University College London

Radical Hydroacylation of C-C and N-N Double Bonds in Air

by

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Declaration

I, Jenna Marie Ahern, 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.

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Abstract

The formation of C-C and C-N bonds in modern organic synthesis is a key target for methodological advancement. Current methods of C-C and C-N bond formation often involve the use of expensive catalysts, or sub-stoichiometric reagents, which can lead to the generation of undesirable waste products. This thesis describes a novel and environmentally benign set of reaction conditions for the formation of C-C and C-N bonds by hydroacylation and this is promoted by mixing two reagents, an aldehyde and an electron-deficient double bond, under freely available atmospheric oxygen at room temperature

Chapter 1 will provide an introduction to the thesis and mainly discusses methods for C-C bond formation, in particular, radical chemistry and hydroacylation. Chapter 2 describes the hydroacylation of vinyl sulfonates and vinyl sulfones (C-C double bonds) with aliphatic and aromatic aldehydes with a discussion and evidence for the mechanism of the transformation. Chapter 3 details the synthesis of precursors for intramolecular cyclisations and studies into aerobic intramolecular cyclisations. Chapter 4 describes the hydroacylation of vinyl phosphonates (C-C double bonds) and diazocarboxylates (N-N double bonds) with aliphatic and aromatic aldehydes bearing functional groups. In addition, the hydroacylation of diazocarboxylates with chiral aldehydes will be discussed.

In conclusion, a new, facile and clean set of reaction conditions for the formation of C-C and C-N bonds has been developed *via* aerobic C-H activation of aldehydes providing access to unsymmetrical ketones.

Contents

Acknowledgments

Abbreviations

$[\alpha]_D$	Specific rotation
AIBN	Azobis(isobutyronitrile)
ACCN	Azobis(cyclohexanecarbonitrile)
BPO	Dibenzoyl peroxide
CO	Carbon monoxide
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarisation transfer
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
E	Entgegen (opposite, *trans*)
ee	Enantiomeric excess
EPHP	1-Ethyl-piperidine hypophosphite
EWG	Electron-withdrawing group
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
LUMO	Lowest unoccupied molecular orbital
m.p	Melting point
MTG	Methyl thioglycolate

NHPI	*N*-hydroxyphthalimide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PFP	Pentafluorophenyl
PPTS	Pyridinium *p*-toluenesulfonate
rt	Room temperature
S_N2	Bimolecular nucleophilic substitution
SOMO	Singly occupied molecular orbital
TBAF	*tetra-n*-Butylammonium fluoride
TBHN	Di-*tert*-butyl hyponitrite
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
TCP	Trichlorophenyl
TDT	*tert*-Dodecanethiol
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TTMSS	Tris(trimethylsilyl)silane
UCL	University College London
Z	Zusammen (together, *cis*)

Chapter 1   Introduction

Radical reactions have become important since the discovery of the triphenylmethyl radical over a century ago.[1]   Radical chemistry complements traditional ionic methods used in organic synthesis as typically they are carried out under neutral reaction conditions, which are tolerated by a wide range of functional groups and they are often insensitive to the type of solvent used. This contrasts to ionic reactions, which often show poorer functional group tolerance and can be critically dependent on correct choice of solvent and sensitive to solvation effects.   For example, an S_N2 displacement can be accelerated by a factor of 10^6 by the use of a polar aprotic solvent in replace of a protic one. It is also worth noting one important general advantage of free-radical reactions is that because of their ambiphilic nature, they can react with both electron rich and electron poor substrates.

1.1 Discovery and history of free radicals

The pioneering study into free radical chemistry was conducted by Gomberg in 1900.[2,3] Whilst investigating the reaction of chlorotriphenylmethane (**1**) with various metals, Gomberg found that, instead of obtaining expected radical recombination product **2**, dialkyl peroxide **3** was isolated instead, whereby oxygen had been incorporated into the product, *via* reaction of tertiary radical **4** with molecular oxygen (Scheme 1). When an analogous reaction was carried out under an atmosphere of carbon dioxide, triene **5**, derived from radical recombination of triphenylmethane radical **4** and **6,** was isolated. Intriguingly, intermediate triphenylmethane radical **4** does not combine to give dimer **2**, and has since been described as being of the class of radicals termed 'persistent'. Persistent radicals are long-lived species that recombine very slowly due to steric crowding around the radical centre. However, such radicals will recombine rapidly with radicals of a different kind e.g. in the case of triphenylmethane radical **4**, recombination with molecular oxygen to give peroxide **3** is rapid
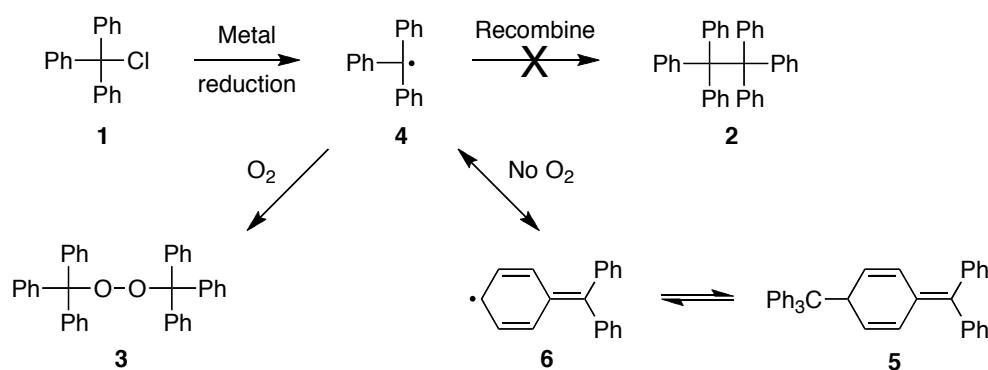
Scheme 1 Attempted synthesis of hexaphenylethane **2**

Despite the initial discovery by Gomberg, the significance of radical chemistry was not realised by chemists until around three decades later. At this time, Kharasch and co-workers discovered that when an olefin **7** was subjected to hydrogen bromide in the absence of oxygen, the ionic Markovnikov product **8** prevails.[4] However, in the presence of molecular oxygen, anti-Markovnikov product **9** was obtained *via* radical intermediate **10** (Scheme 2).
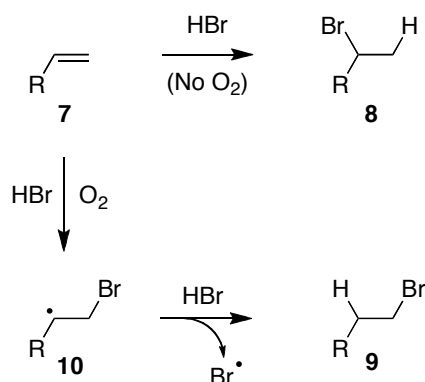
Scheme 2 Formation of Markovnikov and anti-Markovnikov products from hydrobromination of terminal alkene **7**

1.2 Comparison between radical and ionic reactions

One of the main difficulties in utilising radical reactions is that synthetically useful free-radicals are highly reactive, short-lived species and often undergo undesired side-reactions.[5] Ionic reactions on the other hand utilise intermediates that can often be more stable and hence survive for longer periods allowing the desired reaction to take place. Due to the reactivity of radical species, dimer formation (mainly primary and secondary radicals) or disproportionation (mainly tertiary radicals) can be a problem. In order to try and prevent these problems, the concentration of radical species can be kept low to and avoid dimerisation and allow the radical species to

react in the desired fashion. Radicals, being neutral and barely solvated, are not affected to any large extent by the type of solvent used, and the absence of a counterion means that steric factors are relatively less important in radical transformations. Unlike ionic reactions, which proceed through either the HOMO or LUMO of a substrate, radicals always react through their singly occupied molecular orbital (SOMO). This molecular orbital can interact with either a HOMO or a LUMO, as both interactions result in a net stabilisation to the system (Figure 1).
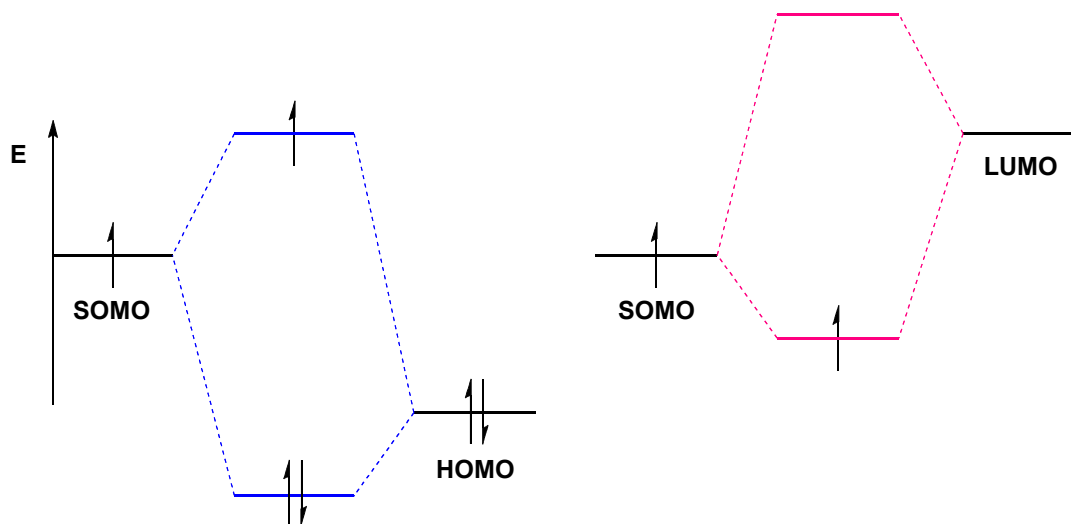
Figure 1 Orbital diagram of SOMO interacting with both a HOMO and a LUMO

1.3 Radical chain reactions

Radical reactions are known to proceed *via* chain processes (Scheme 3).[6] That is, once an initial radical **11** is generated, it will go on to react with a non-radical entity **12**, to form a subsequent radical **13** known as a chain carrier, which will then propagate the chain process. Addition of **13** to an olefin **14** generates adduct radical **15**. For each step in the process, a radical is consumed and a new radical is generated. The chain process is terminated when two free radicals recombine.

Scheme 3 Radical chain process
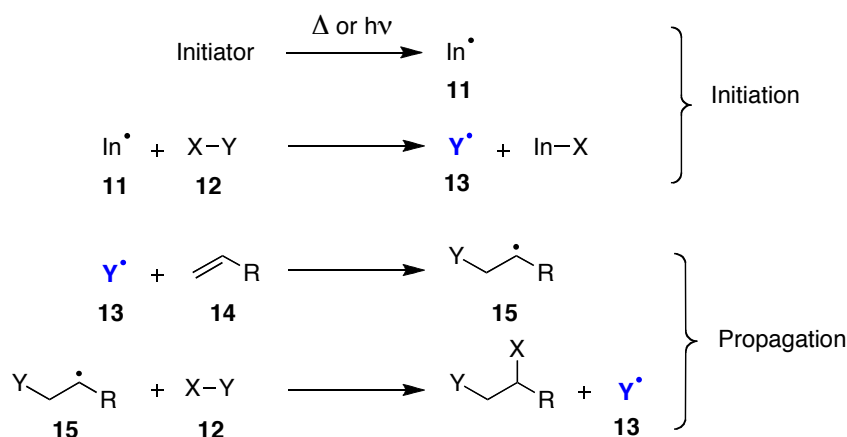
1.3.1 Trialkyltin radicals as chain carriers

One of the most important pieces of work done in the field of radical chemistry, which exploits the radical chain process, was carried out by van der Kerk in 1957.[7] Whilst attempting a Kharasch-type addition of triphenyltin hydride to allyl bromide (**16**), in the presence of oxygen, propene (**17**) was isolated instead of the expected alkyltin **18**, presumably formed *via* abstraction of bromine from allyl bromide (**16**) to give allyl radical **19** and subsequent hydrogen atom abstraction from triphenyltin hydride (Scheme 4). This reduction of halides in the presence of organotin hydrides has since gone on to become one of the most well known radical transformations in modern chemistry.

Scheme 4 Dehalogenation using organotin hydride
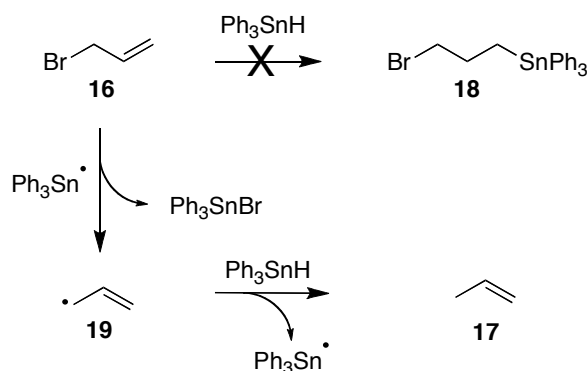
Tributyltin hydride (**20**) is widely used as a chain carrier and often coupled with diazo compounds such as AIBN (**21**) and azobis(cyclohexanecarbonitrile) as initiators since they decompose readily upon heating (Scheme 5).[8] The chain carrier is the tributyltin radical **23** which propagates the chain by abstraction of group X

4

from substrate **24** where X can be I, Br, SePh, xanthate ester, Cl or SPh[9] to generate alkyl radical **25**. Subsequently, abstraction of a hydrogen atom from tributyltin hydride (**20**) gives alkane **26** and regenerates tributyltin radical **23**, propagating the chain process.
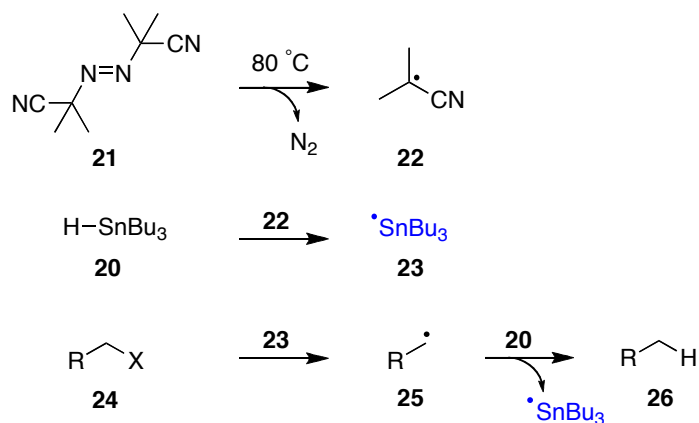
X = I, Br, SePh, Cl, SPh, xanthate esters

Scheme 5 Chain propagation with tributyltin hydride **20**

One major disadvantage of using organotin reagents is their toxicity, and to-date this has limited the use of radical reactions in industry. In addition to their toxicity, they are often used stoichiometrically and it is generally difficult to remove tin containing by-products.[10] In order to circumvent the problems associated with stoichiometric organotin hydride reactions, Fu and co-workers have developed an organotin hydride-catalysed method for the reduction of α,β-unsaturated ketones **27**.[11] It was shown that treatment of α,β-unsaturated ketones **27** with 10 mol% tributyltin hydride and 1.2 equivalents of silicon hydride gave silyl enol ethers **28**, which after base hydrolysis afforded ketones **29** in good yields (>75%).
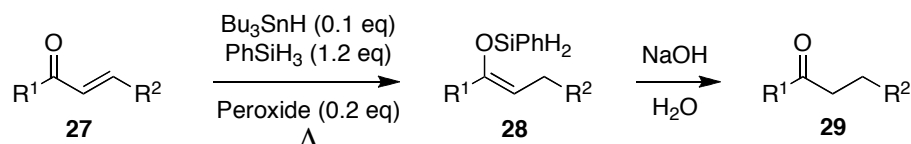
Scheme 6 Reduction of α,β-unsaturated ketones **27** using catalytic organotin hydride

1.4 Radical chemistry in synthesis

One of the first preparatively useful radical reactions, was published by Kharasch and co-workers in 1948; they carried out addition of an aldehyde **30** to an olefin **31** initiated by diacetyl peroxide.[12] A 6:1 aldehyde:olefin stoichiometry was found to

give good yields and a representative example is the reaction of heptanal with 1-octene to give the corresponding ketone in 75% yield. Small amounts of higher boiling point products were observed when reactions were initiated with diacetyl peroxide (derived from reaction of more than one equivalent of alkene **31** with aldehyde **30**). However, the corresponding photochemically initiated reaction provided much cleaner reactions with generation of only the 1:1 adduct **32**.
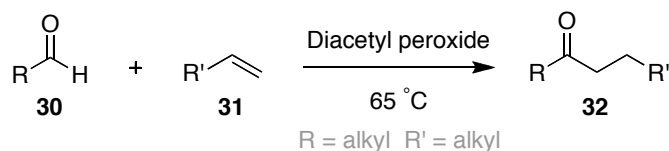
Scheme 7 Kharasch initiation with diacetyl peroxide

1.4.1 Radical initiators

1.4.1.1 AIBN

Azo compounds are a common class of radical initiators and of these azobisisobutyronitrile (**21**, AIBN) is one of the most well known.[13] AIBN readily decomposes upon heating, driven by release of a mole equivalent of nitrogen to generate isobutyronitrile radicals **22**, which can go on to initiate chain processes (Scheme 8).
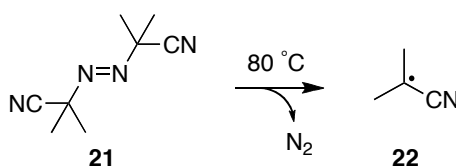
Scheme 8 AIBN (**21**) decomposition to generate isobutyronitrile radicals **22**

1.4.1.2 Diacyl peroxides

Diacyl peroxides **33** are often used to initiate radical chain processes *via* thermal activation and homolysis of the weak O-O bond to give acyloxy radical **34**. (Scheme 9). This oxygen centred radical **34** can initiate radical chain processes itself; however, when R = alkyl, such as in lauroyl peroxide, acyloxy radical **34** rapidly decarboxylates further to give carbon centred radical **35**.[14]
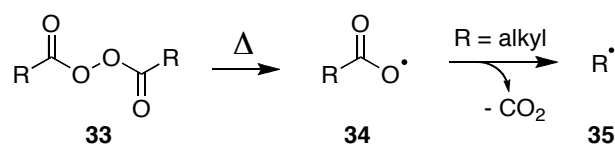
Scheme 9 Decomposition of peroxides **33**

There are a variety of different peroxides employed in radical chemistry; in 2002, Zard and co-workers used lauroyl (dodecanoyl) peroxide and xanthate esters **36** in order to effect a 5-*exo*-trig cyclisation of *N*-(*O*-ethyl thiocarbonylsulfanyl)amides to give various pyrrolidinone derivatives **37**.[15] The chain is initiated by decomposition of lauroyl peroxide, which occurs readily upon heating.
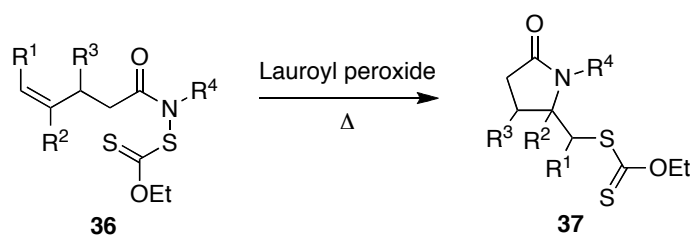
Scheme 10 Intramolecular radical cyclisation

1.4.1.3 Triethylborane/oxygen

Using triethylborane and air to generate ethyl radicals is an attractive system for use as a radical initiator, as it functions at room temperature by the generation of ethyl radicals.[16] However, several problems are associated with the use of triethylborane including reaction reproducibility, and reagent stability. Thus, in 2008, Montgomery and co-workers developed alternative boranes, in particular 2-alkylbenzo[*d*][1,3,2]dioxaboroles.[17] For example, it was possible to reduce bromo-alkanes **38** in good yields (>70%) to give the corresponding alkane **39** using 2-propyl-benzo[*d*][1,3,2]dioxaborole (**40**) in the presence of tributyltin hydride (Scheme 11).
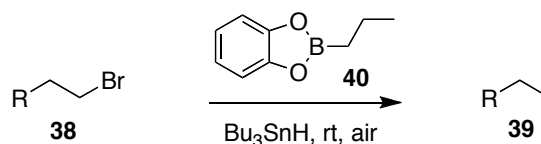
Scheme 11 Reduction of bromo-alkanes **38** using borane derivative **40**

1.4.1.4 Radical reactions promoted by transition metals

Since the mid 1980's, transition metals in radical reactions have been employed as an alternative to toxic stannanes (see section 1.3.1), including titanium, vanadium, manganese, iron, cobalt and copper.[18] Heiba and Dessau showed that radicals can be formed by hydrogen abstraction from the methyl group of acetic acid when Mn(III) acetate, is employed as a reagent.[19,20] Similarly, ketones, esters, and aldehydes can also be oxidised to generate a radical on a carbon atom adjacent to a carbonyl group.[18] Based on this work, McQuillin and Wood showed that substituted tetralones **41** could be synthesised utilising Mn(III) acetate.[21] On addition of Mn(III) acetate to acetophenone (**42**), α-oxyalkyl radical **43** is formed which undergoes intermolecular addition to olefin **44** generating adduct radical **45** which then undergoes intramolecular addition to the aromatic ring. Subsequent oxidation of the resultant radical restores aromaticity and provides tetralone **41**.

42   **43**   **45**   **41**
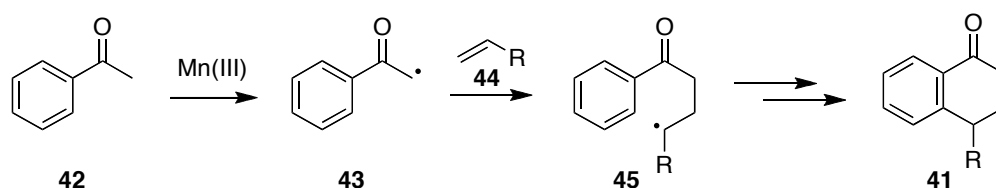
Scheme 12 Synthesis of tetralones **41** using Mn(III) acetate

Skrydstrup and co-workers have reported the use of samarium diiodide in the generaton of ketyl radicals from both thiopyridyl esters and *N*-acyloxazolidinones.[22,23] *N*-acyloxazolidinones **46** were coupled to a range of olefins **47** in moderate yields to give 1,4-dicarbonyls **48** *via* the generation of a ketyl radical.[24]

46   **47**   **48**
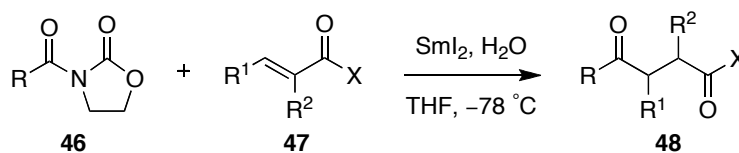
R = benzyl, *t*-butyl X = NH*t*-Bu, OEt

Scheme 13 Coupling of *N*-acyloxazolidinones **46** with acrylates and acrylamides

1.4.2 Non-tin based radical chain carriers

Given the problems associated with organotin reagents (see section 1.3.1), the development of alternative chain carriers for carrying out radical reactions has been a

focus in the radical chemistry community. Other radical chain carriers include hypophosphites, boranes, silanes and germanes to name a few.[25]

1.4.2.1 1-Ethyl-piperidine hypophosphite (EPHP)

1-Ethyl-piperidine hypophosphite (**49**) is considered one of the best substitutes to tin-based chain carriers, not only for the dehalogenation of alkyl halides but also as a radical chain carrier in C-C bond forming processes *via* radical addition to C-C multiple bonds. It has generally been observed that EPHP (**49**) is more effective in halogenation with alkyl iodides than with alkyl bromides.[26] For example, Caddick and co-workers utilised EPHP (**49**) as a radical chain carrier for the addition of alkyl iodides to pentafluorophenyl (PFP) acrylate **50** with the use of triethylborane and air as a radical initiator to generate alkyl PFP esters **51** under mild reaction conditions (Scheme 14).[27]
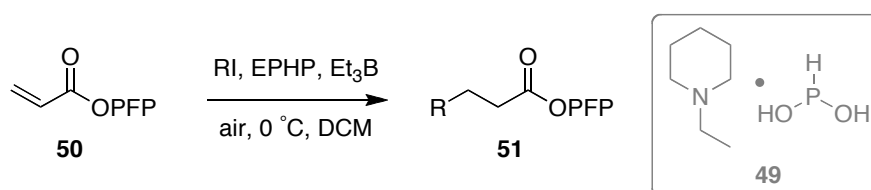
Scheme 14 Addition of alkyl iodides to PFP acrylate **50**

1.4.2.2 Organosilicon hydrides

Silicon and germanium based reagents are noteworthy radical chain carriers. Alkyl silanes have been shown to react through abstraction of hydrogen from the Si-H bond, albeit very slowly at room temperature due to the strength of the Si-H bond. For triethylsilane, the rate of hydrogen abstraction is too slow for the reagent to be employed as a radical chain carrier; however, the Si-H bond can be weakened by changing the substituents on silicon.[28] Thus, tris(trimethylsilyl)silane (TTMSS) has been shown to be a highly successful reagent as its reactivity is similar to tributyltin hydride (**20**). For example, Almirante and Cerri illustrated the use of TTMSS in the synthesis of the natural product digitoxigenin **52** from alkyl iodide **53** (Scheme 15).[29]
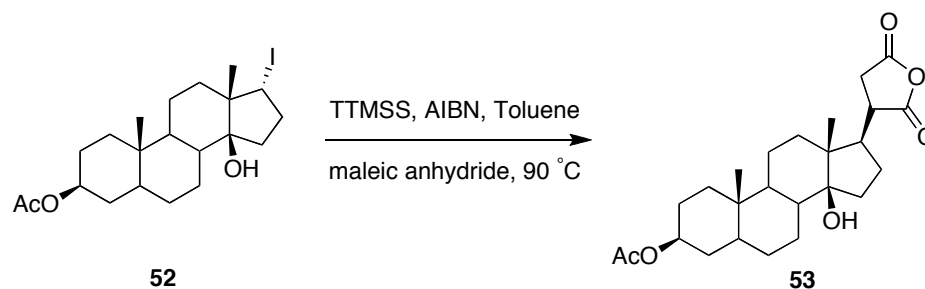
Scheme 15 Use of TTMSS in the synthesis of digitoxigenin **53**

Giese and co-workers have shown TTMSS can be used in some intermolecular radical additions to give isolated yields higher than when using tributyltin hydride. For instance, radical addition of a cyclohexyl radical, derived from cyclohexyl iodide (**54**) in the presence of TTMSS, to acrylonitrile (**55**) gave nitrile **56** in an excellent yield of 90%.[30]
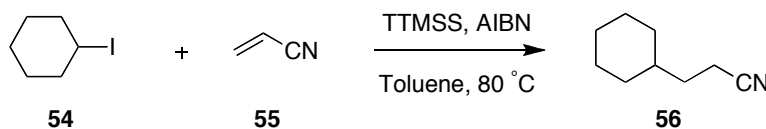
Scheme 16 Reaction of cyclohexyl iodide **54** and acrylonitrile **55**

1.4.3 Radical chemistry in complex molecule synthesis

There have been many total synthesis campaigns that have utilized radical chemistry in order to carry out cascade reactions whereby a complex structure is built up in just a single step. An example of a radical cascade sequence was carried out in 1992 by Parker and co-workers in the synthesis of (–)-morphine (**57**, Scheme 17)[31] In only one step, two rings and a quarternary stereocentre were formed by reaction of **58** with tributyltin hydride and AIBN at elevated temperature. Generation of the aryl radical **59** by abstraction of bromine from aryl bromide **58** led, *via* a 5-*exo*-trig cyclisation, to generation of alkyl radical **60**. Subsequent cyclisation of alkyl radical **60** onto the vinyl sulfide in a 6-*endo*-trig manner, and elimination of a phenyl-sulfinyl radical **61**, led to cyclohexene **62**, which after further manipulation provided the natural product **57**.
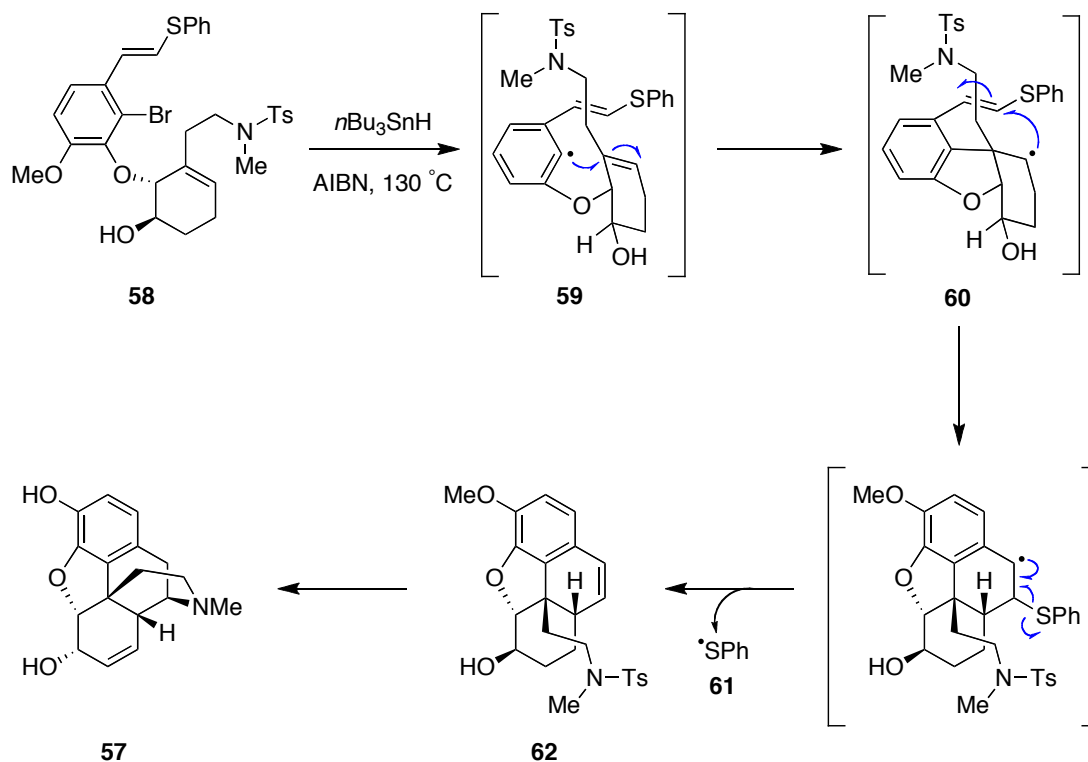
Scheme 17 Radical cascade employed in Parker's total synthesis of (−)-morphine **57**

The total synthesis of 13-deoxyserratine (**63**) was carried out by Zard and co-workers in 2002 using methodology they had developed to generate nitrogen-centred radicals (Scheme 18).[32]   Once nitrogen-centred radical **64** had been formed, the reaction proceeded *via* cyclisation onto the cyclopentenone followed by cyclisation onto the terminal alkene, to furnish tetracycle **65**. Subsequent dechlorination led to tetracycle **66**, a precursor to the natural product **63**. Without the presence of the chlorine atom, an unwanted 5-*exo* closure occurred as expected. However, by placing a chrorine atom on the olefinic trap, this was discouraged and cyclisation took place in a 6-*endo* fashion.

Scheme 18 Radical cascade using a nitrogen-centred radical
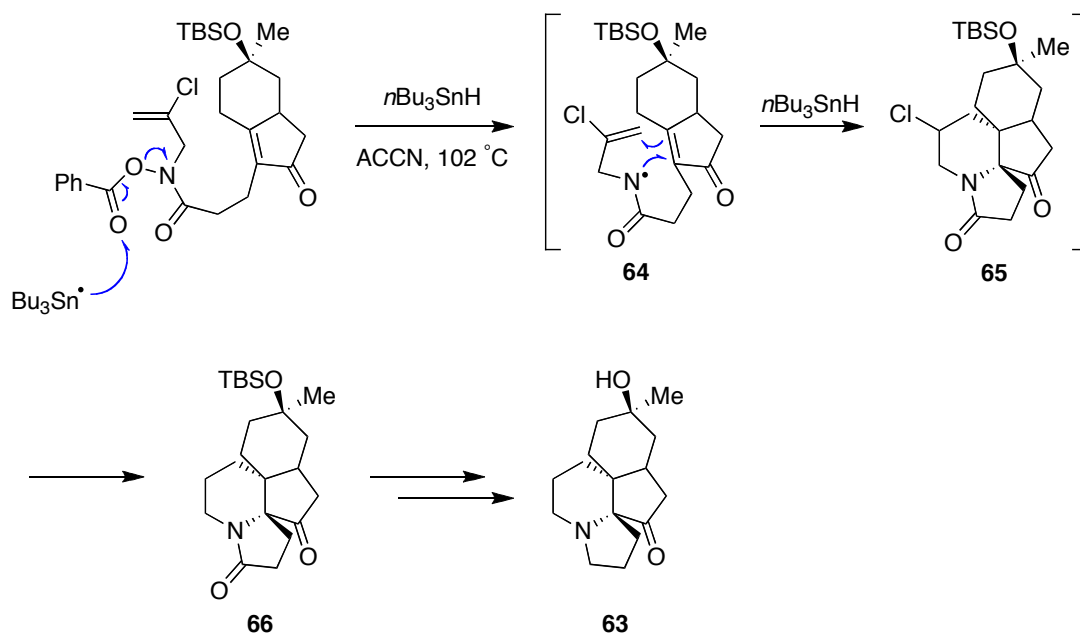
There are many examples of radical cascade cyclisations in the literature, which have been utilised in order to build complex natural products, and without which the total syntheses in question would not proceed with such ease.[33,34,35,36,37]

1.5 Hydroacylation

Formally, hydroacylation is the addition of –H and –C(O)R across a multiple bond; in that both the acyl group and the hydrogen from a starting aldehyde **30** are transferred across a multiple bond A=B **67** to afford hydroacylation product **68**. The term hydroacylation was first coined by Schwartz and Cannon,[38] and the field has since received much attention in the literature, representative examples of which are described below.

Scheme 19 Hydroacylation
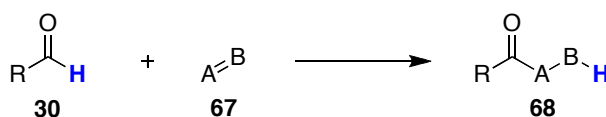
1.5.1 Transition metal catalysed hydroacylation

One common approach to effect the hydroacylation of double and triple bonds is through the use of transition metal catalysis. In this approach, an aldehydic C-H bond can be activated to react with an unsaturated bond by formation of an acyl metal

hydride **69**.[39] This acyl metal hydride **69** then inserts into an unsaturated bond **70** to give metal complex **71** (Scheme 20). Reductive elimination of **71** affords ketone **72**. The main problem faced in metal catalysed hydroacylation reactions is decarbonylation of the acyl metal hydride **69**, which occurs readily due to the stability of metal carbonyl compounds, to give metal carbonyl complex **73** and alkane **74** *via* metal hydride **75**.
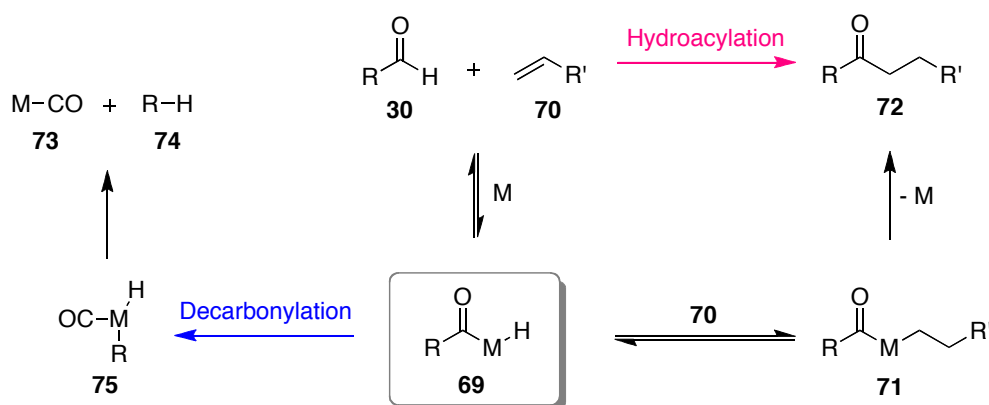
Scheme 20 Transition metal catalysed hydroacylation and decarbonylation

Due to the ease with which decarbonylation occurs, research groups have investigated ways in which it can be avoided in order to facilitate the desired hydroacylation. In 2003, Willis and co-workers showed that using imines of 2-amino-3-picoline **76** as aldehyde equivalents in the hydroacylation of methyl acrylate (**77**), decarbonylation could be avoided because the reaction occurred *via* stable metallocycle **78** (Scheme 21).[40] Subsequent hydrolysis with aqueous hydrochloric acid afforded 1,4-dicarbonyls **79** in excellent yields.
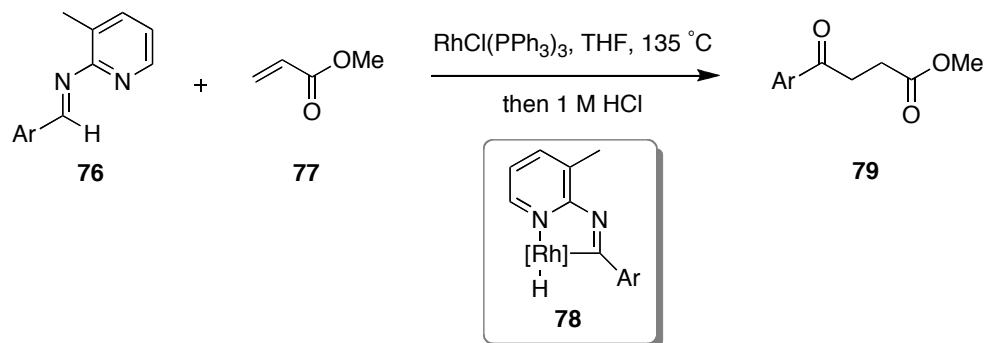
Scheme 21 Hydroacylation of methyl acrylate **77**

Willis and co-workers also reported the use of β-methyl sulfide substituted aldehyde **80** in order to chelate to the metal centre *via* 5-membered metallocycle **81** (Scheme

22).[41,42] Addition of aldehyde **80** to methyl acrylate (**77**) successfully gave ketone **82** in 74% yield. Although the methyl sulfide group functioned well as a coordinating substituent, manipulation of the moiety after hydroacylation was limited. Willis and co-workers have also expanded their work to incorporate hydroacylation with aldehydes containing thio-acetals and to the hydroacylation of triple bonds.[43,44]
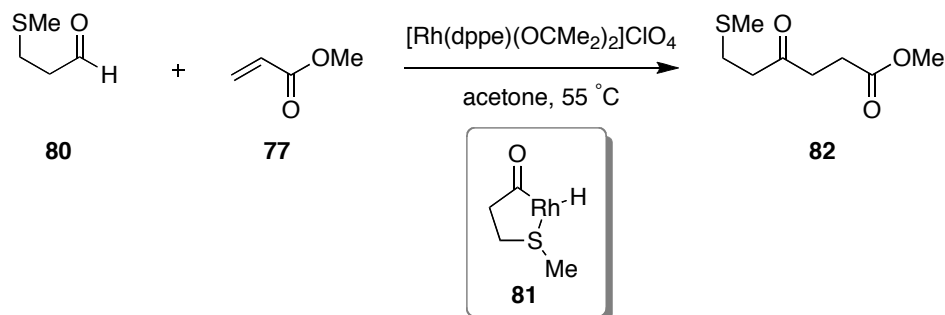
Scheme 22 Hydroacylation of methyl acrylate **77** using sulfur to coordinate to the metal centre

