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A manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols has been developed. This electrochemical method provides access to alkoxy radicals from alcohols and exhibits a broad substrate scope, with various cyclopropanols and cyclobutanols converted into synthetically useful  $\beta$ - and  $\gamma$ -chlorinated ketones (40 examples). Furthermore, the combination of recirculating flow electrochemistry and continuous inline purification was employed to access products on gram scale.

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# Manganese-Catalyzed Electrochemical Deconstructive Chlorination of Cycloalkanols *via* Alkoxy Radicals

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Supporting Information Placeholder

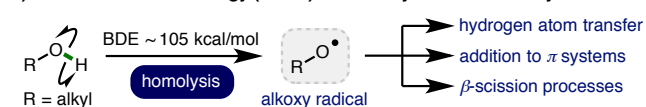
**ABSTRACT:** A manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols has been developed. This electrochemical method provides access to alkoxy radicals from alcohols and exhibits a broad substrate scope, with various cyclopropanols and cyclobutanols converted into synthetically useful  $\beta$ - and  $\gamma$ -chlorinated ketones (40 examples). Furthermore, the combination of recirculating flow electrochemistry and continuous inline purification was employed to access products on gram scale.

Alkoxy radicals are highly transient species that exhibit diverse reactivity, including hydrogen atom transfer,<sup>1</sup> addition to  $\pi$  systems<sup>2</sup> and  $\beta$ -scission processes (Scheme 1A).<sup>3</sup> The generation of alkoxy radicals directly from aliphatic alcohols is challenging, partly due to the high dissociation energy of RO–H bonds (~105 kcal/mol).<sup>2b</sup> As such, traditional methods for alkoxy radical generation involve the homolysis of weak oxygen-heteroatom bonds within pre-functionalized radical precursors in combination with radical initiators and/or thermal or photochemical activation (Scheme 1B).<sup>1,2</sup> Alternatively, transition metal salts can be employed in combination with stoichiometric oxidants (e.g.  $K_2S_2O_8$  or hypervalent iodine reagents) for the generation of alkoxy radicals.<sup>4</sup> Recent advances have developed photocatalytic approaches for alkoxy radical generation employing various radical precursors<sup>5</sup> including peroxides,<sup>6</sup> *N*-alkoxyphthalimides,<sup>7</sup> *N*-alkoxy-pyridiniums,<sup>8</sup> *N*-alkoxybenzimidazoles,<sup>9</sup> *N*-alkoxytriazoliums,<sup>10</sup> and unprotected alcohols.<sup>11</sup> Despite these important advances, many existing approaches require the use of pre-functionalized substrates, (super)stoichiometric reagents (generating waste/by-products) and/or precious metal (photo)catalysts.

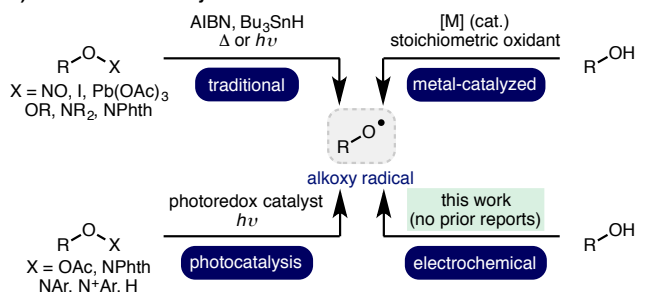
Organic electrochemistry represents one of the cleanest possible chemical processing technologies,<sup>12</sup> which has recently undergone a renaissance due partly to the increasing availability of standardized batch and flow electrochemical reactors.<sup>13</sup> By careful tuning of electrochemical parameters, specific single electron transfer processes can be targeted, accessing powerful radical intermediates.<sup>14</sup> Despite these characteristics, the development of an electrochemical method for the generation of alkoxy radicals from alcohols remains an unsolved problem.<sup>15</sup> To this end, herein we report the manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols *via* alkoxy radical intermediates,<sup>16</sup> accessing synthetically useful  $\beta$ - and  $\gamma$ -

## Scheme 1. Context and Outline of Electrochemical Strategy

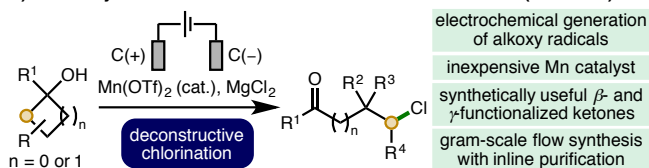
### A) Bond dissociation energy (RO–H) and alkoxy radical reactivity



### B) Generation of alkoxy radicals



### C) Mn-catalyzed electrochemical deconstructive chlorination (this work)



chlorinated ketones (Scheme 1C). Furthermore, by employing microreactor technology and recirculating flow, the electrochemical method can be performed on gram-scale, with continuous inline purification incorporated.

To commence our studies, 1-phenylcyclobutan-1-ol **1** was selected as the model substrate (Table 1). After extensive optimization,<sup>17</sup> it was found that an electrochemical system composed of  $MnCl_2 \cdot 4H_2O$  (10 mol %) as catalyst,<sup>18</sup>  $MgCl_2$  (5 equiv.) as chloride source and  $LiClO_4$  as supporting electrolyte in MeCN/AcOH (7:1, [1] = 0.05 M) using galvanostatic conditions ( $i$  = 10 mA,  $j_{anode}$  = 7.8 mA/cm<sup>2</sup>,  $Q$  = 3.73 F/mol) and graphite electrodes at 25 °C for 3 h under  $N_2$ , enabled the deconstructive chlorination of **1**, giving  $\gamma$ -chlorinated ketone **2** in 82% NMR yield (entry 1). No conversion occurs in the absence of electricity or the manganese catalyst (entries 2 and 3). Employing a constant cell potential ( $E_{cell}$  = 2.4 V) or variation of the current ( $i$  = 12.5 mA or 7.5 mA) lowered the NMR yield of **2** (entries 4–6). Employing TBAPF<sub>6</sub> as electrolyte (entry 7) or substituting the graphite cathode for Pt foil or Ni plate (entries 8 and 9) each had a negligible impact on conversion. However, upon evaluating alternative Mn(II) salts (entries 10 and 11), it was found that

**Table 1. Optimization of Electrochemical Process<sup>a</sup>**

entry	variation from "standard" conditions	yield <sup>b</sup> (%)
1	none	82
2	no electricity	< 2
3	no MnCl <sub>2</sub> ·4H <sub>2</sub> O	< 2
4	<i>E</i> <sub>cell</sub> = 2.4 V	66
5	<i>i</i> = 12.5 mA, <i>j</i> <sub>anode</sub> = 9.8 mA/cm <sup>2</sup>	74
6	<i>i</i> = 7.5 mA, <i>j</i> <sub>anode</sub> = 5.9 mA/cm <sup>2</sup>	80
7	TBAPF <sub>6</sub> instead of LiClO <sub>4</sub>	82
8	Pt foil cathode instead of graphite	82
9	Ni plate cathode instead of graphite	75
10	Mn(OAc) <sub>2</sub> ·4H <sub>2</sub> O instead of MnCl <sub>2</sub> ·4H <sub>2</sub> O	82
11	<b>Mn(OTf)<sub>2</sub> instead of MnCl<sub>2</sub>·4H<sub>2</sub>O</b>	<b>97 (78)</b>
↓ Mn(OTf) <sub>2</sub> as catalyst ↓		
12	LiCl instead of MgCl <sub>2</sub>	64
13	NaCl instead of MgCl <sub>2</sub>	< 2
14	MgCl <sub>2</sub> (2 equiv.)	76
15	Mn(OTf) <sub>2</sub> (5 mol %)	75
16 <sup>c</sup>	Q = 2 F/mol	67

<sup>a</sup>Reactions performed with 0.3 mmol of cyclobutanol **1** using the ElectraSyn 2.0 batch electrochemical reactor. [1] = 0.05 M. <sup>b</sup>Yield after 3 h as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. <sup>c</sup>1 hour 36 minutes reaction time.

97% conversion was obtained using Mn(OTf)<sub>2</sub> as catalyst, which was adopted for further optimization. Employing LiCl or NaCl as the chloride source was detrimental to conversion, presumably due to decreased solubility in MeCN/AcOH (entries 12 and 13). Gratifyingly, the quantities of MgCl<sub>2</sub> and Mn(OTf)<sub>2</sub> could be lowered to 2 equivalents and 5 mol %, respectively, without significant reduction in conversion (entries 14 and 15). A Faradaic efficiency of 67% was obtained when 2 F/mol of charge was passed (entry 16), which indicated that most of the electricity passing through the cell is utilized productively.

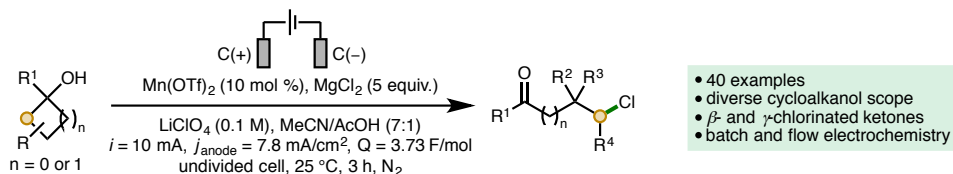
The full scope of the electrochemical process was explored starting with the deconstructive chlorination of cyclobutanols to form  $\gamma$ -functionalized ketones (Scheme 2A). From the outset, it was found that 1-arylcyclobutan-1-ols containing aromatic systems with electron-releasing groups at the 2- or 4-positions (e.g. 4-*t*Bu) or extended  $\pi$  systems (e.g. 4-Ph) undergo decomposition using the optimized reaction conditions (Table 1, entry 11). This instability was attributed to ionization of the C–OH bond in the presence of Brønsted and/or Lewis acids, forming stabilized carbocations that are unproductive for the desired transformation. In such cases, this issue was addressed by employing syringe pump addition of the substrate over 2 h and using TBAOAc as the supporting electrolyte. With a choice of two suitable reaction conditions in hand, a variety of 1-arylcyclobutan-1-ols were converted to the corresponding  $\gamma$ -chlorinated ketone products in good to excellent isolated yields (products **2–20**). Within the aryl unit, various alkyl and aryl substitution was tolerated at the 4-, 3- and 2- positions in addition to halides and electron-withdrawing substituents (e.g. 4-CF<sub>3</sub>). The electrochemical method exhibits good functional group tolerance as demonstrated by the presence of aldehyde,

carboxylic acid, methyl ester, primary amide, nitrile, benzylic primary alcohol and silyl ether functionalities present within products **14–20**. A selection of 1-alkylcyclobutan-1-ols were also converted into the corresponding  $\gamma$ -chlorinated ketones in good isolated yields (products **21–26**). Benzo-fused cyclobutanols participated in deconstructive chlorination, giving benzyl chloride products **27–31**, including the formation of 7-, 8-, 9- and 10-membered rings. This strategy was also applied to the formation of disubstituted cycloheptane **32** in 77% isolated yield. Additional substitution at the 2- and 3-positions of the cyclobutanol was tolerated, accessing  $\gamma$ -chlorinated ketones **33–35** in high yields. We also investigated the deconstructive chlorination of cyclopropanols (Scheme 2B). Gratifyingly, it was found that a representative selection of 1-arylcyclopropan-1-ols and 1-alkylcyclopropan-1-ols could be readily converted to the corresponding  $\beta$ -chlorinated ketones in good yields (**36–39**). Additional substitution is tolerated within the cyclopropanol, giving secondary radical derived product **40** as the major regioisomer. Furthermore, bicyclo[4.1.0]heptan-1-ol was converted to 3-chlorocycloheptan-1-one **41** in 48% isolated yield. At the current stage of development, the electrochemical method does not tolerate larger ring sizes with reduced ring strain. For example, despite assessing various reaction conditions, 1-phenylcyclopentan-1-ol underwent decomposition, whereas 1-phenethylcyclopentan-1-ol was unreactive.<sup>19</sup>

In order to demonstrate scalability, the batch process was translated to a flow electrochemical setup.<sup>20</sup> Employing the commercially available Ammonite8 flow electroreactor,<sup>21</sup> a variety of reaction parameters were evaluated including electrolyte loading, temperature, solvent ratio, residence time, charge and mixing efficiency (Scheme 2C). However, using MnCl<sub>2</sub>·4H<sub>2</sub>O (10 mol %) as catalyst, the conversion to **2** could not be increased beyond 20% using single-pass flow electrochemistry.<sup>17</sup> The yield was increased by applying the optimized reaction parameters to a recirculating flow electrochemical setup, which provided access to **2** in 84% isolated yield (Scheme 2D).<sup>22</sup> Advantageously, due to the decreased distance between the electrodes in flow, a supporting electrolyte was not required. Furthermore, by employing a 6-port 2-position switching valve, the flow could be redirected from recirculation to continuous inline purification (Scheme 2E). Once the electrochemical reaction was complete, the valve was switched from position 1 to position 2 to redirect the flow into the path of work-up solvents. The flow was passed through a mixing unit before entering a liquid/liquid phase separator containing a hydrophobic membrane that allowed separation of the organic layer, which was subsequently dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to provide 1.2 g of product. This flow setup, which combines recirculating flow electrochemistry and continuous inline purification for the first time, enabled the electrochemical process to be performed on gram scale.

Cyclic voltammetry was employed in order to gain mechanistic insight into the electrochemical process.<sup>17</sup> In accordance with the literature,<sup>18d</sup> the combination of Mn(OTf)<sub>2</sub> and MgCl<sub>2</sub> produced a new quasi-reversible redox event at 0.8 V vs Fc/Fc<sup>+</sup>,<sup>23</sup> which provided evidence for the generation of a Mn(III)X<sub>2</sub>Cl species from [Mn(II)X<sub>2</sub>Cl]<sup>−</sup>. Furthermore, a small increase in current was observed upon addition of 1-phenylcyclobutan-1-ol **1**, which suggested that Mn(III)X<sub>2</sub>Cl is consumed by **1**. When methyl ether cyclobutane **42** was employed as the substrate using the standard electrochemical reaction conditions, no  $\gamma$ -chlorinated ketone **2** was observed, with 82% starting material recovered (Scheme 3A). This indicated that the proposed

## Scheme 2. Substrate Scope – Batch and Flow Electrochemistry



### A) $\gamma$ -chlorinated ketones

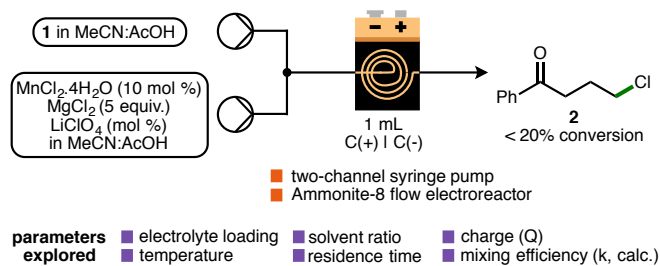
Substrate	Product	Yield	Substrate	Product	Yield	Substrate	Product	Yield
		2, R = H, 78% 3, R = 4-t-Bu, 80% <sup>a</sup> 4, R = 4-Me, 76% <sup>a</sup> 5, R = 3-Me, 44% 6, R = 2-Me, 43% <sup>a</sup>	7, R = 4-Ph, 41% <sup>a</sup> 8, R = 4-I, 62% <sup>b</sup> 9, R = 4-Br, 73% 10, R = 4-Cl, 90% 11, R = 4-F, 84% <sup>a</sup>	12, R = 4-CF <sub>3</sub> , 67% 13, R = 4-OCF <sub>3</sub> , 61% 14, R = 4-CHO, 35% 15, R = 4-CO <sub>2</sub> H, 47% 16, R = 4-CO <sub>2</sub> Me, 57%	17, R = 4-C(O)NH <sub>2</sub> , 61% 18, R = 4-CN, 40% 19, R = 4-CH <sub>2</sub> OH, 58% <sup>a</sup> 20, R = 4-CH <sub>2</sub> OTBS, 47% <sup>a</sup>			21, R = Et, 57% <sup>c</sup> 22, R = n-Bu, 60% 23, R = n-Hex, 47% 24, R = c-Hex, 42% 25, R = Bn, 68% 26, R = CH <sub>2</sub> Bn, 65%
		27, 30% <sup>d</sup>			28, n = 1, 54% 29, n = 2, 42% 30, n = 3, 53% 31, n = 4, 51%			32, 77% <sup>a</sup> (1:1 d.r.)
		33, 57% <sup>a</sup>			34, R = H, 90% 35, R = Me, 58%			

### B) $\beta$ -chlorinated ketones

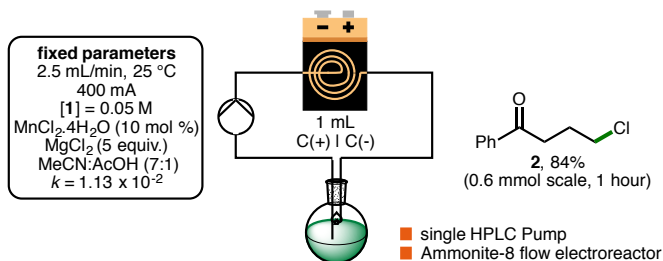
Substrate	Product	Yield	Substrate	Product	Yield	Substrate	Product	Yield
		36, R = Ph, 54% <sup>a</sup> 37, R = Bn, 47% <sup>a</sup> 38, R = CH <sub>2</sub> Bn, 67% <sup>a</sup> 39, R = n-Hex, 66% <sup>a</sup>			40, 70% <sup>a</sup> (93:7 r.r.)			41, 48% <sup>a</sup>

### Translation to Flow

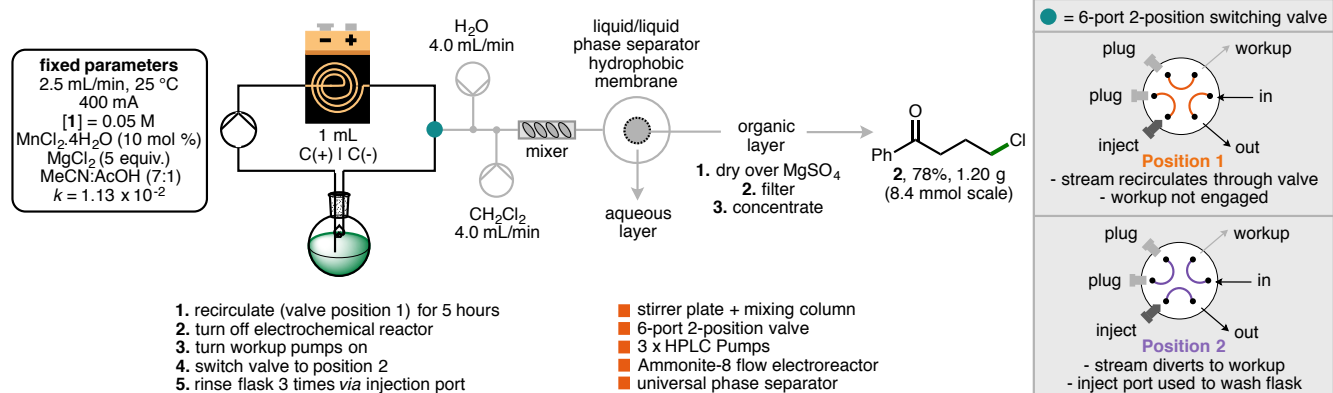
#### C) Parameter assessment - single-pass flow electrochemistry



#### D) Yield optimization - recirculating flow electrochemistry



#### E) Inline purification - recirculating flow electrochemistry + liquid/liquid extraction module

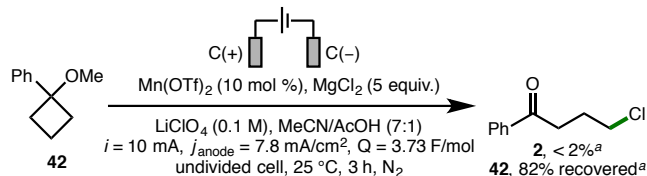


Reactions performed with 0.3 mmol of cycloalkanol using the ElectraSyn 2.0 batch electrochemical reactor with isolated yields after chromatographic purification quoted unless stated otherwise. <sup>a</sup>cycloalkanol was added over 2 h via syringe pump, TBAOAc (0.1 M) as electrolyte; <sup>b</sup>TBAOAc (0.1 M) as electrolyte; <sup>c</sup>yield as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard; <sup>d</sup>6 h

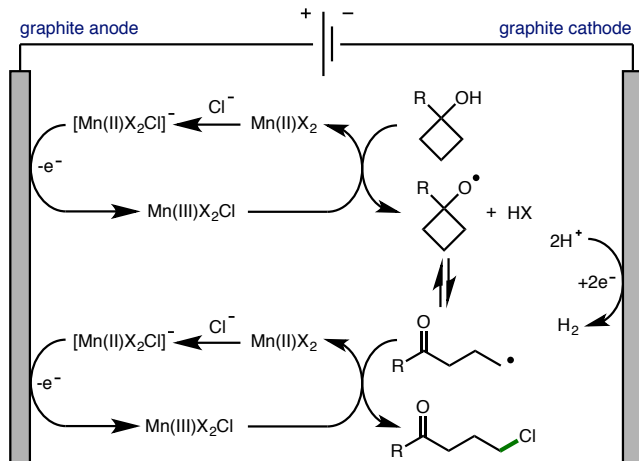


### Scheme 3. Mechanistic Studies

#### A) Mechanistic probe using methyl ether substrate



#### B) Plausible reaction mechanism



<sup>a</sup>Yield as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

Mn(III)X<sub>2</sub>Cl species does not promote cyclobutane ring opening in the absence of a hydroxyl functional group. As such, a plausible reaction mechanism initiates with the formation of [Mn(II)X<sub>2</sub>Cl]<sup>−</sup> from Mn(II)X<sub>2</sub> and MgCl<sub>2</sub>, which is oxidized at the anode to form Mn(III)X<sub>2</sub>Cl (Scheme 3B). This intermediate undergoes ligand exchange with the cycloalkanol, with subsequent homolysis generating an alkoxy radical, which can undergo reversible β-scission. Trapping of the transient primary carbon-centered radical with the persistent Mn(III)X<sub>2</sub>Cl species forms a new C–Cl bond.<sup>24</sup> Hydrogen gas is generated *via* proton reduction at the cathode.

In conclusion, we have developed the first electrochemical method for alkoxy radical generation from alcohols and utilized this for the manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols. The method is applicable across various cyclopropanols and cyclobutanols, accessing a broad range of synthetically useful β- and γ-chlorinated ketones (40 examples). Furthermore, the combination of recirculating flow electrochemistry and continuous inline purification was employed to access products on gram scale. Ongoing studies are focused on further applications of earth-abundant transition metals in synthetic organic electrochemistry and these results will be reported in due course.

### ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXX. Optimization data, experimental procedures, characterization of new compounds and spectral data (PDF)

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### Author Contributions

<sup>#</sup>BDWA and MDH contributed equally to this work.

### Notes

The authors declare no competing financial interest.

Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at <http://doi.org/XXXX> (accessed XXXX).

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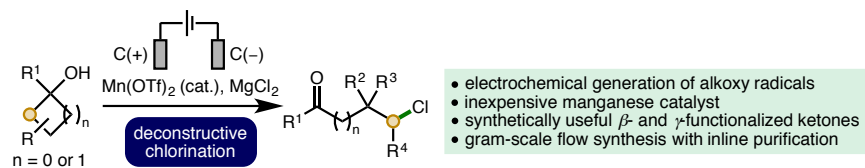
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A manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols has been developed. This electrochemical method provides access to alkoxy radicals from alcohols and exhibits a broad substrate scope, with various cyclopropanols and cyclobutanols converted into synthetically useful  $\beta$ - and  $\gamma$ -chlorinated ketones (40 examples). Furthermore, the combination of re-circulating flow electrochemistry and continuous inline purification was employed to access products on gram scale.



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## SUPPORTING INFORMATION

### Manganese-Catalyzed Electrochemical Deconstructive Chlorination of Cycloalkanols *via* Alkoxy Radicals

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## 1. General Information

Unless otherwise stated, all non-electrochemical reactions were conducted in flame-dried glassware under an atmosphere of dry nitrogen or argon, sealed with septum seals and were stirred with Teflon-coated magnetic stirrer bars. Unless stated otherwise, all electrochemical reactions were performed using oven-dried 10 mL ElectraSyn vials under an atmosphere of dry nitrogen, sealed with an ElectraSyn Teflon cap fitted with a graphite anode and graphite cathode (see Chapter 6 for reaction set-up), and were stirred with Teflon-coated magnetic stirrer bars. Dry tetrahydrofuran (THF), diethyl ether (Et<sub>2</sub>O) and acetonitrile (MeCN) were obtained after passing these previously degassed solvents through activated alumina columns (Mbraun, SPS-800). Tetra-*n*-butylammonium hexafluorophosphate (TBAPF<sub>6</sub>) and tetra-*n*-butylammonium tetrafluoroborate (TBABF<sub>4</sub>) were recrystallised from ethanol or water, respectively, and dried in the oven before use. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

All electrochemical reactions were conducted using an ElectraSyn 2.0 apparatus, purchased from IKA. Graphite, reticulated vitreous carbon (RVC), glassy carbon (GC) and Pt electrodes were purchased from IKA and are of uniform dimensions. Graphite electrodes were used as supplied from IKA or were cut from a sheet of carbon foil (2 mm thickness) purchased from Goodfellow. The electrodes were cut to the dimension of 8 mm × 52 mm using a Dremel 3000 multi-tool fitted with an SC545 EZ SpeedClic Diamond Cutting Wheel (38 mm dia.) attachment. Graphite electrodes could be used several times by renewing the top surface of the graphite. This was achieved by scraping away the top layer with a razor blade, sonicating in MeCN for 5 minutes, followed by oven-drying for 30 mins.

Cyclic voltammetry (CV) experiments were conducted using the ElectraSyn 2.0 CV function. The working electrode was a GC disc (3 mm dia.), the counter electrode was a Pt-plated electrode and the reference electrode was composed of silver wire in a 0.01 M solution of AgNO<sub>3</sub> in MeCN, separated from the bulk solution with a sintered glass frit.

Room temperature (rt) refers to 20-25 °C. Ice/water and CO<sub>2</sub>(s)/acetone baths were used to obtain temperatures of 0 °C and -78 °C respectively. All reactions involving heating were conducted using DrySyn blocks and a contact thermometer. *In vacuo* refers to reduced pressure through the use of a rotary evaporator.

Analytical thin layer chromatography was carried out using aluminium plates coated with silica (Kieselgel 60 F<sub>254</sub> silica) and visualisation was achieved using ultraviolet light (254 nm), followed by staining with a 1% aqueous KMnO<sub>4</sub> solution, or a 10% w/v solution of phosphomolybdic acid in ethanol. Flash column chromatography was performed according to the method of Still<sup>[1]</sup> using Kieselgel 60 silica in the solvent system stated using head-pressure by means of a compressed air line.

Melting points were recorded on an a Gallenkamp melting point apparatus and are reported corrected by linear calibration to benzophenone (47 - 49 °C) and benzoic acid (121 - 123 °C).

Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier Transform ATR spectrometer as thin films using a Pike MIRacle ATR accessory. The most intense peaks and structurally important peaks are quoted. Absorption maxima ( $\nu_{max}$ ) are recorded in wavenumbers ( $\text{cm}^{-1}$ ).

$^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra were obtained on a Bruker Avance 300 (300 MHz  $^1\text{H}$ , 75 MHz  $^{13}\text{C}$ ), Bruker Avance 400 (400 MHz  $^1\text{H}$ , 101 MHz  $^{13}\text{C}$ , 376 MHz  $^{19}\text{F}$ ) or a Bruker Avance 500 (500 MHz  $^1\text{H}$ , 126 MHz  $^{13}\text{C}$ , 471 MHz  $^{19}\text{F}$ ) spectrometer at rt in the solvent stated. Chemical shifts are reported in parts per million (ppm) relative to the residual solvent signal. All coupling constants,  $J$ , are quoted in Hz. Multiplicities are reported with the following symbols: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and combinations of these were used to denote higher order multiplicities.

High resolution mass spectrometry (HRMS,  $m/z$ ) data was acquired at Cardiff University on a Micromass LCT Spectrometer.

“Petrol” refers to the fraction boiling in the range of 40-60 °C unless otherwise stated.

Current density values for the anode,  $j_{anode}$ , were calculated by dividing the current,  $i$ , passed during electrolysis by the exposed active surface area of the electrode. The exposed active surface of the electrode was calculated to be the submerged surface of the electrode that was directly facing the other electrode, since electrons travel through the shortest available circuit (See Figure S1). See relative electrochemical General Procedures for specific current density values.

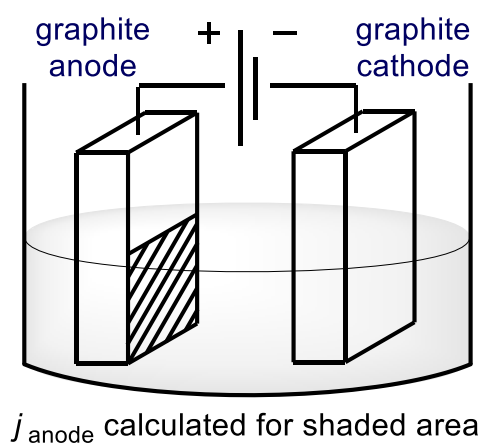


Figure S1 – Current density calculation visual aid

## 2. Experimental and Characterization Data

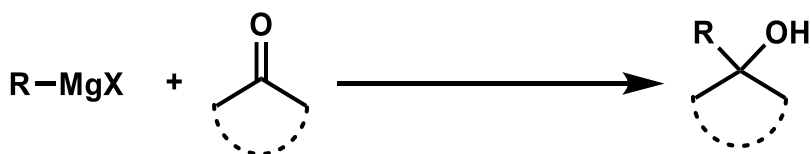
### 2.1 General Procedures – Substrate Synthesis

#### 2.1.1 General Procedure A – Generation and Addition of Grignard Reagents to Cycloalkanones



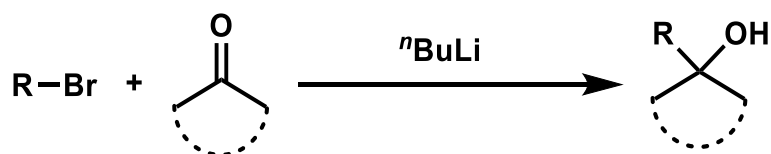
To a three-necked RBF fitted with a condenser, a glass stopper, and a septum seal was added magnesium turnings (1.65 eq.) and the system was flame-dried under a high vacuum. After cooling under a  $\text{N}_2$  atmosphere, a crystal of iodine was added followed by THF (1 M with respect to RBr). RBr (1.5 eq.) was added dropwise and the mixture was stirred at rt for 5 min, or until the exotherm had finished. The reaction mixture was then heated at reflux for 1-3 h. Upon cooling to 0 °C, THF was added (0.2 M with respect to cycloalkanone), followed by drop-wise addition of the cycloalkanone (1.0 eq.). The resulting mixture was left to warm to rt and stirred overnight. A saturated solution of  $\text{NH}_4\text{Cl}$  (aq.) was added and the mixture was diluted with EtOAc. The layers were separated, and the aqueous layer was further extracted with EtOAc ( $\times 2$ ). The combined organics were dried ( $\text{MgSO}_4$ ), filtered, and concentrated under reduced pressure. The resultant crude material was purified by flash column chromatography to afford the desired compound.

#### 2.1.2 General Procedure B – Addition of Commercially-Available Grignard Reagents to Cycloalkanones



To a flame-dried RBF fitted with a septum seal was added a pre-made Grignard reagent (1.5 eq.) under a  $\text{N}_2$  atmosphere. After cooling to 0 °C, the cycloalkanone (1.0 eq.) was added dropwise. After complete addition, the resulting mixture was left to warm to rt and stirred overnight. A saturated solution of  $\text{NH}_4\text{Cl}$  (aq.) was added, followed by a few drops of 1 M  $\text{HCl}$  (aq.), and the mixture was diluted with  $\text{Et}_2\text{O}$ . The layers were separated, and the aqueous layer was further extracted with  $\text{Et}_2\text{O}$  ( $\times 2$ ). The combined organics were dried ( $\text{MgSO}_4$ ), filtered, and concentrated under reduced pressure. The resultant crude material was purified by flash column chromatography to afford the desired compound.

#### 2.1.3 General Procedure C – Generation and Addition of Organolithium Reagents to Cycloalkanones

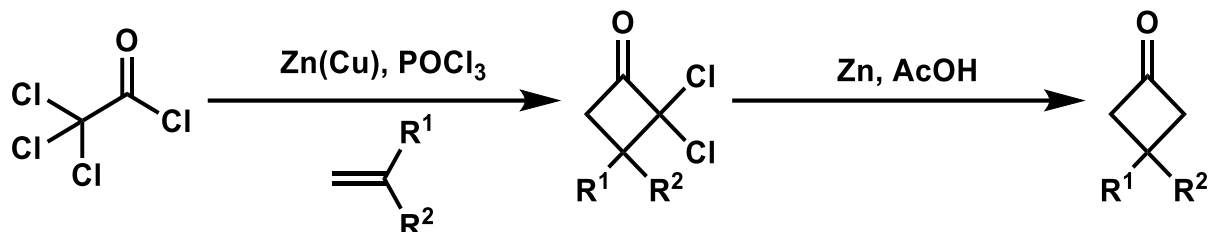


To a flame-dried RBF fitted with a septum seal was added a solution of alkyl or aryl halide (1.3 eq.) in THF (0.3 M). The mixture was cooled to -78 °C, and a solution of *n*-butyllithium (solution in hexanes, 1.3 eq.) was added dropwise. The solution was left to stir for 1-3 h before adding a solution of the cycloalkanone (1.0 eq.) in THF (1.0 M) dropwise. The reaction mixture was left to stir for 1-3 h, whilst



warming to rt. Water was added dropwise, followed by extraction with EtOAc ( $\times 3$ ). The combined organics were dried ( $\text{MgSO}_4$ ), filtered, and concentrated under reduced pressure. The resultant crude material was purified by flash column chromatography to afford the desired compound.

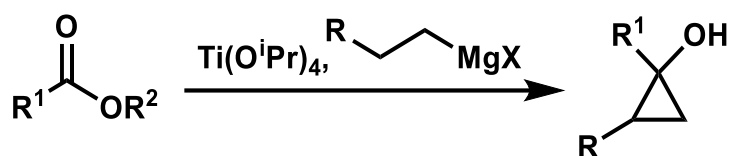
#### 2.1.4 General Procedure D – Synthesis of Substituted Cyclobutanones



To a flame-dried three-necked RBF fitted with an addition funnel, a reflux condenser and a septum seal was added  $\text{Zn}(\text{Cu})$  couple<sup>[2]</sup> (2.5 eq.), alkene (1.0 eq.) and  $\text{Et}_2\text{O}$  (0.5 M). The dropping funnel was charged with trichloroacetyl chloride (2.0 eq.), phosphoryl chloride (2.0 eq.) and  $\text{Et}_2\text{O}$  (1.0 M). The contents of the dropping funnel were added slowly over  $\sim 2$  h. The reaction mixture was stirred at  $70^\circ\text{C}$  for 16 h. Upon cooling, the suspension was filtered through a pad of celite, washing with  $\text{Et}_2\text{O}$  and the filtrate was concentrated to  $\sim 25\%$  of its original volume. To the resultant mixture was cautiously added water and the organic layer was further washed with a saturated solution of  $\text{NaHCO}_3$  (aq.). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $\times 3$ ) and the combined organic layers were dried ( $\text{MgSO}_4$ ), filtered and concentrated. The resultant oil was submitted to the next step without further purification.

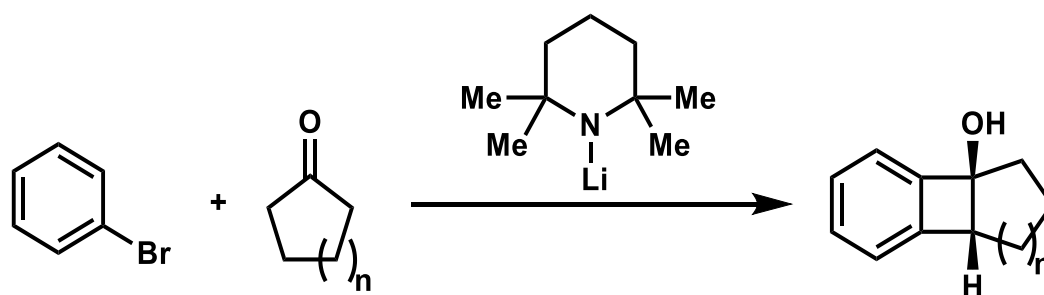
The crude residue from the previous step was dissolved in  $\text{AcOH}$  (0.5 M) and  $\text{Zn}$  dust (4.0 eq.) was added. The reaction mixture was stirred at  $70^\circ\text{C}$  for 2 h. Acetic acid was removed under reduced pressure and the resultant mixture was filtered through a pad of celite, washing with  $\text{Et}_2\text{O}$ . The filtrate was concentrated and the crude residue was purified by flash column chromatography to afford the desired compound.

#### 2.1.5 General Procedure E – Synthesis of Cyclopropanols via Kulinkovich Reaction



To a flame-dried RBF fitted with a septum seal was added the ester (1.0 eq.),  $\text{Ti}(\text{O}^i\text{Pr})_4$  (1.4 eq.), and THF (0.16 M with respect to the ester). The mixture was cooled to  $0^\circ\text{C}$  and a solution of Grignard reagent (2.8 eq.) was added dropwise. After complete addition, the resulting mixture was left to warm to rt and stirred overnight. After completion water was added and the resulting precipitate was filtered under vacuum through celite and washed with EtOAc. The layers of the filtrate were separated, and the aqueous layer was further extracted with EtOAc ( $\times 2$ ). The combined organics were dried ( $\text{MgSO}_4$ ), filtered, and concentrated under reduced pressure. The resultant crude material was purified by flash column chromatography to afford the desired compound.

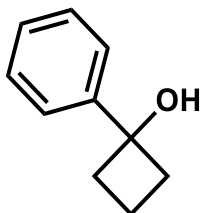
### 2.1.6 General Procedure F – Synthesis of Benzo-fused Cyclobutanols via Benzyne



To a solution of 2,2,6,6-tetramethylpiperidine (2.5 eq.) in THF (0.83 M) at  $-78\text{ }^{\circ}\text{C}$  was added *n*-butyllithium (2.5 eq.) dropwise and the resulting mixture was stirred for 20 min. A solution of ketone (1.0 eq.) in THF (0.67 M) was added dropwise followed by aryl halide (1.0 eq.) and the reaction mixture was stirred for 5 h at  $-78\text{ }^{\circ}\text{C}$ . The reaction was quenched by the addition of a saturated solution of  $\text{NH}_4\text{Cl}$  (aq.) and extracted with EtOAc ( $\times 2$ ). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford the desired compound.

## 2.2 Characterization of Substrates

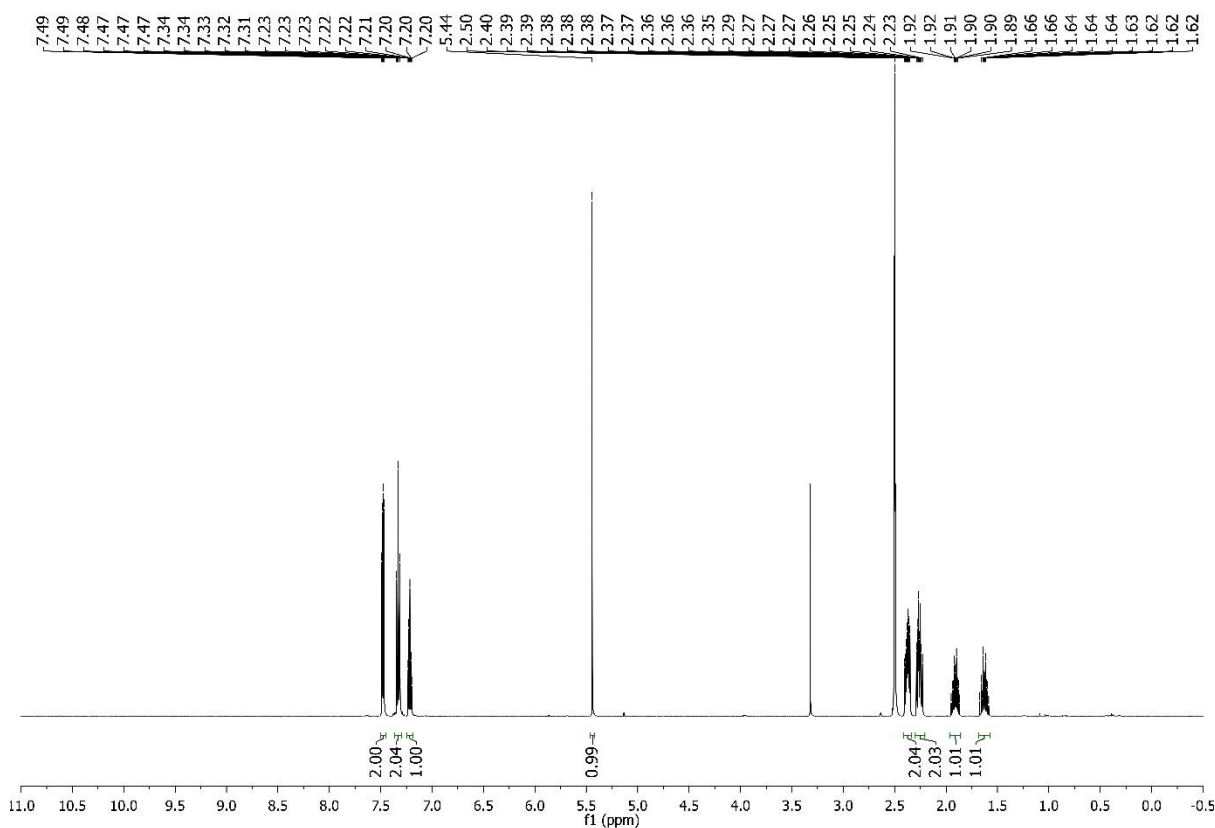
### 1-Phenylcyclobutan-1-ol (**1**)

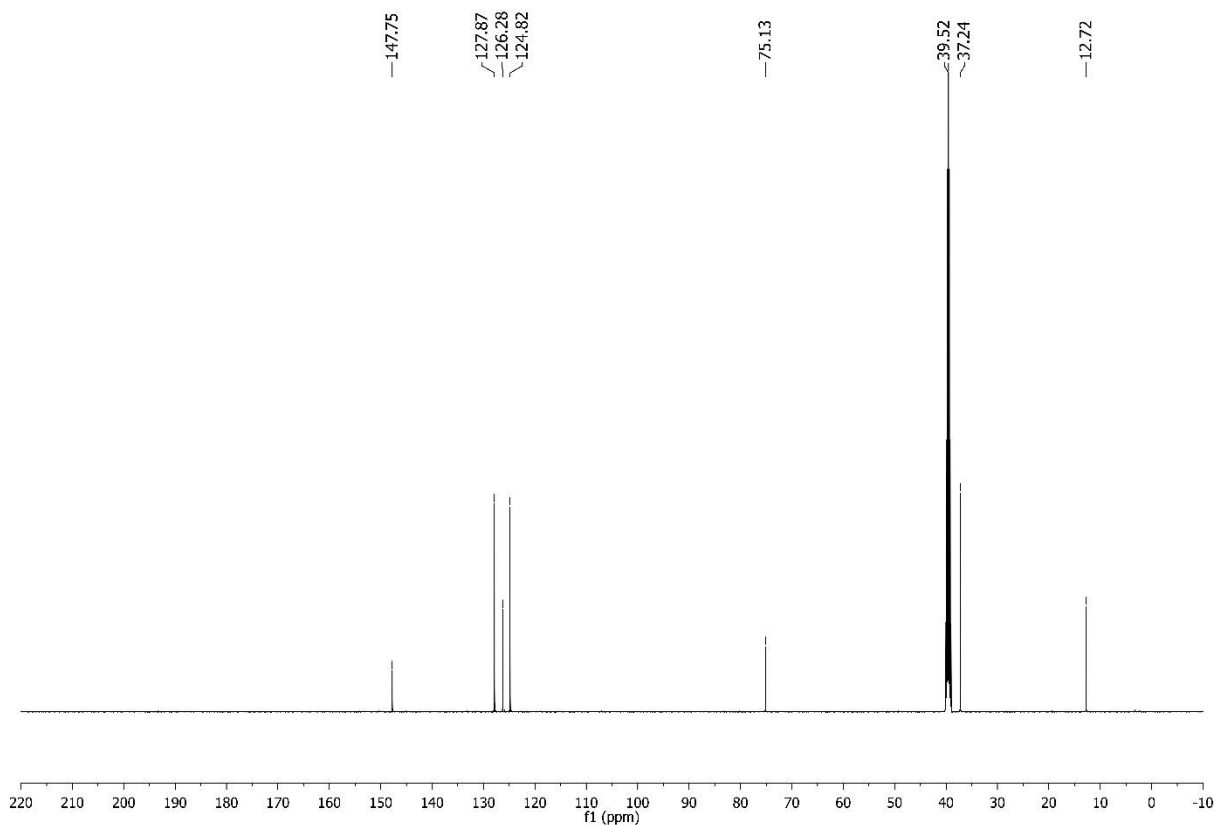


Prepared according to General Procedure A using magnesium turnings (2.01 g, 82.5 mmol), bromobenzene (7.90 mL, 75.0 mmol), and cyclobutanone (3.75 mL, 50.0 mmol). The crude residue was purified by flash column chromatography (5→10% EtOAc/Petrol, silica gel) to afford **1** (5.92 g, 80%) as a colourless solid.

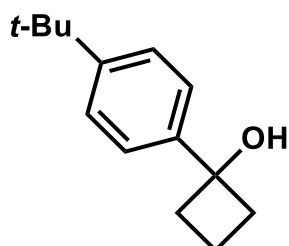
$R_f$  = 0.13 (10% EtOAc/Petrol); **M.p.**: 43–46 °C (lit.<sup>[3]</sup> 41–42 °C);  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  = 7.50 – 7.46 (m, 2H), 7.35 – 7.30 (m, 2H), 7.24 – 7.19 (m, 1H), 5.44 (s, 1H), 2.42 – 2.33 (m, 2H), 2.31 – 2.20 (m, 2H), 1.98 – 1.85 (m, 1H), 1.70 – 1.55 (m, 1H);  $^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  = 147.7, 127.9, 126.3, 124.9, 75.1, 37.2, 12.7.

These data are consistent with those previously reported in the literature.<sup>[4]</sup>



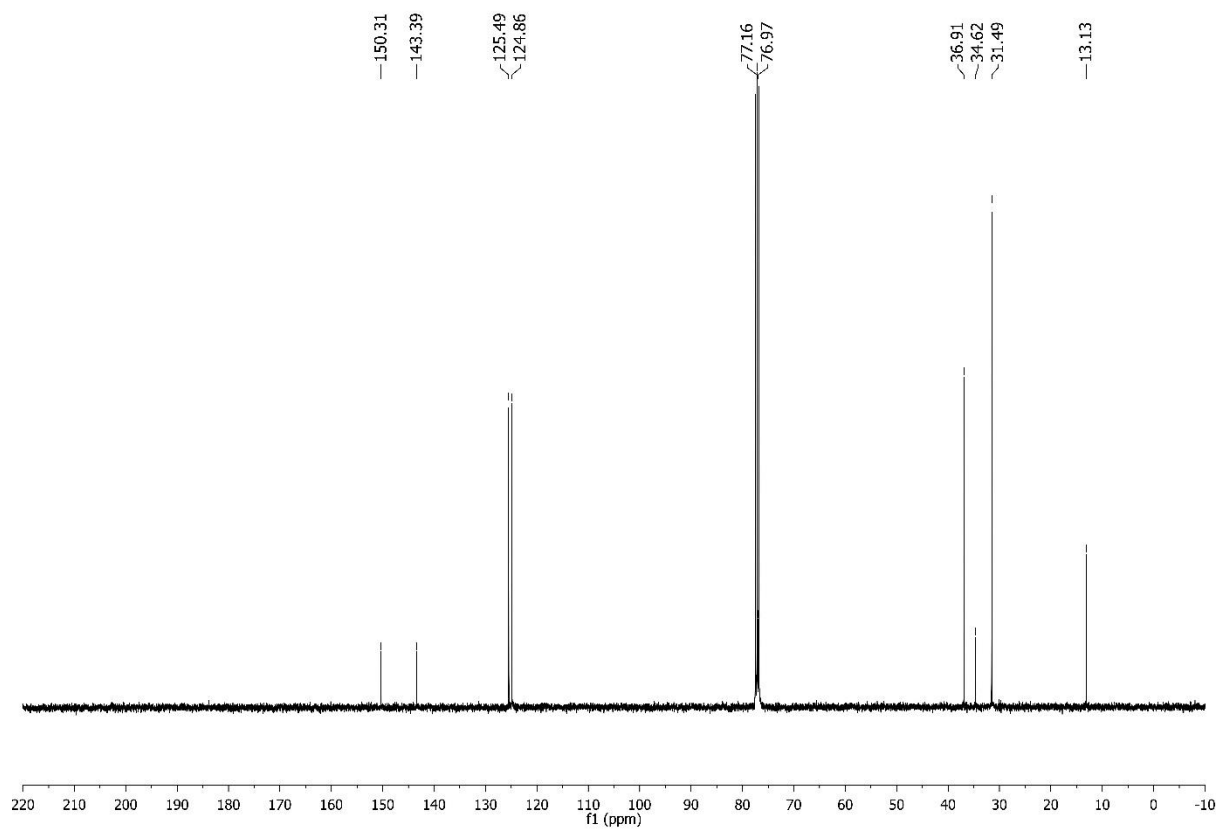
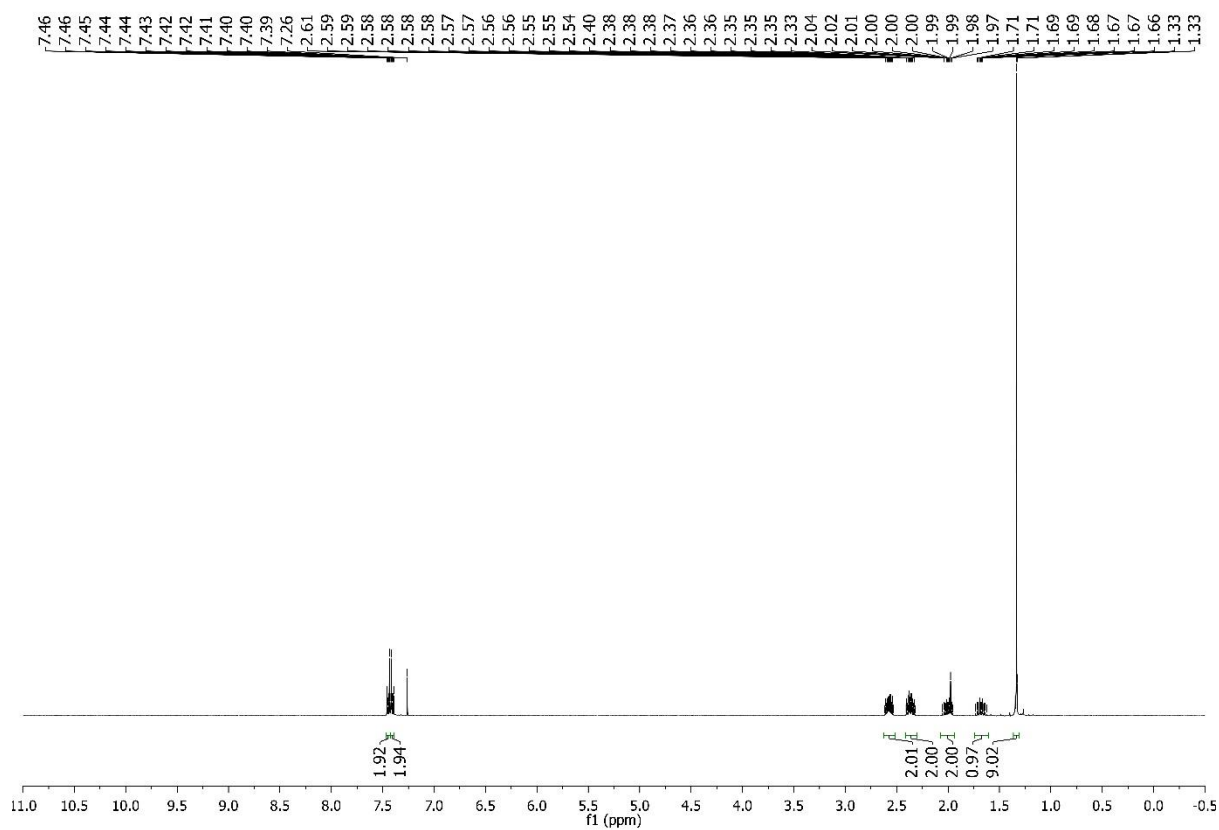


**1-(4-(*Tert*-butyl)phenyl)cyclobutan-1-ol (S1)**



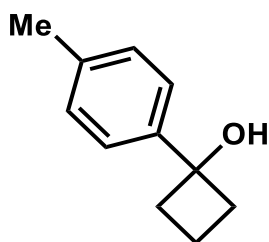
Prepared according to General Procedure A using magnesium turnings (201 mg, 8.25 mmol), 1-bromo-4-(*tert*-butyl)benzene (1.30 mL, 7.50 mmol), and cyclobutanone (374  $\mu$ L, 5.00 mmol). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S1** (571 mg, 56%) as a colourless solid.

**R<sub>f</sub>** = 0.17 (10% EtOAc/Petrol); **M.p.:** 74–77 °C; **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3329 (br), 2961, 2866, 2361, 2342, 1508, 1464, 1395, 1364, 1275, 1261, 1233, 1138, 1111, 961, 845, 839, 764, 750, 567; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.47 – 7.43 (m, 2H), 7.43 – 7.39 (m, 2H), 2.64 – 2.51 (m, 2H), 2.44 – 2.29 (m, 2H), 2.08 – 1.93 (m, 2H), 1.75 – 1.60 (m, 1H), 1.33 (s, 9H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 150.3, 143.4, 125.5, 124.9, 77.0, 36.9, 34.6, 31.5, 13.1; **HRMS** (EI<sup>+</sup>) [C<sub>14</sub>H<sub>20</sub>O] requires [M–H<sub>2</sub>O] 186.1409, found 186.1404.





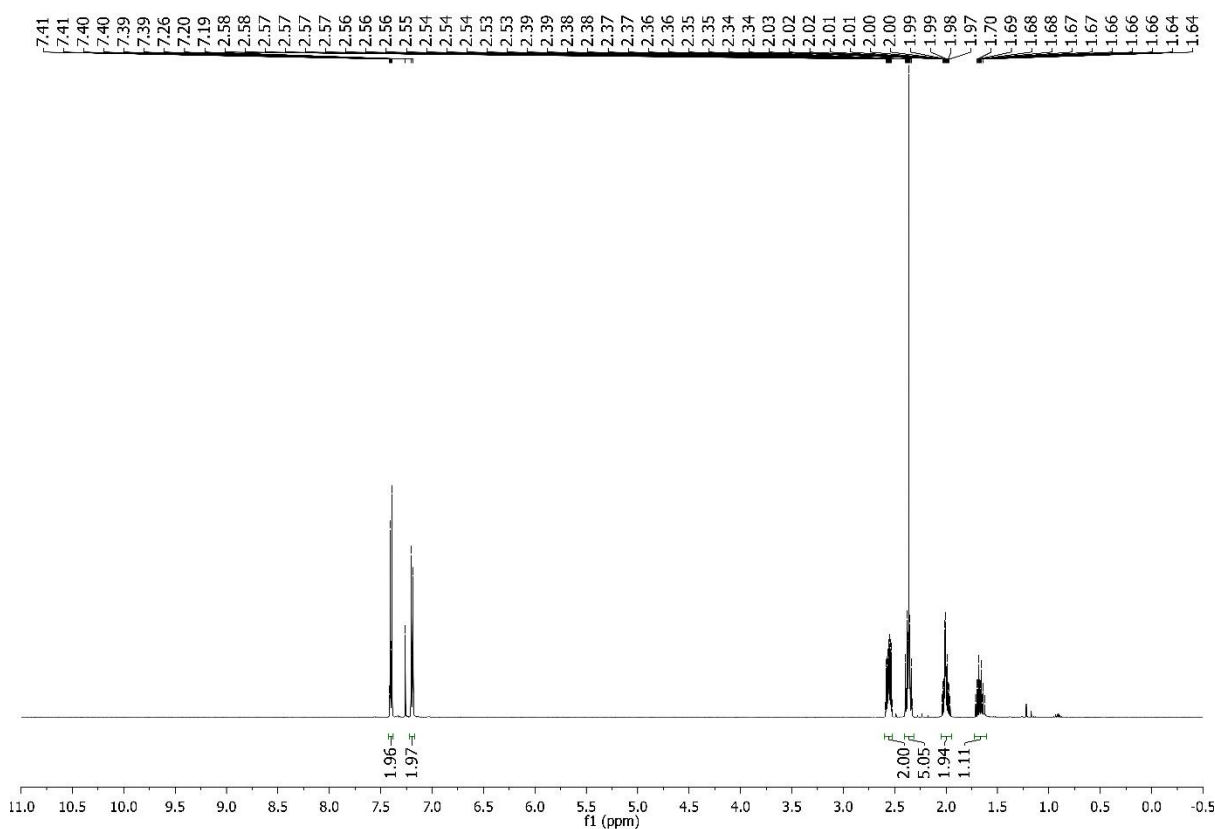
### 1-(*p*-Tolyl)cyclobutan-1-ol (**S2**)

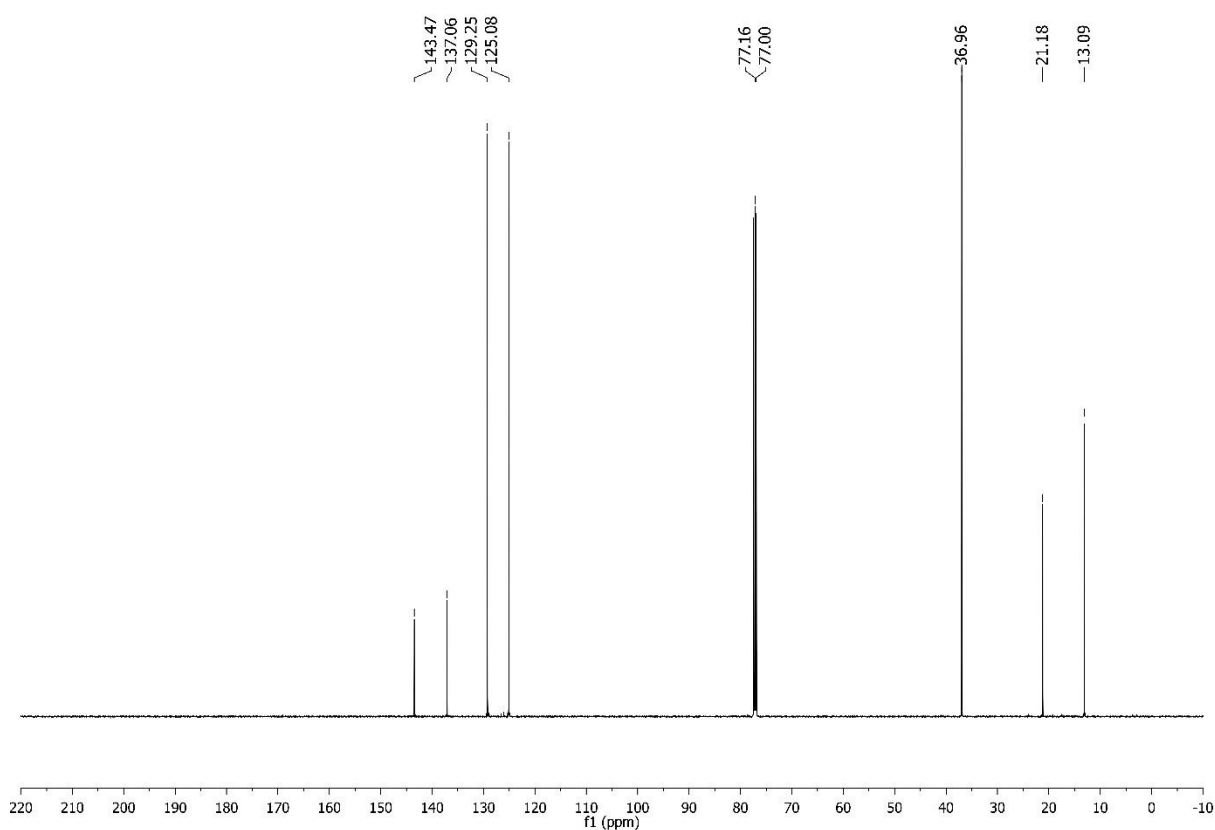


Prepared according to General Procedure A using magnesium turnings (201 mg, 8.25 mmol), 4-bromotoluene (923  $\mu$ L, 7.50 mmol), and cyclobutanone (374  $\mu$ L, 5.00 mmol). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S2** (582 mg, 72%) as a yellow oil.

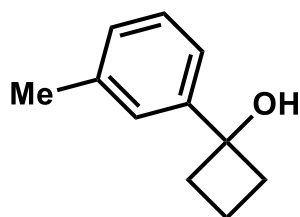
$R_f$  = 0.17 (10% EtOAc/Petrol);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.42 – 7.38 (m, 2H), 7.21 – 7.18 (m, 2H), 2.59 – 2.52 (m, 2H), 2.40 – 2.33 (m, 5H), 2.04 – 1.96 (m, 2H), 1.72 – 1.62 (m, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 143.5, 137.1, 129.3, 125.1, 77.0, 37.0, 21.2, 13.1.

These data are consistent with those previously reported in the literature.<sup>[4]</sup>





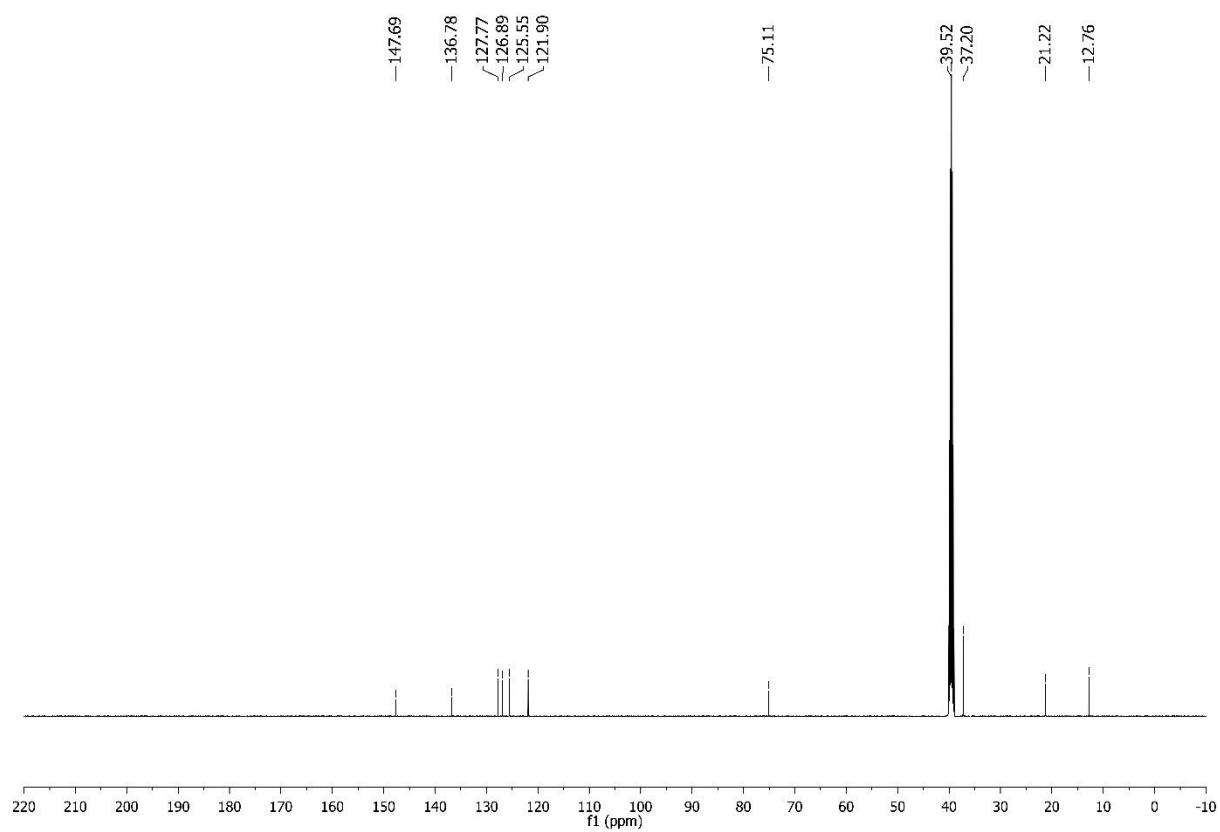
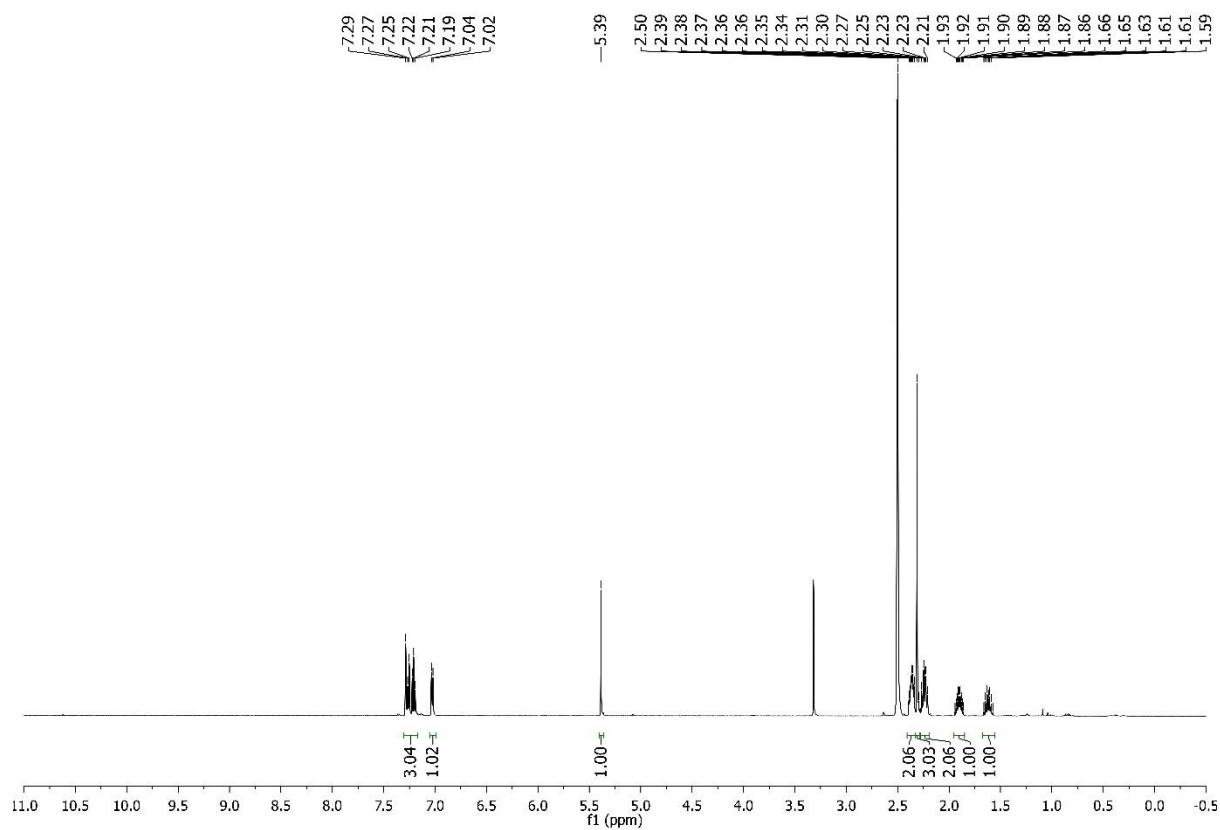
### 1-(*m*-Tolyl)cyclobutan-1-ol (**S3**)



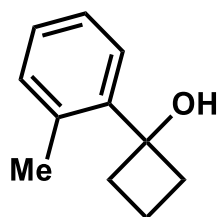
Prepared according to General Procedure A using magnesium turnings (201 mg, 8.25 mmol), 3-bromotoluene (910  $\mu$ L, 7.50 mmol), and cyclobutanone (374  $\mu$ L, 5.00 mmol). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S3** (375 mg, 46%) as a yellow oil.

$R_f$  = 0.36 (10% EtOAc/Petrol);  $^1\text{H NMR}$  (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 7.29 (s, 1H), 7.26 (d,  $J$  = 8.0 Hz, 1H), 7.21 (app. t,  $J$  = 7.5 Hz, 1H), 7.03 (d,  $J$  = 7.5 Hz, 1H), 5.39 (s, 1H), 2.40 – 2.33 (m, 2H), 2.31 (s, 3H), 2.29 – 2.19 (m, 2H), 1.96 – 1.83 (m, 1H), 1.68 – 1.55 (m, 1H);  $^{13}\text{C NMR}$  (126 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 147.7, 136.8, 127.8, 126.9, 125.6, 121.9, 75.1, 37.2, 21.2, 12.8.

These data are consistent with those previously reported in the literature.<sup>[4]</sup>

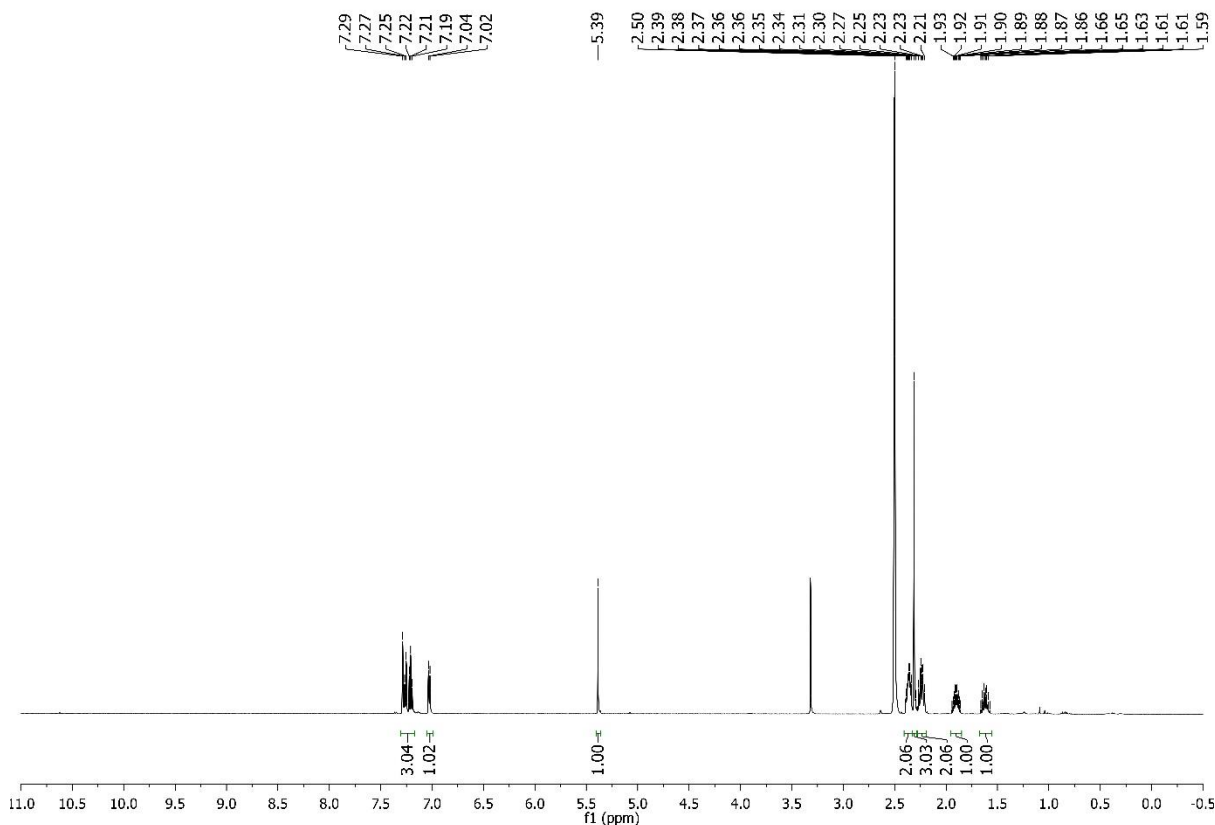


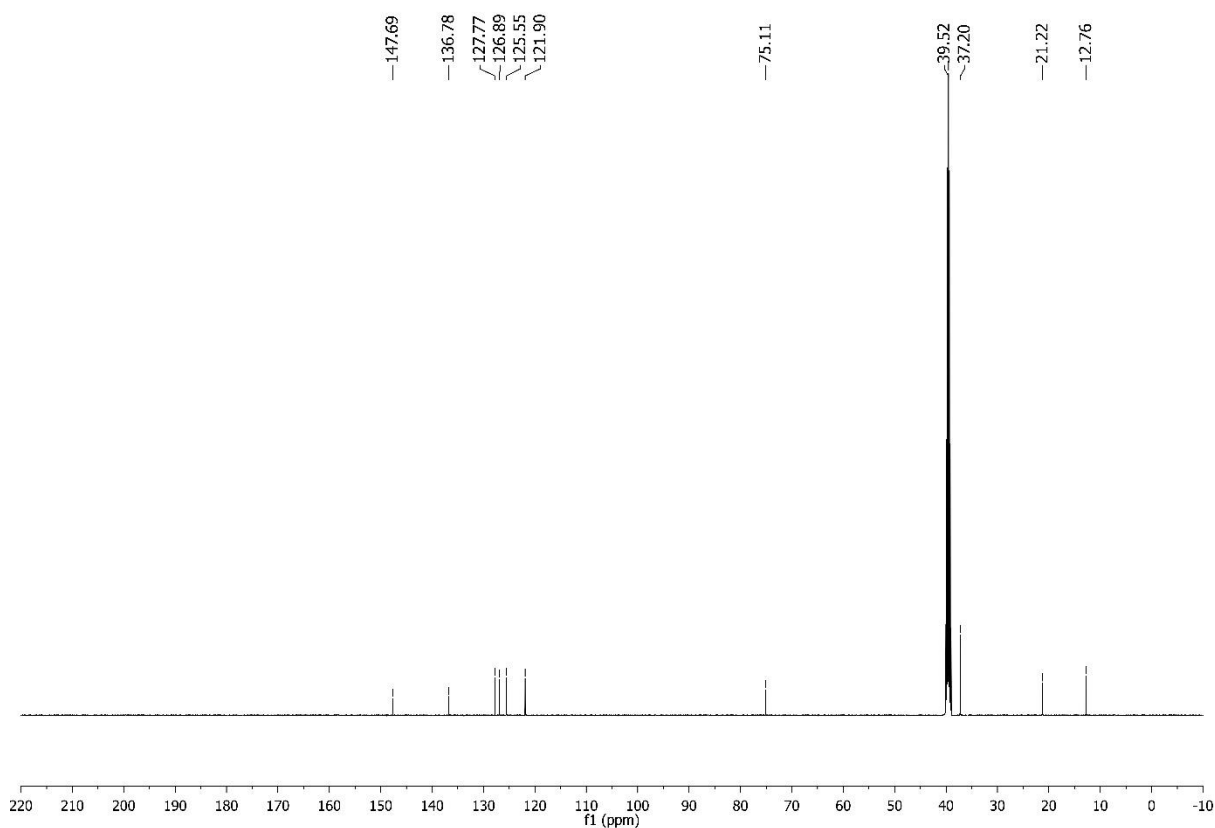
### 1-(*o*-Tolyl)cyclobutan-1-ol (**S4**)



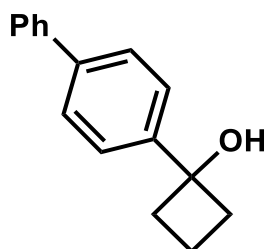
Prepared according to General Procedure A using magnesium turnings (201 mg, 8.25 mmol), 2-bromotoluene (902  $\mu$ L, 7.50 mmol), and cyclobutanone (374  $\mu$ L, 5.00 mmol). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S4** (653 mg, 81%) as a colourless solid.

$R_f$  = 0.22 (10% EtOAc/Petrol); **M.p.**: 75-76  $^{\circ}$ C (lit.<sup>[5]</sup> 73-76  $^{\circ}$ C); **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3333 (br), 2984, 2934, 2361, 2340, 1487, 1456, 1377, 1277, 1231, 1123, 1024, 887, 758, 727;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 7.31 – 7.28 (m, 1H), 7.21 – 7.15 (m, 3H), 2.72 – 2.65 (m, 2H), 2.43 – 2.36 (m, 5H), 2.23 – 2.14 (m, 1H), 1.83 (s, 1H), 1.77 – 1.68 (m, 1H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 143.1, 137.2, 131.9, 127.9, 125.7, 125.3, 79.2, 36.2, 20.3, 14.9; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{11}\text{H}_{14}\text{O}$ ] requires  $[M]$  162.1045, found 162.1040.





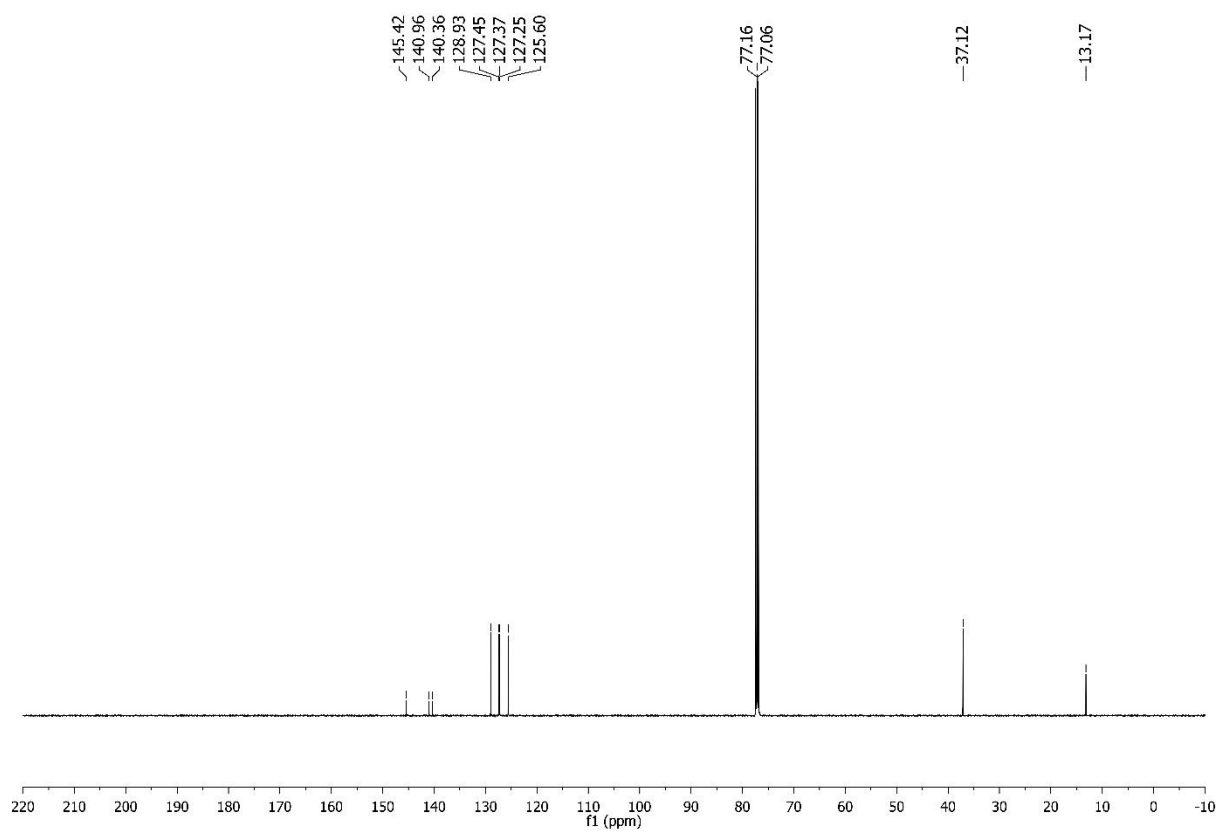
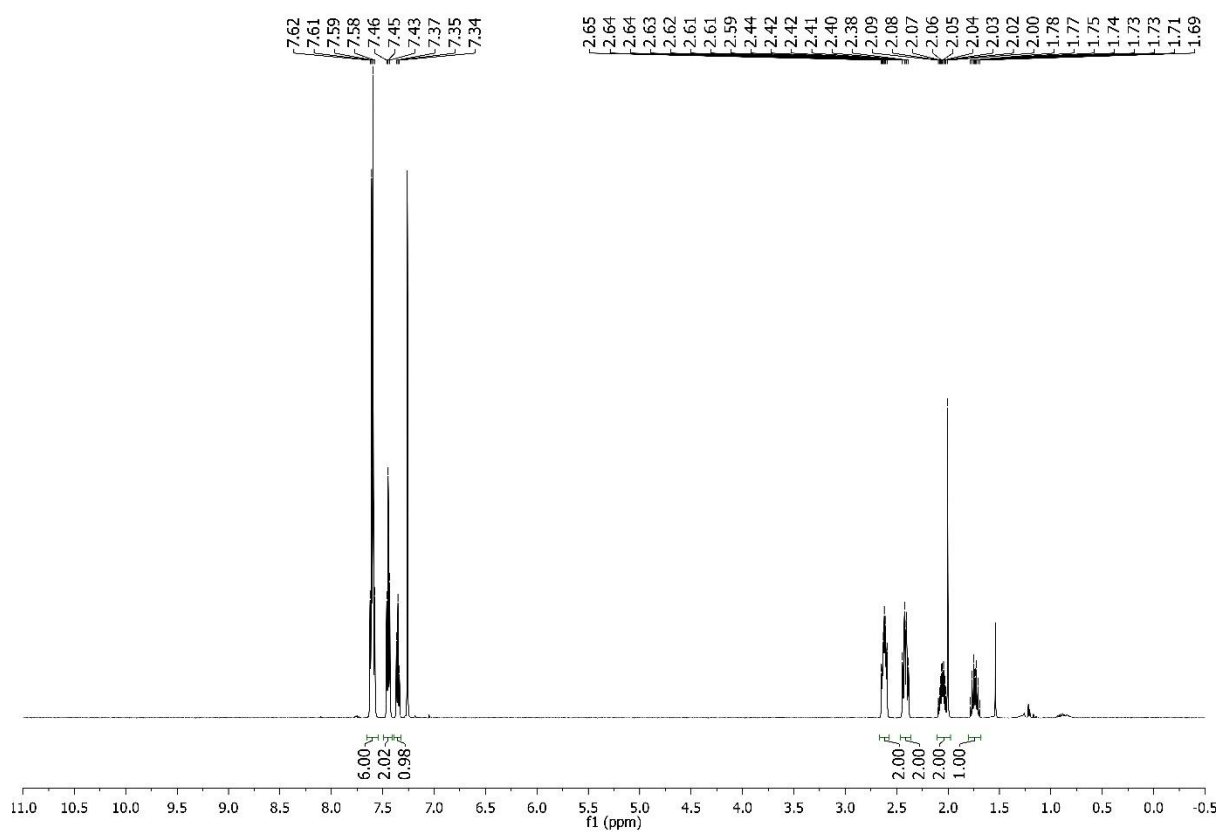
**1-([1,1'-Biphenyl]-4-yl)cyclobutan-1-ol (S5)**



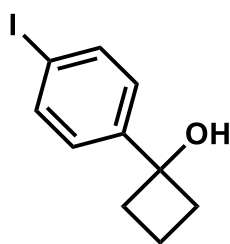
Prepared according to General Procedure C using 4-bromo-1,1'-biphenyl (1.40 g, 6.00 mmol, 1.2 eq.), *n*-butyllithium (3.18 mL, 2.36 M in hexanes, 7.50 mmol, 1.5 eq.) and cyclobutanone (374  $\mu$ L, 5.0 mmol, 1.0 eq.). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S5** (0.97 g, 73%) as a white solid.

$R_f$  = 0.29 (10% EtOAc/Petrol); **M.p.**: 84–86  $^{\circ}$ C; **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3233 (br), 2984, 2938, 1483, 1242, 1140, 1111, 841, 766, 729, 694;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.64 – 7.56 (m, 6H), 7.45 (t,  $J$  = 7.5 Hz, 2H), 7.35 (t,  $J$  = 7.0 Hz, 1H), 2.66 – 2.58 (m, 2H), 2.46 – 2.37 (m, 2H), 2.10 – 1.98 (m, 2H), 1.79 – 1.68 (m, 1H),  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 145.4, 141.0, 140.4, 128.9, 127.5, 127.4, 127.3, 125.6, 77.1, 37.1, 13.2; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{16}\text{H}_{16}\text{O}$ ] requires  $[M]$  224.1201, found 224.1203.



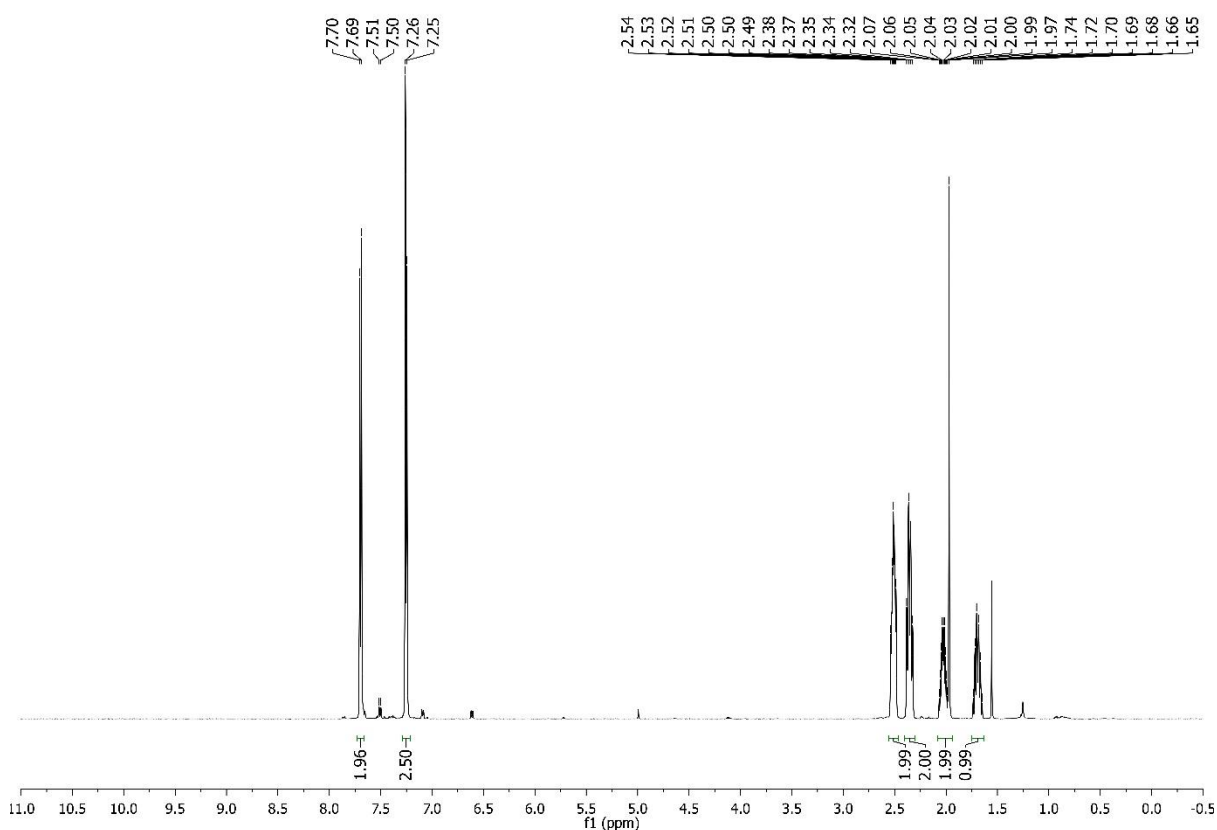


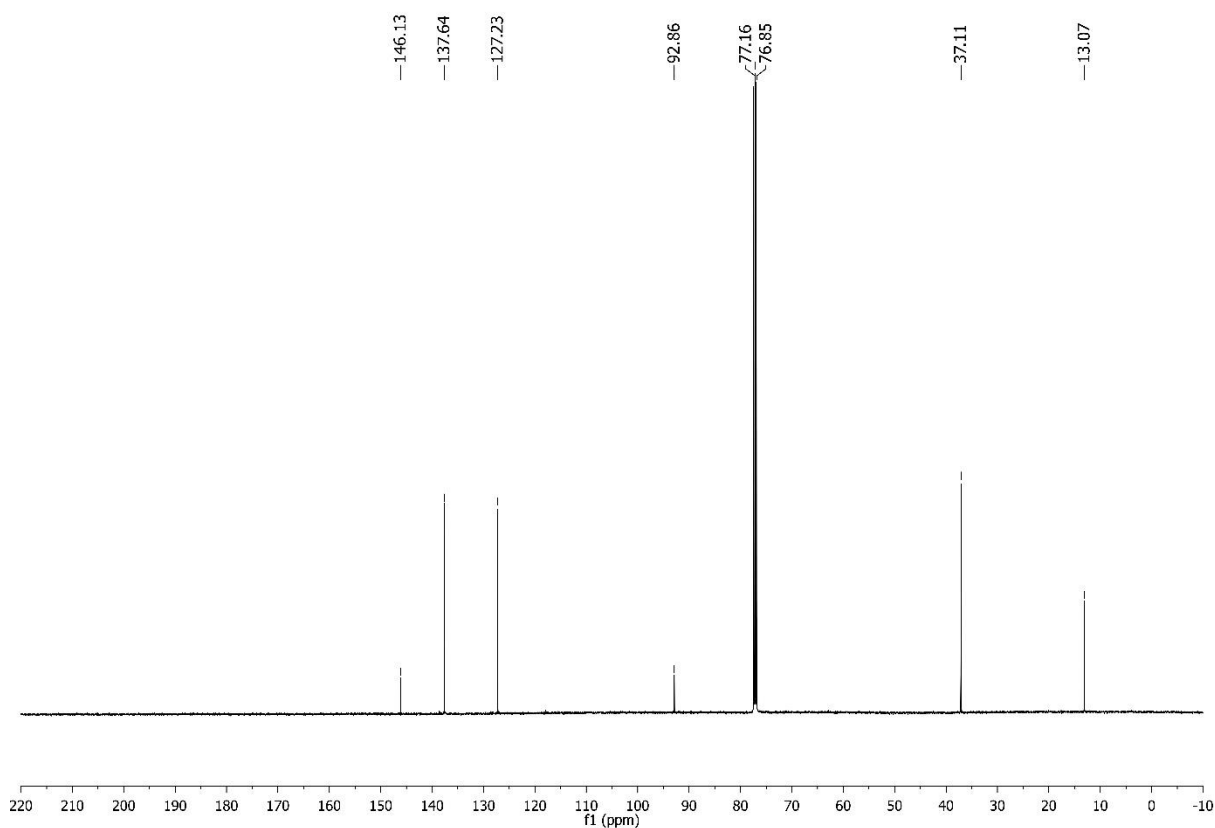
### 1-(4-Iodophenyl)cyclobutan-1-ol (S6)



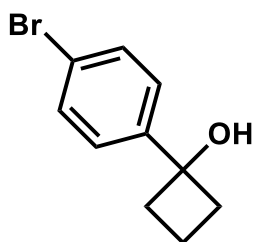
Prepared according to General Procedure C using 1,4-diiodobenzene (2.14 g, 6.50 mmol) *n*-butyllithium (2.83 mL, 2.3 M in hexanes, 6.50 mmol), and cyclobutanone (374  $\mu$ L, 5.00 mmol). The crude residue was purified by flash column chromatography (5% EtOAc/Hexanes, silica gel) to afford **S6** (929 mg, 68%) as an off white solid.

$R_f$  = 0.16 (10% EtOAc/Hexanes); **M.p.**: 66 – 69 °C; **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3335 (br), 2980, 2940, 1489, 1389, 1223, 1128, 1103, 1078, 1005, 961, 839, 812, 642, 523;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.71 – 7.67 (m, 2H), 7.27 – 7.23 (m, 2H), 2.55 – 2.48 (m, 2H), 2.40 – 2.31 (m, 2H), 2.08 – 1.95 (m, 2H), 1.75 – 1.64 (m, 1H);  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 146.1, 137.6, 127.2, 92.9, 76.9, 37.1, 13.1; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{10}\text{H}_{11}\text{IO}$ ] requires [M- $\text{H}_2\text{O}$ ] 255.9749, found 255.9760.



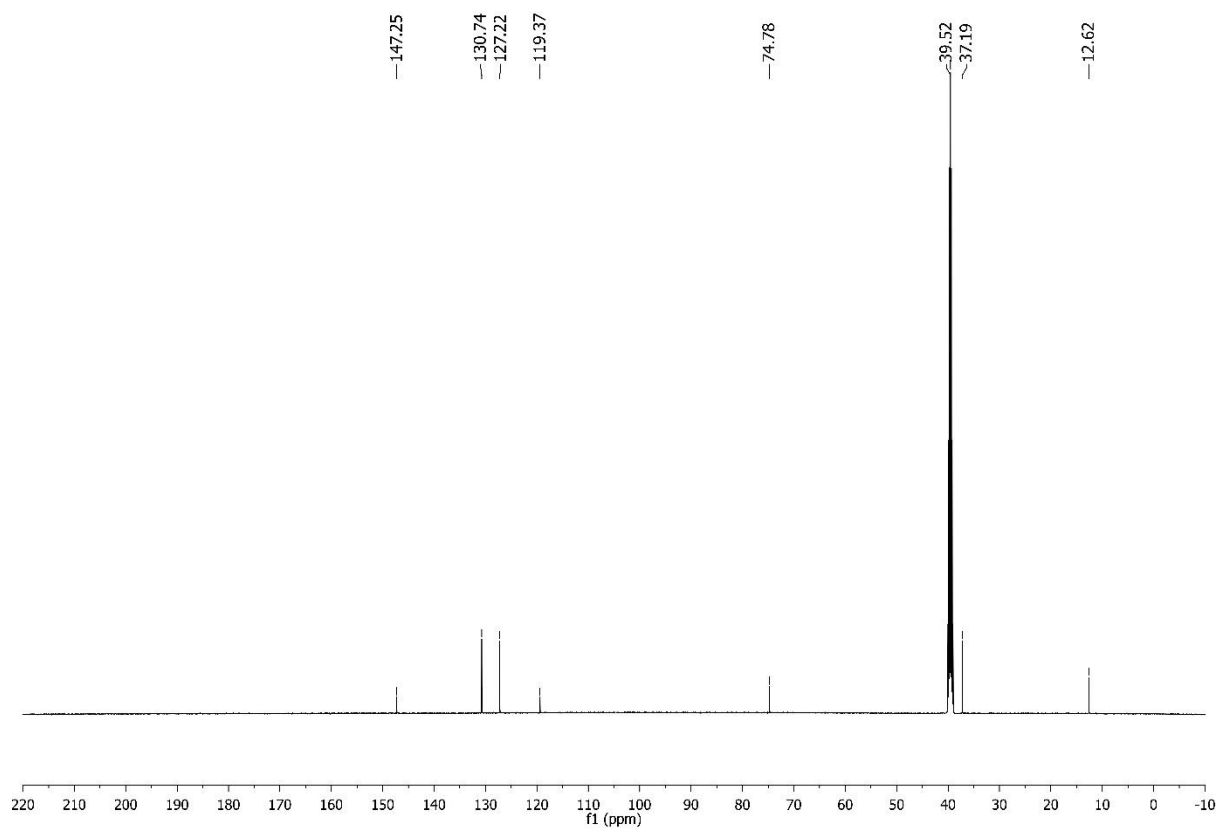
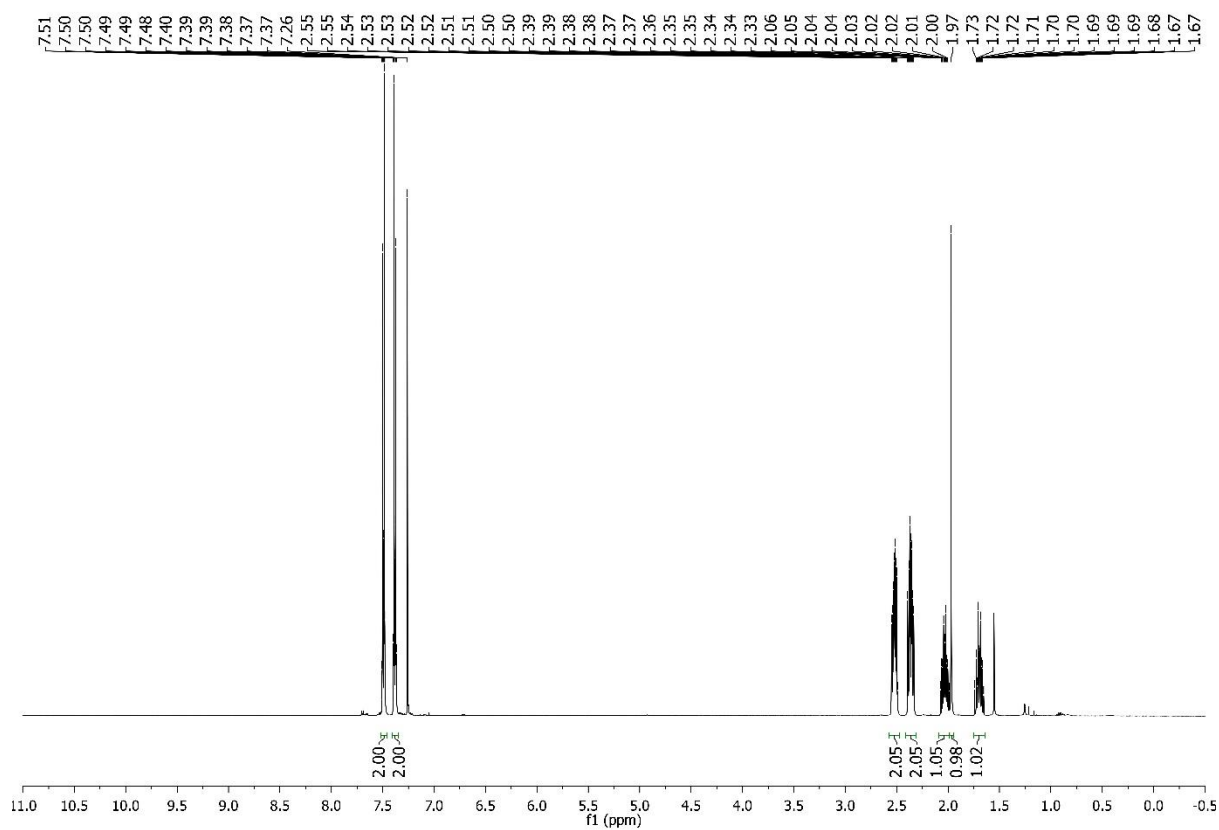


#### 1-(4-Bromophenyl)cyclobutan-1-ol (**S7**)

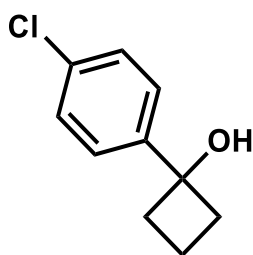


Prepared according to General Procedure C using 1-bromo-4-iodobenzene (1.347 g, 4.76 mmol, 1.00 eq.), *n*-butyllithium (2.35 mL, 2.13 M in hexanes, 5.00 mmol, 1.05 eq.), and cyclobutanone (374  $\mu$ L, 5.00 mmol, 1.05 eq.). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S7** (753 mg, 70%) as a colourless solid.

**R<sub>f</sub>** = 0.31 (10% EtOAc/Petrol); **M.p.**: 46–49 °C; **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3325 (br), 2984, 2938, 2361, 2342, 1489, 1393, 1277, 1244, 1134, 1101, 1076, 1009, 956, 891, 764, 750; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.51 – 7.47 (m, 2H), 7.40 – 7.36 (m, 2H), 2.56 – 2.48 (m, 2H), 2.40 – 2.32 (m, 2H), 2.08 – 1.99 (m, 1H), 1.97 (s, 1H), 1.75 – 1.64 (m, 1H); **<sup>13</sup>C NMR** (126 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 147.3, 130.7, 127.2, 119.4, 74.8, 37.2, 12.6; **HRMS** (EI<sup>+</sup>) [C<sub>10</sub>H<sub>11</sub>BrO] requires [M-H<sub>2</sub>O] 207.9888, found 207.9881.



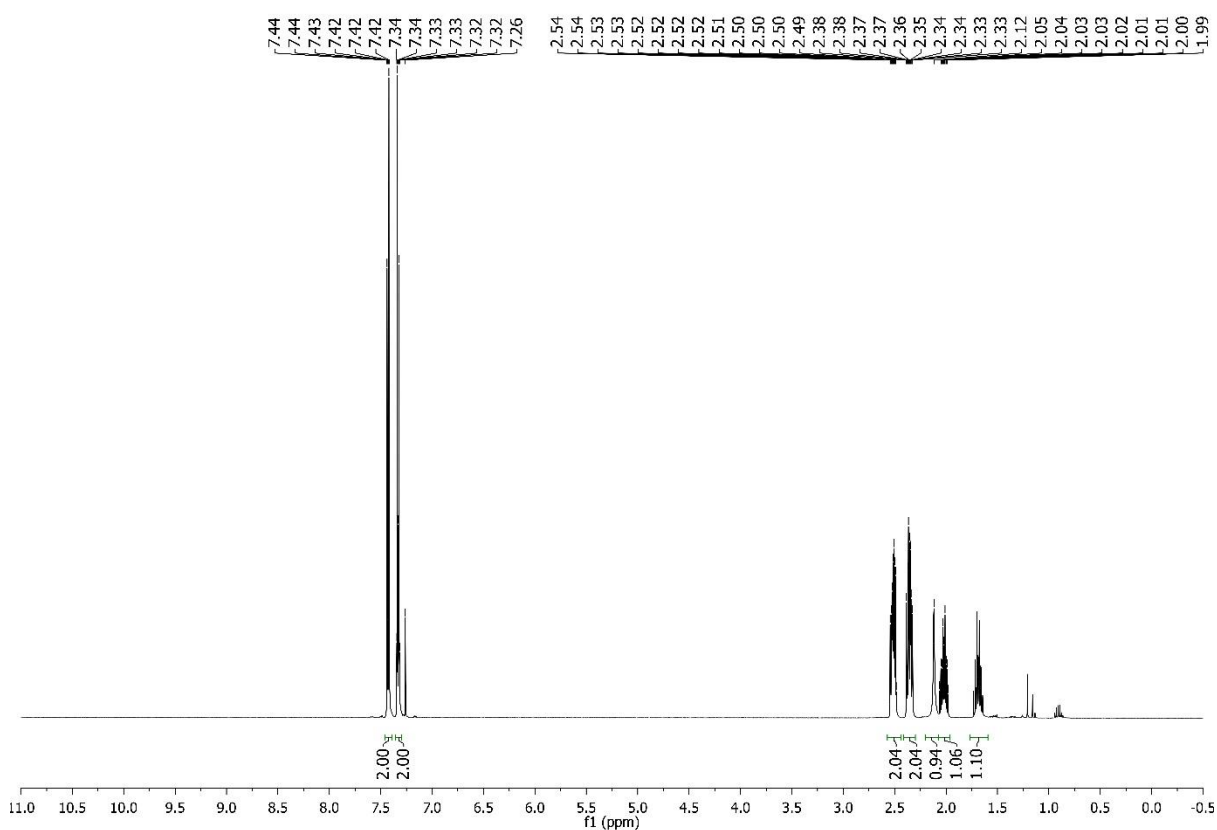
### 1-(4-Chlorophenyl)cyclobutan-1-ol (**S8**)

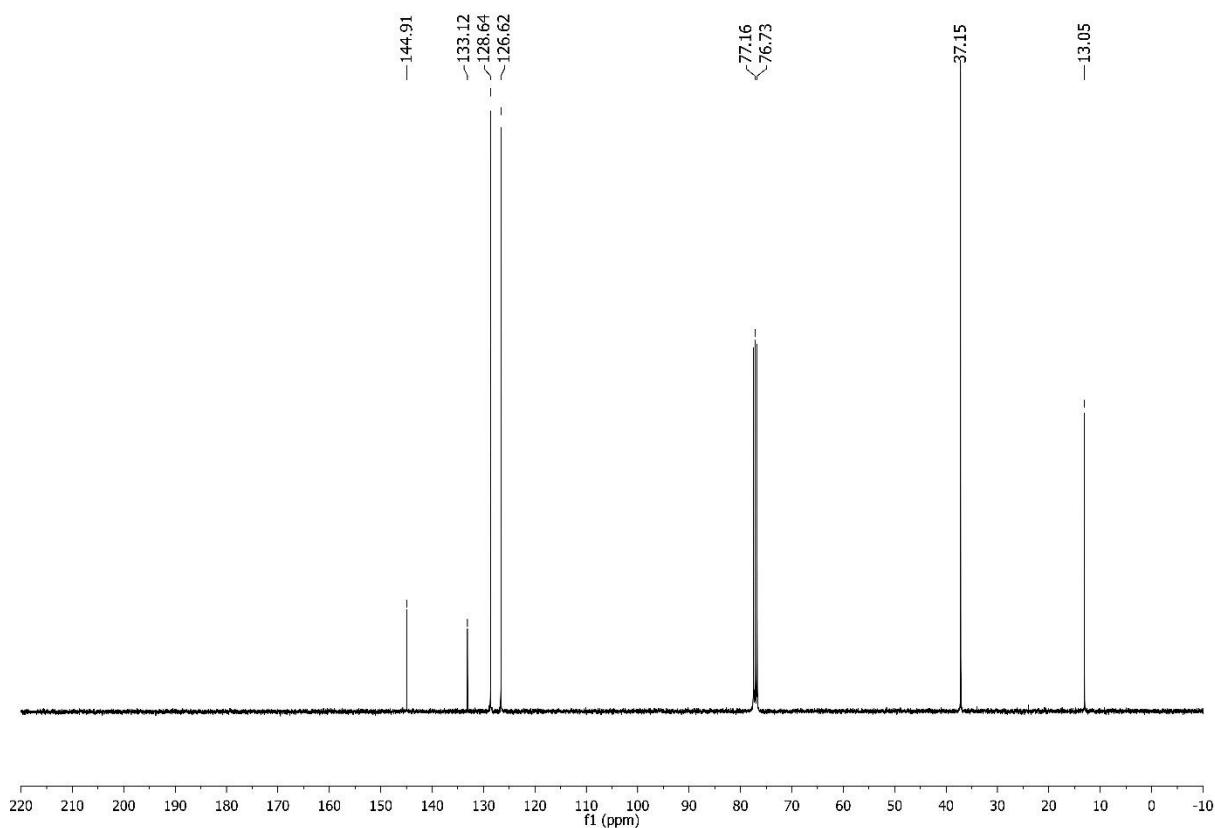


Prepared according to General Procedure C using 1-chloro-4-iodobenzene (1.14 g, 4.76 mmol, 1.00 eq.), *n*-butyllithium (2.25 mL, 2.13 M in hexanes, 4.76 mmol, 1.00 eq.), and cyclobutanone (374  $\mu$ L, 5.00 mmol, 1.05 eq.). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S8** (766 mg, 88%) as a colourless oil.

