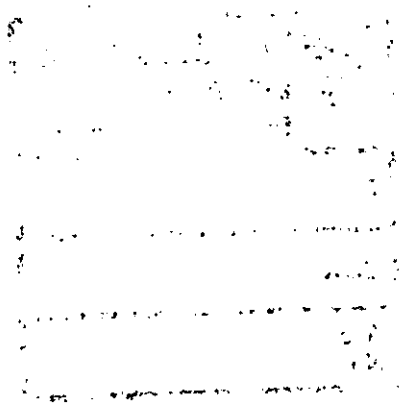
Applications and mechanisms of dioxirane oxidations

APPLICATIONS AND MECHANISMS OF DIOXIRANE OXIDATIONS



CONTENTS

ABSTRACT

Chapter 1 contains a brief introduction to the applications of dioxirane chemistry and outlines the mechanistic investigations carried out to date.

Chapter 2 describes investigations into the dimethyldioxirane oxidation of *para*-substituted N,N-dimethylanilines in acetone. The N-oxides were found to be the only products. Relative rates were determined and compared with those of reactions with methyl iodide and other oxidants. The dimethyldioxirane reactions followed the Hammett relationship with a ρ value of -1.0. The reaction rates are strongly accelerated in the presence of water and the overall reaction mechanism is electrophilic in nature and does not involve free radical species or electron transfer.

Chapter 3 looks at the regioselectivity of dimethyldioxirane when used to oxidise several polyfunctionalised nitrogenous drugs with a view to developing a system for use in oxidative degradation studies.

The regioselectivity of dimethyldioxirane in the oxidation of polyhydroxy steroids, namely a series of bile acid methyl esters, is discussed in chapter 4. No evidence for preferential oxidation of axial over equatorial hydroxyls or vice versa was seen. Instead the least hindered hydroxyl at C3 was oxidised preferentially with some oxidation also occurring at C6 and C7. Hydroxyls at the sterically hindered C12 were not oxidised. This provides further evidence for the proposed butterfly transition state.

Finally, chapter 5 discusses the use of novel trifluoromethyl aryl ketones as promoters for Oxone®-mediated epoxidations. 4-(trifluoroacetyl)benzoic acid was used succesfully and can be readily isolated for re-use by simple base extraction.

ACKNOWLEDGEMENTS

I would like to thank Loughborough University and SmithKline Beecham for financial support.

I would like to thank Professor Brian Marples for his supervision, all the technical staff at Loughborough University, in particular John Kershaw, and also everyone who worked in lab G0001 between October 1993 and January 1997, especially Lesley Walton, Gabrielle Loftus, John Rudderham and Tracey Ross.

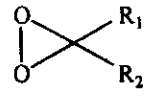
I would also like to thank the following people at SmithKline Beecham for their help during my six month placement at Great Burgh: Chris Buxton, Julie Ennis, Donald Mackenzie, Neil Mortimer, Simon Readshaw, Russell Dennis and Andy West.

Chapter 1

INTRODUCTION

1.1 GENERAL INTRODUCTION

During the last ten years or so, dioxiranes **1** have been used to carry out a wide variety of synthetically useful transformations. The oxidation of a large range of substrates has been extensively investigated, particularly using dimethyldioxirane **1a**, which has shown dioxiranes to be extremely efficient oxygen transfer agents, exhibiting high regio-, chemo- and stereoselectivity. The chemistry of dioxiranes has been the subject of several reviews[1] and interest in them continues.

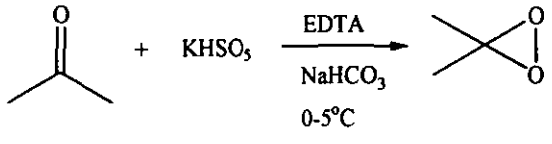


1

1a $R_1 = R_2 = CH_3$

1b $R_1 = CH_3$, $R_2 = CF_3$

Oxidations can be achieved using dioxiranes as isolated species in solutions of the parent ketone or the dioxirane can be generated *in situ*. The *in situ* method can only be used if both substrate and product can tolerate hydrolytic conditions, but it does allow a wider range of ketones to be used for dioxirane generation. The use of isolated dioxirane means that non-aqueous reactions can be performed and it allows the dioxirane to be used more quantitatively as a reagent.
Dimethyldioxirane **1a** was the first dioxirane to be isolated in 1985 by Murray and Jeyeraman.[2] It is prepared from acetone and potassium peroxymonosulfate (otherwise known as potassium caroate, which is commercially sold as Oxone®) under buffered conditions and is isolated by low temperature distillation as an acetone solution.[3]



Scheme 1 : Preparation of dimethyldioxirane

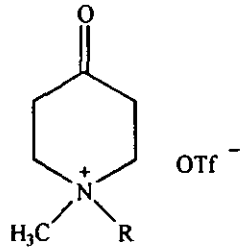
Methyl(trifluoromethyl)dioxirane **1b** was isolated three years later by Curci and coworkers[4] and is about 1000 times more reactive than dimethyldioxirane. Not only this, methyl(trifluoromethyl)-dioxirane can also be prepared as ketone-free solutions in dichloromethane.[5]

In 1992 Murray, Singh and Jeyerman published a method for the preparation of solutions of less volatile dioxiranes, for example the dioxirane derivative of cyclohexanone, which involved salting out the dioxirane / ketone solution from the aqueous phase.[6] In 1993, the first dioxirane stable in the gas phase at room temperature, difluorodioxirane, was synthesised by Russo and DesMarteau,[7] and in 1994 the first solid dioxirane, dimesityldioxirane, was isolated in pure form by Sander *et al.*[8] Although the preparation procedure for dimethyldioxirane / acetone solutions has proved satisfactory for many applications, the conversion yields are poor and often these solutions are too dilute for working at the multigram scale. The distillation procedure also makes it difficult to control the water content of the dimethyldioxirane solution which means drying procedures not always reliable for delicate applications have to be employed. As a result, Messeguer *et al* have devised a procedure for obtaining more concentrated dimethyldioxirane solutions (four to five-fold) using a simple work-up procedure which involves diluting the dimethyldioxirane distillate with water and extracting with dichloromethane, chloroform or carbon tetrachloride.[9] This leads to the quantitative incorporation of dimethyldioxirane into the organic fraction affording solutions containing a higher dimethyldioxirane concentration than that of acetone. These solutions exhibit stability comparable to the conventional dilute ones.

The *in situ* method of dioxirane generation is usually carried out under biphasic conditions (often dichloromethane - water) using excess ketone, Oxone® and a phase transfer catalyst with sodium bicarbonate or phosphate buffer to control the pH to 7.0 - 7.5. Reaction times (0.5 - 72 hours) depend on substrate nature and reaction conditions. Recently, Denmark looked at optimising the conditions of the *in situ* biphasic method and found that there are many key variables which are interdependent.[10] In brief, he found that the stoichiometry of the ketone, the structure of the ketone, the rate of Oxone® addition and the pH all have a dramatic effect on the outcome of the oxidation. This is discussed in more detail in chapter 5.

In situ epoxidations can also be performed in a homogenous aqueous organic solution[11] and the development of a truly general and efficient catalyst remains an important challenge. Much work in this area has been carried out by Denmark. He developed a class of 4-oxopiperidinium salts **2** which can be customised to function as excellent catalysts under either biphasic conditions **2a** or in

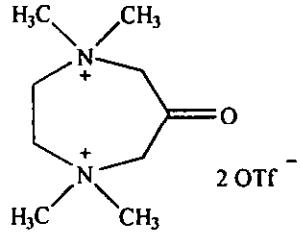
homogenous medium **2b** by simply altering the lipophilicity of the ammonium group.[10] In addition, Denmark has recently reported efficient catalysis with simple fluoroketones[12] (this is discussed in more detail in chapter 5) and also a new class of agents, α,α'-bis(ammonium)ketones **3**.[13]



2

2a R = n-$C_{12}H_{25}$

2b R = CH_3

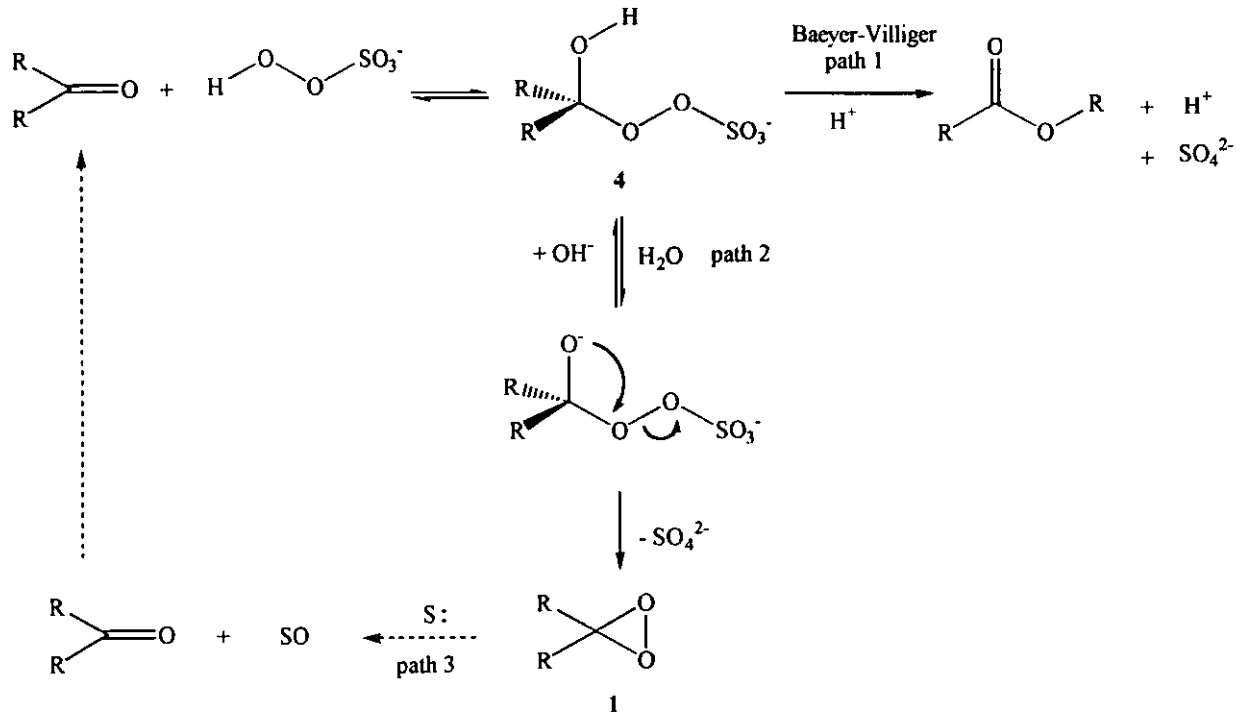


3

1.2 MECHANISM OF DIOXIRANE FORMATION

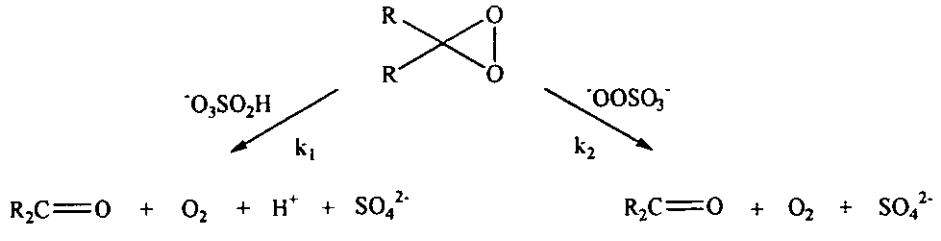
Evidence for the presence of dioxiranes in the ketone / Oxone® system was first presented by Edwards and Curci. They found that by strictly controlling the pH at 7.5, there was little or no competition from the Baeyer-Villiger reaction and the mechanism of dioxirane formation shown in Scheme 2 was postulated.[11b] This accomodates the results of kinetic studies and ^{18}O labelled experiments, confirming the intervention of dioxirane.[11] The ultimate proof was the isolation of dimethyldioxirane and later methyl(trifluoromethyl)dioxirane and their subsequent spectroscopic characterisation.[2,14]

The adduct **4** shown in Scheme 2 is analogous to the adduct formed in the first step of the Baeyer-Villiger oxidation of ketones by organic peroxy acids. Curci found that with small or (to a lesser extent) medium ring cycloalkanes, the reaction is diverted towards the Baeyer-Villiger oxidation (path 1). However, with acyclic dialkyl or aryl alkyl ketones, the loss of ketone via the Baeyer-Villiger oxidation is negligible and adduct **4** takes path 2. The role of the hydroxide ion is crucial. It removes the acidic proton in **4** so that the alkoxide oxygen can perform intramolecular nucleophilic attack on the O-O bond. Concerted ring closure and expulsion of sulfate ion (a good leaving group) generates dioxirane **1** in a slow step. This can then react readily with a variety of nucleophilic substrates S yielding oxygenated products SO (path 3). The ketone is regenerated and returns to the catalytic cycle.



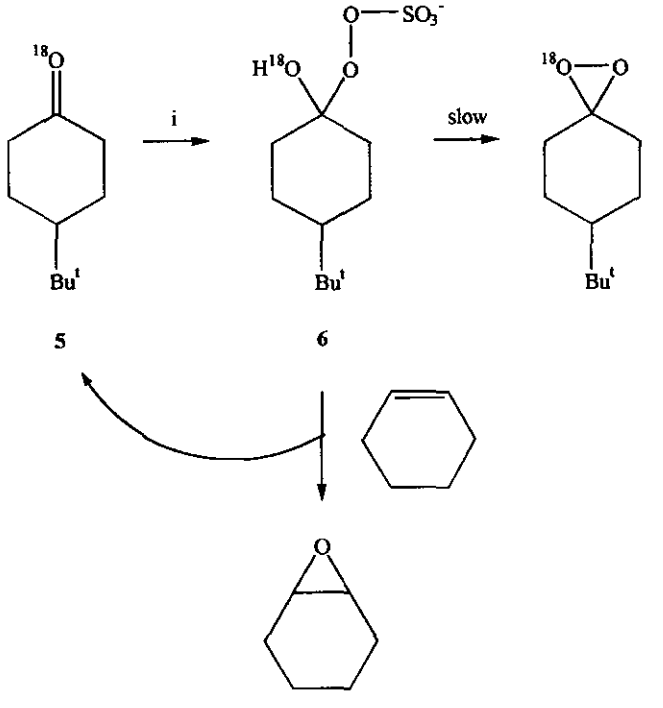
Scheme 2 : Mechanism of dioxirane formation

Competitive with this, however, is the attack on the dioxirane by the peroxy anion, $^{-}OOSO_3^{-}$ according to Scheme 3, yielding sulfate ion and molecular oxygen. In addition to this, the dioxirane can also suffer attack by another caroate species, $^{-}O_3SO_2H$. Therefore, for successful subsequent oxidation to occur *in situ*, the substrate has to compete effectively with $^{-}O_3SO_2H$ and $^{-}O_3SOO^{-}$ and pH plays a key role in this. Although both species are effective nucleophiles, the peroxy anion, $^{-}O_3SOO^{-}$, is about twenty five times more reactive than the peroxy acid $^{-}O_3SO_2H$ ($k_2 > k_1$). At pH 7, pka_2 is approximately equal to 9.4 and so at this pH it is the less nucleophilic peracid species $^{-}O_3SO_2H$ that dominates and the rate of loss of dioxirane is diminished.



Scheme 3 : Competitive attack on dioxirane by other caroate species

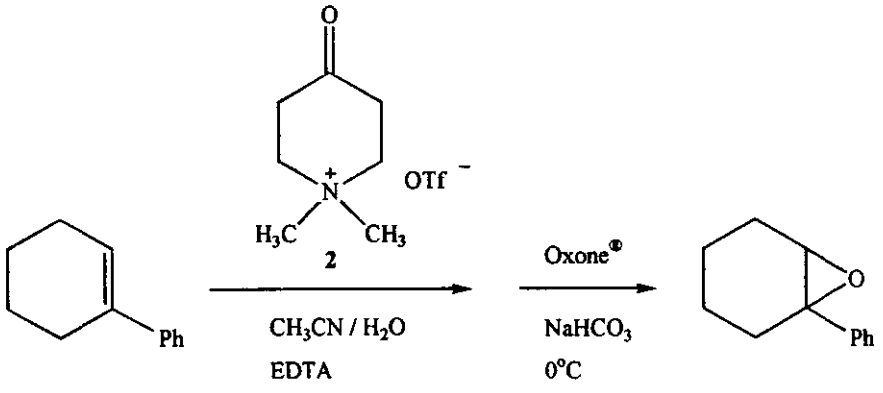
Interestingly, a recent paper by Armstrong *et al* presented the results of an ^{18}O labelling study which led them to conclude that a dioxirane intermediate is probably not responsible for alkene epoxidation in the ketone / Oxone® system.[15] The Armstrong group assumed that addition of Oxone® to the ketone is non-stereoselective and that a dioxirane intermediate would result in 50% label incorporation into the epoxide providing that either of the diastereotopic oxygen atoms is geometrically capable of being transferred to the alkene. However, when ^{18}O labelled 4-tert-butyl-cyclohexanone **5** (Scheme 4) was subjected to the reaction conditions no such label transfer to the epoxide was observed. Also there was no loss of ^{18}O from the ketone carbonyl. The explanation they gave for this was that dioxirane is probably not involved in the epoxidation and that the tetrahedral species **6** resulting from addition of HSO_5^- to the carbonyl group is capable of alkene epoxidation (Scheme 4). Ring closure of **6** is likely to be the rate determining step in dioxirane formation therefore it is possible that epoxidation by **6** is faster than ring closure to the dioxirane.



Scheme 4 : Oxidation of 4-tert-butylcyclohexanone using i. Oxone®, Bu_4NHSO_4, $EDTA.Na_2$, 1M aqueous $NaHCO_3$, dichloromethane, 0°C

However, in a recently published paper by Denmark[16] in which studies on the system shown in Scheme 5 using ^{18}O labelled **2** were described, the author criticises Armstrong's findings and provides evidence that dioxiranes are indeed the intermediates in the ketone / Oxone® *in situ*

epoxidation system. Denmark suggests that the fact that only a low conversion (15%) was obtained with 4-tert-butylcyclohexanone (which implies that this ketone is a poor promoter under biphasic conditions) and the fact that the ^{18}O label is not lost from the ketone in the presence of unlabelled water, casts considerable doubt on the involvement of any tetrahedral intermediate derived from 4-tert-butylcyclohexanone and thus rules out the possibilty that the label could have been transferred in the oxidation process. This is discussed further in chapter 5.



Scheme 5

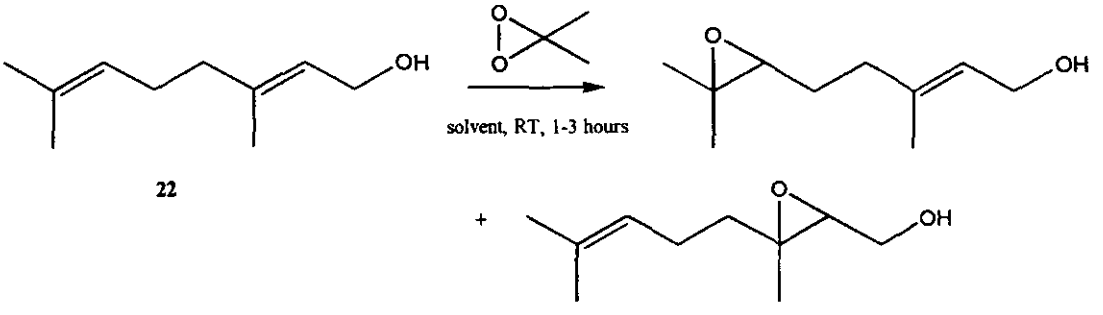
1.3 APPLICATIONS OF DIOXIRANE CHEMISTRY

1.3.1 Epoxidation

The most widespread application of dioxiranes has been to the epoxidation of alkenes. Many examples exist in the literature involving a diverse range of different alkenes, from the structurally simple to the more complex, containing a wide range of functionalities. Yields are high and the higher the degree of alkylation in the alkene the faster the epoxidation. *Cis*-alkenes are epoxidised slightly faster than the corresponding *trans*-alkenes and electron donors activate the double bond towards epoxidation while electron acceptors deactivate it. The reaction is also highly stereo-specific. *Trans*-alkenes yield *trans*-epoxides and *cis*-alkenes produce only *cis*-epoxides. Dimethyldioxirane has been shown to convert enol ethers **7**,[17] 2,3-dimethylbenzofurans **8**,[18] silyl enol ethers **9**,[19,20] enol esters and lactones **10**,[19,21] and enol phosphates **11**[19,22] to the corresponding epoxides, all of which are difficult to isolate through classical routes. In addition, Adam *et al* have

demonstrated that dimethyldioxirane also epoxidises even electron-poor alkenes such as α,β-unsaturated acids, esters and ketones **12**.[23] These epoxidations were then extended to substrates containing both electron-donating and electron-accepting substituents, such as β-oxo enol ethers **13**[24] and flavones **14**,[25] as well as substrates bearing two electron-donating substituents, for example 1,2-bis(trimethylsilyloxy)cycloalkene **15**, which has been epoxidised in excellent yield.[26] Adam *et al* have also achieved the direct epoxidation of various 2'-hydroxychalcones **16** with dimethyldioxirane resulting in acid and base-sensitive epoxides which were hitherto difficult to prepare, thus further illustrating the advantages of this oxidant for the preparation of labile epoxides.[27] Crandell *et al* have shown that dimethyldioxirane provides a route to fragile diepoxides of allenes[28] and have reported the formation of highly functionalised oxygen heterocycles derived from cyclisation of intermediate mono- and di-epoxides.[29] The oxidative cyclisations of allenic aldehydes **17**[30] and allenic sulfonamides **18**[31] have also been studied and it has been found that many furans **19** and **20** are oxidised cleanly and rapidly at room temperature giving one of two product types depending on the substitution pattern.[32] All these epoxidations are featured in Scheme 6.

