The use of aerobic aldehyde C-H activation for the construction of C-C and C-N bonds

By

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Submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy
Declaration

I, Vijay Chudasama, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Vijay Chudasama

August 2011
Abstract

This thesis describes a series of studies directed towards the use of aerobic aldehyde C-H activation for the construction of C-C and C-N bonds by the process of hydroacylation. Chapter 1 provides an introduction to the research project and an overview of strategies for hydroacylation. Chapter 2 describes the application of aerobic aldehyde C-H activation for the hydroacylation of vinyl sulfonates and sulfones. A discussion on the mechanism of the transformation, the effect of using aldehydes with different oxidation profiles and the application of chiral aldehydes is also included. Chapter 3 describes the functionalisation of γ-keto sulfonates with particular emphasis on an elimination/conjugate addition strategy, which provides an indirect approach to the hydroacylation of electron rich alkenes. Chapters 4 and 5 describe the application of aerobic aldehyde C-H activation towards the hydroacylation of α,β-unsaturated esters and vinyl phosphonates, respectively. An in-depth discussion on the mechanism and aldehyde tolerance of each transformation is also included. Chapter 6 describes acyl radical approaches towards C-N bond formation with particular emphasis on the synthesis of amides and acyl hydrazides.
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<th>Definition</th>
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<tr>
<td>$[\alpha]_D$</td>
<td>Specific rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>Boiling point</td>
</tr>
<tr>
<td>BBN</td>
<td>Borabicyclo[3.3.1]-nonane</td>
</tr>
<tr>
<td>BHT</td>
<td>2,6-Di-tert-butyl-4-methylphenol</td>
</tr>
<tr>
<td>BMIM</td>
<td>1-Butyl-3-methylimidazolium</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Cl</td>
<td>Chemical ionisation</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless enhancement by polarisation transfer</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>$E$</td>
<td>Entgegen (opposite, trans)</td>
</tr>
<tr>
<td>EDG</td>
<td>Electron donating group</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EI</td>
<td>Electron ionisation</td>
</tr>
<tr>
<td>EPR</td>
<td>Electron paramagnetic resonance</td>
</tr>
<tr>
<td>ES</td>
<td>Electrospray</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast atom bombardment</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
</tbody>
</table>
Chapter 1  Introduction

1.1 Modern organic synthesis

Modern organic synthesis requires the development of efficient methods for the construction of complex molecules. Chemists aspire to develop reactions that are generic, selective, reliable and scalable. Increasingly chemists are required to conceive of transformations with enhanced atom-economy and minimal waste production.\(^1\) Of central importance in organic synthesis is the development of C-C bond forming reactions and as such there are many examples of elegant and efficient C-C bond forming processes, many of which are promoted with sub-stoichiometric reagents and catalysts.\(^2-4\) Moreover, there are several examples of thermal and photochemical reactions that generate multiple C-C bonds, often as part of polycyclisations or cycloadditions, which are synthetically efficient, generally proceed in the absence of external reagents and produce minimal waste.\(^5-7\) For example, Danishefsky successfully utilised a highly efficient Diels-Alder reaction between diene 1 and dienophile 2 in the synthesis of disodium prephenate 5 and disodium epiprephenate 6 (Scheme 1) to identify the stereochemistry of prephenic acid.\(^8\)

\[
\begin{align*}
&\text{TMSO} \quad \text{OMe} \\
&\text{OMe} \quad \text{CO}_2\text{Me} \\
&\text{MeO} \quad \text{O}\quad \text{Me}_2\text{CO} \\
&\text{AcOH, EtOAc} \\
&\text{100 °C, neat, 26 h} \\
&\text{1} + \text{2} \rightarrow \text{3} \\
&\text{TMSO} \quad \text{OMe} \\
&\text{OMe} \quad \text{CO}_2\text{Me} \\
&\text{SOPh} \\
&\text{SOPh} \\
&\text{4} \rightarrow \text{5} + \text{6} \\
&\text{i) 9-BBN} \\
&\text{ii) NaOH}
\end{align*}
\]

Scheme 1. Use of a Diels-Alder cyclisation *en route* to prephenates 5 and 6.\(^8\)

Despite the successful development of a plethora of useful protocols, it is still the case that numerous synthetic transformations employ a multi-step mode of reactivity (Scheme 2). This common mode of reactivity depends on a number of factors: i) ease
of introduction of precursor 8 from starting material 7, ii) ease of precursor conversion into active species 9 and iii) selectivity and efficiency of the reactivity of active species 9 to produce desired reaction product 10.

![Scheme 2. Common synthetic strategy for chemical transformations.](image)

Each step in the process introduces inefficiencies that multiply through the multi-step conversion and typically involve the use of additional reagents, which inherently results in increased waste production. For example, conversion of cyclohexanone 11 to diene 14 proceeds through conversion to precursor triflate 12, followed by palladium activation and reaction with vinylic tin species 13 (Scheme 3). Despite the disadvantages of the multi-step procedure, some good examples of useful methods employing this approach include metathesis reactions and metal-catalysed coupling. These reactions have been used widely in organic synthesis owing to their invaluable strength in reliably transforming chemical entities.

![Scheme 3. Use of Stille coupling to form diene 14 from cyclohexanone 11.](image)

1.2 C-H activation

A potentially more appealing strategy to those that employ a multi-step protocol is C-H activation, which forms the basis of a good deal of known carbanion methodology. A significant amount of this work involves the use of a directing group (e.g. directed ortho-metalation) or simply utilising the differential acidity associated with activated C-H bonds. For example, imine 15 is used as a directing group to promote ortho-hydroarylation of alkene 16 (Scheme 4). It should also be noted that the use of more elaborate and unusual organometallic complexes to effect C-H activation have recently been reported.
1.2.1 C-H activation of aldehydes

Aldehyde C-H bonds are not very acidic and are therefore not generally perceived as good targets for C-H activation as compared to other C-H bonds. Moreover, aldehydes are extremely good electrophiles and are consequently often employed as the electrophilic component in nucleophilic addition processes. However, despite those factors there are some examples of the use of aldehydes as latent nucleophiles for hydroacylation chemistry.

1.3 Methods for hydroacylation

The hydroacylation of an alkene with an aldehyde to form a ketone (Scheme 5) has generated much attention over the years. In this type of transformation the normal mode of reactivity of an aldehyde is reversed in that it behaves as a nucleophile. As C-C bond forming reactions of this type will form the focus of this thesis, a brief review of what has been achieved in the area of hydroacylation will be presented.

There are a number of methods for hydroacylation, including: the Stetter reaction, dithiane chemistry, transition metal catalysed reactions and hydroacylation via acyl radicals, and each of these methods will be discussed in turn.

1.3.1 The Stetter reaction

One of the earliest known reactions in organic chemistry is the benzoin condensation, in which aromatic and heterocyclic aldehydes are transformed into acyloins on
reaction with cyanide (Scheme 6). A cyanide ion attacks aldehyde 18 to form alkoxide 21, which after proton transfer generates nucleophilic carbanion 22. This species attacks an aldehyde to generate alkoxide 23, which after proton transfer, eliminates cyanide to generate α-hydroxyketone 25.27

![Scheme 6. Benzoin condensation mechanism.]

In 1973, Stetter and Schreckenberg found that carbanion 22 may also add to the double bond of α,β-unsaturated ketones, esters and nitriles via a mechanism analogous to that observed for benzoin condensation (Scheme 7).22 Conjugate addition of carbanion 22 to α,β-unsaturated compound 26, followed by proton transfer and elimination of cyanide, affords 1,4-dicarbonyl 29.

![Scheme 7. Stetter reaction mechanism to form 1,4-carbonyls.]

One of the major failures of early Stetter reactions was the incompatibility of aliphatic aldehydes owing to their propensity to undergo aldol condensation under the influence of the strongly basic cyanide salts.22 However, aldehyde tolerance was soon extended to aliphatic aldehydes by Stetter and Schreckenberg in 1976 via the
application of thiazolium salts in the presence of base (Scheme 8). Thiazolium salt 30 acts as a precursor to nucleophilic carbene 31, which in turn is able to attack an aldehyde to form Breslow intermediate 32. The 1,4-addition of enol 32 to α,β-unsaturated carbonyl compound 26 generates 1,4-dicarbonyl 29 after elimination of carbene species 31.

Scheme 8. Stetter mechanism via the application of thiazolium salt 30.

The scope of the Stetter reaction has further been extended via the use of chiral carbenes to impart stereoselectivity. For example, cyclisation of aldehyde 33 employing a sub-stoichiometric amount of thiazolium salt 34 afforded cyclic ketone 35 with high enantioselectivity and in good yield (Scheme 9). However, despite the advances in the hydroacylation arena with the employment of thiazolium salts in the presence of base, self condensation of aldehydes remains a significant problem.

Scheme 9. Intramolecular enantioselective Stetter reaction.
1.3.2 Dithiane chemistry

A common indirect route to reverse the polarity of an aldehyde is via the conversion of aldehyde 18 to dithiane 37 on application of dithiol 36 and a Lewis acid (Scheme 10). Dithiane 37 may then be deprotonated under strongly basic conditions (e.g. n-butyllithium) to generate metalated intermediate 38, which may undergo conjugate addition to electron poor alkene 39 to give dithiane 40. Finally, this species may be converted to ketone 41 under the appropriate deprotection conditions (i.e. mercuric acetate, Raney Ni/hydrogen). It is for these reasons that the dithiane moiety is generally considered as an acyl anion equivalent. However, as the strongly basic conditions are incompatible with a range of functional groups, this strategy has received relatively modest uptake in the hydroacylation arena. The multi-step protocol and generation of significant amounts of waste may also have contributed to its limited use.

Scheme 10. Hydroacylation of an alkene via dithiane chemistry.

1.3.3 Transition metal catalysed hydroacylation

Many transition metals, in particular rhodium, have been applied as catalysts for the hydroacylation of alkenes (Scheme 11). In general, metal aldehyde C-H oxidative insertion forms acyl metal hydride 42, which inserts into an unsaturated C-C bond to generate alkyl metal complex 44. Reductive elimination from this species affords ketone 45 and regenerates the catalytic metal species. However, transition metal catalysed hydroacylation is significantly complicated by decarbonylation of acyl metal hydride 42 to form metal hydride 46. The resultant alkyl metal hydride can then undergo reductive elimination to afford alkane 47 and metal carbonyl complex 48.
Decarbonylation in transition metal catalysed hydroacylation can be suppressed on coordinative saturation of intermediate acyl metal hydride 49 to form saturated species 50 (Figure 1). Coordinative saturation in this way is often affected by employing a high pressure of ethylene or carbon monoxide.\(^{35-37}\)

Figure 1. Coordinatively unsaturated species 49 and saturated metal species 50.

An intramolecular coordinating group has also been employed to combat the problem of decarbonylation (Scheme 12).\(^ {38-41}\) Thus, aldehyde 51, bearing an appropriately positioned coordinating functional group may coordinatively saturate the metal species, 52. A major limitation of this strategy is that it is restricted to aldehydes that have an appropriately positioned heteroatom.

Scheme 12. Chelation controlled intermolecular hydroacylation.\(^ {40}\)

However, Willis has shown that the β-thioketal and β-sulphide products obtained from hydroacylation using aldehydes with appropriately coordinating thioketal and sulphide functional groups may be cleaved with Raney Ni or eliminated, respectively.
Despite this advance, the work is still very limited with respect to aldehydes that can be applied.

\[
\begin{align*}
\text{Scheme 13. Elimination from } \beta\text{-sulphide } & 54 \text{ and hydrogenation of } \beta\text{-thioketal } 56. \\
\text{Elegantly, Jun developed a general intermolecular hydroacylation strategy using rhodium and 2-amino-3-picoline as a co-catalyst (Scheme 14).}^{42-46} \text{ Key intermediate } 58 \text{ is thought to assist in both C-H activation and rhodium coordinative saturation. This methodology of using a masked form of an aldehyde is highly desirable, as in principle any aldehyde can be employed in hydroacylation of a suitable alkene.}^{42-44,47,48}
\end{align*}
\]

Although the elegance and utility of the hydroacylation strategies discussed thus far are appreciated, there are still many issues associated with the use of metal-based catalysts, multi-step procedures, harsh reaction conditions and/or the production of significant waste. Perhaps for these reasons, the most common way of carrying out hydroacylation is through the formation of acyl radicals.

**1.3.4 Hydroacylation via acyl radicals**

As this method holds the most potential for development and is the most pertinent to this thesis, it will be discussed in depth. Prior to a discussion on hydroacylation via
acyl radicals, a brief overview of current methods for generating acyl radicals and the properties of them will be given.

1.3.4.1 Methods for the generation of acyl radicals

Conceptually three different methods for the generation of acyl radicals may be envisaged: i) homolytic rupture of a RC(O)-X bond, ii) carbonylation of a carbon-centred radical and iii) fragmentation of a C-C bond (e.g. loss of CO$_2$ from an $\alpha$-ketocarboxyl radical or a Norrish-type I cleavage). The latter of these techniques is of importance in yielding acyl radicals for spectroscopic and mechanistic studies and will not be discussed. Although the second method is gaining in prominence in recent years, it is limited by its requirement for a high pressure of carbon monoxide and often employs undesirable toxic reagents such as organotin species. For example, iodobenzene 59 is converted to benzaldehyde 60 via the application of a high pressure of carbon monoxide, AIBN as a radical initiator and tributyltin hydride as a source of hydrogen atoms (Scheme 15). The homolytic rupture of a RC(O)-X bond is by far the most widely applied method to generate acyl radicals and will be discussed in detail herein.

$$\begin{align*}
\text{Iodobenzene 59} & \xrightarrow{\text{AIBN, Bu$_3$SnH, Benzene, 80 ºC, 80 atm CO}} \text{Benzaldehyde 60, 82%} \\
\end{align*}$$

Scheme 15. Conversion of aryl iodide 59 to benzaldehyde 60.$^{49}$

1.3.4.1.1 Generation of acyl radicals from RC(O)-X

In the method of generating an acyl radical from RC(O)-X, X has wide scope as it constitutes any group that will result in the C-X bond being susceptible to homolytic cleavage. As such, acyl radicals may be formed from a wide range of precursors such as acid chlorides and selenoesters. However, despite acid chlorides and selenoesters reliably providing access to acyl radicals, they frequently require the application of undesirable toxic reagents. For example, selenoester 61 may be converted to aldehyde 62 through the use of AIBN and tributyltin hydride (Scheme 16).$^{50-55}$
Other common methods for acyl radical generation from RC(O)-X tend to require photolytic excitation. Using photolytic methods, acyl radicals may be generated from carboxylic acids via ketocarboxyl radicals, thio- and telluro-esters, acylcobalt (III) derivatives, metal carbene complexes and acylphosphine oxides. However, as it is of most relevance, the following section will concentrate on the generation of acyl radicals from aldehydes.

1.3.4.1.2 Generation of acyl radicals from aldehydes

Homolytic scission of an aldehydic C-H bond leads to the formation of an acyl radical and this process is found to be particularly favourable if the abstracting radical is electrophilic. In contrast, application of a nucleophilic alkyl radical for the abstraction of an aldehydic hydrogen atom results in a relatively slow homolytic scission process. This effect is clearly seen in the peroxide induced decarbonylation of aldehydes. This process, in the absence of any external catalysts, is highly unproductive due to the inefficient chain transfer step of aldehydic hydrogen atom abstraction by nucleophilic alkyl radical, derived from decarbonylation of acyl radical (Scheme 17).

![Scheme 17. An inefficient chain transfer process.](image)

However, as initially detailed by Harris and Waters, the presence of a thiol dramatically increases the efficiency of the process. In essence, the inefficient two-step process is superseded by a far more efficient three-step process in which electrophilic thiyl radical abstracts an aldehydic hydrogen atom instead of...
nucleophilic alkyl radical 64 (Scheme 18). In accordance with aldehydic hydrogen atom abstraction being more efficient with more electrophilic radicals, aryl radicals have been shown to be far more efficient aldehydic hydrogen atom abstractors (ca. 3-4 orders of magnitude) when compared with less electrophilic alkyl radicals.\textsuperscript{74,75}

\[
\begin{align*}
R^1\text{H} & \xrightarrow{X^*-\text{HX}} R^1\text{O} & \xrightarrow{\text{CO}} R^1\text{O} & \xrightarrow{R^2\text{S-H}} R^2\text{S}^- & \xrightarrow{\text{efficient}} R^1\text{O}^- + R^2\text{S-H} \\
18 & & 63 & & 64 & & 65 & & 66 & & 63 & & 65
\end{align*}
\]

Scheme 18. Thiol catalysed decarbonylation.

Hydrogen atom abstraction from aldehydes by oxygen centred radicals is a very clean method that has been widely used for analysing acyl radicals via EPR and is by far the most common method for generating acyl radicals from aldehydes.\textsuperscript{26} There are two general methods by which oxygen centred radicals are generated: UV irradiation or thermal decomposition of a peroxide species (Scheme 19).

\[
\begin{align*}
R^1\text{O}-\text{OR}^1 & \xrightarrow{\text{hv or heat}} 2R^1\text{O}^- \\
67 & & 68 \\
R^2\text{H} & \xrightarrow{R^1\text{O}^-} R^2\text{OH} & \xrightarrow{\text{R}^2\text{O}}
\end{align*}
\]

Scheme 19. A common method for generating acyl radicals from aldehydes.

In addition, the aerobic auto-oxidation of aldehydes to carboxylic acids proceeds via an acyl radical intermediate and the general pathway has been known for many years (Scheme 20). Despite the precise details of the initiation step being unknown, molecular oxygen is thought to be essential to generate acyl radical 63 from aldehyde 18. This species then forms peracyl radical 69 on reaction with molecular oxygen, which subsequently abstracts an aldehydic hydrogen atom to re-generate acyl radical 63 and form peroxy acid 70. Reaction of peracid 70 with aldehyde 18 affords intermediate 71, which undergoes decomposition to form two moles of acid 72.
1.3.4.2 Properties of acyl radicals

1.3.4.2.1 Electron Paramagnetic Resonance (EPR)

It is very well established by both theory and experiment that the radical centre of an acyl radical is bent and the unpaired electron occupies an orbital with substantial 2s character, and therefore the acyl radical is a $\sigma$-type radical. In a theoretical study it has been determined by Guerra that for a variety of $\alpha$-substituted acyl radicals (XC(O)$^\cdot$; where X = H, CH$_3$, NH$_2$, OC(CH$_3$)$_3$ and F), angle $a$ lies within a narrow range of 126.6-130.8° (Figure 2, Table 1).

![Figure 2. $\sigma$-Type acyl radical with bond angle $a$.](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Angle $a$ (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>126.6</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>129.4</td>
</tr>
<tr>
<td>NH$_2$</td>
<td>130.8</td>
</tr>
<tr>
<td>OC(CH$_3$)$_3$</td>
<td>128.6</td>
</tr>
<tr>
<td>F</td>
<td>128.1</td>
</tr>
</tbody>
</table>

Table 1. Variation in bond angle $a$ for different R groups.
1.3.4.2.2 Thermodynamic data

An interesting characteristic of aldehydes such as acetaldehyde, \(n\)-propanal, acrolein and benzaldehyde is their similar RC(O)-H bond dissociation enthalpies (Scheme 21, Table 2).\textsuperscript{77-79} Perhaps this is not so surprising since EPR spectroscopy has shown acyl radicals to be \(\sigma\)-type radicals (see Section 1.3.4.2.1). As there is little or no delocalisation of the unpaired electron when there is a neighbouring aromatic or vinylic system, the aldehyde C-H bond strength is likely to be virtually independent of the R group.

![Scheme 21. Aldehyde RC(O)-H dissociation.](image)

<table>
<thead>
<tr>
<th>RC(O)-H</th>
<th>(D^o) (kcal mol(^{-1}))</th>
<th>(E^o) (V) for RC(O)•</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)C(O)-H</td>
<td>89.3</td>
<td>-1.75</td>
</tr>
<tr>
<td>CH(_3)CH(_2)C(O)-H</td>
<td>89.5</td>
<td>-1.75</td>
</tr>
<tr>
<td>CH(_2)=CHC(O)-H</td>
<td>89.1</td>
<td>-1.07</td>
</tr>
<tr>
<td>PhC(O)-H</td>
<td>88.9</td>
<td>-1.13</td>
</tr>
</tbody>
</table>

Table 2. Dissociation enthalpies and reduction potentials for a range of aldehydes and their corresponding acyl radicals, respectively.\textsuperscript{77}

The redox properties of acyl radicals have also been reported (Scheme 21, Table 2).\textsuperscript{80} The acyl radicals were generated indirectly via the electrochemical reduction of acyl chlorides and anhydrides (RC(O)-X) by an aromatic radical anion.\textsuperscript{80,81} The standard potentials of alkyl substituted acyl radicals were shown to be between -1.68 and -1.75 V, whereas for aryl substituted radicals they were between -1.07 and -1.16 V.\textsuperscript{80,81} The 600-700 mV difference may be interpreted as being a consequence of the superior stability of aromatic acyl anions due to the delocalisation of the negative charge into the aromatic ring.
1.3.4.2.3 Infrared and electronic absorption spectra

Ingold and co-workers have reported the IR spectra of a variety of acyl radicals in solution (Table 3).\textsuperscript{82} The C=O stretching frequencies of the corresponding aldehydes have also been included for ease of direct comparison.\textsuperscript{82-84} The larger stretching frequencies observed for acyl radicals over their aldehyde analogues may be attributed to the delocalisation of the unpaired electron into the carbonyl functionality, consequently increasing the carbonyl bond order. The lower C=O stretching frequencies observed for aryl-substituted acyl radicals relative to alkyl-substituted ones may be attributed to conjugation of the carbonyl functionality with the aryl group, consequently reducing bond order.

<table>
<thead>
<tr>
<th>R</th>
<th>$\nu_{\text{C}=\text{O}}$ for RC(O)$^\cdot$ (cm$^{-1}$)</th>
<th>$\nu_{\text{C}=\text{O}}$ for RCHO (cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$</td>
<td>1864</td>
<td>1736</td>
</tr>
<tr>
<td>CH$_3$CH$_2$</td>
<td>1859</td>
<td>1742</td>
</tr>
<tr>
<td>(CH$_3$)$_2$CH</td>
<td>1853</td>
<td>1743</td>
</tr>
<tr>
<td>(CH$_3$)$_3$C</td>
<td>1848</td>
<td>1733</td>
</tr>
<tr>
<td>C$_6$H$_5$</td>
<td>1828</td>
<td>1713</td>
</tr>
<tr>
<td>4-MeOC$_6$H$_4$</td>
<td>1813</td>
<td>1703</td>
</tr>
<tr>
<td>4-BrC$_6$H$_4$</td>
<td>1832</td>
<td>1714</td>
</tr>
<tr>
<td>4-NCC$_6$H$_4$</td>
<td>1824</td>
<td>1716</td>
</tr>
<tr>
<td>mesityl</td>
<td>1805</td>
<td>1742</td>
</tr>
</tbody>
</table>

Table 3. IR stretching frequencies for a range of acyl radicals and aldehydes.\textsuperscript{82}

The electronic absorption spectra of acetyl and pivaloyl radicals show similar characteristics in that they show a broad band at 200-240 nm and do not absorb at $\lambda > 240$ nm.\textsuperscript{85-88} In contrast, aromatic acyl radicals show red-shifted peaks which are attributed to conjugation of the carbonyl moiety with the aryl group.\textsuperscript{88} However, alkyl and aryl substituted acyl radicals show a weak band in the visible region resulting from a $\pi \rightarrow n$ excitation as they are $\sigma$-type radicals.\textsuperscript{89}
1.3.4.3 Intermolecular addition to C-C bonds

The addition of acyl radicals to C-C double bonds provides a useful method for the construction of unsymmetrical ketones (Scheme 22). Generally, acyl radical 63 adds to alkene 43 to form adduct radical 74, which then abstracts an aldehydic hydrogen to form ketone 45 and re-generate 63.

![Scheme 22. General reaction pathway for hydroacylation via acyl radicals.]

In general, acyl radicals add more efficiently to electron poor double bonds than to electron rich alkenes and hence it is for this reason that acyl radicals are viewed as nucleophilic. Furthermore, the abstraction of an aldehydic hydrogen atom by radical 74 is more favourable when the abstracting radical is electrophilic; otherwise the process is inefficient (see Section 1.3.4.1.2).

The earliest report of hydroacylation via an acyl radical intermediate came in 1949; Kharasch reported the formation of unsymmetrical ketones from reaction of aldehydes with alkenes under free-radical conditions.\textsuperscript{90} For example, hex-1-ene 75 was hydroacylated with \textit{n}-butanal 18\textit{a} in the presence of di-acetyl peroxide (Scheme 23).\textsuperscript{90}

![Scheme 23. First report of hydroacylation via an acyl radical.]

Soon after the work by Kharasch, Patrick reported the benzoyl peroxide-initiated addition of \textit{n}-butanal 18\textit{a} to diethyl maleate 77 to give succinate 78\textit{a} (Scheme 24).\textsuperscript{91} Huang later demonstrated the successful addition of aldehydes to numerous electron deficient alkenes under similar reaction conditions. For example, ethyl crotonate 79 underwent hydroacylation with \textit{n}-butanal 18\textit{a} in good yield through the use of di-benzoyl peroxide (Scheme 24).\textsuperscript{92}
Numerous other examples have been reported since these early articles, with strained double bonds\textsuperscript{93-96} and perfluoroalkenes\textsuperscript{97,98} providing particularly good acceptors. For example, perfluorinated alkene \textit{81} was hydroacylated with \textit{n}-butanal \textit{18a} in good yield upon thermal decomposition of di-benzoyl peroxide (Scheme 25).

### 1.3.4.4 Polarity reversal catalysis

A major development in the hydroacylation arena came \textit{via} the application of thiols as polarity reversal catalysts for the hydroacylation of electron neutral and electron rich alkenes (Scheme 26).\textsuperscript{99} As discussed previously (see Section 1.3.4.1.2), if adduct radical \textit{74}, derived from addition of acyl radical \textit{63} to alkene \textit{43}, is not electrophilic, abstraction of an aldehydic hydrogen atom is inefficient. However, in the presence of a thiol, adduct radical \textit{74} readily abstracts a hydrogen atom from a thiol to generate ketone \textit{45} and thiy radical \textit{66}. The electrophilic thiy radical is well polarity matched to abstract an aldehydic hydrogen atom and propagate the chain (see Section 1.3.4.1.2).
Recently, it has been reported that N-hydroxyphthalimide (NHPI) also acts as a polarity reversal catalyst for the hydroacylation of a range of alkenes.\textsuperscript{100,101} For example, NHPI has successfully been employed in the hydroacylation of oct-1-ene \textsuperscript{83} with \textit{n}-butanal \textsuperscript{18a} in good yield (Scheme 27).\textsuperscript{100}

\begin{center}
\textbf{Scheme 27. Hydroacylation of alkene 83 using NHPI as a polarity reversal catalyst.}\textsuperscript{100}
\end{center}

\textbf{1.3.4.5 Intermolecular addition to C-C triple bonds}

Despite there being a limited number of examples in the literature, the first report of the hydroacylation of an alkyne using acyl radical chemistry came as early as 1954.\textsuperscript{102} Hydroacylation of acetylene \textsuperscript{85} gave an \(\alpha,\beta\)-unsaturated ketone, which then underwent selective hydroacylation to afford symmetrical 1,4-diketone \textsuperscript{86} (Scheme 28).\textsuperscript{102} Similar double hydroacylation chemistry on dimethyl acetylenedicarboxylate was reported by Wiley and Harrell in 1960.\textsuperscript{103}

\begin{center}
\textbf{Scheme 28. First example of the hydroacylation of an alkyne.}\textsuperscript{102}
\end{center}
Later, Ryu utilised acyl radical addition to alkynes in a four component coupling protocol to generate β-functionalised δ,ε-unsaturated ketone 91 (Scheme 29).\textsuperscript{104}

\[
\text{Octyl-Br} \quad \text{CO} \quad \text{CO}_2\text{Et} \quad \text{SnBu}_3 \quad \text{AIBN, Benzene} \quad \text{Oct} \text{CO} \text{CO}_2\text{Et}
\]

\begin{align*}
\text{87} & \quad \text{88} & \quad \text{89} & \quad \text{90} & \quad \text{91} \\
80 \degree C, 8 h & \quad 60\% \\
\end{align*}

Scheme 29. Multi-component coupling to generate ketone 91.\textsuperscript{104}

More recently, Fuchs reported an acyl radical transfer reaction from aldehydes to acetylenic trifluoromethylsulfones to afford acetylenic ketones (Scheme 30).\textsuperscript{105} The mechanism is thought to proceed through acyl radical addition to alkyne 92, α to the sulfone, followed by β-scission to generate acetylenic ketone 93.\textsuperscript{106} The resultant trifluoromethylsulfonyl radical may well undergo α-scission to generate sulfur dioxide and a trifluoromethyl radical, which is well polarity matched to abstract an aldehydic hydrogen atom and propagate the chain.

\[
\text{R} \quad \text{Ph} \quad \text{SO}_2\text{CF}_3
\]

\begin{align*}
\text{18} & \quad \text{92} & \quad \text{93} \\
\text{AIBN} & \quad \text{MeCN, reflux} & \quad 84-90\% \\
\end{align*}

Scheme 30. Alkynylation of aldehydic C-H bonds.\textsuperscript{105}

1.3.4.6 Intermolecular addition to non C-C multiple bonds

1.3.4.6.1 Addition to C=O bonds

The addition of an acyl radical to an aldehyde to form an ester was reported in 1948 in the reaction of benzaldehyde 60 and di-\textit{tert}-butyl peroxide to produce 1,2-diphenylethylene glycol di-benzoate 94, incorporating four molecules of benzaldehyde (Scheme 31).\textsuperscript{107} The mechanism is thought to proceed via addition of the acyl radical derived from benzaldehyde to the oxygen atom of another molecule of benzaldehyde. The resultant radical species then undergoes radical recombination to form 1,2-diphenylethylene glycol dibenzoate 94.
The formation of esters is also frequently observed in the reaction of acyl chlorides with aldehydes in the presence of tin hydride and is believed to proceed through acyl radical addition to an aldehyde. Urry has described numerous examples of addition of aliphatic and aromatic aldehydes across perfluorinated ketones with all reactions proceeding in an oxophilic manner to generate esters. For example, benzaldehyde was shown to participate in the hydroacylation of hexafluoroacetone to form ester (Scheme 32).

Scheme 32. An example of ketone hydroacylation reported by Urry.

1.3.4.6.2 Addition to N=N bonds

The intermolecular addition of acyl radicals to N-N double bonds has also been known for many years. In 1953, Kharasch reported the hydroacylation of azobenzene with benzaldehyde to give acyl hydrazide (Scheme 33). Soon after the early work by Kharasch, Horner and Huisgen reported the hydroacylation of azodicarboxylates.
1.3.4.6.3 Addition to C=N bonds

Although there are a large number of examples of intramolecular addition of acyl radicals to C-N double bonds there is a lack of intermolecular examples. However, the addition of acyl radicals to sulfonyl imines outlined by Kim is a notable exception. Kim described acyl radical additions to phenylsulfonyl oxime ethers in a three component coupling protocol. For example, n-octyl iodide 99 was transformed to oxime ether 101 in 80% yield. Presumably, n-octyl radical, which is generated from n-octyl iodide 99, combines with carbon monoxide to form an acyl radical. This acyl radical may then undergo carbophilic addition to imine 100, followed by β-elimination of the sulfonyl group, to form oxime ether 101 (Scheme 34).

1.3.4.7 Cyclisation reactions of acyl radicals

There is extensive literature on cyclisation reactions involving acyl radicals and an in depth discussion can be found in the review by Chatgilialoglu, Crich and Ryu. The cyclisation of acyl radicals onto C-C and C-N multiple bonds, as well as carbonyl groups, has received much attention owing to the orthogonal nature of this type of radical cyclisation chemistry. For example, the use of a 7-endo cyclisation of a
selenide-derived acyl radical for the synthesis of the (+)-Confertin 104 has recently been reported by Shishido (Scheme 35).\(^{115}\)

\[
\begin{array}{c}
\text{O} \quad \text{SePh} \\
\text{O} \quad \text{OPiv} \\
\text{Bu}_3\text{SnH} \\
\text{AIBN, Toluene} \\
85\% \\
\rightarrow \\
\text{O} \quad \text{OPiv} \\
\text{Steps} \\
\end{array}
\]

Scheme 35. Use of acyl radical cyclisation en route to (+)-Confertin 104.\(^{115}\)

1.3.4.8 Hydroacylation work within the Caddick laboratory

Recently, Caddick reported the hydroacylation of pentafluorophenyl (PFP) and trichlorophenyl (TCP) vinyl sulfonates with a range of aldehydes 18 to form unsymmetrical ketones 107 and 108 (Scheme 36).\(^{116}\) Two sets of reaction conditions were developed to achieve good to excellent yields of hydroacylation products 107 and 108: i) use of 5 equivalents of aldehyde in 1,4-dioxane and ii) use of 2 equivalents of aldehyde in water plus 5 mol% hydrogen peroxide. Both reaction conditions were completely inhibited by the addition of a radical inhibitor, 2,6-di-tert-butyl-4-methylphenol (BHT, 5 mol%), thus suggesting a radical mechanism for the hydroacylation.

\[
\begin{array}{c}
\text{O} \\
\text{SO}_3\text{R}^2 \\
\text{R}^1 \text{H} \\
\text{1,4-dioxane or} \\
\text{H}_2\text{O plus 5 mol% H}_2\text{O}_2 \\
\rightarrow \\
\text{R}^1 \text{H} \\
\text{SO}_3\text{R}^2 \\
\end{array}
\]

Scheme 36. Hydroacylation of vinyl sulfonates 105 and 106.\(^{117}\)

Despite the precise mechanism for the formation of ketones 107 and 108 being unknown, reaction was thought to be initiated by molecular oxygen induced conversion of aldehyde 18 to acyl radical 63, as in the case of aldehyde auto-
oxidation (see Section 1.3.4.1.2). Nucleophilic acyl radical 63 may then be trapped by electron deficient alkene 39 to form adduct radical 109, which is well matched in polarity to abstract an aldehydic hydrogen atom to form hydroacylation product 41 and re-generate acyl radical 63 to complete a chain reaction pathway (Scheme 37).

Scheme 37. Trapping of acyl radical intermediate 63 with an electron deficient alkene 39.

The highly electron deficient nature of vinyl sulfonates made them ideal acyl radical acceptor candidates for the methodology, especially as vinyl sulfonates had already been shown to be excellent radical acceptors.\textsuperscript{116,117} For example, protected iodo-sugar derivative 110 has been shown to undergo efficient radical addition to vinyl sulfonate 105 to form sugar 111 (Scheme 38).\textsuperscript{119} Hence, although very interesting, only highly electron deficient vinyl sulfonates had been shown to be effective partners in this hydroacylation methodology. The scope of the acceptor beyond highly electron poor vinyl sulfonates had not been examined. Furthermore, the affect of using more complex aldehydes for hydroacylation had not been studied. Prior to the report by Caddick,\textsuperscript{120} there appears to be only a single example of a similar aerobic initiation methodology being applied in the literature; Vinogradov stated that dimethyl maleate was hydroacylated with \textit{n}-butanal (10 equivalents) in the presence of air in 89% yield (see Chapter 4).\textsuperscript{121}
Overall, the use of aldehyde auto-oxidation to affect hydroacylation (see Scheme 37) generates C-C bonds through the simple mixing of an aldehyde and alkene in the presence of air. This represents a powerful transformation that may have major implications for the way in which aerobic activation could be used to construct bonds.

1.4 Aims

Previously, the efficient hydroacylation of vinyl sulfonate 105 with a range of aldehydes had been demonstrated in water plus 5 mol% hydrogen peroxide (Scheme 39). However, the role of hydrogen peroxide in the transformation was uncertain and one of the primary objectives of the project was to uncover its function.

Owing to acyl radicals being σ-type radicals, the application of chiral aldehydes for the hydroacylation of vinyl sulfonate 105 was to be examined, with a view to analysing if there was any retention of enantiomeric excess (Scheme 40).

A range of γ-keto sulfonates had been prepared within the Caddick group, via the hydroacylation of vinyl sulfonate 105, and the synthetic utility of this novel motif
was to be investigated. An elimination-addition strategy was thought to be very useful as it would provide a powerful indirect alternative to the hydroacylation of electron rich alkenes (Scheme 41).

$$\begin{align*}
\text{R}^1\text{O} & \quad \text{SO}_3\text{R}^2 \\
\text{i) Elimination} & \quad \text{ii) Addition} \\
\rightarrow & \quad \text{Nuc}
\end{align*}$$

Scheme 41. Transformation of sulfonate 112 to ketone 113 via elimination-addition.

Finally, the use of aerobic aldehyde C-H activation for the hydroacylation of a range of other electron poor acceptors for the construction of C-C and C-N bonds was also to be explored (Scheme 42).

$$\begin{align*}
\text{R}^1\text{H} & \quad \text{X} \quad \text{EWG} \\
\rightarrow & \quad \text{R}^1\text{X} \quad \text{EWG}
\end{align*}$$

Scheme 42. Hydroacylation of acceptor 114 with aldehyde 18 to form construct 115.
Chapter 2 Hydroacylation of vinyl sulfonates and sulfones

2.1 Role of hydrogen peroxide

Previously it was reported that vinyl sulfonate 105 may undergo efficient hydroacylation with a range of aldehydes in the presence of water and 5 mol% hydrogen peroxide.\(^{123}\) For example, under such reaction conditions, vinyl sulfonate 105 was converted to ketone 107a in 84% yield on reaction with \(n\)-butanal 18a (Scheme 43, Table 4, Entry 1). Curious of the role of hydrogen peroxide in the transformation, a reaction in the absence of hydrogen peroxide was carried out, and this afforded ketone 107a in 78% yield (Scheme 43, Table 4, Entry 2). Hence, it was concluded that the addition of hydrogen peroxide was not essential for hydroacylation to take place.

Scheme 43. Hydroacylation of vinyl sulfonate 105 with \(n\)-butanal 18a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time/h</th>
<th>Yield 107a/%</th>
<th>Yield 116/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(H_2O), 5 mol% (H_2O_2)</td>
<td>1</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>(H_2O)</td>
<td>3</td>
<td>78</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 4. Yields for the formation of ketone 107a and enol 116.

Although additional hydrogen peroxide was not essential for hydroacylation of vinyl sulfonate 105 with \(n\)-butanal 18a, there were three major differences between reaction with and without hydrogen peroxide (Scheme 43, Table 4). Firstly, a slightly lower yield was observed in the absence of hydrogen peroxide, 78%, compared to in the presence of the peroxide species, 84%. Additionally, reaction was complete in 1 h with hydrogen peroxide and in 3 h without hydrogen peroxide. Finally, a small amount of enol 116\(^ {124,125}\) formed under the neat water conditions, but was not
observed when the reaction was carried out in the presence of hydrogen peroxide. A postulated mechanism by which enol 116 may have formed is given in Scheme 44. 