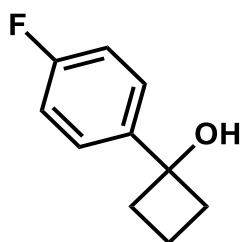
$R_f$  = 0.37 (10 % EtOAc/Petrol);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.45 – 7.40 (m, 2H), 7.36 – 7.31 (m, 2H), 2.56 – 2.47 (m, 2H), 2.40 – 2.31 (m, 2H), 2.12 (s, 1H), 2.07 – 1.97 (m, 1H), 1.75 – 1.63 (m, 1H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 144.9, 133.1, 128.6, 126.6, 76.7, 37.2, 13.1.

These data are consistent with those previously reported in the literature.<sup>[4]</sup>



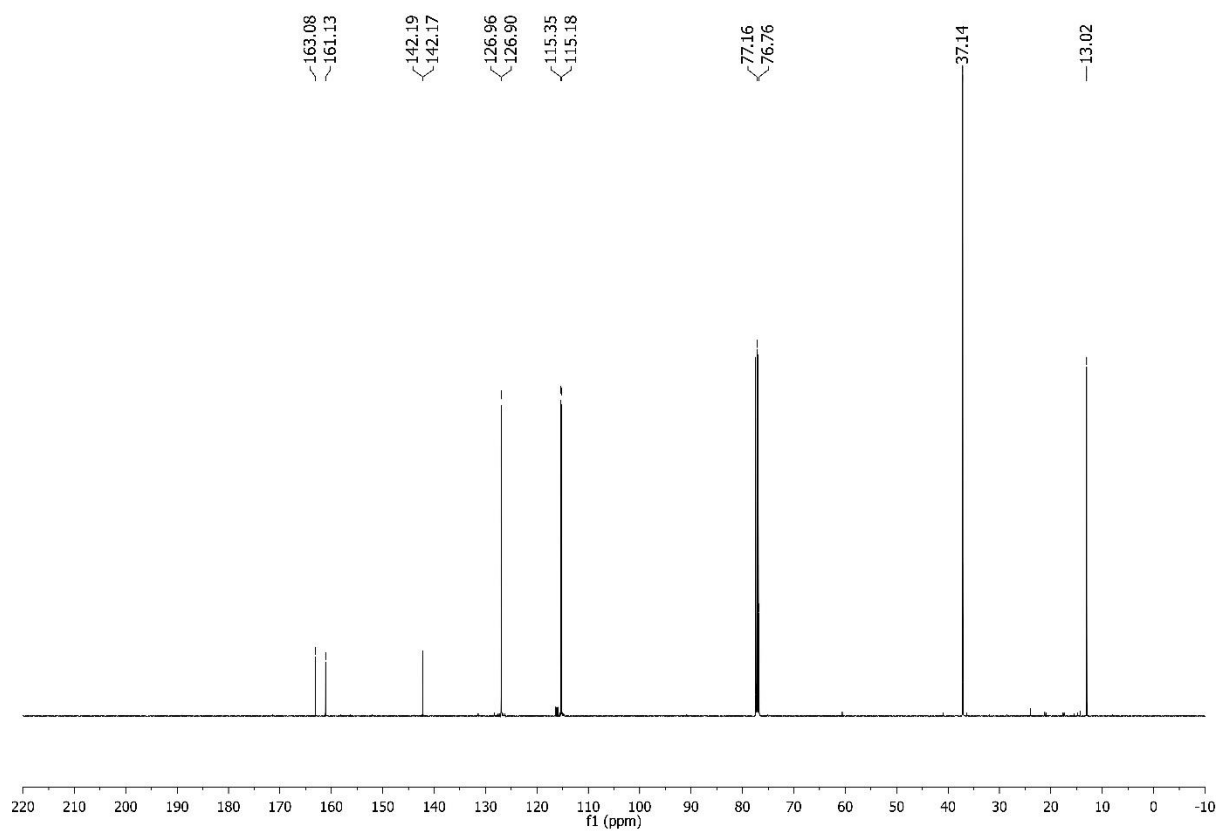
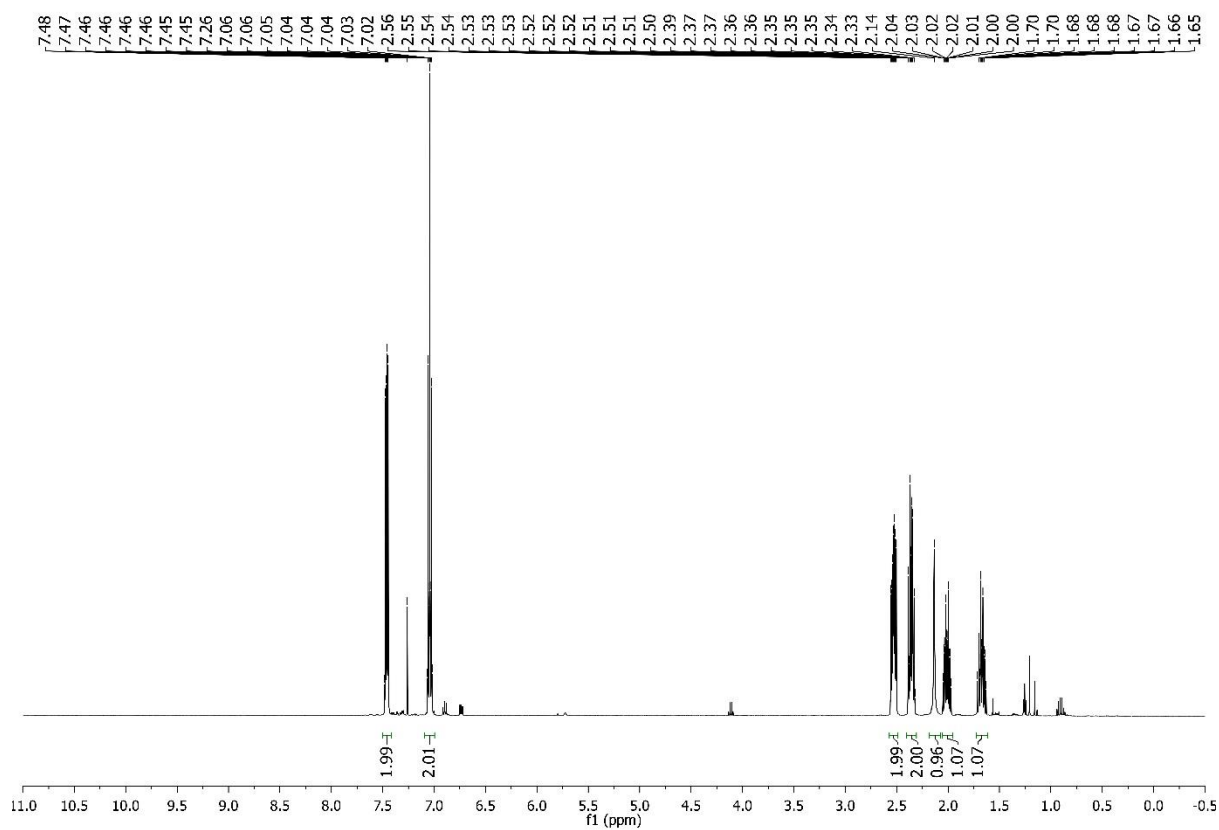


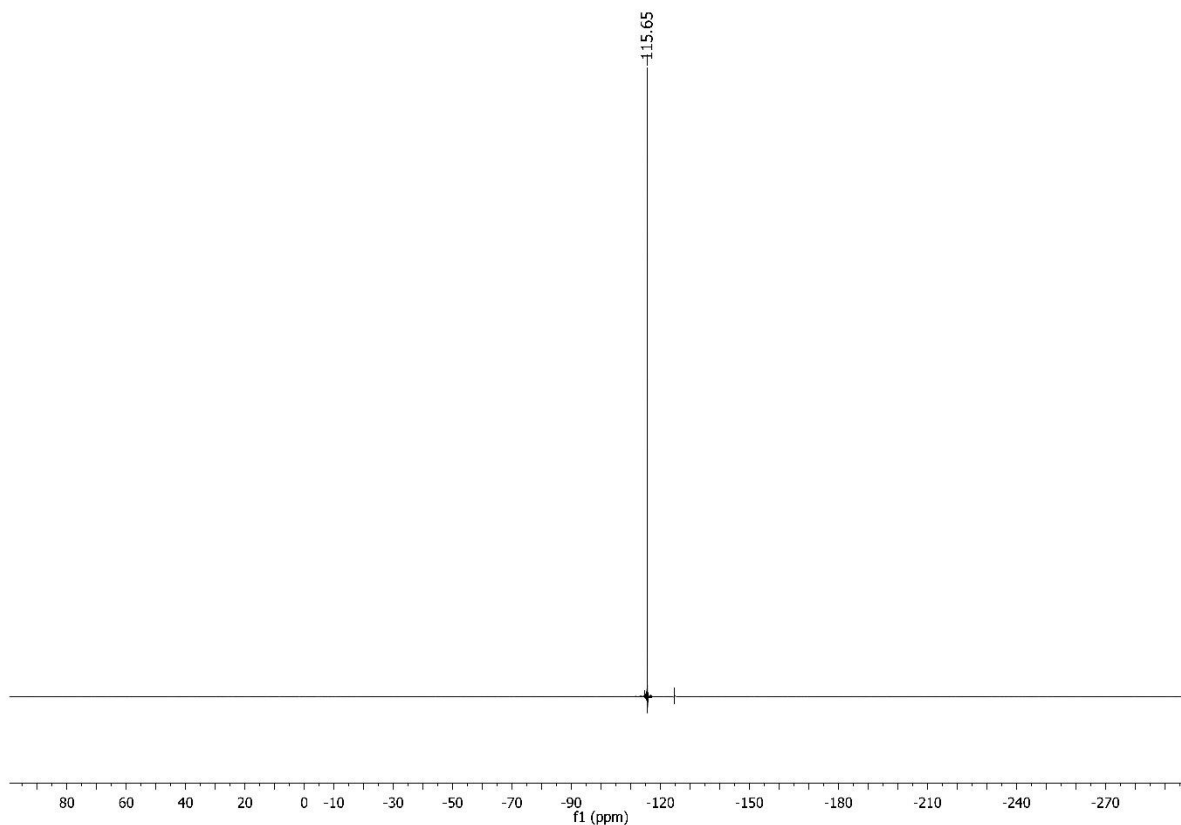
#### 1-(4-Fluorophenyl)cyclobutan-1-ol (S9)



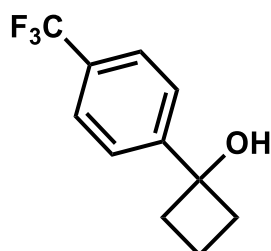
Prepared according to General Procedure A using magnesium turnings (201 mg, 8.25 mmol), 1-bromo-4-fluorobenzene (824  $\mu$ L, 7.50 mmol), and cyclobutanone (374  $\mu$ L, 5.00 mmol). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S9** (652 mg, 78%) as a colourless oil.

$R_f$  = 0.20 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3327 (br), 2940, 2361, 1601, 1508, 1277, 1225, 1159, 1130, 1098, 957, 889, 835, 750, 542;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.50 – 7.42 (m, 2H), 7.08 – 7.00 (m, 2H), 2.58 – 2.48 (m, 2H), 2.41 – 2.31 (m, 2H), 2.14 (s, 1H), 2.07 – 1.96 (m, 1H), 1.74 – 1.61 (m, 1H);  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 162.1 (d,  $J$  = 245.5 Hz), 142.2 (d,  $J$  = 3.0 Hz), 126.9 (d,  $J$  = 8.0 Hz), 115.3 (d,  $J$  = 21.0 Hz), 76.8, 37.1, 13.0;  **$^{19}\text{F}$  NMR** (471 MHz,  $\text{CDCl}_3$ )  $\delta$  = -115.65; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{10}\text{H}_{11}\text{OF}$ ] requires  $[M]$  166.0794, found 166.0790.





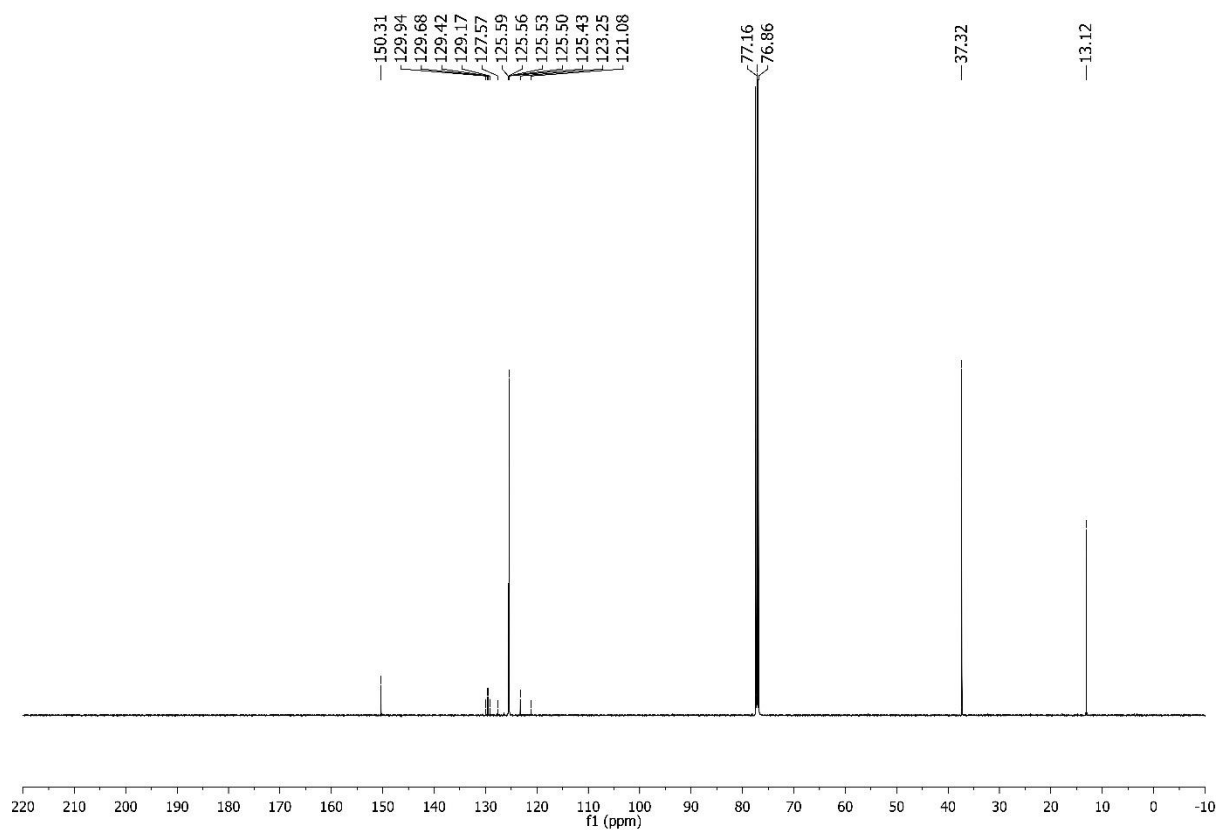
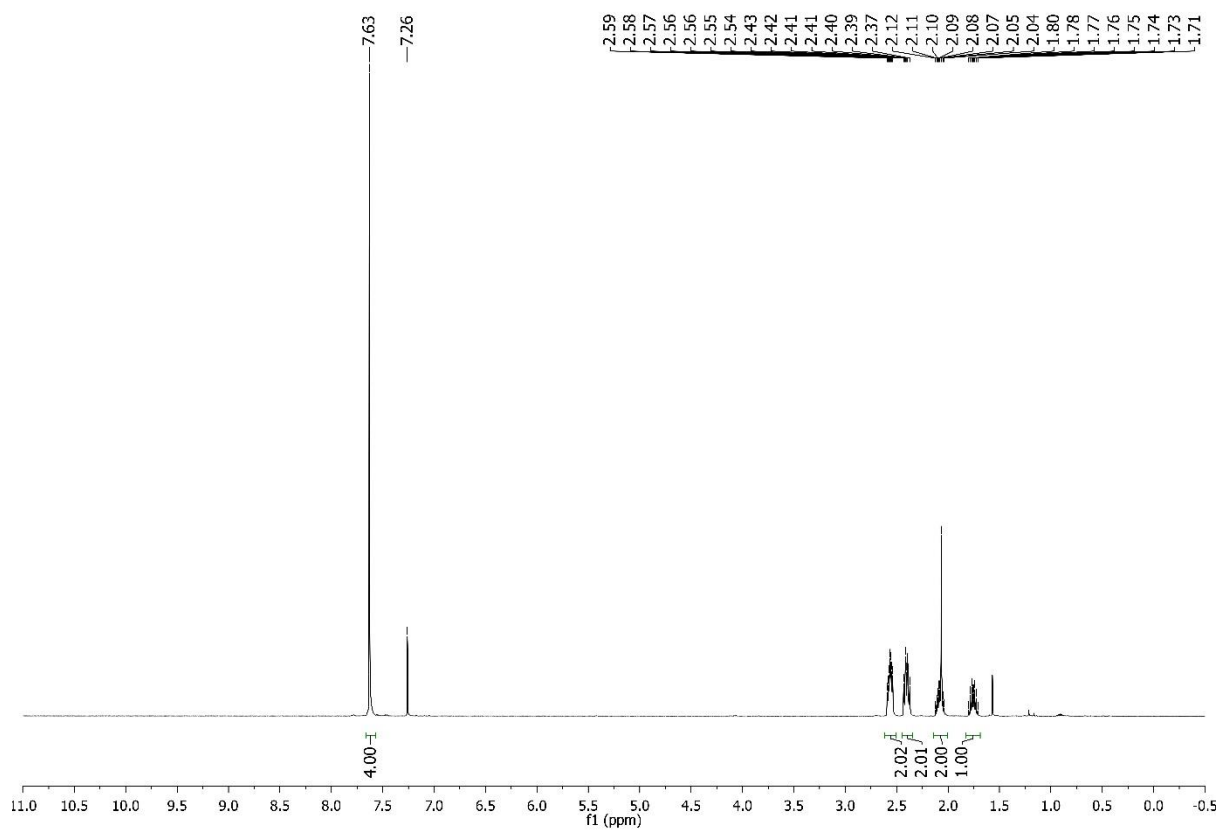
**1-(4-(Trifluoromethyl)phenyl)cyclobutan-1-ol (S10)**

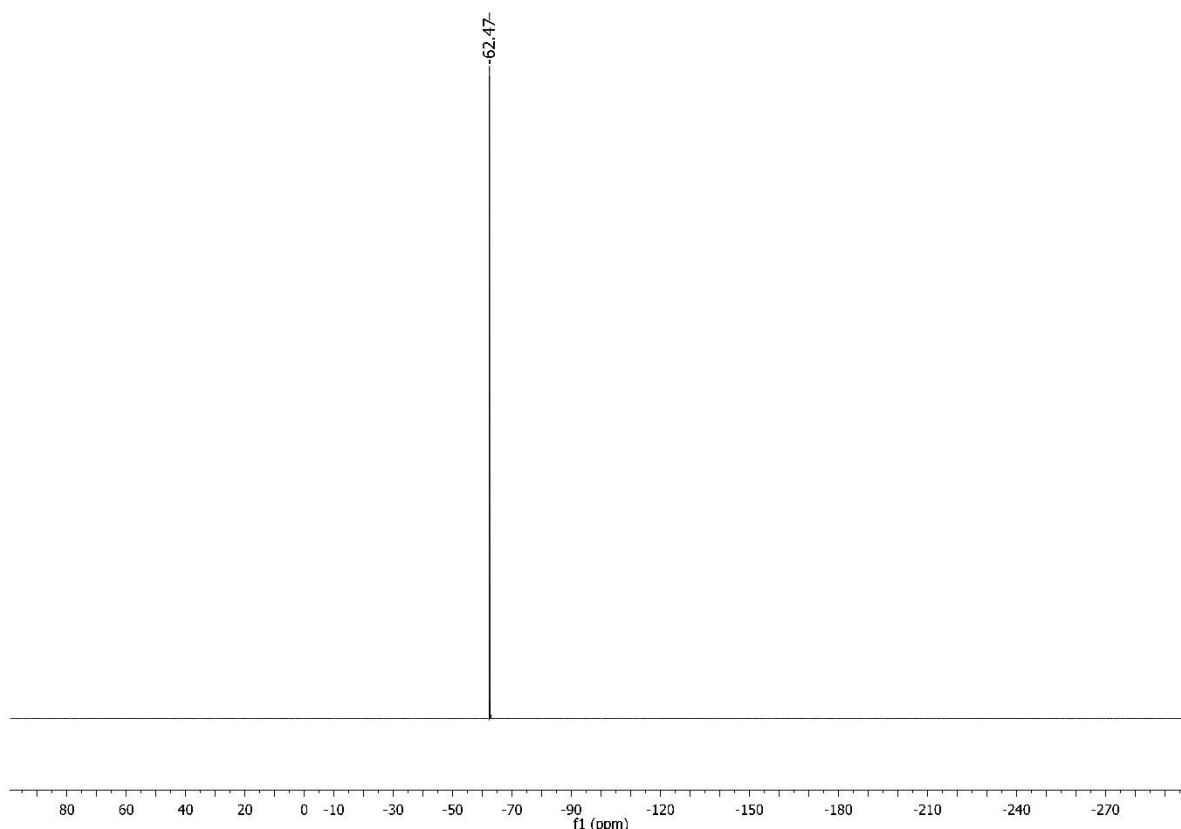


Prepared according to general procedure A using magnesium turnings (438 mg, 18.0 mmol, 1.8 eq.), 1-bromo-4-(trifluoromethyl)benzene (2.10 mL, 15.0 mmol, 1.5 eq.) and cyclobutanone (747  $\mu$ L, 10.0 mmol, 1.0 eq.). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S10** (1.32 g, 61%) as a white solid.

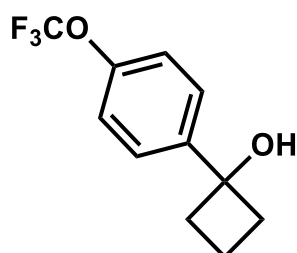
**R<sub>f</sub>** = 0.36 (20% EtOAc/Petrol); **M.p.**: 54-56 °C; **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3240 (br), 2997, 2949, 1620, 1408, 1325, 1155, 1107, 1072, 1012, 835; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 7.63 – 7.63 (m, 4H), 2.64 – 2.50 (m, 2H), 2.47 – 2.32 (m, 2H), 2.19 – 1.99 (m, 2H), 1.85 – 1.68 (m, 1H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 150.3, 129.6 (q, *J* = 32.5 Hz), 125.6 (q, *J* = 4.0 Hz), 125.4, 124.3 (q, *J* = 272.0 Hz), 76.9, 37.3, 13.1; **<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>)**  $\delta$  = -62.47; **HRMS** (EI<sup>+</sup>) [C<sub>11</sub>H<sub>9</sub>F<sub>3</sub>] requires [M-H<sub>2</sub>O] 198.0656, found 198.0661.







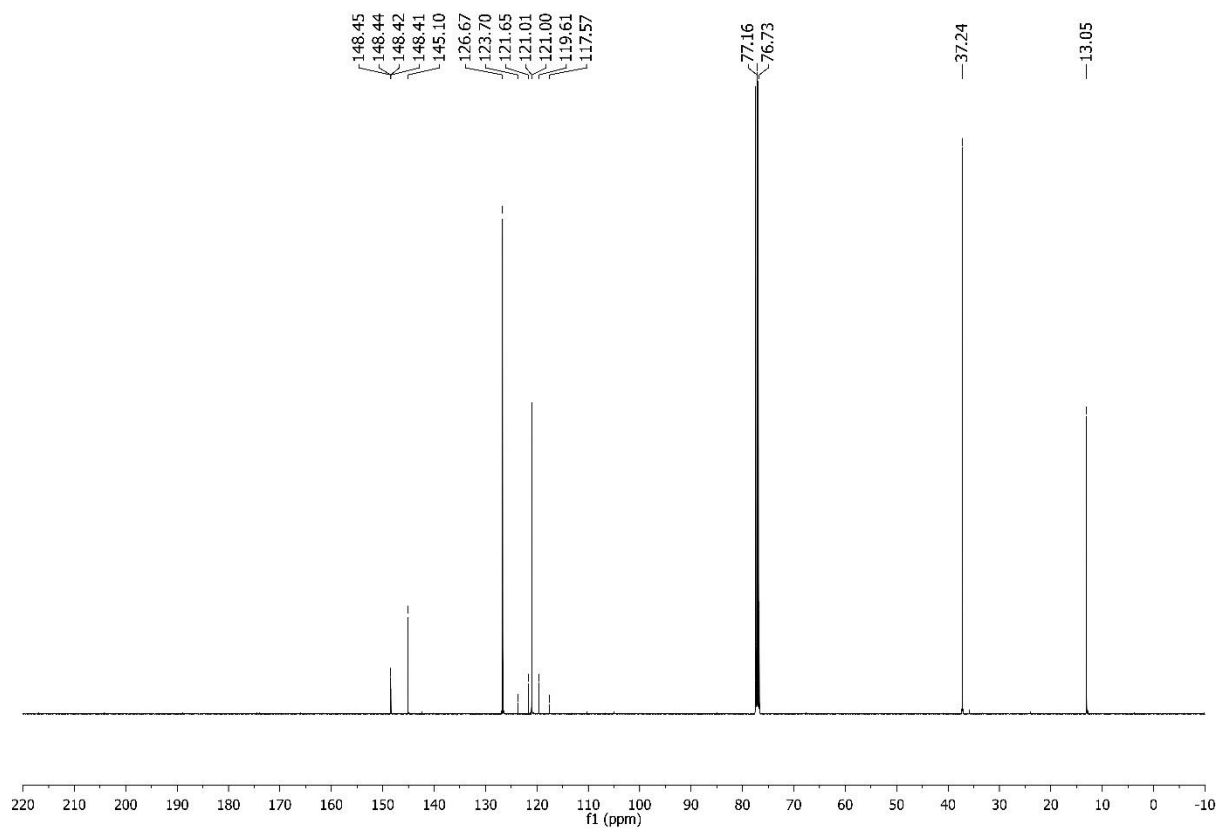
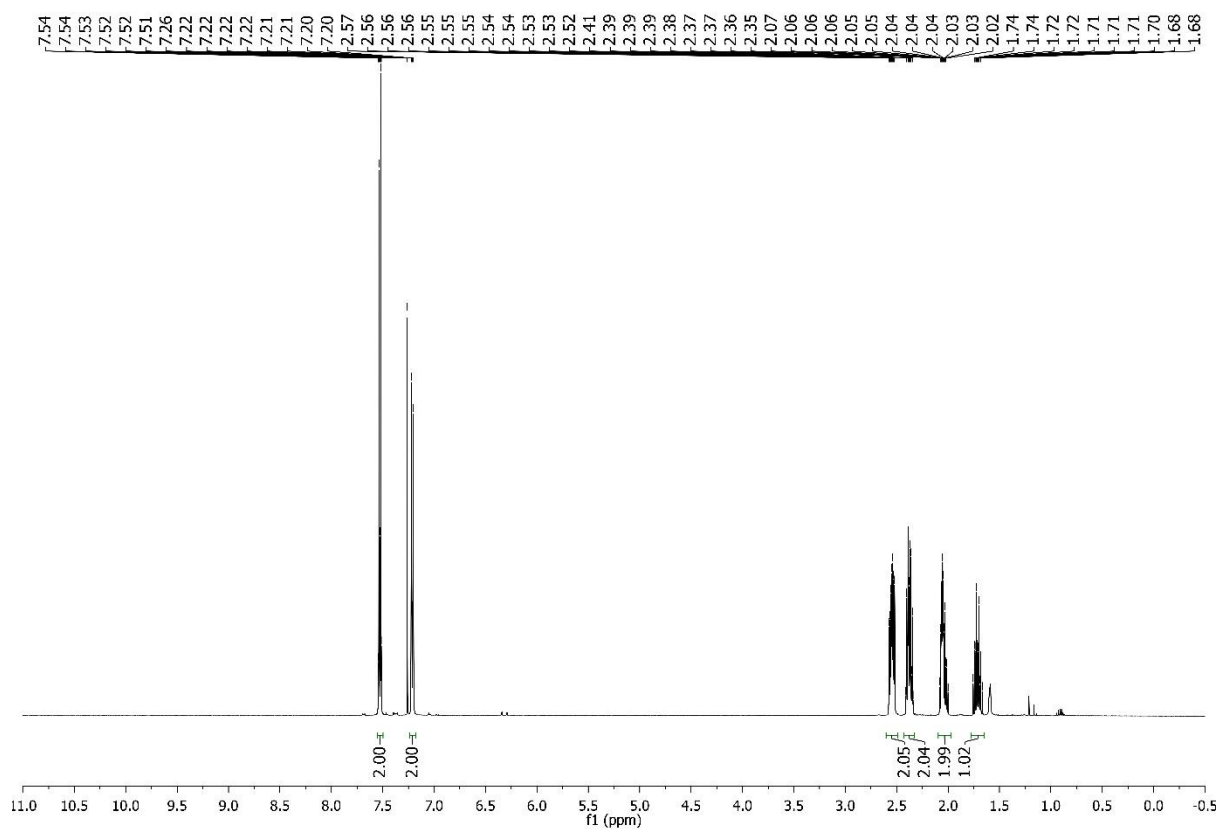
**1-(4-(Trifluoromethoxy)phenyl)cyclobutan-1-ol (S11)**

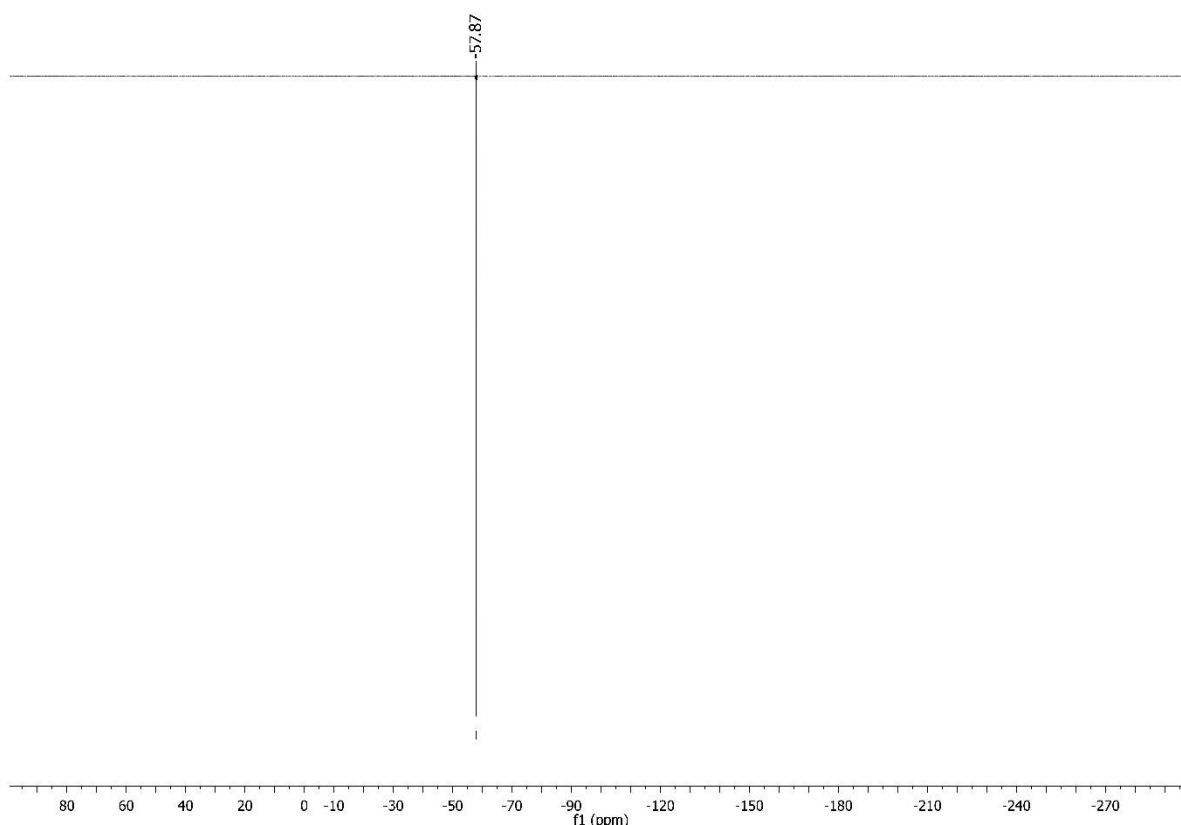


Prepared according to General Procedure C, using 1-bromo-4-(trifluoromethoxy)benzene (1.75 mL, 12.0 mmol, 1.20 eq.), *n*-butyllithium (6.25 mL, 2.3 M in hexanes, 14.3 mmol, 1.43 eq.) and cyclobutanone (747  $\mu$ L, 10.0 mmol, 1.00 eq.). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S11** (1.58 g, 70%) as a white solid.

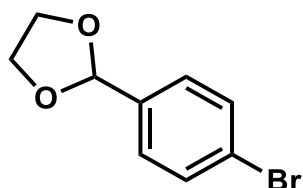
**R<sub>f</sub>** = 0.20 (10% EtOAc/Petrol); **M.p.:** 29-31 °C; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 7.57 – 7.48 (m, 2H), 7.25 – 7.16 (m, 2H), 2.60 – 2.49 (m, 2H), 2.44 – 2.32 (m, 2H), 2.11 – 1.99 (m, 2H), 1.77 – 1.65 (m, 1H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 148.4 (q, *J* = 2.0 Hz), 145.1, 126.7, 121.0, 120.6 (q, *J* = 257.0 Hz), 76.7, 37.2, 13.1; **<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>)**  $\delta$  = -57.9.

These data are consistent with those previously reported in the literature.<sup>[6]</sup>





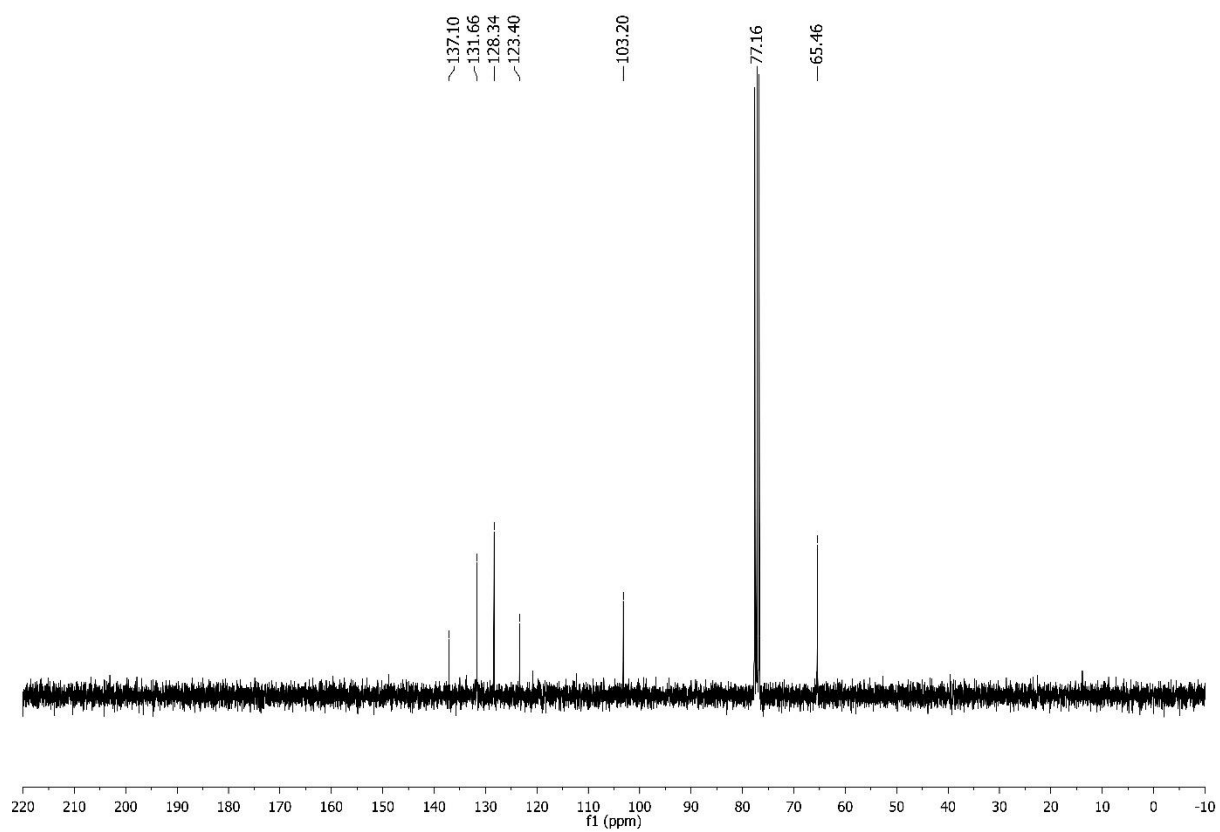
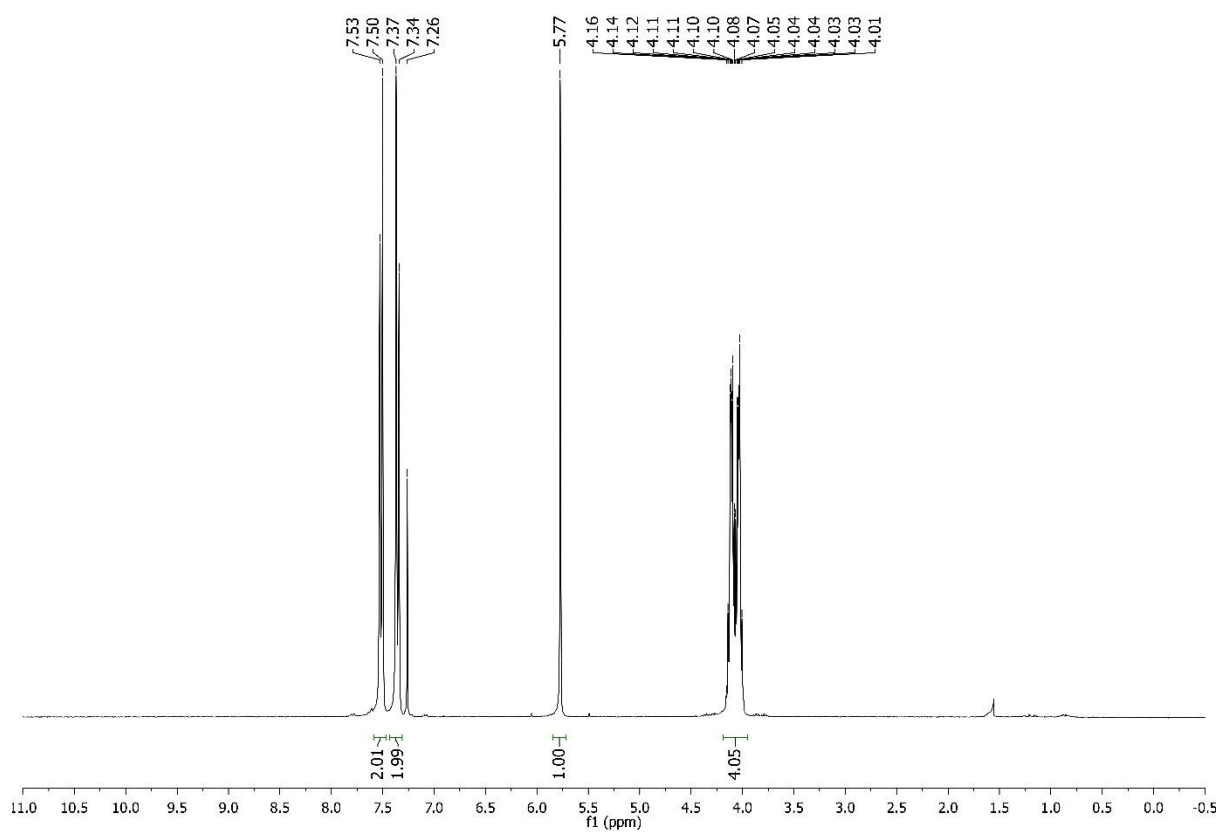
### 2-(4-Bromophenyl)-1,3-dioxolane (**S12**)



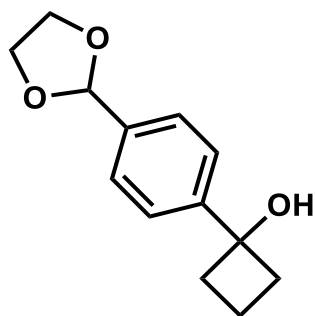
To a 250 mL RBF was added 4-bromobenzaldehyde (4.00 g, 21.6 mmol), *p*-toluenesulfonic acid (100 mg, 0.52 mmol), ethylene glycol (2.40 mL, 34.7 mmol) and toluene (60 mL). The RBF was then fitted with a Dean-Stark condenser and the reaction mixture was refluxed for 10 h and monitored by TLC. Upon completion, the mixture was washed with sat.  $\text{NaHCO}_3$  ( $2 \times 20$  mL) and extracted with EtOAc ( $3 \times 30$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (2% EtOAc/Petrol) to afford **S12** (4.90 g, 97%) as a yellow oil.

$R_f$  = 0.40 (15% EtOAc/Petrol);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.51 (d,  $J$  = 8.5 Hz, 2H), 7.36 (d,  $J$  = 8.5 Hz, 2H), 5.77 (s, 1H), 4.19 – 3.96 (m, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 137.1, 131.6, 128.3, 123.4, 103.2, 65.5.

These data are consistent with those previously reported in the literature.<sup>[7]</sup>

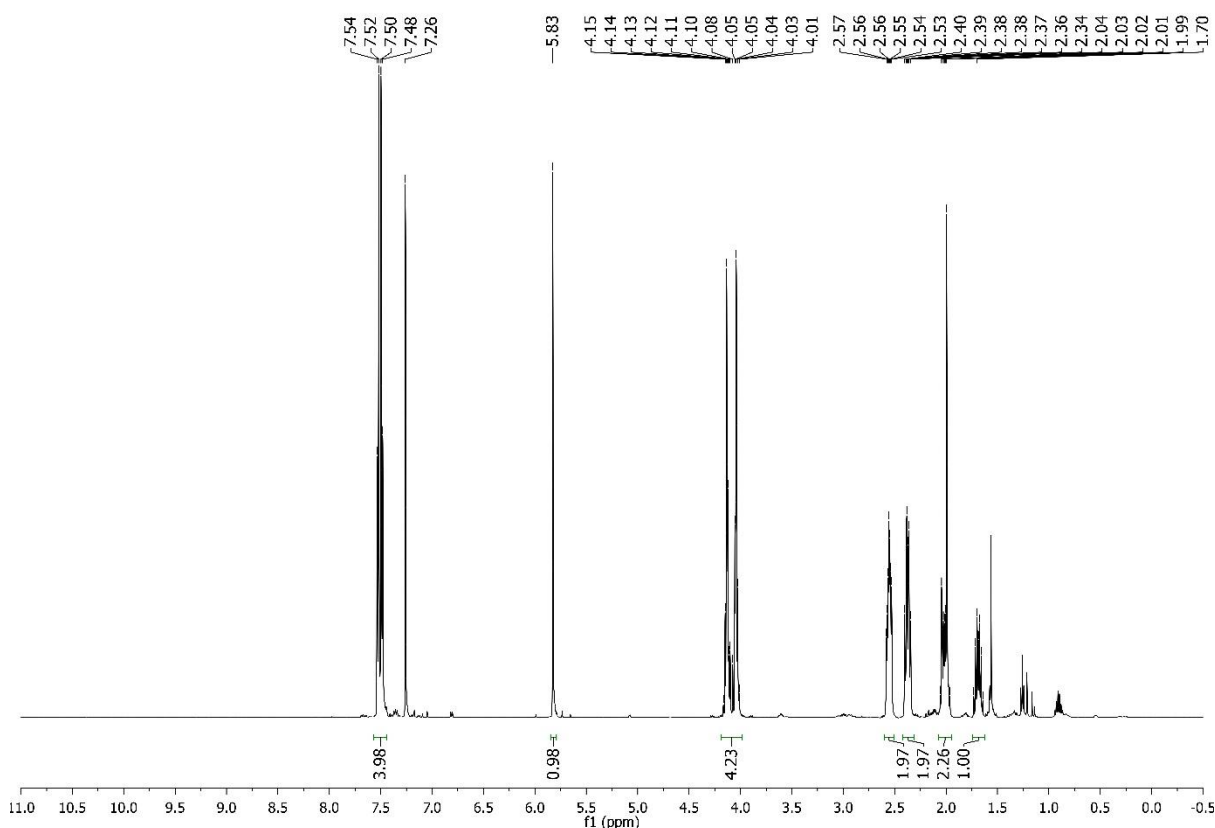


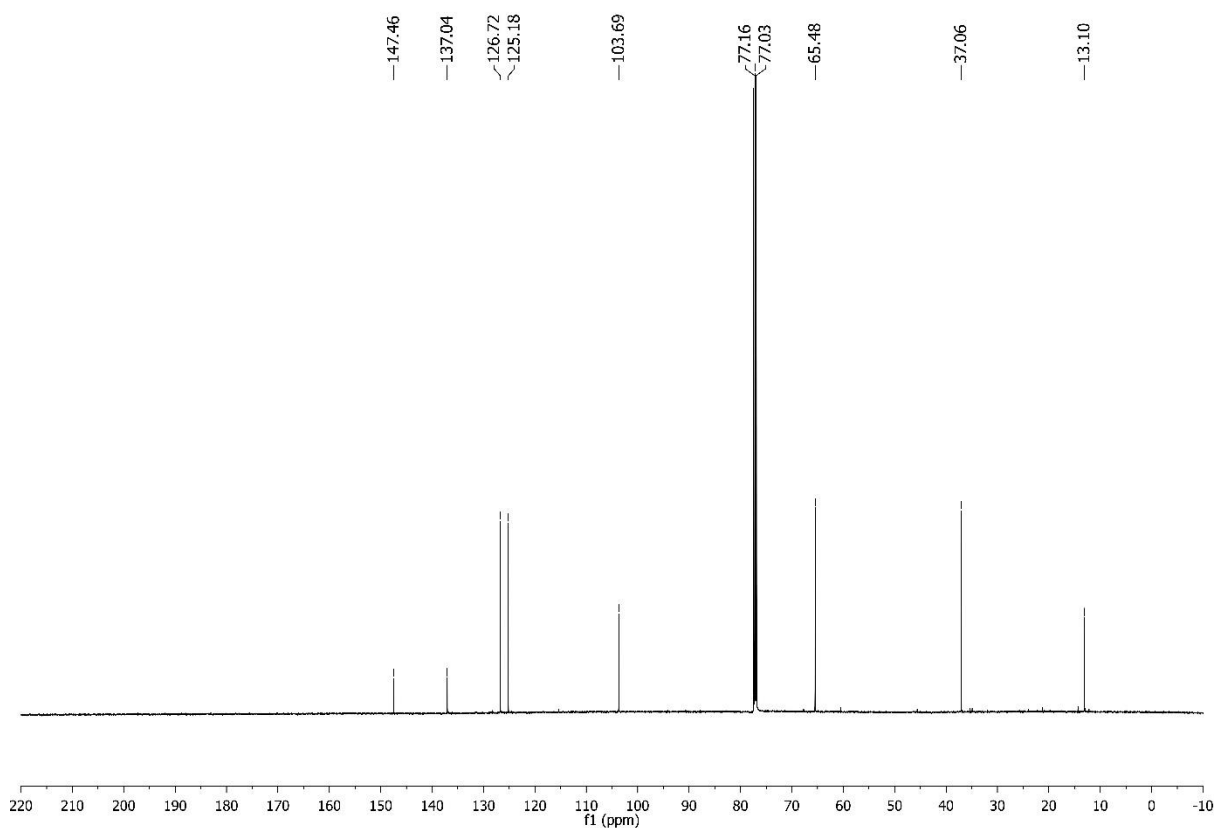
**1-(4-(1,3-Dioxolan-2-yl)phenyl)cyclobutan-1-ol (S13)**



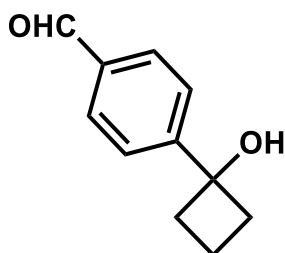
Prepared according to General Procedure C using **S12** (2.74 g, 12 mmol, 1.2 eq.), *n*-butyllithium (6.25 mL, 2.3 M in hexanes, 14.3 mmol, 1.2 eq.) and cyclobutanone (747  $\mu$ L, 10 mmol, 1.0 eq.). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 15% EtOAc/Petrol, silica gel) to afford **S13** (2.04 g, 78%) as a colourless viscous oil.

$R_f$  = 0.48 (30% EtOAc/Petrol); **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3425, 2980, 2889, 1377, 1242, 1078, 939, 827;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 7.56 – 7.44 (m, 4H), 5.83 (s, 1H), 4.19 – 3.98 (m, 4H), 2.61 – 2.50 (m, 2H), 2.43 – 2.31 (m, 2H), 2.06 – 1.95 (m, 2H), 1.76 – 1.61 (m, 1H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 147.4, 137.0, 126.7, 125.1, 103.6, 77.0, 65.4, 37.0, 13.1; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{13}\text{H}_{13}\text{O}_3$ ] requires  $[\text{M}-\text{H}_3\text{O}]$  201.0916, found 201.0911.



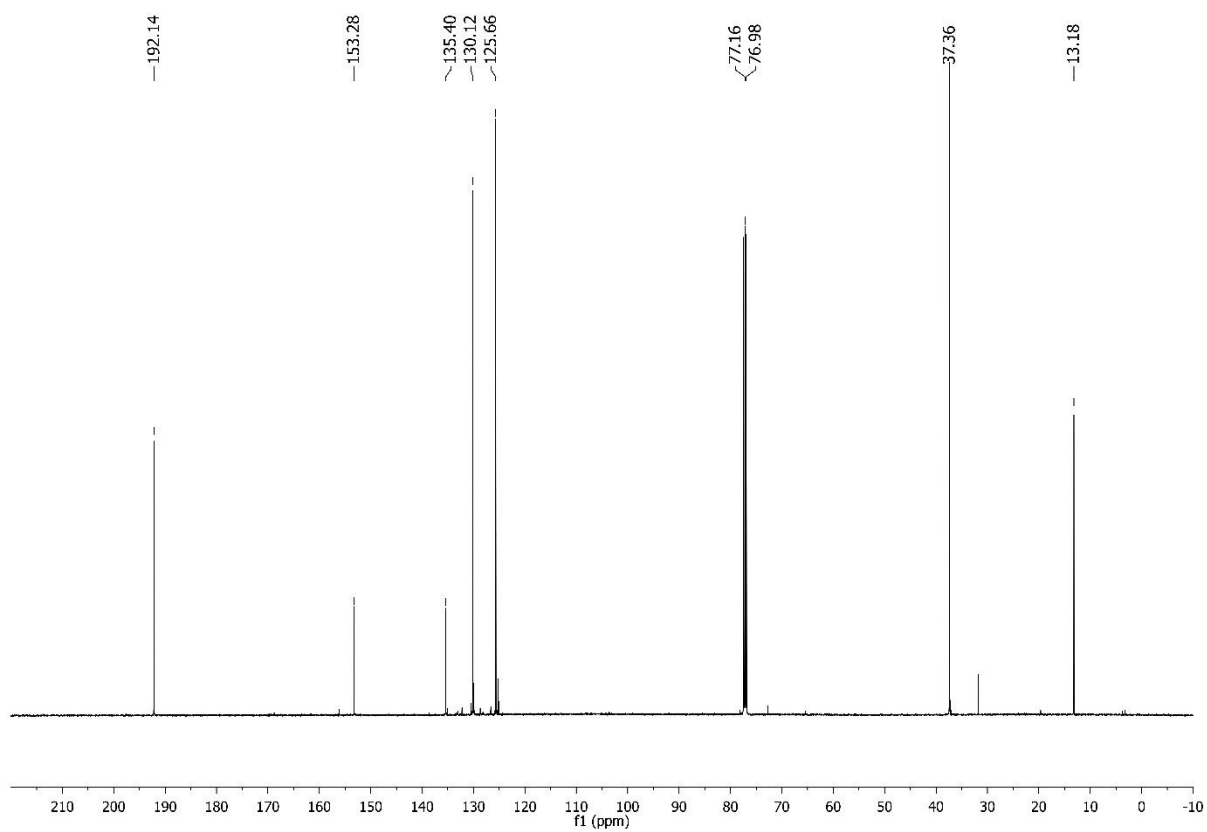
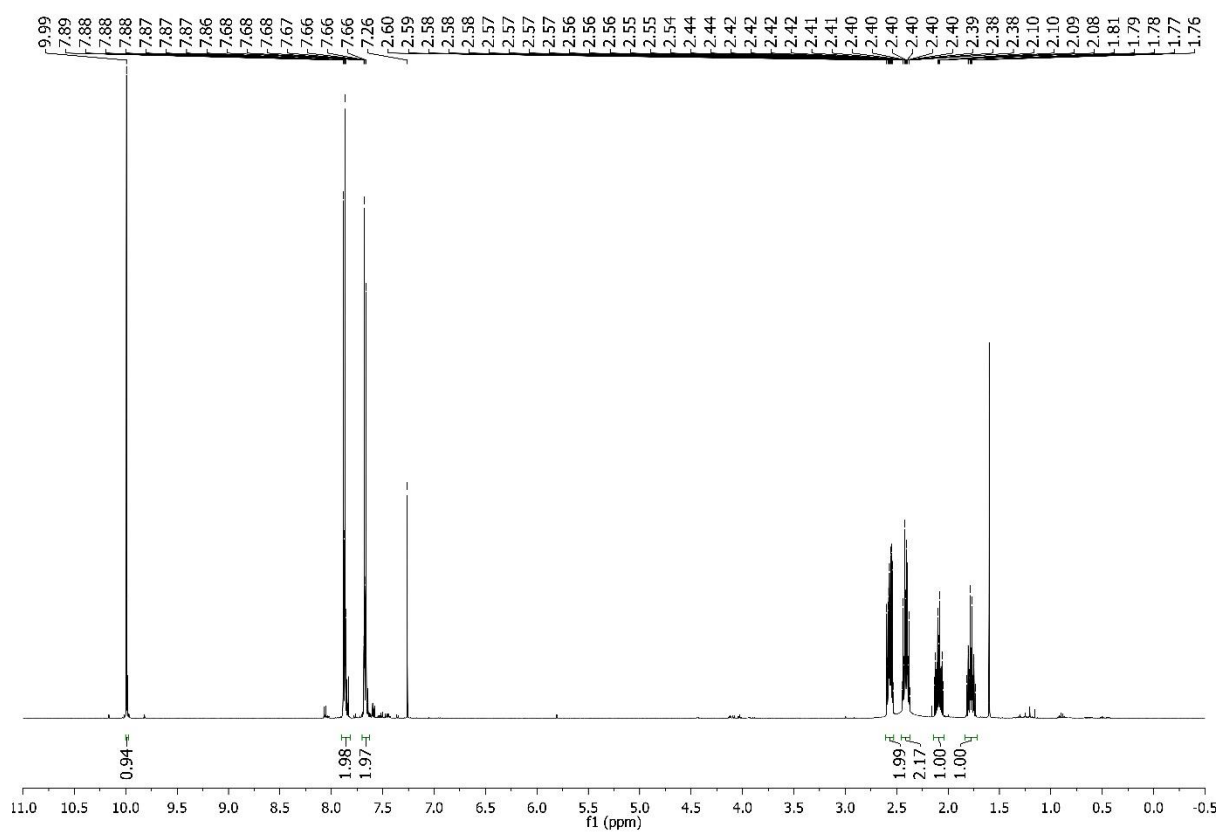


#### 4-(1-Hydroxycyclobutyl)benzaldehyde (**S14**)



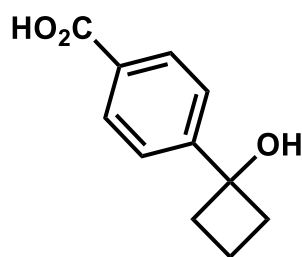
To a solution of **S13** (1.00 g, 4.5 mmol, 1.0 eq.) in THF (5 mL) was added 1 M HCl (2.0 mL) at 0 °C and stirred for 2 h. The reaction was quenched with the addition of sat. NaHCO<sub>3</sub> (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (5→15% EtOAc/Petrol, silica gel) to afford **S14** (450 mg, 56%) as a colourless viscous oil.

**R<sub>f</sub>** = 0.48 (30% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3385 (br), 2988, 2945, 1695, 1603, 1572, 1215, 1136, 1103, 839, 700, 540; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 9.99 (s, 1H), 7.90 – 7.86 (m, 2H), 6.69 – 7.65 (m, 2H), 2.62 – 2.52 (m, 2H), 2.46 – 2.36 (m, 2H), 2.14 – 2.04 (m, 1H), 1.84 – 1.71 (m, 1H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 192.1, 153.2, 135.4, 130.1, 125.6, 76.9, 37.3, 13.1; **HRMS** (EI<sup>+</sup>) [C<sub>11</sub>H<sub>12</sub>O<sub>3</sub>] requires [M-H] 175.0759, found 175.0751.



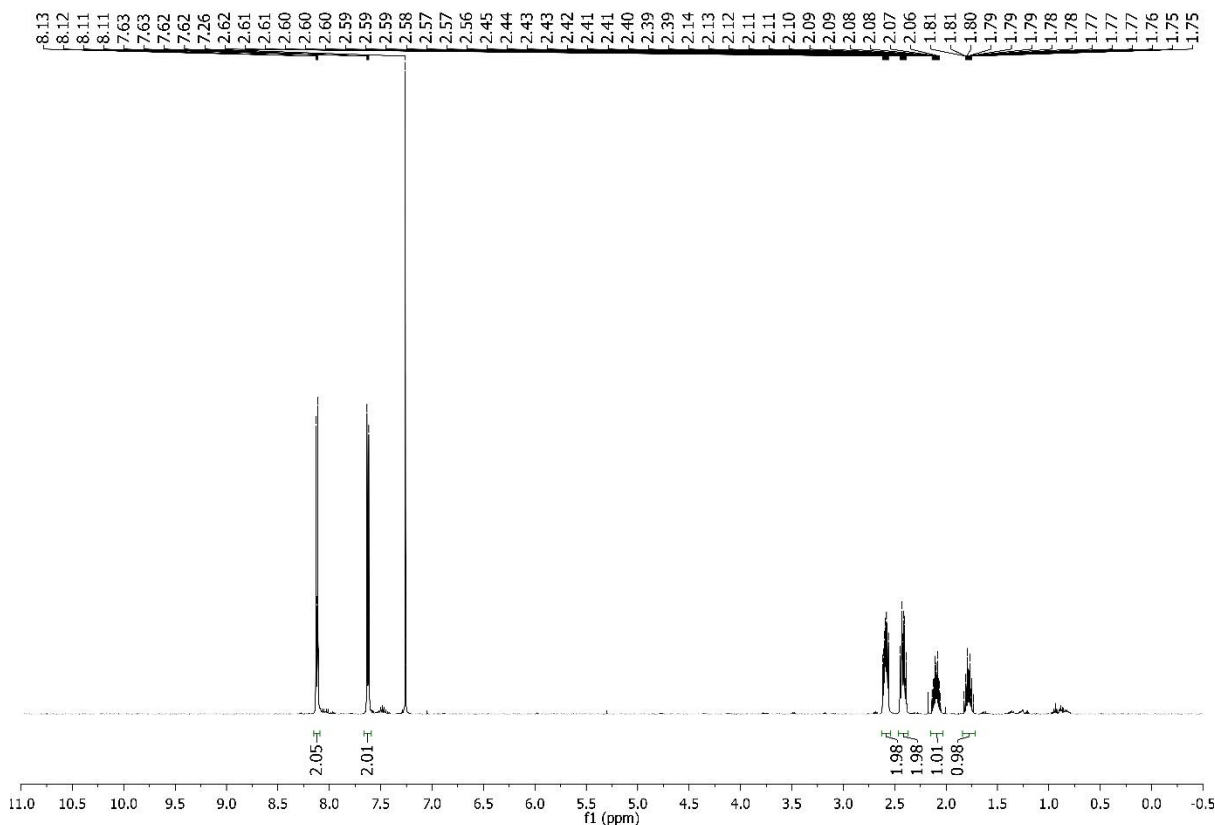


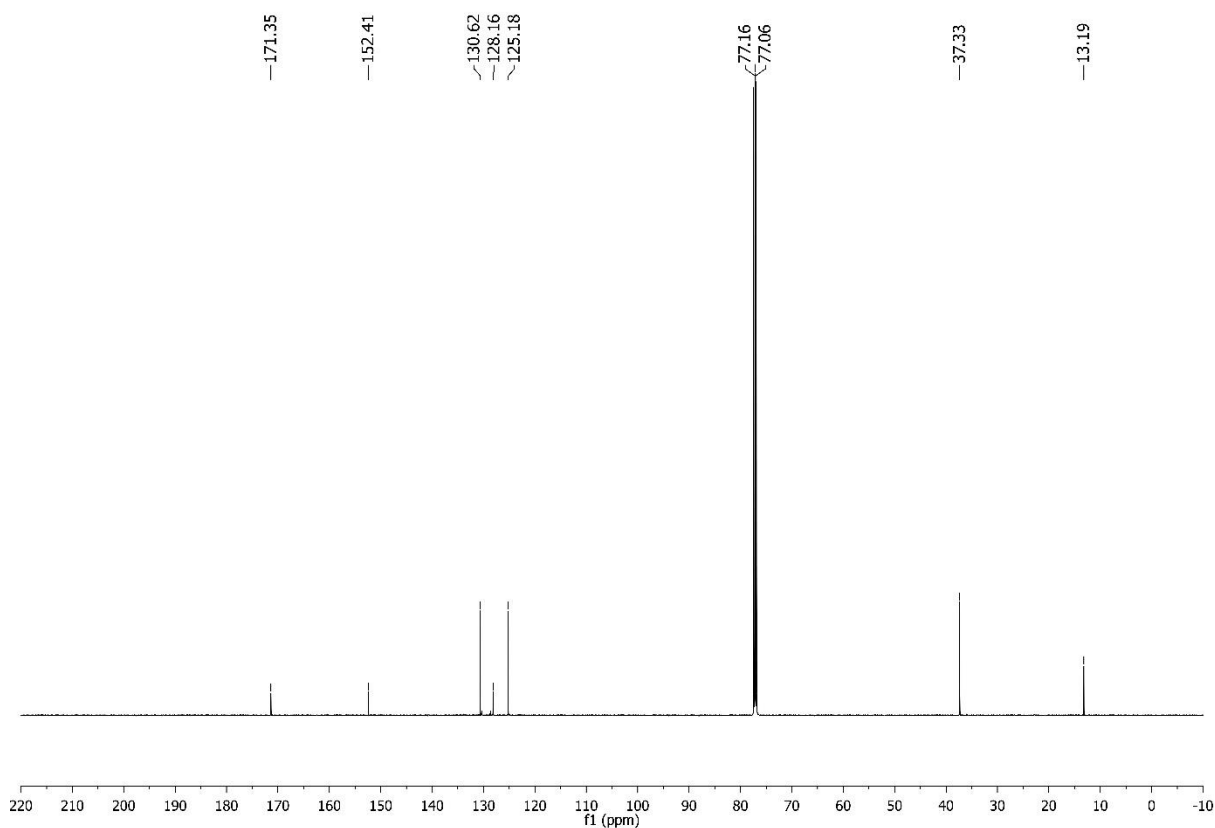
#### 4-(1-Hydroxycyclobutyl)benzoic acid (S15)



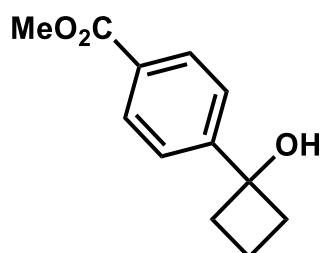
To a solution of 4-bromobenzoic acid (4.0 g, 20 mmol, 1 eq.) in THF (100 mL) at -78 °C was added *n*-butyllithium (17.4 mL, 2.3 M in hexanes, 40.0 mmol, 2.0 eq.) and the resulting mixture was stirred for 30 min. Cyclobutanone (3.3 mL, 44 mmol, 2.2 eq.) was added dropwise to the reaction mixture followed by immediate addition of sat. NH<sub>4</sub>Cl (30 mL) and the resulting mixture was warmed to rt. The reaction mixture was then acidified with 1 M HCl and extracted with EtOAc (3 × 50 mL). The combined organics were dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude residue was suspended in hexanes and stirred vigorously, which resulted in formation of a white solid. The precipitate was filtered and resuspended in CH<sub>2</sub>Cl<sub>2</sub>. Slow addition of hexanes followed resulted in precipitation of the white solid which was filtered and dried under a high vacuum to afford **S15** (1.23 g, 31%) as white solid.

**R<sub>f</sub>** = 0.56 (80% EtOAc/Petrol); **M.p.**: 149-151 °C; **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3264 (br), 2980, 2671, 2561, 1677, 1612, 1420, 1272, 1130, 856, 702, 542; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.15 – 8.08 (m, 2H), 7.47 – 7.41 (m, 2H), 7.66 – 7.59 (m, 1H), 2.64 – 2.53 (m, 2H), 2.47-2.37 (m, 2H), 2.18 – 1.99 (m, 1H), 1.84 – 1.72 (m, 1H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 171.3, 152.4, 130.6, 128.1, 125.1, 77.0, 37.3, 13.1; **HRMS** (EI<sup>+</sup>) [C<sub>11</sub>H<sub>11</sub>O<sub>3</sub>] requires [M-H] 191.0708, found 191.0701.



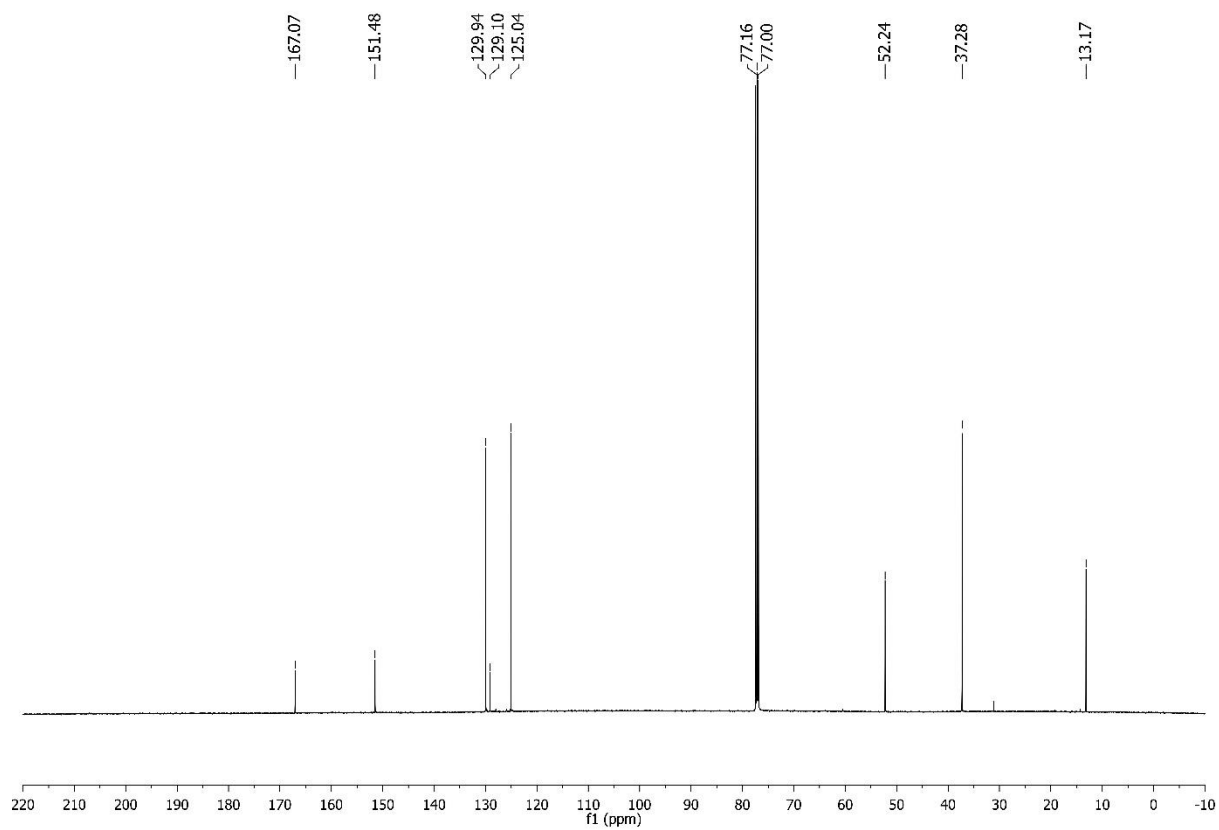
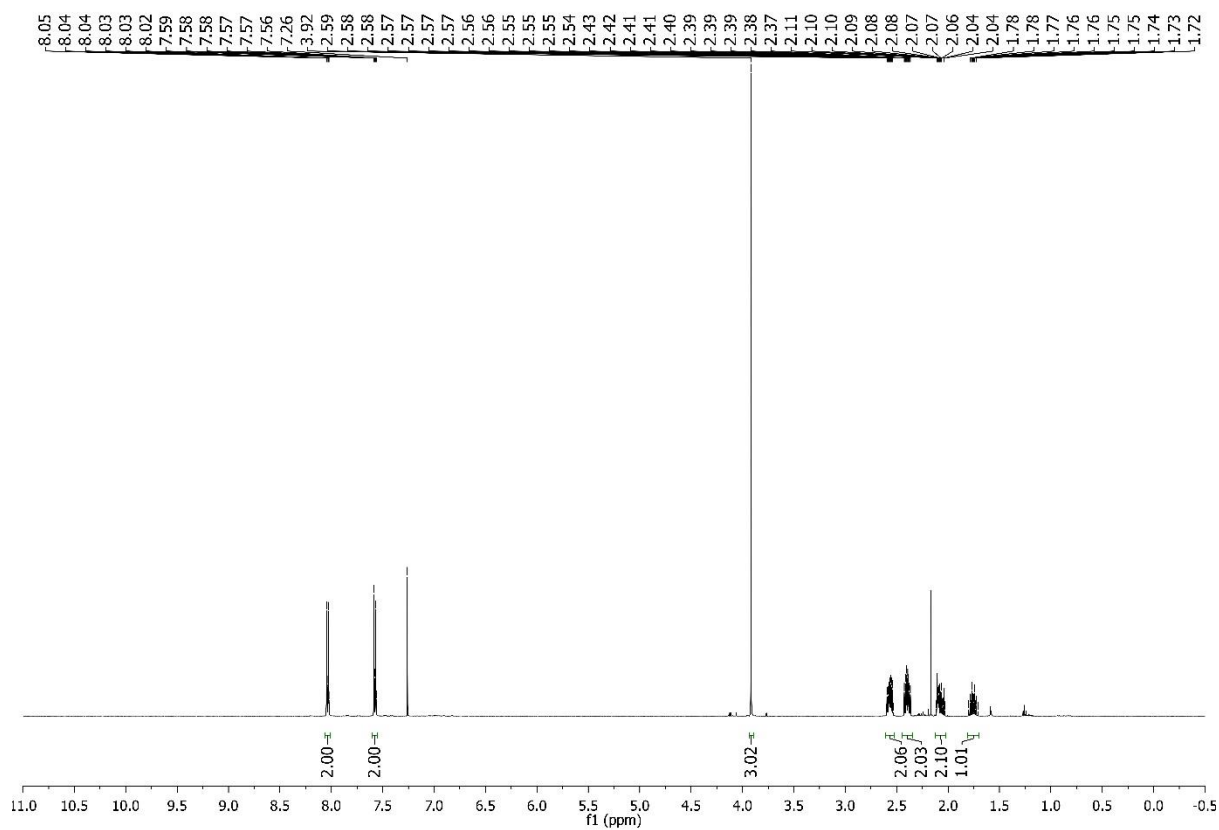


#### Methyl 4-(1-hydroxycyclobutyl)benzoate (**S16**)

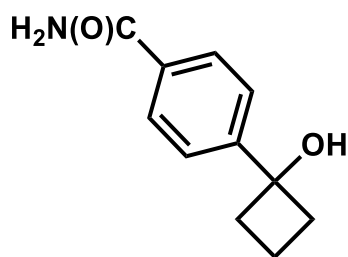


To a solution of **S15** (400 mg, 2.08 mmol, 1.0 eq.) in DMF (5.0 mL, 0.4 M) was added  $K_2CO_3$  (340 mg, 2.50 mmol, 1.2 eq.) and the reaction mixture was stirred for 10 min at rt. Methyl iodide (142  $\mu$ L, 2.28 mmol, 1.1 eq.) was added and the reaction mixture was stirred for 4 h. Brine (10 mL) was added and the aqueous layer was extracted with EtOAc ( $3 \times 10$  mL). The combined organic layers were dried ( $MgSO_4$ ), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (5 $\rightarrow$ 15% EtOAc/Petrol, silica gel) to afford **S16** (350 mg, 83%) as a yellow oil.

$R_f$  = 0.48 (30% EtOAc/Petrol); **FTIR** ( $\nu_{max}$   $cm^{-1}$ , thin film) 3439 (br), 2992, 2945, 1721, 1701, 1607, 1437, 1281, 1105, 1018, 856, 772, 706;  **$^1H$  NMR** (500 MHz,  $CDCl_3$ )  $\delta$  = 8.07–8.00 (m, 2H), 7.60–7.54 (m, 2H), 3.92 (s, 3H), 2.61–2.52 (m, 2H), 2.46–2.34 (m, 2H), 2.13–2.02 (m, 2H), 1.82–1.69 (m, 1H);  **$^{13}C$  NMR** (126 MHz,  $CDCl_3$ )  $\delta$  = 167.0, 151.4, 129.9, 129.1, 125.0, 77.0, 52.2, 37.3, 13.2; **HRMS** ( $El^+$ ) [ $C_{12}H_{13}O_3$ ] requires [M-H] 205.0865, found 205.0863.

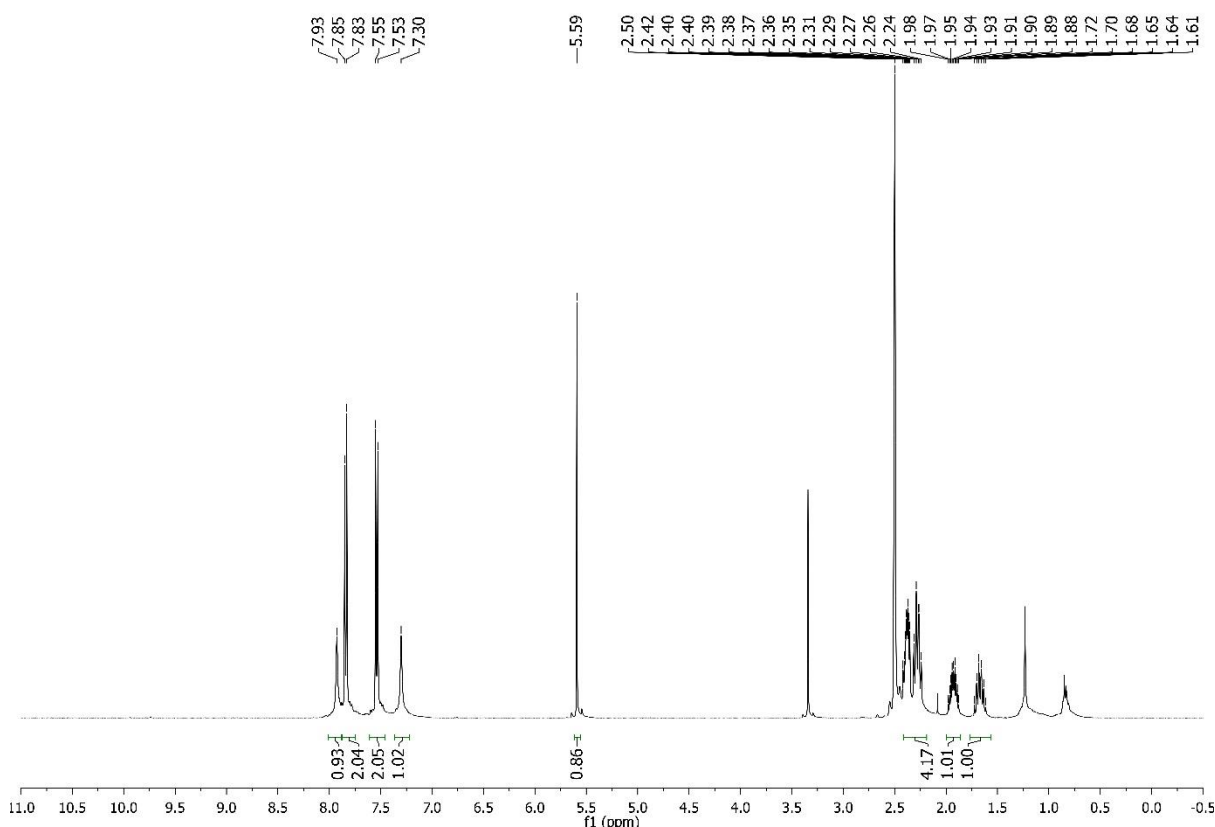


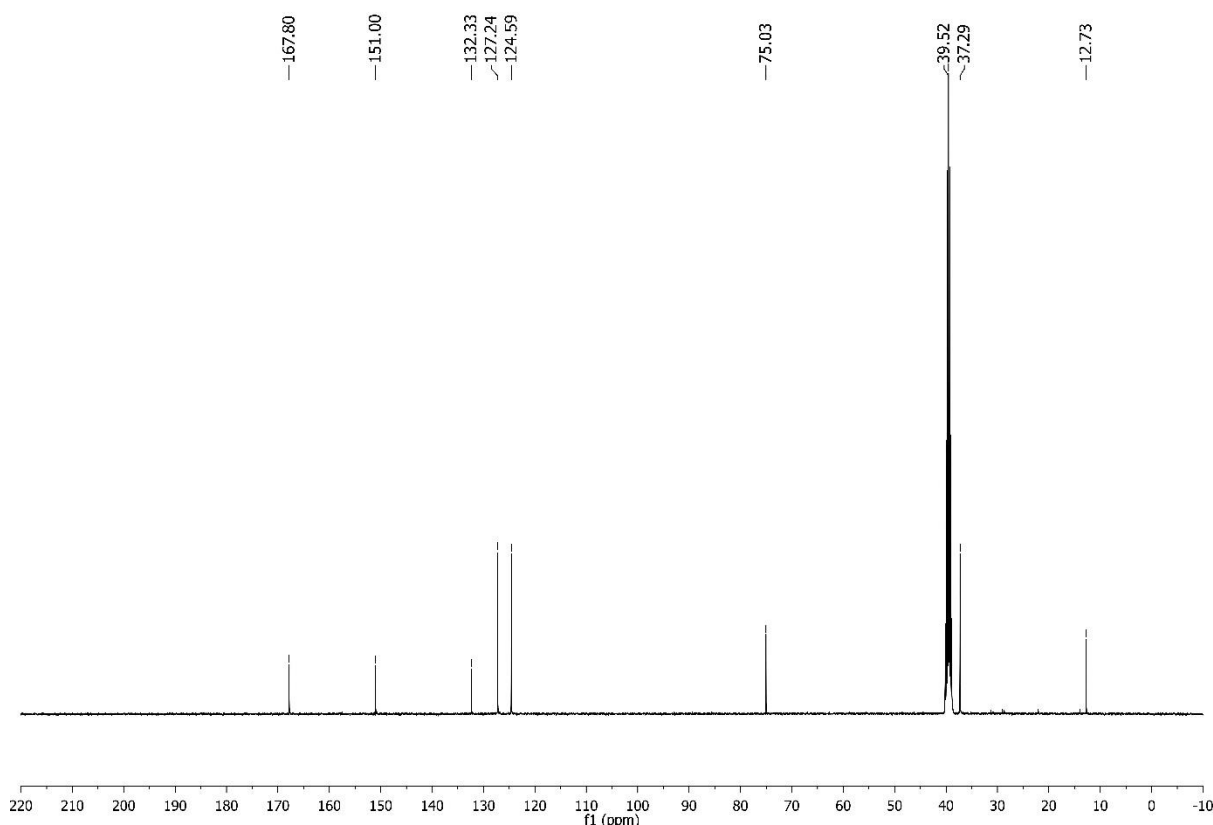
#### 4-(1-Hydroxycyclobutyl)benzamide (**S17**)



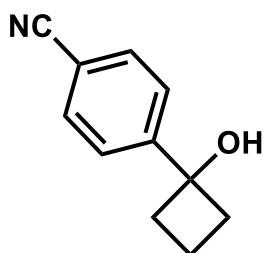
To a stirred solution of **S15** (400 mg, 2.08 mmol, 1.0 eq.) in THF (10 ml) was added  $\text{SOCl}_2$  (0.36 mL, 4.8 mmol, 2.3 eq.) at 0 °C and the reaction mixture was stirred at rt for 1 h. Upon cooling to 0 °C the reaction mixture was poured into an ice-cold solution of  $\text{NH}_4\text{OH}$  (2.40 mL, 35% in water) and stirred for 5 min. The reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 × 15 mL) and the organic layers were dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography (70% EtOAc/hexanes, silica gel) to afford **S17** (56 mg, 15%) as a white amorphous solid.

$R_f$  = 0.32 (100% EtOAc); **M.p.**: 156-158 °C; **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 3267 (br), 3169 (br), 1665, 1607, 1557, 1420, 1290, 1138, 1117, 891, 808, 650;  **$^1\text{H}$  NMR (500 MHz, DMSO)**  $\delta$  = 7.93 (br, 1H), 7.86 – 7.77 (m, 2H), 7.57 – 7.49 (m, 2H), 7.30 (br, 1H), 5.59 (s, 1H), 2.43 – 2.33 (m, 2H), 2.33 – 2.22 (m, 2H), 1.99 – 1.86 (m, 1H), 1.73 – 1.60 (m, 1H);  **$^{13}\text{C}$  NMR (126 MHz, DMSO)**  $\delta$  = 167.8, 151.0, 132.3, 127.2, 124.6, 75.0, 37.3, 12.7; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{11}\text{H}_{13}\text{NO}_2$ ] requires  $[\text{M}+\text{H}]$  192.1025, found 192.1026.





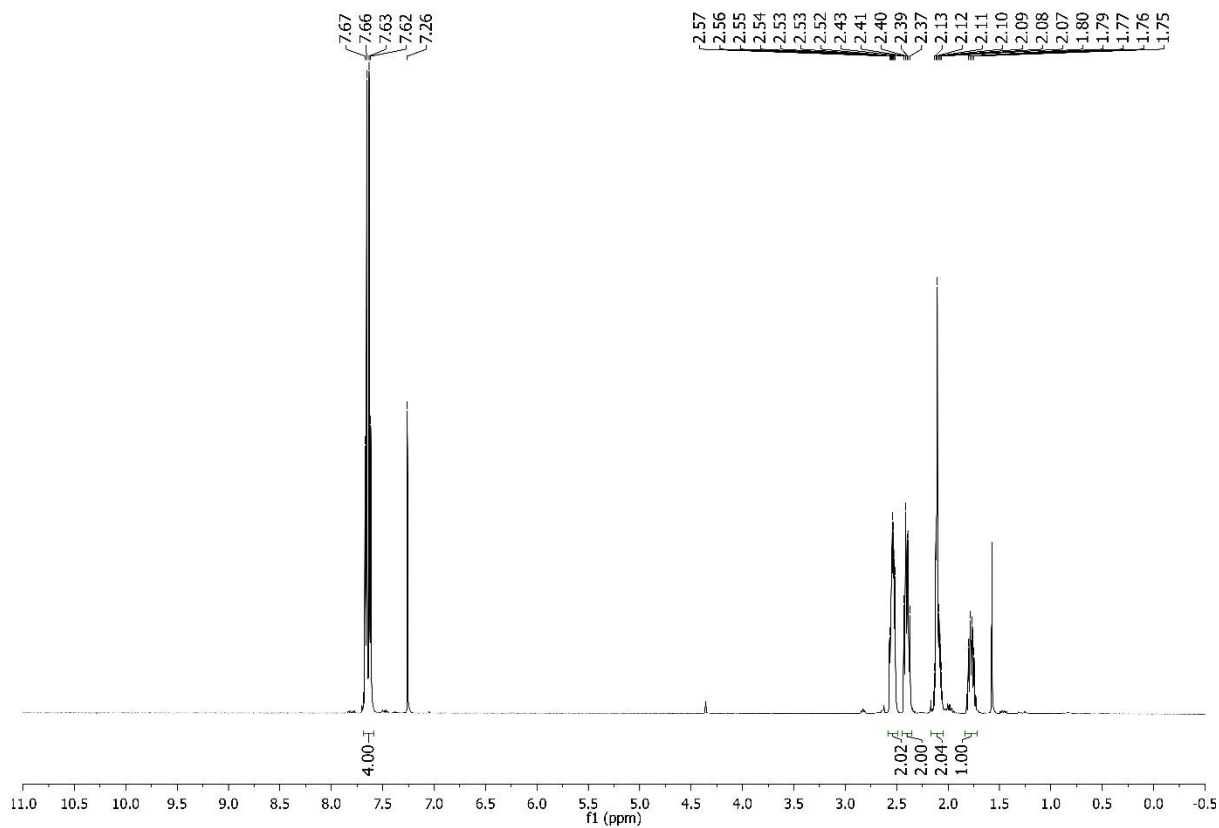
#### 4-(1-Hydroxycyclobutyl)benzonitrile (**S18**)

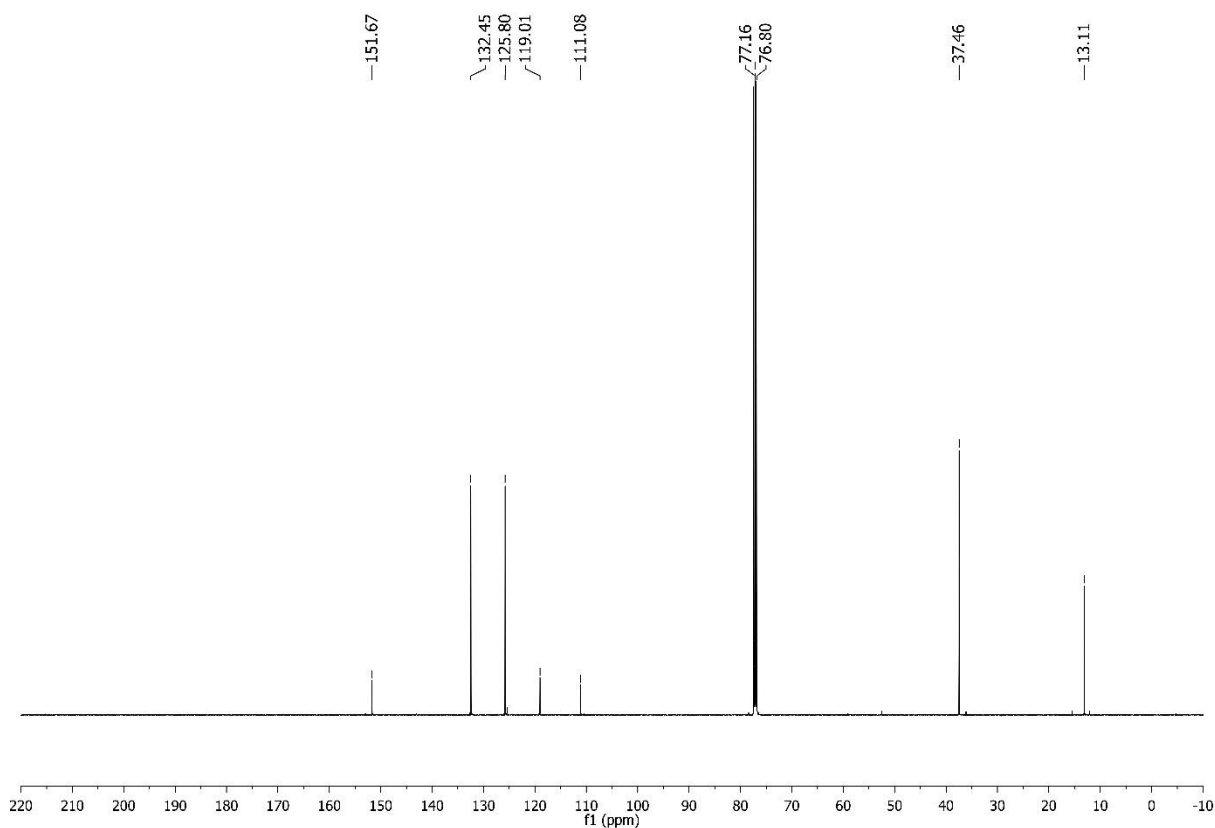


**Preparation of Turbo-Grignard (*i*-PrMgCl.LiCl):** To a flame-dried RBF was added dry LiCl (1.75 g, 38.0 mmol, 1.00 eq.), magnesium turnings (1.20 g, 50.0 mmol, 1.30 eq.) and a crystal of iodine followed by THF (20 mL). The mixture was cooled to 0 °C and 2-chloropropane (3.5 mL, 38.0 mmol, 1.00 eq.) was added dropwise maintaining the temperature of the bath at 0 °C. After the addition was complete, the reaction mixture was brought to rt and stirred for 12 h. The resulting black reaction mixture (1.1 M) was kept under nitrogen and used as such in the following reaction.

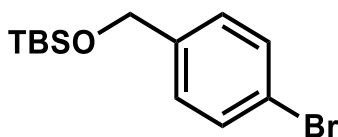
**Preparation of **S18**:** In a flame-dried RBF was added 4-bromobenzonitrile (2.18 g, 12.0 mmol, 1.2 eq.) and THF (20 mL) and cooled to -7 °C. The pre-formed Turbo-Grignard reagent (13.63 mL, 1.1 M, 15.0 mmol, 1.5 eq.) was added dropwise and the resulting mixture was stirred for 4 h at -7 °C. Cyclobutanone (747 µL, 10.0 mmol, 1.0 eq.) was added dropwise and the resulting mixture was stirred for 1 h at -7 °C and then stirred at rt for an additional 2 h. The reaction was quenched with sat. NH<sub>4</sub>Cl (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (5→20% EtOAc/Petrol, silica gel) to afford **S18** (700 mg, 40%) as a colourless liquid.

$R_f = 0.20$  (15% EtOAc/Petrol); **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3333 (br), 2984, 2934, 2361, 2340, 1487, 1456, 1377, 1277, 1231, 1123, 1024, 887, 758, 727;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta = 7.74 - 7.56$  (m, 4H), 2.60 – 2.48 (m, 2H), 2.46 – 2.35 (m, 5H), 2.15 – 2.05 (m, 2H), 1.84 – 1.71 (m, 1H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta = 151.6, 132.5, 125.8, 119.1, 111.1, 76.8, 37.5, 13.1$ ; **HRMS ( $\text{EI}^+$ )** [ $\text{C}_{11}\text{H}_{11}\text{NO}$ ] requires [M] 173.0841, found 173.0841.





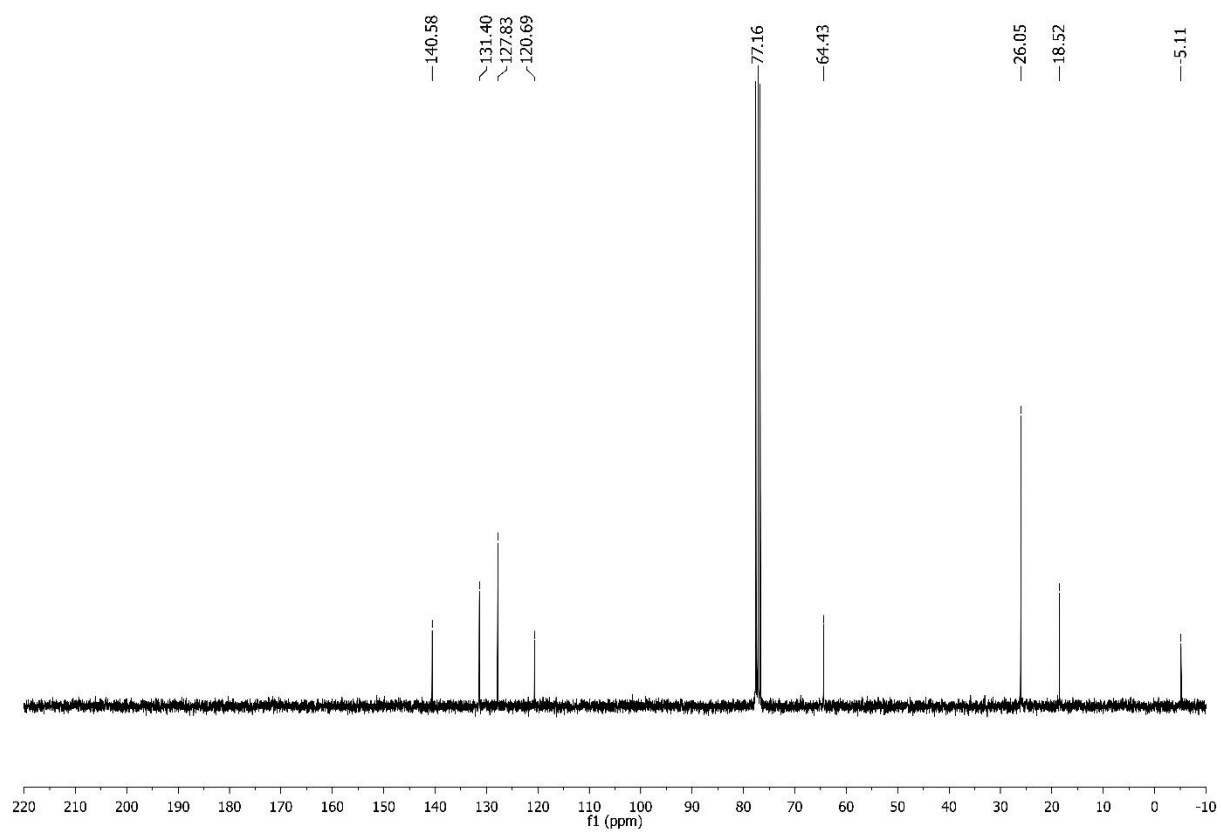
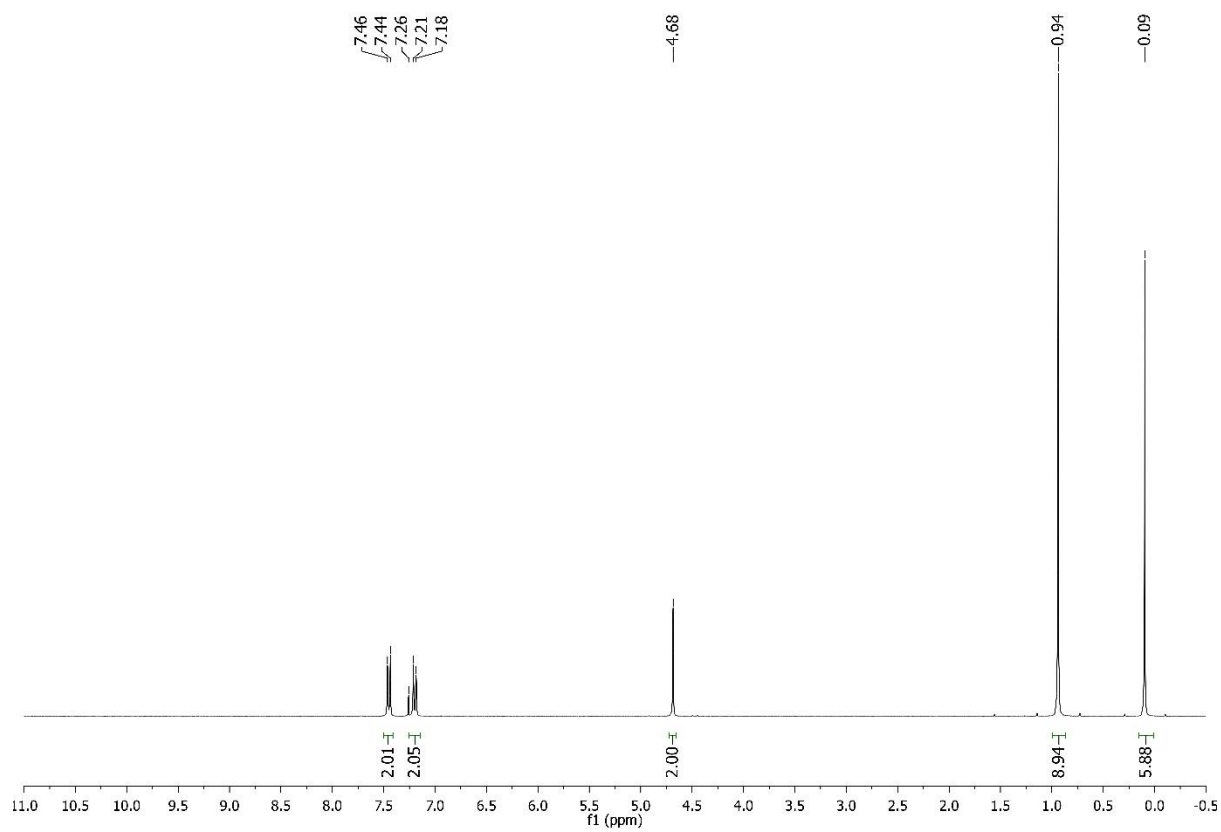
**((4-Bromobenzyl)oxy)(*tert*-butyl)dimethylsilane (S19)**



To a solution of (4-bromophenyl)methanol (4.00 g, 21.3 mmol 1.0 eq.) in  $\text{CH}_2\text{Cl}_2$  was added imidazole (2.91 g, 42.7 mmol, 2.0 eq.) and *tert*-butylchlorodimethylsilane (6.44 g, 42.7 mmol, 2.0 eq.). The resulting mixture was stirred for 14 h at rt, then poured into water (50 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  30 mL). The combined organics were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (5% EtOAc/Petrol) to afford **S19** (5.8 g, 94%) as a colourless liquid.

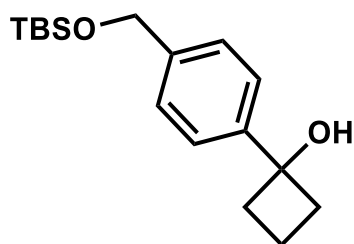
$R_f$  = 0.18 (10% EtOAc/Petrol);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.51 – 7.39 (m, 2H), 7.25 – 7.14 (m, 2H), 4.69 (s, 2H), 0.94 (s, 9H), 0.09 (s, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 140.4, 131.2, 127.7, 120.5, 64.3, 25.9, 18.5, -5.3.