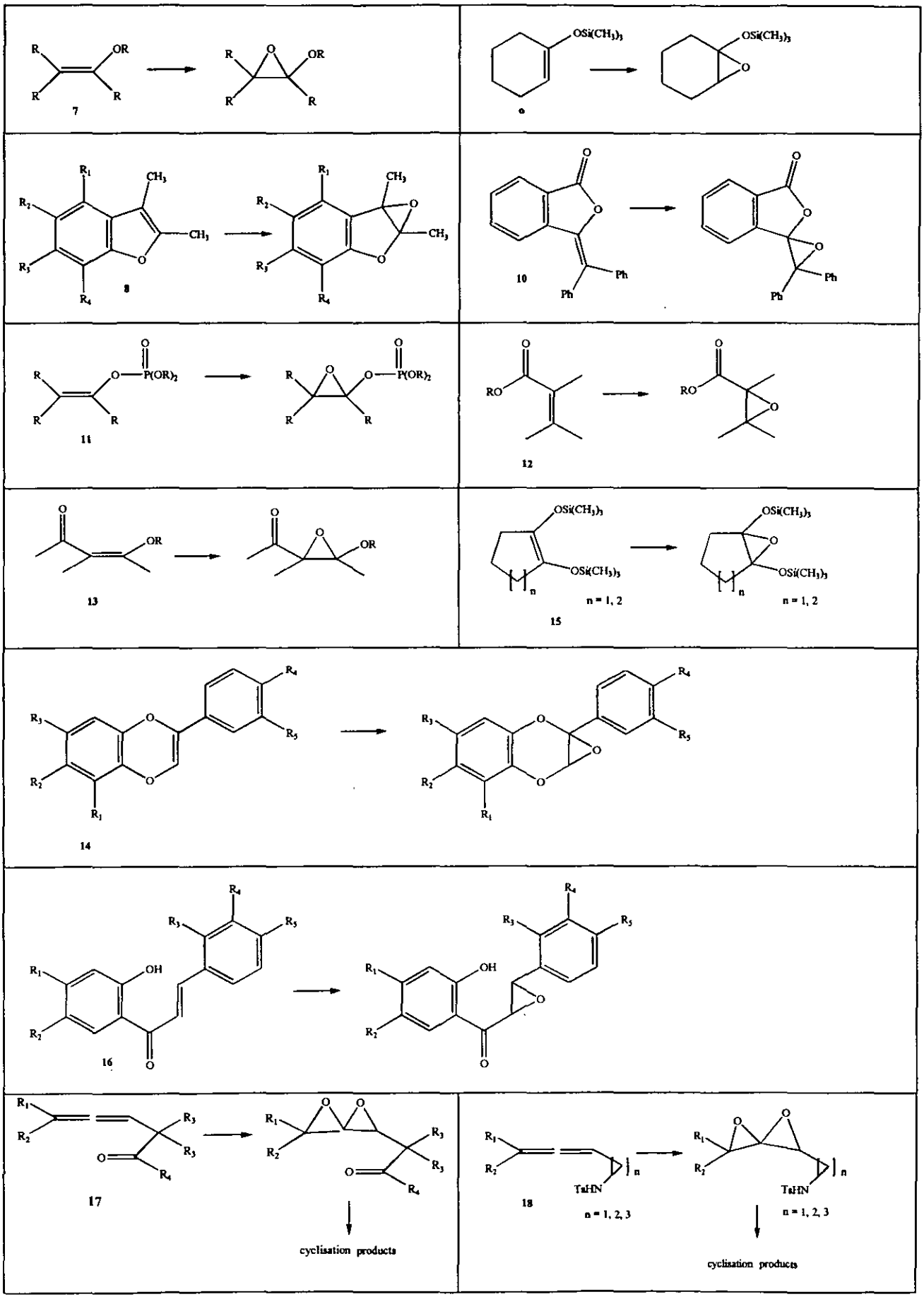
Epoxidations by dioxiranes are particularly sensitive to steric factors[33,88] and solvent effects.[34] The presence of water has been shown to increase the rate of epoxidations[35] and in 1993, Murray reported that the rate of dimethyldioxirane epoxidation is enhanced by hydrogen bonding donor solvents and inhibited by hydrogen bonding acceptor solvents.[34c] In the epoxidation of geraniol **22** by dimethyldioxirane, a mechanistically significant solvent effect is observed on the product distribution of the two regioisomeric epoxides and it is proposed that the hydrogen bonding ability of the solvent is the principal molecular feature in controlling selectivity.[36]

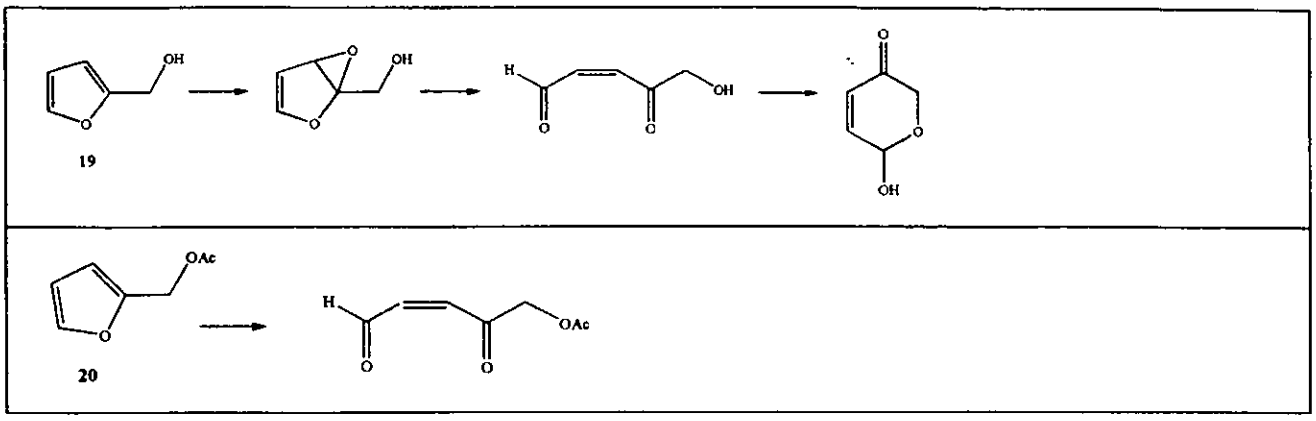


22

Solvent	**Ratio of 6,7-epoxide : 2,3-epoxide**
acetone / methanol 1 : 9	88 : 12
acetone / carbon tetrachloride 1 : 9	51 : 49

Scheme 7 : Epoxidation of geraniol using dimethyldioxirane

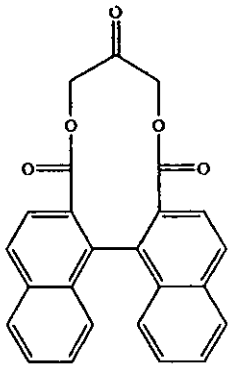

7
8
9
10
11
12
13
14
15
n = 1, 2
16
17
18
n = 1, 2, 3
cyclisation products
cyclisation products



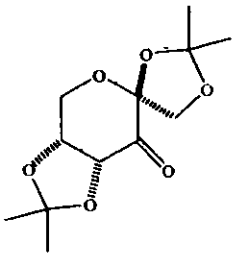
Scheme 6 : Examples of epoxidations carried out using dimethyldioxirane

With regard to stereochemistry, the epoxidations proceed with preservation of initial configuration. Diastereoselectivity is sometimes rather low (~60:40) except when sterically large groups are present when diastereocontrol can be very high (>99:1). Adam also observed a notably higher diastereoselectivity in the dimethyldioxirane epoxidation of chiral allylic alcohols when less polar solvent mixtures are employed[37] and Murray showed a remarkable solvent dependency of the diastereoselectivity of cyclohex-2-en-1-ol.[34a] In a more recent publication, Murray investigated the epoxidation of three series of compounds based on cyclohexene by dimethyldioxirane and found that the diastereoselectivity is subject to a number of substrate and solvent influences, including steric effects, hydrogen-bonding and dipole-dipole interactions. His results suggest that these various factors can be manipulated to give the desired stereocontrol.[34b]

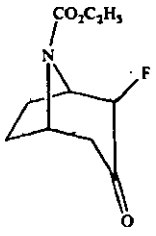
The opportunity that exists for asymmetric epoxidations involving dioxiranes generated *in situ* from suitable chiral ketone precursors has also been recognised although progress in this area has been limited and enantiomeric excesses have generally been low (9-20%).[38] Yang made some progress, reporting an 87% ee in one case using a C2 symmetric cyclic chiral ketone **23**, although in most cases the ees obtained were low (5-50%).[39] Shi *et al* also reported an efficient asymmetric epoxidation method for unfunctionalised *trans*-olefins mediated by a fructose-derived ketone **24**.[40] An ee greater than 91% was achieved for stilbene oxide although it was found the ketone **24** decomposed over time under the reaction conditions. More recently, Armstrong found that enantiomerically pure α-fluoro-N-ethoxycarbonyltropinone **25** is an efficient catalyst for asymmetric epoxidation affording enantioselectivites of up to 83% ee.[41] It can also be recovered and recycled.



23



24

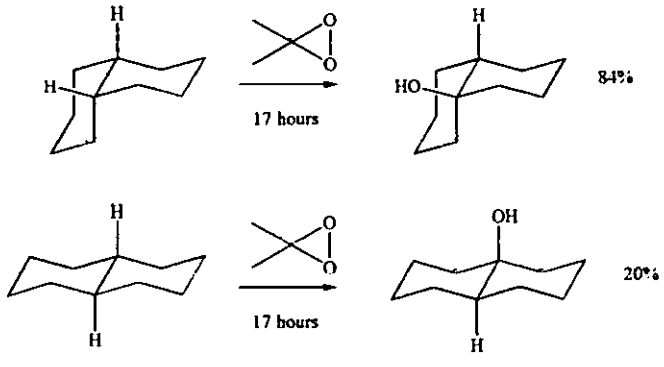


25

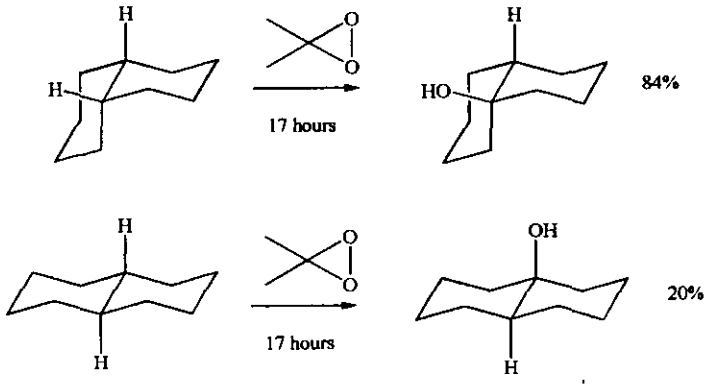
1.3.2 C-H Insertion

The direct oxygen atom insertion into C-H bonds is one of the most unusual oxidations which can be performed by dioxiranes and highly selective oxidation of non-activated C-H bonds has been achieved. The significant feature is the preferential oxidation of tertiary C-H, which give the corresponding alcohol or products arising from further oxidation, over secondary C-H, which give the corresponding ketone from the initially formed secondary alcohol. High retention of configuration is observed and equatorial C-H are oxidised in preference to axial C-H. This is illustrated in the oxidation of *cis*- and *trans*-decalin (Scheme 8).[42]

The high regio- and stereoselectivities achieved when using dimethyldioxirane are not lost when using the more reactive methyl(trifluoromethyl)dioxirane. For example, the selective oxyfunctionalisation at the tertiary C-H of stereomeric 1,2-dimethylcyclohexanes using methyl-(trifluoromethyl)dioxirane is completely stereospecific[43] and optically active 2-phenylbutane **26** can be cleanly converted into 2-phenyl-2-butanol **27** in over 90% yield with complete retention of configuration (Scheme 9).[44]



Scheme 8 : Oxidation of *cis*- and *trans*-decalin by dimethyldioxirane

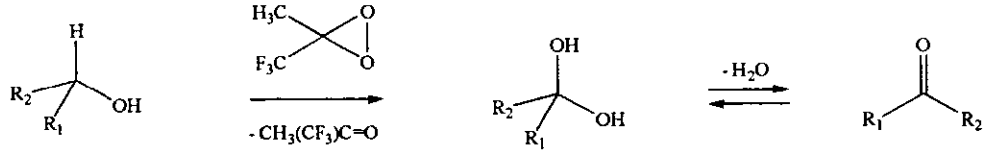


Scheme 8 : Oxidation of *cis*- and *trans*-decalin by dimethyldioxirane

Murray has shown that the C-H insertion reaction is also affected by solvent. Solvents with hydrogen bonding donor capacity favour the reaction although the effect is less pronounced than with epoxidation, which may be attributed to the difference in polarizability of the reacting bonds, i.e. a π bond in the epoxidation reaction versus an sp^3 σ bond in the insertion reaction.[45]

1.3.3 Oxidation of Alcohols

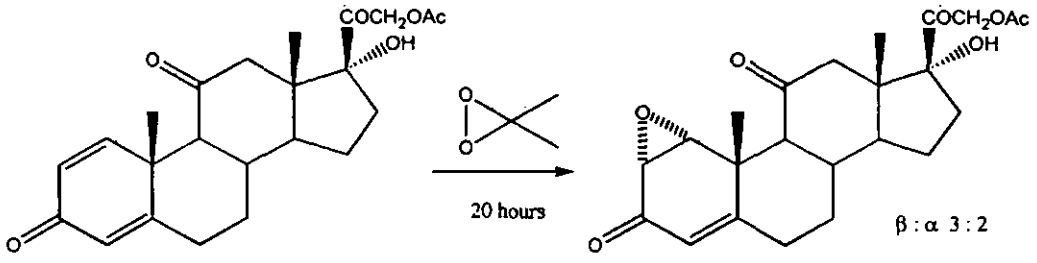
Dioxiranes are also useful for the conversion of alcohols into carbonyl compounds. It was found that a number of secondary alcohols can be oxidised by methyl(trifluoromethyl)dioxirane in a solution of its parent ketone affording the corresponding ketones in high yields (92-99%) under mild conditions and in short reaction times.[46] Aliphatic tertiary alcohols were not appreciably oxidised under the same conditions and the primary alcohol, benzyl alcohol, gave mixtures of benzaldehyde and benzoic acid, depending on the extent of conversion and the reaction time.



Scheme 10 : Oxidation of secondary alcohols by methyl(trifluoromethyl)dioxirane

Dimethyldioxirane will perform selective oxidation of a secondary alcohol in the presence of a primary one.[47] Bovicelli noted that dimethyldioxirane had a very high sensitivity to stereo-

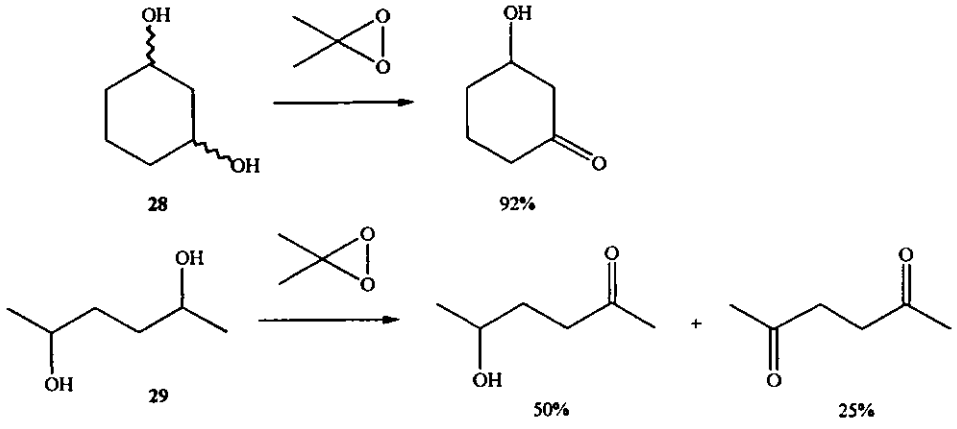
that the observed selectivities might depend on the strong dipolar interaction between dimethyl-dioxirane and the carbonyl moiety present in the substrate. This interaction influences the approach of the dioxirane to the reactive centre favouring or sometimes inhibiting the attack.



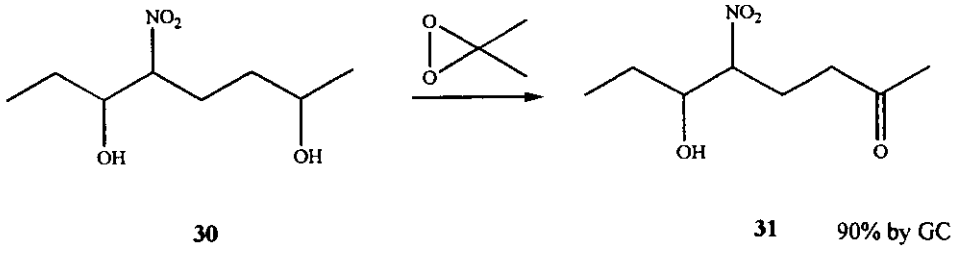
Scheme 11 : Selective epoxidation of the less nucleophilic double bond in prednisone acetate using dimethyldioxirane

Bovicelli also reported the use of dimethyldioxirane to mono-oxidise 1,2- and 1,3-*sec,sec*-diols to the corresponding 2- and 3-ketoalcohols.[47] This appeared to confirm a deactivating effect of the generated carbonyl group lying close to the primary reaction centre. When oxidising compounds such as 1,2-cyclohexandiol and 1,3-cyclohexandiol **28**, which contain two hydroxyl groups of similar reactivity, it was found that dimethyldioxirane gave the ketoalcohols in excellent yields. No appreciable amounts of diketone were observed even when using an excess of dimethyldioxirane and prolonged reaction times. The dipole of the formed carbonyl group modifies the electronic enviroment at the second reactive centre making it unreactive with dimethyldioxirane. Obviously this dipole interaction does not affect diols with distant hydroxyl groups. These compounds, for example **29**, produce a mixture of ketoalcohols and diketones even when the conversions are kept low.

Following this, the same group found they were able to perform selective oxidation of nitrodiols **30** to nitroketols **31**.[50] It was found that the deactivating effect of the nitro group extended to α and β positions.

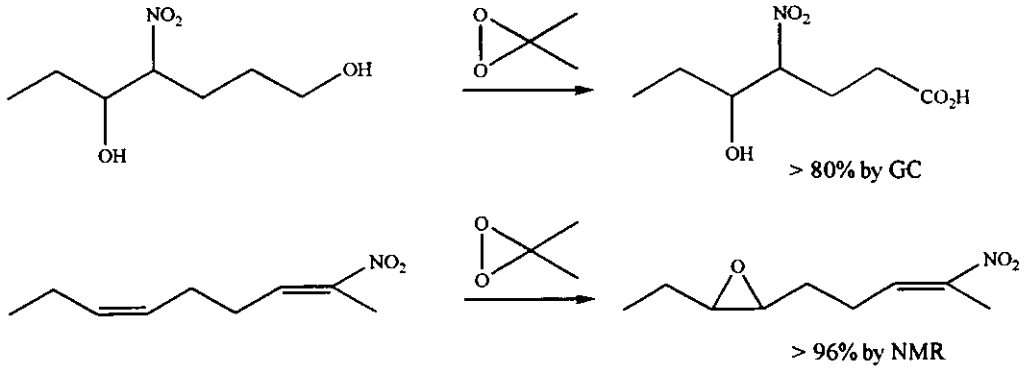


Scheme 12 : Oxidation of 1,2- and 1,4-diols using dimethyldioxirane



Scheme 13 : Selective oxidation of nitrodiols to nitroketols using dimethyldioxirane

The oxidation of a primary hydroxyl group to the corresponding carboxylic acid was carried out in the presence of a secondary alcohol close to a nitro group, and a double bond in a diene which carries a nitro group was also selectively oxidised (Scheme 14).



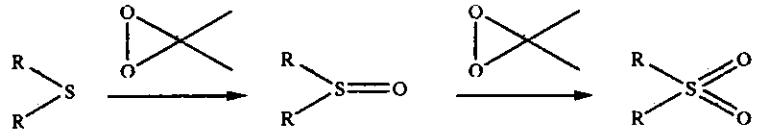
Scheme 14

It has been shown that the oxidation of the hydroxy functionality in secondary allylic alcohols to the ketone by dimethyldioxirane can compete with the epoxidation of the double bond.[51] Nevertheless, the chemoselectivity can be promoted towards epoxide formation by acylation of the alcohol or by employing higher temperatures. The fact that more enone is formed at lower temperatures has been rationalised in terms of entropy control in the epoxidation versus the C-H insertion pathway.

1.3.4 Oxidation of Heteroatoms

1.3.4.1 Oxidation of Sulfur

The oxidation of sulfur is among the earliest studied dioxirane reactions. Dimethyldioxirane reacts with sulfides **32** to give sulfoxides **33** which can react further with dimethyldioxirane to give sulfones **34** in a sequential process.[2,52] The reaction is extremely rapid and yields are practically quantitative. Since sulfides are better nucleophiles than sulfoxides, the oxidation can be controlled at the sulfoxide stage when a stoichiometric amount of dimethyldioxirane is used.

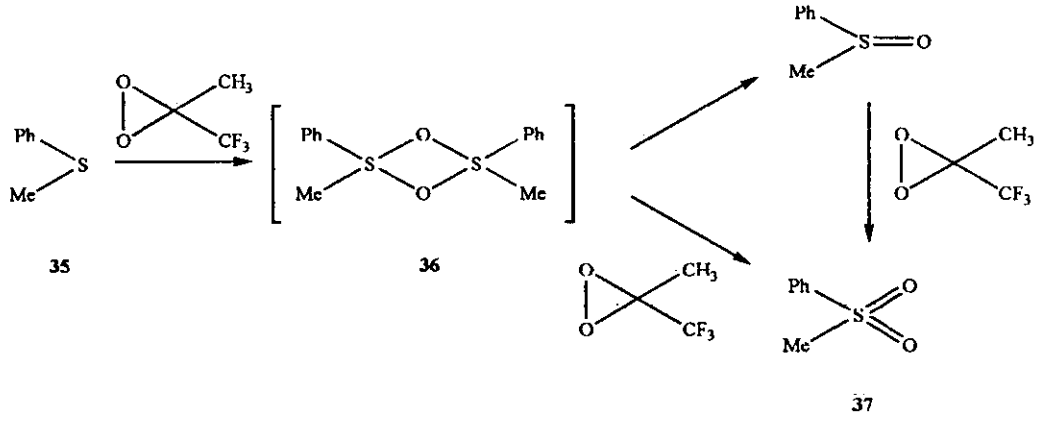


32 **33** **34**

Scheme 15 : Oxidation of sulfides to sulfones via the sulfoxide using dimethyldioxirane

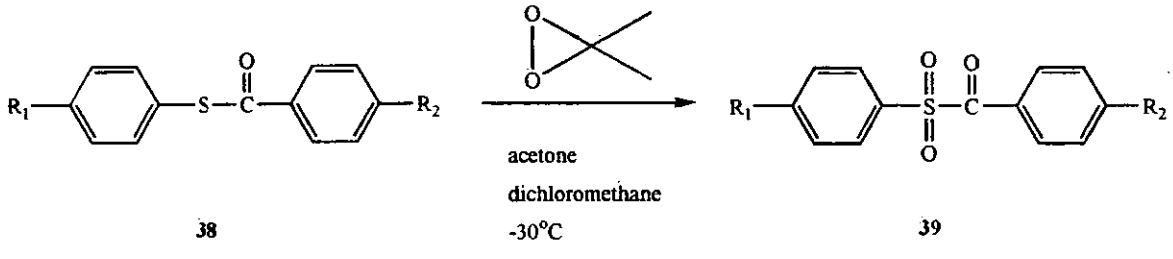
Interestingly, when using methyl(trifluoromethyl)dioxirane the oxidation of phenylmethyl sulfide **35** gave the sulfone **37** as the main product even in the presence of a large excess of sulfide relative to methyl(trifluoromethyl)dioxirane and it was found that the sulfoxide yield increased at the expense of sulfone when 2,2,2-trifluoroethanol was used as co-solvent.[53] It was expected that the oxidation of sulfides to sulfones by methyl(trifluoromethyl)dioxirane follow the same sequence as dimethyl-dioxirane (Scheme 15). If this is the case, these results suggest that sulfoxide reacts faster with methyl(trifluoromethyl)dioxirane than sulfide. To clarify this, Asensio *et al* carried out a series of competitive oxidations on phenyl(trideuteromethyl)sulfide and phenylmethyl sulfoxide.[53] They concluded that the conversion of sulfide to sulfone by methyl(trifluoromethyl)dioxirane cannot occur

only through the oxidation of the intermediate sulfoxide as depicted in Scheme 15 and suggested the involvement of a sulfide-derived reactive intermediate which is oxidised by methyl(trifluoromethyl)-dioxirane faster than either sulfides or sulfoxides and which is readily converted into a sulfoxide by the action of protic acidic solvents such as trifluoroethanol. ^{18}O tracer experiments led to the proposal that the cyclic sulfurane **36** is involved.



Scheme 16 : Proposed pathway for the oxidation of phenylmethylsulfide using methyl(trifluoromethyl)dioxirane

Adam reported the use of dimethyldioxirane in the oxidation of thiol esters **38** to α-oxo sulfones **39** (Scheme 17).[54] Oxidants such as N-bromosuccinimide, iodosobenzene and MCPBA give a complex mixture due to nucleophilic cleavage of the S-CO bond and so compounds such as these have previously been prepared by ozonolysis. However, using dimethyldioxirane, the reagent can simply be added and the solvent evaporated once the reaction is complete.



Scheme 17 : Oxidation of thiol esters using dimethyldioxirane

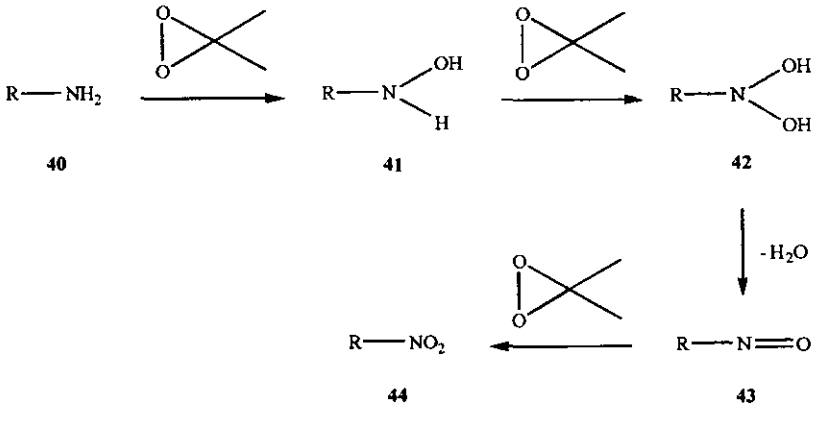
1.3.4.2 Oxidation of Nitrogen

The oxidations of various nitrogen-containing compounds have been carried out using dioxiranes.

