Studies of some novel reagent systems for oxidations and asymmetric epoxidation

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The experimental work in this thesis was carried out in the Department of Chemistry at Loughborough University of Technology by David A. Williams between October 1991 and October 1993. This work has not been previously presented and is not being presented for any other degree.

D. A. Williams

May 1995
Dedication

For Mum, Dad, Melissa, Jill and anyone else who knows me.
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Chapter 1

INTRODUCTION
1. General Introduction.

Oxidation reactions are widespread both in the laboratory and in nature. Inorganic chemists define oxidation in terms of loss of electrons from a particular species, that is an increase in oxidation state e.g. iron (II) to iron (III). However in organic chemistry, where the species under consideration are usually covalent molecules, such concepts of oxidation have little or no meaning.

Organic chemists have devised an arbitrary system for defining organic oxidation reactions. Functional groups have been traditionally assigned an 'oxidation state,' and oxidation is defined as the conversion of a functional group into one of a higher oxidation state. In any case, many oxidation reactions are readily recognisable, and many organic oxidation reactions involve the addition of oxygen itself.

Table 1 shows some examples of functional groups in order of increasing oxidation state.  

<table>
<thead>
<tr>
<th>RH</th>
<th>R₂C=CR₂</th>
<th>RC=CR</th>
<th>R—CO₂H</th>
<th>CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>R—OH</td>
<td>R₂C=O</td>
<td>R—CONH₂</td>
<td>CCl₄</td>
<td></td>
</tr>
<tr>
<td>R—Cl</td>
<td>R₂C&lt; Cl</td>
<td>Cl</td>
<td>R—CCl₃</td>
<td></td>
</tr>
<tr>
<td>R—NH₂</td>
<td>OH OH</td>
<td>R₂C—CR₂</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1.
Many reagents are used in organic oxidations. Often the reagent is inorganic and many of these reagents are very powerful oxidizing agents which require some care in their use to avoid over oxidation. An example is potassium permanganate, which can be used to oxidise alkenes. Selection of the appropriate conditions can give several products as shown in scheme 1. Under acidic conditions the reaction may proceed further leading to cleavage of the olefin.

\[
\begin{align*}
\text{Scheme 1}
\end{align*}
\]

The reagent is also capable if oxidizing a primary amine at a tertiary carbon to a tertiary nitro- compound, a reaction which cannot be achieved by other methods.

However we will only be concerned with peroxycarids which are versatile oxidizing agents.

### 1.1 Structure And Synthesis Of Peroxycarids

The structure of peroxycarids has some bearing on their properties and reactivity. Since they were discovered a variety of physical methods have been used to determine their structure. It has been established, by infrared spectroscopy, that in non-polar
solvents, peroxyacids exist as five membered hydrogen bonded rings. The rings are slightly puckered, and an 'open book' model is often used (Figure 1). The angle between the 'pages,' i.e. the dihedral angle, varies with different peroxyacids, but is generally about 70°.

Figure 1. Dihedral angle in an intramolecularly hydrogen bonded peroxyacid.

In the solid state the dihedral angle opens to 140° due to intermolecular hydrogen bonding.

The synthesis of peroxyacids is straightforward although due consideration to the explosive nature of the product and reagents is necessary. The reaction is itself an example of an organic oxidation involving the addition of oxygen.

Peroxyacids may be synthesised by the careful addition of hydrogen peroxide to a carboxylic acid in a suitable solvent (Scheme 2). The reaction involves an equilibrium, and a strong acid catalyst is required to drive it to completion. For short chain aliphatic carboxylic acids sulfuric acid is normally used. Methanesulfonic acid is used for aromatic carboxylic acids and for
aliphatic carboxylic acids with a chain length longer than about C₈. The peroxyacid may then be isolated or used in solution.

Due to the potentially hazardous nature of this reaction, and the dangers of isolating peracids, a frequently used alternative is *in-situ* peroxyacid formation. *In-situ* peroxyacid formation is usually achieved by the reaction of an acid anhydride and hydrogen peroxide in solution (Scheme 3). The reaction requires no acid catalyst, but buffering may be required since the other product of the reaction is an acid which may attack the ultimate oxidation product e.g. an epoxide. It is also important to have hydrogen peroxide present in excess to avoid production of diacyl peroxides.

\[
R\text{-CO}_2H + H_2O_2 \xrightleftharpoons{H^+} R\text{-CO}_2H + H_2O
\]

Scheme 2

\[
\begin{array}{c}
R
\\downarrow\text{H}_2\text{O}_2
\end{array}
\xrightarrow{H_2O_2} R\text{-CO}_3H + R\text{-CO}_2H
\]

Scheme 3

A third possibility is to use molecular oxygen in place of hydrogen peroxide. The technique is referred to as cooxidation or coupled oxidation.

Oxygen or air is passed through a solution containing an aldehyde, usually butyraldehyde or benzaldehyde to form the peroxyacid.
(Scheme 4). This is a step in the oxidation of aldehydes to carboxylic acids, but in this case the peroxycacid is used to oxidise a second substance such as an olefin. The reaction often utilises a transition metal catalyst to reduce reaction time and increase the yield. 

\[
\text{R-CHO} \rightarrow \text{R-CO}_2\text{H} \quad \text{oxidizable substance} \rightarrow \text{RCO}_2\text{H} + \text{oxidation product}
\]

Scheme 4

**Alternative Sources of H\textsubscript{2}O\textsubscript{2}**.

Hydrogen peroxide, especially when highly concentrated, is a dangerous material to handle. Transition metal contamination will usually cause rapid decomposition and explosion. The material will oxidise organic matter, for example paper, and a fire will result. Fortunately in recent years alternative sources of hydrogen peroxide have become available. Consisting of a complex of hydrogen peroxide and a suitable organic molecule, they represent a much safer way of using hydrogen peroxide.

Of these complexes, urea - hydrogen peroxide ( UHP ) 1 has found the widest use. The complex is readily prepared by recrystallising urea from aqueous hydrogen peroxide. 7 It is a stable white solid, and can only be made to explode under extreme conditions. It is used as a direct replacement for hydrogen peroxide, and gives comparable yields. 8
Two other hydrogen peroxide adducts that have been used are 1,4-diazabicyclo[2.2.2]octane-di-N-oxide-diperhydrate (DABCO.) 2 and triphenylphosphineoxide perhydrate 3.

Commonly Used Peroxyacids.

A great variety of peroxyacids have been used for organic oxidations, however, only a few are commonly in use. Of these the most frequently encountered is meta-chloroperoxybenzoic acid (MCPBA) 4. MCPBA is available as a mixture containing 40-50% of the parent acid, which makes it somewhat more stable. The pure peroxyacid may be obtained by washing the commercial material with an aqueous phosphate buffer. MCPBA has been the reagent of choice for epoxidations since its discovery and use in 1955. 11

Magnesium monoperoxyphthalate (MMPP) 5 is available in 80% purity. It has several advantages over MCPBA, not least its greater stability. The parent acid was first used to synthesise epoxides in 1942. The magnesium salt was developed by Interox (now part of Laporte) as a bleaching agent for detergents for which it was found to be unsuitable.

Peroxyacetic acid 6 is available as a 30% solution containing significant amounts of acetic acid, hydrogen peroxide and a trace of sulfuric acid. Peroxyacetic acid is more conveniently utilised by
in-situ generation from acetic anhydride. The first epoxides produced with this peroxyacid were synthesised in only low yields due to the reaction between the epoxide and acetic acid to yield hydroxy acetates.

Peroxytrifluoroacetic acid 7 is only ever produced in-situ. It is highly electrophilic and reacts rapidly with many substrates that are resistant to attack by other peroxyacids.

Many other peroxyacids have been used, e.g. peroxybenzoic acid, peroxyformic acid, and various aliphatic peroxyacids such as peroxyauric acid. More recently several novel peroxyacids have been developed such as a polymer supported peroxybenzoic acid \( 14 \) and derivatives of peroxycarbonic acid \( 15 \) and derivatives of peroxy carbamic acid. \( 16, 17 \)

\[
\begin{align*}
\text{PhCH}_2\text{CO}_2\text{H} & \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{H} \\
\text{Ph} & \quad \text{NHCO}_2\text{H}
\end{align*}
\]
1.2. Reactions Of Peroxyacids.

There are three significant reactions of peroxyacids. The most important of these is epoxidation (Scheme 5). This reaction is reviewed in the next chapter.

\[ \text{Scheme 5} \]

1.2.1 The Baeyer-Villiger Reaction.

The Baeyer-Villiger reaction is the oxidation of a ketone to an ester using a peroxyacid. In inert solvents, \( \alpha \)-diketones and \( \alpha \)-keto acids can be oxidised to anhydrides. In their paper Baeyer and Villiger described the oxidation of a number of cyclic ketones, e. g. menthone, with Caro’s acid. (Scheme 6).

\[ \text{Scheme 6} \]

Baeyer and Villiger suggested a mechanism involving dioxiranes
This was disproved by Doering and Dorfmann, who showed that no scrambling occurred with O\textsuperscript{18} labelled ketones (Scheme 8).

The generally accepted reaction mechanism was first proposed by Criegee in 1948 (Scheme 9).

The mechanism accounts for the experimental observations.
1. The reaction is 3rd order overall, 1st order with respect to the peroxyacid, the ketone and the acid catalyst.

2. The reaction is susceptible to general acid catalysis.

3. The reaction rate is enhanced by polar solvents, which implies that the reaction has an ionic character.

In addition to these observations, it was discovered that the reaction occurs with retention of configuration 23 (Scheme 10).

![Scheme 10.]

Generally the migratory aptitude of functional groups can be summarised as:

\[
\text{tert-alkyl} > \text{cyclohexyl} > \text{sec-alkyl} > \text{benzyl} > \text{phenyl} > \text{alkyl} > \text{methyl}.
\]

It is found that electron donating \textit{para}-substituents on a phenyl residue enhance its migratory aptitude. Electron donating \textit{ortho}-substituents reduce it relative to \textit{para}-substituted phenyl groups. This sequence can be explained by the migrating atom being that which is best able to support a positive charge.

Such generalisations are only valid for simple systems, and numerous anomalous reactions have been observed. Friess and
Franham showed that cyclohexyl phenyl ketone gives a 5:1 mixture in favour of the expected product \(^{24}\) (Scheme 11).

![Scheme 11.](image)

The peroxyacid also has an effect on the reaction, thus Hawthorne et al showed that in the above reaction peroxyacetic acid gave a 9 : 1 mixture in favour of the product from cyclohexyl migration, whilst peroxytrifluoroacetic acid gave a 4 : 1 mixture. \(^{25}\) Migratory aptitudes are also sensitive to steric and structural effects. An example of this is given by the study of the reactions of camphor derivatives (Scheme 12 ). \(^{26}\)
Baeyer-Villiger type reactions have also been performed using alkaline hydrogen peroxide \(^{27}\) (Scheme 13). A reaction between an acetal and ozone also produces esters \(^{28}\) (Scheme 14).
A similar reaction occurs between aromatic aldehydes possessing ortho- or para- activating groups and alkaline hydrogen peroxide. The reaction is known as the Dakin reaction (Scheme 15, ) and the usual product is a phenol resulting from the hydrolysis of a formate ester. With peroxycarboxylic acid, the normal product is a carboxylic acid, resulting from hydride rather than alkyl or aryl migration.
1.2.2. Heteroatom Oxidations.

The most frequently encountered heteroatoms that are oxidised with peroxyacids are nitrogen and sulfur.

Oxidations Of Sulfur.

Only two oxidations of sulfur are commonly encountered, these are: a) oxidation of sulfides to sulfoxides, and b) oxidation of sulfoxides to sulfones (Scheme 16).

\[
\begin{align*}
R_2S + RCO_3H &\rightarrow R_2SO + RCO_3H \\
R_2SO + RCO_3H &\rightarrow R_2SO_2
\end{align*}
\]

Scheme 16.

