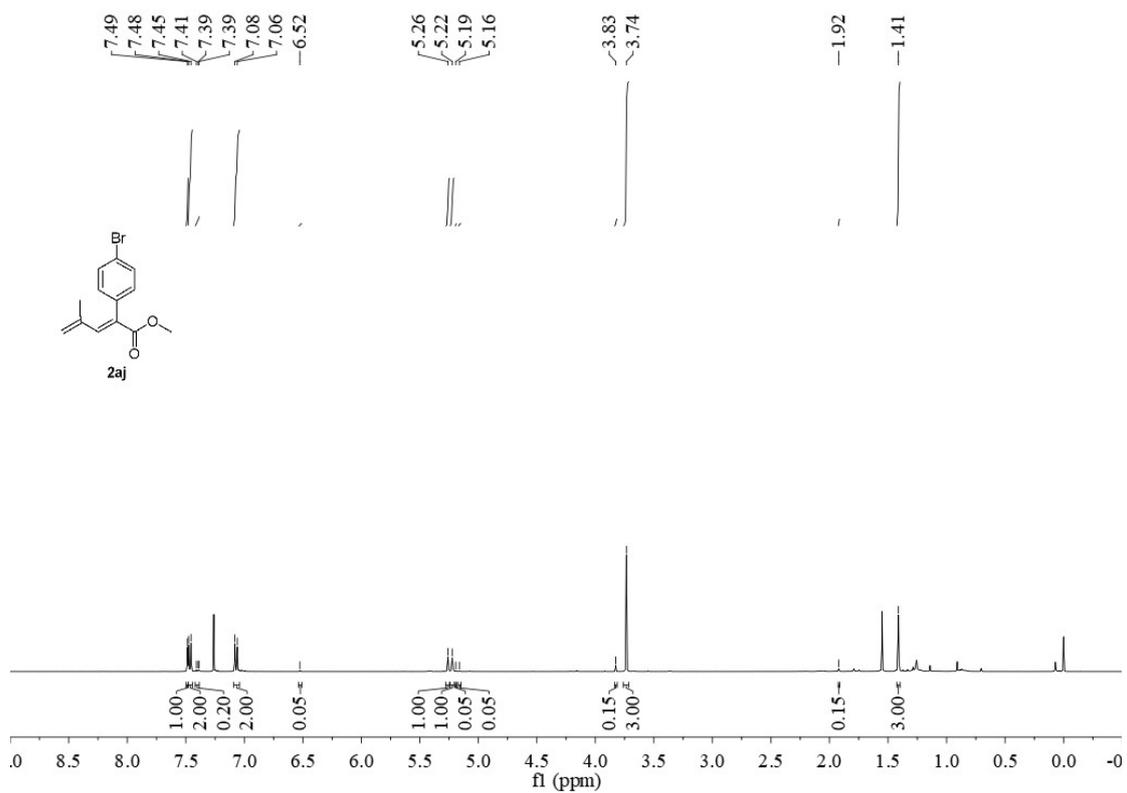
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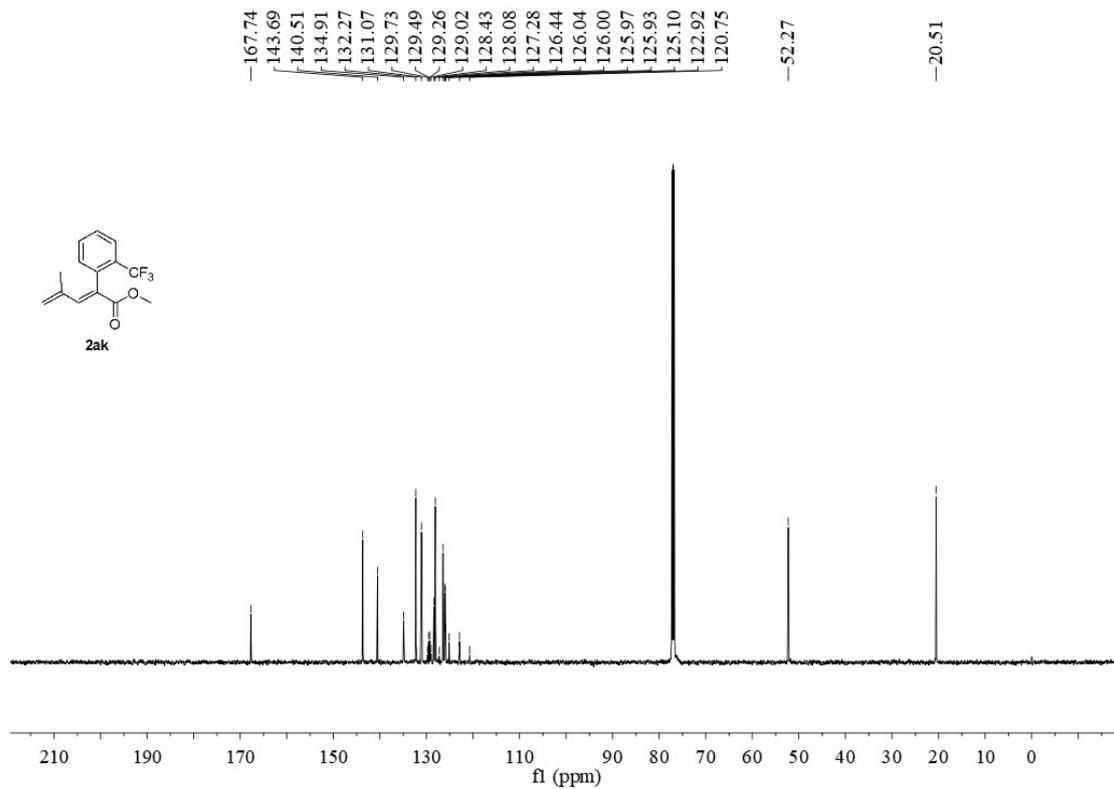
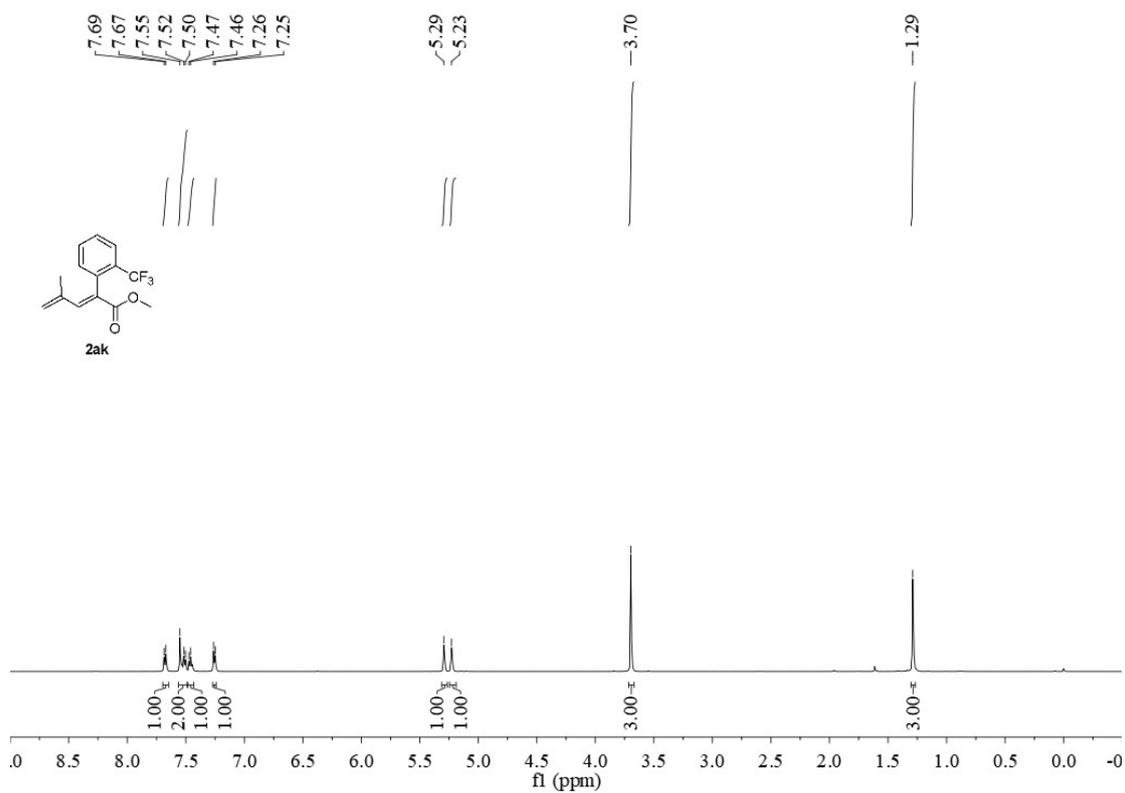
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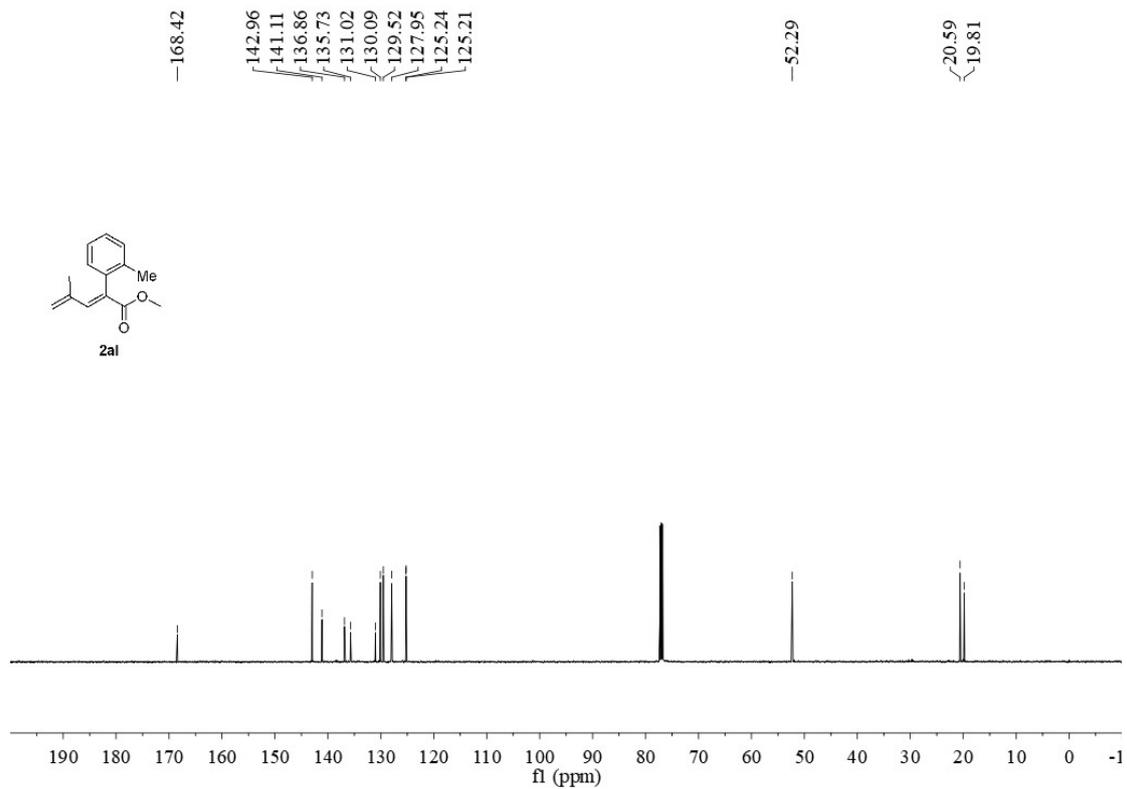
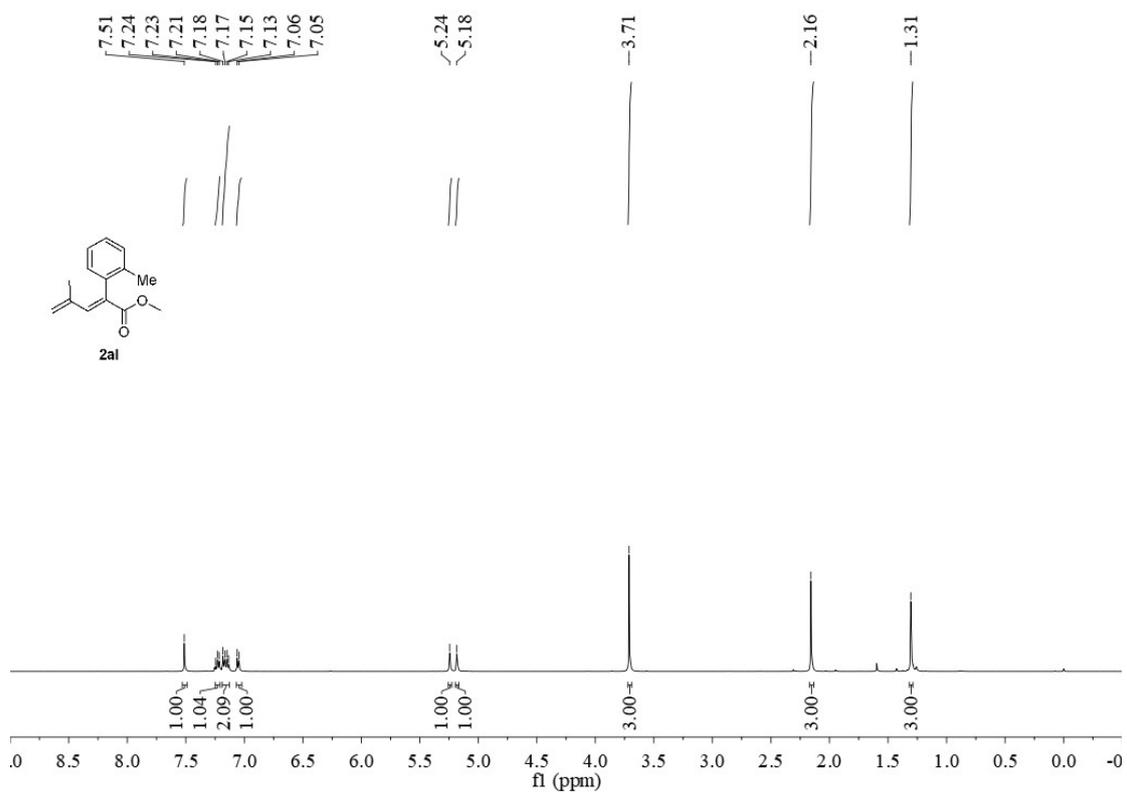
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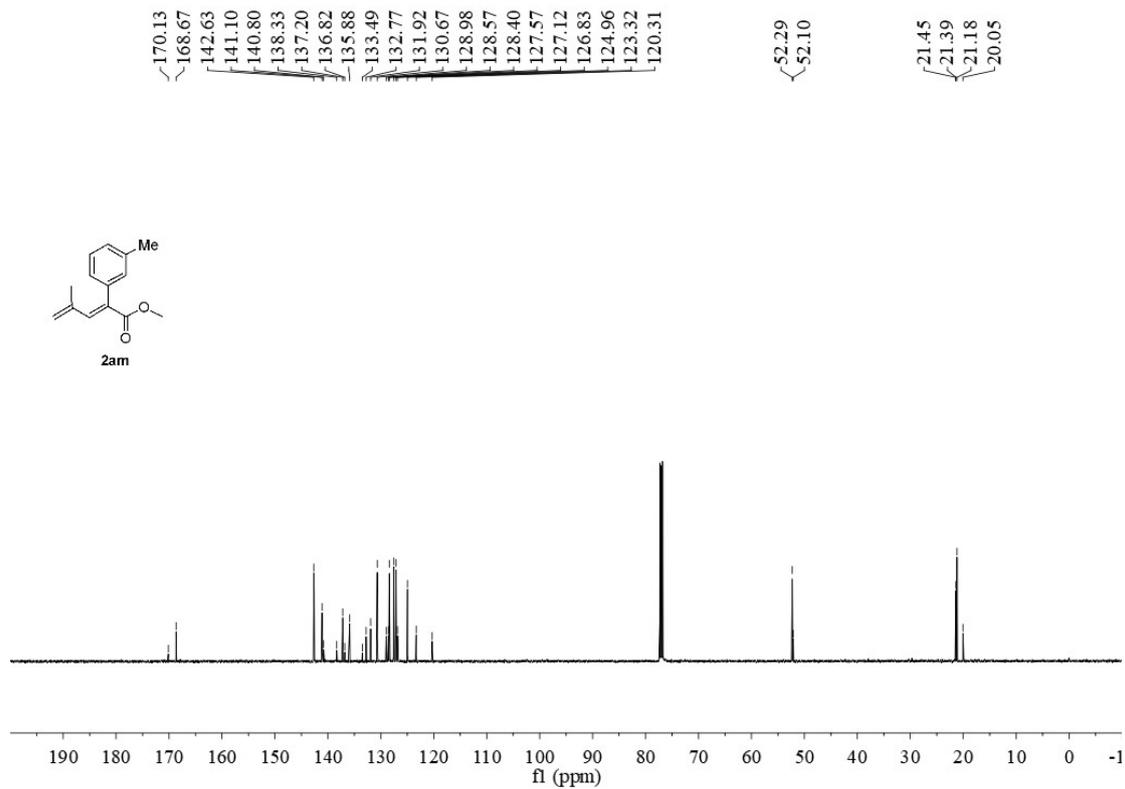