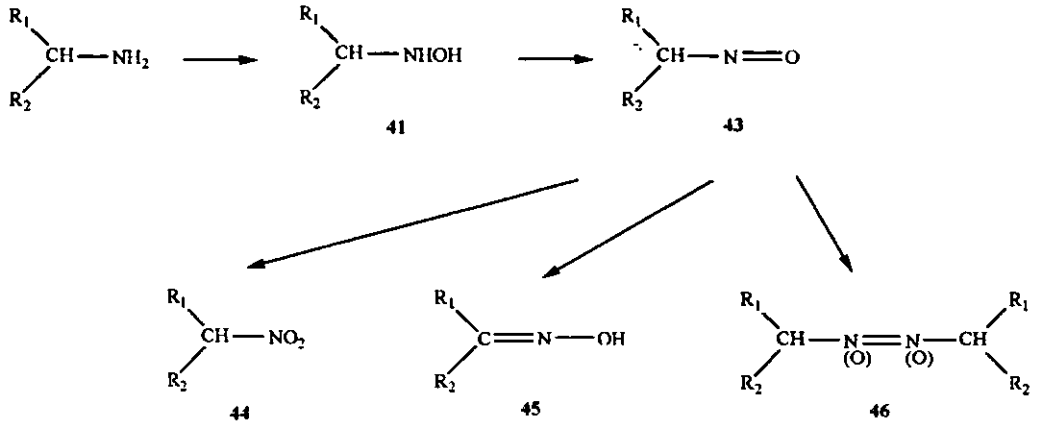
i. Primary amines

Primary amines **40** (primary, secondary and tertiary alkyl and aryl) can be oxidised by dioxiranes to nitro compounds **44** in high yields via the hydroxylamine **41** and the nitroso compound **43** (Scheme 18).[55] The use of stoichiometric amounts of dimethyldioxirane will oxidise most amines to the hydroxylamine **41** without further oxidation to the nitro compound. For example, solutions of dimethyldioxirane have been used for the controlled oxidation of amino sugars and esters of amino acids to the corresponding hydroxylamines.[56]

The final oxidation of the nitroso compound to the nitroalkane is in competition with dimerisation and tautomerisation to the oxime if α hydrogens are available. Mixtures of oximes **45** and nitroso dimers **46** have been typically obtained with solutions of dimethyldioxirane in excess (Scheme 19).[57] It has been found that aromatic amines can be oxidised to the corresponding nitro compound in the presence of highly nucleophilic electron-rich aromatic systems such as indoles and furans.[58] For example, a competitive oxidation using a mixture of furan and aniline gave only nitrobenzene in 78% yield after reaction for 15 minutes with dimethyldioxirane generated *in situ* at 0°C.

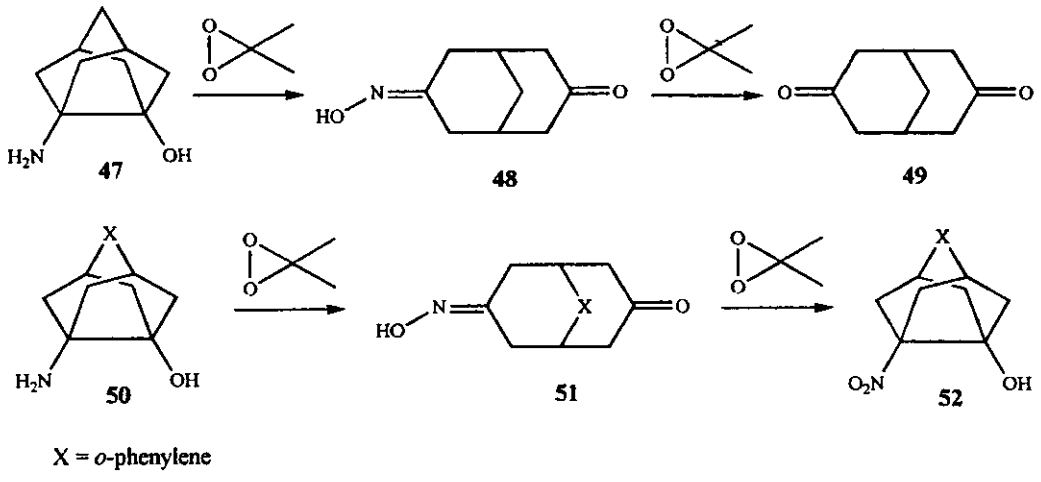


Scheme 18 : Oxidation of primary amines using dimethyldioxirane

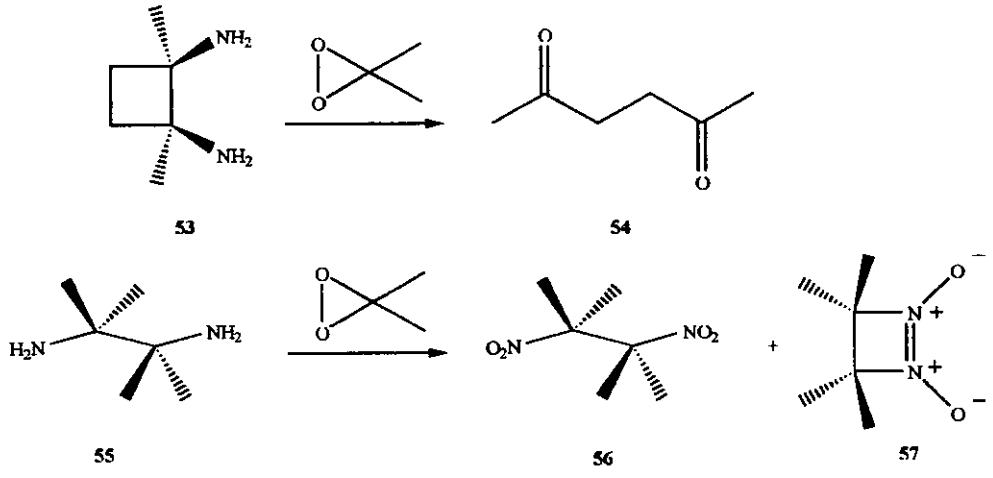


Scheme 19 : Possible products in the oxidation of primary amines using dimethyldioxirane when αH are available

Not all primary amines however are oxidised to the nitroalkane. In 1995, Camps *et al* reported a new kind of oxidation process with dimethyldioxirane.[59] When the aminoalcohol **47** was oxidised with an excess of dimethyldioxirane, the expected nitro alcohol was not formed. Instead the diketone **49** was obtained in quantitative yield. When **47** was oxidised with a stoichiometric amount of dimethyldioxirane, the bicyclic ketone **48** was obtained in excellent yield, showing that the oxidation takes place in an unprecedented way with cleavage of the central carbon-carbon bond bearing the amino and hydroxy functionalities (Scheme 20). Unlike the oxidation of **47**, the treatment of **50** with excess of dimethyldioxirane gave the expected tetracyclic nitro alcohol **52**, although not through the usual series of oxygen transfers which convert primary amines to nitro compounds but through an oxidative coupling of the intermediate oxime ketone **51**, which was obtained quantitatively when **50** was treated with a stoichiometric amount of dimethyldioxirane. Another example is the oxidation of *cis*-1,2-diamino-1,2-dimethylcyclobutane **53** using dimethyldioxirane which results in oxidative cleavage to form the 2,5-hexane-dione **54** rather than 1,2-dinitro-1,2-dimethylcyclobutane (Scheme 21).[60] The open chain analogue, 2,3-diamino-2,3-dimethylbutane **55** yields a mixture of the dinitro compound **56** (13%) and the cyclic nitroso dimer **57** (49%). The oxidative cleavage product in this case would be acetone which cannot be detected since the dimethyldioxirane is prepared as an acetone solution. The amount of strain which can be tolerated within a cyclic system before ring cleavage will occur and the level of oxidation (i.e. hydroxylamino, nitroso or nitro) which has to be attained for cleavage to occur have not yet been established.



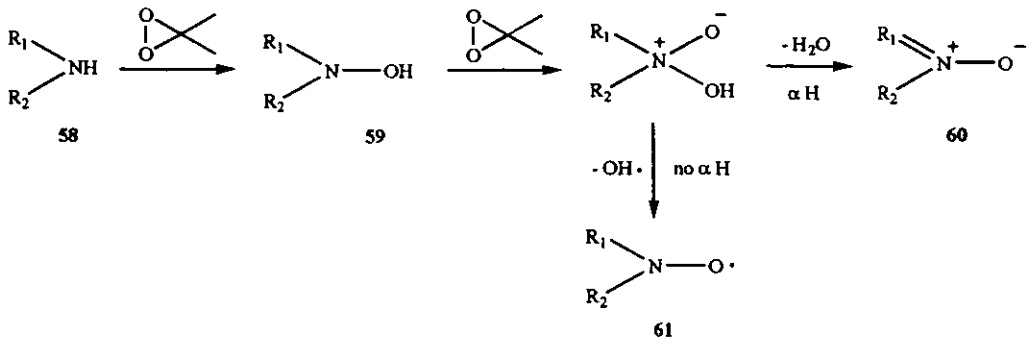
Scheme 20 : Oxidation of polycyclic 2-aminoalcohols using dimethyldioxirane



Scheme 21 : Oxidation of *cis*-1,2-diamino-1,2-dimethylcyclobutane and 2,3-diamino-2,3-dimethylbutane using dimethyldioxirane

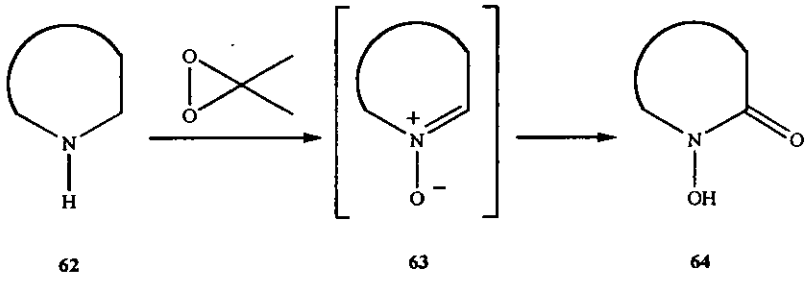
ii. Secondary amines

The oxidation of secondary amines **58** with an equimolar amount of dimethyldioxirane gives the hydroxylamine **59**. A second mole of dioxirane gives the nitrone **60** if α hydrogens are present and the nitroxide **61** if not (Scheme 22).[61]



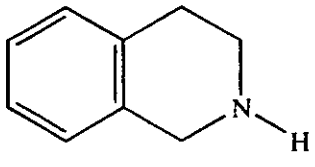
Scheme 22 : Oxidation of secondary amines using dimethyldioxirane

Six-membered cyclic secondary amines **62** such as piperidine and morpholine are readily oxidised to the corresponding hydroxamic acid **64** in acetone by dimethyldioxirane. The reaction proceeds via the nitrone **63**.[62]



Scheme 23 : Oxidation of 6-membered cyclic secondary amines using dimethyldioxirane

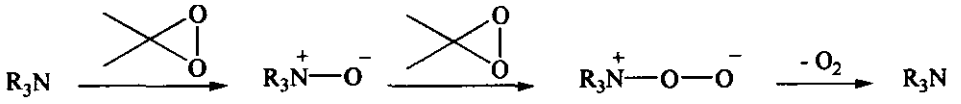
Fused cyclic secondary amines react readily to form the corresponding hydroxamic acids as long as there is no benzylic hydrogen α to the nitrogen atom. With 1,2,3,4-tetrahydroisoquinoline **65** which does have α benzylic hydrogens, oxidation with three equivalents of dimethyldioxirane gives a mixture of the nitrone, the hydroxamic acid plus other unidentified oxidation products. With only two equivalents of dimethyldioxirane, a clean reaction to the nitrone is observed.



65

iii. Tertiary amines

It is well known that aromatic tertiary amines such as pyridines are oxidised by dimethyldioxirane to give the N-oxide. Less work has been reported on other classes of tertiary amine. Murray reports that reaction conditions are critical if the N-oxide is the desired product as excess dioxirane leads to an intermediate which loses oxygen to regenerate the amine (Scheme 24).[1d]



Scheme 24 : Oxidation of tertiary amines using dimethyldioxirane

More recently, Adam reported that 4-dimethylaminopyridine reacts with 1 equivalent of dimethyl-dioxirane to give N-oxide with 57% conversion.[63] Using 3 or 5 equivalents of dimethyldioxirane, a maximum of 84% N-oxide was reached. Nevertheless, the dimethyldioxirane was consumed within a few minutes at 0°C with gas evolution. Adam suspected that the N-oxide decomposed the dioxirane and this was confirmed by reaction of authentic N-oxide with dimethyldioxirane. This gave the same mixture of 84:16 N-oxide / amine using 1, 2 and 5 equivalents of dioxirane, with oxygen gas liberation.

Ammonium chlorides will undergo N-oxidation by dimethyldioxirane[57,64] but it has been reported that tetrafluoroborate salts of primary, secondary and tertiary alkylamines do not.[65] This has led to a procedure for the hydroxylation of amino derivatives which involves performing the reaction in a protic medium. This protects the amino group from oxidation allowing oxygen atom insertion to take place at C-H. In this way, ketone-free solutions of methyl(trifluoromethyl)dioxirane in dichloromethane have been used to selectively oxidise remote unactivated tertiary and secondary C-H bonds in the aliphatic side chain of alkyl amines to give the corresponding aminoalcohols (equation 1, Scheme 25).

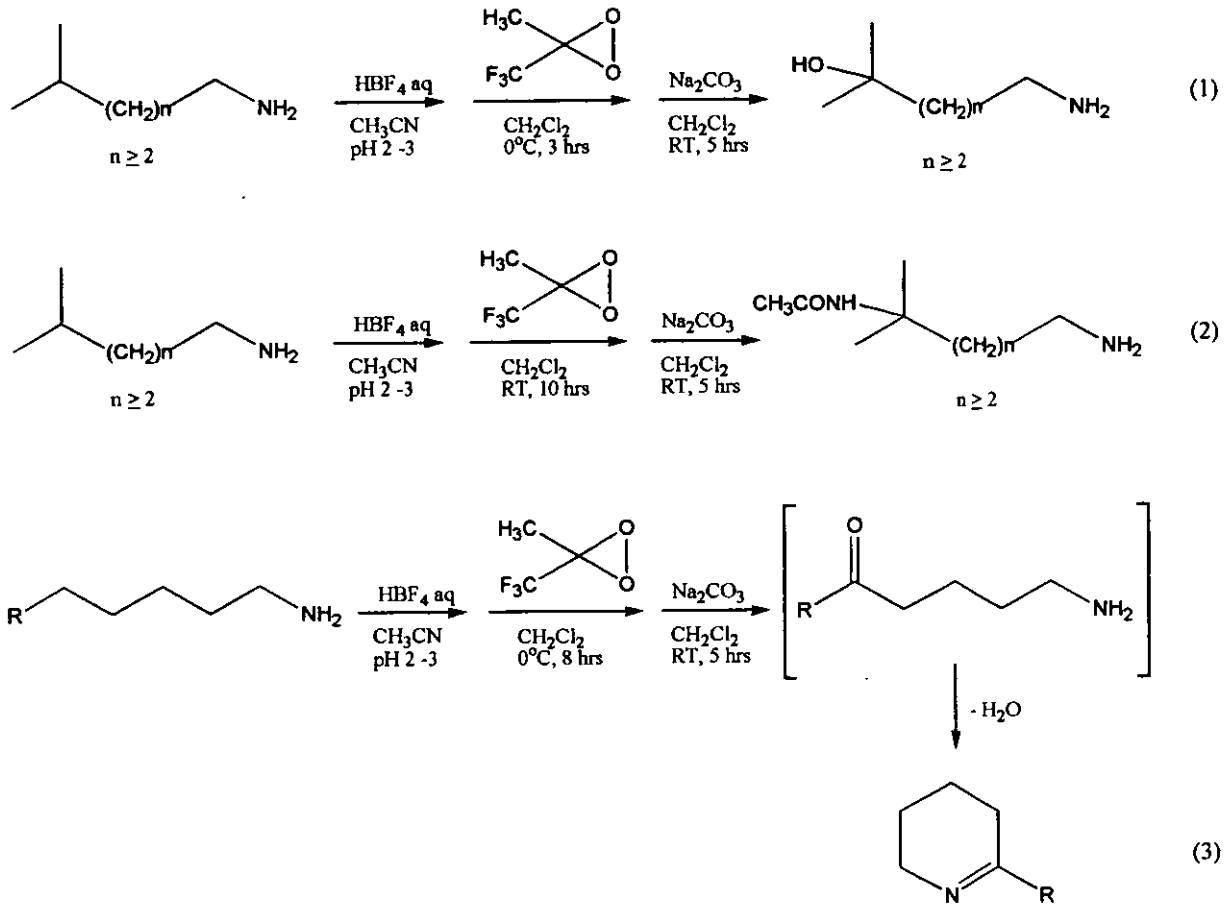
It was found that tertiary C-H bonds of acyclic, cyclic and polycyclic amines separated by at least two carbon atoms from the ammonium group are readily hydroxylated within 3 hours. The α and β positions were found to be deactivated due to the strong electron-withdrawing nature of the ammonium group. Longer reaction times led to the corresponding aminoacetamides (equation 2,

Scheme 25). This is rationalised in terms of a carbocation intermediate produced from the tertiary alcohols in the strong acid medium which is trapped by acetonitrile through the Ritter reaction. Secondary C-H bonds are oxidised exclusively at the ε position to afford 2,3,4,5-tetrahydro-6-alkyl-pyridines after intramolecular condensation of the corresponding amino ketones which are produced by subsequent oxidation of the secondary alcohols (equation 3, Scheme 25).
The high regioselectivity of the oxygen atom insertion (exclusively at the ε methylene group) is thought to be achieved by the cooperative effect of the deactivating effect of the ammonium group, the hydrogen bonding between the dioxirane and the ammonium ion moiety, and the conformational flexibilty of the aliphatic chain which brings the ε methylene group near to the free and activated oxygen atom of methyl(trifluoromethyl)dioxirane.

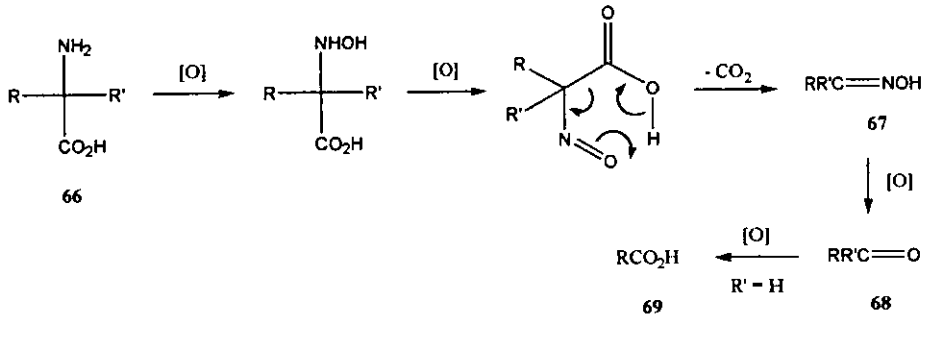
Epoxidation of carbon-carbon double bonds in molecules bearing amino groups has also proved to be troublesome due to the high tendency of the nitrogen atom to undergo preferential oxidation. This is observed with both peroxy-acids and with dioxiranes. The procedure mentioned above cannot be used due to the sensitivity of the epoxides to the acidic medium. Messeguer *et al* therefore solved this problem by quaternisation of the amino moiety through formation of an adduct with a non-protic Lewis acid, such as boron trifluoride. This gives an amine-boron-trifluoride adduct which can then be treated with dimethyldioxirane or methyl(trifluoromethyl)dioxirane to give the epoxide in good to excellent yield.[66] As expected, epoxidations carried out with methyl(trifluoromethyl)-dioxirane take place at higher rates and give higher yields than those performed with dimethyldioxirane.

iv. α-amino acids

When α-amino acids **66** are reacted with *in situ*-generated dimethyldioxirane, the amine nitrogen undergoes direct oxygenation and oxidative decarboxylation takes place.[67] Depending on the structure of the α-amino acid, varying proportions of the oxime **67**, ketone **68** and carboxylic acid **69** with one carbon atom fewer than the starting amino acid are formed. This reaction represented the first example of oxidative decarboxylation of an α-amino acid in which a product other than an aldehyde or a carboxylic acid has been isolated as the major product. The proposed pathway is shown in Scheme 26.



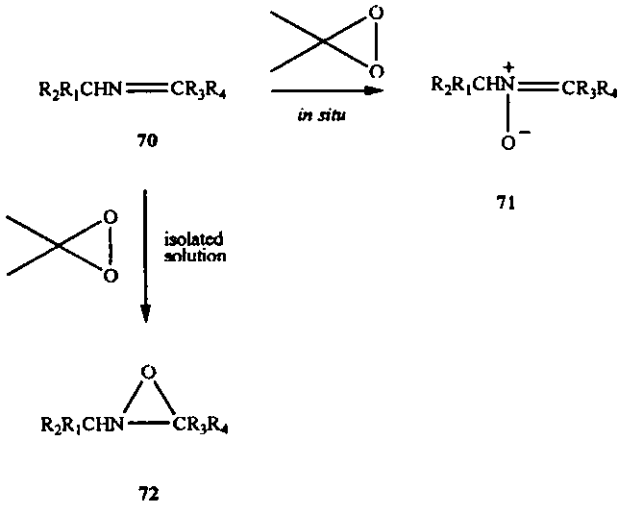
Scheme 25 : Oxidation of remote unactivated tertiary and secondary C-H bonds in the aliphatic side chain of alkylamines using ketone-free solutions of methyl(trifluoromethyl)dioxirane



Scheme 26 : Oxidation of α-amino acids using *in situ*-generated dimethyldioxirane

v. Imines

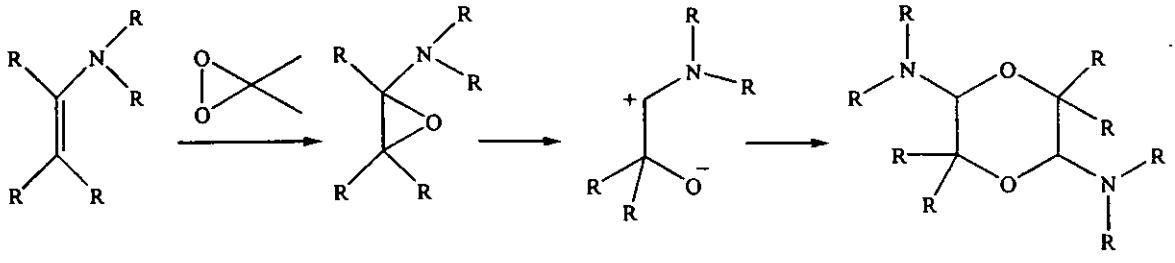
The oxidation of imines **70** with isolated dimethyldioxirane / acetone has been shown to yield nitrones **71**.[57,68] *In situ* oxidation of imines gives the oxaziridine **72**.



Scheme 27 : Oxidation of imines using isolated and *in situ* generated dimethyldioxirane

vi. Enamines

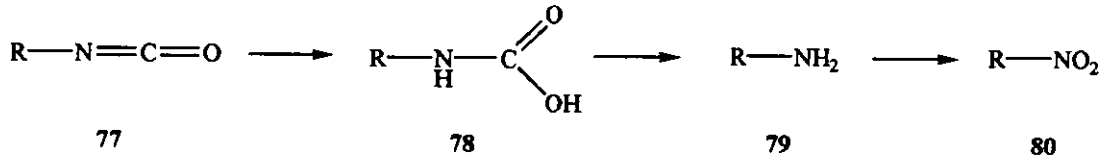
With enamines **73**, oxygen transfers exclusively to the double bond rather than to the nitrogen atom to give the 1,4-dioxane **76** via the α-amino epoxide **74** and 1,3-dipole **75**.[69]



Scheme 28 : Oxidation of enamines using dimethyldioxirane

vii. Isocyanates

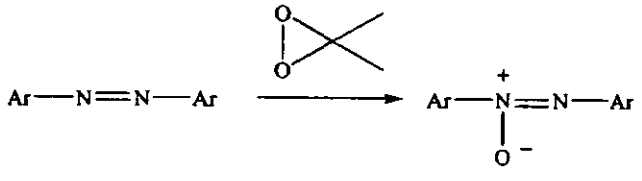
Dimethyldioxirane in wet acetone oxidises isocyanates **77** to nitro compounds **80**.[70] Primary, secondary and tertiary aliphatic isocyanates as well as phenylisocyanates are all cleanly converted to the nitro compound in good yields. Water is an essential ingredient. If the dimethyldioxirane / acetone solution is dried over molecular sieves prior to use, no oxidation will take place. However, if water is purposefully added, the conversions occur quickly at rates roughly dependent on the steric factors. The electron-poor isocyanate is therefore not directly oxidised but is first hydrolysed to the carbamic acid **78** which then undergoes decarboxylation to the amine **79** which is then oxidised. (The fact that amines are easily oxidised to the nitro compounds by dimethyldioxirane and carbamates are not favours this route.)



Scheme 29 : Oxidation of isocyanates using dimethyldioxirane in wet acetone

viii. Azo compounds

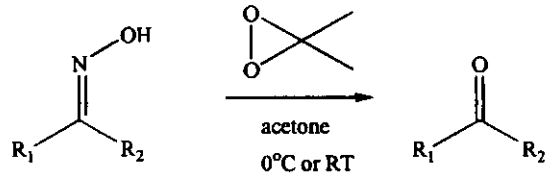
Azo compounds are oxidised to azoxy compounds by dioxiranes.[55a]



Scheme 30 : Oxidation of azo compounds using dimethyldioxirane

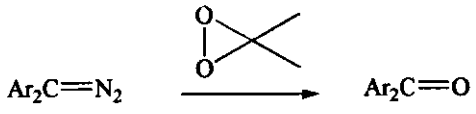
ix. Ketoximes

Olah reported the oxidative hydrolysis of ketoximes to the corresponding carbonyls with dimethyldioxirane in acetone.[71] The ease of hydrolysis varied with the structure of the ketoxime, whereas aldoximes were recovered unchanged.