In 2004, Lee and Otte reported the rhodium catalysed C-H activation of aldehydes **30** in the hydroacylation of diisopropyl azodicarboxylate (**83**, DIAD) to give ketones **84** (Scheme 23).[45] It was found that the reaction was much slower when carried out with α,β-unsaturated and aromatic aldehydes. Yields for hydroacylation with aromatic aldehydes did not exceed 48% except for with 2,6-dichloro-benzaldehyde (78%); in contrast, excellent yields were obtained for aliphatic aldehydes.
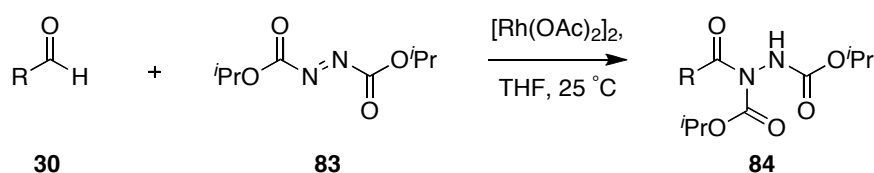
Scheme 23 Rhodium catalysed hydroacylation of DIAD (**83**)

1.5.1.1 Intramolecular rhodium catalysed hydroacylation

Rhodium catalysed hydroacylation of 4-alkenals is a well known method for the generation of cyclopentanones.[46,47] More recently, Tanaka and co-workers have reported intramolecular hydroacylation of 5-alkynals **85** to give cyclopentenones **86** in excellent yields (Scheme 24).[48] However, when R^2 = OMe, only moderate yields were obtained (~55%). In addition, 6-alkynals can be cyclised using a rhodium catalyst in order to afford the corresponding cyclohexanones in excellent yields.
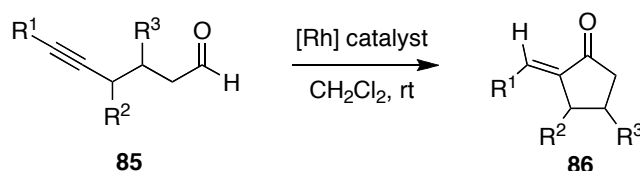
Scheme 24 Rhodium catalysed cyclisation of 5-alkynals **85**

1.5.2 Hydroacylation in ionic liquids

Recently it has been reported by Zhang and co-workers that azodicarboxylates **87** can be converted to there corresponding hydrazine imides **88** *via* hydroacylation with a range of aldehydes **30** in the presence of an ionic liquid at 40 °C (Scheme 25).[49] Hydroacylation of azodicarboxylates **87** with aliphatic aldehydes tends to proceed in high yield (>85%). Interestingly, hydroacylation of benzaldehyde and 4-chlorobenzaldehyde proceeded in good yields whereas Lee and co-workers observed only moderate yields when performing the rhodium acetate catalysed hydroacylation with these substrates.[45] However, yields of less than 10% were observed when employing electron-deficient or electron-rich aromatic aldehydes.
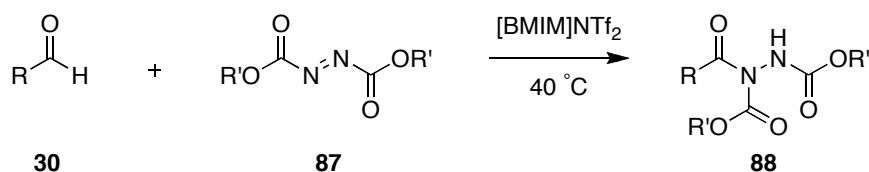
Scheme 25 Hydroacylation of aldehydes **30** with azodicarboxylates **87** in an ionic liquid

1.5.3 Stetter reaction

It was found by Stetter and Schreckenberg in 1973 that ketones were generated from reaction of aldehydes with Michael acceptors catalysed by cyanide ions. Thus, the Stetter reaction, the reaction of an aldehyde with an electron deficient olefin results in overall hydroacylation of the olefin double bond much like rhodium catalysed hydroacylation (see section 1.5.1).[50,51] Stetter has reported reactions proceeded well with aromatic aldehydes and electron deficient alkenes in aprotic solvents such as dimethylformamide (DMF). In addition, the methodology has been extended to aliphatic aldehydes through the use of thiazolium salts **89** as catalysts in place of cyanide.[50] In general, reaction of aldehyde **30** with alkene **90** proceeded to give better yields of 1,4-dicarbonyl **91** where R = aliphatic (Scheme 26).
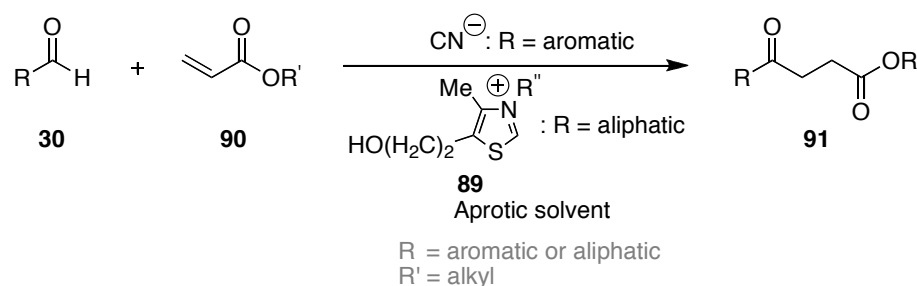
Scheme 26 Stetter reaction to generate 1,4-dicarbonyls **91**

More recently, research groups have shown that the Stetter reaction can be carried out asymmetrically. For example, in 2006, Tomioka and Matsumoto used chiral imidazolium salts **92** as catalysts to carry out intramolecular cyclisations of **93** to give cyclopentanones **94** with good enantiomeric excess.[52]
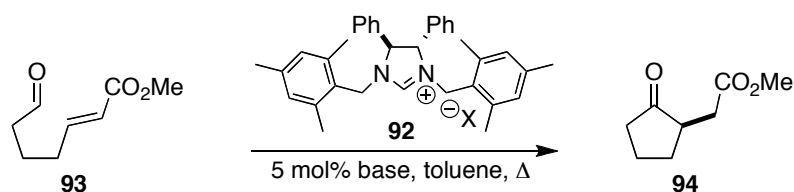
Scheme 27 Imidazolium salt catalysed Stetter reaction

1.6 Chemistry of acyl radicals

In this section, the chemistry of acyl radicals from a range of substrates including aldehydes, acyl chlorides, carboxylic acid derivatives, acylcobalt derivatives and seleno- and telluroesters will be discussed. For further examples the reader is directed to an excellent review by Chatgilialoglu, Crich and Ryu.[53]

It has been well established that acyl radicals are sigma-type radicals due to the unpaired electron occupying an orbital which has substantial 2s character. They are also known to be nucleophilic radicals. It has been shown that there is little or no delocalisation of the unpaired electron when R = aryl or vinyl and therefore the strength of the C-H bond of an aldehyde is likely to be independent of the R group.

Figure 2 σ-Type acyl radical

1.6.1 Acyl radicals *via* carbonylation of alkyl radicals

In 1990, Ryu and co-workers reported the generation of acyl radicals from alkyl radicals using AIBN and tributyltin hydride under a high pressure of carbon monoxide.[54] Thus, alkyl bromides and aromatic iodides can be converted into their corresponding aldehydes. For example, *n*-octyl bromide (**95**) and aromatic iodide **96** were carbonylated to give aldehydes **97** and **98** in 66% and 70% yields respectively under a high pressure of CO (Scheme 28). It was found that relative concentrations of CO and tin hydride played an important role in the success of trapping, and that it was not possible to trap benzyl radicals with carbon monoxide. TTMSS reacts slower with alkyl radicals than Bu$_3$SnH and therefore carbonylation of alkyl radicals can be carried out at lower CO pressures with TTMSS as chain carrier (15 atm).[55] In addition, catalytic Bu$_3$GeH can also be employed as an alternative to tin hydride, although both high pressures of CO and high temperatures are required.[56]
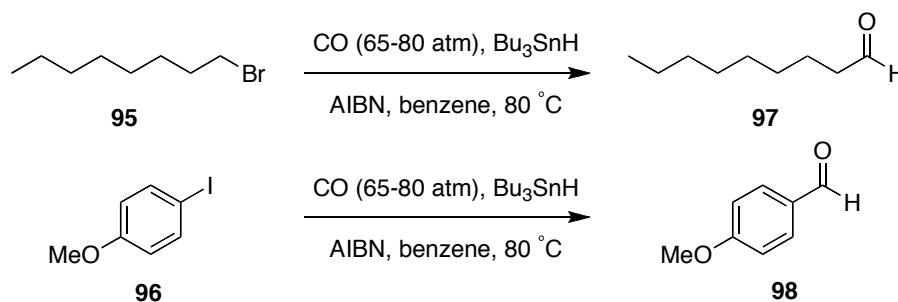
Scheme 28 Carbonylation of alkyl halides to give corresponding aldehydes

1.6.2 Acyl radicals from telluro- and seleno-esters

Tellurium and selenium carboxylates have been employed as precursors to acyl radicals. Evidence for the formation of acyl radicals from telluroesters is given by efficient trapping of the radical, generated by photolysis, with TEMPO, diphenyl disulfide and diphenyl diselenide to generate the corresponding ester, thioester and selenoester in each case. Similarly, benzaldehyde (**30a**) can be formed on photolysis of naphthyl telluride **99** in the presence of thiophenol (Scheme 29).[57]
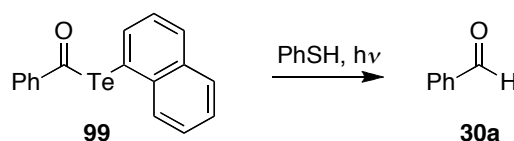
Scheme 29 Photolysis of telluroester **99** to give benzaldehyde **30a**

Thioesters can also be used to generate acyl radicals,[58] but selenoesters are often a better alternative in the generation of acyl radicals due to the weaker carbon-selenium bond.[59] Boger and co-workers have exploited this to effect intramolecular cyclisations *via* acyl radicals to generate various ring structures (Scheme 30); for example, selenoester **100** undergoes intramolecular radical cyclisation *via* the generation of an acyl radical to give ketone **101**.[60]
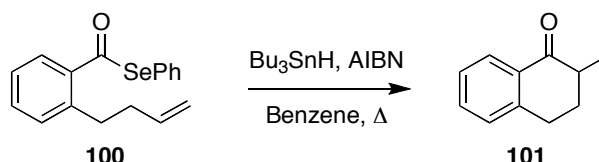
Scheme 30 Generation of acyl radical from a selenoesters

1.7 Acyl radicals from acid chlorides

In 1992, Chatgilialoglu and co-workers reported that acyl radicals could be generated from acid chlorides using TTMSS and AIBN.[61] Subjection of acid chloride **102** to TTMSS and AIBN at elevated temperature in the absence of a radical trap led to a mixture of fully reduced alkane **103** and aldehyde **104**, clearly indicating the formation of an intermediate acyl radical (Scheme 31). At elevated temperature, no reaction took place in the absence of AIBN, however, on addition of AIBN, it was possible to obtain near quantitative overall yields of **103** and **104**.
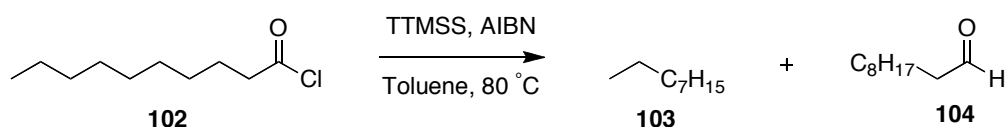
Scheme 31 Reaction of acid chloride with TTMSS and AIBN

1.7.1 Hydroacylation *via* acyl radicals

Although direct addition of both –H and –C(O)R from the same aldehyde molecule is not achieved, the addition of an acyl radical **105** to an unsaturated bond **106** is, in effect, hydroacylation (Scheme 32).
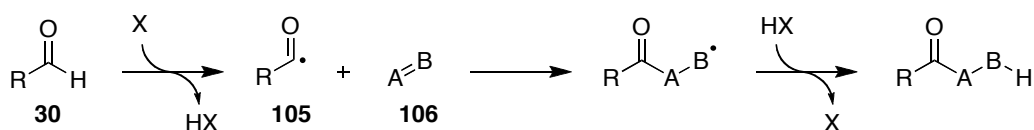
Scheme 32 Addition of an aldehyde to an unsaturated bond

Soon after the work by Kharasch and co-workers (see section 1.4), Patrick reported that acetaldehyde (**30b**) underwent addition to diethyl maleate (**107**) 76-81% yield in the presence of benzoyl peroxide at elevated temperatures (Scheme 33) *via* the corresponding acyl radical.[62,63] Patrick also clearly demonstrated that reactions with an excess of olefin afforded telomers, incorporating multiple equivalents of olefin, as the principal by-products.
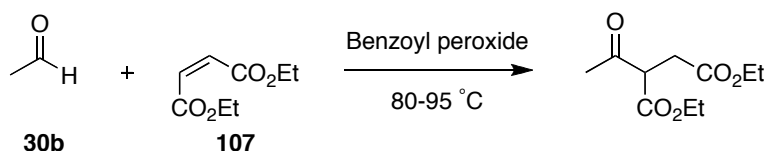
Scheme 33 Addition of acetaldehyde (**30b**) to ethyl maleate (**107**)

In 1967, Vinogradov and co-workers illustrated the use of cobalt acetate in the promotion of the addition of aldehydes to mono-substituted alkenes (Scheme 34).[64,65] A highlight was the addition of acetaldehyde (**30b**) to 1-heptene (**108**) to give ketone **109**. On addition of cobalt acetate to acetaldehyde (**30b**), acyl radical **110** was generated. It was postulated that addition of this acyl radical **110** to the terminal end of 1-heptene (**108**) gives adduct radical **111**, and, after abstraction of aldehydic hydrogen from **30b**, this provides ketone **109** and regeneration of acyl radical **110**.
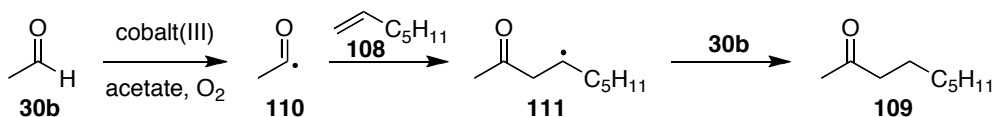
Scheme 34 Addition of acetaldehyde (**30b**) to 1-heptene (**108**)

Vinogradov and co-workers reported the radical addition of aldehydes to a number of unsaturated double bonds catalysed by cobalt salts.[66] For example, stirring butyraldehyde (**30c**) with dimethyl maleate (**112**) at room temperature in the presence of cobalt acetate gave adduct ketone **113** (Scheme 35) in 85% yield. However, without the presence of a cobalt catalyst, a yield of 89% was observed with 92% conversion of the starting material **112**. Vinogradov proposed that in the absence of cobalt the reaction was proceeding *via* an acyl radical generated from auto-oxidation (the conversion of aldehyde to acid *via* acyl and peroxyacyl radicals).[67]
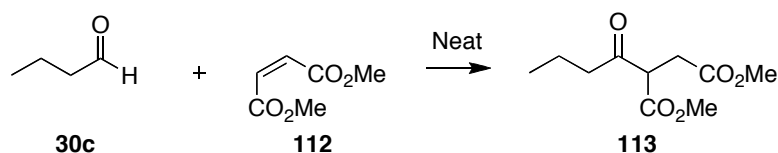
Scheme 35 Addition of butyraldehyde (**30c**) to dimethyl maleate (**112**)

Macias and co-workers were able to furnish a variety of 1,4-dicarbonyls using photochemical conditions to generate acyl radicals from the corresponding aldehyde. In particular, acetaldehyde (**30b**) was used in their study (Scheme 36).[68,69] After generation of acyl radical **110**, addition to substituted olefins **114** gives adduct radical **115**, then abstraction of the aldehydic hydrogen gives 1,4-dicarbonyl **116** and regeneration of acyl radical **110**. However, large excesses of aldehyde were required in order for the reaction to proceed in good yield. It is noteworthy that when Macias and co-workers carried out the reaction under an inert atmosphere, the yield of **116** was suppressed and it is believed that the presence of molecular oxygen is crucial in the generation of acyl radical **110**.
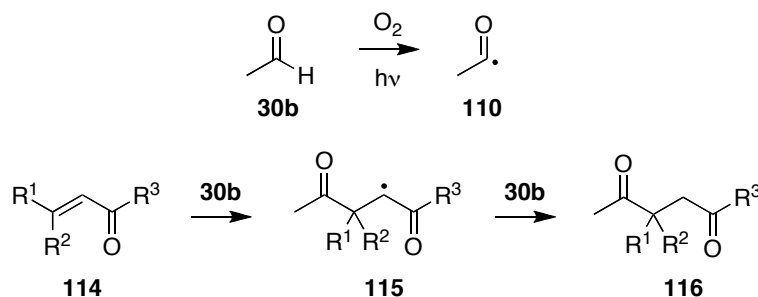
Scheme 36 Acyl radical addition to electron deficient olefins

Following the work by Macias and co-workers, in 1990, Stringat and co-workers used pulsed Nd-YAG lasers to give acyl radicals from butyraldehyde (**30c**); the radicals were trapped using diethyl maleate (**107**) to give diethyl butanoyl succinate (**117**, Scheme 37).[70]
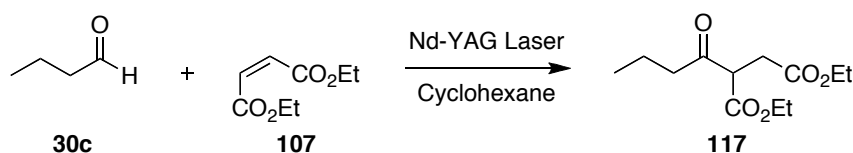
Scheme 37 Addition of butyraldehyde (**30c**) to diethyl maleate (**107**)

More recently in 2007, Albini and co-workers reported decatungstate-photocatalysed activation of aldehydic hydrogen atoms in the generation of acyl radicals, which were then trapped using electrophilic olefins to give unsymmetrical ketones.[71] A

representative example is the addition of hexanal (**118**) to methyl vinyl ketone (**119**) to give ketone **120** in 60% yield.
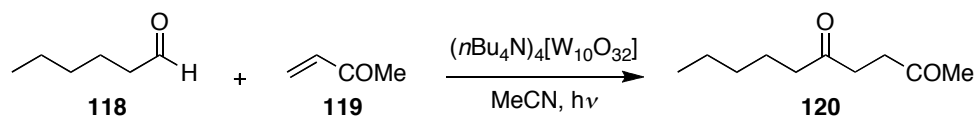
Scheme 38 Decatungstate-photocatalysed addition of hexanal (**118**) to methyl vinyl ketone (**119**)

1.7.1.1 Hydroacylation *via* acyl radicals using polarity reversal catalysis

It is usually the case for electron-rich or electron-neutral olefins, that addition of acyl radicals in the absence of a chain carrier generally gives a low yield of the corresponding ketone products.[72] These poor yields are due, in part, to the nucleophilic nature of adduct radical **121** which cannot efficiently abstract an aldehydic hydrogen to propagate the chain *via* generation of acyl radical **122**. Additionally, the rate of addition of acyl radical **122** will be slow due to the LUMO of an electron-rich or electron-neutral olefin being relatively high in energy with respect to the acyl radical SOMO. However, during the late 1990's, Roberts and co-workers reported the use of thiols **123** as polarity reversal catalysts to carry out hydroacylation of electron rich olefins.[73,74,75] Instead of adduct radical **121** abstracting hydrogen from aldehyde **30**, it abstracts hydrogen from thiol **123** instead, generating thiyl radical **124**. Radical **124** is electrophilic and therefore abstracts hydrogen from aldehyde **30** and generates acyl radical **122**, thus propagating the chain reaction, to generate ketone **125** (Scheme 39). It is also possible to use thiols as catalysts in conjugation with silanes.[76] Roberts and Dang carried out a control study to determine the magnitude of the effect of thiol catalysis. When butyraldehyde (**30c**) and oct-1-ene (**126**) were stirred in dioxane in the presence of di-*tert*-butyl hyponitrite (TBHN) at elevated temperature, ketone **127** was formed in 24% yield (Scheme 40). However, when 5 mol% methyl thioglycolate (MTG) was added, the yield of ketone **127** increased to 67%. A range of thiol catalysts were investigated including *tert*-dodecanethiol (TDT), triisopropylsilanethiol and triphenylsilanethiol; MTG was found to be the most effective.
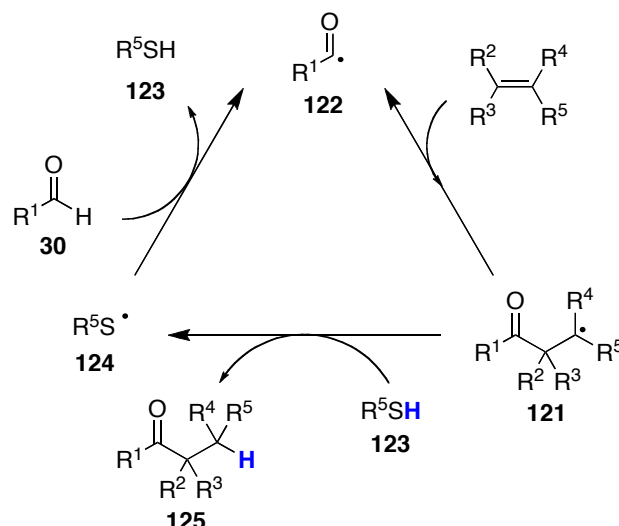
Scheme 39 Mechanistic cycle of polarity reversal catalysis
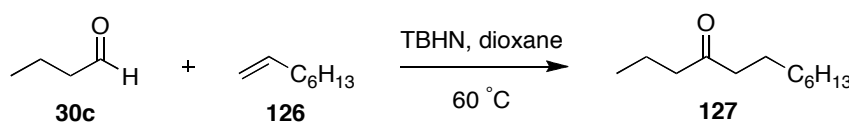
Scheme 40 Reaction of butyraldehyde and oct-1-ene

Roberts and co-workers also carried out investigations into the reaction of butyraldehyde (**30c**) with electron-deficient olefins (Figure 3). In contrast to the reaction of electron-rich olefins, MTG was the least effective thiol catalyst and instead excellent yields were obtained with TDT as catalyst. This can be attributed to the electophilicity of adduct radical **121** (Scheme **39**).

56%	95%	93%	85%
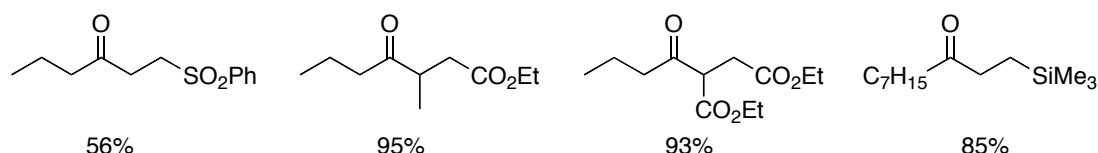
Figure 3 Yields of aldehyde addition to electron-deficient olefins

Ishii and co-workers carried out work on the addition of aldehydes to electron-deficient double bonds using *N*-hydroxyphthalimide (NHPI) as a polarity reversal catalyst at elevated temperature with catalytic amounts of benzoyl peroxide (Scheme 41).[77] In this study the reaction between pentanal (**128**) with a range of olefins **129** was examined. Excellent yields of ketone **130** were obtained when R = CO_2Me and CN (80% and 72% respectively); however, 7.5 equivalents of aldehyde were required. Small amounts of **131** were also isolated which are indicative of polymerisation adducts.
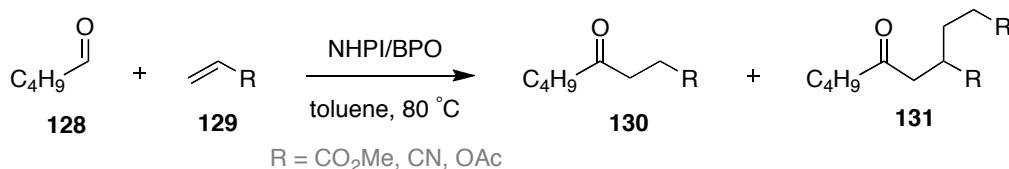
Scheme 41 Hydroacylation of pentanal (**128**) to olefins **129** using NHPI as a polarity reversal catalyst

1.7.2 Intramolecular acyl radical additions to C-C double bonds

In 2005, Tomioka and co-workers utilised thiols as chain carriers in order to carry out acyl radical cyclisations of alkenals.[78] When alkenal **132** was subjected to AIBN and TDT in refluxing chlorobenzene, cyclopentanone **133** was isolated and it was proposed that the reaction proceeded *via* acyl radical **134**. A range of thiols were investigated and it was found that *tert*-dodecanethiol provided the highest yield of cyclopentanone **133** (90%). When benzenethiol was used, only a 16% yield of **133** was observed and it was proposed that this was due to the stability of the phenylthiyl radical. In the absence of thiol and under deoxygenated conditions, no reaction proceeded when stirring with AIBN alone and alkenal **132** was recovered in high yield.
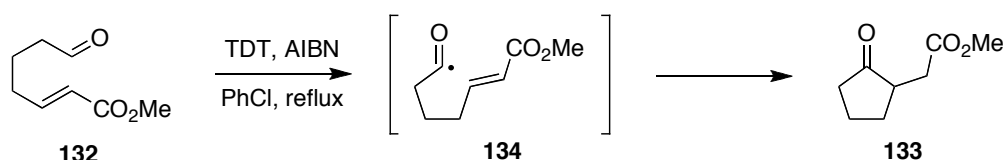
Scheme 42 Cyclisation of acyl radical **134**

Zard and co-workers have shown that acyl radicals **135** can be generated from the corresponding acyl triphenylmethyldiazo derivatives **136**.[79] Oxidation of **136** using phenylseleninic acid gave desired azo derivative **137**, which on heating decomposed to give acyl radical **135** that then underwent cyclisation to give carbon centred radical **138**. Radical **138** was rapidly trapped by diphenyl diselenide to provide **139** (Scheme 43).
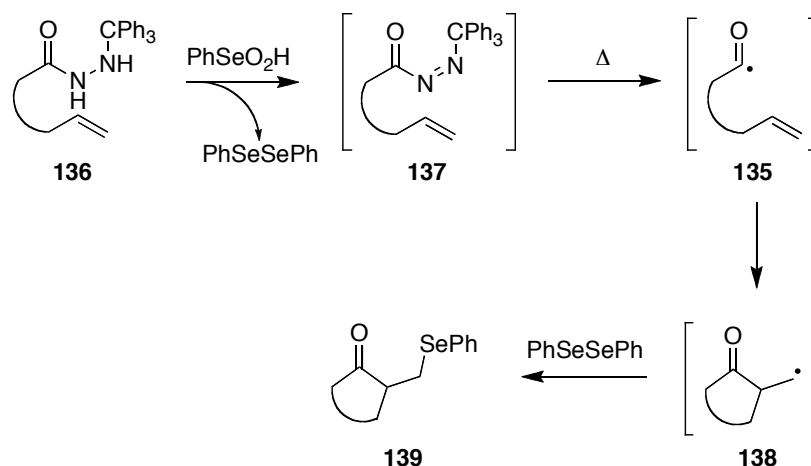
Scheme 43 Cyclisation using acyl hydrazides

An advantage of their approach over stannane-based chemistry in the generation of acyl radicals (from acyl selenides) is that the phenyl selenide can be readily eliminated to give the corresponding unsaturated derivative.   Acyl radical cyclisations have also been achieved by cleavage of C-S,[80,81] C-Se,[82] and other carbon-heteroatom bonds.

1.7.3 Intramolecular acyl radical additions to C-N double bonds

Ryu and co-workers demonstrated that acyl radicals undergo addition to C-N double bonds and reactions occurred with complete selectivity for cyclisation on the nitrogen atom.[83]   Acyl radicals **140**, generated by carbonylation of alkyl radical **141**, cyclised onto the C-N double bond at nitrogen in an exocyclic manner to give pyrrolidinone radical **142**.   Abstraction of hydrogen from tributyltin hydride gave pyrrolidinones **143** in good yields with no evidence for the formation of the corresponding 6-*endo* cyclisation product.
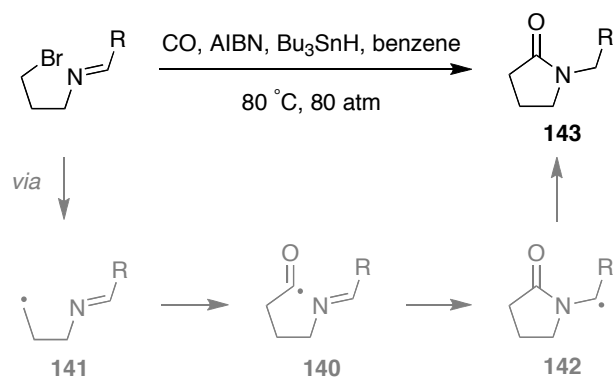
Scheme 44 Nitrogen-philic cyclisation of acyl radicals

1.8 Chemistry 'in the presence of water'

Water is the most readily available solvent in nature and is also the most environmentally friendly. It possesses many desirable properties, including: a high boiling point, high heat capacity, extensive hydrogen bonding and it has optimum oxygen solubility.[84] Due to the fact that organic molecules have limited solubility in water, it has not been used as a solvent of choice by organic chemists to any great extent. However, in recent years, an acceleration in the rate of organic reactions has been observed in the presence of water.[85,86] In most cases, it is difficult to say whether the reaction takes place 'in water' or 'on water' and therefore in this thesis, reactions will be described as taking place 'in the presence of water'.

It is believed that water influences reactions through a hydrophobic effect. 1,3-Dipolar cycloadditions and Diels-Alder reactions in the presence of water have been reported in detail in the literature.[87] For example, in 2005, Sharpless and co-workers demonstrated the rate enhancement when using water in the Diels-Alder reaction between *trans,trans*-2,4-hexadienyl acetate (**144**) and *N*-propylmaleimide (**145**) to give adduct **146** (Scheme 45).[88] The reaction in toluene and acetonitrile took 144 h, whereas when stirring in methanol, the reaction only took 48 h. However, the reaction took place in the shortest time when stirring in the presence of water to give an excellent yield (Table 1).
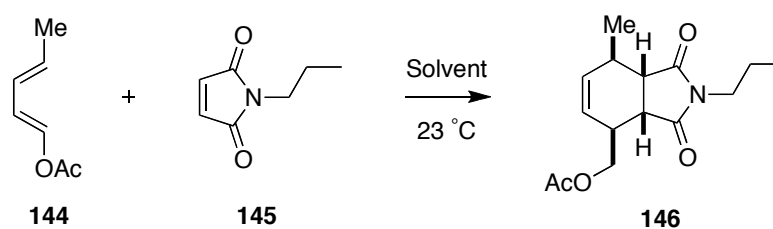
Scheme 45 Diels-Alder cycloaddition

Solvent	Reaction Time / h	Yield of 146 / %
Toluene	144	79
MeCN	>144	43
MeOH	48	82
Neat	10	82

H$_2$O	8	81

Table 1 Effect of solvent on reaction time

For in-depth discussions on the use of water as a solvent to carry out organic reactions see reviews by Chanda and Fokin[84] and Li and co-workers.[89]

1.9 Radical reactions using aryl vinyl sulfonates

The synthesis of sulfonamides from the corresponding sulfonyl chloride is well documented, but sulfonyl chlorides are highly reactive and often unstable.[90,91,92,93] Caddick and co-workers have shown that vinyl sulfonate esters, in particular trichlorophenyl (TCP) and pentafluorophenyl (PFP) sulfonate esters, offer excellent alternatives to sulfonyl chlorides.[94,95,96] For example, vinyl sulfonate **147** is a bifunctional acceptor, which is susceptible to attack by both nucleophilic and radical species in a Michael fashion and to aminolysis at sulfur (Figure 4).
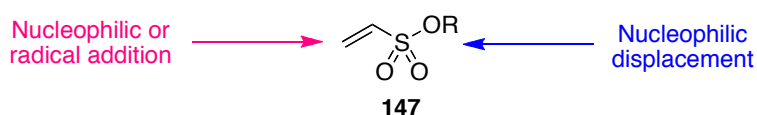
Figure 4 Vinyl sulfonate esters

1.9.1 Functionalisation of vinyl sulfonates *via* alkyl radical additions

Caddick and co-workers showed that PFP vinyl sulfonate **148** is an excellent acceptor for intermolecular radical additions of alkyl radicals derived from alkyl iodides **149** to give alkyl sulfonates **150**.[97] Subsequent addition of a variety of amines to alkyl sulfonate **150** could be used to generate a range of sulfonamides **151** *via* displacement of pentafluorophenol in good yields. Alkyl radical additions to pentafluorophenyl vinyl sulfonate **148** in the presence of tributyltin hydride proceeded in excellent yields with primary, secondary and tertiary iodides. Of particular note were the reactions with derivatised sugars and amino acids, which took place in moderate to good yields.
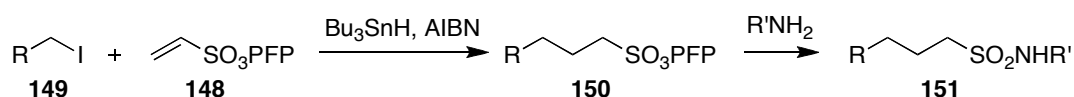
Scheme 46 Radical addition of iodides **149** to PFP vinyl sulfonate **148** and sulfonamide formation

1.9.2 Hydroacylation of vinyl sulfonates

During work on functionalisation of trichlorophenyl vinyl sulfonate **152** using Baylis-Hillman chemistry, Fitzmaurice observed the formation of ketone **153d** in preference to the desired α-substituted Baylis-Hillman product **154** during reaction with isovaleraldehyde (**30d**) in the presence of DABCO (Scheme 47).[98] The hydroacylation of vinyl sulfonate **152** with two equivalents isovaleraldehyde (**30d**) could be effected with or without the presence of DABCO when mixing isovaleraldehyde (**30d**) with TCP vinyl sulfonate **152** in dioxane to provide ketone **153d** in 55% yield at room temperature. This simple hydroacylation, without the need for additional reagents or catalysts, is reminiscent of the work conducted by Vinogradov (see section 1.7.1, Scheme 34 and Scheme 35) and offers an opportunity for green synthesis of functionalised ketones.
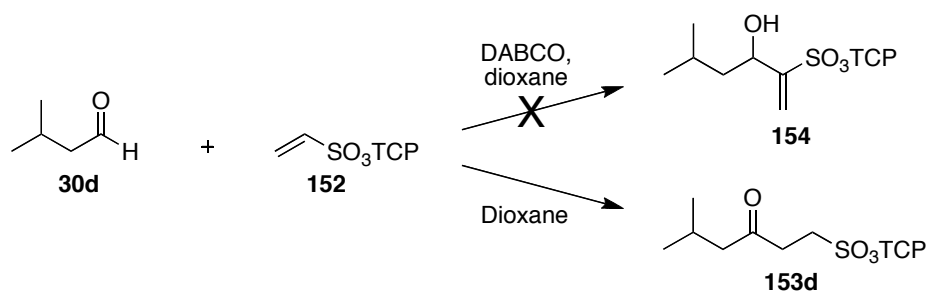
Scheme 47 Attempted Baylis-Hillman reaction

1.10 Aims

The interesting observation that simply stirring isovaleraldehyde (**30d**) with a vinyl sulfonate can afford an unsymmetrical ketone without need for additional reagents (Scheme 47) suggested that there would be merit in further investigation. This thesis presents studies on the scope and limitation of the process for the simple approach for the functionalisation of other aldehydes with vinyl sulfonates (scheme 46, **147**, R = aliphatic and aromatic) and a broader study into the generality of this approach using other electron deficient olefins **155**, EWG = ester, nitrile, phosphonate (Scheme 49).
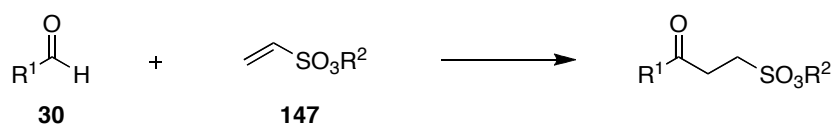
Scheme 48 Hydroacylation of vinyl sulfonates **147**
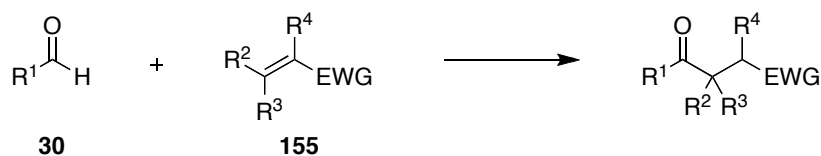
Scheme 49 Hydroacylation of alkenes bearing electron withdrawing substituents

The plethora of recent literature on intramolecular hydroacylation of alkenes suggests continued interest in simple methods for preparation of cyclic ketones. Thus, investigation into the feasibility of intramolecular variants of vinyl sulfonate hydroacylation also appears worthy of further study .

Chapter 2   Hydroacylation of vinyl sulfonates and sulfones

2.1 Introduction

Caddick and co-workers found that when TCP vinyl sulfonate **152** was stirred with isovaleraldehyde (**30d**) in dioxane at room temperature under aerobic conditions, unexpected hydroacylated product **153d** was isolated in 55% yield; small amounts of ketone **158** were also isolated (Scheme 50).
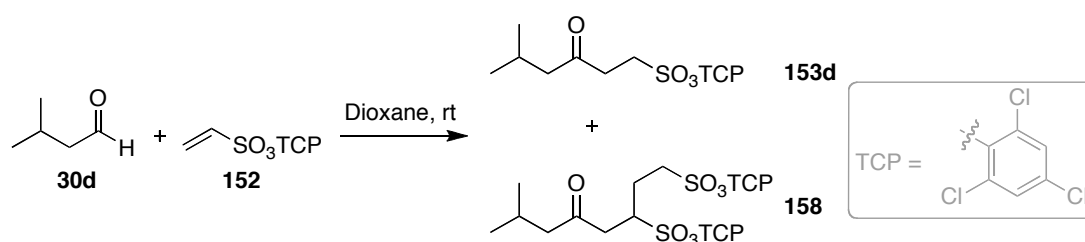
Scheme 50 Reaction of isovaleraldehyde (**30d**) with TCP vinyl sulfonate **152**

As mentioned in section 1.9.2, the group has carried out work on both TCP vinyl sulfonate **152** and PFP vinyl sulfonate **148** and when PFP vinyl sulfonate **148** was used in the reaction (Scheme 50), the corresponding ketone was isolated in 45% yield. It was believed that this type of transformation, in which a C-C bond is formed with significant ease, was an extremely desirable reaction. It was decided to embark upon a program of work in order to study it in more detail; the first part of this work was optimisation of the reaction.