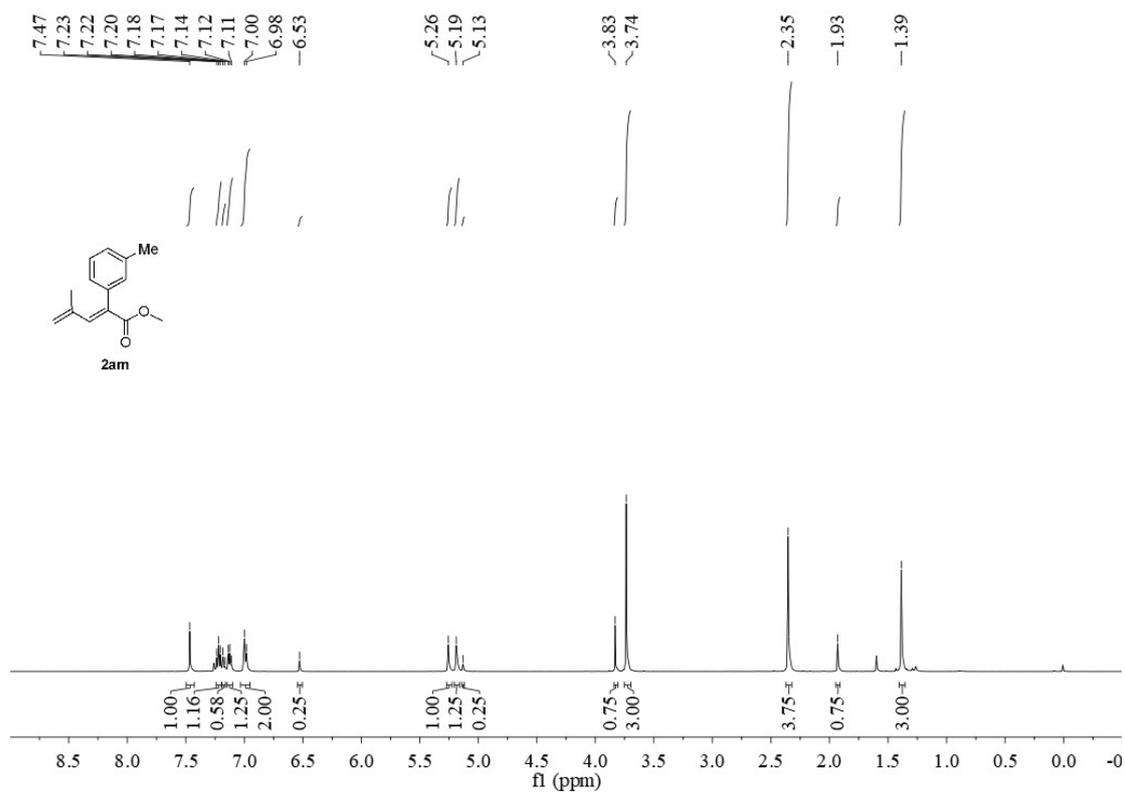
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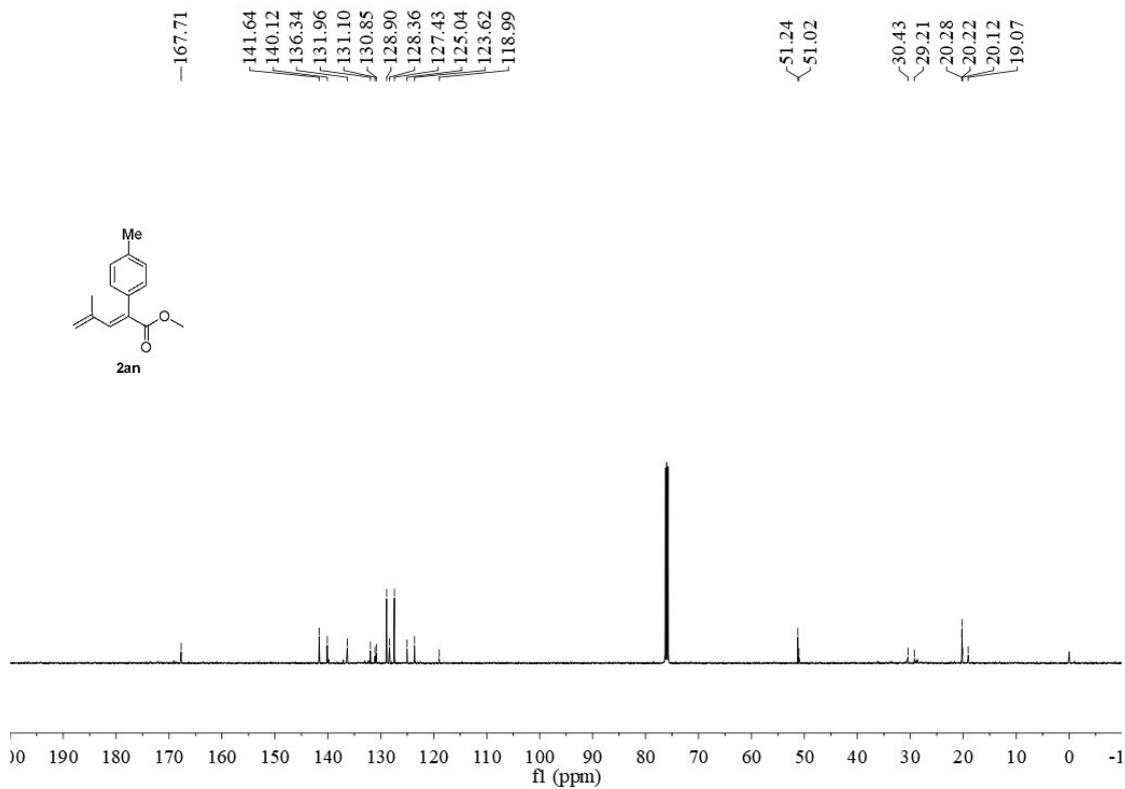
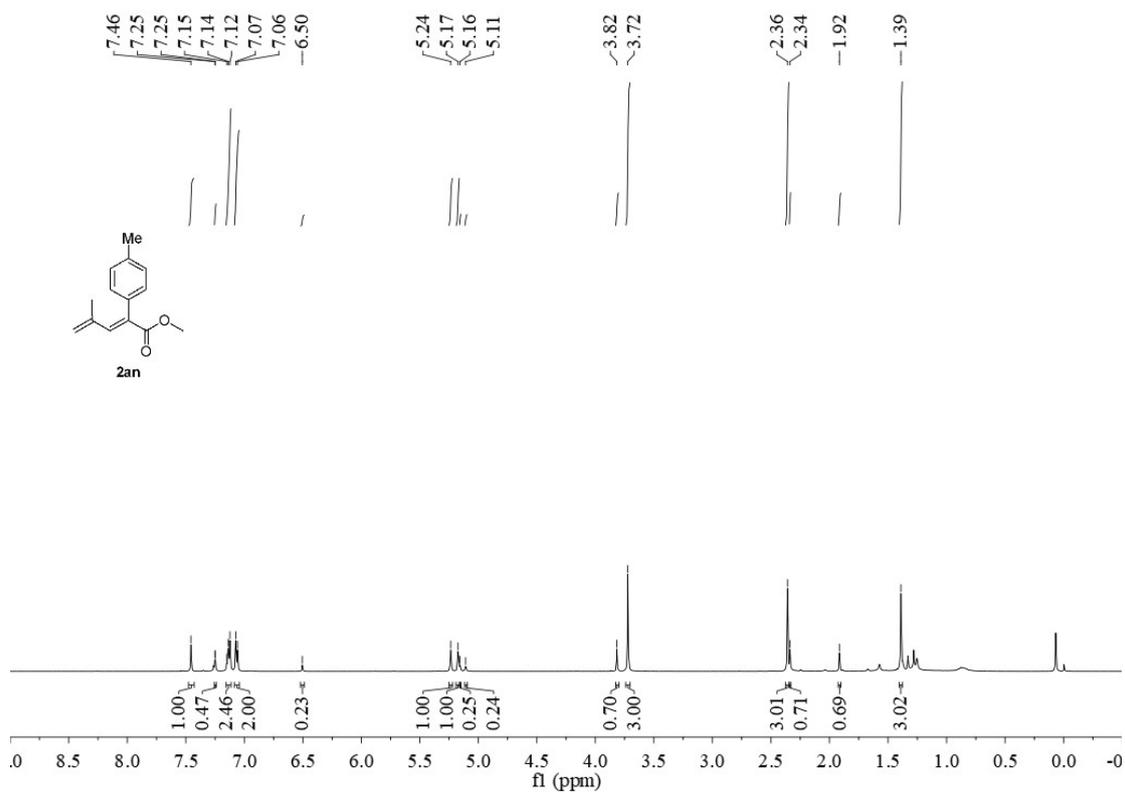
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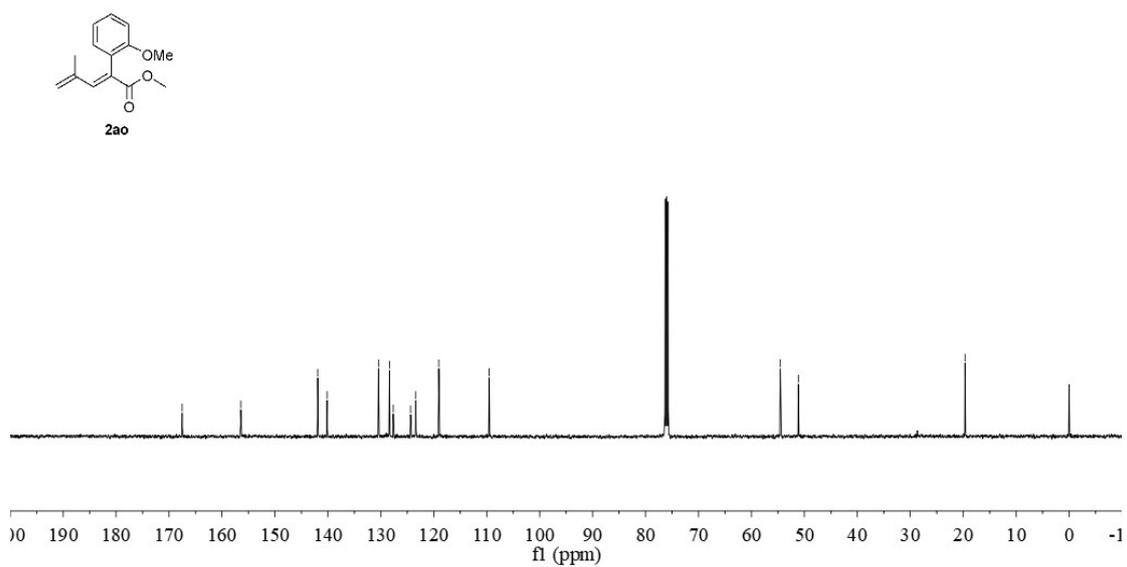
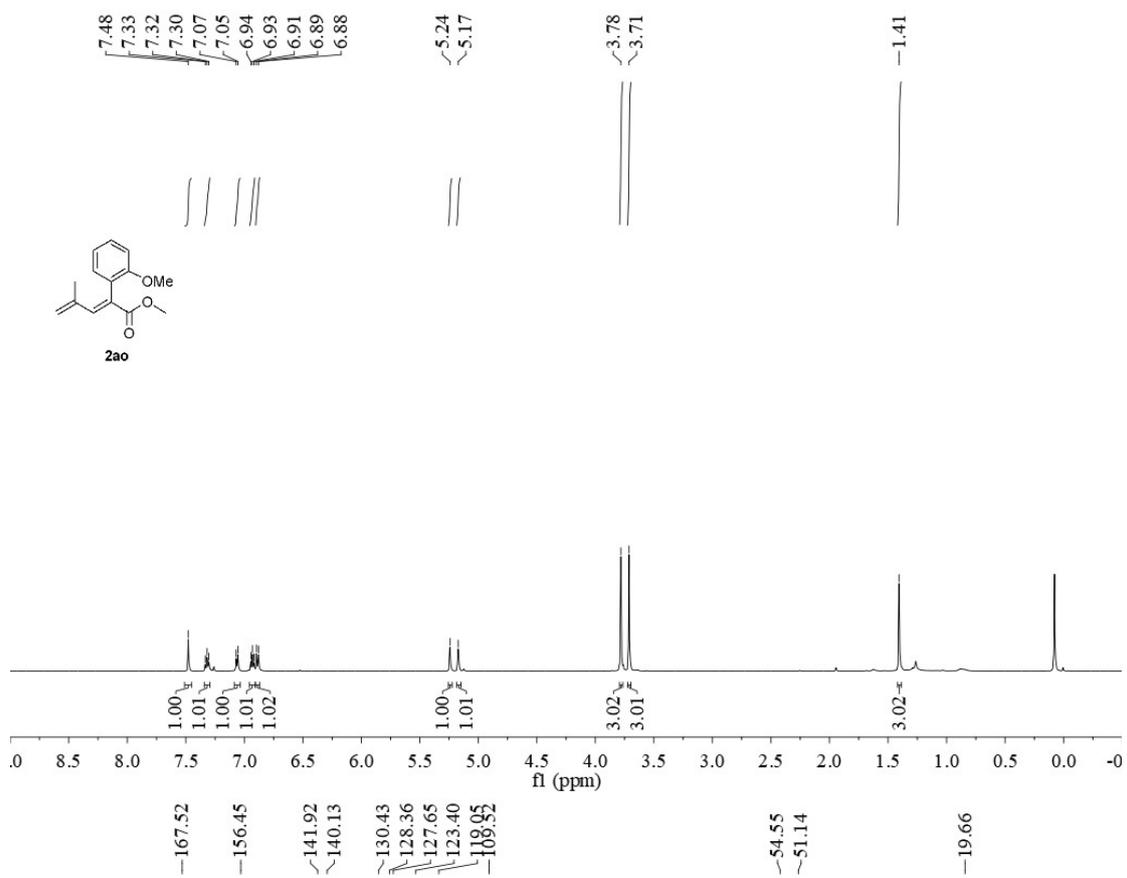
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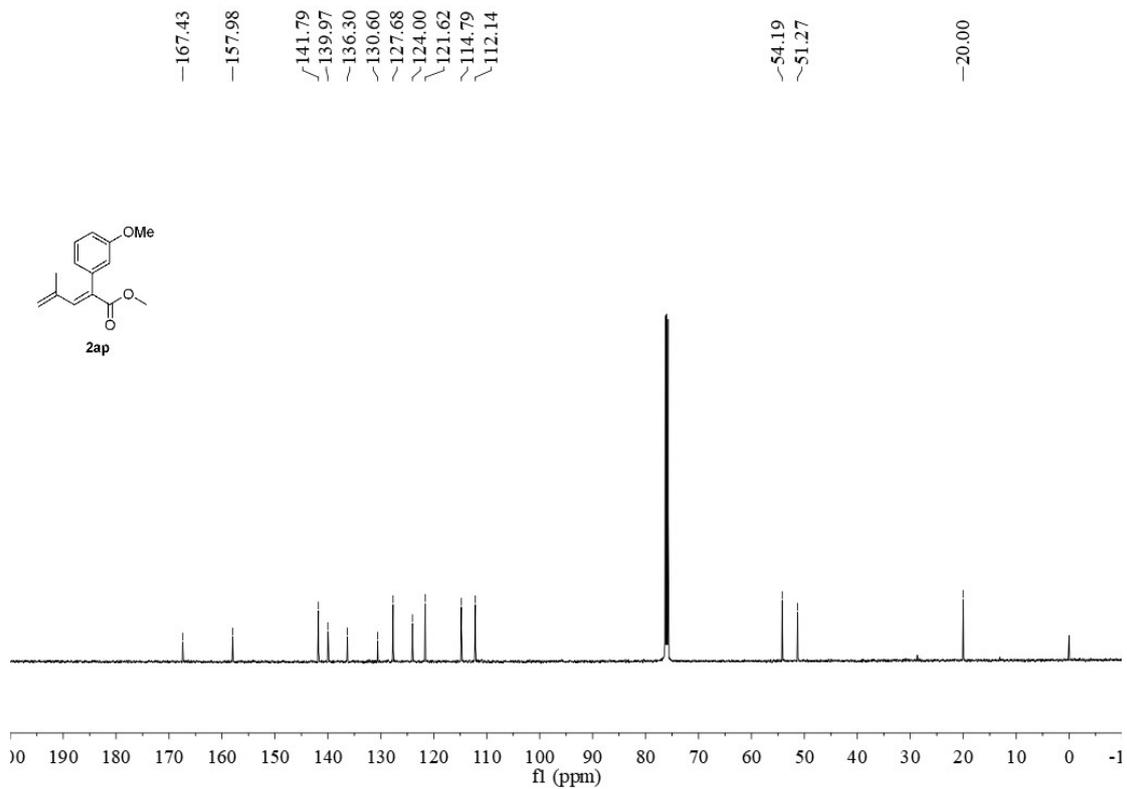