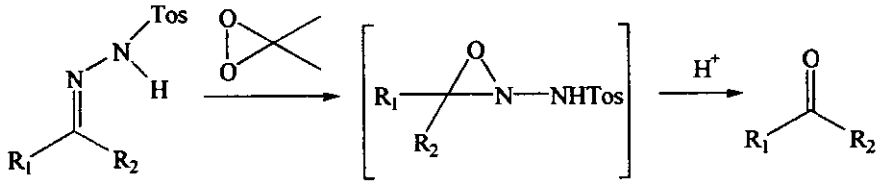


Scheme 31 : Oxidation of ketoxime using dimethyldioxirane

Many other nitrogen-containing compounds undergo similar oxidative cleavage to give the corresponding denitrogenated carbonyls. These include diazo compounds[72] which are oxidised quantitatively with the complete absence of by-products in the crude (Scheme 32) and aryl and dialkyl hydrazones[73] and tosyl hydrazones[74] which react via the oxaziridine (Scheme 33).



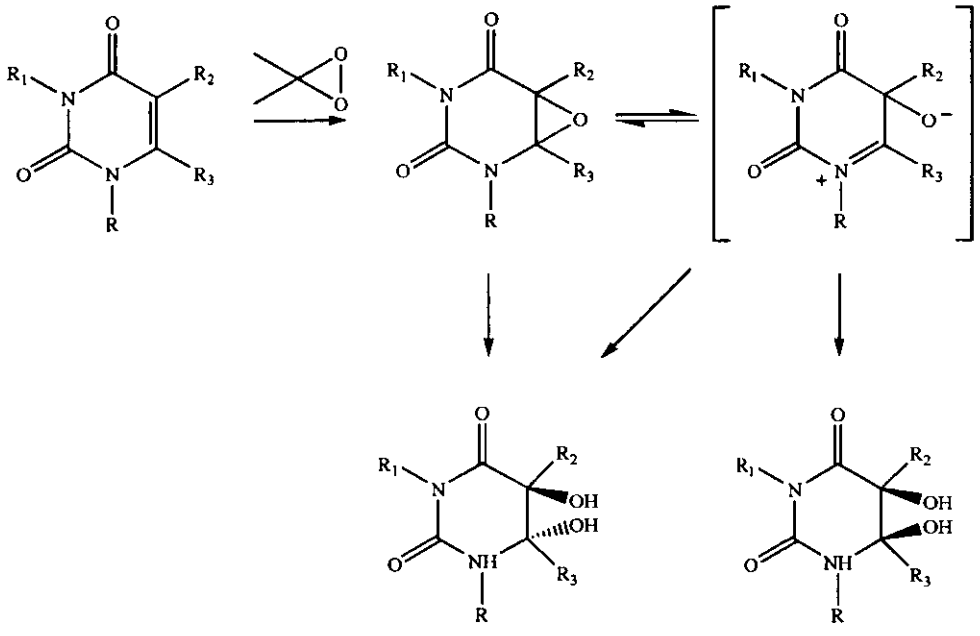
Scheme 32 : Oxidation of diazo compounds using dimethyldioxirane



Scheme 33 : Oxidation of tosyl hydrazones using dimethyldioxirane

x. Uracil derivatives

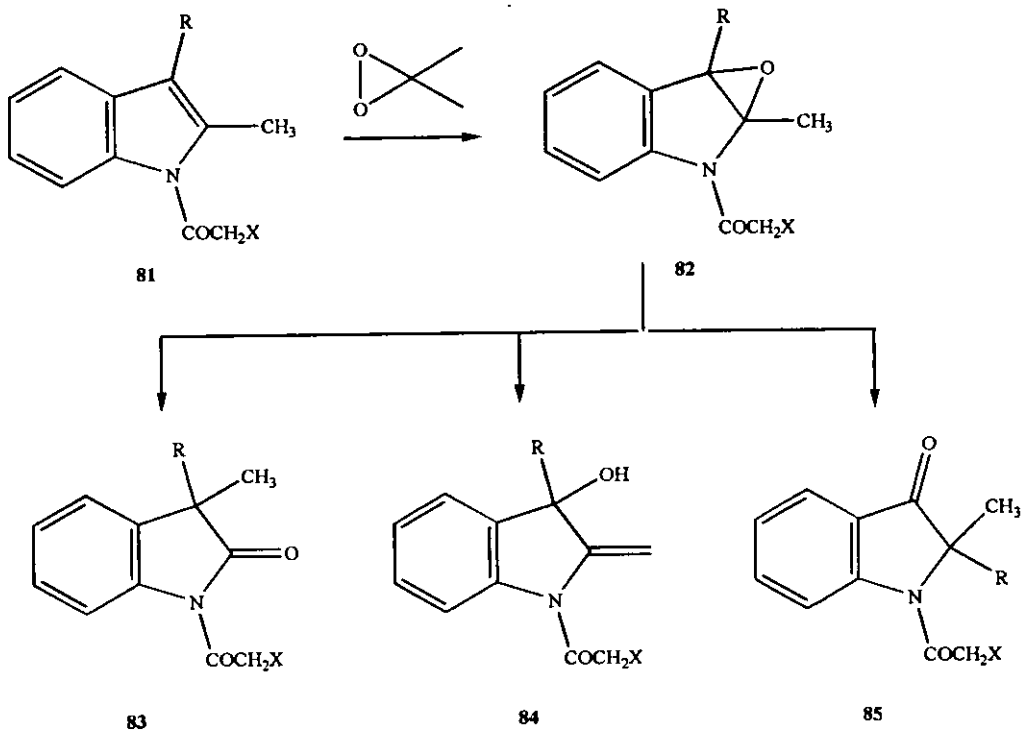
Uracil derivatives and pyrimidine nucleosides are oxidised by dimethyldioxirane as shown in Scheme 34.[75]



Scheme 34 : Oxidation of uracil derivatives using dimethyldioxirane

xi. N-acyl indoles

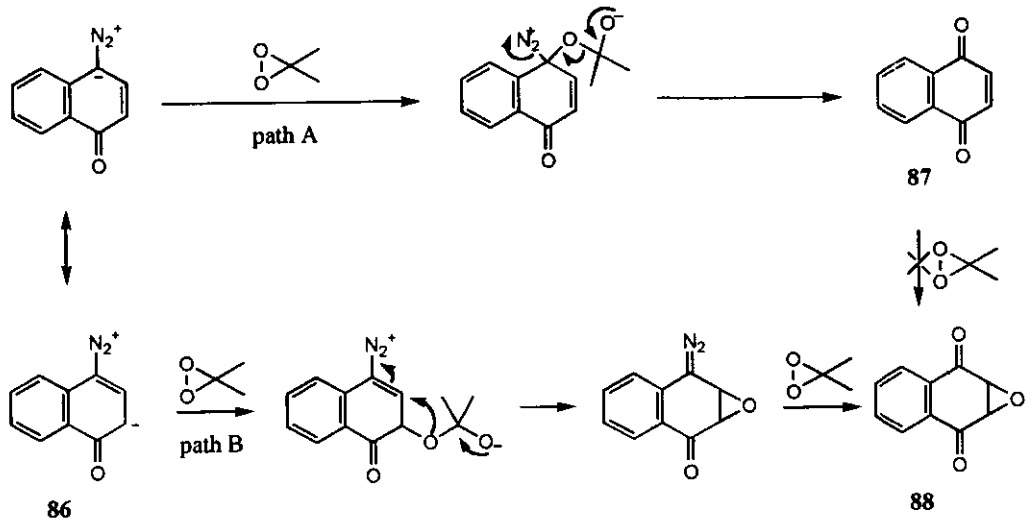
N-acyl indoles **81** are oxidised by dimethyldioxirane to give novel indole-2,3-epoxides **82**.[76] Rearrangement of these epoxides provides a convenient and versatile synthetic route to indolinones **83** and **84** and indolines **85** (Scheme 35). Substitution at C-3 exerts a high degree of regio- and chemoselectivity.



Scheme 35 : Oxidation of N-acyl indoles using dimethyldioxirane

xii. Diazoquinones

In addition to the expected dimethyldioxirane oxidation of electron-poor diazoquinones **86** to their quinones **87**, the corresponding epoxy quinones **88** are formed directly and not as secondary over-oxidation products of the quinones **87**.[77] In this respect, dimethyldioxirane is distinct in its oxidising behaviour from the peroxy acids which exclusively afford the quinones. This novel oxidation has been rationalised in terms of the ambident nucleophilic nature of the diazoquinones and corroborated by molecular orbital (AMI) calculations. It has been proposed that nucleophilic attack of diazo carbon atom (path A, Scheme 36) and subsequent loss of molecular nitrogen and acetone yields the quinone **87** while nucleophilic attack on the α-carbonyl C atom (path B, Scheme 36) results first in the epoxy diazoquinone which is further oxidised by dimethyldioxirane to the epoxy quinone **88**.



Scheme 36 : Oxidation of diazoquinones using dimethyldioxirane

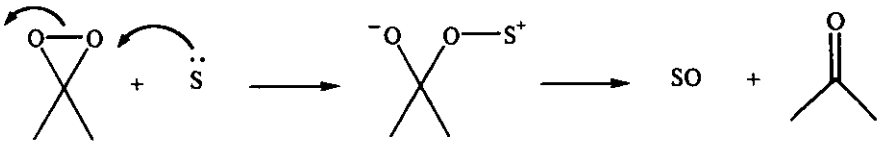
1.3.5 Oxidation of Organometallics

Another application of dioxirane chemistry is the oxidation of organometallic substrates. Examples include the oxidation of silanes (R_3Si-H) to their silanols (R_3Si-OH) by Si-H insertion,[78] the oxidation of silyl enol ethers to the epoxide,[1b] the oxidation of lithium, sodium and titanium enolates to the α hydroxy carbonyl compounds,[1b] the oxidative cleavage of Fischer-carbene complexes to the corresponding carbonyl,[79] and the conversion of arene chrominum tricarbonyl complexes to the corresponding arene derivatives.[80]

1.4 MECHANISMS OF DIOXIRANE REACTIONS

In spite of the numerous applications of dioxirane chemistry to a wide variety of substrates, many mechanistic details are still not fully understood.

Many of the reactions performed by dioxiranes appear to take place by a polar mechanism analogous to the well established mechanism in peroxy acid chemistry, involving nucleophilic attack by the substrate, S at the peroxide O-O bond (Scheme 37).[81]



Scheme 37 : Polar mechanism of oxidation

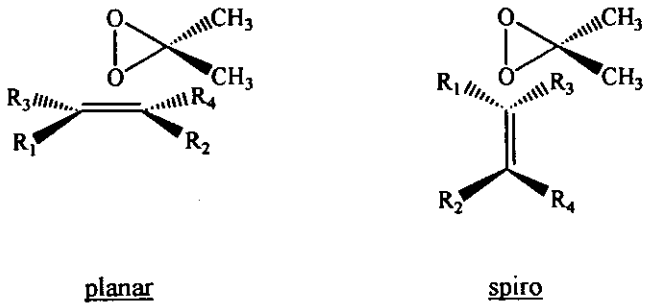
In fact, epoxidation,[82] sulfur oxidation[52a] and C-H insertion[83] reactions of dimethyldioxirane have been shown to be electrophilic by means of linear free energy relationship (LFER) correlations. However, in some cases, more complex electron transfer has been implicated, particularly for substrates with low oxygen potentials[84] and the Minisci group have recently reported evidence of free radical chemistry in the oxidation of alkanes, ethers and aldehydes by dimethyldioxirane involving the bis(oxyl)diradical **89**.[85] This is in contrast with other research groups which exclude a free radical mechanism.

89

Scheme 38 : Formation of the bis(oxyl)diradical

1.4.1 Mechanism of Epoxidation

Several mechanistic studies of dimethyldioxirane epoxidations have been reported which include investigations into stereochemistry,[2,11a,b] kinetics[35,86] and solvent effects.[87] It has been generally accepted that the epoxidation of alkenes by dimethyldioxirane is an electrophilic mechanism involving a spiro "butterfly" type transition state, rather than a planar one (Figure 1). The solvent effect data supports this electrophilic spiro type attack by the dioxirane on the double bond and suggests this leads to partial charge creation at the oxygen atoms of the reacting dioxirane.

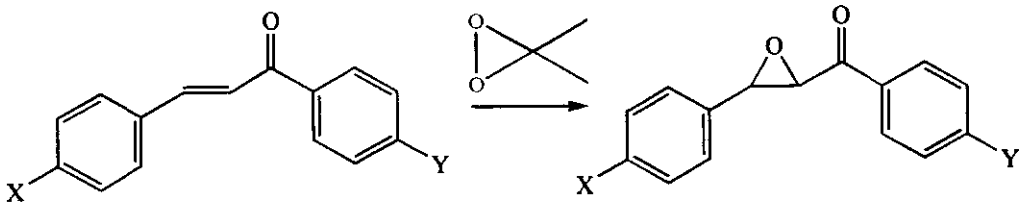


planar spiro

Figure 1 : Mechanistic extremes for the epoxidation transition state

Baumstark studied the epoxidation by dimethyldioxirane of a series of sustituted styrenes and selected di- and mono-substituted alkenes.[35] The fact that for certain *cis* / *trans* dialkylalkenes, the *cis* compounds were found to be of approximately tenfold greater reactivity than the corresponding *trans* alkenes, that kinetic studies on the reaction of the styrene series yielded an excellent LFER with a *p* value of -0.90, and that the addition of water to the dioxirane reactions in acetone increased the observed rates of epoxidation, supported an electrophilic mechanism. The *cis* / *trans* results back up the idea of a spiro transition state as in this arrangement one side of the *cis* compound can be attacked preferentially.

Further work by Baumstark on the reaction of dimethyldioxirane with various chalcones (Scheme 39) provided further evidence of an electrophilic process. Electron-releasing substituents in the *para* positions of the phenyl rings enhanced the rate of epoxidation while electron-withdrawing groups had the opposite effect. Addition of water resulted in a measurable increase in the rate of epoxidation and an excellent LFER against σ^+ in a Hammett type plot was obtained for the 4-substituted chalcones with $\rho^+ = -1.03$.[86a]

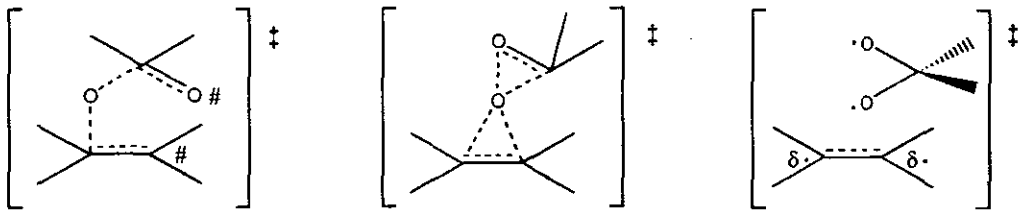


Scheme 39 : Oxidation of chalcones using dimethyldioxirane

Work in our own laboratories provided further insight into the mechanistic aspects of dioxirane epoxidations through a study of the biphasic *in situ* oxidations of Δ5 steroids with a range of ketones.[88] The results obtained were explained by the requirement for a spiro transition state.

However, it has been reported by Minisci and coworkers that dimethyldioxirane is in equilibrium with its bis(oxyl)diradical (Scheme 38) and that epoxidation[89] and certain other oxidations[85,90] proceed by involvement of free radicals (this is dicussed in more detail in section 1.4.2). Earlier, Adam, in a qualitative orbital analysis and energy profile of bis(oxyl)diradical **89**, pointed out the possibility of its intermediacy in epoxidation and C-H bond oxygen insertion reactions,[1d] although this had since been dismissed.

In 1996, Orfanopoulous *et al* addressed the question of whether the dimethyldioxirane epoxidation reaction goes via a concerted or stepwise mechanism.[91] They presented inverse α and β secondary isotope effects to try and elucidate the nature of the transition state. The results obtained were consistent with a concerted mechanism as shown by TS II in Figure 2. However, in light of the results reported by Minisci, Orfanopoulous points out that the bis(oxyl)diradical approach to the double bond in a concerted mechanism shown by TS III in Figure 2 is also consistent with the observed stereospecificity of the epoxidation reaction and certainly not excluded by his results. He suggests that further theoretical calculations are needed to shed light on factors that distinguish TS II and III. He concludes that these results are consistent with oxygen transfer in a non polar concerted transition state which confirms the previous butterfly mechanism derived from stereoelectronic and kinetic studies.



= radicals or ions

TS I TS II TS III

Figure 2

1.4.2 Mechanism of C-H Insertion

The exceptional selectivity in the oxidation of alkanes by dioxirane has led to exclude the involvement of free radicals and a one-step mechanism or "concerted oxenoid O-insertion" mechanism, believed to involve a spiro transition state similar to the one suggested for epoxidation (Figure 3), has been proposed. This is strongly suggested by kinetics, H/D isotope effects, solvent effects and selectivity and stereochemical evidence.[46,92]

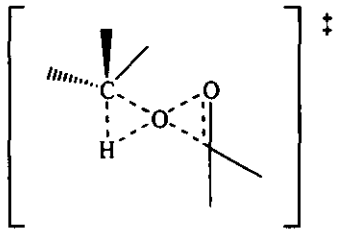
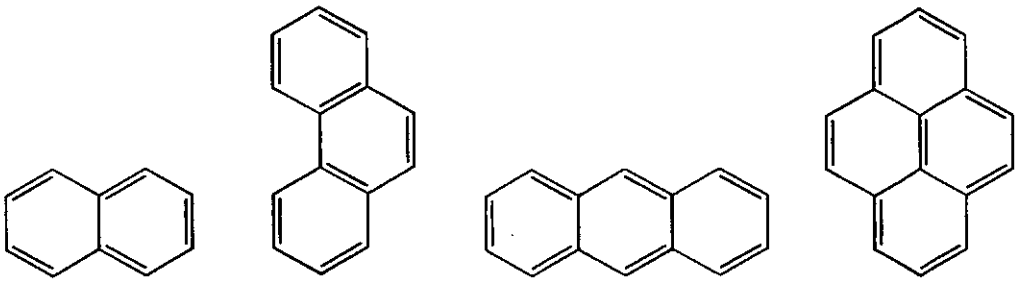


Figure 3 : Proposed transition state for C-H insertion

Murray *et al* investigated the nature of the oxygen atom insertion reaction into C-H bonds by dimethyldioxirane by determining the relative rate of the insertion reaction in a series of related substrates and comparing it to that for a radical process (hydrogen atom abstraction by t-butoxy radicals).[93] The substrates used were toluene, ethylbenzene and cumene. In all cases only the benzylic hydrogen was involved and the data obtained indicated that dimethyldioxirane is considerably more selective than the t-butoxy radical towards these substrates and so is not consistent with a free radical mechanism.

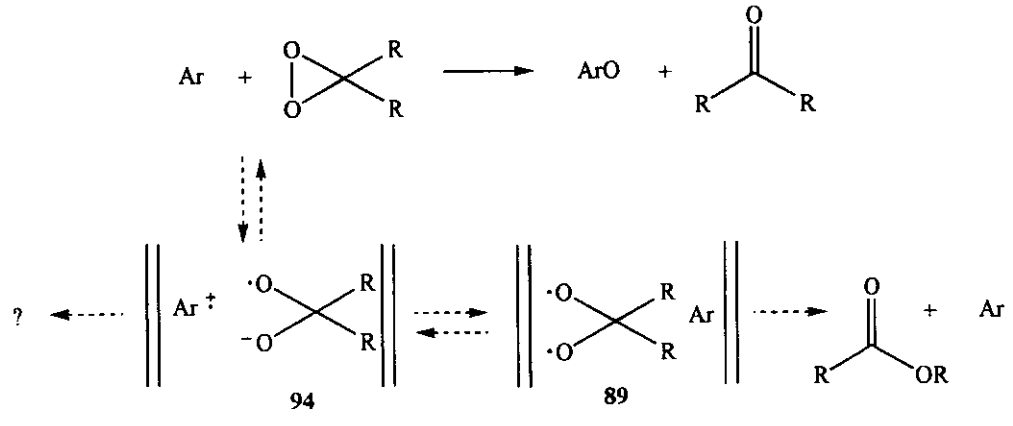
In contrast to this, evidence has been documented which supports electron transfer / radical pathways. In 1990, Curci *et al* reported on the oxyfunctionalisation of aromatic hydrocarbons by methyl(trifluoromethyl)dioxirane.[94] They found the oxidation of naphthalene **90** and phenanthene **91** to be extremely efficient but that it became progressively less effective going onto anthracene **92** and pyrene **93**.



90 91 92 93

In the reaction of pyrene with the dioxirane, some formation of methyl trifluoroacetate occurred. This ester also arises in the decomposition of methyl(trifluoromethyl)dioxirane in the absence of substrate. The rearrangement of dioxiranes into esters is thought to occur via bis(oxyl)diradical which led Curci and coworkers to explain their findings as outlined in Scheme 40.

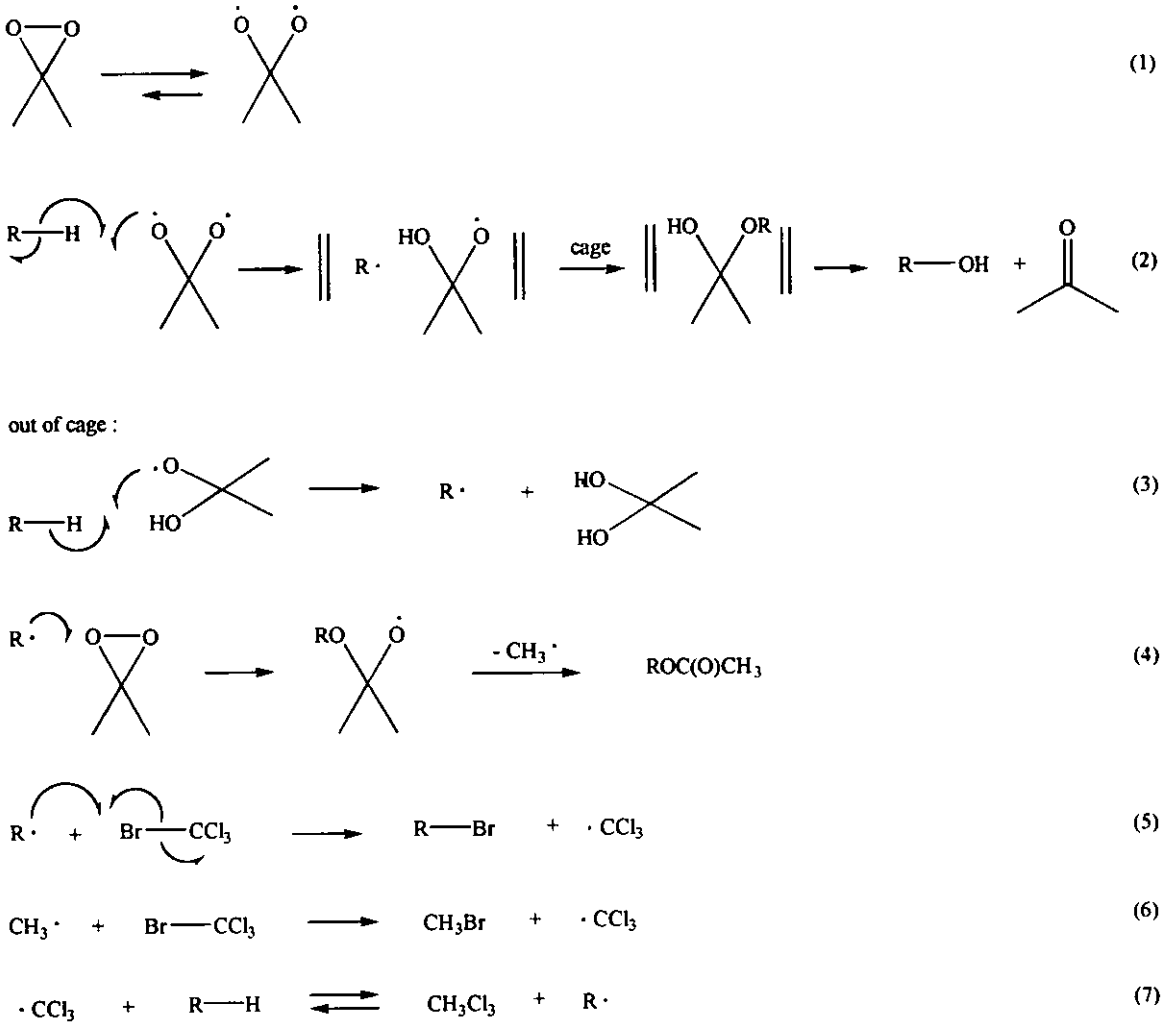
The redox potential for the Ar/Ar+· couple drops on passing from naphthalene to pyrene, so whenever the arene possesses an accessible oxidation potential, Curci postulated a deviation from straightforward oxygen transfer leading to the radical couple **94** which might then generate the bis(oxyl)diradical **89** which in turn would give the ester.



