Photocatalytic Synthesis of 2-Oxabicyclo[2.1.1]hexanes: Cobalt-Enhanced Efficiency

Si-Yuan Tang+,[a] Zhan-Jie Wang+,[a] Jin-Jiao Wu,[a] Zhi-Xi Xing,[a] Ze-Yi Du,[b] and Huan-Ming Huang[a]*

[a]School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, China

[b]Department of Medicinal Chemistry, School of Pharmacy, Fudan University, No. 826 Zhangheng Road, Shanghai 201203, China

+ equal contribution

*Correspondence author. Email: huanghm@shanghaitech.edu.cn

SUPPORTING INFORMATION

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1 General Experimental

All experiments were performed in oven-dried glassware under nitrogen unless otherwise stated. All reagents were purchased from Alfa Aesar, Adamas, Accela, Bidepharm, Energy chemical, J&K chemical, Macklin, TCI, Leyan and used without further purification, unless otherwise stated. Dry solvents were purchased from J&k chemical (Extra Dry, H_2O <10 ppm) in J&KSeal® bottles, stored under molecular sieves and used as received or obtained from commercial sources. Dichloromethane, toluene, diethyl ether, THF were purified by passage through an activated alumina column under nitrogen. Thin-layer chromatography (TLC) analysis of reaction mixtures were performed using Huanghai silica gel HSGF254 TLC plates and Leyan HPTLC Silica Gel 60 GF254, and visualized under UV or by staining with ceric ammonium molybdate or potassium permanganate.

1.1 Data Analysis

Nuclear magnetic resonance (NMR) spectra were recorded using Bruker Avance III HD spectrometer (FT, 400, 500 or 600 MHz for ^{1}H, 101, 126 or 150 MHz for ^{13}C). All spectral data were acquired at 295 K. Chemicals shifts (δ) are quoted in parts per million (ppm) against tetramethylsilane (TMS, δ = 0.00 ppm). The following residual solvent signals were used as references for ^{1}H and ^{13}C NMR spectra: $CDCl_3$, δH 7.26 ppm, δC 77.16 ppm, δC calibrated using absolute referencing to the ^{1}H spectrum). ^{19}F-NMR spectra were calibrated using absolute referencing to the 1H-NMR spectrum, as suggested by IUPAC. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used (or combinations thereof) are: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet. High-resolution mass spectra (HRMS) were obtained from the Agilent Technologies 6230 TOF LC/MS spectrometer in electrospray ionization (ESI^+) mode. Ultraviolet-visible (UV-vis) absorption spectra were recorded by an AgilentCary 3000 UV-vis spectrophotometer at 25 °C. Stern-Volmer luminescence quenching analyses were conducted using an Edinburgh

Instruments FS5 spectrometer. X-Ray structure analyses were performed using a Bruker D8 Venture X-ray single crystal diffractometer.

2 Synthesis of Starting Materials

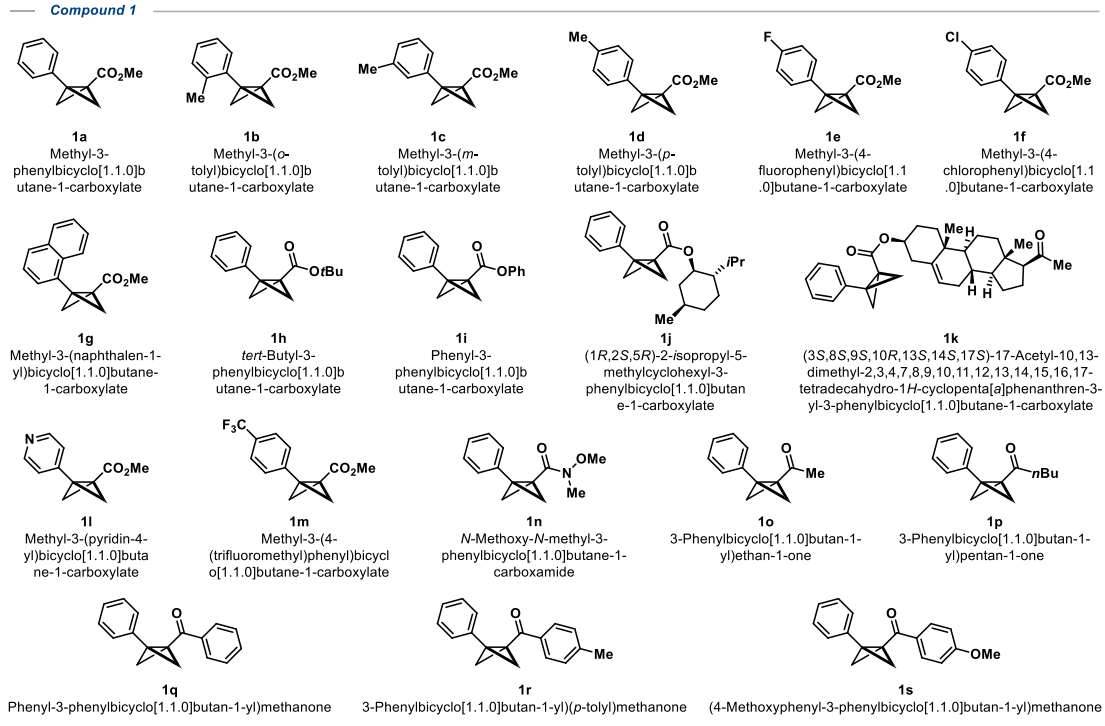


Figure S1. Chemical structures of compound **1**

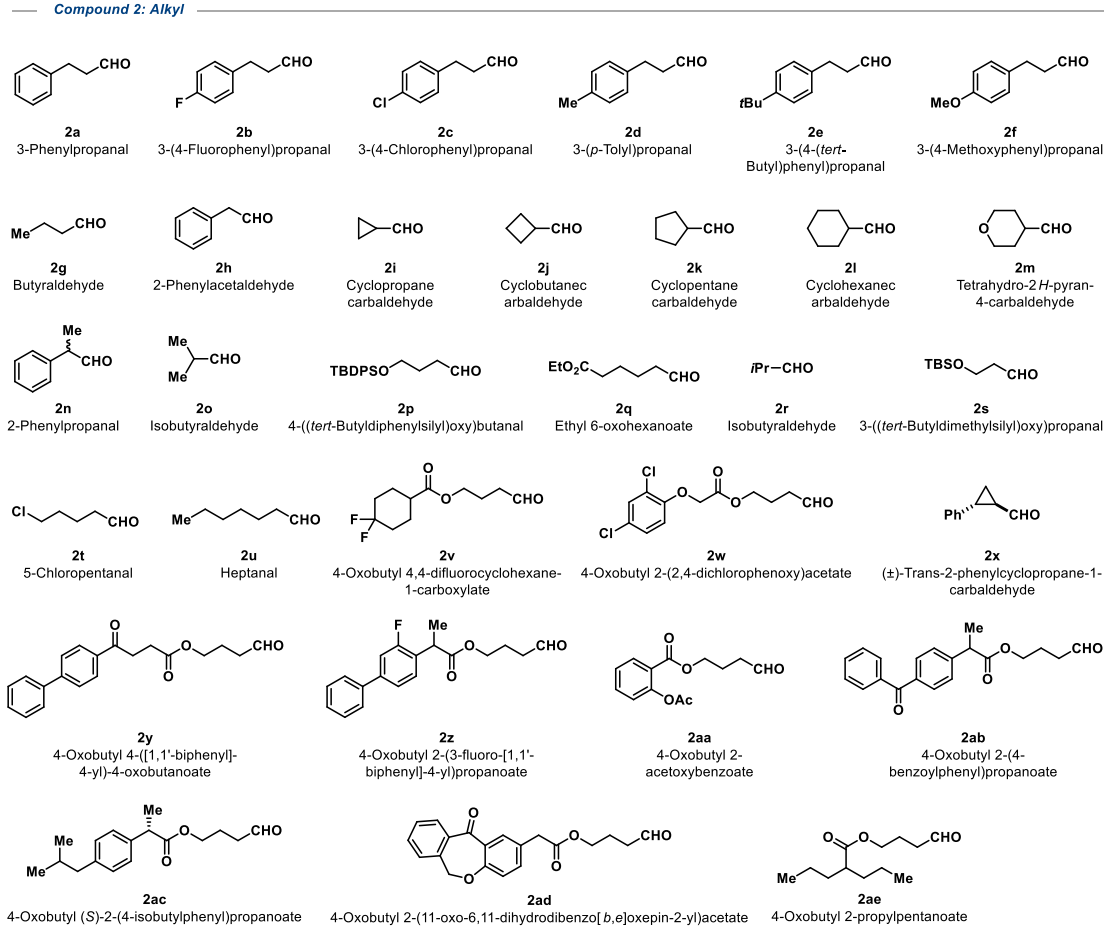


Figure S2. Chemical structures of alkyl compound **2**

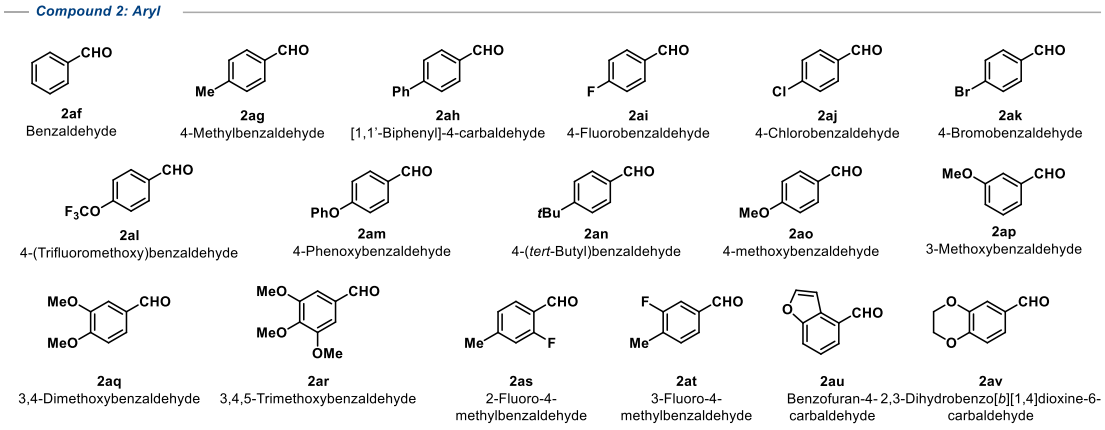


Figure S3. Chemical structures of aryl compound **2**

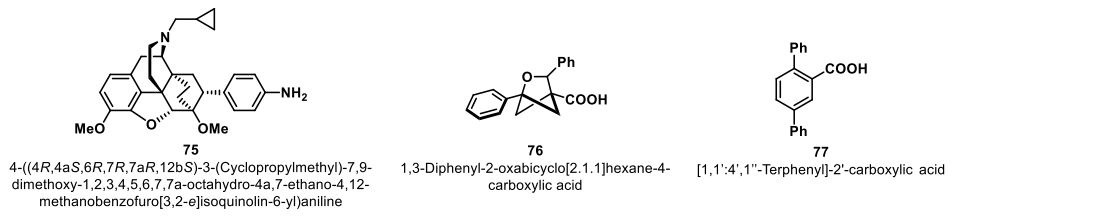
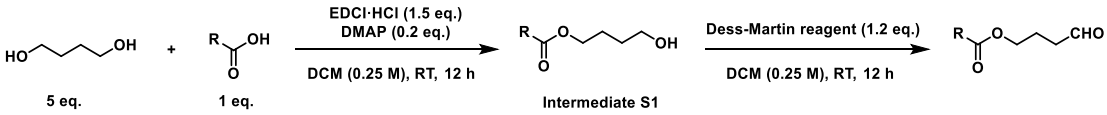


Figure S4. Chemical structures of drug derivatives starting material **75**-**77**

Some compounds were synthesized according to published literature (see General Procedure A for compound **2y**, **2aa**, **2ad** and **2ae**, General Procedure B for compound **76** and **77**).[1,2] Compound **1**, **2q**, **2v**, **2w**, **2x**, **2z**, **2ab**, **2ac** and **75** were synthesized according to published literatures and all analytical data matched the report.[1,3–6] Other reagents were purchased from Alfa Aesar, Adamas, Accela, Bidepharm, Energy chemical, J&K chemical, Macklin, TCI, Leyan and used directly without further purification.

2.1 General Procedure A

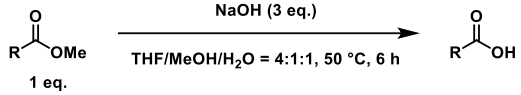


Step1: Butane-1,4-diol (25 mmol) was dissolved in DCM (20 mL). Corresponding acid (5 mmol mmol), EDCI·HCl (7.5 mmol) and DMAP (1 mmol) were added under nitrogen atmosphere. The mixture was stirred for 12 hours under nitrogen atmosphere at RT. The reaction mixture was quenched with H_2O (40 mL) and extracted with EtOAc (3 × 40 mL). The organic phases were combined, dried over

$NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with indicated solvent system to give intermediate S1.

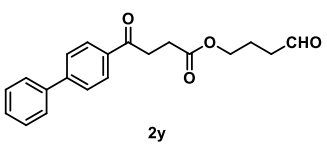
Step2: Intermediate S1 was dissolved in DCM (0.25 M). Dess-Martin reagent (1.2 eq.) was added under nitrogen atmosphere. The mixture was stirred for 12 hours under nitrogen atmosphere at RT. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution (40 mL) and extracted with EtOAc (3 × 40 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with indicated solvent system to give the desired compound.

2.2 General Procedure B



Ester compound (0.5 mmol) was dissolved in a mixture of THF, MeOH and H_2O (8/2/2 mL). NaOH (60 mg, 1.5 mmol) was added under nitrogen atmosphere. The mixture was stirred for 6 hours under nitrogen atmosphere at 50 °C. The reaction mixture was quenched with 2 M HCl aqueous solution (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with indicated solvent system to give the desired compound.

2.3 Experimental Procedures and Spectral Characterization of the Starting Material



2y

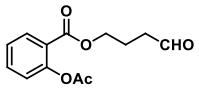
2y was synthesized according to the general procedure A and purified by flash column chromatography (silica gel), eluting with 20% EtOAc in PE to afford the title compound as a colourless oil (1.27 g, 3.92 mmol, 78% over 2-steps).

R_f = 0.5 (40% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.4 Hz, 1H), 8.09 – 8.02 (m, 2H), 7.71 – 7.67 (m, 2H), 7.67 – 7.60 (m, 2H), 7.47 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.44 – 7.38 (m, 1H), 4.16 (t, *J* = 6.3 Hz, 2H), 3.35 (t, *J* = 6.5 Hz, 2H), 2.78 (t, *J* = 6.5 Hz, 2H), 2.61 – 2.53 (m, 2H), 1.99 (app. p, *J* = 6.8 Hz, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.5, 197.8, 173.0, 146.1, 139.9, 135.3, 129.1 (2C), 128.8 (2C), 128.4, 127.4 (3C), 63.7, 40.6, 33.5, 28.3, 21.4 ppm.

HRMS (ESI) calculate: $C_{20}H_{21}O_4^+$ $(M+H)^+$: 325.1434, found: 325.1431.



2aa

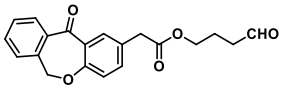
2aa was synthesized according to the general procedure A and purified by flash column chromatography (silica gel), eluting with 20% EtOAc in PE to afford the title compound as a colourless oil (0.91 g, 3.64 mmol, 73% over 2-steps).

R_f = 0.6 (40% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.3 Hz, 1H), 7.98 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.62 – 7.52 (m, 1H), 7.36 – 7.29 (m, 1H), 7.10 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.31 (t, *J* = 6.4 Hz, 2H), 2.61 (td, *J* = 7.2, 1.2 Hz, 2H), 2.34 (s, 3H), 2.07 (t, *J* = 6.8 Hz, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.2, 169.8, 164.4, 150.8, 134.1, 131.7, 126.2, 124.0, 123.2, 64.1, 40.5, 21.4, 21.2 ppm.

HRMS (ESI) calculate: $C_{13}H_{14}O_5^+$ $(M+H)^+$: 251.0914, found: 251.0911.



2ad

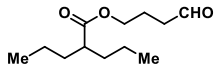
2ad was synthesized according to the general procedure A and purified by flash column chromatography (silica gel), eluting with 12% EtOAc in PE to afford the title compound as a colourless oil (1.02 g, 3.02 mmol, 60%).

R_f = 0.5 (30% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.2 Hz, 1H), 8.10 (d, *J* = 2.4 Hz, 1H), 7.87 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.57 – 7.50 (m, 1H), 7.50 – 7.43 (m, 1H), 7.40 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 5.17 (s, 2H), 4.12 (t, *J* = 6.3 Hz, 2H), 3.62 (s, 2H), 2.55 – 2.47 (m, 2H), 2.00 – 1.91 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.3, 190.9, 171.4, 160.6, 140.5, 136.4, 135.6, 132.9, 132.5, 129.5, 129.4, 127.9, 127.7, 125.2, 121.2, 73.7, 64.0, 40.5, 40.2, 21.3 ppm.

HRMS (ESI) calculate: $C_{20}H_{19}O_5^+$ $(M+H)^+$: 339.1227, found: 339.1223.



2ae

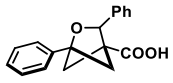
2ae was synthesized according to the general procedure A and purified by flash column chromatography (silica gel), eluting with 5% EtOAc in PE to afford the title compound as a colourless oil (0.63 g, 2.94 mmol, 59%).

R_f = 0.5 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.3 Hz, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 2.56 – 2.49 (m, 2H), 2.37 – 2.30 (m, 1H), 2.00 – 1.92 (m, 2H), 1.61 – 1.51 (m, 2H), 1.40 (dd, *J* = 8.0, 5.3 Hz, 2H), 1.31 – 1.21 (m, 4H), 0.88 (app. t, *J* = 7.3 Hz, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4, 176.6, 63.1, 45.4, 40.6, 34.7 (2C), 21.5, 20.8 (2C), 14.1 (2C) ppm.

HRMS (ESI) calculate: $C_{12}H_{23}O_3^+$ $(M+H)^+$: 215.1642, found: 215.1642.



76

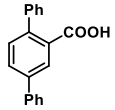
76 was synthesized according to the general procedure B and purified by flash column chromatography (silica gel), eluting with 3% MeOH in DCM to afford the title compound as a white solid (133 mg, 0.48 mmol, 95%).

R_f = 0.7 (8% MeOH in DCM)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 4H), 7.46 – 7.41 (m, 2H), 7.40 – 7.35 (m, 3H), 7.35 – 7.29 (m, 1H), 5.54 (s, 1H), 2.71 – 2.59 (m, 2H), 2.35 (s, 1H), 2.26 (dd, *J* = 8.1, 2.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 139.3, 136.8, 128.6 (3C), 128.3 (2C), 128.0, 126.8 (2C), 126.3 (2C), 87.1, 80.2, 54.6, 51.4, 39.8 ppm.

HRMS (ESI) calculate: $C_{18}H_{17}O_5^+$ $(M+H)^+$: 281.1172, found: 281.1174.



77

77 was synthesized according to the general procedure B and purified by flash column chromatography (silica gel), eluting with 2% MeOH in DCM to afford the title compound as a white solid (130 mg, 0.47 mmol, 95%).

R_f = 0.8 (8% MeOH in DCM)

^{1}H NMR (400 MHz, MeOD) δ 8.03 (d, *J* = 2.1 Hz, 1H), 7.81 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.69 (dd, *J* = 7.1, 1.8 Hz, 2H), 7.51 – 7.45 (m, 3H), 7.43 – 7.35 (m, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 142.3 (2C), 141.4, 141.0, 133.7, 132.5, 130.5, 130.1 (2C), 129.6 (2C), 129.2 (2C), 128.9 (2C), 128.3, 128.0 (2C) ppm.

HRMS (ESI) calculate: $C_{19}H_{15}O_2^+$ $(M+H)^+$: 275.1067, found: 275.1066.

3 Synthesis of Desired Compounds

3.1 General Procedure C: Preparation of Desired Compounds

An oven-dried two-dram vials equipped with PTFE-coated stir bar and Teflon® septum were used. $CoCl_2$ (7.5 mol%), $Mes_2Acr\text{-}tBu_2BF_4$ (**PC1**, 1 mol%), **1** (0.2 mmol, 2 eq.) and **2** (0.1 mmol, 1 eq.) were added into the vial and was dissolved in DCE (0.5 mL, 0.2 M). The vial was set to stir (500 rpm) and irradiated with a 30 W 450 nm blue LED lamp (approximate 3 cm away, with cooling fan to keep the reaction at room temperature). After 12 hours, the reaction mixture was transferred to a 100mL round-bottom flask and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with indicated solvent system to give the desired product.

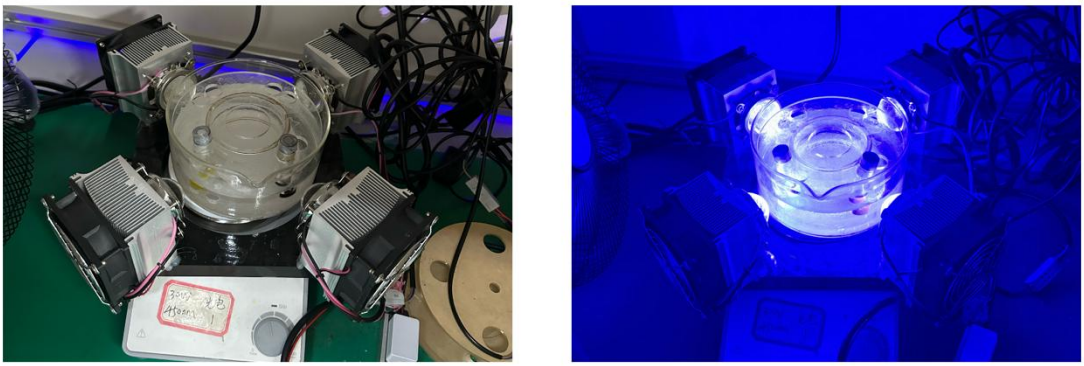
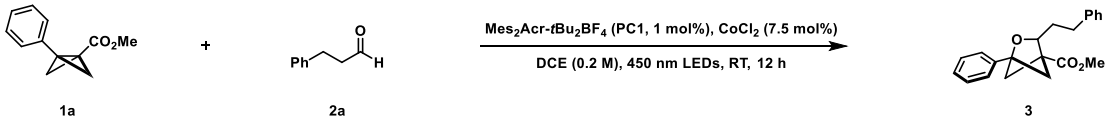


Figure S5. Picture of 30 W 450 nm irradiator

3.2 Experimental Procedures and Spectral Characterization of the Desired Products

Methyl-3-phenethyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2a 3

3 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 3% EtOAc in PE to afford the title compound as a white solid (29 mg, 0.090 mmol, 90%).

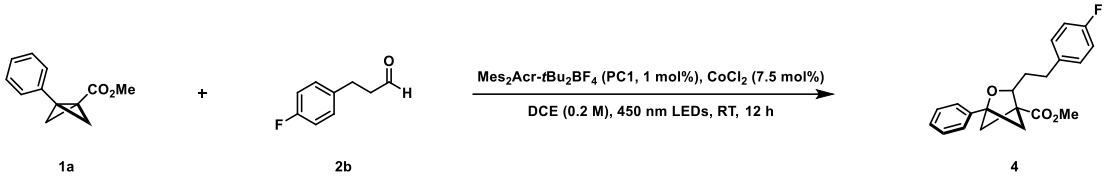
$\mathbf{R}_f$ = 0.6 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.41 – 7.36 (m, 2H), 7.35 – 7.27 (m, 3H), 7.24 (d, *J* = 1.4 Hz, 2H), 7.22 – 7.18 (m, 1H), 4.34 (dd, *J* = 9.5, 3.6 Hz, 1H), 3.75 (s, 3H), 2.99 – 2.90 (m, 1H), 2.78 – 2.69 (m, 1H), 2.43 (d, *J* = 6.9 Hz, 1H), 2.39 – 2.31 (m, 2H), 2.26 (dd, *J* = 10.2, 7.7 Hz, 1H), 2.09 – 2.00 (m, 1H), 1.93 – 1.83 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 142.1, 137.4, 128.6 (2C), 128.5 (4C), 128.4, 126.3 (2C), 126.0, 86.6, 79.7, 52.8, 52.1, 50.1, 42.1, 35.0, 32.3 ppm.

HRMS (ESI) calculate: $C_{21}H_{23}O_3^+$ $(M+H)^+$: 323.1642, found: 323.1641 .

Methyl-3-(4-fluorophenethyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2b 4

4 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a pale-yellow oil. (18 mg, 0.053 mmol, 53%).

R*f* = 0.6 (10% EtOAc in PE).

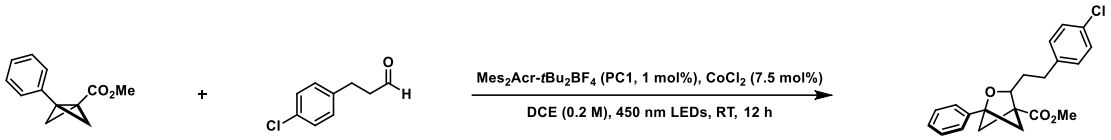
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 5H), 7.23 – 7.17 (m, 2H), 7.00 – 6.94 (m, 2H), 4.30 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.75 (s, 3H), 2.96 – 2.87 (m, 1H), 2.75 – 2.66 (m, 1H), 2.43 (d, *J* = 7.0 Hz, 1H), 2.34 (dd, *J* = 9.9, 7.1 Hz, 2H), 2.24 (dd, *J* = 10.3, 7.7 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.89 – 1.79 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 161.3 (d, *J* = 242.6 Hz), 137.5, 137.2, 129.86 (d, *J* = 7.8 Hz, 2C), 128.4 (2C), 128.3, 126.1 (2C), 115.11 (d, *J* = 21.0 Hz, 2C), 86.5, 79.3, 52.6, 52.0, 50.0, 42.0, 34.9, 31.4. ppm.

^{19}F NMR (471 MHz, $CDCl_3$) δ -117.74 ppm.

HRMS (ESI) calculate: $C_{21}H_{22}FO_3^+$ $(M+H)^+$: 341.1547, found: 341.1545.

Methyl-3-(4-chlorophenethyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



5 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (20 mg, 0.0570 mmol, 57%).

R_f = 0.6 (10% EtOAc in PE).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 4H), 7.27 – 7.23 (m, 1H), 7.20 – 7.16 (m, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 4.22 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.67 (s, 3H), 2.87 – 2.80 (m, 1H), 2.68 – 2.61 (m, 1H), 2.35 (d, *J* = 7.0 Hz, 1H), 2.28 – 2.22 (m, 2H), 2.19 – 2.14 (m, 1H), 1.97 – 1.90 (m, 1H), 1.81 – 1.73 (m, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 140.4, 137.1, 131.6, 129.9 (2C), 128.5 (2C), 128.4 (2C), 128.3, 126.1 (2C), 86.5, 79.2, 52.6, 51.9, 50.0, 42.0, 34.6, 31.5 ppm.

HRMS (ESI) calculate: $C_{21}H_{22}ClO_3^+$ $(M+H)^+$: 357.1252, found: 357.1250.

Methyl-3-(4-methylphenethyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate

6 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a pale-yellow oil. (20 mg, 0.060 mmol, 60%).

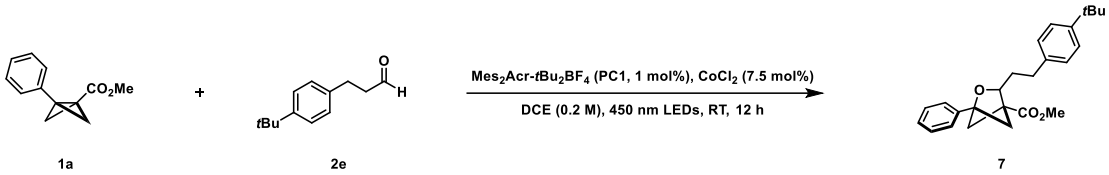
R_f = 0.6 (10% EtOAc in PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 5H), 7.17 – 7.08 (m, 4H), 4.33 (dd, *J* = 9.5, 3.6 Hz, 1H), 3.74 (s, 3H), 2.95 – 2.85 (m, 1H), 2.74 – 2.63 (m, 1H), 2.42 (d, *J* = 6.9 Hz, 1H), 2.37 – 2.29 (m, 5H), 2.25 (dd, *J* = 10.1, 7.6 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.92 – 1.80 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 138.9, 137.2, 135.3, 129.1 (2C), 128.4 (4C), 128.3, 126.1 (2C), 86.4, 79.6, 52.6, 51.9, 50.0, 41.9, 35.0, 31.8, 21.1 ppm.

HRMS (ESI) calculate: $C_{22}H_{25}O_3^+$ $(M+H)^+$: 337.1798, found: 337.1795.

Methyl-3-(4-(*tert*-butyl)phenethyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2e 7

7 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil (29 mg, 0.076 mmol, 76%).

R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 7H), 7.22 – 7.16 (m, 2H), 4.36 (dd, *J* = 9.5, 3.6 Hz, 1H), 3.75 (s, 3H), 2.97 – 2.88 (m, 1H), 2.75 – 2.66 (m, 1H), 2.43 (d, *J* = 7.0 Hz, 1H), 2.39 – 2.30 (m, 2H), 2.26 (dd, *J* = 10.1, 7.7 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.93 – 1.82 (m, 1H), 1.32 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 148.7, 138.9, 137.2, 128.4 (2C), 128.3, 128.2 (2C), 126.1 (2C), 125.3 (2C), 86.4, 79.8, 52.7, 52.0, 50.0, 41.9, 34.9, 34.4, 31.7, 31.5 (3C) ppm.

HRMS (ESI) calculate: $C_{25}H_{31}O_3^+$ $(M+H)^+$: 379.2268, found: 379.2260.

Methyl-3-(4-methoxyphenethyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate

1a 2f 8

8 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (25 mg, 0.070 mmol, 70%).

R*f* = 0.4 (10% EtOAc in PE).

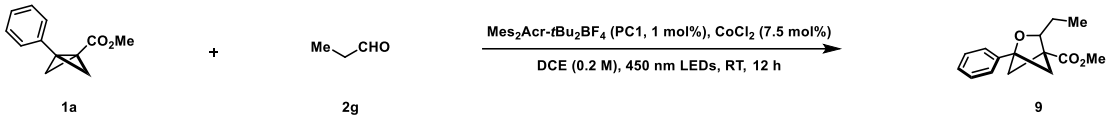
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 5H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.33 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.93 – 2.85 (m,

1H), 2.73 – 2.64 (m, 1H), 2.42 (d, *J* = 7.0 Hz, 1H), 2.34 (dd, *J* = 14.7, 8.5 Hz, 2H), 2.26 (dd, *J* = 10.2, 7.6 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.91 – 1.81 (m, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.8, 156.8, 136.2, 133.0, 128.3 (2C), 127.3 (2C), 127.2, 125.1 (2C), 112.8 (2C), 85.3, 78.5, 54.2, 51.5, 50.8, 48.9, 40.9, 34.0, 30.2 ppm.

HRMS (ESI) calculate: $C_{22}H_{25}O_4^+$ $(M+H)^+$: 353.1747, found: 353.1744.

Methyl-3-ethyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2g 9

9 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (25 mg, 0.098 mmol, 98%).

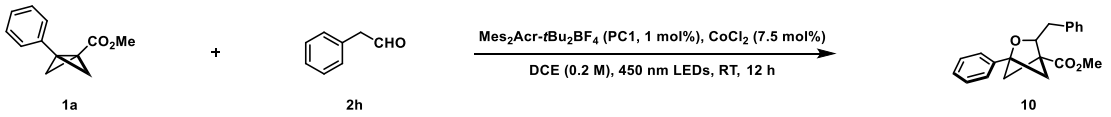
R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 4.22 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.75 (s, 3H), 2.42 – 2.17 (m, 4H), 1.79 – 1.67 (m, 1H), 1.63 – 1.54 (m, 1H), 1.05 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 137.3, 128.4 (2C), 128.2, 126.1 (2C), 86.2, 81.9, 52.5, 51.9, 50.1, 41.6, 26.0, 10.5 ppm.

HRMS (ESI) calculate: $C_{15}H_{19}O_3^+$ $(M+H)^+$: 261.1485, found: 261.1484.

Methyl-3-benzyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2h 10

10 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (16 mg, 0.051 mmol, 51%).

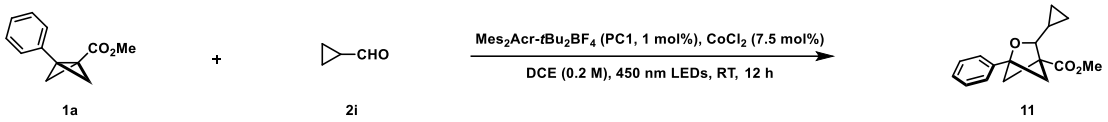
R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.31 – 7.21 (m, 5H), 7.21 – 7.15 (m, 1H), 4.57 – 4.51 (m, 1H), 3.50 (s, 3H), 3.02 (dd, *J* = 14.1, 7.4 Hz, 1H), 2.93 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.38 (d, *J* = 5.8 Hz, 1H), 2.34 – 2.26 (m, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 137.8, 137.1, 129.5 (2C), 128.4 (4C), 128.3, 126.4, 126.1 (2C), 86.6, 80.8, 52.6, 51.7, 50.0, 41.6, 39.5 ppm.

HRMS (ESI) calculate: $C_{20}H_{21}O_3^+$ $(M+H)^+$: 309.1485, found: 309.1483.

Methyl-3-cyclopropyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2i 11

11 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (22 mg, 0.086 mmol, 86%).

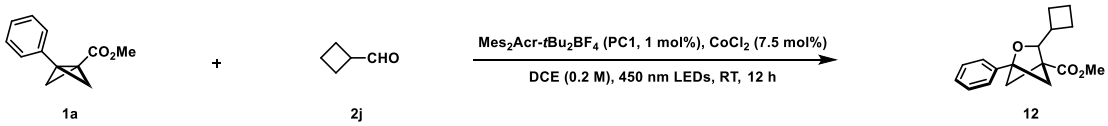
$\mathbf{R_f}$ = 0.6 (10% EtOAc in PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 4.28 (d, *J* = 8.9 Hz, 1H), 3.72 (s, 3H), 2.62 – 2.50 (m, 1H), 2.41 – 2.32 (m, 2H), 2.24 – 2.19 (m, 2H), 2.17 – 2.02 (m, 2H), 1.98 – 1.75 (m, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 137.0, 128.5, 128.4, 126.3, 86.3, 86.0, 53.3, 51.9, 49.8, 41.7, 12.5, 3.1, 2.1 ppm.

HRMS (ESI) calculate: $C_{16}H_{19}O_3^+$ $(M+H)^+$: 259.1329, found: 259.1326.

Methyl-3-cyclobutyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2j 12

12 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (21 mg, 0.077 mmol, 77%).

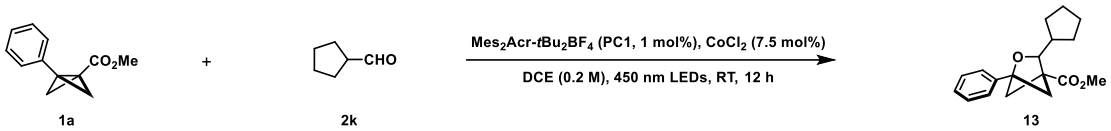
$\mathbf{R_f}$ = 0.6 (10% EtOAc in PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 4.28 (d, *J* = 8.9 Hz, 1H), 3.72 (s, 3H), 2.62 – 2.50 (m, 1H), 2.41 – 2.32 (m, 2H), 2.24 – 2.19 (m, 2H), 2.17 – 2.02 (m, 2H), 1.98 – 1.75 (m, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 137.1, 128.4 (2C), 128.2, 126.2 (2C), 86.0, 84.7, 52.0, 51.8, 49.8, 41.4, 37.9, 25.8, 24.8, 19.1 ppm.

HRMS (ESI) calculate: $C_{17}H_{21}O_3^+$ $(M+H)^+$: 273.1485, found: 273.1481.

Methyl-3-cyclopentyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2k 13

13 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (25 mg, 0.087 mmol, 87%).

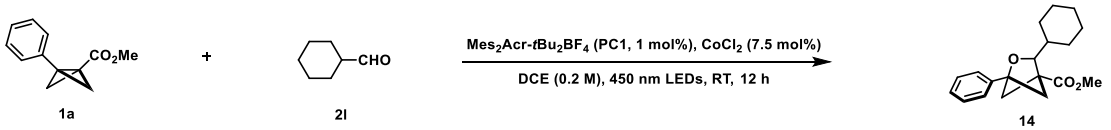
R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 4.07 (d, *J* = 9.4 Hz, 1H), 3.74 (s, 3H), 2.41 – 2.34 (m, 2H), 2.30 – 2.20 (m, 2H), 2.04 – 1.95 (m, 2H), 1.61 – 1.45 (m, 5H), 1.36 – 1.28 (m, 1H), 1.19 – 1.07 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 137.2, 128.3 (2C), 128.2, 126.1 (2C), 85.7, 85.5, 52.5, 51.8, 50.1, 43.5, 41.4, 30.6, 28.3, 25.6, 25.0 ppm.

HRMS (ESI) calculate: $C_{18}H_{23}O_3^+$ $(M+H)^+$: 287.1642, found: 287.1642.

Methyl-3-cyclohexyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2l 14

14 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (25 mg, 0.083 mmol, 83%).

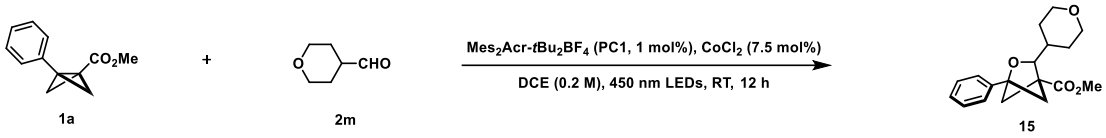
R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 4.00 (d, *J* = 9.1 Hz, 1H), 3.74 (s, 3H), 2.35 (d, *J* = 3.7 Hz, 2H), 2.23 (d, *J* = 5.1 Hz, 2H), 2.12 (d, *J* = 13.0 Hz, 1H), 1.82 – 1.70 (m, 2H), 1.61 – 1.52 (m, 1H), 1.52 – 1.44 (m, 1H), 1.32 – 1.13 (m, 4H), 1.12 – 0.94 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 137.3, 128.4 (2C), 128.1, 126.1 (2C), 85.4, 84.8, 51.9, 51.8, 51.8, 50.9, 41.6, 41.0, 29.8, 28.6, 26.3, 25.8, 25.8 ppm.

HRMS (ESI) calculate: $C_{19}H_{25}O_3^+$ $(M+H)^+$: 301.1798, found: 301.1795.

Methyl-1-phenyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-oxabicyclo[2.1.1]hexane-4-carboxylate



15 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 5% EtOAc in PE to afford the title compound as a colourless oil (19 mg, 0.063 mmol, 63%).

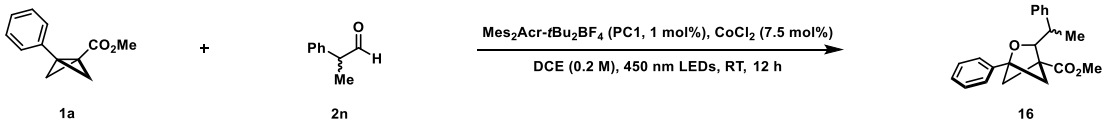
R*f* = 0.4 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 7.33 – 7.29 (m, 1H), 4.04 (d, *J* = 9.2 Hz, 1H), 4.02 – 3.98 (m, 1H), 3.96 – 3.91 (m, 1H), 3.74 (s, 3H), 3.44 – 3.33 (m, 2H), 2.39 – 2.35 (m, 2H), 2.29 (d, *J* = 7.8 Hz, 1H), 2.26 – 2.20 (m, 1H), 2.00 – 1.94 (m, 1H), 1.85 – 1.77 (m, 1H), 1.54 – 1.33 (m, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 137.1, 128.5 (2C), 128.4, 126.2 (2C), 85.9, 84.0, 67.9, 67.3, 52.0, 51.9, 51.0, 41.2, 39.1, 29.8, 28.8 ppm.

HRMS (ESI) calculate: $C_{16}H_{23}O_4^+$ $(M+H)^+$: 303.1591, found: 303.1593.

Methyl-1-phenyl-3-(1-phenylethyl)-2-oxabicyclo[2.1.1]hexane-4-carboxylate



16 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 3% EtOAc in PE to afford the title compound as a colourless oil (18 mg, 0.056 mmol, 56%).

R*f* = 0.6 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.41 – 7.36 (m, 2H), 7.36 – 7.32 (m, 1H), 7.30 (m, 4H), 7.24 – 7.19 (m, 3H), 4.44 (dd, *J* = 9.1, 5.2 Hz, 1H), 3.01 (s, 3H), 2.93 – 2.86 (m, 1H), 2.38 – 2.35 (m, 2H), 2.32 – 2.30 (m, 1H), 2.28 – 2.25 (m, 1H), 1.47 (d, *J* = 6.9 Hz, 3H), 1.30 (d, *J* = 7.1 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 142.6, 137.2, 128.5 (2C), 128.4 (4C), 128.3, 127.0, 126.2 (2C), 85.8, 84.6, 52.4, 51.2, 50.8, 44.3, 41.0, 19.7 ppm.

HRMS (ESI) calculate: $C_{21}H_{23}O_3^+$ $(M+H)^+$: 323.1642, found: 323.1642.

Methyl-3-isopropyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate

1a 2o 17

17 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 3% EtOAc in PE to afford the title compound as a colourless oil (20 mg, 0.077 mmol, 77%).

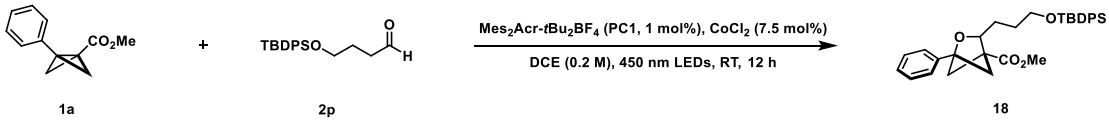
R*f* = 0.7 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 4H), 7.33 – 7.28 (m, 1H), 3.93 (d, *J* = 9.4 Hz, 1H), 3.74 (s, 3H), 2.40 – 2.35 (m, 2H), 2.25 – 2.18 (m, 2H), 1.87 – 1.78 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 137.4, 128.5 (2C), 128.3, 126.2 (2C), 86.2, 85.5, 52.2, 51.9, 51.0, 41.3, 32.1, 20.0, 18.7 ppm.

HRMS (ESI) calculate: $C_{16}H_{21}O_3^+$ $(M+H)^+$: 261.1485, found: 261.1487.

Methyl-3-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-1-phenyl-2-oxabicyclo [2.1.1]hexane-4-carboxylate



1a 2p 18

18 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a colourless oil (32 mg, 0.062 mmol, 62%).

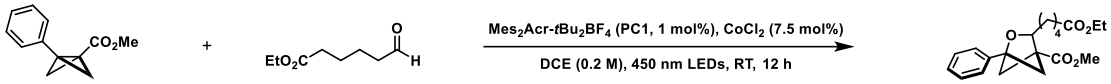
R*f* = 0.8 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 4H), 7.45 – 7.37 (m, 10H), 7.36 – 7.31 (m, 1H), 4.32 (dd, *J* = 9.3, 3.2 Hz, 1H), 3.81 – 3.71 (m, 5H), 2.43 (d, *J* = 6.9 Hz, 1H), 2.35 (dd, *J* = 10.1, 7.0 Hz, 1H), 2.31 (d, *J* = 7.6 Hz, 1H), 2.23 (dd, *J* = 10.2, 7.6 Hz, 1H), 1.93 – 1.83 (m, 2H), 1.75 – 1.61 (m, 2H), 1.08 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 137.4, 135.7 (3C), 134.2, 134.1, 129.7 (2C), 128.4 (2C), 128.3 (2C), 127.7 (4C), 126.2 (2C), 86.4, 80.3, 63.8, 52.8, 51.9, 50.0, 41.9, 29.3, 29.1, 23.0 (3C), 19.4 ppm.

HRMS (ESI) calculate: $C_{32}H_{39}O_4Si^+$ $(M+H)^+$: 515.2539, found: 515.2542.

Methyl-3-(5-ethoxy-5-oxopentyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2q 19

19 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 4% EtOAc in PE to afford the title compound as a colourless oil (22 mg, 0.064 mmol, 64%).

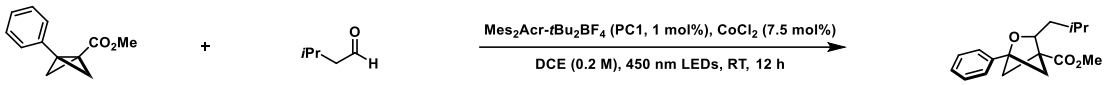
R*f* = 0.5 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 4H), 7.33 – 7.28 (m, 1H), 4.27 (dd, *J* = 9.1, 3.6 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 2.40 (d, *J* = 7.0 Hz, 1H), 2.35 – 2.27 (m, 4H), 2.21 (dd, *J* = 10.2, 7.7 Hz, 1H), 1.75 – 1.67 (m, 3H), 1.65 – 1.53 (m, 2H), 1.48 – 1.40 (m, 1H), 1.27 – 1.23 (m, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 171.0, 137.3, 128.5 (2C), 128.3, 126.2 (2C), 86.5, 80.2, 60.4, 52.7, 52.0, 50.0, 41.9, 34.4, 32.7, 25.8, 25.2, 14.4 ppm.

HRMS (ESI) calculate: $C_{20}H_{28}O_5^+$ $(M+H)^+$: 347.1853, found: 347.1852.

Methyl-3-isobutyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2r 20

20 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a colourless oil (20 mg, 0.073 mmol, 73%).

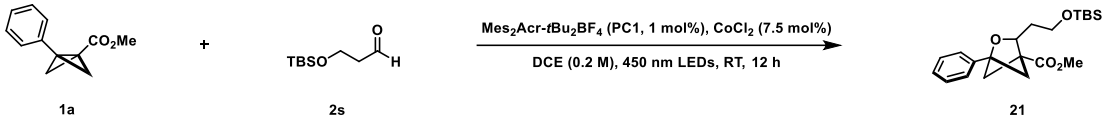
R*f* = 0.8 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.33 (m, 4H), 7.30 (app. t, *J* = 7.2 Hz, 1H), 4.38 (dd, *J* = 9.0, 3.9 Hz, 1H), 3.76 (s, 3H), 2.40 (d, *J* = 6.9 Hz, 1H), 2.36 – 2.30 (m, 1H), 2.27 (d, *J* = 7.5 Hz, 1H), 2.25 – 2.19 (m, 1H), 1.91 – 1.79 (m, 1H), 1.56 – 1.43 (m, 2H), 0.99 (dd, *J* = 6.7, 4.2 Hz, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 137.4, 128.5 (2C), 128.3, 126.2 (2C), 86.4, 78.7, 52.8, 52.0, 49.9, 42.0, 41.9, 25.3, 23.7, 22.4 ppm.

HRMS (ESI) calculate: $C_{17}H_{23}O_3^+$ $(M+H)^+$: 275.1642, found: 275.1642.

Methyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-phenyl-2-oxabicyclo [2.1.1]hexane-4-carboxylate



1a 2s 21

21 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a colourless oil (20 mg, 0.053 mmol, 53%).

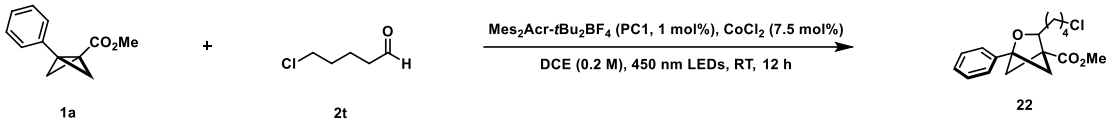
R*f* = 0.6 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 4H), 7.33 – 7.29 (m, 1H), 4.42 (dd, *J* = 9.7, 3.2 Hz, 1H), 3.88 – 3.79 (m, 2H), 3.76 (s, 3H), 2.41 (d, *J* = 6.9 Hz, 1H), 2.32 (dd, *J* = 8.8, 5.4 Hz, 2H), 2.21 (dd, *J* = 10.3, 7.8 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.81 – 1.73 (m, 1H), 0.91 (s, 9H), 0.08 (d, *J* = 1.7 Hz, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 137.4, 128.4 (2C), 128.3, 126.2 (2C), 86.6, 76.9, 60.2, 52.7, 52.0, 50.1, 42.0, 36.4, 26.1 (3C), 18.5, 5.1 (2C) ppm.

HRMS (ESI) calculate: $C_{21}H_{33}O_4Si^+$ $(M+H)^+$: 377.2143, found: 377.2139.

Methyl-(4-chlorobutyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2t 22

22 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 4% EtOAc in PE to afford the title compound as a colourless oil (20 mg, 0.065 mmol, 65%).

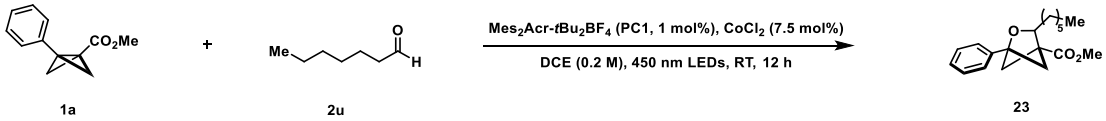
R*f* = 0.4 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 4H), 7.34 – 7.29 (m, 1H), 4.31 – 4.25 (m, 1H), 3.76 (s, 3H), 3.56 (t, *J* = 6.7 Hz, 2H), 2.41 (d, *J* = 7.0 Hz, 1H), 2.35 – 2.29 (m, 2H), 2.21 (dd, *J* = 10.2, 7.7 Hz, 1H), 1.89 – 1.83 (m, 2H), 1.78 – 1.69 (m, 2H), 1.62 – 1.54 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 137.3, 128.5 (2C), 128.4, 126.2 (2C), 86.5, 80.1, 52.7, 52.0, 50.1, 45.0, 41.9, 32.7, 32.3, 23.7 ppm.

HRMS (ESI) calculate: $C_{17}H_{22}ClO_3^+$ $(M+H)^+$: 395.1252, found: 395.1250.

Methyl-hexyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2u 23

23 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a colourless oil (17 mg, 0.056 mmol, 56%).

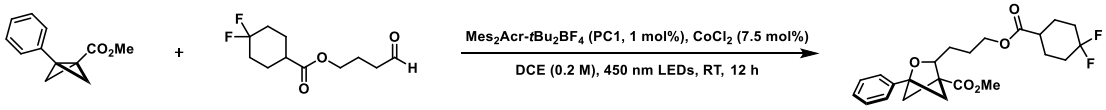
R*f* = 0.8 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.38 – 7.33 (m, 2H), 7.33 – 7.28 (m, 1H), 4.28 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.75 (s, 3H), 2.39 (d, *J* = 6.9 Hz, 1H), 2.33 (dd, *J* = 10.0, 7.0 Hz, 1H), 2.28 (d, *J* = 7.5 Hz, 1H), 2.22 (dd, *J* = 10.0, 7.6 Hz, 1H), 1.72 – 1.64 (m, 1H), 1.57 (m, 2H), 1.41 – 1.33 (m, 3H), 1.32 – 1.25 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 137.4, 128.5 (2C), 128.3, 126.2 (2C), 86.3, 80.6, 52.7, 52.0, 50.1, 41.8, 33.1, 31.9, 29.6, 26.2, 22.8, 14.2 ppm.

HRMS (ESI) calculate: $C_{19}H_{28}O_3^+$ $(M+H)^+$: 303.1955, found: 303.1953.

Methyl-3-(3-((4,4-difluorocyclohexane-1-carbonyl)oxy)propyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2v 24

24 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 8% EtOAc in PE to afford the title compound as a colourless oil (28 mg, 0.066 mmol, 66%).

R*f* = 0.3 (10% EtOAc in PE)

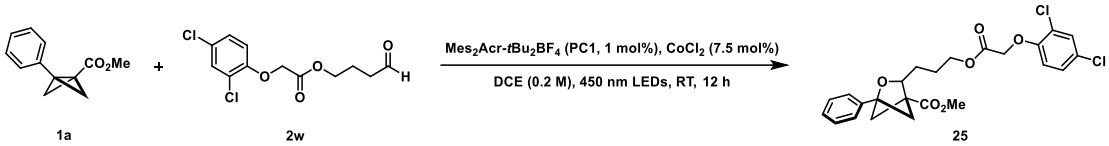
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 4H), 7.34 – 7.29 (m, 1H), 4.29 (dd, *J* = 9.7, 2.9 Hz, 1H), 4.24 – 4.10 (m, 2H), 3.76 (s, 3H), 2.42 (d, *J* = 7.4 Hz, 2H), 2.37 – 2.30 (m, 2H), 2.24 – 2.16 (m, 1H), 2.14 – 2.02 (m, 2H), 2.02 – 1.90 (m, 3H), 1.86 – 1.73 (m, 5H), 1.63 – 1.55 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 170.8, 137.1, 128.5 (2C), 128.4, 126.2 (2C), 122.8 (t, *J* = 240.3 Hz), 86.7, 79.7, 64.6, 52.7, 52.1, 50.1, 41.9, 40.7, 32.7 (t, *J* = 24.4 Hz, 2C), 29.4, 25.5, 25.2 (d, *J* = 7.9 Hz, 2C) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -94.29 (d, *J* = 237.3 Hz), -99.56 (d, *J* = 237.9 Hz) ppm.

HRMS (ESI) calculate: $C_{23}H_{29}F_2O_6^+$ $(M+H)^+$: 423.1978, found: 423.1979.

Methyl-3-(3-(2-(2,4-dichlorophenoxy)acetoxy)propyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2w 25

25 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 10% EtOAc in PE to afford the title compound as a colourless oil (25 mg, 0.052 mmol, 52%).

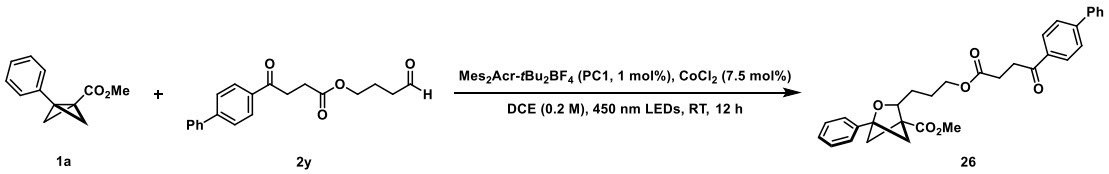
R_f = 0.2 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 6.7 Hz, 5H), 7.34 – 7.29 (m, 1H), 7.16 – 7.11 (m, 1H), 6.77 (dd, *J* = 8.8, 2.1 Hz, 1H), 4.68 (d, *J* = 2.2 Hz, 2H), 4.34 – 4.22 (m, 3H), 3.76 (d, *J* = 2.1 Hz, 3H), 2.42 (dd, *J* = 7.2, 2.0 Hz, 1H), 2.35 – 2.28 (m, 2H), 2.17 (t, *J* = 9.2 Hz, 1H), 2.02 – 1.91 (m, 1H), 1.84 – 1.75 (m, 2H), 1.63 – 1.51 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 168.3, 152.5, 137.1, 130.4, 128.5 (2C), 128.4, 127.7, 127.1, 126.1 (2C), 124.3, 114.8, 86.7, 79.6, 66.5, 65.6, 52.7, 52.1, 50.0, 42.0, 29.3, 25.4 ppm.

HRMS (ESI) calculate: $C_{24}H_{25}Cl_2O_6^+$ $(M+H)^+$: 479.1023, found: 479.1026.

Methyl-3-(3-((4-([1,1'-biphenyl]-4-yl)-4-oxobutanoyl)oxy)propyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2y 26

26 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 12% EtOAc in PE to afford the title compound as a colourless oil (31 mg, 0.060 mmol, 60%).

R_f = 0.3 (20% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 7.3 Hz, 2H), 7.47 (app. t, J = 7.5 Hz, 2H), 7.43 – 7.34 (m, 5H), 7.33 – 7.29 (m,

1H), 4.30 (dd, *J* = 9.5, 3.3 Hz, 1H), 4.25 – 4.15 (m, 2H), 3.77 (s, 3H), 3.35 (t, *J* = 6.7 Hz, 2H), 2.80 (t, *J* = 6.7 Hz, 2H), 2.42 (d, *J* = 7.0 Hz, 1H), 2.36 – 2.28 (m, 2H), 2.21 (dd, *J* = 10.3, 7.7 Hz, 1H), 1.97 (d, *J* = 5.9 Hz, 1H), 1.87 – 1.74 (m, 2H), 1.67 – 1.57 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 173.1, 170.8, 145.9, 140.0, 137.2, 135.4, 129.1 (2C), 128.8 (2C), 128.4 (2C), 128.3, 128.3, 127.4 (4C), 126.2 (2C), 86.6, 79.8, 64.7, 52.7, 52.1, 50.0, 41.9, 33.5, 29.5, 28.4, 25.4 ppm.

HRMS (ESI) calculate: $C_{32}H_{33}O_6$ $(M+H)^+$: 513.2272, found: 513.2269.

Methyl-3-(3-((2-(3-fluoro-[1,1'-biphenyl]-4-yl)propanoyl)oxy)propyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate

27 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 8% EtOAc in PE to afford the title compound as a colourless oil (30 mg, 0.060 mmol, 60%).

R*f* = 0.3 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.43 (app. t, J = 7.8 Hz, 2H), 7.40 – 7.33 (m, 6H), 7.31 (d, *J* = 6.1 Hz, 1H), 7.14 (app. t, J = 11.2 Hz, 2H), 4.27 (d, *J* = 9.4 Hz, 1H), 4.22 – 4.16 (m, 2H), 3.79 – 3.74 (m, 1H), 3.72 (d, *J* = 2.5 Hz, 3H), 2.41 (d, *J* = 7.2 Hz, 1H), 2.33 – 2.26 (m, 2H), 2.14 (s, 1H), 1.99 – 1.89 (m, 1H), 1.76 (d, *J* = 3.5 Hz, 2H), 1.55 (s, 2H), 1.53 (d, *J* = 2.5 Hz, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 170.8, 159.8 (d, *J* = 248.1 Hz), 142.0 (d, *J* = 7.8 Hz), 137.2, 135.6, 130.9 (d, *J* = 3.8 Hz), 129.1 (d, *J* = 2.9 Hz, 2C), 128.5 (2C), 128.5 (2C), 128.4, 127.9, 127.7, 126.1 (2C), 123.7, 115.4 (d, *J* = 23.7 Hz), 86.6, 79.8, 52.7, 52.0, 50.0, 45.2, 41.9, 41.9, 29.3, 25.4, 18.5 ppm.

^{19}F NMR (471 MHz, $CDCl_3$) δ -117.65 ppm.

HRMS (ESI) calculate: $C_{31}H_{32}FO_5^+$ $(M+H)^+$: 503.2228, found: 503.2230.

Methyl-3-(3-((2-acetoxybenzoyl)oxy)propyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate

28 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 10% EtOAc in PE to afford the title compound as a colourless oil (33 mg, 0.075 mmol, 75%).

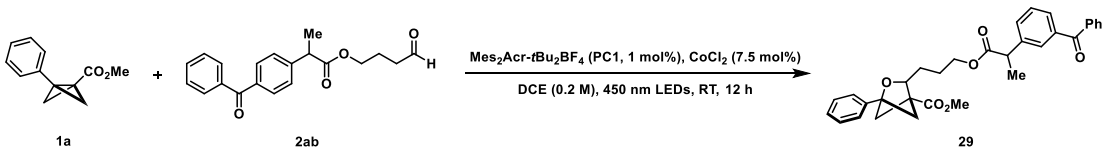
R*f* = 0.4 (20% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.42 – 7.34 (m, 4H), 7.34 – 7.28 (m, 2H), 7.10 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.40 – 4.31 (m, 3H), 3.75 (s, 3H), 2.43 (d, *J* = 7.0 Hz, 1H), 2.33 (d, *J* = 10.2 Hz, 5H), 2.24 (dd, *J* = 10.3, 7.7 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.94 – 1.84 (m, 2H), 1.72 – 1.63 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 169.8, 164.6, 150.7, 137.1, 133.9, 131.9, 128.4 (2C), 128.3, 126.1 (2C), 126.1, 123.9, 123.5, 86.7, 79.7, 65.2, 52.7, 52.0, 50.1, 41.9, 29.5, 25.5, 21.2 ppm.

HRMS (ESI) calculate: $C_{25}H_{27}O_7^+$ $(M+H)^+$: 439.1751, found: 439.1754.

Methyl-3-(3-((2-(4-benzoylphenyl)propanoyl)oxy)propyl)-1-phenyl-2-oxa-bicyclo[2.1.1]hexane-4-carboxylate



29 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 15% EtOAc in PE to afford the title compound as a colourless oil (29 mg, 0.057 mmol, 57%).

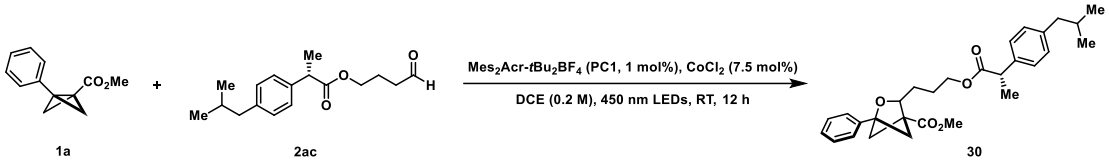
R*f* = 0.3 (20% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 2.5 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.60 – 7.52 (m, 2H), 7.50 – 7.45 (m, 2H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.39 – 7.32 (m, 4H), 7.32 – 7.27 (m, 1H), 4.28 – 4.22 (m, 1H), 4.21 – 4.11 (m, 2H), 3.84 – 3.76 (m, 1H), 3.72 (d, *J* = 2.3 Hz, 3H), 2.40 (dd, *J* = 7.1, 2.3 Hz, 1H), 2.29 (t, *J* = 10.0 Hz, 2H), 2.13 (t, *J* = 9.1 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.78 – 1.70 (m, 2H), 1.54 (d, *J* = 2.3 Hz, 2H), 1.52 (d, *J* = 2.3 Hz, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6, 174.2, 170.8, 141.0, 138.0, 137.6, 137.1, 132.6, 131.7, 130.2 (2C), 129.4, 129.1, 128.7, 128.5 (2C), 128.4 (2C), 128.3, 126.1 (2C), 86.6, 79.7, 65.0, 52.7, 52.0, 50.0, 45.6, 41.9, 29.3, 25.4, 18.6 ppm.

HRMS (ESI) calculate: $C_{32}H_{33}O_6^+$ $(M+H)^+$: 513.2272, found: 513.2274.

Methyl-3-(3-(((*S*)-2-(4-isobutylphenyl)propanoyl)oxy)propyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2ac 30

30 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 5% EtOAc in PE to afford the title compound as a colourless oil (31 mg, 0.067 mmol, 67%).

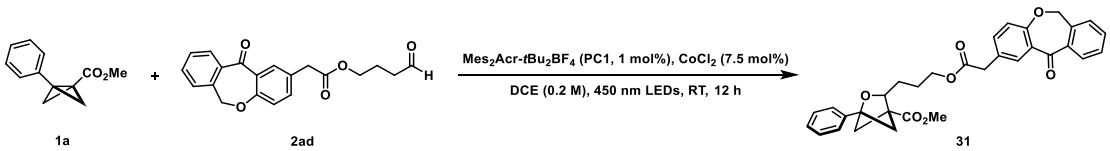
R_f = 0.5 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 7.34 – 7.29 (m, 1H), 7.20 (d, *J* = 7.7 Hz, 2H), 7.07 (dd, *J* = 7.5, 5.0 Hz, 2H), 4.25 (dd, *J* = 9.4, 3.0 Hz, 1H), 4.19 – 4.10 (m, 2H), 3.75 – 3.72 (m, 3H), 3.72 – 3.66 (m, 1H), 2.45 – 2.38 (m, 3H), 2.30 (dd, *J* = 15.7, 8.3 Hz, 2H), 2.17 – 2.10 (m, 1H), 1.94 – 1.86 (m, 1H), 1.86 – 1.78 (m, 1H), 1.77 – 1.67 (m, 2H), 1.57 – 1.46 (m, 4H), 0.90 (d, *J* = 2.4 Hz, 3H), 0.88 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 170.8, 140.6, 137.9, 137.2, 129.4 (2C), 128.5 (2C), 128.3, 127.3 (2C), 126.1 (2C), 86.6, 79.8, 64.7, 52.7, 52.0, 50.0, 45.3, 45.2, 41.9, 30.3, 29.3, 25.4, 22.5 (2C), 18.7 ppm.

HRMS (ESI) calculate: $C_{29}H_{38}O_5^+$ $(M+H)^+$: 465.2636, found: 465.2637.

Methyl-(3-(2-(11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetoxy)propyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2ad 31

31 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 15% EtOAc in PE to afford the title compound as a colourless oil (28 mg, 0.053 mmol, 53%).

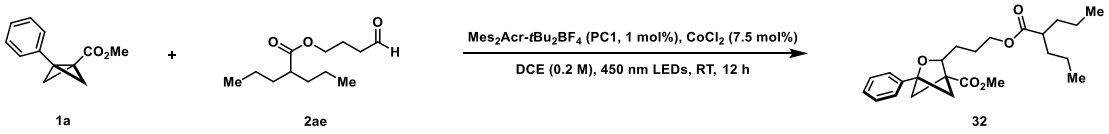
R*f* = 0.5 (30% EtOAc in PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 2.3 Hz, 1H), 7.88 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.60 – 7.52 (m, 1H), 7.50 – 7.40 (m, 2H), 7.40 – 7.27 (m, 6H), 7.02 (d, *J* = 8.5 Hz, 1H), 5.17 (s, 2H), 4.28 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.25 – 4.13 (m, 2H), 3.75 (s, 3H), 3.64 (s, 2H), 2.41 (d, *J* = 7.0 Hz, 1H), 2.35 – 2.25 (m, 2H), 2.18 (dd, *J* = 10.2, 7.7 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.84 – 1.72 (m, 2H), 1.63 – 1.51 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 171.6, 170.8, 160.6, 140.6, 137.2, 136.5, 135.7, 132.9, 132.6, 129.6, 129.4, 128.5 (2C), 128.4, 128.0, 127.9, 126.2 (2C), 125.2, 121.2, 86.6, 79.8, 73.7, 65.0, 52.7, 52.1, 50.0, 42.0, 40.4, 29.4, 25.4 ppm.

HRMS (ESI) calculate: $C_{32}H_{30}O_7^+$ $(M+H)^+$: 527.2064, found: 527.2066.

Methyl-1-phenyl-3-(3-((2-propylpentanoyl)oxy)propyl)-2-oxabicyclo[2.1.1] hexane-4-carboxylate



1a 2ae 32

32 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 3% EtOAc in PE to afford the title compound as a colourless oil (29 mg, 0.072 mmol, 72%).

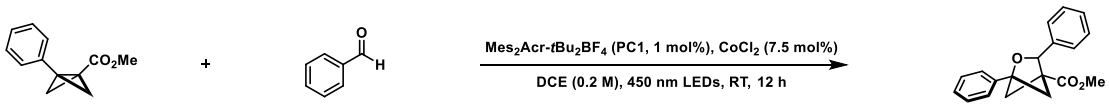
R*f* = 0.4 (10% EtOAc in PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 4.30 (dd, *J* = 9.6, 3.3 Hz, 1H), 4.15 (t, *J* = 6.4 Hz, 2H), 3.76 (s, 3H), 2.42 (d, *J* = 7.0 Hz, 1H), 2.40 – 2.28 (m, 3H), 2.21 (dd, *J* = 10.2, 7.7 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.85 – 1.70 (m, 2H), 1.64 – 1.52 (m, 3H), 1.46 – 1.34 (m, 2H), 1.32 – 1.25 (m, 4H), 0.94 – 0.85 (m, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 170.8, 137.2, 128.5 (2C), 128.4, 126.2 (2C), 86.6, 79.9, 64.0, 52.7, 52.0, 50.0, 45.5, 41.9, 34.8 (2C), 29.5, 25.6, 20.8 (2C), 14.2 (2C) ppm.

HRMS (ESI) calculate: $C_{24}H_{35}O_6^+$ $(M+H)^+$: 403.2479, found: 403.2480.

Methyl-1,3-diphenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2af 33

33 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a pale-yellow solid. (25 mg, 0.085 mmol, 85%).

R*f* = 0.6 (10% EtOAc in PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 2H), 7.48 – 7.39 (m, 4H), 7.39 – 7.32 (m, 3H), 7.32 – 7.27 (m, 1H), 5.51 (s, 1H), 3.74 (s, 3H), 2.64 – 2.58 (m, 1H), 2.55 (d, *J* = 7.0 Hz, 1H), 2.31 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.23 (d, *J* = 8.1 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 139.6, 137.1, 128.6 (2C), 128.5, 128.2 (2C), 127.8, 126.6 (2C), 126.3 (2C), 86.9, 80.4, 54.7, 52.0, 51.0, 39.9 ppm.

HRMS (ESI) calculate: $C_{19}H_{19}O_3^+$ $(M+H)^+$: 295.1329, found: 295.1330.

Methyl-1-phenyl-3-(p-tolyl)-2-oxabicyclo[2.1.1]hexane-4-carboxylate

1a 2ag 34

34 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a pale-yellow solid. (23 mg, 0.076 mmol, 76%).

R*f* = 0.6 (10% EtOAc in PE)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H), 7.46 – 7.30 (m, 5H), 7.16 (d, *J* = 7.9 Hz, 2H), 5.49 (s, 1H), 3.74 (s, 3H), 2.63 – 2.51 (m, 2H), 2.35 (s, 3H), 2.31 (dd, J = 10.1, 8.1 Hz, 1H), 2.22 (d, *J* = 8.0 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 137.4, 137.1, 136.5, 128.9 (2C), 128.5 (2C), 128.4, 126.4 (2C), 126.2 (2C), 86.8, 80.3, 54.6, 51.8, 50.8, 39.9, 21.2 ppm.

HRMS (ESI) calculate: $C_{20}H_{21}O_3^+$ $(M+H)^+$: 309.1485, found: 309.1482.

Methyl-3-([1,1'-biphenyl]-4-yl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate

1a 2ah 35

35 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a pale-yellow solid. (29 mg, 0.079 mmol, 79%).

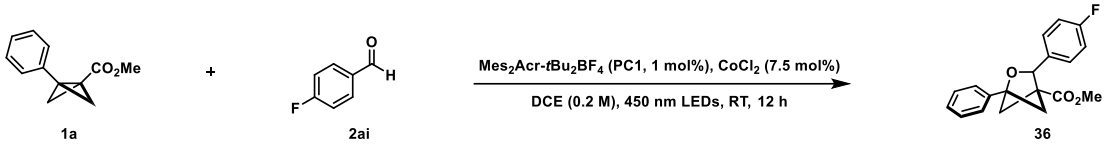
R*f* = 0.6 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 4H), 7.56 – 7.51 (m, 4H), 7.47 – 7.41 (m, 4H), 7.40 – 7.33 (m, 2H), 5.56 (s, 1H), 3.77 (s, 3H), 2.63 (dd, *J* = 10.1, 7.1 Hz, 1H), 2.57 (d, *J* = 7.0 Hz, 1H), 2.35 (dd, *J* = 10.1, 8.1 Hz, 1H), 2.27 (d, *J* = 8.1 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 140.9, 140.6, 138.6, 137.0, 128.8 (2C), 128.5 (2C), 128.4, 127.3, 127.2 (2C), 127.0 (2C), 126.9 (2C), 126.2 (2C), 86.9, 80.2, 54.7, 51.9, 51.0, 40.0 ppm.

HRMS (ESI) calculate: $C_{25}H_{23}O_3^+$ $(M+H)^+$: 371.1642, found: 371.1638.

Methyl-3-(4-fluorophenyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2ai 36

36 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a pale-yellow solid. (22 mg, 0.059 mmol, 59%).

R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 – 7.48 (m, 2H), 7.45 – 7.39 (m, 4H), 7.39 – 7.34 (m, 1H), 7.04 (t, *J* = 8.7 Hz, 2H), 5.47 (s, 1H), 3.74 (s, 3H), 2.61 – 2.52 (m, 2H), 2.28 – 2.22 (m, 2H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.3, 161.4 (d, *J* = 245.8 Hz), 135.8, 134.2 (d, *J* = 3.1 Hz), 127.4 (2C), 127.4, 127.2 (d, *J* = 8.1 Hz, 2C), 125.1 (2C), 114.0 (d, *J* = 21.7 Hz, 2C), 85.9, 78.7, 53.6, 50.8, 49.9, 38.7 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.88 ppm.

HRMS (ESI) calculate: $C_{19}H_{18}FO_3^+$ $(M+H)^+$: 313.1234, found: 313.1227.

Methyl-3-(4-chlorophenyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate

1a 2aj 37

37 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a pale-yellow solid (18 mg, 0.055 mmol, 55%).

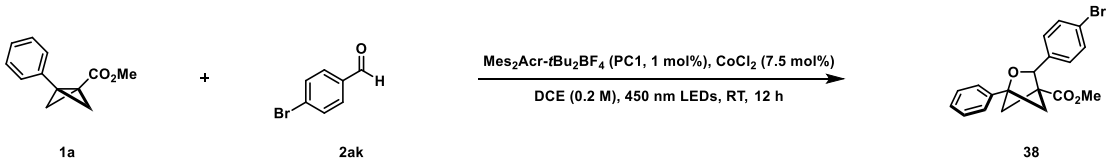
$\mathbf{R_f}$ = 0.6 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.45 – 7.35 (m, 5H), 7.32 (d, *J* = 8.2 Hz, 2H), 5.46 (s, 1H), 3.73 (s, 3H), 2.65 – 2.49 (m, 2H), 2.30 – 2.18 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 138.0, 136.7, 133.6, 128.5, 128.3, 128.0, 126.2, 87.1, 79.7, 54.6, 51.9, 51.0, 39.7 ppm.

HRMS (ESI) calculate: $C_{19}H_{18}ClO_3^+$ $(M+H)^+$: 329.0939, found: 329.0941.

Methyl-3-(4-bromophenyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2ak 38

38 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a pale yellow solid. (23 mg, 0.061 mmol, 61%).

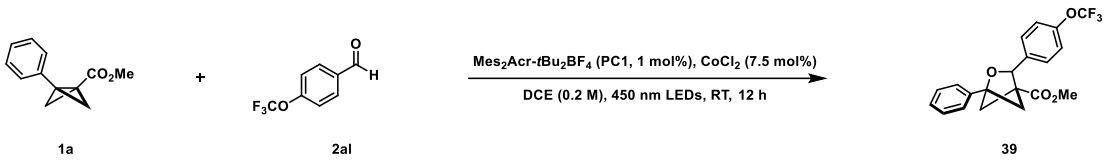
$\mathbf{R_f}$ = 0.6 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 4H), 7.45 – 7.40 (m, 2H), 7.40 – 7.36 (m, 1H), 7.34 (dd, *J* = 8.6, 2.8 Hz, 2H), 5.45 (d, *J* = 2.7 Hz, 1H), 3.74 (s, 3H), 2.62 – 2.52 (m, 2H), 2.26 – 2.19 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 138.6, 136.7, 131.3 (2C), 128.5 (3C), 128.3 (2C), 126.2 (2C), 121.8, 87.1, 79.7, 54.6, 52.0, 51.0, 39.7 ppm.

HRMS (ESI) calculate: $C_{19}H_{18}BrO_3^+$ $(M+H)^+$: 373.0434, found: 373.0428.

Methyl-1-phenyl-3-(4-(trifluoromethoxy)phenyl)-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2al 39

39 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 5% EtOAc in PE to afford the title compound as a pale-yellow oil. (22 mg, 0.058 mmol, 58%).

R*f* = 0.5 (10% EtOAc in PE).

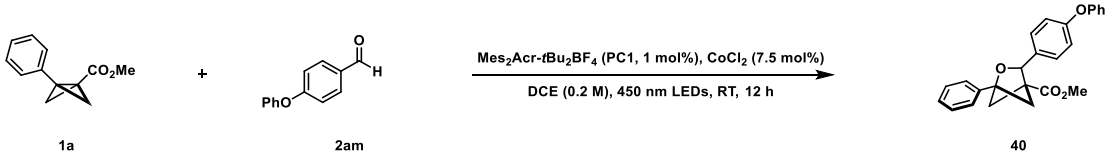
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 4H), 7.46 – 7.34 (m, 3H), 7.20 (d, *J* = 8.3 Hz, 2H), 5.50 (s, 1H), 3.75 (s, 3H), 2.64 – 2.54 (m, 2H), 2.30 – 2.20 (m, 2H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.2, 147.7, 137.1, 135.7, 127.5 (3C), 127.0 (2C), 125.1 (2C), 119.5 (2C), 119.4 (q, *J* = 256.8 Hz), 86.1, 78.5, 53.6, 50.9, 50.0, 38.7 ppm.

^{19}F NMR (471 MHz, $CDCl_3$) δ -57.76 ppm.

HRMS (ESI) calculate: $C_{20}H_{18}F_3O_4^+$ $(M+H)^+$: 379.1152, found: 379.1155.

Methyl-3-(4-phenoxyphenyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2am 40

40 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (23 mg, 0.0609 mmol, 60%).

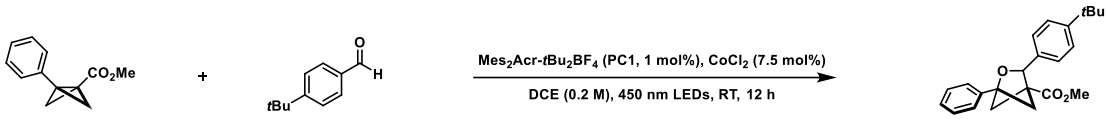
R*f* = 0.5 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.45 – 7.38 (m, 4H), 7.38 – 7.31 (m, 3H), 7.14 – 7.08 (m, 1H), 7.04 – 6.96 (m, 4H), 5.49 (s, 1H), 3.75 (s, 3H), 2.62 – 2.52 (m, 2H), 2.34 – 2.22 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 157.1, 156.9, 136.9, 134.2, 129.8 (2C), 128.5 (2C), 128.4, 128.0 (2C), 126.2 (2C), 123.4, 119.1 (2C), 118.4 (2C), 86.9, 80.0, 54.6, 51.9, 50.9, 39.9 ppm.