\( n \)-Butanal 18a is transformed to acyl radical 63a via the action of molecular oxygen. This acyl radical species may then undergo nucleophilic radical addition to vinyl sulfonate 105 to form adduct radical 117a, which upon reaction with molecular oxygen affords peroxo radical 118a. Finally, aldehydic hydrogen atom abstraction from aldehyde 18a affords hydroperoxide 119a, which may be transformed to enol 116 through elimination of sulfonate, attack of water and loss of hydrogen peroxide. The radical nature of the mechanism is supported by the complete inhibition of reactivity observed upon addition of a radical inhibitor, BHT (5 mol%).

Scheme 44. Postulated mechanism for formation of enol 116.

Since the proposed mechanism for the formation of enol 116 involves loss of hydrogen peroxide, perhaps its formation provides an in-situ source of hydrogen peroxide. Hence, if enol 116 had formed prior to formation of ketone 107a in the neat water conditions, the hydrogen peroxide liberated on formation of enol 116 may be responsible for subsequent hydroacylation. To explore this, reaction of vinyl sulfonate 105 with \( n \)-butanal 18a in the presence of water was monitored by \(^1\)H NMR. As ketone 107a formed in significant quantities prior to formation of enol 116, this suggested that hydrogen peroxide was not required to affect hydroacylation of vinyl sulfonate 105.

Although non-essential, hydrogen peroxide was certainly influencing the hydroacylation of vinyl sulfonate 105 with respect to rate of reaction and yield. To this end, the potential for hydrogen peroxide to be acting as a source of hydroxyl radicals, via a range of different pathways, was explored. Thermolysis of hydrogen
peroxide was excluded as it appears non-viable at room temperature due to the strength of the O-O bond. Photolysis of hydrogen peroxide to form hydroxyl radicals was also excluded as it would require a wavelength of light that is not in the visible range. Finally, decomposition of hydrogen peroxide via the action of Fe$^{2+}$ was also dismissed, as the concentration of Fe$^{2+}$ in water was too low, less than 1 ppt by ICP analysis, for such a pathway to be plausible.

A feasible explanation of the role of hydrogen peroxide is that it may act as a catalyst (Scheme 45). Initially, hydrogen peroxide may donate a hydrogen atom to $\alpha$-sulfonate radical **117a**, which is derived from acyl radical **63a** addition to vinyl sulfonate **105**, to form ketone **107a** and peroxy-radical **121**. This peroxy-radical species may then abstract an aldehydic hydrogen atom to regenerate hydrogen peroxide **120** and complete the chain reaction through the formation of acyl radical **63a**. This overall process may well increase the rate of reaction as peroxy-radicals are known for their excellent ability to abstract aldehydic hydrogen atoms due to their electrophilic character. It may also explain why no enol **116** formed in the presence of hydrogen peroxide. If hydrogen atom abstraction by $\alpha$-sulfonate radical **117a** is faster from hydrogen peroxide than from aldehyde **18a**, the life time of adduct radical **117a** decreases, consequently decreasing the propensity of it to react with molecular oxygen, and thus form enol **116** (see Scheme 44). Furthermore, it has recently been reported that a similar species, N-hydroxyphthalimide (NHPI), acts as a catalyst in the hydroacylation of a range of alkenes (see Scheme 27, Page 17).  

Scheme 45. Postulated role of hydrogen peroxide as a chain carrier.
2.2 Aldehyde auto-oxidation studies

Since hydroacylation of vinyl sulfonate 105 with \( n \)-butanal 18a proceeded in good yield in only 3 h in the presence of only water and air, the scope of this transformation regarding aldehyde variation was explored. At this juncture, in view of testing the methodology with a broad range of aldehydes with respect to auto-oxidation rate, the rates at which different aldehydes auto-oxidised was explored. To obtain a quantitative understanding of how fast different aldehydes auto-oxidised, a volume of 200 \( \mu \)L of aldehyde was stirred at 300 rpm for 2 h and the ratio of aldehyde to acid determined via comparison of the integration signals for the \( \alpha \)-CH\(_2\) protons of each aldehyde and their corresponding acids (Scheme 46, Table 5). Interestingly, aldehydes appeared to auto-oxidise at significantly different rates with only relatively small changes in structure, under the conditions employed. For example, \( n \)-hexanal 18d auto-oxidised to its corresponding acid at a rate far slower to that observed for 2-ethylhexanal 18f (Table 5, Entries 4 and 6).
Scheme 46. Conversion of aldehyde 18 (200 and 500 μL) to acid 72.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 18</th>
<th>18:72 (200 μL)a</th>
<th>18:72 (500 μL)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18a</td>
<td>1:1.08</td>
<td>1:0.37</td>
</tr>
<tr>
<td>2</td>
<td>18b</td>
<td>1:5.11</td>
<td>1:1.04</td>
</tr>
<tr>
<td>3</td>
<td>18c</td>
<td>1:1.20</td>
<td>1:0.39</td>
</tr>
<tr>
<td>4</td>
<td>18d</td>
<td>1:0.37</td>
<td>1:0.27</td>
</tr>
<tr>
<td>5</td>
<td>18e</td>
<td>1:0.66</td>
<td>1:0.34</td>
</tr>
<tr>
<td>6</td>
<td>18f</td>
<td>1:2.16</td>
<td>1:0.50</td>
</tr>
<tr>
<td>7</td>
<td>18g</td>
<td>1:0.04</td>
<td>1:0.04</td>
</tr>
</tbody>
</table>

Conditions: aldehyde (200 and 500 μL) was stirred at 300 rpm for 2 h.

Table 5. Ratio of aldehyde 18 to acid 72 after 2 h for 200 and 500 μL of aldehyde.

The effect of changing the surface area of aldehyde exposed to air relative to the volume of aldehyde was also investigated by comparing the rate of oxidation with different volumes of aldehyde, 200 and 500 μL, at a constant surface area (Scheme 46, Table 5). The faster rate of aldehyde auto-oxidation observed at a higher surface area to volume ratio implies that greater exposure to air, and thus molecular oxygen, increases oxidation rate.
The rate at which a range of other aldehydes auto-oxidised was also determined (Scheme 47, Table 6). Although a significant proportion of aldehydes underwent auto-oxidation (Table 6, Entries 1-14), certain aldehydes did not exhibit any detectable acid formation, even after 24 h (Table 6, Entries 15-16). In addition, it is interesting to note that no radical clock or cyclisation products were observed on application of aldehydes 18m and 18o, respectively.

Scheme 47. Conversion of aldehyde 18 (500 μL) to acid 72.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 18</th>
<th>18:72 (500 μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18h</td>
<td>1:1.54</td>
</tr>
<tr>
<td>2</td>
<td>18i</td>
<td>1:0.17</td>
</tr>
<tr>
<td>3</td>
<td>18j</td>
<td>1:0.12</td>
</tr>
<tr>
<td>4</td>
<td>18k&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1:0.25</td>
</tr>
<tr>
<td>5</td>
<td>18l</td>
<td>1:0.06</td>
</tr>
<tr>
<td>6</td>
<td>18m</td>
<td>1:0.32</td>
</tr>
<tr>
<td>7</td>
<td>18n</td>
<td>1:0.14</td>
</tr>
<tr>
<td>8</td>
<td>18o</td>
<td>1:0.18</td>
</tr>
<tr>
<td>9</td>
<td>18p&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1:0.44</td>
</tr>
</tbody>
</table>
Conditions: aldehyde (500 μL) was stirred at 300 rpm for 2 h. 

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>18q</td>
<td>1:0.99</td>
</tr>
<tr>
<td>18r</td>
<td>1:0.24</td>
</tr>
<tr>
<td>18s</td>
<td>1:0.12</td>
</tr>
<tr>
<td>18t</td>
<td>1:0.04</td>
</tr>
<tr>
<td>18u</td>
<td>1:0.03</td>
</tr>
<tr>
<td>18v</td>
<td>1:0.00b</td>
</tr>
<tr>
<td>18w</td>
<td>1:0.00b</td>
</tr>
</tbody>
</table>

Table 6. Ratio of aldehyde 18 to acid 72 after 2 h unless stated otherwise.

The difference in the rate of auto-oxidation of aldehydes in the presence of water, water plus 5 mol% hydrogen peroxide and in the absence of water was also explored. Aldehyde (200 μL) was stirred at 300 rpm under the appropriate conditions (i.e. water, water plus 5 mol% hydrogen peroxide or in the absence of water) for 2 h and the ratio of aldehyde 18 to acid 72 determined via comparison of the integration signals for the α-CH₂ protons of each aldehyde and their corresponding acids (Table 7). In this study, only aldehydes that had acid analogues that were only sparingly soluble in water were chosen due to solubility issues associated with NMR analysis. For the limited number tested, the rate of auto-oxidation in the presence of water appears to be slightly slower as the aldehyde may be in equilibrium with its hydrate.
2.3 Aldehyde scope

In light of the aldehyde auto-oxidation studies (see Section 2.2), the scope of the hydroacylation of vinyl sulfonate 105 with aldehydes 18a-g, which exhibit a broad range of oxidation rates, was examined (Scheme 49, Table 8). These aldehydes were also selected in view of their wide range of hydration equilibrium constants\(^\text{126,127}\) and their broad range of solubilities in water (see Table 8).\(^\text{128}\) Hydroacylation of vinyl sulfonate 105 with aldehydes 18a-g was also carried out with the addition of 5 mol% hydrogen peroxide for direct comparison (Scheme 49, Table 8).
Scheme 49. Hydroacylation of vinyl sulfonate 105 with a variety of aldehydes 18a-g.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 18</th>
<th>Isolated Yield 107 without H₂O₂/%</th>
<th>Isolated Yield 107 with H₂O₂/%</th>
<th>Solubility of 18 in H₂O at 30 ºC/ mass %&lt;sup&gt;d&lt;/sup&gt;</th>
<th>18:122 in D₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18a</td>
<td>78</td>
<td>84</td>
<td>5.48</td>
<td>1:1.04</td>
</tr>
<tr>
<td>2</td>
<td>18b</td>
<td>40&lt;sup&gt;c&lt;/sup&gt;</td>
<td>56</td>
<td>4.57</td>
<td>1:0.86</td>
</tr>
<tr>
<td>3</td>
<td>18c</td>
<td>74</td>
<td>77</td>
<td>1.78</td>
<td>1:0.66</td>
</tr>
<tr>
<td>4</td>
<td>18d</td>
<td>75&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.44</td>
<td>1:0.98</td>
</tr>
<tr>
<td>5</td>
<td>18e</td>
<td>74</td>
<td>79</td>
<td>0.21</td>
<td>1:0.54</td>
</tr>
<tr>
<td>6</td>
<td>18f</td>
<td>83</td>
<td>87</td>
<td>0.05</td>
<td>1:0.03</td>
</tr>
<tr>
<td>7</td>
<td>18g</td>
<td>62&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.02</td>
<td>1:0.12</td>
</tr>
</tbody>
</table>

Conditions: aldehyde (2 eq) and vinyl sulfonate 105 (1 eq) were stirred at 300 rpm at 21 ºC in H₂O or H₂O plus 5 mol% H₂O₂ for 3 h and 1 h, respectively, with 100% conversion of vinyl sulfonate 105 unless stated otherwise. <sup>a</sup> 6 h reaction time, <sup>b</sup> 2 h reaction time, <sup>c</sup> 60% conversion and <sup>d</sup> details given in reference.<sup>129</sup>

Table 8. Yields of ketones 107a-g, and solubility and hydration data for aldehydes 18a-g.<sup>130-132</sup>

Good yields were obtained across the aldehyde series in the neat water reaction conditions with the exception of reaction of vinyl sulfonate 105 with i-butanal 18b (Table 8, Entry 2). This transformation only reached 60% consumption of vinyl
sulfonate 105 due to rapid oxidation of \(i\)-butanal 18b to its corresponding carboxylic acid, consequently giving a low yield of ketone 107b. The major by-product observed for the hydroacylation of vinyl sulfonate 105 with aldehydes 18a-g was believed to be derived from the addition of the respective acyl radical to two molecules of vinyl sulfonate 105, as evidenced in the crude \(^1\)H NMR (Scheme 50). As previously, adduct radical 117 is generated from addition of acyl radical 63 to vinyl sulfonate 105, but instead of adduct radical 117 undergoing reaction with aldehyde 18, it reacts with another molecule of vinyl sulfonate 105, which after aldehydic hydrogen atom abstraction, affords ketone 124.

Scheme 50. Proposed mechanism for the formation of double addition product 124.

Despite the yields for the hydroacylation reactions in neat water being, in general, slightly lower than when 5 mol% of hydrogen peroxide was added, the hydroacylation reactions still proceeded in good yields, and crucially, without the need for any additives (Scheme 49, Table 8). Furthermore, the tolerance of hydroacylation in the presence of water to \(\alpha\)-branched, sterically hindered and lengthy alkyl chain aliphatic aldehydes was particularly encouraging. Also, as there appeared to be no strong correlation between the solubility and hydration properties of aldehydes 18a-g with yield and/or overall reaction rate, this indicated that the extent of hydration and/or solubility may be insignificant for efficient hydroacylation to transpire. Perhaps, water influences the hydroacylation of vinyl sulfonate 105 with aldehydes 18a-g through a hydrophobic effect.

In line with the previously described mechanism (Scheme 37, Page 22), the slower rates of reaction observed for aldehydes that auto-oxidised at slower rates, \(n\)-hexanal 18d and \(n\)-decanal 18g (see Section 2.2), is to some extent expected. Finally, and again fitting with the proposed mechanism, aldehydes 18v and 18w, which did not
appear to auto-oxidise (Table 6, Entries 15-16), gave 0% conversion of vinyl sulfonate 105, even after 72 h (Scheme 51). Heating to higher temperatures, increasing aldehyde loading or increasing reaction time did not improve conversion and/or yield any detectable hydroacylation products 107v or 107w.

Scheme 51. Hydroacylation of vinyl sulfonate 105 with aldehydes 18v and 18w.

2.4 Extending the scope of vinyl sulfonates

Having determined that vinyl sulfonate 105 may undergo efficient hydroacylation with a range of aldehydes, which have varying oxidation profiles, attention turned to the hydroacylation of other vinyl sulfonates.

2.4.1 Ethyl and phenyl vinyl sulfonates

Initially, the use of n-butanal 18a for the hydroacylation of ethyl vinyl sulfonate 125 in the presence of air and water was explored (Scheme 52, Table 9, Entry 1). The low yields obtained for formation of ketone 126a, 35%, was attributed to formation of significant amounts of double addition product 127a, 17%. One possible explanation is that more electron deficient alkenes, such as PFP-vinyl sulfonate 105, undergo more efficient hydroacylation since the adduct radical that results from acyl radical addition to such alkenes are more electrophilic, and therefore better polarity matched to abstract an aldehydic hydrogen atom.
Scheme 52. Hydroacylation of alkene 125 with n-butanal 18a.

Table 9. Yield for hydroacylation product 126a and double addition product 127a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>18a:125</th>
<th>Yield 126a/%</th>
<th>Yield 127a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2:1</td>
<td>35</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>3:1</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>4:1</td>
<td>47</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>5:1</td>
<td>55</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>6:1</td>
<td>54</td>
<td>14</td>
</tr>
</tbody>
</table>

Conditions: aldehyde and vinyl sulfonate were stirred at 300 rpm at 21 °C in H2O.

Eager to increase the yield of ketone 126a, the affect of increasing aldehyde equivalence was explored (Scheme 52, Table 9, Entries 2-5). Optimal yield for hydroacylation of alkene 125 was achieved with 5 equivalents of n-butanal 18a at 21 °C (Table 9, Entry 4). Additional equivalents of aldehyde had no effect on yield, heating resulted in decomposition of hydroacylation product 126a, and use of hydrogen peroxide as a catalyst and/or 1,4-dioxane as solvent did not have a significant impact on yield. The optimised protocol developed for the hydroacylation of alkene 125 with n-butanal 18a was also applied to a secondary aldehyde, cyclohexanecarboxaldehyde 18e, and to alkene 128 (Scheme 53, Table 10). The modest yields obtained for ketones 126b-d was attributed to the formation of significant amounts double addition products 127b-d.
Scheme 53. Hydroacylation of vinyl sulfonates 125 and 128 with aldehydes 18a and 18e (5 equivalents) in the presence of water at 21 °C.

<table>
<thead>
<tr>
<th>Hydroacylation product 126</th>
<th>Isolated Yield 126/%</th>
<th>Double addition product 127</th>
<th>Yield 127/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>52</td>
<td>O</td>
<td>16&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SO&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td></td>
<td>SO&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td></td>
</tr>
<tr>
<td>126b</td>
<td></td>
<td>127b</td>
<td></td>
</tr>
<tr>
<td>&lt;br&gt;</td>
<td></td>
<td>O</td>
<td>15&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SO&lt;sub&gt;3&lt;/sub&gt;Et</td>
<td>52</td>
<td>SO&lt;sub&gt;3&lt;/sub&gt;Et</td>
<td></td>
</tr>
<tr>
<td>126c</td>
<td></td>
<td>127c</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>57</td>
<td>O</td>
<td>14&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SO&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td></td>
<td>SO&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td></td>
</tr>
<tr>
<td>126d</td>
<td></td>
<td>127d</td>
<td></td>
</tr>
</tbody>
</table>
| Conditions: aldehyde (5 eq) and vinyl sulfonate (1 eq) were stirred at 300 rpm at 21 °C in H<sub>2</sub>O. *Isolated yield and <sup>b</sup>NMR yield by analogy of <sup>1</sup>H NMR shifts for double addition product 127a.

Table 10. Yields for hydroacylation products 126b-d and double addition products 127b-d.

2.4.2 β-Substituted vinyl sulfonates

As a range of vinyl sulfonates had been shown to be tolerant of the aerobic activation hydroacylation methodology, the affect of β-substitution on the vinyl sulfonate motif was explored. β-Phenyl-PFP-vinyl sulfonate 129 was synthesised from trans-β-styrene sulfonyl chloride <i>via</i> the application of pentafluorophenol and triethylamine, and reacted with n-butanal 18a in the presence of air and water. This resulted in 0% conversion of alkene 129, even after 96 h when all the aldehyde had been converted to acid (Scheme 54). Heating to higher temperatures, adding greater equivalents of n-butanal 18a, addition of hydrogen peroxide and/or using 1,4-dioxane as solvent did not improve conversion and the lack of reactivity of alkene 129 was attributed to aryl-alkene conjugation.
To explore how a β-alkyl vinyl sulfonate would be tolerated by the aerobic hydroacylation protocol, β-\(n\)-propyl vinyl sulfonate 133 was to be synthesised via a modified protocol developed by Ghosez (Scheme 55). However, deprotonation of sulfonate 131 with \(n\)-butyllithium or other bases such as LDA resulted in decomposition of sulfonate 131, and thus, this route to β-substituted alkene 133 was abandoned.

Basic decomposition of sulfonate 131 presumably proceeds through deprotonation, followed by elimination of pentafluorophenolate 136 from α-anion-sulfonate 134 to afford highly reactive sulfene 135, which may undergo further reaction (Scheme 56).

As the route to a β-alkyl substituted-PFP-vinyl sulfonate appeared non-trivial, β-\(n\)-propyl-ethyl-vinyl sulfonate 139a was synthesised through the protocol developed by Ghosez. Sulfonate 137 was deprotonated with \(n\)-butyllithium and the resultant α-anion-sulfonate reacted with diethyl chlorophosphonate to form Horner-Wadsworth-Emmons precursor 138. Application of Horner-Wadsworth-Emmons reaction conditions to phosphonate 138 with \(n\)-butyllithium and \(n\)-butanal 18a afforded vinyl sulfonate 139a in 73% overall yield as a mixture of E:Z (2.86:1) isomers (Scheme 57).
Attempted hydroacylation of vinyl sulfonate 139a with n-butanal 18a did not afford ketone 140 and proceeded with only low conversion of alkene 139a, despite complete conversion of aldehyde to acid (Scheme 58). Attempts to yield the formation of ketone 140 by heating to higher temperatures, adding greater quantities of aldehyde, using a catalytic amount of hydrogen peroxide and/or using 1,4-dioxane as solvent were unsuccessful. These results may be explained by unfavourable steric interactions disfavouring acyl radical addition to alkene 139, and thus suppressing formation of ketone 140.

2.5 Vinyl sulfones

Eager to extend the aerobic hydroacylation methodology beyond vinyl sulfonates, the optimised conditions developed for the hydroacylation of PFP-vinyl sulfonate 105 with n-butanal 18a (see Section 2.3) were applied to the hydroacylation of ethyl vinyl sulfone 141 with n-butanal 18a. Despite ethyl vinyl sulfone 141 undergoing hydroacylation with two equivalents of n-butanal 18a at 21 °C in the presence of water and air, the yield of ketone 143a was poor at 32% due to the formation of significant amount of double addition product 144a, 24%. As such, the reaction conditions were optimised with the most favourable yield of ketone 143a, 64%, achieved at 60 °C with 5 equivalents of n-butanal 18a (Scheme 59, Table 11, Entry 1). This optimised protocol was also applied to the hydroacylation of vinyl sulfones 141 and 142 with aldehydes 18a and 18e to afford γ-keto-sulfones 143b-d (Scheme 59, Table 11, Entries 2-4). Although not all double addition products
were isolated, the modest yields obtained for ketones 143a-d was attributed to the formation of significant amounts of them, as observed by crude $^1$H NMR.

\[
\begin{align*}
\text{R}^1
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{SO}_2
\end{align*}
\]

\[
\begin{align*}
\text{Et} & \quad \text{H}
\end{align*}
\]

Scheme 59. Hydroacylation of vinyl sulfones 141 and 142 with aldehydes 18a and 18e (5 equivalents) in the presence of water at 60 °C.

<table>
<thead>
<tr>
<th>Hydroacylation product 143</th>
<th>Isolated Yield 143/%</th>
<th>Double addition product 144</th>
<th>Yield 144/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>143a</td>
<td>64</td>
<td>144a</td>
<td>12\textsuperscript{a}</td>
</tr>
<tr>
<td>143b</td>
<td>56</td>
<td>144b</td>
<td>16\textsuperscript{b}</td>
</tr>
<tr>
<td>143c</td>
<td>57</td>
<td>144c</td>
<td>15\textsuperscript{b}</td>
</tr>
<tr>
<td>143d</td>
<td>61</td>
<td>144d</td>
<td>10\textsuperscript{a}</td>
</tr>
</tbody>
</table>

Conditions: aldehyde (5 eq) and vinyl sulfone (1 eq) were stirred at 300 rpm at 60 °C in H$_2$O.
\textsuperscript{a}Isolated yield and \textsuperscript{b}NMR yield by analogy of $^1$H NMR shifts for double addition product 144a.

Table 11. Yields for hydroacylation products 143a-d and double addition products 144a-d.

2.6 Hydroacylation with chiral aldehydes

To date, the hydroacylation of olefins with chiral aldehydes has not been reported in the literature. This is perhaps rather surprising since if hydroacylation proceeded \textit{via} a $\sigma$-type acyl radical intermediate, the stereochemistry within the aldehyde motif
would likely be retained (see Section 1.3.4.2). Moreover, through the use of chiral aldehydes, a highly desirable connection to the ever expanding area of organocatalysis would be achieved.\textsuperscript{134} Ideally, in order for the hydroacylation of chiral aldehydes to be most synthetically useful, the aldehyde should be used as the limiting reagent. As vinyl sulfonate 105 had previously undergone highly efficient hydroacylation with a range of aldehydes, it was chosen as the acyl radical acceptor with which to explore hydroacylation with chiral aldehydes (Scheme 60).

\begin{center}
\begin{align*}
\text{R}^* & \text{O} \quad \begin{array}{c}
\text{+} \\
\text{SO}_3\text{PFP}
\end{array} \quad \text{R}^* \\
\text{18}\text{*} & \text{105} \quad \rightarrow \quad \text{R}^* \quad \text{SO}_3\text{PFP} \\
\text{107}\text{*}
\end{align*}
\end{center}

Scheme 60. Hydroacylation of vinyl sulfonate 105 with chiral aldehyde 18*.

2.6.1 Unsuccessful hydroacylation of PFP-vinyl sulfonate

To examine the compatibility of chirality with the developed hydroacylation method, it was decided to use aldehydes that were prone to racemisation. Aldehyde 146 was synthesised from commercially available (S)-ethyl lactate 145 via a two-step protocol (Scheme 61).\textsuperscript{135}

\begin{center}
\begin{align*}
\text{OH} & \quad \text{OEt} \\
\text{145} & \quad \rightarrow \\
\text{H} & \quad \text{OEt} \\
\text{146} & \\
\text{i) TBSCI, Imidazole, DMF} & \\
\text{ii) DIBAL, THF, -78 °C}
\end{align*}
\end{center}

Scheme 61. Protection of alcohol 145, followed by DIBAL reduction to afford aldehyde 146.

Reaction of vinyl sulfonate 105 with chiral aldehyde 146 in the presence of water and air resulted in only 10% conversion of vinyl sulfonate 105 (Scheme 62). Furthermore, ketone 147 was not observed when conditions were varied, including increasing amounts of aldehyde 146, addition of hydrogen peroxide as a catalyst, carrying out the reaction in 1,4-dioxane and/or heating.
Scheme 62. Attempted hydroacylation of vinyl sulfonate 105 with aldehyde 146.

Although all aldehyde 146 was consumed on reaction with vinyl sulfonate 105 in the presence of water, none of the corresponding acid was observed. Only acetaldehyde 18h and unreacted vinyl sulfonate 105 were isolated from the product mixture. One possible explanation for the formation of acetaldehyde 18h is via decarbonylation of acyl radical 148, followed by β-TBS-elimination (Scheme 63).

Scheme 63. Postulated pathway via which acetaldehyde 18h may have formed.

2.6.2 Hydroacylation of vinyl sulfonate with (S)-2-methylbutanal

Due to issues associated with aldehyde 146, another system was sought and (S)-2-methylbutanal 152, which was prepared via the TEMPO oxidation of (S)-2-methylbutanol 151, was chosen (Scheme 64). 136

Scheme 64. TEMPO oxidation of (S)-2-methylbutanol 151.

Reaction of a single equivalent of (S)-2-methylbutanal 152 with a single equivalent of vinyl sulfonate 105 in the presence of water and air afforded ketone 153 in only 47% yield (Scheme 65). However, the exceptional retention of enantiomeric excess observed, by chiral HPLC, on transformation of aldehyde 152 to ketone 153 was very encouraging.
The major reason for the low yield of ketone 153 was attributed to carboxylic acid formation, a competing problem that is always likely to exist in any aerobic based hydroacylation protocol. Hence, the application of non-aerobic hydroacylation strategies, which also proceed through an acyl radical intermediate, were investigated.

### 2.6.3 Low temperature thermal initiators

Initially, to minimise decarbonylation of the acyl radical intermediate generated from aldehyde 152, the use of azobisisobutyronitrile (AIBN), a low temperature thermal initiator, for the reaction of (S)-2-methylbutanal 152 with vinyl sulfonate 105 was explored (Scheme 66, Table 12). Reaction at 60 °C with a 1:1 molar ratio of 152:105 resulted in a modest yield of ketone 153, 46%, with the formation of double addition product 154 and decarbonylated addition product 155 also observed (Scheme 66, Table 12, Entry 1). Alkyl sulfonate 155 is likely to have formed via addition of the alkyl radical, which results from decarbonylation of the acyl radical derived from aldehyde 152, to vinyl sulfonate 105. Thus, the effect of lowering temperature to suppress decarbonylation, and therefore formation of alkyl sulfonate 155, was explored. Gratifyingly, lowering the temperature to 40 °C suppressed formation of alkyl sulfonate 155 and increased the yield of ketone 153 to 52% (Scheme 66, Table 12, Entry 2). In an attempt to increase conversion of vinyl sulfonate 105, the effect of altering the 152:105 ratio from 1:1 to 1:2 was explored (Scheme 66, Table 12, Entries 2-5). Despite there being an increase in the formation of double addition product 154, complete conversion was achieved at 1:1.5 and 1:2 molar ratios of 152:105. The increased conversion was attributed to more efficient acyl radical trapping by vinyl sulfonate 105 due to its higher concentration. Unsurprisingly, this also resulted in a higher yield of double addition product 154 as the adduct radical that results from acyl radical addition to vinyl sulfonate 105 is more likely to be trapped by vinyl sulfonate 105 due to its higher concentration. Optimal yield, 64%,
was achieved at a 1:1.5 molar ratio of **152:105** and the enantiomeric excess of ketone **153** determined to be >98% by chiral HPLC (Scheme 66, Table 12, Entry 4).

![Reaction Scheme](image_url)

Scheme 66. Reaction of (S)-2-methylbutanal **152** with vinyl sulfonate **105**.

<table>
<thead>
<tr>
<th>Entry</th>
<th><strong>152:105</strong></th>
<th>Temperature/°C</th>
<th>Conversion <strong>105%/</strong></th>
<th>Isolated Yield <strong>153%/</strong></th>
<th>Yield <strong>154%/</strong></th>
<th>Isolated Yield <strong>155%/</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>60</td>
<td>80</td>
<td>46</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>40</td>
<td>70</td>
<td>52</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>1:1.2</td>
<td>40</td>
<td>84</td>
<td>60</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>4</td>
<td>1:1.5</td>
<td>40</td>
<td>98</td>
<td>64&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>1:2</td>
<td>40</td>
<td>100</td>
<td>60</td>
<td>18</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Conditions: aldehyde **152** and vinyl sulfonate **105** were stirred at 300 rpm. <sup>a</sup> NMR yield by analogy of <sup>1</sup>H NMR shifts for double addition product **127a** and <sup>b</sup>&gt;98% retained enantiomeric excess.

Table 12. Yield of ketone **153**, double addition product **154** and alkyl sulfonate **155** using various amounts of aldehyde and alkene at various temperatures.

The optimised reaction conditions for the hydroacylation of vinyl sulfonate **105** with aldehyde **152** were applied to the use of another low temperature thermal initiator, lauroyl peroxide. Reaction proceeded with 100% conversion of vinyl sulfonate **105** with only a 30% yield of ketone **153**. The low yield of ketone **153** and complete conversion of vinyl sulfonate **105** was due to the formation of a significant amount of alkyl sulfonate **156** (Figure 3); presumably derived from undecyl radical, generated from the decomposition of lauroyl peroxide, addition to vinyl sulfonate **105**. In contrast, only a trace quantity of alkyl sulfonate **157** was isolated on application of AIBN. This may be a consequence of a less nucleophilic and more sterically crowded, tertiary radical, resulting from decomposition of AIBN.
Figure 3. Initiator derived alkyl sulfonates $\textnormal{156}$ and $\textnormal{157}$.

In an attempt to increase yield of ketone $\textnormal{153}$ from reaction of vinyl sulfonate $\textnormal{105}$ with aldehyde $\textnormal{152}$ using $30 \text{ mol}\%$ AIBN in benzene at $40 \degree \text{C}$, the application of polarity reversal catalysts such as $N$-hydroxyphthalimide and $\text{tert}$-dodecylmercaptan was explored.\textsuperscript{99-101} However, use of these catalysts did not effect yield. In view of the work carried out in Section 2.1, the use of hydrogen peroxide as a catalyst for this transformation was also explored, however, this did not improve yield also. As the use of 1,4-dioxane as solvent had provided good yields for a similar transformation,\textsuperscript{137} it was used in place of benzene. However, this significantly suppressed formation of ketone $\textnormal{153}$, <5%, due to reaction of vinyl sulfonate $\textnormal{105}$ with a radical derived from 1,4-dioxane to form alkyl sulfonate $\textnormal{158}$ in 94% yield (Figure 4).

Figure 4. Alkyl sulfonate $\textnormal{158}$, derived from 1,4-dioxane addition to vinyl sulfonate $\textnormal{105}$.

2.7 Conclusion

A novel method for the hydroacylation of vinyl sulfonates and sulfones in the presence of water using only air for aldehyde C-H activation has been developed. Moreover, a broad range of aldehydes with respect to aldehyde auto-oxidation rate have been shown to be compatible with the reaction conditions. In addition, aldehyde hydration and solubility were shown to have minimal impact on the hydroacylation process and water is thought to influence reaction through a hydrophobic effect. The proof of principle for the hydroacylation of an alkene with a chiral aldehyde has also been demonstrated. This chemistry exploits the $\sigma$-type properties of an acyl radical and provides the first example of hydroacylation with a chiral aldehyde with retention of optical purity.
Chapter 3 Functionalisation of γ-keto sulfonates

A range of γ-keto sulfonates had been synthesised via the hydroacylation of vinyl sulfonates and their synthetic utility was to be examined. The bi-functional γ-keto sulfonate motif has appreciable potential for further manipulation. The carbonyl group is a versatile moiety that can be used in subsequent synthetic transformations and, through the work pioneered by Caddick and Wilden,\textsuperscript{138-141} PFP- and TCP-sulfonates have been shown to be useful alternatives to sulfonyl chlorides for the synthesis of sulfonamides. For example, sugar derived PFP-sulfonate \textsuperscript{111} was readily converted to sulfonamide \textsuperscript{159} in good yield (Scheme 67).

Scheme 67. Conversion of sulfonate \textsuperscript{111} to sulfonamide \textsuperscript{152}.

From the outset, the elimination of sulfonate from ketone \textsuperscript{107} to form enone \textsuperscript{160} was seen as a highly desirable transformation as, in conjunction with the hydroacylation chemistry, it would represent a mild method of converting an aldehyde to an enone (Scheme 68).

Scheme 68. Mild alternative for the formation of enones from aldehydes.

Aldehydes are routinely converted to enones via the addition of a vinylic metal species, followed by allylic alcohol oxidation of resultant alcohol \textsuperscript{162} to form enone \textsuperscript{160} (Scheme 69).\textsuperscript{142,143} Due to the harsh reaction conditions, a mild alternative to achieve the same overall transformation would be highly attractive. Moreover,
conjugate addition of nucleophiles to the enones generated by elimination of sulfonate from keto-sulfonate 107 may provide an indirect alternative for the hydroacylation of electron rich alkenes (see Section 3.1.3).

Scheme 69. Common method for the conversion of aldehydes to enones.

3.1 Studies on elimination from keto-sulfonates and its applications

3.1.1 Elimination of PFP-sulfonate

A small amount of elimination was observed when keto-sulfonate 107a was purified using silica-gel chromatography (Scheme 70). However, all attempts to develop a practical elimination protocol using silica gel in numerous solvents (e.g. CH₂Cl₂, petrol, CHCl₃ and Et₂O) were unsuccessful and led to complete recovery of starting material. Since there was literature precedent for the elimination of β-chloroketones with alumina in CHCl₃, sulfonate 107a was subjected to analogous reaction conditions,¹⁴⁴ however, no conversion was observed. Keto-sulfonate 107a was also stable to a range of acidic conditions (acetic acid, para-toluenesulfonic acid and pyridinium para-toluenesulfonate), with complete recovery of keto-sulfonate 107a being observed in all cases.

Scheme 70. Elimination of sulfonate from keto-sulfonate 107a to form enone 160a.

Encouragingly, elimination was achieved under basic conditions, specifically via the application of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 equivalents). However, although the enone could be confirmed by ¹H NMR,¹⁴⁵ it was difficult to isolate as it was prone to oligomerisation. To obviate this problem, the enone was trapped in situ with a thiol (Scheme 71). Gratifyingly, excellent yields were observed for thioethers
163a and 163b, indicating that the elimination was essentially quantitative. Furthermore, elimination and thiol addition proceeded in a range of solvents (i.e. CH₂Cl₂, CHCl₃, MeOH, Et₂O, PhMe and THF) and in good to excellent yields (72-97%), except on application of triethylamine in CH₂Cl₂, 45%. Despite the elimination of sulfonate from keto-sulfonate 107a proceeding in excellent yield with DBU, the overall reaction suffers from poor atom efficiency due to the elimination of a relatively heavy pentafluorophenol group.

\[
\begin{align*}
\text{n-Pr} & \text{O} \\
& \text{SO₃PFP} \\
\text{107a} & \text{i) DBU (2 eq)} \quad \text{ii) RSH SR} \\
& \text{163a, } R = n\text{-C₆H₁₃}, 98\% \\
& \text{163b, } R = \text{CH₃Tol}, 97\%
\end{align*}
\]

Scheme 71. Elimination-thiol addition to form thioethers 163a and 163b.

3.1.2 Elimination of ethyl sulfonate

In order to try and make the overall transformation more atom efficient, the elimination and thiol trapping protocol was applied to γ-keto-ethyl-sulfonate 126a (Scheme 72).

\[
\begin{align*}
\text{n-Pr} & \text{O} \\
& \text{SO₃Et} \\
\text{126a} & \text{i) DBU (2 eq)} \quad \text{ii) RSH SR} \\
& \text{163a, } R = n\text{-C₆H₁₃}, 80\% \\
& \text{163b, } R = \text{CH₃Tol}, 78\%
\end{align*}
\]

Scheme 72. Elimination of sulfonate from keto-sulfonate 126a, followed by thiol trapping to form thioethers 163a and 163b.

In contrast to PFP-sulfonate analogue 107a, slightly lower yields were obtained when the elimination-addition chemistry was applied to ethyl-sulfonate 126a; this was attributed to competitive addition of ethoxide to the enone generated from elimination. To minimise the unfavourable alkoxide conjugate addition pathway, thiol was added prior to base. Gratifyingly, this resulted in higher yields being obtained for thioethers 163a and 163b (Scheme 73).
Scheme 73. Conversion of γ-keto-sulfonate 126a to thioethers 163a and 163b.

Application of weaker bases such as pyridine or triethylamine did not promote elimination and the use of potassium carbonate was thought to generate sulfonate salt 164 through de-alkylation (Scheme 74).

Scheme 74. Application of triethylamine and potassium carbonate to sulfonate 126a.

Although the formation of salt 164 is undesirable in view of the elimination chemistry, conversion of ethyl sulfonate 126a to potassium salt 164 may be useful in context of synthesising β-substituted-PFP-vinyl sulfonates (Scheme 75). The conversion of ethyl sulfonate 137 to β-substituted-vinyl sulfonate 139 has already been demonstrated (see Section 2.4). If potassium salt 165 may be generated from β-substituted-vinyl sulfonate 139 on application of potassium carbonate, transformation to β-substituted-PFP-vinyl sulfonate 166 should be feasible as the conversion of sulfonate salts to PFP-sulfonates has literature precedent.\footnote{As a range of γ-keto-sulfones had also been prepared via the aerobic hydroacylation protocol (see Section 2.5), and due to the vast amount of literature on the elimination of sulfones, the elimination conditions were applied to sulfone 143a (Scheme 76).}

As significantly lower yields were obtained for elimination from keto-sulfone 143a...
when compared to keto-sulfonates 107a and 126a, this highlights an advantage of the keto-sulfonate motif.

\[
\begin{align*}
\text{n-Pr} & \quad \text{SO}_2\text{Et} \\
\text{143a} & \quad \text{i) RSH} \\
& \quad \text{ii) DBU (2 eq)} \\
\text{163a, } R = n\text{-C}_6\text{H}_{13}, 46\% \\
\text{163b, } R = \text{CH}_2\text{Tol}, 34\%
\end{align*}
\]

Scheme 76. Conversion of sulfone 143a to thioethers 163a and 163b.