2.2 Optimisation studies for hydroacylation of vinyl sulfonates

Investigations were initiated to optimise the reaction between isovaleraldehyde (**30d**) and vinyl sulfonate **147** to give ketone **159** and a number of different parameters including stoichiometry, solvent, reaction time and temperature were evaluated (Table 2).
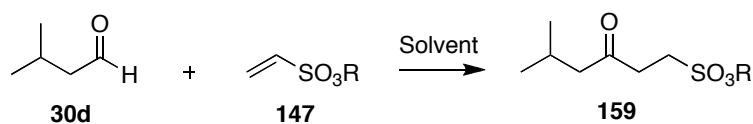
Scheme 51 Reaction of isovaleraldehyde (**30d**) with vinyl sulfonate **147** ([**147**] =1M)

Entry	147, R =	30d eq.	Solvent	T /°C	Time /h	Yield /%
1	TCP	2	1,4-dioxane	21	18	53
2		1				20
3		3				59
4		4				62
5		5				74
6		10				73
7	PFP	5	1,4-dioxane		18	65
8			Et$_2$O			13
9			DCM			39
10			MeOCH$_2$CH$_2$OMe			65
11			THF			28
12			PhMe			25
13			DMF			30
14			MeOH			4
15			1,4-dioxane		0.5	49
16					1	65
17					2	64
18					8	65
19					24	65
20				50	1	40

Table 2 Optimisation study

Reaction of TCP vinyl sulfonate **152** with stoichiometric amount of aldehyde **30d** resulted in a low yield of 20% (entry 2, Table 2). A significant increase in yield was observed when the amount of aldehyde was increased from 1 to 2 equivalents (entries 1 and 2, Table 2). When the amount of aldehyde was increased to 3 or 4

equivalents (entries 4 and 5, Table 2), the yield did not increase substantially, and it was found that 5 equivalents of aldehyde gave the optimum yield with no further increase when more than 5 equivalents of aldehyde were used (entry 6, Table 2). When PFP vinyl sulfonate **148** was used as substrate with 5 equivalents of isovaleraldehyde (**30d**, Scheme 52), an isolated yield of 65% was obtained (entry 7, Table 2).   It was envisaged that the lower yield obtained for reaction of vinyl sulfonate **148** with isovaleraldehyde (**30d**) compared to vinyl sulfonate **152** was due to the propensity of ketone **160d** to eliminate to the corresponding enone (see section 2.6.2). Hence, the remainder of the optimisation studies were carried out with PFP vinyl sulfonate **148** due to the greater synthetic challenge posed by this substrate.
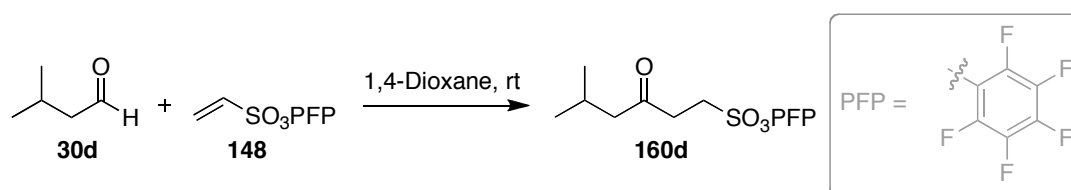
Scheme 52 Reaction of isovaleraldehyde (**30d**) and PFP vinyl sulfonate **148**
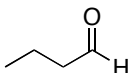
The reaction of isovaleraldehyde (**30d**) and PFP vinyl sulfonate **148** proceeded to give the highest yields in 1,4-dioxane and ethylene glycol dimethyl ether (entries 7 and 10, Table 2). Hence, 1,4-dioxane was used as solvent for subsequent optimisation studies. However, in all cases some of ketone **160d** (Scheme 52) could be isolated derived from the addition of a single molecule of aldehyde to a single molecule of olefin. An investigation towards reaction time was undertaken (entries 16-19, Table 2) and it was found that reaction of PFP vinyl sulfonate **148** and isovaleraldehyde (**30d**) proceeded to completion in just 1 hour and longer reaction had no effect on yield, indicating that ketone **160d** was stable to the reaction conditions. Reaction proceeded much faster with PFP vinyl sulfonate **148** (entry 4, Table 2) as opposed to TCP vinyl sulfonate (entry 5, Table 2), presumably due to the increased electron-withdrawing ability of PFP which renders PFP vinyl sulfonate **148** more reactive. At elevated temperature (entry 20, Table 2), a faster reaction time for reaction with PFP vinyl sulfonate **148** was observed but the isolated yield of ketone **160d** was considerably lower. Hence, the optimised conditions for the reaction of vinyl sulfonates **148** and **152** with isovaleraldehyde (**30d**) were found to be 5 equivalents of aldehyde with 1,4-dioxane as solvent, at room temperature.
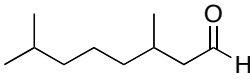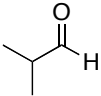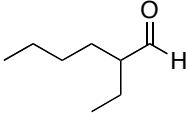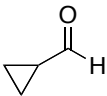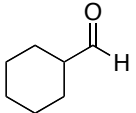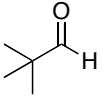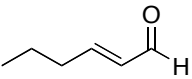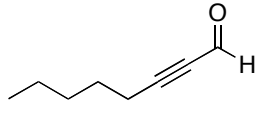
2.3 Aldehyde scope for hydroacylation of vinyl sulfonates

The hydroacylation of both PFP vinyl sulfonate **148** and TCP vinyl sulfonate **152** was found to proceed with a variety of aliphatic aldehydes including straight chained, β-branched, α-branched and tertiary (Scheme 53 and Table 3). It should be noted that the reaction time was dependent on the aldehyde and in some cases, longer reaction times were required. In general, moderate to good yields were observed (entries 1-8, Table 3); higher yields were observed with reactions of TCP vinyl sulfonate **152** than with PFP vinyl sulfonate **148** presumably due to the instability of β-keto-pentafluorophenylsulfonates **160**.   An   exception   to   this   is cyclopropanecarboxaldehyde (**30h**) (entries 12 and 13, Table 3) whereby the yield for reaction with TCP vinyl sulfonate **152** is lower. Reaction of hexen-1-al (entry 18, Table 3) with PFP vinyl sulfonate **148** proceeds in low yield at 100% consumption of starting material and the reaction of octynal (**30l**, entries 19 and 20, Table 3) does not proceed to give any of ketone **160l** and only starting material is visible by ^{1}H NMR.
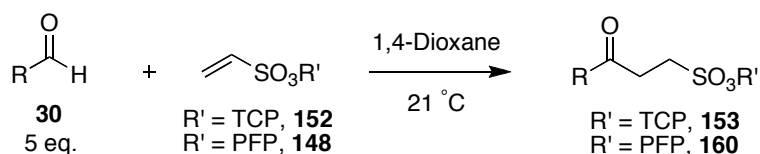
Scheme 53 Reaction of aldehydes with vinyl sulfonates

Entry	Aldehyde	Product	Reaction Time / h	Yield / %
1	O‖–H **30b**	**153b**	20	60
2		**160b**	3	38
3	O‖–H **30c**	**153c**	20	72
4		**160c**	1	65
5	O‖–H **30d**	**153d**	20	76
6		**160d**	3	65

7	**30e**	**160e**	18	72
8	**30f**	**153f**	42	64
9		**160f**	3	58
10	**30g**	**153g**	48	80
11		**160g**	1	69
12	**30h**	**153h**	96	53
13		**160h**	3	66
14	**30i**	**153i**	48	65
15		**160i**	3	47
16	**30j**	**153j**	48	14
17		**160j**	3	5*
18	**30k**	**160k**	24	12
19	**30l**	**153l**	168	0
20		**160l**	168	0

*Pentafluorophenyl 3,3-dimethylbutane-1-sulfonate isolated (53%)

Table 3 Yields for formation of ketones **153** and **160**

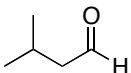Interestingly, when the reaction of isovaleraldehyde (**30d**) and PFP vinyl sulfonate **148** was carried out, a product bearing an enone was visible by ^{1}H NMR, in addition to the desired ketone **160d**. In an attempt to trap the enone, hexanethiol was added to the reaction mixture and sulfide **161** was isolated.

Scheme 54 Generation of sulfide **161**
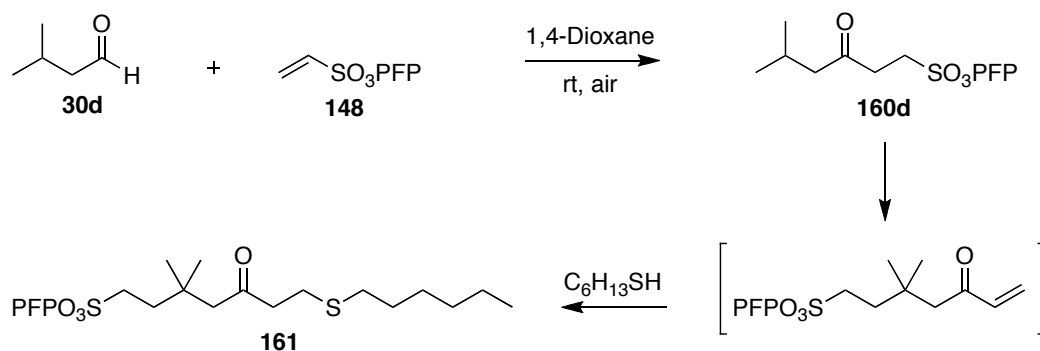
When carrying out reaction with TCP vinyl sulfonate **152** using freshly distilled pivaldehyde (**30j**), at room temperature, only a small amount (14%) of the corresponding ketone **153j** was isolated (Scheme 55). Careful inspection of the crude ^{1}H NMR indicated formation of sulfonate **162** as the major by-product, **153j**:**162** ratio of 1:4

Scheme 55 Reaction of TCP vinyl sulfonate **152** and pivaldehyde (**30j**) to give both acyl and alkyl radical addition
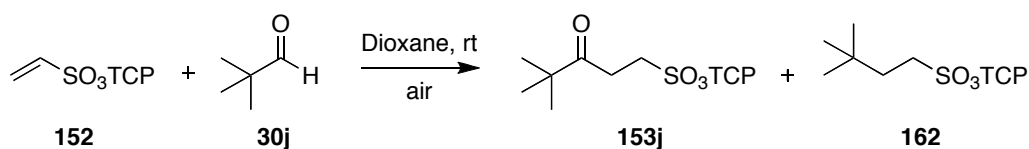
Increasing the reaction temperature to 60 °C afforded a larger proportion of **162** in the reaction mixture (Table 4). Whilst conducting the reaction at −10 °C, it was possible to reverse the ratio of acyl:alkyl addition products **153j**:**162** to 3:2, albeit with a prolonged reaction time of 7 days. The decarbonylation was not observed for any of the other aldehydes examined.

Temperature / °C	Time / h	Ratio of 153j:162
-10	168	3:2
21	48	1:4
60	3	1:8

Table 4 Ratios of **153j**:**162** for reaction of TCP vinyl sulfonate **152** with pivaldehyde (**30j**)

When the reaction was carried out with isovaleraldehyde (**30d**) and TCP vinyl sulfonate **152** (entry 5, Table 3), products **153d** and **163d** were isolated (R = [i]Bu Scheme 56).
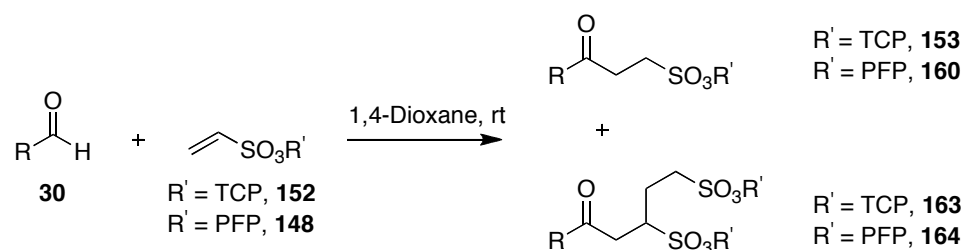
Scheme 56 Generation of single and double addition products

The amount of double addition product **163** and **164** was dependent on the aldehyde used and when reacting PFP vinyl sulfonate **148** with primary aldehydes, the ratio of **160**:**164** was typically 20:1. It was found that for cyclopropanecarboxaldehyde (**30h**) and cyclohexanecarboxaldehyde (**30i**), the ratio decreased to approximately 9:1. For cyclopropanecarboxaldehyde (**30h**), the reaction took notably longer (4 days with TCP vinyl sulfonate **152**) and this could explain the fact that more double addition product **163h** is produced (Scheme 56). An explanation that the reaction of cyclopropanecarboxaldehyde (**30h**) and TCP vinyl sulfonate **152** took longer to go to completion could also be reasoned by the fact that the carbon adjacent to the aldehyde carbon is not 'strictly sp^3' hybridised due to the ring strain in a 3-membered ring causing the sp^3 orbital to be somewhat puckered and hence more sp^2-like in character. When the reaction was carried out with aldehydes that had adjacent sp^2 or sp carbons, it did not proceed e.g. octynal and aromatic aldehydes. However, a low yield of 12% was observed when the reaction was performed with *trans*-2-hexenal (**30k**). It was envisaged at this stage that an sp^3-hybridised carbon adjacent to the aldehyde carbon was required in order to see a reaction take place in good yield.

The amount of double addition product is also dependent on the olefin. For example, in this study, a greater proportion of double addition product was observed when carrying out the reaction with TCP vinyl sulfonate **152** instead of PFP vinyl sulfonate **148**. We envisaged that this was because PFP is more electron-withdrawing than TCP and hence the α-sulfonyl radical is more electrophilic than the adduct radical with TCP vinyl sulfonate **152**. Hence, when reacting PFP vinyl sulfonate **148** with primary aldehydes, little or no double addition product is observed.

2.3.1 Hydroacylation of alternative vinyl sulfonates

In addition to PFP and TCP vinyl sulfonates **148** and **152** discussed above, hydroacylation also proceeds in moderate yields with ethyl vinyl sulfonate (**165**). When reaction of ethyl vinyl sulfonate **165** and butyraldehyde (**30c**) was carried out (Scheme 57), pleasingly it was found that the reaction proceeded in good yield (67%) with a ratio of **166**:**167** of 8:1.
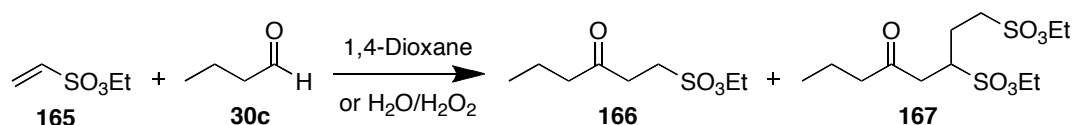
Scheme 57 Reaction of ethyl vinyl sulfonate **165** with butyraldehyde (**30c**)

It was also possible to obtain moderate yields using phenyl vinyl sulfonate **168** as an acceptor giving rise to ketone **169** in 55% yield and also using a sulfonate bearing an ester substituted aryl group **170** to give ketone **171** in 67% yield (Scheme 58).
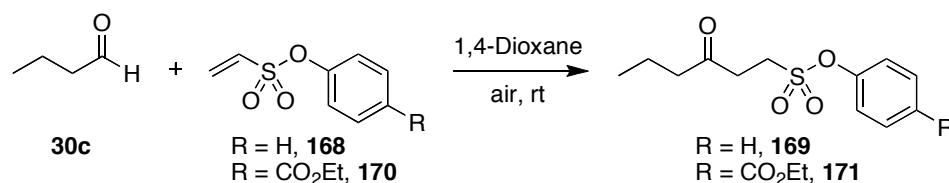
Scheme 58 Yields for hydroacylation of alternative vinyl sulfonates with butyraldehyde (**30c**)

2.4 Reaction mechanism

It is known that over time benzaldehyde (**30a**) oxidises to benzoic acid (**172**) in contact with air (Scheme 59) and it is generally accepted that an acyl radical **173** is generated from benzaldehyde (**30a**) under aerobic conditions.[99] This radical then reacts with triplet oxygen in order to generate peracyl acid **174**, which continues to react with further benzaldehyde (**30a**) to generate benzoic acid (**172**).
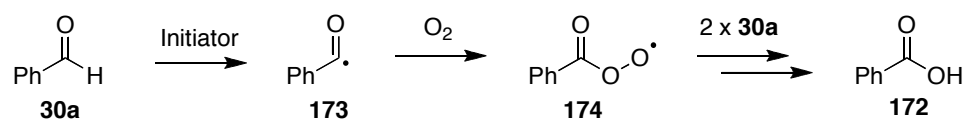
Scheme 59 Auto-oxidation of benzaldehyde (**30a**) to benzoic acid **172**

Given that aliphatic aldehydes also auto-oxidise[100] to their corresponding carboxylic acid **175** *via* acyl radical **176**, peracyl radical **177** and peracid **178**, and based on the

evidence described above, the most likely mechanism for the formation of ketone **179** from vinyl sulfonate **147** is *via* acyl radical **176** and α-sulfonyl radical **180** (Scheme 60). This assertion is supported by the isolation of sulfonate **181** from the reaction of vinyl sulfonate **152** and **30j** and the formation of polymeric ketobissulfonate **182**. Sulfonate **181** is formed *via* decarbonylation of acyl radical **176** to the corresponding alkyl radical **183**, a facile process when forming a *tert*-butyl radical such as in **30j** (Scheme 55)[101], which is then trapped by vinyl sulfonate **147** to afford **181**. The temperature dependence of the ketosulfonate **179** to sulfonate **181** ratio obtained on reaction of vinyl sulfonate **152** with pivaldehyde (**30j**) strongly supports a radical mechanism for the transformation and is consistent with an increased rate of unimolecular decarbonylation at high temperatures (Scheme 55 and Table 4).[102] The formation of ketobis-sulfonate **182** can be rationalised *via* addition of α-sulfonyl radical **180** to a further equivalent of vinyl sulfonate **147**. The dependence of the nature of the aldehyde on the ratio of **179**:**182** obtained suggests that the rate of hydrogen atom transfer from aldehyde **30** is influenced by R. In addition, the increased **179**:**182** ratios observed when R′ = TCP compared to when R′ = PFP suggests that rate of polymerisation is reduced for the more electron poor alkene, R′ = PFP.
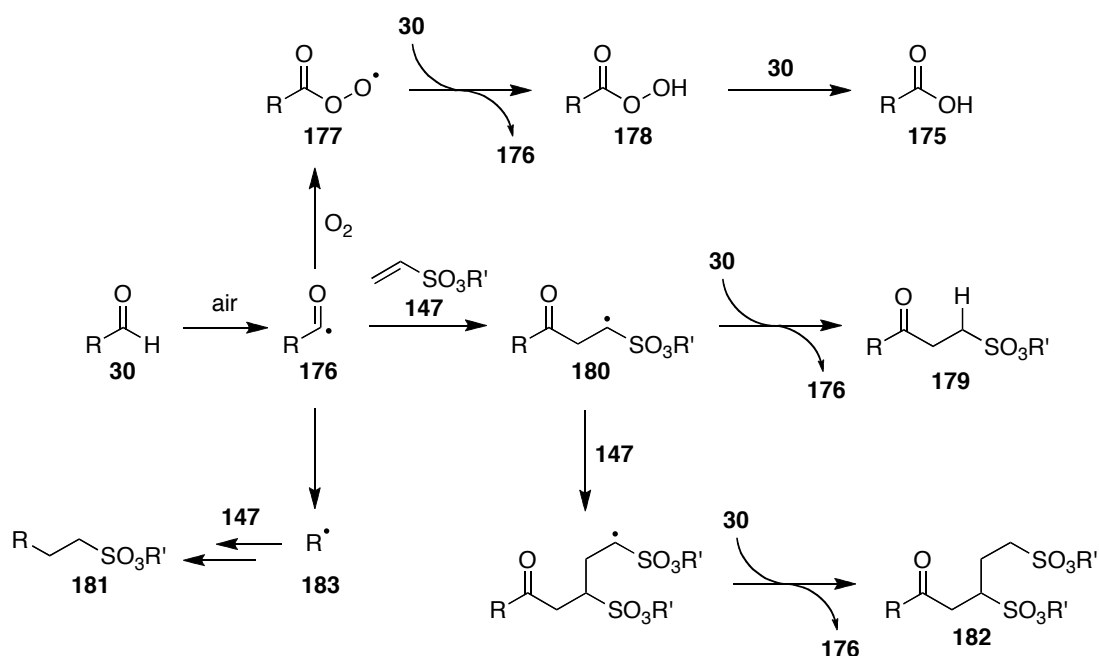
Scheme 60 Proposed mechanistic pathway

In support of the proposal of an acyl radical mechanism for the hydroacylation of vinyl sulfonate **147** in 1,4-dioxane, the addition of 3,5-di-tert-butyl-4-

hydroxytoluene, a known radical inhibitor[103] (10 mol%) to a mixture of vinyl sulfonate **152** and isovaleraldehyde (**30d**) completely inhibited the formation of ketosulfonate **153d**. Also supportive of the proposed mechanism is the almost complete inhibition, <5% conversion of **152** (R′ = TCP) to **153d** (R = $CH_2CH(CH_3)_2$, R′ = TCP) in 24 h, when the reaction was conducted in freshly distilled, freeze thaw degassed 1,4-dioxane under an atmosphere of argon, clearly indicating the importance of air to the success of hydroacylation.

Additional evidence in support of a radical mechanism was isolation of sulfide **161** (as described in section 2.3). It is proposed that a 1,5-hydrogen atom abstraction of adduct radical **184** occurs to give tertiary radical **185** (Scheme 61). Addition of this radical to PFP vinyl sulfonate **148** results in bis-sulfonate **186**, which undergoes elimination to enone **187**. Addition of hexanethiol allows efficient trapping of enone **187** to generate isolable sulfide **161**.
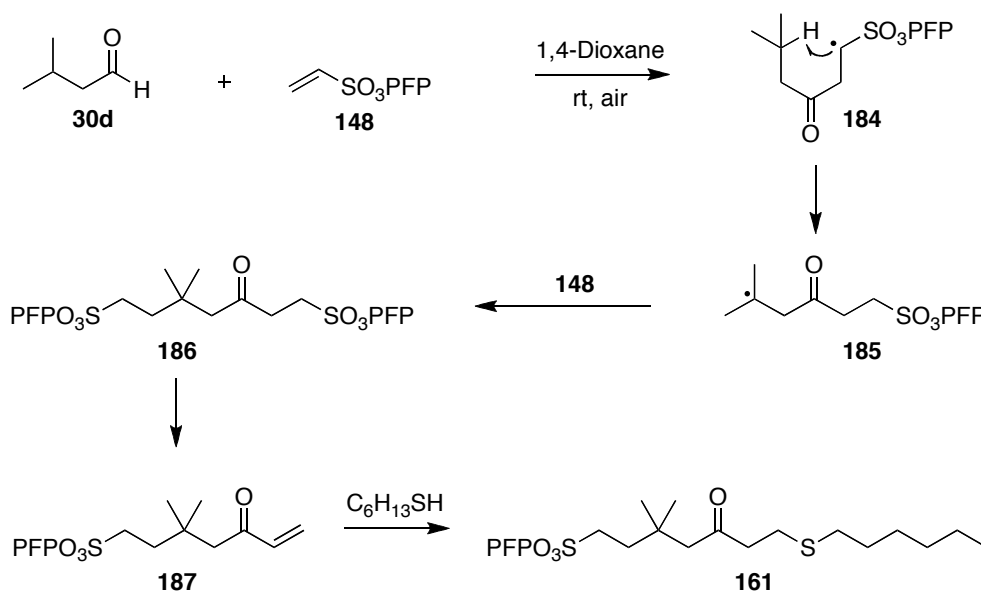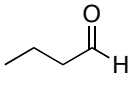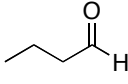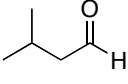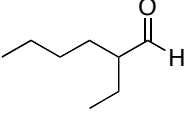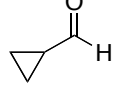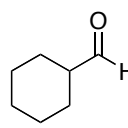
Scheme 61 Example of 1,5-hydrogen atom abstraction in support of a radical mechanism
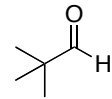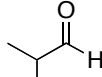
2.5 Further optimisation for hydroacylation of vinyl sulfonates

Although the hydroacylation of vinyl sulfonates in 1,4-dioxane provides unsymmetrical ketones under mild reaction conditions, isolated yields were in some cases poor. Given that, in 1,4-dioxane, hydroacylation of vinyl sulfonates was best at high concentrations (1 M), vinyl sulfonate **148** and isovaleraldehyde (**30d**) were

stirred neat at room temperature under air. However, 100% conversion of PFP vinyl sulfonate **148** was not achieved after stirring for 7 days. It is well known that when water is employed as a solvent for organic reactions, it has an effect on both rate of reaction and selectivity.[84] (see section 1.8). It is believed that water influences the reaction through a hydrophobic effect (the tendency of hydrophobic molecules to associate in order to minimise surface contact with water). Thus, PFP vinyl sulfonate **148** was stirred with butyraldehyde (**30c**) in the presence of water, and ketone **160c** was isolated in excellent yield (entry 1, Table 5). The 1,4-dioxane conditions involved the use of a 5:1 aldehyde:alkene stoichiometry. Gratifyingly, it was found that the reaction proceeded in excellent yields in the presence of water and even more pleasing, only 2 equivalents of aldehyde were required (Table 5). When reaction of PFP vinyl sulfonate **148** was repeated with butyraldehyde (**30c**) and the addition of 5 mol% hydrogen peroxide, the yield was slightly improved and the reaction time reduced from 3 hours to 1 hour.
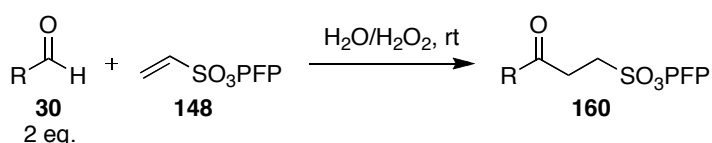
Entry	Aldehyde	Product	mol% H_2O_2	Reaction Time / h	Yield / %
1	**30c**	**160c**	0	-	78
2	**30c**	**160c**	5	1	83
3	**30d**	**160d**	5	1	74
4	**30g**	**160g**	5	3	87
5	**30h**	**160h**	5	3	67
6	**30i**	**160i**	5	3	79

7	 30j	160j	5	3	58*
8	 30b	160b	5	168	0
9	 30f	160f	5	168	0

* Pentafluorophenyl 3,3-dimethylbutane-1-sulfonate isolated (28%)

Table 5 Yields using water as a solvent

Of particular note is the reaction of PFP vinyl sulfonate **148** with cyclohexanecarboxaldehyde (**30i**, entry 6, Table 5), which gave the corresponding ketone **160i** in an excellent 79%, a significant improvement from 47% when the reaction was conducted in 1,4-dioxane. In addition, the reaction of **148** with pivaldehyde (**30j**) (entry 7, Table 5) gave 58% of the acyl addition product **160j** compared to only 5% obtained previously. At high reaction concentrations, the rate of intermolecular reactions is increased and therefore is more likely than unimolecular decarbonylation, hence the better yield obtained in the presence of water. When the mass balance was measured, it was also greatly increased with isolation of 28% of decarbonylated product. It should be noted that the reaction did not proceed with both acetaldehyde (**30b**) and isobutyraldehyde (**30f**, entries 8 and 9 respectively, Table 5) presumably due to the increased solubility and greater degree of hydration of these aldehydes.

2.6 Hydroacylation of vinyl sulfonates using aromatic aldehydes

The intermolecular reaction between PFP vinyl sulfonate **148** and aliphatic aldehydes proceeds well in 1,4-dioxane and in the presence of H_2O/H_2O_2 (5 mol%). However, given the number of commercially available aromatic aldehydes **188**, a simple method for hydroacylation with aromatic aldehydes would be highly desirable (Scheme 62).
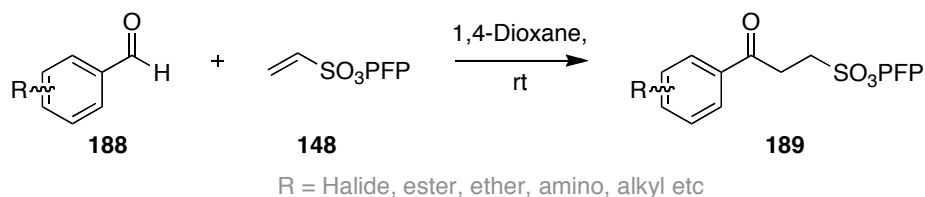
Scheme 62 Reaction of an aromatic aldehyde **188** with PFP vinyl sulfonate **148**
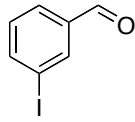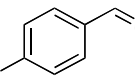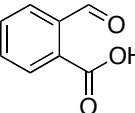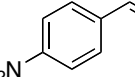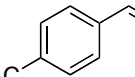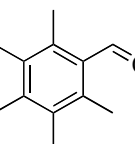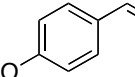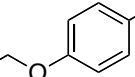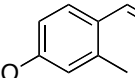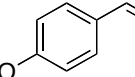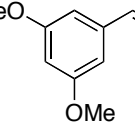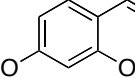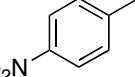
It has been shown that the rate of aldehyde auto-oxidation plays a crucial role in the success of vinyl sulfonate hydroacylation.[104] Therefore, an auto-oxidation study on aromatic aldehydes was implemented.

2.6.1 Auto-oxidation study on aromatic aldehydes

Auto-oxidation studies were carried out on various aromatic aldehydes in 1,4-dioxane at a concentration of 200 mg/mL and percentage carboxylic acid after 16 hours were determined by ^{1}H NMR (Table 6).
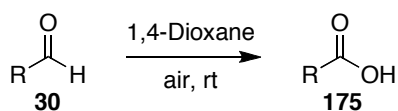
Entry	Aldehyde	% Acid 16 h
1		2.9
2		1.0
3		9.1
4		0
5		19.4
6		0
7		0
8		9.9

#	Structure	%
9		24.2
10		0
11		0
12		0
13		0
14		44.1
15		0
16		0
17		0
18		0
19		0
20		0
21		0

Studies carried out with a stirring rate of 300 rpm. When stirring rate was increased to 900 rpm, the rate of auto-oxidation was slower.

Table 6 Percentage carboxylic acid **175** after 16 hours (concentration of 200 mg/mL in 1,4-dioxane)

It was found that very few solid aromatic aldehydes auto-oxidised (entries 5, 8, 9, 10, 11, 12, 13, 14, 18, 19 and 21, Table 6) and the only observation that was made was that very electron poor e.g. 4-nitro-benzaldehyde and 4-trifluoromethane-benzaldehyde (entries 12 and 13 respectively) or very electron rich (entries 15-21) aldehydes do not appear to oxidise to their corresponding carboxylic acids at room temperature under aerobic conditions.

2.6.2 Hydroacylation of PFP vinyl sulfonate with aromatic aldehydes

4-Fluorobenzaldehyde (**30m**, Entry 3, Table 6) appeared to auto-oxidise at a rate which was comparable to the aliphatic aldehydes used in section 2.3.[104] When 5 equivalents of 4-fluorobenzaldehyde (**30m**) were added to a 1 M solution of PFP vinyl sulfonate **148** in 1,4-dioxane (Scheme 63), ketone **160m** was obtained in a 40% isolated yield after 18 hours, with complete consumption of PFP vinyl sulfonate **148**. In addition, sulfonate **190** was obtained (*ca.* 20% determined by ^{1}H NMR integration).
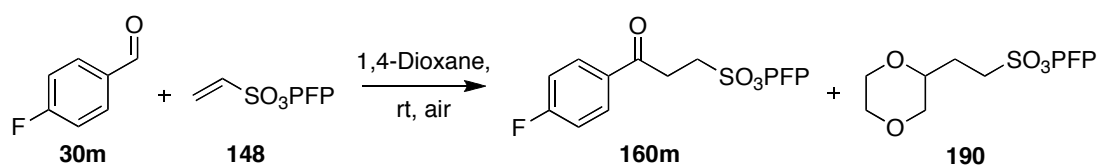
Scheme 63 Reaction of 4-fluorobenzaldehyde (**30m**) and PFP vinyl sulfonate **148**

During our programme of work on aliphatic aldehydes, sulfonate **190** had not been observed. However, similar products have been isolated by other research groups when carrying out reactions in the presence of ethers. For example, Ochiai and co-workers found that reaction of 1,4-dioxane (**191**) and phenyl vinyl sulfone (**192**) in the presence of 1-tert-butylperoxy-1,2-benziodoxol-3(1H)-one (**193**) at elevated temperature gave rise to dioxane addition product **194** (Scheme 64).[105] It was found that **193** serves as a versatile oxidising agent and at elevated temperatures generates α-oxy radicals, which then undergo addition to olefins.
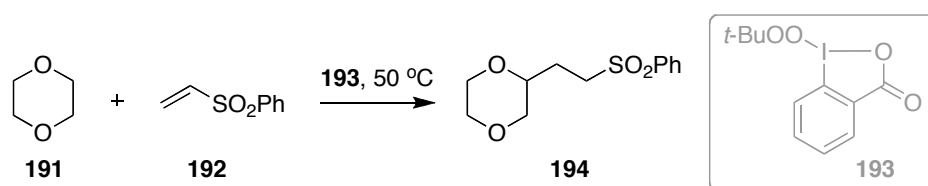
Scheme 64 Reaction of 1,4-dioxane (**191**) with phenyl vinyl sulfone **192**

The poor isolated yield of **160m** (40%) prompted use of an internal standard (pentachlorobenzene) to determine yield by ^{1}H NMR to see if ketone **160m** was being lost during purification. A ^{1}H NMR yield of 50% was obtained for the reaction of 4-fluorobenzaldehyde (**30m**) with PFP vinyl sulfonate **148** suggesting that PFP vinyl sulfonate **148** was particularly unstable to column chromatography. Indeed, when a known amount of ketone **160m** was subjected to column chromatography, evidence for formation of enone **195** and pentafluorophenol (**196**) were observed in the crude ^{1}H NMR along with only 30% of **160m** (Scheme 65).
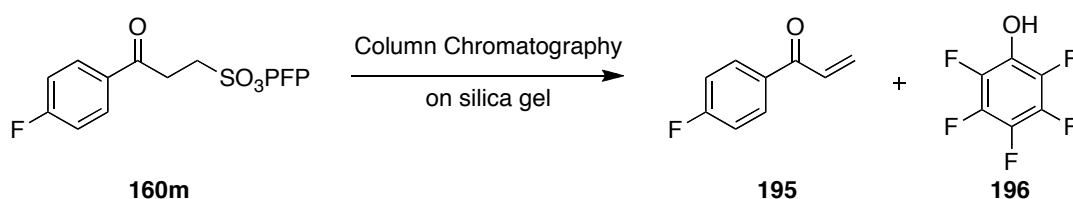
Scheme 65 Elimination of product **160m** to corresponding enone **195**

By monitoring the reaction over a 48 hour period, it became clear that not all of the PFP vinyl sulfonate **148** (PFPVS) was accounted for in products i.e. after 24 hours, 100% PFP vinyl sulfonate **148** was consumed; however, only 71% was present in a combination of ketone **160m** and dioxane addition product **190** (entry 6, Table 7). It is unclear how all of PFP vinyl sulfonate **148** is consumed in the reaction. In addition, when re-subjecting a known amount of ketone **160m** to the reaction conditions it did not appear to decompose.
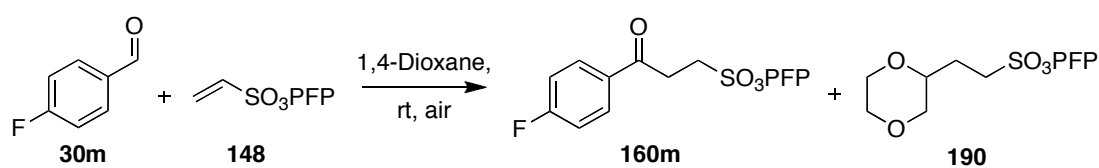
Scheme 66 Reaction of 4-fluorobenzaldehyde (**30m**) with PFP vinyl sulfonate **148**

Entry	Time / h	PFPVS 148 consumption / %	Addition Product 160m / %	Dioxane Addition Product 190 / %
1	0.25	10	3	0
2	1	35	12	7
3	2	76	25	8
4	4	98	42	17
5	8	>99	47	21

| 6 | 24 | 100 | 50 | 21 |
| 7 | 48 | 100 | 50 | 21 |

Percentages calculated by ^{1}H NMR with reference to internal standard (PCB).

Table 7 Reaction of 4-fluorobenzaldehyde (**30m**) and PFP vinyl sulfonate **148** with respect to time

Reaction of TCP vinyl sulfonate **152** (Scheme 67) afforded 9% of ketone **153m** by ^{1}H NMR at 47% conversion of **152** after stirring at room temperature for 18 hours. Therefore, it was deduced that TCP vinyl sulfonate **152** was not compatible in reaction with aromatic aldehydes despite giving good yields for reaction with aliphatic aldehydes.
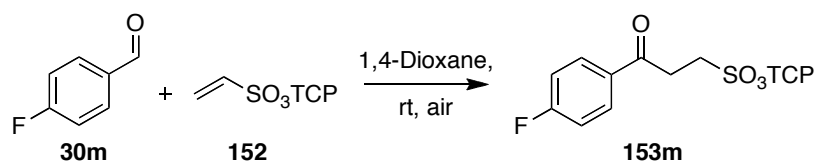
Scheme 67 Reaction of 4-fluorobenzaldehyde (**30m**) with TCP vinyl sulfonate **152**

In a separate programme of work, an elimination-addition sequence employing products derived from the reaction of PFP vinyl sulfonate **148** with aldehydes to give sulfide products **197** (Scheme 68) was developed.[104] It was found that this sequence could be carried out in one-pot i.e sulfonate ester **160** and enone **198** are not isolated. Application of this one-pot elimination-addition sequence on the reaction of 4-fluorobenzaldehyde (**30m**) with **148** was carried out. Pleasingly, a 48% yield of sulfide 1**97m** was obtained (^{1}H NMR yield of 50%).
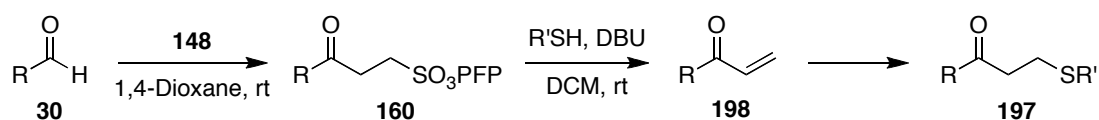
Scheme 68 Elimination-addition sequence

2.6.3 Optimisation of the hydroacylation of aromatic aldehydes

As with the optimisation of hydroacylation of vinyl sulfonates with aliphatic aldehydes (see section 2.3), the effect of stoichiometry, solvent and temperature on hydroacylation of PFP vinyl sulfonate **148** with 4-fluorobenzaldehyde (**30m**) were investigated. Caddick and co-workers proposed that varying the amount of solvent had a direct correlation to the amount of dissolved oxygen present in the reaction

medium and were able to use this to their advantage.[106] It was found in the case of hydroacylation of **148** with **30m** that higher reaction concentrations (2 M compared to 1 M) gave an increased yield of 55% by ^{1}H NMR. Thus a screen of solvents at 2 M concentration was investigated (Table 8). When reaction was conducted at 0.2 M, larger amounts of dioxane addition product **190** were observed as expected.   In solvents other than 1,4-dioxane, PFP vinyl sulfonate **148** was not 100% consumed and very little product was formed (entries 1-8, Table 8).   When mixing 4-fluorobenzaldehyde (**30m**) and PFP vinyl sulfonate **148** in the presence of water (entry 9, Table 8), the reaction failed to reach completion after 7 days at room temperature and a low yield of 40% was observed (entry 9, Table 8). Surprisingly, 0% of ketone **160m** was observed when performing the reaction in ethylene glycol dimethyl ether. Previously, when carrying out the reaction of PFP vinyl sulfonate **148** with aliphatic aldehydes, ketone **160** was isolated in good yield (see section 2.3).

Entry	Solvent	30m eq.	Yield 160m / %
1	MeOCH$_2$CH$_2$OMe	5	0
2	Toluene	5	<1
3	THF	5	14
4	DCM	5	0
5	Benzene	5	<5
6	Et$_2$O	5	14
7	DMF	5	5
8	Methanol	5	0
9	H$_2$O/H$_2$O$_2$	5	40
10	1,4-Dioxane	5	55
11		2	21
12		10	75
13		20	89

Yields calculated by ^{1}H NMR with reference to internal standard (PCB), [**148**] = 2M, Reaction time = 24 h.

Table 8 Solvent and stoichiometry screen

When a large excess of aldehyde was used in 1,4-dioxane (entries 12 and 13, Table 8), excellent ^{1}H NMR yields were observed. However, when attempts were made to isolate product from these reactions, these yields were never obtained and isolation of ketone **160m** became very difficult. When the elimination-addition sequence (Scheme 68) was employed, the excess aldehyde caused problems on isolation of sulfide **197m** and therefore the reaction was less efficient than it was when 5 equivalents were used.

