Supporting Information

KO*t***Bu-Promoted Michael/Aldol/Ring-Opening Cascade Reaction of Cyclobutanones with Chalcones**

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1. General Information

All the Cyclobutanone 1^1 and Chalcone 2^2 have been synthesized following procedures reported in the literature. Other chemical reagent was obtained from commercial sources and was used without further purification. The 1 H and 13 C NMR spectra were recorded on JEOL at 400 MHz for 14 H or at 100 MHz for 13 C, respectively. The chemical shifts (δ) for 14 H and 13 C are given in ppm relative to residual signals of the solvent (CDCl₃: $\delta_{\rm H} = 7.26$ ppm 1 H NMR, $\delta_{\rm C} = 77.16$ ppm 13 C NMR; DMSO- d_6 : $\delta_{\rm H} = 2.50$ ppm 1 H NMR, $\delta_{\rm C} = 39.52$ ppm 13 C NMR). The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, d = doublet of doublets. ESI high-resolution mass spectra were measured on Thermo-DFS mass spectrometer TFor thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF₂₅₄, 0.25 mm) were used, Silica gel 60 H (200-300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China) were used for general chromatography, using UV light as the visualizing agent.

General Procedure for Synthesis of 3

A standard Schlenk tube was charged with cyclobutanone 1 (0.1 mmol), chalcone 2 (0.15 mmol) and KOtBu (13.5 mg, 1.2 equiv) and evacuated under high vacuum and backfilled with N₂ at least three times, followed by the addition of anhydrous CPME (1 mL). The reaction mixture was performed at 140 °C and continuous stirring for 18 hours. After cooling to ambient temperature, the reaction was quenched with HCl/EtOAc (2 mL). Then, the crude mixture was purified first by preparative TLC (DCM/MeOH = 25/1) to remove the major impurities, then the mixture was purified again by preparative TLC (PE/EA = 3/1 to 1/1) to remove the minor impurities to afford the desired product 3.

acid (3aa). The general procedure was followed using substrate 1a (16.0 mg, 0.1 mmol) and 2a (31.2 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded 3aa (25.8 mg, 70%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 7.30 (q, J = 7.6 Hz, 4H), 7.24 - 7.09 (m, 5H), 7.01 (d, J = 7.2 Hz, 2H), 5.98 (s, 1H), 3.28 (dd, J = 16.4, 12.8 Hz, 1H), 3.12 (d, J = 3.6 Hz, 1H), 2.99 – 2.94 (m, 1H), 2.55 (dd, J = 17.2, 5.2 Hz, 1H), 1.49 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 178.7, 148.6, 142.6, 141.5, 138.0, 128.7, 128.6, 128.0, 127.5, 127.4, 127.1, 127.0, 126.8, 125.6, 57.4, 43.9, 38.3, 29.4, 27.1 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{24}O_2$ [M + H]⁺ 369.1849, found

1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carboxylic

369.1851.

1',4-dimethyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'carboxylic acid (3ba). The general procedure was followed using substrate 1b (17.4 mg, 0.1 mmol) and 2a (31.2 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded 3ba (20.0 mg, 52%) as white solid. 1 H NMR (400 MHz,) δ 7.61 – 7.58 (m, 2H), 7.41 – 7.36 (m, 4H), 7.32 – 7.28 (m, 1H), 7.24 - 7.15 (m, 5H), 7.11 - 7.08 (m, 2H), 6.04 (s, 1H), 3.34 (dd, J = 17.2, 12.0 Hz, 1H), 3.17 (d, J = 3.6 Hz, 1H), 3.09 - 3.02 (m, 1H), 2.61 (dd, J = 17.6, 5.6 Hz, 1H), 2.36 (s, 3H), 1.54 (s, 3H) ppm. 13 C NMR (100 MHz,) δ 178.1, 145.7, 142.8, 141.6, 137.8, 136.3, 129.3, 128.7, 128.6, 128.2, 127.5, 127.4, 127.0, 126.9, 125.6, 57.3, 43.6, 38.3, 29.4, 27.2, 21.1 ppm. HR – MS (ESI) m/z calcd for $C_{27}H_{26}O_2$ [M + Na]⁺ 405.1825, found 405.1819.

HOOC.,,,Me Me 3ca

3'-methyl-5'-phenyl-1',2',3',6'-tetrahydro-[1,1':3',1'':4'',1'''-quaterphenyl]-2'-carboxylic acid (3ca). The general procedure was followed using substrate 1c (23.6 mg, 0.1 mmol) and 2a (31.2 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded 3ca (30.2 mg, 68%) as white solid. 1 H NMR (400 MHz, CDCl₃) δ 7.65 – 7.57 (m, 8H), 7.47 – 7.31 (m, 6H), 7.27

-7.16 (m, 3H), 7.14 (d, J = 7.2 Hz, 2H), 6.10 (s, 1H), 3.39 (dd, J = 16.8, 12.8 Hz, 1H), 3.25 (d, J = 2.4 Hz, 1H), 3.17 -3.07 (m, 1H), 2.67 (dd, J = 17.2, 5.2 Hz, 1H), 1.61 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 177.9, 147.8, 142.7, 141.5, 140.8, 139.5, 138.1, 129.0, 128.7, 128.6, 128.0, 127.6, 127.5, 127.4, 127.2, 127.0, 125.7, 57.4, 43.8, 38.4, 29.5, 27.2 ppm. HR - MS (ESI) m/z calcd for $C_{32}H_{28}O_{2}$ [M + Na]⁺ 467.1982, found 467.1974.

HOOC.,, Me

4-fluoro-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carboxylic acid (3da). The general procedure was followed using substrate **1d** (17.8 mg, 0.1 mmol) and **2a** (31.2 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3da** (22.0 mg, 57%) as white solid. 1 H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 7.6 Hz, 2H), 7.47 (dd, J = 8.4, 5.2

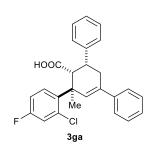
Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.32 (d, J = 7.2 Hz, 1H), 7.24 – 7.19 (m, 3H), 7.09 – 7.03 (m, 4H), 6.02 (s, 1H), 3.34 (dd, J = 17.2, 12.4 Hz, 1H), 3.12 (d, J = 2.8 Hz, 1H), 3.04 – 2.98 (m, 1H), 2.63 (dd, J = 17.6, 5.6 Hz, 1H), 1.54 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 178.0, 161.6 (d, J = 244.4 Hz), 144.4 (d, J = 2.7 Hz), 142.5, 141.3, 138.3, 128.8, 128.7, 128.6, 127.7 (d, J = 8.1 Hz), 127.4, 127.1, 125.6, 115.3 (d, J = 20.9 Hz), 57.6, 43.5, 38.3, 29.4, 27.2 ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ -116.42 ppm. HR – MS (ESI) m/z calcd for C₂₆H₂₃O₂F [M + Na]⁺ 409.1574, found 409.1566.

HOOC, Мe

2-chloro-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'carboxylic acid (3ea). The general procedure was followed using substrate 1e (19.5 mg, 0.1 mmol) and 2a (31.2 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded 3ea (33.8 mg, 84%) as white solid. ¹H NMR $(400 \text{ MHz}, \text{CDCl}_3) \delta 7.54 - 7.51 \text{ (m, 3H)}, 7.40 - 7.36 \text{ (m, 1H)}, 7.32 \text{ (t, } J = 7.6 \text{ Hz, 2H)},$ 7.24 (t, J = 7.6 Hz, 1H), 7.21 - 7.09 (m, 5H), 7.05 (d, J = 7.2 Hz, 2H), 5.95 (s, 1H), 3.97 (d, J = 3.6 Hz, 1H), 3.30 - 3.22 (m, 1H), 2.87 - 2.82 (m, 1H), 2.53 (dd, J = 17.2, 5.6 Hz, 1H), 1.71 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 177.9, 143.8, 142.7, 141.3, 137.6, 132.8, 132.0, 129.3, 128.7, 128.6, 128.5, 127.6, 127.4, 127.0, 126.7, 125.7, 51.3, 44.9, 39.1, 29.4, 24.1 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{23}O_2^{35}Cl$ $[M + Na]^{+}$ 425.1279, found 425.1272; $C_{26}H_{23}O_{2}^{37}Cl$ $[M + Na]^{+}$ 427.1249, found 427.1238.

HOOC, Мe

2-bromo-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'carboxylic acid (3fa). The general procedure was followed using substrate 1f (23.9 mg, 0.1 mmol) and 2a (31.2 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3fa** (30.0 mg, 67%) as white solid. ¹H NMR $(400 \text{ MHz}, \text{CDCl}_3) \delta 7.69 \text{ (d, } J = 7.6 \text{ Hz}, 1\text{H}), 7.63 - 7.60 \text{ (m, 3H)}, 7.40 \text{ (t, } J = 7.6 \text{ Hz}, 1\text{Hz})$ 2H), 7.34 - 7.19 (m, 5H), 7.15 - 7.11 (m, 3H), 6.03 (s, 1H), 4.17 (s, 1H), 3.37 - 3.30 (m, 1H), 2.92 (d, J =11.2 Hz, 1H), 2.61 (dd, J = 17.2, 4.0 Hz, 1H), 1.81 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 177.4, 144.9, 142.6, 141.3, 137.5, 136.6, 132.4, 129.5, 128.73, 128.66, 128.6, 127.6, 127.4, 127.3, 127.0, 125.7, 121.8, 51.1, 45.5, 39.0, 29.3, 24.2 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{23}O_2^{79}Br$ [M + Na]⁺ 469.0774, found 469.0766; $C_{26}H_{23}O_2^{81}Br [M + Na]^+ 471.0753$, found 471.0742.



2-chloro-4-fluoro-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''terphenyl]-2'-carboxylic acid (3ga). The general procedure was followed using substrate 1g (21.3 mg, 0.1 mmol) and 2a (31.2 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded 3ga (29.5 mg, 70%) as white solid. ${}^{1}H$ NMR (400 MHz, CDCl₃) δ 7.60 – 7.54 (m, 3H), 7.42 – 7.38 (m, 2H), 7.34 - 7.31 (m, 1H), 7.29 - 7.20 (m, 4H), 7.13 (d, J = 7.6 Hz, 2H), 6.96 - 6.92 (m, 1H), 5.99 (s, 1H), 3.96(d, J = 3.2 Hz, 1H), 3.33 (dd, J = 17.2, 12.4 Hz, 1H), 2.93 - 2.84 (m, 1H), 2.62 (dd, J = 17.2, 5.2 Hz, 1H),1.76 (s, 3H). 13 C NMR (100 MHz, CDCl₃) δ 178.0, 161.3 (d, J = 248.6 Hz), 142.4, 141.1, 139.7 (d, J = 3.2 Hz), 137.9, 133.4 (d, J = 9.8 Hz), 133.1 (d, J = 8.1 Hz), 129.0, 128.8, 128.7, 127.8, 127.4, 127.1, 125.7, 119.9 (d, J = 24.2 Hz), 113.6 (d, J = 19.7 Hz), 51.4, 44.5, 39.1, 29.3, 24.1 ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ -114.37 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{22}O_2^{35}ClF$ [M + H]⁺ 421.1365, found 421.1356; $C_{26}H_{22}O_2^{37}ClF [M + H]^+ 423.1336$, found 423.1320.

HOOC 3ha

5'-methyl-5'-(naphthalen-2-yl)-2',3',4',5'-tetrahydro-[1,1':3',1''-terphen-yl]-4'-carboxylic acid (3ha). The general procedure was followed using substrate 1h (21.0 mg, 0.1 mmol) and 2a (31.2 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3ha** (21.6 mg, 52%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.90 – 7.81 (dd, J = 21.6, 7.9 Hz, 4H), 7.67

(d, J = 7.6 Hz, 3H), 7.50 - 7.41 (m, 4H), 7.34 (t, J = 7.6 Hz, 1H), 7.23 - 7.15 (m, 3H), 7.07 (d, J = 6.4 Hz, 1H)2H), 6.18 (s, 1H), 3.40 (dd, J = 16.2, 13.0 Hz, 1H), 3.33 (br s, 1H), 3.14 – 3.04 (m, 1H), 2.68 (dd, J = 17.2, 5.2 Hz, 1H), 1.65 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 178.3, 145.9, 142.6, 141.5, 138.3, 133.2, 132.3, 128.7, 128.3, 127.9, 127.6, 127.4, 127.0, 126.7, 126.4, 126.1, 125.7, 124.7, 57.0, 44.2, 38.5, 29.5, 27.1 ppm. HR – MS (ESI) m/z calcd for $C_{30}H_{26}O_2$ [M + Na]⁺ 441.1825, found 441.1813.

HOOC,

2-chloro-3',5'-diphenyl-3',4'-dihydro-2'H-[1,1':1',1''-terphenyl]-2'-carboxylic acid (3ia). The general procedure was followed using substrate 1i (25.7 mg, 0.1 mmol) and 2a (31.2 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3ia** (39.5 mg, 85%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.47 – 7.28 (m, 11H), 7.27 -7.22 (m, 1H), 7.17 - 7.05 (m, 5H), 3.99 (s, 1H), 3.81 (d, J = 10.4 Hz, 1H), 3.41 (dd, J = 16.0, 13.2 Hz,

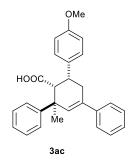
1H), 2.62 (dd, J = 16.8, 5.2 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 175.7, 144.1, 143.1, 142.2, 141.9, 139.3, 134.7, 133.4, 129.0, 128.5, 128.3, 128.1, 127.9, 127.5, 127.4, 127.3, 126.9, 126.6, 125.8, 125.0, 53.6, 52.3, 39.4, 29.7 ppm. HR – MS (ESI) m/z calcd for $C_{31}H_{25}O_2^{35}Cl$ [M + Na]⁺ 487.1435, found 487.1428; $C_{31}H_{25}O_2^{37}Cl [M + Na]^+ 489.1406$, found 489.1386.

HOOC,

1',4''-dimethyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-

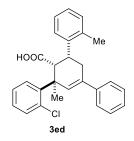
carboxylic acid (**3ab**). The general procedure was followed using substrate **1a** (16.0 mg, 0.1 mmol) and **2b** (33.3 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3ab** (28.2 mg, 73%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.41 – 7.27 (m,

6H), 7.04 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 6.06 (s, 1H), 3.34 (dd, J = 16.0, 13.6 Hz, 1H), 3.17 (s, 1H), 3.00 (d, J = 10.0 Hz, 1H), 2.61 (dd, J = 17.2, 4.4 Hz, 1H), 2.29 (s, 3H), 1.57 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 178.3, 148.6, 141.5, 139.6, 138.0, 136.5, 129.4, 128.6, 128.5, 127.9, 127.5, 127.2, 127.1, 126.7, 125.6, 57.4, 43.9, 37.9, 29.5, 27.1, 21.2 ppm. HR – MS (ESI) m/z calcd for $C_{27}H_{26}O_2$ [M + Na]⁺ 405.1825, found 405.1818.



4"-methoxy-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1"-terphenyl]-2'-ca-rboxylic acid (3ac). The general procedure was followed using substrate 1a (16.0 mg, 0.1 mmol) and 2c (35.7 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded 3ac (28.0 mg, 70%) as white solid. 1 H NMR (400 MHz, CDCl₃) δ 7.63 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.41 (q, J = 8.0

Hz, 4H), 7.36 - 7.27 (q, J = 8.0 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 6.08 (s, 1H), 3.77 (s, 3H), 3.34 (dd, J = 17.2, 12.4 Hz, 1H), 3.19 (d, J = 3.2 Hz, 1H), 3.05 - 3.00 (m, 1H), 2.63 (dd, J = 17.2, 5.2 Hz, 1H), 1.60 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 178.7, 158.5, 148.7, 141.5, 138.1, 134.7, 128.6, 128.6, 128.3, 128.0, 127.5, 127.1, 126.7, 125.6, 114.0, 57.6, 55.3, 43.9, 37.9, 29.7, 27.1 ppm. HR – MS (ESI) m/z calcd for $C_{27}H_{26}O_{3}$ [M + Na]⁺ 421.1774, found 421.1773.