The reaction can usually be controlled since sulfoxides are less reactive than sulfides. The probable reaction mechanism between sulfides and peroxides is shown in scheme 17.

\[
\begin{align*}
\text{R-S-H} &\rightarrow \text{R-SOH + R'OH} \\
\text{R-SOH} &\rightarrow \text{R-S=O + R'OH}
\end{align*}
\]

Scheme 17.

Two possible modes of reaction between sulfoxides and peroxyacids exist, depending upon the pH of the reaction (Scheme 18). 30 Solvent effects in the reaction are minimal. 31
Thiols can be oxidised to sulfonic acids with MCPBA. 32

**Oxidations Of Nitrogen.** 33

The most common oxidation of nitrogen is the production of N-oxides. The reaction occurs with tertiary amines, for which hydrogen peroxide may also be used, and with pyridine derivatives, which can only be oxidised with peroxyc acids. The probable mechanism is shown in scheme 19. Primary alkyl amines and primary aryl amines are oxidised to nitro compounds via a nitroso compound (Scheme 20). If a primary amine has an \( \alpha \) hydrogen present the nitroso compound tautomerises to an oxime (Scheme 21). Secondary amines are oxidised to hydroxylamines which are resistant to further oxidation.

Scheme 18.

Scheme 19.
Azobenzenes can be oxidised to azoxybenzenes.
Chapter 2

STUDIES OF OXIDATION
2.1. Introduction.

An epoxide is a three membered heterocycle containing one oxygen atom (Figure 2). The systematic name for this functional group is oxirane and reactions which produce them are oxirhanations, but the more familiar epoxide and epoxidation will be used.

![Figure 2](image)

Epoxides, like other three membered ring systems, are very reactive due to bond strain. The bond strain has been calculated to be 114 kJ mol$^{-1}$.\(^{34}\) These strains are minimised by changes in the hybridisation so that the bonds forming the ring are not sp\(^3\) hybridised, but have more p character, resulting in so called 'banana' bonds. These bonds can be considered to arise by a) the interaction of an ethylene $\pi$-orbital with an unfilled orbital on oxygen and b) by interaction of a $\pi^*$-orbital with a filled orbital on oxygen (Figure 3). Of these the first is the dominant interaction.

![Figure 3](image)
Epoxides are important for several reasons. They occur in nature, for example in antibiotics such as capsimycin 11 \(^{35}\) and indolomycin 12. \(^{36}\)

Epoxides occur frequently in insect pheromones such as (+)-Disparlure 13. These may be used in pheromone traps which can limit the use of harmful pesticides.
Epoxides also occur in biochemical pathways. Arene oxides are produced in the liver as the first step in the excretion of aromatic compounds. It is believed that these 'arene oxides' that are produced from polycyclic aromatic hydrocarbons are responsible for causing some types of cancer. The mechanism of blood clotting involves vitamin K hydroquinone as a co-factor for a carboxylase. An epoxide is produced during the reaction \(^{(37)}\) (Scheme 22).

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

Scheme 22.

Epoxides are used extensively in industry. Ethylene oxide is produced on a large scale by catalytic reaction between ethylene and atmospheric oxygen (Scheme 23). Ethylene oxide is used in the
preparation of a large number of products such as ethylene glycol and polyethers.

\[ \text{H}_2\text{C} = \text{CH}_2 \xrightarrow{\text{Ag, Alumina, O}_2 \text{, } 260^\circ \text{C}} \text{H}_2\text{C} - \text{CH}_2 \]

Scheme 23.

The major use of epoxides in industry is in the form of epoxidised soya bean oil (ESBO) and other similar oils and esters for use as plasticisers and stabilisers. Their major use is to prevent thermal and photochemical degradation of polyvinyl chloride and its copolymers, presumably by hydrogen chloride scavenging and interruption of free-radical chain reactions. 38

2.2. Epoxidation.

2.2.1 Epoxidation With Peroxyacids.

The epoxidation of alkenes using peroxycacids was discovered by Prileschajew in 1909. 39 The reaction was found to be general and gave high yields, once problems of hydrolysis had been overcome. The reaction has been studied in great detail and the following experimental observations have been made.

1. Electron withdrawing substituents on the peroxycacid enhance the rate of epoxidation, therefore the peroxycacid acts as an electrophilic reagent. 40
2. Electron donating substituents on the olefin enhance its susceptibility to epoxidation, i.e. the olefin behaves as a nucleophile. 41

3. The reaction is stereospecific, \textit{trans} olefins give \textit{trans} epoxides and \textit{cis} olefins give \textit{cis} epoxides. 42 Due to the bulk of the reagent, the peroxyacid generally attacks from the least hindered side.

4. The reaction is 2\textsuperscript{nd} order overall, 1\textsuperscript{st} order in peroxyacid and olefin. 43

5. \textit{Cis} double bonds are epoxidised approximately 1.5 times faster than \textit{trans} double bonds. 44 Some cyclo alkenes such as cyclodecene do not follow this rule.

6. An allylic hydroxyl group increases the rate of epoxidation and also directs attack stereospecifically to the \textit{cis} side of the double bond. 45

The mechanism of the reaction has been debated for many years. Two mechanisms have been seriously considered, a molecular mechanism (Scheme 24) first proposed by Bartlett, 46 and a 1,3-dipolar mechanism proposed by Kwart \textit{et al} 47 (Scheme 25).

![Scheme 24.](image-url)
In the Bartlett mechanism the transition state is non-ionic and a concerted intramolecular process takes place via a spiro transition state as shown above.

Scheme 25.

The Kwart mechanism involves the 1,3-dipolar addition of a hydroxycarbonyl oxide to the olefin as its rate determining step. The Bartlett mechanism is more generally favoured but the 1,3 dipolar mechanism has not been ruled out, and may operate in polar solvents. The cis directing effects of allylic alcohols can be rationalised on the basis of the molecular mechanism (Scheme 26). Such effects have also been seen with carbamates. 48
Steric and solvent effects are well known. Thus epoxidation of norbornylene 14 gives predominantly (96%) the exo epoxide.\textsuperscript{49} Similarly epoxidation of 4-methyl cyclopentene 15 gives the epoxide in a trans to cis ratio of 3:1 independent of the solvent used. However the ratio of epoxides from 4-cyano cyclopentene 16 does depend on the solvent used.\textsuperscript{50}

$\alpha,\beta$-Unsaturated carbonyl compounds react slowly or not at all with peroxyacids, however they may be successfully be epoxidised using basic hydrogen peroxide by a Michael addition (Scheme 27).\textsuperscript{51}
An important difference between peroxyacid epoxidation and alkaline hydrogen peroxide epoxidation is that the latter is not stereospecific. This is due to the fact that the intermediate has a relatively long half life allowing rotation to occur.

### 2.2.2 Other Methods Of Epoxidation

**Payne Reaction.**

The reaction between a nitrile and alkaline hydrogen peroxide in the presence of an olefin is known as the Payne reaction. The nitrile is hydrolysed to an amide during the course of the reaction. The reactive intermediate is believed to be a peroxyimidic acid, however they are unstable and have not been isolated. The reaction offers no advantages for simple epoxidations, but is useful if acidic conditions are precluded. An example is provided by the epoxidation to glycidamide (Scheme 28).
The reaction also provides a method for the selective epoxidation of an unsaturated ketone (Scheme 29).

**Darzens Reaction.**

The reaction between an α-halo carbonyl compound and a ketone or aromatic aldehyde in the presence of a strong base yields an α,β-epoxy carbonyl derivative and is known as the Darzens reaction. The reaction proceeds by a Knoevenagel condensation followed by an internal SN2 reaction. The halogen is normally chlorine. Bromine and iodine have been used, but usually give mixtures of
products due to alkylation. Kinetically, the reaction is 3rd order, 1st order in each of the three components. The reaction is stereoselective giving trans- epoxides although prolonged exposure to the alkali may result in epimerisation. The stereoselectivity is considered to be due to stereoelectronic control of the rate-determining collapse of the α-halohydrin anion (Scheme 30). 54 Analogous reactions occur with cyanide and alkoxide anions (Scheme 31).

\[
\text{Scheme 30.}
\]

\[
\text{Scheme 31.}
\]

Aromatic aldehydes react with phosphorous triamides to give epoxides, and a mechanism has been proposed (Scheme 32). 55 An electronegative group on the aromatic ring enhances epoxide formation, whereas electron releasing substituents favour the formation of adducts.

28
Aldehydes react with a dialkyltelluronium iodide to give $\alpha,\beta$-unsaturated epoxides. 56

Transition Metal Catalysts.

Epoxidation may be achieved using hydrogen peroxide or an organic hydroperoxide and a transition metal catalyst. Electron poor olefins may be epoxidised using hydrogen peroxide and tungstic acid (Scheme 33). 57

$$\text{H}_2\text{WO}_4 + \text{H}_2\text{O}_2 \rightleftharpoons \text{H}_2\text{WO}_5 + \text{H}_2\text{O}$$

Scheme 33.
Other suitable metals include molybdenum, titanium and vanadium. There are drawbacks to this method, which include the problem of removal of the homogenous catalyst, and side reactions. The complex may also be oxidised leading to deactivation. A possible solution to these problems has recently been published. When the complex \( \text{cis- Mn(bpy)}_2 \) is enclosed in a zeolite, side reactions are eliminated and the catalyst may be easily recovered by filtration and reactivated by heating.

Metal catalysts are commonly used with hydroperoxides. For simple olefins no great difference in selectivity over peroxyacids is shown. However in the presence of complexing groups, e. g. allylic alcohols, and with certain catalysts, improved stereo- and regioselectivity is observed (Scheme 34).

\[
\begin{align*}
\text{cis- Mn(bpy)}_2 & \quad \text{Zeolite} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

Scheme 34.

**Cyclisation.**

This is a group of reactions in which an intramolecular nucleophilic substitution occurs. The most familiar and widely used of these reactions is the cyclisation of halohydrins (Scheme 35).
Similar reactions with 1,2-diols are known (Scheme 36). \(^\text{60}\)

![Scheme 35](image)

Epoxides are produced when gem-dihalides are treated with a carbonyl compound and Li or BuLi (Scheme 37). \(^\text{61}\)

![Scheme 36](image)

Sulfur Ylids.

The reaction between sulfur ylids such as dimethylsulphonium methylide \(^\text{17}\) and dimethylsulfoxonium methylide \(^\text{18}\) and carbonyl compounds gives epoxides in good yields, and is sometimes known as the Corey synthesis. \(^\text{62}\)
Usually 18 is the reagent of choice since it is much more stable and may be stored in solution for several days. However if
disastereomeric epoxides are possible 17 gives the kinetic product whereas 18 gives the thermodynamic product (Scheme 38).

Scheme 38.

In addition, with α,β-unsaturated ketones, 18 gives cyclopropanes whereas 17 gives epoxides. The reaction mechanism is similar to the Wittig reaction. The stereochemical difference between 17 and 18 is considered to be due to the formation of the betaine being reversible for 18, but not for 17 (Scheme 39).

Scheme 39.
Alkyl groups can be transferred in a similar way. The reaction may also be done using diazoalkanes, however yields of epoxide are often low since rearrangements to an aldehyde or ketone containing one more carbon than the starting compound are possible (Scheme 40).

Other Methods.

A recent discovery is that epoxides can be produced in a photochemical reaction cycle involving a metal porphyrin, platinum and water as the oxygen source (Scheme 41). 63
Two equivalents of (Triphenylsilyl)-hydroperoxide react with alkenes at room temperature to yield epoxides. 64

Imines can be oxidised to oxaziridines. The reaction mechanism is not the same as epoxidation, and the reaction is not stereospecific and probably has two steps (Scheme 42). The reaction is more rapid than epoxidation and can therefore be carried out in the presence of an alkene. 65
The chief use of epoxides in the laboratory is as synthetic intermediates. Epoxides can be subjected to a wide range of reactions, some of which are detailed below.

