# Supporting Information

## Red-shifted photoredox generation and trapping of alkyl radicals towards bioorthogonality

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# Supporting Information

# 1. General considerations

Unless stated otherwise, all reactions were conducted under air in HPLC-grade solvents. The water used in the reactions was deionized and purified on a Millipore Milli-Q® Integral system. Dry solvents (if needed) were directly purchased from Sigma–Aldrich and used without further purification. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Phosphate buffered saline (PBS, pH 7.4) was prepared following standard procedures. Dulbecco′s Modified Eagle's Medium (GibcoTM DMEM) was purchased from ThermoFisher Scientific. HeLa cell lysates were obtained from 2 days cultured HeLa cells: after two washings with PBS, cells were scraped from the well, sonicated and diluted with PBS to reach the indicated concentration.

$^{1}H$ and $^{13}C$ NMR data were recorded in $CDCl_3$, using a Varian Mercury 300 MHz or Bruker AVIII 500 MHz spectrometer. (at 298–300 K, unless stated otherwise). $^{1}H$ and $^{13}C$ chemical shifts (δ) are reported in ppm relative to the solvent residual peaks as internal reference. For $^{1}H$ NMR, the following residual proton peaks of the deuterated solvents were used: $CDCl_3$, $\delta_H(CHCl_3)$ 7.26. For $^{13}C$ NMR: $CDCl_3$, δ 77.16. $^{13}C$ spectra were acquired with broadband $^{1}H$ decoupling unless mentioned otherwise. Coupling constants (*J*) are provided in Hz, and $^{1}H$-NMR multiplicities are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, td = triple doublet, m = multiplet, br = broad). NMR spectra were analyzed using MestreNova NMR data processing software. GCMS analysis was performed on a 8890 GC System with a 5977B GC/MSD (CI) from Agilent. High-resolution mass spectra (HRMS) were acquired using electrospray ionization (ESI) in a Bruker microTOF (time-of-flight analyzer) instrument in FIA mode (flow-injection analysis).

UV–Vis absorption spectra were recorded on a Jasco V-770 spectrometer using either disposable plastic cuvettes (2x10 mm) or quartz cuvettes (10x10 mm). Emission spectra were recorded on an Edinburgh FS5 Spectrofluorometer using quartz fluorescence cuvettes (10x10 mm). Unless stated otherwise, all spectroscopic studies were performed under air, mimicking the actual reaction conditions.

Thin-layer chromatography (TLC) was performed on pre-coated Merck 60 silica gel $F_{254}$ plates. TLC plates were visualized by observation under UV light and/or staining with either phosphomolybdic acid solution or potassium permanganate solution, followed by heat. Chromatographic purifications were performed by flash column chromatography on silica gel (Merck Geduran® Si 60, 40–63 μm).

Unless stated otherwise, EY, Eosin Y-$Na_2$ or EY-$Na_2$ all refer to Eosin Y disodium salt (**5**), and ZnTPP refers to zinc(II) tetraphenylporphyrin (**6**).

# 2. Light sources and photochemical set-up

## 2.1. Light sources (Kessil LED)

**Kessil PR160L**

Blue, green and red-light irradiation was performed using standardized 456, 525 and 660 nm LED (respectively) PR160L lamps purchased from Kessil, in combination with the PhotoRedOx Duo™ photochemical reactor from HepatoChem (see next section for details). Unless stated otherwise, the lamps were used at full intensity (100%). Intensity maps and more details can be found at the Kessil website: https://kessil.com/products/science_PR160L.php

The emission profile of the three light sources was recorded with a MK350S Premium Handheld Spectrometer from UPRtek, sitting around 20 cm in front of the Kessil LED light at 25% intensity (Figure S1).

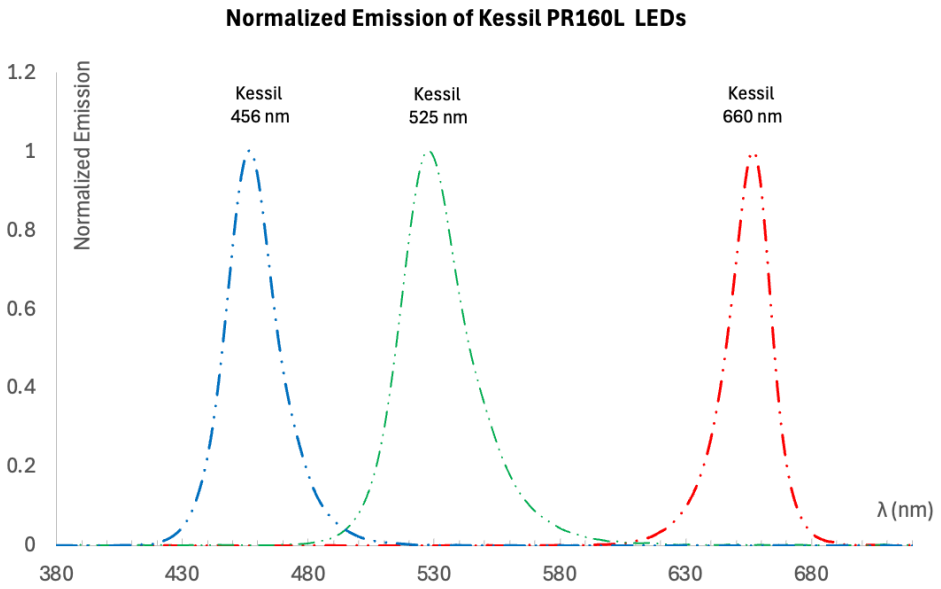



**Figure S1.** Recorded normalized emission of the Kessil LED light sources employed in this study.

## 2.2. Photochemical reactor and set-up

**PhotoRedOx Duo™**

Photochemical reactions were performed using a PhotoRedOx Duo™ reactor from HepatoChem, attaching a single Kessil PR160L lamp of the appropriate wavelength (see previous section for details) at full intensity (100%) to the chamber where the reactions were run (sample holders). If both chambers/holders were employed at the same time, one Kessil lamp of the same color was attached to each of them. The photoreactor is based on a simple mirror set up which directs the light towards the reaction vials (sample holders), and is equipped with an electrical ventilation system to keep the temperature of the chambers below 30 ºC.


**Figure S2.** Schematic representation (left), picture of the photoreactor (center) and sample holder for 8 mL vials (right) provided by HepatoChem.

A detailed description of the photoreactor can be found at the HepatoChem website:

https://hepatochem.com/photoreactors-leds-accessories/photoredox-duo/

The photoreactor was installed on top of a stirring plate in order to stir the reaction solutions using Teflon-coated magnetic stirring bars. The reactions were set up in 6 mL screw-cap vials under ambient atmosphere, with no special precautions taken to exclude air. To ensure efficient irradiation of the solutions, the volume of the vials was always kept between 1.0 and 4.0 mL. A maximum of 4 reaction vials (placed on the row of the sample holder closer the light source) were irradiated at the same time.

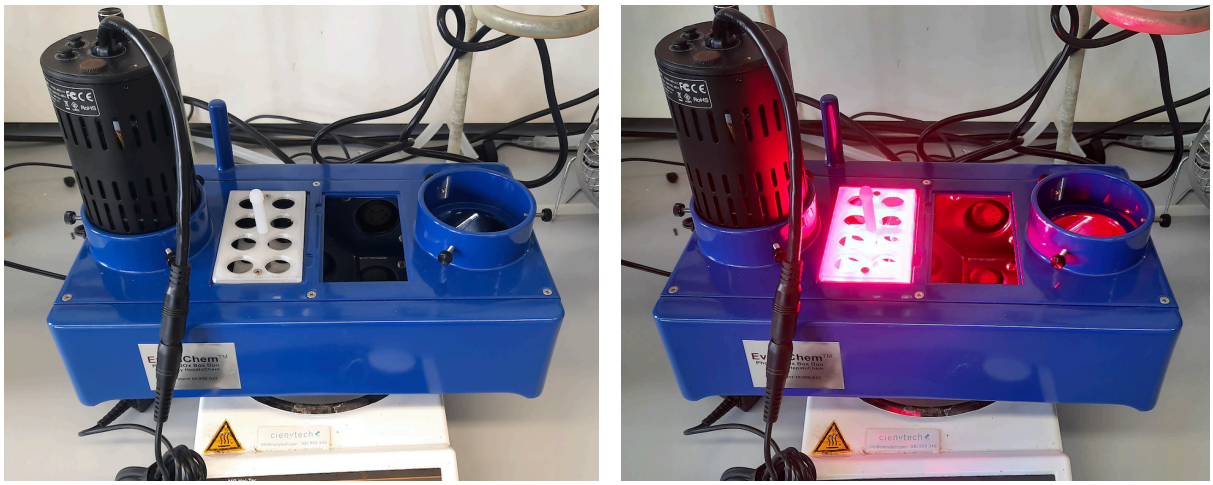
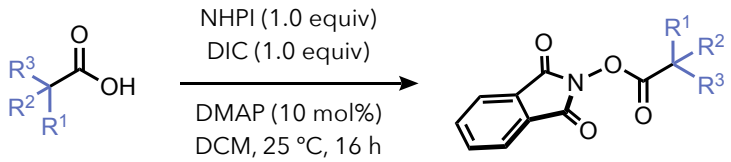


**Figure S3.** Pictures of the photochemical set up with one operative chamber (light off or on).

**Figure S4.** Pictures of the reaction vials and sample holder that is located in the chamber; front (left) or top view (right).

# 3. Synthesis of starting materials (RAEs)

## 3.1. General procedure A for the synthesis of alkyl redox-active esters

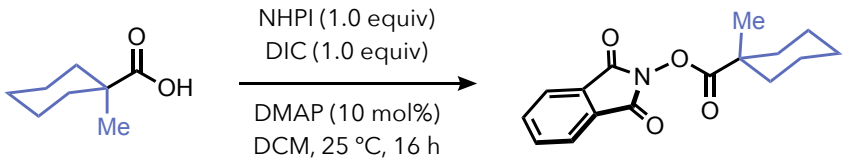



Following typical procedures for the synthesis of alkyl phthalimide esters,[1] a round-bottom flask of the appropriate size (equipped with a Teflon-coated stirring bar) was charged under air atmosphere with the corresponding carboxylic acid (1.0 equiv), *N*-hydroxyphthalimide (1.0 equiv) and 4-dimethylaminopyridine (DMAP, 10 mol%). All reagents were dissolved in HPLC-grade DCM (0.15–0.20 M), before *N,N'*-diisopropylcarbodiimide (DIC, 1.0 equiv) was added in a single portion via syringe. The flask was capped with a rubber septum and the reaction mixture was left stirring at room temperature overnight (ca. 16 h), until TLC revealed consumption of most of the starting carboxylic acid. After this time, the solvent was removed in vacuum and the product **1** was directly purified by flash column chromatography in silica gel, using the appropriate gradients of hexane and EtOAc.

Reaction substrates **1** were prepared from commercially available alkyl carboxylic acids, following General Procedure A. This procedure is based on well-established synthetic methods and, while the used compounds are already known in the literature,[1] for the sake of practicality, exact experimental details and NMR data is reported in the following pages.

## 3.2. Characterization data for alkyl redox-active esters

**1,3-Dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate (1a)**

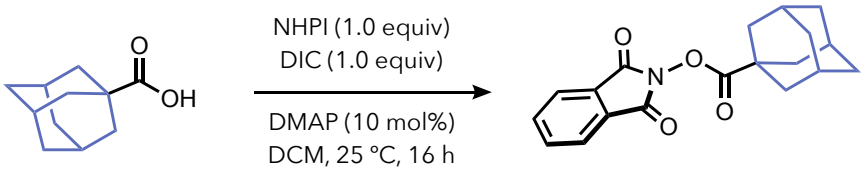



Following General Procedure A, the title product was obtained from 1-methylcyclohexane-1-carboxylic acid (0.71 g, 5.0 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.82 g, 5.0 mmol, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 61 mg, 0.50 mmol, 10 mol%) and *N,N′*-diisopropylcarbodiimide (DIC, 0.63 g, 0.77 mL, 5.0 mmol 1.0 equiv) in DCM (33 mL, 0.15 M). Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 95:5 to 9:1). $R_f$ (9:1 hexane/EtOAc) = 0.4. This gave 1.27 g (88%) of the title product as a colorless oil that solidified upon standing in the fridge to give a white solid.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 (td, *J* = 5.3, 2.1 Hz, 2H), 2.30 – 2.16 (m, 2H), 1.71 – 1.51 (m, 5H), 1.43 (s, 3H), 1.42 – 1.20 (m, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 173.66, 162.22, 134.61, 129.11, 123.82, 43.16, 35.70, 26.69, 25.47, 23.03.

**1,3-Dioxoisoindolin-2-yl adamantane-1-carboxylate (1b)**

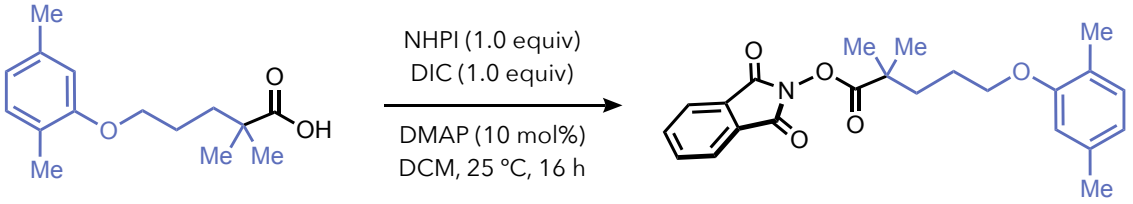



Following General Procedure A, the title product was obtained from 1-adamantanecarboxylic acid (0.72 g, 4.0 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.65 g, 4.0 mmol, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 49 mg, 0.40 mmol, 10 mol%) and *N,N′*-diisopropylcarbodiimide (DIC, 0.51 g, 0.62 mL, 4.0 mmol, 1.0 equiv) in DCM (20 mL, 0.20 M). Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 95:5 to 85:15). $R_f$ (9:1 hexane/EtOAc) = 0.3. This gave 1.10 g (85%) of the title product as a white solid.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 2H), 7.82 – 7.75 (m, 2H), 2.17 – 2.14 (m, 6H), 2.13 – 2.09 (m, 3H), 1.81 – 1.78 (m, 6H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 173.23, 162.13, 134.61, 129.13, 123.82, 40.55, 38.49, 36.23, 27.68.

**1,3-Dioxoisoindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (1c)**

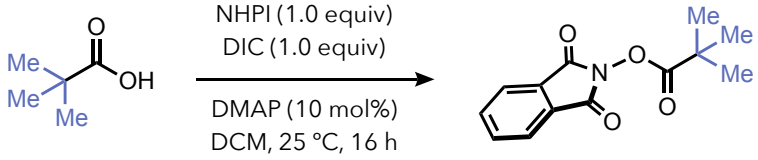



Following General Procedure A, the title product was obtained from gemfibrozil (0.75 g, 3.0 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.49 g, 3.0 mmol, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 37 mg, 0.50 mmol, 10 mol%) and *N,N'*-diisopropylcarbodiimide (DIC, 0.38 g, 0.46 mL, 5.0 mmol 1.0 equiv) in DCM (15 mL, 0.20 M). Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 95:5 to 85:15). $R_f$ (8:2 hexane/EtOAc) = 0.4. This gave 0.93 g (79%) of the title product as a white solid.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 5H), 7.82 – 7.75 (m, 2H), 7.00 (d, $J$ = 8.0 Hz, 1H), 6.68 – 6.63 (m, 2H), 4.01 (d, $J$ = 157.2 Hz, 2H), 2.32 (s, 3H), 2.19 (s, 3H), 1.99 – 1.93 (m, 4H), 1.45 (s, 6H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 173.89, 162.20, 157.12, 136.60, 134.79, 130.40, 129.22, 123.98, 123.76, 120.85, 112.19, 67.90, 42.11, 37.52, 25.26, 25.14, 21.51, 15.89.

**1,3-Dioxoisoindolin-2-yl pivalate (1d)**

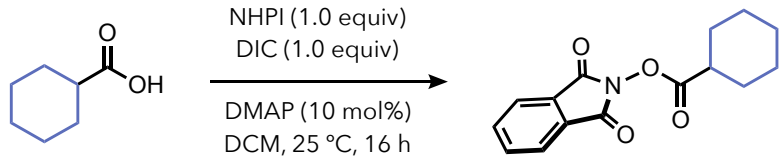



Following General Procedure A, the title product was obtained from pivalic acid (0.15 g, 1.5 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.25 g, 1.5 mmol, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 18 mg, 0.15 mmol, 10 mol%) and *N,N'*-diisopropylcarbodiimide (DIC, 0.19 g, 0.23 mL, 1.5 mmol 1.0 equiv) in DCM (7.5 mL, 0.20 M). Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 9:1 to 7:3). $R_f$ (7:3 hexane/EtOAc) = 0.7. This gave 0.22 g (78%) of the title product as a yellow solid.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 2H), 7.80 – 7.75 (m, 2H), 1.43 (s, 9H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 174.52, 162.23, 134.78, 129.25, 123.99, 38.57, 27.18.

**1,3-Dioxoisoindolin-2-yl cyclohexanecarboxylate (1e)**

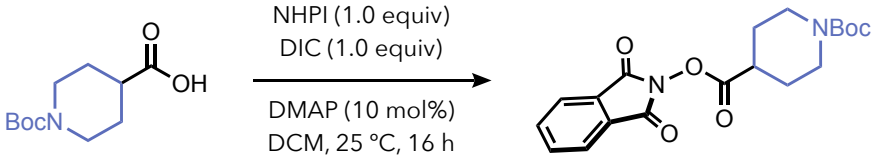



Following General Procedure A, the title product was obtained from cyclohexanecarboxylic acid (0.28 g, 2.18 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.36 g, 2.18 mmol, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 27 mg, 0.28 mmol, 10 mol%) and *N,N'*-diisopropylcarbodiimide (DIC, 0.28 g, 0.34 mL, 2.18 mmol 1.0 equiv) in DCM (11 mL, 0.20 M). Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (9:1). $R_f$ (4:1 hexane/EtOAc) = 0.6. This gave 0.42 g (71%) of the title product as a white solid.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 2H), 7.82 – 7.74 (m, 2H), 2.80 – 2.67 (m, 1H), 2.16 – 2.04 (m, 2H), 1.90 – 1.78 (m, 2H), 1.75 – 1.58 (m, 3H), 1.47 – 1.23 (m, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 72.0, 162.2, 134.8, 129.2, 124.0, 40.7, 29.0, 25.6, 25.2.

**1-(*tert*-Butyl) 4-(1,3-dioxoisoindolin-2-yl) piperidine-1,4-dicarboxylate (1f)**

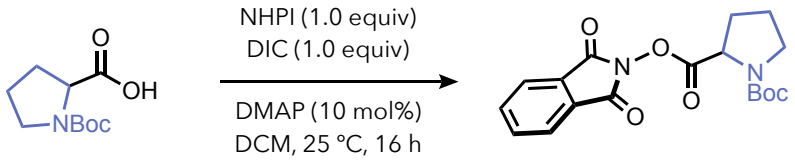



Following General Procedure A, the title product was obtained from 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (0.50 g, 2.18 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.36 g, 2.18 mmol, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 27 mg, 0.28 mmol, 10 mol%) and *N,N'*-diisopropylcarbodiimide (DIC, 0.28 g, 0.34 mL, 2.18 mmol 1.0 equiv) in DCM (11 mL, 0.20 M). Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 9:1 to 7:3). $R_f$ (3:1 hexane/EtOAc) = 0.3. This gave 0.16 g (19%) of the title product as a white solid.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 2H), 7.83 – 7.75 (m, 2H), 4.10 – 3.92 (m, 2H), 3.17 – 2.67 (m, 3H), 2.21 – 1.98 (m, 2H), 1.97 – 1.75 (m, 2H), 1.47 (s, 9H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 170.8, 162.0, 154.7, 134.9, 129.1, 124.1, 79.9, 42.7 (br), 38.7, 28.5, 27.9.

**1-(*tert*-Butyl) 2-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1,2-dicarboxylate (1g)**



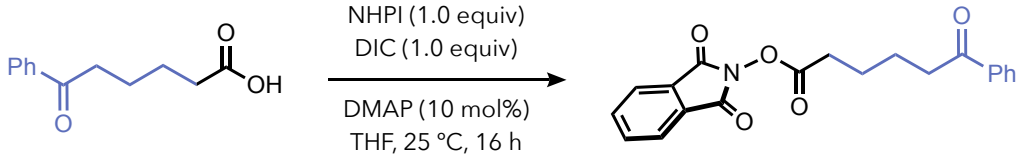

Following General Procedure A, the title product was obtained from *N*-Boc-proline (0.65 g, 3.0 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.51 g, 3.1 mmol, 1.05 equiv), 4-dimethylaminopyridine (DMAP, 37 mg, 0.30 mmol, 10 mol%) and *N,N'*-diisopropylcarbodiimide (DIC, 0.38 g, 0.47 mL, 3.0 mmol 1.0 equiv) in DCM (20 mL, 0.15 M). Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 95:5 to 9:1). This gave 0.85 g (79%) of the title product as a white foam.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.99 – 7.76 (m, 4H), 4.79 – 4.59 (m, 1H), 3.70 – 3.40 (m, 2H), 2.51 – 2.33 (m, 2H), 2.14 – 1.95 (m, 2H), 1.52 (s, 9H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 169.63, 161.67, 153.52, 134.80, 128.91, 123.93, 81.14, 57.22, 46.28, 31.39, 28.09, 23.53.

***** Some NMR signals are broad and split due to the presence of diastereomeric rotamers.

**1,3-Dioxoisoindolin-2-yl 6-oxo-6-phenylhexanoate (1h)**



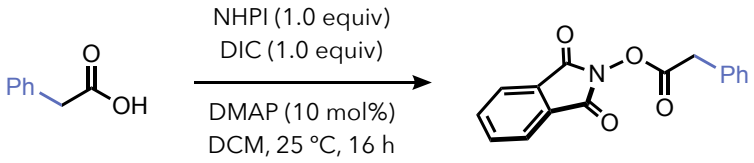

Following General Procedure A, the title product was obtained from 6-oxo-6-phenylhexanoic acid (0.41 g, 2.00 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.33 g, 2.00 mmol, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 24 mg, 0.20 mmol, 10 mol%) and *N,N'*-diisopropylcarbodiimide (DIC, 0.25 g, 0.31 mL, 2.00 mmol 1.0 equiv) in THF (10 mL, 0.20 M).[a] Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (7:3). $R_f$ (3:1 hexane/EtOAc) = 0.7. This gave 0.30 g (42%) of the title product as a white solid.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.06 – 7.93 (m, 2H), 7.95 – 7.83 (m, 2H), 7.85 – 7.73 (m, 2H), 7.63 – 7.50 (m, 1H), 7.52 – 7.41 (m, 2H), 3.14 – 2.98 (m, 2H), 2.85 – 2.66 (m, 2H), 1.98 – 1.86 (m, 4H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 199.6, 169.5, 162.1, 137.0, 134.9, 133.2, 129.1, 128.7, 128.2, 124.1, 38.0, 31.1, 24.4, 23.4.

[a] For this particular compound, THF was used instead of DCM.

**1,3-Dioxoisoindolin-2-yl 2-phenylacetate (1i)**

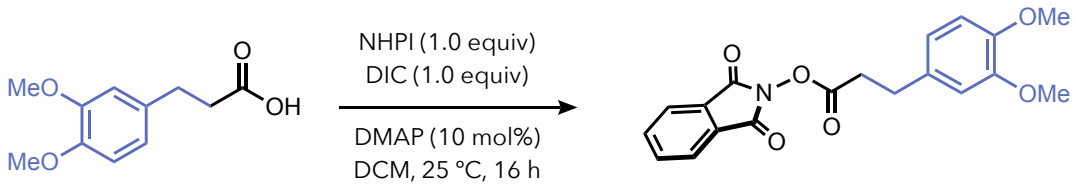



Following General Procedure A, the title product was obtained from 2-phenylacetic acid (0.27 g, 2.00 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.33 g, 2.00 mmol, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 24 mg, 0.20 mmol, 10 mol%) and *N,N'*-diisopropylcarbodiimide (DIC, 0.25 g, 0.31 mL, 2.00 mmol 1.0 equiv) in DCM (10 mL, 0.20 M). Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (7:3). $R_f$ (7:3 hexane/EtOAc) = 0.4. This gave 0.44 g (79%) of the title product as a white solid.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.93 – 7.82 (m, 2H), 7.85 – 7.72 (m, 2H), 7.44 – 7.26 (m, 5H), 4.00 (s, 2H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 167.8, 162.0, 134.9, 131.7, 129.4, 129.1, 129.0, 127.9, 124.1, 37.9.

**1,3-Dioxoisoindolin-2-yl 3-(3,4-dimethoxyphenyl) propanoate (1j)**

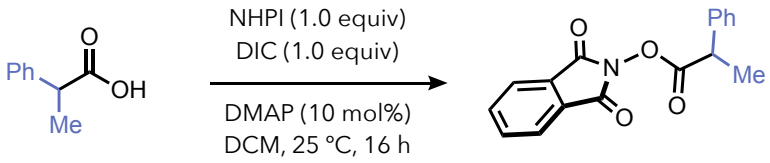



Following General Procedure A, the title product was obtained from 3-(3,4-dimethoxyphenyl)propanoic acid (0.32 g, 1.5 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.25 g, 1.5 mmol, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 18 mg, 0.15 mmol, 10 mol%) and *N,N'*-diisopropylcarbodiimide (DIC, 0.19 g, 0.23 mL, 1.5 mmol, 1.0 equiv) in DCM (7.5 mL, 0.20 M). Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 8:2 to 6:4). $R_f$ (1:1 hexane/EtOAc) = 0.6. This gave 0.53 g (41%) of the title product as a colorless solid.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.89 (dd, $J$ = 5.6, 3.1 Hz, 2H), 7.79 (dd, $J$ = 5.5, 3.2 Hz, 2H), 6.86 – 6.77 (m, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.06 (m, $J$ = 9.5, 6.7 Hz, 2H), 2.96 (m, $J$ = 9.3, 6.5, 1.8 Hz, 2H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ169.06, 162.05, 149.26, 148.01, 134.91, 132.00, 129.10, 124.13, 120.35, 111.81, 111.65, 56.09, 56.04, 33.20, 30.40.

**1,3-Dioxoisoindolin-2-yl 2-phenylpropanoate (SI-1)**



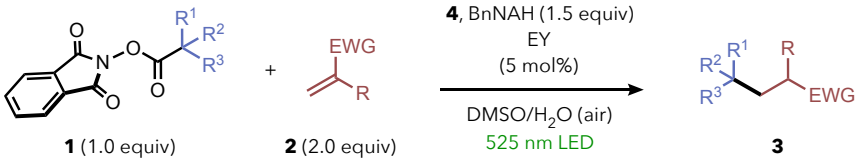

Following General Procedure A, the title product was obtained from 2-phenylpropanoic acid (0.30 g, 2.0 mmol, 1.0 equiv), *N*-hydroxyphthalimide (0.33 g, 2.0 mmol, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 24 mg, 0.20 mmol, 10 mol%) and *N,N'*-diisopropylcarbodiimide (DIC, 0.25 g, 0.31 mL, 2.0 mmol, 1.0 equiv) in DCM (10 mL, 0.20 M). Purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 95:5 to 7:3). $R_f$ (8:2 hexane/EtOAc) = 0.4. This gave 0.39 g (60%, ca. 90% purity) of the title product as a white solid.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.75 (m, 4H), 7.46 – 7.26 (m, 5H), 4.15 (q, 1H), 1.70 (d, J = 1.4 Hz, 3H).

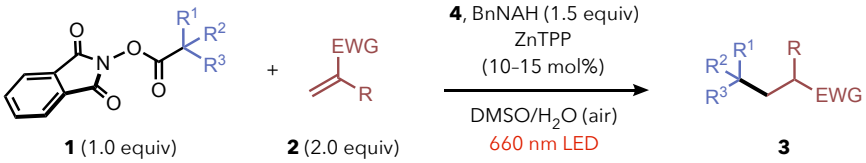
**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 170.92, 161.98, 138.53, 134.86, 129.12, 129.06, 127.95, 127.73, 124.05, 43.13, 19.12.

# 4. Activation and Giese coupling of alkyl redox-active esters

## 4.1. General procedure B for the green-light-promoted coupling reactions




**Coupling at 0.05 mmol scale (for NMR yield):** A 6 mL glass vial equipped with a Teflon-coated stirring bar was charged, under air atmosphere, with the corresponding redox-active ester **1** (0.05 mmol, 1.0 equiv), BnNAH **4** (1.5 equiv), the corresponding Michael acceptor (2.0 equiv) and Eosin Y disodium salt (EY, 5 mol%). This was followed by the addition of DMSO and water (12–25 mM, at the ratio specified for each example, 1:1 or 8:2). The vial was loaded in the sample holder of the HepatoChem PhotoRedOx Duo (see Section 2.2 for details on the set up), which was placed inside the reactor. After ca. 1 min of pre-stirring, the vial was irradiated with a green Kessil LED (525 nm) while stirring and cooling down with the reactor fan system. After the specified reaction time (usually 2 h or 16 h), the vial was extracted from the reactor, and 1.0 equiv of 1,3,5-trimethoxybenzene was added as in internal standard in 1.0 mL of EtOAc. The reaction was further diluted with ca. 2 mL of EtOAc and 2 mL of water and shaken energetically. The organic fraction was dried over anhydrous sodium or magnesium sulfate and centrifuged. The organic fraction was dried in vacuum and the resulted crude product was analyzed by $^1$H NMR.



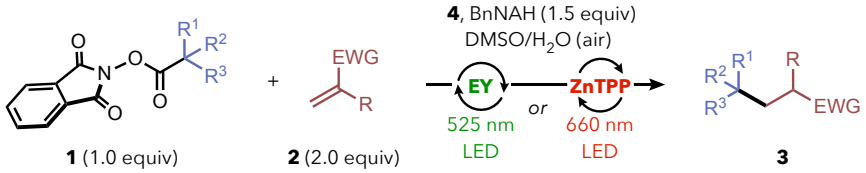

## 4.2. General procedure C for the red-light-promoted coupling reactions

**Coupling at 0.025–0.050 mmol scale (for NMR yield):** A 6 mL glass vial equipped with a Teflon-coated stirring bar was charged, under air atmosphere, with the corresponding redox-active ester **1** (0.025–0.050 mmol, 1.0 equiv), BnNAH **4** (1.5 equiv), the corresponding Michael acceptor (2.0 equiv) and zinc(II) tetraphenylporphyrin (ZnTPP, 010–15 mol%). This was followed by the addition of DMSO and water (12–25 mM, at the ratio specified for each example, 1:1 or 8:2). The vial was loaded in the sample holder of the HepatoChem PhotoRedOx Duo (see Section 2.2 for details on the set up), which was placed inside the reactor. After ca. 1 min of pre-stirring, the vial was irradiated with a red Kessil LED (660 nm) while stirring and cooling down with the reactor fan system. After the specified reaction time (usually 4 h or 16 h), the vial was extracted from the reactor, and 1.0 equiv of 1,3,5-trimethoxybenzene was added as in internal standard in 1.0 mL of EtOAc. The reaction was further diluted with ca. 2 mL of EtOAc and 2 mL of water and shaken energetically. The organic fraction was dried over anhydrous sodium or magnesium sulfate and centrifuged. The organic fraction was dried in vacuum and the resulted crude product was analyzed by $^1$H NMR.

## 4.3. General procedure D for the scale-up and isolation of photochemical reactions

After determining the reaction yield by $^1$H NMR using 1,3,5-trimethoxybenzene as internal standard, one of the two systems (red light or green light) was selected for scale-up (4x), purification, and isolation of each of the alkyl-radical coupling product (based on the highest yield and simplicity of purification as judged by TLC analysis).

Unless stated otherwise, isolation of products was carried out at a 0.20 mmol total scale. To adapt to the vial size required for the sample holder in the photoreactor employed (HepatoChem PhotoRedOx Duo, see Section 2.2 for details) without modifying concentration and ensuring reproducibility of the photochemical method, scale up was performed running the 0.20 mmol reactions separated in 4 different 6 mL reaction vials (i.e.: doing 4 replicates of the same 0.05 mmol scale reaction and combining them before work up). This guarantees an efficient irradiation of the entire reaction mixture within the window directly irradiated by the Kessil lamp in our reaction set up. We found this to be important, particularly in reaction systems that are not fully homogeneous (e.g.: concentrations >10 mM combined with DMSO/water ratios lower than 8:2). Thus, an example of a scale-up reaction would be performed as follows:



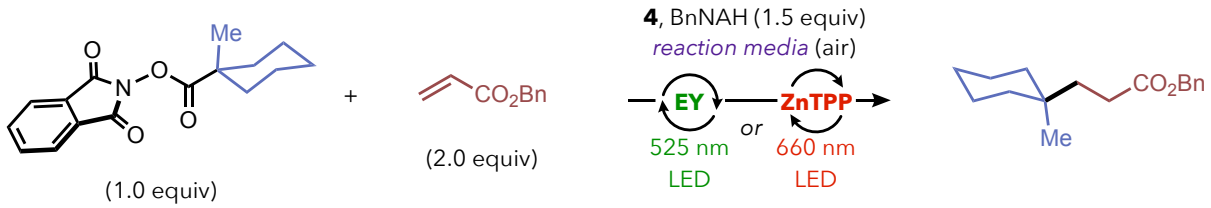

**Coupling at 0.20 mmol scale (for isolation):** Under air, a 20 mL vial was charged, under air atmosphere, with the corresponding redox-active ester **1** (0.20 mmol, 1.0 equiv), BnNAH **4** (0.30 mmol, 1.5 equiv), the corresponding Michael acceptor (0.40 mmol, 2.0 equiv) and the corresponding photocatalyst (EY, 5 mol% or ZnTPP, 10–15 mol%). Everything was dissolved in DMSO (6.4 mL), and four equal parts of this solution (1.6 mL each) were dosed into four 6 mL vials equipped with a Teflon-coated magnetic stirring bar. Then, 0.40 mL of water was added to each vial.[b] The four vials were loaded in the sample holder of the HepatoChem PhotoRedOx Duo (see Section 2.2 for details on the set up), which was placed inside the reactor. After ca. 1 min of pre-stirring, the vials were irradiated with the corresponding Kessil LED (525 nm for EY and 660 nm for ZnTPP) while stirring and cooling down with the reactor fan system. After the specified reaction time (usually 2 h or 16 h), all mixtures were combined in an extraction funnel and diluted with water (ca. 50 mL). The product was extracted with EtOAc (ca. 50 mL), and the organic fraction was washed once with water and once with brine, before drying with anhydrous sodium or magnesium sulfate. After filtration, the crude mixture was concentrated in vacuum. Purification using flash column chromatography in silica gel with the corresponding gradient of hexane/EtOAc afforded the desired product.

Further experimental details and characterization data of the isolated products is reported below.

[b] For reactions using a 1:1 DMSO/water as final solvent mixture, all reagents were dissolved in 4.0 mL of DMSO, and 1.0 mL of this solution was dosed to each vial. This was followed by addition of 1 mL of water to each vial.

## 4.4. Detailed reaction conditions and characterization data for the products

**Benzyl 3-(1-methylcyclohexyl)propanoate (3a)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 75% yield using General Procedure B (5 mol% of EY, 1:1 DMSO/water, 25 mM, green-light irradiation, 1:30 h) or 94% yield using General Procedure C (15 mol% of ZnTPP, 1:1 DMSO/water, 12 mM, red-light irradiation, 4 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate (58 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and benzyl acrylate (65 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (1:1, 4.0 mL, 50 mM) [c] and green-light irradiation (2 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 99:1 to 95:5). This gave 35 mg (67% isolated yield) of the title product as a colorless oil.

$R_f$ (95:5 hexanes/EtOAc): 0.7

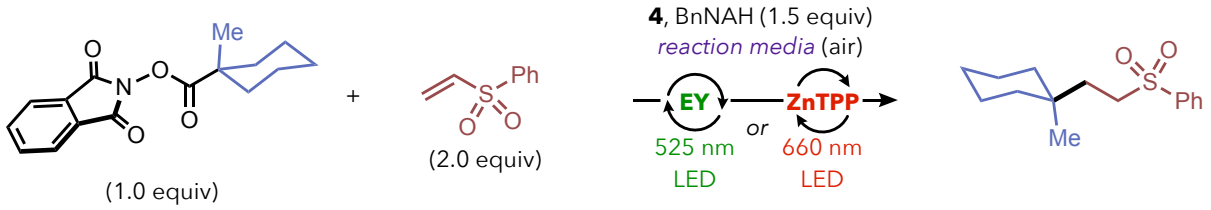
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 5H), 5.11 (s, 2H), 2.38 – 2.25 (m, 2H), 1.64 – 1.57 (m, 2H), 1.43 (q, $J$ = 5.7 Hz, 5H), 1.31 (dd, $J$ = 6.8, 2.7 Hz, 1H), 1.23 (t, $J$ = 5.6 Hz, 4H), 0.85 (s, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 174.45, 136.11, 128.54, 128.21, 128.16, 77.43, 77.01, 76.58, 66.16, 37.47, 36.64, 32.30, 28.97, 26.39, 24.42, 21.94.

**HRMS (ESI)**: calculated for $C_{17}H_{25}O_2$ $[M+H]^+$: 261.1849; found: 261.1839.

[c] Exceptionally, this scale-up reaction was performed in a single 6 mL reaction vial filled with a total volume of 4.0 mL of 1:1 DMSO/water and at a higher concentration than the others (50 mM).

**((2-(1-Methylcyclohexyl)ethyl)sulfonyl)benzene (3b)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 80% yield using General Procedure B (5 mol% of EY, 1:1 DMSO/water, 25 mM, green-light irradiation, 2 h) or 85% yield using General Procedure C (15 mol% of ZnTPP, 1:1 DMSO/water, 12 mM, red-light irradiation, 4 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate (58 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and phenyl vinyl sulfone (67 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (1:1, 8.0 mL, 25 mM), and green-light irradiation (2 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 9:1 to 85:15). This gave 41 mg (77% isolated yield) of the title product as a yellow oil that solidified upon standing in the fridge to give a yellow solid.

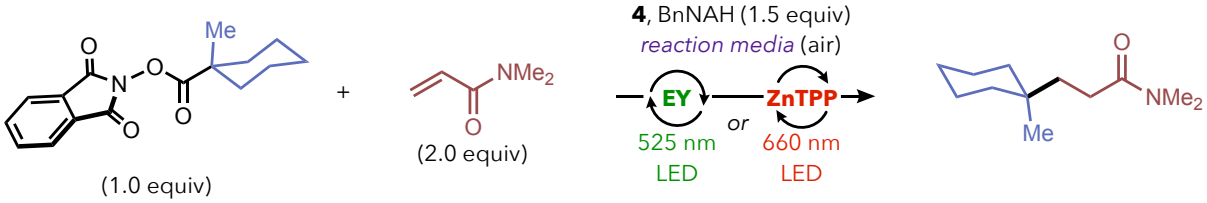
$R_f$ (5:1 hexanes/EtOAc): 0.5

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.98 – 7.83 (m, 2H), 7.71 – 7.49 (m, 3H), 3.13 – 2.98 (m, 2H), 1.71 – 1.53 (m, 2H), 1.50 – 1.07 (m, 10H), 0.80 (s, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 139.4, 133.7, 129.4, 128.2, 52.1, 37.5, 33.8, 32.5, 26.3, 24.6, 21.9.

**HRMS**: calculated for $C_{15}H_{23}O_2S$ $[M+H]^+$: 267.1413; found: 267.1412.

**N,N-Dimethyl-3-(1-methylcyclohexyl)propanamide (3c)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 61% yield using General Procedure B (5 mol% of EY, 1:1 DMSO/water, 25 mM, green-light irradiation, 2 h) or 87% yield using General Procedure C (15 mol% of ZnTPP, 1:1 DMSO/water, 12 mM, red-light irradiation, 4 h).

**Isolated product:** Following General Procedure D, the title product was obtained from dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate (58 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and N,N-dimethylacrylamide (40 mg, 41.2 µL, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (1:1, 8.0 mL, 25 mM), and green-light irradiation (2 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 4:1 to 7:3). This gave 20 mg (52% isolated yield) of the title product as a colorless oil that solidified upon standing in the fridge to give a white solid.

$R_f$ (1:3 hexanes/EtOAc): 0.4

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 3.00 (s, 3H), 2.93 (s, 3H), 2.29 – 2.20 (m, 2H), 1.59 – 1.51 (m, 2H), 1.49 – 1.36 (m, 5H), 1.36 – 1.29 (m, 1H), 1.29 – 1.20 (m, 4H), 0.86 (s, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 174.1, 37.8, 37.5, 37.1, 35.6, 32.5, 28.0, 26.6, 24.7, 22.1.