2-chloro-1',2''-dimethyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphen-yl]-1''

2'-carboxylic acid (3ed). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2d** (33.3 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3ed** (27.2 mg, 65%) as white solid. 1 H NMR (400 MHz, CDCl₃) δ 10.98 (br s, 1H), 7.67 – 7.59 (m, 3H), 7.45 – 7.38 (m, 3H), 7.31

7.34 - 7.28 (m, 2H), 7.26 - 7.21 (m, 2H), 7.15 - 7.06 (m, 3H), 6.03 (s, 1H), 3.80 (s, 1H), 3.50 - 3.37 (m, 1H), 3.17 (dd, J = 12.0, 2.4 Hz, 1H), 2.47 (dd, J = 16.8, 4.0 Hz, 1H), 1.81 (s, 3H), 1.66 (s, 3H) ppm. 13 C NMR (100 MHz, CDCl₃) δ 177.6, 143.6, 141.3, 140.3, 138.1, 136.0, 133.1, 132.6, 132.2, 131.0, 129.2,

128.6, 128.5, 127.6, 126.8, 126.7, 126.3, 125.9, 125.7, 49.8, 45.1, 34.6, 28.9, 23.8, 18.2 ppm. HR - MS (ESI) m/z calcd for $C_{27}H_{25}O_2^{35}Cl$ [M + Na] $^+$ 439.1435, found 439.1429; $C_{27}H_{25}O_2^{37}Cl$ [M + Na] $^+$ 441.1406, found 441.1393.

HOOC,,,,Me
Me
CI
3ee

2-chloro-1',3''-dimethyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphen-yl]- 2'-carboxylic acid (**3ee**). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2e** (33.3 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3ee** (31.5 mg, 76%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.63 – 7.57 (m, 3H), 7.47 – 7.37 (m, 3H), 7.35 – 7.29 (m, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.02 (s, 1H),

7.24 – 7.19 (m, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.02 (s, 1H), 4.02 (d, J = 3.2 Hz, 1H), 3.33 (dd, J = 16.0, 13.2 Hz, 1H), 2.93 – 2.81 (m, 1H), 2.59 (dd, J = 17.2, 5.6 Hz, 1H), 2.26 (s, 3H), 1.78 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 178.0, 143.8, 142.6, 141.3, 138.3, 137.6, 132.8, 132.0, 129.2, 128.6, 128.4, 128.2, 127.8, 127.6, 126.7, 125.7, 124.3, 51.2, 44.9, 39.1, 29.5, 24.1, 21.6 ppm. HR – MS (ESI) m/z calcd for $C_{27}H_{25}O_{2}^{35}Cl$ [M+Na]⁺ 439.1435, found 439.1427; $C_{27}H_{25}O_{2}^{37}Cl$ [M + Na]⁺ 441.1406, found 441.1391.

OMe HOOC.,,Me CI 3ef

2-chloro-2''-methoxy-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carboxylic acid (**3ef**). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2f** (35.7 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3ef** (31.0 mg, 72%) as white solid. 1 H NMR (400 MHz, CDCl₃) δ 7.63 – 7.58 (m, 3H), 7.48 – 7.44 (m, 1H),

7.39 (dd, J = 8.4, 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.25 – 7.15 (m, 4H), 6.86 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.01 (s, 1H), 4.11 (s, 1H), 3.48 (s, 3H), 3.41 – 3.28 (m, 2H), 2.41 (d, J = 14.0 Hz, 1H), 1.75 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 178.0, 157.0, 144.0, 141.6, 137.9, 133.3, 132.1, 130.4, 129.6, 128.6, 128.1, 127.7, 127.5, 126.5, 125.7, 120.5, 110.2, 54.8, 48.6, 45.0, 31.9, 27.6, 23.8 ppm. HR – MS (ESI) m/z calcd for $C_{27}H_{25}O_{3}^{35}Cl$ [M + Na]⁺ 455.1384, found 455.1379; $C_{27}H_{25}O_{3}^{37}Cl$ [M+Na]⁺ 457.1355, found 457.1341.

2-chloro-2''-fluoro-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carboxylic acid (3eg). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2g** (33.9 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3eg** (29.5 mg, 70%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, J = 7.2 Hz, 3H), 7.47 – 7.44 (m, 1H), 7.40 (t, J

= 7.6 Hz, 2H), 7.34 – 7.28 (m, 2H), 7.24 – 7.20 (m, 2H), 7.19 – 7.14 (m, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.94 (t, J = 9.6 Hz, 1H), 6.03 (s, 1H), 4.06 (s, 1H), 3.40 – 3.29 (m, 2H), 2.51 (q, J = 14.0 Hz, 1H), 1.79 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 177.6, 160.9 (d, J = 246.0 Hz), 143.5, 141.3, 137.4, 133.1, 132.7, 131.9, 129.52 (d, J = 13.6 Hz), 129.51, 128.6, 128.5, 128.4, 127.73, 127.66, 126.6, 125.7, 124.2 (d, J = 3.0 Hz), 115.6 (d, J = 22.5 Hz), 49.7, 44.9, 31.6, 28.0, 24.0 ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ -118.55. HR – MS (ESI) m/z calcd for C₂₆H₂₂O₂³⁵ClF [M + Na]⁺ 443.1185, found 443.1178; C₂₆H₂₂O₂³⁷ClF [M + Na]⁺ 445.1155, found 445.1148.

2-chloro-4''-fluoro-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carboxylic acid (3eh). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2h** (33.9 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3eh** (34.5 mg, 82%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.62 – 7.57 (m, 3H), 7.49 – 7.44 (m, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.13 – 7.05 (m, 2H), 6.94 (t,

J = 8.0 Hz, 2H), 6.03 (s, 1H), 4.01 (s, 1H), 3.30 (dd, J = 17.2, 12.0 Hz, 1H), 2.95 – 2.86 (m, 1H), 2.60 (dd, J = 17.2, 5.2 Hz, 1H), 1.77 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 177.7, 161.8 (d, J = 245.0 Hz), 143.5, 141.1, 138.2 (d, J = 2.8 Hz), 137.4, 132.8, 132.7, 132.0, 129.2, 128.9 (d, J = 7.8 Hz), 128.6, 128.5, 127.7, 126.8, 125.6, 115.5 (d, J = 21.0 Hz), 51.4, 44.8, 38.3, 29.3, 24.0 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{22}O_2^{35}\text{CIF} [M + \text{Na}]^+$ 443.1185, found 443.1176; $C_{26}H_{22}O_2^{37}\text{CIF} [M + \text{Na}]^+$ 445.1155, found 445.1141.

2,4''-dichloro-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphen-yl]- 2'-carboxylic acid (3ei). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2i** (36.4 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3ei** (34.8 mg, 80%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (t, J = 7.6 Hz, 3H), 7.47 – 7.38 (m, 3H), 7.32 (t, J = 7.2 Hz,

1H), 7.22 (d, J = 8.0 Hz, 4H), 7.06 (d, J = 8.0 Hz, 2H), 6.02 (s, 1H), 4.01 (d, J = 2.7 Hz, 1H), 3.29 (dd, J = 3.0 Hz, 2H), 6.02 (s, 1H), 4.01 (d, J = 3.0 Hz, 1H), 3.29 (dd, J = 3.0 Hz, 1H), 3.29 (dd, J = 3.0 Hz, 2H), 6.02 (s, 1H), 4.01 (d, J = 3.0 Hz, 1H), 3.29 (dd, J = 3.0 Hz, 2H), 6.02 (s, 1H), 4.01 (d, J = 3.0 Hz, 1H), 3.29 (dd, J = 3.0 Hz, 2H), 6.02 (s, 1H), 4.01 (d, J = 3.0 Hz, 1H), 3.29 (dd, J = 3.0 Hz, 2H), 6.02 (s, 1H), 4.01 (d, J = 3.0 Hz, 1H), 3.29 (dd, J = 3.0 Hz, 2H), 6.02 (s, 1H), 4.01 (d, J = 3.0 Hz, 1H), 3.29 (dd, J = 3.0 Hz, 2H), 6.02 (s, 1H), 4.01 (d, J = 3.0 Hz, 1H), 3.29 (dd, J = 3.0 Hz, 2H), 6.02 (s, 1H), 4.01 (d, J = 3.0 Hz, 1H), 3.29 (dd, J = 3.0 Hz, 1H), 6.02 (s, 1H), 4.01 (d, J = 3.0 Hz, 1H), 6.02 (s, 1H), 16.8, 12.4 Hz, 1H), 2.89 (d, J = 11.6 Hz, 1H), 2.59 (dd, J = 17.2, 5.2 Hz, 1H), 1.77 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 177.8, 143.6, 141.1, 141.1, 137.4, 132.9, 132.7, 132.0, 129.3, 128.9, 128.8, 128.7, 128.6, 127.7, 126.8, 125.7, 51.3, 44.9, 38.5, 29.2, 24.1 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{22}O_2^{35}Cl_2$ $[M + Na]^+$ 459.0889, found 459.0886; $C_{26}H_{22}O_2^{37}Cl^{35}Cl$ $[M + Na]^+$ 461.0860, found 461.0851; $C_{26}H_{22}O_2^{37}Cl_2 [M + Na]^+ 463.0830$, found 463.0810.

HOOC, 3ej

4"-bromo-2-chloro-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1"terphenyl]-2'-carboxylic acid (3ej). The general procedure was followed using substrate 1e (19.5 mg, 0.1 mmol) and 2j (43.1 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3ej** (36.5 mg, 76%) as white solid. ${}^{1}H$ NMR (400 MHz, CDCl₃) δ 7.62 – 7.55 (m, 3H), 7.49 – 7.31 (m, 6H), 7.24 - 7.19 (m, 2H), 7.00 (d, J = 8.0 Hz, 2H), 6.02 (s, 1H), 4.01 (s, 1H), 3.29 (dd, J = 16.8, 12.4 Hz, 1H), 2.94 - 2.82 (m, 1H), 2.58 (dd, J = 17.2, 5.2 Hz, 1H), 1.77 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 177.7, 143.5, 141.6, 141.1, 137.3, 132.9, 132.7, 132.0, 131.8, 129.3, 129.2, 128.7, 128.6, 127.7, 126.8, 125.7, 120.9, 51.2, 44.9, 38.6, 29.1, 24.1 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{22}O_{2}^{79}Br^{35}Cl$ [M + H]⁺ 481.0564, found 481.0560; $C_{26}H_{22}O_2^{81}Br^{35}Cl$ [M + H]⁺ 483.0544 or $C_{26}H_{22}O_2^{79}Br^{37}Cl$ [M + H]⁺ 483.0535, found 483.0536; $C_{26}H_{22}O_2^{81}Br^{37}Cl$ [M + H]⁺ 485.0515, found 485.0498.

HOOC,, 3ek

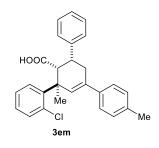
terphen-yl]-4'-carboxylic acid (3ek). The general procedure was followed using substrate 1e (19.5 mg, 0.1 mmol) and 2k (38.8 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded 3ek (32.5 mg, 72%) as white solid. ${}^{1}H$ NMR (400 MHz, CDCl₃) δ 7.83 – 7.71 (m, 3H), 7.65 – 7.55 (m, 3H), 7.47 - 7.30 (m, 8H), 7.13 (t, J = 8.0 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.08 (s, 1H), 4.10 (s, 1H), 3.80 (d, J = 8.8 Hz, 1H), 6.08 (s, 1H), 4.10 (s, 1H), 3.80 (d, J = 8.8 Hz, 1H), 6.08 (s, 1H), 4.10 (s, 1H), 3.80 (d, J = 8.8 Hz, 1H), 6.08 (s, 1H), 4.10 (s, 1H), 3.80 (d, J = 8.8 Hz, 1H), 6.08 (s, 1H), 4.10 (s, 1H), 3.80 (d, J = 8.8 Hz, 1H), 6.08 (s, 1H), 4.10 (s, 1H), 3.80 (d, J = 8.8 Hz, 1H), 6.08 (s, 1H), 4.10 (s, 1H), 3.80 (d, J = 8.8 Hz, 1H), 6.08 (s, 1H), 4.10 (s), 4.10 (

2"-chloro-3'-methyl-5'-(naphthalen-1-yl)-3',4',5',6'-tetrahydro-[1,1':3',1"-

= 11.4 Hz, 1H), 3.61 (t, J = 14.4 Hz, 1H), 2.59 (d, J = 16.4 Hz, 1H), 1.81 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 177.36, 143.63, 141.40, 138.20, 137.70, 134.19, 133.54, 132.61, 132.39, 131.48, 129.40, 129.23, 128.75, 128.63, 127.69, 127.65, 126.95, 126.08, 125.74, 125.50, 125.43, 123.42, 121.88, 77.48, 77.16, 76.84, 50.35, 45.33, 33.84, 28.74, 23.80 ppm. HR – MS (ESI) m/z calcd for $C_{30}H_{25}O_2^{35}Cl$ [M + Na]⁺ 475.1435, found 475.1430; $C_{30}H_{25}O_2^{37}C1 [M + Na]^+ 477.1406$, found 477.1392.

2-chloro-1'-methyl-5'-(m-tolyl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphen-yl]-2'-carboxylic acid (3el). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2l** (33.3 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3el** (28.6 mg, 69%) as white solid. 1 H NMR (400 MHz, CDCl₃) δ 7.59 (s, 1H), 7.47 – 7.38 (m, 3H), 7.33 – 7.10

(m, 9H), 6.00 (s, 1H), 4.03 (s, 1H), 3.40 – 3.24 (m, 1H), 2.91 (d, J = 10.8 Hz, 1H), 2.60 (dd, J = 16.8, 4.0 Hz, 1H), 2.40 (s, 3H), 1.78 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 177.9, 143.8, 142.7, 141.3, 138.2, 137.7, 132.8, 132.1, 129.1, 128.7, 128.5, 128.4, 128.4, 127.4, 127.0, 126.7, 126.4, 122.8, 51.3, 44.9, 39.2, 29.4, 24.1, 21.7 ppm. HR – MS (ESI) m/z calcd for $C_{27}H_{25}O_2^{35}Cl$ [M + Na]⁺ 439.1435, found 439.1429; $C_{27}H_{25}O_2^{37}Cl$ [M + Na]⁺ 441.1406, found 441.1390.



 $\hbox{2-chloro-1'-methyl-5'-(p-tolyl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphen-yl]-1'}$

2'-carboxylic acid (3em). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2m** (33.3 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3em** (30.0 mg, 72%) as white solid. 1 H NMR (400 MHz, CDCl₃) δ 7.61 – 7.56 (m, 1H), 7.50 (d, J = 6.8 Hz, 2H),

7.46 – 7.42 (m, 1H), 7.25 – 7.18 (m, 7H), 7.12 (d, J = 7.2 Hz, 2H), 5.98 (s, 1H), 4.02 (s, 1H), 3.30 (dd, J = 17.2, 12.4 Hz, 1H), 2.95 – 2.84 (m, 1H), 2.59 (dd, J = 17.2, 5.2 Hz, 1H), 2.38 (s, 3H), 1.77 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 178.1, 143.9, 142.7, 138.4, 137.4, 137.3, 132.3, 132.1, 129.3, 128.7, 128.5, 128.4, 127.4, 126.9, 126.7, 125.5, 51.3, 44.9, 39.1, 29.3, 24.1, 21.3 ppm. HR – MS (ESI) m/z calcd for $C_{27}H_{25}O_2^{35}Cl$ [M + Na]⁺ 439.1435, found 439.1428; $C_{27}H_{25}O_2^{37}Cl$ [M + Na]⁺ 441.1406, found 441.1391.

2-chloro-5'-(3-methoxyphenyl)-1'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-

terphenyl]-2'-carboxylic acid (3en). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2n** (35.7 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3en** (31.0 mg, 72%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.55 (m, 1H), 7.49

-7.42 (m, 1H), 7.35 - 7.19 (m, 7H), 7.16 - 7.11 (m, 3H), 6.87 (dd, J = 8.4, 2.4 Hz, 1H), 6.03 (s, 1H), 4.03 (s, 1H), 3.86 (s, 3H), 3.32 (dd, J = 17.2, 12.4 Hz, 1H), 2.97 - 2.86 (m, 1H), 2.60 (d, J = 16.0 Hz, 1H), 1.78

(s, 3H) ppm. 13 C NMR (100 MHz, CDCl₃) δ 177.9, 159.8, 143.7, 142.8, 142.6, 137.4, 132.8, 132.0, 129.6, 129.5, 128.7, 128.5, 127.4, 127.0, 126.7, 118.2, 112.7, 111.7, 55.5, 51.3, 44.9, 39.1, 29.4, 24.0 ppm. HR – MS (ESI) m/z calcd for $C_{27}H_{25}O_3^{35}Cl$ [M + Na]⁺ 455.1384, found 455.1377; $C_{27}H_{25}O_3^{37}Cl$ [M + Na]⁺ 457.1355, found 457.1339.