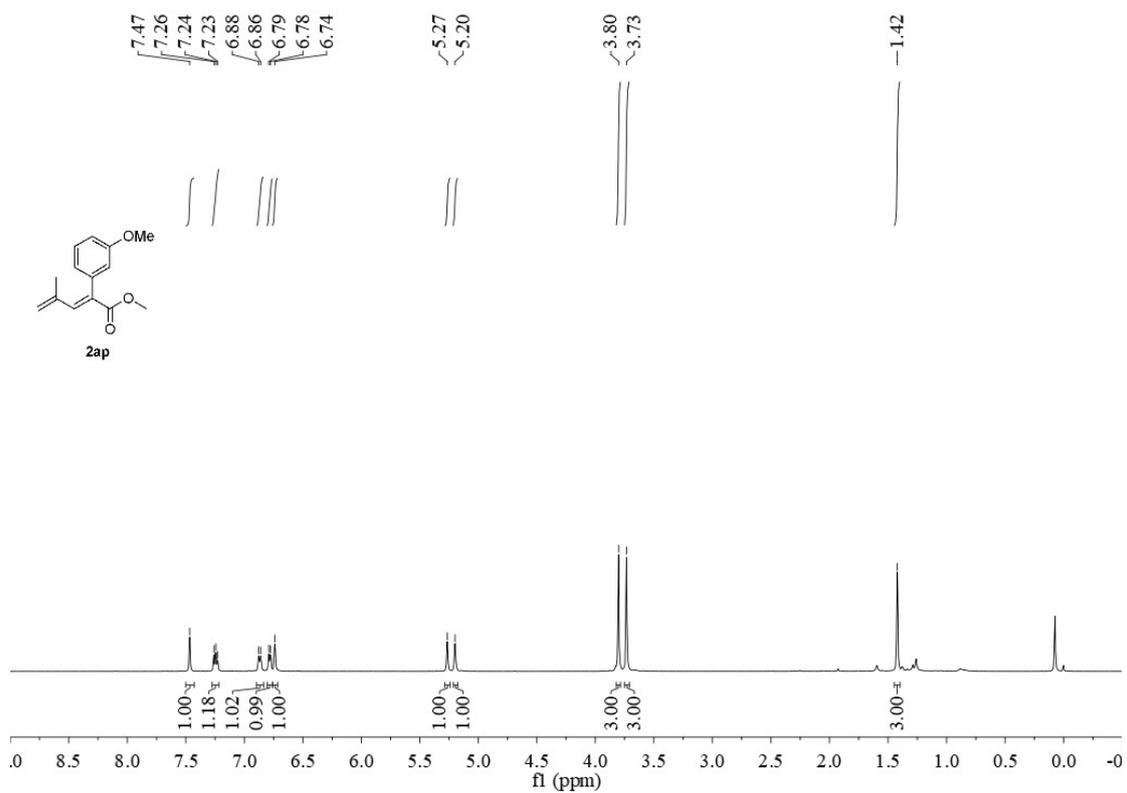
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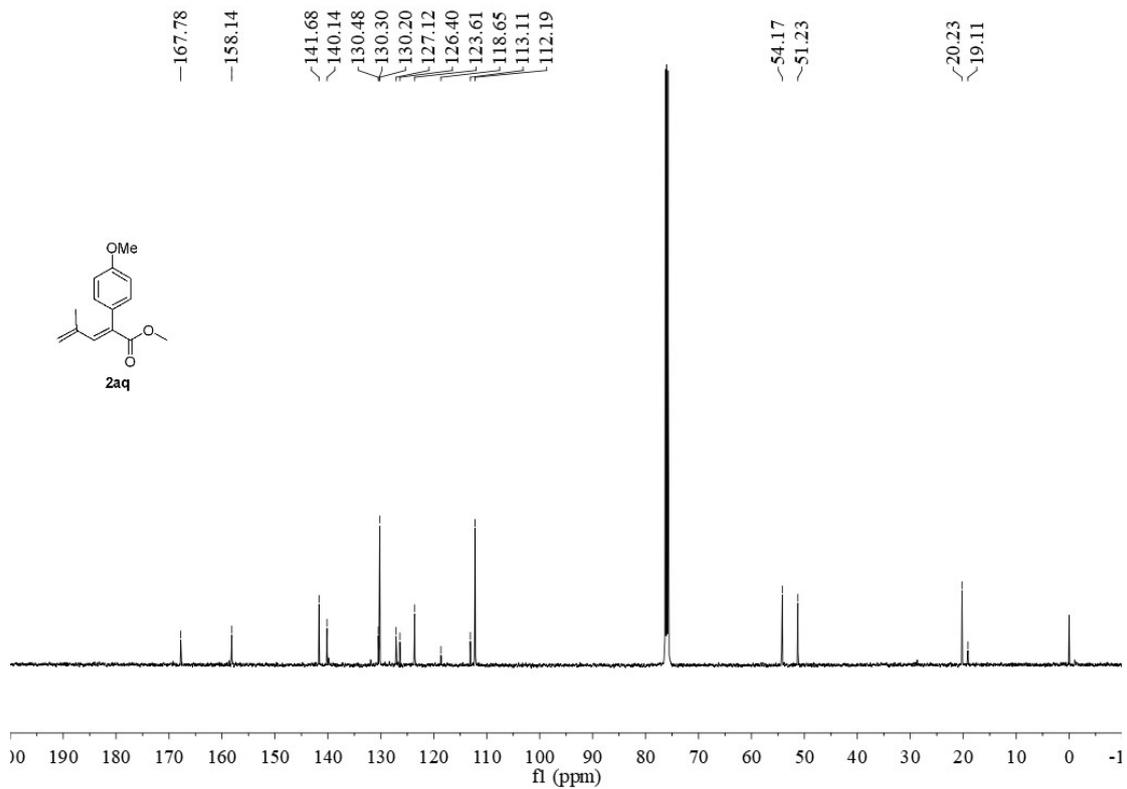
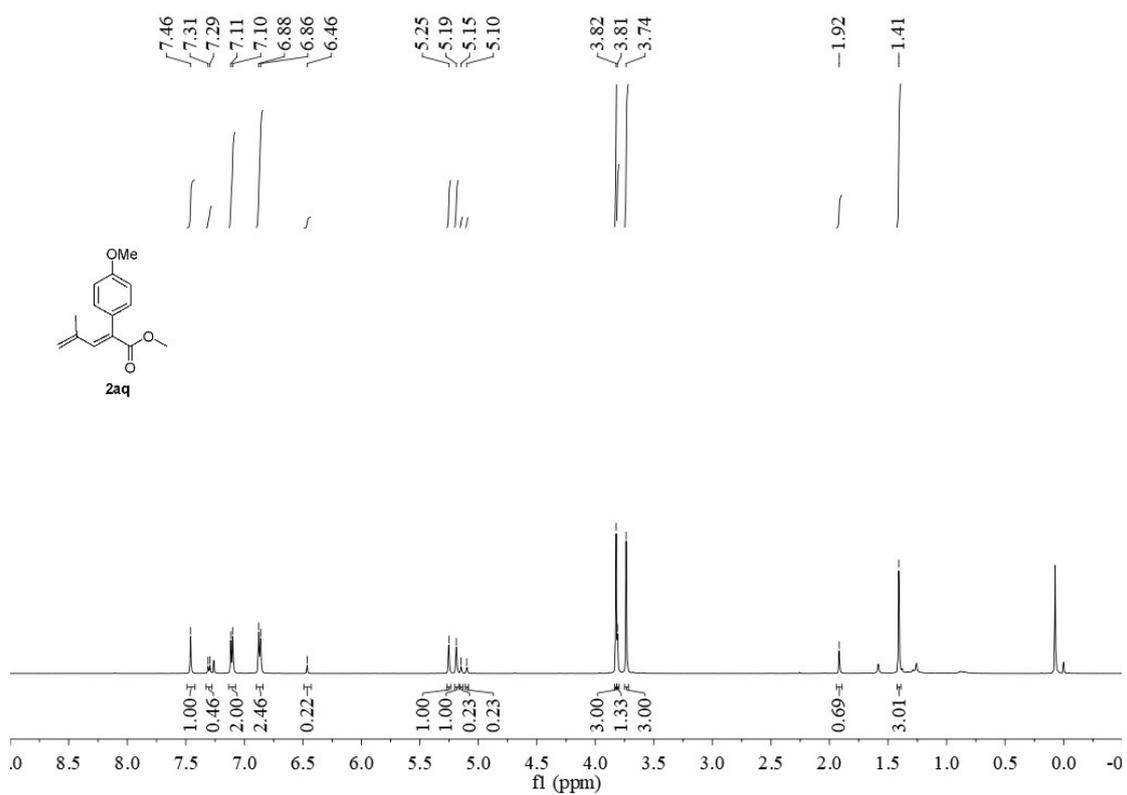
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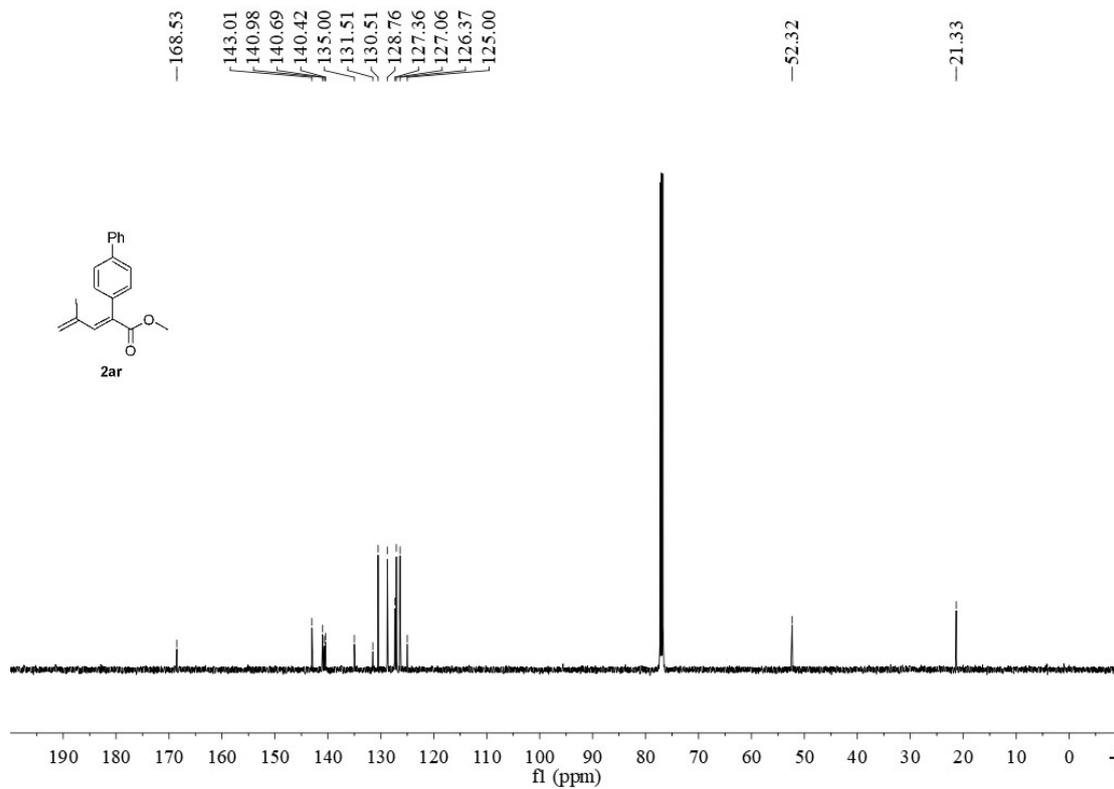
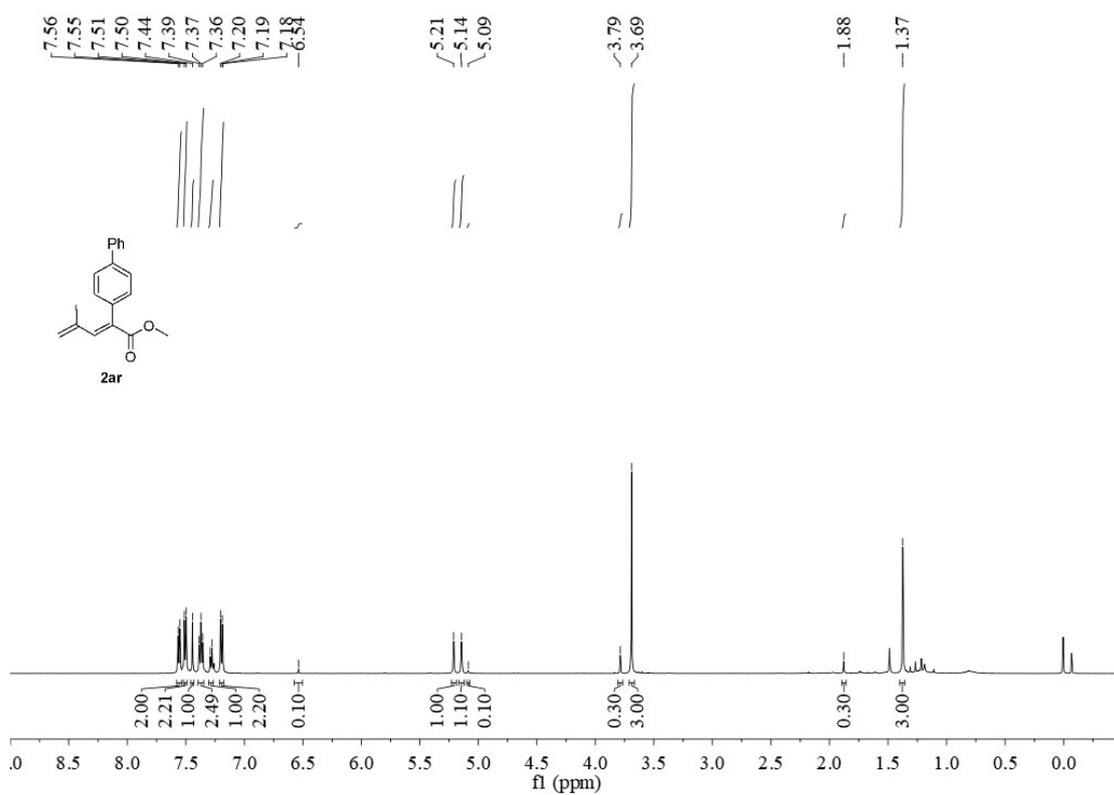
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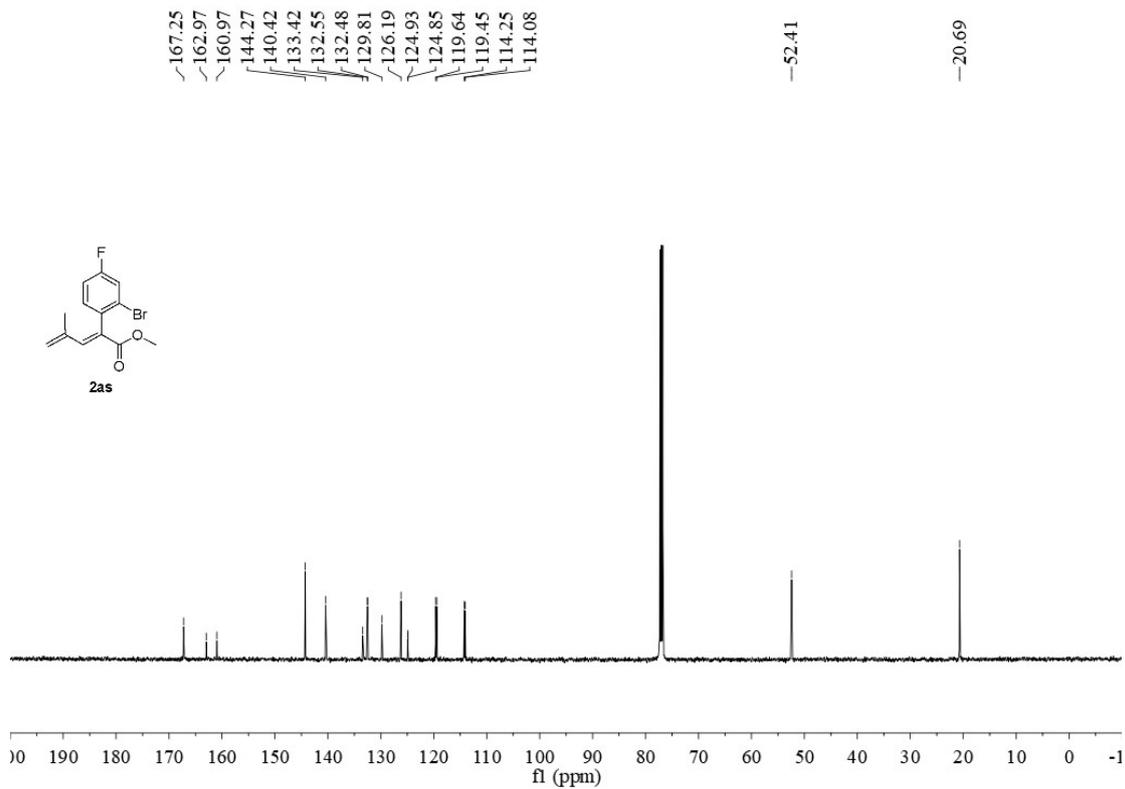
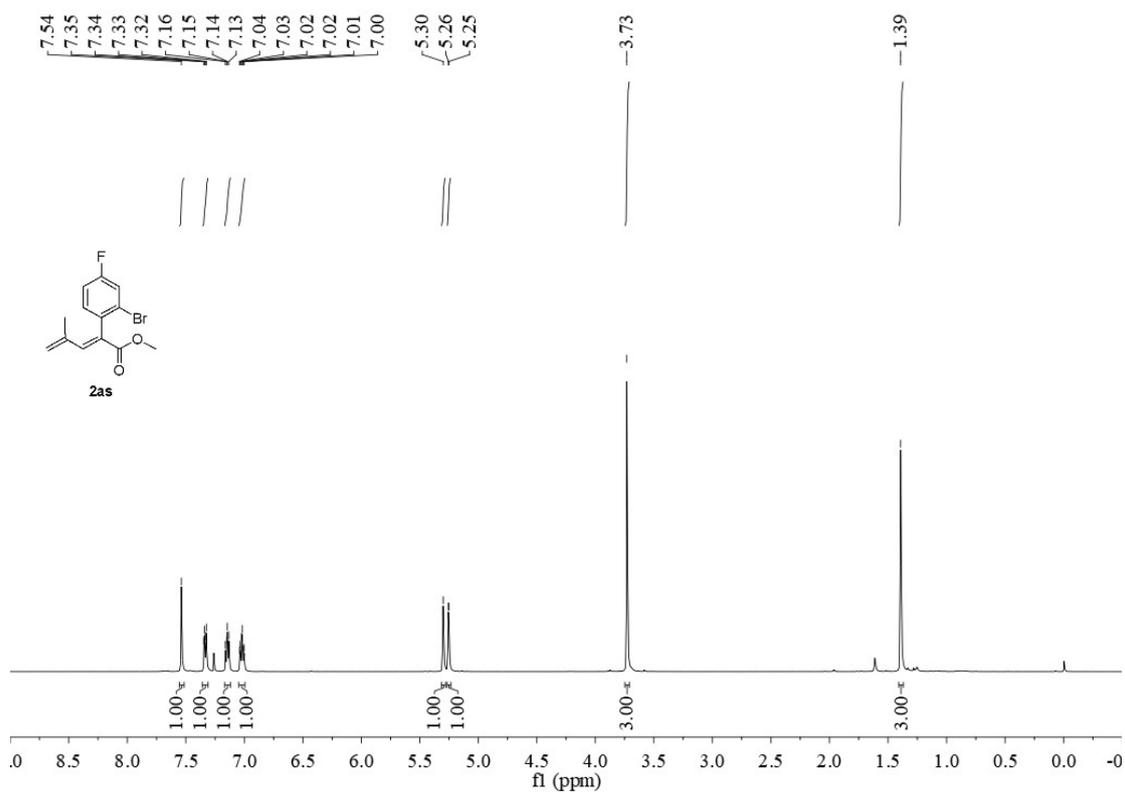