Scheme 40 : Oxyfunctionalisation of aromatic hydrocarbons by methyl(trifluoromethyl)dioxirane

In a more recent study, Minisci *et al* provided evidence that free radicals are involved in the dimethyldioxirane C-H insertion reaction by demonstrating that when oxidising alkanes using dimethyldioxirane, high yields of alkyl bromides could be produced by simply adding a relatively low concentration of CCl_3Br to the reaction medium.[90] The Minisci group showed that free radicals ($R^{\cdot}$) can be formed in dimethyldioxirane / alkane / CCl_3Br reactions and that the formation of

haloderivatives competes with the formation of alcohols and ketones. For example, in the case of adamantane, when reacted with dimethyldioxirane in acetone at room temperature, 51% adamantyl halides and 48% oxygenated products are obtained. The results were rationalised via a free radical-type oxygen rebound mechanism with a radical chain reaction being initiated by escape from the caged radical pair. The "oxygen-rebound" in the solvent cage (equation 2, Scheme 41) explains the oxygenated products while the radical pair escaping from the solvent cage can initiate chain processes according to equation 3-7 (Scheme 41).

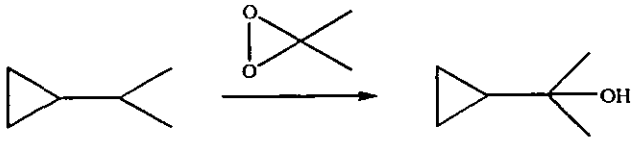


Scheme 41 : Mechanism postulated by the Minisci group for the oxidation of alkanes by dimethyldioxirane in the presence of CCl_3Br

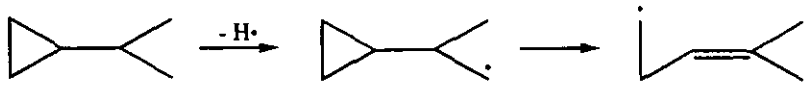
In a further paper, Minisci *et al* reported that when oxidation of cyclohexane, adamantane, ethyl benzene and cumene are oxidised at room temperature in acetone the reaction products and the conversions are quite different depending on whether the reaction is carried out under oxygen or

nitrogen atmospheres.[95] It was found that in the absence of oxygen, conversions are lower and that alkyl acetates (RO-COMe) are the main products, whereas in the presence of oxygen, conversions increase, the formation of acetates is suppressed and the alcohols (or ketones when a CH_2 group is oxidised) are the main products. Minisci again explained the results by the homolysis of dimethyldioxirane induced by the alkane (equation 1, Scheme 41). The radical pair gives rise to a cross-coupling in the solvent cage (equation 2, Scheme 41) while the radicals which have escaped from the cage initiate a free radical chain process leading to the formation of RO-COMe (equation 4, Scheme 41). In the absence of oxygen, methane, methyl acetate, methanol and acetoxyacetone were detected in the reaction mixtures which are formed from dimethyldioxirane by competitive chain processes which do not involve the alkane. In the presence of oxygen, the oxygen intercepts all carbon-centred radicals suppressing these chain processes. The radicals escaping from the solvent cage do not appear to do so in large amounts, thus the cage coupling of equation 2, Scheme 41 is the main reaction in the presence of oxygen. The authors do not believe the previous assumption, that the observed selectivity among toluene, ethylbenzene and cumene excludes a free radical mechanism,[93] is justified. They suggest that a radical such as the bis(oxyl)diradical will be a much more selective hydrogen abstracting species than a simple alkoxy radical for both enthalpic and polar reasons and that this would not be surprising considering the very large differences in selectivity among other oxygen-centred radicals ($ROO^{\cdot} >> R_2C(OH)O^{\cdot} >> RO^{\cdot} >> HO^{\cdot}$). Minisci suggests that this would explain the regio- and chemoselectivity of the oxidation while a very fast oxygen rebound mechanism in the solvent cage (equation 2, Scheme 41) would explain the observed stereo-selectivity.

Ingold, however, challenged this mechanism and applied the radical clock[96] approach to examine further the dimethyldioxirane / alkane reaction.[97] He chose 2-cyclopropylpropane as substrate which contains a tertiary hydrogen atom for relatively easy oxidation by dimethyldioxirane to the corresponding tertiary alcohol with no further oxidation (Scheme 42). 2-Cyclopropylpropane also yields a radical clock sufficiently fast to be suitable for the detection of free radicals but too slow to undergo a rearrangement while still within the solvent cage (Scheme 43).

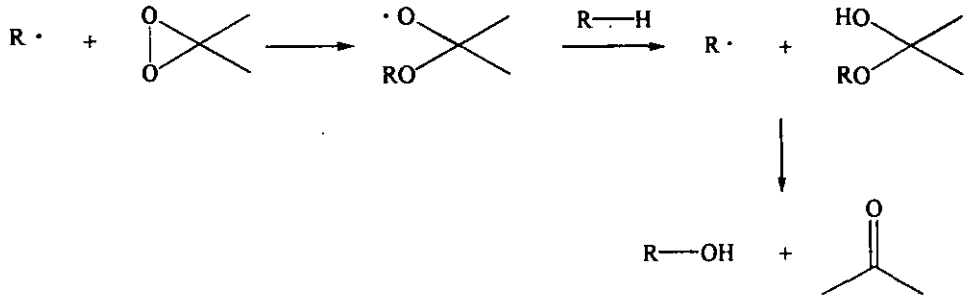


Scheme 42 : Oxidation of 2-cyclopropylpropane using dimethyldioxirane



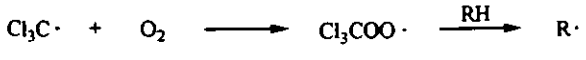
Scheme 43 : Hydrogen atom abstraction from 2-cyclopropylpropane

Ingold carried out reactions using varying concentrations of reagents and found that a 90% change in dimethyldioxirane concentration produced only a 10% difference in the alcohol yield. He concluded therefore that most of the alcohol must be formed by cage collapse (or "oxygen insertion") and not via Scheme 44.

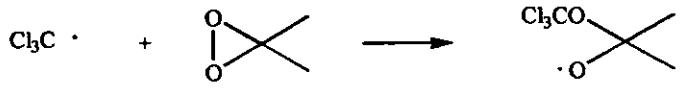


Scheme 44

Thus, Ingold reports, there is a dilemma. These results in agreement with earlier work indicate that oxygenated products are not produced to any significant extent in a free radical chain reaction which implies either that "oxygen insertion" really occurs or that very few radicals escape from the solvent cage. Ingold carried out several reactions to check on the role of oxygen in this reaction and found that there is clearly an oxygen effect on bromide yield. This led him to conclude that the free radical chain observed by Minisci involves the hydrogen atom abstraction from the alkane by $Cl_3COO\cdot$ (Scheme 45) and by $Me_2C(O\cdot)OCCl_3$ (Scheme 46) as well as by the $Cl_3C\cdot$ radical. CCl_3Br appears therefore to "redirect" the dimethyldioxirane / alkane reaction away from a largely in-cage process and towards cage escape and a subsequent radical chain process which consumes dimethyldioxirane and thus reduces the yield of oxygenated alkane products formed via the in-cage collapse reaction.

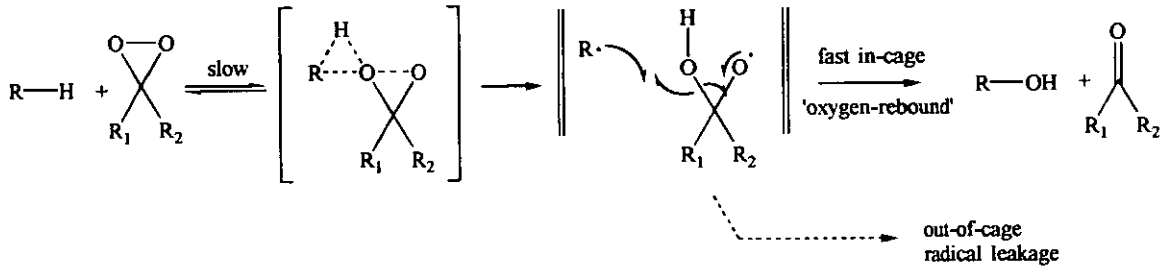


Scheme 45 : Formation of the $Cl_3COO\cdot$ radical in air



Scheme 46 : Formation of the $Me_2C(O^{\cdot})OCCl_3$ radical

In earlier papers, Curci had proposed that the rate determining step in the oxyfunctionalisation of alkanes by dioxiranes presents no distinct radical character or carbenium ion character, although he did point out that after the slow step some radical character may develop as an alternative to direct collapse into products (Scheme 47).[92a,c]

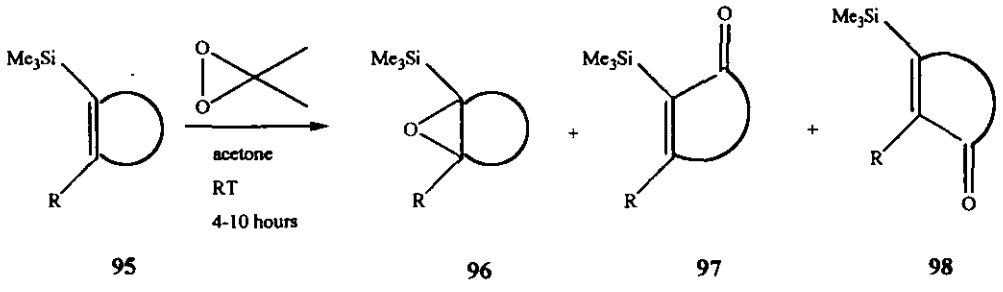


Scheme 47 : Oxyfunctionalisation of alkanes by dioxiranes as proposed by Curci

As result of the Minisci group's findings which led them to rule out this mechanism, Curci undertook a kinetic study of adamantane oxidation by dimethyldioxirane in the presence of CCl_3Br and / or in an inert gas atmosphere.[98] The results of this study led Curci to believe that the alkane oxyfunctionalisation by dioxirane in the absence of conditions and / or reaction partners which promote radical reactivity is still best represented by the process in Scheme 47. He did find, however, that the addition of CCl_3Br led to a dramatic change in the reaction kinetics, rate law and product distribution. It would seem that CCl_3Br serves not only in trapping freely diffusing radicals but it also participates in the primary process by inducing the radical reactivity of the dioxirane. This view is supported by preliminary kinetic data and has led Curci to modify the process established for the thermal decomposition of dioxirane (see section 1.5).[99] The exact nature of the primary interaction between the dioxirane and the bromide that triggers formation of the bis(oxyl)-diradical **89** is still to be established.

Further work by the Minisci group has included the oxidation of alkyl and aryl iodides to iodoso-derivatives, the oxidation of phenylacetaldehyde to phenyl acetic acid or benzyl acetate (depending on the presence or not of oxygen) and the epoxidation and allyl oxidation of alkenes and provides further evidence for the involvement of free radicals in dimethyldioxirane oxidations.[89]

Adam has reported that the epoxidation of acyclic vinylsilanes by dimethyldioxirane proceeds straightforwardly giving the expected α, β epoxysilanes in high yields but that with cyclic vinylsilanes **95** appreciable amounts of allylic oxidation is observed giving the two regioisomeric silylated enones **96** and **97** as well as the epoxide **98**.[100] These competitive pathways become more pronounced when the reactivity of the double bond is decreased by electronic and / or steric factors.

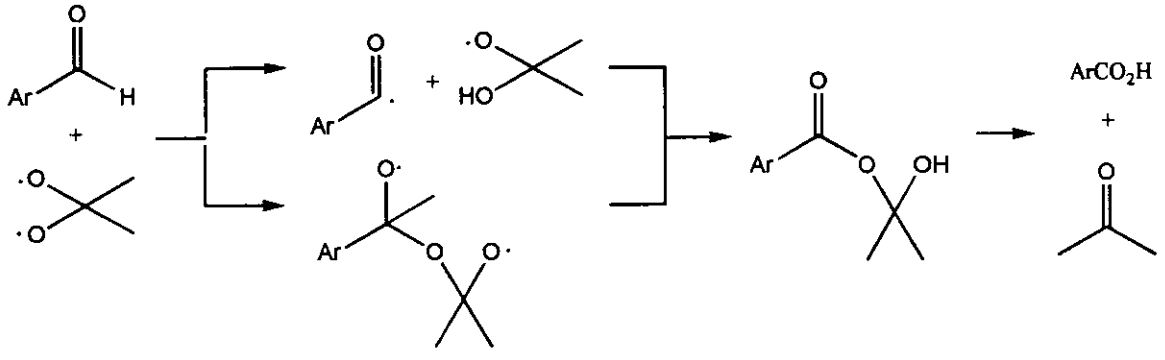


95 **96** **97** **98**

Scheme 48 : Epoxidation of cyclic vinylsilanes using dimethyldioxirane

This fact complicates the straightforward mechanistic rationale of the butterfly mechanism and Adam suggests it would be tempting to propose a free radical mechanism for the allylic oxidation observed here. However, Adam does not believe his results support this but rather that the activation barriers for dimethyldioxirane epoxidation and allylic oxidation lie close together so that subtle structural changes push the chemoselectivity in one or the other oxidation mode through electronic and / or steric effects. Adam also suggests that the radical chain mechanism proposed by Minisci *et al* does not take into account that 100% retention of configuration is documented for the α hydroxylation of 2-phenylbutane,[44] as the intermediary radical generated after benzylic hydrogen atom abstraction by dimethyldioxirane would be expected to racemize appreciably. More studies are therefore required to understand the mechanistic complexities of this type of dioxirane reaction.

Before the early nineties the literature contained only a single report of any radical involvement in dioxirane reactions. This was a study carried out by Baumstark *et al* on the oxidation of *para*-substituted benzaldehydes to the corresponding acids.[101] This represents an oxygen atom insertion into a reactive C-H bond and so the mechanism may be vastly different from the C-H insertion into alkenes. However, it was found that when the reactions of the benzaldehydes, which contain a readily abstractable hydrogen atom, with one equivalent of dimethyldioxirane were done open to the air, yields obtained were 60-70%, whereas under an inert atmosphere (argon or nitrogen), the yields were lower. When a three- to fourfold excess of dimethyldioxirane under argon was employed, the acids were obtained in quantitative yield for all cases. Under an atmosphere of pure oxygen the reactions were faster than those open to the air and more than one equivalent of aldehyde could be oxidised. In the presence of oxygen, aldehydes with electron-donating groups appeared to be more reactive than those with electron-withdrawing groups. However under argon, where dimethyl-dioxirane was the only oxygen-atom source, the yield of acid did not seem to depend on the electronic nature of the aldehyde. These characteristics appeared indicative of a free-radical process and so the diradical pathway shown in Scheme 49 was proposed for oxidation under an inert atmosphere.

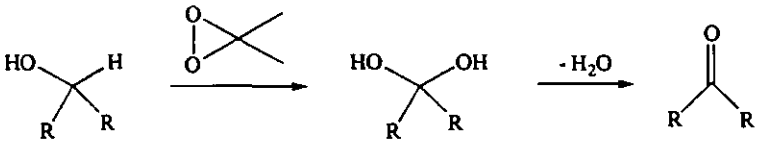


Scheme 49 : Proposed mechanism for benzaldehyde oxidation by dimethyldioxirane under an inert atmosphere

1.4.3 Mechanism of Alcohol Oxidation

As with C-H insertion into alkanes, the most obvious mechanism of alcohol oxidation by dioxiranes is the oxenoid O-atom insertion into the alcohol α C-H bond, followed by elimination of water

(Scheme 50). In these laboratories, the Marples group provided results using ^{18}O labelled substrates in support of this.[88]



Scheme 50 : Dimethyldioxirane oxidation of secondary alcohols

Furthermore the same group found a significant difference in the reaction rate of axial versus equatorial alcohols. It was found that 5α-cholestan-3α-ol (axial hydroxyl) was oxidised one and a half times more quickly than its 3β epimer (equatorial hydroxyl) which may be rationalised assuming butterfly transition states for the oxygen insertion and some intramolecular hydrogen bonding between the second oxygen of the dioxirane and the OH group. A simple explanation using this model would be that the transition states are close to the *gem*-diol on the reaction coordinate so that the higher ground state energy of the 3α-epimer is largely responsible for its enhanced reactivity.[88]

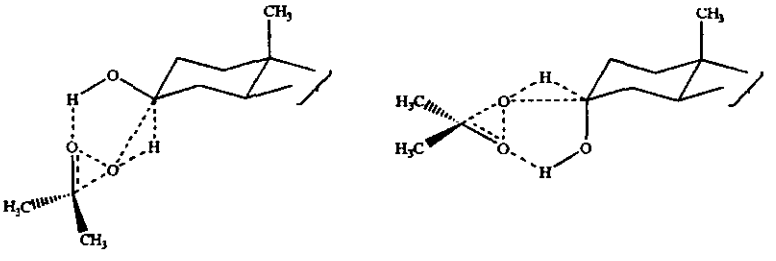
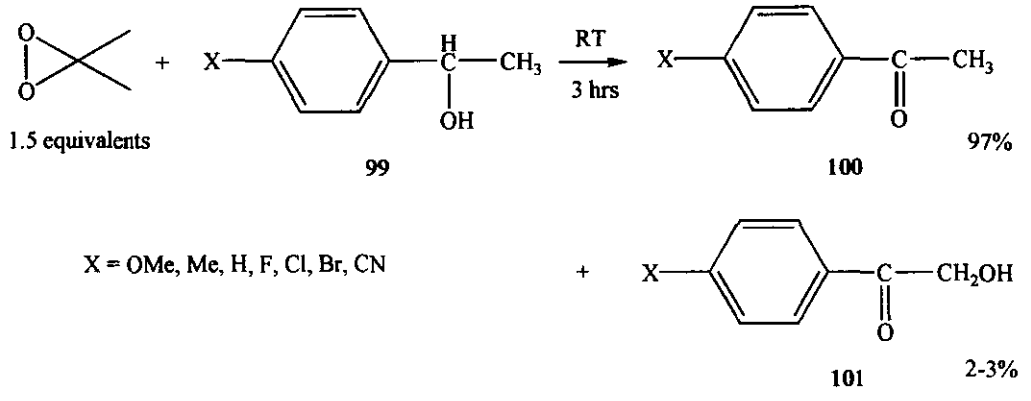


Figure 4 : Butterfly transition states proposed for the oxygen insertion into 5α-cholestan-3-ol

Curci investigated the mechanism of secondary alcohol oxidation with methyl(trifluoromethyl)-dioxirane using cyclobutanol as a mechanistic probe.[46] It is known that cyclobutanol has the unique property of reacting in different ways with one-electron and two-electron oxidants. With one-electron oxidants C-C bond cleavage occurs preferentially leading to acylic products such as γ-hydroxybutyraldehyde. With two-electron oxidants, the product is cyclobutanone and it was found that cyclobutanol is transformed into cyclobutanone only by methyl(trifluoromethyl)dioxirane.
To gain further insight into the reaction mechanism, Curci and his group measured the rates of oxidation of several secondary alcohols by methyl(trifluoromethyl)dioxirane.[46] Clean second order kinetics were observed. This, along with the fact that they found a lack of significant interference by

atmospheric oxygen, plus the remarkable selectivity shown when *endo*- and *exo*-norbornanols were oxidised and it was found that the *endo*-alcohol was about forty times more reactive that the *exo* isomer, suggested that a chain mechanism involving free radicals was not in operation. This is supported by the outcome of the cyclobutanol probe. Further evidence is provided by the fact that Curci *et al* measured a primary kinetic isotope effect, indicating that the C-H bond in the position α to the OH is being broken in the rate determining step. Such a primary kinetic isotope effect is not consistent with a radical-chain mechanism.

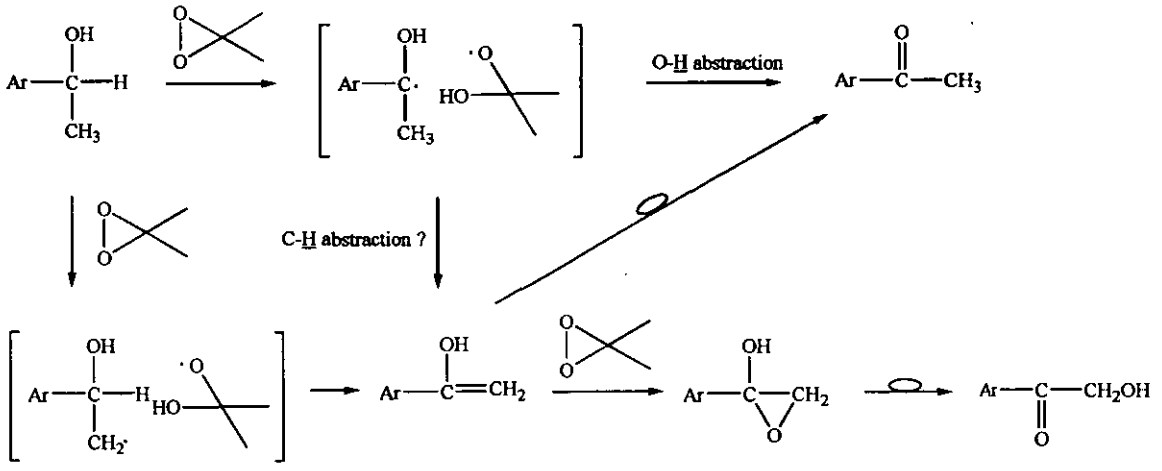
Baumstark studied the oxidation of *para*-substituted α-methylbenzylalcohols **99** using dimethyldioxirane which were found to give the corresponding acetophenones **100** in excellent yield with α-hydroxyacetophenones **101** as minor products.[102] Treatment of acetophenone with excess dimethyldioxirane under the reaction conditions did not yield α-hydroxyphenones indicating that these are direct oxidation products.



Scheme 51 : Oxidation of *para*-substituted α-methylbenzylalcohols using dimethyldioxirane

Kinetic studies were carried out and it was found that addition of water did not result in a measurable increase in rate in contrast to the significant solvent effect observed on the epoxidation of unsaturated carbonyl compounds[86a] and alkenes[35] and the C-H oxidation of alkanes by dimethyldioxirane.[45] It was found however that electron-withdrawing groups in the *para* position decreased the rate of oxidation while electron-releasing groups increased the rate and a Hammett plot of the second order rate constants for the oxidation of *para*-substituted α-methylbenzyl alcohols by dimethyldioxirane showed an excellent LFER against σ giving $\rho = -1.17$ with a correlation coefficient of 0.999. Kinetic studies were also carried out and all this data led Baumstark to suggest

a hydrogen atom abstraction route although concerted insertion could not be ruled out. A cage-radical process as shown in Scheme 52 was proposed consistent with the data.

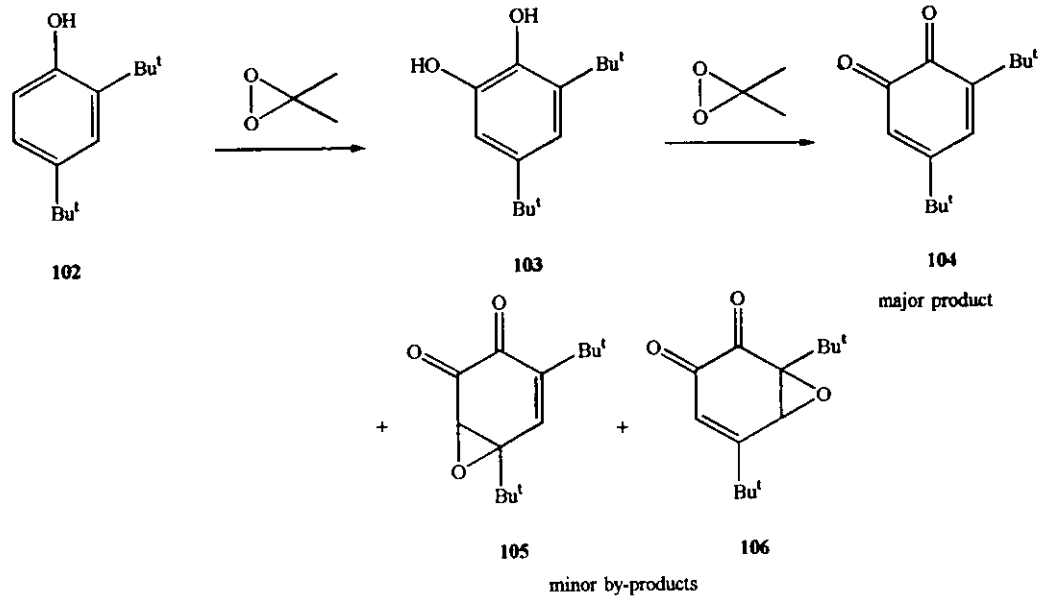


Scheme 52 : Proposed mechanism for the oxidation of *para*-substituted α-methylbenzylalcohols using dimethyldioxirane

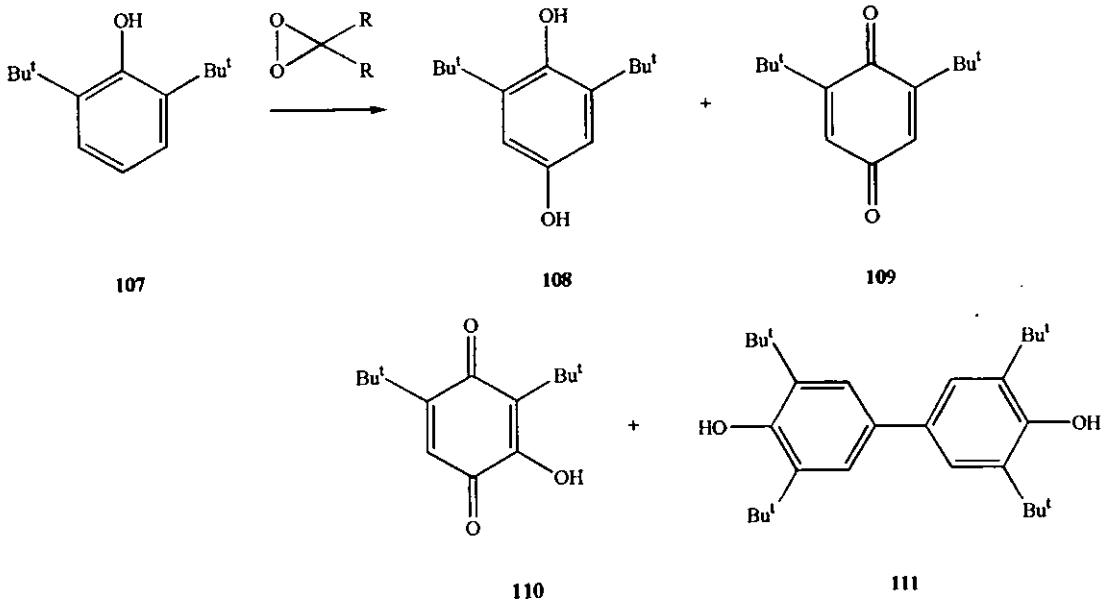
Studies by Crandell[103] and Curci[104] on the dimethyldioxirane oxidation of phenols also suggested electron transfer mechanisms. Crandell showed that dimethyldioxirane oxidises selected phenols to orthoquinones via the related arene diol[103] and that paraquinones can also be obtained where possible. He also showed that whereas simple phenols and anisoles react with dimethyldioxirane to give extremely complex mixtures, hindered phenols, such as 2,4-di-tert-butyl phenol **102**, undergo a more controlled oxidation (Scheme 53). Four equivalents of dimethyldioxirane in acetone were found to give the orthoquinone **104**, via the diol **103**, in 55% yield, with 30% recovered starting material. Alternatively, carrying out this reaction *in situ* gave 72% of the orthoquinone **104** plus a mixture of the epoxides **105** and **106** in minor amounts. Further reaction of **104** with dimethyl-dioxirane gave these by-products in reasonable yield.

