University College London

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

By

Vijay Chudasama

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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

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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.

Contents

Abbreviations

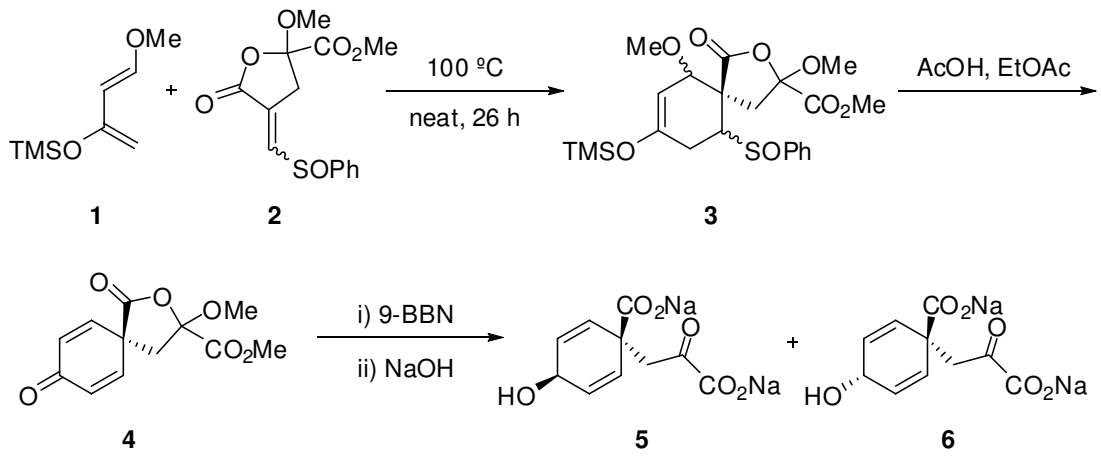
$[\alpha]_D$	Specific rotation
Ac	Acetyl
b.p.	Boiling point
BBN	Borabicyclo[3.3.1]-nonane
BHT	2,6-Di-*tert*-butyl-4-methylphenol
BMIM	1-Butyl-3-methylimidazolium
Bn	Benzyl
Bu	Butyl
CI	Chemical ionisation
Cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarisation transfer
DIBAL	Diisobutylaluminium hydride
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
E	Entgegen (opposite, *trans*)
EDG	Electron donating group
ee	Enantiomeric excess
Et	Ethyl
EI	Electron ionisation
EPR	Electron paramagnetic resonance
ES	Electrospray
EWG	Electron withdrawing group
FAB	Fast atom bombardment
HPLC	High performance liquid chromatography
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
m	Multiplet

m.p.	Melting point
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MW	Microwave
NBS	*N*-Bromosuccinimide
NHPI	*N*-Hydroxyphthalimide
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
PFP	Pentafluorophenyl
Ph	Phenyl
Pr	Propyl
q	Quartet
rt	Room temperature
s	Singlet
sat.	Saturated
t	Triplet
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
TCP	Trichlorophenyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
Tf	Triflate
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Tf	Triflate
UCL	University College London
UV	Ultraviolet
Z	Zusammen (together, *cis*)

Chapter 1 Introduction

1.1 Modern organic synthesis

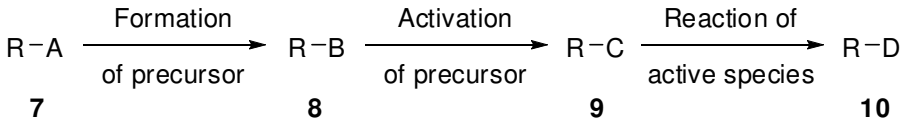
Modern organic synthesis requires the development of efficient methods for the construction of complex molecules. Chemists aspire to develop reactions that are generic, selective, reliable and scalable. Increasingly chemists are required to conceive of transformations with enhanced atom-economy and minimal 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]



Scheme 1. Use of a Diels-Alder cyclisation *en route* to prephenates **5** and **6**.[8]

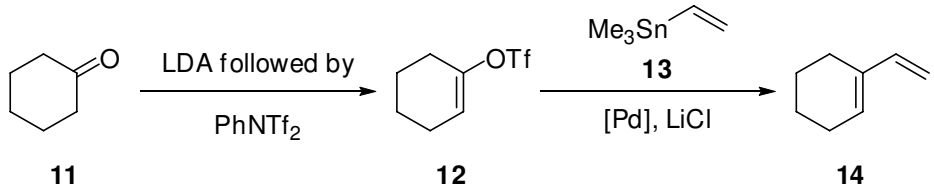
Despite the successful development of a plethora of useful protocols, it is still the case that numerous synthetic transformations employ a multi-step mode of reactivity (Scheme 2). This common mode of reactivity depends on a number of factors: i) ease

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.

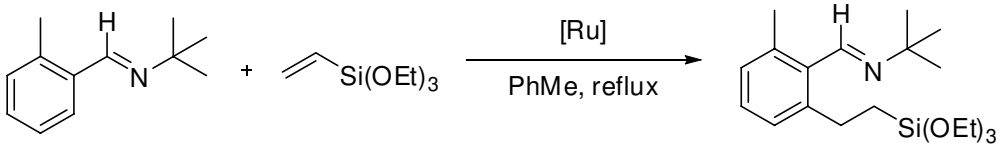
Each step in the process introduces inefficiencies that multiply through the multi-step conversion and typically involve the use of additional reagents, which inherently results in increased waste production.[9] For example, conversion of cyclohexanone **11** to diene **14** proceeds through conversion to precursor triflate **12**, followed by palladium activation and reaction with vinylic tin species **13** (Scheme 3).[10] Despite the disadvantages of the multi-step procedure, some good examples of useful methods employing this approach include metathesis reactions[11,12] and metal-catalysed coupling.[13,14] 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**.[10]

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).[15] It should also be noted that the use of more elaborate and unusual organometallic complexes to effect C-H activation have recently been reported.[16,17]



15 **16** **17**

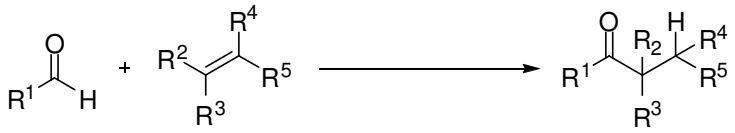
Scheme 4. Chelation assisted C-C bond formation *via* C-H activation.[15]

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.[18] Moreover, aldehydes are extremely good electrophiles and are consequently often employed as the electrophilic component in nucleophilic addition processes.[19-21] However, despite those factors there are some examples of the use of aldehydes as latent nucleophiles for hydroacylation chemistry.[22-26]

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.



18 **19** **20**

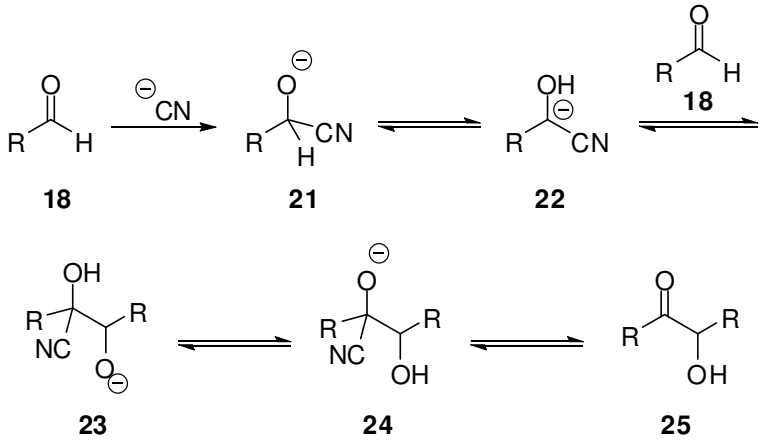
Scheme 5. Hydroacylation of alkene **19** with aldehyde **18**.

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

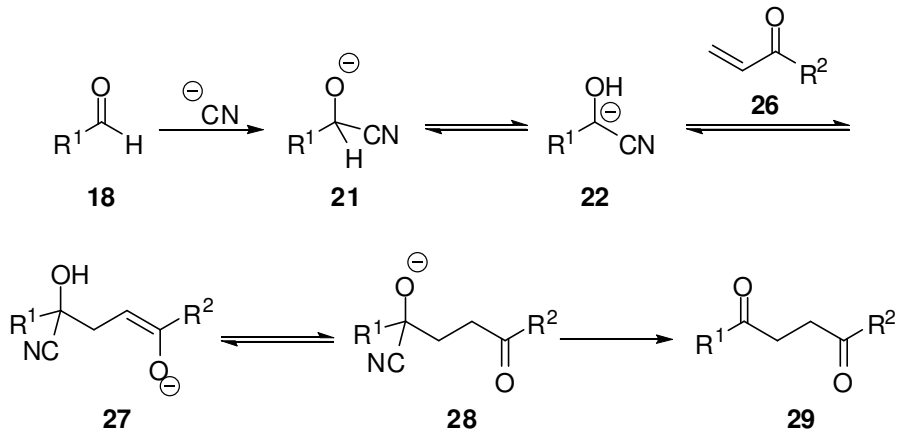
One of the earliest known reactions in organic chemistry is the benzoin condensation, in which aromatic and heterocyclic aldehydes are transformed into acyloins on

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.

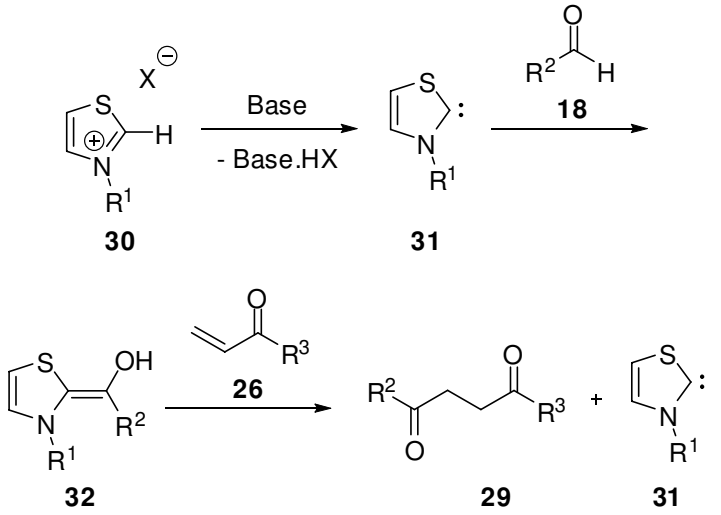
In 1973, Stetter and Schreckenberg found that carbanion **22** may also add to the double bond of α,β-unsaturated ketones, esters and nitriles *via* a mechanism analogous to that observed for benzoin condensation (Scheme 7).[22] Conjugate addition of carbanion **22** to α,β-unsaturated compound **26**,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



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

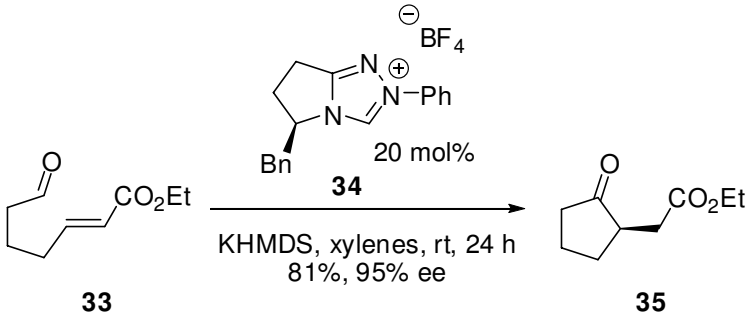
One of the major failures of early Stetter reactions was the incompatibility of aliphatic aldehydes owing to their propensity to undergo aldol condensation under the influence of the strongly basic cyanide salts.[22] However, aldehyde tolerance was soon extended to aliphatic aldehydes by Stetter and Schreckenberg in 1976 *via* the

application of thiazolium salts in the presence of base (Scheme 8).[23] 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**.[28,29] 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**.

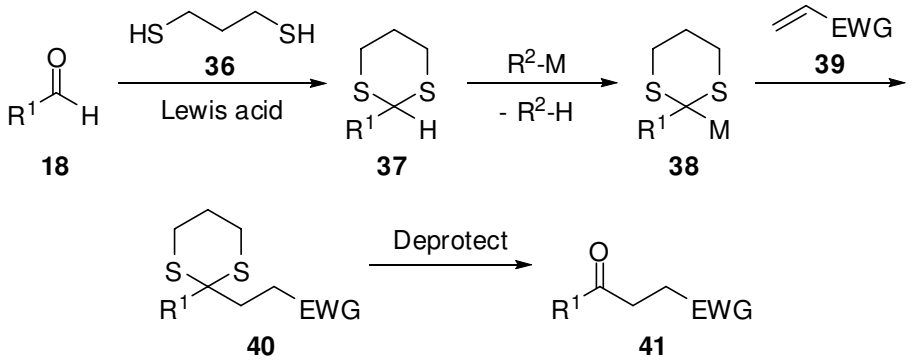
The scope of the Stetter reaction has further been extended *via* the use of chiral carbenes to impart stereoselectivity. For example, cyclisation of aldehyde **33** employing a sub-stoichiometric amount of thiazolium salt **34** afforded cyclic ketone **35** with high enantioselectivity and in good yield (Scheme 9).[30] 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.[31]



Scheme 9. Intramolecular enantioselective Stetter reaction.[30]

1.3.2 Dithiane chemistry

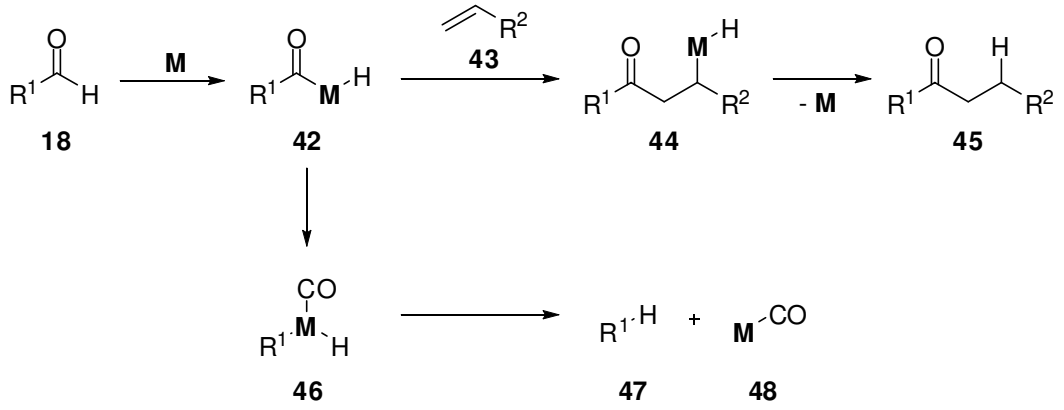
A common indirect route to reverse the polarity of an aldehyde is *via* the conversion of aldehyde **18** to dithiane **37** on application of dithiol **36** and a Lewis acid (Scheme 10).[24] Dithiane **37** may then be deprotonated under strongly basic conditions (e.g. *n*-butyllithium) to generate 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).[24] 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).[25] 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**.[32-34] 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**.

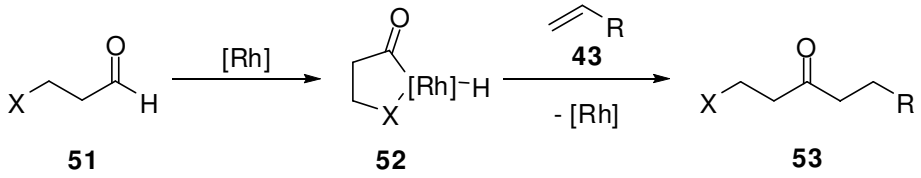


Scheme 11. Generic pathway for the metal mediated hydroacylation of alkenes.

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**.

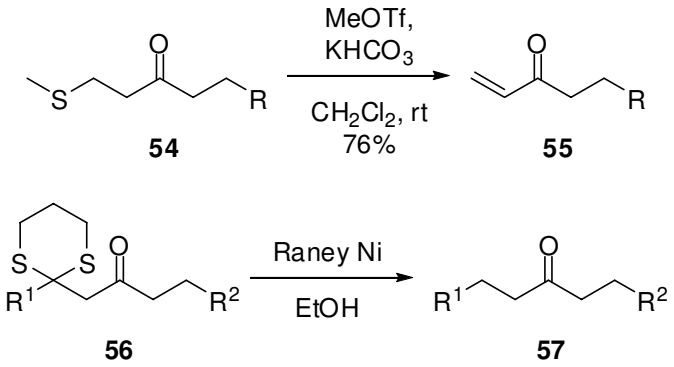
An intramolecular coordinating group has also been employed to combat the problem of decarbonylation (Scheme 12).[38-41] Thus, aldehyde **51**, bearing an appropriately positioned coordinating functional group may coordinatively saturate the metal species, **52**. A major limitation of this strategy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



Scheme 12. Chelation controlled intermolecular hydroacylation.[40]

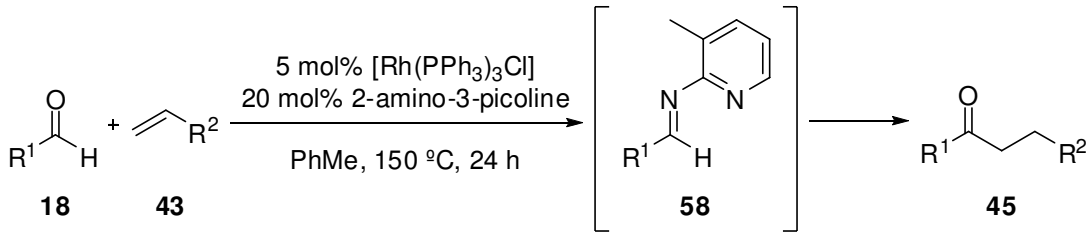
However, Willis has shown that the β-thioketal and β-sulphide products obtained from hydroacylation using aldehydes with appropriately coordinating thioketal and sulphide functional groups may be cleaved with Raney Ni or eliminated, respectively

(Scheme 13).[41] Despite this advance, the work is still very limited with respect to aldehydes that can be applied.



Scheme 13. Elimination from β-sulphide **54** and hydrogenation of β-thioketal **56**.[41]

Elegantly, Jun developed a general intermolecular hydroacylation strategy using rhodium and 2-amino-3-picoline as a co-catalyst (Scheme 14).[42-46] Key intermediate **58** 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]



Scheme 14. Elegant route to hydroacylation using 2-amino-3-picoline and rhodium.[25]

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.

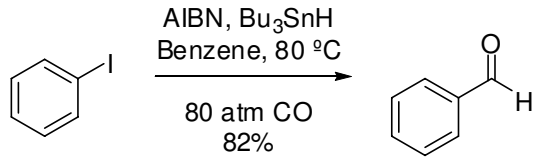
1.3.4 Hydroacylation *via* acyl radicals

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 α-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).[49] 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.

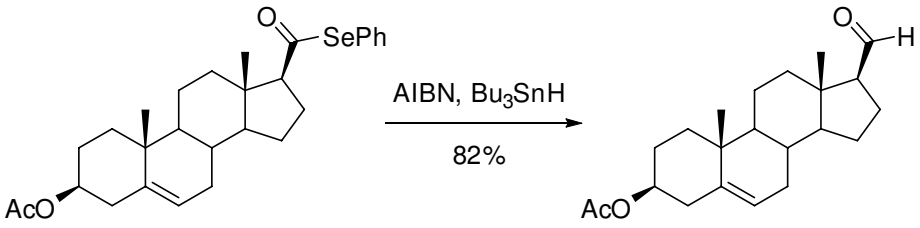


59 **60**

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]



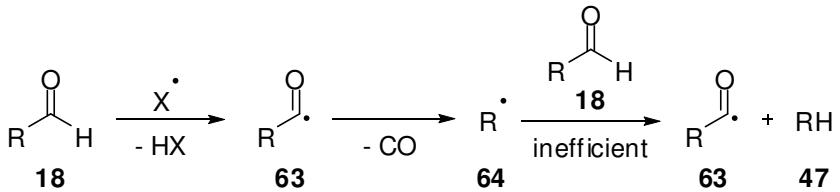
61 **62**

Scheme 16. Formation of aldehyde **62** from selenoester **61**.[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,[56] thio- and telluro-esters,[57-68] acylcobalt (III) derivatives,[69] metal carbene complexes[70,71] and acylphosphine oxides.[72] 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.[26] 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 **64**, derived from decarbonylation of acyl radical **63** (Scheme 17).

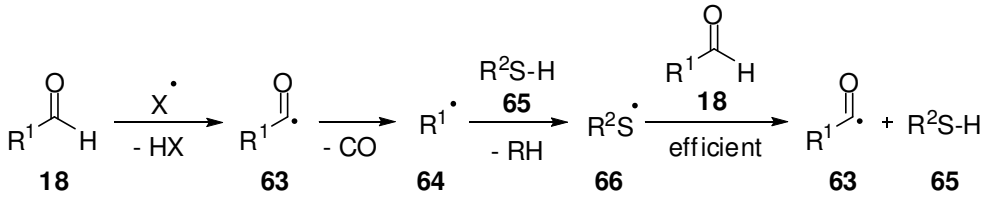


18 **63** **64** **63** **47**

Scheme 17. An inefficient chain transfer process.

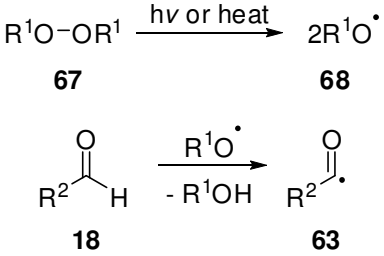
However, as initially detailed by Harris and Waters,[73] the presence of a thiol dramatically increases the efficiency of the process. In essence, the inefficient two-step process is superseded by a far more efficient three-step process in which electrophilic thiyl radical **66** abstracts an aldehydic 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.[74,75]



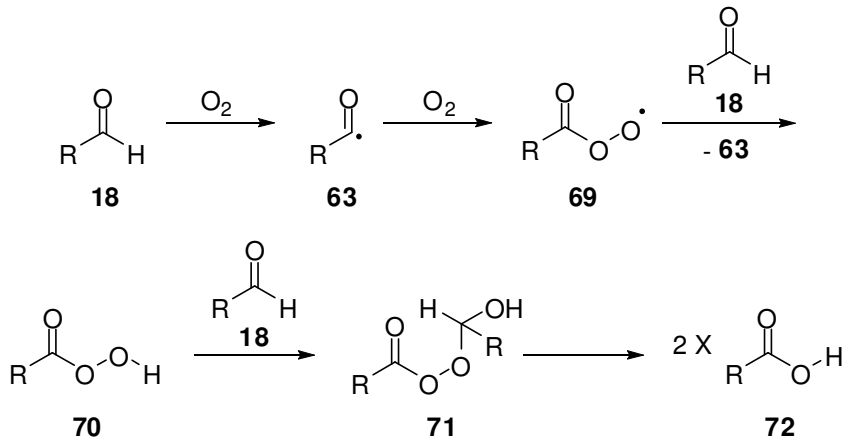
Scheme 18. Thiol catalysed decarbonylation.

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.[26] There are two general methods by which oxygen centred radicals are generated: UV irradiation or thermal decomposition of a peroxide species (Scheme 19).



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**.

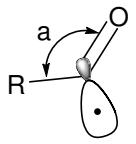


Scheme 20. Mechanism for the auto-oxidation of aldehydes to carboxylic acids.

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 σ-type radical.[26] In a theoretical study it has been determined by Guerra that for a variety of α-substituted acyl radicals ($XC(O)^{\bullet}$; where X = H, CH_3, NH_2, $OC(CH_3)_3$ and F), angle a lies within a narrow range of 126.6-130.8º (Figure 2, Table 1).[76]



63

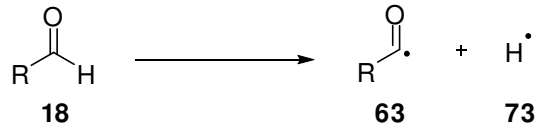
Figure 2. σ-Type acyl radical with bond angle a.

R	Angle a (º)
H	126.6
CH_3	129.4
NH_2	130.8
$OC(CH_3)_3$	128.6
F	128.1

Table 1. Variation in bond angle a for different R groups.[76]

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).[77-79] Perhaps this is not so surprising since EPR spectroscopy has shown acyl radicals to be σ-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.

RC(O)-H	D^o (kcal mol^{-1})	E^o (V) for RC(O)•
$CH_3C(O)$-H	89.3	- 1.75
$CH_3CH_2C(O)$-H	89.5	- 1.75
CH_2=CHC(O)-H	89.1	- 1.07
PhC(O)-H	88.9	- 1.13

Table 2. Dissociation enthalpies and reduction potentials for a range of aldehydes and their corresponding acyl radicals, respectively.[77]

The redox properties of acyl radicals have also been reported (Scheme 21, Table 2).[80] The acyl radicals were generated indirectly *via* the electrochemical reduction of acyl chlorides and anhydrides (RC(O)-X) by an aromatic radical anion.[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.[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).[82] The C=O stretching frequencies of the corresponding aldehydes have also been included for ease of direct comparison.[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.

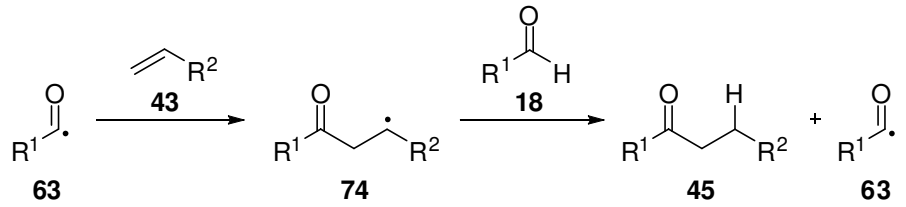
R	$\nu_{C=O}$ for $RC(O)^{\bullet}$ (cm^{-1})	$\nu_{C=O}$ for RCHO (cm^{-1})
CH_3	1864	1736
CH_3CH_2	1859	1742
$(CH3)_2CH$	1853	1743
$(CH_3)_3C$	1848	1733
C_6H_5	1828	1713
4-$MeOC_6H_4$	1813	1703
4-BrC_6H_4	1832	1714
4-NCC_6H_4	1824	1716
mesityl	1805	1742

Table 3. IR stretching frequencies for a range of acyl radicals and aldehydes.[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.[85-88] In contrast, aromatic acyl radicals show red-shifted peaks which are attributed to conjugation of the carbonyl moiety with the aryl group.[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 σ-type radicals.[89]

1.3.4.3 Intermolecular addition to C-C bonds

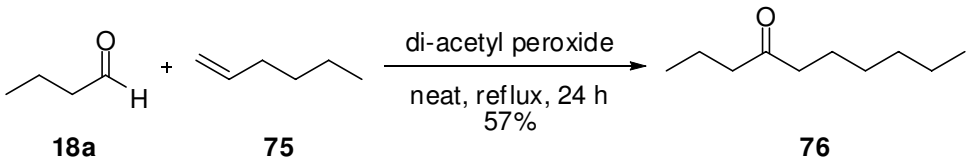
The addition of acyl radicals to C-C double bonds provides a useful method for the construction of unsymmetrical ketones (Scheme 22). Generally, acyl radical **63** adds to alkene **43** to form adduct radical **74**, which then abstracts an aldehydic hydrogen to form ketone **45** and re-generate **63**.



Scheme 22. General reaction pathway for hydroacylation *via* acyl radicals.