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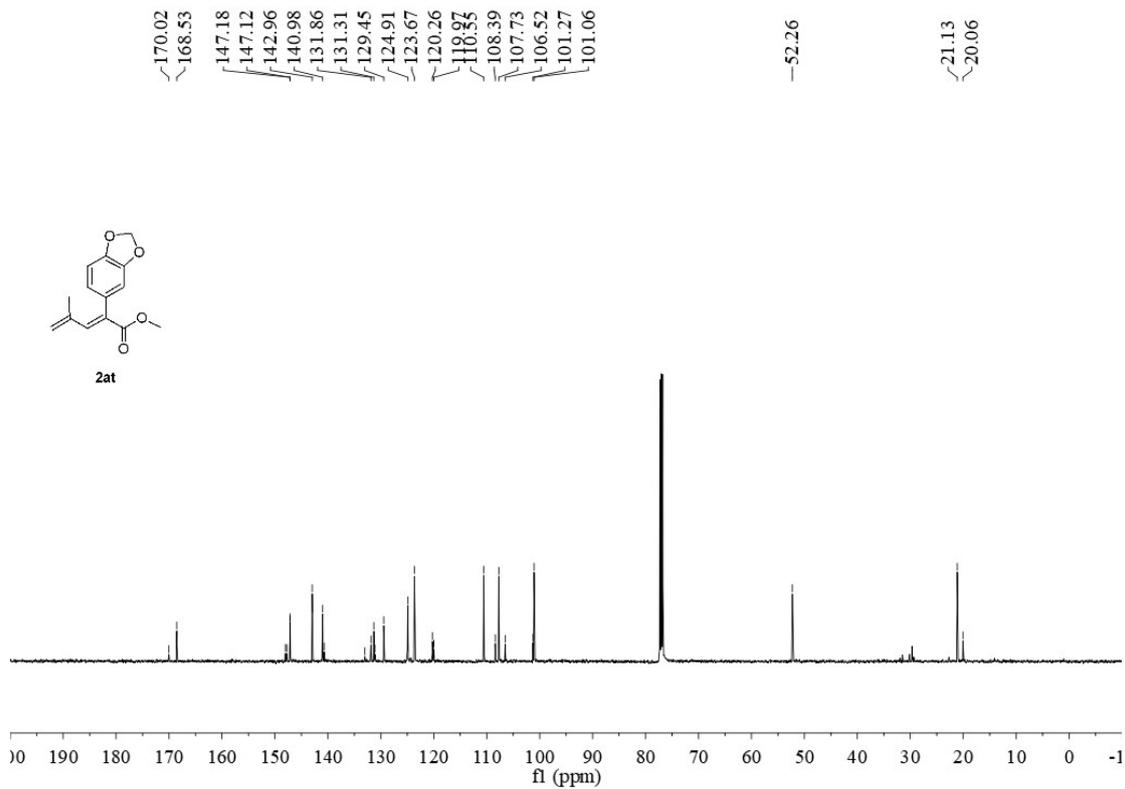
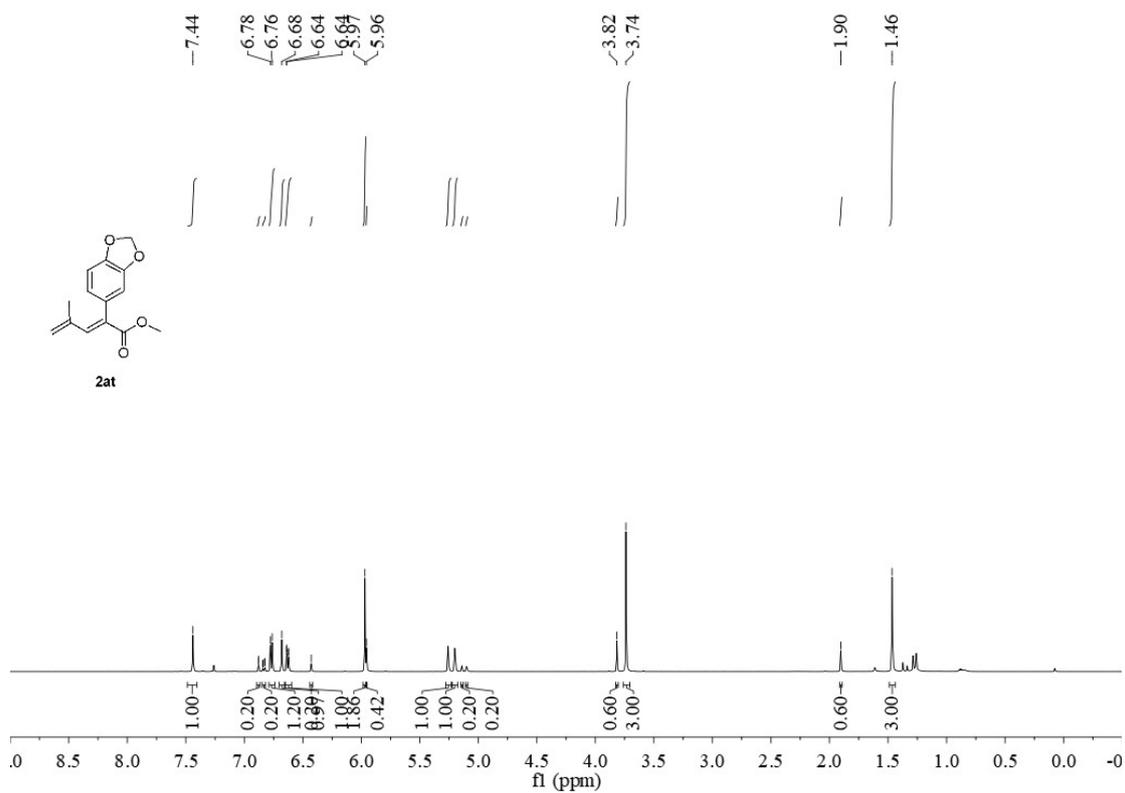
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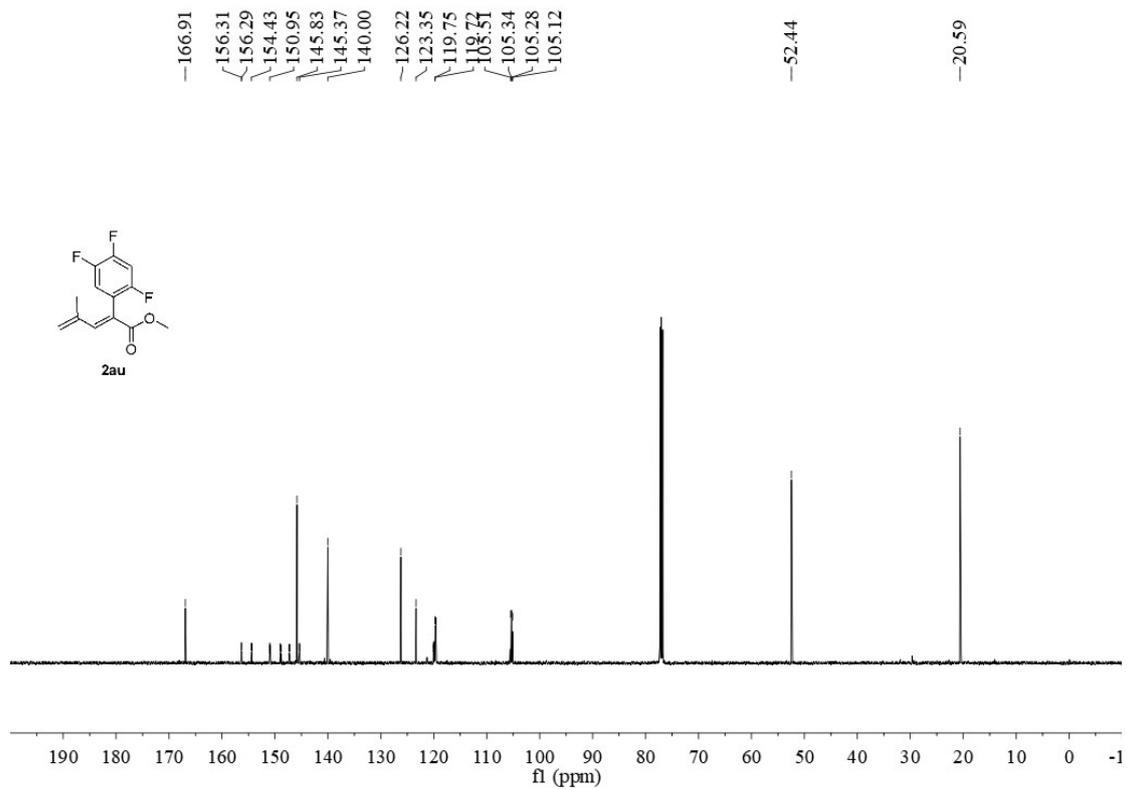
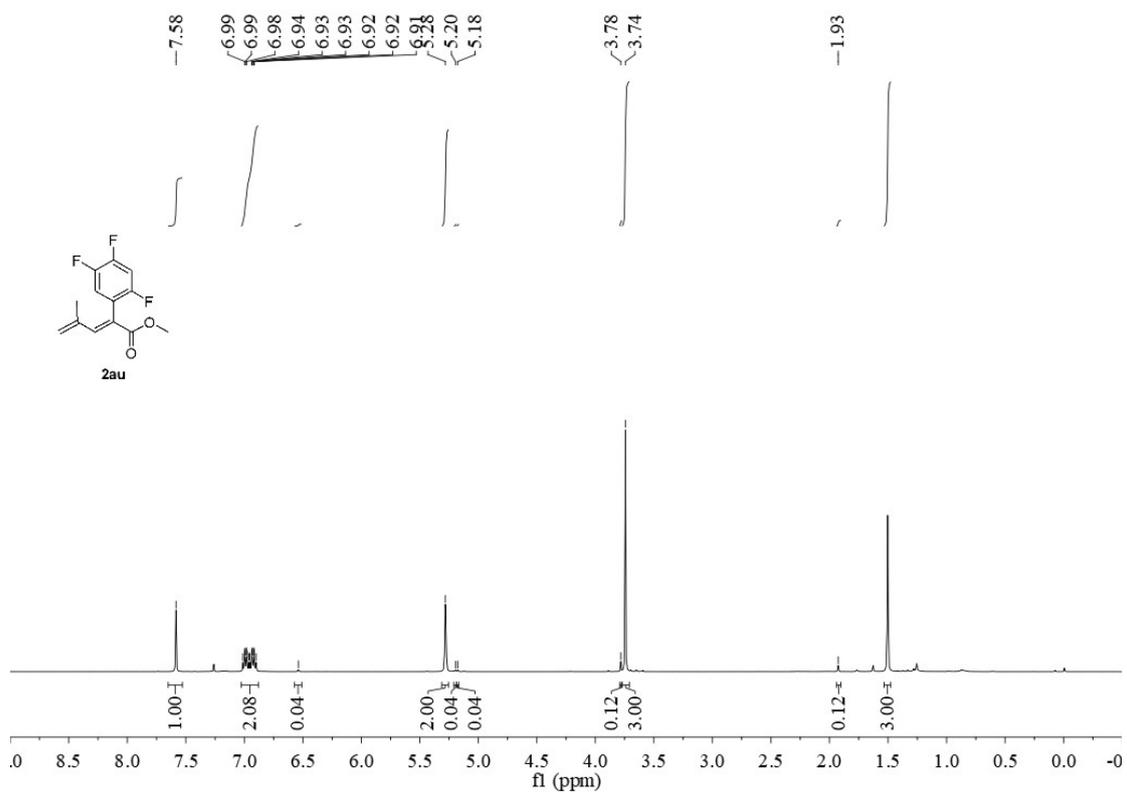
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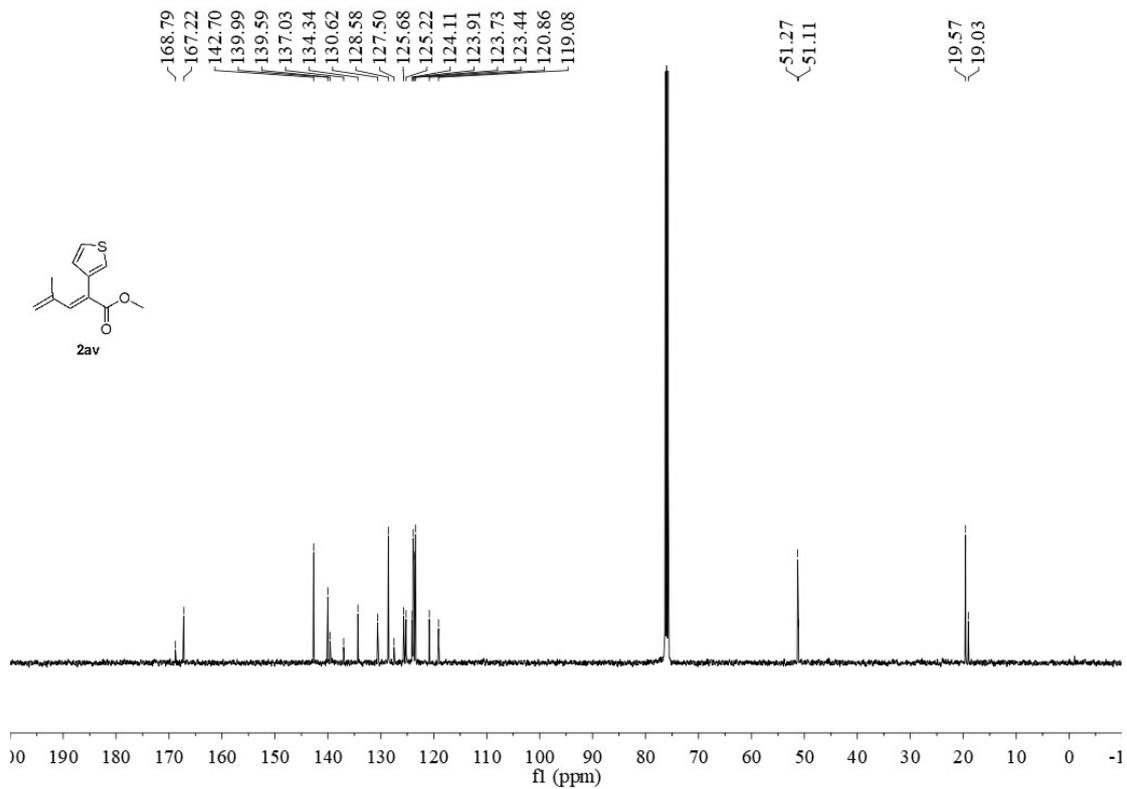
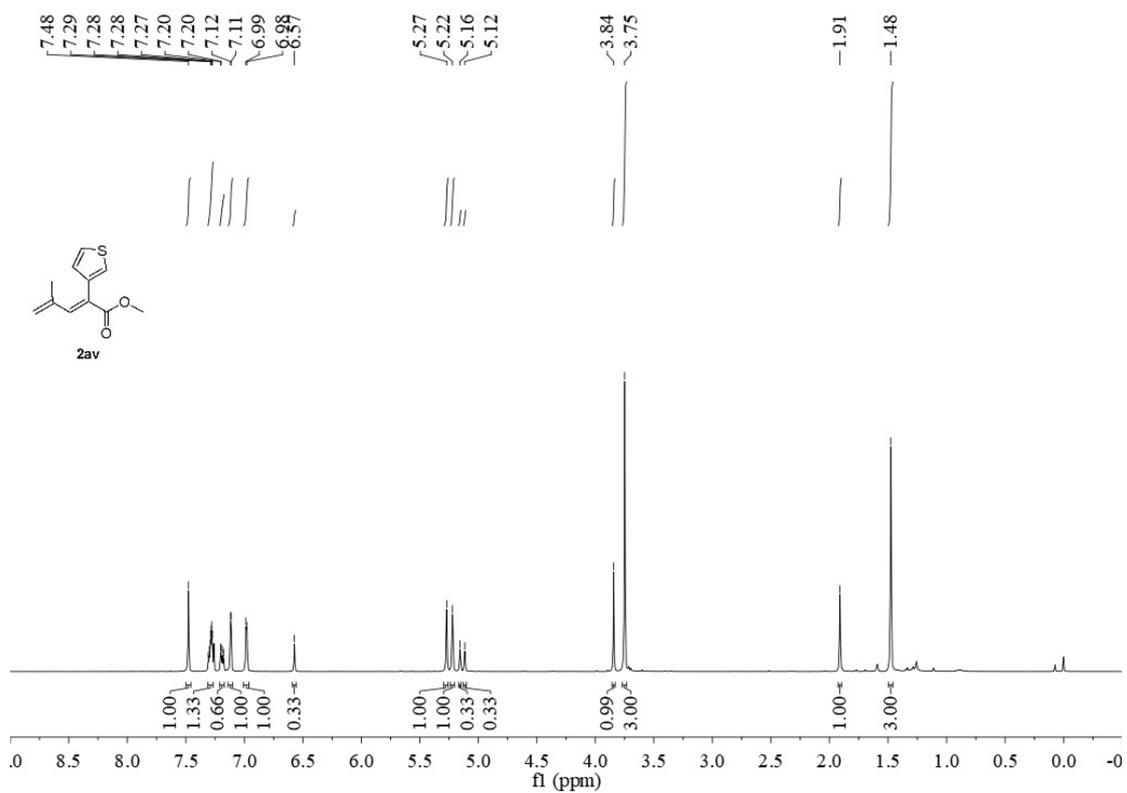