Curci *et al* looked at the oxidation of 2,6-di-tert-butylphenol **107** by both dimethyldioxirane and methyl(trifluoromethyl)dioxirane (Scheme 54).[104] This substrate, with both *ortho* positions blocked by bulky t-butyl groups, was expected to yield product mixtures far less complex than those normally arising from oxidation of simple 'unprotected' phenols[103] and this was found to be the case. With methyl(trifluoromethyl)dioxirane, the hydroxyquinone **110** is the major product, the precursor of which is the hydroquinone **108**. With dimethyldioxirane, products **109** and **110** are accompanied by appreciable amounts of the dimer **111**. Formation of this dimer strongly suggests the radical

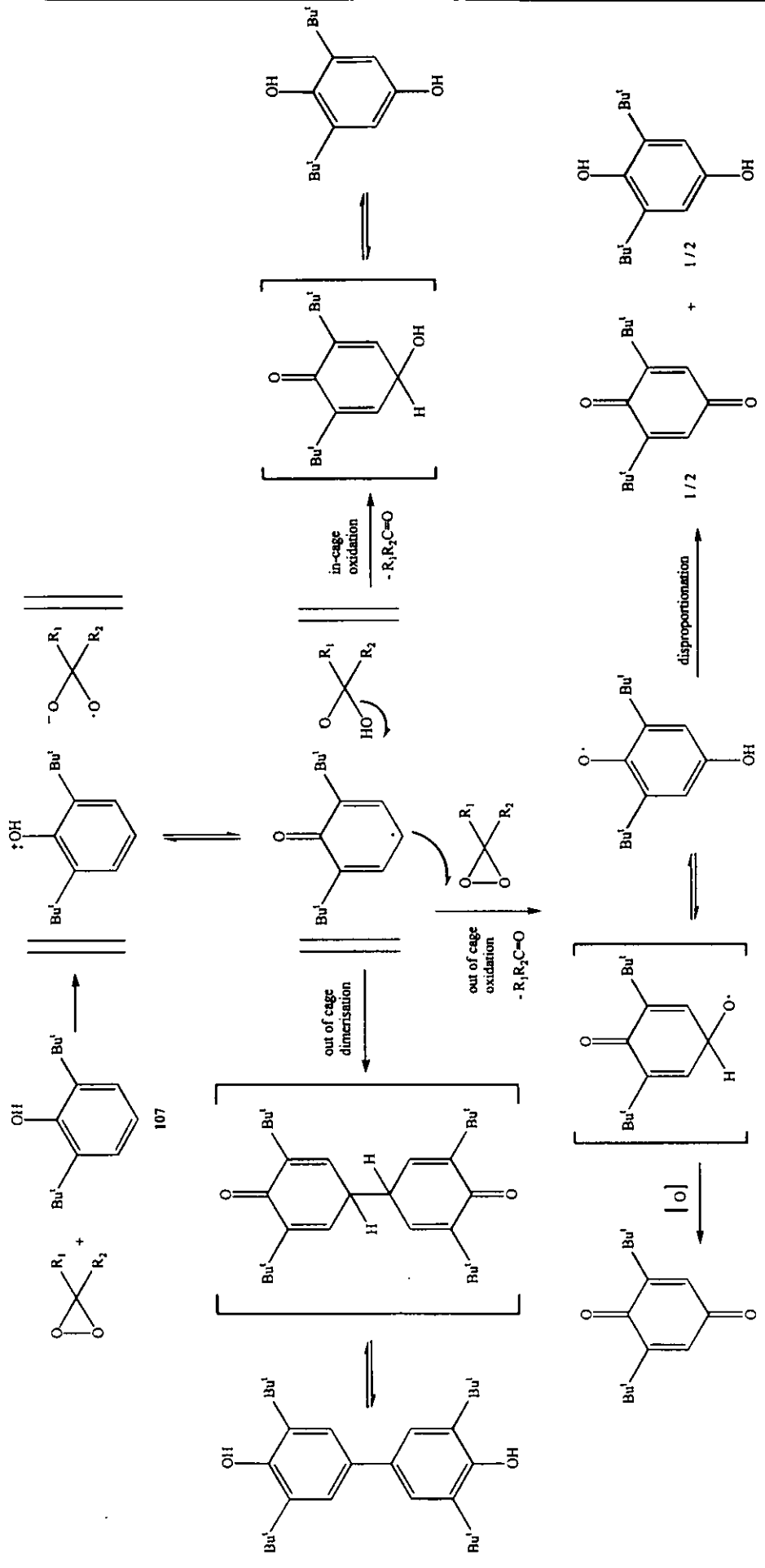
pathway outlined in Scheme 55. This mechanism finds precedence in the phenolic oxidation effected by oxaziridine[105] and by one electron oxidants.[106]



Scheme 53 : Oxidation of 2,4-di-tert-butylphenol using dimethyldioxirane



Scheme 54 : Oxidation of 2,6-di-tert-butylphenol using dimethyldioxirane and methyl(trifluoromethyl)dioxirane

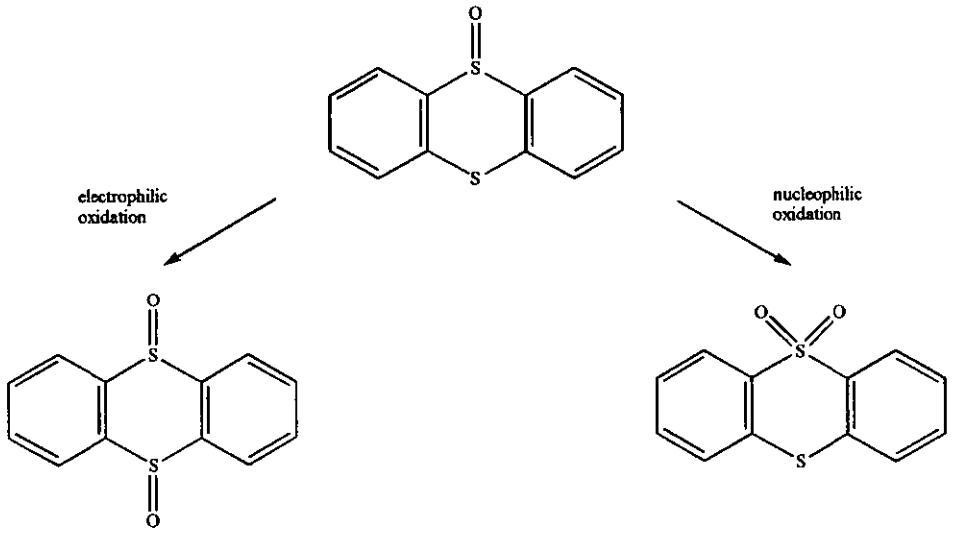


Scheme 55 : Radical pathway proposed for the dioxirane oxidation of 2,6-di-tert-butylphenol

1.4.4 Mechanism of Heteroatom Oxidation

The oxidations of both sulfides and sulfoxides have been shown to be electrophilic. This was established by Murray in 1987.[52a] He used dimethyldioxirane to oxidise a series of aryl methyl sulfides to the corresponding sulfoxides and in a separate series of reactions, sulfoxides were oxidised by dimethyldioxirane to the corresponding sulfones. Treatment of the results with the Hammett relationship gave ρ values of -0.77 and -0.76 respectively.

In an earlier study, Adam *et al*[107] had designed a mechanistic probe, thianthrene-5-oxide, containing both a nucleophilic sulfide and an electrophilic sulfoxide site, to investigate the relative degree of nucleophilic attack in oxygen transfer reactions.



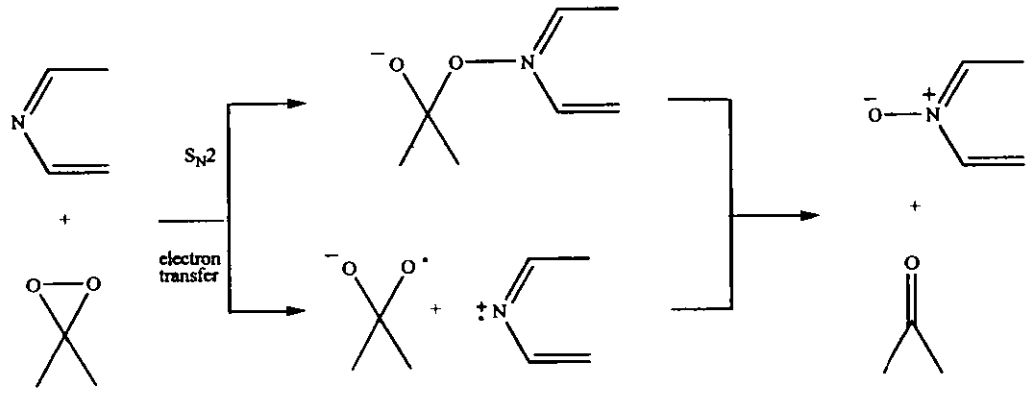
Scheme 56 : Oxidation of thianthrene-5-oxide by electrophilic and nucleophilic reagents

Initial results suggested dominant nucleophilic character (oxidation at the sulfoxide site) over electrophilic character (oxidation at the sulfide site) which was surprising and in light of these findings, McDouall addressed the question of mechanism of oxidation of sulfides to sulfoxides by carrying out an investigation using *ab initio* molecular orbital theory.[108] In a gas phase study, the results suggested that the oxidation of sulfoxide is energetically preferred over the oxidation of sulfide which is in general agreement with the results of Adam. However, in acetone, it was shown that this trend is inverted. More recently, Ballistreri *et al* examined the reactions of both thioethers and sulfoxides with dimethyldioxirane and methyl(trifluoromethyl)dioxirane and they too concluded that both dioxiranes are electrophilic oxidants towards sulfoxides.[109] Regarding Adam's results,

Ballistreri commented that the use of mechanistic probes such as thianthrene 5-oxide under the assumption that nucleophilic oxidants will oxidise the sulfoxide whereas the electrophilic ones will attack the thioether is too simplistic as the reactivity ratio in the competitive oxidation of thioethers and sulfoxides by electrophilic reagents may be small enough to cause the formation of mixtures of products. Ballistreri studied this and found that methyl(trifluoromethyl)dioxirane oxidises both thioethers and sulfoxides whereas dimethyldioxirane oxidises only thioethers. Ballistreri suggested that by applying the logic which has been used to develop mechanistic probes based on such competitive oxidations, the unrealistic conclusion that methyl(trifluoromethyl)dioxirane is less electrophilic than dimethyldioxirane would be reached. On the contrary, however, he showed by means of Hammett plots on substituted sulfoxides that dimethyldioxirane and methyl(trifluoro-methyl)dioxirane are both electrophilic oxidants towards sulfoxides and that methyl(trifluoro-methyl)dioxirane is less selective than dimethyldioxirane being a stronger oxidant. In fact in the same year Adam published further results which obviated all previous considerations of dioxiranes as a nucleophilic oxidant and showed both dimethyldioxirane and methyl(trifluoromethyl)dioxirane to be strongly electrophilic as expected.[110]

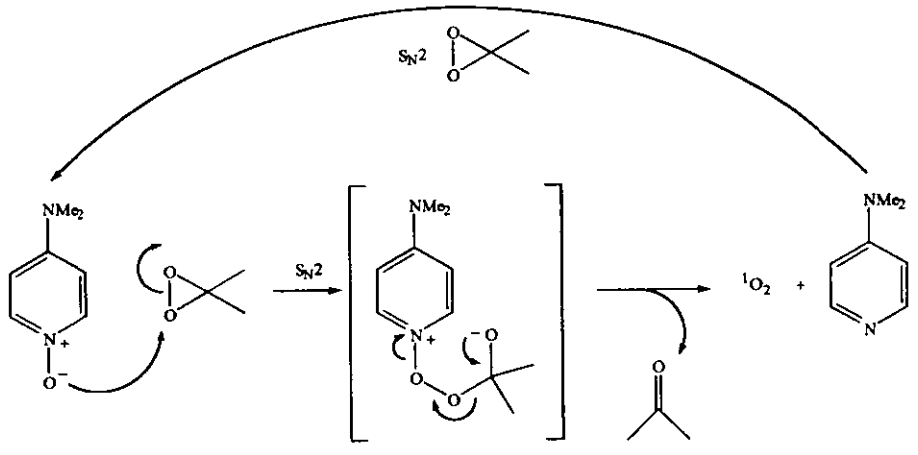
The mechanism of oxidation at nitrogen has also been the subject of several studies. One by Adam involved the investigation of S_N2 versus electron transfer in the oxidation of nitrogenheteroarenes by comparing the relative rates and regioselectivities of dimethyldioxirane oxygen transfer with those of methyl iodide methylation.[111] The results indicated the dimethyldioxirane oxidation of nitrogen-heteroarenes to be S_N2. The heteroarenes used were substituted pyridines and the relative rate constants k_{rel}(dimethyldioxirane) were determined by competition experiments with quinoline as reference substrate. The constants k_{rel}(methyl iodide) were determined from literature data and their correlation with the k_{rel}(dimethyldioxirane) data was found to be good. Excluding sterically encumbered substrates, a good correlation was observed between the k_{rel}(dimethyldioxirane) data and the pka of the nitrogen base and hence its nucleophilicity. When all substrates were considered the correlation was not so good. A very poor correlation was observed between the relative rate constants of dimethyldioxirane and the ionisation potentials of these heteroarenes which measure the removal of an electron out of the lone pair of the nitrogen atom. These reactivity data confirm a clear-cut S_N2 mechanism and not electron transfer.

Adam also looked at the regioselectivity of the dimethyldioxirane oxidation of bidentate nitrogen hereroarenes and found it to be consistent with S_N2 attack on the peroxide bond of dioxirane, with the oxygen transfer being subject to both electronic and steric factors in the heteroarene.



Scheme 57 : Oxidation of nitrogen heteroarenes using dimethyldioxirane - S_N2 or electron transfer?

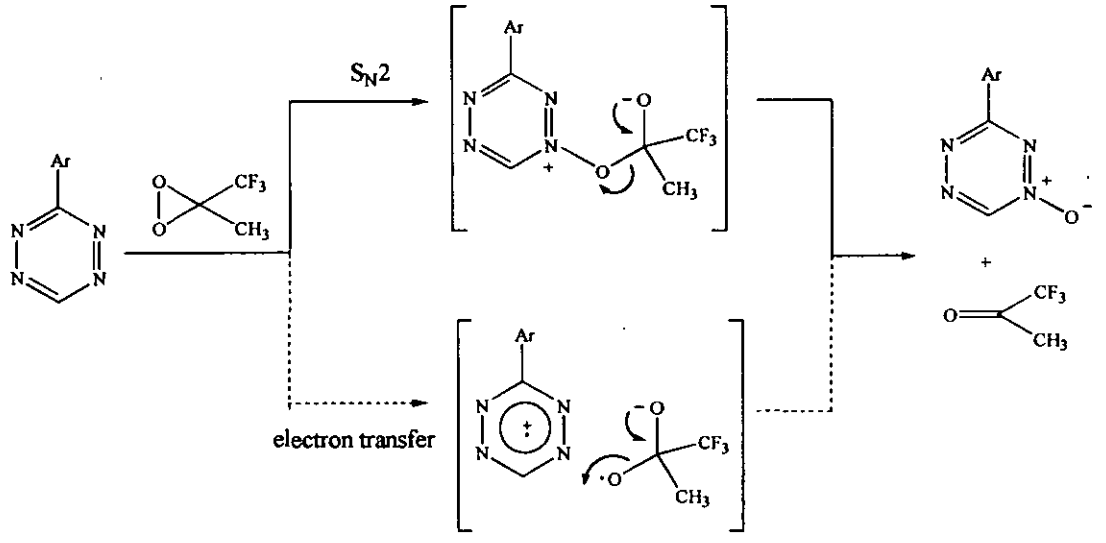
Another study by Adam on the oxidation of aromatic tertiary amines has revealed evidence that at least in some cases the resulting N-oxide decomposes the dioxirane with liberation of oxygen gas and regeneration of the heteroarene.[63] Adam proposed the mechanism in Scheme 58 whereby the decomposition of N-oxide proceeds also by an S_N2 attack of the nucleophilic N-oxide oxygen atom on the dioxirane peroxide bond. If this mechanism applies the proposed dipolar intermediate should lead to the formation of singlet oxygen and this was indeed found to be the case, in support of a S_N2 as apposed to radical mechanism.



Scheme 58 : Decomposition of dimethyldioxirane by N-oxide

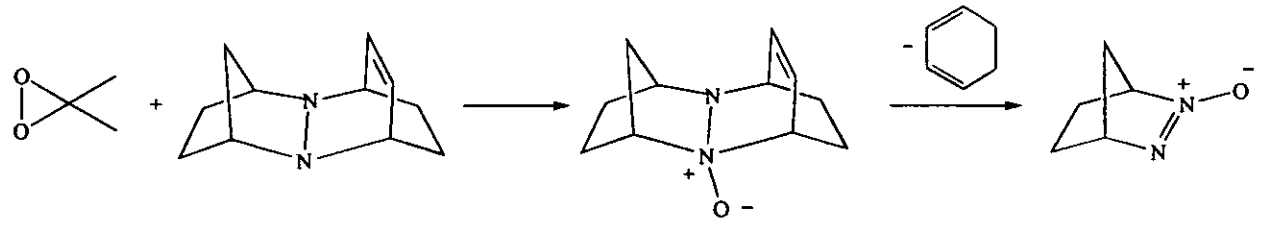
Adam carried out further studies using a series of 3-aryl-1,2,3,4,5-tetrazines. It was found that these compounds were N-oxidised directly by methyl(trifluoromethyl)dioxirane, whereas standard methods, e.g. oxidation with peracetic acid, gave other products.[112] A Hammett plot gave a ρ value

of -1.53 which suggests that the tetrazine serves as the nucleophile despite its electron poor nature and the dioxirane is the electrophile. AMI calculations on both the tetrazines and the N-oxide supported S_N2 attack by the nitrogen lone pair of the tetrazine on the dioxirane peroxide bond and implied that electron transfer is unlikely.



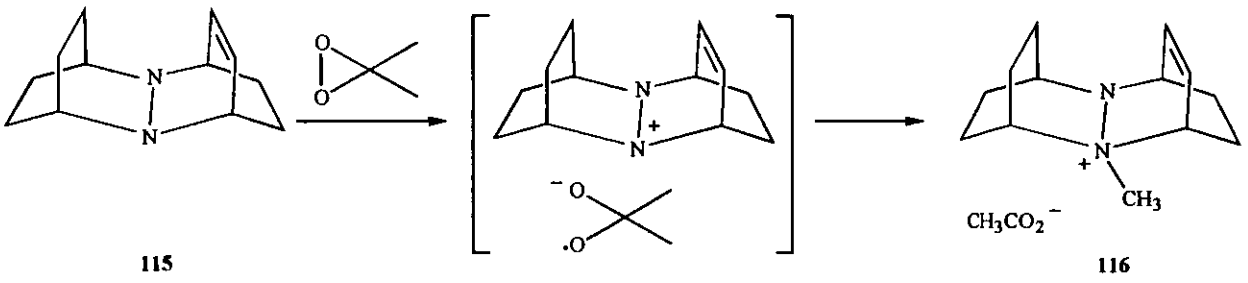
Scheme 59 : Mechanism of oxidation of 3-aryl-1,2,3,4,5-tetrazines using methyl(trifluoromethyl)dioxirane

In contrast, the dimethyldioxirane oxidation of some sesquibicyclic hydrazines has been reported and a surprising dichotomy between the expected formation of hydrazine N-oxides and production of N-methylated hydrazinium cations was discovered.[113] Treatment of hydrazine **112** with dimethyl-dioxirane in acetone gave the thermally labile N-oxide product **113** which undergoes Retro Diels-Alder cleavage to the azo oxide **114**, whereas the homologous unsaturated hydrazine **115** reacts with dimethyldioxirane to give principally N-methyl hydrazinium acetate **116**.



112 **113** **114**

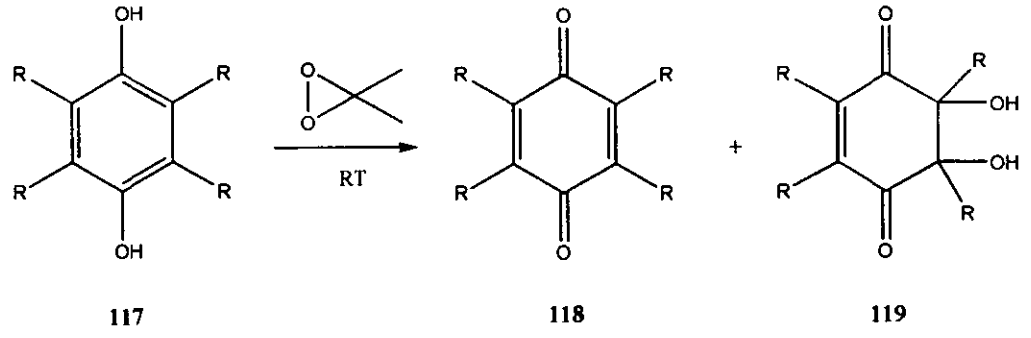
Scheme 60 : Oxidation of sesquibicyclic hydrazine using dimethyldioxirane to give the expected thermally labile hydrazine N-oxide



Scheme 61 : Oxidation of a homologous hydrazine using dimethyldioxirane to give the N-methylated hydrazinium cation acetate

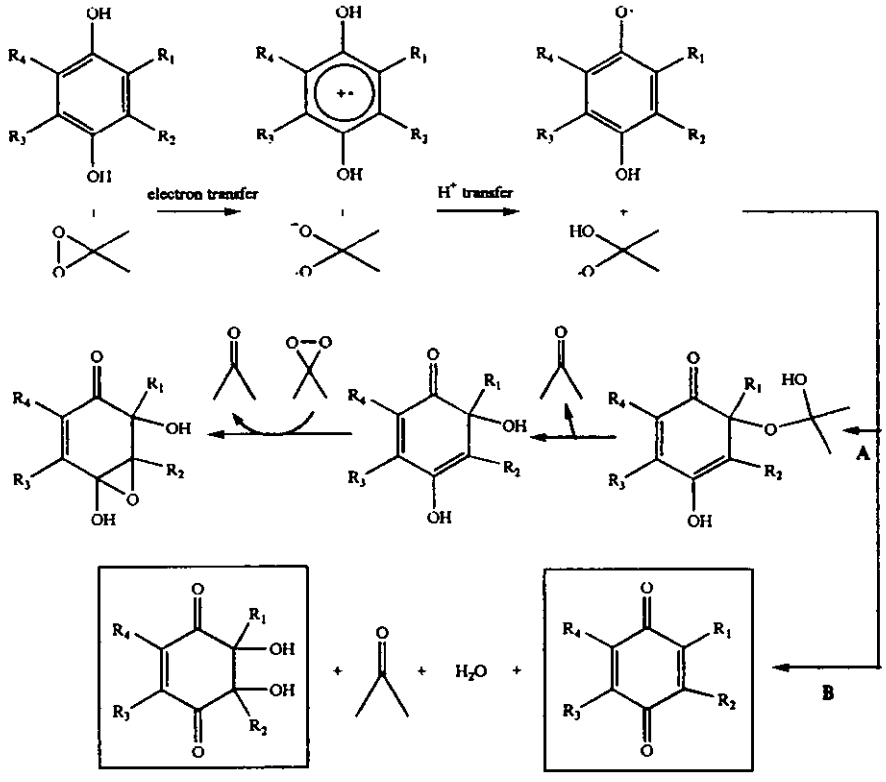
The authors believe that the methyl-transfer reaction can best be rationalized as proceeding by single electron transfer from the hydrazine to the dioxirane in the first step producing an ion pair consisting of the hydrazine radical cation and the O-O cleaved radical anion derived from dimethyldioxirane, shown in Scheme 61. This is based on the observation that methyl(trifluoromethyl)dioxirane undergoes electron transfer with nitroxide in the thermal reaction reported by Adam and coworkers (see section 1.5).[84c] It is suggested that for easily oxidised hydrazines single-electron transfer is more rapid than the usual two-electron oxygen transfer oxidation shown by dimethyldioxirane.