HRMS (ESI) calculate: $C_{25}H_{23}O_4^+$ $(M+H)^+$: 387.1591, found: 387.1589.

Methyl-3-(4-(tert-butyl)phenyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2an 41

41 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow solid. (27 mg, 0.077 mmol, 77%).

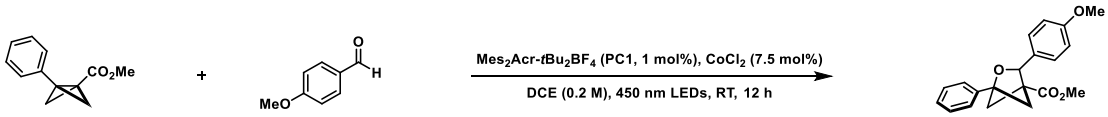
R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.43 – 7.39 (m, 2H), 7.38 – 7.34 (m, 5H), 5.48 (s, 1H), 3.76 (s, 3H), 2.61 – 2.53 (m, 2H), 2.32 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.23 (d, *J* = 8.1 Hz, 1H), 1.32 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 150.5, 137.1, 136.5, 128.4 (2C), 128.3, 126.2 (4C), 125.1 (2C), 86.7, 80.2, 54.5, 51.9, 50.9, 40.1, 34.6, 31.4 (3C) ppm.

HRMS (ESI) calculate: $C_{23}H_{27}O_3^+$ $(M+H)^+$: 351.1955, found: 351.1948.

Methyl-3-(3-methoxyphenyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2ao 42

42 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow solid. (19 mg, 0.063s mmol, 63%).

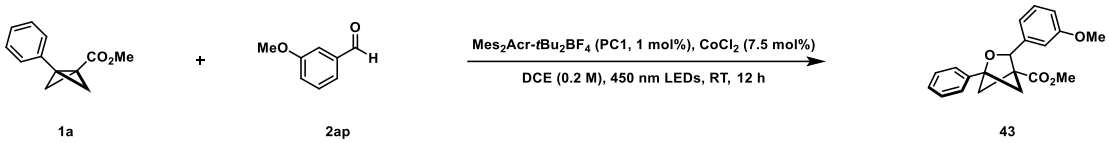
R*f* = 0.5 (10% EtOAc in PE).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.43 – 7.35 (m, 5H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.46 (s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.58 (dd, *J* = 10.1, 7.1 Hz, 1H), 2.53 (d, *J* = 7.0 Hz, 1H), 2.30 (dd, *J* = 10.1, 8.0 Hz, 1H), 2.23 (d, *J* = 8.0 Hz, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.5, 158.1, 136.0, 130.5, 127.4 (2C), 127.3, 126.7 (2C), 125.1 (2C), 112.5 (2C), 85.7, 79.1, 54.2, 53.5, 50.8, 49.8, 38.8 ppm.

HRMS (ESI) calculate: $C_{20}H_{21}O_4^+$ $(M+H)^+$: 325.1434, found: 325.1431.

Methyl-3-(3-methoxyphenyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2ap 43

43 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (20 mg, 0.061 mmol, 61%).

R*f* = 0.5 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.36 – 7.27 (m, 3H), 7.19 – 7.14 (m, 1H), 6.96 – 6.91 (m, 2H), 6.75 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.39 (s, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 2.54 – 2.43 (m, 2H), 2.26 – 2.11 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 159.5, 141.2, 137.0, 129.2, 128.5 (2C), 128.4, 126.2 (2C), 118.7, 113.1, 112.3, 86.9, 80.2, 55.2, 54.6, 51.9, 50.9, 40.0 ppm.

HRMS (ESI) calculate: $C_{20}H_{21}O_4^+$ $(M+H)^+$: 325.1434, found: 325.1431.

Methyl-3-(3,4-dimethoxyphenyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate

1a 2aq 44

44 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 10% EtOAc in PE to afford the title compound as a pale-yellow solid. (22 mg, 0.063 mmol, 63%).

R*f* = 0.3 (10% EtOAc in PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.53 – 7.47 (m, 2H), 7.45 – 7.33 (m, 3H), 7.03 – 6.96 (m, 2H), 6.85 (d, *J* = 8.2 Hz, 1H), 5.46 (s, 1H), 3.87 (d, *J* = 2.6 Hz, 6H), 3.74 (s, 3H), 2.62 – 2.50 (m, 2H), 2.33 – 2.21 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 148.6, 148.5, 137.0, 132.0, 128.5 (2C), 128.4 (2C), 126.2, 118.7, 110.7, 109.7, 86.8, 80.1, 55.9, 55.9, 54.6, 51.9, 50.9, 39.9 ppm.

HRMS (ESI) calculate: $C_{21}H_{23}O_5^+$ $(M+H)^+$: 355.1540, found: 355.1534.

Methyl-1-phenyl-3-(3,4,5-trimethoxyphenyl)-2-oxabicyclo[2.1.1]hexane-4-carboxylate

1a 2ar 45

45 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 10% EtOAc in PE to afford the title compound as a pale-yellow solid. (26 mg, 0.067 mmol, 67%).

R*f* = 0.2 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 2H), 7.45 – 7.35 (m, 3H), 6.68 (s, 2H), 5.45 (s, 1H), 3.84 (s, 9H), 3.75 (s, 3H), 2.63 – 2.51 (m, 2H), 2.33 – 2.22 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 153.0 (2C), 137.3, 136.9, 135.2, 128.5 (2C), 128.5, 126.2 (2C), 103.4 (2C), 86.9, 80.2, 60.9, 56.1 (2C), 54.7, 51.9, 51.1, 39.9 ppm.

HRMS (ESI) calculate: $C_{22}H_{25}O_6^+$ $(M+H)^+$: 385.1646, found: 385.1637.

Methyl-3-(2-fluoro-4-methylphenyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate

1a 2as 46

46 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (21 mg, 0.066 mmol, 66%).

R*f* = 0.5 (10% EtOAc in PE).

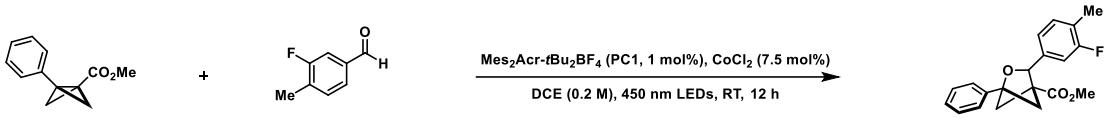
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.32 (m, 7H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 11.5 Hz, 1H), 5.60 (s, 1H), 3.73 (s, 3H), 2.62 – 2.49 (m, 2H), 2.38 – 2.31 (m, 4H), 2.19 (d, *J* = 8.1 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 160.1 (d, *J* = 246.7 Hz), 140.0 (d, *J* = 8.27 Hz), 136.7, 128.6, 128.5 (2C), 128.5, 126.3 (2C), 124.6, 123.4 (d, *J* = 13.8 Hz), 115.5 (d, *J* = 21.2 Hz), 86.4, 76.1, 53.7, 51.9, 49.3, 41.1, 21.1 ppm.

^{19}F NMR (471 MHz, $CDCl_3$) δ -118.31 ppm.

HRMS (ESI) calculate: $C_{20}H_{20}FO_3^+$ $(M+H)^+$: 327.1391, found: 327.1386.

Methyl-3-(3-fluoro-4-methylphenyl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2at 47

47 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a pale-yellow oil. (23 mg, 0.069 mmol, 69%).

R_f = 0.5 (10% EtOAc in PE).

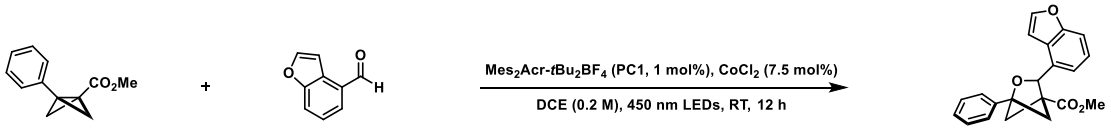
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.32 (m, 6H), 7.24 – 7.17 (m, 1H), 6.97 (app. t, *J* = 8.9 Hz, 1H), 5.44 (s, 1H), 3.74 (s, 3H), 2.61 – 2.49 (m, 2H), 2.30 – 2.22 (m, 5H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 160.9 (d, *J* = 242.6 Hz), 136.9, 134.9, 129.6 (d, *J* = 5.1 Hz), 128.5 (2C), 128.5, 126.2 (2C), 125.4 (d, *J* = 8.4 Hz), 124.6 (d, *J* = 17.5 Hz), 114.7 (d, *J* = 22.5 Hz), 86.9, 79.9, 54.6, 51.9, 51.0, 39.7, 14.8 ppm.

^{19}F NMR (471 MHz, $CDCl_3$) δ -119.16 ppm.

HRMS (ESI) calculate: $C_{20}H_{20}FO_3^+$ $(M+H)^+$: 327.1391, found: 327.1386.

Methyl 3-(benzofuran-4-yl)-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1a 2au 48

48 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 5% EtOAc in PE to afford the title compound as a pale yellow solid. (28 mg, 0.083 mmol, 83%).

R_f = 0.3 (10% EtOAc in PE).

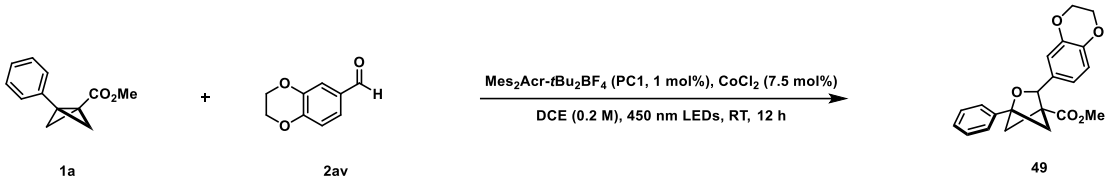
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 1.7 Hz, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.49 – 7.33 (m, 6H), 6.76 (d, *J* = 2.2 Hz, 1H), 5.62 (s, 1H), 3.73 (s, 3H),

2.64 (dd, *J* = 10.2, 7.1 Hz, 1H), 2.56 (d, *J* = 7.0 Hz, 1H), 2.36 (dd, *J* = 10.2, 8.1 Hz, 1H), 2.24 (d, *J* = 8.1 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 154.6, 145.4, 137.0, 134.1, 128.5 (2C), 128.4, 127.3, 126.3 (2C), 122.8, 119.4, 111.0, 106.8, 86.8, 80.6, 54.8, 51.9, 51.0, 39.7 ppm.

HRMS (ESI) calculate: $C_{21}H_{19}O_4^+$ $(M+H)^+$: 335.1278, found: 335.1273.

Methyl-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-phenyl-2-oxabicyclo [2.1.1]hexane-4-carboxylate



1a 2av 49

49 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 5% EtOAc in PE to afford the title compound as a pale yellow solid. (21 mg, 0.063 mmol, 63%).

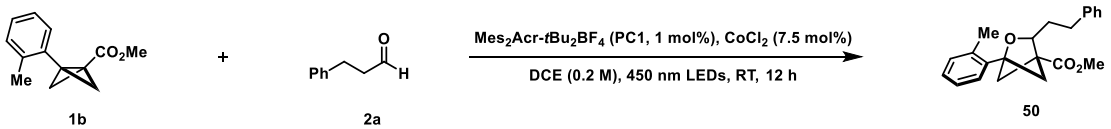
R_f = 0.4 (10% EtOAc in PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H), 7.44 – 7.31 (m, 3H), 6.99 (d, J = 2.1 Hz, 1H), 6.93 – 6.80 (m, 2H), 5.40 (s, 1H), 4.25 (s, 4H), 3.75 (s, 3H), 2.59 – 2.49 (m, 2H), 2.30 (t, J = 9.2 Hz, 1H), 2.21 (d, J = 8.0 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 143.2, 143.1, 137.0, 132.8, 128.4 (2C), 128.3, 126.2 (2C), 119.4, 116.9, 115.6, 86.7, 79.9, 64.4, 54.6, 51.9, 50.8, 39.9 ppm.

HRMS (ESI) calculate: $C_{21}H_{21}O_5^+$ $(M+H)^+$: 353.1384, found: 353.1387.

Methyl-3-phenethyl-1-(o-tolyl)-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1b 2a 50

50 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (21 mg, 0.065 mmol, 65%).

R_f = 0.6 (10% EtOAc in PE).

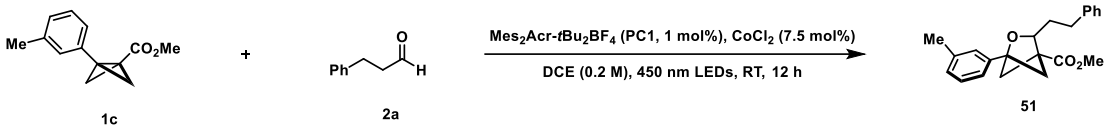
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (app. t, J = 7.5 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 3H), 7.22 – 7.16 (m, 4H), 4.33 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.75 (s, 3H), 2.97 – 2.89 (m, 1H),

2.75 – 2.66 (m, 1H), 2.56 – 2.48 (m, 5H), 2.43 (d, *J* = 6.6 Hz, 1H), 2.28 (d, *J* = 7.3 Hz, 1H), 2.09 – 2.00 (m, 1H), 1.95 – 1.84 (m, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 142.0, 137.9, 134.5, 131.1, 128.9, 128.5 (2C), 128.4 (2C), 127.6, 125.9, 125.7, 87.3, 79.8, 52.2, 51.9, 49.1, 41.3, 34.9, 32.2, 20.1 ppm.

HRMS (ESI) calculate: $C_{22}H_{25}O_3^+$ $(M+H)^+$: 337.1798, found: 337.1794.

Methyl-3-phenethyl-1-(o-tolyl)-2-oxabicyclo[2.1.1]hexane-4-carboxylate



51 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (24 mg, 0.072 mmol, 72%).

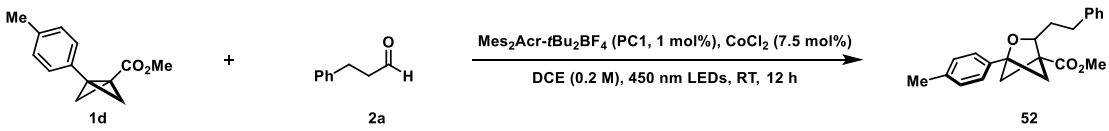
R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.24 (dd, *J* = 8.2, 1.6 Hz, 3H), 7.21 – 7.17 (m, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 4.33 (dd, *J* = 9.5, 3.6 Hz, 1H), 3.74 (s, 3H), 2.98 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.42 – 2.36 (m, 4H), 2.36 – 2.28 (m, 2H), 2.26 – 2.20 (m, 1H), 2.07 – 2.00 (m, 1H), 1.92 – 1.84 (m, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 142.0, 138.1, 137.1, 129.0, 128.5 (2C), 128.4 (2C), 128.3, 126.7, 125.8, 123.1, 86.5, 79.6, 52.6, 51.9, 49.9, 41.9, 34.8, 32.2, 21.4 ppm.

HRMS (ESI) calculate: $C_{22}H_{25}O_3^+$ $(M+H)^+$: 337.1798, found: 337.1792.

Methyl-3-phenethyl-1-(o-tolyl)-2-oxabicyclo[2.1.1]hexane-4-carboxylate



52 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (26 mg, 0.078 mmol, 78%).

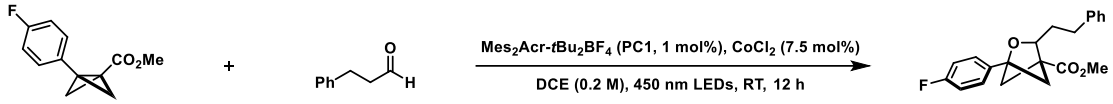
R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 11.0, 7.6 Hz, 4H), 7.27 – 7.23 (m, 2H), 7.23 – 7.17 (m, 3H), 4.33 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.75 (s, 3H), 2.99 – 2.90 (m, 1H), 2.78 – 2.67 (m, 1H), 2.42 – 2.31 (m, 5H), 2.30 (d, *J* = 7.5 Hz, 1H), 2.27 – 2.21 (m, 1H), 2.09 – 1.99 (m, 1H), 1.92 – 1.84 (m, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 142.0, 138.1, 134.3, 129.0 (2C), 128.5 (2C), 128.4 (2C), 126.0 (2C), 125.9, 86.4, 79.5, 52.6, 51.9, 49.9, 41.9, 34.9, 32.2, 21.3 ppm.

HRMS (ESI) calculate: $C_{22}H_{25}O_3^+$ $(M+H)^+$: 337.1798, found: 337.1795.

Methyl-1-(4-fluorophenyl)-3-phenethyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1e 2a 53

53 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (14 mg, 0.040 mmol, 40%).

R_f = 0.6 (10% EtOAc in PE).

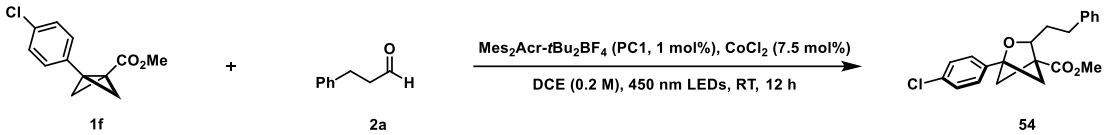
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.31 – 7.27 (m, 2H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.22 – 7.17 (m, 1H), 7.09 – 7.02 (m, 2H), 4.32 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.74 (s, 3H), 2.97 – 2.89 (m, 1H), 2.76 – 2.68 (m, 1H), 2.39 (dd, *J* = 7.0, 1.7 Hz, 1H), 2.35 – 2.28 (m, 2H), 2.26 – 2.20 (m, 1H), 2.05 – 2.00 (m, 1H), 1.91 – 1.81 (m, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 162.6 (d, *J* = 246.9 Hz), 141.9, 133.1 (d, *J* = 3.4 Hz), 128.5 (2C), 128.4 (2C), 127.9 (d, *J* = 8.0 Hz, 2C), 125.9, 115.3 (d, *J* = 21.3 Hz, 2C), 85.8, 79.6, 52.6, 51.9, 49.9, 42.0, 34.7, 32.1 ppm.

^{19}F NMR (471 MHz, $CDCl_3$) δ -113.62 ppm.

HRMS (ESI) calculate: $C_{21}H_{22}FO_3^+$ $(M+H)^+$: 341.1547, found: 341.1544.

Methyl-1-(4-chlorophenyl)-3-phenethyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



54 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (30 mg, 0.084 mmol, 84%).

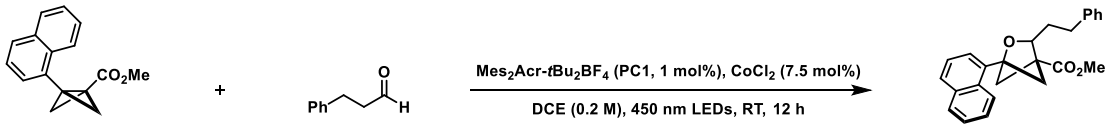
R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (s, 4H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.23 – 7.18 (m, 1H), 4.33 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.75 (s, 3H), 2.98 – 2.90 (m, 1H), 2.78 – 2.70 (m, 1H), 2.41 (d, *J* = 6.9 Hz, 1H), 2.32 (dd, *J* = 9.9, 7.2 Hz, 2H), 2.23 (dd, *J* = 10.3, 7.6 Hz, 1H), 2.10 – 2.00 (m, 1H), 1.93 – 1.83 (m, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 141.8, 135.8, 134.1, 128.6 (2C), 128.5 (2C), 128.4 (2C), 127.6 (2C), 125.9, 85.8, 79.6, 52.6, 52.0, 50.0, 42.1, 34.7, 32.2 ppm.

HRMS (ESI) calculate: $C_{21}H_{22}ClO_3^+$ $(M+H)^+$: 357.1252, found: 357.1254.

Methyl-1-(naphthalen-1-yl)-3-phenethyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



55 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (20 mg, 0.054 mmol, 54%).

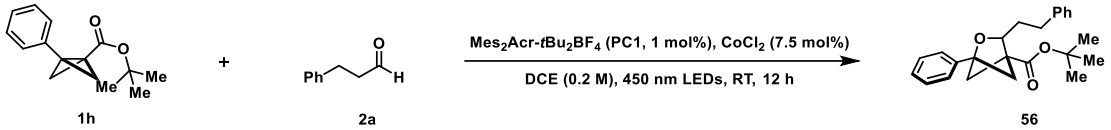
R*f* = 0.6 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.3 Hz, 1H), 7.85 (dd, *J* = 13.5, 8.1 Hz, 2H), 7.57 – 7.48 (m, 2H), 7.46 – 7.41 (m, 1H), 7.37 (d, *J* = 7.0 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.26 (s, 2H), 7.23 – 7.18 (m, 1H), 4.48 (dd, *J* = 9.4, 3.6 Hz, 1H), 3.77 (s, 3H), 3.02 – 2.93 (m, 1H), 2.79 – 2.71 (m, 2H), 2.67 (t, *J* = 8.9 Hz, 1H), 2.53 (d, *J* = 6.9 Hz, 1H), 2.41 (d, *J* = 7.6 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.06 – 1.98 (m, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 142.1, 134.1, 132.9, 131.8, 129.8, 128.7 (2C), 128.6 (2C), 128.6 (2C), 126.3, 126.0, 126.0, 125.7, 125.1, 87.6, 80.4, 52.4, 52.1, 50.0, 42.2, 35.2, 32.3 ppm.

HRMS (ESI) calculate: $C_{25}H_{25}O_3^+$ $(M+H)^+$: 373.1798, found: 373.1800.

***Tert*-Butyl-3-phenethyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate**



1h 2a 56

56 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (31 mg, 0.085 mmol, 85%).

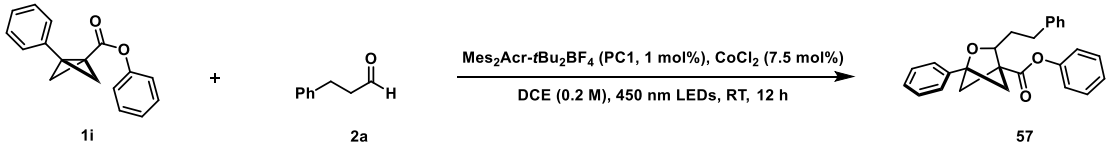
R_f = 0.5 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 6.9 Hz, 2H), 7.39 – 7.35 (m, 2H), 7.33 – 7.27 (m, 3H), 7.26 – 7.23 (m, 2H), 7.21 – 7.17 (m, 1H), 4.28 (dd, *J* = 9.5, 3.5 Hz, 1H), 2.99 – 2.91 (m, 1H), 2.79 – 2.71 (m, 1H), 2.36 (d, *J* = 6.9 Hz, 1H), 2.29 (dd, *J* = 10.1, 7.0 Hz, 1H), 2.25 (d, *J* = 7.6 Hz, 1H), 2.19 (dd, *J* = 10.1, 7.6 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.92 – 1.83 (m, 1H), 1.47 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 142.2, 137.6, 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.2, 126.2 (2C), 125.9, 86.2, 81.4, 79.6, 53.8, 50.0, 41.8, 34.9, 32.3, 28.2 (3C) ppm.

HRMS (ESI) calculate: $C_{24}H_{29}O_3^+$ $(M+H)^+$: 365.2111, found: 365.2113.

Phenyl-3-phenethyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



1i 2a 57

57 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (26 mg, 0.068 mmol, 68%).

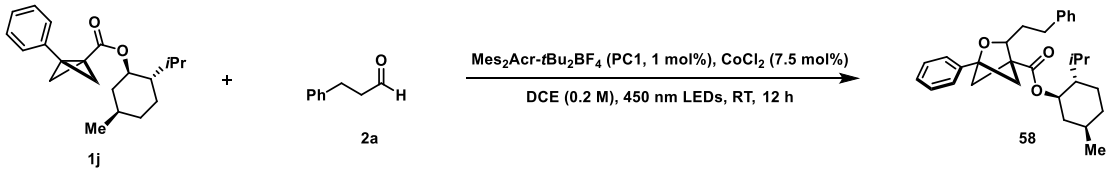
R_f = 0.5 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.2 Hz, 2H), 7.43 – 7.37 (m, 4H), 7.37 – 7.32 (m, 1H), 7.31 – 7.22 (m, 5H), 7.22 – 7.17 (m, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 4.48 (dd, *J* = 9.5, 3.6 Hz, 1H), 3.06 – 2.95 (m, 1H), 2.86 – 2.75 (m, 1H), 2.59 (d, *J* = 7.0 Hz, 1H), 2.49 (dd, *J* = 10.7, 7.2 Hz, 2H), 2.38 (dd, *J* = 10.3, 7.7 Hz, 1H), 2.24 – 2.12 (m, 1H), 2.04 – 1.93 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 150.4, 141.9, 137.1, 129.7 (2C), 128.6 (2C), 128.6 (3C), 128.5, 126.3 (2C), 126.2 (2C), 126.0, 121.5 (2C), 86.7, 79.7, 52.9, 50.3, 42.3, 35.0, 32.3 ppm.

HRMS (ESI) calculate: $C_{26}H_{25}O_3^+$ $(M+H)^+$: 385.1798, found: 385.1796.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl3-phenethyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



58 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford the title compound as a yellow oil. (41 mg, 0.089 mmol, 89%).

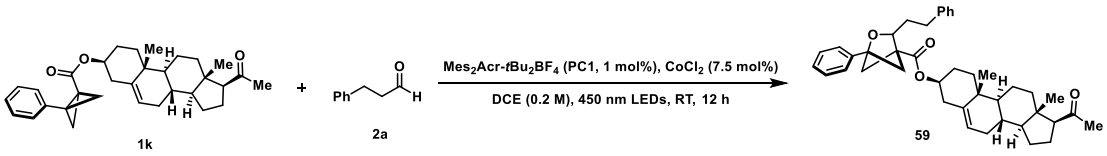
R_f = 0.8 (10% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.5, 2.9 Hz, 2H), 7.41 – 7.35 (m, 2H), 7.35 – 7.27 (m, 3H), 7.24 (dd, *J* = 7.4, 2.5 Hz, 2H), 7.20 (app. t, *J* = 7.3 Hz, 1H), 4.79 – 4.71 (m, 1H), 4.33 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.01 – 2.92 (m, 1H), 2.82 – 2.70 (m, 1H), 2.41 – 2.37 (m, 1H), 2.37 – 2.28 (m, 2H), 2.27 – 2.22 (m, 1H), 2.08 – 1.98 (m, 2H), 1.93 – 1.79 (m, 2H), 1.74 – 1.66 (m, 2H), 1.56 – 1.47 (m, 1H), 1.45 – 1.37 (m, 1H), 1.12 – 1.04 (m, 1H), 1.03 – 0.95 (m, 1H), 0.94 – 0.86 (m, 7H), 0.76 (dd, *J* = 7.0, 3.4 Hz, 3H). ppm.

^{13}C NMR (126 MHz, $CDCl_3$) **Mixer of isomer 1 and isomer 2** δ 170.2, 170.1, 142.1, 137.5, 128.6, 128.6, 128.5, 128.3, 126.3, 126.2, 125.9, 86.5, 86.5, 79.7, 79.6, 74.9, 53.2, 50.1, 50.0, 47.1, 41.9, 41.8, 41.0, 35.0, 34.8, 34.3, 32.4, 32.3, 31.5, 26.7, 26.5, 23.7, 23.5, 22.2, 22.1, 20.9, 20.8, 16.6, 16.3 ppm.

HRMS (ESI) calculate: $C_{30}H_{39}O_3^+$ $(M+H)^+$: 447.2894, found: 447.2896.

(3*S*,8*S*,10*R*,13*S*,14*S*,17*S*)-17-Acetyl-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 3-phenethyl-1-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate



59 was synthesized according to the general procedure C and purified by flash column chromatography (silica gel), eluting with 6% EtOAc in PE to afford the title compound as a yellow oil. (45 mg, 0.076 mmol, 76%).

R*f* = 0.2 (10% EtOAc in PE).

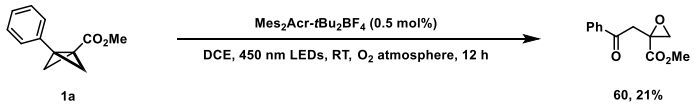
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.40 – 7.35 (m, 2H), 7.34 – 7.27 (m, 3H), 7.25 (d, *J* = 6.7 Hz, 2H), 7.21 – 7.17 (m, 1H), 5.39 (d, *J* = 4.9 Hz, 1H), 4.73 – 4.65 (m, 1H), 4.32 (dd, *J* = 9.4, 3.5 Hz, 1H), 2.95 (s, 1H), 2.79 – 2.70 (m, 1H), 2.57 – 2.51 (m, 1H), 2.40 (d, *J* = 6.9 Hz, 1H), 2.35 – 2.28 (m, 4H), 2.23 (dd, *J* = 10.0, 7.6 Hz, 1H), 2.18 (dd, *J* = 11.1, 1.9 Hz, 1H), 2.13 (s, 3H), 2.08 – 1.98 (m, 3H), 1.93 – 1.84 (m, 3H), 1.72 – 1.60 (m, 4H), 1.54 – 1.44 (m, 3H), 1.28 – 1.13 (m, 4H), 1.03 (s, 4H), 0.64 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.7, 170.0, 142.1, 139.5, 137.4, 128.6 (2C), 128.5 (2C), 128.5 (2C), 128.3, 126.2 (2C), 126.0, 122.7, 86.4, 79.6, 74.4, 63.8, 56.9, 53.0, 50.1, 50.0, 44.1, 41.9, 38.9, 38.1, 37.1, 36.7, 34.8, 32.3, 31.9, 31.9, 31.7, 27.8, 24.6, 23.0, 21.2, 19.5, 13.3 ppm.

HRMS (ESI) calculate: $C_{41}H_{51}O_4^+$ $(M+H)^+$: 607.3782, found: 607.3782.

4 Mechanistic Studies

4.1 Radical cation trapping experiment



1a 60, 21%

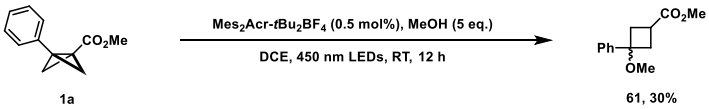
An oven-dried two-dram vials equipped with PTFE-coated stir bar and Teflon® septum were used. $Mes_2Acr\text{-}tBu_2BF_4$ (**PC1**, 0.6 mg, 0.005 mmol) and **1a** (38 mg, 0.2 mmol) were added into the vial and was dissolved in DCE (0.5 mL) under oxygen atmosphere. The vial was set to stir (500 rpm) and irradiated with a 30 W 450 nm blue LED lamp (approximate 3 cm away, with cooling fan to keep the reaction at room temperature). After 12 hours, the reaction mixture was transferred to a 100mL round-bottom flask and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 10% EtOAc in PE to afford **60** as a pale-yellow oil (9 mg, 0.042 mmol, 21%)

$\mathbf{R}_f$ = 0.6 (20% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.92 (m, 2H), 7.63 – 7.56 (m, 1H), 7.48 (app. t, *J* = 7.8 Hz, 2H), 3.76 (s, 3H), 3.61 – 3.51 (m, 2H), 3.29 (d, *J* = 5.6 Hz, 1H), 2.92 (d, *J* = 5.6 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.9, 170.3, 136.2, 133.8, 128.9 (2C), 128.2 (2C), 54.0, 53.0, 51.7, 41.7 ppm.

HRMS (ESI) calculate: $C_{12}H_{13}O_4^+$ $(M+H)^+$: 221.0808, found: 221.0807.



1a 61, 30%

An oven-dried two-dram vials equipped with PTFE-coated stir bar and Teflon® septum were used. $Mes_2Acr\text{-}tBu_2BF_4$ (**PC1**, 0.6 mg, 0.005 mmol), **1a** (38 mg, 0.2 mmol) and MeOH (41 μL, 0.5 mmol) were added into the vial and was dissolved in DCE (1 mL). The vial was set to stir (500 rpm) and irradiated with a 30 W 450 nm blue LED lamp (approximate 3 cm away, with cooling fan to keep the reaction at room temperature). After 12 hours, the reaction mixture was transferred to a 100mL round-bottom flask and concentrated in vacuo. The crude reaction mixture

was purified by flash column chromatography (silica gel), eluting with 3% EtOAc in PE to afford **61** as a pale-yellow oil (13 mg, 0.030 mmol, 30%)

R$_f$ = 0.6 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.32 – 7.26 (m, 3H), 3.66 (s, 3H), 3.41 – 3.33 (m, 1H), 2.98 (s, 3H), 2.65 (d, *J* = 8.8 Hz, 5H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 142.5, 128.4 (2C), 127.6, 126.2 (2C), 80.0, 51.9, 51.1, 35.1 (2C), 32.2 ppm.

HRMS (ESI) calculate: $C_{13}H_{17}O_3^+$ $(M+H)^+$: 221.1172, found: 221.1173.

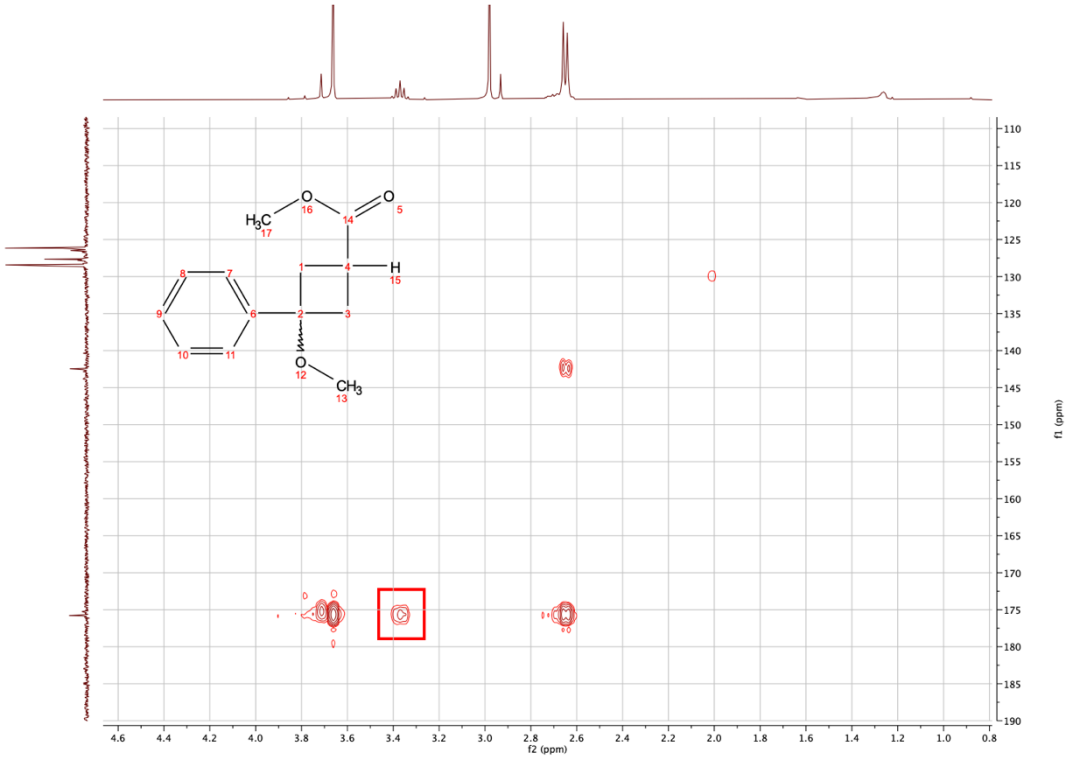


Figure S6. HMBC spectrum of compound **61**

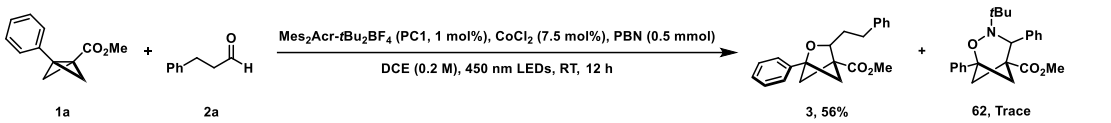
Note: the highlighted correlation (in red square) on the HMBC spectra belongs to H_{15} and C_{14}, and no correlations between H_{15} and any aromatic carbons could be observed. As such, the methoxy group should be adjacent to the benzyl group therefore suggesting the resulted trapping compound by MeOH is **61**.

4.2 Radical trapping experiment

According to general procedure C, depends on specific conditions, Mes_2Acr-*t*Bu_2BF_4 (**PC1**, 0.6 mg, 0.001 mmol), $CoCl_2$ (1 mg, 0.0075 mmol), **1a** (38 mg, 0.2

mmol), **2a** (12 μL, 0.1 mmol), PBN (89 mg, 0.5 mmol) or TEMPO (78 mg, 0.5 mmol) were selectively used.

Condition A: $Mes_2Acr\text{-}tBu_2BF_4$ (**PC1**, 0.6 mg, 0.001 mmol), $CoCl_2$ (1 mg, 0.0075 mmol), **1a** (38 mg, 0.2 mmol), **2a** (12 μL, 0.1 mmol), PBN (89 mg, 0.5 mmol) under reaction conditions in general procedure C.



1a 2a 3, 56% 62, Trace

Chemical Formula: $C_{23}H_{27}NO_3$
Calculated $[M+H]^+$: 366.2064
Found: 366.2064

62 was detected by HRMS as illustrated below. **3** was purified by flash column chromatography (silica gel), eluting with 3% EtOAc in PE to afford **3** as a white solid (18 mg, 0.056 mmol, 56%). All analytical data match to the previous reported **3**.

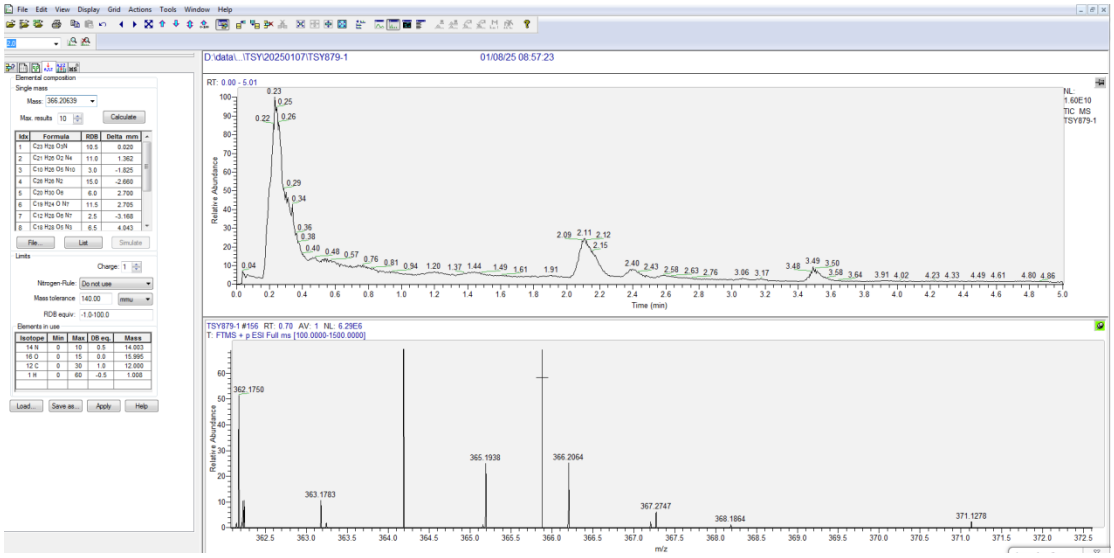
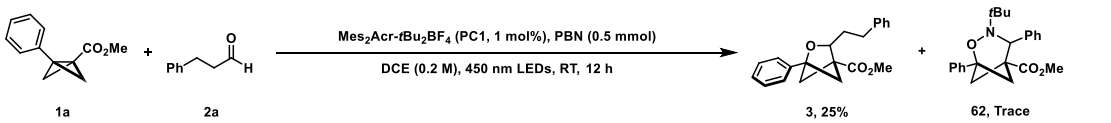


Figure S7. HRMS spectrum and formula prediction of compound **62**

Condition B: $Mes_2Acr\text{-}tBu_2BF_4$ (**PC1**, 0.6 mg, 0.001 mmol), **1a** (38 mg, 0.2 mmol), **2a** (12 μL, 0.1 mmol), PBN (89 mg, 0.5 mmol) under reaction conditions in general procedure C.



1a 2a 3, 25% 62, Trace

Chemical Formula: $C_{23}H_{27}NO_3$
Calculated $[M+H]^+$: 366.2064
Found: 366.2064

62 was detected by HRMS as illustrated below. **3** was purified by flash column chromatography (silica gel), eluting with 3% EtOAc in PE to afford **3** as a white solid (8 mg, 0.025 mmol, 25%). All analytical data match to the previous reported **3**.

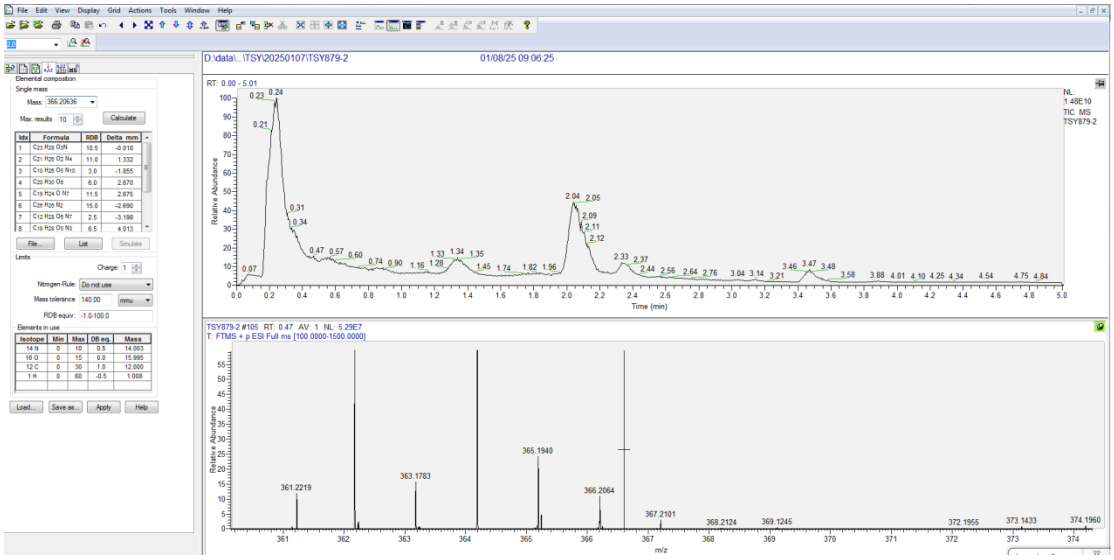
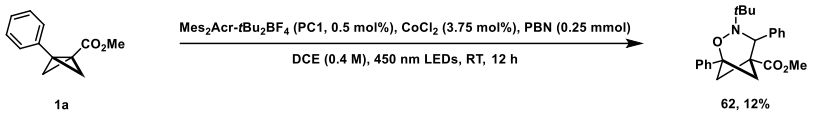


Figure S8. HRMS spectrum and formula prediction of compound **62**

Condition C: Mes_2Acr-*t*Bu_2BF_4 (**PC1**, 0.6 mg, 0.0005 mmol), $CoCl_2$ (1 mg, 0.00375 mmol), **1a** (38 mg, 0.2 mmol), PBN (89 mg, 0.25 mmol) under reaction conditions in general procedure C.



1a

62, 12%

62 was purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford **63** as a pale-yellow oil (9 mg, 0.024 mmol, 12%).

R*f* = 0.7 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 2H), 7.09 – 6.91 (m, 6H), 6.65 – 6.58 (m, 2H), 4.43 (s, 1H), 3.77 (s, 3H), 3.34 – 3.27 (m, 1H), 2.60 (dd, *J* = 9.3, 3.1 Hz, 1H), 2.35 – 2.26 (m, 2H), 1.08 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 144.6, 142.2, 127.9, 127.6 (2C), 127.4 (2C), 126.8, 126.2 (2C), 126.1 (2C), 78.6, 72.6, 60.5, 52.4, 48.0, 45.0, 35.5, 26.8 (3C) ppm.

HRMS (ESI) calculate: $C_{23}H_{27}NO_3^+$ $(M+H)^+$: 366.2064, found: 366.2064.

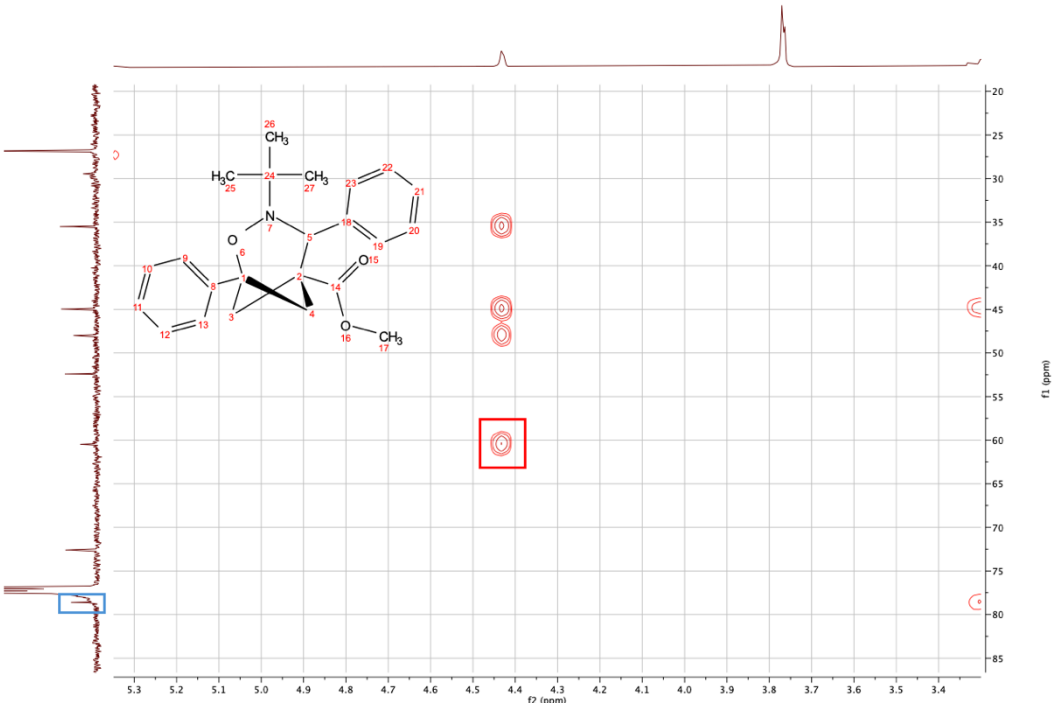
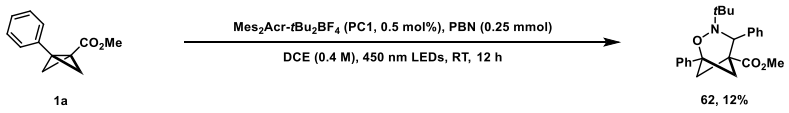


Figure S9. HMBC spectrum of compound **62**

Note: the highlighted correlation (in red square) on the HMBC spectra belongs to H_5 and C_2, and no correlations between H_5 and C_1 (in blue square) could be observed. As such, the oxygen was linked to C_1 therefore suggesting the resulted trapping compound by PBN is **62**.

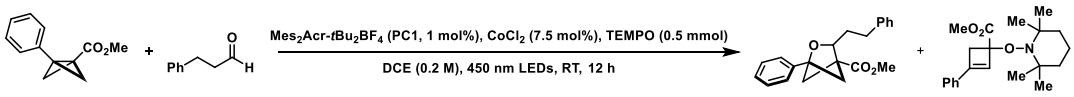
Condition D: Mes_2Acr-tBu$_2BF_4$ (**PC1**, 0.6 mg, 0.0005 mmol), **1a** (38 mg, 0.2 mmol), PBN (87 mg, 0.25 mmol) under reaction conditions in general procedure C.



1a 62, 12%

62 under condition D was purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to afford **62** as a pale-yellow oil (9 mg, 0.024 mmol, 12%). All analytical data match to the previous reported **62**.

Condition E: Mes_2Acr-tBu$_2BF_4$ (**PC1**, 0.6 mg, 0.001 mmol), $CoCl_2$ (1 mg, 0.0075 mmol), **1a** (38 mg, 0.2 mmol), **2a** (12 μL, 0.1 mmol), TEMPO (78 mg, 0.5 mmol) under reaction conditions in general procedure C.



1a 2a 3, ND

Possible structure of **65**
Chemical Formula: $C_{21}H_{29}NO_3$
Calculated $[M+H]^+$: 344.2220
Found: 344.2220

No **3** could be observed but **63** on HRMS was detected as below.

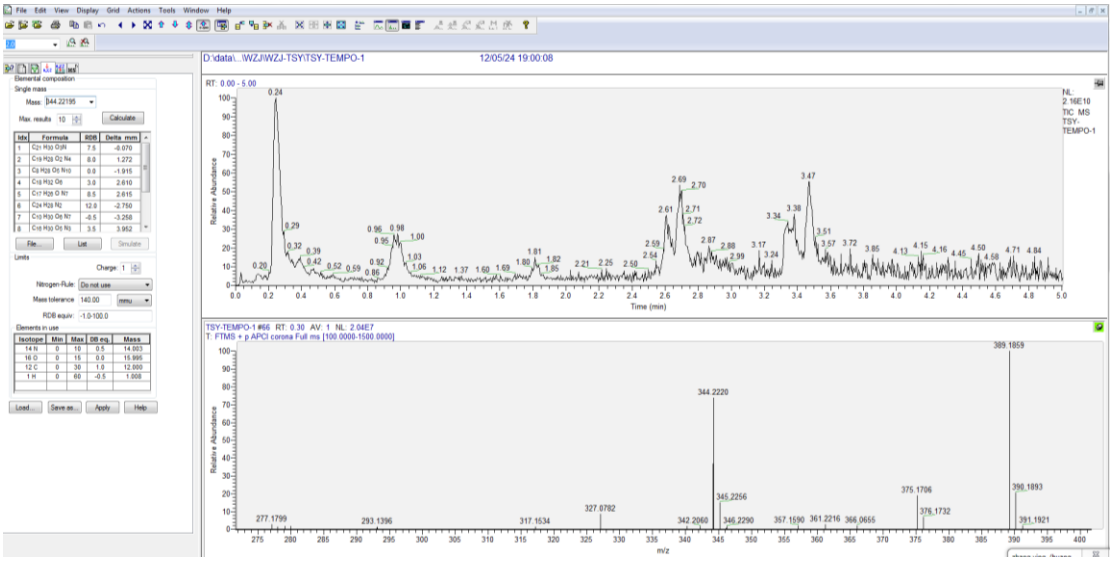


Figure S10. HRMS spectrum and formula prediction of compound **63**

4.3 Ketyl Radical-trapping Experiment

According to general procedure C, Mes_2Acr-*t*Bu_2BF_4 (**PC1**, 0.6 mg, 0.001 mmol), $CoCl_2$ (1 mg, 0.0075 mmol), **1a** (38 mg, 0.2 mmol) and **(±)-trans 2x** (15 mg, 0.1 mmol) were used.

1a (±)-trans 2x 66

64 was purified by flash column chromatography (silica gel), eluting with 3% EtOAc in PE to afford **64** as a pale-yellow oil (21 mg, 0.063 mmol, 63%, 1.2:1 dr).

R*f* = 0.5 (10% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) **Mixer of isomer 1 and isomer 2** δ 7.45 – 7.28 (m, 10H), 7.26 – 7.23 (m, 4H), 7.18 – 7.13 (m, 2H), 7.13 – 7.08 (m, 2H), 7.08 – 7.02 (m, 2H), 3.84 – 3.80 (m, 2H), 3.79 (s, 3H), 3.62 (s, 3H), 2.43 – 2.32 (m, 8H), 1.33 – 1.28 (m, 2H), 1.19 (dd, *J* = 8.8, 5.3 Hz, 1H), 1.17 – 1.13 (m, 1H), 1.03 – 0.95 (m, 2H) ppm. **Isomer 1** δ 2.13 – 2.07 (m, 1H), 1.03 – 0.95 (m, 2H) ppm. **Isomer 2** δ 1.98 – 1.93 (m, 1H), 1.19 (dd, *J* = 8.8, 5.3 Hz, 1H), 1.17 – 1.13 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) **Mixer of isomer 1 and isomer 2** δ 171.1, 170.9, 142.4, 142.0, 137.0, 136.9, 128.5, 128.4, 128.4, 126.3, 126.1, 125.9, 125.8, 86.6, 86.4, 84.6, 84.5, 53.4, 53.3, 52.0, 49.9, 49.7, 42.1, 41.8, 24.7, 24.6, 21.4, 20.9, 13.7, 12.7 ppm.

HRMS (ESI) calculate: $C_{22}H_{23}O_3^+$ $(M+H)^+$: 335.1642, found: 335.1639.

4.4 UV-Vis Absorption Spectra Analysis

UV-visible absorption spectra were carried out on the Agilent Cary 5000 UV-Vis-NIR spectrophotometer, equipped with a temperature control unit at 25 °C. All samples were measured in cuvettes (volume: 2.0 mL, path length: 10 mm) equipped with a PTFE stopper. The spectra were acquired from 350 to 700 nm using 1.0 nm steps. All measurements were performed in 2 mL of dry DCE with consistent concentration of 2.5 mM.

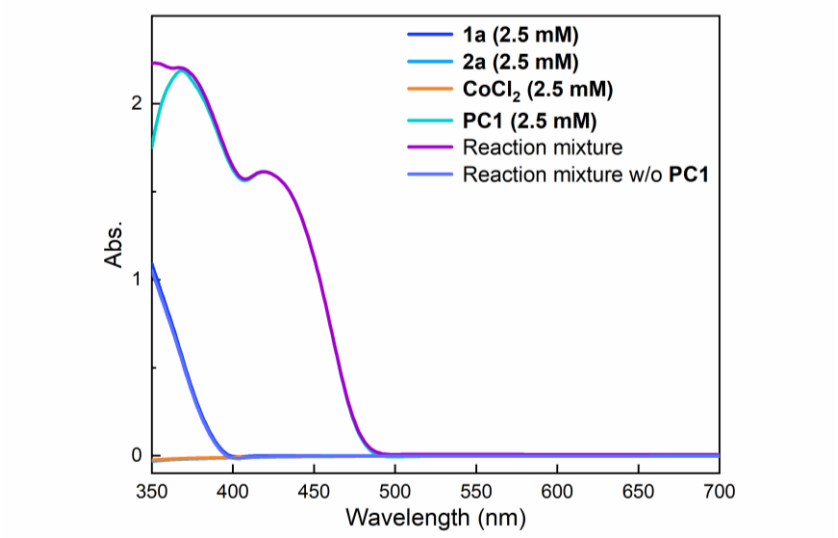


Figure S11. UV-Vis absorption spectra

4.5 Stern-Volmer Luminescence Quenching Analysis

Emission intensities were recorded using a Fluorolog-3 luminescence spectrometer. Solutions of different components were prepared and introduced to a 10 mm path length quartz cuvette in glovebox. Excitation bandwidth = 1 nm, data interval = 0.2 nm, scan speed = 500 nm/min, dwell time = 0.03 s. All the solution was excited at 400 nm and the emission intensity was collected at 510 nm. The solution of **PC1** (0.5 mM, 20 mL), **1a** (50 mM, 20 mL), **2a** (50 mM, 20 mL) were prepared in glovebox using a mixture of dry DCE. I_0 is the luminescence intensity without quenching substrates, and I is the intensity in the presence of quenching substrates. All intensity values were normalized by subtracting the basal intensity of blank DCE solvent.

For Experiment 1: Constant photocatalyst; Varied concentration of **1a**

Add 100 μL of **PC1** solution and 0 μL, 100 μL, 300 μL, 500 μL, 700 μL and 900 μL **1a** solution respectively in the quartz cuvette and then diluted the solution to 2 mL by using the mixture of dry DCE.

Comment: **1a** could quench the excited photocatalyst.

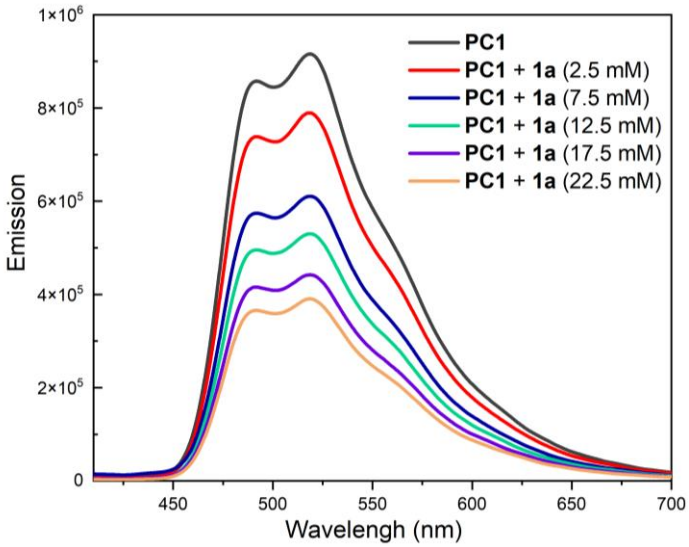


Figure S12. Emission of **PC1** with varying **1a** quencher concentrations

For Experiment 2: Constant photocatalyst; Varied concentration of **2a**

Add 100 μL of **PC1** solution and 0 μL, 100 μL, 300 μL, 500 μL, 700 μL and 900 μL **2a** solution respectively in the quartz cuvette and then diluted the solution to 2 mL by using the mixture of dry DCE.

Comment: **2a** could not quench the excited photocatalyst.

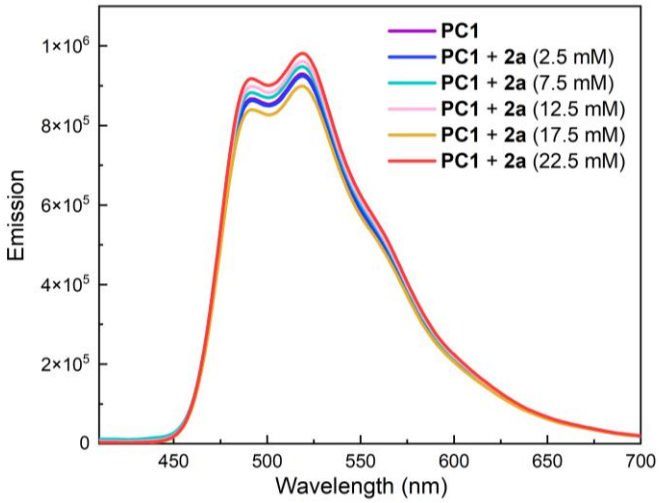


Figure S13. Emission of **PC1** with varying **2a** quencher concentrations

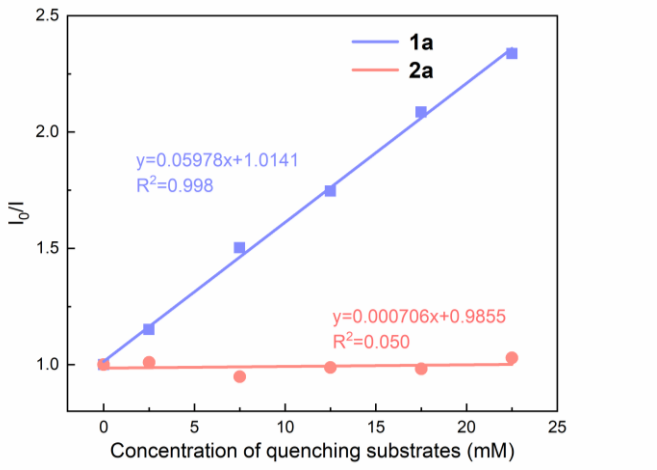


Figure S14. Stern-Volmer plots of **1a** and **2a**

4.6 Quantum Yield Experiment

According to our previous literature procedure, the photo flux of the 30 W 450 nm LED lamp was first determined by standard ferrioxalate actinometry.[7]

Preparation of 0.15 M solution of ferrioxalate (0.15 M):

Potassium ferrioxalate trihydrate (1474 mg) was dissolved in H_2SO_4 aq. (20 mL, 0.2M).

Preparation of buffered solution (0.15 M):

1,10-phenanthroline (541 mg, 3.0 mmol), NaOAc (1.23 g, 15.0 mmol) were dissolved in H_2SO_4 aq. (20 mL, 0.2M). To two 8 mL vials added ferrioxalate solution (1 mL) respectively and irradiated one of the vials with an LED lamp (30W, 450 nm) while the other kept in dark. After 30 s, buffered solution (3 mL) and H_2SO_4 aq. (2 mL, 0.2M) were added immediately to both vials. The resulting mixtures were kept in dark for another 1 h to allow the formed ferrous ions completely coordinate to the phenanthroline. Then, 25 μL of each resulting mixture was transferred to a cuvette (l = 10 mm) and diluted with H_2SO_4 aq. (2 mL, 0.2 M). The absorbance at 510 nm was measured by UV-vis spectrometry. The photo flux was measured by following equation:

$$\text{mol } Fe^{2+} = \frac{V \times \Delta A\ (510\ nm)}{l \times \varepsilon}$$

Where V is the total volume (0.486 L) of the solution after addition of phenanthroline, ΔA = 0.1895 is the difference in absorbance at 510 nm between

the irradiated and non-irradiated solutions, l is the path length (1.0 cm), and ε is the molar absorptivity at 510 nm (11,100 L·mol^{-1}·cm^{-1}). The photon flux can be calculated as following equation:

$$\text{photon flux} = \frac{\text{mol Fe}^{2+}}{\emptyset \times t \times f}$$

Where Φ is the quantum yield for the ferrioxalate actinometer (approximate 0.845 for a 0.15 M solution at λ = 450 nm), t is the time (30 s), and f is the fraction of light absorbed at λ = 450 nm by the ferrioxalate actinometer. This value is calculated using the following equation where A (450 nm) is the absorption of the ferrioxalate solution at 450 nm. An absorption spectrum gave an A (450 nm) = 0.1343, indicating that the fraction of absorbed light (f) = 0.26601.

$$f = 1 - 10^{-A\,(450\,nm)} = 1 - 10^{-0.1343} = 0.2660$$

The photon flux was calculated to be 1.230 × 10^{-6} einstein·s^{-1}.

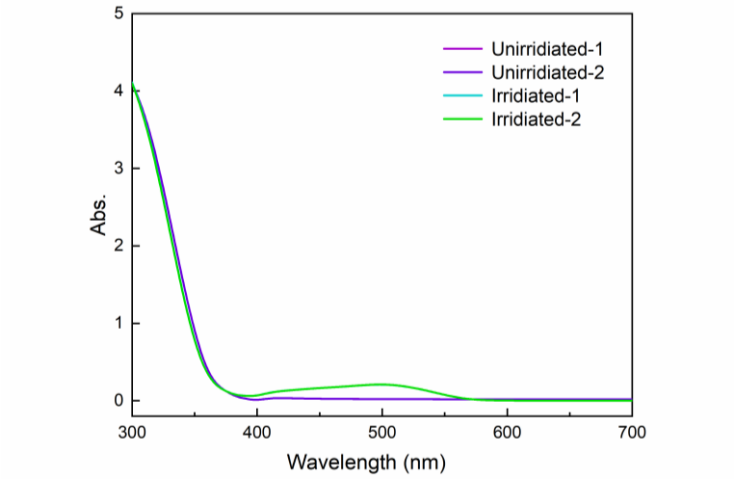


Figure S15. UV-Vis spectrum of quantum yield

Determination of quantum yield

An oven-dried two-dram vials equipped with PTFE-coated stir bar and Teflon® septum were used. To the vial was added **1a** (38 mg, 0.2 mmol), **2a** (13 μL, 0.1 mmol), $CoCl_2$ (1.0 mg, 0.075 mmol), $Mes_2Acr\text{-}tBu_2BF_4$ (**PC1**, 0.7 mg, 0.001 mmol) and were dissolved by DCE (0.5 mL). The mixture was set to stir (500 rpm) and

irradiated with a 30 W 450 nm blue LED lamp (approximate 3 cm away, with cooling fan to keep the reaction at room temperature). After 3 minutes, the reaction mixture was transferred to a 100 mL round-bottom flask and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 2% EtOAc in PE to give the desired product as a pale-yellow oil (10 mg, 0.033 mmol, 33%) and the quantum yield is calculated by the following equation:

$$\emptyset = \frac{\text{mol product}}{flux \times t \times f}$$

where flux is the photon flux determined by ferrioxalate actinometry (1.230×10^{-6} einsteins. s^{-1}), t is the time (180 s), and f is the fraction of light absorbed by the reaction mixture at 450 nm. This value is calculated using eq. 3 where A (450nm) is the absorption of the ferrioxalate solution at 450 nm. f is the fraction of light absorbed at λ = 450 nm (0.935, A= 1.18591).

$$\emptyset = \frac{\text{mol product}}{flux \times t \times f} = \frac{3.3 \times 10^{-5}\ mol}{1.230 \times 10^{-6}\ \text{einstein} \cdot 10^{-1} \times 600\ \text{s} \times 0.935} = 0.1594$$

5 Gram-scale experiment

According to the General procedure C, **1a** (1.88 g, 10 mmol) and **2a** (0.66 mL, 5 mmol) were used and reacted in 200 mL Schlenk tubes instead of two-dram vials. Upon completion, the crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 3% EtOAc in PE to give compound **3** (1.48 g, 4.60 mmol, 92%).

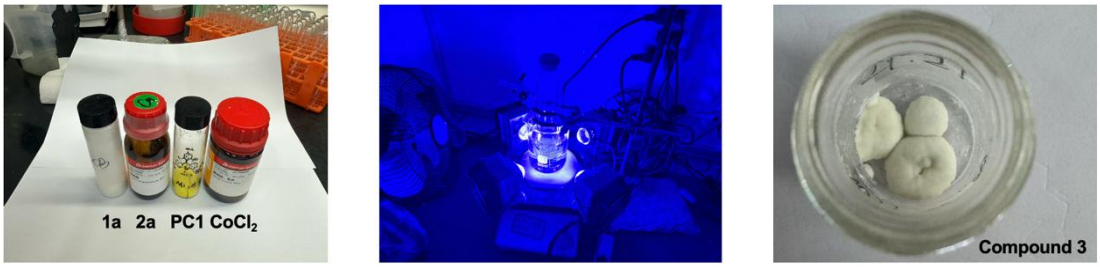
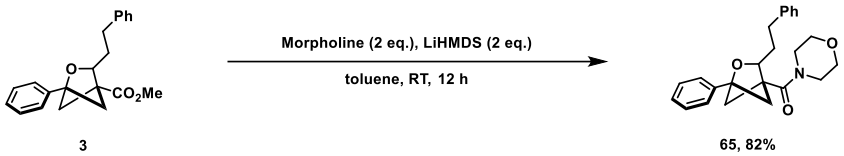


Figure S16. Pictures of gram-scale reaction and compound **3**

6 Synthetic Transformation



3 65, 82%

Compound **65** was synthesized according to published procedures.[2]

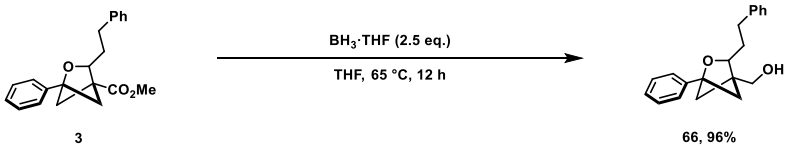
Compound **3** (32 mg, 0.1 mmol) was dissolved in anhydrous toluene (3 mL). Morpholine (18 μL, 0.2 mmol) and LiHMDS (0.2 mL from 1 M solution in THF, 0.2 mmol) were added under nitrogen atmosphere. The mixture was stirred for 12 hours under nitrogen atmosphere at RT. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 15% EtOAc in PE to give **65** (31 mg, 0.082 mmol, 82%) as a pale-yellow oil.

R_f = 0.4 (40% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 13.0, 5.7 Hz, 4H), 7.35 – 7.27 (m, 3H), 7.25 – 7.18 (m, 3H), 4.21 (dd, *J* = 8.9, 3.9 Hz, 1H), 3.75 – 3.67 (m, 2H), 3.67 – 3.53 (m, 3H), 3.39 (dd, *J* = 18.9, 10.4 Hz, 3H), 2.96 – 2.88 (m, 1H), 2.77 – 2.68 (m, 1H), 2.46 (d, *J* = 7.1 Hz, 1H), 2.40 (dd, *J* = 10.3, 7.9 Hz, 1H), 2.30 (dd, *J* = 15.9, 7.3 Hz, 2H), 2.09 – 1.99 (m, 1H), 1.93 – 1.83 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 141.6, 137.0, 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.4, 126.2 (2C), 126.1, 85.4, 79.4, 67.0, 66.9, 54.7, 50.5, 45.8, 43.4, 42.6, 34.6, 32.1 ppm.

HRMS (ESI) calculate: $C_{24}H_{28}NO_3^+$ $(M+H)^+$: 378.2064, found: 378.2058.



3 66, 96%

Compound **66** was synthesized according to adapted procedures.[8]

Compound **3** (32 mg, 0.1 mmol) was dissolved in anhydrous THF (5 mL). BH_3 (0.25 mL from 1 M solution in THF) were added under nitrogen atmosphere. The

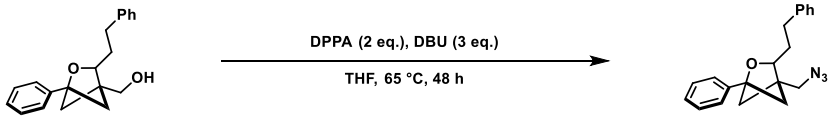
mixture was stirred for 12 hours under nitrogen atmosphere at 60 °C. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 15% EtOAc in PE to give **66** (28 mg, 0.096 mmol, 96%) as a pale-yellow oil.

R_f = 0.5 (30% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.36 (dd, *J* = 8.5, 6.7 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.27 – 7.23 (m, 2H), 7.22 – 7.16 (m, 1H), 4.08 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.83 (d, *J* = 1.3 Hz, 2H), 3.03 – 2.92 (m, 1H), 2.78 – 2.67 (m, 1H), 2.09 (d, *J* = 6.8 Hz, 1H), 2.03 (dd, *J* = 10.1, 7.0 Hz, 1H), 1.99 – 1.86 (m, 3H), 1.85 – 1.76 (m, 1H), 1.70 (s, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 138.3, 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.0, 126.2 (2C), 125.9, 86.8, 79.5, 61.4, 53.2, 46.4, 40.4, 34.8, 32.5 ppm.

HRMS (ESI) calculate: $C_{20}H_{23}O_3^+(M+H)^+$: 295.1693, found: 295.1690.



66 67, 69%

Compound **67** was synthesized according to adapted procedures.[2]

Compound **66** (29 mg, 0.1 mmol) was dissolved in anhydrous THF (5 mL). DPPA (43 µL, 0.2 mmol) and DBU (45 µL, 0.3 mmol) were added under nitrogen atmosphere. The mixture was stirred for 48 hours under nitrogen atmosphere at 60 °C. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 6% EtOAc in PE to give **67** (22 mg, 0.069 mmol, 69%) as a pale-yellow oil.

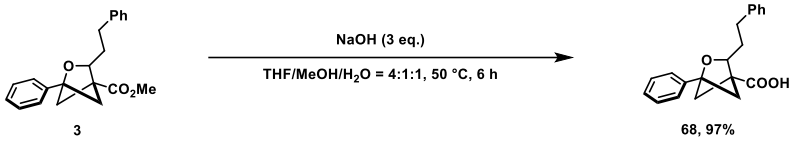
R_f = 0.8 (20% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 6.9 Hz, 2H), 7.30 (app. t, *J* = 7.4 Hz, 2H), 7.24 (dd, *J* = 9.3, 5.4 Hz, 3H), 7.21 – 7.16 (m, 2H), 7.16 – 7.11 (m, 1H), 4.00 (dd, *J* =

9.9, 3.3 Hz, 1H), 3.50 (d, *J* = 5.5 Hz, 2H), 2.92 (dd, *J* = 6.8, 3.6 Hz, 1H), 2.74 – 2.60 (m, 1H), 2.08 (d, *J* = 7.0 Hz, 1H), 2.02 (dd, *J* = 10.1, 6.9 Hz, 1H), 1.95 (dd, *J* = 10.2, 7.2 Hz, 1H), 1.90 (d, *J* = 7.3 Hz, 1H), 1.81 (dd, *J* = 6.6, 3.4 Hz, 1H), 1.78 – 1.67 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2, 137.9, 128.6 (2C), 128.6 (2C), 128.4 (2C), 128.2, 126.2 (2C), 126.0, 87.0, 79.6, 51.4, 51.2, 47.5, 41.6, 34.5, 32.4 ppm.

HRMS (ESI) calculate: $C_{20}H_{22}NO^+(M+H-N_2)^+$: 292.1696, found: 292.1692.



3 68, 97%

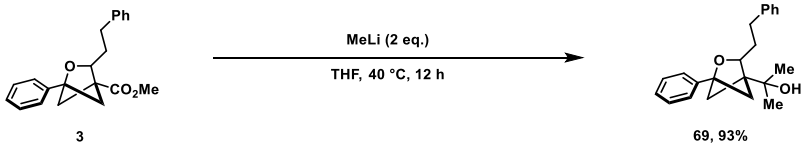
68 was synthesized according to the general procedure B and purified by flash column chromatography (silica gel), eluting with 3% MeOH in DCM to afford **68** as a colourless oil (30 mg, 0.097 mmol, 97%).

R_f = 0.6 (6% MeOH in DCM)

^{1}H NMR (500 MHz, MeOD) δ 7.45 – 7.40 (m, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.29 (m, 1H), 7.29 – 7.22 (m, 4H), 7.18 – 7.13 (m, 1H), 4.26 (dd, *J* = 9.3, 3.7 Hz, 1H), 2.94 – 2.85 (m, 1H), 2.77 – 2.68 (m, 1H), 2.44 (d, *J* = 6.6 Hz, 1H), 2.30 (d, *J* = 7.2 Hz, 1H), 2.29 – 2.19 (m, 2H), 2.09 – 2.00 (m, 1H), 1.92 – 1.82 (m, 1H) ppm.

^{13}C NMR (126 MHz, MeOD) δ 174.6, 143.2, 138.7, 129.5 (2C), 129.4 (2C), 129.3 (2C), 129.2, 127.2 (2C), 126.9, 87.8, 81.0, 54.2, 50.7, 42.6, 36.0, 33.2 ppm.

HRMS (ESI) calculate: $C_{22}H_{27}O_2^+$ $(M+H)^+$: 309.1485, found: 309.1486.



3 69, 93%

Compound **69** was synthesized according to adapted procedures.[9]

Compound **3** (32 mg, 0.1 mmol) was dissolved in anhydrous THF (3 mL). MeLi (0.25 mL from 2 M solution in THF, 0.5 mmol) was added under nitrogen atmosphere. The mixture was stirred for 12 hours under nitrogen atmosphere at 40 °C. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried over $NaSO_4$, filtered

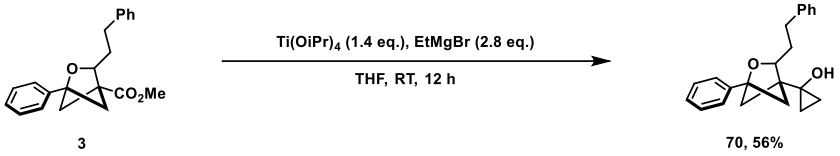
and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 10% EtOAc in PE to give **69** (30 mg, 0.093 mmol, 93%) as a pale-yellow oil.

R_f = 0.5 (20% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 2H), 7.37 (app. t, *J* = 7.5 Hz, 2H), 7.33 – 7.24 (m, 5H), 7.19 (app. t, *J* = 6.8 Hz, 1H), 4.12 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.08 – 2.98 (m, 1H), 2.79 – 2.70 (m, 1H), 2.17 – 2.06 (m, 2H), 2.04 – 1.98 (m, 2H), 1.98 – 1.95 (m, 1H), 1.88 – 1.75 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7, 138.7, 128.7 (2C), 128.5 (2C), 128.4 (2C), 127.9, 126.2 (2C), 125.8, 84.5, 79.5, 70.0, 59.0, 46.5, 38.7, 35.9, 32.7, 27.8, 26.6 ppm.

HRMS (ESI) calculate: $C_{22}H_{27}O_2^+$(M+H)$^+$: 323.2006, found: 323.2004.



3 70, 56%

Compound **70** was synthesized according to published procedures.[10]

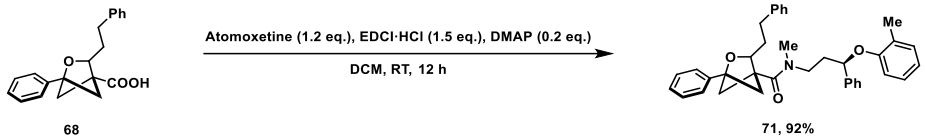
Compound **3** (32 mg, 0.1 mmol) was dissolved in anhydrous THF (5 mL). $Ti(OiPr)_4$ (41 μL, 0.14 mmol) and EtMgBr (0.14 mL from a 2M solution in THF, 0.28 mmol) were added under nitrogen atmosphere. The mixture was stirred for 12 hours under nitrogen atmosphere at RT. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 10% EtOAc in PE to give **70** (18 mg, 0.056 mmol, 56%) as a pale-yellow oil.