Nucleophilic Substitution.

This is the most widespread reaction of epoxides. Unless the epoxide is symmetrical, then two products are possible depending upon which carbon is attacked. Under basic or neutral conditions an $S_{N}2$ mechanism normally occurs and attack at the less highly substituted carbon with inversion. In acidic conditions it is the protonated epoxide that is attacked and either an $S_{N}1$ or an $S_{N}2$ mechanism may operate. However even when an $S_{N}2$ mechanism is operating, attack tends to occur at the more highly substituted carbon. \(^{66}\) When the epoxide is fused to a cyclohexane ring, such as in steroids, $S_{N}2$ ring opening invariably leads to diaxial products. \(^{67}\)
Many substitution reactions are known amongst the most important are:

1. Hydrolysis.

This reaction is a convenient method for the preparation of 1,2-diols. It is also worth noting that the diol will be anti- with respect to the starting alkene, whereas reagents such as osmium tetroxide produce syn-diols (Scheme 43).

![Scheme 43](image)

2. Alcoholysis.

This reaction is analogous to hydrolysis. The products are β-hydroxy ethers, some of which are important industrial solvents such as Cellosolve.

3. Amination.

The reaction between epoxides and ammonia yields a mixture of products, mostly the primary amine (Scheme 44). The ethanolamines produced by this reaction are useful solvents.
Deoxygenation.

Deoxygenation of an epoxide yields an alkene. The reaction occurs via a betaine formed by the attack of a phosphine and subsequent quaternisation and is stereospecific (Scheme 45). 68

Base Catalysed Rearrangements.

The action of a suitable base on an epoxide produces an allylic alcohol (Scheme 46). It is found that trans olefins are produced stereoselectively from open chain epoxides. Either α or β elimination may take place and a elimination occurs via a carbene (Scheme 47).
The reaction has been used for otherwise difficult transformations such as in the synthesis of pentacyclododecanol (Scheme 48).\(^\text{69}\)

Acid Catalysed Rearrangement.

Acid catalysed rearrangement of epoxides produces a carbonyl compound \textit{via} a Pinacol type rearrangement as shown in scheme 49.\(^\text{70}\)
Oxidation.

Terminal epoxides may be oxidised to carbonyl compounds with alkaline hydrogen peroxide (Scheme 50). This reaction may be used to recover a ketone that has been protected as an epoxide with a sulfonium ylide.

Other reactions include periodic acid oxidation in aqueous medium to produce dialdehydes (Scheme 51).
Reduction.

Epoxides may be reduced by a number of methods e.g. metal hydrides, dissolving metals and catalytic hydrogenation. Choice of reagent is important since regioselectivity and stereoselectivity vary. Lithium aluminium hydride reduces epoxides to alcohols. Titanocene dichloride has been used to reduce epoxides to alkanes (Scheme 52). 71

```
\[ \text{Scheme 52.} \]
```

Synthesis of Other Heterocycles.

Epoxides may be used in the synthesis of aziridines and thiiranes. Thiiranes are produced when epoxides react with triphenylphosphine sulfide (Scheme 53). 72
Aziridines may be synthesised by the nucleophilic attack of azide anion followed by reaction with triphenylphosphene (Scheme 54). 73

Scheme 53.

Scheme 54.
2.4. Results And Discussion.

2.4.1. In-situ Peroxyacid Formation In The Presence Of 'Crystal Disrupting Agents'.

Earlier investigations of the UHP - Anhydride system for oxidations have shown the great effectiveness of the reagent. However in order to obtain good yields and to prevent the formation of diacyl peroxides, the reagent is typically used in 8 to 10 fold excess. We believe that the insolubility of UHP in organic solvents is partially responsible for this requirement, and in turn that this insolubility is due to the strong hydrogen bonding in the UHP complex. We decided to investigate the effect of the addition of a small quantity of polyethers, homologues of which have been shown to enhance the reactivity of MMPP. For the study we chose five typical substrates, four solvents of varying polarity and three polyethers of varying molecular mass.

The substrates were oct-1-ene 19, 1-methyl styrene 20, allyl phenyl ether 21, cyclohexanone 22 and nor-camphor 23. Of these the last two were substrates for a Baeyer-Villiger reaction and the others for epoxidation. The expected products are 1,2-epoxyoctane 24, 1-phenyl-1-methyloxirane 25, 1,2-epoxy-3-phenoxypropane 26, ε-caprolactone 27 and 2-oxabicyclo[3.2.1]octan-3-one 28. Allyl phenyl ether was synthesised by reaction between phenol and 3-bromo-1-propene, the other substrates were available commercially. The solvents chosen for study were dichloromethane, tetrahydrofuran, iso-propyl acetate and 1-methyl-2-pyrrolidone.
Crystal disrupting agents examined were the polyethers: polyethylene glycol400 (PEG 400), polypropylene glycol725 (PPG725) and polyethylene glycol400 dimethyl ether (PEG 400 DME.) The last was chosen to test the effect of free OH groups. A typical reaction is shown in Scheme 55.

![Scheme 55.](image)

During the course of these experiments it was found that one of the substrates and two of the solvents were problematic. Allyl phenyl ether was an unsuitable substrate since epoxidations did not go to completion and gave a bright yellow mixture of starting material and product that was difficult to separate. NMP and iso-propyl acetate proved to be unsuitable solvents due to difficulties with their removal from the reaction mixture. Although most of the NMP could be removed by washing with water, a significant amount remained, usually in excess of the volume of product obtained. Iso-propyl acetate has a boiling point sufficiently high for loss of product to occur during rotary evaporation.

The results of the experiments using DCM as the solvent are shown in Table 2, for THF the results are shown in Table 3.
## Table 2: Summary of results with DCM as solvent

<table>
<thead>
<tr>
<th>Substrate</th>
<th>None</th>
<th>PEG 400</th>
<th>PPG 725</th>
<th>PEG 400</th>
<th>DME</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$-methyl styrene</td>
<td>92%</td>
<td>82%</td>
<td>62%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>oct-1-ene</td>
<td>82%</td>
<td>79%</td>
<td>20%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>cyclohexanone</td>
<td>90%</td>
<td>90%</td>
<td>61%</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>nor-camphor</td>
<td>80%</td>
<td>23%</td>
<td>80%</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>

* = Result Not Obtained.

## Table 3: Summary of results with THF as solvent

<table>
<thead>
<tr>
<th>Substrate</th>
<th>NONE</th>
<th>PEG 400</th>
<th>PPG725</th>
<th>PEG 400</th>
<th>DME</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$-methyl styrene</td>
<td>75%</td>
<td>30%</td>
<td>21%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>oct-1-ene</td>
<td>87%</td>
<td>38%</td>
<td>59%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>cyclohexanone</td>
<td>70%</td>
<td>66%</td>
<td>88%</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>nor-camphor</td>
<td>94%</td>
<td>55%</td>
<td>82%</td>
<td>88%</td>
<td></td>
</tr>
</tbody>
</table>
Although each experiment was only performed once and therefore experimental errors may be large, the following observations may be made:

1. Neat DCM is normally a better solvent than THF for performing oxidation reactions using UHP.
2. The use of crystal disrupting polyethers has no beneficial effect on such reactions. In only one case was the yield actually improved.
3. PPG is less detrimental than PEG. It is also possible that the increased molecular mass is beneficial.
4. Free terminal OH groups on the polyether produce a more detrimental effect than capped OH groups.

2. 4. 2. Alternative Sources Of H₂O₂.

Since addition of polyethers had proved to be of no benefit, we decided to turn our attention to alternative H₂O₂ complexes in the hope of finding a stable complex capable of releasing H₂O₂ quantitatively into an organic solvent.

Biuret - H₂O₂ ⁷⁷

Biuret - H₂O₂ 29 (BHP) was the first complex we examined, since it is known that it is an inclusion complex, and that the hydrogen bonds are much weaker than in UHP. For these reasons we believed that BHP might release H₂O₂ into solution more effectively than UHP.
In the complex biuret exists in the $\alpha$- form as shown, the $\beta$- form exists in the anhydrous material. Two complexes are known having compositions of biuret $\cdot$ H$_2$O$_2$ (5 : 1), and biuret $\cdot$ H$_2$O$_2$ (5 : 2). We attempted to synthesise Biuret $\cdot$ H$_2$O$_2$ (BHP) by dissolving biuret in warmed 30% aqueous hydrogen peroxide. We have obtained biuret $\cdot$ H$_2$O$_2$ with an available oxygen content (Av. Ox) of between 1.1 and 8.4. The theoretical Av. Ox. is 2.9 for the 5 : 1 complex and 5.5 for the 5 : 2 complex. Clearly the high value is due to a damp product. We attempted to use the complexes we obtained as a direct replacement for UHP. However the complex appears is insoluble and attempted epoxidations of $\alpha$-methyl styrene using 1 mol equivalent and 5 mol equivalents of BHP both failed, indicating that if anything BHP releases H$_2$O$_2$ into solution even more slowly than UHP.

**Silica-Gel - H$_2$O$_2$.**

We obtained a sample of silica-gel - H$_2$O$_2$ from Interox. It is a stable colourless free running powder and is stable for long periods if kept cold. The complex is prepared by the slow addition of 70% H$_2$O$_2$ hydrophilic silicic acid containing ca. 0.5% hydrophobic silicic acid. The approximate composition of the complex, determined by iodometric titration, is SiO$_2$. 2H$_2$O$_2$. Attempts to synthesise our own
sample using a method provided by Interox failed, yielding a sample of low Av. Ox. and a lumpy rather than free running appearance. We attempted to use the complex as a direct replacement for UHP, but with a smaller excess. However an explosion during distillation of 1,2-epoxycyclohexane produced via this reaction convinced us of the necessity for an excess of oxidant. This, combined with careful work up prevented a reoccurrence.

Quantitative reactions using silica-gel - \( \text{H}_2\text{O}_2 \) in place of UHP have generally been successful in DCM but have consistently failed to work with acetic anhydride. The results are shown in Table 4.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Anhydride</th>
<th>Solvent</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-octene</td>
<td>TFAA</td>
<td>DCM</td>
<td>24</td>
<td>71%</td>
</tr>
<tr>
<td>1-octene</td>
<td>TFAA</td>
<td>DCM</td>
<td>24</td>
<td>24%</td>
</tr>
<tr>
<td>1,7-octadiene</td>
<td>TFAA</td>
<td>DCM</td>
<td>30</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td>47%</td>
</tr>
<tr>
<td>limonene</td>
<td>TFAA</td>
<td>DCM</td>
<td>32</td>
<td>50%</td>
</tr>
<tr>
<td>cyclooctene</td>
<td>TFAA</td>
<td>DCM</td>
<td>33</td>
<td>69%</td>
</tr>
<tr>
<td>( \alpha )-methyl styrene</td>
<td>AA</td>
<td>DCM</td>
<td>25</td>
<td>0%</td>
</tr>
<tr>
<td>( \text{trans} )-stilbene</td>
<td>AA</td>
<td>DCM</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>cholesterol</td>
<td>TFAA</td>
<td>DCM</td>
<td>34</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 4: Silica gel-hydrogen peroxide results.

Results using trifluoroacetic anhydride (TFAA) are generally comparable with those obtained using UHP as the oxidant. Qualitative experiments using GC analysis have also been performed
in order to confirm that reactions using acetic anhydride are really not occurring and to screen alternative reaction conditions.

The GC results confirmed the failure of reactions using acetic anhydride, however if the buffer was omitted, a reaction was observed, but acid catalysed ring opening occurred simultaneously, giving poor selectivity. Refluxing the reaction increased the rate of the reaction but selectivity was not improved. Sodium acetate and sodium hydroxide were tried in place of the disodium hydrogen orthophosphate buffer normally employed, but showed no improvement.

