Supporting Information

Electrochemically Driven Green Synthesis to Unlock Sustainable Routes to β-Keto Spirolactones

Ian MacLean, [†a] Montaña J. García, [†a] Silvia Cabrera,* [bc] Leyre Marzo,* [ac] José Alemán.*[ac]

[a.] Organic Chemistry Department (Módulo 1) Universidad Autónoma de Madrid, 28049 Madrid (Spain).

[b.] Inorganic Chemistry Department (Módulo 7) Universidad Autónoma de Madrid, 28049 Madrid (Spain)

[c.] Institute for Advanced Research in Chemical Sciences (IAdChem) Universidad Autónoma de Madrid, 28049 Madrid (Spain)

[†] I.M. and M.J.G. contributed equally.

Table of Content

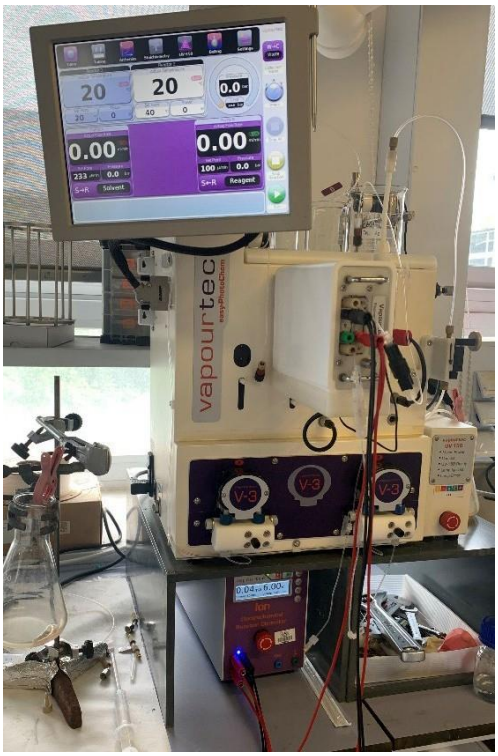
1. General methods and materials

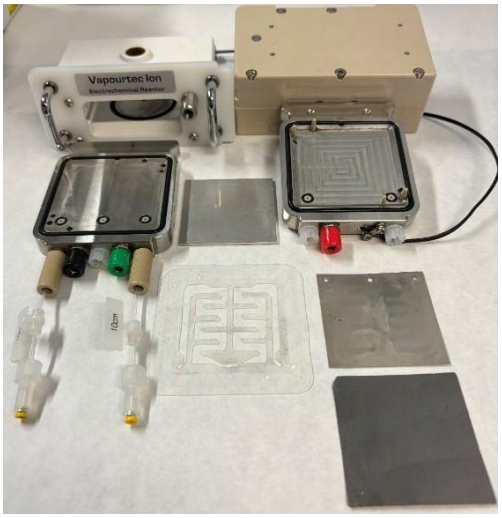
NMR spectra were acquired on a BRUKER AVANCE 300, BRUKER AVANCE-II 300 or BRUKER AVANCE NEO 500 spectrometer running at 300 or 500 MHz for ^{1}H and 75 or 125 MHz for ^{13}C and were internally referenced to residual solvent signals ($CDCl_3$ referenced at δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C-NMR. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, *br* = broad), coupling constant (Hz) and integration. Data for ^{1}H-decoupled and ^{13}C and are reported in terms of chemical shift. The diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture through integration of diagnostic signals. High-Resolution Mass Spectra (HRMS) were obtained on an Agilent Technologies 6120 Quadrupole LC/MS coupled with an SFC Agilent Technologies 1260 Infinity Series instrument for the MS (ESI) (Electrospray Ionization). MassWorks software version 4.0.0.0 (Cerno Bioscience) was used for the formula identification. MassWorks is an MS calibration software which calibrates isotope profiles to achieve high mass accuracy and enables elemental composition determination on conventional mass spectrometers of unit mass resolution allowing highly accurate comparisons between calibrated and theoretical spectra. Commercial grade reagents and solvents were purchased from Acros Organics, Alfa Aesar, Fluorochem, Sigma-Aldrich, BLD Pharm, and TCI Chemicals. Analytical TLC was performed using pre-coated aluminum-backed plates (Merck TLC Silicagel 60 F254) and visualized by ultraviolet irradiation. Chromatographic purification of products was accomplished by flash chromatography using silica gel (Merck Geduran® Si 60) unless another stationary phase is specified.

2. Electrochemical setup

All the electrodes and equipment (ElectraSyn 2.0) used for the batch electrochemical experiments were acquired from IKA.

3. Electrochemical-flow setup



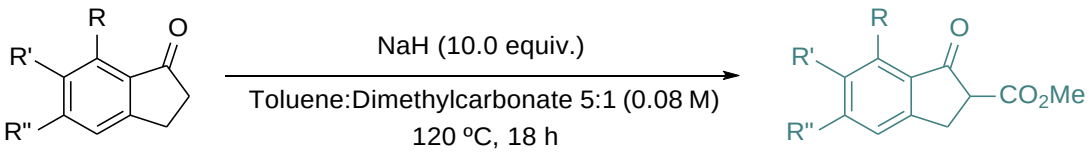


All continuous-flow experiments were carried out using a commercially available Vapourtec Ion electrochemical reactor fixed on an E-series Vapourtec equipment. The reactor has a channel volume of 0.6 mL and was equiped with two electrodes of 5 × 5 cm size with an 0.5 mm spacer. For the study of the flow optimization, the electrodes used were graphite and nickel.

4. General procedures for the synthesis of β-ketoesters and β-ketoamides

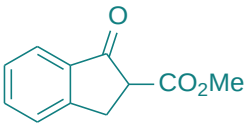
4.1. General procedure A1: Synthesis of β-ketoesters 1a, 1b, 1c, 1e, 1f, 1i

Variation of a procedure described in literature. [1]



The corresponding commercially available ketone (37.8 mmol) was dissolved in a mixture of toluene/dimethyl carbonate (250 mL, 5:1) at room temperature, and then cooled at 0 ºC. Sodium hydride (NaH, 60% in mineral oil, 10.0 equiv.) was added in three portions, and the resulting suspension was stirred at 0 ºC for 10 min. After that time, the reaction was stirred at reflux for 18 h. Then, the reaction mixture was acidified with 1 M aqueous HCl until pH 7 and extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The resulting oily residue was purified by column chromatography to afford the pure β-ketoesters **1a, 1b, 1c, 1e, 1f** and **1i.**

Methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1a)



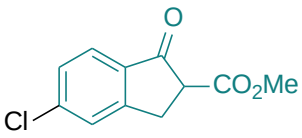
1a

Following the general procedure A1, 2,3-dihydro-1*H*-inden-1-one (5.0 g, 37.8 mmol) and sodium hydride (15.0 g, 378.0 mmol) gave product **1a** (4.6 g, 65 %) as a pale orange solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.63 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 3.75 (dd, *J* = 8.3, 4.0 Hz, 1H), 3.64 – 3.50 (m, 1H), 3.38 (dd, *J* = 17.3, 8.3 Hz, 1H); Representative enol tautomer signals: δ 10.37 (s, 1H), 3.86 (s, 3H).

Spectra data are consistent with those reported in the literature. [1]

Methyl 5-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1b)



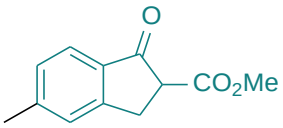
1b

Following the general procedure A1, 5-chloro-1-indanone (1.0 g, 6.0 mmol) and sodium hydride (1.44 g, 60 mmol) gave product **1b** (766 mg, 60 %) as a white solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 1.0 Hz, 1H), 7.31 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.74 (s, 3H), 3.71 (dd, *J* = 8.3, 4.1 Hz, 1H), 3.49 (dd, *J* = 17.5, 4.1 Hz, 1H), 3.30 (dd, *J* = 17.5, 8.3 Hz, 1H); Representative enol tautomer signals: δ 10.25 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 1.1 Hz, 1H), 7.28 – 7.27 (m, 1H), 3.80 (s, 3H), 3.41 (s, 2H).

Spectra data are consistent with those reported in the literature. [2]

Methyl 5-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1c)



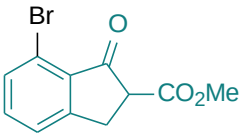
1c

Following the general procedure A1, 5-methyl-1-indanone (1.5 g, 10.3 mmol) and sodium hydride (2.46 g, 102.6 mmol) gave product **1c** (1.01 g, 50%) as an orange solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.29 (s, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 3.78 (s, 3H), 3.72 (dd, *J* = 8.3, 4.0 Hz, 1H), 3.51 (dd, *J* = 17.4, 4.2 Hz, 1H), 3.31 (dd, *J* = 17.2, 8.2 Hz, 1H), 2.44 (s, 3H).

Spectra data are consistent with those reported in the literature. [3]

Methyl 7-bromo-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1e)



1e

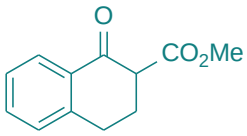
Following the general procedure A1, 7-bromoindan-1-one (0.5 g, 2.4 mmol) and sodium hydride (0.57 g, 23.7 mmol) gave product **1e** (584.9 mg, 92%) as a pale white solid after purification (90:10 CyHex 90:10 EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 6.4, 2.4 Hz, 1H), 7.44 – 7.42 (m, 1H), 7.42 – 7.36 (m, 1H), 3.79 (s, 3H), 3.78 – 3.73 (m, 1H), 3.51 (dd, *J* = 17.5, 4.2 Hz, 1H), 3.32 (dd, *J* = 17.4, 8.5 Hz, 1H);

Representative enol tautomer signals: δ 10.74 (s, 1H), 7.50 – 7.46 (m, 1H), 7.27 – 7.19 (m, 1H), 3.86 (s, 3H), 3.45 (s, 2H).

Spectra data are consistent with those reported in the literature. [2]

Methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (1f)



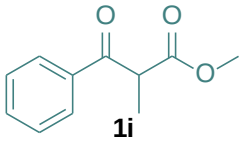
1f

Following the general procedure A1, 1-tetralone (1.0 g, 6.8 mmol) and sodium hydride (1.64 g, 68.4 mmol) gave product **1f** (934.7 mg, 67%) as a white solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) 8.10 – 8.01 (m, 1H), 7.50 (td, *J* = 7.5, 1.5 Hz, 1H), 7.39 – 7.28 (m, 2H), 3.78 (s, 3H), 3.63 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.16 – 2.91 (m, 2H), 2.63 – 2.43 (m, 2H), 2.54 – 2.44 (m, 2H). Representative enol tautomer signals: δ 12.39 (s, 1H), 7.20 – 7.14 (m, 1H), 3.83 (s, 3H).

Spectra data are consistent with those reported in the literature. [1]

Methyl 2-methyl-3-oxo-3-phenylpropanoate (1i)



1i

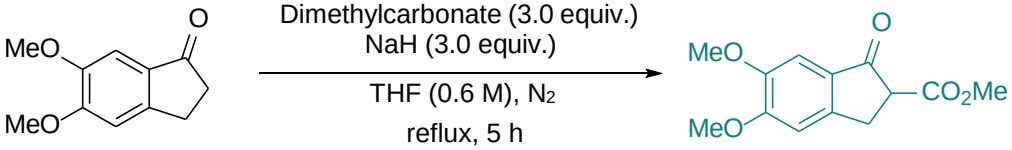
Following the general procedure A1, propiophenone (532.0 μL, 4.0 mmol) and sodium hydride (1.6 g, 40.0 mmol) gave product **1i** (531.0 mg, 69%) as a white solid after purification (90:10 Et_2O/Petroleum ether).

^{1}H NMR (300 MHz, $CDCL_3$) δ 8.03 – 7.93 (m, 2H), 7.65 – 7.53 (m, 1H), 7.54 – 7.42 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 1H), 3.69 (s, 3H), 1.50 (d, *J* = 7.1 Hz, 3H).

Spectra data are consistent with those reported in the literature. [1]

4.2. Synthesis of methyl 5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (1d)

Variation of a procedure described in literature. [4]



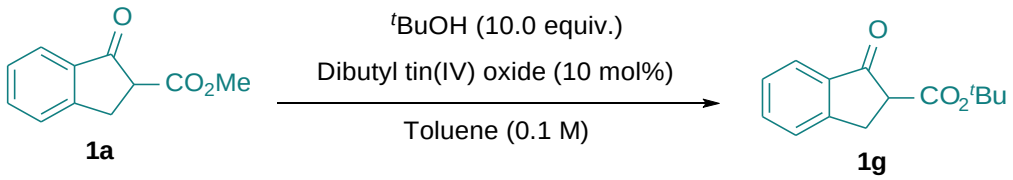
1d

In a round-bottom flask, sodium hydride (60% in mineral oil, 3.0 equiv.) was placed. Then, it was dissolved in dry THF (0.2 mL/mmol NaH) under nitrogen atmosphere, forming a white suspension. Next, dimethyl carbonate (3.0 equiv.) was added to the suspension. Then, a solution of 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (5.0 mmol) in dry THF (1 mL/mol ketone) was added to the reaction mixture dropwise in a period of 3-5 minutes. The reaction mixture was heated to reflux until full conversion of the reagent was observed by TLC (3-5 h). Afterwards, 1 M aq. solution of HCl was added to the mixture until pH=2-3. The aqueous mixture was then extracted with dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (80:20 CyHex/EtOAc) to provide β-keto ester **1d** (985.0 mg, 79%) as a pale brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.91 (s, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 3.79 (s, 3H), 3.73 (dd, *J* = 7.9, 3.6 Hz, 1H), 3.47 (dd, *J* = 17.0, 3.5 Hz, 1H), 3.28 (dd, *J* = 17.0, 7.8 Hz, 1H).

Spectra data are consistent with those reported in the literature. [5]

4.3. Synthesis of tert-butyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (1g) [6]

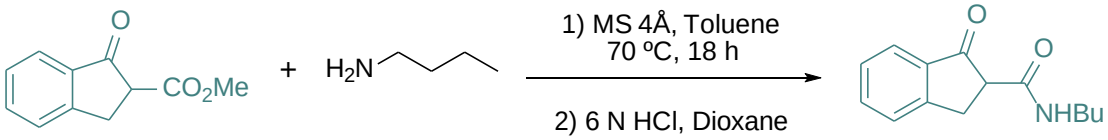


1a **1g**

To a 50 mL round bottom flask **1a** (400 mg, 2.1 mmol), *tert*-butanol (10 equiv.) and dibutyl tin(IV) oxide (10 mol%) were added and dissolved in toluene (0.1 M). The mixture was stirred vigorously at reflux for 3 h. The solution was concentrated til dryness and purified by flash column chromatography on silica gel (95:5 CyHex/EtOAc) to provide the *tert*-butylic β-ketoester (236.1 mg, 48%) as a pink solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.6 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 3.61 (dd, *J* = 8.3, 4.0 Hz, 1H), 3.48 (dd, *J* = 17.3, 4.0 Hz, 1H), 3.31 (dd, *J* = 17.2, 8.2 Hz, 1H), 1.49 (s, 9H); Representative enol tautomer signals: δ 3.43 (s, 2H), 1.58 (s, 9H).

Spectra data are consistent with those reported in the literature.

4.4. Synthesis of N-butyl-1-oxo-2,3-dihydro-1H-indene-2-carboxamide (1h) [7]



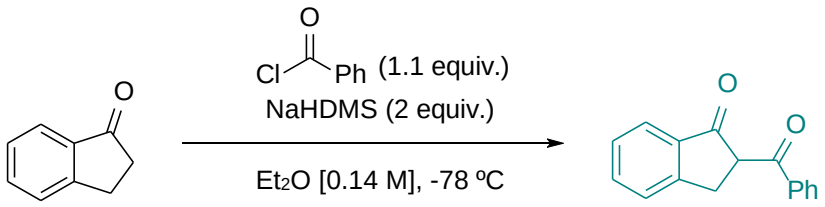
1a **1h**

To a 25 mL round bottom flask, microwave activated MS 4Å, **1a** (1.3 g, 6.8 mmol) and *n*-butylamine (2.37 mL, 24.0 mmol) were dissolved in toluene (22.8 mL) under argon atmosphere. The mixture was heated to 70 ºC and stirred for 18 h. After the completion of the reaction, the mixture was cooled to room temperature and filtered through a pad of Celite®. The filtrate was collected and concentrated until dryness. The residue was purified by column chromatography on silica gel (90:10 CyHex/EtOAc) to give β-ketoamide **1h** (1.1 g, 68%)**.**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.63 (td, *J* = 7.4, 1.3 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.44 – 7.32 (m, 1H), 7.13 (s, 1H), 3.80 (dd, *J* = 17.7, 4.0 Hz, 1H), 3.54 (dd, *J* = 8.3, 3.9 Hz, 1H), 3.41 – 3.34 (m, 1H), 3.36 – 3.25 (m, 2H), 1.59 – 1.48 (m, 2H), 1.44 – 1.31 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H).

Spectra data are consistent with those reported in the literature.

4.5 Synthesis of 2-benzoyl-2,3-dihydro-1H-inden-1-one (1j) [8]



1j

Commercially available 1-Indanone was dissolved in Et_2O (30 mL) under argon atmosphere and was treated with a solution of NaHDMS (3.8 mL of 2 M solution in THF, 7.57 mmol) at -78 ºC. The reaction mixture was stirred for 30 minutes and a solution of the acyl chloride (478 µL, 4.16 mmol) in Et_2O was added dropwise. The reaction mixture was stirred for further 1.5 h. The reaction was quenched with 15 mL of an aqueous solution of NH_4Cl, and the organic layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated until dryness. The crude product was purified by column chromatography on silica gel (97:3 CyHex/EtOAc) to give 2-benzoyl-2,3-dihydro-1H-inden-1-one **1j** (745 mg, 83%) as a brown solid.

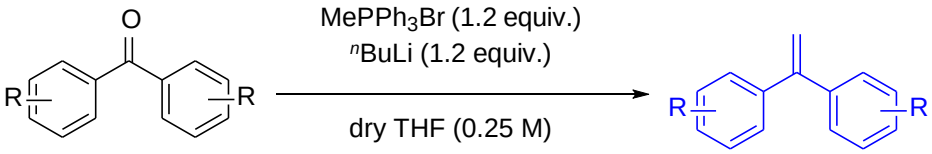
^{1}H NMR (300 MHz, $CDCl_3$) δ 15.07 (s, 1H), 8.06 – 7.81 (m, 3H), 7.70 – 7.34 (m, 6H), 3.92 (s, 2H).

Spectra data are consistent with those reported in the literature.

5. General procedure B: Synthesis of alkenes

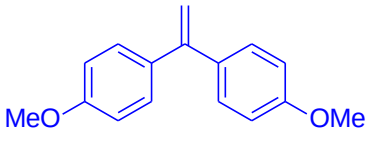
5.1. General procedure B1: Synthesis of aryl alkenes 2b and 2g

Variation of a procedure described in literature. [9]



Methyltriphenylphosphonium bromide (1.9 mmol, 1.2 equiv.) was added to a flame-dried round-bottom flask and dissolved in dry THF (6.3 mL, 0.25 M) under argon atmosphere. To this vigorously stirred heterogeneous solution was added *n*-butyllithium (1.9 mmol of a 2.5 M THF solution, 1.2 equiv.) dropwise at 0 °C. The reaction was allowed to stir at room temperature for 30 min until a bright yellow heterogeneous mixture was achieved. Then, the corresponding 1,1-diarylketone (1.6 mmol) was added slowly at 0 ºC. Upon complete addition, the reaction was stir overnight at room temperature. Then, the reaction mixture was washed with brine and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum until dryness. The residue was purified by silica gel flash chromatography to afford the desired diaryl alkenes **2b, 2g** and **2i**.

4,4'-(Ethene-1,1-diyl)bis(methoxybenzene) (2b)



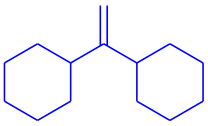
2b

Following the general procedure B1, methyltriphenylphosphonium bromide (685.9 mg, 1.9 mmol), 4,4'-dimethoxybenzophenone (387.6 mg, 1.6 mmol), *n*-buthyllithium (0.77 mL of 2.5 M THF solution, 1.9 mmol) gave product **2b** (299.9 mg, 78%) as a yellow solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 4H), 6.92 – 6.84 (m, 4H), 5.31 (s, 2H), 3.83 (s, 6H).

Spectra data are consistent with those reported in the literature. [10]

Ethene-1,1-diyldicyclohexane (2g)



2g

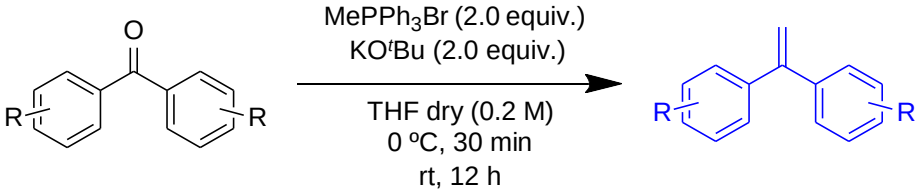
Following the general procedure B1, methyltriphenylphosphonium bromide (2.07 g, 5.8 mmol), ethene-1,1-diyldicyclohexane (582.9 mg, 3.0 mmol), *n*-buthyllithium (2.16 mL of 2.5M THF solution, 5.4 mmol) gave product **2g** (390.2 mg, 68%) as a colourless oil after purification (100 CyHex).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 2H), 1.89 – 1.61 (m, 12H), 1.37 – 1.02 (m, 10H).

Spectra data are consistent with those reported in the literature. [11]

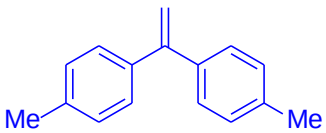
5.2. General procedure B2: Synthesis of aryl alkenes 2c and 2d

Variation of a procedure described in literature. [10]



In a 100 mL round bottom flask with a stirring bar, methyltriphenylphosphonium bromide (2.8 g, 8.0 mmol) and potassium *tert*-butoxide (897.6 mg, 8.0 mmol) were dissolved in 20.0 mL of dry THF at 0 ºC under nitrogen. The reaction mixture was stirred at 0 ºC for 30 min. Then, the corresponding benzophenone (4.0 mmol) was added. The mixture was stirred at room temperature overnight. To quench the reaction, 50 mL of H_2O were added, and the THF was removed under vacuum. 1 M aq. solution of HCl (20.0 mL) was added and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated until dryness. The residue was further purified by flash column chromatography on silica gel (CyHex/EtOAc) to provide the aryl alkenes **2c** and **2d**.

4,4'-(Ethene-1,1-diyl)bis(methoxybenzene) (2c)



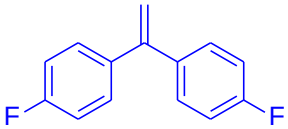
2c

Following the general procedure B2, methyltriphenylphosphonium bromide (2.86 g, 8.0 mmol), di-*p*-tolylmethanone (841.4 mg, 4.0 mmol), potassium *tert*-butoxide (897.7 mg, 8.0 mmol) gave product **2c** (735 mg, 88%) as a colourless oil after purification (99:1 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (dt, *J* = 8.1, 1.9 Hz, 4H), 7.05 (dt, *J* = 7.9, 0.7 Hz, 4H), 5.29 (s, 2H), 2.28 (s, 6H).

Spectra data are consistent with those reported in the literature. [12]

4,4'-(Ethene-1,1-diyl)bis(methoxybenzene) (2d)



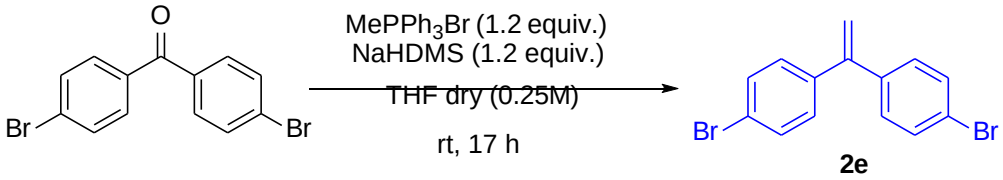
2d

Following the general procedure B2, methyltriphenylphosphonium bromide (2.86 g, 8.0 mmol), di-*p*-tolylmethanone (872.8 mg, 4.0 mmol), potassium *tert*-butoxide (897.7 mg, 8.0 mmol) gave product **2d** (784.9 mg, 91%) as a colourless oil after purification (99:1 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 2H), 7.10 – 6.96 (m, 2H), 5.40 (s, 1H).

Spectra data are consistent with those reported in the literature. [12]

5.3 Synthesis of 4,4'-(ethene-1,1-diyl)bis(bromobenzene) (2e) [13]



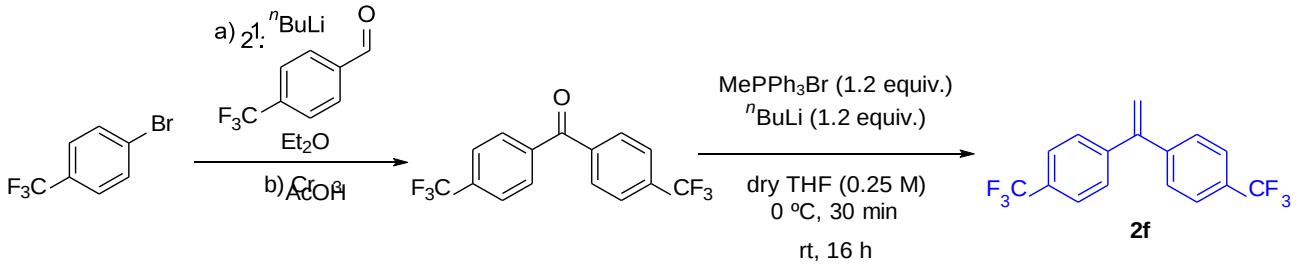
2e

Under argon atmosphere, a 100 mL round bottom flask was charged with methyltriphenylphosphonium bromide (3.5 mmol 1.2 equiv.) and dry THF. Then, sodium hexamethyldisilazide (5.88 mL of 0.6 M THF solution, 3.5 mmol, 1.2 equiv.) was added into the solution and stirred at room temperature for 1 hour. To the solution, 4,4'-dibromobenzophenone (1.00 g, 2.9 mmol) was added and stirred at room temperature for 16 hours. Et_2O was added into the reaction mixture and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (95:5 CyHex/EtOAc) to afford 4,4'-(ethene-1,1-diyl)bis(bromobenzene) **2e** (713.3 mg, 72%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.49 (m, 4H), 7.31 – 7.21 (m, 4H), 5.54 (s, 2H).

Spectra data are consistent with those reported in the literature. [14]

5.4 Synthesis of 4,4'-(ethene-1,1-diyl)bis((trifluoromethyl)benzene) (2f)



2f

1-Bromo-4-(trifluoromethyl)benzene (1.5g, 6.66 mmol) was dissolved in Et_2O (14 mL, 0.5 M) under argon atmosphere. The solution was cooled to -78 ºC and *n*-butyllithium (2.7 mL, 2.5M in *n*-hexane 1.1 equiv.) was added dropwise and stirred for 1 h. A solution of 4-(trifluoromethyl)benzaldehyde (6.7 mmol, 1.1 equiv.) in Et_2O (1.4 mL) was added dropwise at -78 °C and stirred for 3 h. After this time, the solution was able to warm to room temperature. The resulting mixture was quenched with 10 mL of an aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted (3 x 10 mL) with

Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated until dryness under vacuum. The product was used directly for next step without further purification.

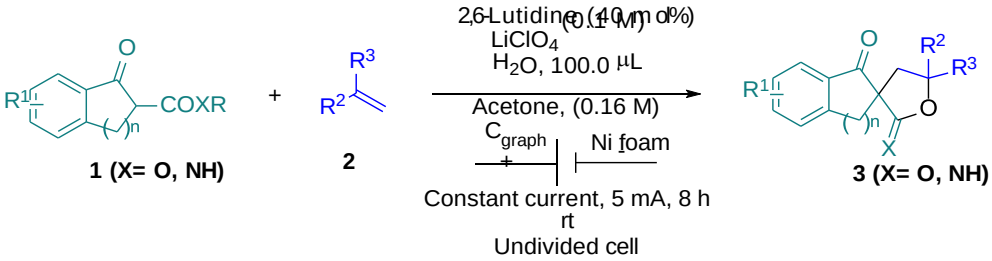
Bis(4-(trifluoromethyl)phenyl)methanol was dissolved in glacial acetic acid (8.5 mL) in a 25 mL round-bottom flask equipped with a condenser. CrO_3 (7.33 mmol, 1.1 equiv.) was added at room temperature and the solution was heated at 70 °C for 2 h. The reaction mixture was diluted with 10 mL of water and extracted with *n*-hexane (3 x 10 mL). The combined organic layers were washed with aqueous solution of NaOH 2M until the washings remained basic, dried over anhydrous $MgSO_4$, filtered, and concentrated until dryness under vacuum. The reaction crude was purified by flash column chromatography on silica gel (98:2 CyHex/EtOAc) to afford a colourless solid (1.32 g, 63%).

Methyltriphenylphosphonium bromide (1.9 mmol, 1.2 equiv.) was added to a flame-dried round-bottom flask and dissolved in THF (6.3 mL, 0.25 M) under argon atmosphere. To this vigorously stirred heterogeneous solution was added *n*-butyllithium (0.75 mL of 2.5M solution in *n*-hexane, 1.2 equiv.) in dropwise at 0 °C. The reaction was allowed to stir at room temperature for 30 min until a bright yellow heterogeneous mixture was achieved. Then, the corresponding 1,1-diarylketone (1.6 mmol) was added slowly. Upon complete addition, the cooling bath was removed, and the reaction was allowed to stir overnight. Then, the reaction mixture was washed with brine and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel flash chromatography (99:1 CyHex/EtOAc) to afford the alkene **2f** (383.4 mg, 77%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.54 (m, 4H), 7.46 – 7.34 (m, 4H), 5.60 (s, 2H).

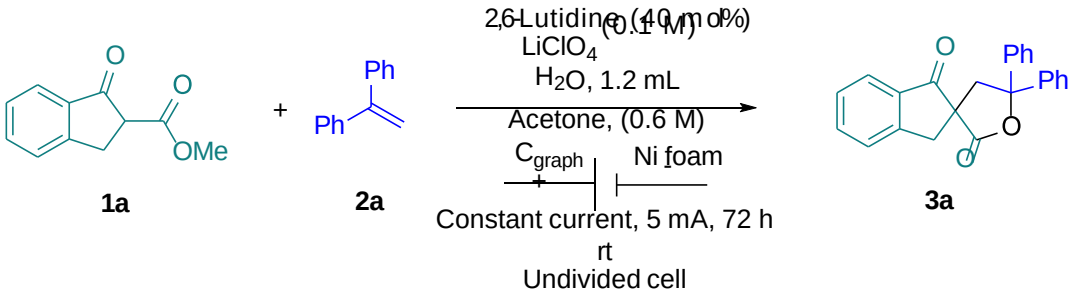
Spectra data are consistent with those reported in the literature. [15]

6 General procedure C for the formation of β-ketospirolactones and acetals



A 5 mL ElectraSyn vial with a stir bar was charged with a solution of the corresponding *β*-ketoester (0.5 mmol, 1.0 equiv.), lithium perchlorate (0.3 mmol, 0.6 equiv.) and the corresponding olefin (1.0 mmol, 2 equiv.) in dry acetone (3.0 mL, 0.16 M). Then, 2,6-lutidine (0.2 mmol, 40 mol%) and H_2O (100.0 µL) were added. The ElectraSyn vial was equipped with a graphite electrode (8 mm wide, 50 mm length, 1 mm thickness, anode), a nickel foam electrode (8 mm wide, 50 mm length, 1 mm thickness, cathode) and sealed. The reaction mixture was electrolyzed under galvanostatic conditions (5 mA, 8 h, 2.94 F/mol). After the reaction completion, the ElectraSyn vial cap was removed and the electrodes were rinsed with acetone, which was combined with the crude mixture. The crude mixture was filtrated over Celite®, washed with acetone and the filtrate was concentrated under reduced pressure. The product was purified by flash column chromatography to give the corresponding β-ketospirolactone.

7 Gram scale batch procedure for the formation of β-ketospirolactone 3a



A 10 mL ElectraSyn vial with a stir bar was charged with a solution of methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1a** (6.0 mmol, 1.0 equiv.), lithium perchlorate (1.0 mmol, 0.16 equiv.) and diphenylethylene **2a** (12.0 mmol, 2 equiv.) in dry acetone (8.8 mL, 0.6 M). Then, 2,6-lutidine (2.4 mmol, 40 mol%) and H_2O (1.2 mL) were added. The ElectraSyn vial was equipped with a graphite electrode (8 mm wide, 50 mm length, 1 mm thickness, anode), a nickel foam electrode (8 mm wide, 50 mm length, 1 mm thickness, cathode) and sealed. The reaction mixture was electrolyzed under galvanostatic conditions (5 mA, 72 h, 2.30 F/mol). After the reaction completion, the ElectraSyn vial cap was removed and the electrodes were rinsed with acetone, which was combined with the crude mixture. The crude mixture was filtrated over Celite®, washed with acetone and the filtrate was concentrated under reduced pressure. The product was purified by flash column chromatography to give 5,5-diphenyl-4,5-dihydro-2H-spiro[furan-3,2'-indene]-1',2(3'H)-dione **3a** (1.8309 g, 86%) as a white solid.

8. Synthesis of β-ketospirolactones under continuous-flow conditions

8.1 Optimization

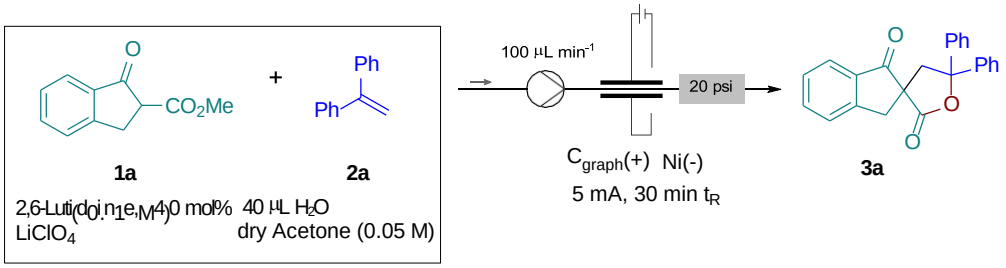
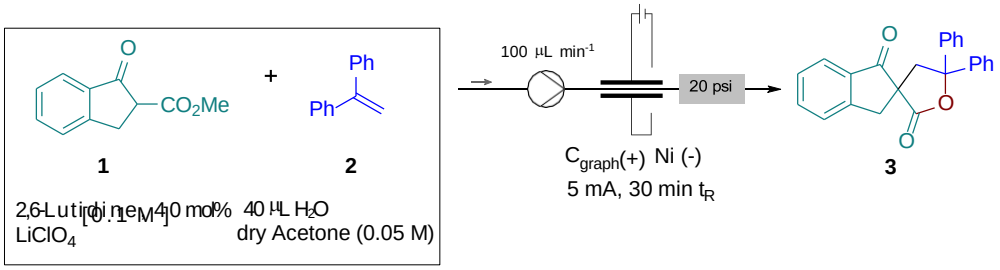


Table S 1. Optimization of the electro-flow synthesis of β-spirolactones[a]

Entry	Deviation from optimized conditions	Yield (%)
1	No deviation	69
2	t_R=80 min	70
3[b]	t_R=45 min	49
4[c]	t_R=6 min	-
5	0.16 M instead of 0.05 M	35
6	7.0 mA instead of 5.0 mA	65

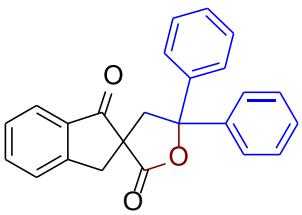
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol). 2,6-lutidine (40 mol %), $LiClO_4$ (0.1 M) and H_2O (40 µL) at constant current (5.0 mA) in dry acetone (0.05 M) at room temperature for 30 min of residence time, using C_{graph} as anode and Ni as cathode in a recirculating system. [b] 40 °C. [c] Single-pass flow setup.

8.2 General procedure D: Electro-flow synthesis of spirolactones



The corresponding β-ketoester (0.2 mmol), lithium perchlorate (0.35 mmol, 0.1 M) and the corresponding olefin (0.4 mmol, 2.0 equiv.) was dissolved in dry acetone (3.6 mL, 0.05 M). Then, 2,6-lutidine (0.08 mmol, 40 mol%) and H_2O (40.0 µL) were added, and the mixture was sonicated prior to the electrolysis to ensure complete dissolution. The mixture was pumped through the electrochemical reactor at 100.0 µL min^{-1} applying a constant current of 5 mA. The pressure of the system was controlled using a 20 psi back pressure regulator (BPR). The resulting solution was recirculated until the reaction finish. The crude mixture was filtrated over Celite®, washed with acetone and the filtrate was concentrated under reduced pressure until dryness. The crude was purified by flash column chromatography to give the corresponding product.

5,5-Diphenyl-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3a)



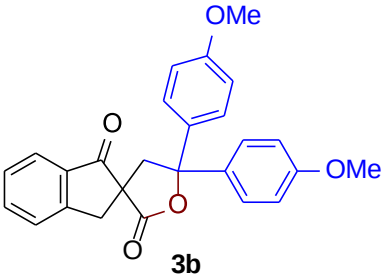
3a

Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol) and diphenylethylene **2a** (177.0 µL, 1.0 mmol) gave product **3a** (136.0 mg, 98%) as a white solid after purification (80:20 CyHex/EtOAc). The compound **3a** (421.0 mg, 45%, 0.1750 mmol/h) was also achieved from **1a** (2.63 mmol) after the scale-up of the reaction under electro-flow conditions (t_R = 6.8 h).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.67 – 7.51 (m, 3H), 7.51 – 7.28 (m, 10H), 3.66 (d, *J* = 13.0 Hz, 1H), 3.24 (d, *J* = 17.5 Hz, 1H), 3.11 (d, *J* = 13.1 Hz, 1H), 2.74 (d, *J* = 17.5 Hz, 1H).

Spectra data are consistent with those reported in the literature. [16]

Methyl 2-(2,2-bis(4-methoxyphenyl)vinyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate--5,5-bis(4-methoxyphenyl)-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3b)



3b

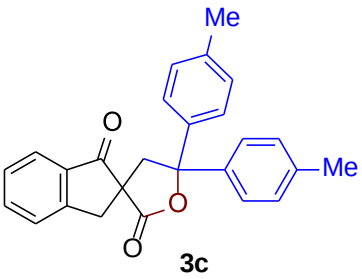
Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (56.1 mg, 0.3 mmol) and 4,4'-(ethene-1,1-diyl)bis(methoxybenzene) **2b** (140.8 mg, 0.6 mmol) gave product **3b** (91.4 mg, 73%) as a white solid after purification (80:20 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.3 Hz, 1H), 7.60 (td, *J* = 7.4, 1.3 Hz, 1H), 7.44 – 7.38 (m, 3H), 7.37 – 7.31 (m, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.60 (d, *J* = 13.0 Hz, 1H), 3.23 (d, *J* = 17.5 Hz, 1H), 3.01 (d, *J* = 13.1 Hz, 1H), 2.75 (d, *J* = 17.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 175.7, 159.4, 159.3, 152.7, 135.9, 135.6, 135.4, 135.3, 128.3, 127.5 (2C), 126.9 (2C), 126.4, 125.1, 114.2 (2C), 113.9 (2C), 88.4, 58.0, 55.5, 55.4, 47.4, 39.8.