These data are consistent with those previously reported in the literature.<sup>[8]</sup>



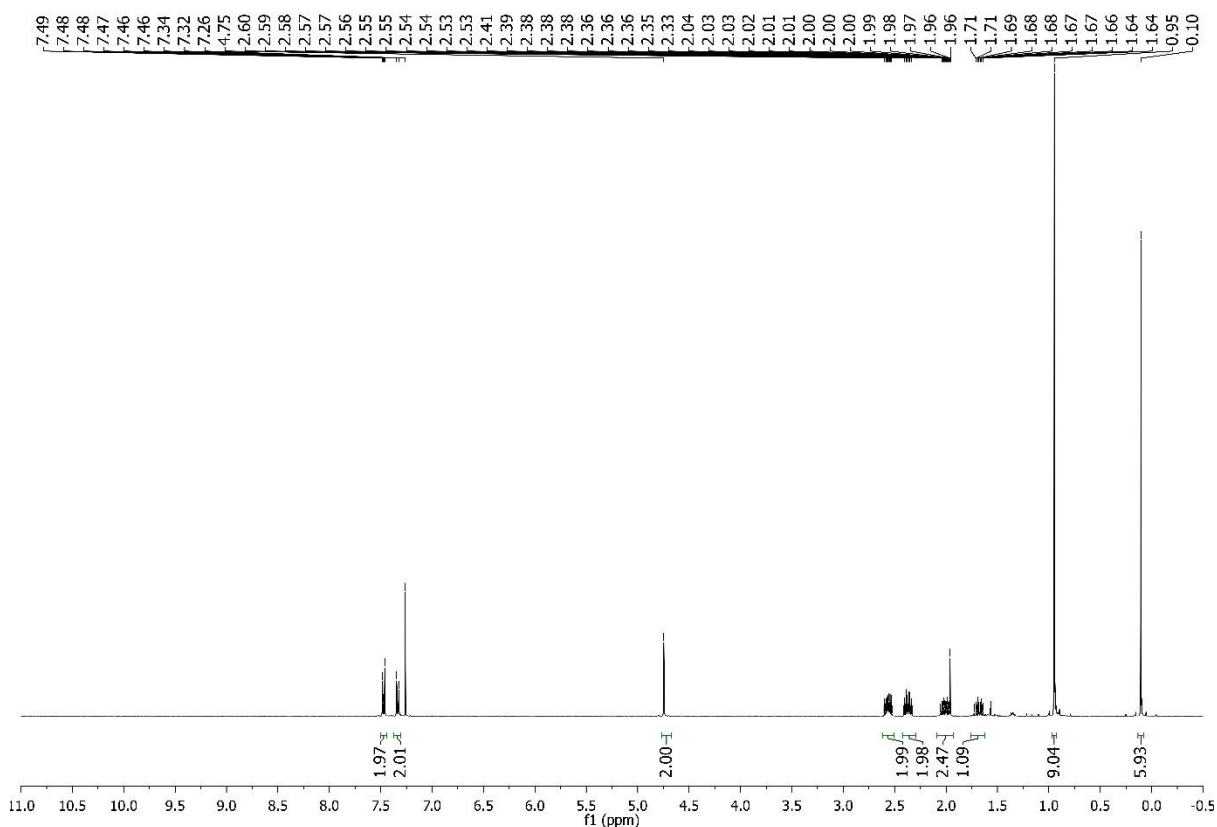


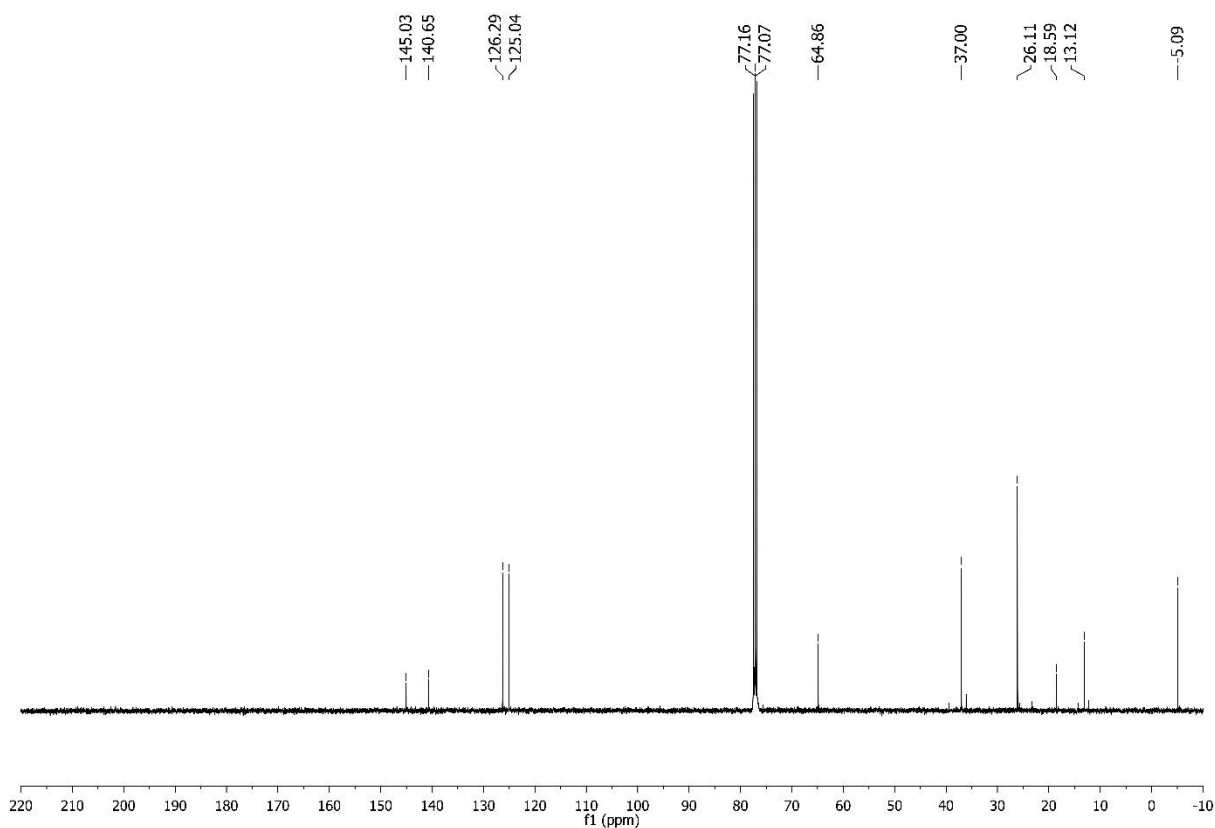
**1-(4-(((*Tert*-butyldimethylsilyl)oxy)methyl)phenyl)cyclobutan-1-ol (**S20**)**



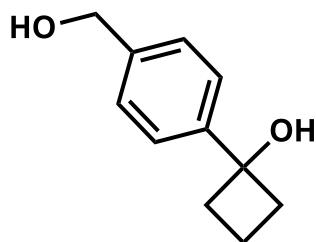
Prepared according to General Procedure C using compound **S19** (1.80 g, 6.00 mmol, 1.2 eq.), *n*-butyllithium (4.10 mL, 2.2 M in hexanes, 9.00 mmol, 1.5 eq.) and cyclobutanone (374  $\mu$ L, 5.00 mmol, 1.0 eq.). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S20** (0.99 g, 57%) as a colourless oil.

$R_f$  = 0.20 (15% EtOAc/Petrol); FTIR ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3354 (br), 2866, 2934, 1460, 1367, 1251, 1089, 833, 771, 667;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.51 – 7.43 (m, 2H), 7.36–7.31 (m, 2H), 4.75 (s, 2H), 2.62 – 2.51 (m, 2H), 2.43 – 2.31 (m, 2H), 2.06 – 1.95 (m, 2H), 1.74 – 1.63 (m, 1H), 0.95 (s, 9H), 0.11 (s, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 145.0, 140.7, 126.3, 125.0, 77.1, 64.9, 37.0, 26.1, 18.6, 13.1, -5.1; HRMS ( $\text{EI}^+$ ) [ $\text{C}_{17}\text{H}_{28}\text{O}_2\text{Si}$ ] requires  $[M-H]$  291.1780, found 291.1779..





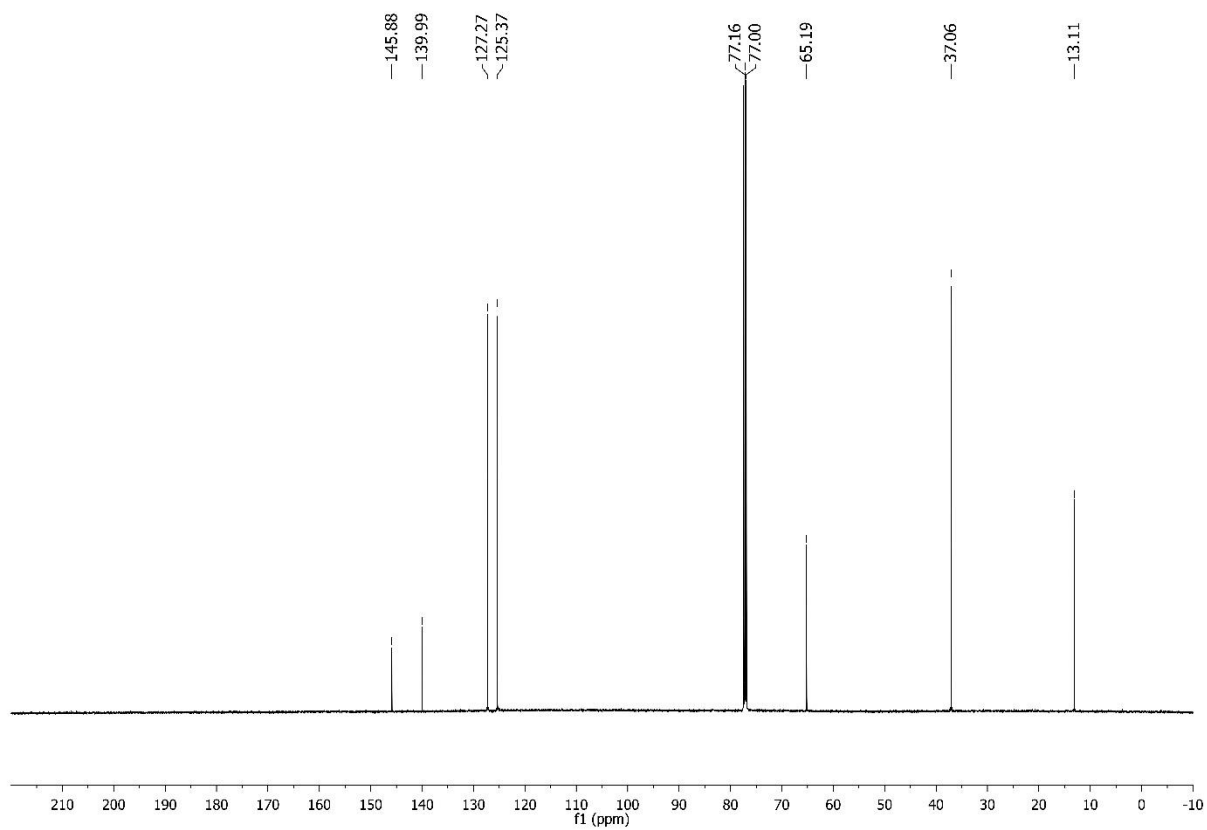
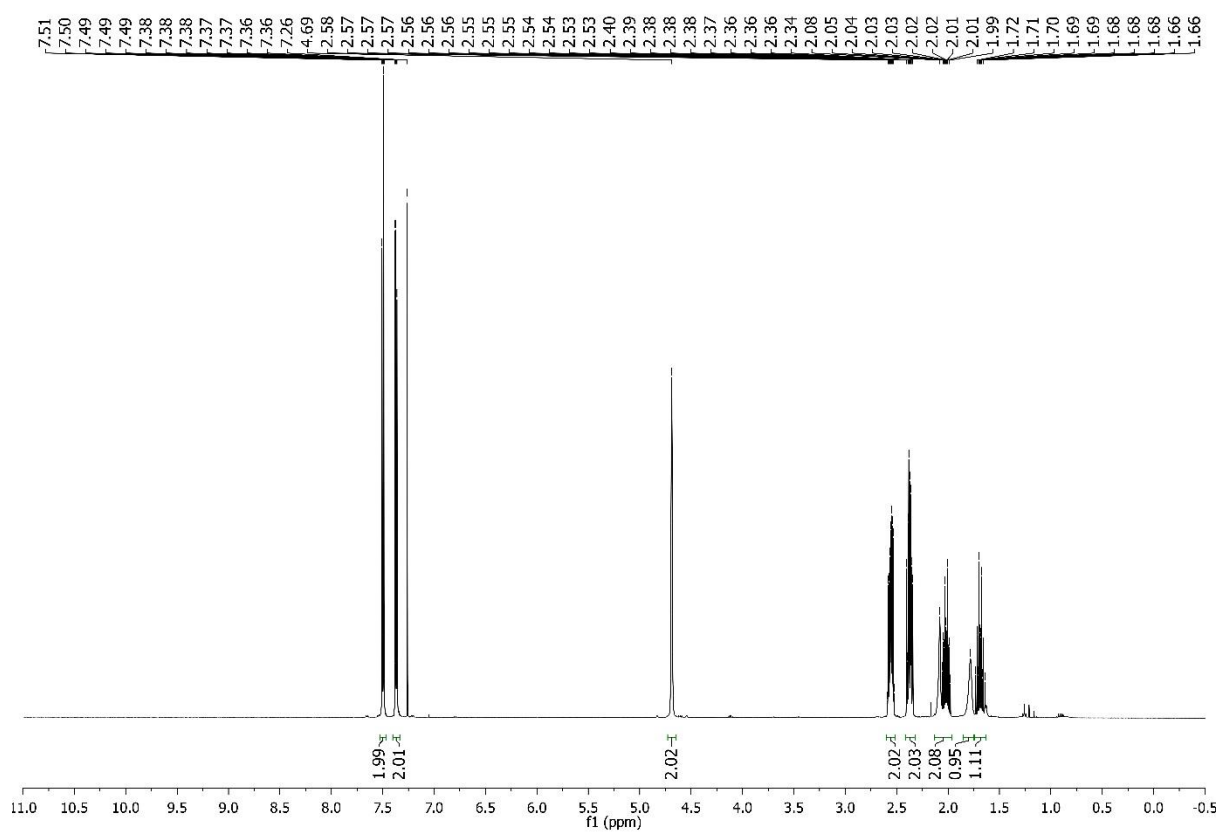
**1-(4-(Hydroxymethyl)phenyl)cyclobutan-1-ol (S21)**



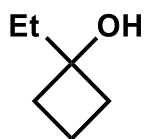
To a solution of **S20** (2.00 g, 6.8 mmol, 1.0 eq.) in dry THF (20 mL, 0.34 M) at 0 °C was added TBAF (13.6 mL, 1 M in THF, 13.6 mmol, 2.0 eq.). The reaction mixture was stirred for 2 h at rt. Water (15 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organics were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30 % EtOAc/Petrol, silica gel) to afford **S21** (800 mg, 66%) as a white solid.

**R<sub>f</sub>** = 0.20 (30% EtOAc/Petrol); **M.p.**: 64–66 °C (lit.<sup>[9]</sup> 63–66 °C); **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ = 7.53 – 7.47 (m, 2H), 7.40–7.34 (m, 2H), 4.69 (s, 2H), 2.61 – 2.51 (m, 2H), 2.42 – 2.32 (m, 2H), 2.08 (s, 1H), 2.06 – 1.97 (m, 1H), 1.79 (s, 1H) 1.75 – 1.62 (m, 1H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ = 145.9, 140.0, 127.3, 125.4, 77.0, 65.2, 37.1, 13.1.

These data are consistent with those previously reported in the literature.<sup>[9]</sup>

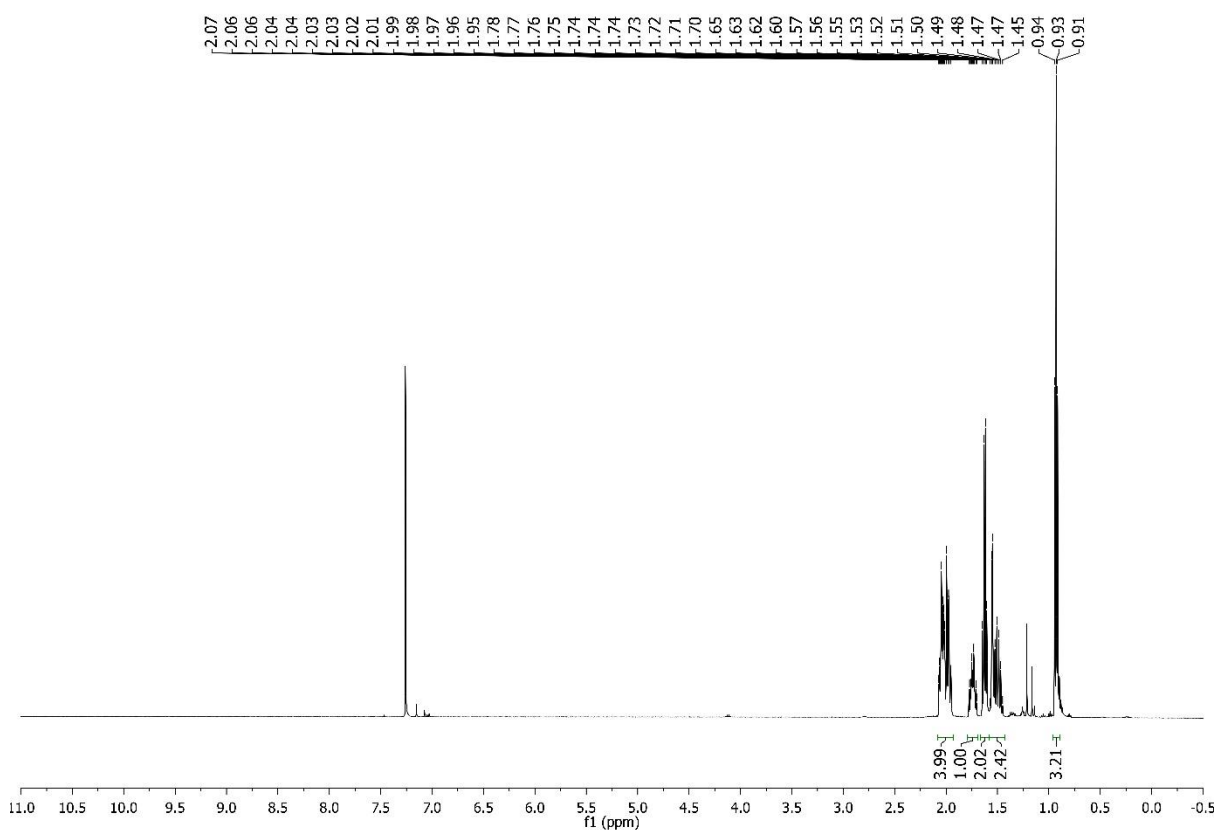


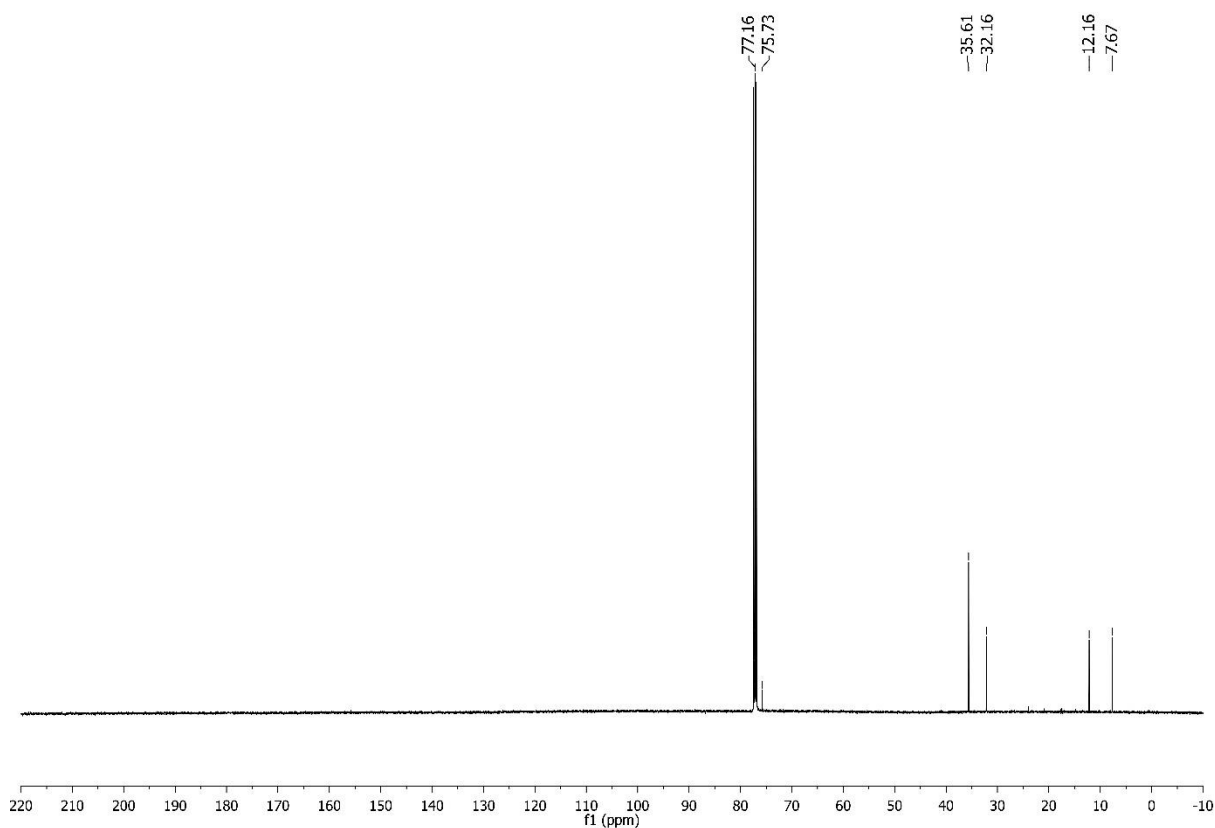
### 1-Ethylcyclobutan-1-ol (S22)



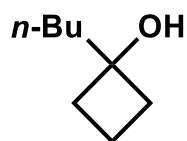
Prepared according to General Procedure B using ethylmagnesium bromide (5.00 mL, 3.0 M in Et<sub>2</sub>O, 15.0 mmol), and cyclobutanone (747  $\mu$ L, 10.0 mmol). The crude residue was purified by flash column chromatography (10 $\rightarrow$ 20% EtOAc/Petrol, silica gel) to afford **14** (323 mg, 32%) as a colourless oil.

$R_f$  = 0.19 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\max}$  cm<sup>-1</sup>, thin film) 3343 (br), 2963, 2932, 2878, 1462, 1296, 1285, 1242, 1173, 1150, 1022, 953, 891, 706, 631; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 2.08 – 1.94 (m, 4H), 1.78 – 1.70 (m, 1H), 1.63 (q,  $J$  = 7.5 Hz, 2H), 1.57 – 1.44 (m, 2H), 0.93 (t,  $J$  = 7.5 Hz, 3H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 75.7, 35.6, 32.2, 12.2, 7.7; **HRMS (EI<sup>+</sup>)** [C<sub>6</sub>H<sub>12</sub>O] requires [M] 100.0888, found 100.0890.





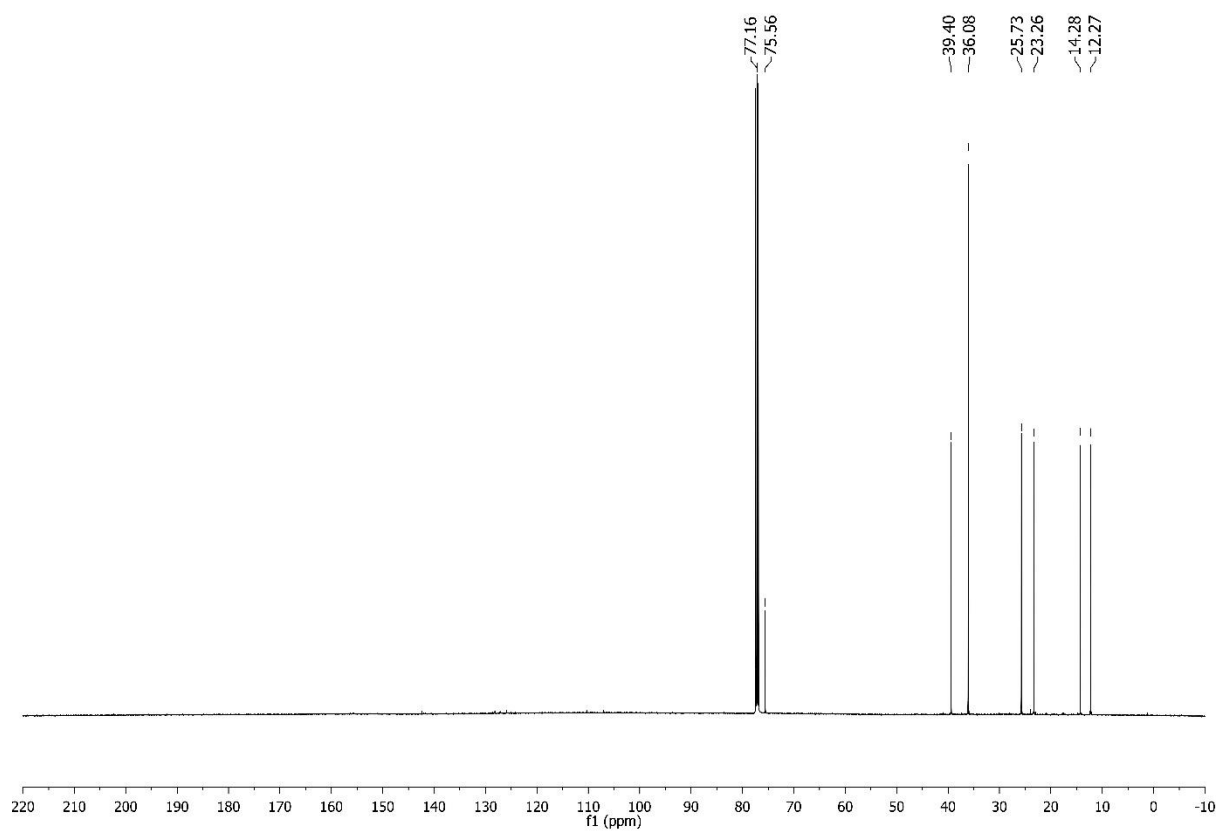
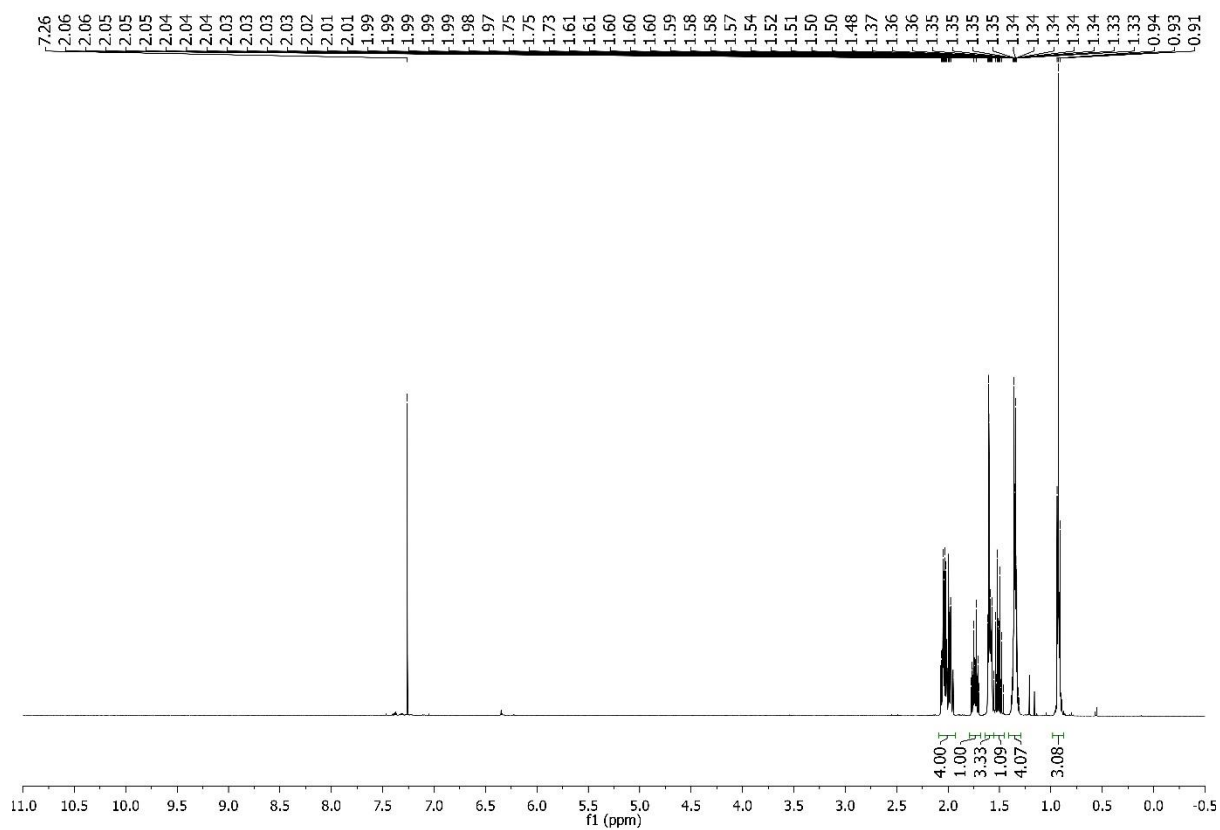
### 1-Butylcyclobutan-1-ol (**S23**)



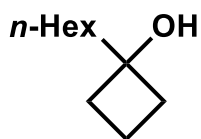
Prepared according to General Procedure B using n-butyilmagnesium chloride (2.00 mL, 20% w/v in THF/Toluene, 3.75 mmol) and cyclobutanone (187  $\mu$ L, 2.50 mmol). The crude residue was purified by flash column chromatography (10% Et<sub>2</sub>O/Petrol, silica gel) to afford **S23** (268 mg, 84%) as a colourless liquid.

$R_f$  = 0.31 (10% EtOAc/Petrol);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 2.09 – 1.93 (m, 4H), 1.79 – 1.69 (m, 1H), 1.63 – 1.45 (m, 4H), 1.40 – 1.30 (m, 4H), 0.97 – 0.89 (m, 3H);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 75.6, 39.4, 36.1, 25.7, 23.3, 14.3, 12.3.

These data are consistent with those previously reported in the literature.<sup>[4]</sup>

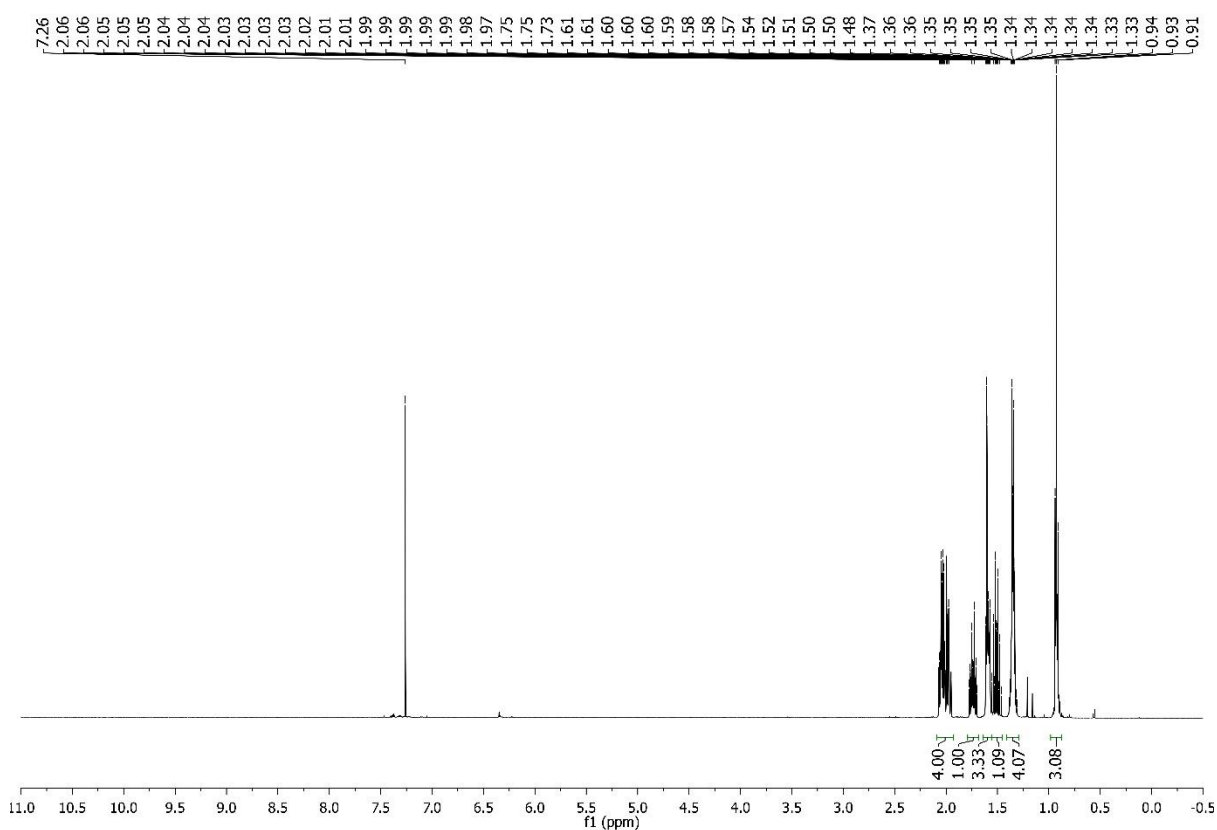


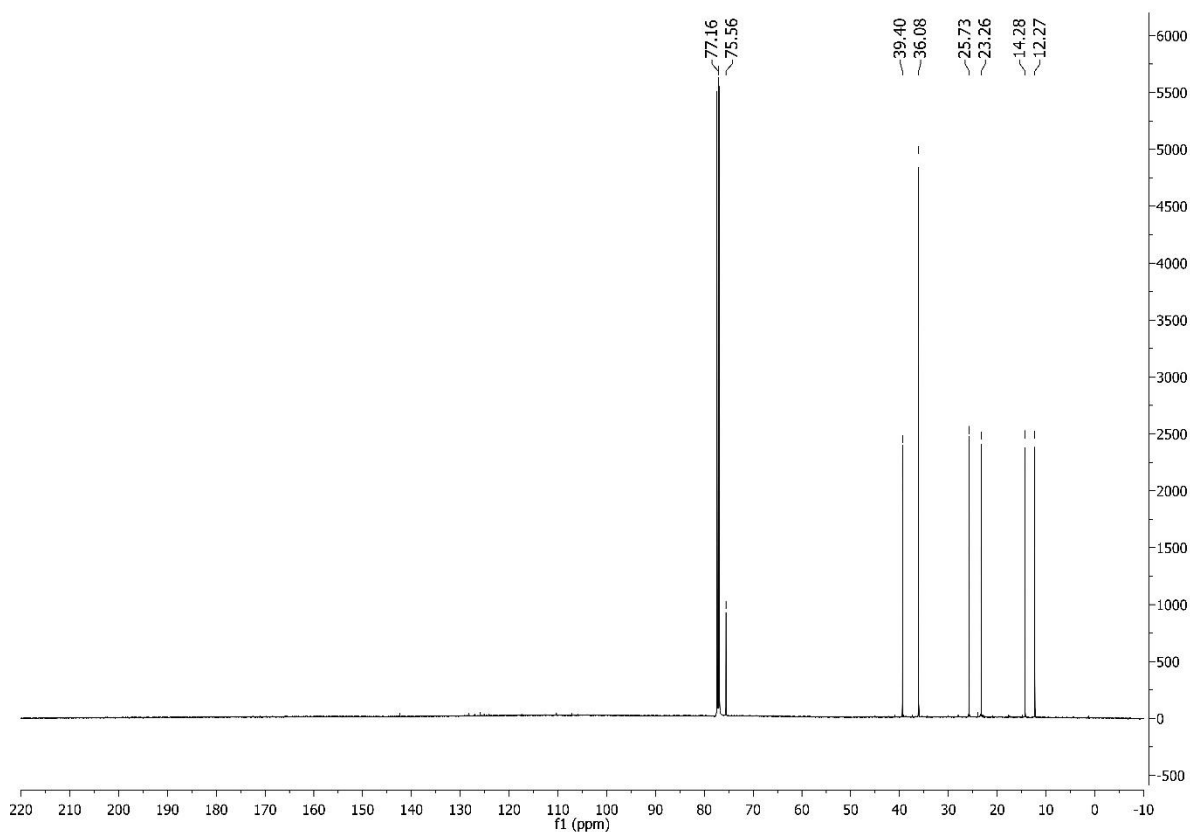
### 1-Hexylcyclobutan-1-ol (**S24**)



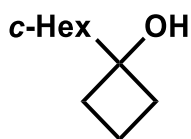
Prepared according to General Procedure A using magnesium turnings (201 mg, 8.25 mmol), 1-bromohexane (1.05 mL, 7.50 mmol), and cyclobutanone (374  $\mu$ L, 5.00 mmol). The crude residue was purified by flash column chromatography (5% EtOAc/Hexanes, silica gel) to afford **S24** (381 mg, 49%) as a colourless oil.

$R_f$  = 0.21 (10% EtOAc, Hexanes); **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3350 (br), 2955, 2928, 2857, 1460, 1377, 1267, 1246, 1167, 1069, 957, 912, 721, 638;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 2.08 – 1.94 (m, 4H), 1.79 – 1.69 (m, 1H), 1.62 – 1.45 (m, 4H), 1.40 – 1.24 (m, 8H), 0.93 – 0.85 (m, 3H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 75.6, 39.7, 36.1, 32.1, 29.9, 23.5, 22.8, 14.3, 12.3; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{10}\text{H}_{20}\text{O}$ ] requires  $[\text{M}-\text{H}_2\text{O}]$  138.1408, found 138.1410.





### 1-Cyclohexylcyclobutan-1-ol (S25)

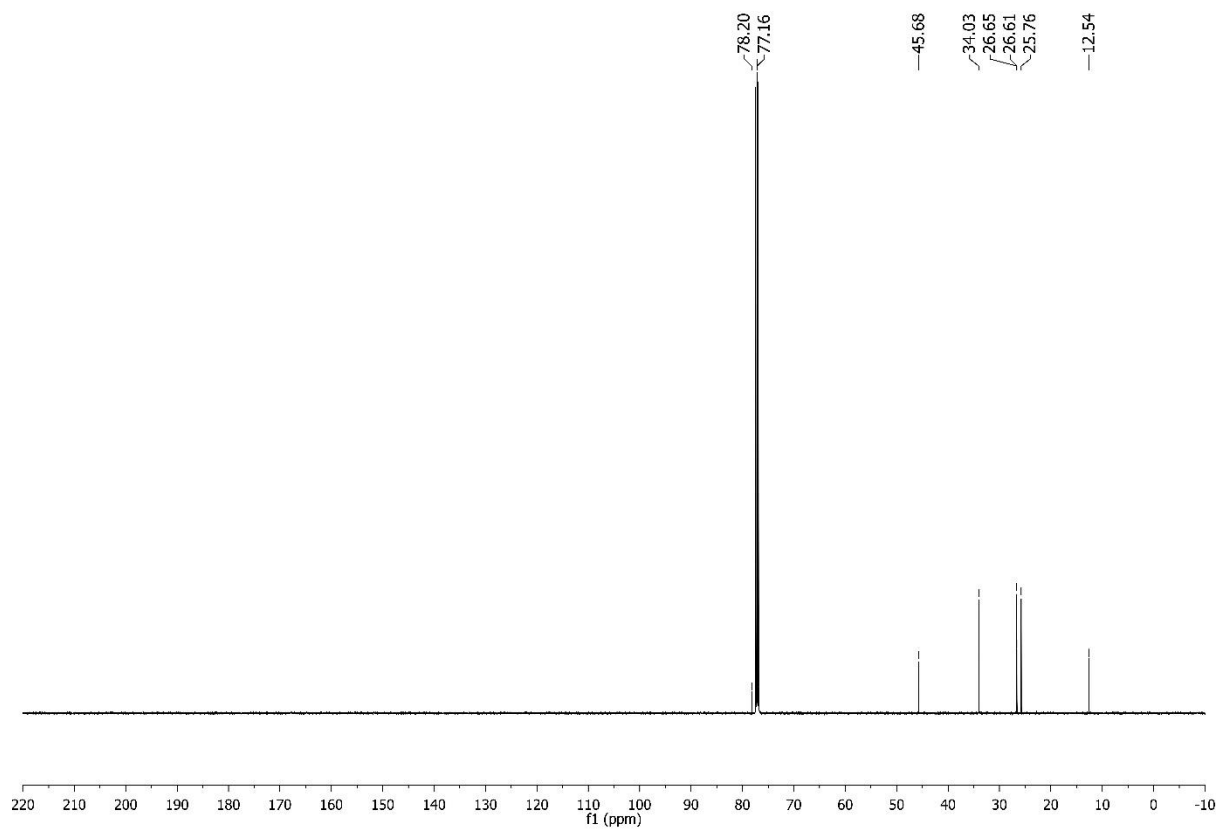
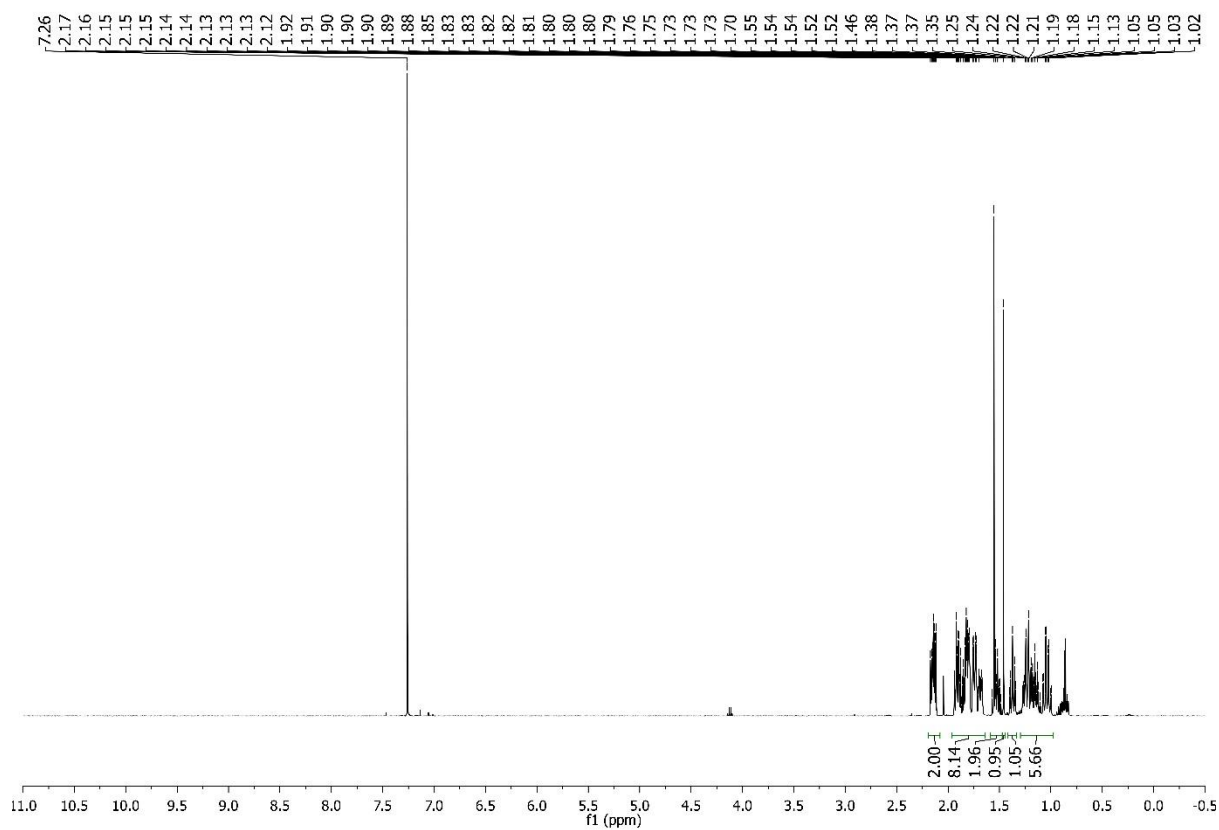


Prepared according to General Procedure B using cyclohexylmagnesium chloride (11.5 mL, 1.3 M in 1:1 THF/Toluene, 15.0 mmol), and cyclobutanone (747  $\mu$ L, 10.0 mmol). The crude residue was purified by flash column chromatography (10% EtOAc/Petrol, silica gel) to afford **S25** (1.18 g, 77%) as a colourless oil.

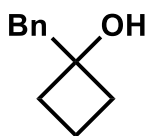
$R_f$  = 0.17 (10% EtOAc/Petrol);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 2.18 – 2.11 (m, 2H), 1.94 – 1.65 (m, 8H), 1.58 – 1.48 (m, 1H), 1.46 (s, 1H), 1.37 (tt,  $J$  = 12.0, 3.0 Hz, 1H), 1.28 – 0.98 (m, 5H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 78.2, 45.7, 34.0, 26.7, 26.6, 25.6, 12.6.

These data are consistent with those previously reported in the literature.<sup>[4]</sup>



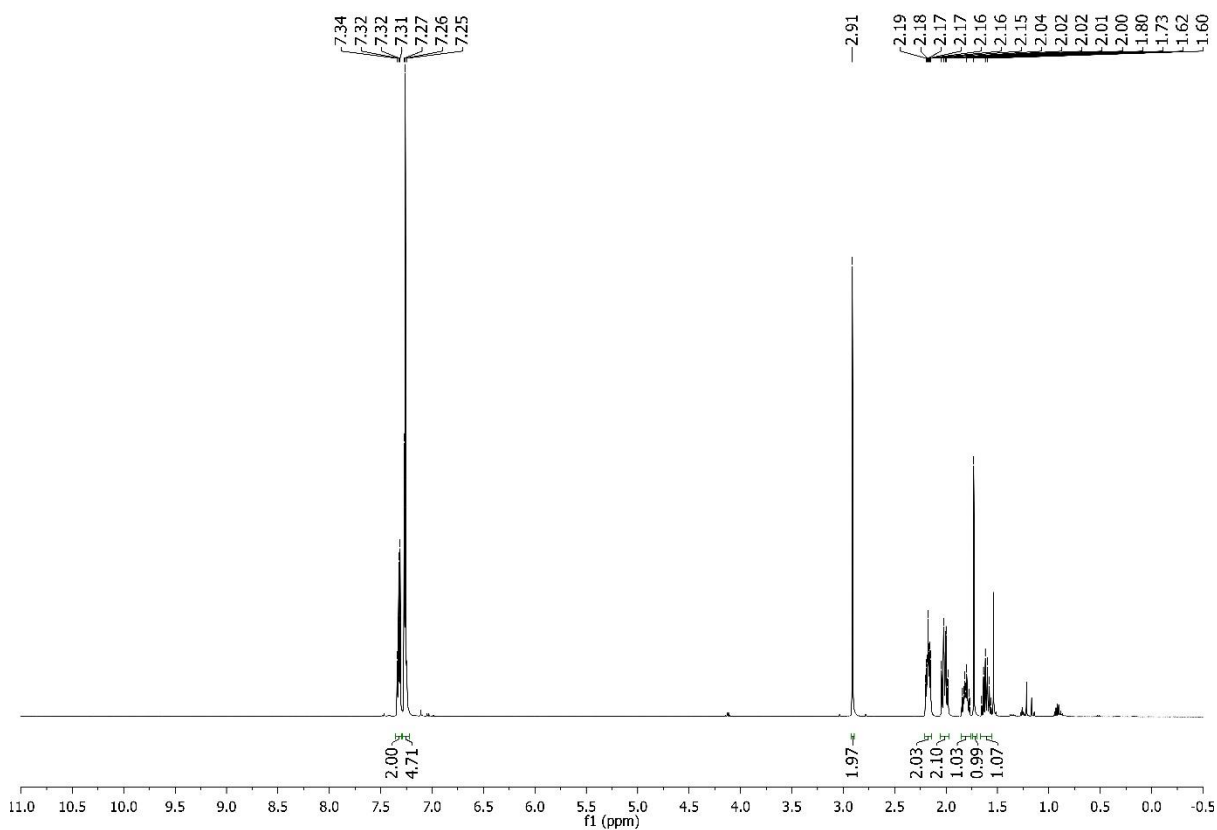


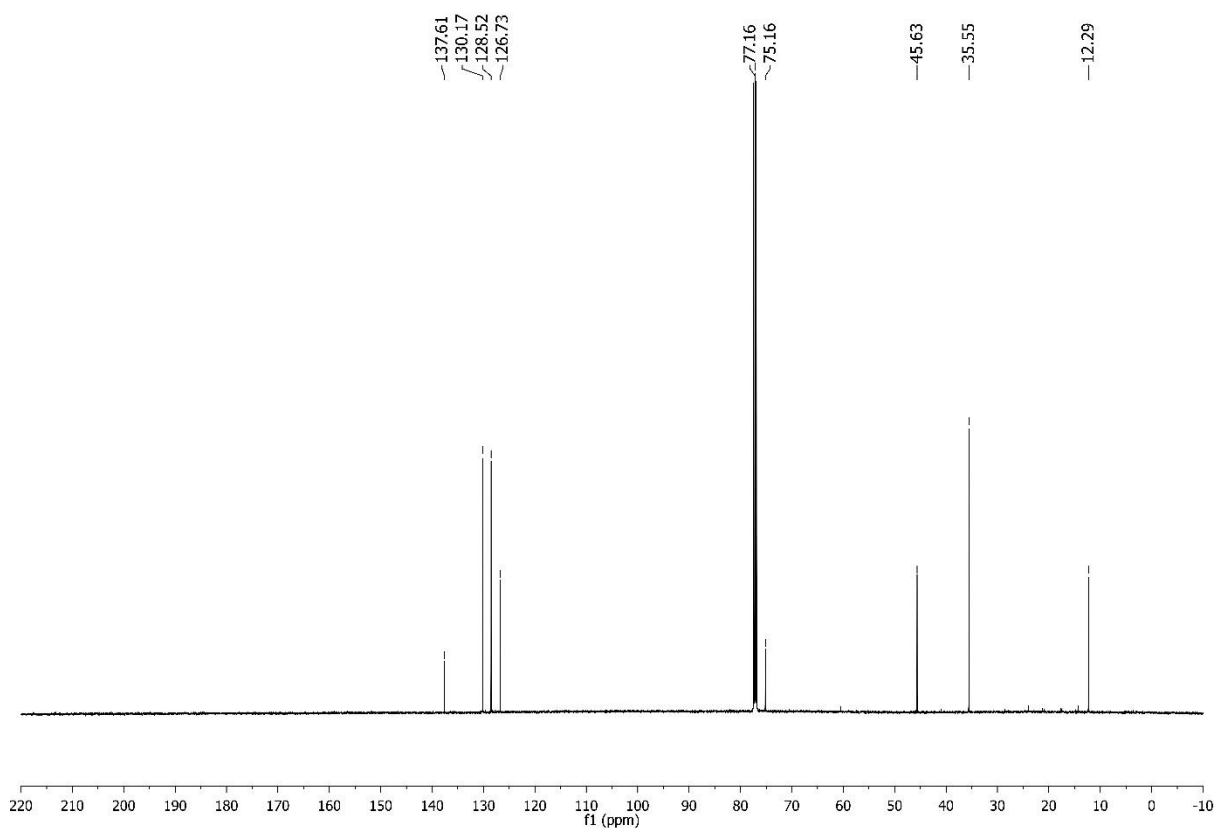
### 1-Benzylcyclobutan-1-ol (S26)



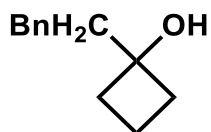
Prepared according to General Procedure B using benzylmagnesium chloride (10.7 mL, 1.4 M in THF, 15.0 mmol), and cyclobutanone (747  $\mu$ L, 10.0 mmol). The crude residue was purified by flash column chromatography (5% EtOAc/Petrol, silica gel) to afford **S26** (1.51 g, 93%) as a colourless oil.

$R_f$  = 0.16 (5% EtOAc/Petrol); **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3372 (br), 2980, 2932, 2495, 1452, 1265, 1098, 1030, 922, 760, 712, 700, 642, 498;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 7.35 – 7.24 (m, 5H), 2.91 (s, 2H), 2.21 – 2.14 (m, 2H), 2.07 – 1.96 (m, 2H), 1.85 – 1.77 (m, 1H), 1.73 (s, 1H), 1.66 – 1.56 (m, 1H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 137.6, 130.2, 128.5, 126.7, 75.2, 45.6, 35.6, 12.3; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{11}\text{H}_{14}\text{O}$ ] requires [M] 162.1045, found 162.1046.



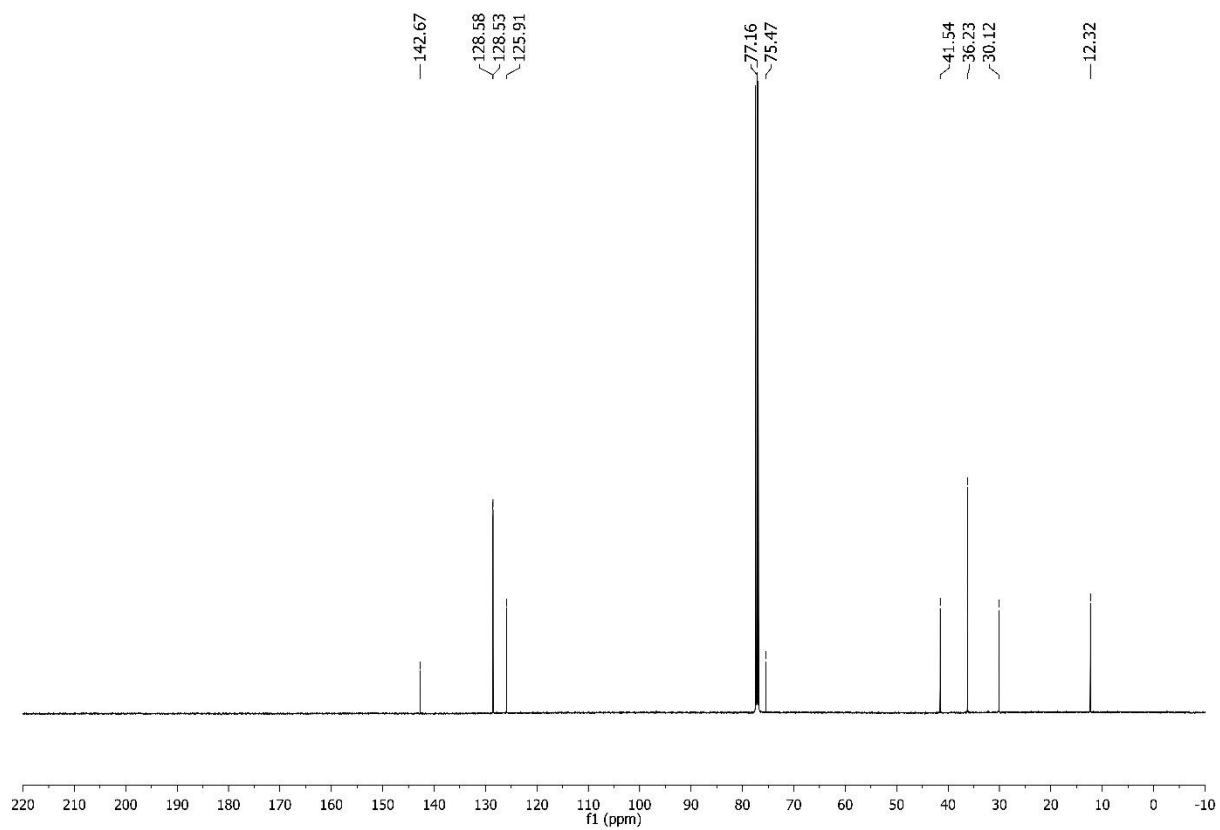
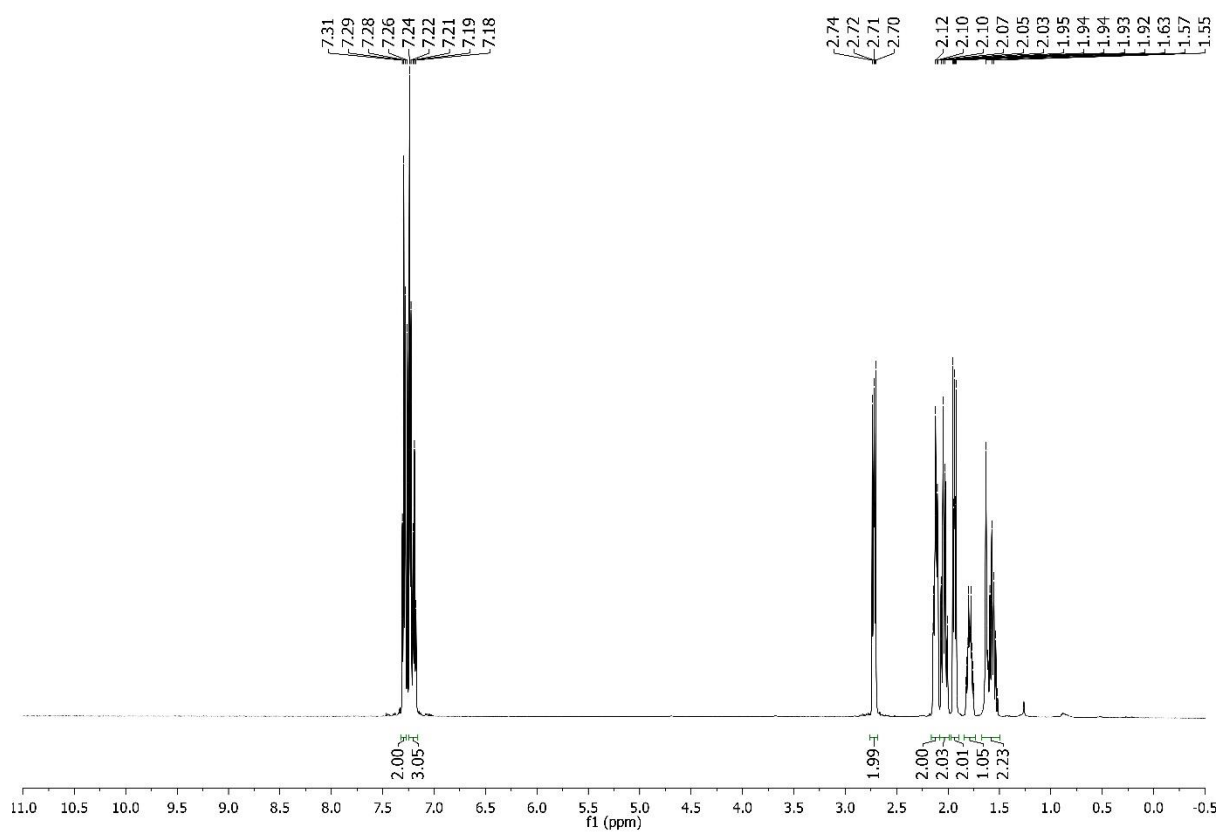


### 1-Phenethylcyclobutan-1-ol (**S27**)

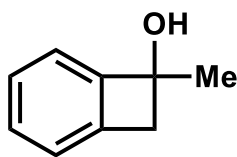


Prepared according to General Procedure A using magnesium turnings (201 mg, 8.25 mmol), (2-bromoethyl)benzene (1.02 mL, 7.50 mmol), and cyclobutanone (374  $\mu$ L, 5.00 mmol). The crude residue was purified by flash column chromatography (10% EtOAc/Hexanes, silica gel) to afford **S27** (552 mg, 63%) as a colourless oil.

$R_f$  = 0.15 (10% EtOAc/Hexanes); **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3325 (br), 2932, 1605, 1497, 1459, 1250, 1158, 1103, 1057, 949, 748, 694;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.32 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 2.74 – 2.70 (m, 2H), 2.15 – 2.09 (m, 2H), 2.09 – 1.99 (m, 2H), 1.96 – 1.91 (m, 2H), 1.83 – 1.75 (m, 1H), 1.65 – 1.51 (m, 2H);  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 142.7, 128.6, 128.5, 125.9, 75.5, 41.5, 36.2, 30.1, 12.3; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{12}\text{H}_{16}\text{O}$ ] requires  $[M]$  176.1201, found 176.1199.

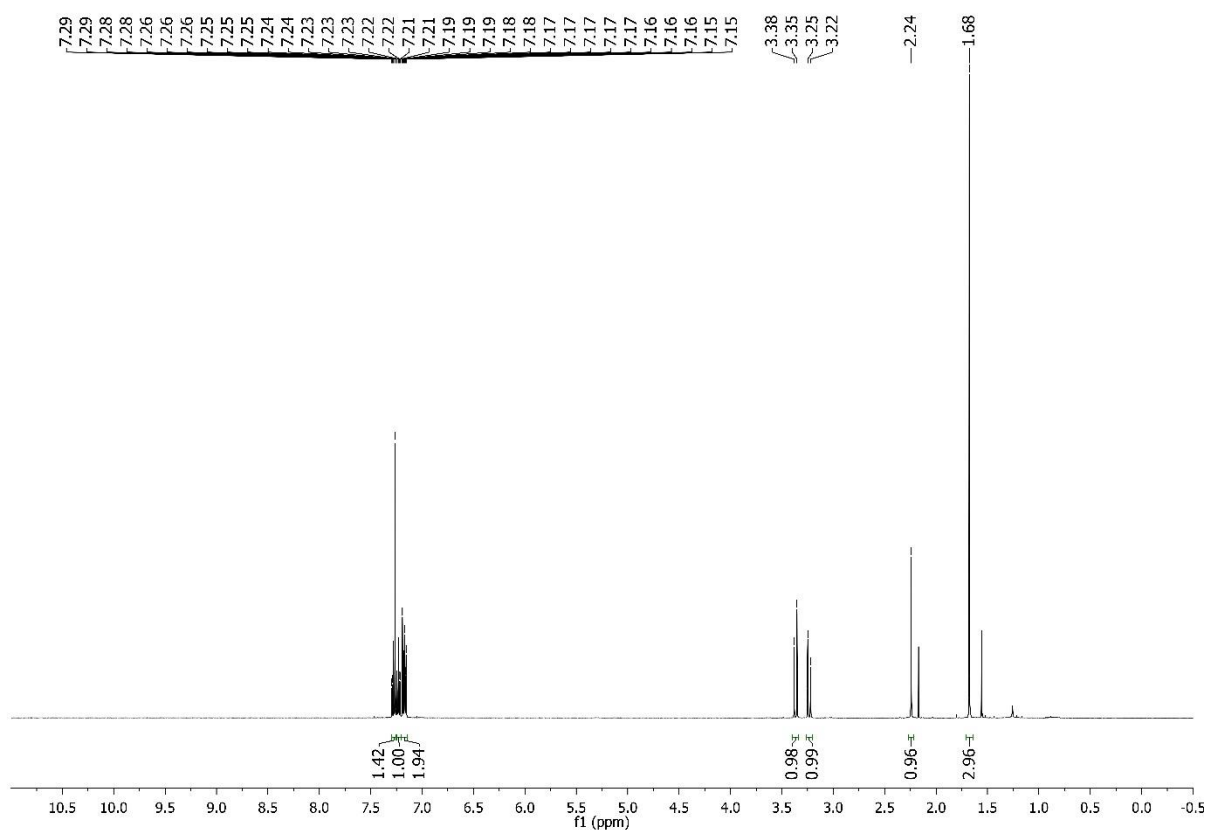


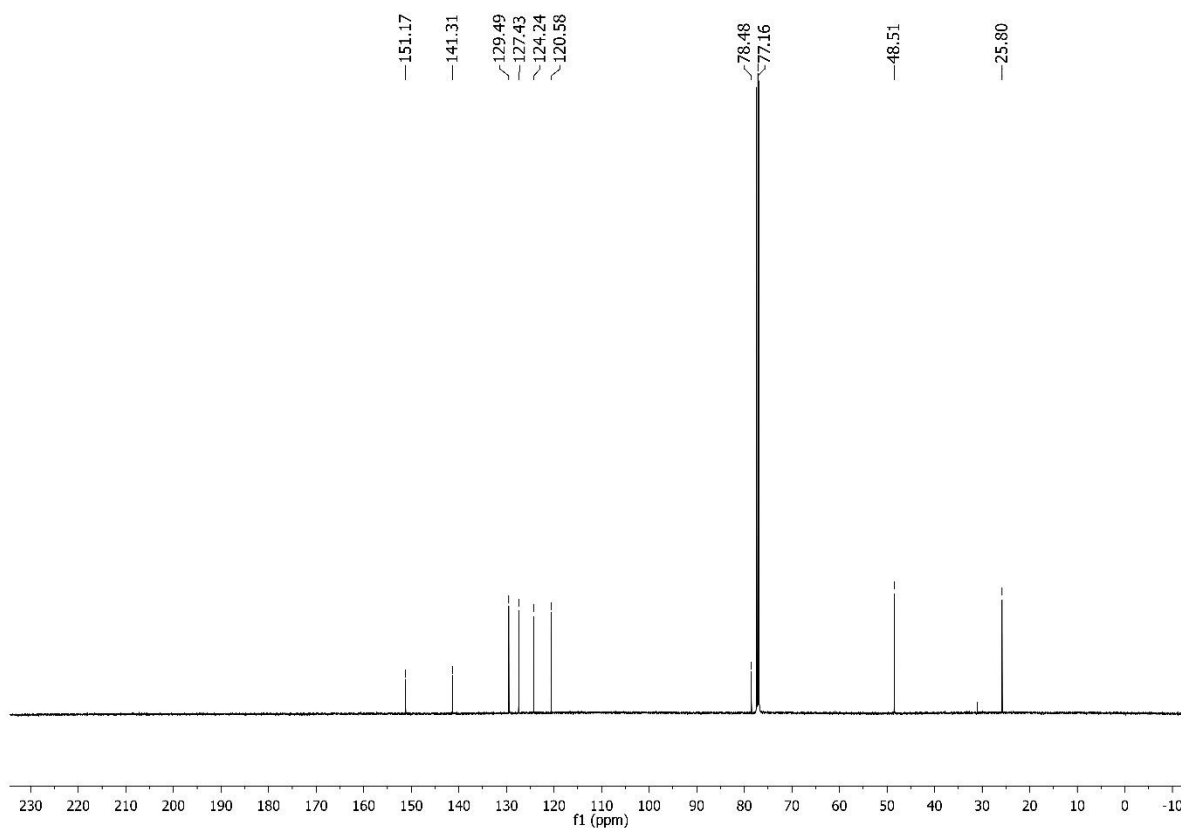
### 7-Methylbicyclo[4.2.0]octa-1,3,5-trien-7-ol (S28)



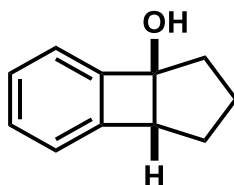
Prepared according to General Procedure B using methylmagnesium bromide (350  $\mu$ L, 3.0 M in Et<sub>2</sub>O, 1.05 mmol), and bicyclo[4.2.0]octa-1,3,5-trien-7-one (83 mg, 0.70 mmol). The crude residue was purified by flash column chromatography (10% EtOAc/Petrol, silica gel) to afford **S28** (63 mg, 67%) as an off-white solid.

$R_f$  = 0.15 (10% EtOAc/Petrol); **M.p.**: 77 – 79 °C; **FTIR** ( $\nu_{\max}$  cm<sup>-1</sup>, thin film) 3304 (br), 2918, 1456, 1366, 1231, 1167, 1061, 947, 758, 714; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.30 – 7.26 (m, 1H), 7.25 – 7.21 (m, 1H), 7.20 – 7.15 (m, 2H), 3.37 (d,  $J$  = 14.0, 1H), 3.23 (d,  $J$  = 14.0, 1H), 2.24 (s, 1H), 1.68 (s, 3H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 151.2, 141.3, 129.5, 127.4, 124.2, 120.6, 78.5, 48.5, 25.8; **HRMS** (EI<sup>+</sup>) [C<sub>9</sub>H<sub>10</sub>O] requires [M] 134.0732, found 134.0738.



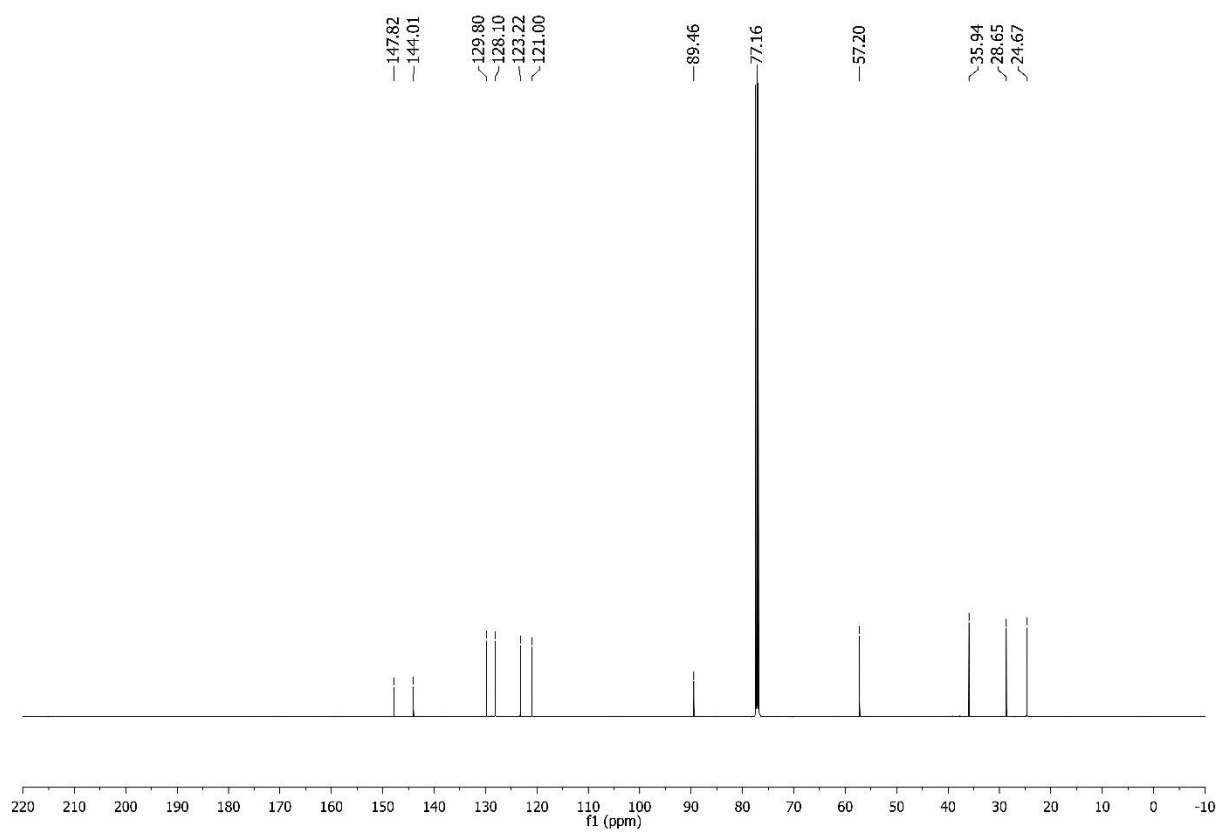
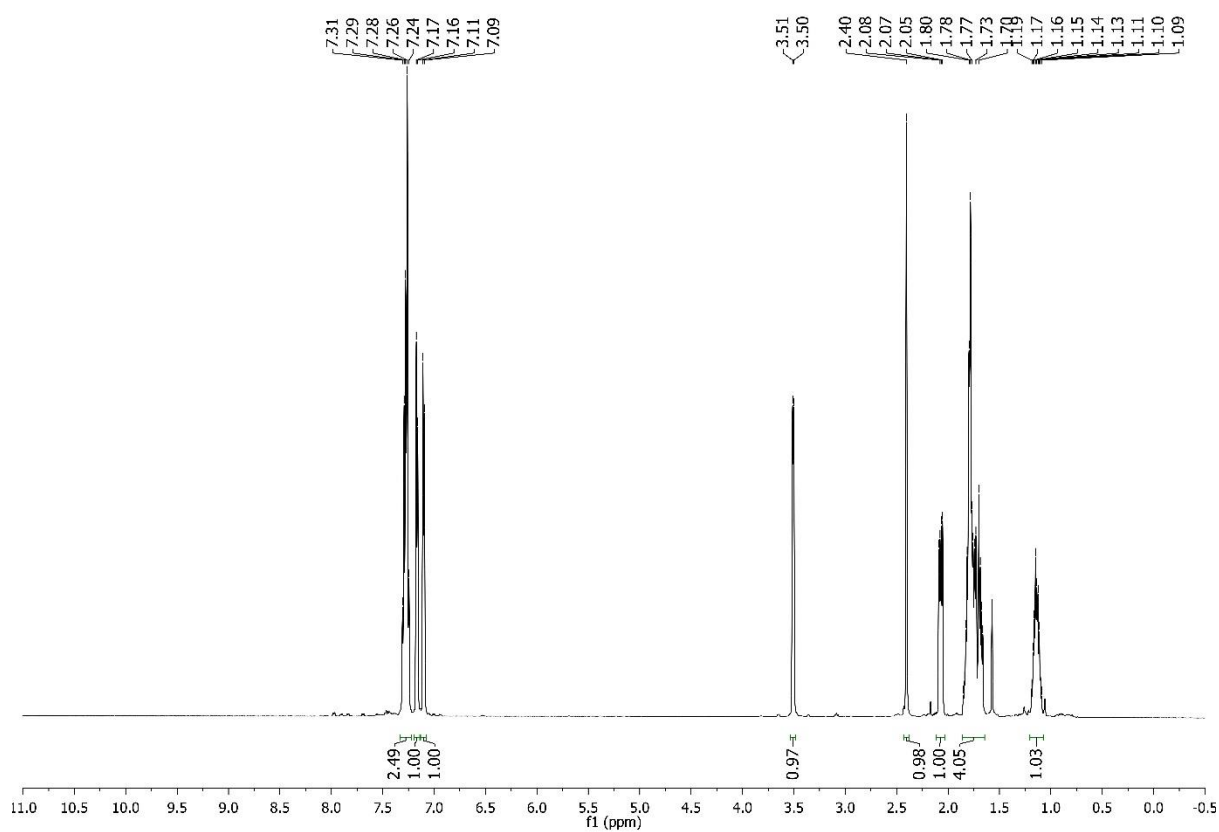


**1,2,3,7b-Tetrahydro-3aH-cyclopenta[3,4]cyclobuta[1,2]benzen-3a-ol (S29)**

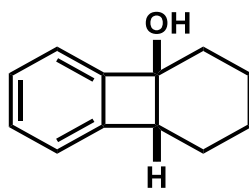


Prepared according to General Procedure F using 2,2,6,6-tetramethylpiperidine (4.21 mL, 25.0 mmol), *n*-butyllithium (11.9 mL, 2.1 M in hexanes, 25.0 mmol), cyclopentanone (0.88 mL, 10.0 mmol) and bromobenzene (1.05 mL, 10.0 mmol). The crude residue was purified by flash column chromatography (5→10% EtOAc/Petrol, silica gel) to afford **S29** (550 mg, 34%) as a white solid.

**R<sub>f</sub>** = 0.50 (15% EtOAc/Petrol); **M.p.**: 55-57 °C; **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3321 (br), 2945, 2855, 1452, 1292, 1221, 1165, 1094, 1038, 756, 737, 658; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.33 – 7.23 (m, 2H), 7.17 (d, *J* = 7.0 Hz, 1H), 7.10 (d, *J* = 7.0 Hz, 1H), 3.51 (d, *J* = 6.0 Hz, 1H), 2.40 (s, 1H), 2.12 – 2.04 (m, 1H), 1.89 – 1.63 (m, 4H), 1.22 – 1.07 (m, 1H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 147.8, 144.0, 129.8, 128.1, 123.2, 121.0, 89.5, 57.2, 35.9, 28.7, 24.7; **HRMS** (EI<sup>+</sup>) [C<sub>11</sub>H<sub>12</sub>O] requires [M] 160.0888, found 160.0888.

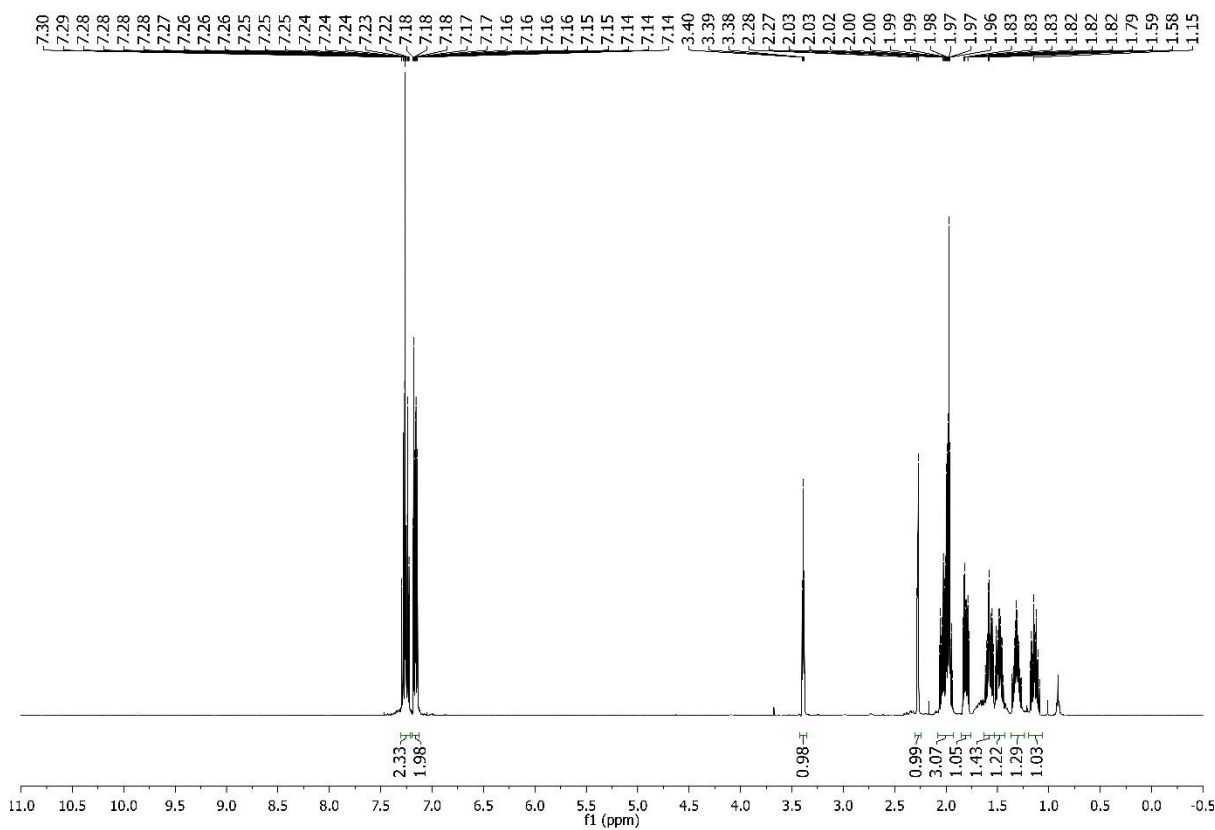


### 1,3,4,8b-Tetrahydrobiphenylen-4a(2H)-ol (S30)

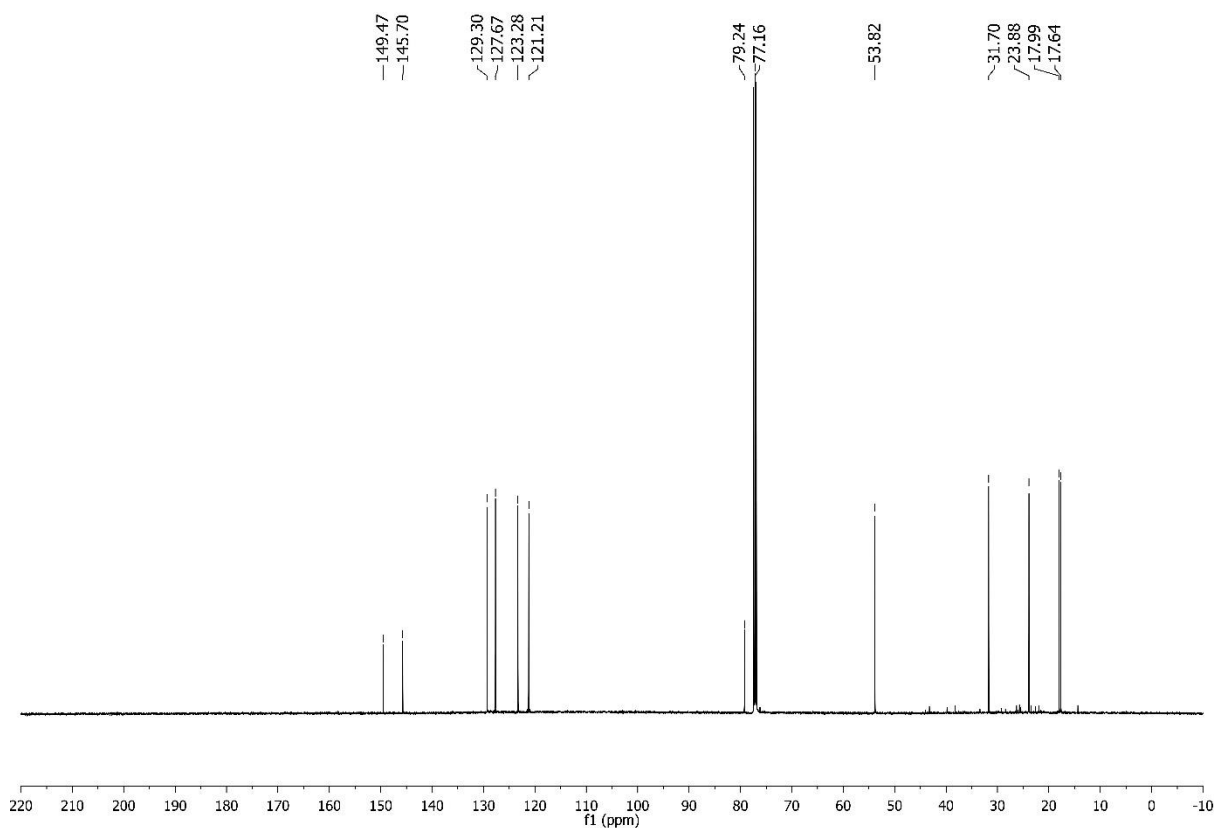


Prepared according to General Procedure F using 2,2,6,6-tetramethylpiperidine (4.21 mL, 25.0 mmol), *n*-butyllithium (11.90 mL, 2.1 M in hexanes, 25.0 mmol), cyclohexanone (1.03 mL, 10.0 mmol) and iodobenzene (2.24 mL, 20.0 mmol). The crude residue was purified by flash column chromatography (5→10 % EtOAc/Petrol, silica gel) to afford **S30** (1.40 g, 80%) as a white solid.

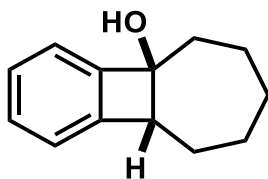
**R<sub>f</sub>** = 0.52 (15% EtOAc/Petrol); **M.p.**: 107-109 °C; **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3231 (br), 2938, 2862, 1456, 1356, 1165, 1076, 1007, 745, 696, 654; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.31 – 7.21 (m, 2H), 7.19 – 7.13 (m, 2H), 3.39 (t, *J* = 5.0 Hz, 1H), 2.27 (s, 1H), 2.08 – 1.92 (m, 3H), 1.86 – 1.76 (m, 1H), 1.64 – 1.42 (m, 2H), 1.37 – 1.08 (m, 2H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 149.5, 145.7, 129.3, 127.7, 123.3, 121.2, 79.2, 53.8, 31.7, 23.9, 17.9, 17.6; **HRMS** (EI<sup>+</sup>) [C<sub>12</sub>H<sub>14</sub>O] requires [M] 174.1045, found 174.1042.





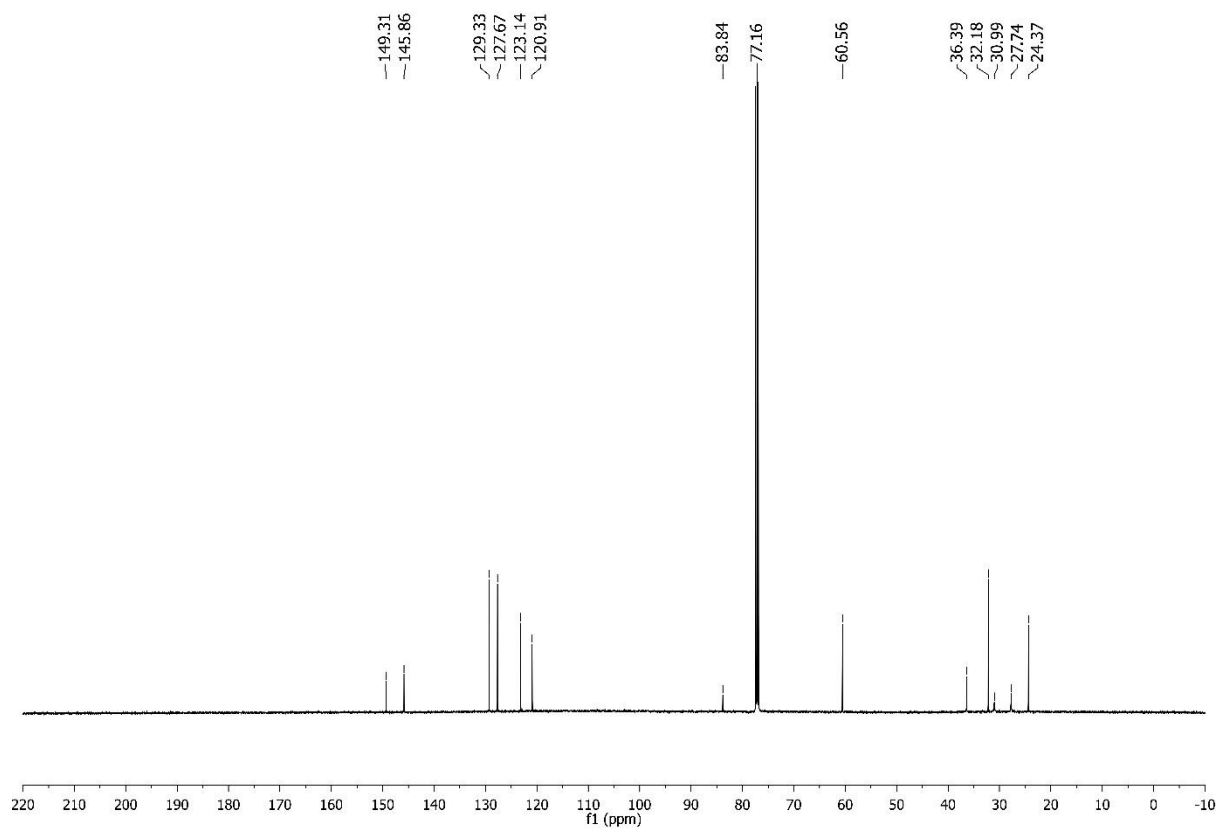
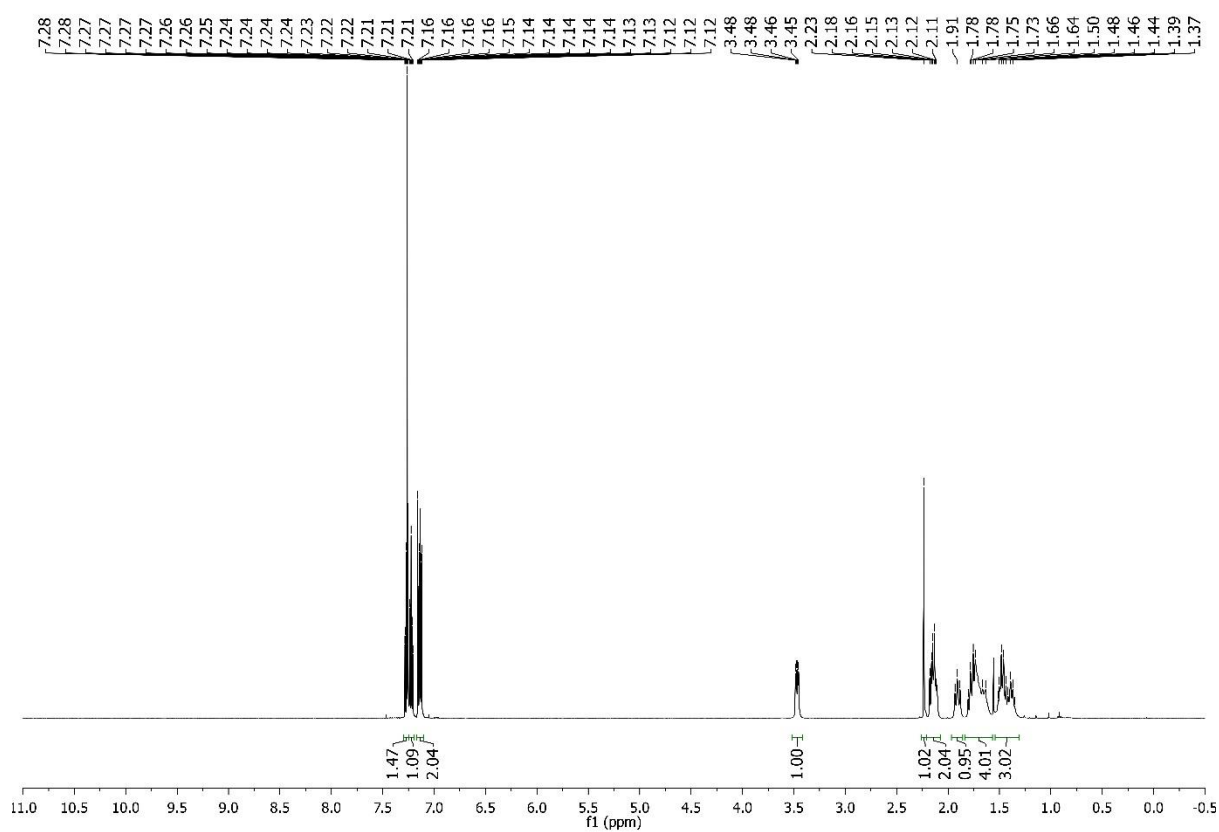


**5,6,7,8,9,9a-Hexahydro-4bH-benzo[3,4]cyclobuta[1,2][7]annulen-4b-ol (S31)**

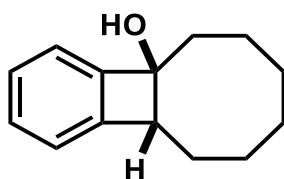


Prepared according to General Procedure F using 2,2,6,6-tetramethylpiperidine (4.21 mL, 25.0 mmol), *n*-butyllithium (11.9 mL, 2.1 M in hexanes, 25.0 mmol), cycloheptanone (1.17 mL, 10.0 mmol) and iodobenzene (1.12 mL, 10.0 mmol). The crude residue was purified by flash column chromatography (5→10% EtOAc/Petrol, silica gel) to afford **S31** (829 mg, 44%) as a white solid.

**R<sub>f</sub>** = 0.48 (15% EtOAc/Petrol); **M.p.**: 96-98 °C; **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3302 (br), 2918, 2843, 1456, 1395, 1333, 1182, 1047, 754, 735; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.31 – 7.19 (m, 2H), 7.18 – 7.10 (m, 2H), 3.56 – 3.37 (m, 1H), 2.31 – 2.21 (m, 1H), 2.20 – 2.07 (m, 2H), 1.99 – 1.86 (m, 1H), 1.84 – 1.30 (m, 7H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 149.3, 145.9, 129.3, 127.7, 123.1, 120.9, 83.8, 60.6, 36.4, 32.2, 31.0, 27.7, 24.4; **HRMS** (EI<sup>+</sup>) [C<sub>13</sub>H<sub>16</sub>O] requires M 188.1201, found 188.1204.

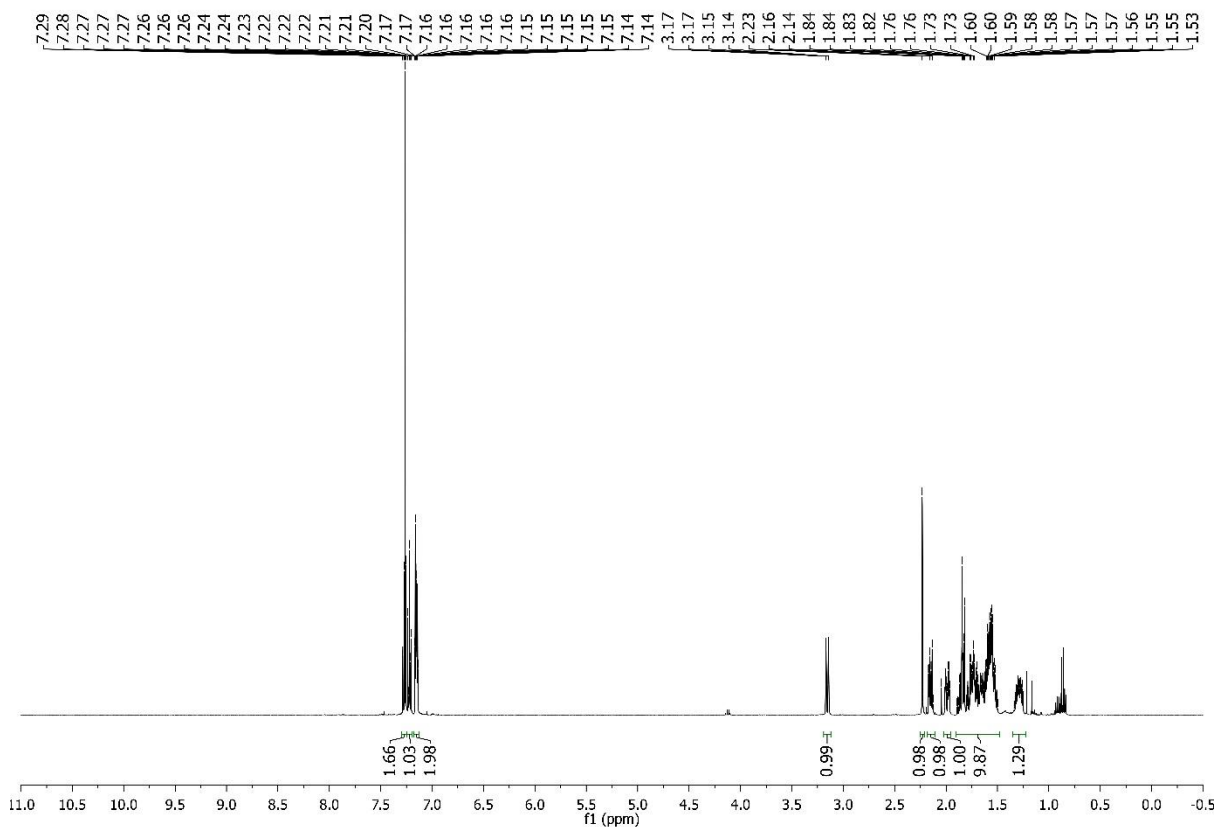


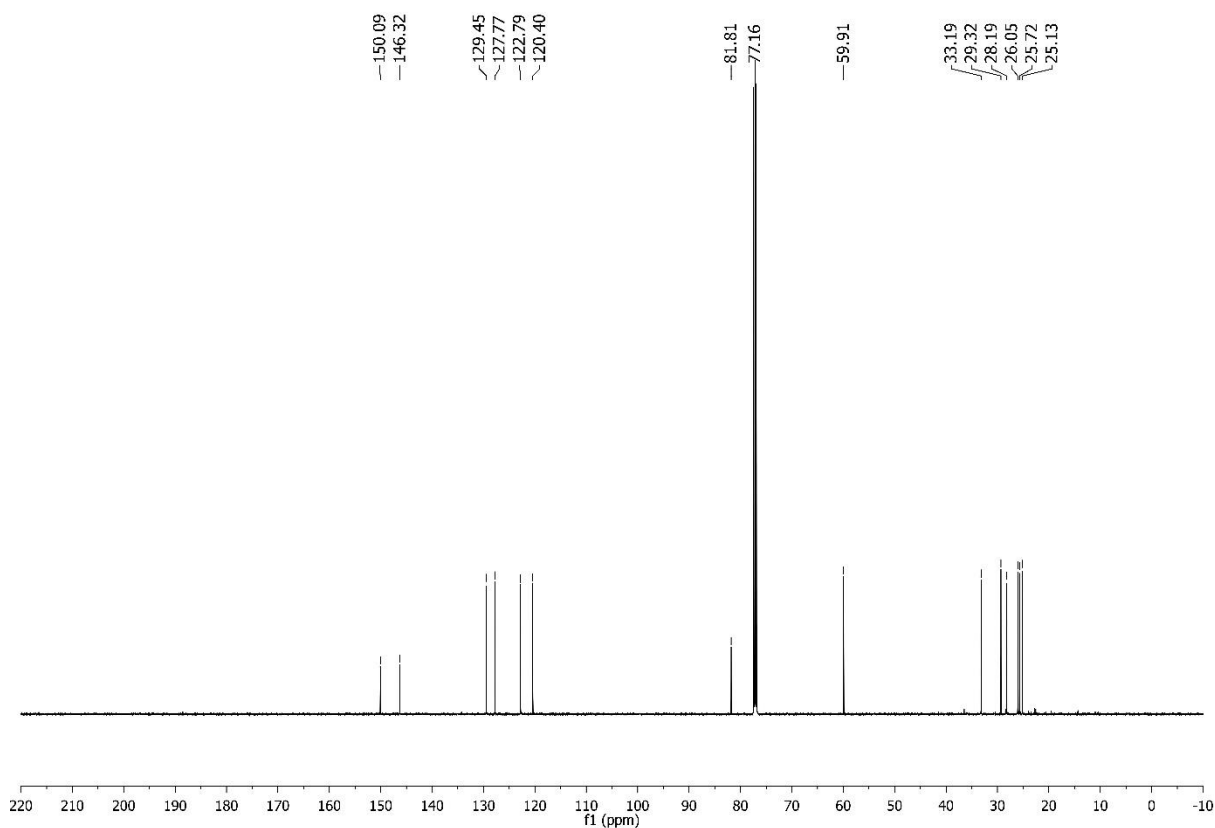
**6,7,8,9,10,10a-Hexahydrobenzo[3,4]cyclobuta[1,2][8]annulen-4b(5H)-ol (S32)**



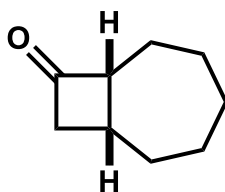
Prepared according to General Procedure F using 2,2,6,6-tetramethylpiperidine (4.21 mL, 25.0 mmol), *n*-butyllithium (11.9 mL, 2.1 M in hexanes, 25.0 mmol), cyclooctanone (1.26 g, 10.0 mmol) and iodobenzene (1.12 mL, 10.0 mmol). The crude residue was purified by flash column chromatography (5→10 % EtOAc/Petrol, silica gel) to afford **S32** (1.19 g, 59%) as a colourless liquid.

$R_f$  = 0.72 (15% EtOAc/Petrol); FTIR ( $\nu_{\max}$  cm<sup>-1</sup>, thin film) 3397 (br), 2926, 2855, 1462, 1445, 1217, 1184, 1115, 1034, 993, 756, 731; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.30 – 7.20 (m, 2H), 7.18 – 7.12 (m, 2H), 3.16 (dd,  $J$  = 12.0, 1.5 Hz, 1H), 2.23 (s, 1H), 2.18 – 2.11 (m, 1H), 2.06 – 1.95 (m, 1H), 1.91 – 1.48 (m, 9H), 1.34 – 1.24 (m, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 150.1, 146.3, 129.4, 127.8, 122.8, 120.4, 81.8, 59.9, 33.2, 29.3, 28.2, 26.1, 25.7, 25.1; HRMS (EI<sup>+</sup>) [C<sub>14</sub>H<sub>18</sub>O] requires [M] 202.1358, found 202.1359.





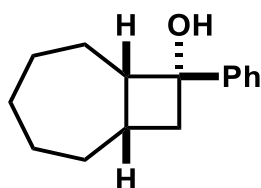
### Bicyclo[5.2.0]nonan-8-one (**S33**)



Following a literature procedure:<sup>[10]</sup> To a solution of cycloheptene (2.33 mL, 20.0 mmol) in hexane (60 mL) was added dichloroacetyl chloride (2.89 mL, 30.0 mmol) and the resulting mixture was heated at reflux for 20 minutes, followed by slow addition of a solution of triethylamine (4.21 mL, 30.2 mmol) in hexane (30 mL). The reaction mixture was stirred at reflux overnight. Upon cooling, the formed precipitate was removed by filtration and the resultant filtrate was washed with sat.  $\text{NaHCO}_3$  ( $2 \times 100$  mL). The organic layer was dried ( $\text{MgSO}_4$ ), filtered and the hexane was removed under vacuum to give a yellow oil.

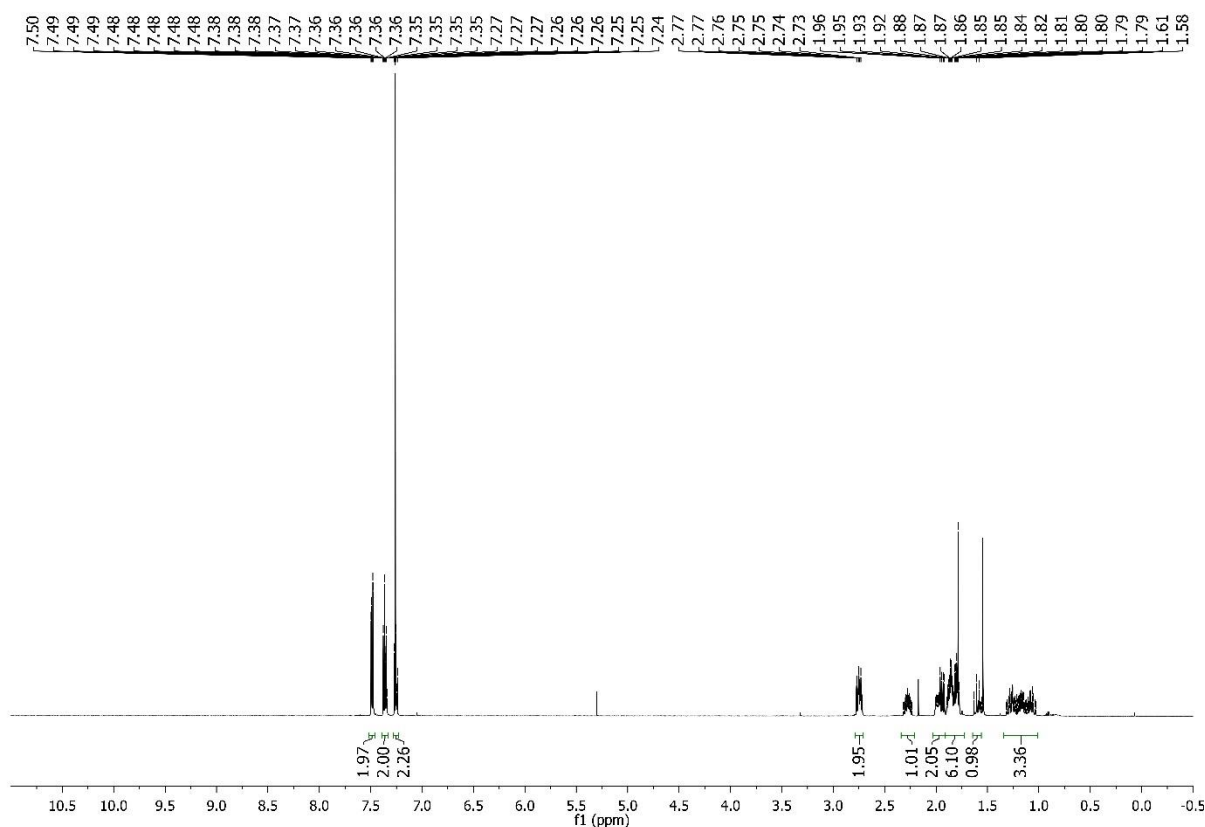
The material from the previous step was taken up in MeOH (140 mL) and stirred at 0 °C. Zinc powder (14.4 g, 220 mmol) was added, followed by  $\text{NH}_4\text{Cl}$  (7.90 g, 148 mmol) and the reaction mixture was allowed to stir at rt overnight. The unreacted zinc was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was taken up in  $\text{Et}_2\text{O}$  (100 mL) and washed with sat.  $\text{NaHCO}_3$  ( $2 \times 100$  mL). The combined aqueous layers were extracted with  $\text{Et}_2\text{O}$  ( $2 \times 100$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (2%  $\text{Et}_2\text{O}$ /Pentane, silica gel) afforded **S33** (1.10 g, 40% over 2 steps) as a yellow oil which was used in the next step without further purification.

