Novel catalysts and mechanistic investigation in dioxirane-mediated oxidations

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For

Dr Boobyer

JK ‘the master’

and

Bryan Davies.
Novel Catalysts and Mechanistic Investigation in Dioxirane Mediated Oxidations.

By

Estella Louise Grocock

A Doctoral Thesis
Submitted in partial fulfilment of the requirements for the award of
Doctor of Philosophy
of
Loughborough University

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I would like to thank the following people for their help during my research

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Todd Boehlow, Richard Toon and Victoria Waddington who were also part of the BAM group and the members of lab F001 and F002

And to my family- Thankyou
Abstract

The work described in this thesis follows the development of a family of achiral trifluoroketones, which were studied for use as ketone catalysts for the *in situ* generation of dioxiranes. One of the ketones investigated was a novel solid phase polymer-bound ketone, which led to a new area for dioxirane generation that could be of particular use in industry.

Oxidations were run under monophasic and biphasic solvent reaction systems, with emphasis on the former. Ranges of reactions, including epoxidation and alcohol oxidations were examined to test the efficiency of each ketone. It was found that epoxidation reactions gave the most efficient oxidations, although secondary benzylic alcohols also gave evidence of oxidation. Epoxidation of some allylic alcohols including geraniol was studied in detail using α,α,α-trifluoroacetophenone as ketone catalyst for *in situ* dioxirane generation and compared with direct reaction with Oxone®. The influence on the epoxidations by protection of the alcohol function was also investigated.

Dioxirane and Oxone® mediated oxidations of the drug Carvedilol were compared *in situ* to examine its oxidative stability.

The preparation and investigation of a group of novel chiral ketone catalysts based on 1-tetralone, 1-indanone, 4-chromanone and 4-*iso*-chromanone was undertaken. One catalyst was successfully synthesised and progress was made towards the synthesis of the 4-*iso*-chromanone. Some evaluation of the catalytic activity of synthetic intermediates and the successfully synthesised catalyst was achieved in epoxidation of *trans*-stilbene.
A mechanistic study of the dimethylidioxirane oxidation of 2,6-dimethyl and 2,2,6-trimethylcyclohexanol in varying solvents lent further support to the proposal that intramolecular hydrogen bonding is involved in a planar transition state for alcohol oxidations, in which the plane contains the CHOH bonds and the dimethylidioxirane oxygens.
Abbreviations

DMD  Dimethyldioxirane
Oxone  Potassium monoperoxy sulphate, Aldrich Chemical Company,
       Triple salt 2KHSO₃ KHSO₄ K₂SO₄
Caroate  Monoperoxy sulphate species (HSO₅⁻)
NMR  Nuclear Magnetic resonance
nm  Nanometers
UV  Ultra Violet
Ref  Reference
Tf  Triflate
rt  Room temperature
h  Hour(s)
ee  Enantiomeric excess
Ac  Acetyl
Bz  Benzoyl
Ts  Tosyl
TBS  tert-Butyldimethylsilyl
SSO  Thianthrene-5-Oxide
SET  Single Electron Transfer
DCM  Dichloromethane
PTC  Phase transfer catalyst
p-TSA  Toluene-4-sulfonic acid
DEAD  Diethylazodicarboxylate
IR  Infrared
DMF  N,N-Dimethylformamide
GC-MS  Gas-Chromatography, Mass spectrometer
Temp  Temperature
Methyl ester  Methyl 4-(Trifluoroacety) benzoate
TFAP  α,α,α-Trifluoroacetophenone also written as
       Trifluoroacetophenone
(EDTA)Na2  Ethylenediaminetetraacetic disodium salt also written as
           EDTA
GLC  Gas Liquid Chromatography
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>Not available</td>
</tr>
<tr>
<td>M</td>
<td>Molarity</td>
</tr>
<tr>
<td>Acid</td>
<td>4-(Trifluoroacetyl) benzoic acid</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulphoxide</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer chromatography</td>
</tr>
<tr>
<td>PPA</td>
<td>Polyphosphoric acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>E I</td>
<td>Electron Impact</td>
</tr>
<tr>
<td>C I</td>
<td>Chemical Ionisation</td>
</tr>
<tr>
<td>Min</td>
<td>Minute(s)</td>
</tr>
<tr>
<td>O/N</td>
<td>Over night</td>
</tr>
<tr>
<td>d r</td>
<td>Diastereomeric ratio</td>
</tr>
</tbody>
</table>
## Contents

Thesis Access Form  
Title Page  
Certificate of Originality  
Acknowledgements  
Abstract  
Abbreviations

### Chapter 1- Review of Dioxirane Chemistry  
1.0  
Dioxirane Discovery  
1.1  
Preparation of Dioxiranes  
1.2  
fluorinated Dioxiranes  
1.3  
Chemical Reactivity  
1.4  
Are Dioxiranes the Active Intermediate  
1.5  
General Dioxirane Oxidation Reactions  
1.5.1  
Epoxidations using Dioxiranes  
1.5.2  
C-H bond insertions using Dioxiranes  
1.5.3  
Alcohol Oxidations using Dioxiranes  
1.6  
Chiral Ketones for asymmetric Oxidations  
1.7  
Mechanism of Dioxiranes  
1.7.1  
Dioxiranes- Nucleophilic or Electrophilic?  
1.7.2  
Heteroatom Oxidation  
1.7.3  
Alkene Oxidation  
1.7.4  
C-H Bond Insertion

### Chapter 2- Project Introduction  
2.1  
New Achiral Catalysts and Applications  
2.2  
New Chiral Catalysts  
2.3  
Mechanistic Investigation of Alcohol Oxidation

### Chapter 3-Synthesis and Evaluation of Novel Achiral Ketones  
3.1  
Synthesis of Derivatives of 4-(Trifluoroacetyl) benzoic Acid
3 11  Synthesis of Methyl 4-(Trifluoroacetyl) benzoate  59
3 12  Synthesis of Dihydrocholesterol 4-(Trifluoroacetyl) benzoate  60
3 13  Synthesis of Benzyl 4-(Trifluoroacetyl) benzoate  61
3 14  Synthesis of Resin-Bound Ketones  62
3 2  Oxidations with New Achiral Catalysts  64
3 21  Epoxidation Reactions  64
3 21 1  Monophasic System Results  67
3 21 2  Biphasic System Results  70
3 21 3  Monophasic Resin-Bound Ketone Results  72
3 21 4  Conclusion to In Situ Epoxidation Work  72
3 22  Effect of Light and pH on Selected Reactions  74
3 22 1  Exclusion of UV Decomposition  74
3 22 2  pH Dependence of Dioxirane Formation  75
3 22 3  Conclusion  77
3 3  Oxidations other than Epoxidation  77
3 31  Conclusion  81
3 4  Epoxidations of Allylic Alcohols  82
4 41  Cyclohexene Epoxidations  83
3 42  Geraniol and Geranyl Acetate Epoxidations  85
3.5  Case Study on Carvedilol  88
3 51  In Situ Dioxirane Oxidation Reactions  88
3 51 1  Conclusion  90
3 52  Other In Situ Oxidations  93
3 52 1  Conclusion  93
3 53  Isolated Dioxirane Oxidation Reactions  95
3 53 1  Conclusion  95
3 54  Other Peroxide Oxidations  96

Chapter 4- Synthesis and Evaluation of Novel Chiral Ketones.  98
4 1  Synthesis of Spiro-Indanone Derivatives  99
4 11  Evaluation of Indanone Derivative  102
4 12  Conclusion  103
4 2  Synthesis and Evaluation of Spiro-Tetralone Derivative  103
4 21  Evaluation of Spiro-Tetralone as a Catalyst  106
CHAPTER 1
Chapter 1

Review of Dioxirane Chemistry

1.0 Dioxirane Discovery

Dioxiranes (Figure 1) are novel three membered strained cyclic organic peroxides. The most commonly used dioxiranes for oxidation are dimethyldioxirane (also known as DMD) and methyl(trifluoromethyl)dioxirane.

![Figure 1](image)

Dimethyldioxirane $R_1=R_2=\text{CH}_3$

Methyl(trifluoromethyl)dioxirane $R_1=\text{CH}_3$, $R_2=\text{CF}_3$

The first literature reference to a dioxirane structure was made by Baeyer and Villiger in 1899. They suggested that the intermediate formed in the conversion of the cyclic ketone, menthone, to its corresponding lactone using monoperoxysulphuric acid, was a dioxirane (Scheme 1). But due to conflict about structure, interest was soon lost in the subject.

In 1974, Montgomery observed that certain ketones at $pH > 7$, in catalytic amounts, will enhance the decomposition of large amounts of monoperoxysulphuric acid and that a number of oxidation reactions of monoperoxysulphuric acid (in future known as caroate or Oxone®) are catalysed by the presence of ketones. He suggested that the adduct formed by the monoperoxysulphate anion adding to the ketone was reacting...
further to give the dioxirane, although he never claimed that a dioxirane was acting as an oxidant.

**Scheme 1**

Proposed dioxirane intermediate in the oxidation of menthone

Edwards, Curci and co-workers expanded Montgomery’s ideas and carried out kinetic studies and $^{18}O$-labelling experiments, which gave them strong evidence that dioxiranes were present in the ketone/caroate system. Reactions were run in an aqueous system that contained the chosen ketone, caroate and the substrate to be oxidised. The pH was strictly maintained at 7.5 for efficient oxidation. At this pH, Curci observed that little or no competition from the Baeyer-Villiger reaction was occurring. From this they proposed that the mechanism of dioxirane formation and decomposition could be as in Scheme 2.

Initial workers ran dioxirane-oxidised oxidations in *in situ* conditions. This involved placing the ketone dioxirane precursor (often acetone is used for this purpose) and caroate in a biphasic solvent system of dichloromethane and aqueous buffer, containing a phase transfer catalyst. To this system the substrate to be oxidised was added. This *in situ* biphasic system theoretically allowed any ketone to be used as a dioxirane catalyst as the system formed the dioxirane *in situ*. However, there have been many debates as to whether actual dioxirane formation is occurring in the *in situ* system.
Scheme 2

\[ \text{Mechanism of dioxirane formation and decomposition} \]

B V is the Baeyer-Villiger reaction
S is the substrate to be oxidised.

In the *in situ* formation of dioxirane it has been noticed that there was a strong pH dependence and generation is optimum at about pH 7.5-8. The pH must constantly be controlled with a base to buffer the system. The pH sensitivity is shown by the fact that you either get caroate self-destruction at a high pH or a loss in reactivity at a lower pH value, where the Baeyer-Villiger reaction takes over.

1.1 Preparation of Dioxiranes

In 1985 Murray and Jeyaraman reported a milestone in dioxirane chemistry. They developed a method to isolate dimethyldioxirane as a solution in the parent ketone. Using a modified ketone/carboxylate system, which was developed by Curci *et al*. the
Dioxirane could be collected by low temperature distillation. These solutions could be kept for several days in a freezer with little or no decomposition.

The isolation method has been improved slightly over the years. In 1991, Adam and co-workers published a simple procedure for the preparation of dimethylidioxirane in its parent ketone (Scheme 3). This method involved the addition of 5 portions of solid Oxone® at three minute intervals, to a vigorously stirred solution of water, commercial acetone and sodium hydrogen carbonate at 0°C. After three minutes from the last addition, cooling was removed and a slight vacuum applied. The dimethylidioxirane, as a solution, in acetone was then distilled into a cooled (-78°C) receiving flask. Concentrations of up to 0.1M were reported and we have found these solutions may be kept up to three months in a freezer without noticeable decomposition.

Scheme 3

\[
\text{CH}_3\text{COCH}_3 + \text{KHSO}_5 \xrightarrow{\text{H}_2\text{O}, \text{NaHCO}_3, \text{pH}\sim 7.5, 5^\circ\text{C}} \text{Me_2C=O} \\
\]

*The formation of isolated dimethyldioxirane*

The isolation of dimethyldioxirane allowed detailed spectral study including \(^{17}\text{O}\) NMR and \(^{13}\text{C}\) NMR analysis, that gave valuable evidence for the dioxirane structure (1) versus the carbonyl oxide structure (2). Other dioxiranes including some less volatile dioxiranes such as that derived from cyclohexanone have also been isolated.
1.2 Fluorinated Dioxiranes

In 1972, a patent by Talbott and Thompson reported the first preparation of a dioxirane. They claimed to have isolated, under low temperature gas chromatography, the unstable and explosive dioxiranes, perfluorodimethylidoxirane (3) and chloro(difluoromethyl)trifluoromethylidoxirane (4).

They were prepared by oxidising the dilithium salts of the corresponding ketone hydrates, using fluorine at -80 to -30°C (Scheme 4).
Three years after Murray’s isolation of dimethyldioxirane, one of the most useful and widely used dioxiranes after dimethyldioxirane was isolated and characterised. This was methyl(trifluoromethyl)dioxirane (Figure 1, page 2). This was reported as being about 1000 times more reactive than its non-fluorinated relative dimethyldioxirane. It will oxidise alkanes to corresponding alcohols and/or ketones within minutes at ambient temperatures. The isolated solution can be stored at -20°C and the stability appears to be at least comparable to dimethyldioxirane. It has been found that solutions of methyl(trifluoromethyl)dioxirane have to be protected from light, since brief exposure to UV or even to 586nm radiation causes the rapid and exothermic decomposition of the dioxirane. In all cases, Curci et al found the decomposition of this dioxirane gave mainly methyl trifluoroacetate (5) and trifluoroacetic acid, the hydrolysis product (Scheme 5).

\[ \text{Decomposition of methyl(trifluoromethyl)dioxirane} \]
In 1993, Russo and DesMarteau \textsuperscript{21} synthesised and characterised difluorodioxirane (6), the first gas phase dioxirane which was stable at room temperature.

![Difluorodioxirane](image)

(6)

The synthesis was thought to proceed via an electron transfer mechanism (Scheme 6)

\textbf{Scheme 6}

\[
\begin{array}{c}
\text{O} \\
\text{F} \\
\text{C} \\
\text{O} \\
\text{F}
\end{array}
\xrightarrow{\text{CsF}}
\begin{array}{c}
\text{O} \\
\text{F} \\
\text{C} \\
\text{O} \\
\text{F}
\end{array}
\xrightarrow{X_2}
\begin{array}{c}
\text{O} \\
\text{F} \\
\text{C} \\
\text{O} \\
\text{F}
\end{array}
\xrightarrow{X_2 + F^-}
\begin{array}{c}
\text{O} \\
\text{F} \\
\text{C} \\
\text{O} \\
\text{F}
\end{array}
\]

Where \(X_2 = \text{Cl}_2, \text{CIF}, \text{F}_2\)

\textit{Synthesis of difluorodioxirane} \textsuperscript{21}

As expected, difluorodioxirane is a powerful oxidant and it will readily transfer oxygen. For example, with \(\text{CF}_3\text{CF}=\text{CF}_2\), \(\text{F}_2\text{C}=\text{CFCI}\) and \(\text{F}_2\text{C}=\text{CHF}\), the respective epoxides are formed in >95% yield in the absence of solvent. When \(\text{CFCl}_3\) is used as a solvent, similar results are observed. These are the first examples of the epoxidation of fluorinated alkenes by a dioxirane \textsuperscript{22}

Cremer noted some properties of difluorodioxirane.
• Its geometry is characterised by a rather long O-O bond of 1.578 Å, which is the longest O-O bond recorded.

• Despite the unusual O-O bond length, the most revealing geometrical parameter as to the electronic nature of difluorodioxirane is the FCF bond angle (108.8°) which is 8° smaller than the HCH bond angle of dimethyldioxirane. This indicates a strong C-F, C-F bond interaction that significantly influences the electronic structure of difluorodioxirane.

• Stabilising bond-bond interactions increase the stability of difluorodioxirane relative to that of dimethyldioxirane by 32 kcal/mol. Part of the increase is due to a decrease in ring strain.

It has been postulated that the major decomposition pathway of difluorodioxirane should be characterised by O-O cleavage and subsequent fluorne shift, thus leading to a somewhat more stable isomer (7). However, this reaction has not been observed experimentally.

\[
\begin{align*}
\text{(7)} \\
F & \quad \text{O} \\
\text{O} & \quad \text{F}
\end{align*}
\]

Although difluorodioxirane reacts in a similar way to methyl(trifluoromethyl)dioxirane, there is probably little or no use for it in synthesis due to it being gaseous at room temperature.

Thus a fluorinated dioxirane seems to be a more powerful oxidant but unfortunately, there are handling problems:

• Difluorodioxirane is gaseous.

• The initial perfluorodimethyldioxirane and chloro(difluoromethyl)dioxirane are explosive in nature.
Methyl(trifluoromethyl)dioxirane,\textsuperscript{19} although an extremely powerful oxidant, has to be handled at low temperatures due to its volatile nature.

1.3 Chemical Reactivity

Dioxiranes are now well known for their novel oxidative properties and Curci and Adam \textit{et al.}\textsuperscript{23} grouped most of the known transformations\textsuperscript{1,2,3} undergone by dioxiranes together (Scheme 7). These include the epoxidation of alkenes\textsuperscript{6,7,15,24-27} (reaction 1, Scheme 7), polycyclic aromatic hydrocarbons\textsuperscript{28,29} (reaction 2, Scheme 7), allenes\textsuperscript{30} (reaction 3, Scheme 7), enol derivatives\textsuperscript{31-34} (reaction 4, Scheme 7), and $\alpha$, $\beta$-unsaturated ketones\textsuperscript{35-37} (reaction 5, Scheme 7). Even insertions into C-H bonds of alkanes\textsuperscript{20,38} (reaction 6, Scheme 7) and of aldehydes\textsuperscript{10,39} (reaction 7, Scheme 7) and into Si-H bonds of silanes\textsuperscript{40} (reaction 8, Scheme 7) have been reported. Sulphides\textsuperscript{14,16,41} were oxidised to sulfoxides or sulphones (reaction 9, Scheme 7), primary amines\textsuperscript{42} to nitro compounds (reaction 10, Scheme 7) and chloride ion\textsuperscript{5} to the hypochlorite ion (reaction 11, Scheme 7). Also phosphine sulphides\textsuperscript{43} to the phosphine oxides (reaction 12, Scheme 7) and imines\textsuperscript{44} to nitrones (reaction 13, Scheme 7).

Furthermore, dimethyldioxirane catalysed the isomerisation of quadricyclane\textsuperscript{45} to norbornadiene, the latter was then epoxidised by the dioxirane\textsuperscript{46}.

The dioxiranes used to undergo these oxidations would be isolated solutions of dimethyldioxirane or methyl(trifluoromethyl)dioxirane in their respective parent ketones.

On account of this widely useful chemistry, dioxiranes have been recognised as one of the most efficient oxygen transfer agents, which are chemo-, regio- and stereo-
selective despite their pronounced reactivity. Dioxirane oxidations are performed under almost neutral conditions (pH ~ 7.5), which is of particular use when sensitive substrates are used.

**Scheme 7**

*Spider diagram to show oxidation potential of dioxiranes*

Most of the reactions shown in Scheme 7 involve isolated dioxiranes. However, *in situ* prepared dioxiranes can also be used, particularly for epoxidations of alkenes. A qualitative comparison of reaction types between isolated and *in situ* generated dioxiranes published in the current literature is shown in Table 1. It is clear that there...
are limited examples for *in situ* dioxiranes outside the scope of epoxidation, yet for isolated dioxiranes there are a bounty of examples

Table 1 - Comparison between isolated and *in situ* dioxirane oxidations

<table>
<thead>
<tr>
<th>Reaction</th>
<th>In situ dioxirane</th>
<th>Isolated dioxirane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoxidation</td>
<td>Many examples</td>
<td>Many examples</td>
</tr>
<tr>
<td></td>
<td>Chiral and achiral ketones</td>
<td>Mainly DMD used</td>
</tr>
<tr>
<td>C-H insertion</td>
<td>Very few examples</td>
<td>Many examples</td>
</tr>
<tr>
<td>Alcohol oxidation</td>
<td>Rare examples</td>
<td>Many examples</td>
</tr>
<tr>
<td></td>
<td>Often by-products of C-H</td>
<td></td>
</tr>
<tr>
<td>Other oxidations</td>
<td>Few examples</td>
<td>Many examples</td>
</tr>
<tr>
<td></td>
<td>Oxidation of sulphides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mainly</td>
<td></td>
</tr>
</tbody>
</table>

Much of the early work that used a biphasic system for *in situ* generation of dioxiranes was initially complicated due to the required strict pH control via a pH titrator. Some examples of ketones used for *in situ* dioxirane generation are shown in Table 2. In 1995 a breakthrough in the use of *in situ* generated dioxiranes was made by Yang *et al.*, which led to a simplified process using a monophasic system. The pH of the system was controlled via the addition of sodium hydrogen carbonate in one portion at the beginning of the reaction. This has caused *in situ* generated dioxirane oxidations to become popular and is the method of choice when asymmetric
ketones are being investigated, as the system is catalytic in regards to the ketone and very easily handled

Table 2- Examples of ketones used under *in situ* oxidation conditions

<table>
<thead>
<tr>
<th>Ketone catalyst</th>
<th>Oxidation</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Ketone 1" /></td>
<td>A wide range of <em>in situ</em> oxidations are published using dimethyl dioxirane and methyl(trifluoromethyl)dioxirane (less so)</td>
<td>1, 3, 7, 22, 23, 24</td>
</tr>
<tr>
<td><img src="image2" alt="Ketone 2" /></td>
<td>adamantane to 1-adamantanol X=Cl, 13% conversion X=F, 11% conversion</td>
<td>48</td>
</tr>
<tr>
<td><img src="image3" alt="Ketone 3" /></td>
<td>For 5,6-steroidal epoxidation R=Me, 70% conversion R=H, 59% conversion R=2-hydroxy-2-methyl, 37%</td>
<td>49, 67</td>
</tr>
<tr>
<td><img src="image4" alt="Ketone 4" /></td>
<td>2-Phenylcyclohexene to 2-phenylcyclohexene oxide 3hr= 90% isolated yield</td>
<td>50, 51</td>
</tr>
<tr>
<td><img src="image5" alt="Ketone 5" /></td>
<td>α-Methylstyrene to α-Methylstyrene oxide 40hr=90% conversion</td>
<td>52</td>
</tr>
</tbody>
</table>
1.4 Are dioxiranes the active intermediate

In 1996 Armstrong et al published papers that indicated evidence that dioxirane is not responsible for alkene epoxidation in a ketone-Oxone® system. It was suggested that tetrahedral Criegee intermediates, not dioxiranes, are the active oxidants for the in situ epoxidation protocol. 53

During 18O-labelling studies of cyclohexene using 4-tert butylcyclohexanone as ketone catalyst under Armstrong et al published biphasic oxidation conditions no 18O-label to the resultant epoxide was observed (Scheme 8-path a). Importantly though there was also no loss of 18O-label from the ketone carbonyl of the catalyst.

Scheme 8

Reagents used, Oxone®, Bu₄NHSO₄ (EDTA)Na₂, 1 mol dm⁻³ aqueous NaHCO₃, CH₂Cl₂, 0°C

Investigation of 18O-label transfer under in situ conditions
A possible explanation for the lack of label transfer is that the tetrahedral species, resulting from addition of HSO$_3^-$ to the carbonyl group, is capable of alkene epoxidation. Ring closure is likely to be the rate-determining step in dioxirane formation and it is possible that in the presence of an alkene, epoxidation by the tetrahedral species is faster than ring closure to the dioxirane (Scheme 8-path a versus path b).

Armstrong and co-workers concluded that it is therefore probable that a dioxirane is not involved in the ketone-accelerated epoxidation of alkenes.

This issue was re-addressed recently by Denmark and co-workers, who carried out $^{18}$O-labeling studies of their own using a 4-oxopiperidinium species (Scheme 9). If the Criegee intermediate (8) is indeed the true oxidant (Scheme 9-path a) then no $^{18}$O-label should be found in the product epoxide. On the other hand, if the dioxirane is in fact involved (Scheme 9-path b) then about 50% of the original label should be transferred to the resultant epoxide.$^{50,54}$

Denmark et al found that the $^{18}$O-label incorporation level in the epoxide increased with loading of ketone catalyst. It was thus established that dioxiranes are the true intermediates in the monophase, in situ generated conditions.$^{50}$

However, due to inconsistencies between the two sets of published results Denmark suggested conditions that need to be fulfilled to obtain the correct conditions for dioxirane intermediates to form. The conditions are as follows:

- Catalytic epoxidation must be rapid and high yielding
- No background pathway can be followed
- There should be no opportunity for scrambling or dilution of label.
- A sensitive analytical method for accurate measurement and isotope enrichment is required.
However, it must be noted that Armstrong and co-workers used biphasic in situ reaction conditions to generate the dioxirane whereas Denmark used monophasic reaction conditions. It may be that this could be relevant to the conflicting results observed.

1.5 General Dioxirane Oxidation Reactions

1.5.1 Epoxidations using Dioxiranes

Epoxidation is the most studied reaction of dioxirane chemistry, mainly because epoxides are useful synthons in synthesis and dioxiranes have been shown to rapidly epoxidise alkenes in high yields and under very mild conditions. The most widely used dioxirane in epoxidations is dimethyldioxirane. As we have previously seen dimethyldioxirane can be both isolated and used as a solution in the parent ketone or it can be generated in situ. The latter either uses a biphasic system.
which is buffered at pH 7.5 or a monophasic system which has pH control included at the beginning of the reaction. The *in situ* protocol is particularly attractive to those wishing to form acid sensitive epoxides, as mild almost neutral conditions are used. It is also practically viable for large-scale preparations and catalytic, therefore allowing a wider range of epoxides to be prepared.

The generally accepted mechanism for *in situ* epoxidation with Oxone® involving dioxirane formation and oxygen transfer is shown in Scheme 10.

![Scheme 10](image)

Dioxiranes are believed to form in two steps from Oxone® and their parent ketone. The nucleophilic attack of peroxomonosulphate anion at the carbonyl carbon of the ketone affords the Criegee intermediate, this intermediate then breaks-down to generate dioxirane, with the loss of KHSO₄.
A single oxygen atom is then transferred to the olefin, whilst regenerating the parent ketone. Therefore, with appropriate choice of reaction conditions the epoxidation could be catalytic in ketone. While this is of little or no consequence when acetone is the promoter, it would be particularly important in the area of asymmetric epoxidation where structurally complex chiral ketones are used.54

The alkene double bond has been investigated thoroughly. Curci and Adam observed the reactivity of the double bond and reported that alkene reactivity follows the order:22

\[
\text{ED-C=C- > -C=C- > EA-C=C-}
\]

Where ED is an electron donating substituent and EA is an electron accepting substituent. It has been seen that the more alkylated the alkene is, the faster it will react.

Edwards et al.6 also demonstrated that olefins were epoxidised in a syn stereospecific manner and in high yield. Baumstark and co-workers later proposed that steric interactions were important in that trans-alkenes are about eight times less reactive than their corresponding cis-isomers and the oxygen transfer is stereoselective, i.e., cis-alkenes will give cis-epoxides.15 This work showed that oxidation reactions are particularly sensitive to steric factors and suggested the involvement of a spiro transition state.

The mechanism of epoxidation by dimethyldioxirane can be viewed in terms of the transition state of the two mechanistic extremes for the electrophilic oxygen atom transfer; planar or spiro (Figure 3). The observed relative reactivity series seems to strongly favour the spiro transition state.16,49
In addition to steric interactions, solvent effects are thought to play a role. The presence of water has been shown to increase the rate of epoxidations. Denmark and co-workers\textsuperscript{54,55} have in a recent study of epoxidation reactions attempted to define optimum conditions. They reported that many variables in the biphasic \textit{in situ} system are interdependent.\textsuperscript{55}

- The stoichiometry of the ketone has a dramatic effect on the overall oxidation.
- The rate of Oxone\textsuperscript{®} addition effects the reaction.
- Oxidation continues long after addition of Oxone\textsuperscript{®} is complete.
- The rate of dioxirane formation exhibited strong pH dependence, with a maximum at pH 7.5-8.0.
- The rate of oxidation increased with increasing olefin substitution, tetra > tri > di > mono and isolated olefin react faster than conjugated alkenes and allylic alcohols.
- The lipophilicity of the ketone and its structure was crucial to success.

A number of ketone structures were also investigated,\textsuperscript{54,55} it was found that the ability to serve as a promoter for epoxidation involves two critical features:

- The ability to efficiently form a dioxirane.
• The ability to efficiently transfer the oxygen to the substrate

• Denmark and co-workers found that the best catalysts used, under biphasic in situ conditions were 4-oxopiperidinium salts (9)

\[
\text{\begin{align*}
\text{O} \\
\text{\text{+}} \\
\text{N} \\
\text{\text{+}} \\
\text{R'} \\
\text{\text{+}} \\
\text{R''}
\end{align*}}
\]

(9)

1.52 C-H bond insertion using Dioxiranes

The ability of dioxiranes to insert into C-H bonds is demonstrative of their remarkable reactivity. Dioxiranes will oxidise tertiary alkanes into their respective alcohols and secondary alkane into ketones via the alcohol. Oxidations with dimethyldioxirane proceed stereoselectively with retention of configuration, as the reactions with cis-decalin and trans-decalin (Scheme 11) demonstrate. This also illustrates that the oxidation of equatorial C-H is preferred to that of axial C-H.