HRMS (ESI$^+$) Calculated for $C_{26}H_{23}O_5$ $[M + H]^+$: 415.1467, found: 415.1540

5,5-Di-*p*-tolyl-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3c)



3c

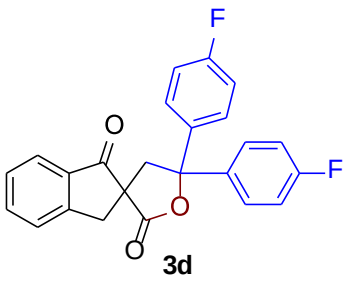
Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), 4,4'-(ethene-1,1-diyl)bis(methylbenzene) **2c** (208.1 mg, 1.0 mmol) and gave product **3c** (145 mg, 76%) as a white solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.60 (td, *J* = 7.5, 1.3 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.37 – 7.30 (m, 3H), 7.27 – 7.12 (m, 4H), 3.62 (d, *J* = 13.0 Hz, 1H), 3.24 (d, *J* = 17.5 Hz, 1H), 3.06 (d, *J* = 13.0 Hz, 1H), 2.75 (d, *J* = 17.5 Hz, 1H), 2.38 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 201.6, 175.6, 152.7, 140.8, 140.5, 138.0, 137.9, 135.7, 135.4, 129.6 (2C), 129.3 (2C), 128.3, 126.4, 125.9 (2C), 125.5 (2C), 125.2, 88.5, 57.9, 5.19, 39.8, 21.2.

HRMS (ESI$^+$): Calculated for $C_{25}H_{21}O_3$ $[M + H]^+$: 369.1412, found: 369.1485

5,5-Bis(4-fluorophenyl)-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3d)



3d

Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol) and 4,4'-(ethene-1,1-diyl)bis(fluorobenzene) **2d** (216.1 mg, 1.0 mmol) gave product **3d** (184.3 mg, 95%) as a white solid after purification (90:10 CyHex/EtOAc).

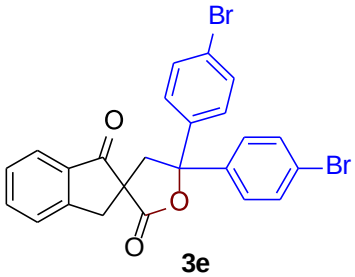
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.62 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.44 – 7.32 (m, 4H), 7.20 – 6.99 (m, 4H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.26 (d, *J* = 17.4 Hz, 1H), 3.05 (d, *J* = 13.2 Hz, 1H), 2.76 (d, *J* = 17.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.2, 175.1, 162.51 (d, $J_{C\text{-}F}$ = 248.1 Hz), 162.49 (d, $J_{C\text{-}F}$ = 248.6 Hz), 152.4, 139.2 (d, *J* = 3.3 Hz), 138.9 (d, *J* = 3.3 Hz), 136.1, 135.0, 128.5, 127.8 (d, $J_{C\text{-}F}$ = 3.3 Hz, 2C), 127.4 (d, $J_{C\text{-}F}$ = 8.2 Hz, 2C), 126.4, 125.2, 116.1 (d, $J_{C\text{-}F}$ = 21.6 Hz, 2C), 115.7 (d, $J_{C\text{-}F}$ = 21.7 Hz, 2C), 87.5, 57.7, 47.2, 39.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -113.42

HRMS (ESI$^+$): Calculated for $C_{24}H_{17}F_2O_3$ $[M + H]^+$: 391.1068, found: 391.1140

5,5-Bis(4-bromophenyl)-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3e)



3e

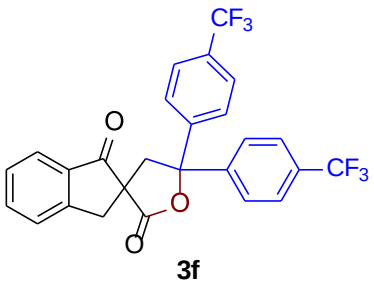
Following the general procedure C, Methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), and 4,4'-(ethene-1,1-diyl)bis(bromobenzene) **2e** (338.0 mg, 1 mmol) gave product **3e** (252.1 mg, 98%) as a white solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.6 Hz, 1H), 7.63 (td, *J* = 7.5, 1.2 Hz, 1H), 7.61 – 7.26 (m, 10H), 3.59 (d, *J* = 13.2 Hz, 1H), 3.27 (d, *J* = 17.4 Hz, 1H), 3.04 (d, *J* = 13.2 Hz, 1H), 2.77 (d, *J* = 17.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 174.9, 152.4, 142.3, 141.7, 136.2, 134.9, 132.4 (2C), 132.0 (2C), 128.6, 127.5 (2C), 127.1 (2C), 126.5, 125.3, 122.7, 87.4, 57.5, 46.8, 39.8.

HRMS (ESI$^+$) Calculated for $C_{24}H_{17}Br_2O_3$ $[M + H]^+$: 510.9466, found: 510.9519

5,5-Bis(4-(trifluoromethyl)phenyl)-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3f)



3f

Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), and 4,4'-(ethene-1,1-diyl)bis((trifluoromethyl)benzene) **2f** (316.0 mg, 1.0 mmol) gave product **3f** (233.3 mg, 94%) as a white solid after purification (80:20 CyHex/EtOAc).

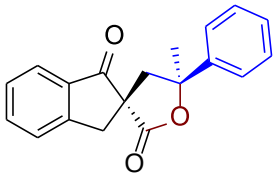
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.76 – 7.55 (m, 9H), 7.52 – 7.34 (m, 2H), 3.68 (d, *J* = 13.2 Hz, 1H), 3.31 (d, *J* = 17.3 Hz, 1H), 3.16 (d, *J* = 13.2 Hz, 1H), 2.80 (d, *J* = 17.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 174.5, 152.2, 147.0, 146.3, 136.3, 134.8, 131.0 (q, *J* = 32.8 Hz) 130.8 (q, *J* = 32.8 Hz), 128.6, 126.5, 126.3 (q, *J* = 3.7 Hz, 4C) 126.0 (m, 4C), 125.8, 125.3, 123.9 (q, *J* = 272.2 Hz), 123.8 (q, *J* = 272.4 Hz), 87.0, 57.3, 46.6, 39.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.68, -62.73.

HRMS (ESI^{+}) Calculated for $C_{26}H_{17}F_6O_3$ $[M + H]^{+}$: 491.1004, found: 491.1076

***trans*-5-(4,4-Methylphenyl)-4,5-dihydro-2*H*-spiro[furan-3,2′-indene]-1′,2(3′*H*)-dione (*trans*-3g)**



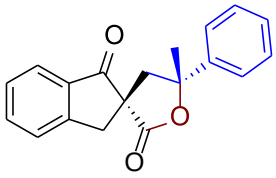
***trans*-3g**

Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), *α*-methylstyrene (130 µL, 1 mmol) gave product ***trans*-3g** (66.5 mg, 46%) as a white solid after purification (80:20 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.59 (td, *J* = 7.5, 1.3 Hz, 1H), 7.46 – 7.30 (m, 7H), 3.33 (d, *J* = 17.4 Hz, 1H), 3.14 (d, *J* = 13.1 Hz, 1H), 2.75 – 2.59 (m, 2H), 1.91 (s, 3H).

Spectra data are consistent with those reported in the literature. [16]

***cis*-5-(4,4-Methylphenyl)-4,5-dihydro-2*H*-spiro[furan-3,2′-indene]-1′,2(3′*H*)-dione (*cis*-3g)**



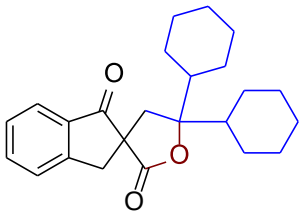
***cis*-3g**

Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), *α*-methylstyrene (130 µL, 1 mmol) gave product ***cis*-3g** (60.2 mg, 41%) as a white solid after purification (80:20 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.65 (td, *J* = 7.4, 1.2 Hz, 1H), 7.56 – 7.27 (m, 7H), 3.87 (d, *J* = 17.0 Hz, 1H), 3.34 (d, *J* = 17.0 Hz, 1H), 3.21 (d, *J* = 13.3 Hz, 1H), 2.55 (d, *J* = 13.2 Hz, 1H), 1.83 (s, 3H).

Spectra data are consistent with those reported in the literature. [16]

5,5-Dicyclohexyl-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3h)



3h

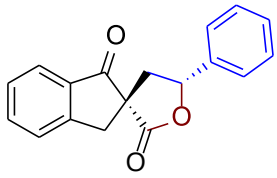
Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), ethene-1,1-diyldicyclohexane **2g** (130.0 µL, 1.0 mmol) gave product **3h** (10.9 mg, 6%) as a white solid after purification (98:2 CyHex/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.64 (td, *J* = 7.5, 1.4 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 3.77 (d, *J* = 16.9 Hz, 1H), 3.20 (d, *J* = 16.8 Hz, 1H), 2.94 (d, *J* = 14.2 Hz, 1H), 2.05 (d, *J* = 14.2 Hz, 1H) 2.07 – 2.00 (m, 1H), 1.88 – 1.69 (m, 10H), 1.30 – 1.06 (m, 11H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2, 176.3, 152.5, 135.8, 135.3, 128.3, 126.2, 125.2, 91.4, 58.2, 43.8, 43.6, 42.9, 36.5, 27.0, 27.0, 26.9, 26.8 (2C), 26.7, 26.6, 26.5 (2C), 26.4.

HRMS (ESI$^+$) Calculated for $C_{24}H_{31}O_3$ $[M + H]^+$: 367.2195, found: 367.2268

***cis*-5-Phenyl-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (*cis*-3i)**



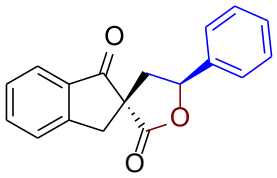
***cis*-3i**

Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), styrene (114.6 µL, 1.0 mmol) gave product ***cis*-3i** (76.6 mg, 55%) as a white solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.57 – 7.30 (m, 7H), 5.60 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.78 (d, *J* = 17.1 Hz, 1H), 3.34 (d, *J* = 17.0 Hz, 1H), 2.99 (dd, *J* = 13.3, 10.0 Hz, 1H), 2.63 (dd, *J* = 13.3, 6.6 Hz, 1H).

Spectra data are consistent with those reported in the literature. [17]

***trans*-5-Phenyl-4,5-dihydro-2H-spiro[furan-3,2'-indene]-1',2(3'H)-dione (*trans*-3i)**



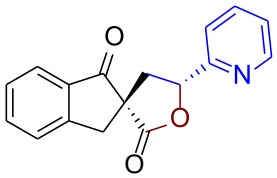
***trans*-3i**

Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), styrene (114.6 µL, 1.0 mmol) gave product ***trans*-3i** (45.1 mg, 33%) as a white solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.48 – 7.34 (m, 6H), 6.08 (dd, *J* = 9.9, 6.6 Hz, 1H), 3.84 (d, *J* = 17.2 Hz, 1H), 3.14 – 2.99 (m, 2H), 2.39 (dd, *J* = 12.9, 9.9 Hz, 1H).

Spectra data are consistent with those reported in the literature. [17]

<u>*cis*-5-(Pyridin-2-yl)-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione</u> (*cis*-3j)



***cis*-3j**

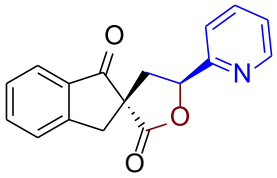
Following the general procedure C, ethyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), 2-vinylpyridine (108.0 µL, 1.0 mmol) gave product ***cis*-3j** (44.7 mg, 32%) as a pale-yellow solid after purification (80:20 Toluene/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.86 – 7.76 (m, 2H), 7.70 – 7.60 (m, 2H), 7.53 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.33 – 7.26 (m, 1H), 5.72 (t, *J* = 7.8 Hz, 1H), 3.79 (d, *J* = 17.0 Hz, 1H), 3.32 (d, *J* = 17.2 Hz, 1H), 3.03 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.84 (dd, *J* = 13.5, 7.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 175.8, 158.6, 152.4, 149.3, 137.3, 136.1, 135.0, 128.5, 126.6, 125.2, 123.4, 120.3, 79.3, 57.3, 40.4, 39.3.

HRMS (ESI$^+$) Calculated for $C_{17}H_{14}NO_3$ $[M + H]^+$: 280.0895, found: 280.0968

***<u>trans</u>*-5-(Pyridin-2-yl)-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (*trans*-3j)**



***trans*-3j**

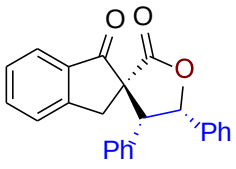
Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), 2-vinylpyridine (108.0 µL, 1.0 mmol) gave product ***trans*-3j** (41.9 mg, 30%) as a pale-yellow solid after purification (80:20 Toluene/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 – 8.61 (m, 1H), 7.85 – 7.73 (m, 2H), 7.70 – 7.63 (m, 1H), 7.55 – 7.40 (m, 3H), 7.30 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 6.06 (dd, *J* = 8.6, 6.9 Hz, 1H), 3.80 (d, *J* = 17.6 Hz, 1H), 3.21 – 3.07 (m, 2H), 2.73 (dd, *J* = 13.1, 8.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 175.0, 157.7, 153.3, 149.9, 137.2, 136.1, 134.3, 128.4, 126.6, 125.3, 123.7, 121.5, 79.2, 58.3, 39.3, 38.1.

HRMS (ESI$^+$) Calculated for $C_{17}H_{14}NO_3$ $[M + H]^+$: 280.0895, found: 280.0968

<u>(3*S*,4*R*,5*S*)*-5-(3-Phenyl-4-phenyl)-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione</u> ((3*S*,4*R*,5*S*)*-3k)



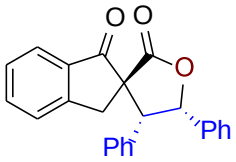
(3*S*,4*R*,5*S*)*-3k

Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), (*E*)-stilbene (158.0 µL, 1.0 mmol) gave product **(3*S*,4*R*,5*S*)*-3k** (28.3 mg, 16%) as a white solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.56 (td, *J* = 7.5, 1.3 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.40 – 7.30 (m, 5H), 7.23 (m, 3H), 7.17 – 7.11 (m, 2H), 5.88 (d, *J* = 10.2 Hz, 1H), 4.59 (d, *J* = 10.3 Hz, 1H), 3.42 (d, *J* = 17.0 Hz, 1H), 3.09 (d, *J* = 17.0 Hz, 1H).

Spectra data are consistent with those reported in the literature. [16]

(3*R*,4*R*,5*S*)*-5-(3-Phenyl-4-phenyl)-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione ((3*R*,4*R*,5*S*)*-3k)



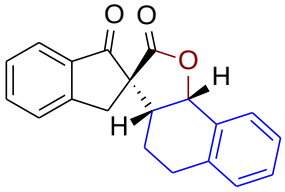
(3*R*,4*R*,5*S*)*-3k

Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), (*E*)-stilbene (158.0 µL, 1.0 mmol) gave product **(3*R*,4*R*,5*S*)*-3k** (65.6 mg, 37%) as a white solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 1H), 7.52 (td, *J* = 7.4, 1.3 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.33 – 7.28 (m, 8H), 7.19 – 7.13 (m, 3H), 6.56 (d, *J* = 11.0 Hz, 1H), 3.92 (d, *J* = 17.2 Hz, 1H), 3.75 (d, *J* = 10.9 Hz, 1H), 3.25 (d, *J* = 17.4 Hz, 1H).

Spectra data are consistent with those reported in the literature. [16]

(2*R*,3*R*,9*S*)*-3a',4',5',9b'-Tetrahydro-2'*H*-spiro[indene-2,1'-naphtho[2,1-b]furan]-1,2'(3*H*)-dione ((2*R*,3*R*,9*S*)*-3l)



(2*R*,3*R*,9*S*)*-3l

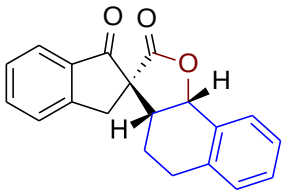
Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), 1,2-dihydronaphthalene (131 µL, 1.0 mmol) gave product **(2*R*,3*R*,9*S*)*-3l** (37.3 mg, 25%) as a white solid after purification (92:8 CyHex/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.66 (td, *J* = 7.4, 1.2 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.17 (d, *J* = 6.7 Hz, 1H), 5.55 (d, *J* = 5.3 Hz, 1H), 3.71 (d, *J* = 16.6 Hz, 1H), 3.46 (d, *J* = 16.8 Hz, 1H), 2.86 (dt, *J* = 16.5, 3.7 Hz, 1H), 2.70 (dt, *J* = 13.0, 5.0 Hz, 1H), 2.60 (ddd, *J* = 16.8, 12.9, 4.4 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.93 – 1.85 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6, 175.4, 151.2, 137.8, 136.5, 135.7, 130.9, 130.3, 129.3, 128.8, 128.5, 126.8, 126.5, 124.7, 77.1, 61.5, 48.1, 39.3, 28.2, 22.0.

HRMS (ESI$^+$) Calculated for $C_{20}H_{17}O_3$ $[M + H]^+$: 305.1099, found: 305.1172

(2*S*,3*R*,9*S*)*-3a',4',5',9b'-Tetrahydro-2'*H*-spiro[indene-2,1'-naphtho[2,1-b]furan]-1,2'(3*H*)-dione ((2*S*,3*R*,9*S*)*-3l)



(2*S*,3*R*,9*S*)*-3l

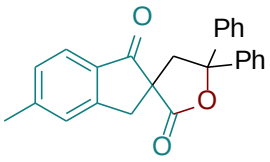
Following the general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), 1,2-dihydronaphthalene (131.0 µL, 1.0 mmol) gave product **(2*S*,3*R*,9*S*)*-3l** (40.8 mg, 27%) as a white solid after purification (92:8 CyHex/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.17 (dd, *J* = 5.4, 3.6 Hz, 1H), 6.25 (d, *J* = 5.5 Hz, 1H), 3.57 (d, *J* = 17.2 Hz, 1H), 3.34 (d, *J* = 17.2 Hz, 1H), 2.96 (dt, *J* = 13.4, 5.0 Hz, 1H), 2.90 (dt, *J* = 16.5, 3.8 Hz, 1H), 2.76 (ddd, *J* = 16.8, 13.0, 4.3 Hz, 1H), 2.05 (dq, *J* = 12.4, 4.3 Hz, 1H), 1.64 – 1.56 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.5, 174.2, 153.3, 137.2, 136.1, 134.2, 131.4, 130.8, 129.1, 128.6, 128.3, 127.0, 126.6, 125.2, 77.2, 64.7, 43.0, 32.1, 28.3, 22.7.

HRMS (ESI$^+$) Calculated for $C_{20}H_{17}O_3$ $[M + H]^+$: 305.1099, found: 305.1172

5'-Methyl-5,5-diphenyl-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3m)



3m

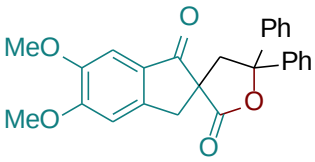
Following the general procedure C, methyl 5-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1c** (102.11 mg, 0.5 mmol), diphenylethylene (177.0 µL, 1.0 mmol) gave product **3m** (162.1 mg, 88%) as a white solid after purification (80:20 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.28 (m, 10H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.12 (s, 1H), 3.64 (d, *J* = 13.0 Hz, 1H), 3.17 (d, *J* = 17.7 Hz, 1H), 3.10 (d, *J* = 13.0 Hz, 1H), 2.68 (d, *J* = 17.5 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 175.6, 153.1, 147.4, 143.6, 143.1, 132.9, 129.6, 128.9 (2C), 128.7 (2C), 128.2, 128.2, 126.7, 125.8 (2C), 125.4 (2C), 124.9, 88.3, 57.8, 47.1, 39.5, 22.2.

HRMS (ESI$^+$) Calculated for $C_{25}H_{21}O_3$ $[M + H]^+$: 369.1412, found: 369.1485

5',6'-Dimethoxy-5,5-diphenyl-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3n)



3n

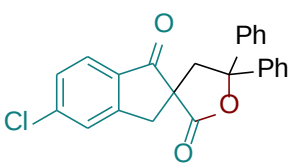
Following the general procedure C, methyl 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1d** (125.04 mg, 0.5 mmol), diphenylethylene (177.0 µL, 1.0 mmol) gave product **3n** (109.7 mg, 53%) as a white solid after purification (80:20 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 – 7.51 (m, 2H), 7.50 – 7.28 (m, 8H), 7.21 (s, 1H), 6.73 (s, 1H), 3.90 (s, 6H), 3.65 (d, *J* = 13.0 Hz, 1H), 3.11 (d, *J* = 17.1 Hz, 1H), 3.09 (d, *J* = 13.0 Hz, 1H), 2.62 (d, *J* = 17.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 199.6, 175.8, 156.6, 150.2, 148.21, 143.7, 143.6, 128.9 (2C), 128.7 (2C), 128.2, 128.1, 128.1, 125.9 (2C), 125.5 (2C), 107.2, 105.2, 88.3, 58.0, 56.5, 56.3, 47.0, 39.5.

HRMS (ESI$^+$): Calculated for $C_{26}H_{23}O_5$ $[M + H]^+$: 415.1467, found: 415.1540.

5'-Chloro-5,5-diphenyl-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3o)



3o

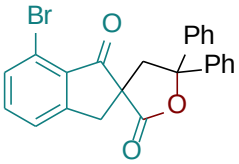
Following the general procedure C, methyl 5-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1b** (90.1 mg, 0.5 mmol), diphenylethylene (177.0 µL, 1.0 mmol) gave product **3o** (113.9 mg, 59%) as a white solid after purification (75:25 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.49 – 7.30 (m, 10H), 3.64 (d, *J* = 13.1 Hz, 1H), 3.23 – 3.09 (m, 2H), 2.71 (d, *J* = 17.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCL_3$) δ 199.9, 175.0, 153.9, 143.3, 142.9, 142.6, 133.6, 129.1, 129.0 (2C), 128.7 (2C), 128.3, 128.3, 126.6, 126.1, 125.7 (2C), 125.4 (2C), 88.4, 57.9, 46.9, 39.1.

HRMS (ESI$^+$) Calculated for $C_{24}H_{18}ClO_3$ $[M + H]^+$: 389.0866, found: 389.0939.

7'-Bromo-5,5-diphenyl-4,5-dihydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (3p)



3p

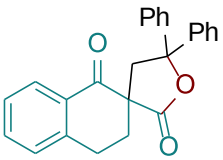
Following the general procedure C, methyl 7-bromo-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1e** (134.54 mg, 0.5 mmol), diphenylethylene (177.0 µL, 1.0 mmol) gave product **3p** (167.9 mg, 77%) as a white solid after purification (85:15 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.23 (m, 13H), 3.67 (d, *J* = 13.1 Hz, 1H), 3.16 (d, *J* = 17.6 Hz, 1H), 3.09 (d, *J* = 13.1 Hz, 1H), 2.69 (d, *J* = 17.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 174.9, 155.2, 143.3, 142.9, 136.1, 133.4, 132.8, 129.0 (2C), 128.7 (2C), 128.3, 128.3, 125.9 (2C), 125.6 (2C), 125.3, 121.0, 88.5, 58.4, 47.2, 38.7.

HRMS (ESI$^+$) Calculated for $C_{24}H_{18}BrO_3$ $[M + H]^+$: 433.0361, found: 433.0434.

5,5-Diphenyl-3',4,4',5-tetrahydro-1'*H*,2*H*-spiro[furan-3,2'-naphthalene]-1',2-dione (3q)



3q

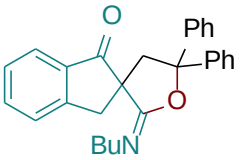
Following the modified general procedure C, methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **1f** (102.0 mg, 0.5 mmol), diphenylethylene (177.0 µL, 1.0 mmol), cesium carbonate (65.1 mg, 0.2 mmol) gave product **3q** (151.5 mg, 82%) as a white solid after purification (92:8 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.58 – 7.45 (m, 3H), 7.47 – 7.34 (m, 4H), 7.39 – 7.25 (m, 5H), 7.22 (d, *J* = 7.4 Hz, 1H), 3.80 (d, *J* = 13.4 Hz, 1H), 3.23 (ddd, *J* = 17.2, 9.1, 4.7 Hz, 1H), 3.02 (d, *J* = 13.4 Hz, 1H), 2.82 (m, 1H), 2.23 (ddd, *J* = 13.8, 6.6, 4.8 Hz, 1H), 1.99 (ddd, *J* = 13.8, 9.1, 4.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 193.6, 173.9, 144.3, 144.0, 143.7, 134.3, 131.0, 128.9 (2C), 128.9, 128.7, 128.6 (2C), 128.1, 128.0, 127.2, 125.7 (2C), 125.4 (2C), 87.6, 56.3, 44.7, 31.7, 25.3.

HRMS (ESI$^+$): Calculated for $C_{25}H_{21}O_3$ $[M + H]^+$: 369.1412, found: 369.1485.

2-(Butylimino)-5,5-diphenyl-4,5-dihydro-2*H*-spiro[furan-3,2'-inden]-1'(3'*H*)-one (3r)



3r

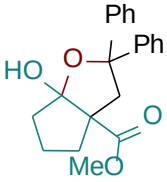
Following the general procedure C, *N*-butyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxamide **1h** (115.65 mg, 0.5 mmol), diphenylethylene (177.0 µL, 1.0 mmol) gave product **3r** (147.4 mg, 72%) as a white solid after purification (90:10 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.55 – 7.22 (m, 13H), 3.57 – 3.42 (m, 2H), 3.38 (d, *J* = 12.7 Hz, 1H), 3.11 (d, *J* = 17.5 Hz, 1H), 2.96 (d, *J* = 12.6 Hz, 1H), 2.65 (d, *J* = 17.4 Hz, 1H), 1.59 – 1.47 (m, 2H), 1.41 – 1.25 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 163.0, 153.2, 144.2, 144.2, 135.7, 135.3, 128.7 (2C), 128.5 (2C), 127.8, 127.8, 126.4, 125.9 (2C), 125.6 (2C), 124.9, 88.8, 57.3, 49.3, 47.9, 41.9, 32.9, 20.7, 14.2.

HRMS (ESI$^+$) Calculated for $C_{28}H_{28}NO_2$ $[M + H]^+$: 410.2042, found: 410.2115.

Methyl 6a-hydroxy-2,2-diphenylhexahydro-3aH-cyclopenta[b]furan-3a-carboxylate (3s)



3s

Following the general procedure C, methyl 2-oxocyclopentanecarboxylate (71.1 mg, 0.5 mmol), diphenylethylene (177.0 µL, 1.0 mmol) gave product **3s** (110.0 mg, 65%) as a white solid after purification (slowly increasing from 5 to 40% EtOAc in CyHex in silica Iatrobeads®).

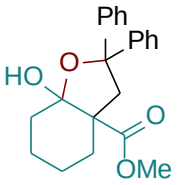
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 2H), 7.51 – 7.43 (m, 2H), 7.33 – 7.26 (m, 4H), 7.23 – 7.13 (m, 2H), 3.65 (d, *J* = 13.7 Hz, 1H), 3.62 (s, 3H), 2.73 (d, *J* = 13.7 Hz, 1H), 2.41 – 2.25 (m, 2H), 1.81 – 1.53 (m, 4H); Representative tautomer signals: δ 3.61 (s, 3H), 3.42 (d, *J* = 13.1 Hz, 1H), 2.88 (d, *J* = 13.1 Hz, 1H).

Hemiketal ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 147.3, 147.1, 128.3 (2C), 128.3 (2C), 127.0, 126.8, 126.0 (2C), 125.1 (2C), 117.4, 88.9, 61.5, 52.4, 48.2, 38.9, 36.3, 21.7.

β-Ketoester ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 174.9, 143.5, 143.4, 128.9, 128.6, 128.1, 128.1, 125.7, 125.4, 88.3, 57.9, 45.7, 37.4, 36.1, 35.5, 19.4.

HRMS (ESI$^+$) Calculated for Calculated for $C_{21}H_{22}O_3$ $[M - OH]^+$: 321.1490, found: 321.1485.

Methyl 7a-hydroxy-2,2-diphenylhexahydrobenzofuran-3a(4*H*)-carboxylate (3t)



3t

Following the general procedure C, methyl 2-oxocyclohexanecarboxylate (78.1 mg, 0.5 mmol), diphenylethylene (177.0 µL, 1.0 mmol) gave product **3t** (89.9 mg, 51%) as a white solid after purification (slowly increasing from 5 to 30% EtOAc in CyHex in silica Iatrobeads®).

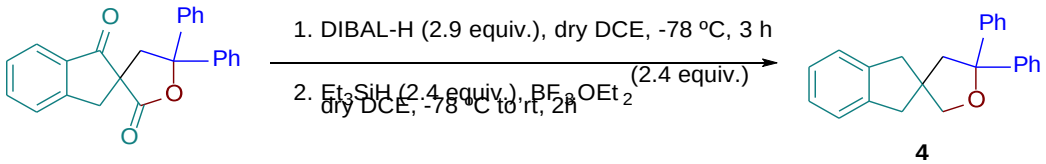
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 4H), 7.33 – 7.21 (m, 4H), 7.18 – 7.07 (m, 2H), 3.66 (s, 3H), 3.50 (d, *J* = 12.7 Hz, 1H), 3.09 (s, 1H), 2.95 (d, *J* = 12.7 Hz, 1H), 2.25 – 2.15 (m, 1H), 2.08 – 1.94 (m, 1H), 1.71 – 1.32 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 150.0, 148.6, 128.4 (2C), 128.3 (2C), 126.5, 126.4, 125.0 (2C), 124.9 (2C), 104.8, 85.4, 56.1, 52.1, 46.9, 34.2, 32.4, 22.9, 21.9.

HRMS (ESI$^+$) Calculated for $C_{22}H_{23}O_3$ [M - OH]$^+$: 335.1675, found: 335.1642.

9. Derivatizations

9.1 Synthesis of 5,5-diphenyl-1',3',4,5-tetrahydro-2H-spiro[furan-3,2'-indene] (4)



3a **4**

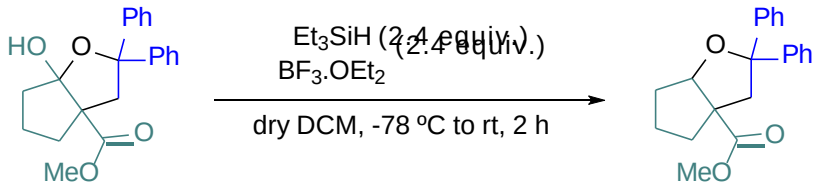
In a 10 mL round bottom flask, **3a** (0.4 mmol) was placed and three vacuum/N_2 cycles were applied. Then, 3.0 mL of dry DCE were added and the solution was cooled at -78 ºC. Diisobutylaluminium hydride (DIBAL-H 1 M in hexane, 1.2 mmol, 2.9 equiv.) was added slowly, and the reaction mixture was stirred at -78 ºC for 3 h, until complete consumption of the starting material by TLC. The reaction was quenched adding 5 mL of a saturated solution of sodium potassium tartrate at -78 ºC. The resulting mixture was allowed to warm to room temperature for 2 h. Then, the organic layer was separated, and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum. The resulting crude product was used directly for the next step without further purification. The crude lactol was dissolved in 5 mL of dry DCE under N_2 and cooled to -78 ºC. Triethylsilane (0.98 mmol, 2.4 equiv.) and boron trifluoride diethyl etherate (BF_3OEt_2 0.98 mmol, 2.4 equiv.) were added simultaneously and the reaction mixture was stirred at -78 ºC for 30 min. The mixture was warmed to room temperature and stirred at this temperature for 1.5 h. Then, the reaction was quenched with a saturated solution of $NaHCO_3$ to pH 7. The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum. The crude product was purified by silica gel flash chromatography (98:2 CyHex/EtOAc) to afford **4** (106.5 mg, 58%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 4H), 7.23 – 7.16 (m, 4H), 7.13 – 7.05 (m, 2H), 7.00 (s, 4H), 3.85 (s, 2H), 2.78 (s, 2H), 2.77 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6 (2C), 142.5 (2C), 128.3 (4 C), 126.7 (2C), 126.5 (2C), 125.7 (4C), 124.6 (2C), 88.3, 79.4, 52.4, 52.1, 44.6 (2C).

HRMS (APCI$^+$) Calculated for $C_{24}H_{23}O$ $[M + H]^+$: 327.1671, found: 327.1743

9.2 Synthesis of ethyl 2,2-diphenylhexahydro-3aH-cyclopenta[b]furan-3a-carboxylate (5)



3s **5**

In a sealed vial under argon atmosphere, lactol **3s** (106.2 mg, 0.31 mmol) was dissolved in DCM dry and cooled to -78 ºC. Triethylsilane (120.3 µL, 0.75 mmol) and $BF_3.OEt_2$ (92.9 µL, 0.75 mmol) were added simultaneously to the solution and stirred for 30 minutes. The mixture was warmed slowly to room temperature and the stirred until the completion of the reaction. Then, the reaction was quenched with a saturated solution of $NaHCO_3$ until it reached pH=7. The solution was extracted three times with DCM. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The volatiles were removed until dryness and the crude mixture was purified by

silica gel flash chromatography (98:2 CyHex/EtOAc) to afford the hexahydro cyclopentafuran carboxylate derivative **5** (48.6 mg, 52%) as a white solid.

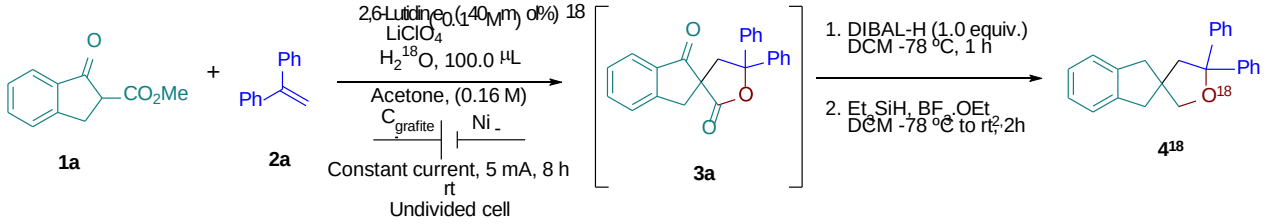
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 7.41 – 7.35 (m, 2H), 7.32 – 7.23 (m, 4H), 7.23 – 7.15 (m, 2H), 4.74 (d, *J* = 5.3 Hz, 1H), 3.78 (d, *J* = 13.1 Hz, 1H), 3.43 (s, 3H), 2.15 (d, *J* = 13.3 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.00 – 1.87 (m, 2H), 1.85 – 1.67 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 146.1, 143.3, 128.2 (2C), 128.2 (2C), 127.1, 126.9, 126.7 (2C), 125.5 (2C), 88.4, 86.1, 60.9, 51.9, 48.9, 39.9, 34.2, 24.8.

HRMS (ESI^{+}) Calculated for $C_{21}H_{23}O_3$ $[M + H]^{+}$: 339.1518, found: 339.1591

10. Mechanism experiments

10.1 Isotopic labelling experiments



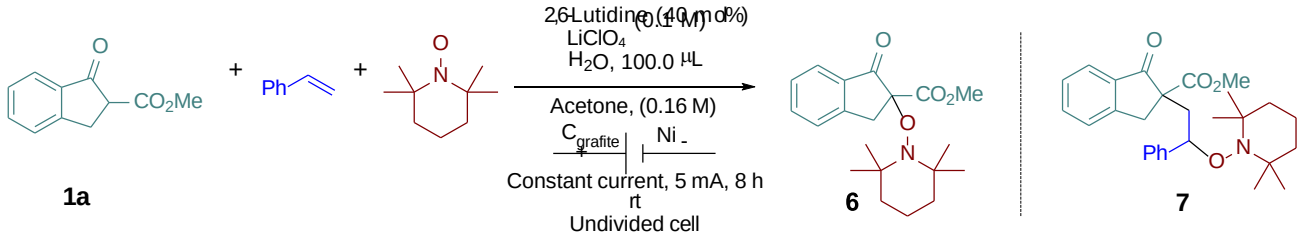
Following the modified general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), diphenylethylene **2a** (177.0 µL, 1.0 mmol) and $H_2{}^{18}O$ (100.0 µL) gave product **3a** (124.0 mg, 90%) as a white solid after purification (80:20 CyHex/EtOAc). Then, the resulting labelled **3a** was used as a starting material to follow the procedure described above for the synthesis of **4**. The product **^{18}4** was achieved (78.1 mg, 58%) as white solid after purification (85:15 CyHex/EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 4H), 7.23 – 7.16 (m, 4H), 7.13 – 7.05 (m, 2H), 7.00 (s, 4H), 3.85 (s, 2H), 2.78 (s, 2H), 2.77 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6 (2C), 142.5 (2C), 128.3 (4 C), 126.7 (2C), 126.5 (2C), 125.7 (4C), 124.6 (2C), 88.3, 79.4, 52.4, 52.1, 44.6 (2C).

HRMS (APCI$^+$) Calculated for $C_{24}H_{23}{}^{18}O$ $[M + H]^+$: 329.1671, found: 329.1790

10.2 Radical intermediates evidences



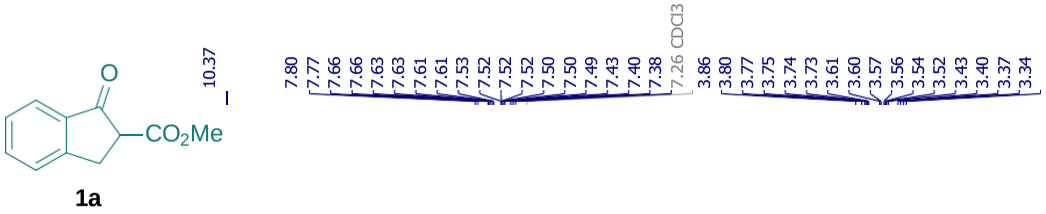
Following the modified general procedure C, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** (95.1 mg, 0.5 mmol), styrene (114.6 µL, 1.0 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 0.5 mmol, 1.0 equiv.) gave product **6** (154.6 mg, 89.6%) as a brown pale oil after purification (90:10 CyHex/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.0 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 4.45 (d, *J* = 17.5 Hz, 1H), 3.57 (s, 3H), 3.31 (d, *J* = 17.6 Hz, 1H), 1.50 – 1.21 (m, 5H), 1.20 – 1.11 (m, 4H), 1.04 (s, 3H), 0.90 (s, 3H), 0.42 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0, 167.7, 150.3, 133.1, 131.1, 124.9, 123.5, 122.0, 87.2, 57.6, 56.6, 50.2, 37.6, 37.4, 30.8, 29.5, 29.3, 18.1, 17.7, 14.2.