Earlier, Adam and Schonberger studied the dimethyldioxirane oxidation of hydroquinones.[114] These compounds are convenient electron donors with which to explore the electron transfer chemistry of dimethyldioxirane as their redox chemistry has been well investigated. It was found that the oxidation of hydroquinones **117** gave quinones **118** and the unusual 2,3-dihydroxycyclohexene-1,4-diones **119** (Scheme 62).



Scheme 62 : Oxidation of hydroquinones using dimethyldioxirane

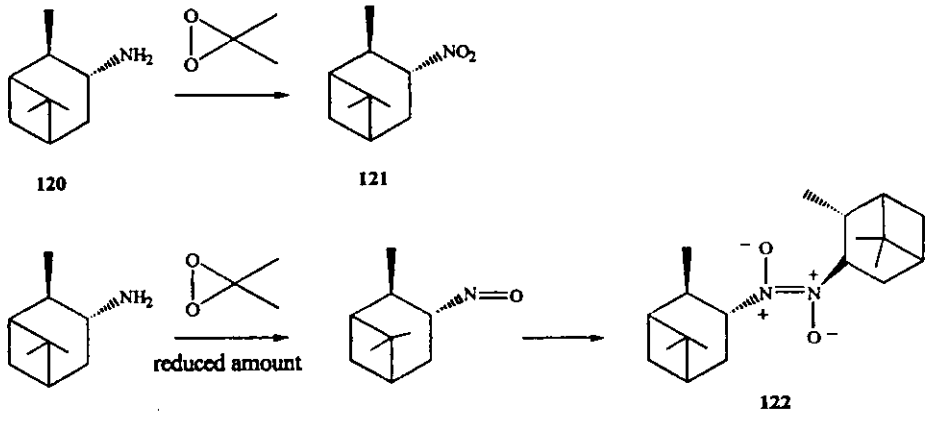
The mechanism shown in Scheme 63 has been suggested, involving an electron transfer process for the dehydration of the hydroquinone to the quinone (path A). For the formation of dihdroxycyclo-hexenediones, the oxygen transfer steps of path B have been proposed.



Scheme 63 : Proposed mechanism for the oxidation of hydroquinones using dimethyldioxirane

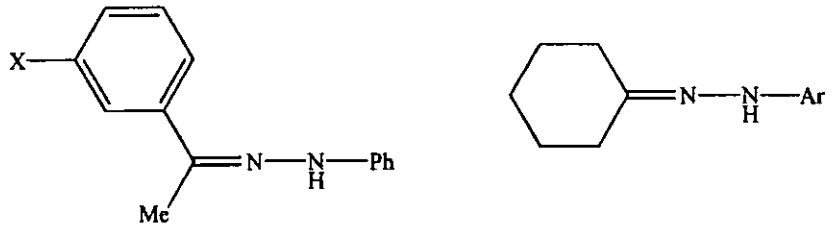
The mechanism of the oxidation of primary amines to nitro compounds has received relatively little atttention. Murray suggested that this transformation goes through a series of individual oxygen atom transfers (Scheme 18) which could involve an insertion reaction of the dioxirane into an N-H bond in a manner analogous to the C-H insertion reaction of dimethyldioxirane or alternatively, since dimethyldioxirane is known to be an electrophilic reagent, the reaction could proceed to give N-oxy type intermediates which could, for example, quickly rearrange to a hydroxylamine in the first step. To investigate this, Murray *et al* oxidised the chiral amines, (+) and (-)-isopinocampheylamine, with dimethyldioxirane to give the corresponding nitro compounds **121** with retention of configuration at the amine-bearing carbon atom.[115] When lower amounts of dimethyldioxirane were used, the amines gave the nitroso dimers **122** as the major products. Treatment of the nitroso dimer from the (-)-amine **120** with additional dimethyldioxirane gave the same nitro compound as obtained from the amine oxidation, indicating that no racemisation was occurring. To further illustrate this, Murray

also synthesised the oxime of the nitroso intermediate and showed that it does not tautomerize under the reaction conditions. Murray concluded that his results were consistent with either a series of N-H insertion reactions or a succession of oxygen transfers to the nitrogen followed by hydrogen atom transfer and not with the intervention of tautomerization in an intervening nitroso compound. Given the results of Adam and Golsch[111], Murray favoured a mechanism involving a series of nucleophilic displacements, believing both a radical process and an N-H insertion reaction to be unlikely.



Scheme 64 : Oxidation of (-)-isopinocampheylamine usimg dimethyldioxirane

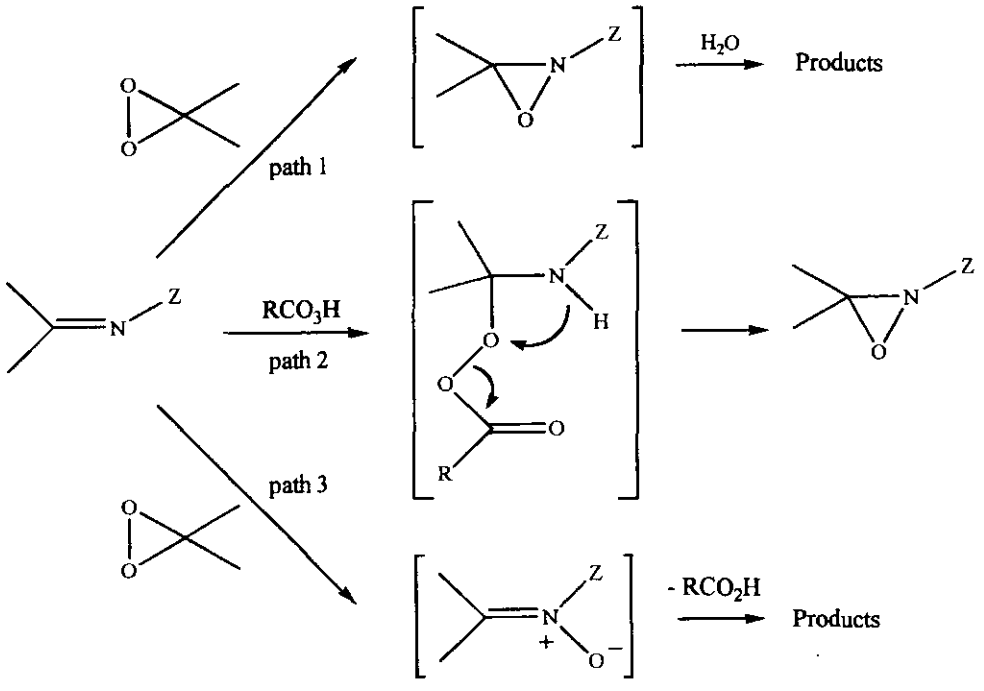
The oxidative cleavage of hydrazones by dimethyldioxirane to give the corresponding ketones is also believed to go via a polar mechanism.[73] Electron withdrawing nitro groups on the phenyl substituent either at the $Ph(CH_3)C{=}N$ moiety of acetophenone phenzylhydrazone **123** or at the nitrogen end of cyclohexanone phenylhydrazone **124** have been shown to have a rate retarding effect.



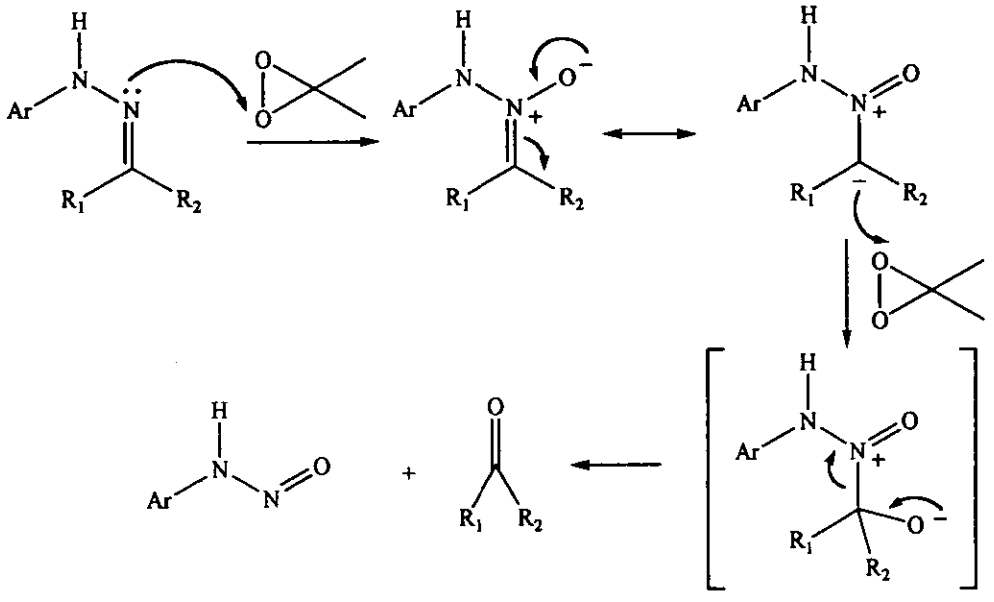
123 **124**

Competitive kinetic experiments showed that the oxidative cleavage of *m*-nitroacetophenone phenylhydrazone (x = NO_2) by dimethyldioxirane is ~1.7 times slower than that of acetophenone

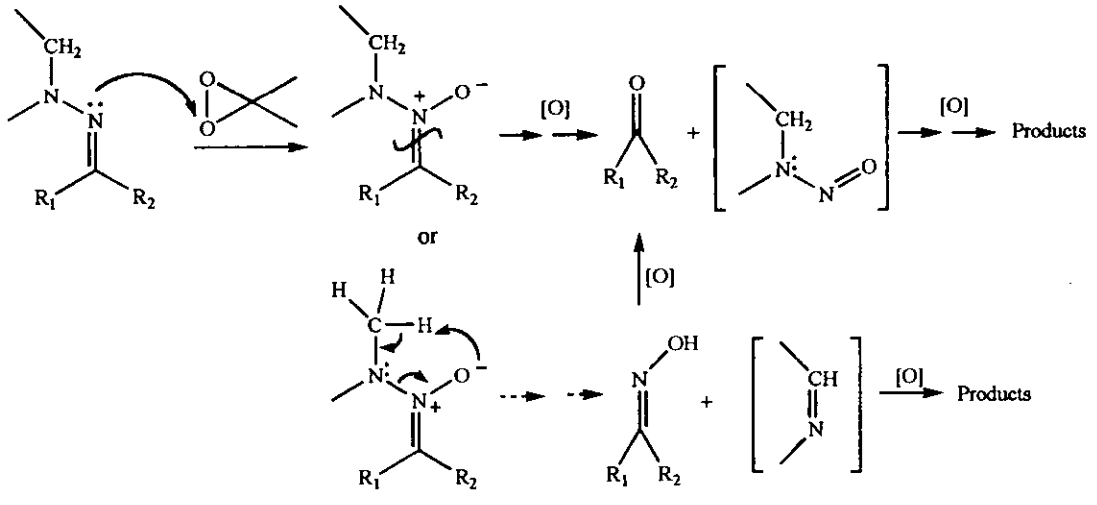
phenylhydrazone (x = H). This demonstrates that the dioxirane acts as an electrophilic oxidant which is reinforced by the observation that the oxidation of more electron-rich hydrazones requires considerably shorter reaction times. Concerning the reaction mechanism, it was at first thought that the cleavage occurred via the oxaziridine (path 1, Scheme 65, Z = NR'R"). However, this is unlikely since formation of oxaziridine from imines, Z = R, normally requires nucleophilic oxidation via an addition-elimination mechanism akin to that envisaged for the peracid conversion (path 2). Furthermore, dioxirane oxidaton of imines has been shown to yield nitrones. Also the cleavage of oximes (Z = OH) by dioxiranes is thought to proceed by direct N-oxidation at the oxime nitrogen (path 3). It is therefore proposed that the oxidative cleavage of hydrazones by dioxiranes initiates with direct electrophilic oxygen transfer to the nitrogen. For aryl hydrazones, the cleavage is envisaged to follow the sequence outlined in Scheme 66. Carbonyl generation is faster with N,N-dialkylhydrazones that N-arylhydrazones, but with dialkylhydrazones, an oxime by-product is formed. The sequence shown in Scheme 67 has been suggested to accommodate this, although a one-electron oxidation pathway has not been ruled out (Scheme 68).



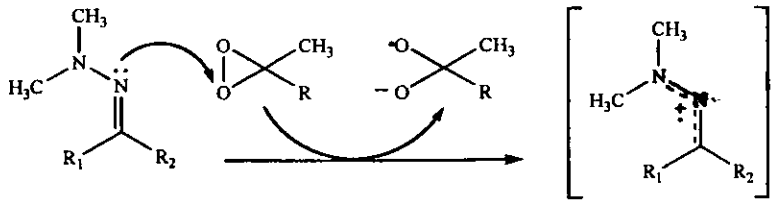
Scheme 65



Scheme 66 : Oxidative cleavage of aryl hydrazones using dimethyldioxirane



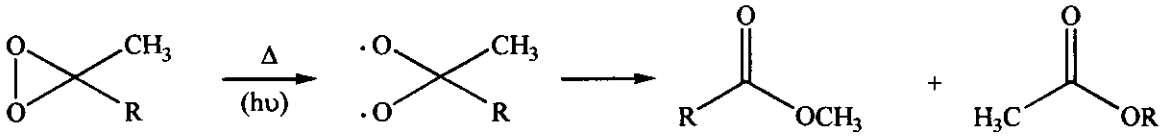
Scheme 67



Scheme 68

1.5 DECOMPOSITION OF DIOXIRANES

There has been much debate about the mechanism of decomposition of dioxiranes. Rearrangement into esters represents a main pathway (Scheme 69) and although the thermal decomposition of dimethyldioxirane is complex, methyl acetate is normally the main decomposition product.[99b] Methyl trifluoroacetate is produced in the thermal and photochemical decompostition of methyl-(trifluoromethyl)dioxirane,[99a] and these products are thought to be the result of rearrangement of the intermediary bis(oxyl)diradical **89**.



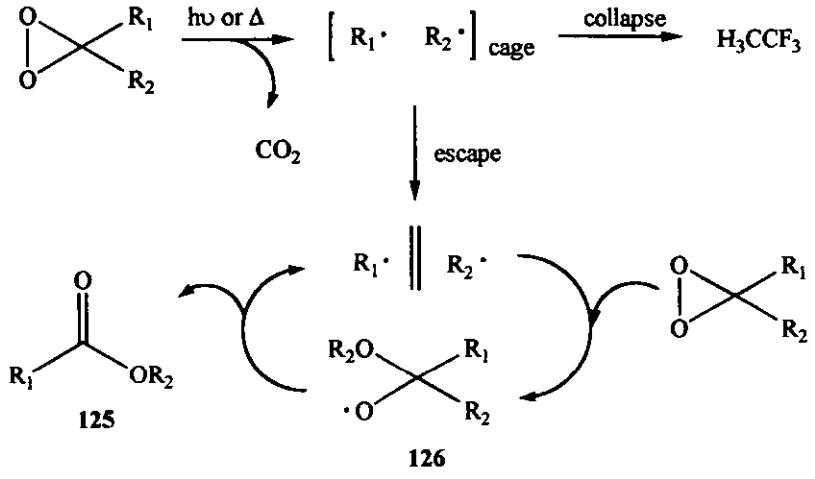
R = CH_3, CF_3 **89**

Scheme 69

The availability of ketone-free solutions of methyl(trifluoromethyl)dioxirane has facilitated the study of this complex free radical process. Adam and Curci carried out investigations into the thermal and photochemical decomposition of methyl(trifluoromethyl)dioxirane in gas, solution and matrix phases.[99a] It was proposed that both gas and liquid phase photolyses and thermal liquid phase decomposition of methyl(trifluoromethyl)dioxirane involve a radical chain process, initiated by attack of methyl and trifluoromethyl radicals on methyl(trifluoromethyl)dioxirane to give α-alkoxy-substituted alkoxy radicals as intermediates which go on to form esters **125a-d**.

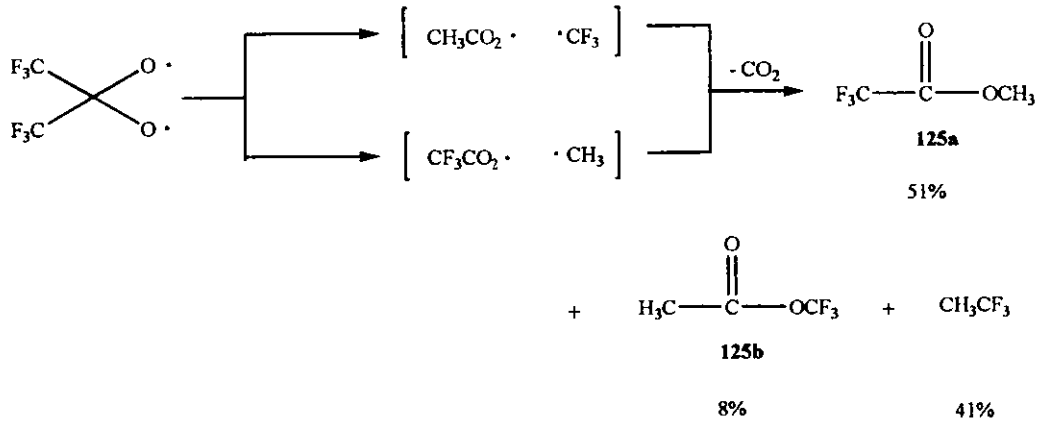
This radical chain process does not operate to any degree in the matrix phase photolysis of methyl-(trifluoromethyl)dioxirane, which gives methyl trifluoroacetate **125a** and 1,1,1-trifluoroethane as the main products (Scheme 71).

More recently, following Minisci's work[90] on the oxidation of adamantane in the presence of CCl_3Br and his own subsequent studies[98] on the triggering of free radical reactivity of dimethyldioxirane, Curci modified the process established for the thermal decomposition of dioxirane to that shown in Scheme 72.[98]

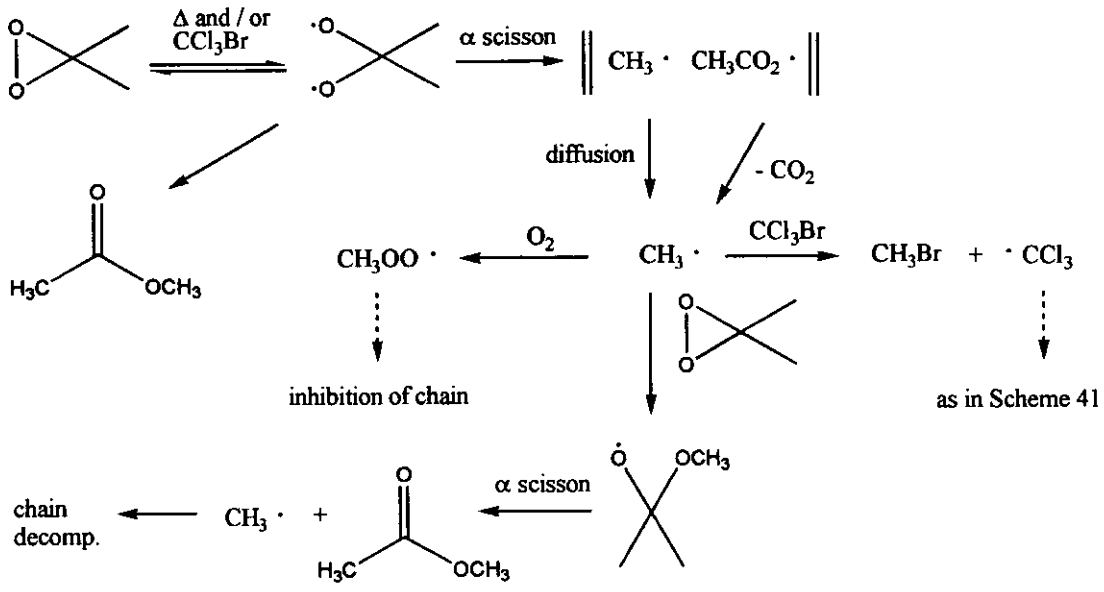


	125a	125b	125c	125d	126a	126b
R_1	CF_3	CH_3	CH_3	CF_3	CF_3	CH_3
R_2	CH_3	CF_3	CH_3	CF_3	CH_3	CF_3

Scheme 70 : Gas and liquid phase photolyses and thermal liquid phase decomposition of methyl(trifluoromethyl)methyldioxirane

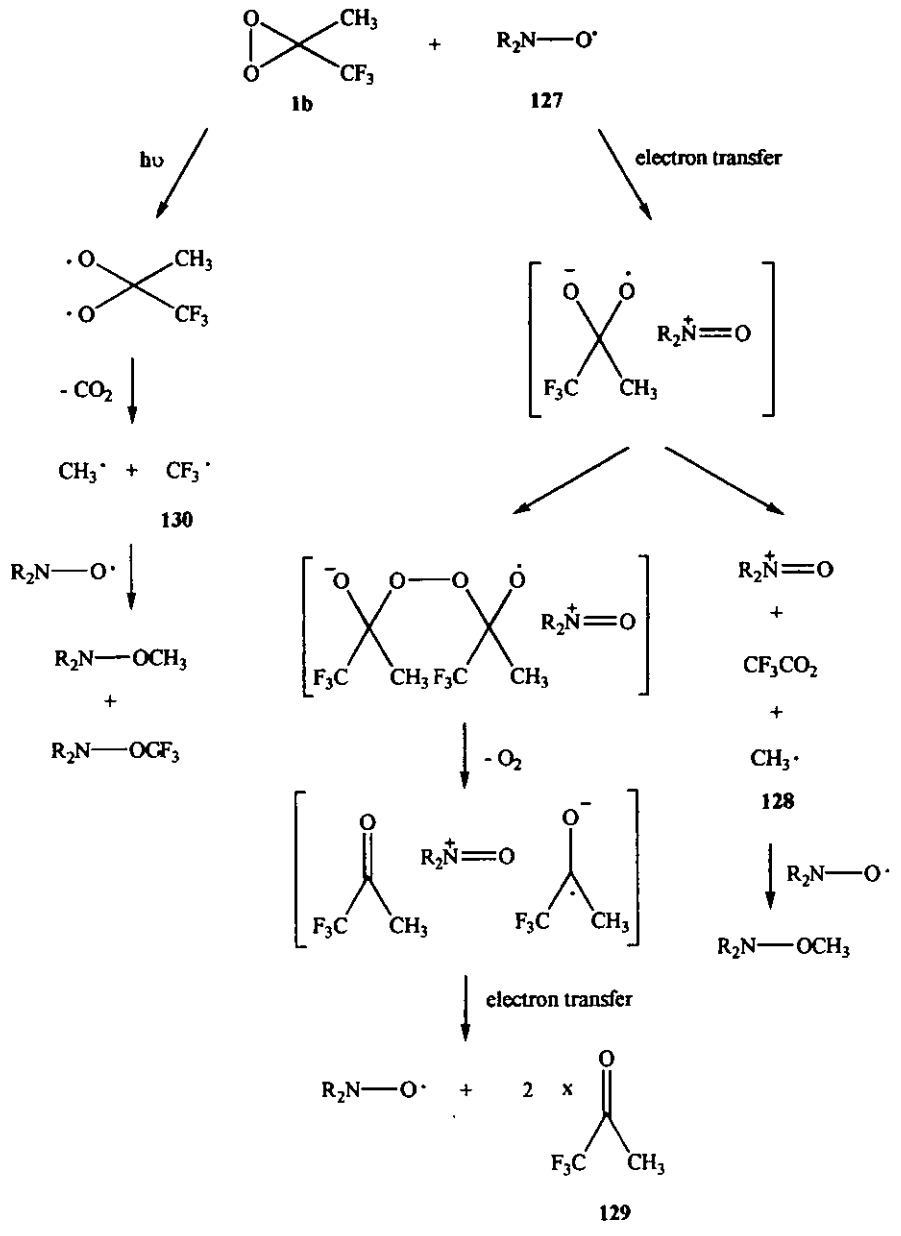


Scheme 71 : Matrix phase photolytic decomposition of methyl(trifluoromethyl)dioxirane