The high selectivity of dimethyldioxirane in its oxidation is also illustrated by its oxygen insertion into toluene, ethylbenzene and isopropylbenzene. The oxidation at the benzylic position is in the order PhCH(CH₃)₂ > PhCH₂CH₃ > PhCH₃. Similarly, in the reaction with saturated hydrocarbons, oxidation has been shown to occur preferentially at the tertiary carbon atom.
Examples of \textit{in situ} generated dioxiranes in C-H oxygen insertions are limited, but recently Yang \textit{et al} published an interesting investigation into intramolecular oxidation of C-H bonds by dioxiranes generated \textit{in situ} \cite{yang2021}. However, first Yang \textit{et al} examined the activities of various ketones in catalysing the oxidation of adamantane under \textit{in situ} conditions (Table 3), before attempting to undertake intramolecular oxidations.

As shown, 1,1,1-trifluoroacetone (entry 1, Table 3) exhibits highest activity. When the ketone units were attached to a series of hydrocarbon skeletons and oxidation reactions were carried out, it was found that the δC-H bonds were selectively oxidised. These results indicate the predominance of stereoelectronic control on the transition state for hydroxylation. Furthermore, the observed regioselectivity (δ-selectivity) is different from that of a typical intramolecular radical reaction (γ-
selectivity), suggesting a non-radical nature of this oxidation reaction. Yang et al proposed a concerted C-H bond mechanism (Scheme 12)

Table 3- Oxidation of adamantane under in situ oxidation conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone catalyst</th>
<th>Product ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>adamantane: 1-adamantanol</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>H₃C CF₃</td>
<td>1 0 22</td>
</tr>
<tr>
<td>2</td>
<td>H₃C OMe</td>
<td>1 0 17</td>
</tr>
<tr>
<td>3</td>
<td>H₃C Cl</td>
<td>1 0 13</td>
</tr>
<tr>
<td>4</td>
<td>H₃C F</td>
<td>1 0 11</td>
</tr>
</tbody>
</table>

Oxidation of a δCH-H bond generates a δ-hydroxy ketone which cyclises to give a hemiketal. The hemiketal formation prevents further oxidation at the δ site. For concerted C-H bond oxidation by dioxiranes, there are two possible transition states, the planar transition state and the spiro transition state. Under a spiro transition state, oxidation of the equatorial δC-H bond (leading to trans-products) is strain free, whereas, oxidation of the axial one (leading to cis-products) is disfavoured. In contrast, under a planar transition state, the cis-product is expected to
be the major product. The observed trans-selectivity in Yang and co-workers study supports the spiro transition state theory.

All the different ketone skeleton endings studied in Table 3 were used and were found to give the same δ selectivity.

Scheme 12

Proposed intramolecular mechanism for C-H bond insertion

1.53 Alcohol oxidation using Dioxiranes

Another main group of oxidations by dioxiranes involves the oxidation of alcohols. Generally, secondary alcohols have been found to react faster than primary alcohols. Tertiary alcohols, however, are not usually oxidised under normal dioxirane conditions.

Secondary alcohols are oxidised to the corresponding ketone and therefore if a product of a C-H bond insertion is a secondary alcohol, often only the ketone will be observed (Scheme 13).
Scheme 13

\[
\begin{align*}
\text{CH}_3\text{CF}_3\text{O} & \to \text{CH}_3\text{O} + \text{CH}_3\text{COCH}_3 \\
& \text{41%} \\
& \text{41%} \\
& \text{18%}
\end{align*}
\]

*C-H bond insertion followed by alcohol oxidation to obtain the relative ketone*

Previous research in our group by Muxworthy on steroidal alcohols were shown to proceed via an oxygen insertion mechanism (Scheme 14) by use of 18O-labelled 5α-cholestan-3β-ol

Scheme 14

\[
\begin{align*}
\text{HO} & \to \text{HO} + \text{R} \text{ R} \\
& \text{R} \text{ R} \\
& \text{R} \text{ R} \\
& \text{R} \text{ R}
\end{align*}
\]

*Proposed mechanism for secondary alcohol oxidation by dioxirane*

Furthermore, significant differences in the reaction rate of axial versus equatorial alcohols (5α-cholestan-3α-ol and its 3β-epimer) were noted. It was proposed that the greater reactivity (>1.5 times) of the axial alcohol may be rationalised assuming
butterfly transition state (Figure 4) for the oxygen insertion and some intramolecular hydrogen bonding between the second oxygen of the dioxirane and the OH group

Figure 4

Diols have also been found to undergo oxidation with dioxiranes and may be used in the stereoselective synthesis of enantiomerically pure \(\alpha\)-hydroxy ketones. A general reaction scheme is shown below (Scheme 14)

Scheme 15

*General reaction scheme for oxidation of a diol with dioxirane*

The oxidative dehydrogenation of chiral \(\textit{\text{vic}}\)-diols into homochiral \(\alpha\)-hydroxy ketones is difficult to achieve in good yield using common oxidative reagents. Curci and coworkers showed that oxidation of \(\textit{\text{vic}}\)-diols by dioxirane led to \(\alpha\)-hydroxy ketones in
good to excellent yields. Very few dioxirane mediated alcohol oxidations reported in the literature use the \textit{in situ} protocol.

1.6 \textbf{Chiral ketones for asymmetric oxidations}

Dimethyldioxirane and methyl(trifluoromethyl)dioxirane are very good general purpose ketones for oxidation. However, in synthesis the requirement of an asymmetric synthetic route is common place. Therefore an asymmetric dioxirane mediated process, would be a very powerful synthetic tool, as the \textit{in situ} procedure is easy and simple to follow.

Until recently, little attention had been devoted to the production and use of a ketone catalyst capable of performing asymmetric epoxidations \textit{via} a dioxirane intermediate. In 1984, Curci et al.\textsuperscript{25} were the first to report an asymmetric epoxidation using a chiral ketone which is used in a biphasic \textit{in situ} system (10 and 11). These dioxiranes were reacted with prochiral alkenes to give epoxides with enantiometric excesses in the 9-12 \% range. The optically active parent ketone can be recovered unchanged at the end of the reaction, hence the reaction is catalytic. Curci continued to study this area of dioxirane chemistry\textsuperscript{19} and nine years later reported the use of two fluorine-substituted ketones.\textsuperscript{52,65} Unfortunately, the levels of selectivity were still low, typically 13-20\% enantiomeric excess (12 and 13).

Curci et al. reported that the adoption of chiral ketones carrying electron-attracting groups as dioxirane precursors was advantageous, as far as reaction times and yields were concerned.\textsuperscript{52}

Marples and co-workers\textsuperscript{66} are also in agreement with results previously found by Curci et al.\textsuperscript{13,25,52}
The chiral ketones, which were investigated by Marples et al., were generated from 1-tetralone and 1-indanone. They were individually substituted at the C-2 position with fluorine and either an alkoxy carbonyl or a 2-hydroxyisopropyl group (Figure 5).

**Figure 5**

1-Tetralone

1-Indanone

\[
R_1 = \text{CO}_2\text{CH}_3, \text{C(CH}_3)_2\text{OH}, \text{CO}_2\text{Men} \\
R_2 = \text{CH}_2\text{CH}_3, \text{CH}_3 \\
R_3 = \text{H}, \text{F}
\]
Published results indicated that both types of ketones were modest as chiral epoxidation promoters. It is accepted that the faster reaction rate and better yields were attributable to the fluorine substitution.

Since 1995, when Yang et al. published their monophasic \textit{in situ} system\textsuperscript{47} a number of attempts at making an asymmetric dioxirane catalyst have been reported. Most ideas are based on C-2 symmetry and some enantioselectivity has been found.

Below are tabulated the percentage conversions and enantiomeric excesses for the epoxidation of \textit{trans}-stilbene (Table 4) with a variety of catalysts.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone catalyst</th>
<th>Trans-Stilbene oxide</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>conversion</td>
<td>% ee</td>
</tr>
<tr>
<td>1</td>
<td><img src="image1" alt="Ketone catalyst" /></td>
<td>X=H, 91%</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X=Cl, 95%</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X=Br, 92%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X=Me, 93%</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X=CH₂OCH₃ 92%</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X=⁻⁻⁻⁻ 95%</td>
<td>71%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Ketone catalyst" /></td>
<td>90% at rt</td>
<td>20% at rt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>79% at 0°C</td>
<td>26% at 0°C</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Ketone catalyst" /></td>
<td>72%</td>
<td>59%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Ketone catalyst" /></td>
<td>Poor catalytic activity</td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>Ketone catalyst</td>
<td>Trans-Stilbene oxide</td>
<td>Ref</td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
<td>---------------------</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td></td>
<td>conversion</td>
<td>% ee</td>
</tr>
<tr>
<td>5</td>
<td><img src="image1" alt="Diagram" /></td>
<td>Poor catalytic activity</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td><img src="image2" alt="Diagram" /></td>
<td>X=F, 88%</td>
<td>76%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image3" alt="Diagram" /></td>
<td>X=H, 21%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X=F, 100%</td>
<td>58%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image4" alt="Diagram" /></td>
<td>trans-stilbene not used, however with trans-2-methyl styrene an ee of 34% was obtained</td>
<td>51, 54</td>
</tr>
<tr>
<td>9</td>
<td><img src="image5" alt="Diagram" /></td>
<td>39%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>67% in dioxane</td>
<td>64% in dioxane</td>
</tr>
<tr>
<td>10</td>
<td><img src="image6" alt="Diagram" /></td>
<td>72%</td>
<td>38%</td>
</tr>
</tbody>
</table>
The best results were found by Yang et al and were obtained with a binaphthol derivative (entry 1, \( X = Cl \), Table 4) yielding an enantiomeric excess of 76%. However for the oxidation of 4,4′-biphenyl-\textit{trans}-stilbene derivative, 87% enantiomeric excess was observed. It should be noted that high enantioselectivities were obtained only in alkenes bearing large aromatic substituents. The 4-step synthesis required to produce the binaphthol derivative (entry 1, Table 4) is also a particular drawback. The studies by Yang and co-workers have shown that when hydrogen was in position \( X \) (entry 1, Table 4, \( X = H \)) it was acting as a steric sensor. When more bulky groups replaced hydrogen it increased enantioselectivity up to a point due to increased steric hindrance in the transition state favouring one enantiomer. However after this point, enantioselectivity rapidly decreases, since groups get so bulky that all reaction orientations become disfavoured. The trends for numerous series of substrates were analysed and it was concluded that the transition state must be spiro in geometry.68

A more recent report of a C-2 symmetric dioxirane catalyst based on a binaphthol derivative was reported by Song et al69 The first ketone derivative (entry 2, Table 4) was produced in two steps from \((R)-(+)\)-1,1′-binaphthol. Two other binaphthol-derived ketones were also synthesised by Song69 (entry 3 and 4, Table 4) These were tested under standard monophasic conditions and oxidations were carried out using a stoichiometric amount of ketone. Song and co-workers69 synthesised a di-ketone (entry 4, Table 4) with the hope that both carbonyl groups would act as catalysts for dioxirane formation and improve the oxidation of olefins. However, the highest enantiomeric excess obtained by Song et al was 59% (entry 3, Table 4) on the oxidation of \textit{trans}-stilbene. X-ray analysis confirmed the C-2 symmetry of these derivatives.
Armstrong and co-workers \textsuperscript{71} also made progress in the synthesis of an asymmetric ketone. His initial 5-membered ring ketone (entry 5, table 4), under Yang monophasic \textit{in situ} reaction conditions, gave no detectable oxidation. However with the tropinone derivative (entry 6, table 4), \textsuperscript{72} a conversion of \textit{trans}-stilbene in 88\% yield was reported with an enantiomeric excess of 76\%. However twice as much ketone and Oxone\textsuperscript{\textregistered} were used compared to the published Yang conditions \textsuperscript{47}.

Armstrong and co-workers tropinone-derived ketones are of similar structure to recently used ketones by Denmark \textit{et al} \textsuperscript{51,54} (entries 7 and 8, table 4), which are asymmetric oxoammonium salts. However, they were both found to be relatively ineffective as epoxidation promoters. Although when \(R=\text{F}\) (entry 7, table 4), some activity was found and a 58\% enantiomeric excess for \textit{trans}-stilbene was obtained, which increased to 85\% with \textit{trans}-2-methylstyrene \textsuperscript{73}.

Denmark suggests their low reactivities most likely result from the unavoidable steric congestion caused by the substitution required to create an asymmetric environment adjacent to the ketone moiety and greater activation of the carbonyl carbon is needed to increase its electrophilicity for the generation of an efficient asymmetric epoxidation catalyst.

Adam and co-workers \textsuperscript{74} also synthesised ketones based on a C-2 symmetric model derived from the sugar mannitol (entry 9, table 4) and tartaric acid (entry 10, table 4). Results were reasonable under catalytic conditions.

A major breakthrough in asymmetric catalysts was made by Shi \textit{et al} with the D-fructose-derived ketone (14). This gave high enantiomeric excesses for epoxidation of \textit{trans}-olefins and tri-substituted alkenes bearing a variety of functional groups. With \textit{trans}-stilbene, (14) gave a 73\% conversion to the corresponding oxide with an.
enantiomeric excess of 95% The following three criteria \(^7\) defined the fructose ketone and its activity

- The stereogenic centres are close to the reacting centre, resulting in efficient stereochemical communication between substrates and catalyst
- The presence of a fused ring and a quaternary centre \(\alpha\) to the carbonyl group are introduced with the intention of maintaining the chiral elements in the ketone by minimising the epimerization.
- One face of the catalyst is sterically blocked to limit the possible competing approaches.

However the usual Yang monophasic procedure \(^47\) was modified to use this ketone by the addition of phase transfer catalyst. These results, using the "Shi ketone" (14), have been verified in our own laboratory and the use of phase transfer catalyst seems crucial to the function of the reaction \(^76\) Initially Shi and co-workers noted that after 2 hours reaction time, the enantiomeric excess tended to drop off. It was speculated that this was due to loss of the ketone catalyst through a Baeyer-Villiger side reaction, possibly yielding the cyclic ester that did not have the desired characteristics to carry out asymmetric epoxidation. In a later publication, \(^77\) Shi \textit{et al} reported that this problem had been overcome by increasing the pH of the reaction from pH7.5 to
pH 10.5, and thus by doing so was able to reduce the oxidation to a catalytic cycle. Again these results were verified in our laboratory.

In another publication, the full investigation as to how the new reaction conditions were achieved and a full pH, solvent and temperature study was given in detail. It can be seen that from the published results just how useful the fructose derived ketone actually is. Another recent publication by Shi et al., shows a new catalyst (Figure 6), which can be used for the oxidation of terminal olefins, di-substituted and tri-substituted olefins. Preliminary results were found to be very respectable in terms of enantiomeric excess.

![Figure 6](image)

With *trans*-stilbene a 60-95% conversion was obtained with an enantiomeric excess of 90-95%. These were carried out under Shi conditions (higher pH) with a solvent system comprised of a dimethoxyethane/ dimethoxymethane mix rather than acetonitrile. When R=OAc the ketone gave the highest enantiomeric excess of 90% and a conversion of 95% to the epoxide. By altering the R group on the parent ketone (Figure 6), differences in conformation and electronic make-up were achieved and it was these that were suggested to lead to the differences in enantiomeric excess. This recent series of ketones are more stable and reactive than the first fructose-derived
ketone (14) and lower quantities are required to achieve good conversions.

Reasonably high enantiomeric excess can be achieved with cis-olefins and terminal olefins, whereas the first catalyst (14) is not suitable for either.

The foregoing studies clearly demonstrate the feasibility of using chiral ketones to effect enantioselective epoxidations with Oxone®. Despite the structural dissimilarity of the compounds discussed one key feature unifies them, namely the presence of strong electron withdrawing substituents in the neighborhood of the carbonyl group.

Recently Shi et al have been investigating ketone structure and determining which groups will lead to enantioselectivity. It was reported that adaptation of the fructose ketone (14) to a simple spiro ketone (15) gave epoxidation of trans-stilbene with 77.5% enantiomeric excess. This observation lead Shi et al to suggest that the methylene (15, A) was important in controlling the epoxidation selectivity, however ketone structure still needs further investigation.

![Diagram of ketone (15)]

It has been shown that achieving the desired outcome from this deceptively simple looking reaction requires a delicate balance among all the possible pathways (Figure 7, a-k). Pathways a-k (a) Nucleophilic attack of the ketone by Oxone®, (b) Deprotonation of the peroxy intermediate; (c) Formation of the dioxirane; (d) Epoxidation of an olefin by the dioxirane, (e) Epimerization of chiral centers of the ketone, (f) Hydration of the ketone, (g) Oxone® self-decomposition, (h) Baeyer-Villiger reaction of the peroxy.
intermediate, (i) Consumption of the dioxirane by Oxone®; (j) Self-decomposition of the dioxirane, (k) Epoxidation of the olefin by Oxone® itself

![Reaction diagram](image)

Figure 7

It is suspected by Shi et al. that high enantioselectivities are more likely to be achieved when the stereogenic centers are closer to the reacting center (carbonyl group) due to more efficient stereochemical communication between substrate and catalyst. A potential problem associated with this type of ketone is the possible racemisation of the chiral centers due to the acidity of the protons at α-positions (Figure 7, path e), which puts restrictions on the choice of groups.
The current studies that have been reported, show that the structural requirements for a chiral ketone catalyst are very stringent in order for it to be effective in terms of both reactivity and selectivity.

1.7 Mechanism of Dioxiranes

The mechanism of oxidation by dioxiranes has been shown to be very complex. There are many papers published in the literature concerning these matters. Here I shall summarise what has been found in recent publications. The mechanistic discussion of dioxirane oxidation is mainly focused on dimethyldioxirane reactions.

1.71 Dioxiranes- Nucleophilic or Electrophilic?

To help us understand dioxirane oxidations we must first investigate how dioxirane transfers oxygen. Thianthrene-5-oxide (SSO) was used as a mechanistic probe to determine the electronic character of an oxidant (Scheme 16). The SSO probe was used to acquire information on the nucleophilic (oxidation at the sulphoxide site, SO in SSO) versus the electrophilic (oxidation at the sulphide site, S in SSO) nature of the oxidants.

The probe was initially developed by Adam and co-workers to differentiate between in situ generated dioxiranes and carbonyl oxides on account of their expected electrophilic versus nucleophilic oxygen transfer nature. The preliminary results obtained implied that dioxiranes and carbonyl oxides are differentiable valence isomers. This has now been established in theoretical, chemical trapping, spectral and recently by preparative work.
Mechanistic probe to determine the electronic character of an oxidant

The electronic character is determined by the parameter, $X_{SO}$, which is obtained from the following equation

$$X_{SO} = \frac{\text{nucleophilic oxidation}}{\text{total oxidation}} = \frac{SSO_2 + SOSO_2}{SSO_2 + SOSO + 2SOSO_2}$$

When a low value is obtained ($X_{SO} < 0.3$) this signifies electrophilic character and for a high value ($X_{SO} > 0.7$) nucleophilic oxidative character. The values found conclude that carbonyl oxides ($X_{SO} \approx 0.9$) are definitely nucleophilic oxygen transfer agents, while dioxiranes ($X_{SO} \approx 0.1$) are definitely electrophilic ones.
1.72 Heteroatom oxidation

Nitrogen and sulphur oxidations are generally explained by an $S_N2$-type attack of the heteroatom lone pair on the dioxirane peroxide bond (Scheme 17)\(^9^5\).

Kinetic experiments have discounted a SET mechanism in nitrogen oxidation.\(^9^6\) This was achieved by comparing the relative rates of dimethyldioxirane oxygen transfer with those of the alkylation by methyl iodide.\(^9^7\) The $S_N2$ behaviour of methyl iodide has been defined, for which electronic and steric factors play their usual role. For the heteroarenes examined by Adam and co-workers,\(^9^7\) a clear-cut $S_N2$ rather than electron transfer mechanism applied in the nitrogen lone pair oxidation by dimethyldioxirane.

Scheme 17

\[ \text{Scheme 17} \]

$S_N2$-type attack of the heteroatom lone pair on the peroxide bond

39
Although this heterolytic mechanism is general, it is supported by the fact that a variety of oxygen type nucleophiles catalytically decompose dioxiranes with evolution of molecular oxygen.

The general mechanism proposed for dioxirane decomposition is depicted in Scheme 18:

**Scheme 18**

![Proposed mechanism for dioxirane decomposition](image)

A study by Marples and co-workers probed the mechanism of amine oxidations and explored the possibility of substituent induced changes of mechanism. Comparative reagents to dimethyldioxirane were needed, therefore methyl iodide, benzyl peroxide and tert-butyl hydroperoxide were chosen. Methyl iodide was used as it was already established as having an $S_{N}2$ mechanism. Benzoyl peroxide is a neutral peroxide like dimethyldioxirane and the rate determining step in its reactions is thought to be electrophilic. Finally, tert-butyl hydroperoxide, which is also a neutral peroxide and is thought to react via a homolytic process involving tert-butylperoxyl radicals was examined.
The results obtained using substituted dimethylanilines indicated a similar qualitative trend for dimethyldioxirane oxidation as for the electrophilic methyl iodide and benzoyl peroxide reactions. Reactions involving tert-butyl hydroperoxide were less susceptible to change in substituent, the difference in rates were less marked, as would be expected for a non-electrophilic reaction. These trends suggest that dimethyldioxirane oxidation of \( N,N \)-dimethylanilines is electrophilic. It was also found that dimethyldioxirane oxidation rates were affected by hydrogen bonding. Hydrogen bonding stabilises both the transition state and the \( N \)-oxide reaction products, hence reactions were very fast in water and were also relatively unaffected by pH and ionic strength (Scheme 19).

Scheme 19

\[
\text{Transition state for the reaction of dimethyl aniline with DMD}
\]

Therefore the study concluded that the reactions were electrophilic and no evidence for either \( \text{bis(oxyl)} \) radicals or electron nature were found.

1.73 Alkene oxidation

For the epoxidation of double bonds, initially concerted mechanisms similar to peracids as well as a diradical mechanism were suggested for dioxiranes.
We have previously discussed initial relative epoxidation rates of differently substituted alkenes, which show a remarkable dependence on steric interactions.\textsuperscript{23,27} This is in contrast to peracids for which the epoxidation rates show a distinct dependence on the degree of substitution of the alkene. Therefore additional alkyl groups have less effect on reaction rates for dimethyldioxirane than would be noticed for peracid oxidations. However Baumstark \textit{et al} \textsuperscript{15} noticed that under dioxirane oxidation the \textit{cis}-isomer of an alkene is significantly more reactive than the corresponding \textit{trans}-isomer, whereas under peracid oxidation the two isomers react about equally as fast. Thus, compared to peracids, dioxiranes have been found to be less susceptible towards the relative nucleophilicity of the double bond, but more sensitive to steric effects \textsuperscript{15} and equally responsive to ring strain effects \textsuperscript{103}

To account for these distinct differences of oxygen transfer in peracids versus dioxiranes a different transition state from the accepted "butterfly" transition state for peracid reactions (Figure 8) was required. It must be noted though that the question of a \textit{planar} or \textit{spiro} geometry remains unsettled.\textsuperscript{82} In the case of a \textit{planar} transition state, similar steric interactions should apply for the corresponding \textit{cis}- and \textit{trans}-isomers. Therefore similar epoxidation rates are to be expected.

\textit{Figure 8}

\begin{center}
\includegraphics[width=0.5\textwidth]{planar_transition_state.png}
\end{center}

\textit{Planar transition state for peracid epoxidation}
However the higher cis/ trans selectivity of dioxiranes suggests this is not true.\textsuperscript{15, 27}

The geometry of the transition state has caused much debate. The general consensus among groups active in dioxirane research is that an oxenoid-type spiro transition state with the plane of the peroxide ring orientated perpendicularly to and bisecting the π-system of the double bond (Figure 9) is the most satisfactory geometry \textsuperscript{49, 104, 105}

![Figure 9](attachment:image.png)

Transition state geometry for dioxirane epoxidations

This geometry explains the cis/ trans selectivity of dioxiranes by allowing approach to a cis-alkene from the unsubstituted side without much steric interference of its methyl groups with the alkyl substituents at the double bond. For the corresponding trans-alkene, the spiro transition state will impose steric interactions between the alkyl groups of the dioxirane and of the trans-alkene. Hence, the attack is more hindered for trans- than for the cis-alkene and the trans isomer should react slower \textsuperscript{92}

The spiro transition state mechanism for dimethyldioxirane epoxidations has also been established with differently substituted dioxiranes, which match the expected transition state geometry. Recently Yang and co-workers \textsuperscript{106} reported enantioselective epoxidations by C-2 symmetric dioxiranes, which also supported the spiro geometry for dioxirane attack \textsuperscript{49}
Theoretical investigations have also reinforced the belief that a spiro transition state is the most probable geometry for oxygen transfer. A diradical mechanism has also been suggested for oxidations. However the fact that no cis/trans isomerisation was observed in the oxygen transfer, certainly speaks against a diradical pathway in the epoxidation by dimethyldioxirane (Figure 10).

**Figure 10**

*Expected transition state geometry for diradical-type attack*

The already mentioned high stereoselectivity of dimethyldioxirane epoxidations could be accommodated by proposing a much faster collapse of the resulting intermediary diradical than isomerisation through bond rotation, but it would be difficult to rationalise the established steric effects i.e. that cis-alkenes react faster than trans-alkenes. The diradical mechanism implies that the relative rates of cis- and trans-alkenes should be nearly the same.

Baumstark *et al* investigated kinetic studies on the epoxidation of a series of Chalcones. It was observed that in the transition state both carbon atoms of the double bond are to the same extent bonded to the transferred oxygen atom of the dioxirane, thus supporting evidence for the concerted oxenoid-type process.

An ultra-fast radical clock (>10^11 s^-1) was used as a mechanistic probe, and provided further evidence towards a concerted oxenoid-type process in the epoxidation of 1-
vinyl-2,2-diphenylcyclopropane the lack of cyclopropyl carbinyl rearrangement suggests that radical intermediates are not involved in dimethyldioxirane epoxidations (Scheme 20)\textsuperscript{82}

Scheme 20

Expected cyclopropyl carbinyl rearrangement in the epoxidation of an ultra-fast radical clock

Hence, in view of these data, the overwhelming evidence favours the concerted oxenoid-type mechanism for dimethyldioxirane epoxidations. However Houk et al concluded a computational study into transition states of epoxidation by saying\textsuperscript{108} "The transition state of the epoxidation by performic acid, dioxirane and oxaziridine are all concerted, but vary from $S_N2$ to homolytic $S_H2$ in character. Substituents on the alkene make the transition structures more asynchronous and diradicaloid in nature. The spiro geometry is highly favoured in all cases. The transition state model
can be used to rationalise the stereoselectivities of oxaziridine and dioxirane epoxidations."

For alcohol oxidation it has also generally been concluded that like epoxidation the mechanism follows a concerted oxenoid-type process.49,56

1.74 C-H bond insertion

A considerable amount of work is reported on of dioxirane reactivity in insertion into C-H bonds of alkanes. Abundant evidence such as kinetics,56 kinetic H/D isotope effects20 and stereoselectivity111 may be cited in support of an oxenoid-type mechanism (Scheme 21).112

![Proposed concerted oxenoid mechanism of insertion into C-H bonds](image)

Nonetheless, recently, Minisci and co-workers have reported the observation that the rigorous exclusion of dioxygen and radical inhibitors can have a dramatic influence upon the reaction pathway.113 This prompted the suggestion that oxidations of alkanes by dimethyldioxirane proceed via a "molecule-induced homolysis" or "radical-oxygen rebound" mechanism (Scheme 22).114 The transition structure for
this reaction pathway should exhibit considerable radical character with some charge separation.

However, a computational study investigated the formation of products derived from free radical intermediates in the absence of dioxygen and lends strong support to the generally accepted, highly exothermic, concerted oxygen insertion mechanism for the oxidation of alkanes with dioxiranes under typical preparative conditions.  

Scheme 22

![Scheme 22](image)

C-H bond insertion via proposed "radical-oxygen rebound" mechanism

Ingold and co-workers by adopting 2-cyclopropyl propane as a radical probe rejected the alkane hydroxylation mechanism in which out-of-cage radicals intervene. This was concluded in view of the absence of oxygenated products derived from cyclopropylcarbinyl radical rearrangement. However, it must be noted that this radical clock is rather slow to compete effectively with the in-cage collapse of the radical pair (oxygen rebound).
Adam and co-workers applied one of the fastest radical clocks (the racemisation of radicals derived from optically active substrates) to investigate C−H insertions by dimethyldioxirane. They had previously shown that hydroxylation of (R)−2-phenylbutane to (S)−2-hydroxy-2-phenylbutane by methyl (trifluoromethyl) dioxirane proceeds with 100% retention. Adam and co-workers claimed that if caged radical pairs are formed after the slow step ($k_{CH}$), their stereoretained collapse ($k_{OH}$) must be faster than diffusion out of the cage ($k_{diff}$) as well as tumbling or in-cage rotation ($k_{rot}$). Their competitive processes should all lead to racemisation (Scheme 23).