HRMS (ESI$^+$) Calculated for $C_{20}H_{28}NO_4$ $[M + H]^+$: 346.1940, found: 346.2013

11. NMR spectral data



1a

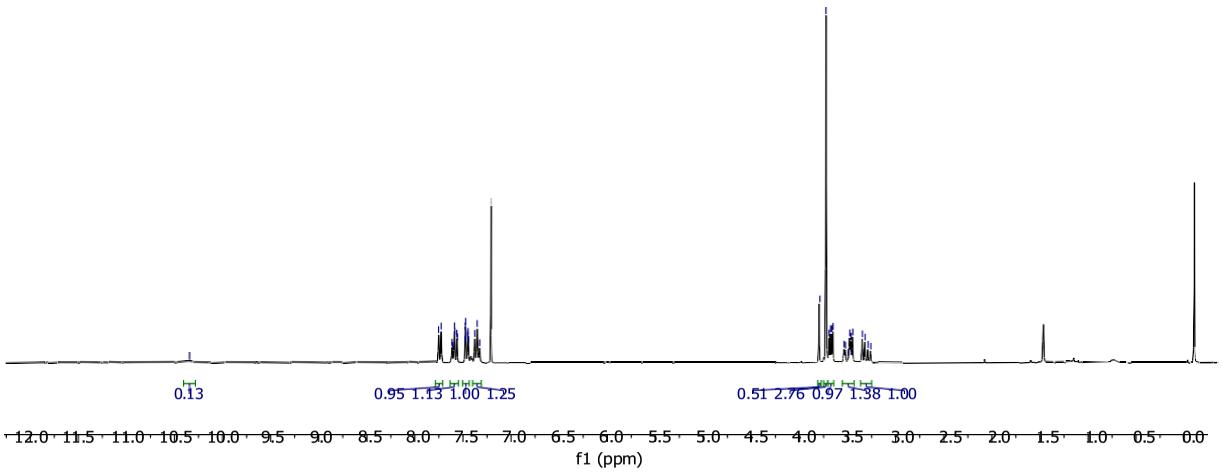
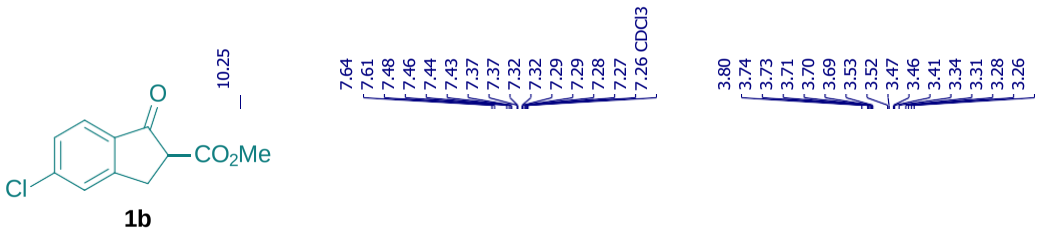


Figure S 1. ^{1}H NMR spectrum of **1a** in $CDCl_3$.



1b

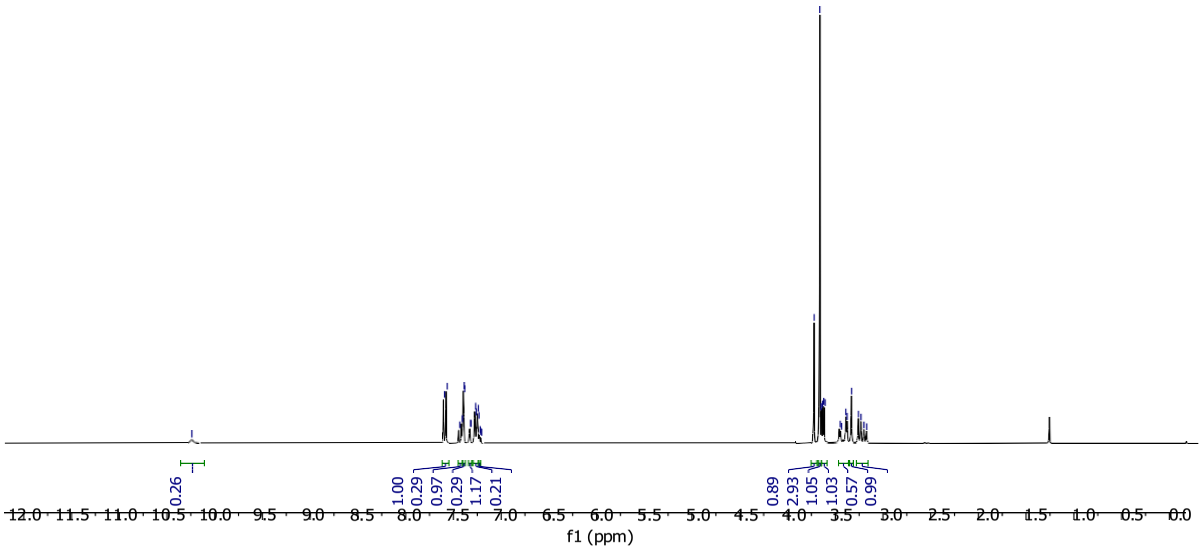


Figure S 2. ^{1}H NMR spectrum of **1b** in $CDCl_3$.

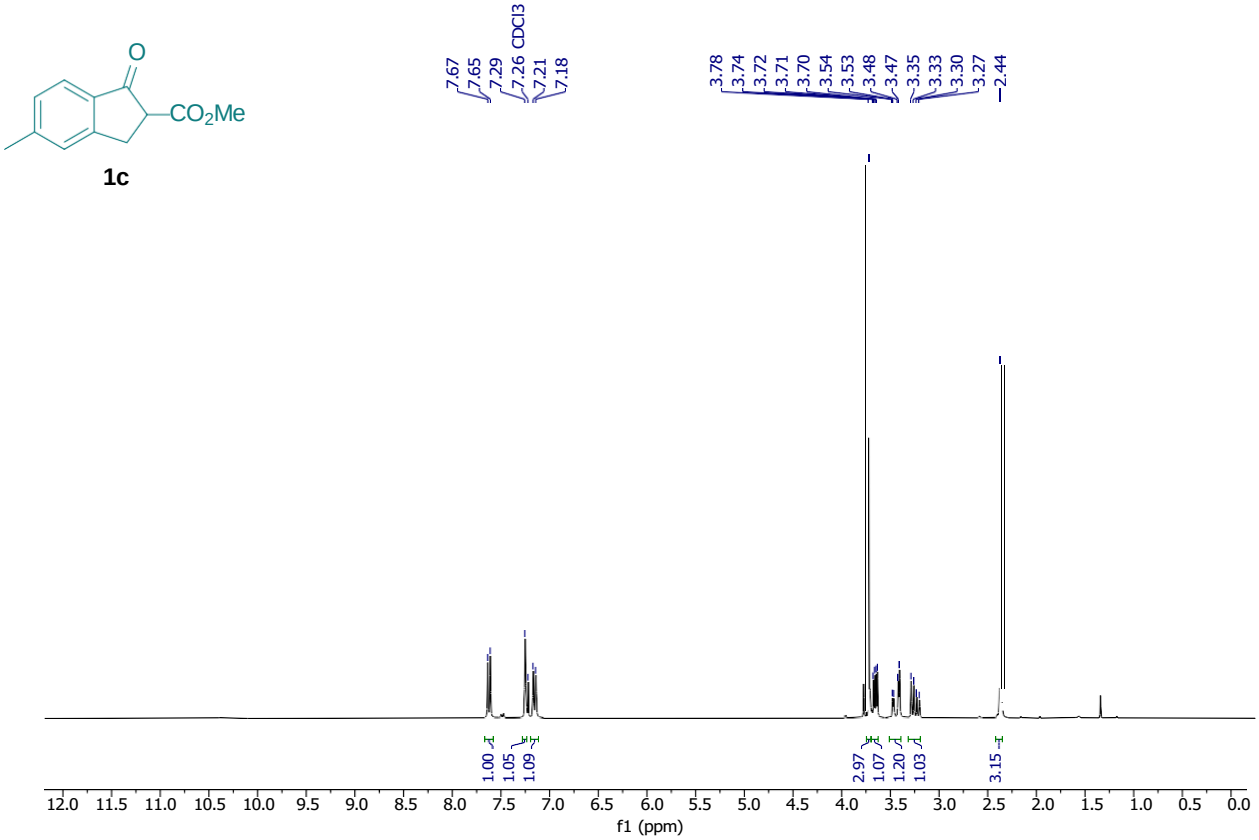


Figure S 3. ^{1}H NMR spectrum of **1c** in $CDCl_3$.

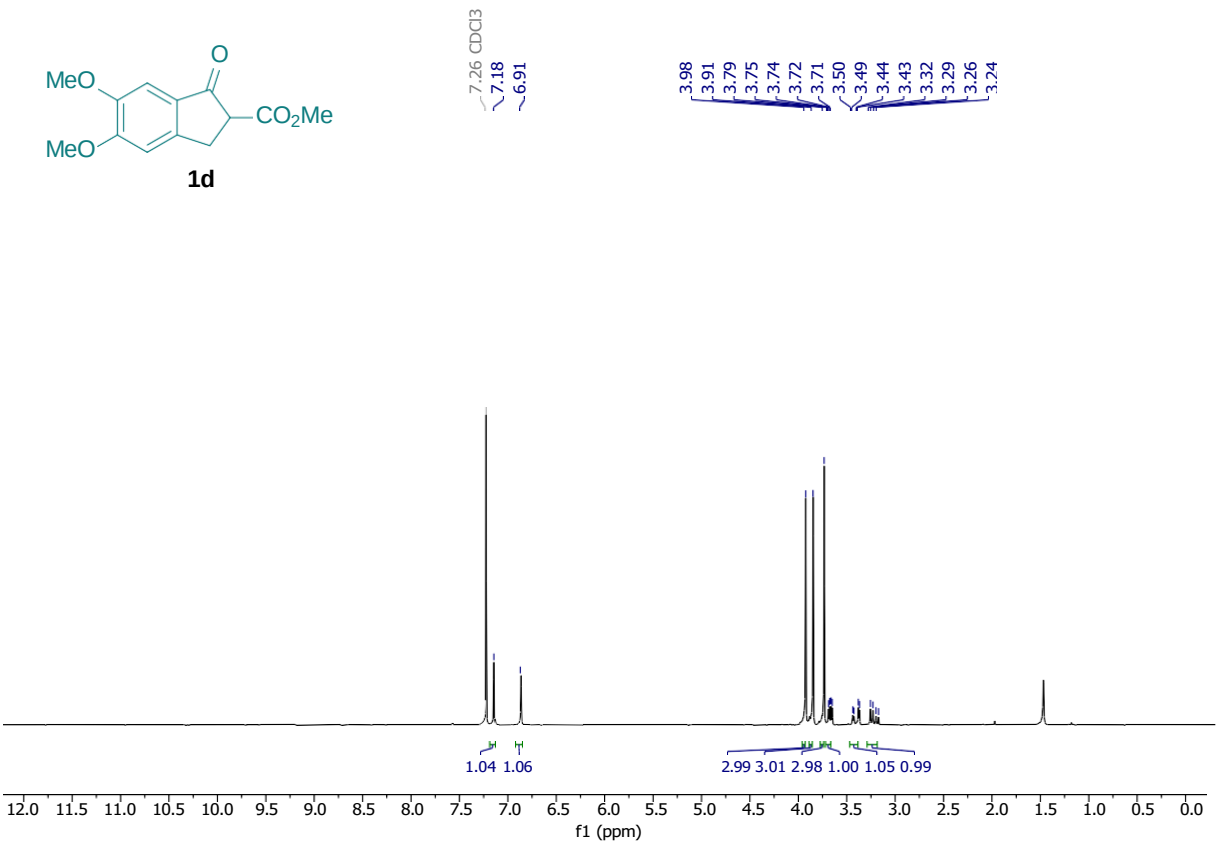


Figure S 4. ^{1}H NMR spectrum of **1d** in $CDCl_3$.

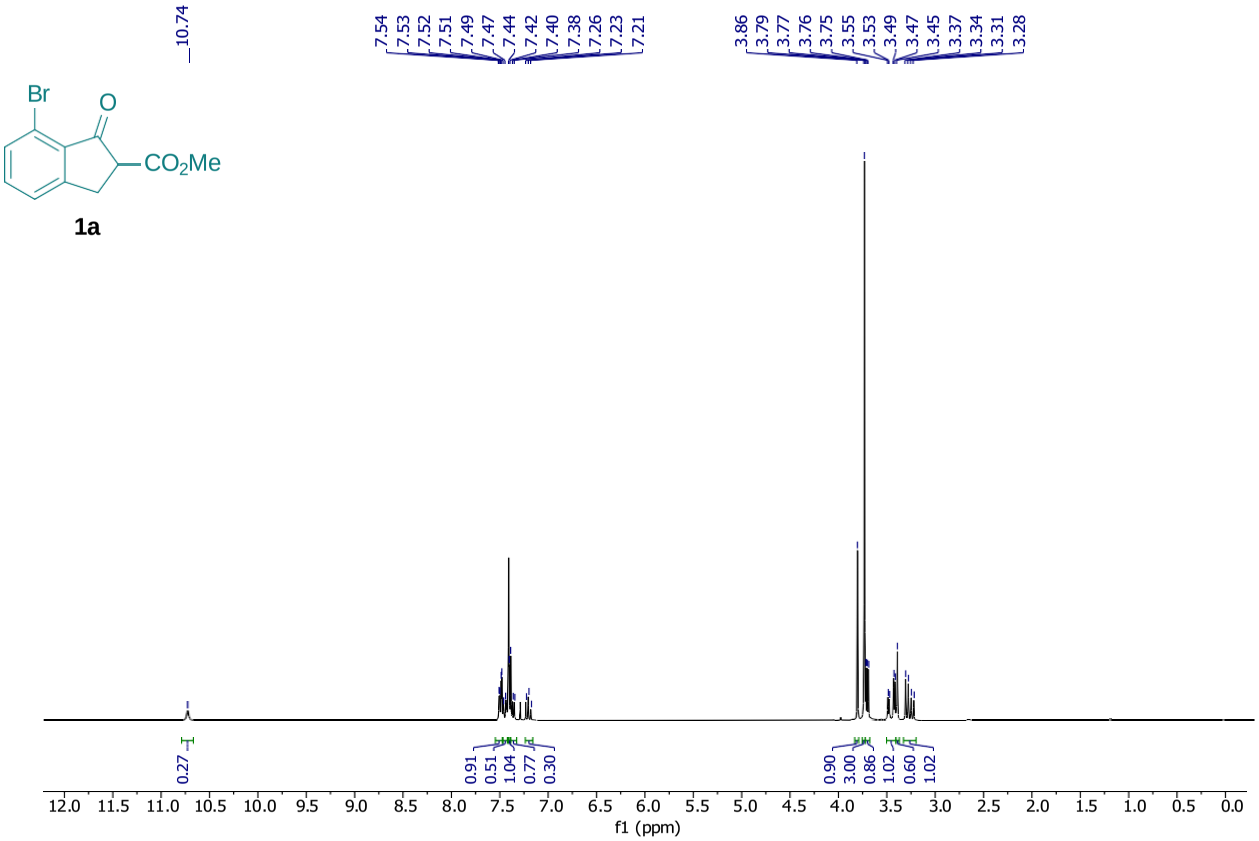


Figure S 5. ^{1}H NMR spectrum of **1e** in $CDCl_3$.

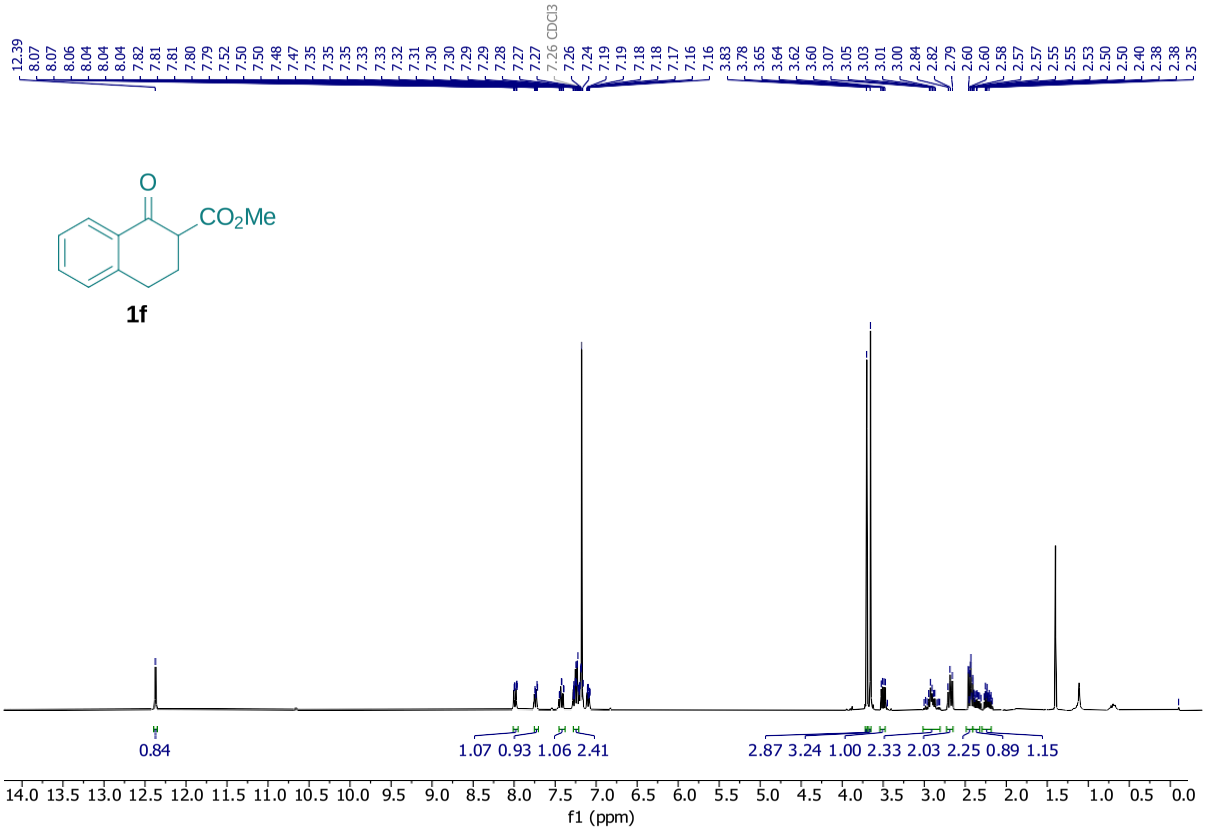


Figure S 6. ^{1}H NMR spectrum of **1f** in $CDCl_3$.

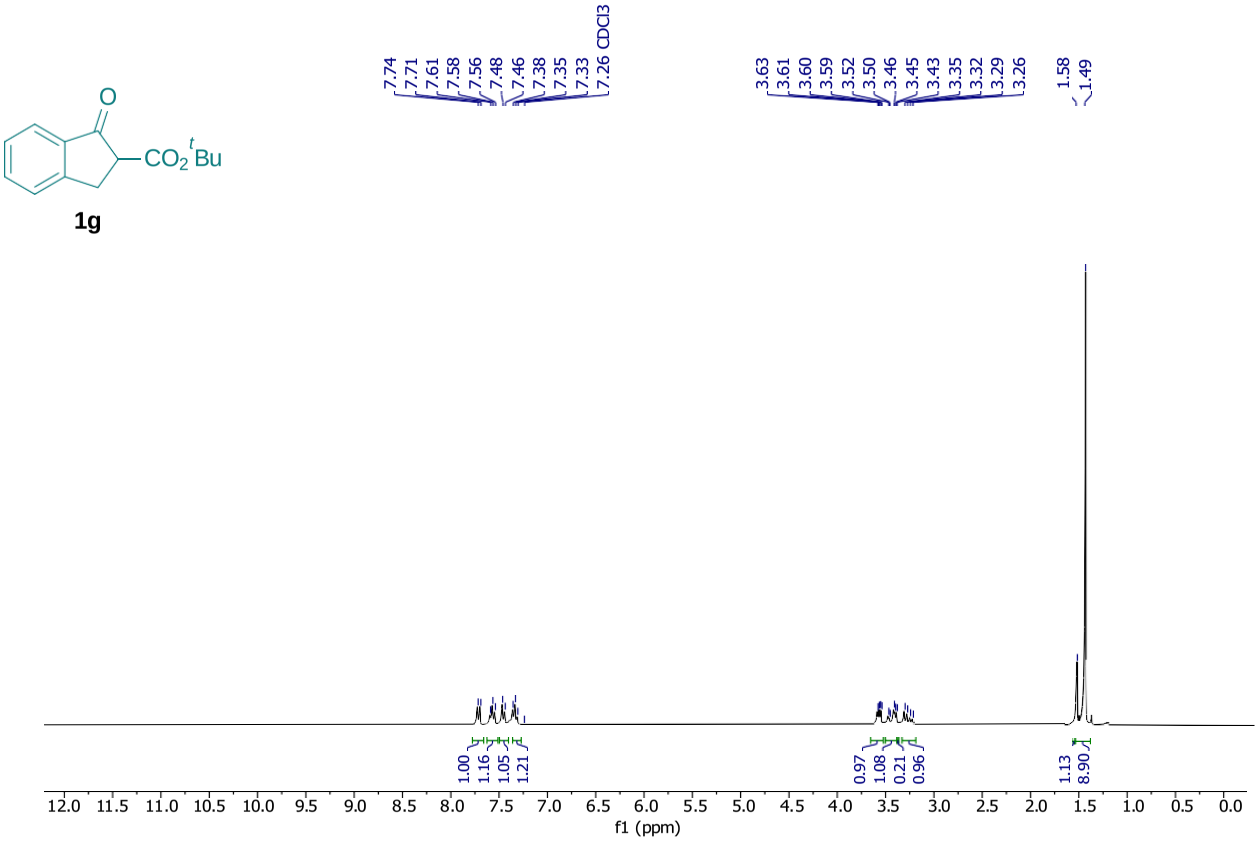


Figure S 7. ^{1}H NMR spectrum of **1g** in $CDCl_3$.

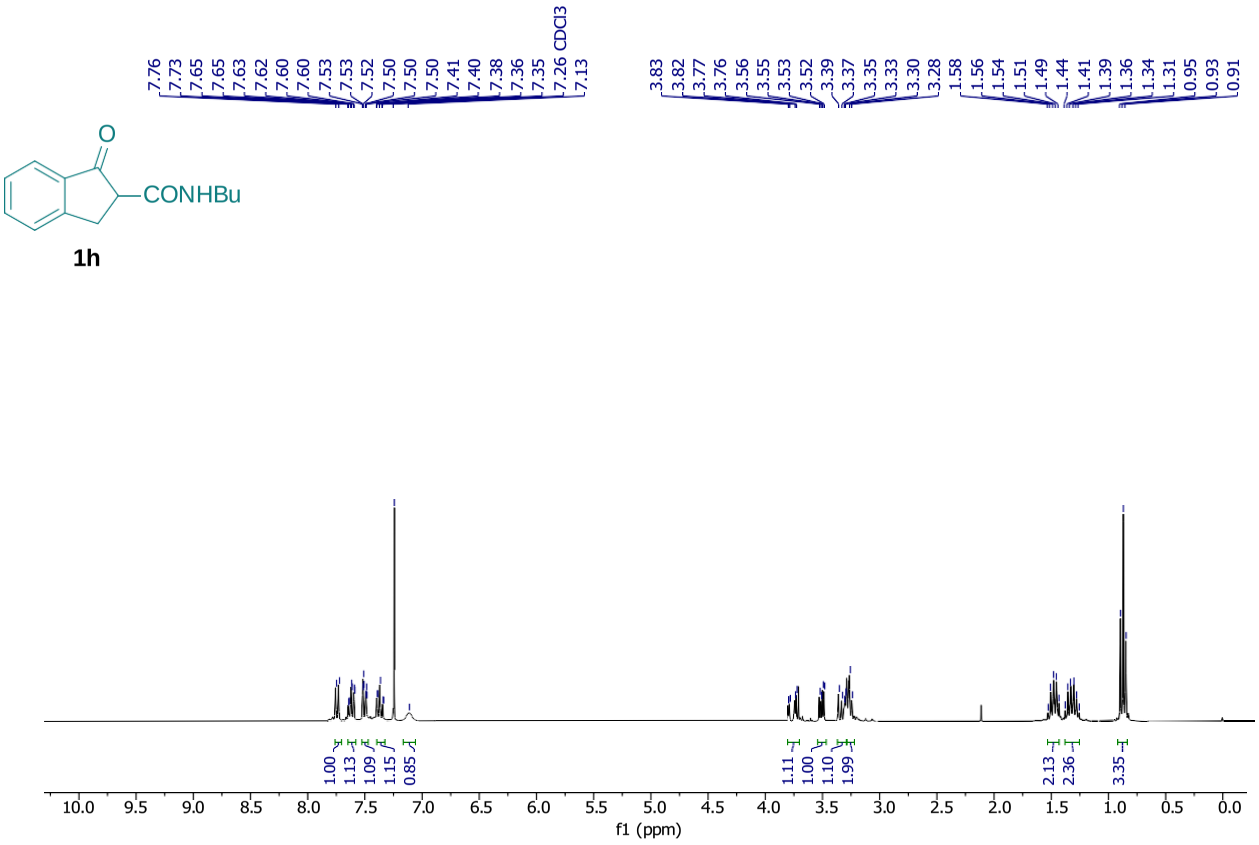


Figure S 8. ^{1}H NMR spectrum of **1h** in $CDCl_3$.

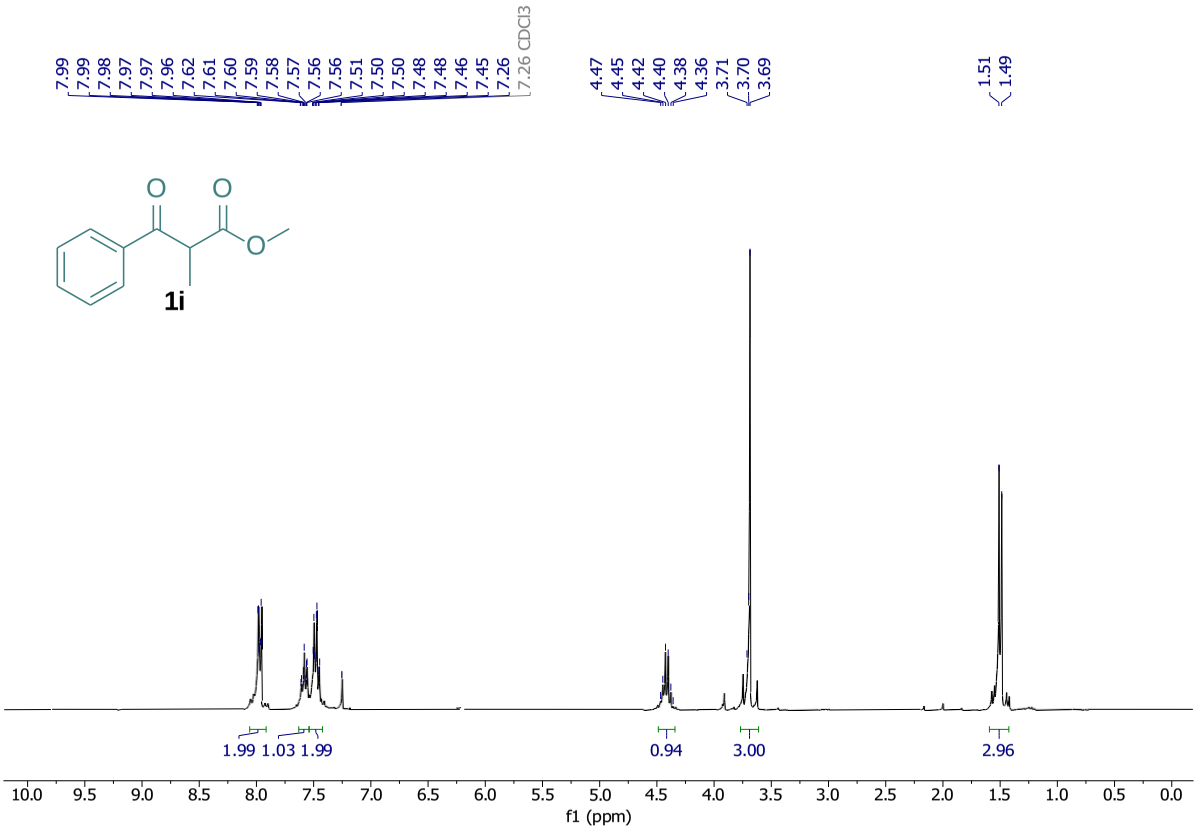
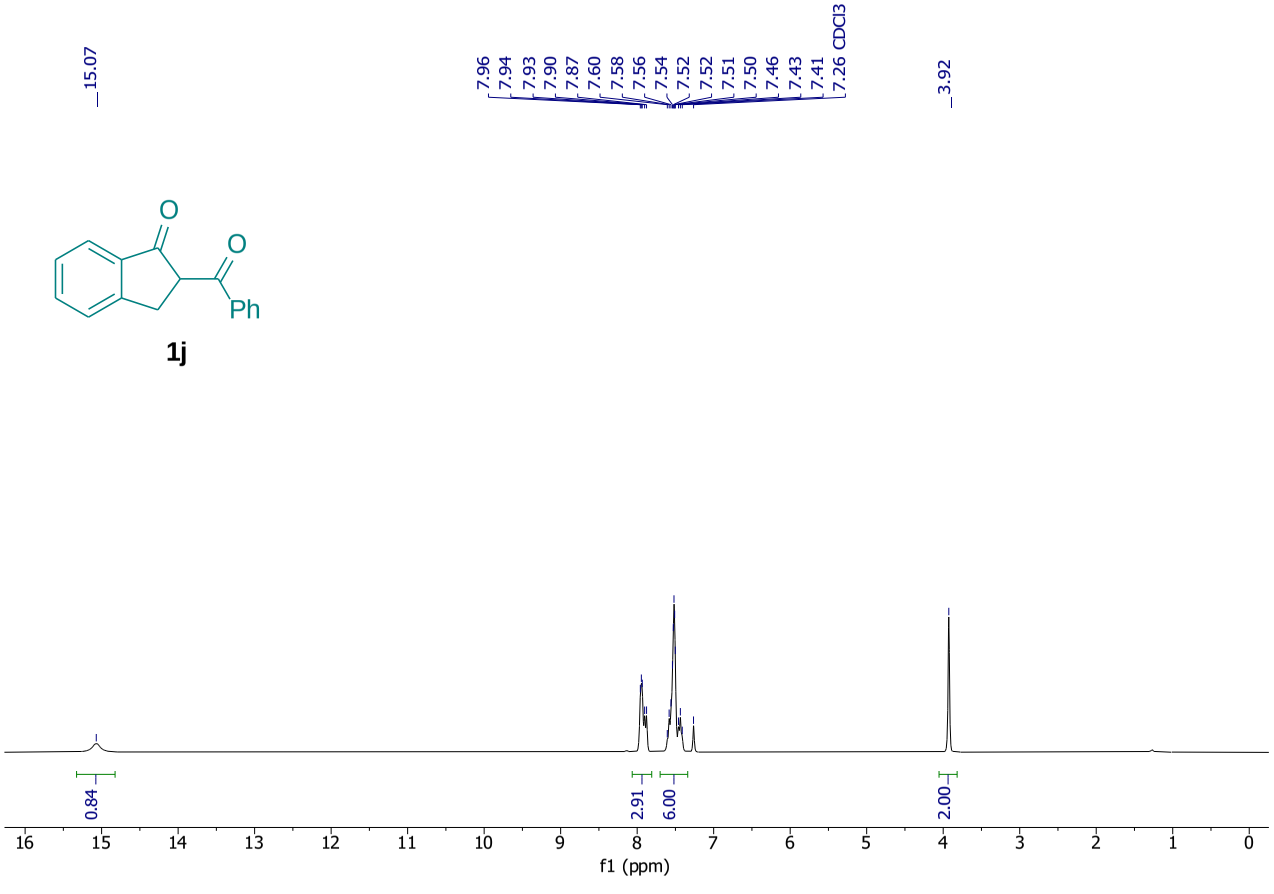


Figure S 9. ^{1}H NMR spectrum of **1i** in $CDCl_3$.



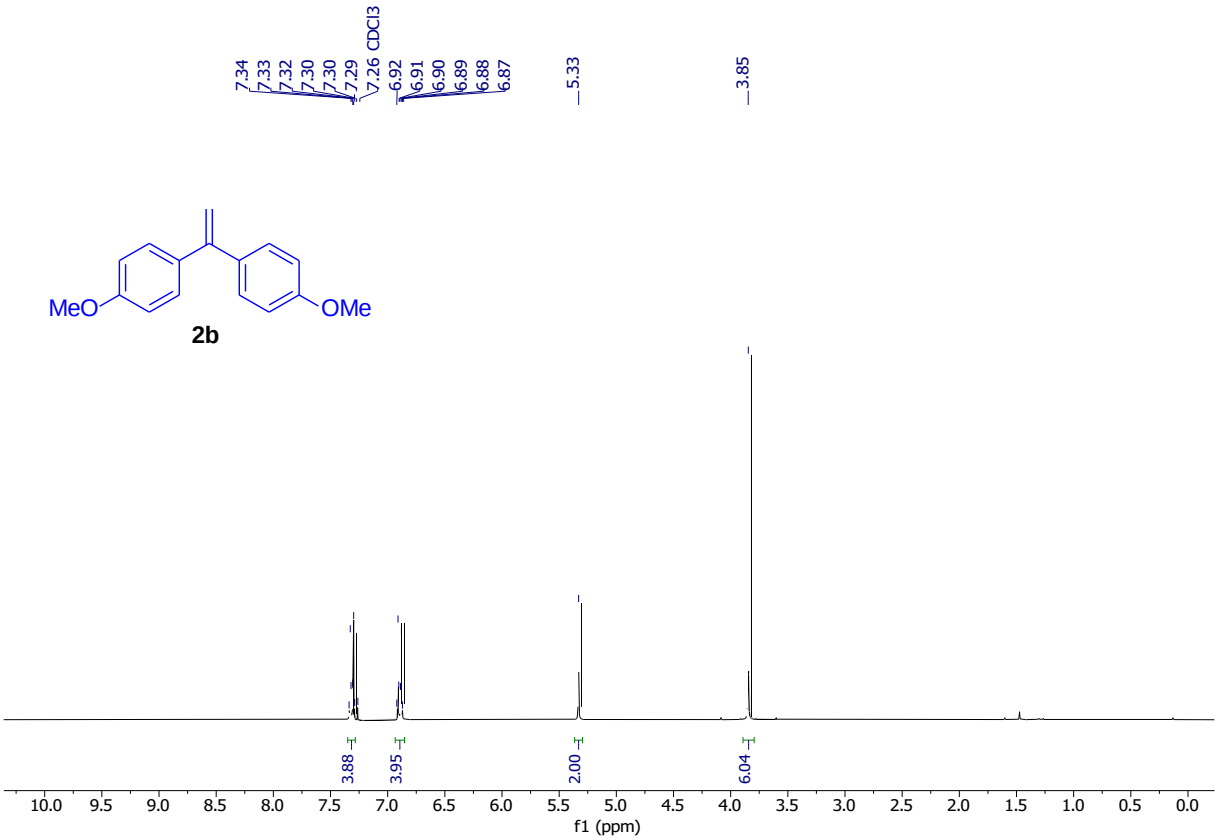


Figure S 10. ^{1}H NMR spectrum of **2b** in $CDCl_3$.

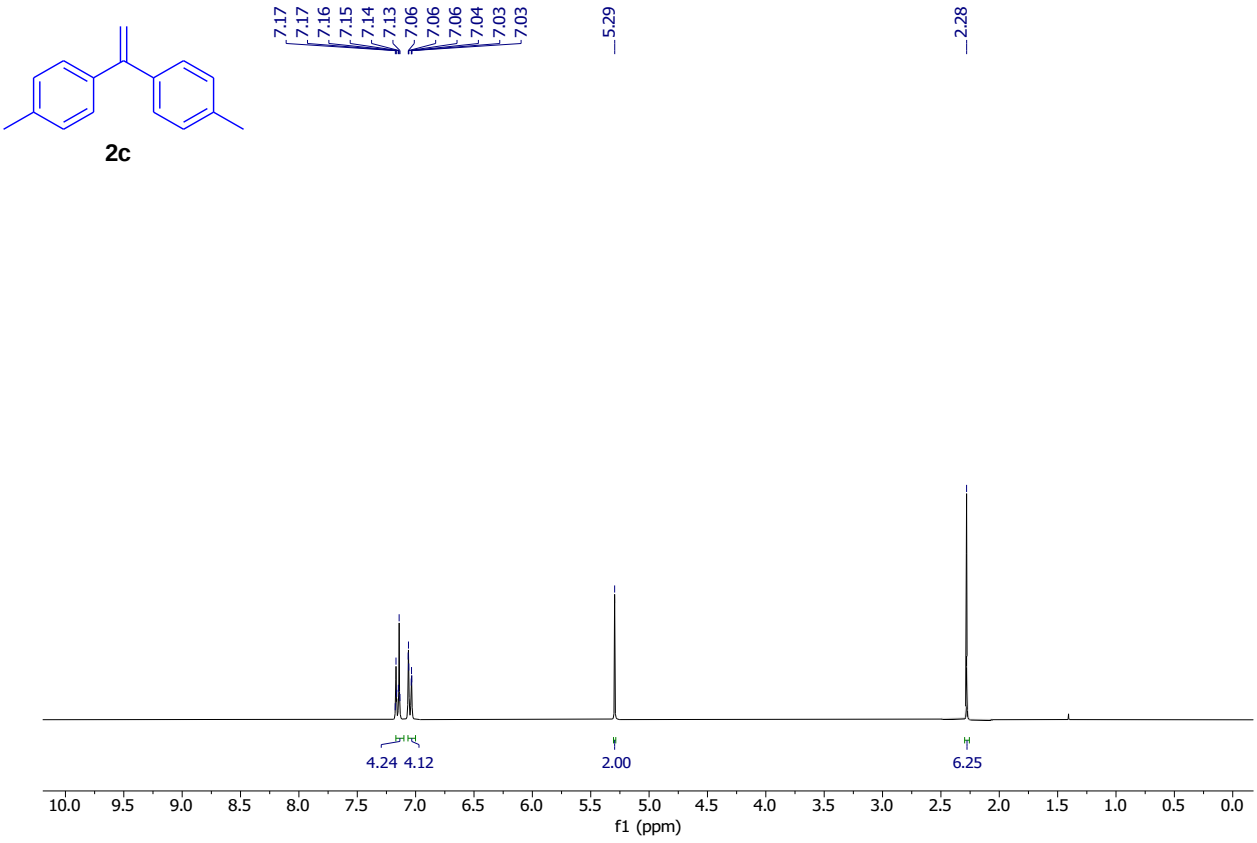


Figure S 11. ^{1}H NMR spectrum of **2c** in $CDCl_3$.