Reactions using trifluoroacetic anhydride were also examined using 1-octene as the substrate. After 3 hours reflux in DCM using sodium carbonate as a buffer, approximately 50% conversion had occurred. Omission of the buffer gave virtually complete reaction in 30 minutes, but after 1 hour some starting material still remained and ring opening of the epoxide was occurring. The same reaction was examined using chloroform as the solvent. After 30 minutes reflux almost complete conversion had occurred. A second experiment thermostatted to 40° C as a direct comparison with DCM gave a similar result, with conversion better than for refluxing DCM, but less than that in refluxing chloroform.

Other H₂O₂ Complexes.

Two other possible complexes of H₂O₂ were considered. A literature report of hexamethylenetetramine . H₂O₂ 35 prompted us to examine this complex. 78 The authors report the preparation of the
complex by dissolving HMTA in 30% H₂O₂ at 0° C and evaporation of the resulting solution under vacuum. We considered this procedure to be too hazardous to perform in our laboratories.

![Diagram of complex](image)

We found that drying the solution under ambient conditions was impractical. An attempt to use a more concentrated (85%) H₂O₂ solution resulted in the rapid decomposition of the solution and no further experimental work was undertaken.

The other potential complex was with Troger’s base 36.

![Diagram of Troger's base](image)

Troger’s base is chiral, and we hoped that a chiral complex analogous to DABCO-di N-oxide di-perhydrate might allow us to perform asymmetric oxidations. Troger’s base was synthesised in 16% yield from p-toluidine and formaldehyde, but proved difficult to purify. All attempts to produce an N-oxide with H₂O₂ or various peracids failed and the work was abandoned.
2. 4. 3. **Epoxidations Of Cholesterol Derivatives.**

It is well known that the epoxidation of steroids by peroxyacids leads to epoxides resulting from attack at the least hindered face. For cholesterol and its ester derivatives this is the α-face (Figure 4). A ratio of about 3 : 1 is normally observed.

![Figure 4](image.png)

We performed a series of experiments in which cholesterol 37, cholesteryl acetate 38 and cholesteryl benzoate 39 were epoxidised with a variety of peroxyacids. The crude products were analysed by NMR spectroscopy. The H₆ proton gives a signal at δ 2.9 for the α-epoxide and at δ 3.1 for the β-epoxide. Similar results are observed for the acetate and the benzoate. We also analysed multiple samples from the same reaction in order to test the repeatability of NMR analysis. The table below shows the results obtained in the cholesterol epoxidations to date. Each α to β ratio was determined three times using separate samples from the same reaction. Each reaction was repeated to minimise experimental error.

Generally the results show that for small α to β ratios, the NMR determinations are fairly repeatable, but for larger α to β ratios, the
errors become quite large, 43\% in an extreme case. The results also show that cholesteryl benzoate gives smaller $\alpha$ to $\beta$ ratios than the other two molecules, i.e. the effect of peroxyacid is smaller although still pronounced, and that MMPP generally gives significantly larger amounts of the $\alpha$ isomer.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Oxidant</th>
<th>$\alpha : \beta$ ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>UHP / TFAA</td>
<td>2.65 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.71 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.19 : 1</td>
</tr>
<tr>
<td></td>
<td>MMPP</td>
<td>8.31 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.71 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.26 : 1</td>
</tr>
<tr>
<td>Cholesteryl acetate</td>
<td>UHP / TFAA</td>
<td>2.08 : 1 ; 1.96 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.03 : 1 ; 1.97 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.42 : 1</td>
</tr>
<tr>
<td></td>
<td>MMPP</td>
<td>9.87 : 1 ; 4.65 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.96 : 1 ; 4.65 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.43 : 1</td>
</tr>
<tr>
<td>Cholesteryl benzoate</td>
<td>UHP / TFAA</td>
<td>1.92 : 1 ; 1.68 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.82 : 1 ; 1.75 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.80 : 1 ; 1.74 : 1</td>
</tr>
<tr>
<td></td>
<td>MMPP</td>
<td>10.21 : 1 ; 10.91 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.84 : 1 ; 17.81 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.99 : 1</td>
</tr>
</tbody>
</table>

Table 5.
Cholesterol has also been epoxidised using UHP / maleic anhydride giving an α to β ratio of 3.39 : 1 and with UHP / glutaric anhydride giving an α to β ratio of 5.24 : 1. Cholesteryl benzoate has been epoxidised using UHP / phthalic anhydride giving an α to β ratio of 13.94 : 1. This result is similar to that obtained with MMPP. These results indicate that, as expected, the larger the peracid, the greater the amount of α isomer that is produced. The free OH group of cholesterol seems to be capable of directing attack to the α-face as shown by the lower α to β ratios observed with this substrate.
Chapter 3

Studies Into Asymmetric Oxidations
3. 1. The Sharpless Epoxidation Reaction.

The reaction now known as the Sharpless Epoxidation was first reported in 1980. The reaction allows the stereoselective epoxidation of allylic alcohols (Scheme 56).

![Scheme 56](image)

DET = Diethyl tartrate

The reaction also allows the kinetic resolution of secondary allylic alcohols and β-amino alcohols. The reagent is a complex formed between a titanium tetraalkoxide and dialkyl esters of tartaric acids and an alkyl hydroperoxide, usually tert-butyl hydroperoxide (TBHP). The catalyst is believed to be the dimer shown below (Figure 5). The alkylperoxo ligand occupies the other coordination site, but has been omitted for clarity.

In his review of the reaction, Sharpless proposed that the attack of the olefin on the peroxy compound takes place along the O-O axis in an SN2 type fashion, and that the hydroxyl group of an allylic alcohol can only participate in a hydrogen bond with the distal peroxy oxygen atom (Figure 6).
The importance of this discovery led to a large amount of research into reaction conditions, the results of which may be summarised as follows: Ti (IV) is the most active catalyst, and gives the highest e.e.'s. Tartrates, tartrate esters and tartramides are the only suitable ligands. Certain substrates give poor results, notably some 2-allylic alcohols and severely hindered molecules, and substrates leading to highly reactive epoxy alcohols. \(^{85}\)
3. 2. Other Methods Of Asymmetric Oxidation.

Other methods of asymmetric oxidation involve either chiral peracids, or chiral metal ligands. Chiral peracids give generally only modest to low e. e.'s except in exceptional circumstances. Rebek et. al. synthesised the chiral peracid shown below 40. Only low e. e.’s were observed. 86

![Chiral Peracid](image1)

40

Pirkle and Rinaldi synthesised monoperoxycamphoric acid 41 and after careful purification found that low e. e.’s could be obtained. Exceptionally 2-tert-butyl-3-(p-bromophenyl)-oxaziridine was obtained with an e. e. of 60%. 87

![Monoperoxycamphoric Acid](image2)

41
Both enantiomers of the oxaziridines 43, 44 shown below have been used to produce chiral sulfoxides with up to 75% e. e. \(^{89}\)

Chiral metal complexes based on either manganese or molybdenum have been successfully used to obtain chiral epoxides. The most successful of these are the Salen manganese complexes which are complexes of a chiral Schiff base 45 obtained from diamine and salicylaldehyde precursors. \(^{90}\)
E. e.'s of up to 93% have been obtained using these ligands. The source of oxygen is iodosomesitylene, which transfers its active oxygen to the metal. The chiral carbon atoms in the vicinity of the metal then favour one transition state during the actual epoxidation.

Chiral molybdenum complexes have been shown to exhibit temperature dependant enantioselective epoxidation. Thus in the reaction shown below (Scheme 57) the e. e. was 53% at -20°C, but increased to 73% at -70°C.
3.3. Synthesis And Reactivity Of 2-oxazolines.

Oxazolines are a class of 5-membered heterocycles containing one double bond. Three distinct ring systems are possible, the 2-oxazolines 46, the 3-oxazolines 47 and the 4-oxazolines 48. 2-oxazolines are the most common system both in the laboratory and in nature.

The 2-oxazolines were first prepared in 1884. Initial interest focused on the use of 2-oxazolines as protecting groups for carboxylic acids. 2-oxazolines are hydrolysed by mineral or Lewis acids, but are resistant to most other reagents. In recent years however, because of the ease with which asymmetry may be
introduced by the synthesis of 2-oxazolines using chiral amino alcohols derived from natural amino acids, 2-oxazolines have found increasing use as chiral catalysts.

The most common preparative route for 2-oxazolines is the reaction of an acid chloride with the appropriate amino alcohol followed by cyclisation with thionyl chloride (Scheme 58). 93

![Scheme 58.](image)

It is occasionally found that problems with the formation of the chloride limit this route. 94 However, it has significant advantages over direct synthesis from the acid and the amino alcohol. Direct synthesis often involves high temperatures and/or azeotropic water removal and can be achieved in a number of ways 95 (Scheme 59).
An alternative and general synthesis of 2-oxazolines is the reaction of an amino alcohol with the imidate of an amide or nitrile (Scheme 60).

The most general synthesis however, is the direct reaction of nitriles and amino alcohols in the presence of catalytic quantities of metal salts. Discovered in 1974, the reaction method was optimised by Bolm et al, and allows the production of 2-oxazolinyl derivatives under mild conditions (Scheme 61). 96
Alternative methods of synthesis include reactions between carboxylic acids and amino alcohols in the presence of DBU and Ph₃P-CCI₄ (Scheme 62).  

The acid is initially converted to the acid chloride which reacts to form the amide. The phosphine activates the hydroxyl group, and ring closure occurs to form the oxazoline. The procedure is analogous to thionyl chloride cyclisation, but the leaving group is different.

An efficient route to chiral aryl oxazolines has recently been described by Meyers. Triflates of phenols are converted to amides in the presence of chiral amino alcohols by palladium catalysed carbon monoxide insertion (Scheme 63).
Our interest in 2-oxazolines is based upon the ease with which asymmetry may be introduced as mentioned above, but also upon another feature of their reactivity, namely their ability to direct metallation of the phenyl residue ortho- to the 2-oxazoline moiety as shown below.

Scheme 64.
3. 4. Results And Discussion.

3. 4. 1. 2-oxazolines.

Because 2-oxazolines are readily synthesised and as there was a body of experience in the department we decided to attempt the synthesis of 2-oxazoline based peroxyacid precursors shown below.

These compounds would allow us to produce peroxyacids, peroxycarbonic acids and peroxycarbamic acids (Payne reagents.) By variation of the amino alcohol, a large number of compounds could be readily produced. Our first synthetic pathway started with the commercially available 2-hydroxy benzonitrile and valinol (Scheme 65).
Scheme 65.

The hydroxy oxazoline 52 was synthesised in 94% yield by this method. Attempts to obtain the chloroformate 50 by action of triphosgene on the hydroxy oxazoline gave a crystalline product. NMR data do not support the formation of 50, but do show the presence of a carbonyl group, but the characteristic signature of the isopropyl group is missing. Attempts to generate a percarbonate from this using hydrogen peroxide \textit{in situ} failed.

In light of our failure, we decided to investigate the synthesis of the acid chloride 49 and nitrile 51 derivatives using oxazolines obtained from the cheap, achiral reagent 2-amino-2-methyl-1-propanol in subsequent investigations. Our first route was via the \textit{ortho} lithiated derivative and subsequent quenching with dry CO$_2$ (Scheme 66).
The method of addition of CO$_2$ is critical to this reaction. Attempted synthesis of the carboxylic acid using lithium and carbon dioxide failed to gave the acid 53. A reaction in which $n$-BuLi was used to generate the organolithium reagent produced the acid in 35% yield.