2.7 Hydroacylation of vinyl sulfones
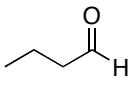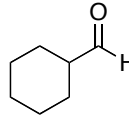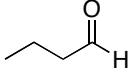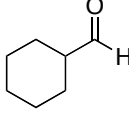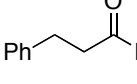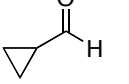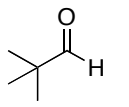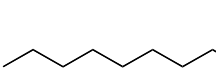
The reaction of vinyl sulfonates with aldehydes to give a hydroacylated product proceeded with such ease that it was decided to investigate the reaction with regards to the alkene. As described in section 1.7.1.1, Roberts and co-workers carried out hydroacylation of phenyl vinyl sulfone **192** using AIBN as a radical initiator and thiols as chain carriers.[75] An investigation was carried out to determine if the methodology developed for the hydroacylation of vinyl sulfonates could be employed in the use of vinyl sulfones without the addition of AIBN and a thiol. Pleasingly, it was found that reactions of both phenyl and ethyl vinyl sulfone (**192** and **199** respectively, Scheme 69) with butyraldehyde proceeded well. A temperature of 60 °C was employed.
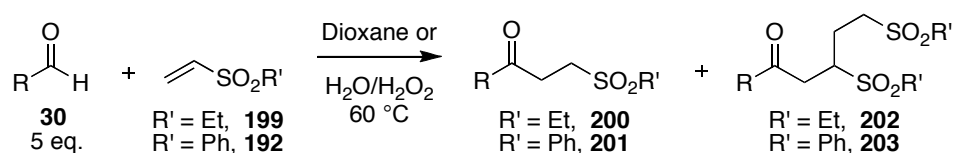
Scheme 69 Reaction of aldehydes with vinyl sulfones

2.7.1 Aldehyde scope

The reaction of phenyl and ethyl vinyl sulfone (**192** and **199** respectively) proceeded both in dioxane and in the presence of water to give comparable yields with both butyraldehyde (**30c**) and cyclohexanecarboxaldehyde (**30i**, entries 1-4, Table 9). However, in order for the reaction to go to completion in 18 hours, a temperature of 60 °C was required; at room temperature the reaction failed to reach completion even after 7 days.

Entry	Aldehyde	Product	Yield / %	
			Dioxane	**H₂O/H₂O₂**
1	![30c] O / H **30c**	**200c**	64	72
2	O / H **30i**	**200i**	-	60
3	O / H **30c**	**201c**	50	52
4	O / H **30i**	**201i**	50	49
5	Ph O H **30n**	**201n**	0	0
6	O / H **30h**	**201h**	0	0
7	O / H **30j**	**201j**	0	0
8	O / H **30o**	**201o**	0	0

Entry 6: 2:1 ratio of single:double addition products. Entry 7: reaction did not go to completion after 5 days. Entry 8: reaction gave multiple products by ¹H NMR. Vinyl sulfone concentration = 1M, Reaction Time = 18 h.

Table 9 Yields for hydroacylation of vinyl sulfones

A greater proportion of double addition product was observed, consistent with the less electron deficient character of vinyl sulfones. When cyclohexanecarboxaldehyde (**30i**) and butyraldehyde (**30c**) were used as aldehydes (entries 1-4, Table 9), the ratio of single to double addition is 3:1 and although this is not optimal it should be noted that the two products are readily separable by column chromatography. The reaction of phenyl vinyl sulfone (**192**) and hydrocinnamaldehyde (**30n**, entry 5, Table 9) appeared to generate many products (tlc analysis) and problems arose on isolation of hydroacylated product **201n** by

column chromatography due to presence of enone **204**. It was not possible to overcome this problem because ketone **201n** and enone **204** appear inseparable by silica-gel chromatography.
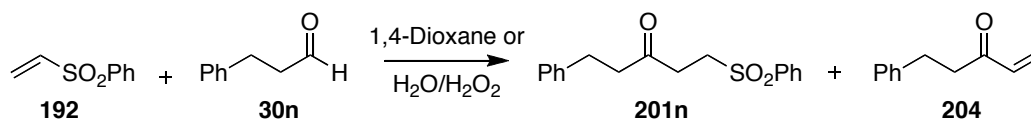
Scheme 70 Reaction of phenyl vinyl sulfone **192** with hydrocinnamaldehyde (**30n**)

2.8 Conclusions

It has been shown that auto-oxidation of aldehydes can be utilized in order to form C-C bonds. The hydroacylation of vinyl sulfonates and vinyl sulfones has been discussed in this chapter and optimisation of the protocol has been achieved.[107] These studies indicate that the scope of aldehydes may be limited to those bearing α-sp^3 centres. In addition, evidence has been gained to support a mechanistic hypothesis invoking an acyl radical intermediate. It was suggested that acyl radical **176** adds to vinyl sulfonate **147** to give adduct radical **180** which abstracts aldehydic hydrogen to give **179** and regeneration of acyl radical **176**.
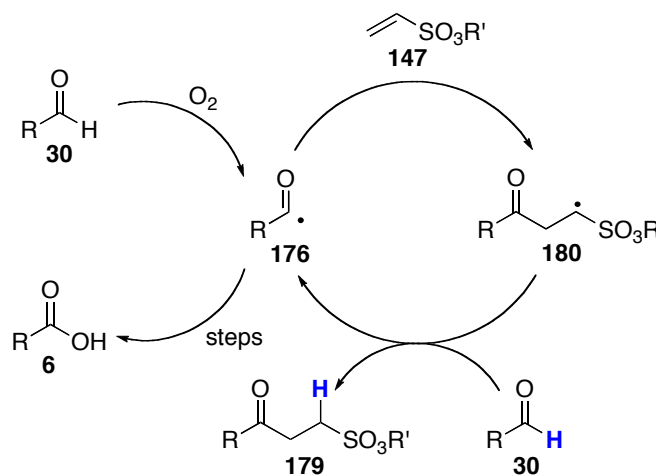
Scheme 71 Proposed mechanism for reaction of vinyl sulfonates

The hydrogen present in product **179** is believed to be that of the aldehyde (shown by **H**). When carrying out hydroacylation of PFP vinyl sulfonate **148** with butyraldehyde (**30c**) in deuterated dioxane or deuterated water, no deuterium was incorporated in the product. Hence, it is likely that the hydrogen atom is abstracted from aldehyde **30** to regenerate acyl radical **176**.

The hydroacylation of aromatic aldehydes has not been successful to-date and it is assumed that this is largely due to the auto-oxidation behaviour of aromatic aldehydes. For example, for aldehydes that do not appear to oxidise to their corresponding carboxylic acids, it is assumed that formation of an acyl radical intermediate does not occur and therefore radical addition to the olefin reacting partner

Figure 5 **Enone**

does not take place. Product isolation was also a problem due to elimination to give enone **205** as a consequence of its increased level of conjugation. The reaction has not been optimised with respect to aromatic aldehydes to date.
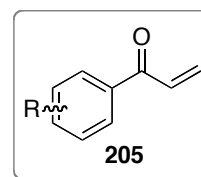
It has also been shown that vinyl sulfones can be hydroacylated under reagent free conditions by just the mixing of two reacting partners (aldehyde and olefin) in dioxane or in the presence of water. However, it was found that the reaction was more challenging with vinyl sulfones and elevated temperatures had to be used. In addition, larger amounts of double addition products were observed and therefore lower yields were observed. This may be a result of the less electron-deficient character of vinyl sulfones compared to vinyl sulfonates.

Chapter 3   Studies on intramolecular hydroacylation of electron deficient alkenes

3.1 Introduction and synthetic approach

Chapter 2 described the intermolecular reaction of vinyl sulfonates and vinyl sulfones with aldehydes *via* aerobically generated acyl radicals. There are a wide variety of intramolecular hydroacylation reactions employing acyl radicals derived from selenoesters and polarity reversal catalysis in the literature (see chapter 1).[78] On the basis of the work that we have developed for intermolecular hydroacylation we considered that it should be possible to promote the intramolecular variant. Thus, cyclisation precursors **206** were envisaged as suitable substrates for 5-*exo*-trig cyclisations to give cyclopentanones **207** (Scheme 72)[108], where cyclisation precursor **207** contains either a vinyl sulfonate (R = OAryl or OAlkyl) or vinyl sulfone (R = Aryl) motif as the radical acceptor and either an alkyl or aryl aldehyde as the acyl radical precursor. Initial studies will begin with the synthesis of 5-*exo*-trig precursors bearing an aliphatic aldehyde, as this will be directly comparable to the intermolecular variants described in chapter 2. A substrate bearing an aromatic aldehyde will also be synthesised.
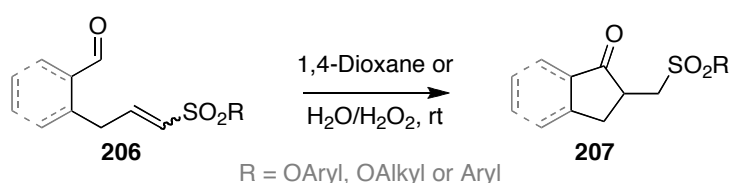
Scheme 72 Intramolecular hydroacylation

The proposed synthesis of **207** commences with preparation of Horner-Wadsworth-Emmons reagent **208** (Scheme 73) from **209**.[109] Subsequent Horner-Wadsworth-Emmons reaction of **208** provides alcohol **210**, oxidation of which would afford the desired cyclisation precursor **211**.
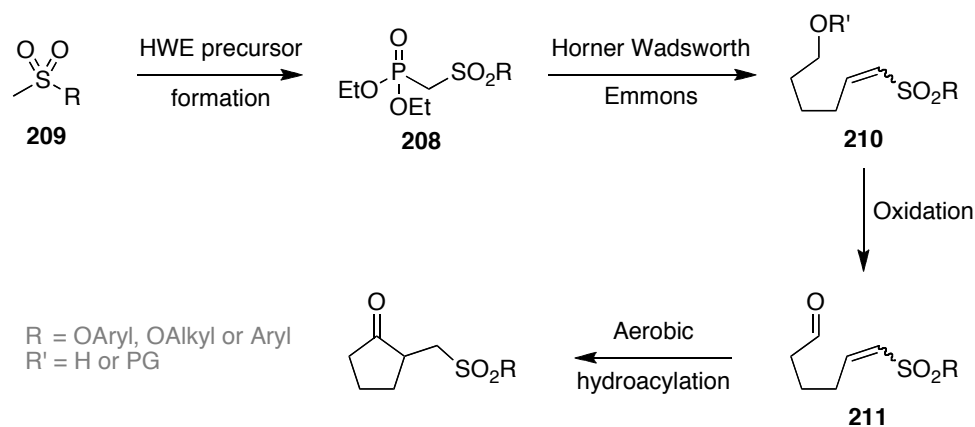
Scheme 73 Proposed synthetic route

3.2 Synthesis of cyclisation precursors

3.2.1 Synthesis of vinyl sulfonate bearing an aliphatic aldehyde

Prior studies showed that intermolecular aerobic hydroacylation proceeded to give the best yields with TCP vinyl sulfonate **152**. Therefore, it was decided that cyclisation precursor **211** (Scheme 73) would be prepared whereby R = OTCP.

3.2.1.1 Synthesis of Horner Wadsworth Emmons reagent

Methanesulfonate **212** (R = OTCP) was readily prepared from mesyl chloride and 2,4,6-trichlorophenol in high yield, 81%. Attempts to prepare Horner Wadsworth Emmons precursor **213** by deprotonation of sulfonate ester **212** with *n*-butyllithium, LDA, LHMDS and KHMDS followed by addition of diethyl chlorophosphate failed to furnish phosphonate **213** (Scheme 74). Attempts to trap the anion generated from deprotonation of **212** with diphenylphosphinic chloride, in an analogous approach to that of Wilden and co-workers[110], afforded none of the desired phosphonate. Trapping of the intermediate α-sulfonyl anion with *p*-chlorobenzaldehyde was also unsuccessful under a range of reaction conditions. When *n*-butyllithium and LDA were used, it is believed that some alkyl (for *n*-BuLi) and amine (for LDA) addition is observed; this was evident from the crude ^{1}H NMR. Difficulties in the preparation of phosphonate **213** may be because of the fact that the sulfur centre is very electrophilic due to the electron-withdrawing nature of the TCP moiety. There are no reports of Horner Wadsworth Emmons precursors bearing an aryl sulfonate. It was therefore decided to determine whether it was the aryl group (in this case TCP)

that was causing problems. When an analogous reaction was carried out with phenyl methanesulfonate **214** and diethyl chlorophosphate, none of Horner Wadsworth Emmons precursor **215** was isolated.

212 R = TCP
214 R = Ph
217 R = Et

213 R = TCP
215 R = Ph
216 R = Et

1) Base, THF, -78 °C
2) (C₂H₅O)P(O)Cl, THF, -78 °C
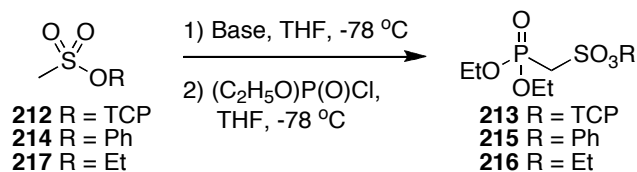
Scheme 74 Preparation of Horner Wadsworth Emmons precursors

In 1987, Ghosez and co-workers reported generation of Horner Wadsworth Emmons precursor **216** (R = **Ethyl**).[109] The reaction of ethyl methanesulfonate (**217**) with diethyl chlorophosphate proceeded in good yield, 65%, as reported to give phosphonate **216**. It was envisaged that the ethyl moiety could be exchanged for an aryl group later in the synthesis after the Horner Wadsworth Emmons reaction had been performed.

3.2.1.2 Synthesis of vinyl sulfonate cyclisation precursor using Horner Wadsworth Emmons reagent

Attempts to isolate alcohol **218** from the reaction of phosphonate **216** with lactol **219** afforded only tetrahydropyran **220** in 60% yield (Scheme 75). Presumably formed *via* cyclisation of the intermediate oxyanion **221** under the reaction conditions. Thus an appropriate protected ring opened form of lactol **219** was envisaged.
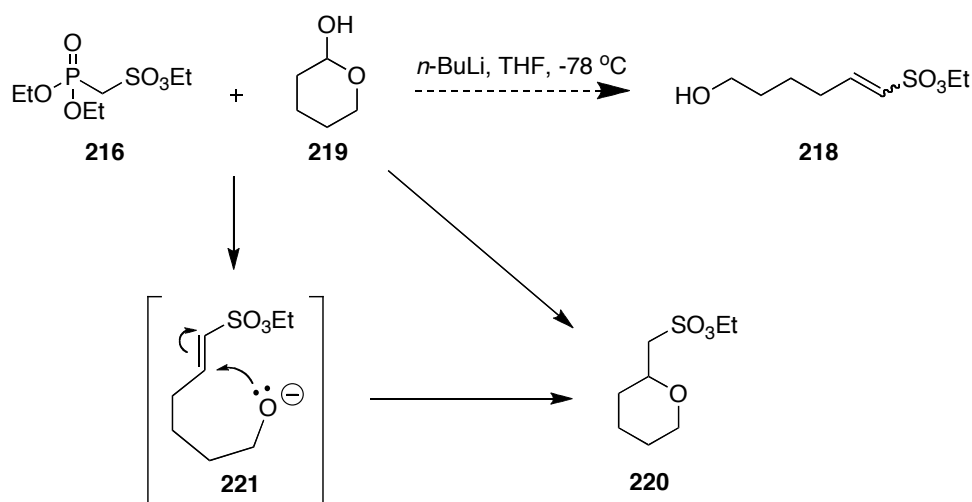
Scheme 75 Horner-Wadsworth-Emmons reaction with lactol **219**

The synthesis of **222** began with mono-protection of 1,5-pentane-diol (**223**) using TBSCl to give alcohol **224** using the method reported by Nicolaou and co-workers.[111]   Subsequent oxidation of alcohol **224** using the Swern oxidation[112] furnished aldehyde **225** in 89% yield, which was successfully coupled with phosphonate **216** in the Horner Wadsworth Emmons reaction to provide β-substituted vinyl sulfonate **226** in a 70% yield with an *E*/*Z* ratio of 3:1. Unfortunately, subjection of ethyl sulfonate ester **226** to TBAI in acetone followed by PPh₃, thionyl chloride and 2,4,6-trichlorophenol under basic conditions[113] (Roush's conditions) failed to give aryl sulfonate ester **227** despite several attempts and so at this stage, intramolecular precursor **222** with an ethyl sulfonate ester moiety was synthesised.
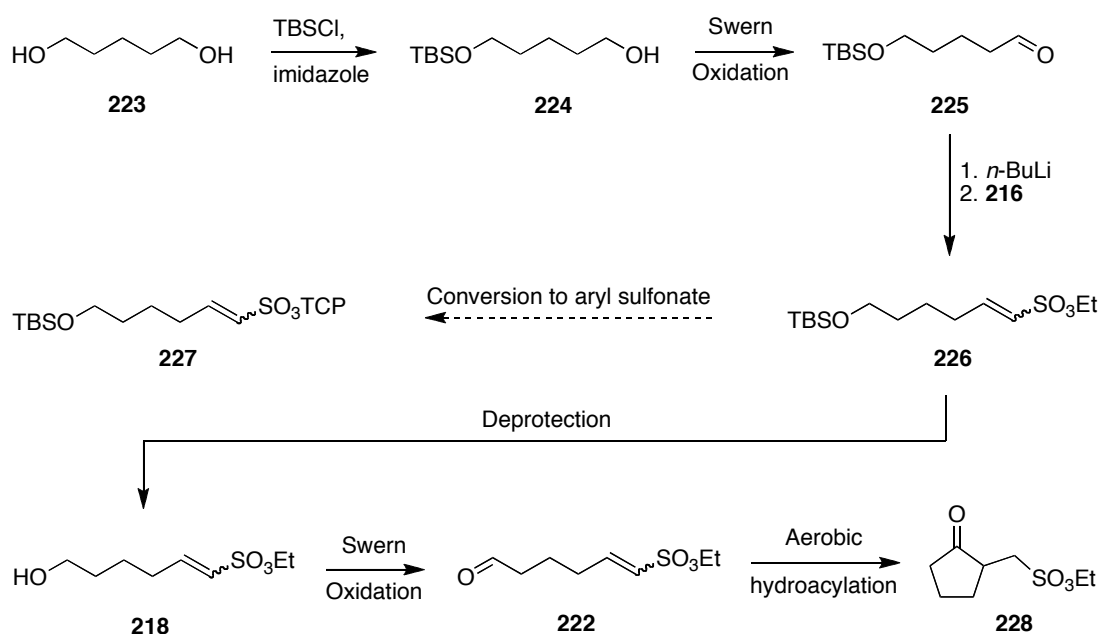
Scheme 76 Revised synthesis of intramolecular cyclisation precursor

Attempts to deprotect silyl ether **226** using TBAF to furnish alcohol **218** (entry 1, Table 10) failed to give desired alcohol **218**, with a variety of products present in the crude ¹H NMR, none of which contained hydrogens in the olefin region. Purification by column chromatography led to isolation of tetrahydropyran **220** (Scheme 75). Treatment of silyl ether **226** with TBAF/acetic acid (entry 2, Table 10) in order to try and circumvent this problem also resulted in formation of tetrahydropyran **220**. A poor yield resulted when the deprotection step was carried out with acetic acid (entry 3, Table 10). However, excellent yields were obtained when performing the reaction with Dowex Resin (a solid supported acid) or iodine in methanol (entries 6 and 7,

Table 10). Thus, deprotection of **226** was carried out with iodine in methanol on large scale; this procedure was reported by Lipshutz and Keith in 1998. Swern oxidation of alcohol **218** provided the desired cyclisation precursor **222** in 73% yield.

Entry	Reagents	Solvent	Yield of 218 / %
1	TBAF[114]	THF	0
2	TBAF/AcOH[115]	THF	0
3	AcOH/H$_2$O[116]	THF	40
4	1M HCl[117]	THF	81
5	PPTS[118]	EtOH	67
6	Dowex Resin[119]	H$_2$O	95
7	I$_2$[120]	MeOH	95

Table 10 Deprotection conditions of silyl ether **226**

3.2.2 Synthesis of vinyl sulfonate bearing aromatic aldehyde

In section 2.6.1, it was shown that the auto-oxidation rates of aromatic aldehydes varied largely in comparison to aliphatic aldehydes and therefore it was envisaged that the synthesis of a cyclisation precursor bearing an aromatic aldehyde would be interesting. Ozonolysis of 1,2-dihydronaphthalene (**229**) followed by Horner Wadsworth Emmons reaction to give **230** is reported in the literature.[78,121] Synthesis of cyclisation precursor **231** bearing an aromatic aldehyde began with ozonolysis of 1,2-dihydronaphthalene (**229**), which proceeded in excellent yield (90%) followed by Horner-Wadsworth-Emmons reaction with **216**. However, Horner Wadsworth Emmons reaction with **216** not only furnished desired sulfonate **231** but also bis-sulfonate **232** whereby Horner Wadsworth Emmons reaction had taken place on both the aliphatic aldehyde and aromatic aldehyde of **233**. Despite numerous attempts, desired sulfonate **231** could not be separated from bis-sulfonate **232** by column chromatography.
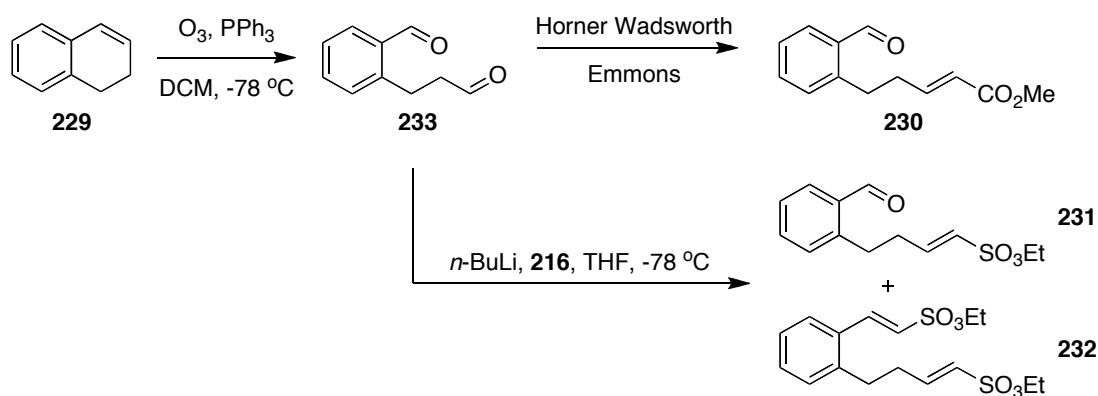
Scheme 77 Synthesis of intramolecular precursor **231** bearing an aromatic aldehyde

3.3 Synthesis of vinyl sulfone bearing an aliphatic aldehyde

The report of Grela and co-workers in 2003 of cross metathesis of phenyl vinyl sulfone (**192**) and 5-hexen-1-ol (**234**) using 10 mol% Grubbs' 2nd generation catalyst to give desired vinyl sulfone **235** in 81% yield (Scheme 78)[122] was intriguing and would allow rapid access to a range of aldehydic vinyl sulfones *via* a subsequent oxidation. Subsequent Swern oxidation would afford desired cyclisation precursor **236**. However, despite several attempts, it proved difficult to repeat the cross metathesis using the conditions reported by Grela and co-workers, with only a 30% conversion obtained even when the reaction was carried out with freshly distilled and degassed CH_2Cl_2. Addition of the catalyst in separate aliquots and dropwise addition of the catalyst also showed no improvement. Even when heating the reaction to 60 °C in chloroform, metathesis between sulfone **192** and alcohol **234** failed to reach completion. A small amount of alcohol **235** could be isolated and subsequent oxidation under Swern conditions afforded desired cyclisation precursor **236** in 86% yield.
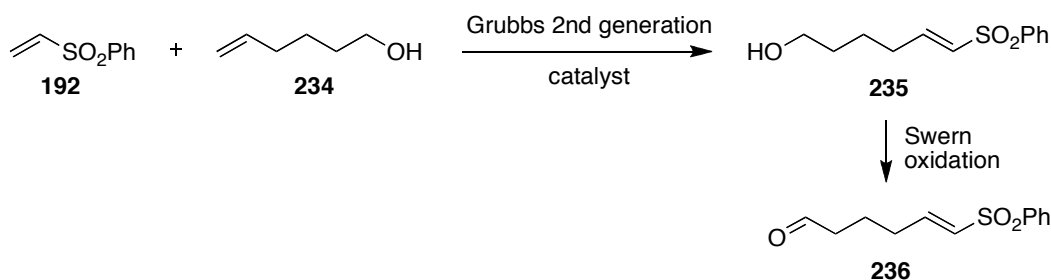
Scheme 78 Cross metathesis of phenyl vinyl sulfone **192** and 5-hexen-1-ol (**234**) followed by Swern oxidation

3.4 Cyclisation studies

With precursor vinyl sulfonate **222** and vinyl sulfone **236** in hand the cyclisation of these substrates to give cyclic ketones (Scheme 72) was investigated employing the aerobic hydroacylation conditions developed in Chapter 2.

3.4.1 Cyclisation of sulfonate ester 222

In order for an olefin to successfully undergo aerobic hydroacylation, (see chapter 2) the rate of auto-oxidation of the aldehyde reaction partner to the corresponding acid is key and the likely major by-product of any intramolecular aerobic hydroacylation reaction. To aid the study of cyclisation of aldehyde **222**, acid **237** was prepared independently *via* Pinnick oxidation of aldehyde **222** in 38% yield (Scheme 79). Disappointingly it was found that by ¹H NMR, carboxylic acid **237** was not present under the aerobic conditions and therefore deduced that aldehyde **222** does not auto-oxidise.
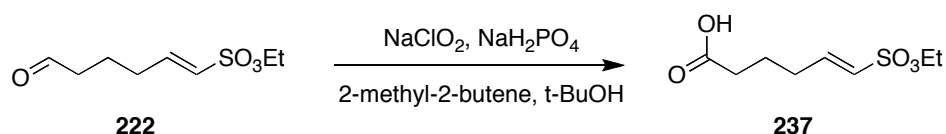
Scheme 79 Pinnick oxidation

We studied the cyclisation using the optimised conditions discussed in Chapter 2, 1,4-dioxane or 5 mol% H_2O_2/H_2O at 21 °C; however, the cyclisation of aldehyde **222** failed to yield isolable quantities of cyclic ketone **228**. The reaction was carried out in dioxane at 0.1 M reaction concentration in order to limit telomerisation of the starting material (Scheme 80). Careful inspection of the crude ¹H NMR failed to reveal the presence of any cyclic ketone **228** or carboxylic acid **237**, with apparently only starting aldehyde **222** and aldol products present even after prolonged stirring (168 h) at 21 °C.
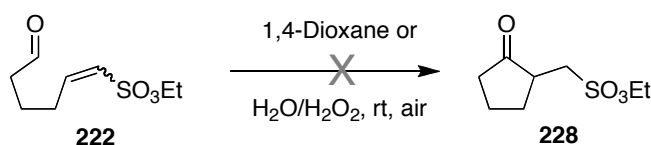
Scheme 80 Cyclisation of precursor **222**

Independent reaction of aldehyde **222** using the method of Tomioka and co-workers[78], using *tert*-dodecanethiol and AIBN in toluene at 80 °C, afforded the desired cyclic ketone **228** in 50%. This independent preparation of ketone **228** *via* radical cyclisation of aldehyde **222** confirmed that the desired 5-*exo*-trig cyclisation was feasible and gave corroboratory evidence that no detectable amount of the desired ketone **228** was formed under the intermolecular aerobic hydroacylation conditions developed in Chapter 2 when applied to intramolecular substrate **222**.

Intramolecular substrate **222** was also subjected to butyraldehyde (**30c**) and PFP vinyl sulfonate **148** in order to determine whether substrate **222** could be trapped *via* intermolecular reaction with either (Scheme 81). However, the aldehyde of **222** failed to react with PFP vinyl sulfonate **148** and the olefin of **222** failed to react with butyraldehyde (**30c**) and starting material was recovered quantitatively.
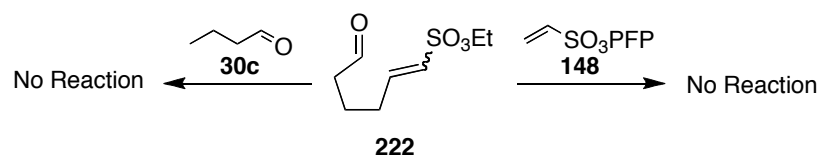
Scheme 81 Intermolecular reactions

3.4.2 Cyclisation of sulfone 236

With aldehyde **236** in hand, a number of reactions in order to investigate the cyclisation were carried out. When stirring aldehyde **236** under the optimised reaction conditions (dioxane or H_2O/H_2O_2 as solvent at 0.1 M concentration), no reaction took place to desired 5-membered ring **238** (Scheme 82). It was expected that the intramolecular reaction would occur more readily than the corresponding intermolecular reaction but even after prolonged heating at 50 °C, no cyclised product **238** was observed. By ^{1}H NMR only the presence of starting material **236** and aldol products were observed and there was no evidence for the formation of the corresponding carboxylic acid *via* aerobic auto-oxidation.
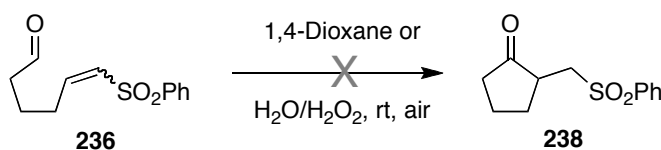
Scheme 82 Attempted cyclisation of intramolecular substrate **236**

3.5 Conclusions

The synthesis of 5-*exo*-trig cyclisation precursor **222** bearing an ethyl sulfonate motif has been described, despite problems which arose throughout the synthesis, especially concerning the formation of Horner-Wadsworth-Emmons precursors. It was not possible however to convert the ethyl sulfonate moiety into an aryl sulfonate moiety and therefore cyclisation studies were carried out using precursor **222**. Alkenal **222** failed to undergo cyclisation when subjected to the aerobic reaction conditions (stirring with 1,4 dioxane or H_2O/H_2O_2) developed in chapter 2. After prolonged reaction times, none of the corresponding carboxylic acid was visible by ^{1}H NMR and it suggested that no acyl radical was generated. When subjected to literature conditions[78], alkenal **222** cyclised in 50% yield to give cyclopentanone **228** clearly indicating that the mode of acyl radical cyclisation is viable and suggesting that the failure of cyclisation under aerobic conditions is due to slow auto-oxidation of **222**. Cyclisation precursor **231** could not be isolated after Horner-Wadsworth-Emmons reaction and hence the cyclisation to give cyclohexanone **239** could not be studied. Subjection of alkenal **236** to the aerobic conditions developed in chapter 2 also failed to give cyclopentanone **238**.
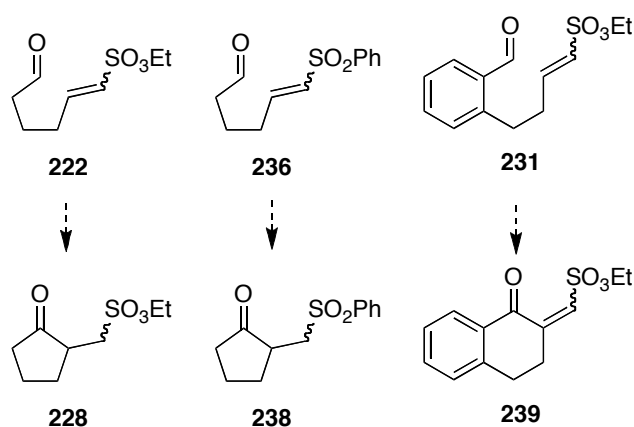
Scheme 83 Cyclisation precursors

Chapter 4   Hydroacylation of vinyl phosphonates and azodicarboxylates

4.1 Introduction

In Chapter 2, the reaction of vinyl sulfonates and vinyl sulfones with aldehydes was discussed in detail. During the period of this work, hydroacylation was also found to proceed with a variety of alkenes including vinyl phosphonates[123] and di-substituted esters.[106] This chapter will discuss the work carried out on the hydroacylation of vinyl phosphonates and azodicarboxylates.

4.2 Hydroacylation of vinyl phosphonates

It was unveiled within the Caddick group that when mixing dimethylvinyl phosphonate (**240**) with butyraldehyde (**30c**) in 1,4-dioxane at 60 °C that hydroacylation of vinyl phosphonate **240** took place in good yield (Scheme 84). In Chapter 2, it was shown that hydroacylation of vinyl sulfonates and vinyl sulfones only proceeded in good yields with simple, non-functionalised aliphatic aldehydes and it was hoped that the aldehyde scope could be expanded to aldehydes bearing functional groups. It was found that the reaction of vinyl phosphonate **240** with 3-phenylbutyraldehyde gave ketone **241p** in 60% yield. Pleasingly, the reaction of vinyl phosphonate **240** with 4-pentenal (**30q**) and an aldehyde bearing an ester moiety (**30r**) gave rise to ketones **241q** and **241r** in 22% and 67% yields respectively.
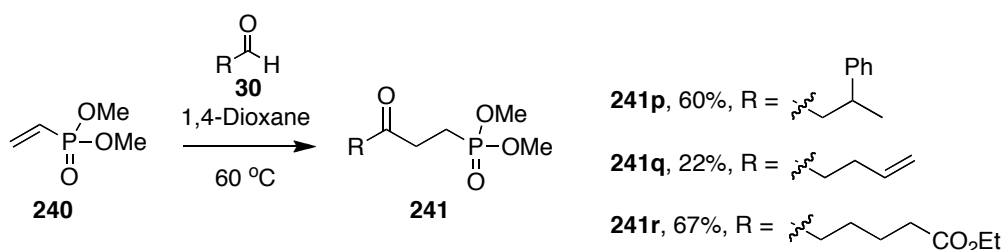
Scheme 84 Hydroacylation of dimethyl vinyl phosphonate (**240**)

4.2.1 Preparation of substituted vinyl phosphonates

It was envisaged that hydroacylation of substituted vinyl phosphonates under aerobic conditions could be investigated; this had not been carried out in the case of vinyl sulfonates and vinyl sulfones. The plethora of literature precedent on the preparation of substituted vinyl phosphonates led to a program of work into the synthesis of α- and β-substituted olefins bearing a phosphonate as the electron withdrawing group. Amri and co-workers reported the preparation of α-substituted vinyl phosphonates *via* Baylis-Hillman reaction on vinyl phosphonate **240**.[124] Addition of acetaldehyde (**30b**) to dimethylvinyl phosphonate (**240**) in the presence of DABCO gave substituted vinyl phosphonate **242** (Scheme 85). Using the procedure outlined by Amri, reaction of aldehyde **30b** with vinyl phosphonate **240** failed to give **242**. The Baylis-Hillman reaction is known to be inherently slow;[125] upon heating the reaction to 60 °C, complete consumption of vinyl phosphonate **240** was observed, but none of the desired α-substituted vinyl phosphonate **242** could be isolated.
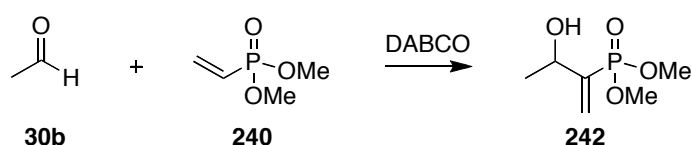
Scheme 85 Baylis-Hillman reaction with vinyl phosphonate **240**

An alternative method for the preparation of α-substituted vinyl phosphonate has been reported by Kreuger and co-workers and utilised nitro-alkenes.[126] For example, *trans*-β-nitrostyrene (**243**) was stirred neat with triethyl phosphite to generate substituted vinyl phosphonate **244** in 85% yield (Scheme 86). Kreuger and co-workers report that no purification was required upon completion of the reaction. However, upon direct repetition of their reaction conditions, this was found not to be the case. By ^{1}H NMR, there was clear evidence for the presence of phosphorus containing impurities. During repeated attempts to purify the crude mixture by column chromatography in a range of solvent systems (including mixtures of diethyl ether, ethyl acetate, methanol, dichloromethane and petrol), the impurity co-eluted with the desired product **244**. Repetition with freshly distilled triethyl phosphite afforded no improvement.
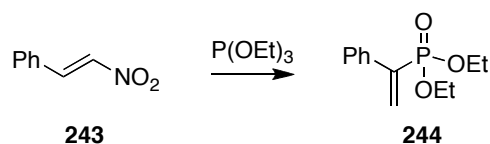
Scheme 86 Synthesis of substituted vinyl phosphonate **244** from *trans*-β-nitrostyrene (**243**)

Knoevenagel-type condensations have also been reported for the preparation of α-substituted vinyl phosphonates (Scheme 87).[127] For example, Taylor and Davies showed that when stirring phosphonate **245** with paraformaldehyde in the presence of piperidine, alkene **246** could be isolated.[127] However, repeated attempts at purification of alkene **246** by distillation led to decomposition and/or failure to separate the desired alkene **246** from paraformaldehyde derived impurities.
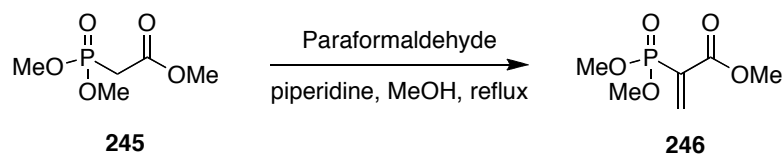
Scheme 87 Taylor's Knoevenagel-type condensation to α-substituted vinyl phosphonates

4.3 Hydroacylation of azodicarboxylates

4.3.1 Introduction

It was reported by Zhang and co-workers in 2009 that azodicarboxylates **87** could be readily hydroacylated by stirring with aldehydes **30** in the presence of ionic liquids (see section 1.5.2).[49] The use of an ionic liquid is much like the use of water as it forms two separate phases due to it having a high dielectric constant. Therefore, it was envisaged that analogous reactions could be carried out in the presence of water. In addition, the range of aldehydes will also be extended.
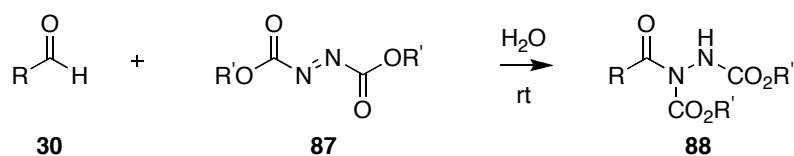
Scheme 88 Hydroacylation of azodicarboxylates

Under a program of work to manipulate **88** (Scheme 89), Lee and Kim found that hydroacylation of DIAD (**83**) using alkenyl aldehydes gave access to **247** and therefore this validates the synthesis of hydrazides **88**. Subsequent alkylation using allyl bromide and caesium carbonate gave ring-closing metathesis (RCM) precursors

248. It was postulated that RCM would proceed with ease due to hindered rotation about the N-N bond. Indeed, using Grubbs' 2nd generation catalyst, it was found that RCM proceeded in good to excellent yields to generate **249** (Scheme 89).[128]
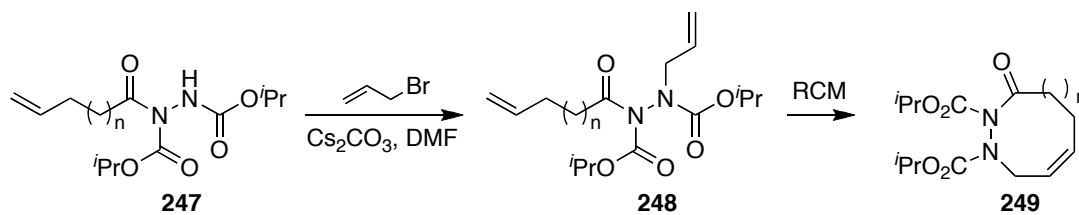
Scheme 89 Ring-closing metathesis in the formation of medium-sized rings

4.3.2 Hydroacylation of DIAD

Others in the Caddick group showed that remarkably, the reaction of DIAD (**83**) with butyraldehyde (**30c**) proceeded in 90% yield with only one equivalent of aldehyde, a stoichiometry yet to be observed for hydroacylation reactions in the literature. The reaction proceeded by simply mixing the two reacting partners together in the presence of water under aerobic conditions at room temperature (Scheme 90).
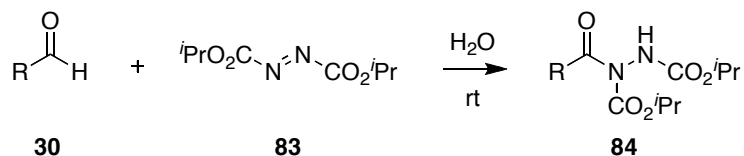
Scheme 90 Hydroacylation of DIAD (**83**)