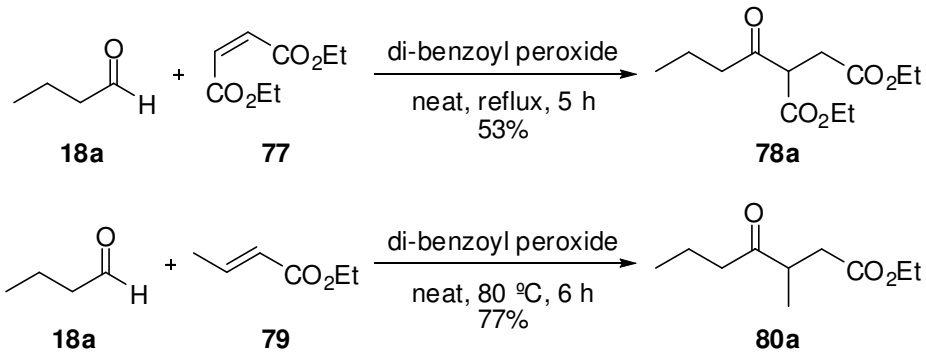
In general, acyl radicals add more efficiently to electron poor double bonds than to electron rich alkenes and hence it is for this reason that acyl radicals are viewed as nucleophilic. Furthermore, the abstraction of an aldehydic hydrogen atom by radical **74** is more favourable when the abstracting 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.[90] For example, hex-1-ene **75** was hydroacylated with *n*-butanal **18a** in the presence of di-acetyl peroxide (Scheme 23).[90]



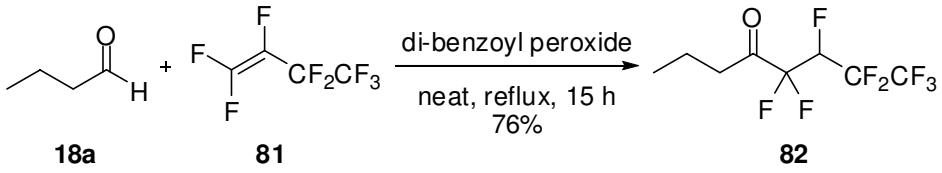
Scheme 23. First report of hydroacylation *via* an acyl radical.[90]

Soon after the work by Kharasch, Patrick reported the benzoyl peroxide-initiated addition of *n*-butanal **18a** to diethyl maleate **77** to give succinate **78a** (Scheme 24).[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 *n*-butanal **18a** in good yield through the use of di-benzoyl peroxide (Scheme 24).[92]



Scheme 24. Early reports of hydroacylation *via* acyl radicals by Patrick and Huang.[91,92]

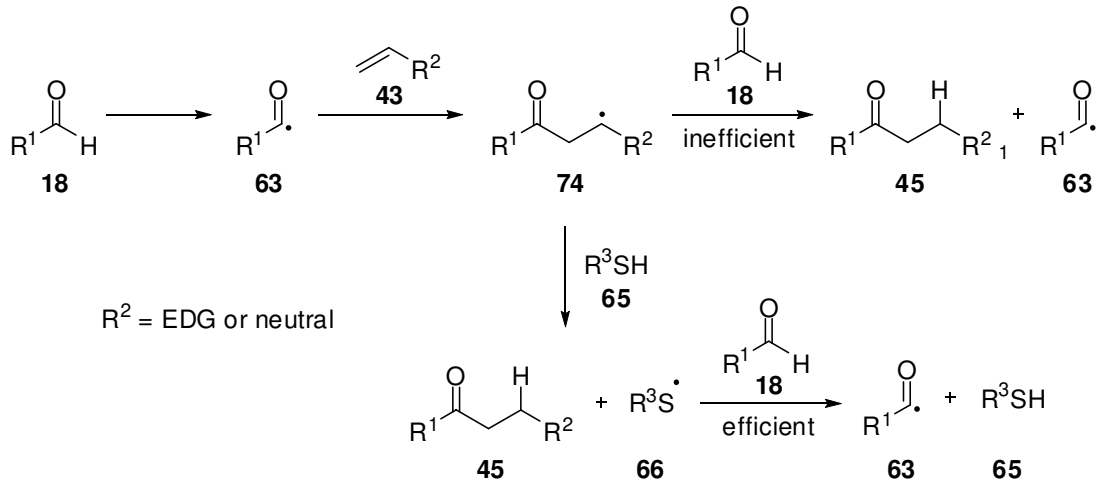
Numerous other examples have been reported since these early articles, with strained double bonds[93-96] and perfluoroalkenes[97,98] providing particularly good acceptors. For example, perfluorinated alkene **81** was hydroacylated with *n*-butanal **18a** in good yield upon thermal decomposition of di-benzoyl peroxide (Scheme 25).



Scheme 25. Hydroacylation of a perfluorinated alkene with acetaldehyde.[97]

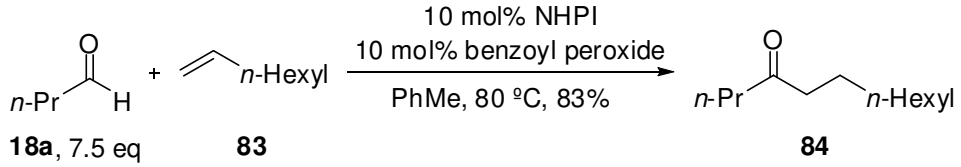
1.3.4.4 Polarity reversal catalysis

A major development in the hydroacylation arena came *via* the application of thiols as polarity reversal catalysts for the hydroacylation of electron neutral and electron rich alkenes (Scheme 26).[99] As discussed previously (see Section 1.3.4.1.2), if adduct radical **74**, derived from addition of acyl radical **63** to alkene **43**, is not electrophilic, abstraction of an aldehydic hydrogen atom is inefficient. However, in the presence of a thiol, adduct radical **74** readily abstracts a hydrogen atom from a thiol to generate ketone **45** and thiyl radical **66**. The electrophilic thiyl radical is well polarity matched to abstract an aldehydic hydrogen atom and propagate the chain (see Section 1.3.4.1.2).



Scheme 26. Thiol catalysis assisted hydroacylation of an alkene.

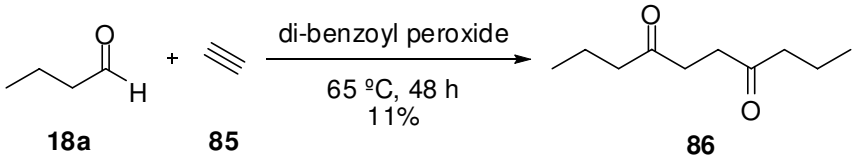
Recently, it has been reported that *N*-hydroxyphthalimide (NHPI) also acts as a polarity reversal catalyst for the hydroacylation of a range of alkenes.[100,101] For example, NHPI has successfully been employed in the hydroacylation of oct-1-ene **83** with *n*-butanal **18a** in good yield (Scheme 27).[100]



Scheme 27. Hydroacylation of alkene **83** using NHPI as a polarity reversal catalyst.[100]

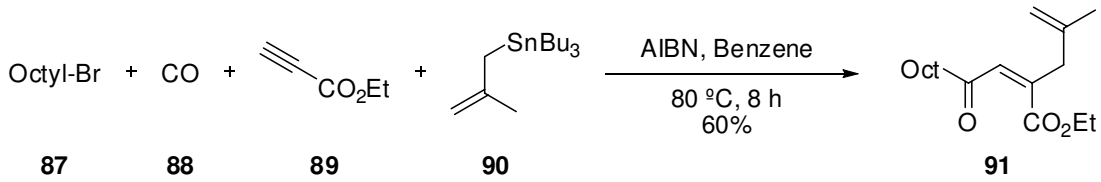
1.3.4.5 Intermolecular addition to C-C triple bonds

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.[102] Hydroacylation of acetylene **85** gave an α,β-unsaturated ketone, which then underwent selective hydroacylation to afford symmetrical 1,4-diketone **86** (Scheme 28).[102] Similar double hydroacylation chemistry on dimethyl acetylenedicarboxylate was reported by Wiley and Harrell in 1960.[103]



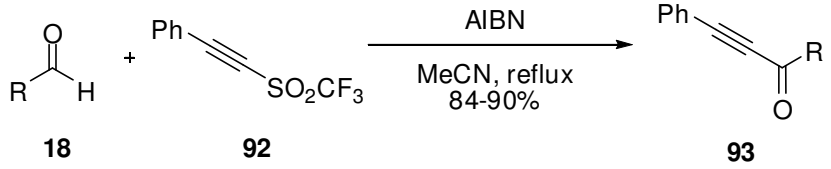
Scheme 28. First example of the hydroacylation of an alkyne. [102]

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).[104]



Scheme 29. Multi-component coupling to generate ketone **91**.[104]

More recently, Fuchs reported an acyl radical transfer reaction from aldehydes to acetylenic trifluoromethylsulfones to afford acetylenic ketones (Scheme 30).[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**.[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.

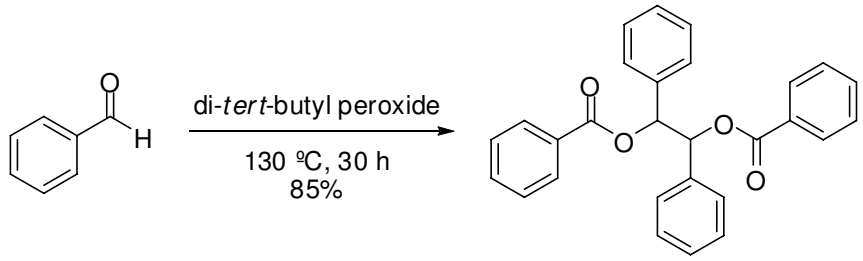


Scheme 30. Alkynylation of aldehydic C-H bonds.[105]

1.3.4.6 Intermolecular addition to non C-C multiple bonds

1.3.4.6.1 Addition to C=O bonds

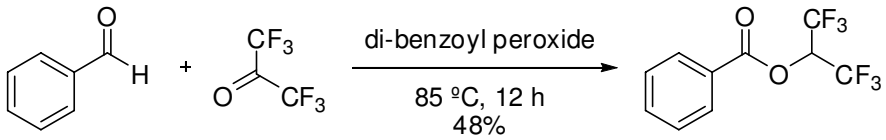
The addition of an acyl radical to an aldehyde to form an ester was reported in 1948 in the reaction of benzaldehyde **60** and di-*tert*-butyl peroxide to produce 1,2-diphenylethylene glycol di-benzoate **94**, incorporating four molecules of benzaldehyde (Scheme 31).[107] The mechanism is thought to 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**.



60 **94**

Scheme 31. Conversion of benzaldehyde **60** to di-benzoate **94**.[107]

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.[108] 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 **60** was shown to participate in the hydroacylation of hexafluoroacetone **95** to form ester **96** (Scheme 32).[109]

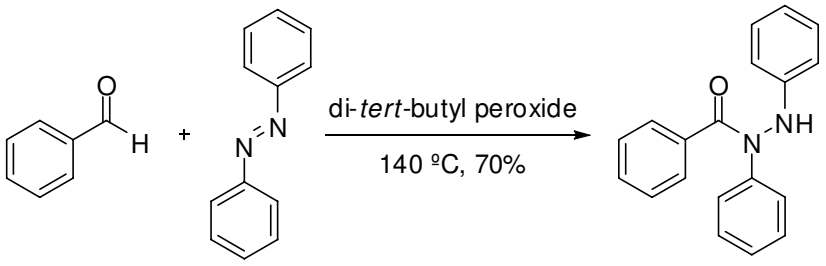


60 **95** **96**

Scheme 32. An example of ketone hydroacylation reported by Urry.[109]

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 **97** with benzaldehyde **60** to give acyl hydrazide **98** (Scheme 33).[110] Soon after the early work by Kharasch,[110] Horner and Huisgen reported the hydroacylation of azo-dicarboxylates.[111,112]

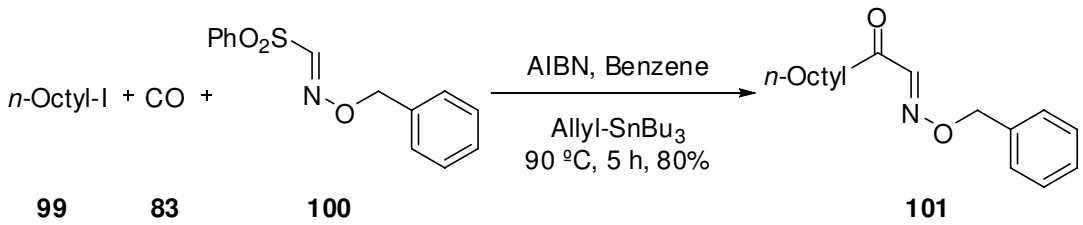


60 **97** **98**

Scheme 33. Hydroacylation of azobenzene **97** with benzaldehyde **60**.[110]

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.[113,114] 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).[114]



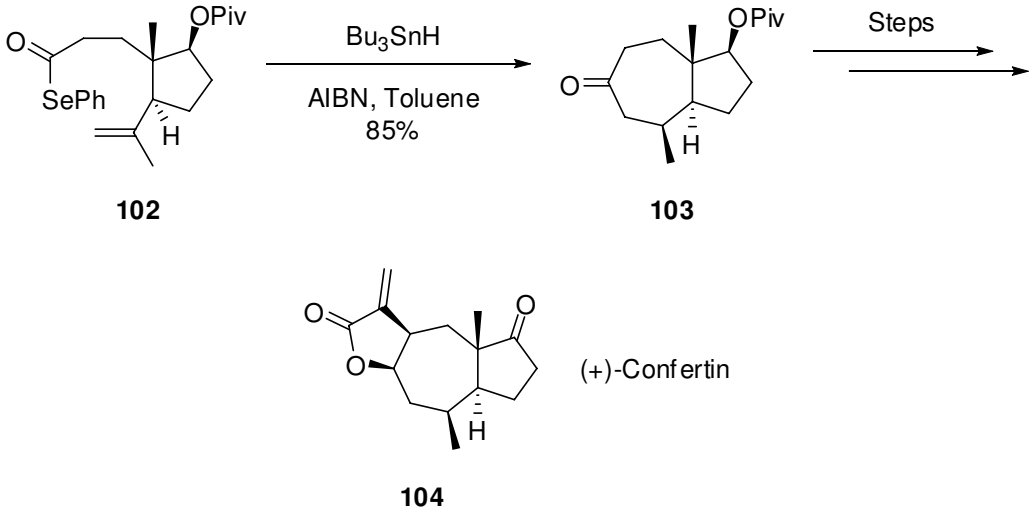
99 **83** **100** **101**

Scheme 34. Three-component coupling leading to oxime ether **101**.[114]

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.[26] 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]

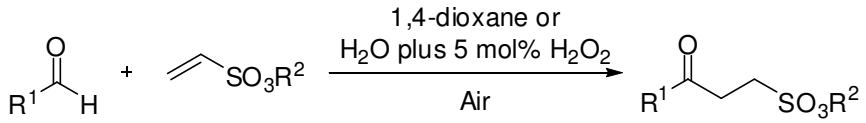


102 **103** **104**

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.



18

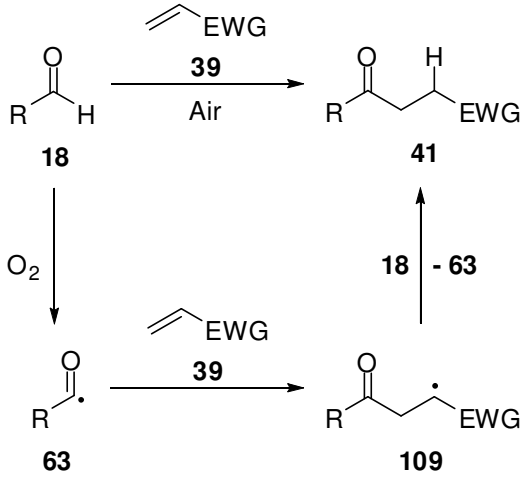
105, R^2 = PFP
106, R^2 = TCP

107, R^2 = PFP
108, R^2 = TCP

Scheme 36. Hydroacylation of vinyl sulfonates **105** and **106**.[117]

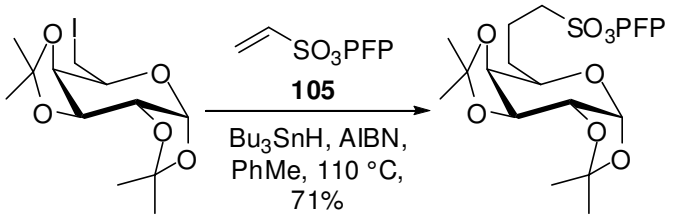
Despite the precise mechanism for the formation of ketones **107** and **108** being unknown, reaction was thought to be initiated by molecular oxygen induced conversion of aldehyde **18** to acyl radical **63**, as in the case of aldehyde auto-

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.[118,119] 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).[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,[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 *n*-butanal (10 equivalents) in the presence of air in 89% yield (see Chapter 4).[121]

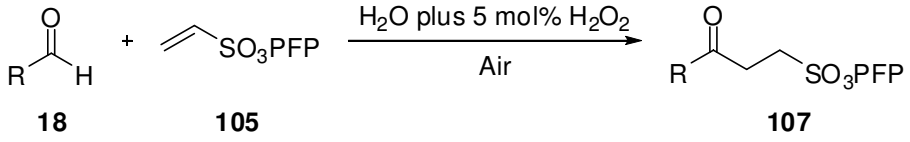


Scheme 38. Tributyltin hydride mediated radical addition to sulfonate **105**.[119]

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.

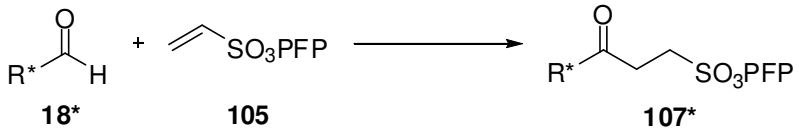
1.4 Aims

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.



Scheme 39. Hydroacylation of alkene **105** with aldehyde **18** to form ketone **107**.[122]

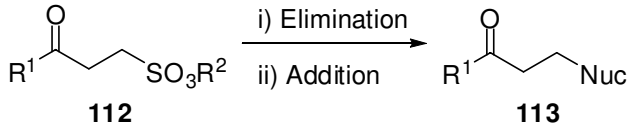
Owing to acyl radicals being σ-type radicals, the application of chiral aldehydes for the hydroacylation of vinyl sulfonate **105** was to be examined, with a view to analysing if there was any retention of enantiomeric excess (Scheme 40).



Scheme 40. Hydroacylation of vinyl sulfonate **105** with chiral aldehyde **18***.

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

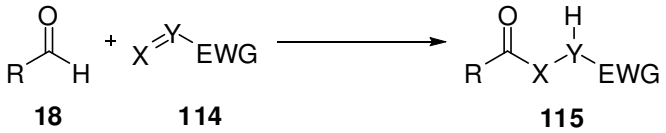
was to be investigated. An elimination-addition strategy was thought to be very useful as it would provide a powerful indirect alternative to the hydroacylation of electron rich alkenes (Scheme 41).



112 **113**

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).



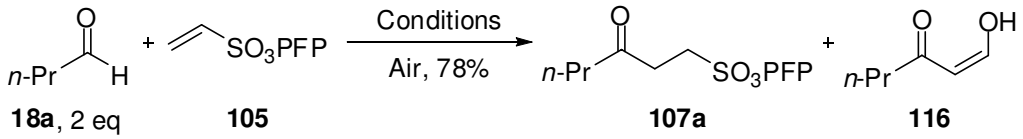
18 **114** **115**

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.



18a, 2 eq **105** **107a** **116**

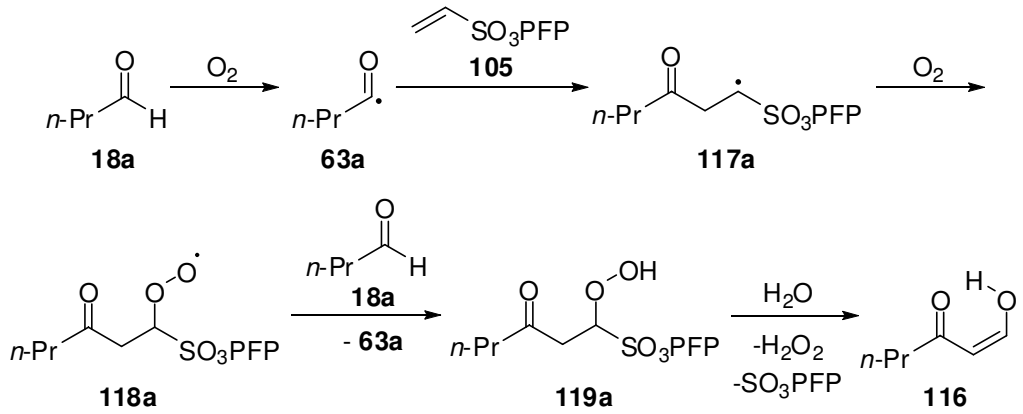
Scheme 43. Hydroacylation of vinyl sulfonate **105** with *n*-butanal **18a**.

Entry	Conditions	Time/h	Yield **107a**/%	Yield **116**/%
1	H_2O, 5 mol% H_2O_2	1	84	0
2	H_2O	3	78	5

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 peroxy 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%).



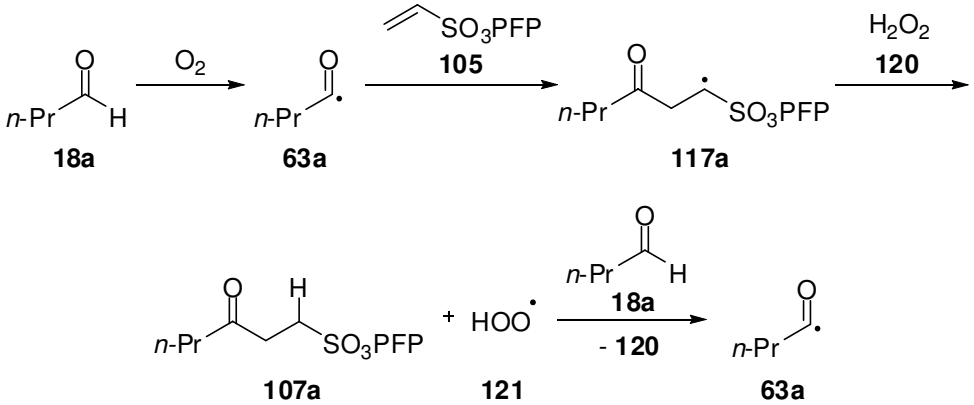
Scheme 44. Postulated mechanism for formation of enol **116**.

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.[26] 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.[26] 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.[26]

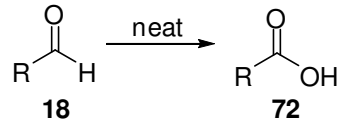
A feasible explanation of the role of hydrogen peroxide is that it may act as a catalyst (Scheme 45). Initially, hydrogen peroxide may donate a hydrogen atom to α-sulfonate radical **117a**, which is derived from acyl radical **63a** addition to vinyl sulfonate **105**, to form ketone **107a** and peroxy-radical **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.[26] It may also explain why no enol **116** formed in the presence of hydrogen peroxide. If hydrogen atom abstraction by α-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).[100,101]



Scheme 45. Postulated role of hydrogen peroxide as a chain carrier.

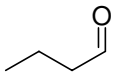
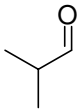
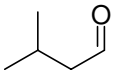
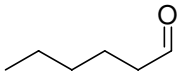
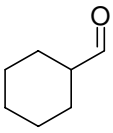
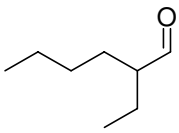
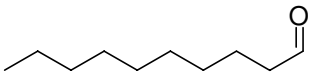
2.2 Aldehyde auto-oxidation studies

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 μL 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 α-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).



18 **72**

Scheme 46. Conversion of aldehyde **18** (200 and 500 μL) to acid **72**.

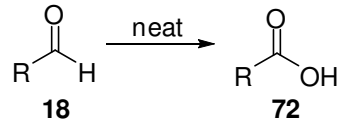
Entry	Aldehyde **18**	**18**:**72** (200 μL)[a]	**18**:**72** (500 μL)[a]
1	 **18a**	1:1.08	1:0.37
2	 **18b**	1:5.11	1:1.04
3	 **18c**	1:1.20	1:0.39
4	 **18d**	1:0.37	1:0.27
5	 **18e**	1:0.66	1:0.34
6	 **18f**	1:2.16	1:0.50
7	 **18g**	1:0.04	1:0.04

Conditions: aldehyde (200 and 500 μL) was stirred at 300 rpm for 2 h.
[a] Surface area (cm^2) to volume (cm^3) ratios at 200 and 500 μL are 1:0.16 and 1:0.06, respectively, where surface area refers to surface area exposed to air. All ratios are quoted as an average of 5 independent experiments with a maximum variation of 10% being observed in all cases.

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

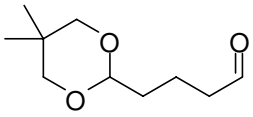
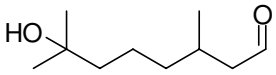
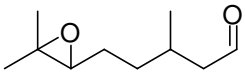
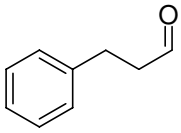
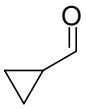
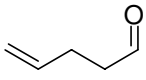
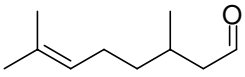
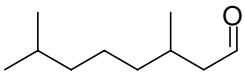
The affect of changing the surface area of aldehyde exposed to air relative to the volume of aldehyde was also investigated by comparing the rate of oxidation with different volumes of aldehyde, 200 and 500 μL, at a constant surface area (Scheme 46, Table 5). The faster rate of aldehyde auto-oxidation observed at a higher surface area to volume ratio implies that greater exposure to air, and thus molecular oxygen, increases oxidation rate.

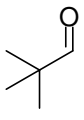
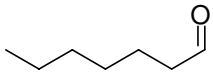
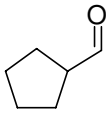
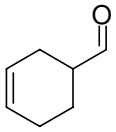
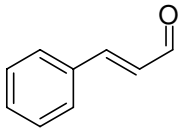
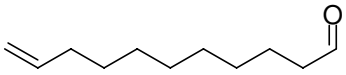
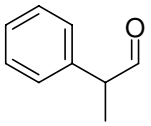
The rate at which a range of other aldehydes auto-oxidised was also determined (Scheme 47, Table 6). Although a significant proportion of aldehydes underwent auto-oxidation (Table 6, Entries 1-14), certain aldehydes did not exhibit any detectable acid formation, even after 24 h (Table 6, Entries 15-16). In addition, it is interesting to note that no radical clock or cyclisation products were observed on application of aldehydes **18m** and **18o**, respectively.



18 **72**

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

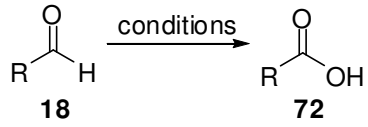
Entry	Aldehyde **18**	**18**:**72** (500 μL)
1	 **18h**	1:1.54
2	 **18i**	1:0.17
3	 **18j**	1:0.12
4	 **18k**[a]	1:0.25
5	 **18l**	1:0.06
6	 **18m**	1:0.32
7	 **18n**	1:0.14
8	 **18o**	1:0.18
9	 **18p**[a]	1:0.44

10	 **18q**	1:0.99
11	 **18r**	1:0.24
12	 **18s**	1:0.12
13	 **18t**	1:0.04
14	 **18u**	1:0.03
15	 **18v**	1:0.00[b]
16	 **18w**	1:0.00[b]

Conditions: aldehyde (500 μL) was stirred at 300 rpm for 2 h. [a] Synthesised from aldehyde **18o** (See Experimental) and [b] after 24 h reaction time. All ratios are quoted as an average of 5 independent experiments with a maximum variation of 12% being observed in all cases.

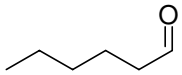
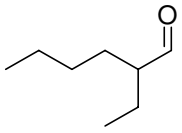
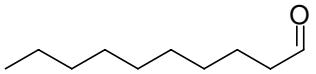
Table 6. Ratio of aldehyde **18** to acid **72** after 2 h unless stated otherwise.

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-CH_2 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.



18 **72**

Scheme 48. Conversion of aldehyde **18** to acid **72** under various conditions.

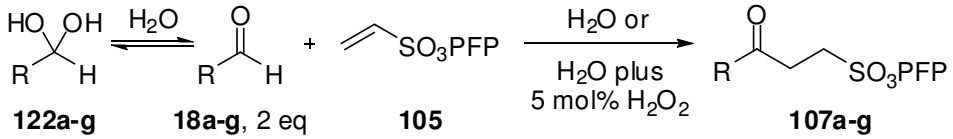
Entry	Aldehyde **18**	**18**:**72** (H_2O)	**18**:**72** (H_2O + 5 mol% H_2O_2)	**18**:**72** (Neat)
1	 **18d**	1:0.29	1:0.28	1:0.37
2	 **18f**	1:1.35	1:1.25	1:2.16
3	 **18g**	1:0.03	1:0.03	1:0.04

Conditions: aldehyde (500 μL) was stirred at 300 rpm for 2 h in the presence of H_2O, H_2O plus 5 mol% H_2O_2 or neat.

Table 7. Ratio of aldehyde **18** to acid **72** under various conditions after 2 h.