As an alternative to the organolithium chemistry we attempted to synthesise Grignard reagents from the ortho bromo oxazoline 54 which is readily synthesised in 59% yield. The ethyl ester of the desired acid 55 was synthesised in 20% yield by the method shown (Scheme 67). The main product of this reaction was due to quenching of the Grignard reagent by water.
Attempts to form the acid by CO$_2$ quench of an organolithium formed from the bromo oxazoline failed.

The methyl ester 56 was synthesised in 30% yield from monomethyl phthalate (Scheme 68).

An attempt to synthesise the acid by permanganate oxidation of the methyl oxazoline 57 failed (Scheme 69).
Having obtained the acid there are three possible routes to the peracid.

1. Conversion to the acid chloride followed by reaction with alkaline H$_2$O$_2$ or sodium peroxide.

2. Conversion to the acid chloride followed by reaction with sodium 4-hydroxy benzenesulfonate. The resulting ester may then be hydrolysed \textit{in situ} by alkaline H$_2$O$_2$.

3. Reaction of the acid with 1,1'-carbonyl diimidazole. The resulting imide may be hydrolysed with alkaline H$_2$O$_2$, and extracted into a suitable solvent for use (Scheme 70.)
A trial reaction using meta chlorobenzoyl chloride and alkaline H₂O₂ gave the peracid as a mixture containing only 24% of the theoretical Av. Ox. An attempted oxidation of α-methyl styrene using a 2 phase system containing perbenzoic acid generated by this method, gave only starting material.

Attempts to form the ester using sodium 4-hydroxy benzenesulfonate and benzoyl chloride in a mixture of iso-octane and n-undecane having a boiling point of ca. 160° C, gave only starting materials.

The nitrile 51 could be made either by introduction of the cyano group via a Sandmeyer reaction or by having the nitrile already present during construction of the oxazoline. The Sandmeyer method was rejected as being too hazardous so the alternative methods were considered. The first method to be attempted was the reaction of phthalonitrile with one equivalent of an amino alcohol (Scheme 71).

![Scheme 71](image)

However the reaction mixture yielded only undesired blue materials, which proved to be phthalocyanins (Figure 7.)
An alternative synthesis reacting phthalonitrile with methanol in the presence of HCl to form a mono imidate ester 58 (Scheme 72) failed.

Scheme 72.

An alternative synthesis would be from 2-cyanobenzoic acid via the acid chloride. However it proved impossible to synthesise the starting material.
3. 4. 2. Chiral Carbamates.

We decided to investigate the possibility that chiral carbamates might transfer chirality during peracid epoxidations since we believed that an interaction of the type shown below might occur (Figure 8.)

![Figure 8.](image)

We synthesised a large number of carbamates which possessed chirality at either the nitrogen or the oxygen by two routes (Scheme 73).

\[
\text{Method 1:} \quad R^2\text{OH} + R^1\text{NCO} \xrightarrow{\text{Et}_3\text{N/Toluene, reflux 24 hr}} R^1\text{NHCO}_2R^2
\]

\[
\text{Method 2:} \quad R^2\text{OCOCl} + R^1\text{NH}_2 \xrightarrow{\text{Na}_2\text{CO}_3/DCM, 24 hr}} R^1\text{NHCO}_2R^2
\]

Scheme 73.

All the carbamates are colourless crystalline solids except N-ethyl-O-iso-menthyl carbamate 64 which is a high boiling liquid. The
fenchyl group gives lower yields possible due to steric hindrance. Other apparent low yields are probably due to the presence of water. Several of the carbamates were then screened for catalytic activity.

The reaction examined was the epoxidation of α-methyl styrene using UHP in DCM with 1 molar equivalent of carbamate. None of the carbamates examined exhibited any ability to induce asymmetry. This result is not particularly surprising in view of the presence of a vast amount of urea which would be expected to swamp any effect of the carbamate. However subsequent experiments using peracetic acid also failed to produce an optically enriched product even with large amounts of carbamate present. In addition it appeared that yields decreased with increasing carbamate concentration (Table 6.)
<table>
<thead>
<tr>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Method</th>
<th>Yield</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menthyl</td>
<td>Phenyl</td>
<td>1</td>
<td>83%</td>
<td>59</td>
</tr>
<tr>
<td>iso-menthyl</td>
<td>Phenyl</td>
<td>1</td>
<td>67%</td>
<td>60</td>
</tr>
<tr>
<td>Fenchyl</td>
<td>Phenyl</td>
<td>1</td>
<td>25%</td>
<td>61</td>
</tr>
<tr>
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Table 6: Chiral carbamates

3.4.3. Miscellaneous Experiments.

Experiments have been undertaken in order to investigate the possibility of tethering a peracid to the hydroxy group of cholesterol in order to epoxidise the double bond, hopefully exclusively on the β-face, a transformation for which there is no simple method. Molecular models indicated that a two carbon spacing group between the ester tether and the free peracid would give a good chance of the desired selectivity as shown in Figure 9.
It was decided to investigate the phthalate group since it offered some rigidity and because cholesteryl hydrogen phthalate is a known compound, and we hoped to use it as shown below (Scheme 74).

Cholesteryl hydrogen phthalate has been successfully synthesised in 70% yield, but attempts to produce the acid chloride or the peroxyacid have been unsuccessful.
Scheme 74.
Chapter 4

EXPERIMENTAL
Commercially available solvents were used throughout without purification, except for those detailed below. 'Light petroleum' refers to the fraction of petroleum ether boiling between 40°C and 60°C, and was distilled through a vigreux column before use. 'Ether' refers to diethyl ether, and was distilled from calcium chloride and stored over sodium. THF was distilled from sodium benzophenone ketal under nitrogen immediately before use. Dichloromethane was distilled from phosphorus pentoxide.

Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 nm) or by staining with phosphomolybdic acid reagent or vanillin reagent, followed by heating.

Infra-red spectra were recorded in the range 4000-600 cm\(^{-1}\) using a Nicolet FT-205 spectrometer, as solutions in chloroform, thin films or as a nujol mull. \(^1\)H and \(^{13}\)C NMR spectra were recorded using a Bruker AC-250 instrument. Mass spectra were recorded on a Kratos MS80 instrument. Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. Optical rotations were determined on an Optical Activity AA100 polarimeter.

Due to the presence of diastereomers, some of the signals in \(^{13}\)C NMR may appear as close doublets. Where this occurs the chemical shifts are separated by an ampersand ('&') and are quoted to two decimal places where necessary.
4.1 Oxidation Studies.

1,2-epoxyoctane (24) 101
To a mixture of oct-1-ene (0.897g, 8 mmol ), di-sodium hydrogen orthophosphate (9.9g, 80 mmol ) and urea-hydrogen peroxide adduct (7.6g, 80 mmol ) in dichloromethane (50ml ) at 0 °C, was added trifluoroacetic anhydride (3ml, 20 mmol ) dropwise with stirring. The mixture was allowed to warm to room temperature and refluxed for 30 min. The mixture was filtered, neutralised by the addition of saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The combined organic layers were washed with saturated sodium metabisulfite solution to remove any diacyl peroxide present, dried over anhydrous MgSO4 and solvent removed under vacuum. The crude material was purified by flash chromatography ( light petroleum/ ether 19:1 ) to give the title compound as a colorless oil (0.73g, 71 % );

\[ \nu_{\text{max}} \text{ (thin film) } / \text{cm}^{-1} \quad 3041, 920 ; \ \delta_H \ (250 \text{ MHz, CDCl}_3 ) \ 2.79 \]
\[ (2H, \text{ m }) , \ 2.41 \ (1H, \text{ m }) , \ 1.34 \ (10H, \text{ br. m }) , \ 0.89 \ (3H, \text{ m }) ; \]
\[ \delta_C \ (62.5 \text{ MHz, CDCl}_3 ) \ 52.4 \ (\text{CH}), \ 47.1 \ (\text{CH}_2), \ 32.5 \ (\text{CH}_2), \ 31.8 \ (\text{CH}_2), \ 29.2 \ (\text{CH}_2), \ 26.0 \ (\text{CH}_2), \ 22.6 \ (\text{CH}_2), \ 14.1 \ (\text{CH}_3) \]

1-methyl-1,2-epoxyethylbenzene (25) 102
To a mixture of α-methyl styrene (0.95g,8 mmol ), di-sodium hydrogen orthophosphate (9.9g, 80 mmol ) and urea gel-hydrogen peroxide adduct (7.6g, 80 mmol ) in dichloromethane (50ml ) at 0 °C, was added acetic anhydride (2.04g, 20 mmol ) dropwise with stirring. The mixture was allowed to warm to
room temperature and stirred overnight. The mixture was filtered, neutralised by the addition of saturated sodium hydrogen carbonate solution, and extracted with dichloromethane. The combined organic layers were washed with saturated sodium metabisulfite solution to remove any diacyl peroxide present, dried over anhydrous MgSO₄ and solvent removed in vacuo. The crude material was purified by kugelrohr distillation to give the title compound as a colourless oil (0.98g, 92%);

$\nu_{\text{max}}$ (thin film)/ cm⁻¹ 3032, 1062;

$\delta_H$ (250 MHz, CDCl₃) 7.30 (5H, m), 2.87 (2H, d, d, J=5), 1.71 (3H, s);

$\delta_C$ (62.5 MHz, CDCl₃) 141.2 (Ar), 128.3 (ArH), 127.4 (ArH), 125.3 (ArH), 57.0 (CH₂), 21.8 (CH₃) 

$\varepsilon$-caprolactone (27) ¹⁰³

To a mixture of cyclohexanone (0.8g, 8 mmol), di-sodium hydrogen orthophosphate (9.9g, 80 mmol) and urea-hydrogen peroxide adduct (7.6g, 80 mmol) in dichloromethane (50ml) at 0 °C, was added trifluoroacetic anhydride (3ml, 20 mmol) dropwise with stirring. The mixture was allowed to warm to room temperature and refluxed for 30 min. The mixture was filtered, neutralised by the addition of saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The combined organic layers were washed with saturated sodium metabisulfite solution to remove any diacyl peroxide present, dried over anhydrous MgSO₄ and solvent removed under vacuum. The crude material was purified by kugelrohr distillation to give the title compound as a colourless oil (0.87g, 90%); $\nu_{\text{max}}$ (thin film)/ cm⁻¹ 2932, 1730;
\[ \delta_H (250 \text{ MHz, CDCl}_3 ) 4.24 (2H, m), 2.65 (2H, m), 0.83 (6H, m) ; \]
\[ \delta_C (62.5 \text{ MHz, CDCl}_3 ) 176.3 (C=O), 69.3(CH_2), 34.6 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 22.9 (CH_2) \]

**2-oxabicyclo[3.2.1]octan-3-one (28)**

To a mixture of nor-camphor (0.897g, 8 mmol ), di-sodium hydrogen orthophosphate (9.9g, 80 mmol ) and urea-hydrogen peroxide adduct (7.6g, 80 mmol ) in dichloromethane (50ml ) at 0 °C, was added trifluoroacetic anhydride (3ml, 20 mmol ) dropwise with stirring. The mixture was allowed to warm to room temperature and refluxed for 30 min. The mixture was filtered, neutralised by the addition of saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The combined organic layers were washed with saturated sodium metabisulfite solution to remove any diacyl peroxide present, dried over anhydrous MgSO\(_4\) and solvent removed under vacuum. The crude material was purified by kugelrohr distillation to give the title compound as a colourless oil (0.90g, 80% ) \( \nu_{\text{max}} \) (thin film )/ cm\(^{-1}\) 2953, 1723;
\[ \delta_H (250 \text{ MHz, CDCl}_3 ) 4.86 (1H, t, J=1 ), 2.19 (9H, m) ; \]
\[ \delta_C (62.5 \text{ MHz, CDCl}_3 ) 171.0 (C=O), 81.0 (CH ), 40.7 (CH_2), 35.8 (CH_2), 32.5 (CH_2), 31.9 (CH ), 29.3 (CH_2) \]

*Note on the use of ' crystal disrupting agents.'*

The above experimental methods were used when evaluating the effect of polyethers as described in chapter 2. The additives were present at a 10 mol% concentration with respect to the
substrate i. e. ca. 0.8 mmol. Addition of the additives took place during the initial mixture of the reagents prior to cooling and addition of the anhydride. In all other respects the experimental procedures were identical.