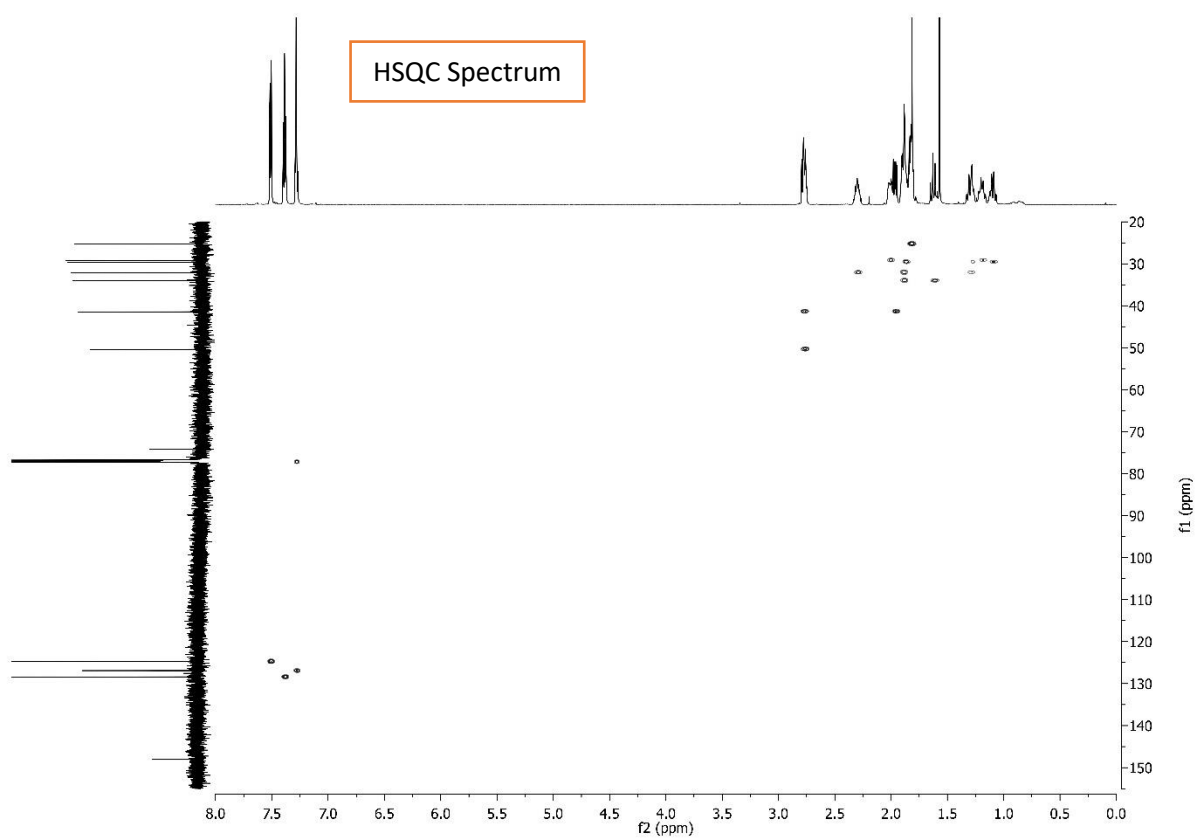
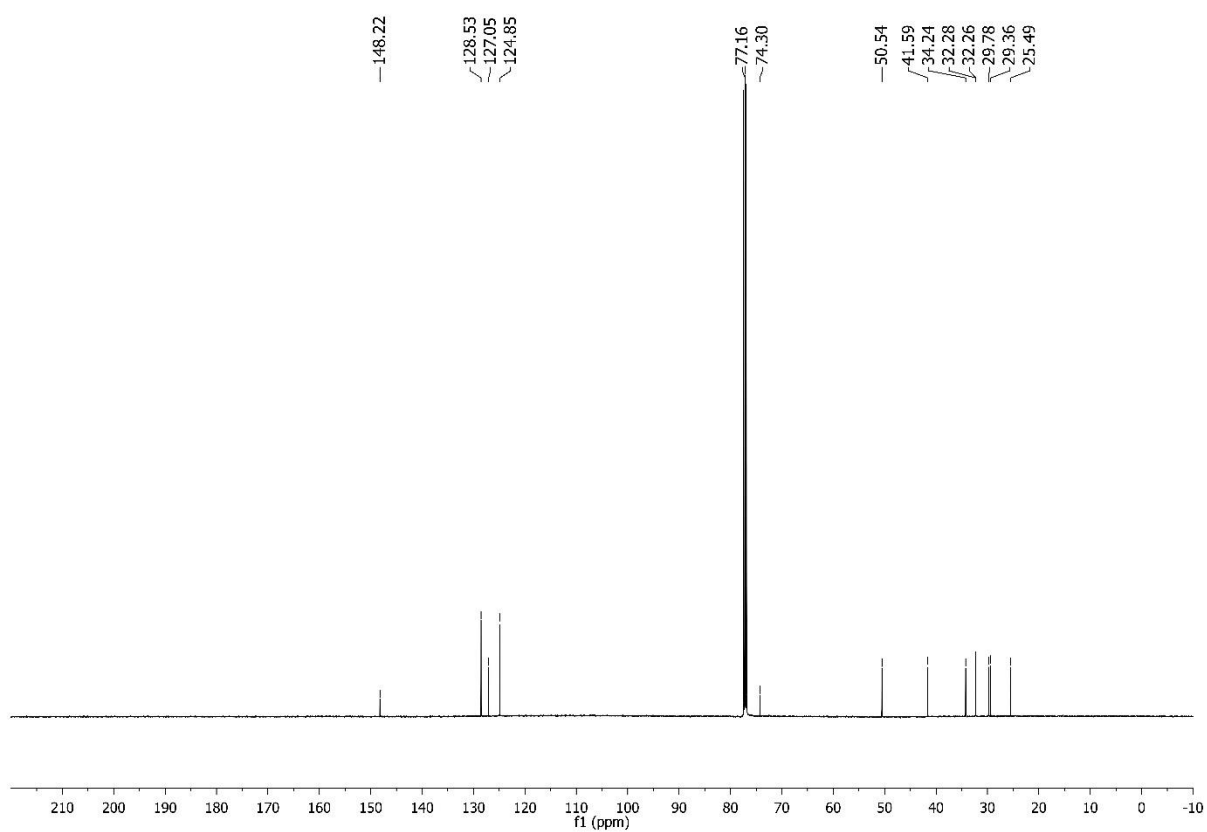
### 8-Phenylbicyclo[5.2.0]nonan-8-ol (**S34**)

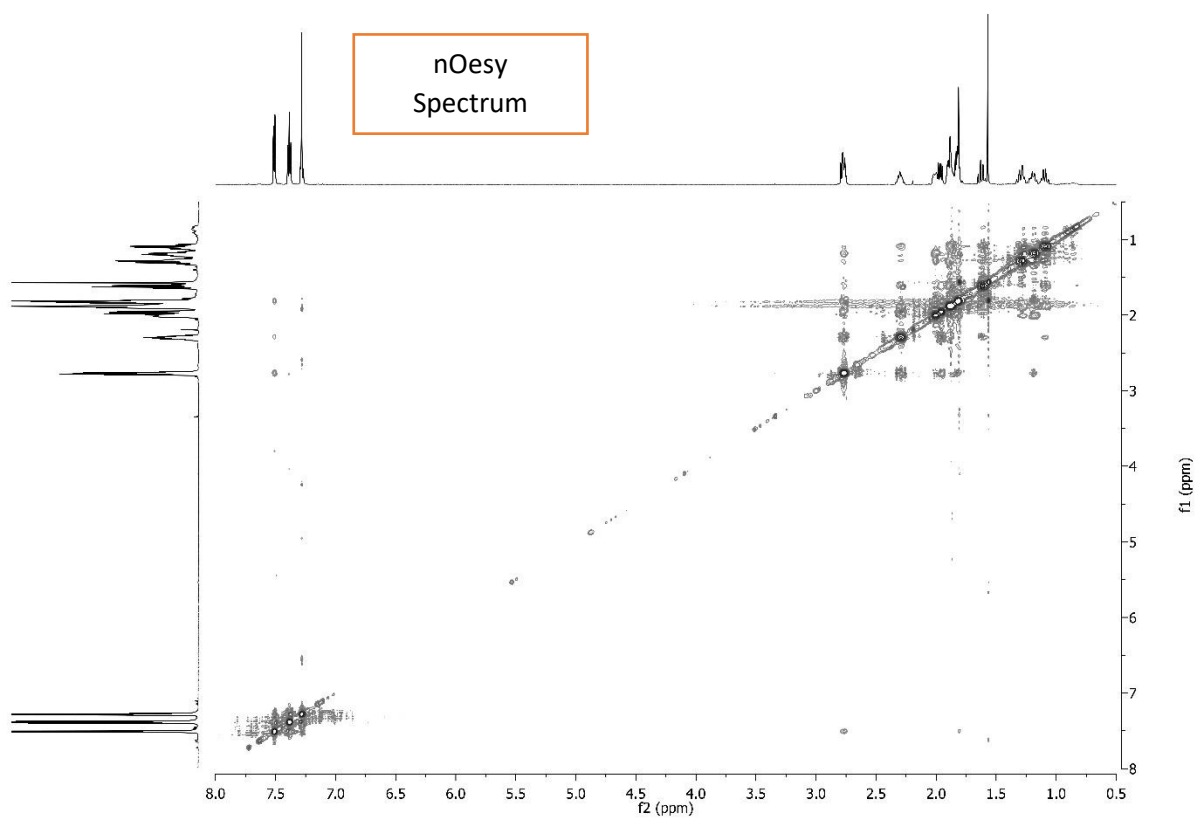
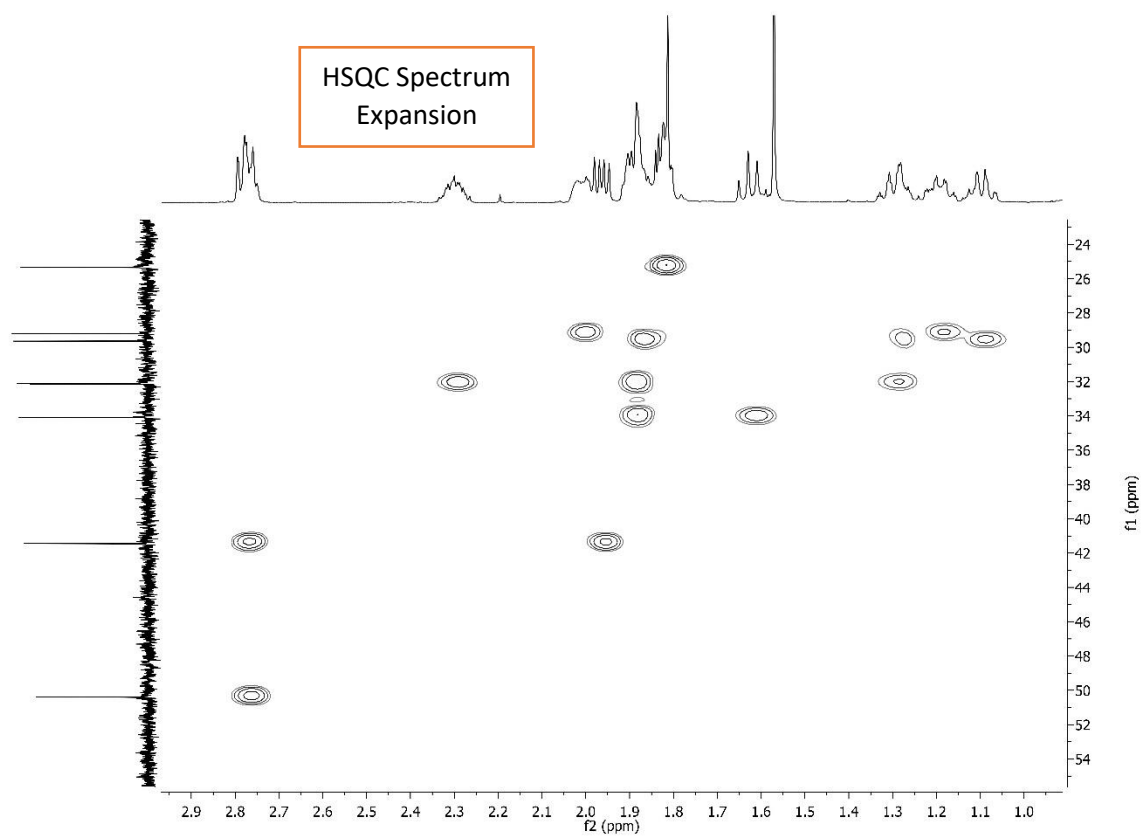


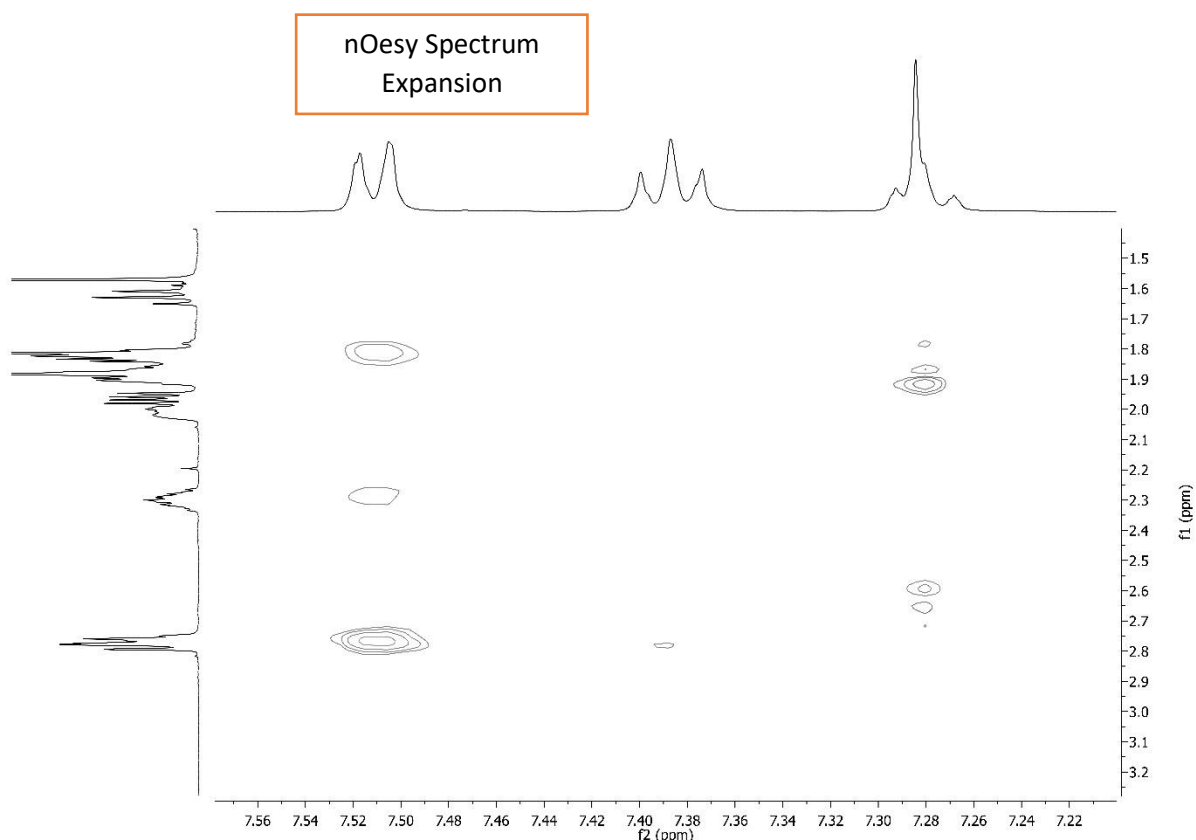
To a solution of **S33** (346 mg, 2.50 mmol) in dry THF (10 mL) at  $-78^{\circ}\text{C}$  was added phenyllithium (1.97 mL, 1.9 M in dibutyl ether, 3.25 mmol) dropwise and the reaction mixture was stirred for 5 h, gradually warming to rt. The reaction was quenched by the addition of sat.  $\text{NH}_4\text{Cl}$  (15 mL) and the aqueous layer was extracted with EtOAc ( $2 \times 15$  mL). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% EtOAc/Petrol, silica gel) to afford **S34** (280 mg, 53%) as a colourless oil.

$R_f$  = 0.41 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 3435 (br), 2922, 2847, 1445, 1223, 1132, 1049, 762, 696;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.50 – 7.47 (m, 2H), 7.38 – 7.34 (m, 2H), 7.28 – 7.24 (m, 1H), 2.79 – 2.70 (m, 2H), 2.33 – 2.22 (m, 1H), 2.02 – 1.75 (m, 8H), 1.65 – 1.55 (m, 1H), 1.32 – 1.02 (m, 3H);  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 148.2, 128.5, 127.1, 124.8, 74.3, 50.5, 41.6, 34.2, 32.3, 32.3, 29.8, 29.4, 25.5; **HRMS** ( $\text{ES}^+$ ) [ $\text{C}_{15}\text{H}_{20}\text{O}$ ] requires [M-OH] 199.1487, found 199.1480.

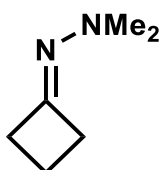






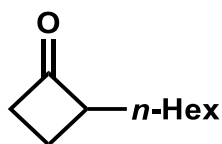


### 2-Cyclobutylidene-1,1-dimethylhydrazine (**S35**)



To a flame-dried RBF was added cyclobutanone (3.00 mL, 40 mmol, 1.0 eq.) and 1,1-dimethylhydrazine (3.65 mL, 48 mmol, 1.2 eq.) and the resulting mixture heated at 70 °C for 5 h. Upon cooling, the reaction mixture was diluted with Et<sub>2</sub>O (50 mL) and washed with ice-cold water (2 × 30 mL). The organic layer was dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to afford **S35** (1.25 g, 28%) as a yellow oil. This material was used in the next step without further purification.

### 2-Hexylcyclobutan-1-one (**S36**)

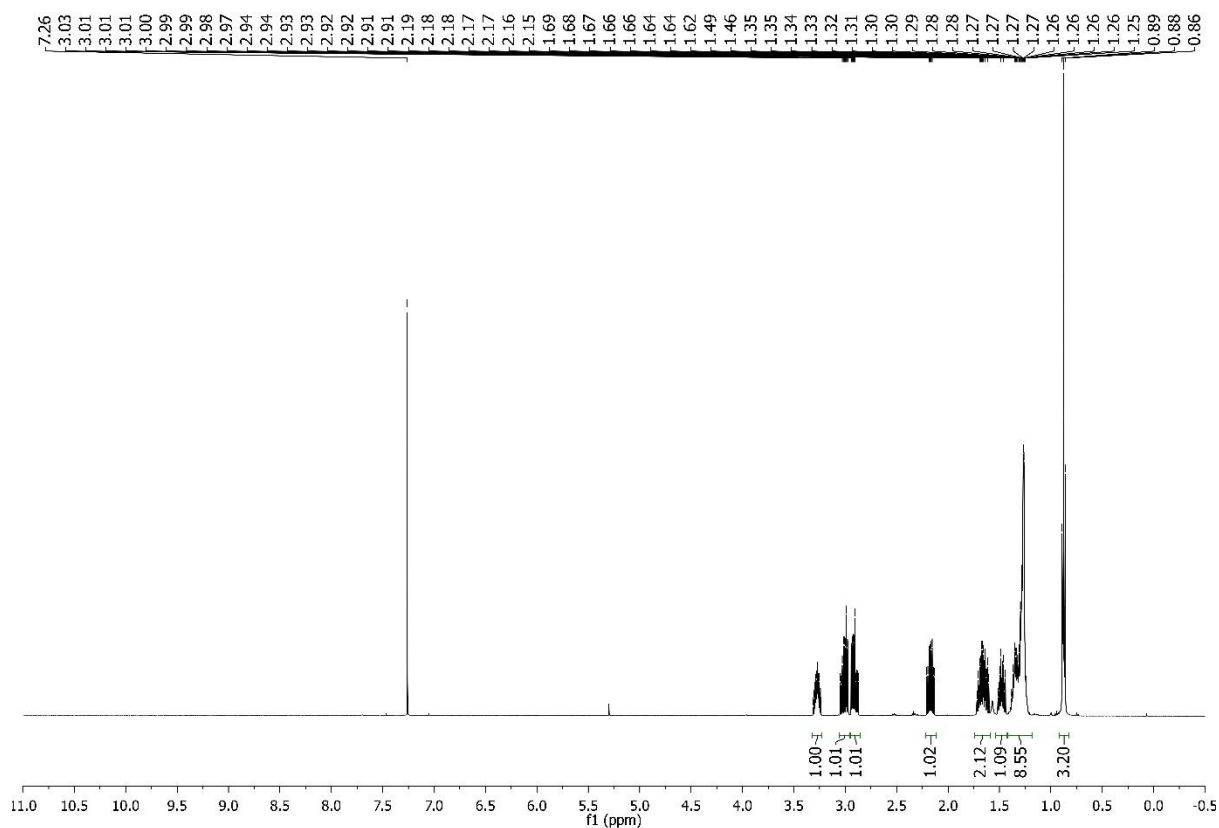


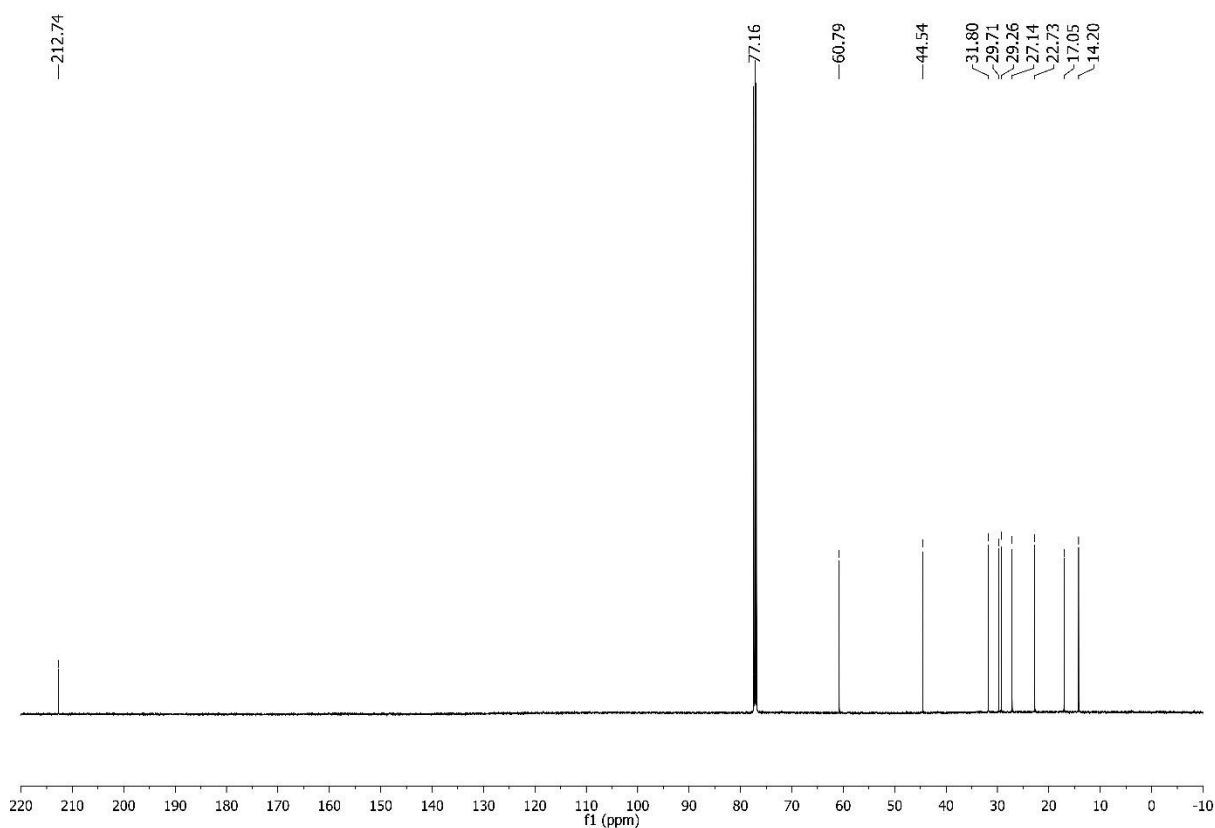
To a solution of **S35** (968 mg, 8.63 mmol, 1.0 eq.) in THF (20 mL) at 0 °C was added *n*-butyllithium (4.30 mL, 2.2 M, 9.49 mmol, 1.1 eq.) and the resulting mixture was left to stir at 0 °C for 1 h. 1-Bromohexane (1.57 mL, 11.22 mmol, 1.3 eq.) was added dropwise and the reaction mixture was left to stir at rt for 3 h. A solution of sat. NH<sub>4</sub>Cl (20 mL) was added and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (2 × 15 mL) and the combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% Et<sub>2</sub>O in petrol, silica gel) to afford **S36** (650 mg, 49%) as a colourless oil.



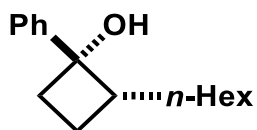
$R_f = 0.43$  (10% Et<sub>2</sub>O/Petrol); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 3.32 - 3.23$  (m, 1H), 3.01 (dddd,  $J = 18.0, 10.5, 8.0, 3.0$  Hz, 1H), 2.91 (dddd,  $J = 18.0, 9.5, 5.5, 2.5$  Hz, 1H), 2.17 (dtd,  $J = 11.0, 10.5, 5.5$  Hz, 1H), 1.73 – 1.59 (m, 2H), 1.52 – 1.43 (m, 1H), 1.41 – 1.21 (m, 8H), 0.88 (t,  $J = 7.0$  Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta = 212.7, 60.8, 44.5, 31.8, 29.7, 29.3, 27.1, 22.7, 17.1, 14.2$ .

These data are consistent with those previously reported in the literature.<sup>[11]</sup>



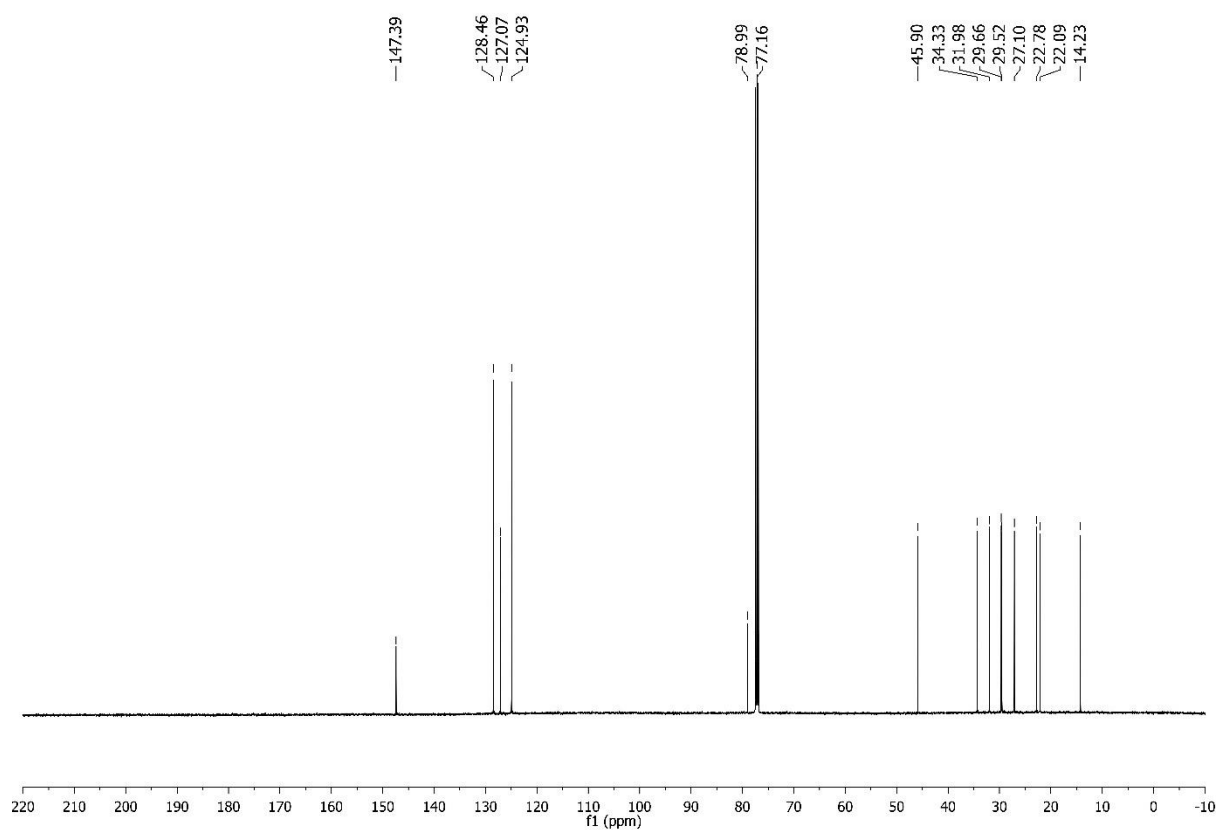
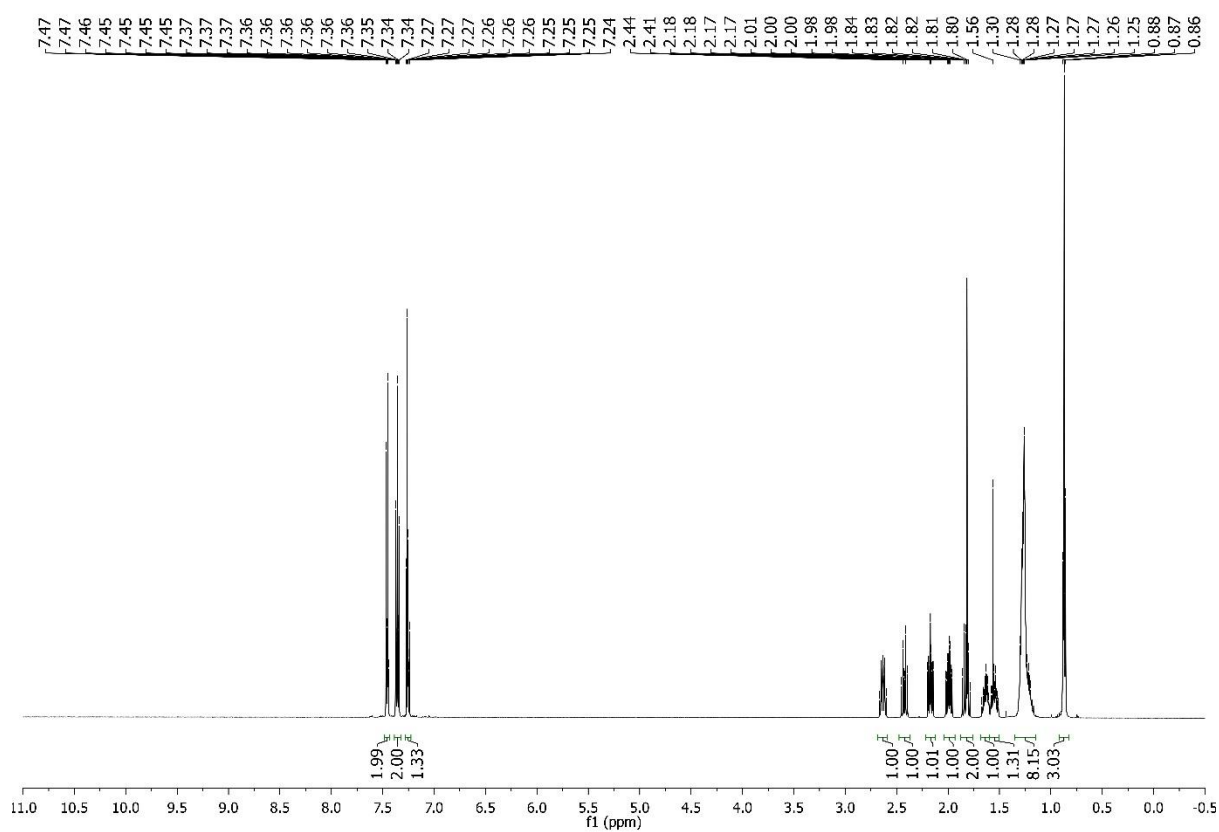


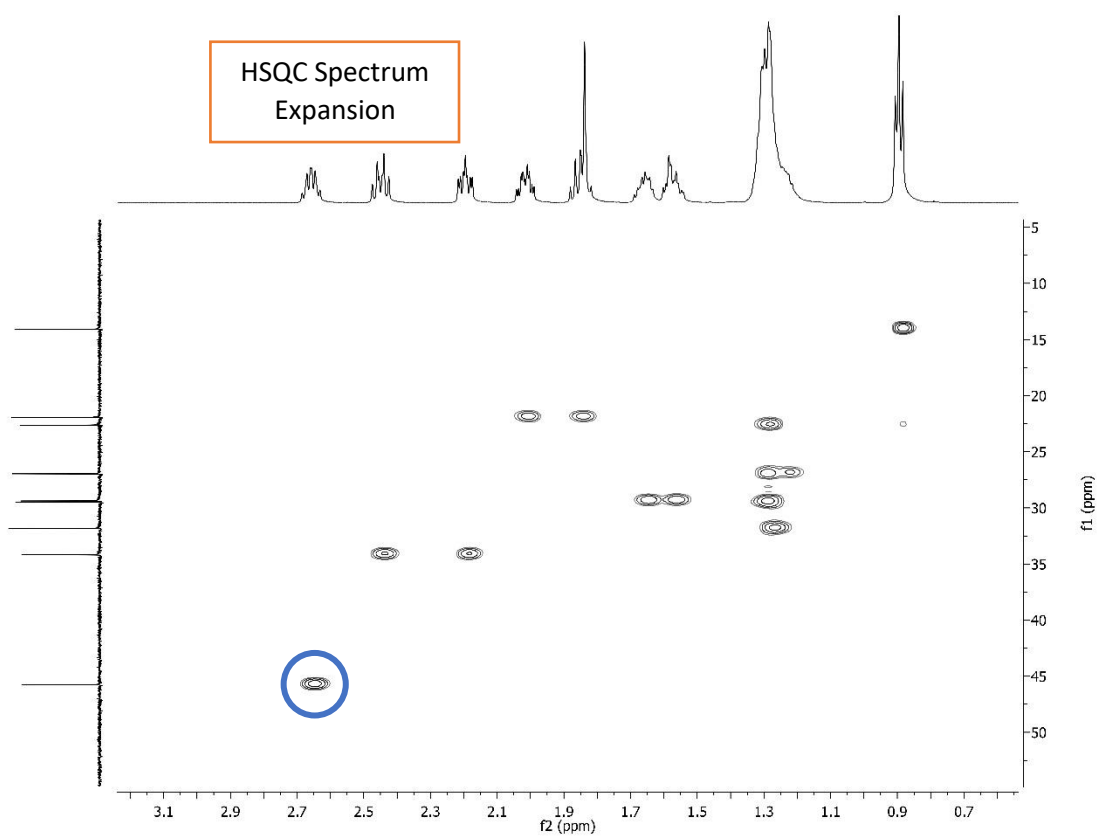
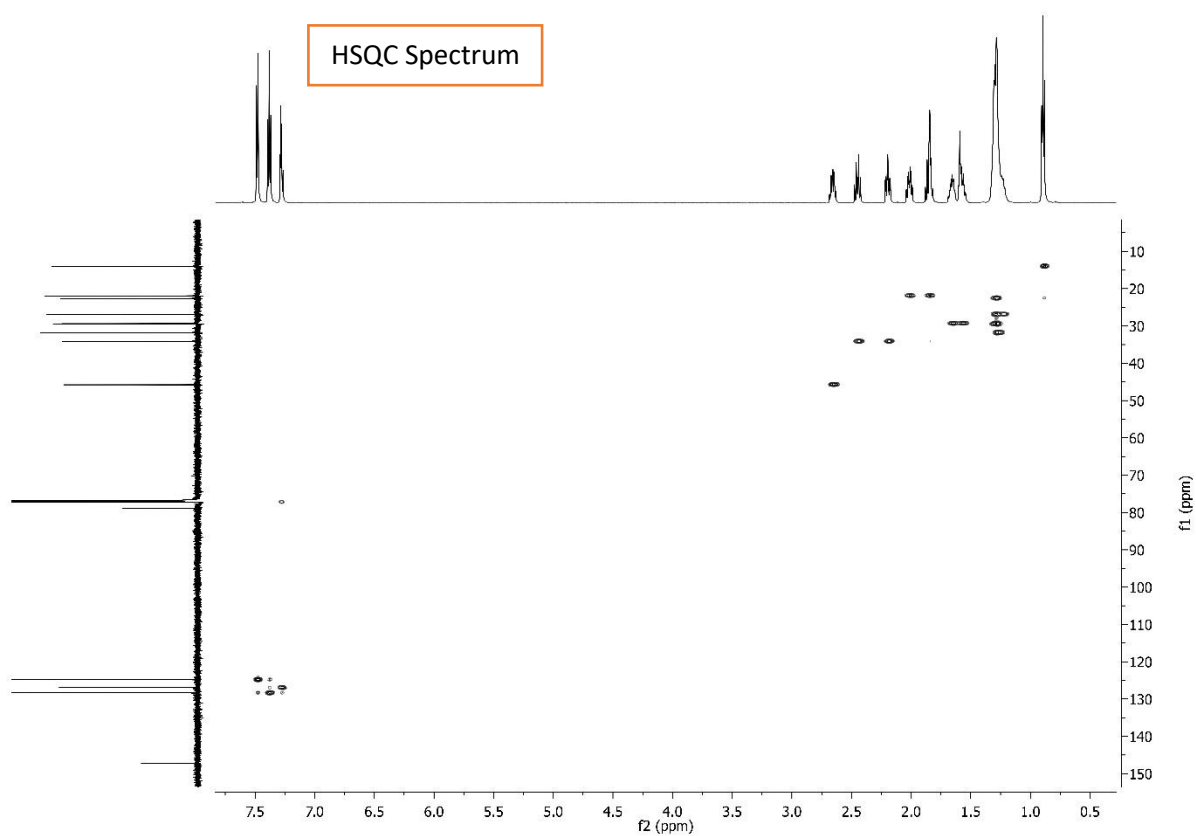
### 2-Hexyl-1-phenylcyclobutan-1-ol (**S37**)

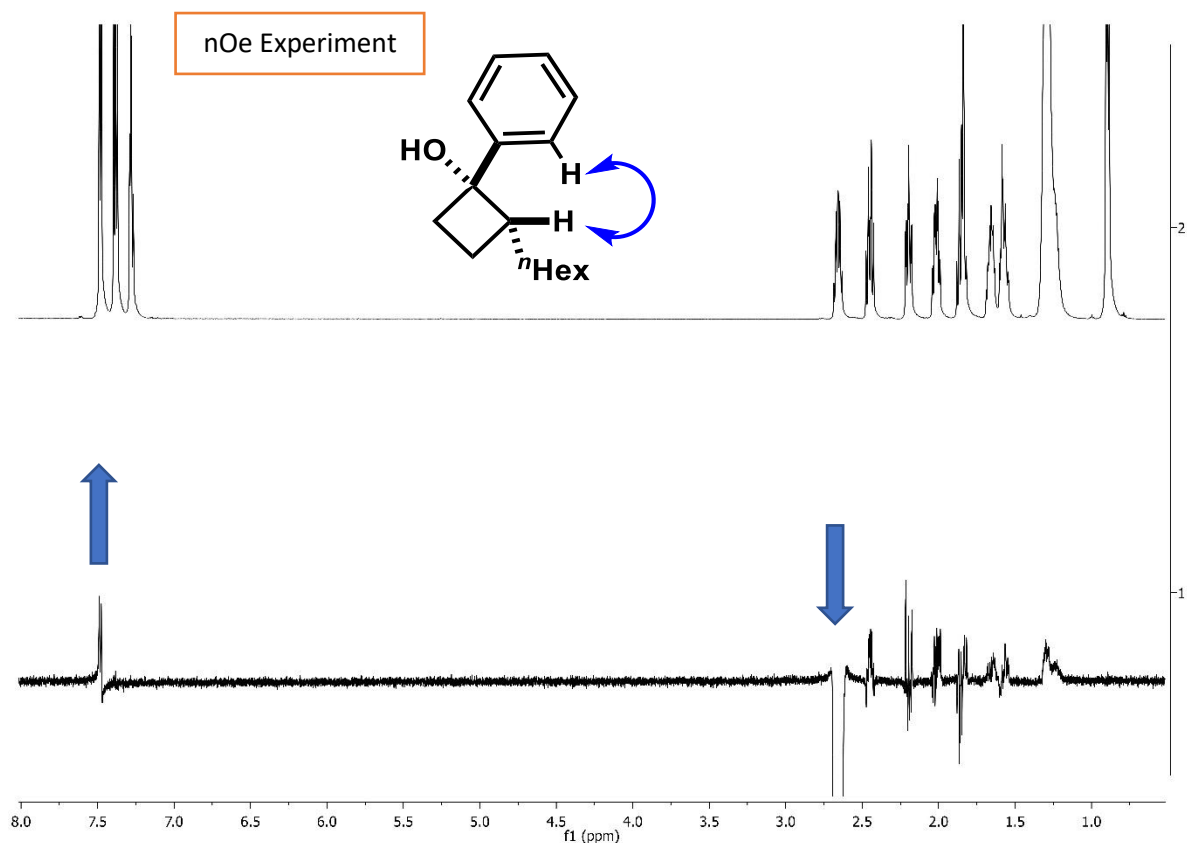


Prepared according to General Procedure A using magnesium turnings (106 mg, 4.34 mmol), bromobenzene (416  $\mu$ L, 3.95 mmol), and **S36** (406 mg, 2.63 mmol). The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10% Et<sub>2</sub>O/Petrol, silica gel) to afford **S37** (493 mg, 81%) as a colourless oil.

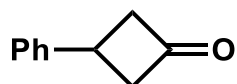
**R<sub>f</sub>** = 0.46 (20% Et<sub>2</sub>O/Petrol); **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3428, 2924, 2853, 1447, 893, 696; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.48–7.44 (m, 2H), 7.38–7.33 (m, 2H), 7.28–7.23 (m, 1H), 2.67–2.59 (m, 1H), 2.43 (dt,  $J$  = 12.0, 8.5 Hz, 1H), 2.17 (dddd,  $J$  = 12.0, 9.5, 4.0, 1.0 Hz, 1H), 1.99 (dtd,  $J$  = 11.0, 8.5, 4.0 Hz, 1H), 1.87–1.77 (m, 2H), 1.68–1.59 (m, 1H), 1.59–1.49 (m, 1H), 1.34–1.15 (m, 8H), 0.87 (t,  $J$  = 7.0 Hz, 3H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 147.4, 128.5, 127.1, 124.9, 79.0, 45.9, 34.3, 32.0, 29.7, 29.5, 27.1, 22.8, 22.1, 14.2; **HRMS** (EI<sup>+</sup>) [C<sub>16</sub>H<sub>24</sub>O] requires [M–H<sub>2</sub>O] 214.1722, found 214.1716.





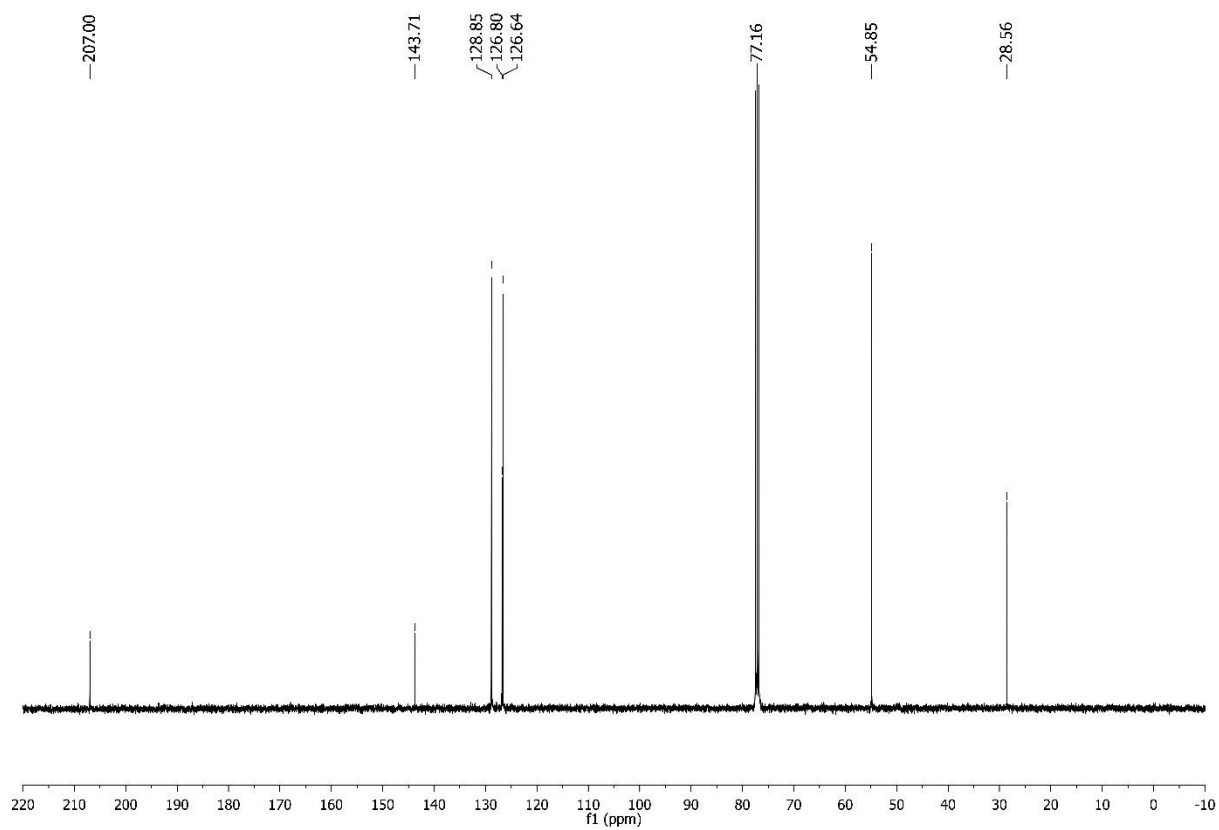
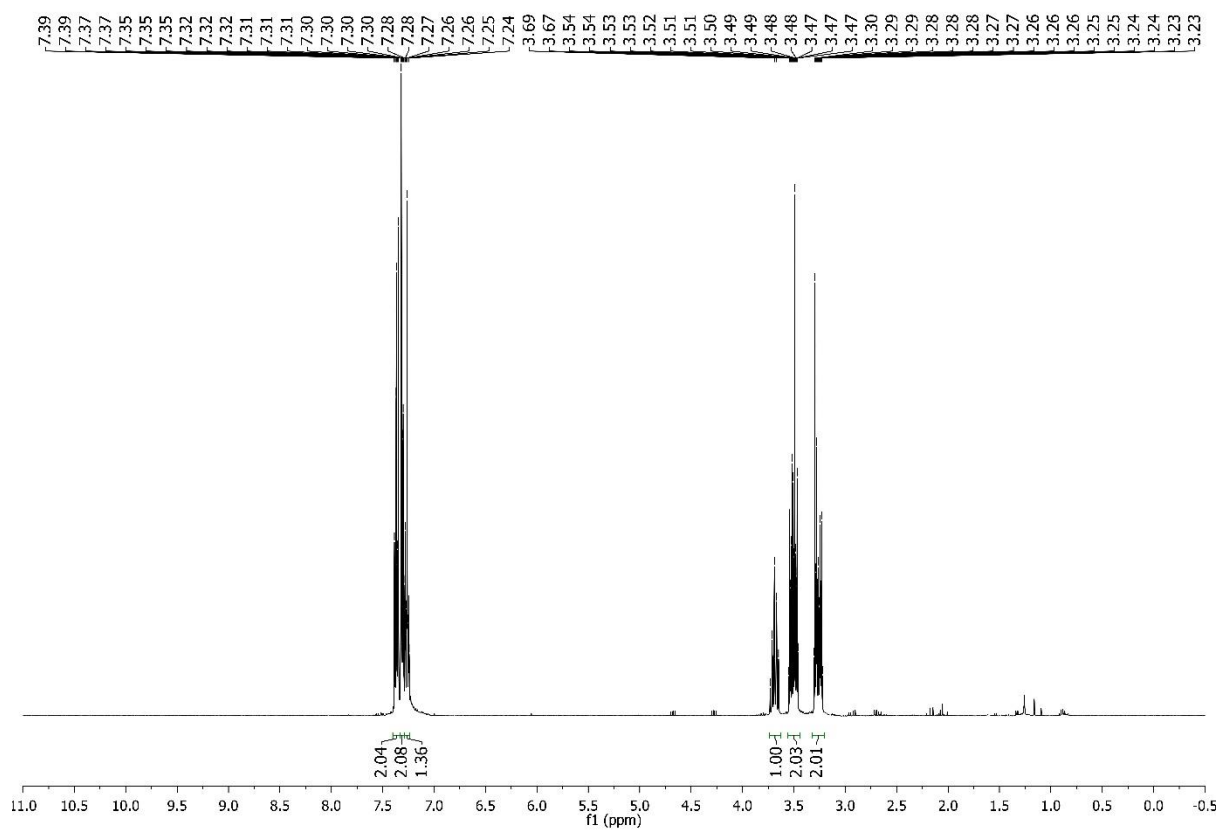


### 3-Phenylcyclobutanone (S38)

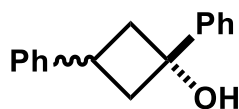


Prepared following General Procedure D using styrene (1.15 mL, 10 mmol), trichloroacetyl chloride (2.23 mL, 20 mmol), Zn(Cu) couple (1.63 g, 25 mmol) and  $\text{POCl}_3$  (1.86 mL, 20 mmol) in  $\text{Et}_2\text{O}$  (30 mL) for the first step. The second step employed Zn dust (2.62 g, 40 mmol) in  $\text{AcOH}$  (20 mL). The crude residue was purified by flash column chromatography (10% ethyl acetate in petrol, silica gel) to afford product **S38** (231 mg, 16% over 2 steps) as a pale yellow oil.

$R_f$  = 0.43 (10%  $\text{EtOAc}$ /Petrol); **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 2974, 2922, 1782, 1495, 1454, 1379, 1103, 758, 700;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.40 – 7.34 (m, 2H), 7.34 – 7.29 (m, 2H), 7.29 – 7.24 (m, 1H), 3.74 – 3.63 (m, 1H), 3.56 – 3.45 (m, 2H), 3.31 – 3.21 (m, 2H);  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 207.0, 143.7, 128.9, 126.8, 126.6, 54.9, 28.6; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{10}\text{H}_{10}\text{O}$ ] requires [M] 146.0732, found 146.0736.



### 1,3-Diphenylcyclobutan-1-ol (S39)

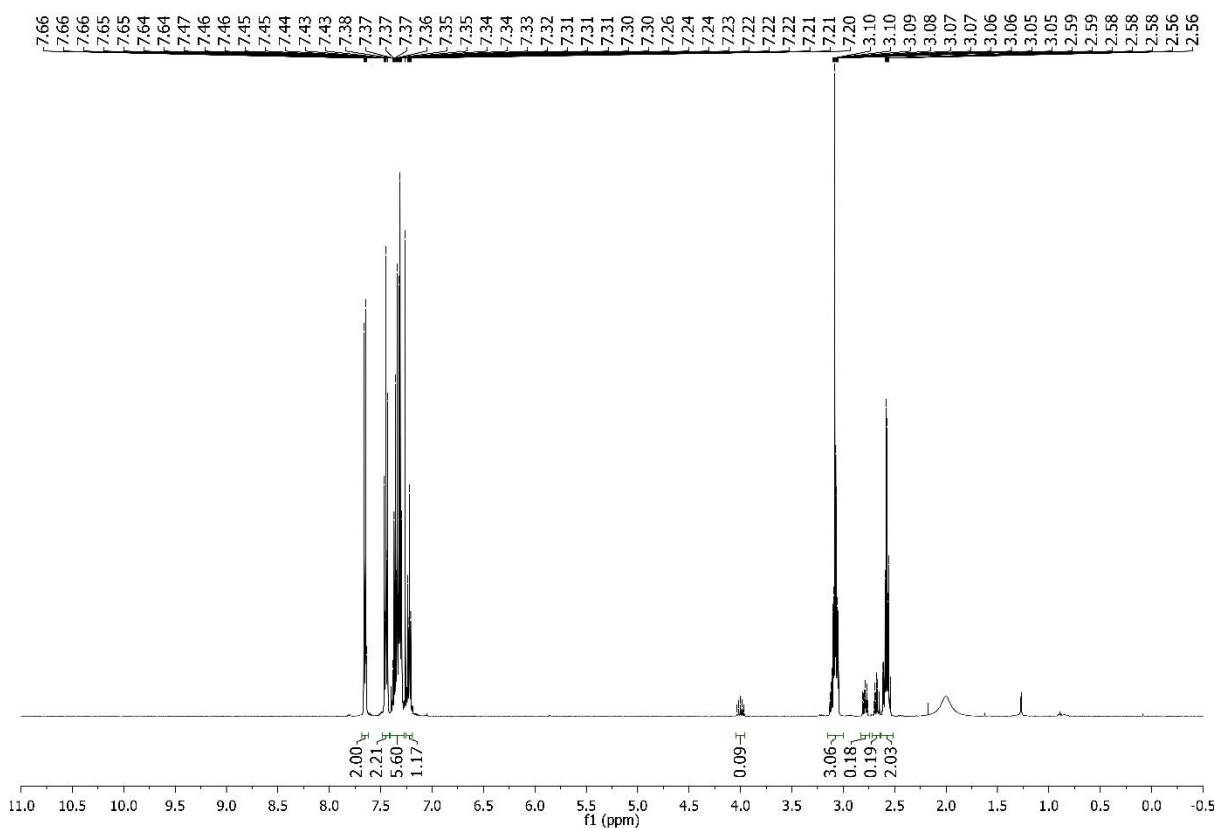


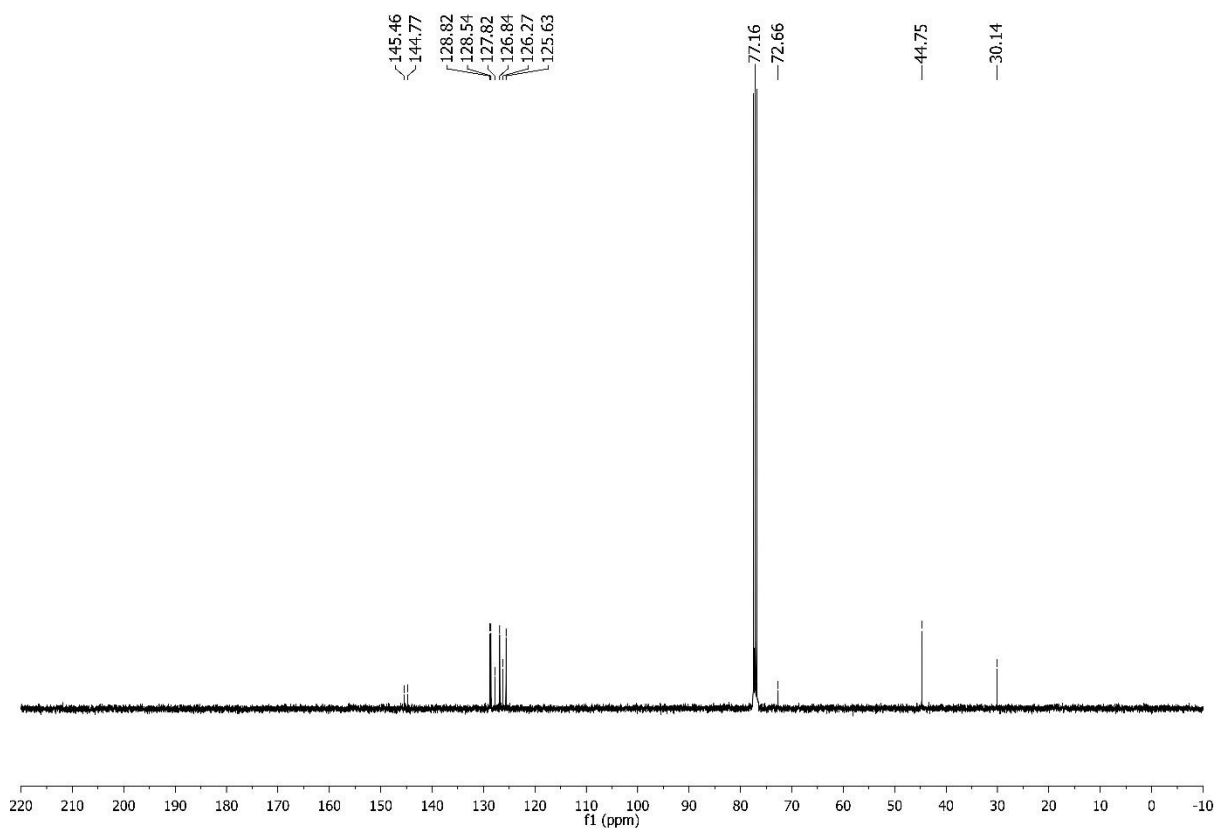
Prepared according to General Procedure C using bromobenzene (216  $\mu\text{L}$ , 2.05 mmol), *n*-butyllithium (865  $\mu\text{L}$ , 2.38 M in hexanes, 2.05 mmol), and **S38** (231 mg, 1.58 mmol). The crude residue was purified by flash column chromatography (10% EtOAc/Petrol, silica gel) to afford **S39** (227 mg, 64%) as a white solid with an approximate d.r. of 90:10.

$R_f$  = 0.21 (10% EtOAc/petrol); **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 3273 (br), 3022, 2978, 1493, 1447, 1242, 1163, 1082, 745, 696; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{16}\text{H}_{16}\text{O}$ ] requires  $[\text{M}-\text{H}_2\text{O}]$  206.1096, found 206.1093.

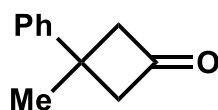
*Data for major diastereoisomer:*  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 7.68 – 7.62 (m, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.28 (m, 5H), 7.25 – 7.18 (m, 1H), 3.12 – 3.02 (m, 3H), 2.63 – 2.51 (m, 2H);  **$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 145.5, 144.8, 128.8, 128.5, 127.8, 126.8, 126.3, 125.6, 72.7, 44.8, 30.1.

*Data for minor diastereoisomer:*  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) (selected)**  $\delta$  = 4.06 – 3.92 (m, 1H), 2.84 – 2.74 (m, 2H), 2.70 – 2.63 (m, 2H).





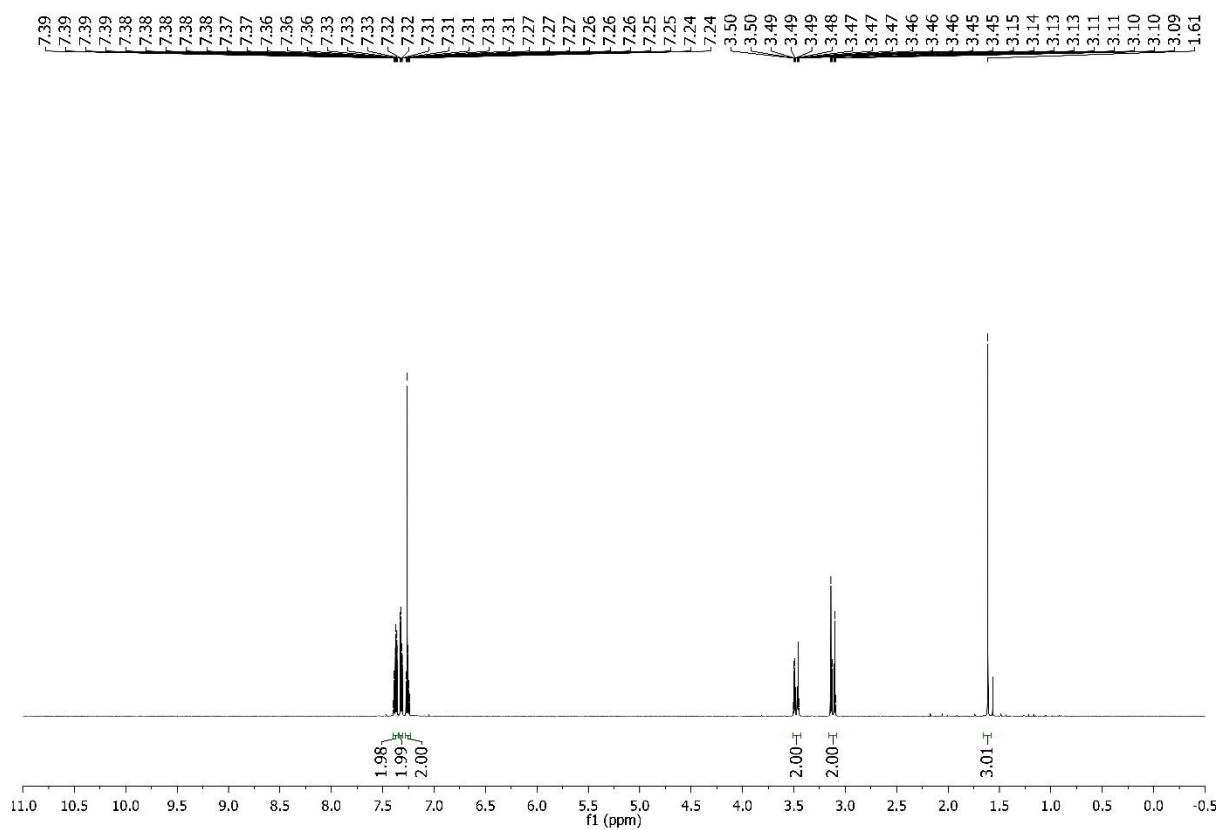
### 3-Methyl-3-phenylcyclobutanone (S40)



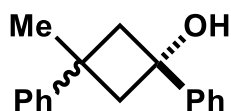
Prepared following General Procedure D using  $\alpha$ -methylstyrene (2.60 mL, 20.0 mmol), trichloroacetyl chloride (4.45 mL, 40.0 mmol), Zn(Cu) couple (3.27 g, 50.0 mmol) and POCl<sub>3</sub> (3.75 mL, 40.0 mmol) in Et<sub>2</sub>O (60 mL) for the first step. The second step employed Zn dust (5.20 g, 80.0 mmol) in AcOH (40 mL). The crude residue was purified by flash column chromatography (10% ethyl acetate in petrol, silica gel) to afford product **S40** (296 mg, 9% over 2 steps) as a colourless oil.

$R_f$  = 0.32 (10% EtOAc/Petrol); FTIR ( $\nu_{\max}$  cm<sup>-1</sup>, thin film) 2954, 2920, 1780, 1497, 1445, 1379, 1302, 1078, 762, 700; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.42 – 7.37 (m, 2H), 7.36 – 7.32 (m, 2H), 7.30 – 7.26 (m, 1H), 3.54 – 3.46 (m, 2H), 3.18 – 3.11 (m, 2H), 1.64 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 206.9, 148.4, 128.7, 126.4, 125.8, 59.4, 34.1, 31.2; HRMS (EI<sup>+</sup>) [C<sub>10</sub>H<sub>10</sub>O] requires [M] 160.0888, found 160.0886.





### 3-Methyl-1,3-diphenylcyclobutanol (**S41**)



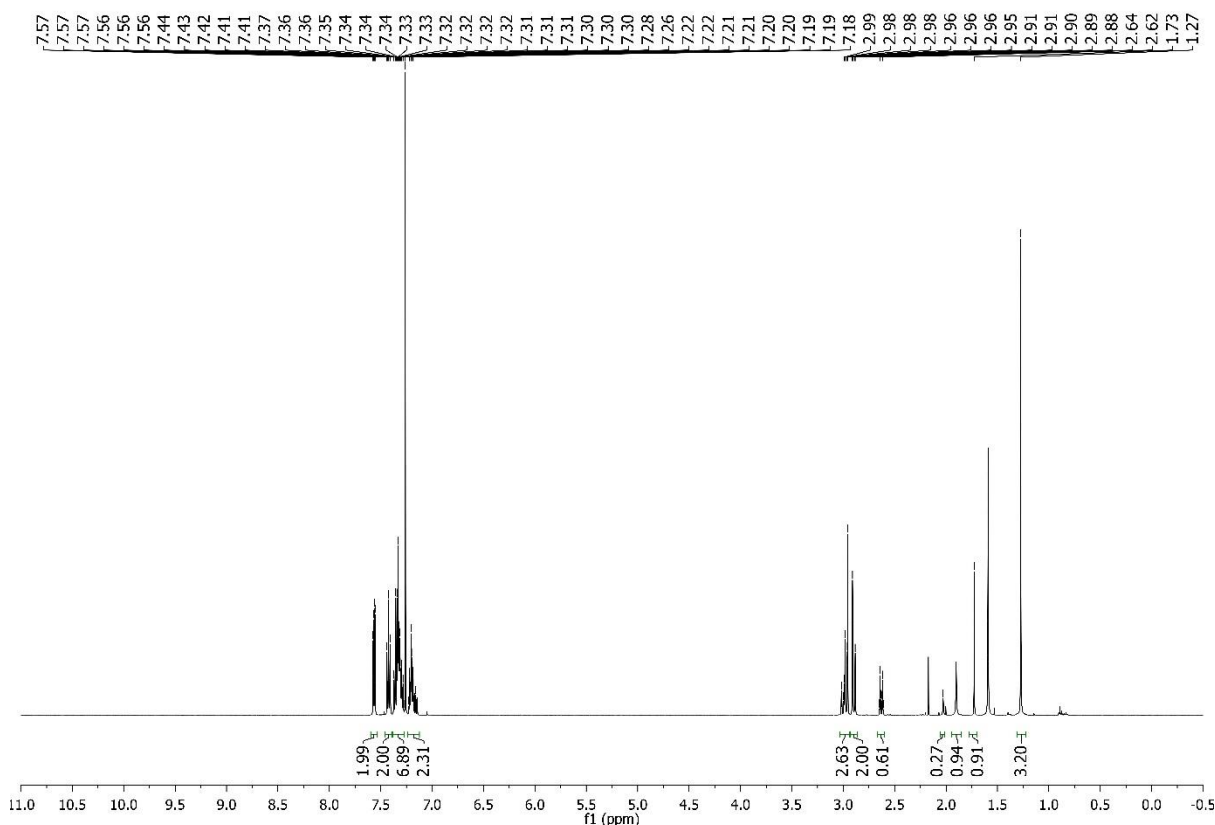
Prepared following General Procedure C using bromobenzene (230  $\mu$ L, 2.18 mmol), *n*-butyllithium (1.10 mL, 2.1 M in hexanes, 2.18 mmol) and **S40** (269 mg, 1.68 mmol). The crude residue was purified by flash column chromatography (10% EtOAc/Petrol, silica gel) to afford **S41** (90 mg, 22%) as a white solid, after recrystallisation from hexanes, with an approximate d.r. of 75:25.

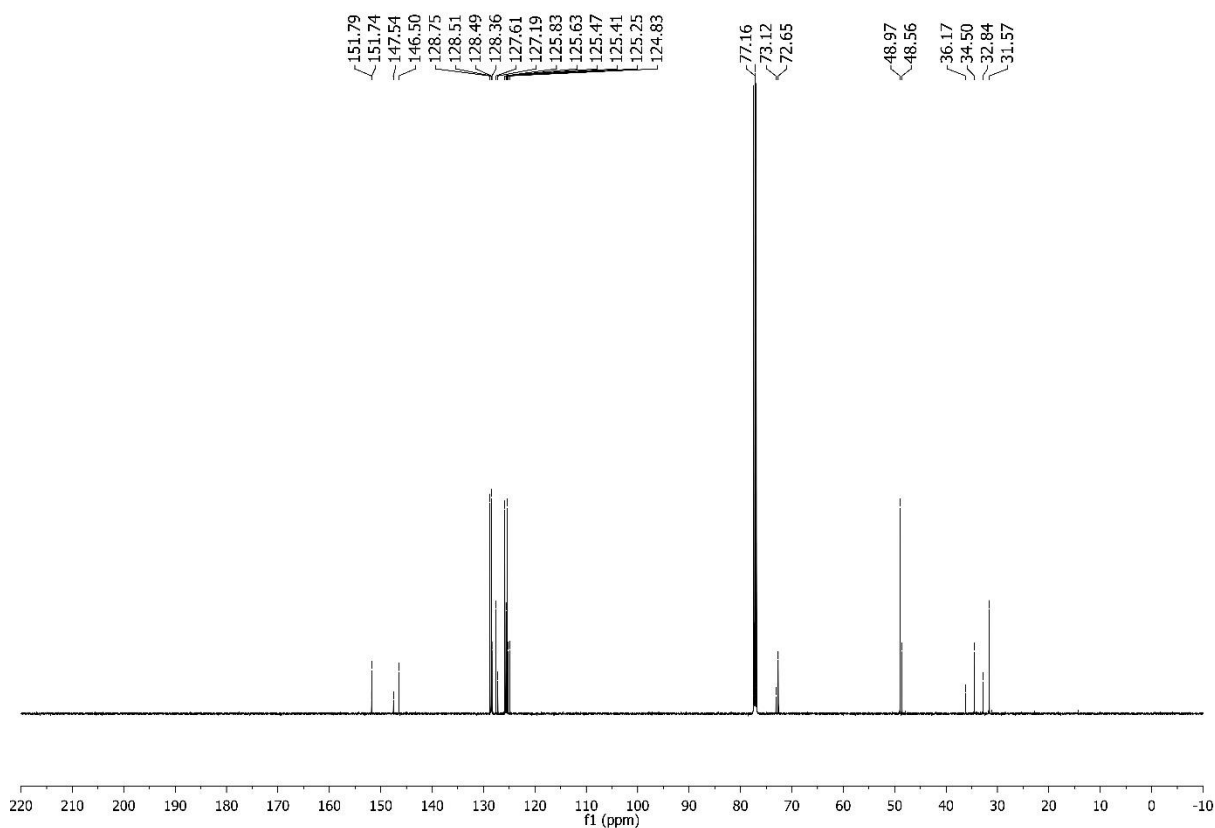
$R_f$  = 0.32 (10% EtOAc/Petrol); **M.p.:** 91-93  $^{\circ}$ C;

*Data for major diastereoisomer:*  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.59 – 7.54 (m, 2H), 7.45 – 7.40 (m, 2H), 7.38 – 7.27 (m, 4H), 7.23 – 7.13 (m, 2H), 3.03 – 2.94 (m, 2H), 2.92 – 2.87 (m, 2H), 1.90 (br. s, 1H), 1.27 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 151.7, 146.5, 128.8, 128.5, 127.6, 125.8, 125.6, 125.4, 72.7, 49.0, 34.5, 31.6.

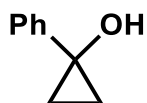
*Data for minor diastereoisomer:*  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) (selected)  $\delta$  = 7.17 – 7.13 (m, 1H), 2.65 – 2.61 (m, 2H), 2.03 (br, 1H), 1.73 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 151.8, 147.5, 128.5, 128.4, 127.2, 125.5, 125.3, 124.8, 73.1, 48.6, 36.2, 32.8.

These data are consistent with those previously reported in the literature.<sup>[12]</sup>



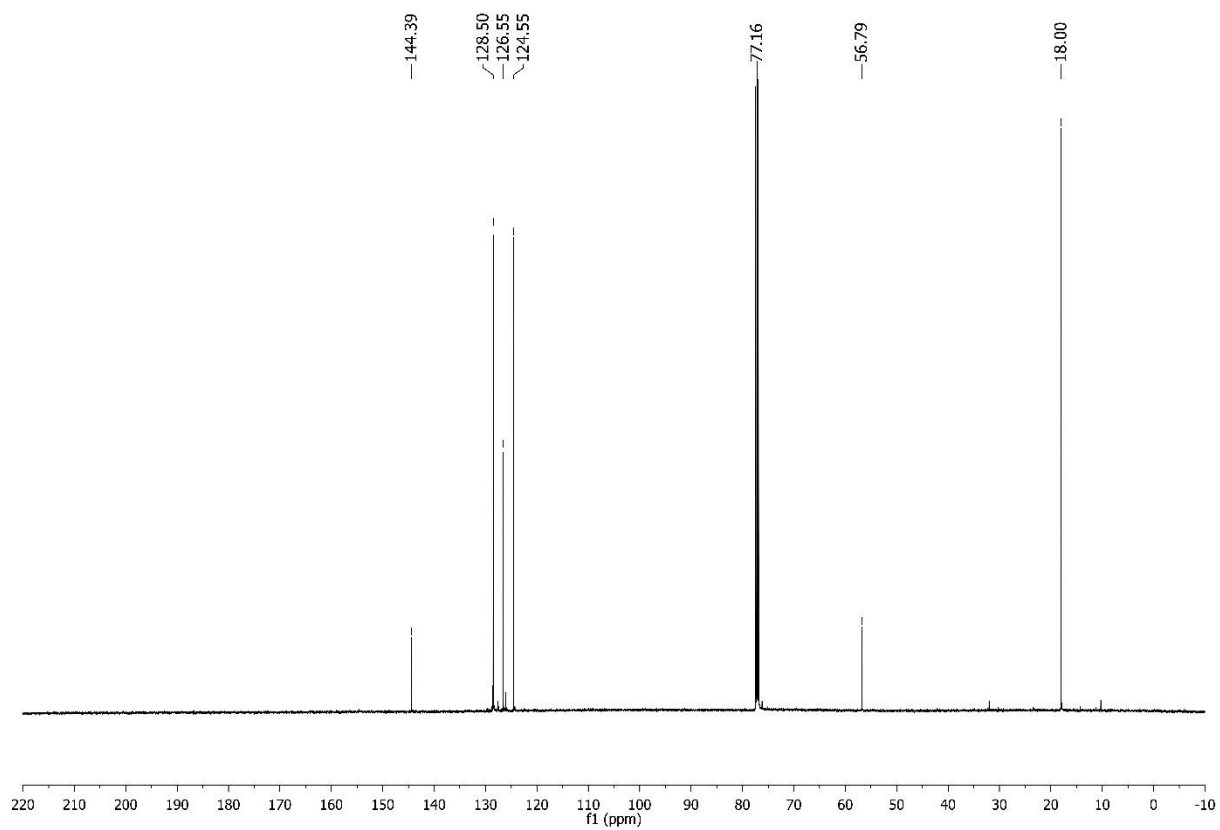
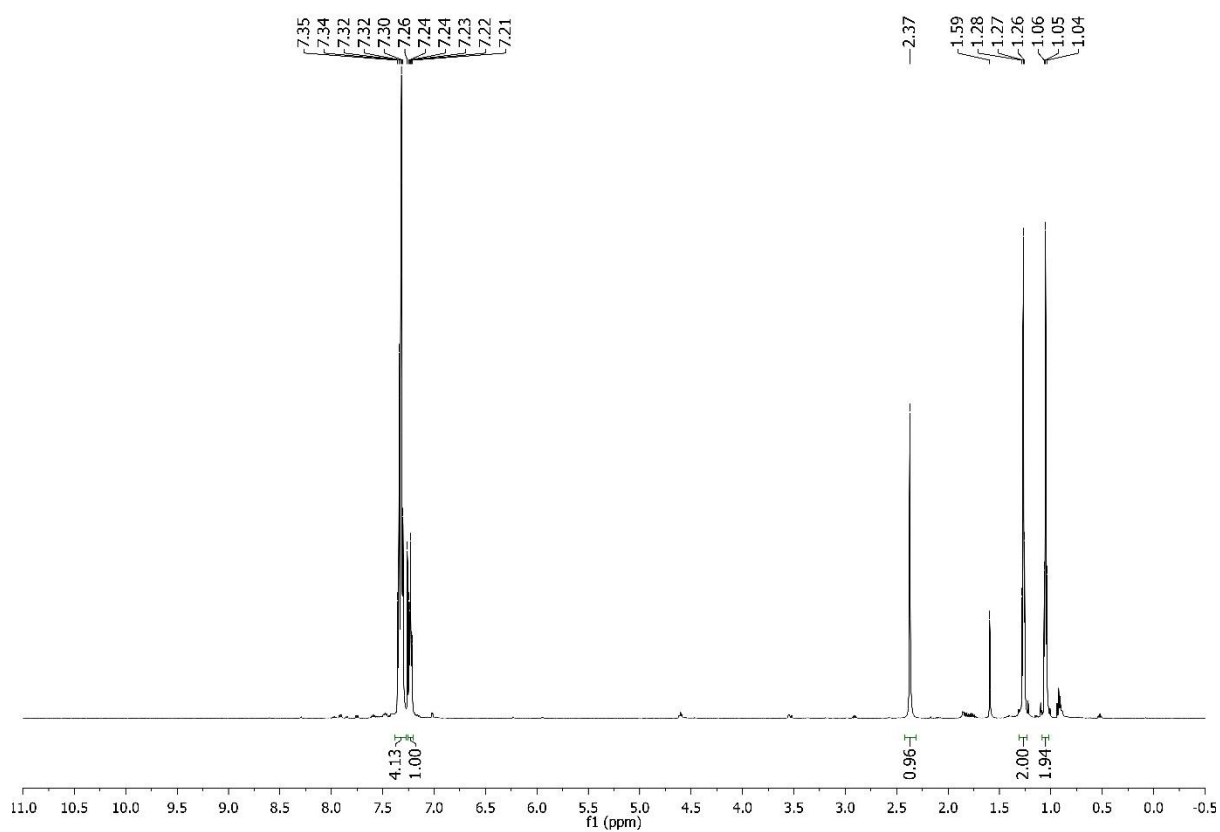


### 1-Phenylcyclopropan-1-ol (S42)

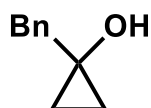


Prepared following General Procedure E using ethyl benzoate (3.16 mL, 25.0 mmol),  $\text{Ti}(\text{O}^i\text{Pr})_4$  (0.74 mL, 2.5 mmol) and ethylmagnesium bromide (17.7 mL, 3 M in diethyl ether, 53 mmol). Purification by flash column chromatography (10% EtOAc/Petrol, silica gel) to afford **18** (2.93 g, 88%) as a yellow oil.

$R_f$  = 0.15 (15% EtOAc/Petrol); FTIR ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) = 3315 (br), 3090, 3028, 1494, 1546, 1230, 1097, 754, 694;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.36 – 7.27 (m, 4H), 7.24 – 7.21 (m, 1H), 2.37 (s, 1H), 1.30 – 1.24 (m, 2H), 1.09 – 1.02 (m, 2H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 144.2, 128.3, 126.4, 124.4, 76.7, 56.6, 17.8; HRMS ( $\text{EI}^+$ ) [ $\text{C}_9\text{H}_9\text{O}$ ] requires [M] 133.0657, found 133.0653.

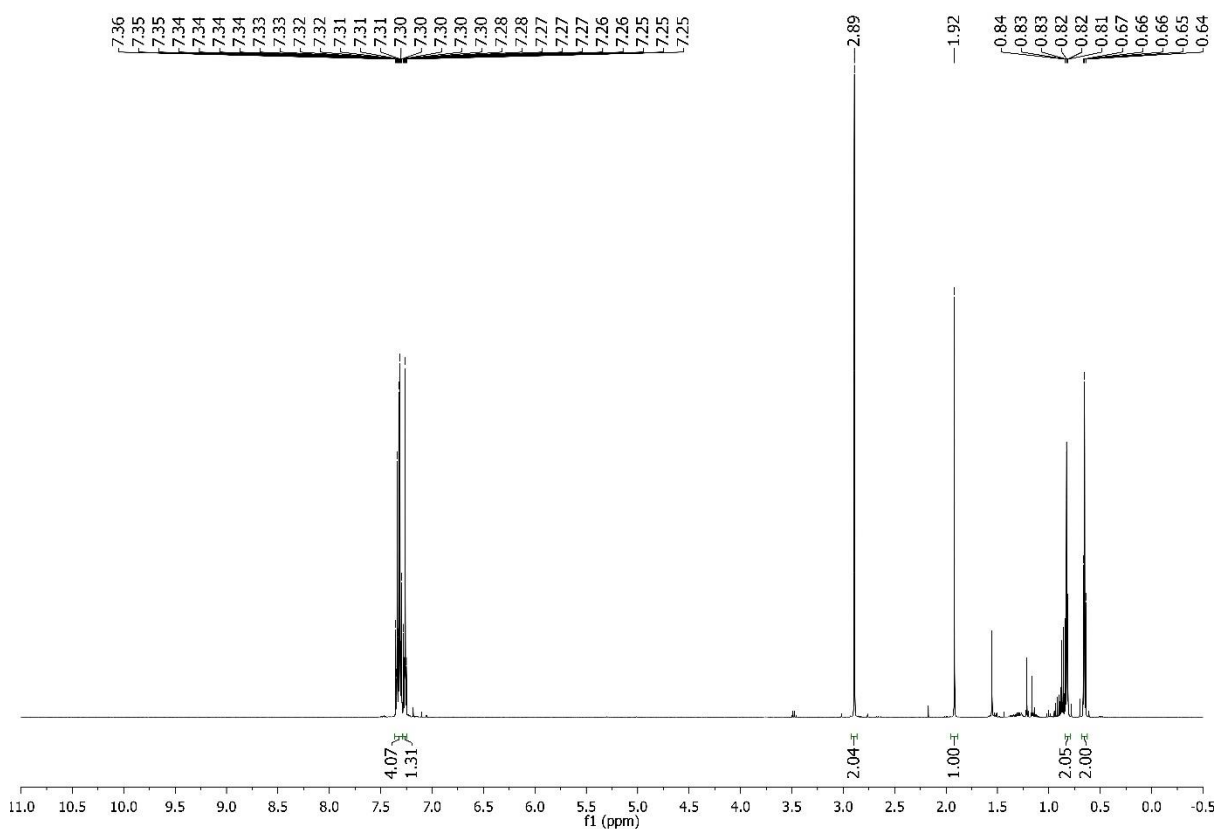


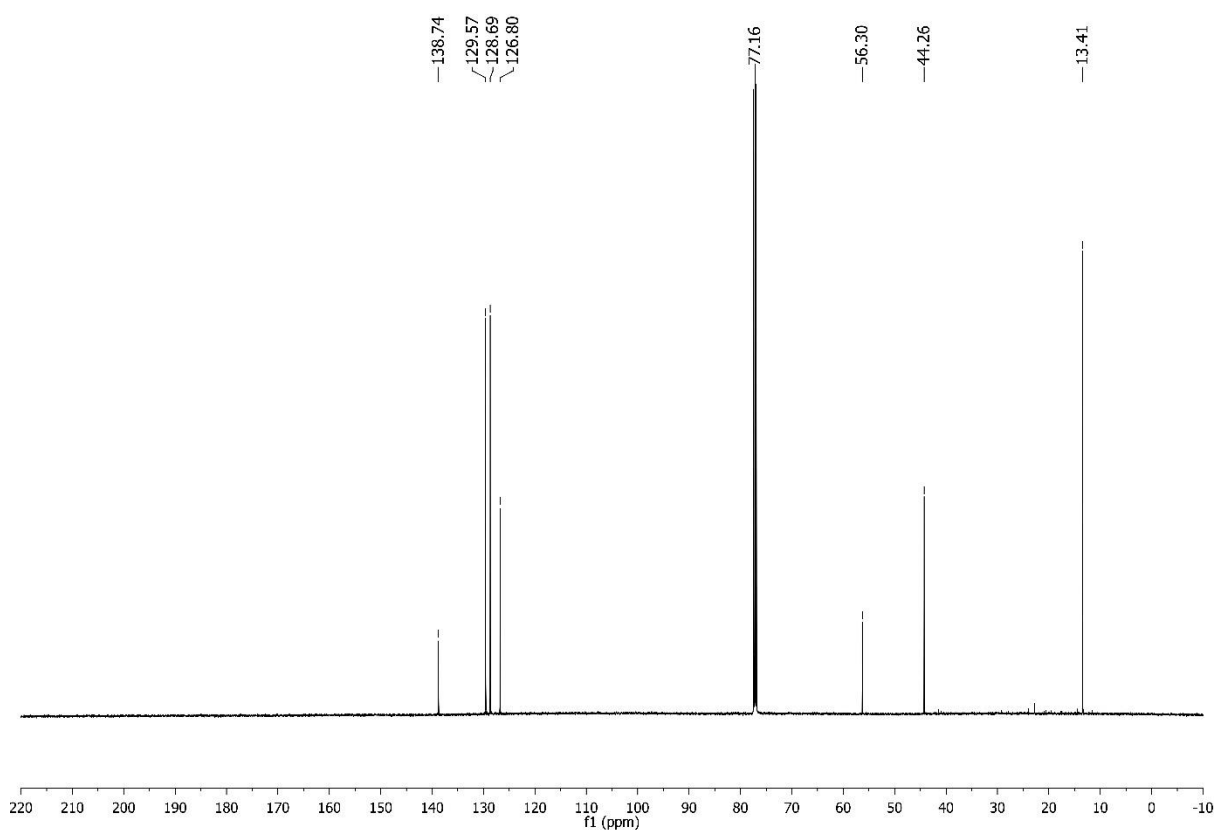
### 1-Benzylcyclopropan-1-ol (**S43**)



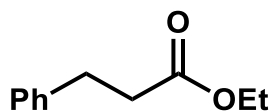
Prepared following General Procedure E using methyl phenylacetate (1.40 mL, 10 mmol),  $\text{Ti}(\text{O}^i\text{Pr})_4$  (4.15 mL, 14 mmol) and ethylmagnesium bromide (9.30 mL, 3.0 M in  $\text{Et}_2\text{O}$ , 28 mmol). Purification by flash column chromatography (10% EtOAc/Petrol, silica gel) afforded **S43** (950 mg, 64%) as a colourless oil.

$R_f$  = 0.34 (10% EtOAc/petrol); **FTIR** 3337, 3005, 1495, 1454, 1011, 953, 926, 486;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 7.37 – 7.29 (m, 4H), 7.29 – 7.24 (m, 1H), 2.89 (s, 2H), 1.92 (s, 1H), 0.84 – 0.81 (m, 2H), 0.68 – 0.63 (m, 2H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 138.7, 129.6, 128.7, 126.8, 56.3, 44.3, 13.4; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{10}\text{H}_{12}\text{O}$ ] requires  $[M]$  148.0888, found 148.0893.



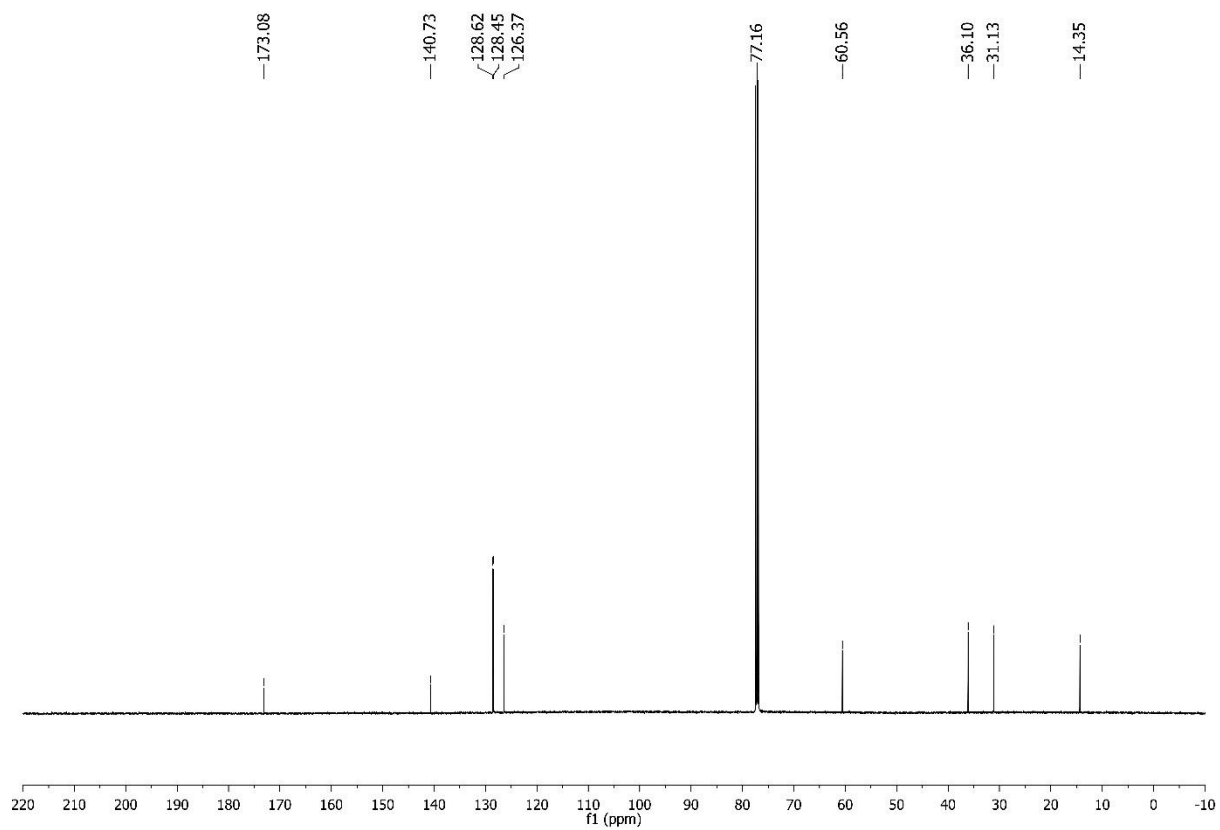
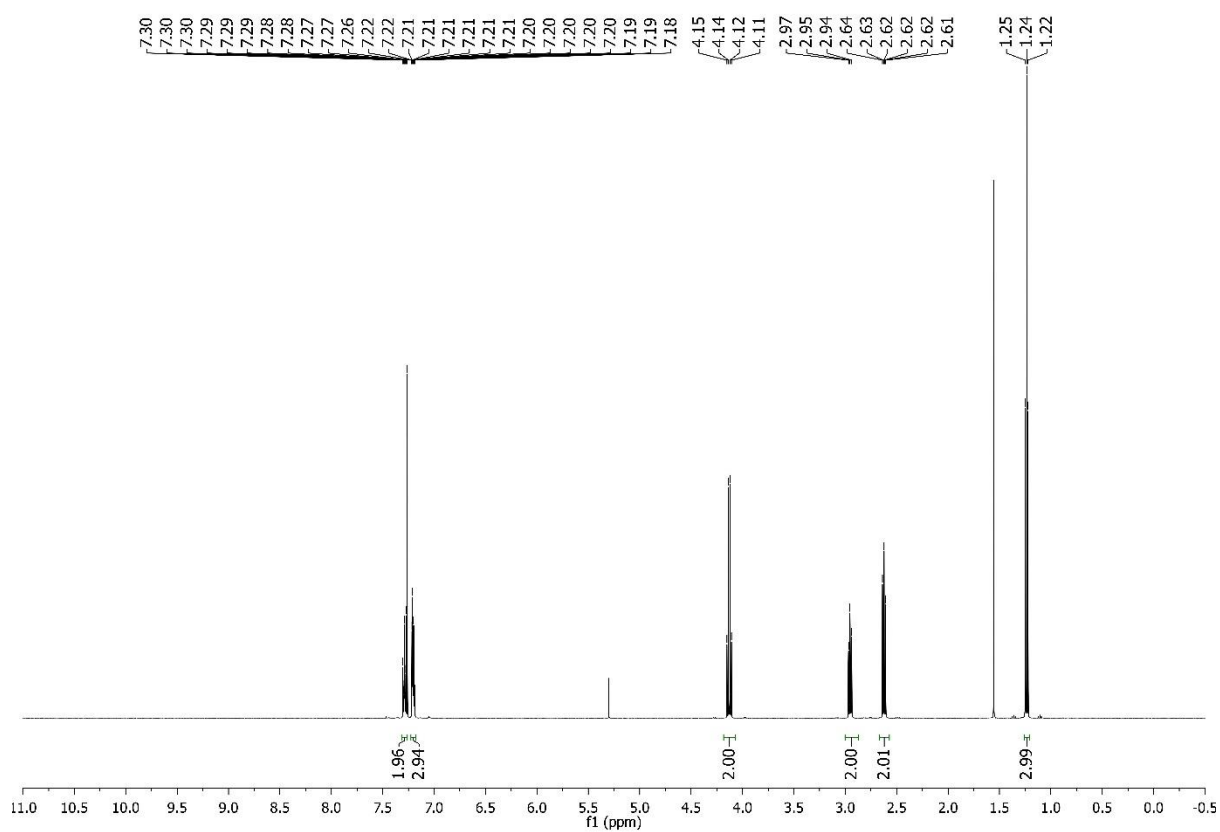


#### Ethyl 3-phenylpropanoate (**S44**)

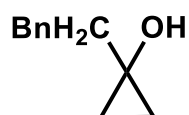


To a solution of 3-phenylpropanoic acid (1.50 g, 10 mmol, 1.0 eq.) in EtOH (12.5 mL) was added conc.  $\text{H}_2\text{SO}_4$  (0.54 mL, 18.4 M, 10 mmol, 1.0 eq.) and the mixture was left to stir at reflux overnight. Upon cooling, the solvent was removed and the residue was taken up in  $\text{CH}_2\text{Cl}_2$  (30 mL). The mixture was washed with 1 M NaOH ( $3 \times 15$  mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure to provide **S44** (1.62 g, 91%) as a colourless oil that was used without further purification.

$R_f$  = 0.40 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 2980, 1730, 1454, 1371, 1159, 1038, 748, 698;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.31 – 7.27 (m, 2H), 7.22 – 7.18 (m, 3H), 4.13 (q,  $J$  = 7.0 Hz, 2H), 2.97 – 2.93 (m, 2H), 2.64 – 2.60 (m, 2H), 1.24 (t,  $J$  = 7.0 Hz, 3H);  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 173.1, 140.7, 128.6, 128.4, 126.4, 60.6, 36.1, 31.1, 14.4; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{11}\text{H}_{14}\text{O}_2$ ] requires  $[M]$  178.0884, found 178.0993.

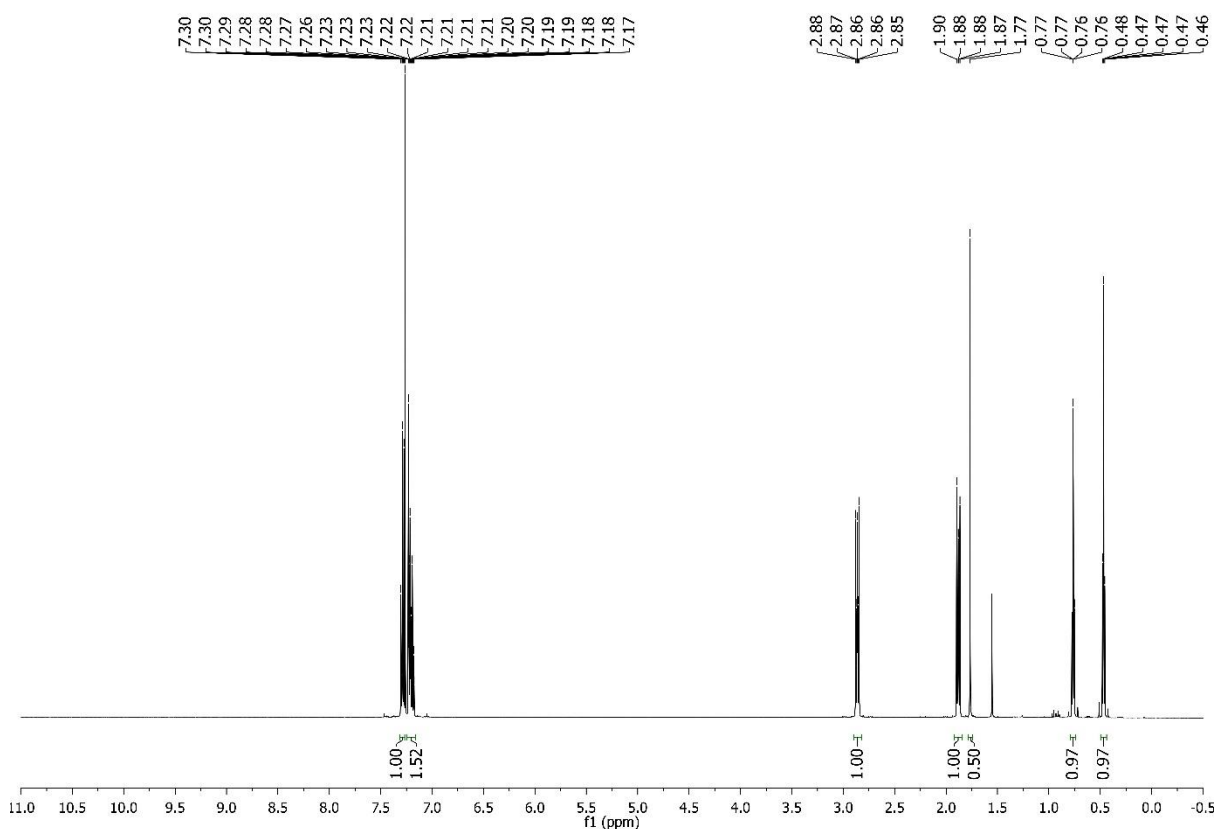


### 1-Phenethylcyclopropan-1-ol (**S45**)

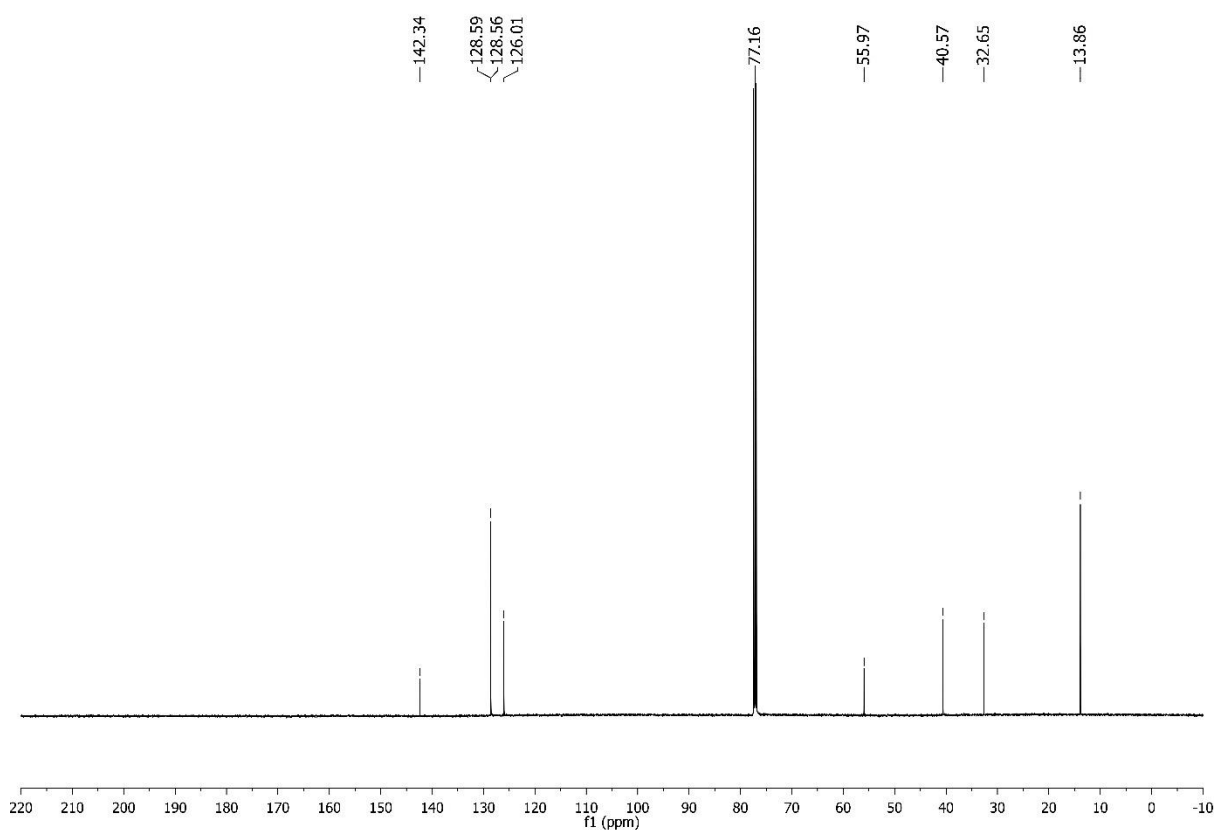


Prepared according to General Procedure E using **S44** (891 mg, 5.00 mmol),  $\text{Ti}(\text{O}^i\text{Pr})_4$  (2.07 mL, 7.00 mmol), and ethyl magnesium bromide (4.67 mL, 3.0 M in  $\text{Et}_2\text{O}$ , 14.0 mmol). The crude residue was purified by flash column chromatography (25% EtOAc/Hexanes, silica gel) to afford **S45** (592 mg, 73%) as a white solid.

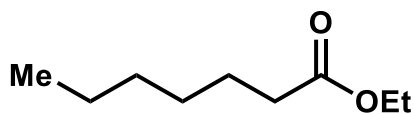
$R_f$  = 0.38 (10% EtOAc/Hexanes); **M.p.**: 49 – 51 °C; **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 3339 (br), 2947, 1493, 1454, 1285, 1248, 1238, 1007, 949, 935, 926, 747, 725, 694, 521;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.31 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 2.88 – 2.84 (m, 2H), 1.90 – 1.86 (m, 2H), 1.77 (s, 1H), 0.78 – 0.75 (m, 2H), 0.48 – 0.45 (m, 2H);  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 142.3, 128.6, 128.5, 126.0, 56.0, 40.6, 32.7, 13.9; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{11}\text{H}_{14}\text{O}$ ] requires [M] 162.1045, found 162.1048.





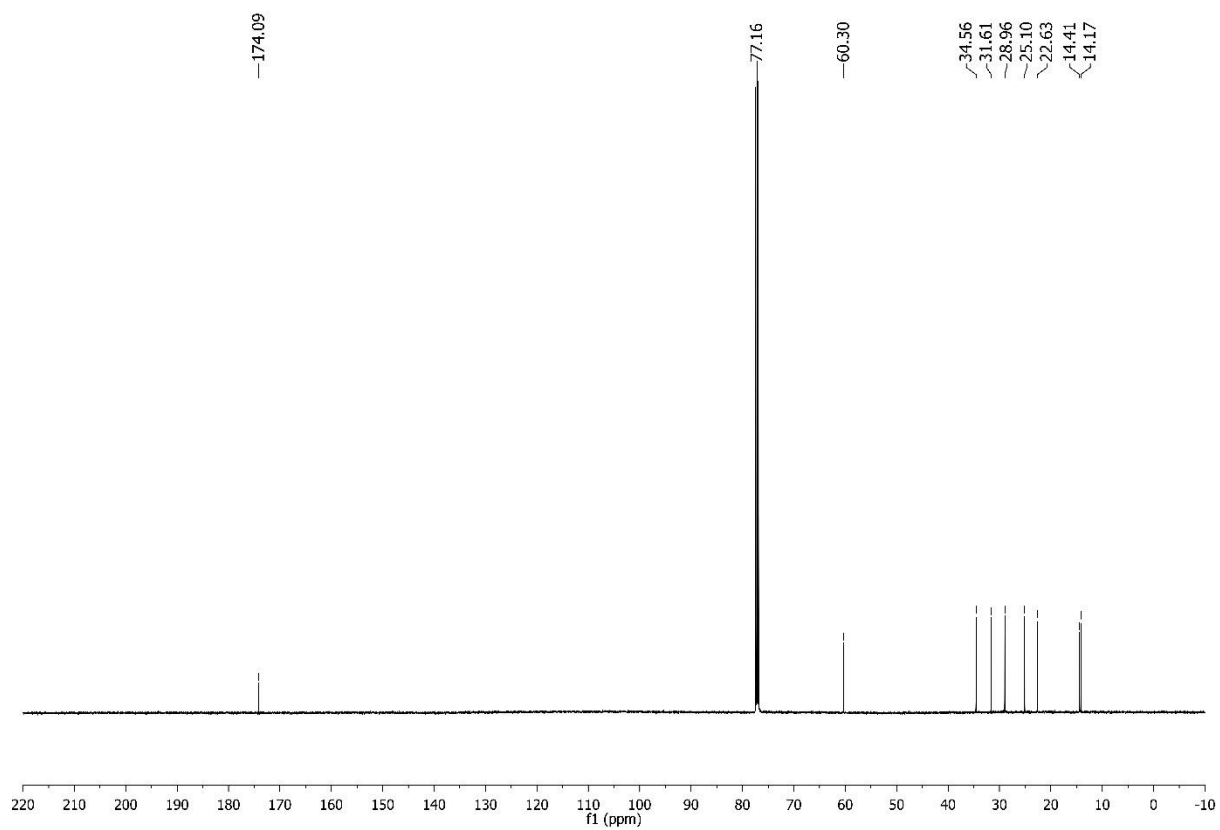
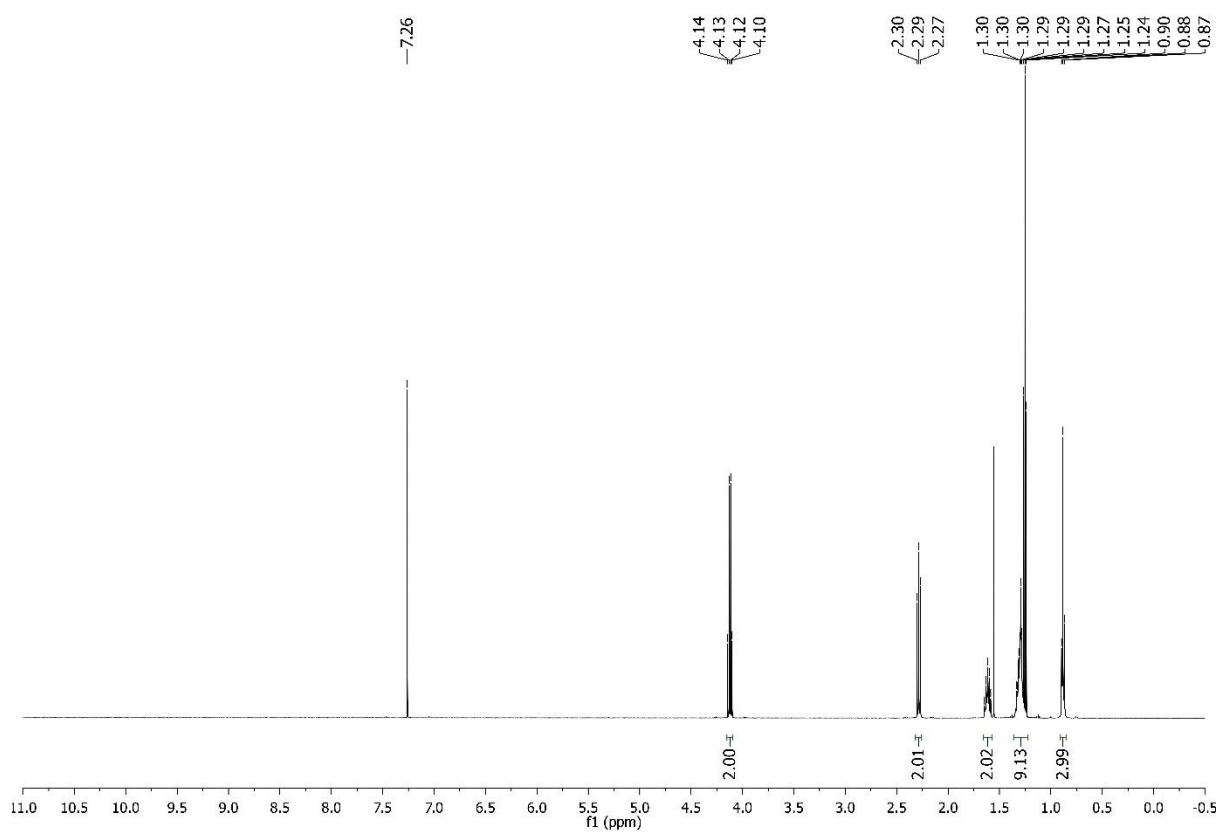


#### Ethyl heptanoate (**S46**)

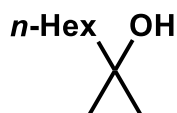


To an RBF charged with heptanoic acid (1.42 mL, 10.0 mmol) in EtOH (12.5 mL, 0.8 M) was added conc.  $\text{H}_2\text{SO}_4$  (0.54 mL, 10 mmol) dropwise at 0 °C. After complete addition, the reaction mixture was allowed to warm to rt, then heated to reflux overnight. After completion of the reaction, the solution was cooled to rt, and then concentrated under reduced pressure. The resulting residue was then dissolved in  $\text{CH}_2\text{Cl}_2$  and washed with 1 M NaOH (3 × 10 mL). The combined organic fractions were dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure to give **S46** (934 mg, 59%) as a colourless oil that was used without further purification.