**HRMS**: calculated for $C_{12}H_{24}NO$ $[M+H]^+$: 198.1852; found: 198.1859.

**3-(1-Methylcyclohexyl)propanenitrile (3d)**


**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 50% yield using General Procedure B (5 mol% of EY, 1:1 DMSO/water, 25 mM, green-light irradiation, 2 h) or 18% yield using General Procedure C (15 mol% of ZnTPP, 1:1 DMSO/water, 12 mM, red-light irradiation, 4 h).

**Isolated product:** Following General Procedure D, the title product was obtained from dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate (58 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and acrylonitrile (21.2 mg, 26.2 µL, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (1:1, 8.0 mL, 25 mM), and green-light irradiation (2 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (85:15). This gave 11 mg (35% isolated yield) of the title product as a colorless oil.

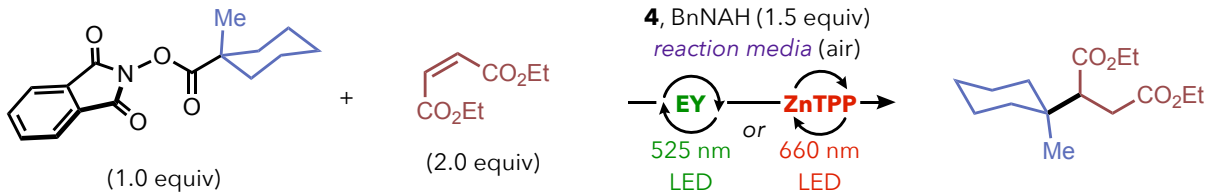
$R_f$ (9:1 hexanes/EtOAc): 0.5

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 2.30 – 2.22 (m, 2H), 1.68 – 1.60 (m, 2H), 1.51 – 1.39 (m, 5H), 1.35 – 1.18 (m, 5H), 0.89 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 120.9, 37.6, 37.3, 32.7, 26.3, 24.2, 21.9, 11.9.

**HRMS**: calculated for $C_{10}H_{18}N$ $[M+H]^+$: 152.1434; found: 152.1438.

**Diethyl 2-(1-methylcyclohexyl)succinate (3e)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 88% yield using General Procedure B (5 mol% of EY, 8:2 DMSO/water, 25 mM, green-light irradiation, 16 h) or 79% yield using General Procedure C (15 mol% of ZnTPP, 8:2 DMSO/water, 25 mM, red-light irradiation, 16 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate (58 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and diethyl maleate (69 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (8:2, 8.0 mL, 25 mM) and green-light irradiation (16 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 95:5 to 9:1). This gave 43 mg (80% isolated yield) of the title product as a yellow oil.

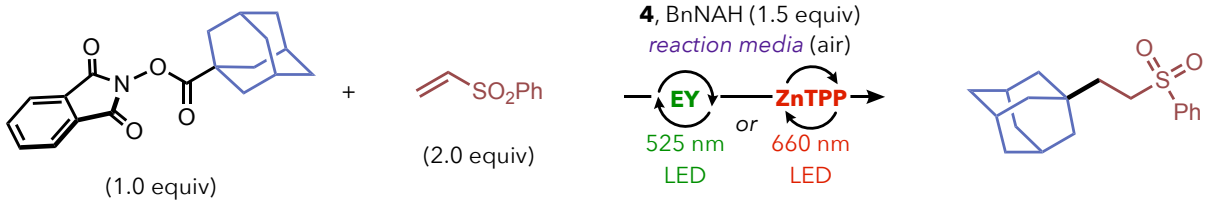
$R_f$ (9:1 hexanes/EtOAc): 0.5

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 4.24 – 4.06 (m, 4H), 2.85 – 2.70 (m, 2H), 2.53 – 2.39 (m, 1H), 1.62 – 1.31 (m, 10H), 1.30 – 1.22 (m, 6H), 0.93 (s, 3H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 174.12, 172.83, 60.51, 60.08, 49.98, 36.29, 36.24, 35.17, 31.97, 26.03, 21.73, 21.67, 20.97, 14.23, 14.13.

**HRMS (ESI)**: calculated for $C_{15}H_{27}O_4$ $[M+H]^+$: 271.1904; found: 271.1908.

**1-(2-(Phenylsulfonyl)ethyl)adamantane (3f)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 72% yield using General Procedure B (5 mol% of EY, 8:2 DMSO/water, 25 mM, green-light irradiation, 16 h) or 69% yield using General Procedure C (15 mol% of ZnTPP, 8:2 DMSO/water, 25 mM, red-light irradiation, 16 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl adamantane-1-carboxylate (65 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and phenyl vinyl sulfone (67 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (8:2, 8.0 mL, 25 mM) and green-light irradiation (16 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 95:5 to 9:1). This gave 41 mg (67% isolated yield) of the title product as a white solid.

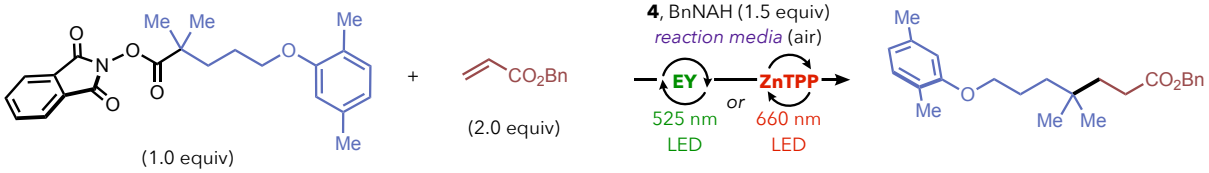
$R_f$ (9:1 hexanes/EtOAc): 0.3

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.93 (dd, $J$ = 8.1, 1.5 Hz, 2H), 7.71 – 7.64 (m, 1H), 7.59 (dd, $J$ = 8.3, 6.7 Hz, 2H), 3.11 – 3.04 (m, 2H), 1.99 – 1.92 (m, 3H), 1.74 – 1.67 (m, 3H), 1.64 – 1.54 (m, 4H), 1.53 – 1.47 (m, 2H), 1.44 – 1.41 (m, 6H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 139.35, 133.55, 129.23, 128.02, 51.29, 41.95, 36.82, 35.88, 31.85, 28.44.

**HRMS (ESI)**: calculated for $C_{18}H_{25}O_2S$ $[M+H]^+$: 305.1570; found: 305.1570.

**Benzyl 7-(2,5-dimethylphenoxy)-4,4-dimethylheptanoate (3g)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 81% yield using General Procedure B (5 mol% of EY, 1:1 DMSO/water, 25 mM, green-light irradiation, 16 h) or 12% yield using General Procedure C (10 mol% of ZnTPP, 1:1 DMSO/water, 25 mM, red-light irradiation, 16 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (79 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and benzyl acrylate (65 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (1:1, 8.0 mL, 25 mM) and green-light irradiation (16 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 99:1 to 97:3). This gave 32 mg (43% isolated yield) of the title product as a white solid.

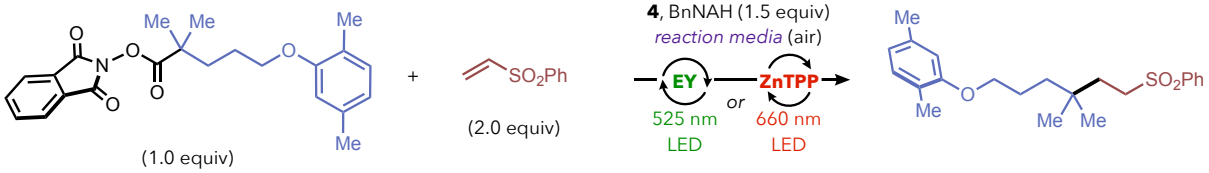
$R_f$ (9:1 hexanes/EtOAc): 0.5

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 5H), 7.01 (d, $J$ = 7.4 Hz, 1H), 6.66 (d, $J$ = 7.7 Hz, 1H), 6.62 (s, 1H), 5.13 (s, 2H), 3.91 (t, $J$ = 6.3 Hz, 2H), 2.39 – 2.33 (m, 2H), 2.32 (s, 3H), 2.18 (s, 3H), 1.82 – 1.70 (m, 2H), 1.67 – 1.60 (m, 2H), 1.41 – 1.34 (m, 2H), 0.92 (s, 6H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ174.28, 157.20, 136.57, 136.24, 130.43, 128.69, 128.36, 128.33, 123.73, 120.79, 112.16, 68.58, 66.35, 38.04, 36.50, 32.42, 29.76, 26.89, 24.39, 21.53, 15.91.

**HRMS (ESI)**: calculated for $C_{24}H_{33}O_3$ $[M+H]^+$: 369.2424; found: 369.2428.

**2-((4,4-Dimethyl-6-(phenylsulfonyl)hexyl)oxy)-1,4-dimethylbenzene (3h)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 92% yield using General Procedure B (5 mol% of EY, 8:2 DMSO/water, 25 mM, green-light irradiation, 16 h) or 88% yield using General Procedure C (10 mol% of ZnTPP, 8:2 DMSO/water, 25 mM, red-light irradiation, 16 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (79 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and phenyl vinyl sulfone (67 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (8:2, 8.0 mL, 25 mM) and green-light irradiation (16 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 95:5 to 85:15). This gave 65 mg (87% isolated yield) of the title product as a white solid.

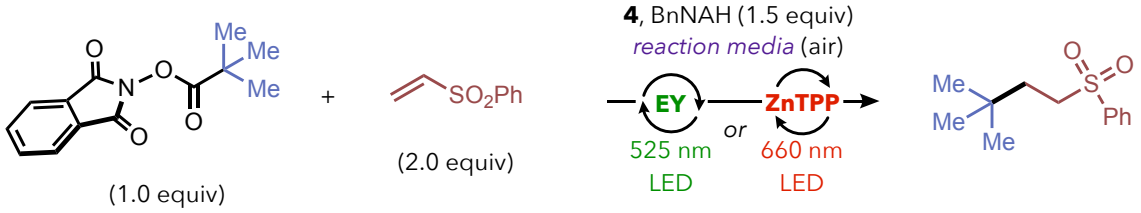
$R_f$ (8:2 hexanes/EtOAc): 0.4

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.92 (d, $J$ = 7.5 Hz, 2H), 7.70 – 7.52 (m, 3H), 7.00 (d, $J$ = 7.5 Hz, 1H), 6.67 (d, $J$ = 7.5 Hz, 1H), 6.60 (s, 1H), 3.88 (t, $J$ = 6.1 Hz, 2H), 3.11 – 3.02 (m, 2H), 2.31 (s, 3H), 2.15 (s, 3H), 1.72 – 1.58 (m, 4H), 1.38 – 1.25 (m, 2H), 0.89 (s, 6H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 157.03, 139.35, 136.60, 133.74, 130.44, 129.38, 128.13, 123.59, 120.87, 112.09, 68.16, 52.56, 37.83, 33.54, 32.38, 26.88, 24.17, 21.50, 15.89.

**HRMS (ESI)**: calculated for $C_{22}H_{31}O_3S$ $[M+H]^+$: 375.1988; found: 375.1983.

**((3,3-Dimethylbutyl)sulfonyl)benzene (3i)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 78% yield using General Procedure B (5 mol% of EY, 8:2 DMSO/water, 25 mM, green-light irradiation, 16 h) or 86% yield using General Procedure C (10 mol% of ZnTPP, 8:2 DMSO/water, 25 mM, red-light irradiation, 16 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl pivalate (50 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and phenyl vinyl sulfone (67 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (8:2, 8.0 mL, 25 mM) and green-light irradiation (16 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 9:1 to 8:2). This gave 40 mg (88% isolated yield) of the title product as a white solid.

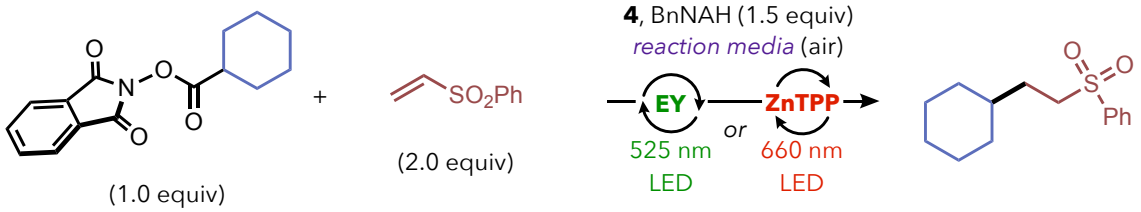
$R_f$ (8:2 hexanes/EtOAc): 0.4

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.90 (d, $J$ = 8.0 Hz, 2H), 7.69 – 7.52 (m, 3H), 3.09 – 3.01 (m, 2H), 1.64 – 1.55 (m, 2H), 0.88 – 0.83 (m, 9H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 139.40, 133.72, 129.38, 128.15, 53.08, 35.77, 30.14, 29.04.

**HRMS (ESI)**: calculated for $C_{12}H_{19}O_2S$ $[M+H]^+$: 227.1100; found: 227.1097.

**((2-Cyclohexylethyl)sulfonyl)benzene (3j)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 48% yield using General Procedure B (5 mol% of EY, 1:1 DMSO/water, 25 mM, green-light irradiation, 2 h) or 74% yield using General Procedure C (10 mol% of ZnTPP, 1:1 DMSO/water, 12 mM, red-light irradiation, 2 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate (55 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and phenyl vinyl sulfone (67 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (8:2, 8.0 mL, 25 mM) and green-light irradiation (16 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 97:3 to 9:1). This gave 29 mg (57% isolated yield) of the title product as a colorless oil that solidified upon standing in the fridge to give a white solid.

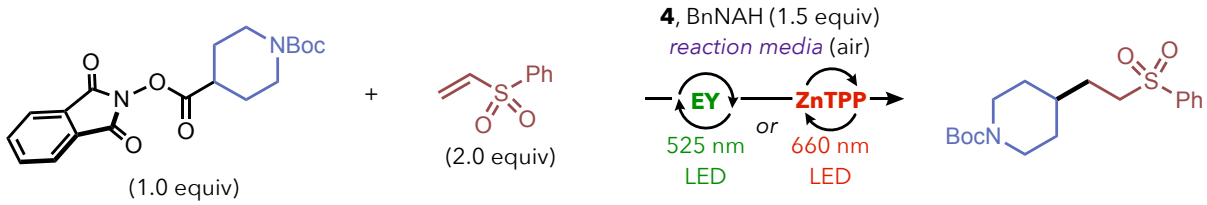
$R_f$ (8:2 hexanes/EtOAc): 0.4

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.91 (d, $J$ = 7.7 Hz, 2H), 7.69 – 7.61 (m, 1H), 7.60 – 7.52 (m, 2H), 3.13 – 3.05 (m, 2H), 1.72 – 1.53 (m, 7H), 1.33 – 1.04 (m, 4H), 0.88 (t, $J$ = 11.5 Hz, 2H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 139.50, 133.70, 129.38, 128.19, 54.55, 36.80, 32.93, 29.77, 26.41, 26.14.

**HRMS (ESI)**: calculated for $C_{14}H_{21}O_2S$ $[M+H]^+$: 253.1257; found: 253.1259.

***tert*-Butyl 4-(2-(phenylsulfonyl)ethyl)piperidine-1-carboxylate (3k)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 46% yield using General Procedure B (5 mol% of EY, 1:1 DMSO/water, 25 mM, green-light irradiation, 2 h) or 79% yield using General Procedure C (15 mol% of ZnTPP, 1:1 DMSO/water, 12 mM, red-light irradiation, 4 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1-(*tert*-butyl) 4-(1,3-dioxoisoindolin-2-yl) piperidine-1,4-dicarboxylate (75 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and phenyl vinyl sulfone (67 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (1:1, 8.0 mL, 25 mM), and green-light irradiation (2 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 8:2 to 7:3). This gave 8.0 mg (11% isolated yield) of the title product as a colorless oil.

$R_f$ (7:3 hexanes/EtOAc): 0.2

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.02 – 7.85 (m, 2H), 7.73 – 7.61 (m, 1H), 7.62 – 7.46 (m, 2H), 4.13 – 3.98 (m, 2H), 3.15 – 3.02 (m, 2H), 2.62 (t, $J$ = 12.0 Hz, 2H), 1.76 – 1.51 (m, 5H), 1.43 (s, 9H), 1.06 (qd, $J$ = 12.1, 4.3 Hz, 2H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 154.8, 139.3, 133.8, 129.4, 128.1, 79.5, 54.0, 43.8 (br), 35.1, 31.8, 29.0, 28.6.

**HRMS**: calculated for $C_{18}H_{28}NO_4S$ $[M+H]^+$: 354.1734; found: 354.1739.

***tert*-Butyl-2-(2-(phenylsulfonyl)ethyl)pyrrolidine-1-carboxylate (3l)**


**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 93% yield using General Procedure B (5 mol% of EY, 1:1 DMSO/water, 25 mM, green-light irradiation, 2 h) or 96% yield using General Procedure C (10 mol% of ZnTPP, 1:1 DMSO/water, 12 mM, red-light irradiation, 2 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1-(*tert*-butyl) 3-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1,3-dicarboxylate (58 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and phenyl vinyl sulfone (67 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (8:2, 2.0 mL, 25 mM) and green-light irradiation (16 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 8:2 to 7:3). This gave 45 mg (66% yield, isolated together with ca. 5 mol% of **SI-2**) of the title product as a white solid.

$R_f$ (6:4 hexanes/EtOAc): 0.4

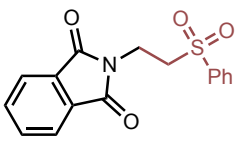
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 2H), 7.72 – 7.61 (m, 1H), 7.60 – 7.49 (m, 2H), 3.81 (s, 1H), 3.35 – 3.01 (m, 4H), 2.07 – 1.53 (m, 6H), 1.36 (s, 9H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 139.33, 133.79, 129.42, 128.15, 55.88, 53.94, 46.59, 31.04, 28.51, 28.09, 23.26.

***** Some NMR signals are broad and split due to the presence of diastereomeric rotamers.

**HRMS (ESI)**: calculated for $C_{17}H_{26}NO_4S$ $[M+H]^+$: 340.1577; found: 340.1575.

Furthermore, a second fraction was isolated from this reaction corresponding to product **SI-2**, **2-(2-(phenylsulfonyl)ethyl)-isoindoline-1,3-dione**, which was obtained as a white solid (39 mg, 62% isolated yield based on **1**). This side-product was observed in all reactions with phenyl vinyl sulfone, arising from the Michael addition of released phthalimide to the acceptor in excess.



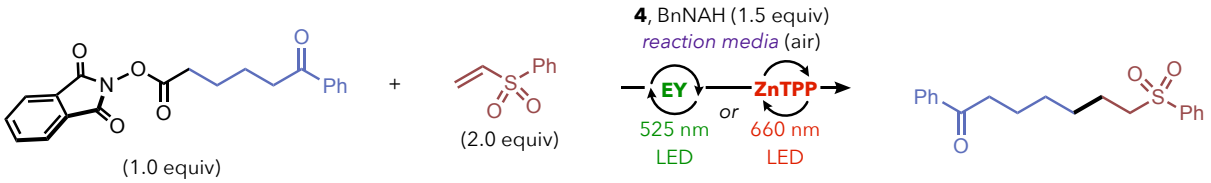

$R_f$ (6:4 hexanes/EtOAc): 0.35

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.82 – 7.77 (m, 2H), 7.73 – 7.68 (m, 2H), 7.60 – 7.52 (m, 2H), 7.52 – 7.47 (m, 1H), 4.06 (t, $J$ = 6.6 Hz, 2H), 3.58 (t, $J$ = 6.6 Hz, 2H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 167.64, 138.81, 133.98, 131.88, 129.48, 128.29, 123.57, 52.82, 32.27, 28.53.

**HRMS (ESI)**: calculated for $C_{16}H_{14}NO_4S$ $[M+H]^+$: 316.0638; found: 316.0642.

**1-Phenyl-7-(phenylsulfonyl)heptan-1-one (3m)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 46% yield using General Procedure B (5 mol% of EY, 1:1 DMSO/water, 25 mM, green-light irradiation, 2 h) or 57% yield using General Procedure C (15 mol% of ZnTPP, 1:1 DMSO/water, 12 mM, red-light irradiation, 4 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl 6-oxo-6-phenylhexanoate (70 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and phenyl vinyl sulfone (67 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 5 mol%) in DMSO/water (1:1, 8.0 mL, 25 mM), and green-light irradiation (2 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (8:2). This gave 19 mg (28% isolated yield) of the title product as a white solid.

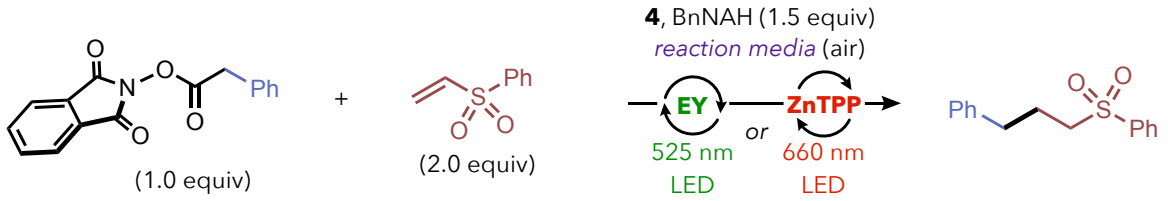
$R_f$ (7:3 hexanes/EtOAc): 0.4

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.95 – 7.86 (m, 4H), 7.69 – 7.61 (m, 1H), 7.60 – 7.51 (m, 3H), 7.45 (t, *J* = 7.4 Hz, 2H), 3.12 – 3.05 (m, 2H), 2.93 (t, *J* = 7.2 Hz, 2H), 1.79 – 1.64 (m, 4H), 1.49 – 1.30 (m, 4H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 200.2, 139.4, 137.1, 133.8, 133.1, 129.4, 128.7, 128.2, 128.1, 56.4, 38.4, 28.8, 28.3, 23.9, 22.7.

**HRMS**: calculated for $C_{19}H_{23}O_3S$ $[M+H]^+$: 331.1362; found: 331.1362.

**(3-Phenylpropyl)sulfonyl]benzene (3n)**




**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 41% yield using General Procedure B (5 mol% of EY, 1:1 DMSO/water, 25 mM, green-light irradiation, 2 h) or 44% yield using General Procedure C (15 mol% of ZnTPP, 1:1 DMSO/water, 12 mM, red-light irradiation, 4 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl 2-phenylacetate (56 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and phenyl vinyl sulfone (67 mg, 0.40 mmol, 2.0 equiv), with Eosin Y disodium salt as photocatalyst (6.9 mg, 0.010 mmol, 10 mol%) in DMSO/water (1:1, 8.0 mL, 25 mM), and green-light irradiation (2 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (85:15).

Chromatographic purification delivered two fractions: first 3.5 mg of pure **3n** as a colorless residue. Second, 34 mg of a 1:5 mixture of **3n** and **2b** (21% total yield of **3n**). Further attempts to fully isolate all **3n** in pure form were unsuccessful. Nevertheless, **3n** is a well-known compound and characterization data matched previously reported ones.[2]

$R_f$ (7:3 hexanes/EtOAc): 0.5

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.94 – 7.85 (m, 2H), 7.65 (t, $J$ = 7.7 Hz, 1H), 7.56 (t, $J$ = 7.8 Hz, 2H), 7.32 – 7.23 (m, 2H), 7.23 – 7.16 (m, 1H), 7.10 (d, $J$ = 7.4 Hz, 2H), 3.11 – 3.04 (m, 2H), 2.70 (t, $J$ = 7.4 Hz, 2H), 2.12 – 1.99 (m, 2H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 140.0, 139.2, 133.8, 129.4, 128.7, 128.5, 128.1, 126.5, 55.5, 34.2, 24.3.

**HRMS**: calculated for $C_{15}H_{17}O_2S$ $[M+H]^+$: 261.0944; found: 261.0940.

**1,2-Dimethoxy-4-(4-(phenylsulfonyl)butyl)benzene (3o)**


**Photocatalytic system comparison:** As determined by NMR using 1,3,5-trimethoxybenzene as internal standard at 0.05 mmol scale, the title product was obtained in 45% yield using General Procedure B (5 mol% of EY, 8:2 DMSO/water, 25 mM, green-light irradiation, 16 h) or 55% yield using General Procedure C (10 mol% of ZnTPP, 8:2 DMSO/water, 25 mM, red-light irradiation, 16 h).

**Isolated product:** Following General Procedure D, the title product was obtained from 1,3-dioxoisoindolin-2-yl 3-(3,4-dimethoxyphenyl)propanoate (71 mg, 0.20 mmol, 1.0 equiv), 1-benzyl-1,4-dihydronicotinamide (BnNAH, 64 mg, 0.30 mmol, 1.5 equiv) and phenyl vinyl sulfone (67 mg, 0.40 mmol, 2.0 equiv), with ZnTPP as photocatalyst (13.6 mg, 0.020 mmol, 10 mol%) in DMSO/water (8:2, 8.0 mL, 25 mM) and red-light irradiation (16 h), after purification by flash column chromatography in silica gel, using hexanes/EtOAc as solvent (gradient from 9:1 to 1:1). This gave 34 mg (51% isolated yield) of the title product as a brown oil.

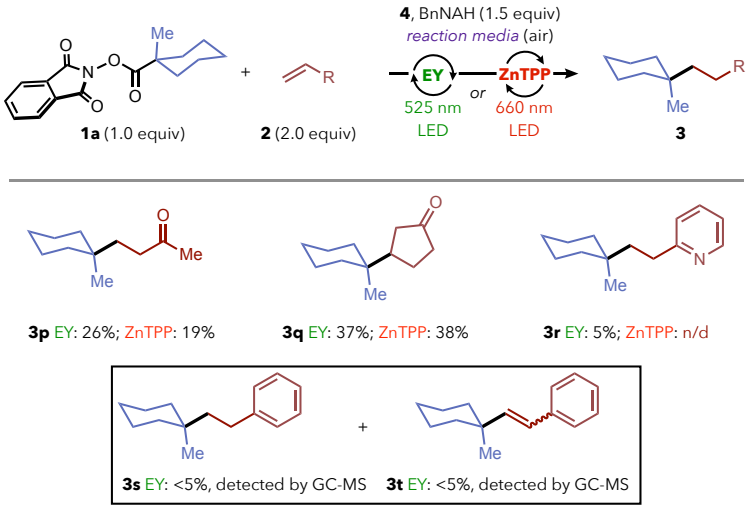
$R_f$ (1:1 hexanes/EtOAc): 0.7

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 2H), 7.68 – 7.61 (m, 1H), 7.59 – 7.52 (m, 2H), 6.78 – 6.73 (m, 1H), 6.66 – 6.61 (m, 2H), 3.84 (s, 6H), 3.14 – 3.04 (m, 2H), 2.54 (t, $J$ = 7.2 Hz, 2H), 1.84 – 1.63 (m, 4H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 149.09, 147.53, 139.38, 134.05, 133.75, 129.38, 128.17, 120.32, 111.87, 111.52, 56.25, 56.10, 55.99, 35.00, 30.28, 22.36.

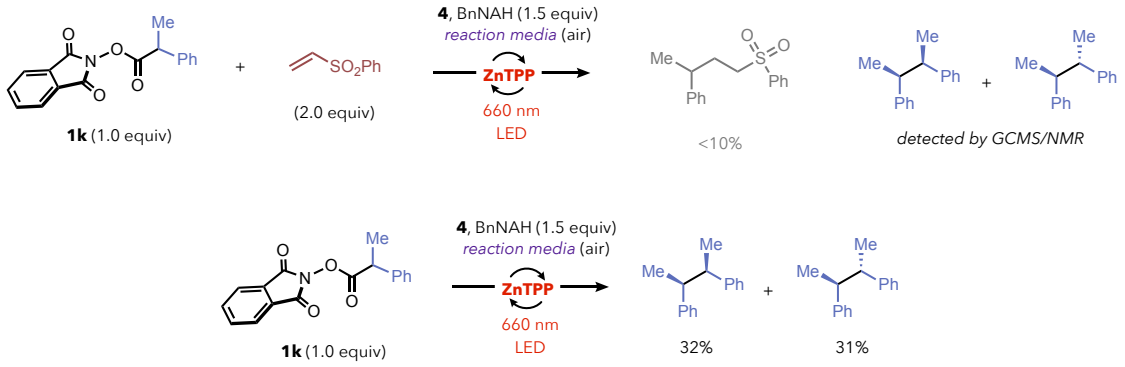
**HRMS (ESI)**: calculated for $C_{18}H_{23}O_4S$ $[M+H]^+$: 335.1312; found: 335.1317.

## 4.5. Low yielding or unsuccessful substrates



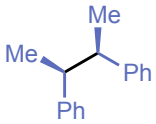

**Scheme S1.** Additional reaction scope with the two photoredox systems. Yields were determined by 1H NMR using 1,3,5-trimethoxybenzene as internal standard. Standard conditions, green light: **1a** (0.05 mmol, 25 mM), **2** (2.0 equiv), **4** (1.5 equiv) and **5** (5 mol%) in DMSO/$H_2O$ (1:1) under 525 nm light irradiation for 120 min; red light: **1a** (0.025 mmol, 12 mM), **2** (2.0 equiv), **4** (1.5 equiv) and **6** (15 mol%) in DMSO/$H_2O$ (1:1) under 660 nm light irradiation for 240 min. n/d = not detected.

The generation of very stabilized alkyl-radical fragments, for example starting from secondary benzylic redox-active esters, leads to diminished yields of the Giese-coupling product. Instead, significat amounts of radical dimerization products were observed.[3]




To fully confirm the formation of these products, we carried out the reaction in the absence of Giese acceptor and determined the yield by crude $^1$H NMR analysis. Furthermore, we isolated the meso dimer by flash column chromatography in silica gel, using hexane as solvent, and NMR data is reported below.

**2,3-Diphenylbutane** (meso form) (**SI-3**)



**$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 4H), 7.22 (d, $J$ = 7.1 Hz, 6H), 2.80 (td, $J$ = 6.2, 4.0 Hz, 2H), 1.09 – 0.90 (m, 6H).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 147.43, 128.43, 127.78, 126.20, 47.42, 21.17.

# 5. Reaction development, optimization and control experiments

Unless stated otherwise, all reaction development was carried out using the standard protocols described in General Procedures B and C (for green or red light, respectively), under the correspondingly modified reaction conditions as described in this section.

Unless stated otherwise, yields were determined by $^{1}$H NMR adding 1 equiv of 1,3,5-trimethoxybenzene as internal standard. In entries were it is indicated, recovery of starting materials was always determined by $^{1}$H NMR with 1,3,5-trimethoxybenzene as internal standard.

Specifically, for some entries of product **3a**, the reaction yields were also determined by GCMS adding 1 equiv of 1,3,5-trimethoxybenzene as internal standard, and according to the following calibration curve (**3a** = PDT in the table), where yield = (area of the product/area of the internal standard) divided by 1.05.

| mmol PDT | mmol IS | area PDT / area IS | mmol PDT/IS |
|---|---|---|---|
| 0.00715 | 0.00411 | 1.85 | 1.74 |
| 0.00358 | 0.00411 | 1.00 | 0.87 |
| 0.00179 | 0.00411 | 0.50 | 0.44 |
| 0.00089 | 0.00411 | 0.24 | 0.22 |

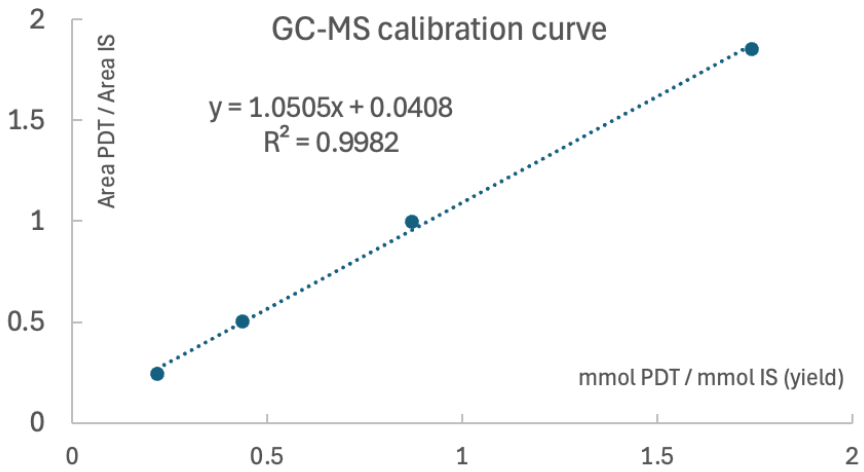
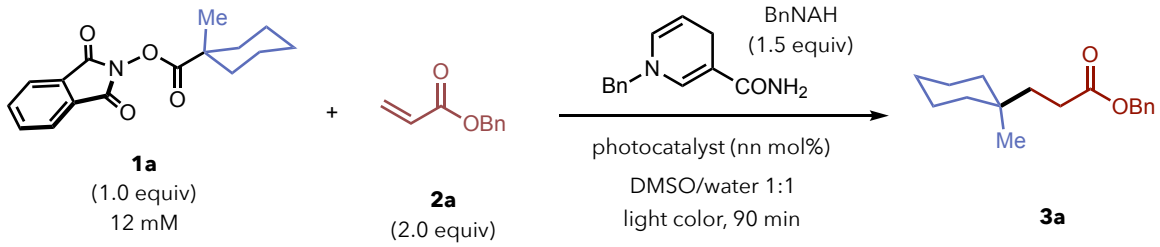



**Figure S5.** Calibration data for the determination of the yield of **3a** (PDT) by GCMS

## Initial reaction development




**1a**
(1.0 equiv)
12 mM

**2a**
(2.0 equiv)

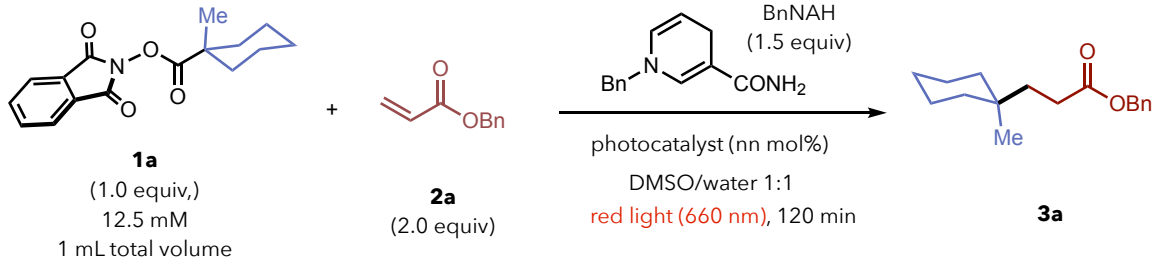
**3a**

| Entry | Conditions / Deviations | Recov. **1a** | Recov. **2a** | **3a** Yield |
|---|---|---|---|---|
| 1 | **Original conditions**: BnNAH, no photocatalyst 1:1 DMSO/water, blue LED (Mendoza, 2020) | 4% | 35% | 70% |
| 2 | **BnNAH**, no photocatalyst, **dark** | 105% | 197% | n/d |
| 3 | **NADH**, no photocatalyst, **dark** | 96% | 173% | n/d |
| 4 | **BnNAH**, EY (5 mol%), green LED | 0% | 28% | 58% |
| 5 | **NADH**, EY (5 mol%), green LED | 11% | 0% | 76% |
| | *green light controls* | | | |
| 6 | BnNAH, **no photocatalyst**, green LED | 59% | 195% | n/d |
| 7 | **no reductant**, EY (5 mol%), green LED | 29% | 4% | n/d |
| 8 | BnNAH, EY (5 mol%), **dark** | 82% | 198% | n/d |

Unless stated otherwise, yields and recoveries estimated by GCMS using 1,3,5-trimethoxybenzene as IS.
n/d = not detected; n/dm = not determined

**Table S1.** Initial reaction development with green light

The conditions in Entry 1 of **Table S1** were adapted from the ones reported by Mendoza and co-workers, and reproduced in our laboratory.[1c]




**1a**
(1.0 equiv,)
12.5 mM
1 mL total volume

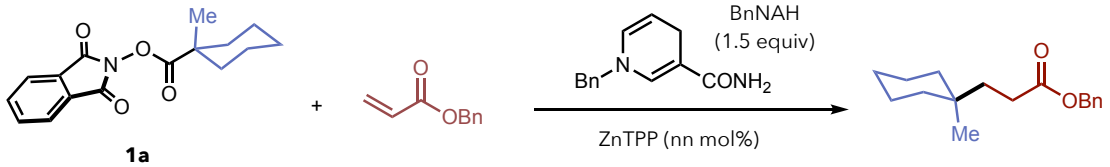
**2a**
(2.0 equiv)

**3a**

| Entry | Conditions / Deviations | Recov. **1a** | Recov. **2a** | **3a** Yield |
|---|---|---|---|---|
| 1 | red light, **no photocatalyst** | 87% | 190% | n/d |
| 2 | red light, methylene blue (10 mol%) | 53% | 174% | 4% |
| 3 | red light, **ZnTPP** (10 mol%), 25 mM (0.5 mL tot. vol.) | n/dm | n/dm | 29% |
| 4 | red light, **ZnTPP** (10 mol%), 12.5 mM (1.0 mL tot. vol.) | 9% | 27% | 55% |

Unless stated otherwise, yields and recoveries estimated by GCMS using 1,3,5-trimethoxybenzene as IS.
n/d = not detected; n/dm = not determined

**Table S2.** Initial reaction development with red light




**1a**
(1.0 equiv)
y mM
2 mL total volume

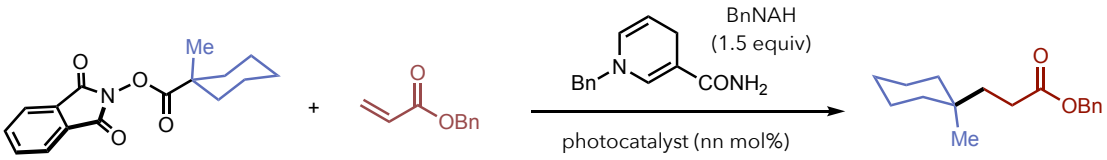
**2a**
(2.0 equiv)

**3a**

| Entry | Conditions / Deviations | **3a** Yield |
|---|---|---|
| 1 | 5 mM, ZnTPP (5 mol%) | 47% |
| 2 | 12.5 mM, ZnTPP (5 mol%) | 59% |
| 3 | 25 mM, ZnTPP (5 mol%) | 32% |
| 4 | 50 mM, ZnTPP (5 mol%) | 22% |
| 5 | 12.5 mM, ZnTPP (2 mol%) | 41% |
| 6 | 12.5 mM, ZnTPP (10 mol%) | 54% |
| 7 | 12.5 mM, ZnTPP (15 mol%) | 60% |

Unless stated otherwise, yields estimated by $^1$H NMR using 1,3,5-trimethoxybenzene as IS.