1,2- epoxyocta-7-ene (30) 112
and 1,2,7,8-diepoxyoctane (31) 113
To 1,7-octadiene (0.88g, 8 mmol) and silica gel / H2O2 (1.85g, 20mmol) in DCM (100ml) was added trifluoroacetic anhydride (3.0ml, 20ml) dropwise. The mixture was refluxed for 3 hr and allowed to cool. Workup and flash chromatography (ether/ light petroleum 4:1) gave the title compound as a colourless oil (0.541g, 47 %) and 1,2- epoxy-7-octene (0.242g, 24 %) also as a colourless oil. v_{max} (thin film)/ cm^{-1} 2978; \delta_H (250 MHz, CDCl_3) 2.91 (2H, m), 2.61 (2H, m), 2.46 (2H, m), 1.45 (8H, br. m); \delta_C (62.5 MHz, CDCl_3) 52.2 (CH), 47.1 (CH_2), 32.44 & 32.38 (CH_2), 25.88 & 25.85 (CH_2)

Data for 1,2- epoxyocta-7-ene:
v_{max} (thin film)/ cm^{-1} 2977; \delta_H (250 MHz, CDCl_3) 4.98 (2H, m), 2.85 (1H, m), 2.75 (1H, m), 2.46 (1H, m), 1.47 (8H, m); \delta_C (62.5 MHz, CDCl_3) 138.7 (CH=), 114.6 (CH2=), 52.3 (CH), 47.1 (CH_2), 33.7 (CH_2), 32.4 (CH_2), 28.7 (CH_2), 25.5 (CH_2)

1,2- epoxylimonene (32) 12
To a mixture of limonene (1.09g, 8 mmol), di-sodium hydrogen orthophosphate (9.9g, 80 mmol) and UHP (7.6g, 80 mmol) in dichloromethane (50ml) at 0 °C, was added acetic anhydride (2.04g, 20 mmol) dropwise with stirring. The mixture was
allowed to warm to room temperature and stirred overnight. The mixture was filtered, neutralised by the addition of saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The combined organic layers were washed with saturated sodium metabisulfite solution to remove any diacyl peroxide present, dried over anhydrous MgSO₄ and solvent removed in vacuo. The crude material was purified by flash chromatography (ether/ light petroleum 4:1) to give the title compound as a colourless oil (0.61 g, 50 %);

νₘₐₓ (thin film) / cm⁻¹ 2931; δₗ (250 MHz, CDCl₃) 4.69 (2H, m), 3.01 (1H, m), 1.68-1.26 (14H, m); δₚ (62.5 MHz, CDCl₃) 120.0 & 109.8 (C=C), 109.11 & 109.06 (C=CH₂), 60.5 & 59.3 (CH), 57.52 & 57.35 (C), 40.7 & 36.2 (CH), 30.77 & 30.06 (CH₂), 28.6 (CH₂), 25.9 & 24.9 (CH₂), 24.8 & 24.3 (CH₃), 18.7 & 18.0 (CH₃).

1-oxa-bicyclo [6.1.0] nonane (33)

To cyclooctene (0.882 g, 8 mmol) and silica gel/H₂O₂ (1.85 g, 20 mmol) in DCM (50 ml) was added trifluoroacetic anhydride (3 ml, 20 mmol) dropwise. The mixture was refluxed for 3 hr. Workup and kugelrohr distillation gave the title compound as a low melting colourless solid (0.651 g, 69 %); νₘₐₓ / cm⁻¹ (thin film) 2968; δₗ (250 MHz, CDCl₃) 2.89 (2H, m), 2.14 (2H, m), 1.48 (10H, m); δₚ (62.5 MHz, CDCl₃) 55.7 (CH), 26.58 (CH₂), 26.3 (CH₂), 25.6 (CH₂)

Trögers Base (2,8-dimethyl-6H,12H-5,11-methanodibenzo-[b,f][1,5]diazocene) (36)
To a solution of $p$-toluidine (3.0g, 28mmol) in 95% ethanol (30ml) was added 37% formaldehyde (13.5ml, 116.5mmol) and the mixture was cooled to 0°C. Concentrated HCl (11.4ml, 136.5mmol) was added dropwise with stirring, the mixture was allowed to warm to room temperature and stirred under nitrogen for 24hr. The mixture was evaporated under reduced pressure to half its original volume and added to water (300ml) and concentrated ammonia (30ml) and extracted into DCM. The organic layer was washed with sodium bicarbonate solution and brine and dried over MgSO$_4$ and the solvent removed in vacuo. The crude product was recrystallised from aqueous ethanol to give the title compound as colourless crystals (1.83g, 53%); $\nu_{\text{max}}$ (nujol mull)/cm$^{-1}$ 1492; $\delta_H$ (250 MHz, CDCl$_3$) 6.95 (4H, m), 6.69 (2H, s), 4.63 (2H, d, J=16.6), 4.28 (2H, s), 4.09 (2H, d, J=16.6), 2.20 (6H, s); $\delta_C$ (62.5 MHz, CDCl$_3$) 145.4 (ArC), 133.4 (ArC), 129.7 (ArC), 128.1 (ArH), 127.5 (ArH), 124.8 (ArH), 67.0 (CH$_2$), 58.7 (CH$_3$), 20.8 (CH$_3$).

5,6-epoxy-cholestan-3β-ol (cholesterol epoxide) (37)$^{1,2}$

a) MMPP method

To a solution of cholesterol (0.77g, 2mmol) in DCM (20ml) at reflux was added a solution of MMPP (1.24g, 2.5mmol) in water (15ml) dropwise. The mixture was refluxed for 1.5 hr and the pH was maintained in the range 4.5-5.0 by addition of 5% NaOH. The solution was washed with water, dried over MgSO$_4$ and the solvent removed in vacuo to yield the title compound (as a mixture of $\alpha$ and $\beta$ isomers) and was analysed by NMR without purification.
b) UHP method.

To a mixture of cholesterol (0.77g, 2mmol), UHP (1.9g, 20mmol) and disodium hydrogen phosphate (2.48g, 17.5mmol) in DCM (50ml) at 0 °C was added trifluoroacetic anhydride (0.75ml, 5mmol) dropwise. The mixture was stirred at room temperature for 17 hr. The mixture was filtered, neutralised by the addition of saturated sodium hydrogen carbonate solution, and extracted with dichloromethane, dried over anhydrous MgSO₄ and solvent removed in vacuo.

δH (250 MHz, CDCl₃) 3.89 (1H, m, α-isomer),
3.49 (1H, m, β-isomer), 3.05 (1H, d, J=4.3, β-isomer),
2.89 (1H, d, J=4.3, α-isomer), 2.15-0.61 (44H, br.m)

5,6-epoxy-3β-acetoxy-cholestanen (epoxy cholesteryl acetate) (38) 106 106

cholesteryl acetate (0.86g, 2mmol) was reacted according to methods (a) and (b) above and the crude material analysed by NMR.

υmax (nujol mull)/ cm⁻¹ 1710; δH (250 MHz, CDCl₃) 4.95 (1H, m, α isomer), 4.76 (1H, m, β isomer), 3.08 (1H, d, J=2.1, β isomer),
2.89 (1H, d, J=2.1, α isomer), 2.27-0.63 (46H, steroid and acetate protons); δC (62.5 MHz, CDCl₃) 170.46 & 170.15 (C=O),
71.3 (CH), 65.1 (CH), 63.5 (C), 62.4 (CH), 59.1 (CH), 56.08 & 55.75 (CH),
50.8 (CH), 42.33 & 42.22 (CH), 39.6 (CH₂), 39.41 & 39.27 (CH₂),
36.6 (CH₂), 36.0 (CH₂), 35.7 (C), 34.9
(CH), 32.4 (CH₂), 32.04 & 29.77 (CH), 28.7 (CH₂), 28.07 & 28.00
(CH₂), 27.9 (CH₃), 27.1 (CH₂), 23.96 & 23.76 (CH₂), 23.71 &
22.75 (CH\textsubscript{2}), 22.5 (CH\textsubscript{2}), 21.3 (CH\textsubscript{3}), 20.5 (CH\textsubscript{3}), 18.59 & 18.56 (CH\textsubscript{3}), 15.8 (CH\textsubscript{3}), 11.77 & 11.67 (CH\textsubscript{3})

5,6-epoxy-3β-benzyloxy-cholestan e
(epoxy cholesteryl benzoate) (39) \textsuperscript{107}

Cholesteryl benzoate (0.98g, 2mmol) was reacted according to methods (a) and (b) above and the crude material analysed by NMR. \textit{v}_{\text{max}} (nujol mull)/ cm\textsuperscript{-1} 1714; \textit{δ}_H (250 MHz, CDCl\textsubscript{3})

8.22 (2H, m), 7.36 (3H, m), 5.21 (1H, m, \textit{α}-isomer), 5.03 (1H, m, \textit{β} isomer), 3.11 (1H, d, J=2, \textit{β}-isomer), 2.92 (1H, d, J=2, \textit{α}-isomer), 2.36-0.62 (43H, steroid protons);

\textit{δ}_C (62.5 MHz, CDCl\textsubscript{3}) 165.9 (C=O), 132.6 (ArH), 130.7 (ArC), 129.5 (ArH), 128.2 (ArH), 74.5 (CH), 56.6 (CH\textsubscript{2}), 56.1 (CH\textsubscript{2}), 55.8 (C), 49.9 (CH), 42.2 (C), 39.7 (CH\textsubscript{2}), 39.5 (CH\textsubscript{2}), 38.2 (CH\textsubscript{2}), 36.9 (CH\textsubscript{2}), 36.6 (C), 36.1 (CH\textsubscript{2}), 36.1 (CH), 31.9 (CH\textsubscript{2}), 31.8 (CH), 28.2 (CH\textsubscript{2}), 27.9 (CH), 27.8 (CH\textsubscript{2}), 27.3 (CH), 24.2 (CH\textsubscript{2}), 23.8 (CH\textsubscript{2}), 22.8 (CH\textsubscript{3}), 22.5 (CH\textsubscript{3}), 20.9 (CH\textsubscript{2}), 19.3 (CH\textsubscript{3}), 18.7 (CH\textsubscript{3}), 11.8 (CH\textsubscript{3})

\textbf{4.2 2-Oxazolines.}

\textbf{Attempted synthesis of}
\textbf{(4S)-4-isopropyl-2-(2-hydroxyphenyl)-1,3-oxazoline chloroformate (50)}

To a solution of (4S)-4-isopropyl-2-(2-hydroxyphenyl)-1,3-oxazoline (2.0g, 10mmol) in pyridine (1.6g, 20mmol) was added triphosgene (2.0g, 2 equivalents) in small portions. The resulting mixture was stirred under nitrogen for 5 hr. The mixture was poured into saturated sodium bicarbonate solution and quickly extracted into ether. The combined ether layers
were dried over MgSO₄ and the solvent removed in vacuo. The crude brown oil was kugelrohr distilled (B.pt. 195°C / 0.4mm ) to give a pale brown syrup that solidified on standing. The solid was recrystallised from light petroleum to yield the title compound as colourless crystals (1.21g, 45% )