2-chloro-5'-(4-methoxyphenyl)-1'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-ter-phenyl]-2'-carboxylic acid (3eo). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2o** (35.7 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3eo** (30.5 mg, 70%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.51 (m, 3H), 7.46

-7.42 (m, 1H), 7.26 - 7.17 (m, 5H), 7.12 (d, J = 7.2 Hz, 2H), 6.93 (d, J = 6.8 Hz, 2H), 5.93 (s, 1H), 4.02 (s, 1H), 3.84 (s, 3H), 3.29 (dd, J = 16.8, 12.8 Hz, 1H), 2.90 (d, J = 11.6 Hz, 1H), 2.58 (dd, J = 17.2, 4.4 Hz, 1H), 1.77 (s, 3H) ppm. 13 C NMR (100 MHz, CDCl₃) δ 177.8, 159.3, 144.0, 142.8, 136.9, 133.9, 132.82, 132.78, 132.1, 128.7, 128.4, 127.8, 127.4, 126.9, 126.7, 114.0, 55.5, 51.3, 44.9, 39.2, 29.4, 24.2 ppm. HR - MS (ESI) m/z calcd for $C_{27}H_{25}O_{3}^{35}$ Cl [M+Na] $^{+}$ 455.1384, found 455.1379; $C_{27}H_{25}O_{3}^{37}$ Cl [M + Na] $^{+}$ 457.1355, found 457.1341.

 $\hbox{$2$-chloro-5'-(3,4-dimethoxyphenyl)-1'-methyl-1',2',3',4'-tetrahydro-1'}$

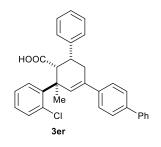
[1,1':3',1''-terphenyl]-2'-carboxylic acid (3ep). The general procedure was

followed using substrate 1e (19.5 mg, 0.1 mmol) and 2p (40.3 mg, 0.15 mmol) to

afford the product. The title compound was isolated by preparative TLC yielded 3ep (33.6 mg, 73%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, J = 6.0, 3.6 Hz, 1H), 7.45 (dd, J = 6.0, 3.6 Hz, 1H), 7.28 – 7.20 (m, 6H), 7.18 – 7.10 (m, 4H), 6.90 (d, J = 8.4 Hz, 1H), 5.95 (s, 1H), 4.02 (d, J = 2.8 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.29 (dd, J = 16.4, 12.8 Hz, 1H), 2.95 – 2.87 (m, 1H), 2.60 (dd, J = 17.2, 5.6 Hz, 1H), 1.79 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 178.2, 149.0, 148.9, 143.8, 142.7, 137.0, 134.2, 132.8, 132.0, 128.7, 128.4, 128.0, 127.4, 127.0, 126.7, 118.1, 111.2, 108.9, 56.2, 56.1, 51.3, 44.9, 39.2, 29.5, 24.1 ppm. HR – MS (ESI) m/z calcd for $C_{28}H_{27}O_4^{35}Cl$ [M + Na]⁺ 485.1490, found 485.1482; $C_{28}H_{27}O_4^{37}Cl$ [M + Na]⁺ 487.1461, found 487.1439.

2-chloro-1'-methyl-5'-(4-propylphenyl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carboxylic acid (**3eq**). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2q** (37.6 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3eq** (33.2 mg, 75%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.62 – 7.42 (m, 4H), 7.27

-7.18 (m, 7H), 7.12 (d, J = 7.6 Hz, 2H), 6.00 (s, 1H), 4.02 (s, 1H), 3.32 (dd, J = 16.4, 12.8 Hz, 1H), 2.90 (d, J = 11.6 Hz, 1H), 2.64 - 2.56 (m, 3H), 1.77 (s, 3H), 1.71 - 1.62 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H) ppm. 13 C NMR (100 MHz, CDCl₃) δ 177.6, 143.9, 142.7, 142.3, 138.6, 137.3, 132.8, 132.8, 132.1, 128.7, 128.5, 128.4, 127.4, 126.9, 126.7, 125.5, 51.3, 44.9, 39.1, 37.9, 29.3, 24.8, 24.1, 14.0 ppm. HR – MS (ESI) m/z calcd for $C_{29}H_{29}O_2^{35}Cl$ [M+Na]⁺ 467.1748, found 467.1742; $C_{29}H_{29}O_2^{37}Cl$ [M+Na]⁺ 469.1719, found 469.1705.



5'-(2-chlorophenyl)-5'-methyl-1',2',5',6'-tetrahydro-[1,1':3',1'':4'',1'''-

quarterphenyl]-6'-carboxylic acid (**3er**). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2r** (42.7 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3er** (35.4 mg, 74%) as white solid. 1 H NMR (400 MHz, CDCl₃) δ 12.19 (s, 1H), 7.79 – 7.70 (m,

6H), 7.61 - 7.47 (m, 4H), 7.40 - 7.27 (m, 5H), 7.21 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.2 Hz, 2H), 6.21 (s, 1H), 3.83 (s, 1H), 3.30 (dd, J = 15.6, 12.4 Hz, 1H), 2.78 (d, J = 10.8 Hz, 1H), 2.62 (dd, J = 16.8, 4.4 Hz, 1H), 1.71 (s, 3H) ppm. 13 C NMR (100 MHz, CDCl₃) δ 172.9, 143.6, 143.0, 139.8, 139.6, 139.1, 136.0, 132.5, 132.0, 131.6, 129.0, 128.8, 128.5, 127.5, 127.2, 127.1, 126.7, 126.63, 126.57, 125.8, 50.9, 44.5, 38.6, 28.6, 23.7 ppm. HR – MS (ESI) m/z calcd for $C_{32}H_{27}O_2^{35}C1$ [M + Na]⁺ 501.1592, found 501.1584; $C_{32}H_{27}O_2^{37}C1$ [M + Na]⁺ 503.1562, found 503.1543.

2-chloro-5'-(3-fluorophenyl)-1'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''-

terphenyl]-2'-carboxylic acid (**3es**). The general procedure was followed using substrate **1e** (19.5 mg, 0.1 mmol) and **2s** (33.9 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3es** (30.0 mg, 71%) as white solid. 1 H NMR (400 MHz, CDCl₃) δ 7.62 – 7.55 (m, 3H), 7.47 – 7.43 (m, 1H),

7.40 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.25 - 7.17 (m, 3H), 6.92 - 6.83 (m, 3H), 6.02 (s, 1H),

4.03 (d, J = 2.8 Hz, 1H), 3.29 (dd, J = 17.2, 12.4 Hz, 1H), 2.97 - 2.86 (m, 1H), 2.60 (dd, J = 17.2, 5.6 Hz, 1H), 1.78 (s, 3H) ppm. 13 C NMR (100 MHz, CDCl₃) δ 178.1, 163.1 (d, J = 245.7 Hz), 145.3 (d, J = 6.9 Hz), 143.6, 141.1, 137.3, 132.9, 132.8, 132.0, 130.2 (d, J = 8.3 Hz), 129.3, 128.6, 128.6, 127.7, 126.8, 125.7, 123.1 (d, J = 2.3 Hz), 114.4 (d, J = 21.5 Hz), 113.9 (d, J = 21.1 Hz), 51.2, 44.9, 38.9, 29.2, 24.0 ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ -112.7 ppm. HR – MS (ESI) m/z calcd for C₂₆H₂₂O₂³⁵ClF [M + H]⁺ 421.1365, found 421.1357; $C_{26}H_{22}O_2^{37}ClF [M + H]^+ 423.1336$, found 423.1319.

2-chloro-5'-(4-fluorophenyl)-1'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''terphen-yl]-2'-carboxylic acid (3et). The general procedure was followed using substrate 1e (19.5 mg, 0.1 mmol) and 2t (33.9 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3et** (28.1 mg, 67%) as white solid. ${}^{1}H$ NMR (400 MHz, CDCl₃) δ 7.58 – 7.52 (m, 3H), 7.48 – 7.42 (m, 1H),

7.29 - 7.17 (m, 5H), 7.13 - 7.05 (m, 4H), 5.95 (s, 1H), 4.03 (s, 1H), 3.29 (dd, J = 16.8, 12.4 Hz, 1H), 2.97-2.85 (m, 1H), 2.56 (dd, J = 16.8, 5.2 Hz, 1H), 1.77 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 178.1, 162.5 (d, J = 246.5 Hz), 143.6, 142.5, 137.4 (d, J = 2.9 Hz), 136.8, 132.9, 132.8, 131.9, 129.2 128.8, 128.5,127.4, 127.2 (d, J = 7.9 Hz), 127.0, 126.8, 115.4 (d, J = 21.3 Hz), 51.2, 44.9, 39.1, 29.5, 24.1 ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ -115.05 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{22}O_2^{35}ClF$ [M + Na]⁺ 443.1185, found 443.1177; $C_{26}H_{22}O_2^{37}ClF [M + H]^+ 445.1155$, found 445.1140.

2-chloro-1'-methyl-5'-(4-(trifluoromethyl)phenyl)-1',2',3',4'-tetrahydro-

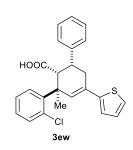
[1,1': 3',1''-terphenyl]-2'-carboxylic acid (3eu). The general procedure was followed using substrate 1e (19.5 mg, 0.1 mmol) and 2u (41.4 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3eu** (40.0 mg, 85%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, J =20.0, 8.0 Hz, 4H), 7.56 - 7.43 (m, 2H), 7.31 - 7.19 (m, 5H), 7.12 (d, J = 7.2 Hz, 2H), 6.10 (s, 1H), 4.06 (d, 2H)

J = 2.4 Hz, 1H), 3.33 (dd, J = 16.4, 12.8 Hz, 1H), 3.00 – 2.88 (m, 1H), 2.61 (dd, J = 17.2, 4.8 Hz, 1H), 1.79 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 177.9, 144.8, 143.3, 142.3, 136.8, 133.0, 132.8, 131.8, 131.3, 129.6 (q, J = 32.4 Hz), 128.8, 128.7, 127.4, 127.1, 126.8, 126.0, 125.58, 125.55, 124.4 (q, J = 272.0 Hz), 51.2, 45.0, 39.1, 29.3, 24.0 ppm. 19 F NMR (376 MHz, CDCl₃) δ -62.31 ppm. HR – MS (ESI) m/z calcd for

495.1111.

2-chloro-5'-(4-chlorophenyl)-1'-methyl-1',2',3',4'-tetrahydro-[1,1':3',1''terph-enyl]-2'-carboxylic acid (3ev). The general procedure was followed using substrate 1e (19.5 mg, 0.1 mmol) and 2v (36.4 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded **3ev** (33.8 mg, 77%) as white solid. ${}^{1}H$ NMR (400 MHz, CDCl₃) δ 7.55 – 7.49 (m, 3H), 7.47 – 7.44 (m,

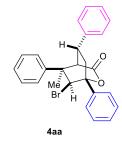
1H), 7.36 (d, J = 8.4 Hz, 2H), 7.29 - 7.19 (m, 5H), 7.11 (d, J = 7.2 Hz, 2H), 6.00 (s, 1H), 4.04 (s, 1H), 3.29(dd, J = 16.0, 13.6 Hz, 1H), 2.91 (dd, J = 6.8, 3.6 Hz, 1H), 2.56 (dd, J = 17.2, 4.0 Hz, 1H), 1.77 (s, 3H)ppm. ¹³C NMR (100 MHz, CDCl₃) δ 178.0, 143.5, 142.4, 139.7, 136.6, 133.4, 132.9, 132.8, 131.9, 123.0, 128.8, 128.7, 128.6, 127.4, 127.1, 126.9, 126.8, 51.2, 45.0, 39.1, 29.3, 24.0 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{22}O_2^{35}Cl_2 [M + Na]^+ 459.0889$, found 459.0881; $C_{26}H_{22}O_2^{37}Cl_2^{35}Cl [M + Na]^+ 461.0860$, found 461.0846; C₂₆H₂₂O₂³⁷Cl₂ [M + Na]⁺ 463.0830, found 463.0806.



2-chloro-1'-methyl-5'-(thiophen-2-yl)-1',2',3',4'-tetrahydro-[1,1':3',1''terphenyl]-2'-carboxylic acid (3ew). The general procedure was followed using substrate 1e (19.5 mg, 0.1 mmol) and 2w (32.1 mg, 0.15 mmol) to afford the product. The title compound was isolated by preparative TLC yielded 3ew (24.0 mg, 59%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.52 (m, 1H), 7.47 – 7.42 (m, 1H), 7.29 - 7.18 (m, 6H), 7.16 - 7.09 (m, 3H), 7.06 - 7.01 (m, 1H), 6.08 (s, 1H), 4.02 (d, J = 2.0 Hz, 1H), 3.32(dd, J = 16.0, 13.2 Hz, 1H), 2.97 - 2.85 (m, 1H), 2.64 (dd, J = 17.2, 5.2 Hz, 1H), 1.77 (s, 3H) ppm.NMR (100 MHz, CDCl₃) δ 177.8, 145.4, 143.5, 142.3, 132.8, 132.7, 132.0, 128.8, 128.5, 128.0, 127.6, 127.4, 127.1, 126.8, 123.9, 122.8, 51.4, 44.9, 38.9, 29.4, 24.0 ppm. HR - MS (ESI) m/z calcd for $C_{24}H_{21}O_{2}^{35}ClS [M + Na]^{+} 431.0843$, found 431.0836; $C_{24}H_{21}O_{2}^{37}ClS [M + Na]^{+} 433.0813$, found 433.0798.

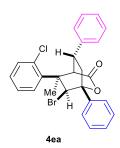
3. Product Derivatization

To a solution of **3** (0.1 mmol) and NBS (19.6 mg, 1.1 equiv) in CH₂Cl₂ (2 mL) was stirred at room temperature overnight. The crude mixture was direct purified by preparative TLC with petroleum ether/ethyl acetate to afford the product **4**.



6-bromo-5-methyl-1,5,8-triphenyl-2-oxabicyclo[2.2.2]octan-3-one (**4aa**). The title compound **4aa** was prepared according to General Procedure and purified by preparative TLC with petroleum ether/ethyl acetate to afford the white solid (43.5 mg, 97% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, J = 7.6 Hz, 2H), 7.44 – 7.36 (m, 9H), 7.33 – 7.27 (m, 4H), 4.54 (s, 1H), 3.93 (t, J = 9.6 Hz, 1H), 3.53 (dd, J = 14.0, 9.6 Hz,

1H), 3.44 (s, 1H), 2.21 (dd, J = 14.0, 9.2 Hz, 1H), 1.72 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 173.1, 144.1, 142.6, 138.7, 129.4, 129.1, 129.0, 128.5, 127.9, 127.6, 127.3, 127.2, 126.6, 86.6, 62.9, 51.1, 45.9, 36.9, 35.9, 34.2 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{23}O_{2}Br$ [M+Na]⁺ 469.0774, found 469.0769; $C_{26}H_{23}O_{2}^{81}Br$ [M+Na]⁺ 471.0753, found 471.0745.



6-bromo-5-(2-chlorophenyl)-5-methyl-1,8-diphenyl-2-oxabicyclo[2.2.2]octan-3-

one (4ea). The title compound 4ea was prepared according to General Procedure and purified by preparative TLC with petroleum ether/ethyl acetate to afford the white solid (47.0 mg, 98% yield). 1 H NMR (400 MHz, CDCl₃) δ 7.62 (d, J = 6.8 Hz, 2H), 7.50 – 7.38 (m, 8H), 7.36 – 7.25 (m, 3H), 7.19 (dd, J = 7.6, 0.8 Hz, 1H), 4.78 (s, 1H), 3.98 (t,

J = 9.6 Hz, 1H), 3.60 (dd, J = 14.0, 9.6 Hz, 1H), 3.45 (s, 1H), 2.20 (dd, J = 12.8, 10.0 Hz, 1H), 1.94 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 142.3, 141.3, 138.4, 136.3, 132.9, 129.4, 129.2, 128.8, 128. 6, 127.7, 127.4, 127.3, 126.9, 126.8, 86.9, 61.9, 52.9, 46.7, 38.8, 35.5, 27.3 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{22}O_2^{79}Br^{35}Cl$ [M + Na]⁺ 503.0384, found 503.0379; $C_{26}H_{22}O_2^{81}Br^{35}Cl$ [M+Na]⁺ 505.0363, found

 $505.0353;\ C_{26}H_{22}O_2{}^{79}Br^{37}Cl\ [M+Na]^+\ 505.0354\ or\ C_{26}H_{22}O_2{}^{81}Br^{35}Cl\ [M+Na]^+\ 505.0363,\ found\ 505.0353;$ $C_{26}H_{22}O_2^{81}Br^{37}Cl [M+Na]^+ 507.0334$ found 507.0319.