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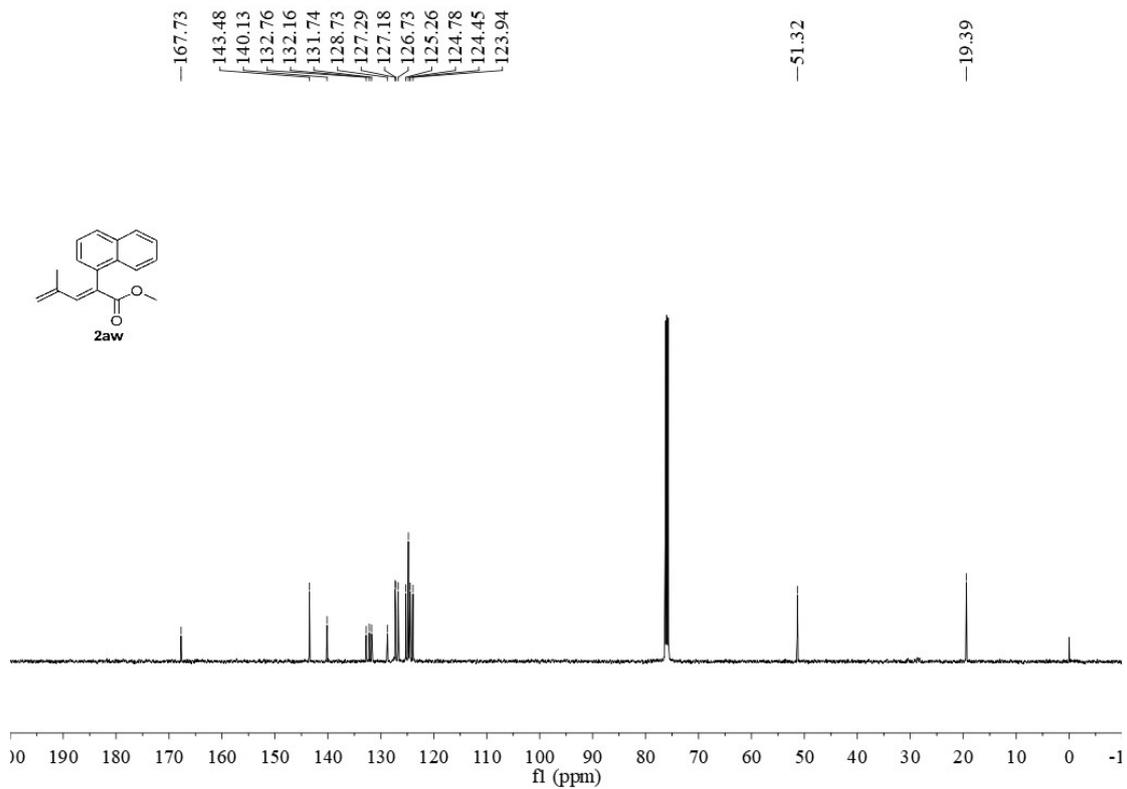
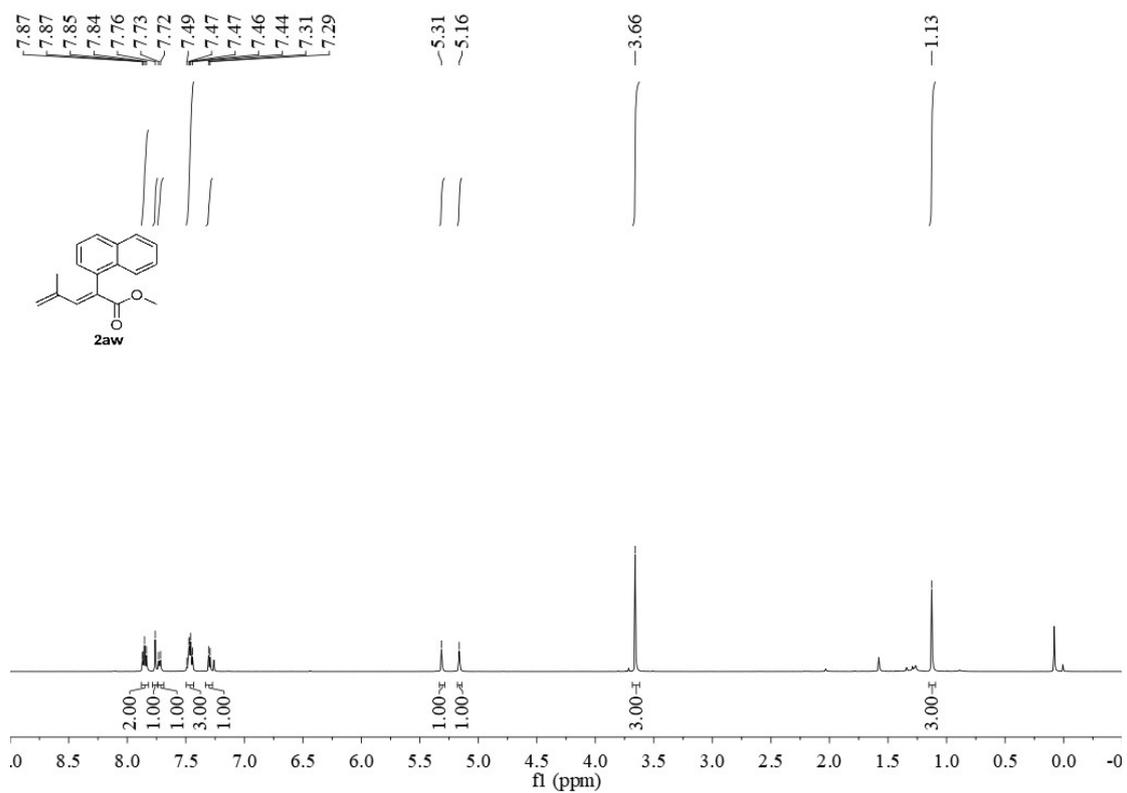
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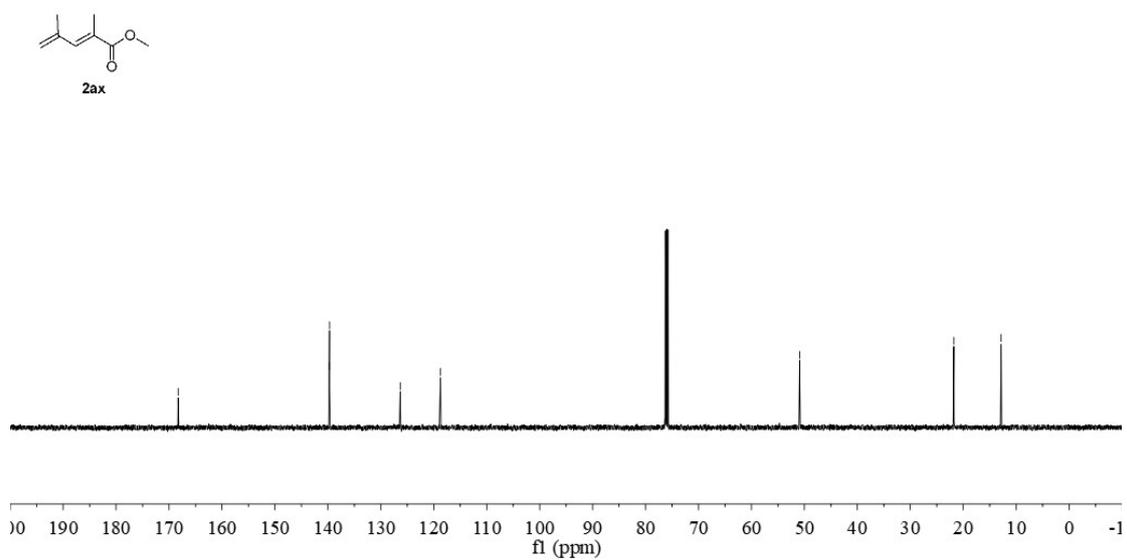
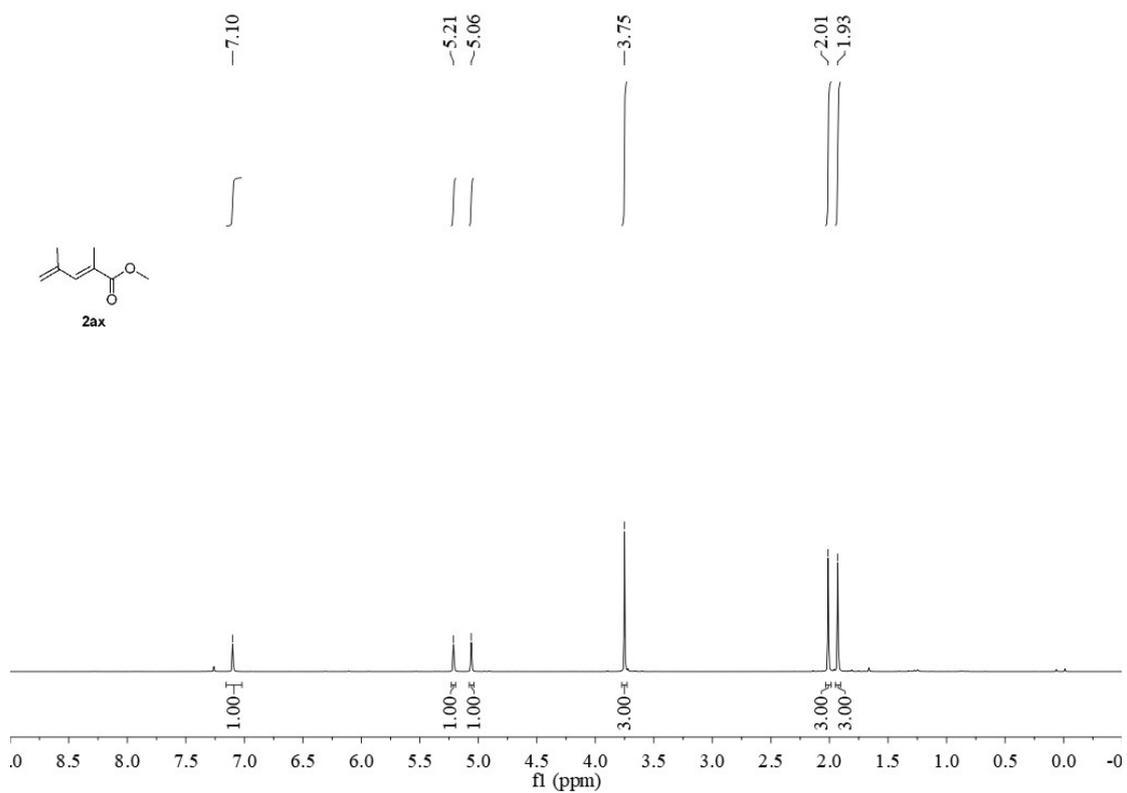
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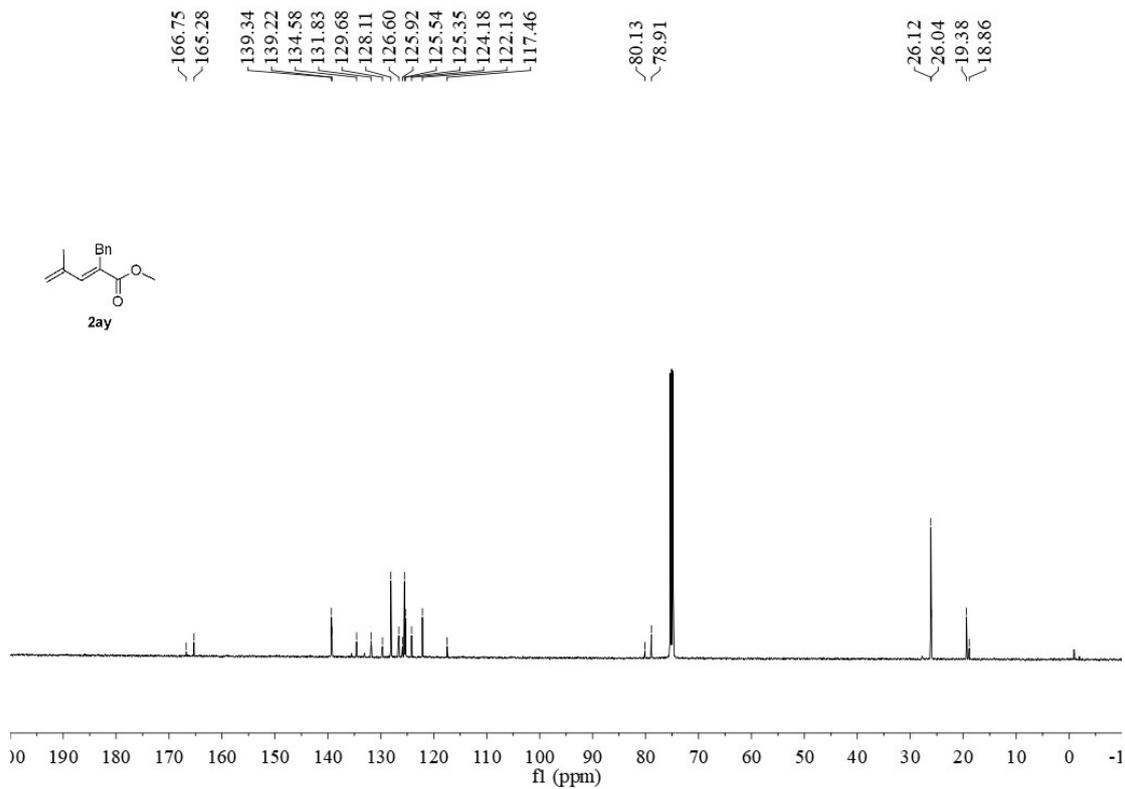
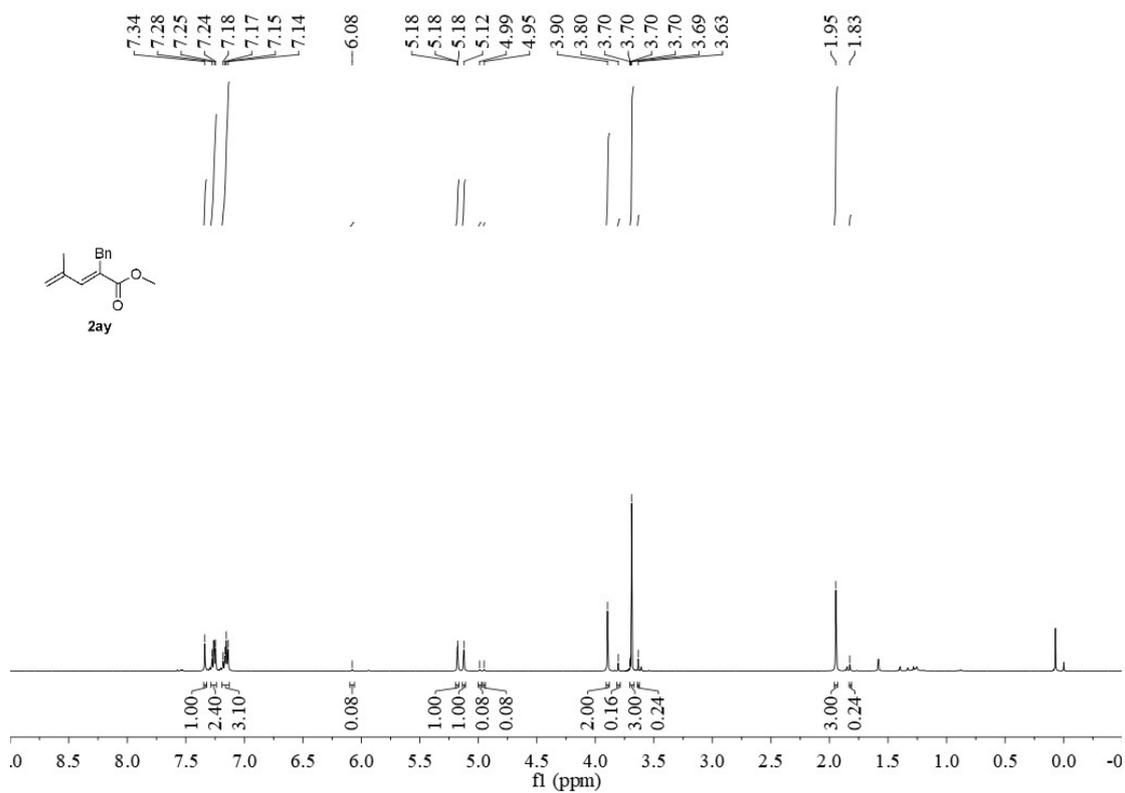