**3.1.3 Alternative to the hydroacylation of electron rich alkenes**

A significant feature of the hydroacylation-elimination-addition chemistry is that it provides an indirect alternative to the hydroacylation of electron-rich alkenes (Scheme 77). Moreover, it should be possible to access a variety of unsymmetrical ketones from aldehydes, which would otherwise represent a significant challenge to current electron rich alkene hydroacylation methodologies. A case in point is the hydroacylation of vinyl sulfides, a transformation that has no literature precedent despite the emergence of thiol catalysis. Encouragingly, the indirect hydroacylation-elimination-addition strategy described above does provide access to these molecules, and in good yields. Most significantly, due to the vast amount of literature on conjugate addition chemistry, access to a range of other compounds not accessible via conventional hydroacylation chemistry may be feasible.

\[
\begin{align*}
\text{R} & \quad \text{H} \\
\text{18} & \quad \text{EDG} \\
\text{i) 105, H}_2\text{O} \quad \text{ii) DBU} \\
\text{43} & \quad \text{R} \quad \text{EDG} \\
\text{167} & \quad \text{Nuc} \\
\text{160} & \quad \text{R} \quad \text{H}
\end{align*}
\]

Scheme 77. Hydroacylation-elimination-addition chemistry as an alternative to the direct hydroacylation of electron rich alkenes.
3.2 Sulfonamide and sultone formation

3.2.1 Sulfonamide formation

The conversion of PFP-sulfonate 107a to its n-hexylamine sulfonamide analogue was attempted using previously reported conditions (DBU, amine in THF).\textsuperscript{130-132} However, perhaps unsurprisingly, keto-sulfonate 107a underwent almost exclusive elimination to its corresponding enone under these reaction conditions.\textsuperscript{150} Application of a weaker base, triethylamine, also appeared to promote enone formation, generated minimal sulfonamide (ca. 10\%) and promoted formation of a structure that has been tentatively assigned as sultone salt 169 (Scheme 78). Sultone salt 169 is presumably derived from attack of triethylamine on the carbonyl functionality, followed by attack of the resulting alkoxide anion to displace pentafluorophenolate.

\begin{equation*}
\begin{align*}
n-\text{Pr} & \quad \text{SO_3PFP} \\
107a & \\
& \quad \text{n-Hexylamine} \\
& \quad \text{NEt}_3, \text{THF} \\
& \quad \text{n-Pr} \\
& \quad \text{O} \\
& \quad \text{S} \\
& \quad \text{O} \\
& \quad \text{NEt}_3 \\
& \quad \text{OPFP} \\
& \quad \text{n-Pr} \\
& \quad 169
\end{align*}
\end{equation*}

Scheme 78. Base promoted formation of sultone 169 from keto-sulfonate 107a.

In an attempt to obviate the formation of sultone 169 more polar solvents were employed to encourage direct displacement of pentafluorophenolate. Encouragingly, application of NMP as a solvent gave desired sulfonamide 170a in 45\% yield, with the major side-product being enone derived. Lowering the temperature at which the amine was added, 0 °C, suppressed elimination and resulted in an improved yield of 64\%. To further suppress elimination, an additional equivalent of n-hexylamine was used in place of triethylamine, as n-hexylamine did not promote any elimination of sulfonate from keto-sulfonate 107a (cf. triethylamine). This resulted in an improved yield of 82\% and the reaction protocol was then applied to a secondary and a sterically encumbered primary amine, morpholine and tert-butylamine, respectively (Scheme 79, Table 13). The poor to modest yields observed on application of morpholine and tert-butylamine showed that the methodology may only be applicable to non-sterically demanding primary amines. Nonetheless, the protocol
has provided access to γ-keto-sulfonamides, which have a range of applications.\textsuperscript{151-155}

\[
\text{n-Pr} \quad \begin{array}{c}
\text{SO}_3PF\text{P} \\
\text{H} \end{array} \xrightarrow{\text{R}_2\text{NH} (2.1 \text{ eq})} \text{n-Pr} \quad \begin{array}{c}
\text{SO}_2\text{NR}_2 \\
\text{H} \end{array}
\]

\text{107a} \quad \text{170a-c}

Scheme 79. Conversion of keto-sulfonate \textbf{107a} to sulfonamides \textbf{170a-c}.

<table>
<thead>
<tr>
<th>Sulfonamide 170</th>
<th>Isolated Yield 170/%</th>
</tr>
</thead>
</table>
| \text{n-Pr} \quad \begin{array}{c}
\text{SO}_3PF\text{P} \\
\text{H} \end{array} \quad \text{NH} \\
\text{O} \quad \text{O} | 82 |
| \text{n-Pr} \quad \begin{array}{c}
\text{SO}_3PF\text{P} \\
\text{H} \end{array} \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \quad \text{O} | 32 |
| \text{n-Pr} \quad \begin{array}{c}
\text{SO}_3PF\text{P} \\
\text{H} \end{array} \quad \begin{array}{c}
\text{O} \\
\text{N} \quad \text{H} | 40 |

Conditions: amine (2.1 eq) was added to a solution of keto-sulfonate \textbf{107a} (1 eq) in NMP at 0 °C, the reaction mixture was left to warm to 21 °C and left to stir for 4 h.

Table 13. Yields for conversion of sulfonate \textbf{107a} to sulfonamides \textbf{170a-c}.

Eager to show the synthetic utility of secondary sulfonamide \textbf{170a}, generated by addition of \textit{n}-hexylamine to keto-sulfonate \textbf{107a}, a one-pot reductive-cyclisation protocol was developed for the synthesis of sultam \textbf{171} in excellent yield (Scheme 80). It is envisaged that a wide range of similar sultams may be synthesised in an analogous manner.

\[
\text{n-Pr} \quad \begin{array}{c}
\text{SO}_3PF\text{P} \\
\text{H} \end{array} \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \quad \text{O} | \text{TFA/NaBH}_3\text{CN} | \text{87\%} |
| \text{n-Hexyl} \quad \begin{array}{c}
\text{S} \\
\text{O} \\
\text{O} | \text{171} |

Scheme 80. Conversion of γ-keto-sulfonamide \textbf{170a} to sultam \textbf{171}.
It has been shown that cyclic 3-substituted N-sulfonyl imines of the form of imine 172 may be used as intermediates for the formation of N-sulfonated β-amino acids (Scheme 81).156

Previously, imines of the form of 172 have been accessed via a three step protocol reported by Freitag in 63-68% overall yield.157 However, direct access to N-sulfonylimine 174 was achieved via the bubbling of ammonia gas into a solution of β-keto-sulfonate 107a in CH₂Cl₂ (Scheme 82). Unlike the protocol outlined by Freitag, this method represents a simple and mild route to N-sulfonylimines in which analogue synthesis should be facile. Furthermore, through the work pioneered by Zhou, access to 3-substituted chiral sultams of the form of sultam 175 should be facile.158 The molecules generated by Zhou’s asymmetric hydrogenation protocol are important organic synthetic intermediates and structural units of agricultural and pharmaceutical agents.159

3.2.2 Sultone formation

It was thought that access to sultones could be achieved by simple reduction of the ketone moiety in keto-sulfonate 107a. Gratifyingly, sodium borohydride reduction of the carbonyl group in keto-sulfonate 107a gave access to sultone 176 in good yield (Scheme 83).
3.3 Conclusion

A series of useful synthetic transformations from the $\gamma$-keto-sulfonate motif have been unearthed. The elimination chemistry to generate enones provides a mild alternative route for the overall conversion of an aldehyde to an enone when taken in conjunction with the hydroacylation chemistry described in Chapter 2. Moreover, the hydroacylation-elimination-addition chemistry represents a powerful indirect alternative for the hydroacylation of electron rich alkenes. Finally, the $\gamma$-keto-sulfonate motif may act as a precursor for the formation of $\gamma$-keto-sulfonamides, sultams, $N$-sulfonylimines and sultones.
Chapter 4 Hydroacylation of α,β-unsaturated esters

Keen to extend the aerobic aldehyde C-H activation chemistry to the hydroacylation of acceptors other than vinyl sulfonates and sulfones, the use of α,β-unsaturated esters as acyl radical acceptors was explored. Hydroacylation of α,β-unsaturated esters would readily generate 1,4-dicarbonyl compounds; a motif that is extensively used in synthetic organic chemistry for the construction of heterocycles. Encouragingly, in 1969 Vinogradov reported the hydroacylation of dimethyl maleate 177 with n-butanal 18a (10 equivalents) to form ketone 178a in 89% yield in the presence of air, and crucially, in the absence of any metal, peroxide or other non-aerobic initiator (Scheme 84).

![Scheme 84. Vinogradov’s reported hydroacylation of alkene 177 with n-butanal 18a.](image)

4.1 Reproduction of Vinogradov result

Several attempts to reproduce the reaction of dimethyl maleate 177 with n-butanal 18a (10 equivalents), under the reported conditions, resulted in only low conversion of dimethyl maleate 177 (ca. 10%). In view of the cobalt(II)-intensive work being undertaken by Vinogradov at the time, it was speculated that the reaction might have been promoted by small quantities of cobalt(II) contamination. To investigate this, the effect of the addition of a small amount of cobalt(II) to the reaction of dimethyl maleate 177 with n-butanal 18a, under the conditions reported by Vinogradov, was explored. Cobalt(II) proved to be a highly effective catalyst for the formation of ketone 178a with only 1 mol% of cobalt(II) required to give complete conversion of dimethyl maleate 177 (Scheme 85). As such, it appears that the non-reproducible nature of the hydroacylation reaction reported by Vinogradov (Scheme 84) may have been due to cobalt(II) contamination.
4.2 Hydroacylation of 1,2-diester-alkenes

In order to investigate the use of 1,2-diester alkenes as acyl radical acceptors, the conditions developed for the hydroacylation of vinyl sulfonates and sulfones were applied to the hydroacylation of dimethyl maleate 177 with n-butanal 18a. Unfortunately, reaction of n-butanal 18a with dimethyl maleate 177 in the presence of water proceeded with only low conversion of alkene (ca. 20%) and no desired hydroacylation product 178a was isolated from the reaction mixture. Moreover, addition of hydrogen peroxide, using greater quantities of aldehyde and/or heating did not yield ketone 178a. However, when dimethyl maleate 177 was treated with n-butanal 18a (5 equivalents) at room temperature in 1,4-dioxane, ketone 178a formed, albeit in low yield and at low conversion (Scheme 86). In addition to the expected alkene hydroacylation product 178a, a significant quantity of another species also formed and was tentatively assigned as cyclic peroxide 179a. Although cyclic peroxide species 179a could not be isolated, $^1$H and COSY NMR data supported the structural assignment. This compound appeared to decompose on silica gel to generate a diastereomeric mixture of epoxides 180a and 180b (Scheme 86). Consistent with prior studies, the hydroacylation reaction was inhibited by a radical inhibitor, BHT (5 mol%).

Scheme 85. Addition of cobalt(II) to a mixture of n-butanal 18a and alkene 177.
Scheme 86. Hydroacylation of alkene 177 with n-butanal 18a to form ketone 178a and peroxide 179a, which decomposed to epoxides 180a and 180b on silica gel.

Hydroacylation product 178a is likely to have formed via aerobically initiated conversion of aldehyde 18 to acyl radical 63, which undergoes addition to alkene 177, followed by hydrogen atom abstraction to form ketone 178 (Scheme 87). Cyclic peroxide is thought to be derived from reaction of molecular oxygen with adduct radical 181, which results from acyl radical addition to dimethyl maleate 177. Resultant peroxo radical 182 may then undergo hydrogen atom abstraction followed by cyclisation to form cyclic peroxide 179 (Scheme 87). The key role of molecular oxygen in the transformation was evidenced by the very low conversion observed when reaction of alkene 177 and n-butanal 18a was carried out under an inert atmosphere; only 5% conversion of alkene was observed after 5 days. Furthermore, when reaction of alkene 177 and n-butanal 18a was carried out under an atmosphere of molecular oxygen, rapid conversion of aldehyde to acid was observed with no conversion of alkene (Scheme 87). Thus, careful control of the exposure of the reaction medium to air was thought to be required for efficient hydroacylation to occur.
4.2.1 Controlling the exposure of reaction medium to air

In an attempt to control the exposure of the reaction medium to air, and hence suppress the formation of cyclic peroxide \(179\) and improve the yield of hydroacylation product \(178\), the effect of increasing temperature was explored. Increasing the temperature from 20 °C to 60 °C gave an increase in the yield of ketone \(178\) (Scheme 88, Table 14), although heating to higher temperatures led to decomposition. The increased yield observed at higher temperature was thought to be a consequence of the lower concentration of dissolved molecular oxygen in solution. This may result in a higher conversion of alkene \(177\) as acyl radical \(63\) is more likely to be trapped by alkene \(177\) than react with molecular oxygen to form acid \(72\) (see Scheme 87). Moreover, the lower concentration of molecular oxygen also decreased the \(178a:179a\) ratio from 1:0.38 to 1:0.15 in the 20-80 °C range as it suppressed formation of peroxide \(179\); consequently encouraging formation of ketone \(178a\). This may be a consequence of adduct radical \(181\) being more likely to abstract an aldehydic hydrogen atom than undergo addition to molecular oxygen (see Scheme 87).
Scheme 88. Hydroacylation of alkene 177 with aldehyde 18a in 1,4-dioxane.

<table>
<thead>
<tr>
<th>Temperature/°C</th>
<th>Conversion $^{177}/%$</th>
<th>Isolated yield $^{178a}/%$</th>
<th>$^{178a}:^{179a}^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>40</td>
<td>21</td>
<td>1:0.38</td>
</tr>
<tr>
<td>40</td>
<td>60</td>
<td>27</td>
<td>1:0.25</td>
</tr>
<tr>
<td>60</td>
<td>60</td>
<td>35</td>
<td>1:0.19</td>
</tr>
<tr>
<td>80</td>
<td>85</td>
<td>24</td>
<td>1:0.15</td>
</tr>
</tbody>
</table>

Conditions: n-butanal 18a (5 eq) and dimethyl maleate 177 (1 eq) were stirred in 1,4-dioxane at various temperatures for 8 days at an initial concentration of 2 mol dm$^{-3}$ of dimethyl maleate 177 in 1,4-dioxane before addition of n-butanal 18a. $^a$ Determined by integration of $^1$H NMR relative to pentachlorobenzene as an internal standard.

Table 14. The effect of temperature on conversion of alkene 177, yield of ketone $^{178a}$ and the ratio of $^{178a}:^{179a}$.

It was also reasoned that the surface area to volume ratio may have a significant impact on the exposure of the reaction medium to air, and thus, the effect of changing solvent volume, and therefore concentration, at constant surface area was explored (Scheme 89, Table 15). As the surface area to volume ratio decreases (i.e. at lower concentrations) there is reduced exposure of the reaction medium to air. Hence, for reasons analogous to those discussed above, this results in higher conversion of alkene 177, suppresses formation of cyclic peroxide $^{179a}$, and thus, increases yield of ketone $^{178a}$. Optimal yield for the hydroacylation of dimethyl maleate 188 with n-butanal 18a was observed at 0.33 mol dm$^{-3}$. 
Scheme 89. Hydroacylation of alkene 177 with aldehyde 18a in 1,4-dioxane.

\[
\text{\textbf{Table 15. The effect of concentration on conversion of alkene 177, yield of ketone 178a and the ratio of 178a:179a.}}
\]

<table>
<thead>
<tr>
<th>[177]/mol dm(^{-3})</th>
<th>Surface area/cm(^2): Volume/cm(^3)</th>
<th>Conversion (177) %</th>
<th>Isolated yield 178a %</th>
<th>178a:179a</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.00</td>
<td>1:0.06</td>
<td>50</td>
<td>37</td>
<td>1:0.34</td>
</tr>
<tr>
<td>2.00</td>
<td>1:0.16</td>
<td>60</td>
<td>35</td>
<td>1:0.19</td>
</tr>
<tr>
<td>1.00</td>
<td>1:0.32</td>
<td>85</td>
<td>50</td>
<td>1:0.07</td>
</tr>
<tr>
<td>0.50</td>
<td>1:0.64</td>
<td>100</td>
<td>64</td>
<td>1:0.05</td>
</tr>
<tr>
<td>0.33</td>
<td>1:0.96</td>
<td>100</td>
<td>77</td>
<td>1:0.04</td>
</tr>
<tr>
<td>0.25</td>
<td>1:1.29</td>
<td>100</td>
<td>74</td>
<td>1:0.03</td>
</tr>
<tr>
<td>0.20</td>
<td>1:1.61</td>
<td>100</td>
<td>70</td>
<td>1:0.03</td>
</tr>
</tbody>
</table>

Conditions: \(n\)-butanal 18a (5 eq) and dimethyl maleate 177 (1 eq) were stirred in 1,4-dioxane at 60 °C for 8 days. \(^{a}\) Concentration refers to initial concentration of dimethyl maleate 177 in 1,4-dioxane before addition of \(n\)-butanal 18a. \(^{b}\) Surface area refers to surface area exposed to air and \(^{c}\) determined by integration of \(^1\)H NMR relative to pentachlorobenzene as an internal standard.

A similar trend in yields, to that obtained for the hydroacylation of dimethyl maleate 177 with \(n\)-butanal 18a with changing solvent volume at constant surface area, was observed for the hydroacylation of diethyl maleate 77 and dimethyl fumarate 184 with \(n\)-butanal 18a (Scheme 90, Table 16). The good yields observed for the hydroacylation of diethyl maleate 77 and dimethyl fumarate 184 also showed that the efficiency of the hydroacylation protocol is independent of the nature of the ester and/or alkene geometry, \(E/Z\).
Scheme 90. Hydroacylation of alkenes 77 and 184 with aldehyde 18a in 1,4-dioxane.

<table>
<thead>
<tr>
<th>[77] or [184]b/mol dm(^{-3})</th>
<th>Surface area(^b/cm^2):</th>
<th>Isolated yield 78a/%</th>
<th>Isolated yield 178a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.00</td>
<td>1:0.16</td>
<td>47</td>
<td>30</td>
</tr>
<tr>
<td>0.33</td>
<td>1:0.96</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td>0.20</td>
<td>1:1.61</td>
<td>55</td>
<td>50</td>
</tr>
</tbody>
</table>

Conditions: \(n\)-butanal 18a (5 eq) and alkene (1 eq) were stirred in 1,4-dioxane at 60 °C for 8 days. \(^a\) Concentration refers to initial concentration of alkene in 1,4-dioxane before addition of \(n\)-butanal 18a and \(^b\) surface area refers to surface area exposed to air.

Table 16. The effect of concentration on yield of ketones 78a and 178a.

### 4.2.2 Aldehyde scope

With optimised conditions in hand, the hydroacylation protocol was applied to the reaction of dimethyl maleate 177 with a selection of aldehydes (Table 17). The aldehydes were specifically chosen in view of their broad auto-oxidation rate profiles (see Section 2.2).

Scheme 91. Hydroacylation of alkene 177 with a range of aldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 18</th>
<th>Time/ days</th>
<th>Yield 178/%</th>
<th>Yield 185/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18a</td>
<td>3</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>18b</td>
<td>5</td>
<td>21(^{a,b})</td>
<td>26(^{a,b})</td>
</tr>
</tbody>
</table>

[1] 18a, 5 eq

[2] 77, (Z) and R = Et

[3] 184, (E) and R = Me
Conditions: aldehyde (5 eq) and dimethyl maleate 177 (1 eq) were stirred in 1,4-dioxane at 60 °C at an initial concentration of dimethyl maleate 177 in 1,4-dioxane of 0.33 mol dm\(^{-3}\) before addition of aldehyde. All reactions proceeded with 100% conversion of dimethyl maleate 177 unless stated otherwise. \(^a\) Determined by integration of \(^1\)H NMR relative to pentachlorobenzene as an internal standard at 100% consumption of aldehyde, \(^b\) 55% conversion of dimethyl maleate 177, \(^c\) significant polymerisation observed under the reaction conditions and \(^d\) 0% conversion of dimethyl maleate 177.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Hydroxyl</th>
<th>Carbonyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{18a})</td>
<td>0(^a)</td>
<td>0(^a)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{18b})</td>
<td>50(^c)</td>
<td>0(^c)</td>
</tr>
<tr>
<td>3</td>
<td>(\text{18c})</td>
<td>57(^0)</td>
<td>0(^0)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{18d})</td>
<td>76(^0)</td>
<td>0(^0)</td>
</tr>
<tr>
<td>5</td>
<td>(\text{18e})</td>
<td>10(^6)</td>
<td>21(^6)</td>
</tr>
<tr>
<td>6</td>
<td>(\text{18f})</td>
<td>25(^6)</td>
<td>36(^6)</td>
</tr>
<tr>
<td>7</td>
<td>(\text{18g})</td>
<td>60(^0)</td>
<td>0(^0)</td>
</tr>
<tr>
<td>8</td>
<td>(\text{18h})</td>
<td>0(^0)</td>
<td>0(^0)</td>
</tr>
<tr>
<td>9</td>
<td>(\text{18i})</td>
<td>0(^0)</td>
<td>0(^0)</td>
</tr>
<tr>
<td>10</td>
<td>(\text{18j})</td>
<td>0(^0)</td>
<td>0(^0)</td>
</tr>
<tr>
<td>11</td>
<td>(\text{18k})</td>
<td>0(^0)</td>
<td>0(^0)</td>
</tr>
</tbody>
</table>

Table 17. Yields for the formation of ketone 178 and decarbonylated addition product 185.

Hydroacylation of dimethyl maleate 177 with primary aldehydes \(\text{18a, 18c, 18d}\) and \(\text{18g}\) gave consistently good yields across the series (Table 17, Entry 1, 3, 4 and 7). However, reaction of alkene 177 with \(i\)-butanal \(\text{18b}\) (Table 17, Entry 2) only reached 55% consumption of alkene due to rapid oxidation of \(i\)-butanal \(\text{18b}\) to its corresponding carboxylic acid \(72b\); thus resulting in a low yield of ketone 178b. As expected at elevated temperature, 60 °C, significant amounts of decarbonylated
addition product 185 was observed upon hydroacylation of 1,2-diester alkene 177 with secondary aldehydes 18b, 18e and 18f (Table 17, Entries 2, 5 and 6), consistent with a radical mechanism. In addition, application of aldehydes bearing an alkene functionality resulted in significant polymerisation (Table 17, Entries 8 and 9), which is also consistent with a radical mechanism. Finally, as expected, application of aldehydes 18v and 18w, which did not appear to auto-oxidise in air (see Section 2.2), yielded no conversion of dimethyl maleate 177 (Table 17, Entries 10 and 11).

4.3 Hydroacylation of 1,1-diester-alkenes

Extension of the methodology to 1,1-diester alkenes was then sought and to this end the reactivity of alkene 186 with n-butanal 18a under aerobic conditions was explored (Scheme 92). Initial studies gave results which were analogous to those obtained for the 1,2-diester alkene 186 in that low conversion (ca. 20%) and no desired hydroacylation product was observed when reaction was carried out in the presence of water. As previously (see Section 4.2), adding hydrogen peroxide, using greater equivalents of aldehyde and/or heating did not afford ketone 187a. However, use of 1,4-dioxane as solvent at room temperature did give rise to the formation of ketone 187a in 30% yield with the major by-product being cyclic peroxide 188 (Scheme 92). Cyclic peroxide 188 is likely to have formed via an analogous reaction pathway to that outlined for cyclic peroxide 179 (Scheme 87).

Heating to 60 °C resulted in complete conversion of alkene 186 and suppressed formation of cyclic peroxide 188, and hence, encouraged formation of the desired hydroacylation product 187a (Scheme 93, Table 18, Entry 2). However, in contrast to the results obtained for the 1,2-diester alkenes (see Table 15), reactions were relatively unaffected by the effect of changing solvent volume, and therefore concentration, at constant surface area (Scheme 93, Table 18). The highest yield observed for the hydroacylation of alkene 186 with n-butanal 18a at 60 °C in
1,4-dioxane was observed at 1 mol dm$^{-3}$, 76%, and was thus chosen as the optimal concentration (Table 18, Entry 3).

![Scheme 93. Hydroacylation of alkene 186 with n-butanal 18a at 60 ºC.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>[186]$^a$/mol dm$^{-3}$</th>
<th>Surface area/cm$^2$: Volume/cm$^3$</th>
<th>Isolated yield 187a/$^a$/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.00</td>
<td>1:0.06</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>2.00</td>
<td>1:0.16</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>1.00</td>
<td>1:0.32</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>0.33</td>
<td>1:0.96</td>
<td>71</td>
</tr>
</tbody>
</table>

Conditions: n-butanal 18a (5 eq) and alkene 186 (1 eq) were stirred in 1,4-dioxane at 60 ºC for 8 days. $^a$ Concentration refers to initial concentration of alkene 186 in 1,4-dioxane before addition of n-butanal 18a.

Table 18. The effect of concentration on yield of ketone 187a.

### 4.3.1 Aldehyde scope

To assess the effect of changing aldehyde upon hydroacylation of alkene 186, the optimised conditions obtained for the hydroacylation of alkene 186 with n-butanal 18a, were applied to a range of other aldehydes (Scheme 94, Table 19). Notably, in most cases, superior yields were observed for the hydroacylation of 1,1-diester alkene 186 in comparison to 1,2-diester alkene 177. This presumably reflects the more electrophilic nature of 1,1-diester alkenes and the greater ability of the more electrophilic adduct radical to propagate the chain reaction.
Scheme 94. Hydroacylation of alkene 186 with a range of aldehydes in 1,4-dioxane.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 18</th>
<th>Time/days</th>
<th>Yield 187/%</th>
<th>Yield 189/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18a</td>
<td>3</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>18b</td>
<td>5</td>
<td>42&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>14&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>18c</td>
<td>3</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>18d</td>
<td>3</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>18e</td>
<td>10</td>
<td>74</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>18f</td>
<td>9</td>
<td>52</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>18g</td>
<td>9</td>
<td>72</td>
<td>0</td>
</tr>
</tbody>
</table>

Conditions: aldehyde (5 eq) and alkene 186 (1 eq) were stirred in 1,4-dioxane at 60 ºC at an initial concentration of alkene 186 in 1,4-dioxane of 1 mol dm<sup>-3</sup> before addition of aldehyde. All reactions proceeded with 100% conversion of alkene 186 unless stated otherwise. <sup>a</sup>Determined by integration of <sup>1</sup>H NMR relative to pentachlorobenzene as an internal standard at 100% consumption of aldehyde and <sup>b</sup> 70% conversion of alkene 186.

Table 19. Yields for the formation of ketone 187 and decarbonylated addition product 189.

Uniformly good yields were obtained for the hydroacylation of alkene 186 with a range of primary aldehydes (Table 19, Entries 1, 3, 4 and 7). However, reaction of alkene 186 with i-butanal 18b (Table 19, Entry 2) resulted in only 42% yield of
ketone 187b due to rapid oxidation of i-butanal 18b to its corresponding carboxylic acid 72b. The influence of unfavourable steric hindrance on reaction with 1,1-diester alkene 186 was displayed by the relatively modest yield obtained on reaction with 2-ethylhexanal 18f (Table 19, Entry 6). To further examine the influence of steric hindrance on the transformation, aldehydes 18e and 18f were applied to the hydroacylation of alkene 190 (Scheme 95). The modest conversions observed for diester 190 on treatment with aldehydes 18e and 18f, 20% and 32% respectively, confirmed that the reaction was sensitive to steric hindrance.

![Scheme 95. Hydroacylation of alkene 190 with aldehydes 18e and 18f (5 equivalents) in 1,4-dioxane.](image)

The effect of changing the ester substituent of the 1,2-diester alkenes was also explored through the hydroacylation of alkene 192 with aldehydes 18a, 18e and 18g (Scheme 96). Since all reactions proceeded with 100% conversion of alkene 192 and in good yield of ketones 193a, 193e and 193g, it was concluded that the reaction was not sensitive to the nature of the ester substituent.
Scheme 96. Hydroacylation of alkene 192 with aldehydes 18a, 18e and 18g in 1,4-dioxane.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 18</th>
<th>Time/ days</th>
<th>Yield 193/%</th>
<th>Yield 194/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18a</td>
<td>3</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>18e</td>
<td>10</td>
<td>71</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>18g</td>
<td>9</td>
<td>67</td>
<td>0</td>
</tr>
</tbody>
</table>

Conditions: aldehyde (5 eq) and alkene 192 (1 eq) were stirred in 1,4-dioxane at 60 ºC at an initial concentration of alkene 192 in 1,4-dioxane of 1 mol dm$^{-3}$ before addition of aldehyde. All reactions proceeded with 100% conversion of alkene 192.

Table 20. Yields for the formation of ketone 193 and decarbonylated addition product 194.

4.3.2 Hydroacylation of 2-alkoxy-1,1-diester alkenes

At this juncture, it was sought to exemplify the mild nature of the aerobic diester alkene hydroacylation protocol via reaction with more challenging substrates. To this end, the hydroacylation of 2-alkoxy-1,1-diester 195 with n-butanal 18a to give corresponding alkoxy-substituted 1,4-dicarbonyl 196a was examined (Scheme 97). Gratifyingly, excellent yields were observed for the hydroacylation of alkene 195 with n-butanal 18a at both 21 ºC and 60 ºC (Scheme 97), which is in sharp contrast to the 2-alkyl-1,1-diester alkenes. Although good yields were observed at both temperatures, reaction at 60 ºC was complete in half the reaction time.
Scheme 97. Hydroacylation of alkene 195 with aldehyde 18a.

In further contrast to the hydroacylation of 2-alkyl-1,1-diester alkenes, there was no evidence for the formation of any cyclic peroxide species (see Section 4.3) at either 21 °C or 60 °C. To explore aldehyde scope, reaction of alkene 195 with a range of aldehydes, with respect to aldehyde auto-oxidation rate, was carried out (Scheme 98, Table 21). Encouragingly, excellent yields were observed for hydroacylation of alkene 195 with primary aldehydes (Table 21, Entries 1-3 and 7). The lower conversions and yields observed for secondary aldehydes (Table 21, Entries 4-5) would appear to indicate sensitivity to steric hindrance and/or unfavourable decarbonylation.
Scheme 98. Hydroacylation of alkene 195 with a range of aldehydes in 1,4-dioxane.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 18</th>
<th>Time/days</th>
<th>Conversion 195/%</th>
<th>Yield 196/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18a</td>
<td>5</td>
<td>100</td>
<td>87&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>18c</td>
<td>5</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>18d</td>
<td>3</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>18e</td>
<td>5</td>
<td>35&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>18f</td>
<td>3</td>
<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>18g</td>
<td>9</td>
<td>100</td>
<td>89</td>
</tr>
</tbody>
</table>

Conditions: aldehyde (5 eq) and alkene 195 (1 eq) were stirred in 1,4-dioxane at 60 °C at an initial concentration of alkene 195 in 1,4-dioxane of 2 mol dm<sup>-3</sup> before addition of aldehyde. 
<sup>a</sup>Determined by integration of <sup>1</sup>H NMR relative to pentachlorobenzene as an internal standard at 100% consumption of aldehyde.

Table 21. Conversions of alkene 195 and yields of ketone 196.

4.4 Hydroacylation of a mono-substituted α,β-unsaturated ester

Finally, the tolerance of the aerobic aldehyde C-H activation chemistry for the hydroacylation of ethyl crotonate 79 was explored. Unfortunately, application of either of the optimised protocols determined for the hydroacylation of α,β-unsaturated-diesters alkenes 177 and 186 resulted in poor yields of ketoester 80 (ca. 20%). However, through the addition of a larger excess of aldehyde, 10
equivalents, an improved yield was obtained (Scheme 99). Although the yield is still modest at 51%, it demonstrates the applicability of the aerobically initiated hydroacylation methodology to encompass a mono-substituted $\alpha,\beta$-unsaturated-ester.

\begin{equation}
\begin{array}{c}
\text{n-Pr} \quad \text{H} \\
\text{18a, 10 eq}
\end{array}
\quad \begin{array}{c}
\text{CO}_2\text{Et} \\
\text{79}
\end{array}
\quad \begin{array}{c}
\text{1,4-Dioxane} \\
\text{Air, 60 °C}
\end{array}
\quad \begin{array}{c}
\text{n-Pr} \quad \text{O} \\
\text{80}
\end{array}
\end{equation}

Scheme 99. Hydroacylation of alkene 79 with aldehyde 18a in 1,4-dioxane at 60 °C at an initial concentration of 0.33 mol dm$^{-3}$ of alkene 79 in 1,4-dioxane before addition of aldehyde 18a.

4.5 Conclusion

Through careful control of the exposure of the reaction medium to air by varying solvent volume and temperature, the application of aerobic aldehyde C-H activation for the hydroacylation of $\alpha,\beta$-unsaturated esters has been achieved. A series of 1,2- and 1,1-diester alkenes have undergone efficient hydroacylation with a range of aldehydes with varying propensity towards auto-oxidation rate. Of particular note is the hydroacylation of 2-alkoxy-1,1-diester alkene 195. This transformation demonstrates the mild nature of the free radical chemistry to give access to products that would otherwise be challenging to synthesise via alternative methods. In addition, the aerobic activation methodology has also been extended to include the hydroacylation of a mono-substituted $\alpha,\beta$-unsaturated-ester, ethyl crotonate 79.
Chapter 5 Hydroacetylation of vinyl phosphonates

5.1 The importance of γ-ketophosphonates

γ-Ketophosphonates, and their corresponding phosphonic acids, have been established as useful tools in both synthetic chemistry\textsuperscript{161-166} and biology as non-hydrolysable phosphate mimetics and inhibitors of phosphoglycerate kinase and β-lactamase\textsuperscript{167-170}. For example, γ-ketophosphonate 197 has been shown to be an effective β-lactamase inhibitor.\textsuperscript{168}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure5.png}
\caption{Effective β-lactamase inhibitor 197.}
\end{figure}

Currently, the most commonly employed method for the preparation of γ-ketophosphonates is based on conjugate addition to an enone\textsuperscript{166,171,172}. Although alternative protocols have been developed for the synthesis of γ-ketophosphonates, including hydroacetylation based strategies, they have not been widely used as they often require noxious precursors, chain carriers that are toxic and/or complicate the purification of reaction products.\textsuperscript{173-177} In view of this, the hydroacetylation of vinyl phosphonates with acyl radicals generated by aldehyde auto-oxidation would provide a mild and clean alternative strategy for the synthesis of γ-ketophosphonates.

5.2 Aerobic hydroacetylation of dimethyl vinyl phosphonate

Initially, hydroacetylation of dimethyl vinyl phosphonate 198 with \textit{n}-butanal 18a at 21 °C in the presence of water was investigated. However, no desired hydroacetylation product and low conversion of vinyl phosphonate 198 were observed (ca. 5%). Application of additional quantities of \textit{n}-butanal 18a, adding hydrogen peroxide
and/or heating did not yield formation of γ-ketophosphonate 199a and/or increase conversion of vinyl phosphonate 198. However, use of 1,4-dioxane as solvent at 21 °C did afford γ-ketophosphonate 199a, albeit in very low yield, <5%, and at low conversion of alkene (Scheme 100). Careful examination of the crude ¹H NMR spectrum of the reaction mixture also indicated the formation of aldehyde 200 and phosphonate 201.

![Scheme 100. Hydroacylation of dimethyl vinyl phosphonate 198 with n-butanal 18a.](image1)

Consistent with previous studies with other alkene acceptors, reaction between n-butanal 18a and vinyl phosphonate 198 was completely suppressed by addition of BHT (5 mol%), which implies a radical mechanism. γ-Ketophosphonate 199a is thought to be formed via a mechanism analogous to that described in Section 1.3.4.8 and phosphonate 201 derived from 1,4-dioxane radical addition to vinyl phosphonate 198. Aldehyde 200 is postulated to have formed via peracyl radical 69a addition to vinyl phosphonate 198, followed by aldehydic hydrogen atom abstraction to form peroxide 203, which decomposes to aldehyde 200 and acid 72a (Scheme 101).

![Scheme 101. Proposed route for the formation of aldehyde 200.](image2)
5.2.1 Optimisation studies

Despite the low yield observed for the hydroacylation of vinyl phosphonate 198 with \( n \)-butanal 18a at 21 °C (Scheme 1) it was sufficiently encouraging to embark upon an optimisation study. As previously, optimisation focused on temperature and concentration in order to attempt to control exposure of the reaction mixture to molecular oxygen and hence suppress formation of aldehyde 200 and phosphonate 201 (Scheme 102, Table 22). Gratifyingly, increasing the reaction temperature had a dramatic impact on yield of \( \gamma \)-ketophosphonate 199a with optimal yield afforded at 60 °C, 70%, at 1.00 mol dm\(^{-3}\) (Table 22, Entry 7); heating to higher temperatures did not affect yield significantly (Table 22, Entries 10 and 11). The increase in yield with increasing temperature was attributed to the lower concentration of dissolved molecular oxygen. This promotes acyl radical trapping by vinyl phosphonate 198 rather than with molecular oxygen, thus promoting higher conversion and a higher yield of \( \gamma \)-ketophosphonate 199a. The lower yields observed at 60 °C at concentrations above and below 1.00 mol dm\(^{-3}\) may be rationalised by increased formation of aldehyde 200 and phosphonate 201, respectively. The higher surface area to volume ratio at higher concentrations results in an increased exposure to air and hence promotes the likelihood of acyl radical 63a being trapped by molecular oxygen than undergoing addition to vinyl phosphonate 198, thus lowering the yield of \( \gamma \)-ketophosphonate 199a and decreasing the 199a:200 ratio (Table 22, Entries 5-7). Unsurprisingly, at lower concentrations a decreased 199a:201 ratio was observed due to the greater concentration of 1,4-dioxane molecules relative to vinyl phosphonate 198 molecules, consequently, lowering the yield of \( \gamma \)-ketophosphonate 199a (Table 22, Entries 7-9).
Scheme 102. Hydroacylation of vinyl phosphonate 198 with n-butanal 18a in 1,4-dioxane.

\[
\text{\textbf{Table 22. Yield of ketone 199a and conversion of vinyl phosphonate 198 under various reaction conditions.}}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature /°C</th>
<th>[198]/mol dm(^{-3})</th>
<th>Conversion 198/%</th>
<th>199a:200:201</th>
<th>Isolated Yield 199a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>1.00</td>
<td>10</td>
<td>-</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>1.00</td>
<td>70</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>0.25</td>
<td>75</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>5.00</td>
<td>100</td>
<td>1:0.27:0.07</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>2.00</td>
<td>100</td>
<td>1:0.19:0.08</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>1.00</td>
<td>100</td>
<td>1:0.18:0.09</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.50</td>
<td>100</td>
<td>1:0.16:0.10</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.25</td>
<td>100</td>
<td>1:0.10:0.14</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>80</td>
<td>1.00</td>
<td>100</td>
<td>-</td>
<td>69</td>
</tr>
<tr>
<td>11</td>
<td>0.25</td>
<td>100</td>
<td>-</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

Conditions: n-butanal 18a (5 eq) and vinyl phosphonate 198 (1 eq) were stirred in 1,4-dioxane.

\(^a\) Concentration refers to initial concentration of vinyl phosphonate 198 in 1,4-dioxane before addition of aldehyde 18a.

**5.3 Aldehyde scope**

The scope of the aldehyde in this hydroacylation protocol was next evaluated using the optimised conditions developed. Hence, aldehydes demonstrating a varying
propensity to undergo auto-oxidation (see Section 2.2) and aldehydes bearing a range of functional groups were selected for the hydroacylation study (Scheme 103, Table 23).