¹⁸O Labeling Experiment 4.

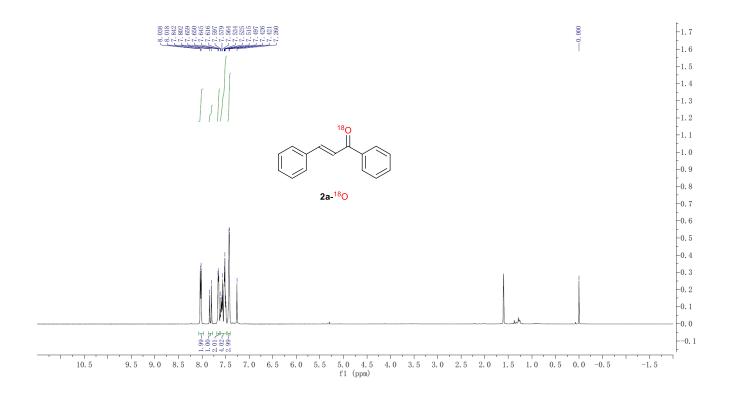
2a-¹⁸O was prepared according to the literatures. ^{2b} The ratio of 2a-¹⁶O and 2a-¹⁸O was 12:88.

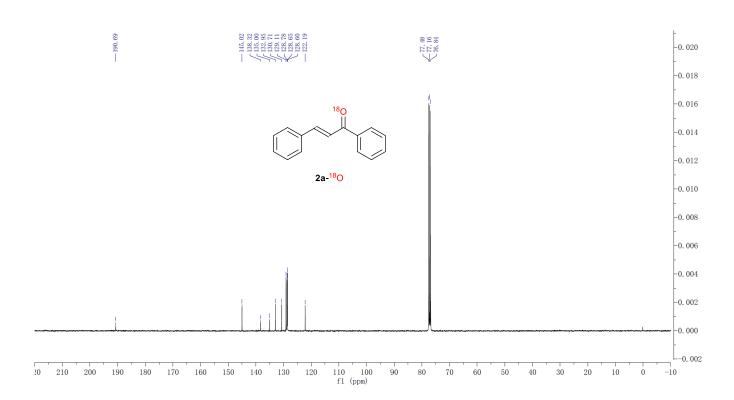
The reaction carried out with Cyclobutanone 1e (19.5 mg, 0.1 mmol), Chalcone 2a-18O (31.5 mg, 0.15 mmol) and KOtBu (13.5 mg, 1.2 equiv). The mixture was added anhydrous CPME (1 mL) at 140 °C and continuous stirring for 18 hours under N2 atmosphere. The reaction was dealt with HCl/EtOAc (2 mL) after cooling to ambient temperature. The crude mixture was purified by preparative TLC to afford product 3ea-¹⁸O. The ratio of **3ea**- 16 O and **3ea**- 18 O was 47 : 53.

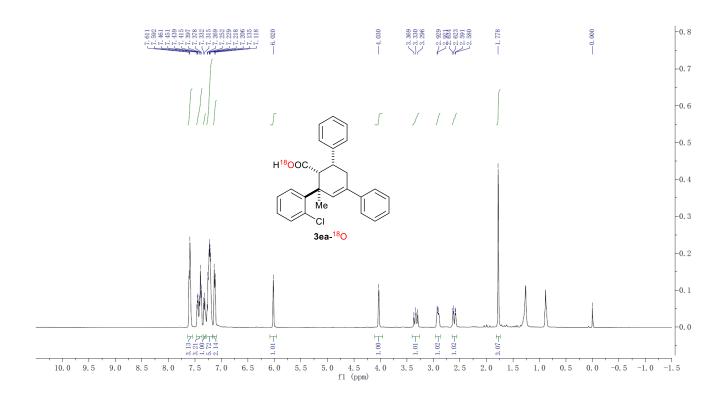
(E)-chalcone-¹⁸O (2a-¹⁸O). ¹H NMR (400 MHz, CDCl₃): δ 8.03 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 16.0 Hz, 1H), 7.68 - 7.63 (m, 2H), 7.62 - 7.50 (m, 4H), 7.46 - 7.40 (d, J = 16.0 Hz, 1H), 7.68 - 7.63 (m, 2H), 7.62 - 7.50 (m, 4H), 7.46 - 7.40 (d, J = 16.0 Hz, 1H), 7.68 - 7.63 (m, 2H), 7.68= 2.3 Hz, 3H) ppm. 13 C NMR (100 MHz, CDCl₃): δ 190.7, 145.0, 138.3, 135.0, 133.0, 2a-18O 130.7, 129.1, 128.8, 128.7, 128.6, 122.2 ppm. HR – MS (ESI) m/z calcd for $C_{15}H_{12}^{18}O$ [M+H]⁺ 211.0823, found 211.1005.

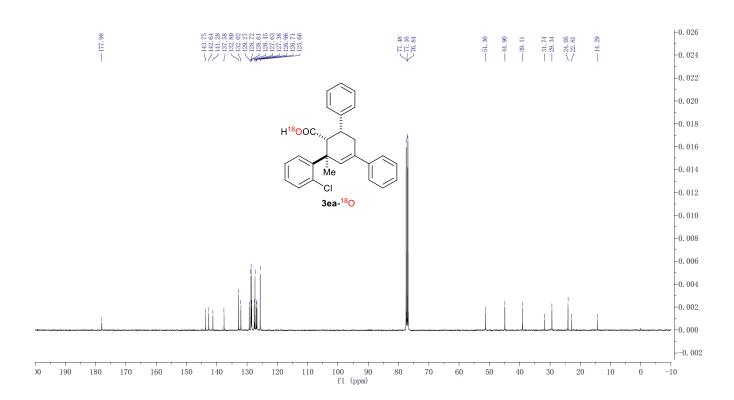
found 427.1327.

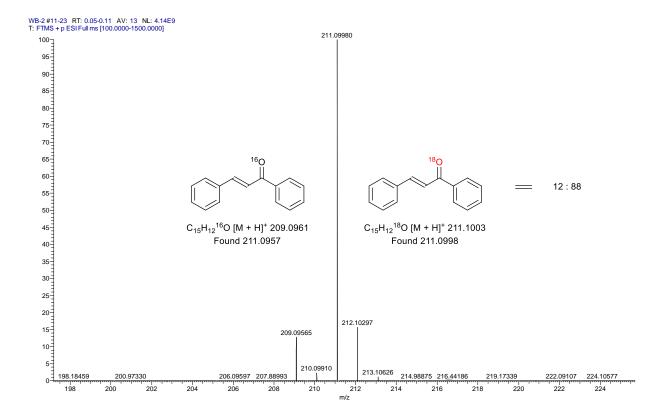
2-chloro-1'-methyl-5'-phenyl-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'carboxylic-¹⁸O acid (3ea-¹⁸O). ¹H NMR (400 MHz, CDCl₃): δ 7.63 – 7.56 (m, 3H), 7.46 - 7.28 (m, 3H), 7.32 (d, J = 6.8 Hz, 1H), 7.28 - 7.17 (m, 5H), 7.13 (d, J = 6.8 Hz, 2H), 6.02 (s, 1H), 4.03 (s, 1H), 3.40 - 3.26 (m, 1H), 2.96 - 2.87 (m, 1H), 2.61 (dd, J= 17.2, 4.4 Hz, 1H), 1.78 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 178.0, 143.8, 142.6, 141.3, 137.6, 132.8, 132.0, 129.3, 128.7, 128.6, 128.5, 127.6, 127.4, 127.0, 126.7, 125.7, 51.3, 44.9, 39.1, 31.7, 29.3, 24.1, 22.8, 14.3 ppm. HR – MS (ESI) m/z calcd for $C_{26}H_{23}OC1^{18}O$ [M+Na]⁺ 427.1321,

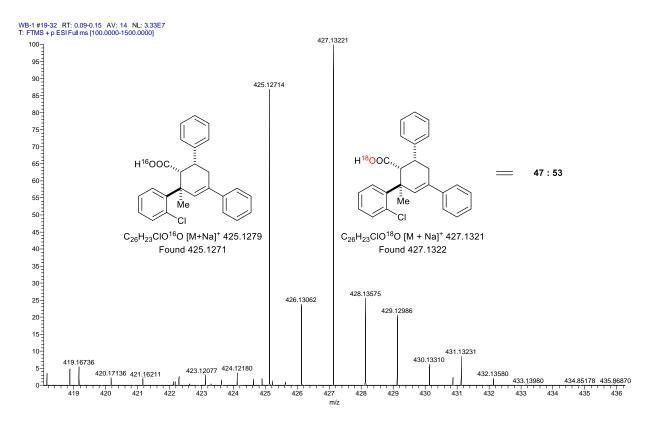




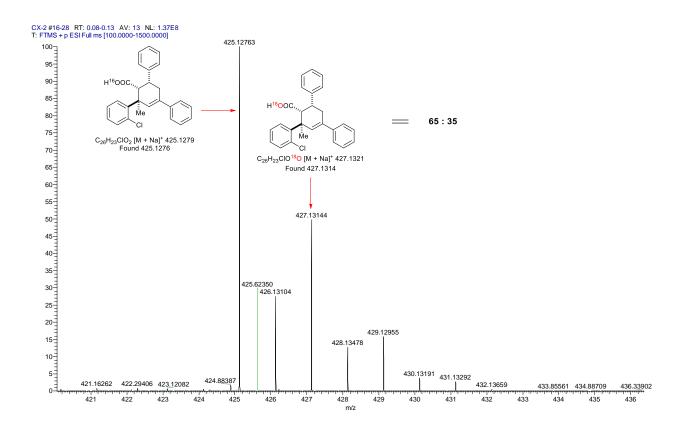




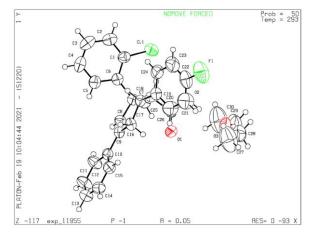




The reaction carried out with Cyclobutanone **1e** (19.5 mg, 0.1 mmol), Chalcone **2a** (31.2 mg, 0.15 mmol), $H_2^{18}O$ (2 mg, 1.0 equiv) and KOtBu (13.5 mg, 1.2 equiv). The mixture was added anhydrous CPME (1 mL) at 140 °C and continuous stirring for 18 hours under N_2 atmosphere. The reaction was dealt with HCl/EtOAc (2 mL) after cooling to ambient temperature. The crude mixture was purified by preparative TLC to afford product **3ea-**¹⁸O (59% yield), which was analyzed HR – MS.



5. Crystal data



Crystal data and structure refinement for 3eh

Empirical formula C₃₀H₃₂O₃FCl

Formula weight 495.00
Temperature/K 293(2)
Crystal system triclinic

Space group P-1

a/Å 9.4244(8) b/Å 9.7735(8) c/Å 16.0599(13)

α/° 105.511(7) β/° 106.708(7)

 $\gamma/^{\circ}$ 93.809(7)

 $Volume/\mathring{A}^3 \hspace{1cm} 1348.7(2)$

 $\begin{array}{ccc} Z & & 2 \\ & & \\ \rho_{cale}g/cm^3 & & 1.219 \end{array}$

 μ /mm⁻¹ 1.538 F(000) 524.0

Crystal size/mm³ $0.140 \times 0.130 \times 0.110$ Radiation $CuK\alpha (\lambda = 1.54184)$

 2Θ range for data collection/° 6.022 to 134.5

Index ranges $-11 \le h \le 11, -11 \le k \le 11, -19 \le l \le 19$

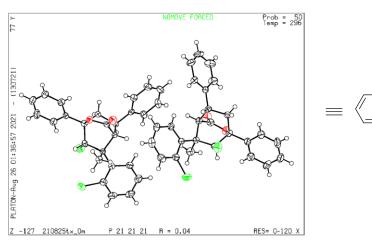
Reflections collected 8428

Independent reflections 4832 [$R_{int} = 0.0344$, $R_{sigma} = 0.0606$]

Data/restraints/parameters 4832/0/321

 $Goodness-of-fit on \ F^2 \\ 1.041$

Largest diff. peak/hole / e $\mbox{Å}^{-3}$ 0.22/-0.24



Crystal data and structure refinement for 4ea

Empirical formula C₂₆H₂₂BrClO₂

Formula weight 481.79

Temperature/K 296.15

Crystal system orthorhombic

Space group P2₁2₁2₁

a/Å 7.0573(7)

b/Å 18.127(2)

c/Å 33.894(4)

α/° 90

β/° 90

 $\gamma/^{\circ}$ 90

Volume/Å³ 4336.0(8)

Z 8

 $\rho_{calc}g/cm^3 \hspace{1.5cm} 1.476$

 μ/mm^{-1} 2.040

F(000) 1968.0

Crystal size/mm³ $0.2 \times 0.15 \times 0.1$

Radiation $MoK\alpha (\lambda = 0.71073)$

 2Θ range for data collection/° 2.548 to 54.906

Index ranges $-8 \leq h \leq 9, -22 \leq k \leq 23, -30 \leq l \leq 43$

Reflections collected 26041

 $\text{Independent reflections} \qquad \qquad 9783 \; [R_{int} = 0.0498, \, R_{sigma} = 0.0923]$

Data/restraints/parameters 9783/0/543

 $Goodness-of-fit \ on \ F^2 \qquad \qquad 0.975$

Final R indexes [I>= 2σ (I)] $R_1 = 0.0418$, $wR_2 = 0.0811$

Final R indexes [all data] $R_1 = 0.0802$, $wR_2 = 0.1079$

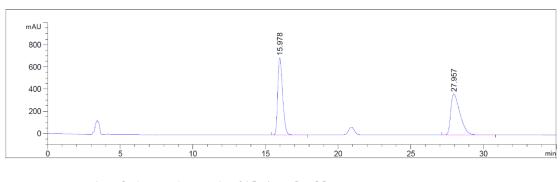
Largest diff. peak/hole / e $\mbox{Å}^{-3}$ 0.28/-0.46

Flack parameter 0.006(5)

4ea

We think the flack parameter [0.006(5)] was probably affected by the crystallization of the racemic mixtures, in some cases, a spontaneous crystallization of a mixture of enantiomerically pure crystals occurs. This method is to mechanically separate the crystals in such a mixture based on differences in their shapes, and it is first used by Louis Pasteur.³ The another is Andreas Seidel-Morgenstern.⁴ In addition, the rest of the crystal **4ea** was analyzed by HPLC, and 75% *ee* was obtained.