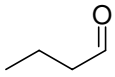
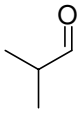
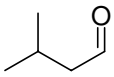
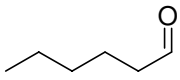
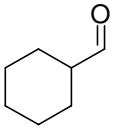
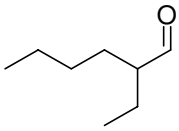
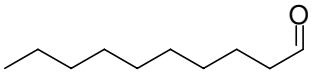
2.3 Aldehyde scope

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[126,127] and their broad range of solubilities in water (see Table 8).[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).



122a-g **18a-g**, 2 eq **105** **107a-g**

Scheme 49. Hydroacylation of vinyl sulfonate **105** with a variety of aldehydes **18a-g**.

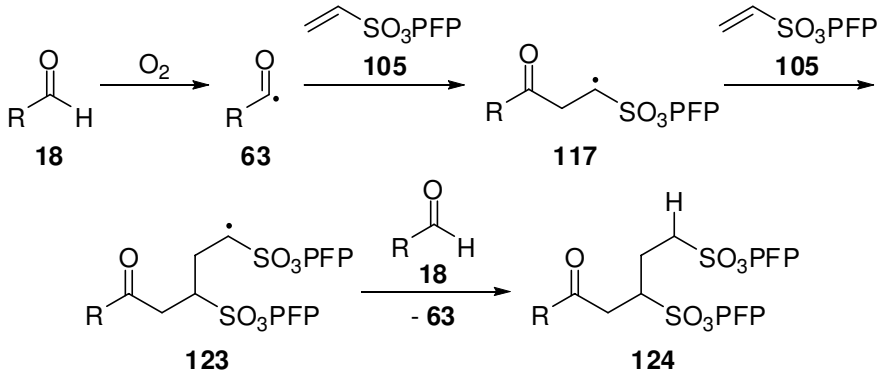
Entry	Aldehyde **18**	Isolated Yield **107** without H_2O_2/%	Isolated Yield **107** with H_2O_2/%	Solubility of **18** in H_2O at 30 ºC/ mass %[d]	**18**:**122** in D_2O
1	 **18a**	78	84	5.48	1:1.04
2	 **18b**	40[c]	56	4.57	1:0.86
3	 **18c**	74	77	1.78	1:0.66
4	 **18d**	75[a]	75[b]	0.44	1:0.98
5	 **18e**	74	79	0.21	1:0.54
6	 **18f**	83	87	0.05	1:0.03
7	 **18g**	62[a]	66[b]	0.02	1:0.12

Conditions: aldehyde (2 eq) and vinyl sulfonate **105** (1 eq) were stirred at 300 rpm at 21 ºC in H_2O or H_2O plus 5 mol% H_2O_2 for 3 h and 1 h, respectively, with 100% conversion of vinyl sulfonate **105** unless stated otherwise. [a] 6 h reaction time, [b] 2 h reaction time, [c] 60% conversion and [d] details given in reference.[129]

Table 8. Yields of ketones **107a-g**, and solubility and hydration data for aldehydes **18a-g**.[130-132]

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**.

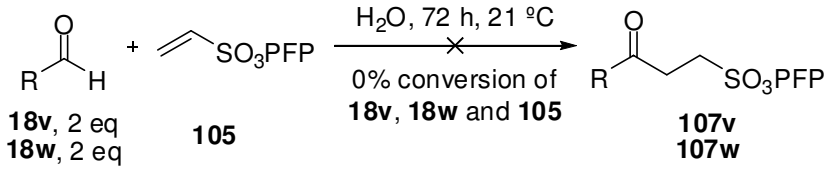


Scheme 50. Proposed mechanism for the formation of double addition product **124**.

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 α-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**.



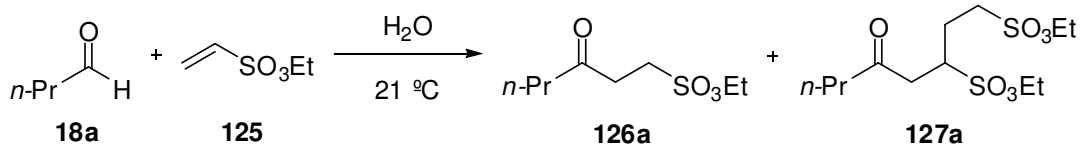
Scheme 51. Hydroacylation of vinyl sulfonate **105** with aldehydes **18v** and **18w**.

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.



18a **125** **126a** **127a**

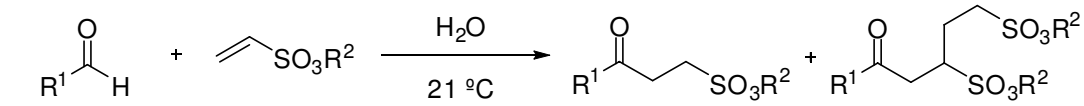
Scheme 52. Hydroacylation of alkene **125** with *n*-butanal **18a**.

Entry	**18a**:**125**	Yield **126a**/%	Yield **127a**/%
1	2:1	35	17
2	3:1	42	15
3	4:1	47	14
4	5:1	55	14
5	6:1	54	14

Conditions: aldehyde and vinyl sulfonate were stirred at 300 rpm at 21 ºC in H_2O.

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

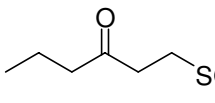
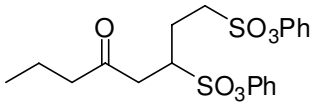
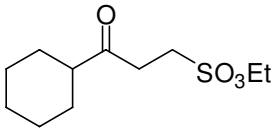
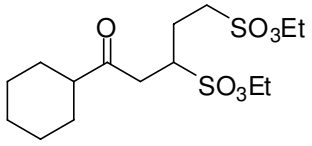
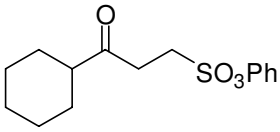
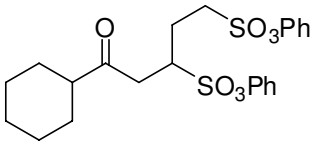
Eager to increase the yield of ketone **126a**, the affect of increasing aldehyde equivalence was explored (Scheme 52, Table 9, Entries 2-5). Optimal yield for hydroacylation of alkene **125** was achieved with 5 equivalents of *n*-butanal **18a** at 21 ºC (Table 9, Entry 4). Additional equivalents of 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**.



18a, R^1 = *n*-Pr **125**, R^2 = Et
18e, R^1 = Cy **128**, R^2 = Ph

126b-d **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 ºC.

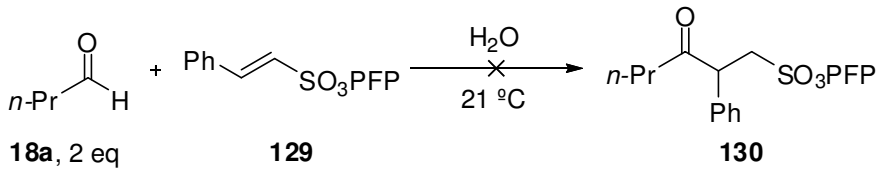
Hydroacylation product **126**	Isolated Yield **126**/%	Double addition product **127**	Yield **127**/%
 **126b**	52	 **127b**	16[b]
 **126c**	52	 **127c**	15[b]
 **126d**	57	 **127d**	14[b]

Conditions: aldehyde (5 eq) and vinyl sulfonate (1 eq) were stirred at 300 rpm at 21 ºC in H_2O.
[a] Isolated yield and [b] NMR yield by analogy of ^{1}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

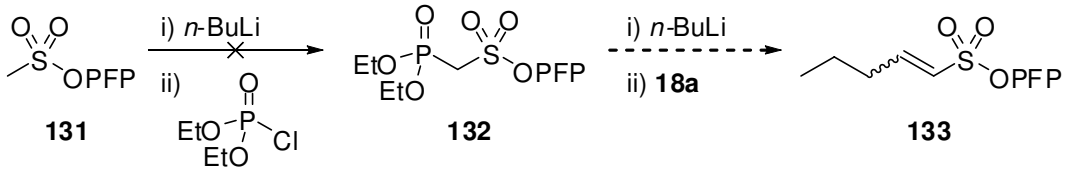
As a range of vinyl sulfonates had been shown to be tolerant of the aerobic activation hydroacylation methodology, the affect of β-substitution on the vinyl sulfonate motif was explored. β-Phenyl-PFP-vinyl sulfonate **129** was synthesised from trans-β-styrene sulfonyl chloride *via* the application 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.



18a, 2 eq **129** **130**

Scheme 54. Hydroacylation of alkene **129** with *n*-butanal **18a**.

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).[133] 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.



131 **132** **133**

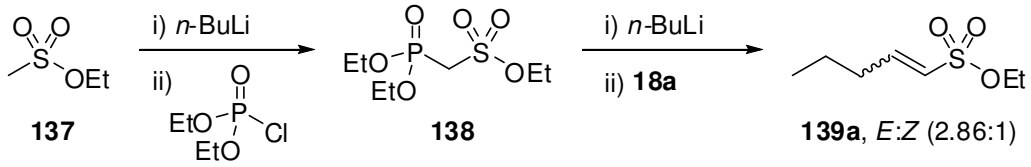
Scheme 55. Proposed route to β-substituted alkene **133** from sulfonate **131**.

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).

131 **134** **135** **136**

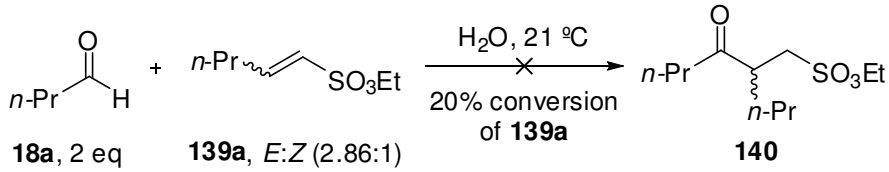
Scheme 56. Proposed decomposition of sulfonate **131** under basic conditions.

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.[133] 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).[133]



Scheme 57. Route to β-substituted vinyl sulfonate **139a**.

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**.

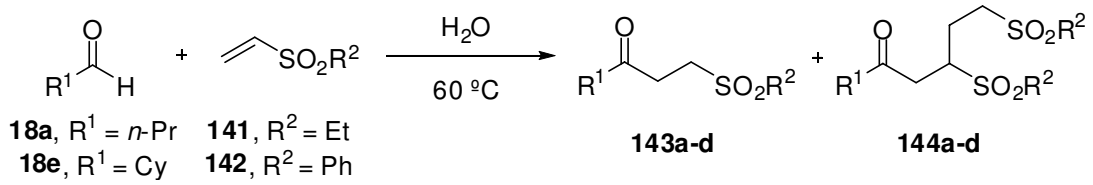


Scheme 58. Hydroacylation of alkene **139a** with *n*-butanal **18a** (2 equivalents).

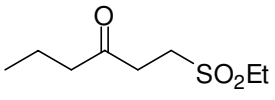
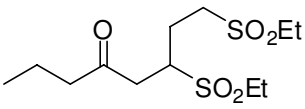
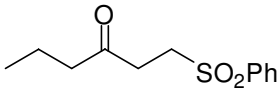
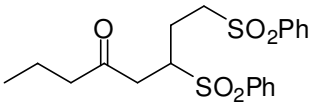
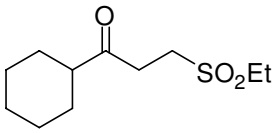
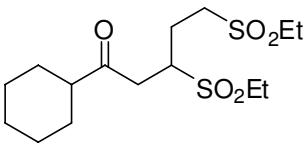
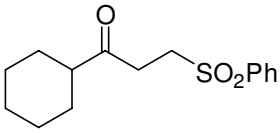
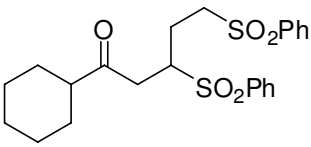
2.5 Vinyl sulfones

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 ºC 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 ºC 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

144a-d 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.



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

Hydroacylation product **143**	Isolated Yield **143**/%	Double addition product **144**	Yield **144**/%
 **143a**	64	 **144a**	12[a]
 **143b**	56	 **144b**	16[b]
 **143c**	57	 **144c**	15[b]
 **143d**	61	 **144d**	10[a]

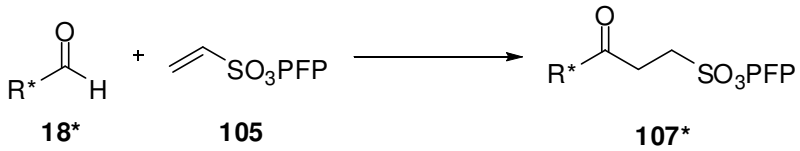
Conditions: aldehyde (5 eq) and vinyl sulfone (1 eq) were stirred at 300 rpm at 60 ºC in H_2O.
[a] Isolated yield and [b] NMR yield by analogy of ^{1}H NMR shifts for double addition product **144a**.

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 *via* a σ-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.[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).

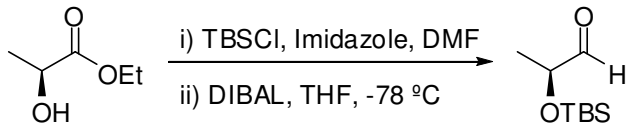


18* **105** **107***

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

2.6.1 Unsuccessful hydroacylation of PFP-vinyl sulfonate

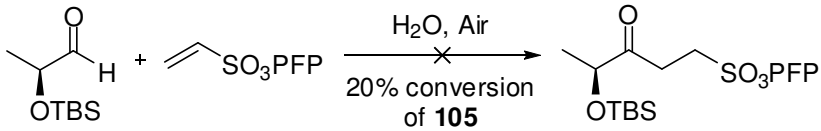
To examine the compatibility of chirality with the developed hydroacylation method, it was decided to use aldehydes that were prone to racemisation. Aldehyde **146** was synthesised from commercially available (*S*)-ethyl lactate **145** *via* a two-step protocol (Scheme 61).[135]



145 **146**

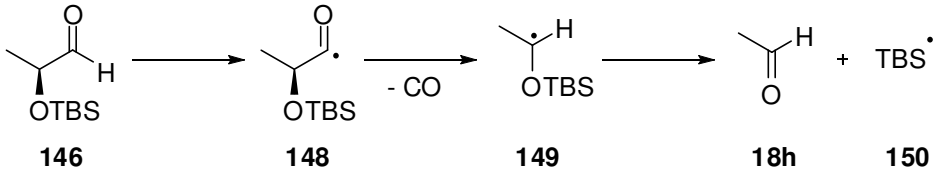
Scheme 61. Protection of alcohol **145**, followed by DIBAL reduction to afford aldehyde **146**.

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**.

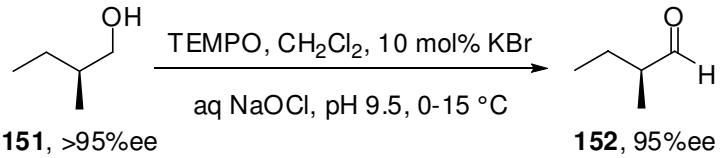
Although all aldehyde **146** was consumed on reaction with vinyl sulfonate **105** in the presence of water, none of the corresponding acid was observed. Only acetaldehyde **18h** and unreacted vinyl sulfonate **105** were isolated from the product mixture. One possible explanation for the formation 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.

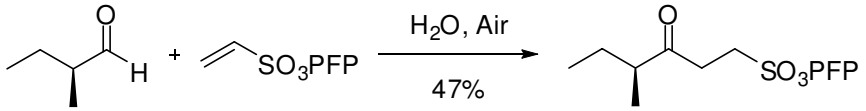
2.6.2 Hydroacylation of vinyl sulfonate with (*S*)-2-methylbutanal

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.



152, 95%ee **105** **153**, 94%ee

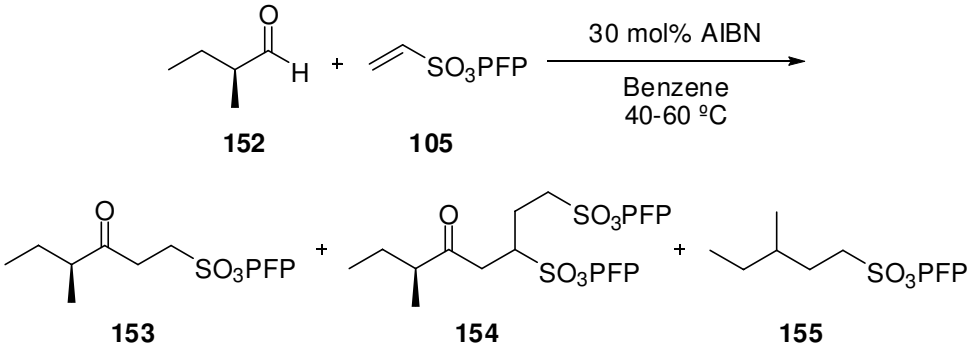
Scheme 65. Hydroacylation of vinyl sulfonate **105** with aldehyde **152**.

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 ºC 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 ºC 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).



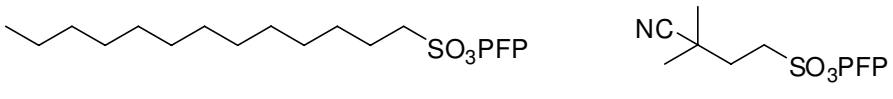
Scheme 66. Reaction of (*S*)-2-methylbutanal **152** with vinyl sulfonate **105**.

Entry	**152**:**105**	Temperature/°C	Conversion **105**/%	Isolated Yield **153**/%	Yield **154**[a]/%	Isolated Yield **155**/%
1	1:1	60	80	46	10	10
2	1:1	40	70	52	8	<1
3	1:1.2	40	84	60	11	<1
4	1:1.5	40	98	64[b]	15	<1
5	1:2	40	100	60	18	<1

Conditions: aldehyde **152** and vinyl sulfonate **105** were stirred at 300 rpm. [a] NMR yield by analogy of ^{1}H NMR shifts for double addition product **127a** and [b] >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.

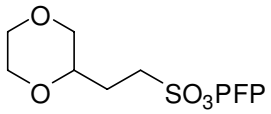
The optimised reaction conditions for the hydroacylation of vinyl sulfonate **105** with aldehyde **152** were applied to the use of another low temperature thermal initiator, lauroyl peroxide. Reaction proceeded with 100% conversion of vinyl sulfonate **105** with only a 30% yield of ketone **153**. 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.



156 **157**

Figure 3. Initiator derived alkyl sulfonates **156** and **157**.

In an attempt to increase yield of ketone **153** from reaction of vinyl sulfonate **105** with aldehyde **152** using 30 mol% AIBN in benzene at 40 ºC, the application of polarity reversal catalysts such as *N*-hydroxyphthalimide and *tert*-dodecylmercaptan was explored.[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,[137] it was used in place of benzene. However, this significantly suppressed formation of ketone **153**, <5%, due to reaction of vinyl sulfonate **105** with a radical derived from 1,4-dioxane to form alkyl sulfonate **158** in 94% yield (Figure 4).



158

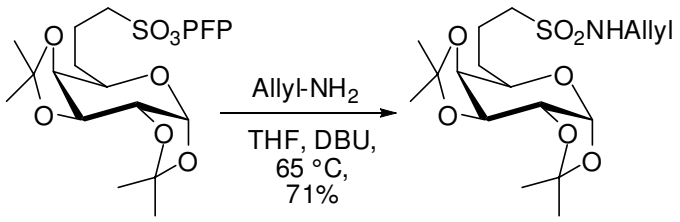
Figure 4. Alkyl sulfonate **158**, derived from 1,4-dioxane addition to vinyl sulfonate **105**.

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 σ-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

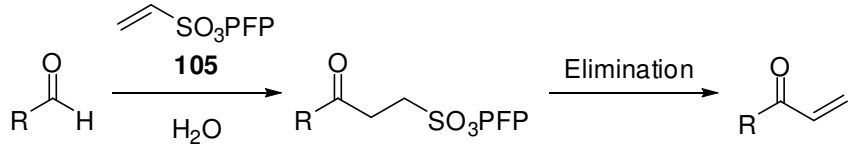
A range of γ-keto sulfonates had been synthesised *via* the hydroacylation of vinyl sulfonates and their synthetic utility was to be examined. The bi-functional γ-keto sulfonate motif has appreciable potential for further manipulation. The carbonyl group is a versatile moiety that can be used in subsequent synthetic transformations and, through the work pioneered by Caddick and Wilden,[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 **111** was readily converted to sulfonamide **159** in good yield (Scheme 67).



111 **159**

Scheme 67. Conversion of sulfonate **111** to sulfonamide **152**.

From the outset, the elimination of sulfonate from ketone **107** to form enone **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).

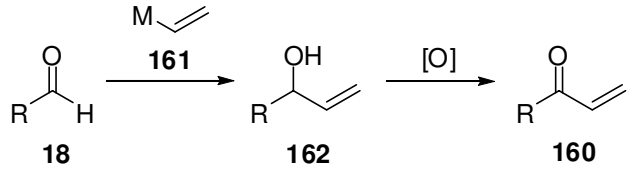


18 **107** **160**

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 **162** to form enone **160** (Scheme 69).[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

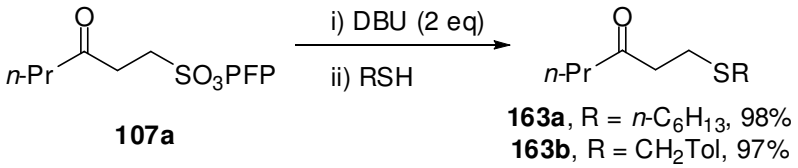
3.1.1 Elimination of PFP-sulfonate

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. CH_2Cl_2, petrol, $CHCl_3$ and Et_2O) were unsuccessful and led to complete recovery of starting material. Since there was literature precedent for the elimination of β-chloroketones with alumina in $CHCl_3$, 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 ^{1}H 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

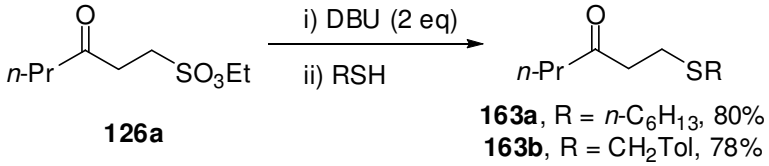
163a and **163b**, indicating that the elimination was essentially quantitative. Furthermore, elimination and thiol addition proceeded in a range of solvents (i.e. CH_2Cl_2, $CHCl_3$, MeOH, Et_2O, PhMe and THF) and in good to excellent yields (72-97%), except on application of triethylamine in CH_2Cl_2, 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.



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).

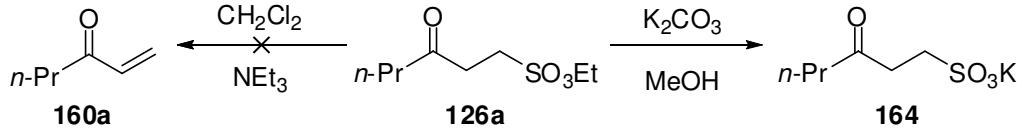


Scheme 72. Elimination of sulfonate from keto-sulfonate **126a**, followed by thiol trapping to form thioethers **163a** and **163b**.

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).

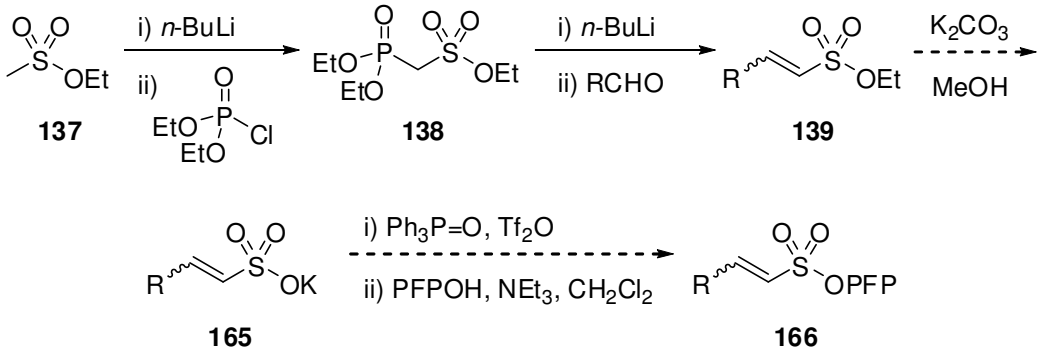
Scheme 73. Conversion of γ-keto-sulfonate **126a** to thioethers **163a** and **163b**.

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**.

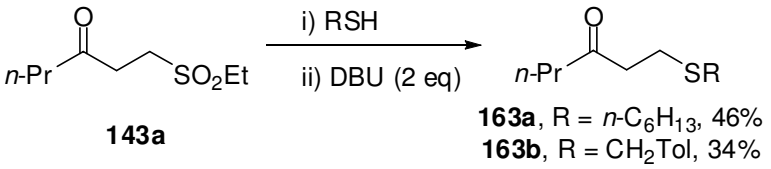
Although the formation of salt **164** is undesirable in view of the elimination chemistry, conversion of ethyl sulfonate **126a** to potassium salt **164** may be useful in context of synthesising β-substituted-PFP-vinyl sulfonates (Scheme 75). The conversion of ethyl sulfonate **137** to β-substituted-vinyl 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.[146]



Scheme 75. Proposed route to vinyl sulfonate **166**.

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,[147] the elimination conditions were applied to sulfone **143a** (Scheme 76). As significantly lower yields were obtained for elimination from keto-sulfone **143a**

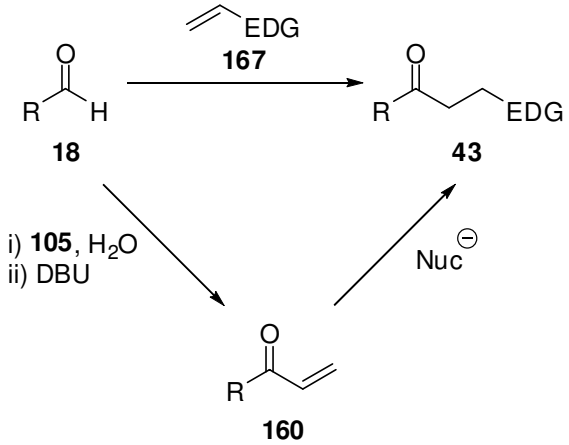
when compared to keto-sulfonates **107a** and **126a**, this highlights an advantage of the keto-sulfonate motif.



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.[99] 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,[148,149] access to a range of other compounds not accessible *via* conventional hydroacylation chemistry may be feasible.

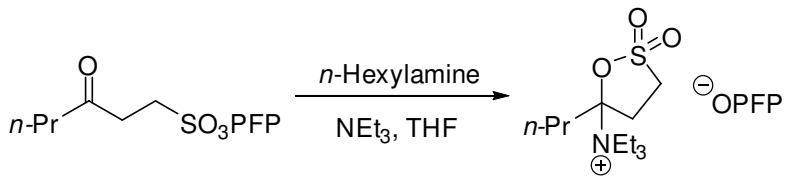


Scheme 77. Hydroacylation-elimination-addition chemistry as an alternative to the direct hydroacylation of electron rich alkenes.

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).[130-132] However, perhaps unsurprisingly, keto-sulfonate **107a** underwent almost exclusive elimination to its corresponding enone under these reaction conditions.[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.

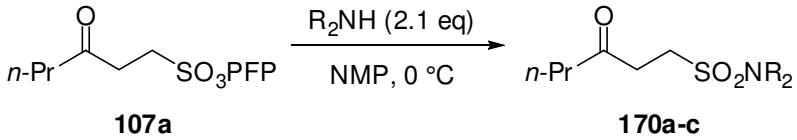


107a **169**

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

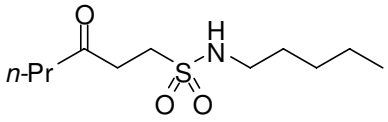
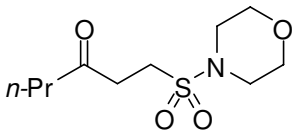
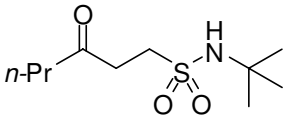
In an attempt to obviate the formation of sultone **169** more polar solvents were employed to encourage direct displacement of pentafluorophenolate. Encouragingly, application of NMP as a solvent gave desired sulfonamide **170a** in 45% yield, with the major side-product being enone derived. Lowering 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.[151-155]



107a **170a-c**

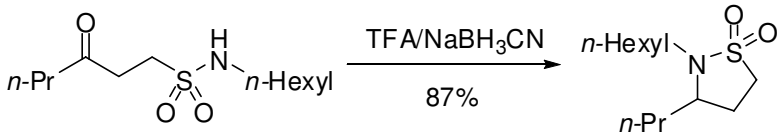
Scheme 79. Conversion of keto-sulfonate **107a** to sulfonamides **170a-c**.