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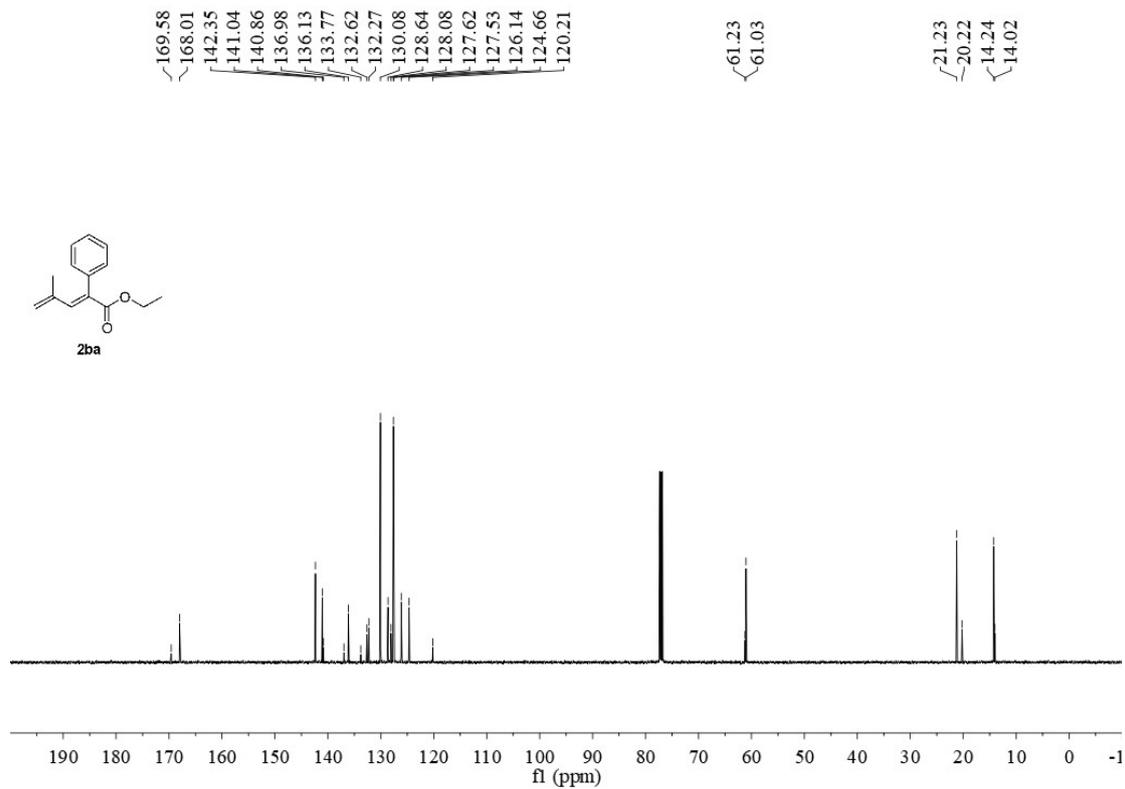
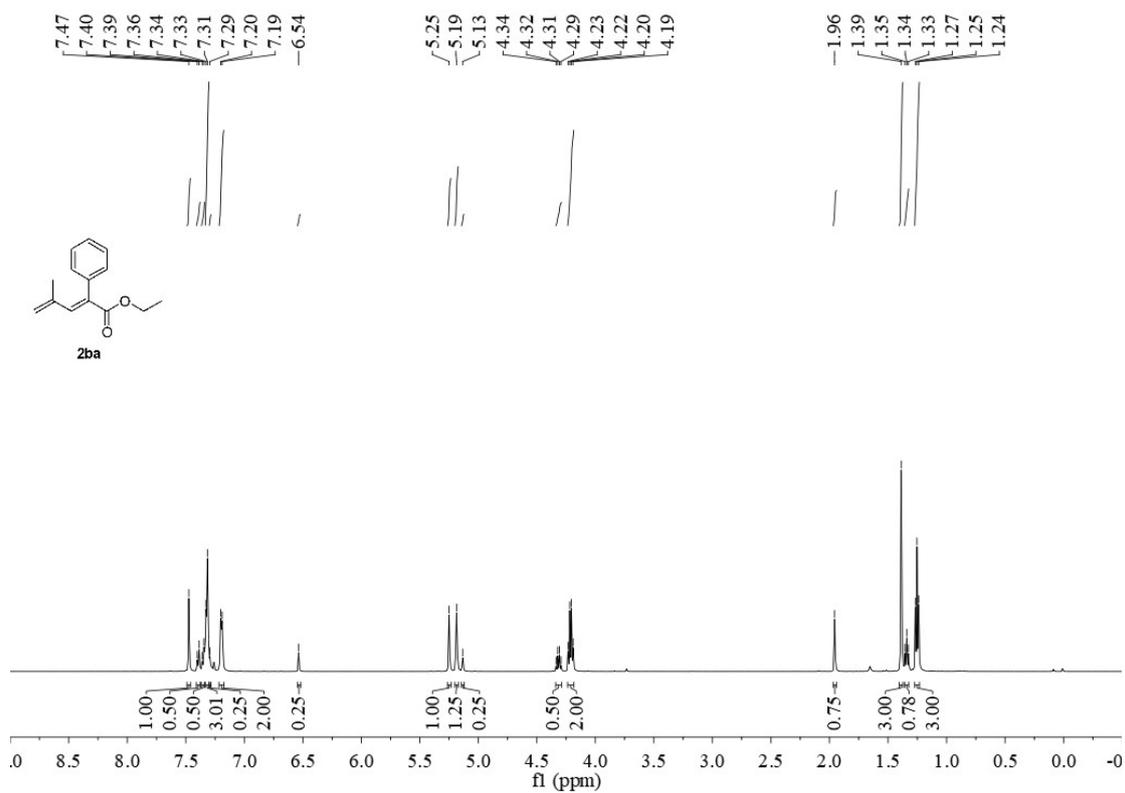
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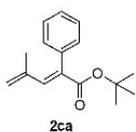
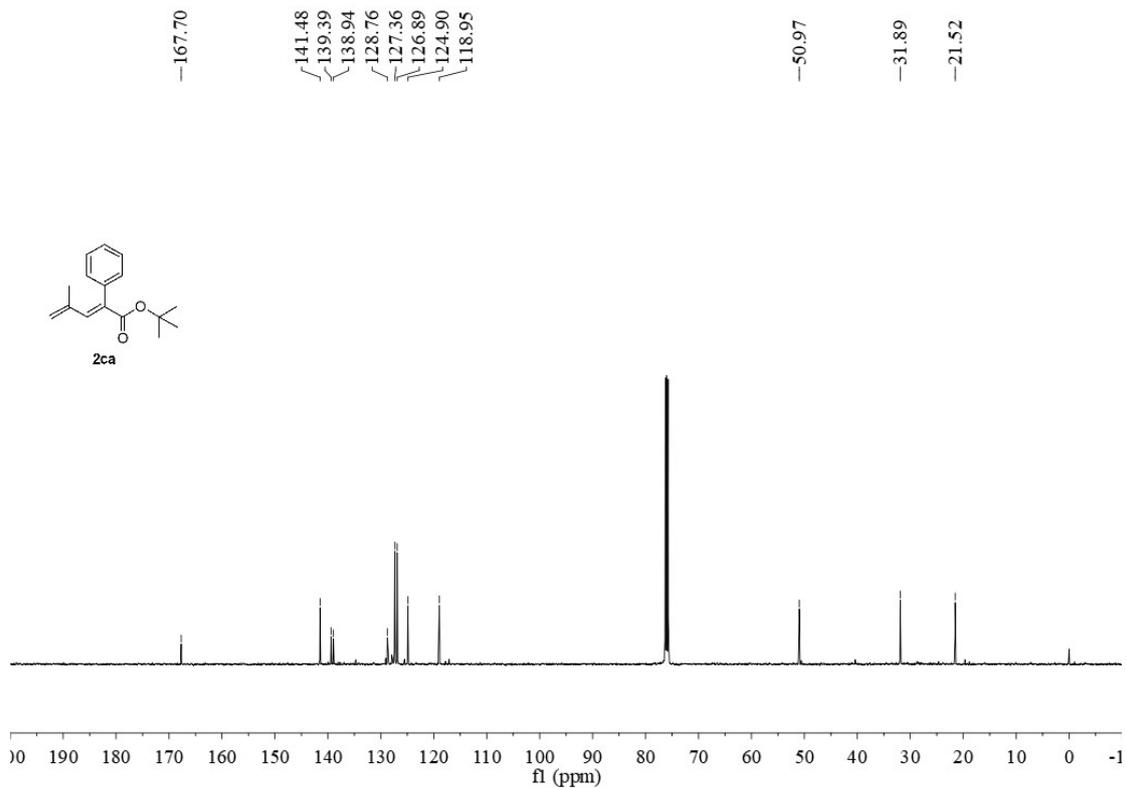
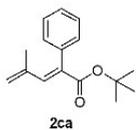
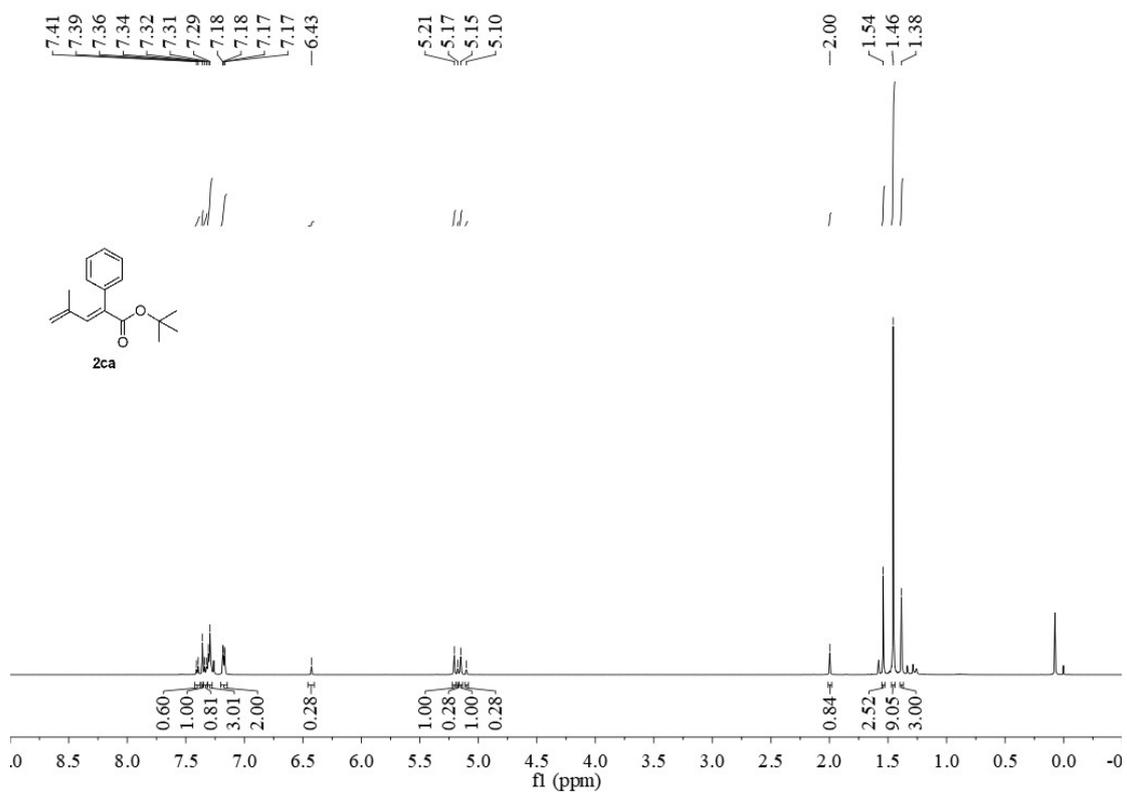
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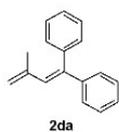