Scheme 23

It is known that increasing temperature would be expected to increase out-of-cage diffusional and in-cage rotational processes relative to recombination and hence, loss of configuration. However when the temperature was increased, it did not result in a detectable change in the stereochemistry. Therefore the optically active radical...
probe confirms that, at least on a time scale of less than a pico-second, stereomemory is retained. Adam could not definitely conclude whether the stereoretained oxygen rebounds or whether the oxenoid mechanism applies, but free radicals or even in-cage rotationally randomising radicals are probably not involved in the C-H insertion by dimethyldioxirane. ¹¹⁷

The mechanism of C-H bond insertion is not as fully understood as previous oxidations were. However, we must conclude by mentioning two recent mathematical modelling studies that probed the mechanism for alkane oxidations under normal laboratory conditions (i.e., in the presence of oxygen).¹¹⁵,¹¹⁹ They conclude that although the mechanism itself was not radical, the highly polarised transition state had some radical character (Figure 11).

Houk et al. concluded that greater OH than CO bonding had been observed than for many previous models.²⁰,¹²⁰ It was therefore concluded that this, combined with the predicted polarised nature of the transition state, caused the concerted oxygen insertion into tertiary C-H bonds to be highly favoured.¹⁰⁸

![Figure 11](image)

Highly polarised transition state showing some radical character
CHAPTER 2
Chapter 2

Project Introduction

Previous work in our group by J. Muxworthy investigated a series of fluorinated aromatic ketones as catalysts. It was known that there was a decrease in reactivity, as the ketone used increases in molecular weight and structural complexity and it was anticipated that introduction of fluorine would increase reactivity. This effect on the reactivity maybe explained by an increase in electrophilicity of the dioxirane. Thus, oxygen transfer maybe assisted by an electron deficient carbonyl carbon atom, hence moving the equilibrium towards ketone formation.

Muxworthy reported results that were carried out in biphasic conditions (DCM/aqueous buffer) and are tabulated as decreasing relative reactivities (Table 5). From the results it was evident that \(\alpha,\alpha,\alpha\)-trifluoroacetophenone was the most reactive ketone examined of the series.

2.1 New achiral catalysts and applications.

The initial proposal of my research was to further develop Muxworthy’s work on fluoro aromatic ketones to explore alternative catalysts and reaction conditions. As \(\alpha,\alpha,\alpha\)-trifluoroacetophenone had already been investigated and found to be reactive, this was further investigated and a family of achiral fluoro aromatic ketones based upon the structure of \(\alpha,\alpha,\alpha\)-trifluoroacetophenone was developed (Figure 12). Their oxidation ability has been explored with particular reference to epoxidation reactions of alkenes, allylic alcohols, secondary alcohols and CH-bond insertions.
Table 5-Muxworthy’s results in biphasic oxidation conditions

<table>
<thead>
<tr>
<th>Entry in decreasing reactivity</th>
<th>Ketone</th>
<th>Reactivity of dioxirane</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Ketone 1" /></td>
<td>Most Reactive ketone</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Ketone 2" /></td>
<td>Ketone entries 2 and 3 are similar in reactivity</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Ketone 3" /></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Ketone 4" /></td>
<td>Ketone entries 4, 5, 6 and 7 are very similar in reactivity</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Ketone 5" /></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Ketone 6" /></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Ketone 7" /></td>
<td>Acetone</td>
</tr>
</tbody>
</table>

Reactions were run in a 1:4 DCM/Phosphate buffer, water solution, using 1 equivalent of cyclohexene, 1 equivalent of ketone, 26 equivalents of Oxone®. 03 equivalents of PTC, at 0°C.
Included in this work is an investigation of resin-bound trifluoroketones as a recyclable dioxirane precursor. The two resins chosen were a TentaGel S-Br resin and a hydroxymethyl resin (see Figure 13, shown attached to the parent ketone structure). The epoxidation catalytic activity of the two resins was evaluated and the TentaGel resin was also evaluated for alcohol oxidation and C-H oxygen insertion. For dioxiranes generated *in situ* there are many variations on the original protocol and the effect of the reaction conditions must be considered to be able to gain maximum potential out of a ketone catalyst. Therefore an investigation of reaction conditions including the effect of light, temperature, pH and organic to aqueous solution ratios has been undertaken.

After identification of an oxidative system and catalyst by oxidising a variety of simple substrates, we chose to use our system and achiral ketones in a study of the oxidative decomposition of Carvedilol (Figure 13-C$_{24}$H$_{26}$NO$_4$) a drug used for heart disease that contains a variety of potential oxidation sites. It was considered that the dioxirane-mediated oxidation might mimic metabolic processes.

**Figure 12**

![Trifluoroacetophenone](image)

4-(Trifluoroacetyl) benzoate ester

4-(Trifluoroacetyl) benzoic acid
2.2 New chiral catalysts

As indicated earlier asymmetric dioxirane-mediated catalytic processes are powerful synthetic tools, but there is still the need to develop new versatile catalysts. Previous work in our research group by Walton\cite{walton} had described how 1-tetralone and 1-indanone derivatives were used to generate \textit{in situ} dioxiranes (Figure 5). This work confirmed that the incorporation of fluorine into an aromatic ring of aryl alkyl ketones increased the reactivity of its dioxirane in alkene epoxidation. Given these results by Walton\cite{walton} and Shi and co-workers recent observations\cite{shi}, it was decided to modify Walton’s chiral ketones, to try and improve the enantioselectivity.
in epoxidation. Use of computer modelling and the basic structural ideas of Shi and co-workers suggested a number of novel ketones. A selection of targets was chosen (16-19), using a spiro ring structure attached to the ketone to the carbonyl to obtain stereochemical control. The incorporation of the heterocyclic oxygen ring as in 4-chromanone and 4-iso-chromanone (18 and 19 respectfully) was thought to be important to provide greater reactivity owing to the electron withdrawing properties of oxygen.

\[ \text{X}=\text{H}/\text{F} \]

(16) (17)

(18) (19)

2.3 Mechanistic investigation of alcohol oxidation

Previously within our research group there has been investigation of the mechanistic details of dimethyldioxirane oxidation of cholestanols and recently of bile acid methyl esters, that have provided further insight into the mechanism of dimethyldioxirane oxidation of alcohols. Effectively the substrates studied are cyclohexanols (Figure 14) with either zero \( \alpha \) substituents (A), one \( \alpha \) substituent (B) or
two α substituents (C) As a result of this work Marples et al proposed that the transition state was planar and included an important hydrogen bond

![Figure 14](image)

However recent reports\(^{45, 119, 120}\) suggested that intramolecular dioxirane mediated oxygen insertions into C-H bonds of alkyl groups are best explained by a \textit{spiro} rather than a \textit{planar} transition state. Therefore a suitable model was proposed to investigate these mechanisms further.

The two substrates chosen for investigation were 2,6-dimethylcyclohexanol (20) and 2,2,6-trimethylcyclohexanol (21) as these extend the range of cyclohexanols studied to include α,α'-disubstituted (D) and α,α,α'-trisubstituted (E).
CHAPTER 3
Chapter 3
Synthesis and Evaluation of novel Achiral ketones

As seen in chapter 2 a family of fluoro aromatic ketones (Figure 12 and 13) were proposed for use as catalysts for in situ dioxirane generation. Each fluoro aromatic ketone was specifically chosen: α,α,α-Trifluoroacetophenone (Figure 12) as the parent fluoro ketone was used as a standard, to compare other fluoro aromatic ketone reactivity. The related 4-(trifluoroacetyl)benzoic acid \(^{123,124}\) (Figure 12) can be reclaimed via a careful work-up procedure and recycled which forms an economic process. Methyl 4-(trifluoroacetyl)benzoate (Figure 12) was initially chosen as a simple ester and because an ester can be synthesised simply from the acid functional group. Therefore it is foreseeable that a range of esters can be synthesised \(^{55}\).

3.1 Synthesis of derivatives of 4-(trifluoroacetyl)benzoic acid

The esters that were chosen to be synthesised were a methyl ester, a steroidal ester and a benzyl ester.

Denmark and co-workers \(^{55}\) observed that by changing the lipophilicity of a ketone an effect on dioxirane formation and oxygen transfer could be achieved. Therefore by altering the ester group chain length, it could be possible to alter the lipophilicity of the fluoroketone to optimise oxidation. Denmark et al. reported that in biphasic systems both highly hydrophilic and highly lipophilic ketones were in active. At one extreme is the organic insoluble/ water soluble promoter, if the resulting dioxirane were also completely soluble then the unproductive pathway of decomposition is expected to dominate as the dioxirane would stay in the aqueous phase with caroate.
and not be transported to the organic phase where the substrate is located. At the other extreme would be an organic soluble/water insoluble promoter. In this example, the biphasic prevents contact of the water-soluble oxidant with the water insoluble dioxirane precursor and will fail to produce a dioxirane unless PTC can be used to shuttle the oxidant into the organic phase.

3.11 Synthesis of methyl 4-(trifluoroacetyl) benzoate

An initial attempt at synthesising methyl 4-(trifluoroacetyl) benzoate was from a literature preparation\textsuperscript{124}. This involved the use of diazomethane, however the method was unsuccessful yielding an inseparable oil. Therefore a standard Fischer esterification procedure was used (Scheme 24) and the product was obtained as a cream solid in varying yields (66-90%).

Scheme 24

\[
\begin{align*}
\text{O} & \text{CF}_3 \\
\text{O} & \text{H} + \text{MeOH} \xrightarrow{\text{Reflux, p-TSA}} \text{O} & \text{CF}_3 \\
\text{O} & \text{OH} & \text{O} & \text{OMe}
\end{align*}
\]

\textit{Fischer esterification to synthesise methyl 4-(trifluoroacetyl) benzoate}

It was observed by NMR analysis that there were two components present in the isolated product, which were similar in structure. The second product was presumed
to be the stable hydrate of the ester that can be detected when halogens are present.

There was a possibility of two hydrates, the hydrate (22) or the hemi-acetal (23):

![Chemical structures of (22) and (23)]

To confirm that hydrate was present, a sample (in CDCl₃) was stood over molecular sieves (4Å) for 48 hours, to allow the sample to dehydrate. On analysis, by proton NMR it was observed that the hydrate peaks were not present and only peaks corresponding to the product ester were present. Re-hydration with water reformed the hydrates (22 and 23).

This information was incorporated into the work-up procedure.

3.12 Synthesis of dihydrocholesterol 4-(trifluoroacetyl) benzoate

A steroidal ester was chosen because of its high lipophilicity. It was initially thought to synthesise the ester via the Mitsunobu reaction (Scheme 24). The Mitsunobu esterification would invert the stereochemistry allowing the ketone moiety to be turned under the main steroid ring system. It was thought that this system was suitable for intermolecular C-H bond insertion.
A number of attempts to synthesise dihydrocholesteryl 4-(trifluoroacetyl) benzoate were made. However the product could not be isolated from the crude reaction mixture. Therefore the Fischer esterification was used, using toluene as a solvent (although no inversion of stereochemistry would be obtained) again isolation proved difficult. Spectroscopy analysis (NMR and IR) of the crude product gave some evidence that the ester structure was present. However due to the difficulty in preparation and isolation of dihydrocholesteryl 4-(trifluoroacetyl) benzoate no further research to synthesise it was attempted.

3.13 Synthesis of benzyl 4-(trifluoroacetyl) benzoate

Due to previously successful experiences with the Fischer esterification procedure, this was used first. Unfortunately nothing was isolated from the crude reaction mixture that could be identified as an ester (24).
Attempts to synthesise the ester (24) through an intermediate acid chloride were also made however no identifiable product was obtained.

3.14 Synthesis of resin bound ketones

A novel resin bound ketone catalyst was theoretically obtainable through the acid functional group of 4-(trifluoroacetyl) benzoic acid, under suitable conditions. This idea had not been attempted before in dioxirane chemistry and a resin that was bound to a ketone that could generate a dioxirane would simplify many oxidations with the additional advantage of being recyclable. However, during our research Sreekumar et al. reported a resin bound ketone, which was pre-treated with Oxone to form the dioxirane and then used to oxidise the substrate. This work did not interfere with our proposed resins because our resins were for in situ generation of dioxirane. The hydroxymethyl resin bound ketone (Figure 13) was prepared by reaction of the hydroxymethyl resin with the acid chloride prepared from 4-(trifluoroacetyl) benzoic acid by reaction with oxalyl chloride/DMF. The alternative resin (Figure 13) was prepared by reaction of TentaGel S-Br with 4-(trifluoroacetyl) benzoic acid under Merrifield conditions. The attachments of the 4-(trifluoroacetyl)
benzoyl group to the resins were confirmed through IR spectra and by isolation of the acid from the resin by treatment of the resin with trifluoroacetic acid in ethyl acetate.

3.15 Conclusion

There were problems in the synthesis of some of the esters in the original group, but a suitable range of ketones were obtained from the parent structure of $\alpha,\alpha,\alpha$-trifluoroacetophenone to partake in evaluation.

The reactivity of the resin bound esters is of particular importance as a resin bound dioxirane has never been generated and used \textit{in situ} before.

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1 It must be noted that initial research and synthesis of the resin bound ketones was by Dr T. Boehlow and published.\textsuperscript{128} The synthesis of the resins has been included as I continued evaluation of the TentaGel resin bound ketone and have subsequently synthesised the resin myself.
3.2 Oxidations with New Achiral Catalysts

3.21 Epoxidation Reactions

A system was needed that gave optimum yields with the chosen fluoroketone family, which could be easily utilised in laboratory conditions. A biphasic system was attractive because work-up would be easily achieved.

In previous in situ biphasic studies (pre 1995) investigations by Curci et al.\textsuperscript{7,13,23} and in previous work in our group, there had always been a need to keep the pH at about 7.5-8.0. Although this method gives good conversions in oxidation\textsuperscript{55} the procedure required use of a pH stat, which is time consuming when the reactions are set up. Armstrong and co-workers\textsuperscript{53} reported that the use a pH stat was not required. Instead sodium hydrogen carbonate was added in one portion to the reaction vessel to buffer the system. However, the reported percentage conversions were lower (GC-MS) than described by Curci\textsuperscript{7} and Denmark\textsuperscript{55}.

The general procedure for in situ oxidation is simple, however there many differences in the ratio of reagents used (typically using molar equivalents, except for the solvent system that is in volume). Reported procedures of Curci\textsuperscript{24}, Denmark\textsuperscript{55}, Armstrong\textsuperscript{53}, Muxworthy\textsuperscript{65} and Yang\textsuperscript{47} are tabulated below (Table 6). It is noted that Yang uses acetonitrile rather than DCM, which leads to a monophasic system (see chapter 1 and later) rather than a biphasic system.
Various reactions were ran altering the ratios of Oxone®, ketone and sodium hydrogen carbonate (based on the information in Table 6) were attempted using α,α,α-trifluoroacetophenone, 4-tert butyl cyclohexanone (Armstrong’s reported ketone) and acetone (the standard ketone used for in situ reactions) to oxidise cyclohexene (Table 7). It was observed (Table 7) that the blank (reaction run in the absence of ketone), acetone and 4-tert-butyl cyclohexanone catalysed reactions gave comparable percentage conversions in each of the systems α,α,α-Trifluoroacetophenone was the most reactive catalyst in all of the systems that indicated the trifluoro group helped in the formation of a dioxirane during the procedure.
### Table 7- In situ oxidation of cyclohexene

<table>
<thead>
<tr>
<th>Method</th>
<th>Conversion after 3 hours</th>
<th>Conversion after 6 hours</th>
<th>Ketone used</th>
<th>Temp</th>
<th>Organic/aqueous Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaHCO$_3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:1 1 2 3 4</td>
<td>6%</td>
<td>10%</td>
<td>4-tert butyl cyclohexanone</td>
<td>0°C</td>
<td>1 1</td>
</tr>
<tr>
<td>1 1 1 2 3 4</td>
<td>12%</td>
<td>17%</td>
<td>trifluoro-acetophenone</td>
<td>0°C</td>
<td>1 1</td>
</tr>
<tr>
<td>1 1 1 2 3 4</td>
<td>7%</td>
<td>11%</td>
<td>Acetone</td>
<td>0°C</td>
<td>1 1</td>
</tr>
<tr>
<td>1 0 1 2 3 4</td>
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<td>9%</td>
<td>Blank</td>
<td>0°C</td>
<td>1 1</td>
</tr>
<tr>
<td>1 5 1 2 3 4</td>
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<td>8%</td>
<td>4-tert butyl cyclohexanone</td>
<td>0°C</td>
<td>1 1</td>
</tr>
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<td>1 5 1 2 3 4</td>
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<td>1 1</td>
</tr>
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<td>47%</td>
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<td>1 7</td>
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<td>1 7</td>
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<td>49%</td>
<td>Acetone</td>
<td>0°C</td>
<td>1 7</td>
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<td>48%</td>
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<td>61%</td>
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<td>89%</td>
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</tr>
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<td>69%</td>
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<td>rt</td>
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<td>46%</td>
<td>65%</td>
<td>Blank</td>
<td>rt</td>
<td>1 7</td>
</tr>
</tbody>
</table>

Equipment and stirring speed was standardised after a brief study on a report by Ford et al.$^{133}$
The observation of high blank reactions were contradictory to previously reported non-catalysed reactions \(^2\), \(^5\), \(^3\), \(^4\) Therefore due to these results, which were constantly obtained, the procedure could not be used for further development of a dioxirane-mediated processes, as the Oxone\(^\circ\) is acting as the oxidant rather than the dioxirane \(^1\)

In chapter 1, the work of Yang and co-workers using the acetonitrile-water-sodium hydrogen carbonate monophasic system was discussed \(^4\), \(^6\), \(^3\) It was thought that this new monophasic system was worth investigation using our fluoro aromatic ketone family since the biphasic system was proving to be difficult to control

Preliminary work by V Waddington in these laboratories established that trans-stilbene could be readily oxidised (96% conversion) using Yang's monophasic system with \(\alpha,\alpha,\alpha\)-trifluoroacetophenone. Also, the corresponding 4-(trifluoroacetyl) benzoic acid gave 97% conversion to the oxide. Importantly, in the absence of a ketone catalyst little conversion (4%) to the oxide was obtained.

This preliminary study has been continued and developed using \(\alpha,\alpha,\alpha\)-trifluoroacetophenone, 4-(trifluoroacetyl) benzoic acid and methyl 4-(trifluoroacetyl) benzoate (often referred to as methyl ester) (Figure 12) as catalysts with a variety of alkene substrates.

### 3.21.1 Monophasic system results

A set of experiments was undertaken, using our newly adopted monophasic system. The substrates and fluoroketones were investigated systematically. The results are in Table 8

It was concluded from Table 8 that most of the substrates investigated gave a good percentage conversion to their corresponding epoxide after 24 hours. Trans-Stilbene gave the best conversion when the methyl ester was used and least when \(\alpha,\alpha,\alpha\)-
trifluoroacetophenone was used. Yet, cis-stilbene gave good results with all three fluoroketones. Therefore this confirmed that a cis-alkene is usually more reactive towards dioxirane oxygen transfer than a trans-alkene. Cholesterol seemed to be less efficient with α,α,α-trifluoroacetophenone and most reactive with 4-(trifluoroactyl) benzoic acid. 

Trans-Chalcone is an anomalous result compared to the other substrates investigated, it gave only low conversions with our ketone family, although in the original Yang et al paper, trans-chalcone gave an isolated yield of 99%. However this was oxidised by in situ generated methyl(trifluoromethyl)dioxirane, which is known to be a powerful oxidant and obviously more reactive than our fluoroketones. Some of the trans-chalcone results are very close to the blanks therefore it was presumed that there was little or no epoxidation occurring via the dioxirane owing to the electron deficiency of the double bond. As expected trans-chalcone gave total conversion with all three fluoroketones. Tri-O-acetyl glucal also reacted well with all three ketones. Cyclohexene had low reactivity with the fluoroketones. 4-(Trifluoroacetyl) benzoic acid and methyl 4-(trifluoroacetyl) benzoate gave almost negligible results and α,α,α-trifluoroacetophenone gave only moderate conversion. The low reactivity may be due to the low solubility of cyclohexene in the system. When following this monophasic procedure using cyclohexene it was observed that when a large quantity of cyclohexene is used the substrate stuck to the wall of the flask in globules, rather than mixing into the homogeneous system. This immiscibility of the system is difficult to observe on a smaller scale.
### Table 8- Monophasic oxidation results

<table>
<thead>
<tr>
<th>Substrates</th>
<th>α,α,α-Trifluoroacetophenone</th>
<th>4-(trifluoroacetyl) benzoic acid</th>
<th>Methyl 4-(trifluoroacetyl) benzoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans-Stilbene a</td>
<td>24 h = 70%</td>
<td>24 h = 81%</td>
<td>24 h = 91%</td>
</tr>
<tr>
<td></td>
<td>48 h = 80%</td>
<td>48 h = 79%</td>
<td></td>
</tr>
<tr>
<td>cts-Stilbene a</td>
<td>24 h = 100%</td>
<td>24 h = 100%</td>
<td>24 h = 97%</td>
</tr>
<tr>
<td></td>
<td>48 h = 100%</td>
<td>48 h = 100%</td>
<td></td>
</tr>
<tr>
<td>Cholesterol b</td>
<td>24 h = 52%</td>
<td>24 h = 100%</td>
<td>24 h = 72%</td>
</tr>
<tr>
<td></td>
<td>48 h = 61%</td>
<td>48 h = 100%</td>
<td></td>
</tr>
<tr>
<td>trans-Chalcone a</td>
<td>24 h = 11%</td>
<td>24 h = 34%</td>
<td>24 h = 7%</td>
</tr>
<tr>
<td></td>
<td>48 hr = 15%</td>
<td>48 h = 27%</td>
<td></td>
</tr>
<tr>
<td>trans-Chalcol b</td>
<td>24 h = 100%</td>
<td>24 h = 100%</td>
<td>24 h = 100%</td>
</tr>
<tr>
<td>Tri-O-acetyl glucal a</td>
<td>24 h = 100%</td>
<td>24 h = 100%</td>
<td>24 h = 100%</td>
</tr>
<tr>
<td>Cyclohexene a</td>
<td>24 h = 38%</td>
<td>24 h = 5%</td>
<td>24 h = 0%</td>
</tr>
</tbody>
</table>

Reactions in the absence of ketone gave little or no conversion (<5%) with the exception of trans-chalcone. Reactions were run in a 15:1 acetonitrile/EDTA solution (4x 10^-3 M), 1 equivalent of alkene, 5 equivalents of ketone, 5 equivalents of Oxone®, 15 5 equivalents of NaHCO₃ at rt.

a) Yields were obtained from GLC analysis of the crude reaction mixture

b) Yields were obtained from proton NMR analysis of the crude reaction mixture

The rate of stirring and equipment used was standardised.
3.21.2 Biphasic system results

Whilst monophasic conditions were being investigated alternative biphasic systems were also developed. These reactions were run under the same conditions as the monophasic system. Acetonitrile was replaced with dichloromethane and a catalytic amount of PTC was added. The results are tabulated in Table 9. Some preliminary results were initially reported by V. Waddington. A trend that is indicated in the observed results (Table 9) is that methyl 4-(trifluoroacetyl) benzoate has a greater reactivity towards the chosen substrates in each case (except for trans-chalcone). A possible explanation to these observed results maybe due to the methyl ester being slightly more soluble in the organic layer of the reaction mixture than a,a,a- trifluoroacetophenone or 4-(trifluoroacetyl) benzoic acid. Trans-chalcone again gave unusually high blanks that were almost comparable to values obtained in the catalysed system. Reactions were not attempted using 4-(trifluoroacetyl) benzoic acid and methyl 4-(trifluoroacetyl) benzoate as catalysts for trans-chalcon and tri-o-acetylglucal due to low conversion values obtained when a,a,a- trifluoroacetophenone was used. Therefore it was considered not valid to running these reactions. In the majority of acid-catalysed reactions the percentage conversions obtained were low. As the biphasic system is complex a possible explanation is that 4-(trifluoroacetyl) benzoic acid could be present in the aqueous layer as the sodium salt therefore not available to react with the substrate to be oxidised in the organic layer.
Table 9-Biphasic oxidation results

<table>
<thead>
<tr>
<th>Substrates</th>
<th>$\alpha,\alpha,\alpha$-Trifluoro-acetophenone</th>
<th>4-(trifluoroacetyl) benzoic acid</th>
<th>Methyl 4-(trifluoroacetyl) benzoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans-Stilbene</td>
<td>24 h = 32%</td>
<td>24 h = 11%</td>
<td>12 h = 90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 h = 98%</td>
</tr>
<tr>
<td>cis-Stilbene</td>
<td>12 h = 77%</td>
<td>48 h = 36%</td>
<td>24 h = 99%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>24 h = 76%</td>
<td>24 h = 69%</td>
<td>24 h = 100%</td>
</tr>
<tr>
<td>trans-Chalcone</td>
<td>24 h = 11%</td>
<td>24 h = 21%</td>
<td>24 h = 8%</td>
</tr>
<tr>
<td>trans-Chalcone</td>
<td>24 h = &lt;5%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Tn-O-acetyl glucal</td>
<td>24 h = &lt;5%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cyclohexene</td>
<td>12 h = 55%</td>
<td>12 h = 65%</td>
<td>12 h = 98%</td>
</tr>
</tbody>
</table>

Reactions in the absence of ketone catalyst gave little or no conversion with the exception of trans-chalcone. Reactions were run in a 1:5 1 DCM/EDTA solution (4x $10^{-4}$M), 1 equivalent of alkene, 5 equivalents of ketone, 5 equivalents of Ozone®, 15 5 equivalents of NaHCO₃ and a catalytic amount of PTC at rt.

a) Yields were obtained from GLC analysis of the crude reaction mixture.
b) Yields were obtained from proton-NMR analysis of the crude reaction mixture.

The formation of a sodium salt of 4-(trifluoroacetyl) benzoic acid had to be overcome. Denmark and co-workers work 55 reported that it was possible to have the ketone catalyst acting as its own PTC in biphasic conditions. Therefore additional PTC would not be needed to 'ferry' Ozone® through to the organic phase, as the ketone would already be in the same phase as the Ozone®. This would lead to formation of the required dioxirane. 
and thus oxidation of the substrate. Therefore it was assumed that if there was more PTC (t-butylammonium hydrogen sulfate) to form the acid-ammonium quaternary salt instead of the acid-sodium salt, more epoxidation should occur. This was attempted by raising the amount of PTC used by a factor of four and the results gave a 53% conversion to trans-stilbene oxide, with a 3% blank, compared to 11% conversion when ordinary amounts of PTC was used (Table 9).

3.21.3 Monophasic Resin-bound ketone results

The resin-bound ketones were investigated in a monophasic system, using the same set of alkenes used during the study of the other fluoro aromatic ketones. The results are given in Table 10. It was found that the Tentagel S-Br resin-bound ketone (chapter 2, Figure 13) was a more efficient oxidising agent than the hydroxymethyl resin-bound ketone. The oxidations gave a better conversion when allowed to react over a longer period of time. Reactions were also run under blank conditions and negligible results were obtained. Trans-Chalcol and tri-O-acetyl glucal were not oxidised with hydroxymethyl resin-bound ketone.

3.21.4 Conclusion to in situ epoxidation work.

It was shown that our modified biphasic procedures were not useful, as the non-catalysed reactions gave high conversions. The monophasic reactions based on Yang's work were extremely useful and good conversions were mainly obtained with all our fluoroketones.

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The results are included for complete detail of our study into fluoroketone catalysed dioxirane oxidations.
family The biphasic system however is more complex and can often lead to poor conversions.

The two resin-bound ketones were found to be promising oxidising agents for *in situ* dioxirane generation. However, their oxidising potential needs to be explored further.

These results obtained from the fluoro aromatic ketone family were published.

**Table 10-Oxidations using resin-bound ketones as catalysts**

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Tentagel S-Br bound resin</th>
<th>Hydroxymethyl bound resin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Trans</em>-Stilbene&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48h = 97%</td>
<td>17h = 41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36h = 64%</td>
</tr>
<tr>
<td><em>Cis</em>-Stilbene&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48h = 61%</td>
<td>38h = 51%</td>
</tr>
<tr>
<td>Cholesterol&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48h = 76%</td>
<td>48h = 37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48h = 70% at 0°C</td>
</tr>
<tr>
<td><em>Trans</em>-chalcone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48h = 13%</td>
<td>48h = 9%</td>
</tr>
<tr>
<td><em>Trans</em>-chalcol&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48h = &gt;90%</td>
<td>-</td>
</tr>
<tr>
<td>Tri-O-acetyl glucal&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48h = 80%</td>
<td>-</td>
</tr>
</tbody>
</table>

Reactions in the absence of ketone catalyst gave little or no conversion with the exception of *trans*-chalcone. Reactions were run in a 1:5 1 DCM/EDTA solution (4x 10^-4M), 1 equivalent of alkene, either 2 equivalents of Tentagel S-Br bound resin or 6 equivalents of hydroxymethyl bound resin, 5 equivalents of Oxone®. 15 5 equivalents of NaHCO₃ at rt unless stated.

a) Yields were obtained from GLC analysis of the crude reaction mixture.
b) Yields were obtained from proton NMR analysis of the crude reaction mixture.
3.22 Effect of light and pH on selected reactions

As the monophasic system investigated gave a reliable oxidation system\textsuperscript{128} it was decided to extend the scope of our system

3.22.1 Exclusion of UV decomposition

Initial focus was investigation of reactions run in the absence of light. This was chosen because solutions of dimethyldioxirane are protected from light, as exposure to UV radiation can cause exothermic decomposition of the dioxirane\textsuperscript{1,2,3} The decomposition of Oxone\textsuperscript{®} was also thought to be UV activated Therefore if it was possible to inhibit Oxone\textsuperscript{®} decomposition due to removal of UV radiation, the process could become more powerful in the oxidation of substrates.