R_f = 0.4 (20% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.37 (app. t, *J* = 7.4 Hz, 2H), 7.30 (d, *J* = 6.7 Hz, 5H), 7.23 – 7.18 (m, 1H), 4.30 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.06 – 2.97 (m, 1H), 2.86 – 2.76 (m, 1H), 2.24 – 2.11 (m, 2H), 1.96 – 1.89 (m, 2H), 1.89 – 1.79 (m, 2H), 1.61 (s, 1H), 0.90 – 0.82 (m, 1H), 0.81 – 0.73 (m, 1H), 0.70 – 0.64 (m, 1H), 0.64 – 0.54 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7, 138.4, 128.7 (2C), 128.5 (2C), 128.4 (2C), 128.1, 126.2 (2C), 125.9, 85.7, 80.2, 54.8, 54.7, 47.1, 41.0, 35.2, 32.7, 12.4, 11.1 ppm.

HRMS (ESI) calculate: $C_{22}H_{24}O_2^+(M+H)^+$: 321.1849, found: 321.1849.



68 71, 92%

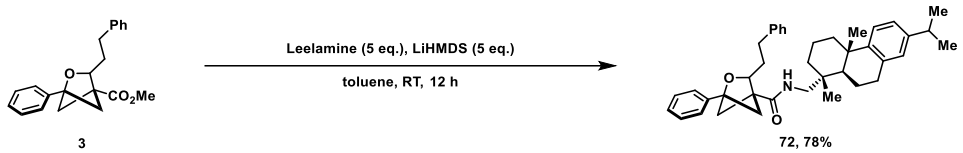
Compound **68** (31 mg, 0.1 mmol) was dissolved in DCM (5 mL). Atomoxetine hydrochloride (35 mg, 0.12 mmol), EDCI·HCl (29 mg, 0.15 mmol) and DMAP (2 mg, 0.02 mmol) were added under nitrogen atmosphere. The mixture was stirred for 12 hours under nitrogen atmosphere at RT. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 20% EtOAc in PE to give **71** (50 mg, 0.092 mmol, 92%) as a colorless oil.

$\mathbf{R}_f$ = 0.6 (50% EtOAc in PE).

^{1}H NMR (500 MHz, $CDCl_3$) **Mixer of isomer 1 and isomer 2** δ 7.42 – 7.29 (m, 15H), 7.28 – 7.21 (m, 10H), 7.21 – 7.15 (m, 5H), 7.12 (dd, *J* = 12.1, 6.0 Hz, 2H), 7.00 – 6.90 (m, 2H), 6.83 – 6.74 (m, 2H), 6.61 – 6.50 (m, 2H), 5.24 – 5.12 (m, 2H), 3.48 – 3.32 (m, 2H), 2.97 – 2.79 (m, 8H), 2.75 – 2.58 (m, 2H), 2.34 (d, *J* = 4.9 Hz, 9H), 2.29 – 2.10 (m, 8H), 2.09 – 1.92 (m, 3H), 1.92 – 1.77 (m, 2H) ppm. **Isomer 1** δ 4.32 – 4.27 (m, 1H), 3.73 – 3.62 (m, 1H) ppm. **Isomer 2** δ 4.23 – 4.12 (m, 1H), 3.59 – 3.48 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) **Mixer of isomer 1 and isomer 2** δ 170.2, 170.1, 155.9, 155.5, 141.9, 141.8, 141.7, 141.7, 140.8, 137.4, 131.1, 130.9, 129.1, 128.9, 128.7, 128.6, 128.5, 128.4, 128.2, 127.9, 127.1, 126.9, 126.9, 126.4, 126.3, 126.1, 125.9, 125.8, 125.7, 120.9, 120.6, 112.9, 112.8, 112.7, 112.6, 85.3, 85.2, 85.2, 79.7, 79.7, 79.4, 77.7, 77.7, 76.8, 55.1, 54.8, 50.6, 50.6, 46.3, 46.0, 45.9, 43.6, 43.5, 43.4, 43.3, 37.9, 37.7, 36.4, 35.4, 35.2, 34.8, 34.7, 34.6, 33.9, 33.9, 32.3, 32.3, 17.1, 17.0, 16.8.

HRMS (ESI) calculate: $C_{37}H_{40}NO_3^+(M+H)^+$: 546.3003, found: 546.3003.



Compound **72** was synthesized according to published procedures.[2]

Compound **3** (32 mg, 0.1 mmol) was dissolved in anhydrous toluene (3 mL). Leelamine (143 mg, 0.5 mmol) and LiHMDS (0.5 mL from 1 M solution in THF, 0.5 mmol) were added under nitrogen atmosphere. The mixture was stirred for 12 hours under nitrogen atmosphere at RT. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 15% EtOAc in PE to give **72** (45 mg, 0.078 mmol, 78%) as a pale-yellow oil.

R_f = 0.7 (30% EtOAc in PE)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 7.24 (d, *J* = 7.0 Hz, 2H), 7.17 (app. t, *J* = 6.9 Hz, 3H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 9.7 Hz, 1H), 5.58 – 5.47 (m, 1H), 4.29 (dd, *J* = 9.9, 3.3 Hz, 1H), 3.32 – 3.11 (m, 2H), 2.95 – 2.85 (m, 2H), 2.85 – 2.63 (m, 3H), 2.40 – 2.32 (m, 1H), 2.32 – 2.21 (m, 3H), 2.13 (dd, *J* = 7.6, 3.0 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.92 – 1.70 (m, 4H), 1.42 – 1.26 (m, 4H), 1.24 – 1.18 (m, 10H), 0.93 (s, 3H) ppm.

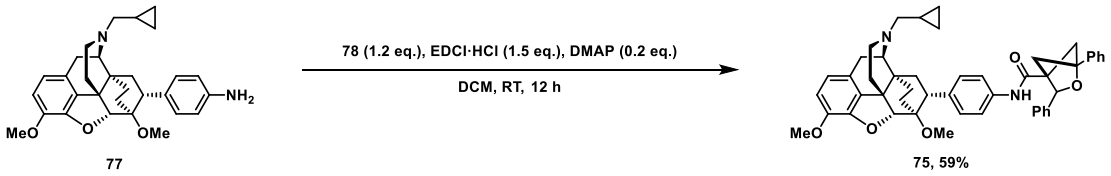
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 147.0, 145.8, 141.9, 137.2, 134.7, 128.6 (2C), 128.5 (3C), 128.4, 127.0, 126.2 (2C), 125.9, 124.4, 124.1, 85.9, 80.2, 80.2, 54.7, 50.0, 49.7, 46.4, 41.5, 38.5, 37.7, 37.5, 36.5, 35.1, 34.9, 33.6, 32.2, 32.2, 30.6, 25.5, 24.1, 19.2, 18.7 ppm.

HRMS (ESI) calculate: $C_{40}H_{50}NO_2^+(M+H)^+$: 576.3836, found: 576.3839.

7 Physicochemical Property Assessment

The physicochemical property of Atomoxetine, **71**, Leelamine and **72** were calculated and predicted by different software and program. ClogP and tPSA values were generated by ChemDraw Office. pKa Values were predicted by a published graph-convolutional neural network program MolGpKa.[11] Human plasma stabilities were predicted by a published attention-based graph neural network program PredPS.[12] **71** and **72** were further measured the stability under different acidic conditions. Compound (55 mg for **71**, 58 mg for **72**, 0.1 mmol) were dissolved in THF (0.5 mL). Different concentration of HCl (2 mL from 0.2 M, 2 M or concentrated HCl aqueous solution) were added under nitrogen atmosphere. The mixture was stirred for 24 hours under nitrogen atmosphere at 37 ℃. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with indicated solvent system to give the desired compound and calculated the recovery ratio based on recovered **71** and **72**.

8 Phrenological Property Assessment



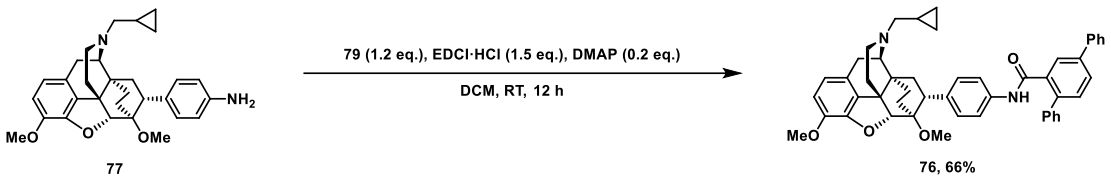
75 (15 mg, 0.032 mmol) was dissolved in DCM (5 mL). **76** (11 mg, 0.038 mmol), EDCI·HCl (9 mg, 0.048 mmol) and DMAP (0.8 mg, 0.006 mmol) were added under nitrogen atmosphere. The mixture was stirred for 12 hours under nitrogen atmosphere at RT. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 1% MeOH in DCM to give **73** (14 mg, 0.019 mmol, 59%) as a colorless oil.

R_f = 0.6 (6% MeOH in DCM)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.4 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.34 (app. t, *J* = 7.5 Hz, 2H), 7.31 – 7.25 (m, 3H), 7.23 (d, *J* = 7.7 Hz, 3H), 7.20 – 7.15 (m, 3H), 6.69 – 6.61 (m, 2H), 6.50 (d, *J* = 8.1 Hz, 1H), 5.47 (s, 1H), 4.51 (s, 1H), 3.78 (s, 3H), 3.19 – 3.06 (m, 4H), 3.02 – 2.91 (m, 3H), 2.65 – 2.54 (m, 2H), 2.51 (d, *J* = 7.4 Hz, 1H), 2.25 (tt, *J* = 33.2, 11.1 Hz, 5H), 2.06 (dd, *J* = 13.0, 7.3 Hz, 2H), 1.66 (d, *J* = 12.7 Hz, 1H), 1.62 – 1.53 (m, 1H), 1.37 (td, *J* = 13.1, 5.7 Hz, 1H), 1.27 – 1.20 (m, 1H), 0.83 – 0.76 (m, 1H), 0.71 – 0.64 (m, 1H), 0.37 (p, *J* = 9.8 Hz, 2H), 0.04 – -0.04 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 147.1, 141.9, 139.4, 138.9, 136.9, 135.3, 132.9, 130.1 (2C), 128.8, 128.6 (2C), 128.6, 128.4 (2C), 128.1, 126.7 (2C), 126.3 (2C), 120.0 (2C), 119.1, 113.7, 93.3, 86.1, 80.9, 77.1, 60.0, 58.7, 57.0, 56.7, 51.2, 49.9, 46.2, 44.0, 43.4, 40.4, 36.5, 36.2, 35.8, 29.8, 22.9, 18.8, 9.6, 4.2, 3.5 ppm.

HRMS (ESI) calculate: $C_{48}H_{51}N_2O_5^+$ $(M+H)^+$: 735.3792, found: 735.3794.



76 (15 mg, 0.032 mmol) was dissolved in DCM (5 mL). **77** (10 mg, 0.038 mmol), EDCI·HCl (9 mg, 0.048 mmol) and DMAP (0.8 mg, 0.006 mmol) were added under nitrogen atmosphere. The mixture was stirred for 12 hours under nitrogen atmosphere at RT. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The organic phases were combined, dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel), eluting with 1% MeOH in DCM to give **74** (15 mg, 0.021 mmol, 66%) as a colorless oil.

R_f = 0.6 (6% MeOH in DCM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 2.0 Hz, 1H), 7.76 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.68 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.54 – 7.37 (m, 9H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.99 (s, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 4.59 (d, *J* = 2.0 Hz, 1H), 3.87 (s, 3H), 3.16 (s, 4H), 3.10 – 2.99 (m, 3H), 2.65 (dd, *J* = 11.9, 5.2 Hz, 1H), 2.32 (d, *J* = 6.5 Hz, 2H), 2.28 (d, *J* = 6.8 Hz, 1H), 2.14 (d, *J* = 5.4 Hz, 1H), 1.77 – 1.71 (m, 1H), 1.59 (dd, *J* = 13.9, 6.0 Hz, 2H), 1.49 – 1.41 (m, 1H), 1.35 – 1.27 (m, 2H), 0.90 – 0.84 (m, 1H), 0.81 – 0.71 (m, 1H), 0.51 – 0.41 (m, 2H), 0.08 (d, *J* = 5.0 Hz, 2H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.1, 147.1, 142.0, 140.9, 139.8, 139.8, 138.7, 138.5, 135.9, 135.9, 133.0, 131.1, 130.0 (2C), 129.2, 129.2 (2C), 129.1 (2C), 129.0 (2C), 128.8, 128.3 (2C), 128.0, 127.2 (2C), 120.0 (2C), 119.1, 113.8, 93.4, 77.1, 60.0, 58.8, 56.8, 51.2, 46.2, 44.0, 43.4, 36.5, 36.2, 35.8, 29.8, 22.9, 18.8, 9.6, 4.2, 3.5 ppm.

HRMS (ESI) calculate: $C_{49}H_{49}N_2O_4^+$ $(M+H)^+$: 729.3684, found: 729.3685.

Cell Membrane Preparation. Chinese hamster ovary (CHO) cells stably expressing human KOR, rat MOR or rat DOR were clustered in F12 medium with 10% fetal calf serum and 0.25 mg/mL G418. Cells were incubated in a humidified atmosphere consisting of 5% CO_2 and 95% air at 37 °C and detached by incubation

with phosphate buffered saline (PBS) containing 1 mM EDTA and then centrifuged at 1000g for 10 min, when cell growth reached 90% confluence. The cell pellets were suspended in ice-cold homogenization buffer (pH 7.4) containing 50 mM HEPES, 1 mM $MgCl_2$ and 1 mM EGTA. After homogenization with a glass dounce homogenizer, the pellets were centrifuged at 40,000 g for 30 min (4 °C). This producer including resuspension, homogenization, and centrifugation was repeated for twice more. The final pellets were resuspended in a 50 mM Tris-HCl buffer, pH 7.4. Protein concentration was determined, and aliquots were stored at -80 °C.

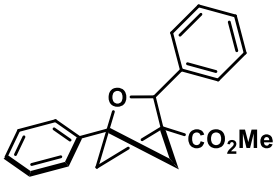
Radioligand Binding Assays. Ki value was measured according to a published literature.[13] Competitive binding assays were carried out using [^{3}H]U69593 (39.1 Ci/mmol) for KOR with Kd values of 0.7 ± 0.2 nM and Bmax values of 871.3 ± 80.4 fmol/mg protein. Competition inhibition by compounds showing [^{3}H]-labeled ligand binding to opioid receptors was performed in the absence or presence of test compounds at various concentrations. U50,488H at a concentration of 10 μM was used to define nonspecific binding. Assay was performed in 50 mM Tris-HCl buffer (pH 7.4) at 37 °C for 30 min in triplicate with a final volume of 0.5 mL containing 30 μg of membrane protein. After reaching equilibrium, bound and free [^{3}H]-labeled ligands were separated by filtration under reduced pressure with GF/B filters. The radioactivity retained on the filters was counted by liquid scintillation counting. Binding data and Ki values were determined using the GraphPad Prism 10.2.

9 Docking Analysis

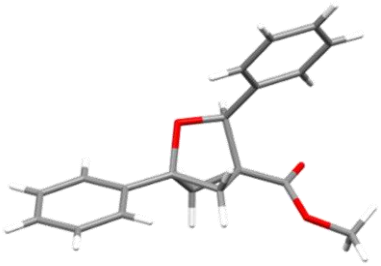
Docking analysis of **73** and **74** were followed to a published protocal.[13] To reveal the binding model of compound **73** and **74**, we built a complex of compound **73** and **74** and opioid receptors based on the published crystal structures of KOR (PDB entry: 6B73). Original compound MP1104 were removed from the crystal structure and all hydrogen atoms added. The chemical structures of compounds **73** and **74** were sketched in SYBYL (Tripos, St Louis, MO, USA) and protonated, if appropriate, before energy minimization using the Tripos force field (Gasteiger–Hückel charges, distance-dependent dielectric constant = 4.0, nonbonded interaction cutoff = 8 Å and termination criterion = energy gradient < 0.05 kcal / (mol × Å) for 10 000 iterations). The molecular docking was performed using GOLD Suite 5.1 (Cambridge Crystallographic Data Centre, Cambridge, U.K.). The original ligand was extracted and the new ligands (compound **73** and **74**) were fit into the binding pocket of MP1104 in KOR. The ChemScore and GoldScore fitness scoring functions were utilized to identify lowest energy binding poses. The exported complexes were edited using UCSF Chimera.

10 X-Ray Structure of Compound 33

CCDC 2389698



33



Bond precision: C-C = 0.0023 A Wavelength=1.34138

Cell: a=10.8872(3) b=8.5462(3) c=32.7304(10)
alpha=90 beta=90 gamma=90
Temperature: 150 K

	Calculated	Reported
Volume	3045.37(17)	3045.37(16)
Space group	P b c a	P b c a
Hall group	-P 2ac 2ab	-P 2ac 2ab
Moiety formula	C19 H18 O3	C19 H18 O3
Sum formula	C19 H18 O3	C19 H18 O3
Mr	294.33	294.33
Dx,g cm-3	1.284	1.284
Z	8	8
Mu (mm-1)	0.440	0.440
F000	1248.0	1248.0
F000'	1250.87	
h,k,lmax	13,10,40	13,10,40
Nref	3129	3104
Tmin,Tmax		0.635,0.751
Tmin'		

Correction method= # Reported T Limits: Tmin=0.635 Tmax=0.751
AbsCorr = NONE

Data completeness= 0.992 Theta(max)= 57.018

R(reflections)= 0.0538(2737) wR2(reflections)= 0.1224(3104)