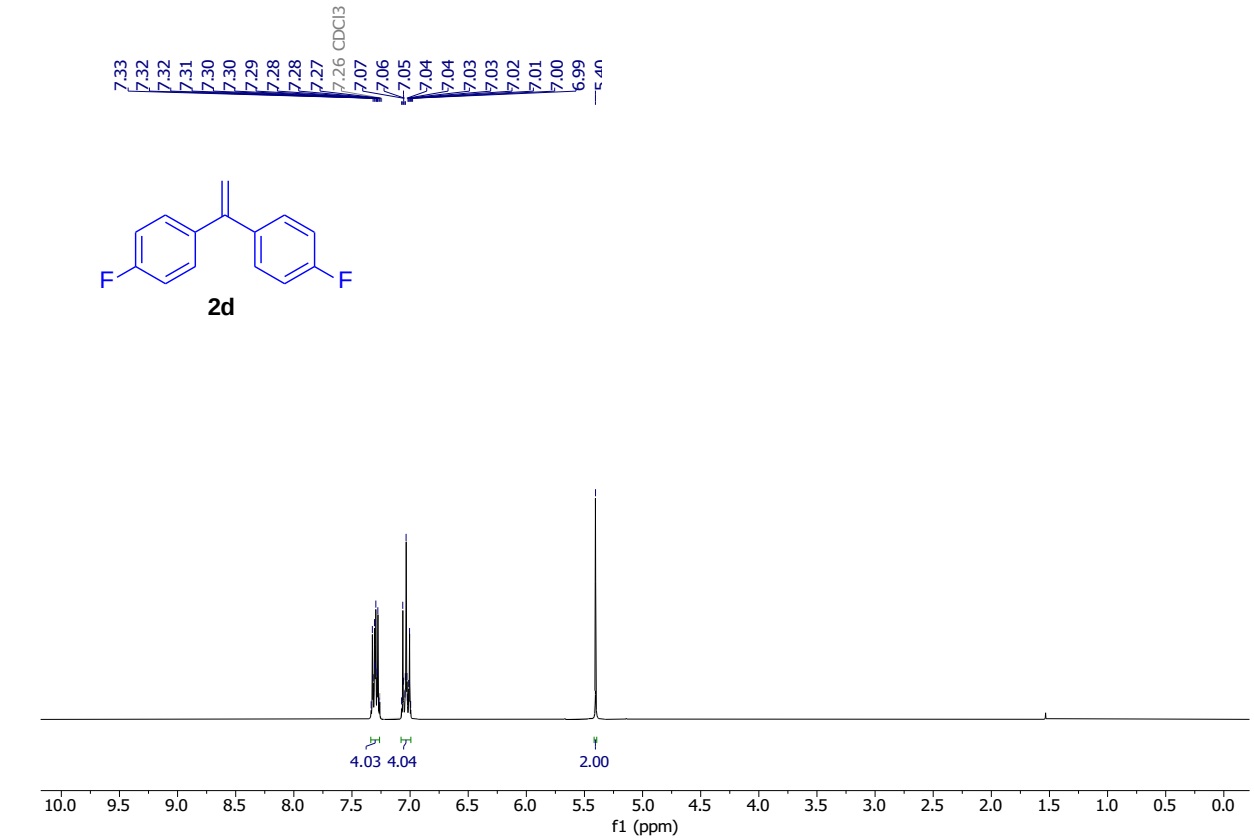


Figure S 12. ^{1}H NMR spectrum of **2d** in $CDCl_3$.

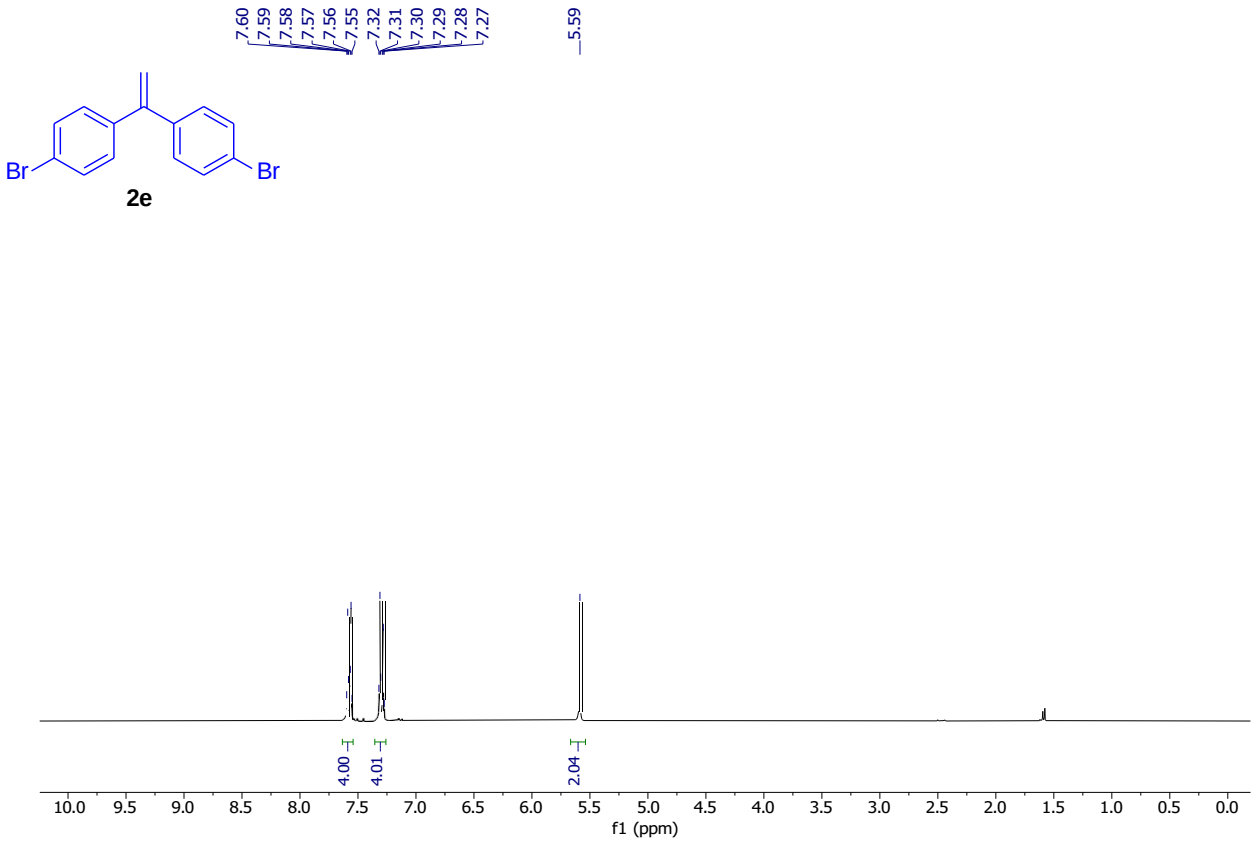


Figure S 13. ^{1}H NMR spectrum of **2d** in $CDCl_3$.

Figure S 14. ^{1}H NMR spectrum of **2f** in $CDCl_3$.

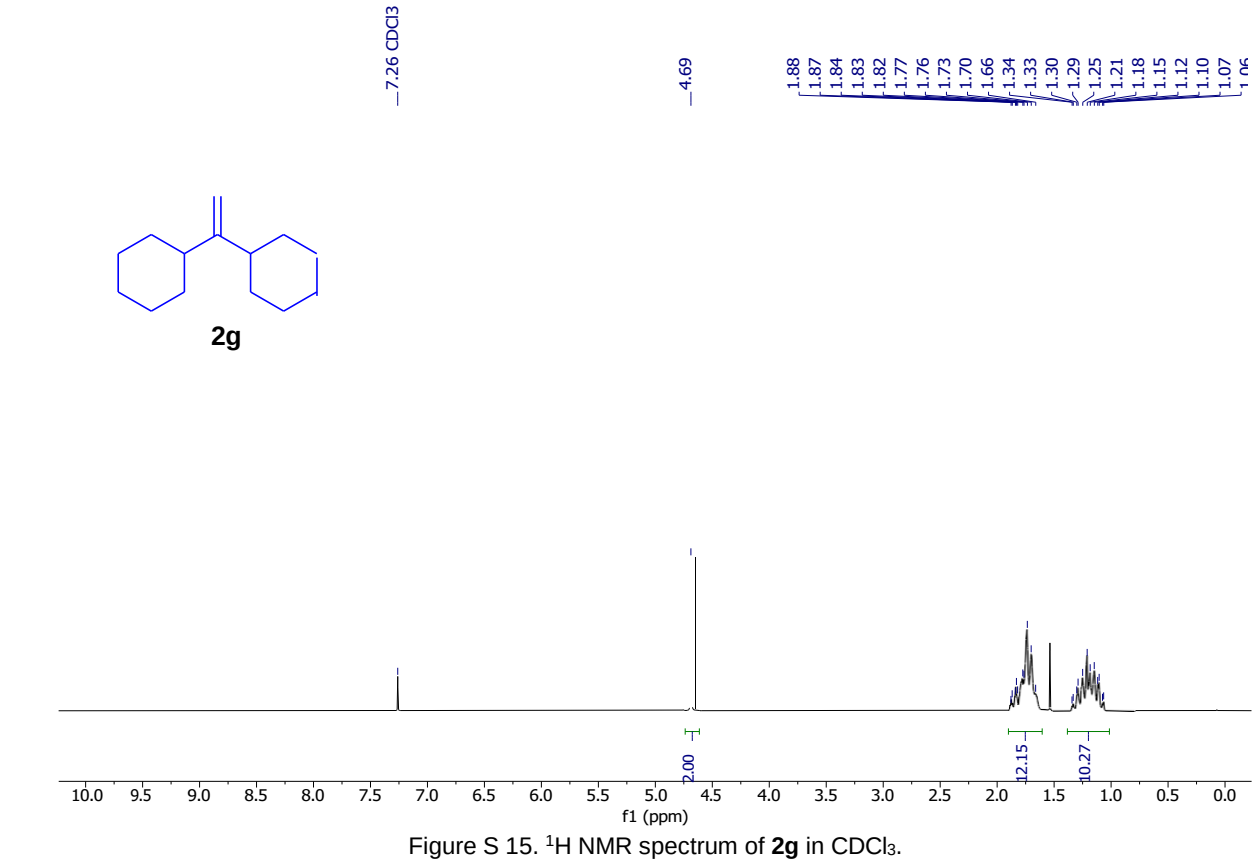


Figure S 15. ^{1}H NMR spectrum of **2g** in $CDCl_3$.

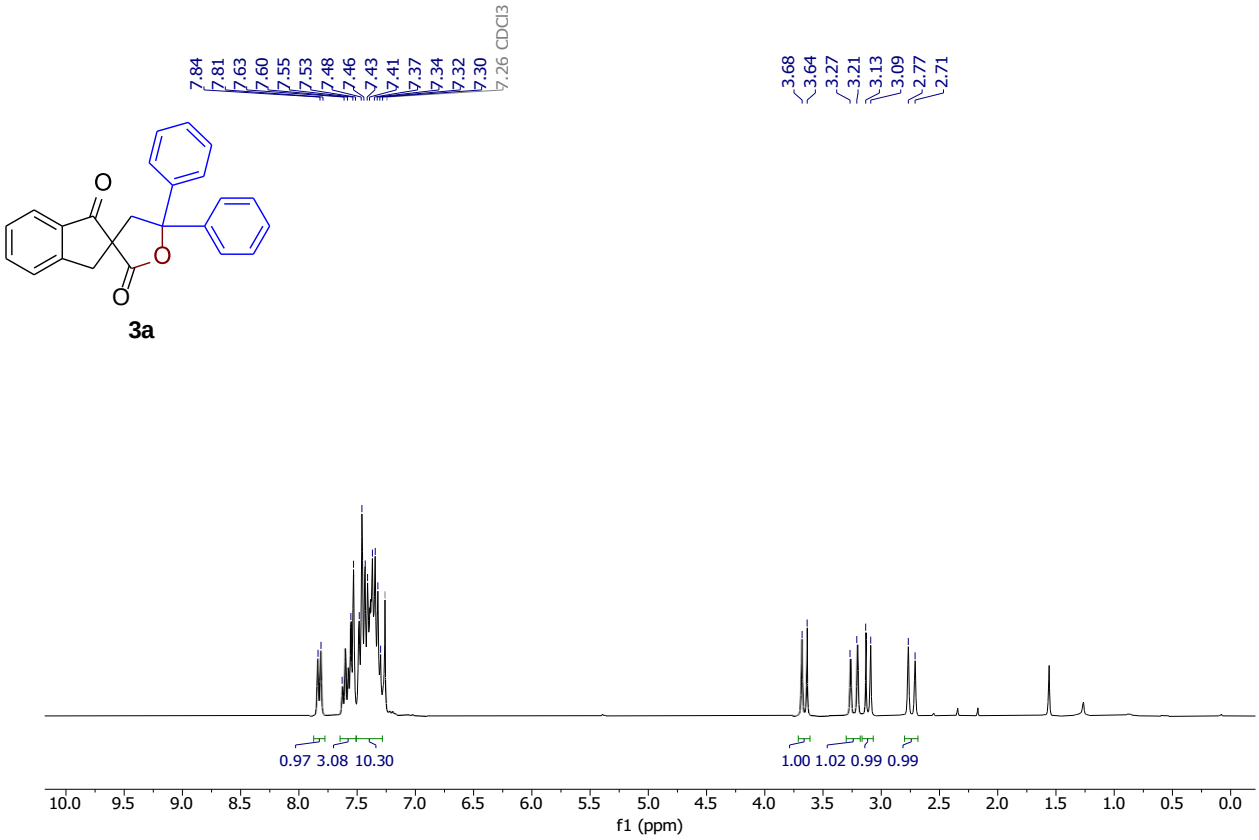


Figure S 16. ^{1}H NMR spectrum of **3a** in $CDCl_3$.

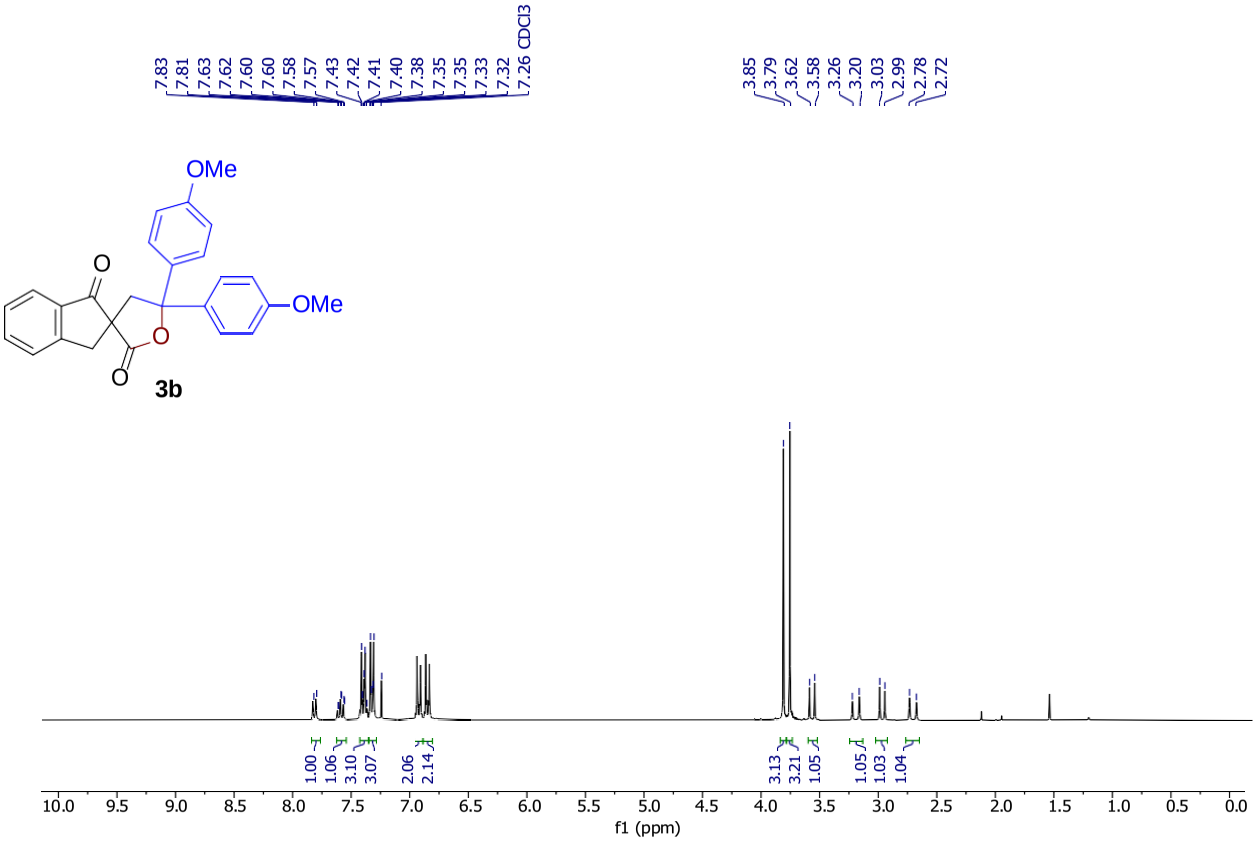


Figure S 17. ^{1}H NMR spectrum of **3b** in $CDCl_3$.

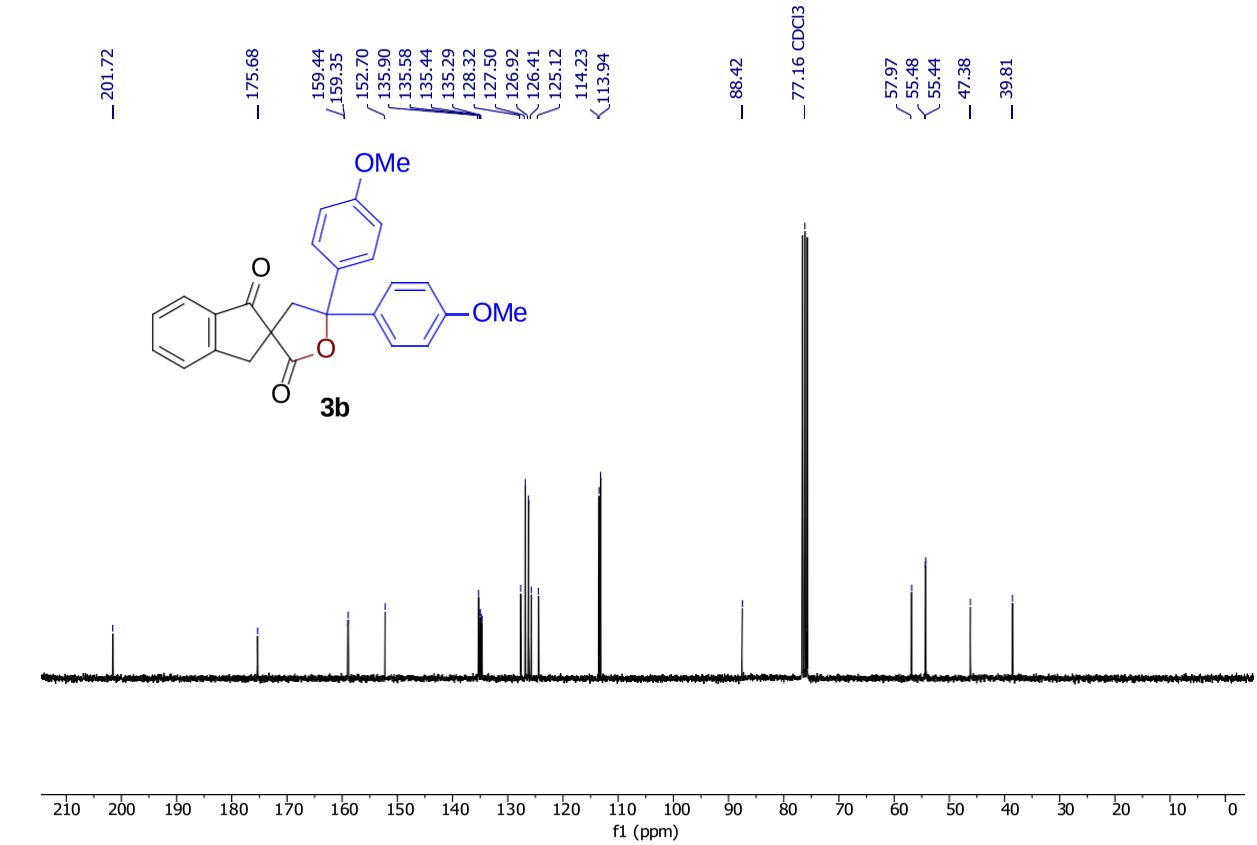


Figure S 18. ^{13}C NMR spectrum of **3b** in $CDCl_3$.

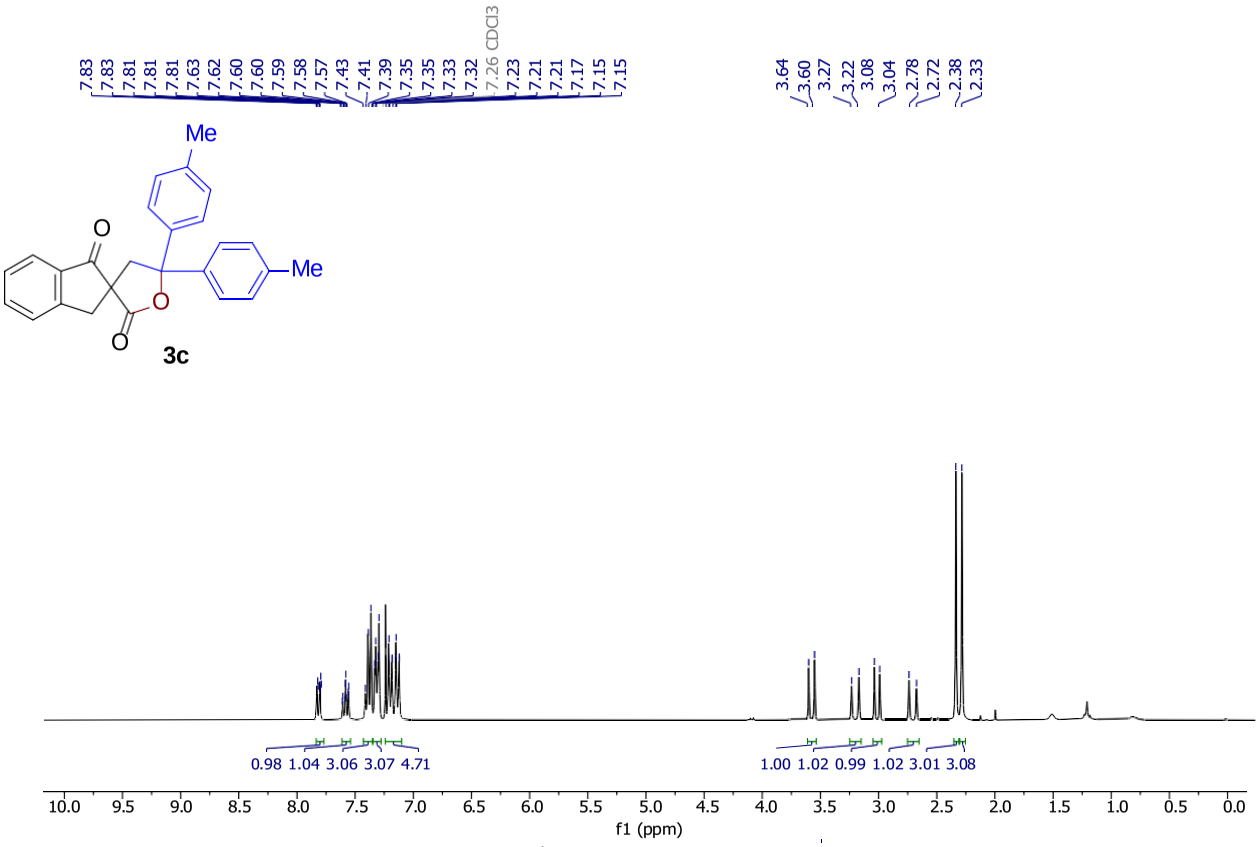


Figure S 19. ^{1}H NMR spectrum of **3c** in $CDCl_3$.

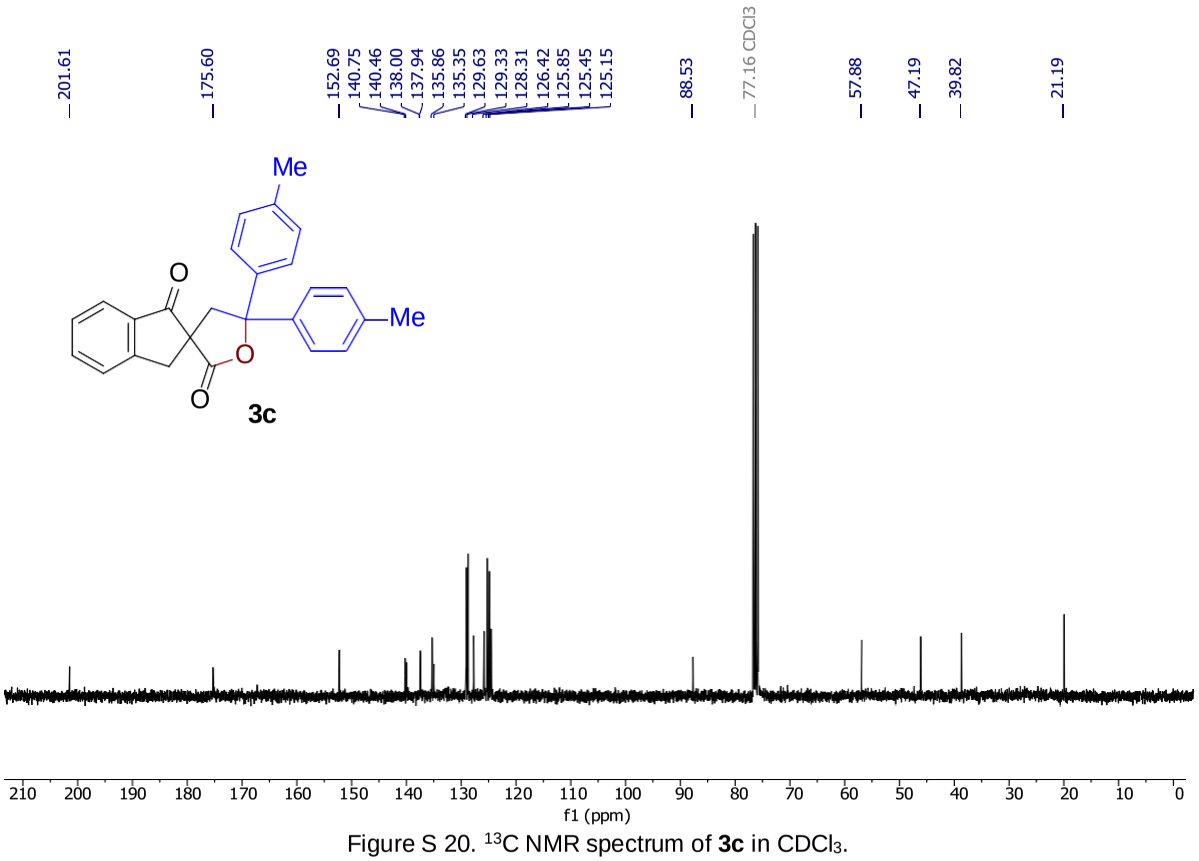


Figure S 20. ^{13}C NMR spectrum of **3c** in $CDCl_3$.

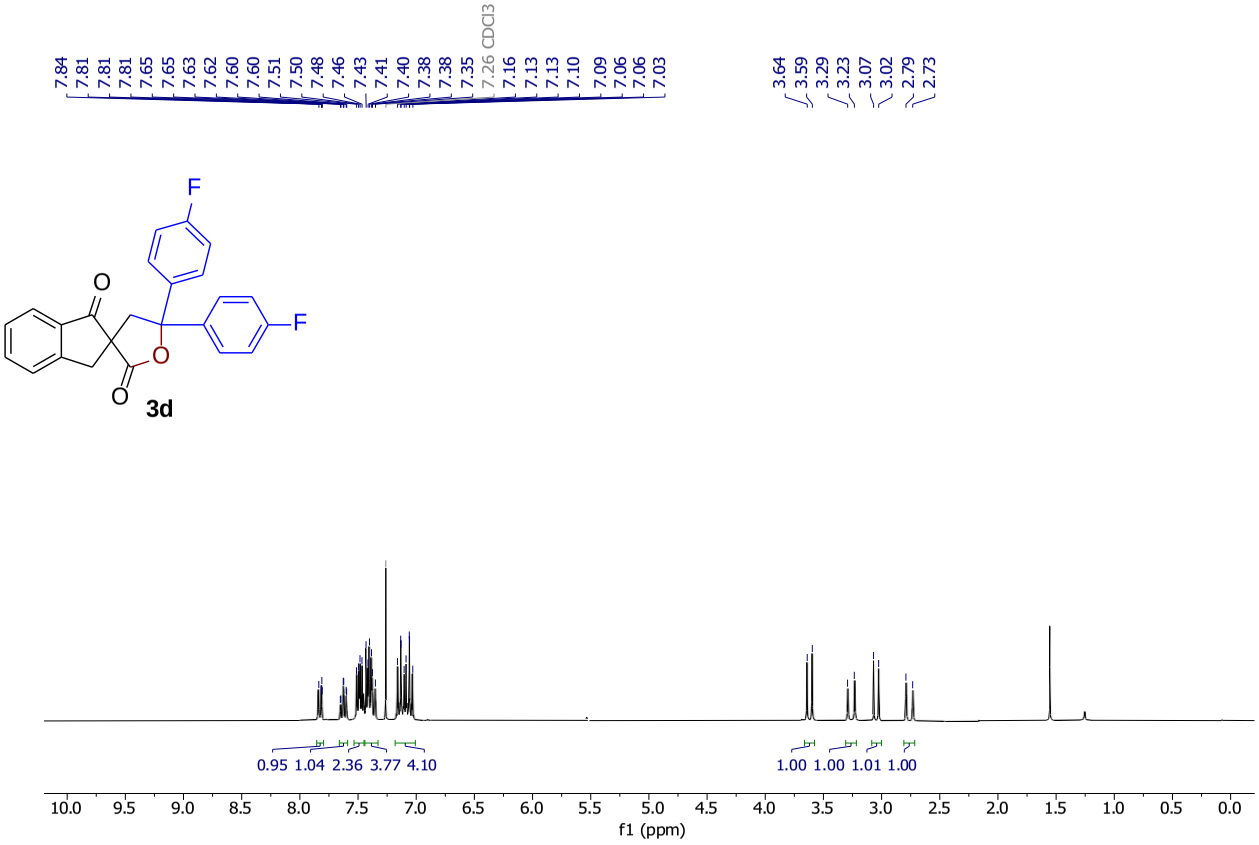


Figure S 21. ^{1}H NMR spectrum of **3d** in $CDCl_3$.

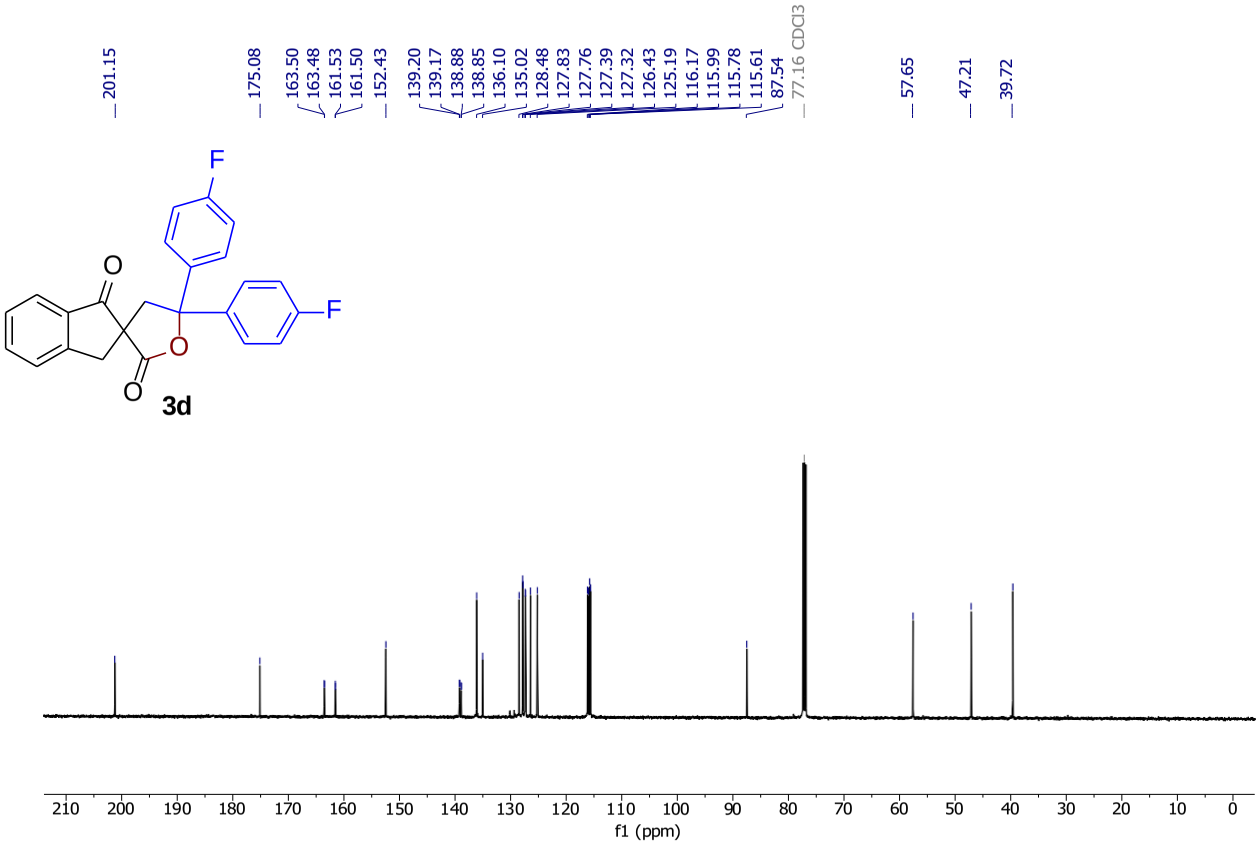


Figure S 22. ^{13}C NMR spectrum of **3d** in $CDCl_3$.

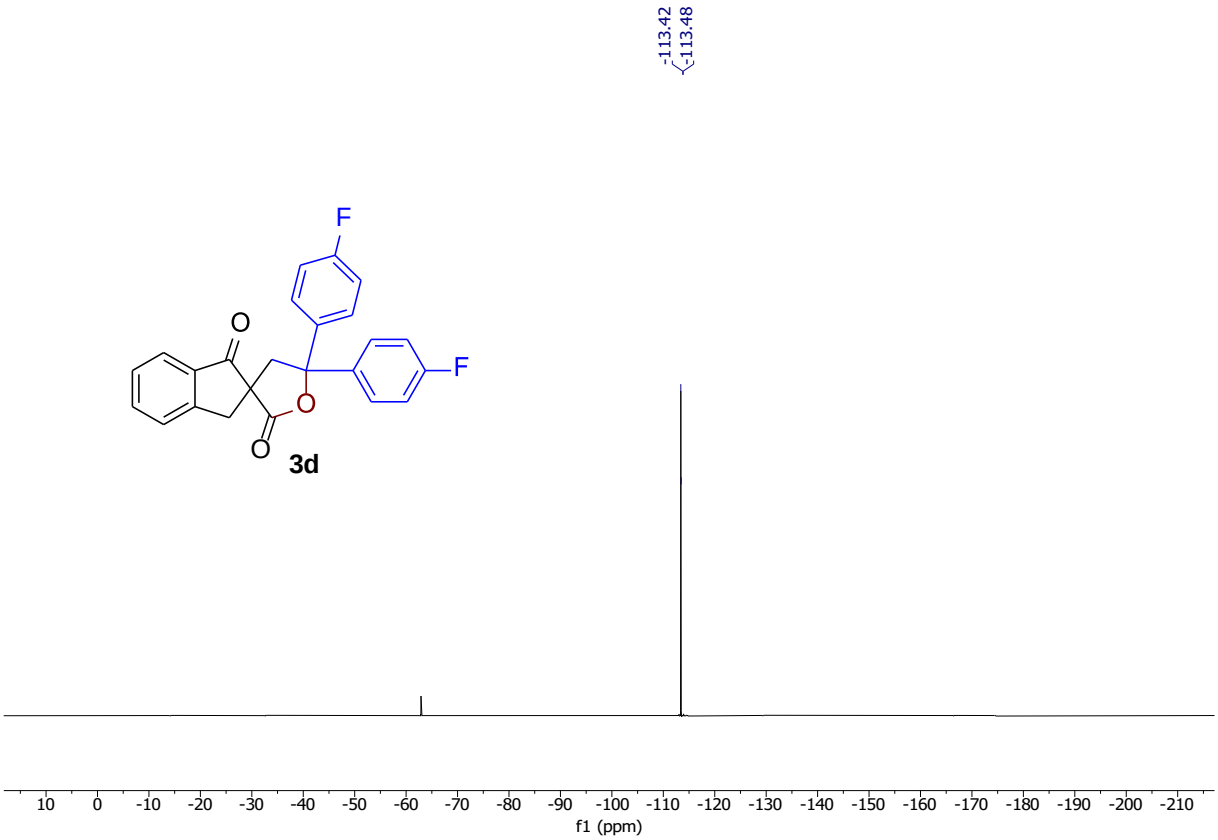


Figure S 23. ^{19}F NMR spectrum of **3d** in $CDCl_3$.

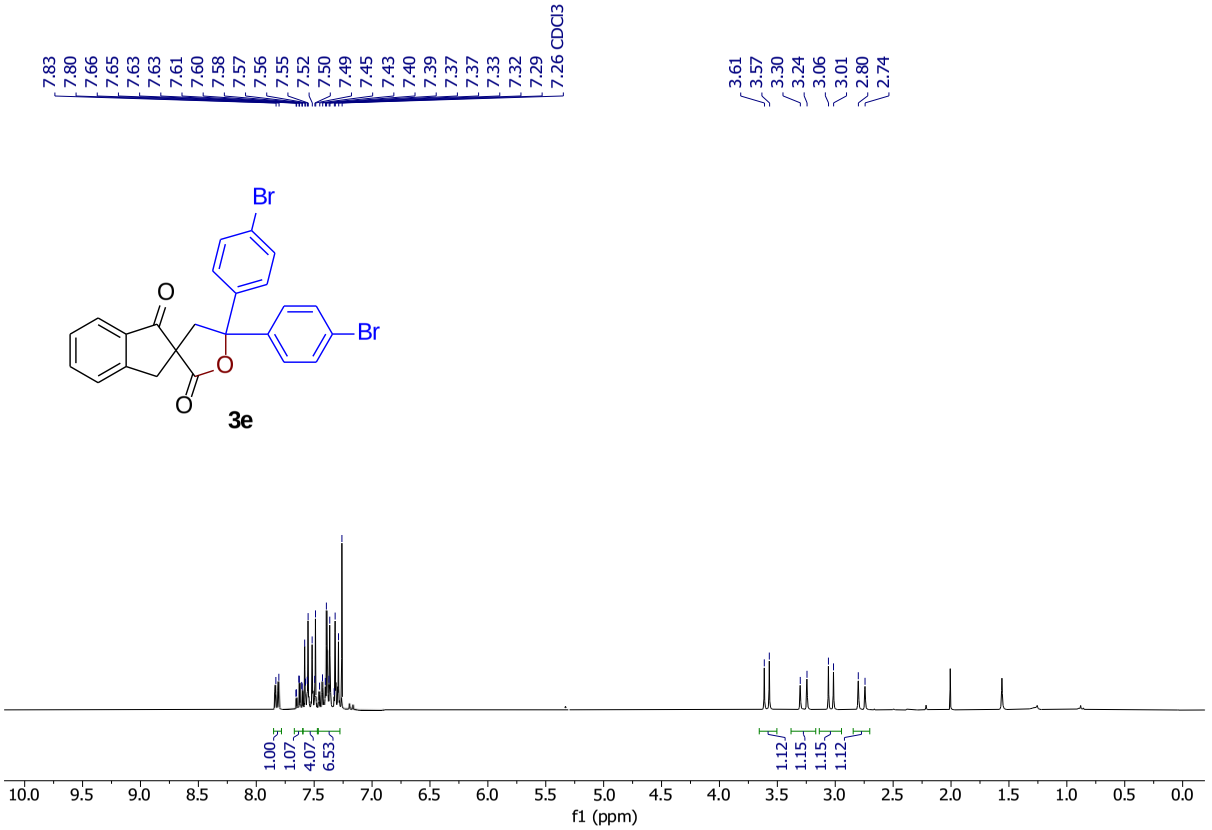


Figure S 24. ^{1}H NMR spectrum of **3e** in $CDCl_3$.