**Table S3.** Reaction optimization with red light




**1a**
(1.0 equiv)
y mM
2 mL total volume

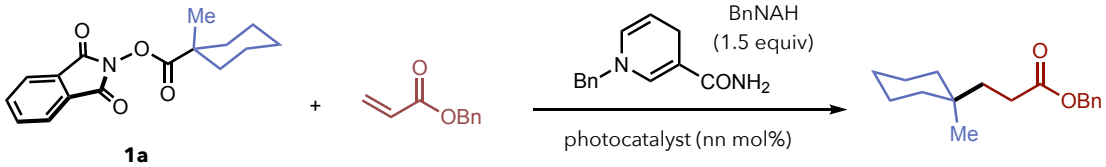
**2a**
(2.0 equiv)

**3a**

| Entry | Conditions / Deviations | **3a** Yield |
|---|---|---|
| 1 | DMSO as solvent (25 mM), open to air, EY (5 mol%), green LED, 2 h | 82% |
| 2 | DMSO as solvent (25 mM), under $N_2$, EY (5 mol%), green LED, 2 h | 49% |
| 3 | MeCN as solvent (25 mM), open to air, EY (5 mol%), green LED, 2 h | 12% |
| 4 | THF as solvent (25 mM), open to air, EY (5 mol%), green LED, 2 h | 10% |
| 5 | DMSO as solvent (12 mM), open to air, ZnTPP (5 mol%), red LED, 4 h | 80% |
| 6 | DMSO as solvent (12 mM), under $N_2$, ZnTPP (5 mol%), red LED, 4 h | 59% |
| 7 | MeCN as solvent (12 mM), open to air, ZnTPP (5 mol%), red LED, 4 h | n/d |
| 8 | THF as solvent (12 mM), open to air, ZnTPP (5 mol%), red LED, 4 h | n/d |

Unless stated otherwise, yields estimated by $^1$H NMR using 1,3,5-trimethoxybenzene as IS. n/d = not detected

**Table S4.** Effect of solvent and air atmosphere in both photocatalytic systems




**1a**
(1.0 equiv)
y mM
2 mL total volume

**2a**
(2.0 equiv)

**3a**

| Entry | Conditions / Deviations | **3a** Yield |
|---|---|---|
| 1 | **15 min**, 25 mM, EY (5 mol%), green LED | 55% |
| 2 | **30 min**, 25 mM, EY (5 mol%), green LED | 57% |
| 3 | **60 min**, 25 mM, EY (5 mol%), green LED | 60% |
| 4 | **120 min**, 25 mM, EY (5 mol%), green LED | 61%, 62%* |
| 5 | **240 min**, 25 mM, EY (5 mol%), green LED | 75% |
| 6 | **15 min**, 12.5 mM, ZnTPP (15 mol%), red LED | 22% |
| 7 | **30 min**, 12.5 mM, ZnTPP (15 mol%), red LED | 43% |
| 8 | **60 min**, 12.5 mM, ZnTPP (15 mol%), red LED | 45% |
| 9 | **120 min**, 12.5 mM, ZnTPP (15 mol%), red LED | 60% |
| 10 | **240 min**, 12.5 mM, ZnTPP (15 mol%), red LED | 94% |

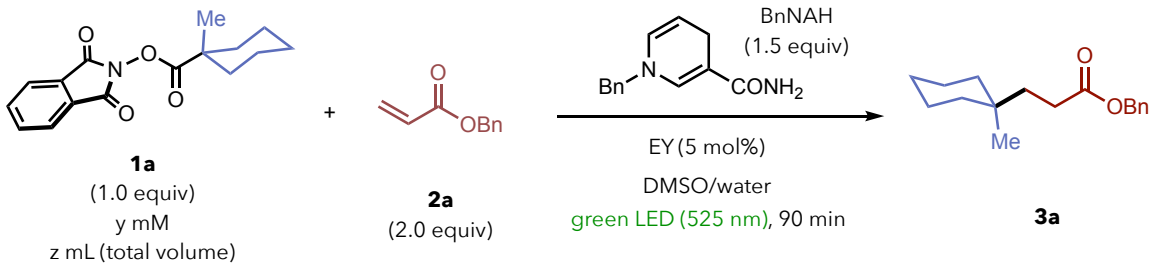
Unless stated otherwise, yields estimated by $^{1}$H NMR using 1,3,5-trimethoxybenzene as IS.
*Independent replicates.

**Table S5.** Effect of the reaction time in both photocatalytic systems

# 6. Biocompatibility experiments

Unless stated otherwise, all biocompatibility experiments were carried out using the standard protocols described in General Procedures B and C (for green or red light, respectively), under the correspondingly modified reaction conditions as described in this section. Unless stated otherwise, yields were determined by $^{1}$H NMR or GCMS (see previous section for deatils) using 1,3,5-trimethoxybenzene as internal standard.

*evaluation of biocompatibility*




**1a**
(1.0 equiv)
y mM
z mL (total volume)

**2a**
(2.0 equiv)

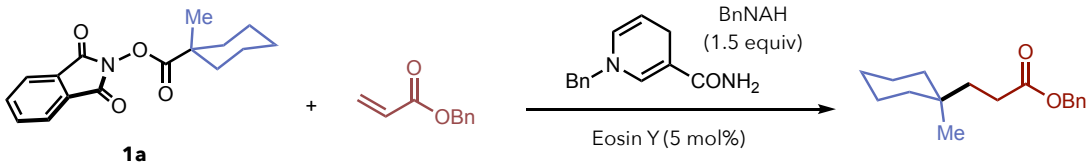
**3a**

| Entry | Conditions / Deviations | Recov. **1a** | Recov. **2a** | **3a** Yield |
|---|---|---|---|---|
| 1 | **Standard "in-vitro" conditons**: BnNAH (1.5 equiv) EY (5 mol%), 1:1 DMSO/water, green LED, 90 min 0.05-mmol scale, 25 mM, 1 mL total volume | 4% | 10% | 63% |
| 2 | **10 mM**, 2 mL total volume, 4:1 water/DMSO | 28% | 2% | 63% |
| 3 | **5 mM**, 2 mL total volume, 4:1 water/DMSO | 4% | 2% | 74% |
| 4 | **1 mM**, 2 mL total volume, 4:1 water/DMSO | 7% | 1% | 19% |
| 5 | 10 mM, 1 mL total volume, **4:1 PBS(1x)/DMSO** | 28% | 2% | 62% |
| 6 | 10 mM, 1 mL total volume, **4:1 CellLys@PBS(1x)/DMSO** | 4% | 2% | 74% |
| 7 | 10 mM, 1 mL total volume, 4:1 PBS(1x)/DMSO, **no photocat.** | 71% | 203% | n/d |
| 8 | 10 mM, 1 mL total volume, 4:1 CellLys@PBS(1x)/DMSO, **no photocat.** | 89% | 205% | n/d |

Unless stated otherwise, yields and recoveries estimated by GCMS using 1,3,5-trimethoxybenzene as IS.
n/d = not detected; n/dm = not determined

**Table S6.** Biocompatibility experiments with green light

The final concentration of cell lysates in entries 6 and 8 was estimated to be 1.5 mg/mL.




**1a**
(1.0 equiv)
y mM
z mL (total volume)

**2a**
(2.0 equiv)

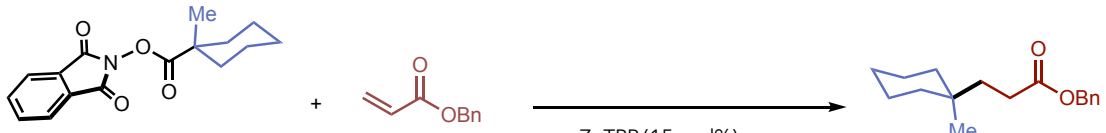
**3a**

| Entry | Conditions / Deviations | **3a** Yield |
|---|---|---|
| 9 | 25 mM, 2 mL total volume, 1:1 water/DMSO | 61% |
| 10 | 25 mM, 2 mL total volume, 1:1 water/DMSO, **NADH instead of BnNAH**, **EY (7 mol%)** | 66% |
| 11 | 10 mM, 2 mL total volume, **1:4 DMEM/DMSO** | 35% |
| 12 | 10 mM, 2 mL total volume, **1:4 DMEM/DMSO, no BnNAH** | 6% |
| 13 | 10 mM, 2 mL total volume, **1:4 DMEM/DMSO**, **no cat.** | <3% |
| 14 | 10 mM, 2 mL total volume, **1:4 DMEM/DMSO**, **no light** | <3% |

Unless stated otherwise, yields estimated by $^{1}$H NMR using 1,3,5-trimethoxybenzene as IS.

**Table S7.** Biocompatibility experiments with green light (continued)

## Biocompatibility experiments with red light




**1a**
(1.0 equiv)
y mM
2 mL (total volume)

**2a**
(2.0 equiv)

**3a**

| Entry | Conditions / Deviations | **3a** Yield |
|---|---|---|
| 1 | **Standard "in-vitro" conditons**: BnNAH (1.5 equiv) ZnTPP (15 mol%), 1:1 DMSO/water, red LED, 240 min 0.025 mmol scale, 12 mM, 2 mL total volume | 94% |
| 2 | 12 mM, **NADH instead of BnNAH** | <3% |
| 3 | **10 mM**, **4:1 water/DMSO** | 72% |
| 4 | **5 mM**, **4:1 water/DMSO** | 45% |
| 5 | **10 mM**, **4:1 PBS(1x)/DMSO** | 20%, 30%* |
| 6 | **10 mM**, **4:1 DMEM/DMSO** | 18% |
| 7 | 10 mM, **4:1 DMEM/DMSO**, **no BnNAH** | n/d |
| 8 | 10 mM, **4:1 DMEM/DMSO**, **no cat.** | <3% |
| 9 | 10 mM, **4:1 DMEM/DMSO**, **no light** | <3% |
| 10 | 10 mM, **4:1 CellLys@PBS(1x)/DMSO** | 19% |
| 11 | 10 mM, **4:1 CellLys@PBS(1x)/DMSO**, **no BnNAH** | n/d |
| 12 | 10 mM, **4:1 CellLys@PBS(1x)/DMSO**, **no cat.** | <3% |
| 13 | 10 mM, **4:1 CellLys@PBS(1x)/DMSO**, **no light** | n/d |

Unless stated otherwise, yields estimated by $^1$H NMR using 1,3,5-trimethoxybenzene as IS.
n/d = not detected
*Independent replicates. Stirring stopped both times by formation of precipitate.

The final concentration of cell lysates in entries 10–13 was estimated to be 0.3 mg/mL.

**Table S8.** Biocompatibility experiments with red light

# 7. Photophysical properties

## 7.1. UV–Vis absorption spectroscopy

**General information**

UV–Vis absorption spectroscopy was performed using a Jasco V-770 UV–Vis spectrophotometer at room temperature (ca. 25 ºC). Sample solutions of the appropriate concentration were freshly prepared in HPLC-grade DMSO. Absorption measurements were performed under air either in 10×2 mm disposable plastic cuvettes ($l$ = 10 mm) or in 10×10 mm quartz cuvettes ($l$ = 10 mm).

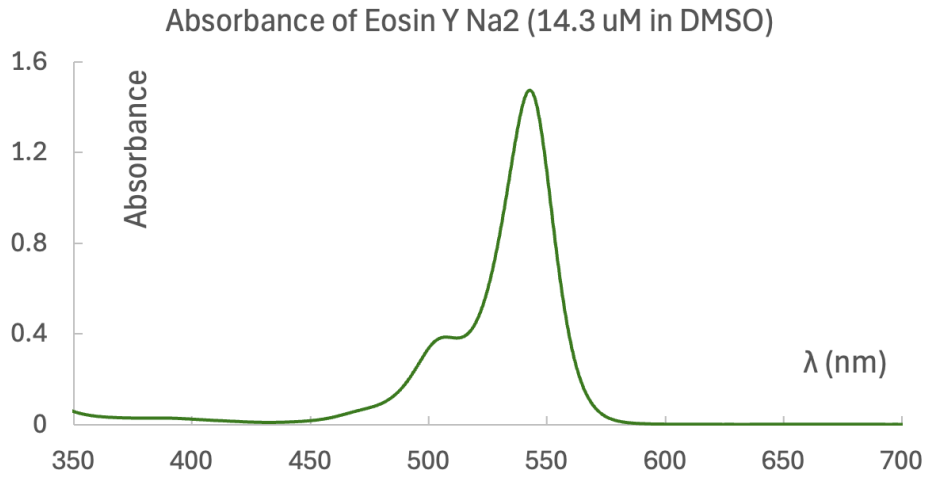



**Figure S6.** UV–Vis absorption spectrum of Eosin Y disodium salt **5** in DMSO (14.3 μM).

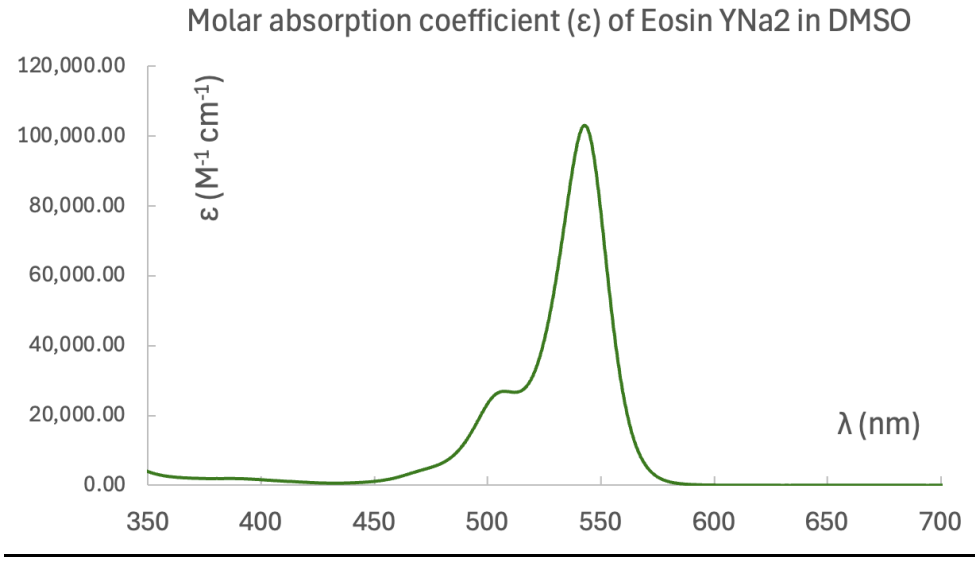



**Figure S7.** Molar absorption coefficient of Eosin Y disodium salt **5** in DMSO (recorded at 14.3 μM, $l$ = 10 mm).

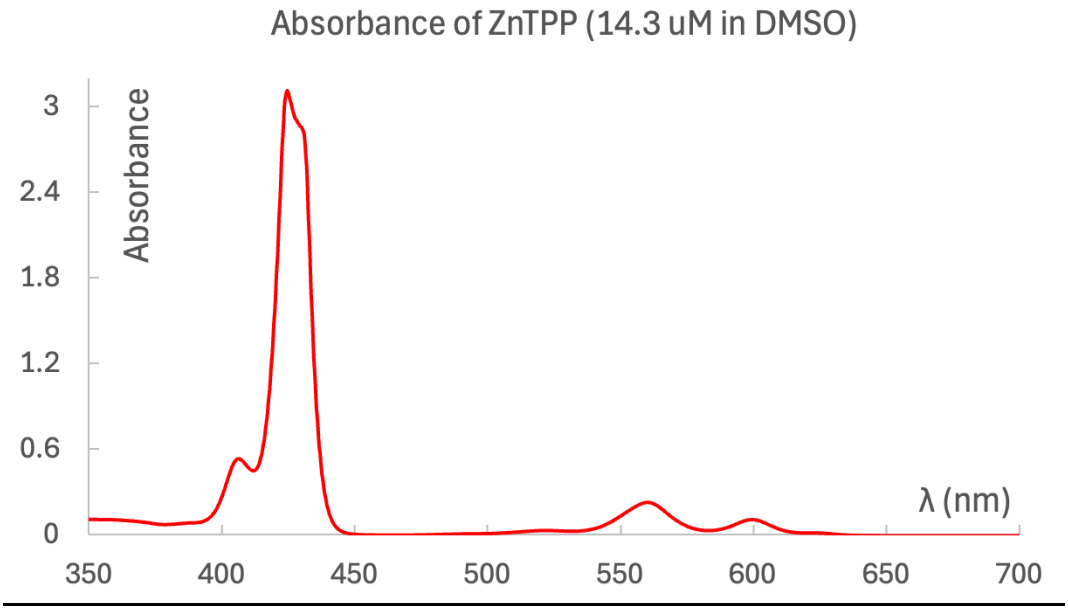



**Figure S8.** UV–Vis absorption spectrum of ZnTPP **6** in DMSO (14.3 μM).

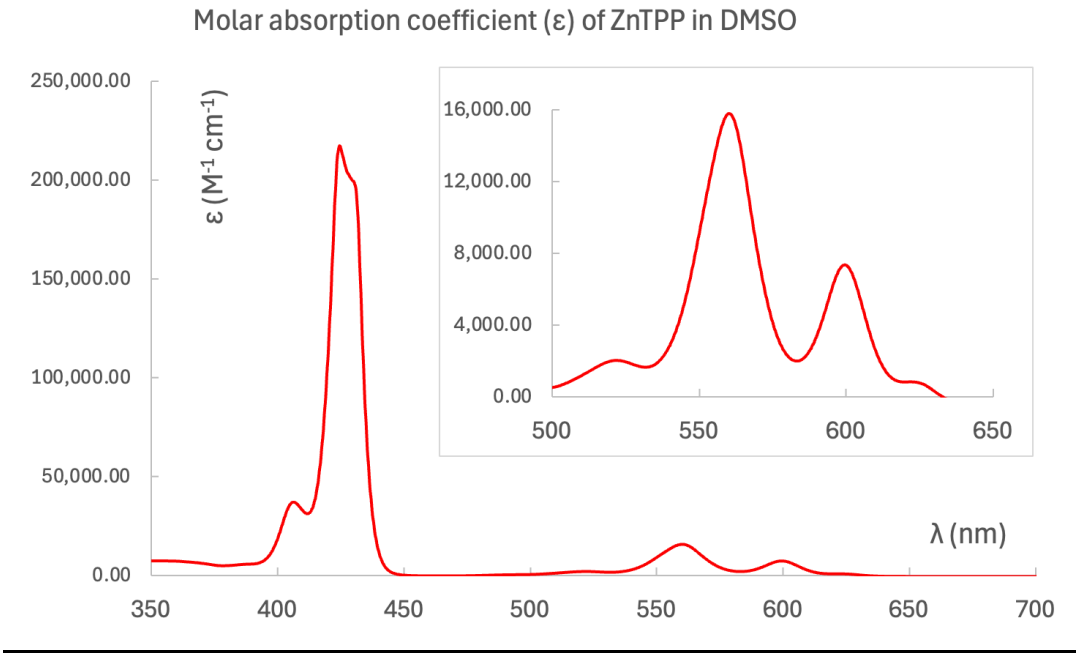



**Figure S9.** Molar absorption coefficient of ZnTPP **6** in DMSO (recorded at 14.3 μM, $l$ = 10 mm).

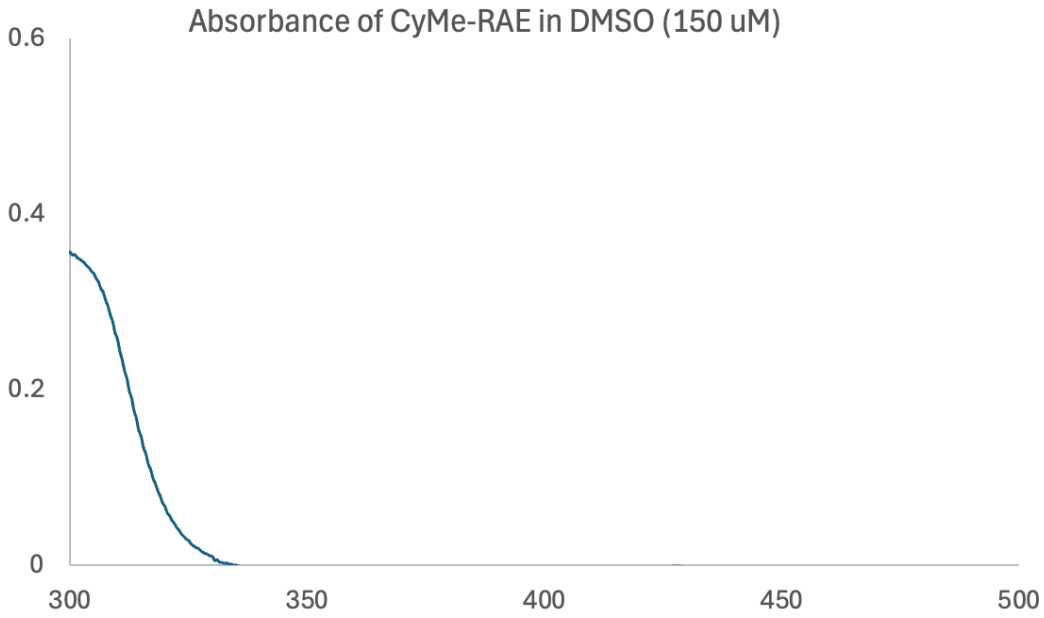



**Figure S10.** UV–Vis absorption spectrum of RAE **1a** in DMSO (150 μM).

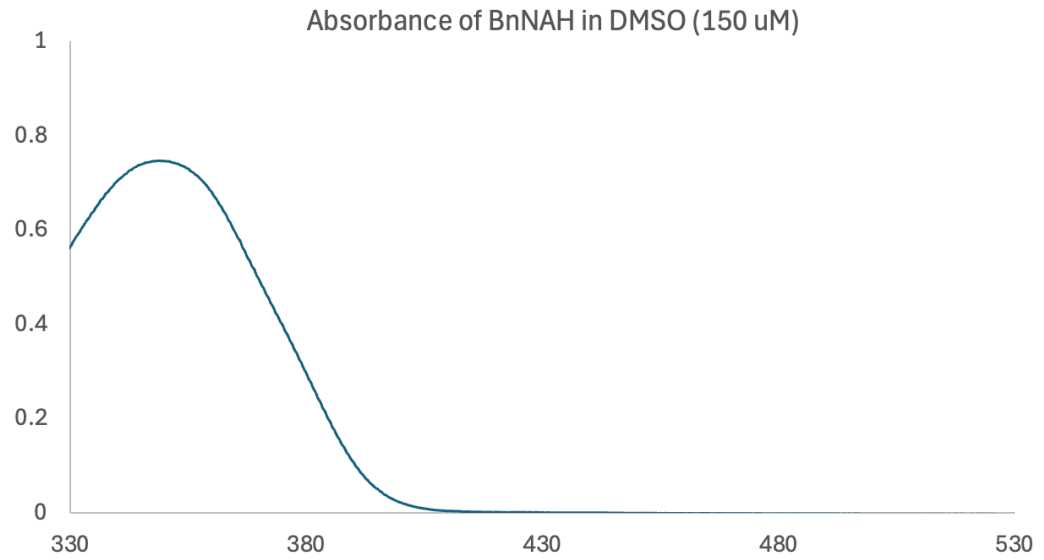



**Figure S11.** UV–Vis absorption spectrum of BnNAH **4** in DMSO (150 μM).

* The absorbance of these compounds was recorded in plastic cuvettes, which do no transmit light below 300 nm.

## 7.2. Emission spectroscopy (fluorescence)

**General information**

Fluorescence spectroscopy was performed using a FS5 spectrofluorometer at room temperature (ca. 25 ºC). Sample solutions of the appropriate concentration were freshly prepared in HPLC-grade DMSO. Emission measurements were performed under air in 10×10 mm quartz cuvettes ($l$ = 10 mm). For specific parameters for each compound, see Section 8.2.

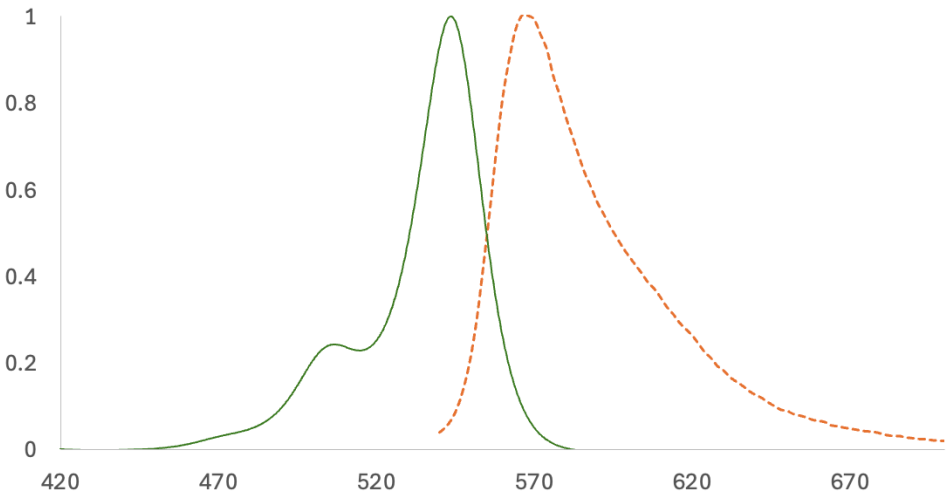



**Figure S12.** Normalized emission (orange dashed trace; excitation wavelength = 530 nm) and UV–Vis absorption (green trace) spectra of Eosin Y disodium salt **5** in DMSO.

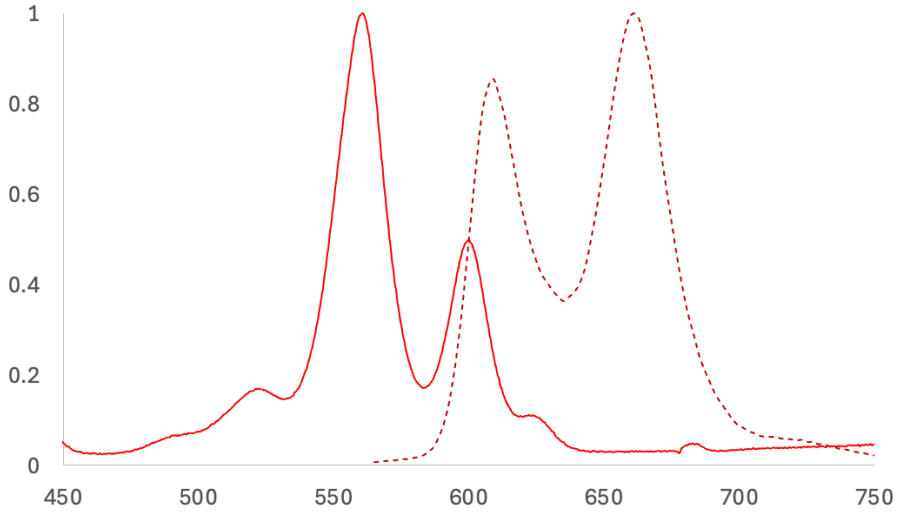



**Figure S13.** Normalized emission (excitation wavelength = 560 nm) and UV–Vis absorption spectra of ZnTPP **6** in DMSO.

# 8. Mechanistic experiments

## 8.1. Overlap of absorption spectra and emission of the light sources

**Absorption of the reaction components vs emission of the LEDs**

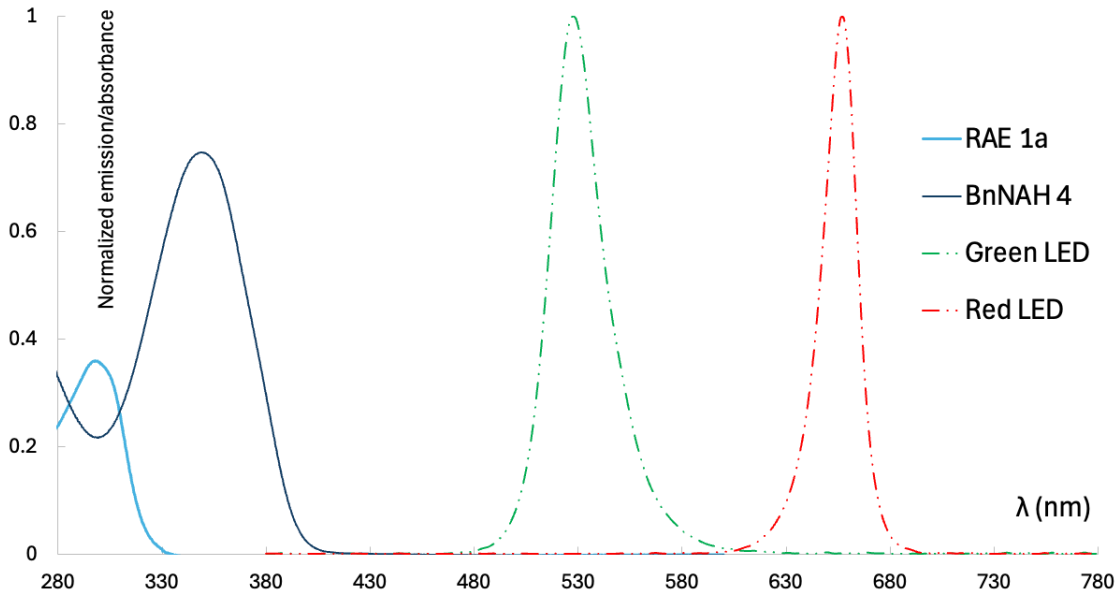



**Figure S14.** Normalized UV–Vis absorption spectra of RAE **1a** and BnNAH **4** in DMSO and emission spectra of the green and red LED used in this study.

Neither the reaction substrate nor the reactant absorb at the wavelengths of emission of the two LEDs used in this study, justifying the requirement of photocatalysts.

**Absorption of the photocatalysts vs emission of the corresponding light source**

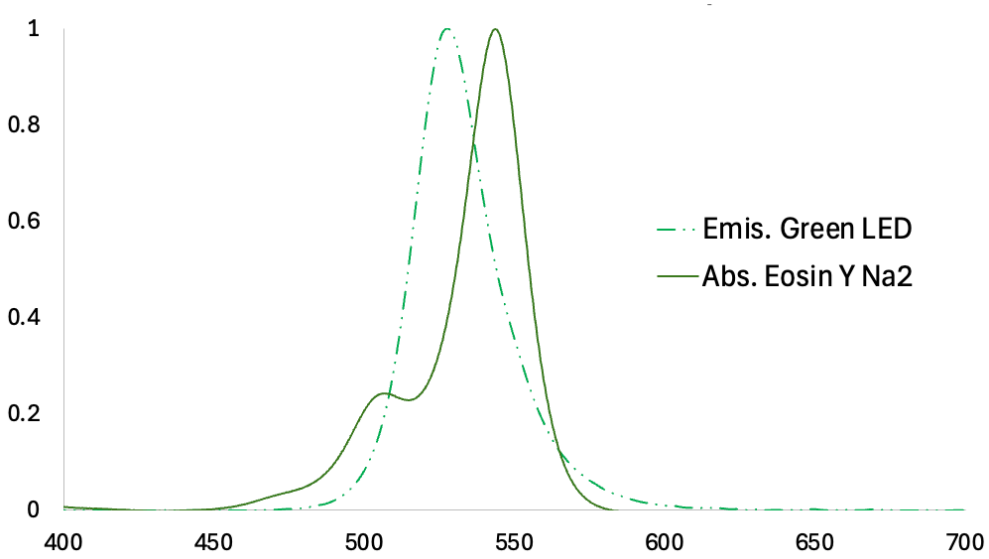



**Figure S15.** Normalized UV–Vis absorption spectrum of Eosin Y disodium salt **5** in DMSO and emission spectra of the green LED used in this study.

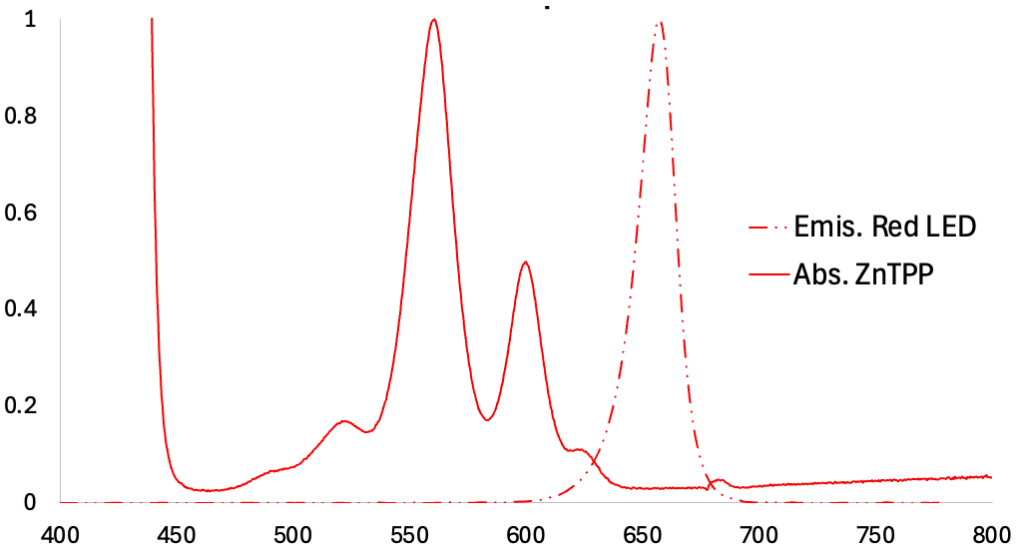



**Figure S16.** UV–Vis absorption spectrum of ZnTPP **6** in DMSO and emission spectra of the red LED used in this study.

## 8.2. Fluorescence quenching studies

Fluorescence spectroscopy was performed using a FS5 spectrofluorometer at room temperature (ca. 25 ºC), according to typical procedures.[4] Sample solutions of the appropriate concentration were freshly prepared in HPLC-grade DMSO. Emission measurements were performed under air in 10×10 mm quartz cuvettes ($l$ = 10 mm).

In order to minimize inner filter effects, the following excitation wavelengths with absorption values between 0.1–0.2 at the photocatalyst concentration were selected:

- Eosin Y disodium salt **5** in DMSO: Excitation at 490 nm (Absorbance = 0.19 14.3 μM)
- ZnTPP **6** in DMSO: Excitation at 550 nm (Absorbance = 0.15 at 14.3 μM)

The following additional experimental settings were employed:

- Eosin Y **5**: 495–750 nm scan range (step = 1 nm). Scan slit: 1.2 nm. Fixed/offset slit: 1.0 nm.
- ZnTPP **6**: 555–750 nm scan range (step = 1 nm). Scan slit: 4.0 nm. Fixed/offset slit: 2.0 nm.

Fluorescence quenching experiments were performed under air, simulating the reaction experimental conditions. The following stock solutions were prepared in DMSO:

- A) 10 mL of a 0.0005 M solution of Eosin Y disodium salt **5**.
- B) 10 mL of a 0.0005 M solution of ZnTPP **6**.
- C) 20 mL of a 0.02 M solution of redox-active ester **1a**.
- D) 20 mL of a 0.02 M solution of BnNAH **4**.

From this stock solutions, the following set of final solutions were prepared for each combination of photocatalyst and quencher (3.5 mL total volume for the cuvette).

- I) 14.3 μM in photocatalyst + 498 μM of quencher.
- II) 14.3 μM in photocatalyst + 956 μM of quencher.
- III) 14.3 μM in photocatalyst + 1811 μM of quencher.
- IV) 14.3 μM in photocatalyst + 3339 μM of quencher.
- V) 14.3 μM in photocatalyst + 6670 μM of quencher.

The 3.5 mL 10×10 mm fluorescence quartz cuvettes were filled with the corresponding solution, starting from I and up to V. Between cuvettes of the same set, the cuvette was rinsed twice with DMSO before the addition of the next solution. After a set of fluorescence measurements, the cuvette was fully washed with water, acetone and Hellmanex™, followed by another water and then acetone rinse. Fluorescence emission was recorded for each solution and the results for each combination of photocatalyst/quencher is reported in the following pages. For Stern–Volmer analysis, the fluorescence intensity value at the emission maximum was used.

## Quenching of Eosin Y

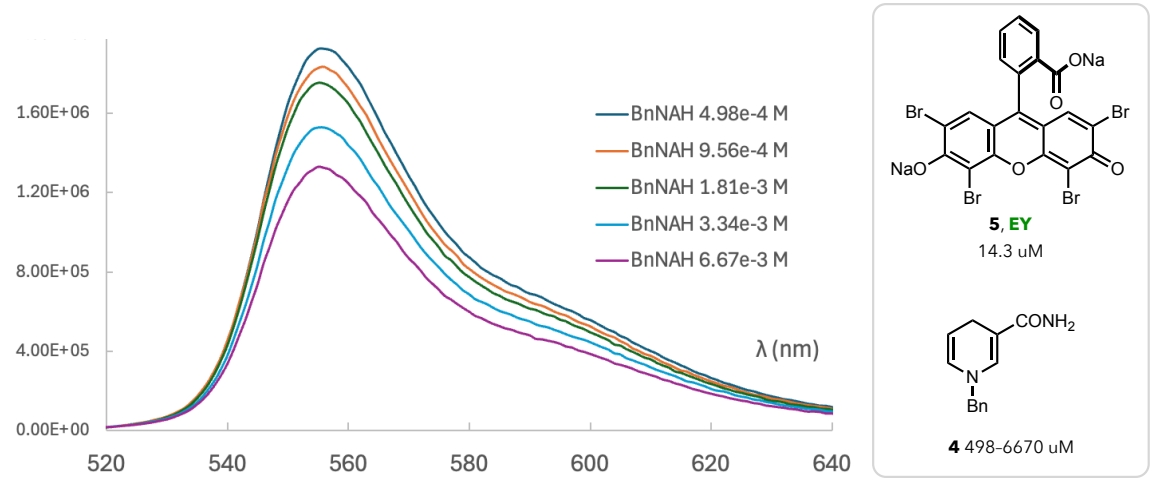



**Figure S17.** Overlapped steady-state fluorescence emission spectra of Eosin Y disodium salt **5** (14.3 μM) in the presence of different concentrations of quencher **4** (498–6670 μM). $\lambda_{ex}$ = 490 nm.

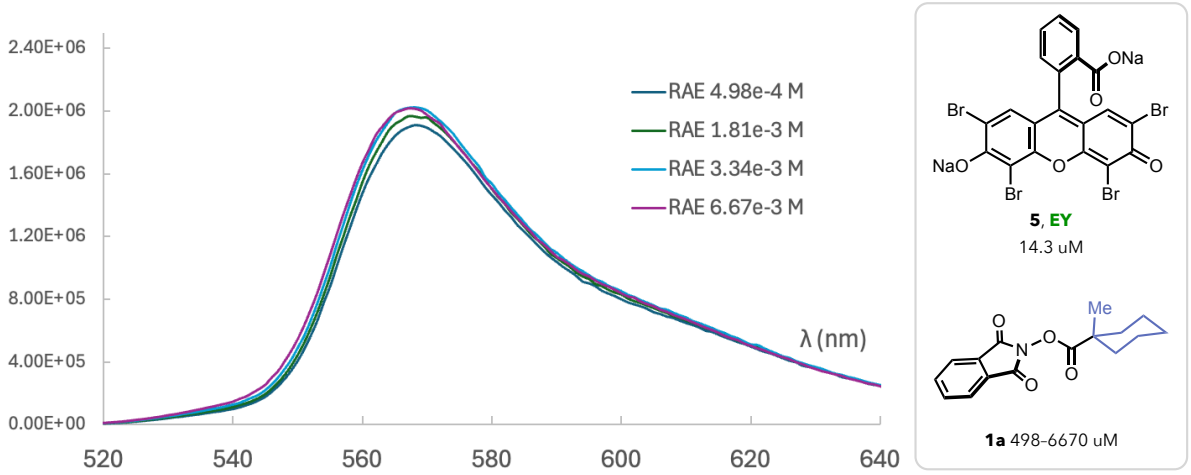



**Figure S18.** Overlapped steady-state fluorescence emission spectra of Eosin Y disodium salt **5** (14.3 μM) in the presence of different concentrations of RAE **1a** (498–6670 μM). $\lambda_{ex}$ = 490 nm.

A significant quenching effect was observed for BnNAH **4** with Eosin Y, while no quenching effect was detected with RAE **1a**. This suggests that a reductive-quenching photoredox mechanism is at least operative to some extent, while a hypothetical oxidative-quenching could not be identified.

It is worth noting that steady-state fluorescence quenching analysis only delivers direct information about the reactivity of *singlet* excited states (which for Eosin Y are long-lived enough [ca. 5 ns][5] to engage in bimolecular interactions). *Triplet*-state reactivity could also be operative.

**Attempted quenching of ZnTPP**

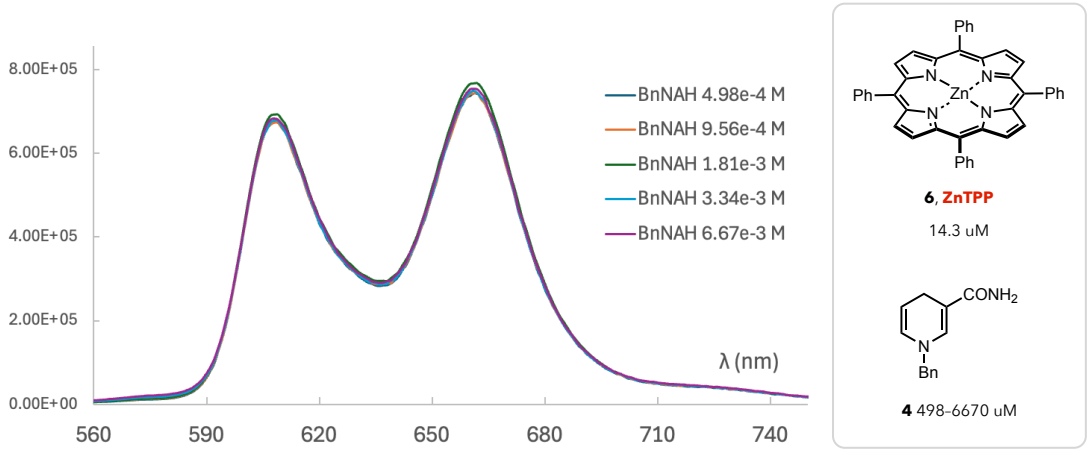



**Figure S19.** Overlapped steady-state fluorescence emission spectra of ZnTPP **6** (14.3 μM) in the presence of different concentrations of quencher **4** (498–6670 μM). $\lambda_{ex}$ = 550 nm.