Sulfonamide **170**	Isolated Yield **170**/%
 **170a**	82
 **170b**	32
 **170c**	40

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

Table 13. Yields for conversion of sulfonate **107a** to sulfonamides **170a-c**.

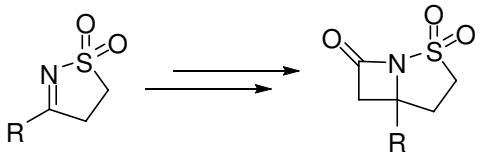
Eager to show the synthetic utility of secondary sulfonamide **170a**, generated by addition of *n*-hexylamine to keto-sulfonate **107a**, a one-pot reductive-cyclisation protocol was developed for the synthesis of sultam **171** in excellent yield (Scheme 80). It is envisaged that a wide range of similar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



170a **171**

Scheme 80. Conversion of γ-keto-sulfonamide **170a** to sultam **171**.

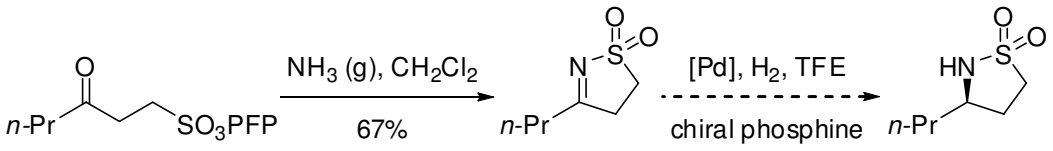
It has been shown that cyclic 3-substituted *N*-sulfonyl imines of the form of imine **172** may be used as intermediates for the formation of *N*-sulfonated β-amino acids (Scheme 81).[156]



172 **173**

Scheme 81. Formation of *N*-sulfonated β-amino acid **173** from imine **172**.

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 CH_2Cl_2 (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]

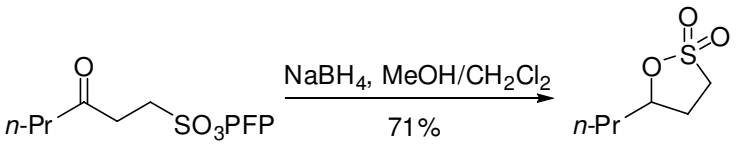


107a **174** **175**

Scheme 82. Application of ammonia to convert keto-sulfonate **107a** to imine **174**, which may be converted to sultam **175**.

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).



107a **176**

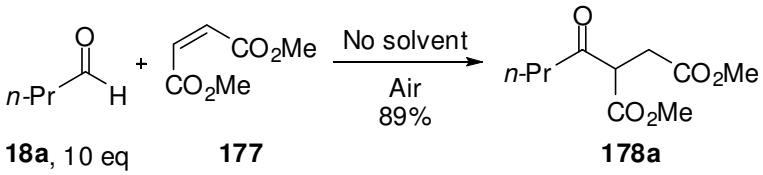
Scheme 83. Facile formation of sultone **176** *via* ketone reduction.

3.3 Conclusion

A series of useful synthetic transformations from the γ-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 γ-keto-sulfonate motif may act as a precursor for the formation of γ-keto-sulfonamides, sultams, *N*-sulfonylimines and sultones.

Chapter 4 Hydroacylation of α,β-unsaturated esters

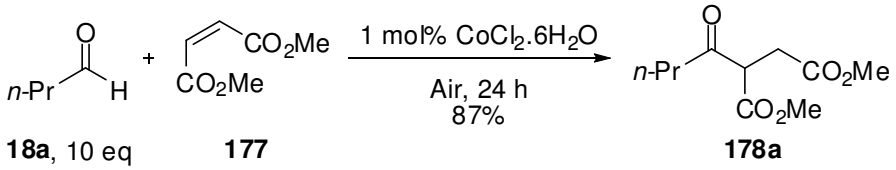
Keen to extend the aerobic aldehyde C-H activation chemistry to the hydroacylation of acceptors other than vinyl sulfonates and sulfones, the use of α,β-unsaturated esters as acyl radical acceptors was explored. Hydroacylation of α,β-unsaturated esters would readily generate 1,4-dicarbonyl compounds; 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).[160]



Scheme 84. Vinogradov's reported hydroacylation of alkene **177** with *n*-butanal **18a**.

4.1 Reproduction of Vinogradov result

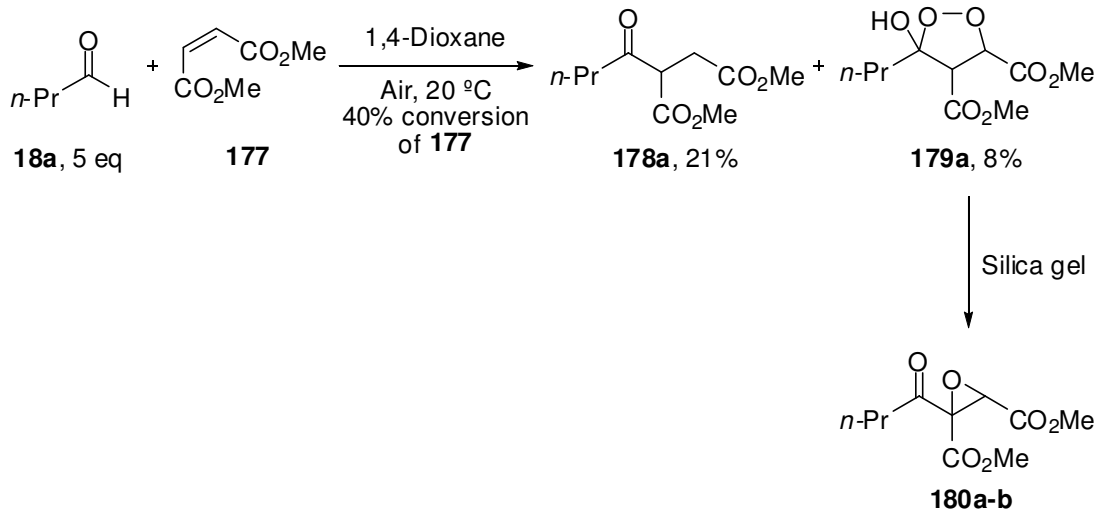
Several attempts to reproduce the reaction of dimethyl maleate **177** with *n*-butanal **18a** (10 equivalents), under the reported conditions, resulted in only low conversion of dimethyl maleate **177** (*ca.* 10%). In view of the cobalt(II)-intensive work being undertaken by Vinogradov at the time, 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.



Scheme 85. Addition of cobalt(II) to a mixture of *n*-butanal **18a** and alkene **177**.

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%).

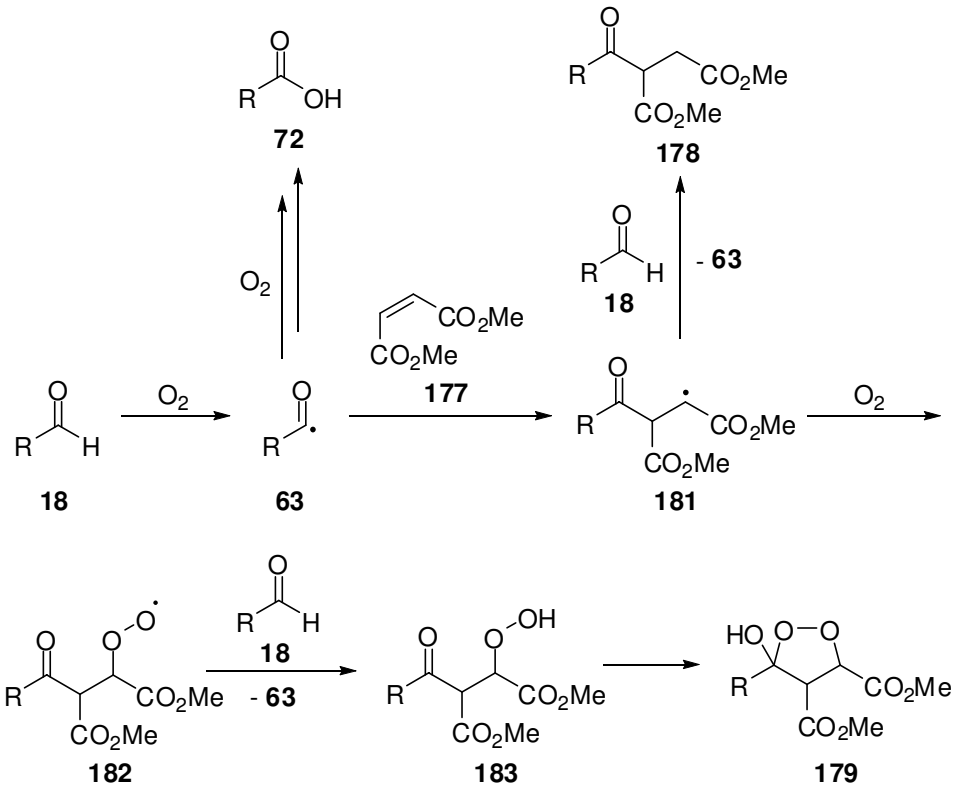


18a, 5 eq **177** **178a**, 21% **179a**, 8%

180a-b

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.

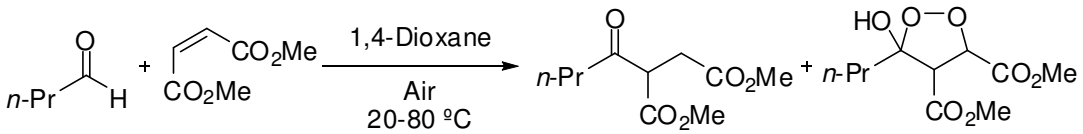
Hydroacylation product **178a** is likely to have formed *via* aerobically initiated conversion of aldehyde **18** to acyl radical **63**, which undergoes addition to alkene **177**, followed by hydrogen atom abstraction to form ketone **178** (Scheme 87). Cyclic peroxide is thought to be derived from reaction of molecular oxygen with adduct radical **181**, which results from acyl radical addition to dimethyl maleate **177**. Resultant peroxy 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.



Scheme 87. Proposed route for the formation of ketone **178**, cyclic peroxide **179** and acid **72**.

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 **179a** and improve the yield of hydroacylation product **178a**, the effect of increasing temperature was explored. Increasing the temperature from 20 ºC to 60 ºC gave an increase in the yield of ketone **178a** (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 **63a** is more likely to be trapped by alkene **177** than react with molecular oxygen to form acid **72a** (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 ºC range as it suppressed formation of peroxide **179a**; consequently encouraging formation of ketone **178a**. This may be a consequence of adduct radical **181a** being more likely to abstract an aldehydic hydrogen atom than undergo addition to molecular oxygen (see Scheme 87).



18a, 5 eq **177** **178a** **179a**

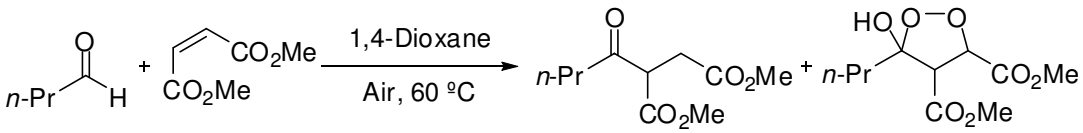
Scheme 88. Hydroacylation of alkene **177** with aldehyde **18a** in 1,4-dioxane.

Temperature/ºC	Conversion **177**[b]/%	Isolated yield **178a**/%	**178a**:**179a**[a]
20	40	21	1:0.38
40	60	27	1:0.25
60	60	35	1:0.19
80	85	24	1:0.15

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}.



18a, 5 eq **177** **178a** **179a**

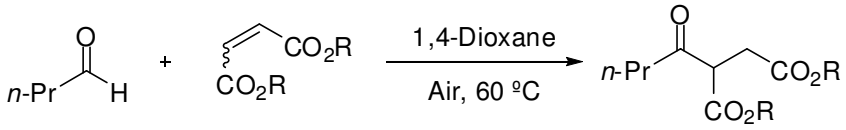
Scheme 89. Hydroacylation of alkene **177** with aldehyde **18a** in 1,4-dioxane.

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

Conditions: *n*-butanal **18a** (5 eq) and dimethyl maleate **177** (1 eq) were stirred in 1,4-dioxane at 60 ºC 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.

Table 15. The effect of concentration on conversion of alkene **177**, yield of ketone **178a** and the ratio of **178a**:**179a**.

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*.



18a, 5 eq | **77**, (*Z*) and R = Et; **184**, (*E*) and R = Me | **78a**, R = Et; **178a**, R = Me

Scheme 90. Hydroacylation of alkenes **77** and **184** with aldehyde **18a** in 1,4-dioxane.

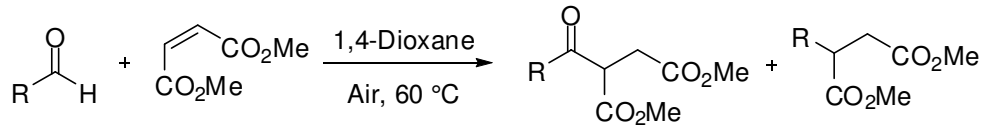
[**77**] or [**184**][a]/mol dm^{-3}	Surface area[b]/cm^2: Volume/cm^3	Isolated yield **78a**/%	Isolated yield **178a**/%
2.00	1:0.16	47	30
0.33	1:0.96	68	62
0.20	1:1.61	55	50

Conditions: *n*-butanal **18a** (5 eq) and alkene (1 eq) were stirred in 1,4-dioxane at 60 ºC 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**.

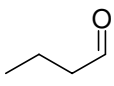
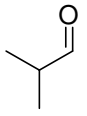
4.2.2 Aldehyde scope

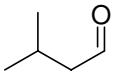
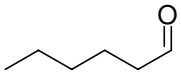
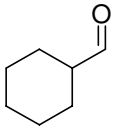
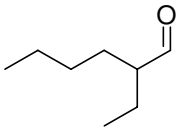
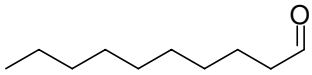
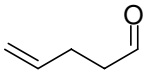
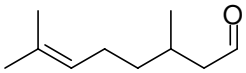
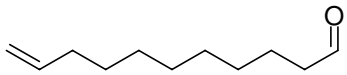
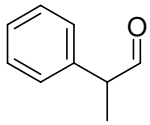
With optimised conditions in hand, the hydroacylation protocol was applied to the reaction of dimethyl maleate **177** with a selection of aldehydes (Table 17). The aldehydes were specifically chosen in view of their broad auto-oxidation rate profiles (see Section 2.2).



18, 5 eq | **177** | **178** | **185**

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

Entry	Aldehyde **18**	Time/ days	Yield **178**/%	Yield **185**/%
1	 **18a**	3	70	0
2	 **18b**	5	21[a,b]	26[a,b]

3	 **18c**	3	57	0
4	 **18d**	3	76	0
5	 **18e**	10	56[a]	21[a]
6	 **18f**	9	25[a]	36[a]
7	 **18g**	9	60	0
8	 **18n**	5	0[c]	0[c]
9	 **18o**	5	0[c]	0[c]
10	 **18v**	10	0[d]	0[d]
11	 **18w**	10	0[d]	0[d]

Conditions: aldehyde (5 eq) and dimethyl maleate **177** (1 eq) were stirred in 1,4-dioxane at 60 ºC 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 ^1H 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**.

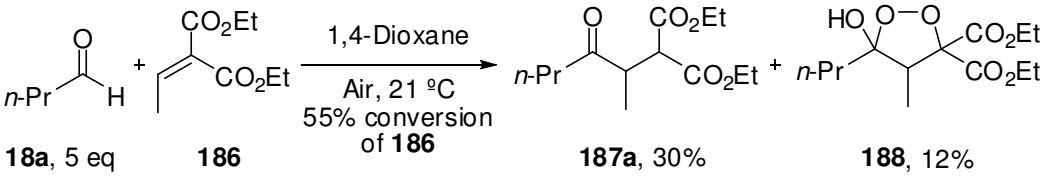
Table 17. Yields for the formation of ketone **178** and decarbonylated addition product **185**.

Hydroacylation of dimethyl maleate **177** with primary aldehydes **18a, 18c**, **18d** and **18g** gave consistently good yields across the series (Table 17, Entry 1, 3, 4 and 7). However, reaction of alkene **177** with *i*-butanal **18b** (Table 17, Entry 2) only reached 55% consumption of alkene due to rapid oxidation of *i*-butanal **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).

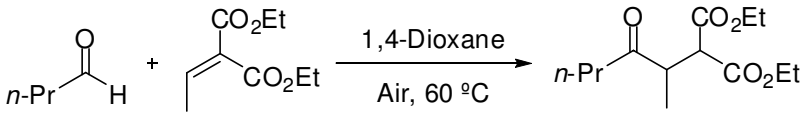


18a, 5 eq **186** **187a**, 30% **188**, 12%

Scheme 92. Hydroacylation of alkene **186** with aldehyde **18a** in 1,4-dioxane.

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).



18a, 5 eq **186** **187a**

Scheme 93. Hydroacylation of alkene **186** with *n*-butanal **18a** at 60 ºC.

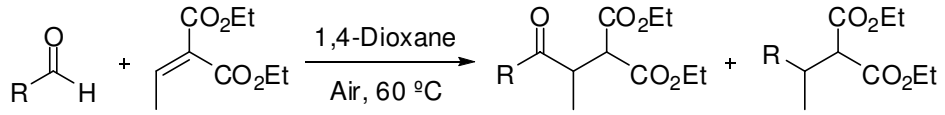
Entry	[**186**][a]/mol dm^{-3}	Surface area/cm^2: Volume/cm^3	Isolated yield **187a**/%
1	5.00	1:0.06	71
2	2.00	1:0.16	70
3	1.00	1:0.32	76
4	0.33	1:0.96	71

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**.

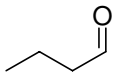
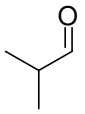
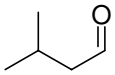
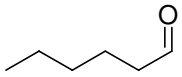
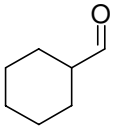
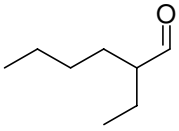
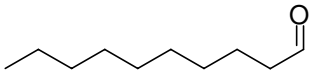
4.3.1 Aldehyde scope

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.



18, 5 eq **186** **187** **189**

Scheme 94. Hydroacylation of alkene **186** with a range of aldehydes in 1,4-dioxane.

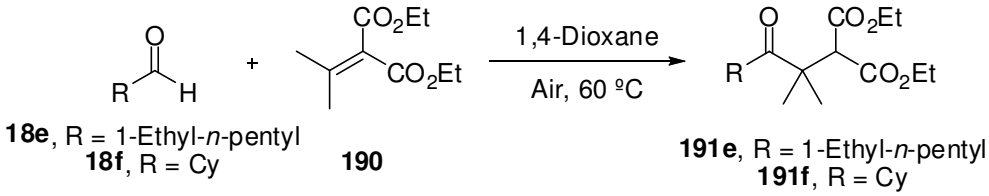
Entry	Aldehyde **18**	Time/ days	Yield **187**/%	Yield **189**/%
1	 **18a**	3	76	0
2	 **18b**	5	42[a,b]	14[a,b]
3	 **18c**	3	60	0
4	 **18d**	3	72	0
5	 **18e**	10	74	5
6	 **18f**	9	52	20
7	 **18g**	9	72	0

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^{-3} before addition of aldehyde. All reactions proceeded with 100% conversion of alkene **186** unless stated otherwise. [a] Determined by integration of ^1H NMR relative to pentachlorobenzene as an internal standard at 100% consumption of aldehyde and [b] 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.



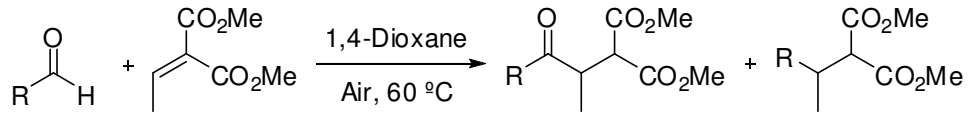
18e, R = 1-Ethyl-*n*-pentyl
18f, R = Cy

190

191e, R = 1-Ethyl-*n*-pentyl
191f, R = Cy

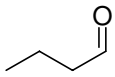
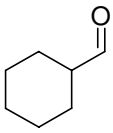
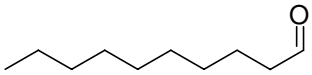
Scheme 95. Hydroacylation of alkene **190** with aldehydes **18e** and **18f** (5 equivalents) in 1,4-dioxane.

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.



18, 5 eq **192** **193** **194**

Scheme 96. Hydroacylation of alkene **192** with aldehydes **18a**, **18e** and **18g** in 1,4-dioxane.

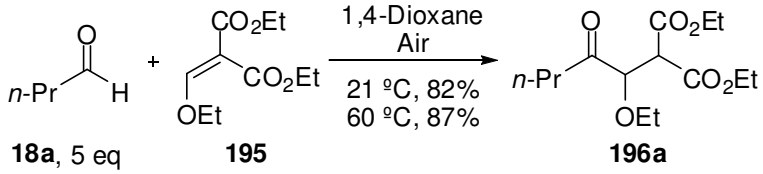
Entry	Aldehyde **18**	Time/ days	Yield **193**/%	Yield **194**/%
1	 **18a**	3	70	0
2	 **18e**	10	71	6
3	 **18g**	9	67	0

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**.

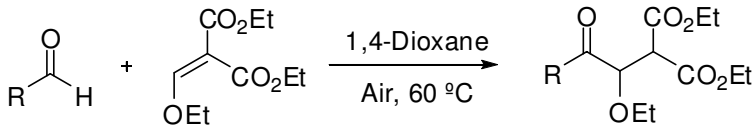
4.3.2 Hydroacylation of 2-alkoxy-1,1-diester alkenes

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.



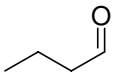
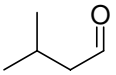
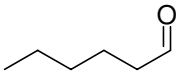
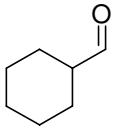
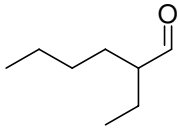
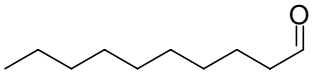
Scheme 97. Hydroacylation of alkene **195** with aldehyde **18a**.

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.



18, 5 eq **195** **196**

Scheme 98. Hydroacylation of alkene **195** with a range of aldehydes in 1,4-dioxane.

Entry	Aldehyde **18**	Time/ days	Conversion **195**/%	Yield **196**/%
1	 **18a**	5	100	87[a]
2	 **18c**	5	100	85
3	 **18d**	3	100	87
4	 **18e**	5	35[a]	24[a]
5	 **18f**	3	10[a]	0[a]
6	 **18g**	9	100	89

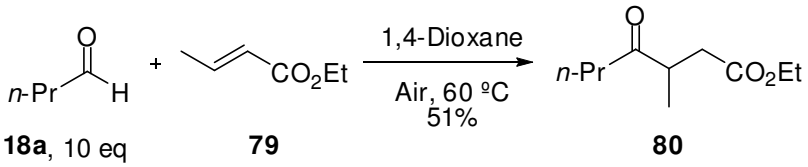
Conditions: aldehyde (5 eq) and alkene **195** (1 eq) were stirred in 1,4-dioxane at 60 ºC at an initial concentration of alkene **195** in 1,4-dioxane of 2 mol dm^{-3} before addition of aldehyde.
[a] Determined by integration of ^{1}H NMR relative to pentachlorobenzene as an internal standard at 100% 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 α,β-unsaturated-ester.



18a, 10 eq **79** **80**

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

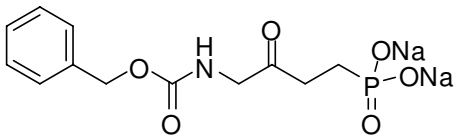
4.5 Conclusion

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 α,β-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 α,β-unsaturated-ester, ethyl crotonate **79**.

Chapter 5 Hydroacylation 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[161-166] and biology as non-hydrolysable phosphate mimetics and inhibitors of phosphoglycerate kinase and β-lactamase.[167-170] For example, γ-ketophosphonate **197** has been shown to be an effective β-lactamase inhibitor.[168]



197

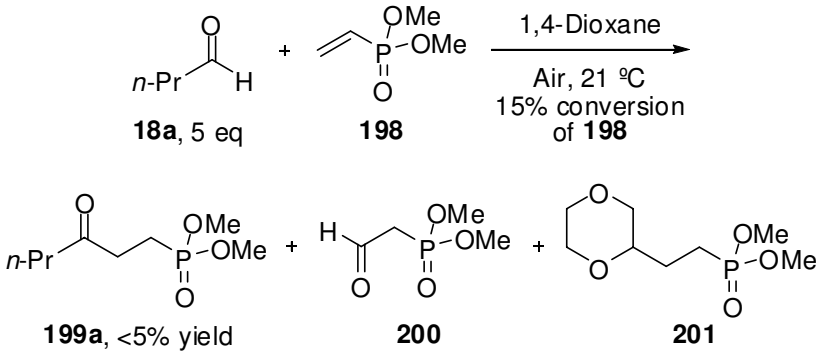
Figure 5. Effective β-lactamase inhibitor **197**.

Currently, the most commonly employed method for the preparation of γ-ketophosphonates is based on conjugate addition to an enone.[166,171,172] Although alternative protocols have been developed for the synthesis of γ-ketophosphonates, including hydroacylation 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.[173-177] In view of this, the hydroacylation 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 hydroacylation of dimethyl vinyl phosphonate

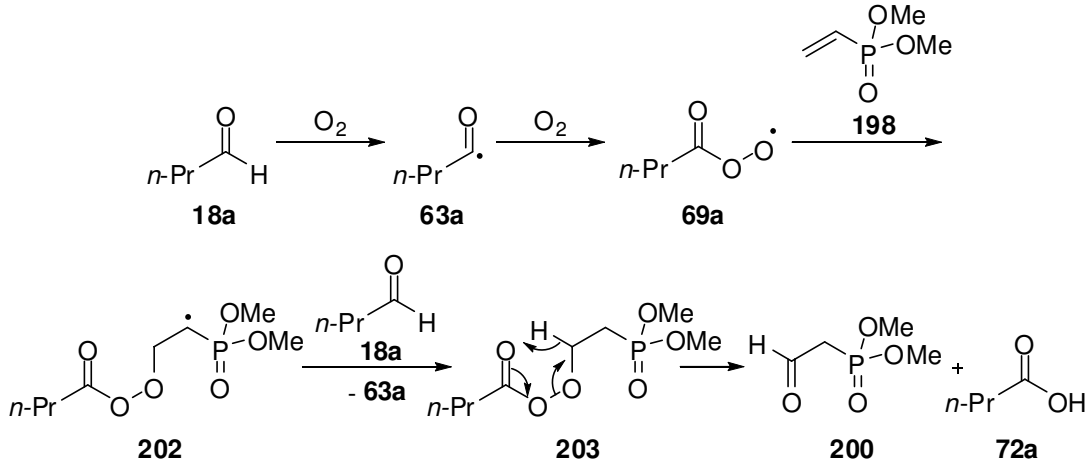
Initially, hydroacylation of dimethyl vinyl phosphonate **198** with *n*-butanal **18a** at 21 °C in the presence of water was investigated. However, no desired hydroacylation product and low conversion of vinyl phosphonate **198** were observed (*ca.* 5%). Application of additional quantities of *n*-butanal **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 ^{1}H 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**.

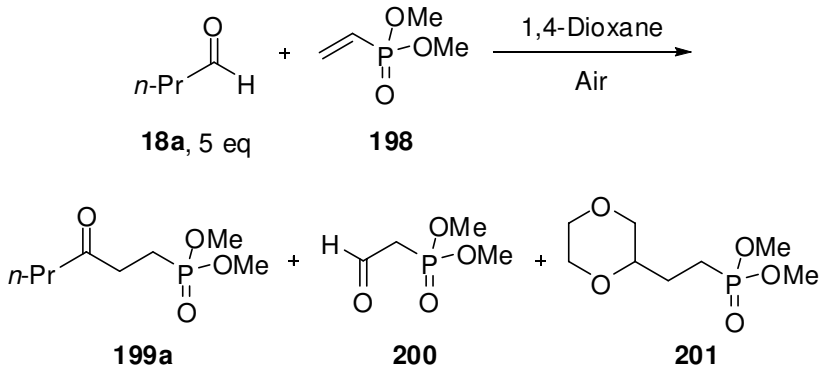
Consistent with previous studies with other alkene acceptors, reaction between *n*-butanal **18a** and vinyl phosphonate **198** was completely suppressed by addition of BHT (5 mol%), which implies a radical mechanism. γ-Ketophosphonate **199a** is thought to be formed *via* a mechanism analogous to 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**.