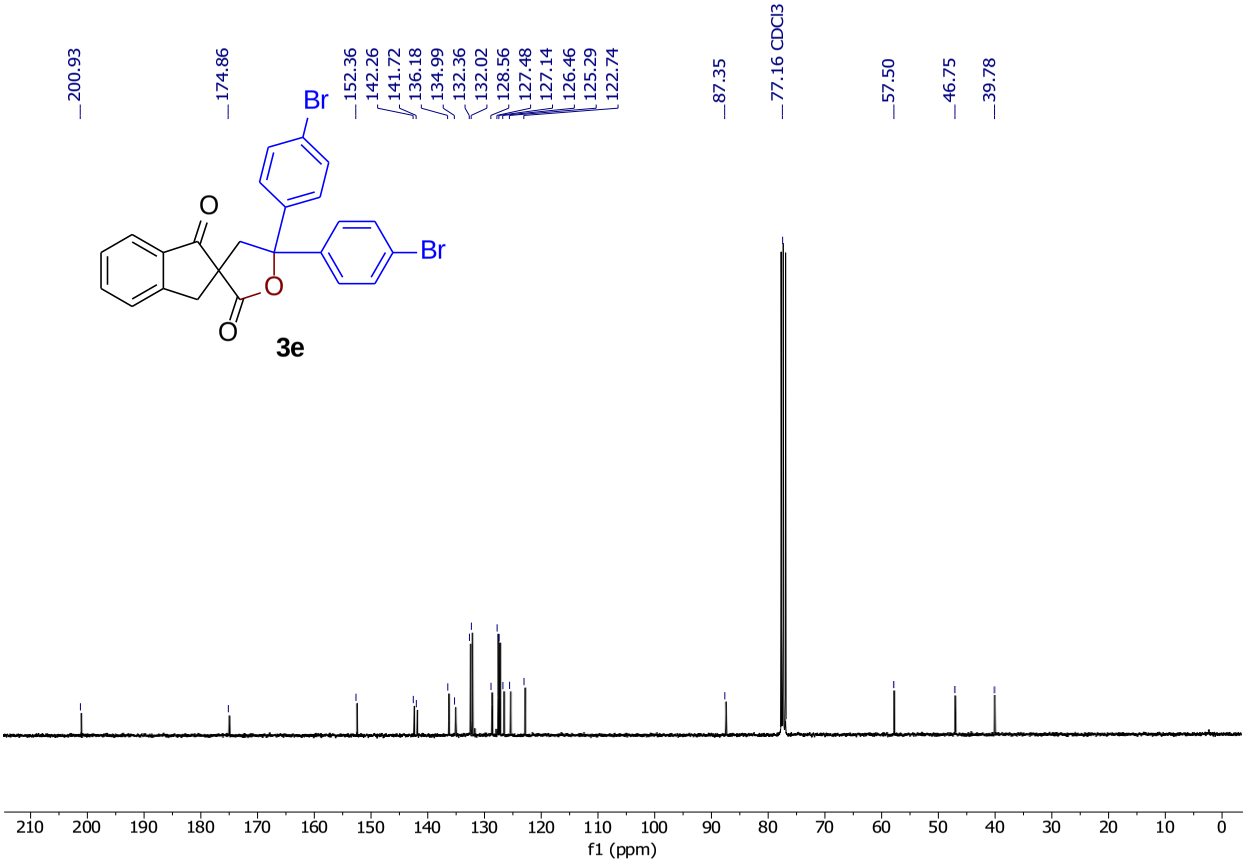


Figure S 25. ^{13}C NMR spectrum of **3e** in $CDCl_3$.

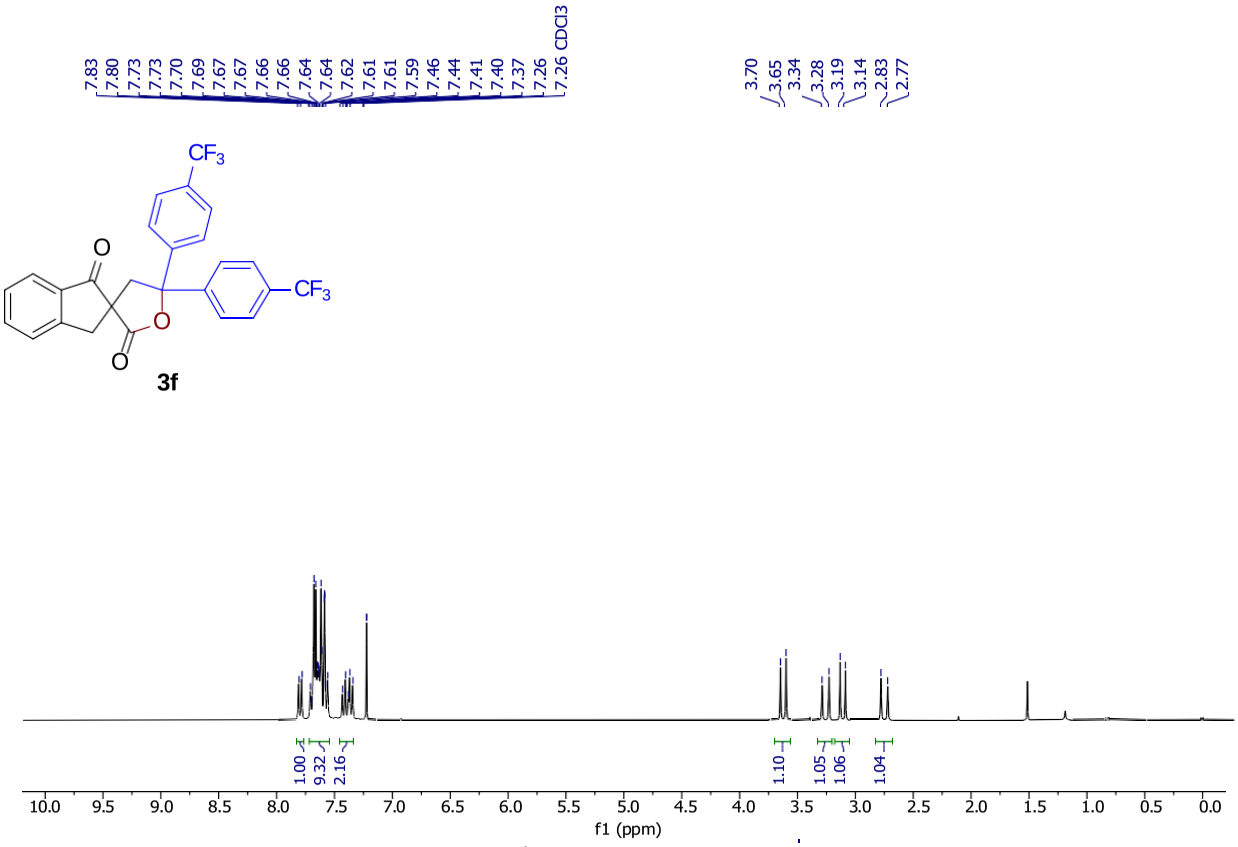


Figure S 26. ^{1}H NMR spectrum of **3f** in $CDCl_3$.

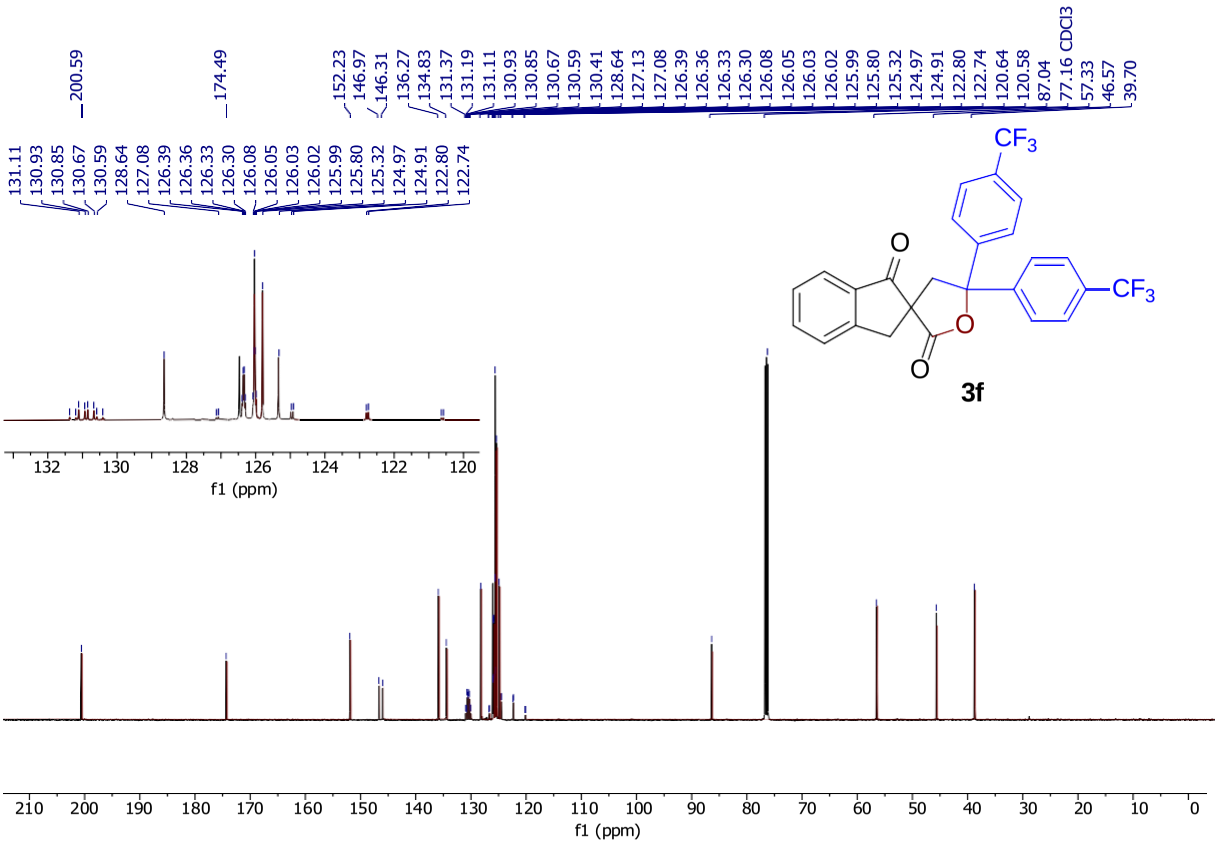


Figure S 27. ^{13}C NMR spectrum of **3f** in $CDCl_3$.

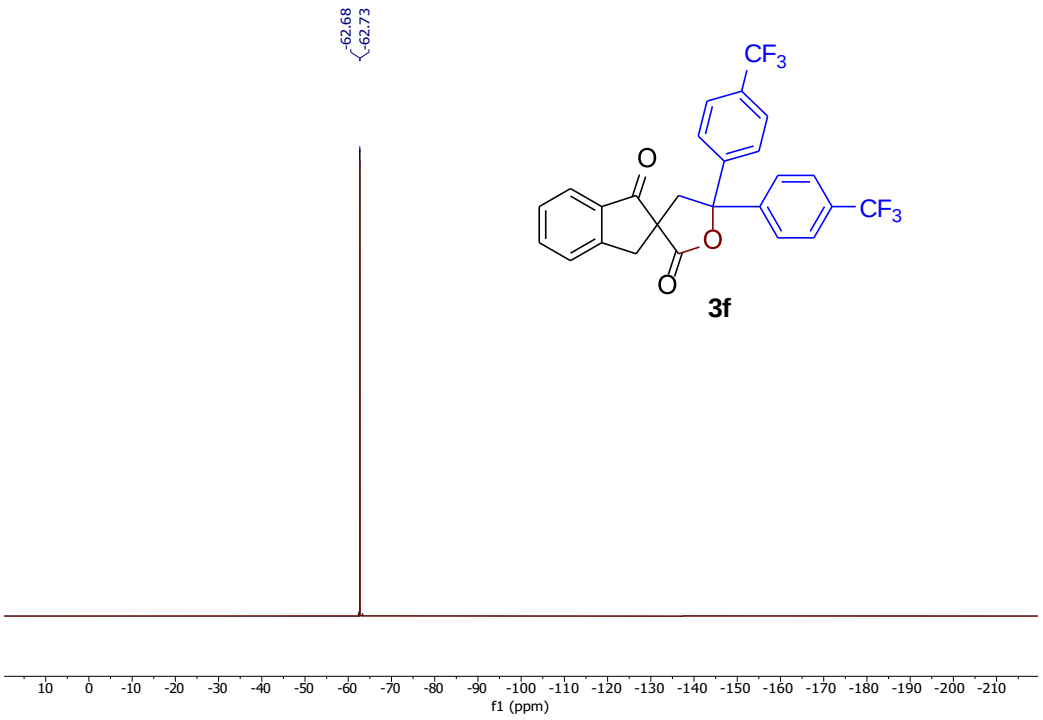


Figure S 28. ^{19}F NMR spectrum of **3f** in $CDCl_3$.

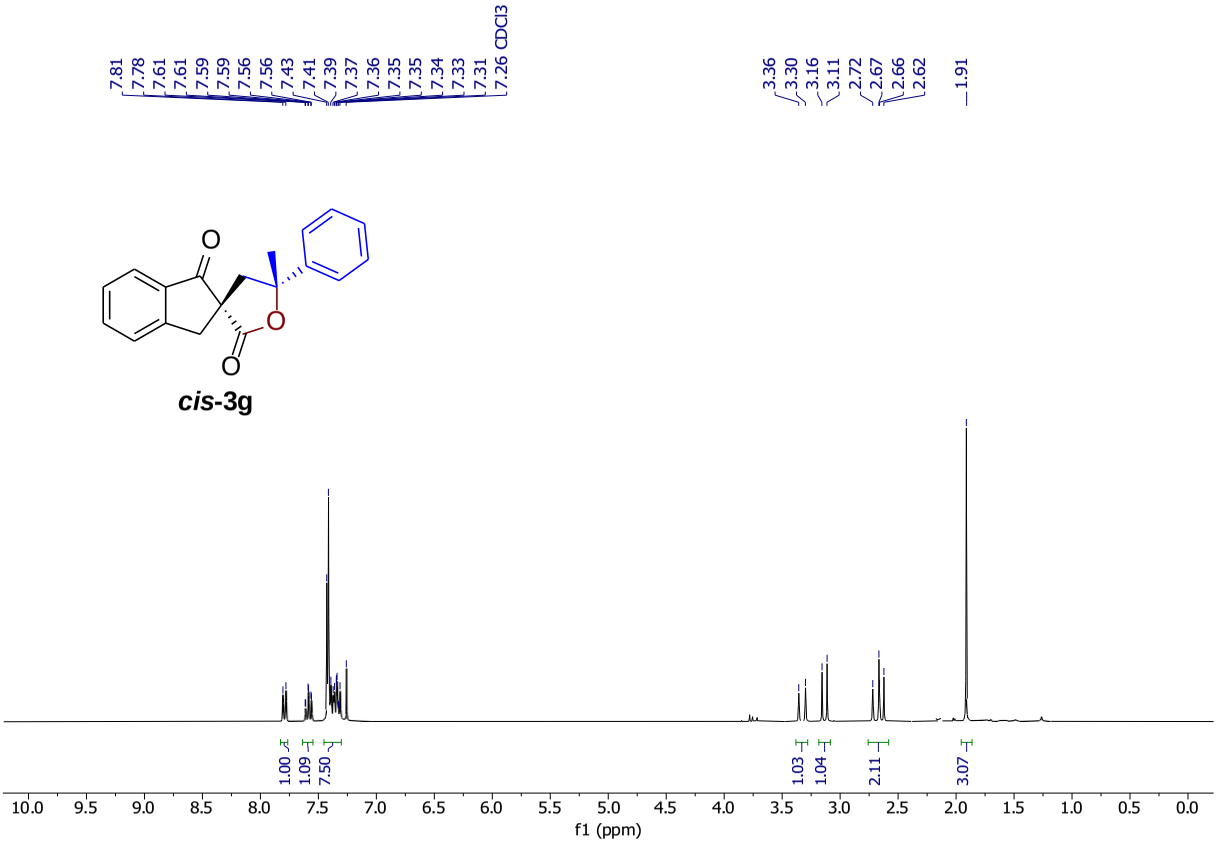


Figure S 29. ^{1}H NMR spectrum of ***cis*-3g** in $CDCl_3$.

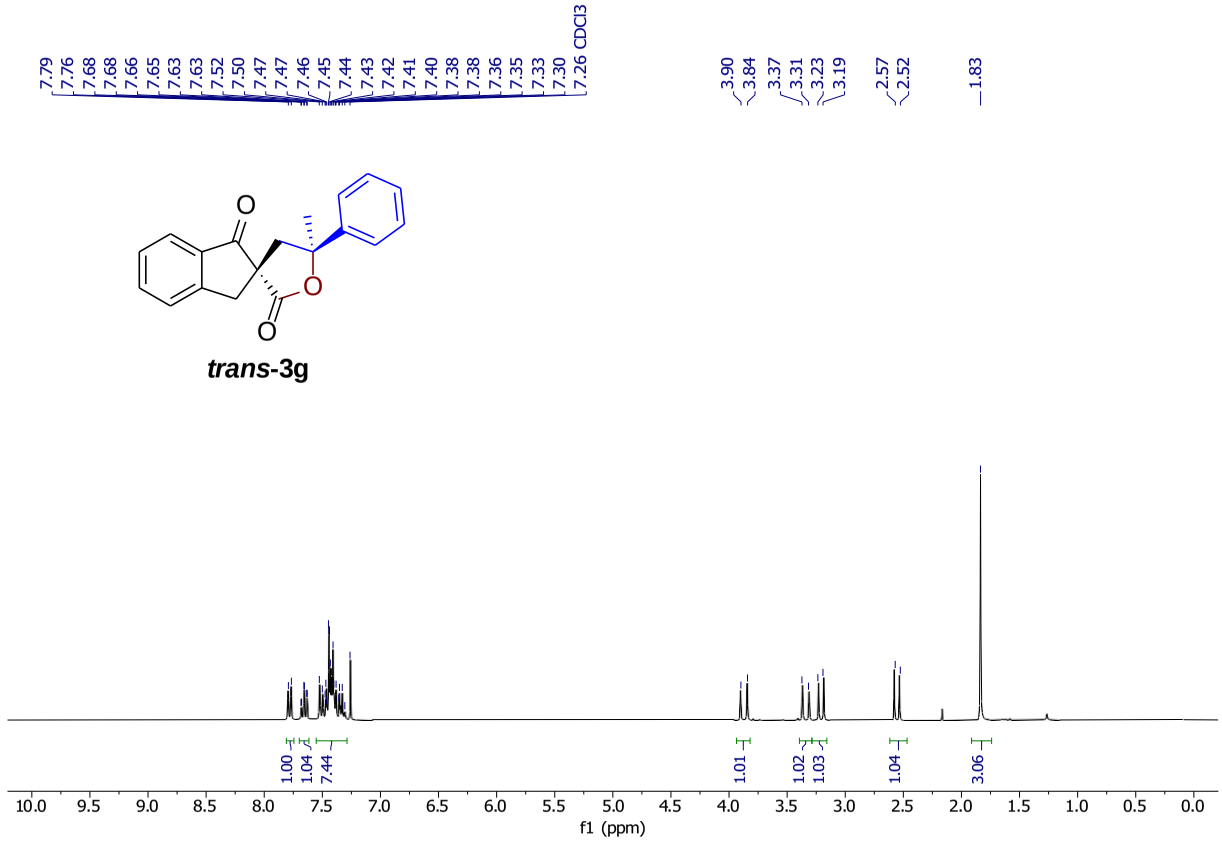


Figure S 30. ^{1}H NMR spectrum of ***trans*-3g** in $CDCl_3$.

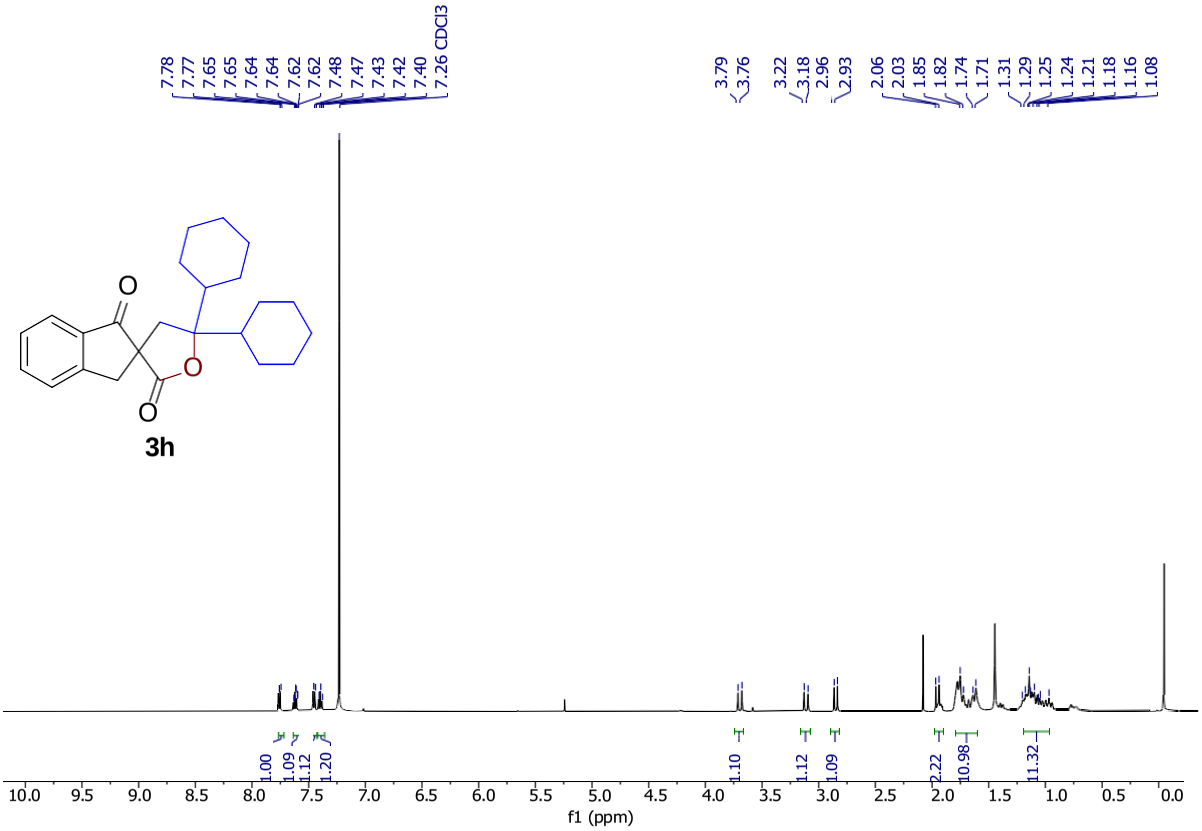


Figure S 31. ^{1}H NMR spectrum of **3h** in $CDCl_3$.

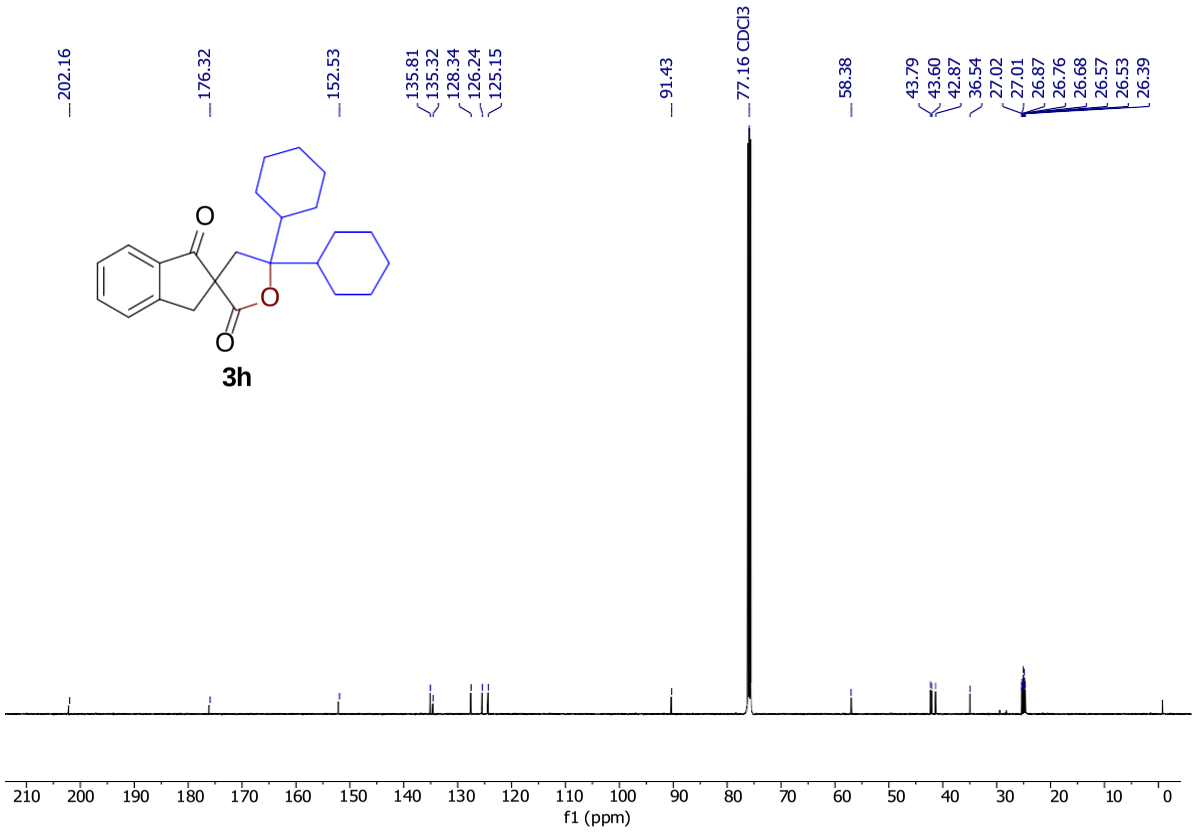
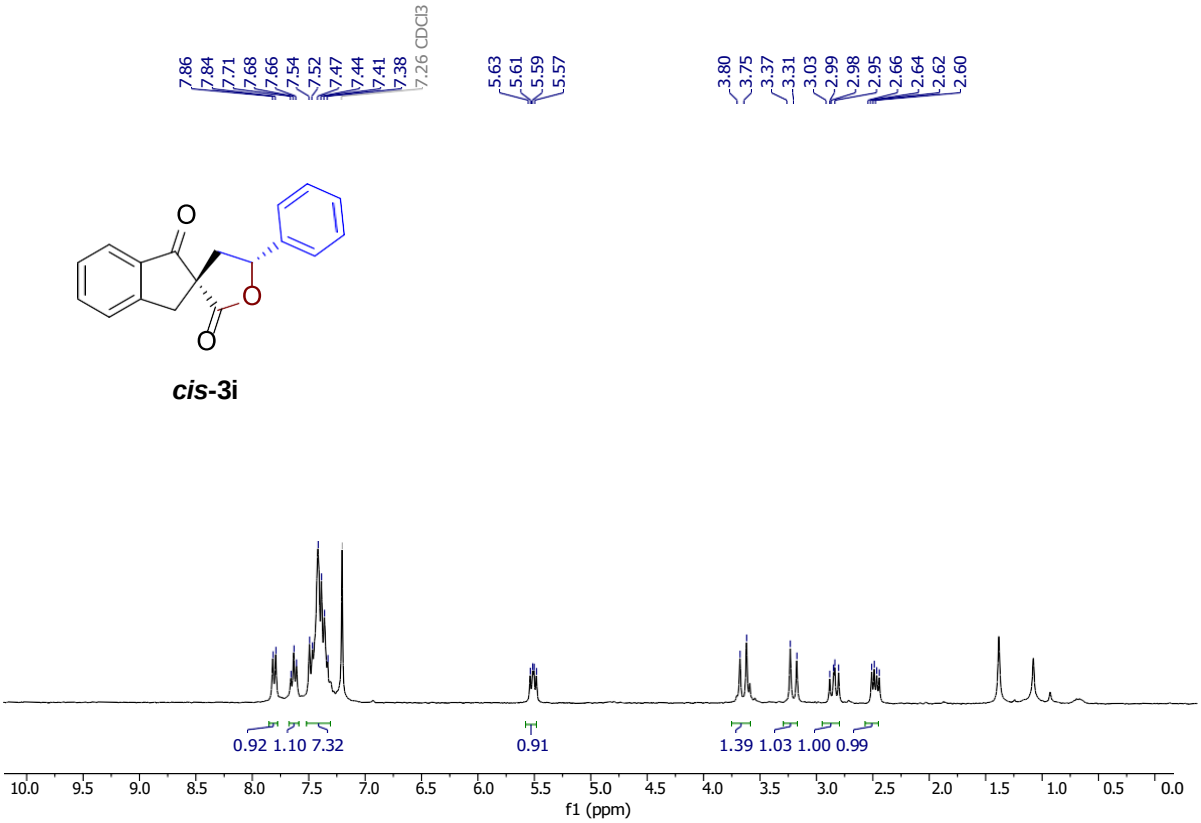
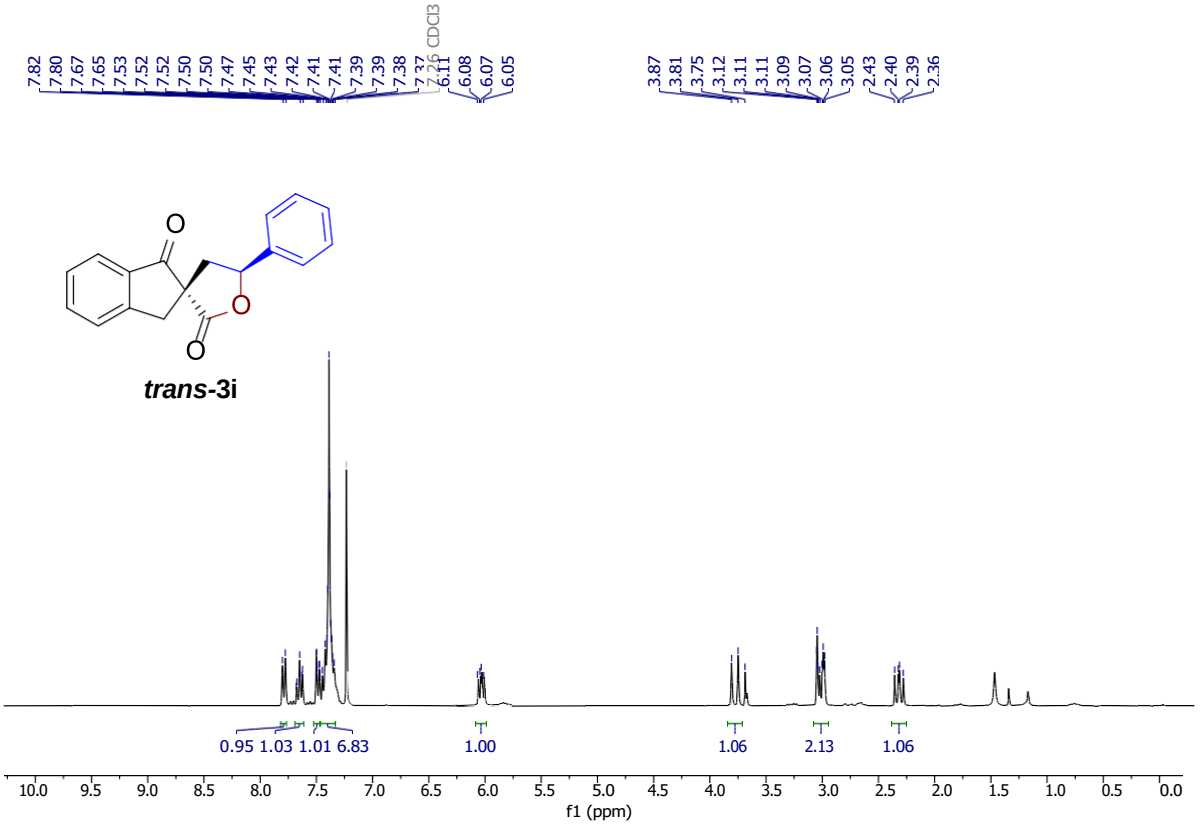


Figure S 32. ^{13}C NMR spectrum of **3h** in $CDCl_3$.



***cis*-3i**

Figure S 33. ^{1}H NMR spectrum of ***cis*-3i** in $CDCl_3$.



***trans*-3i**

Figure S 34. ^{1}H NMR spectrum of ***trans*-3i** in $CDCl_3$.

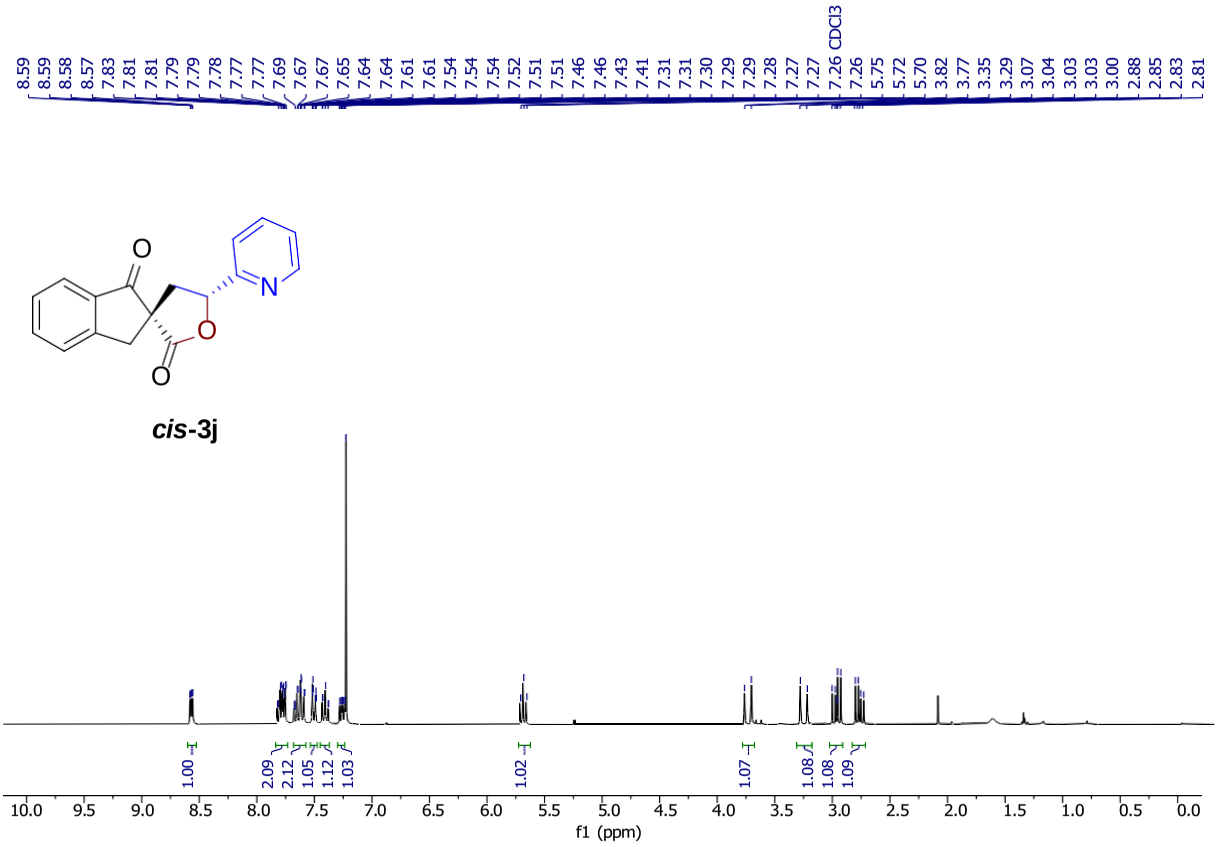


Figure S 35. ^{1}H NMR spectrum of ***cis*-3j** in $CDCl_3$.

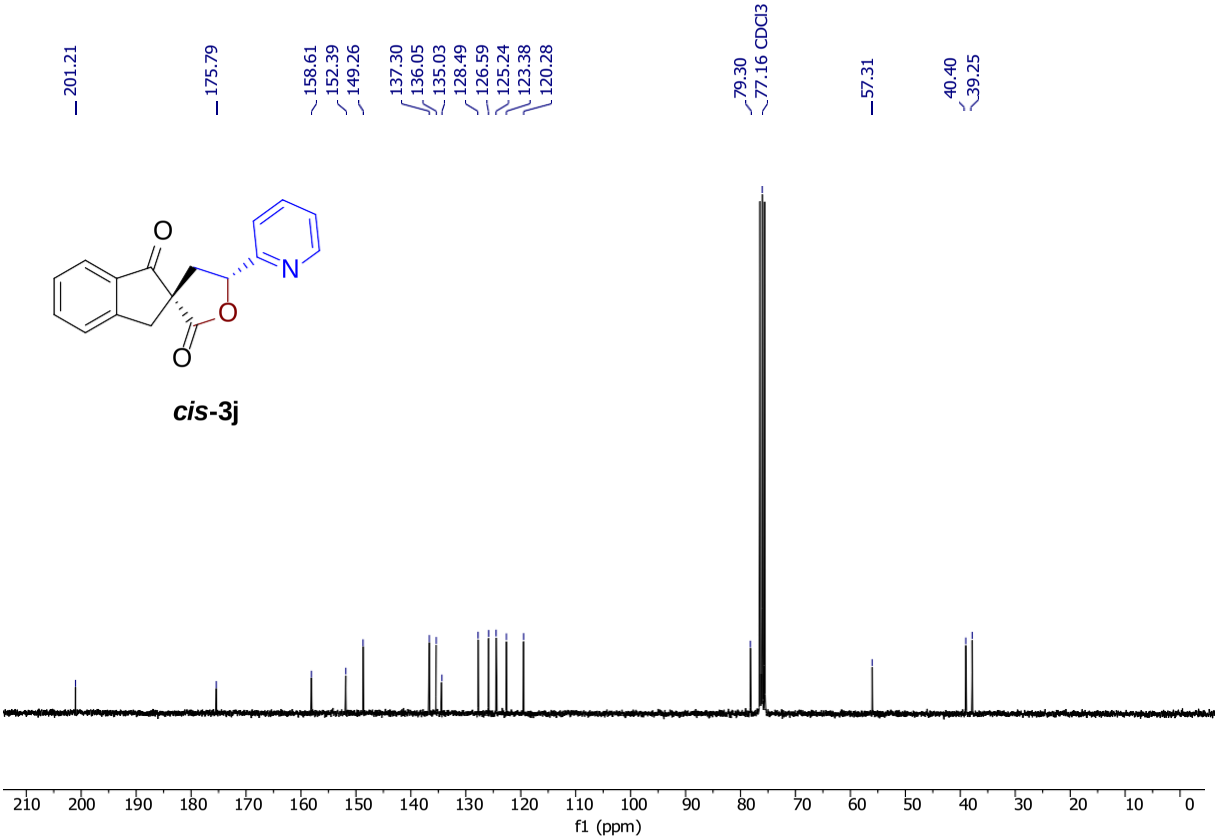


Figure S 36. ^{13}C NMR spectrum of ***cis*-3j** in $CDCl_3$.