Table 11 shows a comparison of some of the previous epoxidation results and one oxidation of benzhydrol where no attempt was made to exclude light with those where reaction flasks were enclosed in foil

It was found (Table 11) that benzhydrol and \textit{trans}-chalcone gave a considerable improvement of oxidation However the most dramatic result was for \textit{trans}-stilbene using the TentaGel resin-bound ketone, which gave a 61-76\% conversion to the epoxide after only 6 hours, whereas, previously a 97\% conversion was recorded after 48 hours reaction time. The hydroxymethyl resin-bound ketone was not reacted under these light excluded conditions

Curiously cholesterol conversions were much lower than our standard results, when both \textit{\alpha,\alpha,\alpha}-trifluoroacetophenone and methyl 4-(trifluoroacetyl) benzoate were used

These results suggested that our monophasic procedure should be modified to exclude light, which generally improved the oxidative potential of the system
Table 11- Comparison of oxidations in light excluded and light not excluded conditions

Non-catalysed reaction results are in parenthesis

<table>
<thead>
<tr>
<th>Substance</th>
<th>Light excluded Results</th>
<th>Light not excluded Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzhydrol</td>
<td>17% (0%)&lt;sup&gt;1, a, e&lt;/sup&gt;</td>
<td>8.7% (0%)&lt;sup&gt;1, a, e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>1% (1%)&lt;sup&gt;2, a, e&lt;/sup&gt;</td>
<td>3% (1%)&lt;sup&gt;2, a, e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trans-Chalcone</td>
<td>20% (0%)&lt;sup&gt;1, a, d&lt;/sup&gt;</td>
<td>11% (8%)&lt;sup&gt;1, a, e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>12% (0%)&lt;sup&gt;2, a, e&lt;/sup&gt;</td>
<td>11% (8%)&lt;sup&gt;2, a, e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trans-Stilbene</td>
<td>61% (0%)&lt;sup&gt;1, b, d&lt;/sup&gt;</td>
<td>97% (0%)&lt;sup&gt;1, b, e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>76% (0%)&lt;sup&gt;1, b, d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>34% (0%)&lt;sup&gt;1, a, e&lt;/sup&gt;</td>
<td>52% (0%)&lt;sup&gt;1, a, e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>36% (0%)&lt;sup&gt;1, c, e&lt;/sup&gt;</td>
<td>72% (0%)&lt;sup&gt;1, a, e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1) Monophasic conditions were used. 2) Biphasic conditions were used, a) reaction with α,α,α-trifluoroacetophenone, b) reaction with TentaGel resin-bound ketone, c) reaction with methyl 4-(trifluoracetyl) benzoate, d) 6 hour reaction time, e) 24 hour reaction time f) 48 hour reaction time

3.22.2 pH Dependence of dioxirane formation

When Shi et al used their fructose derived ketone (14) a powerful catalytic system was obtained when the pH of the system was raised<sup>77, 135</sup>. Therefore it was suggested that a raised pH could possibly improve conversions of olefins to their corresponding epoxides.

Shown in Table 12 are the results of our observations on oxidations by changing the pH.
The results that were obtained indicated that for $\alpha,\alpha,\alpha$-trifluoroacetophenone the pH conditions and equivalents that were previously used were already satisfactory and no improvement was observed when the pH was raised.

Table 12- Comparison of oxidations as pH is altered

<table>
<thead>
<tr>
<th>Substrate</th>
<th>% Conversion</th>
<th>pH before Oxone®</th>
<th>pH during Oxone®</th>
<th>pH after Oxone®</th>
<th>pH end reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans-stilbene ¹,a</td>
<td>100%</td>
<td>2.36</td>
<td>7.8</td>
<td>7.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Trans-stilbene ²,a</td>
<td>76%</td>
<td>9.6</td>
<td>10.6</td>
<td>10.1</td>
<td>9.8</td>
</tr>
<tr>
<td>Trans-stilbene ³,a</td>
<td>73%</td>
<td>10</td>
<td>9.8</td>
<td>9.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Trans-stilbene ⁴,a</td>
<td>69%</td>
<td>9.9</td>
<td>9.7</td>
<td>8.9</td>
<td>8.6</td>
</tr>
<tr>
<td>Trans-stilbene ³,b</td>
<td>4%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Trans-stilbene ³,b</td>
<td>54%</td>
<td>5.2</td>
<td>8.0</td>
<td>7.9</td>
<td>7.8</td>
</tr>
<tr>
<td>Trans-Chalcone ³,a</td>
<td>0%</td>
<td>10.2</td>
<td>9.8</td>
<td>9.8</td>
<td>9.8</td>
</tr>
<tr>
<td>Cholesterol ³,a</td>
<td>0%</td>
<td>10.1</td>
<td>9.8</td>
<td>9.8</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Monophasic conditions, 1 equivalent substrate 5 equivalent ketone 5 equivalent Oxone® 15.5 equivalent NaHCO₃ Shi conditions, 1 equivalent substrate 0.3 equivalent ketone 1.38 equivalent Oxone® 5.8 equivalents K₂CO₃ 0.04 equivalents PTC

1) Monophasic conditions, 2) Shi pH conditions, 0.3 equivalents of ketone, 3) Shi pH conditions, 5 equivalents of ketone, 4) Shi pH conditions, monophasic equivalents

a) Reaction with $\alpha,\alpha,\alpha$-trifluoroacetophenone, b) reaction with 4-(trifluoroacetyl) benzoic acid
3.22.3 Conclusion

It was concluded through our work\textsuperscript{128} and Shi \textit{et al}\textsuperscript{77} that different ketone catalysts must be effectively “tuned” to optimise their oxidative property, thus making it increasingly difficult to find an overall general ketone for synthetic use.

3.3 Oxidations other than Epoxidation

It has been previously observed that there are limited references for the oxidation of substrates other than alkenes in \textit{in situ} dioxirane system (page 12), usually isolated dimethyldioxirane and methyl(trifluoromethyl)dioxirane are used for oxidation of a variety of substrates. Therefore to expand the investigation of trifluoroketones, in particular $\alpha,\alpha,\alpha$-trifluoroacetophenone (TFAP) and the TentaGel resin-bound ketone, it was decided to examine the oxidation of secondary alcohols because there had been some success previously with benzhydrol oxidation. A C-H bond insertion (\textit{cis-decalin}) and an allylic alcohol (cinnamyl alcohol) were also chosen for investigation.

The results that were obtained are tabulated (Table 13).

The data obtained gave evidence that $\alpha,\alpha,\alpha$-trifluoroacetophenone was an overall better catalyst to use than the TentaGel resin-bound ketone and 4-(trifluoroacetyl) benzoic acid. When methyl 4-(trifluoroacetyl) benzoate was used as a catalyst for oxidation of phenylethanol a conversion of 28\% was obtained; this result was similar to that obtained when $\alpha,\alpha,\alpha$-trifluoroacetophenone was used. Given the similarity of this result and previous epoxidation results\textsuperscript{128} methyl 4-(trifluoroacetyl) benzoate was not investigated further.

The TentaGel resin-bound ketone and 4-(trifluoroacetyl) benzoic acid had unexplained poor reactivity with all of the secondary alcohols tested.
Table 13-Comparison of trifluoroketones in oxidising alcohols, allylic alcohols and alkanes

<table>
<thead>
<tr>
<th>Substrate/Product</th>
<th>TFAP</th>
<th>Tentagel Resin</th>
<th>4-(trifluoroacetyl) benzoic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenyl ethanol</td>
<td>29% (3%) (cf methyl 4-(trifluoroacetyl) benzoate =28%)</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Benzhydrol</td>
<td>17%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Cyclopropyl benzyl alcohol</td>
<td>19%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Cinnamyl alcohol</td>
<td>2hr= 75% (12%) 24hr= 99% (59-80%)</td>
<td>91%</td>
<td>99%</td>
</tr>
<tr>
<td>Cis-Decalin</td>
<td>58%</td>
<td>6%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Monophasic conditions with exclusion of light for 24 hours unless stated. Non-catalysed reaction values were negligible, except for those in parentheses. Conversions determined by GLC.
The reaction with cis-decalin gave good oxidation results when \( \alpha,\alpha,\alpha \)-trifluoroacetophenone was used as the ketone catalyst. However, cis-decalin is particularly receptive to C-H bond insertion and other substrates should be explored further with \( \alpha,\alpha,\alpha \)-trifluoroacetophenone.

The allylic alcohol, cinnamyl alcohol gave readily epoxidised results with all the trifluoroketones tested and was also reactive enough to be oxidised by Oxone\(^\text{®}\) itself. However, better values were obtained when reaction time was reduced to 2 hours and an acceptable blank (12%) was obtained.

In conjunction with these results, a final year undergraduate student (D. Hobson) investigated \( \alpha,\alpha,\alpha \)-trifluoroacetophenone to catalyse the oxidation of another set of secondary alcohols. The results that were obtained are tabulated (Table 14).

As with isolated dimethyldioxirane oxidation of cyclopropylcarbinols\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) the oxidation of cyclopropylbenzylic alcohol (Table 13) and \( \alpha \)-methylcyclopropanemethanol (Table 14) gave no evidence (GLC) of ring opening (Scheme 26). This adds further support to an electrophilic oxidation mechanism (see chapter 1) rather than one involving free radicals.

\[ \text{Scheme 26} \]

\[ \text{Proposed radical and electrophilic pathways for C-H bond insertion} \]
Table 14-Oxidation of alcohols using α,α,α-trifluoroacetophenone

<table>
<thead>
<tr>
<th>Substrate/ Product</th>
<th>% conversion using TFAP after 18 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Methylcyclopropanemethanol</td>
<td>35%</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>15%</td>
</tr>
<tr>
<td>Cyclohexanol</td>
<td>7%</td>
</tr>
<tr>
<td><em>Endo</em>-Norborneol</td>
<td>38%</td>
</tr>
<tr>
<td>3β-Cholestanol</td>
<td>0%</td>
</tr>
</tbody>
</table>

Work by D Hobson, with confirmation of α-methylcyclopropanemethanol by myself.

Standard monophasic conditions, excluding light were used. All non-catalysed reactions less than 2% oxidation.
3.31 Conclusion

Both sets of results (Table 13 and 14) showed that α,α,α-trifluoroacetophenone will catalyse oxidation of secondary alcohols, although the conversions are generally poor compared to epoxidations and tertiary C-H bond insertions. However no attempts were undertaken to optimise conditions such as pH and concentration to effectively ‘tune the catalyst’ Therefore it seemed that for secondary alcohols the oxidation applications are limited for α,α,α-trifluoroacetophenone compared to isolated dimethyldioxirane. However this would allow the in situ procedure to be used as a regioselective epoxidation method and a possible useful alternative to isolated dimethyldioxirane if an alkene and an alcohol were both present in a substrate. It may be that the relatively sluggish alcohol oxidation is in part owed to the aqueous environment disrupting the intramolecular hydrogen bonding between the alcohol function and the electrophilic dioxirane (see later)
3.4 **Epoxidations of Allylic Alcohols**\(^{137}\)

Reactions of allylic alcohols with *in situ*-generated dioxiranes are relatively few and are complicated by reaction with Oxone\(^*\) directly \(^{70, 78, 138, 139}\). Although such direct reaction may in some cases be avoided by adjusting the pH of the reaction medium\(^{78}\), little detailed mechanistic evaluation has been reported. Recent work\(^ {70, 138, 139}\) suggested that diastereoselectivity and regioselectivity in direct Oxone\(^*\) mediated epoxidation are determined by intramolecular hydrogen bonding in cyclohexanols (25 and 26) and 1-methylgeraniol (31), although in all of these reactions low conversions were observed.

These results lead us to evaluate geraniol (32), isophorol (27), 3-phenylcyclohex-2-en-1-ol (28) and the related acetates (29, 30, 33)

![Chemical structures](image)

\[
25 \text{ R}_1=\text{R}_2=\text{R}_3=\text{H} \\
26 \text{ R}_1=\text{R}_2=\text{H}, \text{ R}_3=\text{Me} \\
27 \text{ R}_1=\text{H}, \text{ R}_2=\text{R}_3=\text{Me} \\
28 \text{ R}_1=\text{R}_2=\text{H}, \text{ R}_3=\text{Ph} \\
29 \text{ R}_1=\text{Ac}, \text{ R}_2=\text{R}_3=\text{Me} \\
30 \text{ R}_1=\text{Ac}, \text{ R}_2=\text{H}, \text{ R}_3=\text{Ph} \\
31 \text{ R}_1=\text{H}, \text{ R}_2=\text{Me} \\
32 \text{ R}_1=\text{R}_2=\text{H} \\
33 \text{ R}_1=\text{Ac}, \text{ R}_2=\text{H} \\
34 \text{ R}_1=\text{TBS}, \text{ R}_2=\text{H} \\
35 \text{ R}_1=\text{Me}, \text{ R}_2=\text{H}
\]
3.41 Cyclohexene Epoxidations

The reactions were run in a non-catalysed and an α,α,α-trifluoroacetophenone catalysed system. The results of the epoxidation reactions are shown in Table 15.

**Table 15—Results of cyclohexene epoxidation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time</th>
<th>Temp</th>
<th>% Conversion</th>
<th>cis trans epoxides</th>
<th>% conversion</th>
<th>cis trans epoxides</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>24 h</td>
<td>rt</td>
<td>100</td>
<td>14 86</td>
<td>80</td>
<td>74 26</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>45 h</td>
<td>0°C</td>
<td>91</td>
<td>21 79</td>
<td>38</td>
<td>69 31</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>15 h</td>
<td>0°C</td>
<td>82</td>
<td>22 78</td>
<td>25</td>
<td>71 29</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>24 h</td>
<td>rt</td>
<td>100</td>
<td>19 81</td>
<td>10</td>
<td>21 79</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>15 h</td>
<td>0°C</td>
<td>50*</td>
<td>25 75</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>24 h</td>
<td>rt</td>
<td>100</td>
<td>53 47</td>
<td>100</td>
<td>97 3</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>24 h</td>
<td>rt</td>
<td>100</td>
<td>43 57</td>
<td>10</td>
<td>50 50</td>
</tr>
</tbody>
</table>

*Somewhat variable but consistently < that for alcohol*

Conversions and ratios determined by $^1$H-NMR spectra of the crude mixtures.

Oxidations in Table 15 were run by Dr. R. C. Toon, with the exception of the isolation and characterisation of trans-2,3-epoxy-3-phenylcyclohexanol and trans-1-(acetoxy)-2,3-epoxy-3-phenylcyclohexane.
The greater conversions for the partial reactions of 3-phenylcyclohex-2-en-1-ol (28) versus its acetate (30) (Table 15 entries 3 and 5) presumably arise from the lower nucleophtlticity of the double bond which is due to the greater electron withdrawing properties of OAc verses OH. The high trans-selectivity for (28) and the much lower selectivity for (27) confirmed the controlling importance of steric effects rather than intramolecular hydrogen bonding for in situ dioxirane epoxidations. The trans-selectivity might be expected to be greater than that observed were it not for background cis-selective and intramolecular hydrogen bond-mediated direct reactions with Oxone® (Table 15 entries 1 and 6). However, this looks to be only significant for (27) and may be a reflection of the greater rate of the catalysed reaction for (28) versus (27), the latter being subject to much more steric hindrance to approach on the trans-face.

In general the direct Oxone® reactions with (27 and 28) are relatively slow and the reactions with the acetates (29 and 30) even slower. Both of the acetates show similar trans-selectivity in the α,α,α-trifluoroacetophenone mediated and direct Oxone® reactions (Table 15 entries 4 and 7) in contrast to the parent alcohols (27 and 28) where intramolecular hydrogen bonding facilitates the cis-selectivity for the direct reaction. It is clear that Oxone® is a reasonable reagent in its own right for epoxidation but particularly for allylic alcohols.

The presence of the bulky phenyl group in the dioxirane generated from α,α,α-trifluoroacetophenone seemed to have a minor effect on diastereoselectivity. Since, with isophorol (27) this [53:47, cis: trans] is not markedly different from that observed [62:38] with isolated dimethyldioxirane in acetone:methanol solvent system (1:9) in which the effects of intramolecular hydrogen bonding are minimised. Furthermore, the high trans-selectivity [86:14] for the reaction of (28)
in α,α,α-trifluoroacetophenone mediated reactions is similar to that observed [82 18] for the reaction of dimethyldioxirane in the same solvent with 3-methylcyclohex-2-en-1-ol (26) \(^{146}\). *In situ* reactions for (26) with a variety of ketones excluding acetone and cyclohexanone gave *trans*-selectivities >74% and that closest to the α,α,α-trifluoroacetophenone value with (28) was with 1,3-dichloropropanone \(^{139}\). The results with α,α,α-trifluoroacetophenone are probably best explained through the spiro transition states depicted in Figure 15 in which the phenyl group is remote from the ring substituent (\(R_3\)) \(^{128,147}\). Polar effects appear to make no major contributions to diastereoselectivity \(^{139}\).

**Figure 15**

**Predicted spiro transition states**

### 3.42 Geraniol and geranyl acetate epoxidations

Shi *et al* reported \(^{78}\) that background epoxidation of geraniol (32) by Oxone\(^{®}\) reduced the enantioselectivity in using the catalyst (14).

The reactions were run in a non-catalysed and a α,α,α-trifluoroacetophenone catalysed system. The results of the epoxidation reactions are shown in Table 16. These results (Table 16) confirm that Oxone\(^{®}\) readily oxidises both double bonds of
geraniol (32) and suggested that the 6,7-double bond oxidises first. We have used considerably more Oxone® than Shi et al in accordance with our previously published procedure with α,α,α-trifluoroacetophenone128 and did not detect the 2,3-epoxide (36)

As expected from observations with geranyl TBS ether (Figure 16, number 21), the acetate (20) was much less reactive with Oxone® than geraniol (Table 16, entries 1, 2 and 4) However, even this can be used to oxidise the 6,7-double bond essentially to give (25, R=Ac) (Table 16, entry 5) The use of α,α,α-trifluoroacetophenone allows complete oxidation of geraniol (32) to the bis-epoxide (38, R=H) at 0°C in 2 hours (Table 16, entry 2) The greater nucleophilicity of the 6,7-double bond seemed to be the controlling feature in all of these reactions in common with those observed in the reactions of geraniol (32) and its methyl ether (35) with dimethyldioxirane in acetone methanol solvent system (1 9) 82,144,148
Table 16-Results of geraniol epoxidation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time h</th>
<th>Temp</th>
<th>% conversion</th>
<th>% 6,7-epoxide</th>
<th>% bis-epoxide</th>
<th>OXIDANT:</th>
<th>% conversion</th>
<th>% 6,7-epoxide</th>
<th>% bis-epoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>1</td>
<td>0°C</td>
<td>89</td>
<td>46</td>
<td>43</td>
<td>TFAP/Oxone®</td>
<td>84</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>2</td>
<td>0°C</td>
<td>100</td>
<td>Trace</td>
<td>&gt;97</td>
<td>Oxone®</td>
<td>93</td>
<td>34</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>24</td>
<td>rt</td>
<td>100</td>
<td>0</td>
<td>&gt;99</td>
<td>Oxone®</td>
<td>100</td>
<td>0</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>2</td>
<td>0°C</td>
<td>76</td>
<td>76</td>
<td>-</td>
<td>Oxone®</td>
<td>15</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>24</td>
<td>rt</td>
<td>100</td>
<td>41</td>
<td>59</td>
<td>Oxone®</td>
<td>100</td>
<td>98</td>
<td>2</td>
</tr>
</tbody>
</table>

Conversions and ratios determined by proton-NMR spectra of the crude mixtures
3.5 Case study on Carvedilol

In continuation of the exploration in these laboratories\textsuperscript{128} of the potential of dioxiranes in oxidative degradation of nitrogenous drugs some reactions of Carvedilol (Figure 16) with \textit{in situ} and isolated dioxiranes have been investigated. Carvedilol is a cardiovascular drug having use in the treatment of hypertension, angina and heart failure and has a number of possible oxidation sites.

\textbf{Figure 16}

\textit{Hydrogens of interest and possible oxidation sites (OX) are labelled.}

3.51 \textit{In situ} dioxirane oxidation reactions

Initial oxidation reactions on Carvedilol were under our published monophasic conditions,\textsuperscript{128} using \(\alpha,\alpha,\alpha\)-trifluoroacetophenone as dioxirane catalyst in an \textit{in situ} monophasic system of acetonitrile/ aqueous EDTA solution. The reaction flask was covered in tinfoil to exclude light. Column chromatography was undertaken of the crude mixture to isolate the major product (Table 17, entry 1). The proton NMR spectrum of this isolated spot is very different to the
starting material The main difference was the absence of the aliphatic protons between δ 2.9 and δ 4.5. However, two other peaks appear in the new spectra at δ 4.7 and δ 4.9, both split into doublets. The new material is thought to be a possible mixture of two products owing to the appearance of what seems to be two methoxy peaks at δ 3.87 and δ 3.89. The absence of the H5 proton on the carbazole ring indicates that this part of the molecule is not present and has been fragmented during oxidation.

By GC/MS the purified sample shows two peaks with M/Z 181 and 163. However, the baseline is very uneven and thus difficult to quantify, this is thought to be due to the polarity of the fragments.

Initially a speculative structure (39) that fit the mass spectral data and the loss of the carbazole ring was proposed.

![Structural formula](image)

This could possibly arise from a hydroperoxide cleavage (Scheme 27).

However, this did not fit the proton NMR data, in which the protons H1 and H2 are at δ 4.7 and δ 4.9 and should be split into triplets. The COSY spectrum also showed no coupling between the protons at δ 4.7 and δ 4.9 and only coupling to low field protons.
Key bands in the IR spectrum are a very broad peak at 3424.5 cm\(^{-1}\) (OH moiety) and a very strong sharp signal at 1504 4 cm\(^{-1}\) (possibly R=N-, oxime type). There is another strong signal at 1253 3 cm\(^{-1}\) (possibly N-O type stretch).

In the \(^{13}\)C NMR spectrum there is only one peak for the methoxy carbon at 854.8, which is surprising since the proton spectrum suggests the possibility of two products. However, it may be possible that there are two isomers of the product. A peak in the \(^{13}\)C NMR at \(\delta 146.7\) is thought to be a possible oxime carbon signal, hence supporting IR data.

3.51.1 Conclusion

The data seemed to support that the isolated material is a mixture of oximes (syn and anti) (40). It is possible that dehydration to the nitrile (41) could occur in the injection port of the GC/MS thereby giving the minor peak at m/z 163 (Scheme 28)
Further support for this assignment was provided by the coupling constants of the CH\(_2\) doublet (H2) on the oximes (J=3.49\,Hz) and (J=2.2\,Hz), at \(\delta 4.7\) and \(\delta 4.9\) respectively. The COSY spectrum shows this coupling to a single proton (H1) at \(\delta 7.6\) (triplet, \(J=3.49\,\text{Hz}\)) and \(\delta 7.1\) (broad singlet).

The oximes may arise from the nitroso compound (42) through the hydroxylamine hydroperoxide (or persulphate) (43) as indicated in Scheme 29.

Other mechanisms are possible.
Possible fragmentation mechanism
3.52 Other in situ oxidations

The blank oxidation (oxidation in the absence of a ketone) gave exactly the same products by proton NMR (Table 17, entry 2). Therefore Oxone® was the main oxidative reagent and seemed to fragment Carvedilol. Many reactions were attempted that varied reaction conditions (reaction time, temperature, pH and amounts of Oxone® used) in an attempt to inhibit the non-catalysed system. However proton NMR evidence gathered on the crude products was the same as previously observed. It seemed as though Oxone® in our monophasic system is too powerful an oxidant in it’s own right for Carvedilol. All reactions completed on Carvedilol are summarised in Table 17.

4-(Trifluoroacetyl) benzoic acid (Figure 12) was also used as a catalyst (Table 17, entry 5) but after 5 hours at 0°C the crude NMR data showed the same fragmentation pattern. It was considered that may be reactions in a biphasic system would give greater control. Dichloromethane and a phase transfer catalyst as previously described in our work at 0°C in the absence of ketone and after only 1 hour gave the same NMR evidence as was previously observed (Table 17, entry 7).

3.52.1 Conclusion

It was concluded that the in situ system was not ideal to evaluate the effect of dioxirane oxidation on Carvedilol.

As the Oxone® oxidised the system in the absence of ketone, the oxidation potential of our substituted TentaGel resin-bound ketone could not be evaluated and no further investigation of the in situ system for Carvedilol oxidation was undertaken.
Table 17—Reactions run in an *in situ* system for the oxidation of Carvedilol

<table>
<thead>
<tr>
<th>Entry/ Catalyst</th>
<th>Reactions run</th>
<th>Analysis of crude product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1)</strong> Trifluoroacetophenone</td>
<td>Monophasic conditions, 24 hours at room temperature</td>
<td>Oxime</td>
</tr>
<tr>
<td><strong>2)</strong> Blank</td>
<td></td>
<td>Oxime</td>
</tr>
<tr>
<td><strong>3)</strong> Trifluoroacetophenone</td>
<td>Monophasic conditions, 5 hours in an ice bath</td>
<td>Oxime</td>
</tr>
<tr>
<td><strong>4)</strong> Blank</td>
<td></td>
<td>Oxime</td>
</tr>
<tr>
<td><strong>5)</strong> 4-(trifluoroacetyl) benzoic acid</td>
<td>Monophasic conditions, 1 hour in an ice bath</td>
<td>Oxime</td>
</tr>
<tr>
<td><strong>6)</strong> Blank</td>
<td>Biphasic conditions, 1 hour in an ice bath</td>
<td>Oxime</td>
</tr>
<tr>
<td><strong>7)</strong> Blank</td>
<td>Increased pH conditions (pH=10 5), 1½ hours in an ice bath</td>
<td>Oxime</td>
</tr>
<tr>
<td><strong>9)</strong> Trifluoroacetophenone</td>
<td>Monophasic conditions, 2 hours in an ice bath using 1 equivalent of Oxone®</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>10)</strong> Blank</td>
<td></td>
<td>Unknown</td>
</tr>
</tbody>
</table>
3.53 Isolated dioxirane oxidation reactions

It was decided to examine direct dioxirane oxidation by treatment with isolated dimethyldioxirane solution.

Carvedilol was treated with 1 equivalent of dimethyldioxirane solution in acetone; the proton NMR of the crude product showed that the whole molecule was intact and had not been fragmented as previously.

Some chemical shifts and other changes were noted including evidence that H4 had been shifted slightly down field to 84.5 but the evidence is inconclusive. These results suggested that a product could be the ketone derived from oxidation of the hydroxyl group. Evidence of this possible oxidation is in the 13C NMR spectrum of the crude product, which showed the presence of a carbonyl signal at 8211.

This reaction was also tried with 3 equivalents of dimethyldioxirane. The NMR spectrum of the crude product, although difficult to assess, showed that there may be a possibility of the methoxy peaks being duplicated suggesting multiple products from fragmentation again. As it seemed that 3 equivalents of dimethyldioxirane solution was too harsh for Carvedilol, a reaction was run with 2 equivalents added in two equal aliquots. The second aliquot was added after the first was consumed (starch iodide paper) NMR data of the crude product gave evidence that the molecule was being destroyed.

3.53.1 Conclusion

The use of isolated dimethyldioxirane solution seemed more promising than the in situ oxidation. However by column chromatography no pure product was isolated.
3.54 Other Peroxide Oxidations

Oxidations using benzoyl peroxide and t-butyl hydroperoxide\textsuperscript{122} were performed on Carvedilol. These have been summarised in Table 18.

Oxidation with benzoyl peroxide gave a complex mixture of products, whilst oxidation with t-butyl hydroperoxide showed varying amounts of oxidation depending on the quantity of oxidant used. The oxidation product with t-butyl hydroperoxide was clearly identifiable in the proton NMR spectrum and shows a distinct H5 doublet (δ 285) and separate methoxyl peak (δ 762). However, on standing the material appeared to decompose and \textsuperscript{13}C NMR spectra only showed traces of other than the starting material.

In addition Jones oxidation was also tried. A solid was obtained which was only sparingly soluble in DMSO and no other solvent. No proton NMR analysis was obtained due to paramagnetism (possibly due to chromium co-ordination).
Table 18-Other peroxide oxidations on Carvedilol

<table>
<thead>
<tr>
<th>TLC eluent, 20% methanol in ethyl acetate</th>
<th>Benzoyl peroxide</th>
<th>t-Butyl hydroperoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult to determine the number of products due to spreading up the plate</td>
<td>Several spots-$R_f$=0.71 (oxidation products-some seemingly common with DMD products) $R_f$=0.23 (starting material)</td>
<td>Starting material spreads</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NMR analysis</th>
<th>NMR analysis (CDCl₃) shows a complex mixture No starting material is evident</th>
<th>NMR analysis (CDCl₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 equivalent-12% oxidation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 equivalents-33% oxidation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 equivalents-47% oxidation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 equivalents-48% oxidation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 equivalents-24% oxidation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-signs of further degradation</td>
</tr>
</tbody>
</table>

| Observations | Orange solution which, on evaporation, gives a dark brown residue A repeat work-up, washing the crude in DCM with saturated sodium thiosulfate shows similar degradation | Clear, colourless residue NMR spectroscopic and TLC evidence of decomposition |

All the oxidations in Table 18 were performed by Dr R. C. Toon, they are included in this Chapter to complete the oxidation study of Carvedilol

* In Solvent system (75 35 25 8 5 v v v v v chloroform methanol acetone water acetic acid) there is less spreading but no well-defined product was apparent
CHAPTER 4
As indicated in chapter 1, there is still a need to improve and extend the chiral catalytic approach. The targets identified in chapter 2 were substituted systems of 1-indanone (16), 1-tetralone (17), 4-chromanone (18) and iso-4-chromanone (19).