![Scheme 103. Hydroacylation of vinyl phosphonate 198 with a range of aldehydes in 1,4-dioxane at 60 °C.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 18</th>
<th>Time/h</th>
<th>Yield 199/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18a</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>18c</td>
<td>24</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>18d</td>
<td>24</td>
<td>72</td>
</tr>
<tr>
<td>4a</td>
<td>18e</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>18h</td>
<td>24</td>
<td>68a</td>
</tr>
<tr>
<td>6</td>
<td>18i</td>
<td>24</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>18j</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>18k</td>
<td>24</td>
<td>62b</td>
</tr>
<tr>
<td>9</td>
<td>18l</td>
<td>72</td>
<td>62b</td>
</tr>
</tbody>
</table>
Conditions: aldehyde (5 eq) and vinyl phosphonate \(198\) (1 eq) were stirred at 60 °C in 1,4-dioxane at an initial concentration of 1 mol dm\(^{-3}\) of vinyl phosphonate \(198\) in 1,4-dioxane before addition of aldehyde. All reactions proceeded with 100% conversion of vinyl phosphonate \(198\) unless stated otherwise. \(^{a}\) 10 equivalents of acetaldehyde \(18h\) were required due to its low boiling point, \(^{b}\) determined by integration of \(^1\)H NMR relative to pentachlorobenzene as an internal standard and \(^{c}\) 0% conversion of vinyl phosphonate \(198\). Similar reactions have been carried out by others within the Caddick group (see Appendix).

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Time (min)</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>(18m)</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>11</td>
<td>(18n)</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>(18o)</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>(18p)</td>
<td>24</td>
<td>68</td>
</tr>
<tr>
<td>14</td>
<td>(18q)</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>(18v)</td>
<td>120</td>
<td>0(^c)</td>
</tr>
<tr>
<td>16</td>
<td>(18w)</td>
<td>120</td>
<td>0(^c)</td>
</tr>
</tbody>
</table>

Table 23. Yields and reaction times for formation of ketone \(199\).

Hydroacylation of vinyl phosphonate \(198\) was achieved with aldehydes exhibiting a range of auto-oxidation rates (Table 23, Entries 1-14). Moreover, hydroacylation of vinyl phosphonate \(198\) under the optimised conditions could also be achieved with aldehydes bearing acetal, alcohol, epoxide and aryl functionalities (Table 23, Entries 6-9), exemplifying the mild, orthogonal nature of the reaction. Also encouraging was the success of cyclopropyl aldehyde \(18m\) (Table 23, Entry 10), as well as \(\beta\)-branched aldehydes (Table 23, Entries 2, 7-8 and 13). Consistent with a radical mechanism was the poor tolerance of the methodology to aldehydes bearing an alkene functionality (Table 23, Entries 11-12). For example, in reactions of vinyl phosphonate \(198\) with 4-pentenal \(18n\) or citronellal \(18o\) there was no evidence for the formation of the corresponding hydroacylation products, despite consumption of all of the vinyl phosphonate. This is presumably due to polymerisation of the alkene.
under the reaction conditions. In support of this, the corresponding saturated citronellal, aldehyde 18p, underwent successful hydroacylation of vinyl phosphonate 198, to afford ketone 199p in good yield (Table 23, Entry 13). The absence of the formation of γ-ketophosphonate 199q for the hydroacylation of vinyl phosphonate 198 with pivaldehyde 18q was due to the significant amount of tert-butyl radical addition that took place under the reaction conditions to form phosphonate 204 (Table 23, Entry 14). The tert-butyl radical is presumably derived from decarbonylation of the acyl radical formed from pivaldehyde oxidation. Indeed, complete decarbonylation of pivaldehyde 18q and trapping of the intermediate tert-butyl radical could be achieved in 68% yield when reaction was conducted at 100 °C for 24 h (Scheme 104).

As expected, application of aldehydes 18v and 18w, which did not appear to auto-oxidise in air (see Section 2.2), yielded no conversion of alkene 198 (Table 23, Entries 15 and 16). Finally, changing the ester substituent of dimethyl vinyl phosphonate 198 to an ethyl group did not have a significant impact on hydroacylation (Scheme 105).

5.4 Hydroacylation of α- and β-substituted vinyl phosphonates

With a view to synthesising further functionalised γ-ketophosphonates the tolerance of α- and β-substituted vinyl phosphonates was investigated. Alkenes 210 and 211
were prepared by a modified protocol of that described by Stawinski (Scheme 106).

\[
\text{EtO}_2P\overset{\text{H}}{\underset{\text{O}}{\text{O}}}\text{BrH}
\]

\[
\text{R}^1 = \text{Me}, \text{R}^2 = \text{H}
\]

\[
\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}, 39\%
\]

\[
\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}, 40\%
\]

Scheme 106. Route to α- and β-methyl substituted vinyl phosphonates 210 and 211.

Vinyl phosphonates 210 and 211 were treated with \(n\)-butanal 18a under the optimised conditions developed for the aerobic hydroacylation of vinyl phosphonate 198 (Scheme 107). Hydroacylation of β-methyl γ-ketophosphonate 210 proceeded with 80% conversion of vinyl phosphonate and in 60% NMR yield\(^*\) of ketone 212. This provided evidence that β-substituted vinyl phosphonates may be applied to the aerobic hydroacylation methodology. In contrast, no desired γ-ketophosphonate 213 was isolated from reaction of alkene 211 with aldehyde 18a despite complete consumption of alkene. This may be attributed to poor aldehydic hydrogen atom abstraction from the relatively more nucleophilic adduct radical that results from acyl radical addition to α-methyl vinyl phosphonate 211 compared with addition to β-methyl vinyl phosphonate 210. This poor chain transfer step may result in unfavourable polymerisation, which may indicate a general limitation of the aerobic hydroacylation methodology.

\[
n\text{Pr}O\overset{\text{H}}{\underset{\text{O}}{\text{O}}}\text{P}
\]

\[
\text{R}^1 = \text{Me}, \text{R}^2 = \text{H}
\]

\[
\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}, 60\%\ *
\]

\[
\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}, 0\%
\]

Scheme 107. Hydroacylation of vinyl phosphonates 210 and 211 with \(n\)-butanal 18a.

The optimised conditions were also used in an attempt to affect the hydroacylation of α-bromo-vinyl phosphonate 214 with \(n\)-butanal 18a but with little success despite complete consumption of alkene. Only γ-ketophosphonate 199a was isolated from the reaction mixture in 10% yield. As this species is likely to have been derived from

\(^*\) Determined by integration of \(^1\)H NMR relative to pentachlorobenzene as an internal standard.
γ-ketophosphonate 215, the failure to isolate ketone 215 may be attributed to the propensity of γ-ketophosphonate 215 to undergo further transformations under the reaction conditions.

Scheme 108. Hydroacylation of α-bromo-vinyl phosphonate 214 with n-butanal 18a.

5.5 Conclusion

Through careful optimisation, vinyl phosphonates have been shown to undergo aerobic hydroacylation. Moreover, a range of aldehydes, including those with acetal, alcohol, epoxide and aryl functionalities, are shown to be tolerant of the methodology. Finally, although no α-substituted vinyl phosphonates were shown to undergo hydroacylation, β-methyl vinyl phosphonate 212 was efficiently hydroacylated with n-butanal 18a.
Chapter 6  Acyl radical approaches to C-N bond formation

Thus far, studies have focused on the application of aldehyde auto-oxidation to C-C bond formation. Eager to extend the application of aerobic aldehyde C-H activation, methods for the construction of C-N bonds were explored.

6.1 Conversion of aldehydes to amides

Marko previously reported the conversion of aldehydes to amides through the treatment of aldehydes with NBS and 5 mol% AIBN, followed by addition of an amine.\(^{179}\) For example, \(n\)-hexanal 18d was converted to amide 216 in 78% yield (Scheme 109).\(^{179}\)

```
\[
\begin{align*}
\text{1. NBS (1.2 eq), AIBN (5 mol%),} \\
90^\circ \text{C, CCl}_4 \\
\text{2. n-Butylamine (2 eq)}
\end{align*}
\]
```

Scheme 109. Conversion of aldehyde 18d to amide 216.

Presumably, conversion of aldehyde 18d to amide 216 proceeds through an acyl radical that is trapped by bromine to form an acid bromide, which is then converted to an amide on treatment with \(n\)-butylamine. As reaction proceeds through an acyl radical intermediate, the use of aerobic aldehyde C-H activation for the formation of amides in an analogous manner was investigated (Scheme 110). An aldehyde 18 may undergo aerobic activation to an acyl radical, which may then be converted to an acid bromide 217 in the presence of a source of bromine. The resultant acid bromide may then be converted to an amide 218 with an amine.

```
\begin{align*}
\text{R}^1\text{H} & \xrightarrow{\text{Air}} \text{R}^1\text{O} \\
\text{NBS} & \xrightarrow{\text{H}_2\text{N}^+\text{R}^2} \text{R}^1\text{O}^+\text{Br} \\
\text{217} & \xrightarrow{\text{218}} \text{R}^1\text{N}^+\text{R}^2
\end{align*}
```

Scheme 110. Proposed conversion of an aldehyde 18 to an amide 218 via acid bromide 217.
Initially, the conversion of an aldehyde to an acid bromide was investigated through the reaction of \( n\)-butanal \( 18a \) with NBS (1.2 equivalents) in the presence of air (Scheme 111). Although \( n\)-butanal \( 18a \) was completely consumed after 2 h, almost exclusive formation of ester \( 219 \) was observed, 95% isolated yield. Formation of ester \( 219 \) is undesirable since it consumes two molecules of aldehyde \( 18a \). As ester \( 219 \) reacts with an amine to form only a single molecule of amide, overall, two molecules of aldehyde \( 18a \) are consumed for the formation of one molecule of amide. Attempts to minimise formation of ester \( 219 \) and increase yield of acid bromide \( 217a \), through the addition of tetrabutylammonium bromide or lithium bromide, failed, with a similar ratio of \( 219:217a \) being observed in either case. Heating the reaction mixture to 60 °C, or use of \( \text{CH}_2\text{Cl}_2 \), benzene, THF, \( \text{Et}_2\text{O} \) or EtOAc as solvent, also had no positive impact on the formation of acid bromide \( 217a \) in preference to ester \( 219 \).

\[
\begin{align*}
\text{\text{H}} & \quad \text{\text{O}} \\
\text{\text{18a}} & \quad \text{\text{NBS (1.2 eq)}} & \quad \text{\text{\text{219}}, 95\%} & \quad \text{\text{\text{217a}}, <2\%}} \\
\text{21 ^\circ C, CCl}_4 &
\end{align*}
\]

Scheme 111. Reaction of aldehyde \( 18a \) with NBS at 21 °C in \( \text{CCl}_4 \).

As expected, addition of \( n\)-hexylamine (2 equivalents) to the crude product mixture that resulted from complete conversion of aldehyde \( 18a \) on reaction with NBS, resulted in a low yield of amide \( 220a \), 43%, based on aldehyde as the limiting reagent. Also as expected, reaction with \( n\)-hexylamine afforded a similar ratio of amide \( 220a \) and aldehyde \( 18a \).

\[
\begin{align*}
\text{\text{H}} & \quad \text{\text{O}} \\
\text{\text{18a}} & \quad \text{\text{NBS (1.2 eq)}} & \quad \text{\text{\text{\text{219}}, 95\%}} \\
\text{\text{n-Hexylamine (2 eq)}} & \quad \text{\text{\text{219}}, 95\%} & \quad \text{\text{\text{220a}, 43\%}} & \quad \text{\text{\text{18a}, 40\%}} \\
\end{align*}
\]

Scheme 112. Reaction of \( n\)-butanal \( 18a \) with NBS, followed by addition of \( n\)-hexylamine to form amide \( 220a \) and \( n\)-butanal \( 18a \).
Due to the almost exclusive formation of ester 219 on reaction of n-butanal 18a with NBS, there is limited support for the conversion of aldehydes to amides through a route analogous to that reported by Marko. As such, an alternative method for C-N bond formation through acyl radicals, generated by aldehyde auto-oxidation, was explored.

### 6.2 Hydroacylation of azodicarboxylates

Recently, methods to affect the hydroacylation of azodicarboxylates to construct hydrazides have been reported.\textsuperscript{180,181} For example, diethyl azodicarboxylate 221 was hydroacylated with n-propanal 18x (2 equivalents) in the presence of an ionic liquid at 40 °C in 94% yield (Scheme 113). However, to date, approaches have focused on the functionalisation of azodicarboxylates whilst employing an excess of aldehyde, thus, precluding the use of these methods for the functionalisation of valuable aldehydes.

```
\[ \text{H}_2\text{O}^{18x}, 2 \text{ eq} \quad \text{EtO}_2\text{C}-\text{N}^+\text{N}^-\text{CO}_2\text{Et} \underset{\text{[BMIM]NTf}_2}{\text{40 °C, 94%}} \rightarrow \text{H}_2\text{N}-\text{N}\text{CO}_2\text{Et} \quad 222x \]
```

Scheme 113. Hydroacylation of diethyl azodicarboxylate 221 with n-propanal 18x.

Initially the investigation focused on optimisation of the hydroacylation of diethyl azodicarboxylate 221 with n-butanal 18a to form hydrazide 222a. Application of previously optimised conditions for the hydroacylation of vinyl sulfonate 105 in the presence of water, 2 equivalents of aldehyde at 21 °C (see Section 2.3), afforded hydrazide 222a in excellent yield, 92%, based on azodicarboxylate 221 as limiting reagent (Scheme 114, Table 24, Entry 1). Although further reducing the ratio of 18a:221 ratio from 2:1 to 1.5:1 resulted in similarly high yield (Scheme 114, Table 24, Entry 2), modest conversions (70%) were achieved with stoichiometric reaction conditions (Scheme 114, Table 24, Entry 3). The lower yield observed on reaction with a 1:1 stoichiometry of 18a:221 was attributed to conversion of diethyl azodicarboxylate 221 to diethyl hydrazinedicarboxylate 223. To combat this, the amount of diethyl azodicarboxylate 221 was increased (Scheme 114, Table 24, Entry 4).
4), and gratifyingly, afforded hydrazide 222a in excellent yield, 90%, based on
\(n\)-butanal 18a as the limiting reagent.

```
\[
\begin{align*}
\text{Scheme 114. Hydroacylation of azodicarboxylate 221 with } n\text{-butanal 18a.}
\end{align*}
\]
```

<table>
<thead>
<tr>
<th>Entry</th>
<th>18a/eq</th>
<th>221/eq</th>
<th>Isolated Yield 222a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1.2</td>
<td>90</td>
</tr>
</tbody>
</table>

Conditions: \(n\)-butanal 18a and diethyl azodicarboxylate 221 were
reacted in the presence of \(\text{H}_2\text{O}\) at 21 ºC.

Table 24. Isolated yield of hydrazide 222a with varying equivalents of \(n\)-butanal 18a
and azodicarboxylate 221.

As with previous hydroacylation strategies based on aerobic aldehyde C-H
activation, hydroacylation was completely inhibited by BHT (5 mol%), consistent
with a radical mechanism. It is proposed that aldehyde 18a is converted to acyl
radical 63a, which undergoes radical addition to diethyl azodicarboxylate 221,
followed by aldehyde hydrogen atom abstraction to form hydrazide 222a and
regenerate acyl radical 63a (Scheme 115).

```
\[
\begin{align*}
\text{Scheme 115. Proposed mechanism for the formation hydrazide 222a.}
\end{align*}
\]
```
No evidence of the formation of butanoic acid 72a, from aerobic oxidation of
n-butanal 18a, or telomeric products, from reaction of multiple equivalents of diethyl
azodicarboxylate 221 with n-butanal 18a, were observed whilst employing n-butanal
18a as the limiting reagent on reaction with diethyl azodicarboxylate 221. This result
implies that azodicarboxylates, such as diethyl azodicarboxylate 221, have an
exceptional ability to trap acyl radicals and the N-based adduct radical 224 is very
well polarity matched to abstract an aldehydic hydrogen atom.

6.2.1 Aldehyde scope

At this juncture, the optimised conditions developed for the conversion of n-butanal
18a to hydrazide 222a were applied to a range of aldehydes to hydroacylate diethyl
azodicarboxylate 221 (Scheme 116, Table 25).

![Scheme 116. Hydroacylation of diethyl azodicarboxylate 221 with a range of
aldehydes.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Time/h</th>
<th>Isolated Yield 222a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(18a)</td>
<td>24</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>(18b)</td>
<td>24</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>(18c)</td>
<td>24</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>(18f)</td>
<td>24</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>(18g)</td>
<td>24</td>
<td>82</td>
</tr>
</tbody>
</table>
Conditions: aldehyde (1 eq) and diethyl azodicarboxylate 221 (1.2 eq) were reacted in the presence of H₂O at 21 ºC. Unless otherwise stated and 98% ee. Similar reactions have been carried out by others within the Caddick group (see Appendix).

Table 25. Yields and reaction time for formation of hydrazides 222 and 225.

The aerobic activation protocol showed excellent tolerance to a broad range of aldehydes with respect to aldehyde auto-oxidation rate (Table 25, Entries 1-7). Previously, the aerobic activation methodology for the hydroacylation of other acceptors has shown poor applicability to i-butanal 18b as it rapidly auto-oxidises to its corresponding acid 72b in air (see Sections 2.3 and 4.2.2). However, in the case of diethyl azodicarboxylate 221, i-butanal 18b was readily functionalised to hydrazide 222b in good yield (Table 25, Entry 2). Moreover, pivaldehyde 18q, which has previously shown a tendency to undergo rapid decarbonylation (see Section 5.3), was also efficiently converted to its corresponding hydrazide 222q (Table 25, Entry 6). Aldehydes bearing an alkene functional group, which have been poorly tolerated on hydroacylation of α,β-unsaturated ester 177 and vinyl phosphonate 198 (see Sections 4.2.2 and 5.3), afforded good yields of hydrazides 222n and 222y on reaction with diethyl azodicarboxylate 221 (Table 25, Entries 7-8). Aldehydes 18v and 18w, which did not appear to auto-oxidise (Table 6, Entries 15-16) or react with vinyl sulfonates, vinyl sulfones, α,β-unsaturated esters and vinyl phosphonates (see Sections 2.3, 4.2.2 and 5.3), efficiently underwent hydroacylation with diethyl azodicarboxylate 221 to
generate hydrazides 222v and 222w in good yields (Table 25, Entries 9-10). These results highlight the exceptional ability of azodicarboxylates to undergo efficient hydroacylation. Finally, diethyl azodicarboxylate 221 underwent efficient hydroacylation with chiral aldehyde 152 with a high retention of enantiomeric excess, 98% ree (Table 25, Entry 11).

6.3 Reactions of acyl hydrazides

Since a range of aldehydes were successfully functionalised to form hydrazides, the synthetic utility of these hydrazides was explored, with initial focus on Krapcho decarboxylation. However, attempts to convert hydrazide 222a with lithium chloride, under Krapcho decarboxylation conditions, to its corresponding mono-acylated hydrazide yielded a mixture of compounds containing heterocycle 226, hydrazide 227 and hydrazine 223 (Scheme 117).

As hydrazine 223 was presumably derived from an addition-elimination reaction of chloride with hydrazide 222a, the efficacy of hydrazide 222a as an acyl donor for the formation of amides was investigated. Gratifyingly, treatment of hydrazide 222a with n-hexylamine or allylamine in CH₂Cl₂ for 16 h afforded the corresponding amides 220a and 220b in excellent yields, respectively, with concurrent isolation of diethyl hydrazinedicarboxylate 223 (Scheme 118). Unfortunately, presumably due to unfavourable steric interactions, treatment of hydrazide 222a with diethylamine or tert-butylamine resulted in very low conversion of hydrazide 222a, <10% in either case, after 48 h. Nonetheless, the conversion of hydrazide 222a to amides 220a and 220b represents the first examples of the use of acyl hydrazides as acyl donors.
Additionally, enantioenriched hydrazide 225 was converted to benzyl amide 228 in good yield, 84%, and with retention of stereochemical information at the α carbon atom (Scheme 119). It is envisaged that a range of enantioenriched amides may be prepared in similarly high enantiomeric excess.

6.4 Conclusion

A benign, atom economical method for the functionalisation of aldehydes through the hydroacylation of azodicarboxylates in the presence of water has been demonstrated. The use of aldehyde as the limiting reagent is in sharp contrast to previous methods that have been used to affect the hydroacylation of azodicarboxylates.\(^\text{182,183}\) Moreover, the resultant hydrazides may be used as acyl donors for the construction of amides in excellent yields. The overall conversion of an aldehyde to an amide, represents an overall oxidation of aldehydes to amides, which is both mild and high yielding, and offers a complementary approach to the metal catalysed oxidation of imines.\(^\text{184-186}\) Finally, the overall conversion of an aldehyde to an amide has been shown to be tolerant of an α-centred enantioenriched aldehyde with exceptional retention of enantiomeric excess.

Scheme 118. Conversion of hydrazide 222a to amides 220a and 220b.

Scheme 119. Conversion of hydrazide 225 to amide 228.
Conclusions and Further Work

This thesis has described the use of aerobic aldehyde C-H activation for the construction of C-C and C-N bonds through the hydroacylation of vinyl sulfonates, sulfones and phosphonates, \(\alpha,\beta\)-unsaturated esters and azodicarboxylates. Of particular note is the hydroacylation of azodicarboxylates, which proceeded with aldehyde as limiting reagent, a stoichiometry not previously observed in the literature. Hydroacylation, in all acceptor cases, was shown to proceed in good yields for a range of aldehydes with respect to aldehyde auto-oxidation rate, as well as being tolerant of aldehydes bearing alcohol, epoxide, acetal and other functionalities. Moreover, the use of chiral aldehydes for hydroacylation, which has not been reported in the literature, was shown to be applicable to the aerobic activation protocol with exceptional retention of enantiomeric excess observed in all cases. Throughout, evidence of a radical mechanism for hydroacylation, proceeding through acyl radical generation, addition to a double bond followed by hydrogen atom abstraction, has been compiled through the isolation of various telomeric, decarbonylation and molecular oxygen adducts. Furthermore, complete inhibition of reactivity was observed in all cases in the presence of a radical inhibitor.

In addition to using aerobic aldehyde C-H activation to affect hydroacylation of a range of acyl radical acceptors, the reactivity of the resultant hydroacylation products was explored. The \(\gamma\)-keto-sulfonate motif may act as a precursor for the formation of \(\gamma\)-keto-sulfonamides, sultams, \(N\)-sulfonylimines and sultones. Perhaps most significantly, the \(\gamma\)-keto-sulfonate motif may undergo quantitative elimination to generate enones, providing a mild alternative route for the overall conversion of an aldehyde to an enone when taken in conjunction with the hydroacylation chemistry. Moreover, the hydroacylation-elimination-addition chemistry represents a powerful indirect alternative for the hydroacylation of electron rich alkenes. The acyl hydrazide motif has also been highlighted as an intermediate for the construction of amides.

Future work on this project should include exploring the diastereoselectivity observed, if any, on hydroacylation of asymmetric acyl radical acceptors with enantioenriched aldehydes; a reaction that has not previously been explored in the
literature. For example, it would be interesting to explore the diastereoselectivity observed for hydroacylation of alkene 186 with (S)-2-methylbutanal 152 (Scheme 120). The use of enantioenriched acyl radical acceptors, such as Ellman’s enantioenriched tert-butylsulfinyl imines, may also be of interest.

Scheme 120. Hydroacylation of alkene 186 with (S)-2-methylbutanal 152.
Experimental

General Experimental

Chemicals

All reagents were purchased from Sigma Aldrich, Alfa Aesar, Acros and Avocado and used as received unless otherwise stated.

Solvents

Solvents were used as received unless otherwise stated. Petrol refers to petroleum ether (b.p. 40-60 °C).

Chromatography

All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates (254 µm). Silica gel plates were initially examined under UV light and then developed using aqueous potassium permanganate stain. Column chromatography was carried out silica gel (33-70 µm) supplied by VWR. Normal phase High Performance Liquid Chromatography (HPLC) was measured using a UV detector prostar/dynamic system24 (2 volts) absorbance at 214 nm and 254 nm. The analytes were separated and enantiomeric excess determined using a CHIRALCEL-OD column (Daicel; Chiral Technologies Group, France) 25 × 0.46 cm.

Spectroscopy

Quoted yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. $^1$H NMR spectra were recorded at 300 MHz, 400 MHz, 500 MHz and 600 MHz and $^{13}$C NMR at 75 MHz, 100 MHz, 125 MHz and 150 MHz on a Bruker AMX300, AMX400, AMX500 and AMX600 at 25 °C in CDCl$_3$ as described below. The chemical shifts (δ) for $^1$H and $^{13}$C are quoted relative to residual signals of the solvent on the parts per million (ppm) scale. In the case of multiple amide rotamers, only the major rotamer has been assigned. Coupling
constants ($J$ values) are reported in Hertz (Hz) and are reported as $J_{H-H}$ couplings unless otherwise stated. Due to the broadness of the $^{13}$C NMR signals in the pentafluorophenyl moiety these peaks have not been assigned. Signal multiplicities were determined using the distortionless enhancement by phase transfer (DEPT) spectral editing technique. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode. Mass spectra were obtained at UCL on either a VG70-SE (FAB), Thermo Finnigan MAT900Xp (EI and CI) or Waters LCT Premier XE (ES) mass spectrometer.

**Hydroacylation reactions**

All hydroacylation reactions were carried out in a carousel tube (15 cm × 2 cm) equipped with an octagon-shaped magnetic stirrer bar (12.7 mm × 3 mm) fitted with a carousel tube screw cap lid (carousel equipment purchased from Radleys Discovery Technologies).

**Miscellaneous**

Melting points were measured with a Gallenkamp apparatus and are uncorrected. Optical rotations ([α]$_D$) were recorded with a Perkin Elmer 343 polarimeter. All reactions were carried out under atmospheric air and stirred at 300 revolutions per minute (rpm) unless otherwise stated.

**Experimental for Chapter 2**

**Pentafluorophenyl ethenesulfonate 105**

\[
\text{SO}_3\text{PFP}
\]

A solution of NEt$_3$ (13.9 g, 19.2 mL, 137.5 mmol) in CH$_2$Cl$_2$ (100 mL) was added dropwise over 1 h to a solution of 2-chloroethane-1-sulfonyl chloride (10.2 g, 62.5 mmol) and pentafluorophenol (11.5 g, 62.5 mmol) in CH$_2$Cl$_2$ (100 mL) at -15 °C. The reaction mixture was allowed to warm to 21 °C, diluted with CH$_2$Cl$_2$ (100 mL), washed with sat. NaHCO$_3$ (2 × 250 mL) and the solvent removed in vacuo. The reaction mixture was diluted with Et$_3$O (250 mL), washed with 2M HCl (2 × 250 mL) and sat. NaCl (250 mL), dried (MgSO$_4$) and the solvent removed in vacuo.
Purification by column chromatography (5%-10% Et₂O/petrol) and recrystallisation (petrol) gave pentafluorophenyl ethenesulphonate as white crystals (13.6 g, 49.6 mmol, 79%).

¹H NMR (500 MHz, CDCl₃) δ 6.79 (dd, J = 16.5 and 10.0 Hz, 1H), 6.53 (dd, J = 16.5 and 1.0 Hz, 1H), 6.34 (dd, J = 10.0 and 1.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 133.3 (CH₂), 131.8 (CH); IR (solid) 3078, 1652, 1514, 1385, 1183 cm⁻¹; LRMS (EI) 274 (24, [M]+), 184 (100); HRMS (EI) calcd for C₈H₃F₅O₃S [M]+ 273.9718, observed 273.9725.

5-(3,3-dimethyloxiran-2-yl)-3-methylpentanal 18k

To a stirring solution of (±)-citronellal (771 mg, 902 µL, 5 mmol) in CH₂Cl₂ (20 mL) was added dropwise a solution of m-CPBA (1.04 g, 6 mmol) in CH₂Cl₂ (10 mL) at 0 °C under an atmosphere of argon. The reaction mixture was allowed to warm to 21 °C and stirred for a further 90 min. The reaction mixture was filtered and the filtrate washed with sat. K₂CO₃ (3 × 30 mL), dried (MgSO₄) and the solvent removed in vacuo to afford 5-(3,3-dimethyloxiran-2-yl)-3-methylpentanal (809 mg, 4.75 mmol, 95%) as a 50:50 mixture of diastereoisomers.

¹H NMR (600 MHz, CDCl₃) δ 9.76 (t, J = 2.0 Hz, 1H), 2.70-2.68 (m, 1H), 2.42 (ddd, J = 11.0, 3.5 and 2.0 Hz, 1H), 2.30-2.25 (m, 1H), 2.14-2.09 (m, 1H), 1.60-1.42 (m, 4H), 1.30 (s, 3H), 1.26 (s, 3H), 0.98 (d, J = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃)† δ 202.7 (CH), 202.6 (CH), 64.3 (CH), 64.2 (CH), 58.4 (C), 58.3 (C), 51.0 (CH₂), 50.9 (CH₂), 33.5 (CH₂), 27.9 (CH), 26.4 (CH₂), 26.4 (CH₂), 25.0 (CH₃), 19.9 (CH₃), 19.8 (CH₃), 18.7 (CH₃), 18.7 (CH₃); IR (thin film) 2960, 2927, 1722 cm⁻¹; LRMS (FAB) 193 (100, [M+Na]⁺); HRMS (FAB) calcd for C₁₀H₁₆O₂Na [M+Na]⁺ 193.1205, observed 193.1208.

† 20C expected, 17C observed.
3,7-Dimethyloctanal 18\textsuperscript{189}

A stirring solution of (±)-citronellal (771 mg, 902 µL, 5 mmol) and Pd on activated C (1%, 250 mg) in MeOH (15 mL) was successively degassed and purged with H\textsubscript{2} three times and the solution left to stir under a H\textsubscript{2} atmosphere for 20 h. To work-up, the reaction mixture was filtered through a 50:50 mixture of silica and celite, and the filtrate solvent removed \textit{in vacuo} to afford 3,7-dimethyloctanal as a colourless oil (546 mg, 3.50 mmol, 70%).

\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta\) 9.76 (t, \(J = 2.5\) Hz, 1H), 2.38 (ddd, \(J = 16.0, 5.5\) and 2.5 Hz, 1H), 2.22 (ddd, \(J = 16.0, 8.0\) and 2.5 Hz, 1H), 2.08-2.02 (m, 1H), 1.52 (nonet, \(J = 6.5\) Hz, 1H), 1.36-1.12 (m, 6H), 0.95 (d, \(J = 6.5\) Hz, 3H), 0.86 (d, \(J = 6.5\) Hz, 6H); \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) \(\delta\) 203.4 (CH), 51.2 (CH\textsubscript{2}), 39.1 (CH\textsubscript{2}), 37.2 (CH\textsubscript{2}), 28.3 (CH), 28.0 (CH), 24.8 (CH\textsubscript{2}), 22.8 (CH\textsubscript{3}), 22.7 (CH\textsubscript{3}), 20.1 (CH\textsubscript{3}); IR (thin film) 2955, 2927, 2870, 1726 cm\textsuperscript{-1}.

**Typical procedure for the synthesis of ketone sulfonate esters – Method A**

5% H\textsubscript{2}O\textsubscript{2} (0.05 mmol) and aldehyde (2 mmol) were added to a solution of pentafluorophenyl ethenesulfonate 105 (1 mmol) on H\textsubscript{2}O (500 µL) and the reaction mixture stirred at 21 °C for the time specified (see below). The reaction mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} (50 mL), washed with H\textsubscript{2}O (50 mL), dried (MgSO\textsubscript{4}), the solvent removed \textit{in vacuo} and purified as described below to afford the desired ketone sulfonate ester.

**Typical procedure for the synthesis of ketone sulfonate esters – Method B**

Aldehyde (2 mmol) was added to a solution of pentafluorophenyl ethenesulfonate 105 (1 mmol) on H\textsubscript{2}O (500 µL) and the reaction mixture stirred at 21 °C for the time specified (see below). The reaction mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} (50 mL), washed with H\textsubscript{2}O (50 mL), dried (MgSO\textsubscript{4}), the solvent removed \textit{in vacuo} and purified as described below to afford the desired ketone sulfonate ester.
**Pentafluorophenyl 3-oxohexane-1-sulfonate 107a**

Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH$_2$Cl$_2$/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-oxohexane-1-sulfonate as white crystals (291 mg, 0.84 mmol, 84%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH$_2$Cl$_2$/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-oxohexane-1-sulfonate as white crystals (270 mg, 0.78 mmol, 78%).

m.p. 47-49 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.76-3.74 (m, 2H), 3.13-3.11 (m, 2H), 2.51 (t, $J = 7.5$ Hz, 2H), 1.64 (sextet, $J = 7.5$ Hz, 2H), 0.93 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 205.0 (C), 47.0 (CH$_2$), 44.7 (CH$_2$), 36.0 (CH$_2$), 17.2 (CH$_2$), 13.6 (CH$_3$); IR (solid) 2968, 1719, 1515, 1381, 1182 cm$^{-1}$; LRMS (CI) 347 (90, [M+H]$^+$), 163 (100); HRMS (CI) calcd for C$_{12}$H$_{12}$F$_5$O$_4$S [M+H]$^+$ 347.0371, observed 347.0369.

**Pentafluorophenyl 4-methyl-3-oxopentane-1-sulfonate 107b**

Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH$_2$Cl$_2$/petrol) and recrystallisation (petrol) gave pentafluorophenyl 4-methyl-3-oxopentane-1-sulfonate as white crystals (194 mg, 0.56 mmol, 56%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH$_2$Cl$_2$/petrol) and recrystallisation (petrol) gave pentafluorophenyl 4-methyl-3-oxopentane-1-sulfonate as white crystals (138 mg, 0.40 mmol, 40%).
Pentafluorophenyl 5-methyl-3-oxohexane-1-sulfonate 107c

Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH₂Cl₂/petrol) and recrystallisation (petrol) gave pentafluorophenyl 5-methyl-3-oxohexane-1-sulfonate as white crystals (277 mg, 0.77 mmol, 77%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH₂Cl₂/petrol) and recrystallisation (petrol) gave pentafluorophenyl 5-methyl-3-oxohexane-1-sulfonate as white crystals (266 mg, 0.74 mmol, 74%).

Pentafluorophenyl 3-oxooctane-1-sulfonate 107d

Using Method A, the reaction was complete after 2 h. Purification by column chromatography (30%-70% CH₂Cl₂/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-oxooctane-1-sulfonate as white crystals (281 mg, 0.75 mmol, 75%).
Using Method B, the reaction was complete after 6 h. Purification by column chromatography (30%-70% CH₂Cl₂/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-oxooctane-1-sulfonate as white crystals (280 mg, 0.75 mmol, 75%).

m.p. 45-47 °C; ¹H NMR (500 MHz, CDCl₃) δ 3.77-3.75 (m, 2H), 3.14-3.12 (m, 2H), 2.51 (t, J = 7.5 Hz, 2H), 1.63 (quintet, J = 7.5 Hz, 2H), 1.34-1.26 (m, 4H), 0.94 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 205.1 (C), 47.1 (CH₂), 42.8 (CH₂), 36.0 (CH₂), 31.3 (CH₂), 23.4 (CH₂), 22.4 (CH₂), 13.9 (CH₃); IR (solid) 2937, 2871, 1721, 1520, 1388, 1183 cm⁻¹; LRMS (CI) 375 (100, [M+H]⁺); HRMS (CI) calcd for C₁₄H₁₆F₅O₄S [M+H]⁺ 375.0690, observed 375.0685.

**Pentafluorophenyl 3-cyclohexyl-3-oxopropane-1-sulfonate 107e**

Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH₂Cl₂/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-cyclohexyl-3-oxopropane-1-sulfonate as white crystals (305 mg, 0.79 mmol, 79%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH₂Cl₂/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-cyclohexyl-3-oxopropane-1-sulfonate as white crystals (286 mg, 0.74 mmol, 74%).

m.p. 65-67 °C; ¹H NMR (500 MHz, CDCl₃) δ 3.76-3.74 (m, 2H), 3.18-3.16 (m, 2H), 2.43 (tt, J = 11.0 and 3.0 Hz, 1H), 1.92-1.87 (m, 2H), 1.84-1.78 (m, 2H), 1.74-1.68 (m, 1H), 1.40-0.85 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 208.1 (C), 50.8 (CH), 47.2 (CH₂), 34.0 (CH₂), 28.4 (CH₂), 25.7 (CH₂), 25.5 (CH₂); IR (solid) 2936, 2858, 1714, 1519, 1388, 1183 cm⁻¹; LRMS (CI) 387 (100, [M+H]⁺); HRMS (CI) calcd for C₁₅H₁₆F₅O₄S [M+H]⁺ 387.0690, observed 387.0689.
Pentafluorophenyl 4-ethyl-3-oxooctane-1-sulfonate 107f\textsuperscript{194}

Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH\textsubscript{2}Cl\textsubscript{2}/petrol) gave pentafluorophenyl 4-ethyl-3-oxooctane-1-sulfonate as a colourless oil (350 mg, 0.87 mmol, 87%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH\textsubscript{2}Cl\textsubscript{2}/petrol) gave pentafluorophenyl 4-ethyl-3-oxooctane-1-sulfonate as a colourless oil (334 mg, 0.83 mmol, 83%).

\begin{center}
\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) $\delta$ 3.73-3.71 (m, 2H), 3.13-3.11 (m, 2H), 2.47-2.44 (m, 1H), 1.65-1.60 (m, 2H), 1.59-1.40 (m, 2H), 1.31-1.27 (m, 2H), 1.22-1.19 (m, 2H), 0.87 (t, $J = 7.0$ Hz, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) $\delta$ 208.9 (C), 53.9 (CH), 47.0 (CH\textsubscript{2}), 35.6 (CH\textsubscript{2}), 30.9 (CH\textsubscript{2}), 29.6 (CH\textsubscript{2}), 24.6 (CH\textsubscript{2}), 22.8 (CH\textsubscript{2}), 13.8 (CH\textsubscript{3}), 11.7 (CH\textsubscript{3}); IR (thin film) 2962, 2935, 2877, 1714, 1516, 1384, 1183 cm\textsuperscript{-1}; LRMS (CI) 403 (51, [M+H]$^+$), 216 (100); HRMS (CI) calcd for C\textsubscript{16}H\textsubscript{20}F\textsubscript{5}O\textsubscript{4}S [M+H]$^+$ 403.0997, observed 403.0981.
\end{center}

Pentafluorophenyl 3-oxododecane-1-sulfonate 107g

Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH\textsubscript{2}Cl\textsubscript{2}/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-oxododecane-1-sulfonate as white crystals (284 mg, 0.66 mmol, 66%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH\textsubscript{2}Cl\textsubscript{2}/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-oxododecane-1-sulfonate as white crystals (267 mg, 0.62 mmol, 62%).

m.p. 68-70 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) $\delta$ 3.77-3.75 (m, 2H), 3.14-3.12 (m, 2H), 2.51 (t, $J = 7.5$ Hz, 2H), 2.16 (quintet, $J = 7.5$ Hz, 2H), 1.33-1.27 (m, 12H), 0.94 (t, $J$
= 7.5 Hz, 3H); \( ^{13} \text{C} \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 205.1 (C), 47.0 (CH\(_2\)), 35.9 (CH\(_2\)), 31.9 (CH\(_2\)), 29.6 (CH\(_2\)), 29.4 (CH\(_2\)), 29.3 (CH\(_2\)), 29.1 (CH\(_2\)), 23.7 (CH\(_2\)), 22.7 (CH\(_2\)), 14.1 (CH\(_3\)); IR (solid) 2954, 2918, 2849, 1710, 1518, 1378, 1178 cm\(^{-1}\); LRMS (Cl) 431 (100, [M+H]\(^+\)); HRMS (Cl) calcd for C\(_{18}\)H\(_{24}\)F\(_5\)O\(_4\)S [M+H]\(^+\) 431.1310, observed 431.1290.