S = 1.112 Npar= 200

Figure S17. Crystal structure of compound **33** and XRD information

11 Unsuccessful Cases

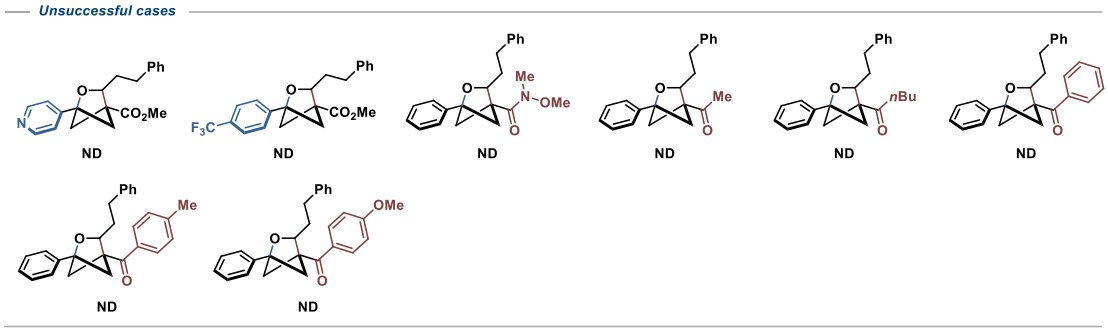


Figure S18. Unsuccessful cases in scope section

12 NMR Spectra of Starting Materials

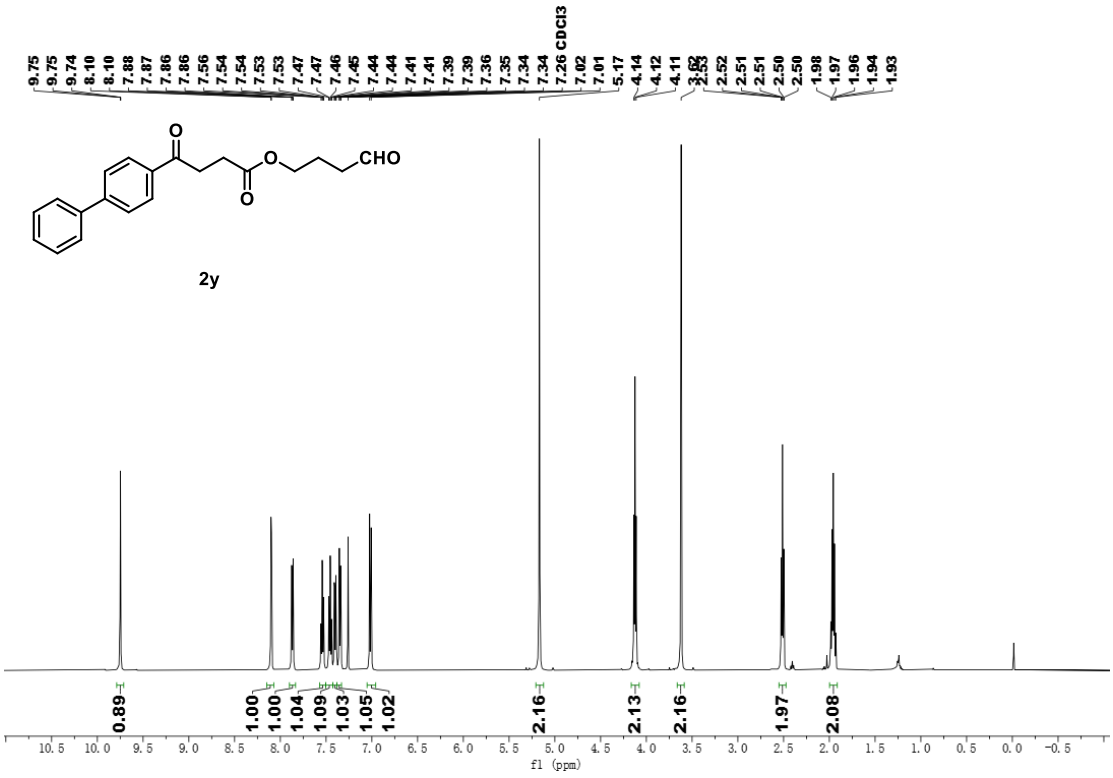


Figure S19. ^{1}H NMR spectra of **2y**

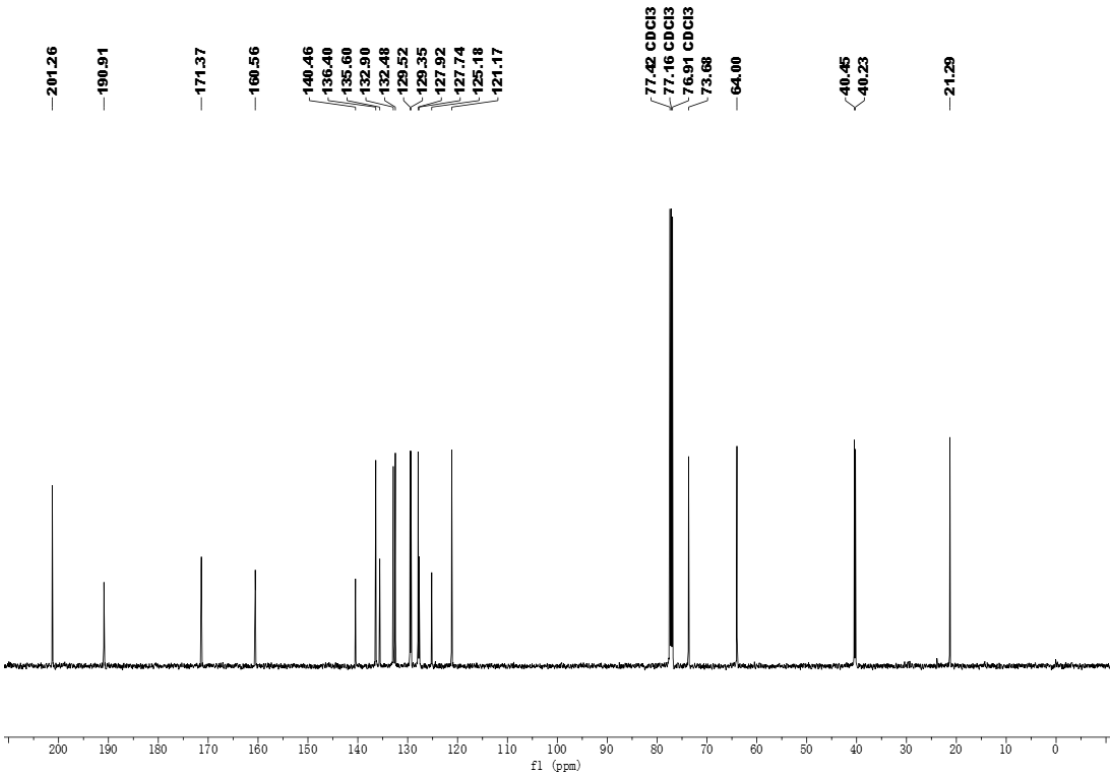


Figure S20. ^{13}C NMR spectra of **2y**

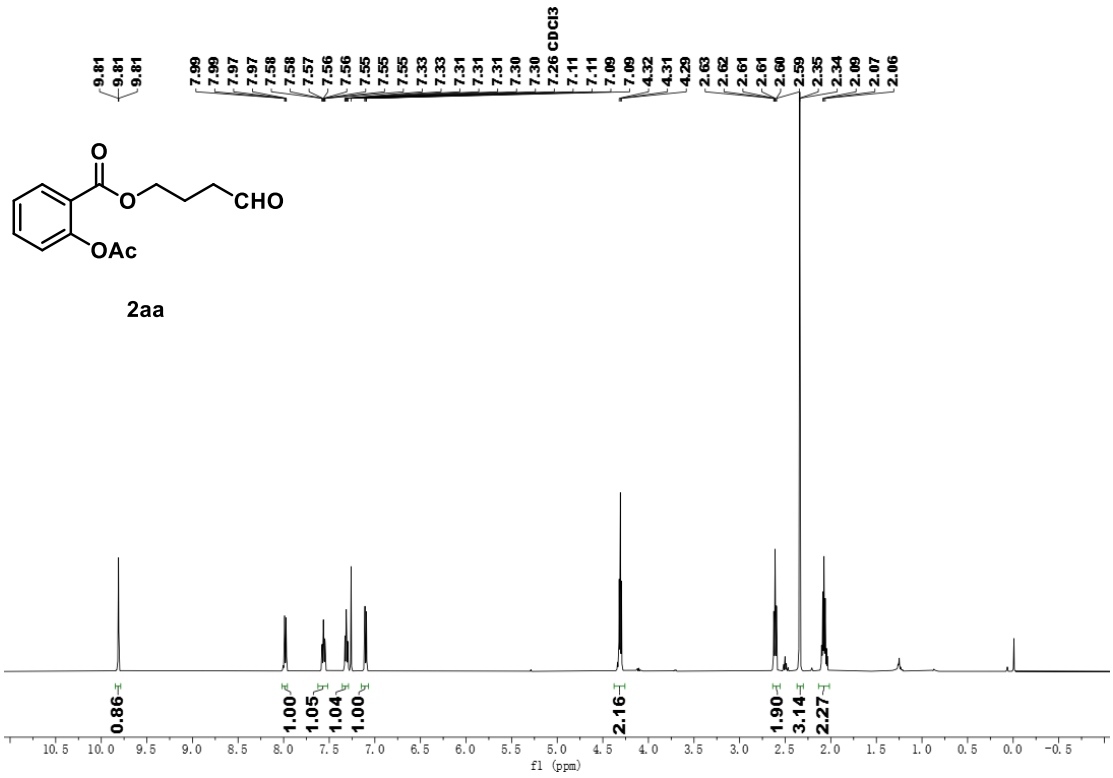


Figure S21. ^{1}H NMR spectra of **2aa**

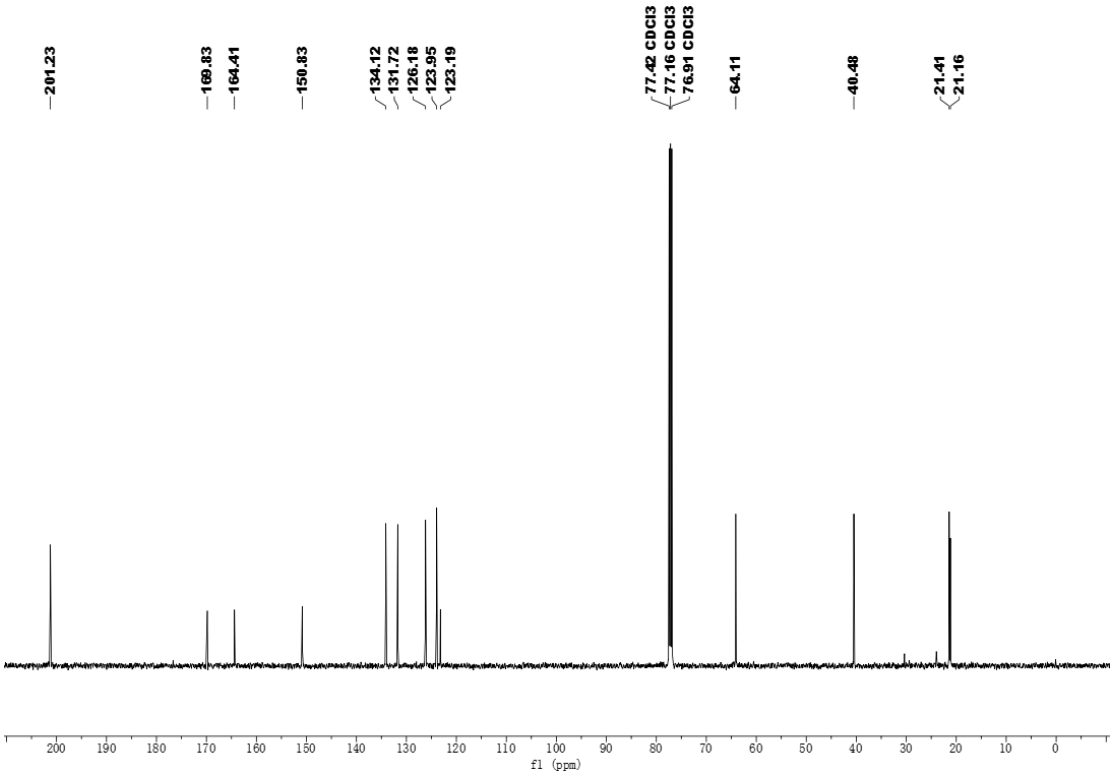


Figure S22. ^{13}C NMR spectra of **2aa**

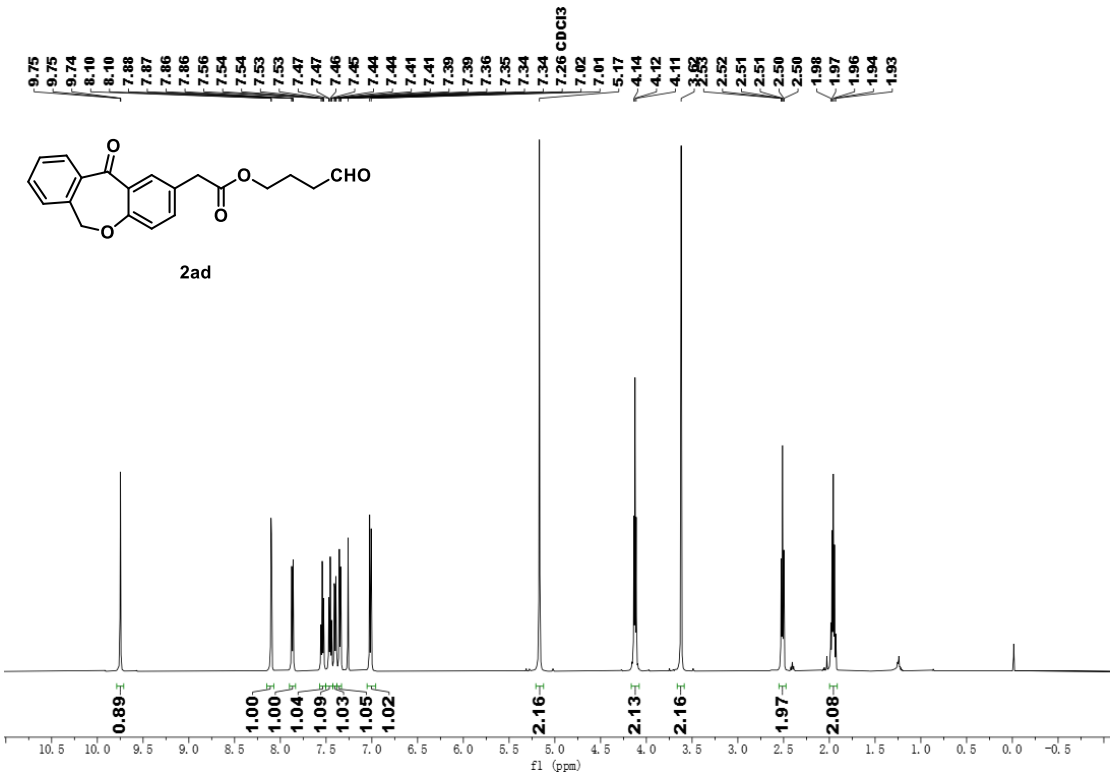


Figure S23. ^{1}H NMR spectra of **2ad**

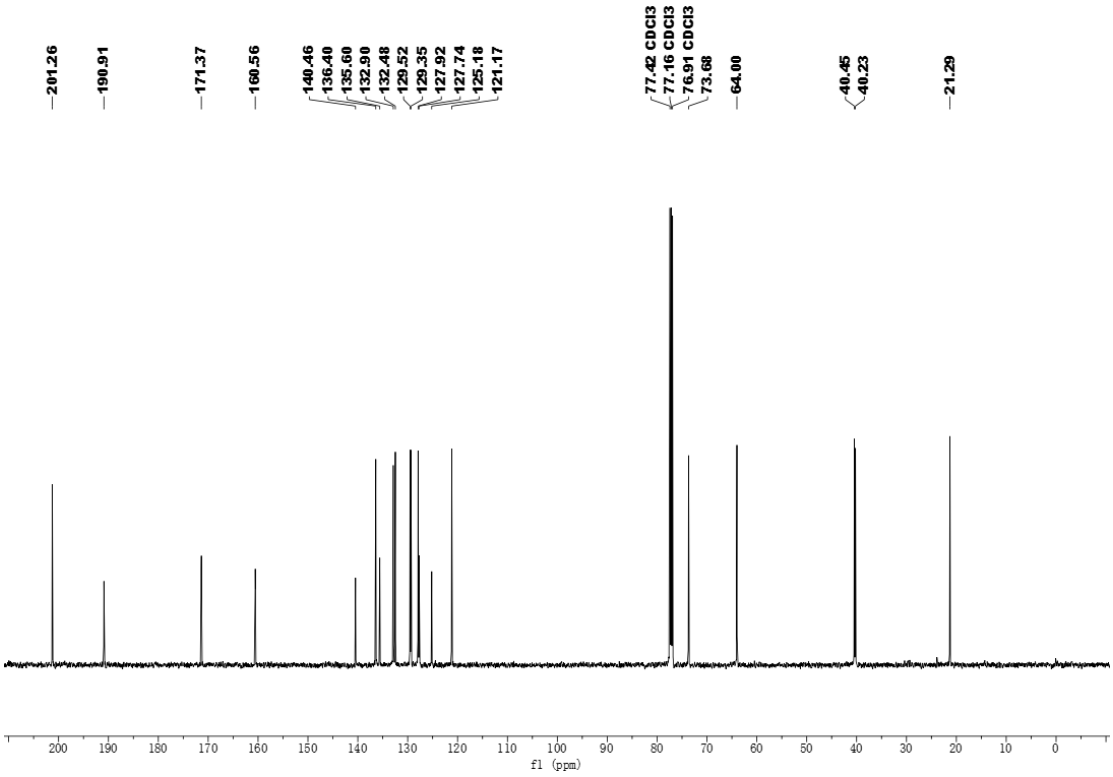


Figure S24. ^{13}C NMR spectra of **2ad**

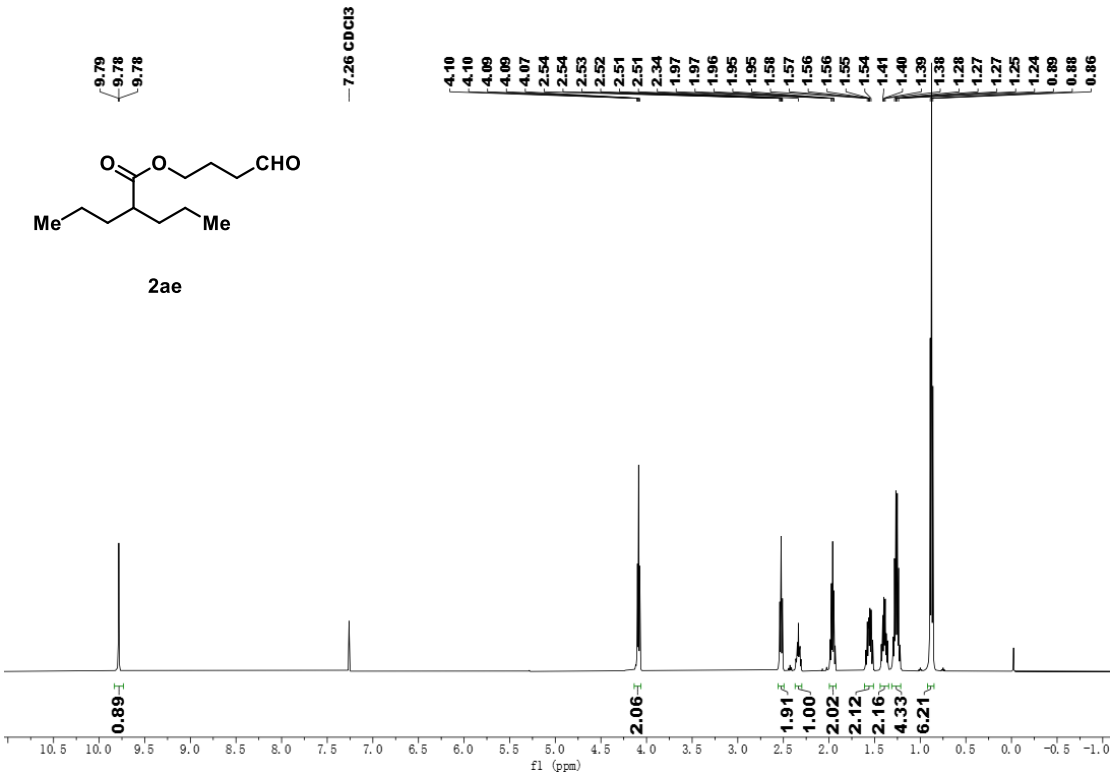


Figure S25. ^{1}H NMR spectra of **2ae**

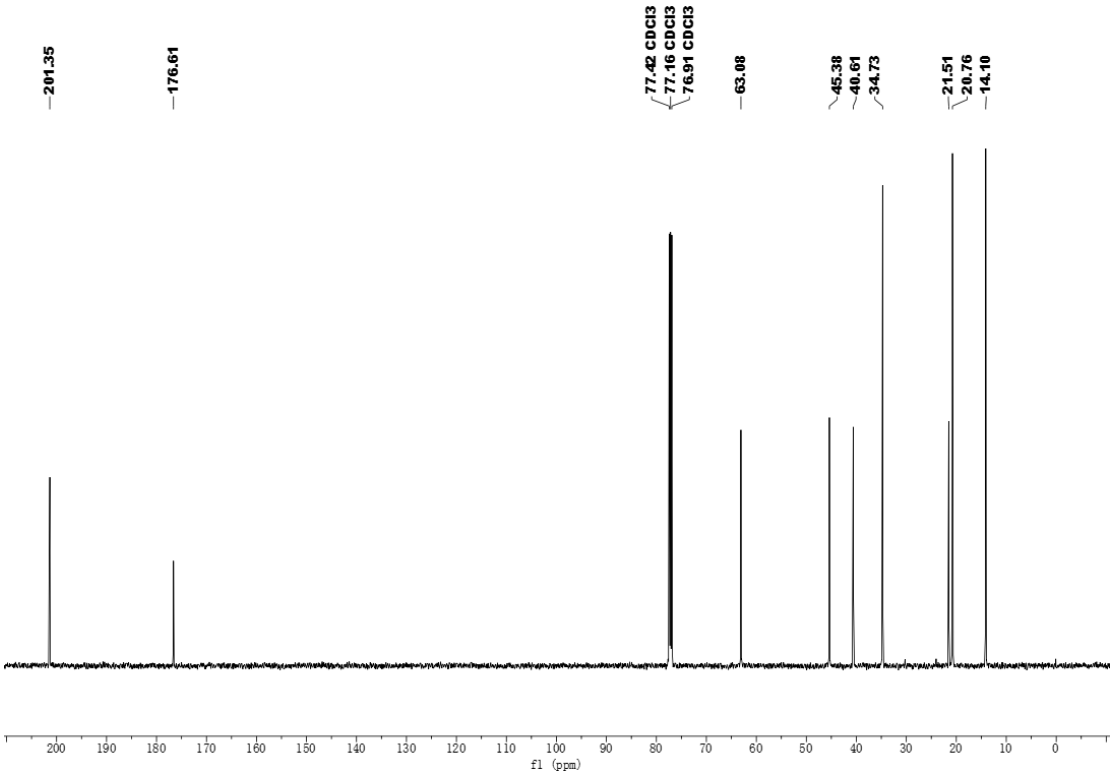


Figure S26. ^{13}C NMR spectra of **2ae**

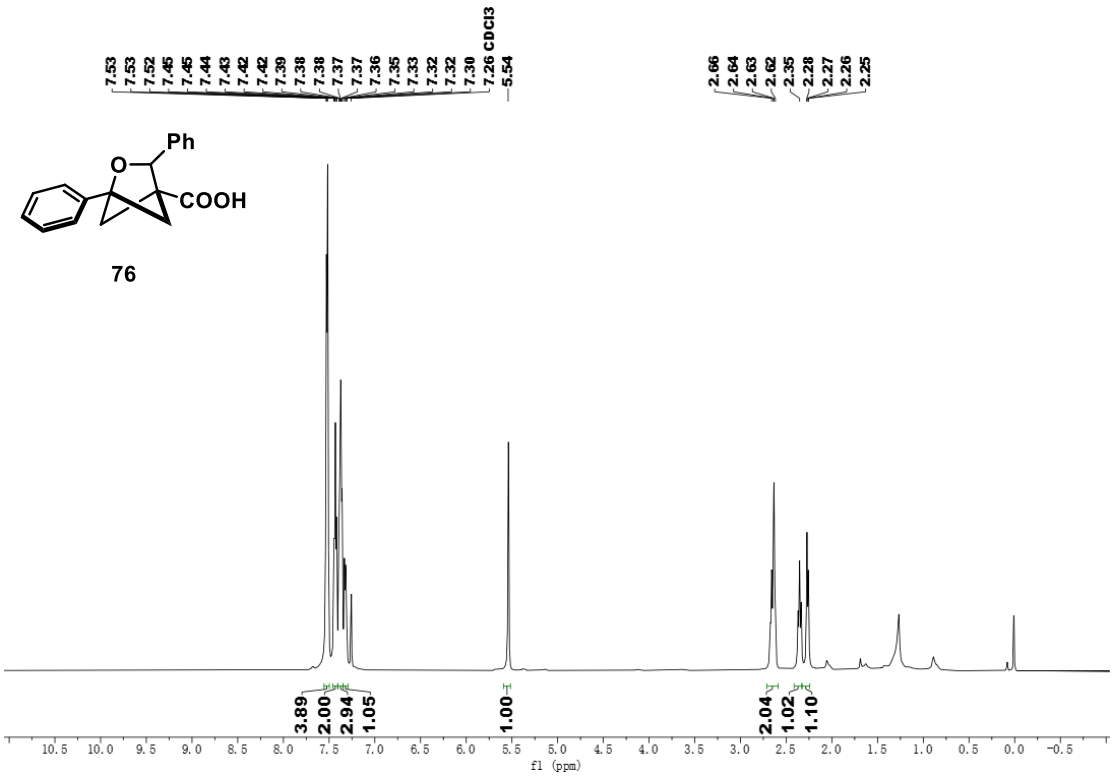


Figure S27. ^{1}H NMR spectra of **76**

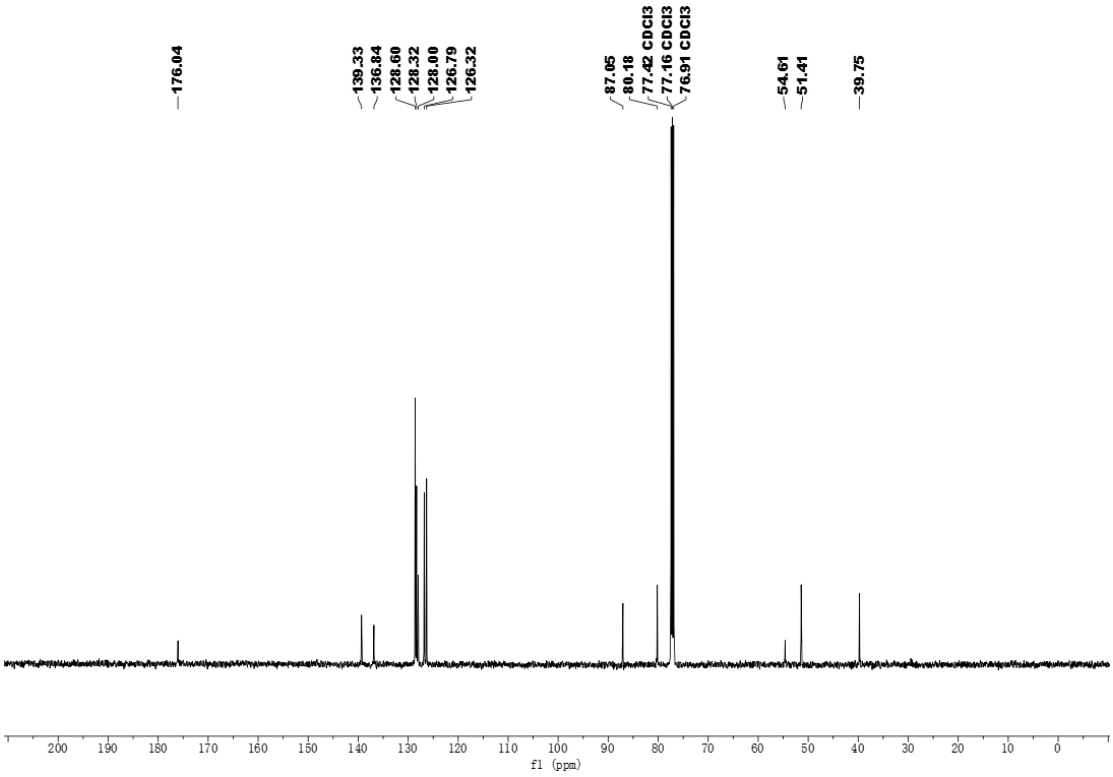


Figure S28. ^{13}C NMR spectra of **76**

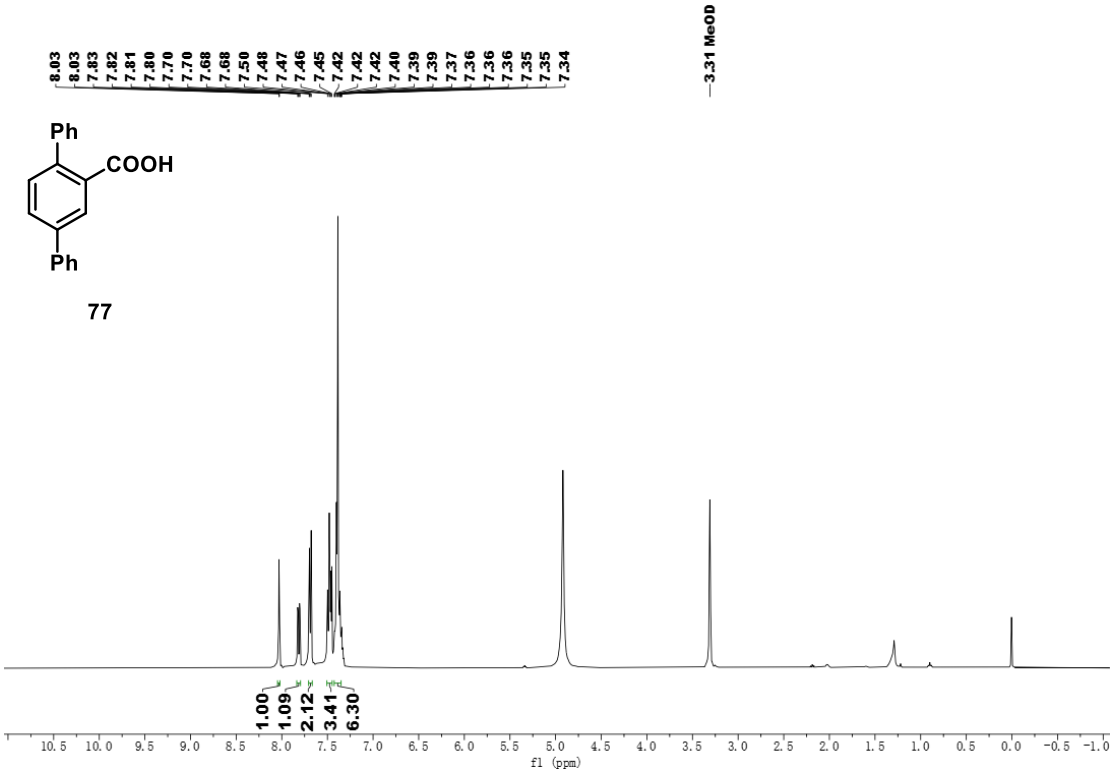


Figure S29. ^{1}H NMR spectra of **77**

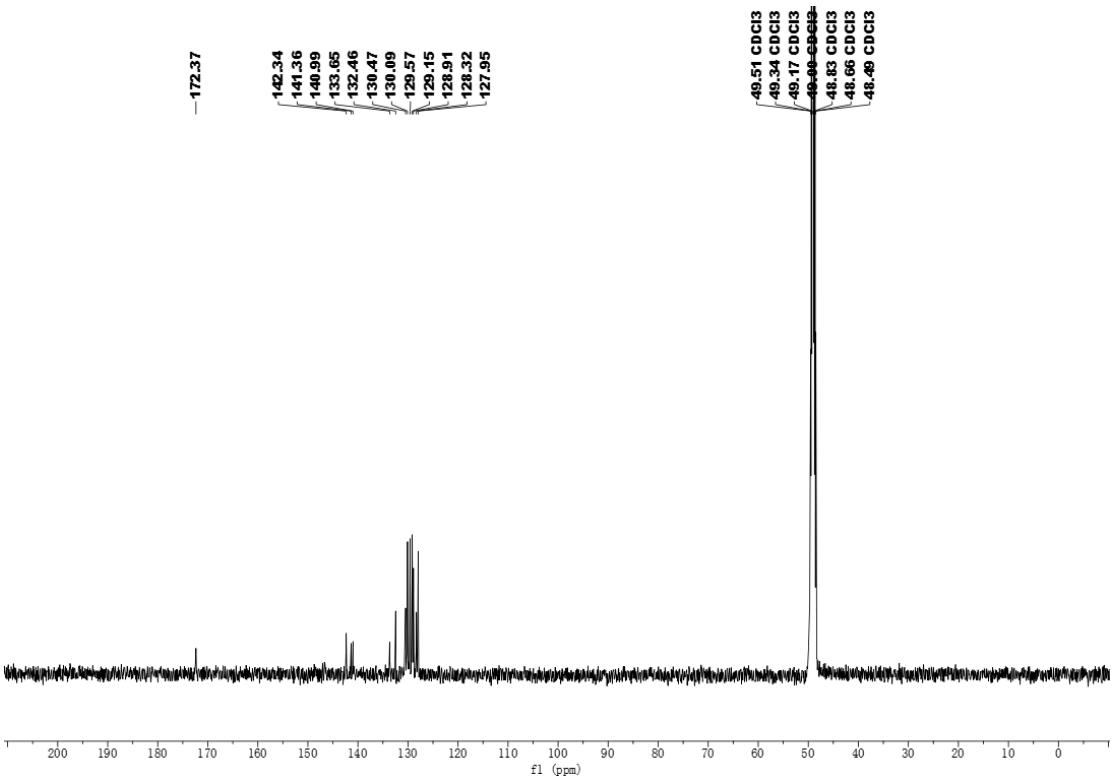


Figure S30. ^{13}C NMR spectra of **77**

13 NMR Spectra of Desired Compounds

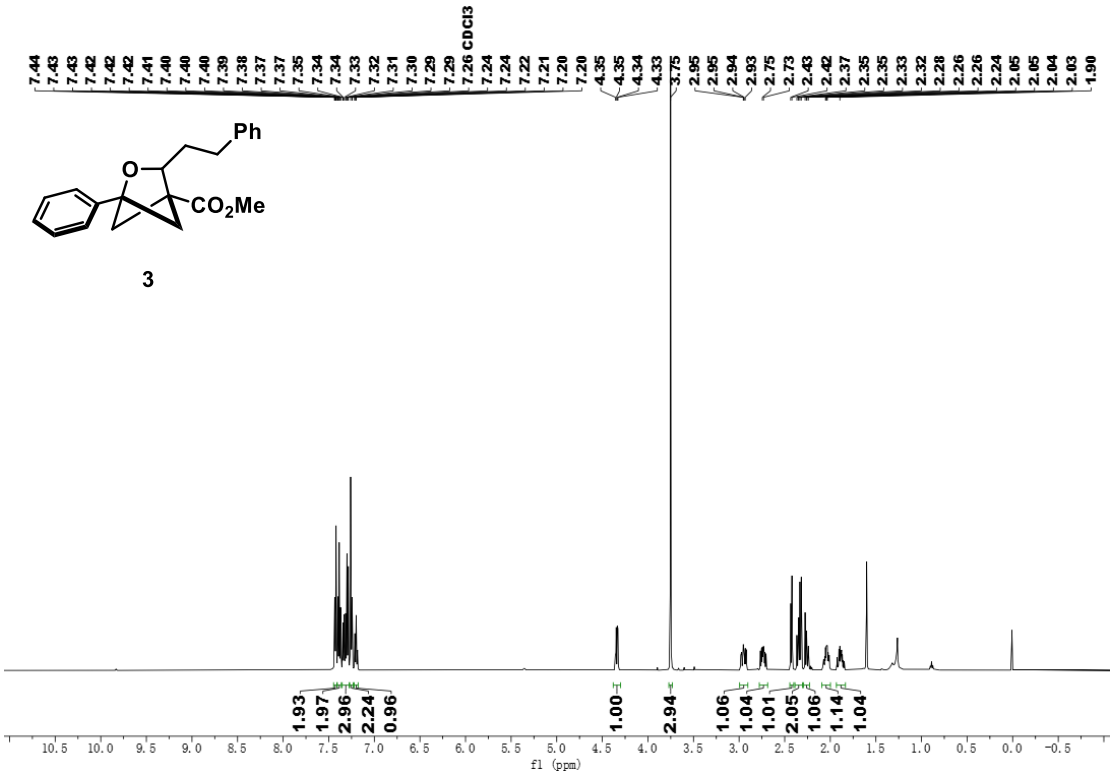


Figure S31. ^{1}H NMR spectra of **3**

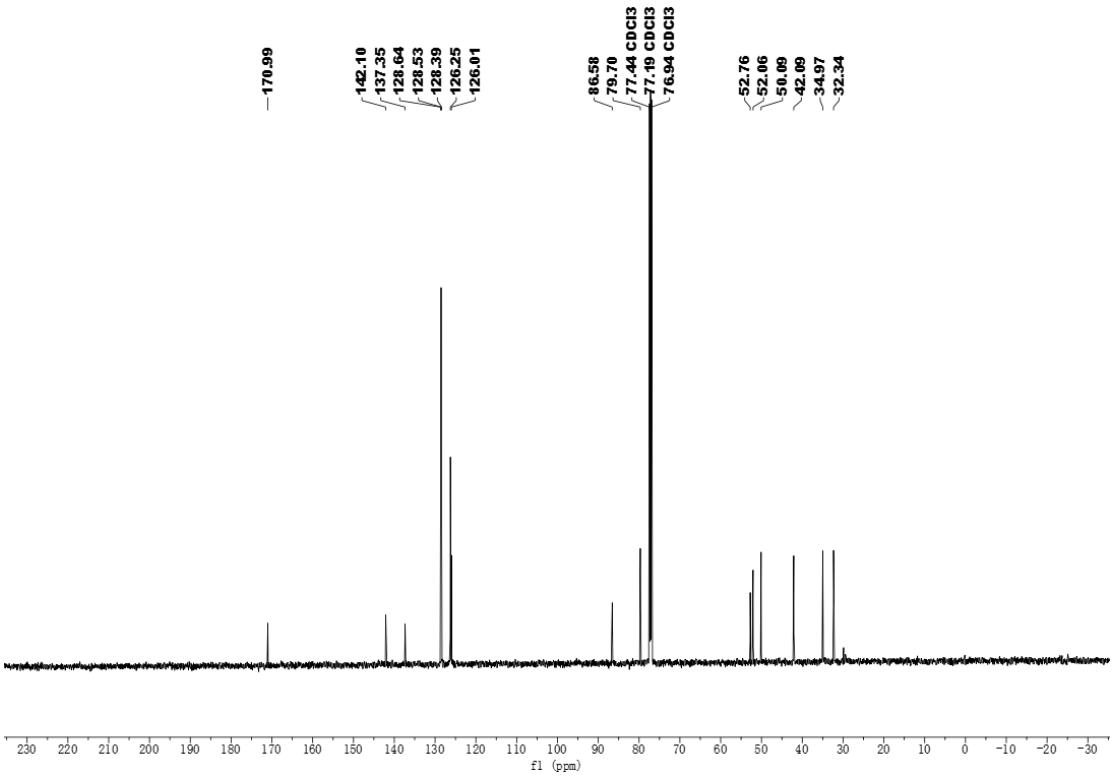


Figure S32. ^{13}C NMR spectra of **3**

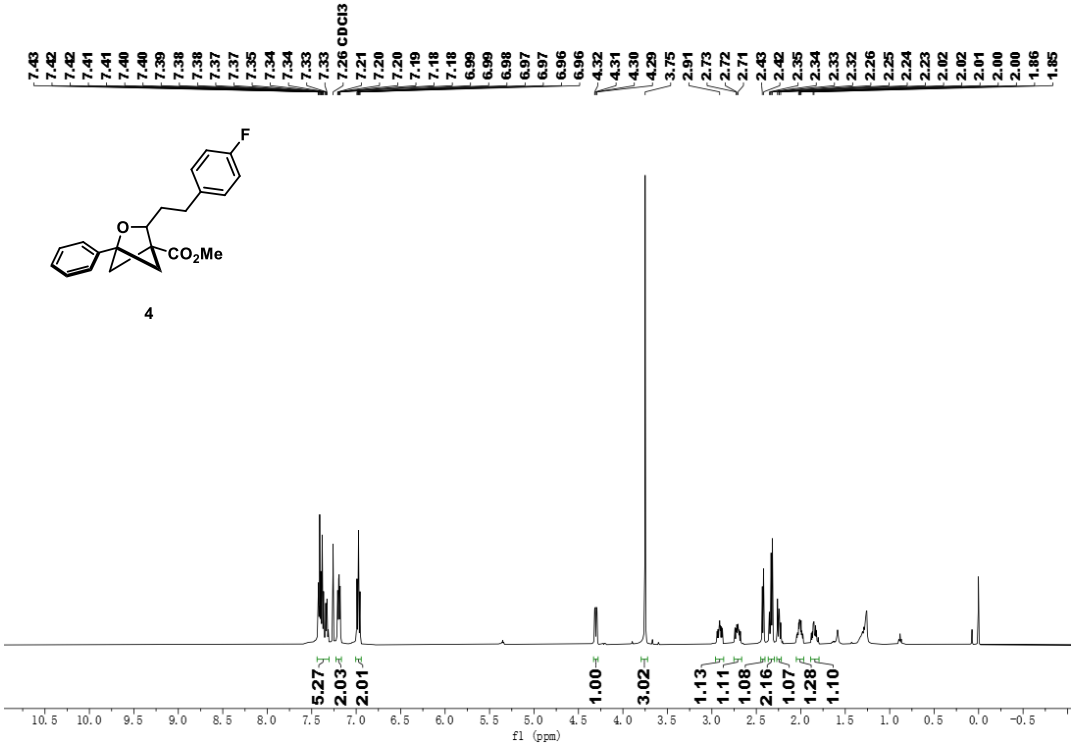


Figure S33. ^{1}H NMR spectra of **4**

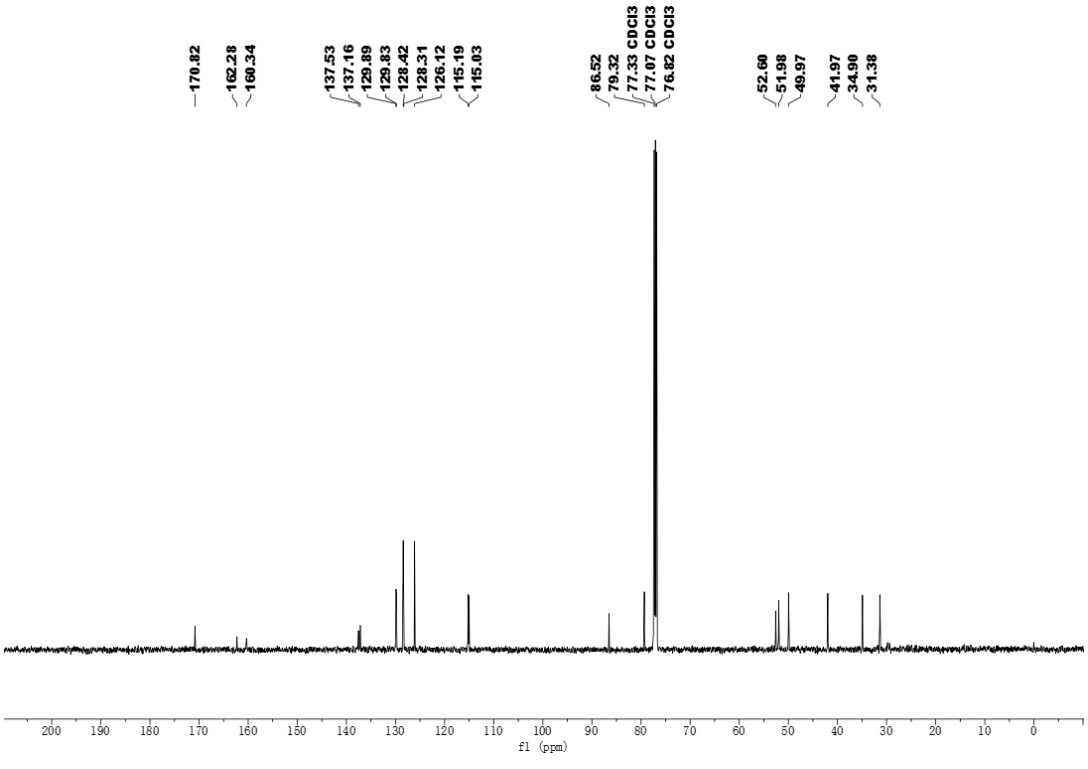


Figure S34. ^{13}C NMR spectra of **4**

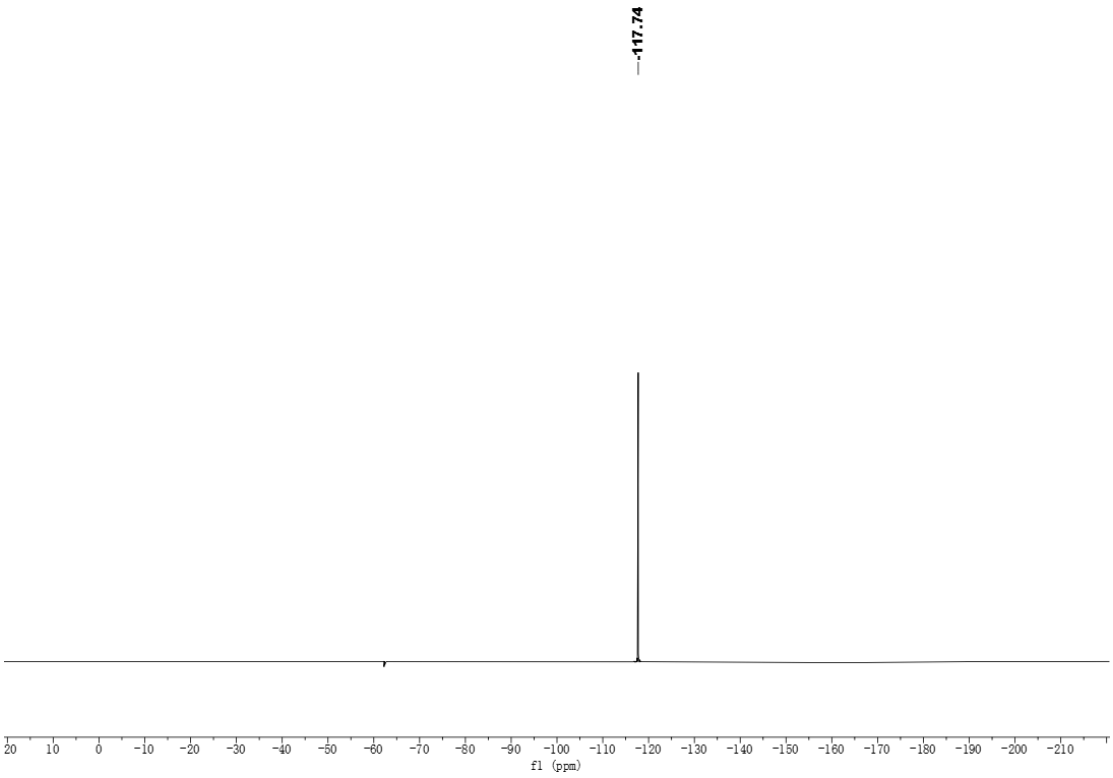


Figure S35. ^{19}F NMR spectra of **4**

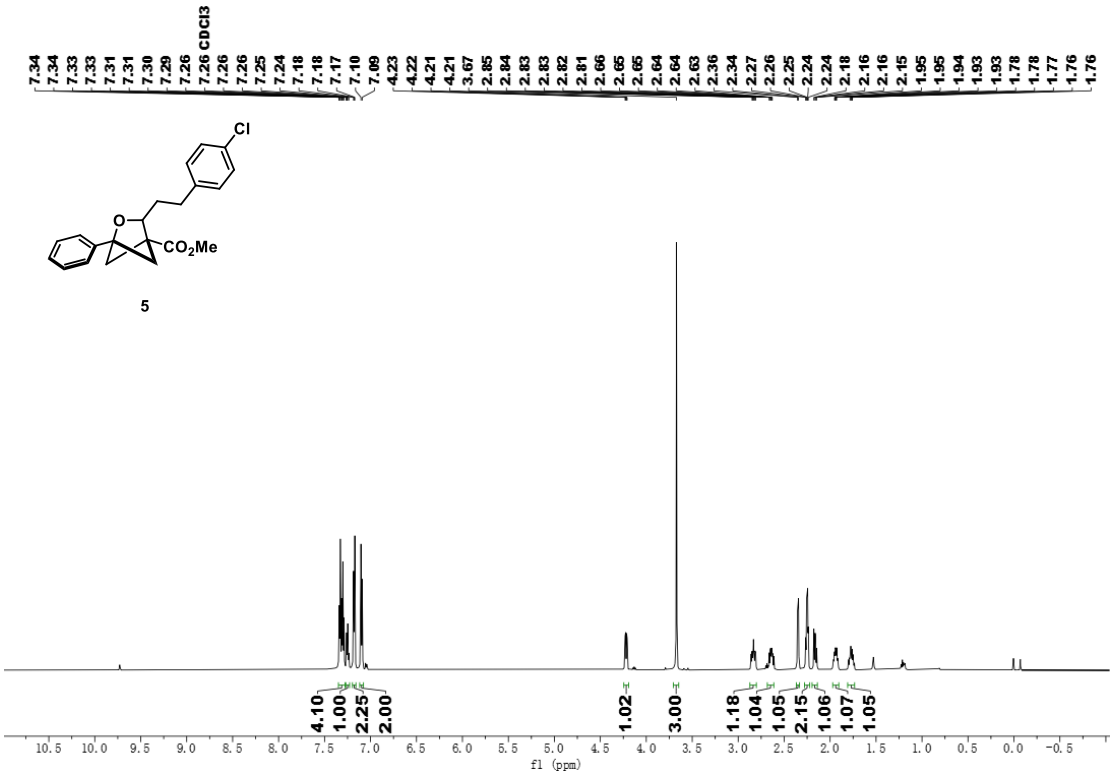


Figure S36. ^{1}H NMR spectra of **5**

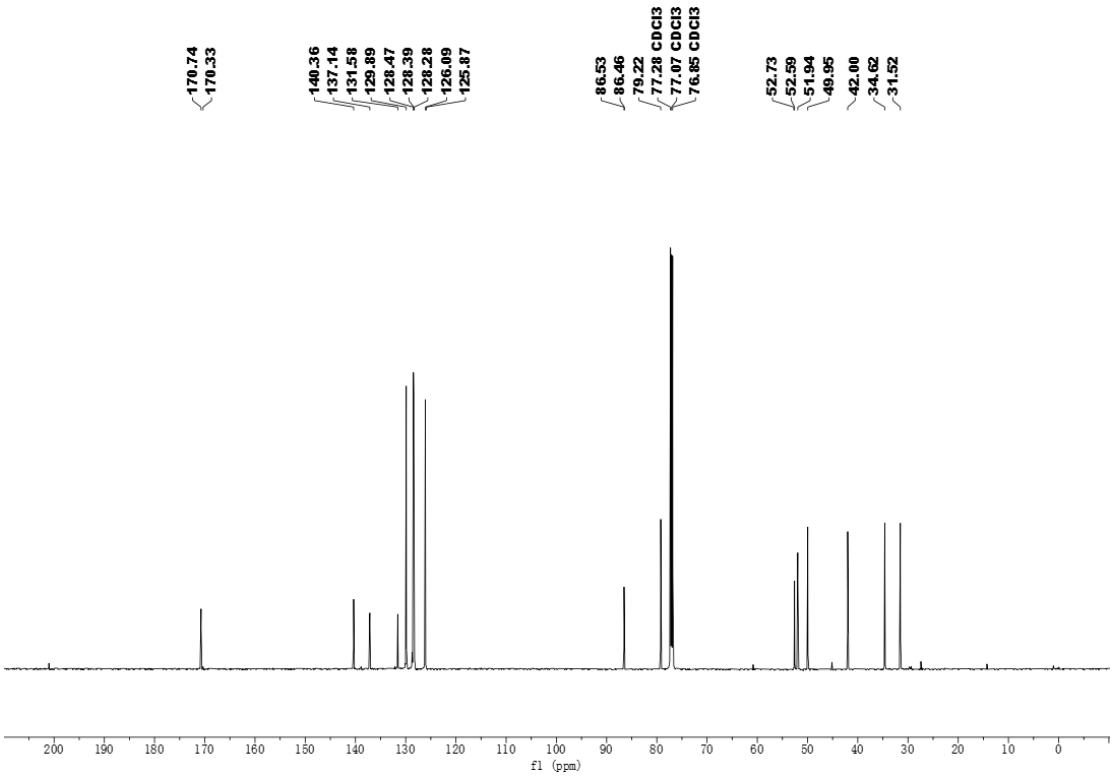


Figure S37. ^{13}C NMR spectra of **5**

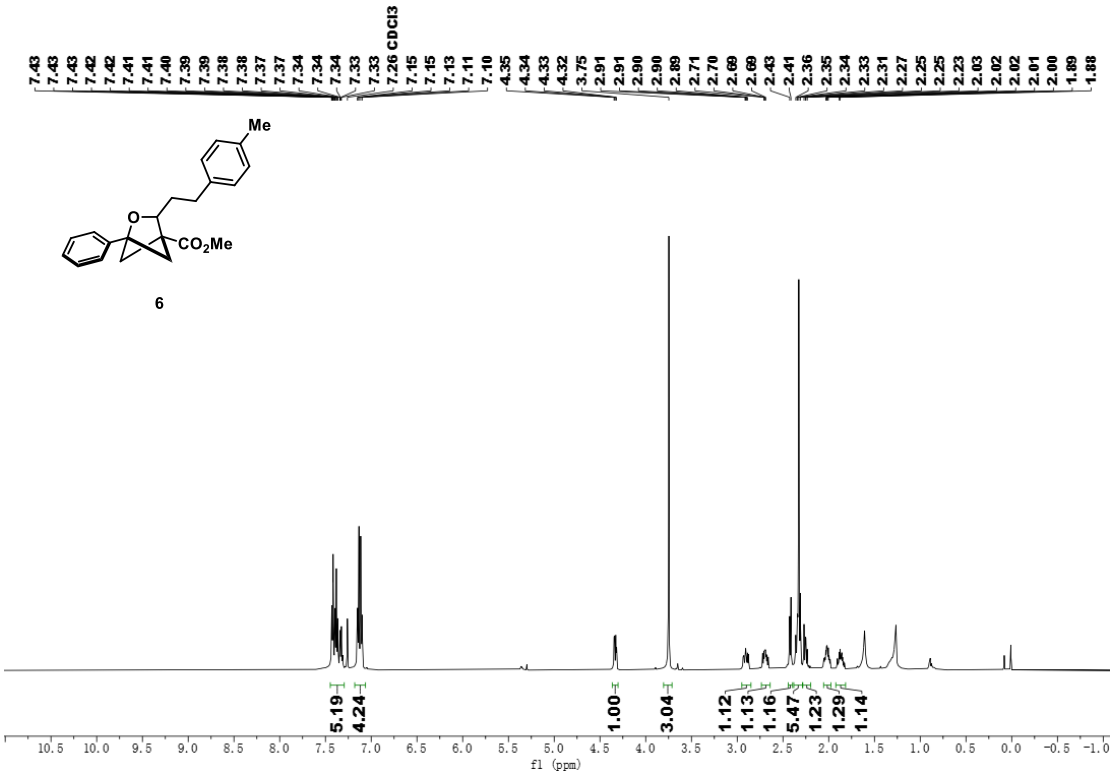


Figure S38. ^{1}H NMR spectra of **6**

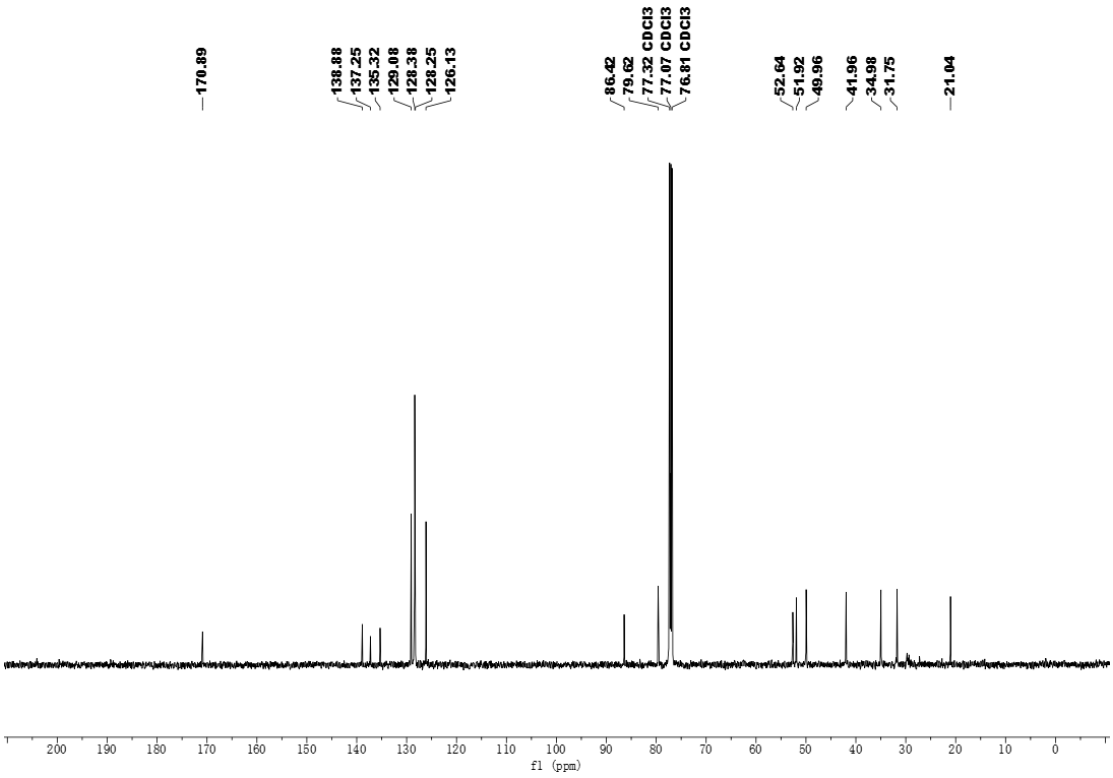


Figure S39. ^{13}C NMR spectra of **6**

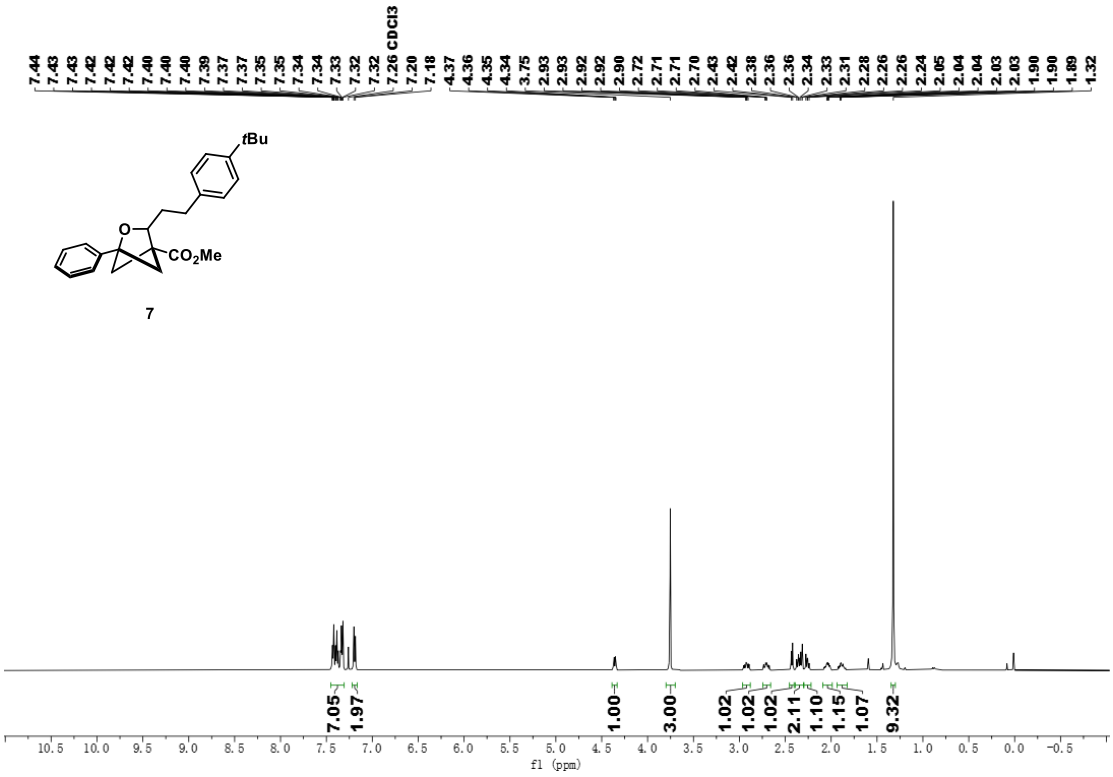


Figure S40. ^{1}H NMR spectra of **7**

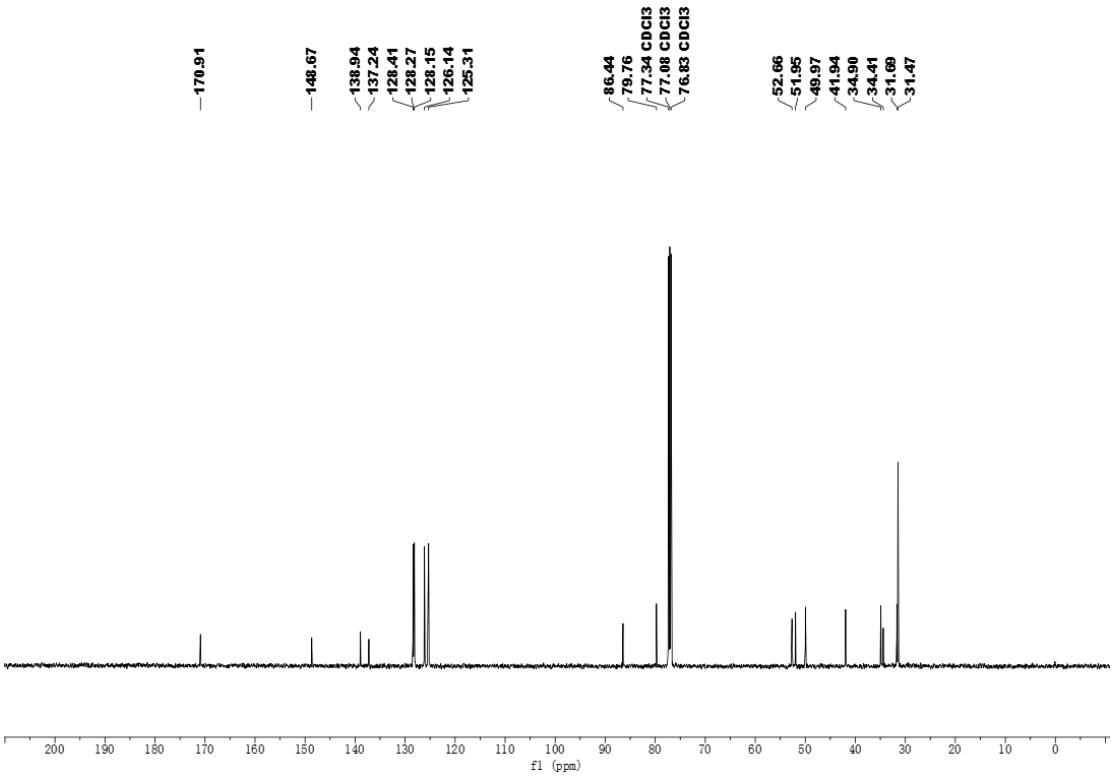


Figure S41. ^{13}C NMR spectra of **7**

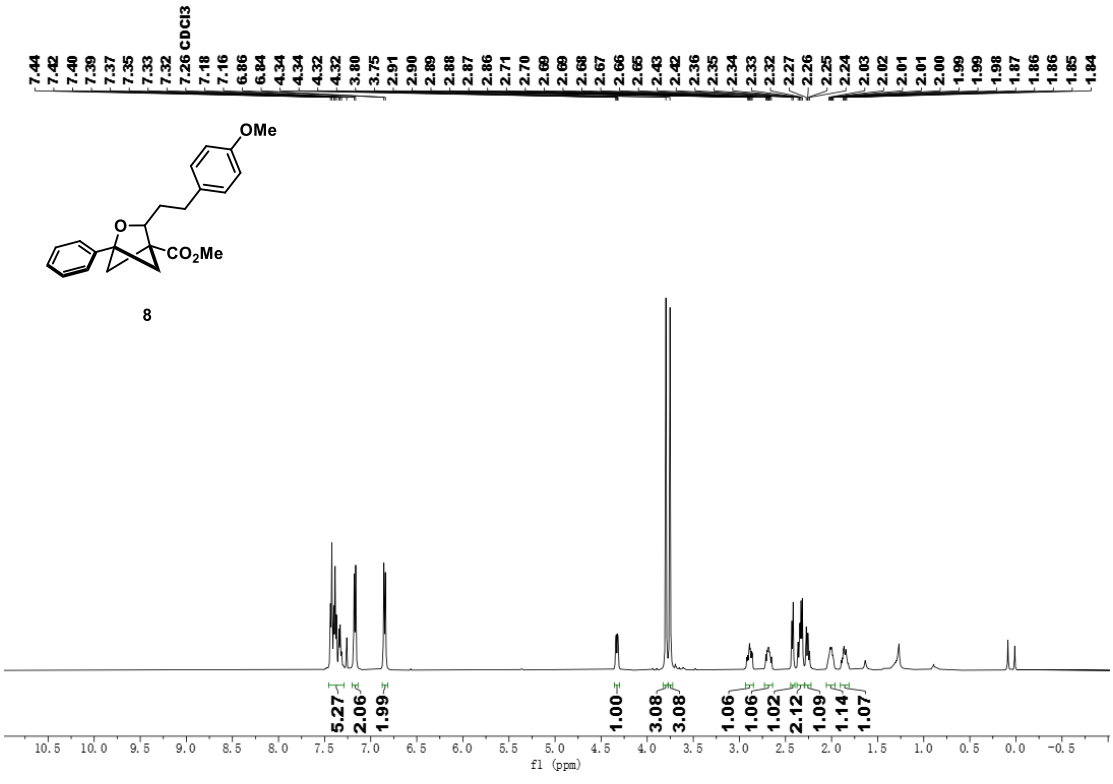


Figure S42. ^{1}H NMR spectra of **8**