The HPLC spectrum of 4ea

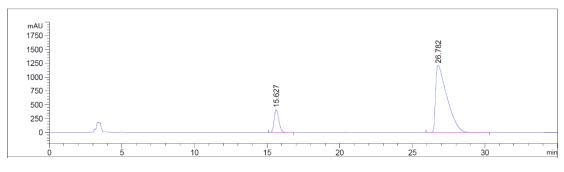


Signal 1: DAD1 A, Sig=215,4 Ref=off

Peak RetTime	e Type	Width	Area	Height	Area
# [min]		[min]	[mAU*s]	[mAU]	엉
	-				
1 15.978	BB	0.3596	1.60727e4	695.54797	49.9248
2 27.95	BB	0.6665	1.61211e4	369.89978	50.0752

Totals: 3.21939e4 1065.44775

The HPLC spectrum of crystal 4ea



Signal 1: DAD1 A, Sig=215,4 Ref=off

RetTime	Type	Width	Area	Height	Area	
[min]		[min]	[mAU*s]	[mAU]	용	
15.627	BB	0.3500	9211.55469	410.15604	12.1985	
26.782	BB	0.7942	6.63023e4	1215.77380	87.8015	
	[min] 15.627	[min]	[min] [min] 	[min] [min] [mAU*s] 	[min] [min] [mAU*s] [mAU] 	[min] [min] [mAU*s] [mAU] %

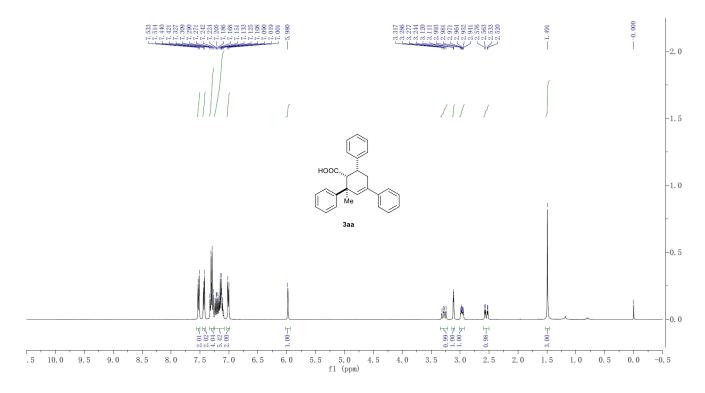
Totals: 7.55138e4 1625.92984

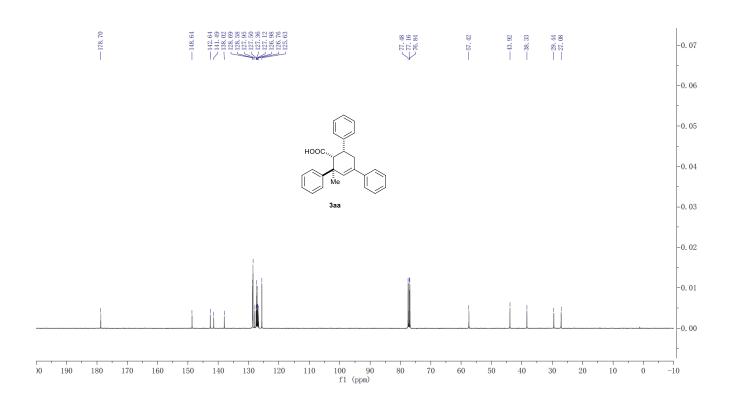
6. References

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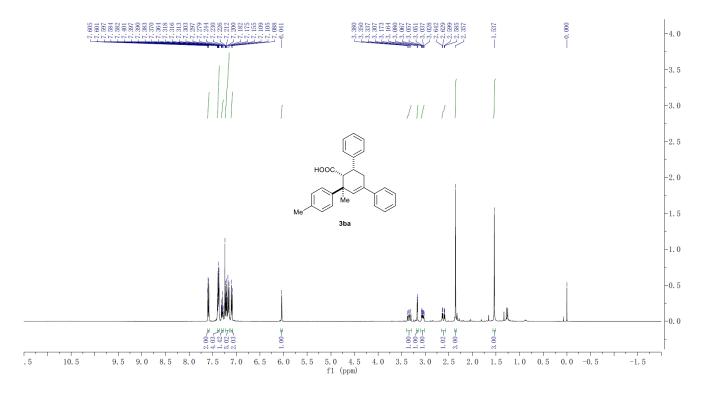
7. NMR Spectra

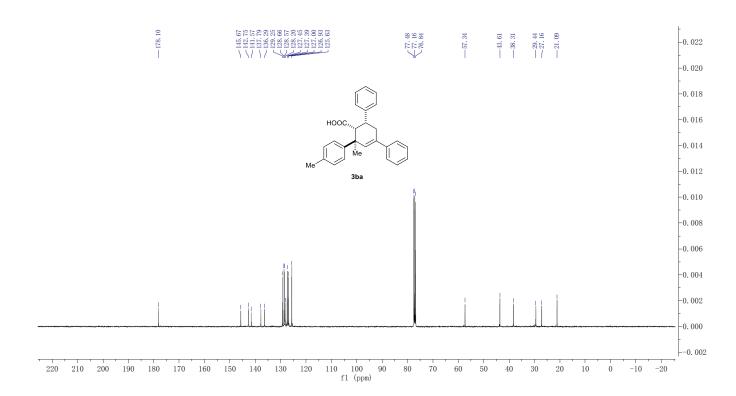
3aa



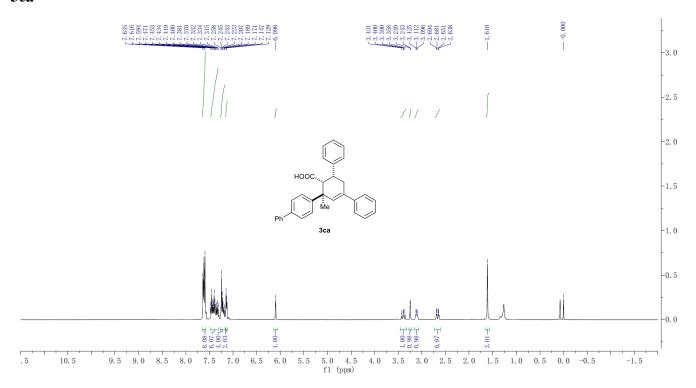


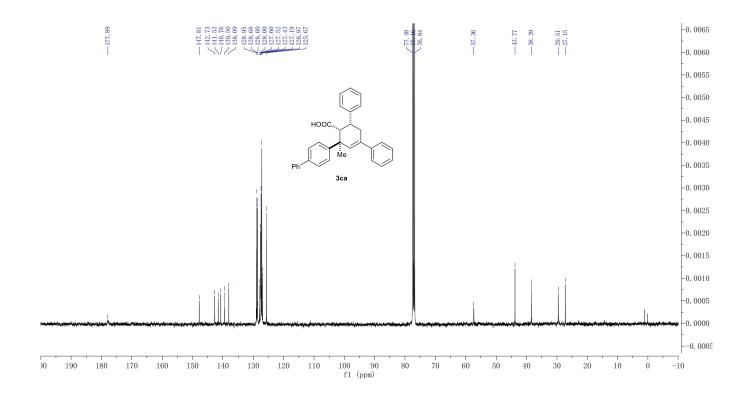
3ba



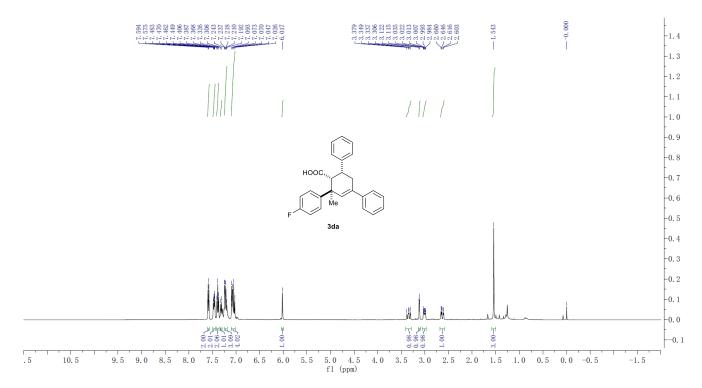


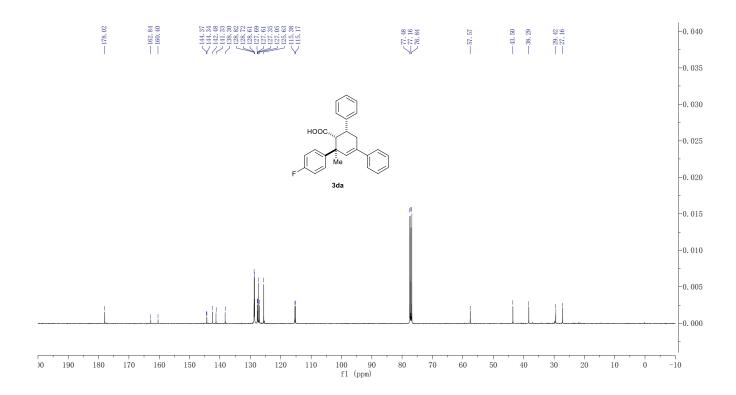
3ca

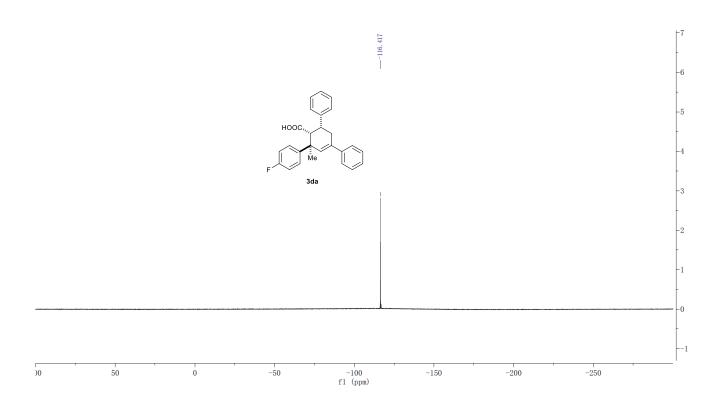




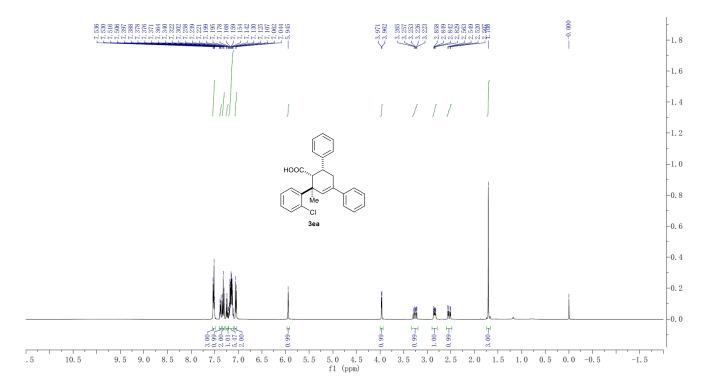
3da

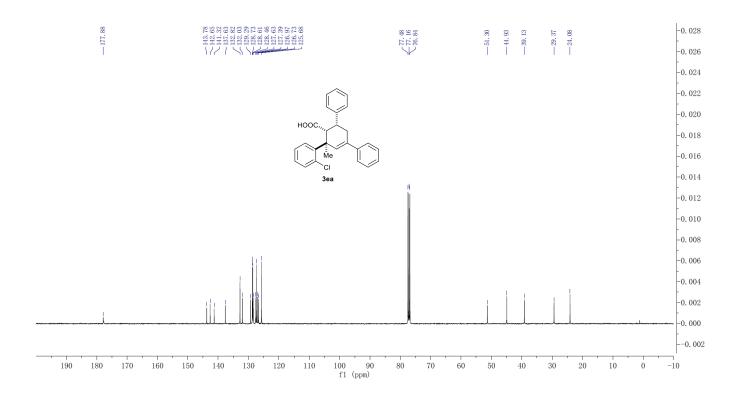


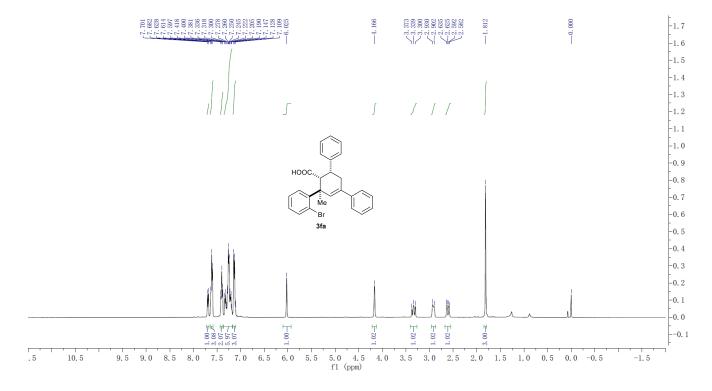


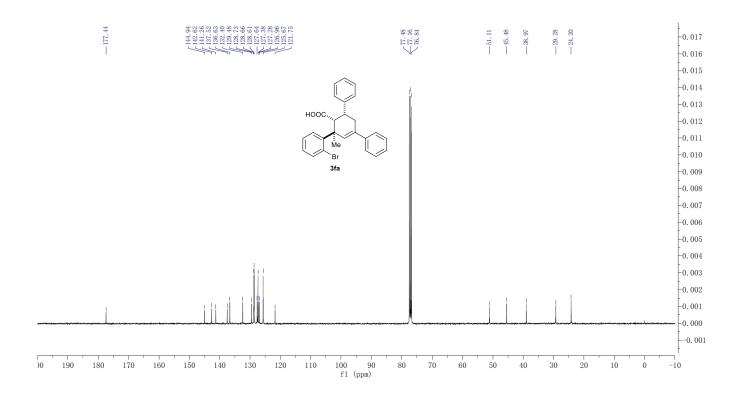


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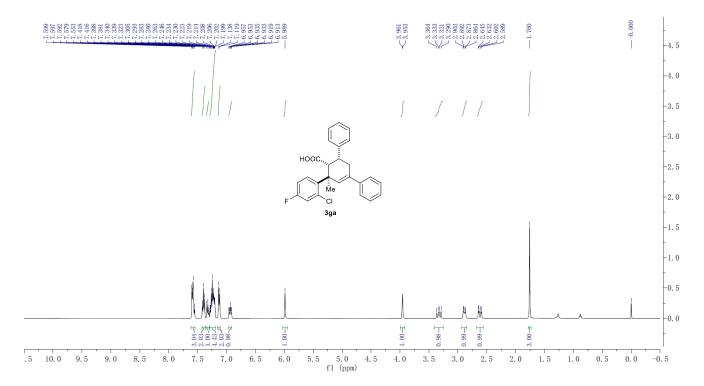


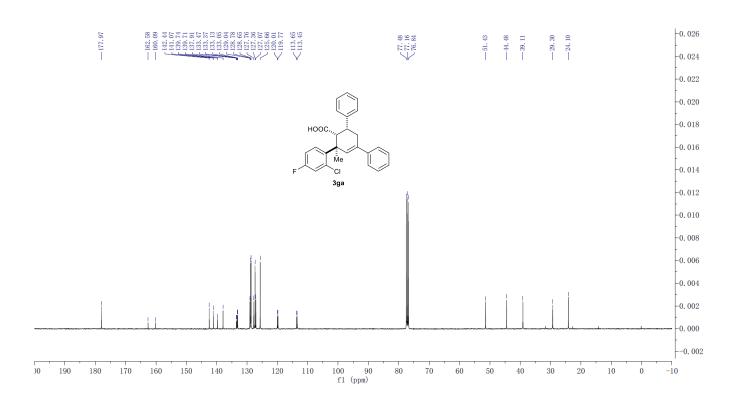


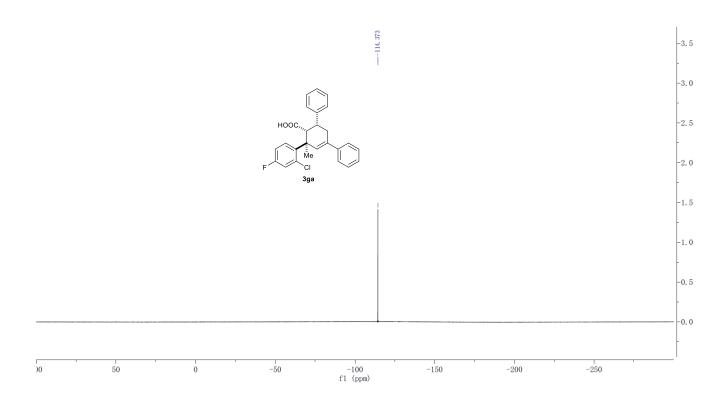




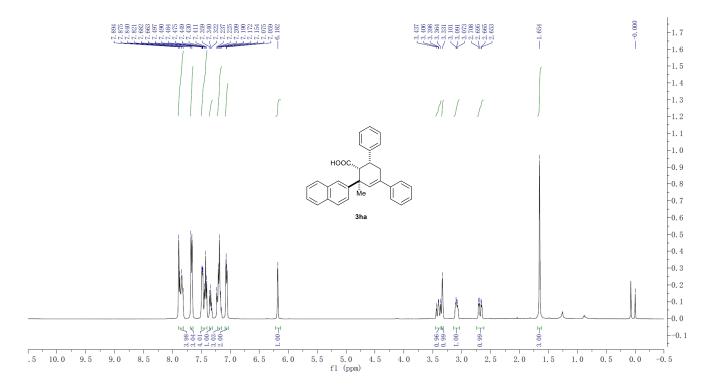
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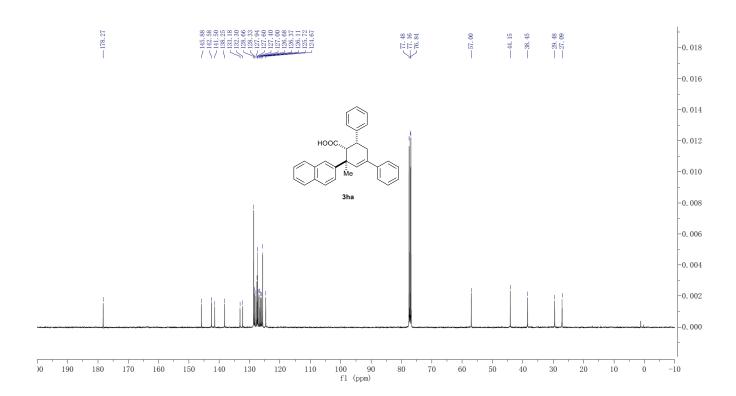