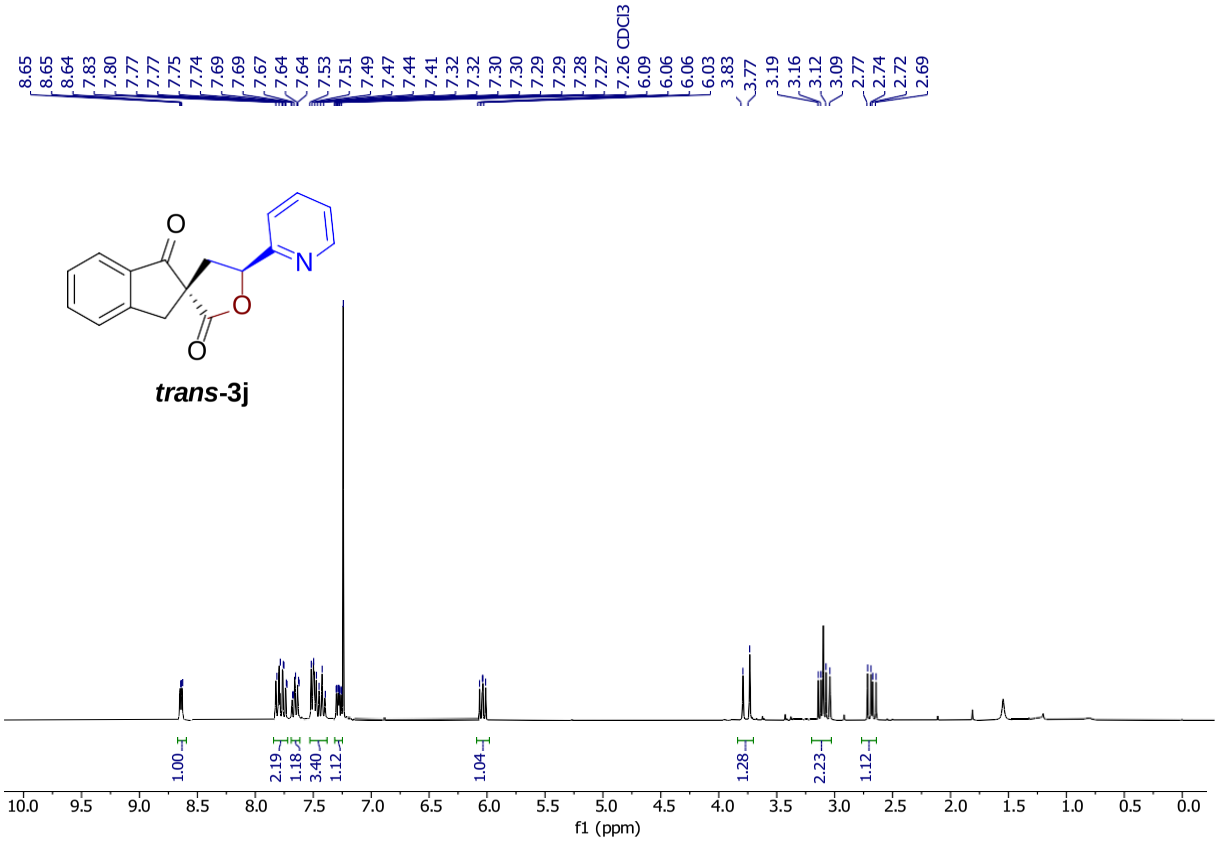


Figure S 37. ^{1}H NMR spectrum of ***trans*-3j** in $CDCl_3$.

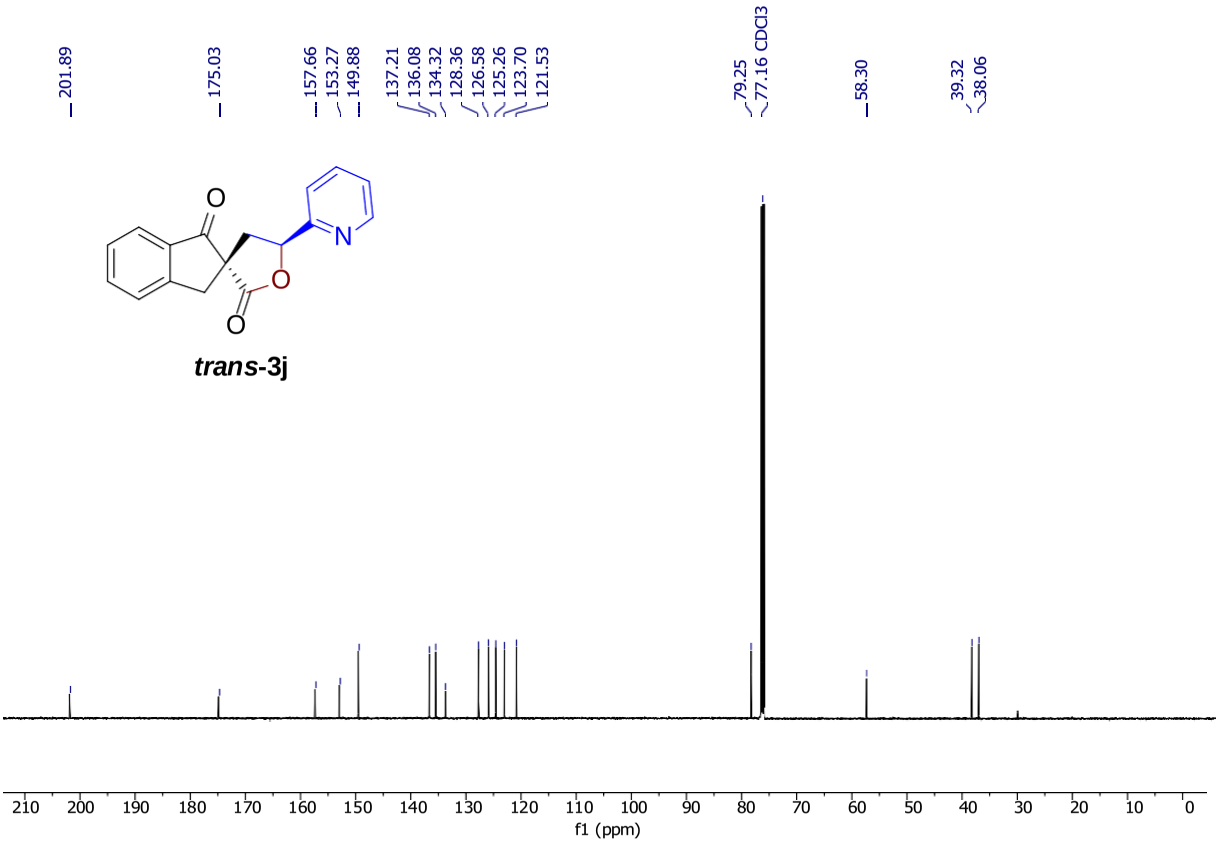


Figure S 38. ^{13}C NMR spectrum of ***trans*-3j** in $CDCl_3$.

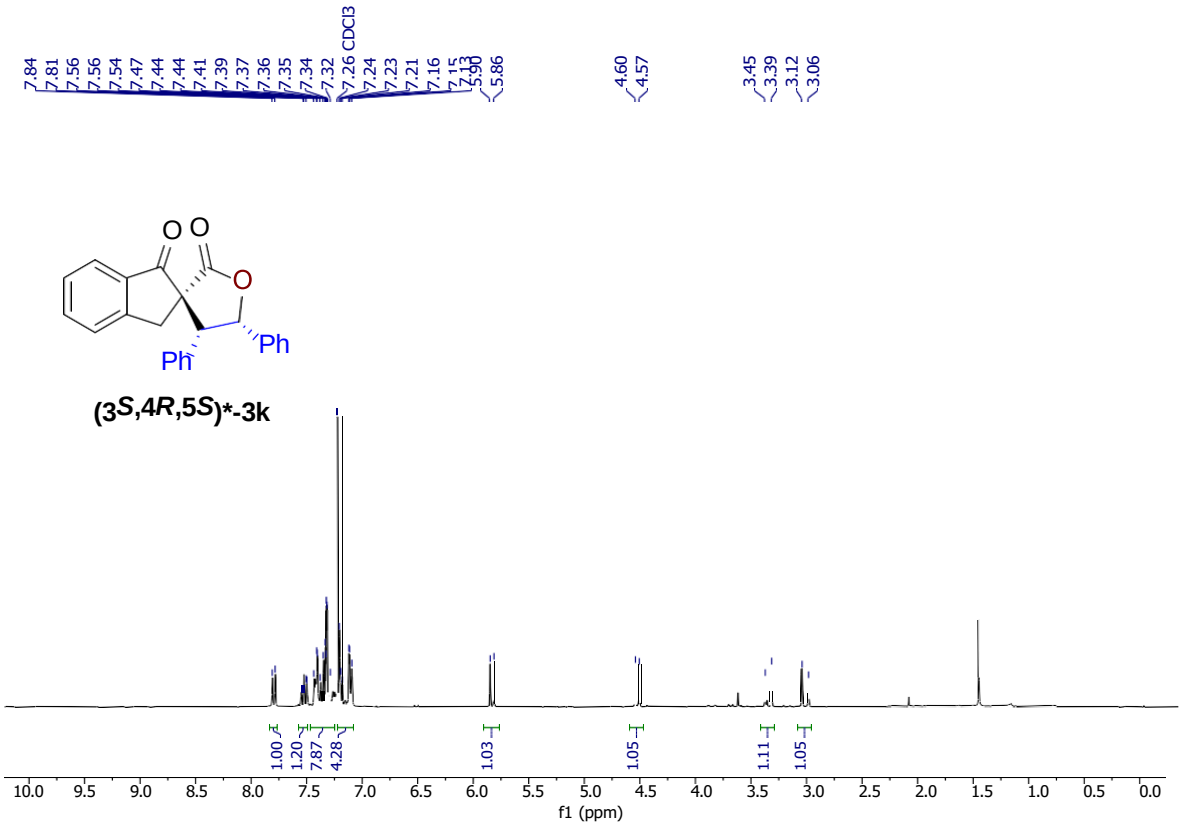


Figure S 39. ^{1}H NMR spectrum of **(3*S*,4*R*,5*S*)*-3k** in $CDCl_3$

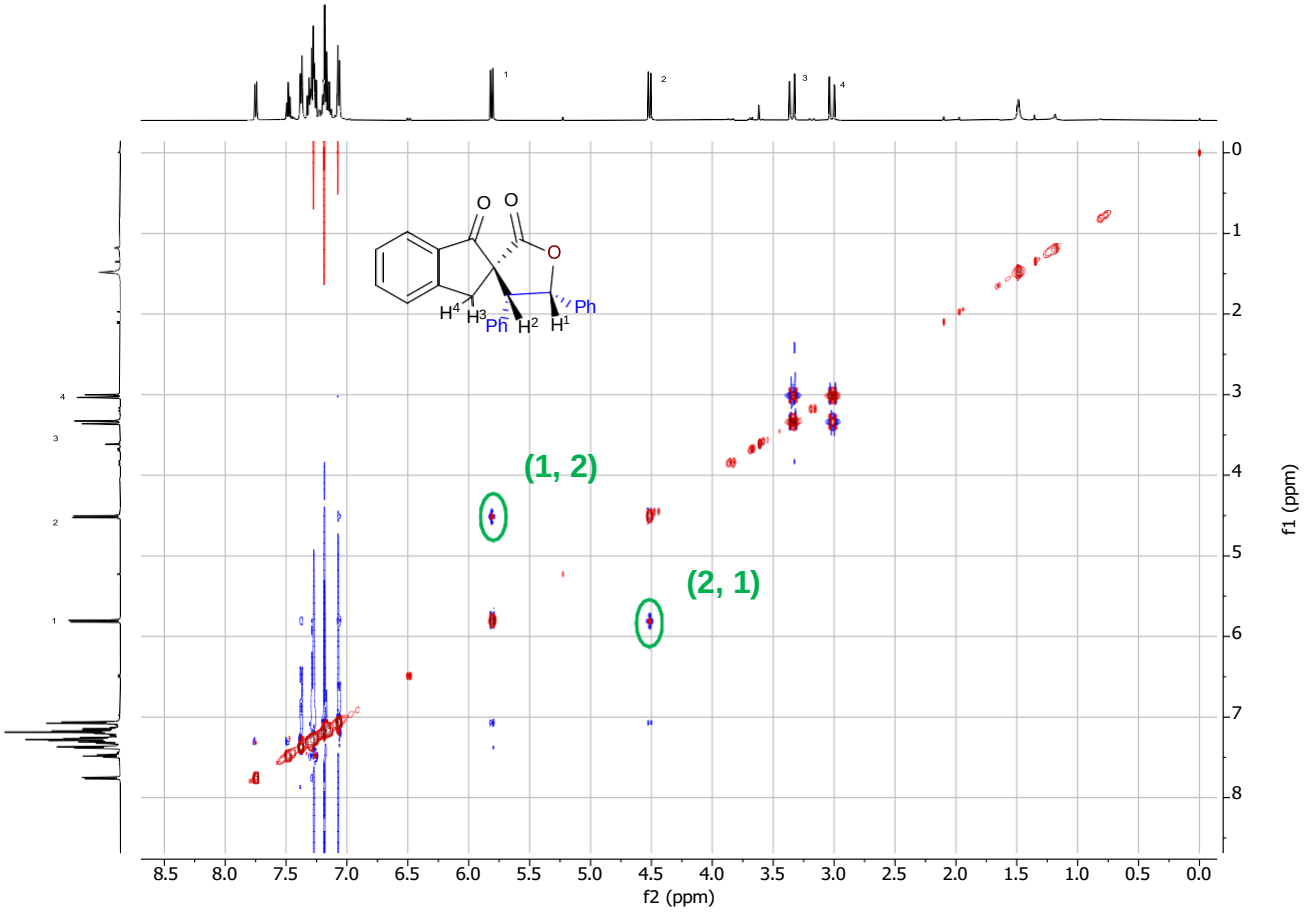
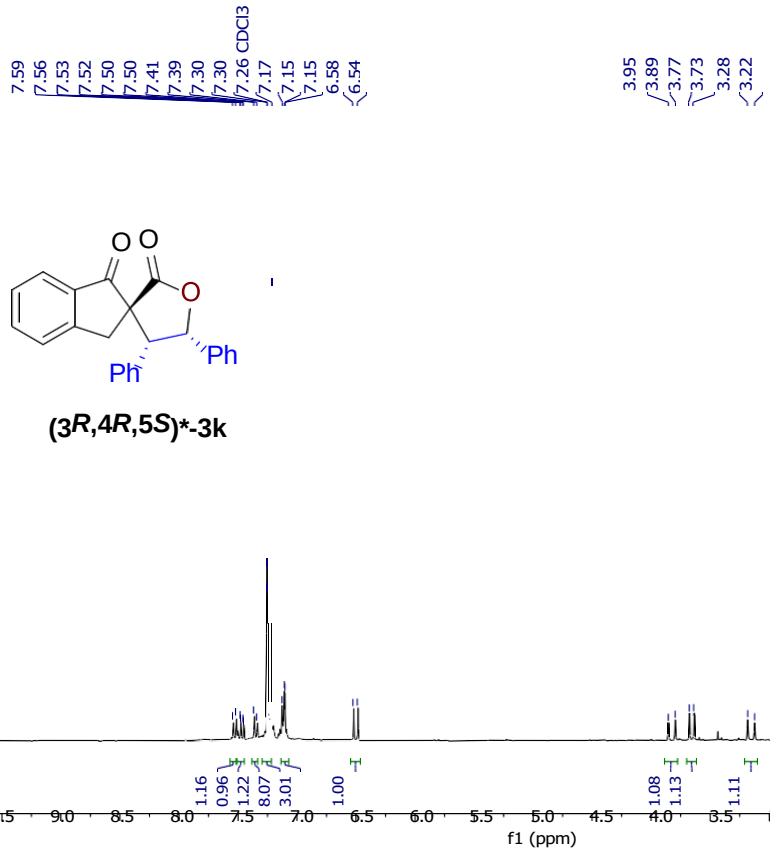


Figure S 40. 2D ^{1}H-^{1}H NOESY spectrum of **(3*S*,4*R*,5*S*)*-3k** in $CDCl_3$



(3*R*,4*R*,5*S*)*-3k

Figure S 41. ^{1}H NMR spectrum of **(3*S*,4*R*,5*S*)*-3k** in $CDCl_3$

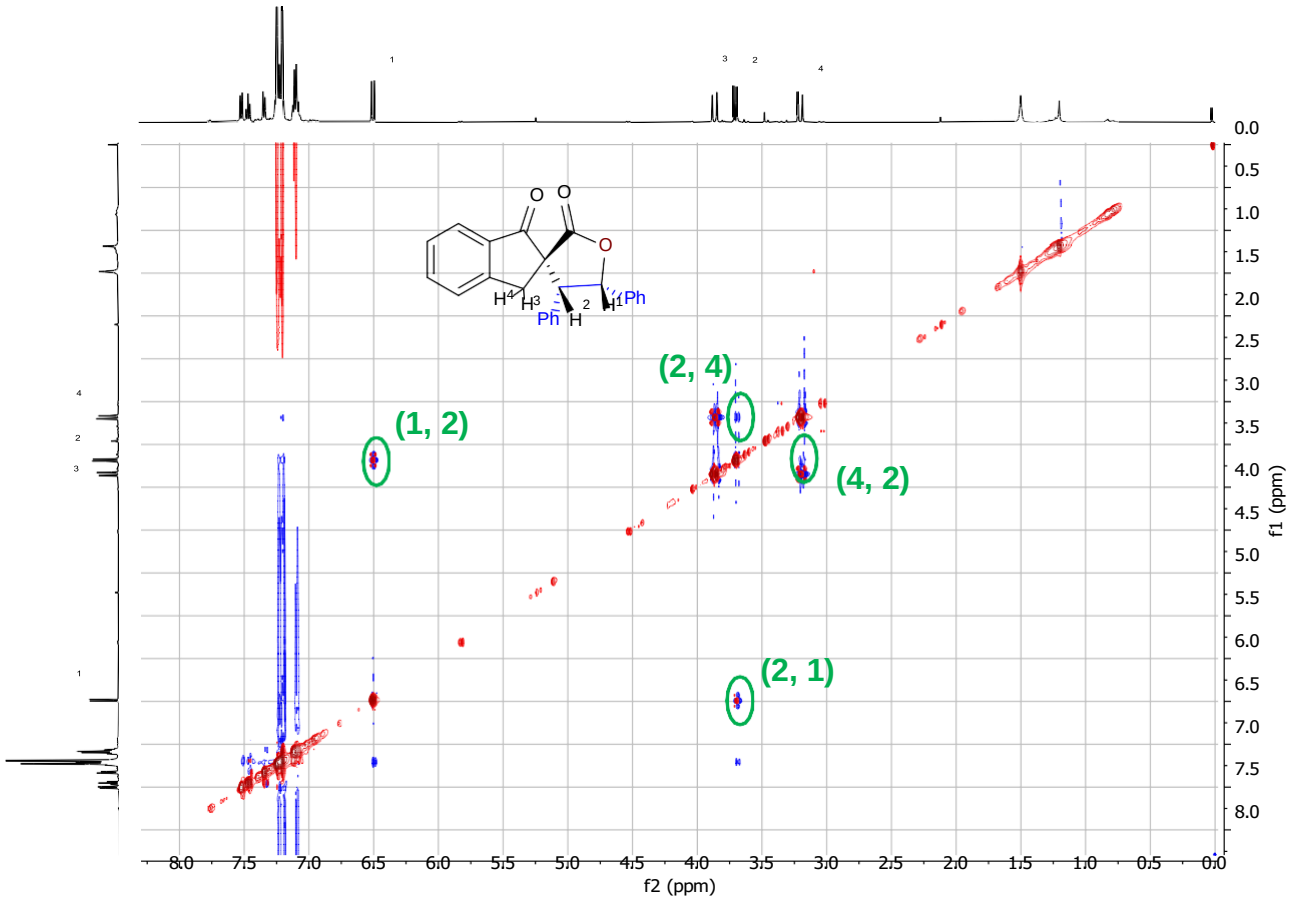


Figure S 42. 2D ^{1}H-^{1}H NOESY spectrum of **(3*S*,4*R*,5*S*)*-3k** in $CDCl_3$

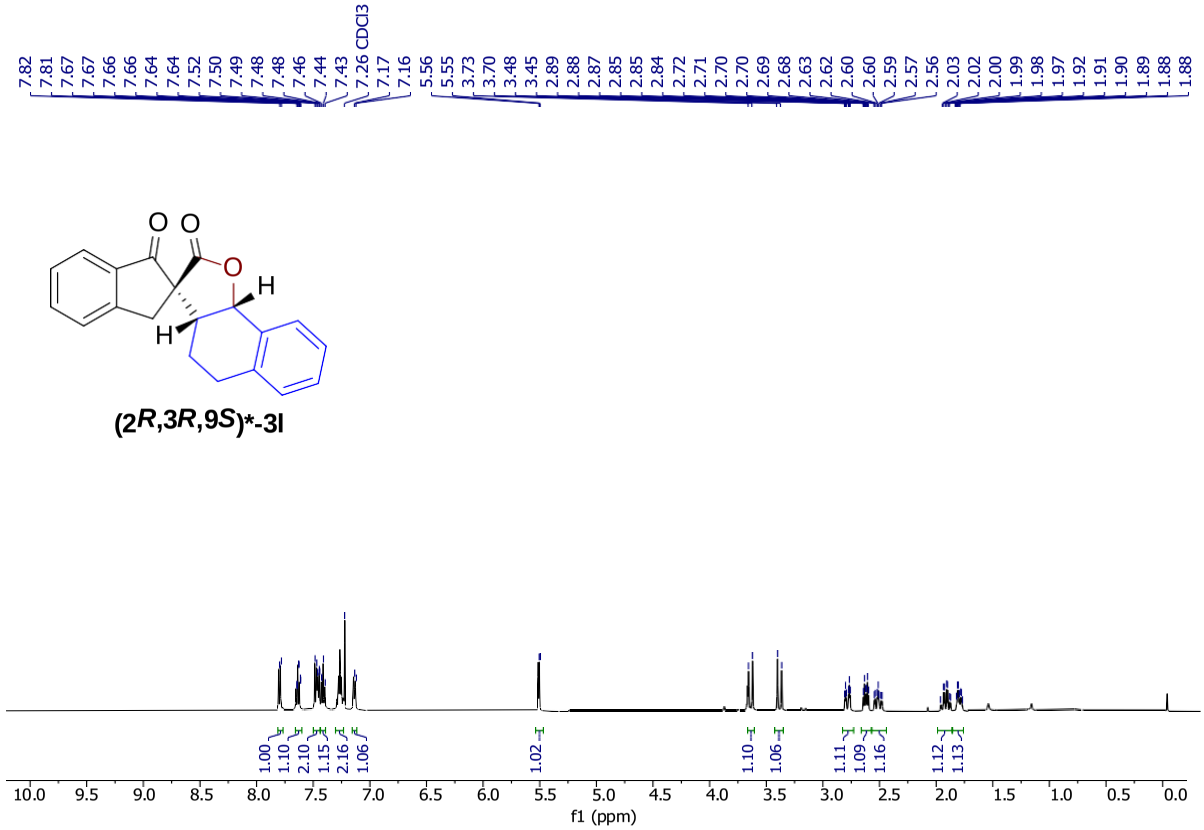


Figure S 43. ^{1}H NMR spectrum of **(2*R*,3*R*,9*S*)*-3l** in $CDCl_3$

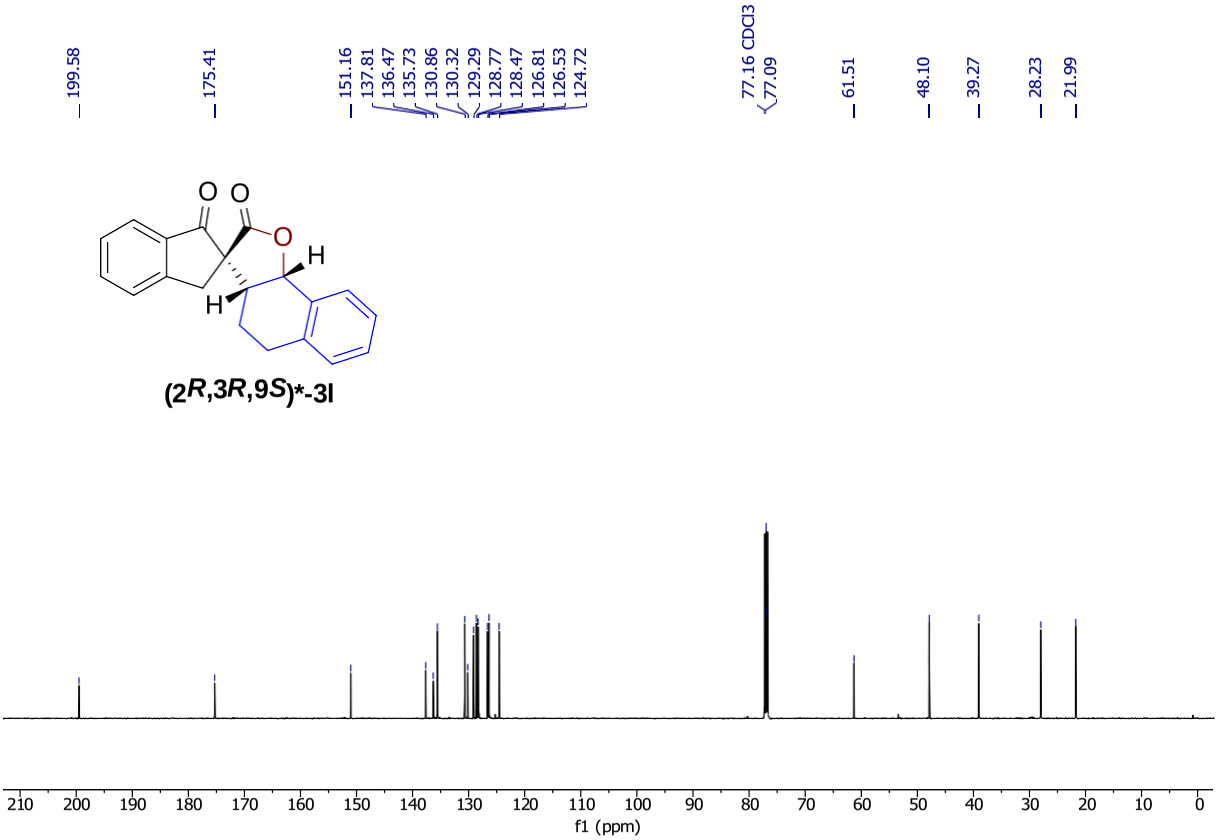


Figure S 44. ^{13}C NMR spectrum of **(2*R*,3*R*,9*S*)*-3l** in $CDCl_3$

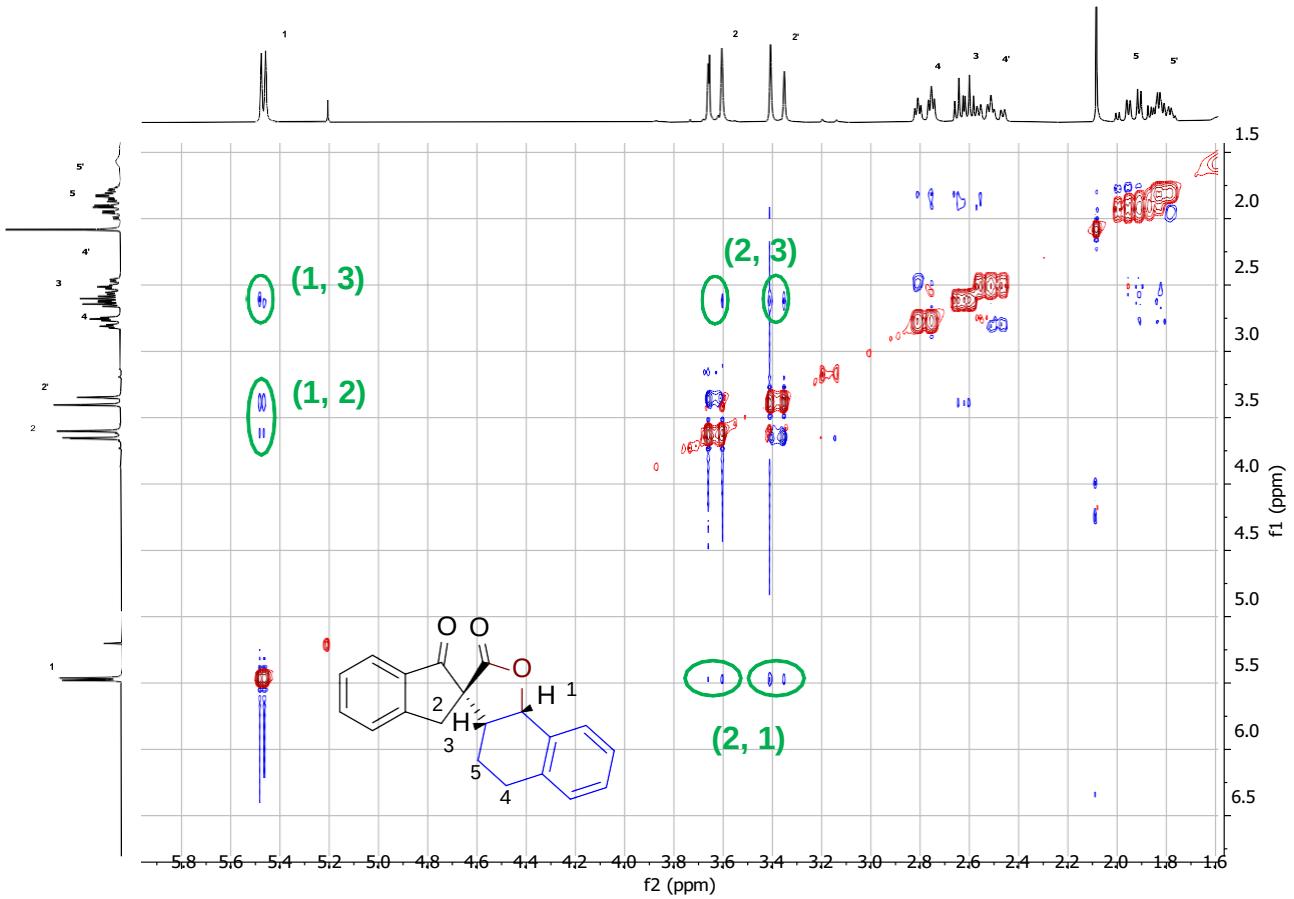


Figure S 45. 2D ^{1}H-^{1}H NOESY spectrum of **(2*R*,3*R*,9*S*)*-3l** in $CDCl_3$