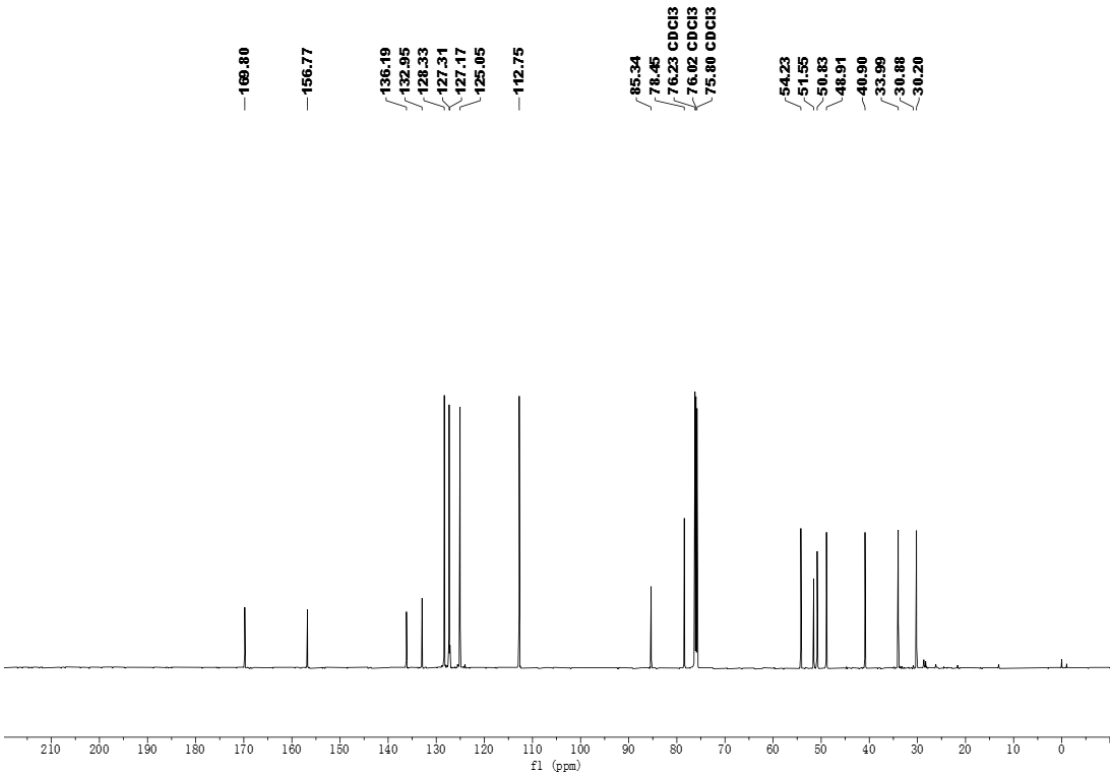


Figure S43. ^{13}C NMR spectra of **8**

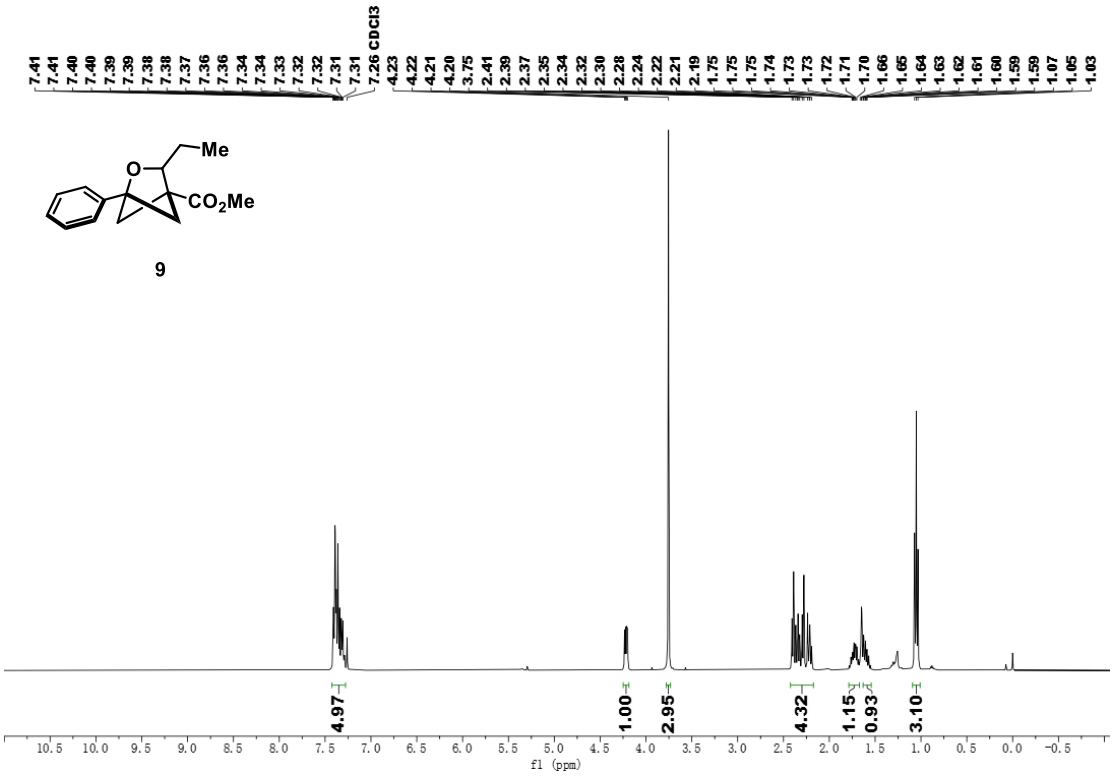


Figure S44. ^{1}H NMR spectra of **9**

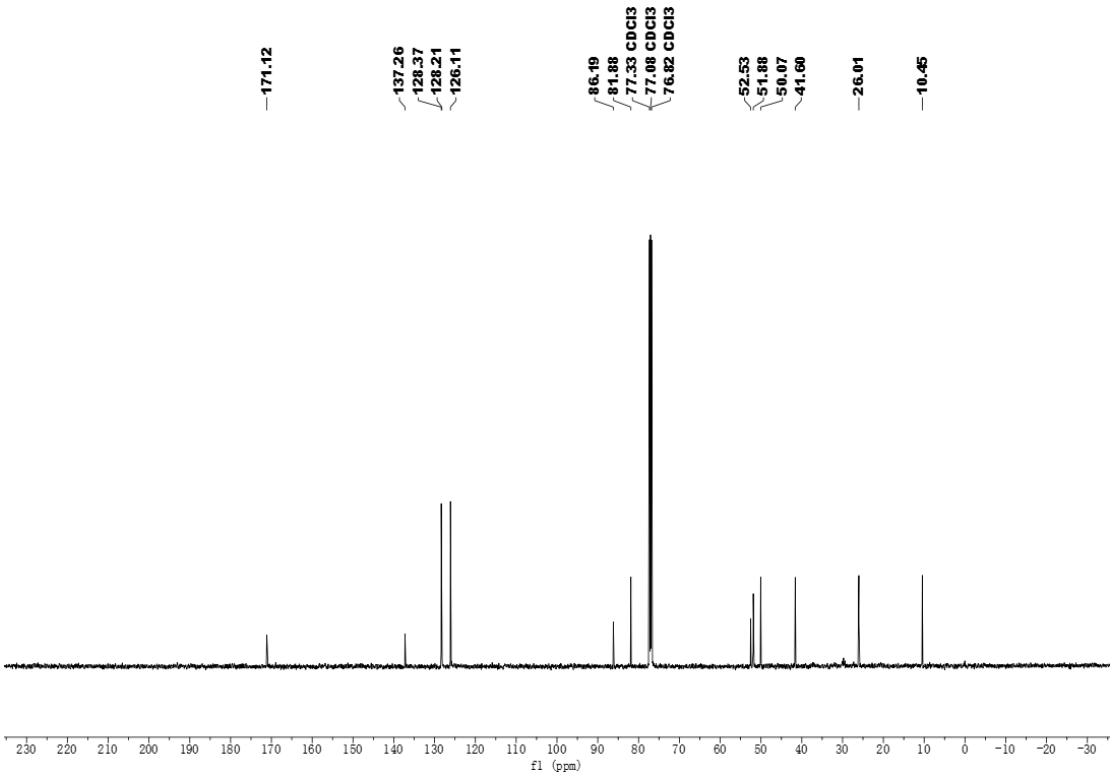


Figure S45. ^{13}C NMR spectra of **9**

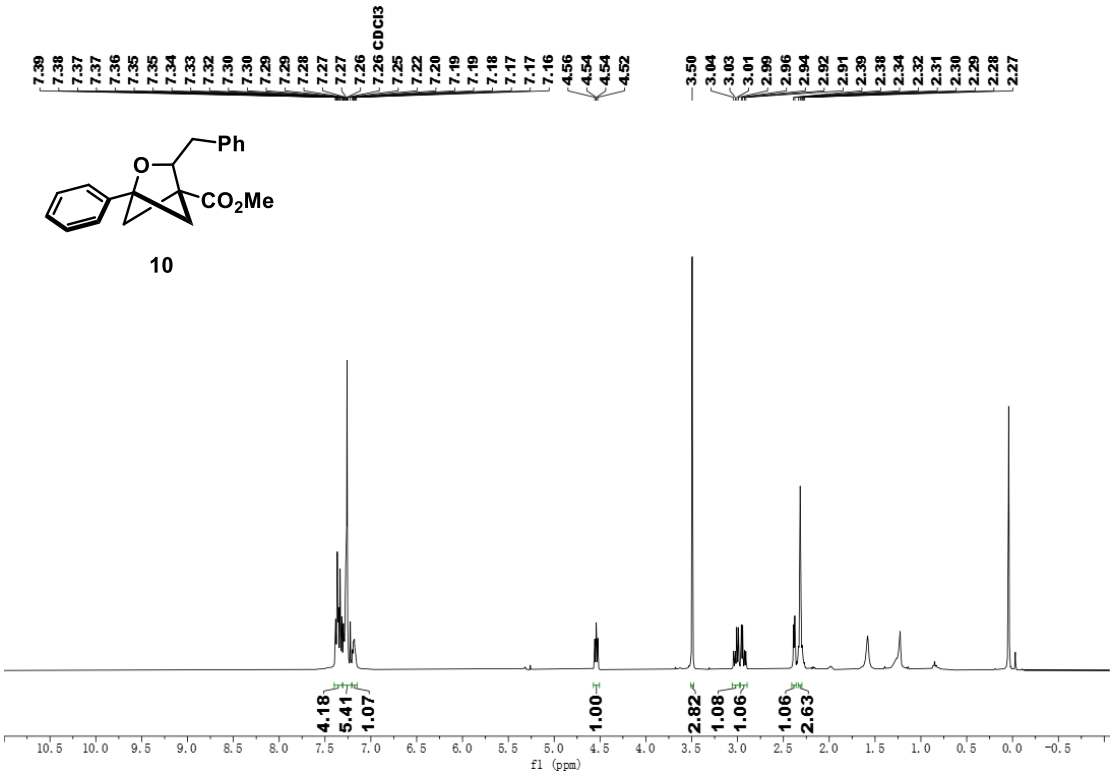


Figure S46. ^{1}H NMR spectra of **10**

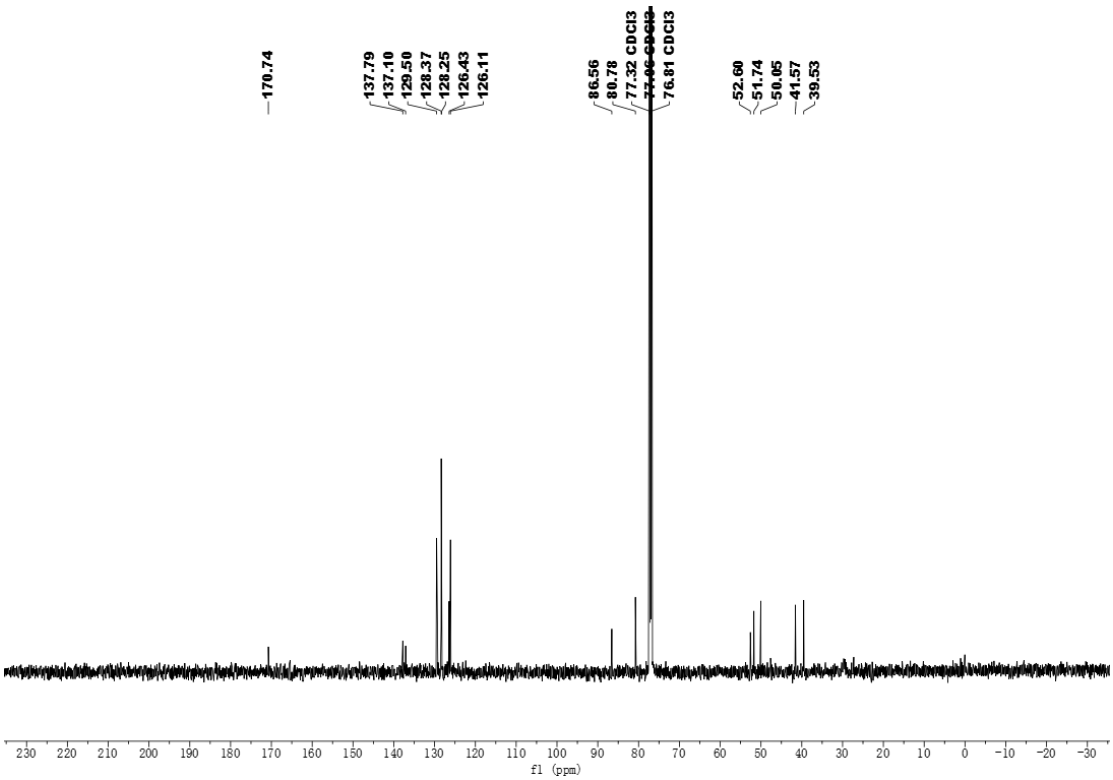


Figure S47. ^{13}C NMR spectra of **10**

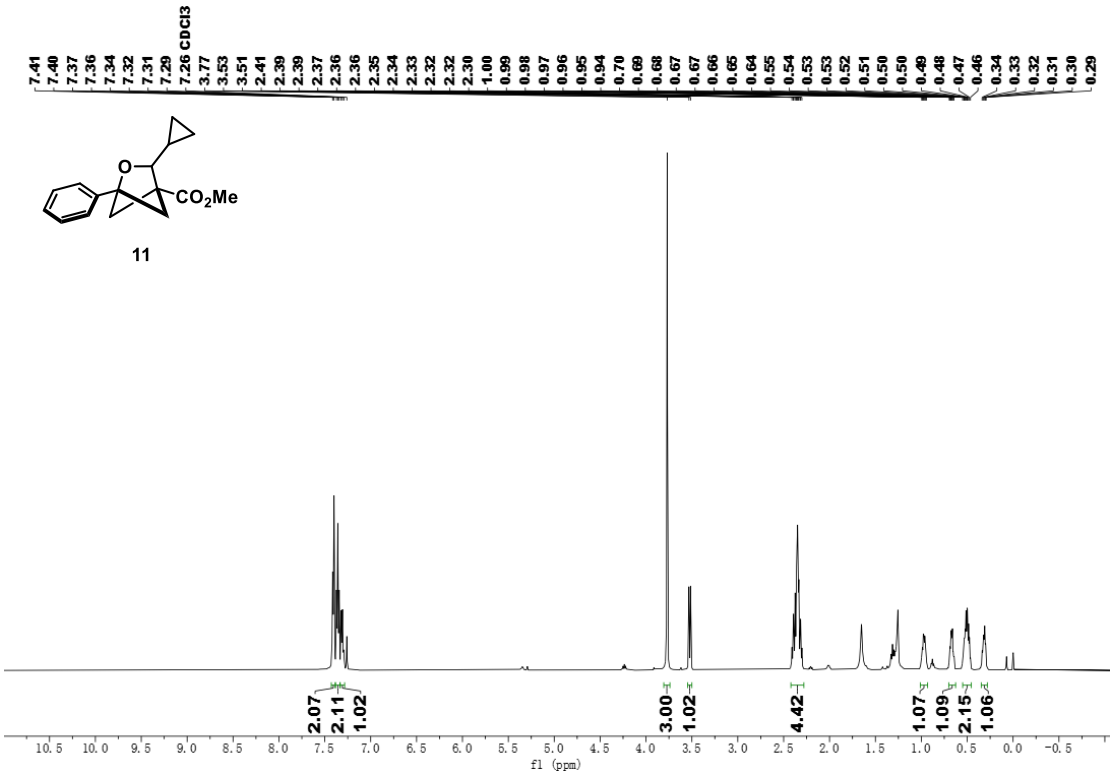


Figure S48. ^{1}H NMR spectra of **11**

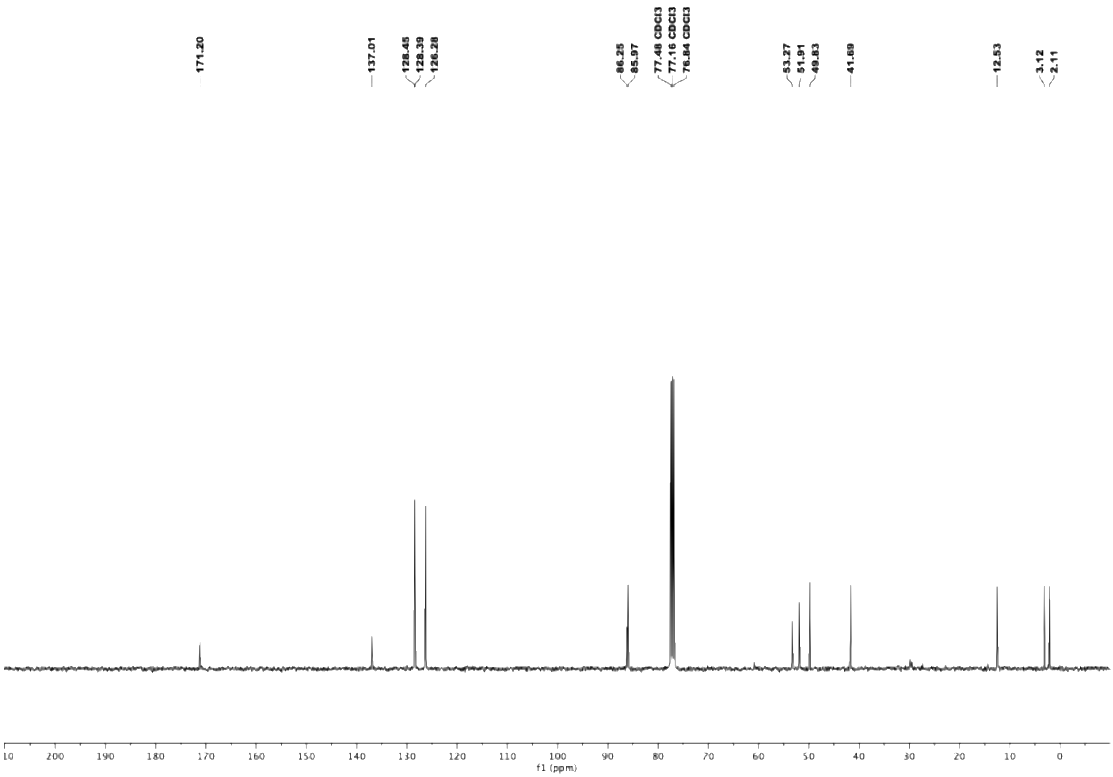


Figure S49. ^{13}C NMR spectra of **11**

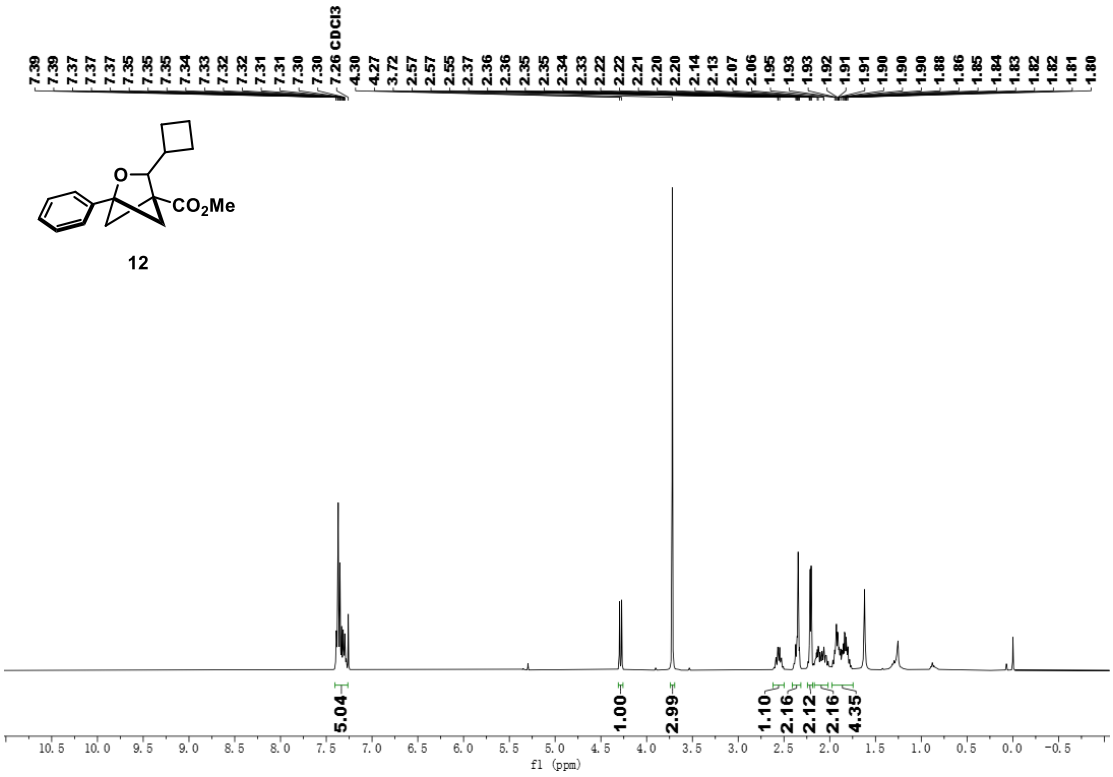


Figure S50. ^{1}H NMR spectra of **12**

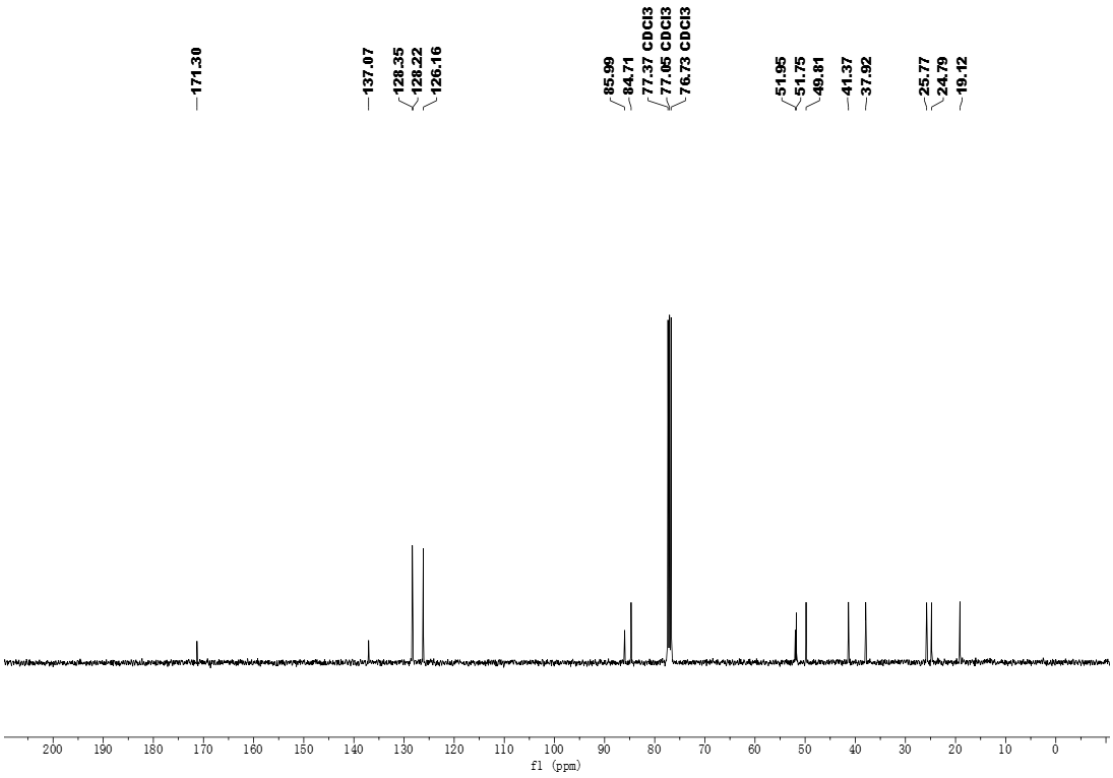
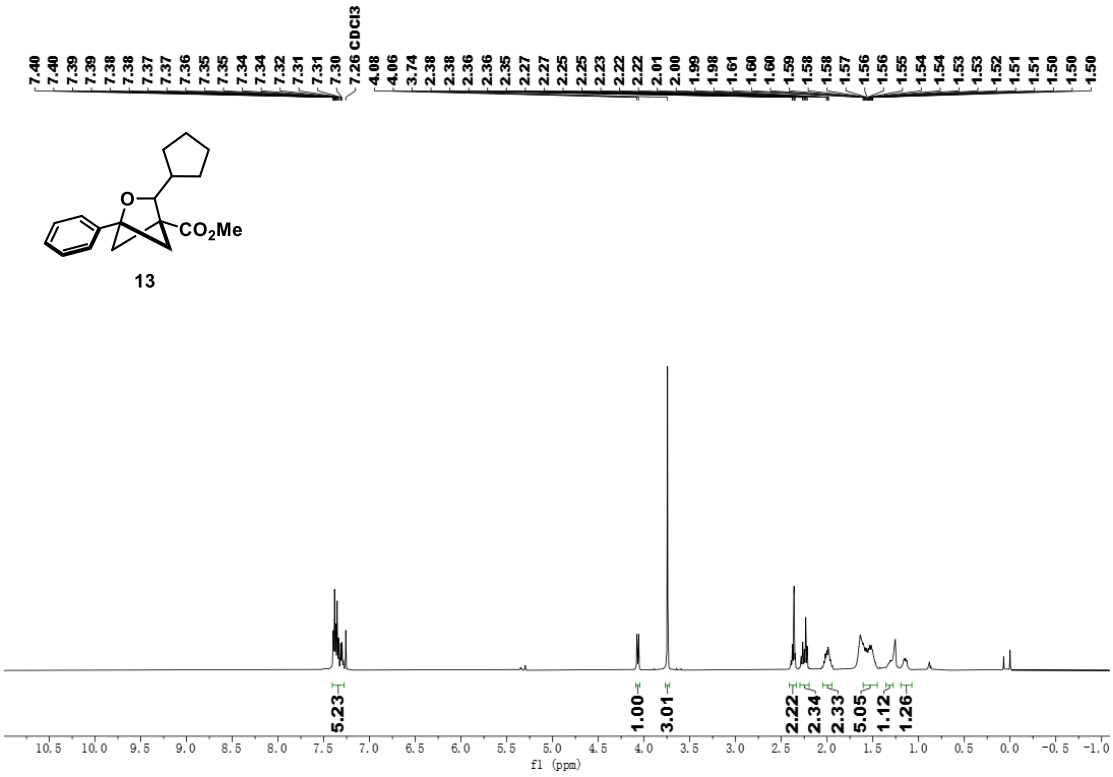


Figure S51. ^{13}C NMR spectra of **12**



13

Figure S52. ^{1}H NMR spectra of **13**

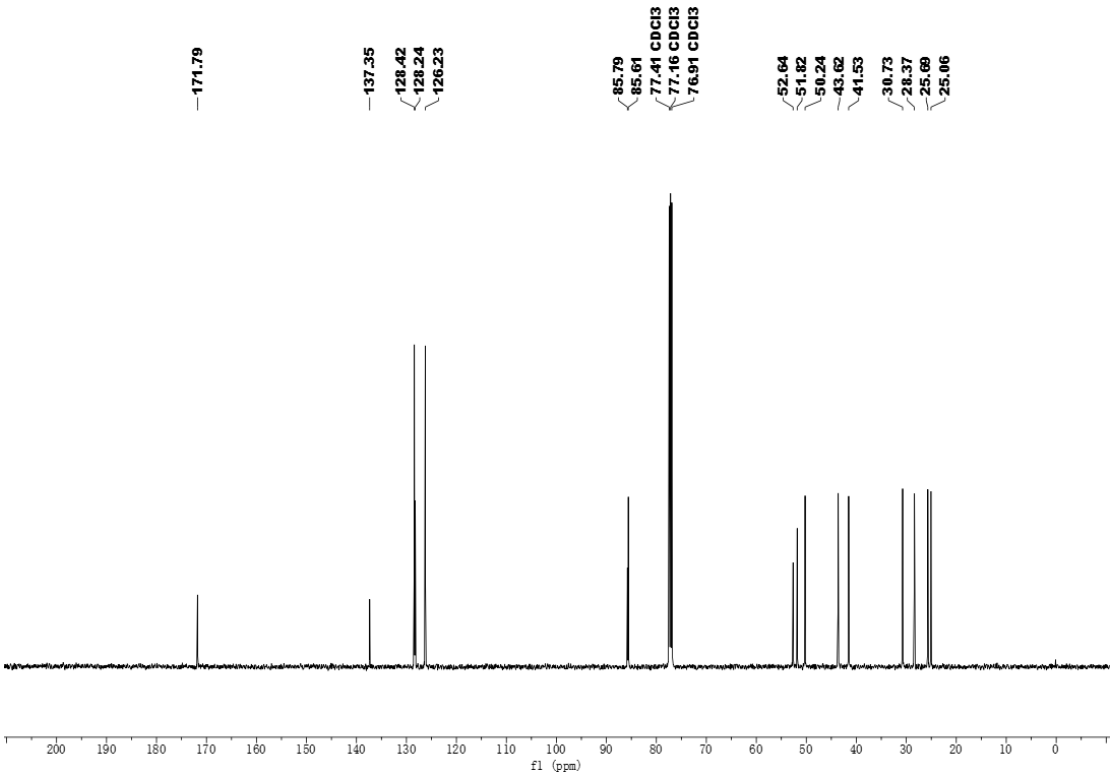


Figure S53. ^{13}C NMR spectra of **13**

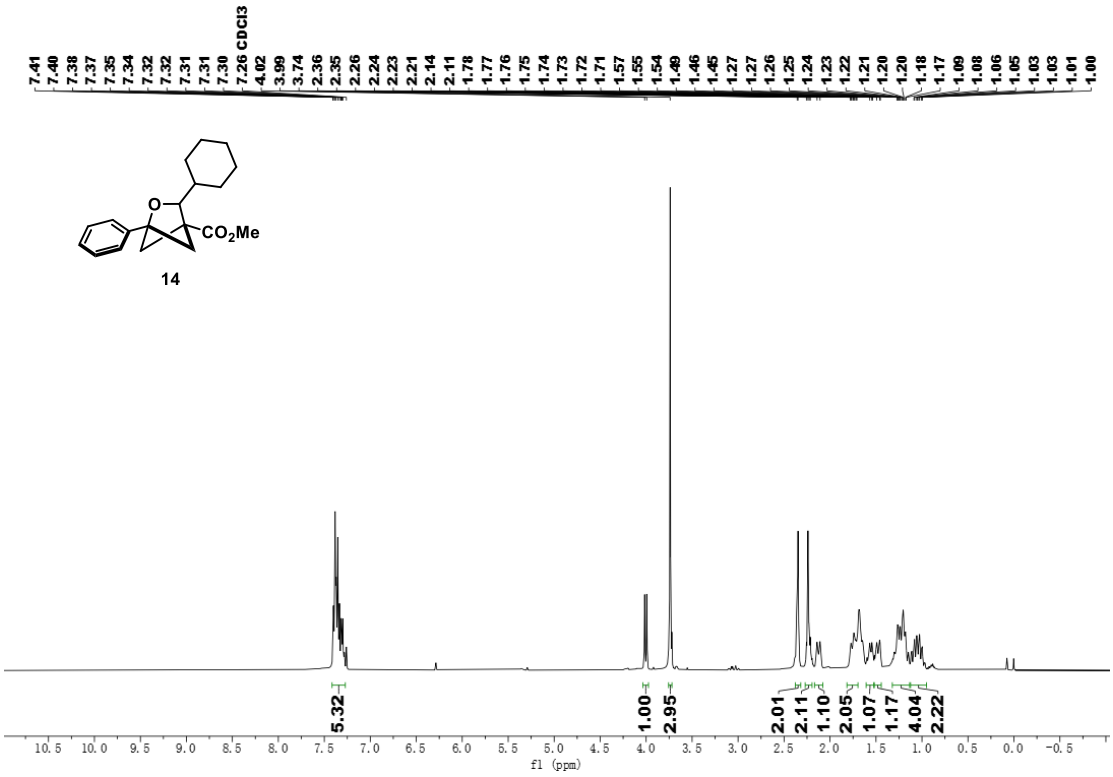


Figure S54. ^{1}H NMR spectra of **14**

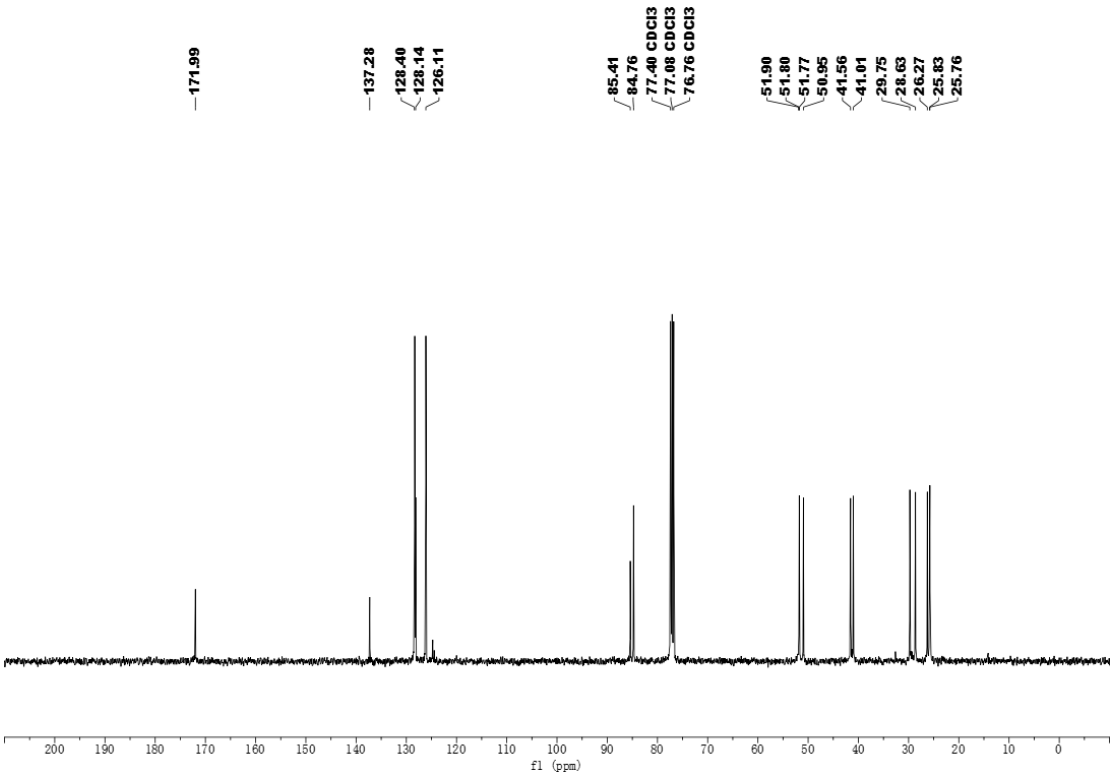


Figure S55. ^{13}C NMR spectra of **14**

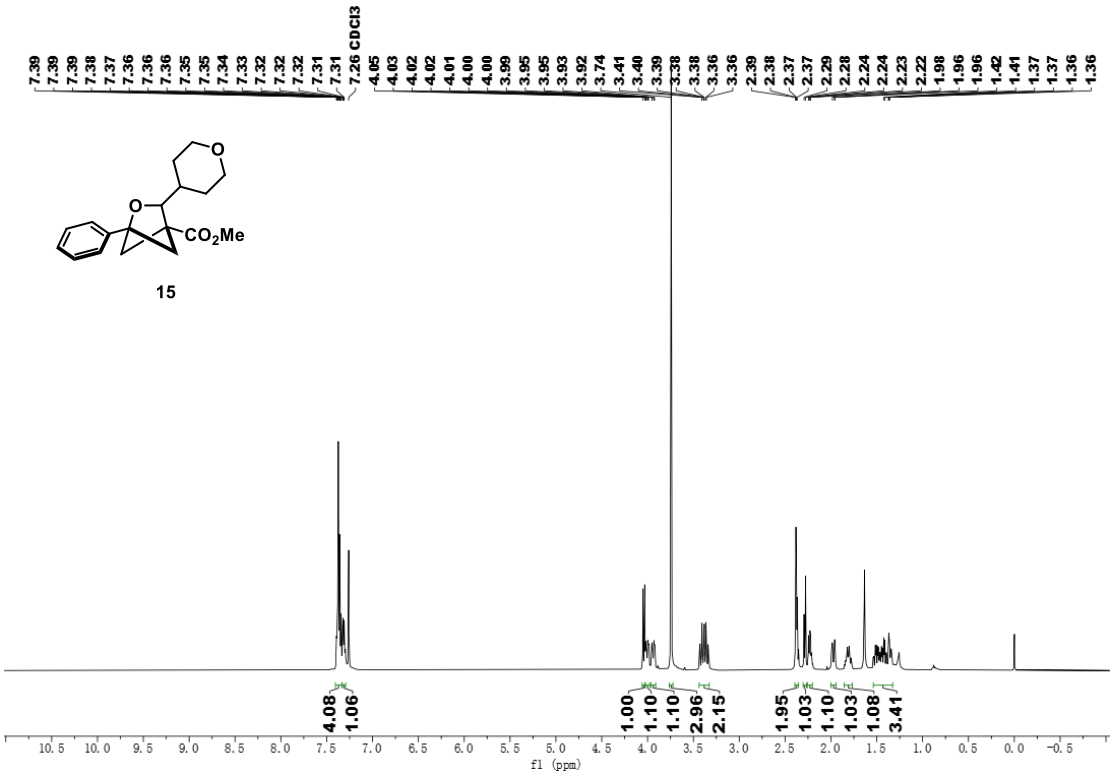


Figure S56. ^{1}H NMR spectra of **15**

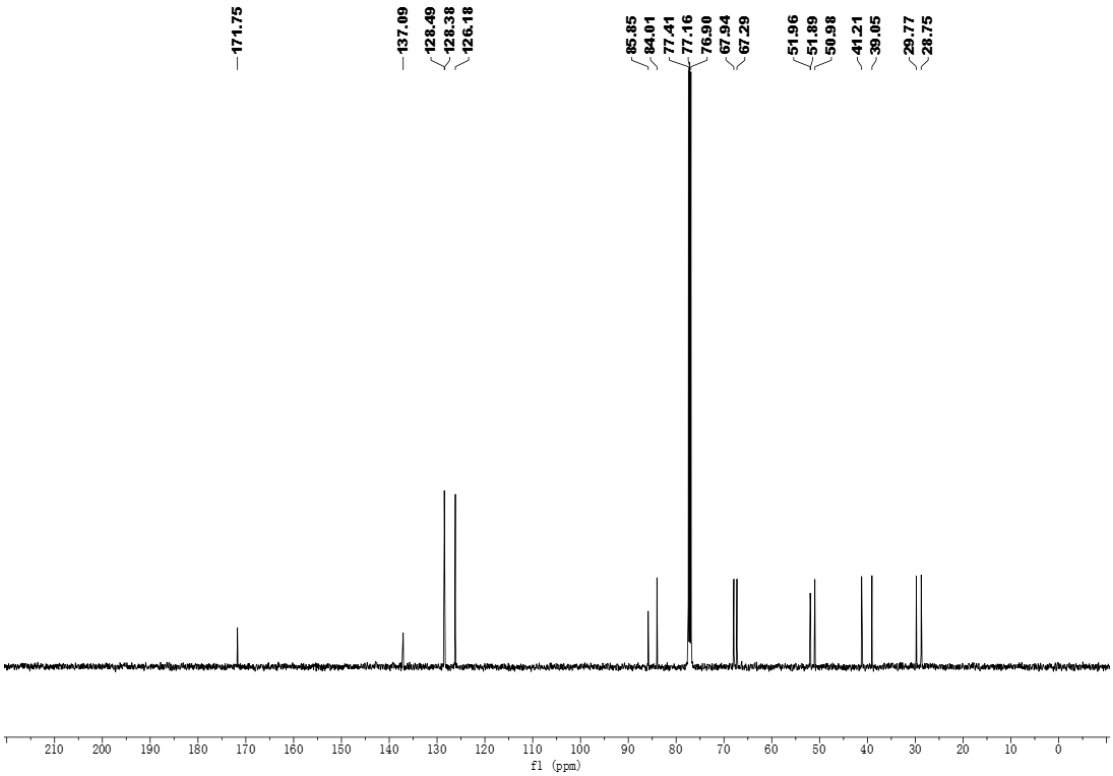


Figure S57. ^{13}C NMR spectra of **15**

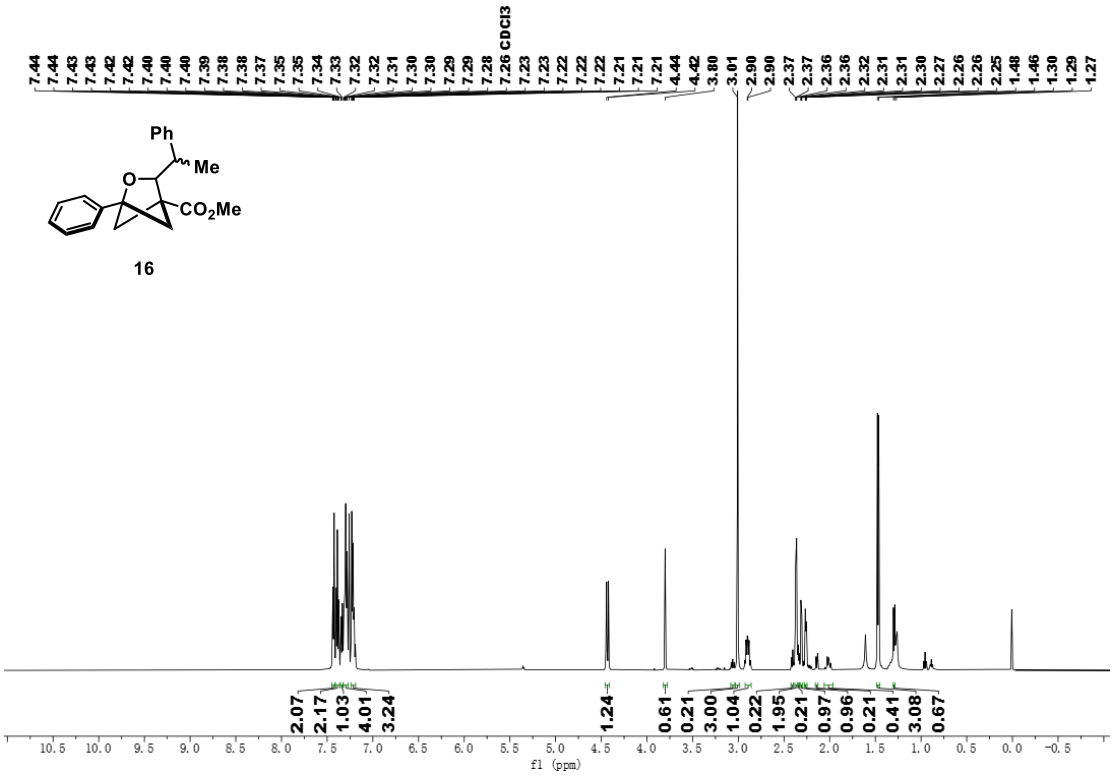


Figure S58. ^{1}H NMR spectra of **16**

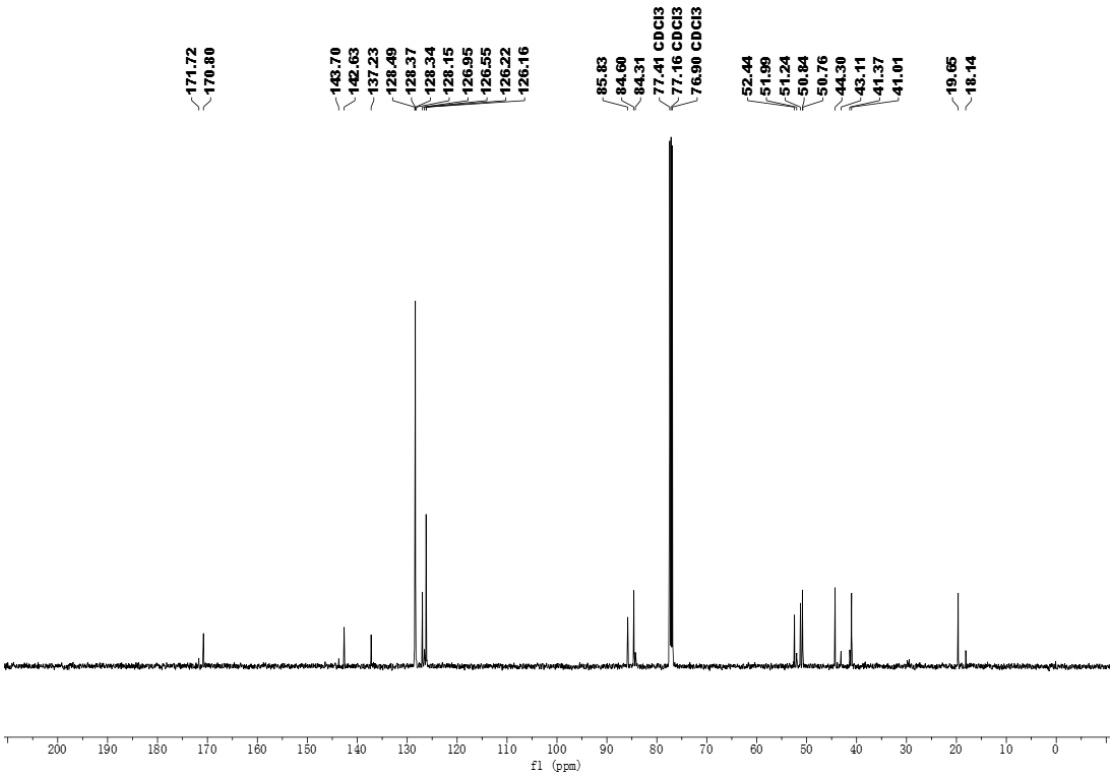


Figure S59. ^{13}C NMR spectra of **16**

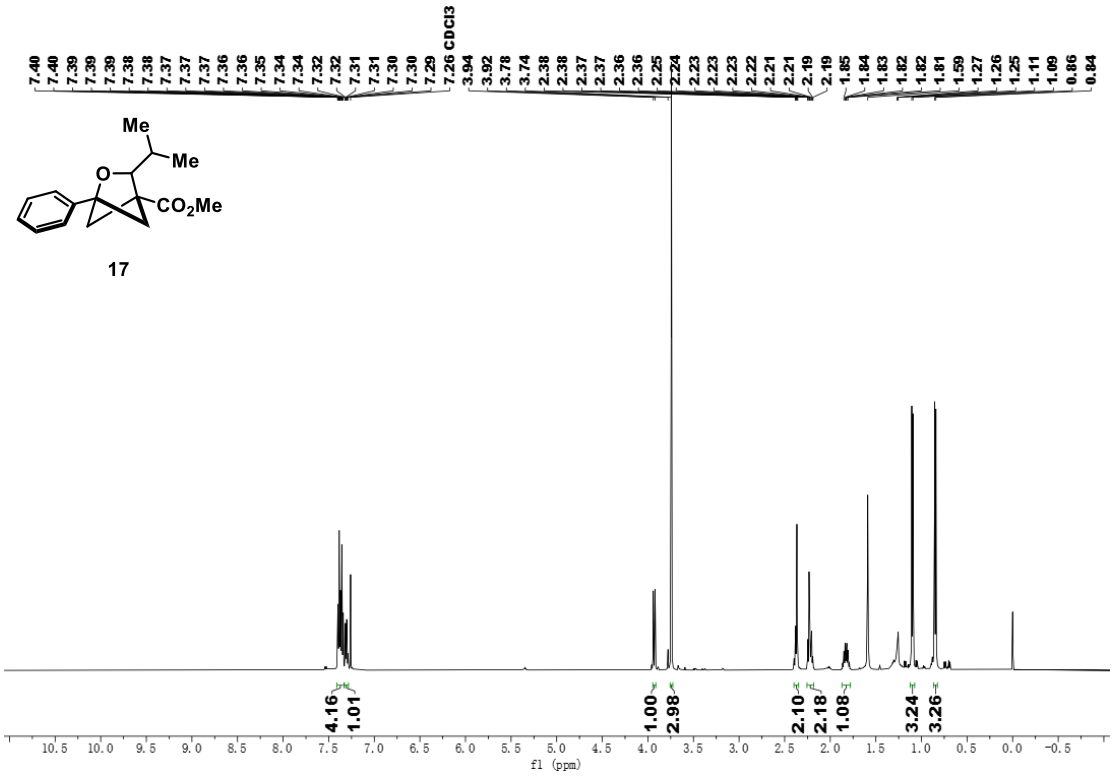


Figure S60. ^{1}H NMR spectra of **17**

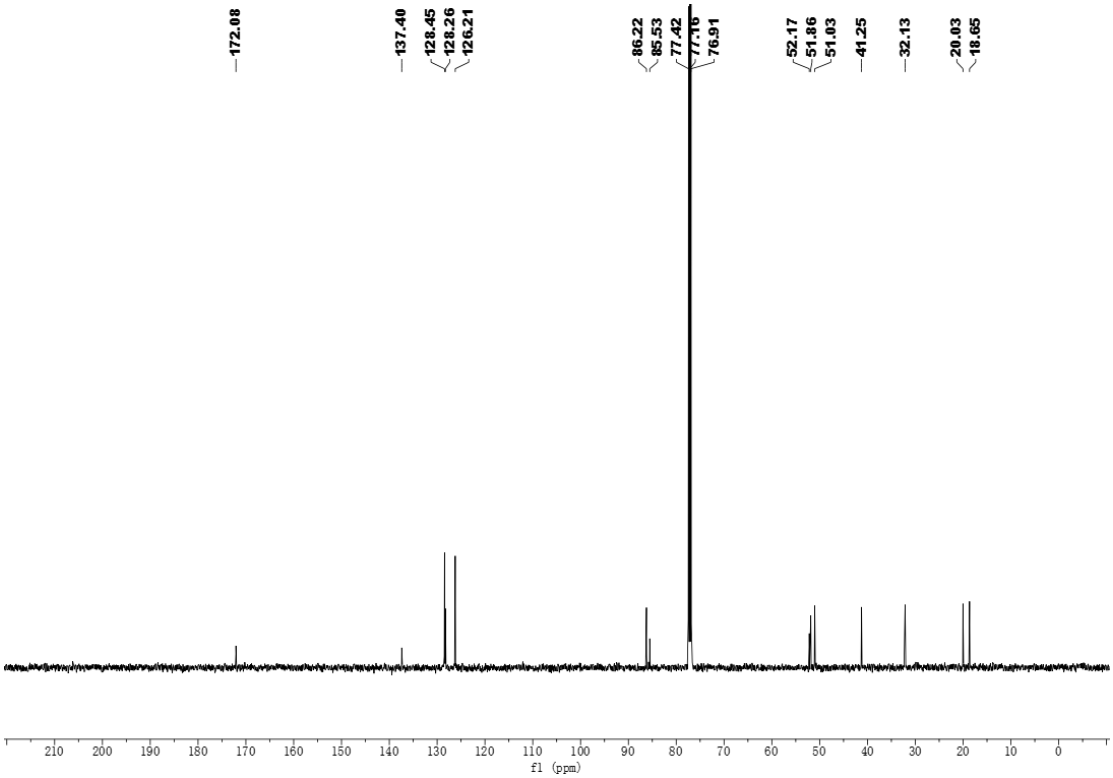


Figure S61. ^{13}C NMR spectra of **17**

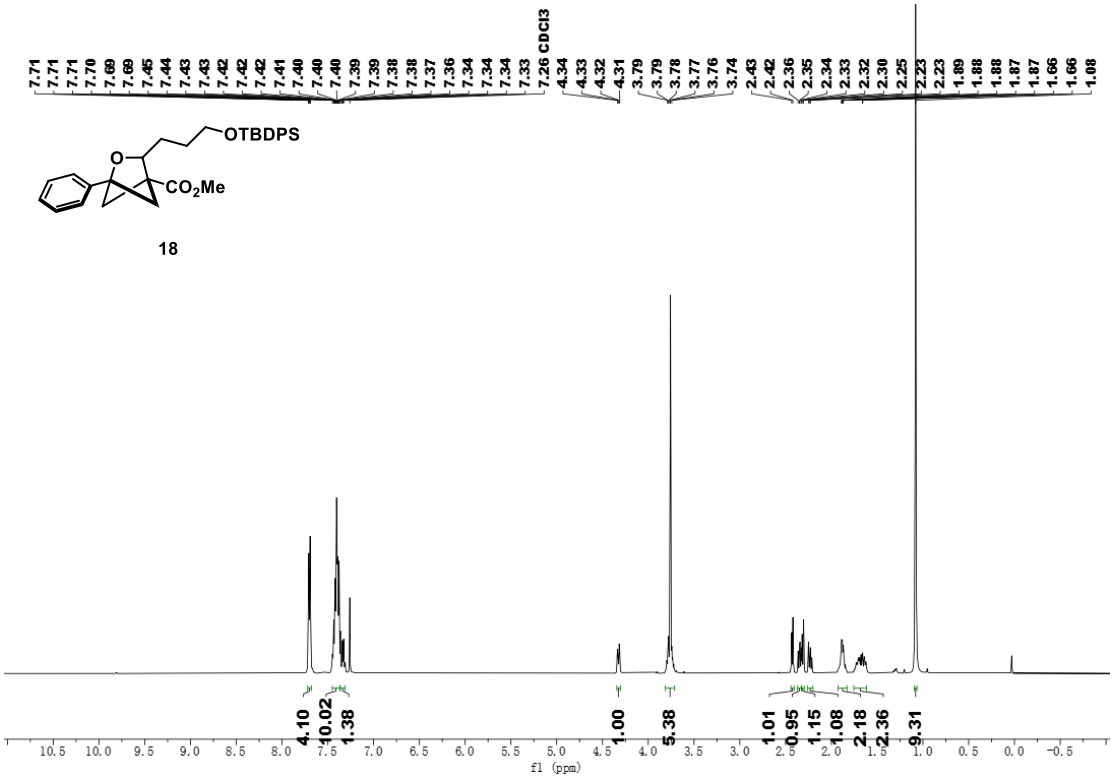


Figure S62. ^{1}H NMR spectra of **18**

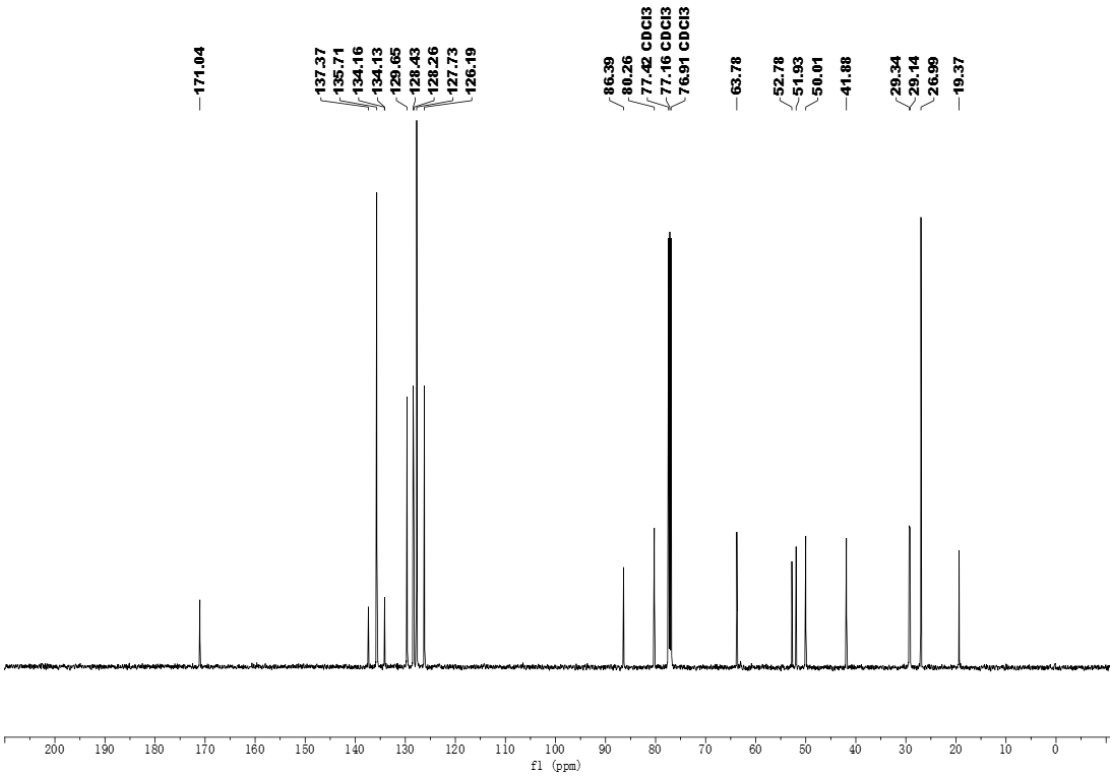


Figure S63. ^{13}C NMR spectra of **18**

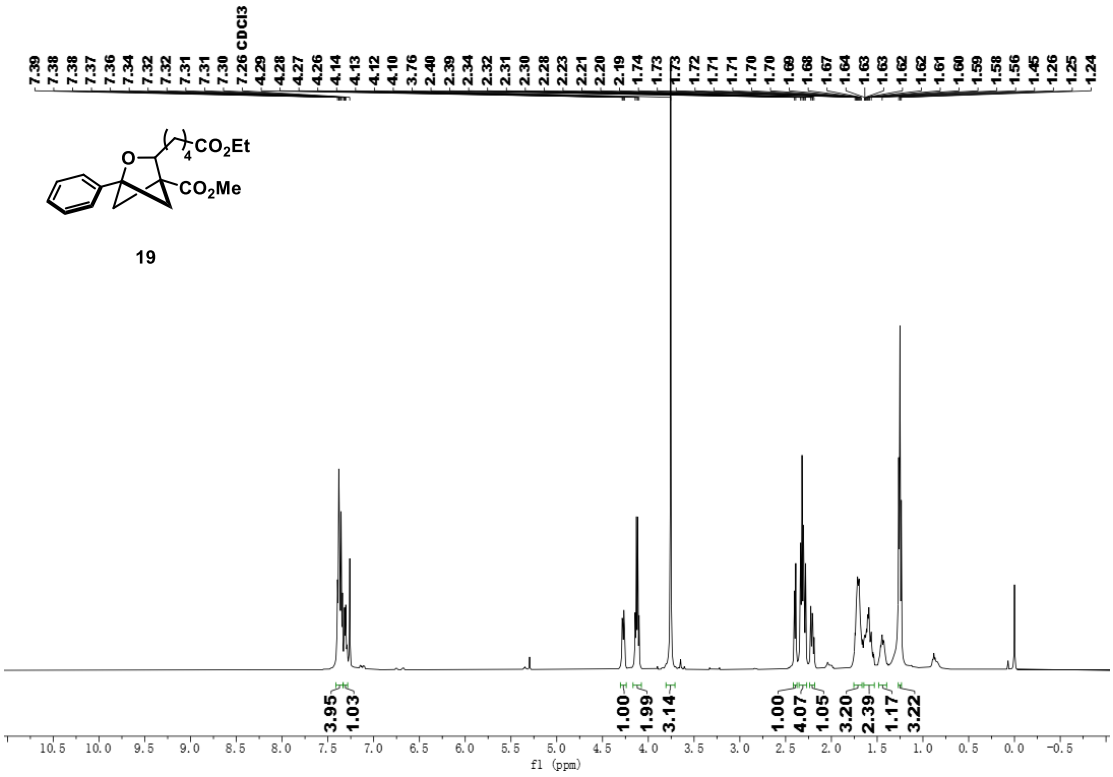


Figure S64. ^{1}H NMR spectra of **19**

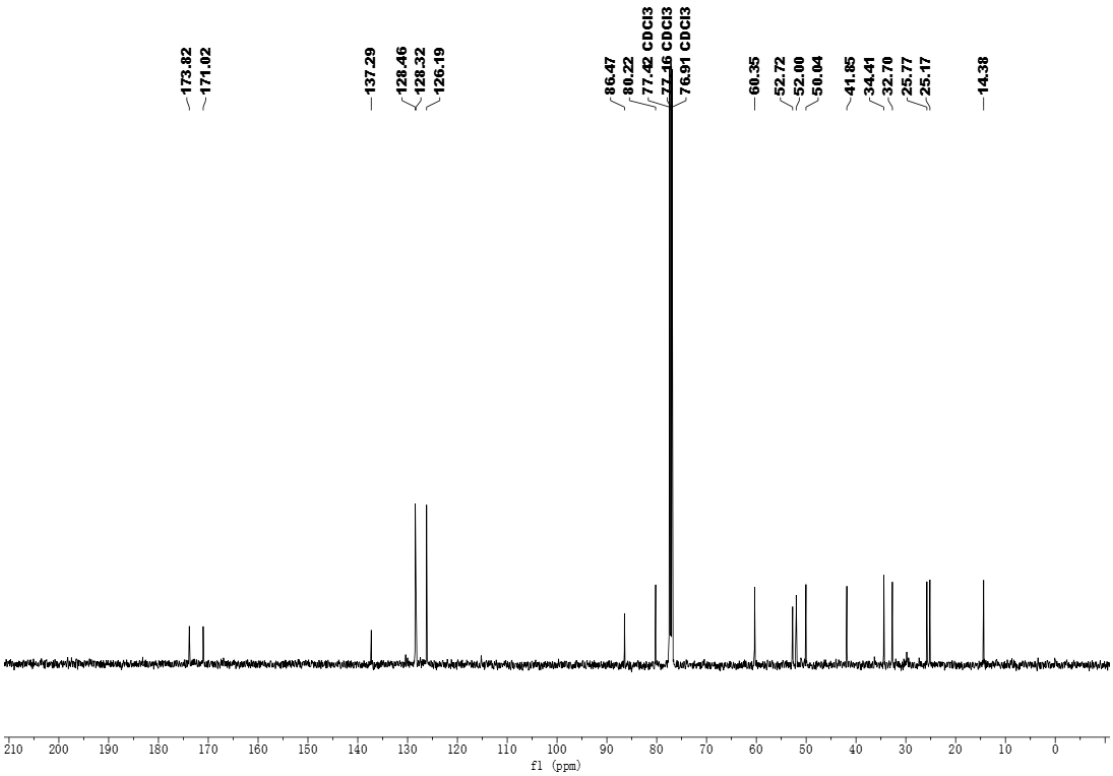


Figure S65. ^{13}C NMR spectra of **19**

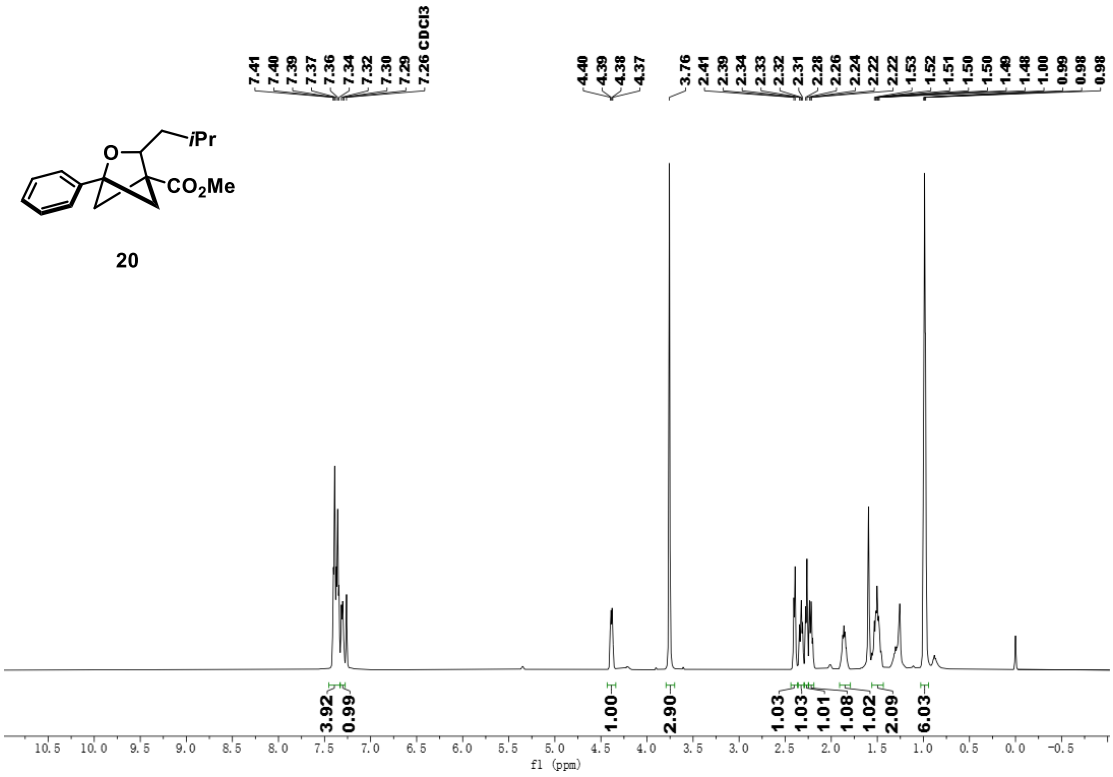


Figure S66. ^{1}H NMR spectra of **20**

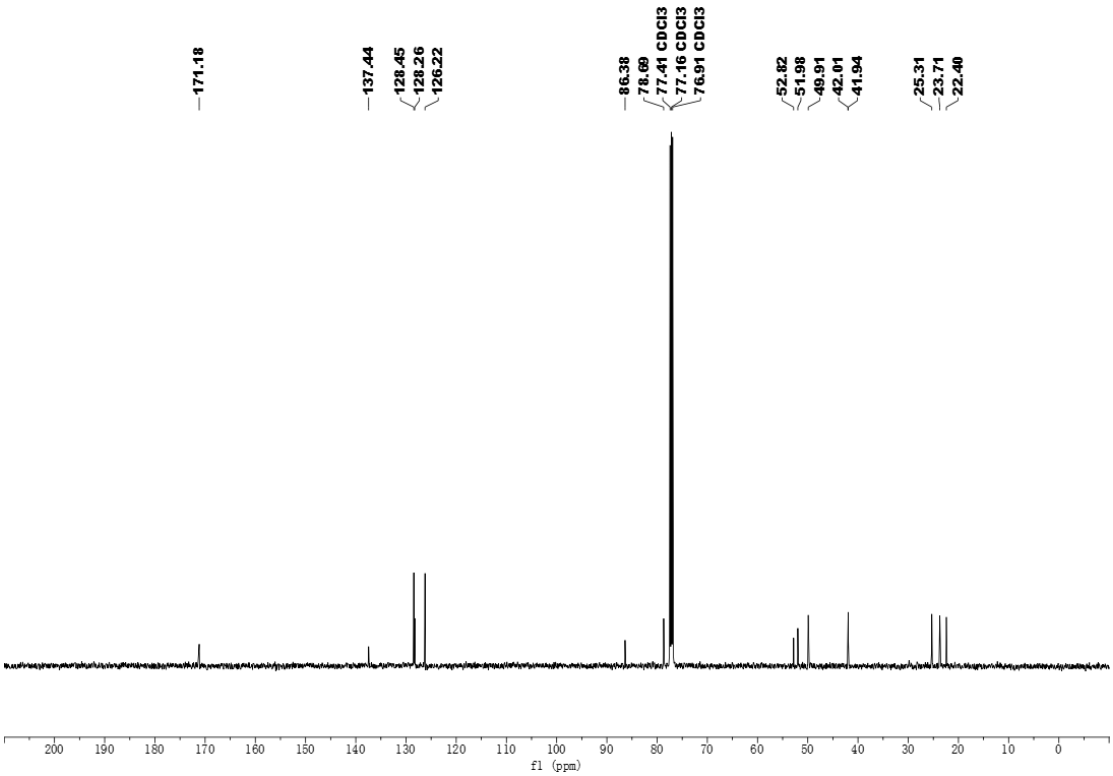


Figure S67. ^{13}C NMR spectra of **20**

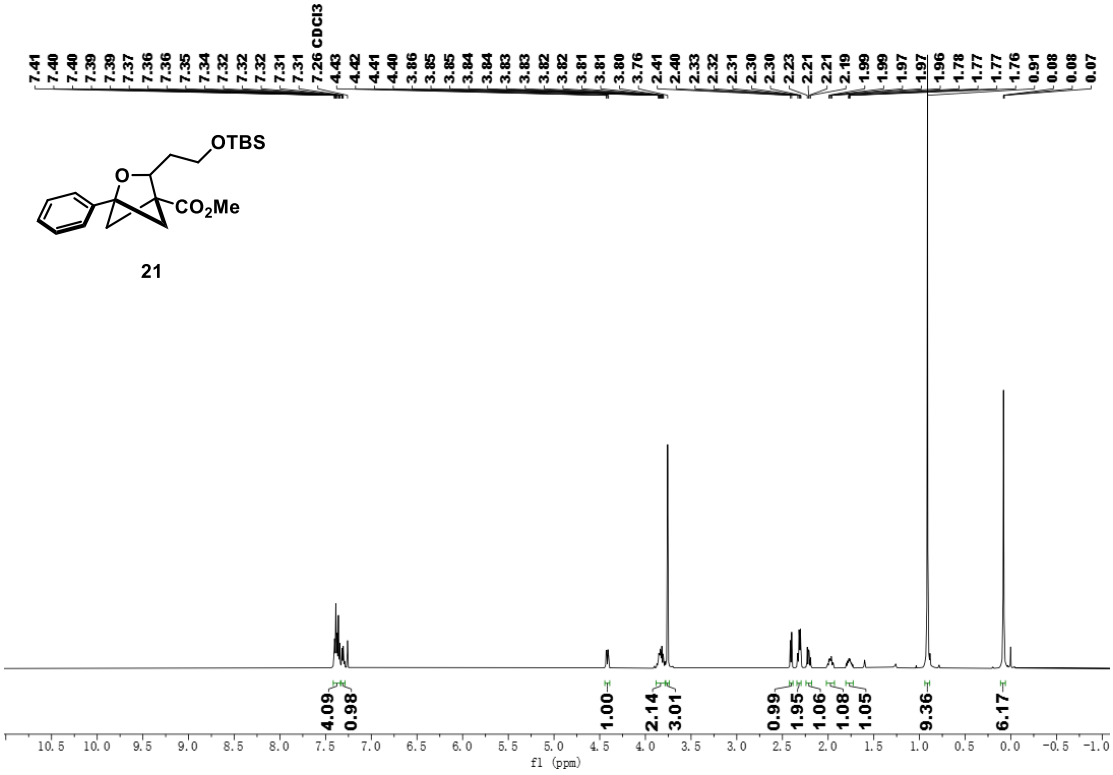


Figure S68. ^{1}H NMR spectra of **21**

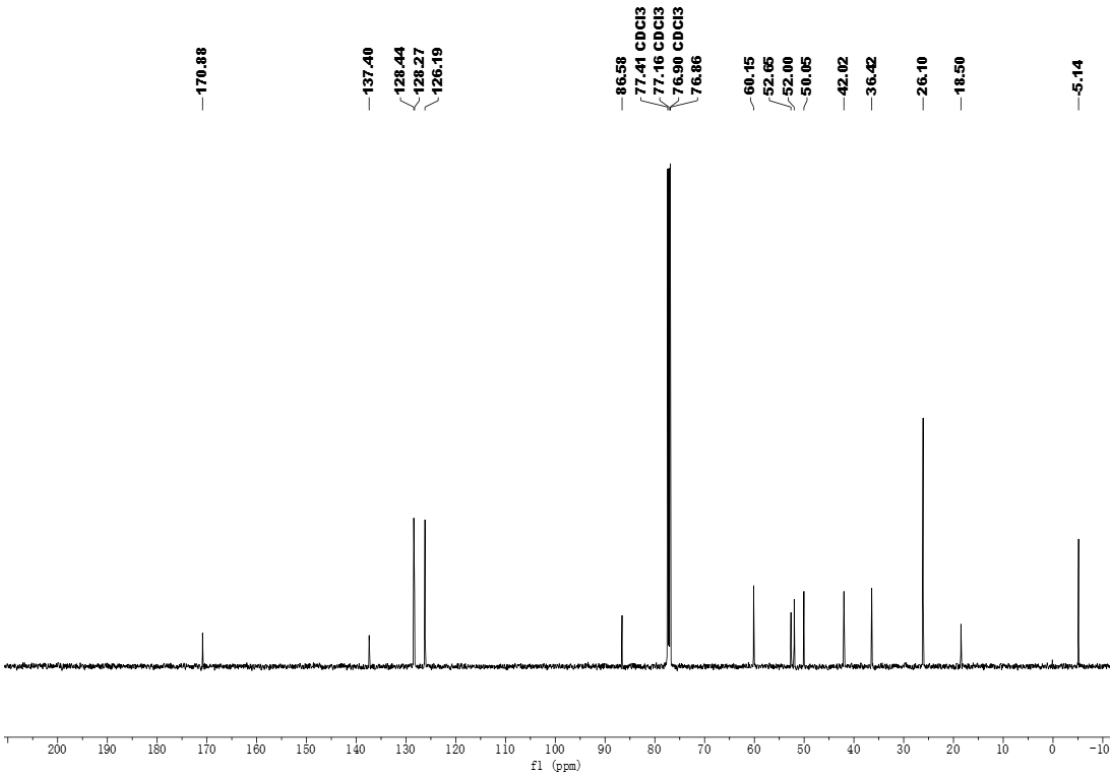
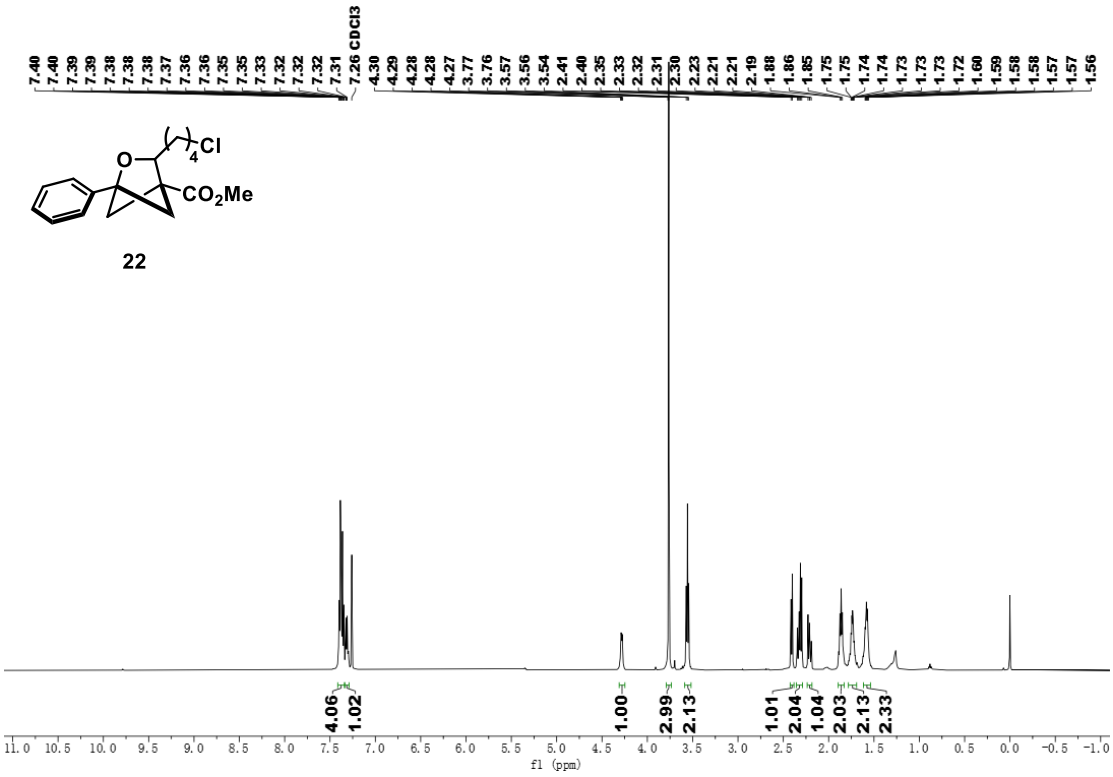