It seems logical to assert, based on the evidence gathered for the mechanism of aerobic hydroacylation of vinyl sulfonates (see section 2.4), that the mechanism for the hydroacylation of DIAD (**83**) also proceeds *via* a radical process (Scheme 91). Thus, acyl radical **176**, generated from auto-oxidation of aldehyde **30** is trapped by azodicarboxylate **83** to give adduct radical **250**. Adduct radical **250** then abstracts aldehydic hydrogen from **30** in order to form product **84** and regenerate acyl radical **176**.
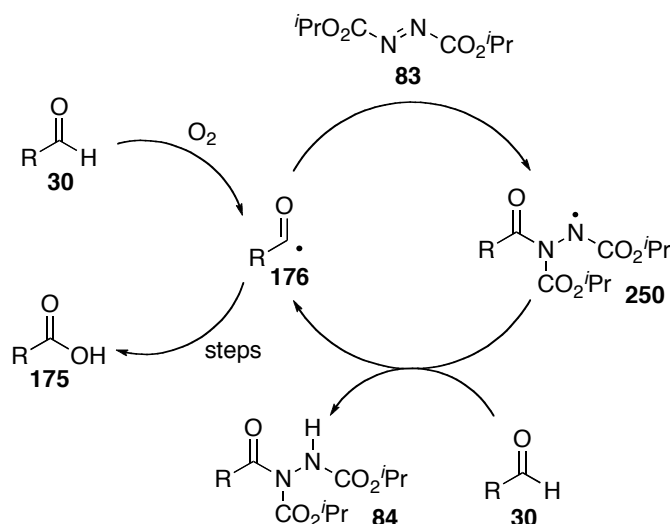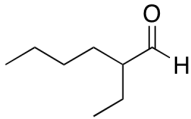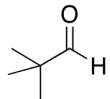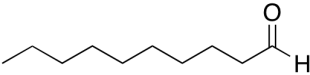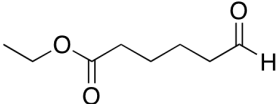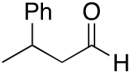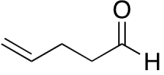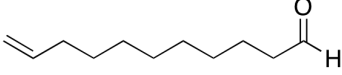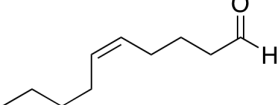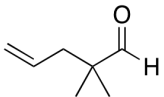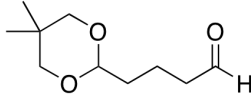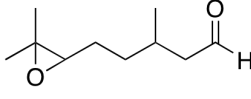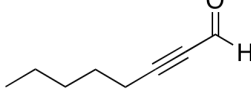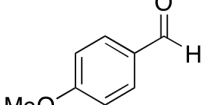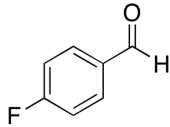
Scheme 91 Proposed mechanism for reaction of DIAD (**83**) with aldehydes

4.3.3 Aldehyde tolerance for hydroacylation of DIAD

As described previously, hydroacylation of vinyl sulfonates and vinyl sulfones proceeded well with only simple aliphatic aldehydes (see chapter 2). However, hydroacylation of vinyl phosphonates (see section 4.2) suggests that with a suitable reaction partner, aerobic hydroacylation can be carried out successfully with functionalised aldehydes. Gratifyingly, it was found that hydroacylation of DIAD (**83**) proceeded with a wide range of aldehydes (Table 11) and that only a single equivalent of aldehyde could be used.
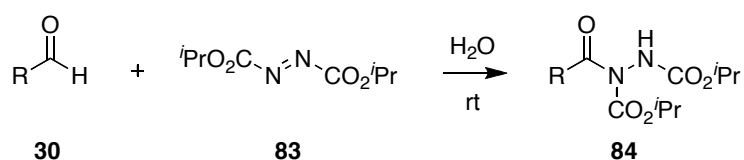
Entry	Aldehyde	Product	Reaction time / h	Yield / %
1		**84c**	24	91
2		**84d**	48	79
3		**84s**	24	88
4		**84f**	48	79

5		**84g**	48	87
6		**84j**	48	69
7		**84o**	48	85
8		**84r**	96	80
9		**84p**	24	80
10		**84q**	48	42
11		**84t**	72	77
12		**84u**	48	47
13		**84v**	48	48
14		**84w**	24	70
15		**84x**	48	74
16		**84l**	72	55
17		**84y**	48	44
18		**84m**	48	75
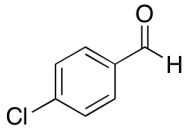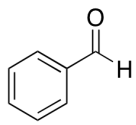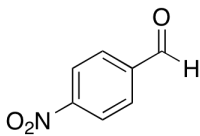
19		**84z**	48	63
20		**84a**	48	79
21		-	168	0

Table 11 Yields for hydroacylation reactions with DIAD (**83**)

With simple aliphatic aldehydes, the hydroacylation of DIAD (**83**) proceeds in excellent yields (entries 1-7, Table 11). The reaction times vary for different aldehydes; presumably this is due to differing rates of auto-oxidation. Notably, reaction with pivaldehyde (**30j**, entry 6, Table 11) generates acyl addition product to give the desired ketone; no decarbonylation is observed suggesting that intermolecular addition to DIAD (**83**) is faster than decarbonylation to tertiary alkyl radical. Hydroacylation of DIAD (**83**) also proceeds with aldehydes bearing alkene moieties (entries 10-13, Table 11), a functional group that has not been tolerated before due to oligomerisation. Good yields are observed for the reaction of DIAD (**83**) with aldehydes bearing an acetal and an epoxide (entries 14 and 15, Table 11). Most pleasingly, it has been shown that aromatic aldehydes can be used in the hydroacylation of DIAD (**83**) and the products thereof can be isolated in good yields (entries 17-20, Table 11), unlike with PFP vinyl sulfonate **148** (see section 2.6). However, reaction does not proceed with 4-nitrobenzaldehyde (entry 21) and no conversion is observed after 168 h; this could be due to solubility of the aldehyde under the reaction conditions. Despite the fact that octynal (**30l**) did not appear to auto-oxidise to octanoic acid by ^{1}H NMR when stirring under aerobic conditions for 18 h (see section 2.3), when DIAD (**83**) was stirred on water with octynal (**30l**), the desired addition product **84l** was isolated in 55% yield (entry 16, Table 11). This suggests that efficient trapping of a low concentration of acyl radicals formed by auto-oxidation is key to a general method for aerobic hydroacylation. In addition, when auto-oxidation studies were carried out on anisaldehyde (chapter 2), none of the corresponding carboxylic acid was observed. However, when anisaldehyde (**30y**)

was stirred on water with DIAD (**83**, entry 17, Table 11), the hydroacylated product **84y** was observed albeit in a relatively modest 44% yield.

4.3.3.1 Hydroacylation of DIAD with aldehyde 222

As described above, the hydroacylation of DIAD (**83**) with octynal (**30l**) and anisaldehyde (**30y**) proceeds to give desired ketones **84** albeit in modest yields. This was not observed for the corresponding reaction with PFP vinyl sulfonate **148**. In chapter 2, auto-oxidation was discussed; octynal and anisaldehyde did not appear to auto-oxidise and therefore it was assumed that no acyl radical was being generated. In chapter 3, aldehyde **222** was synthesised and its cyclisation under the radical hydroacylation conditions investigated. It was found that aldehyde **222** did not appear to auto-oxidise to its corresponding carboxylic acid **237**. Aldehyde **222** was stirred with DIAD (**83**) in order to determine if it could be trapped and there was some evidence for hydroacylation taking place even though hydrazide **251** could not be isolated. Consumption of both DIAD (**83**) and aldehyde **222** was observed by ^{1}H NMR. In addition, a signal typical of an NH was present by ^{1}H NMR and mass spectroscopy confirmed presence of a compound with the same molecular mass as hydrazide **251**, hence suggesting the formation of **251**.
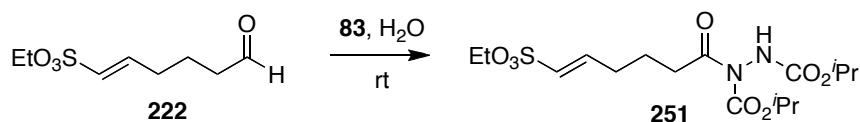
Scheme 92 Hydroacylation of DIAD (**83**) with intramolecular precursor **222**

4.3.4   Hydroacylation of DIAD with chiral aldehydes

Given the sigma-type nature of an acyl radical, it was envisaged that hydroacylation of DIAD (**83**) with chiral aldehydes would not cause racemisation of a sensitive alpha chiral centre. In addition, given that hydroacylation of DIAD (**83**) requires only 1 equivalent of aldehyde to generate acyl hydrazides in good yields, the application of radical hydroacylation as a general method for the functionalisation of valuable aldehydes is feasible.

4.3.4.1 Alpha substituted chiral aldehydes

Investigations into hydroacylation with chiral aldehydes began with reaction of 2-methyl-butyraldehyde (**30s**) with DIAD (**83**). The reaction of DIAD (**83**) and racemic

2-methyl-butyraldehyde (**30s**) proceeded well to give hydrazide **84s** in an excellent 88% yield (Scheme 93).
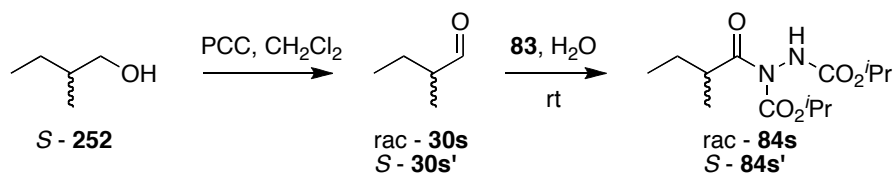
Scheme 93 Reaction of DIAD (**83**) with racemic and enantiopure 2-methyl-butyraldehyde

By surveying a range of chiral HPLC columns including CHIRALPAK-AK, CHIRALCEL-OA, -OB, and –OJ, it was possible to get baseline separation of the two enantiomers using CHIRALCEL-OD with a solvent mix of hexane/*i*-PrOH of 99:1 and flow rate of 0.6 mL/min (Figure 6). The enantiopure aldehyde **30s′** can be accessed in one step from oxidation of the commercially available corresponding alcohol **252** (Scheme 93). Hydroacylation of DIAD (**83**) with *S*-2-methyl-butyraldehyde (**30s′**) also proceeded in excellent yield (88%). Pleasingly, when enantiopure hydrazide **84s′** was subjected to chiral HPLC, it was found that the enantiomeric excess was 98% and hence retained during hydroacylation (Figure 7).
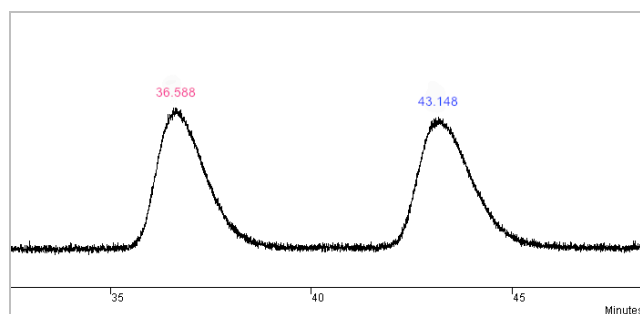
Figure 6 HPLC chromatogram of racemic product **84s**
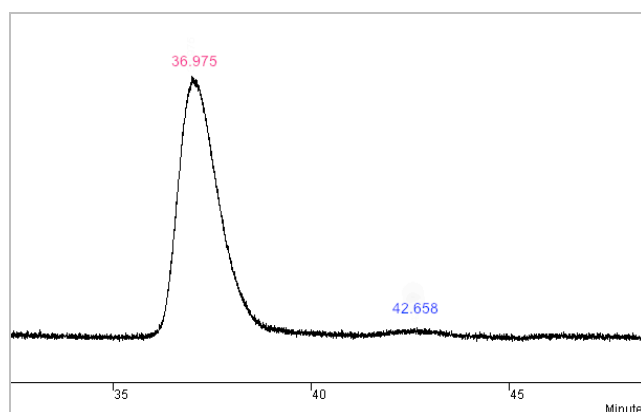
Figure 7 HPLC chromatogram of enantiomer **84s′**

Given the success of hydroacylation of DIAD (**83**) with *S*-2-methyl-butyraldehyde (**30s′**) with retained enantiomeric excess, aldehyde **253** bearing a α-silyl ether was chosen for evaluation in reaction with **83**. Racemic aldehyde **253** is available in two steps from commercially available DL-methyl-lactate (**254**) *via* TBS protection to give **255** and DIBAL reduction[129] at −78 °C in 49% overall yield. Pleasingly, when subjected to the hydroacylation reaction conditions, hydrazide **256** was isolated in 61% yield. It was possible to get baseline separation of the two enantiomers using CHIRALCEL-OD with a solvent mix of hexane/*i*-PrOH of 99:1 and flow rate of 0.6 mL/min (Figure 8). Enantiopure aldehyde **253′** was synthesised in an analogous fashion and on reaction with DIAD (**83**), hydrazide **256′** was isolated in 61% yield. On subjection of hydrazide **256′** to chiral HPLC, it was found that the enantiomeric excess was 99% and hence retained during hydroacylation (Figure 9).
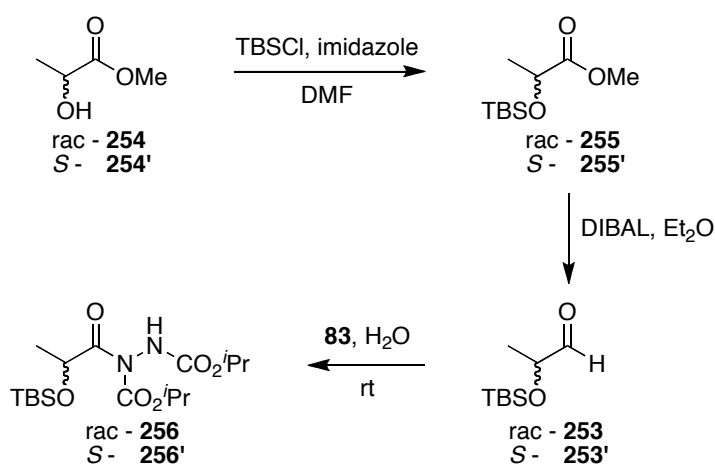
Scheme 94 Hydroacylation of DIAD **83** with chiral aldehyde
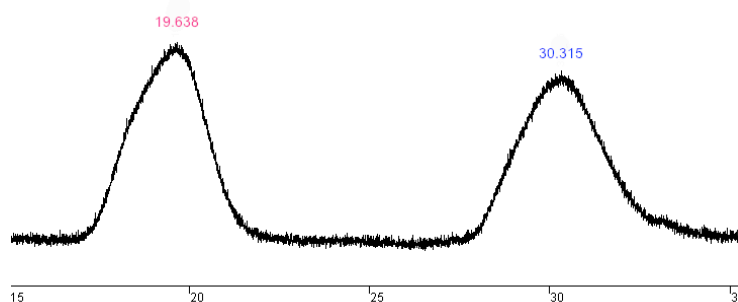
Figure 8 HPLC chromatogram of racemic product **256**
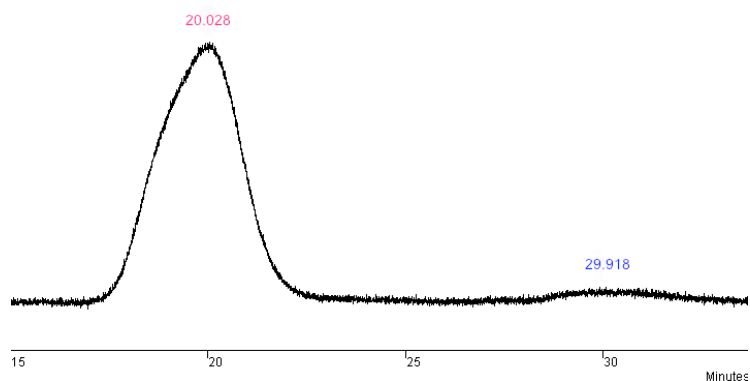
Figure 9 HPLC chromatogram for enantiomer **256′**

4.3.4.2 Beta substituted chiral aldehydes

With the success achieved with α-substituted aldehydes, investigations moved onto β-substituted chiral aldehydes.   Initially, racemic analogues were synthesised in order to determine whether separation was possible using chiral HPLC.

4.3.4.2.1 β-Substituted aldehyde derived from β-citronellal

Investigations began with hydroacylation of DIAD (**83**) with aldehyde **257**, derived from the hydrogenation of commercially available β-citronellal (**258**, Scheme 95). Pleasingly, the hydroacylation reaction proceeded in an excellent 91% yield. However, when hydrazide **259** was subjected to a range of chiral chromatography columns including CHIRALPAK-AK and CHIRALCEL-OD, -OJ, -OA and -OB, with a solvent mix of hexane/*i*-PrOH of 99:1 and flow rate of 0.6 mL/min, no separation of the two enantiomers was observed.
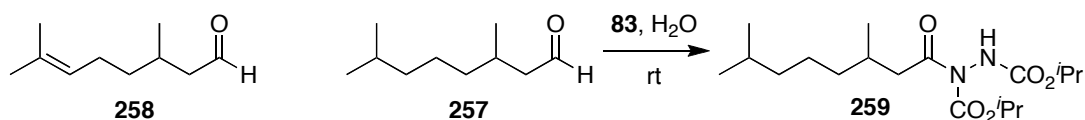
Scheme 95 Hydroacylation of DIAD (**83**) with beta-substituted aldehyde **257**

It was envisaged that hydrazide **259** could be reduced using LiAlH$_4$ to generate alcohol **260**, and that this would not affect the enantiomeric excess of the beta chiral centre to allow ee determination.   Hydrogenation of commercially available β-citronellol (**261**) gave alcohol **260** and derivatisation using tosyl chloride, gave sulfonate **262** and acetic anhydride, gave ester **263**, compounds bearing suitable chromophores for HPLC evaluation.   Screening a range of chiral HPLC columns

(CHIRALPAK-AK and CHIRALCEL-OA, -OB, -OJ and –OD) gave no separation for either sulfonate **262** or ester **263**.
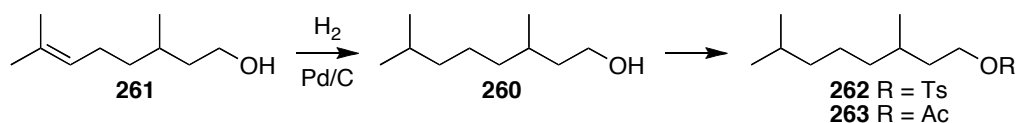
Scheme 96 Derivatisation of alcohol **260**

4.3.4.2.2 β-Substituted aldehyde derived from DL-*iso*leucine

Kumaraswamy and Markondaiah reported a concise synthesis of aldehyde **264** *via* de-amination of DL-*iso*leucine **265** to give carboxylic acid **266**.[130] Esterification with methyl iodide gave ester **267** and reduction with lithium aluminium hydride afforded desired aldehyde **264** after PCC oxidation (Scheme 97). Addition of aldehyde **264** to DIAD (**83**) gave hydrazide **268** in 80% yield. Disappointingly, subjection of hydrazide **268** to a range of chiral HPLC columns (CHIRALPAK-AK and CHIRALCEL-OA, -OB, -OJ and –OD) with a hexane/*i*-PrOH solvent mix at a flow rate of 0.6 mL/min failed to give separation of the two enantiomers.
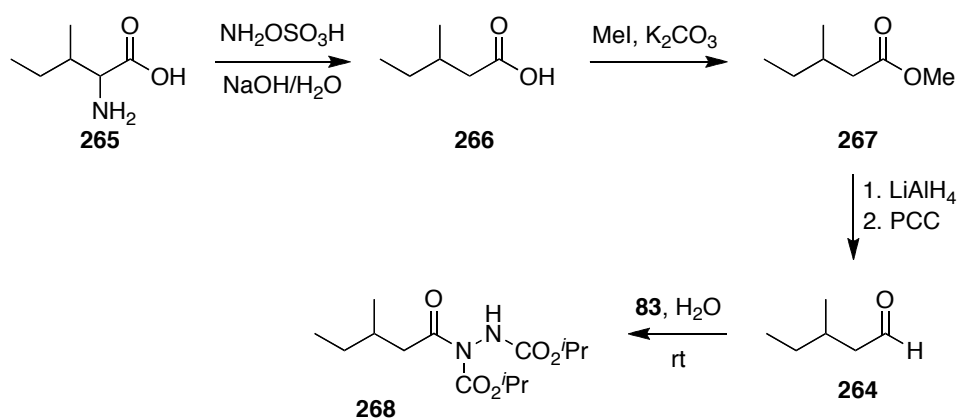
Scheme 97 Synthesis of beta-substituted aldehyde **264** and reaction with DIAD (**83**)

4.3.4.3 Gamma substituted chiral aldehyde

Due to the lack of success obtained in the determination of ee's for β-substituted aldehydes, it was decided that γ-substituted aldehydes should also be evaluated. It was foreseen that γ-substituted aldehyde **269** could be accessed from commercially available β-citronellol (**270**) by ozonolysis. However, ozonolysis of alkene **270** led to a mixture of aldehyde **271** and lactol **272** by ^{1}H NMR. The alcohol present in alkene **270** was TBS protected to give silyl ether **273** which was subjected to

potassium manganate to give a diol *in situ* followed by sodium periodate in order to cleave the diol. However, ketone **274** was isolated in 70% yield instead of desired aldehyde **269**. Presumably ketone **274** formed *via* oxidation of the diol before cleavage occurred. Ozonolysis of silyl ether **273** provided aldehyde **269** in 81% yield. Addition of aldehyde **269** to DIAD (**83**) gave hydrazide **275** in a pleasing 74% yield. However, evaluation with a range of chiral HPLC columns (CHIRALPAK-AK and CHIRALCEL-OA, -OB, -OD, -OJ)) with a hexane/*i*-PrOH solvent mix and flow rate of 0.6 mL/min showed that it was not possible to separate the two enantiomers of hydrazide **275**.
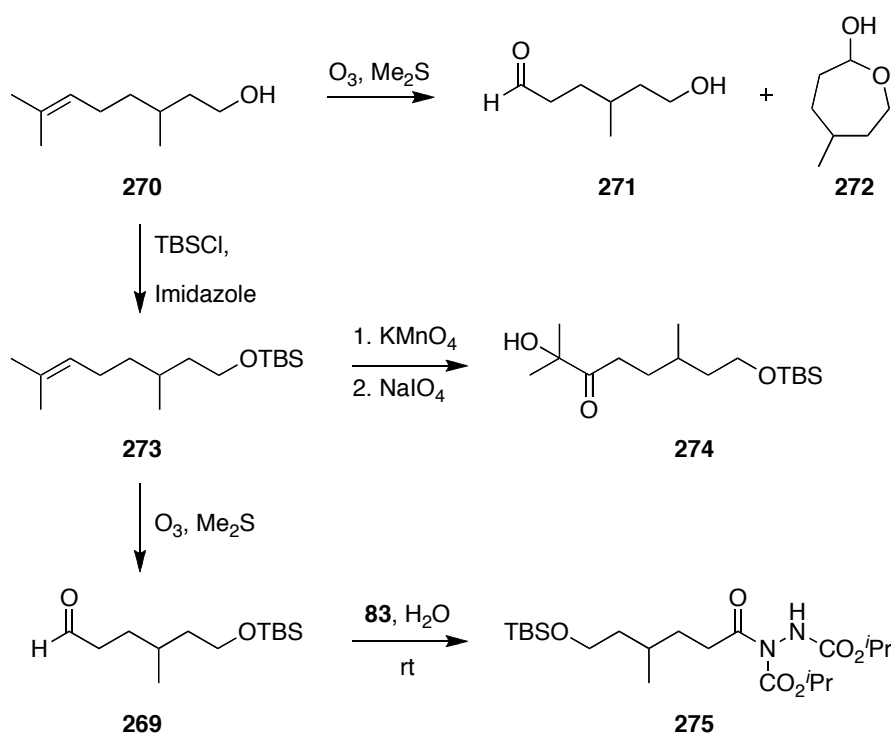
Scheme 98 Synthesis of γ-substituted aldehyde **269** and subsequent reaction with DIAD (**83**)

4.4 Conclusions

The hydroacylation of vinyl phosphonates **240** has been achieved with aldehydes bearing functional groups including ester, alkene and aryl moieties, although the reaction only proceeds at elevated temperature. It has not been possible to prepare substituted vinyl phosphonates; this has proved difficult using a range of methods.

Hydroacylation of DIAD (**83**) has been carried out at room temperature employing water as a solvent.[131] This is comparable to the work by Zhang and co-workers, which proceeds in moderate to excellent yields with 2 equivalents of aldehyde using

an ionic liquid;[49] hydroacylation in the presence of water only requires 1 equivalent of aldehyde. The hydroacylation of DIAD (**83**) proceeds with a variety of aldehydes in good yields including aldehydes bearing alkenes, aromatics, alkynes, esters, acetals, epoxides and silyl ethers. It was also possible to trap intramolecular precursor **222** using DIAD (**83**) and some evidence for the hydroacylation addition product **251** has been provided despite not being able to isolate the addition product.

It has been shown that the reaction of DIAD (**83**) with α-substituted chiral aldehydes proceeds well with retained enantiomeric excess. The reaction of DIAD (**83**) with β- and γ-substituted aldehydes proceeds in good yields; however, it has not been possible to determine enantiomeric excesses by chiral HPLC or by derivatisation.

Conclusions and Further Work

This thesis has described a method for the aerobic radical hydroacylation of vinyl sulfonates, vinyl sulfones, vinyl phosphonates and azo-dicarboxylates. The hydroacylation of vinyl sulfonates with simple aliphatic aldehydes proceeds in good yields in dioxane with 5 equivalents of aldehyde. Excellent yields can be obtained if the solvent is switched to water in the presence of 5 mol% hydrogen peroxide with only 2 equivalents of aldehyde. Disappointingly, under similar conditions, hydroacylation with aromatic aldehydes was unsuccessful. The success of aerobic radical hydroacylation appears to be closely linked to the rate of aldehyde auto-oxidation. Thus, the failure of intramolecular examples of aerobic hydroacylation seems to be attributable to the slow rate of aldehyde auto-oxidation.

Finally, hydroacylation of DIAD has been carried out in excellent yields with a variety of functionalised aldehydes including aromatic aldehydes and aldehydes that show no auto-oxidation by ^{1}H NMR. Remarkably, hydroacylation of DIAD requires only 1 equivalent of aldehyde; a stoichiometry not previously observed in the literature. During the preparation of this thesis, Zhang and co-workers published similar work whereby DIAD was hydroacylated with a range of simple aliphatic and aromatic aldehydes. However, their work requires 2 equivalents of aldehyde and in addition, they do not report hydroacylation with functionalised or chiral aldehydes.[132] Hydroacylation has also been carried out with α-substituted chiral aldehydes with excellent retained ee. Disappointingly, it has not been possible to obtain an ee for β- and γ-substituted aldehydes due to the inability to obtain baseline separation using chiral HPLC. In order to study the hydroacylation of DIAD with chiral aldehydes in greater detail, a general method for determination of ee needs to be developed.

Future work on this project should include investigations into the reactivity of C-N double bonds (Figure 10) under the aerobic radical hydroacylation conditions that have been developed throughout this project. It would be interesting to determine if the reactivity of the double bond can be reversed depending on where the electron-withdrawing group (EWG) is placed. For example, it is expected that when the EWG is attached on nitrogen (**276**), acyl radical addition would take place at the carbon atom to generate a nitrogen adduct radical much like that implicated in the

DIAD reaction. If this reaction took place more readily than when the EWG is attached on the carbon atom (**277**) thus generating a carbon-centred radical after the first addition, it would suggest that the nitrogen-centred radical is better polarity matched to abstract hydrogen from the aldehyde hence explaining the effectiveness of DIAD in the aerobic hydroacylation. It would also be interesting to study compounds with structure **278**, whereby EWG's are attached on both nitrogen and carbon in order to determine whether addition is faster at nitrogen or at carbon.
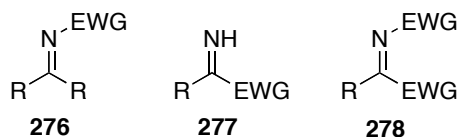
Figure 10 C-N double bonds to be investigated

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, boiling point = 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. Flash chromatography was carried out with 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. The analytes were separated and *enantiomeric excess* determined by using a CHIRALCEL-OD column (Daicel; Chiral Technologies Group, France) 25 × 0.46 cm with solvent mixes of *iso*-propanol and hexane.

Spectroscopy

Quoted yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AMX 300, Bruker AVANCE 400, Bruker AVANCE 500 or Bruker AVANCE 600 and chemical shifts (δ values) are reported in parts per million (ppm), relative to $CHCl_3$ (δ 7.26) or C_6H_6 (δ 7.14). Coupling constants (*J* values) are reported in Hertz (Hz) and are reported as J_{H-H} couplings unless otherwise specified. Carbon signals for the pentafluorophenyl moiety are not reported. Signal multiplicities were determined using the distortionless enhancement by phase transfer (DEPT) spectral

editing technique. Infrared spectra were recorded on a Perkin Elmer FTIR (ATR mode). Mass spectra were obtained at UCL on either a VG70-SE (FAB) mass spectrometer, Thermo Finnigan MAT900Xp (CI and EI), Waters LCT Premier XE (ES) or measured at EPSRC Mass Spectrometry Service, University of Swansea on either a MAT95 XP or MAT900 XLT using ammonium acetate as an additive.

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 in 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 unless otherwise stated.

Experimental for Chapter 2

Pentafluorophenyl ethene-1-sulfonate (148)[107]

Pentafluorophenol (11.5 g, 63 mmol) and NEt_3 (19.0 mL, 138 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1 h to a solution of 2-chloroethane sulfonyl chloride (10.1 g, 62.5 mmol) in CH_2Cl_2 (100 mL) at −10 °C. The mixture was allowed to warm slowly to 21 °C and stirring continued for 1 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with water (×1), 2 M HCl (×3), sat. $NaHCO_3$ (×3), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by column chromatography on silica gel (10% Et_2O/petrol) gave title compound **148** as a colourless oil (13.7 g, 50 mmol, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dd, J = 16.5, 10.0 Hz, 1H), 6.53 (dd, J = 16.5, 0.5 Hz, 1H), 6.34 (dd, J = 10.0, 0.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2

(C), 133.2 (CH), 131.7 (CH$_2$); IR (thin film) 2963, 1650, 1625, 1520 cm^{-1}; LRMS (EI) 274 (46%, [M]$^{+\cdot}$), 184 (47), 136 (17), 91 (100).

2,4,6-Trichlorophenyl 5-methyl-3-oxohexane-1-sulfonate (153d)
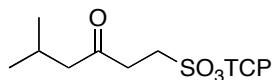
Isovaleraldehyde (540 μL, 5.0 mmol) was added to a stirred solution of trichlorophenyl vinyl sulfonate (287 mg, 1.0 mmol) in dioxane (1 mL) and the reaction mixture stirred at 21 °C for 18 h. The solvent was removed *in vacuo* and purification by column chromatography (20-60% CH$_2$Cl$_2$/Petrol) gave title compound **153d** as a white solid (254 mg, 0.74 mmol, 74%).

m.p. 59-62 °C (CH$_2$Cl$_2$/Hexane); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40 (s, 2H), 3.86-3.83 (m, 2H), 3.18-3.15 (m, 2H), 2.40 (d, *J* = 7.0 Hz, 2H), 2.18 (app. sept, *J* = 7.0 Hz, 1H), 0.95 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.2 (C), 141.9 (C), 133.2 (C), 130.7 (C), 129.3 (CH), 51.8 (CH$_2$), 48.7 (CH$_2$), 36.8 (CH$_2$), 24.8 (CH), 22.6 (CH$_3$); IR (thin film) 3081, 2959, 2873, 1717, 1560 cm^{-1}; LRMS (CI) 401 (19%, [M(^{35}Cl$_3$)+Et]$^+$), 377 (5, [M(^{37}Cl$_2$^{35}Cl)+H]$^+$), 375 (17, [M(^{37}Cl^{35}Cl$_2$)+H]$^+$), 373 (19, [M(^{35}Cl$_3$)+H]$^+$) 177 (100); HRMS (CI) calcd for C$_{13}$H$_{16}$Cl$_3$O$_4$S [M+H]$^+$ 372.9835; observed 372.9829.

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

5% H$_2$O$_2$ (0.05 mmol) and aldehyde (2.0 mmol) were added to a solution of pentafluorophenyl ethene-1-sulfonate **148** (1.0 mmol) on H$_2$O (1 mL) and the reaction mixture stirred at 21 °C for the time specified. The reaction mixture was concentrated *in vacuo* and purified as described.

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

Aldehyde (5.0 mmol) was added to a solution of pentafluorophenyl ethene-1-sulfonate **148** (1.0 mmol) in dioxane (1 mL) and the reaction mixture stirred at 21 °C

for the time specified. The reaction mixture was concentrated *in vacuo* and purified as described.

Pentafluorophenyl 3-oxobutane-1-sulfonate (160b)
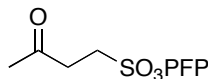
Using Method B, the reaction was complete after 3 h. Purification by column chromatography (20-80% CH_2Cl_2/Petrol) gave title compound **160b** as a pale yellow oil (119 mg, 0.38 mmol, 38%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.78-3.75 (m, 2H), 3.21-3.17 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.4 (C), 46.9 (CH), 36.8 (CH$_2$), 29.8 (CH$_3$); IR (neat) 1724 cm^{-1}; LRMS (CI) 366 (100%, [M+NH$_4$]$^+$); HRMS (ES) calcd for $C_{10}H_{11}F_5NO_4S$ [M+NH$_4$]$^+$ 366.0323, observed 366.0323.

Pentafluorophenyl 3-oxohexane-1-sulfonate (160c)

Using Method A, the reaction was complete after 1 h. Purification by column chromatography (20-80% CH_2Cl_2/Petrol) gave title compound **160c** as an off-white crystalline solid (287 mg, 0.83 mmol, 83%).

m.p 44-46 °C (hexane); ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.77-3.73 (m, 2H), 3.15-3.10 (m, 2H), 2.50 (t, *J* = 7.5 Hz, 2H), 1.71-1.59 (app. sextet, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 204.9 (C), 47.0 (CH$_2$), 44.6 (CH$_2$), 35.9 (CH$_2$), 17.2 (CH$_2$), 13.6 (CH$_3$); IR (neat) 2964, 1716 cm^{-1}; LRMS (CI) 364 (100%, [M+NH$_4$]$^+$); HRMS (ES) calcd for $C_{12}H_{15}F_5NO_4S$ [M+NH$_4$]$^+$ 364.0636, observed 364.0636.

Pentafluorophenyl   5-methyl-3-oxohexane-1-sulfonate   (160d)   and pentafluorophenyl 5-methyl-3-oxohexane-1-sulfonate (161)

Using Method A, the reaction was complete after 1 h. Purification by column chromatography (20-80% CH_2Cl_2/Petrol) gave title compound **160d** as an off-white

crystalline solid (266 mg, 0.74 mmol, 74%). Further elution gave a mixture of products. To this was added a few drops of hexanethiol. Removal of the solvent *in vacuo* and purification of the crude residue (30-60% CH_2Cl_2/Petrol) gave title compound **161** as a pale yellow oil (<5%).

Data for **160d**: m.p. 56-59 °C hexane); ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.78-3.73 (m, 2H), 3.14-3.09 (m, 2H), 2.40 (d, J = 7.0 Hz, 2H), 2.18 (app. sept, J = 6.5 Hz, 1H), 0.95 (d, J = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 204.7 (C), 51.6 (CH$_2$), 46.9 (CH$_2$), 36.4 (CH$_2$), 24.7 (CH), 22.5 (CH$_3$); IR (neat) 2964, 1720 cm^{-1}; LRMS (CI) 378 (100%, [M+NH$_4$]$^+$); HRMS (ES) calcd for C$_{13}$H$_{17}$F$_5$NO$_4$S [M+NH$_4$]$^+$ 378.0793, observed 378.0796.

Data for **161**: ^{1}H NMR (600 MHz, CDCl$_3$) δ 3.49-3.46 (m, 2H), 2.76-2.69 (m, 2H), 2.53 (t, J = 7.5 Hz, 2H), 2.41 (s, 2H), 2.15-2.13 (m, 2H), 1.60-1.56 (m, 2H), 1.40-1.27 (m, 7H), 1.10 (s, 6H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 207.7 (C), 52.5 (CH$_2$), 49.2 (CH$_2$), 44.5 (CH$_2$), 34.3 (CH$_2$), 33.1 (CH$_2$), 32.6 (CH$_2$), 31.4 (CH$_2$), 29.5 (CH$_2$), 28.6 (CH$_2$), 27.0 (CH$_3$), 25.7 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$) ; IR (thin film) 2959, 2854, 1715, 1520, 1182 cm^{-1}; LRMS (CI) 505 (100%, [M+H]$^+$; HRMS (CI) calcd for C$_{21}$H$_{30}$F$_5$O$_4$S$_2$ [M+H]$^+$ 505.1506, observed 505.1487.

Pentafluorophenyl 5,9-dimethyl-3-oxodecane-1-sulfonate (160e)
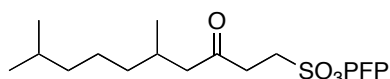
Using Method B, the reaction was complete after 18 h. Purification by column chromatography (30-80% CH_2Cl_2/Petrol) gave title compound **160e** as a white solid (248 mg, 0.72 mmol, 72%).

m.p. 49-51 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 3.75 (t, J = 7.5 Hz, 2H), 3.14-3.11 (m, 2H), 2.50 (dd, J = 16.0 and 5.5 Hz, 1H), 3.32 (dd, J = 16.0 and 8.0 Hz, 1H), 2.06-2.01 (m, 1H), 1.51 (septet, J = 6.5 Hz, 1H), 1.36-1.12 (m, 4H), 0.91 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 205.1 (C), 50.3 (CH$_2$), 47.1 (CH$_2$), 39.1 (CH$_2$), 37.1 (CH$_2$), 36.6 (CH$_2$), 29.5 (CH), 28.0 (CH), 24.8 (CH$_2$), 22.8 (CH$_3$), 22.7 (CH$_3$), 19.9 (CH$_3$); IR (thin film) 2959, 1720, 1516, 1380, 1187 cm^{-1}; LRMS (CI) 431 (20%, [M+H]$^+$), 184 (100); HRMS (CI) calcd for C$_{18}$H$_{24}$O$_4$SF$_5$ [M+H]$^+$ 431.1315, observed 431.1319.

Pentafluorophenyl 4-methyl-3-oxopentane-1-sulfonate (160f)
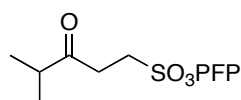
Using Method B, the reaction was complete after 3 h. Purification by column chromatography (10-80% CH_2Cl_2/Petrol) gave title compound **160f** as a colourless oil (200 mg, 0.58 mmol, 58%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.78-3.74 (m, 2H), 3.21-3.18 (m, 2H), 2.74-2.67 (app. sept, J = 7.0 Hz, 1H), 1.18 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 208.7 (C), 47.2 (CH$_2$), 41.0 (CH), 33.7 (CH$_2$), 18.1 (CH$_3$); IR (neat) 2976, 1716 cm^{-1}; LRMS (CI) 364 (100%, [M+NH$_4$]$^+$); HRMS (ES) calcd for C$_{12}$H$_{15}$F$_5$NO$_4$S [M+NH$_4$]$^+$ 364.0636, observed 364.0635.