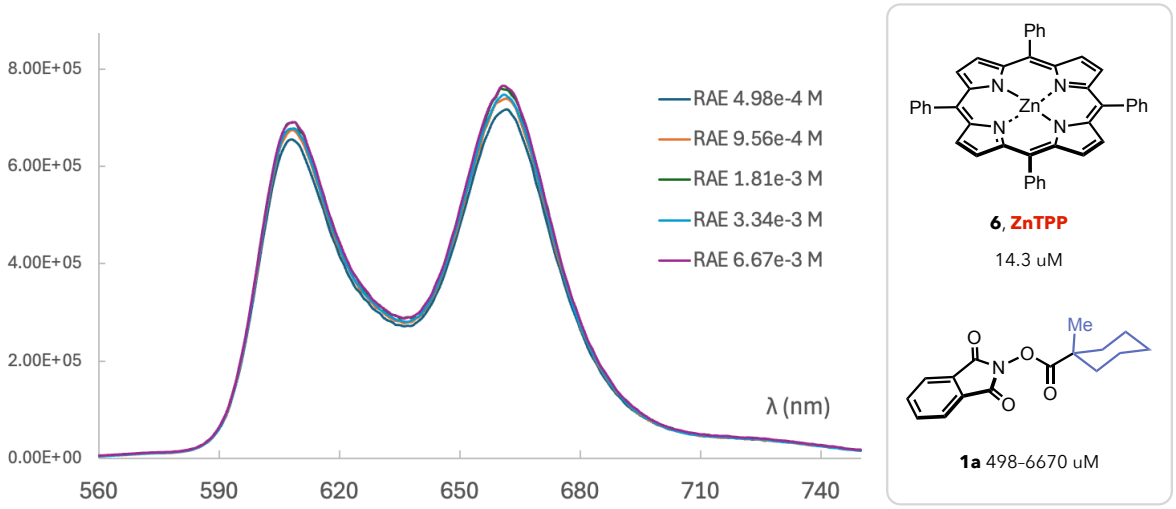



**Figure S20.** Overlapped steady-state fluorescence emission spectra of ZnTPP **6** (14.3 μM) in the presence of different concentrations of RAE **1a** (498–6670 μM). $\lambda_{ex}$ = 550 nm.

No steady-state quenching of the fluorescence of ZnTPP was observed with neither of the two potential quenchers. This strongly suggests that all the observed photoreactivity involves triplet excited states of the red-light absorbing photocatalyst, and that ISC (inter-system crossing) is faster than any bimolecular quenching of the singlet (fluorescent) excited states with **1a** or **4**.

## Stern–Volmer analysis

We constructed Stern–Volmer plots based on the fluorescence intensity at the emission maximum of Eosin Y in DMSO upon addition of increasing concentrations of quenchers **1a** and BnNAH **4**. The fluorescence intensity value at the emission maximum was used. This ratio was plotted as a function of the quencher concentration [Q] as shown in Figure S21.

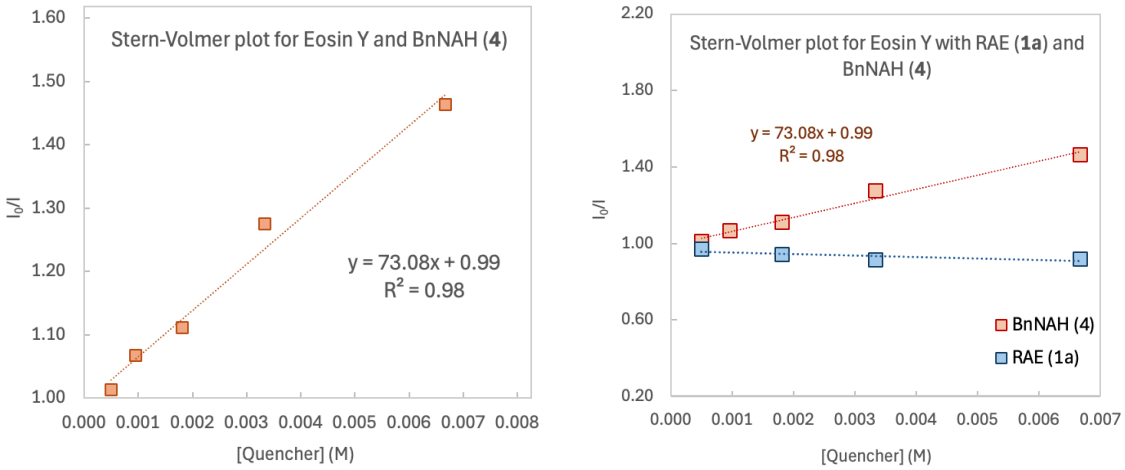



**Figure S21.** Stern–Volmer plot for the fluorescence quenching of Eosin Y disodium salt **5** with BnNAH **4** (left) and overlapped effect of BnNAH **4** vs RAE **1a** (right).

The rate of the quenching process was calculated according to the Stern–Volmer equation:

$$\frac{I_0}{I} = 1 + K_{SV}[Q] = 1 + k_q \tau_0 [Q]$$

where $\mathbf{K_{SV}}$ is the Stern–Volmer constant (slope), $k_q$ is the bimolecular quenching rate and $\tau_0$ is the excited state lifetime.

Linear fitting of the data points (Figure S21) with the Stern–Volmer equation provided a value of $\mathbf{K_{SV}}$ **= 73.1** $\mathbf{M^{-1}}$ for Eosin Y disodium salt **5** in DMSO with BnNAH **4**. Considering a reported value of singlet-state lifetime for Eosin Y of $\tau_0 = 4.5$ ns,[5] a bimolecular quenching rate constant of $\boldsymbol{k_q}$ **= 1.6 x** $\mathbf{10^{10}}$ $\mathbf{M^{-1}s^{-1}}$ was calculated. This value can be consistent with a diffusion-controlled bimolecular quenching (i.e.: all collisions between excited photocatalyst and quencher **4** results in reactivity). Alternatively, this could also be consistent with a static quenching process, which cannot be discarded before studying the system with fluorescence lifetime analysis.

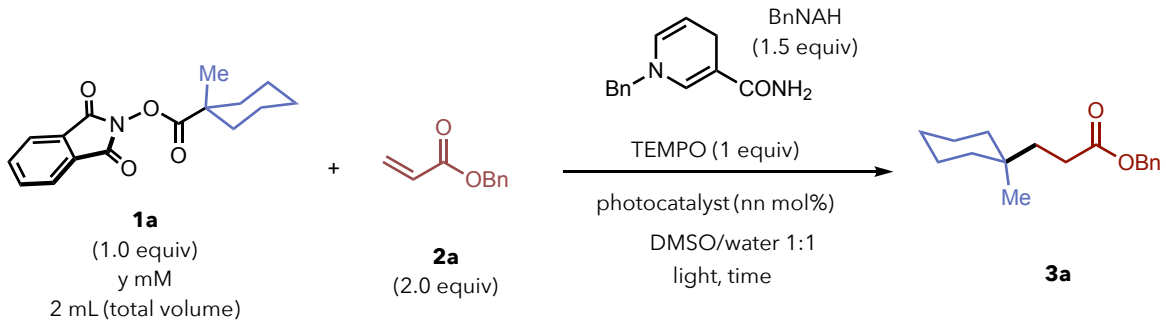
Significant fluorescence quenching with RAE **1a** was not observed at the explored concentrations.

## 8.3. Radical inhibition experiments

Following General procedures B or C, **1a** (0.025–0.050 mmol, 1.0 equiv), BnNAH **4** (1.5 equiv), **2a** (2.0 equiv) photocatalyst (5–15 mol%) and TEMPO (1 equiv) in a mixture of DMSO and water 1:1 were irradiated for 120–240 min with green or red light.

The yield of product **3a** was determined by $^1$H NMR using 1,3,5-trimethoxybenzene as IS.

Significant inhibition of the reactivity was observed with the green-based system, while full inhibition was observed using red light and ZnTPP.

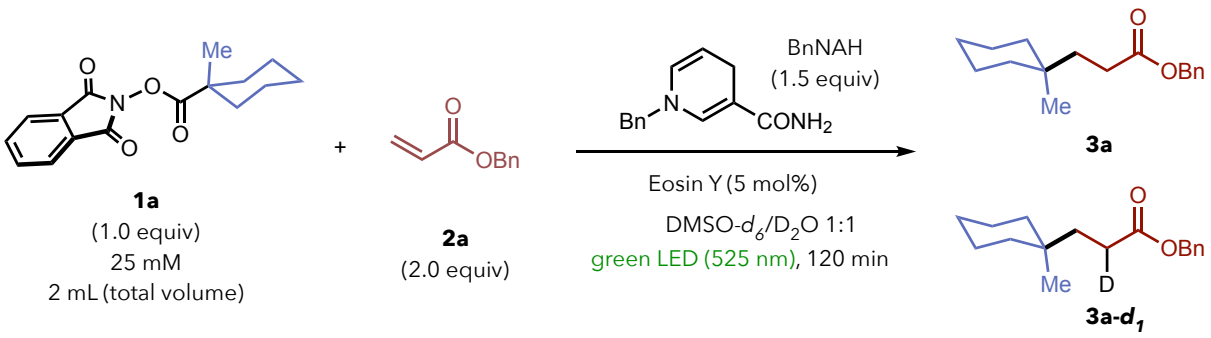



| Entry | Conditions / Deviations | **3a** Yield |
|---|---|---|
| 1 | EY (5 mol%), green LED, 120 min, 25 mM | 46% |
| 2 | ZnTPP (15 mol%), red LED, 240 min, 12 mM | n/d |

Unless stated otherwise, yields estimated by $^1$H NMR using 1,3,5-trimethoxybenzene as IS. n/d: not detected.

**Table S9.** TEMPO inhibition experiments.

## 8.4. Deuterium labelling experiments




Following General procedure B, **1a** (0.050 mmol, 1.0 equiv), BnNAH **4** (1.5 equiv), **2a** (2.0 equiv) and Eosin Y (5 mol%) in a mixture of DMSO-$d_6$ and $D_2O$ 1:1 were irradiated for 120 min with green light. A total yield of 75% was determined by $^1H$ NMR using 1,3,5-trimethoxybenzene as IS.

The crude $^1H$ NMR spectrum was then compared with that of the reaction performed in non-deuterated solvents, see next page for details.

No significant incorporation of deuterium from the solvent was observed (see next page), which indirectly suggests that BnNAH is the source of hydrogen in products **3** after radical addition.

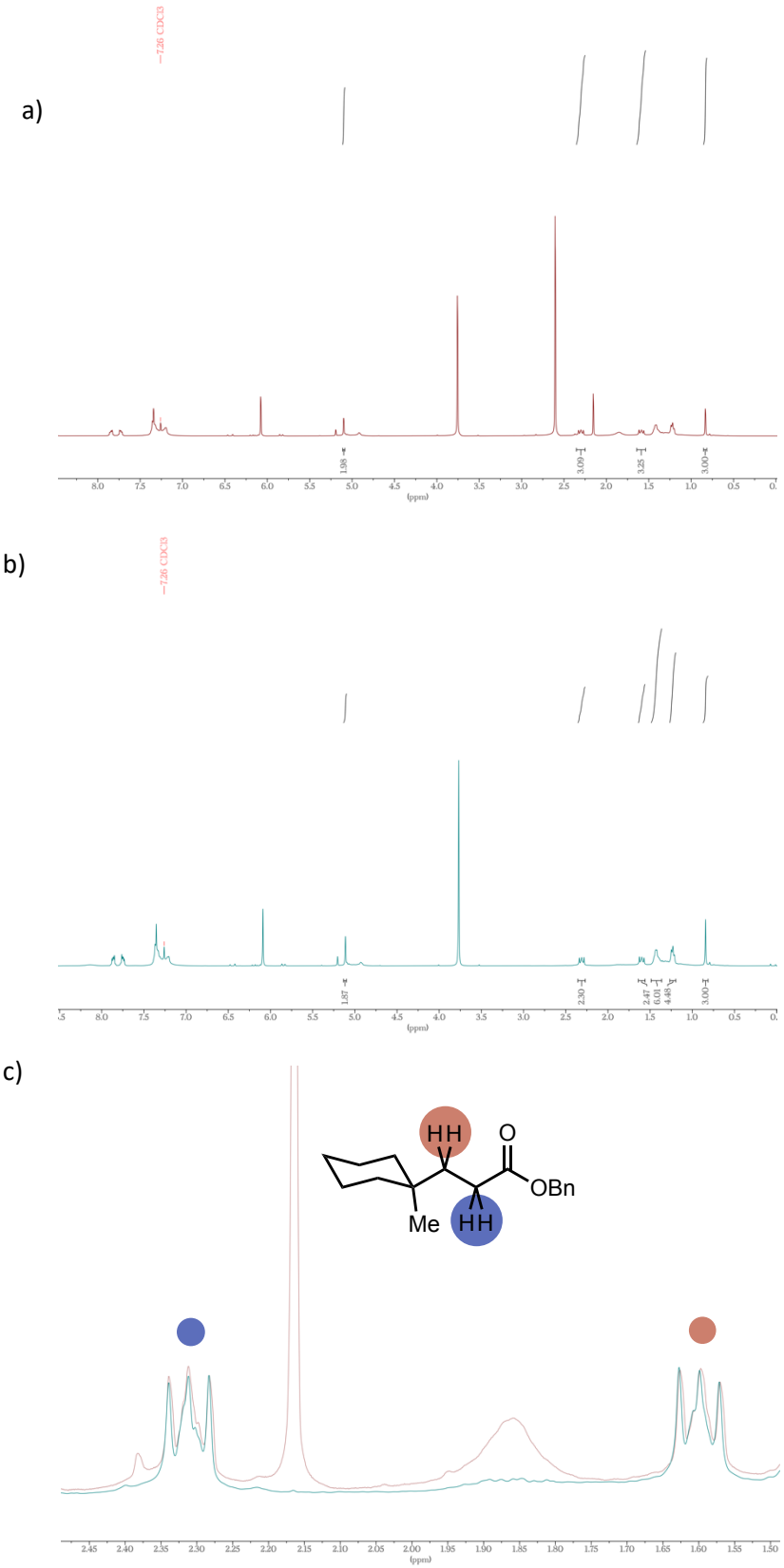
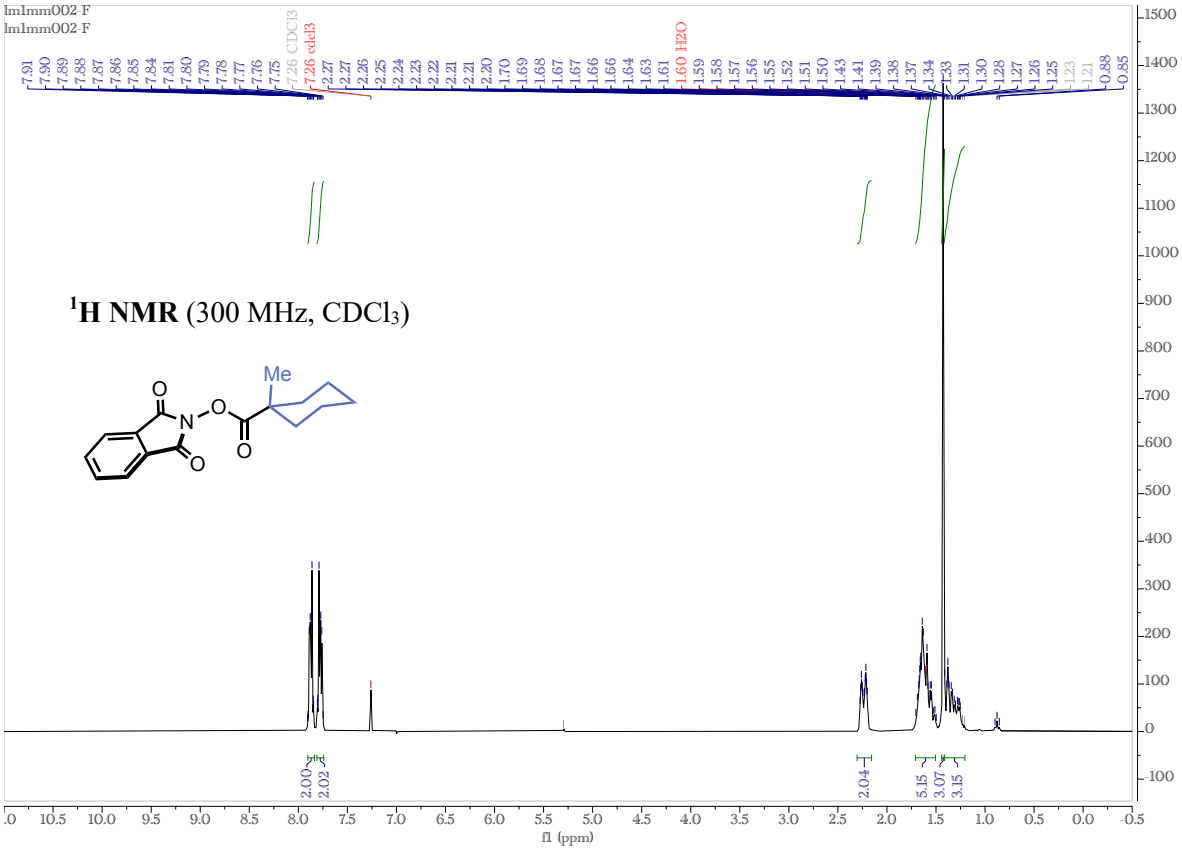
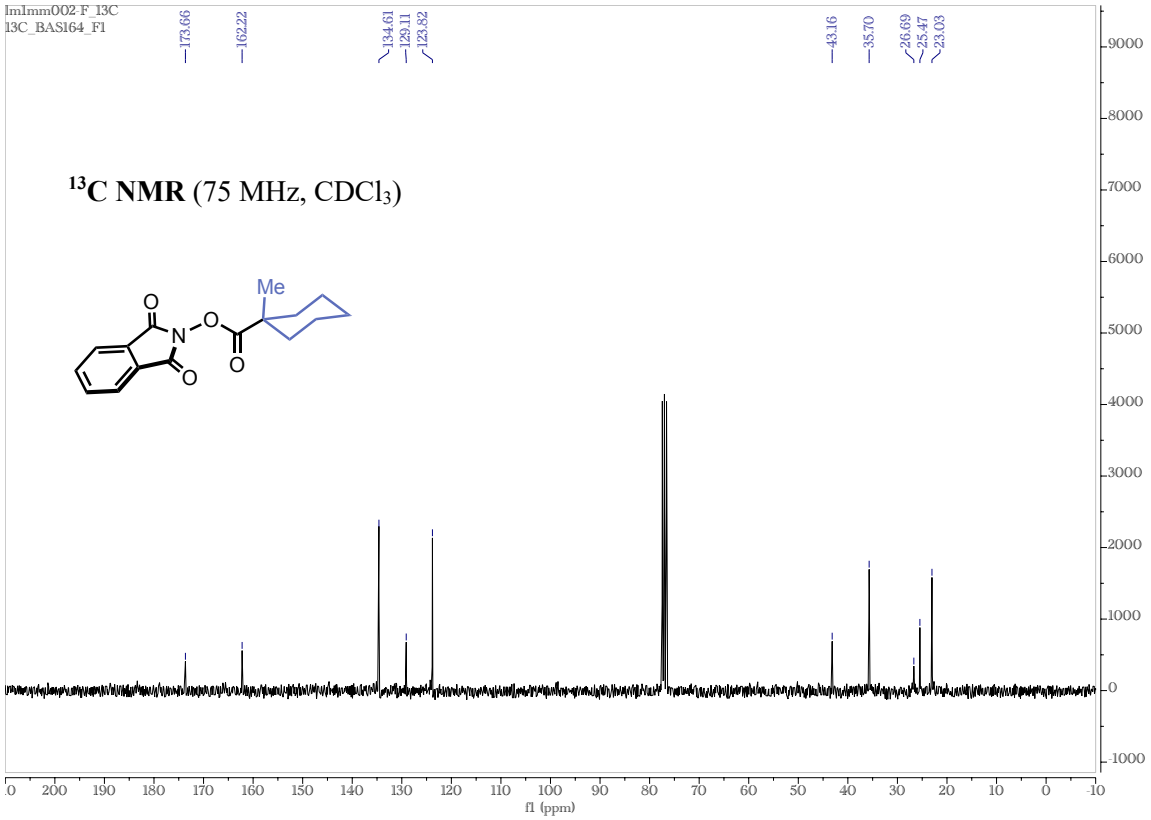



**Figure S22.** (a) Crude $^{1}$H NMR spectrum of the reaction performed in DMSO/$H_2O$. (b) Crude $^{1}$H NMR spectrum of the reaction performed in DMSO-$d_6$/$D_2O$. (c) Superimposed spectra.

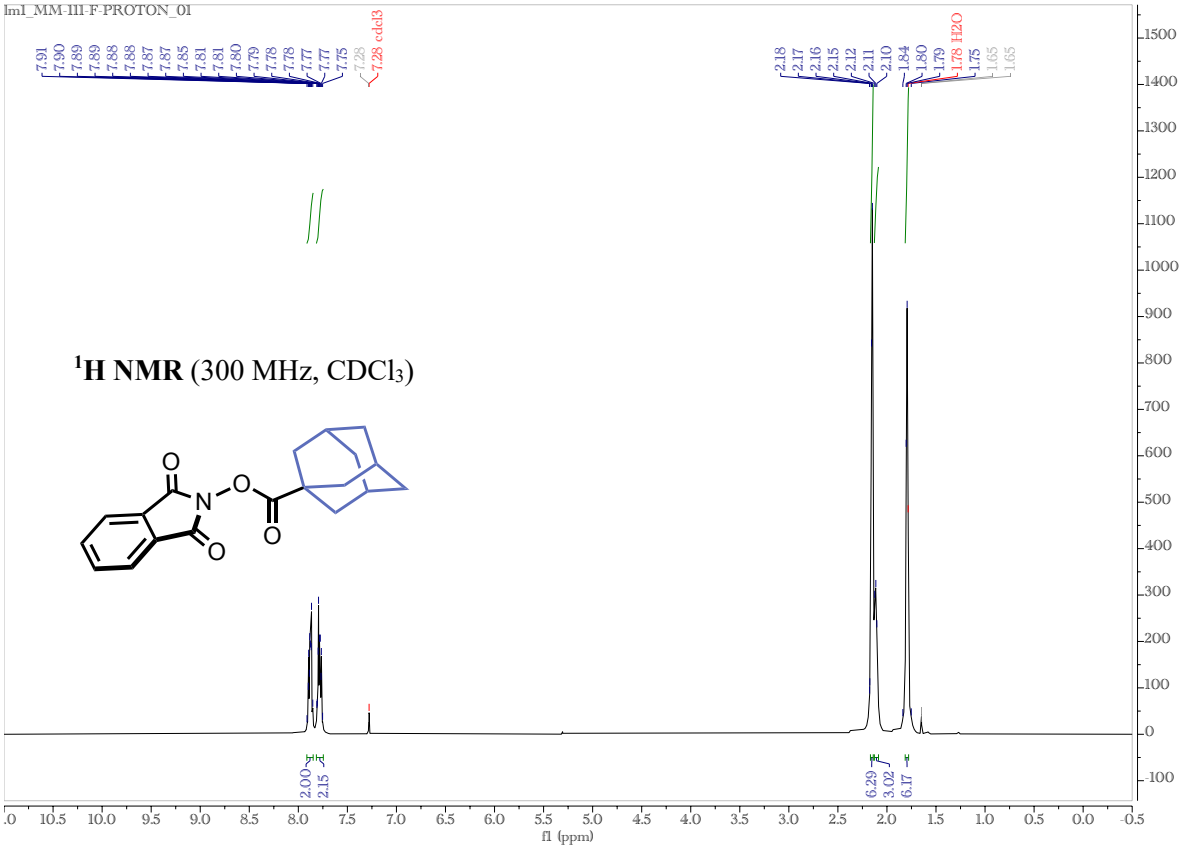
# 9. NMR spectra

## 1,3-Dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate (1a)



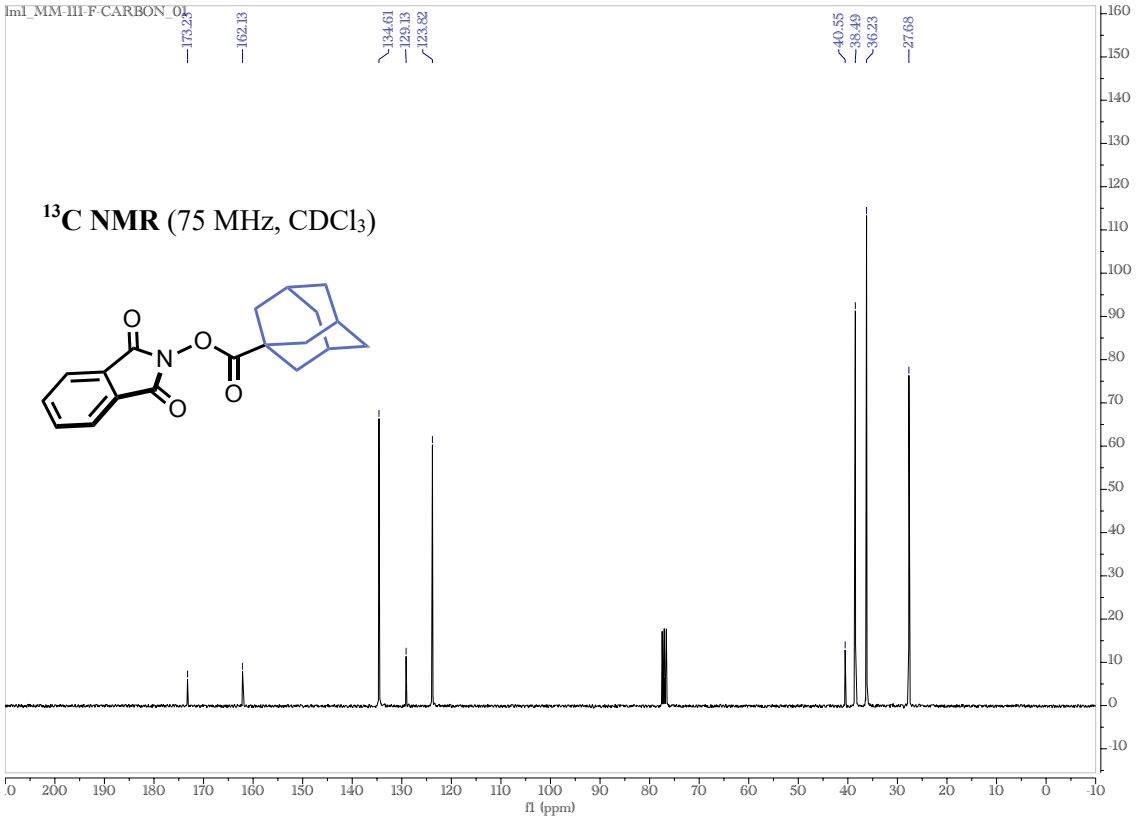



## 1,3-Dioxoisoindolin-2-yl adamantane-1-carboxylate (1b)



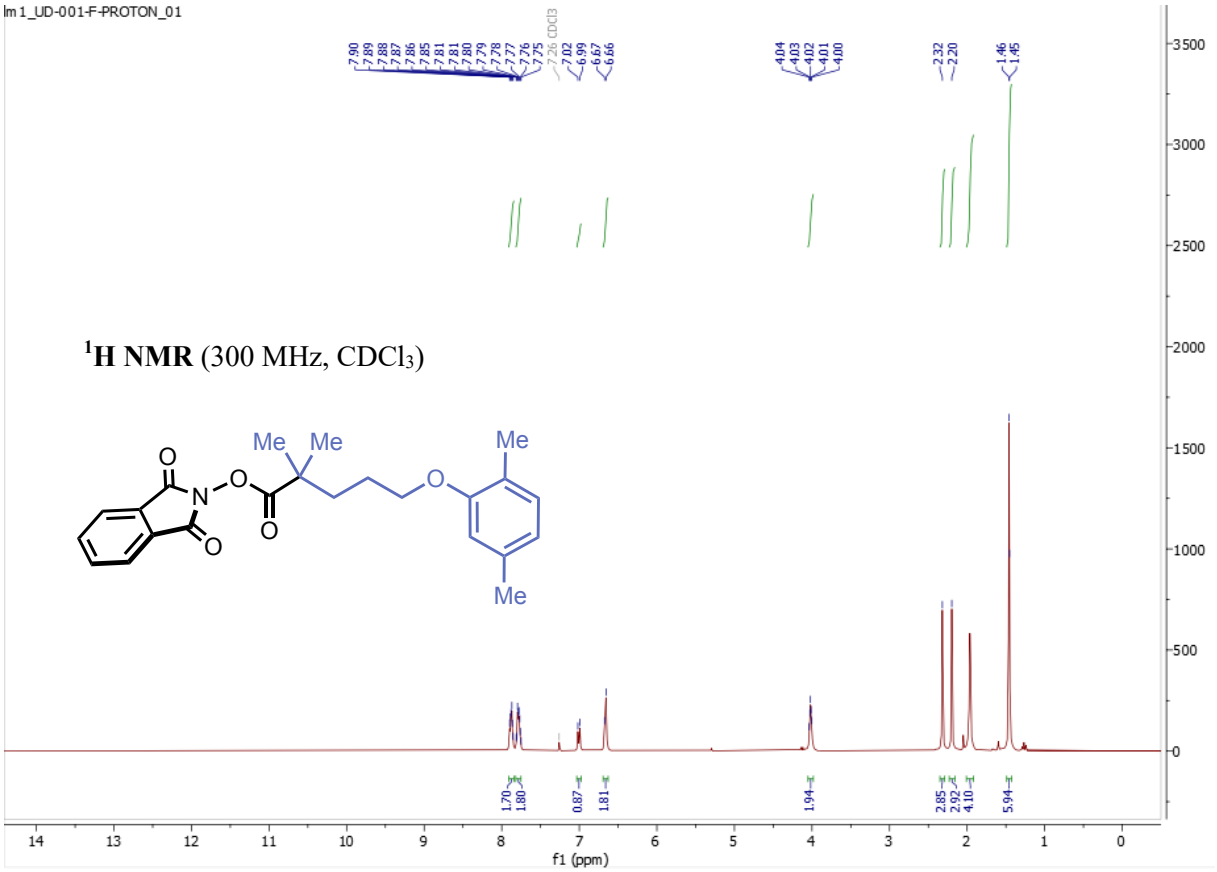

$^{1}$**H NMR** (300 MHz, $CDCl_3$)



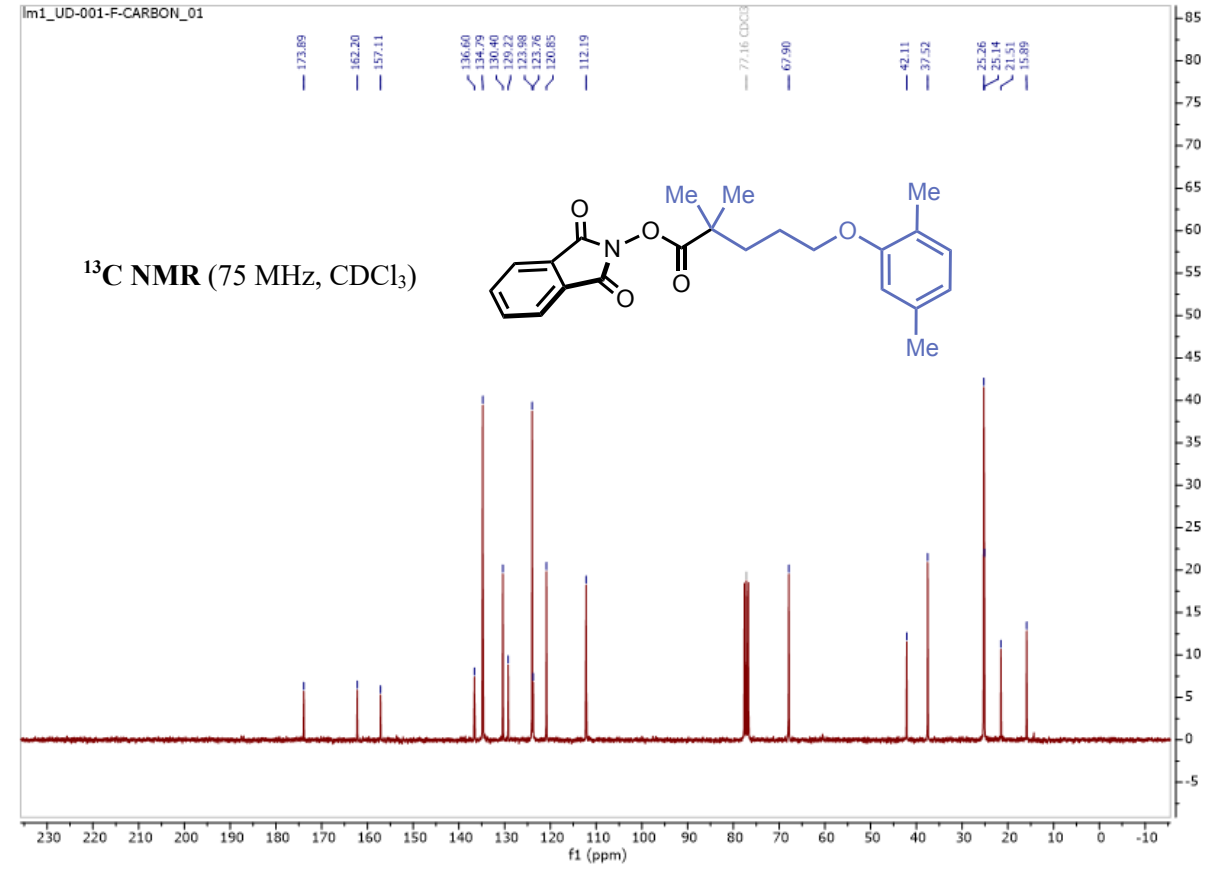



$^{13}$**C NMR** (75 MHz, $CDCl_3$)

**1,3-Dioxoisoindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (1c)**

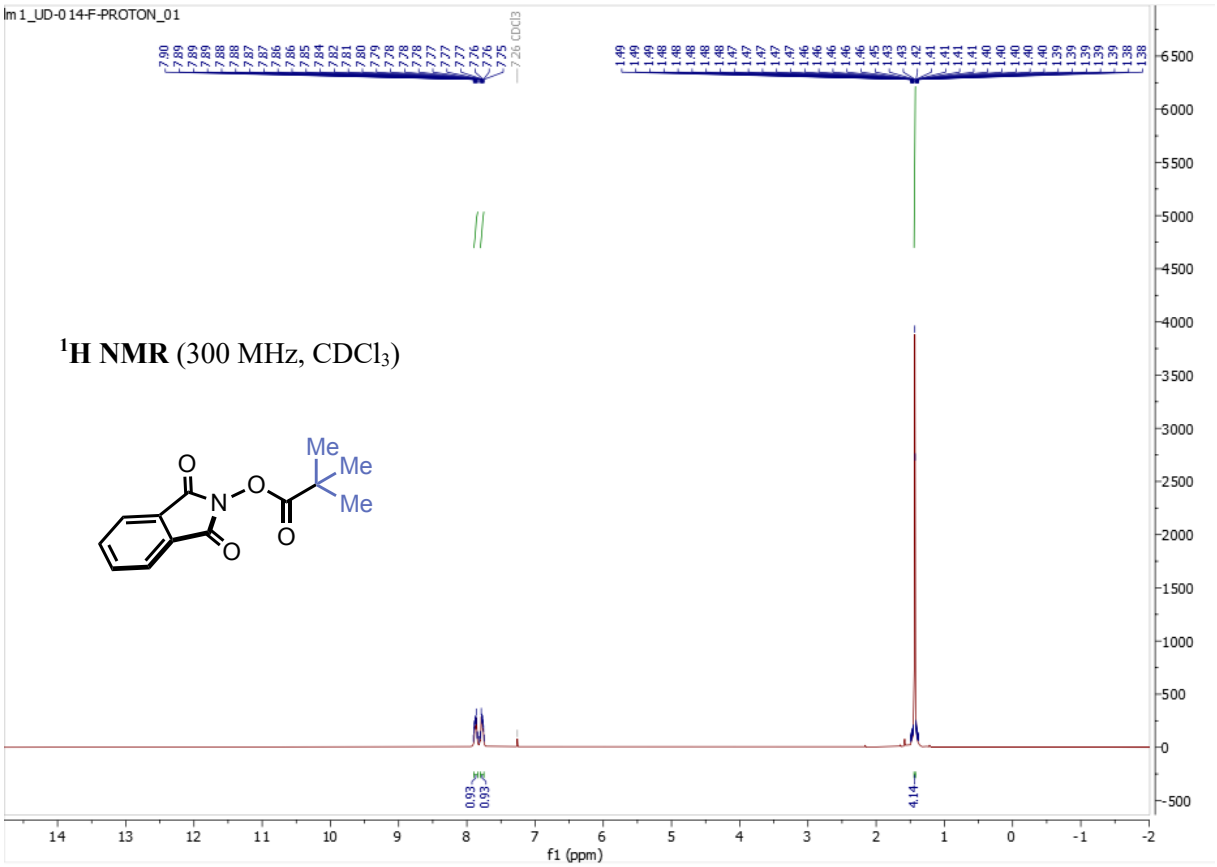


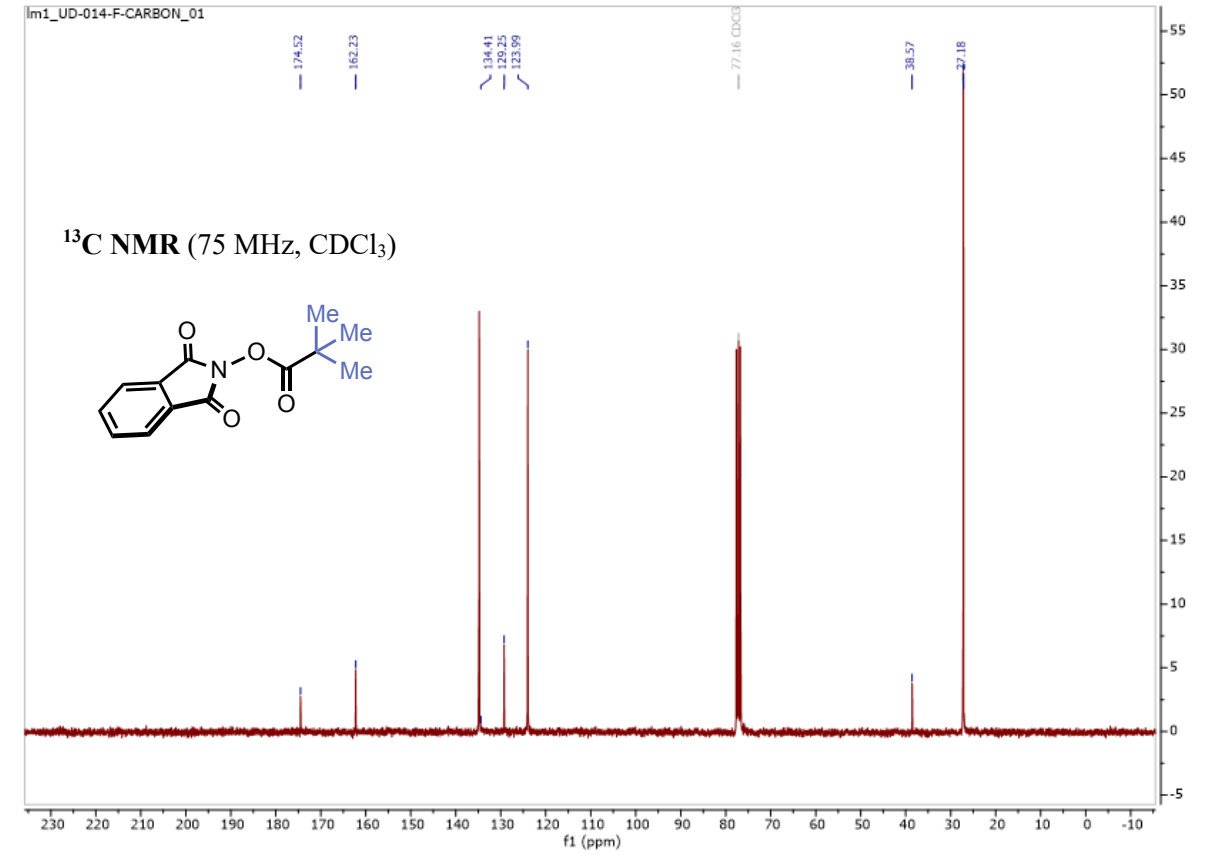

$^{1}$**H NMR** (300 MHz, $CDCl_3$)