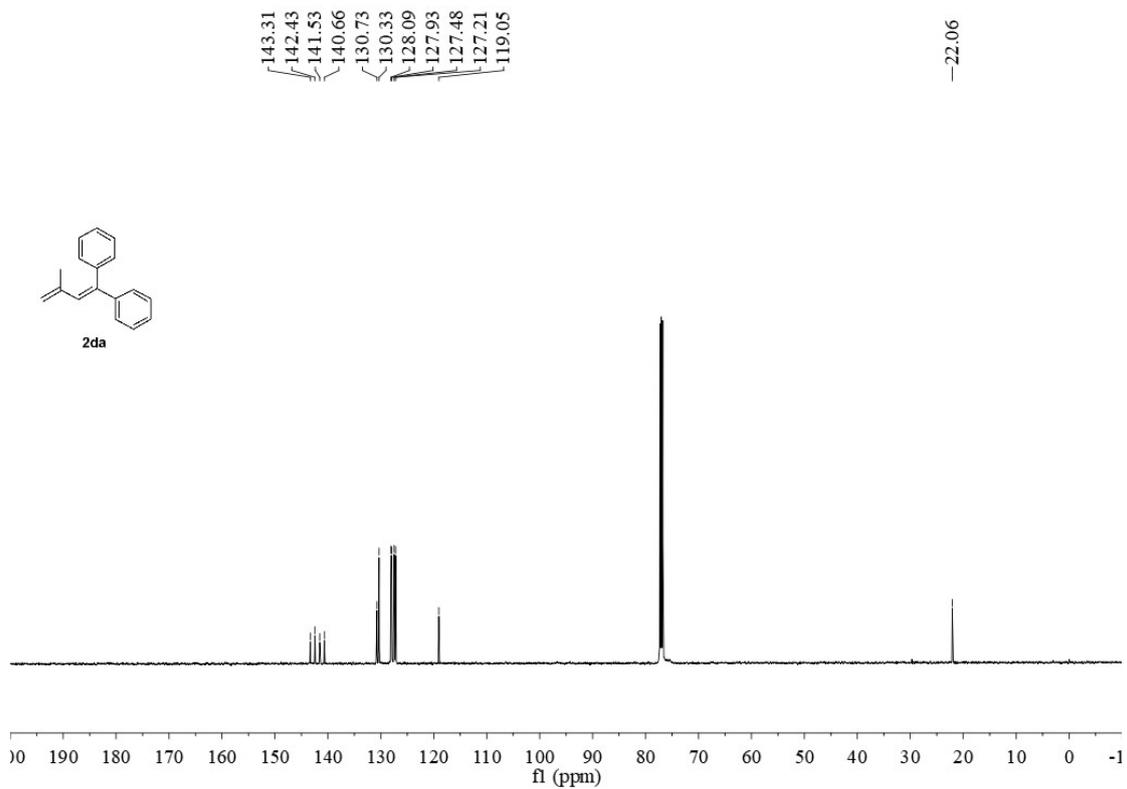
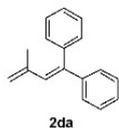
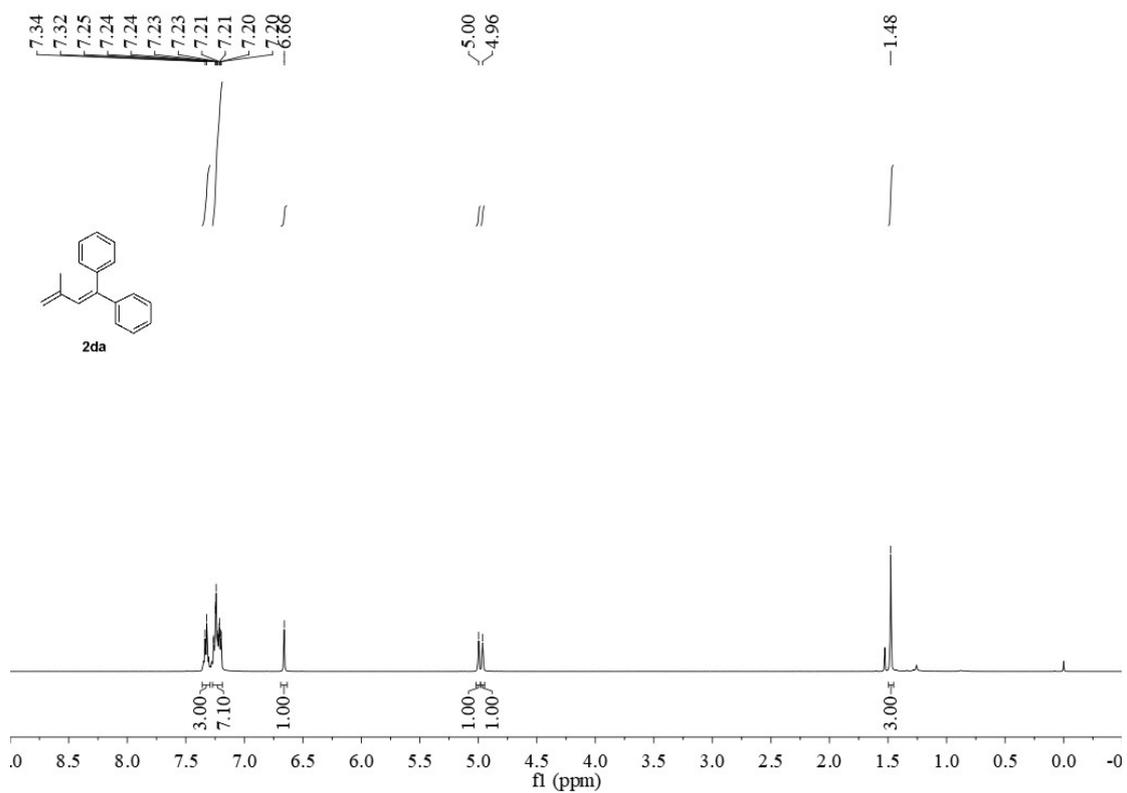
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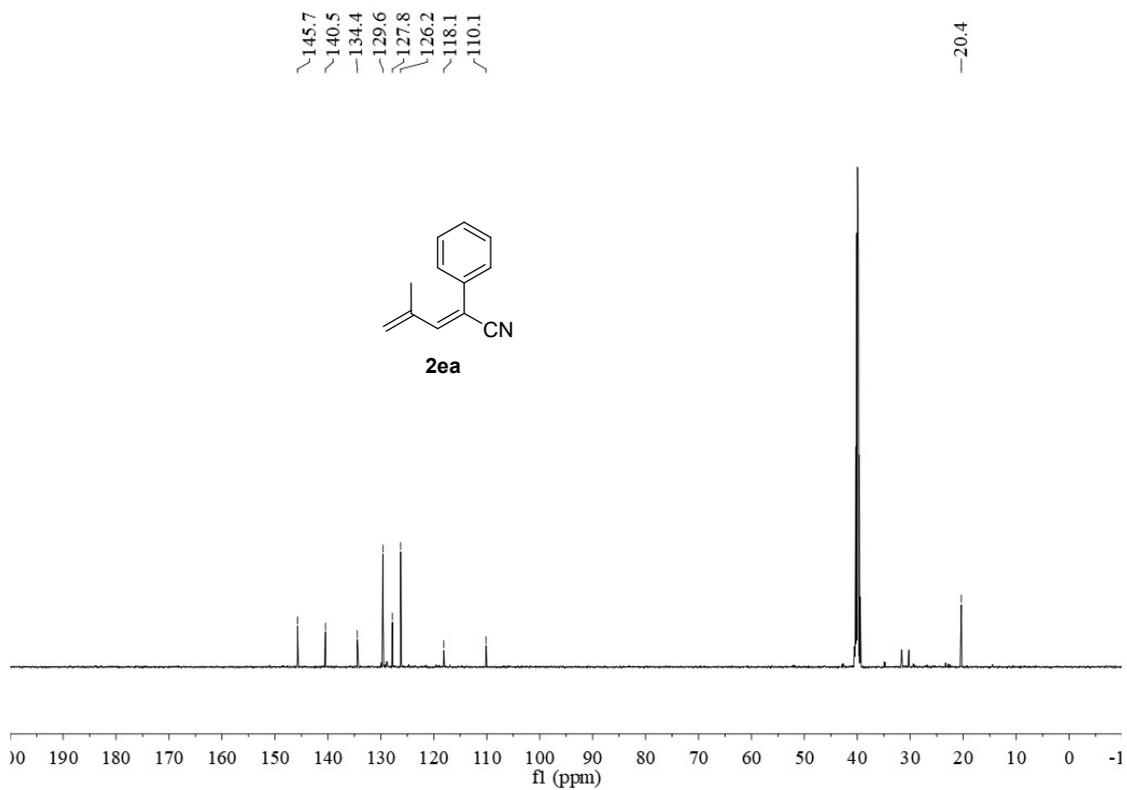
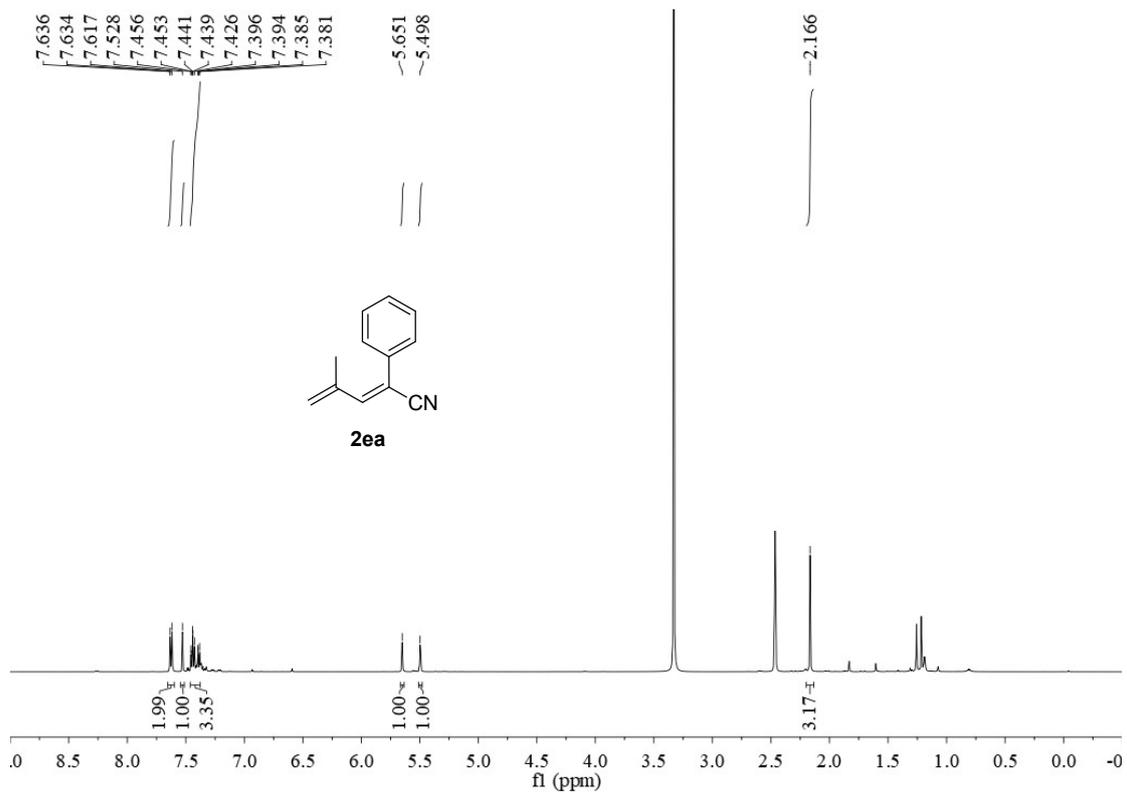
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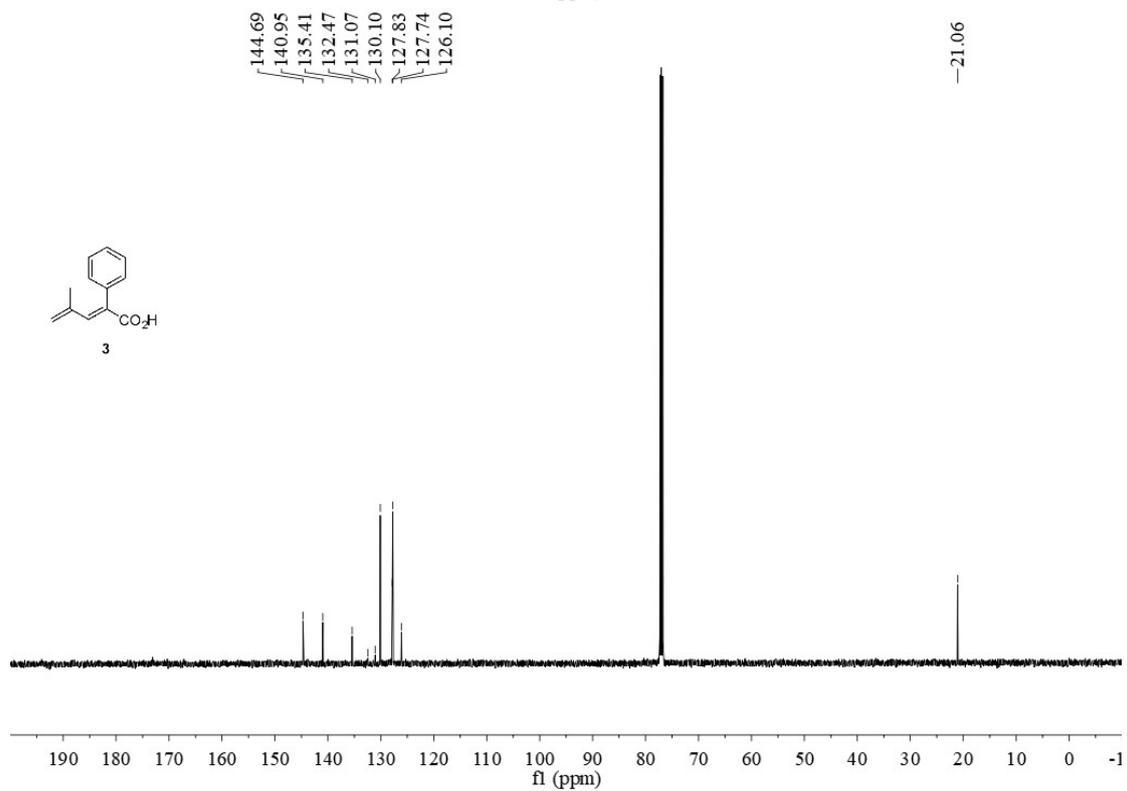
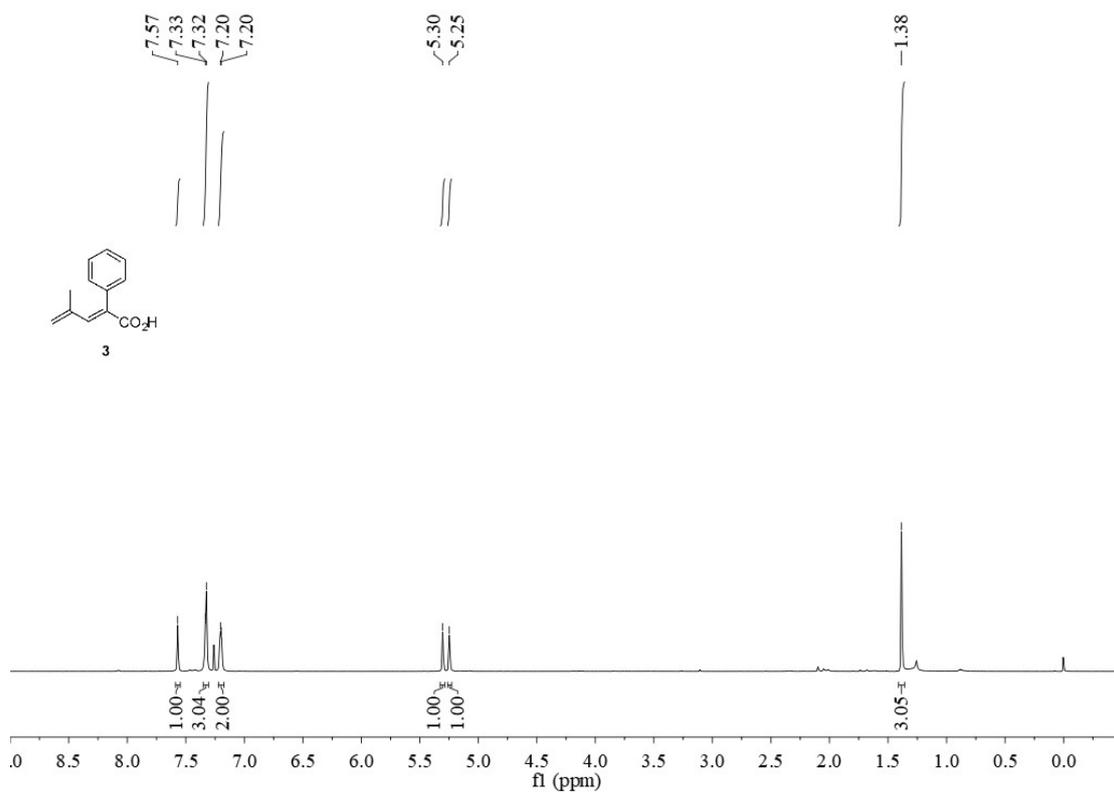