Figure S69. ^{13}C NMR spectra of **21**



22

Figure S70. ^{1}H NMR spectra of **22**

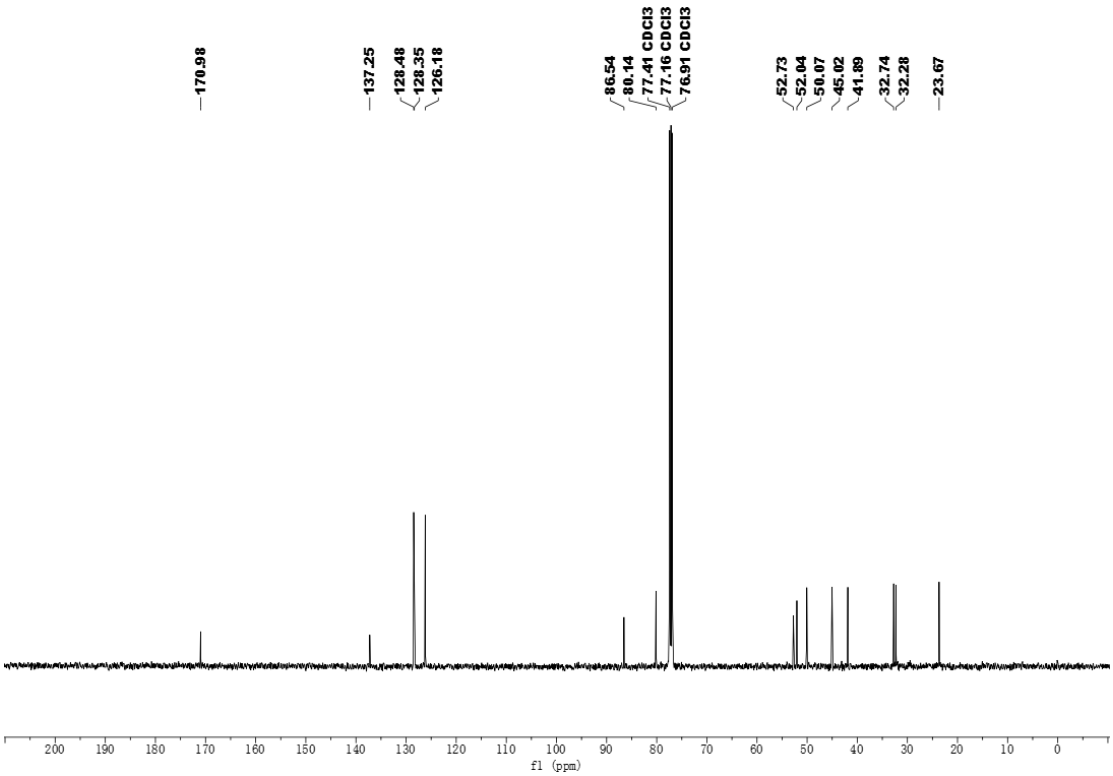


Figure S71. ^{13}C NMR spectra of **22**

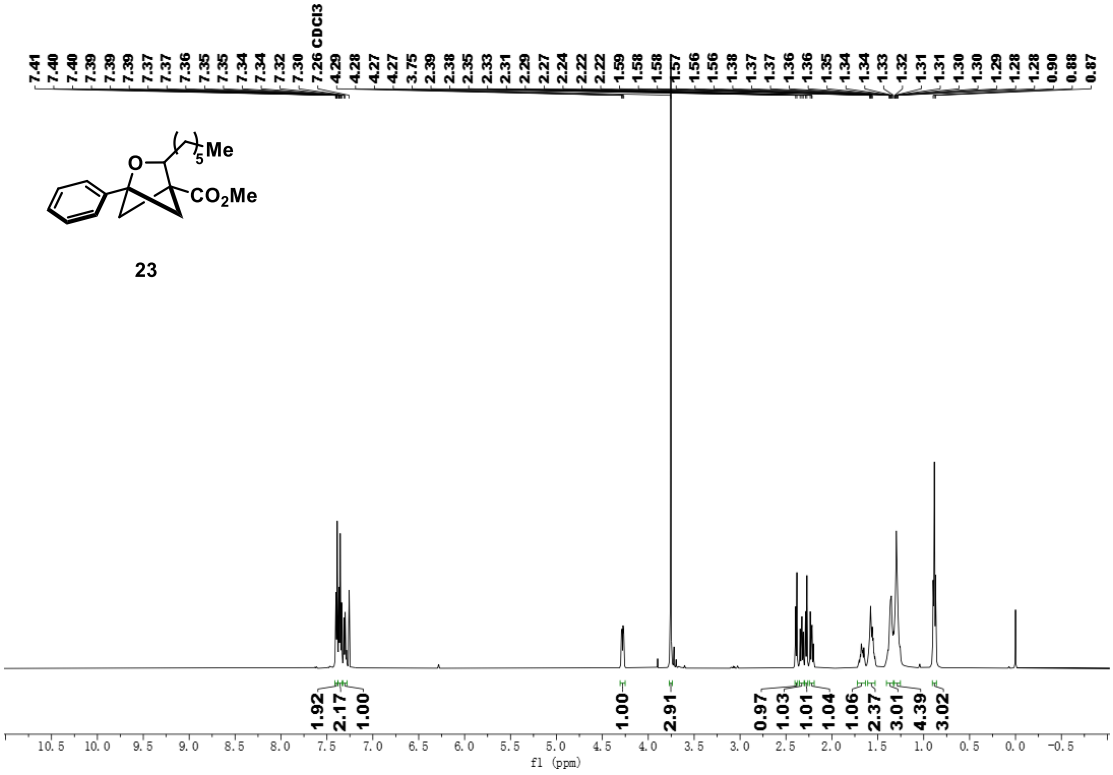


Figure S72. ^{1}H NMR spectra of **23**

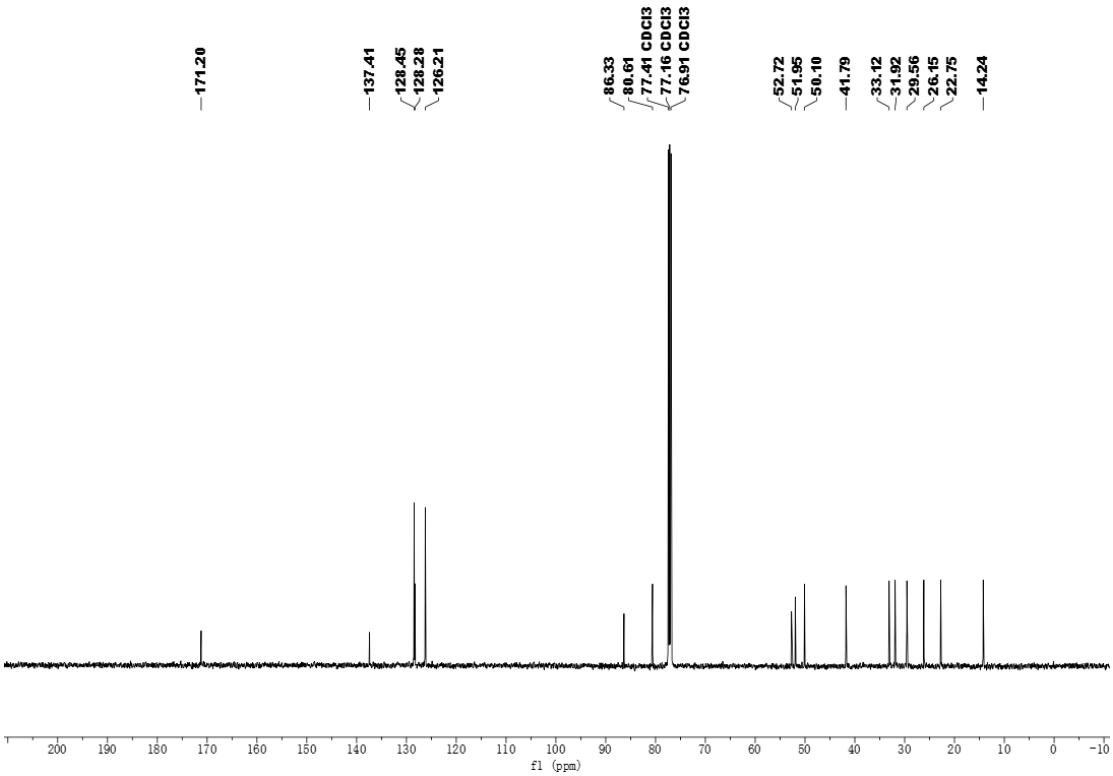


Figure S73. ^{13}C NMR spectra of **23**

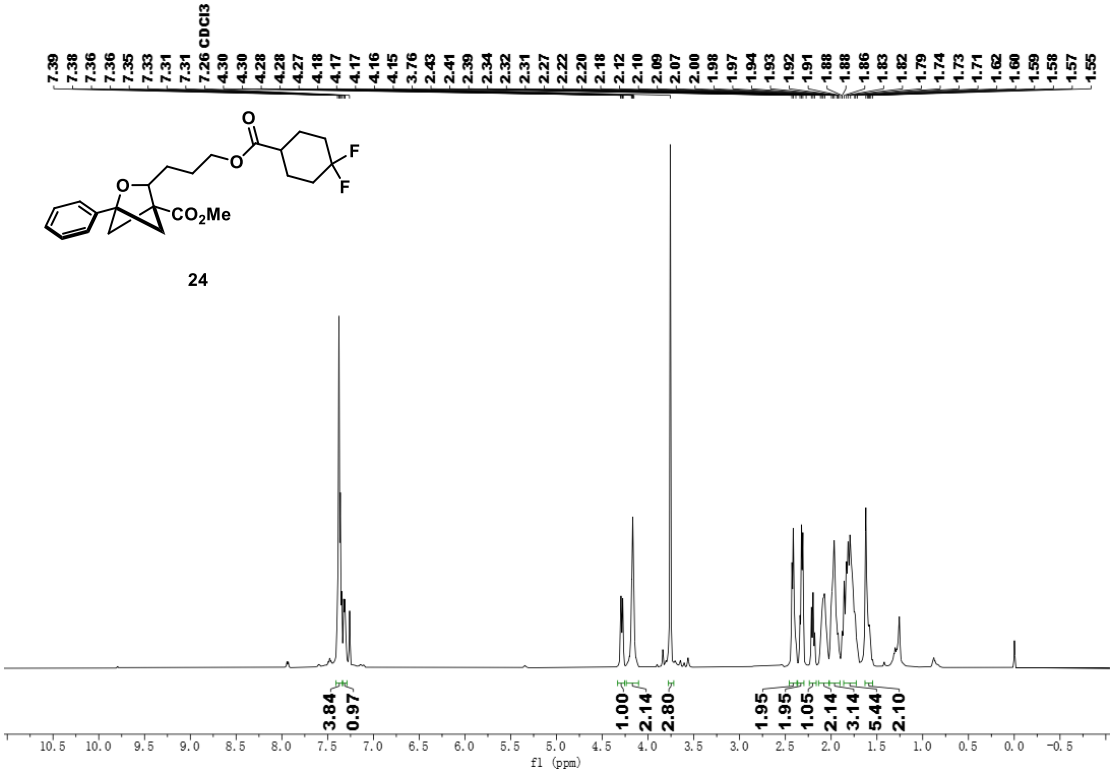


Figure S74. ^{1}H NMR spectra of **24**

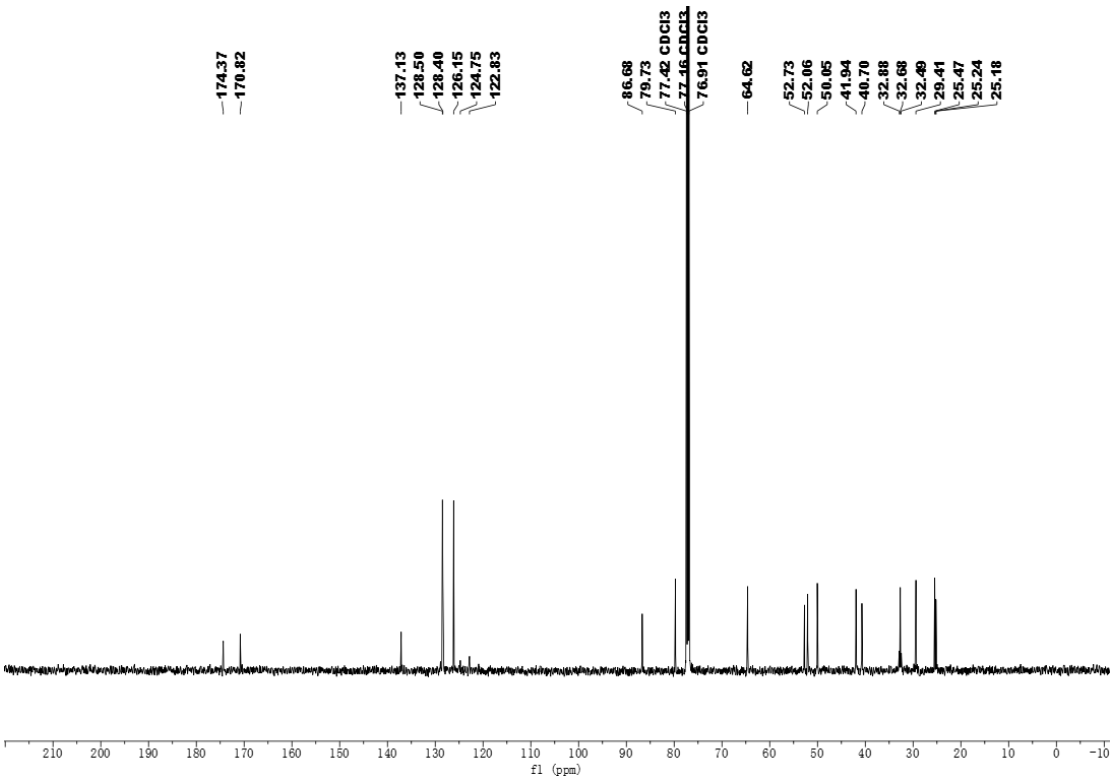


Figure S75. ^{13}C NMR spectra of **24**

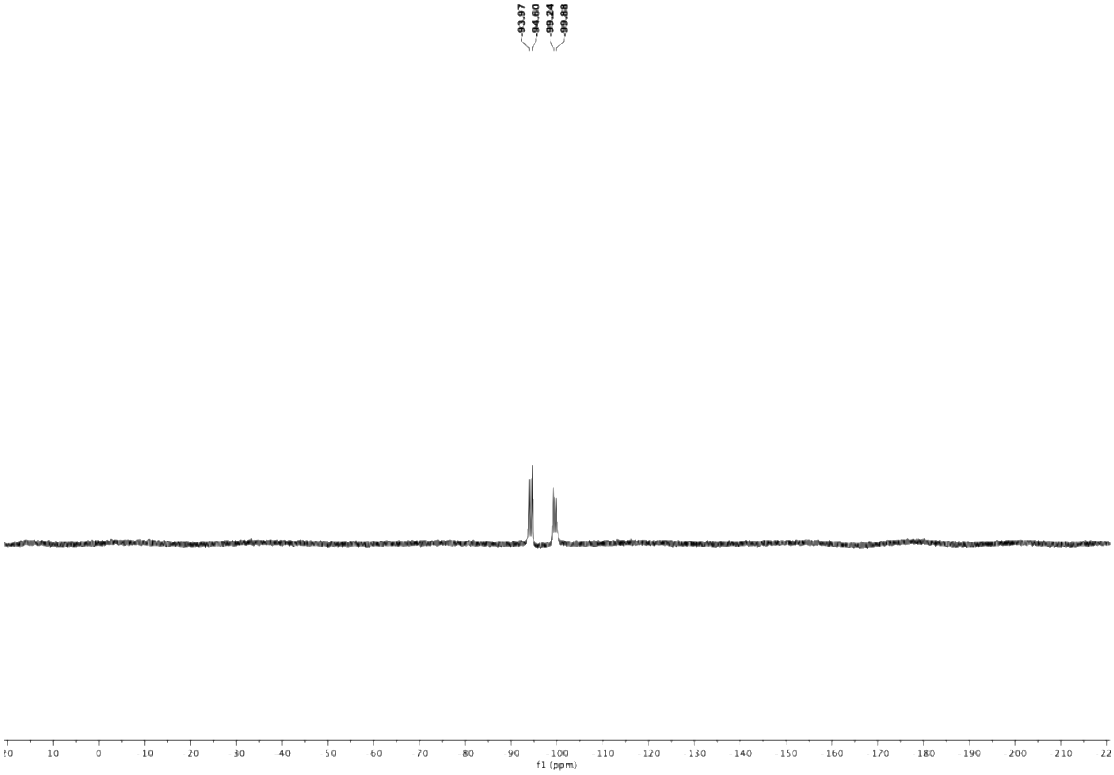


Figure S76. ^{19}F NMR spectra of **24**

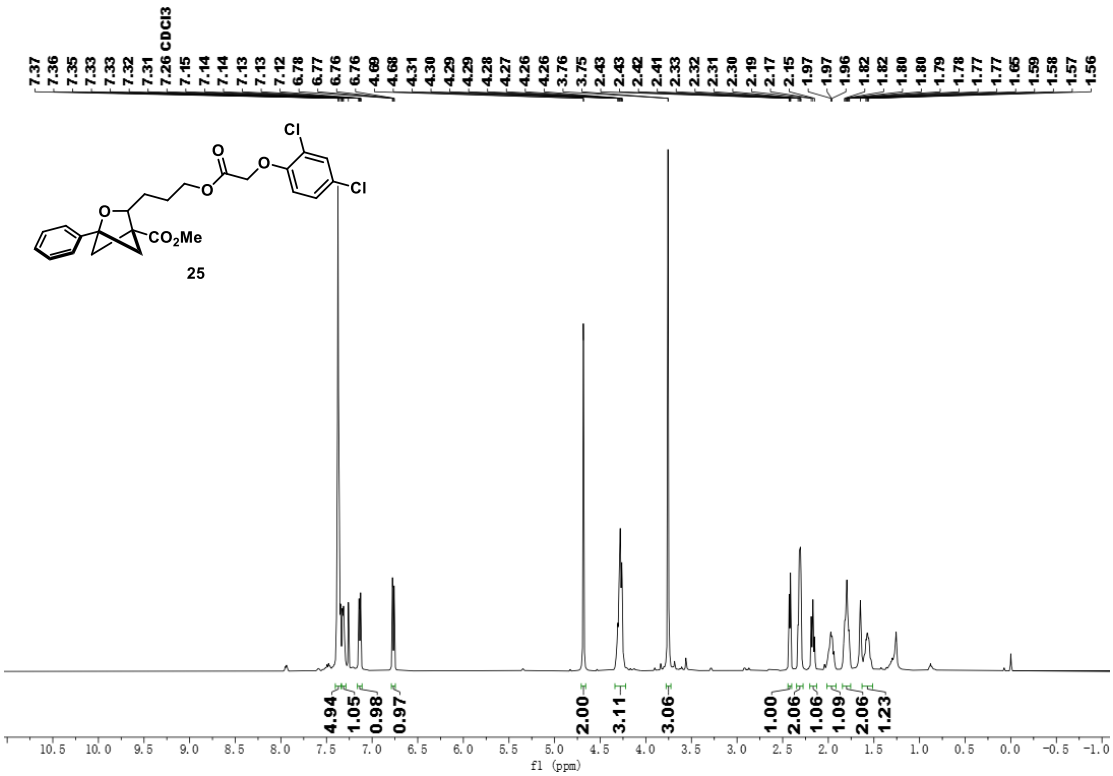


Figure S77. ^{1}H NMR spectra of **25**

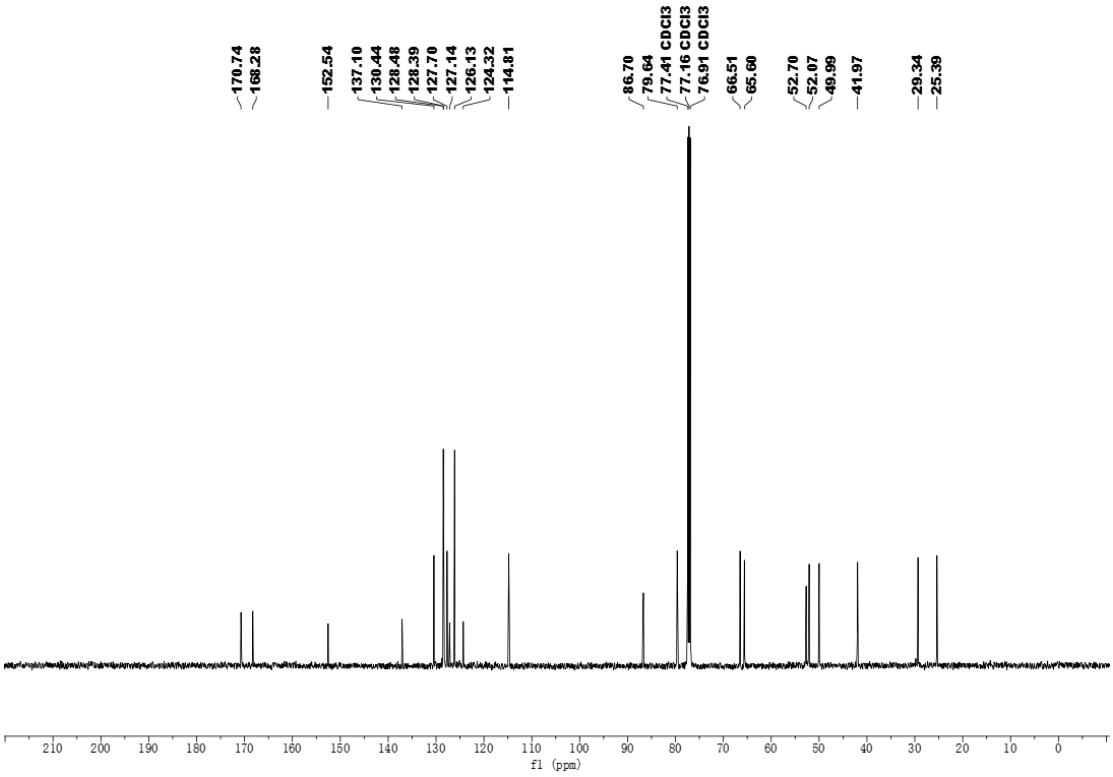


Figure S78. ^{13}C NMR spectra of **25**

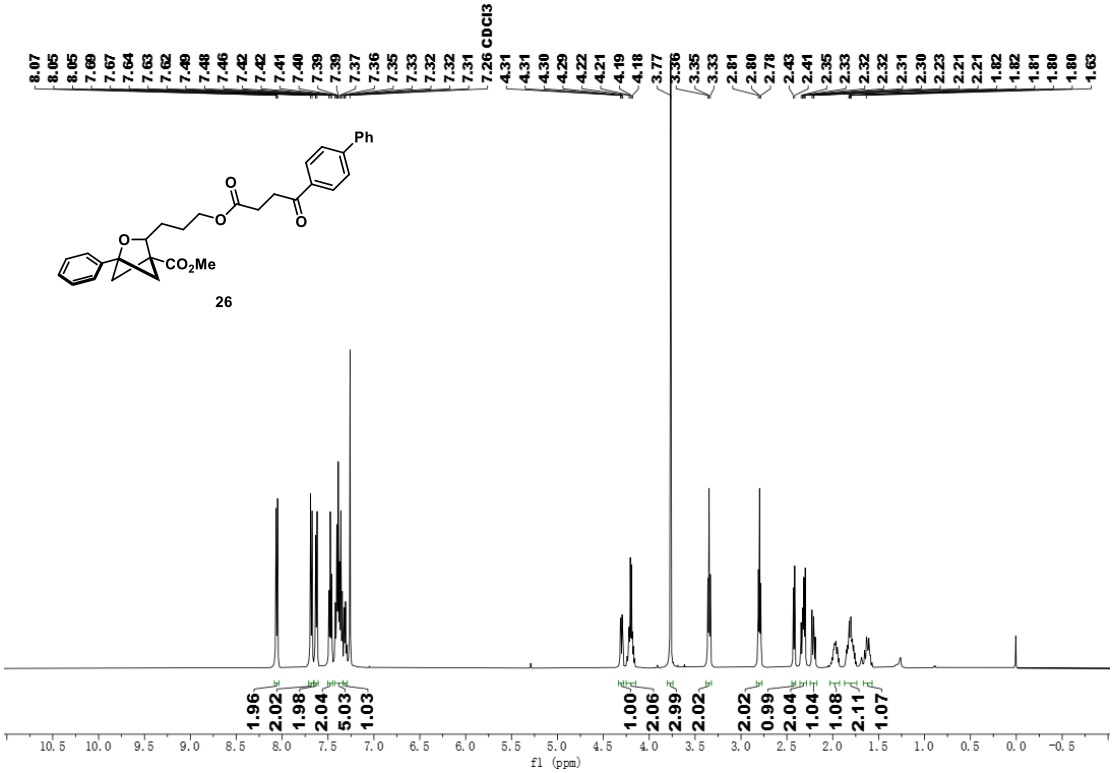


Figure S79. ^{1}H NMR spectra of **26**

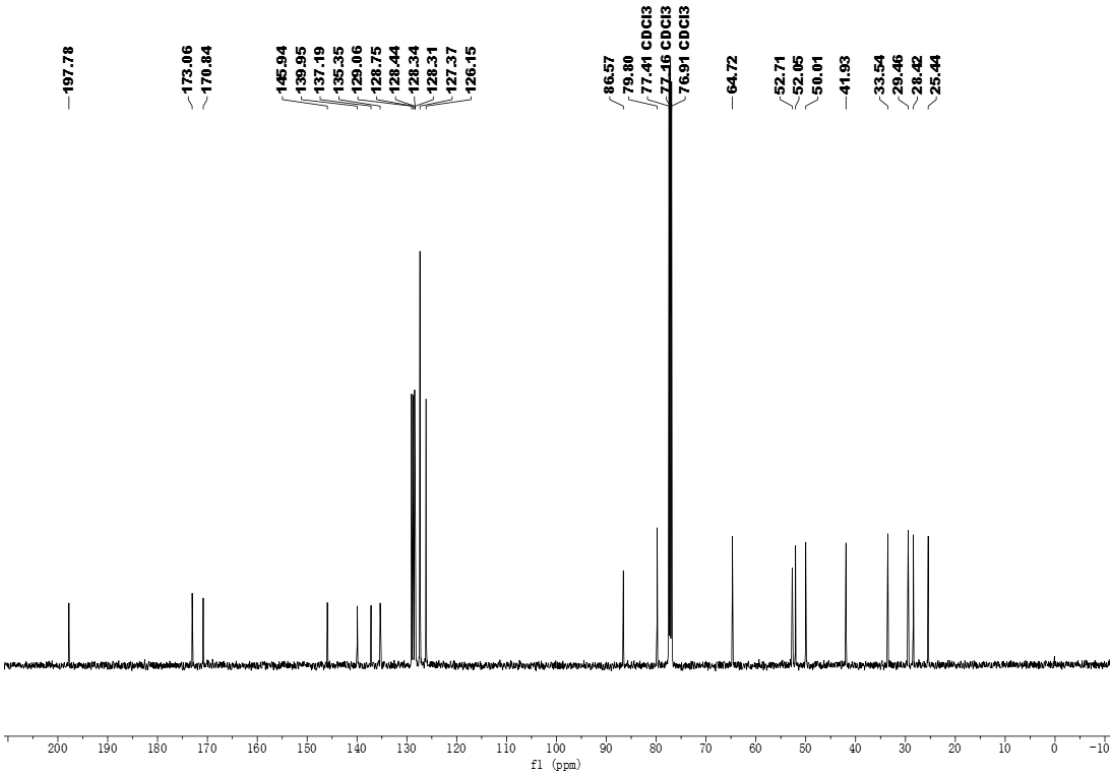


Figure S80. ^{13}C NMR spectra of **26**

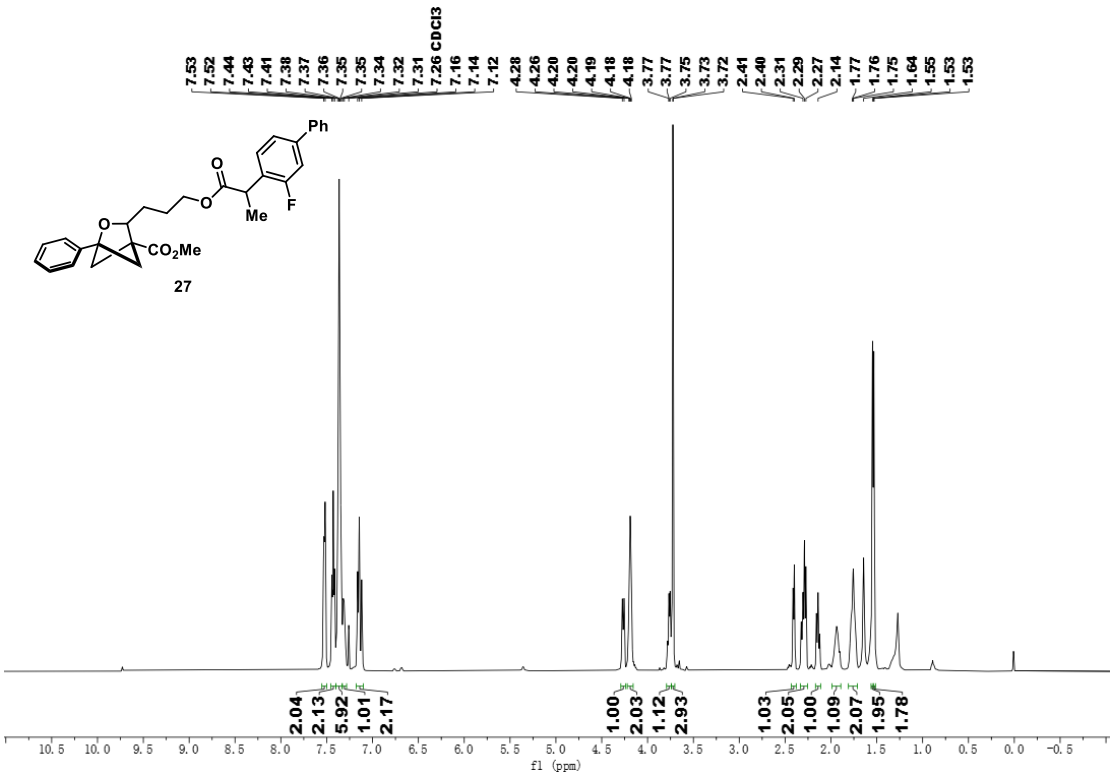


Figure S81. ^{1}H NMR spectra of **27**

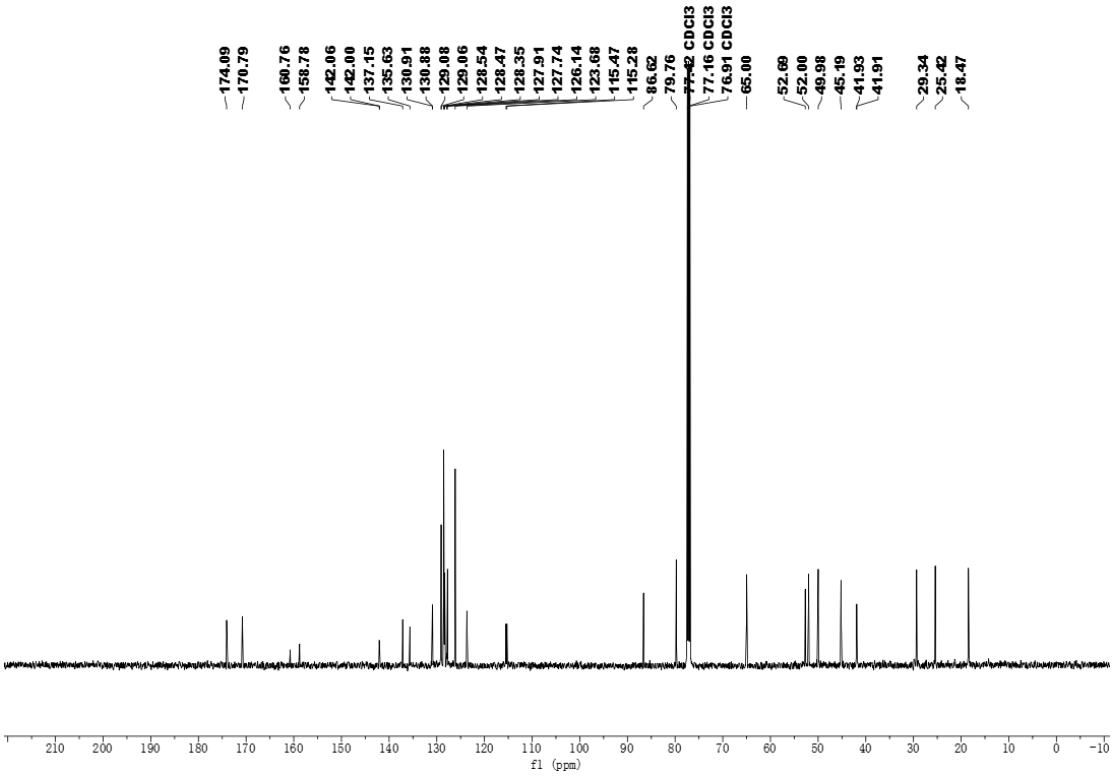


Figure S82. ^{13}C NMR spectra of **27**

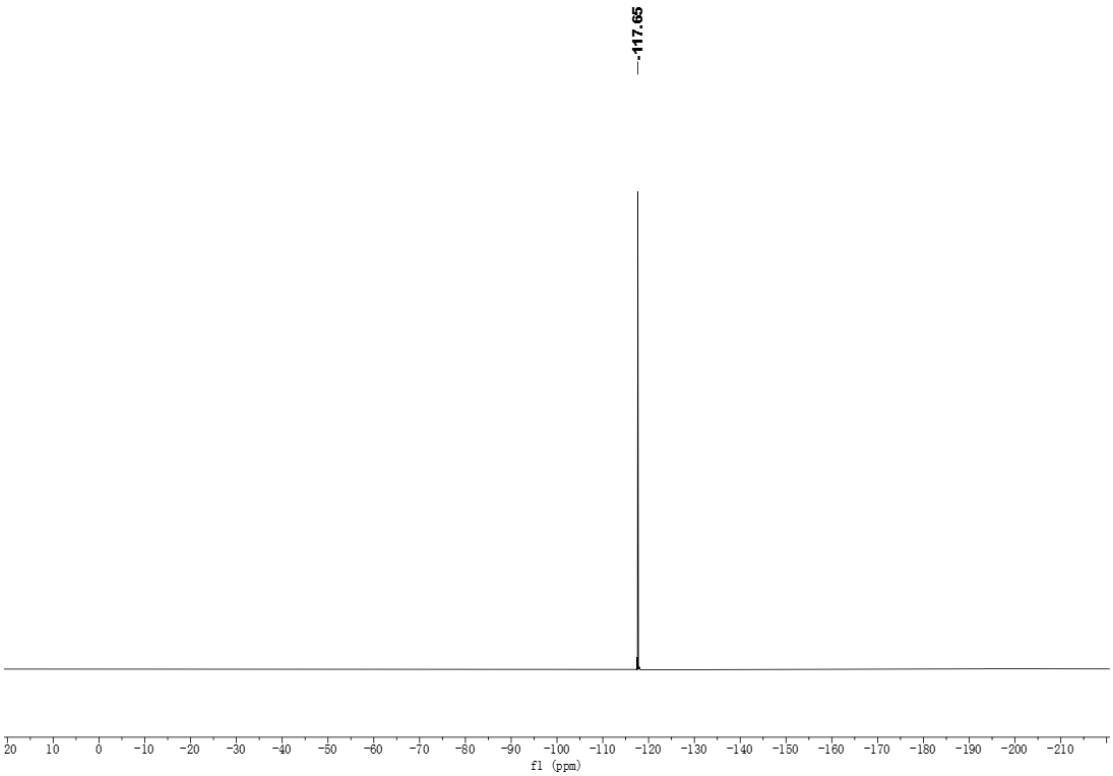


Figure S83. ^{19}F NMR spectra of **27**

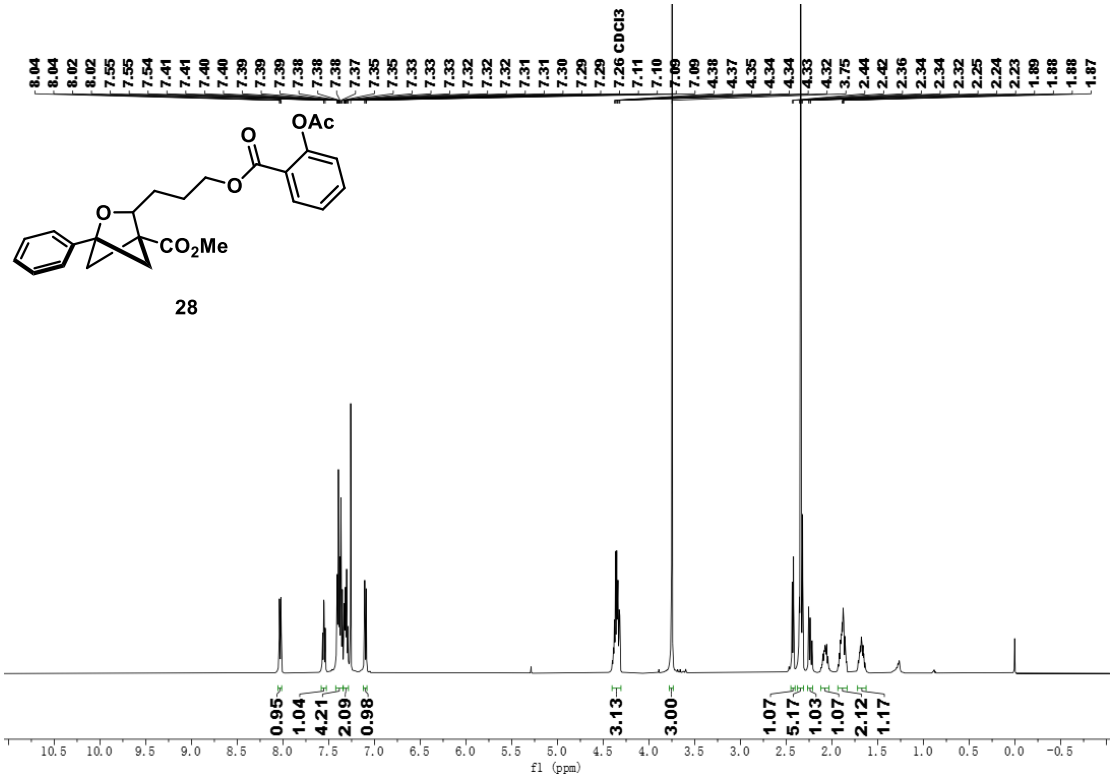


Figure S84. ^{1}H NMR spectra of **28**

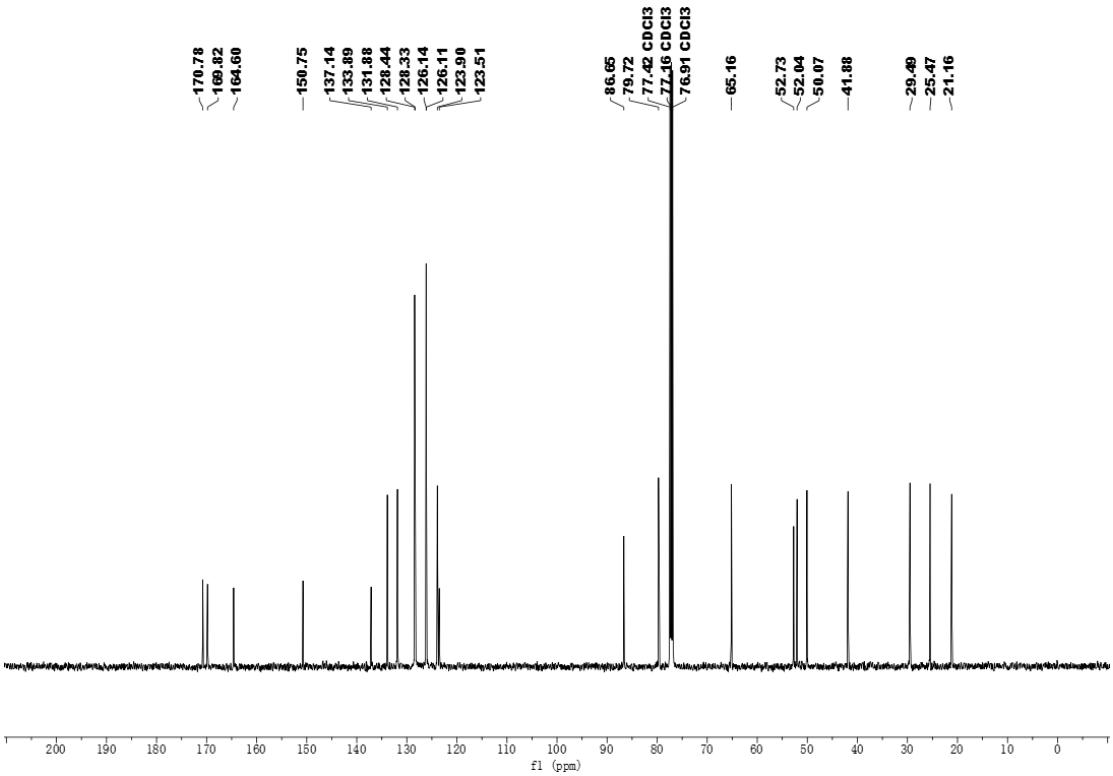


Figure S85. ^{13}C NMR spectra of **28**

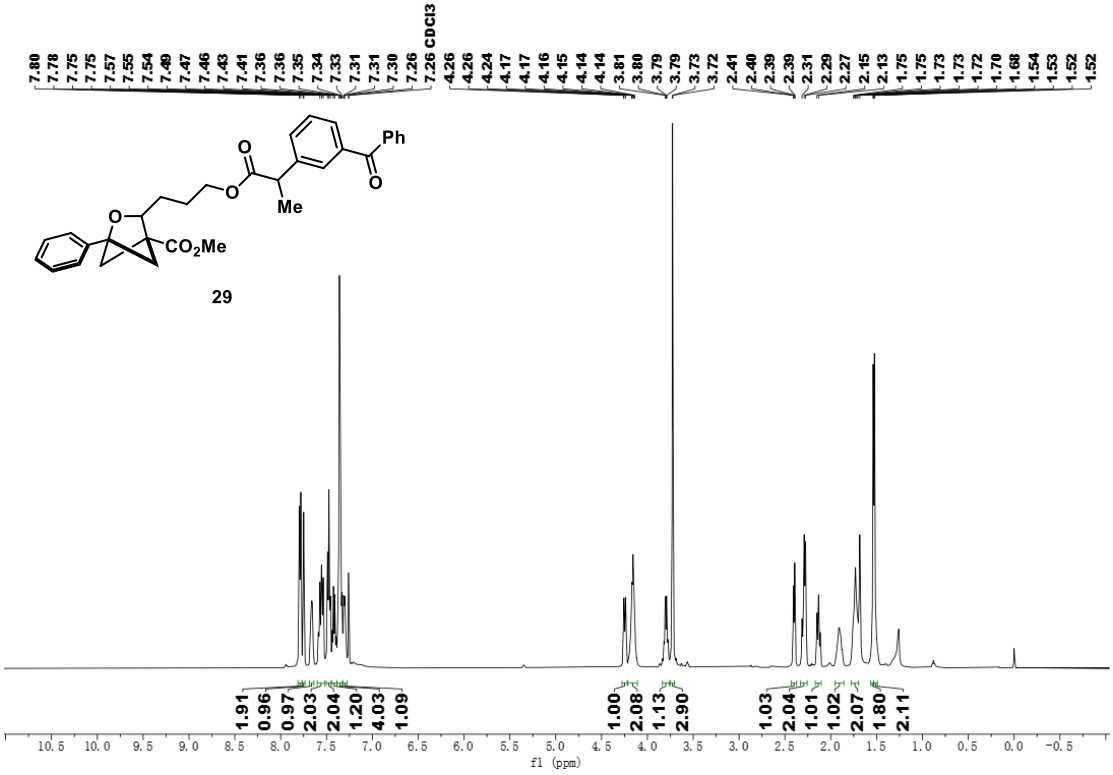


Figure S86. ^{1}H NMR spectra of **29**

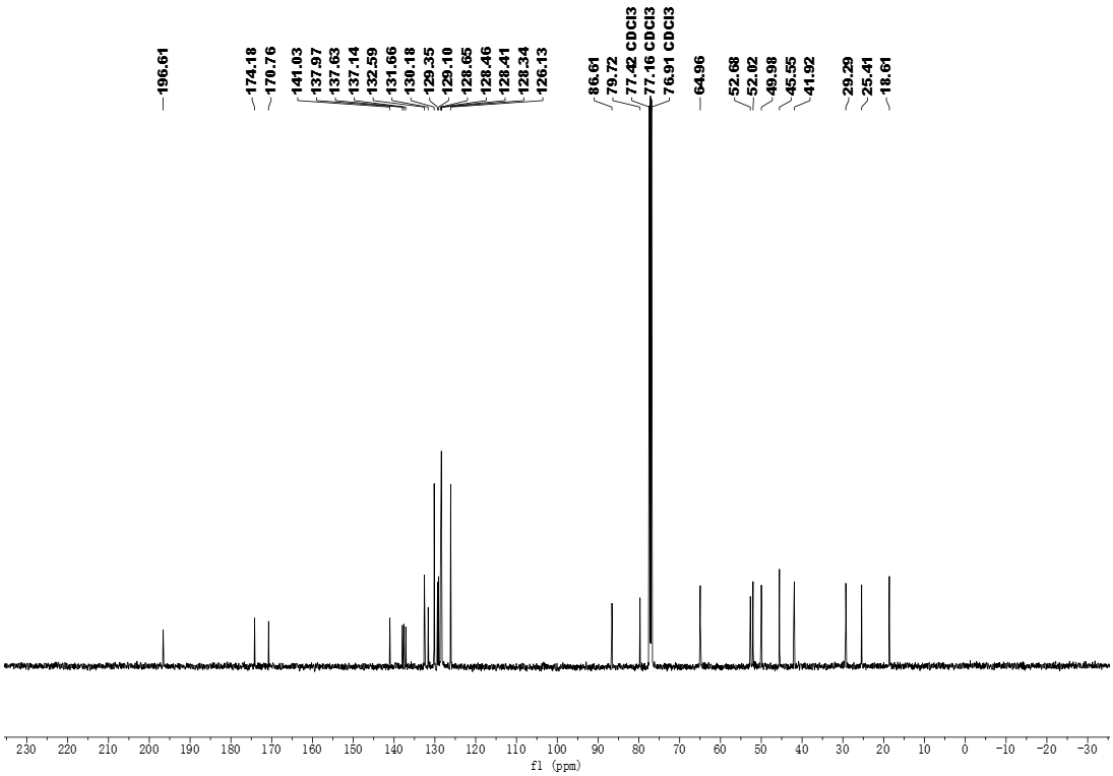


Figure S87. ^{13}C NMR spectra of **29**

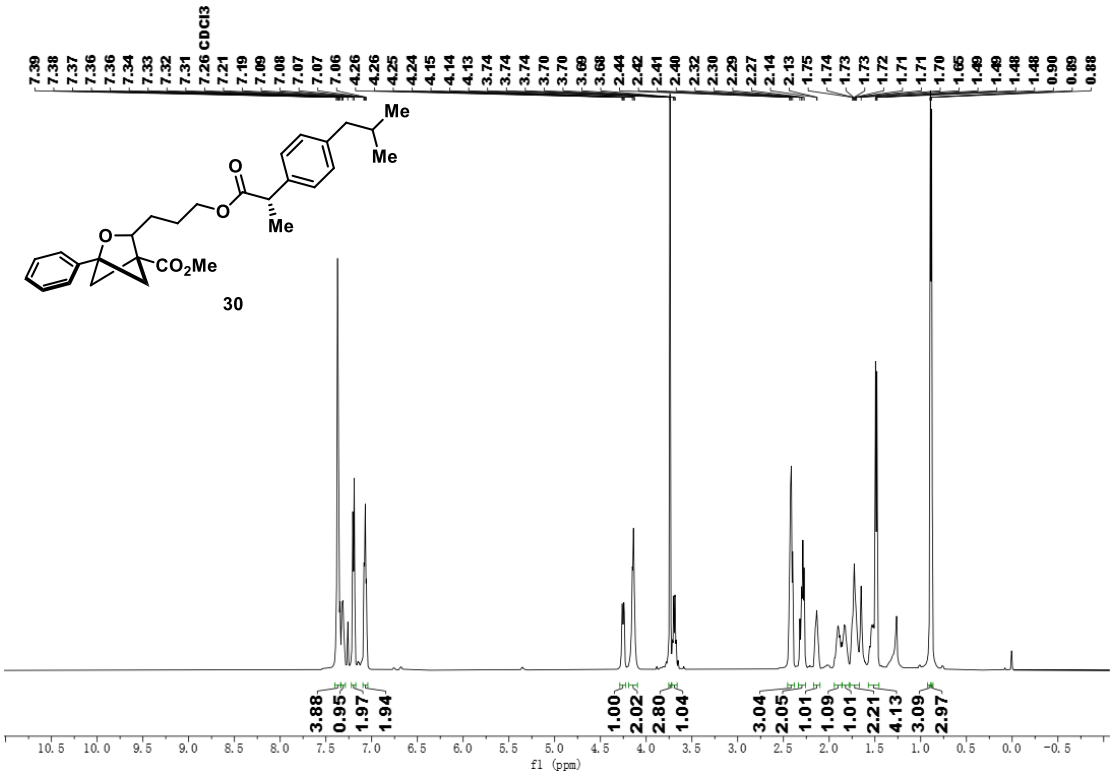


Figure S88. ^{1}H NMR spectra of **30**

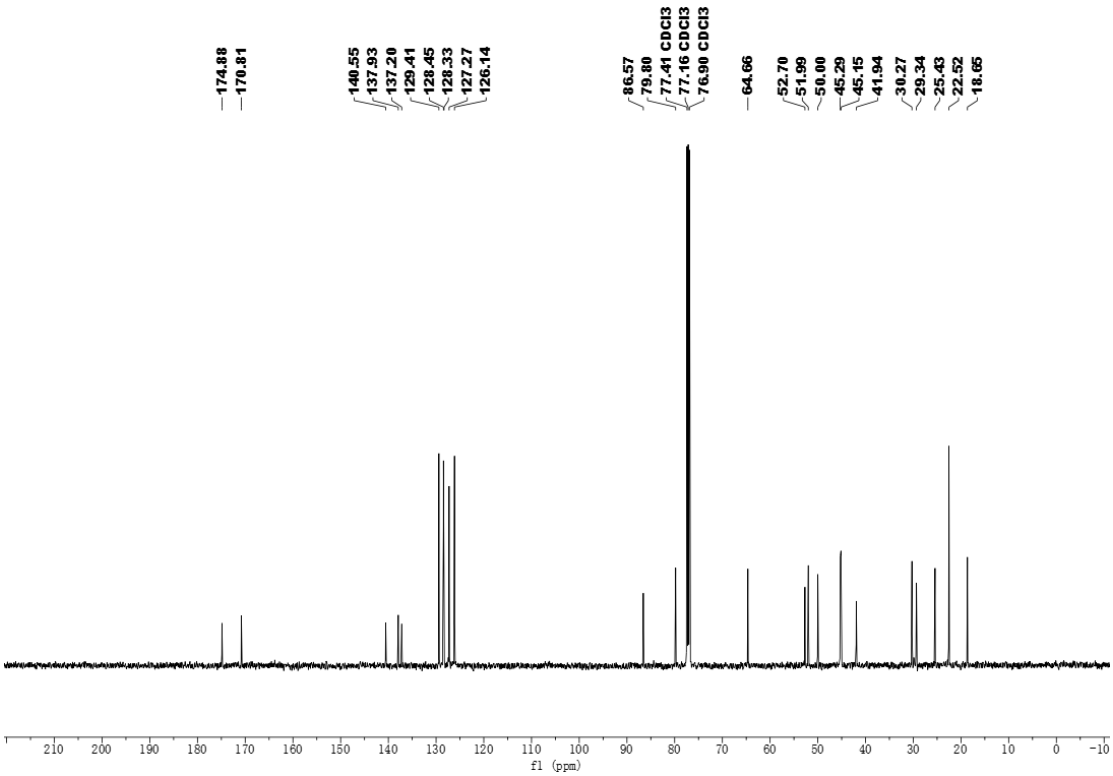


Figure S89. ^{13}C NMR spectra of **30**

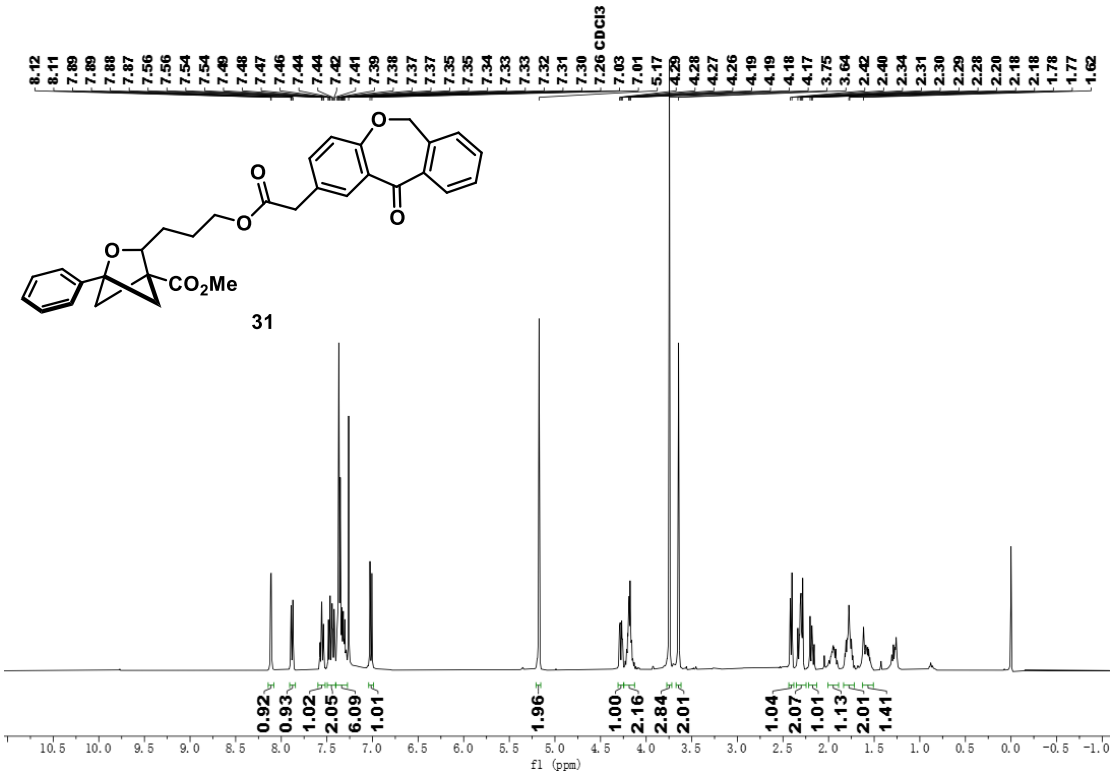


Figure S90. ^{1}H NMR spectra of **31**

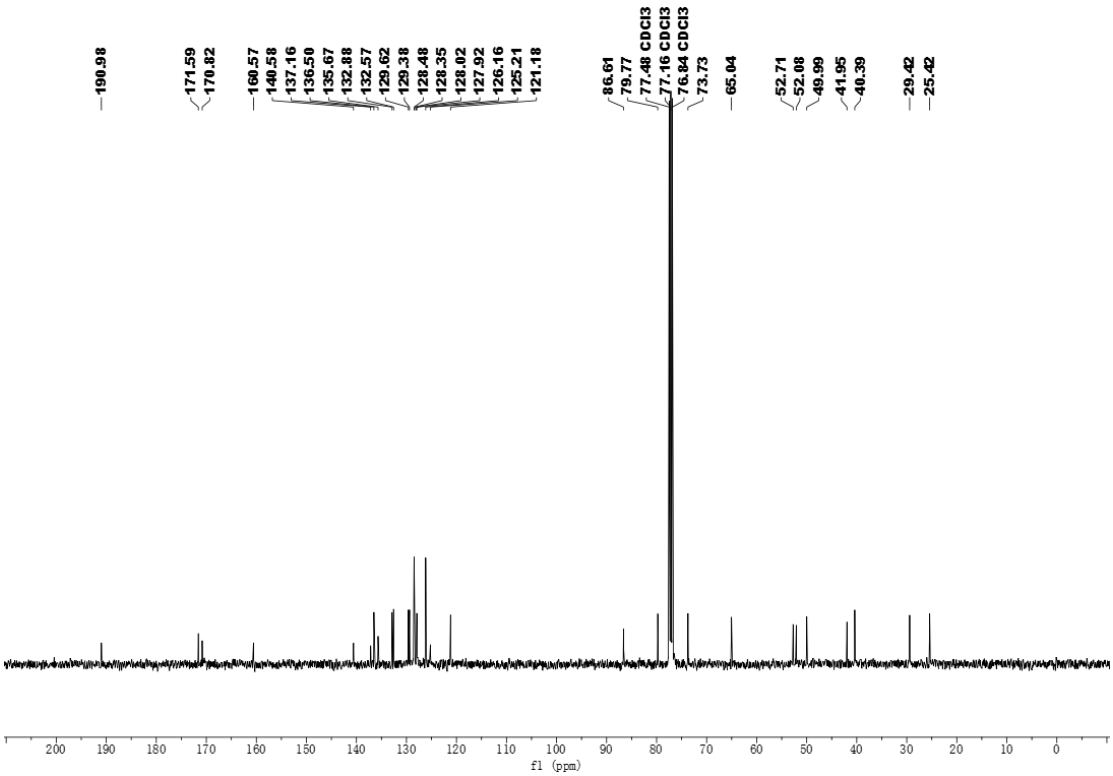


Figure S91. ^{13}C NMR spectra of **31**

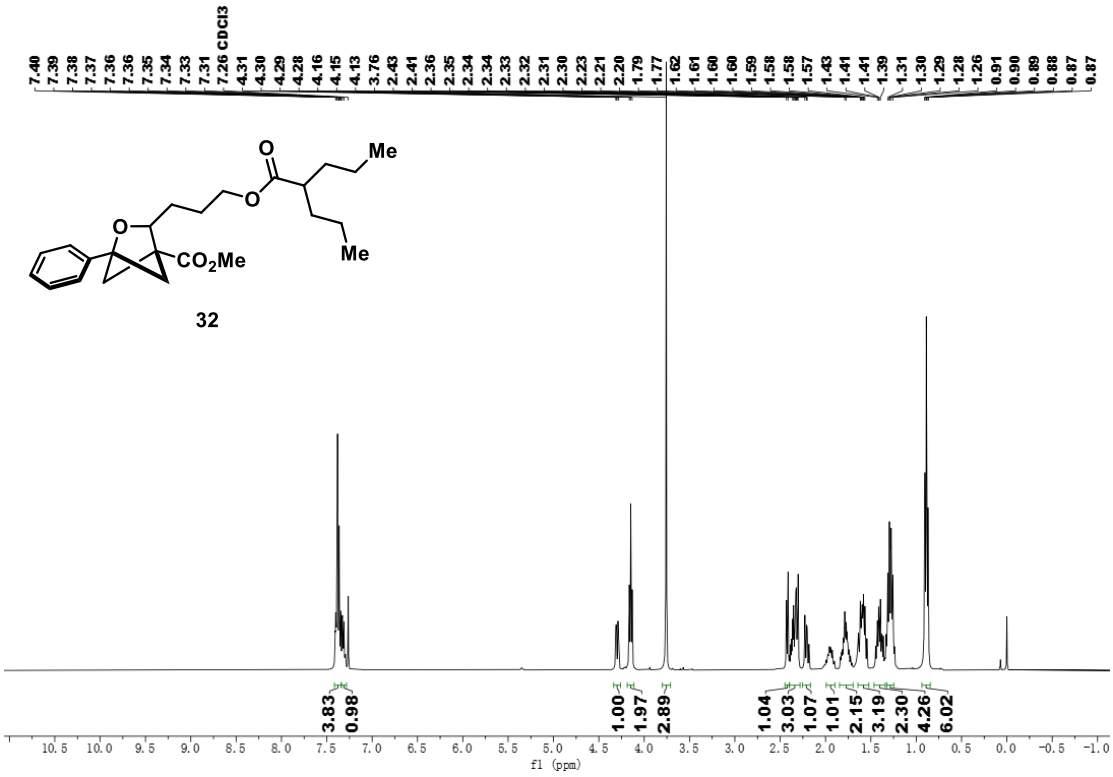


Figure S92. ^{1}H NMR spectra of **32**

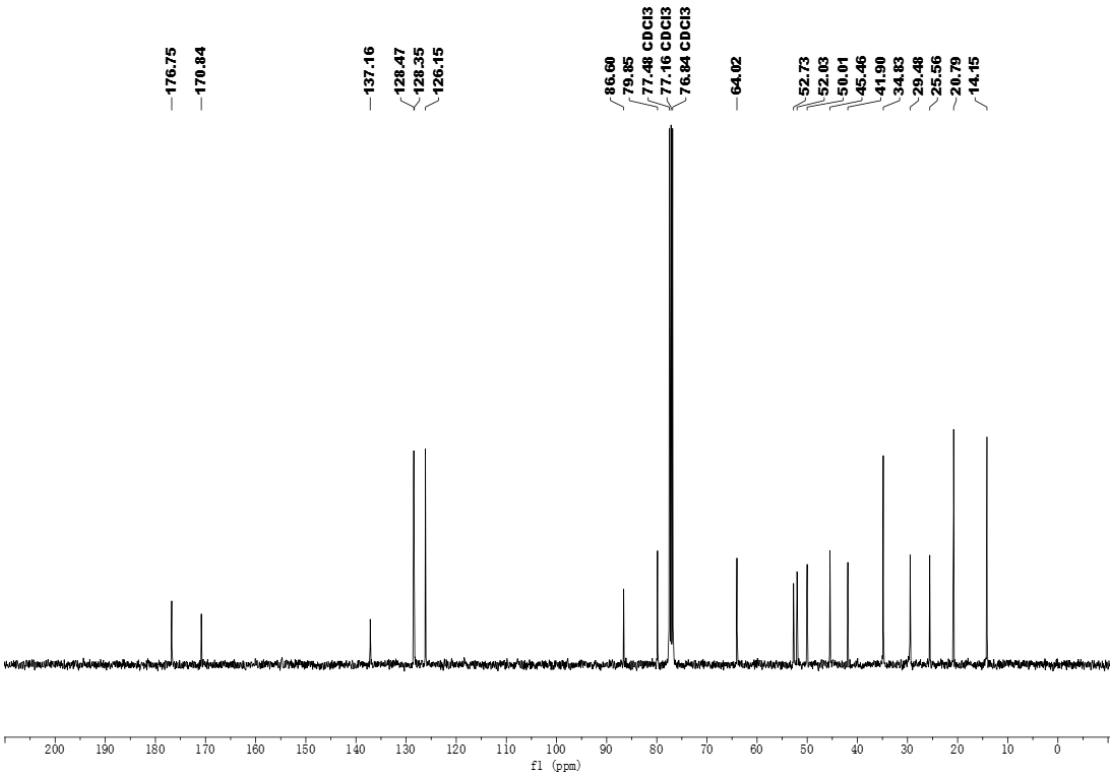


Figure S93. ^{13}C NMR spectra of **32**

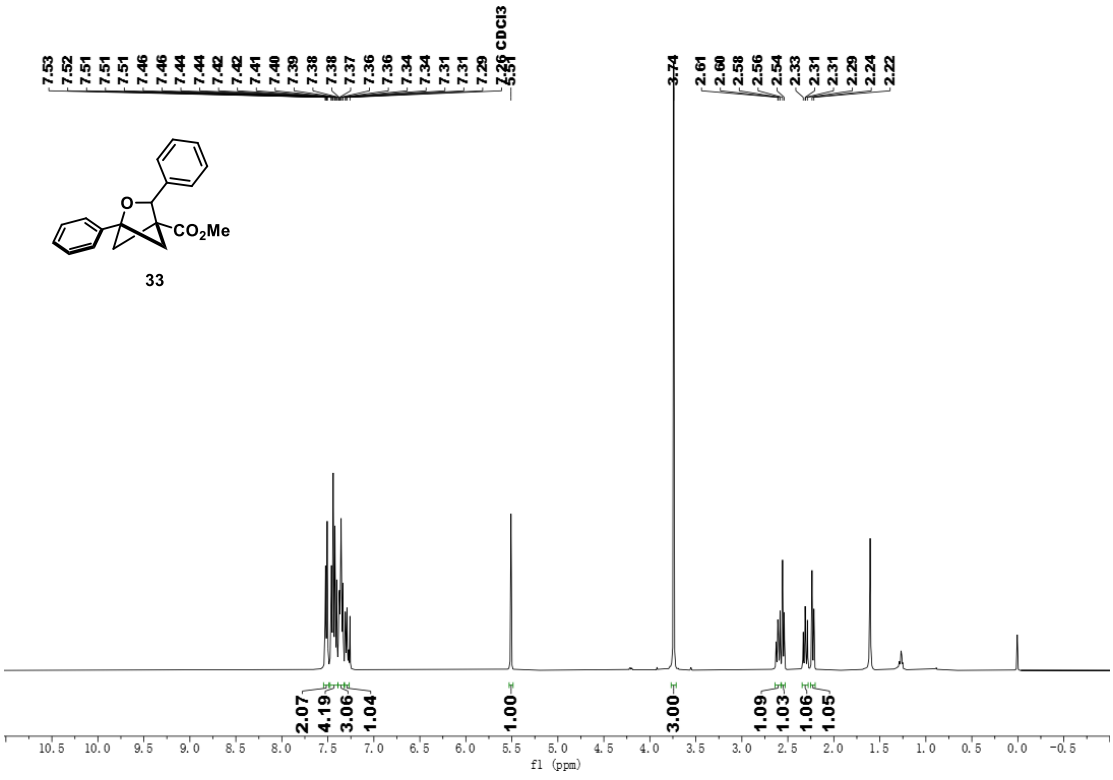


Figure S94. ^{1}H NMR spectra of **33**

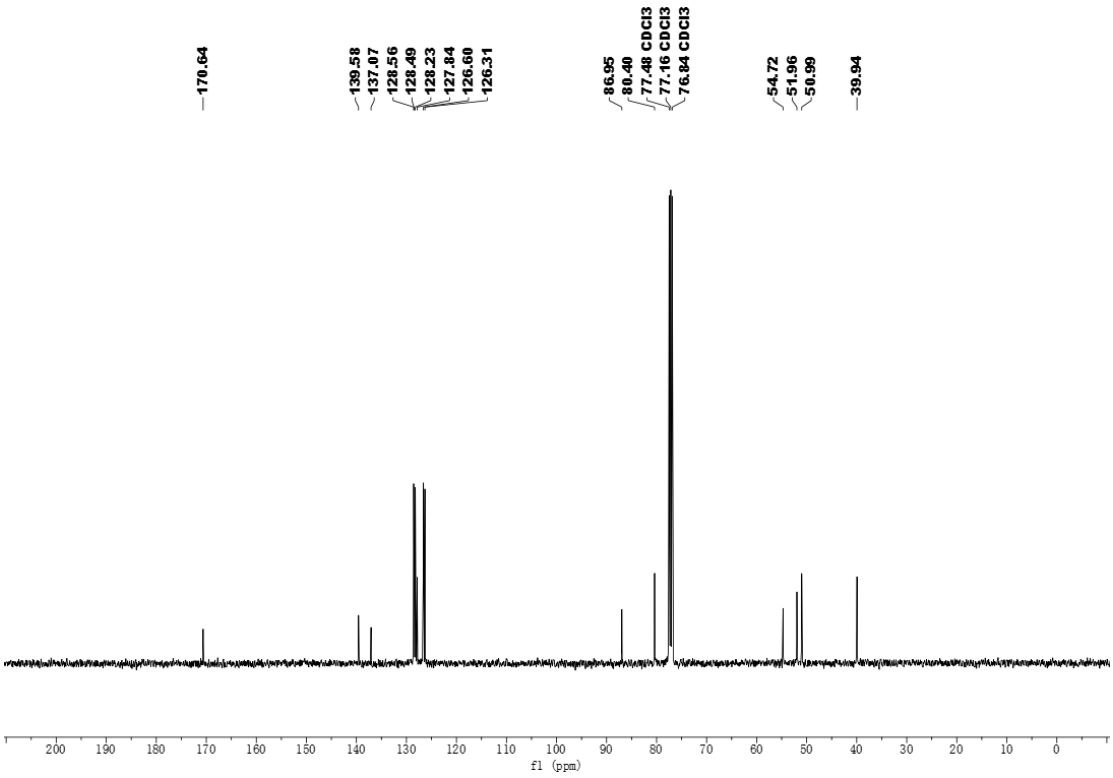


Figure S95. ^{13}C NMR spectra of **33**

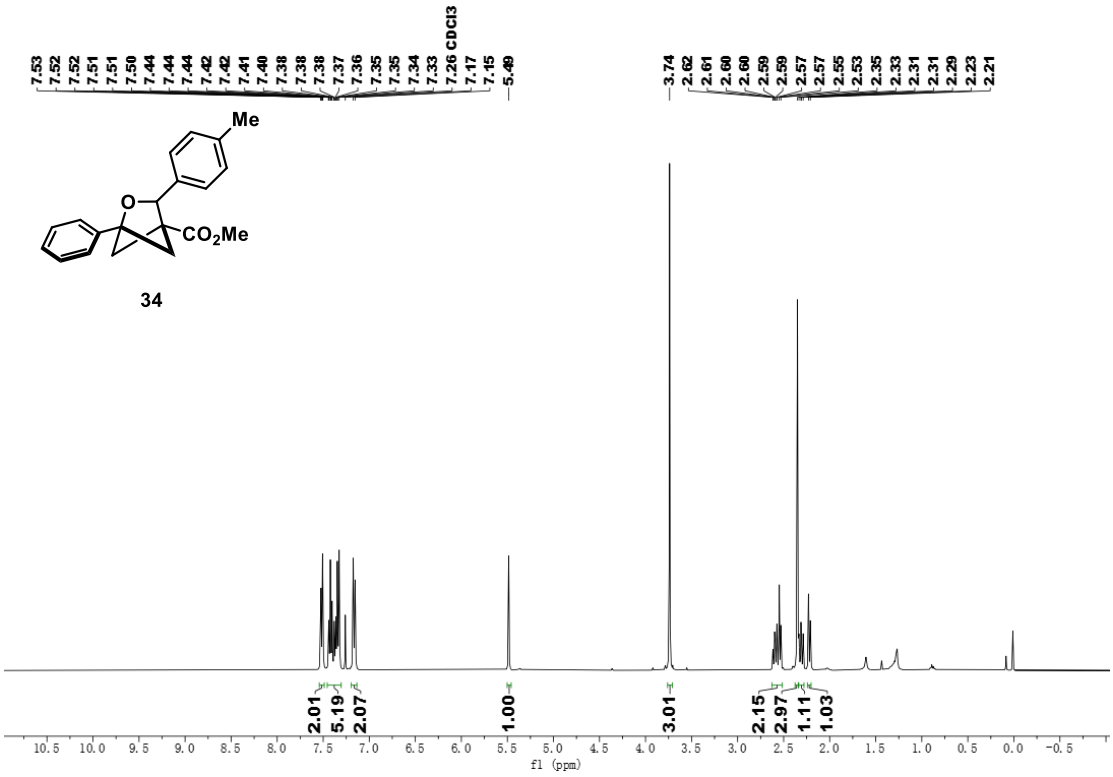


Figure S96. ^{1}H NMR spectra of **34**

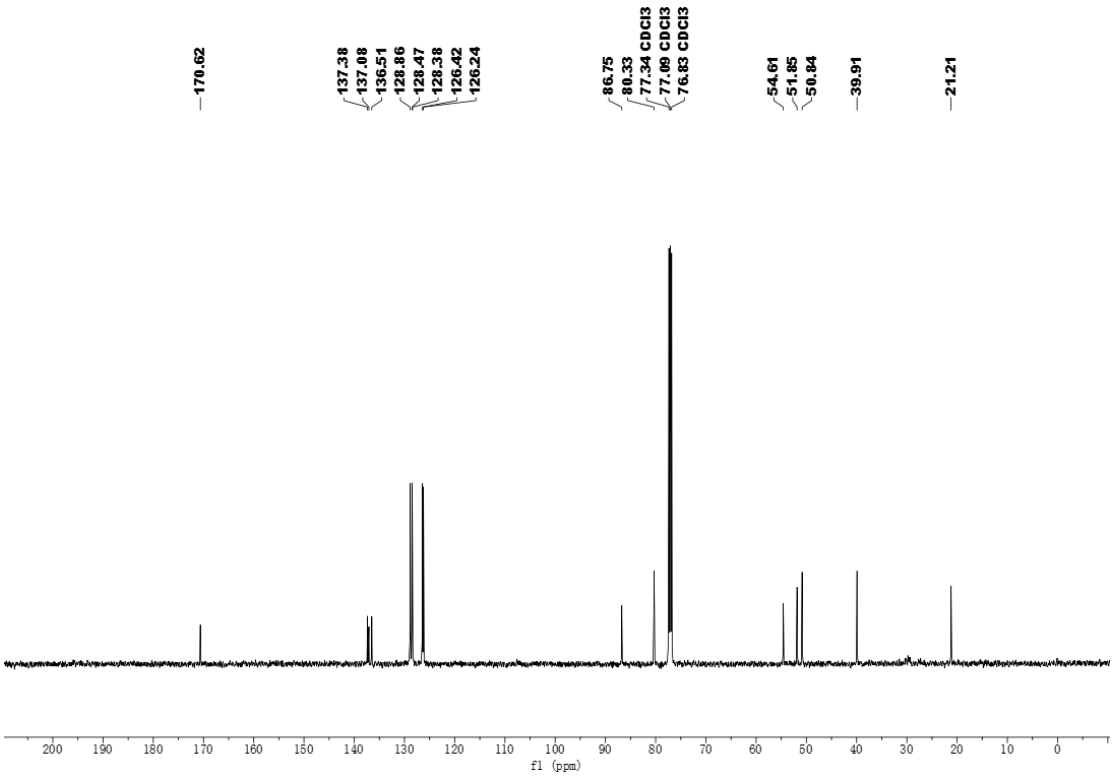


Figure S97. ^{13}C NMR spectra of **34**

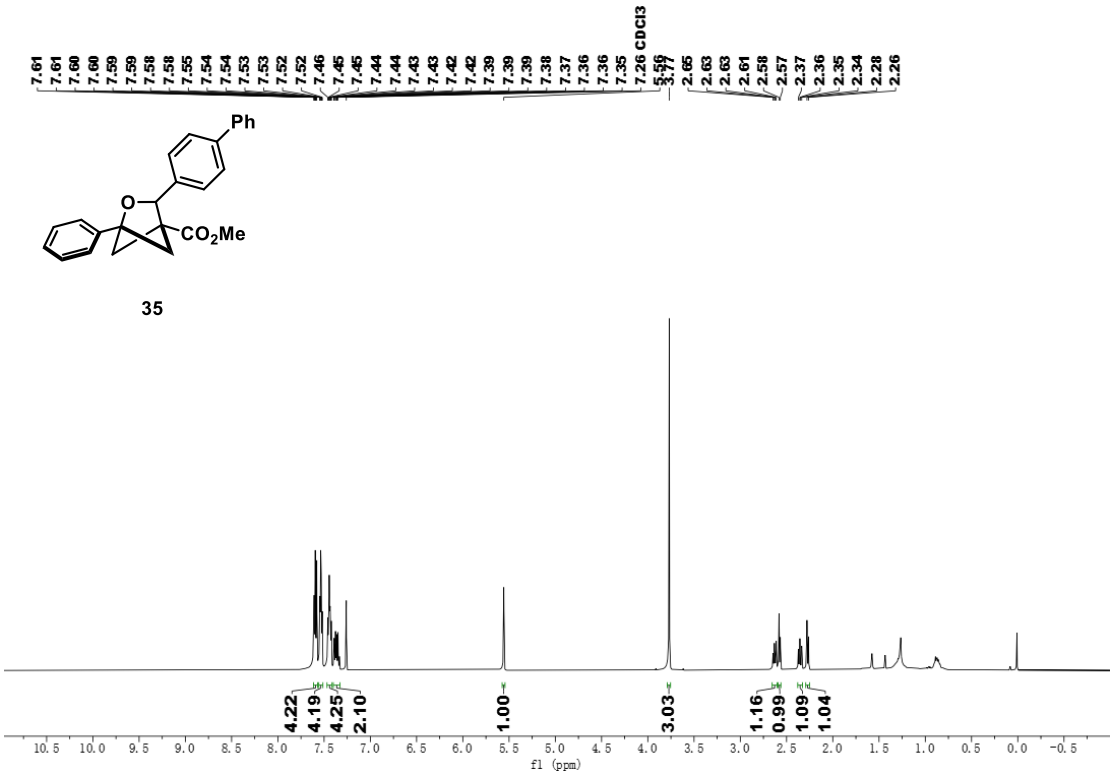


Figure S98. ^{1}H NMR spectra of **35**

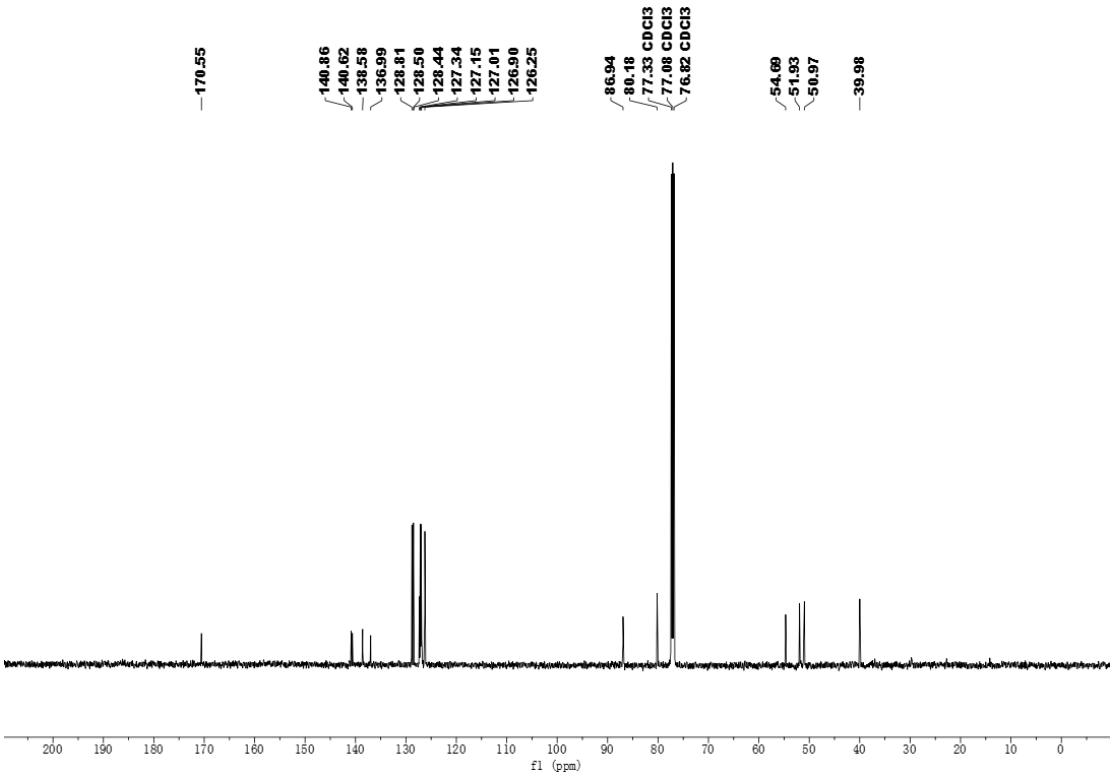


Figure S99. ^{13}C NMR spectra of **35**

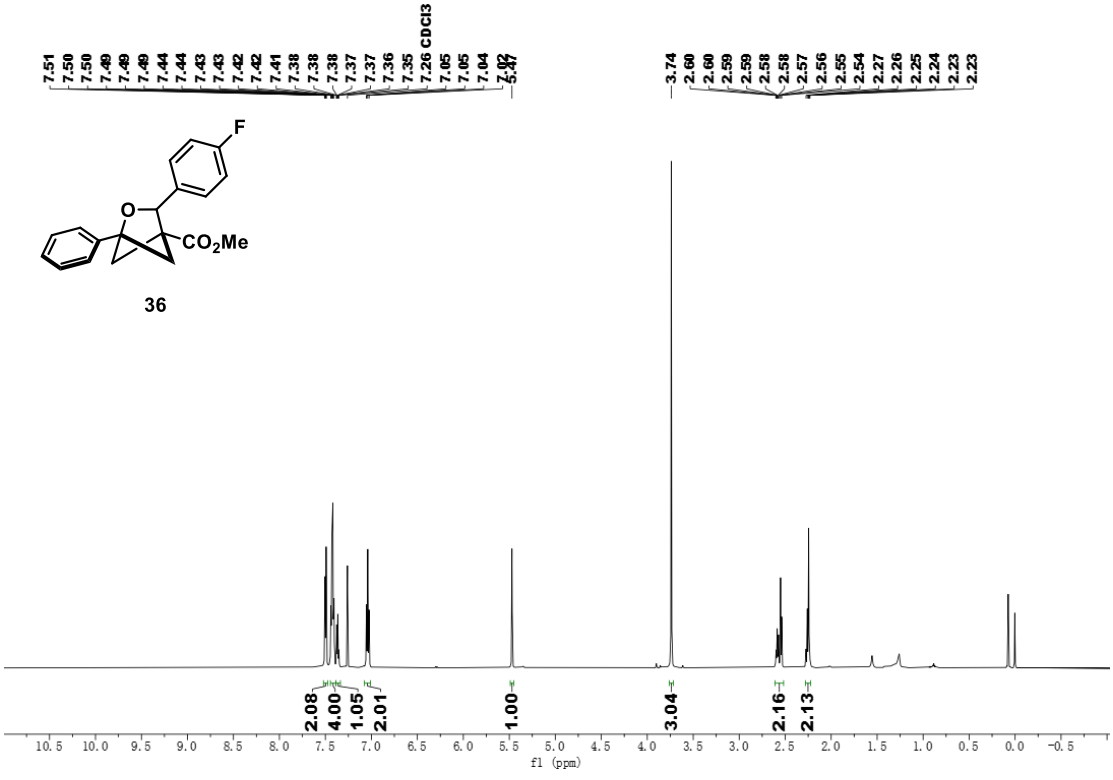


Figure S100. ^{1}H NMR spectra of **36**

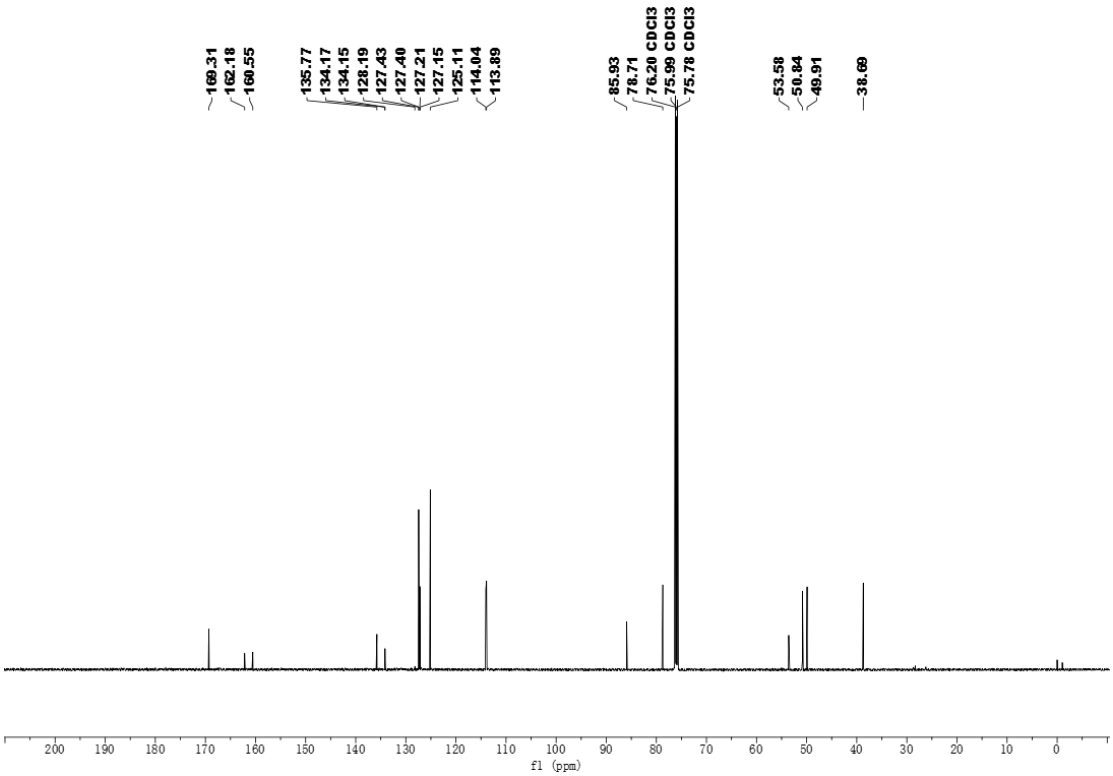


Figure S101. ^{13}C NMR spectra of **36**

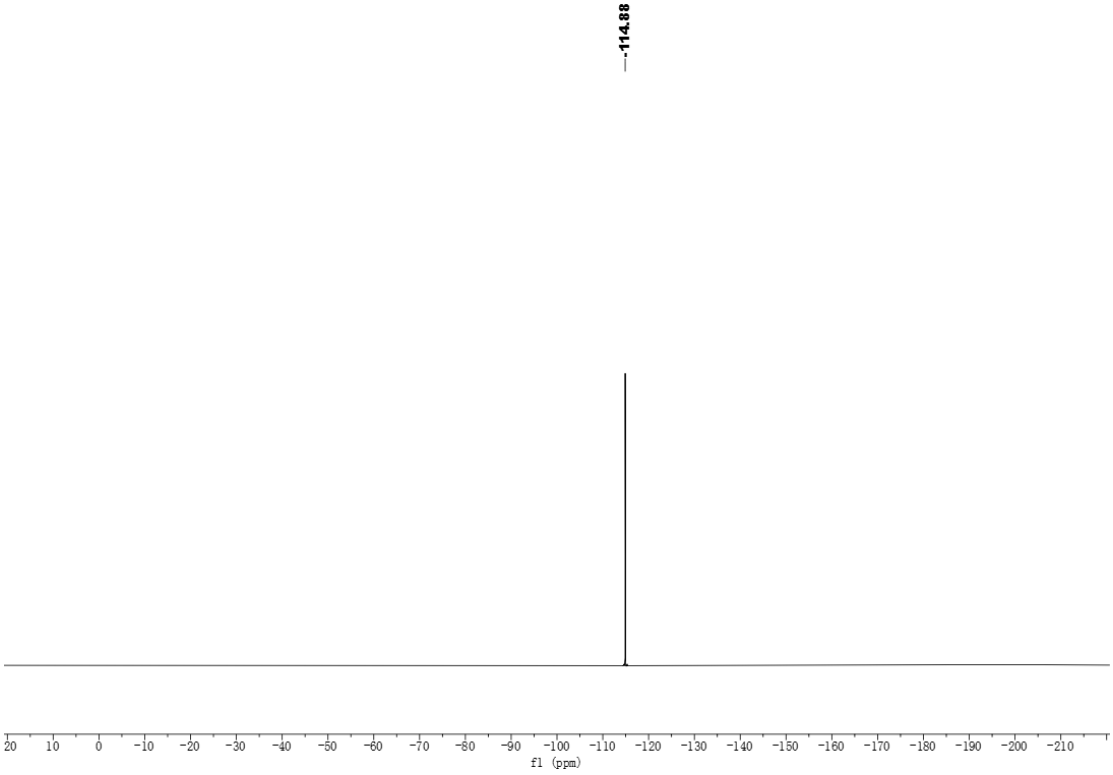


Figure S102. ^{19}F NMR spectra of **36**

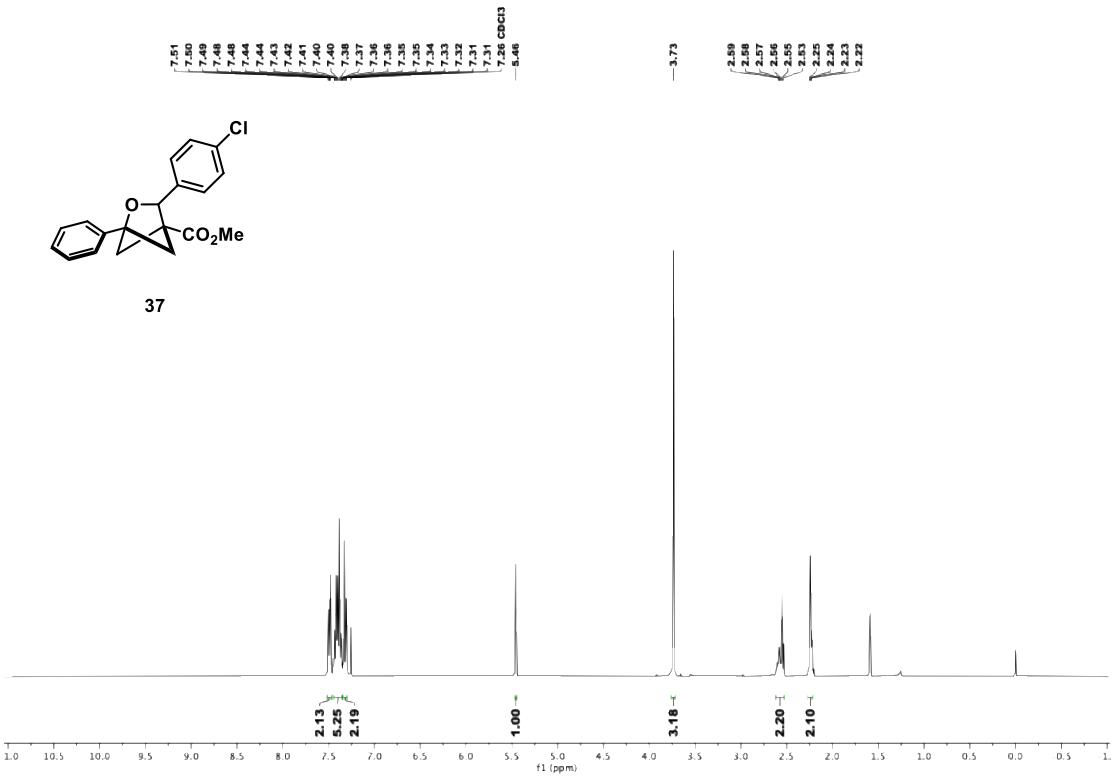


Figure S103. ^{1}H NMR spectra of **37**