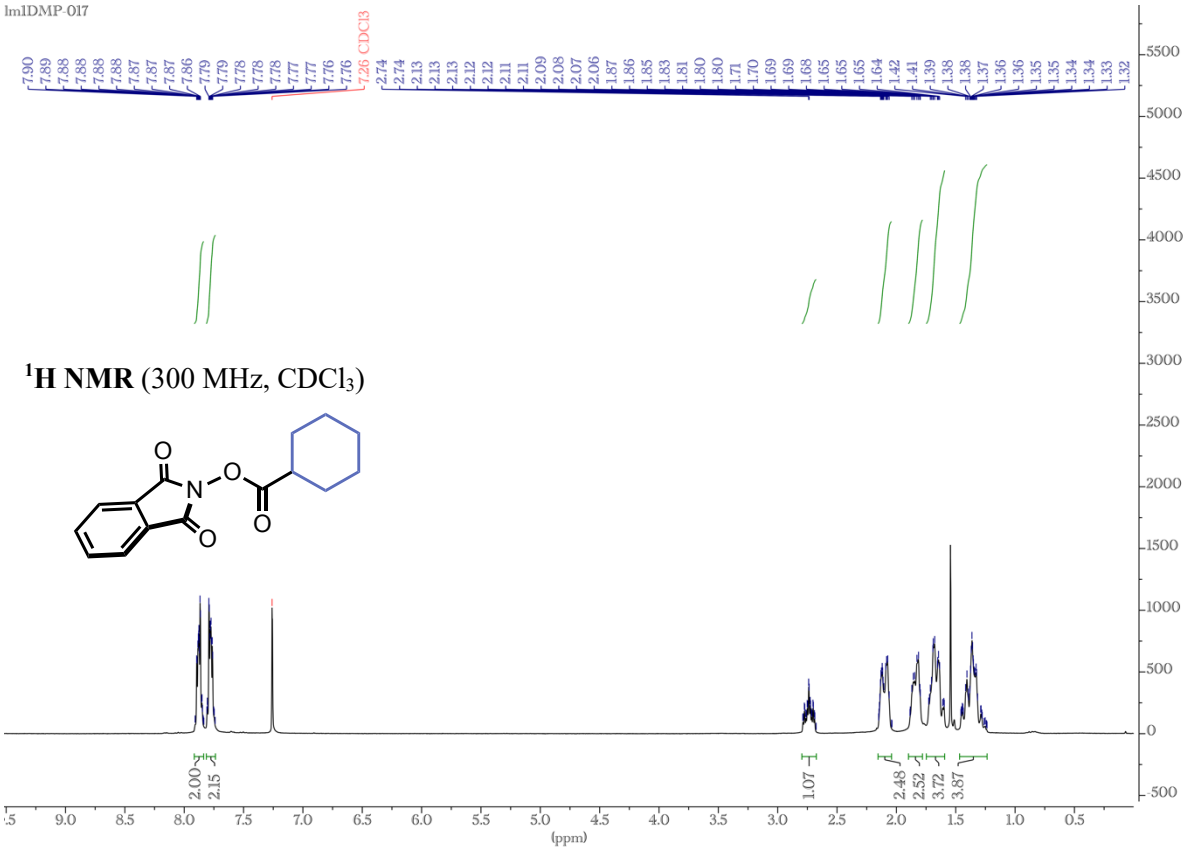

$^{13}$**C NMR** (75 MHz, $CDCl_3$)

**1,3-Dioxoisoindolin-2-yl pivalate (1d)**

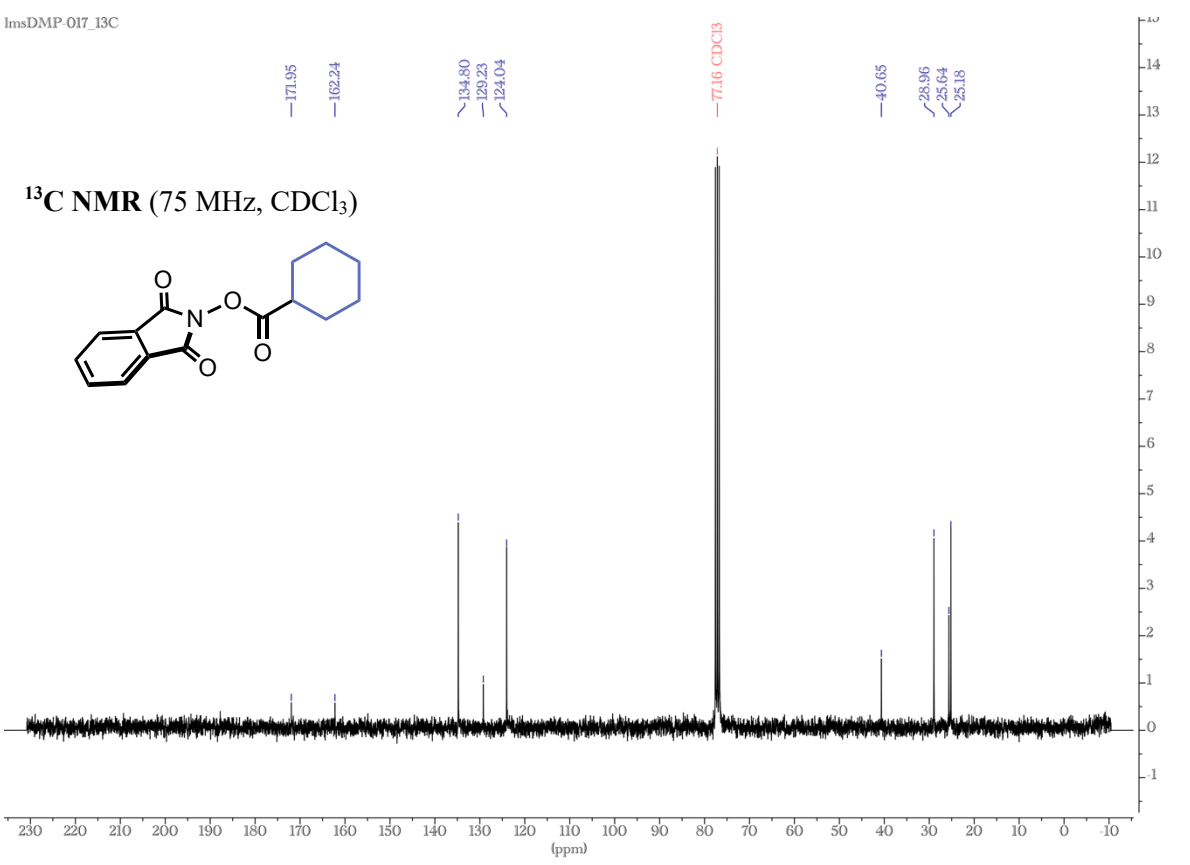


## 1,3-Dioxoisoindolin-2-yl cyclohexanecarboxylate (1e)

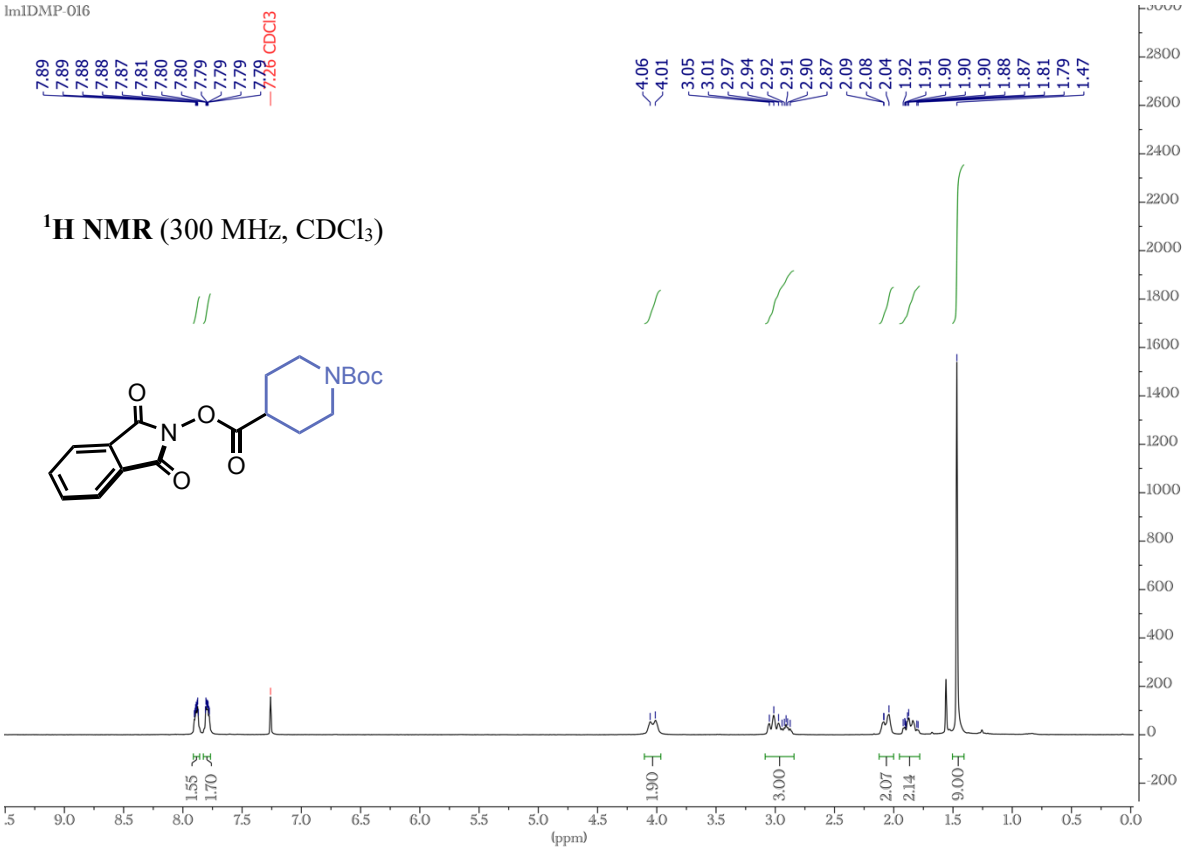



**$^{1}$H NMR** (300 MHz, $CDCl_3$)

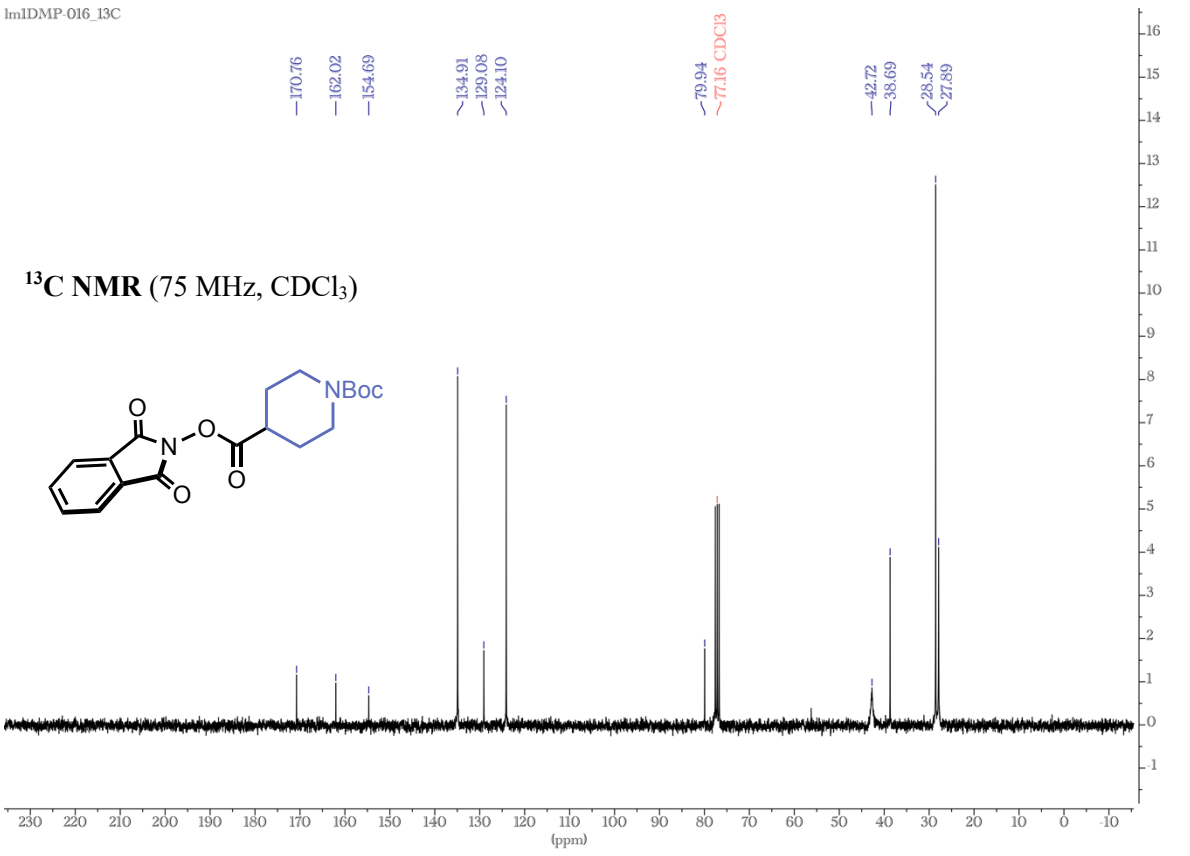



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

**1-(*tert*-Butyl)-4-(1,3-dioxoisoindolin-2-yl) piperidine-1,4-dicarboxylate (1f)**

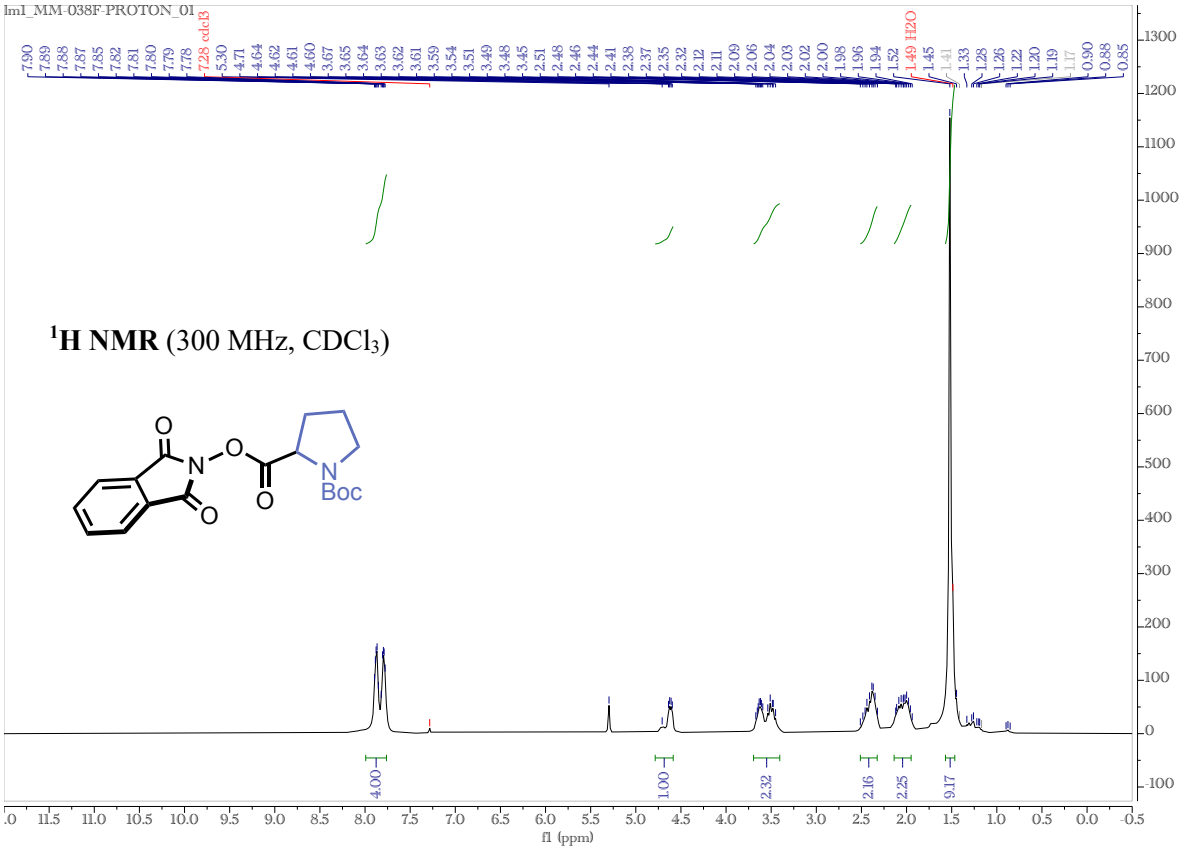



**$^{1}$H NMR** (300 MHz, $CDCl_3$)

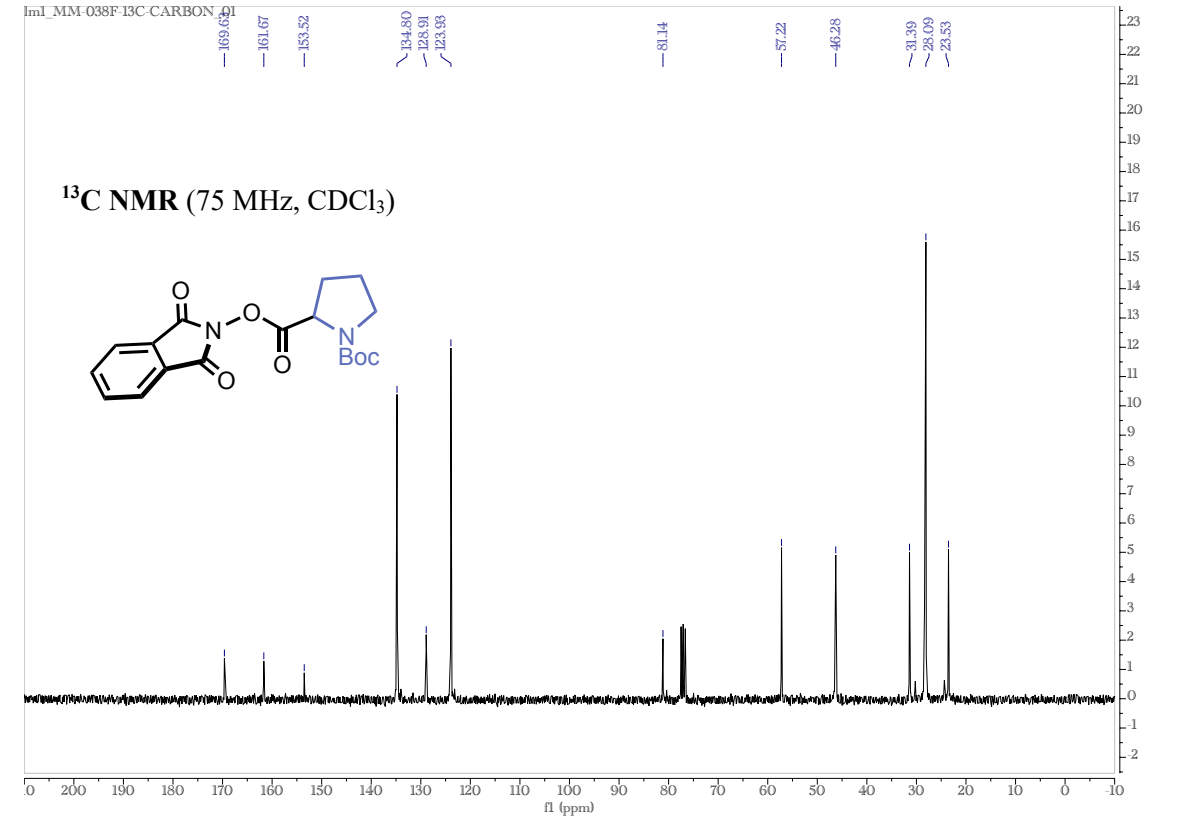



**$^{13}$C NMR** (75 MHz, $CDCl_3$)

**1-(*tert*-Butyl) 2-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1,2-dicarboxylate** (**1g**) – some signals are broad and split due to the presence of diastereomeric rotamers.