4.1 Synthesis of Spiro-Indanone derivatives

The spiro-indanone (16, X=H) was synthesised by Dr. T. Boehlow as outlined in Scheme 30. Unfortunately when the catalyst was used in the monophasic system\textsuperscript{47, 128} and also in the higher pH conditions of Shi \textit{et al} (pH 10.5)\textsuperscript{78} no oxidation occurred with either \textit{trans}-stilbene or cholesterol.
However an X-ray structure was obtained (see appendix A), which showed the orientation of the methyl groups protecting one face of the carbonyl moiety and therefore suggests that it may provide appropriate enantioselectivity as a catalyst provided it could be further activated. Therefore the difluoro analogue (16, X=F) was thought to be a reasonable target.
It was proposed that the fluoroketone (16, X=F) would be synthesised by starting with difluorocinnamic acid by the synthetic route shown in Scheme 31.

Scheme 31

\[
\begin{align*}
\text{F-CO}_2\text{H} & \xrightarrow{\text{H}_2, \text{Pd/C}} \text{F-CO}_2\text{H} \quad \text{(44)} \\
\text{F-CO}_2\text{H} & \xrightarrow{\text{PPA, Heat}} \text{F} \quad \text{(45)} \\
\text{F} & \xrightarrow{\text{1) LDA/THF, 2) NCCO}_2\text{CH}_3, 3) H^+}} \text{F} \quad \text{(47)} \\
\text{F} & \xrightarrow{\text{NaBH}_4, \text{EtOH}} \text{F} \quad \text{(48)} \\
\text{F} & \xrightarrow{\text{Sodium dichromate}} \text{F} \quad \text{(16, X=F)}
\end{align*}
\]
Hydrogenation of 3,5-difluorocinnamic acid using 10% palladium on carbon catalyst in ethyl acetate gave 3-(3,5-difluorophenyl) propionic acid (44) This was cyclised by using polyphosphoric acid with gentle warming, to give 5,7-difluoroindanone (45) in 64% yield. Acylation using LDA followed, by the addition of Mander's reagent (NCCO₂CH₃) gave the required methyl 5,7-difluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (46), which after chromatography was sufficiently pure for the next stage.

Compound (46) was then allylated using sodium hydride in DMF and allyl bromide to yield the allyl-indanone, methyl 5,7-difluoro-1-oxo-2-prop-2-enyl-2,3-dihydro-1H-indene-2-carboxylate (47). Some difficulty was experienced in purification of (47) by chromatography. However, material sufficiently pure for the next step was obtained and reduction of this using sodium borohydride in ethanol gave the secondary alcohol, methyl 5,7-difluoro-1-hydroxy-2-prop-2-enyl-2,3-dihydro-1H-indene-2-carboxylate (48), which was more easily purified (yield 61%). Reaction of (48) with methyl magnesium bromide and with methyl lithium unfortunately was unsuccessful and gave no evidence of the desired product (49).

4.11 Evaluation of indanone derivative

Although the target (16, X=F) was unavailable some evidence of the reactivity of the related system (47) was tried.

It was decided to attempt an oxidation reaction of trans-stilbene using the fluoro allyl ketone (47). These oxidations were performed using our published conditions, but with the inclusion of a catalytic amount of phase transfer catalyst. However, due to limited quantities of ketone (47) only 3 equivalents were used instead of the usual 5.
equivalents and unfortunately no evidence of epoxidation was observed (proton NMR)

4.12 Conclusion

The lack of reactivity found in the spiro-indanone (16, X=H) and the difluoro-allyl ketone derivative (47) was disappointing in view of Walton’s observations of the use of α-fluoro-indanones (50) (100% conversion of trans-β-methylstyrene). However the result is in agreement with Armstrong and co-workers 5-membered ketone (Table 4, entry 5) which also gave no reaction. It has been suggested that the limited reactivity maybe due to enhanced strain in the five membered ring during dioxirane formation.

Therefore it was decided to investigate the use of spiro-tetralone which would be a more favoured six membered cyclic ketone.

\[ \text{(50)} \]

4.2 Synthesis and Evaluation of Spiro-Tetralone derivative

The spiro-tetralone derivative (17) (Scheme 32) was synthesised in a similar fashion to that used for the spiro-indanone (16)(Scheme 30).
Diethyl carbonate was used as the solvent for the acylation of α-tetralone (51) as described by Walton,\textsuperscript{66} after an hour a very thick deep lilac precipitate was formed. The reaction was cooled to room temperature and DMF was added to dissolve the precipitate. Extra sodium hydride was then added to ensure the deprotonation for allylation. Allyl bromide was added, the mixture was stirred at room temperature over night. Chromatography of the crude product, ethyl 1-oxo-2-prop-2-enyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (53) gave material contaminated with diethyl carbonate which was not removed prior to the next step. Reduction of this material using sodium borohydride in ethanol gave the secondary alcohol, ethyl 1-hydroxy-2-prop-2-enyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (54), in high yields (63\%) after column chromatography. The reaction of (54) with methyl lithium which had failed in the difluoroindanone (16, X=F) synthesis worked well and reasonable yields of 2-(1-hydroxy-1-methylethyl)-2-prop-2-enyl-1,2,3,4-tetrahydronaphthalen-1-ol (55) was obtained after purification (63\%). The secondary alcohol (55) was then oxidised to ketone (56) using a standard sodium dichromate method.\textsuperscript{156} This worked well and the product, 2-(1-hydroxy-1-methylethyl)-2-prop-2-enyl-1,2,3,4-tetrahydronaphthalen-1-one (56) was isolated in 64\% yield after purification. The final step of the spiro-tetralone (17) synthesis was the ozonolysis of (56).
Synthetic route to obtain the spiro-tetralone (17) derivative
After ozonolysis a variety of work-up procedures were attempted, including the use of triethylamine and acetic anhydride in methanol \(^{157}\) that would give the corresponding ester in situ \(^{(57)}\). Jones reagent was also tried.\(^{158, 159}\)

\[\text{OMe}\]

The most satisfactory was using the standard hydrogen peroxide procedure \(^{160}\). The ozonolysis product was then converted to the lactone \((17)\) by heating (80-110°C) with pTSA in toluene following the reaction by TLC. The crude material was filtered through either silica gel or charcoal and crystallised from hexane/ethyl acetate. Although the yield of crystalline lactone \((17)\) was low (10-16%), the spectroscopic evidence of the mother liquors suggested the presence of a further substantial amount of the desired lactone \((17)\). Purification of this was not further attempted following the disappointing evaluation of \((17)\) as a dioxirane catalyst (section 4.21).

An X-ray structure was obtained of the crystalline spiro-tetralone \((17)\) confirming its structure and the positioning of the methyl groups on the lactone ring protecting one face of the ketone carbonyl [cf. the indanone] (see appendix B).

4.21 Evaluation of Spiro-tetralone \((17)\) as a catalyst

Even though yields were low, enough spiro-tetralone \((17)\) was isolated to undertake a preliminary oxidation study.
The oxidation of trans-stilbene using the spiro-tetralone (17) as a catalyst for dioxirane formation was attempted, the results are shown in Table 19. Oxidation using α,α,α-trifluoroacetophenone and non-catalysed systems were used as reference oxidations.

It can be seen that the spiro-tetralone (17) gave a small amount of oxidation which was significant compared to that with the spiro-indanone (16, X=H), however compared to the catalyst of Shi and co-workers the conversions are very disappointing.

Table 19—Oxidation of trans-stilbene using (17)

<table>
<thead>
<tr>
<th>Method of reaction</th>
<th>Spiro-tetralone (17) % conversion</th>
<th>Comparison reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 equivalents of ketone</td>
<td>7%</td>
<td>Trifluoroacetophenone 99%</td>
</tr>
<tr>
<td>3 equivalents of ketone and PTC</td>
<td>10%</td>
<td>Blank 9%</td>
</tr>
<tr>
<td>3 equivalents of ketone</td>
<td>Trace</td>
<td>Trifluoroacetophenone 99%</td>
</tr>
<tr>
<td>5 equivalents of ketone and PTC</td>
<td>8%</td>
<td>Blank Trace</td>
</tr>
</tbody>
</table>

Oxidations were run under usual monophasic conditions (see experimental), changes made are noted in Table 19. Analysis was by GLC.
4.22 Conclusion

It was perceived that there were two options to improve activity of the ketone (a) by the addition of fluorine atoms around the tetralone ring and (b) by the inclusion of oxygen atoms in the ketone-containing ring, as effectively Shi et al had achieved in their fructose derived ketone catalyst (14) The second option was chosen as a priority given the possible difficulties of synthesis of the fluorinated derivatives as experienced in the indanone series The following sections deal with our attempts to synthesise 4-chromanone (18) and 4-iso-chromanone (19)

4.3 Synthesis of the Spiro-Chromanone (18) derivative

The spiro-chromanone (18) synthesis was undertaken to see if the extra reactivity of the oxygen and its similarity to Shi et al fructose catalyst would improve oxidation potential The synthetic route (Scheme 33) that was proposed was similar to that of the spiro-tetralone (Scheme 32), as reactivities were expected to be similar

The synthesis was started with acylation of the 4-chromanone (58) via the Walton method using distilled diethyl carbonate as the solvent An orange precipitate was formed under reaction conditions This was then allylated by addition of DMF to dissolve the precipitate followed by extra sodium hydride and 1.2 equivalents of allyl bromide The reaction mixture was worked up as usual, but it was not clear that the expected product (59) was present as the proton NMR spectrum was difficult to interpret
Scheme 33

Proposed synthetic route to spiro-chromanone (18)
In the expectation that the alcohol (60) would be easier to purify, reduction was undertaken with sodium borohydride in ethanol. After several attempts to chromatograph the product (60) only material which gave very broad uninterpretable peaks in the proton NMR spectrum was isolated.

In view of these unpromising results, a new route to the spiro 4-chromanone (18) was sought.

**4.31 New route to spiro-chromanone (18) derivative**

It was decided to build the substitution into the C-2 position before ring closure to obtain (59) and then return to Scheme 33 to synthesise (18). A relevant approach to Scheme 34 was found in the literature leading a series of chromanones related to our target (59). Although there was some difficulty reported in cyclising (using AlCl₃) an allyl derivative (61, R=CH₂CH=CH₂) owing to HCl addition of the double bond it was felt that a PPA-mediated cyclisation may be more promising.

![Scheme 34](image_url)

Z₁=H, Cl or Me
Z₂=H or Cl
R=Me, Et, CH₂CH₂CH(CH₃)₂ or CH₂CH=CH₂

*Literature procedure for 4-chromanone synthesis*
To obtain the relevant disubstituted chromanone (59) a synthetic route was proposed from literature procedures (Scheme 35)\(^{161, 163, 164}\). This method also seemed promising in providing the opportunity to obtain the optically active ketone through the resolved acid (path b, Scheme 35) which could be obtained by enzymatic hydrolysis\(^{162}\). However, attempts to follow the synthetic route for the preparation of (59) were unsuccessful and this approach was abandoned in favour of the 4-isochromanone (19) target.

**Scheme 35**

![Proposed synthetic route to (59)](attachment:image.png)
4.4 Synthesis of the spiro iso-chromanone (19) derivative

The spiro iso-chromanone derivative (19) was proposed as a good model for a catalyst as its structure had a number of structural features similar to the fructose derived catalyst (14) of Shi et al.

The preparation of the key intermediate (62) in our proposed synthetic route of the spiro iso-chromanone (Scheme 36) is reported in the literature (Scheme 37). \(^{165,166}\)

\[\text{Scheme 36}\]

Proposed Synthetic scheme for spiro iso-chromanone (19)
Scheme 37

\[
\text{Phthalide} + \text{Ph}_3\text{PCl}_2 \xrightarrow{180^\circ C, 4h} \text{PhCl} \xrightarrow{\text{EtOH} \ 50^\circ C, O/N} 49\%
\]

\[
\text{EtO} \xrightarrow{\text{Na}^+\text{OCH}_2\text{CO}_2\text{Et}} \xrightarrow{40\%} \text{EtO}
\]

\[
\text{(65)} \xrightarrow{\text{Dieckmann}} \text{(62)}
\]

**Synthetic route to carboxylated iso-chromanone (62)**

Preparation of ethyl 2-(chloromethyl) benzene-1-carboxylate (64) was effected by melting phthalide and dichlorotriphenylphosphorane together followed by treatment *in-situ* with ethanol to form the ester required (64) in a 49% yield. However, after isolation (one spot TLC) there was always an extra singlet peak (δ3 90ppm) present in the proton NMR spectrum. GC-MS showed this to be a small amount of the methyl ester, which co-elutes with the product during column chromatography.
But as the ester group is lost in the final step of the Dieckmann cyclization it was not seen as a problem.

The next step was the formation of the ester linkage to form ethyl 2-({2-(ethyloxy)-2-oxoethyl}oxy)methyl) benzene-1-carboxylate (65) by addition of the sodium salt of ethyl glycolate. A yield of 40% was obtained after isolation.

The final step was Dieckmann cyclisation to form ethyl 4-oxo-3, 4-dihydro-1H-isochromene-3-carboxylate (62). Although Norman et al.\textsuperscript{165} used metallic sodium in toluene for their preparation, it was decided to use potassium hydride in THF\textsuperscript{169, 170} since this is more convenient and is reported to be at least as effective in similar cyclisations. However, none of the desired product was identified in the proton NMR spectrum of the reaction mixture. Attempts using sodium hydride in THF gave similar results.

Attempts to trap the enolate (Scheme 38) by addition of allyl bromide to the Dieckmann reaction mixture (cf. allylation in the tetralone series, Scheme 32) gave no indication (proton NMR) of the incorporation of the allyl group. The crude product seemed to be similar to that obtained when no allyl bromide was added.
It is known in the literature that thermal decomposition of chromenes is possible.

(Scheme 39) \(^{171}\)

**Trapping the enolate of (62) with allyl bromide**

**Scheme 38**

**Scheme 39**

*Thermal decomposition of chromene* \(^{174}\)
It could be argued that a similar to decomposition of the enolate anion (Scheme 40) could be possible and could lead to decomposition.

**Scheme 40**

Possible route of decomposition of the enolate anion of (62)

The decision was taken to incorporate the allyl group into the ether precursor (65) prior to cyclisation. A new synthetic scheme was proposed (Scheme 41). It had been previously reported that cyclisation of an equivalent phenyl substituted ester (66) had been achieved although the yield was not high\textsuperscript{165}

![Scheme 40](image)
Scheme 41

New proposed route to obtain disubstituted iso-chromanone (63)

The starting material, ethyl 2-hydroxypent-4-enoate (67) was synthesised as reported in the literature (Scheme 42) \(^{172}\)
However it was noted that the new scheme initially consisted of forming the hemi-acetal and hydrate of ethyl glyoxylate followed by distillation over phosphorus pentoxide to form ethyl glyoxylate (69). This step proved difficult to achieve and a mixture of products were obtained after distillation. Since the next step was in an aqueous medium, it was assumed probable that the reaction did not require pure ethyl glyoxylate (69). The Indium catalysed reaction was attempted and was successful, a yield was given after purification of 52%.
A sodium salt of ethyl 2-hydroxypent-4-enoate (67) was formed, which reacted with ethyl 2-(chloromethyl) benzene-1-carboxylate (64) to obtain ethyl 2-[[1-[(ethyloxy)carbonyl]but-3-enyl]oxy)methyl] benzene-1-carboxylate (68) in 43% yield (Scheme 41).

Ring closure to ethyl 4-oxo-3-prop-2-enyl-3, 4-dihydro-1H-isochromene-3-carboxylate (63) was initially attempted using potassium hydride in THF. However, the crude reaction was messy and intractable (TLC). Sodium hydride was used as an alternative base. After column chromatography a proton NMR spectrum was obtained which recorded allyl peaks and aromatic peaks present but no ethyl ester peaks were detected. The literature procedure using sodium metal in toluene was also tried, the results obtained were similar to those using sodium hydride. Therefore it was decided to investigate using a stronger base; LDA was chosen. After column chromatography, a 26% yield of material was obtained, which gave peaks in the proton NMR spectrum that corresponded to those expected for an aromatic group, allyl group and ethyl ester group all of which would be in the product (63). Although the material was not pure and further attempts at purification were unsuccessful, the presence of the required product was confirmed by mass spectrometry (M⁺ 260 10484, C₁₅H₁₆O₄ requires M⁺ 260 10486).

4.41 Conclusion

Although isolation of the pure isochromanone (63) was not achieved the work described does suggest that this approach could be further developed into a successful synthesis.
CHAPTER 5
Chapter 5

Alcohol oxidation by Dimethyldioxirane

In chapter 2 reference was made to previous investigation within our research group of the mechanistic details of dimethyldioxirane oxidation of cholestanols and bile acid methyl esters

Hydrogen bonding has been recognised as being an important influence in dioxirane reactions in general and intramolecular hydrogen bonding has been observed to be influential in dimethyldioxirane mediated C-H oxygen insertion reactions. If intramolecular hydrogen bonding facilitates the oxidation of secondary alcohols, it would be expected that the use of a hydrogen bonding solvent would inhibit the oxidation by disruption of the intramolecular hydrogen bond. This prediction was confirmed by the observation in the oxidation of methyl deoxycholate in methanol acetone which was reduced from 63% to 30% and in chloroform, acetone to 44%

It was proposed that the transition state was planar and contained the CHOH atoms and the OOC plane of the dioxirane and an important hydrogen bond (Figure 17)
To investigate these issues further we have examined the dimethylidioxirane oxidation of 2,6-dimethylcyclohexanol (20) and 2,2,6-trimethylcyclohexanol (21)

![Structures](image)

5.1 Synthesis of 2,2,6-trimethylcyclohexanol and 2,6-dimethylcyclohexanol

2,2,6-Trimethylcyclohexanol (21) was synthesised by the reduction of 2,2,6-trimethylcyclohexanone with sodium borohydride in ethanol (Scheme 43)

**Scheme 43**

Reduction of 2,2,6-trimethylcyclohexanone

After purification by column chromatography an isomeric mixture was obtained (74% yield) that consisted mainly of a major isomer (70) with a minor impurity of the second isomer (71) present in a percentage ratio of 93% 7% Both isomers were identified by proton NMR spectroscopic data available in the literature \(^{181}\)
In the same manner, 2,6-dimethylcyclohexanol (20) was synthesised by reduction of 2,6-dimethylcyclohexanone with sodium borohydride (Scheme 44)

Scheme 44

Reduction of 2,6-dimethylcyclohexanone

Three isomeric alcohols were obtained (84% yield) in a percentage ratio of 38% 53% 9% determined by GLC. These isomers (72, 73 and 74) were identified from NMR spectroscopic data available in the literature.
5.2 Dimethyldioxirane Oxidation

5.21 Oxidation of 2,2,6-Trimethylcyclohexanol

2,2,6-Trimethylcyclohexanol (21) has a degree of hindrance to its structure that could limit the ways in which the dimethyldioxirane can attack in the transition state. The high restriction is caused by the presence of two methyl groups on a single carbon. Figure 18 shows the different transition states for attack of dimethyldioxirane along the CHOH plane and the CCH plane of the major isomer of the alcohol (70).

Figure 18

Planar (CHOH)– favoured

Spiro (CHOH)– disfavoured

Planar (CCH)– disfavoured

Spiro (CCH)– disfavoured
It was observed that the most favoured transition state is a planar approach of dimethyldioxirane in the CHOH plane of the alcohol (70) this transition state is also favourable for intramolecular hydrogen bonding. The other transition states have either oxygen or methyls of the dimethyldioxirane interacting with the methyl groups of the trisubstituted cyclohexanol (70).

Oxidation of 2,2,6-trimethylcyclohexanol (21) was undertaken and the results obtained are tabulated (Table 20).

### Table 20- Oxidation of 2,2,6-trimethylcyclohexanol with DMD

<table>
<thead>
<tr>
<th>Solvent used</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 ml acetone 5 ml DMD solution</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td>66%</td>
</tr>
<tr>
<td>5 ml chloroform 5 ml DMD solution</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>5 ml methanol 5 ml DMD solution</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>7%</td>
</tr>
</tbody>
</table>

Standardised equipment and procedure was used (see experimental), 50mgs of starting material were used. Samples were taken straight out of the reaction flask for analysis by GLC.

Changing the solvent used from acetone to mixture of chloroform/acetone (1:1) to methanol/acetone (1:1) increased the hydrogen bonding capacity of the solvent system and was accompanied by a decrease in percentage conversion.

These results were similar to those with bile acids previously published by our group, suggesting support for the proposed mechanism for dimethyldioxirane mediated alcohol oxidations (Figure 17) 49,122
5.22 Oxidation of 2,6-dimethylcyclohexanol

The same ideas were applied to 2,6-dimethylcyclohexanol (20) and proposed transition states for dimethyldioxirane attack were identified (Figure 19) for the major isomer (73).

![Figure 19](image)

Planar (CHOH)- favoured          Spiro (CHOH)- disfavoured

Planar (CCH)- disfavoured          Spiro (CCH)- disfavoured

It was observed that the proposed planar transition state containing the CHOH plane is favoured in this system and it is also favourable for intramolecular hydrogen bonding. The other transition states have either oxygen or methyls of the dimethyldioxirane interacting with the methyl groups of the disubstituted cyclohexanol (73) which causes disfavoured transition states.
Oxidation of 2,6-dimethylcyclohexanol (20) was undertaken and the results obtained are tabulated (Table 21). As each isomer (72, 73 and 74) is oxidised in different quantities a column has been included in Table 21, which shows the ratio of the total amount left of 2,6-dimethylcyclohexanol against the total oxidation to 2,6-dimethylcyclohexanone.

Table 21 - Oxidation of 2,6-dimethylcyclohexanol with DMD

<table>
<thead>
<tr>
<th>Solvent used</th>
<th>% 2,6-dimethylcyclohexanol remaining</th>
<th>% 2,6-dimethylcyclohexanone obtained</th>
<th>% ratio of total conversion (Product / Starting material)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5ml acetone 5ml DMD solution</td>
<td>24% 8% 0%</td>
<td>59% 9%</td>
<td>68% / 32%</td>
</tr>
<tr>
<td>5ml chloroform 5ml DMD solution</td>
<td>30% 22% 0%</td>
<td>40% 8%</td>
<td>48% / 52%</td>
</tr>
<tr>
<td>5ml methanol 5ml DMD solution</td>
<td>35% 46% 4%</td>
<td>11% 4%</td>
<td>15% / 85%</td>
</tr>
</tbody>
</table>

The results obtained confirmed those previously observed for the oxidation of 2,2,6-trimethylcyclohexanol (Table 20). Thus increasing the hydrogen bonding capacity of the solvent system (methanol/ acetone 1:1) can effect a decrease in percentage conversion to 2,6-dimethylcyclohexanone.
It was noted that 2,6-dimethylcyclohexanol was slightly more reactive than 2,2,6-
trimethylcyclohexanol (cf. Table 20 and 21) but this would be expected due to less
steric hindrance

5.3 Conclusion

The two cyclohexanol structures (20 and 21) investigated have suggested further
support for our previously proposed mechanism for dimethyldioxirane mediated
alcohol oxidations (Figure 17). It was observed that both cyclohexanols (see
Table 20 and 21) were oxidised in substantial amounts, which suggests that
dimethyldioxirane attack can occur via a planar transition state (Figure 18 and 19) in
the oxidation of secondary alcohol and that intramolecular hydrogen bonding is
involved. It is impossible to say that no spiro attack took place but from proposed
transition states (Figure 18 and 19) it can be seen that for spiro attack the transition
state is very hindered in these systems
CHAPTER 6
6.1 General Information
6.11 Solvents and Reagents
Solvents were purified prior to use as follows: Dichloromethane was distilled from phosphorus pentoxide, petroleum and ethyl acetate was distilled from anhydrous calcium chloride and methanol was distilled from magnesium and iodine. Acetonitrile, ethanol, tetrahydrofuran, toluene, hexane, diethyl ether, dimethylformamide and acetone were purchased from Aldrich either in anhydrous form or HPLC grade. The (EDTA)Na₂ solution used in the monophasic and biphasic oxidation reactions was of concentration 4x10⁻⁴M aqueous solution. The buffer used in increased pH studies (Shi-type) was 0.05M Na₂B₄O₇·10H₂O in 4x10⁻⁴M aqueous (EDTA)Na₂ solution.

6.12 Spectroscopic Techniques
Infra red spectra were recorded on a Nicolet 205 series FT-IR spectrometer. ¹H, ¹³C and cosy spectra were recorded on either a Bruker AC-250 or a DPX-400 spectrometer in deuteriochloroform (unless stated otherwise). Chemical shifts are reported as delta (δ) values in ppm relative to tetramethylsilane (δ0 00) as the internal standard. Spectroscopic data are annotated with the following abbreviations: br broad, s singlet, d doublet, t triplet, q quartet, m multiplet, cm complex multiplet and combinations thereof. Mass spectra were recorded on a Kratos MS80 or a VG Analytical ZAB-E spectrometer.
6.13 Chromatographic Procedures

Thin layer chromatography (preparative and analytical) was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Flash chromatography was carried out using Matrex silica 60, 35-70 micron (Fisons Scientific Equipment).

GLC Chromatograms were recorded on a Perkin Elmer GC8700, 25m capillary column, Pye Unicam series 104 (carbonwax 20m column) and Pye Unicam series 104 (5% apeizion 20m column). Optimisation of each substrate was carried out using the substrate and its oxidised form.

GC-MS data was recorded on a Fisons GC 8000, 15m DB5ms (J+W) column with a MD800 (EI) detector.

6.14 Other Information

In all oxidation reactions (unless stated) the standardised equipment was used, 50ml round bottom flask and a 25ml magnetic stir bar, stirring at maximum revolutions.

Melting points were measured on an Electrothermal digital melting point apparatus.

The measurement of pH was on Metrohm 691 pH meter.

X-ray crystallographic structures were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.
6.2 Synthesis of Achiral Ketones

6.21 Synthesis of Methyl 4-(trifluoroacetyl) benzoate (Scheme 24)\textsuperscript{124}

\[\text{CF}_3\]
\[\text{O} \quad \text{O} \quad \text{Me} \]

To a solution of 4-(trifluoroacetyl) benzoic acid (2.0 g, 0.9 mmol) in excess methanol, was added p-TSA (50 mg). The solution was refluxed for 48 hours. After this time, the methanol was removed \textit{in vacuo} and the crude material worked up in ethyl acetate washing with sat. sodium hydrogen carbonate (2 x 50 ml) and water (2 x 50 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. To remove the hydrate, the product was taken up in chloroform and dried for 48 hours over molecular sieves (4 Å). The solution was then filtered and evaporated to dryness, to give a cream solid (1.93 g, 90\%) m p 60-62°C (Literature gave m p 37-39°C\textsuperscript{183}, after Kugelrohr distillation, the value that I obtained indicates that hydrate is still present, all other data corresponds).

\(\nu_{\text{max}}/\text{cm}^{-1}\) (KBr disk), 3064, 2679, 2562, 1724 (C=O), 1693 (C=O), 1432, 1289, 1210, 1185, 1153, 948

\(\delta_{\text{H}}\) (250 MHz, CDCl\textsubscript{3}), 8.22-8.18 (2H, d, \(J=8.4\) Hz, ArH), 8.15-8.11 (2H, d, \(J=8.5\) Hz, ArH), 3.97 (3H, s, OMe) Hydrate peaks; 8.10-8.06 (2H, d, \(J=8.3\) Hz, ArH), 7.81-7.26 (2H, d, \(J=8.3\) Hz, ArH), 3.94 (3H, s, OMe)

\(\delta_{\text{C}}\) (100 MHz, CDCl\textsubscript{3}), 180 7-179.6 (trifluoro C=O, q, \(J=35\) 6Hz), 165 6 (ester C=O), 136 0 (C), 133 1 (C), 130 1-130 0 (4CH), 120 8-112.1 (CF\textsubscript{3}, q, \(J=291\) Hz), 52 7 (OMe)
6.22 Synthesis of dihydrocholesteryl 4-(trifluoroacetyl) benzoate (Scheme 25)

To a solution of 4-(trifluoroacetyl) benzoic acid (50 mg, 0.229 mmol) and
dihydrocholesterol (89 mg, 0.229 mmol) in toluene (25 ml) was added p-TSA
(~50 mg) and refluxed for 48 hours.
The toluene was removed in vacuo and the crude product was taken-up in ethyl
acetate (50 ml). This was then washed with sat. sodium hydrogen carbonate
(2 x 25 ml) and water (2 x 25 ml) and the organic layer dried over anhydrous sodium
sulfate and evaporated to dryness in vacuo. The crude product was partially purified
by column chromatography (eluent 9:1, petroleum: ethyl acetate) to give material that
was suspected to be the title compound (0.090 g, 67%).
The analysis of the partially pure product gave evidence of peaks that were expected
to be present.