(4S)-4-isopropyl-2-(2-hydroxyphenyl)-1,3-oxazoline (52) 96

To freshly dried zinc chloride (68mg, 0.5mmol ) was added chlorobenzene (30 ml) followed by 2-hydroxybenzonitrile (1.19g, 10 mmol ) and valinol (1.56g, 15 mmol ). The mixture was heated under reflux for 48-60 hours. The solvent was removed in vacuo to give an oily residue, which was dissolved in DCM (30ml ). The solution was extracted with water (3x 20ml ) and dried over MgSO₄ and the solvent removed in vacuo. The residue was purified by flash chromatography (DCM ) to give the title compound as a colourless oil (1.93g, 94% ); \( \nu_{\text{max}} \) (thin film )/ cm\(^{-1}\) 1643; \( \delta_H \) (250 MHz, CDCl₃ ) 7.63 (1H, m ), 7.34 (1H, m ), 6.99 (1H, m ), 6.85 (1H, m ), 4.41 (1H, m ), 4.12 (2H, m ), 1.78 (1H, sept, J=6.7 ), 0.98 (6H, d . d, J=17.6, 6.7 ); \( \delta_C \) (62.5 MHz, CDCl₃ ) 165.5 (C=N ), 159.9 (ArC ), 133.2 (ArH ), 127.9 (ArH ), 118.5 (ArH ), 116.6 (ArH ), 111.5 (ArC ), 71.5 (CH ), 69.8 (CH₂ ), 33.0 (CH ), 18.7 (CH₃ ), 18.6 (CH₃)

2-(4,4-dimethyl-1,3-oxazolin-2-yl)-benzoic acid (53) 108

To a solution of 4,4-dimethyl-2-(2-bromophenyl)-1,3-oxazoline (1.0g, 3.7mmol ) in dry THF under nitrogen at -40°C was added n-butyllithium (3ml, 4.8mmol ) dropwise, and the mixture was stirred at -40°C for 2 hr. A 1 litre conical containing dry solid CO₂ was
prepared, and the solution poured into it. The resulting solution was filtered and washed with a small amount of ice water, dried over MgSO₄ and the solvent removed in vacuo. The crude product was recrystallised twice from ether to yield the title compound as colourless crystals (0.29g, 35%); \( \delta_H \) (250 MHz, CDCl₃) 8.55 (1H, d, J=1.9, 6.6), 8.04 (1H, d, J=1.9, 7.2), 7.64 (2H, m), 4.31 (2H, s), 1.42 (6H, s); \( \delta_C \) (62.5 MHz, CDCl₃) 167.2 (C=O), 164.5 (C=N), 135.1 (ArH), 133.0 (ArC), 132.5 (ArH), 131.6 (ArH), 130.5 (ArH), 124 (ArC), 79.7 (CH₂), 27.9 (CH₃)

**4,4-dimethyl-2-(2-bromophenyl)-1,3-oxazoline (54)**

Bromobenzoyl chloride (2.0g, 9mmol) was added dropwise to 2-amino-2-methyl-1-propanol (1.6g, 18mmol) in DCM (50ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 4 hr. The solvent was removed in vacuo and the residue was washed with water and dried to give the crude benzamide. The crude solid was placed in a 150ml conical flask and thionyl chloride was added dropwise until the vigorous reaction ceased. Dry ether (50ml) was added and the precipitate was neutralised with 2M sodium hydroxide. The aqueous layer was extracted with ether (2x 50 ml) and the combined organic layers were dried over MgSO₄ and the solvent removed in vacuo. The crude residue was purified by flash chromatography (ether) to give the title compound as a pale yellow oil (1.24g, 52%); \( \delta_H \) (250 MHz, CDCl₃) 7.62 (2H, m), 7.29 (2H, m), 4.14 (2H, s), 1.41 (6H, s); \( \delta_C \) (62.5 MHz, CDCl₃) 162.5 (C=N), 133.5 (ArH), 131.4 (ArH), 131.2 (ArH), 126.7 (ArH), 121.7 (ArC), 79.3 (CH₂), 68.0 (C), 28.2 (CH₃)
4,4-dimethyl-2-(2-ethoxycarbonyl phenyl)-1,3-oxazoline (55) \(^{109}\)

To a solution of 4,4-dimethyl-2-(2-bromophenyl)-1,3-oxazoline (2.5g, 9.8mmol) in THF (100ml) was added magnesium turnings (0.24g, 9.8 mmol) in small portions. The sluggish reaction eventually produced a brown solution. The solution was quenched with excess ethyl chloroformate and stirred for 1 hr. The solvent was removed in vacuo and the crude product was purified by flash chromatography (ether / light petroleum 3 : 2) to yield the title compound (0.48g, 20 %) as a yellow oil.

\( \nu_{\text{max}} \) (thin film) / cm\(^{-1}\) 1698; \( \delta_H \) (250 MHz, CDCl\(_3\)) 7.72 (2H, m), 7.40 (2H, m), 4.37 (2H, q, J=4), 4.12 (2H, s), 1.39 (9H, m); \( \delta_C \) (62.5 MHz, CDCl\(_3\)) 167.7 (C=O), 162.2 (C=N), 132.4 (ArC), 130.9 (ArH), 130.3 (ArH), 129.9 (ArH), 128.9 (ArH), 128.4 (ArC), 79.7 (CH\(_2\)), 67.9 (C), 61.4 (CH\(_2\)), 28.2 (CH\(_3\)), 14.2 (CH\(_3\))

4,4-dimethyl-2-(2-methoxycarbonyl phenyl)-1,3-oxazoline (56) \(^{110}\)

To mono methyl phthalic acid (3.28g, 20mmol) was added thionyl chloride (2.97g, 25mmol). The mixture was heated for 2 hrs and then distilled to remove excess thionyl chloride. The resulting crude acid chloride was used without further purification. To the acid chloride in DCM (50mls) was added a solution of 2-amino-2-methyl-1-propanol (Excess in DCM) and the resulting mixture was stirred at room temperature for 2 hrs. The solvent was removed in vacuo and the residue washed with water and dried. Thionyl chloride was added dropwise to the residue until no further gas evolution occurred. Ether (50ml)
was added and the solution was neutralised with 2M NaOH. The solution was extracted with ether dried over MgSO₄ and the solvent removed in vacuo to yield the title compound as a pale yellow oil (1.39g, 30%); δₓ (250 MHz, CDCl₃) 7.50 (2H, m), 7.27 (2H, m), 4.09 (2H, s), 3.87 (3H, s), 1.39 (6H, s); δc (62.5 MHz, CDCl₃) 168.0 (C=O), 162.5 (C=N), 133.9 (ArC), 130.9 (ArH), 130.3 (ArH), 129.7 (ArH), 128.9 (ArH), 122.9 (ArC), 79.8 (CH₂), 52.3 (C), 28.1 (CH₃), 23.0 (CH₃)

4,4-dimethyl-2-(2-methyl phenyl)-1,3-oxazoline (57)

To a solution of 2-amino-2-methyl-1-propanol (1.78g, 20mmol) in DCM (20ml) at 0°C was added 2-methylbenzoyl chloride (1.55g, 10mmol) dropwise with stirring. The mixture was stirred for 2 hrs at room temperature and the solvent removed in vacuo. The residue was washed with water and dried under vacuum to give the benzamide (1.04g, 50%) which was used without purification.

To the benzamide (1.04g, 5mmol) was added thionyl chloride until gas evolution ceased. Dry ether (20mls) was added and the mixture was acidified with 2M HCl. The solution was washed with sodium chloride solution and water and dried over MgSO₄. The solvent was removed in vacuo to yield the title compound as a pale yellow oil (0.73g, 77%); δₓ (250 MHz, CDCl₃) 7.74 (1H, m), 7.24 (3H, m), 4.04 (2H, s), 2.56 (3H, s), 1.38 (6H, s); δc (62.5 MHz, CDCl₃) 164.0 (C=N), 138.4 (ArC), 131.0 (ArH), 130.3 (ArH), 129.8 (ArH), 128.0 (ArC), 125.5 (ArH), 78.6 (CH₂), 67.9 (C), 28.5 (CH₃), 21.4 (CH₃)
4.3 Carbamates.

**N-phenyl-O-menthyl carbamate (59)**

To phenyl isocyanate (3.0g, 25mmol) in toluene (100ml) was added (-)-menthol (3.9g, 25mmol) and triethylamine (2ml). The mixture was refluxed for 14 hr and the solvent was removed *in vacuo*. The crude product was recrystallised 3 times from light petroleum to give the title compound as colourless crystals (6.06g, 83%); M.pt. 110-112 °C; M+: 275.1875, C\textsubscript{17}H\textsubscript{25}N\textsubscript{2}O\textsubscript{2} requires 275.3900; \( \nu_{\text{max}} \) (nujol mull) / cm\(^{-1}\) 2990, 1691; \( \alpha_{D}^{25} \) -67.6° [c=1.02 in EtOH]; \( \delta_{H} \) (250 MHz, CDCl\textsubscript{3}) 7.31 (4H, m), 7.03 (1H, m), 6.65 (1H, br. s), 4.66 (1H, t. d, J=11, 4), 1.99 (2H, m), 1.68 (2H, m), 1.38 (2H, m), 1.02 (12H, m); \( \delta_{C} \) (62.5 MHz, CDCl\textsubscript{3}) 154.0 (C=O), 138.2 (ArC), 129.0 (ArH), 123.1 (ArH), 118.5 (ArH), 75.1 (CH), 47.3 (CH), 41.4 (CH\textsubscript{2}), 34.2 (CH\textsubscript{2}), 31.4 (CH), 26.3 (CH), 23.5 (CH\textsubscript{2}), 27.0 (CH\textsubscript{3}), 20.8 (CH\textsubscript{3}), 16.4 (CH\textsubscript{3}).

**N-phenyl-O-isomenthyl carbamate (60)**

To phenyl isocyanate (3.0g, 25mmol) in toluene (100ml) was added (+)-isomenthol (3.9g, 25mmol) and triethylamine (1ml). The mixture was refluxed for 15 hr and the solvent was removed *in vacuo*. The crude product was recrystallised 3 times from light petroleum to give the title compound as colourless crystals (4.58g, 67%); M.pt. 65-66 °C; M+: 275.1899, C\textsubscript{17}H\textsubscript{25}N\textsubscript{2}O\textsubscript{2} requires 275.3900 \( \nu_{\text{max}} \) (nujol mull) 2924, 1687; \( \alpha_{D}^{25} \) +12.5° [c=0.8 in EtOH]; \( \delta_{H} \) (250 MHz, CDCl\textsubscript{3}) 7.29 (4H, m), 7.03 (1H, m), 6.63 (1H, s), 5.03 (1H, t. d, J=6, 4), 1.40 (18H, br. m); \( \delta_{C} \) (62.5 MHz, CDCl\textsubscript{3}) 154.0 (C=O), 138.2 (ArC), 129.0 (ArH),
123.1 (ArH ), 118.5 (ArH ), 72.8 (CH ), 45.9 (CH ), 36.1 (CH₂ ), 29.9 (CH₂ ), 27.6 (CH₂ ), 26.3 (CH₂ ), 25.8 (CH ), 20.9 (CH₃ ), 20.8 (CH₃ ), 20.5 (CH₃ ), 19.1 (CH₃ ).

**N-phenyl-O-fenchylcarbamate (61)**

To phenyl isocyanate (3.0g, 25mmol ) in toluene (100ml ) was added fenchol (3.9g, 25mmol ) and triethylamine (1ml. ) The mixture was refluxed for 15 hr and the solvent was removed *in vacuo*. The crude product was recrystallised 3 times from light petroleum to give the title compound as colourless crystals (1.71g, 25% ); M.pt. 94-95 °C; M+: 273.1721, C₁₇H₂₃NO₂ requires 273.3742; $\nu_{\text{max}}$/ cm⁻¹ (nujol mull ) 2924, 1694; $\alpha_D^{25}$ +38.1° $\delta_H$ (250 MHz, CDCl₃ ) 7.30 (4H, m ), 7.04 (1H, m ), 6.66 (1H, s ), 4.38 (1H, d, J=2 ), 1.62 (5H, m ), 1.17 (8H, m ), 0.86 (3H, s ); $\delta_C$ (62.5 MHz, CDCl₃ ) 154.0 (C=O), 138.0 (ArC), 129.0 (ArH), 123.3 (ArH), 118.6 (ArH), 87.0 (CH), 48.3 (CH), 41.3 (CH₂ ), 39.6 (CH), 29.7 (CH₃ ), 26.7 (CH₂ ), 25.8 (CH₂ ), 20.1 (CH₃ ), 19.5 (CH₃ ).