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 γ-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 γ-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 γ-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 γ-ketophosphonate **199a** (Table 22, Entries 7-9).



Scheme 102. Hydroacylation of vinyl phosphonate **198** with *n*-butanal **18a** in 1,4-dioxane.

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

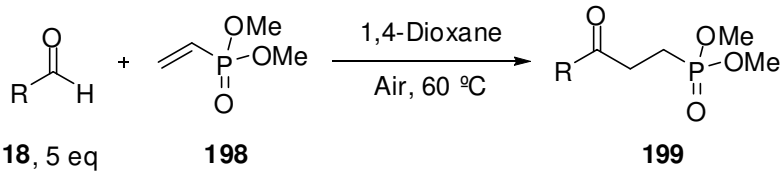
Conditions: *n*-butanal **18a** (5 eq) and vinyl phosphonate **198** (1 eq) were stirred in 1.4-dioxane.
[a] Concentration refers to initial concentration of vinyl phosphonate **198** in 1,4-dioxane before addition of aldehyde **18a**.

Table 22. Yield of ketone **199a** and conversion of vinyl phosphonate **198** under various reaction conditions.

5.3 Aldehyde scope

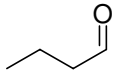
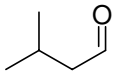
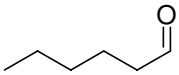
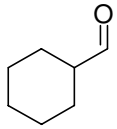
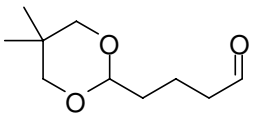
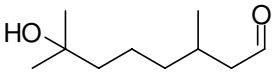
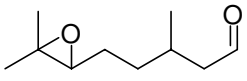
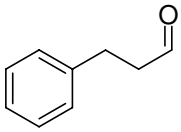
The scope of the aldehyde in this hydroacylation protocol was next evaluated using the optimised conditions developed. Hence, aldehydes demonstrating a varying

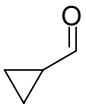
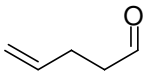
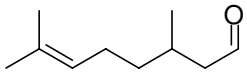
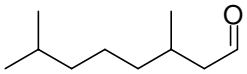
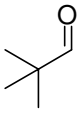
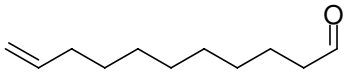
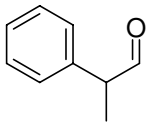
propensity to undergo auto-oxidation (see Section 2.2) and aldehydes bearing a range of functional groups were selected for the hydroacylation study (Scheme 103, Table 23).



18, 5 eq **198** **199**

Scheme 103. Hydroacylation of vinyl phosphonate **198** with a range of aldehydes in 1,4-dioxane at 60 °C.

Entry	Aldehyde **18**	Time/h	Yield **199**/%
1	 **18a**	24	70
2	 **18c**	24	65
3	 **18d**	24	72
4[a]	 **18e**	24	60
5	 **18h**	24	68[a]
6	 **18i**	24	71
7	 **18j**	24	74
8	 **18k**	24	62[b]
9	 **18l**	72	62[b]

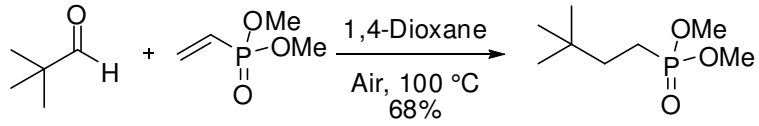
10	 **18m**	60	57
11	 **18n**	24	0
12	 **18o**	72	0
13	 **18p**	24	68
14	 **18q**	24	0
15	 **18v**	120	0[c]
16	 **18w**	120	0[c]

Conditions: aldehyde (5 eq) and vinyl phosphonate **198** (1 eq) were stirred at 60 ºC 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 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 β-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

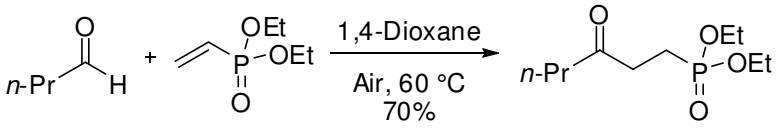
under the reaction conditions. In support of this, the corresponding saturated citronellal, aldehyde **18p**, underwent successful hydroacylation of vinyl phosphonate **198**, to afford ketone **199p** in good yield (Table 23, Entry 13). The absence of the formation of γ-ketophosphonate **199q** for 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).



18q, 5 eq **198** **204**

Scheme 104. *tert*-Butyl radical addition to vinyl phosphonate **198**.

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).



18a, 5 eq **205** **206**

Scheme 105. Hydroacylation of vinyl phosphonate **205** with *n*-butanal **18a**.

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).[178]

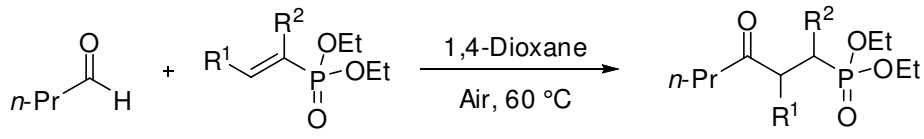
207

208, R^1 = Me, R^2 = H
209, R^1 = H, R^2 = Me

210, R^1 = Me, R^2 = H, 39%
211, R^1 = H, R^2 = 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.



18a, 5 eq

210, R^1 = Me, R^2 = H
211, R^1 = H, R^2 = Me

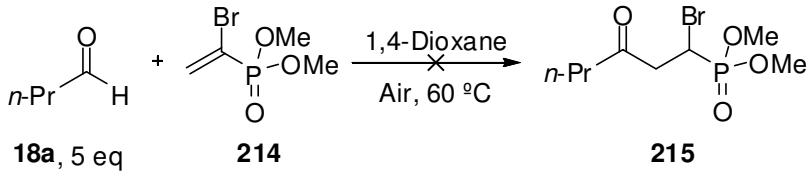
212, R^1 = Me, R^2 = H, 60%*
213, R^1 = H, R^2 = Me, 0%

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.



18a, 5 eq **214** **215**

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

5.5 Conclusion

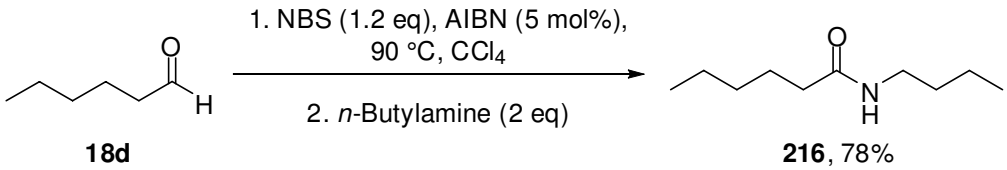
Through careful optimisation, vinyl phosphonates have been shown to undergo aerobic hydroacylation. Moreover, a range of aldehydes, including those with acetal, alcohol, epoxide and aryl functionalities, are shown to be tolerant of the methodology. Finally, although no α-substituted vinyl phosphonates 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

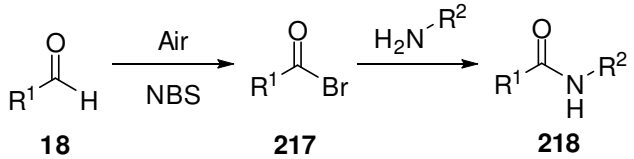
Marko previously reported the conversion of aldehydes to amides through the treatment of aldehydes with NBS and 5 mol% AIBN, followed by addition of an amine.[179] For example, *n*-hexanal **18d** was converted to amide **216** in 78% yield (Scheme 109).[179]



18d **216**, 78%

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

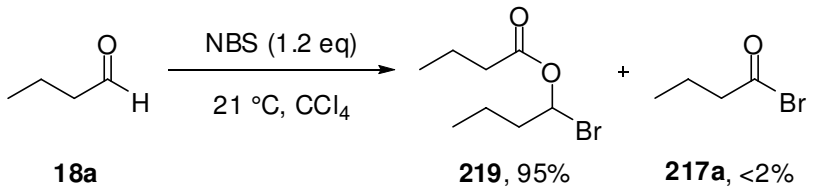
Presumably, conversion of aldehyde **18d** to amide **216** proceeds through an acyl radical that is trapped by bromine to form an acid bromide, which is then converted to an amide on treatment with *n*-butylamine. As reaction proceeds through an acyl radical intermediate, the use of aerobic aldehyde 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.



18 **217** **218**

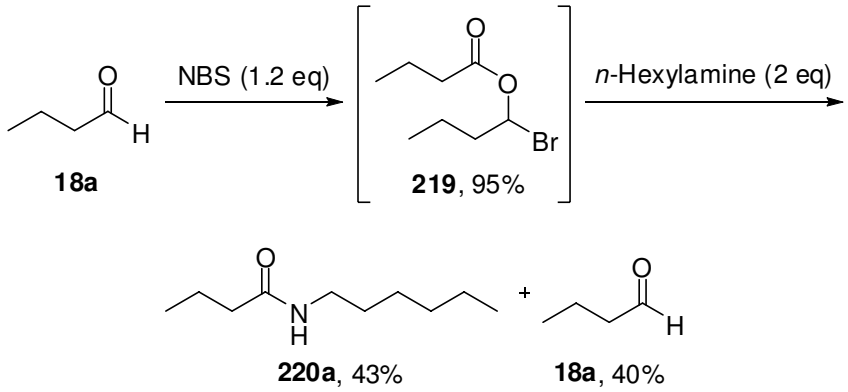
Scheme 110. Proposed conversion of an aldehyde **18** to an amide **218** *via* acid bromide **217**.

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 ºC, or use of CH_2Cl_2, benzene, THF, Et_2O or EtOAc as solvent, also had no positive impact on the formation of acid bromide **217a** in preference to ester **219**.



Scheme 111. Reaction of aldehyde **18a** with NBS at 21 ºC in 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**.

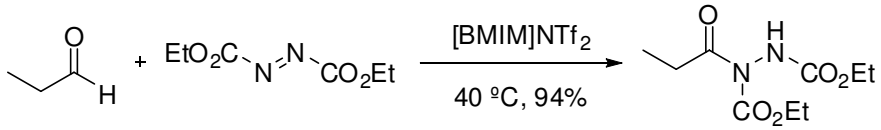


Scheme 112. Reaction of *n*-butanal **18a** with NBS, followed by addition of *n*-hexylamine to form amide **220a** and *n*-butanal **18a**.

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.[180,181] For example, diethyl azodicarboxylate **221** was hydroacylated with *n*-propanal **18x** (2 equivalents) in the presence of an ionic liquid at 40 ºC 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.

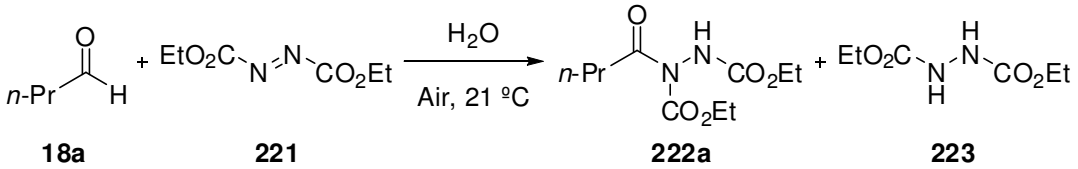


18x, 2 eq **221** **222x**

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 ºC (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), and gratifyingly, afforded hydrazide **222a** in excellent yield, 90%, based on *n*-butanal **18a** as the limiting reagent.



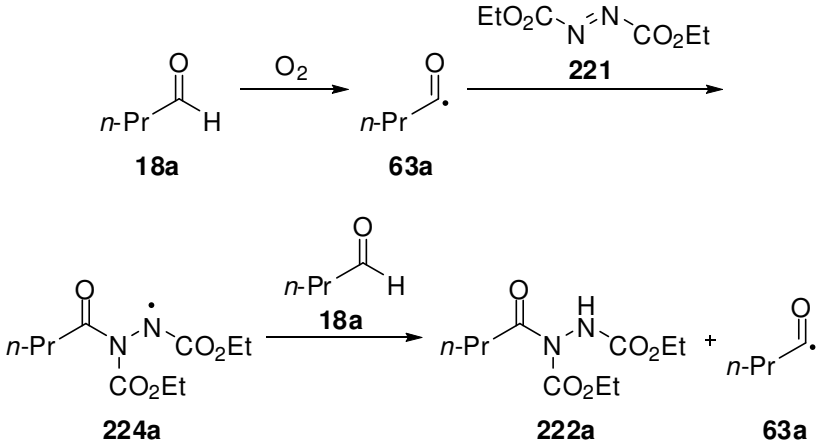
Scheme 114. Hydroacylation of azodicarboxylate **221** with *n*-butanal **18a**.

Entry	**18a**/eq	**221**/eq	Isolated Yield **222a**/%
1	2	1	92
2	1.5	1	90
3	1	1	70
4	1	1.2	90

Conditions: *n*-butanal **18a** and diethyl azodicarboxylate **221** were reacted in the presence of H_2O 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).

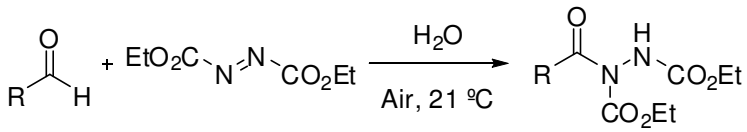


Scheme 115. Proposed mechanism for the formation hydrazide **222a**.

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.

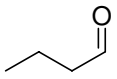
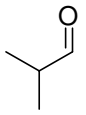
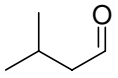
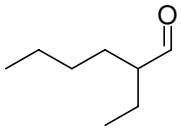
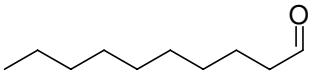
6.2.1 Aldehyde scope

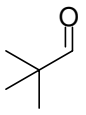
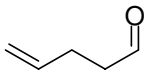
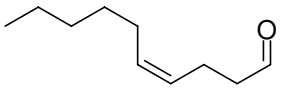
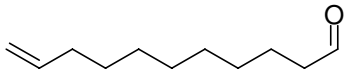
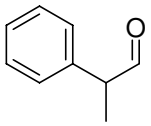
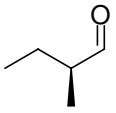
At this juncture, the optimised conditions developed for the conversion of *n*-butanal **18a** to hydrazide **222a** were applied to a range of aldehydes to hydroacylate diethyl azodicarboxylate **221** (Scheme 116, Table 25).



18 **221** **222**

Scheme 116. Hydroacylation of diethyl azodicarboxylate **221** with a range of aldehydes.

Entry	Aldehyde	Time/h	Isolated Yield **222**[a]/%
1	 **18a**	24	90
2	 **18b**	24	72
3	 **18c**	24	92
4	 **18f**	24	90
5	 **18g**	24	82

6	 **18q**	24	64
7	 **18n**	24	60
8	 **18y**	48	70
9	 **18v**	48	85
10	 **18w**	72	67
11	 **152**[b]	24	88,[b] **225**

Conditions: aldehyde (1 eq) and diethyl azodicarboxylate **221** (1.2 eq) were reacted in the presence of H_2O at 21 ºC. [a] Unless otherwise stated and [b] 98% ee. Similar reactions have been carried out by others within the Caddick group (see Appendix).

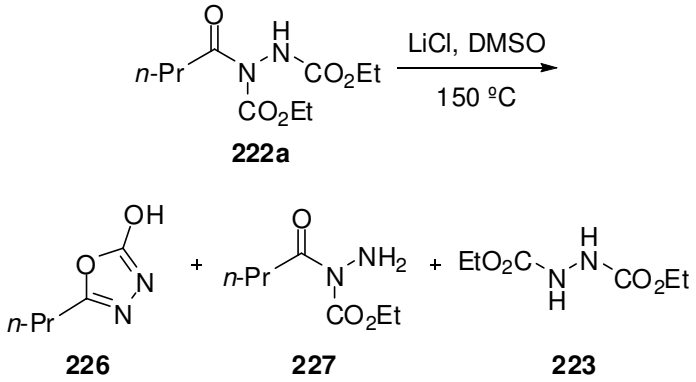
Table 25. Yields and reaction time for formation of hydrazides **222** and **225**.

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).

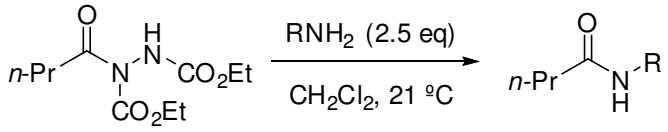
6.3 Reactions of acyl hydrazides

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).



Scheme 117. Attempted Krapcho decarbonylation of hydrazide **222a**.

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 CH_2Cl_2 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.

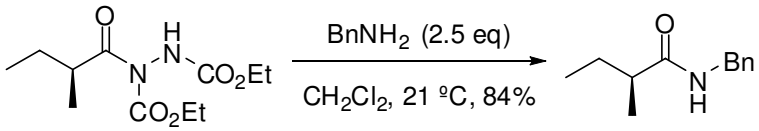


222a

220a, R = *n*-hexyl, 96%
220b, R = allyl, 95%

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

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.



225 **228**

Scheme 119. Conversion of hydrazide **225** to amide **228**.

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.[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.[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.

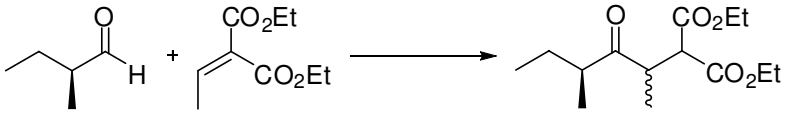
Conclusions and Further Work

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, α,β-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 γ-keto-sulfonate motif may act as a precursor for the formation of γ-keto-sulfonamides, sultams, *N*-sulfonylimines and sultones. Perhaps most significantly, the γ-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,[187] may also be of interest.



152 **186** **229**

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 ºC).

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 ºC 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 $J_{H\text{-}H}$ 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

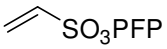
All hydroacylation reactions were carried out in a carousel tube (15 cm × 2 cm) equipped with an octagon-shaped magnetic stirrer bar (12.7 mm × 3 mm) fitted with a carousel tube screw cap lid (carousel equipment purchased from Radleys Discovery Technologies).

Miscellaneous

Melting points were measured with a Gallenkamp apparatus and are uncorrected. Optical rotations ($[\alpha]_D$) 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[188]

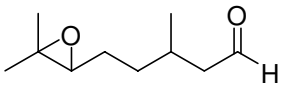


A solution of NEt_3 (13.9 g, 19.2 mL, 137.5 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1 h to a solution of 2-chloroethane-1-sulfonyl chloride (10.2 g, 62.5 mmol) and pentafluorophenol (11.5 g, 62.5 mmol) in CH_2Cl_2 (100 mL) at -15 °C. The reaction mixture was allowed to warm to 21 °C, diluted with CH_2Cl_2 (100 mL), washed with sat. $NaHCO_3$ (2 × 250 mL) and the solvent removed *in vacuo*. The reaction mixture was diluted with Et_2O (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% Et_2O/petrol) and recrystallisation (petrol) gave pentafluorophenyl ethenesulfonate as white crystals (13.6 g, 49.6 mmol, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.3 (CH_2), 131.8 (CH); IR (solid) 3078, 1652, 1514, 1385, 1183 cm^{-1}; LRMS (EI) 274 (24, $[M]^{+\cdot}$), 184 (100); HRMS (EI) calcd for $C_8H_3F_5O_3S$ $[M]^{+\cdot}$ 273.9718, observed 273.9725.

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

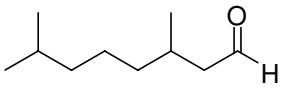


To a stirring solution of (±)-citronellal (771 mg, 902 μL, 5 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of *m*-CPBA (1.04 g, 6 mmol) in CH_2Cl_2 (10 mL) at 0 °C under an atmosphere of argon. The reaction mixture was allowed to warm to 21 °C and stirred for a further 90 min. The reaction mixture was filtered and the filtrate washed with sat. K_2CO_3 (3 × 30 mL), dried ($MgSO_4$) 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.

^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$)[†] δ 202.7 (CH), 202.6 (CH), 64.3 (CH), 64.2 (CH), 58.4 (C), 58.3 (C), 51.0 (CH_2), 50.9 (CH_2), 33.5 (CH_2), 27.9 (CH), 26.4 (CH_2), 26.4 (CH_2), 25.0 (CH_3), 19.9 (CH_3), 19.8 (CH_3), 18.7 (CH_3), 18.7 (CH_3); IR (thin film) 2960, 2927, 1722 cm^{-1}; LRMS (FAB) 193 (100, $[M+Na]^+$); HRMS (FAB) calcd for $C_{10}H_{18}O_2Na$ $[M+Na]^+$ 193.1205, observed 193.1208.

[†] 20C expected, 17C observed.

3,7-Dimethyloctanal 18p[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_2 three times and the solution left to stir under a H_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 *in vacuo* to afford 3,7-dimethyloctanal as a colourless oil (546 mg, 3.50 mmol, 70%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 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); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.4 (CH), 51.2 (CH_2), 39.1 (CH_2), 37.2 (CH_2), 28.3 (CH), 28.0 (CH), 24.8 (CH_2), 22.8 (CH_3), 22.7 (CH_3), 20.1 (CH_3); IR (thin film) 2955, 2927, 2870, 1726 cm^{-1}.

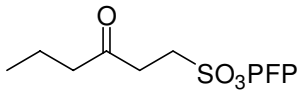
Typical procedure for the synthesis of ketone sulfonate esters – Method A

5% H_2O_2 (0.05 mmol) and aldehyde (2 mmol) were added to a solution of pentafluorophenyl ethenesulfonate **105** (1 mmol) on H_2O (500 μL) and the reaction mixture stirred at 21 °C for the time specified (see below). The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with H_2O (50 mL), dried ($MgSO_4$), the solvent removed *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_2O (500 μL) and the reaction mixture stirred at 21 °C for the time specified (see below). The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with H_2O (50 mL), dried ($MgSO_4$), the solvent removed *in vacuo* and purified as described below to afford the desired ketone sulfonate ester.

Pentafluorophenyl 3-oxohexane-1-sulfonate 107a[190]

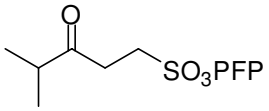


Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-oxohexane-1-sulfonate as white crystals (291 mg, 0.84 mmol, 84%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH_2Cl_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{12}H_{12}F_5O_4S$ $[M+H]^+$ 347.0371, observed 347.0369.

Pentafluorophenyl 4-methyl-3-oxopentane-1-sulfonate 107b[191]

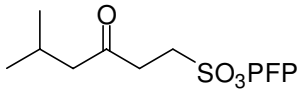


Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) and recrystallisation (petrol) gave pentafluorophenyl 4-methyl-3-oxopentane-1-sulfonate as white crystals (194 mg, 0.56 mmol, 56%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) and recrystallisation (petrol) gave pentafluorophenyl 4-methyl-3-oxopentane-1-sulfonate as white crystals (138 mg, 0.40 mmol, 40%).

m.p. 53-55 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76-3.74 (m, 2H), 3.19-3.17 (m, 2H), 2.68 (septet, *J* = 7.0 Hz, 1H), 1.17 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8 (C), 47.3 (CH_2), 41.1 (CH), 33.8 (CH_2), 18.2 (CH_3); IR (solid) 2976, 2937, 1716, 1518, 1385, 1186 cm^{-1}; LRMS (CI) 347 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{12}H_{12}F_5O_4S$ $[M+H]^+$ 347.0371, observed 347.0385.

Pentafluorophenyl 5-methyl-3-oxohexane-1-sulfonate 107c[192]

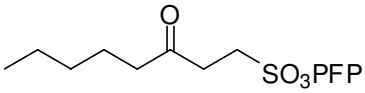


Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) and recrystallisation (petrol) gave pentafluorophenyl 5-methyl-3-oxohexane-1-sulfonate as white crystals (277 mg, 0.77 mmol, 77%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) and recrystallisation (petrol) gave pentafluorophenyl 5-methyl-3-oxohexane-1-sulfonate as white crystals (266 mg, 0.74 mmol, 74%).

m.p. 62-64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75-3.73 (m, 2H), 3.11-3.09 (m, 2H), 2.40 (d, *J* = 7.0 Hz, 2H), 2.16 (nonet, *J* = 6.5 Hz, 1H), 0.94 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7 (C), 51.7 (CH_2), 47.0 (CH_2), 36.5 (CH_2), 24.7 (CH), 22.5 (CH_3); IR (solid) 2963, 1722, 1518, 1379, 1186 cm^{-1}; LRMS (CI) 361 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{13}H_{14}F_5O_4S$ $[M+H]^+$ 361.0528, observed 361.0537.

Pentafluorophenyl 3-oxooctane-1-sulfonate 107d

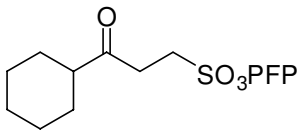


Using Method A, the reaction was complete after 2 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-oxooctane-1-sulfonate as white crystals (281 mg, 0.75 mmol, 75%).

Using Method B, the reaction was complete after 6 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-oxooctane-1-sulfonate as white crystals (280 mg, 0.75 mmol, 75%).

m.p. 45-47 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1 (C), 47.1 (CH_2), 42.8 (CH_2), 36.0 (CH_2), 31.3 (CH_2), 23.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3); IR (solid) 2937, 2871, 1721, 1520, 1388, 1183 cm^{-1}; LRMS (CI) 375 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{14}H_{16}F_5O_4S$ $[M+H]^+$ 375.0690, observed 375.0685.

Pentafluorophenyl 3-cyclohexyl-3-oxopropane-1-sulfonate 107e[193]

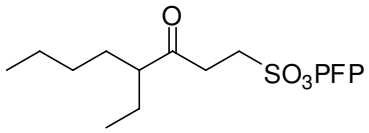


Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-cyclohexyl-3-oxopropane-1-sulfonate as white crystals (305 mg, 0.79 mmol, 79%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH_2Cl_2/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; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1 (C), 50.8 (CH), 47.2 (CH_2), 34.0 (CH_2), 28.4 (CH_2), 25.7 (CH_2), 25.5 (CH_2); IR (solid) 2936, 2858, 1714, 1519, 1388, 1183 cm^{-1}; LRMS (CI) 387 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{15}H_{16}F_5O_4S$ $[M+H]^+$ 387.0690, observed 387.0689.

Pentafluorophenyl 4-ethyl-3-oxooctane-1-sulfonate 107f[194]

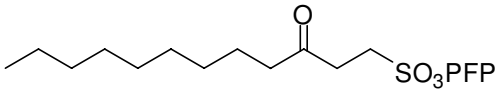


Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) gave pentafluorophenyl 4-ethyl-3-oxooctane-1-sulfonate as a colourless oil (350 mg, 0.87 mmol, 87%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) gave pentafluorophenyl 4-ethyl-3-oxooctane-1-sulfonate as a colourless oil (334 mg, 0.83 mmol, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9 (C), 53.9 (CH), 47.0 (CH_2), 35.6 (CH_2), 30.9 (CH_2), 29.6 (CH_2), 24.6 (CH_2), 22.8 (CH_2), 13.8 (CH_3), 11.7 (CH_3); IR (thin film) 2962, 2935, 2877, 1714, 1516, 1384, 1183 cm^{-1}; LRMS (CI) 403 (51, $[M+H]^+$), 216 (100); HRMS (CI) calcd for $C_{16}H_{20}F_5O_4S$ $[M+H]^+$ 403.0997, observed 403.0981.

Pentafluorophenyl 3-oxododecane-1-sulfonate 107g



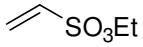
Using Method A, the reaction was complete after 1 h. Purification by column chromatography (30%-70% CH_2Cl_2/petrol) and recrystallisation (petrol) gave pentafluorophenyl 3-oxododecane-1-sulfonate as white crystals (284 mg, 0.66 mmol, 66%).