**Ethyl ethenesulfonate 125**

\[
\begin{align*}
\text{SO}_3\text{Et}
\end{align*}
\]

A solution of EtOH (5.6 g, 7.2 mL, 123 mmol) and NEt\(_3\) (18.7 g, 25.6 mL, 184 mmol) in CH\(_2\)Cl\(_2\) (100 mL) was added dropwise over 1 h to a solution of 2-chloroethane-1-sulfonyl chloride (10 g, 61.3 mmol) in CH\(_2\)Cl\(_2\) (100 mL) at -15 °C. The reaction mixture was allowed to warm to 21 °C, diluted with CH\(_2\)Cl\(_2\) (100 mL), washed with sat. NaHCO\(_3\) (2 × 250 mL) and the solvent removed in vacuo. The reaction mixture was diluted with Et\(_2\)O, washed with 2M HCl (2 × 250 mL) and sat. NaCl (250 mL), dried (MgSO\(_4\)) and the solvent removed in vacuo to afford ethyl ethenesulfonate as a colourless oil (6.6 g, 48.4 mmol, 79%).

\(^1\text{H} \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.55 (dd, \( J = 16.5 \) and 10.0 Hz, 1H), 6.40 (dd, \( J = 16.5 \) and 0.5 Hz, 1H), 6.11 (dd, \( J = 10.0 \) and 0.5 Hz, 1H), 4.21 (q, \( J = 7.0 \) Hz, 2H), 1.39 (t, \( J = 7.0 \) Hz, 3H); \(^{13} \text{C} \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 132.8 (CH), 130.0 (CH\(_2\)), 67.2 (CH\(_2\)), 15.0 (CH\(_3\)); IR (thin film) 3068, 2990, 1614, 1351, 1168 cm\(^{-1}\); LRMS (Cl) 137 (26, [M+H]\(^+\)), 109 (100); HRMS (Cl) calcd for C\(_4\)H\(_9\)O\(_2\)S [M+H]\(^+\) 137.0272, observed 137.0273.

**Phenyl ethenesulfonate 128**

\[
\begin{align*}
\text{SO}_3\text{Ph}
\end{align*}
\]

A solution of NEt\(_3\) (31.2 g, 43 mL, 307 mmol) in CH\(_2\)Cl\(_2\) (100 mL) was added dropwise over 1 h to a solution of 2-chloroethane-1-sulfonyl chloride (10 g, 61.3 mmol) and phenol (6.9 g, 74 mmol) in CH\(_2\)Cl\(_2\) (100 mL) at -15 °C. The reaction mixture was allowed to warm to 21 °C, The solvent was removed in vacuo, the crude residue diluted with Et\(_2\)O (200 mL), washed with 2M HCl (2 × 250 mL), sat. NaHCO\(_3\) (2 × 250 mL) and sat. NaCl (250 mL), dried (MgSO\(_4\)) and the solvent
removed in vacuo. Purification by column chromatography (20%-30% Et₂O/Petrol) gave phenyl ethenesulfonate as a white solid (8.4 g, 50 mmol, 82%).

m.p. 39-42 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.39 (m, 2H), 7.35-7.30 (m, 1H), 7.26-7.23 (m, 2H), 6.69 (dd, J = 16.5 and 10.0 Hz, 1H), 6.38 (dd, J = 16.5 and 0.5 Hz, 1H), 6.18 (dd, J = 10.0 and 0.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 149.5 (C), 132.2 (C), 131.7 (CH₂), 129.9 (CH), 127.4 (CH), 122.3 (CH); IR (solid) 3065, 1586, 1487, 1359, 1140 cm⁻¹; LRMS (CI) 185 (45, [M+H]^+), 94 (100); HRMS (CI) calcd for C₈H₉O₃S [M+H]^+ 185.0189, observed 185.0190.

**Typical procedure for the synthesis of ketone sulfonate esters – Method C**

Aldehyde (5 mmol) was added to a solution of alkene (1 mmol) on H₂O (500 μL) and the reaction mixture stirred at 21 °C for the time specified (see below). The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with H₂O (50 mL), dried (MgSO₄), the solvent removed in vacuo and purified as described below to afford the desired ketone sulfonate ester.

**Ethyl 3-oxohexane-1-sulfonate 126a and 1,3-diethyl 5-oxooctane-1,3-disulfonate 127a**

Using Method C, the reaction was complete after 96 h. Purification by column chromatography (20%-60% EtOAc/petrol) gave ethyl 3-oxohexane-1-sulfonate as a yellow oil (114 mg, 0.55 mmol, 55%) and 1,3-diethyl 5-oxooctane-1,3-disulfonate as a colourless oil (48 mg, 0.14 mmol, 14%).

Data for 126a: ¹H NMR (300 MHz, CDCl₃) δ 4.27 (q, J = 7.0 Hz, 2H), 3.40-3.36 (m, 2H), 2.96-2.92 (m, 2H), 2.44 (t, J = 7.0 Hz, 2H), 1.60 (sextet, J = 7.0 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 206.1 (C), 66.7 (CH₂), 44.7 (CH₂), 44.3 (CH₂), 36.0 (CH₂), 17.1 (CH₂), 15.0 (CH₃), 13.6 (CH₃); IR (thin film) 2964, 2873, 1716, 1350, 1168 cm⁻¹; LRMS (CI) 209 (100, [M+H]^+); HRMS (CI) calcd for C₈H₁₇O₄S [M+H]^+ 209.0848, observed 209.0850.
Data for 127a: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.45-4.28 (m, 4H), 3.89-3.86 (m, 1H), 3.48-3.30 (m, 2H), 3.20 (dd, $J = 18.5$ and 4.5 Hz, 1H), 2.68 (dt, $J = 18.5$ and 7.0 Hz, 1H), 2.50-2.36 (m, 3H), 2.31-2.15 (m, 1H), 1.65 (sextet, $J = 7.5$ Hz, 2H), 1.47-1.37 (m, 6H), 0.95 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 205.7 (C), 67.3 (CH$_2$), 66.8 (CH$_2$), 53.9 (CH), 47.5 (CH$_2$), 45.0 (CH$_2$), 42.2 (CH$_2$), 24.5 (CH$_2$), 17.2 (CH$_2$), 15.2 (CH$_3$), 15.2 (CH$_3$), 13.7 (CH$_3$); IR (thin film) 2934, 1716, 1344, 1166 cm$^{-1}$; LRMS (CI) 345 (15, [M+H]$^+$), 235 (100); HRMS (CI) calcd for C$_{12}$H$_{25}$O$_7$S$_2$ [M+H]$^+$ 345.1042; observed 345.1036.

Phenyl 3-oxohexane-1-sulfonate 126b

Using Method C, the reaction was complete after 120 h. Purification by column chromatography (50%-95% CH$_2$Cl$_2$/petrol) and recrystallisation (petrol) gave phenyl 3-oxohexane-1-sulfonate as a white solid (133 mg, 0.52 mmol, 52%).

m.p. 28-30 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41 (td, $J = 7.0$ and 1.5 Hz, 2H), 7.32 (tt, $J = 7.0$ and 1.0 Hz, 1H), 7.27 (dd, $J = 7.0$ and 1.0 Hz, 2H), 3.57-3.54 (m, 2H), 3.08-3.04 (m, 2H), 2.48 (t, $J = 7.5$ Hz, 2H), 1.65 (sextet, $J = 7.5$ Hz, 2H), 0.94 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 205.7 (C), 149.1 (C), 130.1 (CH), 127.5 (CH), 122.0 (CH), 44.9 (CH$_2$), 44.8 (CH$_2$), 36.1 (CH$_2$), 17.3 (CH$_2$), 13.7 (CH$_3$); IR (solid) 2964, 2934, 2875, 1718, 1588, 1489, 1489, 1370, 1145 cm$^{-1}$; LRMS (CI) 257 (45, [M+H]$^+$), 163 (100); HRMS (CI) calcd for C$_{12}$H$_{17}$O$_4$S [M+H]$^+$ 257.0848, observed 257.0850.

Ethyl 3-cyclohexyl-3-oxopropane-1-sulfonate 126c

Using Method C, the reaction was complete after 96 h. Purification by column chromatography (20%-60% EtOAc/petrol) gave ethyl 3-cyclohexyl-3-oxopropane-1-sulfonate as a colourless oil (129 mg, 0.52 mmol, 52%).
Phenyl 3-cyclohexyl-3-oxopropane-1-sulfonate 126d

Using Method C, the reaction was complete after 120 h. Purification by column chromatography (50%-95% CH$_2$Cl$_2$/petrol) and recrystallisation (petrol) gave phenyl 3-cyclohexyl-3-oxopropane-1-sulfonate as a white solid (169 mg, 0.57 mmol, 57%).

m.p. 62-64 °C; $^1$H NMR (600 MHz, CDCl$_3$) δ 7.47-7.42 (m, 2H), 7.38-7.34 (m, 1H), 7.32-7.28 (m, 2H), 3.59-3.55 (m, 2H), 3.17-3.12 (m, 2H), 2.44 (tt, $J = 11.0$ and 3.0 Hz, 1H), 1.92-1.86 (m, 2H), 1.84-1.78 (m, 2H), 1.72-1.66 (m, 1H), 1.44-1.18 (m, 5H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 208.9 (C), 149.0 (C), 130.1 (CH), 127.4 (CH), 122.0 (CH), 50.8 (CH), 44.9 (CH$_2$), 34.0 (CH$_2$), 28.4 (CH$_2$), 25.7 (CH$_2$), 25.5 (CH$_2$); IR (solid) 2930, 2855, 1711, 1588, 1488, 1370, 1144 cm$^{-1}$; LRMS (FAB) 319 (17, [M+Na]$^+$), 297 (18, [M+H]$^+$), 176 (52), 154 (100); HRMS (FAB) calcd for C$_{15}$H$_{21}$O$_4$S [M+H]$^+$ 297.1161, observed 297.1167.

Pentafluorophenyl (E)-2-phenylethenesulfonate 129

A solution of NEt$_3$ (2.0 g, 2.8 mL, 19.74 mmol) and pentafluorophenol (2.2 g, 11.8 mmol) in CH$_2$Cl$_2$ (20 mL) was added dropwise over 1 h to a solution of 2-phenylethenesulfonyl chloride (2.0 g, 9.87 mmol) in CH$_2$Cl$_2$ (100 mL) at -15 °C and the reaction mixture left to stir at this temperature for 20 min. The reaction mixture was left to warm to 21 °C, left to stir for a further 30 min, diluted with CH$_2$Cl$_2$ (100 mL), washed with sat. NaHCO$_3$ (3 × 200 mL), 2M HCl (3 × 200 mL) and sat. NaCl (250
mL), dried (MgSO₄) and the solvent removed in vacuo. The crude residue was triturated with 5% CH₂Cl₂/petrol and dried under vacuum to afford pentafluorophenyl (E)-2-phenylethenesulfonate as white crystals (3.20 g, 9.14 mmol, 91%).

m.p. 104-106 ºC; ¹H NMR (500 MHz, CDCl₃) δ 7.70 (d, J = 15.5 Hz, 1H), 7.56-7.51 (m, 3H), 7.47 (td, J = 5.0 and 1.5 Hz, 2H), 6.95 (d, J = 15.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 147.9 (CH), 132.5 (CH), 131.3 (C), 129.5 (CH), 129.0 (CH), 119.8 (CH); IR (solid) 3067, 1613, 1576, 1516, 1393, 1174 cm⁻¹; LRMS (CI) 351 (100, [M+H]⁺); HRMS (CI) calcd for C₁₄H₈F₅O₃S [M+H]⁺ 351.0114, observed 351.0126.

**Ethyl methanesulfonate 137**

A solution of EtOH (40.2 g, 51 mL, 524 mmol) and NEt₃ (19.4 g, 26.8 mL, 192 mmol) in CH₂Cl₂ (100 mL) was added dropwise over 30 min to a stirring solution of methanesulfonyl chloride (20 g, 13.6 mL, 175 mmol) at 0 ºC. The reaction mixture was allowed to warm to 21 ºC, stirred for a further 1 h, diluted with CH₂Cl₂ (100 mL), washed with 2M HCl (3 × 250 mL), dried (MgSO₄) and the solvent removed in vacuo to afford ethyl methanesulfonate as a colourless oil (17.1 g, 139 mmol, 79%).

¹H NMR (500 MHz, CDCl₃) δ 4.30 (q, J = 7.0 Hz, 2H), 3.00 (s, 3H), 1.42 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 66.3 (CH₂), 37.6 (CH₃), 15.1 (CH₃); IR (thin film) 2988, 2943, 1343, 1169 cm⁻¹; LRMS (CI) 125 (7, [M+H]⁺), 109 (100); HRMS (CI) calcd for C₃H₉O₃S [M+H]⁺ 125.0189, observed 125.0190.

**Ethyl (diethoxyphosphoryl)methanesulfonate 138**

A solution of n-butyllithium (1.6M in hexanes, 0.67 g, 6.5 mL, 10.4 mmol) was added to a stirring solution of methanesulfonic acid ethyl ester 137 (1.17 g, 1.0 mL, 9.43 mmol) in dry THF (30 mL) at -78 ºC under an argon atmosphere and the reaction mixture left to stir at -78 ºC for 15 min. Ethyl chlorophosphate (0.90 g, 0.77 mL, 5.20 mmol) was added at -78 ºC, the reaction mixture left to stir at -78 ºC for 30
min, warmed to -50 ºC and stirred at -50 ºC for a further 1 h. 4.4M NH₄Cl (2.58 mL, 10.4 mmol) was added cautiously, the reaction mixture left to warm to 21 ºC and the solvent removed in vacuo. The crude residue was diluted with H₂O (100 mL), extracted with CH₂Cl₂ (3 × 50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography (50% Et₂O/CH₂Cl₂) gave ethyl (diethoxyphosphoryl)methanesulfonate as a colourless oil (1.02 g, 3.9 mmol, 76%).

¹H NMR (500 MHz, CDCl₃) δ 4.41 (q, J = 7.0 Hz, 2H), 4.24 (dq, JₗH-P = 14.0 and J = 6.0 Hz, 4H), 3.71 (d, JₗC-P = 17.0 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H), 1.38 (t, J = 7.0 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 68.4 (CH₂), 63.8 (d, JₗC-P = 6.0 Hz, CH₂), 48.0 (d, JₗC-P = 139.5 Hz, CH₂), 16.3 (d, JₗC-P = 6.0 Hz, CH₃), 15.1 (CH₃); IR (thin film) 2985, 2907, 1358, 1263, 1180 cm⁻¹; LRMS (CI) 261 (100, [M+H]+); HRMS (CI) calcd for C₇H₁₈O₇PS [M+H]+ 261.0562, observed 261.0555.

Ethyl (E,Z)-pent-1-ene-1-sulfonate 139a

A solution of (diethoxy-phosphoryl)-methanesulfonic acid ethyl ester 138 (3.0 g, 11.52 mmol) and 1,10-phenantroline (1 mg) in dry THF (50 mL) was cooled to -78 ºC under an atmosphere of argon. A solution of n-butyllithium (2.5M in hexanes, 4.61 mL, 11.52 mmol) was added dropwise until a persistent orange colour appeared, the reaction mixture left to stir at -78 ºC for 10 min, freshly distilled n-butanal 18a (0.83 g, 1.04 mL, 11.52 mmol) added and the reaction mixture left to stir at -78 ºC for 45 min. The reaction mixture was allowed to warm to 21 ºC, left to stir for 16 h and the solvent removed in vacuo. The crude residue was diluted with H₂O (200 mL), extracted with CH₂Cl₂ (3 × 200 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography (50%-75% Et₂O/CH₂Cl₂) gave ethyl (E,Z)-pent-1-ene-1-sulfonate (1.97 g, 11.06 mmol, 96%) as a mixture of E:Z (2.86:1) isomers.

Data for E-isomer: ¹H NMR (500 MHz, CDCl₃) δ 6.91 (dt, J = 15.0 and 7.0 Hz, 1H), 6.19 (d, J = 15.0 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 2.26 (qd, J = 7.0 and 1.5 Hz, 2H), 1.54 (sextet, J = 7.0 Hz, 2H), 1.38 (t, J = 7.0 Hz, 3H), 0.97 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 148.8 (CH), 124.9 (CH), 66.4 (CH₂), 30.2 (CH₂), 21.0
(CH₂), 15.0 (CH₃), 13.7 (CH₃); IR (thin film) 2963, 1630, 1352, 1167 cm⁻¹; LRMS (CI) 179 (37, [M+H]⁺), 151 (100); HRMS (CI) calcd for C₇H₁₅O₂S [M+H]⁺ 179.0742, observed 179.0745.

Data for Z-isomer: ¹H NMR (500 MHz, CDCl₃) δ 6.38 (dt, J = 11.0 and 7.5 Hz, 1H), 6.19 (dt, J = 11.0 and 1.5 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 2.58 (qd, J = 7.5 and 1.5 Hz, 2H), 1.54 (sextet, J = 7.5 Hz, 2H), 1.40 (t, J = 7.0 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 149.3 (CH), 124.6 (CH), 66.5 (CH₂), 33.5 (CH₂), 22.0 (CH₂), 15.0 (CH₃), 13.6 (CH₃); IR (thin film) 2963, 1630, 1352, 1167 cm⁻¹; LRMS (CI) 179 (37, [M+H]⁺), 151 (100); HRMS (CI) calcd for C₇H₁₅O₂S [M+H]⁺ 179.0742, observed 179.0745.

Typical procedure for the synthesis of ketone sulfones – Method D

Aldehyde (5 mmol) was added to a solution of alkene (1 mmol) on H₂O (500 μL) and the reaction mixture stirred at 60 °C for the time specified (see below). The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with H₂O (50 mL), dried (MgSO₄), the solvent removed in vacuo and purified as described below to afford the desired ketone sulfone.

1-(Ethylsulfonyl)hexan-3-one 143a and 6,8-bis(ethanesulfonyl)octan-4-one 144a

Using Method D, the reaction was complete after 24 h. Purification by column chromatography (50% EtOAc/petrol) and recrystallisation (CH₂Cl₂/petrol) gave 1-(ethylsulfonyl)hexan-3-one as a white solid (123 mg, 0.64 mmol, 64%) and 6,8-bis(ethanesulfonyl)octan-4-one as a yellow oil (37 mg, 0.12 mmol, 12%).

Data for 143a: m.p. 70-73 °C; ¹H NMR (400 MHz, CDCl₃) δ 3.29-3.26 (m, 2H), 3.06-2.98 (m, 4H), 2.51-2.47 (m, 2H), 1.58 (sextet, J = 7.5 Hz, 2H), 1.44 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 206.8 (C), 48.2 (CH₂), 46.0 (CH₂), 44.7 (CH₂), 34.1 (CH₂), 17.2 (CH₂), 13.7 (CH₃), 6.72 (CH₃); IR (solid) 2961, 2874, 1712, 1293, 1127 cm⁻¹; LRMS (CI) 193 (5, [M+H]⁺), 109 (68), 99 (100); HRMS (ES) calcd for C₈H₁₇O₃S [M+H]⁺ 193.0898; observed 193.0901.
Data for **144a**: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.65-3.60 (m, 1H), 3.23-3.18 (m, 3H), 3.04-3.00 (m, 4H), 2.69 (dd, $J = 18.5$ and 6.5 Hz, 1H), 2.49 (dt, $J = 16.5$ and 7.5 Hz, 1H), 2.40 (dt, $J = 16.5$ and 7.0 Hz, 1H), 1.65 (sextet, $J = 7.5$ Hz, 2H), 1.55-1.37 (m, 8H), 0.93 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 206.5 (C), 54.3 (CH), 48.5 (CH$_2$), 47.5 (CH$_2$), 46.5 (CH$_2$), 44.9 (CH$_2$), 41.1 (CH$_2$), 21.7 (CH$_2$), 17.1 (CH$_2$), 13.7 (CH$_3$), 6.7 (CH$_3$), 6.1 (CH$_3$); IR (thin film) 2934, 1714, 1300, 1125 cm$^{-1}$; LRMS (ES) 335 (100, [M+Na]$^+$); HRMS (ES) calcd for C$_{12}$H$_{24}$O$_5$S$_2$Na [M+Na]$^+$ 335.0963; observed 335.0951.

**1-(Phenylsulfonyl)hexan-3-one 143b**

Using Method D, the reaction was complete after 24 h. Purification by column chromatography (10-30% EtOAc/petrol) gave 1-(phenylsulfonyl)hexan-3-one as a yellow oil (134 mg, 0.56 mmol, 56%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.94-7.88 (m, 2H), 7.68-7.64 (m, 1H), 7.62-7.58 (m, 2H), 3.42-3.28 (m 2H), 2.92-2.88 (m, 2H), 2.40 (t, $J = 7.5$ Hz, 2H), 1.58 (sextet, $J = 7.5$ Hz, 2H), 0.90 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 206.2 (C), 139.1 (C), 134.0 (CH), 129.5 (CH), 128.0 (CH), 50.6 (CH$_2$), 44.8 (CH$_2$), 35.0 (CH$_2$), 17.2 (CH$_2$), 13.7 (CH$_3$); IR (thin film) 2965, 1716, 1308, 1150 cm$^{-1}$; LRMS (CI) 258 (100, [M+NH$_4$]$^+$); HRMS (ES) calcd for C$_{12}$H$_{20}$NO$_3$S [M+NH$_4$]$^+$ 258.1158; observed 258.1160.

**1-Cyclohexyl-3-ethanesulfonylpropan-1-one 143c**

Using Method D, the reaction was complete after 24 h. Purification by column chromatography (10-30% EtOAc/petrol) and recrystallisation (CH$_2$Cl$_2$/petrol) gave 1-cyclohexyl-3-ethanesulfonylpropan-1-one as a white solid (132 mg, 0.57 mmol, 57%).
m.p. 82-84 °C; $^1$H NMR (600 MHz, CDCl$_3$) δ 3.28-3.24 (m, 2H), 3.05-3.00 (m, 4H), 2.43 (tt, $J = 11.0$ and 3.5, 1H), 1.92-1.87 (m, 2H), 1.83-1.78 (m, 2H), 1.72-1.68 (m, 1H), 1.44 (t, $J = 7.5$, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 209.9 (C), 50.8 (CH), 48.2 (CH$_2$), 46.1 (CH$_2$), 32.1 (CH$_2$), 28.5 (CH$_2$), 25.7 (CH$_2$), 25.5 (CH$_2$), 6.7 (CH$_3$); IR (solid) 2929, 2854, 1702, 1300, 1130 cm$^{-1}$; LRMS (EI) 232 (12, [M$^+$]), 204 (55), 139 (100); HRMS (EI) calcd for C$_{11}$H$_{20}$O$_3$S [M$^+$] 232.1128; observed 232.1117.

3-Benzylsulfonyl-1-cyclohexylpropan-1-one 143d and 3,5-bis(benzylsulfonyl)-1-cyclohexylpentan-1-one 144d

Using Method D, the reaction was complete after 24 h. Purification by column chromatography (10-30% EtOAc/petrol) and recrystallisation (petrol) gave 3-benzylsulfonyl-1-cyclohexylpropan-1-one as a white solid (171 mg, 0.61 mmol, 61%) and 3,5-bis(benzylsulfonyl)-1-cyclohexylpentan-1-one as white solid (45 mg, 0.10 mmol, 10%).

Date for 143d: m.p. 78-80 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.92-7.88 (m, 2H), 7.68-7.64 (m, 1H), 7.60-7.56 (m, 2H), 3.39-3.34 (m 2H), 2.97-2.92 (m, 2H), 2.35 (tt, $J = 11.0$ and 3.0 Hz, 1H), 1.82-1.67 (m, 5H), 1.32-1.18 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 209.3 (C), 139.2 (C), 134.0 (CH), 129.5 (CH), 128.0 (CH), 50.9 (CH), 50.7 (CH$_2$), 32.9 (CH$_2$), 28.5 (CH$_2$), 25.7 (CH$_2$), 25.6 (CH$_2$); IR (solid) 2929, 1709, 1308, 1151 cm$^{-1}$; LRMS (Cl) 298 (100, [M+NH$_4$]$^+$); HRMS (ES) calcd for C$_{15}$H$_{24}$NO$_3$S [M+NH$_4$]$^+$ 298.1471; observed 298.1473.

Data for 144d: m.p. 130-132 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.88-7.84 (m, 4H), 7.69-7.64 (m, 2H), 7.64-7.58 (m, 4H), 3.72 (ddddd, $J = 8.5$, 6.5, 5.5 and 4.5 Hz, 1H), 3.29 (ddd, $J = 14.0$, 11.5 and 5.0 Hz, 1H), 3.19 (ddd, $J = 14.0$, 11.5 and 4.5 Hz, 1H), 2.29 (tt, $J = 11.0$ and 3.5 Hz, 1H), 2.17 (dd, $J = 11.5$ and 6.5 Hz, 1H), 1.91 (dd, $J = 11.5$ and 5.5 Hz, 1H), 1.82-1.55 (m, 7H), 1.30-1.12 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 208.7 (C), 138.4 (C), 136.6 (C), 134.3 (CH), 133.9 (CH), 129.5 (CH), 129.4 (CH), 128.8 (CH), 128.1 (CH), 57.6 (CH), 52.9 (CH$_2$), 50.9 (CH), 38.5 (CH$_2$),
28.4 (CH₂), 28.2 (CH₂), 25.6 (CH₂), 25.5 (CH₂), 25.3 (CH₂), 22.4 (CH₂); IR (solid) 2922, 1721, 1312, 1140 cm⁻¹; LRMS (CI) 449 (100, [M+H]+); HRMS (ES) calcd for C₂₃H₂₉O₅S [M+H]⁺ 449.1378; observed 449.1387.

(2S)-2-[(tert-Butyldimethylsilyl)oxy]propanal 146

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2-tert-Butylchlorodimethylsilane (7.95 g, 53.0 mmol) was added to a stirring solution of (S)-ethyl lactate 145 (5 mL, 44.2 mmol) and imidazole (4.51 g, 67.1 mmol) in DMF (44 mL) and the reaction mixture left to stir at 21 °C for 30 min. The reaction mixture was diluted with H₂O (100 mL), extracted with Et₂O (3 × 100 mL), the combined organics washed with sat. NaCl (100 mL), dried (MgSO₄) and the solvent removed in vacuo to give crude ethyl (2S)-2-[(tert-butyldimethylsilyl)oxy]propanoate (12 g). Diisobutylaluminium hydride (1.5 M in PhMe, 19.0 mL, 28.9 mmol) was added at 0.5 mL/min to a solution of (2S)-2-[(tert-butyldimethylsilyl)oxy]-propionic acid ethyl ester (4.42 g, 18.2 mmol) in Et₂O (150 mL) at -85 °C under an inert atmosphere. After addition was complete, the reaction was stirred for a further 10 min at -78 °C then quenched by the dropwise addition of MeOH (1.1 mL) and H₂O (3 mL). After warming to 21 °C and stirring for 90 min, finely ground Na₂SO₄ and MgSO₄ were added and the suspension stirred for 15 min, then filtered through a short plug of celite and silica, eluting with Et₂O. The solvents were removed in vacuo and the crude residue purified by vacuum distillation to give (2S)-2-[(tert-butyldimethylsilyl)oxy]propanal as a colourless oil (2.10 g, 11.1 mmol, 61%).

¹H NMR (400 MHz, CDCl₃) δ 9.62 (d, J = 1.5 Hz, 1H), 4.10 (qd, J = 7.0 and 1.5 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 204.3 (CH), 73.8 (CH), 25.7 (CH₃), 18.5 (CH₃), 18.2 (CH₃), -4.8 (CH₃), -4.8 (CH₃); IR (thin film) 2952, 2931, 2859, 1742 cm⁻¹; [α]D = -11.0 (c 2.51, CHCl₃, 22.0 °C), Lit. [α]D = -11.1 (c 1.50, CHCl₃, 20.0 °C).
(2S)-2-Methylbutanal 152

A two-necked flask was fitted with a pressure-equalising dropping funnel and a thermometer. The flask was charged with (2S)-2-methylbutanol 151 (13.5 mL, 11.0 g, 0.13 mol), 2,2,6,6-tetramethylpiperidin-1-oxyl (0.2 g, 1.3 mmol), CH₂Cl₂ (40 mL), and a solution of KBr (1.48 g, 0.013 mol) in H₂O (6 mL). The reaction mixture was vigorously stirred and cooled to -10 °C, then aqueous NaOCl (2.4 M, 115 mL, 0.14 mol, pH 9.5) was added over 20 min, keeping the temperature of the reaction mixture between 10 and 15 °C. The mixture was stirred for a further 15 min, the orange organic phase was separated and the aqueous phase extracted with CH₂Cl₂ (15 mL). The combined organic extracts were washed with 10% aqueous HCl (50 mL) containing KI (0.40 g, 0.03 mol), 10% aqueous Na₂S₂O₃ (50 mL) and H₂O (30 mL). The organic phase was dried over MgSO₄ and then distilled at atmospheric pressure through a 20 cm Vigreux distillation column to give (2S)-2-methylbutanal as a colourless oil (8.8 g, 0.10 mol, 82%).

b.p. 90-92 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.59 (d, J = 2.0 Hz, 1H), 2.24 (sextet of doublets, J = 7.0 and 2.0 Hz, 1H), 1.75-1.67 (m, 1H), 1.45-1.36 (m, 1H), 1.05 (d, J = 7.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 205.4 (C), 47.8 (CH), 23.5 (CH₂), 12.9 (CH₃), 11.3 (CH₃); IR (thin film) 2970, 2938, 2878, 1705 cm⁻¹; LRMS (CI) 87 (30, [M+H]⁺), 74 (100); HRMS (CI) caleld for C₅H₁₁O [M+H]⁺ 87.0804, observed 87.0809; [α]D = +35.0 (c 2.04, Acetone, 22.0 °C), Lit. [α]D = +35.5 (c 2.50, Acetone, 20.0 °C).²⁹⁷

Pentafluorophenyl (4S)-4-methyl-3-oxohexane-1-sulfonate 153, pentafluorophenyl 3-methylpentane-1-sulfonate 154 and pentafluorophenyl 3-cyano-3-methylbutane-1-sulfonate 155

A solution of pentafluorophenyl ethenesulfonate 105 (411 mg, 1.5 mmol) in benzene (1 mL) was freeze-thaw degassed three times and then stirred under an atmosphere of
argon. Then was added (2S)-2-methylbutanal 152 (86 mg, 107 µL, 1 mmol) and AIBN (49 mg, 0.30 mmol) and the reaction mixture stirred at 40 °C for 72 h. The solvent was removed in vacuo and the crude residue purified by column chromatography (20%-90% CH₂Cl₂/petrol) to afford pentafluorophenyl (4S)-4-methyl-3-oxohexane-1-sulfonate as a colourless oil (231 mg, 0.64 mmol, 64%), pentafluorophenyl 3-methylpentane-1-sulfonate as a colourless oil (2 mg, 0.01 mmol, <1%) and pentafluorophenyl 3-cyano-3-methylbutane-1-sulfonate as a colourless oil (2 mg, 0.01 mmol, <1%).

Data for 153: ¹H NMR (400 MHz, CDCl₃) δ 3.79-3.73 (m, 2H), 3.24-3.14 (m, 2H), 2.57 (sextet, J = 7.5 Hz, 1H), 1.75 (doublet of quintets, J = 14.0 and 7.5 Hz, 1H), 1.48 (doublet of quintets, J = 14.0 and 7.5 Hz, 1H), 1.16 (d, J = 7.5 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 208.8 (C), 47.9 (CH), 47.1 (CH₂), 34.5 (CH₂), 25.9 (CH₂), 15.7 (CH₃), 11.5 (CH₃); IR (solid) 2970, 2940, 1716, 1516, 1384, 1184 cm⁻¹; LRMS (CI) 361 (100, [M+H]+); HRMS (CI) calcd for C₁₃H₁₄F₅O₄S [M+H]+ 361.0533, observed 361.0526; [α]D = +9.76 (c 18.9, CHCl₃, 23.5 °C); HPLC conditions: CHIRALCEL-OD column, hexane:i-PrOH 97:3, 1.2 mL/min, retention time: 16.3 min.

Data for 154: ¹H NMR (600 MHz, CDCl₃) δ 3.51-3.40 (m, 2H), 2.11-2.05 (m, 1H), 1.87 (ddddd, J = 19.0, 13.5, 7.5 and 5.0 Hz, 1H), 1.61-1.55 (m, 1H), 1.46-1.38 (m, 1H), 1.31-1.24 (m, 1H), 0.98 (d, J = 7.5 Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 51.2 (CH₂), 33.5 (CH), 29.7 (CH₂), 28.9 (CH₂), 18.6 (CH₃), 11.2 (CH₃); IR (thin film) 2966, 2880, 1515, 1390, 1178 cm⁻¹; LRMS (CI) 333 (100, [M+H]+); HRMS (CI) calcd for C₁₂H₁₄F₃O₃S [M+H]+ 333.0584, observed 333.0574.

Data for 155: ¹H NMR (600 MHz, CDCl₃) δ 3.66-3.63 (m, 2H), 2.31-2.28 (m, 2H), 1.49 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 121.1 (C), 49.3 (CH₂), 34.5 (CH₂), 26.5 (CH₃), 23.5 (CH₃); IR (thin film) 2983, 2234, 1515, 1390, 1184 cm⁻¹; LRMS (CI) 344 (100, [M+H]+); HRMS (CI) calcd for C₁₂H₁₁F₃NO₃S [M+H]+ 344.0380, observed 344.0386.
Pentafluorophenyl tridecane-1-sulfonate 156

A solution of pentafluorophenyl ethenesulfonate 105 (411 mg, 1.5 mmol) in benzene (1 mL) was freeze-thaw degassed three times and then stirred under an atmosphere of argon. Then was added (2S)-2-methylbutanal 152 (86 mg, 107 µL, 1 mmol) and lauroyl peroxide (120 mg, 0.30 mmol) and the reaction mixture stirred at 40 °C for 72 h. The solvent was removed in vacuo and the crude residue purified by column chromatography (20%-90% CH₂Cl₂/petrol) to afford pentafluorophenyl tridecane-1-sulfonate as a colourless oil (413 mg, 0.96 mmol, 96%).

$^1$H NMR (500 MHz, CDCl₃) δ 3.46-3.41 (m, 2H), 2.06-2.00 (m, 2H), 1.55-1.47 (m, 2H), 1.40-1.23 (m, 18H), 0.88 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl₃) δ 52.9 (CH₂), 32.0 (CH₂), 29.7 (CH₂), 29.7 (CH₂), 29.6 (CH₂), 29.5 (CH₂), 29.4 (CH₂), 29.3 (CH₂), 28.9 (CH₂), 28.1 (CH₂), 23.6 (CH₂), 22.8 (CH₂), 14.2 (CH₃); IR (thin film) 2922, 2852, 1519, 1384, 1185 cm⁻¹; LRMS (Cl) 431 (100, [M+H]⁺); HRMS (Cl) calcd for C₁₉H₂₈F₅O₃S [M+H]⁺ 431.1679, observed 431.1685.

Pentafluorophenyl 2-(1,4-dioxan-2-yl)ethane-1-sulfonate 158

A solution of pentafluorophenyl ethenesulfonate 105 (411 mg, 1.5 mmol) in 1,4-dioxane (1 mL) was freeze-thaw degassed three times and then stirred under an atmosphere of argon. Then was added (2S)-2-methylbutanal 152 (86 mg, 107 µL, 1 mmol) and AIBN (49 mg, 0.30 mmol) and the reaction mixture stirred at 40 °C for 72 h. The solvent was removed in vacuo and the crude residue purified by column chromatography (20%-90% CH₂Cl₂/petrol) to afford pentafluorophenyl 2-(1,4-dioxan-2-yl)ethane-1-sulfonate as a colourless oil (340 mg, 0.94 mmol, 94%).

$^1$H NMR (600 MHz, CDCl₃) δ 3.83-3.69 (m, 6H), 3.66-3.60 (m, 1H), 3.55 (ddd, $J = 16.0$, 10.0 and 6.0 Hz, 1H), 3.35 (dd, $J = 10.0$, 11.5 Hz, 1H), 2.15-2.03 (m, 2H); $^{13}$C NMR (125 MHz, CDCl₃) δ 72.6 (CH), 70.6 (CH₂), 66.7 (CH₂), 66.4 (CH₂), 49.0

$^2$ 19C expected, 13C observed.
(CH₂), 25.6 (CH₂); IR (thin film) 2960, 1381, 1183 cm⁻¹; LRMS (FAB) 385 (100, [M+Na⁺]); HRMS (FAB) calcd for C₁₂H₁₁F₅O₅SNa [M+Na]⁺ 385.0145, observed 385.0152.

**Experimental for Chapter 3**

**Typical procedure for the synthesis of thioethers – Method E**

To a stirring solution of pentafluorophenyl 3-oxohexane-1-sulfonate 107a (79 mg, 0.29 mmol) in CH₂Cl₂ (3 mL) was added thiol (0.32 mmol) and then DBU (129 mg, 127 μL, 0.58 mmol) and the reaction mixture stirred at 21 °C for the time specified (see below). The solvent was removed *in vacuo* and purified as described below to afford the desired thioether.

**1-(Hexylsulfanyl)hexan-3-one 163a**

Using Method E, the reaction was complete after 1 h. Purification by column chromatography (60% CH₂Cl₂/petrol-neat CH₂Cl₂) gave 1-(hexylsulfanyl)hexan-3-one as a colourless oil (61 mg, 0.28 mmol, 98%).