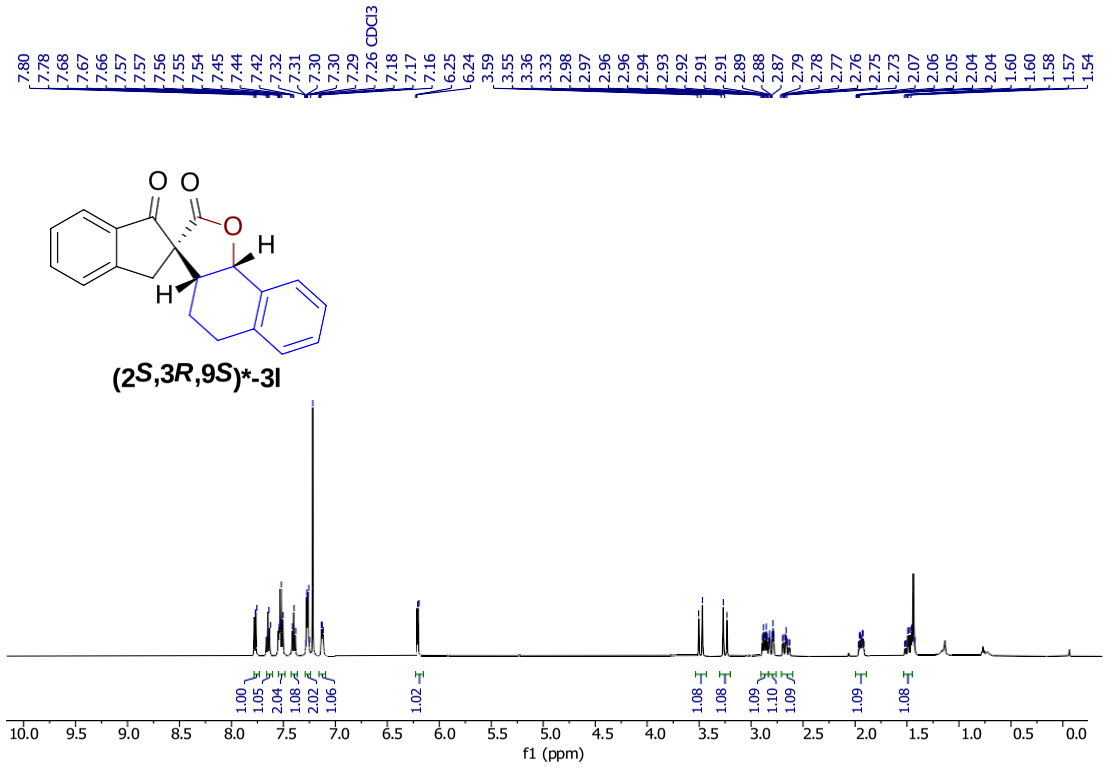


Figure S 46. ^{1}H NMR spectrum of **(2*S*,3*R*,9*S*)*-3l** in $CDCl_3$

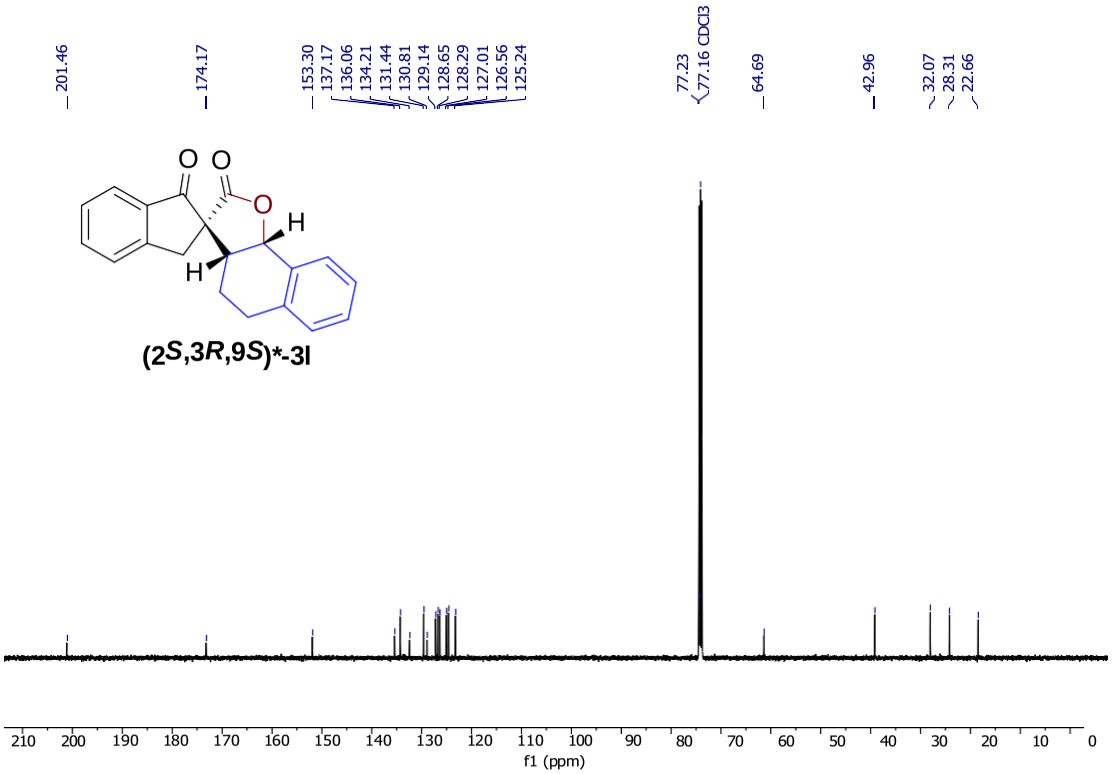


Figure S 47. ^{13}C NMR spectrum of **(2*S*,3*R*,9*S*)*-3l** in $CDCl_3$

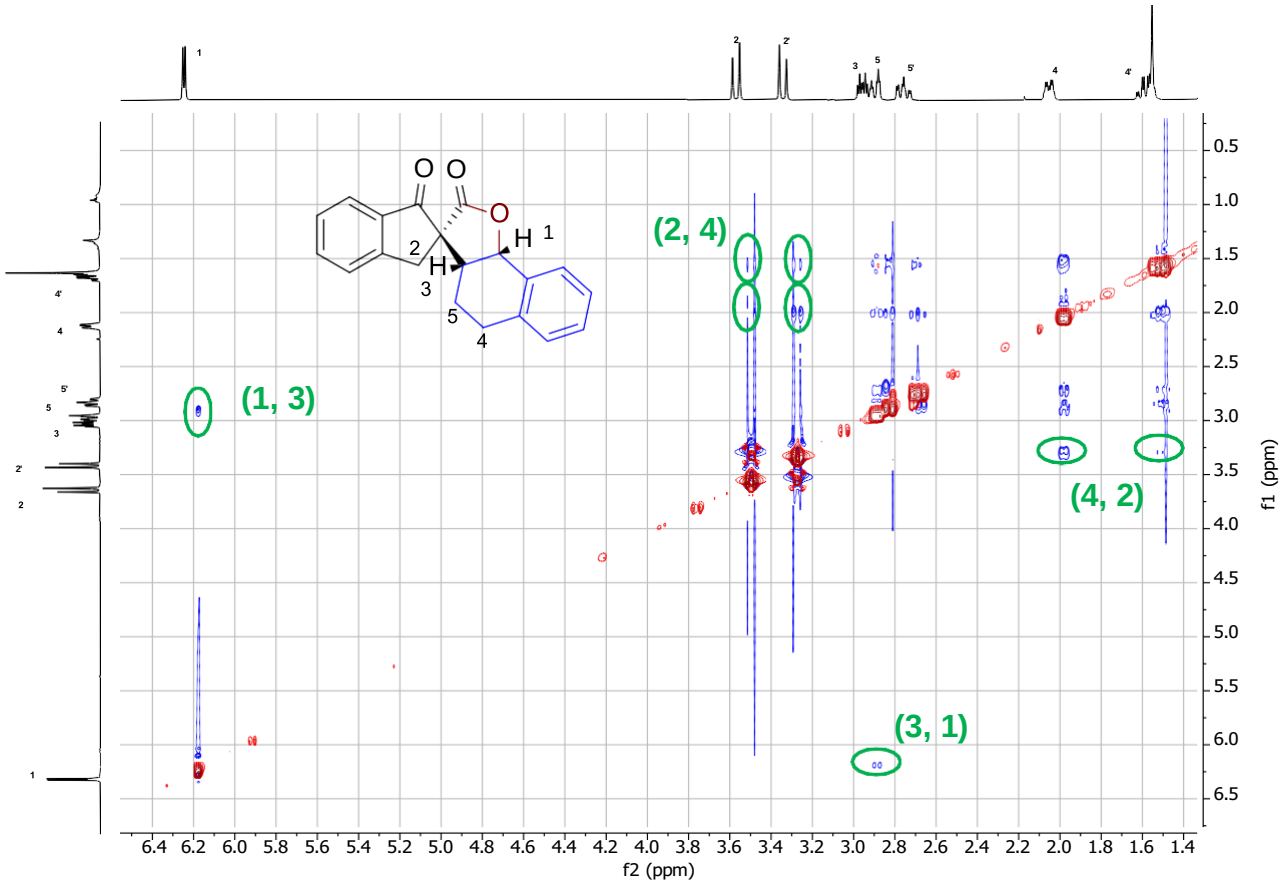
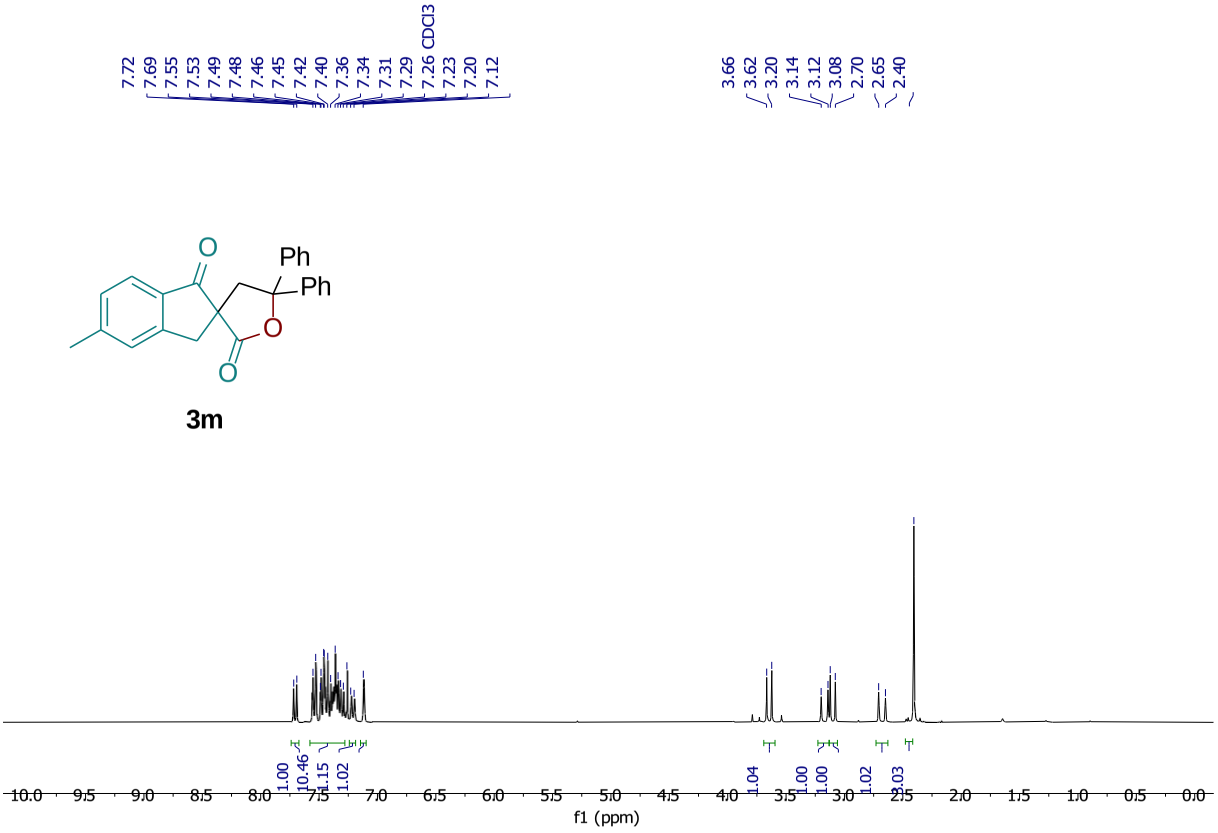
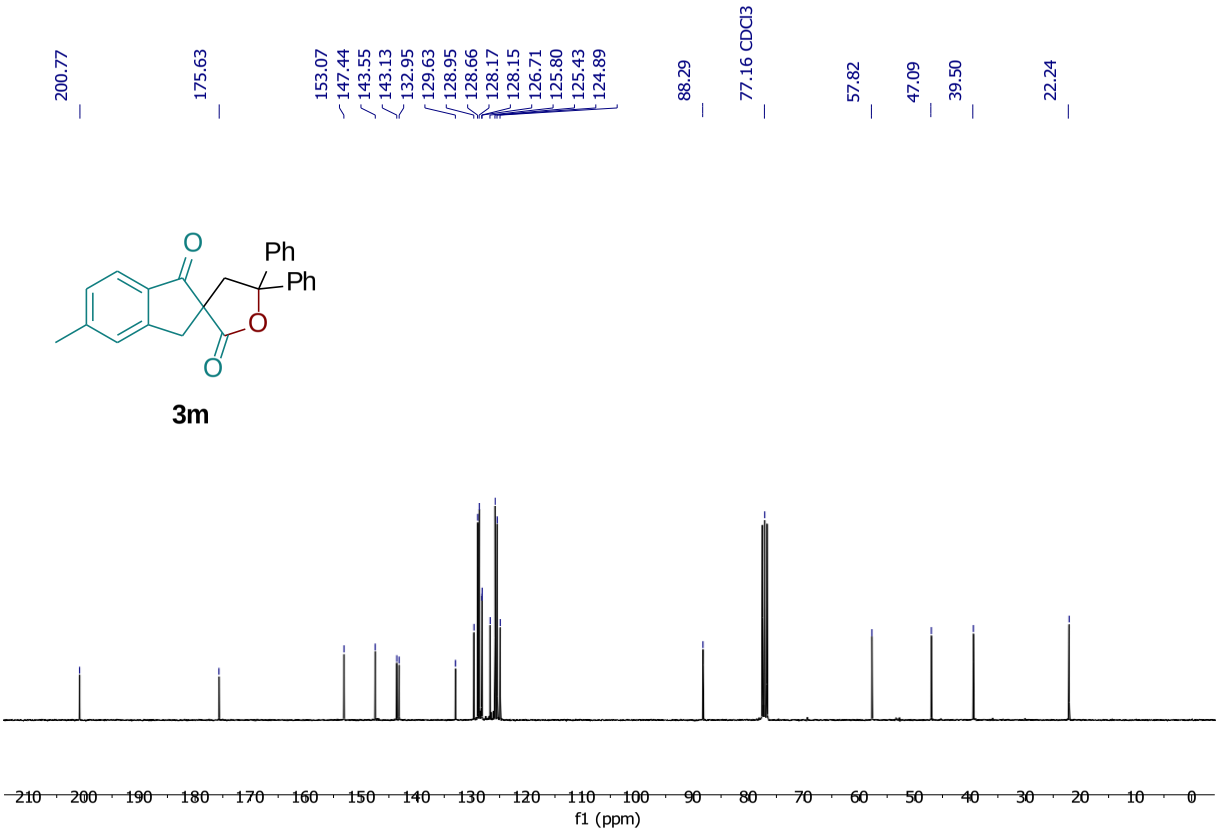


Figure S 48. 2D ^{1}H-^{1}H NOESY spectrum of **(2*S*,3*R*,9*S*)*-3l** in $CDCl_3$



3m

Figure S 49. ^{1}H NMR spectrum of **3m** in $CDCl_3$



3m

Figure S 50. ^{13}C NMR spectrum of **3m** in $CDCl_3$.

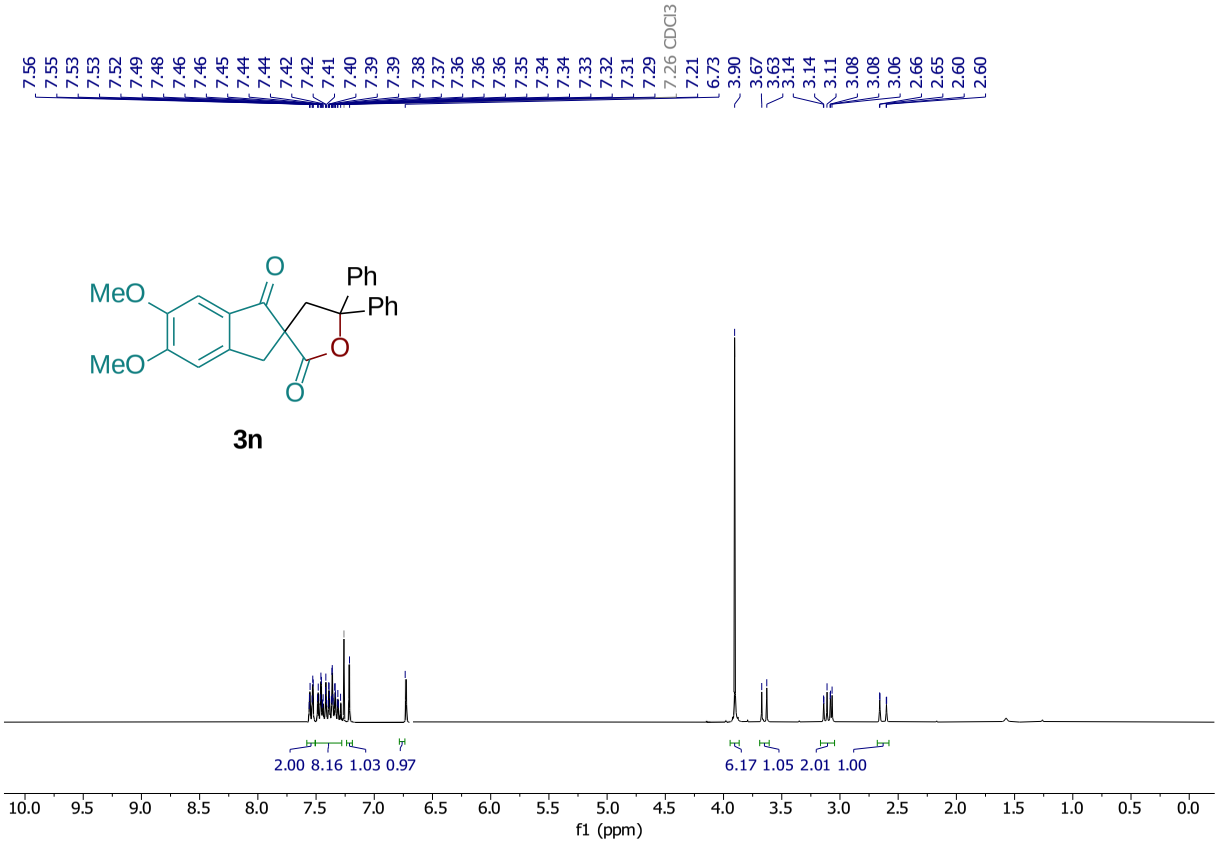


Figure S 51. ^{1}H NMR spectrum of **3n** in $CDCl_3$

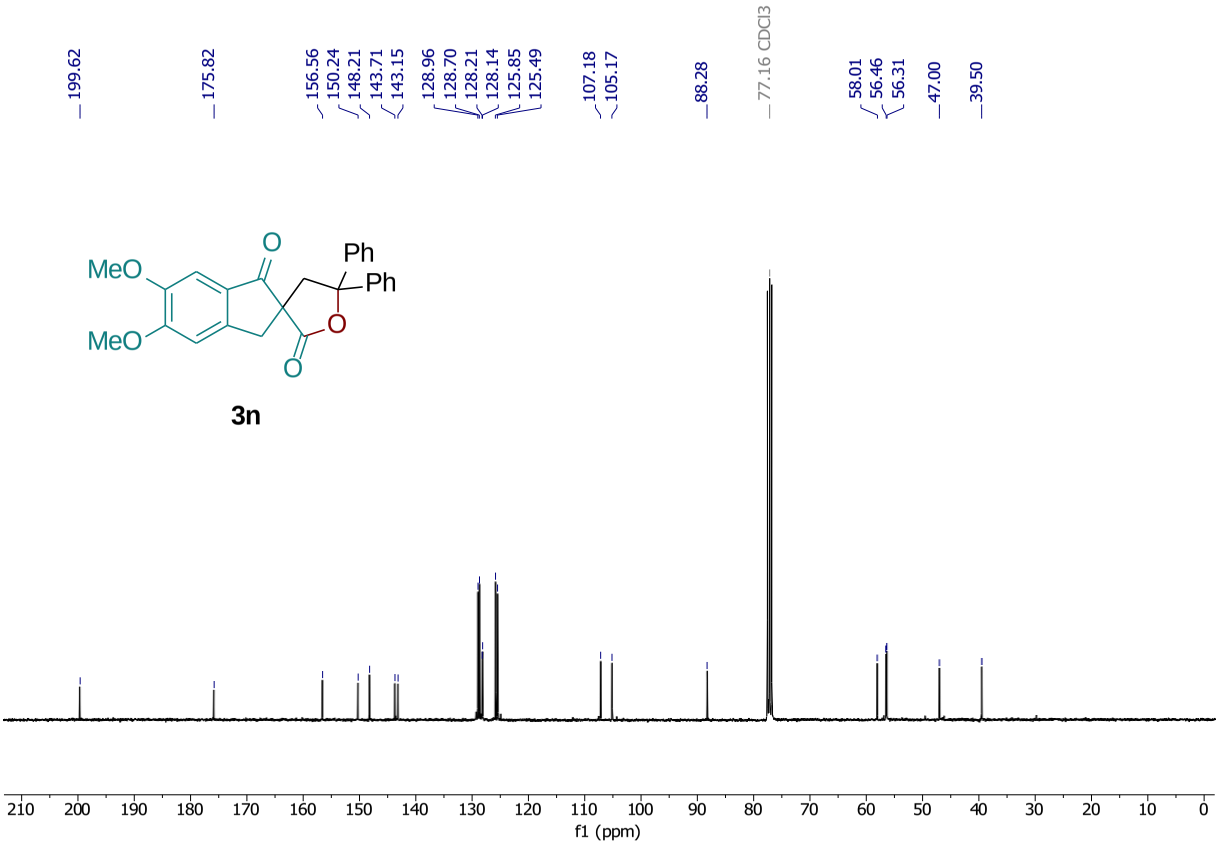
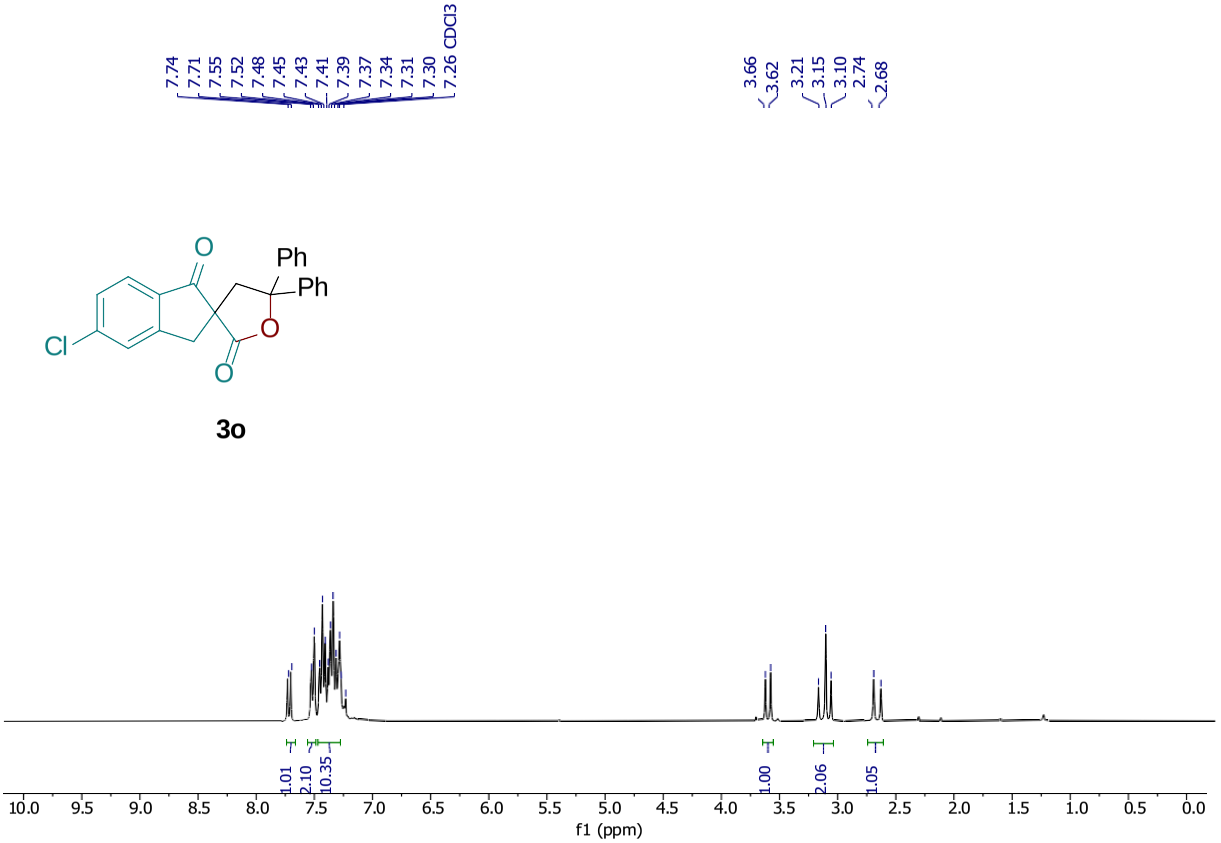
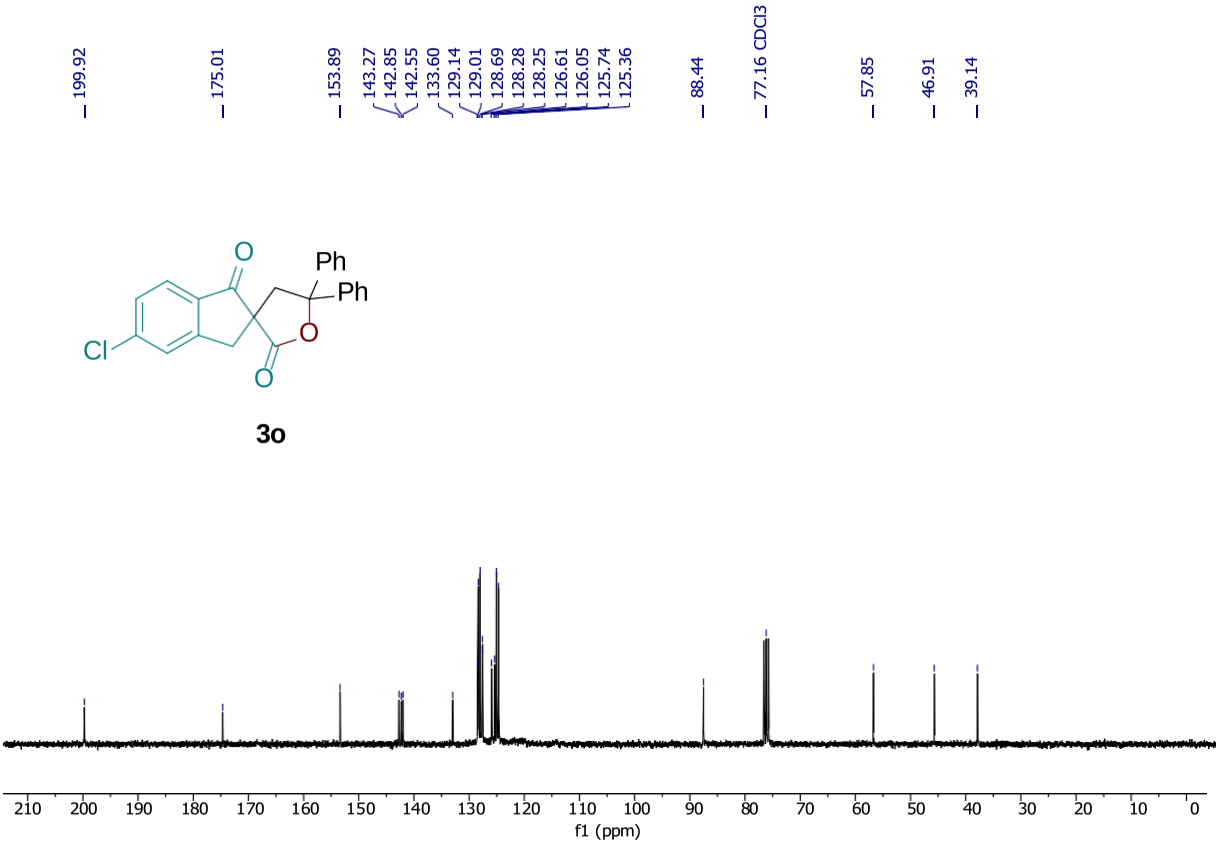


Figure S 52. ^{13}C NMR spectrum of **3n** in $CDCl_3$.



3o

Figure S 53. ^{1}H NMR spectrum of **3o** in $CDCl_3$



3o

Figure S 54. ^{13}C NMR spectrum of **3o** in $CDCl_3$.

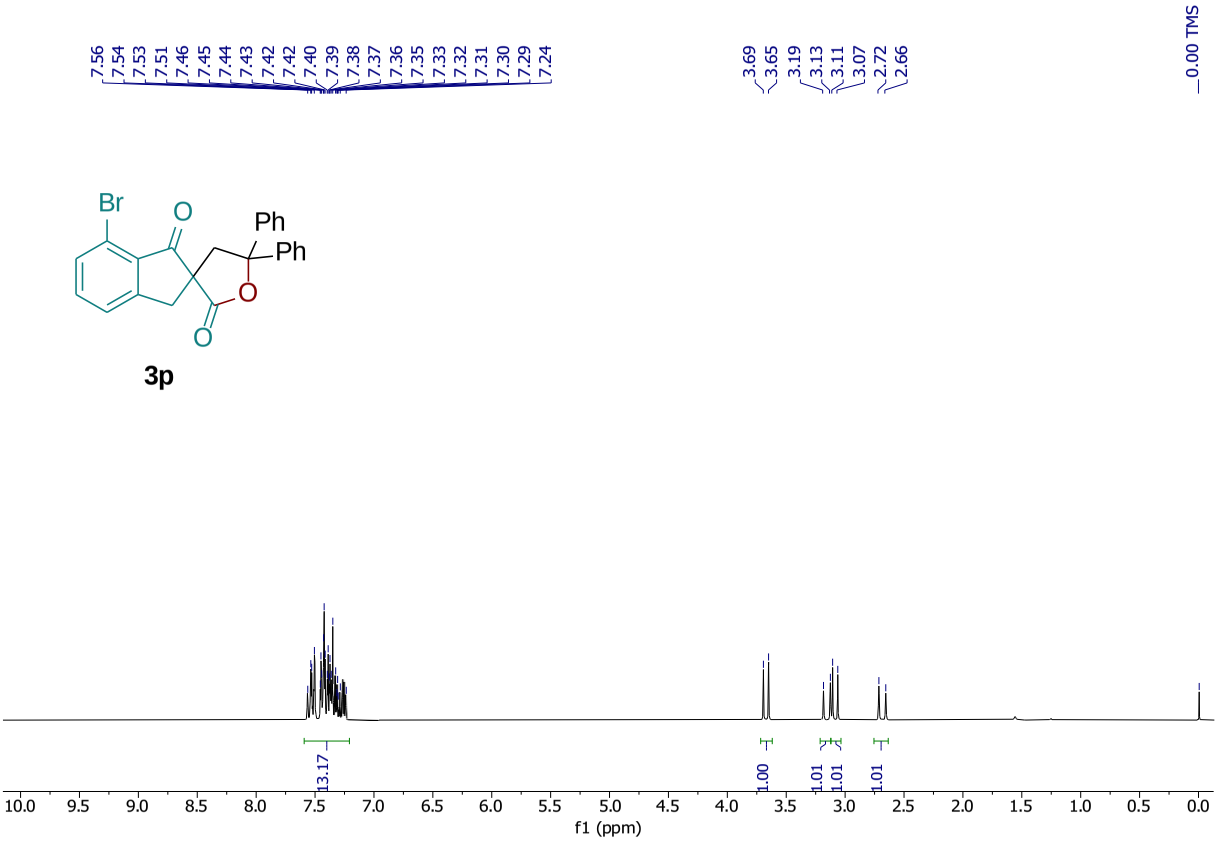


Figure S 55. ^{1}H NMR spectrum of **3p** in $CDCl_3$

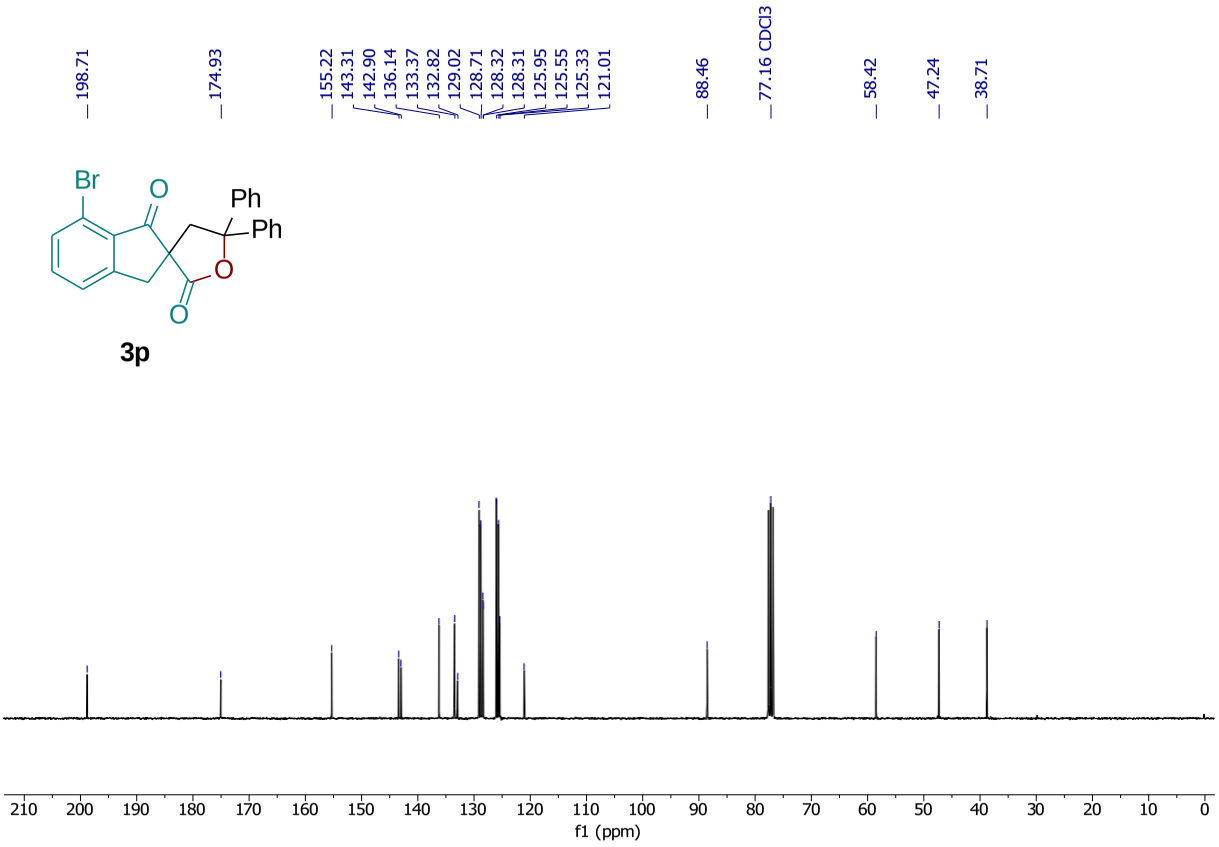


Figure S 56. ^{13}C NMR spectrum of **3p** in $CDCl_3$.

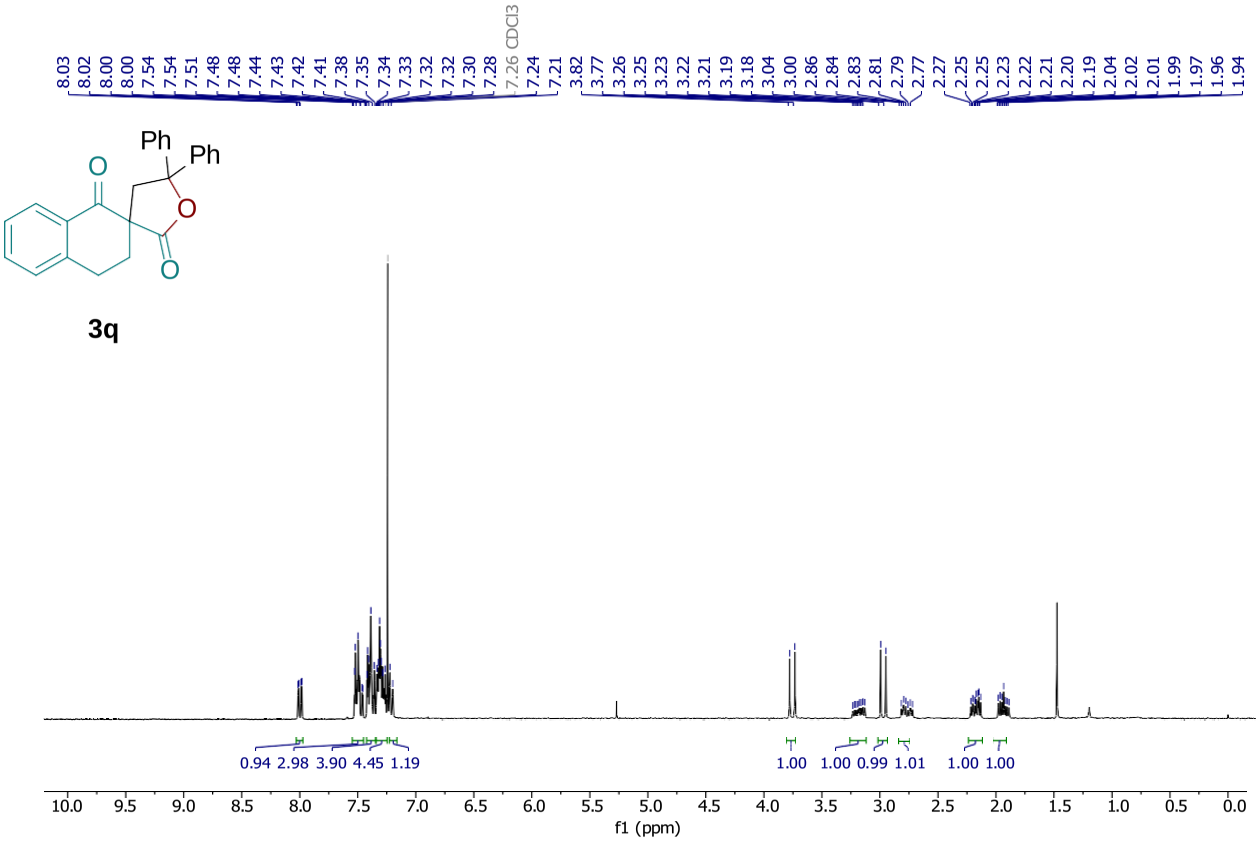


Figure S 57. ^{1}H NMR spectrum of **3q** in $CDCl_3$

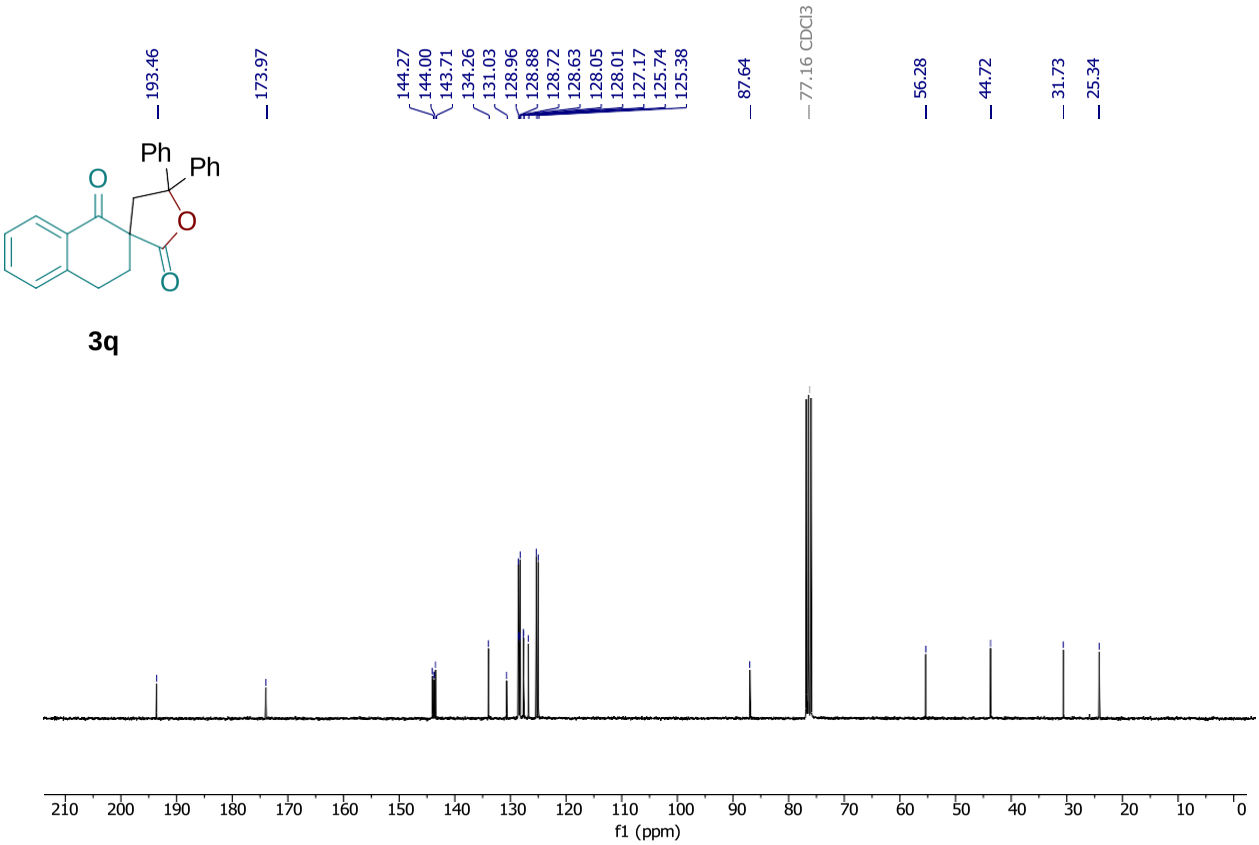


Figure S 58. ^{13}C NMR spectrum of **3q** in $CDCl_3$.

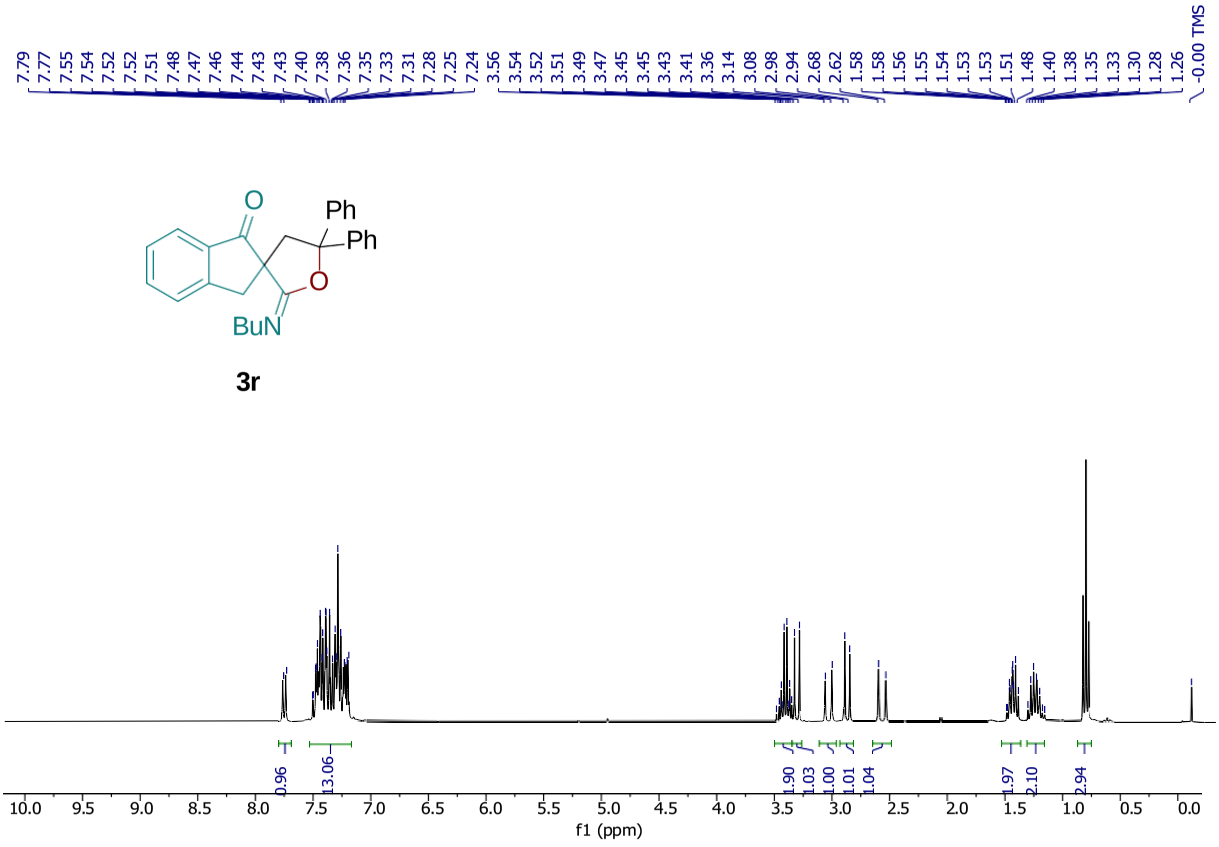


Figure S 59. ^{1}H NMR spectrum of **3r** in $CDCl_3$

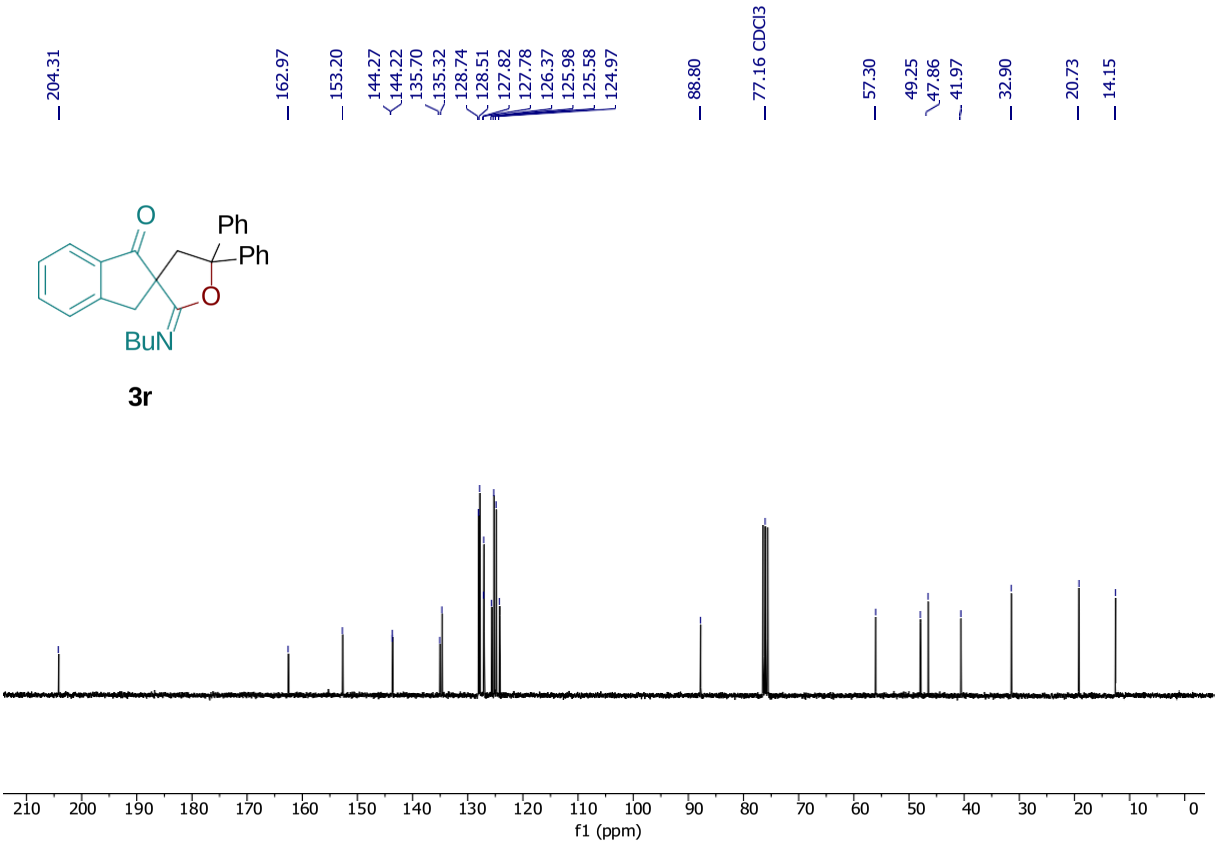


Figure S 60. ^{13}C NMR spectrum of **3r** in $CDCl_3$.