Using Method B, the reaction was complete after 3 h. Purification by column chromatography (30%-70% CH_2Cl_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; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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}C NMR (125 MHz, $CDCl_3$) δ 205.1 (C), 47.0 (CH_2), 42.8 (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 (CI) 431 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{18}H_{24}F_5O_4S$ $[M+H]^+$ 431.1310, observed 431.1290.

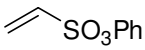
Ethyl ethenesulfonate 125



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_2Cl_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_2Cl_2 (100 mL) at -15 °C. The reaction mixture was allowed to warm to 21 °C, diluted with CH_2Cl_2 (100 mL), washed with sat. $NaHCO_3$ (2 × 250 mL) and the solvent removed *in vacuo*. The reaction mixture was diluted with Et_2O, 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}H NMR (500 MHz, $CDCl_3$) δ 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}C NMR (125 MHz, $CDCl_3$) δ 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 (CI) 137 (26, $[M+H]^+$), 109 (100); HRMS (CI) calcd for $C_4H_9O_3S$ $[M+H]^+$ 137.0272, observed 137.0273.

Phenyl ethenesulfonate 128



A solution of NEt_3 (31.2 g, 43 mL, 307 mmol) in CH_2Cl_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_2Cl_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_2O (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

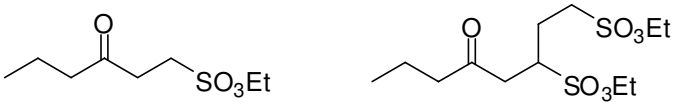
removed *in vacuo*. Purification by column chromatography (20%-30% Et_2O/Petrol) gave phenyl ethenesulfonate as a white solid (8.4 g, 50 mmol, 82%).

m.p. 39-42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5 (C), 132.2 (C), 131.7 (CH_2), 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 $C_8H_9O_3S$ $[M+H]^+$ 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 H_2O (500 μL) and the reaction mixture stirred at 21 °C for the time specified (see below). The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with H_2O (50 mL), dried ($MgSO_4$), 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

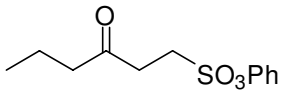


Using Method C, the reaction was complete after 96 h. Purification by column chromatography (20%-60% EtOAc/petrol) gave ethyl 3-oxohexane-1-sulfonate as a yellow oil (114 mg, 0.55 mmol, 55%) and 1,3-diethyl 5-oxooctane-1,3-disulfonate as a colourless oil (48 mg, 0.14 mmol, 14%).

Data for **126a**: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1 (C), 66.7 (CH_2), 44.7 (CH_2), 44.3 (CH_2), 36.0 (CH_2), 17.1 (CH_2), 15.0 (CH_3), 13.6 (CH_3); IR (thin film) 2964, 2873, 1716, 1350, 1168 cm^{-1}; LRMS (CI) 209 (100, $[M+H]^+$); HRMS (CI) calcd for $C_8H_{17}O_4S$ $[M+H]^+$ 209.0848, observed 209.0850.

Data for **127a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{12}H_{25}O_7S_2$ $[M+H]^+$ 345.1042; observed 345.1036.

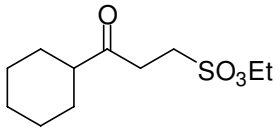
Phenyl 3-oxohexane-1-sulfonate 126b



Using Method C, the reaction was complete after 120 h. Purification by column chromatography (50%-95% CH_2Cl_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, 1370, 1145 cm^{-1}; LRMS (CI) 257 (45, $[M+H]^+$), 163 (100); HRMS (CI) calcd for $C_{12}H_{17}O_4S$ $[M+H]^+$ 257.0848, observed 257.0850.

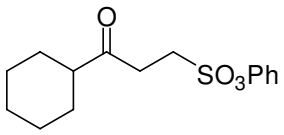
Ethyl 3-cyclohexyl-3-oxopropane-1-sulfonate 126c



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%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.30 (q, *J* = 7.0 Hz, 2H), 3.42-3.39 (m, 2H), 3.04-3.00 (m, 2H), 2.41 (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, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2 (C), 66.7 (CH_2), 50.8 (CH), 44.4 (CH_2), 34.1 (CH_2), 28.4 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 15.0 (CH_3); IR (thin film) 2930, 2855, 1710, 1352, 1168 cm^{-1}; LRMS (EI) 248 (10, $[M]^{+\cdot}$), 139 (100); HRMS (EI) calcd for $C_{11}H_{20}O_4S$ $[M]^{+\cdot}$ 248.1077, observed 248.1066.

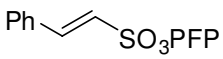
Phenyl 3-cyclohexyl-3-oxopropane-1-sulfonate 126d



Using Method C, the reaction was complete after 120 h. Purification by column chromatography (50%-95% CH_2Cl_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 $C_{15}H_{21}O_4S$ $[M+H]^+$ 297.1161, observed 297.1167.

Pentafluorophenyl (*E*)-2-phenylethenesulfonate 129

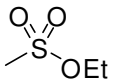


A solution of NEt_3 (2.0 g, 2.8 mL, 19.74 mmol) and pentafluorophenol (2.2 g, 11.8 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 1 h to a solution of 2-phenyl-ethenesulfonyl chloride (2.0 g, 9.87 mmol) in CH_2Cl_2 (100 mL) at -15 °C and the reaction mixture left to stir at this temperature for 20 min. The reaction mixture was left to warm to 21 °C, left to stir for a further 30 min, diluted with CH_2Cl_2 (100 mL), washed with sat. $NaHCO_3$ (3 × 200 mL), 2M HCl (3 × 200 mL) and sat. NaCl (250

mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude residue was triturated with 5% CH_2Cl_2/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 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_8F_5O_3S$ $[M+H]^+$ 351.0114, observed 351.0126.

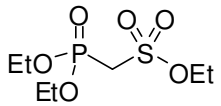
Ethyl methanesulfonate 137[133]



A solution of EtOH (40.2 g, 51 mL, 524 mmol) and NEt_3 (19.4 g, 26.8 mL, 192 mmol) in CH_2Cl_2 (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 °C, stirred for a further 1 h, diluted with CH_2Cl_2 (100 mL), washed with 2M HCl (3 × 250 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford ethyl methanesulfonate as a colourless oil (17.1 g, 139 mmol, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (q, *J* = 7.0 Hz, 2H), 3.00 (s, 3H), 1.42 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.3 (CH_2), 37.6 (CH_3), 15.1 (CH_3); IR (thin film) 2988, 2943, 1343, 1169 cm^{-1}; LRMS (CI) 125 (7, $[M+H]^+$), 109 (100); HRMS (CI) calcd for $C_3H_9O_3S$ $[M+H]^+$ 125.0189, observed 125.0190.

Ethyl (diethoxyphosphoryl)methanesulfonate 138[133]

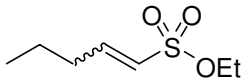


A solution of *n*-butyllithium (1.6M in hexanes, 0.67 g, 6.5 mL, 10.4 mmol) was added to a stirring solution of methanesulfonic acid ethyl ester **137** (1.17 g, 1.0 mL, 9.43 mmol) in dry THF (30 mL) at -78 ºC under an argon atmosphere and the reaction mixture left to stir at -78 ºC for 15 min. Ethyl 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 NH_4Cl (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 H_2O (100 mL), extracted with CH_2Cl_2 (3 × 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (50% Et_2O/CH_2Cl_2) gave ethyl (diethoxyphosphoryl)methanesulfonate as a colourless oil (1.02 g, 3.9 mmol, 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (q, J = 7.0 Hz, 2H), 4.24 (dq, $J_{H\text{-}P}$ = 14.0 and J = 6.0 Hz, 4H), 3.71 (d, $J_{H\text{-}P}$ = 17.0 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H), 1.38 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.4 (CH_2), 63.8 (d, $J_{C\text{-}P}$ = 6.0 Hz, CH_2), 48.0 (d, $J_{C\text{-}P}$ = 139.5 Hz, CH_2), 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz, CH_3), 15.1 (CH_3); IR (thin film) 2985, 2907, 1358, 1263, 1180 cm^{-1}; LRMS (CI) 261 (100, $[M+H]^+$); HRMS (CI) calcd for $C_7H_{18}O_6PS$ $[M+H]^+$ 261.0562, observed 261.0555.

Ethyl (*E*,*Z*)-pent-1-ene-1-sulfonate 139a[133]



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 °C 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 °C 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 °C for 45 min. The reaction mixture was allowed to warm to 21 °C, left to stir for 16 h and the solvent removed *in vacuo*. The crude residue was diluted with H_2O (200 mL), extracted with CH_2Cl_2 (3 × 200 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (50%-75% Et_2O/CH_2Cl_2) 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: ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8 (CH), 124.9 (CH), 66.4 (CH_2), 30.2 (CH_2), 21.0

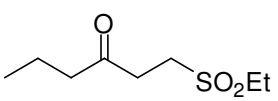
(CH_2), 15.0 (CH_3), 13.7 (CH_3); IR (thin film) 2963, 1630, 1352, 1167 cm^{-1}; LRMS (CI) 179 (37, $[M+H]^+$), 151 (100); HRMS (CI) calcd for $C_7H_{15}O_3S$ $[M+H]^+$ 179.0742, observed 179.0745.

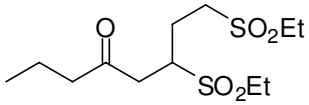
Data for *Z*-isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 6.38 (dt, *J* = 11.0 and 7.5 Hz, 1H), 6.19 (dt, *J* = 11.0 and 1.5 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 2.58 (qd, *J* = 7.5 and 1.5 Hz, 2H), 1.54 (sextet, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3 (CH), 124.6 (CH), 66.5 (CH_2), 33.5 (CH_2), 22.0 (CH_2), 15.0 (CH_3), 13.6 (CH_3); IR (thin film) 2963, 1630, 1352, 1167 cm^{-1}; LRMS (CI) 179 (37, $[M+H]^+$), 151 (100); HRMS (CI) calcd for $C_7H_{15}O_3S$ $[M+H]^+$ 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 H_2O (500 μL) and the reaction mixture stirred at 60 °C for the time specified (see below). The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with H_2O (50 mL), dried ($MgSO_4$), 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



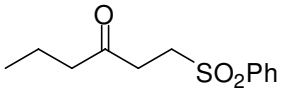


Using Method D, the reaction was complete after 24 h. Purification by column chromatography (50% EtOAc/petrol) and recrystallisation (CH_2Cl_2/petrol) gave 1-(ethylsulfonyl)hexan-3-one as a white solid (123 mg, 0.64 mmol, 64%) and 6,8-bis(ethanesulfonyl)octan-4-one as a yellow oil (37 mg, 0.12 mmol, 12%).

Data for **143a**: m.p. 70-73 °C; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.8 (C), 48.2 (CH_2), 46.0 (CH_2), 44.7 (CH_2), 34.1 (CH_2), 17.2 (CH_2), 13.7 (CH_3), 6.72 (CH_3); IR (solid) 2961, 2874, 1712, 1293, 1127 cm^{-1}; LRMS (CI) 193 (5, $[M+H]^+$), 109 (68), 99 (100); HRMS (ES) calcd for $C_8H_{17}O_3S$ $[M+H]^+$ 193.0898; observed 193.0901.

Data for **144a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{12}H_{24}O_5S_2Na$ $[M+Na]^+$ 335.0963; observed 335.0951.

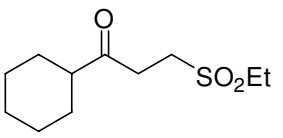
1-(Phenylsulfonyl)hexan-3-one 143b



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{12}H_{20}NO_3S$ $[M+NH_4]^+$ 258.1158; observed 258.1160.

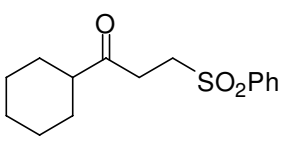
1-Cyclohexyl-3-ethanesulfonylpropan-1-one 143c

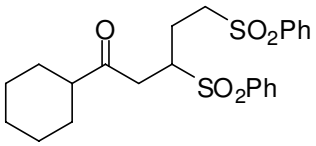


Using Method D, the reaction was complete after 24 h. Purification by column chromatography (10-30% EtOAc/petrol) and recrystallisation (CH_2Cl_2/petrol) gave 1-cyclohexyl-3-ethanesulfonylpropan-1-one as a white solid (132 mg, 0.57 mmol, 57%).

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). 1.42-1.17 (m, 5H); ^{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, $[M]^{+\cdot}$), 204 (55), 139 (100); HRMS (EI) calcd for $C_{11}H_{20}O_3S$ $[M]^{+\cdot}$ 232.1128; observed 232.1117.

3-Benzenesulfonyl-1-cyclohexylpropan-1-one 143d and 3,5-bis(benzenesulfonyl)-1-cyclohexylpentan-1-one 144d





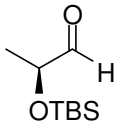
Using Method D, the reaction was complete after 24 h. Purification by column chromatography (10-30% EtOAc/petrol) and recrystallisation (petrol) gave 3-benzenesulfonyl-1-cyclohexylpropan-1-one as a white solid (171 mg, 0.61 mmol, 61%) and 3,5-bis(benzenesulfonyl)-1-cyclohexylpentan-1-one as white solid (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 (CI) 298 (100, $[M+NH_4]^+$); HRMS (ES) calcd for $C_{15}H_{24}NO_3S$ $[M+NH_4]^+$ 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 (dddd, *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 (CH_2), 28.2 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 22.4 (CH_2); IR (solid) 2922, 1721, 1312, 1140 cm^{-1}; LRMS (CI) 449 (100, $[M+H]^+$); HRMS (ES) calcd for $C_{23}H_{29}O_5S$ $[M+H]^+$ 449.1378; observed 449.1387.

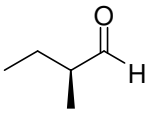
(2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]propanal 146[135]



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 H_2O (100 mL), extracted with Et_2O (3 × 100 mL), the combined organics washed with sat. NaCl (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to give crude ethyl (2*S*)-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 (2*S*)-2-[(*tert*-butyldimethylsilanyl)oxy]-propionic acid ethyl ester (4.42 g, 18.2 mmol) in Et_2O (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 H_2O (3 mL). After warming to 21 °C and stirring for 90 min, finely ground Na_2SO_4 and $MgSO_4$ were added and the suspension stirred for 15 min, then filtered through a short plug of celite and silica, eluting with Et_2O. The solvents were removed *in vacuo* and the crude residue purified by vacuum distillation to give (2*S*)-2-[(*tert*-butyldimethylsilyl)oxy]propanal as a colourless oil (2.10 g, 11.1 mmol, 61%).

^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3 (CH), 73.8 (CH), 25.7 (CH_3), 18.5 (CH_3), 18.2 (CH_3), -4.8 (CH_3), -4.8 (CH_3); IR (thin film) 2952, 2931, 2859, 1742 cm^{-1}; $[\alpha]_D$ = -11.0 (*c* 2.51, $CHCl_3$, 22.0 ºC), Lit. $[\alpha]_D$ = -11.1 (*c* 1.50, $CHCl_3$, 20.0 °C).[195]

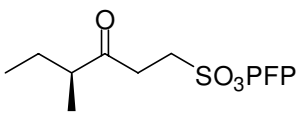
(2*S*)-2-Methylbutanal 152[196]

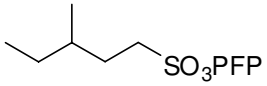


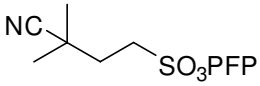
A two-necked flask was fitted with a pressure-equalising dropping funnel and a thermometer. The flask was charged with (2*S*)-2-methylbutanol **151** (13.5 mL, 11.0 g, 0.13 mol), 2,2,6,6-tetramethylpiperidin-1-oxyl (0.2 g, 1.3 mmol), CH_2Cl_2 (40 mL), and a solution of KBr (1.48 g, 0.013 mol) in H_2O (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 CH_2Cl_2 (15 mL). The combined organic extracts were washed with 10% aqueous HCl (50 mL) containing KI (0.40 g, 0.03 mol), 10% aqueous $Na_2S_2O_3$ (50 mL) and H_2O (30 mL). The organic phase was dried over $MgSO_4$ and then distilled at atmospheric pressure through a 20 cm Vigreux distillation column to give (2*S*)-2-methylbutanal as a colourless oil (8.8 g, 0.10 mol, 82%).

b.p. 90-92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4 (C), 47.8 (CH), 23.5 (CH_2), 12.9 (CH_3), 11.3 (CH_3); IR (thin film) 2970, 2938, 2878, 1705 cm^{-1}; LRMS (CI) 87 (30, $[M+H]^+$), 74 (100); HRMS (CI) calcd for $C_5H_{11}O$ $[M+H]^+$ 87.0804, observed 87.0809; $[\alpha]_D$ = +35.0 (*c* 2.04, Acetone, 22.0 ºC), Lit. $[\alpha]_D$ = +35.5 (*c* 2.50, Acetone, 20.0 °C).[197]

Pentafluorophenyl (4*S*)-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

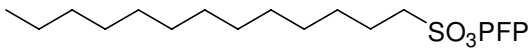
argon. Then was added (2*S*)-2-methylbutanal **152** (86 mg, 107 μL, 1 mmol) and AIBN (49 mg, 0.30 mmol) and the reaction mixture stirred at 40 °C for 72 h. The solvent was removed *in vacuo* and the crude residue purified by column chromatography (20%-90% CH_2Cl_2/petrol) to afford pentafluorophenyl (4*S*)-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**: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.8 (C), 47.9 (CH), 47.1 (CH_2), 34.5 (CH_2), 25.9 (CH_2), 15.7 (CH_3), 11.5 (CH_3); IR (solid) 2970, 2940, 1716, 1516, 1384, 1184 cm^{-1}; LRMS (CI) 361 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{13}H_{14}F_5O_4S$ $[M+H]^+$ 361.0533, observed 361.0526; $[\alpha]_D$ = +9.76 (c 18.9, $CHCl_3$, 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**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.51-3.40 (m, 2H), 2.11-2.05 (m, 1H), 1.87 (dddd, *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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.2 (CH_2), 33.5 (CH), 29.7 (CH_2), 28.9 (CH_2), 18.6 (CH_3), 11.2 (CH_3); IR (thin film) 2966, 2880, 1515, 1384, 1178 cm^{-1}; LRMS (CI) 333 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{12}H_{14}F_5O_3S$ $[M+H]^+$ 333.0584, observed 333.0574.

Data for **155**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.66-3.63 (m, 2H), 2.31-2.28 (m, 2H), 1.49 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 121.1 (C), 49.3 (CH_2), 34.5 (CH_2), 26.5 (CH_3), 23.5 (CH_3); IR (thin film) 2983, 2234, 1515, 1390, 1184 cm^{-1}; LRMS (CI) 344 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{12}H_{11}F_5NO_3S$ $[M+H]^+$ 344.0380, observed 344.0386.

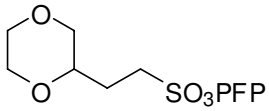
Pentafluorophenyl tridecane-1-sulfonate 156



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 (2*S*)-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% CH_2Cl_2/petrol) to afford pentafluorophenyl tridecane-1-sulfonate as a colourless oil (413 mg, 0.96 mmol, 96%).

^{1}H NMR (500 MHz, $CDCl_3$) 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, $CDCl_3$)‡ δ 52.9 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 28.1 (CH_2), 23.6 (CH_2), 22.8 (CH_2), 14.2 (CH_3); IR (thin film) 2922, 2852, 1519, 1384, 1185 cm^{-1}; LRMS (CI) 431 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{19}H_{28}F_5O_3S$ $[M+H]^+$ 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 (2*S*)-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% CH_2Cl_2/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, $CDCl_3$) 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, $CDCl_3$) δ 72.6 (CH), 70.6 (CH_2), 66.7 (CH_2), 66.4 (CH_2), 49.0

‡ 19C expected, 13C observed.

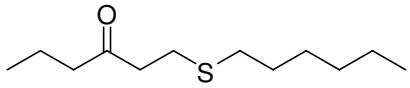
(CH_2), 25.6 (CH_2); IR (thin film) 2960, 1381, 1183 cm^{-1}; LRMS (FAB) 385 (100, $[M+Na]^+$); HRMS (FAB) calcd for $C_{12}H_{11}F_5O_5SNa$ $[M+Na]^+$ 385.0145, observed 385.0152.

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 CH_2Cl_2 (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.

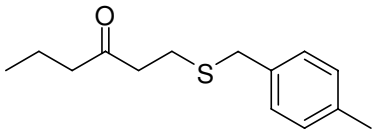
1-(Hexylsulfanyl)hexan-3-one 163a



Using Method E, the reaction was complete after 1 h. Purification by column chromatography (60% CH_2Cl_2/petrol-neat CH_2Cl_2) gave 1-(hexylsulfanyl)hexan-3-one as a colourless oil (61 mg, 0.28 mmol, 98%).

^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8 (C), 45.1 (CH), 42.9 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 29.6 (CH_2), 28.6 (CH_2), 25.9 (CH_2), 22.6 (CH_2), 17.3 (CH_2), 14.1 (CH_3), 13.8 (CH_3); IR (thin film) 2959, 2927, 1714 cm^{-1}; LRMS (CI) 217 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{12}H_{25}OS$ $[M+H]^+$ 217.1626, observed 217.1621.

1-(4-Methyl-benzylsulfanyl)-hexan-3-one 163b



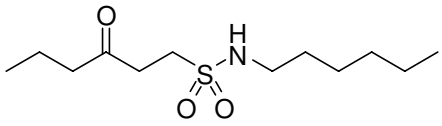
Using Method E, the reaction was complete after 1 h. Purification by column chromatography (60% CH_2Cl_2/petrol to neat CH_2Cl_2) gave 1-(4-methyl-benzylsulfanyl)-hexan-3-one as a colourless oil (66 mg, 0.28 mmol, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6 (C), 136.8 (C), 135.2 (C), 129.3 (CH), 128.8 (CH), 45.0 (CH_2), 42.5 (CH_2), 36.5 (CH_2), 25.3 (CH_2), 21.1 (CH_3), 17.3 (CH_2), 13.8 (CH_3); IR (thin film) 2962, 2928, 2871, 1712, 1535, 1516 cm^{-1}; LRMS (CI) 237 (100, $[M+H]^+$); 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 dropwise 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_2O (20 mL), washed with sat. LiCl (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL), 2M HCl (3 × 20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the desired sulfonamide.

N-Hexyl-3-oxohexane-1-sulfonamide 170a

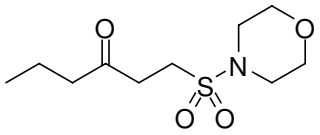


Using Method F, *N*-hexyl-3-oxohexane-1-sulfonamide was isolated as a white solid (64 mg, 0.25 mmol, 82%).

m.p. 67-69 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 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),

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), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 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 $C_{12}H_{26}NO_3S$ $[M+H]^+$ 264.1633, observed 264.1624.

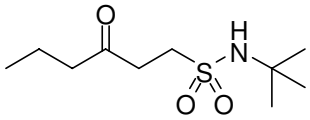
1-(Morpholin-4-ylsulfonyl)hexan-3-one 170b



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{10}H_{20}NO_4S$ $[M+H]^+$ 250.1113, observed 250.1107.

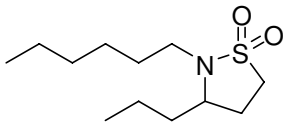
N-tert-Butyl-3-oxohexane-1-sulfonamide 170c



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{10}H_{22}NO_3S$ $[M+H]^+$ 236.1320, observed 236.1325.

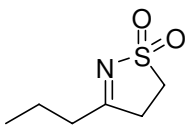
2-Hexyl-3-propyl-1,2-thiazolidine 1,1-dioxide 171



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. $NaHCO_3$ (3 × 100 mL) and 2M HCl (3 × 100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (50% Et_2O/petrol) to afford 2-hexyl-3-propyl-isothiazolidine 1,1-dioxide as a colourless oil (41 mg, 0.17 mmol, 87%).

^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) δ 58.1 (CH), 46.5 (CH_2), 43.8 (CH_2), 36.0 (CH_2), 31.5 (CH_2), 28.6 (CH_2), 26.7 (CH_2), 25.0 (CH_2), 22.6 (CH_2), 17.8 (CH_2), 14.1 (CH_3), 14.1 (CH_3); IR (thin film) 2957, 2930, 2872, 1305, 1134 cm^{-1}; LRMS (CI) 248 (60, $[M+H]^+$), 204 (100); HRMS (CI) calcd for $C_{12}H_{26}NO_2S$ $[M+H]^+$ 248.1684, observed 248.1686.

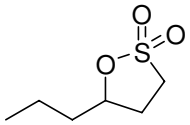
3-Propyl-4,5-dihydro-1,2-thiazole 1,1-dioxide 174



To a solution of pentafluorophenyl 3-oxohexane-1-sulfonate **107a** (0.29 mmol) in CH_2Cl_2 (2 mL) was bubbled through NH_3 (g) for 45 min at 0 °C. Then the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with 2M HCl (3 × 20 mL) and sat. K_2CO_3 (3 × 20 mL), dried ($MgSO_4$) 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_6H_{12}NO_2S$ $[M+H]^+$ 162.0589, observed 162.0591.

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

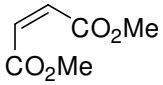


To a mixture of pentafluorophenyl 3-oxohexane-1-sulfonate **107a** (100 mg, 0.29 mmol) and sodium borohydride (22 mg, 0.58 mmol) was added CH_2Cl_2 (4 mL) and MeOH (12 mL) and the reaction mixture left to stir for 30 min. Then was added further sodium borohydride (22 mg, 0.58 mmol) and the reaction mixture left to stir for a further 10 min. The solvents were removed *in vacuo*, the crude residue diluted with Et_2O (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, $CDCl_3$) δ 4.66 (ddt, *J* = 12.0, 8.5 and 5.0 Hz, 1H), 3.34 (ddd, *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, $CDCl_3$) δ 82.6 (CH), 45.7 (CH_2), 37.2 (CH_2), 29.6 (CH_2), 18.5 (CH_2), 13.6 (CH_3); IR (thin film) 2963, 2877, 1340, 1157 cm^{-1}; LRMS (CI) 165 (100, $[M+H]^+$); HRMS (CI) calcd for $C_6H_{13}O_3S$ $[M+H]^+$ 165.0585, observed 165.0587.

Experimental for Chapter 4

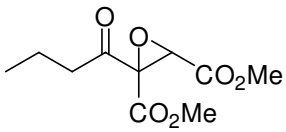
Dimethyl maleate 177



A solution of maleic acid (10 g, 86.2 mmol) and conc. H_2SO_4 (2 mL) in excess MeOH (200 mL) was heated under reflux for 5 h. The solvent was removed *in vacuo*, diluted with Et_2O (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 $C_6H_9O_4$ $[M+H]^+$ 145.0501, observed 145.0503.

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

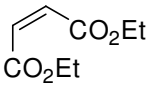


n-Butanal (361 mg, 451 μL, 5 mmol) was added to a solution of dimethyl maleate (144 mg, 1 mmol) in 1,4-dioxane (0.5 mL) and the reaction mixture stirred at 21 °C for 8 days. The solvent was removed *in vacuo* to give crude 5-hydroxy-5-propyl-1,2-dioxolane-3,4-dicarboxylate. Purification by column chromatography (10%-90% Et_2O/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, CDCl3) 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



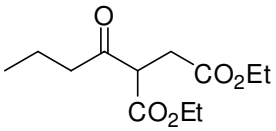
A solution of maleic acid (10 g, 86.2 mmol), conc. H_2SO_4 (2 mL) and excess EtOH (200 mL) in PhMe (200 mL) was heated under reflux for 3 days. The solvent was removed *in vacuo*, diluted with Et_2O (200 mL), washed with sat. $NaHCO_3$ (250 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to 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 $C_8H_{13}O_4$ $[M+H]^+$ 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.