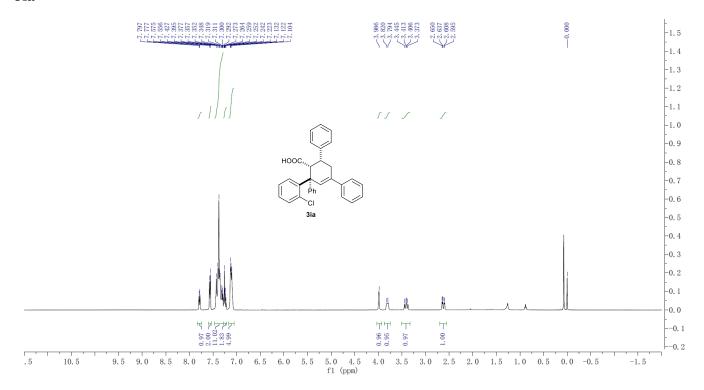


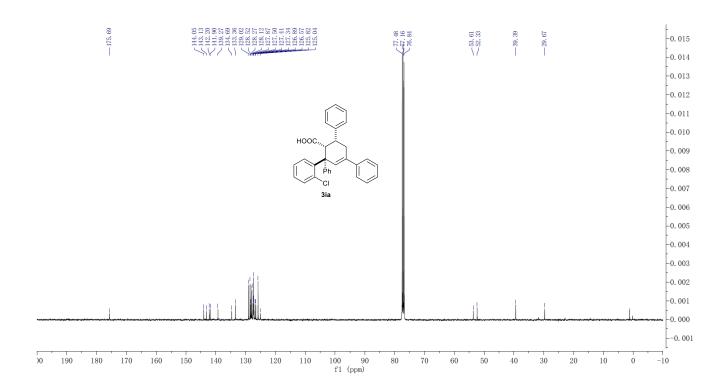


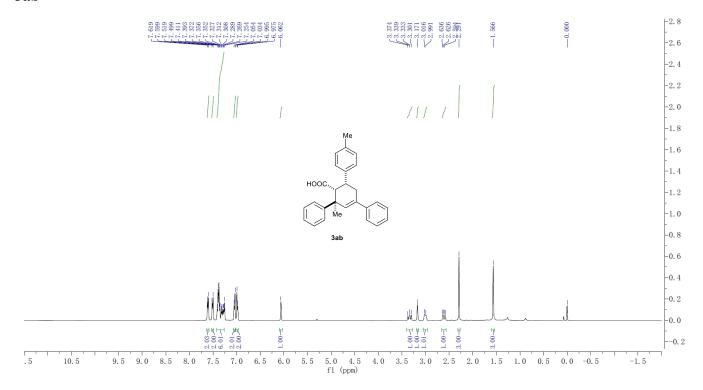
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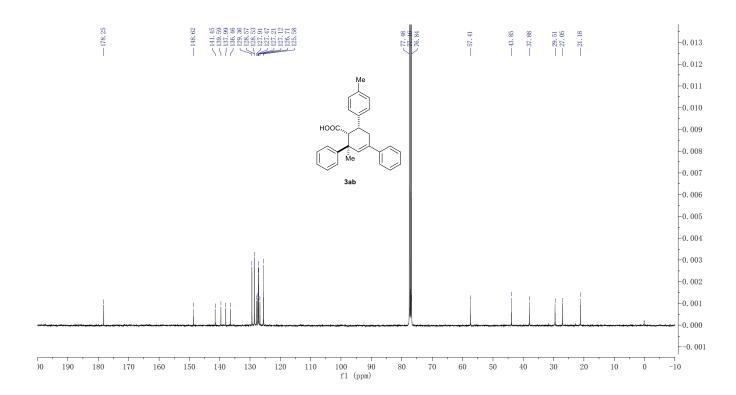




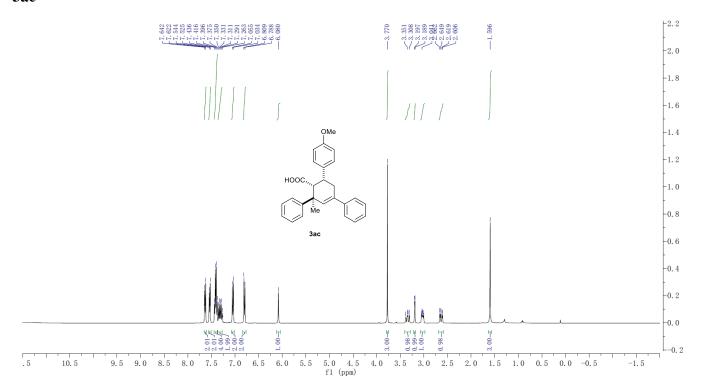


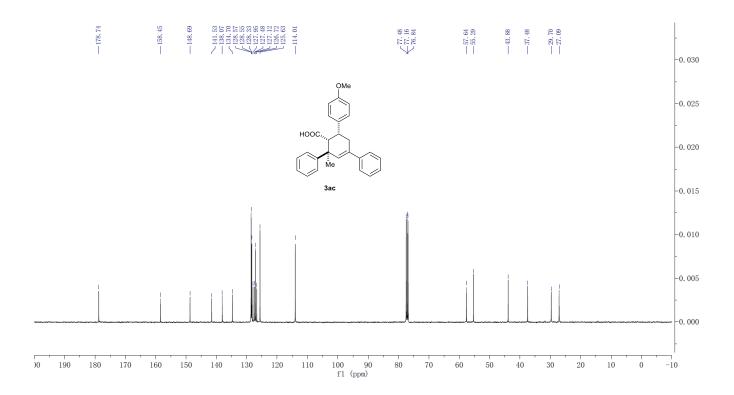




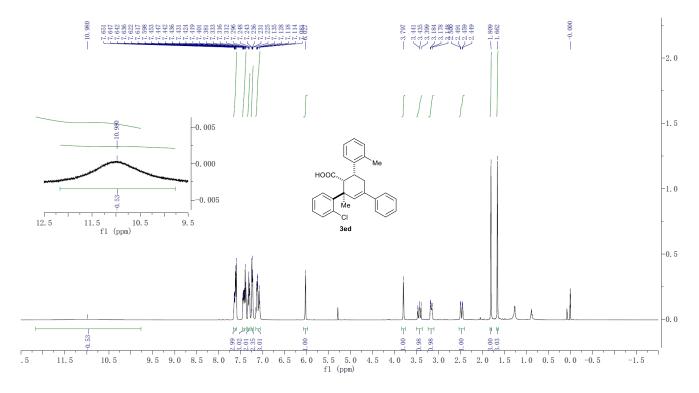


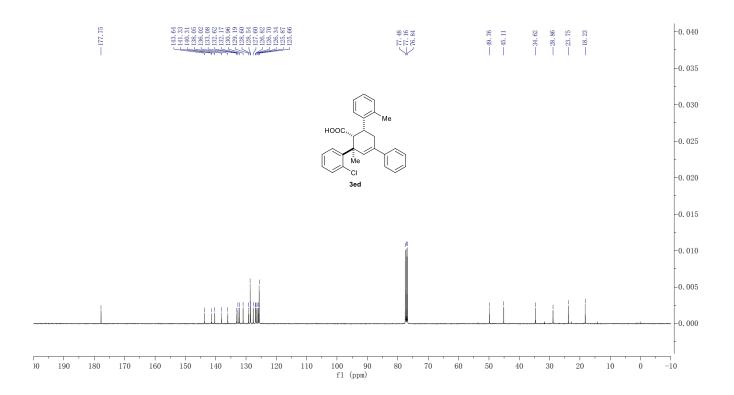
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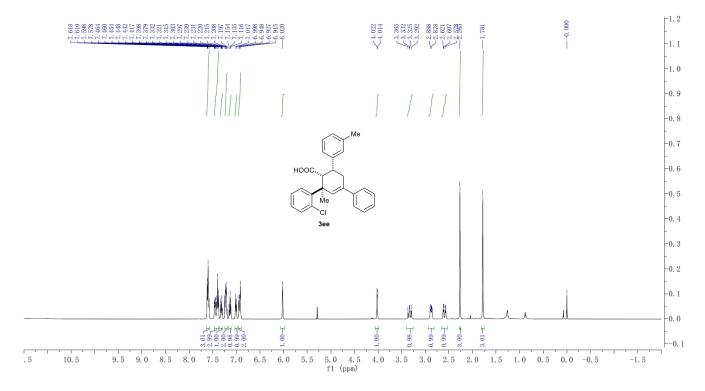


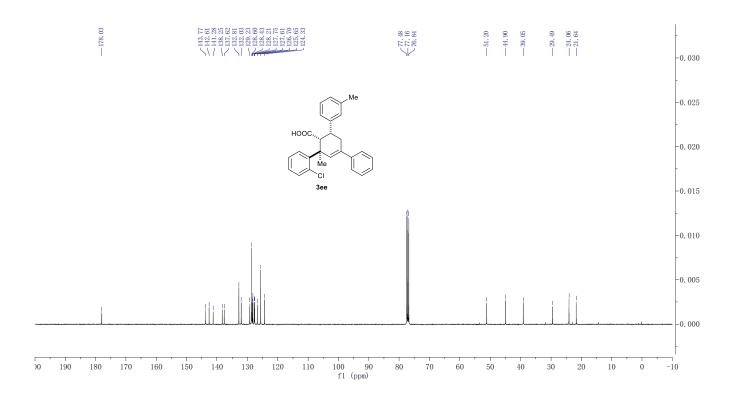
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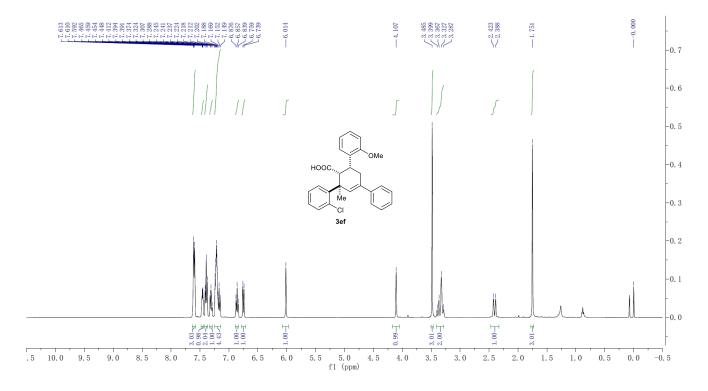


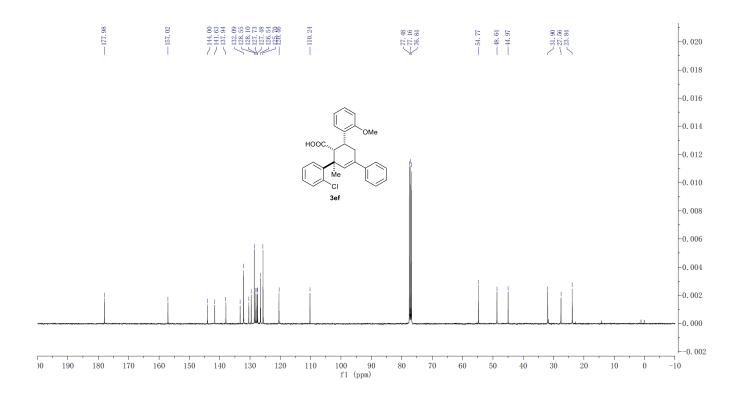
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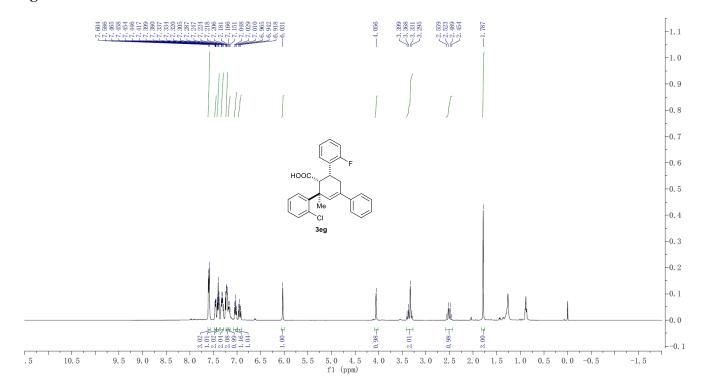


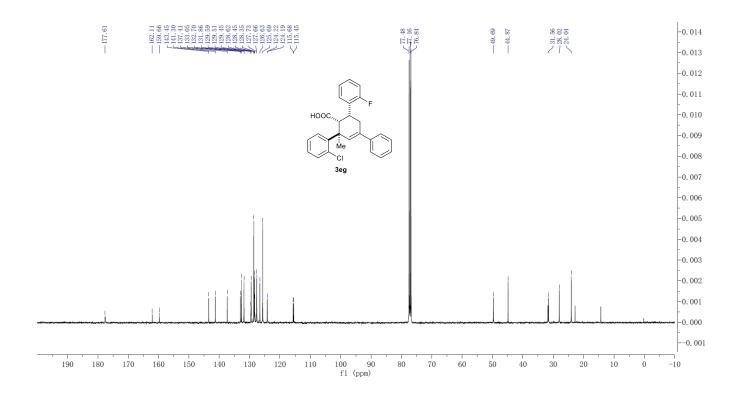
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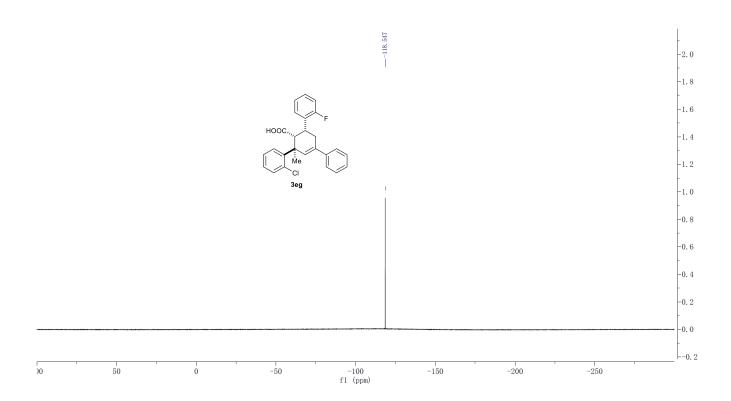