¹H NMR (500 MHz, CDCl₃) δ 2.71 (m, 2H), 2.67 (m, 2H), 2.49 (t, J = 7.5, 2H), 2.39 (t, J = 7.5 Hz, 2H), 1.62-1.55 (m, 4H), 1.38-1.23 (m, 6H), 0.90 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 209.8 (C), 45.1 (CH), 42.9 (CH₂), 32.6 (CH₂), 31.5 (CH₂), 29.6 (CH₂), 28.6 (CH₂), 25.9 (CH₂), 22.6 (CH₂), 17.3 (CH₂), 14.1 (CH₃), 13.8 (CH₃); IR (thin film) 2959, 2927, 1714 cm⁻¹; LRMS (CI) 217 (100, [M+H]⁺); HRMS (CI) calcd for C₁₂H₂₅OS [M+H]⁺ 217.1626, observed 217.1621.
1-(4-Methyl-benzylsulfanyl)-hexan-3-one 163b

Using Method E, the reaction was complete after 1 h. Purification by column chromatography (60% CH₂Cl₂/petrol to neat CH₂Cl₂) gave 1-(4-methyl-benzylsulfanyl)-hexan-3-one as a colourless oil (66 mg, 0.28 mmol, 97%).

\[ \text{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) } \delta 7.19 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 3.68 (s, 2H), 2.66-2.58 (m, 4H), 2.34 (t, J = 7.5 Hz, 2H), 2.32 (s, 3H), 1.59 (sextet, J = 7.5 Hz, 2H), 0.88 (t, J = 7.5 Hz, 3H); \text{\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) } \delta 209.6 (C), 136.8 (C), 135.2 (C), 129.3 (CH), 128.8 (CH), 45.0 (CH\textsubscript{2}), 42.5 (CH\textsubscript{2}), 36.5 (CH\textsubscript{2}), 25.3 (CH\textsubscript{2}), 21.1 (CH\textsubscript{3}), 17.3 (CH\textsubscript{2}), 13.8 (CH\textsubscript{3}); \text{IR (thin film) 2962, 2928, 2871, 1712, 1535, 1516 cm}^{-1}; \text{LRMS (CI) 237 (100, [M+H]}^+\text{); HRMS (CI) calcd for C}_{14}H_{21}OS [M+H]^+ 237.1313, observed 237.1318.\]

Typical procedure for the synthesis of sulfonamides – Method F

To a stirring solution of pentafluorophenyl 3-oxohexane-1-sulfonate 107a (79 mg, 0.29 mmol) in NMP (2.5 mL) was added drop wise a solution of amine (0.61 mmol) in NMP (1 mL) at 0 °C. After addition was complete, the reaction mixture was left to warm to 21 °C and stirred for 4 h. To work-up, the reaction mixture was diluted with Et\textsubscript{2}O (20 mL), washed with sat. LiCl (3 × 20 mL), sat. NaHCO\textsubscript{3} (3 × 20 mL), 2M HCl (3 × 20 mL), dried (MgSO\textsubscript{4}) and the solvent removed \textit{in vacuo} to afford the desired sulfonamide.

\[ \text{\textit{N-Hexyl-3-oxohexane-1-sulfonamide 170a}} \]

\[ \text{Using Method F, N-hexyl-3-oxohexane-1-sulfonamide was isolated as a white solid (64 mg, 0.25 mmol, 82%).} \]

\[ \text{m.p. 67-69 °C; \text{\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) } \delta 4.12 (br t, J = 6.0 Hz, 1H, NH), 3.34-3.31 (m, 2H), 3.12 (q, J = 7.0 Hz, 2H), 2.97-2.94 (m, 2H), 2.47 (t, J = 7.5 Hz, 2H),} \]

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1.63 (sextet, \( J = 7.5 \) Hz, 2H), 1.57 (quintet, \( J = 7.5 \) Hz, 2H), 1.38-1.24 (m, 6H), 0.94 (t, \( J = 7.5 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\( _3 \)) \( \delta \) 207.1 (C), 46.6 (CH\(_2\)), 44.8 (CH\(_2\)), 43.4 (CH\(_2\)), 36.5 (CH\(_2\)), 33.3 (CH\(_2\)), 30.2 (CH\(_2\)), 26.3 (CH\(_2\)), 22.5 (CH\(_2\)), 17.2 (CH\(_2\)), 14.0 (CH\(_3\)), 13.7 (CH\(_3\)); IR (solid) 3288, 2957, 2930, 2859, 1703, 1312, 1136 cm\(^{-1}\); LRMS (CI) 264 (45, [M+H]+), 102 (100); HRMS (CI) calcd for C\(_{12}\)H\(_{26}\)NO\(_3\)S [M+H]+ 264.1633, observed 264.1624.

**1-(Morpholin-4-ylsulfonyl)hexan-3-one 170b**

![Chemical Structure](image)

Using Method F, 1-(morpholin-4-ylsulfonyl)hexan-3-one was isolated as a yellow solid (23 mg, 0.09 mmol, 32%).

m.p. 45-48 °C; \(^1\)H NMR (600 MHz, CDCl\( _3 \)) \( \delta \) 3.78-3.75 (m, 4H), 3.27-3.25 (m, 4H), 3.21 (m, 2H), 2.96 (m, 2H), 2.48 (t, \( J = 7.0 \) Hz, 2H), 1.67 (sextet, \( J = 7.0 \) Hz, 2H), 0.93 (t, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\( _3 \)) \( \delta \) 206.8 (C), 66.5 (CH\(_2\)), 45.7 (CH\(_2\)), 44.8 (CH\(_2\)), 42.6 (CH\(_2\)), 35.5 (CH\(_2\)), 17.2 (CH\(_2\)), 13.7 (CH\(_3\)); IR (solid) 2964, 2926, 2860, 1716, 1344, 1157 cm\(^{-1}\); LRMS (CI) 250 (20, [M+H]+), 163 (35), 99 (100); HRMS (CI) calcd for C\(_{10}\)H\(_{20}\)NO\(_4\)S [M+H]+ 250.1113, observed 250.1107.

**N-tert-Butyl-3-oxohexane-1-sulfonamide 170c**

![Chemical Structure](image)

Using Method F, **N-tert**-butyl-3-oxohexane-1-sulfonamide was isolated as a colourless oil (27 mg, 0.11 mmol, 40%).

\(^1\)H NMR (600 MHz, CDCl\( _3 \)) \( \delta \) 4.18 (br s, NH, 1H), 3.37-3.33 (m, 2H), 2.96-2.92 (m, 2H), 2.46 (t, \( J = 7.0 \) Hz, 2H), 1.64 (sextet, \( J = 7.0 \) Hz, 2H), 1.41 (s, 9H), 0.93 (t, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\( _3 \)) \( \delta \) 207.2 (C), 54.9 (C), 50.4 (CH\(_2\)), 44.8 (CH\(_2\)), 36.8 (CH\(_2\)), 30.3 (CH\(_3\)), 17.2 (CH\(_2\)), 13.7 (CH\(_3\)); IR (thin film) 3288, 2966, 2940, 2875, 1716, 1316, 1135 cm\(^{-1}\); LRMS (CI) 236 (15, [M+H]+), 220 (25), 163 (100); HRMS (CI) calcd for C\(_{10}\)H\(_{22}\)NO\(_3\)S [M+H]+ 236.1320, observed 236.1325.
2-Hexyl-3-propyl-1,2-thiazolidine 1,1-dioxide 171

A solution of N-hexyl-3-oxohexane-1-sulfonamide 170a (50 mg, 0.19 mmol) in TFA (4 mL) was left to stir at 21 °C for 15 min. Then was added sodium cyanoborohydride (12 mg, 0.19 mmol) and the reaction mixture left to stir for 30 min. Then was added further sodium cyanoborohydride (24 mg, 0.38 mmol) and the reaction mixture left to stir for a further 20 min. The solvent was removed in vacuo, the crude residue diluted with EtOAc (50 mL), washed with sat. NaHCO₃ (3 × 100 mL) and 2M HCl (3 × 100 mL), dried (MgSO₄) and the solvent removed in vacuo. The crude residue was purified by column chromatography (50% Et₂O/petrol) to afford 2-hexyl-3-propyl-isothiazolidine 1,1-dioxide as a colourless oil (41 mg, 0.17 mmol, 87%).

¹H NMR (600 MHz, CDCl₃) δ 3.34-3.30 (m, 1H), 3.22 (ddd, J = 12.5, 8.0 and 4.5 Hz, 1H), 3.16 (ddd, J = 12.5, 8.0 and 7.0 Hz, 1H), 3.03-2.97 (m, 1H), 2.44-2.37 (m, 1H), 2.06-2.00 (m, 1H), 1.75-1.70 (m, 1H), 1.65-1.24 (m, 11H), 0.98 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 58.1 (CH), 46.5 (CH₂), 43.8 (CH₂), 36.0 (CH₂), 31.5 (CH₂), 28.6 (CH₂), 26.7 (CH₂), 25.0 (CH₂), 22.6 (CH₂), 17.8 (CH₂), 14.1 (CH₃), 14.1 (CH₃); IR (thin film) 2957, 2930, 2872, 1305, 1134 cm⁻¹; LRMS (CI) 248 (60, [M+H]+), 204 (100); HRMS (CI) calcd for C₁₂H₂₆NO₂S [M+H]+ 248.1684, observed 248.1686.

3-Propyl-4,5-dihydro-1,2-thiazole 1,1-dioxide 174

To a solution of pentafluorophenyl 3-oxohexane-1-sulfonate 107a (0.29 mmol) in CH₂Cl₂ (2 mL) was bubbled through NH₃ (g) for 45 min at 0 °C. Then the reaction mixture was diluted with CH₂Cl₂ (20 mL), washed with 2M HCl (3 × 20 mL) and sat. K₂CO₃ (3 × 20 mL), dried (MgSO₄) and the solvent removed in vacuo to afford 3-propyl-4,5-dihydro-isothiazole 1,1-dioxide as a white solid (31 mg, 0.19 mmol, 67%).
m.p. 68-70 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.28-2.24 (m, 2H), 3.20-3.16 (m, 2H), 2.54 (t, $J = 7.5$ Hz, 2H), 1.77 (sextet, $J = 7.5$ Hz, 2H), 1.02 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 184.9 (C), 44.0 (CH$_2$), 37.5 (CH$_2$), 36.8 (CH$_2$), 18.9 (CH$_2$), 13.7 (CH$_3$); IR (solid) 2966, 2929, 2872, 1617, 1326, 1144 cm$^{-1}$; LRMS (CI) 162 (100, [M+H]$^+$); HRMS (CI) calcd for C$_6$H$_{12}$NO$_2$S [M+H]$^+$ 162.0589, observed 162.0591.

5-Propyl-1,2-oxathiolane 2,2-dioxide 176

To a mixture of pentafluorophenyl 3-oxohexane-1-sulfonate 107a (100 mg, 0.29 mmol) and sodium borohydride (22 mg, 0.58 mmol) was added CH$_2$Cl$_2$ (4 mL) and MeOH (12 mL) and the reaction mixture left to stir for 30 min. Then was added further sodium borohydride (22 mg, 0.58 mmol) and the reaction mixture left to stir for a further 10 min. The solvents were removed in vacuo, the crude residue diluted with Et$_2$O (50 mL), washed with sat. NaHCO$_3$ (3 × 100 mL), dried (MgSO$_4$) and the solvent removed in vacuo to afford 5-propyl-1,2-oxathiolane 2,2-dioxide as a colourless oil (33 mg, 0.20 mmol, 71%).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 4.66 (ddt, $J = 12.0, 8.5$ and 5.0 Hz, 1H), 3.34 (dd, $J = 12.0, 9.0$ and 4.0 Hz, 1H), 3.27 (ddd, $J = 12.0, 9.5$ and 8.0 Hz, 1H), 2.64-2.57 (m, 1H), 2.34-2.37 (m, 1H), 1.89-1.84 (m, 1H), 1.71-1.65 (m, 1H), 1.57-1.42 (m, 2H), 0.98 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 82.6 (CH), 45.7 (CH$_2$), 37.2 (CH$_2$), 29.6 (CH$_2$), 18.5 (CH$_3$), 13.6 (CH$_3$); IR (thin film) 2963, 2877, 1340, 1157 cm$^{-1}$; LRMS (CI) 165 (100, [M+H]$^+$); HRMS (CI) calcd for C$_6$H$_{13}$O$_3$S [M+H]$^+$ 165.0585, observed 165.0587.
**Experimental for Chapter 4**

**Dimethyl maleate 177**

A solution of maleic acid (10 g, 86.2 mmol) and conc. H$_2$SO$_4$ (2 mL) in excess MeOH (200 mL) was heated under reflux for 5 h. The solvent was removed *in vacuo*, diluted with Et$_2$O (200 mL), washed with sat. NaHCO$_3$ (250 mL), dried (MgSO$_4$) and the solvent removed *in vacuo* to afford dimethyl maleate as a colourless oil (9.7 g, 67.4 mmol, 78%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.25 (s, 2H), 3.79 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 165.7 (C), 129.8 (CH), 52.3 (CH$_3$); IR (thin film) 3004, 2956, 1721, 1646 cm$^{-1}$; LRMS (CI) 145 (7, [M+H]$^+$), 113 (100); HRMS (CI) calcd for C$_6$H$_9$O$_4$ [M+H]$^+$ 145.0501, observed 145.0503.

**Dimethyl 2-butanoyloxirane-2,3-dicarboxylate 180a-b**

$n$-Butanal (361 mg, 451 µL, 5 mmol) was added to a solution of dimethyl maleate (144 mg, 1 mmol) in 1,4-dioxane (0.5 mL) and the reaction mixture stirred at 21 °C for 8 days. The solvent was removed *in vacuo* to give crude 5-hydroxy-5-propyl-1,2-dioxolane-3,4-dicarboxylate. Purification by column chromatography (10%-90% Et$_2$O/petrol) gave dimethyl 2-butanoyloxirane-2,3-dicarboxylate (12 mg, 0.05 mmol, 5%) as a 50:50 mixture of diastereoisomers 180a and 180b.

Data for 180a: $^1$H NMR (300 MHz, CDCl$_3$) δ 4.00 (s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.88-2.79 (m, 1H), 2.68-2.56 (m, 1H), 1.69-1.62 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 200.2 (C), 165.7 (C), 165.2 (C), 62.9 (C), 56.9 (CH), 53.7 (CH$_3$), 53.1 (CH$_3$), 42.3 (CH$_2$), 16.0 (CH$_2$), 13.5 (CH$_3$); IR (thin film) 2964, 2892, 1734, 1712 cm$^{-1}$; LRMS (CI) 231 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{10}$H$_{15}$O$_6$ [M+H]$^+$ 231.0790, observed 231.0801.
Data for **180b**: $^1$H NMR (300 MHz, CDCl$_3$) δ 3.84 (s, 3H), 3.83 (s, 1H), 3.76 (s, 3H), 2.64-2.53 (m, 1H), 2.43-2.32 (m, 1H), 1.67-1.57 (m, 2H), 0.92 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 200.1 (C), 165.5 (C), 165.0 (C), 62.6 (C), 56.4 (CH), 53.9 (CH$_3$), 53.5 (CH$_3$), 42.7 (CH$_2$), 15.8 (CH$_2$), 13.5 (CH$_3$); IR (thin film) 2964, 2892, 1734, 1712 cm$^{-1}$; LRMS (CI) 231 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{10}$H$_{15}$O$_6$ [M+H]$^+$ 231.0790, observed 231.0798.

**Diethyl maleate 77**

\[
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et}
\end{array}
\]

A solution of maleic acid (10 g, 86.2 mmol), conc. H$_2$SO$_4$ (2 mL) and excess EtOH (200 mL) in PhMe (200 mL) was heated under reflux for 3 days. The solvent was removed *in vacuo*, diluted with Et$_2$O (200 mL), washed with sat. NaHCO$_3$ (250 mL), dried (MgSO$_4$) and the solvent removed *in vacuo* to afford diethyl maleate as a colourless oil (13.8 g, 80.1 mmol, 93%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 6.25 (s, 2H), 4.26 (q, $J = 7.0$ Hz, 4H), 1.33 (t, $J = 7.0$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 165.3 (C), 129.9 (CH), 61.3 (CH$_2$), 14.1 (CH$_3$); IR (thin film) 2987, 1721, 1639 cm$^{-1}$; LRMS (CI) 173 (30, [M+H]$^+$), 127 (72), 99 (100); HRMS (CI) calcd for C$_8$H$_{13}$O$_4$ [M+H]$^+$ 173.0814, observed 173.0811.

**Typical procedure for the synthesis of ketone diesters – Method G**

Aldehyde (5 mmol) was added to a solution of alkene (1 mmol) in 1,4-dioxane (3 mL) and the reaction mixture stirred at 60 °C for the time specified (see below). The solvent was removed *in vacuo* and purified as described below to afford the desired ketone diester.
Diethyl 2-butanoylbutanedioate 78a

Using Method G, the reaction was complete after 4 days. Purification by column chromatography (10%-20% Et₂O/petrol) gave diethyl 2-butanoylbutanedioate as a colourless oil (165 mg, 0.68 mmol, 68%).

\[ ^1H \text{NMR (400 MHz, CDCl}_3\] \( \delta \) 4.21 (q, \( J = 7.0, 2H \)), 4.12 (q, \( J = 7.0 \text{ Hz}, 2H \)), 3.97 (dd, \( J = 8.5 \text{ and } 6.0 \text{ Hz}, 1H \)), 2.98 (dd, \( J = 17.5 \text{ and } 8.5 \text{ Hz}, 1H \)), 2.83 (dd, \( J = 17.5 \text{ and } 6.0 \text{ Hz}, 1H \)), 2.70 (dt, \( J = 17.5 \text{ and } 7.0 \text{ Hz}, 1H \)), 2.61 (dt, \( J = 17.5 \text{ and } 7.0 \text{ Hz}, 1H \)), 1.65 (sextet, \( J = 7.0 \text{ Hz}, 2H \)), 1.27 (t, \( J = 7.0 \text{ Hz}, 3H \)), 1.24 (t, \( J = 7.0 \text{ Hz}, 3H \)), 0.93 (t, \( J = 7.0 \text{ Hz}, 3H \)); \( ^{13}C \text{NMR (150 MHz, CDCl}_3\] \( \delta \) 204.0 (C), 171.4 (C), 168.5 (C), 61.8 (CH₂), 61.0 (CH₂), 54.0 (CH), 44.6 (CH₂), 32.4 (CH₂), 16.8 (CH₂), 14.1 (CH₃), 14.0 (CH₃), 13.5 (CH₃); IR (thin film) 2967, 2881, 1736, 1719 cm⁻¹; LRMS (Cl) 245 (60, [M+H]⁺), 199 (100); HRMS (Cl) calcd for C₁₂H₂₁O₅ [M+H]⁺ 245.1389, observed 245.1382.

Dimethyl 2-butanoylbutanedioate 178a

Using Method G, the reaction was complete after 3 days. Purification by column chromatography (10%-30% Et₂O/petrol) gave dimethyl 2-butanoylbutanedioate as a colourless oil (151 mg, 0.70 mmol, 70%).

\[ ^1H \text{NMR (500 MHz, CDCl}_3\] \( \delta \) 3.95 (dd, \( J = 8.0 \text{ and } 6.5 \text{ Hz}, 1H \)), 3.71 (s, 3H), 3.64 (s, 3H), 2.94 (dd, \( J = 17.5 \text{ and } 8.0 \text{ Hz}, 1H \)), 2.80 (dd, \( J = 17.5 \text{ and } 6.5 \text{ Hz}, 1H \)), 2.65 (dt, \( J = 17.5 \text{ and } 7.5 \text{ Hz}, 1H \)), 2.61 (dt, \( J = 17.5 \text{ and } 7.5 \text{ Hz}, 1H \)), 1.59 (sextet, \( J = 7.5 \text{ Hz}, 2H \)), 0.91 (t, \( J = 7.5 \text{ Hz}, 3H \)); \( ^{13}C \text{NMR (75 MHz, CDCl}_3\] \( \delta \) 203.8 (C), 171.8 (C), 168.9 (C), 53.8 (CH), 52.7 (CH₃), 52.0 (CH₂), 44.6 (CH₂), 32.1 (CH₂), 16.8 (CH₂), 13.4 (CH₃); IR (thin film) 2959, 2880, 1734, 1717 cm⁻¹; LRMS (Cl) 217 (100, [M+H]⁺); HRMS (Cl) calcd for C₁₀H₁₇O₅ [M+H]⁺ 217.1076, observed 217.1072.
Dimethyl 2-(2-methylpropanoyl)butanedioate 178b and dimethyl 2-(propan-2-yl)butanedioate 185b

Using Method G, the reaction was complete after 9 days. Purification by column chromatography (5%-30% Et<sub>2</sub>O/petrol) gave dimethyl 2-(2-methylpropanoyl)butanedioate as a colourless oil and dimethyl 2-(propan-2-yl)butanedioate as a colourless oil.

Data for 178b: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 4.20 (dd, J = 8.0 and 6.5 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 2.99-2.94 (m, 2H), 2.65 (dd, J = 17.5 and 6.5 Hz, 1H), 1.18 (d, J = 7.0 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 207.8 (C), 171.8 (C), 169.1 (C), 52.8 (CH), 52.1 (CH<sub>3</sub>), 52.0 (CH<sub>3</sub>), 40.7 (CH<sub>2</sub>), 32.3 (CH), 18.6 (CH<sub>3</sub>), 17.8 (CH<sub>3</sub>); IR (thin film) 2949, 2886, 1736, 1714 cm<sup>-1</sup>; LRMS (CI) 217 (15, [M+H]<sup>+</sup>), 86 (100); HRMS (CI) calcd for C<sub>10</sub>H<sub>17</sub>O<sub>5</sub> [M+H]<sup>+</sup> 217.1076, observed 217.1066.

Data for 185b: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 3.72 (s, 3H), 3.69 (s, 3H), 2.78-2.72 (m, 2H), 2.47-2.41 (m, 1H), 1.98-2.02 (m, 1H), 0.96-0.92 (m, 6H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 175.0 (C), 173.0 (C), 51.8 (CH<sub>3</sub>), 51.7 (CH<sub>3</sub>), 47.4 (CH), 32.9 (CH<sub>2</sub>), 30.1 (CH), 20.1 (CH<sub>3</sub>), 19.6 (CH<sub>3</sub>); IR (thin film) 2952, 2930, 2865, 1732 cm<sup>-1</sup>; LRMS (CI) 189 (10, [M+H]<sup>+</sup>), 157 (100); HRMS (CI) calcd for C<sub>9</sub>H<sub>17</sub>O<sub>4</sub> [M+H]<sup>+</sup> 189.1049, observed 189.1055.

Dimethyl 2-(3-methylbutanoyl)butanedioate 178c

Using Method G, the reaction was complete after 3 days. Purification by column chromatography (10%-30% Et<sub>2</sub>O/petrol) gave dimethyl 2-(3-methylbutanoyl)butanedioate as a colourless oil (131 mg, 0.57 mmol, 57%).
\[^1\text{H} \text{NMR (600 MHz, CDCl}_3\text{)} \delta 3.98 \text{ (dd, } J = 8.0 \text{ and } 6.5 \text{ Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.01 \text{ (dd, } J = 17.0 \text{ and } 8.0 \text{ Hz, 1H), 2.85 (dd, } J = 17.0 \text{ and } 6.5 \text{ Hz, 1H), 2.58 (dd, } J = 17.0 \text{ and } 7.5 \text{ Hz, 1H), 2.53 (dd, } J = 17.0 \text{ and } 6.5 \text{ Hz, 1H), 2.24-2.17 \text{ (m, 1H), 0.94 (d, } J = 7.0 \text{ Hz, 3H), 0.92 (d, } J = 7.0 \text{ Hz, 3H); } ^{13}\text{C NMR (150 MHz, CDCl}_3\text{)} \delta 203.4 \text{ (C), 171.8 (C), 168.9 (C), 54.2 (CH), 52.7 (CH}_3\text{), 52.1 (CH}_3\text{), 51.5 (CH}_2\text{), 32.1 (CH}_2\text{), 24.1 (CH), 22.5 (CH}_3\text{), 22.2 (CH}_2\text{); IR (thin film) 2957, 1738, 1719 cm}^{-1}; \text{ LRMS (EI) 230 (15, [M]^+)}, 199 (100); \text{ HRMS (EI) calcd for C}_{11}H_{18}O_5 \text{ [M]^+} 230.1149, \text{ observed 230.1143.}

\textbf{Dimethyl 2-hexanoylbutanedioate 178d}

\[
\begin{align*}
\text{Using Method G, the reaction was complete after 3 days. Purification by column chromatography (10\%-30\% Et}_2\text{O/petrol) gave dimethyl 2-hexanoylbutanedioate as a colourless oil (185 mg, 0.76 mmol, 76%).}
\end{align*}
\]

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{)} \delta 4.00 \text{ (dd, } J = 8.0 \text{ and } 6.5 \text{ Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.00 \text{ (dd, } J = 17.5 \text{ and } 8.0 \text{ Hz, 1H), 2.84 (dd, } J = 17.5 \text{ and } 6.5 \text{ Hz, 1H), 2.71 (dt, } J = 17.5 \text{ and } 7.5 \text{ Hz, 1H), 2.61 (dt, } J = 17.5 \text{ and } 7.5 \text{ Hz, 1H), 1.59 (sextet, } J = 7.5 \text{ Hz, 2H), 1.36-1.22 \text{ (m, 4H) 0.91 (t, } J = 7.5 \text{ Hz, 3H); } ^{13}\text{C NMR (150 MHz, CDCl}_3\text{)} \delta 204.0 \text{ (C), 171.9 (C), 169.0 (C), 53.8 (CH}_3\text{), 52.8 (CH}_3\text{), 52.1 (CH), 42.8 (CH}_2\text{), 32.2 (CH}_2\text{), 31.1 (CH}_2\text{), 23.1 (CH)_2\text{), 22.4 (CH}_2\text{), 13.9 (CH}_3\text{); IR (thin film) 2959, 2934, 1738, 1720 cm}^{-1}; \text{ LRMS (CI) 245 (15, [M+H]^+)}, 213 (100); \text{ HRMS (CI) calcd for C}_{12}H_{21}O_5 \text{ [M+H]^+} 245.1389, \text{ observed 245.1382.}

\textbf{Dimethyl 2-(cyclohexylcarbonyl)butanedioate 178e}

\[
\begin{align*}
\text{Using Method G, the reaction was complete after 10 days. Purification by column chromatography (10\%-30\% Et}_2\text{O/petrol) gave dimethyl 2-(cyclohexylcarbonyl)butanedioate as a colourless oil.}
\end{align*}
\]
H NMR (600 MHz, CDCl$_3$) δ 3.95 (dd, $J = 8.0$ and 6.5 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.96 (dd, $J = 17.5$ and 8.0 Hz, 1H), 2.84 (dd, $J = 17.5$ and 6.5 Hz, 1H), 2.68 (tt, $J = 11.0$ and 3.5 Hz, 1H), 2.03-1.97 (m, 1H), 1.84-1.77 (m, 3H), 1.72-1.67 (m, 1H), 1.47-1.40 (m, 1H), 1.35-1.19 (m, 4H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 207.0 (C), 171.8 (C), 169.1 (C), 52.8 (CH), 52.1 (CH$_3$), 50.6 (CH), 32.3 (CH$_2$), 28.9 (CH$_2$), 27.9 (CH$_2$), 25.8 (CH$_2$), 25.7 (CH$_2$), 25.3 (CH$_2$); IR (thin film) 2934, 2855, 1740, 1711 cm$^{-1}$; LRMS (ES$^-$) 255 (70, [M-H]), 208 (100); HRMS (ES$^-$) calcd for C$_{13}$H$_{19}$O$_5$ [M-H] 255.1232, observed 255.1234.

Dimethyl 2-(2-ethylhexanoyl)butanedioate 178f and dimethyl 2-(heptan-3-yl)butanedioate 185f

Using Method G, the reaction was complete after 9 days. Purification by column chromatography (5%-30% Et$_2$O/petrol) gave dimethyl 2-(2-ethylhexanoyl)butanedioate as a mixture of diastereoisomers and dimethyl 2-(heptan-3-yl)butanedioate as a mixture of diastereoisomers.

Data for 178f: $^1$H NMR (400 MHz, CDCl$_3$) δ 4.14 (m, 1H), 3.78-3.68 (m, 6H), 2.95-2.73 (m, 3H), 1.74-1.61 (m, 2H), 1.55-1.20 (m, 6H), 0.96-0.80 (m, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$)$^8$ δ 206.7 (C), 206.6 (C), 171.8 (C), 171.8 (C), 168.9 (C), 168.8 (C), 54.4 (CH), 54.3 (CH), 52.7 (CH), 52.6 (CH$_3$), 52.5 (CH), 52.1 (CH$_3$), 31.9 (CH$_2$), 31.9 (CH$_2$), 31.0 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 24.6 (CH$_2$), 23.5 (CH$_2$), 22.8 (CH$_2$), 13.9 (CH$_3$), 11.7 (CH$_3$), 11.4 (CH$_3$); IR (thin film) 2957, 2932, 2855, 1740, 1717 cm$^{-1}$; LRMS (ES$^-$) 271 (100, [M-H]); HRMS (ES$^-$) calcd for C$_{14}$H$_{23}$O$_5$ [M-H] 271.1545, observed 271.1558.

Data for 185f: $^1$H NMR (600 MHz, CDCl$_3$) δ 3.70 (s, 3H), 3.69 (s, 3H), 3.05-3.00 (m, 1H), 2.78-2.72 (m, 1H), 2.36-2.32 (m, 1H), 1.67-1.58 (m, 1H), 1.39-1.19 (m, 8H), 0.94-0.87 (m, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$)$^{**}$ δ 175.4 (C), 173.2 (C), 51.8 (CH$_3$), 51.7 (CH$_3$), 43.1 (CH), 43.1 (CH), 41.5 (CH), 41.4 (CH), 31.9 (CH$_2$), 31.8

$^1$ 28C expected, 24C observed.

$^{**}$ 26C expected, 21C observed.
(CH₂), 30.6 (CH₂), 30.3 (CH₂), 29.5 (CH₂), 29.3 (CH₂), 24.1 (CH₂), 23.7 (CH₂), 22.8 (CH₂), 14.1 (CH₃), 14.0 (CH₃), 11.8 (CH₃), 11.7 (CH₃); IR (thin film) 2957, 2932, 2875, 1734 cm⁻¹; LRMS (CI) 245 (10, [M+H]⁺), 213 (100); HRMS (CI) calcd for C₁₃H₂₅O₄ [M+H]⁺ 245.1753, observed 245.1748.

**Dimethyl 2-decanoylbutanedioate 178g**

Using Method G, the reaction was complete after 9 days. Purification by column chromatography (10%-30% Et₂O/petrol) gave dimethyl 2-decanoylbutanedioate as a colourless oil (180 mg, 0.60 mmol, 60%).

¹H NMR (500 MHz, CDCl₃) δ 4.00 (dd, J = 8.5 and 6.5 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 2.99 (dd, J = 17.5 and 8.0 Hz, 1H), 2.85 (dd, J = 17.5 and 6.5 Hz, 1H), 2.65 (dt, J = 17.5 and 7.5 Hz, 1H), 2.61 (dt, J = 17.5 and 7.5 Hz, 1H), 1.59 (sextet, J = 7.5 Hz, 2H), 1.33-1.23 (m, 12H), 0.89 (t, J = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 204.0 (C), 171.9 (C), 167.0 (C), 53.8 (CH), 52.7 (CH₃), 52.0 (CH₃), 42.8 (CH₂), 32.2 (CH₂), 31.9 (CH₂), 29.4 (CH₂), 29.4 (CH₂), 29.3 (CH₂), 29.0 (CH₂), 23.4 (CH₂), 22.7 (CH₂), 14.1 (CH₃); IR (thin film) 2959, 2926, 2856, 1742, 1720 cm⁻¹; LRMS (ES⁻) 299 (100, [M-H]⁻); HRMS (ES⁻) calcd for C₁₆H₂₇O₅ [M-H]⁻ 299.1858, observed 299.1860.

**Typical procedure for the synthesis of ketone diesters – Method H**

Aldehyde (5 mmol) was added to a solution of alkene (1 mmol) in 1,4-dioxane (1 mL) and the reaction mixture stirred at 60 °C for the time specified (see below). The solvent was removed *in vacuo* and purified as described below to afford the desired ketone diester.
Diethyl (3-oxohexan-2-yl)propanedioate 187a and diethyl 5-hydroxy-4-methyl-5-propyl-1,2-dioxolane-3,3-dicarboxylate 188

Using Method H, the reaction was complete after 3 days. Purification by column chromatography (10%-50% Et<sub>2</sub>O/petrol) gave diethyl (3-oxohexan-2-yl)propanedioate as a colourless oil (181 mg, 0.70 mmol, 70%) and diethyl 5-hydroxy-4-methyl-5-propyl-1,2-dioxolane-3,3-dicarboxylate as a colourless oil (2 mg, 0.01 mmol, 1%).

Data for 187a: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.26-4.11 (m, 4H), 3.77 (d, <i>J</i> = 10.5 Hz, 1H), 3.27 (dq, <i>J</i> = 10.5 and 7.0 Hz, 1H), 2.58 (t, <i>J</i> = 7.0 Hz, 2H), 1.65 (sextet, <i>J</i> = 7.0 Hz, 2H), 1.29 (t, <i>J</i> = 7.0 Hz, 3H), 1.24 (t, <i>J</i> = 7.0 Hz, 3H), 1.12 (d, <i>J</i> = 7.0 Hz, 3H), 0.92 (t, <i>J</i> = 7.0 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 211.7 (C), 168.7 (C), 168.6 (C), 62.0 (CH<sub>2</sub>), 61.6 (CH<sub>2</sub>), 54.5 (CH), 45.0 (CH), 43.4 (CH<sub>2</sub>), 16.9 (CH<sub>2</sub>), 14.7 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>), 14.0 (CH<sub>3</sub>), 13.8 (CH<sub>3</sub>); IR (thin film) 2967, 2933, 1759, 1733, 1715 cm<sup>-1</sup>; LRMS (CI) 259 (15, [M+H]<sup>+</sup>), 213 (100); HRMS (CI) calcd for C<sub>13</sub>H<sub>23</sub>O<sub>5</sub>[M+H]<sup>+</sup> 259.1545, observed 259.1548.

Data for 188: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.69 (br s, 1H, OH), 4.36-4.25 (m, 4H), 3.44 (q, <i>J</i> = 7.0 Hz, 1H), 1.81 (td, <i>J</i> = 11.0 and 4.5 Hz, 1H), 1.68-1.42 (m, 3H), 1.31 (t, <i>J</i> = 7.0 Hz, 6H), 1.17 (d, <i>J</i> = 7.0 Hz, 3H), 0.92 (t, <i>J</i> = 7.0 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 167.9 (C), 167.5 (C), 107.5 (C), 89.1 (C), 63.4 (CH<sub>2</sub>), 62.7 (CH<sub>2</sub>), 56.1 (CH), 35.5 (CH<sub>2</sub>), 16.8 (CH<sub>2</sub>), 14.4 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>), 14.0 (CH<sub>3</sub>), 10.6 (CH<sub>3</sub>); IR (thin film) 3466, 2967, 2938, 1732 cm<sup>-1</sup>; LRMS (ES) 313 (40, [M+Na]<sup>+</sup>), 278 (100); HRMS (ES) calcd for C<sub>13</sub>H<sub>22</sub>O<sub>7</sub>Na [M+Na]<sup>+</sup> 313.1263, observed 313.1247.

Diethyl (5-methyl-3-oxohexan-2-yl)propanedioate 187c

Using Method H, the reaction was complete after 3 days. Purification by column chromatography (5%-20% Et<sub>2</sub>O/petrol) gave diethyl (5-methyl-3-oxohexan-2-yl)propanedioate as a colourless oil (163 mg, 0.60 mmol, 60%).
$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 4.24-4.12 (m, 4H), 3.74 (d, $J = 10.5$ Hz, 1H), 3.22 (dq, $J = 10.5$ and 7.5 Hz, 1H), 2.50 (dd, $J = 17.0$ and 6.0 Hz, 1H), 2.44 (dd, $J = 17.0$ and 7.5 Hz, 1H), 2.17 (nonet, $J = 7.0$ Hz, 1H), 1.27 (t, $J = 7.0$ Hz, 3H), 1.22 (t, $J = 7.0$ Hz, 3H), 1.10 (d, $J = 7.0$ Hz, 3H), 0.95 (d, $J = 7.0$ Hz, 3H), 0.90 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 211.1 (C), 168.6 (C), 168.5 (C), 61.6 (CH$_2$), 61.5 (CH$_2$), 54.3 (CH), 50.3 (CH$_2$), 45.3 (CH), 23.8 (CH), 22.6 (CH$_3$), 22.4 (CH$_3$), 14.5 (CH$_3$), 14.1 (CH$_3$), 14.0 (CH$_3$); IR (thin film) 2960, 2870, 1746, 1733, 1713 cm$^{-1}$; LRMS (EI) 272 (10, [M]$^+$), 227 (85), 189 (100); HRMS (EI) calcd for C$_{14}$H$_{24}$O$_5$ [M]$^+$ 272.1618, observed 272.1621.

**Diethyl (3-oxooctan-2-yl)propanedioate 187d**

![Diethyl (3-oxooctan-2-yl)propanedioate 187d](image)

Using Method H, the reaction was complete after 3 days. Purification by column chromatography (5%-20% Et$_2$O/petrol) gave diethyl (3-oxooctan-2-yl)propanedioate as a colourless oil (206 mg, 0.72 mmol, 72%).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 4.25-4.10 (m, 4H), 3.74 (d, $J = 10.5$ Hz, 1H), 3.27 (dq, $J = 10.5$ and 7.5 Hz, 1H), 2.57 (t, $J = 7.5$ Hz, 2H), 1.65-1.56 (m, 2H), 1.35-1.22 (m, 10H), 1.11 (t, $J = 7.5$ Hz, 3H), 0.89 (d, $J = 7.5$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 211.8 (C), 168.7 (C), 168.5 (C), 61.6 (CH$_2$), 61.5 (CH$_2$), 54.4 (CH), 44.9 (CH), 41.4 (CH$_2$), 31.3 (CH$_2$), 23.1 (CH$_2$), 22.5 (CH$_2$), 14.7 (CH$_3$), 14.1 (CH$_3$), 14.0 (CH$_3$), 14.0 (CH$_3$); IR (thin film) 2963, 2935, 1749, 1733, 1717 cm$^{-1}$; LRMS (CI) 287 (12, [M+H]$^+$), 241 (85), 230 (70), 187 (100); HRMS (CI) calcd for C$_{15}$H$_{27}$O$_5$ [M+H]$^+$ 287.1853, observed 287.1859.

**Diethyl (1-cyclohexyl-1-oxopropan-2-yl)propanedioate 187e and diethyl (1-cyclohexylethyl)propanedioate 189e**

![Diethyl (1-cyclohexyl-1-oxopropan-2-yl)propanedioate 187e and diethyl (1-cyclohexylethyl)propanedioate 189e](image)

Using Method H, the reaction was complete after 10 days. Purification by column chromatography (5%-20% Et$_2$O/petrol) gave diethyl (1-cyclohexyl-1-oxopropan-2-
yl)propanedioate as a colourless oil (221 mg, 0.74 mmol, 74%) and diethyl (1-cyclohexylethyl)propanedioate as a colourless oil (14 mg, 0.05 mmol, 5%).

Data for 187e: $^1$H NMR (600 MHz, CDCl$_3$) δ 4.22 (qd, $J = 7.0$ and 2.0 Hz, 2H), 4.17-4.10 (m, 2H), 3.75 (d, $J = 10.5$ Hz, 1H), 3.41 (dq, $J = 10.5$ and 7.5 Hz, 1H), 2.62 (tt, $J = 11.5$ and 3.0 Hz, 1H), 2.04 (m, 1H), 1.83-1.78 (m, 3H), 1.69-1.64 (m, 1H), 1.46-1.38 (m, 1H), 1.34-1.17 (m, 10H), 0.92 (d, $J = 7.5$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 214.6 (C), 168.8 (C), 168.4 (C), 61.6 (CH$_2$), 61.5 (CH$_2$), 54.5 (CH), 49.6 (CH), 43.7 (CH), 29.1 (CH$_2$), 28.3 (CH$_2$), 25.9 (CH$_2$), 25.8 (CH$_2$), 25.6 (CH$_2$), 14.9 (CH$_3$), 14.1 (CH$_3$), 14.0 (CH$_3$); IR (thin film) 2981, 2932, 2856, 1749, 1732, 1709 cm$^{-1}$; LRMS (ES) 321 (100, [M+Na]$^+$); HRMS (ES) calcd for C$_{16}$H$_{26}$O$_5$Na [M+Na]$^+$ 321.1666, observed 321.1678.