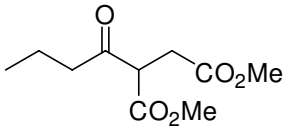
Diethyl 2-butanoylbutanedioate 78a



Using Method G, the reaction was complete after 4 days. Purification by column chromatography (10%-20% Et_2O/petrol) gave diethyl 2-butanoylbutanedioate as a colourless oil (165 mg, 0.68 mmol, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.0, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.97 (dd, *J* = 8.5 and 6.0 Hz, 1H), 2.98 (dd, *J* = 17.5 and 8.5 Hz, 1H), 2.83 (dd, *J* = 17.5 and 6.0 Hz, 1H), 2.70 (dt, *J* = 17.5 and 7.0 Hz, 1H), 2.61 (dt, *J* = 17.5 and 7.0 Hz, 1H), 1.65 (sextet, *J* = 7.0 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.0 (C), 171.4 (C), 168.5 (C), 61.8 (CH_2), 61.0 (CH_2), 54.0 (CH), 44.6 (CH_2), 32.4 (CH_2), 16.8 (CH_2), 14.1 (CH_3), 14.0 (CH_3), 13.5 (CH_3); IR (thin film) 2967, 2881, 1736, 1719 cm^{-1}; LRMS (CI) 245 (60, $[M+H]^+$), 199 (100); HRMS (CI) calcd for $C_{12}H_{21}O_5$ $[M+H]^+$ 245.1389, observed 245.1382.

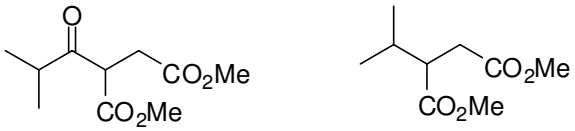
Dimethyl 2-butanoylbutanedioate 178a



Using Method G, the reaction was complete after 3 days. Purification by column chromatography (10%-30% Et_2O/petrol) gave dimethyl 2-butanoylbutanedioate as a colourless oil (151 mg, 0.70 mmol, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (dd, *J* = 8.0 and 6.5 Hz, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 2.94 (dd, *J* = 17.5 and 8.0 Hz, 1H), 2.80 (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), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8 (C), 171.8 (C), 168.9 (C), 53.8 (CH), 52.7 (CH_3), 52.0 (CH_3), 44.6 (CH_2), 32.1 (CH_2), 16.8 (CH_2), 13.4 (CH_3); IR (thin film) 2959, 2880, 1734, 1717 cm^{-1}; LRMS (CI) 217 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{10}H_{17}O_5$ $[M+H]^+$ 217.1076, observed 217.1072.

Dimethyl 2-(2-methylpropanoyl)butanedioate 178b and dimethyl 2-(propan-2-yl)butanedioate 185b

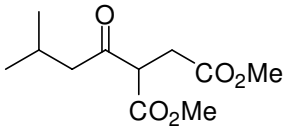


Using Method G, the reaction was complete after 9 days. Purification by column chromatography (5%-30% Et_2O/petrol) gave dimethyl 2-(2-methylpropanoyl)butanedioate as a colourless oil and dimethyl 2-(propan-2-yl)butanedioate as a colourless oil.

Data for **178b**: ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.8 (C), 171.8 (C), 169.1 (C), 52.8 (CH), 52.1 (CH_3), 52.0 (CH_3), 40.7 (CH_2), 32.3 (CH), 18.6 (CH_3), 17.8 (CH_3); IR (thin film) 2949, 2886, 1736, 1714 cm^{-1}; LRMS (CI) 217 (15, $[M+H]^+$), 86 (100); HRMS (CI) calcd for $C_{10}H_{17}O_5$ $[M+H]^+$ 217.1076, observed 217.1066.

Data for **185b**: ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.0 (C), 173.0 (C), 51.8 (CH_3), 51.7 (CH_3), 47.4 (CH), 32.9 (CH_2), 30.1 (CH), 20.1 (CH_3), 19.6 (CH_3); IR (thin film) 2952, 2930, 2865, 1732 cm^{-1}; LRMS (CI) 189 (10, $[M+H]^+$), 157 (100); HRMS (CI) calcd for $C_9H_{17}O_4$ $[M+H]^+$ 189.1049, observed 189.1055.

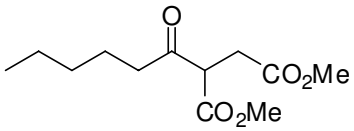
Dimethyl 2-(3-methylbutanoyl)butanedioate 178c



Using Method G, the reaction was complete after 3 days. Purification by column chromatography (10%-30% Et_2O/petrol) gave dimethyl 2-(3-methylbutanoyl)butanedioate as a colourless oil (131 mg, 0.57 mmol, 57%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.98 (dd, *J* = 8.0 and 6.5 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.01 (dd, *J* = 17.0 and 8.0 Hz, 1H), 2.85 (dd, *J* = 17.0 and 6.5 Hz, 1H), 2.58 (dd, *J* = 17.0 and 7.5 Hz, 1H), 2.53 (dd, *J* = 17.0 and 6.5 Hz, 1H), 2.24-2.17 (m, 1H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.4 (C), 171.8 (C), 168.9 (C), 54.2 (CH), 52.7 (CH_3), 52.1 (CH_3), 51.5 (CH_2), 32.1 (CH_2), 24.1 (CH), 22.5 (CH_3), 22.2 (CH_3); IR (thin film) 2957, 1738, 1719 cm^{-1}; LRMS (EI) 230 (15, $[M]^{+\cdot}$), 199 (100); HRMS (EI) calcd for $C_{11}H_{18}O_5$ $[M]^{+\cdot}$ 230.1149, observed 230.1143.

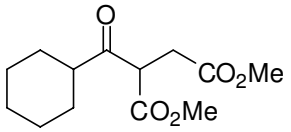
Dimethyl 2-hexanoylbutanedioate 178d



Using Method G, the reaction was complete after 3 days. Purification by column chromatography (10%-30% Et_2O/petrol) gave dimethyl 2-hexanoylbutanedioate as a colourless oil (185 mg, 0.76 mmol, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (dd, *J* = 8.0 and 6.5 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.00 (dd, *J* = 17.5 and 8.0 Hz, 1H), 2.84 (dd, *J* = 17.5 and 6.5 Hz, 1H), 2.71 (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), 1.36-1.22 (m, 4H) 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.0 (C), 171.9 (C), 169.0 (C), 53.8 (CH_3), 52.8 (CH_3), 52.1 (CH), 42.8 (CH_2), 32.2 (CH_2), 31.1 (CH_2), 23.1 (CH_2), 22.4 (CH_2), 13.9 (CH_3); IR (thin film) 2959, 2934, 1738, 1720 cm^{-1}; LRMS (CI) 245 (15, $[M+H]^+$), 213 (100); HRMS (CI) calcd for $C_{12}H_{21}O_5$ $[M+H]^+$ 245.1389, observed 245.1382.

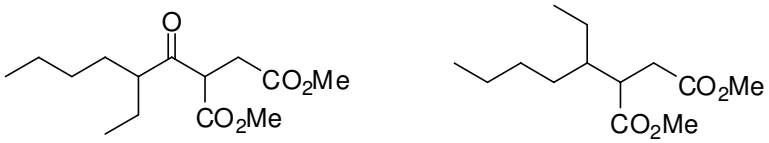
Dimethyl 2-(cyclohexylcarbonyl)butanedioate 178e



Using Method G, the reaction was complete after 10 days. Purification by column chromatography (10%-30% Et_2O/petrol) gave dimethyl 2-(cyclohexylcarbonyl)butanedioate as a colourless oil.

^{1}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), 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_2O/petrol) gave dimethyl 2-(2-ethylhexanoyl)butanedioateas as a mixture of diastereoisomers and dimethyl 2-(heptan-3-yl)butanedioateas 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, $CDCl_3$)[§] 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, 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.

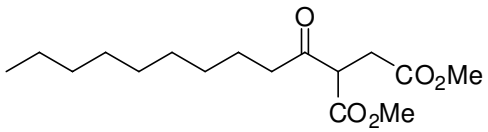
Data for **185f**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.69 (s, 3H), 3.05-3.00 (m, 1H), 2.78-2.72 (m, 1H), 2.36-2.32 (m, 1H), 1.67-1.58 (m, 1H), 1.39-1.19 (m, 8H), 0.94-0.87 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$)[**] δ 175.4 (C), 173.2 (C), 51.8 (CH_3), 51.7 (CH_3), 43.1 (CH), 43.1 (CH), 41.5 (CH), 41.4 (CH), 31.9 (CH_2), 31.8

[§] 28C expected, 24C observed.

[**] 26C expected, 21C observed.

(CH_2), 30.6 (CH_2), 30.3 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 24.1 (CH_2), 23.7 (CH_2), 22.8 (CH_2), 14.1 (CH_3), 14.0 (CH_3), 11.8 (CH_3), 11.7 (CH_3); IR (thin film) 2957, 2932, 2875, 1734 cm^{-1}; LRMS (CI) 245 (10, $[M+H]^+$), 213 (100); HRMS (CI) calcd for $C_{13}H_{25}O_4$ $[M+H]^+$ 245.1753, observed 245.1748.

Dimethyl 2-decanoylbutanedioate 178g



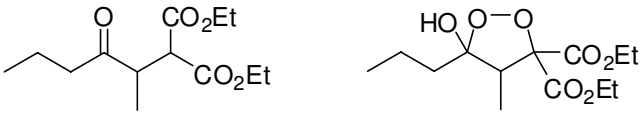
Using Method G, the reaction was complete after 9 days. Purification by column chromatography (10%-30% Et_2O/petrol) gave dimethyl 2-decanoylbutanedioate as a colourless oil (180 mg, 0.60 mmol, 60%).

^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0 (C), 171.9 (C), 167.0 (C), 53.8 (CH), 52.7 (CH_3), 52.0 (CH_3), 42.8 (CH_2), 32.2 (CH_2), 31.9 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 23.4 (CH_2), 22.7 (CH_2), 14.1 (CH_3); IR (thin film) 2959, 2926, 2856, 1742, 1720 cm^{-1}; LRMS (ES^-) 299 (100, $[M-H]^-$); HRMS (ES^-) calcd for $C_{16}H_{27}O_5$ $[M-H]^-$ 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

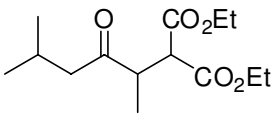


Using Method H, the reaction was complete after 3 days. Purification by column chromatography (10%-50% Et_2O/petrol) gave diethyl (3-oxohexan-2-yl)propanedioateas a colourless oil (181 mg, 0.70 mmol, 70%) and diethyl 5-hydroxy-4-methyl-5-propyl-1,2-dioxolane-3,3-dicarboxylate as a colourless oil (2 mg, 0.01 mmol, 1%).

Data for **187a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26-4.11 (m, 4H), 3.77 (d, *J* = 10.5 Hz, 1H), 3.27 (dq, *J* = 10.5 and 7.0 Hz, 1H), 2.58 (t, *J* = 7.0 Hz, 2H), 1.65 (sextet, *J* = 7.0 Hz, 2H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7 (C), 168.7 (C), 168.6 (C), 62.0 (CH_2), 61.6 (CH_2), 54.5 (CH), 45.0 (CH), 43.4 (CH_2), 16.9 (CH_2), 14.7 (CH_3), 14.2 (CH_3), 14.0 (CH_3), 13.8 (CH_3); IR (thin film) 2967, 2933, 1759, 1733, 1715 cm^{-1}; LRMS (CI) 259 (15, $[M+H]^+$), 213 (100); HRMS (CI) calcd for $C_{13}H_{23}O_5$ $[M+H]^+$ 259.1545, observed 259.1548.

Data for **188**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (br s, 1H, OH), 4.36-4.25 (m, 4H), 3.44 (q, *J* = 7.0 Hz, 1H), 1.81 (td, *J* = 11.0 and 4.5 Hz, 1H), 1.68-1.42 (m, 3H), 1.31 (t, *J* = 7.0 Hz, 6H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9 (C), 167.5 (C), 107.5 (C), 89.1 (C), 63.4 (CH_2), 62.7 (CH_2), 56.1 (CH), 35.5 (CH_2), 16.8 (CH_2), 14.4 (CH_3), 14.1 (CH_3), 14.0 (CH_3), 10.6 (CH_3); IR (thin film) 3466, 2967, 2938, 1732 cm^{-1}; LRMS (ES) 313 (40, $[M+Na]^+$), 278 (100); HRMS (ES) calcd for $C_{13}H_{22}O_7Na$ $[M+Na]^+$ 313.1263, observed 313.1247.

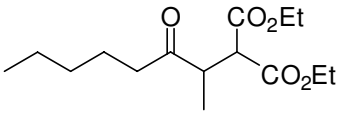
Diethyl (5-methyl-3-oxohexan-2-yl)propanedioate 187c



Using Method H, the reaction was complete after 3 days. Purification by column chromatography (5%-20% Et_2O/petrol) gave diethyl (5-methyl-3-oxohexan-2-yl)propanedioateas as a colourless oil (163 mg, 0.60 mmol, 60%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $[M]^{+\cdot}$), 227 (85), 189 (100); HRMS (EI) calcd for $C_{14}H_{24}O_5$ $[M]^{+\cdot}$ 272.1618, observed 272.1621.

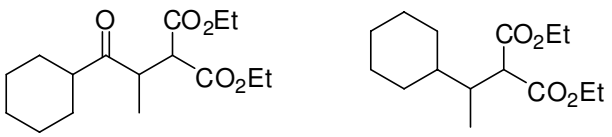
Diethyl (3-oxooctan-2-yl)propanedioate 187d



Using Method H, the reaction was complete after 3 days. Purification by column chromatography (5%-20% Et_2O/petrol) gave diethyl (3-oxooctan-2-yl)propanedioate as a colourless oil (206 mg, 0.72 mmol, 72%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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



Using Method H, the reaction was complete after 10 days. Purification by column chromatography (5%-20% Et_2O/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 $C_{16}H_{26}O_5Na$ $[M+Na]^+$ 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 $C_{15}H_{26}O_4Na$ $[M+Na]^+$ 293.1741, observed 293.1729.

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

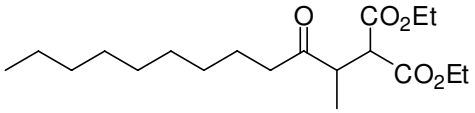
Using Method H, the reaction was complete after 9 days. Purification by column chromatography (5%-20% Et_2O/petrol) gave diethyl (4-ethyl-3-oxooctan-2-yl)propanedioate (163 mg, 0.52 mmol, 52%) as a 50:50 mixture of diastereoisomers and diethyl (3-ethylheptan-2-yl)propanedioate (57 mg, 0.20 mmol, 20%) 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, $CDCl_3$)[††] 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), 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 $C_{17}H_{30}O_5Na$ $[M+Na]^+$ 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, $CDCl_3$)[‡‡] 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 $C_{16}H_{30}O_4Na$ $[M+Na]^+$ 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_2O/petrol) gave diethyl (3-oxododecan-2-yl)propanedioate as a colourless oil (246 mg, 0.72 mmol, 72%).

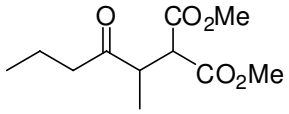
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (d, *J* = 7.0 Hz, 2H), 4.17-4.11 (m, 2H), 3.75 (d, *J* = 10.5 Hz, 1H), 3.22 (dq, *J* = 10.5 and 7.5 Hz, 1H), 2.57 (t, *J* = 7.5 Hz, 2H), 1.61-1.54 (m, 2H), 1.32-1.21 (m, 18H), 1.10 (d, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8 (C), 168.7 (C), 168.6 (C), 61.7 (CH_2), 61.6

[††] 34C expected, 29C observed.

[‡‡] 32C expected, 25C observed.

(CH_2), 54.5 (CH), 45.0 (CH), 41.5 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 23.5 (CH_2), 22.7 (CH_2), 14.8 (CH_3), 14.1 (CH_3), 14.1 (CH_3), 14.0 (CH_3); IR (thin film) 2927, 2855, 1750, 1734, 1717 cm^{-1}; LRMS (ES) 365 (100, $[M+Na]^+$); HRMS (ES) calcd for $C_{19}H_{34}O_5Na$ $[M+Na]^+$ 365.2318, observed 365.2304.

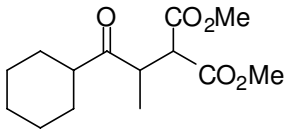
Dimethyl (3-oxohexan-2-yl)propanedioate 193a

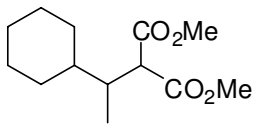


Using Method H, the reaction was complete after 3 days. Purification by column chromatography (10%-20% Et_2O/petrol) gave dimethyl (3-oxohexan-2-yl)propanedioate as a colourless oil (161 mg, 0.70 mmol, 70%).

^1H NMR (500 MHz, $CDCl_3$) 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), 0.93 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6 (C), 169.1 (C), 168.9 (C), 54.1 (CH), 52.8 (CH_3), 52.7 (CH_3), 45.2 (CH), 43.3 (CH_2), 17.0 (CH_2), 14.7 (CH_3), 13.7 (CH_3); IR (thin film) 2960, 1752, 1737, 1715 cm^{-1}; LRMS (CI) 231 (25, $[M+H]^+$), 199 (100); HRMS (CI) calcd for $C_{11}H_{19}O_5$ $[M+H]^+$ 231.1232, observed 231.1236.

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





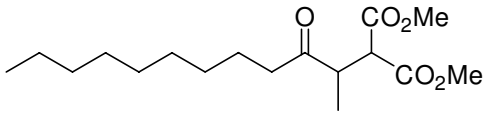
Purification by column chromatography (5%-20% Et_2O/petrol) gave dimethyl (1-cyclohexyl-1-oxopropan-2-yl)propanedioate as a colourless oil (192 mg, 0.71 mmol, 71%) and dimethyl (1-cyclohexylethyl)propanedioate as a colourless oil (15 mg, 0.06 mmol, 6%).

Data for **193e**: ^1H NMR (600 MHz, $CDCl_3$) 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, $CDCl_3$) δ 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 $C_{14}H_{22}O_5Na$ $[M+Na]^+$ 293.1365, observed 293.1379.

Data for **194e**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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



Purification by column chromatography (5%-20% Et_2O/petrol) gave dimethyl (3-oxododecan-2-yl)propanedioate as a colourless oil (210 mg, 0.67 mmol, 67%).

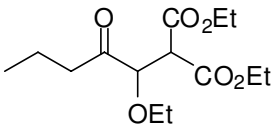
^{1}H NMR (600 MHz, $CDCl_3$) δ 3.81 (d, J = 10.5 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.29 (dq, J = 10.5, 7.0 Hz, 1H), 2.59 (td, J = 7.0, 2.0 Hz, 2H), 1.62 (sextet, J = 7.0 Hz, 2H), 1.32-1.26 (m, 12H), 1.11 (d, J = 7.0 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$)[§§] δ 211.9 (C), 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, 2855, 1754, 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.

[§§] 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.

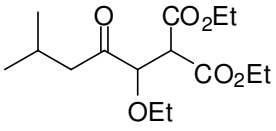
Diethyl (1-ethoxy-2-oxopentyl)propanedioate 196a



Using Method I, the reaction was complete after 7 days. Purification by column chromatography (5%-20% Et_2O/petrol) gave diethyl (1-ethoxy-2-oxopentyl)propanedioate as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) 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), 2.68 (dt, *J* = 18.0 and 7.0 Hz, 1H), 2.51 (dt, *J* = 18.0 and 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, $CDCl_3$) δ 209.5 (C), 167.0 (C), 167.0 (C), 82.4 (CH), 67.8 (CH_2), 61.8 (CH_2), 61.7 (CH_2), 54.5 (CH), 41.1 (CH_2), 16.5 (CH_2), 15.4 (CH_3), 14.1 (CH_3), 14.0 (CH_3), 13.8 (CH_3); IR (thin film) 2978, 2934, 2873, 1744, 1724 cm^{-1}; LRMS (CI) 289 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{14}H_{25}O_6$ $[M+H]^+$ 289.1651, observed 289.1648.

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

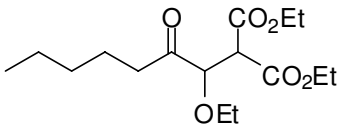


Using Method I, the reaction was complete after 5 days. Purification by column chromatography (5%-20% Et_2O/petrol) gave diethyl (1-ethoxy-4-methyl-2-oxopentyl)propanedioate as a colourless oil (257 mg, 0.85 mmol, 85%).

^{1}H NMR (600 MHz, $CDCl_3$) 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), 2.68 (dd, *J* = 17.5 and 7.0 Hz, 1H), 2.52 (dt, *J* =

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, $CDCl_3$) δ 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 $C_{15}H_{27}O_6$ $[M+H]^+$ 303.1808, observed 303.1805.

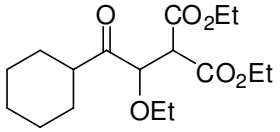
Diethyl (1-ethoxy-4-methyl-2-oxopentyl)propanedioate 196d



Using Method I, the reaction was complete after 3 days. Purification by column chromatography (5%-20% Et_2O/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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{16}H_{28}O_6Na$ $[M+Na]^+$ 339.1784, observed 339.1769.

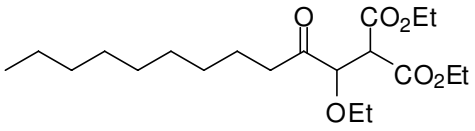
Diethyl (2-cyclohexyl-1-ethoxy-2-oxoethyl)propanedioate 196e



Using Method I, the reaction was complete after 3 days. Purification by column chromatography (5%-20% Et_2O/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), 3.71-3.62 (m, 2H), 2.86 (tt, *J* = 11.5 and 2.0 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), 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 $C_{17}H_{28}O_6Na$ $[M+Na]^+$ 351.1784, observed 351.1773.

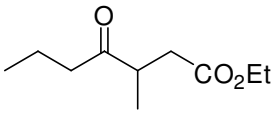
Diethyl (1-ethoxy-4-methyl-2-oxononyl)propanedioate 196g



Using Method I, the reaction was complete after 5 days. Purification by column chromatography (5%-20% Et_2O/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, 1749, 1733 cm^{-1}; LRMS (ES) 395 (100, $[M+Na]^+$); HRMS (ES) calcd for $C_{20}H_{36}O_6Na$ $[M+Na]^+$ 395.2410, observed 395.2423.

Ethyl 3-methyl-4-oxoheptanoate 80



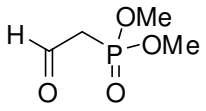
n-Butanal (721 mg, 901 μL,10 mmol) was added to a solution of ethyl crotonate **79** (114 mg, 1 mmol) in 1,4-dioxane (3 mL) and the reaction mixture stirred at 60 °C for 96 h. The solvent was removed *in vacuo* and purification by column chromatography

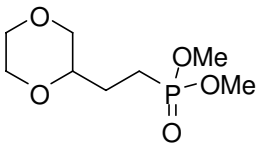
(5%-20% Et_2O/petrol) gave ethyl 3-methyl-4-oxoheptanoate as a colourless oil (95 mg, 0.51 mmol, 51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.0 Hz, 2H), 2.99 (ddq, *J* = 17.0, 12.5 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, $CDCl_3$) δ 213.0 (C), 172.5 (C), 60.6 (CH_2), 43.2 (CH_2), 42.1 (CH), 37.1 (CH_2), 17.1 (CH_2), 16.8 (CH_3), 14.2 (CH_3), 13.8 (CH_3); IR (thin film) 2965, 2938, 2879, 1735, 1715 cm^{-1}; LRMS (CI) 187 (40, $[M+H]^+$), 141 (100); HRMS (CI) calcd for $C_{10}H_{19}O_3$ $[M+H]^+$ 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





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 *in vacuo* and purification by column chromatography (neat CH_2Cl_2-5% MeOH/CH_2Cl_2) 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%).

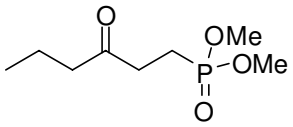
Data for **200**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (td, *J* = 3.0 Hz, J_{H-P} = 1.5 Hz, 1H), 3.81 (d, J_{H-P} = 11.5 Hz, 6H), 3.10 (dd, J_{H-P} = 22.0 and *J* = 3.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6 (d, J_{C-P} = 6.5 Hz, CH), 53.1 (d, J_{C-P} = 6.5 Hz, CH_3), 42.1 (d, J_{C-P} = 128.0 Hz, CH_2); IR (thin film) 2954, 2859, 1720, 1240 cm^{-1}; LRMS (CI) 153 (100, $[M+H]^+$); HRMS (CI) calcd for $C_4H_{10}O_4P$ $[M+H]^+$ 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, $J_{C\text{-}P}$ = 16.0 Hz, CH), 70.9 (CH_2), 66.7 (CH_2), 66.5 (CH_2), 52.3 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 52.3 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 24.4 (d, $J_{C\text{-}P}$ = 4.5 Hz, CH_2), 20.2 (d, $J_{C\text{-}P}$ = 142.0 Hz, CH_2); IR (thin film) 2957, 2853, 1244 cm^{-1}; LRMS (FAB) 247 (100, $[M+Na]^+$); HRMS (FAB) calcd for $C_8H_{17}O_5PNa$ $[M+Na]^+$ 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 *in vacuo* and purified as described below to afford the desired ketone phosphonate.

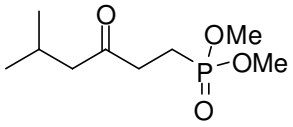
Dimethyl (3-oxohexyl)phosphonate 199a



Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_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, $J_{H\text{-}P}$ = 11.0 Hz, 6H), 2.67 (dt, $J_{H\text{-}P}$ = 15.5 and J = 7.5 Hz, 2H), 2.38 (t, J = 7.5 Hz, 2H), 2.00 (dt, $J_{H\text{-}P}$ = 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, $J_{C\text{-}P}$ = 14.0 Hz, C), 52.5 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 44.6 (CH_2), 35.3 (d, $J_{C\text{-}P}$ = 4.0 Hz, CH_2), 18.3 (d, $J_{C\text{-}P}$ = 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 $C_8H_{18}O_4P$ $[M+H]^+$ 209.0943, observed 209.0947.

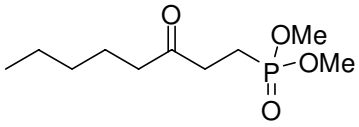
Dimethyl (5-methyl-3-oxohexyl)phosphonate 199c



Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_2) gave (dimethyl (5-methyl-3-oxohexyl)phosphonate as a colourless oil (144 mg, 0.65 mmol, 65%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (d, $J_{H\text{-}P}$ = 11.0 Hz, 6H), 2.69 (dt, $J_{H\text{-}P}$ = 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, $J_{H\text{-}P}$ = 18.0 and J = 7.5 Hz, 2H), 0.89 (d, J = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.3 (d, $J_{C\text{-}P}$ = 14.0 Hz, C), 52.4 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 51.6 (CH_2), 35.7 (d, $J_{C\text{-}P}$ = 4.0 Hz, CH_2), 24.7 (CH), 22.5 (CH_3), 18.2 (d, $J_{C\text{-}P}$ = 144.0 Hz, CH_2); IR (thin film) 2957, 2873, 1714, 1245 cm^{-1}; LRMS (ES) 245 (100, [M+Na]$^+$); HRMS (ES) calcd for $C_9H_{19}O_4PNa$ [M+Na]$^+$ 245.0919, observed 245.0915.

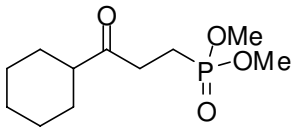
Dimethyl (3-oxooctyl)phosphonate 199d



Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_2) gave dimethyl (3-oxooctyl)phosphonate as a colourless oil (170 mg, 0.72 mmol, 72%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (d, $J_{H\text{-}P}$ = 11.0 Hz, 6H), 2.72 (dt, $J_{H\text{-}P}$ = 15.5 and J = 7.5 Hz, 2H), 2.43 (t, J = 7.5 Hz, 2H), 2.00 (dt, $J_{H\text{-}P}$ = 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, $CDCl_3$) δ 208.3 (d, $J_{C\text{-}P}$ = 14.0 Hz, C), 52.4 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 42.6 (CH_2), 35.2 (d, $J_{C\text{-}P}$ = 4.0 Hz, CH_2), 31.4 (CH_2), 23.5 (CH_2), 22.4 (CH_2), 18.2 (d, $J_{C\text{-}P}$ = 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 $C_{10}H_{21}O_4PNa$ [M+Na]$^+$ 259.1076, observed 259.1070.