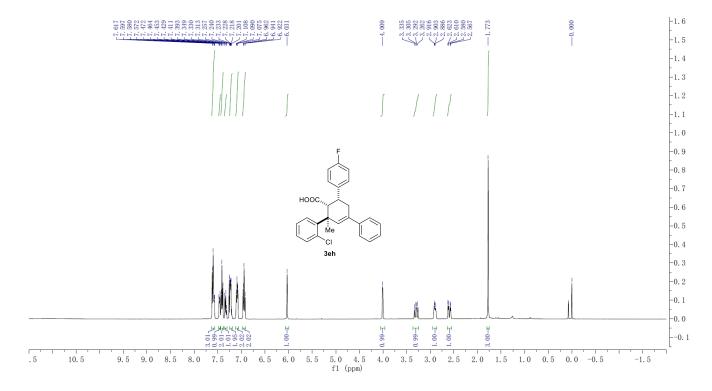


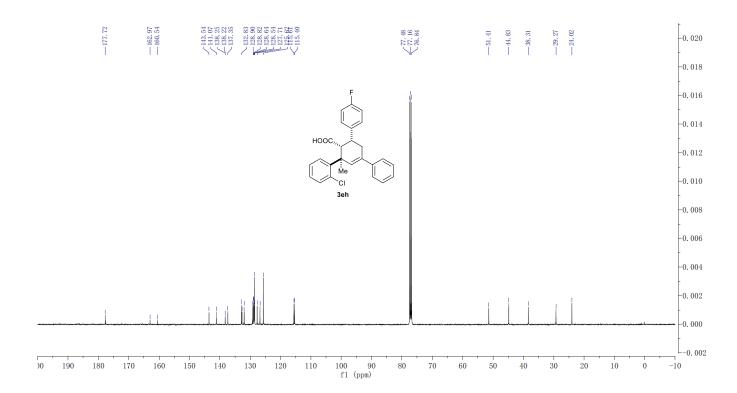


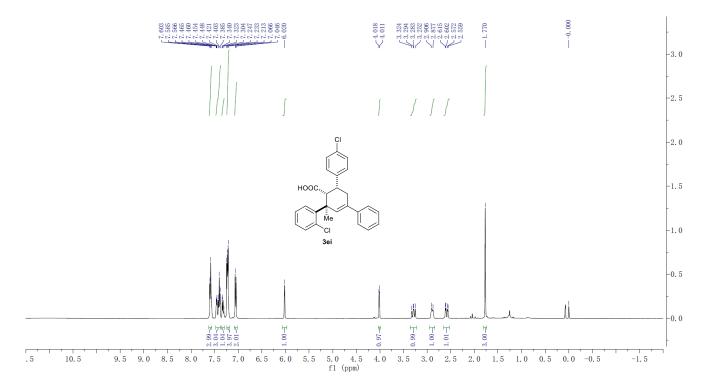


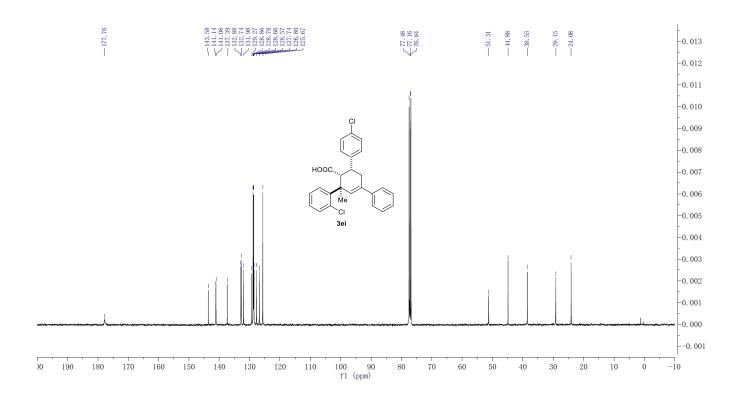


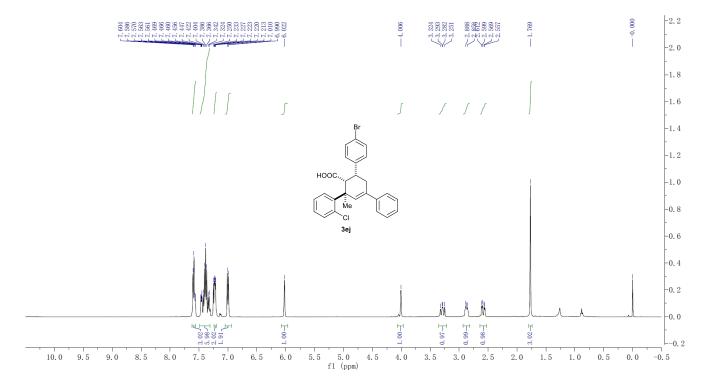
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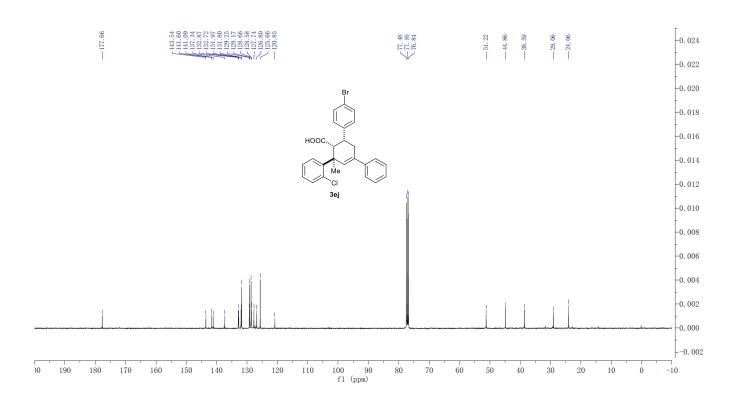




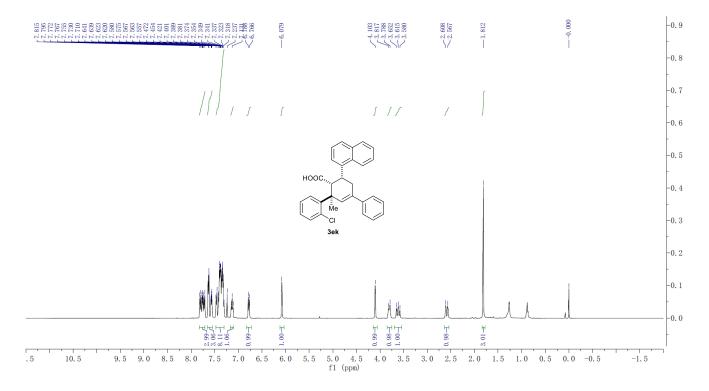


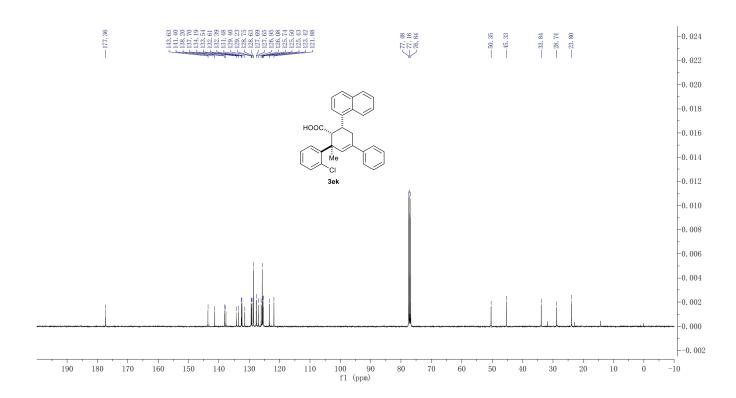


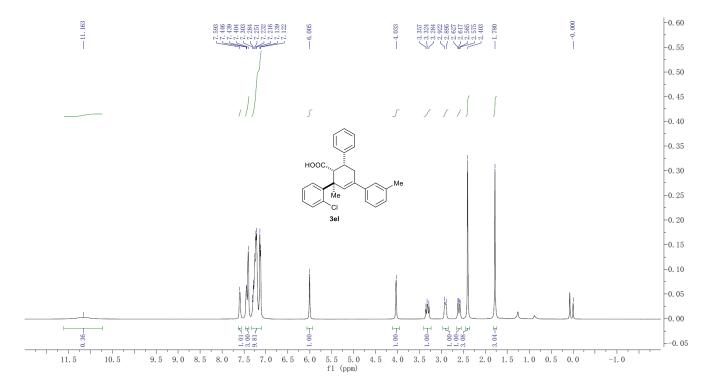


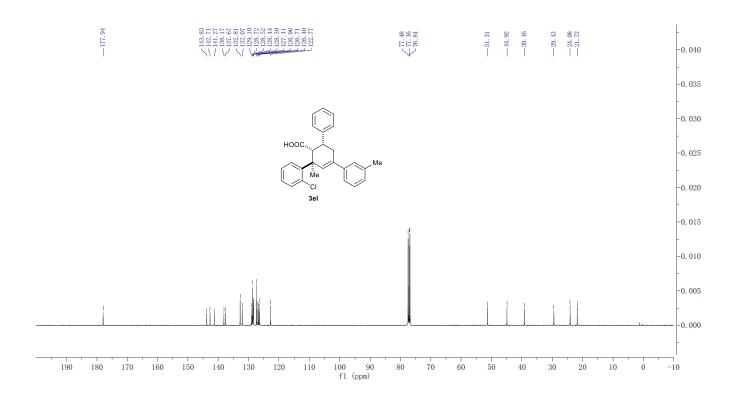


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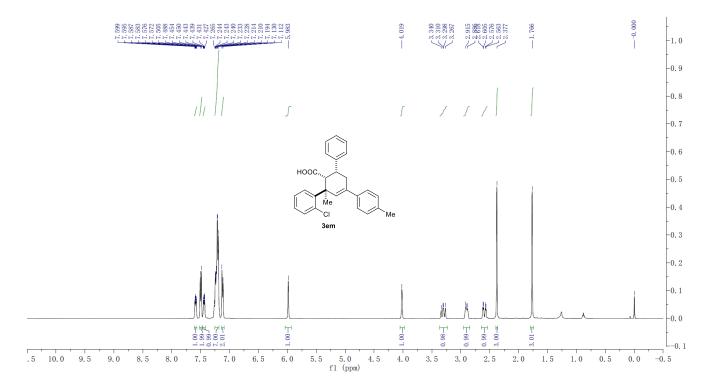


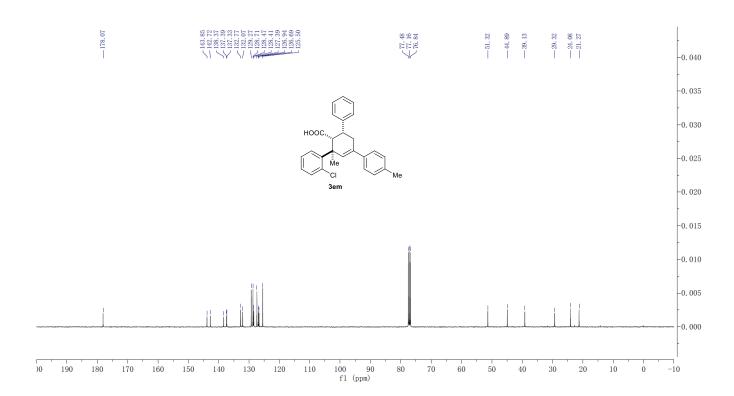




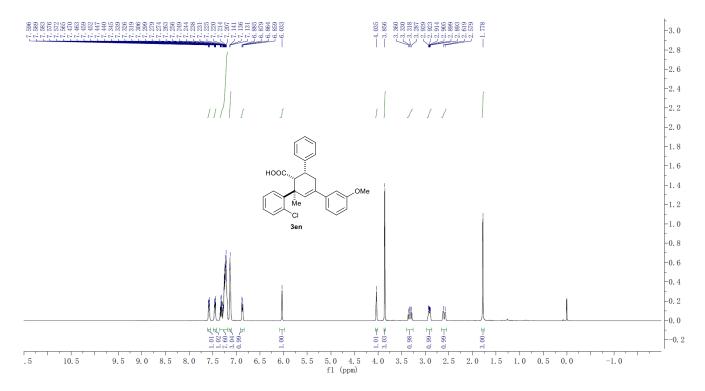


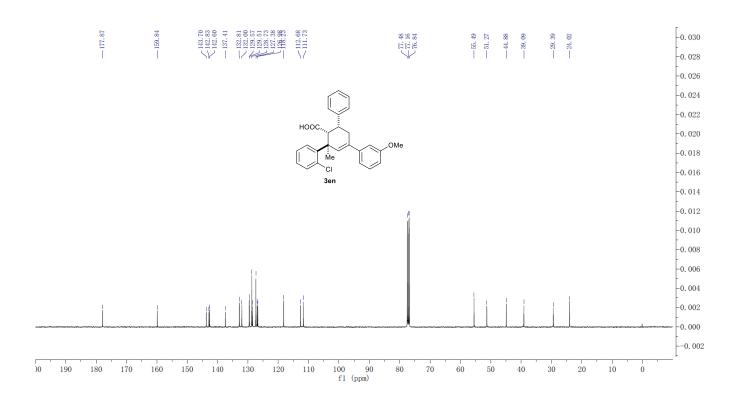
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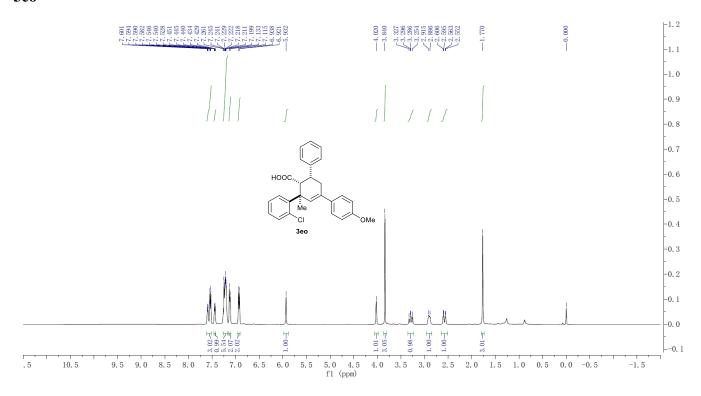


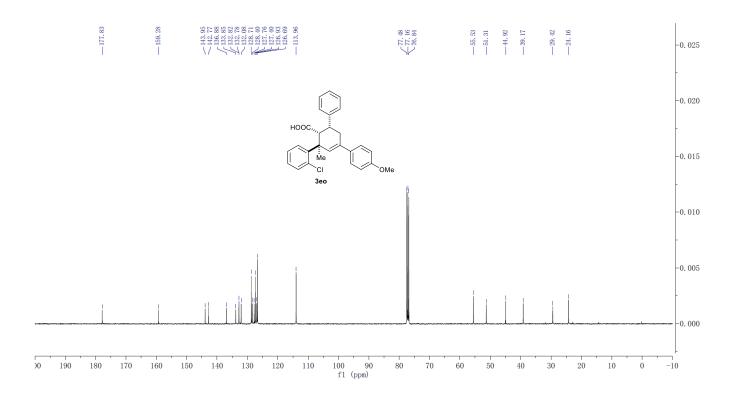
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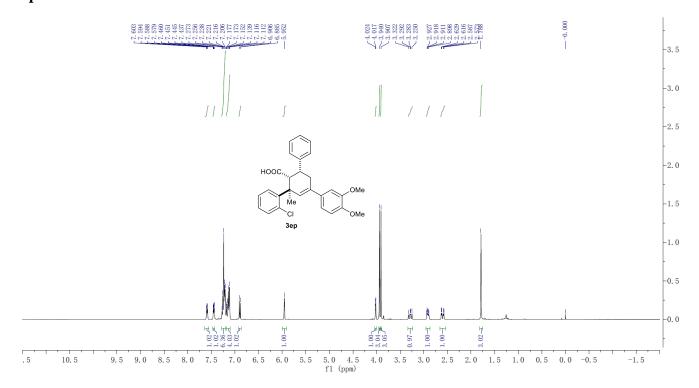


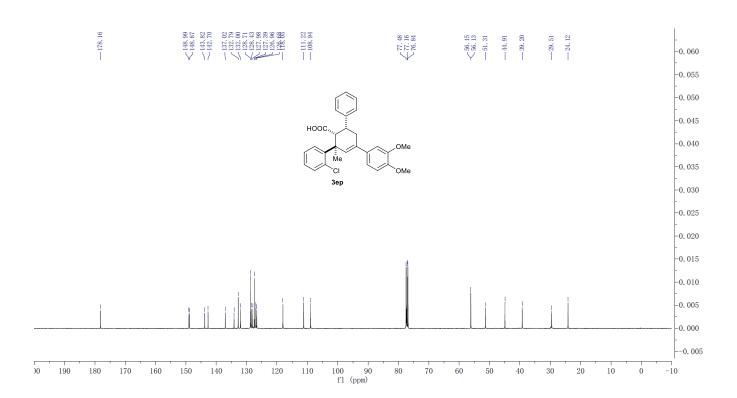


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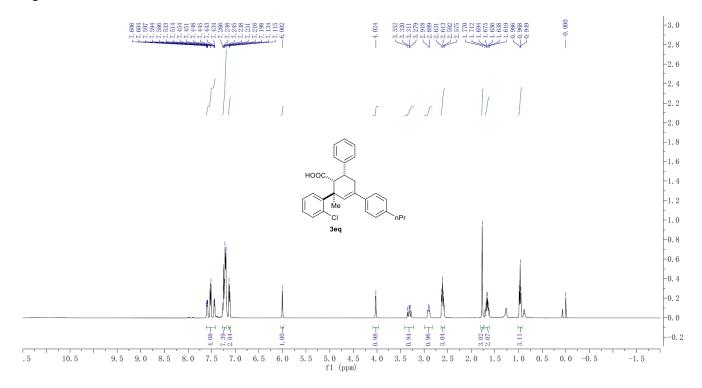