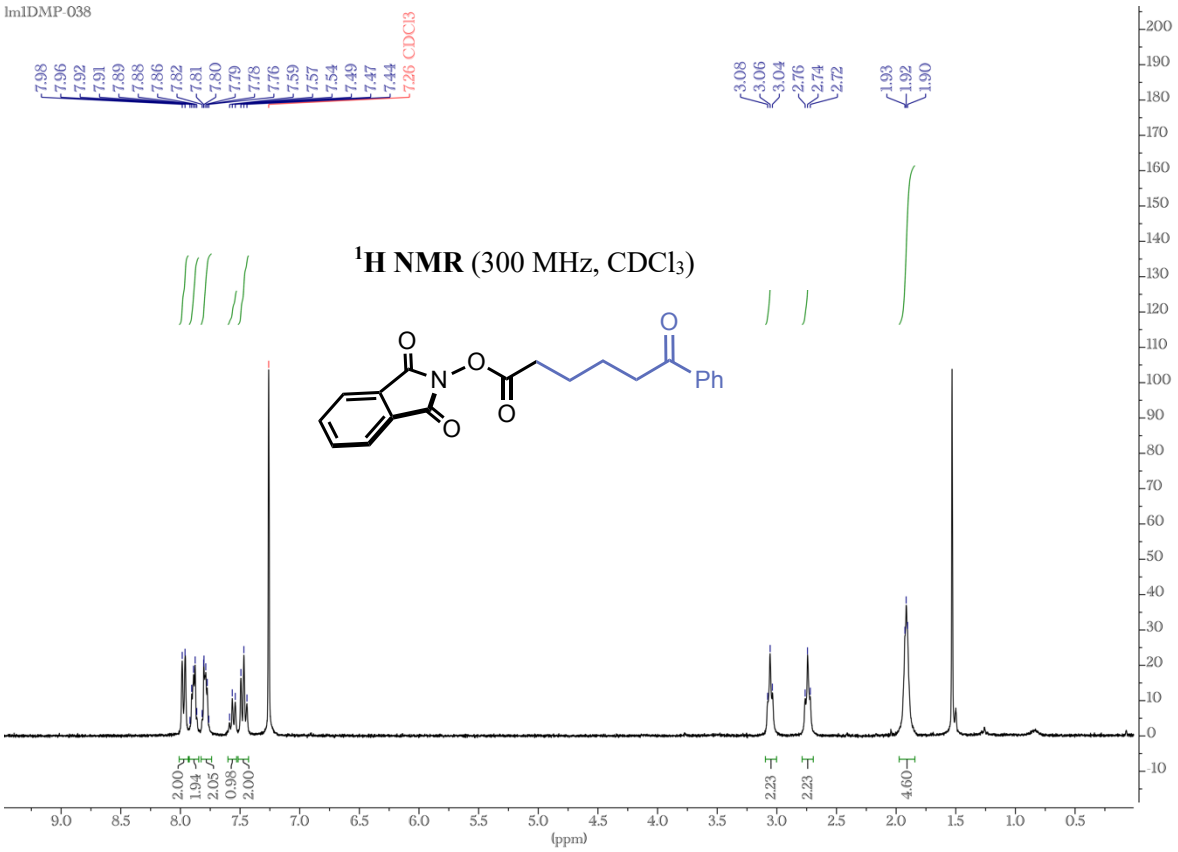



**$^{1}$H NMR** (300 MHz, $CDCl_3$)



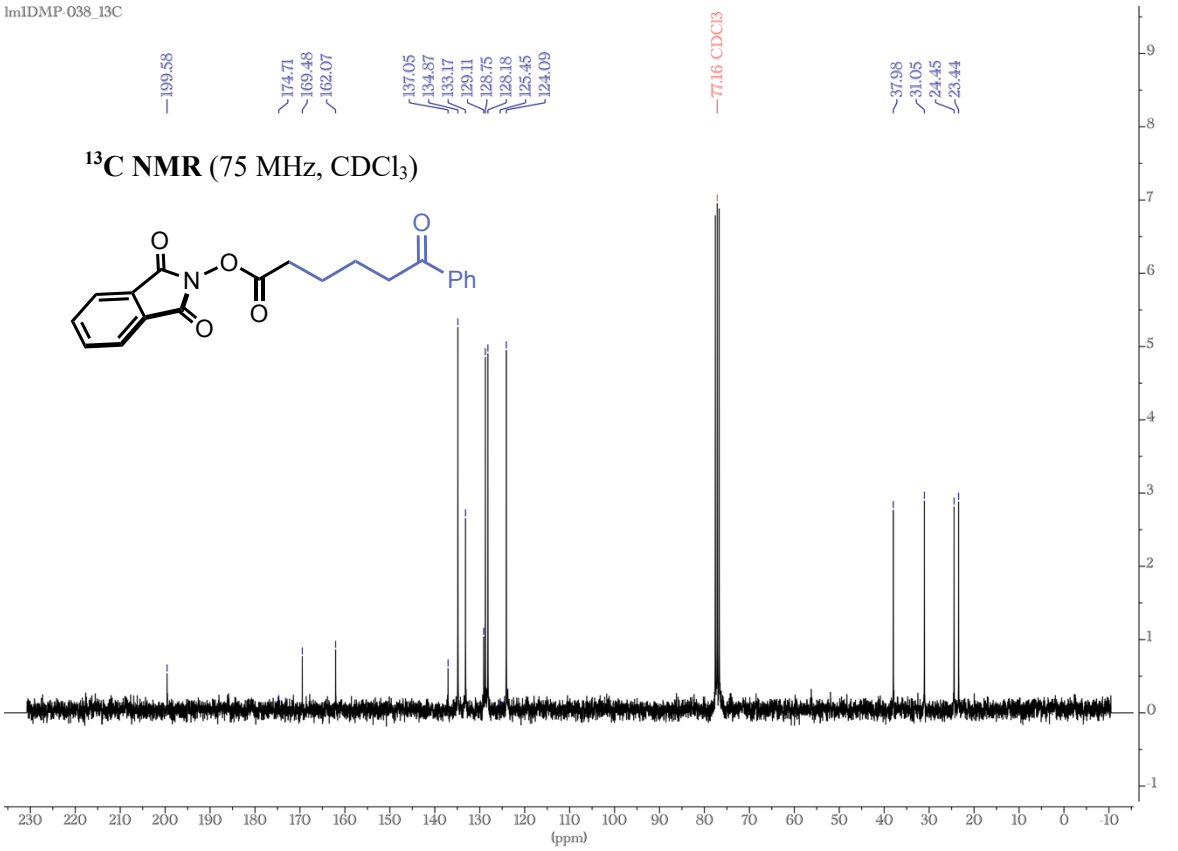

**$^{13}$C NMR** (75 MHz, $CDCl_3$)

## 1,3-Dioxoisoindolin-2-yl 6-oxo-6-phenylhexanoate (1h)



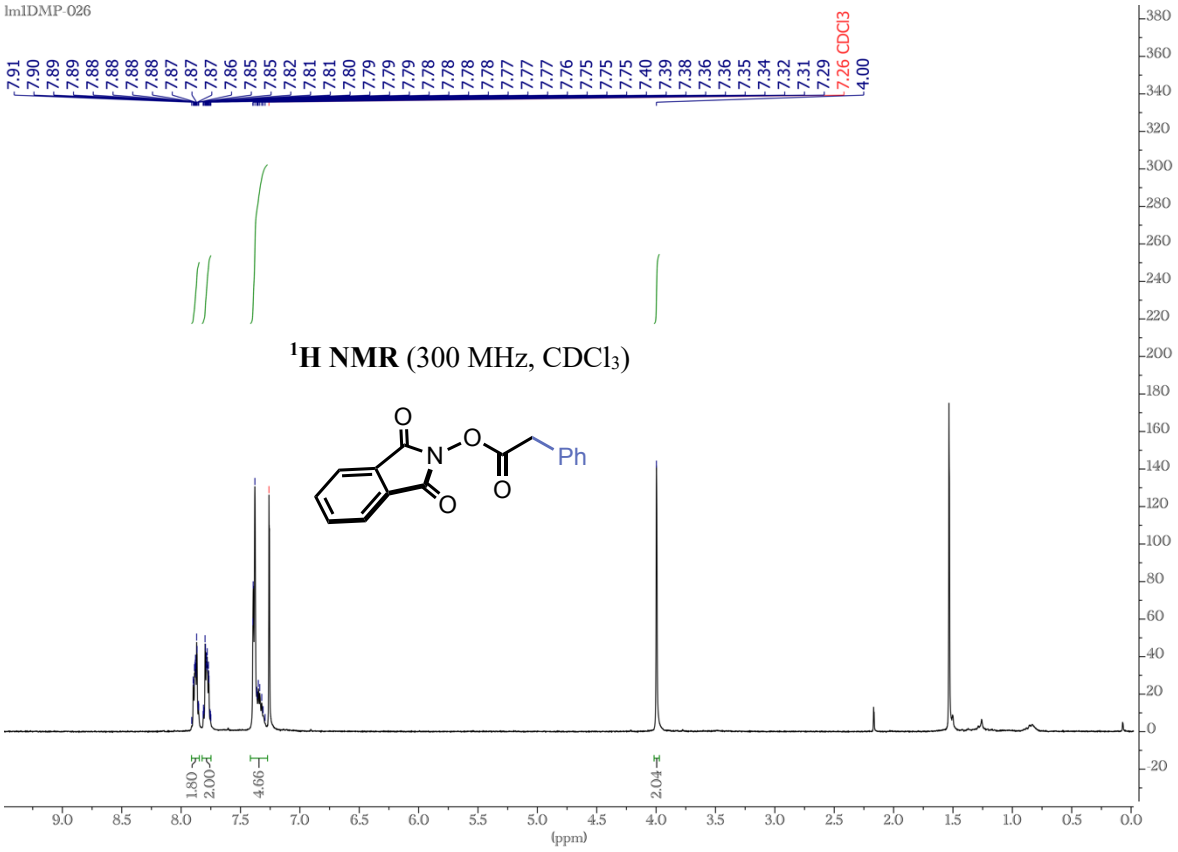

**$^{1}$H NMR** (300 MHz, $CDCl_3$)



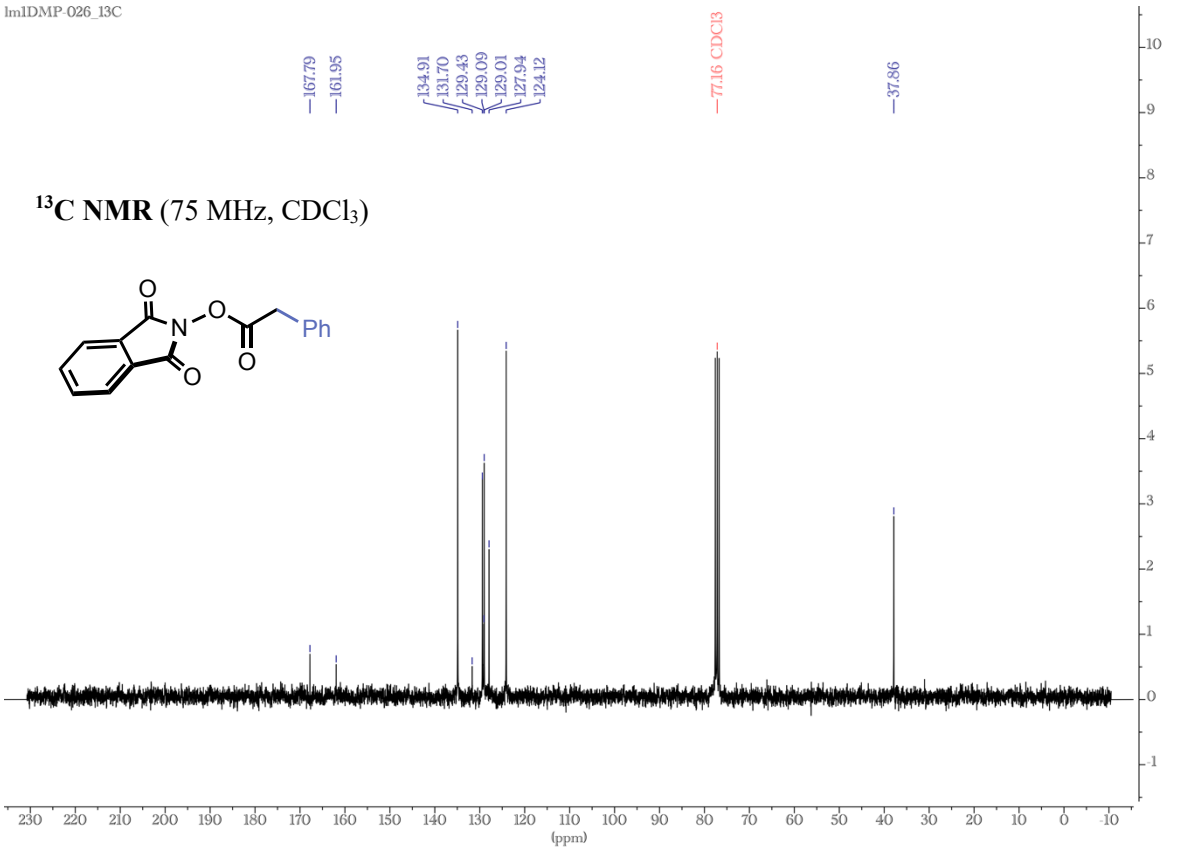

**$^{13}$C NMR** (75 MHz, $CDCl_3$)

## 1,3-Dioxoisoindolin-2-yl 2-phenylacetate (1i)



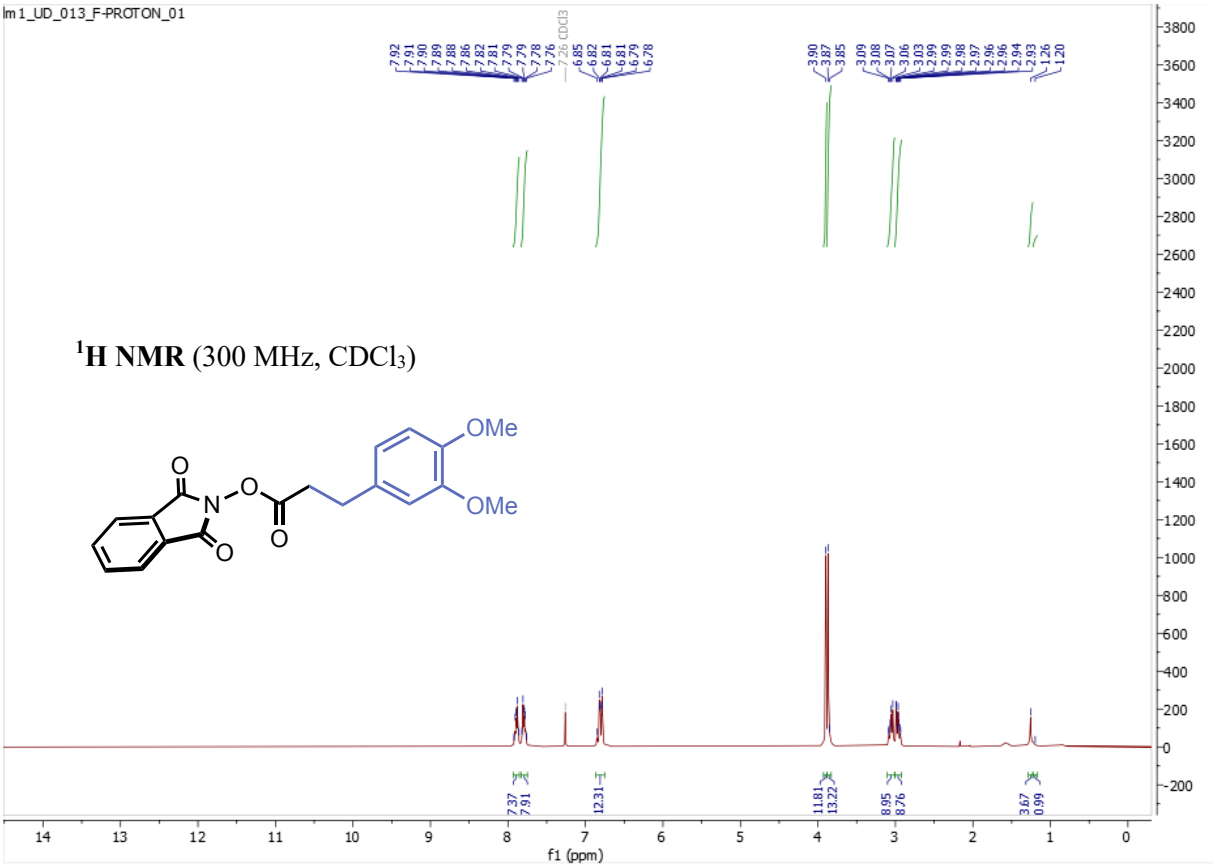

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

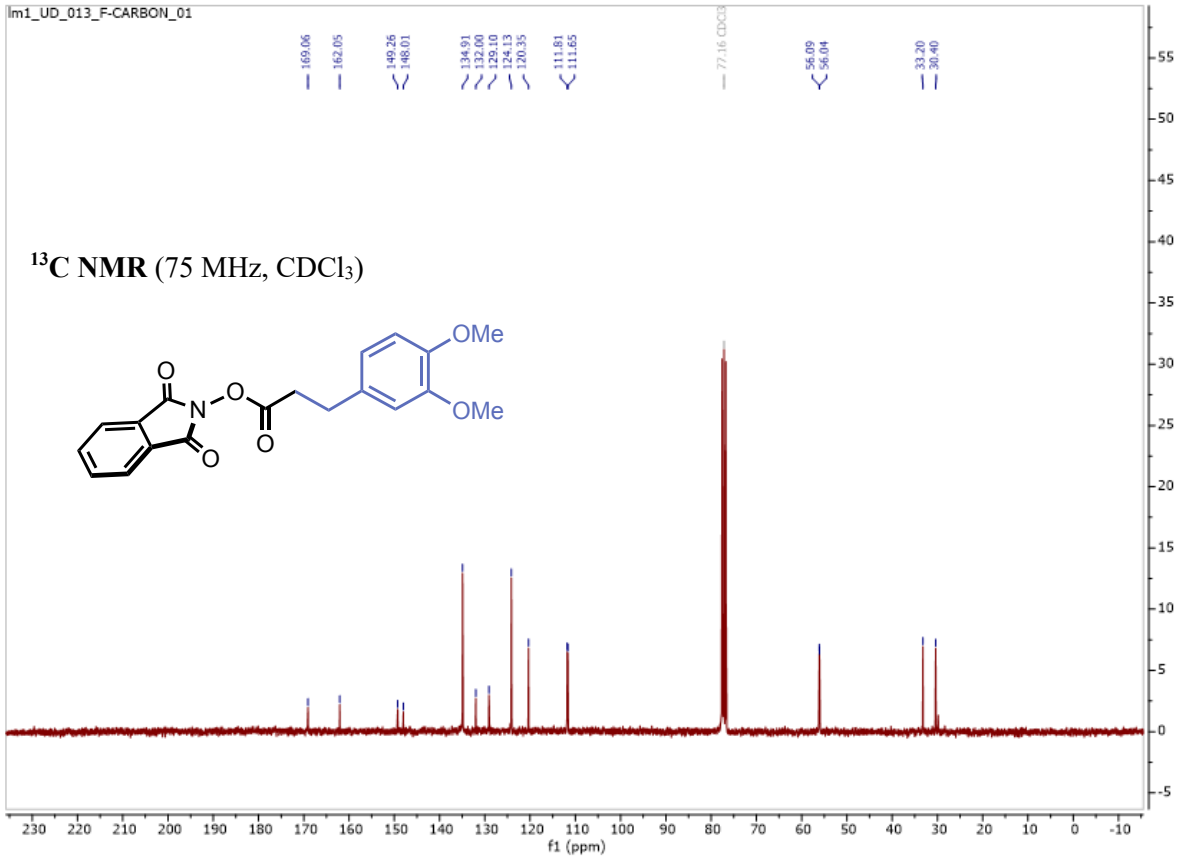


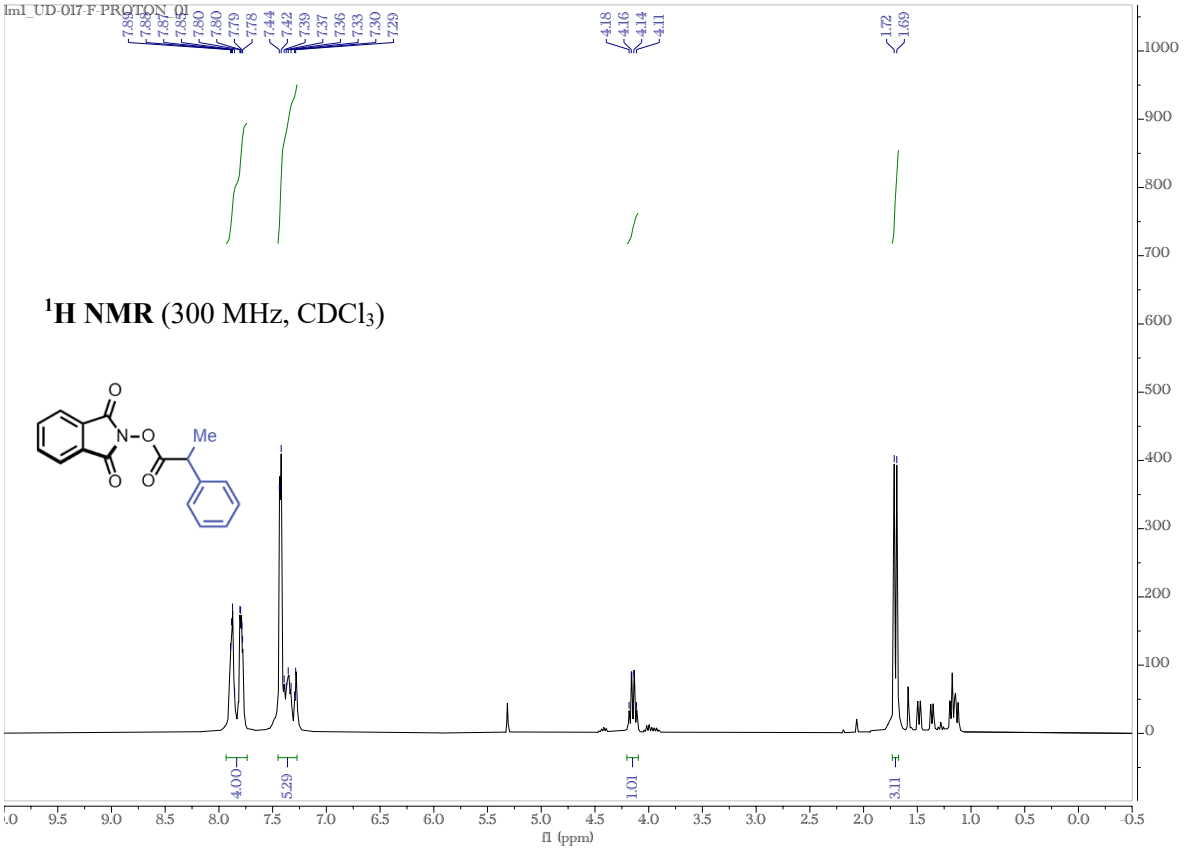

**$^{13}$C NMR** (75 MHz, $CDCl_3$)

**1,3-Dioxoisoindolin-2-yl 3-(3,4-dimethoxyphenyl) propanoate (1j)**



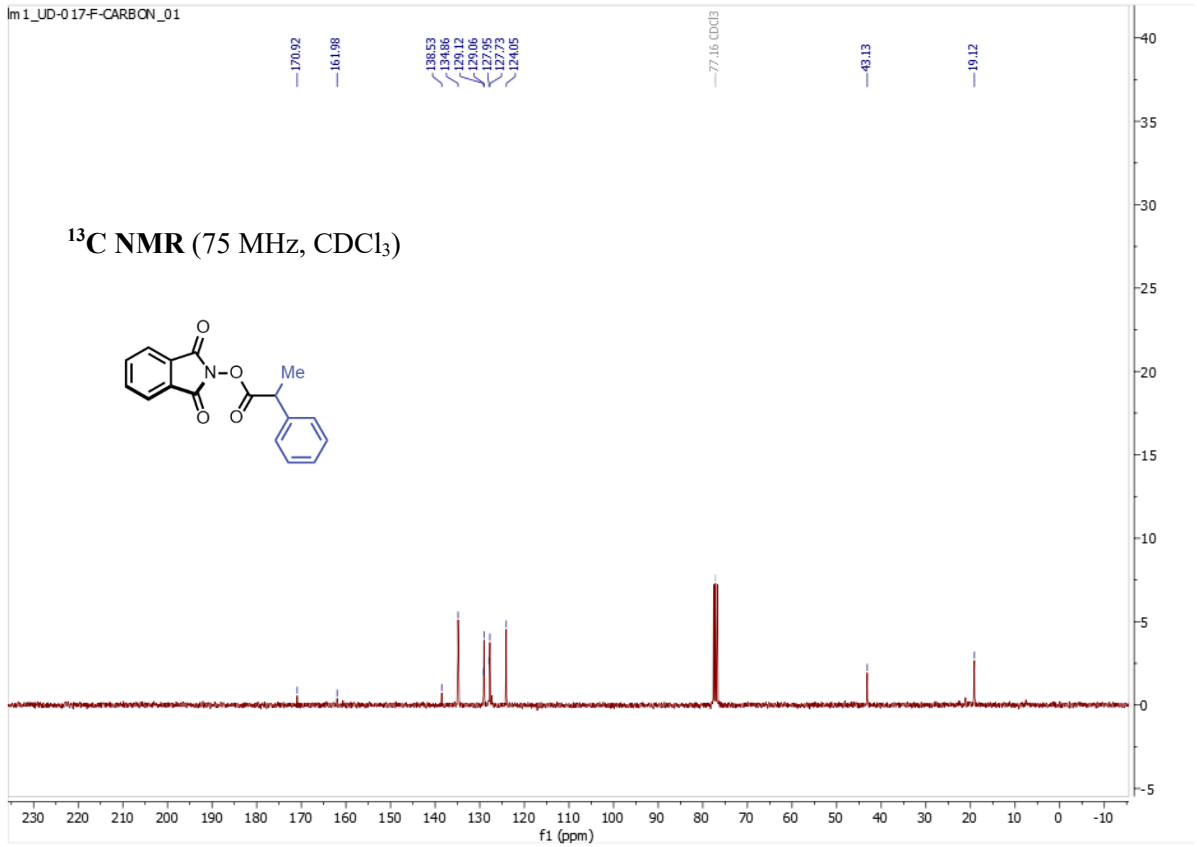



## 1,3-Dioxoisoindolin-2-yl 2-phenylpropanoate (SI-1)



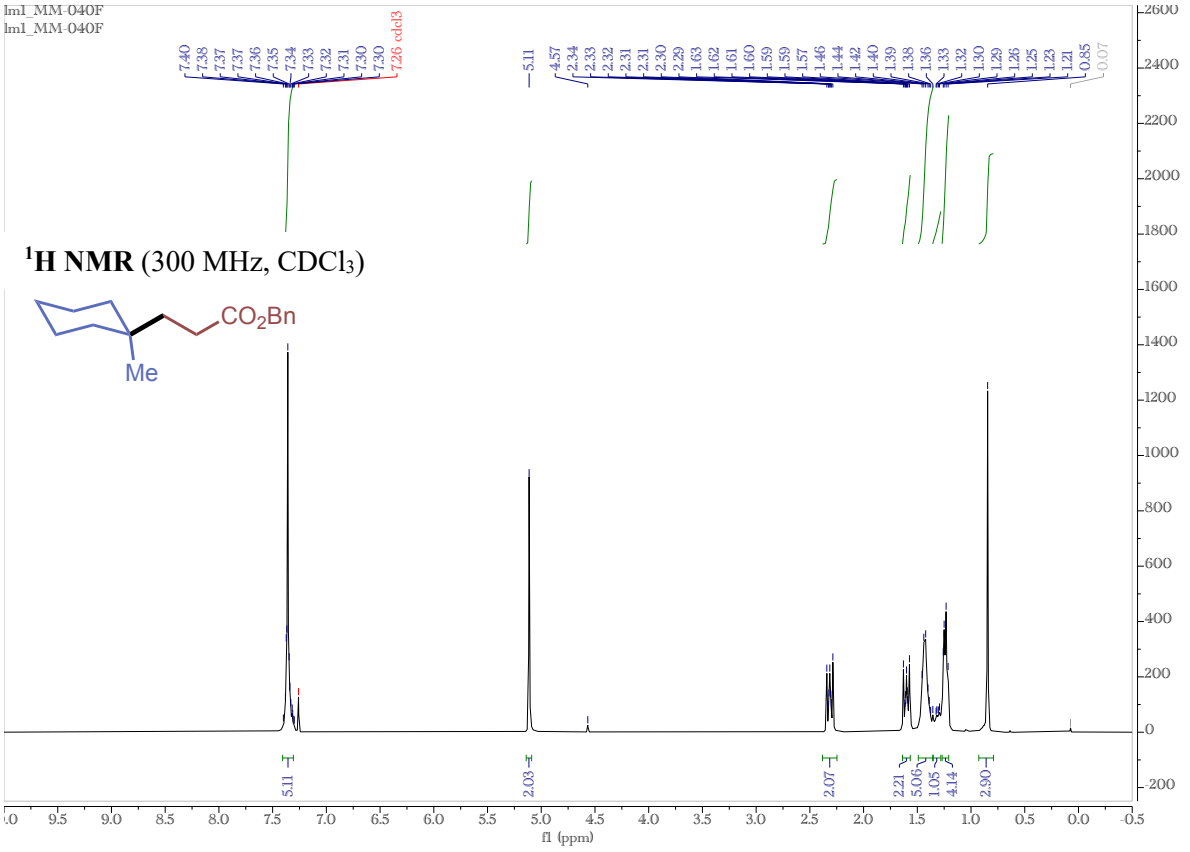

**$^{1}$H NMR** (300 MHz, $CDCl_3$)

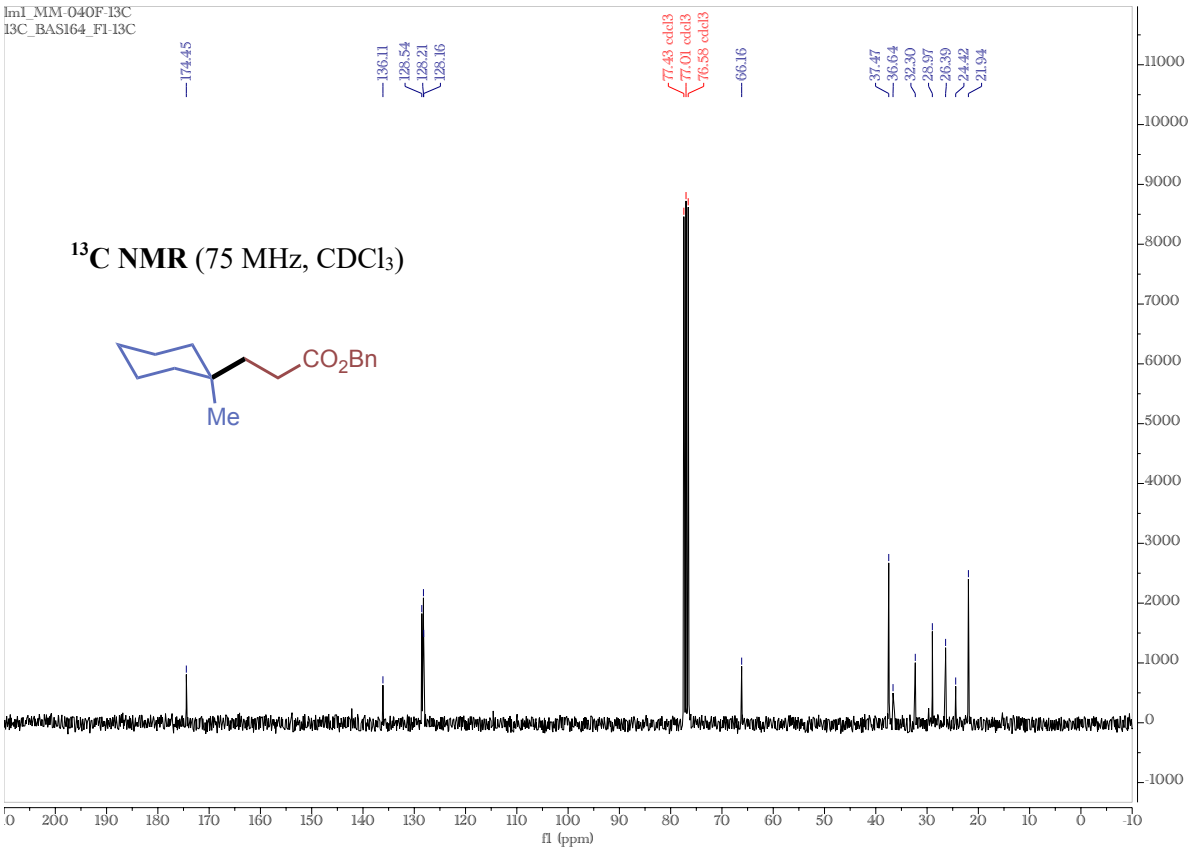


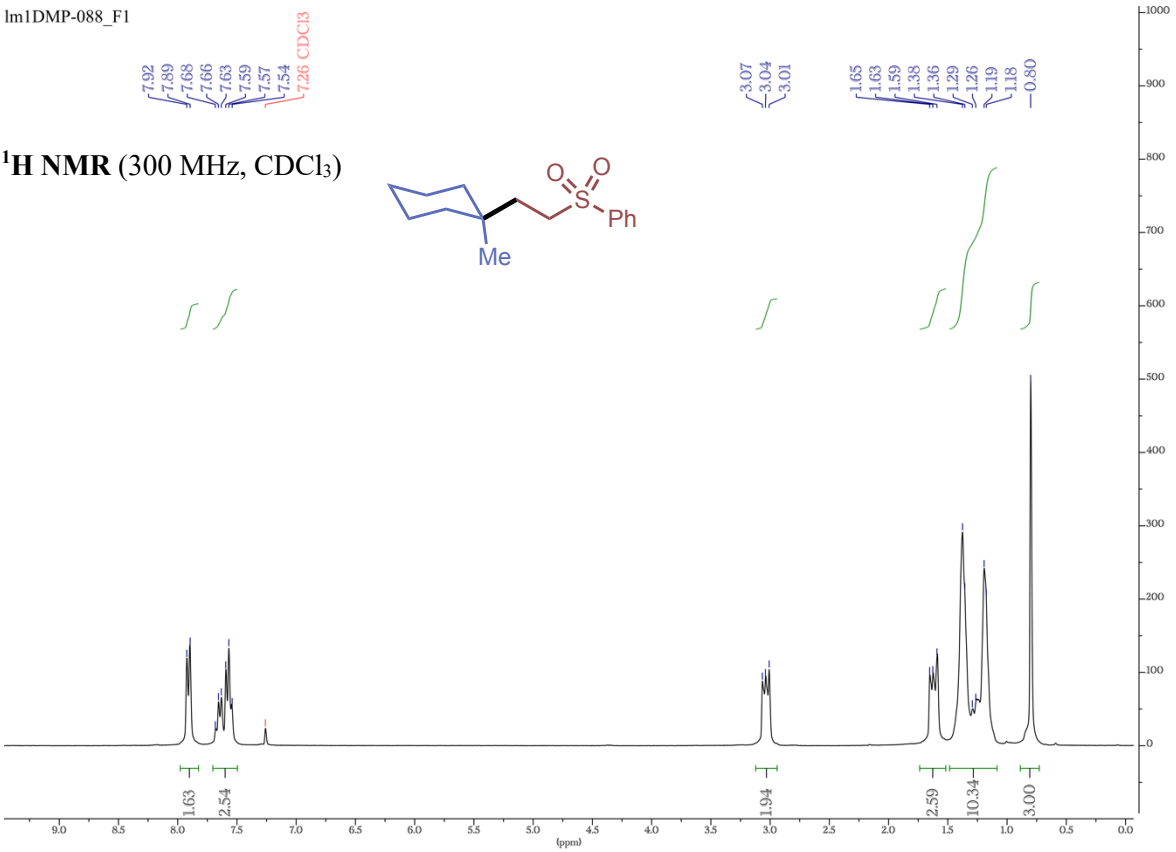

**$^{13}$C NMR** (75 MHz, $CDCl_3$)

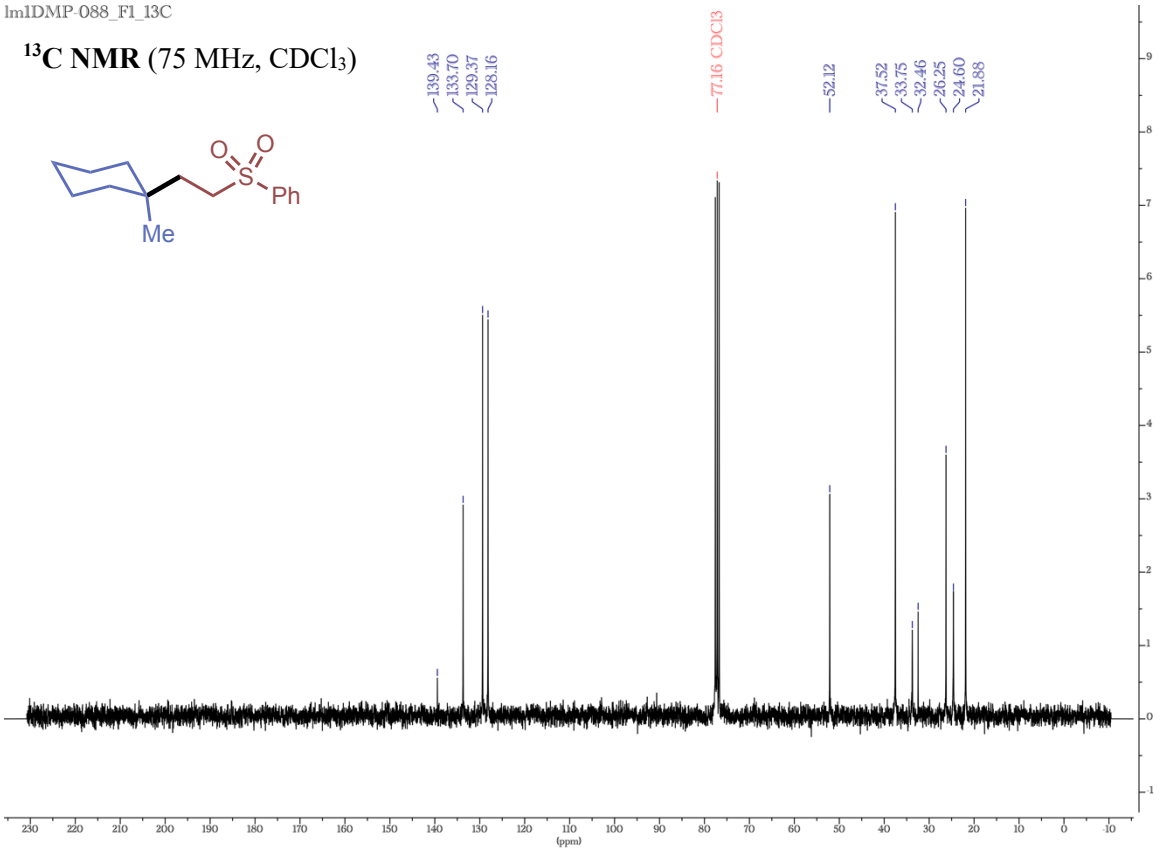
**Benzyl 3-(1-methylcyclohexyl)propanoate (3a)**



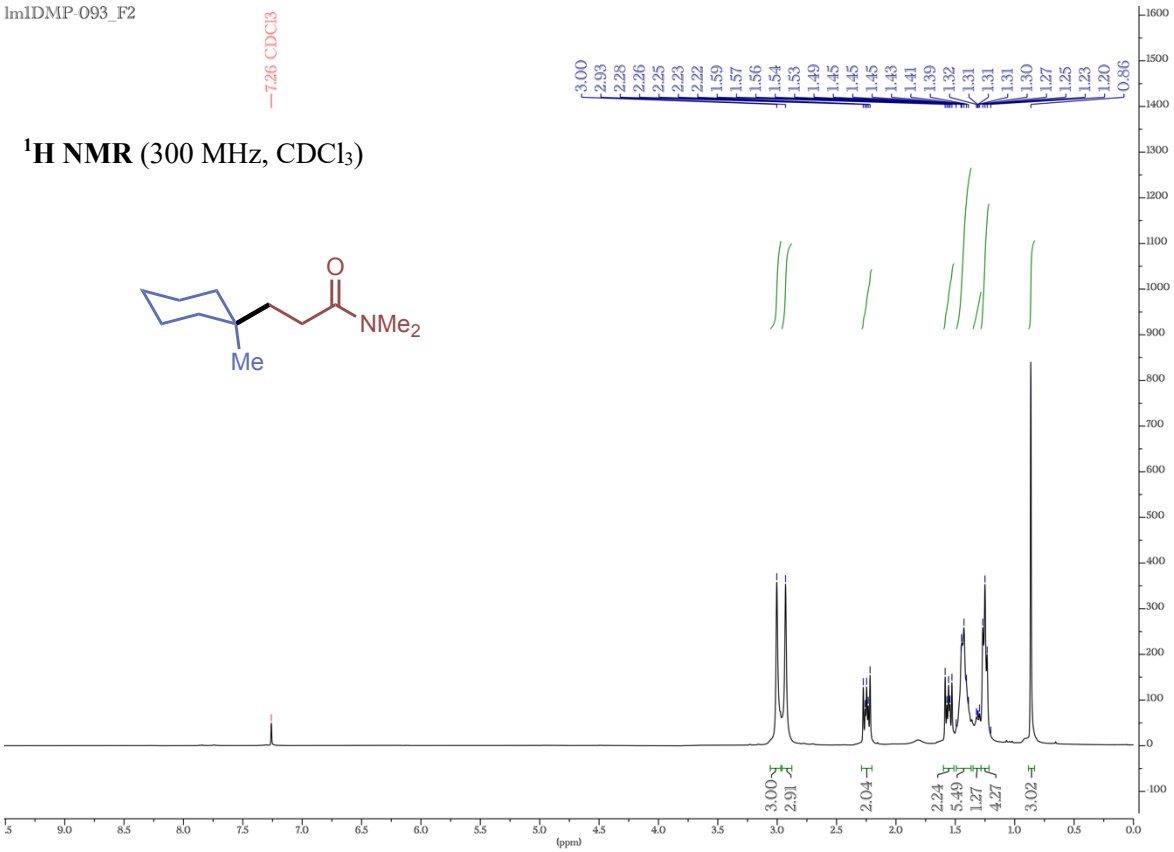



**((2-(1-Methylcyclohexyl)ethyl)sulfonyl)benzene (3b)**

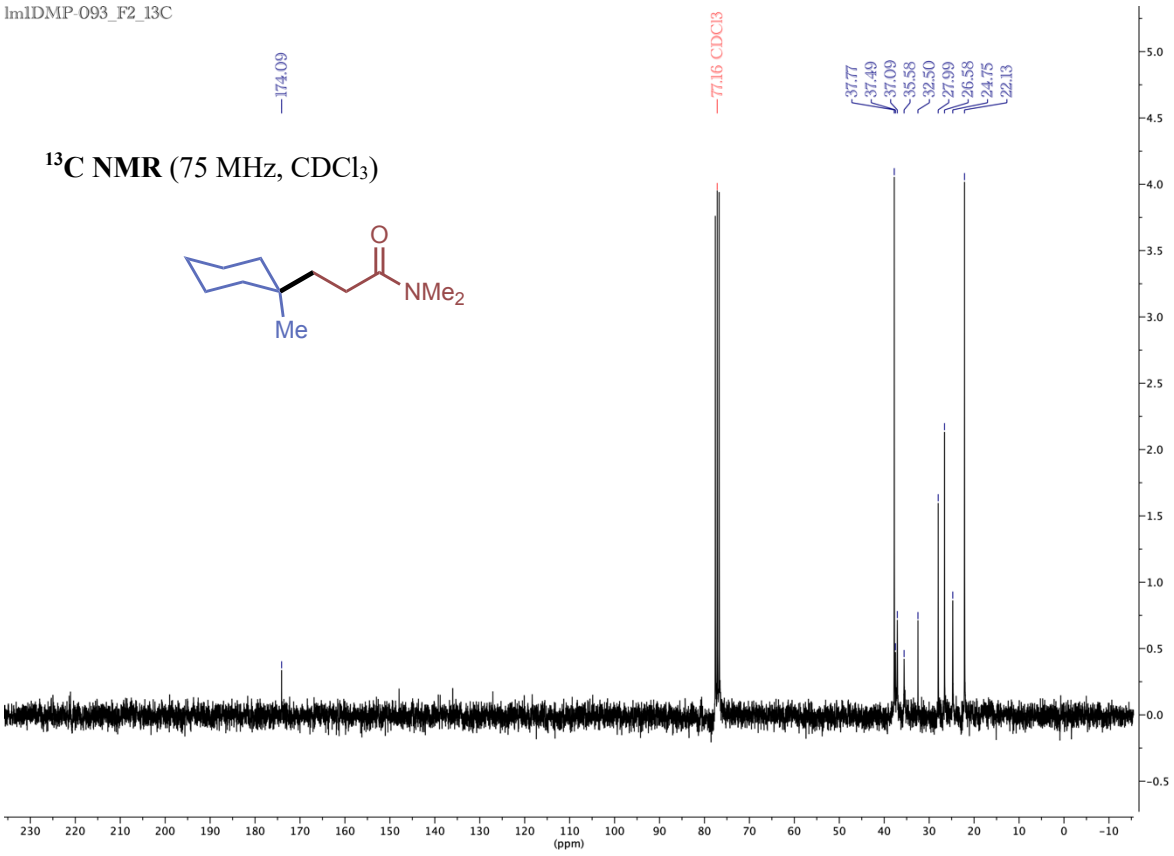


## *N*,*N*-Dimethyl-3-(1-methylcyclohexyl)propanamide (3c)



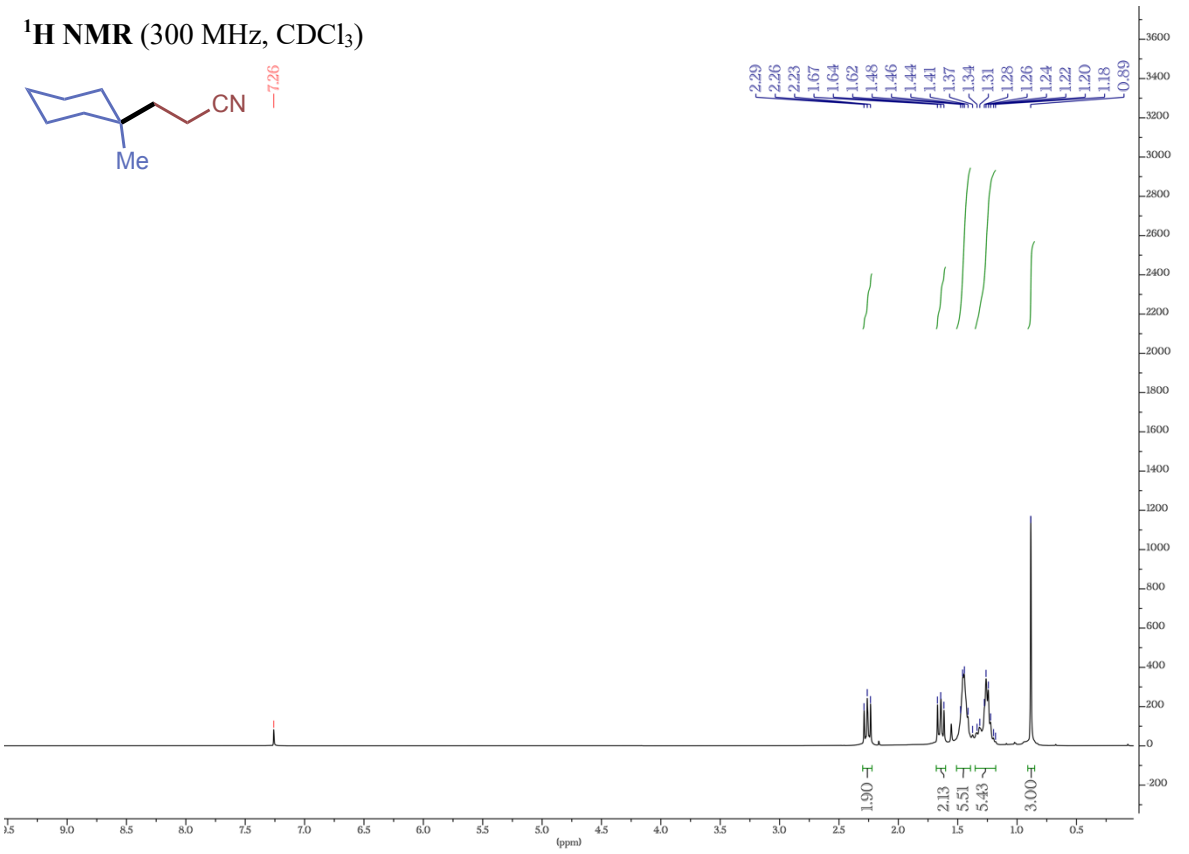

**$^{1}$H NMR** (300 MHz, $CDCl_3$)



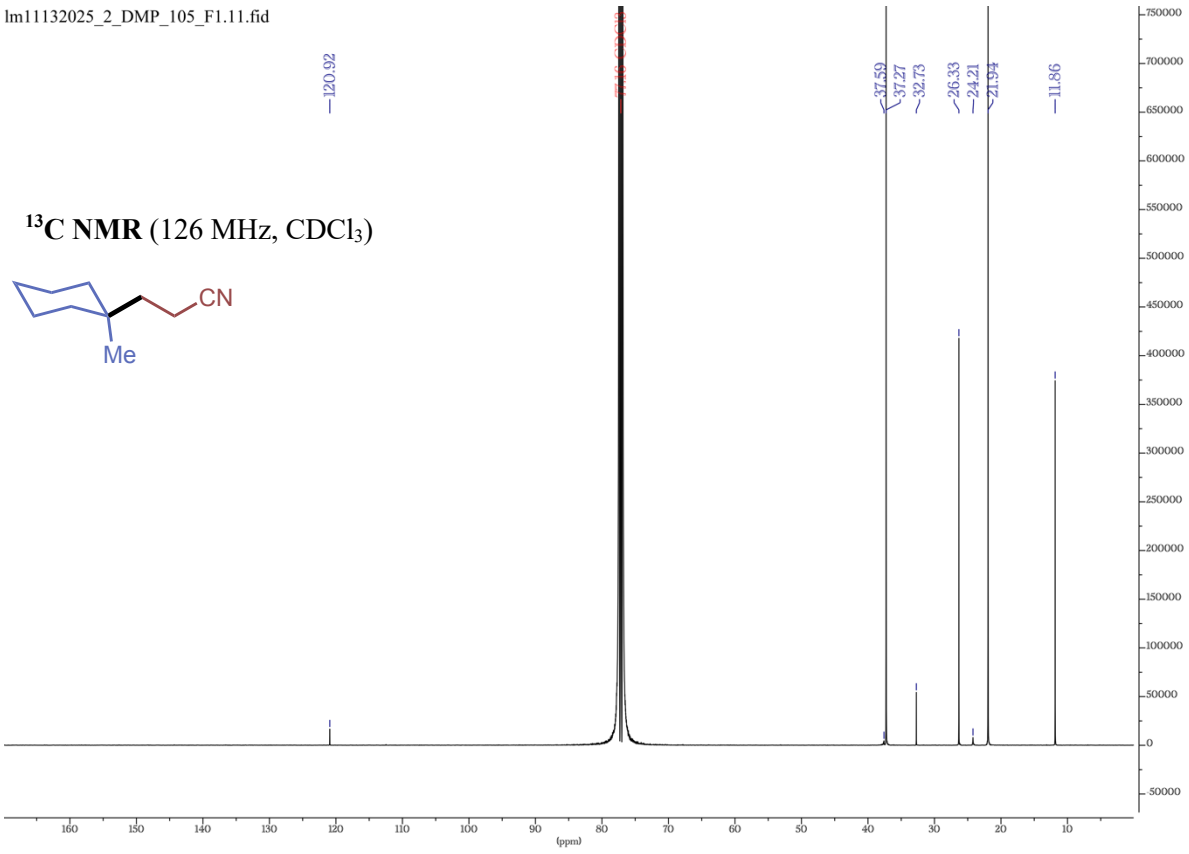

**$^{13}$C NMR** (75 MHz, $CDCl_3$)

**3-(1-Methylcyclohexyl)propanenitrile (3d)**

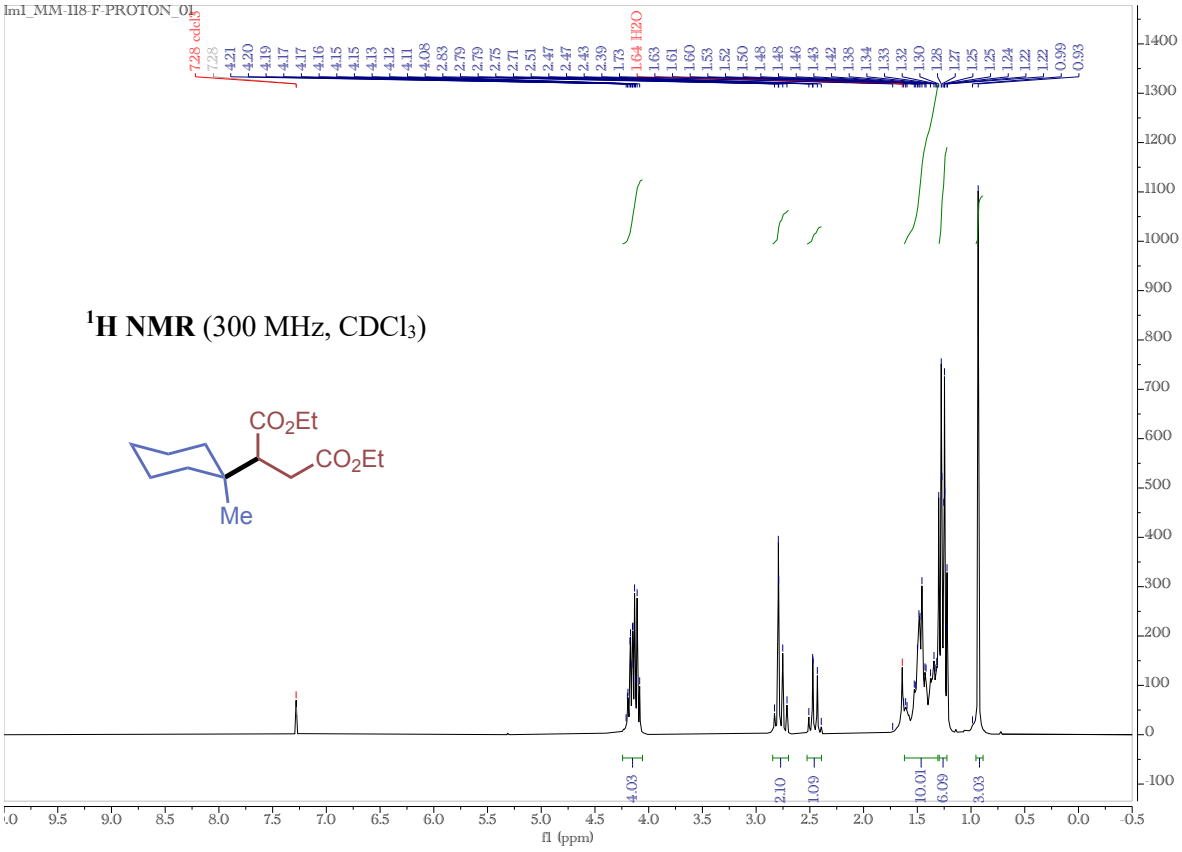
**$^{1}$H NMR** (300 MHz, $CDCl_3$)

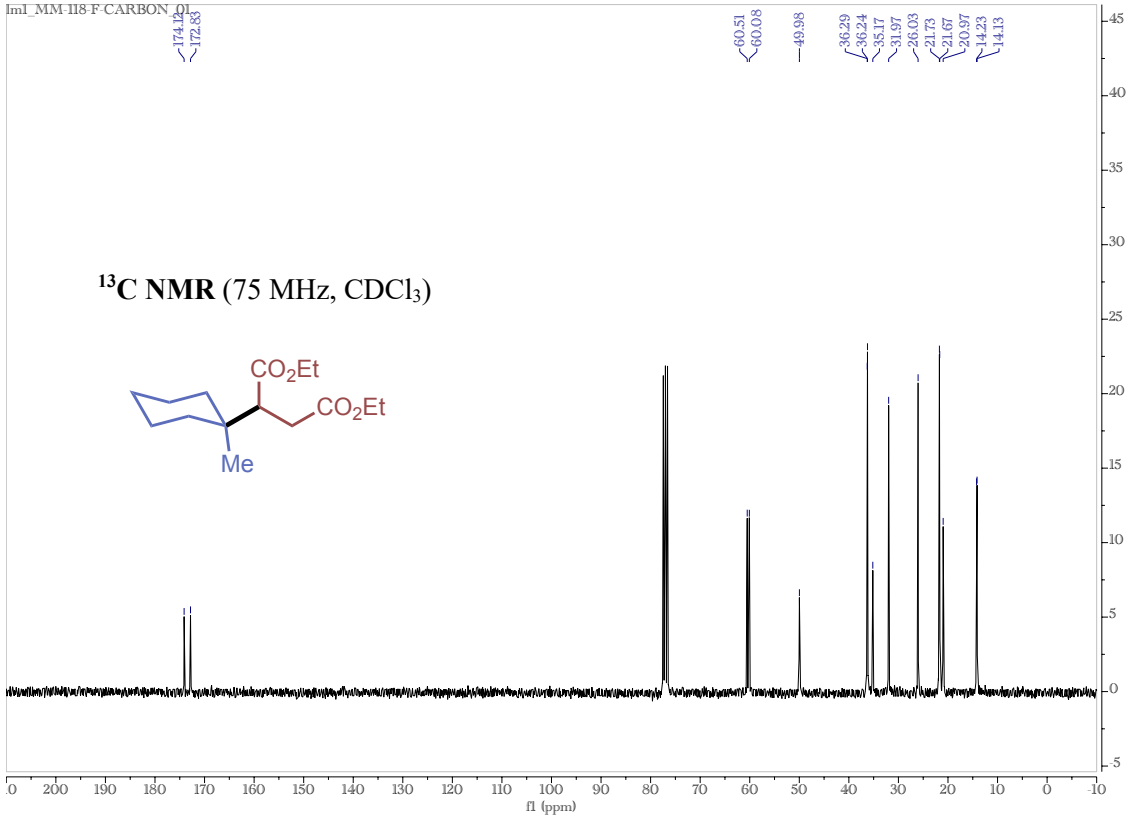



**$^{13}$C NMR** (126 MHz, $CDCl_3$)

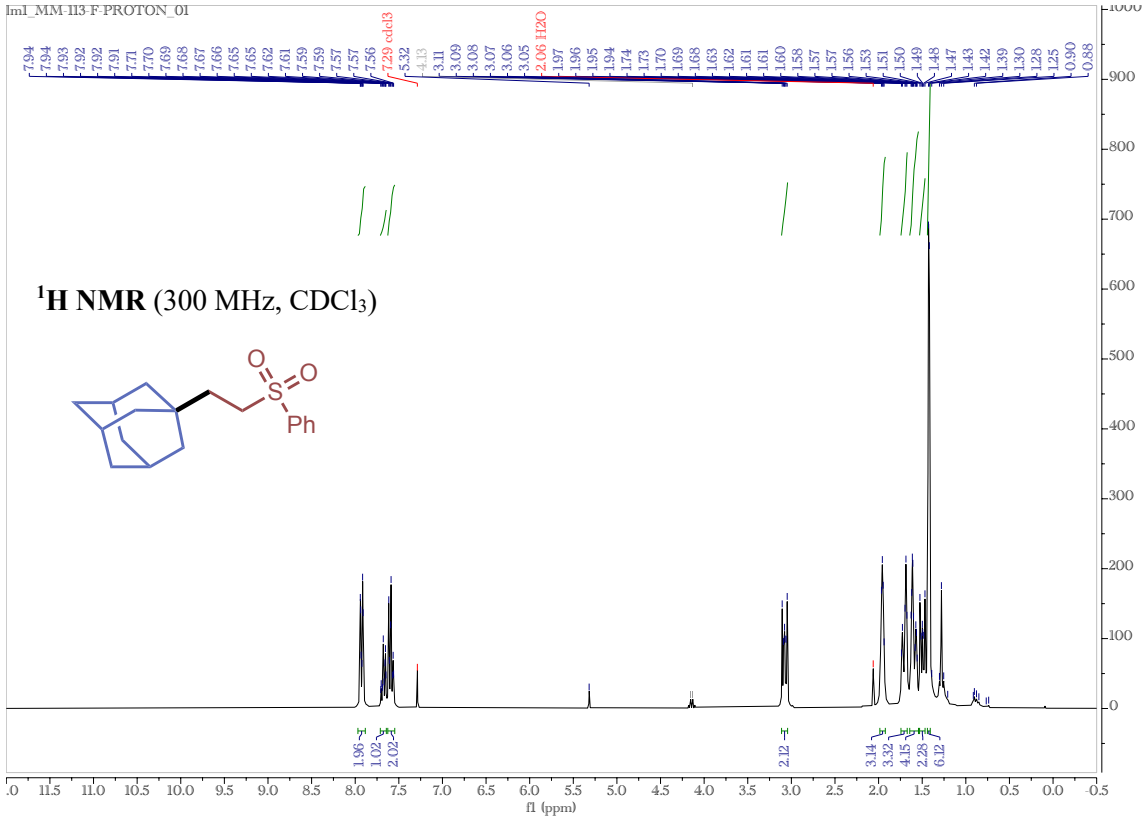


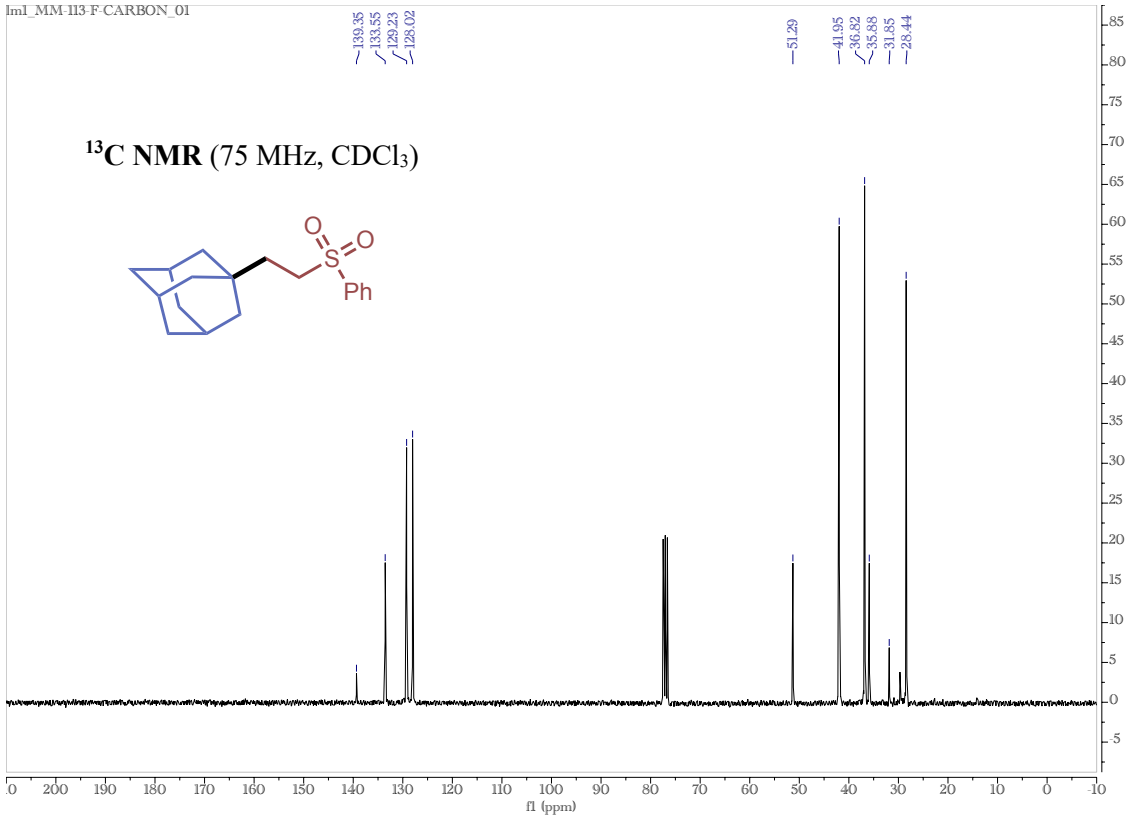
**Diethyl 2-(1-methylcyclohexyl)succinate (3e)**