Pentafluorophenyl 4-ethyl-3-oxooctane-1-sulfonate (160g)

Using Method A, the reaction was complete after 3 h. Purification by column chromatography (20-80% CH_2Cl_2/Petrol) gave title compound **160g** as a colourless oil (350 mg, 0.87 mmol, 87%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.87-3.83 (m, 2H), 3.23-3.19 (m, 2H), 2.49 (tt, J = 8.0 and 5.5 Hz, 1H), 1.68-1.45 (m, 4H), 1.31-1.20 (m, 4H), 0.90 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 208.9 (C), 54.0 (CH), 47.1 (CH$_2$), 35.6 (CH$_2$), 31.0 (CH$_2$), 29.8 (CH$_2$), 24.7 (CH$_2$), 22.8 (CH$_2$), 14.0 (CH$_3$), 11.8 (CH$_3$); IR (neat) 2934, 2962, 2875, 1714 cm^{-1}; LRMS (CI) 420 (14%, [M+NH$_4$]$^+$), 172 (100); HRMS (ES) calcd for C$_{16}$H$_{23}$F$_5$NO$_4$S [M+NH$_4$]$^+$ 420.1262, observed 420.1265.
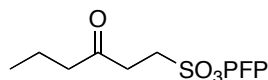
Pentafluorophenyl 3-cyclopropyl-3-oxopropane-1-sulfonate (160h)

Using Method A, the reaction was complete after 3 h. Purification by column chromatography (20-80% CH_2Cl_2/Petrol) gave title compound **160h** as an off-white solid (230 mg, 0.67 mmol, 67%).

m.p. 52-54 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82-3.74 (m, 2H), 3.38-3.31 (m, 2H), 2.06-1.97 (tt, J = 8.0 and 4.5 Hz, 1H), 1.18-1.12 (m, 2H), 1.06-0.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9 (C), 47.1 (CH_2), 36.5 (CH_2), 20.7 (CH), 11.8 (CH_2); IR (neat) 1702 cm^{-1}; LRMS (CI) 362 (100%, $[M+NH_4]^+$); HRMS (ES) calcd for $C_{12}H_{13}F_5NO_4S$ $[M+NH_4]^+$ 362.0480, observed 362.0484.

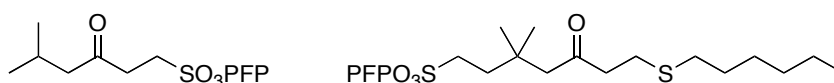**Pentafluorophenyl 3-cyclohexyl-3-oxopropane-1-sulfonate (160i)**

Using Method A, the reaction was complete after 3 h. Purification by column chromatography (20-80% CH_2Cl_2/Petrol) gave title compound **160i** as an off-white solid (304 mg, 0.79 mmol, 79%).

m.p. 62-64 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79-3.72 (m, 2H), 3.22-3.16 (m, 2H), 2.49-2.40 (tt, J = 11.0 and 3.5 Hz, 1H), 1.97-1.64 (m, 5H), 1.48-1.15 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1 (C), 50.7 (CH), 47.1 (CH_2), 34.0 (CH_2), 28.4 (CH_2), 25.6 (CH_2), 25.5 (CH_2); IR (neat) 2934, 2855, 1706 cm^{-1}; LRMS (CI) 404 (100%, $[M+NH_4]^+$); HRMS (ES) calcd for $C_{15}H_{19}F_5NO_4S$ $[M+NH_4]^+$ 404.0949, observed 404.0949.

Pentafluorophenyl   4,4-dimethyl-3-oxopentane-1-sulfonate   (160j)   and pentafluorophenyl 3,3-dimethylbutane-1-sulfonate (162)

Using Methods A and B, the reaction was complete after 3 h and 24 h respectively. Purification by column chromatography (20-80% CH_2Cl_2/Petrol) gave title

compound **160j** as a white solid (208 mg and 18 mg, 0.58 and 0.05 mmol, 58 and 5% respectively) and title compound **162** as a colourless oil (93 mg and 192 mg, 0.28 and 0.58 mmol, 28 and 58% respectively).

Data for **160j**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.75-3.72 (m, 2H), 3.25-3.22 (m, 2H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 210.4 (C), 47.5 (CH$_2$), 44.3 (C), 30.8 (CH$_2$), 26.3 (CH$_3$); IR (neat) 2971, 1710 cm^{-1}; LRMS (CI) 378 (65%, [M+NH$_4$]$^+$); HRMS (ES) calcd for C$_{13}$H$_{17}$F$_5$NO$_4$S [M+NH$_4$]$^+$ 378.0793, observed 378.0797.

Data for **162**: m.p. 40-43 °C (hexane); ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.51-3.33 (m, 2H), 2.02-1.85 (m, 2H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 49.7 (CH$_2$), 36.5 (CH$_2$), 31.0 (C), 28.8 (CH$_3$); IR (neat) 2958, 1519 cm^{-1}; LRMS (EI) 332 (20%, [M]$^{+\cdot}$), 57 (100); HRMS (ES) calcd for C$_{12}$H$_{13}$F$_5$O$_3$S [M+]$^{+\cdot}$ 332.0533, observed 332.0541.

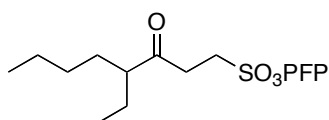**Pentafluorophenyl (4***E***)-3-oxooct-4-ene-1-sulfonate (160k)**
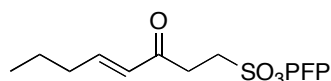
Using Method B, the reaction was complete after 24 h. Purification by column chromatography (20-80% CH$_2$Cl$_2$/Petrol) gave title compound **160k** as a yellow oil (45 mg, 0.12 mmol, 12%).

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.98 (dt, J = 14.0 and 7.0 Hz, 1H), 6.20-6.17 (m, 1H), 3.82-3.78 (m, 2H), 3.33-3.30 (m, 2H), 2.27-2.25 (m, 2H), 1.55-1.50 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.0 (C), 150.0 (CH), 129.2 (CH), 47.2 (CH$_2$), 34.6 (CH$_2$), 33.4 (CH$_2$), 21.2 (CH$_2$), 13.7 (CH$_3$); IR (neat) 2962, 1676 cm^{-1}; LRMS (CI) 389 (100%, [M+NH$_4$]$^+$), 142.2 (30).

Pentafluorophenyl 3-(4-fluorophenyl)-3-oxopropane-1-sulfonate (160m) and pentafluoro- phenyl 2-(1,4-dioxan-2-yl)ethane-1-sulfonate (190)
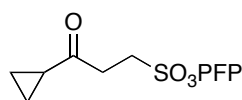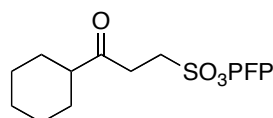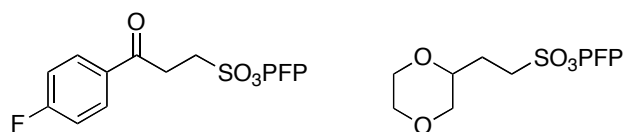

Using Method B, the reaction was complete after 18 h. Purification by column chromatography (5% Et$_2$O/Petrol) gave title compound **160m** as a white solid (135 mg, 0.34 mmol, 34%) and title compound **190** as a colourless oil.

Data for **160m**: m.p. 102-105 °C (hexane); ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.05-8.03 (m, 2H), 7.22-7.19 (m, 2H), 3.96-3.94 (m, 2H), 3.75-7.71 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 192.7 (C), 166.3 (d, J_{C-F} = 255 Hz, C), 138.8 (C), 137.1 (d, J_{C-F} = 13.5 Hz, CH), 116.2 (d, J_{C-F} = 22.5 Hz, CH), 47.4 (CH$_2$), 32.6 (CH$_2$); IR (neat) 3069, 2960, 1684, 1381, 1183 cm^{-1}; LRMS (CI) 399 (10%, [M+H]$^+$), 215 (47%), 123 (100%); HRMS (CI) calcd for C$_{15}$H$_9$F$_6$O$_4$S [M+H]$^+$ 399.01257, observed 399.01198.

Data for **190**: ^{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, 1H), 3.35 (dd, J = 11.4, 9.8, 1H), 2.15-2.03 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 72.6 (CH), 70.6 (CH$_2$), 66.7 (CH$_2$), 66.4 (CH$_2$), 49.0 (CH$_2$), 25.6 (CH$_2$); IR (neat) 3069, 2960, 1684, 1381, 1183 cm^{-1}; LRMS (FAB) 385 (20%, [M+Na]$^+$), 326 (20%), 176 (100%); HRMS (FAB) calcd for C$_{12}$H$_{11}$F$_5$O$_5$SNa [M+Na]$^+$ 385.0145, observed 385.0152.

Ethyl ethene-1-sulfonate (165)
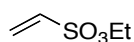
Ethanol (1.07 mL, 18.4 mmol) and NEt$_3$ (5.64 mL, 40.5 mmol)) in CH$_2$Cl$_2$ (50 mL) was added dropwise over 1 h to a solution of 2-chloroethane sulfonyl chloride (1.92 mL, 18.4 mmol) in CH$_2$Cl$_2$ (50 mL) at −10 °C. The reaction mixture was allowed to warm slowly to 21 °C and diluted with CH$_2$Cl$_2$ (50 mL), washed with water (×1), 2 M HCl (×3), sat. NaHCO$_3$ (×3), dried (MgSO$_4$) and solvent removed *in vacuo* to give title compound 7 (1.80 g, 13.2 mmol, 72%) as colourless oil. This material was used without further purification.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.54 (dd, J = 16.5 and 10.0 Hz, 1H), 6.41 (d, J = 16.5 Hz, 1H), 6.11 (d, J = 10.0 Hz, 1H), 4.20 (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 (neat) 2989, 1389, 1351 cm^{-1}; LRMS (CI) 137 (26%, [M+H]$^+$), 109 (100); HRMS (CI) calcd for C$_4$H$_9$O$_3$S [M+H]$^+$ 137.0272; observed 137.0273.

Ethyl 3-oxohexane-1-sulfonate (166) and 1,3-diethyl 5-oxooctane-1,3-disulfonate (167)
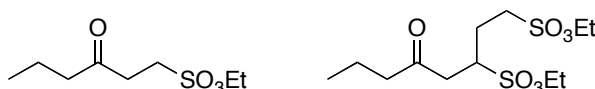
Butyraldehyde (0.45 mL, 5.0 mmol) was added to a stirred solution of ethyl vinyl sulfonate **165** (136 mg, 1.0 mmol) in dioxane and the reaction mixture stirred at 50 °C for 4 h. The solvent was removed *in vacuo*; purification by column chromatography (20-50% EtOAc/Petrol) gave title compound **166** (139 mg, 0.67 mmol, 67%) as a yellow oil and title compound **167** (33 mg, 0.10 mmol, 10%) as a colourless oil.

Data for **166**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.30 (q, J = 7.0 Hz, 2H), 3.40-3.36 (m, 2H), 2.96-2.91 (m, 2H), 2.48 (t, J = 7.5 Hz, 2H), 1.65 (app. sex, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 206.2 (C), 66.8 (CH$_2$), 44.8 (CH$_2$), 44.2 (CH$_2$), 36.1 (CH$_2$), 17.2 (CH$_2$), 15.1 (CH$_3$) 13.7 (CH$_3$); IR (neat) 2965, 2878, 1716, 1349, 1244 cm^{-1}. LRMS (CI) 209 (100%, [M+H]$^+$), 163 (22); HRMS (CI) calcd for C$_8$H$_{17}$O$_4$S [M+H]$^+$ 209.0848, observed 209.0850.

Data for **167**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.45-4.28 (m, 4H), 3.90-3.86 (m, 1H), 3.42 (ddd, J = 14.5, 10.5 and 5.5 Hz, 1H), 3.34 (ddd, J = 14.5, 10.5 and 6.0 Hz, 1H), 3.20 (dd, J = 18.5 and 4.5 Hz, 1H), 2.68 (dd, J = 18.5 and 7.5 Hz, 1H), 2.50-2.36 (m, 3H), 2.25-2.21 (m, 1H), 1.65 (app. sextet, J = 8.0 Hz, 2H), 1.49-1.42 (m, 6H), 0.95 (t, J = 8.0 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$_3$), 15.1 (CH$_3$), 13.7 (CH$_3$); IR (neat) 2934, 1716, 1344, 1166 cm^{-1}; LRMS (CI) 345 (15%, [M+H]$^+$), 235 (100), 127 (87); HRMS (CI) calcd for C$_{12}$H$_{25}$O$_7$S$_2$ [M+H]$^+$ 345.1042, observed 345.1037.

Phenyl ethene-1-sulfonate (168)

$$\diagup\diagup\text{SO}_3\text{Ph}$$
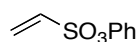
Phenol (6.90 g, 74 mmol) and NEt$_3$ (43.0 mL, 307 mmol) in CH$_2$Cl$_2$ (100 mL) was added dropwise over 1 h to a solution of 2-chloroethane sulfonyl chloride (10.0 g, 61.3 mmol) in CH$_2$Cl$_2$ (100 mL) at −10 °C. After complete addition, the mixture was allowed to warm to 21 °C and diluted with CH$_2$Cl$_2$ (50 mL), washed with 2 M HCl (×2), sat. NaHCO$_3$ (×2), brine (×1), dried (MgSO$_4$) and the solvent removed *in vacuo* to give title compound **168** as a white solid (8.40 g, 50 mmol, 82%). The compound was used without further purification.

^{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 (d, *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) 184 (45%, [M+H]$^+$), 94 (100); HRMS (CI) calcd for C$_8$H$_9$O$_3$S [M+H]$^+$ 184.0189, observed 184.0190.

Phenyl 3-oxohexane-1-sulfonate (169)

$$\diagup\diagdown\diagup\overset{\overset{\displaystyle O}{\|}}{}\diagdown\diagup\text{SO}_3\text{Ph}$$
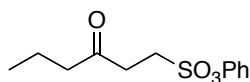
Butyraldehyde (450 µL, 5.0 mmol) was added to a stirred solution of phenyl vinyl sulfonate **168** (184 mg, 1.0 mmol) in water (1 mL) and H$_2$O$_2$ (5.0 µL, 5 mol%) and the reaction stirred at 21 °C for 3 days. The solvent was removed *in vacuo*; purification by column chromatography (20-60% CH$_2$Cl$_2$/Petrol) gave title compound **10** as a yellow oil (140 mg, 0.58 mmol, 55%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45-7.29 (m, 5H), 3.60-3.57 (m, 2H), 3.11-3.08 (m, 2H), 2.50 (t, *J* = 7.0 Hz, 2H), 1.65 (dt, *J* = 7.5 and 7.0 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 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$_2$), 17.3 (CH$_2$), 13.7 (CH$_3$); IR (neat) 2956, 1713 cm^{-1}; LRMS (CI) 257 (45%, [M+H]$^+$), 163 (100); HRMS (CI) calcd for C$_{12}$H$_{17}$O$_4$S [M+H]$^+$ 257.0848, observed 257.0850.

Ethyl 4-[(ethenesulfonyl)oxy]benzoate (170)
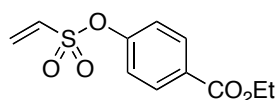
4-Hydroxy-benzoic acid ethyl ester (4.28 g, 26 mmol) and NEt_3 (9.8 mL, 70 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 1 h to a solution of 2-chloroethane sulfonyl chloride (3.8 g, 23 mmol) in CH_2Cl_2 (50 mL) at −10 °C. The reaction mixture was allowed to warm slowly to 21 °C and diluted with CH_2Cl_2 (50 mL), washed with water (×1), 2 M HCl (×3), sat. $NaHCO_3$ (×3), dried ($MgSO_4$) and solvent removed *in vacuo* to give title compound 7 (5.38 g, 21 mmol, 90%) as colourless oil. This material was used without further purification.

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.06 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 6.68 (dd, *J* = 16.5, 10.0 Hz, 1H), 6.40 (dd, *J* = 16.6, 0.5 Hz, 1H), 6.19 (dd, *J* = 10.0, 0.5 Hz, 1H), 4.38 (q, *J* = 7.5 Hz, 2H), 1.39 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.6 (C), 152.6 (C), 132.3 (CH$_2$), 131.8 (CH), 131.6 (CH), 129.6 (C), 122.2 (CH), 61.4 (CH$_2$), 14.3 (CH$_3$); IR (neat) 3112, 1712 cm^{-1}; LRMS (EI) 256 (100%, [M]$^{+\cdot}$); HRMS (EI) calcd for C$_{11}$H$_{12}$O$_5$S [M]$^{+\cdot}$ 256.0405, observed 256.0408.

Ethyl 4-{[(3-oxohexane)sulfonyl]oxy}benzoate (171)
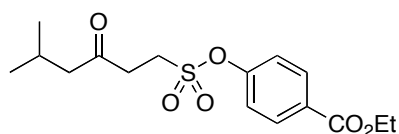
Butyraldehyde (460 μL, 5.0 mmol) was added to a stirred solution of ethyl 4-[(ethenesulfonyl)oxy]benzoate **170** (256 mg, 1.0 mmol) in dioxane (1 mL) and the reaction was stirred at 21 °C for 2 d. The solvent was removed *in vacuo*; purification by column chromatography (30-70% CH_2Cl_2/Petrol) gave title compound **12** as a yellow oil (220 mg, 0.67 mmol, 67 %).

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.11 (d, *J* = 9.0 Hz), 7.34 (d, *J* = 9.0 Hz, 2H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.60-3.57 (m, 2H), 3.09-3.06 (m, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 1.66 (app. sext, *J* = 7.5 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.5 (C), 165.4 (C), 152.3 (C), 131.7 (CH), 129.6 (C), 121.9 (CH), 61.4 (CH$_2$), 45.4 (CH$_2$), 44.8 (CH$_2$), 36.0 (CH$_2$), 17.2 (CH$_2$), 14.4 (CH$_3$), 13.7 (CH$_3$); IR (neat) 2962, 1713 cm^{-1}.

Typical procedure for the synthesis of ketone sulfones – Method C

5% H_2O_2 (0.05 mmol) and aldehyde (2.0 mmol) were added to a solution of vinyl sulfone (1.0 mmol) on H_2O (1 mL) and the reaction mixture stirred at 60 °C for the time specified. The reaction mixture was concentrated *in vacuo* and purified as described.

1-(ethanesulfonyl)hexan-3-one (200c) and 6,8-bis(ethanesulfonyl)octan-4-one (202c)
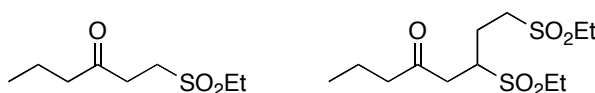
Using Method C, the reaction was complete after 18 h. Purification by column chromatography (10-50% EtOAc/Petrol) gave title compound **200c** as an off-white crystalline solid (138 mg, 0.72 mmol, 72%) and title compound **202c** as a yellow oil (<5%).

Data for **200c**: m.p. 70-73 °C (CH_2Cl_2); ^{1}H 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 (CI) calcd for $C_8H_{17}O_3S$ [M+H]$^+$ 193.0898; observed 193.0901.

Data for **202c**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.65-3.60 (m, 1H), 3.23-3.19 (m, 3H), 3.04-3.01 (m, 4H), 2.69 (dd, J = 18.5 and 6.5 Hz, 1H), 2.49 (td, J = 7.1 and 3.0 Hz, 2H), 2.45-2.38 (m, 1H) 2.25-2.16 (m, 1H), 1.63-1.59 (m, 2H), 1.41 (t, J = 7.5 Hz, 3H), 1.41 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 206.5 (C), 54.3 (CH), 48.5 (CH$_2$), 47.5 (CH$_2$), 47.4 (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 (neat) 2943, 1714, 1300, 1125 cm^{-1}; LRMS (ES) 335 (100%, [M+Na]$^+$); HRMS (ES) calcd for $C_{12}H_{24}O_5NaS_2$ [M+Na]$^+$ 335.0963, observed 335.0951.

1-Cyclohexyl-3-(ethanesulfonyl)propan-1-one (200i)
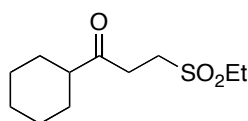
Using Method C, the reaction was complete after 18 h. Purification by column chromatography (10-30% EtOAc/Petrol) gave title compound **200i** as a white solid (139 mg, 0.60 mmol, 60%).

m.p. 82-84 °C (CH$_2$ Cl$_2$/petrol); ^{1}H NMR (600 MHz, CDCl$_3$) δ 3.27-3.24 (m, 2H), 3.04-2.99 (m, 4H), 2.43 (tt, J = 11.0 and 3.5 Hz, 1H), 1.92-1.87 (m, 2H), 1.83-1.78 (m, 2H), 1.72-1.69 (m, 1H), 1.44 (t, J = 7.5 Hz, 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$_3$S [M]$^{+\cdot}$ 232.1128; observed 232.1117.

1-(Benzenesulfonyl)hexan-3-one (201c)
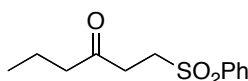
Using Method C, the reaction was complete after 16 h. Purification by column chromatography (20-50% CH$_2$Cl$_2$/Petrol) gave title compound **201c** as a yellow oil (125 mg, 0.52 mmol, 52%).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93-7.90 (m, 2H), 7.68-7.66 (m, 1H), 7.60-7.58 (m, 2H), 3.40-3.37 (m, 2H), 2.91-2.88 (m, 2H), 2.40 (t, J = 7.5 Hz, 2H), 1.56 (app. sext, 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 (CH), 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 cm^{-1}; LRMS (CI) 258 (100%, [M+NH$_4$]$^+$), 116 (55); HRMS (ES) calcd for C$_{12}$H$_{20}$O$_3$SN [M+NH$_4$]$^+$ 258.1158, observed 258.1160.

3-(Benzenesulfonyl)-1-cyclohexylpropan-1-one   (201i)   and   3,5-bis(benzenesulfonyl)-1-cyclohexylpentan-1-one (203i)
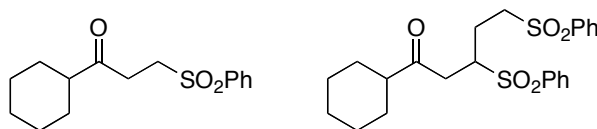
Using Method C, the reaction was complete after 18 h. Purification by column chromatography (10-30% EtOAc/Petrol) gave title compound **201i** as a white solid (140 mg, 0.50 mmol, 50%). Further elution gave title compound **203i** (<5%) as a white solid.

Data for **201i**: m.p. 78-80 ºC (hexane); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93-7.90 (m, 2H), 7.68-6.66 (m, 1H), 7.60-7.57 (m, 2H), 3.38-3.35 (m, 2H), 2.96-2.93 (m, 2H), 2.35 (tt, J = 11.0 and 3.0 Hz, 1H), 1.82-1.65 (m, 5H), 1.32-1.16 (m, 5H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 209.3 (C), 139.2 (C), 134.0 (CH), 129.5 (CH), 128.0 (CH), 50.9 (CH$_2$), 50.7 (CH), 32.9 (CH$_2$), 28.5 (CH$_2$), 25.7 (CH$_2$), 25.6 (CH$_2$); IR (thin film) 2929, 2855, 1709 cm^{-1}; LRMS (CI) 298 (100%, [M+NH$_4$]$^+$), 156 (90); HRMS (ES) calcd for C$_{15}$H$_{24}$O$_3$SN [M+NH$_4$]$^+$ 298.1471, observed 298.1473.

Data for **203i**: m.p. 130-132 °C (hexane); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 (d, J = 9.5 Hz, 2H), 7.76 (d, J = 9.5 Hz, 1H), 7.68 (m, 2H), 7.56 (m, 2H), 3.72 (dddd, J = 8.5, 6.5, 5.0 and 4.0 Hz, 1H), 3.29 (ddd, J = 14.0, 11.5 and 5.0 Hz, 1H), 3.19 (ddd, J = 14.0, 11.5 and 5.0 Hz, 1H), 2.29 (tt, J = 11.0 and 3.5 Hz, 1H), 2.17 (dtd, J = 11.5, 6.5 and 5.0 Hz, 1H), 1.91 (dtd, J = 11.5, 6.5 and 5.0 Hz, 1H), 1.83-1.60 (m, 5H), 1.27-1.14 (m, 5H); ^{13}C NMR (151 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 (thin film) 1740 cm^{-1}; LRMS (CI) 466 (28%, [M+NH$_4$]$^+$), 324 (100); HRMS (ES) calcd for C$_{23}$H$_{32}$O$_5$S$_2$N [M+NH$_4$]$^+$ 466.1716, observed 466.1720.

Experimental for Chapter 3

2,4,6-Trichlorophenyl methanesulfonate (212)
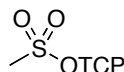
To a stirred solution of methane sulfonyl chloride (2.59 mL, 33 mmol) in CH_2Cl_2 (100 mL) at -78 °C, was added dropwise a solution of NEt_3 (8.36 mL, 60 mmol) and trichlorophenol (6.0 g, 30 mmol) in CH_2Cl_2 (100 mL). After complete addition, the reaction was diluted with CH_2Cl_2 (*ca.* 50 mL), washed with 1M $NaHCO_3$ (×3), 2M HCl (×3), brine (×1), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **212** as a white solid (6.70 g, 24 mmol, 81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 2H), 3.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.3 (CH), 41.1 (CH_3); IR (neat) 3075, 1365, 1328 cm^{-1}; LRMS (CI) 296 (30%, $[M(^{37}Cl_2{}^{35}Cl)+NH_4]^+$), 294 (100, $[M(^{37}Cl^{35}Cl_2)+NH_4]^+$), 292 (100, $[M(^{35}Cl_3)+NH_4]^+$); HRMS (CI) calcd for $C_7H_6Cl_3O_3S$ $[M+H]^+$ 274.9333, observed 274.9334.

Phenyl methanesulfonate (214)
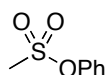
To a stirred solution of methane sulfonyl chloride (5.45 mL, 70 mmol) in CH_2Cl_2 (100 mL) at -78 °C, was added a solution of NEt_3 (17.8 mL, 128 mmol) and trichlorophenol (6.00 g, 64 mmol) in CH_2Cl_2 (100 mL) dropwise. After complete addition, the reaction was diluted with CH_2Cl_2 (*ca.* 50 mL), washed with 1M $NaHCO_3$ (×3), 2M HCl (×3), brine (×1), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **214** as a white solid (8.10 g, 47 mmol, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.25 (m, 5H), 3.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.1 (CH), 127.5 (CH), 122.1 (CH), 37.4 (CH_3); IR (neat) 3075, 1365, 1327 cm^{-1}; LRMS (ES) 190 (100%, $[M+NH_4]^+$); HRMS (ES) calcd for $C_7H_{12}O_3SN$ $[M+NH_4]^+$ 190.0532; observed 190.0529.

Ethyl (diethoxyphosphoryl)methanesulfonate (216)[109]
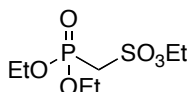
Ethyl methanesulfonate **217** (15.0 g, 121 mmol) was dissolved in dry THF (400 mL) and cooled to −78 °C under argon. To this was added *n*-BuLi (2.5 M in hexanes, 53.2 mL, 133 mmol) and the reaction stirred for 15 min. Diethylchlorophosphate (10.5 mL, 72.6 mmol) was added and the reaction stirred at −78 ºC for 30 min, warmed to −50 ºC and stirred for a further 1 h. Saturated NH_4Cl was added, the reaction mixture allowed to warm to 21 °C and the THF removed under reduced pressure. The residue was diluted with H_2O (200 mL), extracted with CH_2Cl_2 (×3), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (2:3:2 CH_2Cl_2/Et_2O/Petrol) gave title compound **216** as a colourless oil (12.3 g, 47.3 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (q, *J* = 7.0 Hz, 2H), 4.24 (dq, J_{H-P} = 14.0 Hz and *J* = 6.0 Hz, 4H), 3.71 (d, J_{H-P} = 17.0 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.37 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.4 (CH_2), 63.8 (d, J_{C-P} = 6.0 Hz, CH_2), 48.1 (d, J_{C-P} = 140.0 Hz, CH_2), 16.3 (d, J_{C-P} = 6.0 Hz, CH_3), 15.0 (CH_3); IR (neat) 2984, 1358, 1180 cm^{-1}; LRMS (CI) 261 (100%, $[M+H]^+$), 233 (87); HRMS (CI) calcd for $C_7H_{17}O_6PS$ $[M+H]^+$ 261.0562, observed 261.0555.

Ethyl methanesulfonate (217)[109]
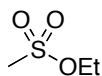
To a stirred solution of methane sulfonyl chloride (16.0 g, 140 mmol) in CH_2Cl_2 (100 mL) at −78 °C, was added dropwise a solution of NEt_3 (39.0 mL, 280 mmol) and ethanol (7.48 mL, 128 mmol) in CH_2Cl_2 (100 mL). After complete addition, the reaction was stirred at 21 °C for 1 h followed by dilution with CH_2Cl_2 (100 mL). The reaction mixture was washed with 1M $NaHCO_3$ (×3), 2M HCl (×3), brine (×1), dried ($MgSO_4$) and the solvent removed *in vacuo* to give title compound **217** (14.2 g, 115 mmol, 90%). No further purification was required.

^{1}H NMR (500 MHz, CDCl$_3$) δ 4.28 (q, J = 8.0 Hz, 2H), 3.00 (s, 3H), 1.41 (t, J = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 66.3 (CH$_2$), 37.6 (CH$_3$), 15.1 (CH$_3$); IR (neat) 2943, 1342 cm^{-1}.

Ethyl (1*E*)-6-hydroxyhex-1-ene-1-sulfonate (218)
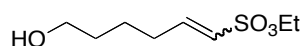
To a solution of silyl ether **226** (100 mg, 0.31 mmol) in MeOH (0.31 mL, 0.1 M) was added I$_2$ (3.1 mg, 0.12 mmol) and the reaction mixture stirred at 21 °C for 4 h. The solvent was removed *in vacuo* and the crude residue dissolved in EtOAc, washed with saturated Na$_2$S$_2$O$_3$ (×3), dried (MgSO$_4$) and the solvent removed *in vacuo*. Purification by column chromatography (50% EtOAc/Petrol) gave title compound **218** as a colourless oil (62 mg, 0.30 mmol, 93%) as a mixture of *E:Z* isomers, 3:1.

^{1}H NMR (600 MHz, C$_6$D$_6$) δ 6.65 (dt, J = 15.0 and 7.0 Hz, 1H$_{maj}$), 5.80 (dt, J = 15.0 and 1.5 Hz, 1H$_{maj}$), 5.76 (dt, J = 11.0 and 1.5, 1H$_{min}$), 5.54 (dt, J = 11.0 and 8.0 Hz, 1H$_{min}$), 3.75 (q, J = 7.0 Hz, 2H$_{maj}$), 3.74 (q, J = 7.0 Hz, 2H$_{min}$), 3.22 (t, J = 6.0 Hz, 2H$_{min}$), 3.12 (t, J = 6.0 Hz, 2H$_{maj}$), 2.39 (ddd, J = 15.0, 7.5 and 1.5 Hz, 2H$_{min}$), 1.51 (ddd, J = 16.5, 7.0 and 1.5 Hz, 2H$_{maj}$), 1.23-1.15 (m, 4H$_{min}$), 1.06-1.01 (m, 2H$_{maj}$), 0.97-0.92 (m, 2H$_{maj}$), 0.87 (t, J = 7.0 Hz, 3H$_{maj}$), 0.82 (t, J = 7.0 Hz, 3H$_{min}$); ^{13}C NMR$_{major}$ (125 MHz, C$_6$D$_6$) δ 147.9 (CH), 125.2 (CH), 65.4 (CH$_2$), 61.6 (CH$_2$), 31.6 (CH$_2$), 30.6 (CH$_2$), 23.6 (CH$_2$), 14.4 (CH$_3$); IR (neat) 3600-3200, 2938, 1632, 1346, 1164 cm^{-1}; LRMS (ES) 207 (40%, [M-H]$^-$), 179 (100); HRMS (ES) calcd for C$_8$H$_{15}$O$_4$S [M-H]$^-$ 207.0691, observed 207.0705.

Ethyl oxan-2-ylmethanesulfonate (220)
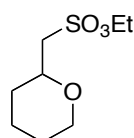
Tetrahydro-pyran-2-ol was prepared *via* DIBAL reduction of the corresponding lactone.[133] To a solution of phosphonate **216** (33 mg, 0.13 mmol) in dry THF (0.5 mL) at −78 °C under argon was added a solution of *n*-BuLi (2.5 M in hexanes, 56 μL, 0.14 mmol) and the reaction mixture stirred for 10 min. After this time, the solution was added *via* cannula to a solution of tetrahydro-pyran-2-ol (12 mg, 0.12 mmol) in dry THF (0.5 mL) at −78 °C and the mixture stirred at for 45 min at −78 °C

and then at 21 °C for 18 h. The reaction was quenched with saturated NH_4Cl and THF removed *in vacuo*. H_2O (10 mL) was added and the organic material extracted with CH_2Cl_2 (×3), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (20-50% EtOAc/Petrol) gave title compound **220** as a colourless oil (15 mg, 0.072 mmol, 60%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.43 (q, *J* = 7.0 Hz, 2H), 4.03-4.01 (m, 1H), 3.89 (dddd, *J* = 13.5, 7.5, 4.0 and 2.0 Hz, 1H), 3.51-3.49 (m, 1H), 3.35 (dd, *J* = 14.5 and 7.5 Hz, 1H), 3.14 (dd, *J* = 14.5 and 4.0 Hz, 1H), 1.89-1.87 (m, 1H), 1.77-1.75 (m, 1H), 1.62-1.53 (m, 4H), 1.41 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.6 (CH), 68.6 (CH_2), 66.9 (CH_2), 56.3 (CH_2), 31.4 (CH_2), 25.3 (CH_2), 23.0 (CH_2), 15.1 (CH_3); IR (neat) 2939, 2857, 1346, 1162 cm^{-1}; LRMS (CI) 209 (70%, [M+H]$^+$), 181 (100), 163 (60), 81 (45); HRMS (CI) calcd for $C_8H_{17}O_4S$ [M+H]$^+$ 209.0848, observed 209.0846.

Ethyl (1*E*)-6-oxohex-1-ene-1-sulfonate (222)
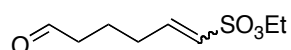
To a solution of DMSO (0.61 mL, 8.7 mmol) in CH_2Cl_2 (18 mL) at −78 °C was added oxalyl chloride (0.34 mL, 4.0 mmol) followed by alcohol **218** (550 mg, 2.6 mmol) under argon. After stirring at −78 °C for 1 h, NEt_3 (1.10 mL, 7.9 mmol) was added and the reaction mixture warmed to 21 °C, diluted with Et_2O (150 mL), washed with H_2O (×1), dried ($MgSO_4$) and solvent removed *in vacuo* to give title compound **222** as a colourless oil (390 mg, 1.90 mmol, 73%) as a mixture of *E:Z* isomers, 3:1. The compound was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (m, 1H$_{maj + min}$), 6.91 (dt, *J* = 15.0 and 7.0 Hz, 1H$_{maj}$), 6.37 (dt, *J* = 11.0 and 8.0 Hz, 1H$_{min}$), 6.27 (dt, *J* = 11.0 and 1.5 Hz, 1H$_{min}$), 6.25 (dt, *J* = 15.0 and 1.5 Hz, 1H$_{maj}$), 4.24 (q, *J* = 7.0 Hz, 2H$_{min}$), 4.19 (q, *J* = 7.0 Hz, 2H$_{maj}$), 2.57-2.54 (m, 2H$_{maj + min}$), 2.37-2.33 (m, 2H$_{maj + min}$) 1.88-1.83 (m, 2H$_{maj + min}$), 1.42-1.39 (m, 3H$_{maj + min}$); ^{13}C NMR$_{major}$ (125 MHz, $CDCl_3$) δ 201.2 (C), 147.7 (CH), 125.4 (CH), 66.7 (CH_2), 42.8 (CH_2), 30.6 (CH_2), 19.9 (CH_2), 14.9 (CH_3); IR (neat) 2938, 2729, 1721, 1351, 1168 cm^{-1}; LRMS (ES) 207 (10%, [M+H]$^+$), 180 (100); HRMS (ES) calcd for $C_8H_{15}O_4S$ [M+H]$^+$ 207.0691, observed 207.0695.

Ethyl (2-oxocyclopentyl)methanesulfonate (228)
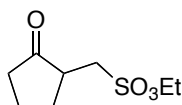
To a solution of aldehyde **222** (50 mg, 0.24 mmol) in toluene (2.5 mL) was added *tert*-dodecanethiol (20 µL, 0.09 mmol) followed by AIBN (13 mg, 0.79 mmol). The solution was degassed three times by the freeze-pump-thaw procedure and then heated to 80 °C for 18 h. Purification by column chromatography (0-30% Et_2O/Petrol) gave title compound **228** as a colourless oil (20 mg, 0.097 mmol, 40%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.37-4.35 (m, 2H), 3.70 (dd, *J* = 14.5 and 2.5 Hz, 2H), 2.95 (dd, *J* = 14.5 and 9.5 Hz, 1H), 2.65-2.63 (m, 2H), 2.44-2.42 (m, 1H), 2.17-2.14 (m, 2H), 1.88-1.86 (m, 1H), 1.74-1.72 (m, 1H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.1 (C), 66.7 (CH_2), 50.3 (CH_2), 45.0 (CH), 36.8 (CH_2), 29.7 (CH_2), 20.4 (CH_2), 15.1 (CH_3); IR (neat) 2974, 1742, 1353, 1164 cm^{-1}; LRMS (EI) 206 (100%, [M][+•]), 161 (37); HRMS (EI) calcd for $C_8H_{14}O_4S$ [M][+•] 206.0607, observed 206.0610.

5-[(*tert*-Butyldimethylsilyl)oxy]pentan-1-ol (224)[111]
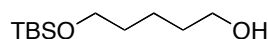
1,5-Pentanediol (41.7 g, 400 mmol) was added to a solution of imidazole (6.80 g, 100 mmol) in DMF (150 mL). The reaction mixture was cooled to 0 ºC and TBSCl (12.0 g, 80 mmol) added. The reaction was allowed to stir for 15 min at 21 °C then diluted with Et_2O (300 mL), washed with H_2O (×1) followed by brine (×1), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (15-20% EtOAc/Petrol) gave title compound **224** as a colourless oil (14.1 g, 65 mmol, 65%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.60-3.65 (m, 4H), 1.72 (br s, 1H), 1.53-1.65 (m, 4H), 1.36-1.44 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 63.5 (CH_2), 63.2 (CH_2), 33.0 (CH_2), 32.9 (CH_2), 26.4 (CH_2), 22.2 (C), 18.8 (CH_3), −5.0 (CH_3); IR (neat) 3300, 2898, 1240 cm^{-1}.

5-[(*tert*-Butyldimethylsilyl)oxy]pentanal (225)[112]
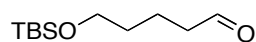
Oxalyl chloride (0.96 mL, 11.0 mmol) was dissolved in CH_2Cl_2 (9 mL) and cooled to -78 °C under argon. To this was added a solution of DMSO (1.44 mL, 10.1 mmol) in CH_2Cl_2 (5 mL). After 5 min, alcohol **224** (2.0 g, 9.2 mmol) in CH_2Cl_2 (11 mL) was added and stirring continued for 15 min. The reaction mixture was quenched with NEt_3 (6.2 mL, 45 mmol), allowed to warm to 21 °C, diluted with H_2O, extracted with CH_2Cl_2 (×3) and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford **225** as a yellow oil (1.76 g, 8.1 mmol, 89%). The material was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, $J = 1.5$ Hz, 1H), 3.60 (t, $J = 6.0$ Hz, 2H), 2.42 (dt, $J = 7.0$ and 1.5 Hz, 2H), 1.17-1.60 (m, 2H), 1.58-1.44 (m, 2H), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0 (C), 62.5 (CH_2), 42.8 (CH_2), 32.0 (CH_2), 25.9 (CH_3), 18.6 (CH_2), 18.3 (C), -5.4 (CH_3); IR (neat) 2952, 1749 cm^{-1}.