$R_f$  = 0.92 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 2930, 2859, 1736, 1456, 1371, 1165, 1099, 1034;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 4.12 (t,  $J$  = 7.1, 2H), 2.32 – 2.35 (m, 2H), 1.66 – 1.58 (m, 2H), 1.35 – 1.23 (m, 9H), 0.91 – 0.85 (m, 3H);  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 174.1, 60.3, 34.6, 31.6, 29.0, 25.1, 22.6, 14.4, 14.2; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_9\text{H}_{18}\text{O}_2$ ] requires  $[M]$  158.1307, found 158.1306.

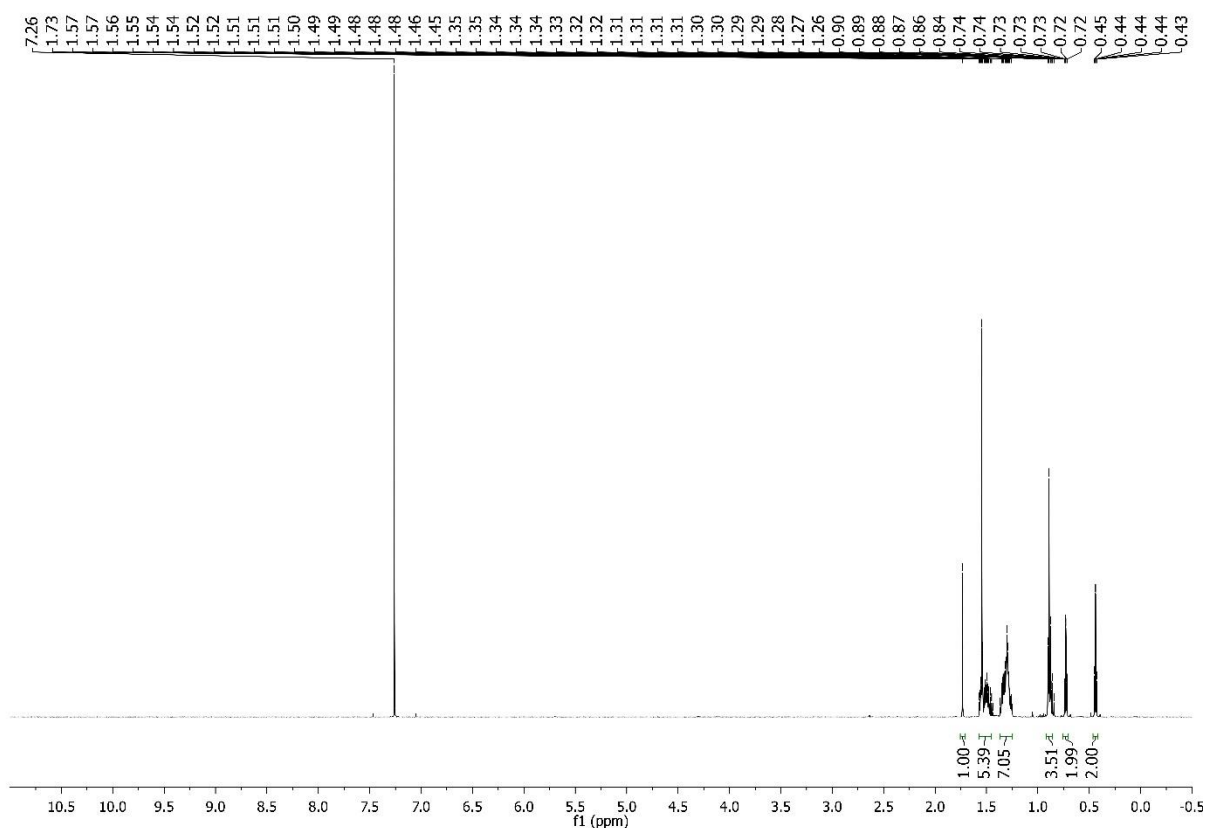


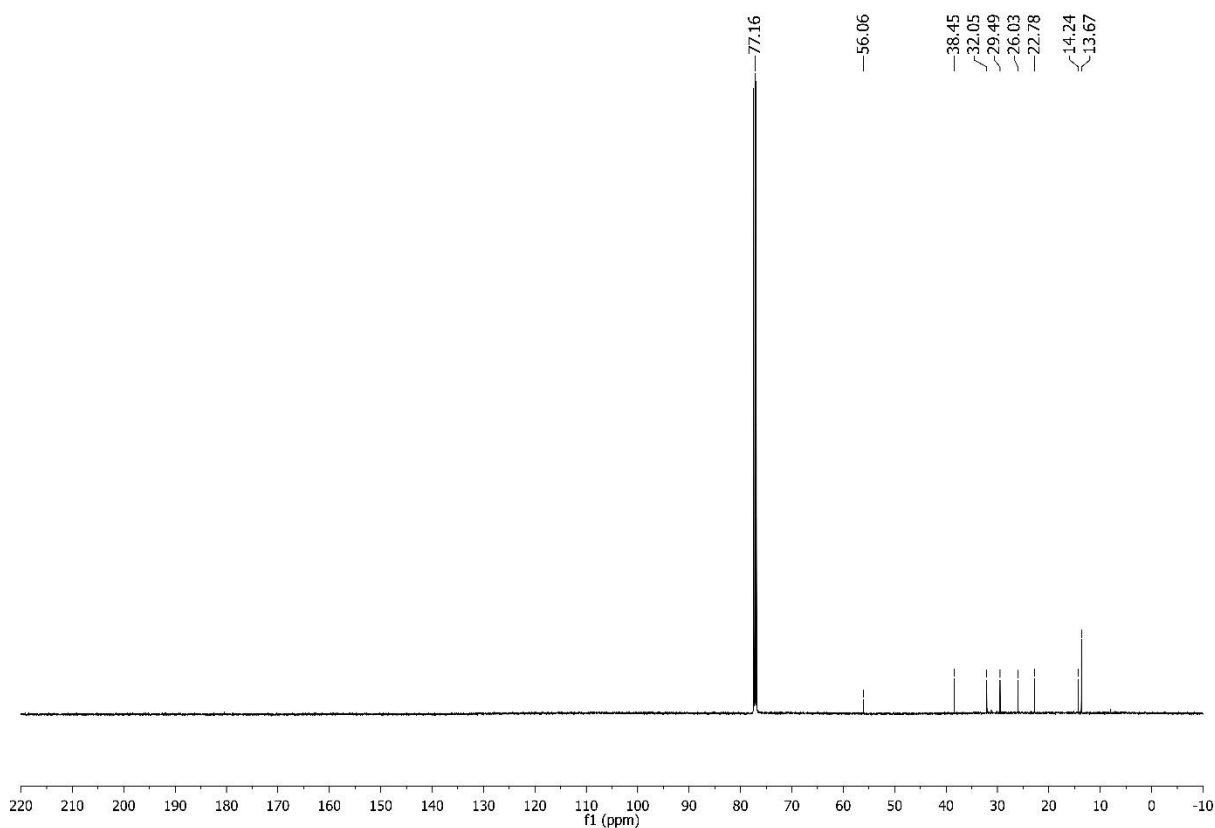
### 1-Hexylcyclopropan-1-ol (**S47**)



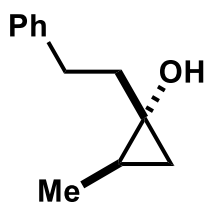
Prepared according to General Procedure E using **S46** (792 mg, 5.00 mmol),  $\text{Ti}(\text{O}^i\text{Pr})_4$  (2.07 mL, 7.00 mmol), and ethyl magnesium bromide (4.67 mL, 3.0 M in  $\text{Et}_2\text{O}$ , 14.0 mmol). The crude residue was purified by flash column chromatography (10% EtOAc/Petrol, silica gel) to afford **S47** (287 mg, 40%) as a colourless oil.

$R_f$  = 0.29 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 3306 (br), 1456, 1267, 1236, 1096, 1007, 955, 926, 721;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 1.73 (s, 1H), 1.59 – 1.44 (m, 3H), 1.37 – 1.24 (m, 7H), 0.93 – 0.86 (m, 3H), 0.75 – 0.70 (m, 2H), 0.46 – 0.42 (m, 2H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 56.1, 38.5, 32.1, 29.5, 26.0, 22.8, 14.3, 13.7; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_9\text{H}_{18}\text{O}$ ] requires  $[M]$  142.1358, found 142.1365.



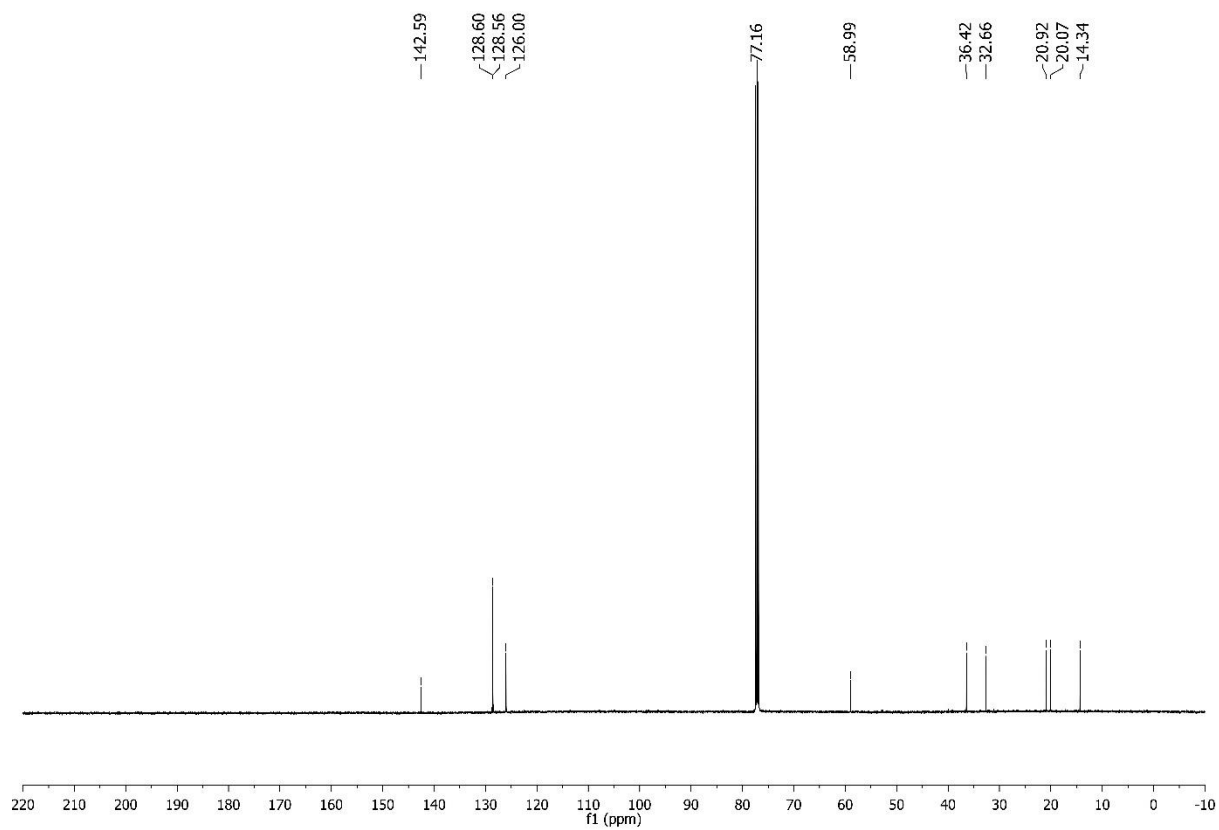
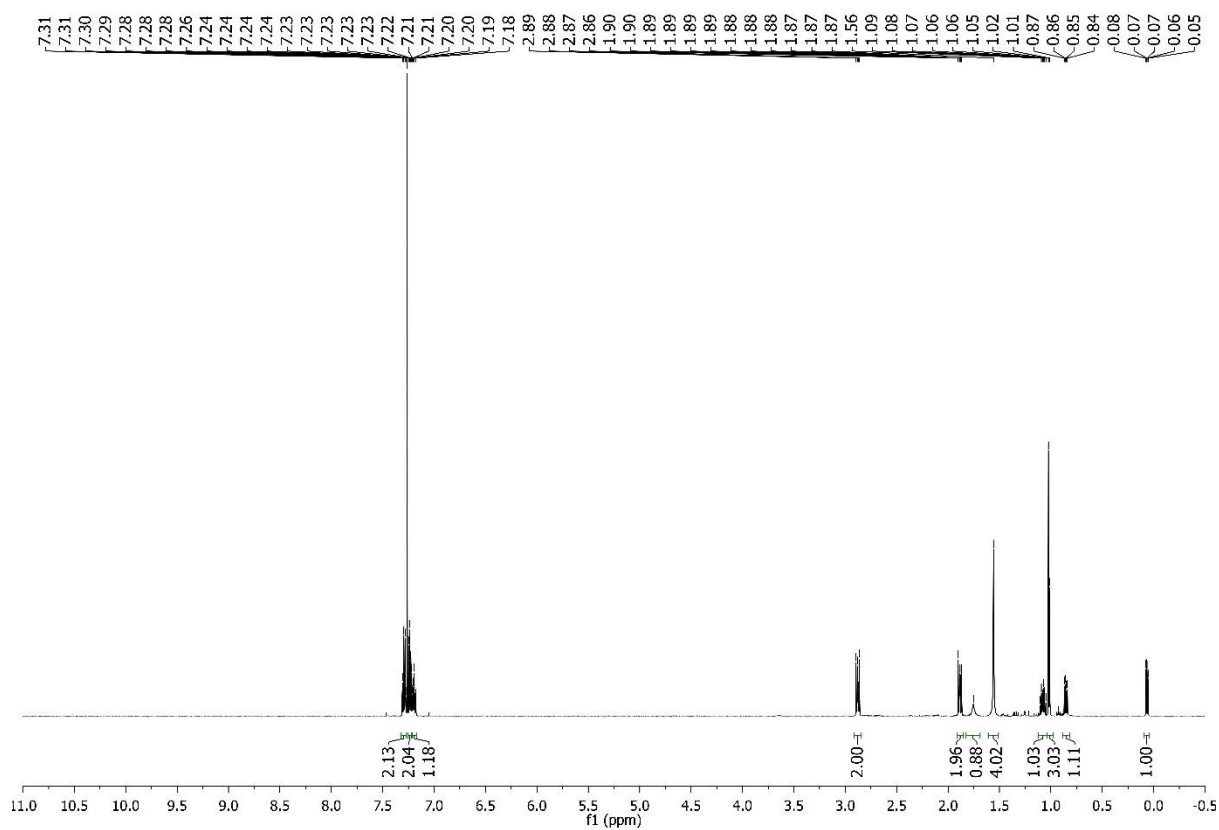


#### 2-Methyl-1-phenethylcyclopropan-1-ol (**S48**)

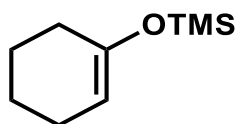


Prepared according to General Procedure E using **S44** (891 mg, 5.00 mmol),  $\text{Ti}(\text{O}^i\text{Pr})_4$  (2.07 mL, 7.00 mmol), and isopropylmagnesium chloride (7.00 mL, 2.0 M in THF, 14.0 mmol). The crude residue was purified by flash column chromatography (10→15% EtOAc/Petrol, silica gel) to afford **S48** (245 mg, 28%) as a colourless oil.

$R_f$  = 0.18 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 3294 (br), 2949, 2924, 1495, 1452, 1219, 1061, 907, 750, 698;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 7.31 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 2.90 – 2.86 (m, 2H), 1.90 – 1.86 (m, 2H), 1.76 (br. s, 1H), 1.12 – 1.05 (m, 1H), 1.02 (d,  $J$  = 6.0, 3H), 0.85 (dd,  $J$  = 10.0, 5.5, 1H), 0.10 – 0.03 (m, 1H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 142.6, 128.6, 128.6, 126.0, 59.0, 36.4, 32.7, 20.9, 20.1, 14.3; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{12}\text{H}_{16}\text{O}$ ] requires  $[M]$  176.1201, found 176.1197.



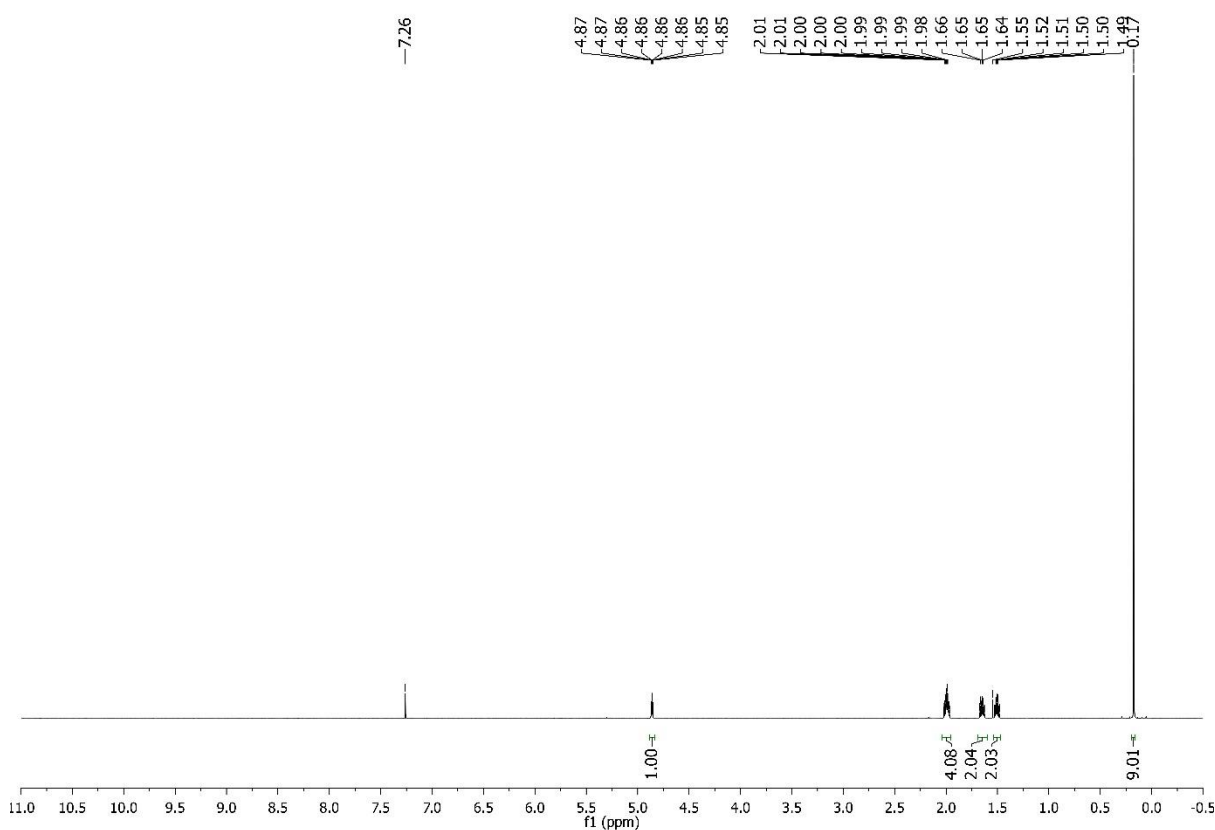
(Cyclohex-1-en-1-yloxy)trimethylsilane (**S49**)

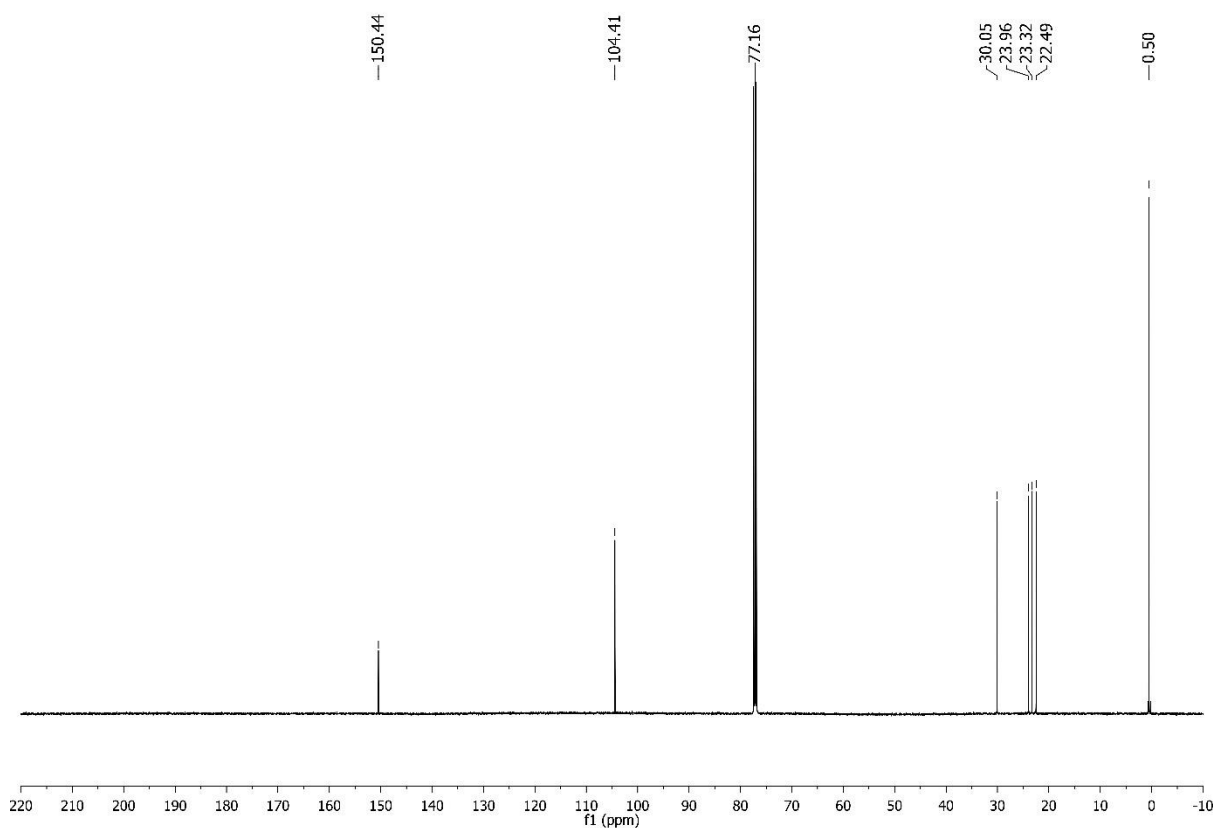


A RBF charged with NaI (3.60 g, 24 mmol, 1.2 eq.) was flame-dried and placed under an atmosphere of N<sub>2</sub>. MeCN (30 mL) was added followed by cyclohexanone (2.07 mL, 20 mmol, 1.0 eq.) and Et<sub>3</sub>N (4.18 mL, 30 mmol, 1.5 eq.). TMSCl (3.05 mL, 24 mmol, 1.2 eq.) was added dropwise and the reaction mixture was left to stir at rt for 16 h. The reaction was quenched by the addition of sat. NH<sub>4</sub>Cl (50 mL) and petrol (50 mL). The aqueous layer was extracted with petrol (2 × 30 mL) and the combined organic layers were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. High vacuum distillation afforded **S49** (2.89 g, 85%) as a colourless oil.

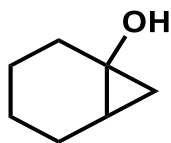
R<sub>f</sub> = 0.28 (100% Petrol); B.p.: 69-70 °C (18 mmHg) (Lit.<sup>[13]</sup> 75-76 °C (20 mmHg)); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 4.88 – 4.84 (m, 1H), 2.03 – 1.96 (m, 4H), 1.68 – 1.61 (m, 2H), 1.54 – 1.47 (m, 2H), 0.17 (s, 9H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ = 150.4, 104.4, 30.1, 24.0, 23.3, 22.5, 0.5.

These data are consistent with those previously reported in the literature.<sup>[14]</sup>



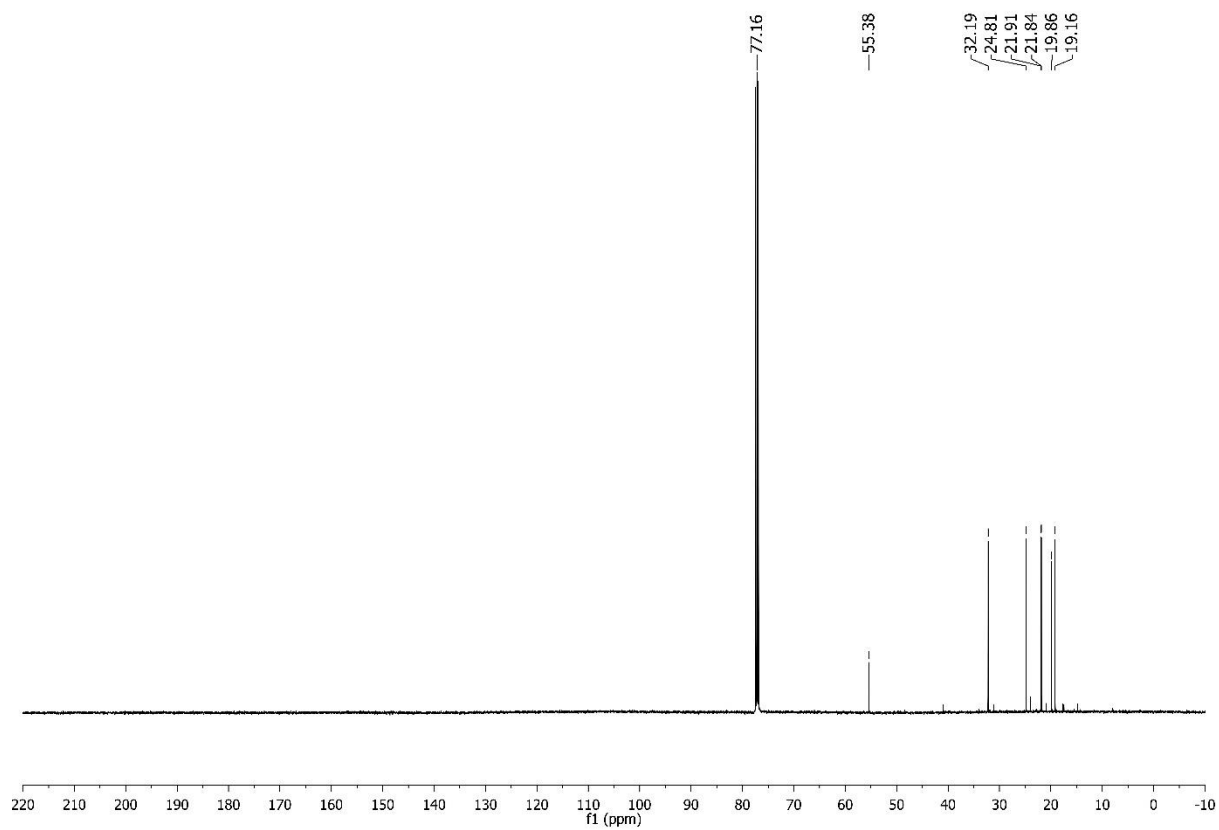
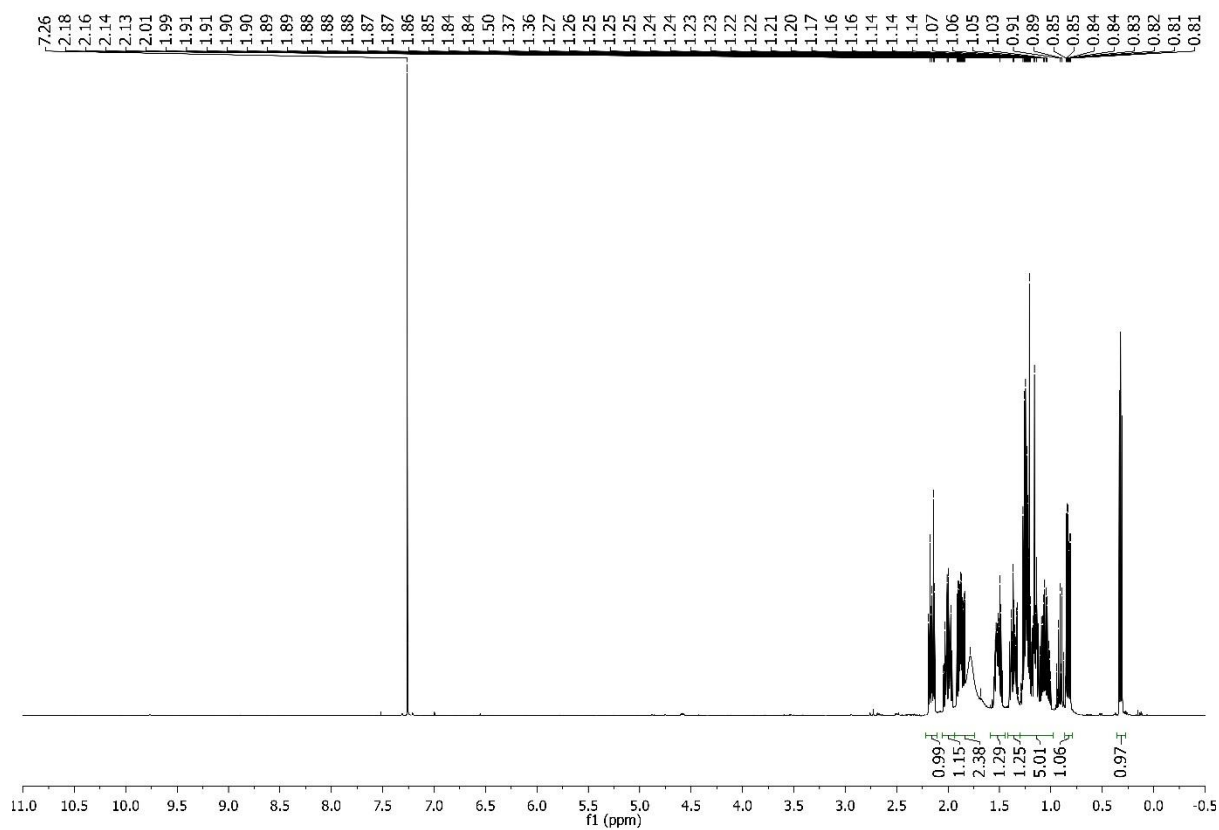


#### Bicyclo[4.1.0]heptan-1-ol (**S50**)



To a solution of **S49** (852 mg, 5 mmol, 1.0 eq.) and diethylzinc (7.8 mL, 7 mmol, 0.9 m in hexane, 1.4 eq.) in Et<sub>2</sub>O (5 mL) at 0 °C was added a solution of diiodomethane (565 µL, 7 mmol, 1.4 eq.) in Et<sub>2</sub>O (5 mL) dropwise and the reaction mixture was heated at reflux for 3 h. After cooling, the reaction was quenched by the dropwise addition of pyridine (1.0 mL) and the mixture was filtered through a pad of celite, washing with Et<sub>2</sub>O. The filtrate was concentrated and the resulting residue was taken up in MeOH (15 mL). K<sub>2</sub>CO<sub>3</sub> (69 mg, 0.5 mmol, 10 mol %) was added and the reaction mixture was left to stir for 30 min at rt. Water (15 mL) and EtOAc (50 mL) were added and the layers separated. The aqueous layer was further extracted with EtOAc (2 × 15 mL). The combined organics were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% Et<sub>2</sub>O in petrol, silica gel) to afford **S50** (347 mg, 62%) as a colourless oil.

**R<sub>f</sub>** = 0.25 (20% Et<sub>2</sub>O/Petrol); **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3323, 2928, 2857, 2359, 1449, 1362, 1198, 1094, 1070, 914; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 2.16 (dt, *J* = 13.0, 5.0 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.88 (dddd, *J* = 13.0, 10.0, 5.5, 1.5 Hz, 1H), 1.78 (br. s, 1H), 1.57 – 1.46 (m, 1H), 1.41 – 1.31 (m, 1H), 1.29 – 0.98 (m, 5H), 0.83 (ddd, *J* = 10.5, 5.5, 1.5 Hz, 1H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 55.4, 32.2, 24.8, 21.9, 21.8, 19.9, 19.2; **HRMS** (EI<sup>+</sup>) [C<sub>7</sub>H<sub>12</sub>O] requires [M] 112.0888, found 112.0890.





## 2.3 General Procedures – Electrochemical Deconstructive-Chlorination of Cycloalkanols

### 2.3.1 General Procedure G – Standard Procedure

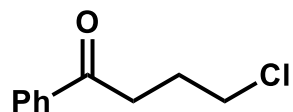
To an oven-dried 10 mL ElectraSyn vial equipped with a magnetic stirrer bar, was added substrate (0.30 mmol), Mn(OTf)<sub>2</sub> (11 mg, 0.03 mmol), MgCl<sub>2</sub> (143 mg, 1.50 mmol) and LiClO<sub>4</sub> (64 mg, 0.60 mmol). The threaded glass was wrapped with PTFE tape and connected to the ElectraSyn cap, which was fitted with a graphite anode and a graphite cathode. The vial was purged with N<sub>2</sub> gas *via* evacuate-refill cycles (× 3). MeCN (5.25 mL) was added, followed by AcOH (0.75 mL) and the mixture was stirred for a minute to ensure solvation of the MgCl<sub>2</sub>. The mixture was then purged *via* bubbling with N<sub>2</sub> gas for 10 minutes. During this time, the vial was connected to an ElectraSyn GoGo module and submerged in a 25 °C water bath mounted on a magnetic stirrer. Electrolysis at 10 mA was conducted for 3 h under N<sub>2</sub> with continuous stirring. After electrolysis was complete, the reaction mixture was left to stir at 25 °C for an additional 30 minutes. The crude reaction mixture was diluted with Et<sub>2</sub>O (10 mL) and washed with sat. NaHCO<sub>3</sub> (2 × 15 mL). The aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 mL) and the combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the pure product. ***N.B.***: If the substrate is an oil, it is weighed directly into the ElectraSyn vial before addition of solid reactants.

### 2.3.2 General Procedure H – Syringe Pump Addition of Substrate

To an oven-dried 10 mL ElectraSyn vial equipped with a magnetic stirrer bar, was added Mn(OTf)<sub>2</sub> (11 mg, 0.03 mmol), MgCl<sub>2</sub> (143 mg, 1.50 mmol) and TBAOAc (181 mg, 0.60 mmol). The threaded glass was wrapped with PTFE tape and connected to the ElectraSyn cap, which was fitted with a graphite anode and a graphite cathode. The vial was purged with N<sub>2</sub> gas *via* evacuate-refill cycles (× 3). MeCN (3.25 mL) was added, followed by AcOH (0.75 mL) and the mixture was stirred for one minute to ensure solvation of the MgCl<sub>2</sub>. The mixture was then purged *via* bubbling with N<sub>2</sub> gas for 10 minutes. During this time, the vial was connected to an ElectraSyn GoGo module and submerged in a 25 °C water bath mounted on a magnetic stirrer. In a separate 5 mL vial, substrate (0.30 mmol) and MeCN (2 mL) was added and the mixture was purged *via* bubbling with N<sub>2</sub> gas for 2 minutes before it was transferred into a 3 mL disposable syringe and connected to a syringe pump. Electrolysis at 10 mA was conducted for 3 h under N<sub>2</sub> with continuous stirring, while syringe pump addition of the tertiary alcohol solution in MeCN (1 mL/h) was started after 2 minutes of electrolysis. After electrolysis was complete, the reaction mixture was left to stir at 25 °C for an additional 30 minutes. The crude reaction mixture was diluted with Et<sub>2</sub>O (10 mL) and washed with sat. aq. NaHCO<sub>3</sub> (2 × 15 mL). The aqueous layer was further extracted with Et<sub>2</sub>O (3 × 10 mL) and the combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the pure product.

## 2.4 Characterization of Products

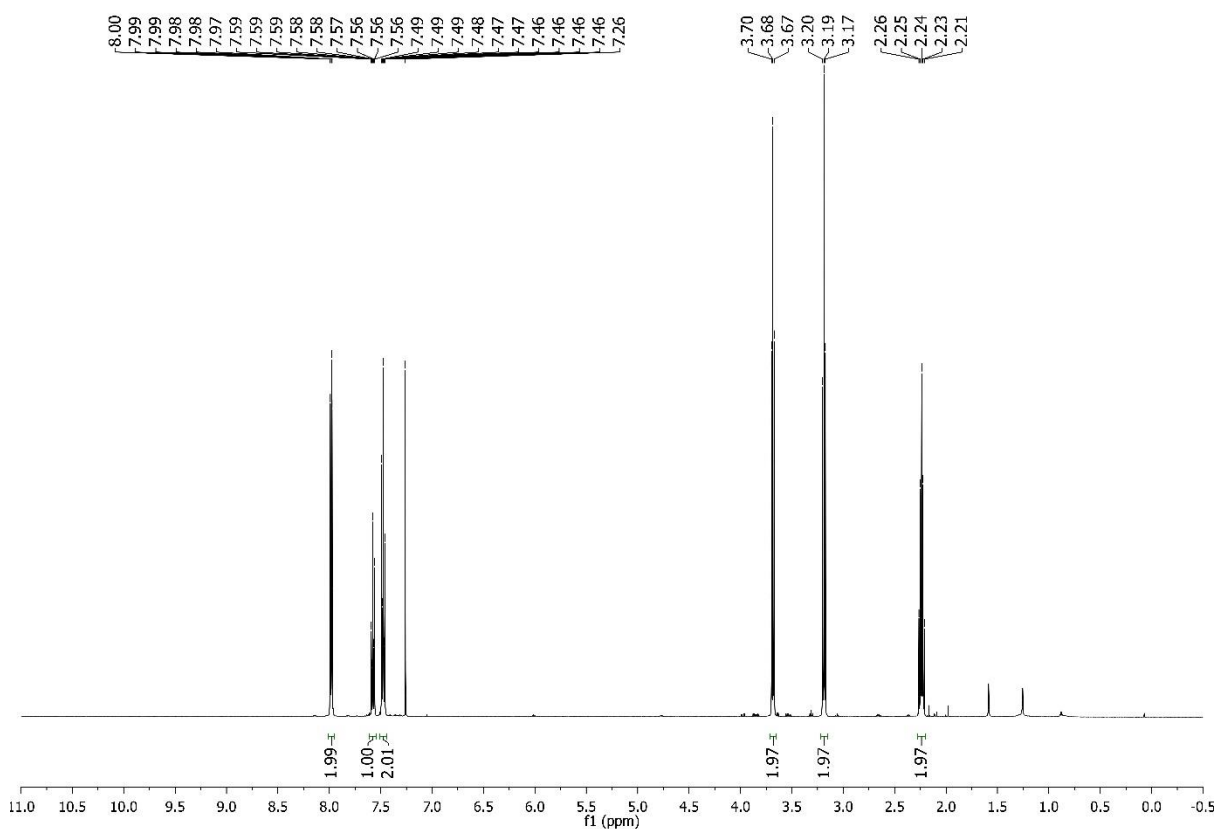
### 4-Chloro-1-phenylbutan-1-one (2)

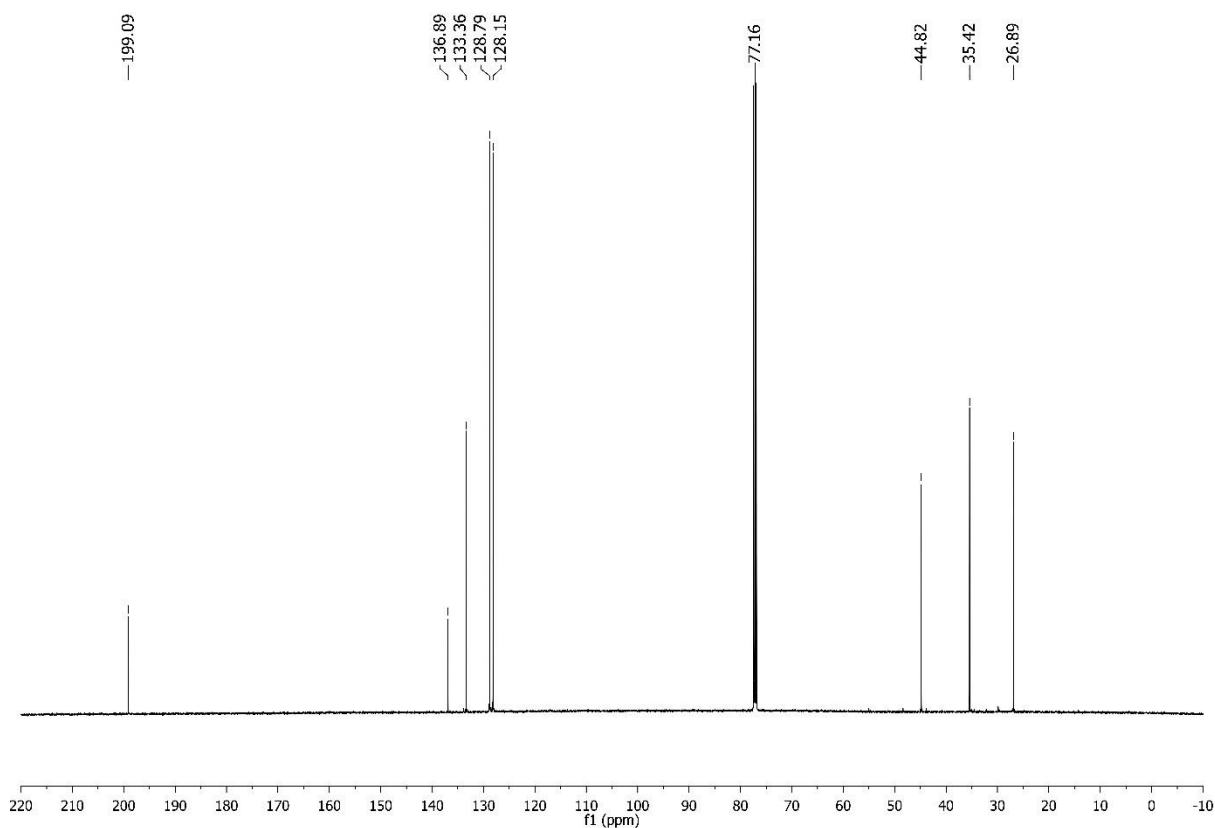


Prepared following General Procedure G using **1** (44 mg). The crude residue was purified by flash column chromatography (5% EtOAc/Petrol, silica gel) to afford **2** (43 mg, 78%) as a colourless oil.

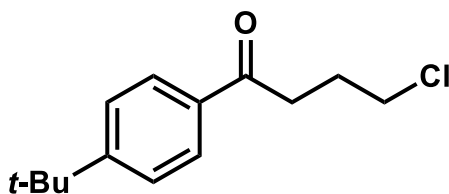
$R_f$  = 0.30 (5% EtOAc/Petrol);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.01 – 7.95 (m, 2H), 7.60 – 7.55 (m, 1H), 7.50 – 7.45 (m, 2H), 3.68 (t,  $J$  = 6.0 Hz, 2H), 3.19 (t,  $J$  = 7.0 Hz, 2H), 2.27 – 2.20 (m, 2H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 199.1, 136.9, 133.4, 128.8, 128.2, 44.8, 35.4, 26.9.

These data are consistent with those previously reported in the literature.<sup>[15]</sup>





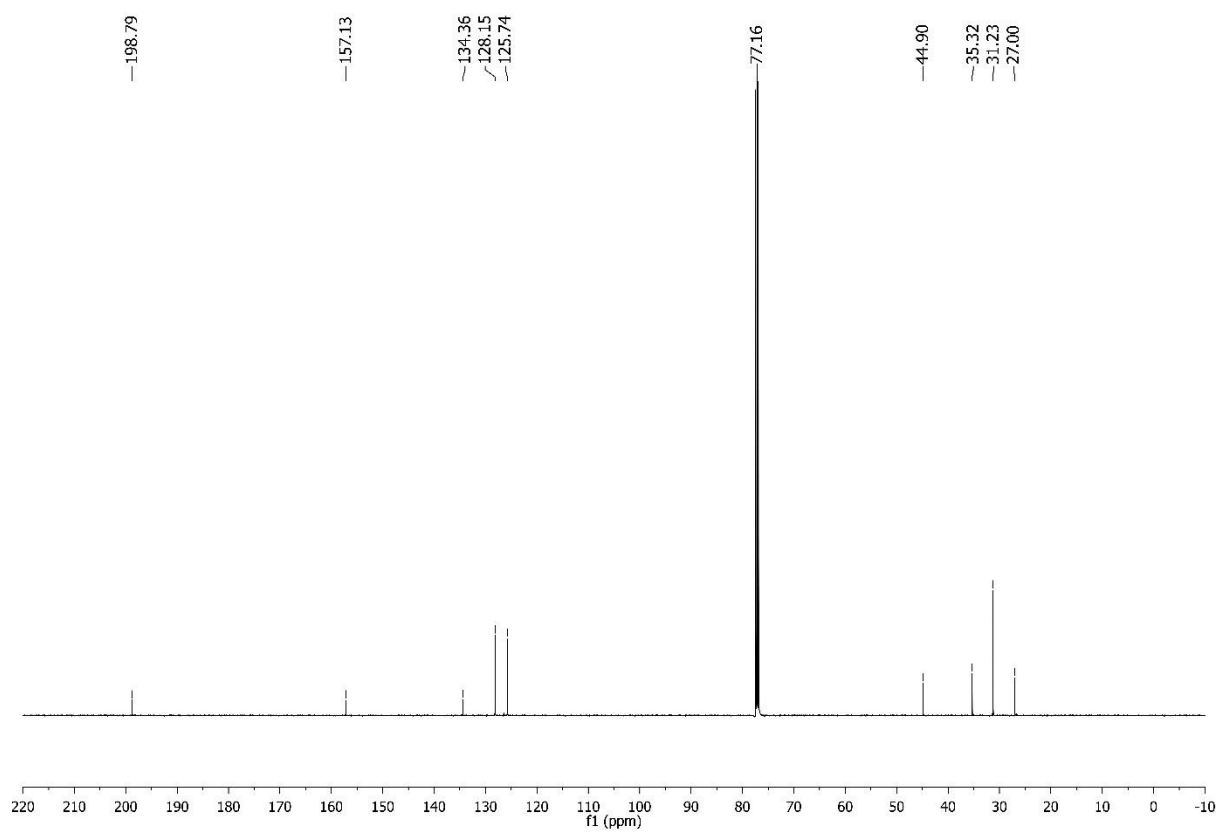
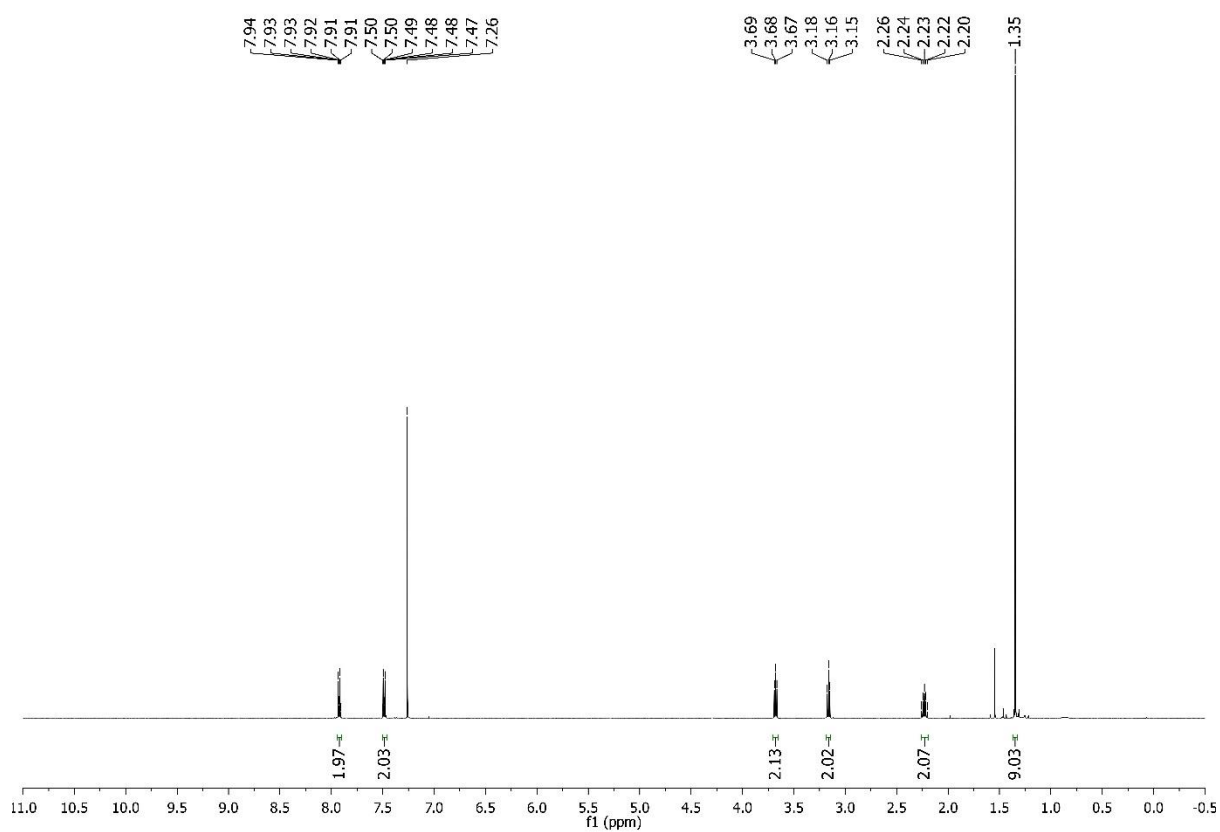
**1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-one (3)**



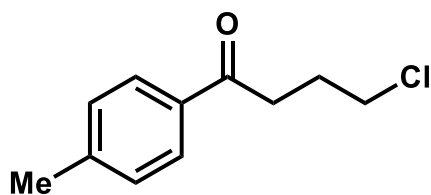
Prepared following General Procedure H using **S1** (61 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **3** (57 mg, 80%) as a colourless oil.

**R<sub>f</sub>** = 0.87 (15% EtOAc/Petrol); **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ = 7.94 – 7.90 (m, 2H), 7.50 – 7.46 (m, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.26 – 2.20 (m, 1H), 1.35 (s, 9H).; **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ = 198.8, 157.1, 134.4, 128.2, 125.7, 44.9, 35.3, 35.3, 31.1, 26.8.

These data are consistent with those previously reported in the literature.<sup>[16]</sup>



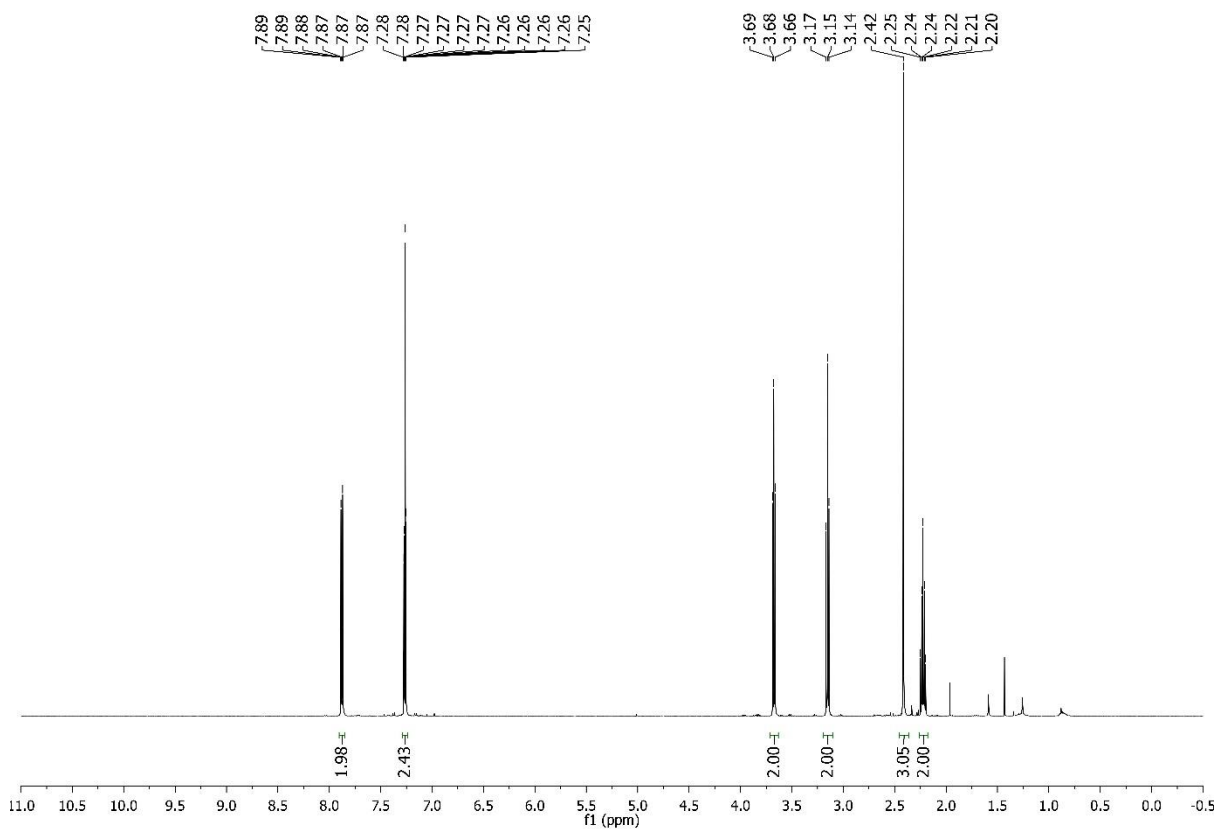
#### 4-Chloro-1-(*p*-tolyl)butan-1-one (**4**)

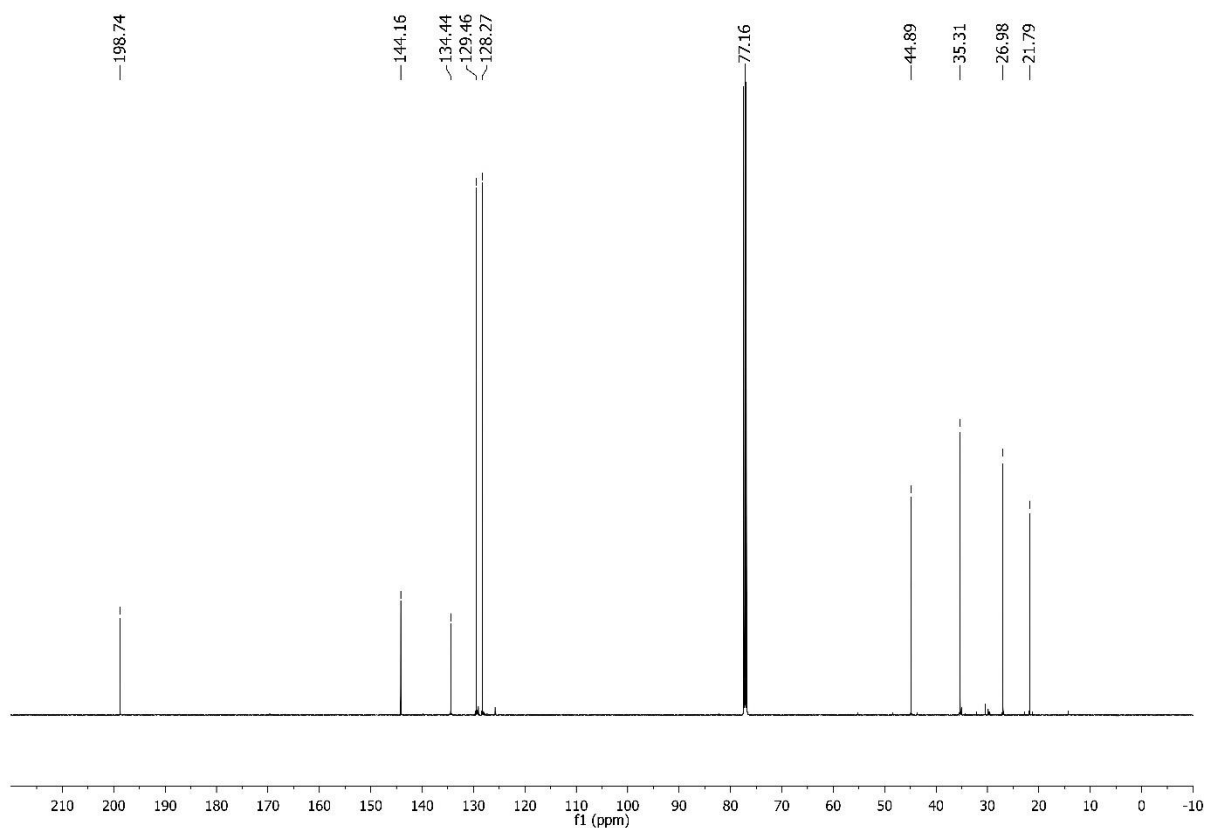


Prepared following General Procedure H using **S2** (49 mg). The crude residue was purified by flash column chromatography (6% Et<sub>2</sub>O/Pentane, silica gel) to afford **4** (45 mg, 76%) as a white solid.

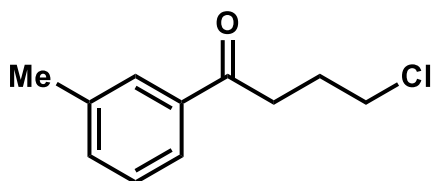
$R_f$  = 0.75 (15% EtOAc/Petrol); **M.p.**: 28-31 °C;  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.90 – 7.85 (m, 2H), 7.29 – 7.24 (m, 2H), 3.68 (t,  $J$  = 6.5 Hz, 2H), 3.15 (t,  $J$  = 7.0 Hz, 2H), 2.42 (s, 3H), 2.25 – 2.19 (m, 2H);  $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 198.7, 144.2, 134.4, 129.5, 128.3, 44.9, 35.3, 27.0, 21.8.

These data are consistent with those previously reported in the literature.<sup>[17]</sup>



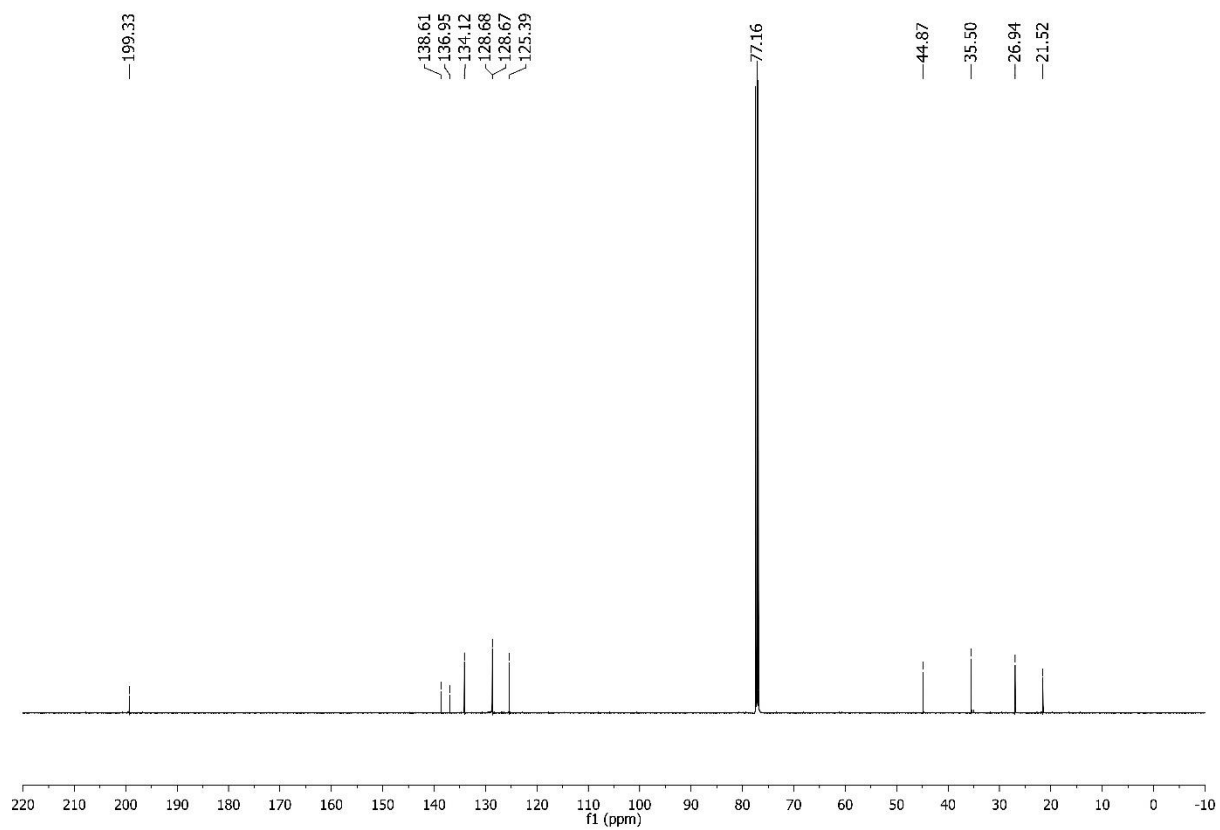
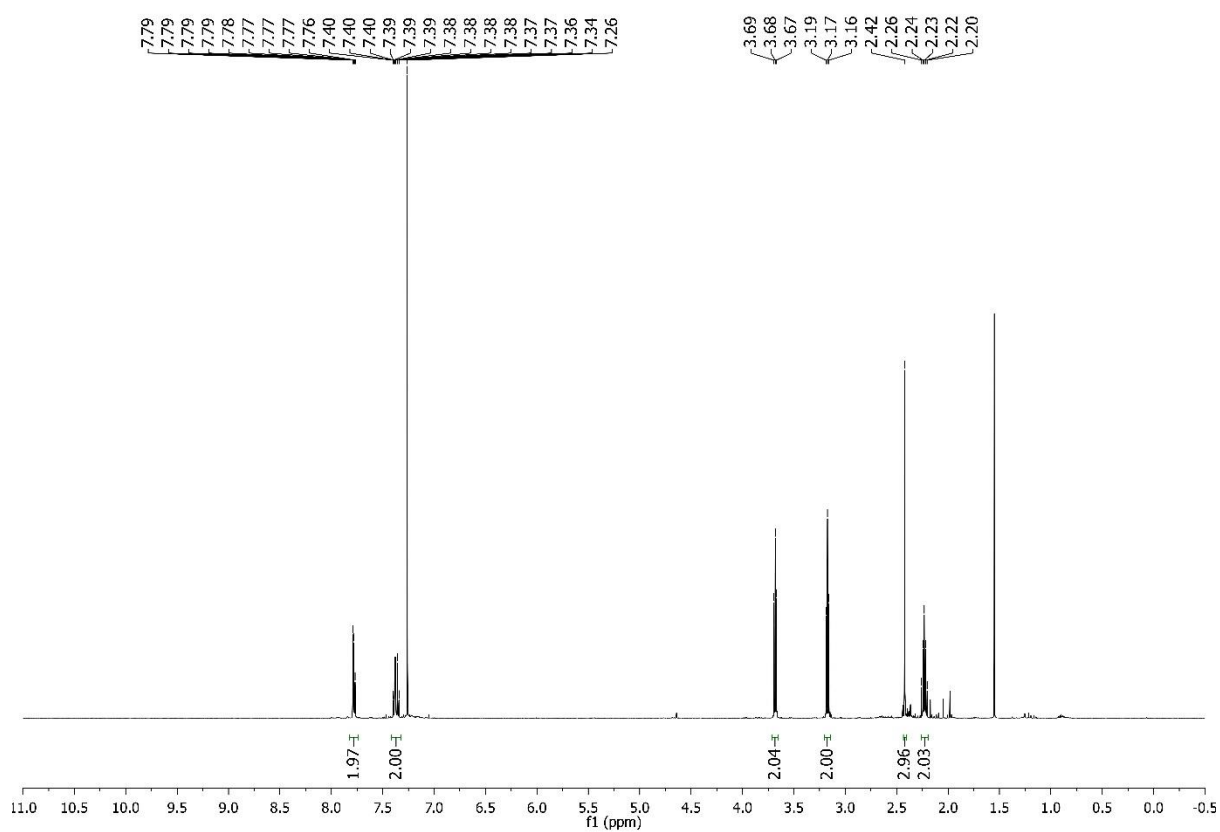


**4-chloro-1-(*m*-tolyl)butan-1-one (5)**

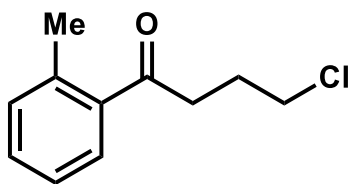


Prepared following General Procedure G using **S3** (48 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **5** (26 mg, 44%) as a colourless oil.

**R<sub>f</sub>** = 0.78 (15% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 2358, 1681, 1558, 1539, 1506, 1460, 738, 692; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 7.80 – 7.75 (m, 2H), 7.41 – 7.33 (m, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.17 (t, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 2.26 – 2.20 (m, 2H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 199.1, 138.4, 136.7, 133.9, 128.5, 128.5, 125.2, 44.7, 35.3, 26.7, 21.3; **HRMS** (EI<sup>+</sup>) [C<sub>11</sub>H<sub>14</sub>ClO] requires [M+H] 197.0733, found 197.0727.

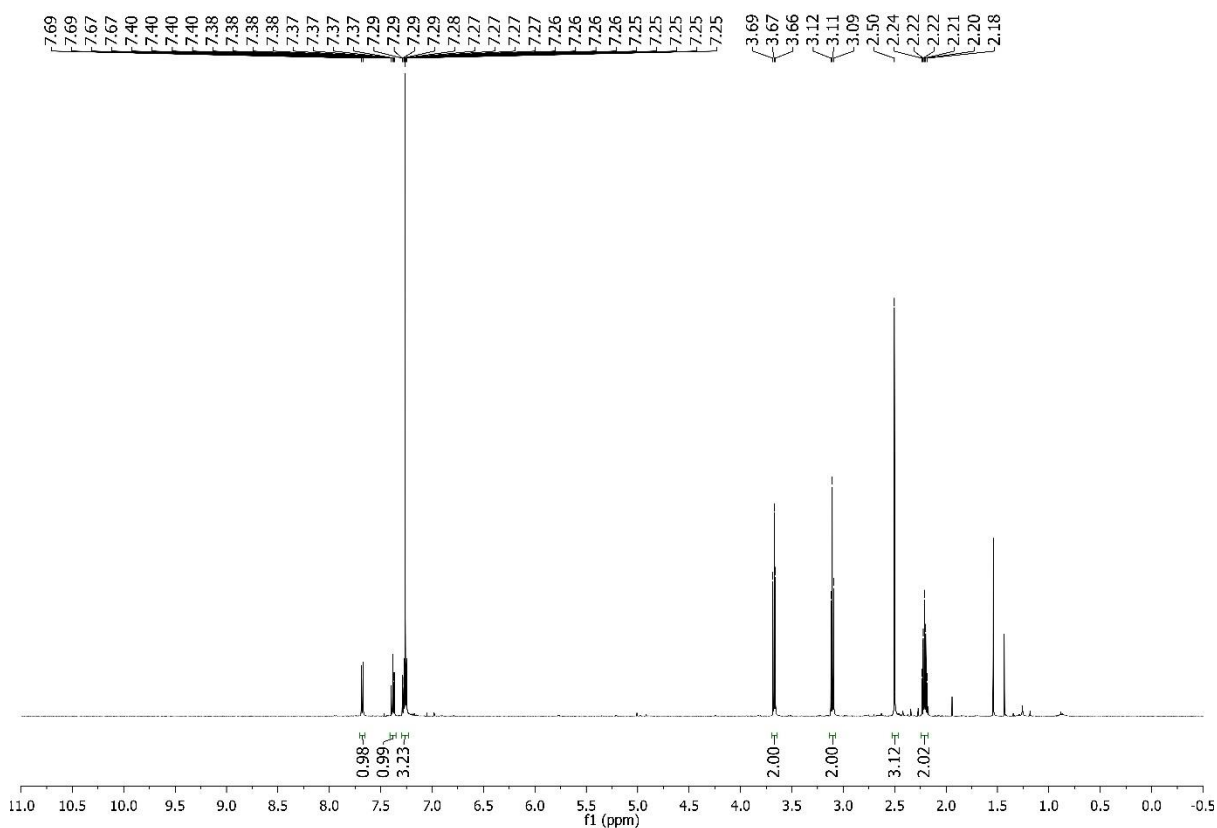


#### 4-Chloro-1-(*o*-tolyl)butan-1-one (**6**)

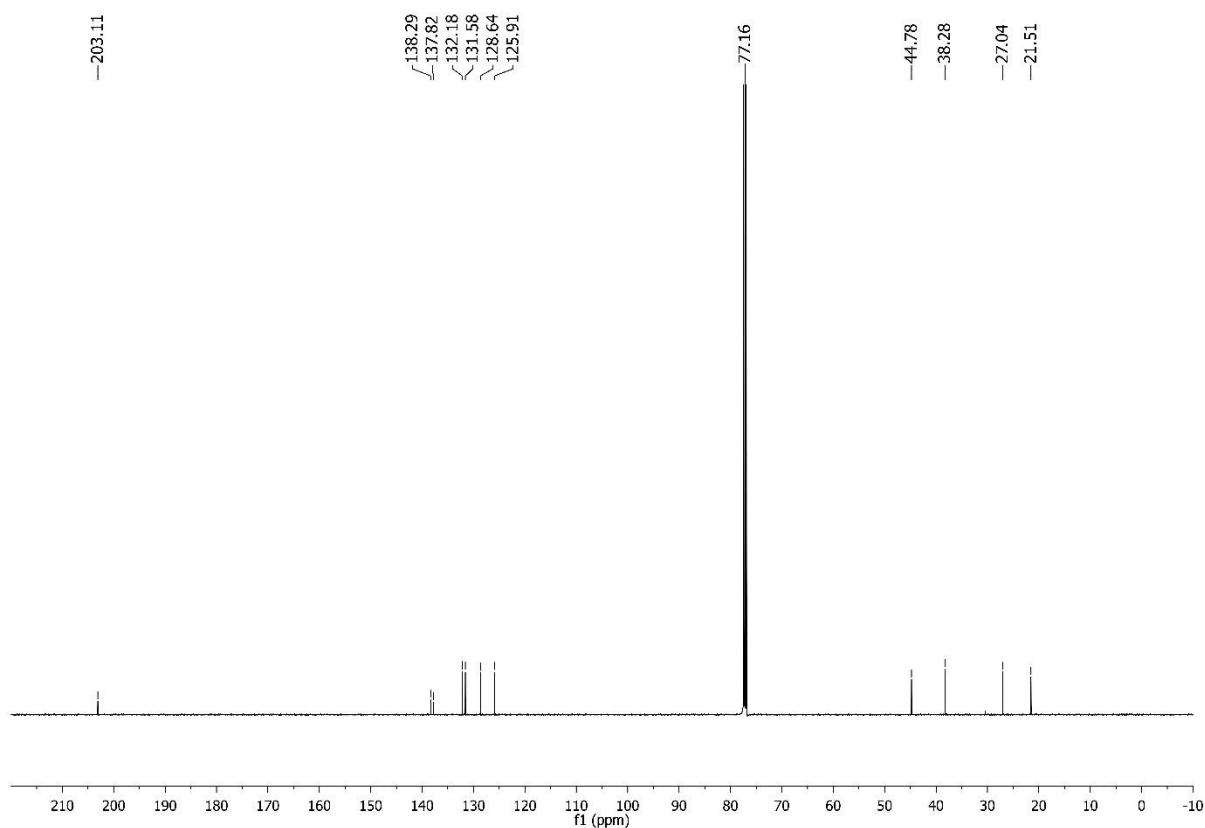


Prepared following General Procedure H using **S4** (49 mg). The crude residue was purified by flash column chromatography (0→6% Et<sub>2</sub>O/Hexanes, silica gel) to afford **6** (26 mg, 43%) as a light red oil.

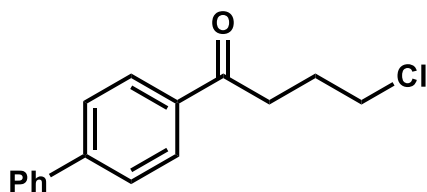
$R_f$  = 0.40 (10% EtOAc/Hexanes); **FTIR** ( $\nu_{\max}$  cm<sup>-1</sup>, thin film) 2963, 1682, 1570, 1449, 1300, 1221, 972, 754; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.71 – 7.65 (m, 1H), 7.42 – 7.35 (m, 1H), 7.31 – 7.22 (m, 2H), 3.67 (t,  $J$  = 6.5 Hz, 2H), 3.11 (t,  $J$  = 7.0 Hz, 2H), 2.50 (s, 3H), 2.24 – 2.18 (m, 2H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 203.1, 138.3, 137.8, 132.2, 131.6, 128.6, 125.9, 44.8, 38.3, 27.1, 21.5; **HRMS** (EI<sup>+</sup>) [C<sub>11</sub>H<sub>13</sub>ClO] requires [M] 196.0655, found 196.0647.







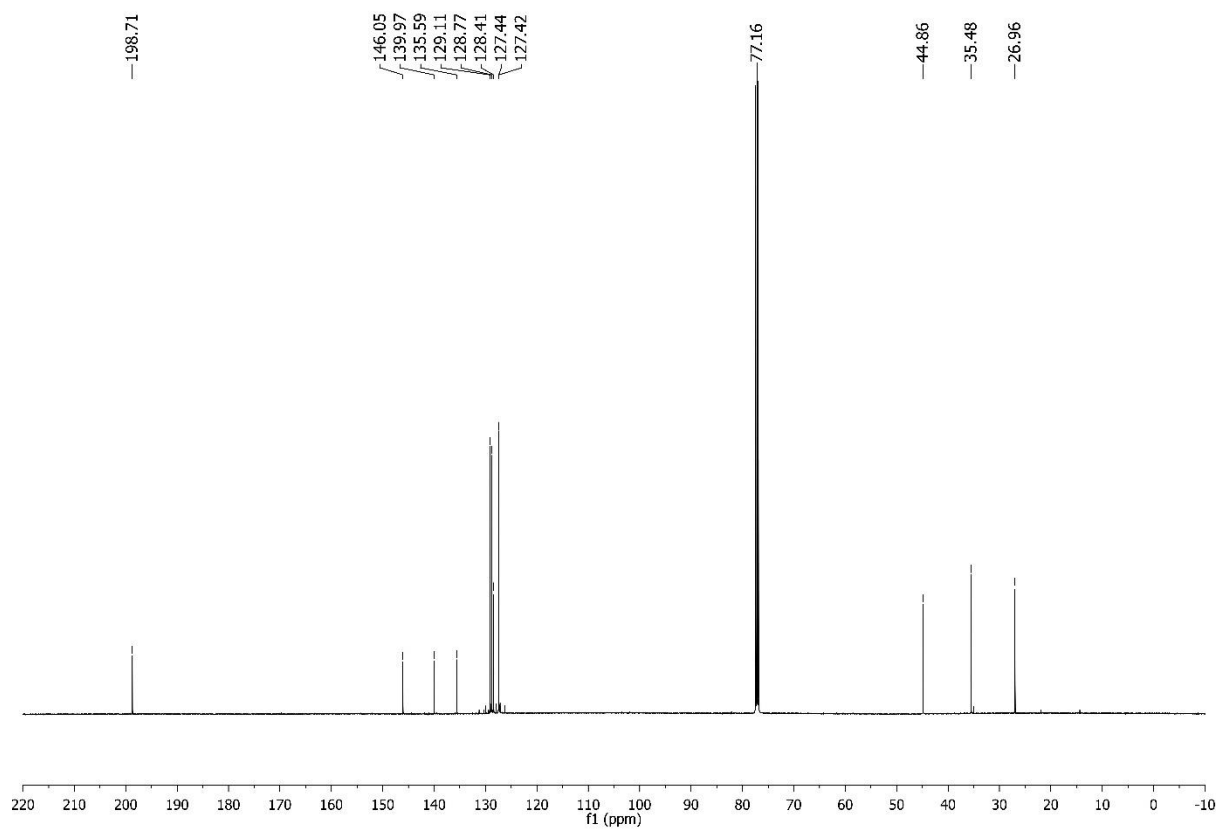
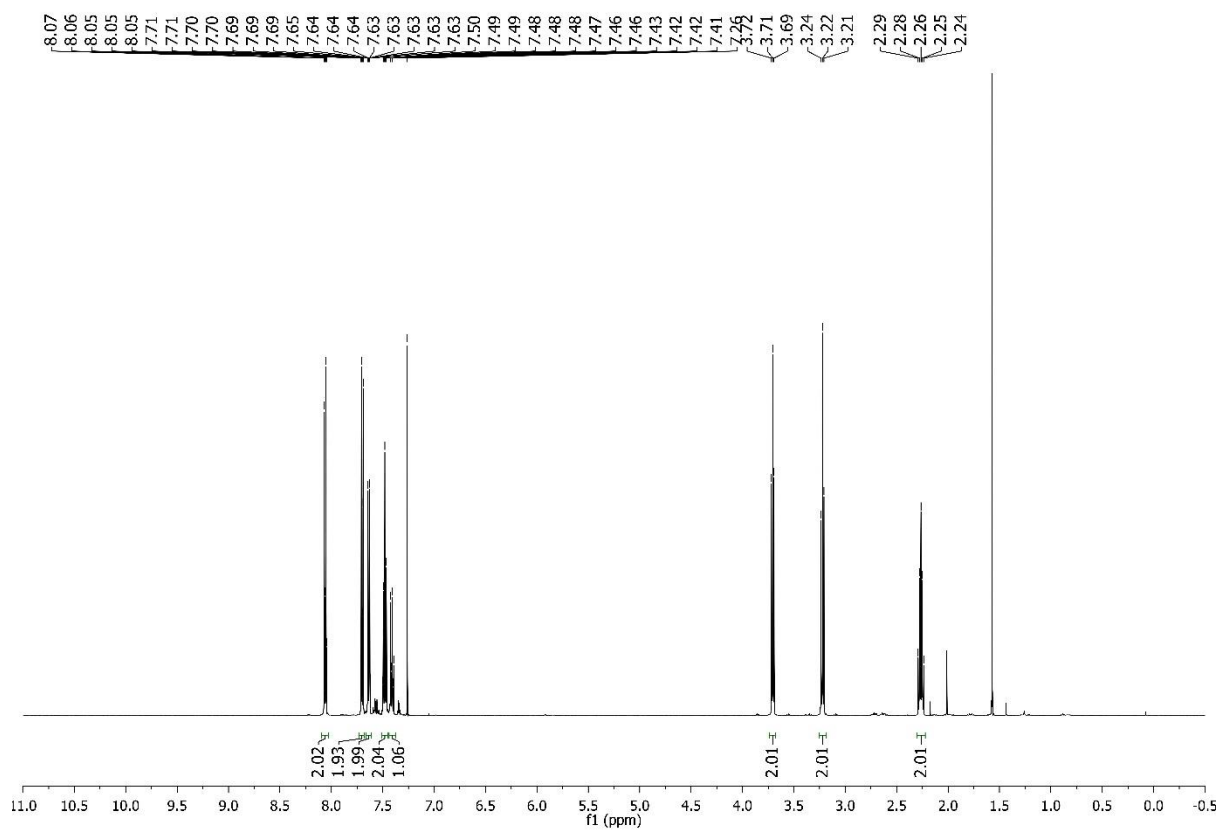
**1-([1,1'-Biphenyl]-4-yl)-4-chlorobutan-1-one (7)**



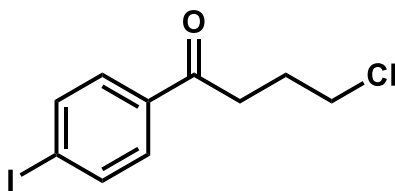
Prepared following General Procedure H using **S5** (67 mg). The crude residue was purified by flash column chromatography (8% EtOAc/Petrol, silica gel) to afford **7** (32 mg, 41%) as a white solid.

$R_f$  = 0.82 (15% EtOAc/Petrol); **M.p.:** 120-122 °C (lit.<sup>[18]</sup> 119-121 °C);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.09 – 8.03 (m, 2H), 7.74 – 7.67 (m, 2H), 7.66 – 7.60 (m, 2H), 7.51 – 7.45 (m, 2H), 7.43 – 7.39 (m, 1H), 3.70 (t,  $J$  = 6.0 Hz, 2H), 3.22 (t,  $J$  = 7.0 Hz, 2H), 2.31 – 2.22 (m, 2H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 198.7, 146.0, 139.9, 135.6, 129.1, 128.8, 128.4, 127.4, 127.4, 44.9, 35.5, 26.9.

These data are consistent with those previously reported in the literature.<sup>[15]</sup>

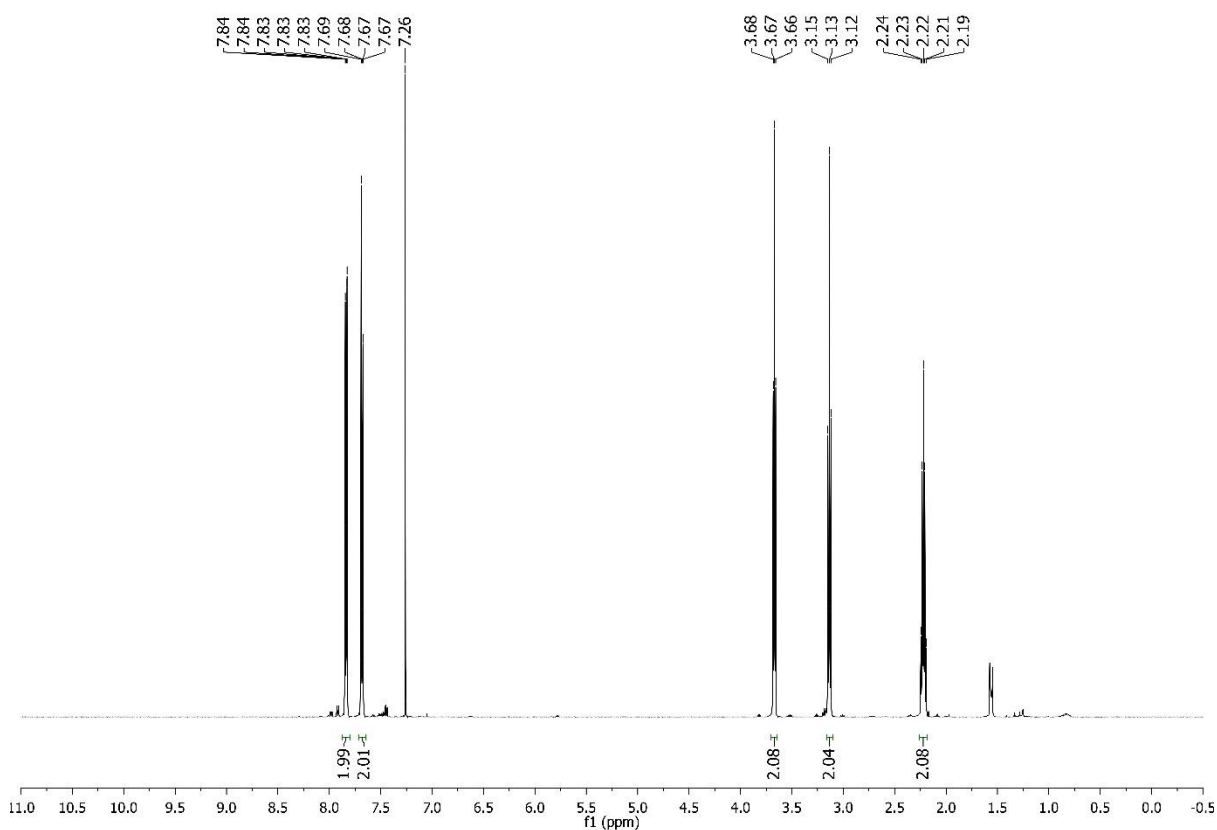


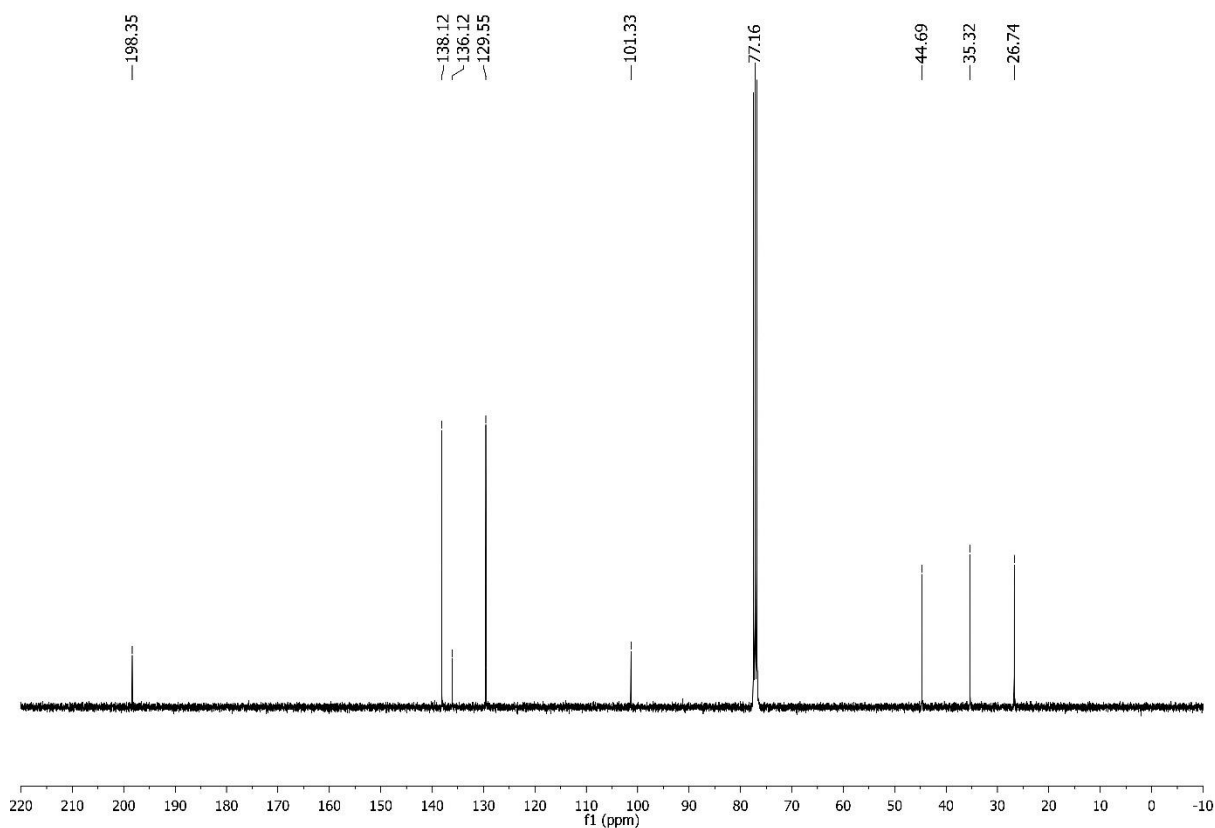
#### 4-Chloro-1-(4-iodophenyl)butan-1-one (**8**)



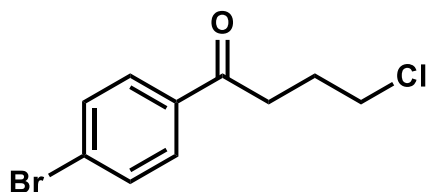
Prepared following General Procedure G using **S6** (82 mg) and tetra-*n*-butylammonium acetate (181 mg, 0.60 mmol) instead of LiClO<sub>4</sub>. The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Hexane, silica gel) to afford **8** (58 mg, 62%) as an amorphous white solid.

**R<sub>f</sub>** = 0.69 (15% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 2926, 2899, 1685, 1577, 1560, 1481, 1452, 1388, 1354, 1300, 1215, 1178, 1149, 1056, 1001, 983; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.88 – 7.80 (m, 2H), 7.72 – 7.63 (m, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.13 (t, *J* = 7.0 Hz, 2H), 2.27 – 2.18 (m, 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  198.4, 138.1, 136.1, 129.5, 101.3, 44.7, 35.3, 26.7; **HRMS** (EI<sup>+</sup>) [C<sub>10</sub>H<sub>10</sub>ClOI] requires [M+H] 308.9543, found 308.9538.





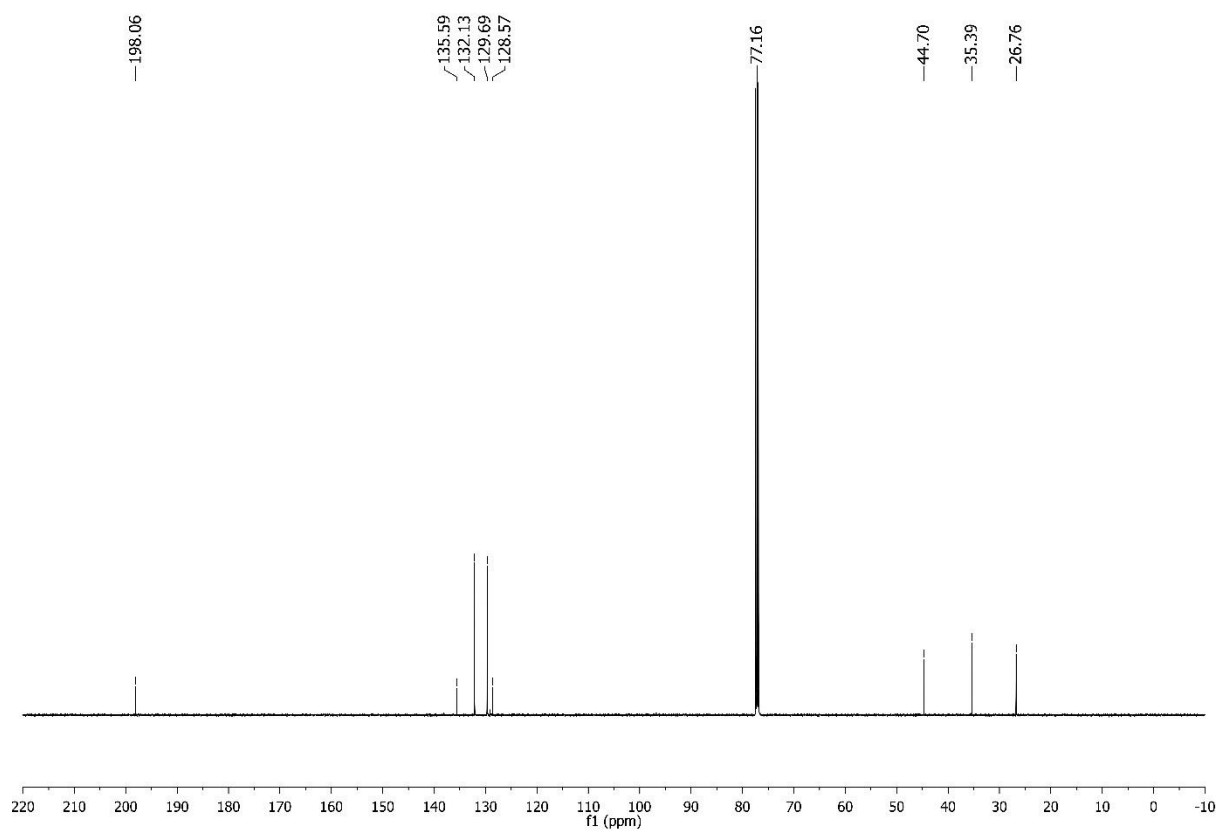
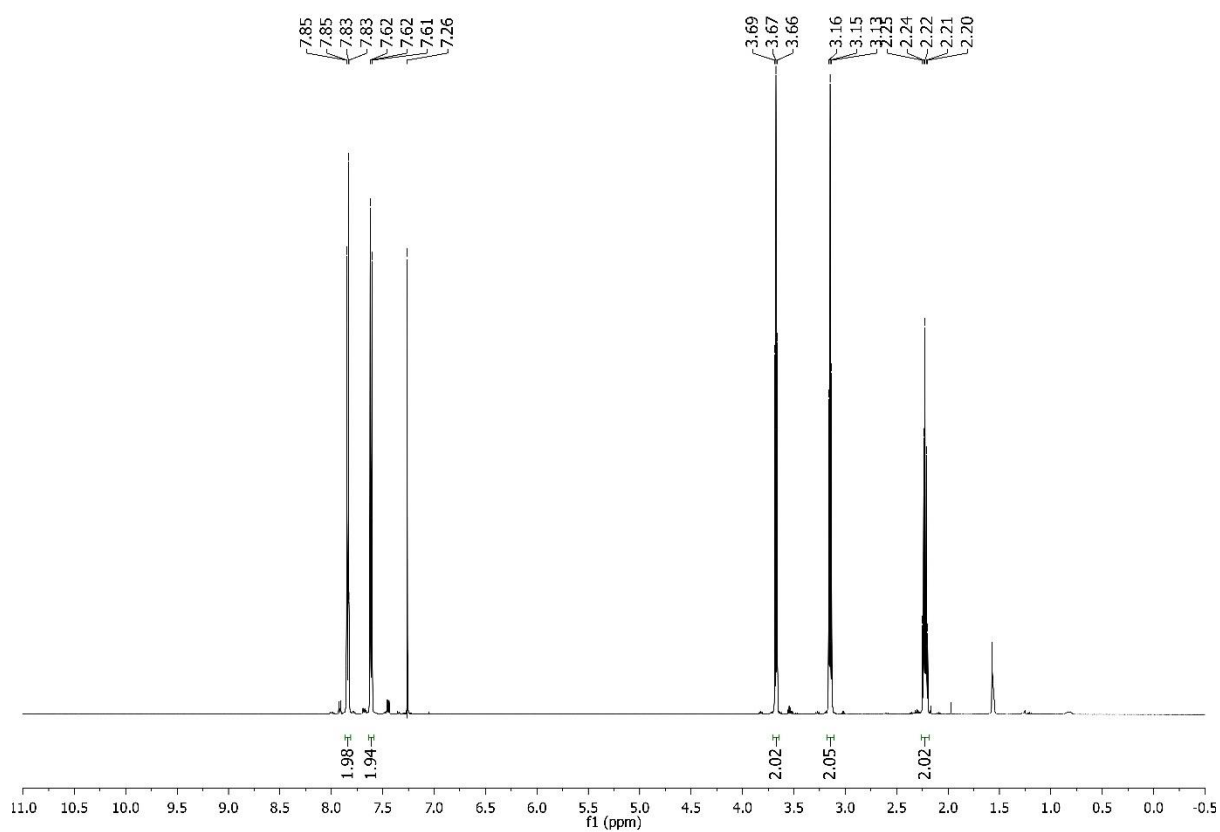
**1-(4-Bromophenyl)-4-chlorobutan-1-one (9)**



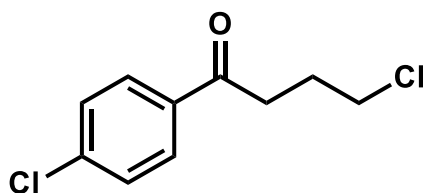
Prepared following General Procedure G using **S7** (68 mg). The crude residue was purified by flash column chromatography (5% EtOAc/Petrol, silica gel) to afford **9** (57 mg, 73%) as a white solid.

**R<sub>f</sub>** = 0.35 (5% EtOAc/Petrol); **M.p.**: 37-39 °C (lit.<sup>[15]</sup> 33-35 °C) **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 7.87 – 7.82 (m, 2H), 7.64 – 7.59 (m, 2H), 3.68 (t, *J* = 6.0 Hz, 1H), 3.15 (t, *J* = 7.0 Hz, 1H), 2.26 – 2.19 (m, 1H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 198.1, 135.6, 132.1, 129.7, 128.6, 44.7, 35.4, 26.8.

These data are in agreement with those previously reported in the literature.<sup>[15]</sup>



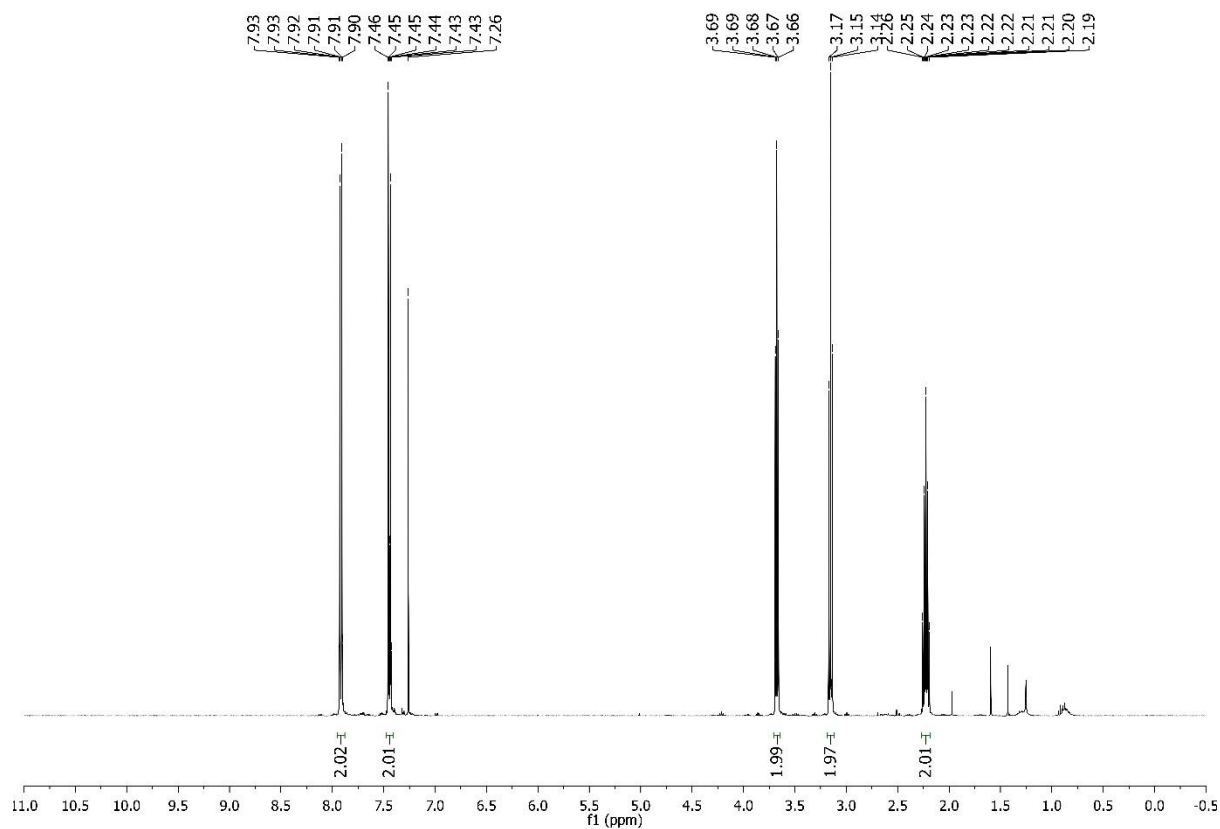
#### 4-Chloro-1-(4-chlorophenyl)butan-1-one (10)

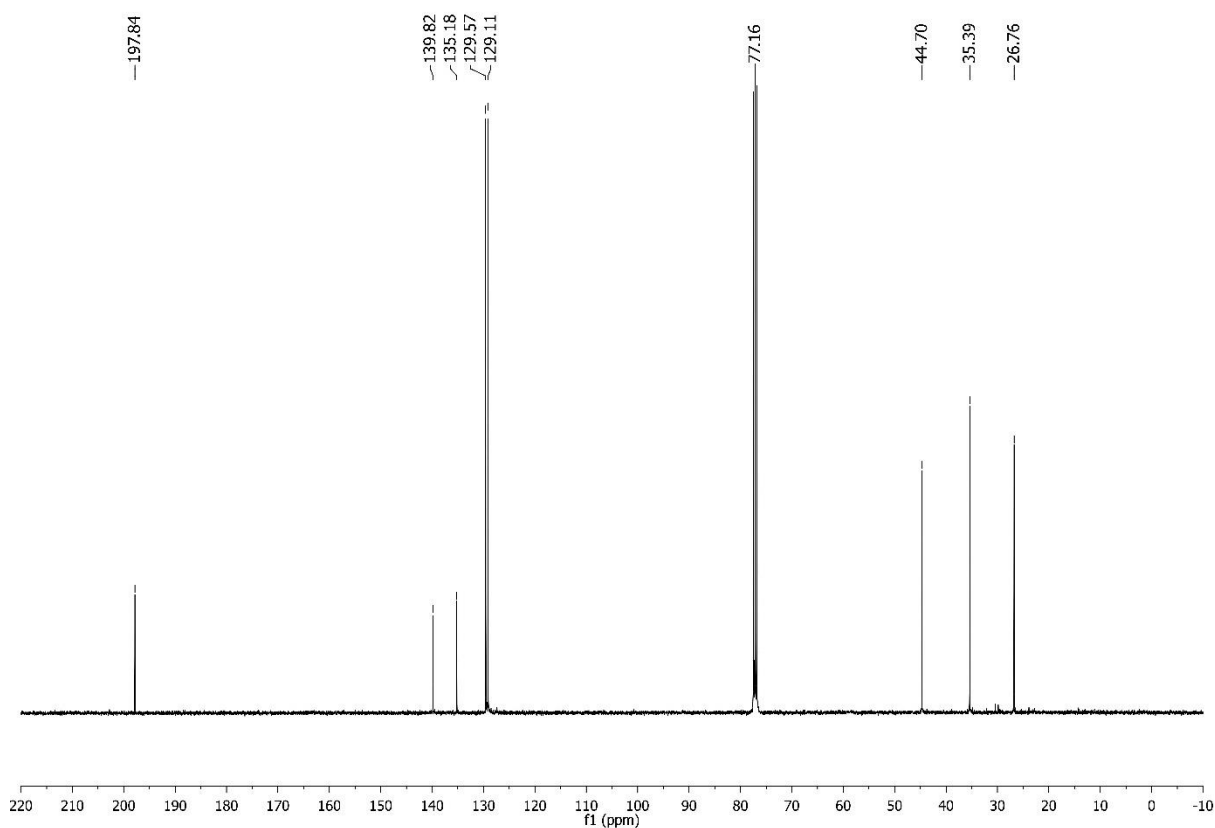


Prepared following General Procedure G using **S8** (55 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **10** (59 mg, 90%) as a colourless oil.