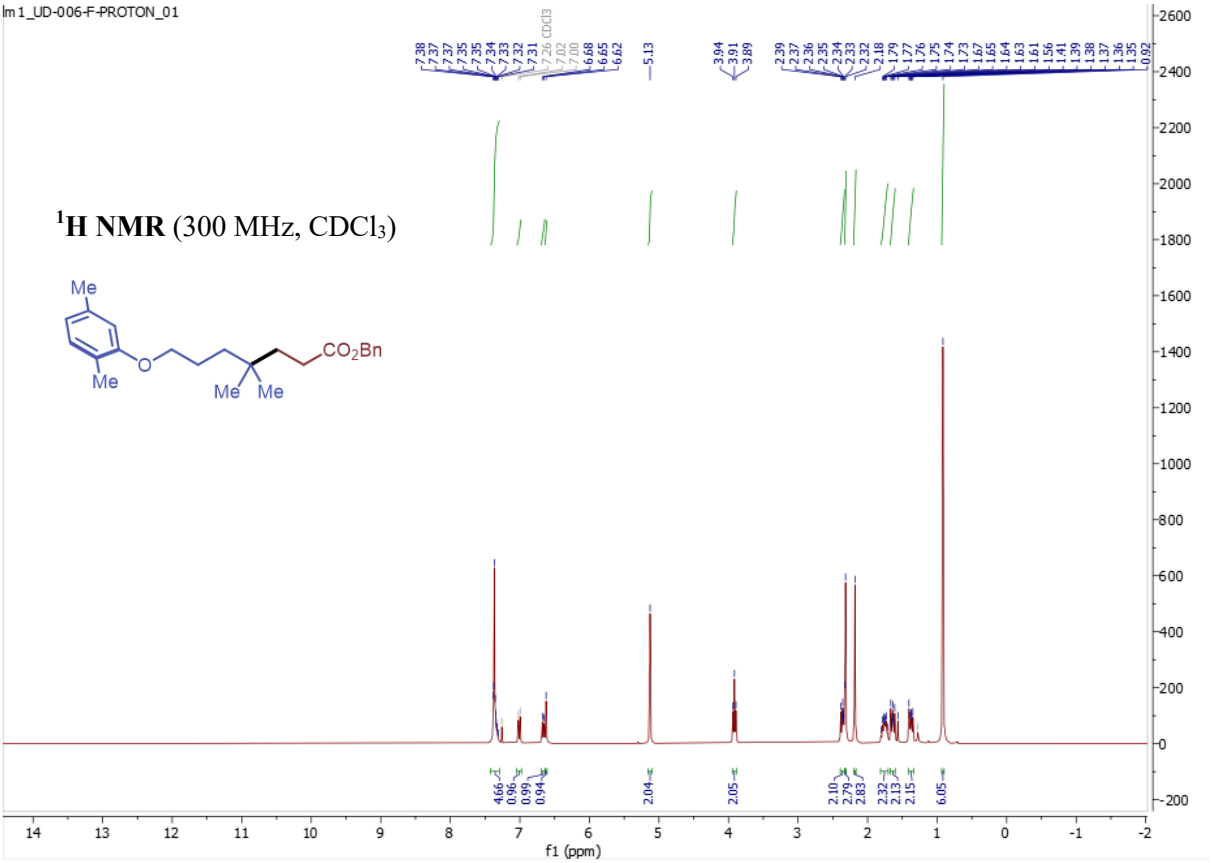



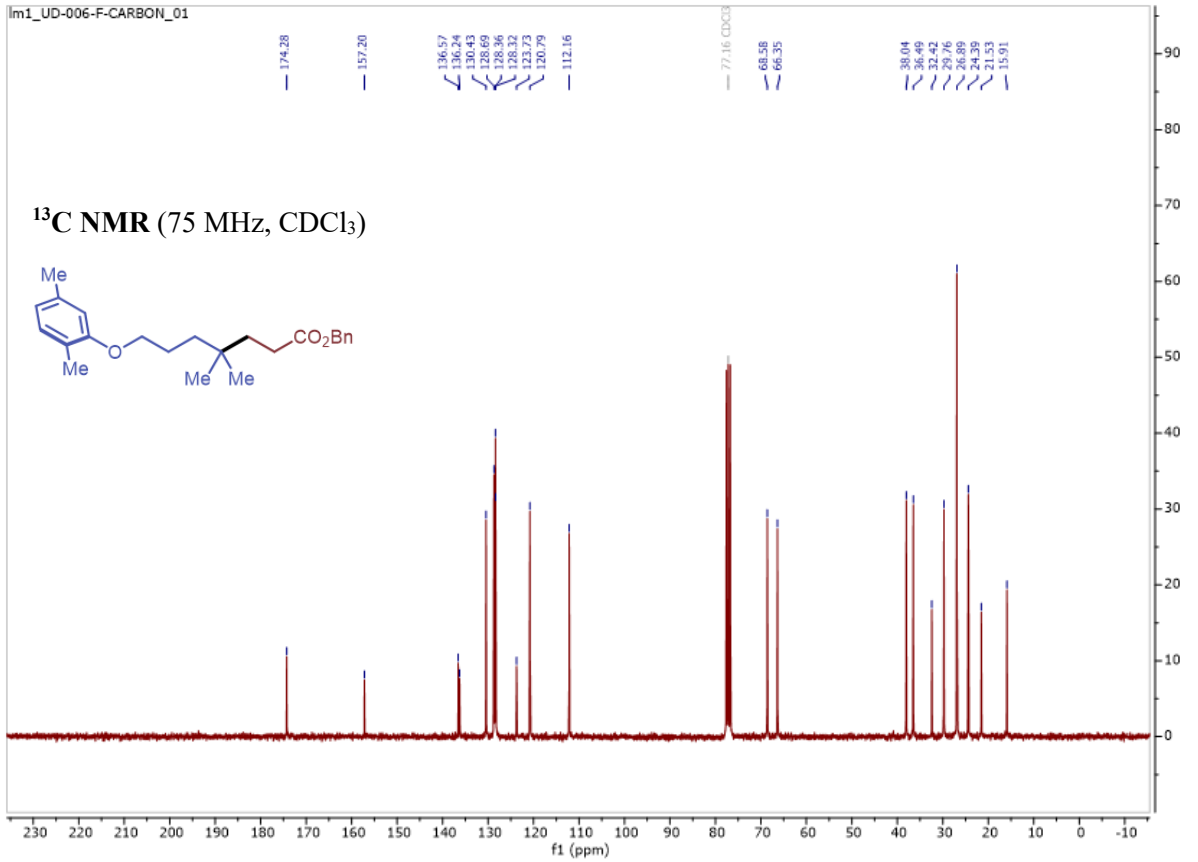
## 1-(2-(Phenylsulfonyl)ethyl)adamantane (3f)



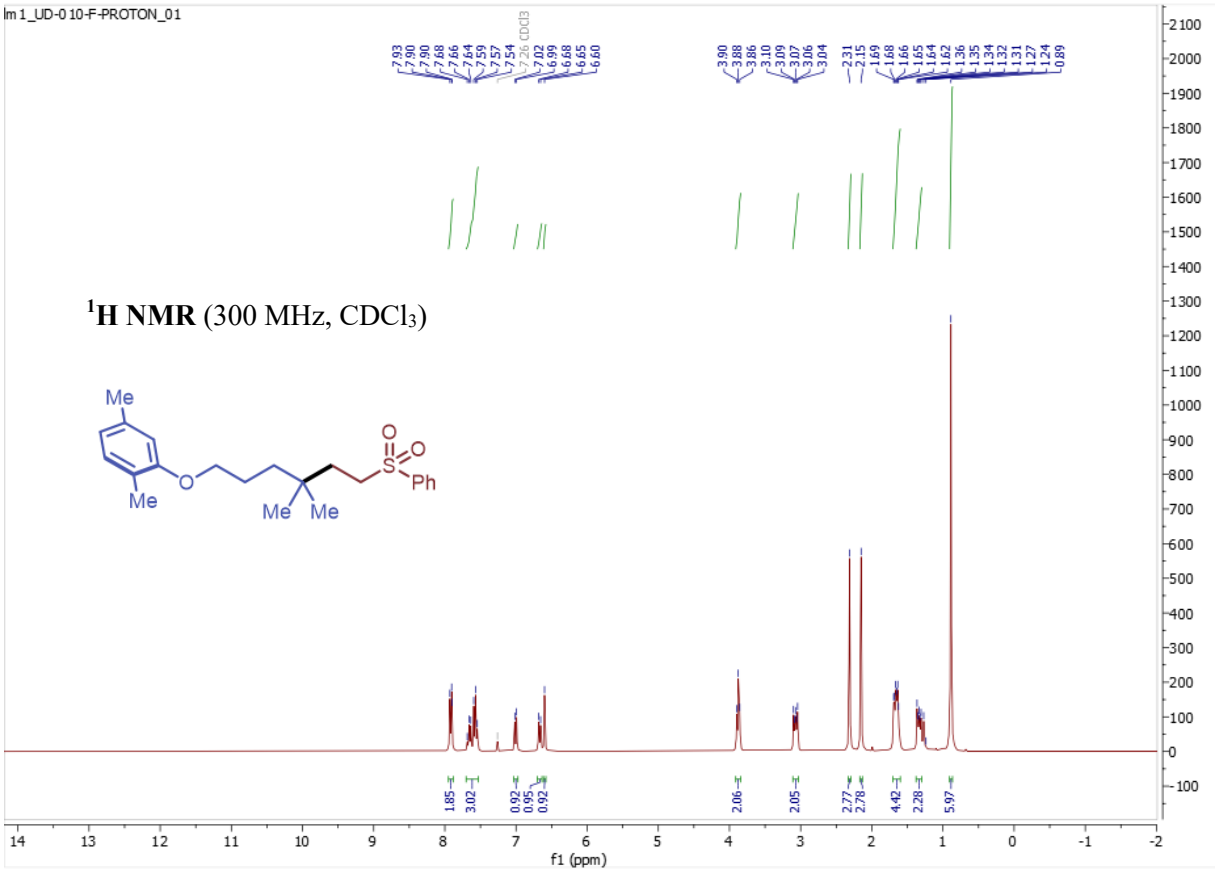



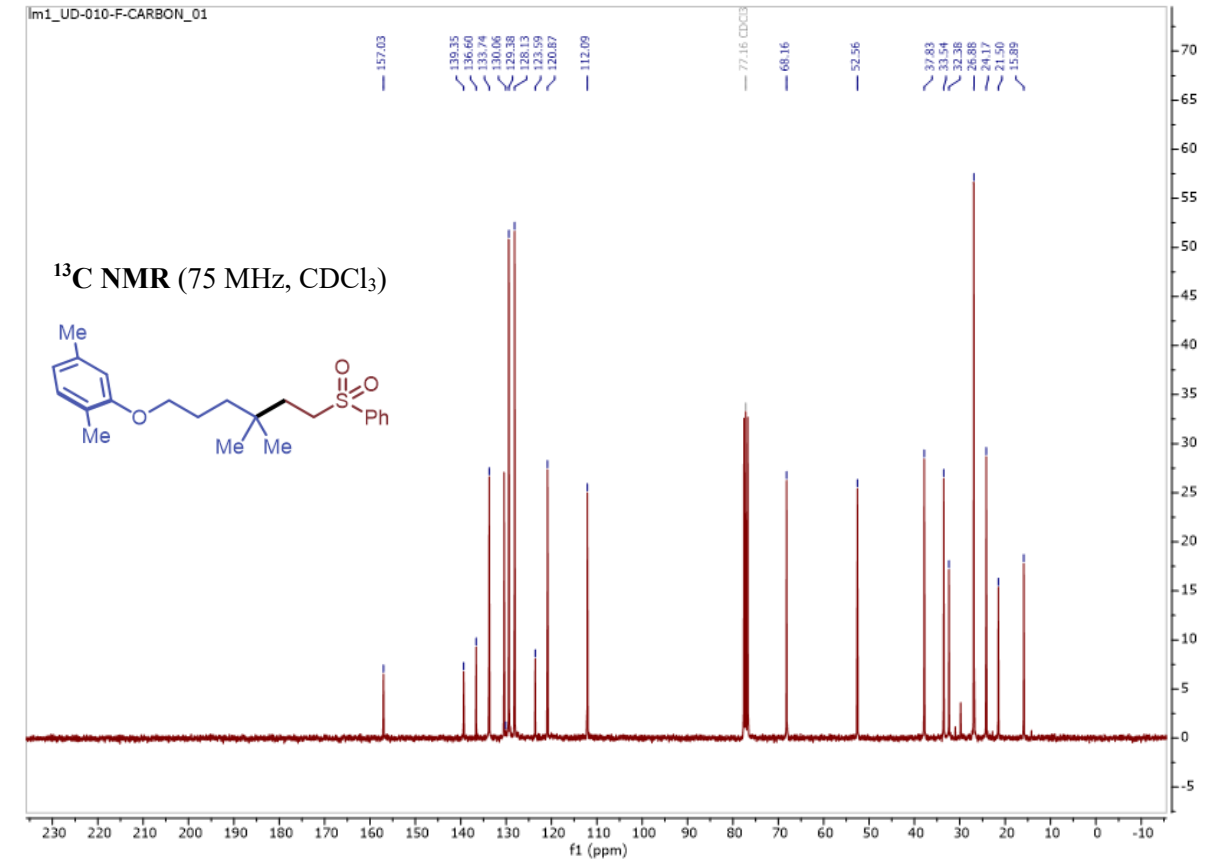
**Benzyl 7-(2,5-dimethylphenoxy)-4,4-dimethylheptanoate (3g)**



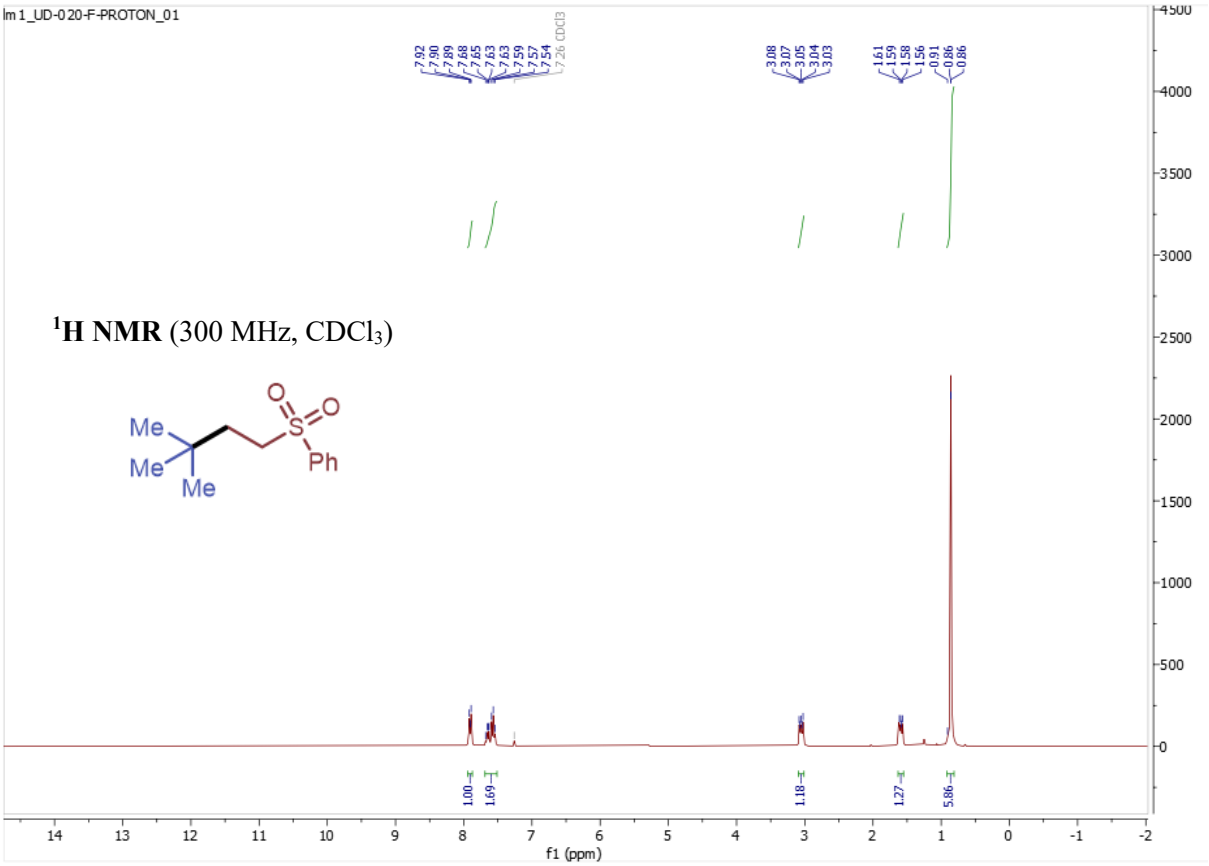



**2-((4,4-Dimethyl-6-(phenylsulfonyl)hexyl)oxy)-1,4-dimethylbenzene (3h)**



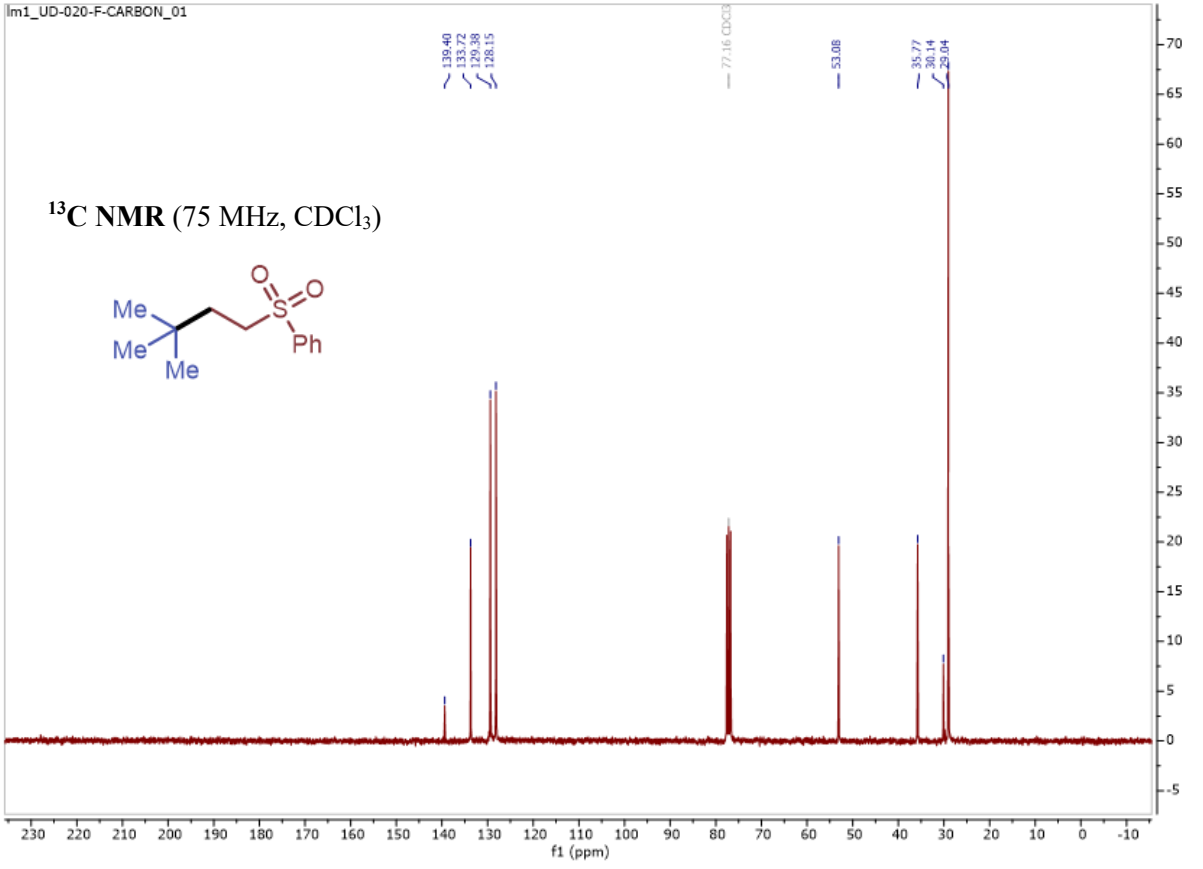



**((3,3-Dimethylbutyl)sulfonyl)benzene (3i)**



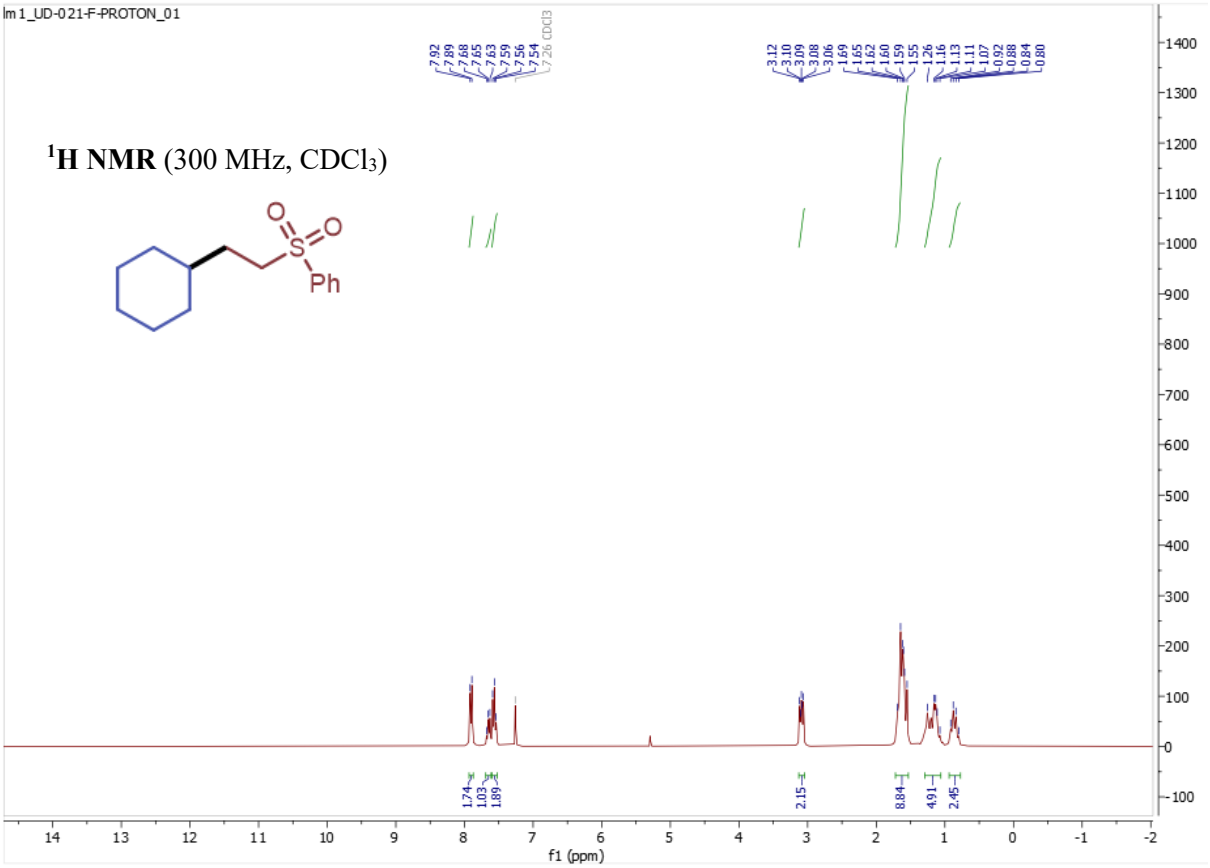

$^{1}$**H NMR** (300 MHz, $CDCl_3$)

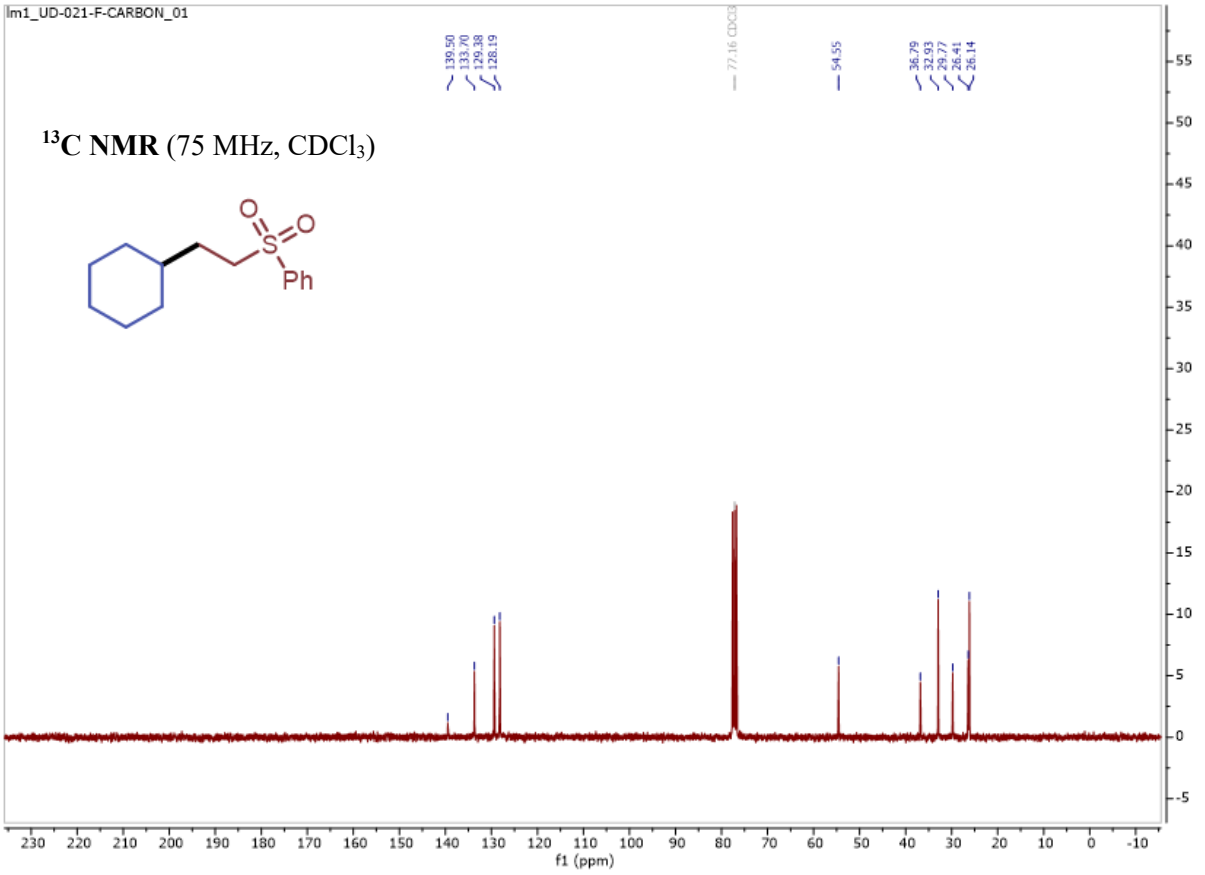


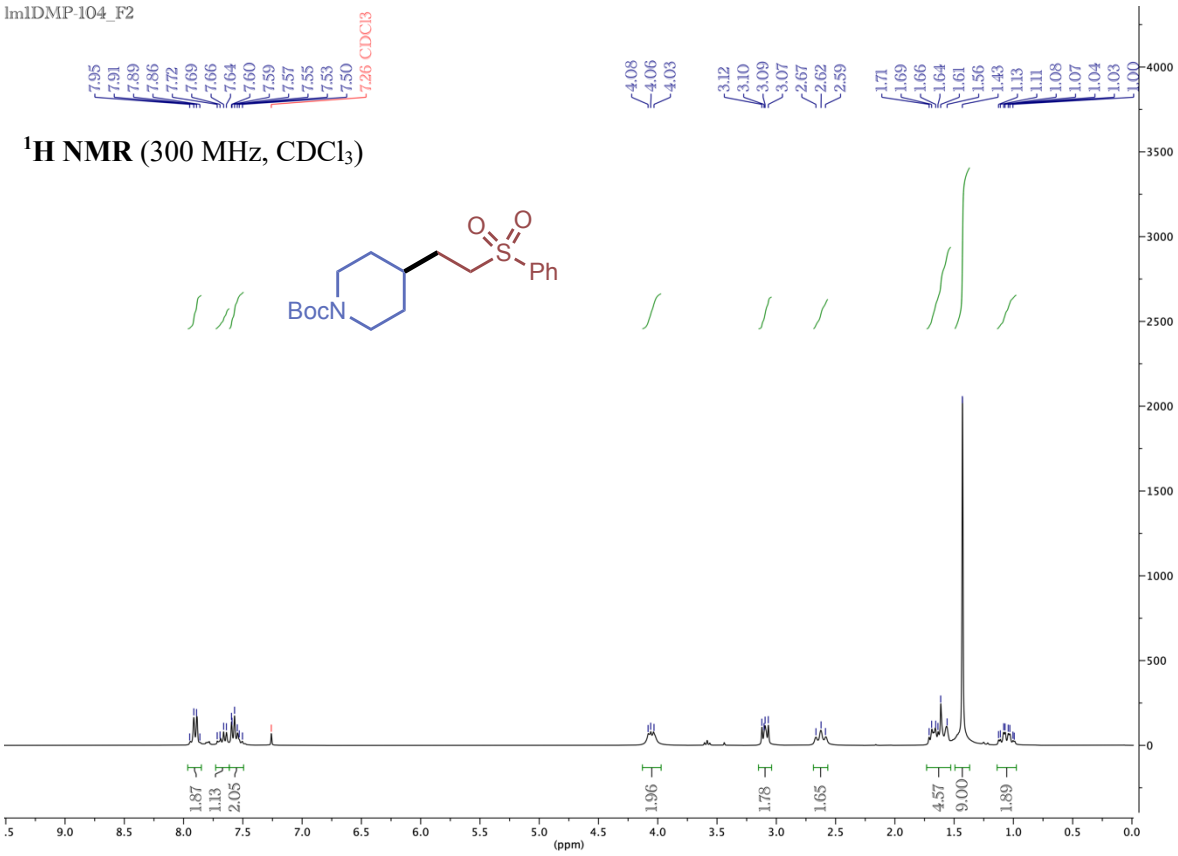

$^{13}$**C NMR** (75 MHz, $CDCl_3$)

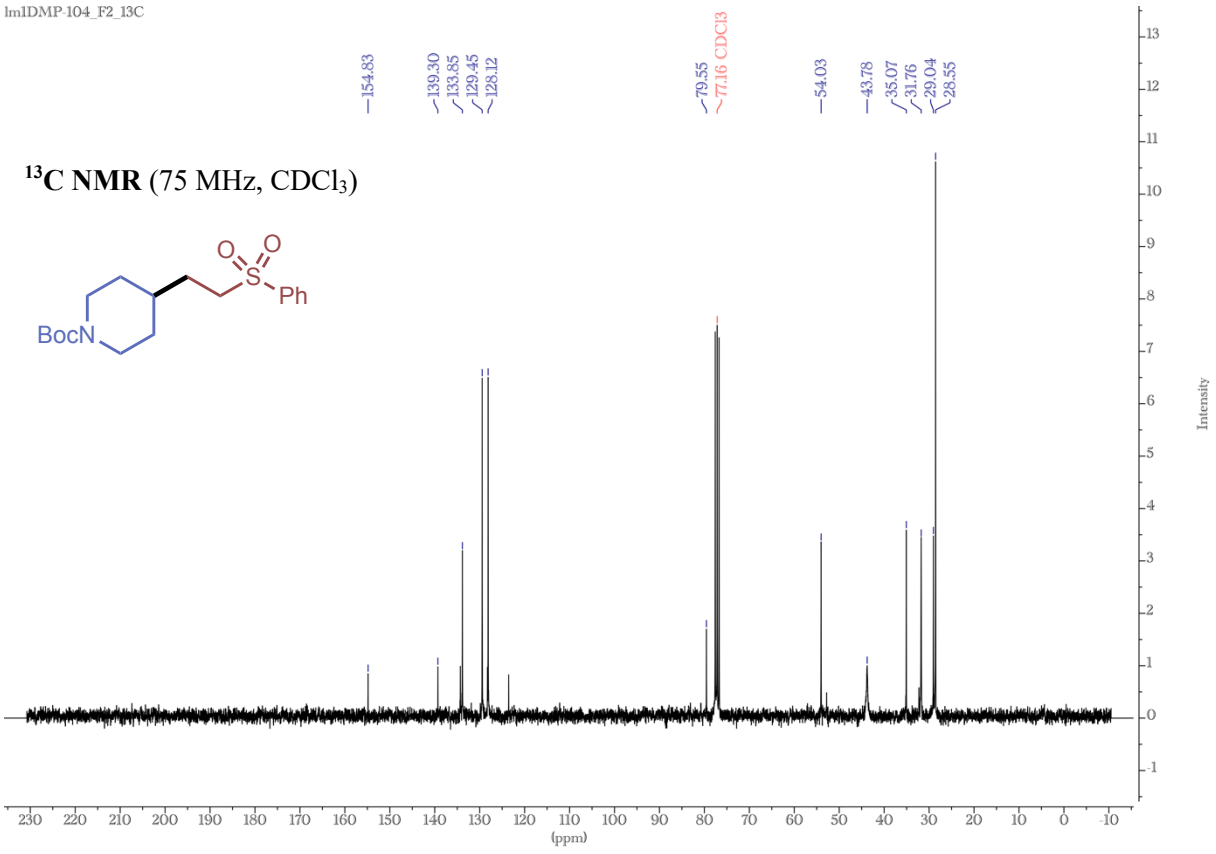
**((2-Cyclohexylethyl)sulfonyl)benzene (3j)**