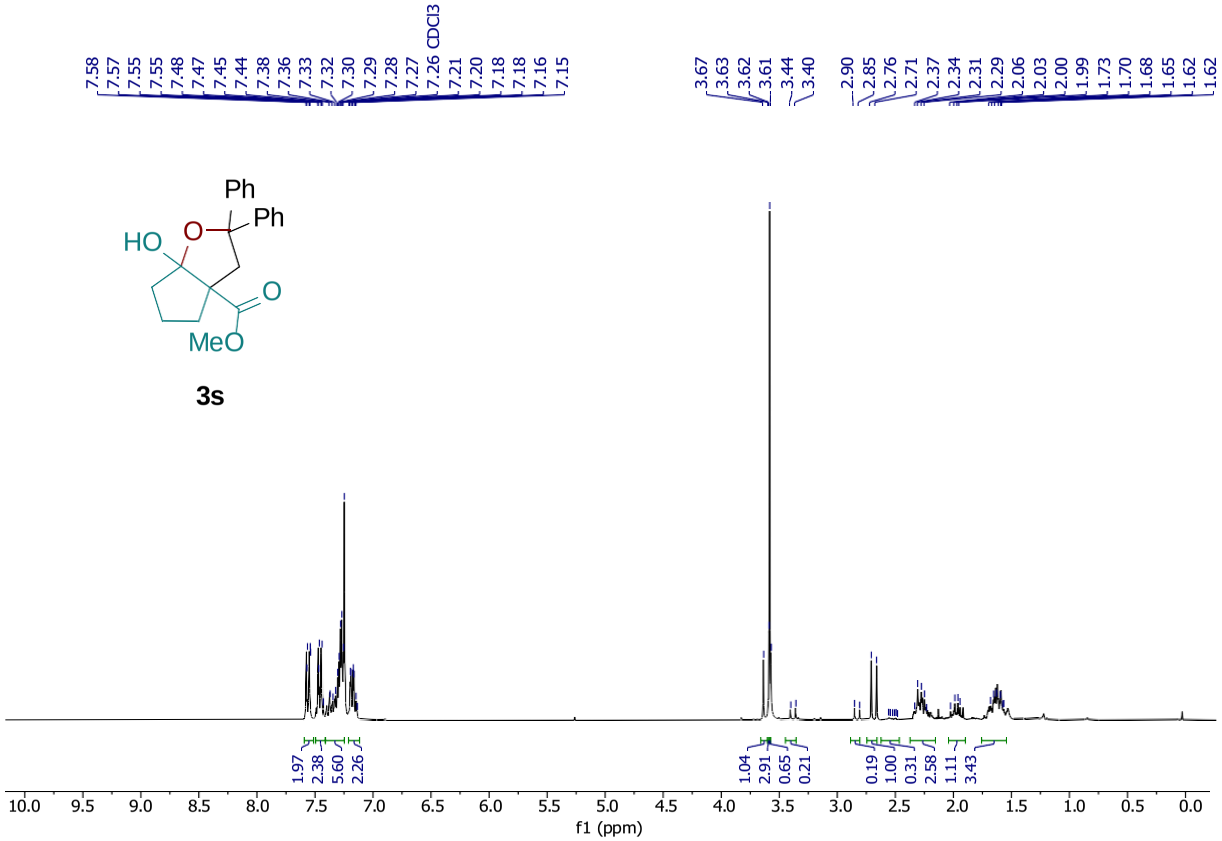


Figure S 61. ^{1}H NMR spectrum of **3s** in $CDCl_3$

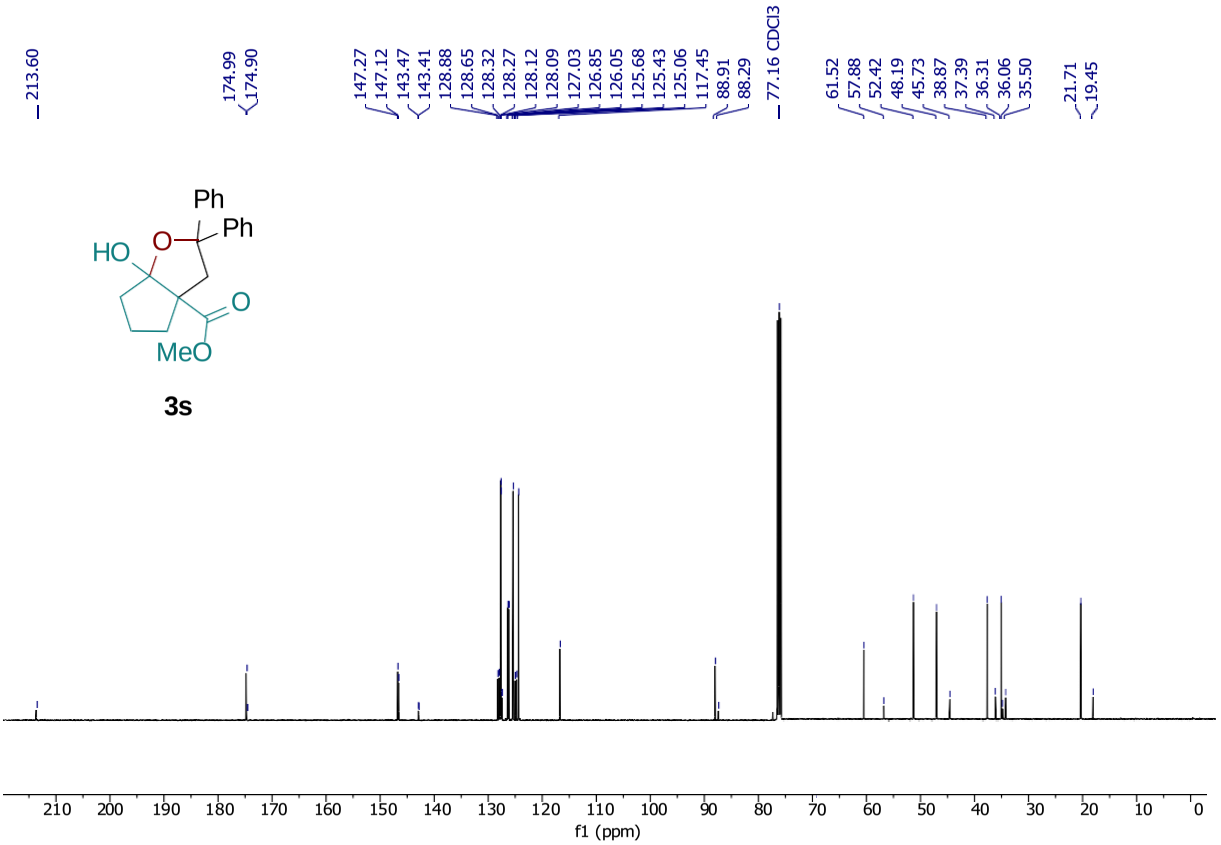


Figure S 62. ^{13}C NMR spectrum of **3s** in $CDCl_3$.

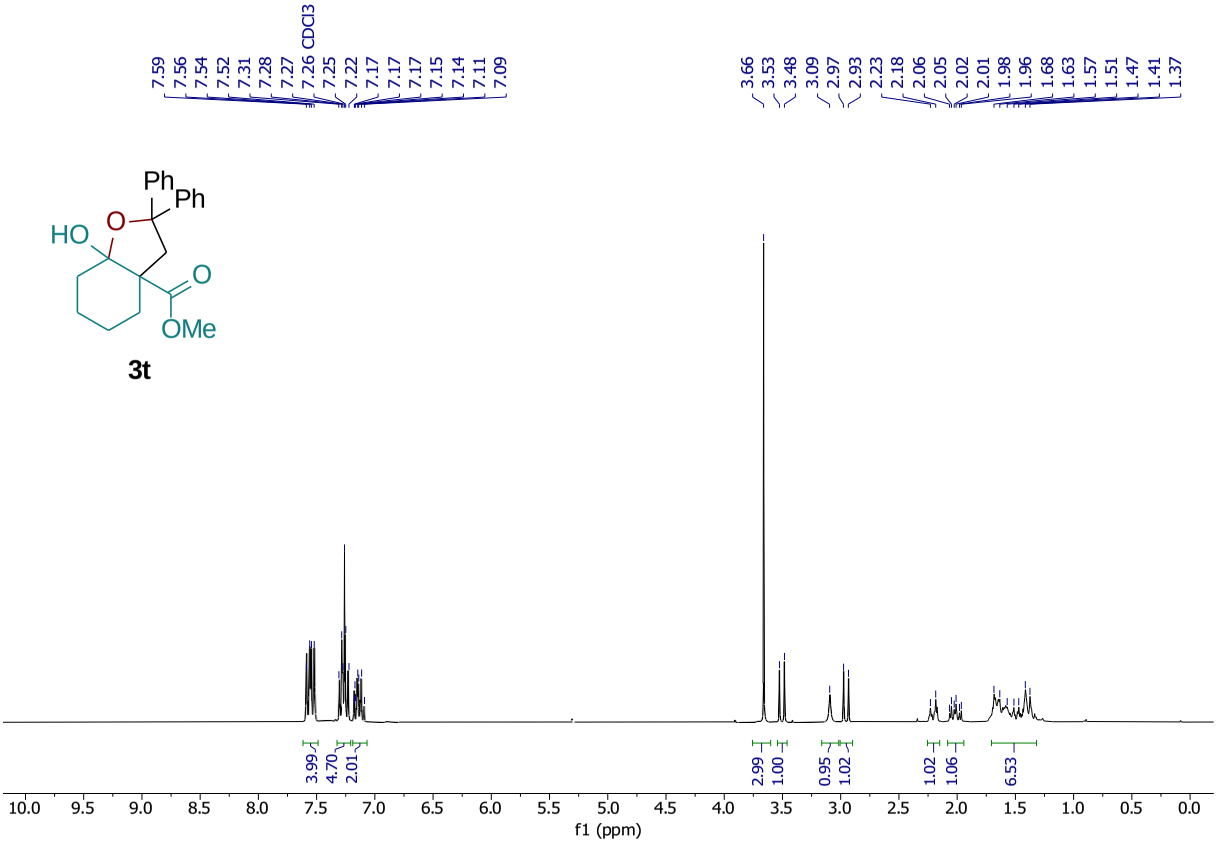


Figure S 63. ^{1}H NMR spectrum of **3t** in $CDCl_3$

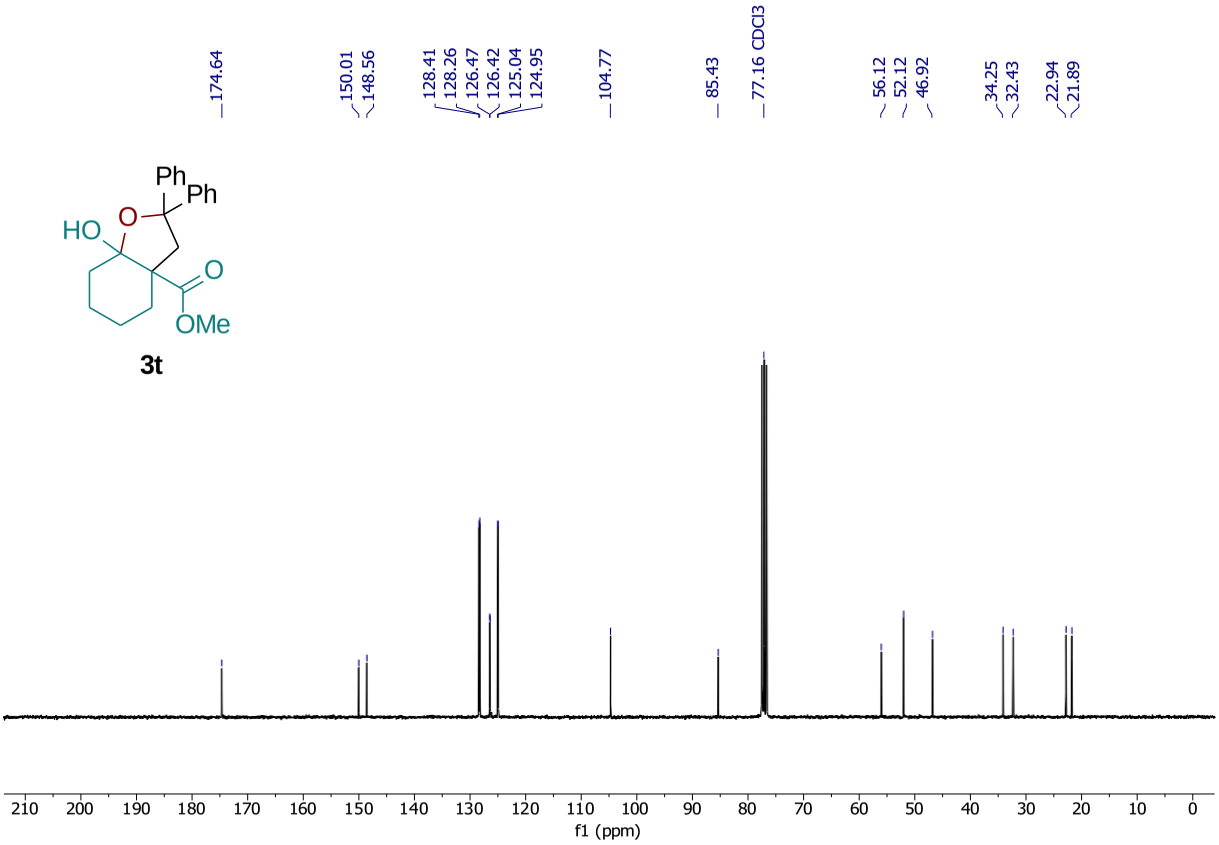


Figure S 64. ^{13}C NMR spectrum of **3t** in $CDCl_3$.

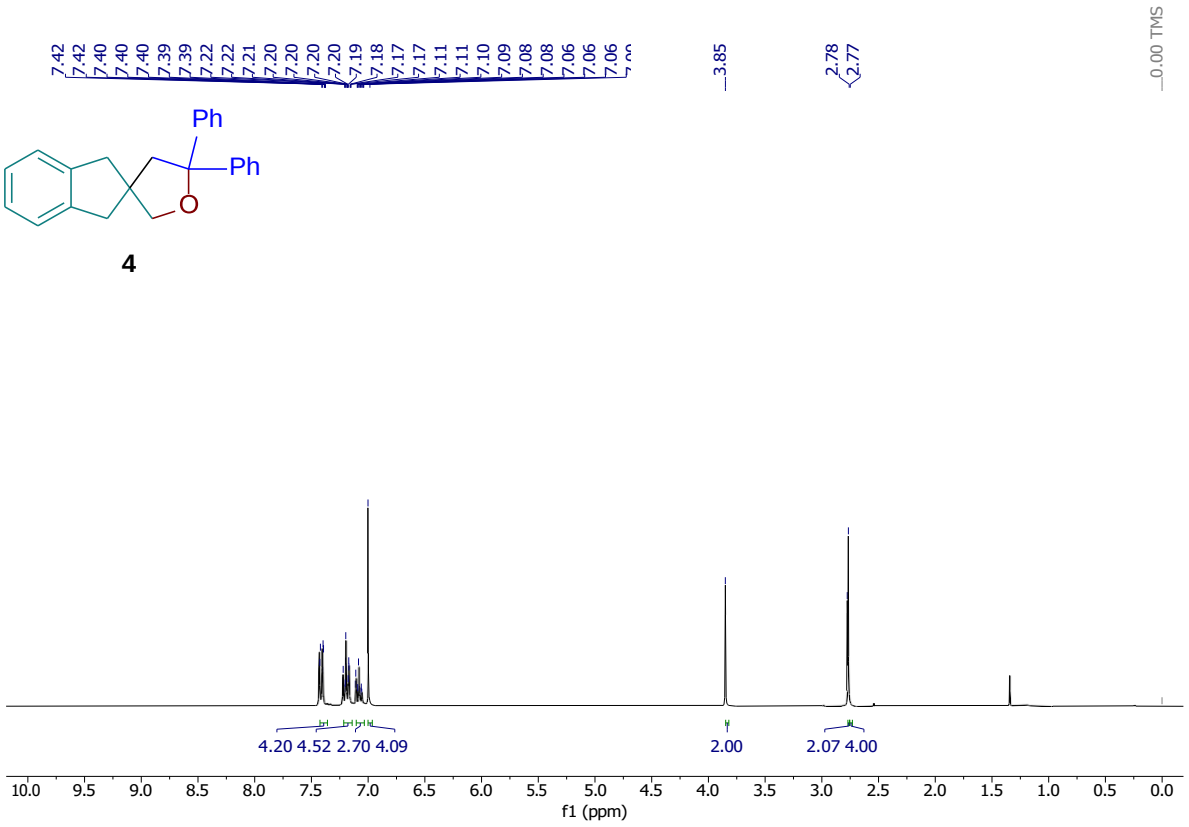


Figure S 65. ^{1}H NMR spectrum of **4** in $CDCl_3$

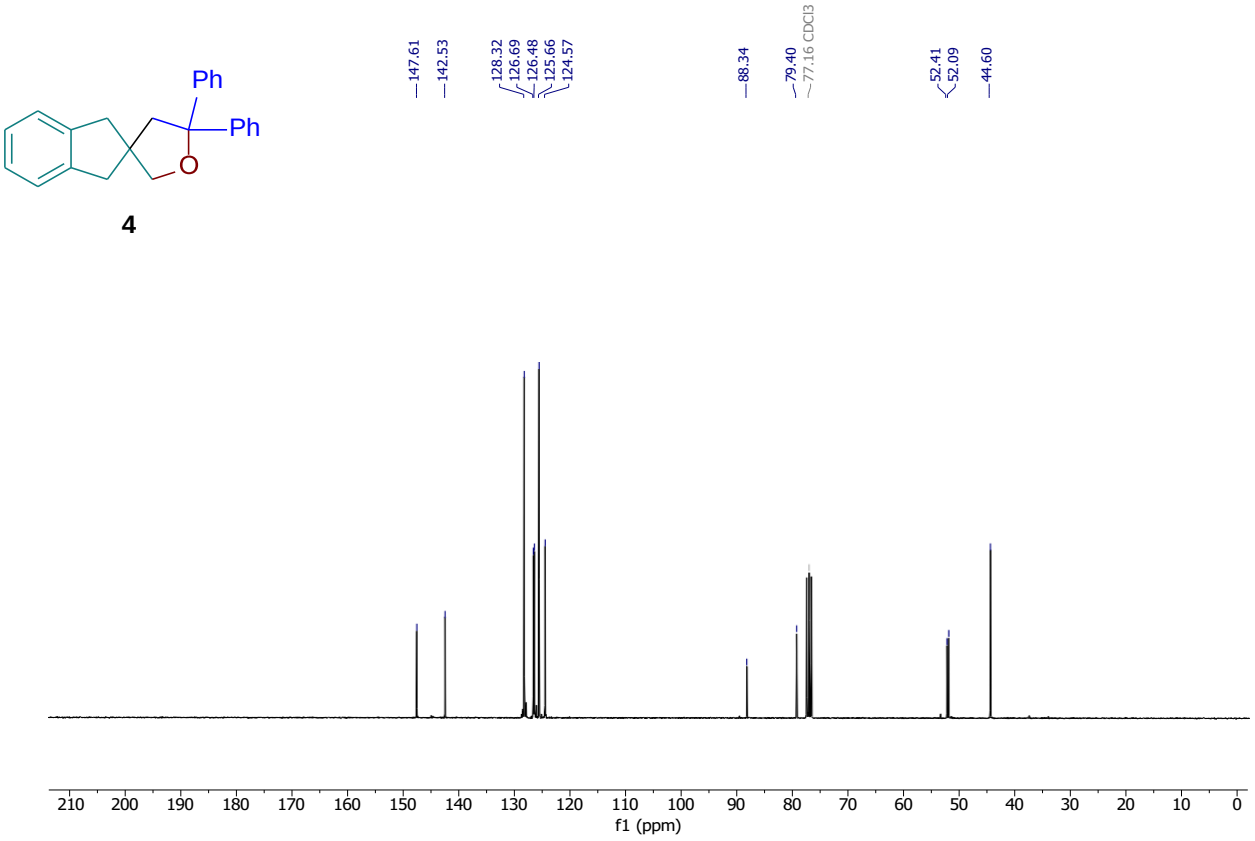
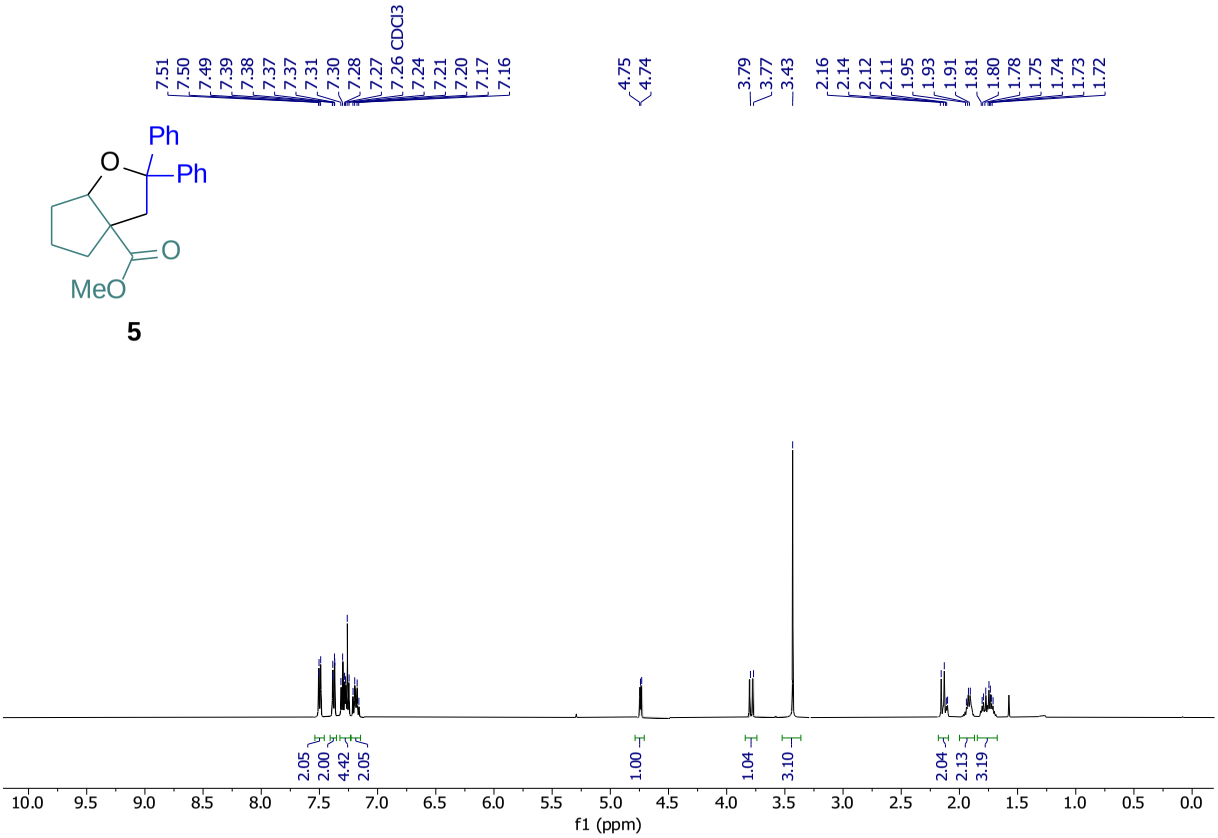
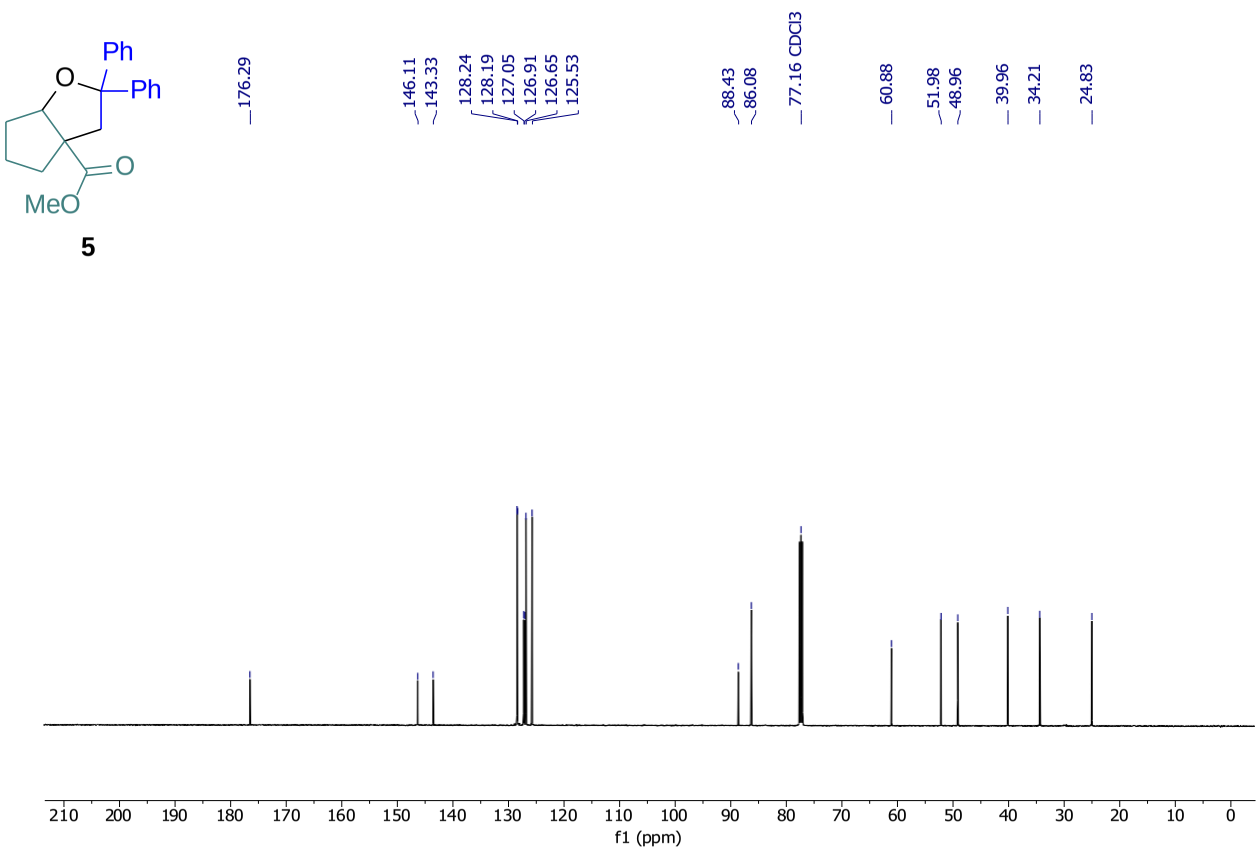


Figure S 66. ^{13}C NMR spectrum of **4** in $CDCl_3$.



5

Figure S 67. ^{1}H NMR spectrum of **5** in $CDCl_3$



5

Figure S 68. ^{13}C NMR spectrum of **5** in $CDCl_3$.

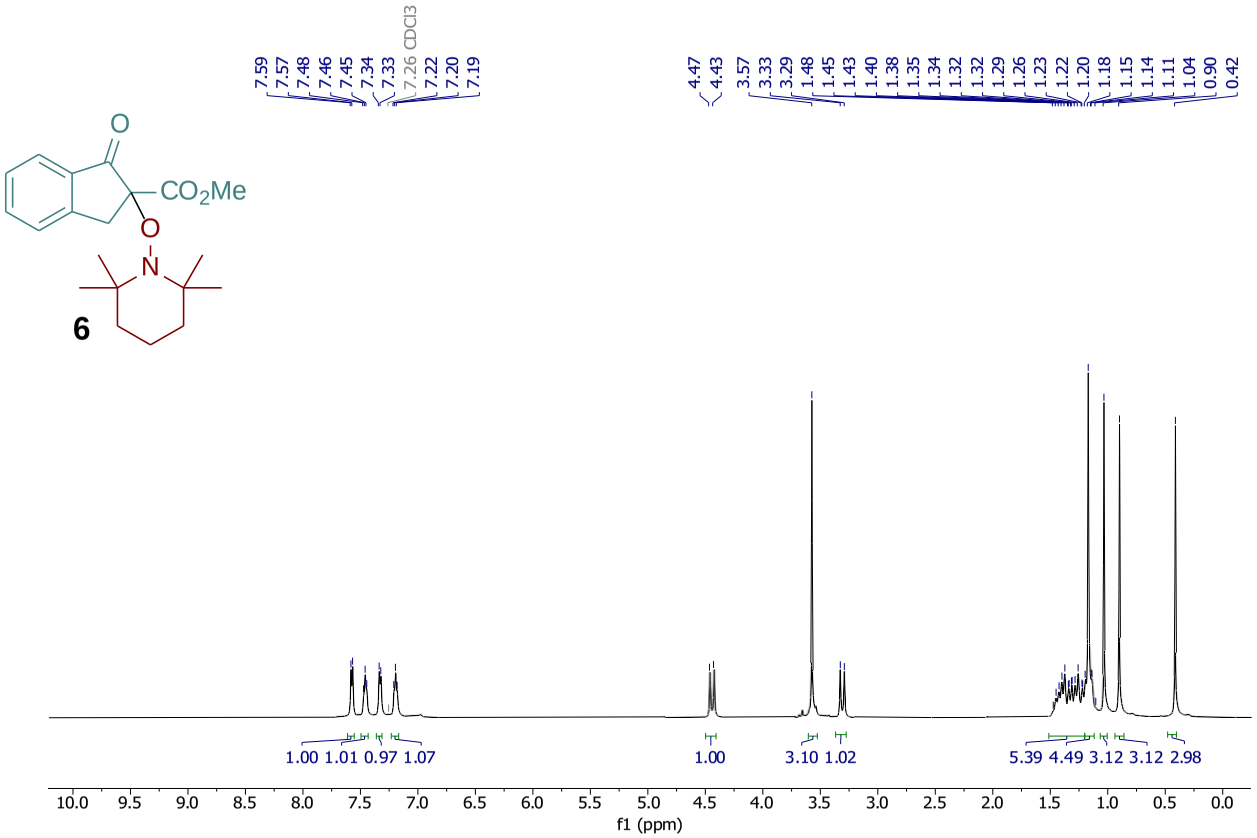


Figure S 69. ^{1}H NMR spectrum of **6** in $CDCl_3$

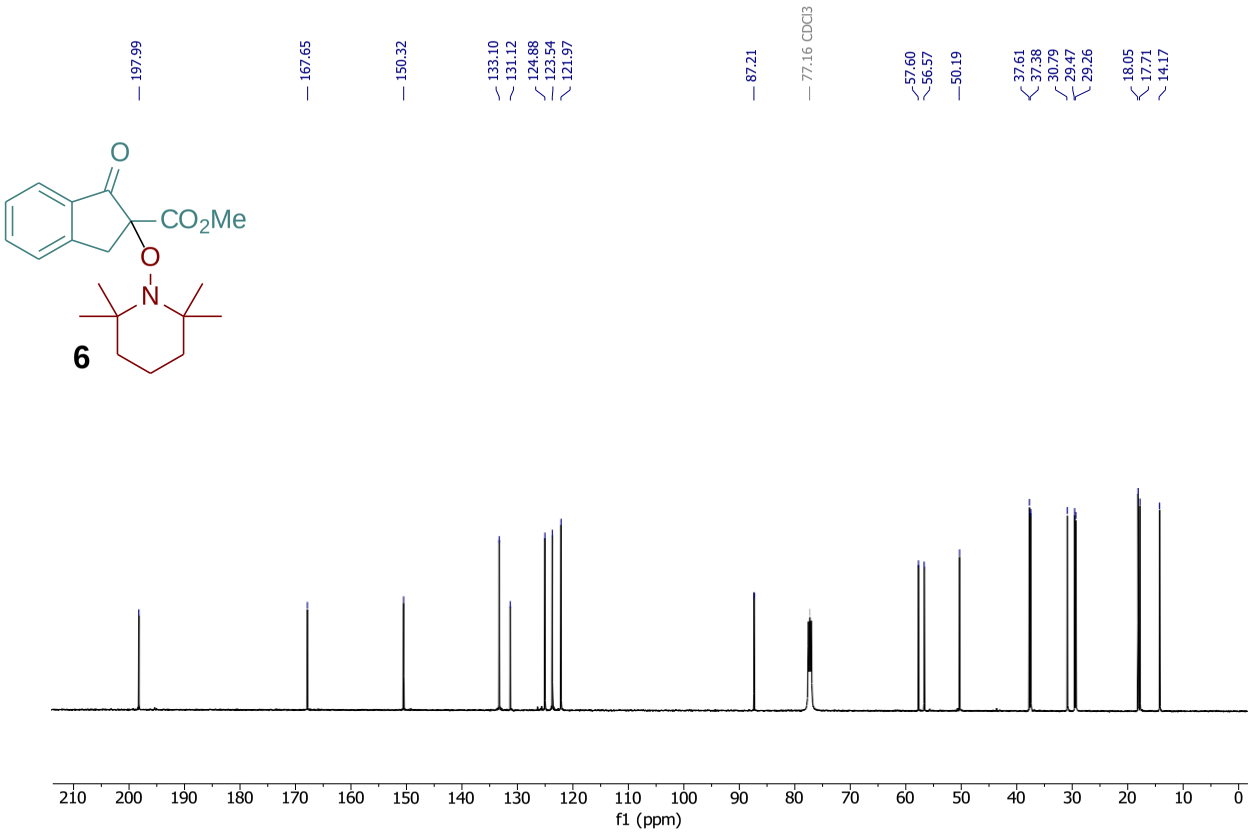


Figure S 70. ^{13}C NMR spectrum of **6** in $CDCl_3$.

11. References

1. Companys, S.; Peixoto, P. A.; Bosset, C.; Chassaing, S.; Miqueu, K.; Sotiropoulos, J.; Pouységu, L.; Quideau, S. Asymmetric Alkynylation of β-Ketoesters and Naphthols Promoted by New Chiral Biphenylic Iodanes. *Chem. Eur. J.* **2017***, 23*, 13309-13313.

2. Dong, X.; Lv, S.; Qi, Q.; Gu, Y.; Wu, P.; Zhang, W.; Zhang, Z.; Yang, L.; Li, J.; Chen, Y.; Wang, C. Cyclic Dinucleotide-Based Enantioselective Fluorination in Water. *J. Org. Chem.* **2023***, 88*, 189-197.

3. Chen, J.; Gu, H.; Zhu, X.; Nam, W.; Wang, B. Zirconium-Salan Catalyzed Enantioselective α-Hydroxylation of β-Keto Esters. *Adv. Synth. Catal.* **2020***, 362*, 2976-2983.

4. Granados, A.; Sarró, P.; Vallribera, A. Catalytic Asymmetric Fluorination of Alkyl 1-indanone-2-carboxylates Ruled by Pybox-Eu(III) Combination. *Molecules* **2019***, 24*.

5. Ding, T.; Jiang, L.; Yang, J.; Xu, Y.; Wang, G.; Yi, W. Highly Carbon-Selective Monofluoromethylation of β-Ketoesters with Fluoromethyl Iodide. *Org. Lett.* **2019***, 21*, 6025-6028.

6. Smith, A. M. R.; Billen, D.; Hii, K. K. (. Palladium-catalysed enantioselective α-hydroxylation of β-ketoesters. *Chem. Commun.* **2009**, 3925-3927.

7. Yasui, K.; Kato, T.; Kojima, K.; Nagasawa, K. Guanidinium iodide-catalyzed oxidative α-nitroalkylation of β-ketoamides. *Chem. Commun.* **2015***, 51*, 2290-2293.

8. Liu, Y.; Mao, Y.; Hu, Y.; Gui, J.; Wang, L.; Wang, W.; Zhang, S. The Employment of Sodium Hydride as a Michael Donor in Palladium-catalyzed Reductions of α, β-Unsaturated Carbonyl Compounds. *Adv. Synth. Catal.* **2019***, 361*, 1554-1558.

9. Zhang, G.; Bai, R.; Li, C.; Feng, C.; Lin, G. Halogenation of 1,1-diarylethylenes by N-halosuccinimides. *Tetrahedron* **2019***, 75*, 1658-1662.

10. Liwosz, T. W.; Chemler, S. R. Copper-Catalyzed Oxidative Amination and Allylic Amination of Alkenes. *Chem. Eur. J.* **2013***, 19*, 12771-12777.

11. Wu, X.; Gannett, C. N.; Liu, J.; Zeng, R.; Novaes, L. F. T.; Wang, H.; Abruña, H. D.; Lin, S. Intercepting Hydrogen Evolution with Hydrogen-Atom Transfer: Electron-Initiated Hydrofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2022***, 144*, 17783-17791.

12. Mejri, E.; Higashida, K.; Kondo, Y.; Nawachi, A.; Morimoto, H.; Ohshima, T.; Sawamura, M.; Shimizu, Y. Visible-Light-Induced Aminochlorination of Alkenes. *Org. Lett.* **2023***, 25*, 4581-4585.

13. Tomita, R.; Yasu, Y.; Koike, T.; Akita, M. Direct C–H trifluoromethylation of di- and trisubstituted alkenes by photoredox catalysis. *Beilstein J. Org. Chem.* **2014***, 10*, 1099-1106.

14. Xie, K.; Kemper, S.; Oestreich, M. Dehydrative Coupling of 1,1-Diarylalkenes and Cyclohexa-2,5-diene-1-carbaldehyde Derivatives Induced by a B(C6F5)3-Initiated [1,2]-Alkyl Migration. *J. Org. Chem.* **2023***, 88*, 10310-10313.

15. Zhang, G.; Bai, R.; Li, C.; Feng, C.; Lin, G. Halogenation of 1,1-diarylethylenes by N-halosuccinimides. *Tetrahedron* **2019***, 75*, 1658-1662.

16. Maejima, S.; Yamaguchi, E.; Itoh, A. Visible Light/Molecular-Iodine-Mediated Intermolecular Spirolactonization Reaction of Olefins with Cyclic Ketones. *J. Org. Chem.* **2019***, 84*, 9519-9531.

17. Ko, T. Y.; Youn, S. W. Cooperative Indium(III)/Silver(I) System for Oxidative Coupling/Annulation of 1,3-Dicarbonyls and Styrenes: Construction of Five-Membered Heterocycles. *Adv. Synth. Catal.* **2016***, 358*, 1934-1941.