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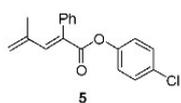
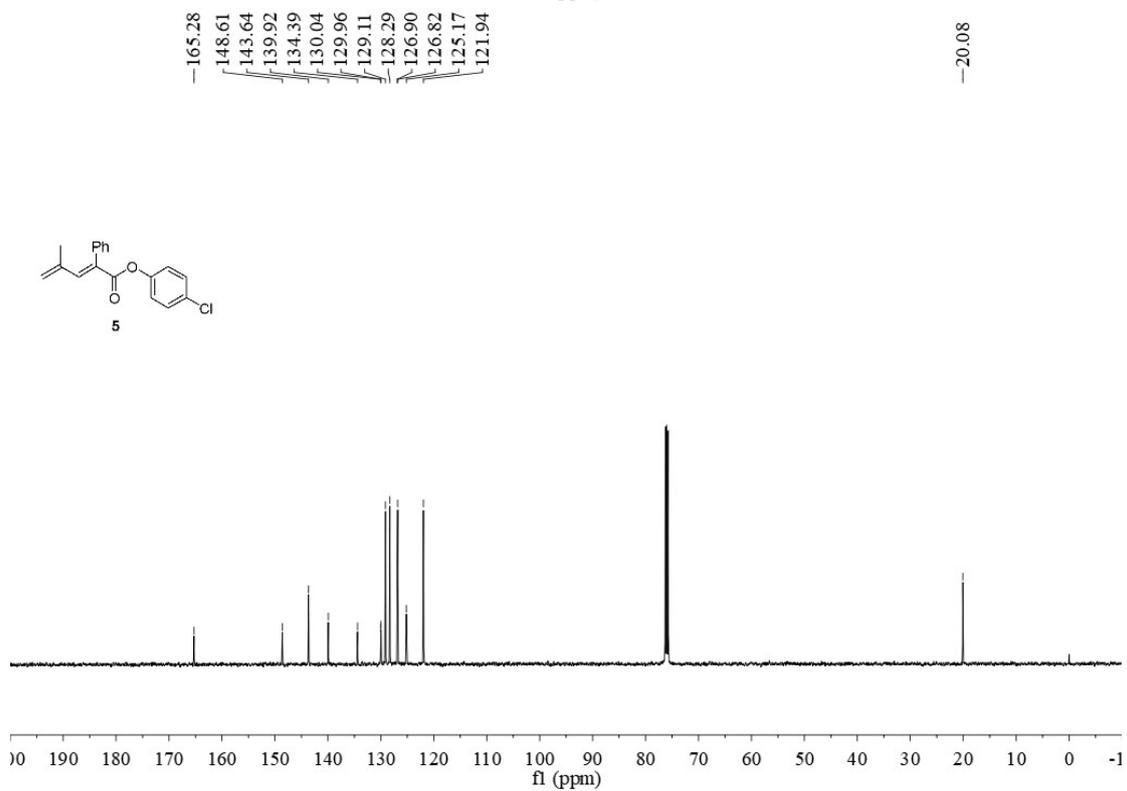
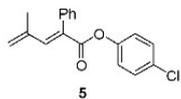
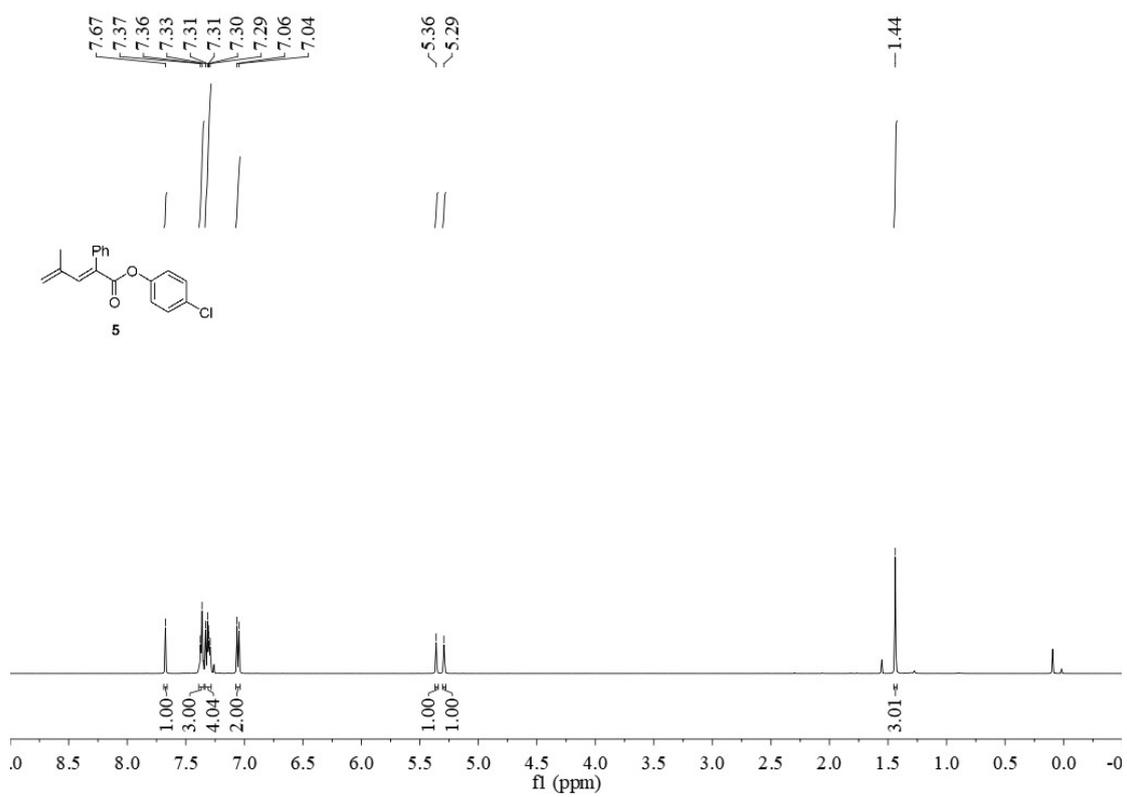
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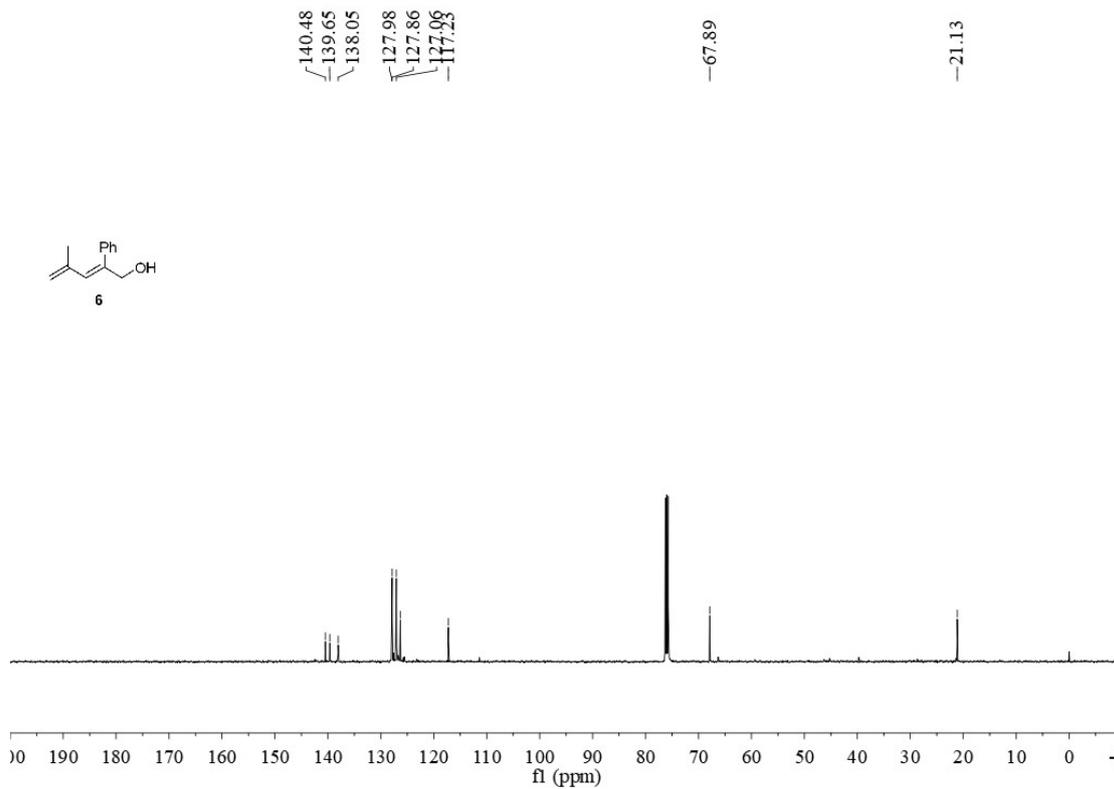
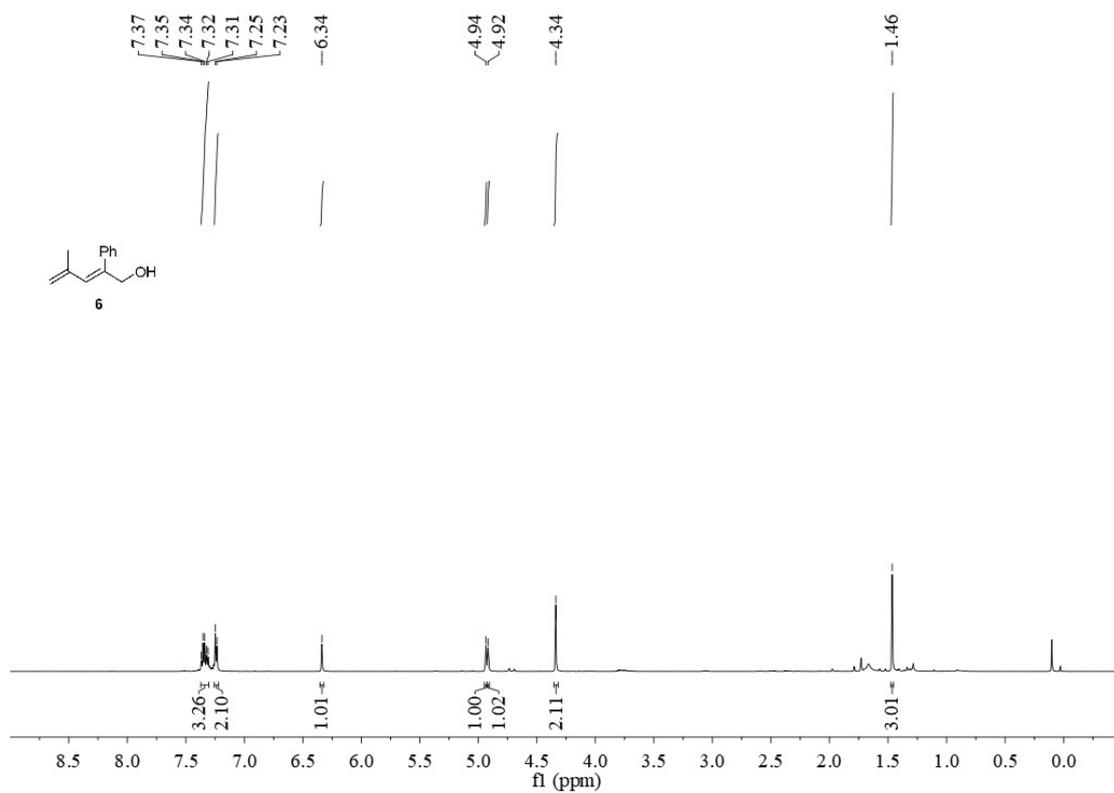
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