$\nu_{\text{max}}/\text{cm}^{-1}$ (KBr disk); 2932, 1718 (C=O), 1280, 1184, 1148.

$\delta^H$ (250 MHz, CDCl$_3$); 8 20-8.17 (2H, d, $J=8.6$ Hz, ArH), 8 13-8 10 (2H, d, $J=8.4$ Hz,
ArH), 4 97 (1H, m, $\beta$-H), 2 0-0.85 (cm, steroidal protons)
6.13 Synthesis of TentaGel S-Br resin-bound ketone

Dr T Boehlow initially developed the experimental for this product.

To a suspension of TentaGel S-Br resin (0.7 g) in ethyl acetate (10ml), was added a solution of 4-(trifluoroacetyl) benzoic acid (0.32 g, 1.46 mmol) in ethyl acetate (10ml) and triethylamine (205 μl). The reaction mixture was refluxed for 48 hours. After this time the reaction mixture was filtered and the residue washed with ethyl acetate (25ml), water (25ml) and acetone (25ml). The white solid was allowed to vacuum dry.

\[ \nu_{\text{max}}/\text{cm}^{-1} (\text{Nujol}) \]: 1718, 1636

IR analysis shows two carbonyl peaks present of the attached trifluoroketone. The data obtained corresponded to data previously recorded by Dr. T. Boehlow. The preferred method of analysis is to run an oxidation on trans-stilbene under standard monophasic conditions (for experimental see later). Typical epoxidation results obtained gave a conversion of 75% to trans-stilbene oxide by GLC.
6.3 General oxidation procedures used

When blank reactions are recorded in the result chapters (3, 4 and 5), the experimental procedure is identical to a catalysed reaction except that no ketone is added.

6.31 Oxidation methods used for Tables 7, 8 and 9

6.31.1 General Armstrong epoxidation procedure \(^{53}\) (method ratio 1:1:1.2.3.4)

To a biphasic solution of cyclohexene (0.52 ml, 5 mmol), tetrabutylammonium hydrogen sulphate (400 mg, 1 mmol) and ketone (5 mmol) in DCM (50 ml) and 1 moldm\(^{-3}\) aqueous sodium hydrogen carbonate (17 ml) at 0°C, was added a solution of Oxone\(^\circledR\) (3.68 g, 6 mmol) in distilled water (30 ml) and (EDTA)Na\(_2\) (20 mg) in one portion. The reaction was stirred at 0°C and followed at intervals (3 and 6 hours) by GLC and expressed as percentage conversions.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Retention time (min)</th>
<th>Typical % conversion of oxidised product obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexene</td>
<td>0.83</td>
<td>17% (with TFAP)</td>
</tr>
<tr>
<td>Cyclohexene oxide</td>
<td>4.01</td>
<td></td>
</tr>
</tbody>
</table>

Column used: Carbowax 20m.

Conditions were obtained with standards before use to determine retention times of substrates.

6.31.2 Optimum yield epoxidation procedure \((method ratio 1:1:10:27)\)

- Note very high blanks obtained

To a biphasic solution of alkene (2.74 mmol), tetrabutylammonium hydrogen sulphate (500 mg) and ketone (2.74 mmol) in DCM (30 ml) and 1 moldm\(^{-3}\) aqueous sodium hydrogen carbonate (74.8 ml) at room temperature, was added a solution of Oxone\(^\circledR\)
(16.84 g, 27 mmol) in distilled water (138 ml) and (EDTA)Na₂ (500 mg) in one portion. The reaction was stirred and followed at intervals (3 and 6 hours) by GLC and expressed as percentage conversions.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Retention time (min)</th>
<th>Typical % conversion of oxidised product obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexene</td>
<td>0.83</td>
<td>17% (with TFAP)</td>
</tr>
<tr>
<td>Cyclohexene oxide</td>
<td>4.01</td>
<td></td>
</tr>
</tbody>
</table>

Column used, Carbowax 20m

Conditions were obtained with standards before use to determine retention times of substrates.

6.31.3 Monophasic epoxidation procedure (Table 8)

To a monophasic system consisting of substrate (0.27 mmol), acetonitrile (7.5 ml), ketone (1.3 mmol) and (EDTA)Na₂ solution (5 ml of 4x10⁻⁴ M), was added a solid mixture of Oxsone® (0.85 g, 1.3 mmol) and sodium hydrogen carbonate (0.36 g, 4.2 mmol) over 30 minutes. This was stirred vigorously at room temperature for 24 hours. After such time the reaction mixture was worked up by taking the reaction mixture into ethyl acetate and washing with water and sat. sodium hydrogen carbonate. The organic layer was dried over sodium sulfate and evaporated to dryness in vacuo. The crude products were analysed by GLC or proton NMR spectroscopy and expressed as percentage conversions.

The table below only shows a typical percentage conversion for the substrate, for full results using alternative ketone catalysts see Table 8.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Retention time (min)</th>
<th>Typical % conversion of oxidised product obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans-stilbene</td>
<td>7.91</td>
<td>70% (with TFAP)</td>
</tr>
<tr>
<td>Trans-stilbene oxide</td>
<td>8.93</td>
<td></td>
</tr>
<tr>
<td>Cis-stilbene</td>
<td>3.62</td>
<td>100% (with TFAP)</td>
</tr>
<tr>
<td>Cis-stilbene oxide</td>
<td>5.60</td>
<td></td>
</tr>
<tr>
<td>Trans-chalcone</td>
<td>3.28</td>
<td>11% (with TFAP)</td>
</tr>
<tr>
<td>Trans-chalcone oxide</td>
<td>2.23</td>
<td></td>
</tr>
<tr>
<td>Cyclohexene</td>
<td>0.83</td>
<td>38% (with TFAP)</td>
</tr>
<tr>
<td>Cyclohexene oxide</td>
<td>4.01</td>
<td></td>
</tr>
</tbody>
</table>

Column used for cyclohexene was Carbowax 20m all other substrates were on 5% apiezon 20m column. Conditions were obtained with standards before use to determine retention times of substrates.

Approximate ratios of conversion were also obtained from proton NMR analysis of the crude reaction mixture.

$\delta_H$ (250MHz; CDCl$_3$), **Cholesterol** (only peaks of interest listed) 5 35-5.34 (1H, brs, 6-H), 3 56-3 48 (1H, m, 3-H). **5,6-Cholesterol oxide** (only peaks of interest listed) 3.93-3.87 (1H, m, $\beta$3-H), 3.72-3.66 (1H, m, $\alpha$3-H), 3 06-3.05 (1H, d, $J$= 2.2Hz, $\beta$6-H), 2 90-2.89 (1H, d, $J$=4.3Hz, $\alpha$6-H) $\alpha$: $\beta$ ratio about 50 50. Typical epoxidation with TFAP was 52% (determined by integration of 6-H peaks).

**Trans-Chalcol** 7 45-7.20 (10H, cm, ArH), 6 63-6.57 (1H, d, $J$=13.3Hz, 3-H), 6 41-6 33 (1H, td, $J$=13 0Hz, 2-H), 5 12-5 07 (1H, t, $J$=5 0Hz, 1-H), 1 75 (1H, bs, OH)

**Trans-chalcol oxide** Crude reaction mixture gave difficulty in determining peaks, however percentage conversion was determined by the disappearance of olefinic
peaks and in all spectra obtained no olefinic peaks were observed therefore 100% oxidation of the substrate had taken place. Therefore it is possible that the keto-epoxide may be present in small amount.

**Tri-O-acetyl Glucal** 6 48-6 45 (1H, dd, J=6 1Hz, 1.2Hz, 2-H), 5 36-5 32 (1H, m, ring CH), 5 28-5 20 (1H, m, ring CH), 4 87-4 83 (1H, dd, J=6 2Hz, 3 2Hz, 3-H), 4 44-4 10 (3H, m, ring CH and CH₂), 2 10 (3H, s, OAc), 2 08 (3H, s, OAc), 2 05 (3H, s, OAc) **Tri-O-acetyl Glucal oxide** Crude reaction mixture caused difficulty in assigning peaks, however it was observed that there was no evidence of olefinic protons and 2 new multiplets that correspond with expected values for epoxide protons were present 5.32-5.24ppm and 5.10-4.98ppm. Therefore typical percentage conversion assigned was 100% with TFAP

6.31.4 Biphasic epoxidation procedure (Table 9) To a biphasic system consisting of substrate (0.27 mmol), tetrabutylammonium hydrogen sulphate (50 mg), DCM (7.5 ml), ketone (1.3 mmol) and (EDTA)Na₂ solution (5 ml of 4x10⁻⁴M), was added a solid mixture of Oxone® (0.85 g, 1.3 mmol) and sodium hydrogen carbonate (0.36 g, 4.2 mmol) over 30 minutes. This was stirred vigorously at room temperature for 24 hours. After such time the reaction mixture was worked up by taking the reaction mixture into ethyl acetate and washing with water and sat sodium hydrogen carbonate. The organic layer was dried over sodium sulphate and evaporated to dryness in vacuo. The crude products were analysed by GLC or proton NMR spectroscopy and expressed as percentage conversions.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Retention time (min)</th>
<th>Typical % conversion of oxidised product obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans-stilbene</td>
<td>7.91</td>
<td>32% (with TFAP)</td>
</tr>
<tr>
<td>Trans-stilbene oxide</td>
<td>8.93</td>
<td></td>
</tr>
<tr>
<td>Cis-stilbene</td>
<td>3.62</td>
<td>77% (with TFAP)</td>
</tr>
<tr>
<td>Cis-stilbene oxide</td>
<td>5.60</td>
<td></td>
</tr>
<tr>
<td>Trans-chalcone</td>
<td>3.28</td>
<td>11% (with TFAP)</td>
</tr>
<tr>
<td>Trans-chalcone oxide</td>
<td>2.23</td>
<td></td>
</tr>
<tr>
<td>Cyclohexene</td>
<td>0.83</td>
<td>55% (with TFAP)</td>
</tr>
<tr>
<td>Cyclohexene oxide</td>
<td>4.01</td>
<td></td>
</tr>
</tbody>
</table>

Column used for cyclohexene was Carbowax 20m all other substrates were on 5% apiezon 20m column. Conditions were obtained with standards before use to determine retention times of substrates.

Approximate ratios of conversion were also obtained from proton NMR analysis of the crude reaction mixture.

δ_H (250MHz; CDCl3), Cholesterol (only peaks of interest listed) 5.35-5.34 (1H, brs, 6-H), 3.56-3.48 (1H, m, 3-H). 5,6-Cholesterol oxide (only peaks of interest listed) 3.93-3.87 (1H, m, β3-H), 3.72-3.66 (1H, m, α3-H), 3.06-3.05 (1H, d, J= 2.2Hz, β6-H), 2.90-2.89 (1H, d, J=4.3Hz, α6-H) α: β ratio about 50:50  Typical epoxidation with TFAP was 76% (determined by integration of 6-H peaks).

Trans-Chalcol 7.45-7.20 (10H, cm, ArH), 6.63-6.57 (1H, d, J=13 3Hz, 3-H), 6.41-6.33 (1H, td, J=13.0Hz, 2-H), 5.12-5.07 (1H, t, J=5 0Hz, 1-H), 1.75 (1H, bs, OH).

Trans-chalcone oxide: Crude reaction mixture gave difficulty in determining peaks, however percentage conversion was determined by the disappearance of olefinic
peaks and in all spectra no olefinic peaks were observed to be declining therefore little or no oxidation of the substrate had taken place

**Tri-O-acetyl Glucal**  6 48-6 45 (1H, dd, J=6.1Hz, 1 2Hz, 2-H), 5 36-5 32 (1H, m, ring CH), 5 28-5 20 (1H, m, ring CH), 4 87-4.83 (1H, dd, J=6 2Hz, 3.2Hz, 3-H), 4 44-4 10 (3H, m, ring CH and CH₂), 2 10 (3H, s, OAc), 2 08 (3H, s, OAc), 2 05 (3H, s, OAc). **Tri-O-acetyl Glucal oxide** Crude reaction mixture caused difficulty in assigning peaks, however it was observed that there was no evidence of declining olefinic protons therefore typically there was little or no oxidation with TFAP

6.32  **Alterations made on pH and exclusion of light in the monophasic oxidation system (Tables 11 and 12).**

6.32.1  **Monophasic epoxidation with the absence of light (Table 11)**

To a monophasic system consisting of substrate (0 27 mmol), acetonitrile (7 5 ml), ketone (1 3 mmol) and (EDTA)Na₂ solution (5 ml of 4x10⁻⁴M), was added a solid mixture of Oxone® (0 85 g, 1.3 mmol) and sodium hydrogen carbonate (0 36 g, 4 2 mmol) over 30 minutes. This was stirred vigorously at room temperature for specified times. After such times the reaction mixture was worked up by taking the reaction mixture into ethyl acetate and washing with water. The organic layer was dried over anhydrous sodium sulphate and evaporated to dryness in vacuo. The crude products were analysed by GC-MS and expressed as percentage conversions

*For experiments in the absence of light, the apparatus was liberally covered in tin foil.*
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Retention time (min)</th>
<th>Typical % conversion of oxidised product obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans-stilbene</td>
<td>16 128</td>
<td>76% (with TentaGel resin-bound ketone)</td>
</tr>
<tr>
<td>Trans-stilbene oxide</td>
<td>16 328</td>
<td></td>
</tr>
<tr>
<td>Benzhydrol</td>
<td>15 553</td>
<td>17% (with TFAP)</td>
</tr>
<tr>
<td>Diphenyl methyl ketone</td>
<td>15 203</td>
<td></td>
</tr>
<tr>
<td>Trans-chalcone</td>
<td>19 352</td>
<td>20% (with TFAP)</td>
</tr>
<tr>
<td>Trans-chalcone oxide</td>
<td>19 477</td>
<td></td>
</tr>
</tbody>
</table>

Samples were run on a GC-MS and determined by using mass spectra.

Approximate ratios of conversion were also obtained from proton NMR analysis of the crude reaction mixture.

δH (250MHz, CDCl3), Cholesterol (only peaks of interest listed): 5.35-5.34 (1H, brs, 6-H), 3.56-3.48 (1H, m, 3-H)
5,6-Cholesterol oxide (only peaks of interest listed): 3.93-3.87 (1H, m, β3-H), 3.72-3.66 (1H, m, α3-H), 3.06-3.05 (1H, d, J=2 2Hz, β6-H), 2.90-2.89 (1H, d, J=4.3Hz, α6-H) α:β ratio about 50:50

Typical epoxidation with TFAP was 34% (determined by integration of 6-H peaks)

6.32.2 Biphasic epoxidation with the absence of light (Table 11)

To a biphasic system consisting of substrate (0.27 mmol), dichloromethane (7.5 ml), ketone (1.3 mmol), tetrabutylammoniumhydrogen sulphate (catalytic) and (EDTA)Na2 solution (5 ml of 4x10^-4M), was added a solid mixture of Oxone® (0.85 g, 1.3 mmol) and sodium hydrogen carbonate (0.36 g, 4.2 mmol) over 30 minutes. This was stirred vigorously at room temperature for specified times. After such times the reaction mixture was worked up by taking the reaction mixture into dichloromethane and washed with water. The organic layer was dried over anhydrous sodium sulfate.
and evaporated to dryness *in vacuo*. The crude products were analysed by GC-MS and expressed as percentage conversions

*For experiments in the absence of light, the apparatus was covered in tin-foil.*

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Retention time (min)</th>
<th>Typical % conversion of oxidised product obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Trans</em>-stilbene</td>
<td>16 128</td>
<td>32% (with TFAP)</td>
</tr>
<tr>
<td><em>Trans</em>-stilbene oxide</td>
<td>16 328</td>
<td></td>
</tr>
<tr>
<td>Benzhydrol</td>
<td>15 553</td>
<td>1% (with TFAP)</td>
</tr>
<tr>
<td>Diphenyl methyl ketone</td>
<td>15 203</td>
<td></td>
</tr>
<tr>
<td><em>Trans</em>-chalcone</td>
<td>19.352</td>
<td>12% (with TFAP)</td>
</tr>
<tr>
<td><em>Trans</em>-chalcone oxide</td>
<td>19 477</td>
<td></td>
</tr>
</tbody>
</table>

Samples were run on a GC-MS and determined by using mass spectra.

Approximate ratios of conversion were also obtained from proton NMR analysis of the crude reaction mixture

δ_{H} (250MHz; CDCl₃), *Cholesterol* (only peaks of interest listed) 5 35-5 34 (1H, brs, 6-H), 3.56-3.48 (1H, m, 3-H). *5,6-Cholesterol oxide* (only peaks of interest listed).

δ_{H} 3.93-3.87 (1H, m, β3-H), 3.72-3.66 (1H, m, α3-H), 3.06-3.05 (1H, d, J= 2 2Hz, β6-H), 2.90-2.89 (1H, d, J= 4 3Hz, α6-H) α: β ratio about 50.50. Typical epoxidation with TFAP was 76% (determined by integration of 6-H peaks).

### 6.32.3 Monophasic epoxidation TentaGel resin-bound ketone (Table 11)

*TentaGel loading is 0.26mmol/g, and 2 equivalents are used.*

To a monophasic system consisting of substrate (0.13 mmol), acetonitrile (6 ml), TentaGel resin (1.03g) and (EDTA)Na₂ solution (4 ml of 4x10⁻⁴M), was added a solid
mixture of Oxone® (0.414 g, 0.65 mmol) and sodium hydrogen carbonate (0.175 g, 2.1 mmol) over 30 minutes. This was stirred vigorously at room temperature for specified times. After such times the reaction mixture was worked up filtering the reaction mixture and washing thoroughly with ethyl acetate and water. The organic layer was separated and dried over anhydrous sodium sulfate and evaporated to dryness in vacuo. The crude products were analysed by GC-MS and expressed as percentage conversions (for retention times see trans-stilbene in 6.32.1).

For experiments in the absence of light, the apparatus was covered in tin foil.

For the next set of reactions three substrates were used, trans-stilbene, trans-chalcone and cholesterol, GC-MS and NMR were used for analysis and the data corresponded with that previously seen therefore retention and ppm values are not quoted.

6.32.4 Oxidation under altered pH conditions (Table 12)

Using 0.3 equivalents of ketone

To a round bottom flask (50 ml) was added buffer (10 ml) (see general information 6.11), acetonitrile (15 ml), substrate (1 mmol), tetrabutylammoniumhydrogen sulphate (0.04 mmol) and ketone (0.3 mmol). The reaction mixture was cooled with an ice bath. A solution of Oxone® (0.85 g, 1.38 mmol) in aqueous (EDTA)Na₂ (6.5 ml) and a solution of potassium carbonate (0.8 g, 5.8 mmol) in water (6.5 ml) were added dropwise through separate needles over a period of 1.5 hours (under this condition, the reaction pH is ~10.5, it is recommended that both Oxone® and potassium carbonate be added uniformly over 1.5 hours) The reaction mixture was stirred...
vigorously at 0°C, for a further 1.5 hours. The pH was measured periodically through out the reaction. After 3 hours reaction time work up was undertaken by partitioning the reaction mixture between ethyl acetate and water. The organic layer was separated and dried over anhydrous sodium sulfate then evaporated to dryness in vacuo. The crude products were analysed by GC-MS and expressed as percentage conversions.

**Using 5 equivalents of ketone**

To a round bottom flask (50ml) was added buffer (10ml) (see 6.11), acetonitrile (15ml), substrate (1 mmol), tetrabutylammoniumhydrogen sulphate (0.04 mmol) and ketone (5 mmol). The reaction mixture was cooled with an ice bath. A solution of Oxone® (0.85g, 1.38 mmol) in aqueous (EDTA)Na₂ (6.5ml) and a solution of potassium carbonate (0.8g, 5.8 mmol) in water (6.5ml) were added dropwise through separate needles over a period of 1.5 hours (under this condition, the reaction pH is ~10.5, it is recommended that both Oxone® and potassium carbonate be added uniformly over 1.5 hours). The reaction mixture was stirred vigorously at 0°C, for a further 1.5 hours. The pH was measured periodically throughout the reaction. After 3 hours reaction time work up was undertaken by partitioning the reaction mixture between ethyl acetate and water. The organic layer was separated and dried over anhydrous sodium sulfate then evaporated to dryness in vacuo. The crude products were analysed by GC-MS and expressed as percentage conversions.

**Monophasic reaction equivalents with increased pH (Table 12)**

To a round bottom flask (50ml) was added buffer (5ml) (see 6.11), acetonitrile (7.5ml), substrate (0.27 mmol), tetrabutylammoniumhydrogen sulphate (0.04 mmol) and ketone (5 mmol). The reaction mixture was cooled with an ice bath.
A solution of Oxone® (0.85 g, 1.38 mmol) in aqueous (EDTA)Na₂ (6.5 ml) and a solution of potassium carbonate (0.578 g, 4.2 mmol) in water (6.5 ml) were added dropwise through separate needles over a period of 1.5 hours (under this condition, the reaction pH is ~10.5, it is recommended that both Oxone® and potassium carbonate be added uniformly over 1.5 hours) The reaction mixture was stirred vigorously at 0°C, for a further 1.5 hours. The pH was measured periodically throughout the reaction.

After 3 hours reaction time work up was undertaken by partitioning the reaction mixture between ethyl acetate and water. The organic layer was separated and dried over anhydrous sodium sulfate then evaporated to dryness in vacuo. The crude products were analysed by GC-MS and expressed as percentage conversions.

6.33 Monophasic Oxidation for substrates other than alkenes (Table 13)

To a monophasic system consisting of substrate (0.27 mmol), acetonitrile (7.5 ml), ketone (1.3 mmol) and (EDTA)Na₂ solution (5 ml of 4x10⁻⁴ M), was added a solid mixture of Oxone® (0.85 g, 1.3 mmol) and sodium hydrogen carbonate (0.36 g, 4.2 mmol) over 30 minutes. This was stirred vigorously in darkness for 24 hours at room temperature. After such times the reaction mixture was worked up by taking the reaction mixture into ethyl acetate and washing with water. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness in vacuo. The crude products were analysed by GLC and expressed as percentage conversions (see below).
6.33.1 Monophasic Oxidation using TentaGel resin-bound ketone (Table 13)

TentaGel loading is 0.26mmol/g, and 2 equivalents are used.

To a monophasic system consisting of substrate (0.13 mmol), acetonitrile (6 ml), TentaGel resin (1.03 g) and (EDTA)Na₂ solution (4 ml of 4x10⁻⁴M), was added a solid mixture of Oxone® (0.414 g, 0.65 mmol) and sodium hydrogen carbonate (0.175 g, 2.1 mmol) over 30 minutes. This was stirred vigorously in darkness for 24 hours at room temperature. After such times the reaction mixture was worked up filtering the reaction mixture and washing thoroughly with ethyl acetate and water. The organic layer was separated and dried over anhydrous sodium sulfate and evaporated to dryness in vacuo. The crude products were analysed by GLC and expressed as percentage conversions.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Retention time (min)</th>
<th>Typical % conversion of oxidised product obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenyl ethanol</td>
<td>7.50</td>
<td>29% (with TFAP)</td>
</tr>
<tr>
<td>Acetophenone</td>
<td>7.70</td>
<td></td>
</tr>
<tr>
<td>Benzhydrol</td>
<td>25.11</td>
<td>17% (with TFAP)</td>
</tr>
<tr>
<td>Diphenyl methyl ketone</td>
<td>24.15</td>
<td></td>
</tr>
<tr>
<td>Cyclopropyl benzyl alcohol</td>
<td>7.01</td>
<td>19% (with TFAP)</td>
</tr>
<tr>
<td>Cyclopropyl benzyl ketone</td>
<td>7.34</td>
<td></td>
</tr>
<tr>
<td>Cinnamyl alcohol</td>
<td>4.21</td>
<td>75% (with TFAP)</td>
</tr>
<tr>
<td>Cinnamyl alcohol oxide</td>
<td>4.98</td>
<td></td>
</tr>
<tr>
<td>Cis-decalin</td>
<td>2.95</td>
<td>58% (with TFAP)</td>
</tr>
<tr>
<td>Cis-9-decalol</td>
<td>5.04</td>
<td></td>
</tr>
</tbody>
</table>

All GLC ran on Perkin Elmer 25m capillary column, conditions were identified against purchased standards.
6.34 **General Oxidation procedure for allylic alcohols and their acetates**

A mixture of Oxone\(^\circledast\) (0.85g, 1.38mmol) and sodium hydrogen carbonate (0.39g, 4.5mmol) was added to a mixture of the alcohol or its acetate (0.27mmol), \(\alpha,\alpha,\alpha\)-trifluoroacetophenone (0.185ml, 1.32mmol) and (EDTA)\(\text{Na}_2\) (5ml of a \(4 \times 10^{-4}\)M solution) in acetonitrile (7.5ml). The solution was stirred rapidly overnight excluding light and at room temperature except where indicated otherwise. The reactions with Oxone\(^\circledast\) alone were performed in the same manner but \(\alpha,\alpha,\alpha\)-trifluoroacetophenone was omitted. After the stated time water (100ml) was added and the solution was extracted with DCM (3x20ml), the combined extracts then being dried over magnesium sulfate and evaporated to dryness. Product ratios were determined from proton NMR spectra of the crude products.

The allylic alcohols and their acetates are all literature compounds as are all the isolated epoxides except the trans-epoxide (28, \(R^1=R^2=H, R^3=\text{Ph}\)) and the trans-epoxide from (30).

**Characterisation of trans-epoxides 28 and 30**

In a slightly modified procedure, oxidation of 3-phenylcyclohex-2-en-1-ol (28) (500mg, 2.87mmol) was carried out at room temperature and excluding light in a rapidly stirred reaction mixture containing \(\alpha,\alpha,\alpha\)-trifluoroacetophenone (0.805ml, 5.74mmol), (EDTA)\(\text{Na}_2\) (20ml of \(4 \times 10^{-4}\)M solution) in acetonitrile (30ml), Oxone\(^\circledast\) (8.81g, 14.3mmol) and sodium hydrogen carbonate (3.69g, 44.4mmol). After ca. 18 hours, water (100ml) was added and the solution was extracted with DCM (3x30ml), the combined extracts were dried over sodium sulfate and evaporated to dryness. Careful chromatography of the reaction mixture, using diethyl ether-hexane mixtures.
as eluent, afforded the trans-epoxide of (28, $R^1=R^2=H$, $R^3=Ph$) (23%), mp 75-76°C (white crystalline solid, from diethyl ether: hexane).

$\nu_{\text{max}}$ cm$^{-1}$ (CDCl$_3$ film) 3406 (OH), 2941, 1495, 1447, 1067, 960

$\delta_H$ (250MHz; CDCl$_3$): 7 40-7.27 (5H, m, Ph), 4 13-4 05 (1H, dt, $J=8$ 8Hz, 5.6Hz, 1-CH), 3 07 (1H, s, 2-CH), 2 33-1 99 (3H, cm, CH$_3$), 1 78-1 76 (1H, d, $J=5$ 2Hz, OH), 1.69-1 19 (3H, cm, CH$_2$)

$\delta_C$ (62 9MHz, CDCl$_3$) 141 1 (Ar-C), 128 3 (Ar-CH), 127 5 (Ar-CH), 125 4 (Ar-CH), 66 8 (CH), 65 5 (CH), 61 4 (3-C), 30 2 (CH$_2$), 28 4 (CH$_2$), 15 8 (CH$_2$)

m/z (E I) $M^+_{\text{EI}}$ 190 0993 C$_{12}$H$_{14}$O$_2$ requires $M^+_{\text{EI}}$ 190 0994, 105 (100)

Acetylation of the trans-epoxide of (28, $R^1=R^2=H$, $R^3=Ph$) with acetic anhydride in pyridine, afforded a quantitative yield of the trans-epoxide acetate (30, $R^1=Ac$, $R^2=H$, $R^3=Ph$) as an oil

$\nu_{\text{max}}$ cm$^{-1}$ (CDCl$_3$ film). 2944, 2872, 1738 (C=O), 1448, 1372, 1237 (C-O), 1038.

$\delta_H$ (400MHz; CDCl$_3$): 7 39-7.25 (5H, m, Ph), 5.11-5 07 (1H, dd, $J=8$ 8Hz, 6 4Hz, 1-CH), 3 04 (1H, brs 2-CH), 2.34-2 27 (1H, m, CH$_2$), 2.20-2 14 (1H, m, CH$_2$), 2 06 (3H, s, CH$_3$), 2 04-1.98 (1H, m, CH$_2$), 1 68-1.59 (1H, m, CH$_2$), 1.57-1.46 (1H, m, CH$_2$), 1.40-1.31 (1H, m, CH$_2$)

$\delta_C$ (100MHz; CDCl$_3$). 170.1 (C), 140.7 (Ar-C), 128 3 (Ar-CH), 127.6 (Ar-CH), 125 3 (Ar-CH), 68.7 (CH), 62 9 (CH), 60 9 (3-C), 28 0 (CH$_2$), 26 4 (CH$_2$), 21.1 (CH$_3$), 15 7 (CH$_2$).

m/z (C I) $M+H_{\text{EI}}$ 233.1177 C$_{12}$H$_{14}$O$_2$ requires $M+H_{\text{EI}}$ 233.1178, 173 (100).
6.4 Experimental for Carvedilol

6.41 Monophasic oxidation conditions

To a monophasic system consisting of Carvedilol (0.27 mmol, 0.109 g), acetonitrile (7.5 ml), \( \alpha,\alpha,\alpha \)-trifluoroacetophenone (1.3 mmol, 0.23 g, 0.189 ml) and (EDTA)\( \text{Na}_2 \) (5 ml of 4 x 10^-4 M solution), was added a solid mixture of Oxone® (1.3 mmol, 0.85 g) and sodium hydrogen carbonate (4.2 mmol, 0.36 g) over 30 minutes. The reaction mixture was allowed to stir vigorously with the exclusion of light for the 24 hours. After such time the reaction mixture was partitioned between diethyl ether and water and the diethyl ether layer separated. This was then dried over anhydrous sodium sulfate and evaporated in vacuo.