Ethyl (1*E*)-6-[(*tert*-butyldimethylsilyl)oxy]hex-1-ene-1-sulfonate (226)
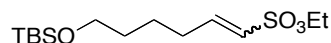
To a solution of phosphonate **216** (3.00 g, 9.3 mmol) in dry THF (30 mL) at -78°C under argon, was added *n*-BuLi (2.2 M in hexanes, 4.6 mL, 10.1 mmol). After 15 min, aldehyde **225** (2.4 g, 11.1 mmol) was added and the reaction mixture stirred at -78 °C for 45 min. The reaction mixture was stirred at 21 °C overnight, quenched with saturated NH_4Cl and THF removed under reduced pressure. H_2O (50 mL) was added and the organic material extracted with CH_2Cl_2 (×3), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (0-50% EtOAc in Petrol) gave title compound **226** as a colourless oil (2.10 g, 6.5 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dt, $J = 15.0$ and 7.0 Hz, 1H), 6.22 (d, $J = 15.0$ Hz, 1H), 4.16 (q, $J = 7.0$ Hz, 2H), 3.64-3.62 (m, 2H), 2.35-2.32 (m, 2H), 1.57-1.52 (m, 4H), 1.39 (t, $J = 7.0$ Hz, 3H), 0.93 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3 (CH), 124.6 (CH), 66.5 (CH_2), 62.6 (CH_2), 32.1 (CH_2), 31.4 (CH_2), 26.0 (CH_3), 24.2 (CH_2), 18.4 (C), 15.0 (CH_3), -5.2 (CH_3); IR (neat) 2954, 1423,

1344 cm^{-1}; LRMS (ES) 340 (100%, [M+NH$_4$]$^+$); HRMS (ES) calcd for C$_{14}$H$_{34}$O$_4$SSiN [M+NH$_4$]$^+$ 340.1972, observed 340.1975.

2-(3-Oxopropyl)benzaldehyde (233)[78,121]
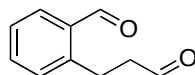
1,2-Dihydronaphthalene (0.50 g, 3.84 mmol) was dissolved in CH$_2$Cl$_2$ (150 mL) and cooled to −78 °C. A stream of ozone-enriched oxygen was bubbled through the solution until a blue colour persisted. After stirring for a further 5 min, argon was bubbled through the solution until the blue colour disappeared. PPh$_3$ (2.01 g, 7.68 mmol) was added and the reaction mixture allowed to warm to 21 °C and stirred for 2 h. The solvent was removed *in vacuo* and purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **233** as a colourless oil (0.45 g, 2.78 mmol, 90%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 10.18 (s, 1H), 9.84 (t, *J* = 1.5 Hz, 1H), 7.82 (dd, *J* = 7.5 and 1.5 Hz, 1H), 7.54 (dt, *J* = 9.0 and 1.5 Hz, 1H), 7.45 (dt, *J* = 9.0 and 1.5 Hz, 1H), 7.35-7.33 (m, 1H), 3.37 (t, *J* = 8.0 Hz, 2H), 2.80 (dt, *J* = 8.0 and 1.5 Hz, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 201.3 (CH), 193.1 (CH), 142.8 (C), 134.6 (CH), 133.9 (CH), 133.7 (C), 131.4 (CH), 127.1 (CH), 45.0 (CH$_2$), 21.1 (CH$_2$); LRMS (CI) 163 (90%, [M+H]$^+$), 117 (100); HRMS (CI) calcd for C$_{10}$H$_{11}$O$_2$ [M+H]$^+$ 163.0759, observed 163.0726.

(5*E*)-6-(Benzenesulfonyl)hex-5-enal (236)[134]
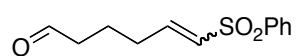
To a solution of DMSO (0.10 mL, 1.5 mmol) in CH$_2$Cl$_2$ (3 mL) was added oxalyl chloride (60 µL, 0.70 mmol) at −78 °C under argon, followed by a solution of alcohol **235** (prepared *via* literature procedure)[122] (130 mg, 0.54 mmol) in CH$_2$Cl$_2$ (1.5 mL). The reaction mixture was stirred at −78 °C for 40 min. NEt$_3$ (0.25 mL, 3.4 mmol) was added and the mixture warmed to 21 °C. The reaction mixture was diluted with CH$_2$Cl$_2$, washed with H$_2$O (×3), dried (MgSO$_4$) and the solvent removed *in vacuo* to give title compound **236** a yellow oil (112 mg, 0.47 mmol, 86%). The material was used without further purification.

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.78 (t, J = 1.0 Hz, 2H), 7.90-7.88 (m, 2H), 7.66-7.62 (m, 1H), 7.58-5.53 (m, 2H), 6.97 (dt, J = 16.5 and 6.0 Hz, 1H), 6.37 (d, J = 16.5 Hz, 1H), 2.50 (t, J = 7.0 Hz, 2H), 2.31 (app. q, J = 7.0 Hz, 2H), 1.84 (quin, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 201.3 (C), 133.5 (C), 131.2 (CH), 129.4 (CH), 127.6 (CH), 100.7 (CH), 77.3 (CH), 42.8 (CH$_2$), 30.6 (CH$_2$), 19.9 (CH$_2$); IR (neat) 3300, 2934, 2864, 1725, 1449 cm^{-1}.

(5*E*)-6-(Ethoxysulfonyl)hex-5-enoic acid (237)[135]
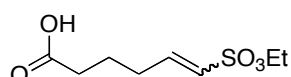
To a solution of **222** (20 mg, 0.096 mmol) and 2-methyl-2-butene (0.51 mL, 4.8 mmol) in *t*-BuOH (2 mL) was added a solution of sodium chlorite (96 mg, 0.89 mmol) and sodium dihydrogen phosphate (104 mg, 0.67 mmol) in H$_2$O (0.9 mL). The reaction mixture was stirred at 21 °C for 18 h and volatiles removed *in vacuo.* The mixture was acidified to pH 2 with 10% aqueous HCl and the organic material extracted with EtOAc (×3), washed with brine (×1), dried (MgSO$_4$) and solvent removed *in vacuo*. Purification by column chromatography (10-50% EtOAc/Petrol) gave title compound **237** as a colourless oil (8 mg, 0.036 mmol, 38%) as a mixture of *E:Z* isomers, 3:1.

^{1}H NMR (600 MHz, C$_6$D$_6$) δ 6.53 (dt, J = 15.0 and 7.0 Hz, 1H$_{maj}$), 5.74 (dt, J = 15.0 and 1.5 Hz, 1H$_{maj}$), 5.73 (dt, J = 11.0 and 1.5 Hz, 1H$_{min}$), 5.37 (dt, J = 11.0 and 8.0 Hz, 1H$_{min}$), 3.74 (q, J = 7.0 Hz, 2H$_{maj}$), 3.72 (q, J = 7.0 Hz, 1H$_{min}$), 2.33 (ddd, J = 15.0, 8.0 and 1.5 Hz, 2H$_{min}$), 1.91 (t, J = 7.0 Hz, 2H$_{min}$), 1.74 (t, J = 7.0 Hz, 2H$_{maj}$), 1.46-1.42 (m, 2H$_{maj}$ + 2H$_{min}$), 1.37-1.27 (m, 2H$_{maj}$ + 2H$_{min}$), 0.86 (t, J = 7.0 Hz, 3H$_{maj}$), 0.83 (t, J = 7.0 Hz, 3H$_{min}$); ^{13}C NMR$_{major}$ (150 MHz, C$_6$D$_6$) δ 176.8 (C), 146.6 (CH), 125.8 (CH), 65.5 (CH$_2$), 32.2 (CH$_2$), 29.9 (CH$_2$), 22.0 (CH$_2$), 14.4 (CH$_3$); IR (thin film) 3600-3000, 2919, 1711, 1351, 1167 cm^{-1}; LRMS (ES) 221 (100%, [M-H]$^-$); HRMS (ES) calcd for C$_8$H$_{13}$O$_5$S [M-H]$^-$ 221.0475, observed 221.0484.

Experimental for Chapter 4

Typical procedure for the synthesis of ketone phosphonate esters – Method D

Aldehyde (5.0 mmol) was added to a solution of vinyl phosphonate (1.0 mmol) in dioxane (1 mL) and the reaction mixture stirred at 60 °C for the time specified. The reaction mixture was concentrated *in vacuo* and purified as described.

Dimethyl (3-oxo-5-phenylhexyl)phosphonate (241p)
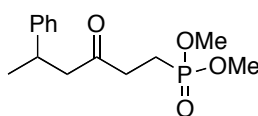
Using method D, the reaction was complete after 18 h. Purification by column chromatography (0-4% MeOH/CH$_2$Cl$_2$) gave title compound **241p** as a colourless oil (170 mg, 0.60 mmol, 60%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.33-7.29 (m, 2H), 7.23-7.20 (m, 3H), 3.70 (d J_{H-P} = 11.0 Hz, 3H), 3.70 (d, J_{H-P} = 11.0 Hz, 3H), 2.78 (dd, J = 16.0 and 7.0 Hz, 1H), 2.70-2.52 (m, 3H), 2.04-1.91 (m, 2H), 1.28 (d, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 206.9 (d, J_{C-P} = 13.5 Hz, C) 145.8 (C), 128.6 (CH), 126.8 (CH), 126.5 (CH), 52.5 (d, J_{C-P} = 6.5 Hz, CH$_3$), 52.5 (d, J_{C-P} = 6.5 Hz, CH$_3$), 50.9 (CH$_2$), 36.0 (d, J_{C-P} = 6.5 Hz, CH$_2$), 35.5 (CH), 22.0 (CH$_3$), 18.0 (d, J_{C-P} = 144.0 Hz, CH$_2$); IR (thin film) 2958, 1716, 1240, 1024 cm^{-1}; LRMS (EI) 284 (26%, [M]$^{+\cdot}$), 138 (100); HRMS (EI) calcd for C$_{14}$H$_{21}$O$_4$P [M]$^{+\cdot}$ 284.1172, observed 284.1186.

Dimethyl (3-oxohept-6-en-1-yl)phosphonate (241q)

Using method D, the reaction was complete after 48 h. Purification by column chromatography (0-4% MeOH/CH$_2$Cl$_2$) gave title compound **241q** as a colourless oil (132 mg, 0.60 mmol 60%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 5.80 (ddt, J = 17.0, 10.0 and 6.5 Hz, 1H), 5.04 (dq, J = 17.0 and 1.5 Hz, 1H), 5.00 (dq, J = 10.0 and 1.5 Hz, 1H), 3.74 (d, J_{H-P} = 11.0 Hz,

6H), 2.73 (m, 2H), 2.55 (t, J = 15.0 Hz, 2H), 2.35-2.32 (m, 2H), 2.07-2.01 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 207.3 (d, J_{C-P} = 13.5 Hz. C), 136.8 (CH), 115.5 (CH$_2$), 52.5 (d, J_{C-P} = 6.5 Hz, CH$_3$), 41.6 (CH$_2$), 35.4 (d, J_{C-P} = 6.5 Hz, CH$_2$), 27.7 (CH$_2$), 18.0 (d, J_{C-P} = 144 Hz, CH$_2$); IR (thin film) 2956, 1716, 1415, 1237, 1027 cm^{-1}; LRMS (EI) 220 (24%, [M]$^{+\cdot}$), 165 (100), 138 (98); HRMS (EI) calcd for C$_9$H$_{17}$O$_4$P [M]$^{+\cdot}$ 220.0859, observed 220.0853.

Ethyl 6-oxohexanoate (30r)[136]
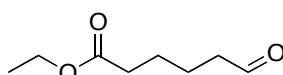
To a solution of PCC (8.08 g, 37.5 mmol) in CH$_2$Cl$_2$ (40 mL) at 0 °C was added a solution of ethyl-6-hydroxy-hexanoate (4.00 g, 25 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C and the reaction mixture stirred at 21 °C for 1 h. When the reaction was complete (monitored by TLC), the mixture was diluted with Et$_2$O and filtered through a plug of silica gel. The solution was concentrated *in vacuo* to give title compound **30r** as a colourless oil (2.65 g, 16.6 mmol, 66%). The compound was used without further purification.

^{1}H NMR (600 MHz, CDCl$_3$) δ 9.78 (t, J = 1.5 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 2.51-2.45 (m, 2H), 2.37-2.30 (m, 2H), 1.70-1.65 (m, 4H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 202.3 (C), 173.4 (C), 60.5 (CH$_2$), 43.6 (CH$_2$), 34.1 (CH$_2$), 24.5 (CH$_2$), 21.6 (CH$_2$), 14.4 (CH$_3$); LRMS (CI) 157 (100%, [M+H]$^+$), 143 (80), 111 (85), 101 (50); HRMS (CI) calcd for C$_8$H$_{13}$O$_3$ [M+H]$^+$ 157.0865, observed 157.0868.

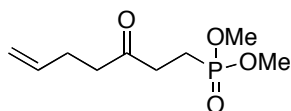**Ethyl 8-(dimethoxyphosphoryl)-6-oxooctanoate (241r)**
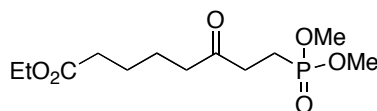
Using method D, the reaction was complete after 18 h. Purification by column chromatography (0-4% MeOH/CH$_2$ Cl$_2$) gave title compound **241r** as a colourless oil (197 mg, 0.67 mmol, 67 %).

^{1}H NMR (600 MHz, CDCl$_3$) δ 4.10 (q, J = 7.0 Hz, 2H), 3.71 (d, J_{H-P} = 11.0 Hz, 6H), 2.69 (dt, J_{H-P} = 15.5 and 7.5 Hz, 2H), 2.45-2.43 (m, 2H), 2.31-2.29 (m, 2H), 2.03-

2.00 (m, 2H), 1.61-1.59 (m, 4H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 207.7 (d, J_{C-P} = 14.0 Hz, C), 173.5 (C) 60.5 (CH$_2$), 52.5 (d, J_{C-P} = 6.0 Hz, CH$_3$), 42.3 (CH$_2$), 35.4 (d, J_{C-P} = 3.0 Hz, CH$_2$), 34.1 (CH$_2$), 24.5 (CH$_2$), 23.2 (CH$_2$), 18.3 (d, J_{C-P} = 144.0 Hz, CH$_2$), 14.3 (CH$_3$); IR (thin film) 2955, 1730, 1717, 1244 cm^{-1}; LRMS (ES) 317 (100%, [M+Na]$^+$); HRMS (ES) calcd for C$_{12}$H$_{23}$O$_6$NaP [M+Na]$^+$ 317.1130, observed 317.1120.

Typical Procedure for the Synthesis of Hydroacylated DIAD – Method E

Aldehyde (1.0 mmol) was added to a solution of DIAD (1.2 mmol) on H$_2$O (500 μL) and the reaction mixture stirred at 21 °C until the time specified. The solvent was removed *in vacuo* and the product purified as specified.

### *N,N'*-bis[(propan-2-yloxy)carbonyl]benzohydrazide (84a)
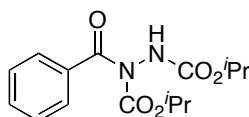
Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **84a** as a white solid (243 mg, 0.79 mmol, 79%).

m.p. 98-101 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.72-7.59 (m, 2H), 7.52-7.48 (m 1H), 7.43-7.37 (m, 2H), 7.03-6.97 (br s, NH, 1H), 5.00 (septet, J = 6.5 Hz, 1H), 4.92-4.84 (m, 1H), 1.31-1.23 (m, 6H), 1.10-1.02 (m, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 171.3 (C), 155.4 (C), 152.9 (C), 135.2 (C), 131.9 (CH), 128.2 (CH), 128.1 (CH), 72.5 (CH), 70.6 (CH), 21.9 (CH$_3$), 21.3 (CH$_3$); IR (thin film) 3265, 2988, 1755, 1738, 1682, 1601, 1519 cm^{-1}; LRMS (ES) 307 (100, [M−H]$^-$); HRMS (ES) calcd for C$_{15}$H$_{19}$N$_2$O$_5$ [M−H]$^-$ 307.1294, observed 307.1289.

N,N'-Bis[(propan-2-yloxy)carbonyl]butanehydrazide (84c)
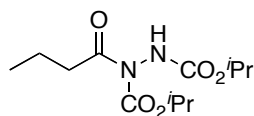
Using method E, the reaction was complete after 24 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave title compound **84c** as a colourless oil (249 mg, 0.91 mmol, 91%).

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.62-6.34 (br s, NH, 1H), 5.03 (septet, J = 6.5 Hz, 1H), 4.97 (septet, J = 6.5 Hz, 1H), 2.94-2.74 (m, 2H), 1.69 (sextet, J = 7.5 Hz, 2H), 1.34-1.17 (m, 12H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.9 (C), 155.2 (C), 152.8 (C), 72.2 (CH), 70.5 (CH), 39.1 (CH$_2$), 22.0 (CH$_3$), 21.8 (CH$_3$), 18.2 (CH$_2$), 13.8 (CH$_3$); IR (thin film) 3317, 2982, 2938, 1736, 1717 cm^{-1}; LRMS (CI) 275 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{12}$H$_{23}$N$_2$O$_5$ [M+H]$^+$ 275.1607, observed 275.1609.

3-Methyl-*N,N'*-bis[(propan-2-yloxy)carbonyl]butanehydrazide (84d)

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave title compound **84d** as a colourless oil (228 mg, 0.79 mmol, 79%).

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.67-6.37 (br s, NH, 1H), 5.02 (septet, J = 6.5 Hz, 1H), 4.96 (septet, J = 6.5 Hz, 1H), 2.92-2.57 (m, 2H), 2.18 (nonet, J = 6.5 Hz, 1H), 1.33-1.17 (m, 12H), 0.97 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.2 (C), 155.2 (C), 152.7 (C), 72.1 (CH), 70.4 (CH), 45.7 (CH$_2$), 25.3 (CH), 22.6 (CH$_3$), 21.9 (CH$_3$), 21.8 (CH$_3$); IR (thin film) 3317, 2982, 2874, 1736, 1718 cm^{-1}; LRMS (CI) 289 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{13}$H$_{25}$N$_2$O$_5$ [M+H]$^+$ 289.1764, observed 289.1760.

2-Methyl-*N*,*N'*-bis[(propan-2-yloxy)carbonyl]propanehydrazide (84f)

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave title compound **84f** as a colourless oil (217 mg, 0.79 mmol, 79%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.78-6.60 (br s, NH, 1H), 5.00 (septet, J = 6.5 Hz, 1H), 4.93 (septet, J = 6.5 Hz, 1H), 3.60 (septet, J = 7.0 Hz, 1H), 1.33-1.12 (m, 18H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 178.4 (C), 155.3 (C), 152.7 (C), 72.2 (CH), 70.4 (CH), 34.4 (CH), 22.0 (CH$_3$), 21.8 (CH$_3$), 19.4 (CH$_3$); IR (thin film) 3322, 2982, 2938, 1736, 1718 cm^{-1}; LRMS (CI) 275 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{12}$H$_{23}$N$_2$O$_5$ [M+H]$^+$ 275.1607, observed 275.1598.

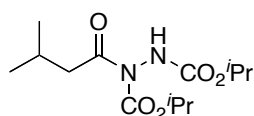## 2-Ethyl-*N*,*N'*-bis[(propan-2-yloxy)carbonyl]hexanehydrazide (84g)

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave title compound **84g** as a colourless oil (287 mg, 0.87 mmol, 87%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.60-6.30 (br s, NH, 1H), 5.04 (septet, J = 6.5 Hz, 1H), 4.96 (septet, J = 6.5 Hz, 1H), 3.53 (app. quintet, J = 6.0 Hz, 1H), 1.75-1.66 (m, 2H), 1.57-1.42 (m, 2H), 1.33-1.17 (m, 16H), 0.90 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 177.5 (C), 155.3 (C), 152.8 (C), 72.2 (CH), 70.5 (CH), 46.1 (CH), 31.7 (CH$_2$), 29.5 (CH$_2$), 25.5 (CH$_2$), 22.9 (CH$_2$), 22.0 (CH$_3$), 21.8 (CH$_3$), 14.1 (CH$_3$), 11.7 (CH$_3$); IR (thin film) 3317, 2963, 2935, 2875, 1736, 1721 cm^{-1}; LRMS (FAB) 353 (100, [M+Na]$^+$); HRMS (FAB) calcd for C$_{16}$H$_{30}$N$_2$NaO$_5$ [M+Na]$^+$ 353.2052, observed 353.2053.

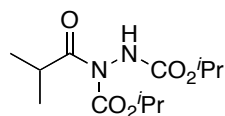## 2,2-Dimethyl-*N,N'*-bis[(propan-2-yloxy)carbonyl]propanehydrazide (84j)

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave title compound **84j** as a colourless oil (228 mg, 0.79 mmol, 79%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.62-6.55 (br s, NH, 1H), 5.04 (septet, J = 6.5 Hz, 1H), 4.99 (septet, J = 6.5 Hz, 1H), 1.33-1.18 (m, 21H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 179.9 (C), 155.8 (C), 153.4 (C), 72.4 (CH), 70.7 (CH), 42.2 (C), 27.6 (CH$_3$), 22.0 (CH$_3$), 21.8 (CH$_3$); IR (thin film) 3293, 2982, 2937, 1777, 1734, 1721 cm^{-1}; LRMS (FAB) 311 (100, [M+Na]$^+$); HRMS (FAB) calcd for C$_{13}$H$_{24}$N$_2$NaO$_5$ [M+Na]$^+$ 311.1583, observed 311.1588.

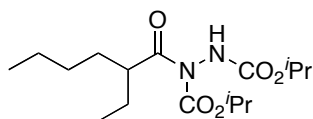## *N,N'*-Bis[(propan-2-yloxy)carbonyl]oct-2-ynehydrazide (84l)

Using method E, the reaction was complete after 72 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave title compound **84l** as a colourless oil (179 mg, 0.55 mmol, 55%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.67-6.59 (br s, NH, 1H), 5.08 (septet, J = 6.5 Hz, 1H), 4.99 (septet, J = 6.5 Hz, 1H), 2.39 (t, J = 7.0 Hz, 2H), 1.62-1.55 (m, 2H), 1.42-1.22 (m, 16H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 154.7 (C), 152.4 (C), 151.4 (C), 98.8 (C), 74.3 (C), 72.8 (CH), 70.8 (CH), 31.1 (CH$_2$), 27.3 (CH$_2$), 22.2 (CH$_2$), 22.0 (CH$_3$), 21.8 (CH$_3$), 19.4 (CH$_2$), 14.0 (CH$_3$); IR (thin film) 3314, 2983, 2936, 2873, 2229, 1741, 1724, 1687 cm^{-1}; LRMS (FAB) 349 (100, [M+Na]$^+$); HRMS (FAB) calcd for C$_{16}$H$_{26}$N$_2$NaO$_5$ [M+Na]$^+$ 349.1739, observed 349.1733.

4-Fluoro-*N*,*N*'-bis[(propan-2-yloxy)carbonyl]benzohydrazide (84m)
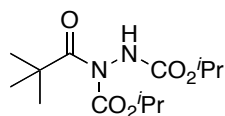

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **84m** as a colourless oil (245 mg, 0.75 mmol, 75%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.76-7.69 (m, 2H), 7.10 (m, 2H), 6.95-6.85 (br s, NH, 1H), 5.00 (septet, J = 6.5 Hz, 1H), 4.90 (septet, J = 6.5 Hz, 1H), 1.30-1.22 (m, 6H), 1.20-1.05 (m, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 170.3 (C), 165.1 (d, J_{C-F} = 252 Hz, C), 155.4 (C), 153.0 (C), 131.3 (C), 131.0 (d, J_{C-F} = 8.0 Hz, CH), 115.5 (d, J_{C-F} = 21.0 Hz, CH), 72.8 (CH), 70.9 (CH), 22.0 (CH$_3$), 21.5 (CH$_3$); IR (thin film) 3313, 2984, 2938, 1734, 1705, 1603, 1507 cm^{-1}; LRMS (FAB) 349 (100, [M+Na]$^+$); HRMS (FAB) calcd for C$_{15}$H$_{19}$FN$_2$NaO$_5$ [M+Na]$^+$ 349.1176, observed 349.1171.

_N_,_N_'-Bis[(propan-2-yloxy)carbonyl]decanehydrazide (84o)
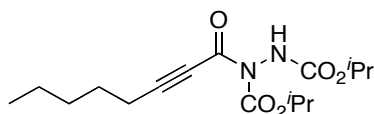

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave title compound **84o** as a colourless oil (304 mg, 0.85 mmol, 85%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.61-6.53 (br s, NH, 1H), 5.03 (septet, J = 6.5 Hz, 1H), 4.97 (septet, J = 6.5 Hz, 1H), 2.96-2.84 (m, 2H), 1.69-1.62 (m, 2H), 1.37-1.15 (m, 24H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 174.0 (C), 155.2 (C), 152.8 (C), 72.2 (CH), 70.5 (CH), 37.2 (CH$_2$), 32.0 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 24.7 (CH$_2$), 22.8 (CH$_2$), 22.0 (CH$_3$), 21.8 (CH$_3$), 14.2 (CH$_3$); IR (thin film) 3323, 2982, 2924, 2855, 1737, 1720 cm^{-1}; LRMS (FAB) 381 (100, [M+Na]$^+$); HRMS (FAB) calcd for C$_{18}$H$_{34}$N$_2$NaO$_5$ [M+Na]$^+$ 381.2365, observed 381.2365.

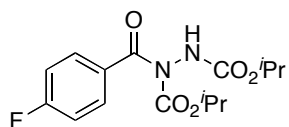### 3-Phenyl-*N,N'*-bis[(propan-2-yloxy)carbonyl]butanehydrazide (84p)

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **84p** as a colourless oil (280 mg, 0.80 mmol, 80%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.32-7.17 (m, 5H), 6.65-6.42 (br s, NH, 1H), 5.02 (septet, *J* = 6.0 Hz, 1H), 4.95 (app. quin, *J* = 6.0 Hz, 1H), 3.38 (app. sextet, *J* = 7.0 Hz, 1H), 3.32-3.14 (m, 2H), 1.33-1.24 (m, 15H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 172.5 (C), 155.1 (C), 152.7 (C), 146.2 (C), 128.6 (CH), 127.0 (CH), 126.4 (CH), 72.3 (CH), 70.6 (CH), 45.3 (CH$_2$), 36.0 (CH), 22.0 (CH$_3$), 21.8 (CH$_3$); IR (thin film) 3312, 2937, 1787, 1732, 1721, 1103 cm^{-1}; LRMS (CI) 351 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{18}$H$_{27}$N$_2$O$_5$ [M+H]$^+$ 351.1920, observed 351.1916.

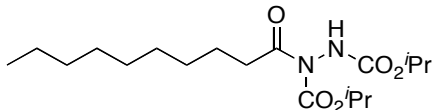### *N,N'*-Bis[(propan-2-yloxy)carbonyl]pent-4-enehydrazide (84q)

Using method E, the reaction was complete after 48 h. Purification by column chromatography (5-10% EtOAc/Petrol) gave title compound **84q** as a colourless oil (120 mg, 0.42 mmol, 42%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.60-6.53 (br s, NH, 1H), 5.85 (ddt, *J* = 17.0, 10.0 and 6.5 Hz, 1H), 5.09-4.94 (m, 4H), 3.02 (m, 2H), 2.42 (q, *J* = 7.0 Hz, 2H), 1.31 (d, *J* = 6.5 Hz, 6H), 1.30-1.25 (m, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 173.3 (C), 155.2 (C), 152.7 (C), 136.9 (CH), 115.6 (CH$_2$), 72.3 (CH), 70.6 (CH), 36.5 (CH$_2$), 28.6 (CH$_2$), 22.0 (CH$_3$), 21.8 (CH$_3$); IR (neat) 3308, 2982, 2941, 1787, 1734, 1718, 1103 cm^{-1}; LRMS (CI) 287 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{13}$H$_{23}$N$_2$O$_5$ [M+H]$^+$ 287.1607, observed 287.1612.

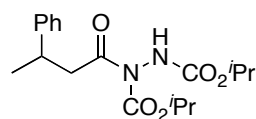## Ethyl-5-{*N,N'*-bis[(propan-2-yloxy)carbonyl]hydrazinecarbonyl}pentanoate (84r)
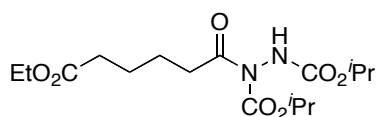
Using method E, the reaction was complete after 4 d. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **84r** as a colourless oil (288 mg, 0.80 mmol, 80%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.60-6.52 (br s, NH, 1H), 5.03 (septet, J = 6.0 Hz, 1H), 4.97 (septet, J = 6.0 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 2.97-2.82 (m, 2H), 2.32 (t, J = 7.0 Hz, 2H), 1.73-1.65 (m, 2H), 1.32-1.23 (m, 14H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 173.5 (C), 173.4 (C), 155.2 (C), 152.7 (C), 72.3 (CH), 70.6 (CH), 60.4 (CH$_2$), 36.8 (CH$_2$), 34.2 (CH$_2$), 24.4 (CH$_2$), 24.2 (CH$_2$), 22.0 (CH$_3$), 21.8 (CH$_3$), 14.4 (CH$_3$); IR (thin film) 3321, 2982, 1788, 1727, 1725 cm^{-1}; LRMS (ES) 359 (100, [M–H]$^-$); HRMS (ES) calcd for C$_{16}$H$_{27}$N$_2$O$_7$ [M–H]$^-$ 359.1818, observed 359.1826.

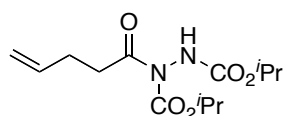## 2-Methyl-*N,N'*-bis[(propan-2-yloxy)carbonyl]butanehydrazide (84s)

Using method E, the reaction was complete after 24 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave title compound **84s** as a colourless oil (254 mg, 0.88 mmol, 88%).

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.70-6.45 (br s, NH, 1H), 5.05 (septet, J = 6.5 Hz, 1H), 4.97 (septet, J = 6.5 Hz, 1H), 3.55-3.47 (m, 1H), 1.80 (doublet of quintets, J = 14.5, 7.5 Hz, 1H), 1.46 (doublet of quintets, J = 14.5, 7.0 Hz, 1H), 1.34-1.17 (m, 15H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 178.0 (C), 155.3 (C), 152.7 (C), 72.2 (CH), 70.4 (CH), 41.0 (CH), 27.1 (CH$_2$), 22.0 (CH$_3$), 21.8 (CH$_3$), 16.9 (CH$_3$), 11.7 (CH$_3$); IR (thin film) 3313, 2981, 2938, 1736, 1718 cm^{-1}; LRMS (CI) 289 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{13}$H$_{25}$N$_2$O$_5$ [M+H]$^+$ 289.1764, observed 289.1757; HPLC conditions: CHIRALCEL-OD column, hexane:*i*-PrOH 99:1, 0.6 mL/min, retention times: 36.8 min and 43.1 min.

(2S)-2-Methyl-*N,N'*-bis[(propan-2-yloxy)carbonyl]butanehydrazide (84s′)

Using method E, the reaction was complete after 24 h. Purification by column chromatography (10%-40% EtOAc/Petrol) gave title compound **84s′** as a colourless oil (254 mg, 0.88 mmol, 88%).

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.70-6.45 (br s, NH, 1H), 5.05 (septet, *J* = 6.5 Hz, 1H), 4.97 (septet, *J* = 6.5 Hz, 1H), 3.55-3.47 (m, 1H), 1.80 (doublet of quintets, *J* = 14.5, 7.5 Hz, 1H), 1.46 (doublet of quintets, *J* = 14.5, 7.0 Hz, 1H), 1.34-1.17 (m, 15H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 178.0 (C), 155.3 (C), 152.7 (C), 72.2 (CH), 70.4 (CH), 41.0 (CH), 27.1 (CH$_2$), 22.0 (CH$_3$), 21.8 (CH$_3$), 16.9 (CH$_3$), 11.7 (CH$_3$); IR (thin film) 3313, 2981, 2938, 1736, 1718 cm^{-1}; LRMS (CI) 289 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{13}$H$_{25}$N$_2$O$_5$ [M+H]$^+$ 289.1764, observed 289.1757; $[\alpha]_D^{20}$ = +20.0 (*c* 0.48, CHCl$_3$); HPLC conditions: CHIRALCEL-OD column, hexane:*i*-PrOH 99:1, 0.6 mL/min, retention time: 36.8 min.

_N,N'_-bis[(propan-2-yloxy)carbonyl]undec-10-enehydrazide (84t)

Using method E, the reaction was complete after 72 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **84t** as a colourless oil (285 mg, 0.77 mmol, 77%).
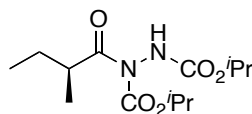
^{1}H NMR (600 MHz, CDCl$_3$) δ 6.61-6.53 (br s, NH, 1H), 5.80 (ddt, *J* = 17.0, 10.0 and 6.5 Hz 1H), 5.03 (septet, *J* = 6.0 Hz, 1H), 5.01-4.90 (m, 3H), 2.94-2.89 (m, 2H), 2.03 (app. q, *J* = 7.0 Hz, 2H), 1.65 (app. quin, *J* = 6.9 Hz, 2H), 1.38-1.22 (m, 21H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 174.0 (C), 155.2 (C), 152.8 (C), 139.4 (CH), 114.2 (CH$_2$), 72.2 (CH), 70.5 (CH), 37.2 (CH$_2$), 33.9 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 24.7 (CH$_2$), 22.0 (CH$_3$), 21.8 (CH$_3$); IR (thin film) 3313, 2981, 2855, 1788, 1736, 1722 cm^{-1}; LRMS (CI) 371 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{19}$H$_{35}$N$_2$O$_5$ [M+H]$^+$ 371.2546, observed 371.2548.

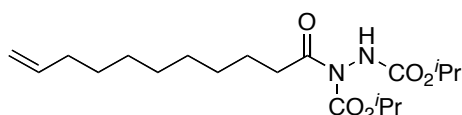## (4*Z*)-*N*,*N*'-Bis[(propan-2-yloxy)carbonyl]dec-4-enehydrazide (84u)

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave title compound **84u** as a colourless oil (167 mg, 0.47 mmol, 47%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.67-6.37 (br s, NH, 1H), 5.43-5.38 (m, 1H), 5.37-5.32 (m, 1H), 5.03 (septet, J = 6.5 Hz, 1H), 4.97 (septet, J = 6.5 Hz, 1H), 2.98-2.68 (m, 2H), 2.39 (q, J = 7.5 Hz, 1H), 2.03 (q, J = 7.5 Hz, 1H), 1.34-1.17 (m, 18H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 173.5 (C), 155.2 (C), 152.7 (C), 131.7 (CH), 127.5 (CH), 72.3 (CH), 70.6 (CH), 37.3 (CH$_2$), 31.6 (CH$_2$), 29.4 (CH$_2$), 27.3 (CH$_2$), 22.7 (CH$_2$), 22.6 (CH$_2$), 22.0 (CH$_3$), 21.8 (CH$_3$), 14.2 (CH$_3$); IR (thin film) 3317, 2983, 2930, 2858, 1736, 1721 cm^{-1}; LRMS (FAB) 379 (100, [M+Na]$^+$); HRMS (FAB) calcd for C$_{18}$H$_{32}$N$_2$NaO$_5$ [M+Na]$^+$ 379.2209, observed 379.2203.

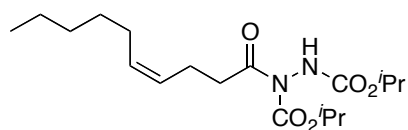## 2,2-Dimethyl-*N*,*N*'-bis[(propan-2-yloxy)carbonyl]pent-4-enehydrazide (84v)

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **84v** as a colourless oil (151 mg, 0.48 mmol, 48%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.56-6.51 (br s, NH, 1H), 5.80-5.71 (m, 1H), 5.08-4.97 (m, 4H), 2.44 (d, J = 7.5 Hz, 2H), 1.31 (d, J = 6.5 Hz, 6H), 1.30-1.25 (m, 12H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 178.6 (C), 155.6 (C), 153.2 (C), 134.3 (CH), 118.0 (CH$_2$), 72.3 (CH), 70.7 (CH), 45.5 (C), 44.7 (CH$_2$), 25.3 (CH$_3$), 21.9 (CH$_3$), 21.7 (CH$_3$); IR (thin film) 3296, 2982, 2938, 1778, 1771, 1734, 1641 cm^{-1}; LRMS (CI) 315 (85, [M+H]$^+$), 205 (100); HRMS (CI) calcd for C$_{15}$H$_{27}$N$_2$O$_5$ [M+H]$^+$ 315.1920, observed 315.1915.

4-(5,5-Dimethyl-1,3-dioxan-2-yl)-*N*,*N'*-bis[(propan-2-yloxy)carbonyl]butane-hydrazide (84w)
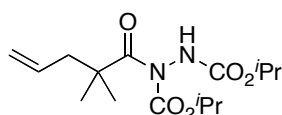

Using method E, the reaction was complete after 24 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **84w** as a colourless oil (288 mg, 0.80 mmol, 80%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.62-6.53 (br s, NH, 1H), 5.03 (septet, *J* = 6.0 Hz, 1H), 4.96 (septet, *J* = 6.0 Hz, 1H), 4.43 (t, *J* = 5.0 Hz, 1H), 3.57 (d, *J* = 10.5 Hz, 2H), 3.40 (d, *J* = 11.0 Hz, 2H), 2.97-2.87 (m, 2H), 1.82-1.77 (m 2H), 1.70-1.67 (m, 2H), 1.32-1.20 (m, 12H), 1.17 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 173.6 (C), 155.2 (C), 152.7 (C), 101.9 (CH), 77.5 (CH$_2$), 72.1 (CH), 70.2 (CH), 36.7 (CH$_2$), 33.9 (CH$_2$), 30.2 (C), 23.0 (CH$_3$), 21.9 (CH$_3$), 21.8 (CH$_3$), 21.7 (CH$_3$), 19.2 (CH$_2$); IR (thin film) 3299, 2955, 2848, 1780, 1738, 1734, 1105 cm^{-1}; LRMS (ES) 411 (100, [M+Na]$^+$);   HRMS (ES) calcd for C$_{18}$H$_{32}$N$_2$O$_7$Na [M+Na]$^+$ 411.2107, observed 411.2116.

5-(3,3-Dimethyloxiran-2-yl)-3-methyl-1-{[(propan-2-yloxy)carbonyl]({[(propan-2-yloxy)carbonyl]amino})amino}pentan-1-one (84x)
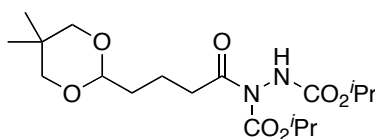

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **84x** as a colourless oil as a 1:1 mixture of diastereoisomers (249 mg, 0.67 mmol, 67%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.61-6.54 (br s, NH, 1H), 5.02 (septet, *J* = 6.0 Hz, 1H), 4.97 (septet, *J* = 6.5 Hz, 1H), 2.97-2.73 (m, 2H), 2.70 (q, *J* = 6.0 Hz, 1H), 2.11 (m, 1H), 1.62-1.35 (m, 4H), 1.33-1.23 (m, 18H), 0.96 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 173.2 (C), 155.2 (C), 152.7 (C), 72.3 (CH), 70.6 (CH), 64.6 (CH), 64.4 (CH), 58.5 (C), 58.4 (C), 44.2 (CH$_2$), 33.5 (CH$_2$), 33.4 (CH$_2$), 29.8 (CH), 29.8 (CH), 26.53 (CH$_2$), 26.51 (CH$_2$), 25.0, 22.0, 21.8, 19.8, 19.7, 18.8, 18.7; IR (thin

film) 3298, 2932, 1788, 1736, 1722, 1104 cm^{-1}; LRMS (ES) 395 (100, [M+Na]$^+$); HRMS (ES) calcd for $C_{18}H_{32}N_2O_6Na$ [M+Na]$^+$ 395.2158, observed 395.2150.