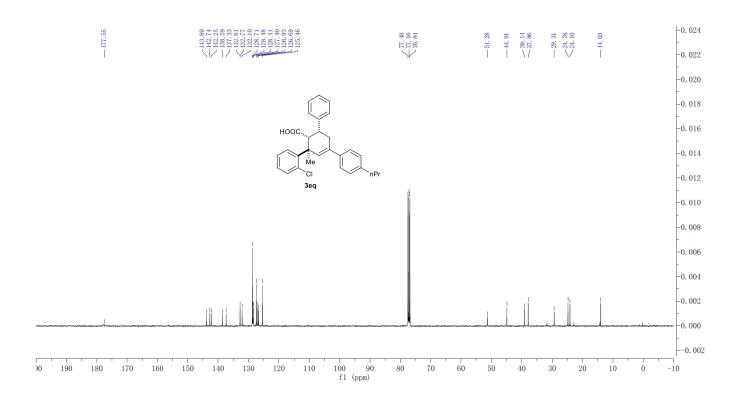




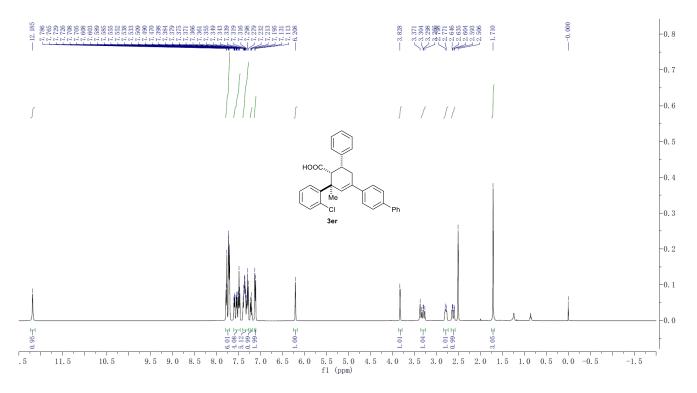


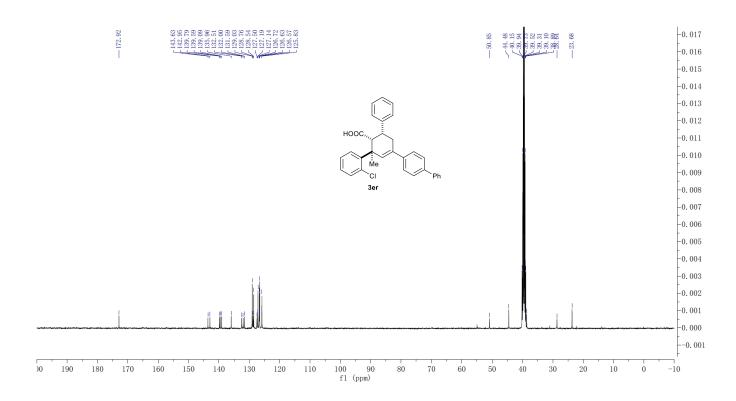


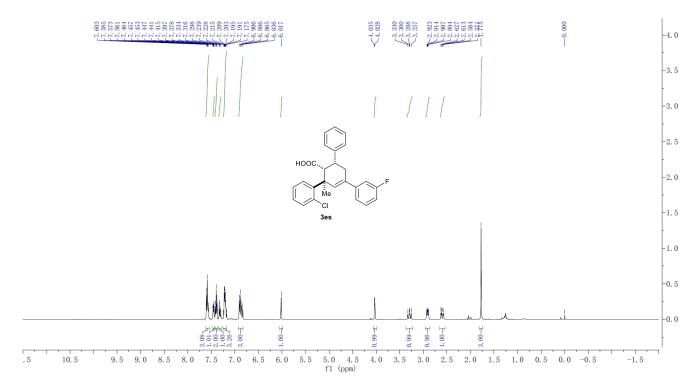


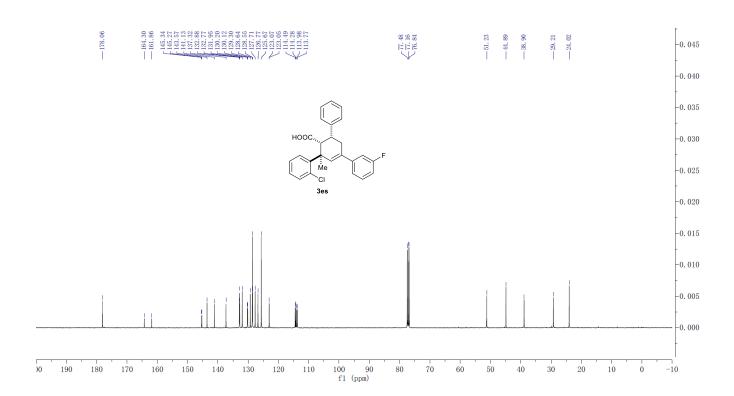


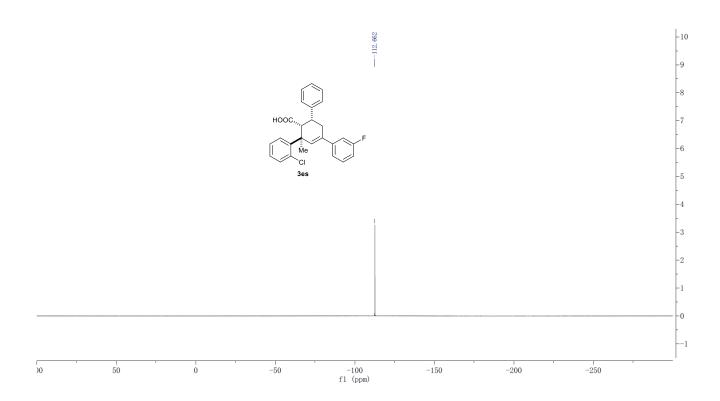
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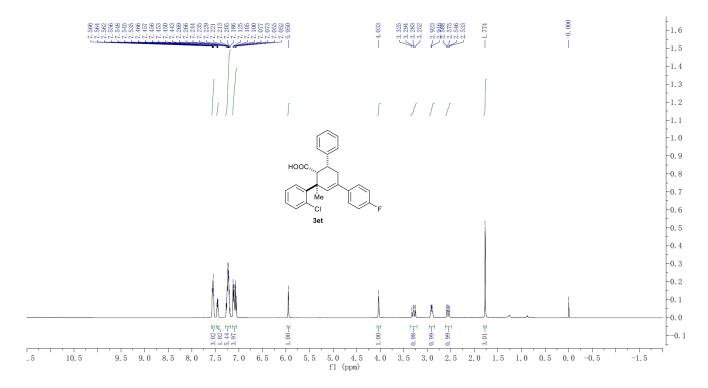


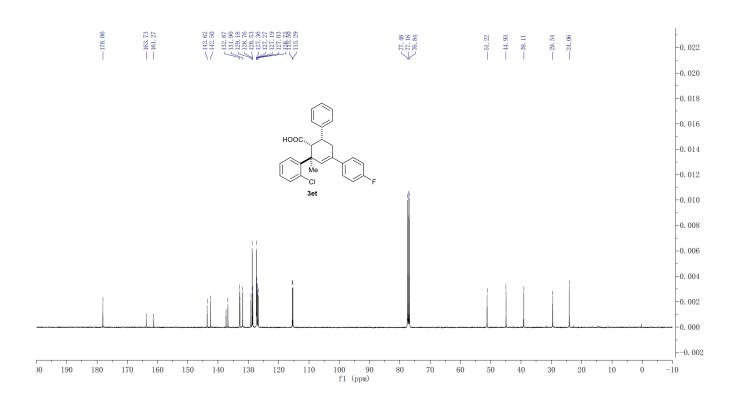


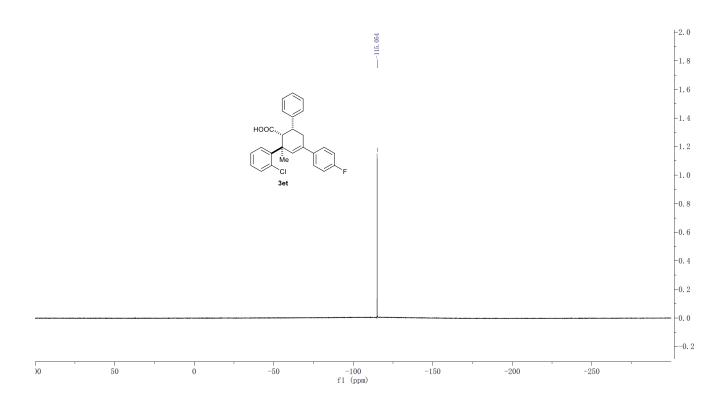




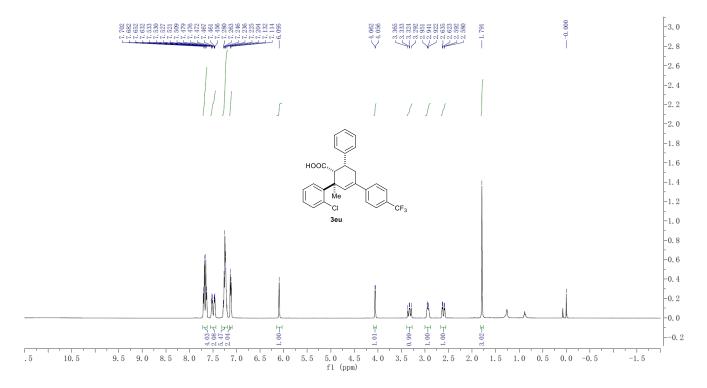


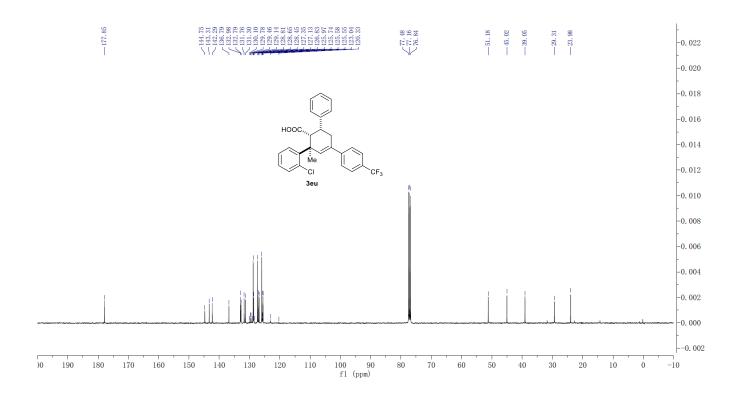


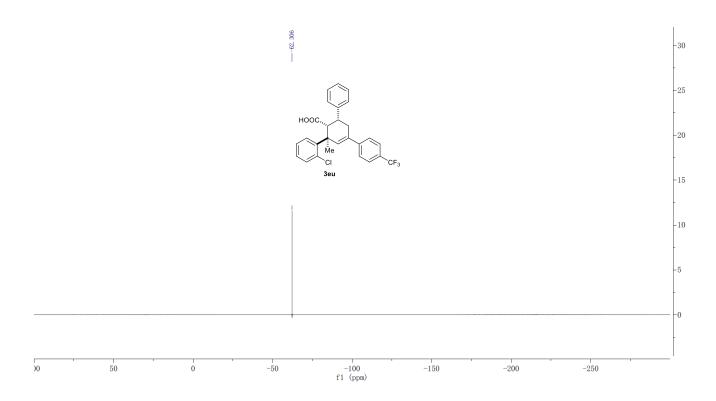




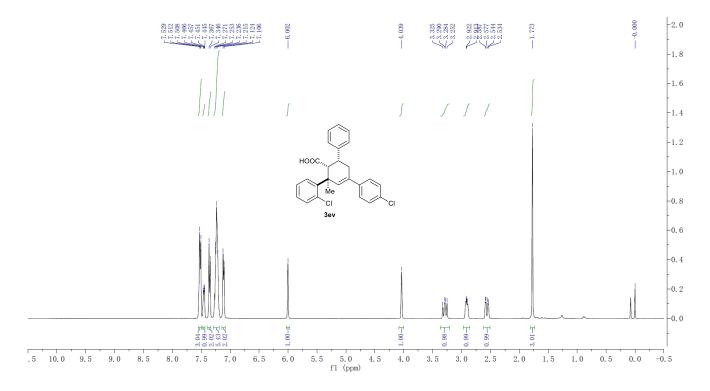
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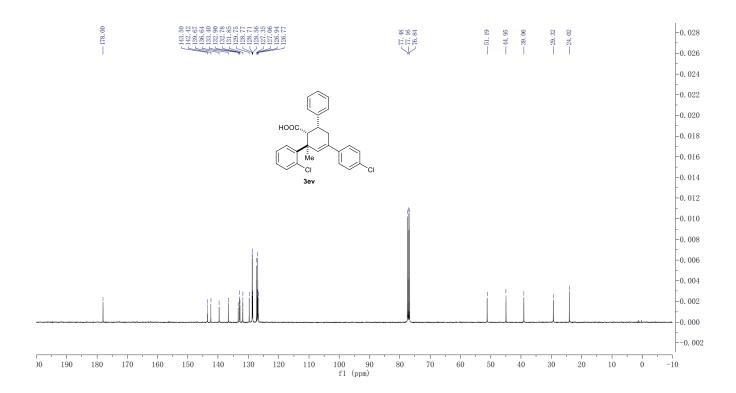




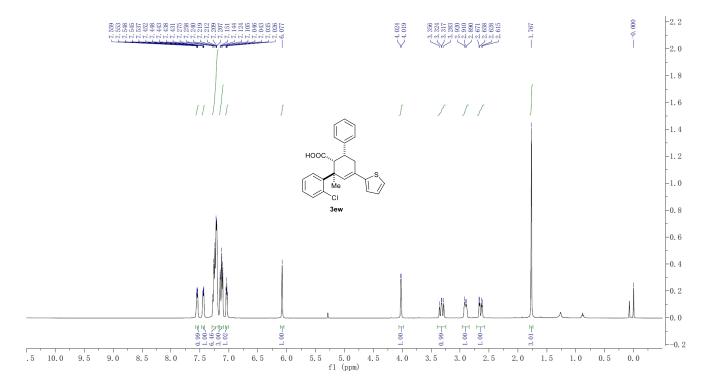


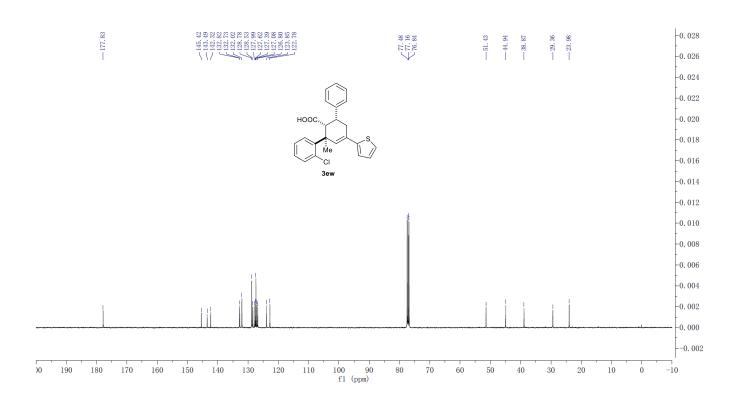
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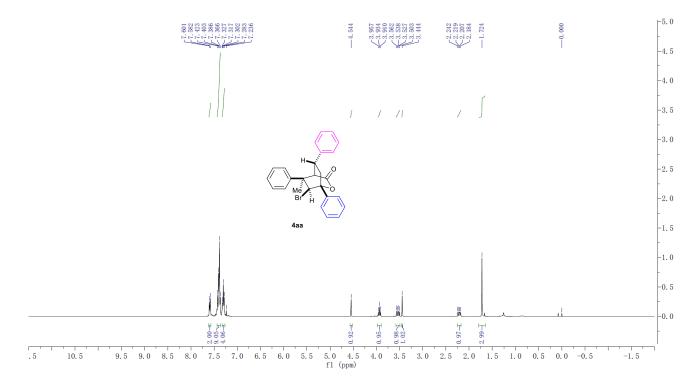


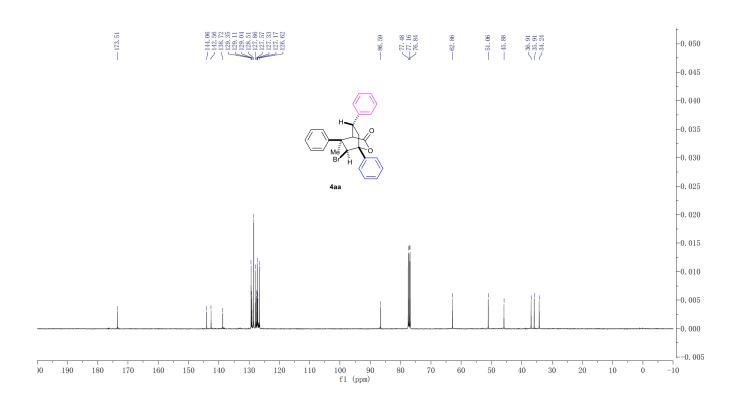
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