Column chromatography was undertaken on the crude material (silica gel using an initial elution system of 9:1 hexane:diethyl ether, progressing through to 100% diethyl ether. TLC system used was 8:2 ethyl acetate:hexane). This gave the oxime isomeric degradation product (40) (48 mg, 98%)

\( \nu_{\text{max}}/\text{cm}^{-1} \) (CDCl₃ film), 3424, 1593, 1504, 1457, 1253, 1125

\( \delta_H \) (400 MHz, CDCl₃), 7.67-7.64 (1H, t, \( J=3.49 \text{ Hz} \), oxime-H), 7.08 (1H, brs, isomeric oxime-H), 6.97-6.87 (4H, m, ArH), 4.97-4.96 (2H, d, \( J=2.2 \text{ Hz} \), isomeric CH₂), 4.71-4.70 (2H, d, \( J=3.5 \text{ Hz} \), CH₂), 3.88 (3H, s, OMe), 3.87 (3H, s, isomeric OMe).

\( \delta_C \) (100 MHz, CDCl₃), 149.2 (isomeric oxime C), 148.6 (ArC), 148.4 (ArC), 146.7 (oxime C), 146.4 (ArC), 146.3 (ArC), 121.2 (ArCH), 121.0 (ArCH), 119.9 (ArCH), 119.8 (ArCH), 113.3 (ArCH), 112.3 (ArCH), 110.9 (2ArCH), 65.0 (CH₂), 61.9 (CH₂), 54.8 (OMe).

GC-MS (EI); \( M^+ \) 181 (retention time 15.27 min), \( M^+ \) 163 (retention time 13.70 min)
6.41.1 Altered time monophasic conditions (Table 17)

Reaction times used were 5 hours, 2 hours and 1 hour.

To a monophasic system, at 0°C, consisting of Carvedilol (0.27mmol, 0.109g), acetonitrile (7.5ml), trifluoroacetophenone (1.3mmol, 0.23g, 0.189ml) and (EDTA)Na₂ (5ml of 4x10⁻⁴M solution), was added a solid mixture of Oxone® (1.3mmol, 0.85g) and sodium hydrogen carbonate (4.2mmol, 0.36g) over 30 minutes. The reaction mixture was allowed to vigorously stir with the exclusion of light, for the required time. After such time the reaction mixture was partitioned between diethyl ether and water and the diethyl ether layer separated. This was then dried over anhydrous sodium sulfate and evaporated *in vacuo*. Proton NMR analysis of the crude product showed oxime to be mainly present.

6.41.2 Biphasic oxidation conditions (Table 17)

To a biphasic system, at 0°C, consisting of Carvedilol (0.27mmol, 0.109g), tetra butyl ammonium sulphate (catalytic amount), dichloromethane (7.5ml), trifluoroacetophenone (1.3mmol, 0.23g, 0.189ml) and (EDTA)Na₂ (5ml of 4x10⁻⁴M solution), was added a solid mixture of Oxone® (1.3mmol, 0.85g) and sodium hydrogen carbonate (4.2mmol, 0.36g) over 30 minutes. The reaction mixture was allowed to vigorously stir with the exclusion of light for an hour. After such time the reaction mixture was partitioned between dichloromethane and water and the organic layer separated. This was then dried over anhydrous sodium sulfate and evaporated *in vacuo*. Proton NMR analysis of the crude product showed oxime to be mainly present.
6.41.3 Increased pH monophasic oxidation conditions (Table 17)

To a monophasic system, at 0°C, consisting of Carvedilol (0.27mmol, 0.109g), tetrabutyl ammonium hydrogen sulphate (0.04mmol, 0.015g), acetonitrile (10ml) and freshly prepared aqueous potassium carbonate (7ml, 0.5ml of glacial acetic acid was added to 100ml of 0.1M potassium carbonate) The pH of the mixture was adjusted with 1M potassium carbonate until pH~11

A solution of Oxone® (1.3mmol, 0.85g) in aqueous (EDTA)Na₂ (5ml) was added to the reaction mixture, by syringe over 90 minutes. The reaction mixture pH was constantly monitored and adjusted to pH11

Immediately after Oxone® addition the reaction mixture was partitioned between dichloromethane and water. The organic layer was separated and dried over anhydrous sodium sulfate and evaporated in vacuo. Proton NMR analysis of the crude product showed oxime to be mainly present

6.42 Formation of Dimethyldioxirane

A dry 1000ml three necked flask was charged with a mixture of distilled water (254ml), commercial acetone (192ml) and sodium hydrogen carbonate (58g) and cooled to 0°C, whilst being vigorously stirred. In a 250ml round bottomed flask (attached to the three-necked flask by flexible tubing) solid Oxone® (0.195mol, 120g) was added in five portions to the reaction vessel via the tubing, at three-minute intervals. After three minutes of the last portion being added a moderate vacuum was applied and the cooling bath around the three-necked flask removed. The dimethyldioxirane as an acetone solution quickly distilled over into the collection flask
(-78°C), and the characteristic yellow solution of dimethyldioxirane was then tested with starch paper for the presence of peroxide. The dimethyldioxirane solution was finally filtered through magnesium sulfate and collected in a dry flask which was placed in the freezer.

**Standardisation of DMD solution**

Potassium iodide solution (10% W/V, 5ml) and an acetic acid / acetone solution (3ml, 3:2 solution) was placed in a conical flask and mixed thoroughly. Dioxirane solution (0.2ml) was pipetted into the flask. The solution turns brown. Sodium thiosulphate solution (0.01M) was titrated in until the solution becomes colourless. (See appendix C for chemical equations and calculations of the molarity of dimethyldioxirane solutions).

6.43 Oxidation using isolated dimethyldioxirane solution

In a flask charged with Carvedilol (0.492mmol, 0.2g) in HPLC grade acetone (5ml), cooled to 0°C, was added an aliquot of dimethyldioxirane solution (5.17ml of 0.095M solution). This was gradually allowed to warm to room temperature and stirred overnight.

The acetone was removed *in vacuo*. Column chromatography (8:2, hexane: ethyl acetate) gave 60mg of material which was speculated to be the ketone form of Carvedilol.

Preparative TLC in the same solvent system did not improve the purity and a crude analysis was performed

\[ \nu_{\text{max}}/\text{cm}^{-1} (\text{CDCl}_3 \text{ film}) ; 1506, 1457, 1381, 1253, 1097. \]
δ<sub>H</sub> (250MHz, CDCl<sub>3</sub>); 8 68 (1H, brs, NH), 8 27-8 24 (1H, d, <i>J</i>=7 7Hz, H5), 7 31-7 10 (m, ArH), 6 97-6 79 (m, ArH), 6 58-6 55 (1H, d, <i>J</i>=7 8Hz), 4 50-4.48 (m), 4.23-4 14 (m), 3 75 (3H, s, OMe), 3 73-3 63 (m), 3 17-3 02 (m)

A further oxidation under identical conditions gave a crude product, the <sup>13</sup>C NMR spectrum of which showed it to contain a carbonyl at δ211 and significant changes in the region δ50-75 compared to Carvedilol, but no assignments were possible
6.5 Synthesis of Chiral ketones

6.51 Synthesis of difluoro-indanone derivative

6.51.1 Synthesis of 3-(3, 5-difluorophenyl) propionic acid (44)

\[
\begin{array}{c}
\text{F} \\
\text{O} \\
\text{H} \\
\text{F}
\end{array}
\]

A solution of 3, 5-difluorocinnamic acid (1 020 g, 5.5 mmol) in an excess of ethyl acetate was hydrogenated with palladium (10% on carbon) for 12 hours. The crude product was passed through celite and evaporated \textit{in vacuo}. This was recrystallised from hexane to yield the \textit{title compound} as a colourless solid (0.92 g, 89%) m.p. 57-58°C (literature value 59-60°C).

\[\delta_{\text{H}}(250\text{MHz}; \text{CDCl}_3); 11.15 (1\text{H, brs, OH}), 6.76-6.60 (3\text{H, m, ArH}), 2.96-2.90 (2\text{H, t, } J=7.5 \text{ Hz, CH}_2), 2.69-2.63 (2\text{H, t, } J=7.5 \text{ Hz, CH}_2).\]

Data consistent with literature values. 66

6.51.2 Synthesis of 5,7-Difluoro-1-indanone (45)

\[
\begin{array}{c}
\text{F} \\
\text{O} \\
\text{F}
\end{array}
\]
To 3-(3,5- difluorophenyl) propionic acid (44) (2.04 g, 10.9 mmol) was added polyphosphoric acid (excess) and the reaction mixture warmed for 24 hours. The crude product was worked up diluting with water (50 ml) and extracting with ethyl acetate (2 x 40 ml). The combined organic layer was washed with sodium hydrogen carbonate solution (2 x 20 ml) and water (2 x 20 ml) dried over anhydrous sodium sulfate and evaporated *in vacuo*.

The crude product was purified by column chromatography (eluent 50:50 ethyl acetate:hexane) to yield the *title compound* as a colourless solid (1.17 g, 64%) m.p. 80-81°C (literature value 66 81-81.5°C).

δ*H* (250 MHz; CDCl₃) 6.99-6.94 (1H, m, ArH), 6.78-6.69 (1H, m, ArH), 3.18-3.13 (2H, m, CH₂), 2.76-2.71 (2H, m, CH₂)

δ*C* (62.9 MHz; CDCl₃) 202 (C=O), 169.5-166 (dd, ̂J=251 Hz, 12 Hz, CF), 162-159 (dd, ̂J=235 Hz, 12 Hz, CF), 157.5 (C), 121 (C), 109.7-109.2 (dd, ̂J=224 Hz, 4.6 Hz, ArCH), 103.8-103.0 (dd, ̂J=27.1 Hz, 23.2 Hz, ArCH), 36.8 (2-CH₂), 26.0 (3-CH₂).

Data consistent with literature values 66.

6.51.3 Synthesis of methyl-5,7-difluoro-1-indanone-2-carboxylate (46)

![Image of molecular structure]

To a solution of diisopropylamine (0.77 ml, 5.5 mmol) in THF (4 ml) at -78°C was added n-BuLi (3.43 ml, 5.5 mmol, 1.6 M in hexane). A solution of 5,7-Difluoro-1-indanone (45)
(0.775 g, 4.6 mmol) in THF (3 ml) was slowly added to the LDA/THF mixture and stirred for 30 minutes. Methylcyanoforomate (0.435 ml, 5.5 mmol) was added and the reaction mixture stirred at -78°C for a further 30 minutes.

The reaction mixture was warmed to room temperature and diluted with water (100 ml) and extracted using ethyl acetate (4 x 60 ml). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo.

Attempted purification on the crude product by column chromatography (eluent 50:50 ethyl acetate:hexane) did not surrender the title compound in pure form, however proton NMR analysis of the crude material gave evidence that the product required was present (crude 0.43 g, 41%).

δH (250 MHz, CDCl3) 7.01-6.94 (1H, m, ArH), 6.86-6.69 (1H, m, ArH), 3.86 (3H, s, enol-OMe), 3.80 (3H, s, keto-OMe), 3.12 (2H, m, enol-aliphatic), 2.73 (2H, m, keto-aliphatic).

Although only crude data was obtained literature values gave confirmation of proton NMR values for (46).

6.5.1.4 Synthesis of methyl 5,7-difluoro-1-oxo-2-prop-2-enyl-2,3-dihydro-1H-indene-2-carboxylate (47)

![Chemical Structure]

To a suspension of sodium hydride (3.49 mmol, 0.083 g) in anhydrous DMF (6 ml) at 0°C was added a solution of semi-crude methyl 5,7-difluoro-1-oxo-2,3-dihydro-1H-indene-2-
carboxylate (46) (2.9mmol, 0.657g) in anhydrous DMF (6ml). The reaction mixture was warmed to room temperature and stirred for 1 hour. Allyl bromide (4.64mmol, 0.56g) was added at 0°C and the reaction mixture rewarmed to room temperature and stirred overnight.

The reaction mixture was diluted with water (50ml) and extracted using ethyl acetate (2x25ml). The organic layers were combined and dried over anhydrous sodium sulfate and evaporated _in vacuo._

The crude product was purified by column chromatography (eluent 9:1 petroleum ether:ethyl acetate) to yield a partially purified compound that was the _title compound_ (0.524g, 64%).

\[\delta_H (250MHz; CDCl_3) 7.01-6.98 (1H, dd, J=7.8Hz, 1.1Hz, ArH), 6.82-6.74 (1H, td, J=9 1Hz, 2 0Hz, ArH), 5.72-5.56 (1H, m, CH-allylic), 5.20-5.06 (2H, m, CH_2-allylic), 3.72 (3H, s, OMe), 3.69-3.62 (1H, d, J=17.9Hz, CH_2), 3.19-3.12 (1H, d, J=17.9Hz, CH_2), 2.92-2.83 (1H, ddt, J=13.9Hz, 7.4Hz, 1.0Hz, CH_2), 2.69-2.60 (1H, ddt, J=13.9Hz, 7.0Hz, 1.1Hz, CH_2)\] COSY confirmed coupling

\[\delta_C (62.9MHz; CDCl_3) 196.4 (d, J=2.9Hz, C=O), 170.3 (C=O), 170.0-165.7 (dd, J=259Hz, 10Hz, CF), 162.0-157.6 (dd, J=267Hz, 13Hz, CF), 157.0-156.7 (dd, J=11.8Hz, 3.9Hz, C), 132.0 (CH-allylic), 119.7 (CH_2-allylic), 119.6 (C), 109.5-109.1 (dd, J=22.1Hz, 4.1Hz, ArCH), 104.2-103.4 (dd, J=27.5Hz, 22.6Hz, ArCH), 60.6 (C), 52.8 (OMe), 38.6 (CH_2), 35.7 (CH_2)\]

The spectral data that was collected on the partial purified product (47) was consistent to the related structure (16, X=H).
65.1.5 Synthesis of Methyl 5,7-difluoro-1-hydroxy-2-prop-2-enyl-2,3-dihydro-1H-indene-2-carboxylate (48)

To a solution of partially pure methyl 5,7-difluoro-1-oxo-2-prop-2-enyl-2,3-dihydro-1H-indene-2-carboxylate (47) (0.524g, 1.97mmol) in ethanol (20ml) at 0°C was added a suspension of sodium borohydride (0.089g, 2.36mmol) in ethanol (6ml). This was warmed to room temperature and stirred overnight. The reaction mixture was quenched with 2M HCl to pH1 and extracted with ethyl acetate (2x40ml). The combined organic layer was then washed (2x20ml), sodium hydrogen carbonate solution (2x20ml) and water (2x10ml) dried over anhydrous sodium sulfate and evaporated in vacuo.

The crude product was purified by column chromatography (eluent hexane diethylether mixtures). This was recrystallised from hexane to yield the title compound as a white solid (0.322g, 61%) m p 89-90°C

$\nu_{\text{max}}$/cm$^{-1}$ (CDCl$_3$ film): 3448 (OH), 2954, 1730 (C=O), 1630, 1601, 1486, 1444, 1338 (OMe), 1220, 1112, 1018

$\delta$(H) (250MHz, CDCl$_3$) 6.73-6.71 (1H, m, ArH), 6.65-6.60 (1H, m, ArH), 5.80-5.69 (1H, m, CH-allylic), 5.54 (1H, s, CHOH), 5.14-5.05 (2H, m, CH$_2$-allylic), 3.67 (3H, s, OMe), 3.40-3.36 (1H, d$_{\text{HH}}, J=16$ 6Hz, CH$_2$-ring), 3.01-2.97 (1H, d$_{\text{HH}}, J=16$ 5Hz, CH$_2$-ring),
2.76-2.71 (1H, ddt, J=13.9Hz, 6.9Hz, 1.1Hz, CH₂-allylic), 2.6 (1H, brs, OH), 2.51-2.45 (1H, ddt, J=13.9Hz, 7.5Hz, 1.0Hz, CH₂-allylic) COSY confirmed coupling.

δc (100MHz, CDCl₃) 175.6 (C=O), 165.4-162.9 (dd, J=247Hz, 10.9Hz, CF), 161.1-158.5 (dd, J=251Hz, 13.2Hz, CF), 146.5-146.2 (dd, J=10Hz, 6.5Hz, C), 134.2 (CH-allylic), 125.3-125.1 (dd, J=16.2Hz, 2.9Hz, C), 118.7 (CH₂-allylic), 108.6-108.1 (dd, J=23.4Hz, 3.8Hz, ArCH), 103.1-102.5 (dd, J=26.5Hz, 24.3Hz, ArCH), 76.0 (CH(OH)), 61.6 (C), 52.7 (OMe), 40.8 (CH₂-ring), 37.3 (CH₂-allylic)

m/z (EI) M⁺ 268 09110  C₁₄H₁₄O₃F₂ requires M⁺ 268 0925; 227 (100), 191 (30)

6.5.1.6 Synthesis of 5,7-difluoro-2-(1-hydroxy-1-methylethyl)-2-prop-2-enyl-2,3-dihydro-1H-inden-1-ol (49)

A solution of methyl iodide (0.305g, 2.1mmol) in anhydrous diethyl ether (5ml) was slowly added to a stirring mixture of magnesium (0.0516g, 2.1mmol) in anhydrous diethyl ether (6ml). The Grignard solution was added to a solution of methyl 5,7-difluoro-1-hydroxy-2-prop-2-enyl-2,3-dihydro-1H-indene-2-carboxylate (48) (0.322g, 1.2mmol) in diethyl ether (5ml) and stirred overnight.

The reaction mixture was quenched with 2M HCl and extracted with ethyl acetate (2x40ml). The combined organic layer was washed with water (2x20ml), sodium
hydrogen carbonate solution (2x20ml) and water (2x10ml) dried over anhydrous sodium sulfate and evaporated in vacuo.

No methylation had occurred by proton NMR analysis. Therefore a reaction using methyl lithium as the alkylating agent was attempted. To a solution of (48) (0.114g, 0.425mmol) in diethyl ether (5ml) at -78°C was added methyl lithium (1.42ml, 2.13mmol). This was stirred at -78°C for 30 minutes then warmed to room temperature to stir for a further 16 hours. After this time the reaction mixture was quenched and extracted in the same way to the above Grignard reaction. Upon analysis by proton NMR it was observed that no methylation had occurred.

6.5.1.7 Evaluation of difluoro-indanone ketone (47)

The oxidation conditions that were used for the evaluation of the catalyst was the monophasic epoxidation conditions (see section 6.3.1.3) using trans-stilbene as substrate for oxidation. However two changes were made, one was the inclusion of phase transfer catalyst and the other the amount of ketone used was only 3 equivalents to 1 equivalent of substrate whereas it is usually 5 equivalents. Analysis by GLC, GC-MS and proton NMR saw no trans-stilbene oxide formed. Therefore it was concluded that this ketone was inactive to dioxirane reaction conditions.
6.52 Synthesis of spiro tetralone derivative (17)

6.52.1 Synthesis of Ethyl 1-oxo-2-prop-2-enyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (53)

To a suspension of sodium hydride (0.82g 34.2mmol) in dry diethyl carbonate (39g, 330mmol, 40ml, pre-dried overnight over sodium hydride) was added dry α-tetralone (1.99g, 13.6mmol, 1.81ml, pre-dried over sodium hydride). This was warmed for 10 minutes until the thick purple solid had formed. To the cooled solid DMF (20ml) was added to dissolve the precipitate. Sodium hydride (0.46g, 19.1mmol) was added to the solution, followed by allyl bromide (5.59g, 46.2mmol). The reaction mixture was stirred at room temperature overnight. After this time the reaction mixture was quenched with 50% acetic acid and extracted with diethyl ether. The organic layer was washed with 2M HCl, sodium hydrogen carbonate solution (2×50ml) and water (2×50ml). The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo.

The crude mixture was partially purified by column chromatography (eluent 8:2 petrol. diethyl ether), however the diethyl carbonate co-eluted with the product, which gave increased yield (11.4g, 325%).
Although there was excess diethyl carbonate in the sample and no pure material was isolated, crude NMR analysis gave evidence that the required product was present

\[ \delta_H(250\text{MHz}, \text{CDCl}_3), 8.05-8.01 (1\text{H}, \text{dd}, J=7.8\text{Hz}, 1.5\text{Hz}, \text{ArH}), 7.49-7.43 (1\text{H}, \text{td}, J=7.5\text{Hz}, 1.3\text{Hz}, \text{ArH}), 7.34-7.19 (2\text{H}, \text{m}, \text{ArH}), 5.92-5.75 (1\text{H}, \text{M}, \text{allyl-CH}), 5.17-5.08 (2\text{H}, \text{m}, \text{allyl-CH}_2), 4.18-4.09 (2\text{H}, \text{q}, J=7.1\text{Hz}, \text{CH}_2), 2.99-2.93 (1\text{H}, \text{m}, \text{CH}_2), 2.73-2.63 (1\text{H}, \text{m}, \text{CH}_2), 2.57-2.48 (1\text{H}, \text{m}, \text{CH}_2), 2.19-2.08 (1\text{H}, \text{m}, \text{CH}_2), 1.19-1.13 (3\text{H}, \text{t}, J=7.1\text{Hz}, \text{CH}_3) \]

6.52.2 Synthesis of Ethyl 1-hydroxy-2-prop-2-enyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (54)

![Chemical structure of ethyl 1-hydroxy-2-prop-2-enyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate](image)

A solution of crude ethyl 1-oxo-2-prop-2-enyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (53) (7.24mmol, 1.87g) in ethanol (14ml) was cooled to 0°C. To this a suspension of sodium borohydride (8.6mmol, 0.329g) in ethanol (20ml) was added, warmed to room temperature and stirred overnight. The reaction mixture was quenched with 2M HCl and extracted using ethyl acetate (2x40ml). The combined organic layer was then washed with water (2x20ml), sodium hydrogen carbonate solution (2x20ml) and water (2x20ml) and dried over anhydrous sodium sulfate and evaporated \textit{in vacuo}.
The crude product was purified by column chromatography (eluent 95 5 petroleum ethyl acetate) to yield the title compound as a colourless oil (1.22g, 64%)

$\nu_{\text{max}}/\text{cm}^{-1}$ (CDCl$_3$ film) 3494 (OH), 2978, 2934, 1724 (C=O), 1640, 1454, 1217, 1023, 916, 773, 738

$\delta$H (250MHz, CDCl$_3$) 7 48-7 46 (1H, m, ArH), 7 21-7 18 (2H, m, ArH), 7 09-7 08 (1H, m, ArH), 5 82-5 73 (1H, m, CH-allyl), 5 09-5 05 (2H, m, CH$_2$-allyl), 4 66 (1H, s, CHOH), 4 20-4 14 (2H, q, $J$=7 1Hz, CH$_2$-ester), 2 89-2 78 (3H, m, CH$_2$-ring and OH), 2 49-2 43 (1H, dd, $J$=13 9Hz, 6 9Hz, CH$_2$-allyl), 2 33-2 25 (2H, m, CH$_2$-allyl), 1 93-1 88 (1H, dt, $J$=13 2Hz, 6 6Hz, CH$_2$-ring), 1 26-1 23 (3H, t, $J$=7 1Hz, Me)

COSY confirmed coupling that enabled assignment of allyl CH$_2$ and ring CH$_2$

$\delta$C (100MHz, CDCl$_3$) 176 0 (C=O), 137 7 (ArC), 135 6 (ArC), 133 4 (CH-allyl), 129 4 (ArCH), 129 0 (ArCH), 128 1 (ArCH), 126 7 (ArCH), 118 9 (CH$_2$-allyl), 73 3 (CHOH), 61 1 (CH$_2$-ester), 50 7 (C), 38 7 (CH$_2$-allylic), 25 7 (CH$_2$-ring), 24 8 (CH$_2$-ring), 14 6 (Me)

m/z (EI) M$^+$ 260.1409 C$_{16}$H$_{20}$O$_3$ requires M$^+$ 260.1412, 219 (100)

6.52.3 Synthesis of 2-(1-Hydroxy-1-methylethyl)-2-prop-2-enyl-1,2,3,4-tetrahydronapthalen-1-ol (55)
To a solution of ethyl 1-hydroxy-2-prop-2-enyl-1,2,3,4-tetranaphthalene-2-carboxylate (54) (0.508g, 1.95mmol) in diethyl ether (10ml) at -78°C was added methyl lithium (6.51ml, 9.76mmol). This was stirred at -78°C for 30 minutes then warmed to room temperature and stirred overnight.

The reaction mixture was quenched with saturated ammonium chloride solution (40ml) and extracted using ethyl acetate (2x30ml). The combined organic layers were washed with sodium hydrogen carbonate solution (2x20ml) and water (2x20ml) and dried over anhydrous sodium sulfate and evaporated in vacuo. The crude product was purified by column chromatography (eluent 9:1 petroleum ether:ethyl acetate) to yield the title compound as a colourless oil (0.305g, 63%).

$\nu_{\text{max}}/\text{cm}^{-1}$ (CDCl$_3$ film) 3347 (OH), 2973, 1459, 1387, 1172, 1041, 748

$\delta_H$ (400MHz, CDCl$_3$) 7.63-7.61 (1H, dd, $J=7.8$Hz, 1.0Hz, ArH), 7.25-7.15 (2H, m, ArH), 7.07-7.05 (1H, dd, $J=7.4$Hz, 0.6Hz, ArH), 6.26-6.15 (1H, m, CH$_2$-allyl), 5.18 (1H, s, CHOH), 5.01-4.92 (2H, m, CH$_2$-allyl), 4.0 (1H, brs, OH), 2.87-2.82 (1H, m, CH$_2$-ring), 2.75-2.70 (1H, m, CH$_2$-ring), 2.56-2.50 (1H, dt, $J=15$ 2Hz, 1.4Hz, CH$_2$-allyl), 2.33-2.27 (1H, dt, $J=15$ 2Hz, 0.5Hz, CH$_2$-allyl), 1.74-1.69 (2H, m, CH$_2$-ring), 1.5 (1H, brs, OH), 1.41 (3H, s, Me), 1.38 (3H, s, Me)

COSY confirmed coupling.

$\delta_C$ (100MHz; CDCl$_3$) 139.3 (ArC), 139.0 (CH$_2$-allyl), 135.0 (ArC), 127.6 (ArCH), 126.4 (ArCH), 126.2 (ArCH), 125.7 (ArCH), 116.5 (CH$_2$-allyl), 79.1 (C), 73.7 (CHOH), 45.7 (C), 33.6 (CH$_2$-allyl), 28.3 (CH$_2$-ring), 26.5 (2xMe), 25.9 (CH$_2$-ring),

m/z (EI) $M^+$ 246.16232 C$_{16}$H$_{25}$O$_2$ requires $M^+$ 246.16198; 170 (100), 187 (75).
6.52.4 Synthesis of 2-(1-Hydroxy-1-methylethyl)-2-prop-2-enyl-1,2,3,4-tetrahydronaphthalen-1-one (56)

To a solution of sodium dichromate dihydrate (0.394 g, 1.3 mmol) in water (10 ml) at 0°C was slowly added concentrated sulphuric acid (2.4 ml), water (15 ml) was then added and the mixture stirred for 30 minutes. Separately a solution of 2-(1-hydroxy-1-methylethyl)-2-prop-2-enyl-1,2,3,4-tetrahydronaphthalen-1-ol (55) (0.495 g, 2.0 mmol) in diethyl ether (27 ml) was cooled for 15 minutes.

After cooling, the aqueous solution was slowly added to the ethereal solution and the ice bath removed, the biphasic system was stirred vigorously for 24 hours at room temperature.

The reaction mixture was separated and the organic layer was washed with sodium hydrogen carbonate solution (2×10 ml) and water (2×20 ml) and dried over anhydrous sodium sulfate and evaporated in vacuo.

The crude product was partially purified by column chromatography (eluent 95.5 petroleum:ethyl acetate). Analysis by proton NMR and IR indicated that the title compound was the main product, however unknown impurities were also obtained (0.317 g, 64%, purity ~ 80-90%).

ν\text{max}/\text{cm}^{-1} \ (\text{CDCl}_3 \ \text{film}) \ 3459 \ (\text{OH}), \ 2929, \ 1681 \ (\text{C}=\text{O}), \ 1599, \ 1454, \ 1222, \ 745
δ_H (250MHz, CDCl₃) 8 02-7 99 (1H, dd, J=7 8Hz, 1 3Hz, ArH), 7 51-7 44 (1H, dt, J=7 4Hz, 1 5Hz, ArH), 7 33-7 27 (1H, m, ArH), 7.22-7.19 (1H, d, J=7 5Hz, ArH), 5 92-5 75 (1H, m, CH-allyl), 5 14-4 91 (2H, m, CH2-allyl), 4 50 (1H, brs, OH), 3 23-3 05 (1H, m, CH₂), 2 95-2 81 (2H, m, CH₂), 2.58-2.48 (1H, m, CH₂), 2 17-2.12 (2H, m, CH₂), 1.23 (3H, s, Me), 1 22 (3H, s, Me)

6.52.5 Synthesis of the spiro Tetralone derivative (17)

Ozone was bubbled through a solution of partially purified 2-(1-hydroxy-1-methylethyl)-2-prop-enyl-1,2,3,4-tetrahydronaphthalen-1-one (56) (0 850g, 3 48mmol) in anhydrous DCM (35ml) at -78°C, until a blue colouration appeared. 30% Hydrogen peroxide solution (1ml) was added and the reaction mixture stirred at room temperature overnight. The reaction mixture was then washed with water (2x25ml) and the organic layer dried over anhydrous sodium sulfate and evaporated in vacuo.