**N-phenyl-O-bornylcarbamate (62)**

To phenyl isocyanate (3.0g, 25mmol ) in toluene (100ml ) was added borneol (3.9g, 25mmol ) and triethylamine (1ml. ) The mixture was refluxed for 14 hr and the solvent was removed *in vacuo*. The crude product was recrystallised 3 times from light petroleum to give the title compound as colourless crystals (6.15g, 90% ); M.pt. 137-138 °C; M+: 273.1720, C₁₇H₂₃NO₂ requires 273.3742; $\nu_{\text{max}}$/ cm⁻¹ (nujol mull ) 2924, 1687; $\alpha_D^{25}$ -36.3° $\delta_H$ (250 MHz, CDCl₃ ) 7.30 (4H, m ), 7.04 (1H, m ), 6.65 (1H, s ), 4.94 (1H, d . q, J=10, 2 ), 2.38
N-ethyl-O-menthylcarbamate (63)
To menthol (3.9g, 25mmol) was added ethyl isocyanate (1.9g, 25mmol), toluene (20ml) and triethylamine (1ml). The mixture was refluxed for 15 hr and the solvent was removed in vacuo. The resulting crude product was kugelrohr distilled (B.pt. 120°C @ 1 mm) and recrystallised 3 times from ether to give the title compound as colourless crystals (5.59g, 98%); M.pt. 63-65 °C; M+: 228.1948, C_{13}H_{25}NO_{2} requires 227.3460; \nu_{\text{max}} / \text{cm}^{-1} \text{ (nujol mull) 1686; } \alpha_D^{25} \text{ -78.0° [c=1.0 in EtOH ]; } \delta_H (250 \text{ MHz, CDCl}_3) 4.54 (2H, m), 3.26 (2H, m), 1.92 (2H, m), 1.66 (2H, m), 1.09 (3H, m), 0.88 (12H, m); \delta_C (62.5 \text{ MHz, CDCl}_3) 156.0 (C=O), 74.8 (CH), 47.5 (CH), 41.6 (CH₂), 35.8 (CH₂), 34.4 (CH₂), 22.1 (CH₃), 20.9 (CH₃), 16.5 (CH₃), 15.3 (CH₃)

N-ethyl-O-isomenthyl carbamate (64)
To isomenthol (3.9g, 25mmol) was added ethyl isocyanate (1.9g, 25mmol), toluene (20ml) and triethylamine (1ml). The mixture was refluxed for 4 hr and the solvent was removed in vacuo. The resulting crude product was kugelrohr distilled (B.pt. 135°C @ 0.7mm) to give the title compound as a colourless oil (4.97g, 87%); \nu_{\text{max}} / \text{cm}^{-1} \text{ (thin film) 1690; } \delta_H (250 \text{ MHz, CDCl}_3) 4.91 (1H, m), 4.65 (1H, s), 3.20 (2H, m), 1.37 (21H, m);
\[ \delta_C \text{ (62.5 MHz, CDCl}_3 \text{) } 156.0 \text{ (C=O), 71.8 \text{ (CH), 46.0 \text{ (CH)}, 36.2 \text{ (CH}_2 \text{), 35.7 \text{ (CH}_2 \text{), 30.0 \text{ (CH}_2 \text{), 27.6 \text{ (CH}_2 \text{), 26.3 \text{ (CH}_2 \text{), 20.9 \text{ (CH}_3 \text{), 20.6 \text{ (CH}_3 \text{), 19.2 \text{ (CH}_3 \text{), 15.3 \text{ (CH}_3 \text{) )}}}}}

N-ethyl-O-fenchyl carbamate (65)
To fenchol (3.9g, 25mmol) was added ethyl isocyanate (1.9g, 25mmol), toluene (20ml) and triethylamine (1ml). The mixture was refluxed for 17 hr and the solvent was removed \textit{in vacuo}. The resulting crude product was kugelrohr distilled (B.pt. 125°C @ 1mm) and recrystallised 3 times from ether to give the title compound as colourless crystals (5.52g, 98%); M.pt. 59-61 °C; \( \nu_{\text{max}} / \text{cm}^{-1} \text{ (nujol mull) } 1687; \alpha_D^{25} +31.0^\circ \text{ (c=1.02 in EtOH) } \); \( \delta_H \text{ (250 MHz, CDCl}_3 \text{) } 5.30 \text{ (1H, m), 4.34 \text{ (1H, s), 3.25 \text{ (2H, m), 1.57 \text{ (4H, m), 1.12 \text{ (13H, m), 0.84 \text{ (2H, m) } \); \delta_C \text{ (62.5 MHz, CDCl}_3 \text{) } 167 \text{ (C=O), 86.2 \text{ (CH), 48.3 \text{ (CH}_2 \text{), 41.3 \text{ (CH}_2 \text{), 39.5 \text{ (C), 35.8 \text{ (CH), 29.7 \text{ (CH}_3 \text{), 26.6 \text{ (CH}_2 \text{), 25.9 \text{ (CH}_2 \text{), 20.0 \text{ (CH}_3 \text{), 19.4 \text{ (CH}_3 \text{), 15.3 \text{ (CH}_3 \text{) )}}}}}

N-ethyl bornylcarbamate (66)
To borneol (3.9g, 25mmol) was added ethyl isocyanate (1.9g, 25mmol), toluene (20ml) and triethylamine (1ml). The mixture was refluxed for 15 hr and the solvent was removed \textit{in vacuo}. The resulting crude product was kugelrohr distilled (B.pt. 120°C @ 1mm) and recrystallised 3 times from ether to give the title compound as colourless liquid that solidified on standing (5.59g, 98%); M.pt. 45-49 °C; M+: 225.1728, \( C_{13}H_{23}NO_2 \) requires 225.3302; \( \nu_{\text{max}} / \text{cm}^{-1} \text{ (nujol mull) } 1686; \delta_H \text{ (250 MHz, CDCl}_3 \text{) } 4.83 \text{ (1H, d, q, J=10, 2), 4.65 \text{ (1H, s), 3.21 \text{ (2H, m) }, 9.3} \]
2.33 (1H, m), 1.73 (3H, m), 1.05 (15H, m); δC (62.5 MHz, CDCl₃) 157.0 (C=O), 79.9 (CH), 48.7 (C), 47.7 (C), 44.9 (CH), 36.7 (CH₂), 35.8 (CH₂), 28.1 (CH₂), 27.1 (CH₂), 19.8 (CH₃), 16.9 (CH₃), 15.3 (CH₃), 13.5 (CH₃)

N-((S)-phenylethyl)-O-menthylcarbamate (67)
To a solution of menthol (1.56g, 10mmol) in toluene (100ml) was added triethylamine (1ml) and a solution of (S)-methylbenzylisocyanate (1.47g, 10mmol) in toluene (20ml). The mixture was refluxed for 14hr and the solvent removed in vacuo. The crude product was purified by flash chromatography (light petroleum / ether 3:2) to give the title compound as colourless crystals. M.pt. 97-99 °C; M+ : 304.2292, C₁₉H₂₉N₂O₂ requires 303.4436; [α]D°²⁵ -106.9° [c=1.02 in EtOH]; δH (250 MHz, CDCl₃) 7.28 (5H, m), 4.86 (1H, s), 4.53 (1H, t.d, J=11, 4), 1.55 (22H, m); δC (62.5 MHz, CDCl₃) 155.7 (C=O), 144.0 (ArC), 128.6 (ArH), 127.2 (ArH), 125.9 (ArH), 74.7 (CH), 50.6 (CH), 47.7 (CH), 41.4 (CH₂), 34.3 (CH₂), 31.4 (CH), 26.3 (CH), 23.6 (CH₂), 22.6 (CH₃), 22.0 (CH₃), 20.8 (CH₃), 16.5 (CH₃)

N-((S)-phenylethyl)-O-methylcarbanate (68)
To a mixture of sodium carbonate (15.9g, 150mmol) and (S)-α-phenethylamine (6.06g, 50mmol) in dry DCM (50ml) under nitrogen at 0°C was added methyl chloroformate (4.1ml, 60mmol) dropwise with stirring. The mixture was stirred at room temperature for 2 days and then filtered and the solvent removed in vacuo. The crude product was recrystallised 3 times from ether to yield the title compound as a colourless solid
To a mixture of sodium carbonate (15.9 g, 150 mmol) and (S)-α-phenylethylamine (6.06 g, 50 mmol) in dry DCM (50 ml) under nitrogen at 0°C was added phenyl chloroformate (6.8 ml, 55 mmol) dropwise with stirring. The mixture was stirred at room temperature for 2 days and then filtered and the solvent was removed *in vacuo*. The crude product was recrystallised 3 times from ether to yield the title compound as a colourless solid (8.99 g, 75%); M.pt. 80-81°C; M⁺: 242.1175, C₁₅H₁₅N₂O₂ requires 241.4084; αD²⁵ -54.0° [c=1.0 in EtOH]; δH (250 MHz, CDCl₃) 7.26 (1OH, m), 5.35 (1 H, s), 4.95 (1H, quin, J=7); δC (62.5 MHz, CDCl₃) 154.0 (C=O), 151.0 (ArC), 143.0 (ArC), 129.2 (ArH), 128.7 (ArH), 127.5 (ArH), 126.1 (ArH), 125.3 (ArH), 121.6 (ArH), 50.9 (CH), 22.2, (CH₃)
hr. Cholesterol (4.4g, 11mmol) and n-butanol (2 drops) were added and the mixture refluxed for a further 1.5 hr. The mixture was filtered and a small amount of water was added. The resulting precipitate was dissolved in 2M HCl and extracted with ether. The ether layer was washed with water and dried over MgSO4. Removal of solvent in vacuo and recrystallisation from light petroleum gave the title compound as colourless crystals (4.29g, 70%); M.pt. 149-151°C; M+: 534.3709, C35H50O4 requires 534.7776; \( v_{\text{max}} \) (nujol mull)/cm\(^{-1}\) 2925, 1702; \( \delta_H \) (250 MHz, CDCl\(_3\)) 10.10 (1H, br.), 7.91 (2H, m.), 7.63 (2H, m.), 5.43 (1H, d, J=4.7), 4.85 (1H, m), 2.47 (2H, m), 2.04-0.68 (41H, br. m); \( \delta_C \) (62.5 MHz, CDCl\(_3\)) 172.5 (C=O), 167.5 (C=O), 139.4 (ArC), 133.8 (ArC), 132.2 (ArC), 130.7 (ArH), 129.8 (ArH), 128.8 (ArH), 125.7 (ArH), 122.9 (CH=), 77.5 (CH), 56.7 (CH\(_2\)), 56.1 (CH\(_2\)), 50.0 (CH\(_2\)), 42.3 (C), 39.7 (CH\(_2\)), 39.5 (CH\(_2\)), 37.8 (CH\(_2\)), 37.0 (C), 36.6 (CH\(_2\)), 36.2 (CH\(_2\)), 35.8 (CH), 31.9 (CH\(_2\)), 31.6 (CH), 28.2 (CH\(_2\)), 28.0 (CH), 27.4 (CH\(_2\)), 24.3 (CH\(_2\)), 23.8 (CH\(_2\)), 22.9 (CH\(_3\)), 22.6 (CH\(_3\)), 21.0 (CH\(_2\)), 19.3 (CH\(_3\)), 18.7 (CH\(_3\)), 11.9 (CH\(_3\))
Chapter 5

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