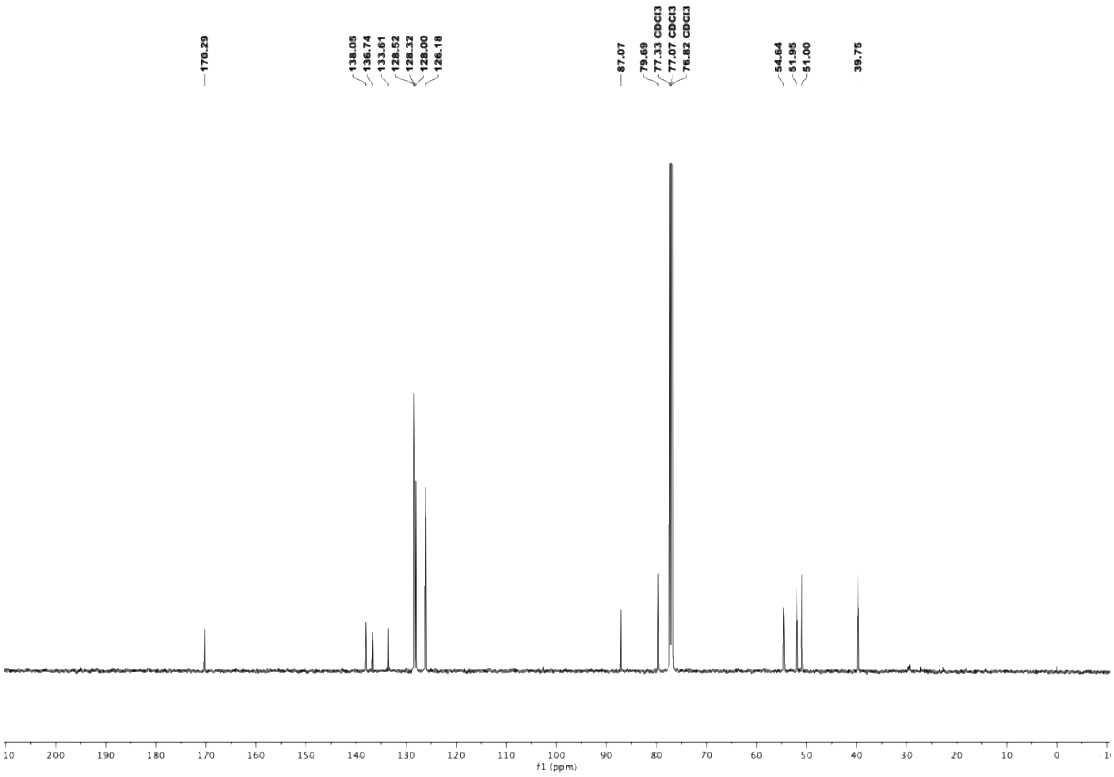


Figure S104. ^{13}C NMR spectra of **37**

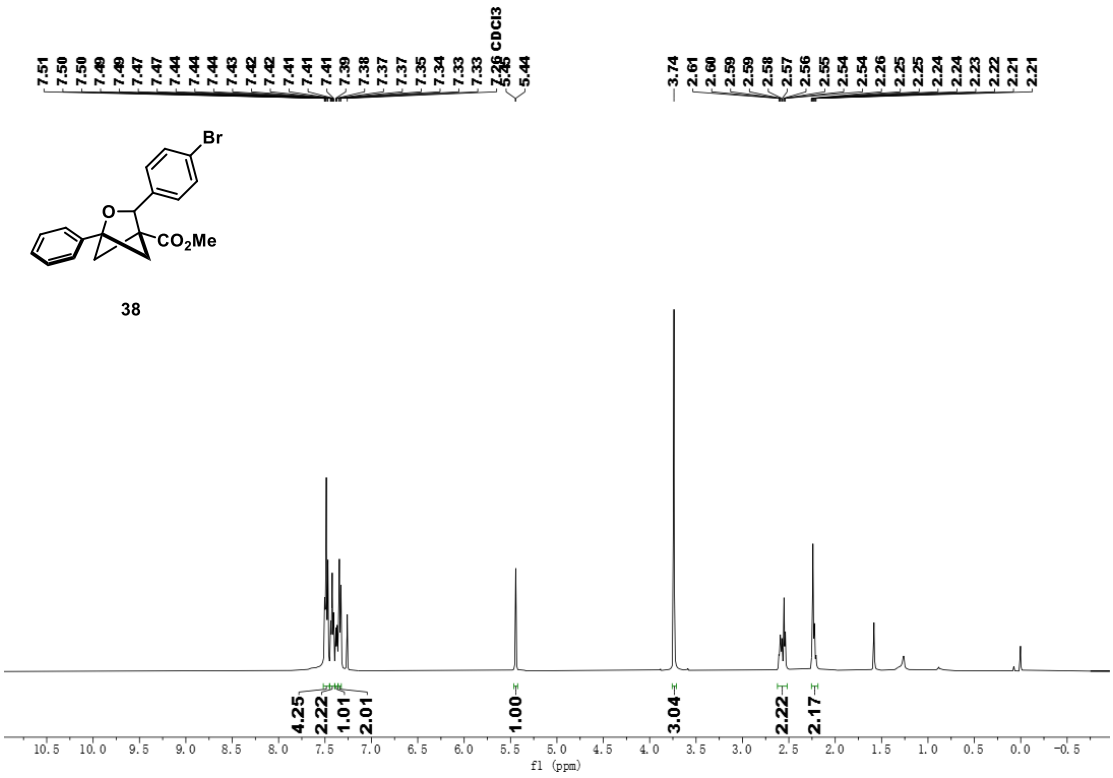


Figure S105. ^{1}H NMR spectra of **38**

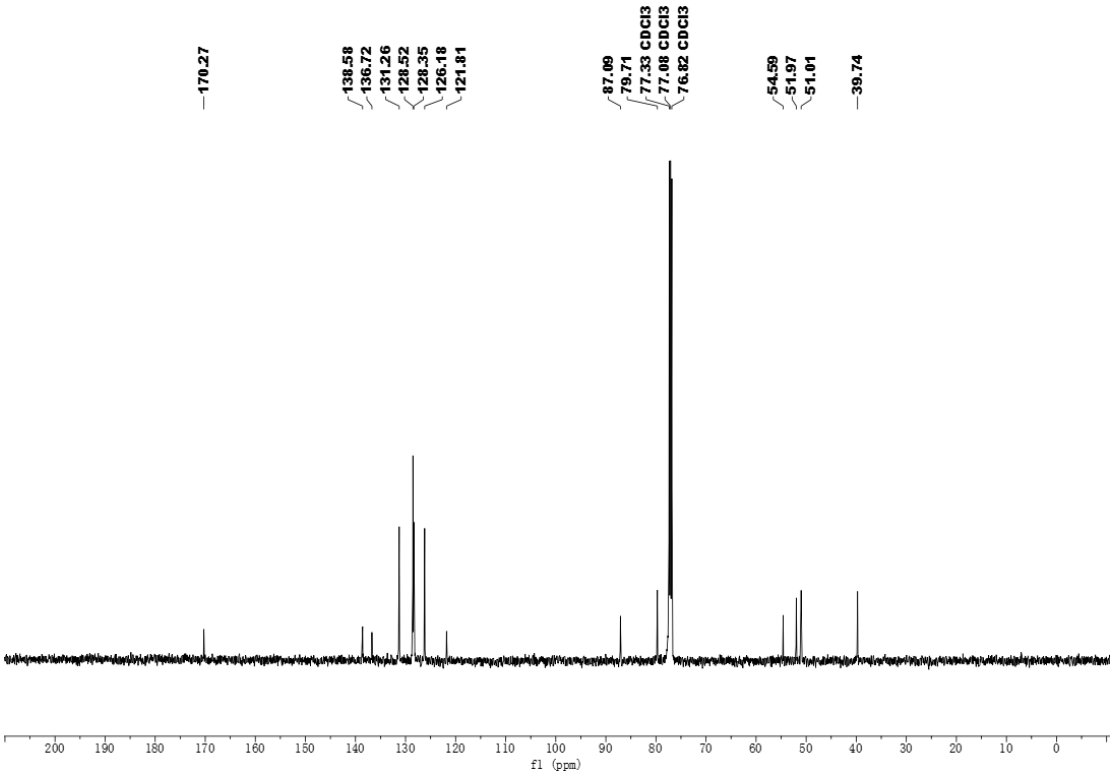


Figure S106. ^{13}C NMR spectra of **38**

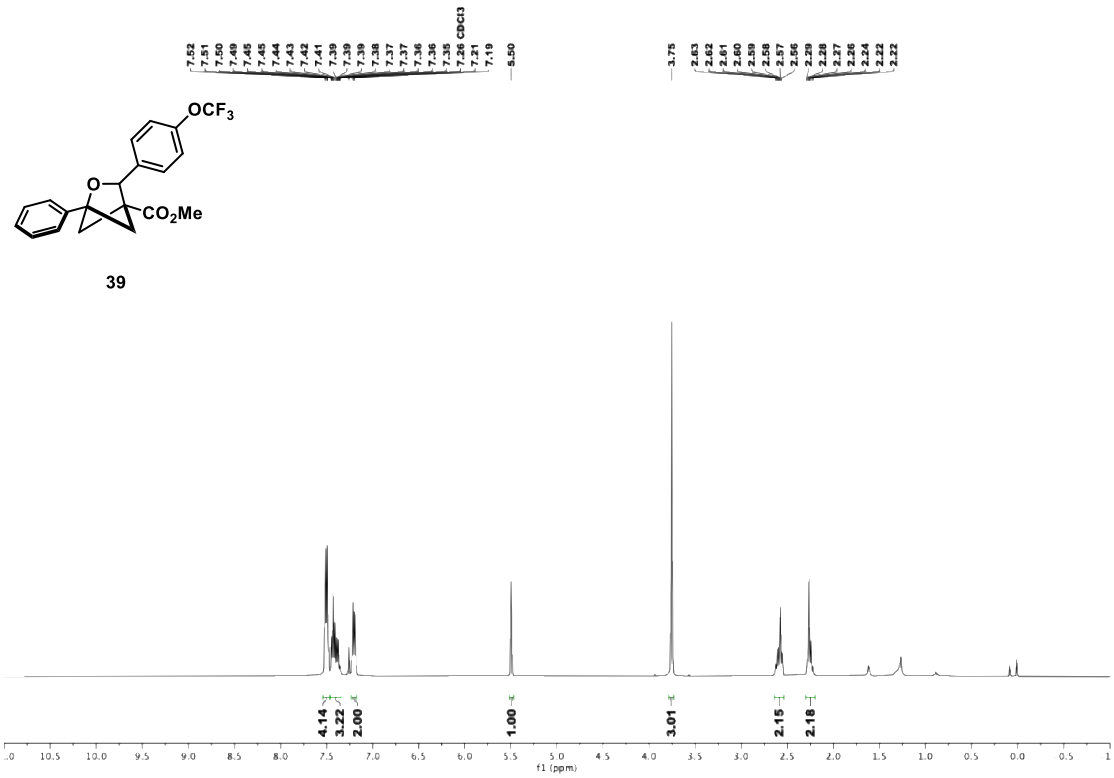


Figure S107. ^{1}H NMR spectra of **39**

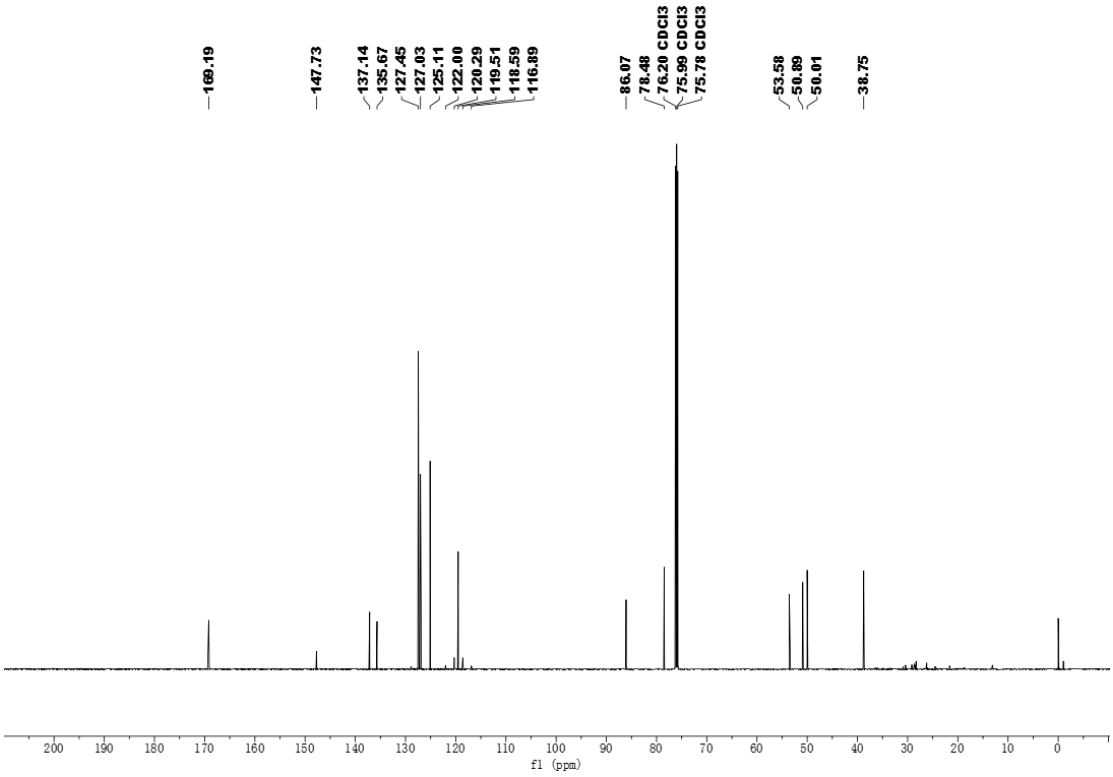


Figure S108. ^{13}C NMR spectra of **39**

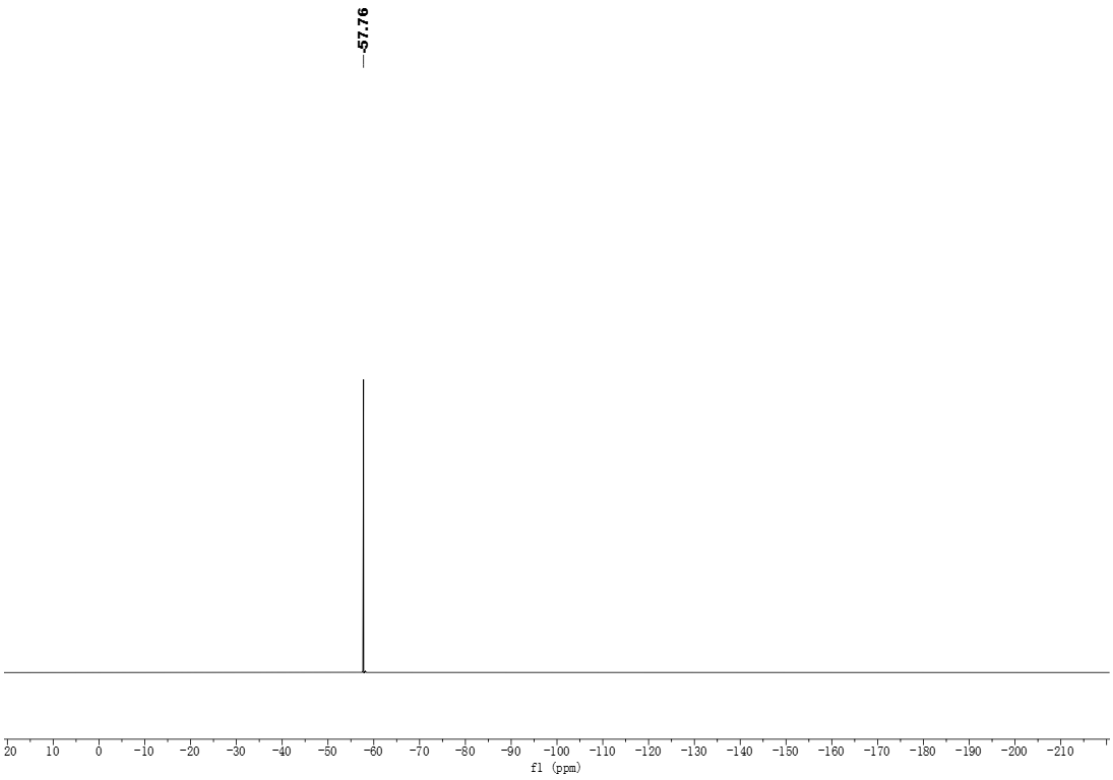


Figure S109. ^{19}F NMR spectra of **39**

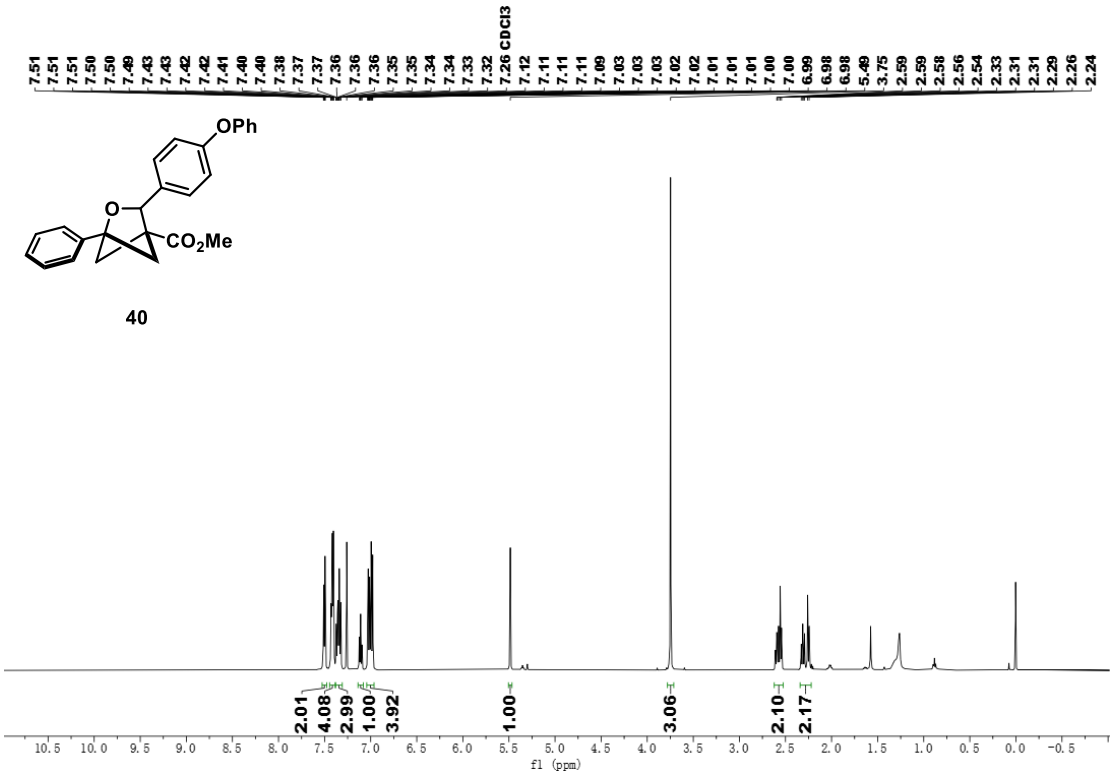


Figure S110. ^{1}H NMR spectra of **40**

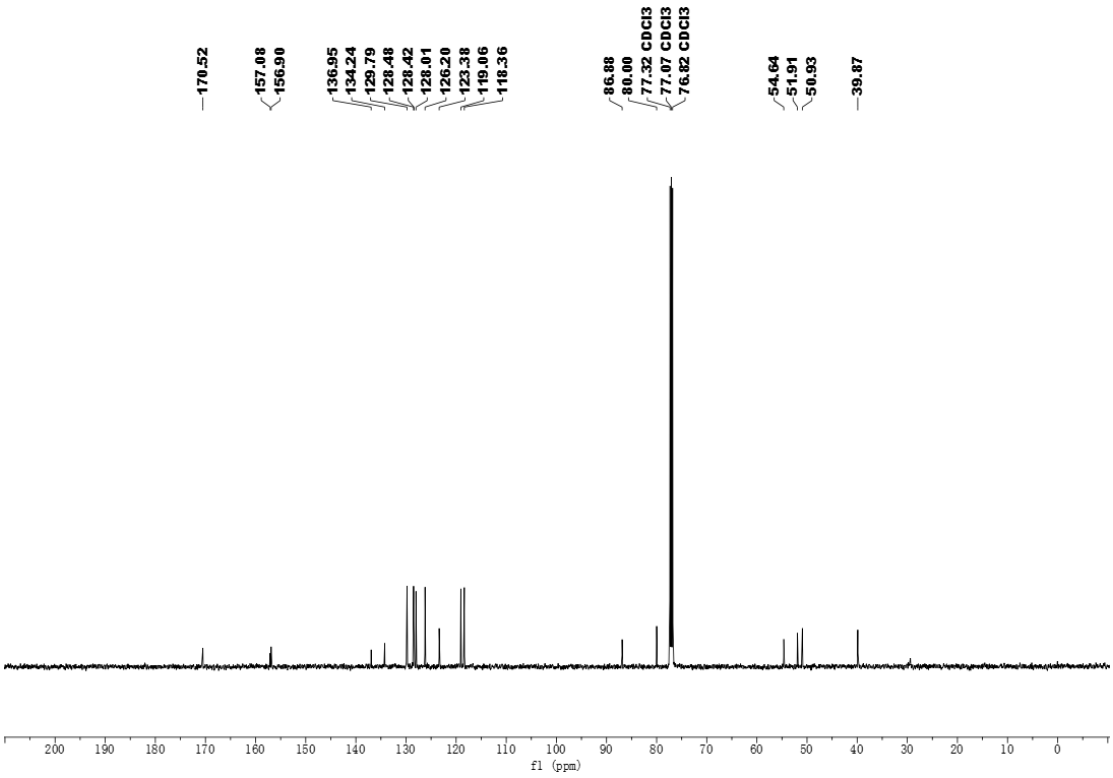


Figure S111. ^{13}C NMR spectra of **40**

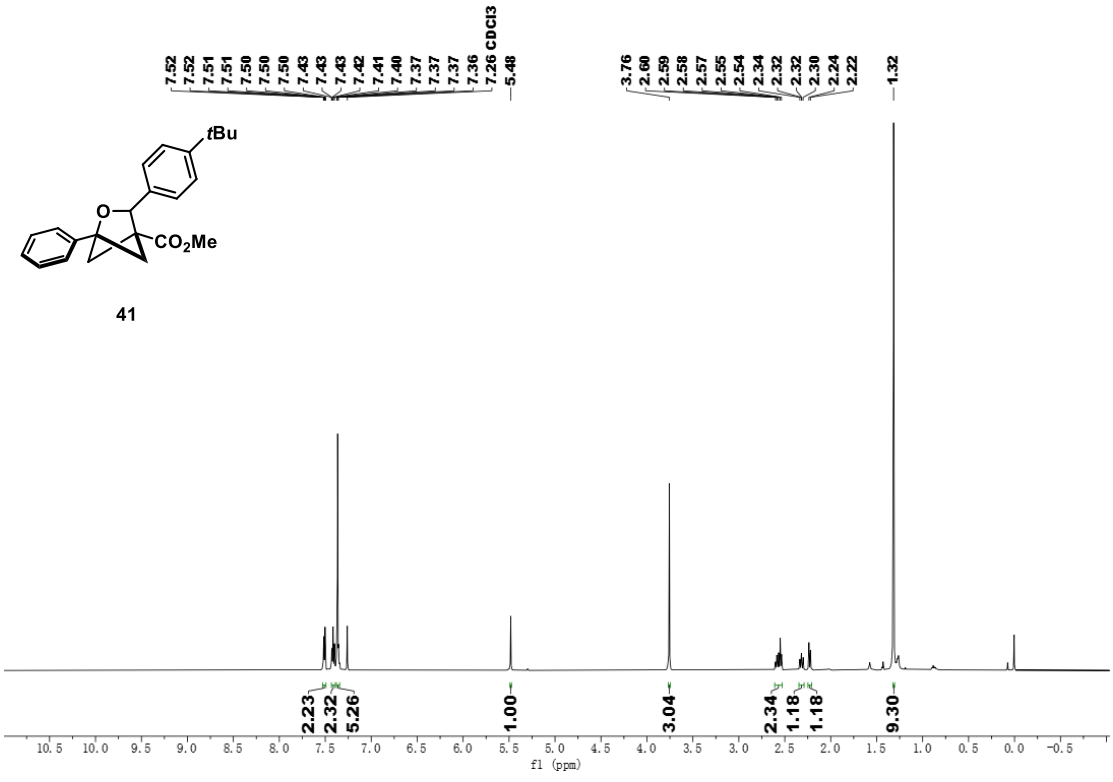


Figure S112. ^{1}H NMR spectra of **41**

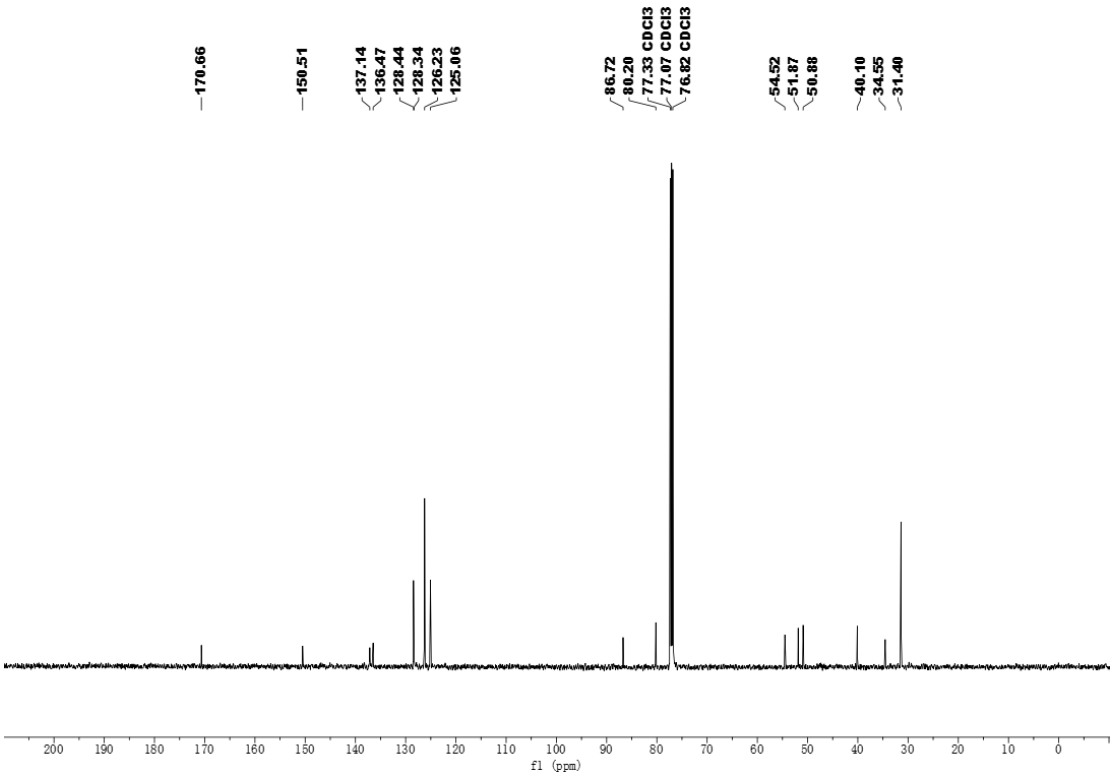


Figure S113. ^{13}C NMR spectra of **41**

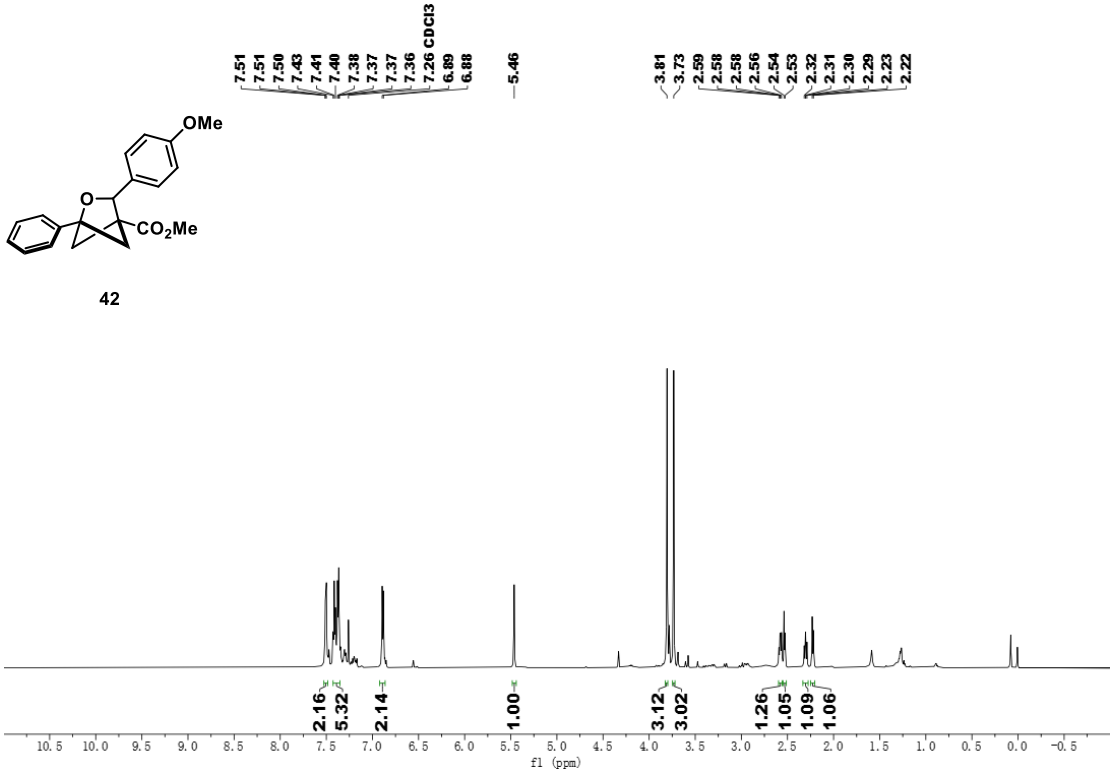


Figure S114. ^{1}H NMR spectra of **42**

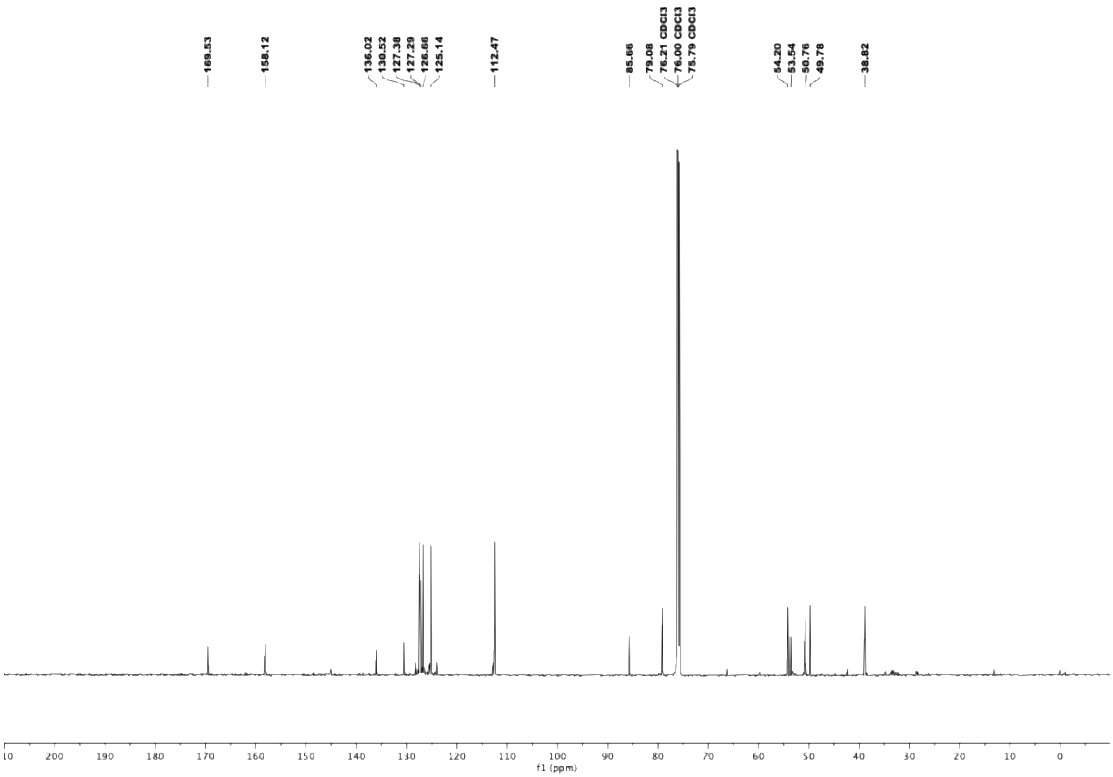


Figure S115. ^{13}C NMR spectra of **42**

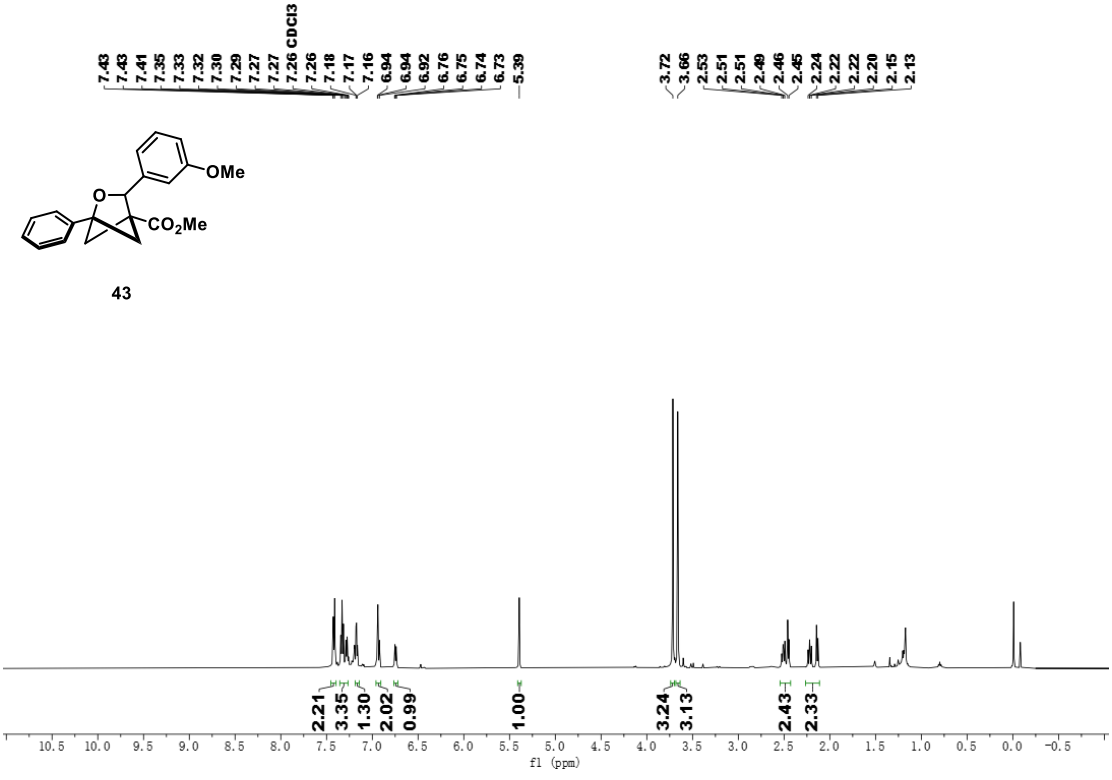


Figure S116. ^{1}H NMR spectra of **43**

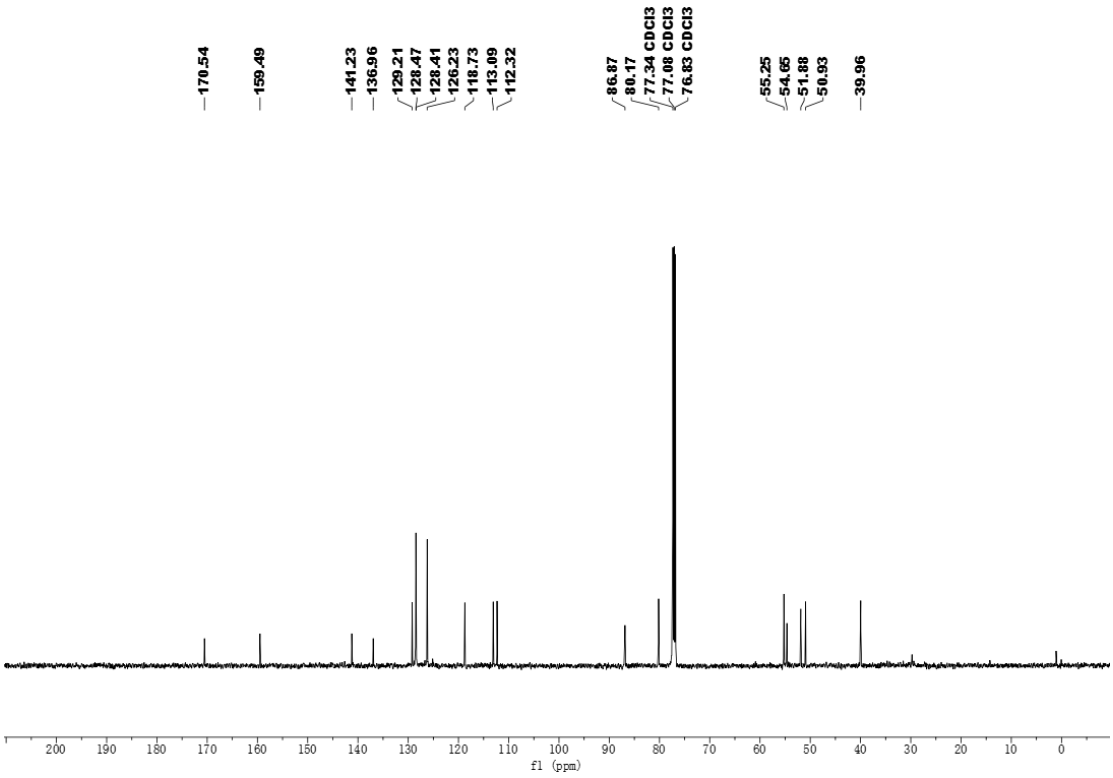


Figure S117. ^{13}C NMR spectra of **43**

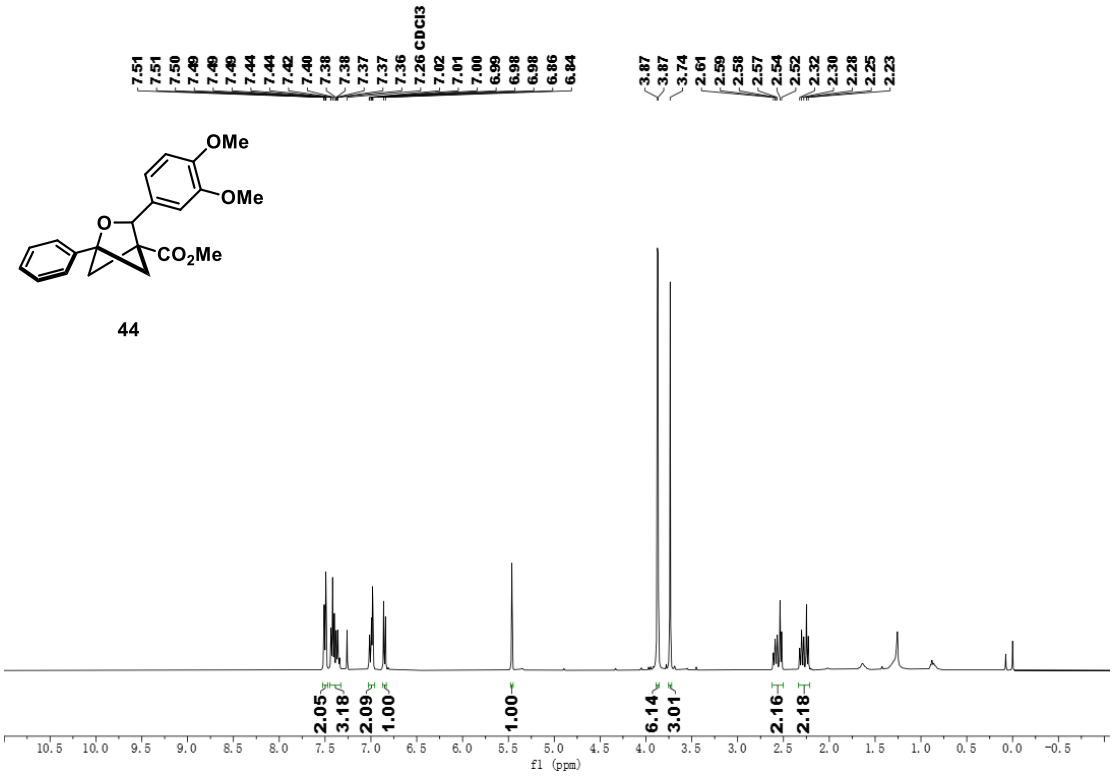


Figure S118. ^{1}H NMR spectra of **44**

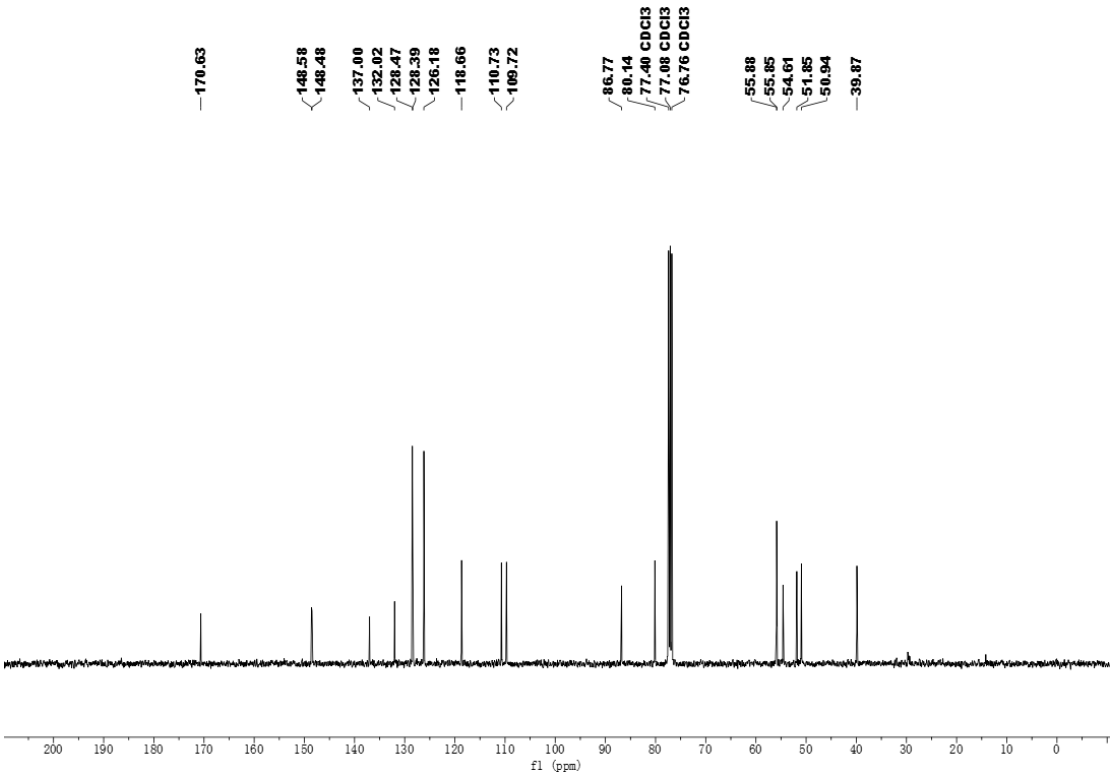


Figure S119. ^{13}C NMR spectra of **44**

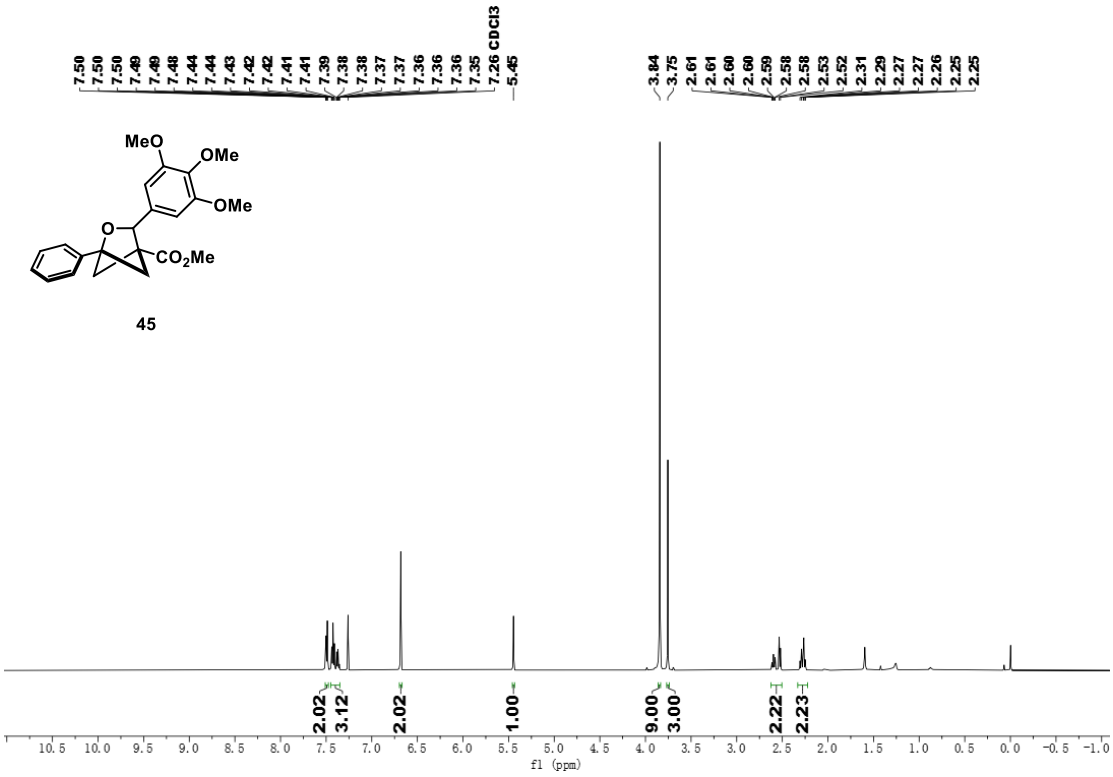


Figure S120. ^{1}H NMR spectra of **45**

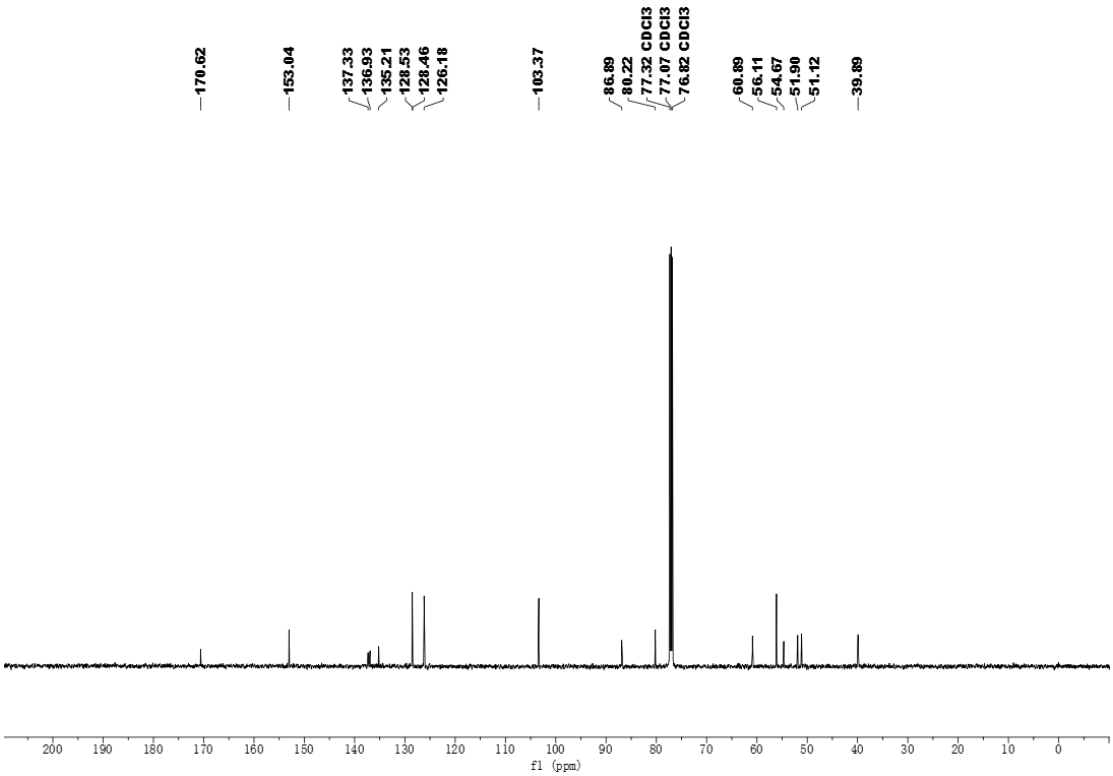


Figure S121. ^{13}C NMR spectra of **45**

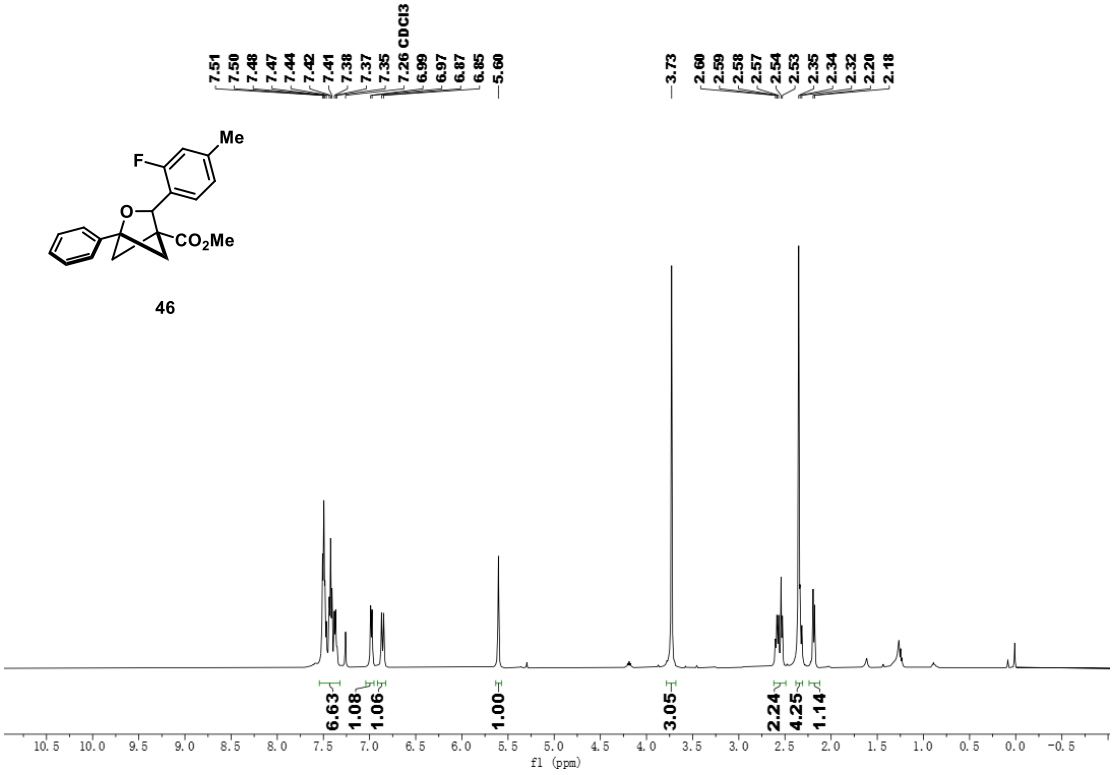


Figure S122. ^{1}H NMR spectra of **46**

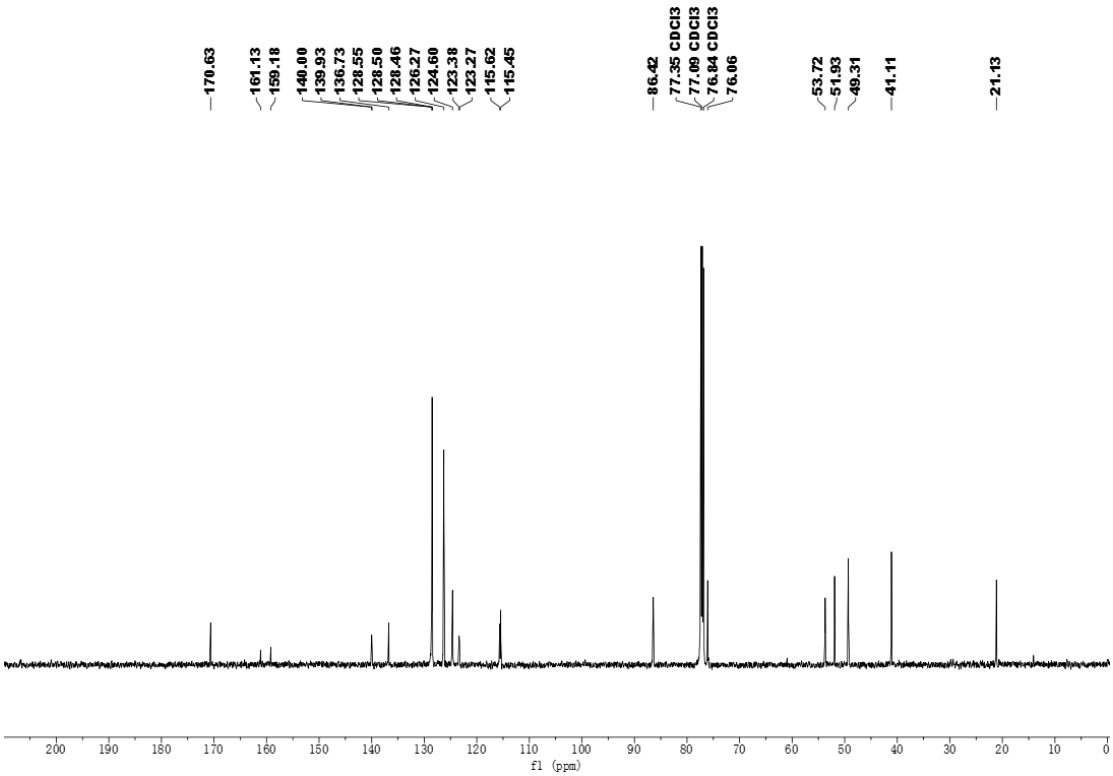


Figure S123. ^{13}C NMR spectra of **46**

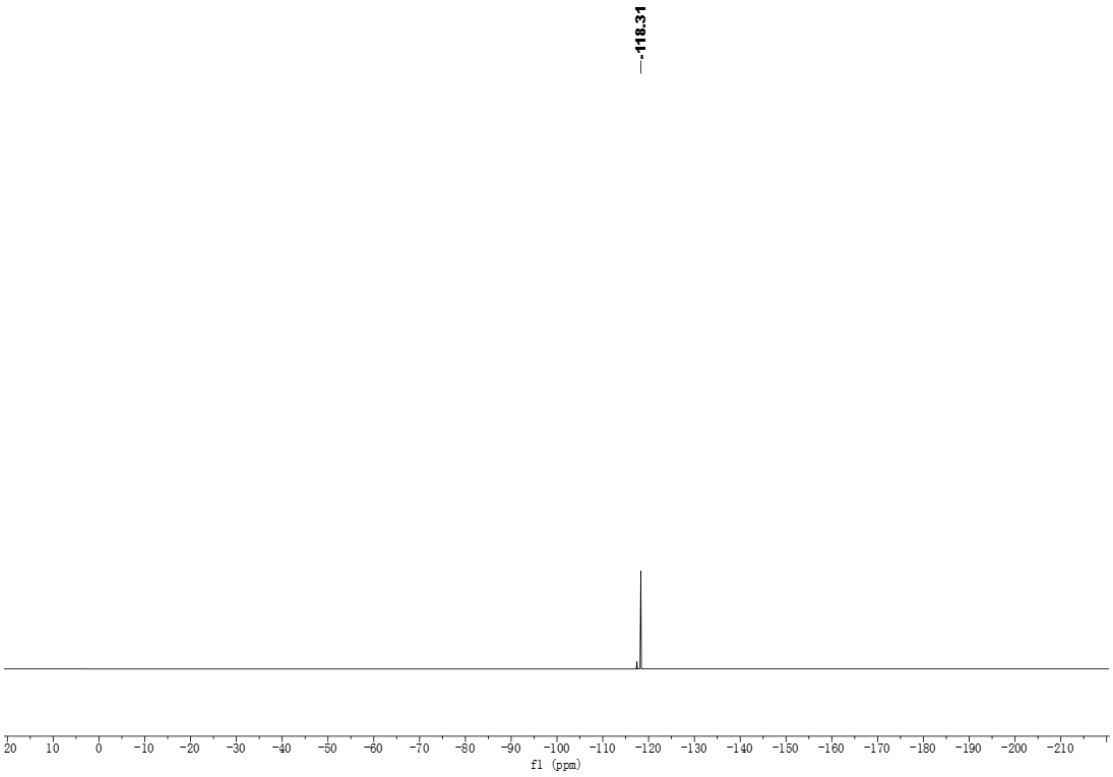


Figure S124. ^{19}F NMR spectra of **46**

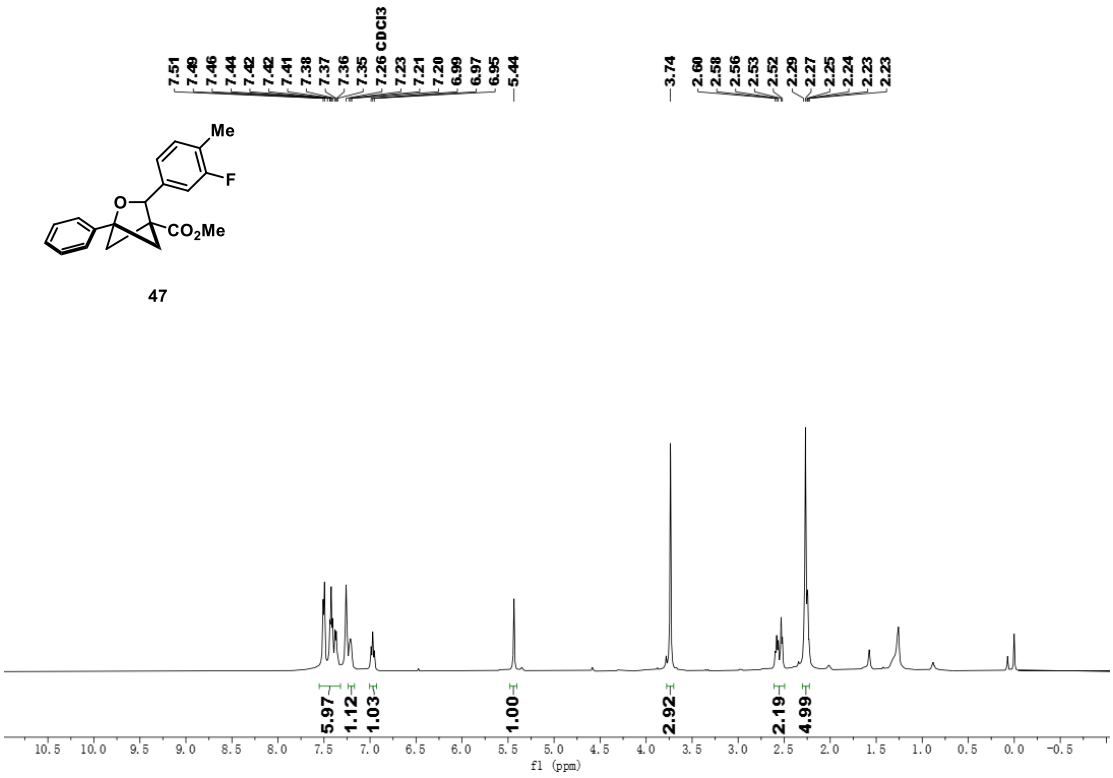


Figure S125. ^{1}H NMR spectra of **47**

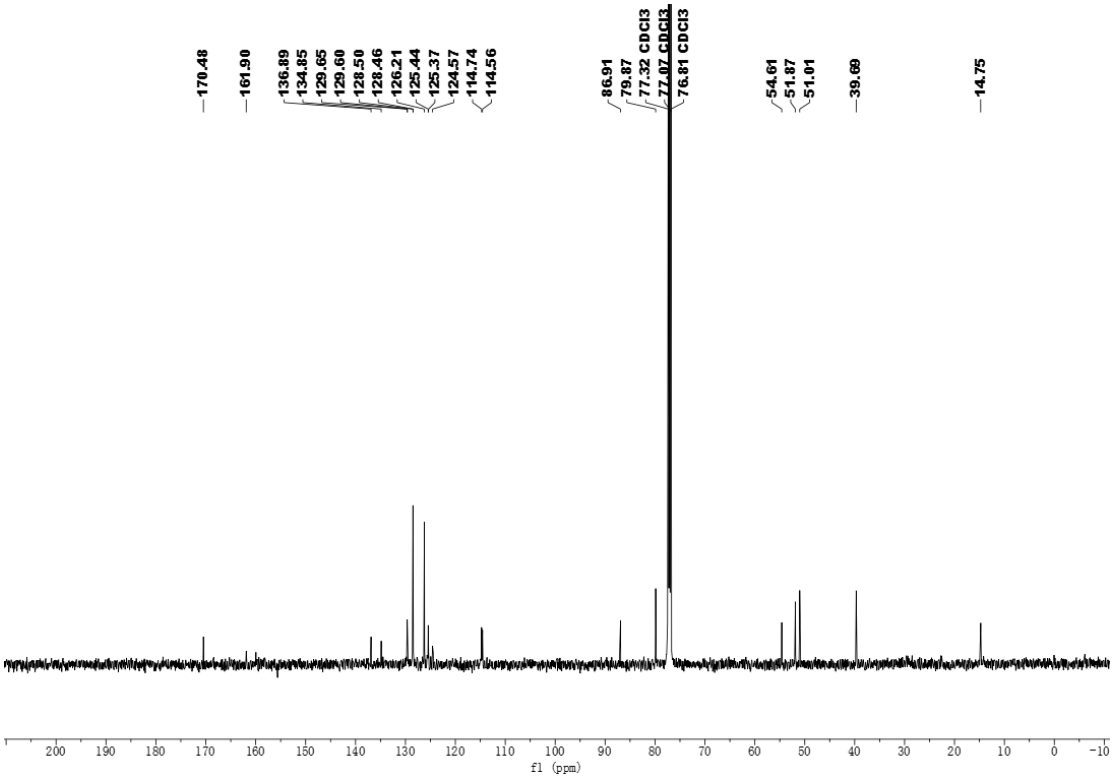


Figure S126. ^{13}C NMR spectra of **47**

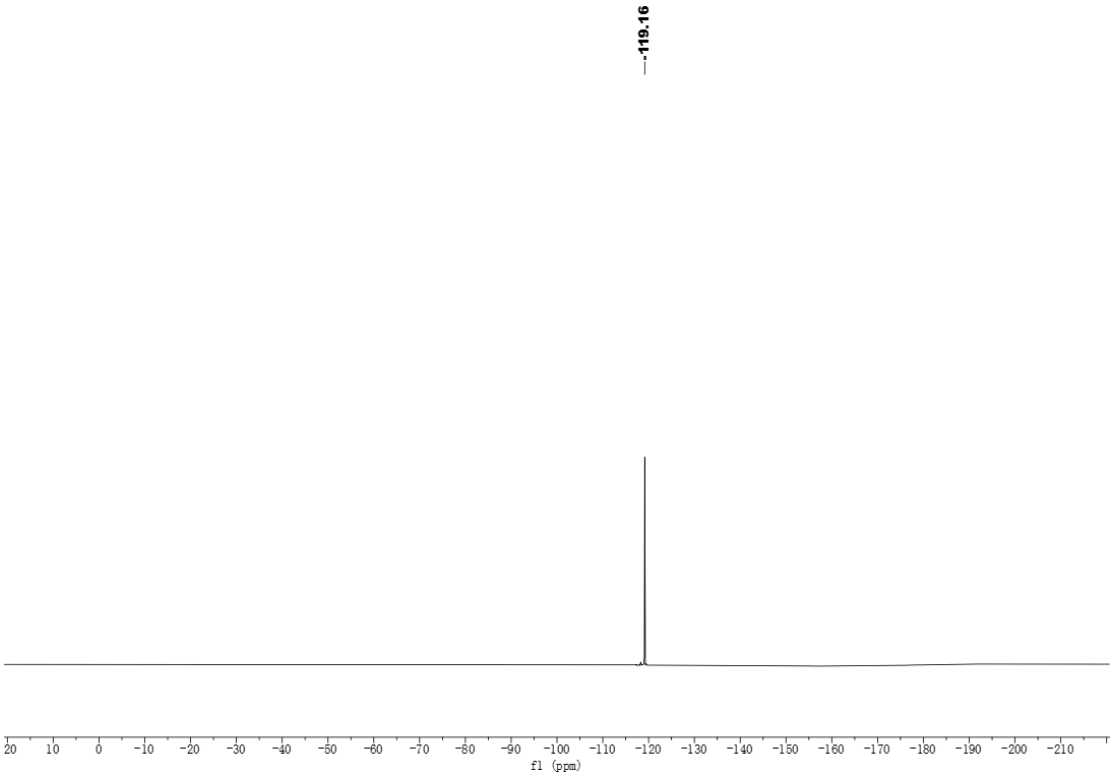


Figure S127. ^{19}F NMR spectra of **47**

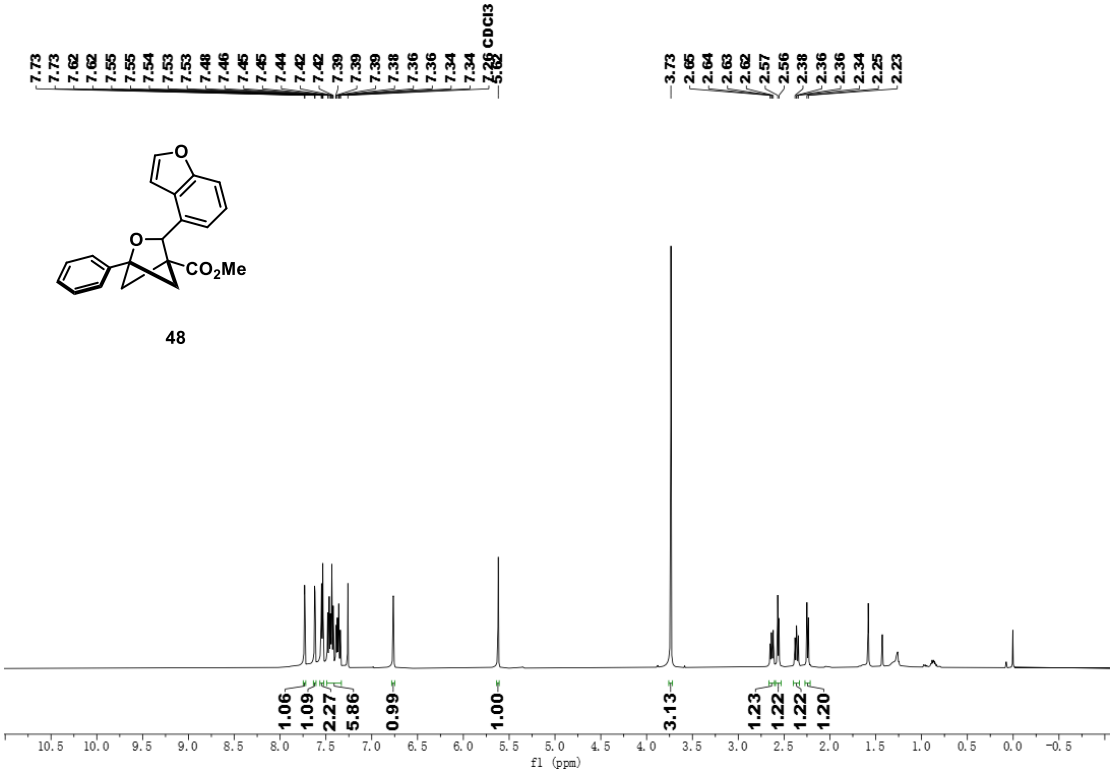


Figure S128. ^{1}H NMR spectra of **48**

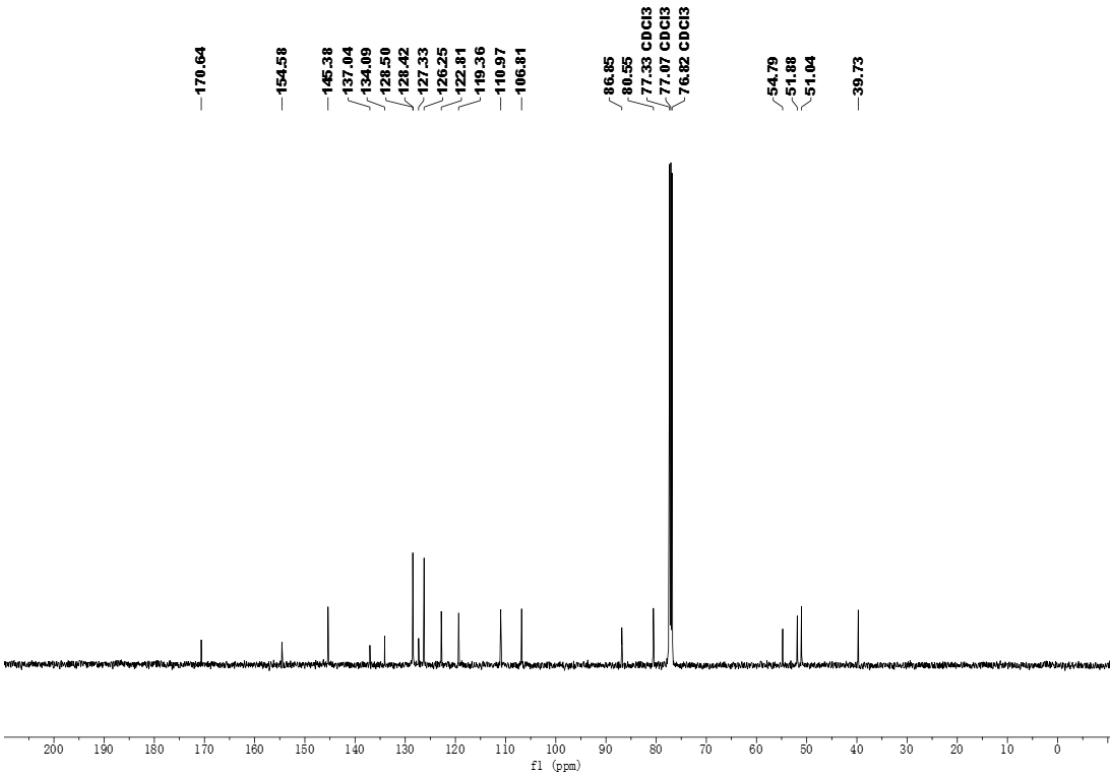


Figure S129. ^{13}C NMR spectra of **48**

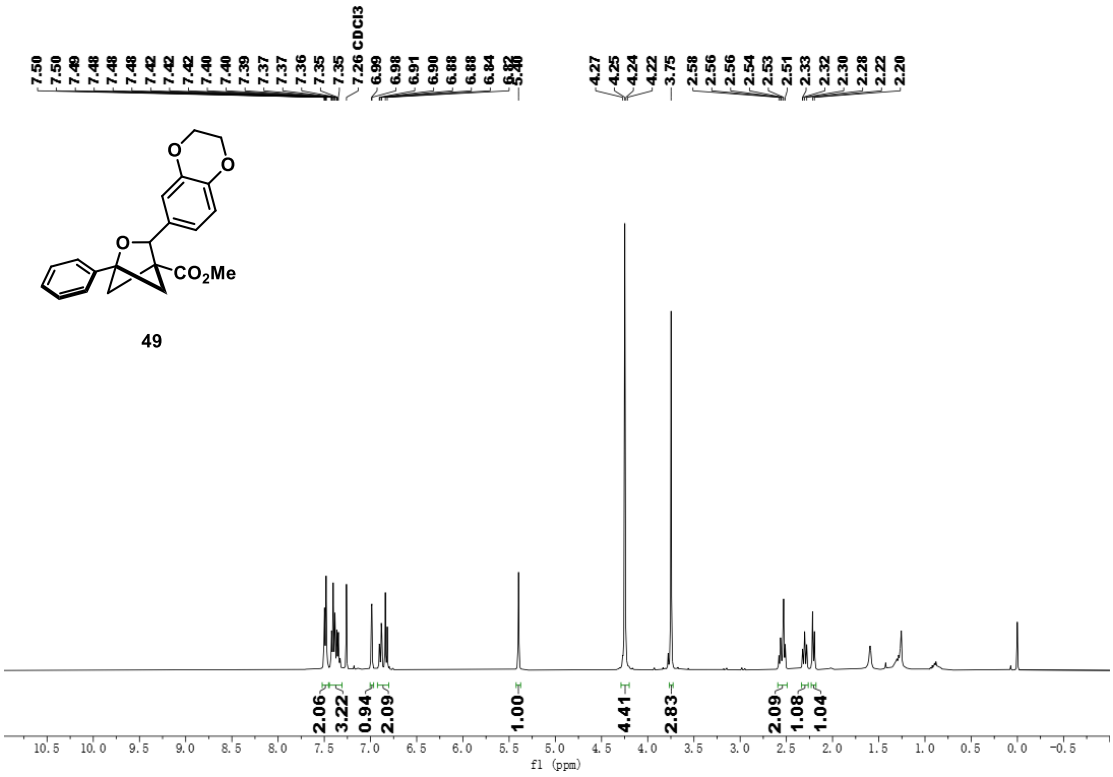


Figure S130. ^{1}H NMR spectra of **49**

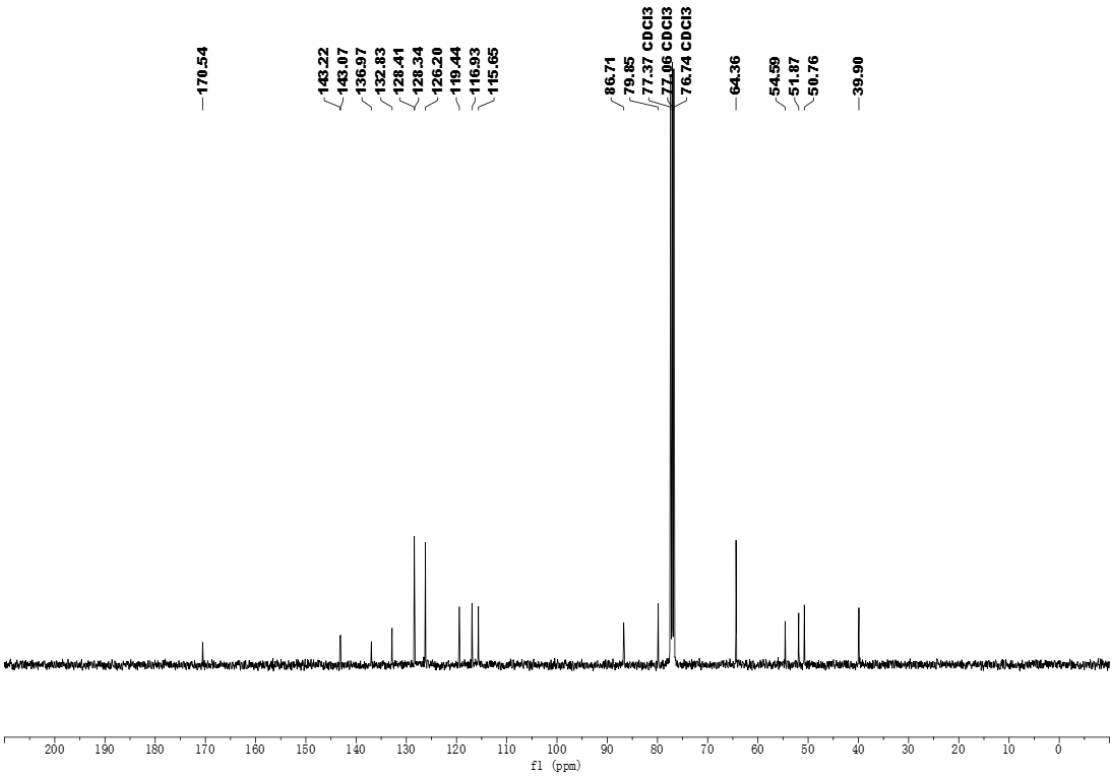


Figure S131. ^{13}C NMR spectra of **49**

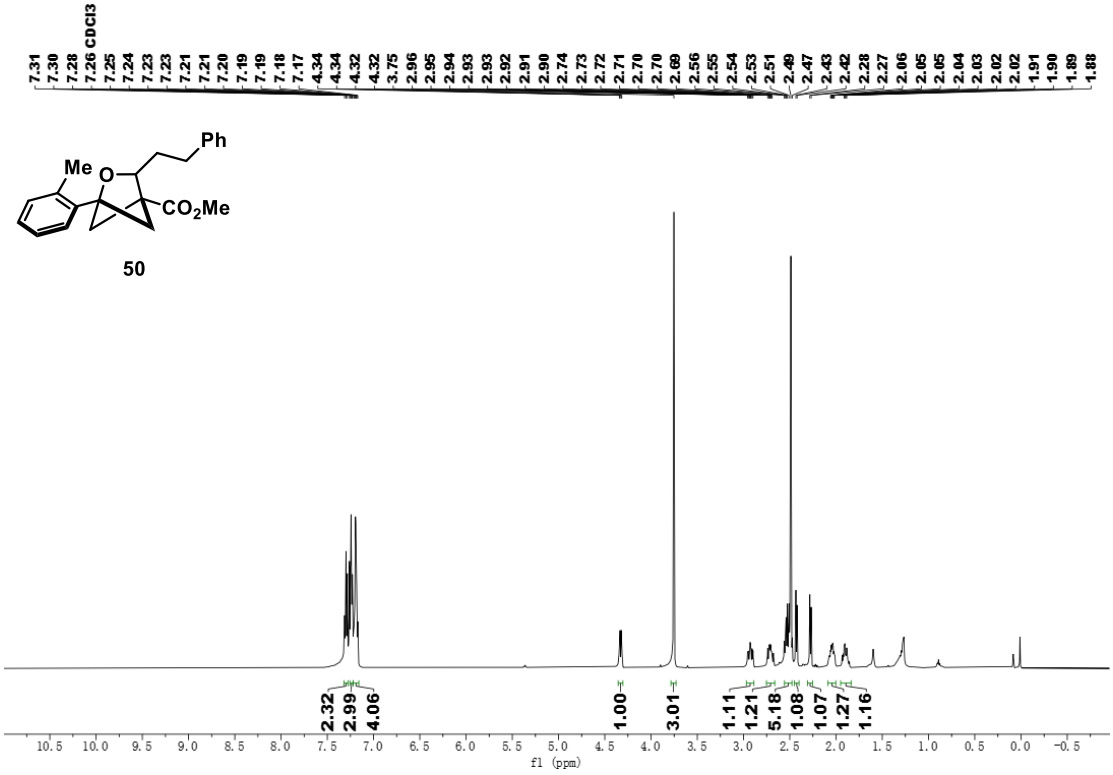


Figure S132. ^{1}H NMR spectra of **50**

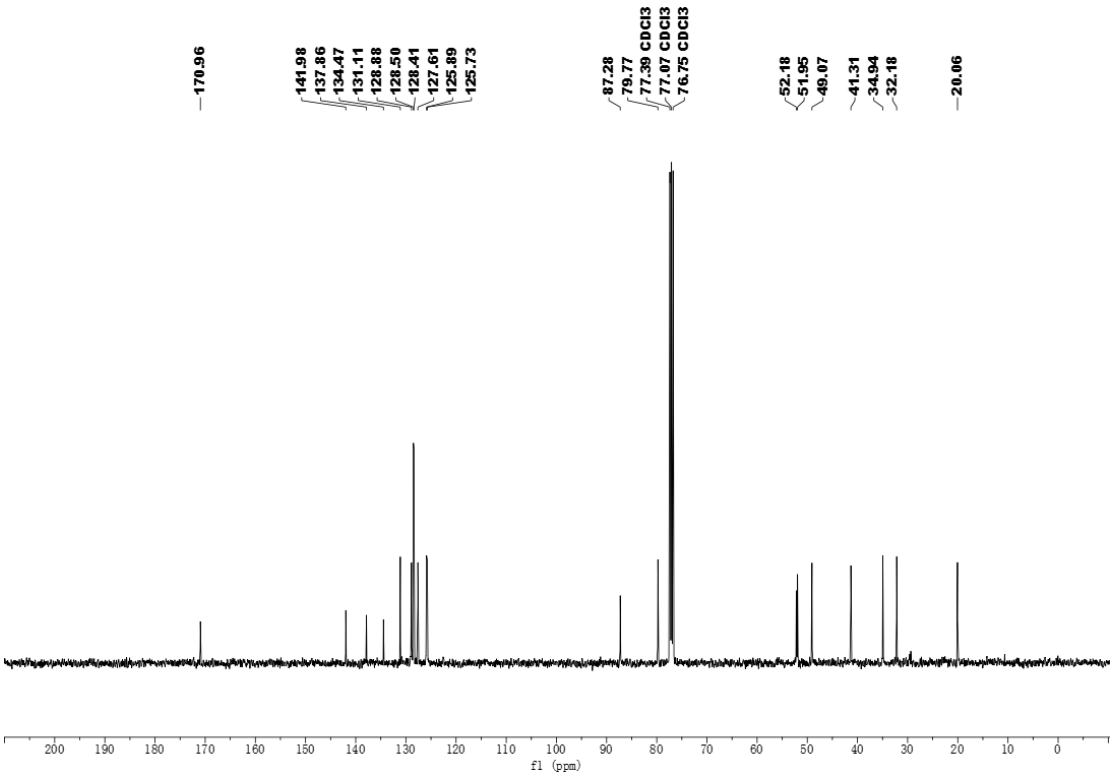


Figure S133. ^{13}C NMR spectra of **50**

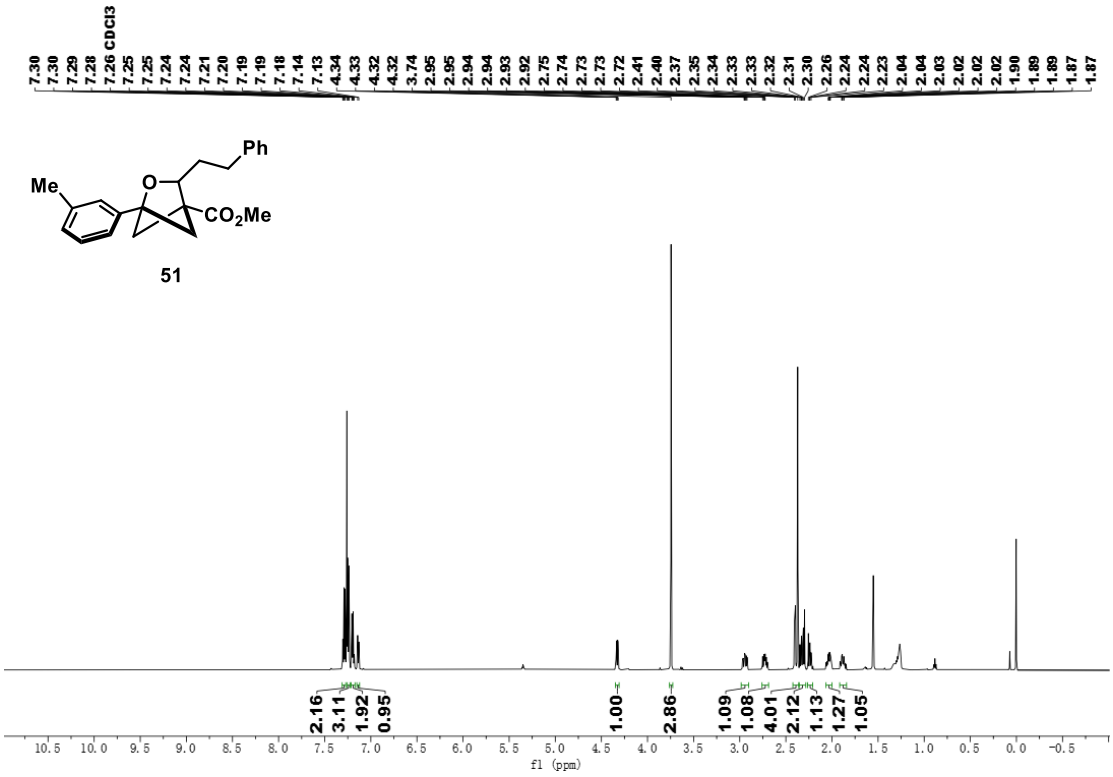


Figure S134. ^{1}H NMR spectra of **51**

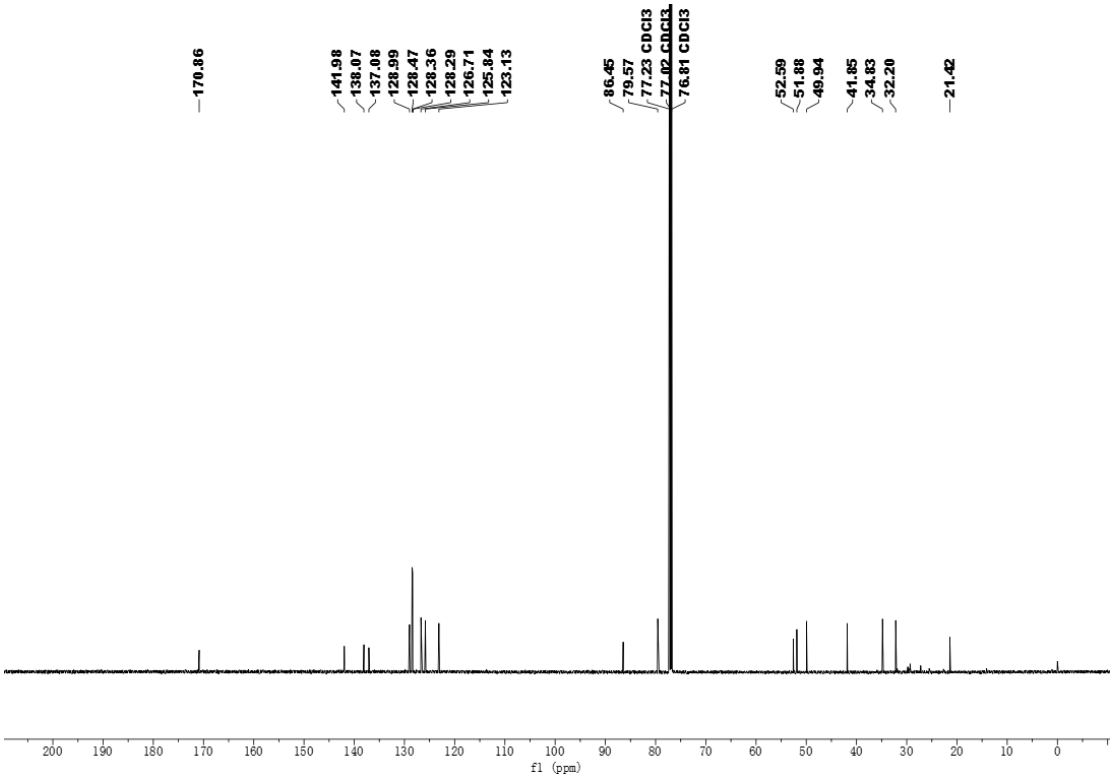


Figure S135. ^{13}C NMR spectra of **51**

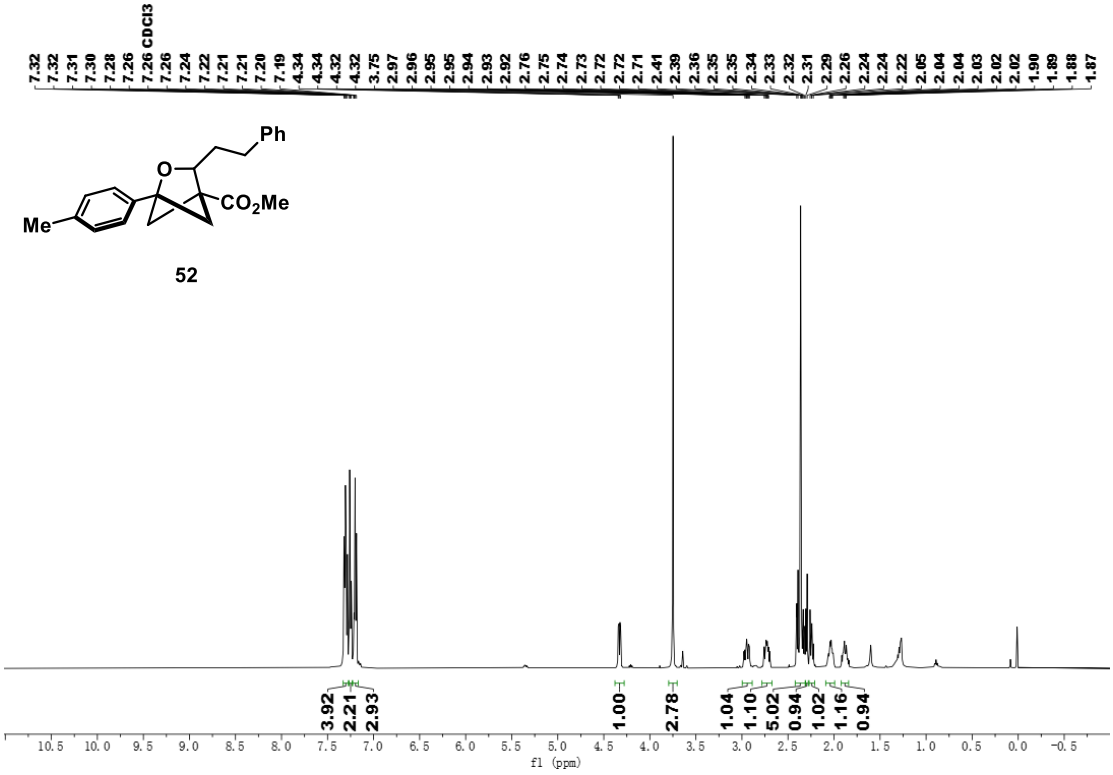


Figure S136. ^{1}H NMR spectra of **52**

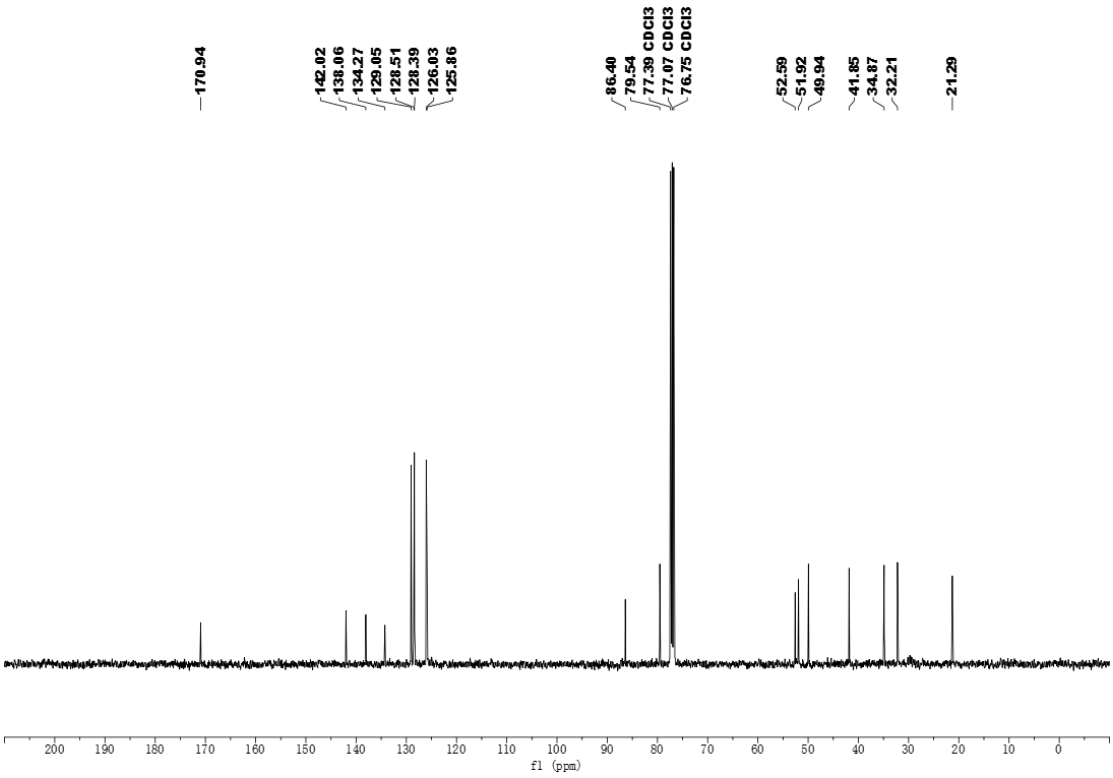
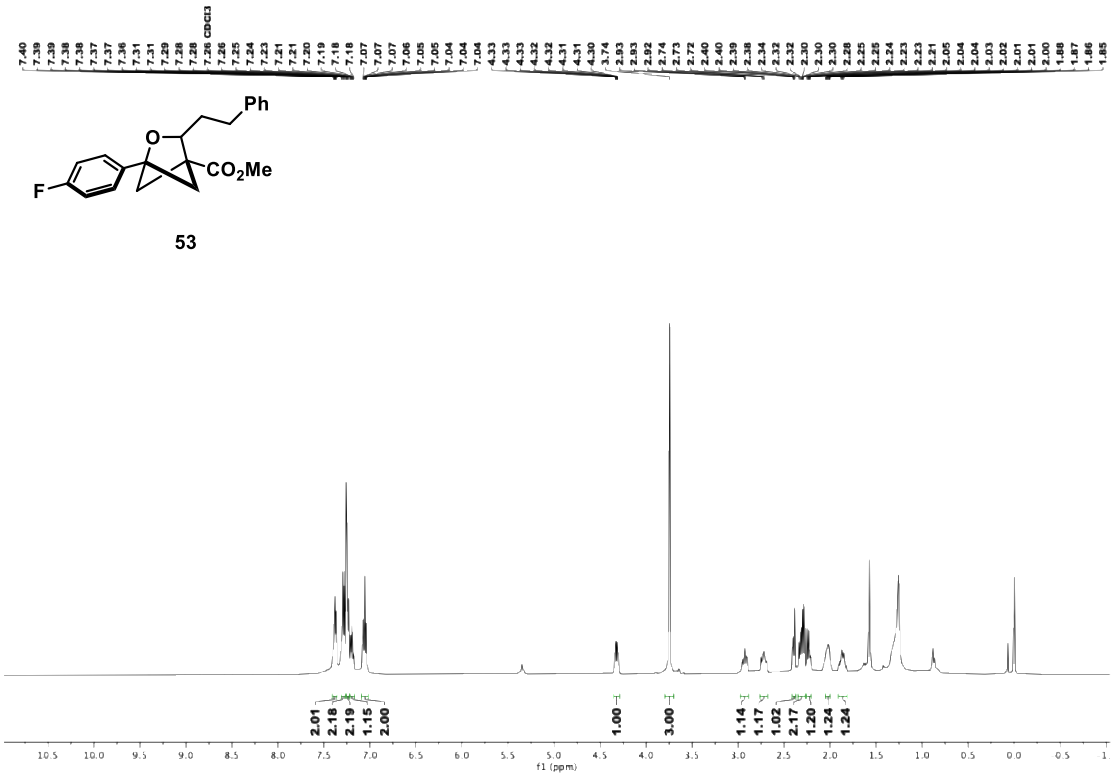