The crude product (0 792g) was immediately dissolved in toluene (30ml) and a catalytic amount of pTSA added, this was warmed to 80°C for 24 hours. The reaction mixture was diluted with DCM (3x40ml) and washed with water (2x20ml) then dried over anhydrous sodium sulfate and evaporated in vacuo.

166
The crude product underwent hot filtration through charcoal and crystallisation (ethyl acetate: hexane) to yield the title compound as white crystals (0.085 g, 10%) m p 207-208°C.

$\nu_{\text{max}}/\text{cm}^{-1}$ (CDCl$_3$ film), 2982, 2624, 1776 (C=O), 1675 (C=O), 1453, 1256, 968, 752

$\delta_{\text{H}}$ (250 MHz, CDCl$_3$), 8.11-8.07 (1H, dd, $J$=7.9 Hz, 1 2Hz, ArH), 7.55-7.49 (1H, dt, $J$=7 4Hz, 1 5Hz, ArH), 7.39-7.33 (1H, t, $J$=7 5Hz, ArH), 7.26-7.24 (1H, d, $J$=6 1Hz, ArH), 3.14-2.92 (2H, m, CH$_2$), 2.97-2.90 (1H, d, $J$=16 9Hz, CH$_2$-lactone), 2.50-2.43 (1H, d, $J$=16 9Hz, CH$_2$-lactone), 2.35-2.29 (2H, m, CH$_2$), 1.55 (3H, s, Me), 1.25 (3H, s, Me)

$\delta_{\text{C}}$ (62.9 MHz, CDCl$_3$) 198.0 (C=O), 173.1 (C=O), 142.3 (ArC), 133.9 (ArCH), 132.6 (ArC), 128.7 (ArCH), 127.7 (ArCH), 127.3 (ArCH), 86.5 (C), 53.8 (C), 39.6 (CH$_2$), 29.5 (CH$_2$), 26.0 (CH$_2$), 25.3 (Me), 25.2 (Me)

m/z (EI) M$^+$ 244 1105 C$_{13}$H$_{16}$O$_3$ requires M$^+$ 244.1099, 186 (100)

X-ray available in appendix B and confirms the identification of the structure

6.52.6 Evaluation of spiro tetralone (17) as a catalyst

To a monophasic system consisting of trans-stilbene (0.27 mmol, 50 mg), acetonitrile (7.5 ml), spiro tetralone (17) (1.3 mmol, 317 mg for 5 equivalents or 0.81 mmol, 197 mg for 3 equivalents) and (EDTA)$_2$Na$_2$ solution (5 ml of 4x10$^{-4}$M). Was added a solid mixture of Oxone® (1.3 mmol, 0.85 g) and sodium hydrogen carbonate (4.2 mmol, 0.36 g) over 30 minutes. This was stirred vigorously with the exclusion of light at room temperature for 24 hours.
After such time the reaction mixture was worked up by taking the reaction mixture into ethyl acetate and washing with water and sat sodium hydrogen carbonate. The organic layer was dried over sodium sulfate and evaporated to dryness in vacuo.

The crude products were analysed by GC-MS and expressed as percentage conversion. When TFAP replaced the spiro tetralone (17) for comparative purposes the equivalent amounts were kept the same but masses were different due to differences in molecular weight. The blank reactions were run under the same reaction conditions with the exception that no ketone was added. PTC was also added in some of the reactions (see Table 19 for details).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Retention time (min)</th>
<th>Typical % conversion of oxidised product obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans-stilbene</td>
<td>16.228</td>
<td>8% (with (17))</td>
</tr>
<tr>
<td>Trans-stilbene oxide</td>
<td>16.353</td>
<td>99% (with TFAP)</td>
</tr>
</tbody>
</table>

GC-MS used for determination of peaks on mass.
6.53 Synthesis of 4-chromanone derivative (18)

6.53.1 Synthesis of Sodium chloromethanesulphonate (Scheme 35) \(^{163}\)

\[
\text{Na}^+\text{O} \quad \text{S} \quad \text{Cl}
\]

To a solution of sodium sulphite (0.2 mol, 25.2 g) in water (50 ml) and ethanol (3 ml) was added dichloromethane (0.1 mol, 8.5 g) and a catalytic amount of copper (II) chloride crystals. The reaction mixture was refluxed for 30 hours followed by a further 12 hours at room temperature.

The reaction mixture evaporated \textit{in vacuo} to give a solid which was extracted using ethanol (soxhlet apparatus, 6 hour reflux) on cooling a white precipitate formed and was isolated via filtration to yield the assumed \textit{title compound} (3.24 g, 25%).

\(\nu_{\text{max}}/\text{cm}^{-1}\) (Nujol) 3423, 2572, 1205, 1050, 740.

\(\delta_{\text{H}}\) (250 MHz, D\(_2\)O) 4.79 (s), 4.51 (s).

6.53.2 Synthesis of Sodium phenoxy methanesulphonate (Scheme 35) \(^{164}\)

\[
\text{O} \quad \text{S} \quad \text{O}^+\text{Na}
\]
To a mixture of sodium chloromethanesulphonate (21.2 mmol, 3.2 g) and phenol crystals (53.1 mmol, 4.99 g) was added 50% w/v solution of sodium hydroxide (2.97 g in 151 ml). The reaction mixture was heated until no more water distilled off and then continued for 4 hours, which gave a purple solid.

The reaction mixture was allowed to cool and the solid dissolved in water (100 ml) which was acidified to pH 1 and extracted using diethyl ether (2 x 30 ml). The remaining aqueous layer was boiled and treated with charcoal and filtered. The colourless filtrate was evaporated *in vacuo*.

Analysis by proton NMR was very poor and indicated that the reaction had not occurred.
6.54 Synthesis of iso-4-chromanone (19)

6.54.1 Synthesis of Ethyl 2-(chloromethyl)benzene-1-carboxylate (64)\textsuperscript{167,168}

A solid mixture of triphenyl dichlorophosphorane (20.3g, 63mmol) and phthalide (8.04g, 60mmol) was heated to 180°C for 4 hours to cause mass liquidation. The reaction mixture then cooled to 50°C and ethanol (100ml) was added and the reaction mixture allowed to stir overnight.

The reaction mixture was then cooled to room temperature and poured onto ice. The crude product was extracted using diethyl ether (4x25ml). The combined organic extract then washed with water (2x50ml), sodium hydrogen carbonate solution (2x50ml) and water (2x25ml). The diethyl ether layer was then dried over anhydrous sodium sulfate and evaporated \textit{in vacuo}

A solid by-product was precipitated out in hexane. The liquor containing the required product was purified using column chromatography (eluent 80 20 hexane: diethyl ether) to yield the \textit{title compound} as a yellow oil (5.9g, 49%).

By GC-MS the methyl ester is also present in a small quantity. m/z (E I) M\textsuperscript{+} 184; 89 (100), retention time 12.126 min

\begin{align*}
\nu_{\text{max}}/\text{cm}^{-1} (\text{CDCl}_3 \text{ film}) & : 2982, 1717 (\text{C=O}), 1601, 1449, 1366, 1267, 1130, 1079, 714
\end{align*}
δ_H (250MHz, CDCl₃) 7.98-7.94 (1H, m, ArH), 7.51-7.47 (2H, m, ArH), 7.39-7.33 (1H, m, ArH), 5.03 (2H, s, CH₂), 4.42-4.33 (2H, q, J=7.1Hz, CH₂-ester), 1.42-1.36 (3H, t, J=7.1Hz, Me) Methyl ester impurity singlet falls at 3.90ppm (OMe)

δ_C (62.9MHz; CDCl₃) 166.4 (C=O), 138.4 (ArC), 132.2 (ArCH), 130.8 (ArCH), 130.6 (ArCH), 129.3 (ArC), 128.2 (ArCH), 61.1 (CH₂Cl), 44.3 (CH₂-ester), 14.0 (Me) Methyl ester impurity falls at 52.0ppm (OMe)

GC-MS, Product (64) m/z (E I) M⁺ 198, 133(100), retention time 13.15

6.54.2 Synthesis of Ethyl 2-({[2-(ethyloxy)-2-oxoethyl]oxy}methyl)benzene-1-carboxylate (65)¹⁶⁵,¹⁶⁶

Ethyl glycolate (5g, 48mmol) was added to sodium ethoxide (1.82g, 26mmol) this was heated at 50°C for 5 hours. The ethanol was removed and replaced with DMSO (25ml) and heated to 50°C. A solution of ethyl 2-(chloromethyl) benzene-1-carboxylate (64) (5g, 25mmol) in DMSO (6ml) was added and the reaction mixture stirred overnight. After cooling the mixture was poured onto ice and extracted using diethyl ether (4x50ml) the combined extract was then washed with water (2x50ml). The diethyl ether layer was dried over anhydrous sodium sulfate and evaporated in vacuo

The crude product was purified by column chromatography (eluent hexane:diethyl ether mixtures) to yield the title compound as a yellow oil (2.7g, 40%)
$\nu_{\text{max}}/\text{cm}^{-1}$ (CDCl$_3$ film) 2982, 1754 (C=O), 1715 (C=O), 1448, 1367, 1262, 1202, 1140, 1080, 742

$\delta_H$ (250MHz, CDCl$_3$) 7.97-7.93 (1H, dd, $J=7.8\text{Hz}$, 1.3Hz, ArH), 7.74-7.71 (1H, d, $J=7.8\text{Hz}$, ArH), 7.56-7.49 (1H, dt, $J=7.5\text{Hz}$, 1.4Hz, ArH), 7.36-7.30 (1H, dt, $J=7.5\text{Hz}$, 0.7Hz, ArH), 5.04 (2H, s, CH$_2$), 4.38-4.30 (2H, q, $J=7.1\text{Hz}$, CH$_2$-ester), 4.27-4.18 (2H, q, $J=7.1\text{Hz}$, CH$_2$-ester), 4.20 (2H, s, CH$_2$), 1.41-1.35 (3H, t, $J=7.1\text{Hz}$, Me-ester), 1.31-1.25 (3H, t, $J=7.1\text{Hz}$, Me-ester)

$\delta_C$ (100MHz, CDCl$_3$) 170.2 (benzylic C=O), 166.9 (C=O), 139.9 (ArC), 132.4 (ArCH), 130.4 (ArCH), 128.4 (ArC), 128.0 (ArCH), 127.1 (ArCH), 71.2 (CH$_2$), 68.2 (CH$_2$), 60.9 (CH$_2$-ester), 60.7 (CH$_2$-ester), 14.2 (Me), 14.2 (Me).

$m/z$ (CI) M+H 267.1233 C$_{14}$H$_{18}$O$_5$ requires M+H 267 1232, 133 (100)

Dieckmann cyclisation to form ethyl 4-oxo-3, 4-dihydro-1H-isochromene-3-carboxylate (62) was attempted with different bases (KH/THF$^{169}$, Na/ toluene$^{165}$ and NaH/ THF$^{166}$).

However none of the desired product (62) was identified in the proton NMR spectrum of the reaction mixture.

6.54.3 Synthesis of Ethyl glyoxylate (69)$^{173}$

![Ethyl glyoxylate](image)

Ethyl diethoxyacetate (12.9g, 0.073mol), glyoxylic acid monohydrate (6.5g, 0.07mol) and pTSA (100mg) were combined and heated at 90°C for 24 hours.
The resultant syrup was cooled in ice and stirred vigorously while phosphorus pentoxide (9g) was added. The reaction mixture was then heated for a further 2 hours at 90°C. The crude product then cooled and distilled under vacuum to yield a colourless oil (9.3g, 129%).

Upon analysis a mixture of the hydrated and hemi-acetal forms of the product (69) were suspected to be present. However the product was used in this form in the next step. A small sample was dehydrated with molecular sieves (over 80 hours) which was upon analysis identified as the required aldehyde (69).

\[ \nu_{\text{max}}/\text{cm}^{-1} (\text{neat}) 3428 (\text{H-bonding}), 1745 (\text{C}=\text{O}), 1447, 1301, 1225, 1096 \]

\[ \delta_{\text{H}} (250\text{MHz, CDCl}_3) \ 9.40 \text{ (s, aldehyde-H), 4.43-4.24 (2H, dq, \ J=7 1\text{Hz, 0 5Hz, CH}_2), 1.42-1.35 (3H, dt, J=7 1\text{Hz, 0 5Hz, Me})} \]

6.54.4 Synthesis of Ethyl 2-hydroxypent-4-enoate (67)

To a slurry of indium powder (100 mesh, 2g, 17.5mmol) in water (158ml) was added a 50% solution of crude ethyl glyoxylate (22.8mmol, 2.33g, in hydrated and hemi-acetal form) in toluene. Allyl bromide (23mmol, 2.87g) was slowly added and the reaction mixture stirred for 24 hours. During this time a white precipitate formed. Ethyl acetate (40ml) was added and the reaction stirred for 30 min, the precipitate was dissolved by the addition of HCl (2M) to ~pH1. The crude product was extracted using
ethyl acetate (2x40ml) and washed with water (2x40ml) The combined ethyl acetate
layer was dried over anhydrous sodium sulfate and evaporated in vacuo.
The crude product was purified using column chromatography (eluent 7.3 hexane : diethyl ether) to yield the title compound as a colourless oil (1.7g, 52%)

$\nu_{\text{max}}/\text{cm}^{-1}$ (CDCl$_3$ film) 3483 (OH), 2981, 1734 (C=O), 1213, 1087

$\delta_{\text{H}}$ (250MHz, CDCl$_3$) 5.90-5.73 (1H, m, CH-allyl), 5.19-5.10 (2H, m, CH$_2$-allyl), 4.30-4.18 (3H, m, CH$_2$-ester, CHOH), 3.12-3.10 (1H, d, $J=5.8$Hz, OH), 2.64-2.39 (2H, m, CH$_2$), 1.32-1.26 (3H, dt, $J=7.1$Hz, 0.5Hz, Me-ester)

$\delta_{\text{C}}$ (62.9MHz, CDCl$_3$) 174.6 (C=O), 132.8 (CH), 118.6 (CH$_2$), 70.2 (CHOH), 61.8 (CH$_2$), 38.9 (CH$_2$), 14.4 (Me)

6.54.5 Synthesis of Ethyl 2-[[{(1-[(ethyloxy)carbonyl]but-3-enyl}oxy)methyl] benzene-1-carboxylate (68)

Ethyl 2-hydroxypent-4-enoate (67) (1.49g, 10.3mmol) was added to sodium ethoxide (0.41g, 6.0mmol) this was heated for 5 hours at 50°C. The ethanol was removed and replaced with DMSO (5ml) and reheated to 50°C. A solution of ethyl 2-(chloromethyl) benzene-1-carboxylate (64) (6.2mmol, 1.24g) in DMSO (2ml) was added and the reaction mixture stirred overnight.
After cooling, the mixture was poured into ice and extracted using diethyl ether (4x25ml) the combined extract was then washed with water (2x20ml). The diethyl ether layer was dried over anhydrous sodium sulfate and evaporated in vacuo.

The crude product was purified by column chromatography (eluent hexane: diethyl ether mixtures) to yield the title compound as a yellow oil (0.83g, 43%).

$\nu_{\text{max}}$ cm$^{-1}$ (CDCl$_3$ film) 3076, 2981, 1748 (C=O), 1716 (C=O), 1447, 1367, 1262, 1194, 1139, 1080, 741.

$\delta_{\text{H}}$ (250MHz, CDCl$_3$) 7.95-7.92 (1H, dd, $J$=7.8Hz, 1 3Hz, ArH), 7.77-7.74 (1H, dd, $J$=7.8Hz, 0 6Hz, ArH), 7.55-7.48 (1H, dt, $J$=7.5Hz, 1 4Hz, ArH), 7.35-7.28 (1H, dt, $J$=7.5Hz, 1 1Hz, ArH), 5.95-5.79 (1H, m, CH-allyl), 5.18-5.07 (2H, m, CH$_2$-allyl), 5.09-4.89 (2H, dd, $J$=35.7Hz, 14 0Hz, CH$_2$-benzyl), 4.37-4.29 (2H, q, $J$=7.12Hz, CH$_2$-benzyl ester), 4.26-4.16 (2H, dq, $J$=7.1Hz, 2 5Hz, CH$_2$-chiral ester), 4.10-4.05 (1H, t, $J$=6.1Hz, CH-chiral), 2.62-2.56 (2H, dt, $J$=6.3Hz, 1.2Hz, CH$_2$), 1.40-1.34 (3H, t, $J$=7.1Hz, Me-ester), 1.30-1.25 (3H, t, $J$=7.1Hz, Me-ester).

$\delta_{\text{C}}$ (100MHz, CDCl$_3$) 172.0 (benzyl C=O), 167.0 (C=O), 140.2 (ArC), 133.2 (chiral CH), 132.2 (ArCH), 130.3 (ArCH), 128.2 (ArC), 127.9 (ArCH), 127.0 (ArCH), 117.9 (CH$_2$-benzyl), 78.6 (CH-allyl), 70.1 (CH$_2$-allyl), 60.87 (CH$_2$-ester), 60.82 (CH$_2$-ester), 37.4 (CH$_2$), 14.30 (Me-ester), 14.28 (Me-ester).

m/z (EI) $M^+$ 306.14631 C$_{17}$H$_{22}$O$_3$ requires $M^+$ 306.14673, 134(100).
6.54.6 Synthesis of Ethyl 4-oxo-3-prop-2-enyl-3,4-dihydro-1H-isochromene-3-carboxylate (63)

![Chemical Structure]

To a solution of ethyl 2-[(1-[(ethyloxy)carbonyl]but-3-enyl]oxy)methyl] benzene-1-carboxylate (68) (0.3g, 0.98mmol) in THF (5ml) at -78°C was added LDA (1.96ml, 2.0M solution) and stirred for 2 hours. Diethyl ether (5ml) was added and the reaction mixture warmed to 0°C. Acetic acid (50% aqueous solution) was added to obtain pH5 and the aqueous layer extracted in diethyl ether (3x10ml). The combined organic layers were washed with water (2x10ml), sodium hydrogen carbonate solution (2x5ml) and water (2x10ml), dried over anhydrous sodium sulfate and evaporated in vacuo. The crude product was partially purified through silica (eluent 7.3 hexane: diethyl ether) (65mg, 26%). This was further purified using a preparative TLC system (95:5:5 hexane:diethyl ether:acetone, run three times). A product was isolated that was thought to be the title compound (11mg) however the sample was still impure. Analysis of the partially purified sample gave confirmation that the product required (63) was present.

**ν<sub>max</sub>/cm<sup>-1</sup>** (CDCl<sub>3</sub> film): 2981, 1736 (C=O), 1701 (C=O), 1601, 1288, 1212, 1026, 753

**δ<sub>H</sub>** (250MHz, CDCl<sub>3</sub>) 8.10-8.03 (1H, m, ArH), 7.61-7.14 (3H, m, ArH), 6.07-5.77 (1H, m, CH-allyl), 5.38-4.89 (2H, q<sub>ab</sub>, J<sub>H,H</sub>= 89Hz, J<sub>H,H</sub>=16Hz, CH<sub>2</sub>-ring), 5.26-5.05 (2H, m, CH<sub>2</sub>-allyl). The remaining CH<sub>2</sub> and CH<sub>3</sub> peaks were not assigned due to impurities overlapping suspected product peaks, which caused assignment difficulties.
$\delta_C$ (100MHz, CDCl$_3$), very difficult to interpret the two ketones were established though at 193.3 and 190.1.

$m/z$ (EI) $M^+ 260$ 10484 $C_{15}H_{18}O_4$ requires $M^+ 260$ 10486, 187 (100)
6.6 Alcohol oxidation by dimethyldioxirane

For the formation of dimethyldioxirane used in these following experiments see section 6 42. The concentration of the dimethyldioxirane used was 0 07 M.

6.61 Synthesis of 2,2,6-Trimethylcyclohexanol (21)

To a solution of 2,2,6-trimethylcyclohexanone (0.903 g, 6.4 mmol) in ethanol (11 ml) at 0°C was slowly added a suspension of sodium borohydride (0.29 g, 7.7 mmol) in ethanol (15 ml). The reaction mixture was stirred overnight at room temperature. After this time, the reaction mixture was diluted with diethyl ether (50 ml) and quenched with 50% aqueous acetic acid to pH 5. The organic layer was separated and washed with water (2 x 20 ml), sodium hydrogen carbonate (2 x 20 ml) and finally with water (2 x 20 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to dryness.

The crude product was purified using column chromatography (eluent 8:2, Hexane: diethyl ether) to yield the title compound as a pale yellow oil (0.67 g, 74%).

As expected both isomers were present in the product and were identified by correspondence of analytical data to literature values. The isomers were calculated to be present in a percentage ratio of 93%: 7%

ν max/cm⁻¹ (neat film) 3405 (OH), 2927, 1457, 1058, 1041, 974.

δ H (250 MHz, CDCl₃) 3.14 (1H, brs, 1-CH-minor isomer), 2.83-2.79 (1H, d, J=10 Hz, 1-CH-major isomer), 1.7-1.0 (cm, 6-CH, 3-, 4-, 5-CH₂+OH-both isomeric
forms), 0 98-0 96 (3H, d, J=6 3Hz, 6-Me), 0 98 (3H, s, 2-Me), 0 87 (3H, s, 2-Me),
0 95-0 92 (3H, d, J=6 8Hz, 6-Me-minor isomer), 0 91 (3H, s, 2-Me-minor isomer)
δc (100MHz, CDCl₃) 83 7 (1-CH), 39 9 (CH₂), 35 7 (2-C), 34 6 (6-CH, CH₂), 29 4 (Me), 21 5 (CH₂), 19 1 (Me), 18 3 (Me) Minor isomer; 79 1 (1-CH), 35 1 (2-C), 32 4 (CH₂), 31 6 (6-CH), 28 4 (Me), 27 4 (CH₂), 24 4 (Me), 21 6 (CH₂), 18 8 (Me)

6.62 Synthesis of 2,6-dimethylcyclohexanol (20)

To a solution of 2, 6-dimethylcyclohexanone (5g, 39.6mmol) in ethanol (37ml) at
0°C, was slowly added a suspension of sodium borohydride (1.79g, 47 5mmol) in
ethanol (53ml) The reaction mixture was stirred overnight at room temperature.
After this time, the reaction mixture was diluted with diethyl ether (100ml) and
quenched with 50% aqueous acetic acid to pH5 The organic layer was separated and
washed with water (2x50ml), sodium hydrogen carbonate (2x50ml) and finally with
water (2x50ml) The organic layer was dried over anhydrous sodium sulfate and
evaporated in vacuo to dryness.
The crude product was purified using column chromatography (eluent 8 2, Hexane:
diethyl ether) to yield the title compound as a pale yellow oil (4.2g, 84%)
As expected all isomers were present in the product and were identified by
correspondence of analytical data to literature values and by GLC data, run against
standards of purchased 2,6-dimethylcyclohexanol including the spiking of synthesised
product (20) Isomer ratio of 72, 73, and 74 obtained by GLC was 38% (72) 53% (73) 9% (74)

νmax/cm⁻¹ (neat film), 3385 (OH), 2951, 2872, 1454, 1044, 969, 944

δ_H (250MHz, CDCl₃) 4.3 (s, brs, OH), 3 52-3 51 (1H, t, J=2 0Hz, 1-CH (73)), 3 35-3 30 (1H, dd, J=7.5Hz, 1-CH (74)), 2 71-2 63 (1H, t, J=9 6Hz, 1-CH (72)), 1 7-1.1 (cm, CH, CH₂+OH-all isomers), 1 01 (3H, s, Me (72)), 0 99 (3H, s, Me (72)), 0.97 (3H, s, Me (73)), 0.96 (3H, s, Me (74)), 0.94 (3H, s, Me (73)), 0.93 (3H, m, Me (74))

δ_C (100MHz, CDCl₃) 182 82 2 (1-CH (72)), 77 8 (1-CH (74)), 75 2 (1-CH (73)), 39 8 (2-CH+6-CH (72)), 37 4 (2-CH+6-CH (73)), 34 4 (3-CH₂+5-CH₂ (72)), 33 5 (2-CH (74)), 33 3 (6-CH (74)), 30 7 (5-CH₂ (74)), 27.5 (3-CH₂+5-CH₂ (73)), 26 0 (4-CH₂ (73)), 25 7 (4-CH₂ (72)), 20 0 (4-CH₂ (74)), 18 9 (2xMe (72)), 18 7 (2xMe (73)), 18 2 (Me (74)), 13 7 (Me (74))

6.63 Oxidation of 2,2,6-Trimethylcyclohexanol (21)

To a solution of 2,2,6-trimethylcyclohexanol (50mg, 0.35mmol) in acetone (5ml) at 0°C, was added dimethyldioxirane solution (isolated in acetone, 0.35mmol, 5ml). The reaction mixture was stirred at room temperature, in complete darkness for 24 hours. Samples for GLC analysis were taken out of the reaction flask without preparative work up. Purchased standards verified the samples.

For oxidations run in chloroform and methanol mixed solvent systems, the starting material was made into solution by the addition of either chloroform (5ml) or methanol (5ml) instead of acetone (5ml). The standard procedure is then followed as above.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Retention time (mins)</th>
<th>Typical % conversion to product</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,2,6-Trimethylcyclohexanol</td>
<td>6.33 no minor isomer observed</td>
<td>61-66% with 100% acetone</td>
</tr>
<tr>
<td>2,2,6-Trimethylcyclohexanone</td>
<td>6.08 no minor isomer observed</td>
<td></td>
</tr>
</tbody>
</table>

25m capillary column used, optimisation of GC conditions were determined with purchased standards.

6.64 Oxidation of 2, 6-dimethylcyclohexanol (20)

To a solution of 2, 6-dimethylcyclohexanol (44mg, 0.35mmol) in acetone (5ml) at 0°C, was added dimethyldioxirane solution (isolated in acetone, 0.35mmol, 5ml). The reaction mixture was stirred at room temperature, in complete darkness for 24 hours. Samples for GLC analysis were taken out of the reaction flask without preparative work up. Purchased standards verified the samples.

For oxidations run in chloroform and methanol mixed solvent systems, the starting material was made into solution by the addition of either chloroform (5ml) or methanol (5ml) instead of acetone (5ml). The standard procedure is then followed as above.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Retention time (mins)</th>
<th>Typical % conversion to product</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,6-Dimethylecyclohexanol</td>
<td>9.27</td>
<td>9.49</td>
</tr>
<tr>
<td>2,6-Dimethylecyclohexanone</td>
<td>10.09</td>
<td>10.69</td>
</tr>
</tbody>
</table>

25m capillary column used, optimisation of GC conditions were determined with purchased standards
CHAPTER 7
Chapter 7

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Appendix A

X-Ray structure of spiro-indanone derivative (16, X=H)
Appendix B

X-Ray structure of spiro-tetralone derivative (17)
Appendix C

**Determination of Dioxirane Molarity by Titration**

The molarity of the dioxirane solution was determined by iodometric titration. Iodine, liberated from potassium iodide by a known volume of dioxirane solution, was titrated against a thiosulfate solution of known molarity.

The chemical equations for the titration are shown below.

**Reaction of dioxirane with iodine:**

\[
2 \text{KI} + \begin{array}{c}
\text{O} \\
\text{Me}
\end{array} + \text{H}_2\text{O} \rightarrow \text{I}_2 + \begin{array}{c}
\text{O} \\
\text{Me}
\end{array} + 2 \text{KOH}
\]

**Reaction of the iodine with sodium thiosulfate:**

\[
\text{I}_2 + 2\text{Na}_2\text{S}_2\text{O}_3 \rightarrow \text{Na}_2\text{S}_4\text{O}_6 + 2\text{NaI}
\]

The molarity of the dioxirane solution is calculated as follows:

Number of moles of sodium thiosulfate solution used = \( \frac{V_{\text{Na}_2\text{S}_2\text{O}_3} \times M_{\text{Na}_2\text{S}_2\text{O}_3}}{1000} \)

Since two moles of potassium iodide react with one mole of dioxirane to give one mole of iodine, and the iodine reacts with two moles of sodium thiosulfate

1 mole dioxirane = 2 moles of sodium thiosulfate

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Number of moles of dioxirane used = \( \frac{V_{Na,S} x MNa,S_2O_3}{1000 \times 2} \)

Therefore, molarity of the dioxirane solution = \( \frac{V_{Na,S} x MNa,S_2O_3 x 1000}{1000 \times 2 x V_{dioxirane}} \)

Where,

- \( MNa,S_2O_3 \) = molarity of the sodium thiosulfate solution
- \( V_{Na,S} \) = volume of the sodium thiosulfate solution
- \( V_{dioxirane} \) = volume of dioxirane solution (usually predetermined at 0 2 ml)