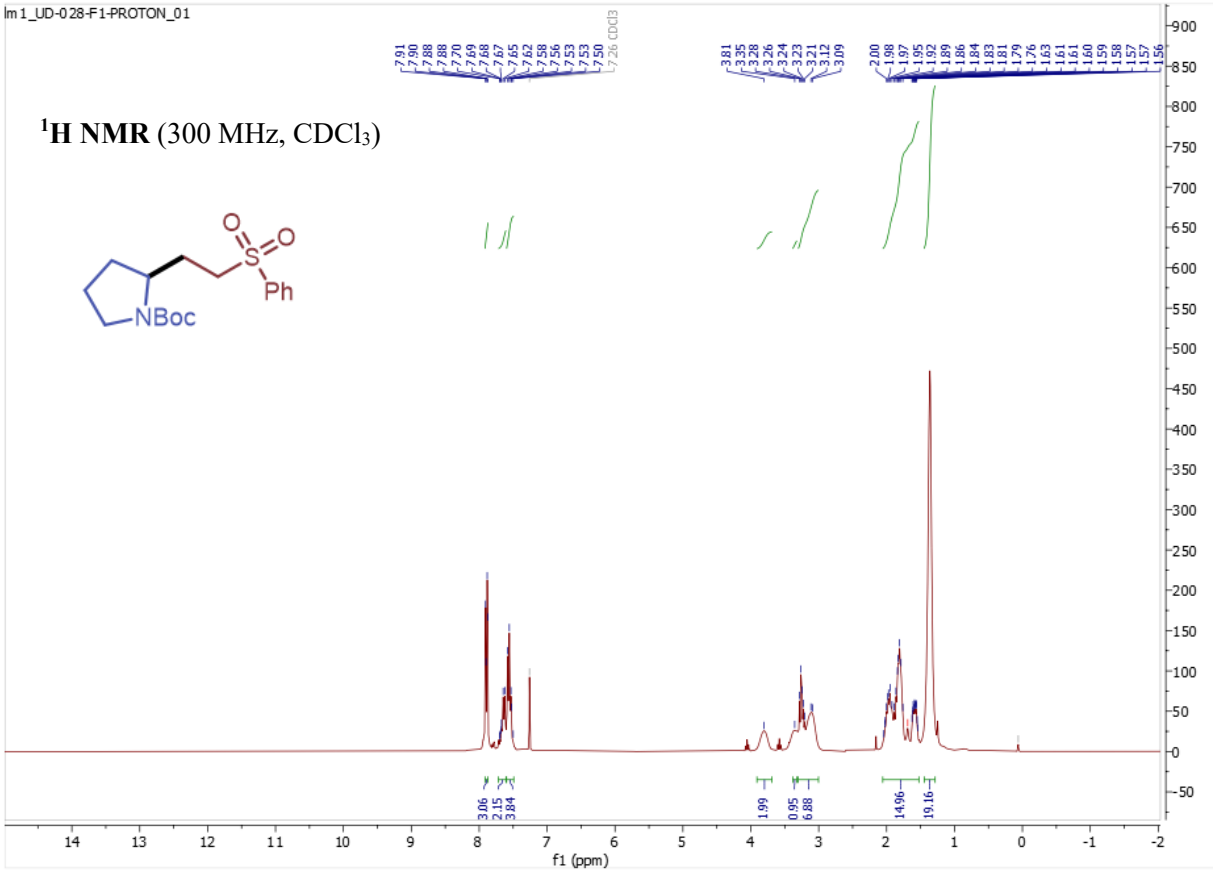



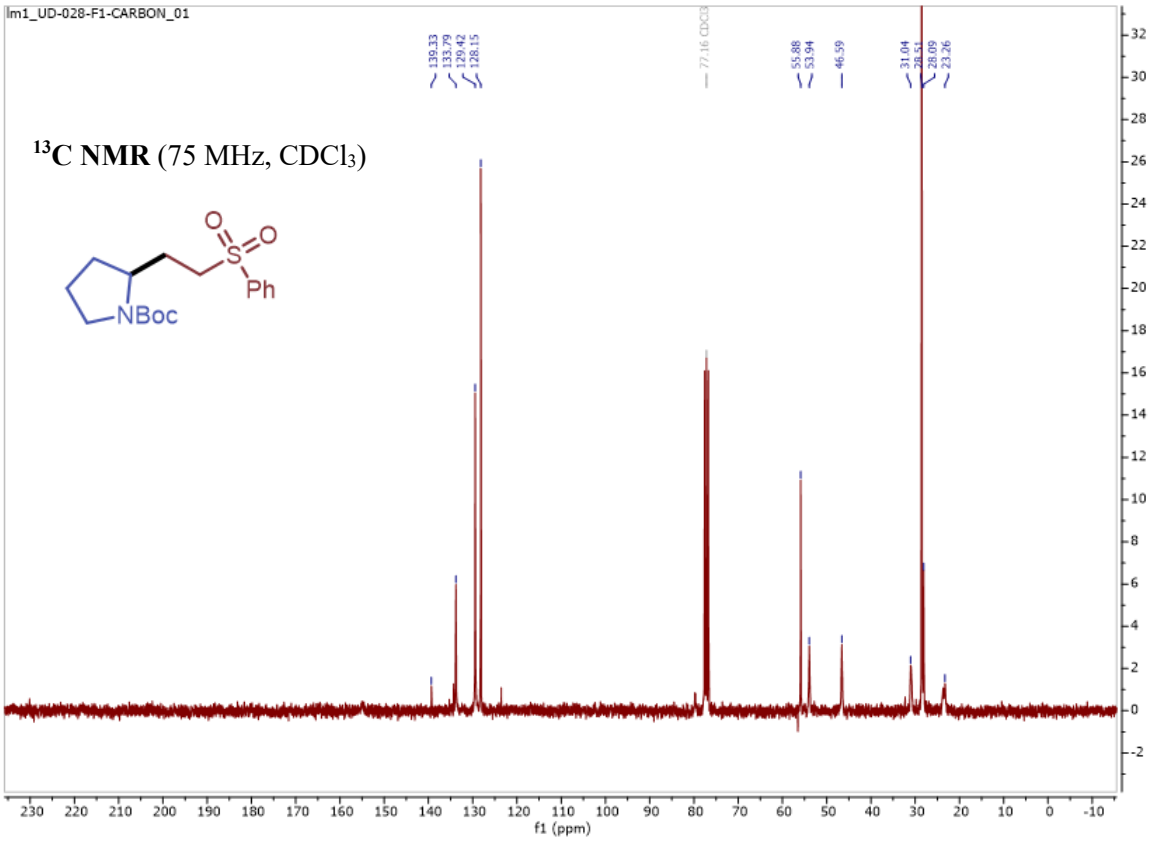
***tert*-Butyl 4-(2-(phenylsulfonyl)ethyl)piperidine-1-carboxylate (3k)**



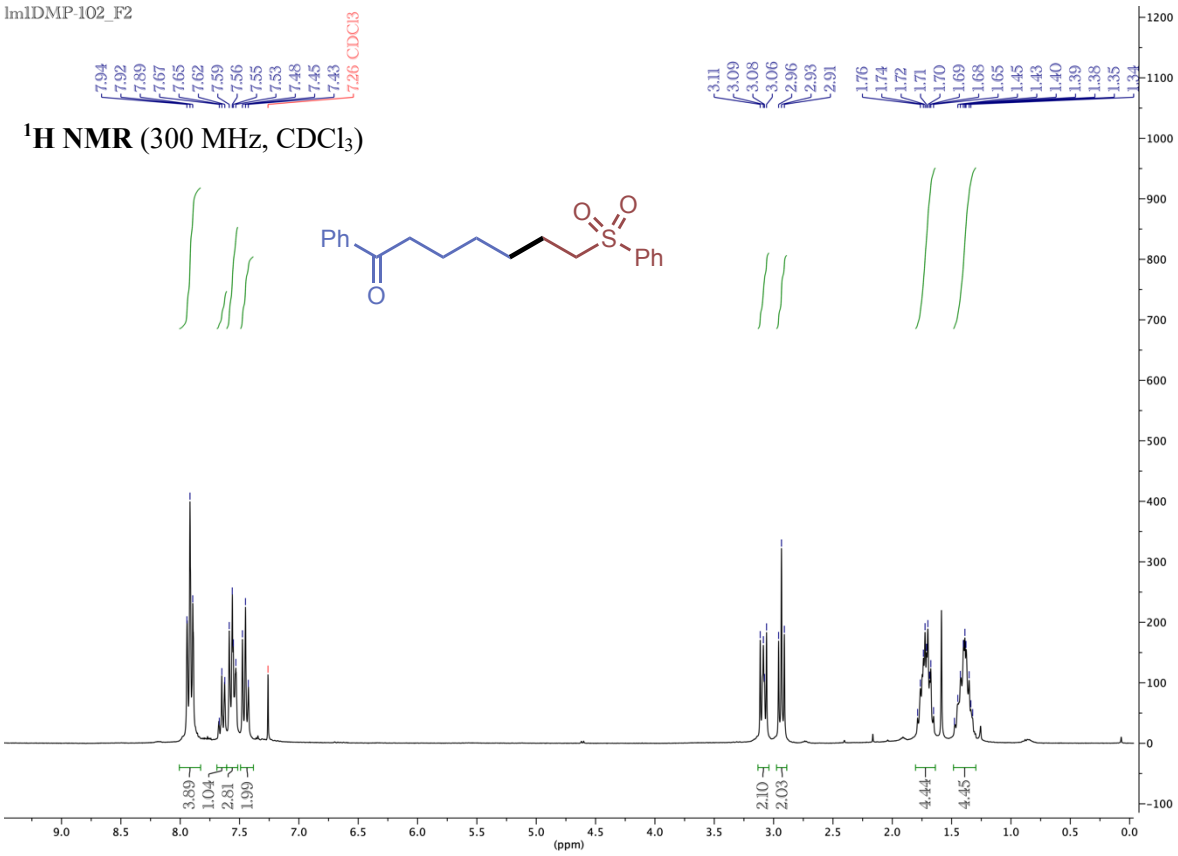



***tert*-Butyl-2-(2-(phenylsulfonyl)ethyl)pyrrolidine-1-carboxylate (3l) –** some signals are broad and split due to the presence of diastereomeric rotamers.

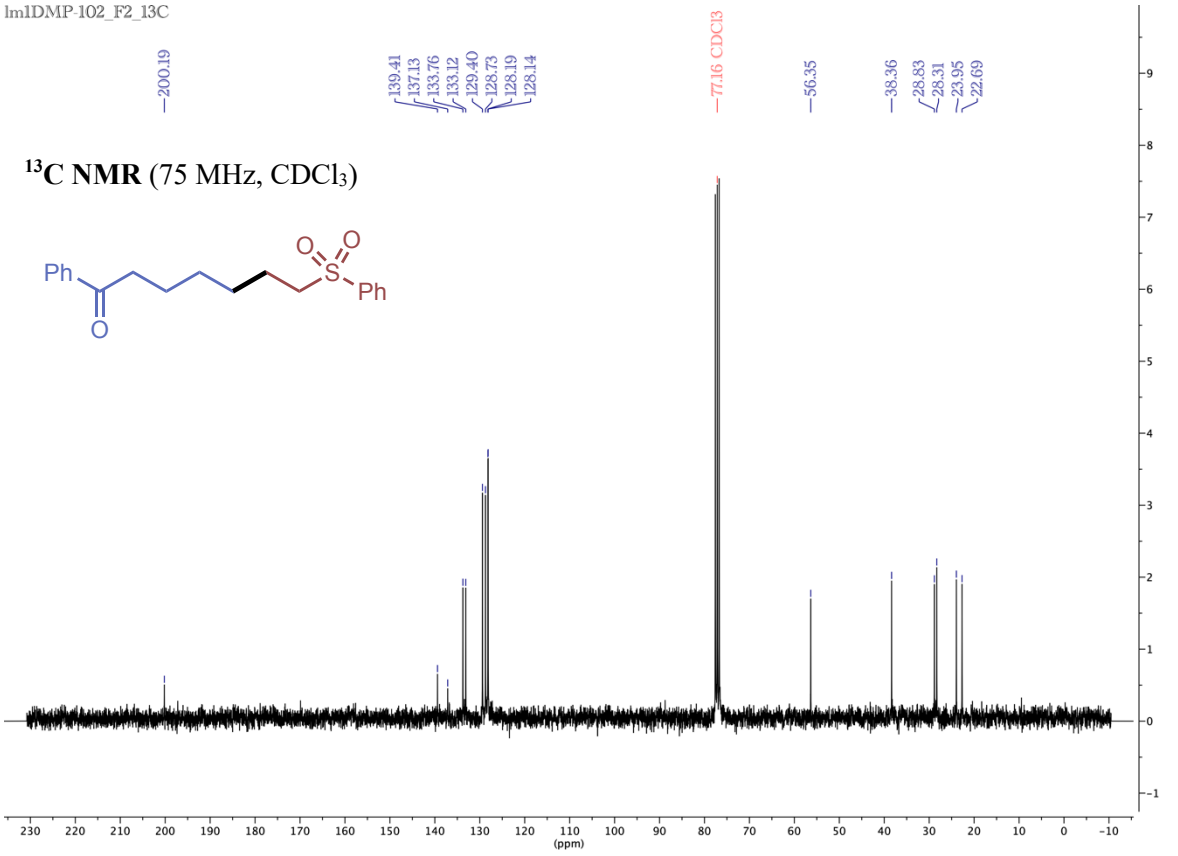


**1-Phenyl-7-(phenylsulfonyl)heptan-1-one (3m)**

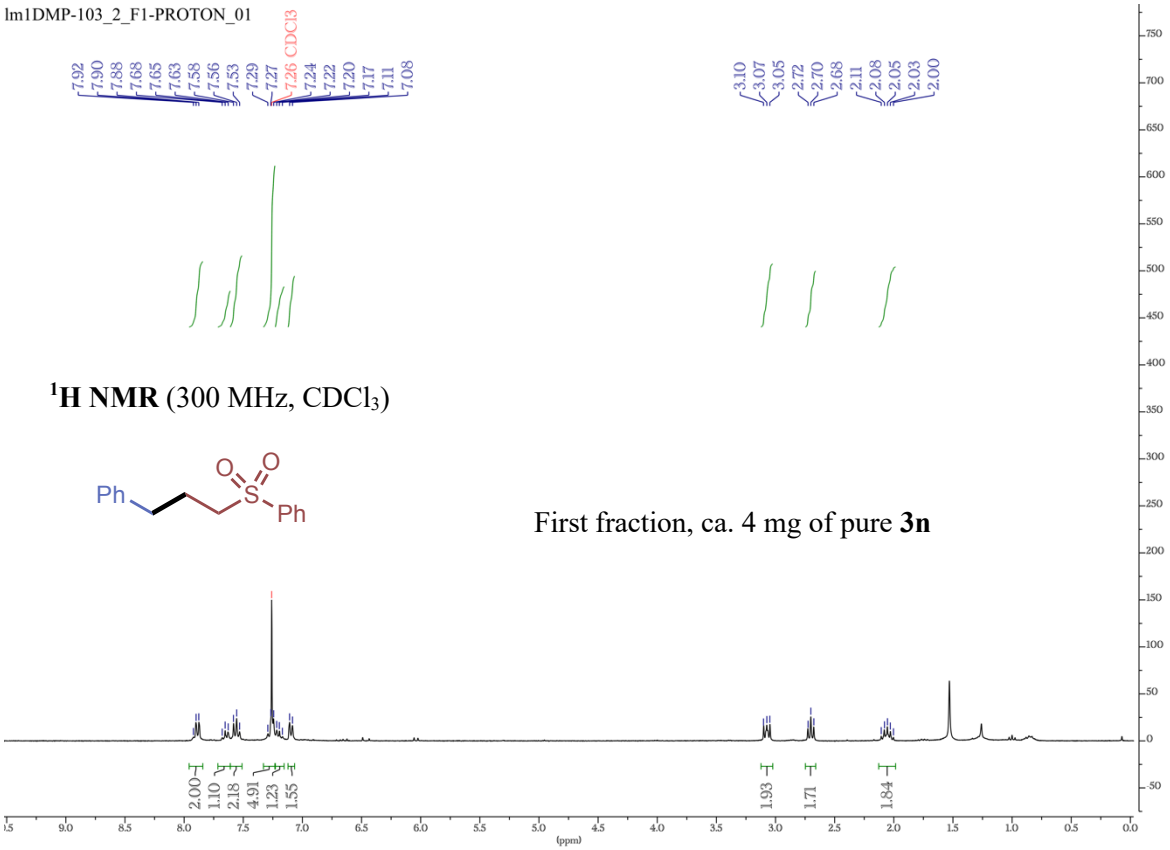



**$^{1}$H NMR** (300 MHz, $CDCl_3$)




**$^{13}$C NMR** (75 MHz, $CDCl_3$)

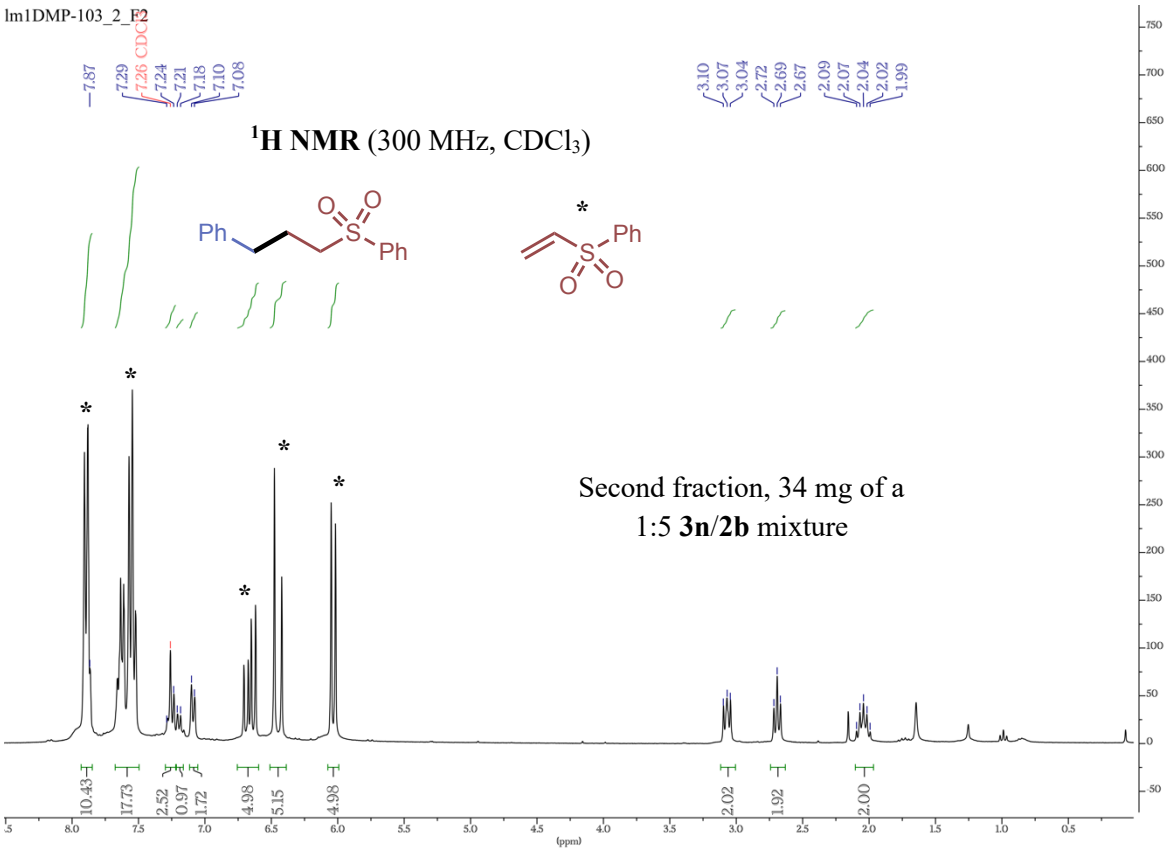
**(3-Phenylpropyl)sulfonyl]benzene (3n)**




$^1$**H NMR** (300 MHz, $CDCl_3$)



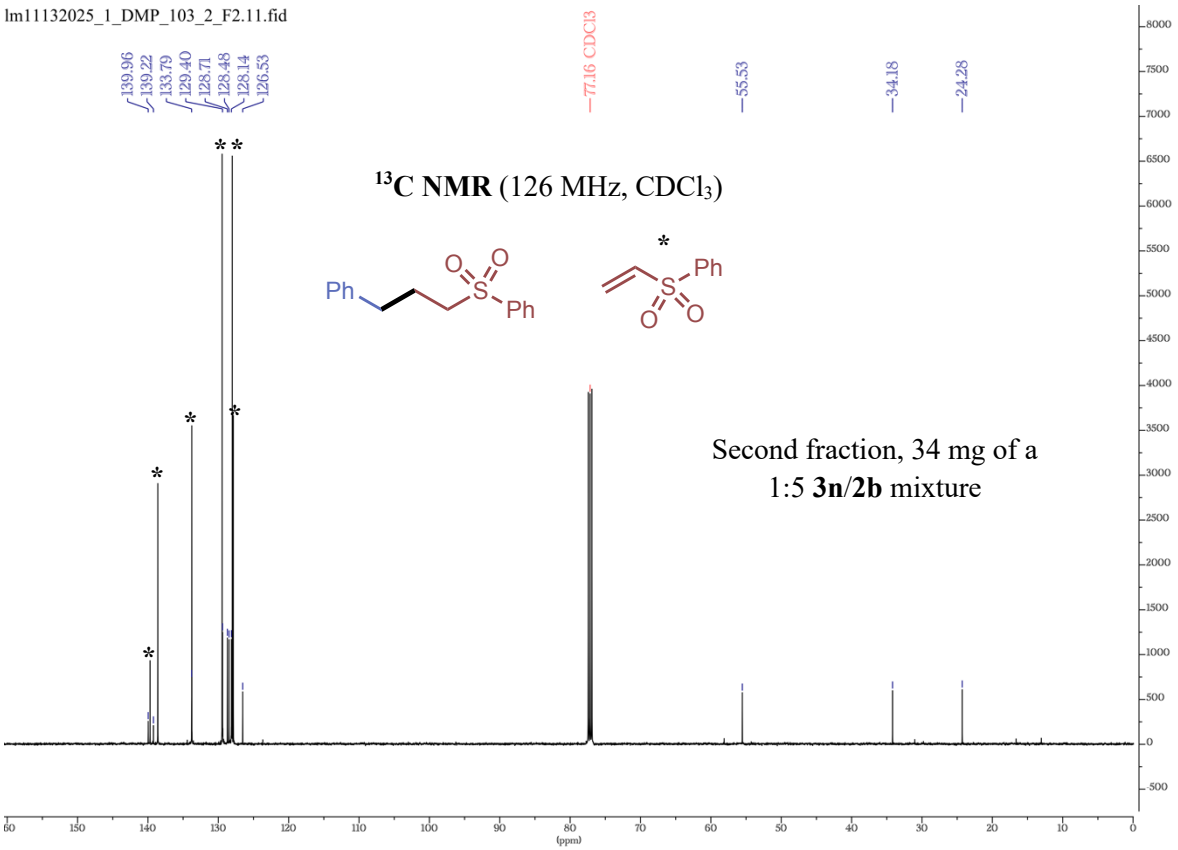

First fraction, ca. 4 mg of pure **3n**



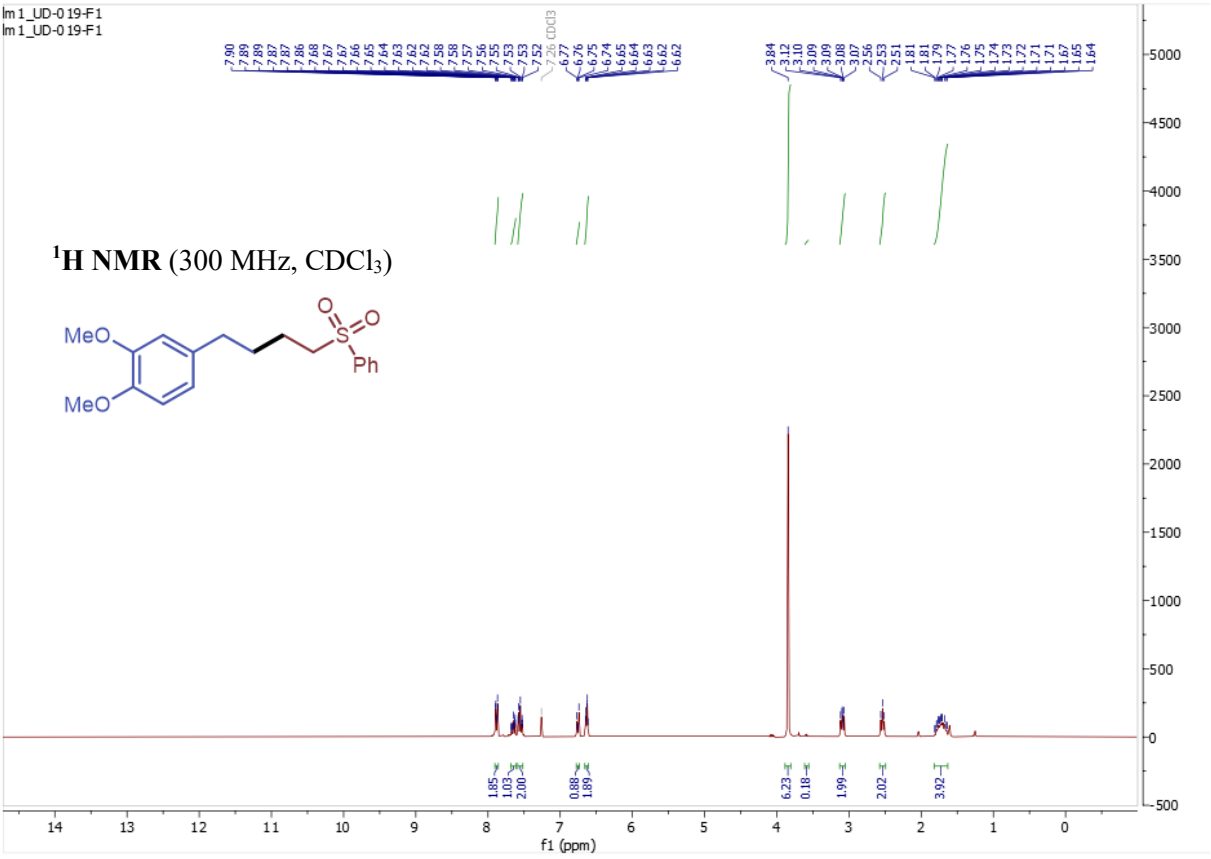

$^1$**H NMR** (300 MHz, $CDCl_3$)

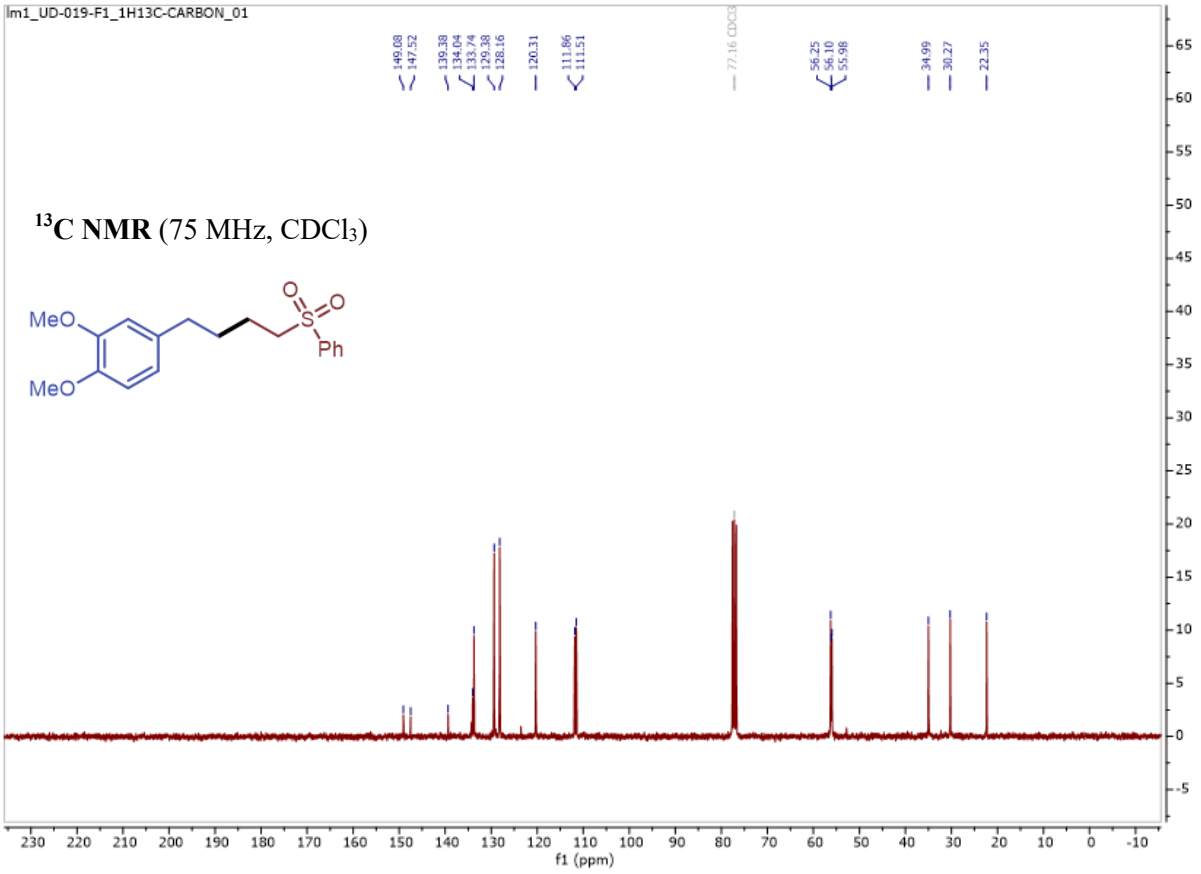



Second fraction, 34 mg of a
1:5 **3n**/**2b** mixture

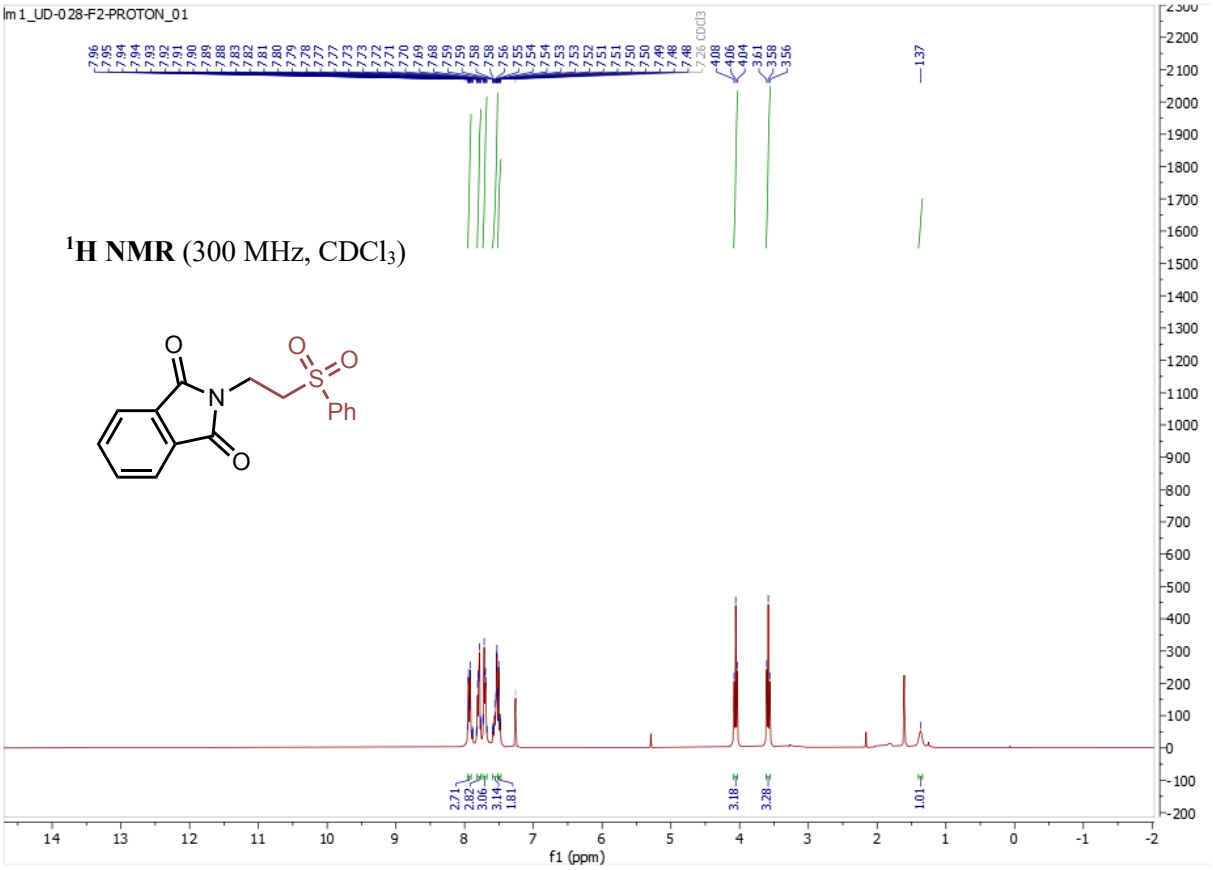

lm11132025_1_DMP_103_2_F2.11.fid
139.96
139.22
133.79
129.40
128.71
128.48
128.14
126.53
77.16 CDCl3
55.53
34.18
24.28
13C NMR (126 MHz, CDCl3)
Ph
O
O
S
Ph
Ph
S
O
O
Second fraction, 34 mg of a
1:5 3n/2b mixture
(ppm)

**1,2-Dimethoxy-4-(4-(phenylsulfonyl)butyl)benzene (3o)**



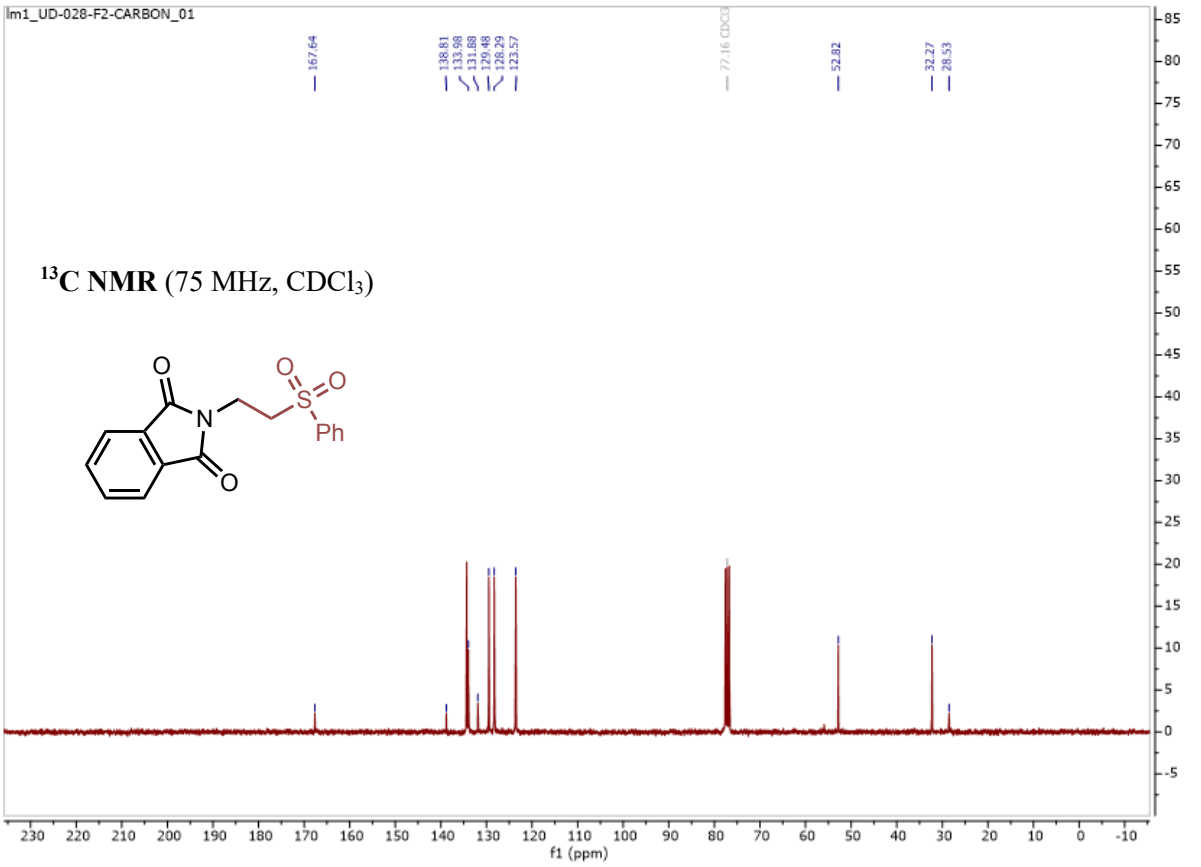



**2-(2-(Phenylsulfonyl)ethyl)isoindoline-1,3-dione (SI-2)**



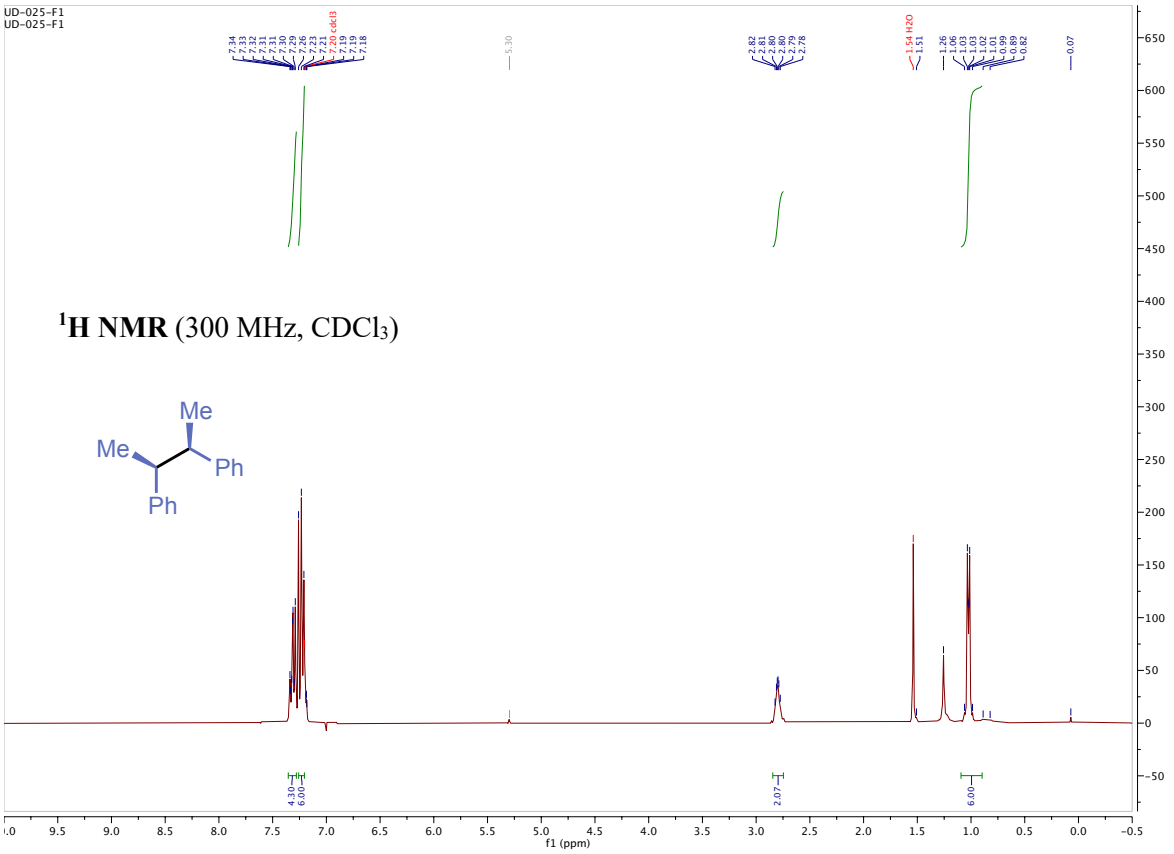

$^{1}$**H NMR** (300 MHz, $CDCl_3$)



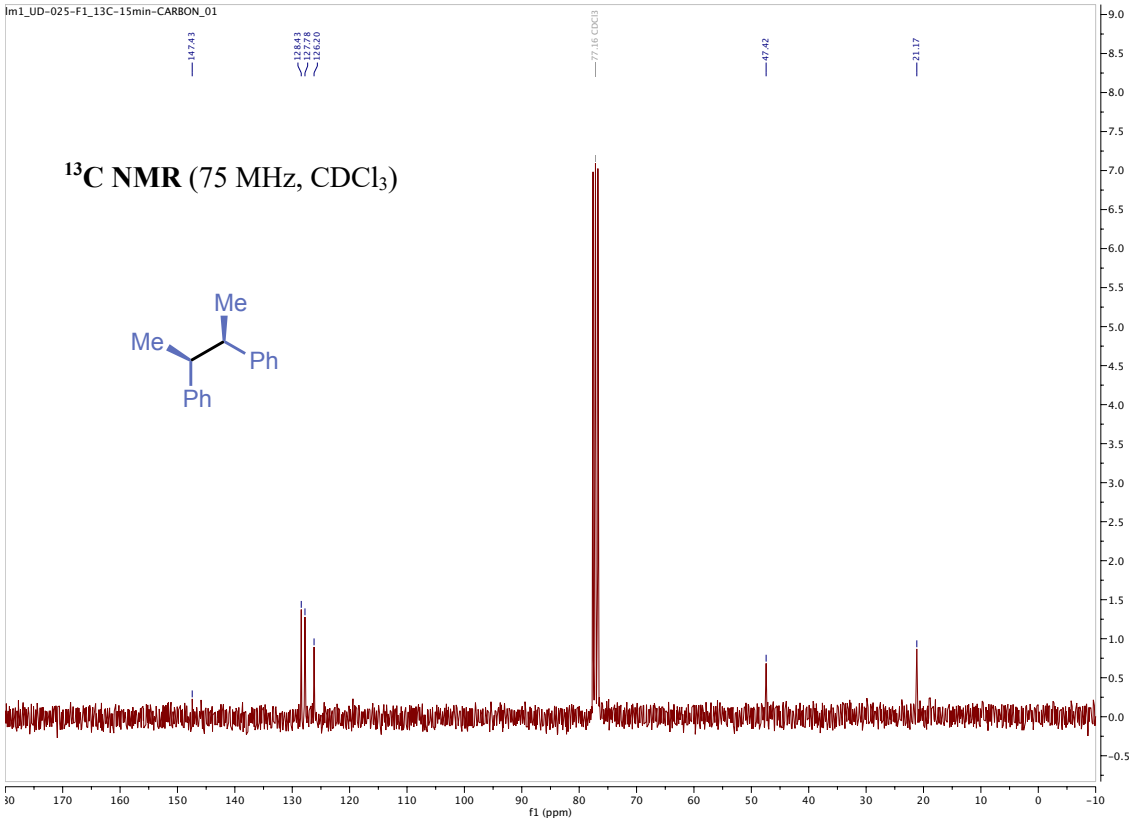

$^{13}$**C NMR** (75 MHz, $CDCl_3$)

**2,3-Diphenylbutane** (meso form) (**SI-3)**




**$^{1}$H NMR** (300 MHz, $CDCl_3$)




**$^{13}$C NMR** (75 MHz, $CDCl_3$)

# 10. References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