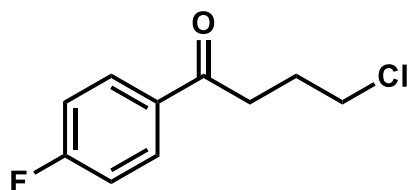
$R_f$  = 0.75 (15% EtOAc/Petrol); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.96 – 7.88 (m, 2H), 7.48 – 7.41 (m, 2H), 3.73 – 3.61 (m, 2H), 3.15 (t,  $J$  = 7.0 Hz, 2H), 2.27 – 2.17 (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 197.8, 139.8, 135.2, 129.6, 129.1, 44.7, 35.4, 26.8.

These data are in agreement with those previously reported in the literature.<sup>[15]</sup>





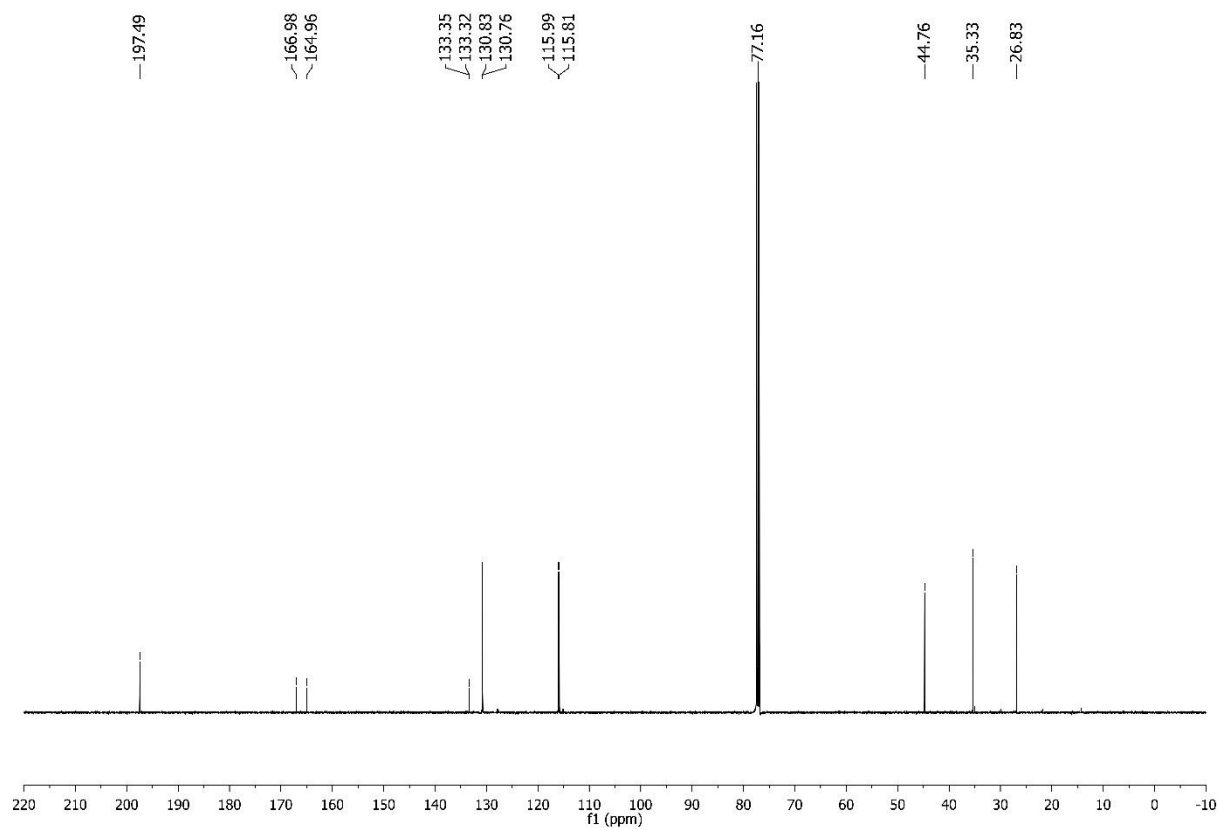
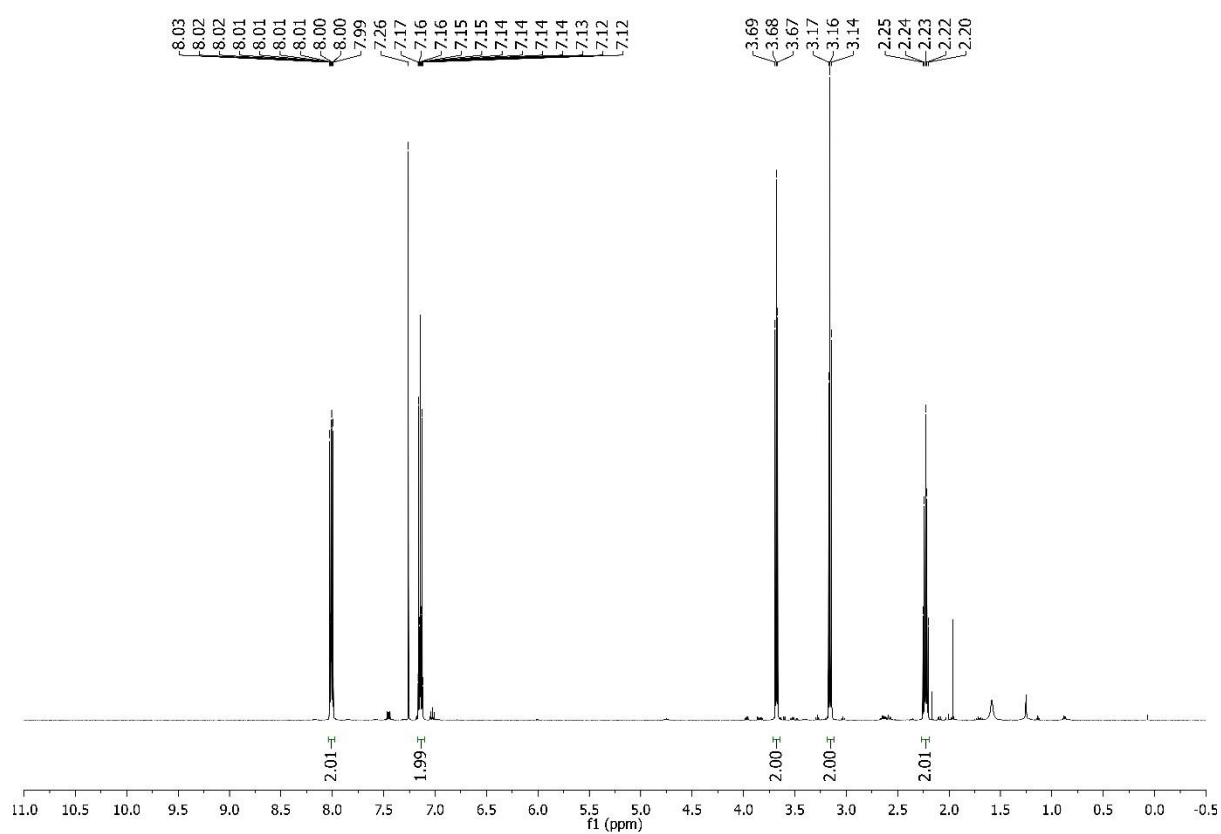
#### 4-Chloro-1-(4-fluorophenyl)butan-1-one (**11**)



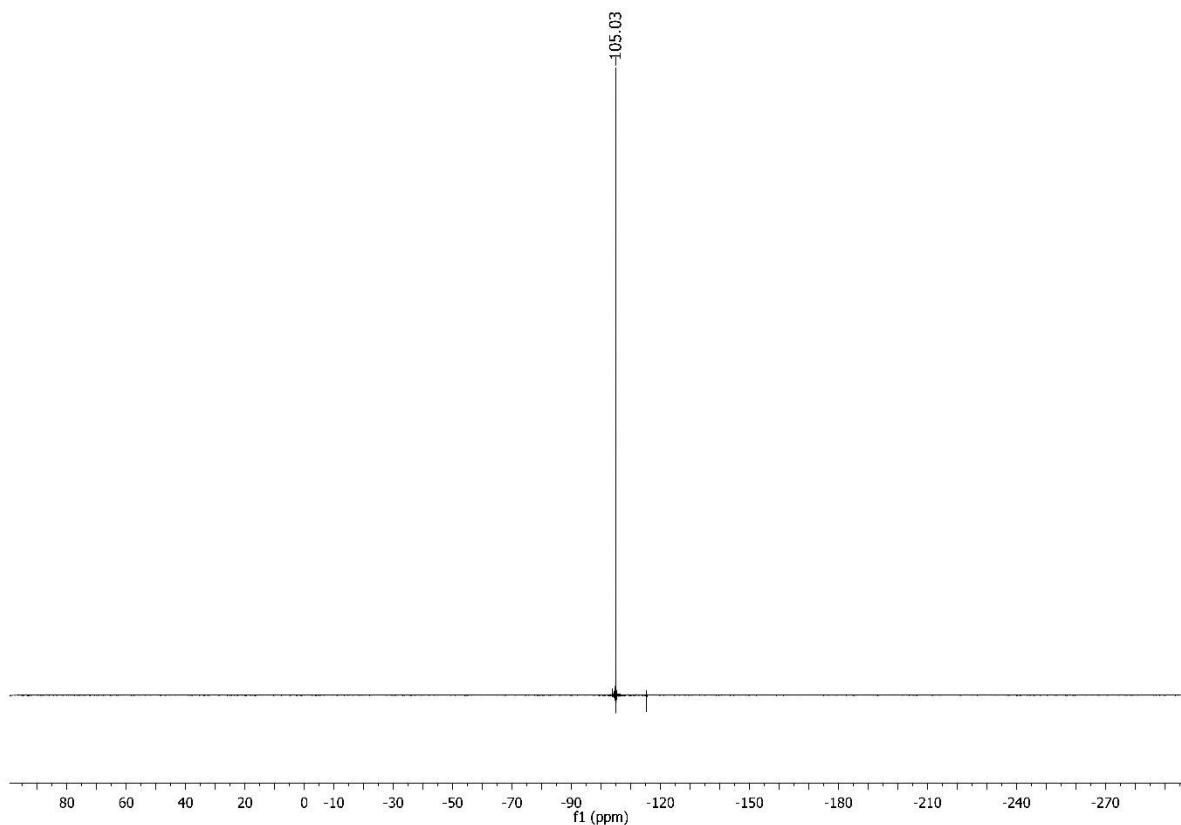
Prepared following General Procedure H using **S9** (50 mg). The crude residue was purified by flash column chromatography (5% EtOAc/Petrol, silica gel) to afford **11** (51 mg, 84%) as a colourless oil.

$R_f$  = 0.32 (5% EtOAc/Petrol);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.04 – 7.98 (m, 2H), 7.17 – 7.11 (m, 2H), 3.68 (t,  $J$  = 6.0 Hz, 2H), 3.16 (t,  $J$  = 7.0 Hz, 2H), 2.26 – 2.20 (m, 2H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 197.5, 166.0 (d,  $J$  = 255.0 Hz), 133.3 (d,  $J$  = 3.0 Hz), 130.80 (d,  $J$  = 9.5 Hz), 115.90 (d,  $J$  = 22.0 Hz), 44.8, 35.3, 26.8;  $^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$  = -105.00.

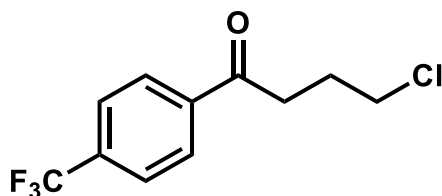
These data are in agreement with those previously reported in the literature.<sup>[15]</sup>







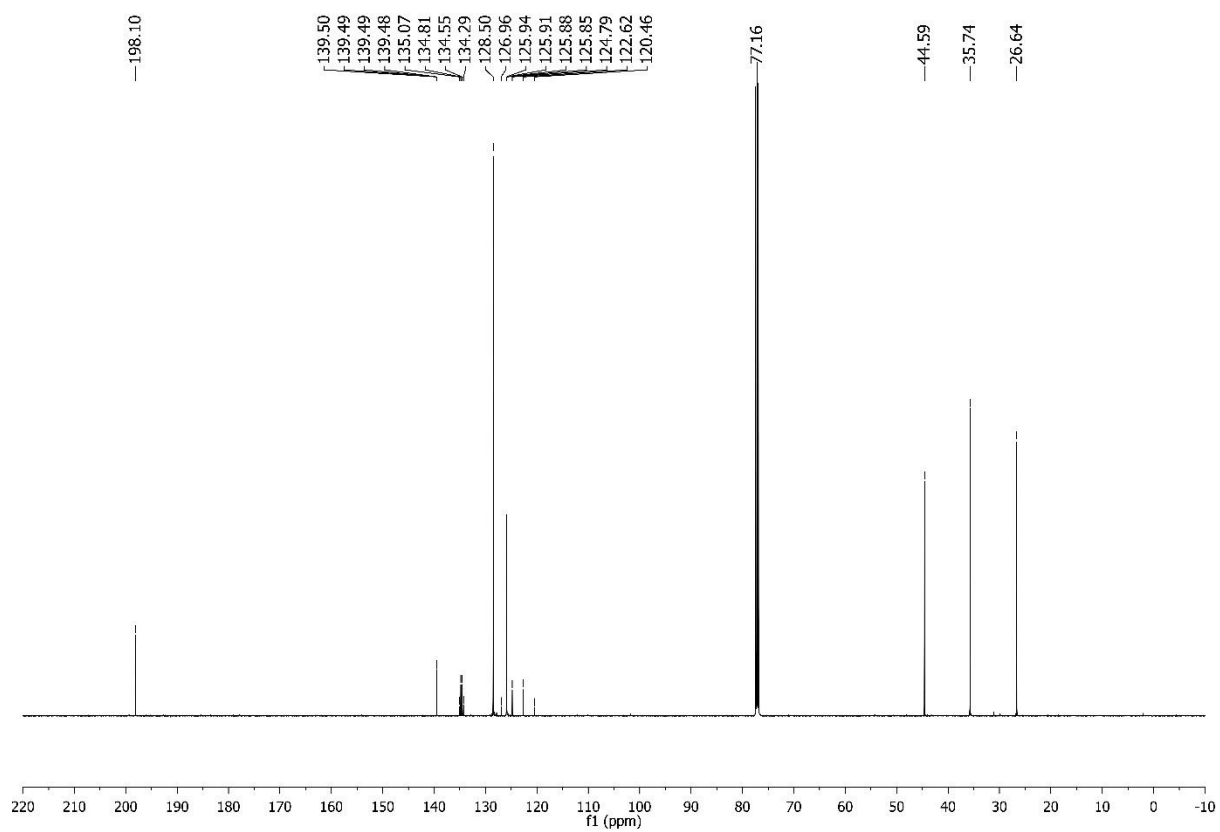
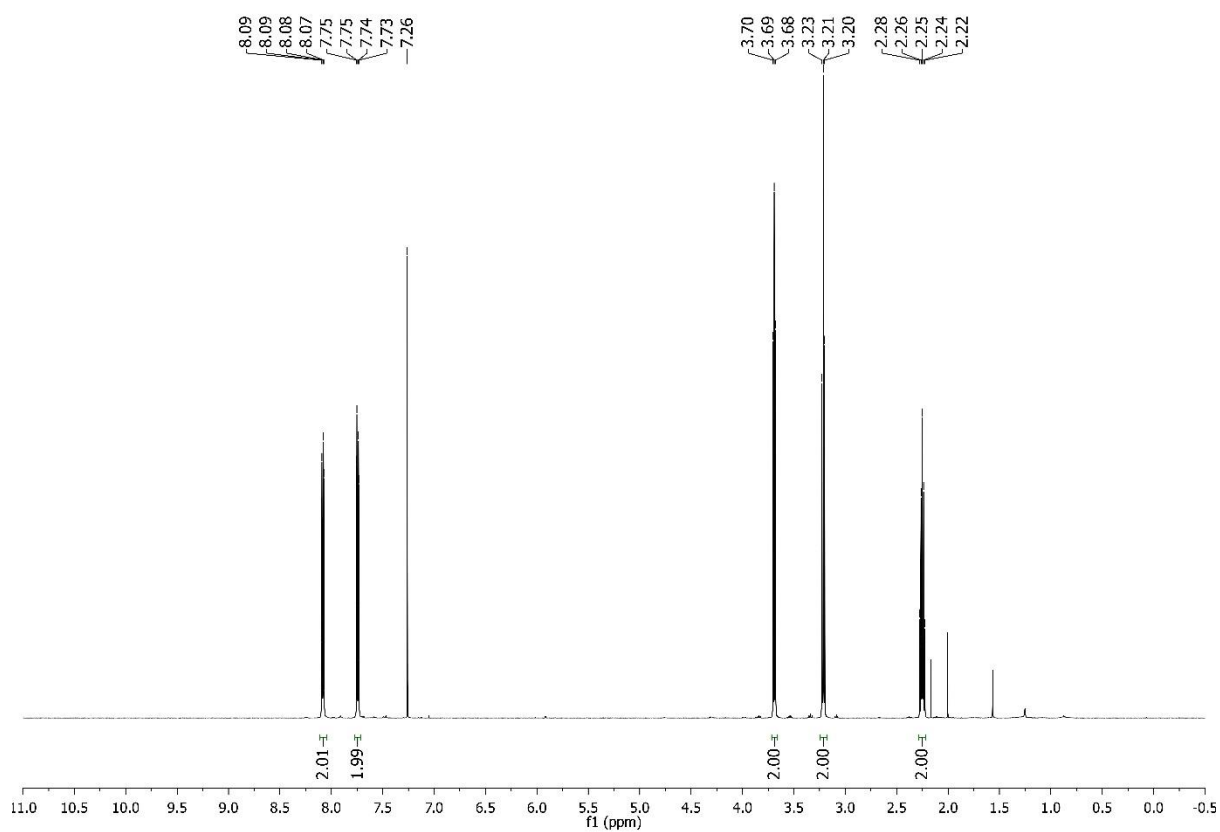
**4-Chloro-1-(4-(trifluoromethyl)phenyl)butan-1-one (12)**

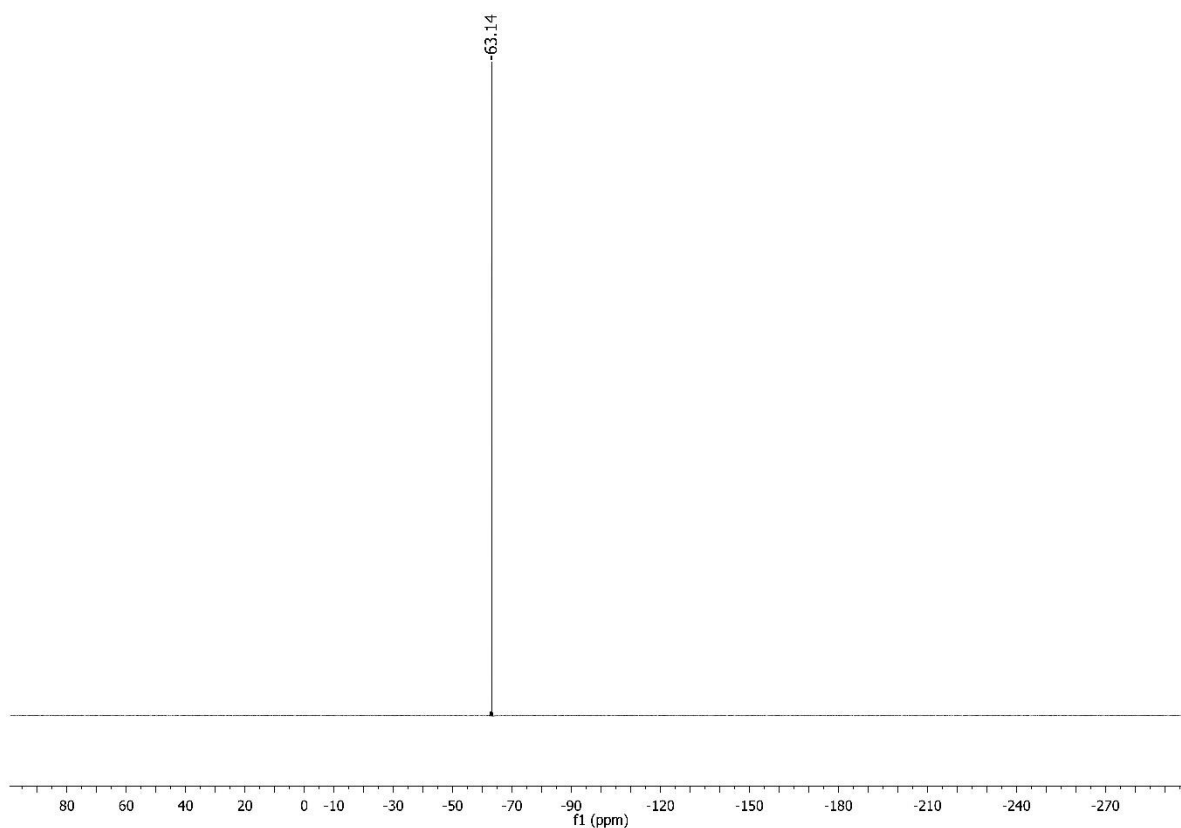


Prepared following General Procedure G using **S10** (65 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **12** (49 mg, 67%) as a colourless oil.

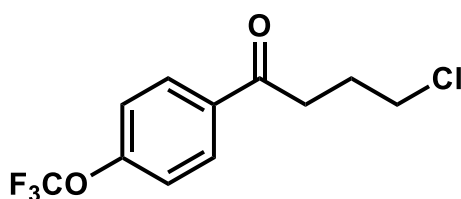
**R<sub>f</sub>** = 0.71 (15% EtOAc/Petrol); **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ = 8.09 – 8.07 (m, 2H), 7.77 – 7.71 (m, 2H), 3.69 (t, *J* = 6.0 Hz, 2H), 3.20 (t, *J* = 7.0 Hz, 2H), 2.28 – 2.22 (m, 2H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ = 198.1, 139.5 (q, *J* = 1.0 Hz), 134.7 (q, *J* = 32.5 Hz), 128.5, 125.9 (q, *J* = 3.5 Hz), 123.7 (q, *J* = 272.5 Hz), 44.4, 35.6, 26.5; **<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>)** δ = -63.1.

These data are in agreement with those previously reported in the literature.<sup>[15]</sup>





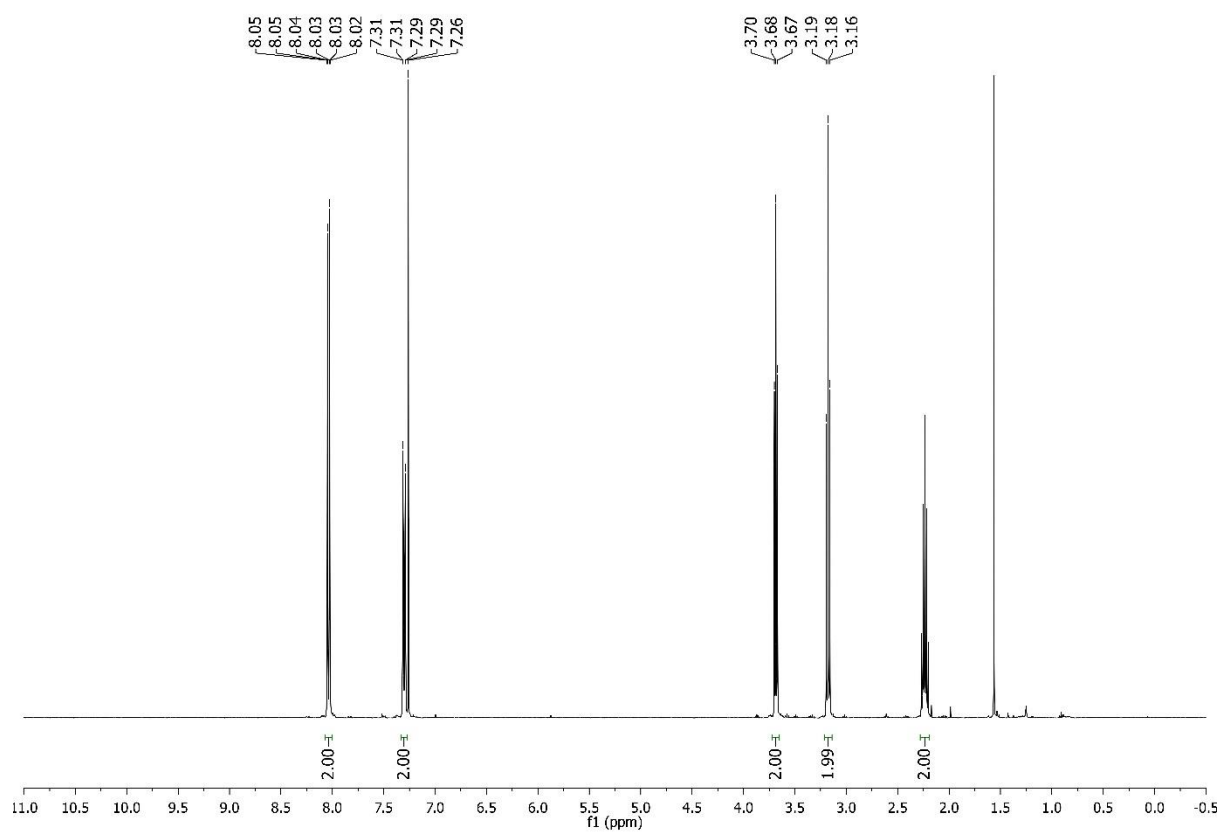
**4-Chloro-1-(4-(trifluoromethoxy)phenyl)butan-1-one (13)**

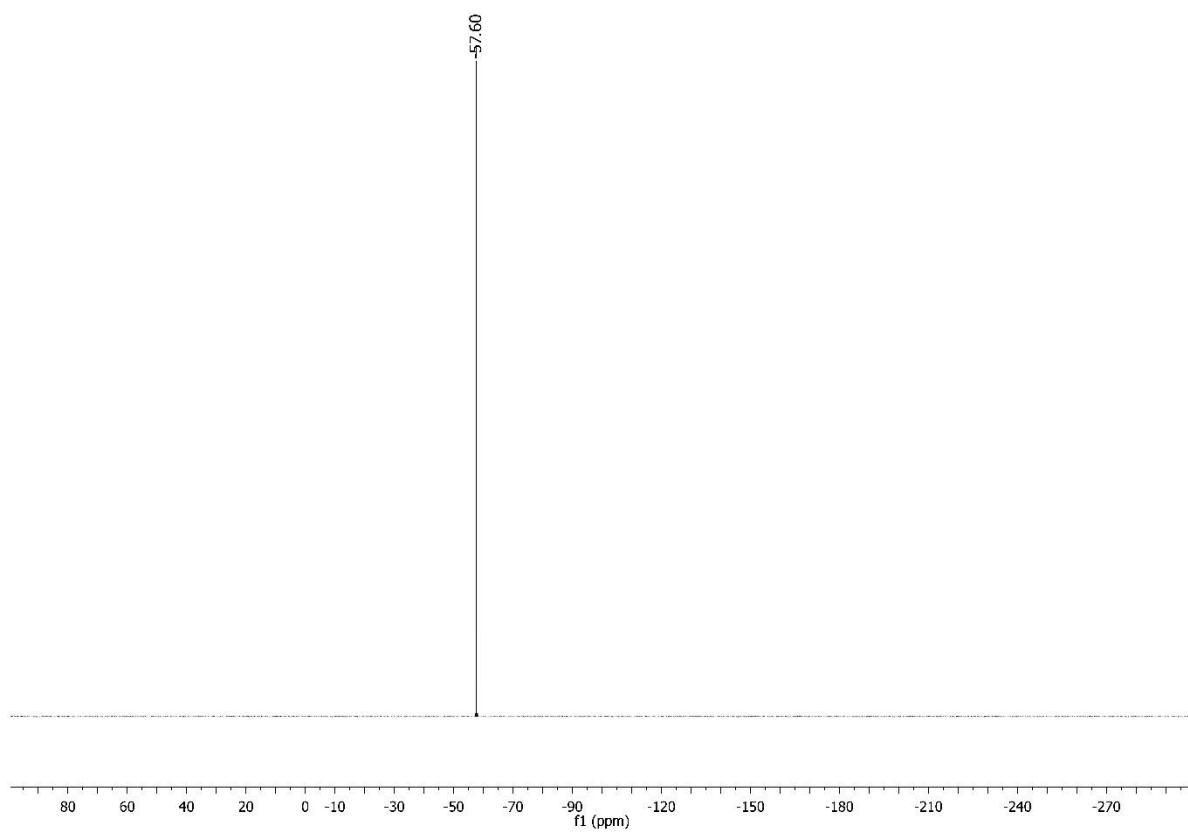
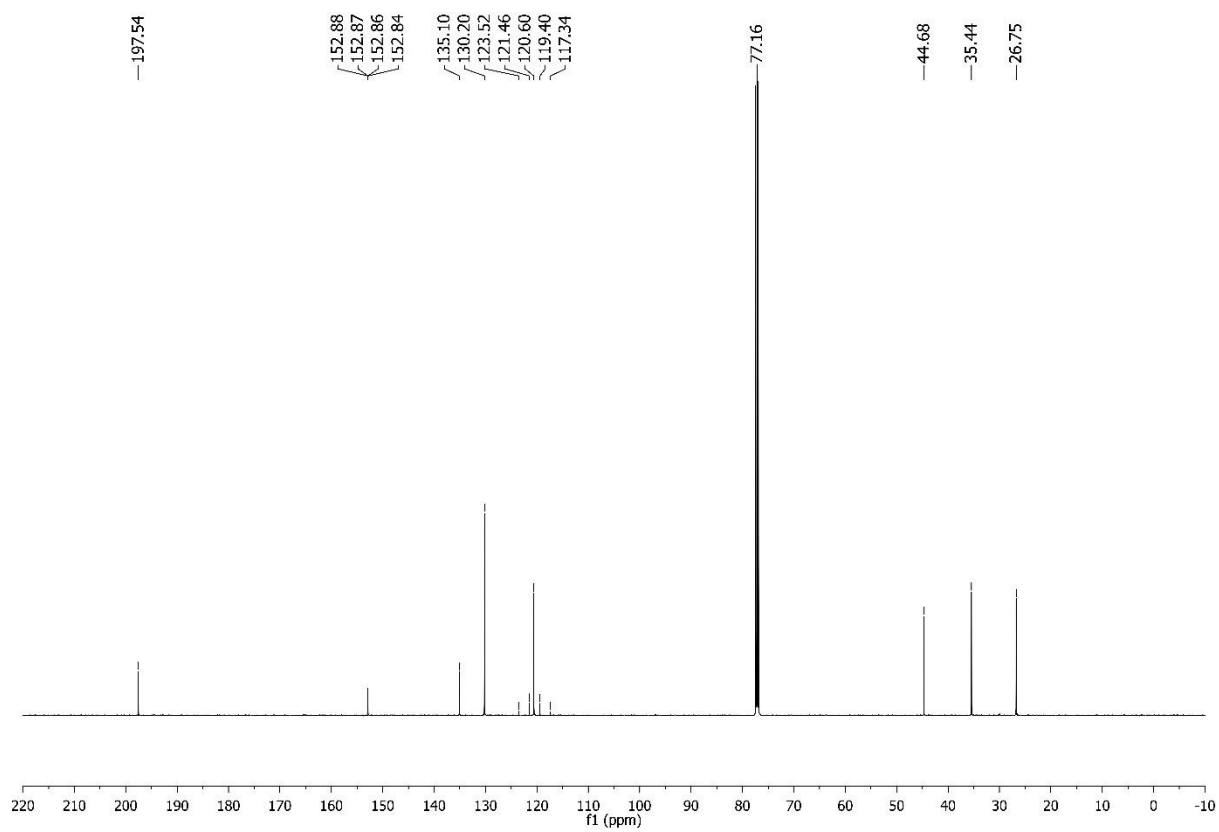


Prepared following General Procedure G using **S11** (70 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **13** (49 mg, 61%) as a colourless oil.

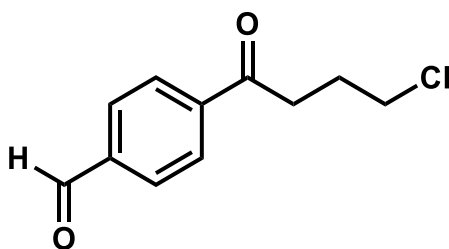
**R<sub>f</sub>** = 0.78 (15% EtOAc/Petrol); **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ = 8.07 – 8.00 (m, 2H), 7.33 – 7.27 (m, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 2.29 – 2.19 (m, 2H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ = 197.5, 152.9 (q, *J* = 1.5 Hz), 135.1, 130.2, 120.6, 120.4 (q, *J* = 259.0 Hz), 44.7, 35.4, 26.8; **<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)** δ -57.6.

These data are consistent with those previously reported in the literature.<sup>[18]</sup>



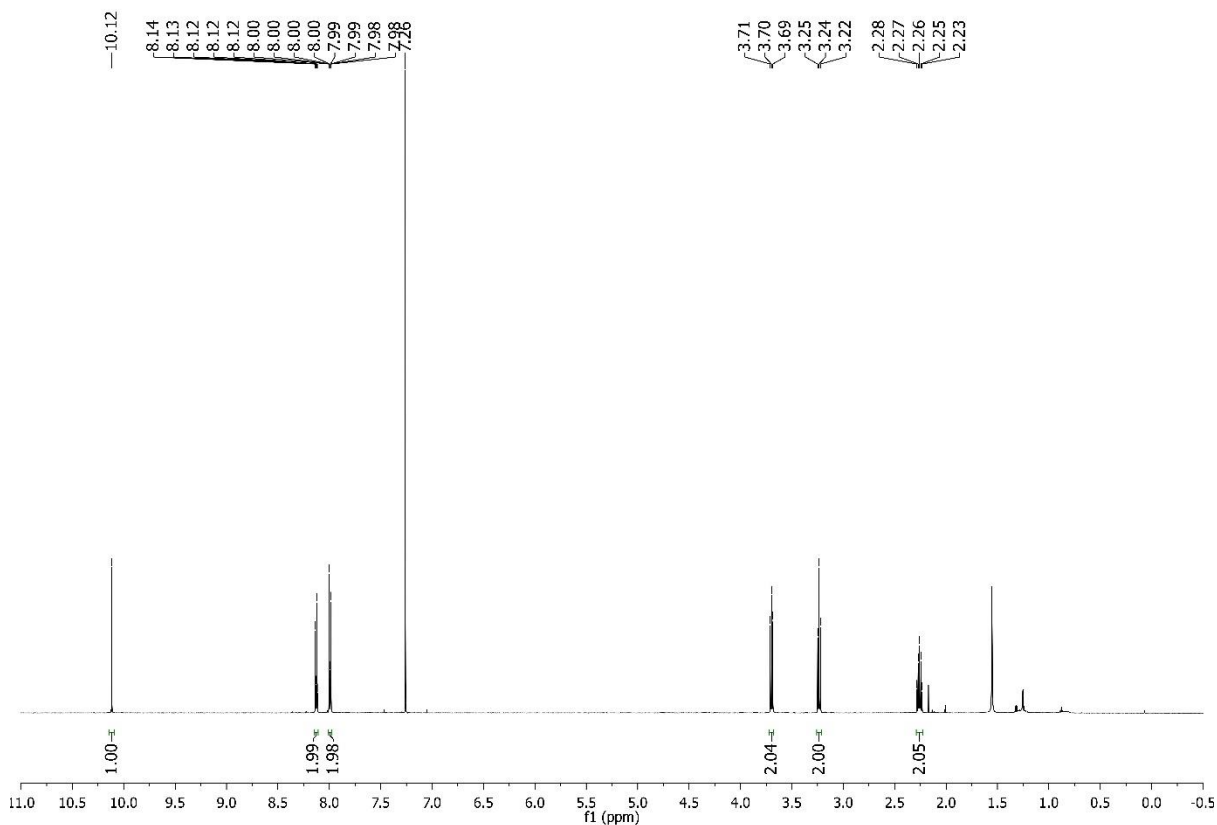


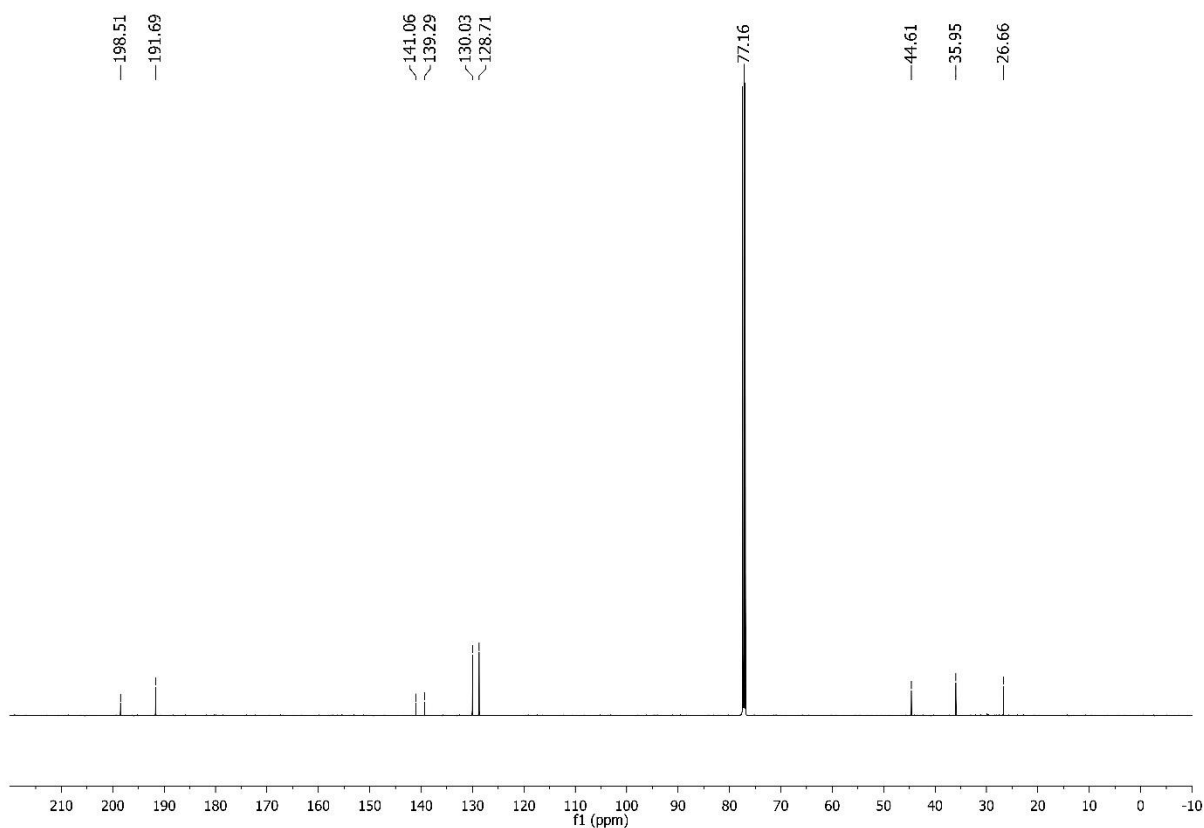
#### 4-(4-Chlorobutanoyl)benzaldehyde (**14**)



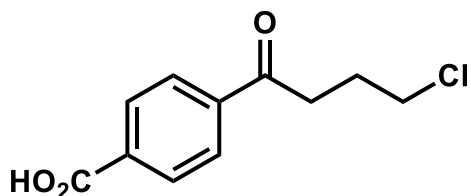
Prepared following General Procedure G using **S14** (53 mg). The crude residue was purified by flash column chromatography (15% EtOAc/Hexane, silica gel) to afford **14** (22 mg, 35%) as a colourless liquid.

$R_f$  = 0.36 (15% EtOAc/Petrol); FTIR ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 2938, 2843, 1705, 1688, 1572, 1499, 1387, 1227, 1200, 997, 835;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 10.12 (s, 1H), 8.15 – 8.10 (m, 2H), 8.02 – 7.97 (m, 2H), 3.70 (t,  $J$  = 6.0 Hz, 2H), 3.23 (t,  $J$  = 7.0 Hz, 2H), 2.30 – 2.22 (m, 2H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 198.5, 191.7, 141.0, 139.3, 130.0, 128.7, 44.6, 35.9, 26.7; HRMS ( $\text{EI}^+$ ) [ $\text{C}_{11}\text{H}_{11}\text{O}_2\text{Cl}$ ] requires [M] 210.0448, found 210.0446.



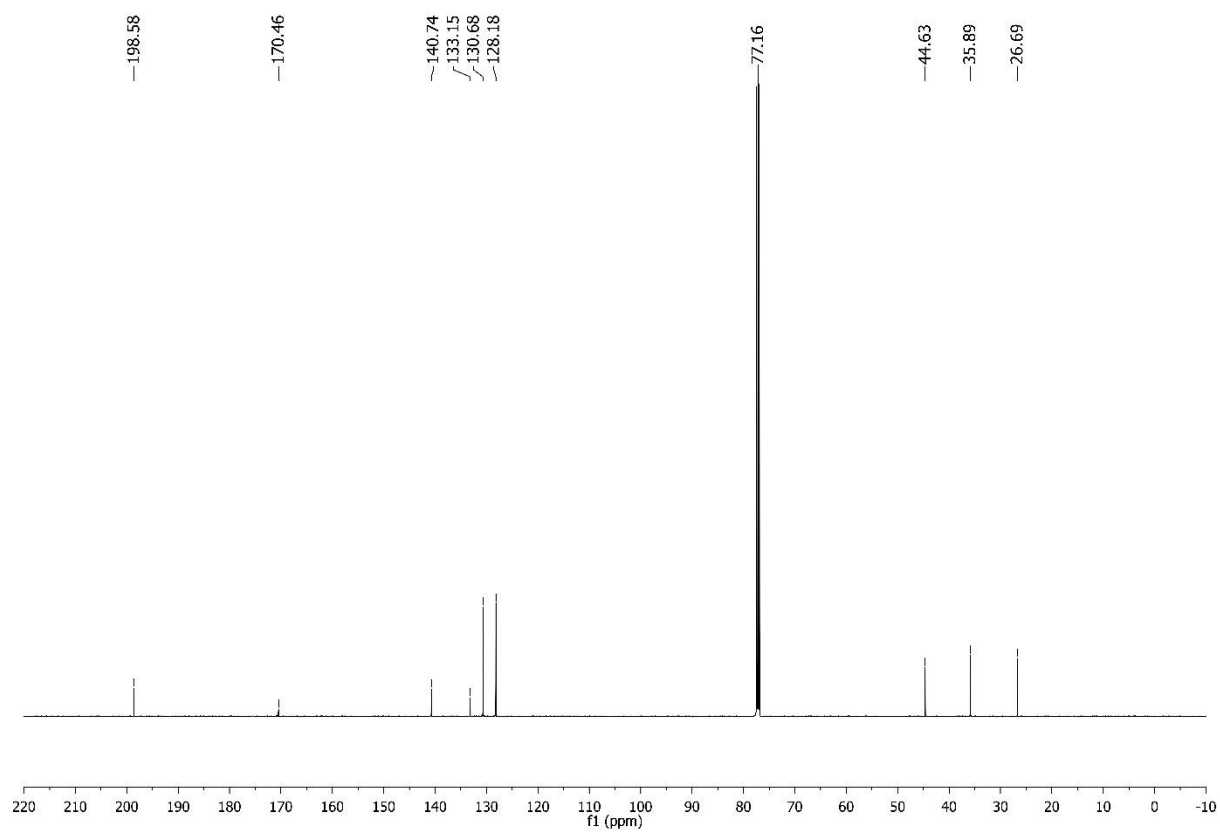
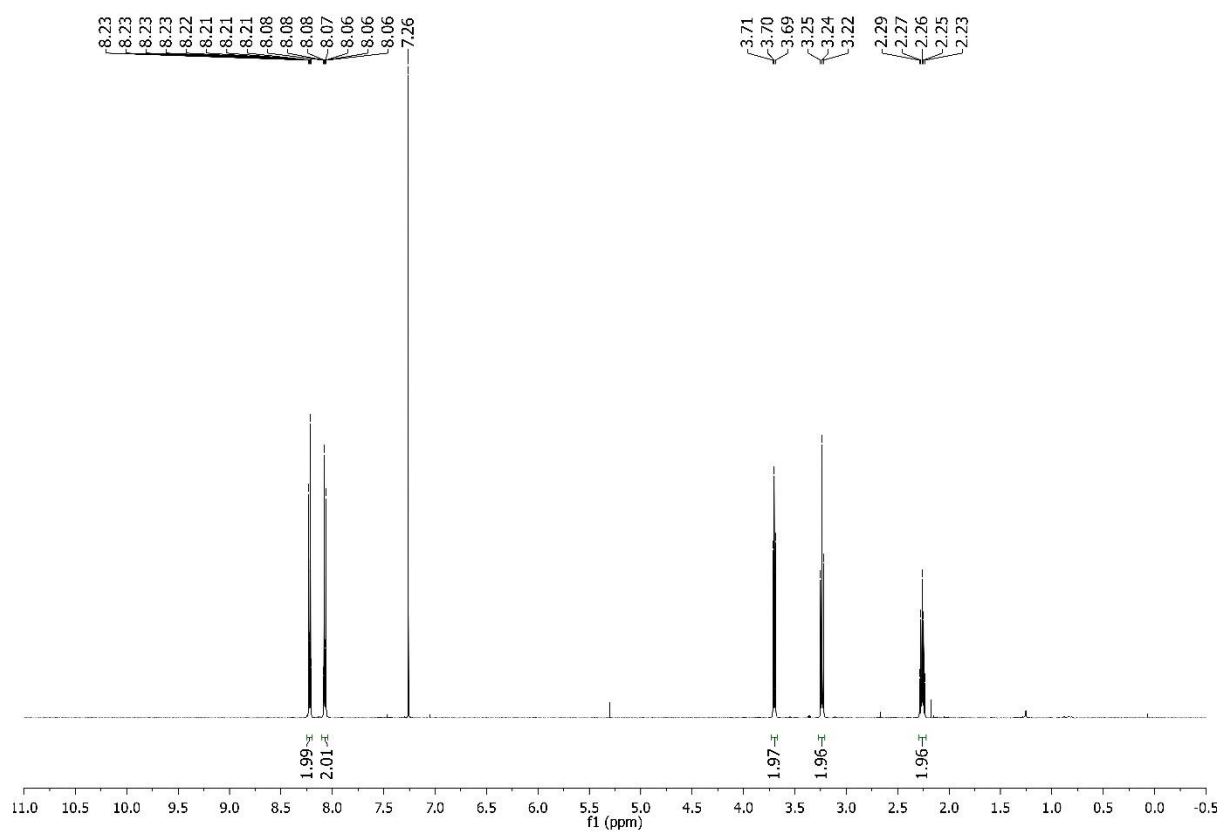


#### 4-(4-Chlorobutanoyl)benzoic acid (**15**)



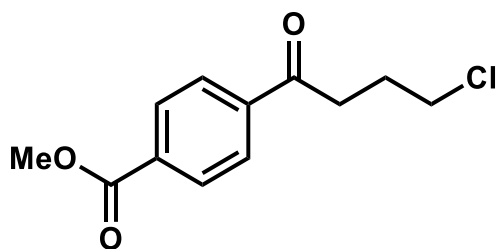
Prepared following General Procedure G using **S15** (58 mg). For this example, the reaction mixture was washed with distilled water instead of sat. NaHCO<sub>3</sub>. The crude residue was purified by flash column chromatography (70% EtOAc/Petrol, silica gel) to afford **15** (30 mg, 47%) as a white solid.

**R<sub>f</sub>** = 0.29 (50% EtOAc); **M.p.**: 137-139 °C; **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 2888, 2865, 1699, 1676, 1574, 1431, 1412, 1290, 1223, 934, 772, 735; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.24–8.19 (m, 2H), 8.10–8.04 (m, 2H), 3.70 (t,  $J$  = 6.0 Hz, 2H), 3.23 (t,  $J$  = 7.0 Hz, 2H), 2.30–2.21 (m, 2H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 198.58, 170.5, 140.7, 133.1, 130.7, 128.2, 44.6, 35.9, 26.7; **HRMS** (EI<sup>+</sup>) [C<sub>11</sub>H<sub>11</sub>ClO<sub>3</sub>] requires [M+H] 225.0323, found 225.0318.



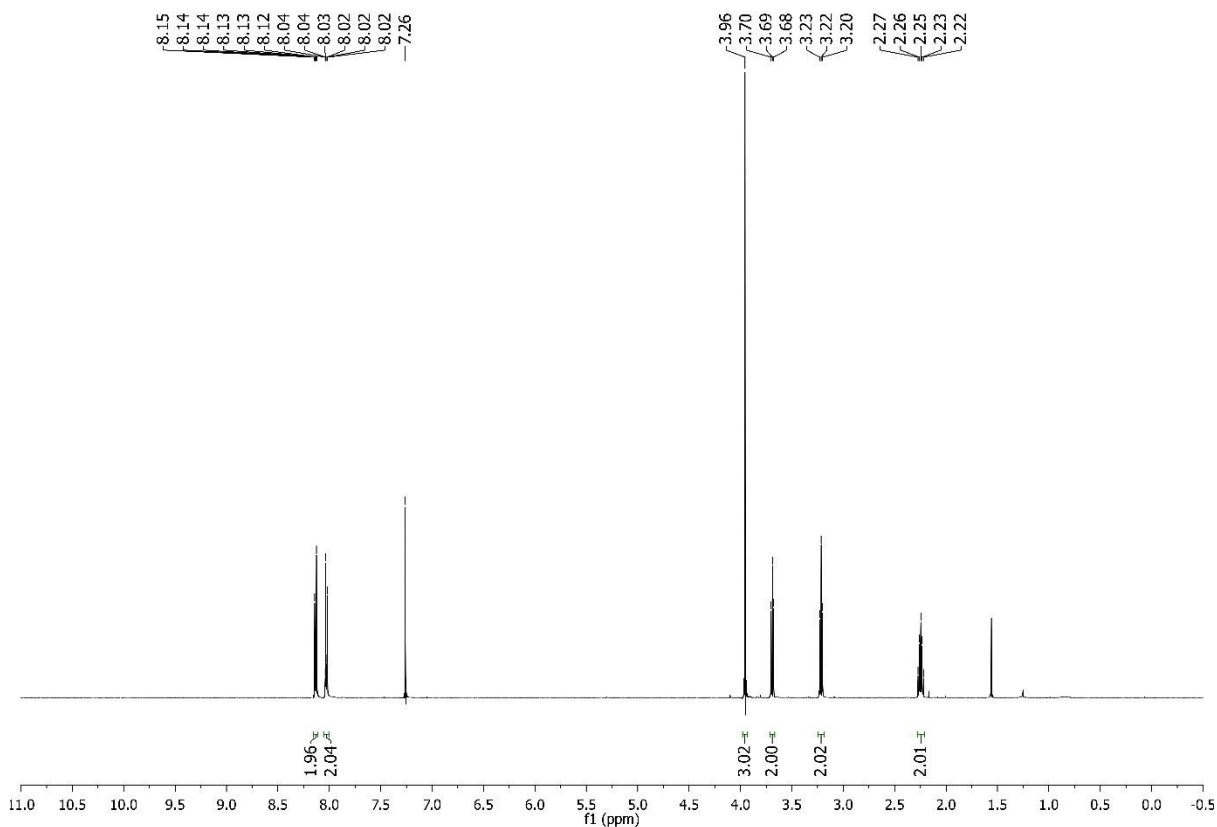


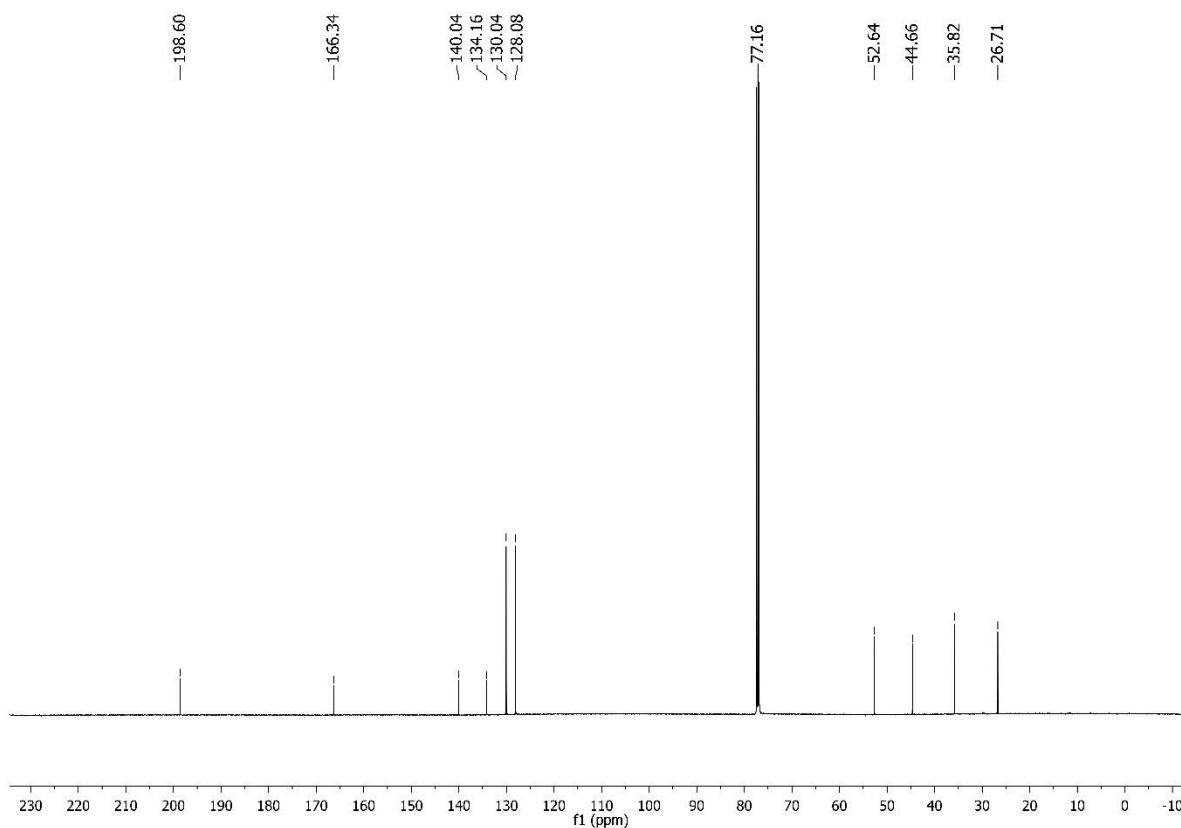
**Methyl 4-(4-chlorobutanoyl)benzoate (16)**



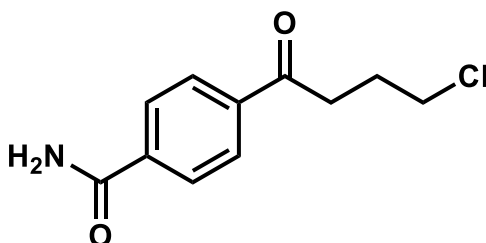
Prepared following General Procedure G using **S16** (62 mg). The crude residue was purified by flash column chromatography (10% Et<sub>2</sub>O/Pentane, silica gel) to afford **16** (41 mg, 57%) as a colourless oil.

**R<sub>f</sub>** = 0.36 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 2949, 1726, 1688, 1506, 1435, 1410, 1278, 1221, 1107, 758, 694; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 8.16 – 8.11 (m, 2H), 8.05 – 8.00 (m, 2H), 3.95 (s, 3H), 3.69 (t, *J* = 6.0 Hz, 2H), 3.22 (t, *J* = 7.0 Hz, 2H), 2.29 – 2.20 (m, 2H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 198.6, 166.3, 140.0, 134.2, 130.0, 128.0, 52.6, 44.7, 35.8, 26.7; **HRMS (EI<sup>+</sup>)** [C<sub>12</sub>H<sub>13</sub>ClO<sub>3</sub>] requires [M+H] 241.0628, found 241.0631.



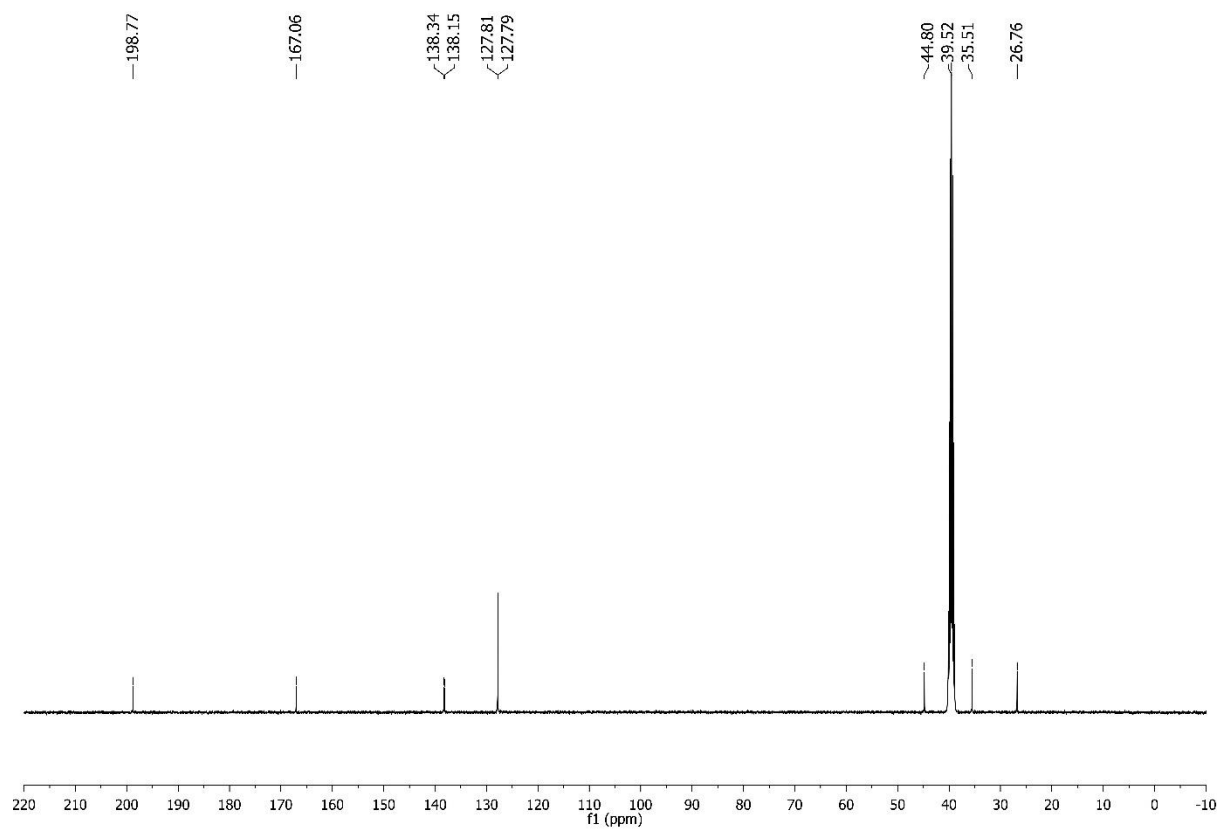
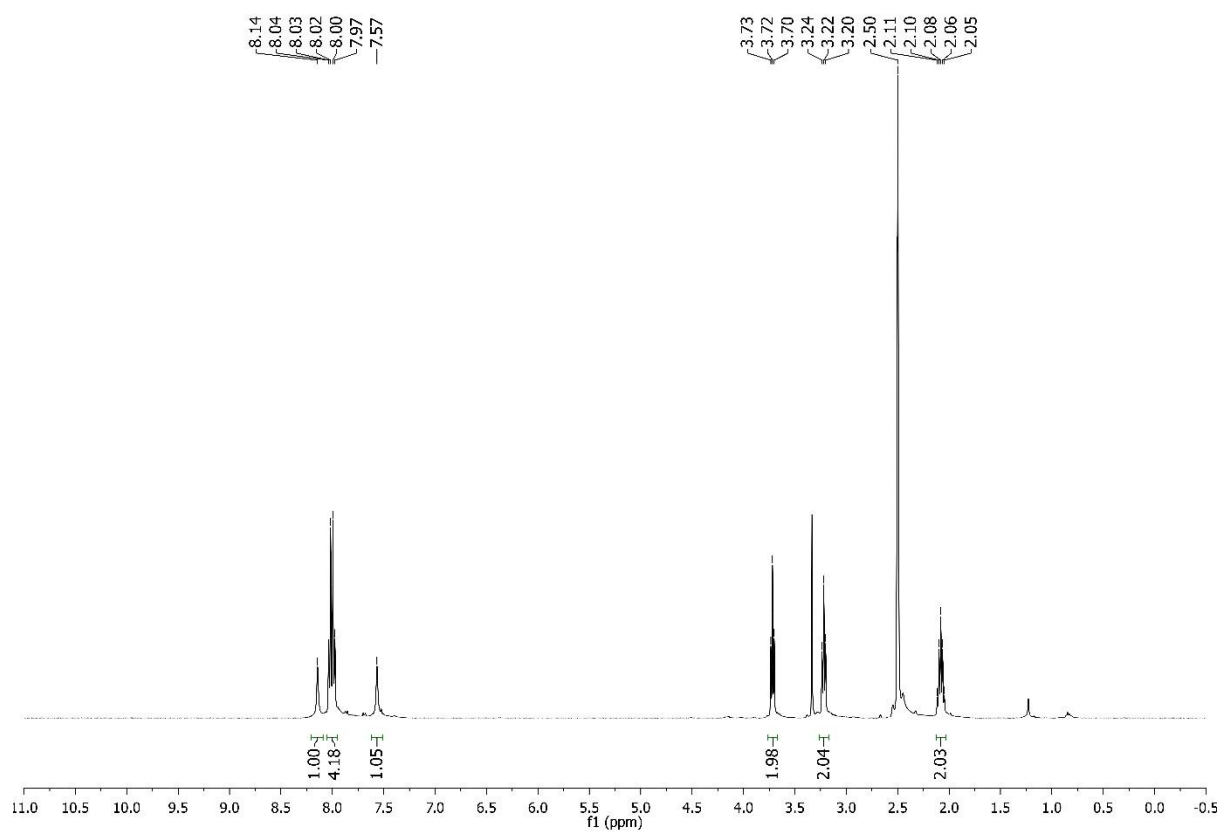


#### 4-(4-Chlorobutanoyl)benzamide (**17**)

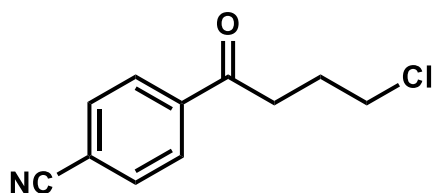


Prepared following General Procedure G using **S17** (57 mg). The crude residue was purified by flash column chromatography (80% EtOAc/Petrol, silica gel) to afford **17** (41 mg, 61%) as a white solid.

$R_f$  = 0.60 (100% EtOAc/Hexanes); **M.p.**: 173-175 °C; **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) 3408 (br), 3157 (br), 1674, 1653, 1618, 1562, 1506, 1411, 1379, 1224, 1188, 1143, 1112, 997, 777;  **$^1\text{H}$  NMR (400 MHz, DMSO)**  $\delta$  = 8.14 (s, 1H), 8.07 – 7.94 (m, 4H), 7.57 (s, 1H), 3.72 (t,  $J$  = 6.5 Hz, 2H), 3.22 (t,  $J$  = 7.0 Hz, 2H), 2.16 – 2.01 (m, 2H);  **$^{13}\text{C}$  NMR (101 MHz, DMSO)**  $\delta$  = 198.8, 167.1, 138.3, 138.1, 127.8, 127.8, 44.8, 35.5, 26.8; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{11}\text{H}_{12}\text{ClNO}_2$ ] requires  $[\text{M}+\text{H}]$  226.0638, found 226.0635.

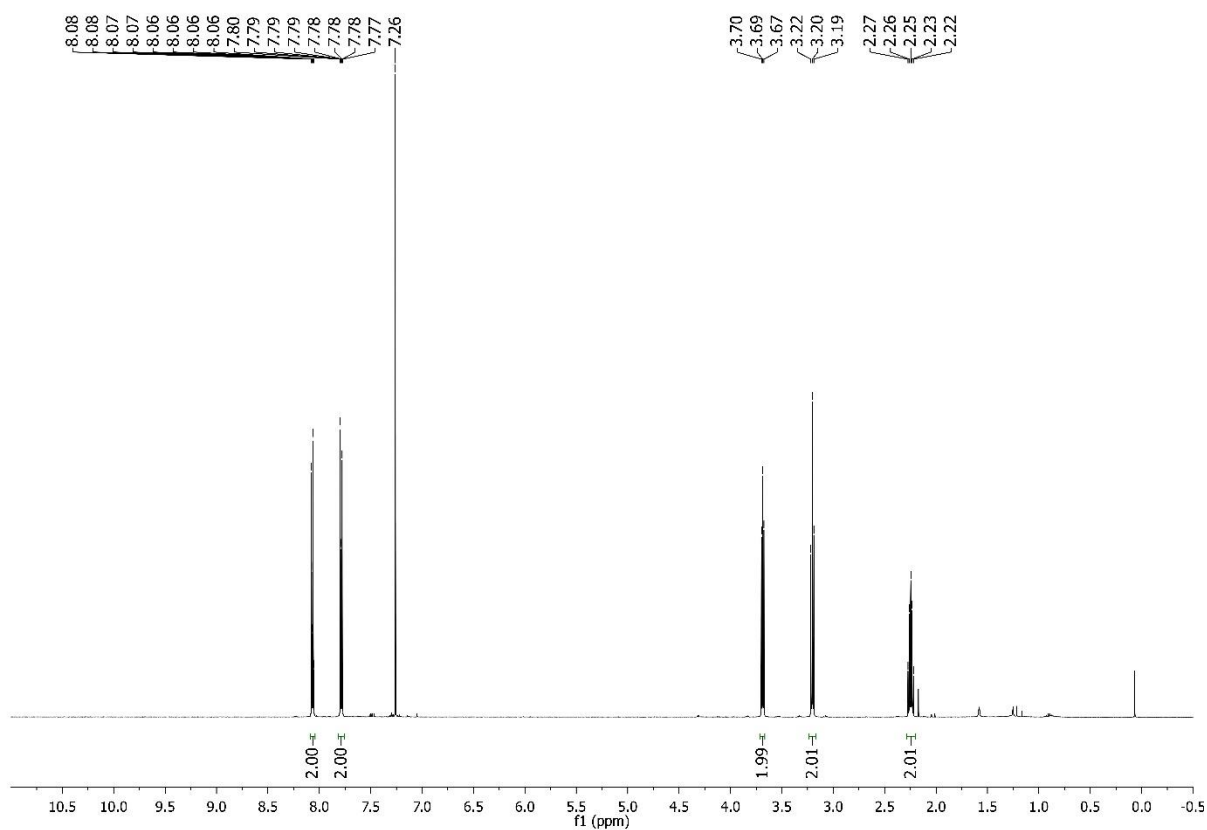


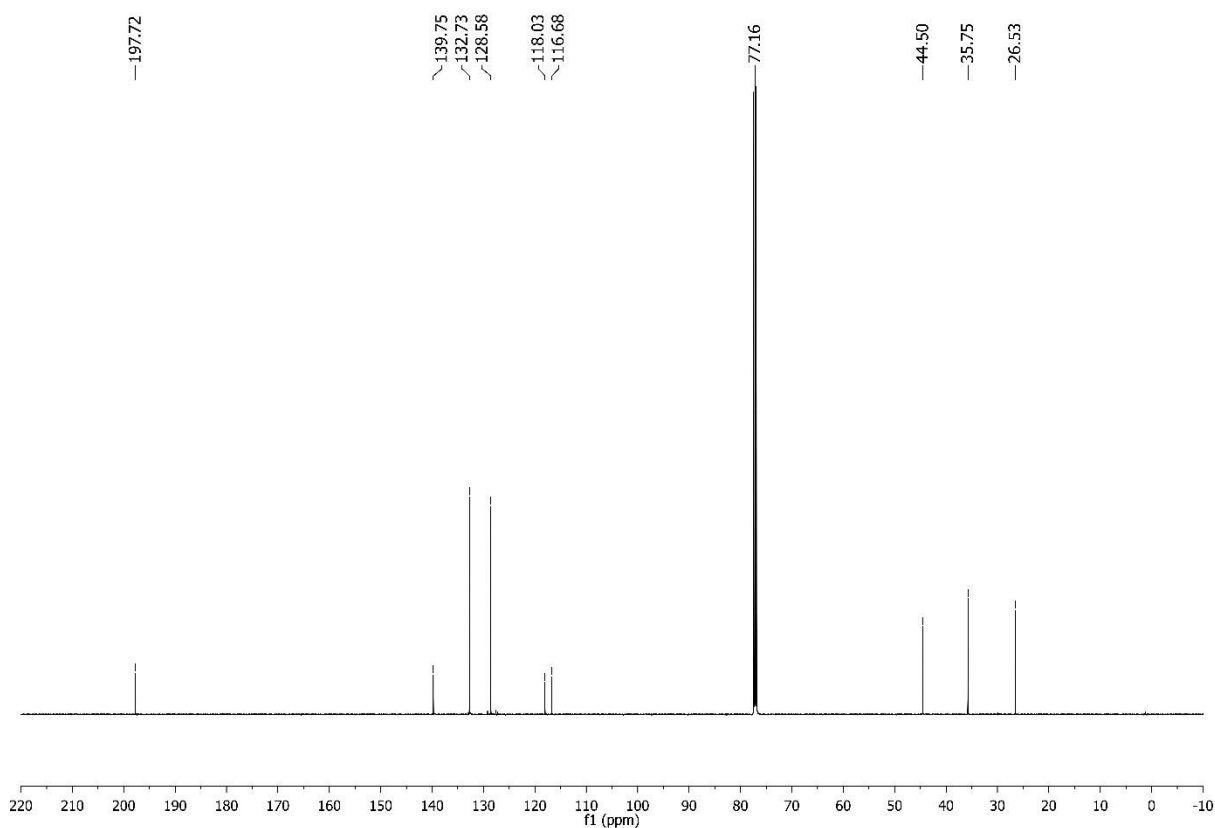
#### 4-(4-Chlorobutanoyl)benzonitrile (**18**)



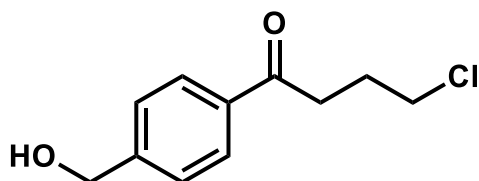
Prepared following General Procedure G using **S18** (52 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **18** (25 mg, 40%) as a white solid.

**R<sub>f</sub>** = 0.27 (10% EtOAc/Petrol); **M.p.**: 84-86 °C; **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 3090, 2965, 2934, 2236, 1688, 1603, 1404, 1315, 1229, 997, 853, 779, 646, 577; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.09 – 8.04 (m, 2H), 7.81 – 7.75 (m, 2H), 3.69 (t, *J* = 6.5 Hz, 2H), 3.20 (t, *J* = 7.0 Hz, 2H), 2.25 – 2.22 (m, 2H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 197.6, 139.6, 132.6, 128.4, 117.9, 116.5, 44.3, 35.6, 26.4; **HRMS** (EI<sup>+</sup>) [C<sub>11</sub>H<sub>10</sub>ClNO] requires [M+H] 208.0529, found 208.0535.



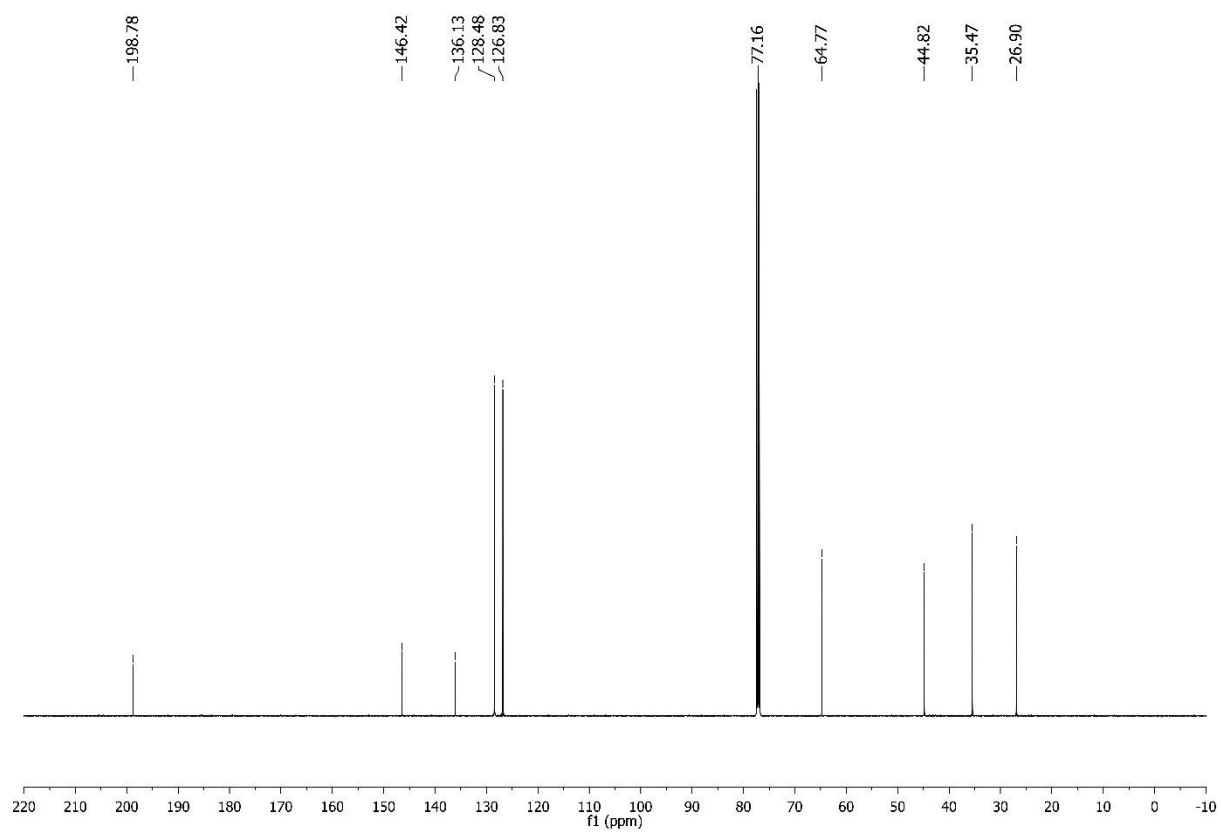
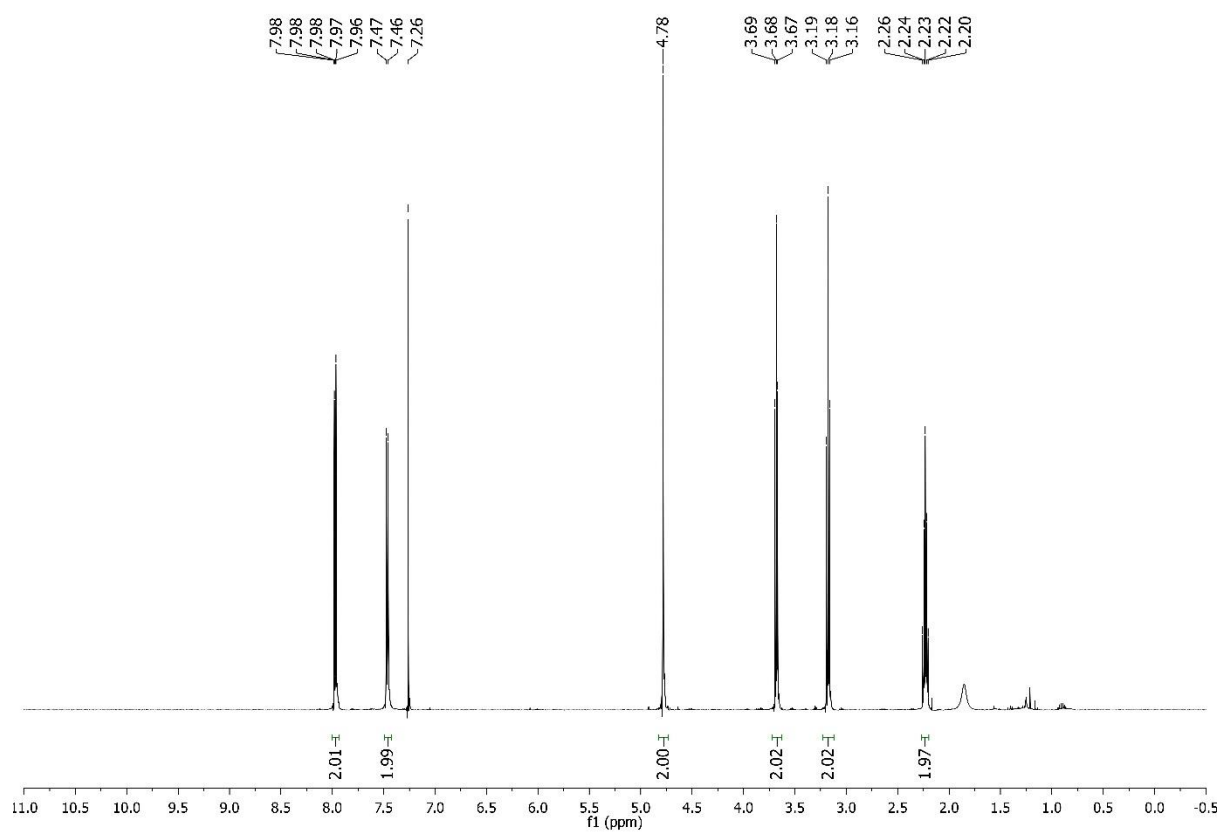


**4-Chloro-1-(4-(hydroxymethyl)phenyl)butan-1-one (19)**

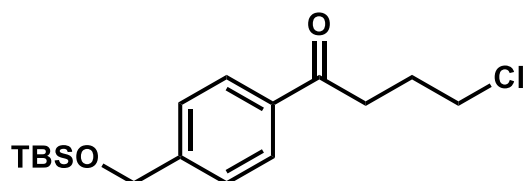


Prepared following General Procedure H using **S21** (54 mg). The crude residue was purified by flash column chromatography (50% EtOAc/Petrol, silica gel) to afford **19** (37 mg, 58%) as a colourless oil.

$R_f$  = 0.48 (50% EtOAc/Petrol); **FTIR** ( $\nu_{\max}$   $\text{cm}^{-1}$ , thin film) = 3415 (br), 2929, 2858, 1705, 1606, 1570, 1413, 1319, 1228, 1045, 810, 779, 648, 569;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 7.99 – 7.94 (m, 2H), 7.50 – 7.42 (m, 2H), 4.78 (s, 2H), 3.68 (t,  $J$  = 6.0 Hz, 2H), 3.18 (t,  $J$  = 7.0 Hz, 2H), 2.28 – 2.19 (m, 2H), 1.85 (s, 1H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 198.8, 146.4, 136.1, 128.5, 126.8, 64.8, 44.8, 35.5, 26.9; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{11}\text{H}_{13}\text{O}_2\text{Cl}$ ] requires  $[M+H]$  213.0682, found 213.0687.

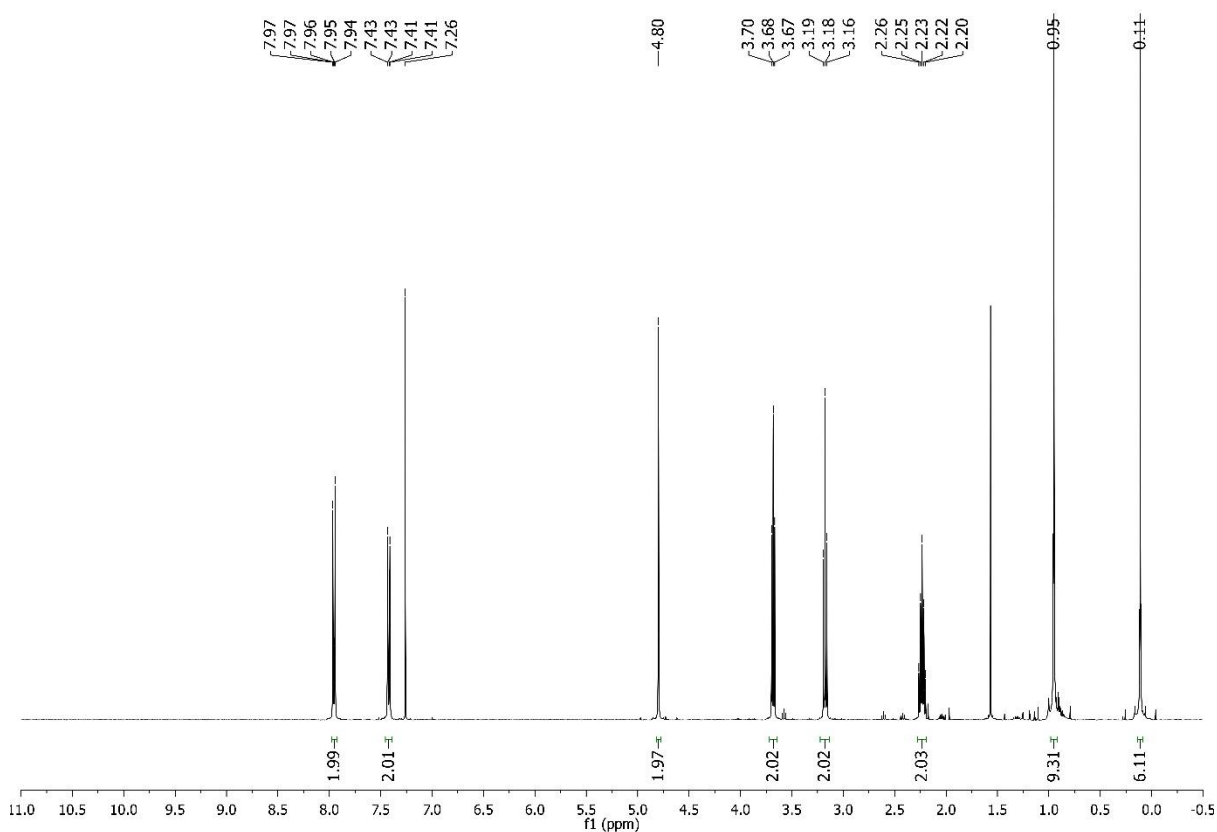


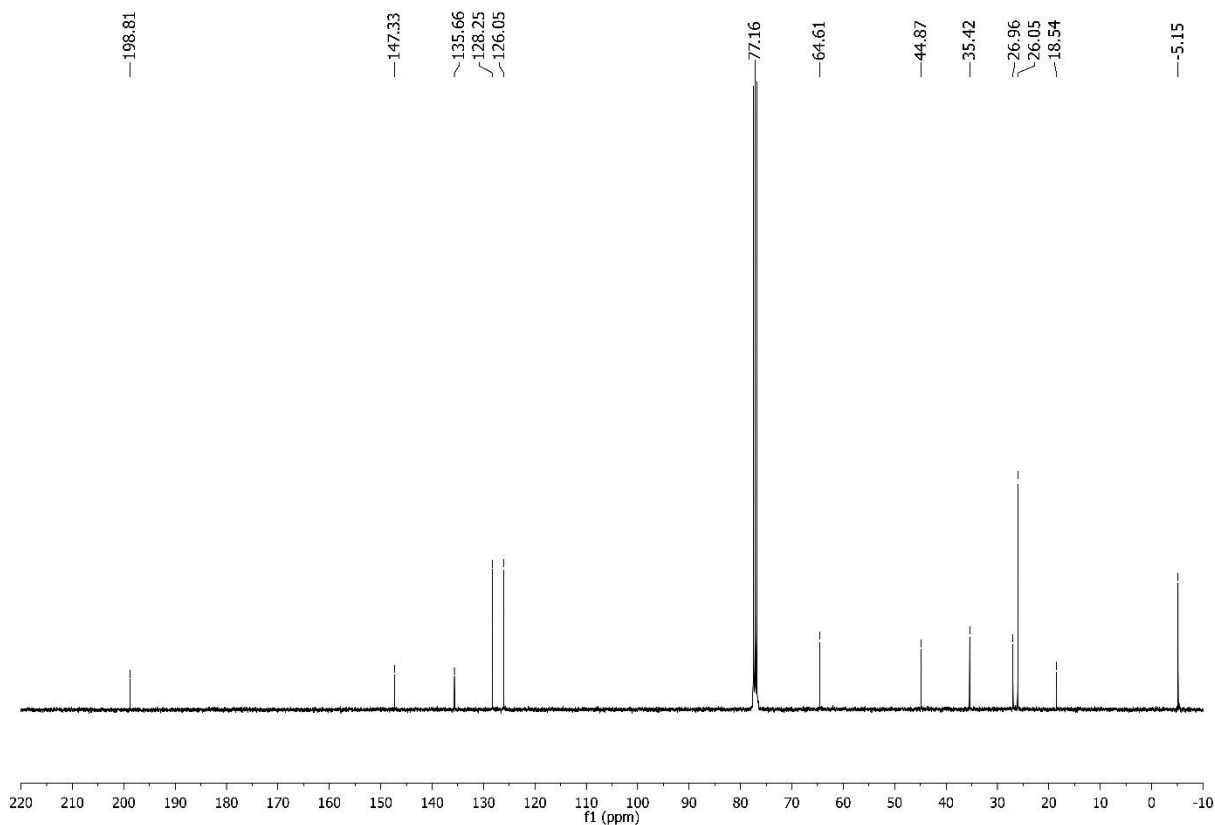
**1-(4-(((*Tert*-butyldimethylsilyl)oxy)methyl)phenyl)-4-chlorobutan-1-one (20)**



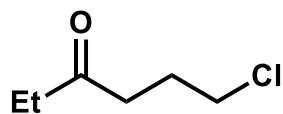
Prepared following General Procedure H using **S20** (88 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **20** (46 mg, 47%) as a colourless oil.

**R<sub>f</sub>** = 0.15 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 2930, 1688, 1607, 1410, 1227, 1047, 810; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.98 – 7.93 (m, 2H), 7.45 – 7.39 (m, 2H), 4.80 (s, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 2.29 – 2.18 (m, 2H), 0.95 (s, 9H), 0.11 (s, 6H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 198.8, 147.3, 135.7, 128.3, 126.1, 64.6, 44.9, 35.4, 27.0, 26.1, 18.5, -5.2; **HRMS** (EI<sup>+</sup>) [C<sub>17</sub>H<sub>27</sub>ClO<sub>2</sub>Si] requires [M+H] 327.1547, found 327.1543.





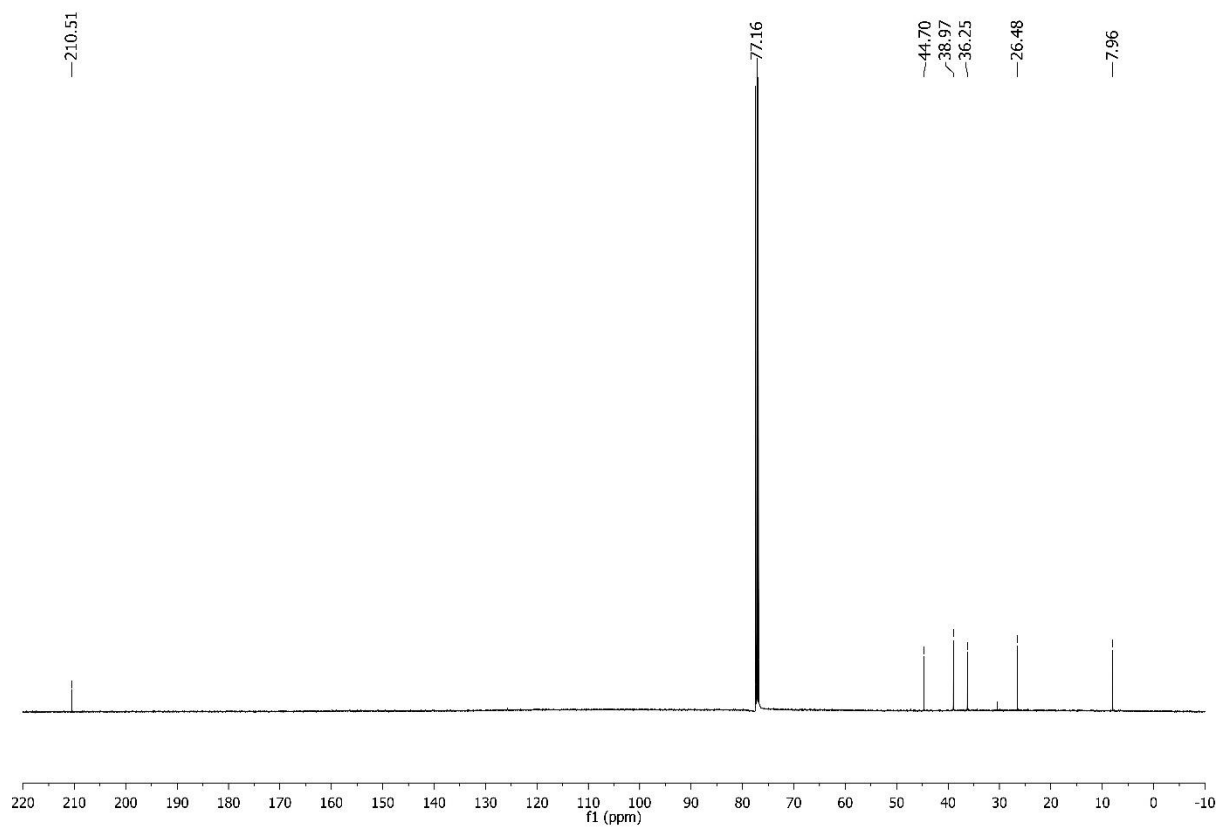
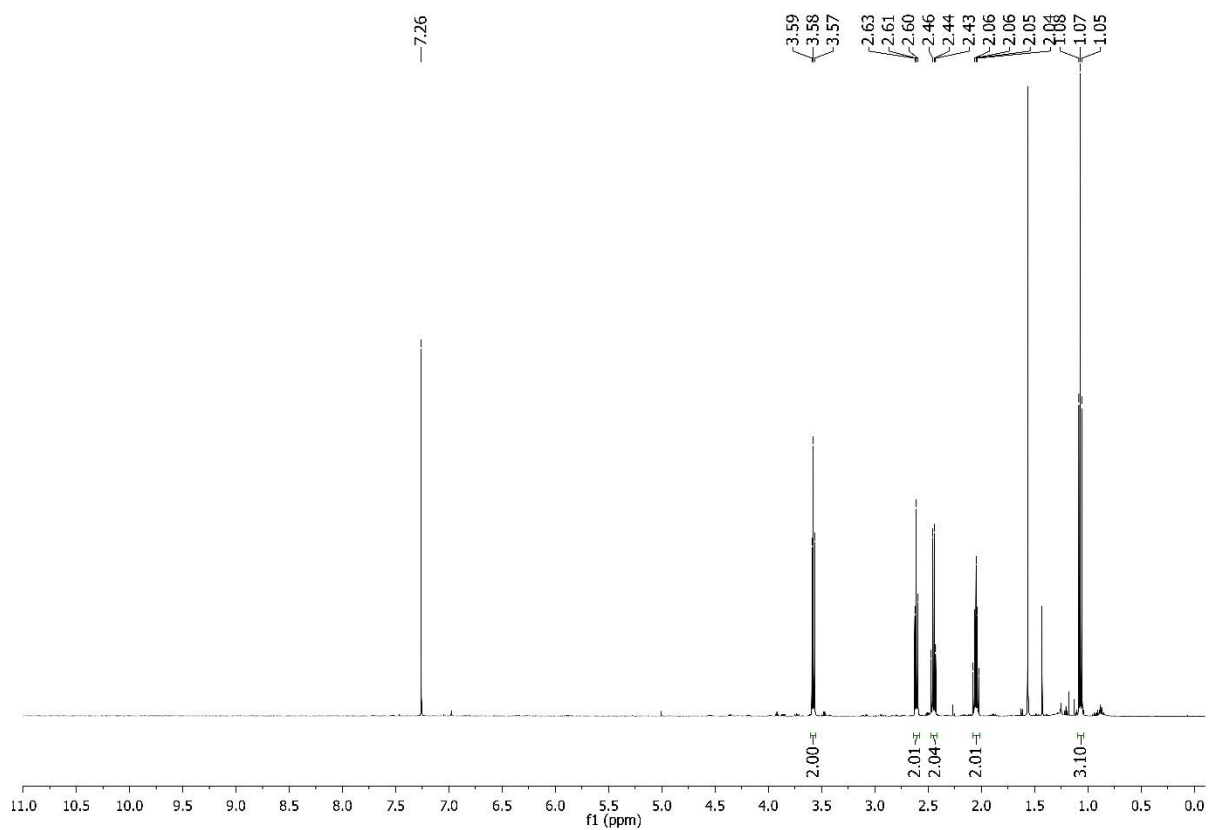
### 6-Chlorohexan-3-one (**21**)



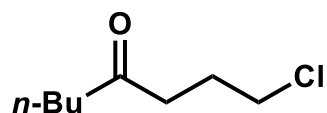
Prepared according to General Procedure G using **S22** (30 mg). The crude residue was purified by flash column chromatography (0→6% Et<sub>2</sub>O/Pentane, silica gel) to afford **21** (8 mg, 19%) as a colourless oil. <sup>1</sup>H NMR analysis of the crude reaction mixture with an internal standard indicated a 57% yield.

**R<sub>f</sub>** = 0.27 (10% EtOAc/Hexanes); **FTIR** (ν<sub>max</sub> cm<sup>-1</sup>, thin film) 1713, 1445, 1354, 1206, 1034, 861; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ = 3.58 (t, *J* = 6.5 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.45 (q, *J* = 7.5 Hz, 2H), 2.10 – 2.00 (m, 2H), 1.07 (t, *J* = 7.5 Hz, 3H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ = 210.5, 44.7, 39.0, 36.3, 26.5, 8.0; **HRMS** (EI<sup>+</sup>) [C<sub>6</sub>H<sub>11</sub>OCl] requires [M] 134.0498, found 134.0497.



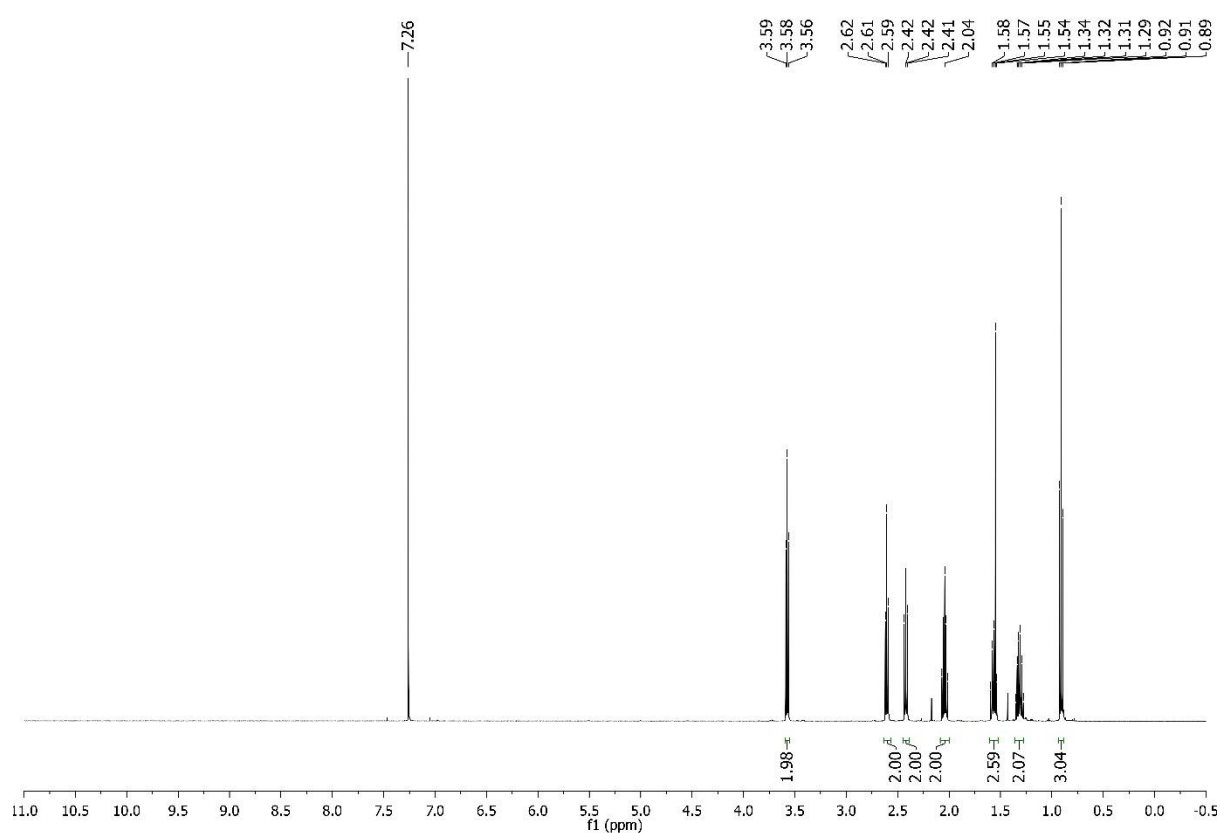


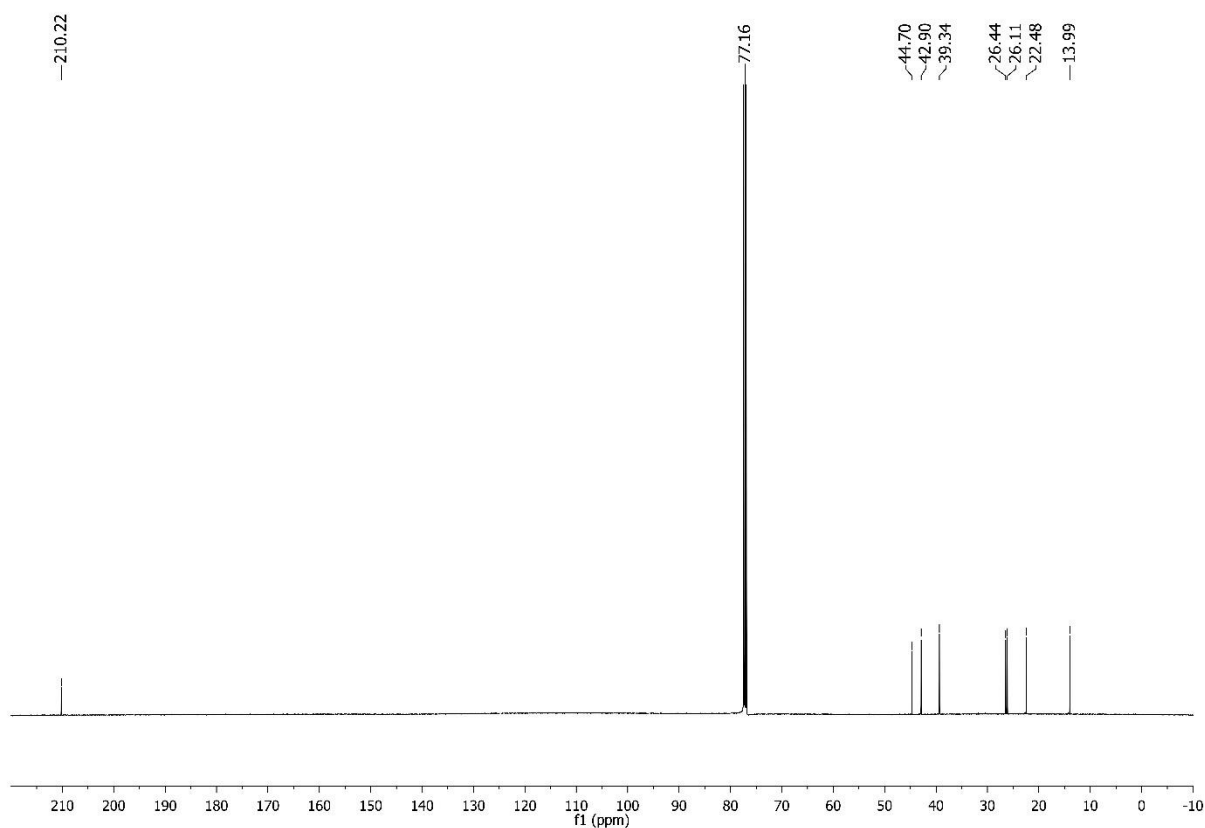
### 1-Chlorooctan-4-one (22)



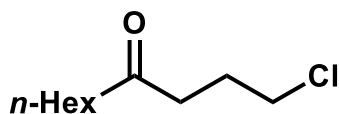
Prepared following General Procedure G using **S23** (38 mg). The crude residue was purified by flash column chromatography (4% Et<sub>2</sub>O/Pentane, silica gel) to afford **22** (29 mg, 60%) as a colourless oil.

**R<sub>f</sub>** = 0.60 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 2972, 2895, 1714, 1384, 1251, 1157, 958; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.58 (t,  $J$  = 6.0 Hz, 2H), 2.61 (t,  $J$  = 7.0 Hz, 2H), 2.42 (t,  $J$  = 7.5 Hz, 2H), 2.09 – 2.00 (m, 2H), 1.61 – 1.54 (m, 2H), 1.37 – 1.27 (m, 2H), 0.91 (t,  $J$  = 7.5 Hz, 3H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 210.2, 44.7, 42.9, 39.4, 26.4, 26.1, 22.5, 13.9; **HRMS** (EI<sup>+</sup>) [C<sub>8</sub>H<sub>15</sub>OC] requires [M] 162.0811, found 162.0807.