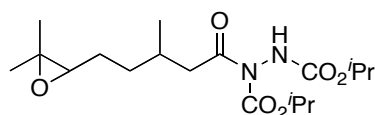## 4-Methoxy-*N,N'*-bis[(propan-2-yloxy)carbonyl]benzohydrazide (84y)
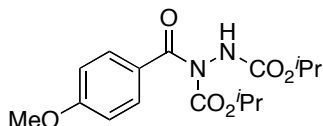
Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **84y** as a white solid (149 mg, 0.44 mmol, 44%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.73-7.60 (m, 2H), 7.15-7.09 (br s, NH, 1H) 6.87 (d, *J* = 8.5 Hz, 2H), 4.97 (septet, *J* = 6.5 Hz, 1H), 4.89 (septet, *J* = 6.5 Hz, 1H) 3.82 (s, 3H), 1.29-1.07 (m, 12H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 170.8 (C), 163.1 (C), 155.5 (C), 153.4 (C), 131.1 (CH), 127.0 (C), 113.5 (CH), 72.4 (CH), 70.6 (CH), 55.6 (CH$_3$), 22.0 (CH$_3$), 21.6 (CH$_3$); IR (thin film) 3309, 2982, 2938, 1733, 1701, 1604, 1579 cm^{-1}; LRMS (ES) 337 (100, [M−H]$^-$); HRMS (ES) calcd for $C_{16}H_{21}N_2O_6$ [M−H]$^-$ 337.1400, observed 337.1406.

4-Chloro-*N,N'*-bis[(propan-2-yloxy)carbonyl]benzohydrazide (84z)
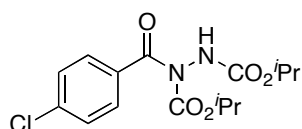
Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **84z** as a white solid (216 mg, 0.63 mmol, 63%).

m.p. 87-90 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.68-7.59 (m, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 6.85-6.80 (br s, NH, 1H), 5.00 (septet, *J* = 6.0 Hz, 1H), 4.91 (septet, *J* = 6.0 Hz, 1H), 1.32-1.25 (m, 6H), 1.15-1.11 (m, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 170.3 (C), 155.3 (C), 152.8 (C), 138.2 (C), 133.5 (C), 129.8 (CH), 128.6 (CH), 72.9 (CH), 71.0 (CH), 22.0 (CH$_3$), 21.5 (CH$_3$); IR (thin film) 3307, 2989, 2939, 1732, 1708, 1595 cm^{-1}; LRMS (ES) 343 (30%, [M(^{37}Cl)−H]$^-$), 341 (100, [M(^{35}Cl)−H]$^-$); HRMS (ES) calcd for $C_{15}H_{18}N_2O_5Cl$ [M−H]$^-$ 341.0904, observed 341.0909.

2-[(*tert*-Butyldimethylsilyl)oxy]propanal (253)[137]
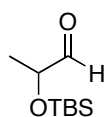
2-*tert*-Butylchlorodimethylsilane (5.70 g, 38.0 mmol) was added to a solution of DL-methyl lactate (3.0 mL, 31.0 mmol) and imidazole (3.88 g, 57.0 mmol) in DMF (100 mL) and the reaction mixture stirred at 21 °C for 30 min. The reaction mixture was diluted with H_2O (100 mL), extracted with Et_2O (×3), the combined organics washed with brine (×1), dried ($MgSO_4$) and the solvent removed *in vacuo* to give DL-2-(*tert*-butyldimethylsilanyloxy)-propionic acid ethyl ester (6.35 g, 29 mmol, 94%). Diisobutylaluminium hydride (1.0 M in heptane, 30.6 mL, 30.6 mmol) was added at 0.5 mL/min to a solution of DL-2-(*tert*-butyldimethylsilanyloxy)-propionic acid ethyl ester (4.45 g, 20.4 mmol) in Et_2O (150 mL) at −85 °C under argon. After addition was complete, the reaction was stirred for a further 10 min at −78 °C then quenched by the dropwise addition of MeOH (20 mL) and H_2O (20 mL). After warming to room temperature and stirring for 1 h and 30 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 residue purified by column chromatography to give title compound **253** as a colourless oil (1.99 g, 10.6 mmol, 52%).

^{1}H 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}.

(2S)-2-[(*tert*-Butyldimethylsilyl)oxy]propanal (253′)[137]
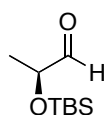
2-*tert*-Butylchlorodimethylsilane (5.70 g, 38.0 mmol) was added to a solution of L-methyl lactate (3.0 mL, 31 mmol) and imidazole (3.88 g, 57.0 mmol) in DMF (100 mL) and the reaction mixture stirred at 21 °C for 30 min. The reaction mixture was diluted with H_2O (100 mL), extracted with Et_2O (×3), the combined organics washed

with brine (×1), dried (MgSO$_4$) and the solvent removed *in vacuo* to give L-2-(*tert*-butyldimethylsilanyloxy)-propionic acid ethyl ester (6.22 g, 29 mmol, 92%). Diisobutylaluminium hydride (1.0 M in heptane, 30.6 mL, 30.6 mmol) was added at 0.5 mL/min to a solution of L-2-(*tert*-butyldimethylsilanyloxy)-propionic acid ethyl ester (4.45 g, 20.4 mmol) in Et$_2$O (150 mL) at –85 °C under argon. After addition was complete, the reaction was stirred for a further 10 min at –78 °C then quenched by the dropwise addition of MeOH (20.0 mL) and H$_2$O (20 mL). After warming to room temperature and stirring for 1 h and 30 min, finely ground Na$_2$SO$_4$ 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$_2$O. The solvents were removed *in vacuo* and the residue purified by column chromatography to give title compound **253′** as a colourless oil (2.10 g, 11.1 mmol, 61%).

$[\alpha]_D^{20}$ = +11.0 (*c* 2.51, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.62 (d, *J* = 1.5 Hz, 1H), 4.10 (qd, *J* = 7.0, 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}.

2-[(*tert*-Butyldimethylsilyl)oxy]-*N,N′*-bis[(propan-2-yloxy)carbonyl]propane hydrazide (256)


Using method E, the reaction was complete after 4 d. Purification by column chromatography (5-10% EtOAc/Petrol) gave title compound **256** as a colourless oil (238 mg, 0.61 mmol, 61%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.65-6.55 (br s, NH, 1H), 5.38 (q, *J* = 6.5 Hz, 1H), 5.04 (septet, *J* = 6.5 Hz, 1H), 4.98-4.92 (m, 1H), 1.47-1.40 (m, 3H), 1.34-1.17 (m, 12H), 0.91 (s, 9H), 0.09 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 175.7 (C), 155.1 (C), 152.6 (C), 72.5 (CH), 70.7 (CH), 69.5 (CH), 25.9 (CH$_3$), 22.0 (CH$_3$), 22.0 (CH$_3$), 21.8 (CH$_3$), 21.8 (CH$_3$), 21.6 (CH$_3$), 18.5 (C), –4.7 (CH$_3$), –5.1 (CH$_3$); IR (thin film) 3309, 2931, 2858, 1788, 1741, 1727, 1103 cm^{-1}; LRMS (ES) 413

(100%, [M+Na]$^+$); HRMS (ES) calcd for C$_{17}$H$_{34}$N$_2$O$_6$NaSi [M+Na]$^+$ 413.2084, observed 413.2069; HPLC conditions: CHIRALCEL-OD column, hexane:i-PrOH 99:1, 0.6 mL/min, retention times: 19.6 min and 30.3 min.

(2S)-2-[(tert-Butyldimethylsilyl)oxy]-N,N'-bis[(propan-2-yloxy)carbonyl] propane hydrazide (256′)

Using method E, the reaction was complete after 4 d. Purification by column chromatography (5-10% EtOAc/Petrol) gave title compound **256′** as a colourless oil (238 mg, 0.61 mmol, 61%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.65-6.55 (br s, NH, 1H), 5.38 (q, J = 6.5 Hz, 1H), 5.04 (septet, J = 6.5 Hz, 1H), 4.98-4.92 (m, 1H), 1.47-1.40 (m, 3H), 1.34-1.17 (m, 12H), 0.91 (s, 9H), 0.09 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 175.7 (C), 155.1 (C), 152.6 (C), 72.5 (CH), 70.7 (CH), 69.5 (CH), 25.9 (CH$_3$), 22.0 (CH$_3$), 22.0 (CH$_3$), 21.8 (CH$_3$), 21.8 (CH$_3$), 21.6 (CH$_3$), 18.5 (C), −4.7 (CH$_3$), −5.1 (CH$_3$); IR (thin film) 3309, 2931, 2858, 1788, 1741, 1727, 1103 cm^{-1}; LRMS (ES) 413 (100, [M+Na]$^+$); HRMS (ES) calcd for C$_{17}$H$_{34}$N$_2$O$_6$NaSi [M+Na]$^+$ 413.2084, observed 413.2069. $[\alpha]_D^{20}$ = +22.7 (c 0.55, CHCl$_3$); HPLC conditions: CHIRALCEL-OD column, hexane:i-PrOH 99:1, 0.6 mL/min, retention time: 19.6 min.

3,7-dimethyloctanal (257)[138]
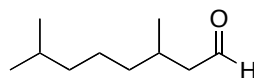
A stirring solution of (±)-citronellal (771 mg, 902 µL, 5.0 mmol) and Pd on activated C (1%, 250 mg) in MeOH (15 mL) was successively degassed and purged with H$_2$ (×3) and the solution stirred under a H$_2$ atmosphere for 20 h. The organic material was collected by filtering the mixture through a 50:50 mixture of silica and celite and the filter cake was washed with MeOH. The filtrate washings were concentrated *in vacuo* and purification of the residue by column chromatography (5-10%

EtOAc/Petrol) gave title compound **257** 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}.

3,7-Dimethyl-*N,N'*-bis[(propan-2-yloxy)carbonyl]octanehydrazide (259)
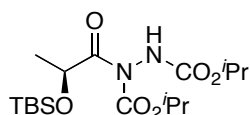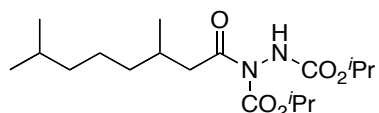

Using method E, the reaction was complete after 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **259** as a colourless oil (326 mg, 0.91 mmol, 91%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.62-6.52 (br s, NH, 1H), 5.03 (septet, J = 6.0 Hz, 1H), 4.97 (septet, J = 6.0 Hz, 1H), 2.95-2.65 (m, 2H), 2.13 (m, 1H), 1.51 (septet, J = 7.0 Hz, 1H), 1.35-1.11 (m, 16H), 0.94 (d, J = 7.0 Hz, 3H), 0.86-0.84 (m, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 173.5 (C), 155.2 (C), 152.8 (C), 72.2 (CH), 70.5 (CH), 44.3 (CH$_2$), 39.2 (CH$_2$), 37.2 (CH$_2$), 29.9 (CH), 28.0 (CH), 24.8 (CH$_2$), 22.8 (CH$_3$), 22.7 (CH$_3$), 22.0 (CH$_3$), 21.8 (CH$_3$), 19.8 (CH$_3$); IR (thin film) 3325, 2926, 2159, 1740 cm^{-1}; LRMS (CI) 359 (100, [M+H]$^+$); HRMS (CI) calcd for C$_{18}$H$_{35}$N$_2$O$_5$ [M+H]$^+$ 359.2546, observed 359.2550.

3,7-Dimethyloctan-1-ol (260)[139]
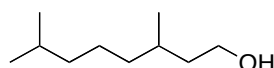
A stirring solution of (±)-citronellol (1.00 g, 6.4 mmol) and Pd on activated C (1%, 250 mg) in MeOH (15 mL) was successively degassed and purged with H$_2$ (×3) and the solution left to stir under a H$_2$ atmosphere for 20 h. To organic material was filtered through a 50:50 mixture of silica and celite and the filter cake was washed with MeOH. The filtrate washings were concentrated *in vacuo* and purification of

the residue by column chromatography (10-20% EtOAc/Petrol) gave title compound **260** as a colourless oil (887 mg, 5.6 mmol, 88%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 3.69 (ddd, J = 10.0, 7.0 and 6.0 Hz, 1H), 3.66 (dt, J = 10.0 and 7.0 Hz, 1H), 1.63-1.47 (m, 3H), 1.40-1.22 (m, 5H), 1.51 -1.09 (m, 3H), 0.88 (d, J = 6.5 Hz, 3H), 0.85, (d, J = 6.5 Hz, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 61.4 (CH$_2$), 40.1 (CH$_2$), 39.4 (CH$_2$), 37.5 (CH$_2$), 29.6 (CH), 28.1 (CH), 24.8 (CH$_3$), 22.8 (CH$_2$), 22.7 (CH$_3$), 19.8 (CH$_3$); IR (neat) 3600-3200, 2953, 2920, 2870, 1052 cm^{-1}; LRMS (CI) 159 (5%, [M+H]$^+$), 141 (35), 85 (100); HRMS (CI) calcd for C$_{10}$H$_{23}$O [M+H]$^+$ 159.1749, observed 159.1741.

3,7-Dimethyloctyl 4-methylbenzene-1-sulfonate (262)[140]
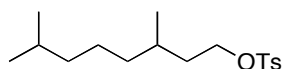
To a solution of *para*-toluenesulfonyl chloride (596 mg, 3.1 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C was added a solution of **260** (450 mg, 2.8 mmol) and NEt$_3$ (0.79 mL, 5.7 mmol) in CH$_2$Cl$_2$ (5 mL). The reaction mixture was stirred at 21 °C for 18 h, followed by dilution with CH$_2$Cl$_2$ (20 mL). The reaction mixture was then washed with 2M HCl (×3), 1M NaHCO$_3$ (×3), brine (×1), dried (MgSO$_4$) and the solvent removed *in vacuo*. Purification by column chromatography (10% EtOAc/Petrol) gave title compound **262** as a colourless oil (708 mg, 2.3 mmol, 81%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.80 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.09-4.01 (m, 2H), 2.45 (s, 3H), 1.69-1.62 (m, 1H), 1.52-1.38 (m, 3H), 1.24-1.01 (m, 6H), 0.85 (d, J = 6.5 Hz, 6H), 0.79 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 144.7 (C), 133.3 (C), 130.0 (CH), 128.0 (CH), 69.2 (CH$_2$), 39.2 (CH$_2$), 36.9 (CH$_2$), 35.8 (CH$_2$), 29.2 (CH), 28.0 (CH), 24.6 (CH$_2$), 22.8 (CH$_3$), 22.7 (CH$_3$), 21.8 (CH$_3$), 19.3 (CH$_3$); IR (neat) 2954, 2927, 2869, 1359, 1188 cm^{-1}; LRMS (CI) 313 (10%, [M+H]$^+$), 141 (100); HRMS (CI) calcd for C$_{17}$H$_{29}$O$_3$S [M+H]$^+$ 313.1837, observed 313.1842.

3,7-Dimethyloctyl acetate (263)[141]
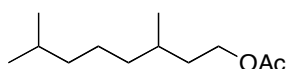
To a solution of **260** (150 mg, 0.95 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added DMAP (23 mg, 0.02 mmol) and acetic anhydride (178 µL, 1.89 mmol) and the reaction was stirred at 21 °C for 1 h. Then the solvent was removed *in vacuo* and purification by column chromatography (10% EtOAc/Petrol) gave title compound **263** as a colourless oil (159 mg, 0.79 mmol, 84%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.11-4.02 (m, 2H), 2.04 (s, 3H), 1.68-1.62 (m, 1H), 1.55-1.48 (m, 2H), 1.45-1.38 (m, 1H), 1.33-1.09 (m, 6H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4 (C), 63.2 (CH_2), 39.3 (CH_2), 37.2 (CH_2), 35.6 (CH_2), 29.9 (CH), 28.1 (CH), 24.7 (CH_2), 22.8 (CH_3), 22.7 (CH_3), 21.2 (CH_3), 19.6 (CH_3); IR (neat) 2955, 2927, 2870, 1741 cm^{-1}; LRMS (CI) 201 (100%, [M+H]$^+$); HRMS (CI) calcd for $C_{12}H_{25}O_2$ [M+H]$^+$ 201.1855, observed 201.1850.

3-Methyl-*N,N'*-bis[(propan-2-yloxy)carbonyl]pentanehydrazide (268)
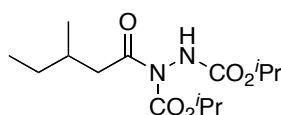
Using method E, the reaction was complete after 48 h. Purification by column chromatography (5-10% EtOAc/Petrol) gave title compound **268** as a colourless oil (251 mg, 0.83 mmol, 83%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.60-6.52 (br s, NH, 1H), 5.02 (septet, *J* = 6.5 Hz, 1H), 4.97 (septet, *J* = 6.5 Hz, 1H), 2.98-2.67 (m, 2H), 1.98 (app. octet, *J* = 7.0 Hz, 1H), 1.44-1.37 (m, 1H), 1.31 (d, *J* = 6.5 Hz, 6H), 1.30-1.20 (m, 6H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.5 (C), 155.2 (C), 152.8 (C), 72.2 (CH), 70.5 (CH), 43.9 (CH_2), 31.5 (CH), 29.5 (CH_2), 22.0 (CH_3), 21.8 (CH_3), 19.3 (CH_3), 11.4 (CH_3); IR (neat) 3333, 2982, 2936, 1787, 1739, 1722, 1106 cm^{-1}; LRMS (CI) 303 (100, [M+H]$^+$); HRMS (CI) calcd for $C_{14}H_{27}N_2O_5$ [M+H]$^+$ 303.1920, observed 303.1924.

6-(*tert*-Butyldimethylsilyloxy)-4-methylhexanal (269)
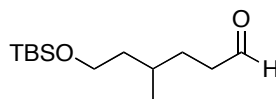
Alkene **273** (1.00 g, 3.7 mmol) was dissolved in CH_2Cl_2 (80 mL) and cooled to −78 °C. A stream of ozone-enriched oxygen was bubbled through the solution until a blue colour persisted. After which, stirring was continued for 5 min, then argon was bubbled through the solution until the blue colour disappeared. Dimethyl sulfide (816 μL, 11 mmol) was added and the reaction mixture allowed to warm to 21 °C. Stirring was continued for 18 h and the solvent was removed *in vacuo* to give the crude residue. Purification by column chromatography (5% Et_2O/Petrol) gave title compound **269** as a colourless oil (735 mg, 3.0 mmol, 81%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.66 (ddd, J = 10.0, 7.0 and 6.0 Hz, 1H), 3.61 (dt, J = 10.0 and 7.0 Hz, 1H), 2.47 (dddd, J = 17.0, 9.0, 6.0 and 2.0 Hz, 1H), 2.41 (dddd, J = 17.0, 9.0, 6.0 and 2.0 Hz, 1H), 1.69-1.52 (m, 2H), 1.51-1.44 (m, 1H), 1.41-1.33 (m, 1H), 0.89 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.1 (C), 61.2 (CH_2), 41.8 (CH_2), 39.6 (CH_2), 29.3 (CH), 29.0 (CH_2), 26.1 (CH_3), 19.5 (CH_3), 18.4 (C), −5.2 (CH_3); IR (neat) 2955, 2857, 1727, 1472, 1092 cm^{-1}; LRMS (CI) 245 (53%, [M+H]$^+$), 243 (40), 129 (36), 113 (100); HRMS (CI) calcd for $C_{13}H_{29}O_2Si$ [M+H]$^+$ 245.1937, observed 245.1947.

tert-Butyl[(3,7-dimethyloct-6-en-1-yl)oxy]dimethylsilane (273)[142]
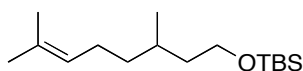
To a solution of (±)-β-citronellol (5.00 g, 32 mmol) in DMF (200 mL) was added imidazole (3.26 g, 48 mmol), followed by *tert*-butyl(chloro)dimethylsilane (7.25 g, 48 mmol) and the solution stirred for 24 h at 21 °C. The reaction mixture was diluted with H_2O (200 mL) and the organic material extracted Et_2O (×3). The extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (5% Et_2O/Petrol) gave title compound **273** as a colourless oil (7.40 g, 27.4 mmol, 86%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.09 (t, J = 7.0 Hz, 1H), 3.68-3.59 (m, 2H), 2.20-1.90 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.59-1.51 (m, 2H), 1.36-1.28 (m, 2H), 1.18-1.11

(m, 1H), 0.89 (s, 9H), 0.87 (d, J = 6.5 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 131.2 (C), 125.0 (CH), 61.6 (CH$_2$), 40.0 (CH$_2$), 37.3 (CH$_2$), 29.2 (CH), 26.1 (CH$_3$), 25.9 (CH$_3$), 25.6 (CH$_2$), 19.7 (CH$_3$), 18.5 (C), 17.8 (CH$_3$), −5.2 (CH$_3$); IR (neat) 2955, 2857, 1471, 1094 cm^{-1}; LRMS (CI) 271 (25%, [M+H]$^+$), 213 (80), 139 (80), 137 (100); HRMS (CI) calcd for C$_{16}$H$_{25}$OSi [M+H]$^+$ 271.2457, observed 271.2446.

8-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxy-2,6-dimethyloctan-3-one (274)
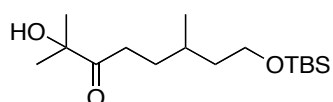
To a solution of alkene **273** (1.00 g, 3.7 mmol) in THF (40 mL) at 0 °C was added NaOH (72 mg, 1.85 mmol), followed by dropwise addition of a solution of KMnO$_4$ (880 mg, 5.6 mmol) in H$_2$O (25 mL). The reaction mixture was stirred for 18 h at 21 °C, filtered through celite and the solvent removed *in vacuo*. The organic material was extracted with EtOAc (×3), dried (MgSO$_4$) and the solvent removed *in vacuo*. Purification by column chromatography (0-50% EtOAc/Petrol) gave title compound **274** as a colourless oil (782 mg, 2.6 mmol, 70%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 3.66 (ddd, J = 10.0, 7.0 and 6.0 Hz, 1H), 3.62 (dt, J = 10.0 and 7.0 Hz, 1H), 2.57 (ddd, J = 17.5, 9.0 and 6.0 Hz, 1H), 2.52 (ddd, J = 17.5, 9.0 and 6.0 Hz, 1H), 1.68-1.62 (m, 1H), 1.60-1.53 (m, 2H), 1.49-1.43 (m, 1H), 1.38 (s, 3H), 1.37 (s, 3H), 1.36-1.31 (m, 1H), 0.89 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 214.9 (C), 76.3 (C), 61.2 (CH$_2$), 39.6 (CH$_2$), 33.3 (CH$_2$), 30.9 (CH$_2$), 29.3 (CH), 26.7 (CH$_3$), 26.1 (CH$_3$), 19.6 (CH$_3$), 18.4 (C), −5.2 (CH$_3$); IR (neat) 3475, 2955, 2858, 1708, 1463, 1092 cm^{-1}; LRMS (CI) 303 (100%, [M+H]$^+$), 171 (27), 153 (30); HRMS (CI) calcd for C$_{16}$H$_{35}$O$_3$Si [M+H]$^+$ 303.2356, observed 303.2355.

6-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-*N*,*N*'-bis[(propan-2-yloxy)carbonyl] hexanehydrazide (275)
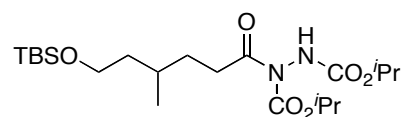
Using method E, the reaction was complete after 72 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave title compound **275** as a colourless oil (330 mg, 0.74 mmol, 74%).

^{1}H NMR (600 MHz, CDCl$_3$) δ 6.65-6.57 (br s, NH, 1H), 5.04 (septet, J = 6.5 Hz, 1H), 4.97 (septet, J = 6.5 Hz, 1H), 3.69-3.60 (m, 2H), 3.01-2.81 (m, 2H), 1.75-1.51 (m, 4H), 1.38-1.20 (m, 13H), 0.91 (d, J = 6.5 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 174.2(C), 155.2 (C), 152.7 (C), 72.2 (CH), 70.5 (CH), 61.3 (CH$_2$), 39.7 (CH$_2$), 34.9 (CH$_2$), 31.7(CH$_2$), 29.8 (CH$_3$), 29.2 (CH), 26.1 (CH$_3$), 22.0 (CH$_3$), 21.8 (CH$_3$), 19.5 (CH$_3$), 18.4 (C), −5.2 (CH$_3$); IR (thin film) 3318, 2955, 2858, 1790, 1738, 1726, 1103 cm^{-1}; LRMS (ES) 469 (100%, [M+Na]$^+$); HRMS (ES) calcd for C$_{21}$H$_{42}$N$_2$O$_6$NaSi [M+Na]$^+$ 469.2710, observed 469.2699.

References

1. Zard, S. Z. *Radical Reactions in Organic Synthesis*. Oxford University Press: **2003**.

2. Gomberg, M. *J. Am. Chem. Soc.* **1900**, 757.

3. McBride, J. M. *Tetrahedron*. **1974**, 2009.

4. Kharasch, M. S.; Mayo. *J. Am. Chem. Soc.* **1933**, 2468.

5. Hart, D. J. *Science*. **1984**, 883.

6. Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*. John Wiley & Sons: **1995**.

7. van der Kerk, G. J. M.; Noltes, J. G.; Luijten, J. G. S. *J. App. Chem.* **1957**, 356.

8. Curran, D. P. *Synthesis*. **1988**, 417.

9. Beckwith, A. L. J.; Pigou, P. E. *Aust. J. Chem.* **1986**, 1151.

10. Studer, A.; Amrein, S. *Synthesis*. **2002**, 835.

11. Hays, D. S.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, 6751.

12. Kharasch, M. S.; Urry, W. H.; Kuderna, B. M. *J. Org. Chem.* **1949**, 248.

13. Hinz, J.; Oberliner, A.; Ruchardt, C. *Tetrahedron Lett.* **1973**, 1975.

14. Guillet, J. E.; Gilmer, J. C. *Can. J. Chem.* **1969**, 4405.

15. Gagosz, F.; Moutrille, C.; Zard, S. Z. *Org. Lett.* **2002**, 2707.

16. Darmency, V.; Renaud, P. *Radicals in Synthesis I: Methods and Mechanisms*, **2006**, 71.

17. Montgomery, I.; Parsons, A. F.; Ghelfi, F.; Roncaglia, F. *Tetrahedron Lett.* **2008**,628.

18. Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, 519.

19. Heiba, E. I.; Dessau, R. M.; Koehl, W. J. *J. Am. Chem. Soc.* **1968**, 2706.

20. Heiba, E. I.; Dessau, R. M, *J. Am. Chem. Soc.* **1971**, 524.

21. McQuillin, F. J.; Wood, M. *J. Chem. Soc., Perkin Trans. 1*. **1976**, 1762.

22. Blakskjaer, P.; Hoj, B.; Riber, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2003**, 4030.

23. Hansen, A. M.; Lindsay, K. B.; Sudhadevi Antharjanam, P.K.; Karaffa, J.; Dassbjerg, K.; Flowers, R. A.; Skrydstrup, T. *J. Am. Chem. Soc.* **2006**, 9616.

24. Jensen, C. M.; Lindsay, K. B.; Taaning, R. H.; Karaffa, J.; Hansen, A. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2005**, 6544.

25. Rowlands, G. J. *Tetrahedron.* **2009**, 8603.

26. Francisco, C. G.; Gonzalez, C. C.; Herrera, A. J.; Paz, N. R.; Suarez, E. *Tetrahedron Lett.* **2006**, 9057.

27. Caddick, S.; Hamza, D.; Judd, D. B.; Reich, M. T.; Wadman, S. N.; Wilden, J. D. *Tetrahedron Lett.* **2004**, 2363.

28. Chatgilialoglu, C. *Chem. Rev.* **1995**, 1229.

29. Almirante, N.; Cerri, A. *J. Org. Chem.* **1997**, 3402.

30. Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, 681.

31. Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, 9688.

32. Cassayre, J.; Gagosz, F.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2002**, 1783.

33. Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem. Int. Ed.* **2007**, 7629.

34. Crimmins, M. T.; Wang, Z.; McKerlie, L. A. *J. Am. Chem. Soc.* **1998**, 1747.

35. Pattenden, G.; Reddy, L. K.; Walter, A. *Tetrahedron Lett.* **2004**, 4027.

36. Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett.* **1999**, 4443.

37. Nicolaou, K. C.; Follmann, M.; Roecker, A. J.; Hunt, K. W. *Angew. Chem. Int. Ed.* **2002**, 2103.

38. Schwartz, J.; Cannon, J. B. *J. Am. Chem. Soc.* **1974**, 4721.

39. Jun, C. H.; Jo, E. A.; Park, J. W. *Eur. J. Org. Chem.* **2007**, 1869.

40. Willis, M. C.; Sapmaz, S. *Chem. Commun.* **2001**, 2558.

41. Willis, M. C.; McNally, S. J.; Beswick, P. J. *Angew. Chem. Int. Ed.* **2004**, 340.

42. Moxham, G. L.; Randell-Sly, H. E.; Brayshaw, S. K.; Woodward, R. L.; Weller, A. S.; Willis, M. C. *Angew. Chem. Int. Ed.* **2006**, 7618.

43. Willis, M. C.; Randell-Sly, H. E.; Woodward, R. L.; Currie, G. S. *Org. Lett.* **2005**, 2249.

44. Willis, M. C.; Randell-Sly, H. E.; Woodward, R. L.; McNally, S. J.; Currie, G. S. *J. Org. Chem.* **2006**, 5291.

45. Lee, D.; Otte, R. D. *J. Org. Chem.* **2004**, 3569.

46. Sakai, K.; Ide, J.; Oda, O.; Nakamura, N. *Tetrahedron Lett.* **1972**, 1287.

47. Fairlie, D. P.; Bosnich, B. *Organometallics.* **1988**, 936.

48. Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chemistry A European Journal.* **2004**, 5681.

49. Ni, B.; Zhang, Q.; Garre, S.; Headley, A. D. *Adv. Synth. Catal.* **2009**, 875.

50. Stetter, H. *Angew. Chem. Int. Ed.* **1976**, 639.

51. Stetter, H.; Schrecke, M. *Angew. Chem. Int. Ed.* **1973**, 81.

52. Matsumoto, Y.; Tomioka, K. *Tetrahedron Lett.* **2006**, 5843.

53. Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, 1991.

54. Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, 1295.

55. Ryu, I.; Hasegawa, M.; Kurihara, A.; Ogawa, A.; Tsunoi, S.; Sonoda, N. *Synlett* **1993**, 143.

56. Gupta, V.; Kahne, D. *Tetrahedron Lett.* **1993**, 591.

57. Petragnani, N.; Stefani, H. A. *Tetrahedron.* **2005**, 1613.

58. Penn, J. H.; Liu, F. *J. Org. Chem.* **1994**, 2608.

59. Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, 3377.

60. Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, 1429.

61. Ballestri, M.; Chatgilialoglu, C.; Cardi, N.; Sommazzi, A. *Tetrahedron Lett.* **1992**, 1787.

62. Patrick, T. M. *J. Org. Chem.* **1952**, 1009.

63. Patrick,T. M. *J. Org. Chem.* **1952**, 1269.

64. Nikishin, G. I.; Vinogradov, M. G.; Kereseelidze, R. V. *Bul. Acad. Sci. USSR, Div. Chem. Sci.* **1967**, 1570.

65. Nikishin, G. I.; Vinogradov, M. G.; Verenchikov, S. P. *Bul. Acad. Sci. USSR, Div. Chem. Sci.* **1969**, 1698.

66. Nikishin, G. I.; Vinogradov, M. G.; Kereseelidze, R. V. *Russ. Chem. Bull.* **1966**, 1973.

67. McNesby, J. R.; Heller, C. A. *Chem. Rev.* **1954**, 325.

68. Macias, F. D.; Molinillo, J. M. G.; Massenet, G. M.; Rodriguez-Luis, F. *Tetrahedron.* **1992**, 3345.

69. Macias, F. D.; Molinillo, J. M. G.; Collado, I. G.; Massenet, G. M.; Rodriguez-Luis, F. *Tetrahedron Lett.* **1990**, 3063.

70. Stringat, R.; Fabre, G.; Alessandri, M. *Laser Chem.* **1994**, 55.

71. Esposti, S.; Dondi, D.; Fagnoni, M.; Albini, A. *Angew. Chem. Int. Ed.* **2007**, 2531.

72. Roberts, B. P. *Chem. Soc. Rev.* **1999**, 25.

73. Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2.* **1996**, 2719.

74. Dang, H. S.; Roberts, B. P. *Chem. Commun.* **1996**, 2201.

75. Dang, H. S.; Roberts, B. P. *J. Chem. Soc. Perkin Trans. 1.* **1998**, 67.

76. Dang, H. S.; Kim, K. M.; Roberts, B. P. *Chem. Commun.* **1998**, 1413.

77. Tsujimoto, S.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, 5601.

78. Yoshikai, K.; Hayama, T.; Nishimura, K.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2005**, 681.

79. Bath, S.; Laso, N. M.; Lopez-Ruiz, H.; Quiclet-Sire, B.; Zard, S. Z. *Chem. Commun.* **2003**, 204.

80. Crich, D.; Hao, X. *J. Org. Chem.* **1997**, 5982.

81. Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S.; Zanardi, G. *Org. Lett.* **2002**, 3079.

82. Evans, P. A.; Roseman, J. D. *J. Org. Chem.* **1996**, 2252.

83. Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, 5838.

84. Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, 725.

85. Klijn, J. E.; Engberts, J. B. F. N. *Nature.* **2005**, 746.

86. Hailes, H. C. *Org. Process Res. Dev.* **2007**, 114.

87. Breslow, R.; Rideout, D. C. *J. Am. Chem. Soc.* **1980**, 7816.

88. Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, 3275.

89. Herrerias, C. I.; Yao, X.; Li, Z.; Li, C. J. *Chem. Rev.* **2007**, 2546.

90. Wright, S. W.; Hallstrom, K. N. *J. Org. Chem.* **2006**, 1080.

91. Deng, X. H.; Mani, N. S. *Green Chem.* **2006,** 835.

92. Zhou, G.; Ting, P.; Aslanian, R.; Piwinski, J. J. *Org. Lett.* **2008**, 2517.

93. Zanon, J.; Klapers, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, 2890.

94. Caddick, S.; Wilden, J. D.; Judd, D. B. *Chem. Commun.* **2005**, 2727.

95. Wilden, J. D.; Geldeard, L.; Lee, C. C.; Judd, D. B.; Caddick, S. *Chem. Commun.* **2007**, 1074.

96. Caddick, S.; Wilden, J. D.; Judd, D. B. *J. Am. Chem. Soc.* **2004**, 1024.

97. Caddick, S.; Wilden, J. D.; Bush, H. D.; Wadman, S. N.; Judd, D. B. *Org. Lett.* **2002**, 2549.

98. Fitzmaurice, R. J. *Unpublished results.*

99. C. S. Foote, J. S. V.; A. Greenberg, J. F. *Active Oxygen in Chemistry*, Liebman, Ed. Blackie Academic and Professional. **1995**, Vol. 2.

100. Milas, N. A. *Chem. Rev.* **1932**, 295.

101. Schuh, H.; Edwin, J. H.; Henning, P.; Fischer, H. *Helv. Chim. Acta.* **1974**, 2011.

102. Vollenweider, J. K.; Paul, H. *Int. J. Chem. Kinet.* **2004**, 791.

103. Fujisawa, S.; Kadoma, Y.; Yokoe, I. *Chem. Phys. Lipids.* **2004**, 189.

104. Chudasama, V.; Fitzmaurice, R. J.; Ahern, J. M.; Caddick, S. *Chem. Commun.* **2010**, 133.

105. Sueda, T.; Takeuchi, Y.; Suefuji, T.; Ochiai, M. *Molecules.* **2005**, 195.

106. Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nature Chem.* **2010**, 592.

107. Fitzmarice, R. J.; Ahern, J. M.; Caddick, S. *Org. Biomol. Chem.* **2009**, 235.

108. Baldwin, J. E. *Chem. Commun.* **1976**, 734.

109. Carretero, J. C.; Demillequand, M.; Ghosez, L. *Tetrahedron*. **1987**, 5125.

110. Wilden, J. D. *Unpublished results.*

111. Nicolaou, K. C.; Hwang, C. K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, 3040.

112. Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aube, J. *J. Am. Chem. Soc.* **2008**, 6018.

113. Roush, W. R.; Gwaltney, J. C.; Schneidt, K. A.; McKerrow, J. H.; Hansell, E. *J. Am. Chem. Soc.* **1998**, 10994.

114. Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, 2549.

115. Xu, Y.; Qian, L.; Prestwich, G. D. *Org. Lett.* **2003**, 2267.

116. Gaul, C.; Njardarson, J. T.; Shan, D.; Dorn, D. C.; Wu, K. D.; Tong, W. P.; Huang, X. Y.; Moore, M. A. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, 11326.

117. Takebayashi, M.; Hiranama, S.; Kanie, Y.; Kajimoto, T.; Kanie, O.; Wong, C. H. *J. Org. Chem.* **1999**, 5280.

118. Fuerstner, A.; Larionov, O.; Fluegge, S. *Angew. Chem. Int. Ed.* **2007**, 5641.

119. Bousquie, I.; Madiot, V.; Florent, J. C.; Monneret, C. *Bioorg. Med. Chem. Lett.* **1996**, 1815.

120. Lipshutz, B. H.; Keith, J. *Tetrahedron Lett.* **1998**, 4407.

121. Sieber, F.; Wentworth, P.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. *J. Org. Chem.* **1999**, 5188.

122. Michrowska, A.; Bieniek, M.; Kim, M.; Klajn, R.; Grela, K. *Tetrahedron.* **2003**, 4525.

123. Chudasama, V.; Ahern, J. M.; Fitzmaurice, R. J.; Caddick, S. *Tetrahedron Lett.* **2010**, submitted for publication.

124. Amri, H.; El Gaied, M. M.; Villeras, J. *Synth. Commun.* **1990**, 659.

125. Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, 1581.

126. Kreuger, W. E.; McLean, M. B.; Rizwaniuk, A.; Maloney, J. R.; Behalfer, G. L.; Boland, B. E. *J. Org. Chem.* **1978**, 2877.

127. Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1986**, 1537.

128. Kim, Y. J.; Lee, D. *Org. Lett.* **2004**, 4351.

129. Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1993**, 4452.

130. Kumaraswamy, G.; Markondaiah, B. *Tetrahedron Lett.* **2007**, 1707.

131. Chudasama, V.; Ahern, J. M.; Dhokia, D. V.; Fitzmaurice, R. J.; Caddick, S. *Chem. Commun.* **2010**, submitted for publication.

132. Zhang, Q.; Parker, E.; Headley, A. D.; Ni, B. *Synlett.* **2010**, 2453.

133. Brunel, Y.; Rousseau, G. *J. Org. Chem.* **1996**, 5793.

134. Trost, B. M.; Grese, T. A.; Chan, D. M. T. *J. Am. Chem. Soc.* **1991**, 7350.

135. Hale, K. J.; Manaviazar, S.; George, J. H.; Walters, M. A.; Dalby, S. M. *Org. Lett.* **2009**, 733.

136. Banerji, A.; Bandyopadhyay, D.; Sarkar, M.; Siddhanta, A. K.; Pal, S. C.; Ghosh, S.; Abraham, K.; Shoolery, J. N. *Phytochemistry*. **1985**, 279.

137. Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, 7652.

138. Yasumoto, K.; Nishigami, A.; Aoi, H.; Tsuchihashi, C.; Kasai, F.; Kusumi, T.; Ooi, T. *Chem. Pharm. Bull.* **2008**, 129.

139. Tietze, L. F.; Schiemann, K.; Wegner, C.; Wulff, C. *Chem. Eur. J.* **1996**, 1164.

140. Wong, M. K.; Chung, N. W.; He, L.; Yang, D. *J. Am. Chem. Soc.* **2003**, 158.

141. Gomez, L.; Garcia-Bosch, I.; Company, A.; Polo, A.; Ribas, X.; Costas, M.; Benet-Buchholz, J.; Sala, X. *Angew. Chem. Int. Ed.* **2009**, 5830.

142. Queron, E.; Lett, R. *Tetrahedron Lett.* **2004**, 4527.