Data for 189e: $^1$H NMR (600 MHz, CDCl$_3$) δ 4.25-4.17 (m, 4H), 3.41 (d, $J = 9.0$ Hz, 1H), 2.22-2.16 (m, 1H), 1.76-1.73 (m, 2H), 1.67-1.65 (m, 2H), 1.62-1.56 (m, 1H), 1.31-1.07 (m, 5H), 1.29 (t, $J = 7.0$ Hz, 6H), 0.96 (td, $J = 12.5$ and 3.5 Hz, 1H), 0.92 (d, $J = 7.5$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 169.3 (C), 169.1 (C), 61.2 (CH$_2$), 61.1 (CH$_2$), 55.8 (CH), 40.2 (CH), 38.6 (CH), 31.5 (CH$_2$), 27.4 (CH$_2$), 26.7 (CH$_2$), 26.5 (CH$_2$), 26.5 (CH$_2$), 14.1 (CH$_3$), 14.1 (CH$_3$), 12.9 (CH$_3$); IR (thin film) 2981, 2927, 2854, 1754, 1733 cm$^{-1}$; LRMS (ES) 293 (100, [M+Na]$^+$), 271 (40); HRMS (ES) calcd for C$_{15}$H$_{26}$O$_4$Na [M+Na]$^+$ 293.1741, observed 293.1729.

**Diethyl (4-ethyl-3-oxooctan-2-yl)propanedioate 187f and diethyl (3-ethylheptan-2-yl)propanedioate 189f**

![Chemical Structure](image)

Using Method H, the reaction was complete after 9 days. Purification by column chromatography (5%-20% Et$_2$O/petrol) gave diethyl (4-ethyl-3-oxooctan-2-yl)propanedioate (163 mg, 0.52 mmol, 52%) as a 50:50 mixture of diastereoisomers and diethyl (3-ethylheptan-2-yl)propanedioate (57 mg, 0.20 mmol, 20%) as a 50:50 mixture of diastereoisomers.

Data for 187f: $^1$H NMR (600 MHz, CDCl$_3$) δ 4.26-4.19 (m, 2H), 4.18-4.23 (m, 2H), 3.75-3.71 (m, 1H), 3.41-3.24 (m, 1H), 2.68-2.62 (m, 1H), 1.82-1.63 (m, 2H), 1.51-
1.44 (m, 1H), 1.42-1.10 (m, 5H), 1.29 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.16-1.13 (m, 3H), 0.95-0.82 (m, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$) $^{\ddagger\ddagger}$ δ 214.1 (C), 168.8 (C), 168.4 (C), 168.3 (C), 61.6 (CH$_2$), 61.5 (CH$_2$), 61.5 (CH$_2$), 54.1 (CH), 54.0 (CH), 51.5 (CH), 51.2 (CH), 45.0 (CH), 44.9 (CH), 31.0 (CH$_2$), 29.9 (CH$_2$), 29.2 (CH$_2$), 22.8 (CH$_2$), 24.6 (CH$_2$), 23.0 (CH$_2$), 22.9 (CH$_2$), 22.8 (CH$_2$), 14.5 (CH$_3$), 14.4 (CH$_3$), 14.1 (CH$_3$), 14.0 (CH$_3$), 14.0 (CH$_3$), 12.1 (CH$_3$), 11.4 (CH$_3$); IR (thin film) 2962, 2934, 2875, 1753, 1734, 1710 cm$^{-1}$; LRMS (ES) 337 (100, [M+Na]$^+$), 269 (30); HRMS (ES) calcd for C$_{17}$H$_{30}$O$_5$Na [M+Na]$^+$ 337.1991, observed 337.2011.

Data for 189f: $^1$H NMR (600 MHz, CDCl$_3$) δ 4.23-4.16 (m, 4H), 3.37 (d, J = 8.5 Hz, 1H), 2.49-2.41 (m, 1H), 1.50-1.43 (m, 1H), 1.41-1.10 (m, 13H), 1.05-0.98 (m, 1H), 0.93-0.86 (m, 6H), 0.84-0.81 (m, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $^{\ddagger\ddagger}$ δ 169.1 (C), 169.1 (C), 169.0 (C), 169.0 (C), 61.2 (CH$_2$), 56.6 (CH), 56.6 (CH), 41.5 (CH), 41.5 (CH), 35.1 (CH), 34.6 (CH), 30.8 (CH$_2$), 30.3 (CH$_2$), 29.6 (CH$_2$), 28.8 (CH$_2$), 24.3 (CH$_2$), 23.1 (CH$_2$), 23.0 (CH$_2$), 21.9 (CH$_2$), 14.1 (CH$_3$), 14.1 (CH$_3$), 12.5 (CH$_3$), 12.0 (CH$_3$), 11.7 (CH$_3$), 11.6 (CH$_3$); IR (thin film) 2961, 2932, 2874, 1757, 1734 cm$^{-1}$; LRMS (ES) 309 (90, [M+Na]$^+$), 304 (100); HRMS (ES) calcd for C$_{16}$H$_{30}$O$_4$Na [M+Na]$^+$ 309.2042, observed 309.2058.

**Diethyl (3-oxododecan-2-yl)propanedioate 187g**

Using Method H, the reaction was complete after 9 days. Purification by column chromatography (5%-20% Et$_2$O/petrol) gave diethyl (3-oxododecan-2-yl)propanedioate as a colourless oil (246 mg, 0.72 mmol, 72%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.21 (d, J = 7.0 Hz, 2H), 4.17-4.11 (m, 2H), 3.75 (d, J = 10.5 Hz, 1H), 3.22 (dq, J = 10.5 and 7.5 Hz, 1H), 2.57 (t, J = 7.5 Hz, 2H), 1.61-1.54 (m, 2H), 1.32-1.21 (m, 18H), 1.10 (d, J = 7.5 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 211.8 (C), 168.7 (C), 168.6 (C), 61.7 (CH$_2$), 61.6

$^{\ddagger\ddagger}$ 34C expected, 29C observed.

$^{\ddagger\ddagger}$ 32C expected, 25C observed.
Dimethyl (3-oxohexan-2-yl)propanedioate 193a

Using Method H, the reaction was complete after 3 days. Purification by column chromatography (10%-20% Et<sub>2</sub>O/petrol) gave dimethyl (3-oxohexan-2-yl)propanedioate as a colourless oil (161 mg, 0.70 mmol, 70%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.79 (d, J = 10.5 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.27 (dq, J = 10.5 and 7.0 Hz, 1H), 2.56 (t, J = 7.0 Hz, 2H), 1.62 (sextet, J = 7.0 Hz, 2H), 1.09 (d, J = 7.0 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 211.6 (C), 169.1 (C), 168.9 (C), 54.1 (CH), 52.8 (CH<sub>3</sub>), 52.7 (CH<sub>3</sub>), 45.2 (CH), 43.3 (CH<sub>2</sub>), 17.0 (CH<sub>2</sub>), 14.7 (CH<sub>3</sub>), 13.7 (CH<sub>3</sub>); IR (thin film) 2960, 1752, 1737, 1715 cm<sup>-1</sup>; LRMS (CI) 231 (25, [M+H]<sup>+</sup>), 199 (100); HRMS (CI) calcd for C<sub>11</sub>H<sub>19</sub>O<sub>5</sub> [M+H]<sup>+</sup> 231.1232, observed 231.1236.

Dimethyl (1-cyclohexyl-1-oxopropan-2-yl)propanedioate 193e and dimethyl (1-cyclohexylethyl)propanedioate 194e

Purification by column chromatography (5%-20% Et<sub>2</sub>O/petrol) gave dimethyl (1-cyclohexyl-1-oxopropan-2-yl)propanedioate as a colourless oil (192 mg, 0.71 mmol, 71%) and dimethyl (1-cyclohexylethyl)propanedioate as a colourless oil (15 mg, 0.06 mmol, 6%).

Data for 193e: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 3.80 (d, J = 10.5 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.44 (dq, J = 10.5 and 7.0 Hz, 1H), 2.62 (tt, J = 11.5 and 3.0 Hz, 1H), 2.07-2.03 (m, 1H), 1.86-1.77 (m, 3H), 1.71-1.67 (m, 1H), 1.48-1.41 (m, 1H), 1.34-
1.20 (m, 4H), 1.11 (d, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 214.5 (C), 169.2 (C), 168.8 (C), 54.1 (CH), 52.7 (CH\(_3\)), 52.7 (CH\(_3\)), 49.5 (CH), 43.8 (CH), 29.1 (CH\(_2\)), 28.2 (CH\(_2\)), 25.9 (CH\(_2\)), 25.8 (CH\(_2\)), 25.5 (CH\(_2\)), 15.0 (CH\(_3\)); IR (thin film) 2932, 2855, 1756, 1738, 1709 cm\(^{-1}\); LRMS (ES) 293 (100, [M+Na]\(^+\)); HRMS (ES) calcd for C\(_{14}\)H\(_{22}\)O\(_5\)Na [M+Na]\(^+\) 293.1365, observed 293.1379.

Data for 194e: \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 3.75 (s, 3H), 3.74 (s, 3H), 3.74 (d, \( J = 9.0 \) Hz, 1H), 2.21-2.17 (m, 1H), 1.77-1.72 (m, 2H), 1.67-1.57 (m, 3H), 1.29-1.07 (m, 5H), 0.96 (td, \( J = 12.5 \) and 3.0, 1H), 0.91 (d, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \( \delta \) 169.7 (C), 169.5 (C), 55.5 (CH), 52.4 (CH\(_3\)), 52.3 (CH\(_3\)), 40.3 (CH), 38.7 (CH), 31.5 (CH\(_2\)), 27.4 (CH\(_2\)), 26.7 (CH\(_2\)), 26.5 (CH\(_2\)), 26.5 (CH\(_2\)), 12.9 (CH\(_3\)); IR (thin film) 2927, 2853, 1756, 1737 cm\(^{-1}\); LRMS (ES) 243 (20, [M+H]\(^+\)), 180 (100); HRMS (ES) calcd for C\(_{13}\)H\(_{23}\)O\(_4\) [M+H]\(^+\) 243.1596, observed 243.1601.

**Dimethyl (3-oxododecan-2-yl)propanedioate 193g**

![Dimethyl (3-oxododecan-2-yl)propanedioate](image)

Purification by column chromatography (5%-20% Et\(_2\)O/petrol) gave dimethyl (3-oxododecan-2-yl)propanedioate as a colourless oil (210 mg, 0.67 mmol, 67%).

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 3.81 (d, \( J = 10.5 \) Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.29 (dq, \( J = 10.5, 7.0 \) Hz, 1H), 2.59 (td, \( J = 7.0, 2.0 \) Hz, 2H), 1.62 (sextet, \( J = 7.0 \) Hz, 2H), 1.32-1.26 (m, 12H), 1.11 (d, \( J = 7.0 \) Hz, 3H), 0.93 (t, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\))\(^\dagger\) \( \delta \) 211.9 (C), 169.1 (C), 168.9 (C), 54.0 (CH), 52.8 (CH\(_3\)), 52.7 (CH\(_3\)), 45.1 (CH), 41.4 (CH\(_2\)), 31.9 (CH\(_2\)), 29.5 (CH\(_2\)), 29.3 (CH\(_2\)), 29.2 (CH\(_2\)), 23.4 (CH\(_2\)), 22.7 (CH\(_2\)), 14.8 (CH\(_3\)), 14.2 (CH\(_3\)); IR (thin film) 2927, 2853, 1756, 1738, 1716 cm\(^{-1}\); LRMS (ES') 313 (100, [M-H]); HRMS (ES') calcd for C\(_{17}\)H\(_{29}\)O\(_5\) [M-H] 313.2015, observed 313.2018.

\(^\dagger\) 17C expected, 16C observed.
Typical procedure for the synthesis of ketone alkoxy diesters – Method I

Aldehyde (5 mmol) was added to a solution of alkene (1 mmol) in 1,4-dioxane (0.5 mL) and the reaction mixture stirred at 60 °C for the time specified (see below). The solvent was removed in vacuo and purified as described below to afford the desired ketone alkoxy diester.

**Diethyl (1-ethoxy-2-oxopentyl)propanedioate 196a**

Using Method I, the reaction was complete after 7 days. Purification by column chromatography (5%-20% Et₂O/petrol) gave diethyl (1-ethoxy-2-oxopentyl)propanedioate as a colourless oil.

**¹H NMR (500 MHz, CDCl₃) δ 4.29 (d, J = 7.5 Hz, 1H), 4.25-4.17 (m, 4H), 3.91 (d, J = 7.5 Hz, 1H), 3.69-3.60 (m, 2H), 2.51 (dt, J = 7.0 Hz, 1H), 1.65 (sextet, J = 7.0 Hz, 2H), 1.28-1.24 (m, 6H), 1.19 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 209.5 (C), 167.0 (C), 167.0 (C), 82.4 (CH), 67.8 (CH₂), 61.8 (CH₂), 61.7 (CH₂), 54.5 (CH), 41.1 (CH₂), 16.5 (CH₂), 15.4 (CH₃), 14.1 (CH₃), 14.0 (CH₃), 13.8 (CH₃); IR (thin film) 2978, 2934, 2873, 1744, 1724 cm⁻¹; LRMS (CI) 289 (100, [M+H]+); HRMS (CI) calcd for C₁₄H₂₂O₆ [M+H]+ 289.1651, observed 289.1648.

**Diethyl (1-ethoxy-4-methyl-2-oxopentyl)propanedioate 196c**

Using Method I, the reaction was complete after 5 days. Purification by column chromatography (5%-20% Et₂O/petrol) gave diethyl (1-ethoxy-4-methyl-2-oxopentyl)propanedioate as a colourless oil (257 mg, 0.85 mmol, 85%).

**¹H NMR (600 MHz, CDCl₃) δ 4.31 (d, J = 7.5 Hz, 1H), 4.26-4.17 (m, 4H), 3.94 (d, J = 7.5 Hz, 1H), 3.72-3.62 (m, 2H), 2.52 (dt, J = 7.0 Hz, 1H), 2.10 (dt, J = 7.0 Hz, 1H), 1.99 (m, 2H), 1.65 (m, 6H), 1.19 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 209.6 (C), 167.0 (C), 167.0 (C), 82.4 (CH), 67.8 (CH₂), 61.8 (CH₂), 61.7 (CH₂), 54.5 (CH), 41.1 (CH₂), 16.5 (CH₂), 15.4 (CH₃), 14.1 (CH₃), 14.0 (CH₃), 13.8 (CH₃); IR (thin film) 2978, 2934, 2873, 1744, 1724 cm⁻¹; LRMS (CI) 289 (100, [M+H]+); HRMS (CI) calcd for C₁₄H₂₄O₆ [M+H]+ 291.1772, observed 291.1772.
17.5 and 6.5 Hz, 1H), 2.19 (nonet, J = 6.5 Hz, 1H), 1.30 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H), 0.95 (d, J = 6.5 Hz, 6H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 208.7 (C), 167.0 (C), 167.0 (C), 82.4 (CH), 67.8 (CH\(_2\)), 61.8 (CH\(_2\)), 61.7 (CH\(_2\)), 54.1 (CH), 47.9 (CH\(_2\)), 23.6 (CH), 22.7 (CH\(_3\)), 22.5 (CH\(_3\)), 15.4 (CH\(_3\)), 14.0 (CH\(_3\)), 13.9 (CH\(_3\)); IR (thin film) 2978, 2960, 2874, 1744, 1732 cm\(^{-1}\); LRMS (CI) 303 (5, [M+H]\(^+\)), 285 (10), 211 (100); HRMS (CI) calcd for C\(_{15}\)H\(_{22}\)O\(_6\) [M+H]\(^+\) 303.1808, observed 303.1805.

**Diethyl (1-ethoxy-4-methyl-2-oxopentyl)propanedioate 196d**

Using Method I, the reaction was complete after 3 days. Purification by column chromatography (5%-20% Et\(_2\)O/petrol) gave diethyl (1-ethoxy-4-methyl-2-oxopentyl)propanedioate as a colourless oil (275 mg, 0.87 mmol, 87%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.32 (d, J = 7.5 Hz, 1H), 4.25-4.17 (m, 4H), 3.93 (d, J = 7.5 Hz, 1H), 3.69-3.61 (m, 2H), 2.74 (dt, J = 18.0 and 7.5 Hz, 1H), 2.60 (dt, J = 18.0 and 7.5 Hz, 1H), 1.60 (quintet, J = 7.5 Hz, 2H), 1.34-1.24 (m, 10H), 1.21 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 209.7 (C), 167.0 (C), 167.0 (C), 82.3 (CH), 67.7 (CH\(_2\)), 61.7 (CH\(_2\)), 61.7 (CH\(_2\)), 54.5 (CH), 39.1 (CH\(_2\)), 31.3 (CH\(_2\)), 22.7 (CH\(_2\)), 22.5 (CH\(_2\)), 15.4 (CH\(_3\)), 14.0 (CH\(_3\)), 14.0 (CH\(_3\)), 14.0 (CH\(_3\)); IR (thin film) 2978, 2959, 2932, 1750, 1736 cm\(^{-1}\); LRMS (ES) 339 (100, [M+Na]\(^+\)); HRMS (ES) calcd for C\(_{16}\)H\(_{26}\)O\(_8\)Na [M+Na]\(^+\) 339.1784, observed 339.1769.

**Diethyl (2-cyclohexyl-1-ethoxy-2-oxoethyl)propanedioate 196e**

Using Method I, the reaction was complete after 3 days. Purification by column chromatography (5%-20% Et\(_2\)O/petrol) gave diethyl (2-cyclohexyl-1-ethoxy-2-oxoethyl)propanedioate as a colourless oil.
$^1$H NMR (600 MHz, CDCl$_3$) δ 4.52 (d, $J = 8.0$ Hz, 1H), 4.27-4.15 (m, 4H), 3.98 (d, $J = 8.0$ Hz, 1H), 1.94-1.89 (m, 1H), 1.85-1.79 (m, 3H), 1.72-1.67 (m, 1H), 1.44-1.19 (m, 14H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 211.4 (C), 167.2 (C), 167.1 (C), 81.0 (CH), 67.3 (CH$_2$), 61.7 (CH$_2$), 53.7 (CH), 46.8 (CH), 29.0 (CH$_2$), 27.8 (CH$_2$), 25.9 (CH$_2$), 25.8 (CH$_2$), 25.5 (CH$_2$), 15.5 (CH$_3$), 14.1 (CH$_3$), 14.0 (CH$_3$); IR (thin film) 2979, 2933, 2856, 1747, 1734, 1716 cm$^{-1}$; LRMS (ES) 351 (100, [M+Na]$^+$); HRMS (ES) calcd for C$_{17}$H$_{28}$O$_6$Na [M+Na]$^+$ 351.1784, observed 351.1773.

Diethyl (1-ethoxy-4-methyl-2-oxononyl)propanedioate 196g

Using Method I, the reaction was complete after 5 days. Purification by column chromatography (5%-20% Et$_2$O/petrol) gave diethyl (1-ethoxy-4-methyl-2-oxononyl)propanedioate as a colourless oil (331 mg, 0.89 mmol, 89%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.35 (d, $J = 7.0$ Hz, 1H), 4.25-4.15 (m, 4H), 3.91 (d, $J = 7.0$ Hz, 1H), 3.69-3.60 (m, 2H), 2.68 (dt, $J = 18.0$ and 7.0 Hz, 1H), 2.51 (dt, $J = 18.0$ and 7.0 Hz, 1H), 1.60-1.55 (m, 2H), 1.28-1.18 (m, 21H), 0.87 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 209.7 (C), 167.0 (C), 167.0 (C), 82.4 (CH), 67.8 (CH$_2$), 61.8 (CH$_2$), 61.8 (CH$_2$), 54.5 (CH), 39.3 (CH$_2$), 31.9 (CH$_2$), 29.5 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 29.3 (CH$_2$), 23.1 (CH$_2$), 22.7 (CH$_2$), 15.4 (CH$_3$), 14.2 (CH$_3$), 14.1 (CH$_3$), 14.0 (CH$_3$); IR (thin film) 2926, 2856, 1747, 1734, 1716 cm$^{-1}$; LRMS (ES) 395 (100, [M+Na]$^+$); HRMS (ES) calcd for C$_{20}$H$_{36}$O$_6$Na [M+Na]$^+$ 395.2410, observed 395.2423.

Ethyl 3-methyl-4-oxoheptanoate 80

$n$-Butanal (721 mg, 901 μL, 10 mmol) was added to a solution of ethyl crotonate 79 (114 mg, 1 mmol) in 1,4-dioxane (3 mL) and the reaction mixture stirred at 60 °C for 96 h. The solvent was removed in vacuo and purification by column chromatography
(5%-20% Et₂O/petrol) gave ethyl 3-methyl-4-oxoheptanoate as a colourless oil (95 mg, 0.51 mmol, 51%).

\(^1\)H NMR (500 MHz, CDCl₃) δ 4.10 (q, J = 7.0 Hz, 2H), 2.99 (ddq, J = 17.0 and 5.5 Hz, 1H), 2.76 (dd, J = 17.0 and 9.0 Hz, 1H), 2.50 (m, 2H), 2.27 (dd, J = 17.0 and 5.5 Hz, 1H), 1.61 (sextet, J = 7.5 Hz, 2H), 1.23 (t, J = 7.0 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 213.0 (C), 172.5 (C), 60.6 (CH₂), 43.2 (CH₂), 42.1 (CH), 37.1 (CH₂), 17.1 (CH₂), 16.8 (CH₃), 14.2 (CH₃), 13.8 (CH₃); IR (thin film) 2965, 2938, 2879, 1735, 1715 cm⁻¹; LRMS (CI) 187 (40, [M+H]+), 141 (100); HRMS (CI) calcd for C₁₀H₁₉O₃ [M+H]⁺ 187.1334, observed 187.1337.

**Experimental for Chapter 5**

**Dimethyl (2-oxoethyl)phosphonate 200 and dimethyl [2-(1,4-dioxan-2-yl)ethyl]phosphonate 201**

\[\text{H} \quad \text{O} \quad \text{P} \quad \text{OMe} \quad \text{OMe} \]
\[\text{O} \quad \text{OMe} \quad \text{P} \quad \text{OMe} \]

\(n\)-Butanal 18a (361 mg, 451 μL, 5 mmol) was added to a solution of dimethyl vinyl phosphonate 198 (136 mg, 1 mmol) in 1,4-dioxane (1 mL) and the reaction mixture stirred at 60 °C for 5 days. The solvent was removed \textit{in vacuo} and purification by column chromatography (neat CH₂Cl₂-5% MeOH/CH₂Cl₂) gave dimethyl (2-oxoethyl)phosphonate as a colourless oil (2 mg, 0.02 mmol, 2%) and dimethyl [2-(1,4-dioxan-2-yl)ethyl]phosphonate as a colourless oil (2 mg, 0.01 mmol, 1%).

Data for 200: \(^1\)H NMR (500 MHz, CDCl₃) δ 9.68 (td, J = 3.0 Hz, J₈₋₆ = 1.5 Hz, 1H), 3.81 (d, J₈₋₆ = 11.5 Hz, 6H), 3.10 (dd, J₈₋₆ = 22.0 and J = 3.0 Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 192.6 (d, J₆₋₇ = 6.5 Hz, CH), 53.1 (d, J₆₋₇ = 6.5 Hz, CH₃), 42.1 (d, J₆₋₇ = 128.0 Hz, CH₂); IR (thin film) 2954, 2859, 1720, 1240 cm⁻¹; LRMS (CI) 153 (100, [M+H]⁺); HRMS (CI) calcd for C₄H₁₀O₄P [M+H]⁺ 153.0317, observed 153.0318.
Data for 201: $^1$H NMR (600 MHz, CDCl$_3$) δ 3.80-3.69 (m, 10H), 3.62-3.53 (m, 2H), 3.27 (dd, $J = 11.5$ and $10.0$ Hz, 1H), 2.04-1.95 (m, 1H), 1.82-1.62 (m, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 74.7 (d, $J_{C-P} = 16.0$ Hz, CH), 70.9 (CH$_2$), 66.7 (CH$_2$), 66.5 (CH$_2$), 52.3 (d, $J_{C-P} = 6.5$ Hz, CH$_3$), 52.3 (d, $J_{C-P} = 6.5$ Hz, CH$_3$), 24.4 (d, $J_{C-P} = 4.5$ Hz, CH$_2$), 20.2 (d, $J_{C-P} = 142.0$ Hz, CH$_2$); IR (thin film) 2957, 2853, 1244 cm$^{-1}$; LRMS (FAB) 247 (100, [M+Na]$^+$); HRMS (FAB) calcd for C$_8$H$_{17}$O$_3$PNa [M+Na]$^+$ 247.0711, observed 247.0714.

**Typical procedure for the synthesis of ketone phosphonates – Method J**

Aldehyde (5 mmol) was added to a solution of alkene (1 mmol) in 1,4-dioxane (1 mL) and the reaction mixture stirred at 60 °C for the time specified (see below) unless otherwise stated. The solvent was removed \textit{in vacuo} and purified as described below to afford the desired ketone phosphonate.

**Dimethyl (3-oxohexyl)phosphonate 199a**

![Chemical Structure](attachment:image.png)

Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH$_2$Cl$_2$-2.5% MeOH/CH$_2$Cl$_2$) gave dimethyl (3-oxohexyl)phosphonate as a colourless oil (146 mg, 0.70 mmol, 70%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 3.70 (d, $J_{H-P} = 11.0$ Hz, 6H), 2.67 (dt, $J_{H-P} = 15.5$ and $J = 7.5$ Hz, 2H), 2.38 (t, $J = 7.5$ Hz, 2H), 2.00 (dt, $J_{H-P} = 18.0$ and $J = 7.5$ Hz, 2H), 1.59 (sextet, $J = 7.5$ Hz, 2H), 0.89 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 208.1 (d, $J_{C-P} = 14.0$ Hz, C), 52.5 (d, $J_{C-P} = 6.5$ Hz, CH$_3$), 44.6 (CH$_2$), 35.3 (d, $J_{C-P} = 4.0$ Hz, CH$_2$), 18.3 (d, $J_{C-P} = 143.0$ Hz, CH$_2$), 17.3 (CH$_2$), 13.7 (CH$_3$); IR (thin film) 2960, 1715, 1245 cm$^{-1}$; LRMS (CI) 209 (100, [M+H]$^+$); HRMS (CI) calcd for C$_8$H$_{18}$O$_4$P [M+H]$^+$ 209.0943, observed 209.0947.
Dimethyl (5-methyl-3-oxohexyl)phosphonate 199c

Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH$_2$Cl$_2$-2.5% MeOH/CH$_2$Cl$_2$) gave (dimethyl (5-methyl-3-oxohexyl)phosphonate as a colourless oil (144 mg, 0.65 mmol, 65%).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 3.74 (d, $J_{H-P}$ = 11.0 Hz, 6H), 2.69 (dt, $J_{H-P}$ = 15.5 and $J$ = 7.5 Hz, 2H), 2.31 (d, $J$ = 7.0 Hz, 2H), 2.15 (nonet, $J$ = 7.0 Hz, 1H), 2.03 (dt, $J_{H-P}$ = 18.0 and $J$ = 7.5 Hz, 2H), 0.89 (d, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 208.3 (d, $J_{C-P}$ = 14.0 Hz, C), 52.4 (d, $J_{C-P}$ = 6.5 Hz, CH$_3$), 51.6 (CH$_2$), 35.7 (d, $J_{C-P}$ = 4.0 Hz, CH$_2$), 24.7 (CH), 22.5 (CH$_3$), 18.2 (d, $J_{C-P}$ = 144.0 Hz, CH$_2$); IR (thin film) 2957, 2873, 1714, 1245 cm$^{-1}$; LRMS (ES) 245 (100, [M+Na]$^+$); HRMS (ES) calcd for C$_9$H$_{19}$O$_4$PNa [M+Na]$^+$ 245.0919, observed 245.0915.

Dimethyl (3-oxooctyl)phosphonate 199d

Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH$_2$Cl$_2$-2.5% MeOH/CH$_2$Cl$_2$) gave dimethyl (3-oxooctyl)phosphonate as a colourless oil (170 mg, 0.72 mmol, 72%).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 3.74 (d, $J_{H-P}$ = 11.0 Hz, 6H), 2.72 (dt, $J_{H-P}$ = 15.5 and $J$ = 7.5 Hz, 2H), 2.43 (t, $J$ = 7.5 Hz, 2H), 2.00 (dt, $J_{H-P}$ = 18.0 and $J$ = 7.5 Hz, 2H), 1.59 (quintet, $J$ = 7.5 Hz, 2H), 1.35-1.24 (m, 4H), 0.89 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 208.3 (d, $J_{C-P}$ = 14.0 Hz, C), 52.4 (d, $J_{C-P}$ = 6.5 Hz, CH$_3$), 42.6 (CH$_2$), 35.2 (d, $J_{C-P}$ = 4.0 Hz, CH$_2$), 31.4 (CH$_2$), 23.5 (CH$_2$), 22.4 (CH$_2$), 18.2 (d, $J_{C-P}$ = 143.0 Hz, CH$_2$), 13.9 (CH$_3$); IR (thin film) 2956, 2934, 2856, 1717, 1243 cm$^{-1}$; LRMS (FAB) 259 (100, [M+Na]$^+$); HRMS (FAB) calcd for C$_{10}$H$_{21}$O$_4$PNa [M+Na]$^+$ 259.1076, observed 259.1070.
Dimethyl (3-cyclohexyl-3-oxopropyl)phosphonate 199e

Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH₂Cl₂-2.5% MeOH/CH₂Cl₂) gave dimethyl (3-cyclohexyl-3-oxopropyl)phosphonate as a colourless oil (149 mg, 0.60 mmol, 60%).

¹H NMR (400 MHz, CDCl₃) δ 3.74 (d, J_H-P = 11.0 Hz, 6H), 2.75 (dt, J_H-P = 15.5 and J = 7.5 Hz, 2H), 2.36 (tt, J = 11.0 and 3.0 Hz, 1H), 2.00 (dt, J_H-P = 18.0 and J = 7.5 Hz, 2H), 1.87-1.18 (m, 10H); ¹³C NMR (150 MHz, CDCl₃) δ 211.1 (d, J_C-P = 14.0 Hz, C), 52.4 (d, J_C-P = 6.5 Hz, CH₃), 50.7 (CH), 33.2 (d, J_C-P = 4.0 Hz, CH₂), 28.5 (CH₂), 25.8 (CH₂), 25.6 (CH₂), 18.2 (d, J_C-P = 143.0 Hz, CH₂); IR (thin film) 2930, 2854, 1709, 1243 cm⁻¹; LRMS (EI) 248 (100, [M]⁺); HRMS (EI) calcd for C₁₁H₂₁O₄P [M]⁺ 248.1172, observed 248.1172.

Dimethyl (3-oxobutyl)phosphonate 199h

Using Method J, but with 10 equivalents of acetaldehyde, the reaction was complete after 24 h. Purification by column chromatography (neat CH₂Cl₂-2.5% MeOH/CH₂Cl₂) gave dimethyl (3-oxobutyl)phosphonate as a colourless oil (122 mg, 0.68 mmol, 68%).

¹H NMR (600 MHz, CDCl₃) δ 3.74 (d, J_H-P = 11.0 Hz, 6H), 2.76 (dt, J_H-P = 15.5 and J = 7.5 Hz, 2H), 2.18 (s, 3H), 2.02 (dt, J_H-P = 18.0 and J = 7.5 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 205.7 (d, J_C-P = 14.0 Hz, C), 52.5 (d, J_C-P = 6.5 Hz, CH₃), 36.2 (d, J_C-P = 4.0 Hz, CH₂), 29.7 (CH₃), 18.2 (d, J_C-P = 143.0 Hz, CH₂); IR (thin film) 2958, 1717, 1239 cm⁻¹; LRMS (EI) 180 (5, [M]⁺), 110 (100); HRMS (EI) calcd for C₆H₁₃O₄P [M]⁺ 180.0546, observed 180.0548.
**Dimethyl [6-(5,5-dimethyl-1,3-dioxan-2-yl)-3-oxohexyl]phosphonate 199i**

Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH$_2$Cl$_2$-2.5% MeOH/CH$_2$Cl$_2$) gave dimethyl [6-(5,5-dimethyl-1,3-dioxan-2-yl)-3-oxohexyl]phosphonate as a colourless oil (228 mg, 0.71 mmol, 71%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.40 (t, $J = 5.0$ Hz, 1H), 3.73 (d, $J_{H-P} = 11.0$ Hz, 6H), 3.57 (d, $J = 10.0$ Hz, 2H), 3.40 (d, $J = 11.0$ Hz, 2H), 2.70 (dt, $J_{H-P} = 15.5$ and $J = 7.5$ Hz, 2H), 2.47 (t, $J = 7.0$ Hz, 2H), 2.02 (dt, $J_{H-P} = 18.0$ and $J = 7.5$ Hz, 2H), 1.78-1.60 (m, 4H), 1.17 (s, 3H), 0.71 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.7 (d, $J_{C-P} = 14.0$ Hz, C), 101.9 (CH), 77.2 (CH$_2$), 52.4 (d, $J_{C-P} = 6.0$ Hz, CH$_3$), 42.3 (CH$_2$), 35.2 (d, $J_{C-P} = 4.0$ Hz, CH$_2$), 34.1 (CH$_2$), 30.1 (C), 23.1 (CH$_3$), 21.9 (CH$_3$), 18.4 (CH$_2$), 18.3 (d, $J_{C-P} = 144.0$ Hz, CH$_2$); IR (thin film) 2955, 2850, 1717, 1244 cm$^{-1}$; LRMS (EI) 321 (15, [M-H]$^-$), 219 (65), 115 (100); HRMS (EI) calcd for C$_{14}$H$_{26}$O$_8$P [M-H]$^-$ 321.1461, observed 321.1465.

**Dimethyl (9-hydroxy-5,9-dimethyl-3-oxodecyl)phosphonate 199j**

Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH$_2$Cl$_2$-7.5% MeOH/CH$_2$Cl$_2$) gave dimethyl (9-hydroxy-5,9-dimethyl-3-oxodecyl)phosphonate as a colourless oil (228 mg, 0.74 mmol, 74%).

$^1$H NMR (600 MHz, CDCl$_3$) δ 3.74 (d, $J_{H-P} = 11.0$ Hz, 3H), 3.74 (d, $J_{H-P} = 11.0$ Hz, 3H), 2.75-2.65 (m, 2H), 2.43 (dd, $J = 16.0$ and 6.0 Hz, 1H), 2.26 (dd, $J = 16.0$ and 8.0 Hz, 1H), 2.03 (dt, $J_{H-P} = 18.0$ and $J = 8.0$ Hz, 2H), 1.48-1.14 (m, 14H), 0.91 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 208.0 (d, $J_{C-P} = 14.0$ Hz, C), 70.9 (C), 52.5 (d, $J_{C-P} = 6.5$ Hz, CH$_3$), 52.4 (d, $J_{C-P} = 6.5$ Hz, CH$_3$), 50.0 (CH$_2$), 43.8 (CH$_2$), 37.3 (CH$_2$), 35.8 (d, $J_{C-P} = 4.0$ Hz, CH$_2$), 29.4 (CH$_3$), 29.3 (CH$_3$), 29.2 (CH), 21.6
(CH₃), 19.9 (CH₃), 18.1 (d, J_C-P = 143.0 Hz, CH₂); IR (thin film) 3409, 2960, 2928, 2848, 1715, 1238 cm⁻¹; LRMS (FAB) 331 (100, [M+Na]⁺); HRMS (FAB) calcd for C₁₄H₂₀O₅PNa [M+Na]⁺ 331.1650, observed 331.1653.

**Dimethyl [7-(3,3-dimethyloxiran-2-yl)-5-methyl-3-oxoheptyl]phosphonate 199k**

Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH₂Cl₂-3% MeOH/CH₂Cl₂) gave dimethyl [7-(3,3-dimethyloxiran-2-yl)-5-methyl-3-oxoheptyl]phosphonate as a 50:50 mixture of diastereoisomers as a colourless oil.

¹H NMR (600 MHz, CDCl₃) δ 3.71 (d, J_H-P = 11.0 Hz, 6H), 2.71-2.64 (m, 3H), 2.44-2.38 (m, 1H), 2.28-2.23 (m, 1H), 2.06-1.98 (m, 3H), 1.56-1.21 (m, 10H), 0.88 (d, J = 7.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 207.7 (d, J_C-P = 14.0 Hz, C), 207.7 (d, J_C-P = 14.0 Hz, C), 64.4 (CH), 58.5 (C), 58.4 (C), 52.6 (d, J_C-P = 6.5 Hz, CH₃), 50.0 (CH₂), 49.9 (CH₂), 36.0 (CH₂), 35.9 (CH₂), 33.5 (CH₂), 29.2 (CH), 29.1 (CH), 26.6 (CH₂), 26.5 (CH₂), 25.0 (CH₃), 19.8 (CH₃), 19.8 (CH₃), 18.8 (CH₃), 18.7 (CH₃), 18.2 (d, J_C-P = 143.0 Hz, CH₃); IR (thin film) 2958, 2927, 1716, 1248 cm⁻¹; LRMS (CI) 307 (100, [M+H]⁺); HRMS (CI) calcd for C₁₄H₂₈O₅P [M+H]⁺ 307.1674, observed 307.1683.

**Dimethyl (3-oxo-5-phenylpentyl)phosphonate 199l**

Using Method J, the reaction was complete after 72 h. Purification by column chromatography (neat CH₂Cl₂-2.5% MeOH/CH₂Cl₂) gave dimethyl (3-oxo-5-phenylpentyl)phosphonate as a colourless oil.

*** 28C expected, 21C observed.
\[ ^1 \text{H NMR (500 MHz, CDCl}_3 \] \delta 7.29-7.25 (m, 2H), 7.21-7.16 (m, 3H), 3.71 (d, \( J_{\text{H-P}} = 11.0 \text{ Hz}, \) 6H), 2.91 (t, \( J = 7.5 \text{ Hz}, \) 2H), 2.76 (t, \( J = 7.5 \text{ Hz}, \) 2H), 2.68 (dt, \( J_{\text{H-P}} = 15.5 \) and \( J = 7.5 \text{ Hz}, \) 2H), 2.01 (dt, \( J_{\text{H-P}} = 18.0 \) and \( J = 7.5 \text{ Hz}, \) 2H); \[ ^{13} \text{C NMR (125 MHz, CDCl}_3 \] \delta 207.1 (d, \( J_{\text{C-P}} = 14.0 \text{ Hz}, \) C), 140.7 (C), 128.6 (CH), 128.4 (CH), 126.3 (CH), 52.5 (d, \( J_{\text{C-P}} = 6.5 \text{ Hz}, \) CH\(_3\)), 44.1 (CH\(_2\)), 35.8 (d, \( J_{\text{C-P}} = 4.0 \text{ Hz}, \) CH\(_2\)), 29.8 (CH\(_2\)), 18.3 (d, \( J_{\text{C-P}} = 143.0 \text{ Hz}, \) CH\(_2\)); IR (thin film) 2955, 2926, 1717, 1243 cm\(^{-1}\); LRMS (ES) 271 (100, [M+H]\(^+\)); HRMS (ES) calcd for C\(_{13}\)H\(_{20}\)O\(_4\)P [M+H]\(^+\) 271.1099, observed 271.1103.