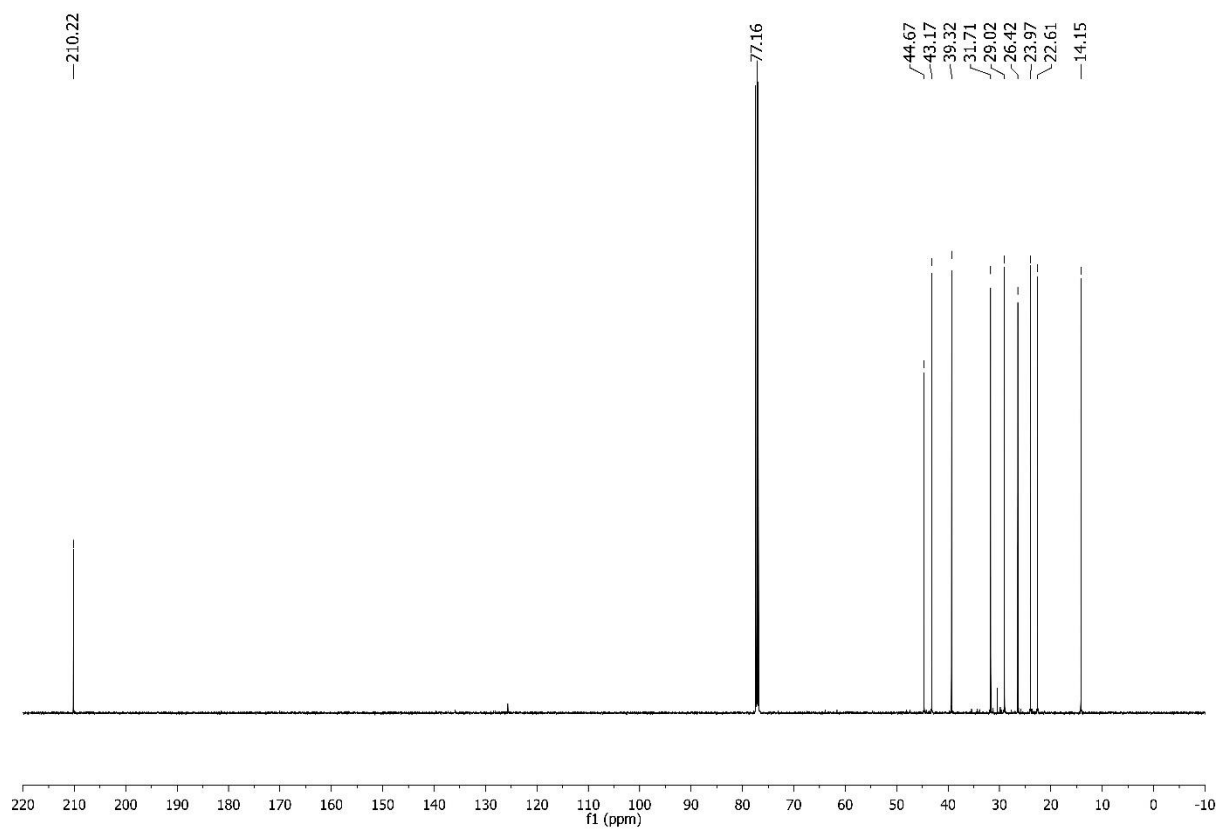
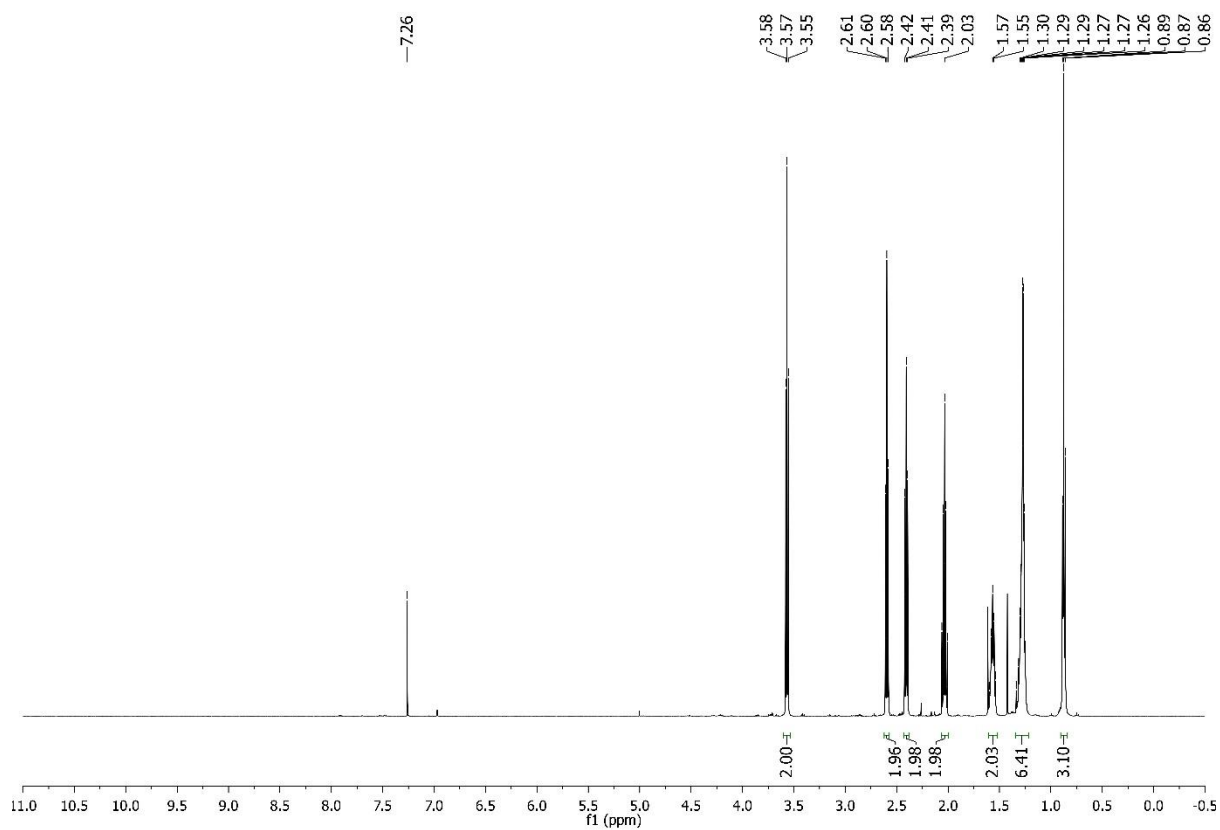
### 1-Chlorodecan-4-one (23)



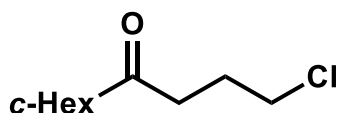
Prepared following General Procedure G using **S24** (47 mg). The crude residue was purified by flash column chromatography (10% Et<sub>2</sub>O/Pentane, silica gel) to afford **23** (27 mg, 47%) as a colourless oil.

**R<sub>f</sub>** = 0.43 (10% EtOAc/Hexanes); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 3.57 (t, *J* = 6.5 Hz, 2H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.06 – 2.00 (m, 2H), 1.60 – 1.53 (m, 2H), 1.32 – 1.23 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ = 210.2, 44.7, 43.2, 39.3, 31.7, 29.0, 26.4, 24.0, 22.6, 14.2.

These data are in agreement with those previously reported in the literature.<sup>[15]</sup>



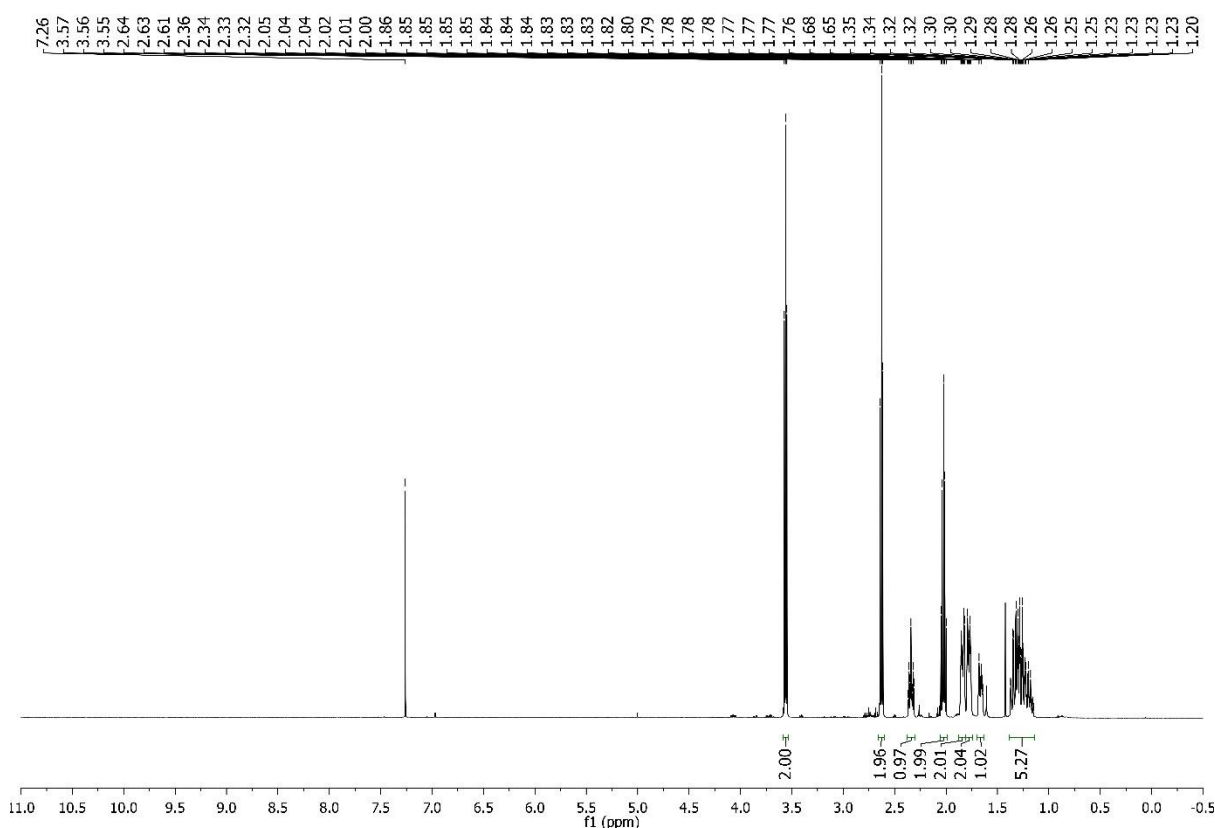
#### 4-Chloro-1-cyclohexylbutan-1-one (**24**)

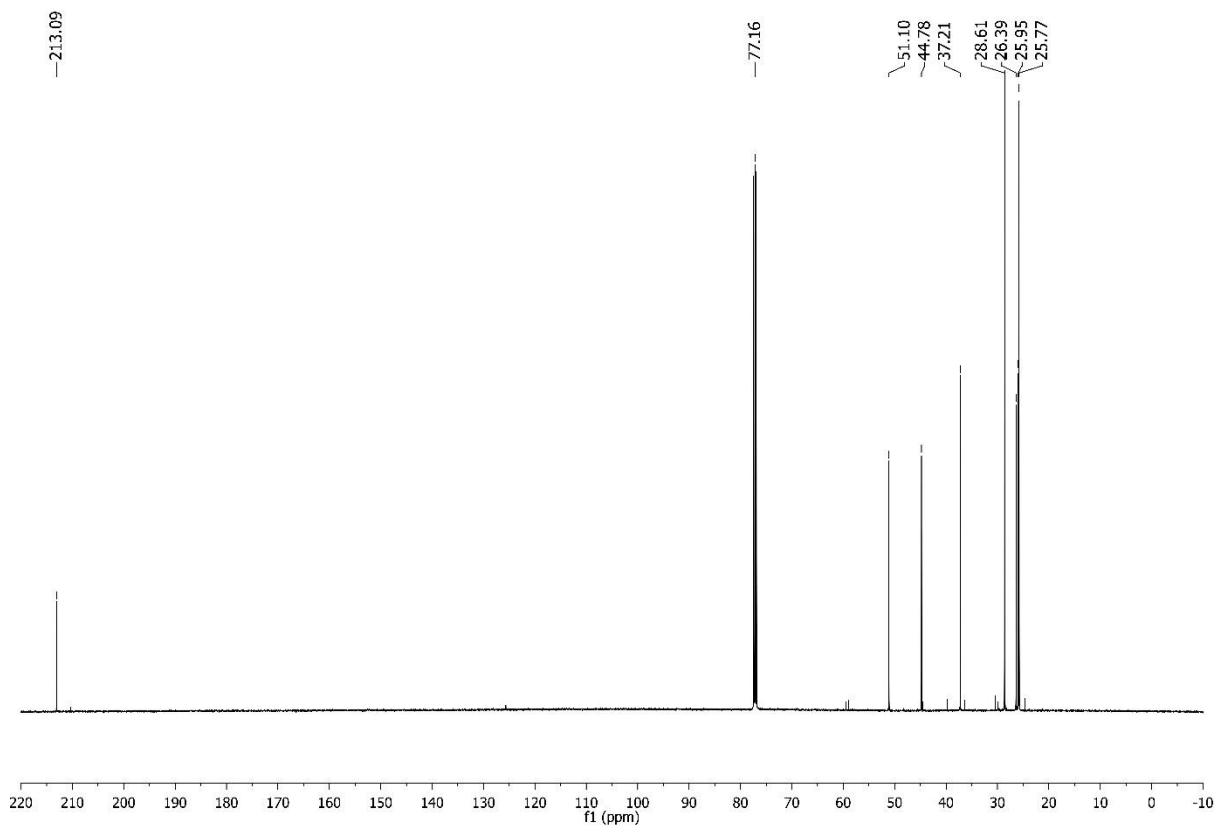


Prepared following General Procedure G using **S25** (46 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **24** (24 mg, 42%) as a colourless oil.

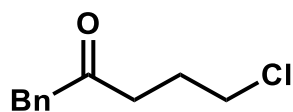
$R_f$  = 0.36 (10% Et<sub>2</sub>O/Petrol); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.59 – 3.52 (t,  $J$  = 6.5 Hz, 2H), 2.63 (t,  $J$  = 7.0 Hz, 2H), 2.37 – 2.30 (m, 1H), 2.06 – 1.99 (m, 2H), 1.87 – 1.81 (m, 2H), 1.81 – 1.74 (m, 2H), 1.71 – 1.63 (m, 1H), 1.39 – 1.14 (m, 5H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 213.1, 51.1, 44.8, 37.2, 28.6, 26.4, 26.0, 25.8.

These data are consistent with those previously reported in the literature.<sup>[15]</sup>





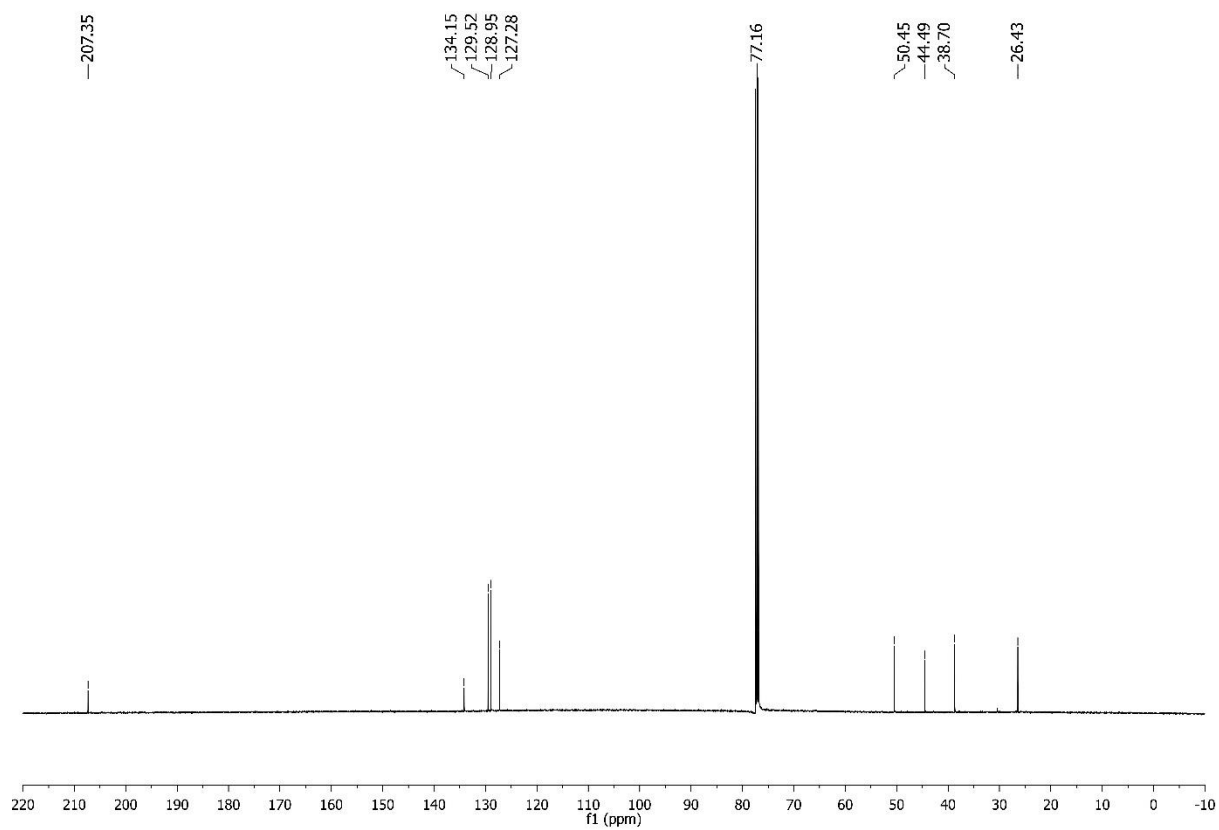
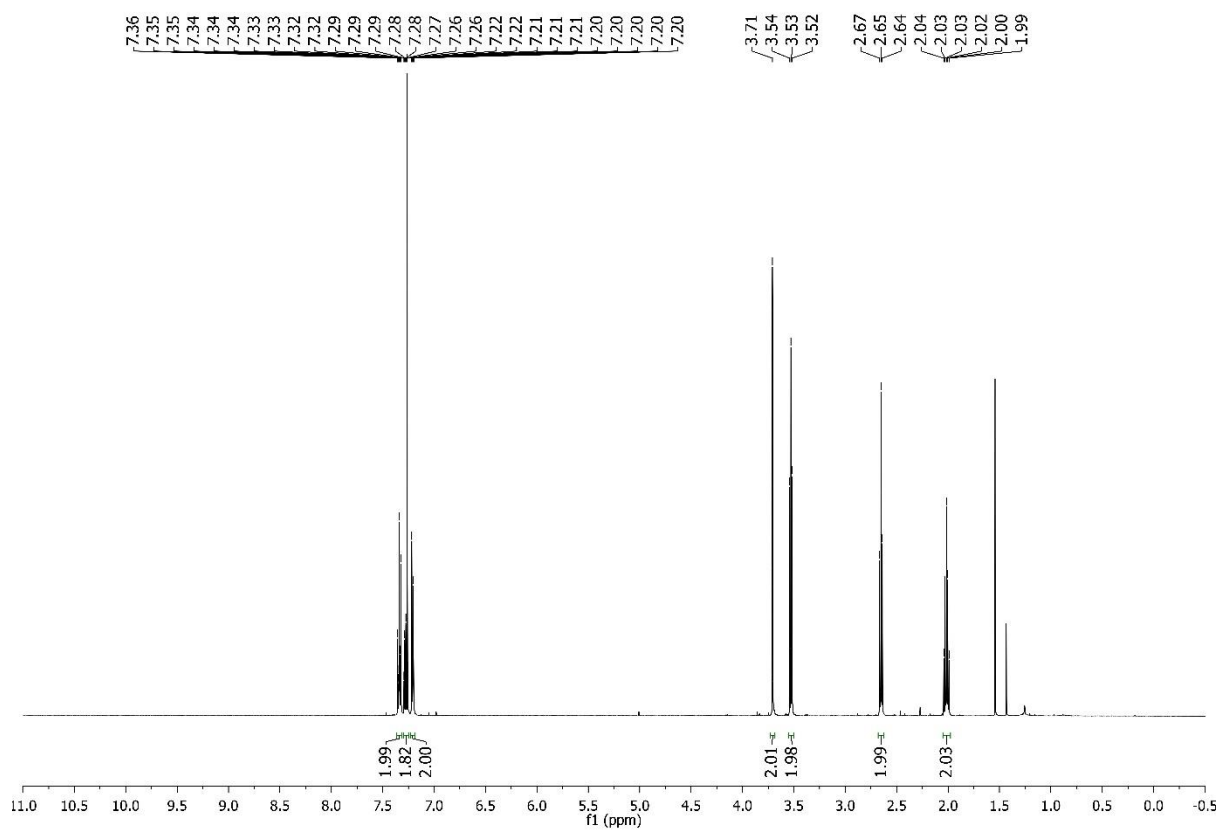
### 5-Chloro-1-phenylpentan-2-one (**25**)



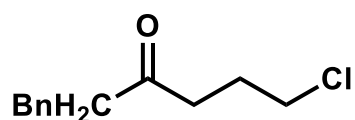
Prepared following General Procedure G using **S26** (49 mg). The crude residue was purified by flash column chromatography (10% Et<sub>2</sub>O/Pentane, silica gel) to afford **25** (40 mg, 68%) as a colourless oil.

**R<sub>f</sub>** = 0.29 (10% EtOAc/Hexanes); **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 7.36 – 7.31 (m, 2H), 7.30 – 7.25 (m, 1H), 7.23 – 7.19 (m, 2H), 3.71 (s, 2H), 3.53 (t, *J* = 6.5 Hz, 2H), 2.65 (t, *J* = 7.0 Hz, 2H), 2.05 – 1.98 (m, 2H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 207.4, 134.2, 129.5, 129.0, 127.3, 50.5, 44.5, 38.7, 26.4.

These data are in agreement with those previously reported in the literature.<sup>[19]</sup>

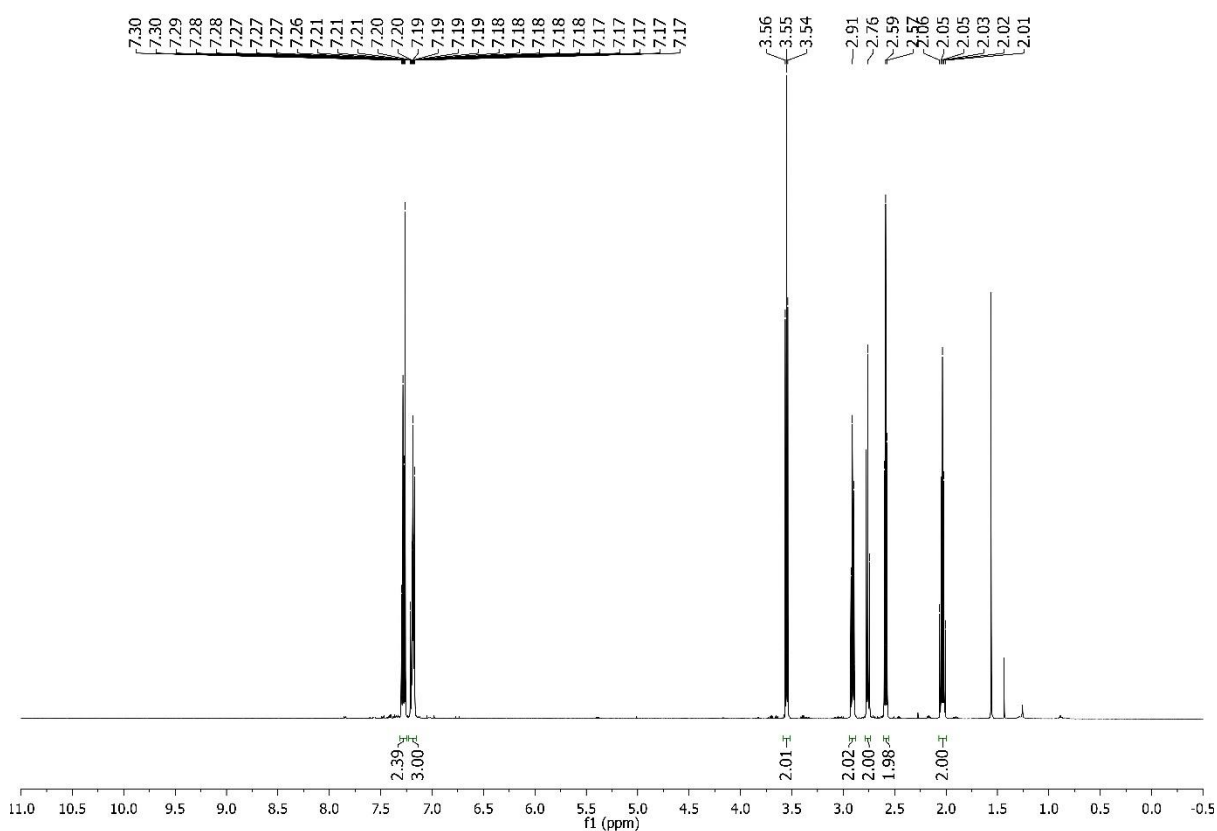


### 6-Chloro-1-phenylhexan-3-one (26)

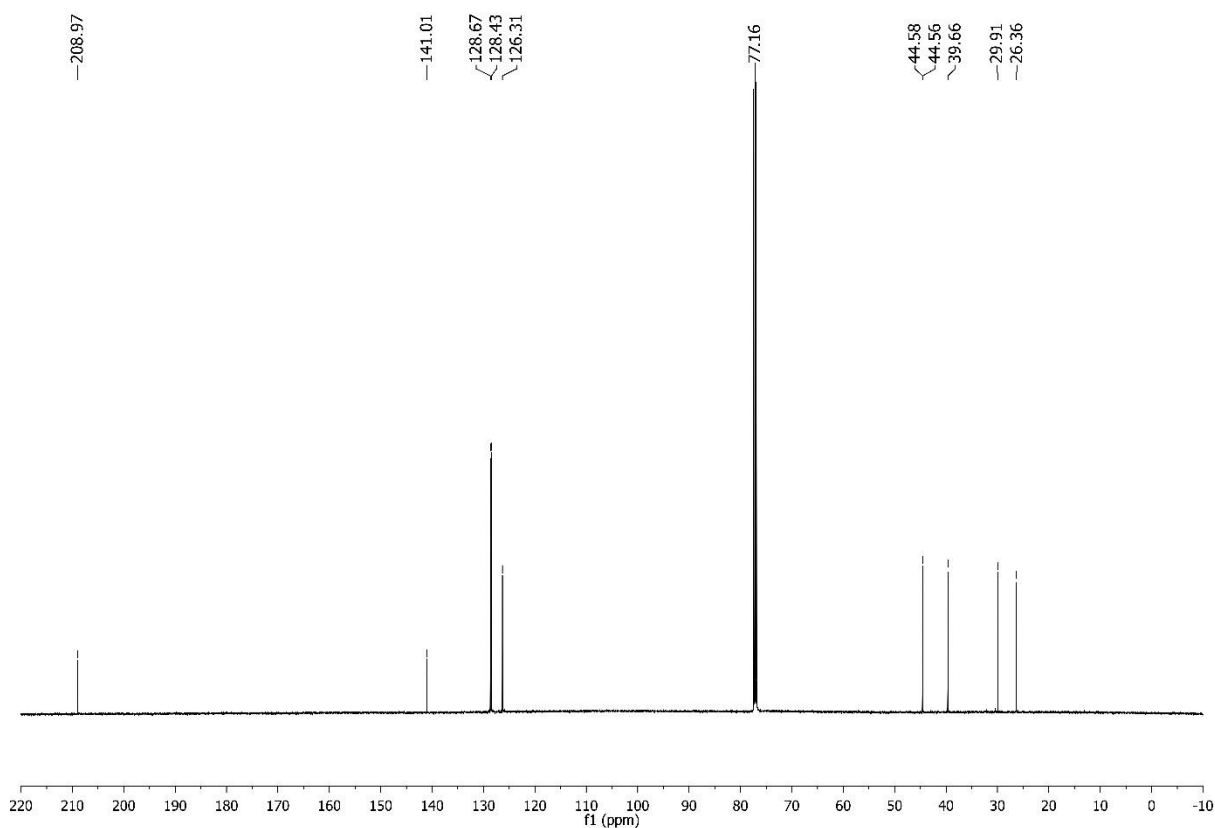


Prepared following General Procedure G using **S27** (53 mg). The crude residue was purified by flash column chromatography (0→8% Et<sub>2</sub>O/Hexanes, silica gel) to afford **26** (41 mg, 65%) as a colourless oil.

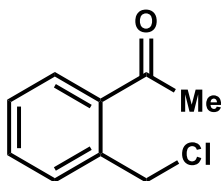
$R_f$  = 0.31 (10% EtOAc/Hexanes); FTIR ( $\nu_{\max}$  cm<sup>-1</sup>, thin film) 2918, 1711, 1495, 1452, 1408, 1092, 748, 700; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.30 – 7.26 (m, 2H), 7.22 – 7.16 (m, 3H), 3.55 (t,  $J$  = 6.5 Hz, 2H), 2.91 (t,  $J$  = 7.5 Hz, 2H), 2.76 (t,  $J$  = 7.5 Hz, 2H), 2.59 (t,  $J$  = 7.0 Hz, 2H), 2.08 – 1.99 (m, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 209.0, 141.0, 128.7, 128.4, 126.3, 44.6, 44.6, 39.7, 29.9, 26.4; HRMS (EI<sup>+</sup>) [C<sub>12</sub>H<sub>15</sub>ClO] requires [M] 210.0811, found 210.0808.





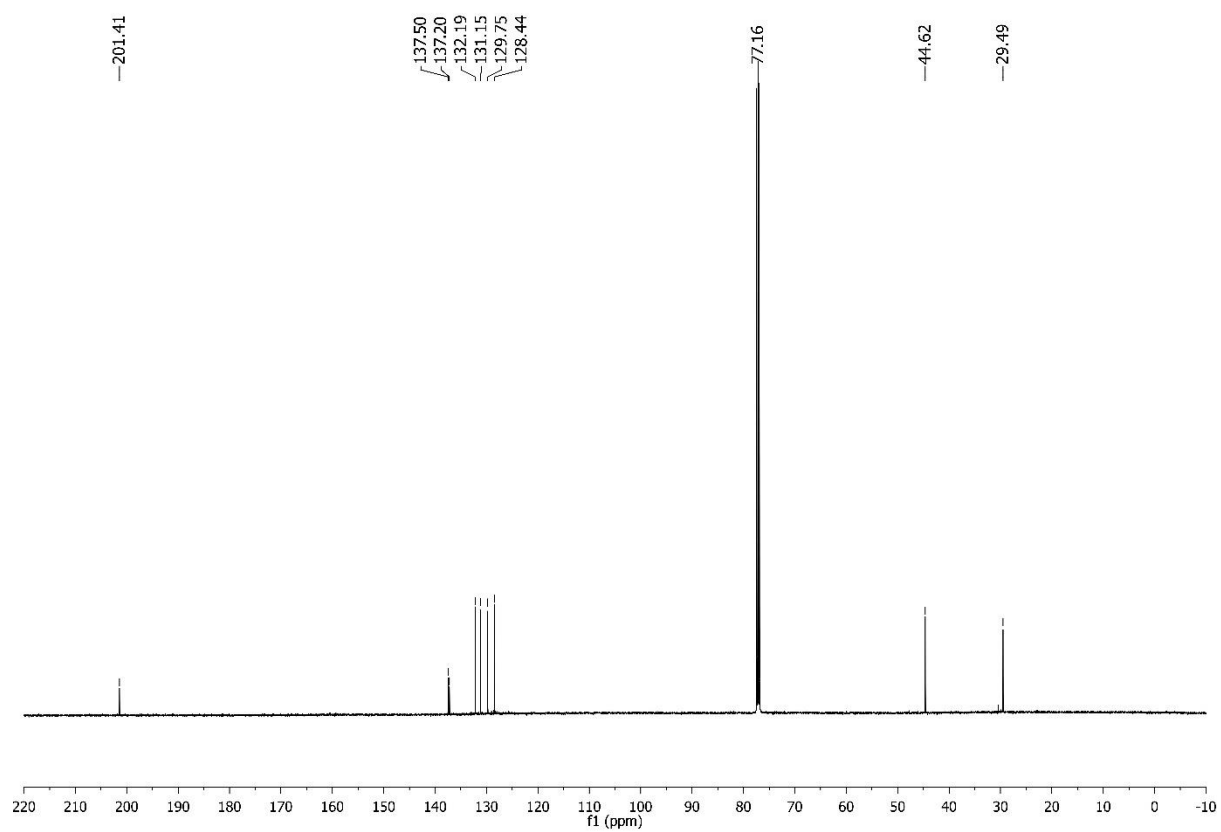
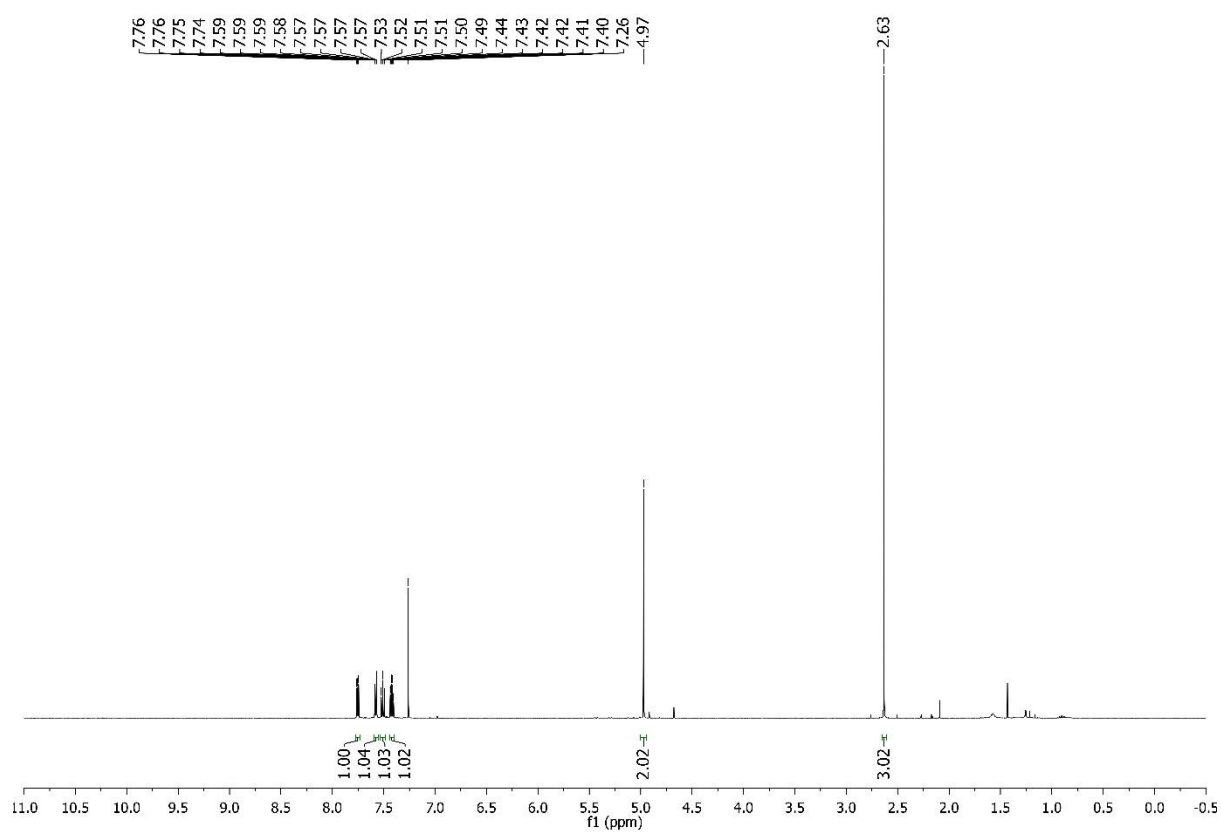


### 1-(2-(Chloromethyl)phenyl)ethan-1-one (**27**)

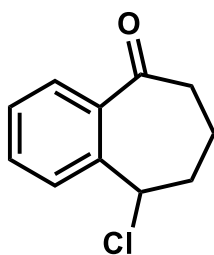


Prepared following General Procedure G using **S28** (40 mg), but electrolysis was run for 6 h instead of 3 h. For this example, the reaction mixture was washed with distilled water instead of sat.  $\text{NaHCO}_3$ . The crude residue was purified by flash column chromatography (10%  $\text{Et}_2\text{O}$ /Hexanes, silica gel) to afford **27** (15 mg, 30%) as a colourless oil.

$R_f$  = 0.33 (10%  $\text{Et}_2\text{O}$ /Petrol); **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 2967, 2930, 1680, 1572, 1356, 1250, 957, 756, 675;  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.75 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 7.58 (ddd,  $J$  = 7.5, 1.5, 0.5 Hz, 1H), 7.51 (td,  $J$  = 7.5, 1.5 Hz, 1H), 7.42 (td,  $J$  = 7.5, 1.5 Hz, 1H), 4.97 (s, 2H), 2.63 (s, 3H);  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 201.4, 137.5, 137.2, 132.2, 131.2, 129.8, 128.4, 44.6, 29.5; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_9\text{H}_9\text{OCl}$ ] requires  $[M]$  168.0342, found 168.0345.



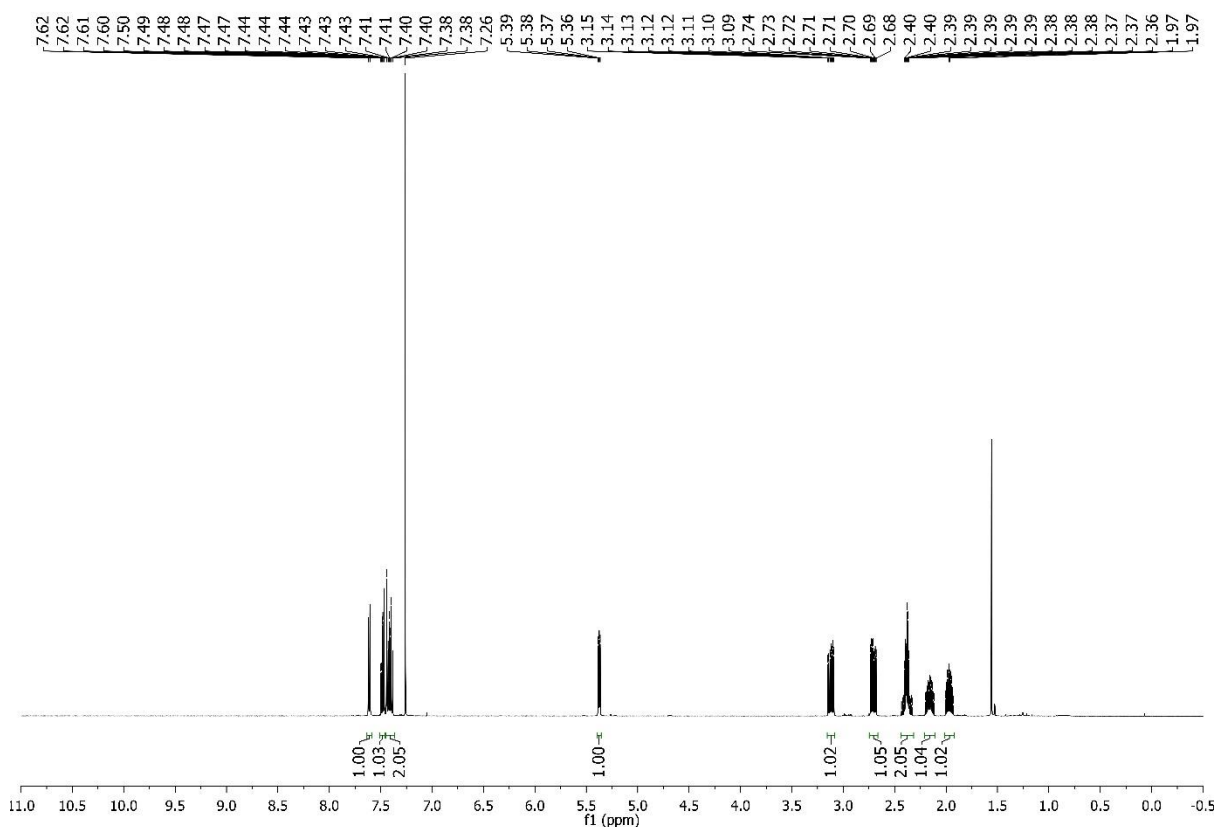
**9-Chloro-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (28)**

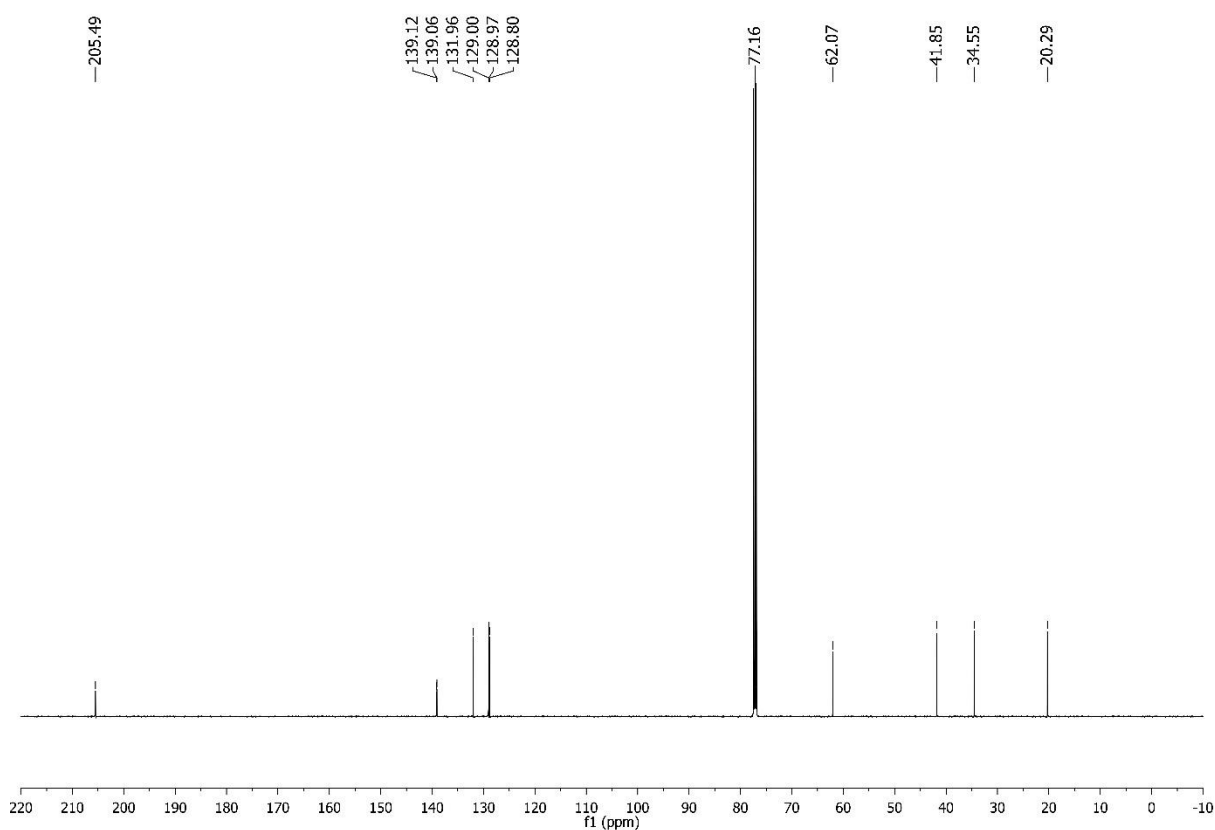


Prepared following General Procedure G using **S29** (48 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **28** (32 mg, 54%) as a colourless oil.

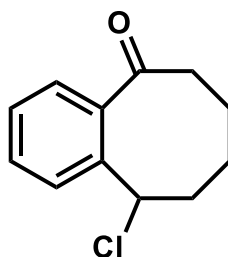
**R<sub>f</sub>** = 0.47 (10% EtOAc/Petrol); **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 7.64 – 7.58 (m, 1H), 7.52 – 7.36 (m, 3H), 5.40 – 5.35 (m, 1H), 3.17 – 3.07 (m, 1H), 2.76 – 2.66 (m, 1H), 2.45 – 2.31 (m, 2H), 2.22 – 2.10 (m, 1H), 2.02 – 1.91 (m, 1H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 205.5, 139.1, 139.1, 132.0, 129.0, 129.0, 128.8, 62.1, 41.9, 34.6, 20.3.

These data are consistent with those previously reported in the literature.<sup>[17]</sup>





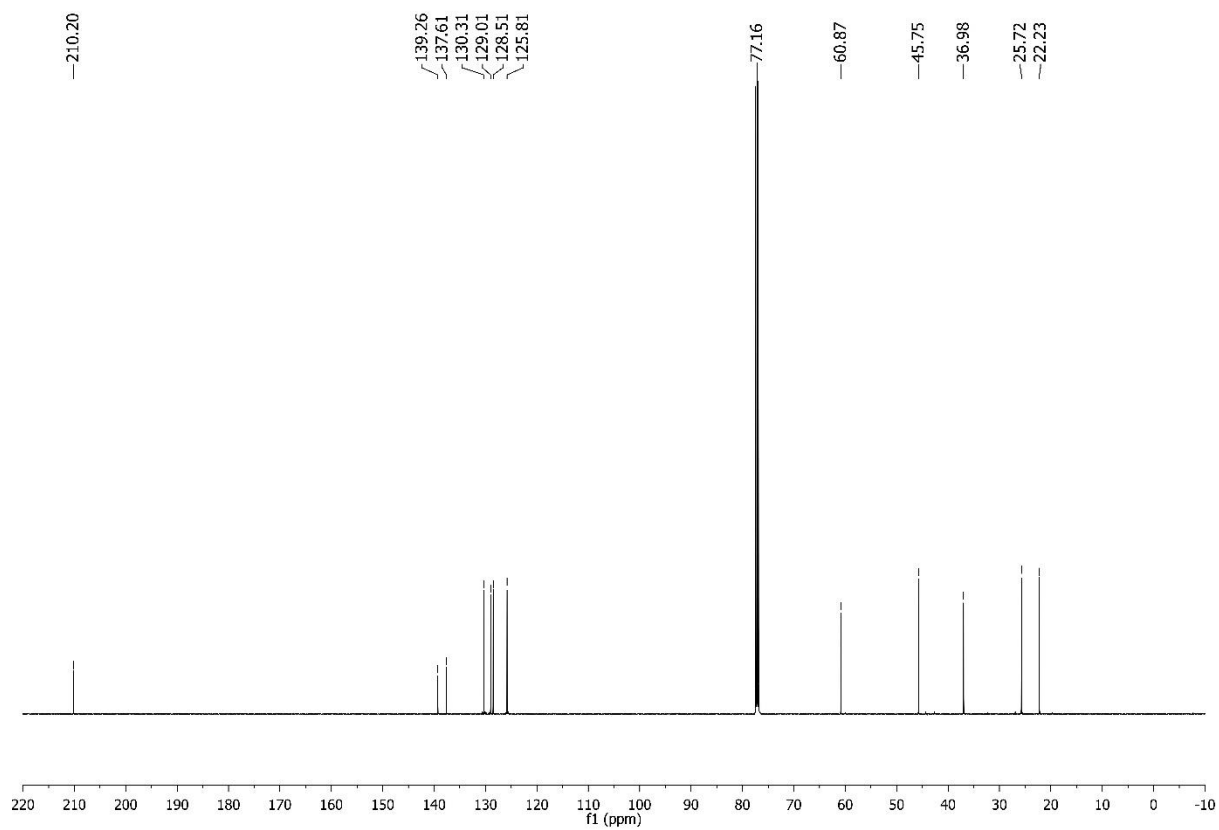
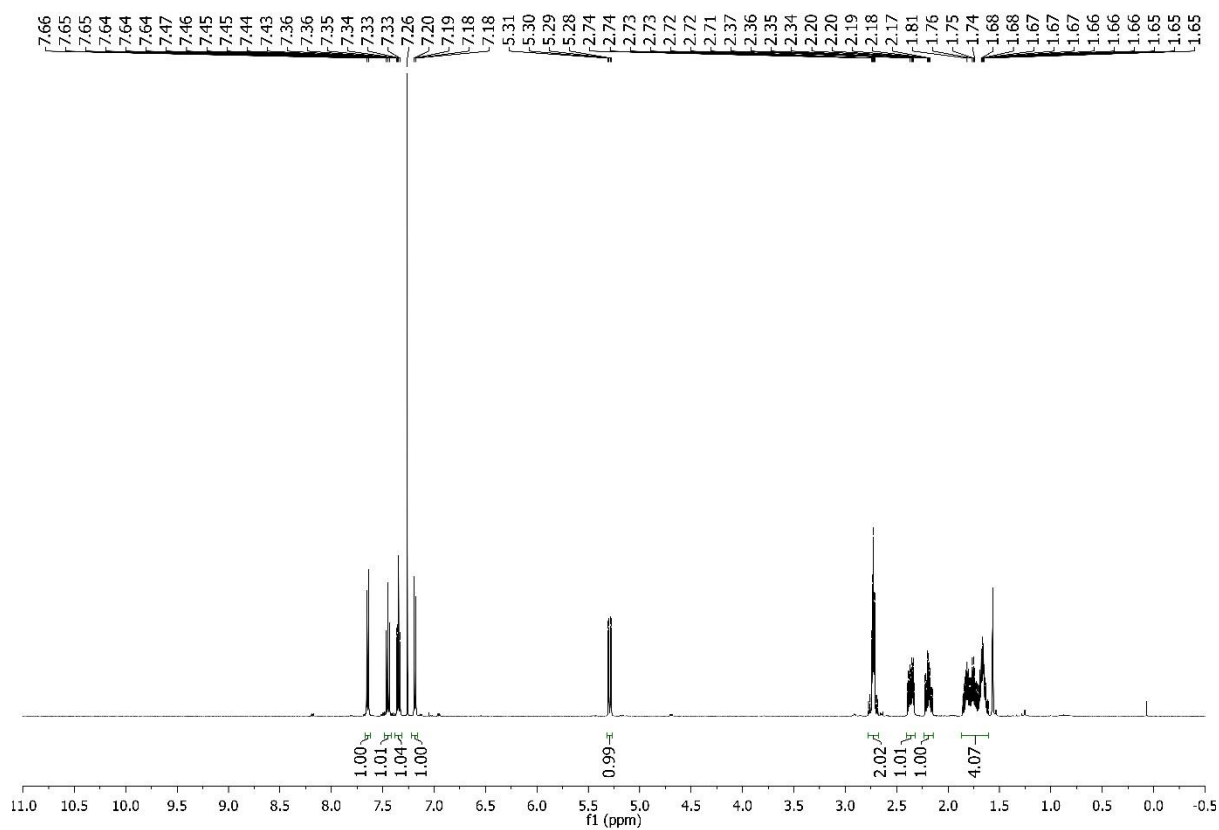
**10-Chloro-7,8,9,10-tetrahydrobenzo[8]annulen-5(6*H*)-one (29)**



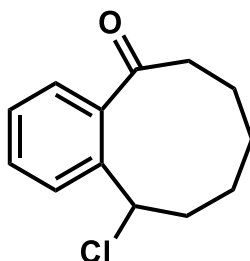
Prepared following General Procedure H using **S30** (52 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **29** (26 mg, 42%) as a colourless oil.

**R<sub>f</sub>** = 0.50 (10% EtOAc/Petrol); **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 7.68 – 7.62 (m, 1H), 7.48 – 7.41 (m, 1H), 7.38 – 7.31 (m, 1H), 7.21 – 7.16 (m, 1H), 5.29 (dd, *J* = 11.0, 4.0 Hz, 1H), 2.76 – 2.70 (m, 2H), 2.42 – 2.31 (m, 1H), 2.25 – 2.13 (m, 1H), 1.87 – 1.60 (m, 4H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 210.2, 139.3, 137.6, 130.3, 129.0, 128.5, 125.8, 60.9, 45.8, 37.0, 25.7, 22.2.

These data are consistent with those previously reported in the literature.<sup>[15]</sup>



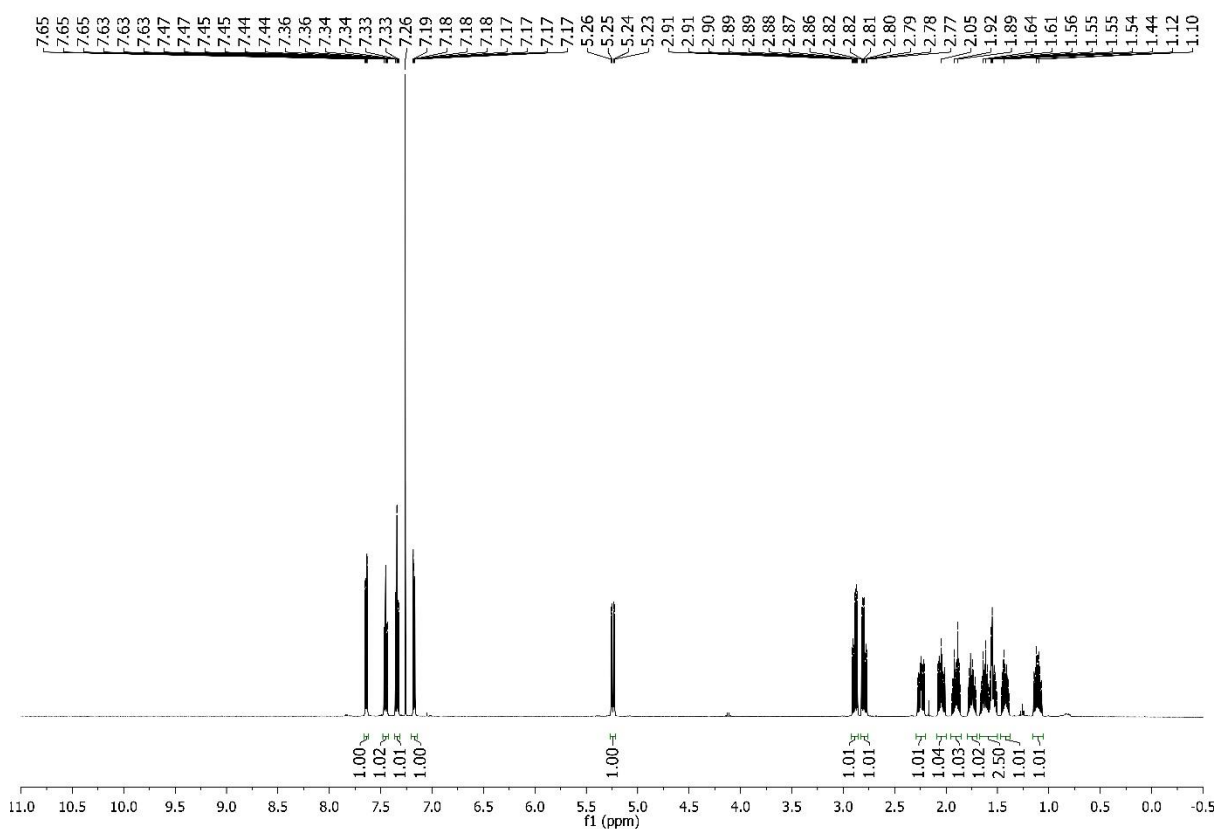
**11-chloro-6,7,8,9,10,11-hexahydro-5H-benzo[9]annulen-5-one (30)**

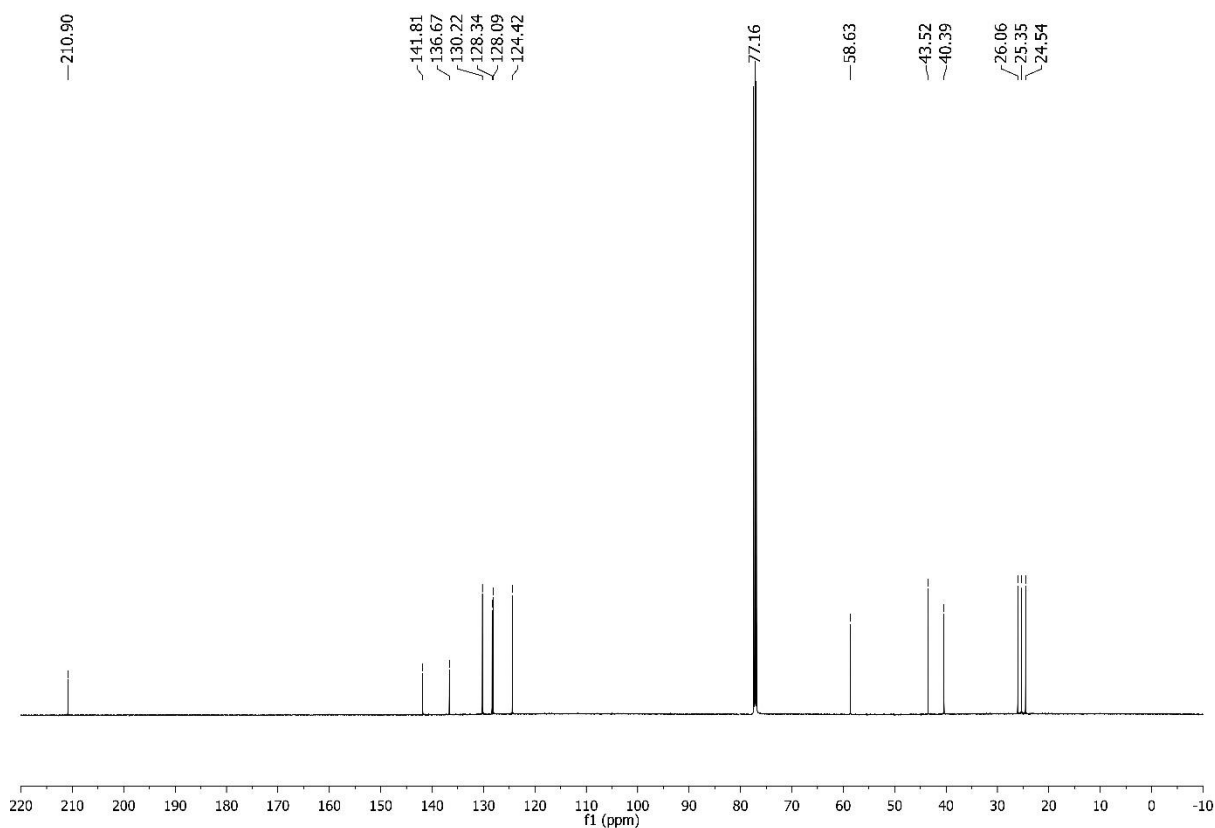


Prepared following General Procedure G using **S31** (57 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **30** (35 mg, 53%) as a yellow solid.

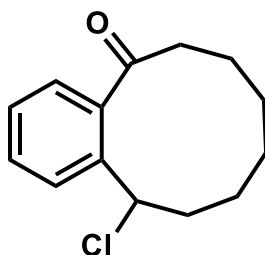
**R<sub>f</sub>** = 0.45 (10% EtOAc/Petrol); **M.p.:** 63-65 °C; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 7.67 – 7.61 (m, 1H), 7.49 – 7.42 (m, 1H), 7.38 – 7.31 (m, 1H), 7.20 – 7.14 (m, 1H), 5.24 (dd, *J* = 11.5, 5.0 Hz, 1H), 2.89 (ddd, *J* = 14.5, 8.5, 3.5 Hz, 1H), 2.80 (ddd, *J* = 14.5, 9.0, 4.0 Hz, 1H), 2.24 (dddd, *J* = 14.0, 11.5, 5.0, 4.0 Hz, 1H), 2.09 – 2.00 (m, 1H), 1.97 – 1.85 (m, 1H), 1.81 – 1.69 (m, 1H), 1.69 – 1.49 (m, 2H), 1.49 – 1.37 (m, 1H), 1.17 – 1.05 (m, 1H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 210.9, 141.8, 136.7, 130.2, 128.3, 128.1, 124.4, 58.6, 43.5, 40.4, 26.1, 25.4, 24.5.

These data are consistent with those previously reported in the literature.<sup>[17]</sup>





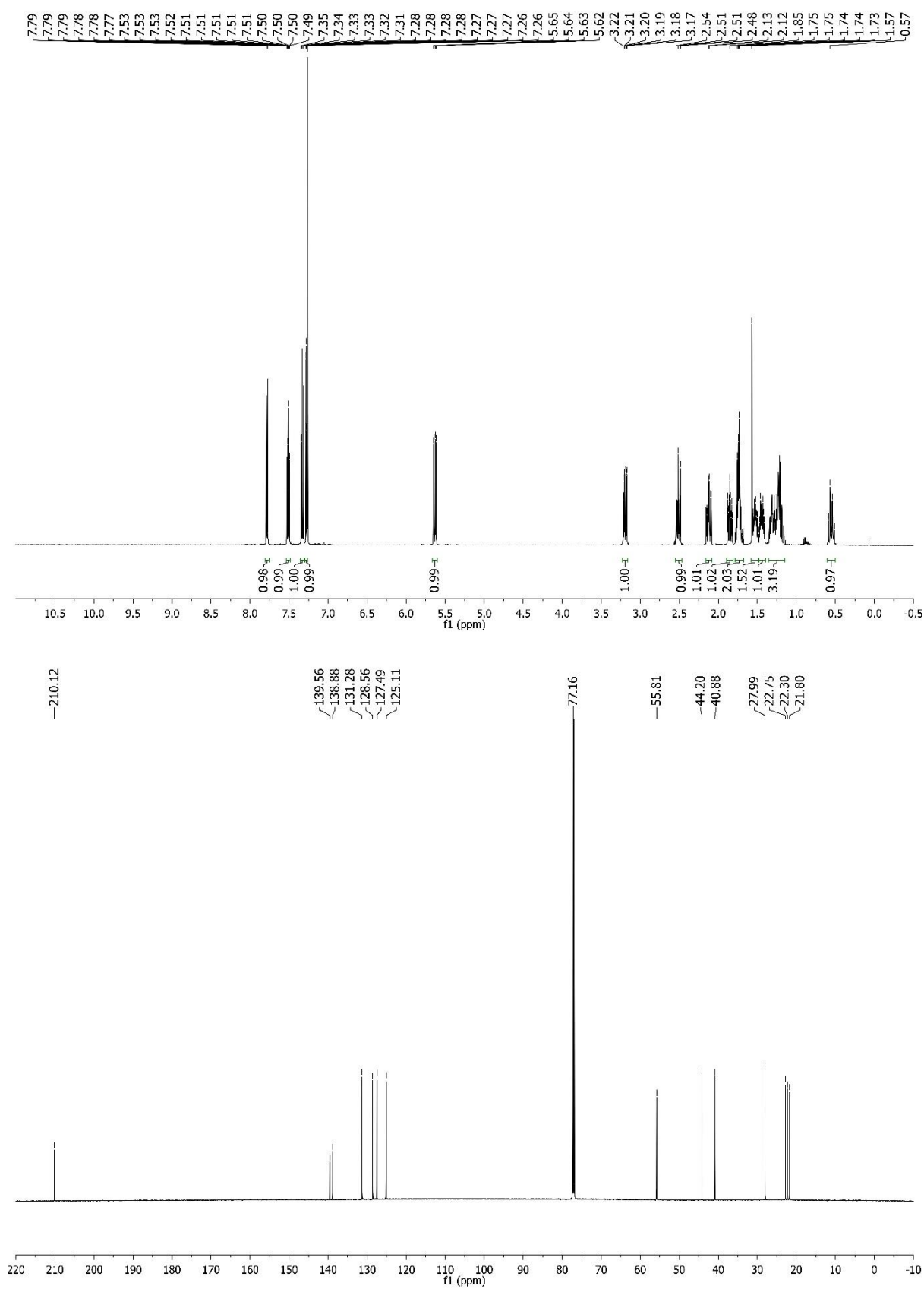
**12-chloro-7,8,9,10,11,12-hexahydrobenzo[10]annulen-5(6H)-one (31)**



Prepared following General Procedure G using **S32** (60 mg). The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **31** (36 mg, 51%) as a white solid.

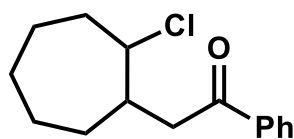
**R<sub>f</sub>** = 0.52 (10% EtOAc/Petrol); **M.p.:** 85-87 °C; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 7.81 – 7.74 (m, 1H), 7.55 – 7.47 (m, 1H), 7.37 – 7.24 (m, 2H), 5.63 (dd,  $J$  = 12.0, 5.0 Hz, 1H), 3.25 – 3.15 (m, 1H), 2.58 – 2.45 (m, 1H), 2.18 – 2.07 (m, 1H), 1.90 – 1.67 (m, 3H), 1.56 – 1.14 (m, 5H), 0.62 – 0.49 (m, 1H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 210.1, 139.6, 138.9, 131.3, 128.6, 127.5, 125.1, 55.8, 44.2, 40.9, 28.0, 22.8, 22.3, 21.8.

These data are consistent with those previously reported in the literature.<sup>[15]</sup>





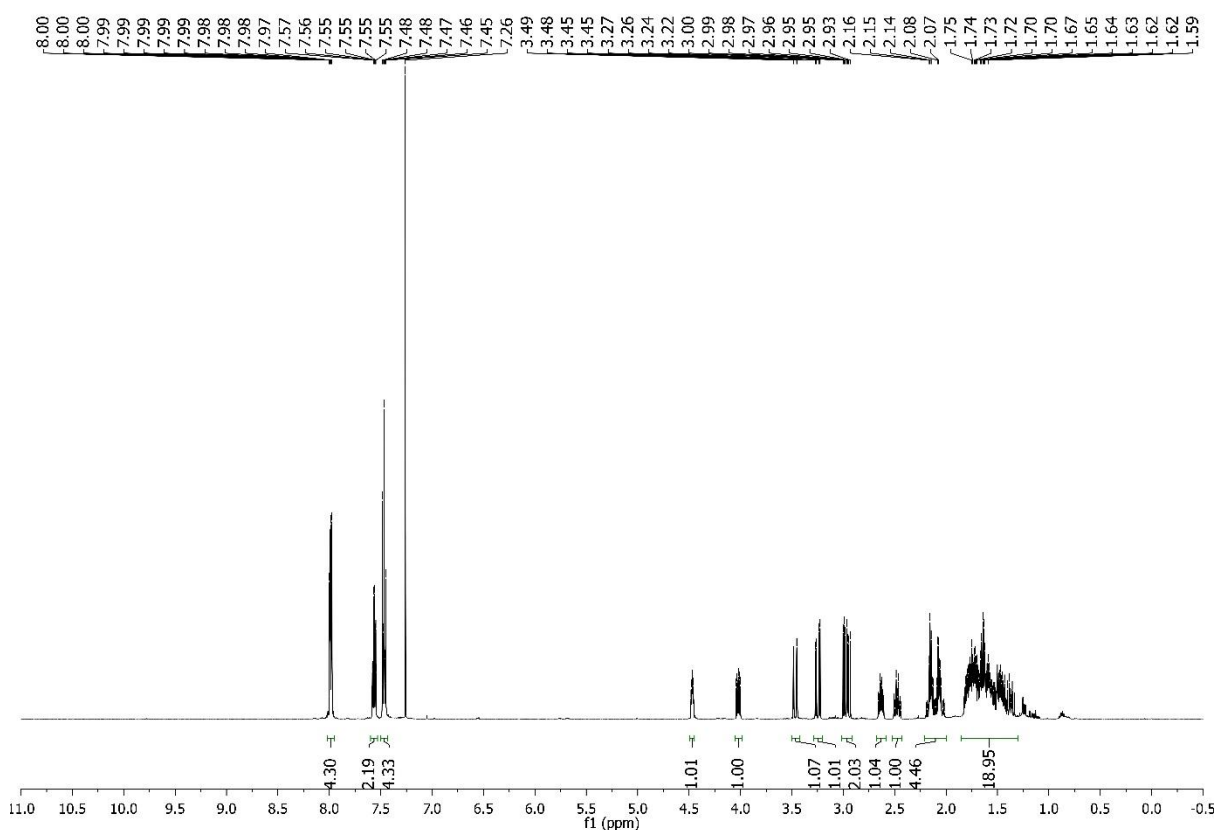
## 2-(2-Chlorocycloheptyl)-1-phenylethan-1-one (32)

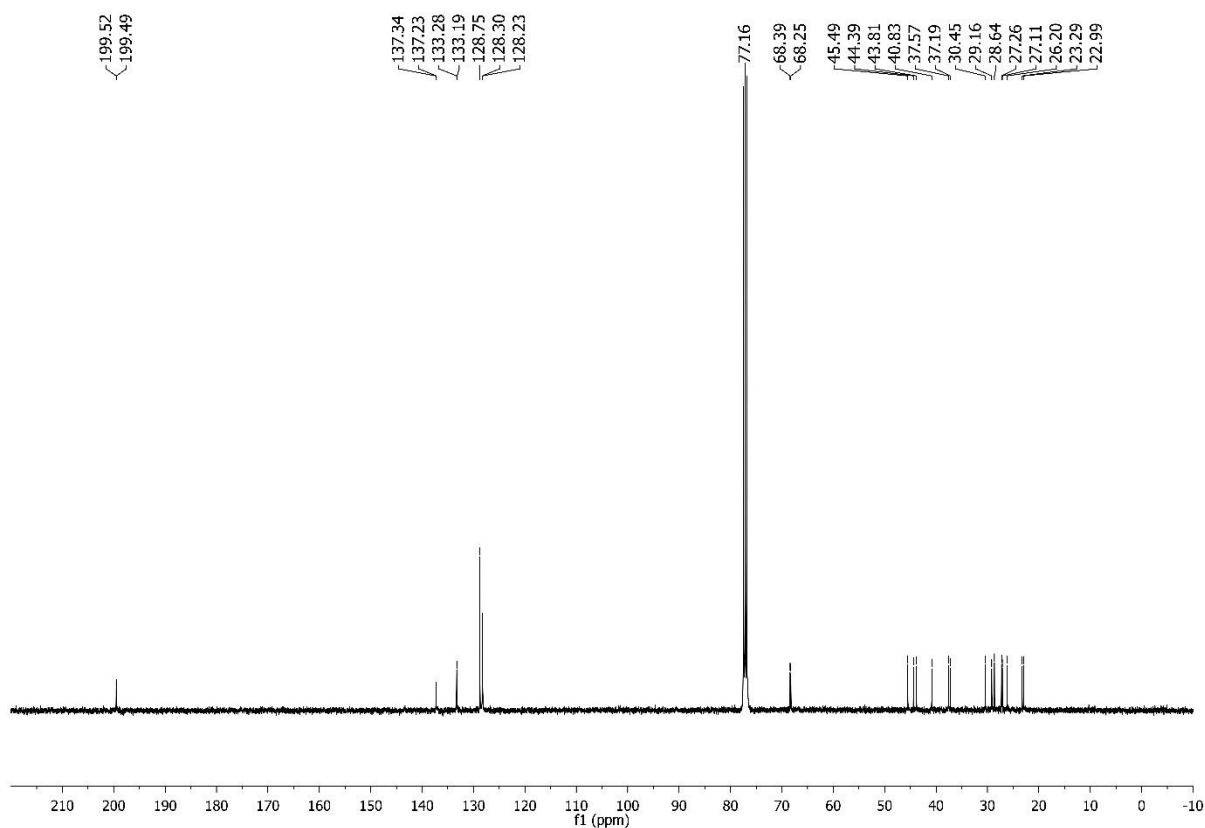


Prepared following General Procedure H using **S34** (65 mg). The crude residue was purified by flash column chromatography (4% Et<sub>2</sub>O/Pentane, silica gel) to afford **32** (58 mg, 77%) as a colourless oil. The compound was obtained as a 1:1 inseparable mixture of diastereoisomers.

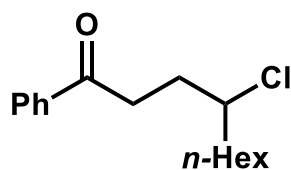
**R<sub>f</sub>** = 0.56 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 2929, 2862, 1683, 1598, 1579, 1450, 1361, 1282, 1211, 985, 752, 690; **HRMS** (ES<sup>+</sup>) [C<sub>15</sub>H<sub>19</sub>OCl] requires [M+H] 251.1203, found 251.1203.

*Data for both diastereoisomers:* **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 8.03 – 7.94 (m, 4H), 7.60 – 7.53 (m, 2H), 7.50 – 7.44 (m, 4H), 4.52 – 4.41 (m, 1H), 4.07 – 3.96 (m, 1H), 3.47 (dd,  $J$  = 16.5, 3.0 Hz, 1H), 3.25 (dd,  $J$  = 17.5, 6.5 Hz, 1H), 2.97 (ddd,  $J$  = 16.5, 11.0, 8.0 Hz, 2H), 2.69 – 2.58 (m, 1H), 2.54 – 2.42 (m, 1H), 2.21 – 2.00 (m, 4H), 1.86 – 1.31 (m, 16H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 199.5, 199.5, 137.3, 137.2, 133.3, 133.2, 128.8, 128.8, 128.3, 128.2, 68.4, 68.3, 45.5, 44.4, 43.8, 40.8, 37.6, 37.2, 30.5, 29.2, 28.6, 27.3, 27.1, 26.2, 23.3, 23.0.



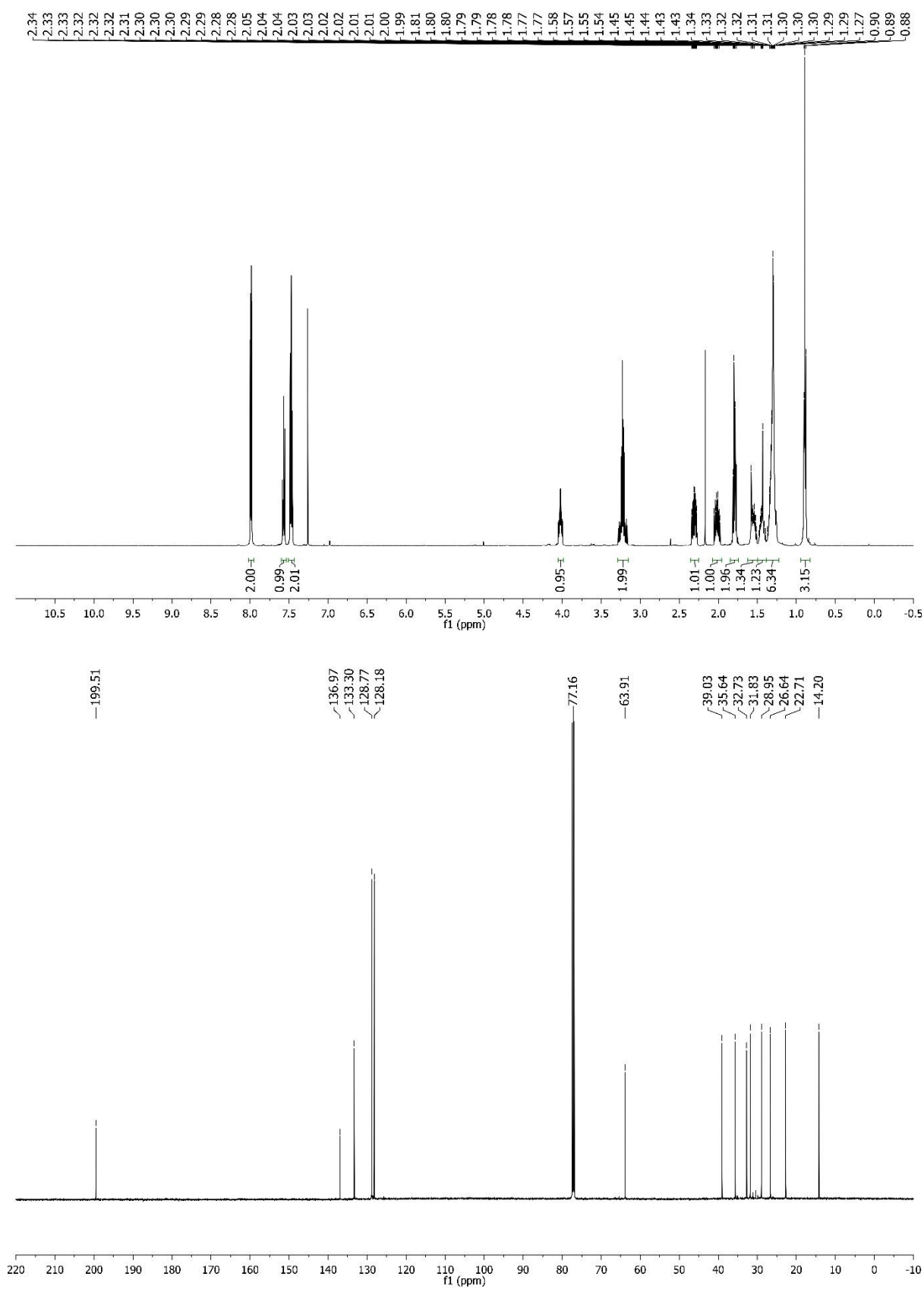


#### 4-Chloro-1-phenyldecan-1-one (**33**)

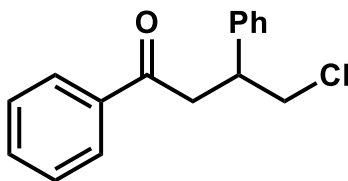


Prepared following General Procedure H using **S37** (70 mg). The crude residue was purified by flash column chromatography (2→4% Et<sub>2</sub>O/Petrol, silica gel) to afford **33** (46 mg, 57%) as a colourless oil.

$R_f$  = 0.50 (5% Et<sub>2</sub>O/Petrol); **FTIR** ( $\nu_{\max}$  cm<sup>-1</sup>, thin film) 2953, 2926, 2857, 2361, 1686, 1449, 1225, 1202, 689, 413; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.02 – 7.95 (m, 2H), 7.60 – 7.54 (m, 1H), 7.51 – 7.43 (m, 2H), 4.05 – 3.99 (m, 1H), 3.29 – 3.16 (m, 2H), 2.36 – 2.25 (m, 1H), 2.06 – 1.97 (m, 1H), 1.84 – 1.73 (m, 2H), 1.61 – 1.50 (m, 1H), 1.49 – 1.39 (m, 1H), 1.38 – 1.23 (m, 6H), 0.89 (t,  $J$  = 7.0 Hz, 3H); **<sup>13</sup>C NMR** (126 Hz, CDCl<sub>3</sub>)  $\delta$  = 199.5, 137.0, 133.3, 128.8, 128.2, 63.9, 39.0, 35.6, 32.7, 31.8, 29.0, 26.6, 22.7, 14.2; **HRMS** (EI<sup>+</sup>) [C<sub>16</sub>H<sub>23</sub>ClO] requires [M-Cl] 231.1749, found 231.1758.



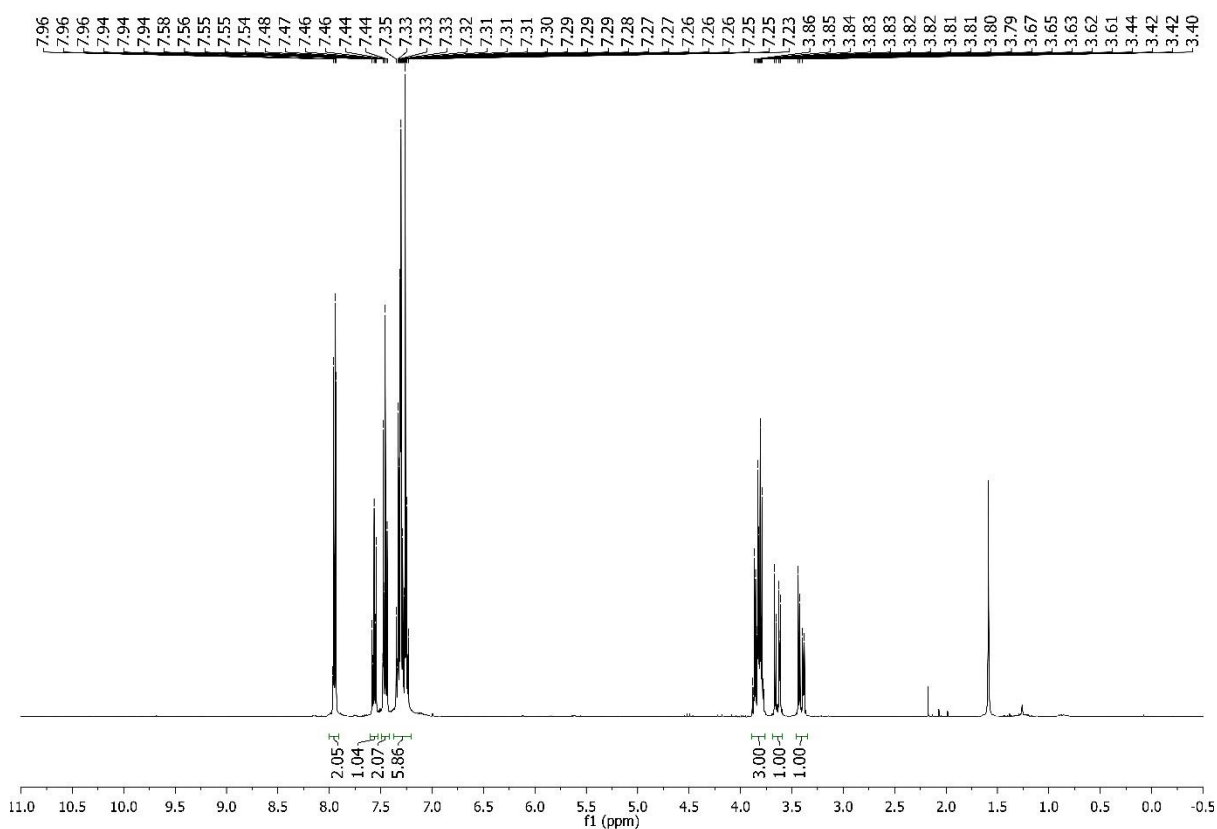
#### 4-Chloro-1,3-diphenylbutan-1-one (34)

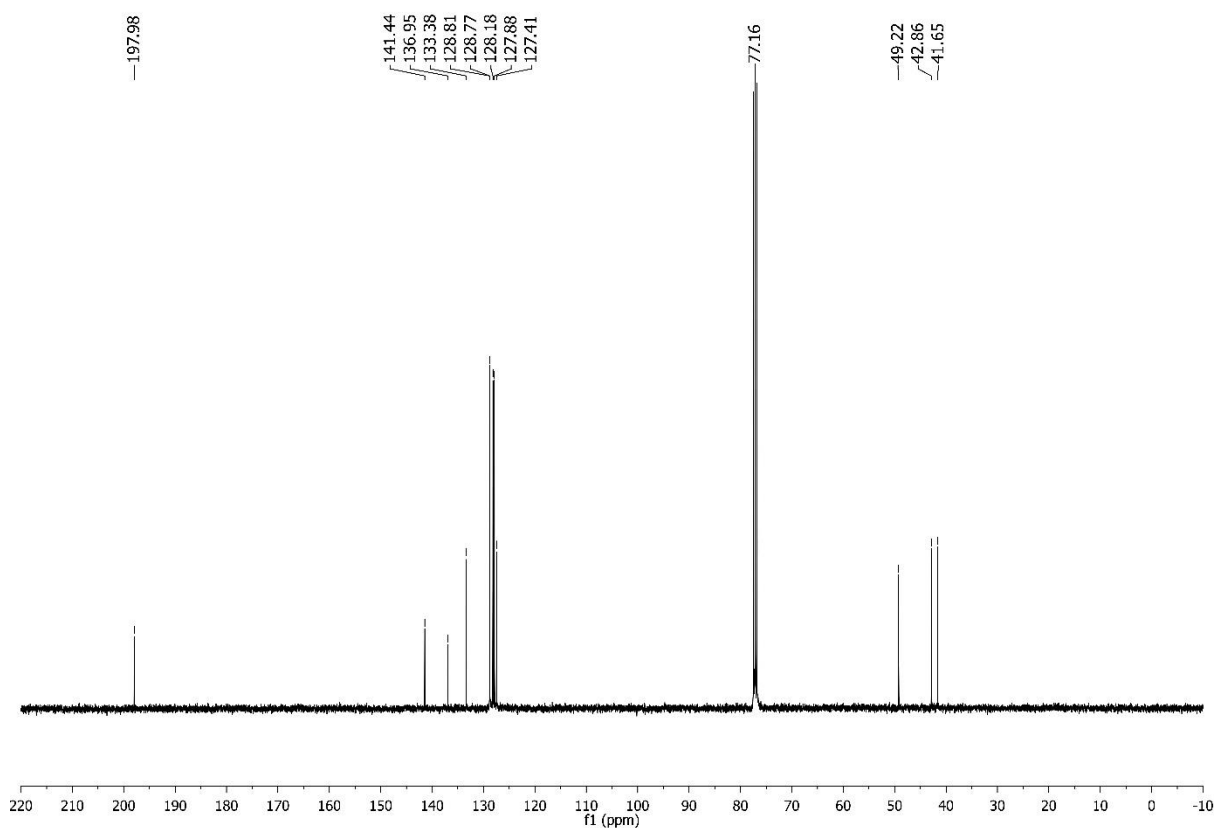


Prepared following General Procedure G using **S39** (67 mg). The crude residue was purified by flash column chromatography (5% EtOAc/Petrol, silica gel) to afford **34** (70 mg, 90%) as a white solid.

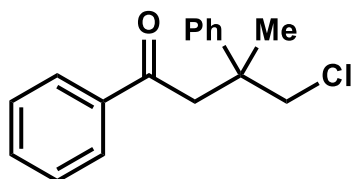
$R_f$  = 0.36 (10% EtOAc/Petrol); **M.p.**: 80-82 °C (lit.<sup>[15]</sup> 74-75 °C);  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 7.99 – 7.90 (m, 2H), 7.60 – 7.53 (m, 1H), 7.50 – 7.41 (m, 2H), 7.37 – 7.20 (m, 5H), 3.90 – 3.75 (m, 3H), 3.69 – 3.59 (m, 1H), 3.47 – 3.35 (m, 1H);  **$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 198.0, 141.4, 137.0, 133.4, 128.8, 128.8, 128.2, 127.9, 127.4, 49.2, 42.9, 41.7.

These data are consistent with those reported in the literature.<sup>[18]</sup>Error! Bookmark not defined.





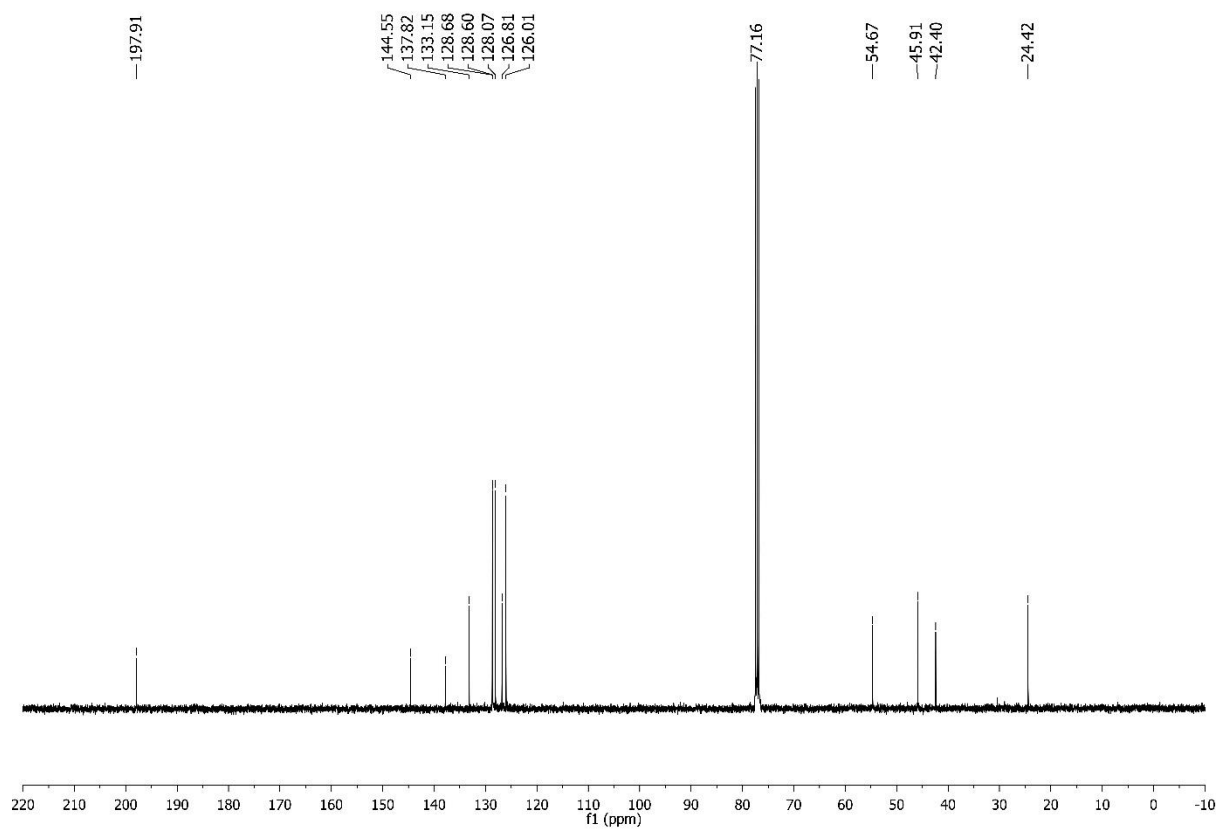
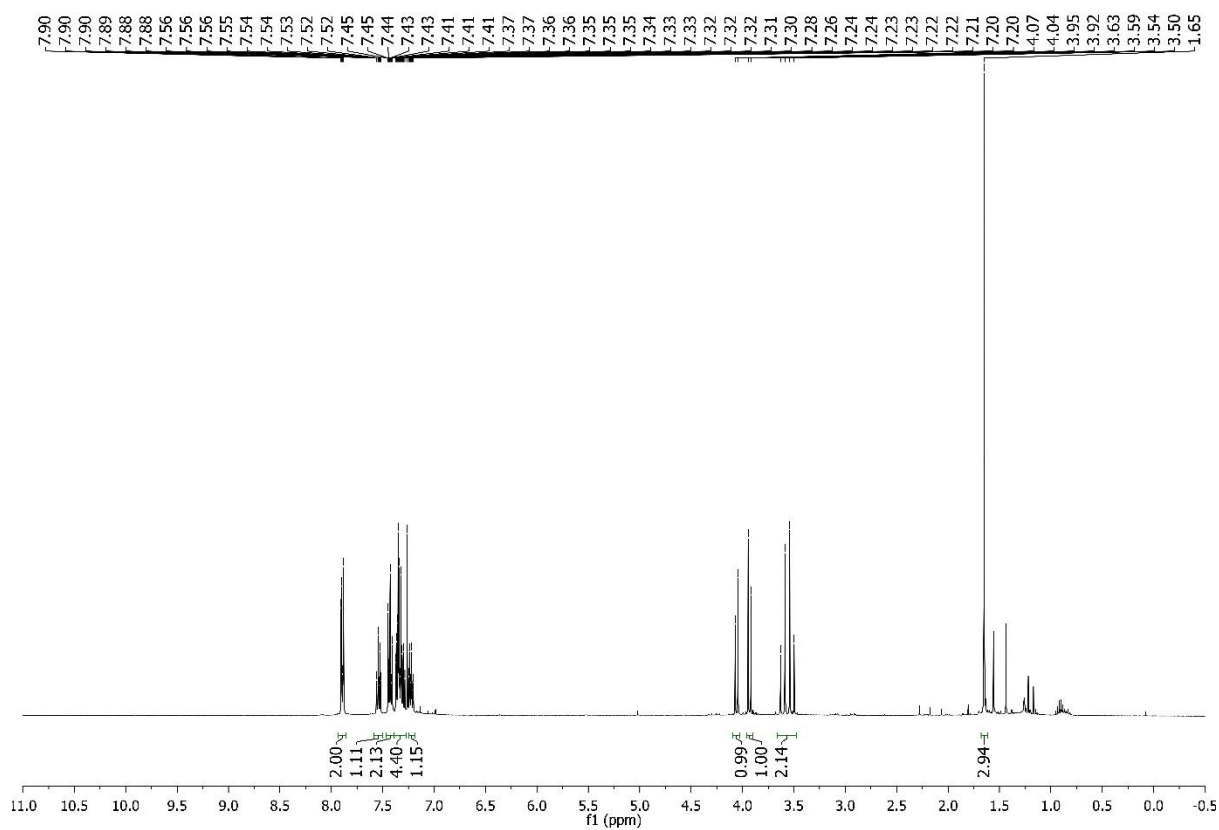
#### 4-Chloro-3-methyl-1,3-diphenylbutan-1-one (**35**)



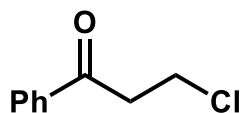
Prepared following General Procedure G using **S41** (56 mg, 0.235 mmol),  $\text{Mn}(\text{OTf})_2$  (8 mg, 0.024 mmol),  $\text{MgCl}_2$  (112 mg, 1.175 mmol),  $\text{LiClO}_4$  (50 mg, 0.470 mmol), MeCN (4.1 mL) and AcOH (0.6 mL). The crude residue was purified by flash column chromatography (5→10% EtOAc/Petrol, silica gel) to afford **35** (37 mg, 58%) as a colourless oil.

$R_f$  = 0.43 (10% EtOAc/Petrol);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.92 – 7.86 (m, 2H), 7.58 – 7.50 (m, 1H), 7.47 – 7.39 (m, 2H), 7.39 – 7.28 (m, 4H), 7.25 – 7.19 (m, 1H), 4.06 (d,  $J$  = 11.0 Hz, 1H), 3.93 (d,  $J$  = 11.0 Hz, 1H), 3.61 (d,  $J$  = 17.0 Hz, 1H), 3.52 (d,  $J$  = 17.0 Hz, 1H), 1.65 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 197.9, 144.6, 137.8, 133.2, 128.7, 128.6, 128.1, 126.8, 126.0, 54.7, 45.9, 42.4, 24.4.

These data are consistent with those previously reported in the literature.<sup>[15]</sup>



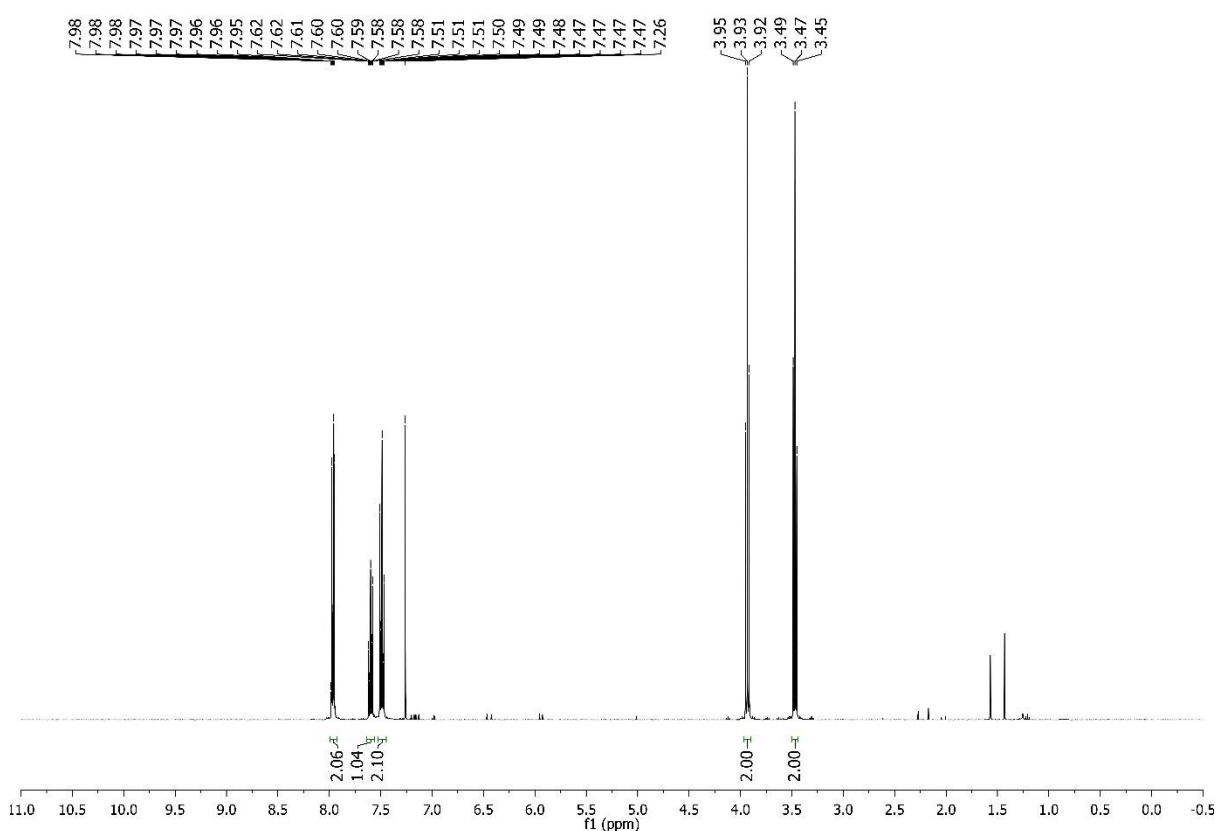
### 3-Chloro-1-phenylpropan-1-one (36)

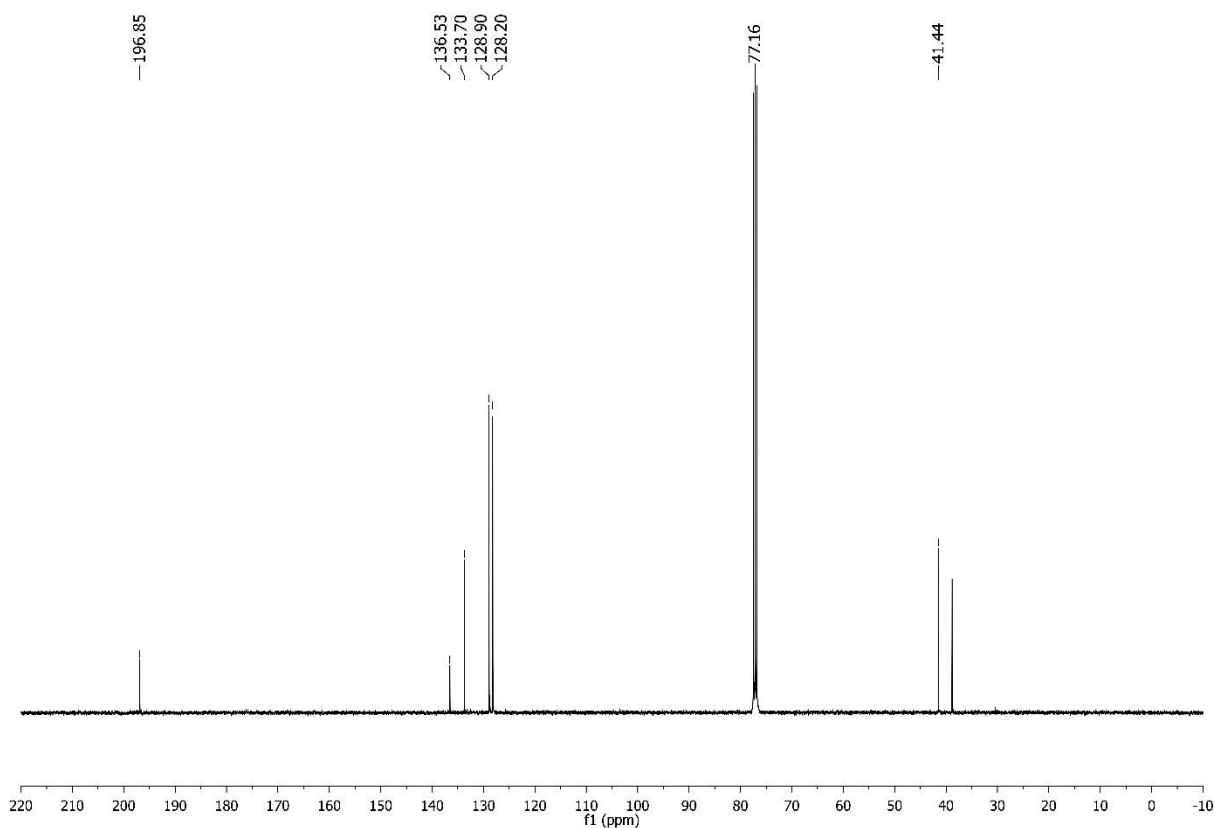


Prepared following General Procedure H using **S42** (40 mg). For this example, the reaction mixture was washed with distilled water instead of sat. NaHCO<sub>3</sub>. The crude residue was purified by flash column chromatography (5% Et<sub>2</sub>O/Pentane, silica gel) to afford **36** (27 mg, 54%) as a colourless oil.

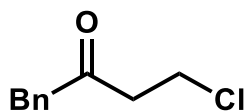
$R_f$  = 0.69 (10% EtOAc/Petrol); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.00 – 7.93 (m, 2H), 7.63-7.57 (m, 1H), 7.52 – 7.45 (m, 2H), 3.93 (t,  $J$  = 7.0 Hz, 2H), 3.47 (t,  $J$  = 7.0 Hz, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 196.7, 136.5, 133.7, 128.9, 128.2, 41.4, 38.8.

These data are consistent with those previously reported in the literature.<sup>[19]</sup>





#### 4-Chloro-1-phenylbutan-2-one (**37**)

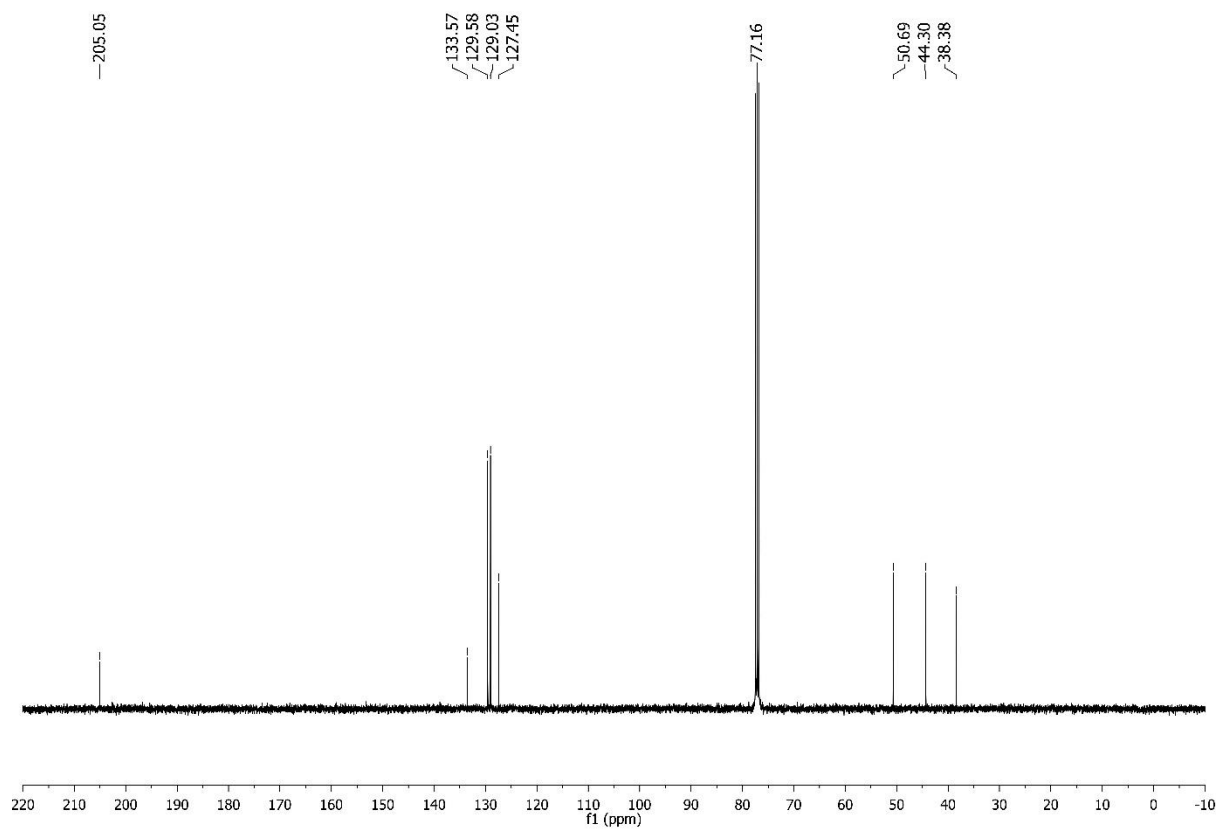
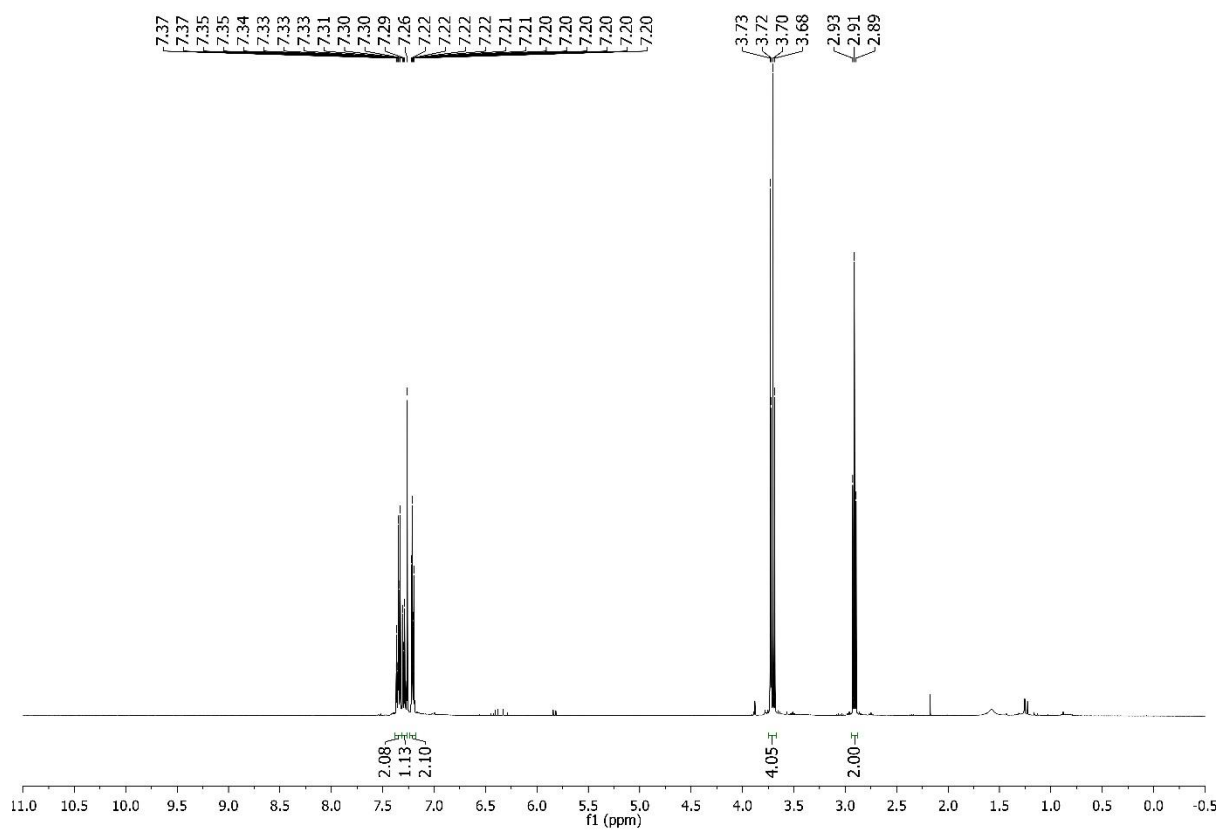


Prepared following General Procedure H using **S43** (44 mg). For this example, the reaction mixture was washed with distilled water instead of sat.  $\text{NaHCO}_3$ . The crude residue was purified by flash column chromatography (10%  $\text{Et}_2\text{O}$ /Petrol, silica gel) to afford **37** (26 mg, 47%) as a colourless oil.