Figure S137. ^{13}C NMR spectra of **52**



53

Figure S138. ^{1}H NMR spectra of **53**

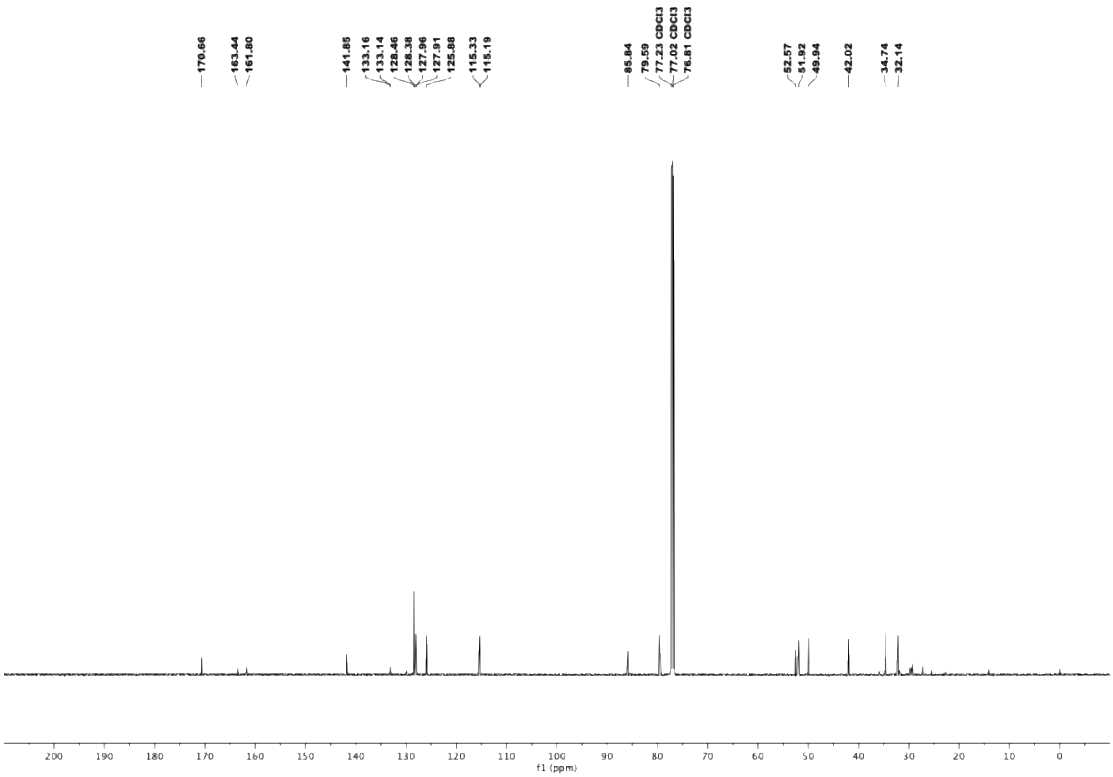


Figure S139. ^{13}C NMR spectra of **53**

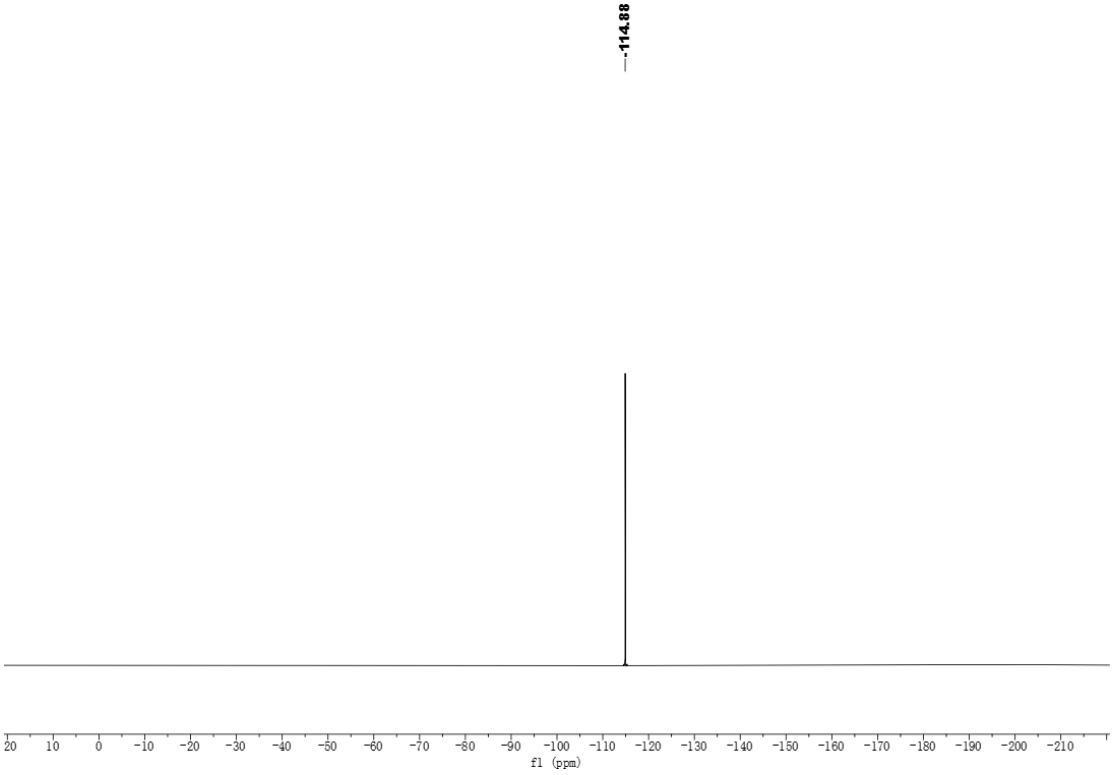


Figure S140. ^{19}F NMR spectra of **53**

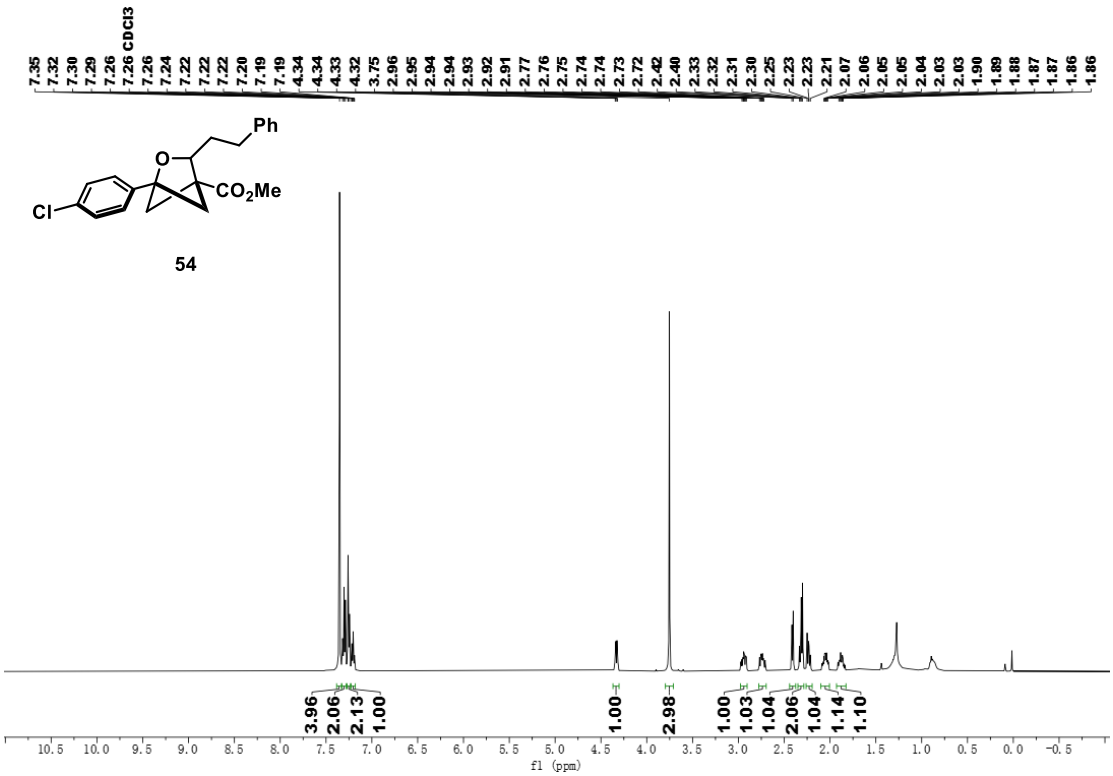


Figure S141. ^{1}H NMR spectra of **54**

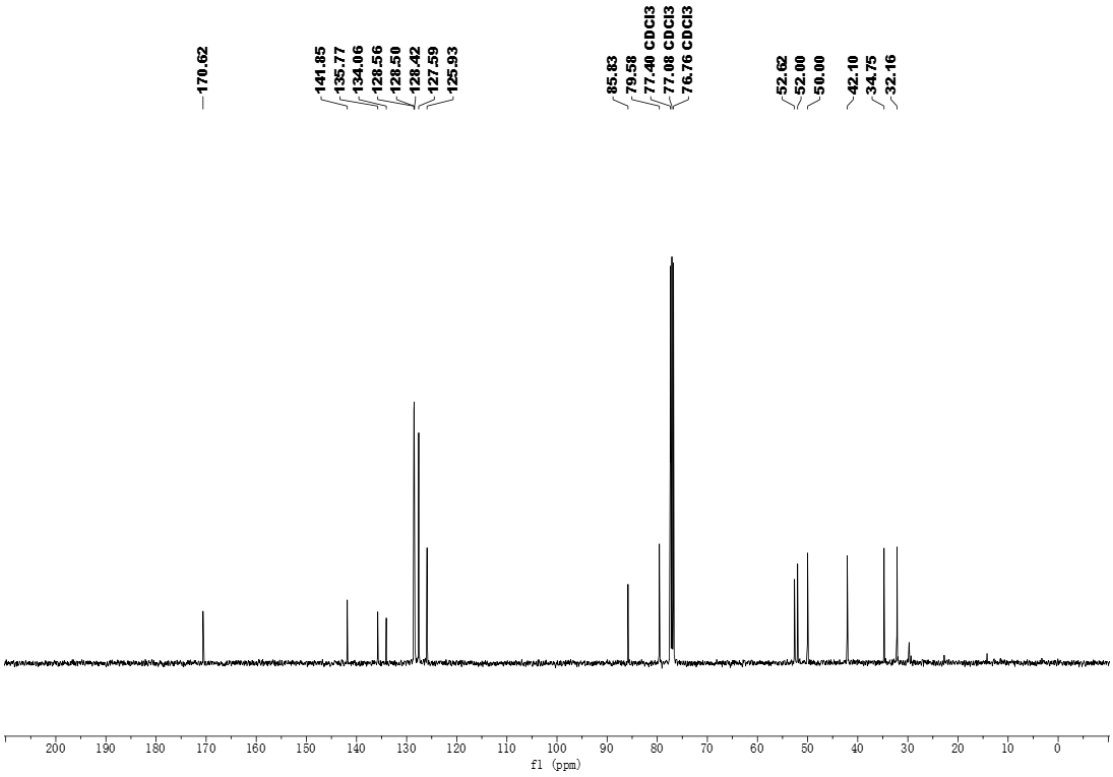


Figure S142. ^{13}C NMR spectra of **54**

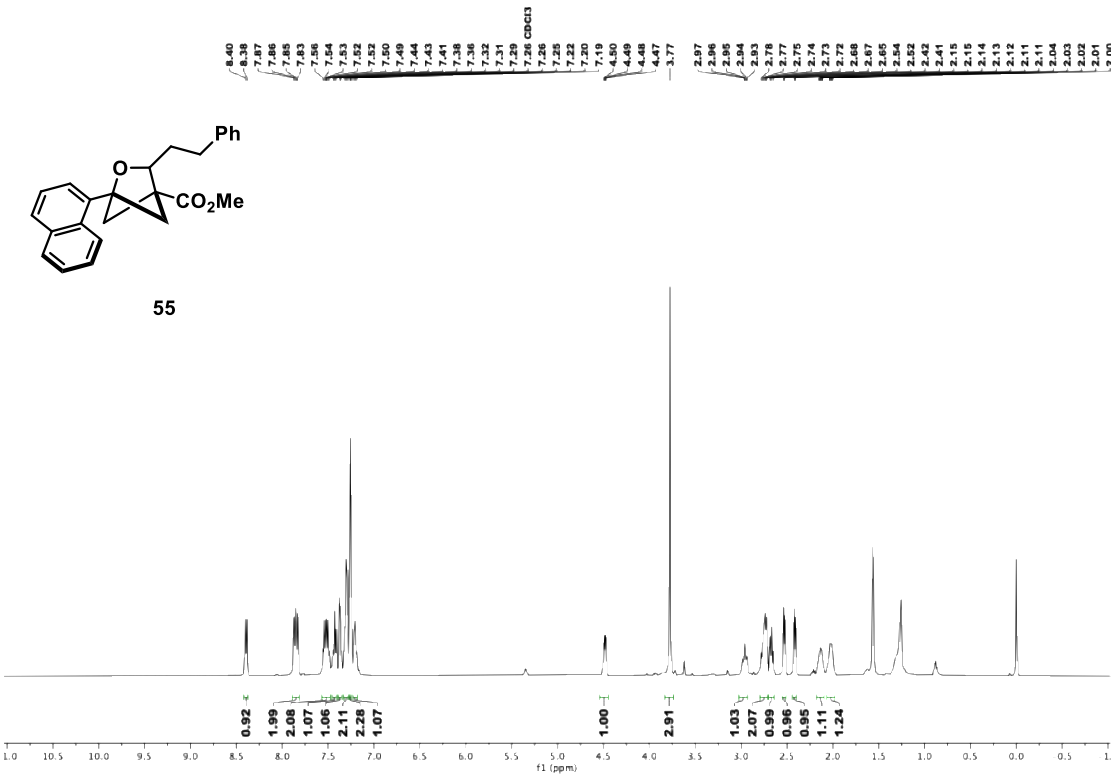


Figure S143. ^{1}H NMR spectra of **55**

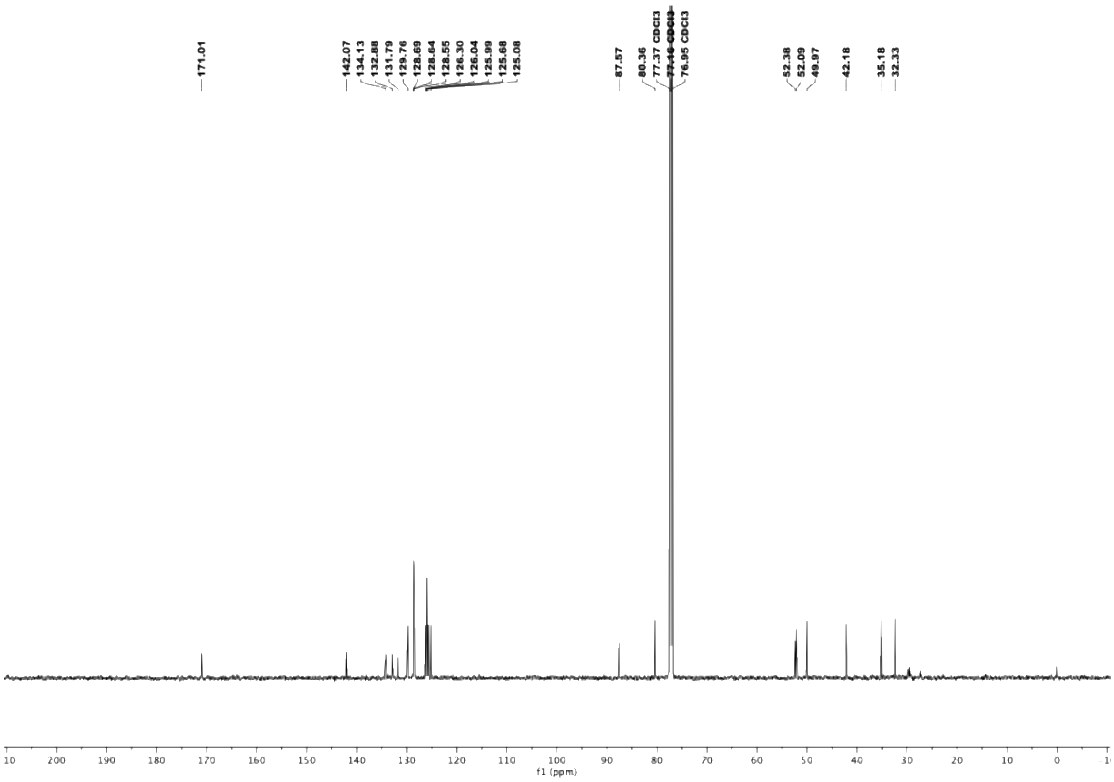


Figure S144. ^{13}C NMR spectra of **55**

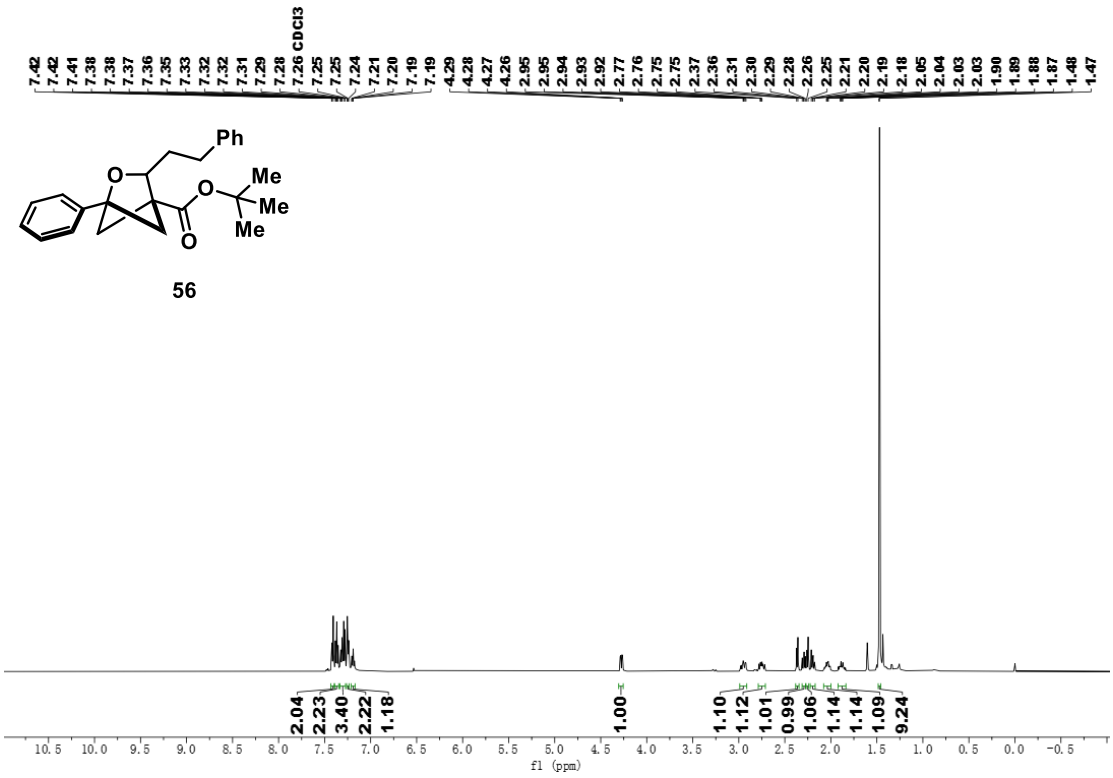


Figure S145. ^{1}H NMR spectra of **56**

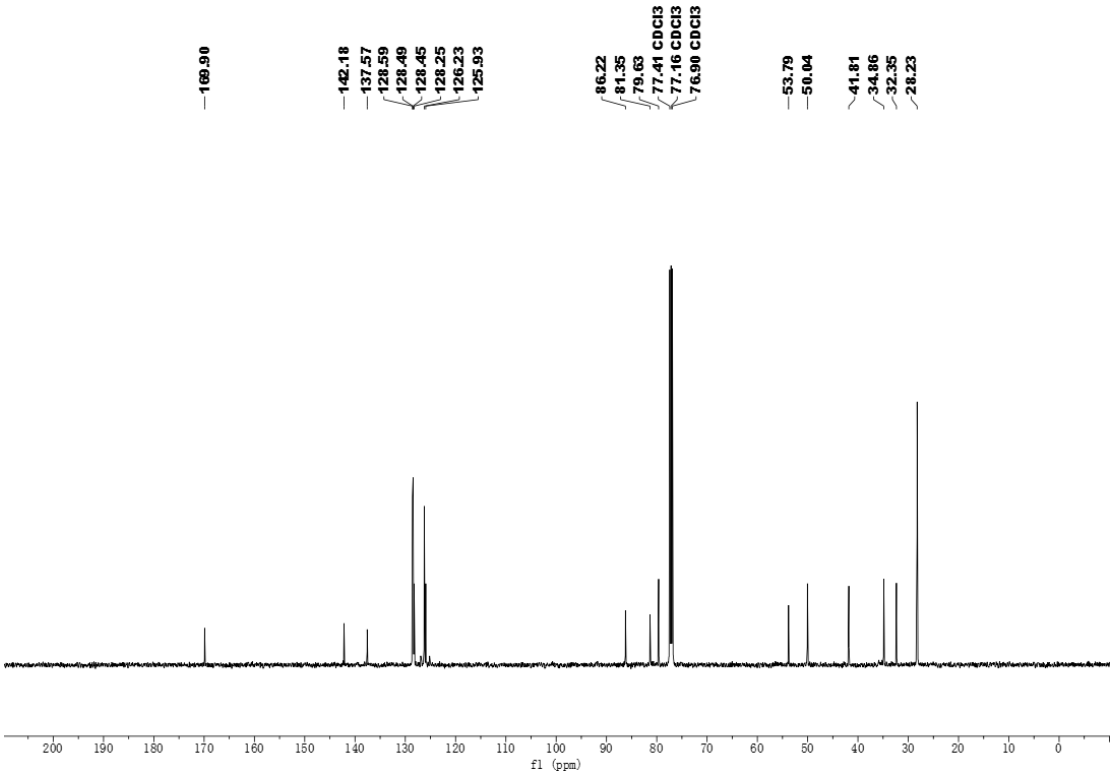


Figure S146. ^{13}C NMR spectra of **56**

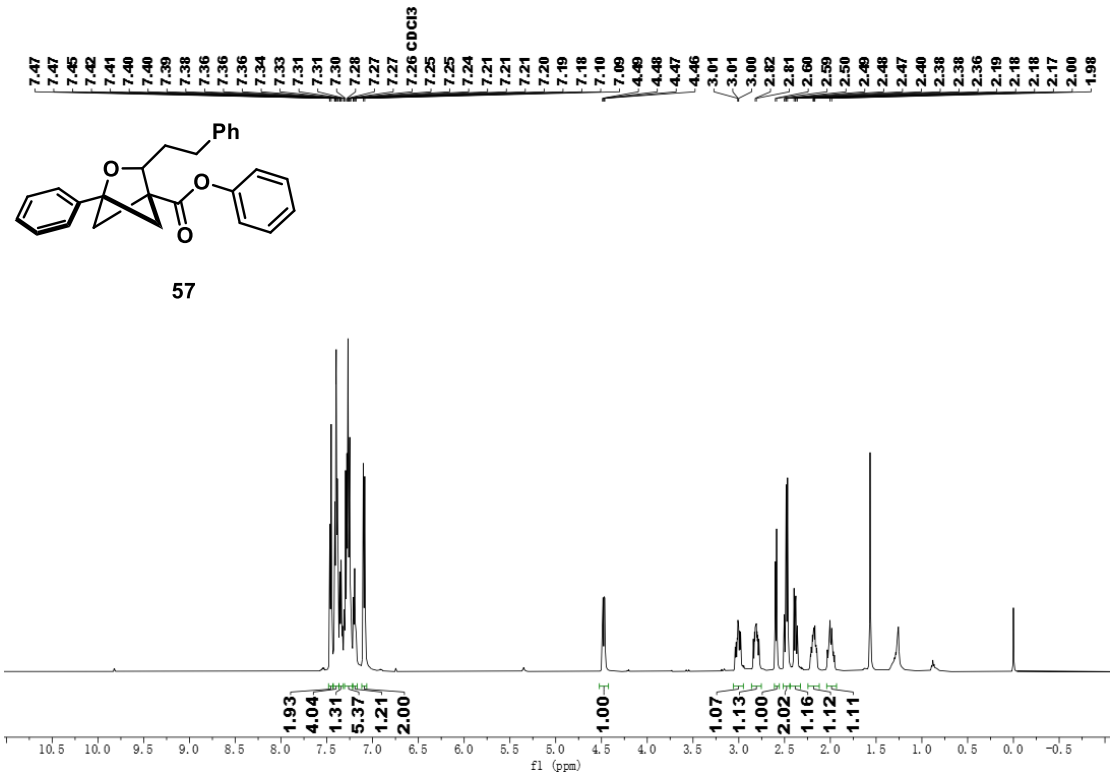


Figure S147. ^{1}H NMR spectra of **57**

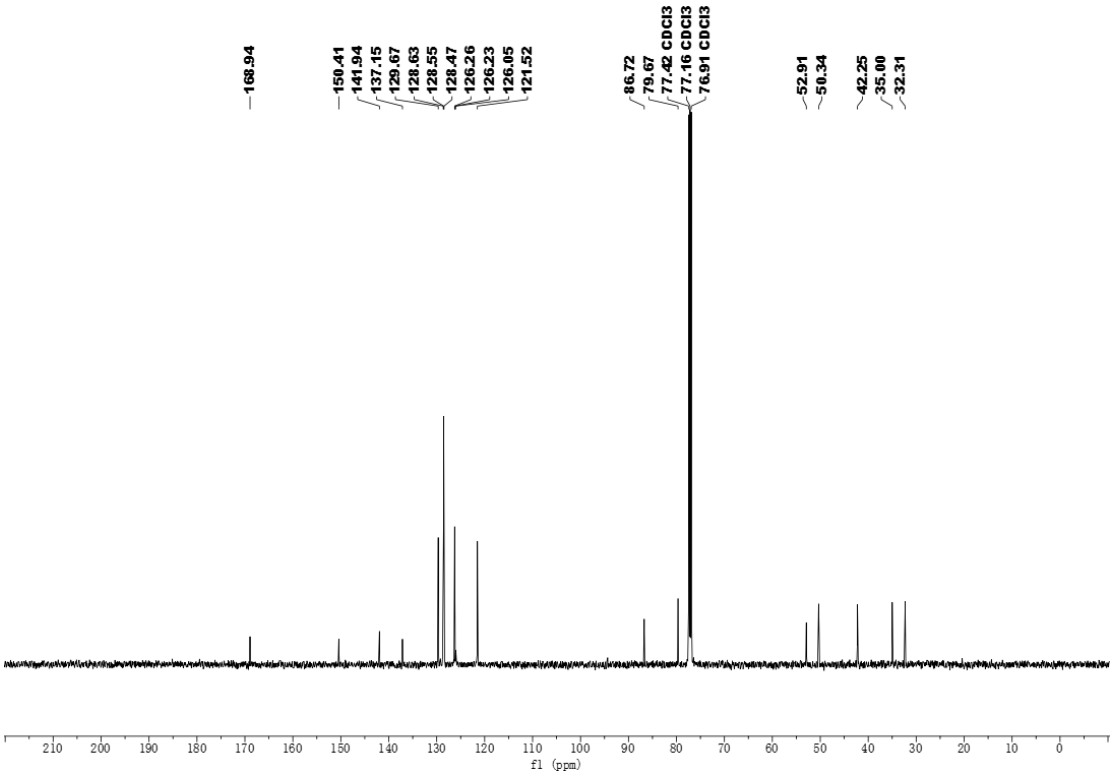


Figure S148. ^{13}C NMR spectra of **57**

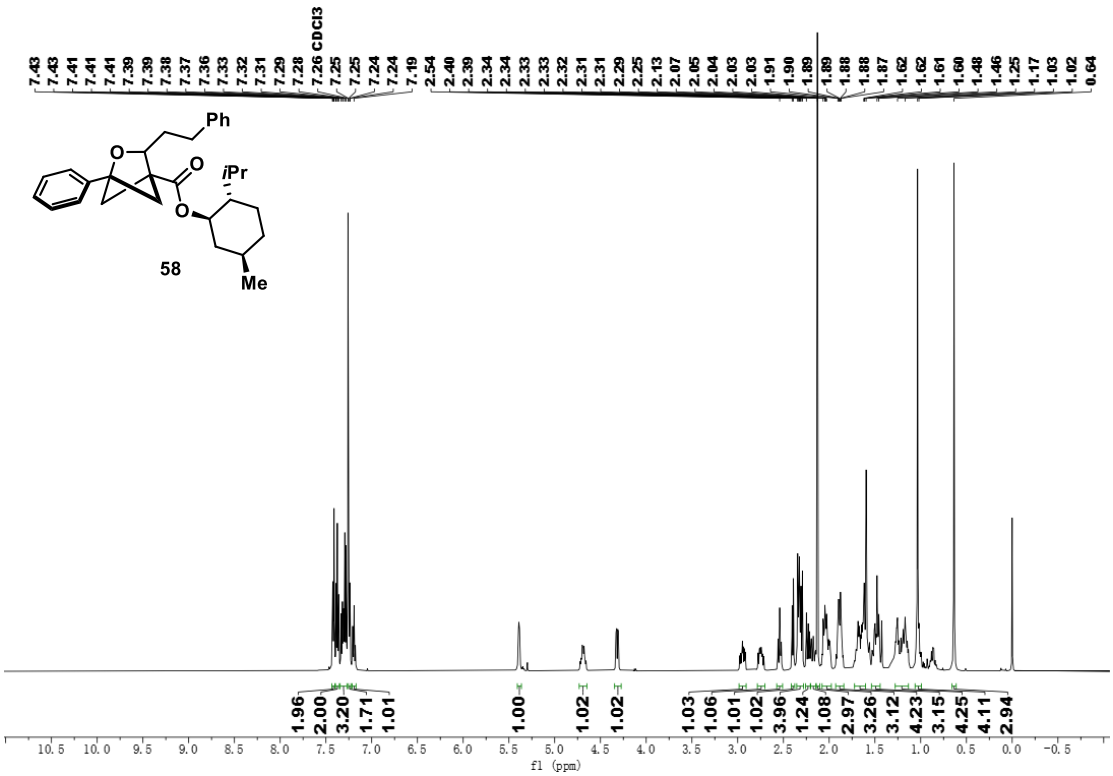


Figure S149. ^{1}H NMR spectra of **58**

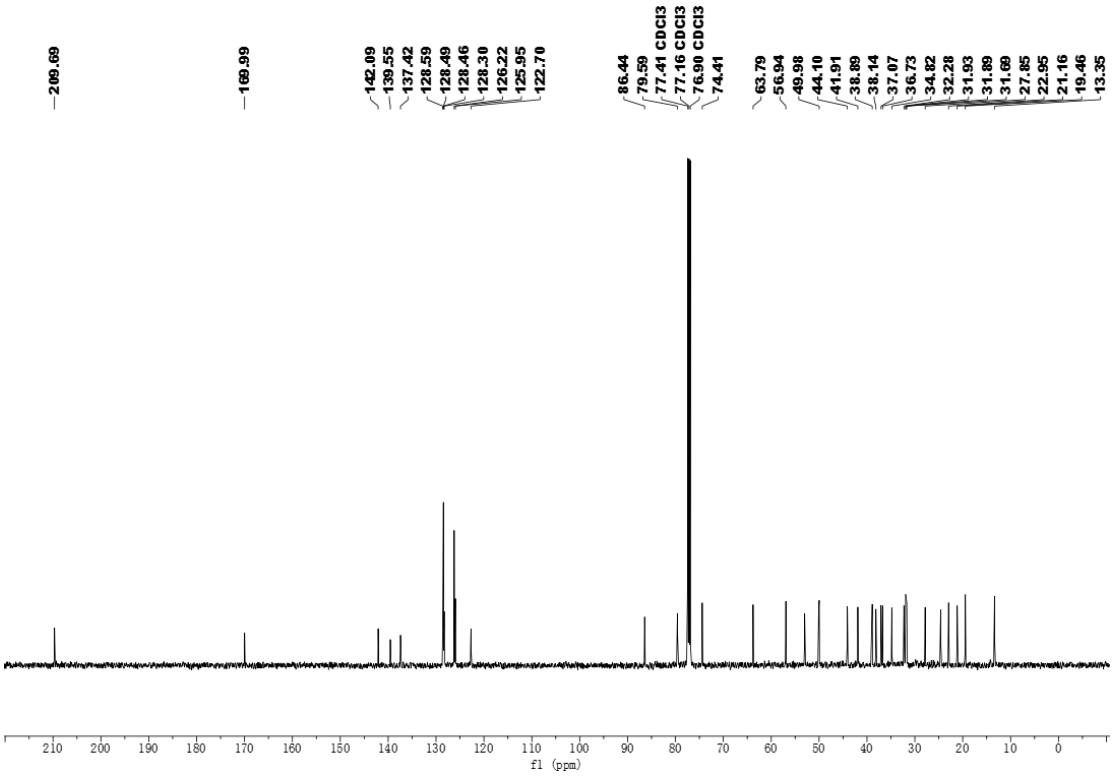


Figure S150. ^{13}C NMR spectra of **58**

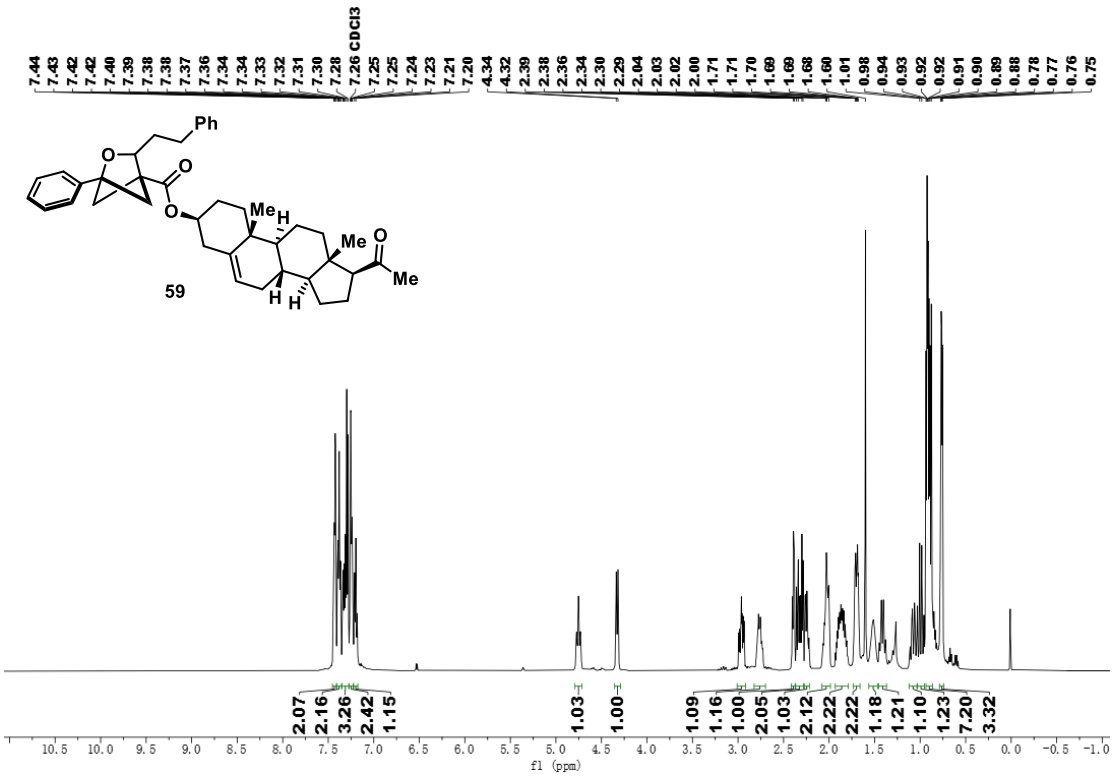


Figure S151. ^{1}H NMR spectra of **59**

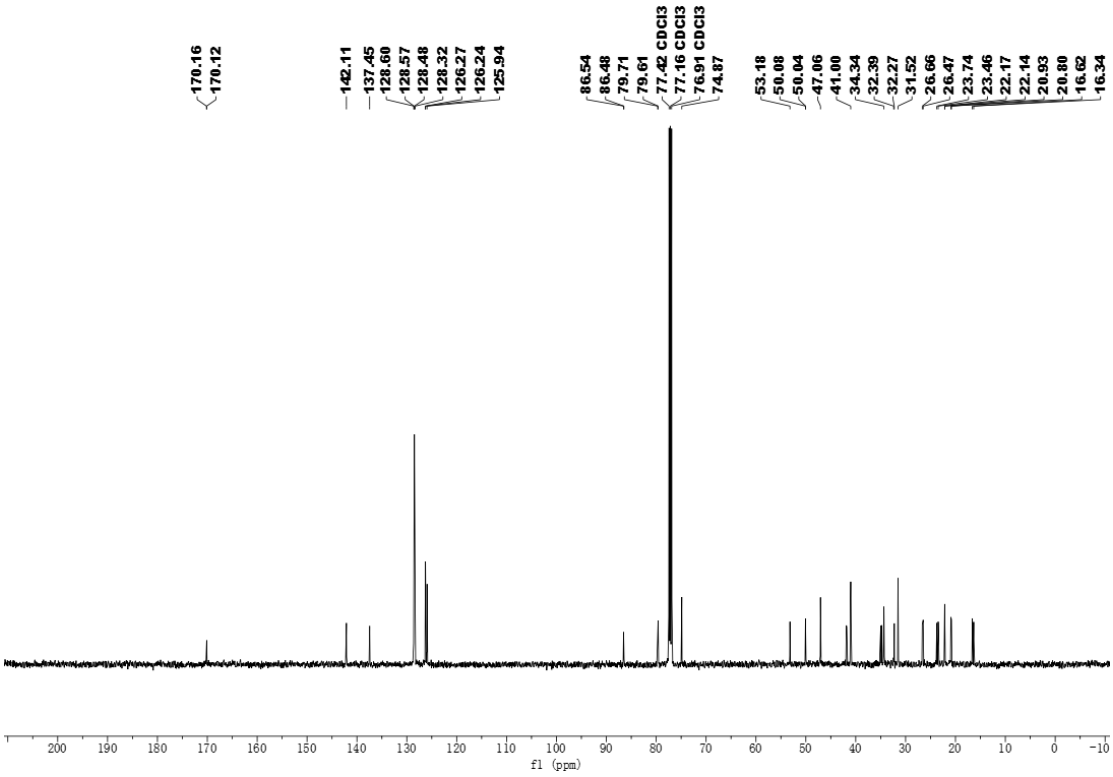


Figure S152. ^{13}C NMR spectra of **59**

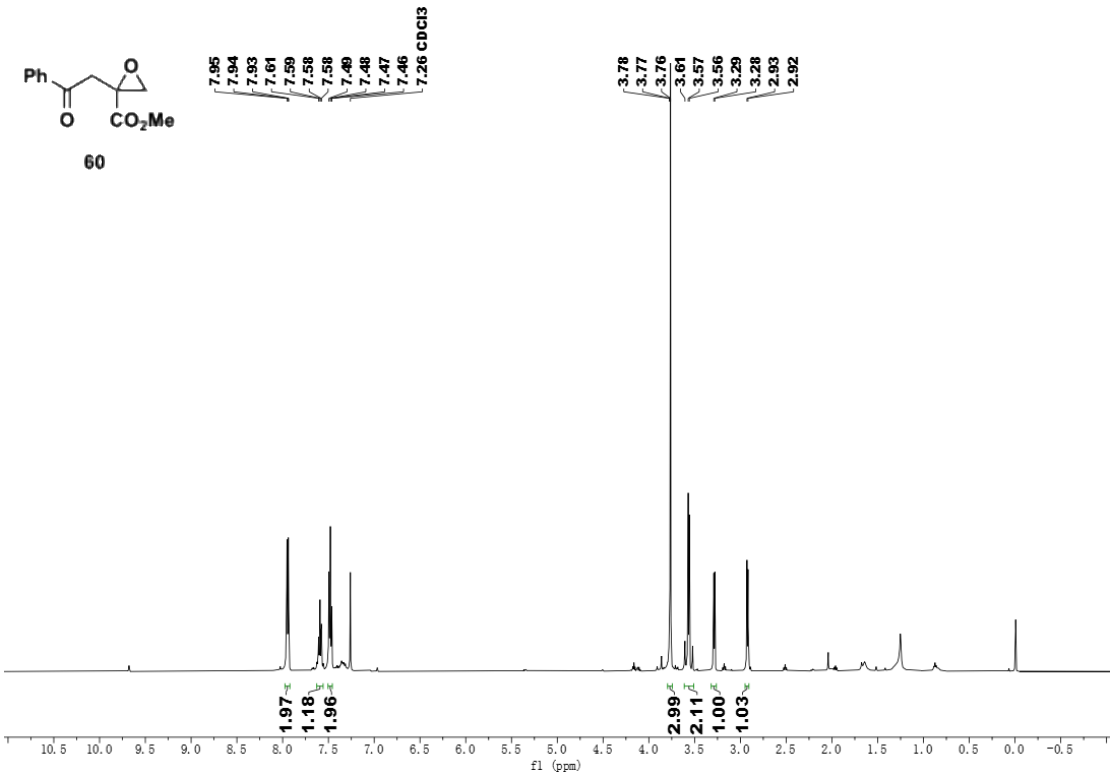


Figure S153. ^{1}H NMR spectra of **60**

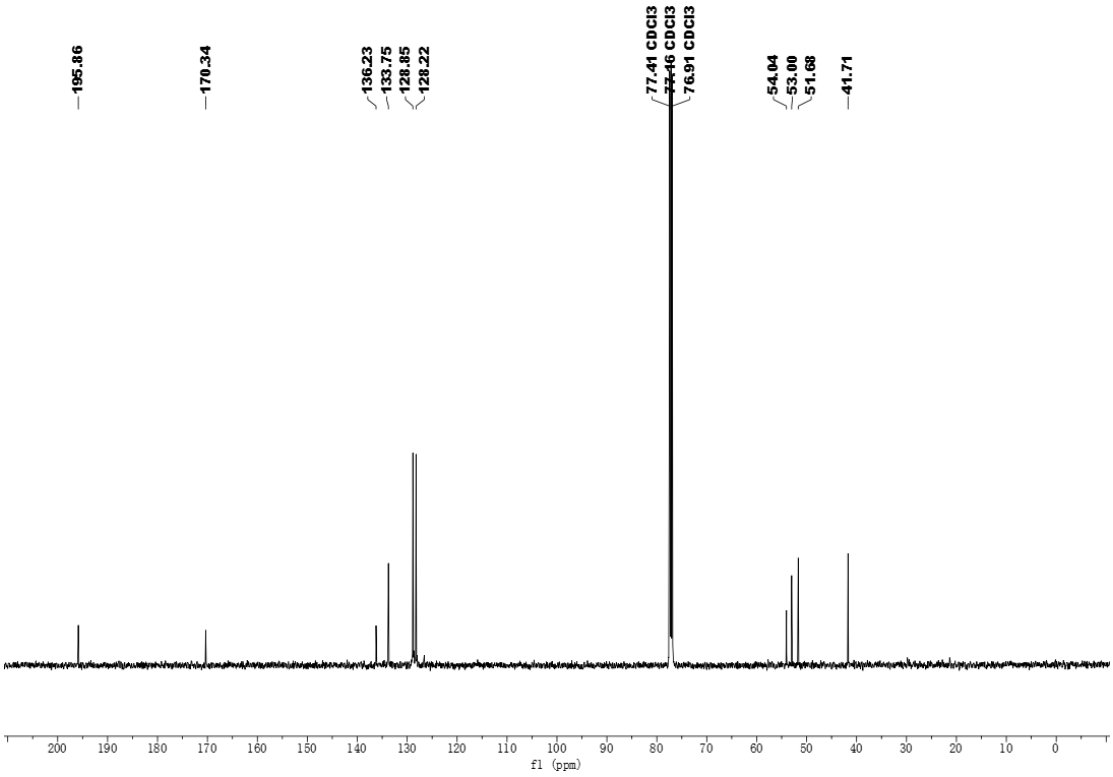


Figure S154. ^{13}C NMR spectra of **60**

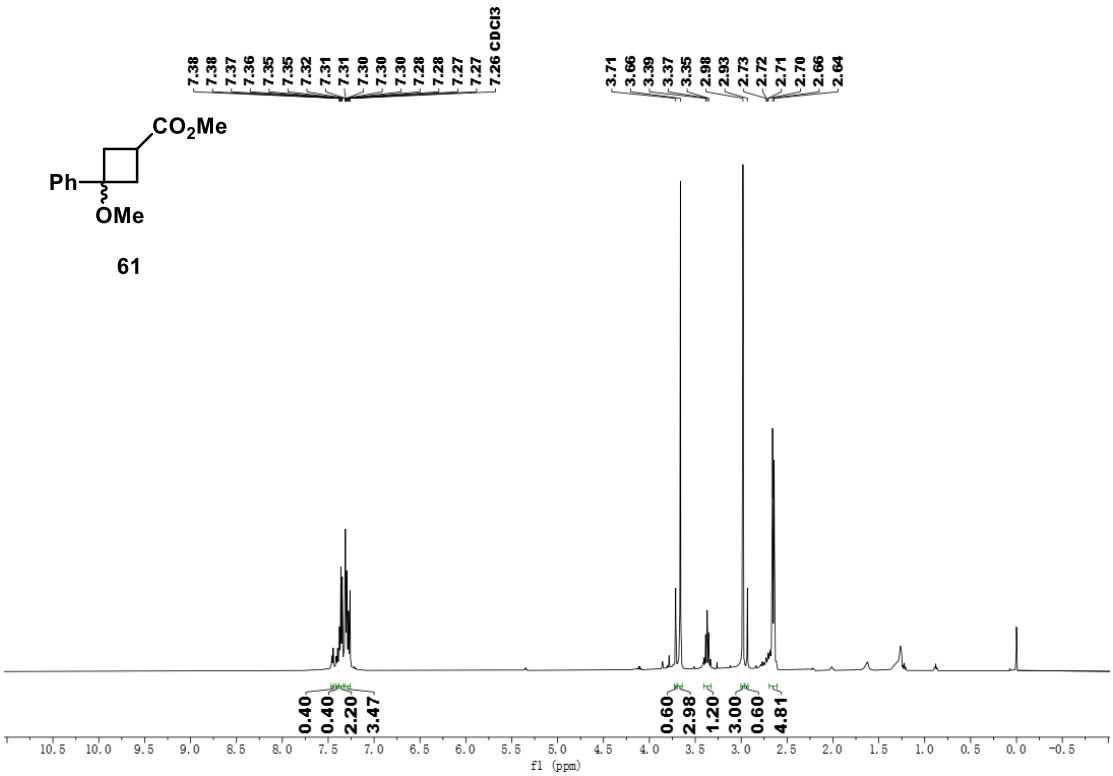


Figure S155. ^{1}H NMR spectra of **61**

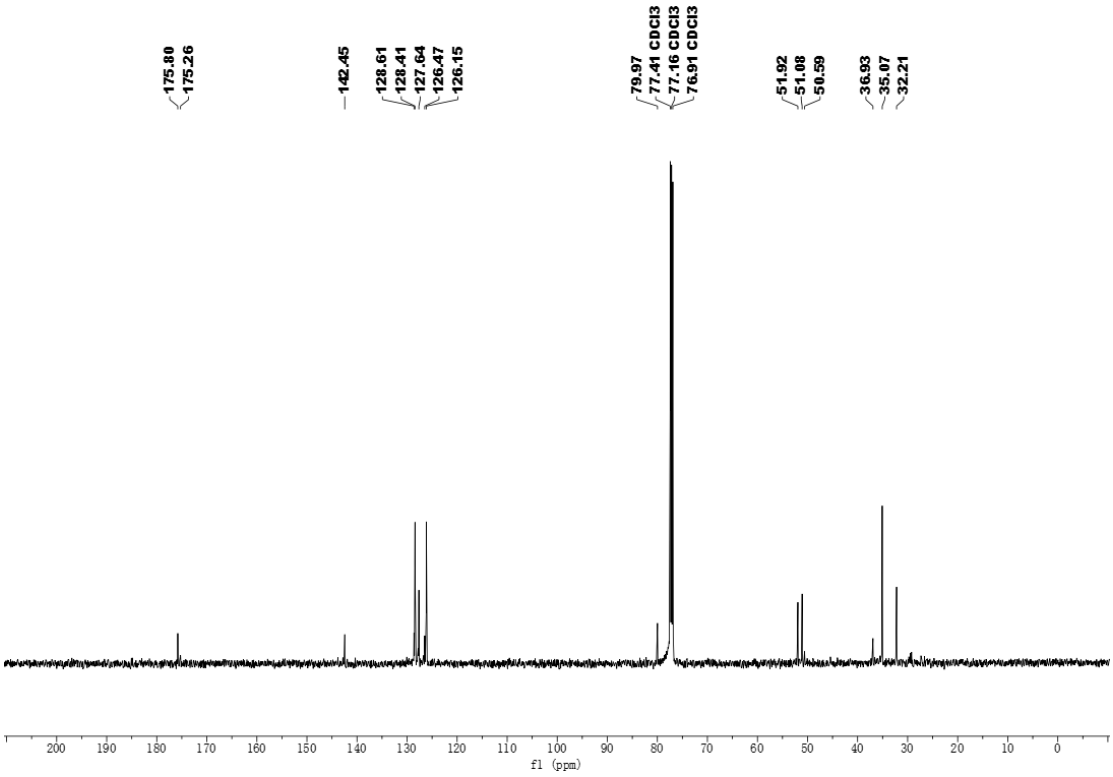


Figure S156. ^{13}C NMR spectra of **61**

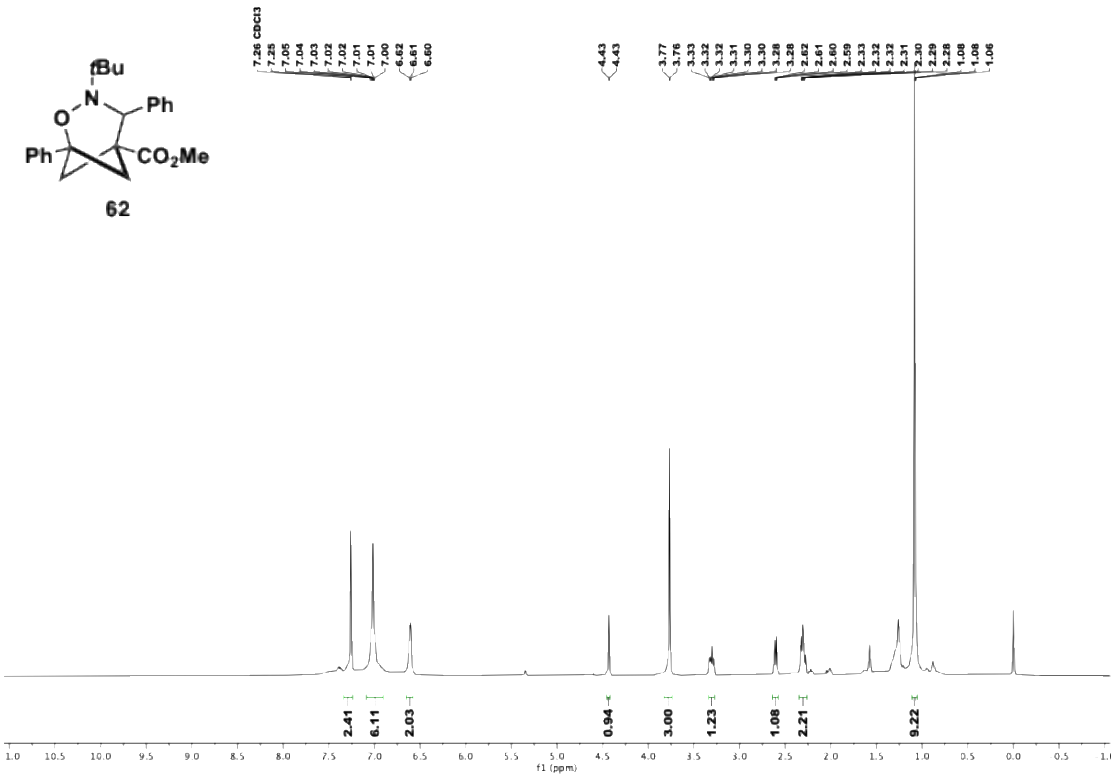


Figure S157. ^{1}H NMR spectra of **62**

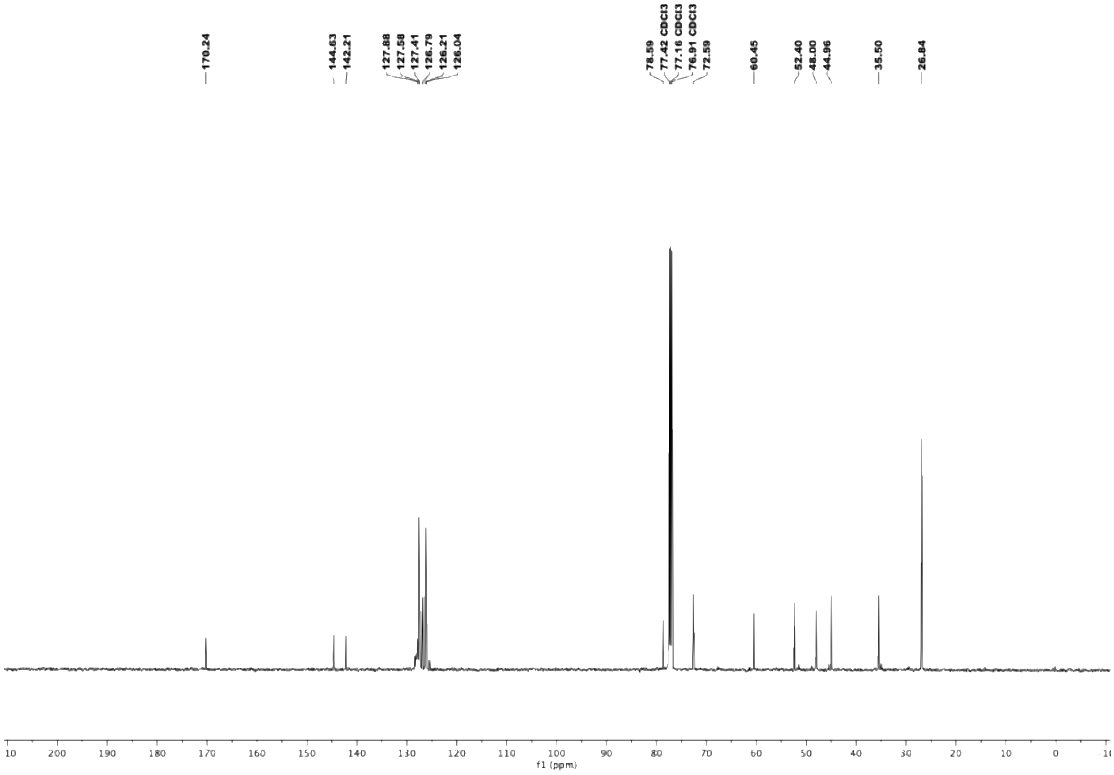


Figure S158. ^{13}C NMR spectra of **62**

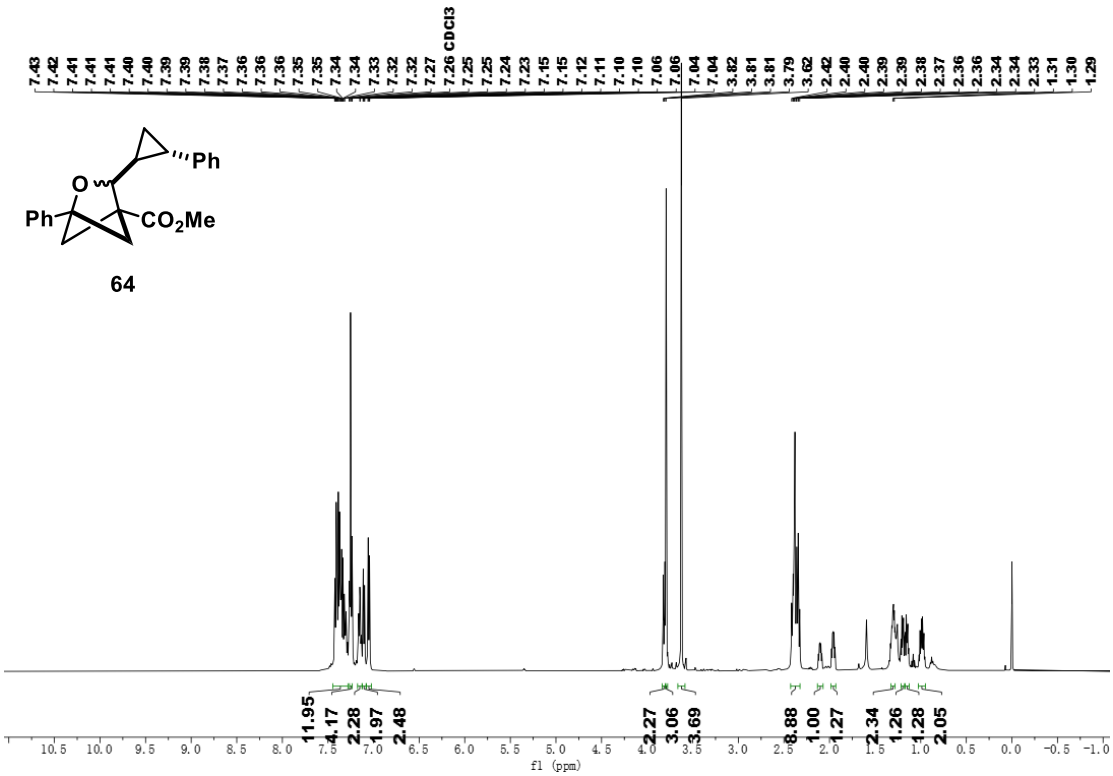


Figure S159. ^{1}H NMR spectra of **64**

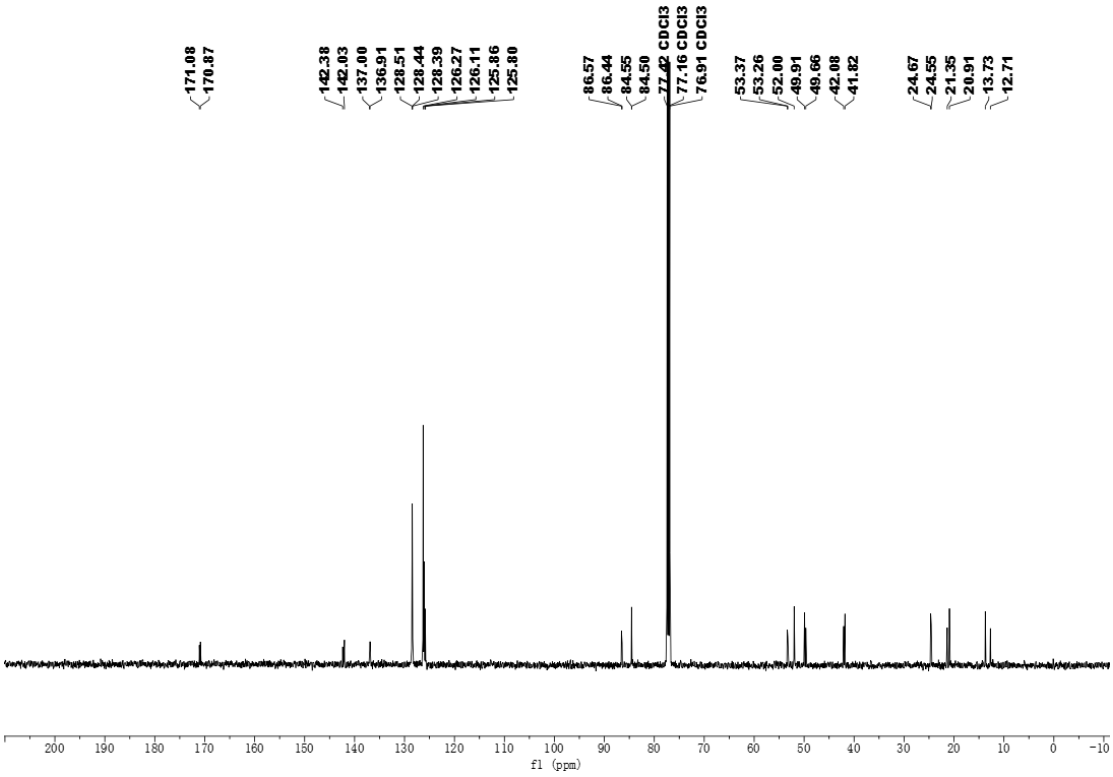


Figure S160. ^{13}C NMR spectra of **64**

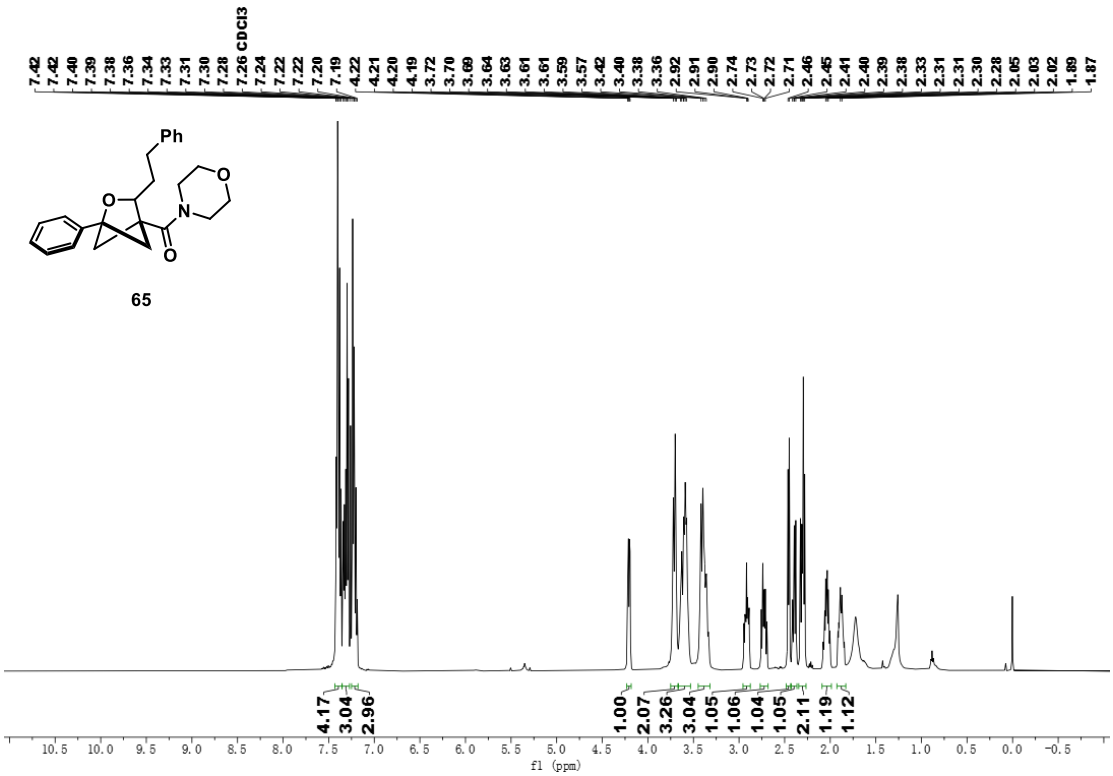


Figure S161. ^{1}H NMR spectra of **65**

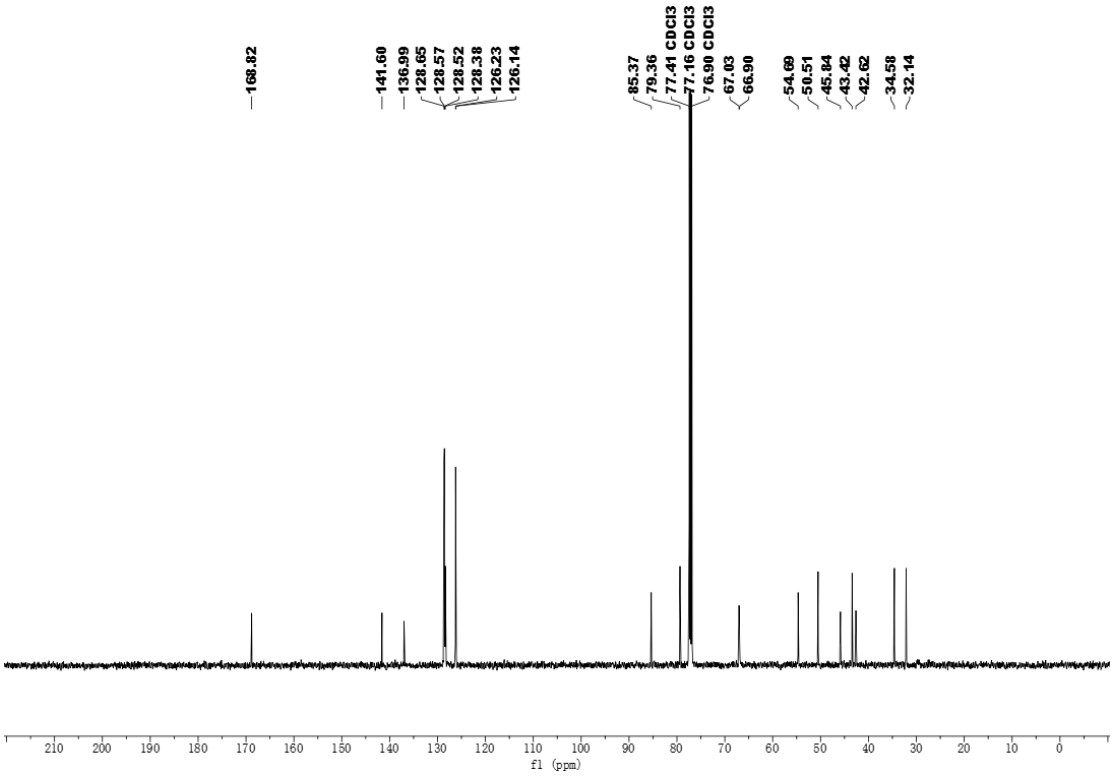


Figure S162. ^{13}C NMR spectra of **65**

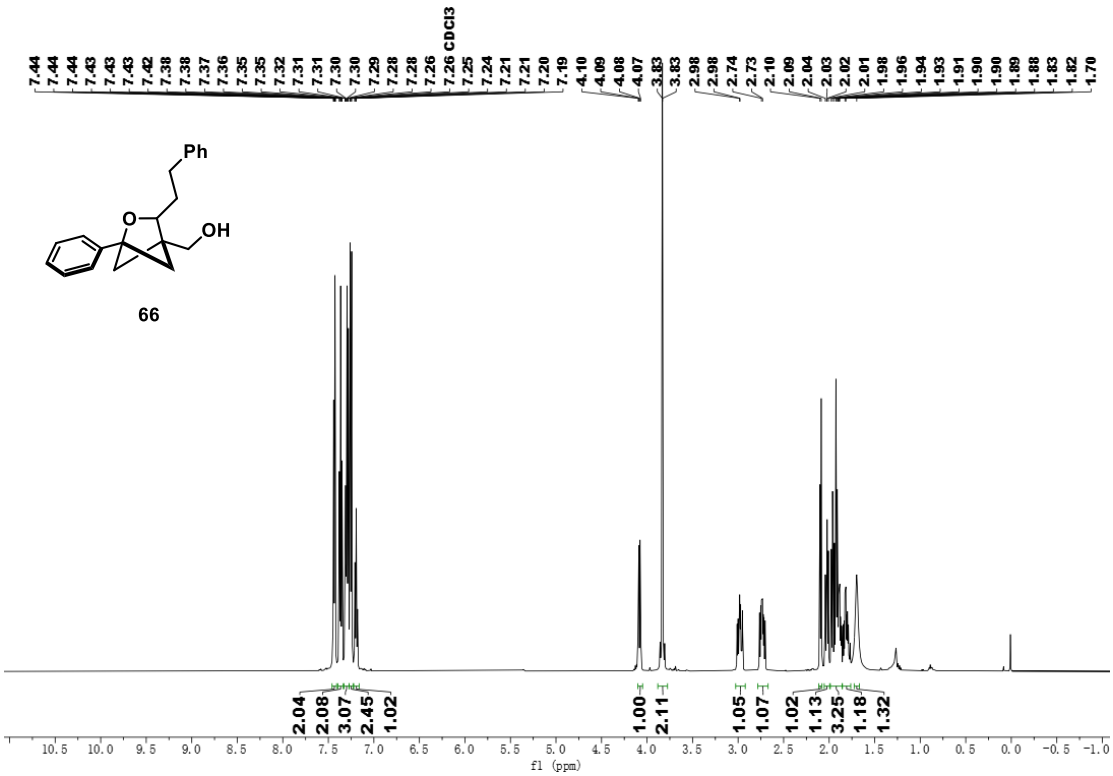


Figure S163. ^{1}H NMR spectra of **66**

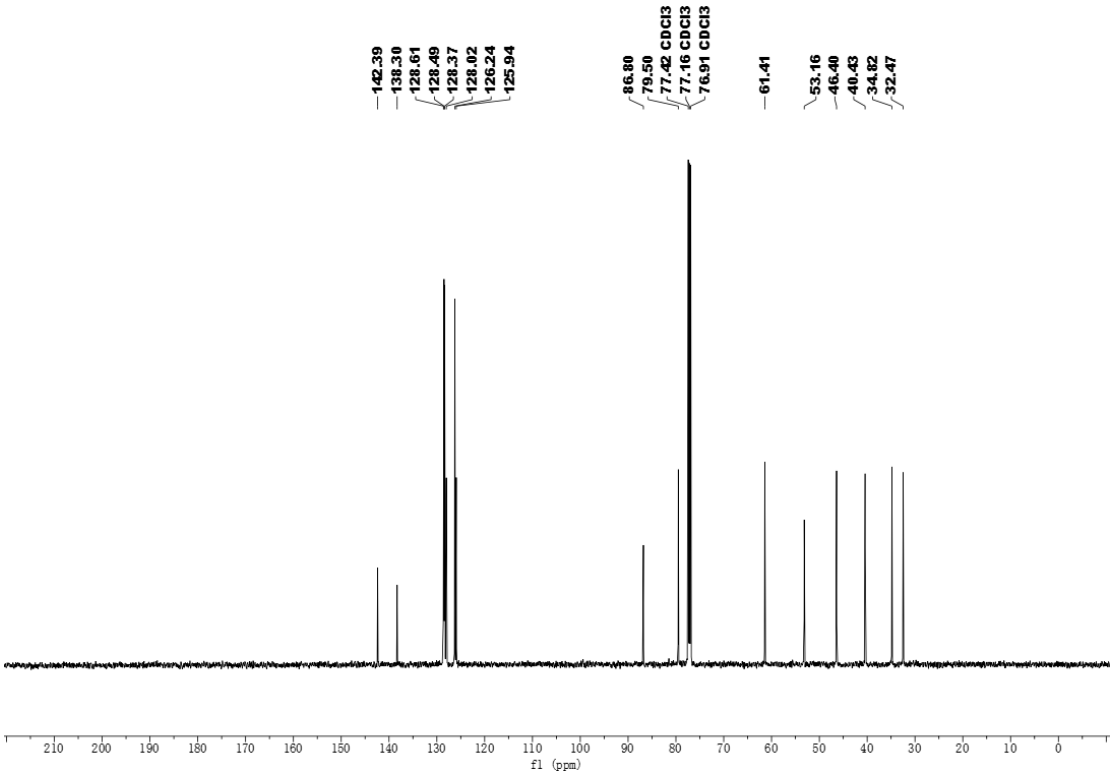


Figure S164. ^{13}C NMR spectra of **66**

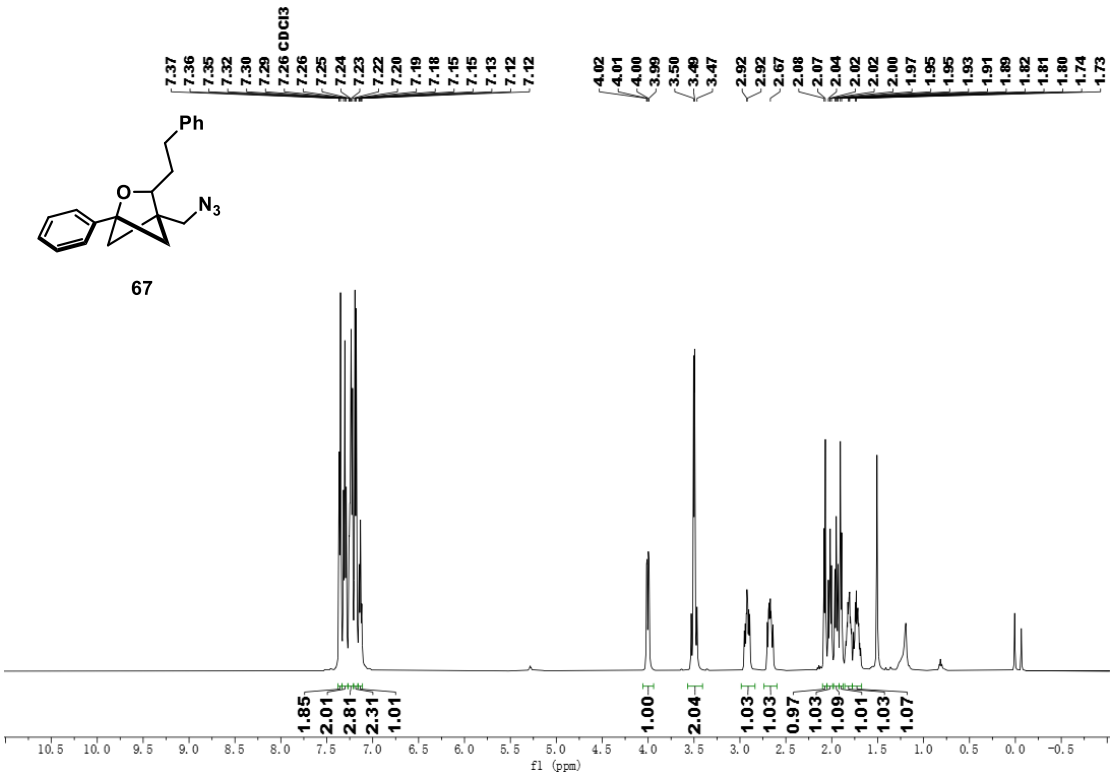


Figure S165. ^{1}H NMR spectra of **67**

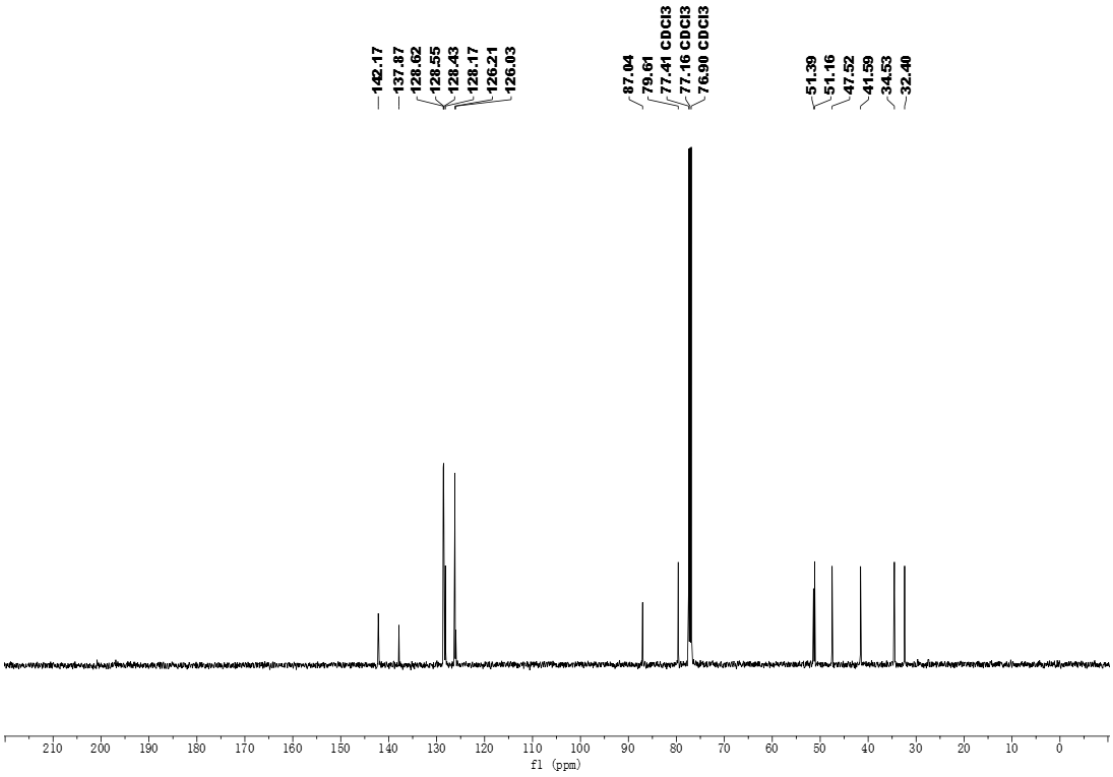


Figure S166. ^{13}C NMR spectra of **67**

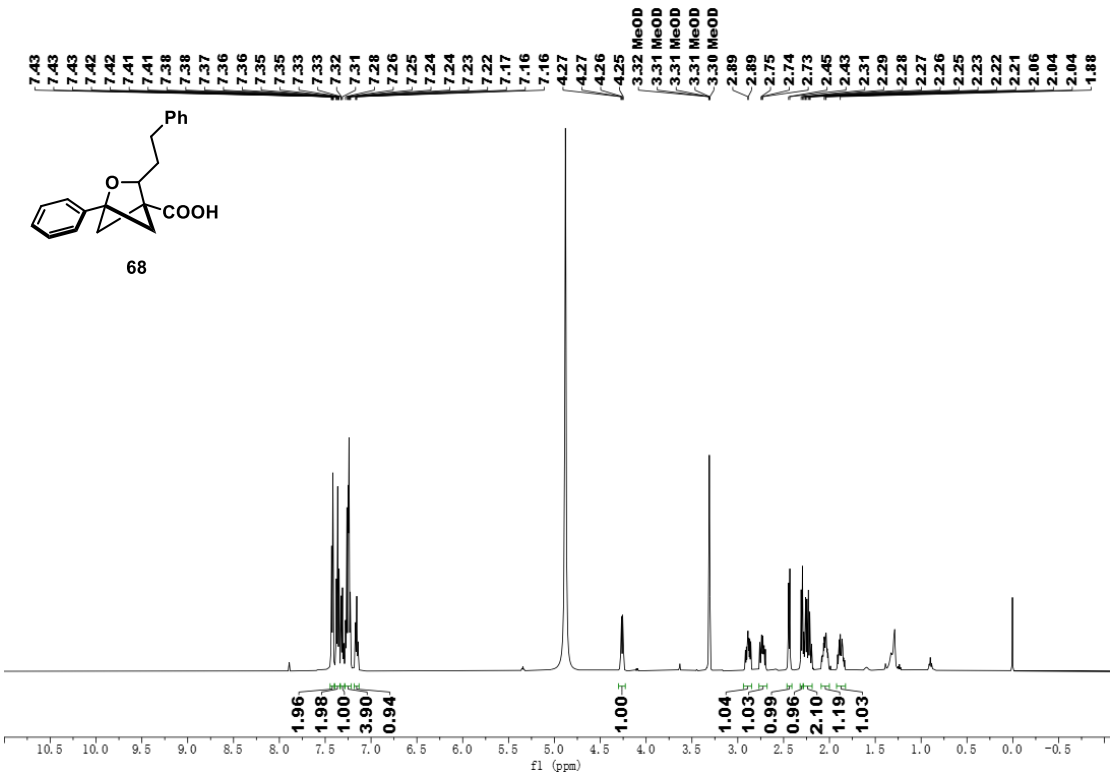


Figure S167. ^{1}H NMR spectra of **68**

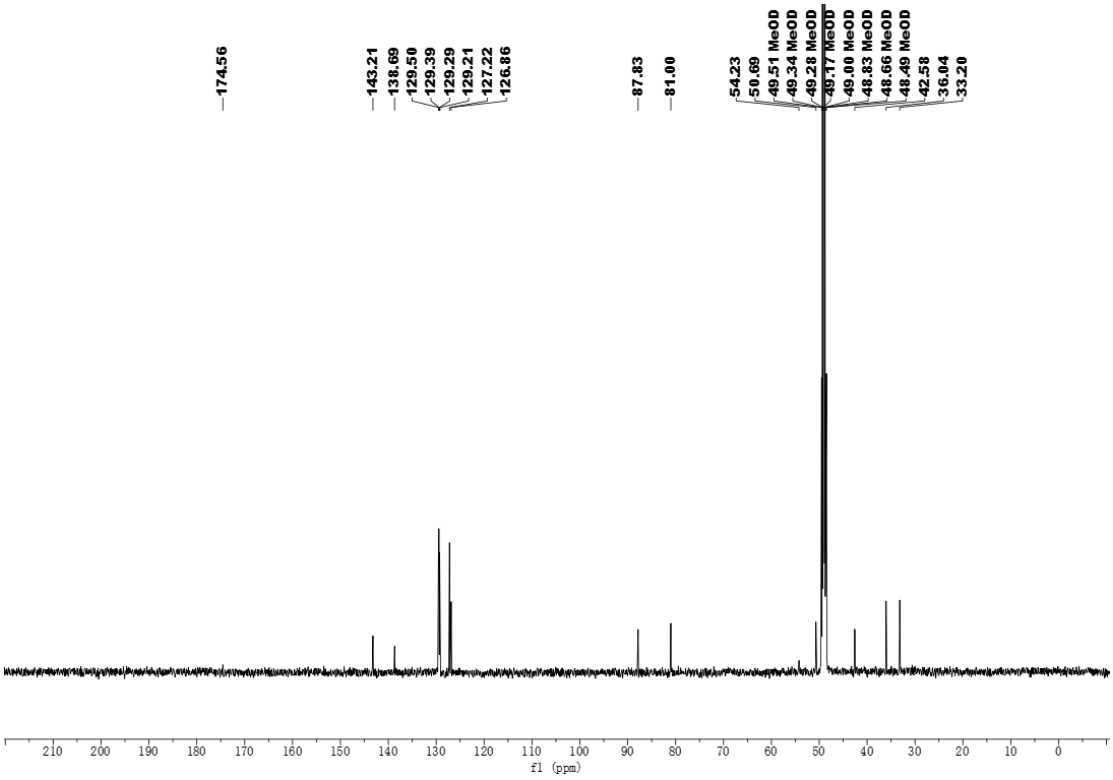


Figure S168. ^{13}C NMR spectra of **68**

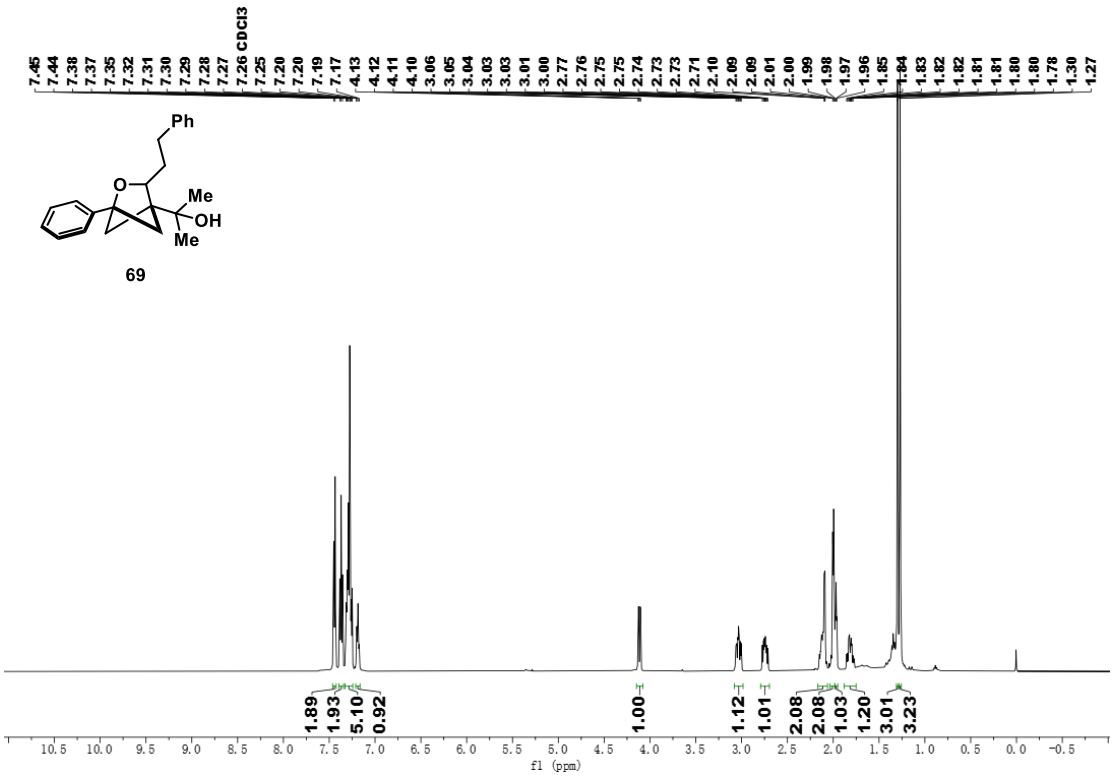


Figure S169. ^{1}H NMR spectra of **69**

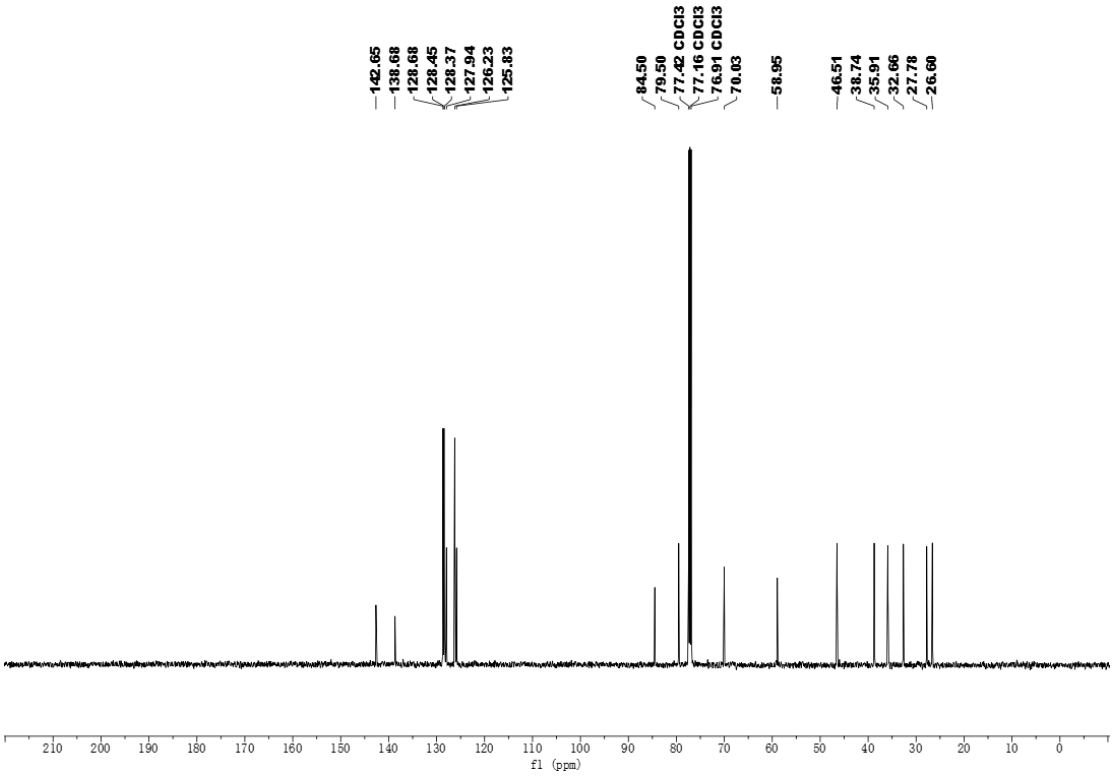


Figure S170. ^{13}C NMR spectra of **69**

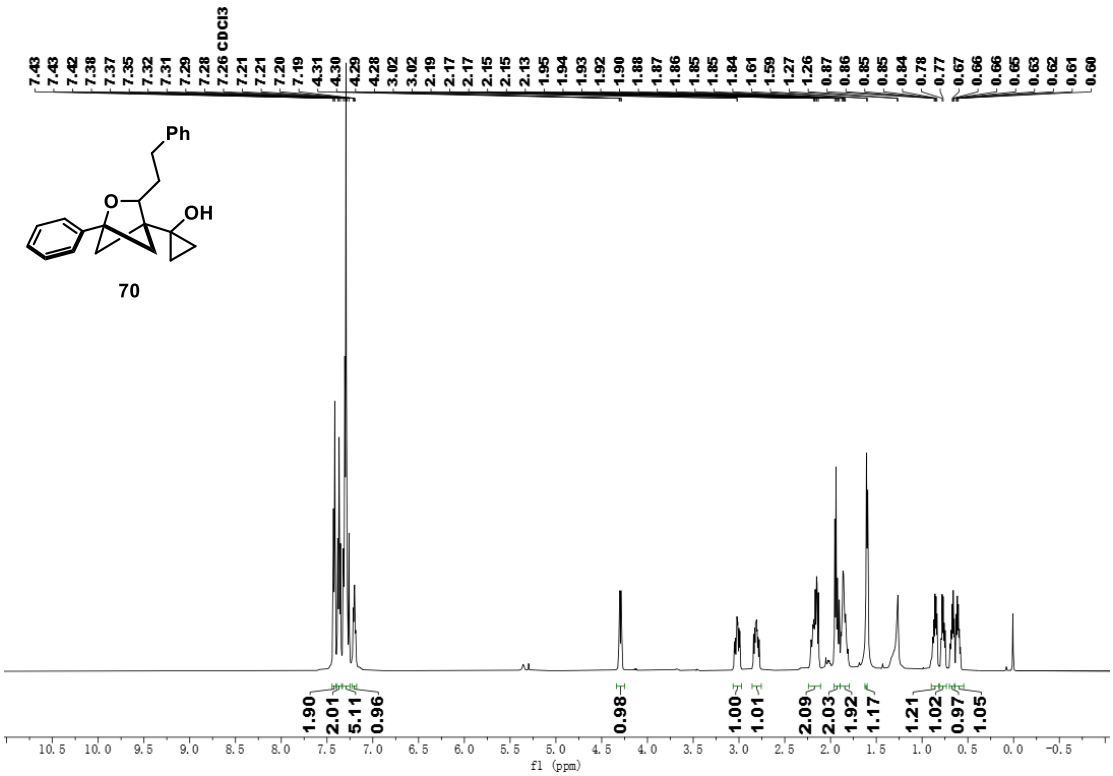


Figure S171. ^{1}H NMR spectra of **70**

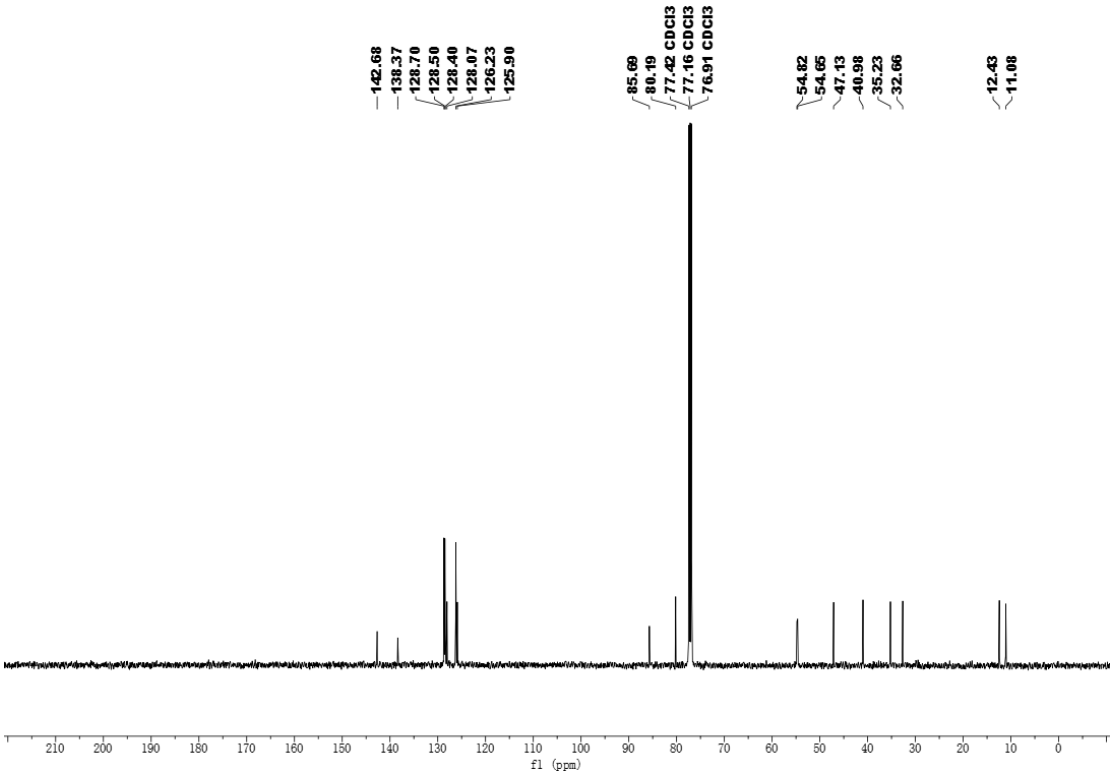


Figure S172. ^{13}C NMR spectra of **70**

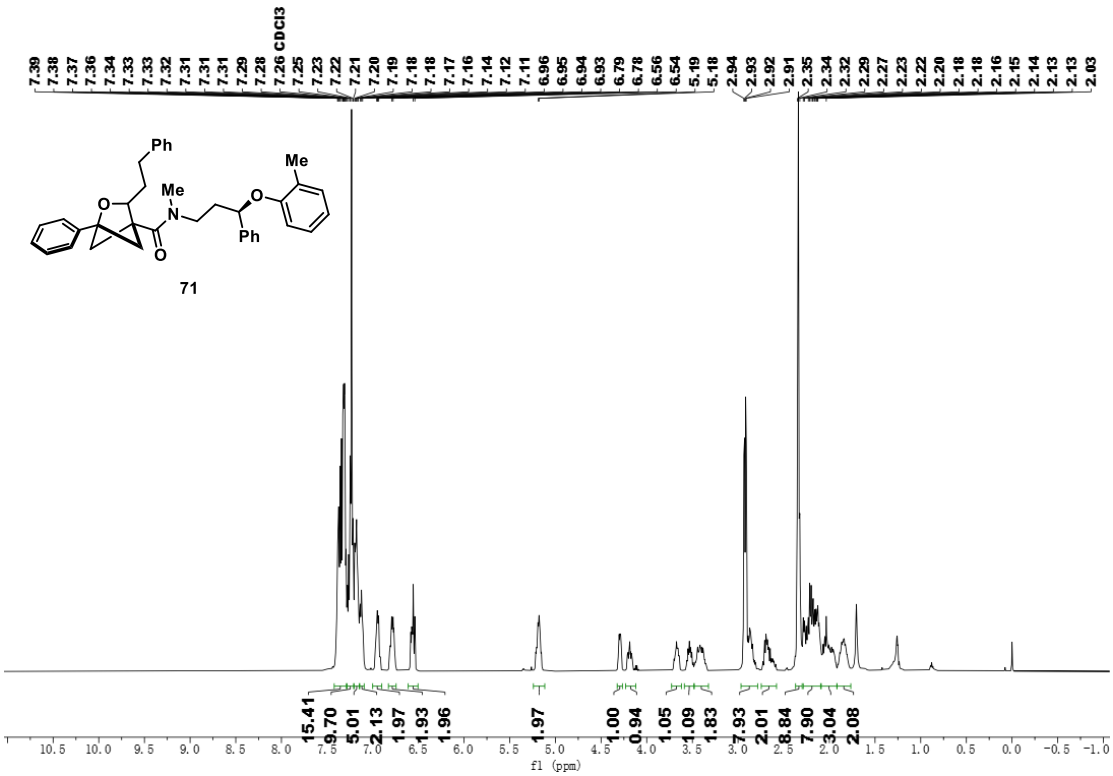


Figure S173. ^{1}H NMR spectra of **71**

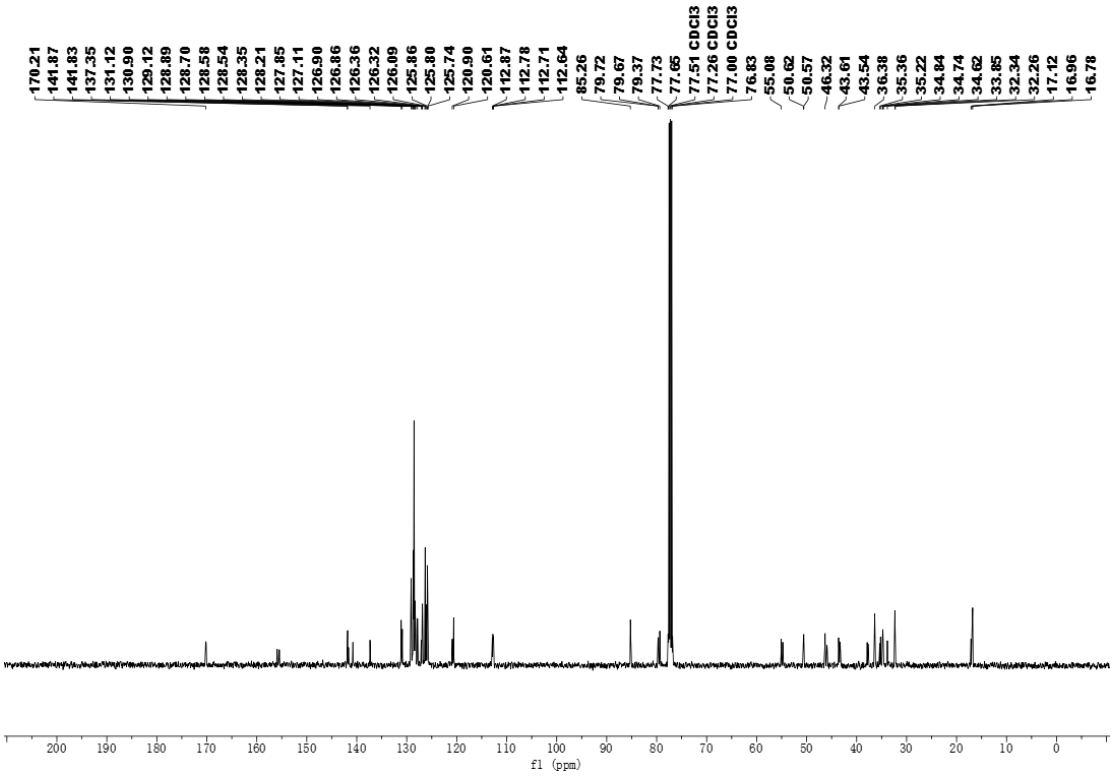


Figure S174. ^{13}C NMR spectra of **71**

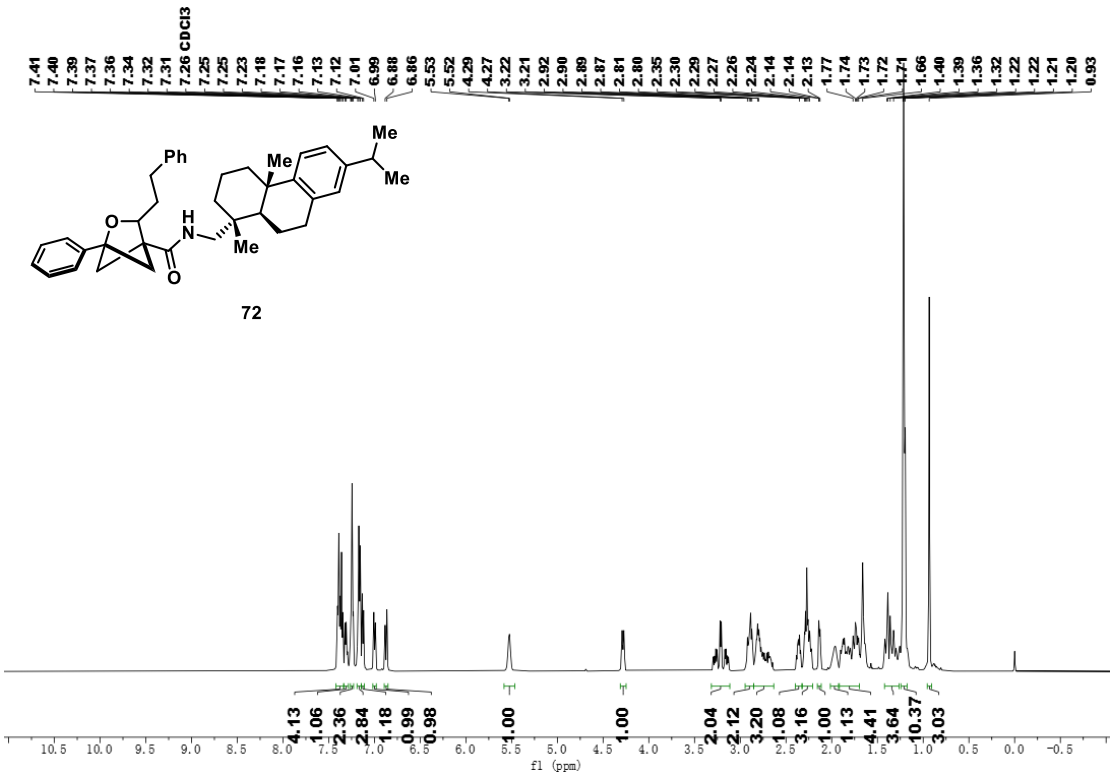


Figure S175. ^{1}H NMR spectra of **72**

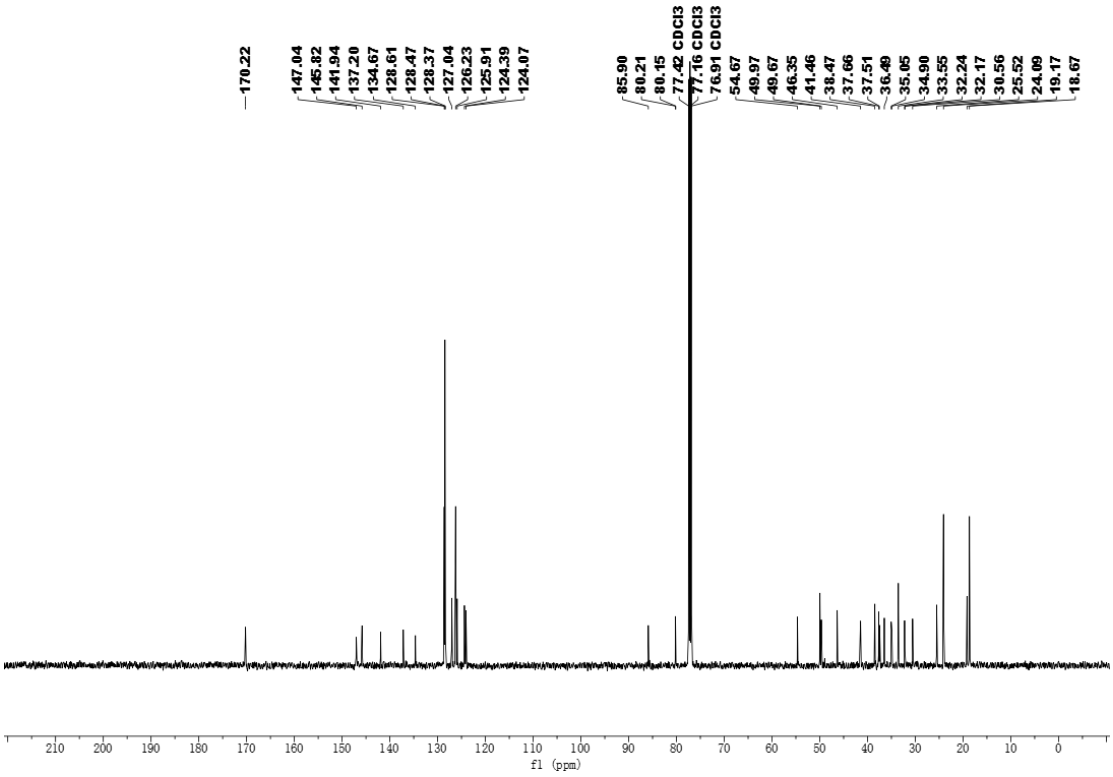


Figure S176. ^{13}C NMR spectra of **72**

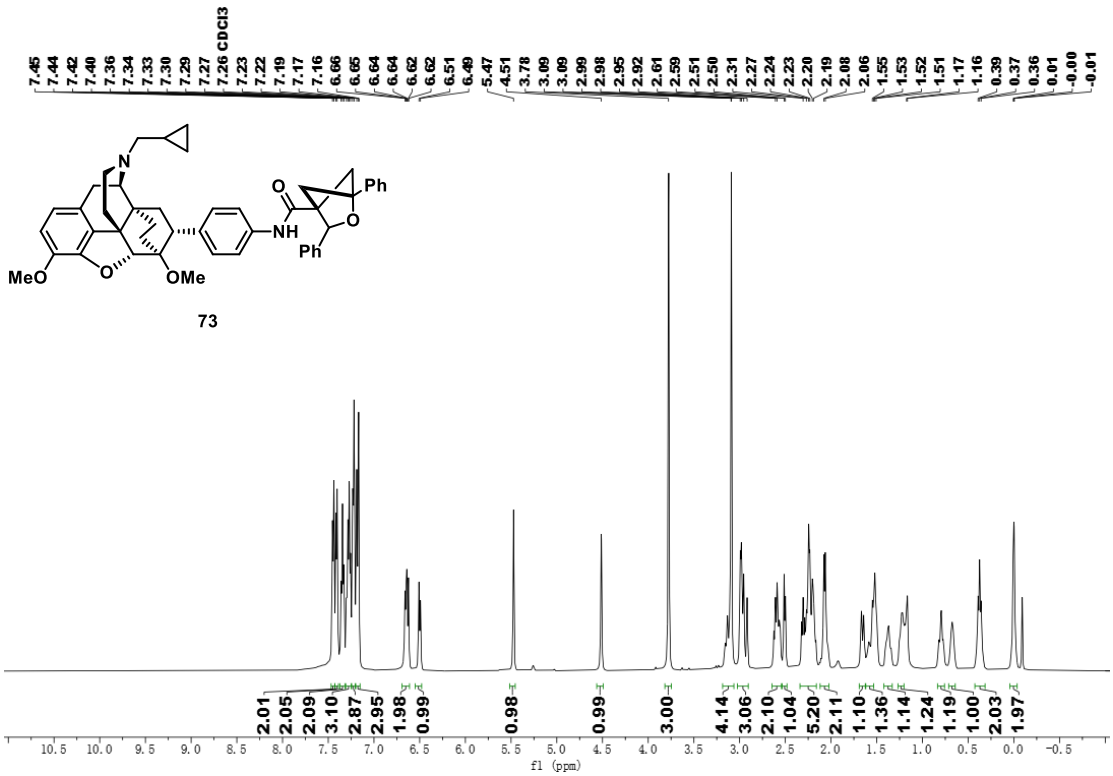


Figure S177. ^{1}H NMR spectra of **73**

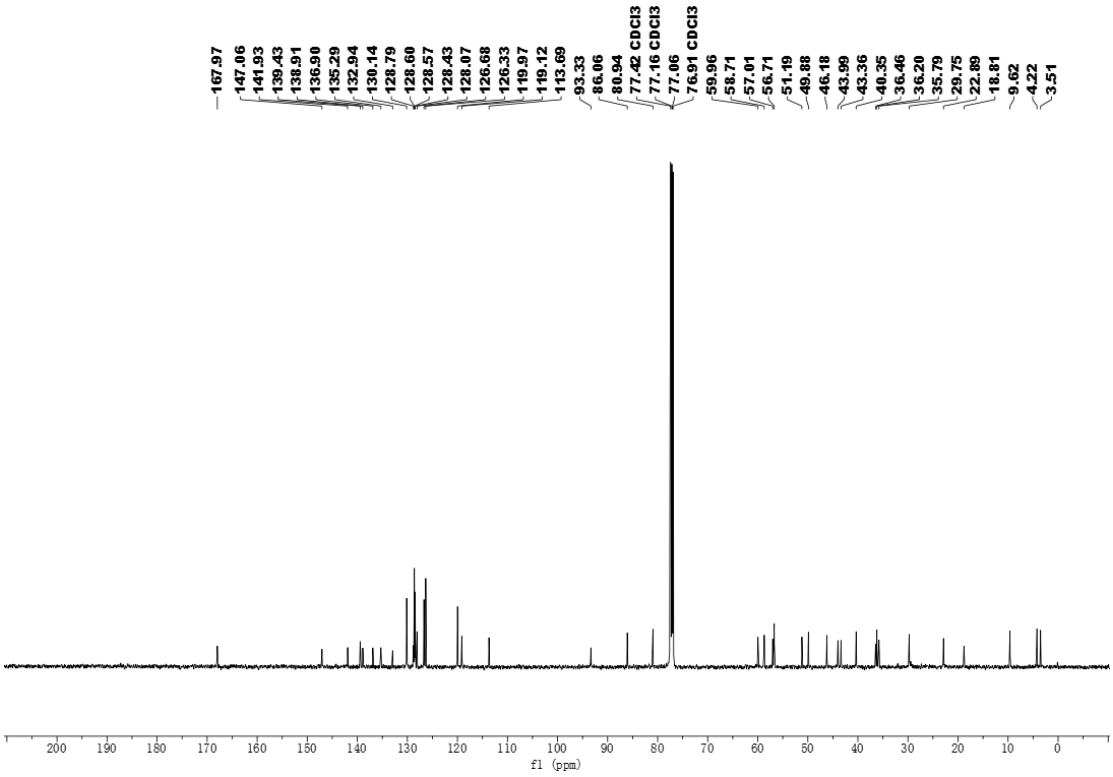


Figure S178. ^{13}C NMR spectra of **73**

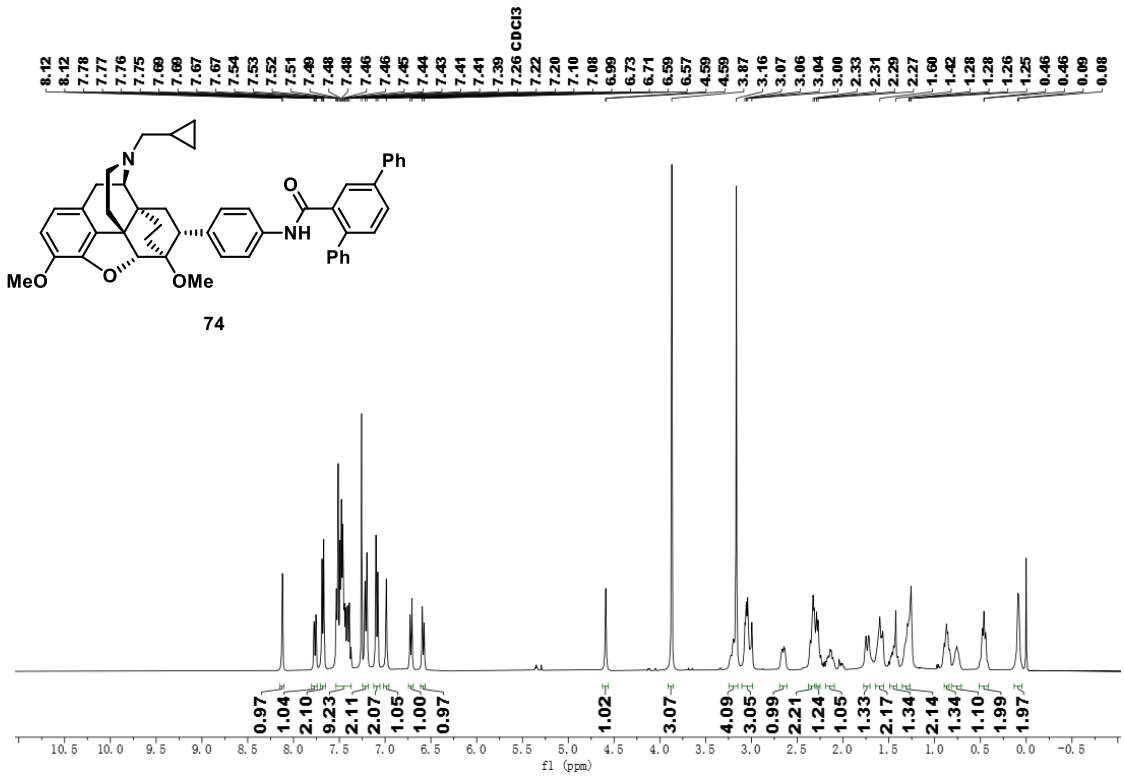


Figure S179. ^{1}H NMR spectra of **74**

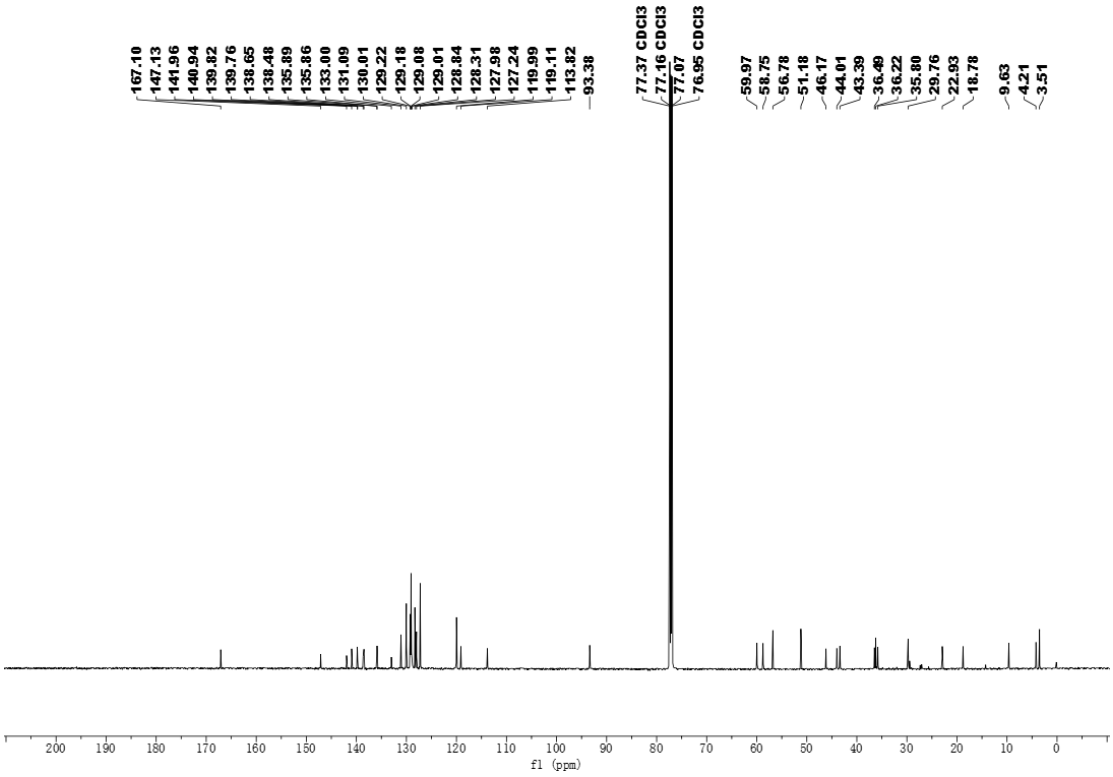


Figure S180. ^{13}C NMR spectra of **74**

14 References

[1] Z. X. Xing, S. S. Chen, H. M. Huang, *Org. Lett.* **2024**, 0–5.

[2] X. W. Chen, C. Li, Y. Y. Gui, J. P. Yue, Q. Zhou, L. L. Liao, J. W. Yang, J. H. Ye, D. G. Yu, *Angew. Chemie - Int. Ed.* **2024**, *63*, 1–8.

[3] J. L. Tyler, F. Schäfer, H. Shao, C. Stein, A. Wong, C. G. Daniliuc, K. N. Houk, F. Glorius, *J. Am. Chem. Soc.* **2024**, *146*, 16237–16247.

[4] L. Xiao, Y. Wang, M. Zhang, W. Wu, L. Kong, Y. Ma, X. Xu, X. Liu, Q. He, Y. Qian, H. Sun, H. Wu, C. Lin, H. Huang, R. Ye, S. Jiang, R. F. Ye, C. Yuan, S. Fang, D. Xue, X. Yang, H. Chen, Y. Zheng, L. Yu, Q. Xie, L. Zheng, W. Fu, W. Li, Z. Qiu, J. Liu, L. Shao, *J. Med. Chem.* **2019**, *62*, 11054–11070.

[5] M. Golfmann, M. Reinhold, J. D. Steen, M. S. Deike, B. Rodemann, C. Golz, S. Crespi, J. C. L. Walker, *ACS Catal.* **2024**, 13987–13998.

[6] M. Xu, Z. Wang, Z. Sun, Y. Ouyang, Z. Ding, T. Yu, L. Xu, P. Li, *Angew. Chemie - Int. Ed.* **2022**, *61*, DOI 10.1002/anie.202214507.

[7] Y. Zhang, S. S. Chen, K. D. Li, H. M. Huang, *Angew. Chemie - Int. Ed.* **2024**, e202401671.

[8] Z. Huang, J. E. Reilly, R. N. Buckle, *Synlett* **2007**, 1026–1030.

[9] A. Iwanami, S. Komori, Y. Ura, *Chem. Commun.* **2024**, *60*, 7495–7498.

[10] D. A. V. Oleg G. Kulinkovich* , Sergei V. Sviridov, *Synthesis (Stuttg).* **1991**, *3*, 234.

[11] X. Pan, H. Wang, C. Li, J. Z. H. Zhang, C. Ji, *J. Chem. Inf. Model.* **2021**, *61*, 3159–3165.

[12] W. D. Jang, J. Jang, J. S. Song, S. Ahn, K. S. Oh, *Comput. Struct. Biotechnol. J.* **2023**, *21*, 3532–3539.

[13] L. Kong, X. Shu, S. Tang, R. Ye, H. Sun, S. Jiang, Z. Li, J. Chai, Y. Fang, Y. Lan, L. Yu, Q. Xie, W. Fu, Y. Wang, W. Li, Z. Qiu, J. Liu, L. Shao, *J. Med. Chem.* **2022**, *65*, 10377–10392.