**Dimethyl (3-cyclopropyl-3-oxopropyl)phosphonate 199m**

![Diagram of dimethyl (3-cyclopropyl-3-oxopropyl)phosphonate 199m]

Using Method J, the reaction was complete after 60 h. Purification by column chromatography (neat CH\(_2\)Cl\(_2\)-2.5% MeOH/CH\(_2\)Cl\(_2\)) gave dimethyl (3-cyclopropyl-3-oxopropyl)phosphonate as a colourless oil (117 mg, 0.57 mmol, 57%).

\[ ^1 \text{H NMR (600 MHz, CDCl}_3 \] \delta 3.75 (d, \( J_{\text{H-P}} = 11.0 \text{ Hz}, \) 6H), 2.91-2.87 (m, 2H), 2.08-2.02 (m, 2H), 1.95-1.92 (m, 1H), 1.06-1.03 (m, 2H), 0.94-0.90 (m, 2H); \[ ^{13} \text{C NMR (150 MHz, CDCl}_3 \] \delta 208.0 (d, \( J_{\text{C-P}} = 14.0 \text{ Hz}, \) C), 52.5 (d, \( J_{\text{C-P}} = 6.5 \text{ Hz}, \) CH\(_3\)), 35.8 (d, \( J_{\text{C-P}} = 4.0 \text{ Hz}, \) CH\(_2\)), 20.4 (CH), 18.3 (d, \( J_{\text{C-P}} = 143.0 \text{ Hz}, \) CH\(_2\)), 11.1 (CH\(_2\)); IR (thin film) 2962, 1699, 1238 cm\(^{-1}\); LRMS (FAB) 229 (100, [M+Na]\(^+\)); HRMS (FAB) calcd for C\(_8\)H\(_{15}\)O\(_4\)PNa [M+Na]\(^+\) 229.0606, observed 229.0601.

**Dimethyl (5,9-dimethyl-3-oxodecyl)phosphonate 199p**

![Diagram of dimethyl (5,9-dimethyl-3-oxodecyl)phosphonate 199p]

Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH\(_2\)Cl\(_2\)-4% MeOH/CH\(_2\)Cl\(_2\)) gave dimethyl (5,9-dimethyl-3-oxodecyl)phosphonate as a colourless oil (198 mg, 0.68 mmol, 68%).

\[ ^1 \text{H NMR (600 MHz, CDCl}_3 \] \delta 3.72 (d, \( J_{\text{H-P}} = 11.0 \text{ Hz}, \) 6H), 2.74-2.64 (m, 2H), 2.40 (dd, \( J = 16.0 \) and 5.5 Hz, 1H), 2.22 (dd, \( J = 16.0 \) and 8.0 Hz, 1H), 2.05-1.96 (m, 3H), 1.49 nonet, \( J = 6.5 \text{ Hz}, \) 1H), 1.32-1.08 (m, 6H), 0.87 (d, \( J = 6.5 \text{ Hz}, \) 3H), 0.84 (d, \( J =
6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 208.2 (d, J$_{C-P}$ = 14.0 Hz, C), 52.5 (d, J$_{C-P}$ = 6.5 Hz, CH$_3$), 50.3 (CH$_2$), 39.1 (CH$_2$), 37.2 (CH$_2$), 35.9 (d, J$_{C-P}$ = 4.0 Hz, CH$_2$), 29.5 (CH), 28.0 (CH), 24.8 (CH$_2$), 22.8 (CH$_3$), 22.7 (CH$_3$), 19.9 (CH$_3$), 18.3 (d, J$_{C-P}$ = 143.0 Hz, CH$_2$); IR (thin film) 2955, 2928, 1716 cm$^{-1}$; LRMS (Cl) 293 (100, [M+H]$^+$); HRMS (Cl) calcd for C$_{14}$H$_{30}$O$_4$P [M+H]$^+$ 293.1882, observed 293.1884.

**Dimethyl (3,3-dimethylbutyl)phosphonate 204**

![Dimethyl (3,3-dimethylbutyl)phosphonate](image)

Using Method J, but at 100 °C, the reaction was complete after 24 h. Purification by column chromatography (neat CH$_2$Cl$_2$-2.5% MeOH/CH$_2$Cl$_2$) gave dimethyl (3,3-dimethylbutyl)phosphonate as a colourless oil (132 mg, 0.68 mmol, 68%).

$^1$H NMR (600 MHz, CDCl$_3$) δ 3.75 (d, J$_{H-P}$ = 11.0 Hz, 6H), 1.74-1.67 (m, 2H), 1.50-1.46 (m, 2H), 0.89 (s, 9H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 52.4 (d, J$_{C-P}$ = 6.5 Hz, CH$_3$), 35.7 (d, J$_{C-P}$ = 4.0 Hz, CH$_2$), 30.4 (d, J$_{C-P}$ = 18.0 Hz, C), 28.7 (CH$_3$), 20.1 (d, J$_{C-P}$ = 140.0 Hz, CH$_2$); IR (thin film) 2955, 2868, 1245 cm$^{-1}$; LRMS (Cl) 195 (100, [M+H]$^+$); HRMS (Cl) calcd for C$_8$H$_{20}$O$_3$P [M+H]$^+$ 195.1150, observed 195.1153.

**Diethyl (3-oxohexyl)phosphonate 206**

![Diethyl (3-oxohexyl)phosphonate](image)

Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH$_2$Cl$_2$-2.5% MeOH/CH$_2$Cl$_2$) gave diethyl (3-oxohexyl)phosphonate as a colourless oil (146 mg, 0.70 mmol, 70%).

$^1$H NMR (600 MHz, CDCl$_3$) δ 4.12-4.03 (m, 4H), 2.68 (d, J$_{H-P}$ = 11.5 and J = 7.5 Hz, 2H), 2.41 (t, J = 7.5 Hz, 2H), 2.00 (m, 2H), 1.61 (sextet, J = 7.5 Hz, 2H), 1.30 (t, J = 7.0 Hz, 6H), 0.90 (t, J = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 208.4 (d, J$_{C-P}$ = 14.0 Hz, C), 61.8 (d, J$_{C-P}$ = 6.5 Hz, CH$_2$), 44.6 (CH$_2$), 35.5 (d, J$_{C-P}$ = 4.0 Hz, CH$_2$), 19.4 (d, J$_{C-P}$ = 144.0 Hz, CH$_2$), 17.4 (CH$_2$), 16.5 (d, J$_{C-P}$ = 6.0 Hz, CH$_3$), 13.8 (CH$_3$);
IR (thin film) 2967, 1716, 1240 cm\(^{-1}\); LRMS (EI) 236 (15, [M]\(^+\)), 166 (100); HRMS (EI) calcd for C\(_{10}\)H\(_{21}\)O\(_4\)P [M]\(^+\) 236.1172, observed 236.1165.

**Diethyl (E)-prop-1-en-1-ylphosphonate 210**

![Chemical Structure](image)

Pd\(_2\)(dba)\(_3\) (57 mg, 0.06 mmol, 5 mol\%) and Cs\(_2\)CO\(_3\) (489 mg, 1.50 mmol) were placed in a microwave tube. The tube was sealed with a lid and filled with argon, by applying 3 cycles of vacuum, followed by argon. Dry THF (5 mL) was introduced via the septum, followed by *trans*-1-bromo-1-propene 208 (167 mg, 139 \(\mu\)L, 1.38 mmol) and hydrogen phosphonate diester (172 mg, 161 \(\mu\)L, 1.25 mmol). The tube was then heated in a microwave oven for 10 min at 120 °C. After cooling down, the solids were filtered off and washed with CH\(_2\)Cl\(_2\). The filtrate solvent was removed *in vacuo* and the crude residue purified by column chromatography (20-70\% EtOAc/Petrol) to give diethyl (E)-prop-1-en-1-ylphosphonate as a pale yellow oil (87 mg, 0.49 mmol, 39%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.75 (ddq, \(J_{H,P} = 52.0\) and \(J = 13.0\) and 7.0 Hz, 1H), 5.67 (ddq, \(J_{H,P} = 20.0\) and \(J = 13.0\) and 1.5 Hz, 1H), 4.09-4.02 (m, 4H), 1.91 (ddd, \(J_{H,P} = 3.5\) and \(J = 7.0\) and 1.5 Hz, 3H), 1.27 (t, \(J = 1.0\) Hz, 6H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 149.3 (d, \(J_{C,P} = 6.0\) Hz, CH), 118.5 (d, \(J_{C-P} = 188.0\) Hz, CH), 61.7 (d, \(J_{C-P} = 6.0\) Hz, CH\(_2\)), 20.3 (d, \(J_{C-P} = 24.0\) Hz, CH\(_3\)), 16.3 (d, \(J_{C-P} = 6.0\) Hz, CH\(_3\)); HRMS (CI) calcd for C\(_7\)H\(_{16}\)O\(_3\)P [M+H]\(^+\) 179.0837, observed 179.0834.

**Diethyl prop-1-en-2-ylphosphonate 211**

![Chemical Structure](image)

Pd\(_2\)(dba)\(_3\) (57 mg, 0.06 mmol, 5 mol\%) and Cs\(_2\)CO\(_3\) (489 mg, 1.50 mmol) were placed in a microwave tube. The tube was sealed with a lid and filled with argon, by applying 3 cycles of vacuum, followed by argon. Dry THF (5 mL) was introduced *via* the septum, then was added 2-bromo-1-propene 209 (167 mg, 117 \(\mu\)L, 1.38 mmol) and hydrogen phosphonate diester (172 mg, 161 \(\mu\)L, 1.25 mmol). The tube was then heated in a microwave oven for 10 min at 120 °C. After cooling down, the
solids were filtered off and washed with CH$_2$Cl$_2$. The filtrate solvent was removed in vacuo and the crude residue purified by column chromatography (20-70% EtOAc/Petrol) to give diethyl prop-1-en-2-ylphosphonate as a pale yellow oil (89 mg, 0.50 mmol, 40%).

$^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.94 (doublet of quintets, $J_{H-P}$ = 22.0 and $J$ = 1.5 Hz, 1H), 5.72 (doublet of quintets, $J_{H-P}$ = 48.5 and $J$ = 1.5 Hz, 1H), 4.09-4.02 (m, 4H), 1.91 (dt, $J_{H-P}$ = 14.0 and $J$ = 1.5 Hz, 3H), 1.30 (t, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 134.8 (d, $J_{C-P}$ = 174.0 Hz, C), 130.0 (d, $J_{C-P}$ = 10.0 Hz, CH$_2$), 61.7 (d, $J_{C-P}$ = 6.0 Hz, CH$_2$), 18.8 (d, $J_{C-P}$ = 11.0 Hz, CH$_3$), 16.3 (d, $J_{C-P}$ = 6.0 Hz, CH$_3$); HRMS (FAB) calcd for C$_7$H$_{15}$O$_3$PNa $[M+Na]^+$ 201.0673, observed 201.0679.

**Diethyl (2-methyl-3-oxohexyl)phosphonate 212**

Using Method J, the reaction was complete after 120 h. Purification by column chromatography (neat CH$_2$Cl$_2$-2.5% MeOH/CH$_2$Cl$_2$) gave diethyl (2-methyl-3-oxohexyl)phosphonate as a colourless oil.

$^{1}$H NMR (600 MHz, CDCl$_3$) $\delta$ 4.10-4.01 (m, 4H), 2.98-2.89 (m, 1H), 2.52 (dt, $J$ = 17.5 and 7.0 Hz, 1H), 2.44 (dt, $J$ = 17.5 and 7.0 Hz, 1H), 2.28 (ddd, $J_{H-P}$ = 22.0 and $J$ = 15.5 and 7.0 Hz, 1H), 1.70-1.57 (m, 3H), 1.30 (t, $J$ = 7.0 Hz, 3H), 1.29 (t, $J$ = 7.0 Hz, 3H), 1.20 (dd, $J_{H-P}$ = 0.5 and $J$ = 7.0 Hz, 3H), 0.91 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 212.4 (d, $J_{C-P}$ = 9.0 Hz, C), 61.7 (d, $J_{C-P}$ = 7.0 Hz, CH$_2$), 61.7 (d, $J_{C-P}$ = 7.0 Hz, CH$_2$), 43.2 (CH$_2$), 40.6 (d, $J_{C-P}$ = 2.5 Hz, CH), 28.0 (d, $J_{C-P}$ = 140.0 Hz, CH$_2$), 18.6 (d, $J_{C-P}$ = 11.0 Hz, CH$_3$), 17.1 (CH$_2$), 16.5 (d, $J_{C-P}$ = 7.0 Hz, CH$_3$), 13.8 (CH$_3$); IR (thin film) 2965, 2937, 1715, 1238 cm$^{-1}$; LRMS (FAB) 273 (100, [M+Na]$^+$); HRMS (FAB) calcd for C$_{11}$H$_{23}$O$_4$PNa $[M+Na]^+$ 273.1232, observed 273.1227.
**Dimethyl (1-bromoethenyl)phosphonate 214**

To a stirring solution of dimethyl vinyl phosphonate 198 (680 mg, 5.0 mmol) in CH$_3$Cl (10 mL) was added excess bromine (5 mL) and the reaction mixture left to stir at 21 °C for 16 h. The solvent and excess bromine were removed *in vacuo*, PhMe (20 mL) added and then was added NEt$_3$ (607 mg, 840 µL, 6.0 mmol) and the reaction mixture left to stir at 21 °C for 4 h. To work-up, the solvent was removed *in vacuo*, the reaction mixture diluted with Et$_2$O (50 mL), washed with sat. K$_2$CO$_3$ (3 × 100 mL), 2M HCl (3 × 100 mL) and sat. NaCl (150 mL), dried (MgSO$_4$) and the solvent removed *in vacuo*. Purification by column chromatography (neat CH$_2$Cl$_2$-2% MeOH/ CH$_2$Cl$_2$) gave dimethyl (1-bromoethenyl)phosphonate as a yellow oil (484 mg, 2.25 mmol, 45%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.92 (dd, $J_{H-P} = 3.5$ and $J = 0.5$ Hz, 1H), 6.49 (dd, $J_{H-P} = 9.5$ and $J = 0.5$ Hz, 1H), 3.74 (d, $J_{H-P} = 11.0$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 135.9 (dt, $J_{C-P} = 14.0$ Hz), 117.4 (ds, $J_{C-P} = 200.0$ Hz), 53.3 (dq, $J_{C-P} = 5.0$ Hz); IR (thin film) 2957, 1600, 1259 cm$^{-1}$; LRMS (CI) 217 (100, [M$^{81}$Br +H]$^+$), 215 (100, [M$^{79}$Br +H]$^+$); HRMS (CI) calcd for C$_4$H$_9$BrO$_3$P [M$^{79}$Br +H]$^+$ 214.9473, observed 214.9468.

**Experimental for Chapter 6**

**1-Bromobutyl butanoate 219**

$n$-Butanal 18a (72 mg, 90 µL, 1 mmol) was added to a solution of NBS (214 mg, 1.2 mmol) in CCl$_4$ (2 mL) and the reaction mixture left to stir at 21 °C for 2 h. The solvent was removed *in vacuo*, the solids filtered off, washed with CCl$_4$ (10 mL) and the filtrate solvent removed *in vacuo* to afford 1-bromobutyl butanoate as a yellow oil (211 mg, 0.95 mmol, 95%).
\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 6.66 (t, \( J = 8.0 \) Hz, 1H), 2.33 (dt, \( J = 8.0 \) and 7.5 Hz, 2H), 2.12-2.07 (m, 2H), 1.67 (sextet, \( J = 7.5 \) Hz, 2H), 1.49 (sextet, \( J = 7.5 \) Hz, 2H), 0.98-0.94 (m, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 171.3 (C), 76.2 (CH), 41.3 (CH\textsubscript{2}), 36.1 (CH\textsubscript{2}), 19.3 (CH\textsubscript{2}), 18.2 (CH\textsubscript{2}), 13.6 (CH\textsubscript{3}), 13.3 (CH\textsubscript{3}); IR (thin film) 2934, 1732 cm\textsuperscript{-1}; LRMS (EI) 143 (100, [M-Br]+); HRMS (EI) calcd for C\textsubscript{8}H\textsubscript{15}O\textsubscript{2}[M-Br]+ 143.1066; observed 143.1060.

**Typical procedure for the synthesis of acyl hydrazides – Method K**

Aldehyde (1 mmol) was added to a solution of azodicarboxylate (1.2 mmol) on H\textsubscript{2}O (500 \( \mu \)L) and the reaction mixture stirred at 21 \( ^\circ \)C for the time specified (see below). The solvent was removed \textit{in vacuo} and purified as described below to afford the desired acyl hydrazide.

**Diethyl 1-butanoylhydrazine-1,2-dicarboxylate 222a**

\[
\begin{align*}
\text{N} & \quad \text{CO}_2\text{Et} \\
& \quad \text{CO}_2\text{Et}
\end{align*}
\]

Using Method K, the reaction was complete after 24 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave diethyl 1-butanoylhydrazine-1,2-dicarboxylate as a colourless oil (221 mg, 0.90 mmol, 90%).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 6.77 (br s, NH, 1H), 4.28 (q, \( J = 7.0 \) Hz, 2H), 4.19 (q, \( J = 7.0 \) Hz, 2H), 2.90-2.80 (m, 2H), 1.68 (sextet, \( J = 7.5 \) Hz, 2H), 1.35-1.17 (m, 6H), 0.97 (t, \( J = 7.5 \) Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 173.8 (C), 155.6 (C), 153.3 (C), 63.9 (CH\textsubscript{2}), 62.6 (CH\textsubscript{2}), 38.9 (CH\textsubscript{2}), 18.1 (CH\textsubscript{2}), 14.4 (CH\textsubscript{3}), 14.2 (CH\textsubscript{3}), 13.6 (CH\textsubscript{3}); IR (thin film) 3309, 2968, 2877, 1738, 1717 cm\textsuperscript{-1}; LRMS (FAB) 269 (100, [M+Na]+); HRMS (FAB) calcd for C\textsubscript{10}H\textsubscript{18}N\textsubscript{2}O\textsubscript{5}Na [M+Na]+ 269.1113, observed 269.1118.
Diethyl 1-(2-methylpropanoyl)hydrazine-1,2-dicarboxylate 222b

Using Method K, the reaction was complete after 24 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave diethyl 1-(2-methylpropanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (177 mg, 0.72 mmol, 72%).

$^1$H NMR (600 MHz, CDCl$_3$) δ 6.55 (br s, NH, 1H), 4.29 (q, $J = 7.0$ Hz, 2H), 4.21 (q, $J = 7.0$ Hz, 2H), 3.65 (br septet, $J = 6.5$ Hz, 1H), 1.35-1.24 (m, 6H), 1.20 (d, $J = 6.5$ Hz, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 178.4 (C), 155.7 (C), 153.2 (C), 64.0 (CH$_2$), 62.7 (CH$_2$), 34.4 (CH), 19.4 (CH$_3$), 14.5 (CH$_3$), 14.3 (CH$_3$); IR (thin film) 3312, 2984, 2938, 1742, 1725 cm$^{-1}$; LRMS (FAB) 247 (100, [M+H]$^+$); HRMS (FAB) calcd for C$_{10}$H$_{19}$N$_2$O$_5$ [M+H]$^+$ 247.1294, observed 247.1284.

Diethyl 1-(3-methylbutanoyl)hydrazine-1,2-dicarboxylate 222c

Using Method K, the reaction was complete after 24 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave diethyl 1-(3-methylbutanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (239 mg, 0.92 mmol, 92%).

$^1$H NMR (600 MHz, CDCl$_3$) δ 6.63 (br s, NH, 1H), 4.29 (q, $J = 7.0$ Hz, 2H), 4.21 (q, $J = 7.0$ Hz, 2H), 2.88-2.72 (m, 2H), 2.19 (nontet, $J = 6.5$ Hz, 2H), 1.33 (t, $J = 7.0$ Hz, 3H), 1.32-1.27 (m, 3H), 0.97 (d, $J = 6.5$ Hz, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 173.2 (C), 155.7 (C), 153.3 (C), 64.0 (CH$_2$), 62.7 (CH$_2$), 45.7 (CH$_2$), 25.3 (CH), 22.6 (CH$_2$), 14.5 (CH$_3$), 14.3 (CH$_3$); IR (thin film) 3312, 2961, 2874, 1742, 1723 cm$^{-1}$; LRMS (CI) 261 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{11}$H$_{21}$N$_2$O$_5$ [M+H]$^+$ 261.1451, observed 261.1442.
Diethyl 1-(2-ethylhexanoyl)hydrazine-1,2-dicarboxylate 222f

Using Method K, the reaction was complete after 24 h. Purification by column chromatography (10%-40% EtOAc/petrol) gave diethyl 1-(2-ethylhexanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (272 mg, 0.90 mmol, 90%).

\[\text{1H NMR (600 MHz, CDCl}_3\text{)} \delta 6.73 \text{ (br s, NH, 1H)}, 4.28 \text{ (q, \text{J} = 7.0 \text{ Hz, 2H})}, 4.23-4.14 \text{ (m, 2H), 3.56-3.47 (m, 1H), 1.74-1.65 (m, 2H), 1.57-1.42 (m, 2H), 1.32 (t, \text{J} = 7.0 \text{ Hz, 3H), 1.30-1.18 (m, 7H), 0.89 (t, \text{J} = 7.5 \text{ Hz, 3H}), 0.85 (t, \text{J} = 7.0 \text{ Hz, 3H})}; \]
\[\text{13C NMR (150 MHz, CDCl}_3\text{)} \delta 177.5 \text{ (C), 155.7 \text{ (C), 153.3 (C), 64.0 (CH\text{)}), 62.6 (CH\text{)}), 46.1 (CH\text{}), 31.6 (CH\text{)}, 29.5 (CH\text{)}, 25.5 (CH\text{)}, 22.9 (CH\text{), 14.5 (CH\text{)}, 14.2 (CH\text{)}, 14.1 (CH\text{)}, 11.7 (CH\text{)); IR (thin film) 3305, 2962, 2934, 2874, 1740, 1720 cm}^{-1}; \]
\[\text{LRMS (CI) 303 (100, [M+H]}^{+}; \text{ HRMS (CI) calcd for C}_{14}\text{H}_{27}\text{N}_{2}\text{O}_{5} \text{[M+H]}^{+} 303.1920, \text{observed 303.1925.} \]

Diethyl 1-decanoylhydrazine-1,2-dicarboxylate 222g

Using Method K, the reaction was complete after 24 h. Purification by column chromatography (10%-50% EtOAc/petrol) gave diethyl 1-decanoylhydrazine-1,2-dicarboxylate as a colourless oil (271 mg, 0.82 mmol, 82%).

\[\text{1H NMR (600 MHz, CDCl}_3\text{)} \delta 6.73 \text{ (br s, NH, 1H)}, 4.28 \text{ (q, \text{J} = 7.0 \text{ Hz, 2H})}, 4.21 \text{ (q, \text{J} = 7.0 \text{ Hz, 2H})}, 2.97-2.89 \text{ (m, 2H), 1.64 (quintet, \text{J} = 7.0 \text{ Hz, 2H}), 1.35-1.24 (m, 18H), 0.86 (t, \text{J} = 7.0 \text{ Hz, 3H}); \]
\[\text{13C NMR (150 MHz, CDCl}_3\text{)} \delta 174.0 \text{ (C), 155.7 (C), 153.3 (C), 64.0 (CH\text{)}, 62.7 (CH\text{)}, 37.1 (CH\text{)}, 32.0 (CH\text{)}, 29.5 (CH\text{)}, 29.5 (CH\text{)}, 29.4 (CH\text{)}, 29.1 (CH\text{)}, 24.7 (CH\text{)}, 22.8 (CH\text{)}, 14.5 (CH\text{)}, 14.3 (CH\text{)}, 14.2 (CH\text{}); \]
\[\text{IR (thin film) 3311, 2924, 2855, 1740, 1722 cm}^{-1}; \text{ LRMS (ES) 329 (100, [M-H]}^{-}; \text{ HRMS (ES) calcd for C}_{16}\text{H}_{29}\text{N}_{2}\text{O}_{5} \text{[M-H]}^{-} 329.2076, \text{observed 329.2084.} \]
Diethyl 1-(2,2-dimethylpropanoyl)hydrazine-1,2-dicarboxylate 222q

Using Method K, the reaction was complete after 24 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave diethyl 1-(2,2-dimethylpropanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (166 mg, 0.64 mmol, 64%).

$^1$H NMR (600 MHz, CDCl$_3$) δ 6.90 (br s, NH, 1H), 4.29 (q, $J = 7.0$ Hz, 2H), 4.21 (q, $J = 7.0$ Hz, 2H), 1.34-1.20 (m, 15H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 180.0 (C), 156.2 (C), 154.2 (C), 64.2 (CH$_2$), 62.8 (CH$_2$), 42.2 (C), 27.5 (CH$_3$), 14.5 (CH$_3$), 14.3 (CH$_3$); IR (thin film) 3295, 2982, 2938, 1782, 1734, 1715 cm$^{-1}$; LRMS (FAB) 283 (100, [M+Na]$^+$); HRMS (FAB) calcd for C$_{11}$H$_{20}$N$_2$O$_5$ [M+Na]$^+$ 283.1270, observed 283.1270.

Diethyl 1-(pent-4-enoyl)hydrazine-1,2-dicarboxylate 222n

Using Method K, the reaction was complete after 24 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave diethyl 1-(pent-4-enoyl)hydrazine-1,2-dicarboxylate as a colourless oil (155 mg, 0.60 mmol, 60%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.70 (br s, NH, 1H), 5.84 (ddt, $J = 17.0$, 10.5 and 6.5 Hz, 1H), 5.08 (dq, $J = 17.0$ and 1.5 Hz, 1H), 4.99 (dq, $J = 10.5$ and 1.5 Hz, 1H), 4.29 (q, $J = 7.0$ Hz, 2H), 4.21 (q, $J = 7.0$ Hz, 2H), 3.10-2.90 (m, 2H), 1.68 (q, $J = 6.5$ Hz, 2H), 1.34-1.16 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.2 (C), 155.6 (C), 153.2 (C), 136.8 (CH), 115.6 (CH$_2$), 64.0 (CH$_2$), 62.7 (CH$_2$), 36.3 (CH$_2$), 28.6 (CH$_2$), 14.4 (CH$_3$), 14.2 (CH$_3$); IR (thin film) 3309, 2983, 1738, 1718, 1642 cm$^{-1}$; LRMS (CI) 259 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{11}$H$_{19}$N$_2$O$_5$ [M+H]$^+$ 259.1294, observed 259.1289.
Diethyl 1-[(4Z)-dec-4-enoyl]hydrazine-1,2-dicarboxylate 222y

Using Method K, the reaction was complete after 48 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave diethyl 1-[(4Z)-dec-4-enoyl]hydrazine-1,2-dicarboxylate as a colourless oil (230 mg, 0.70 mmol, 70%).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.63 (br s, NH, 1H), 5.44-5.38 (m, 1H), 5.37-5.32 (m, 1H), 4.30 (q, $J$ = 7.0 Hz, 2H), 4.22 (q, $J$ = 7.0 Hz, 2H), 3.01-2.92 (m, 2H), 2.40 (q, $J$ = 7.5 Hz, 2H), 2.03 (q, $J$ = 7.0 Hz, 2H), 1.35-1.22 (m, 12H), 0.88 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 174.4 (C), 155.6 (C), 153.2 (C), 131.7 (CH), 127.4 (CH), 64.1 (CH$_2$), 62.7 (CH$_2$), 37.2 (CH$_2$), 31.6 (CH$_2$), 29.4 (CH$_2$), 27.3 (CH$_2$), 22.7 (CH$_2$), 22.5 (CH$_2$), 14.5 (CH$_3$), 14.3 (CH$_3$), 14.2 (CH$_3$); IR (thin film) 3316, 2958, 2928, 1742, 1722 cm$^{-1}$; LRMS (CI) 329 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{16}$H$_{29}$N$_2$O$_5$ [M+H]$^+$ 329.2077, observed 329.2083.

Diethyl 1-[undec-10-enoyl]hydrazine-1,2-dicarboxylate 222v

Using Method K, the reaction was complete after 48 h. Purification by column chromatography (10%-30% EtOAc/petrol) gave diethyl 1-[undec-10-enoyl]hydrazine-1,2-dicarboxylate as a colourless oil (291 mg, 0.85 mmol, 85%).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.82 (br s, NH, 1H), 5.78 (ddt, $J$ = 17.0, 10.0 and 6.5 Hz, 1H), 4.96 (dq, $J$ = 17.0 and 1.0 Hz, 1H), 4.90 (dq, $J$ = 10.0 and 1.0 Hz, 1H), 4.27 (q, $J$ = 7.0 Hz, 2H), 4.20 (q, $J$ = 7.0 Hz, 2H), 2.93-2.84 (m, 2H), 2.01 (q, $J$ = 7.0 Hz, 2H), 1.63 (quintet, $J$ = 7.0 Hz, 2H), 1.35-1.23 (m, 16H); $^{13}$C NMR (150 MHz, CDCl$_3$)$^{†††}$ $\delta$ 174.0 (C), 155.7 (C), 153.3 (C), 139.3 (CH), 114.2 (CH$_2$), 64.0 (CH$_2$), 62.6 (CH$_2$), 37.1 (CH$_2$), 33.9 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 24.6 (CH$_2$), 14.5 (CH$_3$), 14.3 (CH$_3$); IR (thin film) 3312, 2980, 2926, 2855, 1741, 1725, 1640

$^{†††}$ 17C expected, 15C observed.
cm$^{-1}$; LRMS (ES) 365 (100, [M+Na]$^+$); HRMS (ES) calcd for C$_{17}$H$_{30}$N$_2$NaO$_5$ [M+Na]$^+$ 365.2052, observed 365.2034.

**Diethyl 1-(2-phenylpropanoyl)hydrazine-1,2-dicarboxylate 222w**

![Chemical structure](image)

Using Method K, the reaction was complete after 72 h. Purification by column chromatography (10%-30% EtOAc/petrol) gave diethyl 1-(2-phenylpropanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (206 mg, 0.67 mmol, 67%).

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.33-7.22 (m, 5H), 6.56 (br s, NH, 1H), 4.25-4.21 (m, 4H), 1.56 (br q, $J = 7.0$ Hz, 1H), 1.49 (t, $J = 7.0$ Hz, 3H), 1.32-1.23 (m, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 174.8 (C), 155.4 (C), 152.8 (C), 140.4 (C), 128.7 (CH), 127.8 (CH), 127.1 (CH), 64.0 (CH$_2$), 62.6 (CH$_2$), 45.5 (CH), 20.1 (CH$_3$), 14.4 (CH$_3$), 14.1 (CH$_3$); IR (thin film) 3294, 2982, 1743, 1720, 1495 cm$^{-1}$; LRMS (ES) 331 (100, [M+Na]$^+$); HRMS (ES) calcd for C$_{15}$H$_{20}$N$_2$NaO$_5$ [M+Na]$^+$ 331.1270, observed 331.1283.

**(2S)-Diethyl 1-(2-methylbutanoyl)hydrazine-1,2-dicarboxylate 225**

![Chemical structure](image)

Using Method K, the reaction was complete after 24 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave (2S)-diethyl 1-(2-methylbutanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (229 mg, 0.88 mmol, 88%).

$^1$H NMR (600 MHz, CDCl$_3$) δ 6.58 (br s, NH, 1H), 4.30 (q, $J = 7.0$ Hz, 2H), 4.21 (q, $J = 7.0$ Hz, 2H), 3.58-3.44 (m, 1H), 1.79 (doublet of quintets, $J = 14.5$ and 7.0 Hz, 1H), 1.46 (doublet of quintets, $J = 14.5$ and 7.5 Hz, 1H), 1.34-1.22 (m, 6H), 1.18 (d, $J = 7.0$ Hz, 3H), 0.92 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 177.9 (C), 155.7 (C), 153.3 (C), 64.0 (CH$_2$), 62.7 (CH$_2$), 41.0 (CH), 27.1 (CH$_2$), 16.9 (CH$_3$), 148
14.5 (CH₃), 14.3 (CH₃), 11.7 (CH₃); IR (thin film) 3313, 2979, 2938, 1742, 1724 cm⁻¹; LRMS (CI) 261 (100, [M+H]+); HRMS (CI) calcd for C₁₃H₂₁N₂O₅ [M+H]+ 261.1450, observed 261.1445; [α]D = +20.5 (c 0.50, CHCl₃, 20.5 °C); HPLC conditions: CHIRALCEL-OD column, hexane:i-PrOH 99:1, 0.6 mL/min, retention time: 34.8 min.

**5-Propyl-1,3,4-oxadiazol-2-ol 226, N-butyryl-hydrazinecarboxylic acid ethyl ester 227 and diethyl hydrazine-1,2-dicarboxylate 223**

To a solution of diethyl 1-butanoylhydrazine-1,2-dicarboxylate 222a (246 mg, 1 mmol) in DMSO (1 mL) was added LiCl (212 mg, 5 mmol) and the reaction mixture stirred at 150 °C for 16 h. To work-up, the reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (5 × 50 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by column chromatography (1%-5% MeOH/CH₂Cl₂) gave trace quantities of 5-propyl-1,3,4-oxadiazol-2-ol, N-butyryl-hydrazinecarboxylic acid ethyl ester and diethyl hydrazine-1,2-dicarboxylate.

Data for 226: ¹H NMR (600 MHz, CDCl₃) δ 8.68 (br s, OH, 1H), 2.53 (t, J = 7.5 Hz, 2H), 1.72 (sextet, J = 7.5 Hz, 2H), 1.00 (t, J = 7.5 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 158.4 (C), 155.2 (C), 28.4 (CH₂), 19.0 (CH₂), 13.5 (CH₃); IR (thin film) 3300, 2959, 2872, 1670, 1640 cm⁻¹; LRMS (CI) 129 (100, [M+H]+); HRMS (CI) calcd for C₅H₉N₂O₂ [M+H]+ 129.0664, observed 129.0660.

Data for 227: ¹H NMR (600 MHz, CDCl₃) δ 3.72 (q, J = 7.5 Hz, 2H), 2.52 (t, J = 7.5 Hz, 2H), 1.71 (sextet, J = 7.5 Hz, 2H), 1.28 (t, J = 7.5 Hz, 3H), 1.00 (t, J = 7.5 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 177.0 (C), 154.0 (C), 40.7 (CH₂), 28.3 (CH₂), 19.1 (CH₂), 13.6 (CH₃), 13.5 (CH₃); IR (thin film) 3350, 3300, 2967, 1782, 1720 cm⁻¹; LRMS (CI) 175 (100, [M+H]+); HRMS (CI) calcd for C₇H₁₅N₂O₃ [M+H]+ 175.1004, observed 175.1014.

Data for 223: ¹H NMR (600 MHz, CDCl₃) δ 4.21 (q, J = 7.0 Hz, 4H), 1.26 (t, J = 7.0 Hz, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 154.1 (C), 62.4 (CH₂), 14.5 (CH₃); IR
Typical procedure for the synthesis of amides – Method L

Amine (2.5 mmol) was added to a solution of acyl hydrazide (1 mmol) in CH$_2$Cl$_2$ (2.0 mL) and the reaction mixture stirred at 21 °C for the time specified (see below). The solvent was removed in vacuo and purified as described below to afford the desired amide.

**N-Hexylbutanamide 220a**

Using Method L, the reaction was complete after 16 h. Purification by column chromatography (20%-60% EtOAc/petrol) gave N-hexylbutanamide as a colourless oil (164 mg, 0.96 mmol, 96%).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 5.45-5.35 (m, NH, 1H), 3.26 (q, $J = 7.0$ Hz, 2H), 2.16 (t, $J = 7.5$ Hz, 2H), 1.68 (sextet, $J = 7.5$ Hz, 2H), 1.51 (quintet, $J = 7.0$ Hz, 2H), 1.36-1.24 (m, 6H), 1.00 (t, $J = 7.5$ Hz, 3H), 0.95 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 172.9 (C), 39.6 (CH$_2$), 38.9 (CH$_2$), 31.5 (CH$_2$), 29.7 (CH$_2$), 26.6 (CH$_2$), 22.6 (CH$_2$), 19.3 (CH$_2$), 14.1 (CH$_3$), 13.8 (CH$_3$); IR (thin film) 3290, 3083, 2959, 2929, 2872, 1643, 1550 cm$^{-1}$; LRMS (CI) 172 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{10}$H$_{22}$NO [M+H]$^+$ 172.1701, observed 172.1698.

**N-(Prop-2-en-1-yl)butanamide 220b**

Using Method L, the reaction was complete after 16 h. Purification by column chromatography (20%-60% EtOAc/petrol) gave N-(prop-2-en-1-yl)butanamide as a colourless oil (121 mg, 0.95 mmol, 95%).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 5.83 (ddt, $J = 17.0$, 11.5 and 6.0 Hz, 1H), 5.64-5.56 (m, NH, 1H), 5.08 (dq, $J = 17.0$ and 1.5 Hz, 1H), 4.99 (dq, $J = 11.5$ and 1.5 Hz, 1H),
3.88 (tt, J = 6.0 and 1.5 Hz, 2H), 2.17 (t, J = 7.5 Hz, 2H), 1.67 (sextet, J = 7.5 Hz, 2H), 0.94 (t, J = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.0 (C), 134.5 (CH), 116.4 (CH$_2$), 42.0 (CH$_2$), 38.8 (CH$_2$), 19.3 (CH$_2$), 13.9 (CH$_3$); IR (thin film) 3290, 3083, 2964, 2930, 2874, 1643, 1548 cm$^{-1}$; LRMS (EI) 127 (100, [M]$^+$); HRMS (EI) calcd for C$_7$H$_{13}$NO [M]$^+$ 127.0992, observed 127.0995.

(2S)-N-Benzyl-2-methylbutanamide 228

Using Method L, the reaction was complete after 16 h. Purification by column chromatography (50% Et$_2$O/petrol) gave (2S)-N-benzyl-2-methylbutanamide as a colourless oil (160 mg, 0.84 mmol, 84%).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.35-7.32 (m, 2H), 7.29-7.25 (m, 3H), 5.70-5.62 (m, NH, 1H), 4.49-4.42 (m, 2H), 2.12 (quintet, J = 7.0 Hz, 2H), 1.74-1.66 (m, 1H), 1.45 (ddq, J = 14.5, 7.5 and 7.0 Hz, 1H), 1.16 (d, J = 7.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 176.4 (C), 138.6 (C), 128.8 (CH), 127.9 (CH), 127.6 (CH), 43.6 (CH$_3$), 43.4 (CH), 27.5 (CH$_2$), 17.7 (CH$_3$), 12.1 (CH$_3$); IR (thin film) 3282, 2965, 2929, 2876, 1646, 1548 cm$^{-1}$; LRMS (CI) 192 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{12}$H$_{18}$NO [M+H]$^+$ 192.1388, observed 192.1392; [$\alpha$]$_D$ = +16.4 (c 1.08, Acetone, 20.0 °C), Lit. [$\alpha$]$_D$ = +16.9 (Acetone, 20.0 °C).
References


Appendix