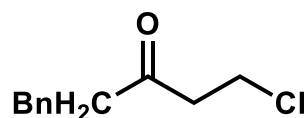
$R_f$  = 0.25 (10%  $\text{Et}_2\text{O}$ /Petrol);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.38 – 7.26 (m, 3H), 7.23 – 7.18 (m, 2H), 3.73 (s, 2H), 3.70 (t,  $J$  = 6.5 Hz, 2H), 2.91 (t,  $J$  = 6.5 Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 205.2, 133.6, 129.6, 129.0, 127.5, 50.7, 44.3, 38.4.

These data are consistent with those previously reported in the literature.<sup>[19]</sup>





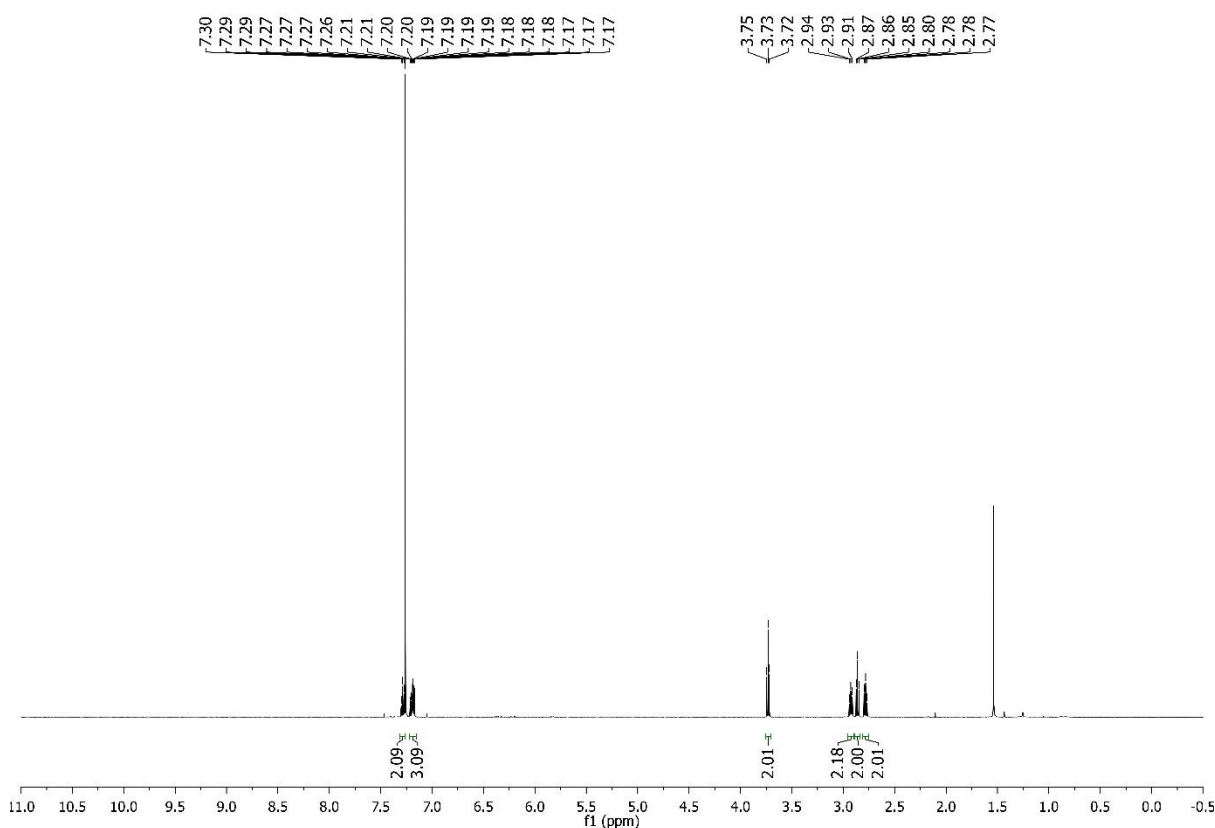
### 1-Chloro-5-phenylpentan-3-one (**38**)

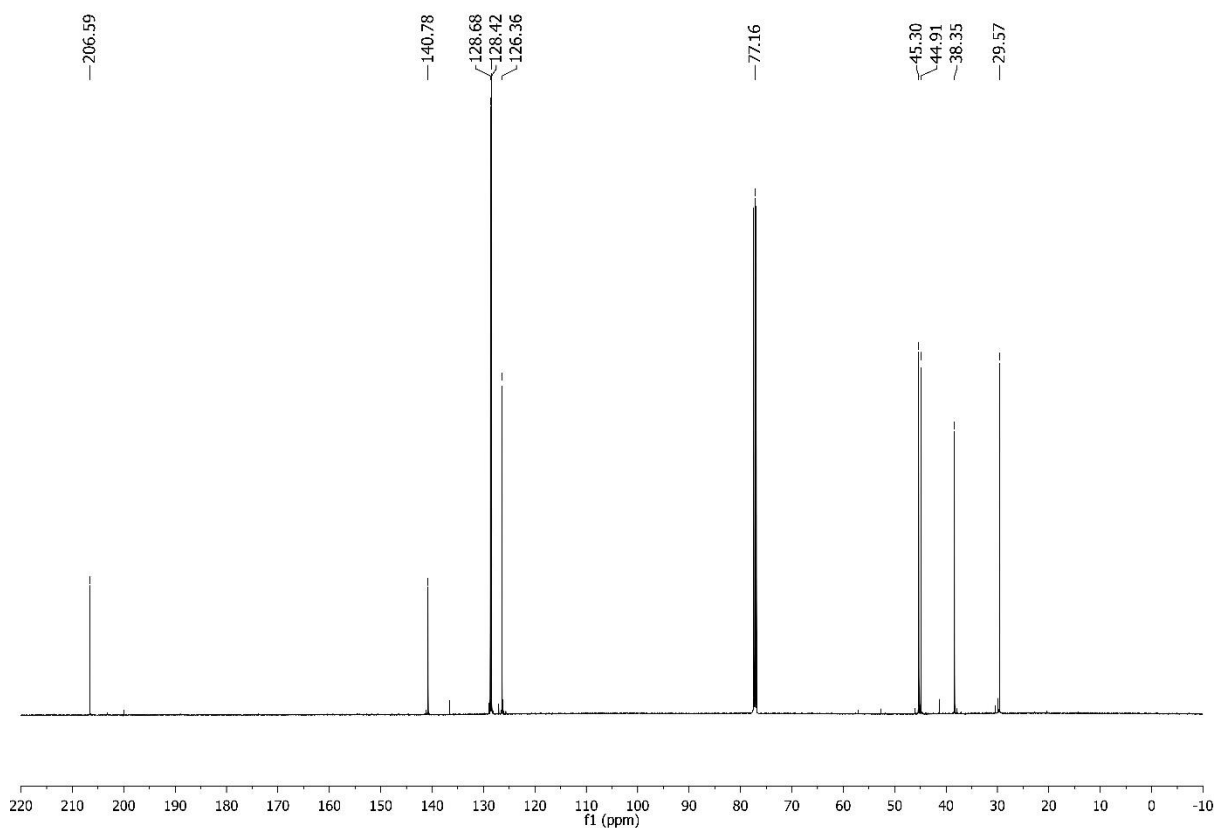


Prepared according to General Procedure H using **S45** (49 mg). For this example, the reaction mixture was washed with distilled water instead of sat.  $\text{NaHCO}_3$ . The crude residue was purified by flash column chromatography (10%  $\text{Et}_2\text{O}$ /Pentane, silica gel) to afford **38** (39 mg, 67%) as a colourless oil.

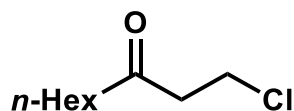
$R_f$  = 0.21 (10%  $\text{EtOAc}$ /Petrol),  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.32 – 7.27 (m, 2H), 7.22 – 7.17 (m, 3H), 3.73 (t,  $J$  = 6.5 Hz, 2H), 2.93 (t,  $J$  = 7.5 Hz, 2H), 2.86 (t,  $J$  = 6.5 Hz, 2H), 2.78 (t,  $J$  = 7.5 Hz, 2H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 206.6, 140.8, 128.7, 128.4, 126.4, 45.3, 44.9, 38.4, 29.6.

These data are in agreement with those previously reported in the literature.<sup>[15]</sup>



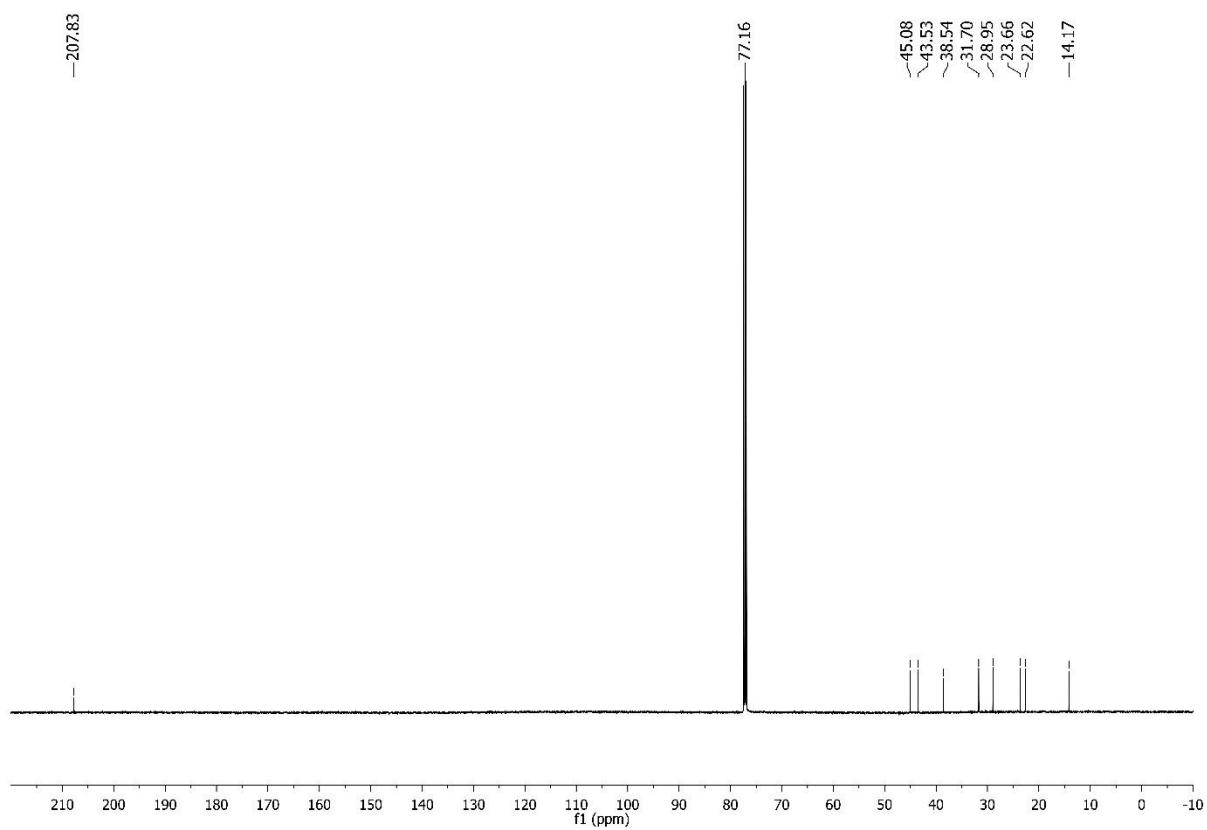
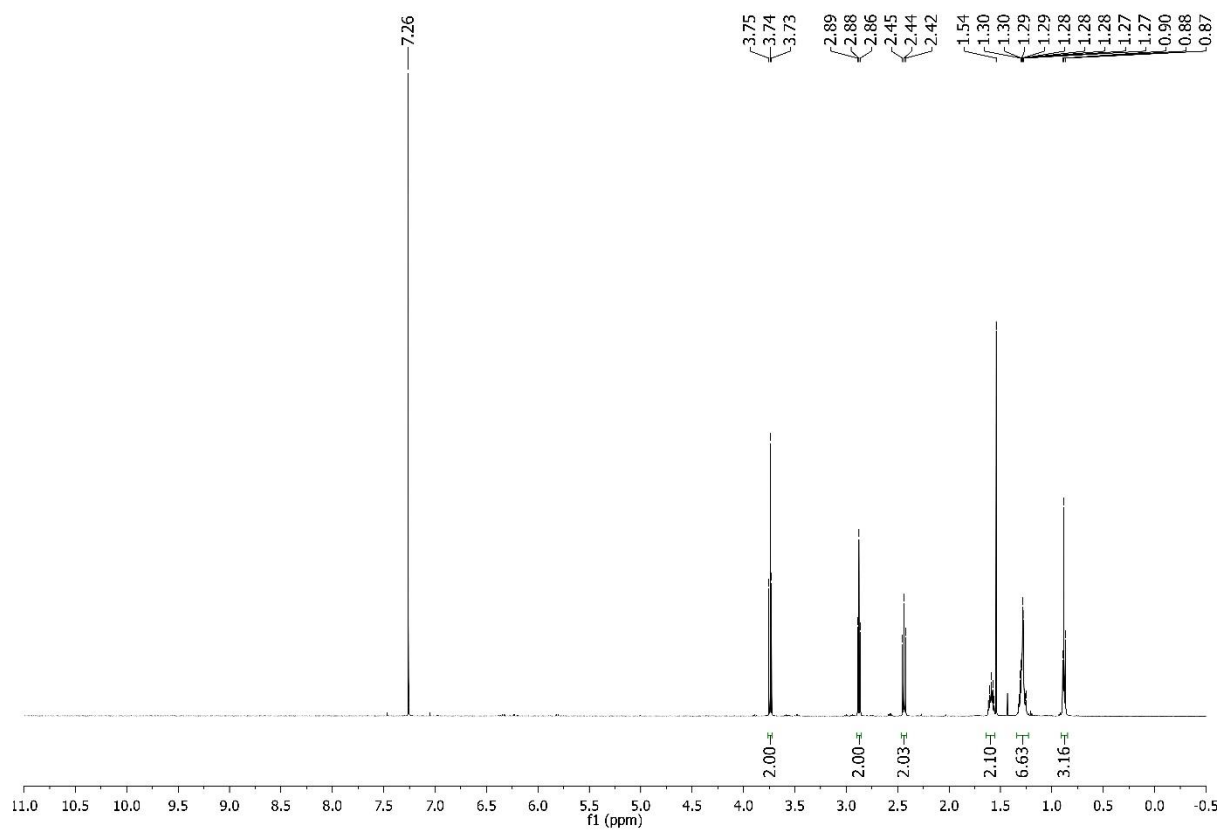


### 1-Chlorononan-3-one (39)

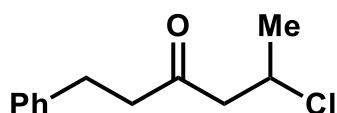


Prepared according to General Procedure H using **S47** (43 mg). For this example, the reaction mixture was washed with distilled water instead of sat. NaHCO<sub>3</sub>. The crude residue was purified by flash column chromatography (10% Et<sub>2</sub>O/Pentane, silica gel) to afford **39** (35 mg, 66%) as a colourless oil.

**R<sub>f</sub>** = 0.34 (10% EtOAc/Petrol); **FTIR** ( $\nu_{\max}$  cm<sup>-1</sup>, thin film) 1717, 1456, 1368, 1216, 1078, 718, 656; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  = 3.74 (t, *J* = 6.5 Hz, 2H), 2.88 (t, *J* = 6.5 Hz, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 1.62 – 1.56 (m, 2H), 1.35 – 1.24 (m, 6H), 0.90 – 0.86 (m, 3H); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta$  = 207.8, 45.1, 43.5, 38.5, 31.7, 29.0, 23.7, 22.6, 14.2; **HRMS** (EI<sup>+</sup>) [C<sub>9</sub>H<sub>17</sub>OCl] requires [M] 176.0968, found 176.0975.



### 5-Chloro-1-phenylhexan-3-one (40)

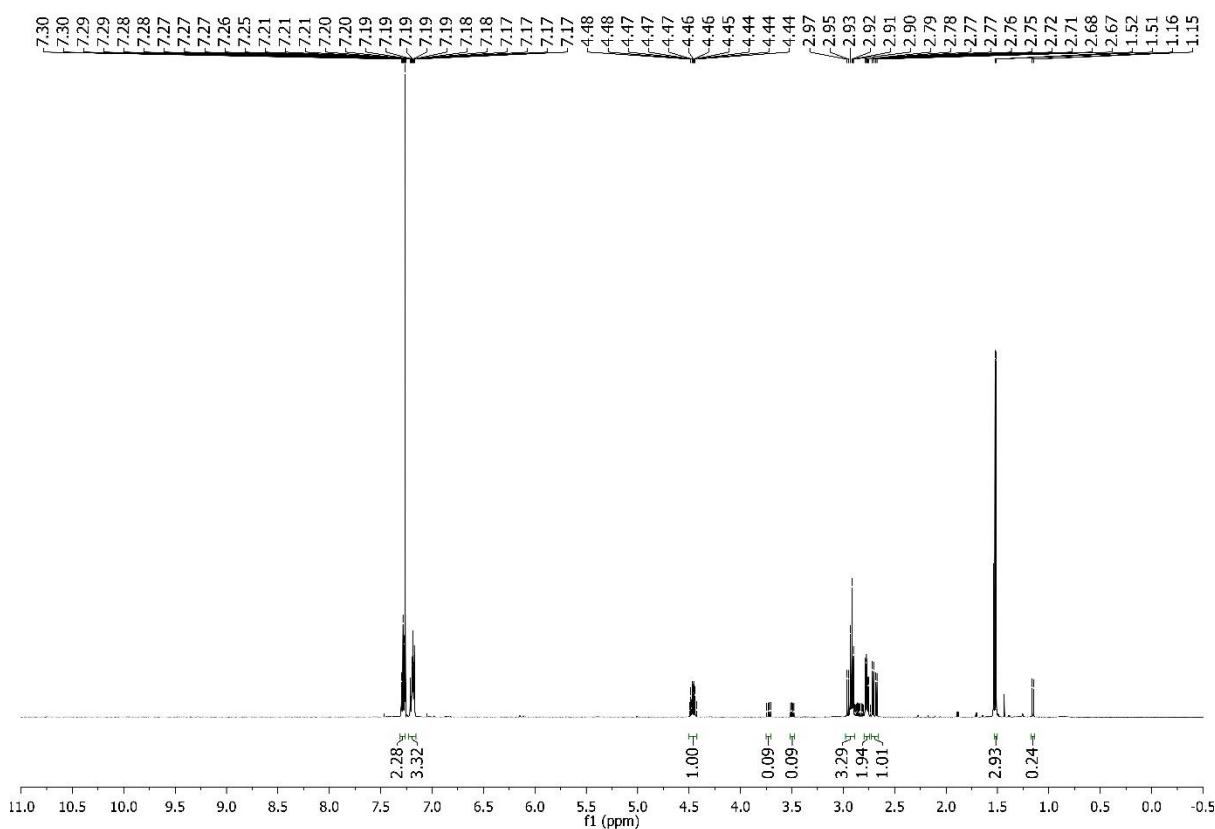


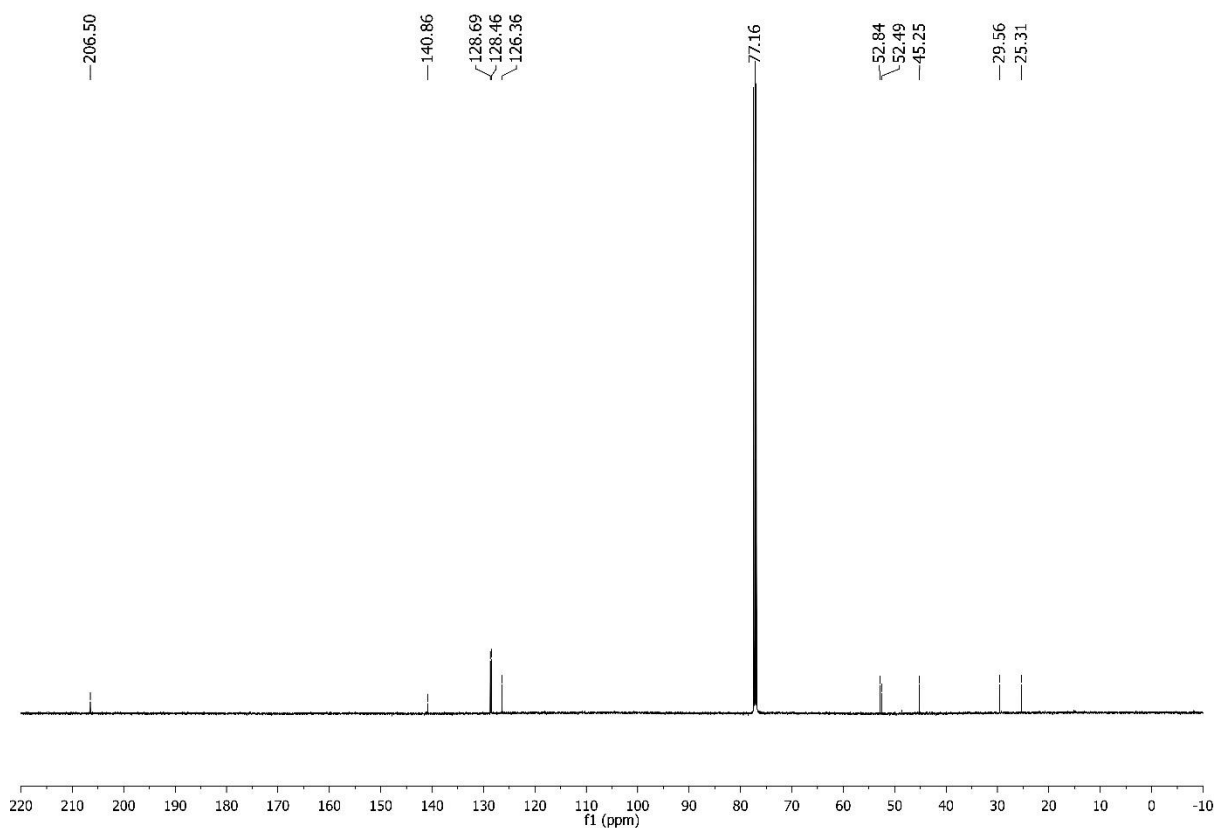
Prepared according to General Procedure H using **S48** (53 mg). For this example, the reaction mixture was washed with distilled water instead of sat.  $\text{NaHCO}_3$ . The crude residue was purified by flash column chromatography (10%  $\text{Et}_2\text{O}$ /Pentane, silica gel) to afford **40** (44 mg, 70%) as a colourless oil. This compound was obtained as a 93:7 inseparable mixture of regioisomers.

$R_f$  = 0.29 (10%  $\text{EtOAc}$ /Petrol); **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 2934, 1713, 1498, 1452, 1406, 1375, 1128, 1028, 989, 750, 698, 613; **HRMS** ( $\text{EI}^+$ ) [ $\text{C}_{12}\text{H}_{15}\text{OCl}$ ] requires  $[M]$  210.0811, found 210.0815.

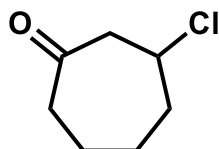
*Data for major regioisomer:*  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.30 – 7.26 (m, 2H), 7.22 – 7.17 (m, 3H), 4.46 (dq,  $J$  = 7.5, 6.5, 5.5, 1H), 2.99 – 2.88 (m, 3H), 2.81 – 2.73 (m, 2H), 2.69 (dd,  $J$  = 17.0, 5.5, 1H), 1.52 (d,  $J$  = 6.5, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 206.5, 140.9, 128.7, 128.5, 126.4, 52.8, 52.5, 45.3, 29.6, 25.3.

*Data for minor regioisomer:*  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) (selected)  $\delta$  = 3.73 (dd,  $J$  = 11.0, 7.5, 1H), 3.50 (dd,  $J$  = 11.0, 6.0, 1H), 1.15 (d,  $J$  = 7.0, 3H).



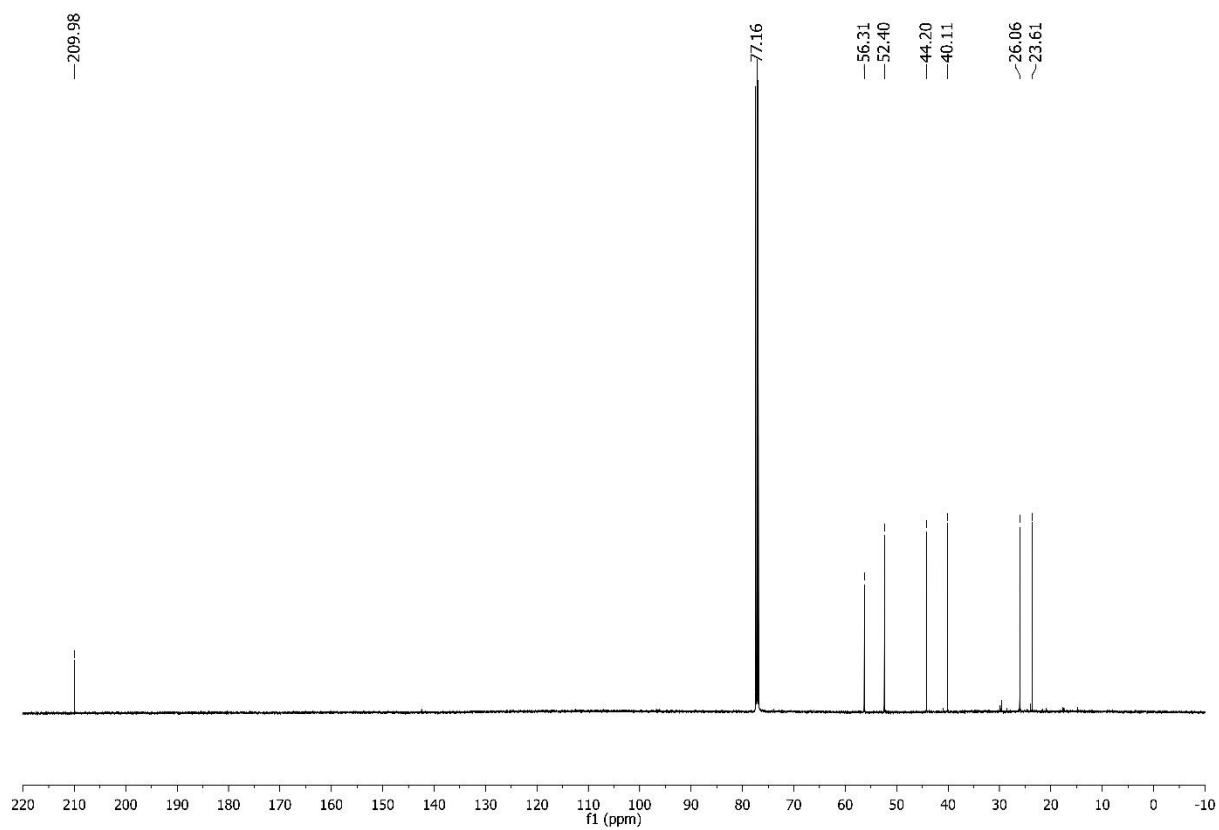
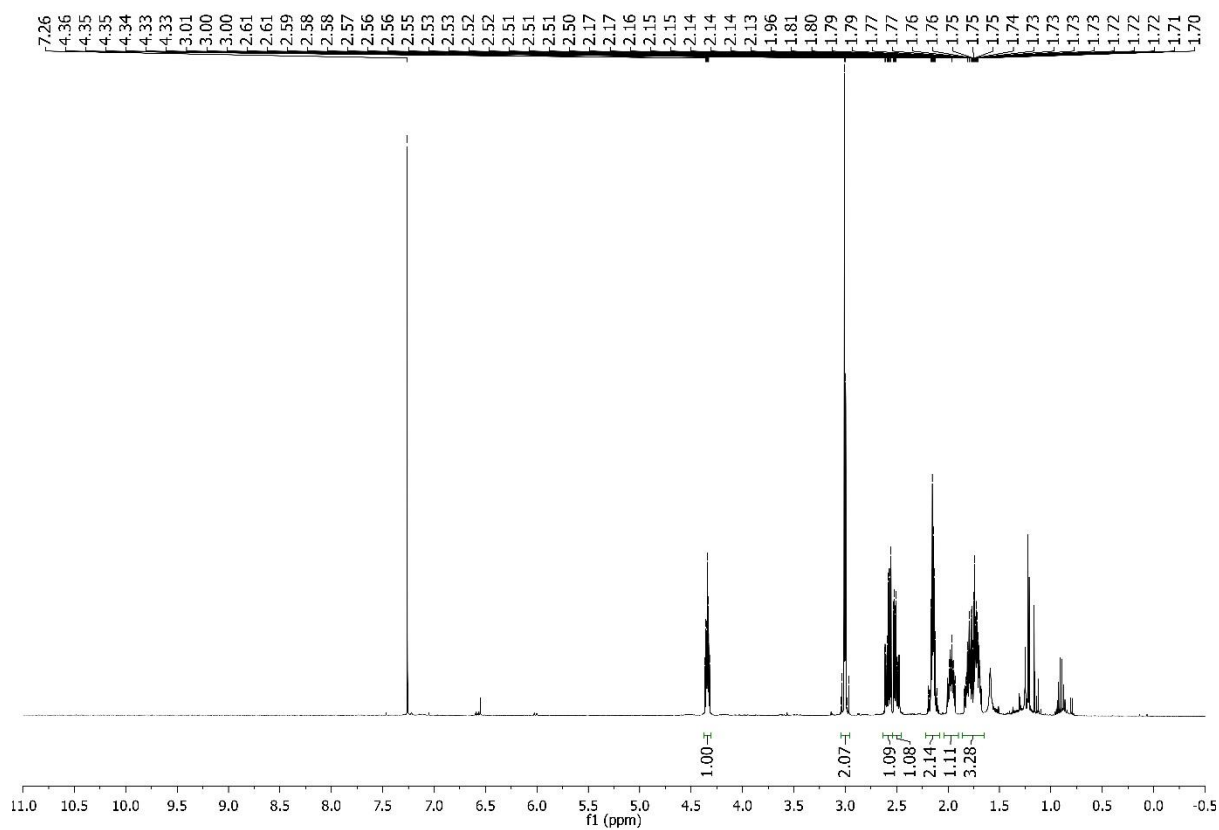


### 3-Chlorocycloheptan-1-one (**41**)



Prepared according to General Procedure H using **S50** (34 mg). For this example, the reaction mixture was washed with distilled water instead of sat.  $\text{NaHCO}_3$ . The crude residue was purified by flash column chromatography (5 $\rightarrow$ 10%  $\text{Et}_2\text{O}$ /Pentane, silica gel) to afford **41** (21 mg, 48%) as a colourless oil.

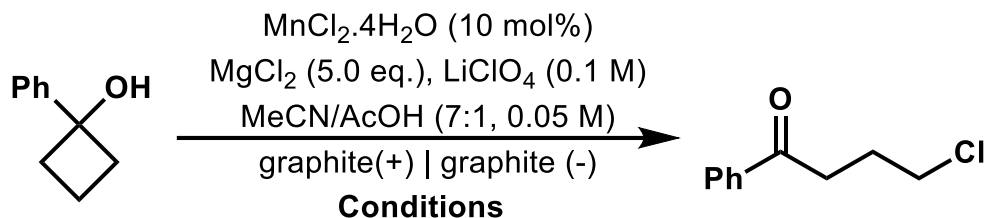
$R_f$  = 0.16 (10%  $\text{Et}_2\text{O}$ /Petrol); **FTIR** ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ , thin film) 2934, 2363, 1701, 1449, 1348, 1196, 1165, 964, 584;  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 4.37 – 4.31 (m, 1H), 3.04 – 2.96 (m, 2H), 2.62 – 2.55 (m, 1H), 2.53 – 2.47 (m, 1H), 2.20 – 2.10 (m, 2H), 2.02 – 1.92 (m, 1H), 1.85 – 1.67 (m, 3H);  **$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )**  $\delta$  = 210.0, 56.3, 52.4, 44.2, 40.1, 26.1, 23.6; **HRMS** [ $\text{C}_7\text{H}_{11}\text{OCl}$ ] requires [M] 146.0498, found 146.0499.



### 3. Optimization Studies

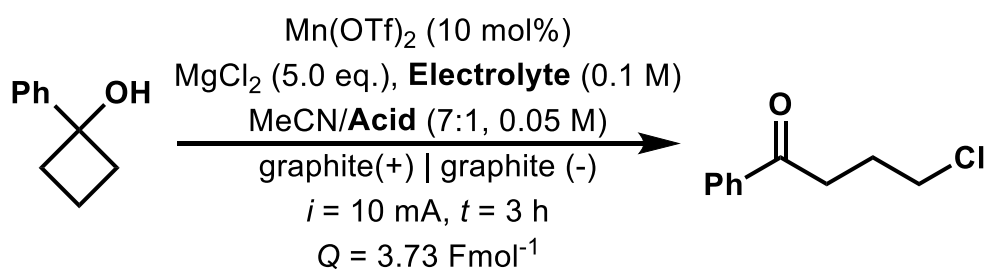
#### 3.1 Optimization using 1-phenylcyclobutan-1-ol (1)

##### 3.1.1 Electrochemical Conditions Screen



Entry	Conditions	NMR Yield / %
1	$i = 7.5 \text{ mA}; Q = 2.00 \text{ Fmol}^{-1}$	73
2	$i = 10 \text{ mA}; Q = 2.00 \text{ Fmol}^{-1}$	74
3	$i = 12.5 \text{ mA}; Q = 2.00 \text{ Fmol}^{-1}$	70
4	$i = 15 \text{ mA}; Q = 2.00 \text{ Fmol}^{-1}$	70
5	$i = 17.5 \text{ mA}; Q = 2.00 \text{ Fmol}^{-1}$	68
6	$i = 7.5 \text{ mA}; t = 3 \text{ h}; Q = 2.80 \text{ Fmol}^{-1}$	80
<b>7</b>	<b><math>i = 10 \text{ mA}; t = 3 \text{ h}; Q = 3.73 \text{ Fmol}^{-1}</math></b>	<b>82</b>
8	$i = 12.5 \text{ mA}; t = 3 \text{ h}; Q = 4.66 \text{ Fmol}^{-1}$	74
9	$i = 7.5 \text{ mA}; t = 3 \text{ h}; Q = 2.80 \text{ Fmol}^{-1}; \text{LiClO}_4 (0.2 \text{ M})$	68
10	$i = 10 \text{ mA}; t = 3 \text{ h}; Q = 3.73 \text{ Fmol}^{-1}; \text{LiClO}_4 (0.2 \text{ M})$	69
11	$i = 12.5 \text{ mA}; t = 3 \text{ h}; Q = 4.66 \text{ Fmol}^{-1}; \text{LiClO}_4 (0.2 \text{ M})$	72
12	$E_{\text{cell}} = 2.40 \text{ V}; Q = 2.00 \text{ Fmol}^{-1}$	62
13	$E_{\text{cell}} = 2.40 \text{ V}; Q = 3.00 \text{ Fmol}^{-1}$	73
14	$E_{\text{cell}} = 2.40 \text{ V}; Q = 4.00 \text{ Fmol}^{-1}$	66
15	$E_{\text{cell}} = 2.40 \text{ V}, 3 \text{ h}$	66

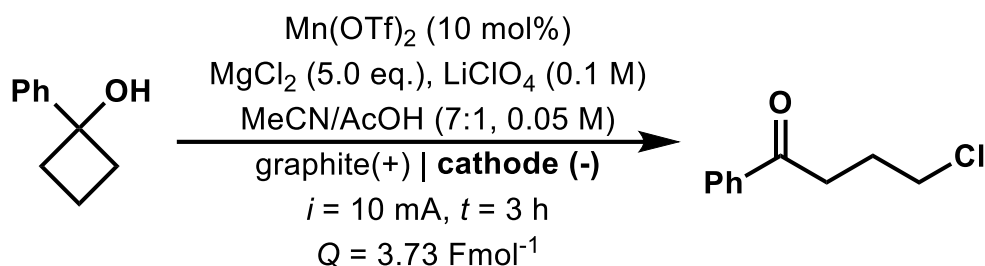
##### 3.1.2 Electrolyte and Acid Screen



Entry	Conditions	NMR Yield / %
<b>1</b>	<b>LiClO<sub>4</sub>; AcOH</b>	<b>82</b>
2	<sup>n</sup> Bu <sub>4</sub> NPF <sub>6</sub> ; AcOH	82
3	LiClO <sub>4</sub> ; 1.2 M H <sub>3</sub> PO <sub>4</sub>	<2
4	LiClO <sub>4</sub> ; TFA	<2

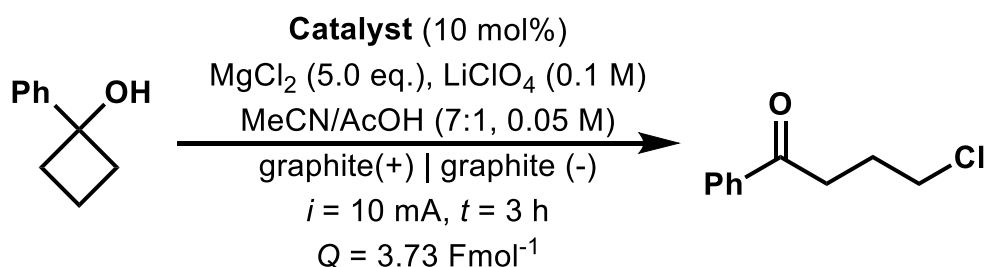


### 3.1.3 Cathode Screen



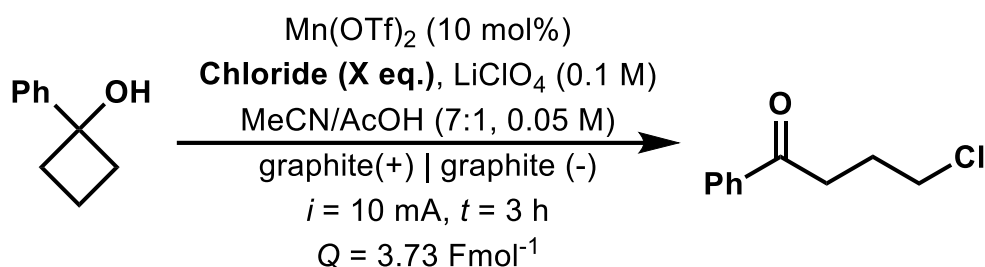
Entry	Cathode	NMR Yield / %
1	graphite	82
2	Pt foil	82
3	Ni plate	75

### 3.1.4 Catalyst Screen



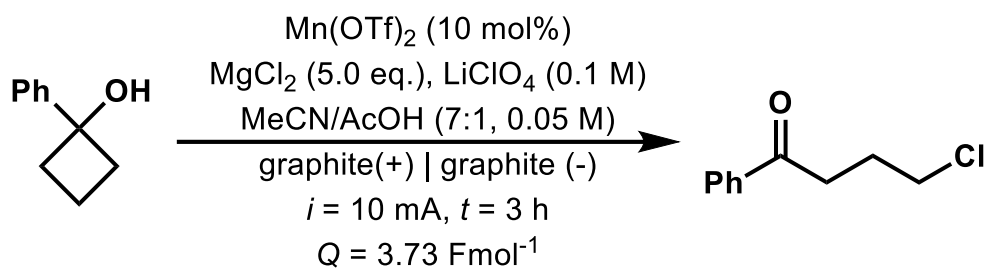
Entry	Cathode	NMR Yield / %
1	MnCl <sub>2</sub> ·4H <sub>2</sub> O	82
2	Mn(OAc) <sub>2</sub> ·4H <sub>2</sub> O	82
3	<b>Mn(OTf)<sub>2</sub></b>	<b>97</b>
4	Mn(OTf) <sub>2</sub> + bipyridine (12 mol%)	43

### 3.1.5 Chloride Screen



Entry	Cathode	NMR Yield / %
1	<b>MgCl<sub>2</sub> (5.0 eq.)</b>	<b>97</b>
2	NaCl (5.0 eq.)	<2
3	LiCl (5.0 eq.)	64
4	MgCl <sub>2</sub> (3.0 eq.)	73
5	MgCl <sub>2</sub> (2.0 eq.)	76

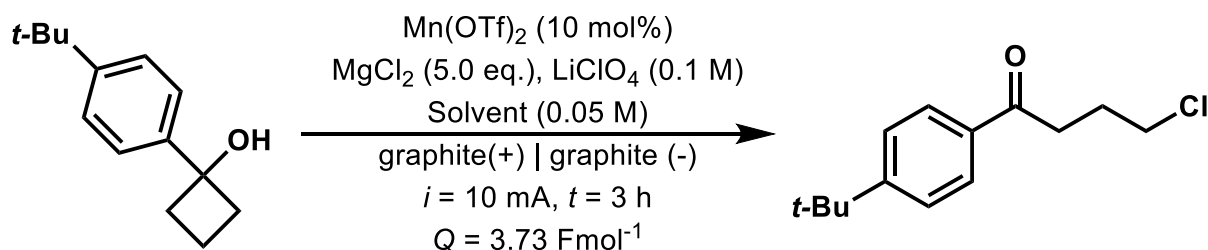
### 3.1.6 Final Permutations



Entry	Deviation from Standard Conditions	NMR Yield / %
1	None	97
2	Mn(OTf) <sub>2</sub> (5 mol%)	75
3	Q = 2.0 Fmol <sup>-1</sup>	67
4	LiClO <sub>4</sub> (0.2 M); MgCl <sub>2</sub> (3.0 eq.)	91

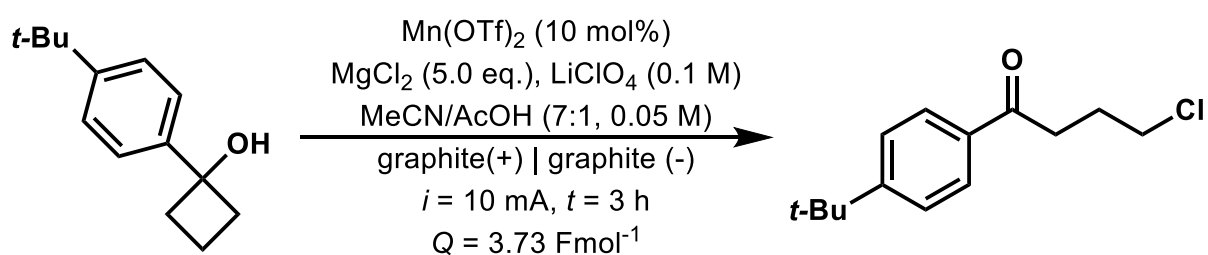
### 3.2 Optimization using 1-(4-(*tert*-butyl)phenyl)cyclobutan-1-ol (S1)

#### 3.2.1 Investigating Solvent Effect



Entry	Solvent	NMR Yield / %
1	MeCN/AcOH (7:1)	14
2	MeCN/AcOH (20:1)	29
3	MeCN/AcOH (50:1)	36
4	MeCN/HFIP (7:1)	56
5	MeCN/TFE (7:1)	55
6	MeCN/MeOH (7:1)	10
7	MeCN/H <sub>2</sub> O (7:1)	<2
8	MeCN/DMF (7:1)	4
9	MeCN/DMA (7:1)	34
10	MeCN/DMSO (7:1)	<2
11	MeCN/HFIP (3:1)	26
12	MeCN/HFIP (20:1)	36
13	MeCN/HFIP (50:1)	66
14	MeCN	8
15	MeCN, HFIP (5 eq.)	61

#### 3.2.2 Investigating Slow Addition



Entry	Conditions	NMR Yield / %
1	Addition of substrate in MeCN (2 mL) to reaction mixture in MeCN (3.25 mL) and AcOH (0.75 mL) over 2 h	61
2	As in entry 1, but TBAOAc as electrolyte	80
3	As in entry 2, but 2 minute delay between start of electrolysis and addition of substrate	91

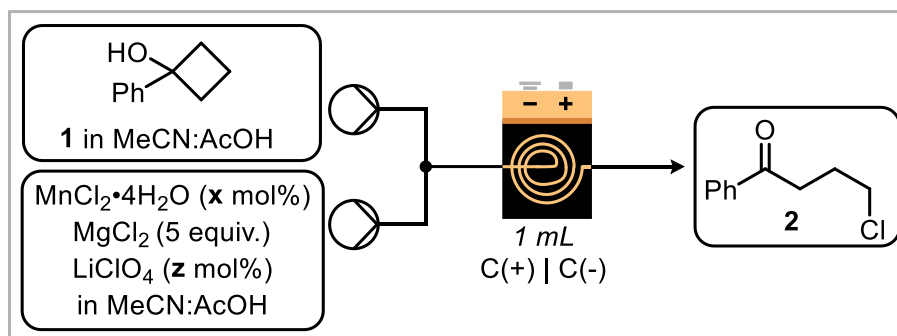
## 4. Flow Optimization and Experimental

### 4.1 General Information

The flow set-up used PFA tubing with a  $0.79 \pm 0.1$  mm internal diameter and  $1.58 \pm 0.1$  mm outer diameter supplied by Polyflon. All flow fittings and connections were purchased from Kinesis (Gripper fitting nuts, part number: 002103; Adapters, part number: P-618; Omnilok type-p fitting ferrule, part number: 008FT16; Y-Connector, part number: P-512; Threaded union, part number: P-623; 40 psi Back pressure regulator (used as check valve for DCM pump; part number: P-785). Pumps used were the Chemyx Fusion 100 syringe pump; Knauer P4.1S and P2.1S Azura HPLC pumps (⑥ + ⑦), and SSI Series 1 PEEK HPLC pump (①). The residence coils were made from the tubing by taking the appropriate length for the desired volume. Pumps ⑥, ⑦ and ① were calibrated by pumping solvent into a measuring cylinder, recording the time taken for the desired volume to be dispensed and then adjusting the pump's flow rate to the correct value, if required. The power supply (③) used was a Voltcraft LRP-1205 that supplied DC to the electrochemical system. The electrochemical flow cell was purchased from Cambridge Reactor Design, the Ammonite 8 (part number: 74660; ③). The electrochemical flow cell consists of two carbon/PVDF electrodes that are fixed either side of a FFKM gasket with a channel groove length of 1000 mm and an internal volume of 2.5 mL, of which 1 mL is exposed to the electrodes. The inlet and outlet fittings of the ammonite 8 cell were modified from 1/16" ID to accommodate 1/32" ID PFA tubing using Swagelok reducers, nuts and ferrules. The electrochemical cell was not dismantled, nor were the electrodes polished, for the duration of this project. The 6-port 2-position injection valve (④) was purchased from Kinesis (part number: V-451) and mounted on a stainless-steel plate for ease of handling. The mixer unit (⑧) was made from a 150 x 10 mm Omnifit Column charged with 10 stirrer bars; the filter frits were removed for reduced back pressure. The universal liquid-liquid phase separator (⑨) was obtained from Biotage (part number: 120-1930V) and modified with a side-arm tap (part number: 121-0001) inserted through the outside wall. The tap was connected by drilling a hole into the plastic cup where the PTFE tap was pushed through and held in place *via* friction, no leakage was observed throughout the project. 25 °C means isothermally controlled whereas 'rt' means the reaction is being held at ambient UK temperatures.

The electrochemical reactor was used in three modes of operation, **mode 1** for exploring single pass parameters, **mode 2** for recirculating experiments and **mode 3** for scale up and continuous extraction.

## 4.2 Single Pass Flow Electrochemistry (Mode 1)



### 4.2.1 Experimental

#### Preparation of reagent solutions:

Three 25 mL round-bottom flasks were flame dried; one was charged with 1-phenyl cyclobutanol (0.6 mmol, 0.0890 g) and sealed with a Suba-seal and parafilm. The second RBF was charged with  $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$  (0.06 mmol, 0.0119 g),  $\text{MgCl}_2$  (3 mmol, 0.2865 g) and  $\text{LiClO}_4$  (1.2 mmol, 0.1279 g). Both reagent flasks were evacuated on a Schlenk line and back filled with nitrogen gas for three cycles. The third RBF was charged with dry degassed MeCN (12.25 mL) and glacial acetic acid (1.75 mL). After deoxygenating, (bubbling with nitrogen for 15 min), the solvent mixture (6 mL) was added to each reagent flask under a nitrogen atmosphere and swirled until dissolution occurred.

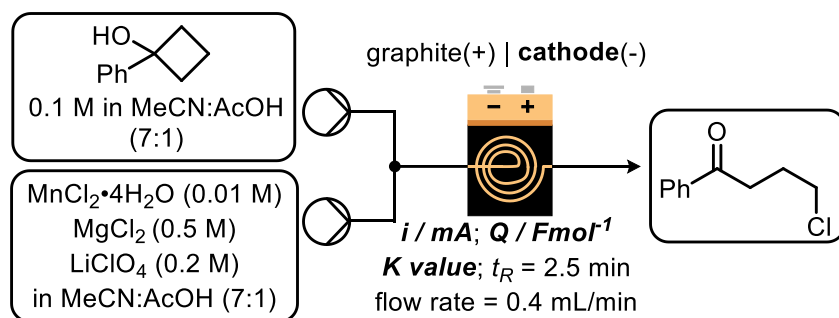
#### Flow running order:

The electrochemical flow system was flushed with nitrogen gas for 5 min by connecting the inlet tubing directly to the dry nitrogen line. The reagent solutions were drawn up into 10 mL syringes and promptly connected to the flow system. The syringe pumps were set to 1.125 mL/min, giving a combined total flow rate of 2.5 mL/min at the mixing-tee. Syringe pumping was initiated, and the outlet of the flow system was set to waste for the first 3.46 mL (representing 1 whole flow path volume, inclusive of tubing, connectors and reactor) of reaction mixture to allow the flow system to be filled. After this initial priming, the power supply was switched on and the electrolysis commenced at a constant current with the system outlet still set to waste for a further 2.5 mL (representing a total volume from 'in' to 'out' of the electrochemical reactor; exposed electrochemical path = 1 mL). The outlet stream of the flow system was then collected for 6 mL (representing 0.3 mmol of **A** processed). Mesitylene (0.1 mmol, 13.9  $\mu\text{L}$ ) was added to the product mixture, stirred for 5 min and then the  $^1\text{H}$  NMR spectrum was recorded to give a crude reaction yield.

### 4.2.2 Optimization

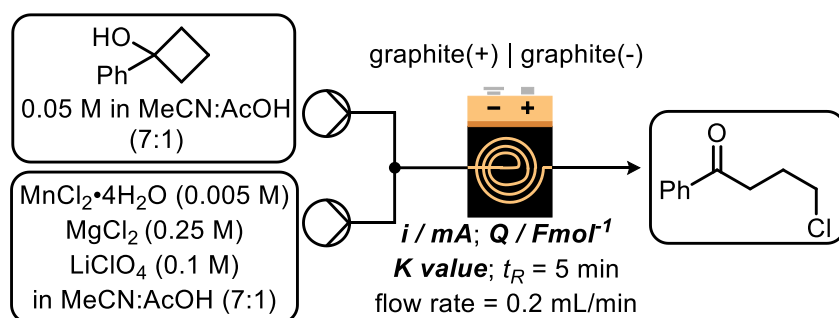
Single pass electrochemical flow was explored initially to see whether the reaction would proceed successfully *via* this mode. The optimisation allowed for physical parameters to be screened using a simple flow system. Initially, mass balance was optimised to give a clean reaction with a high productivity and an efficient mixing regime ( $k$  value). These parameters were met, however, when optimising for yield, the reaction required prolonged exposure to the electrochemical system therefore mode 2, recirculation, was explored. Italicised conditions in bold (4.2.2.6, entry 1) were carried forward into mode 2, recirculation.

#### 4.2.2.1 Initial Experiments



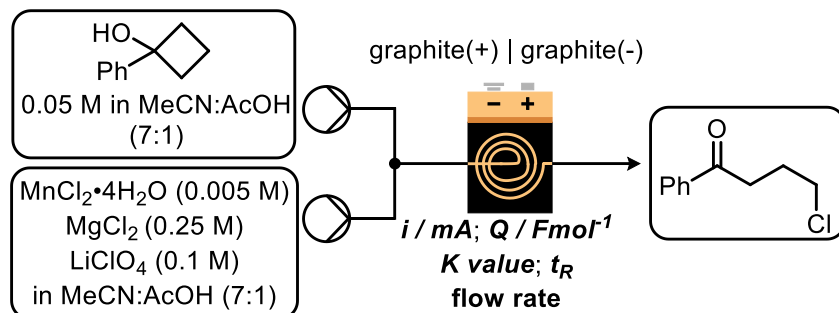
Entry	Cathode	Current / mA	Charge / Fmol <sup>-1</sup>	K value	Yield / %	RSM / %
1	Stainless steel	70	1.1	$9.87 \times 10^{-4}$	0	0
2	Graphite	70	1.1	$9.87 \times 10^{-4}$	0	-
3	Graphite	100	1.6	$1.41 \times 10^{-3}$	9	41
4	Graphite	120	1.9	$1.69 \times 10^{-3}$	0	0

#### 4.2.2.2 Current Screen



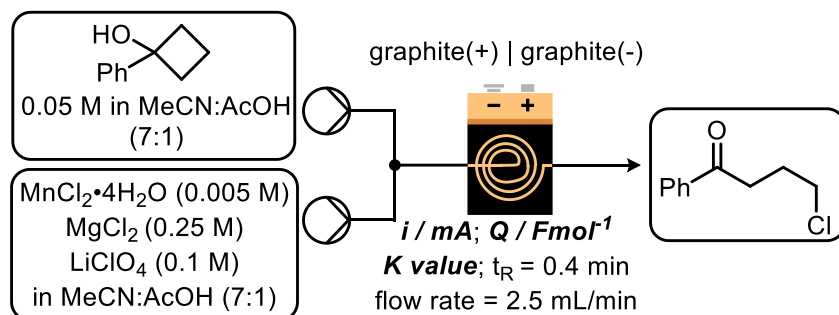
Entry	Current / mA	Charge / Fmol <sup>-1</sup>	K value	Yield / %	RSM / %
1	30	1.9	$8.46 \times 10^{-4}$	6	73
2	40	2.5	$1.13 \times 10^{-3}$	19	55
3	60	3.7	$1.69 \times 10^{-3}$	12	61
4	80	5.0	$2.26 \times 10^{-3}$	14	48
5	100	6.2	$2.82 \times 10^{-3}$	11	40
6	120	7.5	$3.38 \times 10^{-3}$	10	39

#### 4.2.2.3 Retention Time Screen



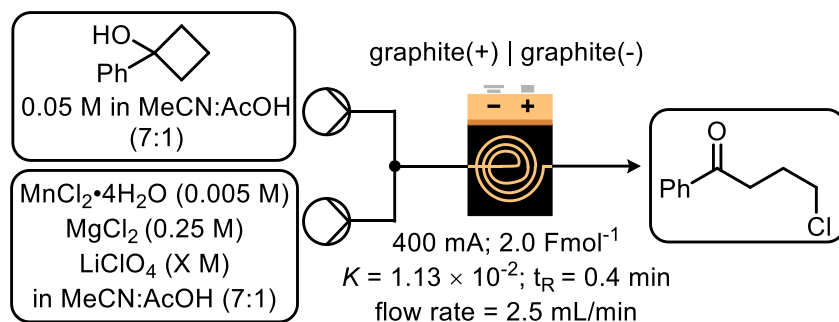
Entry	Current / mA	Charge / Fmol <sup>-1</sup>	$t_R$ / min	Flow rate / mL/min	K value	Yield / %	RSM / %
1	30	3.7	10	0.1	$8.46 \times 10^{-4}$	12	70
2	100	3.1	2.5	0.4	$2.82 \times 10^{-3}$	5	0
3	200	2.5	1	1	$5.64 \times 10^{-3}$	9	79
4	160	2.0	1	1	$4.51 \times 10^{-3}$	6	85
5	400	2.0	0.4	2.5	$1.13 \times 10^{-2}$	14	83
6	480	2.0	0.33	3	$1.35 \times 10^{-2}$	8	92

#### 4.2.2.4 Current Screen



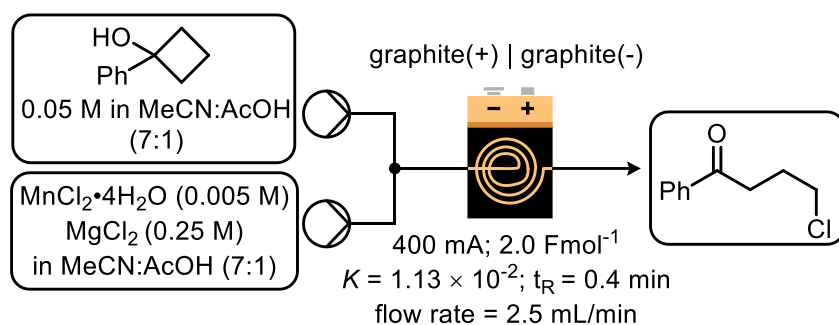
Entry	Current / mA	Charge / Fmol <sup>-1</sup>	K value	Yield / %	RSM / %
1	370	1.8	$1.04 \times 10^{-2}$	12	84
2	420	2.1	$1.18 \times 10^{-2}$	15	74
3	440	2.2	$1.24 \times 10^{-2}$	13	73
4	460	2.3	$1.30 \times 10^{-2}$	16	64
5	480	2.4	$1.35 \times 10^{-2}$	12	63
6	500	2.5	$1.41 \times 10^{-2}$	12	68

#### 4.2.2.5 Electrolyte Loading



Entry	LiClO <sub>4</sub> / M	Yield / %	RSM / %
1	0.1	14	83
2	-	11	88

#### 4.2.2.6 Temperature Screen

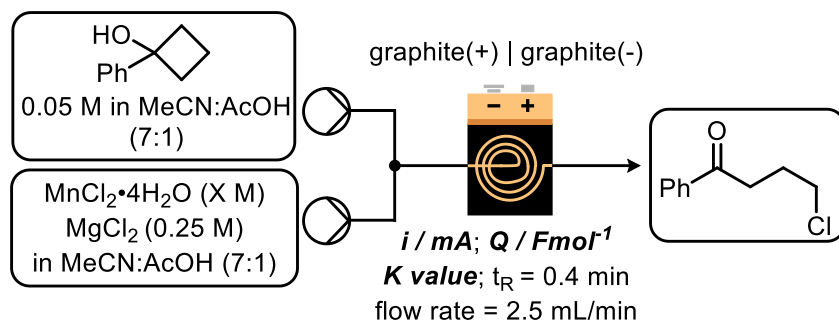


Entry	T / °C	Yield / %	RSM / %
1	25	14	80
2	35	14	72
3	45	11	70
4	55	18	60
5 <sup>[a]</sup>	25	15	80

[a] Run with MeCN/AcOH (1:1) solvent ratio.



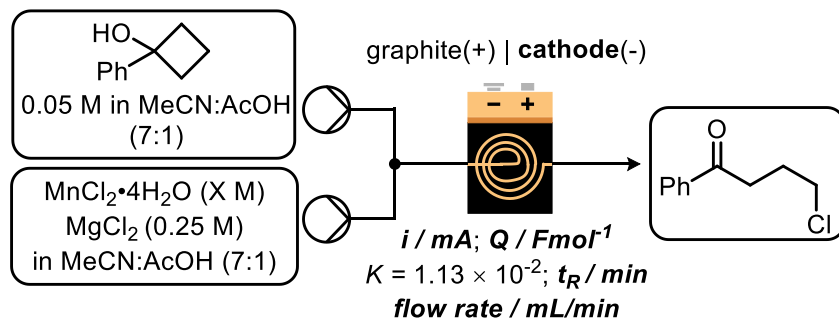
#### 4.2.2.7 Catalyst Loading



Entry	MnCl <sub>2</sub> ·4H <sub>2</sub> O / M	Current / mA	Charge / Fmol <sup>-1</sup>	K value	Yield / %	RSM / %
1 <sup>[a]</sup>	0.01	370	1.8	$1.04 \times 10^{-2}$	12	70
2 <sup>[a]</sup>	0.02	200	1.0	$5.64 \times 10^{-3}$	9	71
3	0.01	400	2.0	$1.13 \times 10^{-2}$	19	76
4	0.02	400	2.0	$1.13 \times 10^{-2}$	20	65
5 <sup>[b]</sup>	0.02	400	2.0	$1.13 \times 10^{-2}$	25	65
6 <sup>[b]</sup>	0.05	400	2.0	$1.13 \times 10^{-2}$	34	0

[a] Run with LiClO<sub>4</sub> (0.1 M); [b] Run with MeCN/AcOH (1:1) solvent ratio.

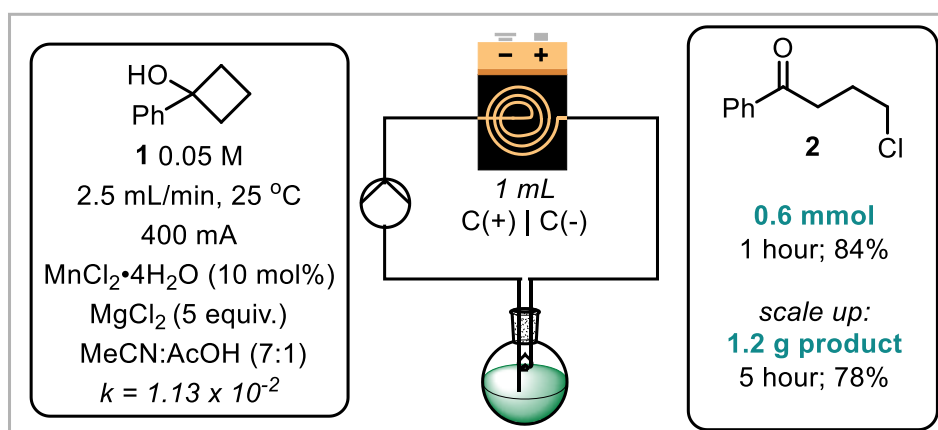
#### 4.2.2.8 Final Iterations



Entry	Cathode	MnCl <sub>2</sub> ·4H <sub>2</sub> O / M	Current / mA	Charge / Fmol <sup>-1</sup>	Flow rate / mLmin <sup>-1</sup>	$t_R / \text{min}$	Yield / %	RSM / %
1 <sup>[a]</sup>	graphite	0.05	400	5.0	1.0	1.0	12	70
2	Pt plate	0.05	400	2.0	2.5	0.4	19	76

[a] Run with MeCN/AcOH (1:1) solvent ratio.

### 4.3 Recirculating Flow System (Mode 2)



#### 4.3.1 Experimental

##### 0.6 mmol scale

A 25 mL round-bottom flask and stirrer bar was flame dried and charged with 1-phenyl cyclobutanol (0.6 mmol, 0.0890 g), MnCl<sub>2</sub>•4H<sub>2</sub>O (0.06 mmol, 0.0119 g), MgCl<sub>2</sub> (3 mmol, 0.2865 g) and sealed with a Suba-seal and parafilm. The reagent flask was evacuated on a Schlenk line and back filled with nitrogen gas for three cycles. Both the inlet and outlet tubing of the electrochemical flow system were pushed through the Suba-seal and the reagents dissolved with dry degassed MeCN (11.5 mL) and glacial acetic acid (1.5 mL). The HPLC pump was primed with the reaction mixture and set to recirculate at 2.5 mL/min while the contents of the flask were degassed by bubbling nitrogen for 15 min. The electrolysis was then commenced and conducted at a constant current of 400 mA, the recirculated reaction was monitored by TLC until completion, which, at this scale required 1 hour.

Upon completion, electrolysis was turned off and the product mixture was transferred to a 100 mL separatory funnel. The flow system was purged and flushed with clean solvent (7:1 MeCN:AcOH; 3 x 20 mL), into the separatory funnel. The crude reaction mixture was washed with a saturated solution of NaHCO<sub>3</sub> (25 mL) and Et<sub>2</sub>O (25 mL). The aqueous layer was extracted with Et<sub>2</sub>O (3 x 25 mL) and the organic layer dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography and eluted with a gradient of Et<sub>2</sub>O in hexane (2% to 6%) to afford compound **A** as a colourless oil (0.0920 g, 0.5037 mmol, 84% yield).

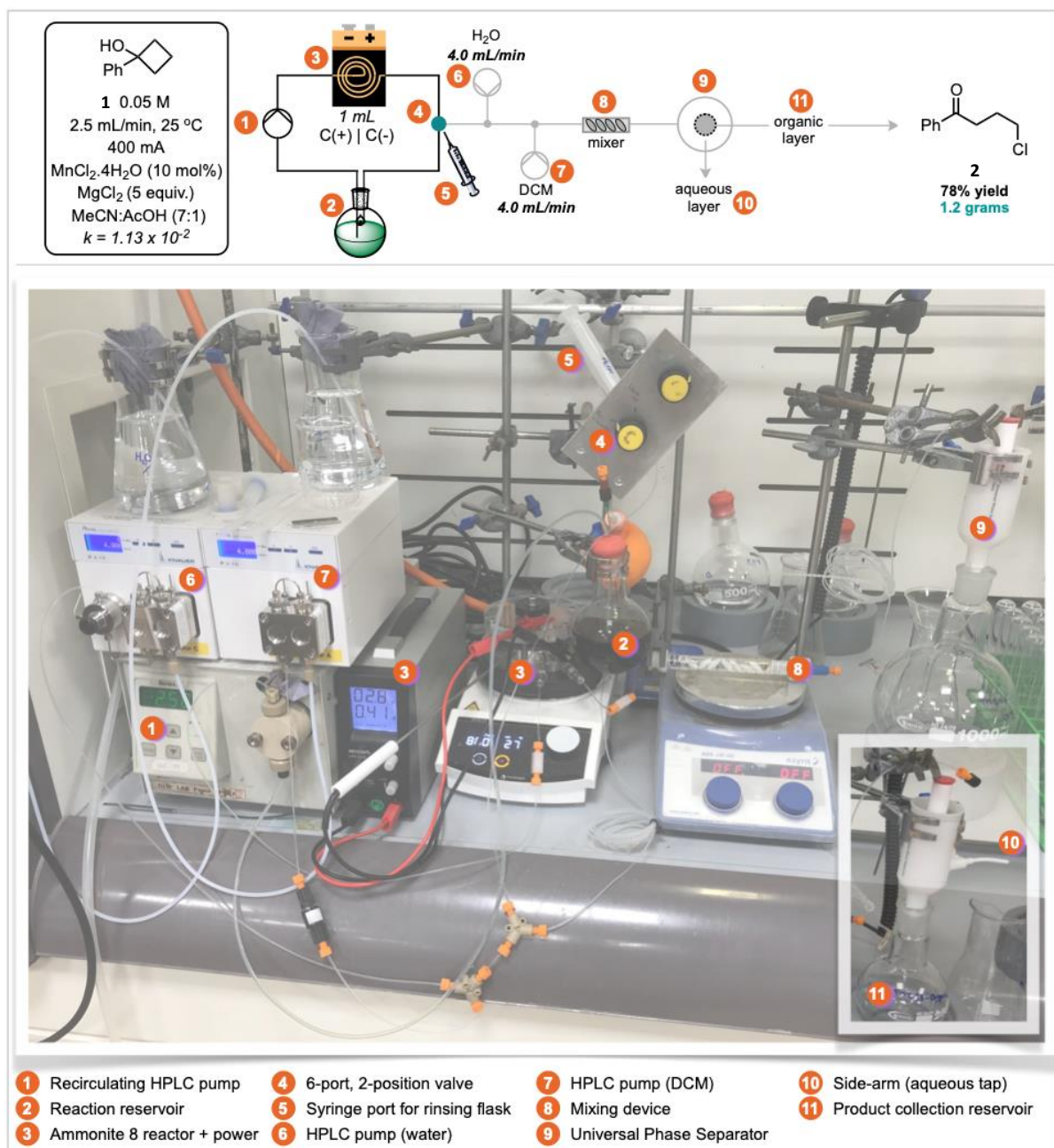
##### Gram scale

A 250 mL round-bottom flask and stirrer bar was flame dried and charged with 1-phenyl cyclobutanol (8.44 mmol, 1.25 g), MnCl<sub>2</sub>•4H<sub>2</sub>O (0.844 mmol, 0.1670 g), MgCl<sub>2</sub> (42.2 mmol, 4.0179 g) and sealed with a Suba-seal and parafilm. The reagent flask was evacuated on a Schlenk line and back filled with nitrogen gas for three cycles. Both the inlet and outlet tubing of the electrochemical flow system were pushed through the Suba-seal and the reagents dissolved with dry degassed MeCN (147.87 mL) and glacial acetic acid (21.13 mL). The HPLC pump was primed with the reaction mixture and set to recirculate at 2.5 mL/min while the contents of the flask were degassed by bubbling nitrogen for 30 min. The electrolysis was then commenced and conducted at a constant current of 400 mA, the recirculated reaction was monitored by TLC until completion, which, at this scale required 5 hours.

Upon completion, electrolysis was turned off and the product mixture was transferred to a 1 L separatory funnel. The flow system was purged and flushed, with clean solvent (7:1 MeCN:AcOH; 3 x

20 mL), into the separatory funnel. The crude reaction mixture was washed with a saturated solution of  $\text{NaHCO}_3$  (2 x 100 mL) and  $\text{Et}_2\text{O}$  (100 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 100 mL) and the organic layer dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude product was purified by column chromatography and eluted with a gradient of  $\text{Et}_2\text{O}$  in hexane (2% to 10%) to afford compound **A** as a colourless oil (1.2 g, 6.57 mmol, 78% yield).

#### 4.4 Recirculating Flow System with In-Line Extraction (Mode 3)

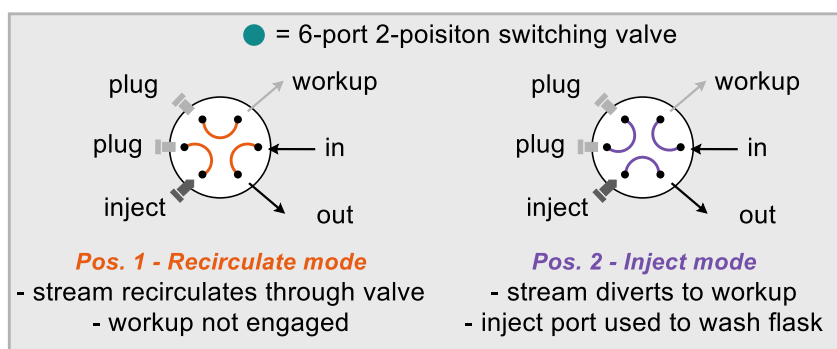


##### 4.4.2 Experimental

###### Gram scale

A 250 mL round-bottom flask and stirrer bar was flame dried and charged with 1-phenyl cyclobutanol (8.44 mmol, 1.25 g), MnCl<sub>2</sub>•4H<sub>2</sub>O (0.844 mmol, 0.1670 g), MgCl<sub>2</sub> (42.2 mmol, 4.0179 g) and sealed with a Suba-seal and parafilm. The reagent flask was evacuated on a Schlenk line and back filled with nitrogen gas for three cycles. Both the inlet and outlet tubing of the electrochemical flow system were pushed through the Suba-seal and the reagents dissolved with dry degassed MeCN (147.87 mL) and glacial acetic acid (21.13 mL). The HPLC pump (①) was primed with the reaction mixture and set to recirculate at 2.5 mL/min while the contents of the flask were degassed by bubbling nitrogen for 30 min. The electrolysis was commenced and conducted at a constant current of 400 mA, the recirculated reaction was monitored by TLC until completion, which, at this scale required 5 hours.

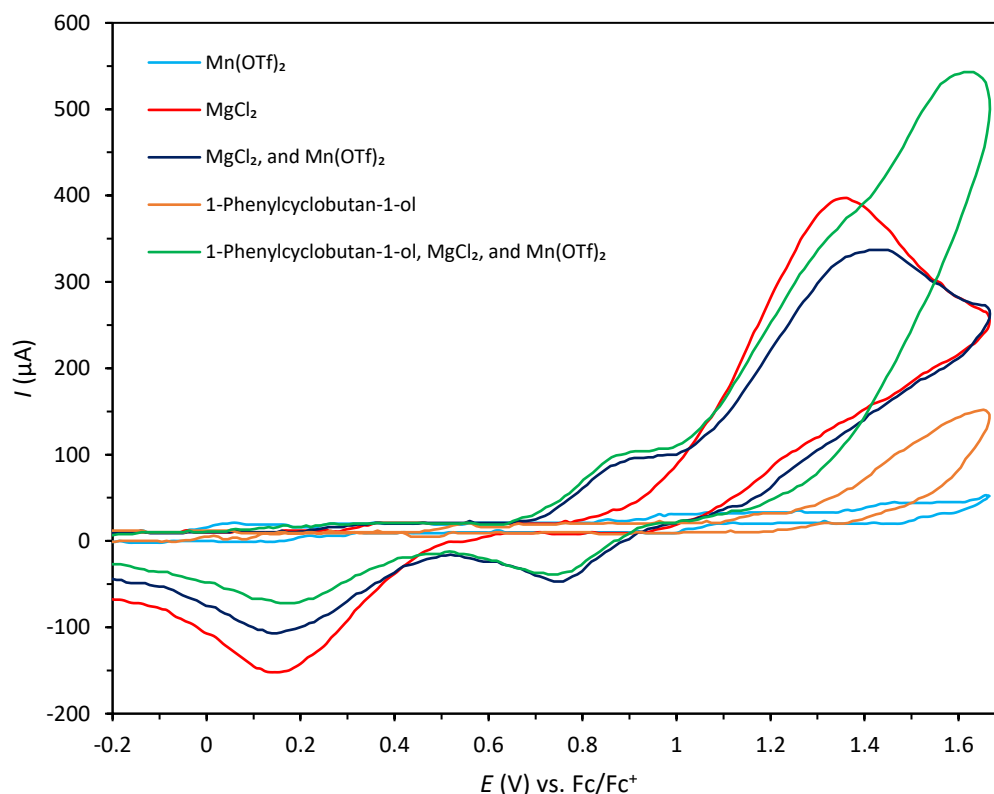
Once judged as complete, electrolysis was turned off, pump ① was set to 4 mL/min and pumps ⑥ and ⑦ were turned on and set to 4 mL/min, the mixing device (⑧) was switched on and set to mix at 1500 rpm. The 6-port, 2-position valve (④) was switched to the inject position, thus diverting the recirculating stream into the in-line work up. Upon depletion of the reaction mixture from the flask, the flask was washed and rinsed with clean solvent three times (20 mL 7:1 MeCN:AcOH). The in-line workup took 60 minutes for the entire reaction mixture to be processed, (42 min reaction mixture processing, 10 min rinse of flow system, 8 min solvent flush for work up line cleaning). The separated organic layer (⑪) was dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography and eluted with a gradient of Et<sub>2</sub>O in hexane (2% to 10%) to afford compound **A** as a colourless oil (1.2 g, 6.57 mmol, 78% yield).



## 5. Mechanistic Studies

### 5.1 Cyclic Voltammetry Studies

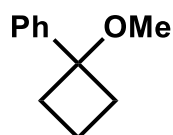
General Information: Cyclic Voltammetry (CV) experiments were conducted with ElectroSyn 2.0 package (IKA) using the CV function. The experiments were conducted in a 10 mL ElectroSyn vial fitted with a glassy carbon disk (diameter 3 mm) working electrode, a platinum-plated counter electrode, and a Ag/AgNO<sub>3</sub> reference electrode. The solution of interest was purged with N<sub>2</sub> for 5 minutes before data collection.



**Fig SX.** Cyclic Voltammogram of (a) Mn(OTf)<sub>2</sub> (3.0 mM); (b) MgCl<sub>2</sub> (12 mM); (c) Mn(OTf)<sub>2</sub> (3.0 mM) and MgCl<sub>2</sub> (12 mM); (d) 1-phenylcyclobutan-1-ol (6.0 mM) or (e) 1-phenylcyclobutan-1-ol (6.0 mM), Mn(OTf)<sub>2</sub> (3.0 mM) and MgCl<sub>2</sub> (12 mM) in MeCN/AcOH (7:1) with LiClO<sub>4</sub> (0.10 M). **Scan rate: 200 mV/s.**

### 5.2 Experimental Evidence

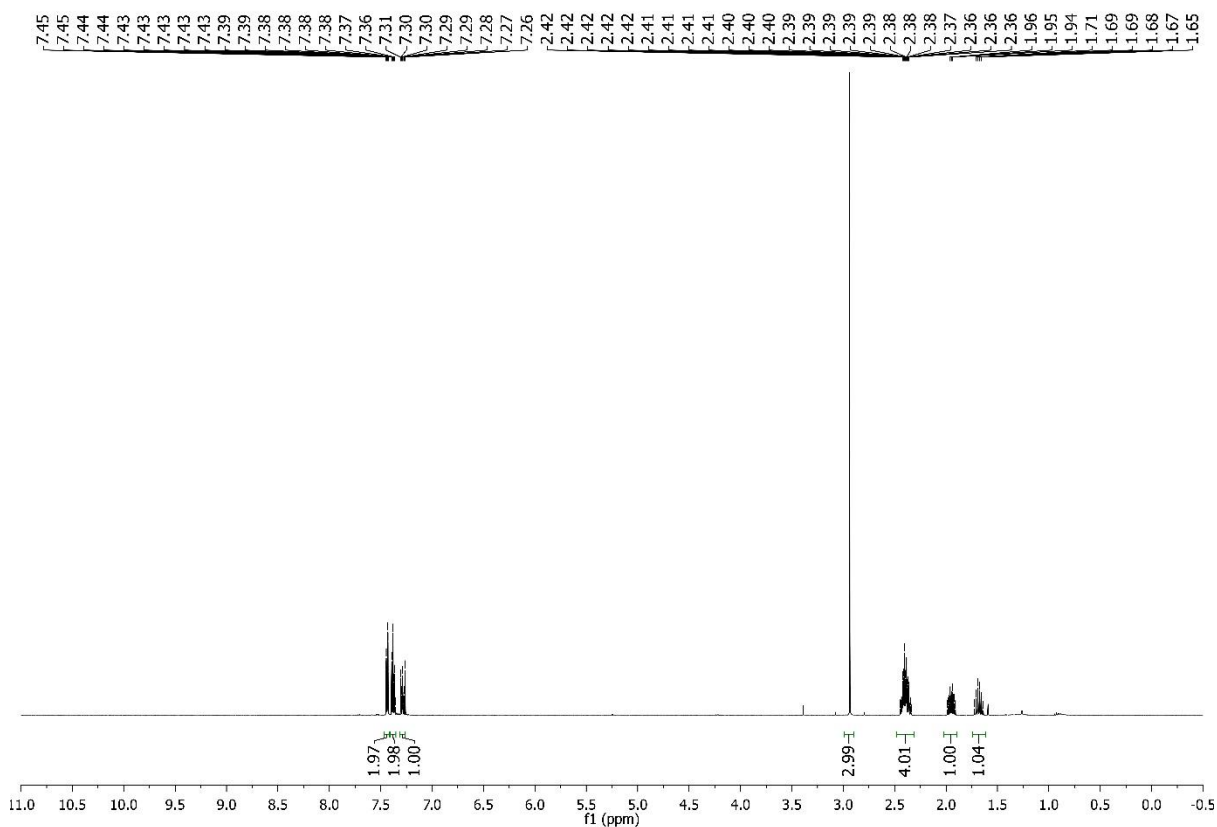
#### 5.2.1 Synthesis of (1-methoxycyclobutyl)benzene (42)

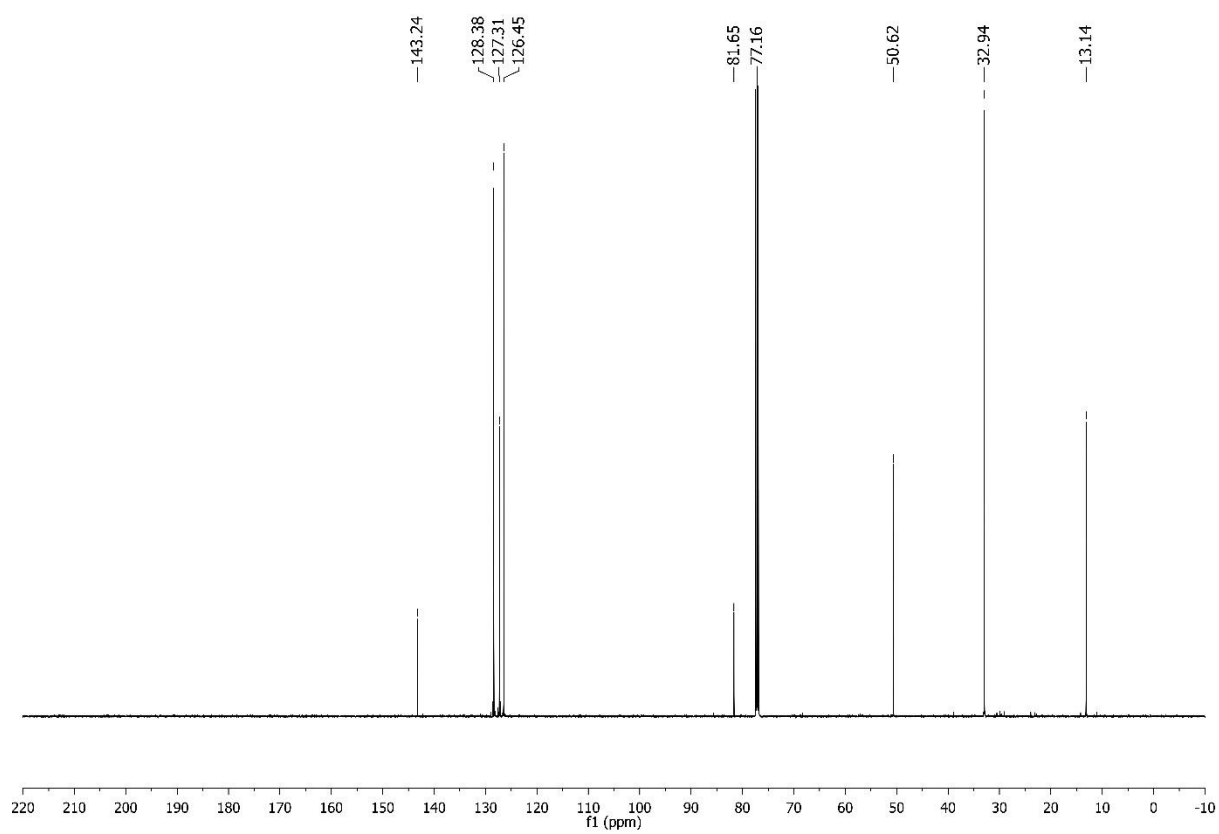


To a solution of **1** (445 mg, 3.00 mmol) in THF (15 mL) was slowly added NaH (60% dispersed in mineral oil, 156 mg, 3.90 mmol, 1.30 eq.). Once gas evolution had ceased, the solution was cooled to 0 °C and methyl iodide (933 μL, 15.0 mmol, 5.0 eq.) was added slowly. The reaction mixture was stirred at rt for 7 h, before being cooled to 0 °C and H<sub>2</sub>O (15 mL) was added. The layers were separated, and the aqueous layer was further extracted with Et<sub>2</sub>O (2 × 20 mL). The combined organics were then washed

with H<sub>2</sub>O and brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (5% EtOAc/Hexanes, silica gel) to afford **42** (314 mg, 65%) as a colourless oil.

**R<sub>f</sub>** = 0.46 (10% EtOAc/Hexanes); **FTIR** ( $\nu_{\text{max}}$  cm<sup>-1</sup>, thin film) 2978, 2940, 2816, 1443, 1281, 1242, 1126, 1088, 1042, 756, 694; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.45 – 7.42 (m, 2H), 7.40 – 7.36 (m, 2H), 7.31 – 7.27 (m, 1H), 2.94 (s, 3H), 2.46 – 2.34 (m, 4H), 1.99 – 1.91 (m, 1H), 1.73 – 1.64 (m, 1H); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 143.2, 128.4, 127.3, 126.5, 81.7, 50.6, 32.9, 13.2; **HRMS** (EI<sup>+</sup>) [C<sub>11</sub>H<sub>14</sub>O] requires [M] 162.1045, found 162.1047.







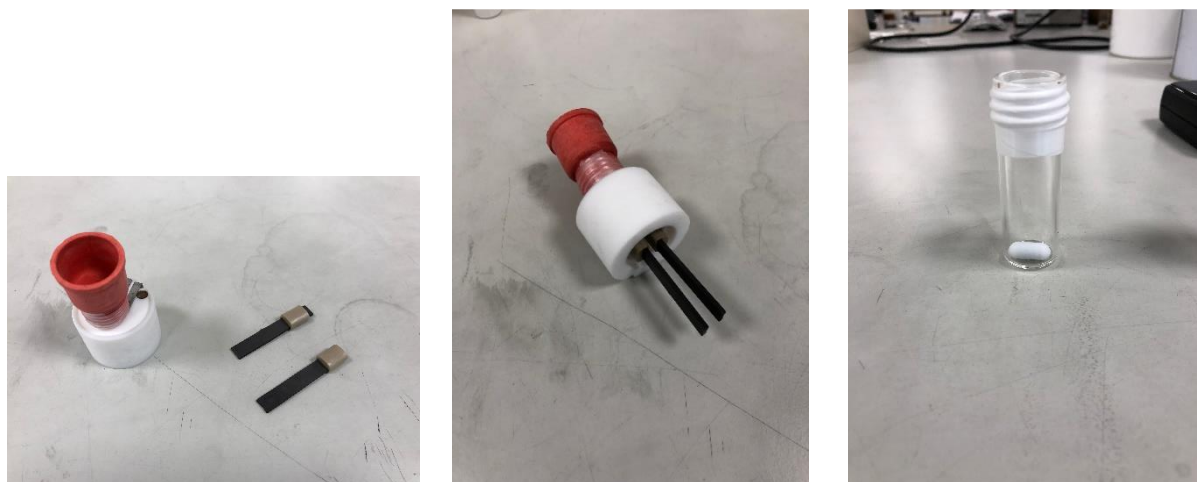
## 6. Graphical Set-Up Guide

### 6.1 Graphical Guide for Set-Up of Electrochemical Mn-Catalyzed Deconstructive Chlorination of Cycloalkanols

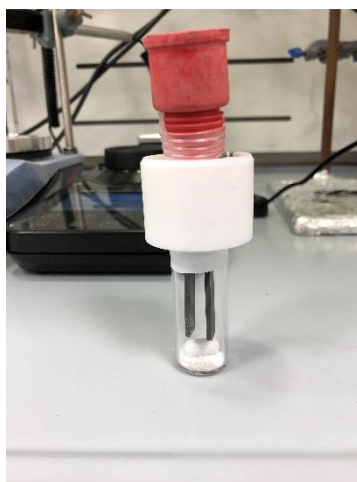
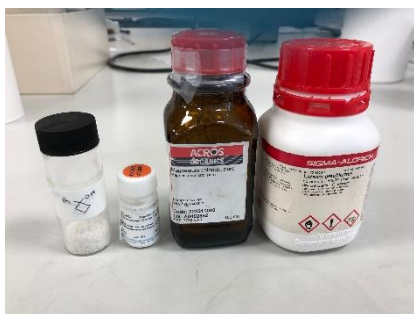
Photos were taken from the deconstructive chlorination reaction of [1-phenylcyclobutan-1-ol](#) (**1**) using [General Procedure G](#).



**LEFT.** Subaseal (size 41), ElectraSyn (ES) Teflon tube, ES cap, parafilm. **MIDDLE.** The Teflon tube is inserted into the Subaseal and the joint is wrapped with parafilm, ensuring an overlap of at least 1 cm of the parafilm over the Teflon tube – this helps to keep a good air-tight seal during the reaction. **RIGHT.** The Teflon tube is then inserted into the cap.



**LEFT.** Two graphite electrodes are inserted into electrode holders. **MIDDLE.** The graphite electrodes are then connected to the ES cap. **RIGHT.** An oven-dried 10 mL ES vial and stirrer bar are cooled in a desiccator and the glass thread is subsequently wrapped with Teflon tape to help create a better seal.

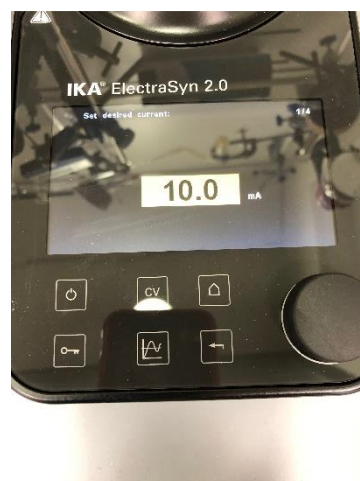
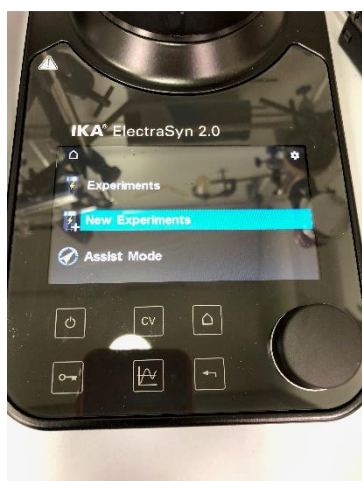


**LEFT.** Reagents used in this procedure – substrate is home-made (see [1](#));  $\text{Mn}(\text{OTf})_2$  is purchased from Apollo Scientific and used as found (stored under  $\text{N}_2$ );  $\text{MgCl}_2$  is purchased from Acros Organics and used as found (stored under  $\text{N}_2$ );  $\text{LiClO}_4$  is purchased from Sigma-Aldrich (now Merck) and is used as found. **MIDDLE.** All solid reagents are added to the dried ES vial and the cap is screwed tightly in place. Any liquid substrates are weighed directly into the ES vial before addition of the other reagents. **RIGHT.** The solid reagents are subjected to three evacuate-refill cycles using an atmosphere of  $\text{N}_2$ . MeCN and AcOH are added. The  $\text{MgCl}_2$  is not usually dissolved until addition of the AcOH. However, sometimes, it does not fully dissolve, giving a suspension. In these cases, we proceed as normal and have not noticed any detriment to the reaction.

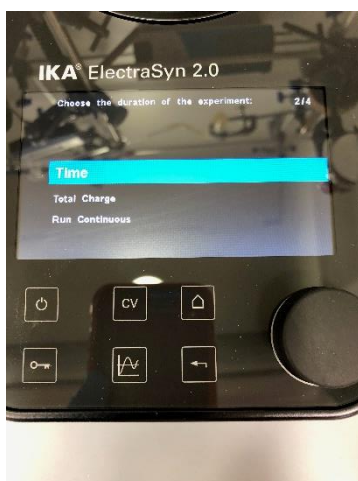
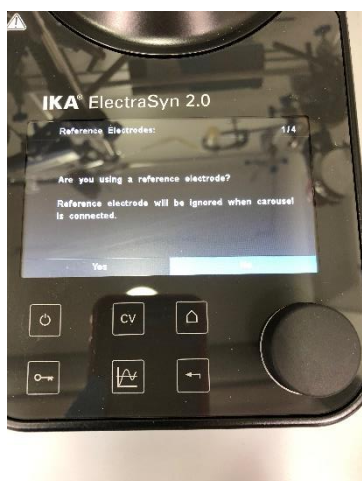


**LEFT.** The reaction mixture is purged with  $\text{N}_2$ , ensuring the needle spewing  $\text{N}_2$  gas is kept at the bottom of the vial. The reaction is vented to the atmosphere during this time with another needle. Take care not to bubble the  $\text{N}_2$  too vigorously or the solvent can begin to evaporate. The purging takes place for 10 minutes. **MIDDLE.** During the purge, the ElectraSyn 2.0 is switched on and arranged as pictured using a GOGO module to position the vial in a water bath, set at  $25\text{ }^\circ\text{C}$ . **RIGHT.** Once the reaction mixture is purged, it is placed onto the GOGO module and positioned in the water bath, under a  $\text{N}_2$  atmosphere, either by balloon or connected to a Schlenk line.

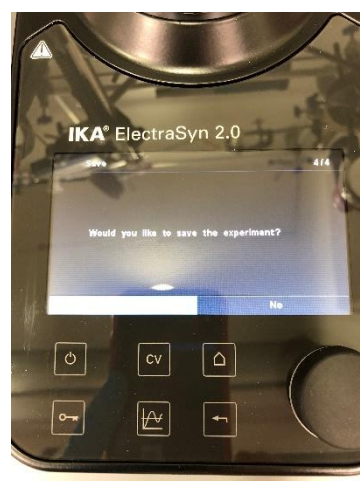
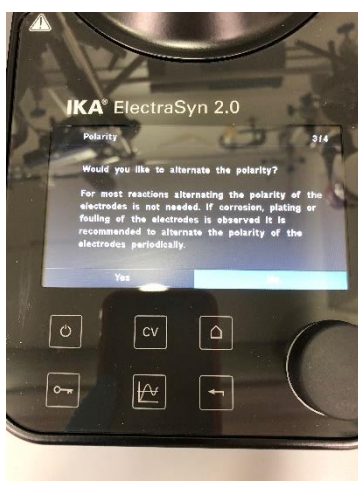
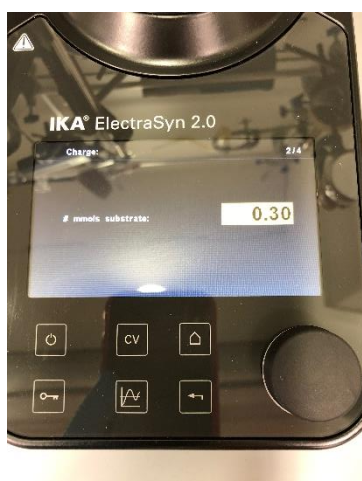




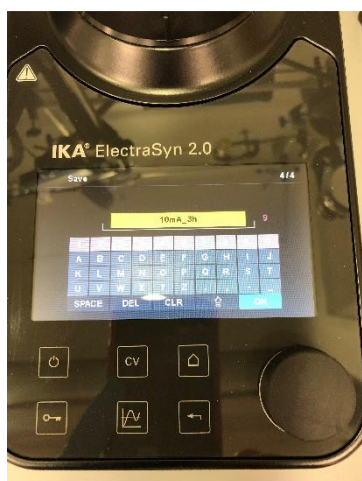
**LEFT.** On the ElectraSyn, select “New Experiments”. **MIDDLE.** Select “Constant Current”. **RIGHT.** Input “10.0 mA” as the reaction current.



**LEFT.** Select “No” for using a reference electrode. **MIDDLE.** Select “Time” to control the reaction duration. **RIGHT.** Input “3 h: 00 m: 00s” as the reaction time.



**LEFT.** Input “0.30 mmol” for the amount of substrate. **MIDDLE.** Select “No” for alternation of polarity. **RIGHT.** It is advised to select “Yes” to save the experiment, to avoid previous steps.



**LEFT.** Input title of experiment. Here we have selected “10mA\_3h”. **MIDDLE.** Screen displaying reaction conditions. Select “Start”. **RIGHT.** After a few minutes have passed, the reaction mixture will typically turn green. This is indicative of the formation of Mn(III) catalyst. There are some examples where this green colour is not observed, or does not persist, until towards the end of the experiment, but good yields are still obtained in these instances. This is presumably due to a faster reaction rate resulting in faster consumption of the electrogenerated catalyst.



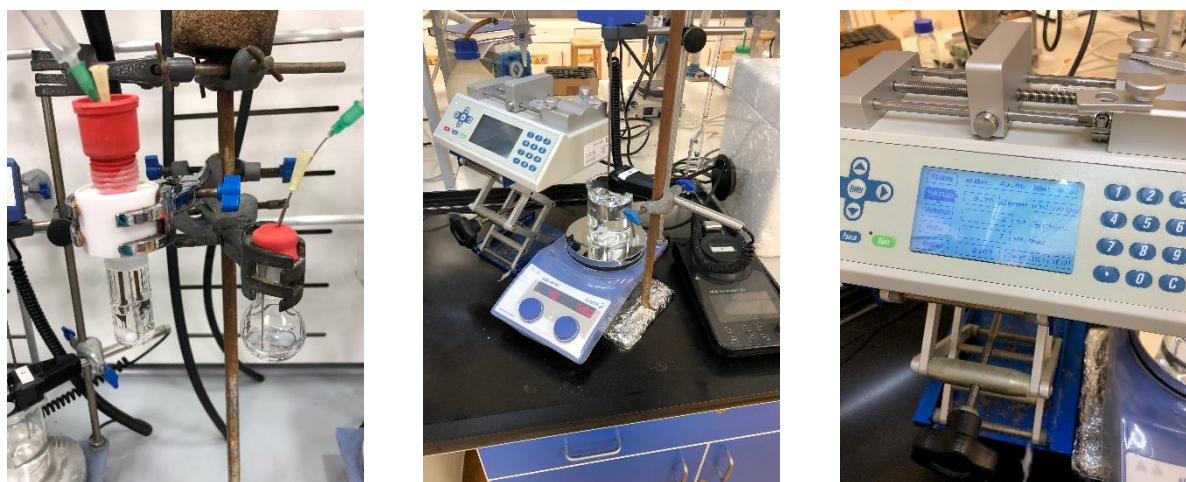
## 6.2 Graphical Guide for Set-Up of Electrochemical Mn-Catalyzed Deconstructive Chlorination of Cycloalkanols Using Syringe Pump Addition of Substrate

Photos were taken from the deconstructive chlorination reaction of 1-(4-(*tert*-butyl)phenyl)cyclobutan-1-ol using [General Procedure H](#).

The reaction vial was set-up in the same way as in [Graphical Guide 5.1](#).



**LEFT.** Reagents used in this procedure – substrate is home-made (see [S1](#));  $\text{Mn}(\text{OTf})_2$  is purchased from Apollo Scientific and used as found (stored under  $\text{N}_2$ );  $\text{MgCl}_2$  is purchased from Acros Organics and used as found (stored under  $\text{N}_2$ ); TBAOAc is purchased from Apollo Scientific and is used as found. **MIDDLE.** The substrate is added to a flame-dried 10 mL RBF and all other reagents are added to the oven-dried ES vial. **RIGHT.** MeCN (3.25 mL) and AcOH (0.75 mL) are added to the ES vial and MeCN (2 mL) is added to the 10 mL RBF.

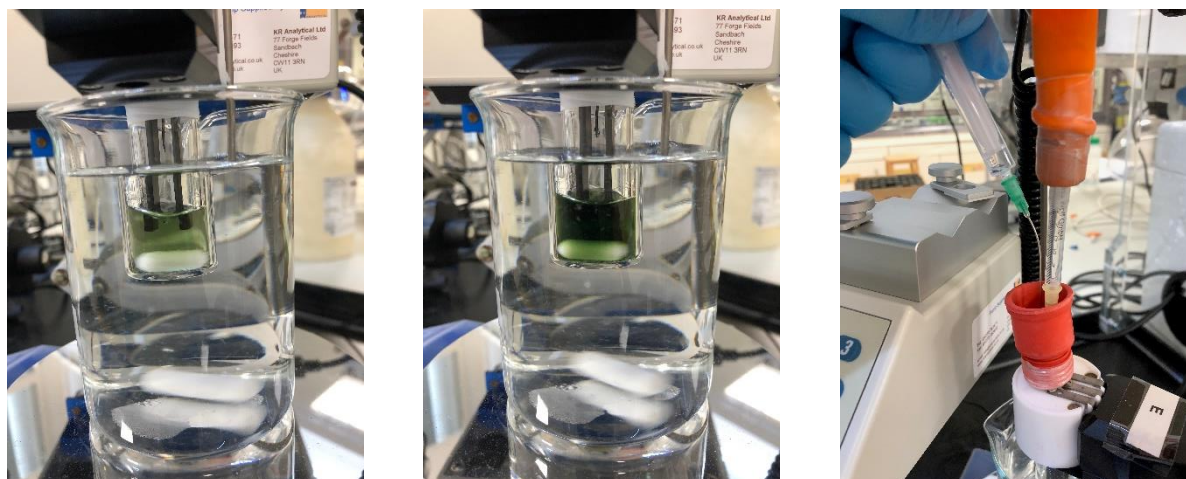


**LEFT.** The reaction mixture is purged with  $\text{N}_2$ , ensuring the needle spewing  $\text{N}_2$  gas is kept at the bottom of the vial. The reaction mixture is vented to the atmosphere during this time with another needle. Take care not to bubble the  $\text{N}_2$  too vigorously or the solvent can begin to evaporate. The purging takes place for 10 minutes in the ES vial. For the solution in the RBF, purging is conducted for 2 minutes, after which a slow  $\text{N}_2$  stream is introduced just above the solvent level to avoid evaporation/concentration of the solution. **MIDDLE.** During the purge, the ElectraSyn 2.0 is switched on and arranged as pictured using a GOGO module to position the vial in a water bath, set at 25 °C. Next to this arrangement, a syringe pump is placed on a lab jack just above the level of the GOGO adapter. **RIGHT.** The settings of the syringe pump are set. The internal diameter of the syringe (brand

and volume exclusive) is input. The volume is set to 2.5 mL. The flow rate is set to 1 mL/h. The delay is set to 2 minutes. These parameters are not changed on occasions where the substrate solution is greater or less than 2 mL. The ElectraSyn 2.0 is also set up in the same as way as General Guide 5.1. If the experiment has been saved, this can be accessed in the “Experiments” section from the “Main Menu”.



**LEFT.** Once the reaction mixture is purged, it is placed onto the GOGO module and positioned in the water bath, under a  $N_2$  atmosphere, either by balloon or connected to a Schlenk line. The substrate solution is drawn up into a NORM-JECT® 2 mL disposable syringe, fitted with a Sterican® 120 mm, 21-gauge needle. The syringe is positioned into the syringe pump with the needle inserted through the septum of the ES cap, ensuring that the end of the needle can be seen through the side of the reaction vial – this ensures efficient addition to the reaction mixture. Balloon omitted for clarity. **MIDDLE.** Close-up of LEFT image. **RIGHT.** Full set-up with balloon. The ElectraSyn experiment is started at the same time as the start of the syringe pump program.



**LEFT.** Reaction mixture after 60 seconds of experiment. Note the needle tip between the electrodes. **MIDDLE.** Reaction mixture after 5 minutes – substrate addition has begun. Usually, the reaction mixture turns a darker green initially indicating a higher concentration of Mn(III) catalyst. Depending on the substrate, this may disappear or become less persistent. **RIGHT.** After the syringe pump program has complete, the pump will stall. At this point, the syringe is backfilled with the  $N_2$  atmosphere, and re-injected into the reaction mixture to help clear the head space of the syringe/needle and ensure complete addition of substrate.

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