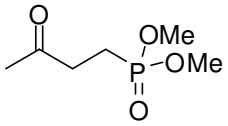
Dimethyl (3-cyclohexyl-3-oxopropyl)phosphonate 199e



Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_2) gave dimethyl (3-cyclohexyl-3-oxopropyl)phosphonate as a colourless oil (149 mg, 0.60 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (d, $J_{H\text{-}P}$ = 11.0 Hz, 6H), 2.75 (dt, $J_{H\text{-}P}$ = 15.5 and J = 7.5 Hz, 2H), 2.36 (tt, J = 11.0 and 3.0 Hz, 1H), 2.00 (dt, $J_{H\text{-}P}$ = 18.0 and J = 7.5 Hz, 2H), 1.87-1.18 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.1 (d, $J_{C\text{-}P}$ = 14.0 Hz, C), 52.4 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 50.7 (CH), 33.2 (d, $J_{C\text{-}P}$ = 4.0 Hz, CH_2), 28.5 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 18.2 (d, $J_{C\text{-}P}$ = 143.0 Hz, CH_2); IR (thin film) 2930, 2854, 1709, 1243 cm^{-1}; LRMS (EI) 248 (100, $[M]^{+\cdot}$); HRMS (EI) calcd for $C_{11}H_{21}O_4P$ $[M]^{+\cdot}$ 248.1172, observed 248.1176.

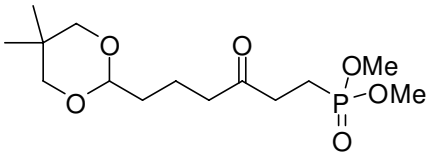
Dimethyl (3-oxobutyl)phosphonate 199h



Using Method J, but with 10 equivalents of acetaldehyde, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_2) gave dimethyl (3-oxobutyl)phosphonate as a colourless oil (122 mg, 0.68 mmol, 68%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (d, $J_{H\text{-}P}$ = 11.0 Hz, 6H), 2.76 (dt, $J_{H\text{-}P}$ = 15.5 and J = 7.5 Hz, 2H), 2.18 (s, 3H), 2.02 (dt, $J_{H\text{-}P}$ = 18.0 and J = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7 (d, $J_{C\text{-}P}$ = 14.0 Hz, C), 52.5 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 36.2 (d, $J_{C\text{-}P}$ = 4.0 Hz, CH_2), 29.7 (CH_3), 18.2 (d, $J_{C\text{-}P}$ = 143.0 Hz, CH_2); IR (thin film) 2958, 1717, 1239 cm^{-1}; LRMS (EI) 180 (5, $[M]^{+\cdot}$), 110 (100); HRMS (EI) calcd for $C_6H_{13}O_4P$ $[M]^{+\cdot}$ 180.0546, observed 180.0548.

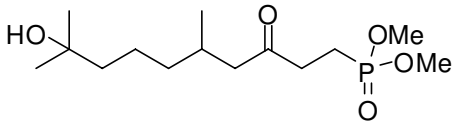
Dimethyl [6-(5,5-dimethyl-1,3-dioxan-2-yl)-3-oxohexyl]phosphonate 199i



Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_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, $J_{H\text{-}P}$ = 11.0 Hz, 6H), 3.57 (d, J = 10.0 Hz, 2H), 3.40 (d, J = 11.0 Hz, 2H), 2.70 (dt, $J_{H\text{-}P}$ = 15.5 and J = 7.5 Hz, 2H), 2.47 (t, J = 7.0 Hz, 2H), 2.02 (dt, $J_{H\text{-}P}$ = 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, $J_{C\text{-}P}$ = 14.0 Hz, C), 101.9 (CH), 77.2 (CH_2), 52.4 (d, $J_{C\text{-}P}$ = 6.0 Hz, CH_3), 42.3 (CH_2), 35.2 (d, $J_{C\text{-}P}$ = 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, $J_{C\text{-}P}$ = 144.0 Hz, CH_2); IR (thin film) 2955, 2850, 1717, 1244 cm^{-1}; LRMS (EI) 321 (15, $[M\text{-}H]^{+\cdot}$), 219 (65), 115 (100); HRMS (EI) calcd for $C_{14}H_{26}O_6P$ $[M\text{-}H]^{+\cdot}$ 321.1461, observed 321.1465.

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

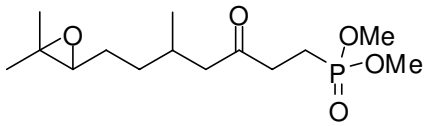


Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-7.5% MeOH/CH_2Cl_2) gave dimethyl (9-hydroxy-5,9-dimethyl-3-oxodecyl)phosphonate as a colourless oil (228 mg, 0.74 mmol, 74%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (d, $J_{H\text{-}P}$ = 11.0 Hz, 3H), 3.74 (d, $J_{H\text{-}P}$ = 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, $J_{H\text{-}P}$ = 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, $J_{C\text{-}P}$ = 14.0 Hz, C), 70.9 (C), 52.5 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 52.4 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 50.0 (CH_2), 43.8 (CH_2), 37.3 (CH_2), 35.8 (d, $J_{C\text{-}P}$ = 4.0 Hz, CH_2), 29.4 (CH_3), 29.3 (CH_3), 29.2 (CH), 21.6

(CH_2), 19.9 (CH_3), 18.1 (d, $J_{C\text{-}P}$ = 143.0 Hz, CH_2); IR (thin film) 3409, 2960, 2928, 2848, 1715, 1238 cm^{-1}; LRMS (FAB) 331 (100, $[M+Na]^+$); HRMS (FAB) calcd for $C_{14}H_{29}O_5PNa$ $[M+Na]^+$ 331.1650, observed 331.1653.

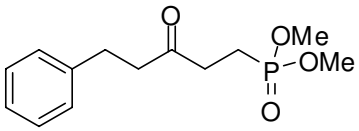
Dimethyl [7-(3,3-dimethyloxiran-2-yl)-5-methyl-3-oxoheptyl]phosphonate 199k



Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-3% MeOH/CH_2Cl_2) gave dimethyl [7-(3,3-dimethyloxiran-2-yl)-5-methyl-3-oxoheptyl]phosphonate as a 50:50 mixture of diastereoisomers as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.71 (d, $J_{H\text{-}P}$ = 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); ^{13}C NMR (150 MHz, $CDCl_3$)[***] δ 207.7 (d, $J_{C\text{-}P}$ = 14.0 Hz, C), 207.7 (d, $J_{C\text{-}P}$ = 14.0 Hz, C), 64.4 (CH), 58.5 (C), 58.4 (C), 52.6 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 50.0 (CH_2), 49.9 (CH_2), 36.0 (CH_2), 35.9 (CH_2), 33.5 (CH_2), 29.2 (CH), 29.1 (CH), 26.6 (CH_2), 26.5 (CH_2), 25.0 (CH_3), 19.8 (CH_3), 19.8 (CH_3), 18.8 (CH_3), 18.7 (CH_3), 18.2 (d, $J_{C\text{-}P}$ = 143.0 Hz, CH_3); IR (thin film) 2958, 2927, 1716, 1248 cm^{-1}; LRMS (CI) 307 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{14}H_{28}O_5P$ $[M+H]^+$ 307.1674, observed 307.1683.

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

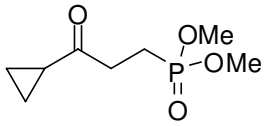


Using Method J, the reaction was complete after 72 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_2) gave dimethyl (3-oxo-5-phenylpentyl)phosphonate as a colourless oil.

[***] 28C expected, 21C observed.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.21-7.16 (m, 3H), 3.71 (d, $J_{H\text{-}P}$ = 11.0 Hz, 6H), 2.91 (t, J = 7.5 Hz, 2H), 2.76 (t, J = 7.5 Hz, 2H), 2.68 (dt, $J_{H\text{-}P}$ = 15.5 and J = 7.5 Hz, 2H), 2.01 (dt, $J_{H\text{-}P}$ = 18.0 and J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1 (d, $J_{C\text{-}P}$ = 14.0 Hz, C), 140.7 (C), 128.6 (CH), 128.4 (CH), 126.3 (CH), 52.5 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 44.1 (CH_2), 35.8 (d, $J_{C\text{-}P}$ = 4.0 Hz, CH_2), 29.8 (CH_2), 18.3 (d, $J_{C\text{-}P}$ = 143.0 Hz, CH_2); IR (thin film) 2955, 2926, 1717, 1243 cm^{-1}; LRMS (ES) 271 (100, $[M+H]^+$); HRMS (ES) calcd for $C_{13}H_{20}O_4P$ $[M+H]^+$ 271.1099, observed 271.1103.

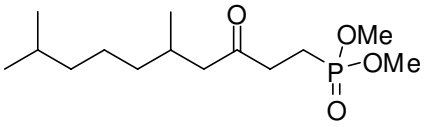
Dimethyl (3-cyclopropyl-3-oxopropyl)phosphonate 199m



Using Method J, the reaction was complete after 60 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_2) gave dimethyl (3-cyclopropyl-3-oxopropyl)phosphonate as a colourless oil (117 mg, 0.57 mmol, 57%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.75 (d, $J_{H\text{-}P}$ = 11.0 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}C NMR (150 MHz, $CDCl_3$) δ 208.0 (d, $J_{C\text{-}P}$ = 14.0 Hz, C), 52.5 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 35.8 (d, $J_{C\text{-}P}$ = 4.0 Hz, CH_2), 20.4 (CH), 18.3 (d, $J_{C\text{-}P}$ = 143.0 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 $C_8H_{15}O_4PNa$ $[M+Na]^+$ 229.0606, observed 229.0601.

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

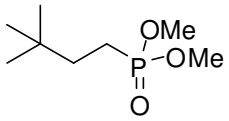


Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-4% MeOH/CH_2Cl_2) gave dimethyl (5,9-dimethyl-3-oxodecyl)phosphonate as a colourless oil (198 mg, 0.68 mmol, 68%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.72 (d, $J_{H\text{-}P}$ = 11.0 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 Hz, 1H), 1.32-1.08 (m, 6H), 0.87 (d, J = 6.5 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, $J_{C\text{-}P}$ = 14.0 Hz, C), 52.5 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 50.3 (CH_2), 39.1 (CH_2), 37.2 (CH_2), 35.9 (d, $J_{C\text{-}P}$ = 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, $J_{C\text{-}P}$ = 143.0 Hz, CH_2); IR (thin film) 2955, 2928, 1716 cm^{-1}; LRMS (CI) 293 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{14}H_{30}O_4P$ $[M+H]^+$ 293.1882, observed 293.1884.

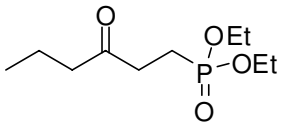
Dimethyl (3,3-dimethylbutyl)phosphonate 204



Using Method J, but at 100 °C, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_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, $J_{H\text{-}P}$ = 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, $J_{C\text{-}P}$ = 6.5 Hz, CH_3), 35.7 (d, $J_{C\text{-}P}$ = 4.0 Hz, CH_2), 30.4 (d, $J_{C\text{-}P}$ = 18.0 Hz, C), 28.7 (CH_3), 20.1 (d, $J_{C\text{-}P}$ = 140.0 Hz, CH_2); IR (thin film) 2955, 2868, 1245 cm^{-1}; LRMS (CI) 195 (100, $[M+H]^+$); HRMS (CI) calcd for $C_8H_{20}O_3P$ $[M+H]^+$ 195.1150, observed 195.1153.

Diethyl (3-oxohexyl)phosphonate 206

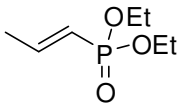


Using Method J, the reaction was complete after 24 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_2) gave diethyl (3-oxohexyl)phosphonate as a colourless oil (146 mg, 0.70 mmol, 70%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.12-4.03 (m, 4H), 2.68 (d, $J_{H\text{-}P}$ = 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, $J_{C\text{-}P}$ = 14.0 Hz, C), 61.8 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_2), 44.6 (CH_2), 35.5 (d, $J_{C\text{-}P}$ = 4.0 Hz, CH_2), 19.4 (d, $J_{C\text{-}P}$ = 144.0 Hz, CH_2), 17.4 (CH_2), 16.5 (d, $J_{C\text{-}P}$ = 6.0 Hz, CH_3), 13.8 (CH_3);

IR (thin film) 2967, 1716, 1240 cm^{-1}; LRMS (EI) 236 (15, $[M]^{+\cdot}$), 166 (100); HRMS (EI) calcd for $C_{10}H_{21}O_4P$ $[M]^{+\cdot}$ 236.1172, observed 236.1165.

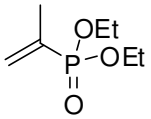
Diethyl (*E*)-prop-1-en-1-ylphosphonate 210[198]



$Pd_2(dba)_3$ (57 mg, 0.06 mmol, 5 mol%) and Cs_2CO_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 µL, 1.38 mmol) and hydrogen phosphonate diester (172 mg, 161 µL, 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_2Cl_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%).

^1H NMR (500 MHz, $CDCl_3$) δ 6.75 (ddq, $J_{H\text{-}P}$ = 52.0 and J = 13.0 and 7.0 Hz, 1H), 5.67 (ddq, $J_{H\text{-}P}$ = 20.0 and J = 13.0 and 1.5 Hz, 1H), 4.09-4.02 (m, 4H), 1.91 (ddd, $J_{H\text{-}P}$ = 3.5 and J = 7.0 and 1.5 Hz, 3H), 1.27 (t, J = 1.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.3 (d, $J_{C\text{-}P}$ = 6.0 Hz, CH), 118.5 (d, $J_{C\text{-}P}$ = 188.0 Hz, CH), 61.7 (d, $J_{C\text{-}P}$ = 6.0 Hz, CH_2), 20.3 (d, $J_{C\text{-}P}$ = 24.0 Hz, CH_3), 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz, CH_3); HRMS (CI) calcd for $C_7H_{16}O_3P$ $[M+H]^+$ 179.0837, observed 179.0834.

Diethyl prop-1-en-2-ylphosphonate 211[178]

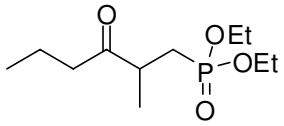


$Pd_2(dba)_3$ (57 mg, 0.06 mmol, 5 mol%) and Cs_2CO_3 (489 mg, 1.50 mmol) were placed in a microwave tube. The tube was sealed with a lid and filled with argon, by applying 3 cycles of vacuum, followed by argon. Dry THF (5 mL) was introduced *via* the septum, then was added 2-bromo-1-propene **209** (167 mg, 117 µL, 1.38 mmol) and hydrogen phosphonate diester (172 mg, 161 µL, 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_2Cl_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, $CDCl_3$) δ 5.94 (doublet of quintets, $J_{H\text{-}P}$ = 22.0 and J = 1.5 Hz, 1H), 5.72 (doublet of quintets, $J_{H\text{-}P}$ = 48.5 and J = 1.5 Hz, 1H), 4.09-4.02 (m, 4H), 1.91 (dt, $J_{H\text{-}P}$ = 14.0 and J = 1.5 Hz, 3H), 1.30 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8 (d, $J_{C\text{-}P}$ = 174.0 Hz, C), 130.0 (d, $J_{C\text{-}P}$ = 10.0 Hz, CH_2), 61.7 (d, $J_{C\text{-}P}$ = 6.0 Hz, CH_2), 18.8 (d, $J_{C\text{-}P}$ = 11.0 Hz, CH_3), 16.3 (d, $J_{C\text{-}P}$ = 6.0 Hz, CH_3); HRMS (FAB) calcd for $C_7H_{15}O_3PNa$ $[M+Na]^+$ 201.0673, observed 201.0679.

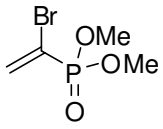
Diethyl (2-methyl-3-oxohexyl)phosphonate 212



Using Method J, the reaction was complete after 120 h. Purification by column chromatography (neat CH_2Cl_2-2.5% MeOH/CH_2Cl_2) gave diethyl (2-methyl-3-oxohexyl)phosphonate as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $J_{H\text{-}P}$ = 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, $J_{H\text{-}P}$ = 0.5 and J = 7.0 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.4 (d, $J_{C\text{-}P}$ = 9.0 Hz, C), 61.7 (d, $J_{C\text{-}P}$ = 7.0 Hz, CH_2), 61.7 (d, $J_{C\text{-}P}$ = 7.0 Hz, CH_2), 43.2 (CH_2), 40.6 (d, $J_{C\text{-}P}$ = 2.5 Hz, CH), 28.0 (d, $J_{C\text{-}P}$ = 140.0 Hz, CH_2), 18.6 (d, $J_{C\text{-}P}$ = 11.0 Hz, CH_3), 17.1 (CH_2), 16.5 (d, $J_{C\text{-}P}$ = 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 $C_{11}H_{23}O_4PNa$ $[M+Na]^+$ 273.1232, observed 273.1227.

Dimethyl (1-bromoethenyl)phosphonate 214

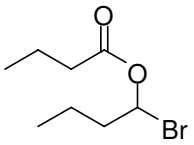


To a stirring solution of dimethyl vinyl phosphonate **198** (680 mg, 5.0 mmol) in CH_3Cl (10 mL) was added excess bromine (5 mL) and the reaction mixture left to stir at 21 °C for 16 h. The solvent and excess bromine were removed *in vacuo*, PhMe (20 mL) added and then was added NEt_3 (607 mg, 840 μL, 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_2O (50 mL), washed with sat. K_2CO_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_2Cl_2-2% MeOH/ CH_2Cl_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, $J_{H\text{-}P}$ = 3.5 and J = 0.5 Hz, 1H), 6.49 (dd, $J_{H\text{-}P}$ = 9.5 and J = 0.5 Hz, 1H), 3.74 (d, $J_{H\text{-}P}$ = 11.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9 (dt, $J_{C\text{-}P}$ = 14.0 Hz), 117.4 (ds, $J_{C\text{-}P}$ = 200.0 Hz), 53.3 (dq, $J_{C\text{-}P}$ = 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 $C_4H_9BrO_3P$ $[M^{79}Br + H]^+$ 214.9473, observed 214.9468.

Experimental for Chapter 6

1-Bromobutyl butanoate 219



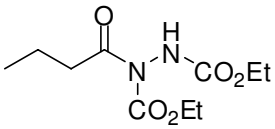
n-Butanal **18a** (72 mg, 90 μL, 1 mmol) was added to a solution of NBS (214 mg, 1.2 mmol) in CCl_4 (2 mL) and the reaction mixture left to stir at 21 °C for 2 h. The solvent was removed *in vacuo*, the solids filtered off, washed with CCl_4 (10 mL) and the filtrate solvent removed *in vacuo* to afford 1-bromobutyl butanoate as a yellow oil (211 mg, 0.95 mmol, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (C), 76.2 (CH), 41.3 (CH_2), 36.1 (CH_2), 19.3 (CH_2), 18.2 (CH_2), 13.6 (CH_3), 13.3 (CH_3); IR (thin film) 2934, 1732 cm^{-1}; LRMS (EI) 143 (100, $[M\text{-}Br]^{+\cdot}$); HRMS (EI) calcd for $C_8H_{15}O_2$ $[M\text{-}Br]^{+\cdot}$ 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_2O (500 μL) 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 acyl hydrazide.

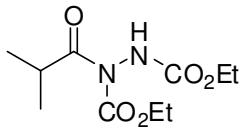
Diethyl 1-butanoylhydrazine-1,2-dicarboxylate 222a



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%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (C), 155.6 (C), 153.3 (C), 63.9 (CH_2), 62.6 (CH_2), 38.9 (CH_2), 18.1 (CH_2), 14.4 (CH_3), 14.2 (CH_3), 13.6 (CH_3); IR (thin film) 3309, 2968, 2877, 1738, 1717 cm^{-1}; LRMS (FAB) 269 (100, $[M+Na]^{+}$); HRMS (FAB) calcd for $C_{10}H_{18}N_2O_5Na$ $[M+Na]^{+}$ 269.1113, observed 269.1118.

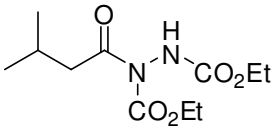
Diethyl 1-(2-methylpropanoyl)hydrazine-1,2-dicarboxylate 222b



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 $C_{10}H_{19}N_2O_5$ $[M+H]^+$ 247.1294, observed 247.1284.

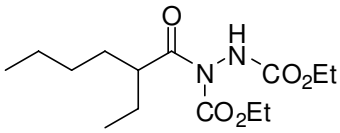
Diethyl 1-(3-methylbutanoyl)hydrazine-1,2-dicarboxylate 222c



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 $C_{11}H_{21}N_2O_5$ $[M+H]^+$ 261.1451, observed 261.1442.

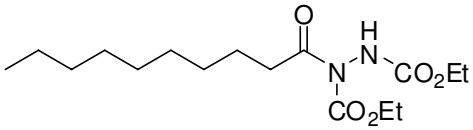
Diethyl 1-(2-ethylhexanoyl)hydrazine-1,2-dicarboxylate 222f



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%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.73 (br s, NH, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 4.23-4.14 (m, 2H), 3.56-3.47 (m, 1H), 1.74-1.65 (m, 2H), 1.57-1.42 (m, 2H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.30-1.18 (m, 7H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.5 (C), 155.7 (C), 153.3 (C), 64.0 (CH_2), 62.6 (CH_2), 46.1 (CH), 31.6 (CH_2), 29.5 (CH_2), 25.5 (CH_2), 22.9 (CH_2), 14.5 (CH_3), 14.2 (CH_3), 14.1 (CH_3), 11.7 (CH_3); IR (thin film) 3305, 2962, 2934, 2874, 1740, 1720 cm^{-1}; LRMS (CI) 303 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{14}H_{27}N_2O_5$ $[M+H]^+$ 303.1920, observed 303.1925.

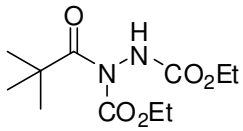
Diethyl 1-decanoylhydrazine-1,2-dicarboxylate 222g



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%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.73 (br s, NH, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 4.21 (q, *J* = 7.0 Hz, 2H), 2.97-2.89 (m, 2H), 1.64 (quintet, *J* = 7.0 Hz, 2H), 1.35-1.24 (m, 18H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0 (C), 155.7 (C), 153.3 (C), 64.0 (CH_2), 62.7 (CH_2), 37.1 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 24.7 (CH_2), 22.8 (CH_2), 14.5 (CH_3), 14.3 (CH_3), 14.2 (CH_3); IR (thin film) 3311, 2924, 2855, 1740, 1722 cm^{-1}; LRMS (ES^-) 329 (100, $[M-H]^-$); HRMS (ES^-) calcd for $C_{16}H_{29}N_2O_5$ $[M-H]^-$ 329.2076, observed 329.2084.

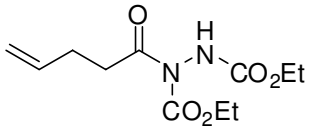
Diethyl 1-(2,2-dimethylpropanoyl)hydrazine-1,2-dicarboxylate 222q



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 $C_{11}H_{20}N_2NaO_5$ $[M+Na]^+$ 283.1270, observed 283.1270.

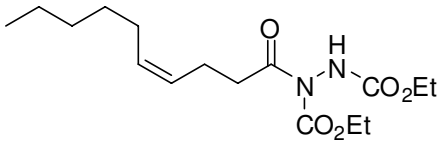
Diethyl 1-(pent-4-enoyl)hydrazine-1,2-dicarboxylate 222n



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 $C_{11}H_{19}N_2O_5$ $[M+H]^+$ 259.1294, observed 259.1289.

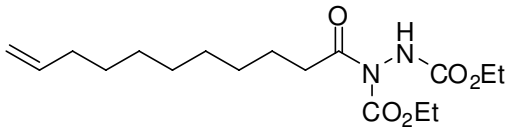
Diethyl 1-[(4*Z*)-dec-4-enoyl]hydrazine-1,2-dicarboxylate 222y



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

^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 173.4 (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 $C_{16}H_{29}N_2O_5$ $[M+H]^+$ 329.2077, observed 329.2083.

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



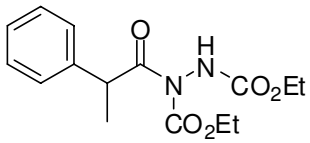
Using Method K, the reaction was complete after 48 h. Purification by column chromatography (10%-30% EtOAc/petrol) gave diethyl 1-[undec-10-enoyl]hydrazine-1,2-dicarboxylate as a colourless oil (291 mg, 0.85 mmol, 85%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$)[†††] δ 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 $C_{17}H_{30}N_2NaO_5$ $[M+Na]^+$ 365.2052, observed 365.2034.

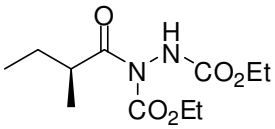
Diethyl 1-(2-phenylpropanoyl)hydrazine-1,2-dicarboxylate 222w



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 $C_{15}H_{20}N_2NaO_5$ $[M+Na]^+$ 331.1270, observed 331.1283.

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

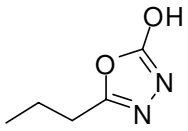


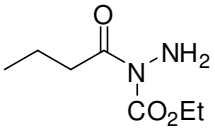
Using Method K, the reaction was complete after 24 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave (2*S*)-diethyl 1-(2-methylbutanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (229 mg, 0.88 mmol, 88%).

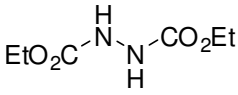
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (br s, NH, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.58-3.44 (m, 1H), 1.79 (doublet of quintets, *J* = 14.5 and 7.0 Hz, 1H), 1.46 (doublet of quintets, *J* = 14.5 and 7.5 Hz, 1H), 1.34-1.22 (m, 6H), 1.18 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.5 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),

14.5 (CH_3), 14.3 (CH_3), 11.7 (CH_3); IR (thin film) 3313, 2979, 2938, 1742, 1724 cm^{-1}; LRMS (CI) 261 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{11}H_{21}N_2O_5$ $[M+H]^+$ 261.1450, observed 261.1445; $[\alpha]_D$ = +20.5 (c 0.50, $CHCl_3$, 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 H_2O (10 mL) and extracted with EtOAc (5 × 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (1%-5% MeOH/CH_2Cl_2) 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**: ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.4 (C), 155.2 (C), 28.4 (CH_2), 19.0 (CH_2), 13.5 (CH_3); IR (thin film) 3300, 2959, 2872, 1670, 1640 cm^{-1}; LRMS (CI) 129 (100, $[M+H]^+$); HRMS (CI) calcd for $C_5H_9N_2O_2$ $[M+H]^+$ 129.0664, observed 129.0660.

Data for **227**: ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.0 (C), 154.0 (C), 40.7 (CH_2), 28.3 (CH_2), 19.1 (CH_2), 13.6 (CH_3), 13.5 (CH_3); IR (thin film) 3350, 3300, 2967, 1782, 1720 cm^{-1}; LRMS (CI) 175 (100, $[M+H]^+$); HRMS (CI) calcd for $C_7H_{15}N_2O_3$ $[M+H]^+$ 175.1004, observed 175.1014.

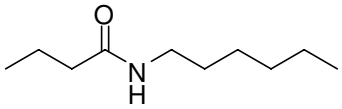
Data for **223**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.0 Hz, 4H), 1.26 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.1 (C), 62.4 (CH_2), 14.5 (CH_3); IR

(solid) 2934, 1737 cm^{-1}; LRMS (CI) 177 (100, $[M+H]^+$); HRMS (CI) calcd for $C_6H_{13}N_2O_4$ $[M+H]^+$ 177.0875; observed 177.0879.

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_2Cl_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.

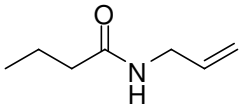
N-Hexylbutanamide 220a



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%).

^1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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

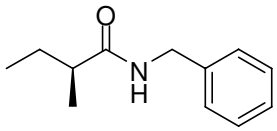


Using Method L, the reaction was complete after 16 h. Purification by column chromatography (20%-60% EtOAc/petrol) gave *N*-(prop-2-en-1-yl)butanamide as a colourless oil (121 mg, 0.95 mmol, 95%).

^1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $[M]^{+\cdot}$); HRMS (EI) calcd for $C_7H_{13}NO$ $[M]^{+\cdot}$ 127.0992, observed 127.0995.

(2*S*)-*N*-Benzyl-2-methylbutanamide 228[199]



Using Method L, the reaction was complete after 16 h. Purification by column chromatography (50% Et_2O/petrol) gave (2*S*)-*N*-benzyl-2-methylbutanamide as a colourless oil (160 mg, 0.84 mmol, 84%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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).[199]

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Appendix