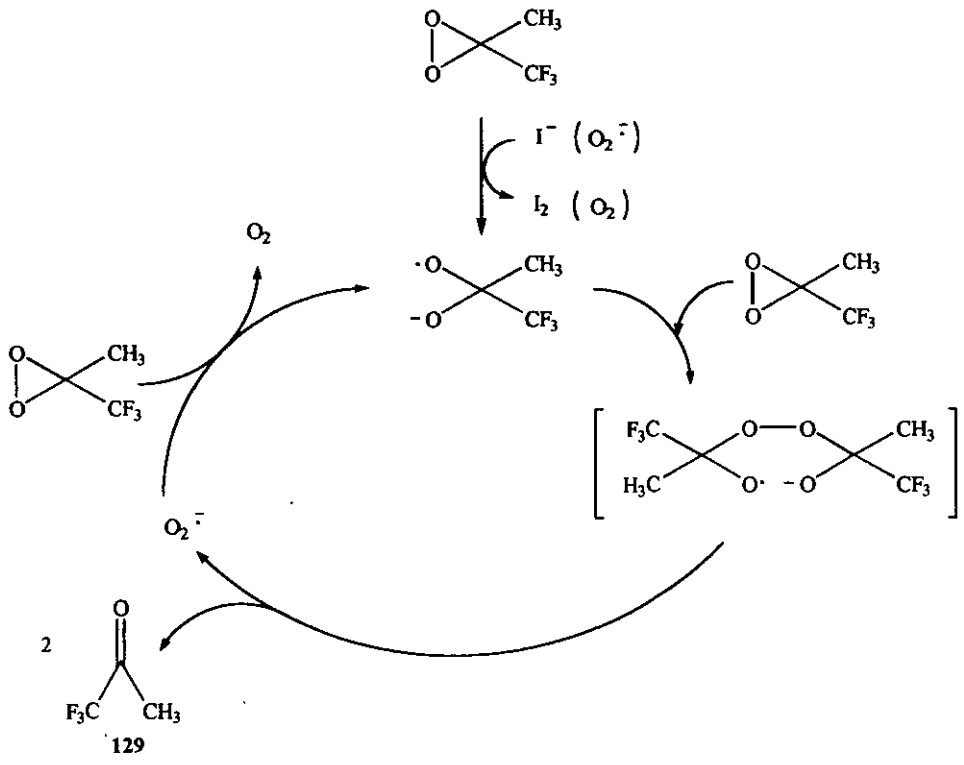
Scheme 72 : Thermal decomposition of dioxirane

In an earlier study by Adam,[84c] using nitroxides, it was proposed that methyl(trifluoromethyl)-dioxirane may act as a one electron acceptor leading to trifluoroacetone **129**. Methyl(trifluoro-methyl)dioxirane reacts with a nitroxide **127** to produce methyl radicals **128** which are readily trapped by the nitroxide radical scavenger (Scheme 73). However, photolysis of methyl(trifluoro-methyl)dioxirane with $\lambda > 300$nm in the presence of a nitroxide involves a completely different mechanism with trifluoromethyl radicals **130** also being produced (Scheme 73). The photolysis affects the dioxirane directly by inducing both methyl and trifluoromethyl cleavage and the electron transfer process is a minor side process. However, in the absence of light, the dioxirane radical anion, produced by electron transfer between dioxirane and nitroxide, predominantly generates the radicals. This non-photolytic production of methyl radicals, as detected by nitroxide trapping, represents an unusual pathway for these species and this electron transfer process is not only mechanistically important but also synthetically important, especially in view of the preparation of nitroxides from secondary amines by oxidation with dioxiranes. It is recommended therefore that dimethyldioxirane should be used for such oxidations.



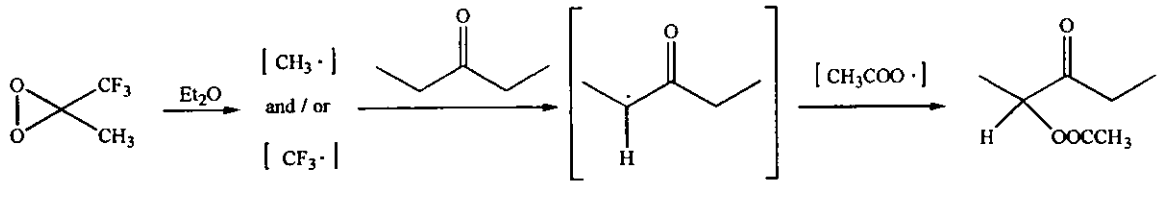
Scheme 73 : Reaction of methyl(trifluoromethyl)dioxirane with nitroxides in the presence and absence of light

In another study by Adam and Curci, again using ketone-free solutions, the ability of dioxirane to act as a one electron acceptor was established.[84d] This was achieved by investigating the reduction of methyl(trifluoromethyl)dioxirane with iodide ion - a one electron reductant which does not undergo oxygen transfer by the dioxirane. An electron transfer chain reaction mediated by the superoxide anion was proposed (Scheme 74) leading to the conversion of methyl(trifluoromethyl)dioxirane into trifluoroacetone and dioxygen.



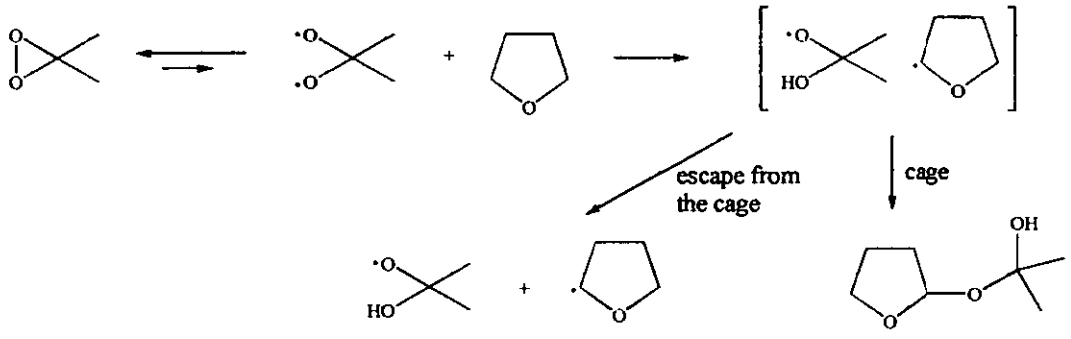
Scheme 74 : Reduction of methyl(trifluoromethyl)dioxirane with iodide ion

It has been reported by Messeguer *et al* that ethers can induce the free radical decomposition of dimethyldioxirane.[116] In the presence of 3-pentanone, the formation of 2-acetyloxy-3-pentanone was explained by the free radical mechanism (Scheme 75) which had previously been suggested for the thermal decomposition of dimethyldioxirane in the presence of ketones.[99b] It was not certain whether the radical species which induce the decomposition originate from the ether itself or from a product derived from its oxidative cleavage.



Scheme 75 : Proposed ether-induced decomposition of dimethyldioxirane

However, Minisci *et al*[85] reported this mechanism to be inconsistent with rate constant data[117] and a free radical mechanism had also been excluded for the oxidation of ethers by dimethyldioxirane[118] due to the high selectivity for a C-H bonds and the assumption that all the oxygen-centred radicals must have similar selectivity. The Minisci group however, as already mentioned, do not agree with this assumption, therefore to obtain evidence about the mechanism of this oxidation, they attempted to trap the possible intermediate carbon-centred radicals by protonated quinolines, which represents a powerful diagnostic criterion for the interception of nucleophilic free radicals.[85] They concluded that methyl and ethyl, and respectively methyl and α-tetrahydrofuranyl, radicals are certainly formed in the oxidation of diethyl ether and tetrahydrofuran by dimethyldioxirane, explained by the free radical mechanism of Scheme 76.



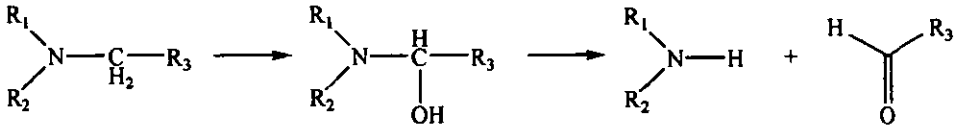
Scheme 76 : Proposed mechanism of oxidation of diethyl ether and tetrahydrofuran by dimethyldioxirane

1.6 INTRODUCTION TO THE PROJECT

It can be seen from the discussion above that the use of dioxiranes in organic synthesis can be extremely advantageous due to the high regio- and stereoselective oxyfunctionalisations which can be attained. However, much work remains to be done in order to fully understand the intricate mechanistic aspects of dioxirane oxidations.

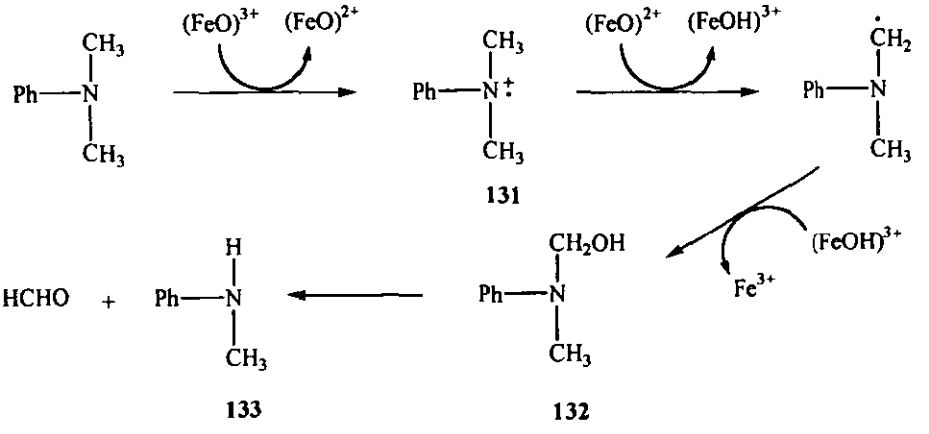
There were several areas of dioxirane chemistry which were of particular interest to us. At the outset of the project, we were interested in exploring the potential use of dioxiranes in studies of oxidative degradation of nitrogenous drugs, particularly tertiary amines, with a view to providing a greater understanding of these processes and possibly developing a biometic procedure to be used

in the testing of new and existing drugs. Oxidative dealkylation is a common pathway in the metabolism of tertiary amines. *In vivo* the reaction is mediated by cytochrome P450 enzymes and has an absolute requirement for both molecular oxygen and NADPH. The pathway goes via an unstable intermediate which dissociates to give the dealkylated amine.



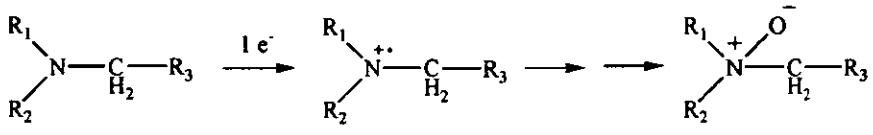
Scheme 77 : The metabolic pathway of tertiary amines

Amine oxidations are important in the metabolism of both chemicals endogenous to cells and those introduced as drugs, pesticides etc. Not only do biomimetic models help in the prediction of metabolites, some of which may prove to be carcinogenic, but they are also indispensible for the development of pro-drugs. Biomimetic models also provide a route for the synthesis of large quantities of metabolites which would be difficult to isolate solely from tissue and / or urine.
The mechanism of the N-dealkylation of tertiary amines by cytochrome P450 enzymes has been widely investigated and is believed to involve stepwise electron transfer and base catalysis. A current view of the mechanism is shown in Scheme 78.[119] A porphyrin $(FeO)^{3+}$ complex is formed which is involved in a one electron oxidation to give an aminium radical **131**. Abstraction of an α hydrogen atom with base catalysis follows and radical recombination then generates an oxidised product **132** and Fe^{3+} which leads to the final dealkylated product **133**.



Scheme 78 : Mechanism of N-dealkylation of tertiary amines by cytochrome P450s

P450s can lead to the formation of N-oxides but these are not favoured whenever N-dealkylation is possible, i.e. when α protons are accessible. However if the previous scheme (Scheme 78) involving one electron oxidation is valid then some partitioning of aminium radicals between N-oxygenation and N-dealkylation might be expected. In fact this has found to be the case and some N-oxide is formed even in the presence of accessible α protons.[120] The aminium radical is formed as before but then follows a different pathway to give the N-oxide (Scheme 79). This is more complex than a direct transfer of oxygen to the aminium radical and several possible mechanisms have been postulated.[120] The ratio of N-dealkylation to N-oxygenation varies by 200-fold depending on the structure of the substrate.



Scheme 79 : N-oxidation mediated by cytochrome P450s

The initial aim of the project was to investigate whether it would be possible to mimic the N-dealkylation reactions of the P450 enzymes using dimethyldioxirane as the oxidant. It is reported that tertiary amines undergo N-oxygenation when reacted with dimethyldioxirane via a polar mechanism but, as discussed in the previous section, it is apparent that in some instances dioxiranes will react via alternative free radical / electron transfer pathways. The possibility of changing the course of the reaction by employing certain conditions, for example, heat, light or even transition metal catalysis, and hence induce a reaction which mimics that of the P450 enzymes, was therefore to be investigated.

While reviewing the dioxirane literature, it was found that little work has been done on the oxidation of non-pyridine based tertiary amines by dioxiranes and although it is presumed that the mechanism is straightforward S_N2, the exact nature of this oxygen transfer reaction had not been defined in these particular substrates. This prompted us therefore to begin our work with a study of the oxidation of simple tertiary amines.

Chapter 2 begins by describing the results of a competitive study of the relative rates of oxygen transfer to a series of *para*-substituted N,N-dimethylanilines and the subsequent application of the Hammett relationship to these results. This work has recently been published.[121] An investigation into the dimethyldioxirane oxidation of the same series of N,N-dimethylanilines under various

different reaction conditions then follows. The conditions employed were:

1. 0-5°C / dark
2. room temperature / daylight
3. in the presence of water
4. at reflux
5. photochemical

In each case, the products obtained were carefully monitored and any evidence of dealkylation versus N-oxidation was noted. In addition, the dimethyldioxirane oxidation of a similar series of N,N-dimethylbenzylamines was carried out to investigate the effect if any of the benzylic methylene group.

Chapter 3 investigates the regioselectivity of the dimethyldioxirane oxygen transfer reaction in the oxidation of polyfunctionalised nitrogenous drugs to assess the potential of using dimethyl-dioxirane as a simple, easy to use reagent in oxidative degradation studies.

Chapter 4 investigates the regioselectivity of the dimethyldioxirane oxygen transfer to polyhydroxy steroids. The products obtained when several bile acid methyl ester derivatives were oxidised with one or two equivalents of dimethyldioxirane were determined and any selectivity shown by the dioxirane noted.

Finally, chapter 5 describes the development of an *in situ* Oxone®-mediated epoxidation method using 4-(trifluoroacetyl)benzoic acid as the dioxirane precursor. This work has also recently been published.[177]

Chapter 2

OXIDATION OF TERTIARY AMINES USING DIMETHYLDIOXIRANE

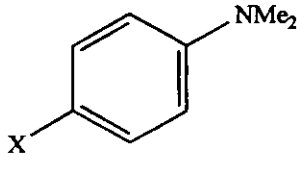
2.1 INTRODUCTION

The aim of the work described in this chapter was to investigate the nature of the dimethyldioxirane oxidation of a series of simple tertiary amines in an attempt to further probe the mechanism of these oxidations and explore the possibility of substituent-induced and reaction condition-induced changes of mechanism.

Adam reported that when oxidised by dimethyldioxirane, nitrogen heteroarenes give the N-oxide by an electrophilic S_N2 mechanism.[111] However, in many dioxirane oxygen transfer reactions, free radical or electron transfer mechanisms cannot be completely ruled out and it is known that the breakdown of dioxiranes into radical species can be promoted by thermal and photochemical means.[99] The following work investigates whether the reaction of dimethyldioxirane with simple tertiary amines is indeed electrophilic or whether there is a possibility that electron transfer or free radical species are involved.

2.2 RELATIVE RATE STUDY ON THE OXYGEN TRANSFER BY DIMETHYLDIOXIRANE TO A SERIES OF N,N-DIMETHYLANILINES

The results of a study of the relative rates of oxygen transfer by dimethyldioxirane to the nitrogen of several N,N-dimethylanilines **134** are described. The rates obtained for the dimethyldioxirane reaction were then compared to the relative rates obtained for methyl iodide methylation, benzoyl peroxide oxidation and t-butyl hydroperoxide oxidation.

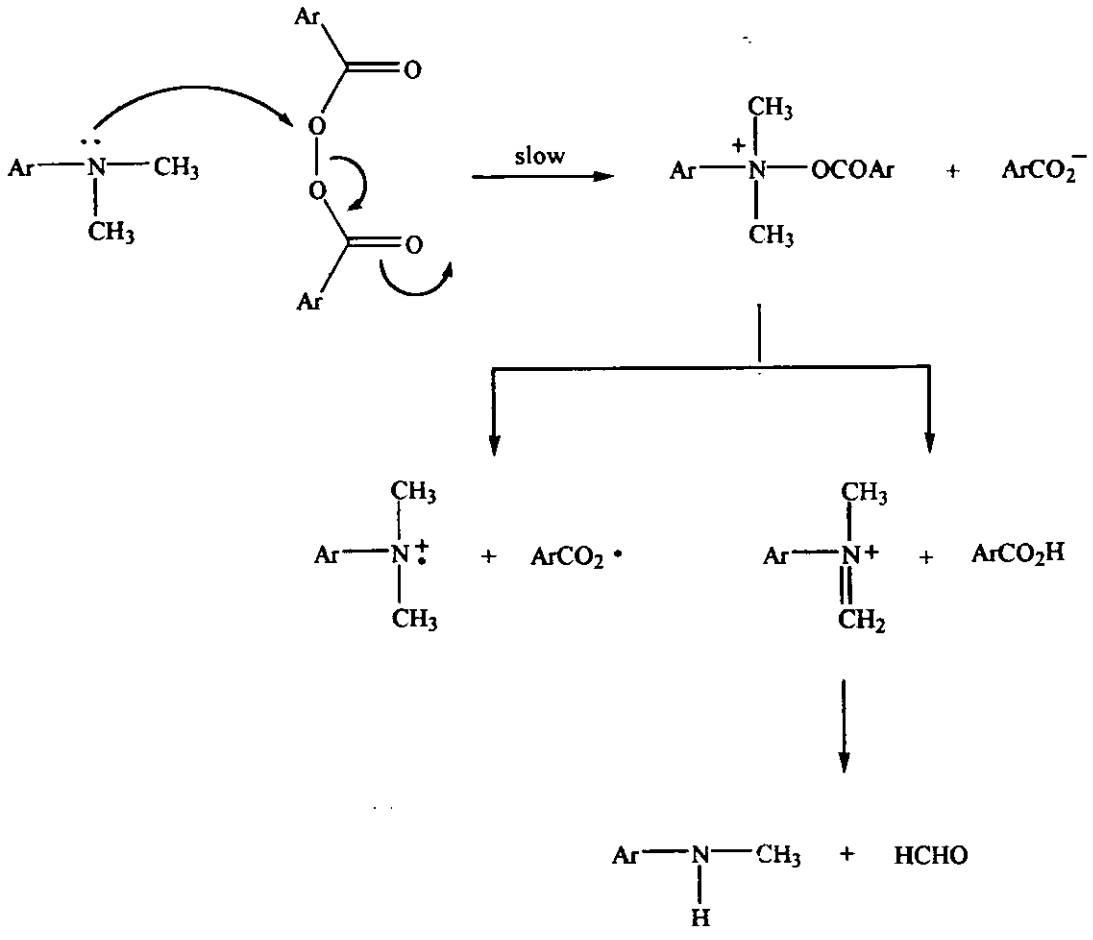


X = H
MeO
Cl
NO_2

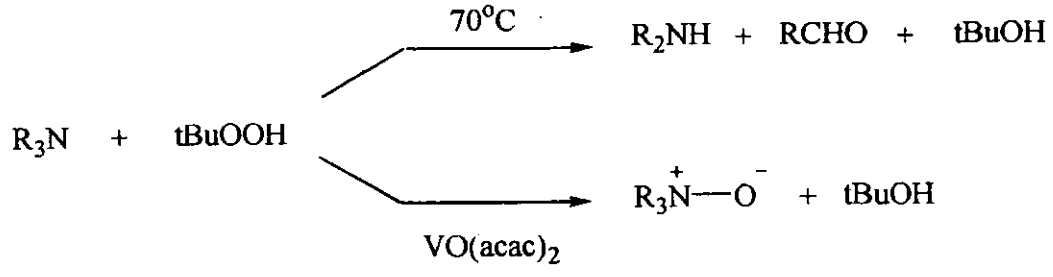
134

Methyl iodide was used as a comparison because it reacts with tertiary amines via a well established S_N2 mechanism[122] We thought it would also be interesting to compare dimethyldioxirane with other peroxides. Benzoyl peroxide and t-butyl hydroperoxide were chosen because, like dimethyl-dioxirane, both are neutral peroxides. (Acidic peroxides may cause protonation of the aniline and so affect the rate and mechanism of reaction.) Benzoyl peroxide dealkylates tertiary amines and provides another comparison to an S_N2 type mechanism as its rate-determining step is known to be electrophilic.[123] It goes via attack by the peroxide on the amine to give a quaternary hydroxyamine derivative which goes on to form the dealkylated product (Scheme 80). The rest of the mechanism is complicated by two competing pathways - one ionic and one radical, however it is the rate-determining step which is important in this study. t-Butyl hydroperoxide also dealkylates tertiary amines but is thought to react via a homolytic process involving t-butoxy radicals.[124] t-Butyl hydroperoxide was also used in the presence of a vanadium catalyst which leads to N-oxidation rather than dealkylation (Scheme 81).[125]

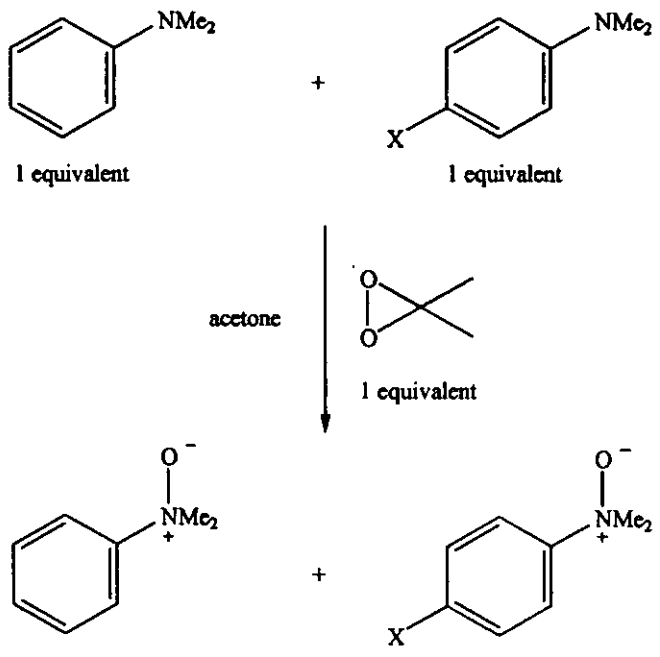
The relative rates of N-oxidation were determined by carrying out a series of competition reactions using N,N-dimethylaniline as the reference substrate in each case. The substrates are all sterically identical around the nitrogen so the only factor affecting the rate of reaction is the electron demand of the *para* substituent, unlike in Adam's study[111] where methyl and benzo substitution in the proximity of the nitrogen heteroatom hindered the oxygen transfer by the dioxirane to some substrates and so these had to be excluded when correlating the results.
The basic procedure for the competition reactions is outlined in Scheme 82. One equivalent of *para*-substituted N,N-dimethylaniline was taken with one equivalent of the unsubstituted N,N-dimethylaniline in an acetone solution and one equivalent of dimethyldioxirane added. The reactions were run at 0-5°C for approximately 6 hours before being allowed to slowly warm to room temperature overnight, thus ensuring total consumption of the dimethyldioxirane.
Relative rates of reaction were determined by monitoring the consumption of the starting materials by HPLC. Each reaction was carried out in duplicate as was each HPLC determination. This procedure was repeated using all three substituted anilines. In each case, the N-oxide was the only product and no evidence was found for dealkylation. The reactions of dimethyldioxirane with the individual N,N-dimethylanilines were carried out to confirm this and the products obtained compared with N-oxides prepared using performic acid[126] (see section 2.3.1).



Scheme 80 : Oxidation of tertiary amines by benzoyl peroxide



Scheme 81 : Oxidation of tertiary amines by t-butyl hydroperoxide

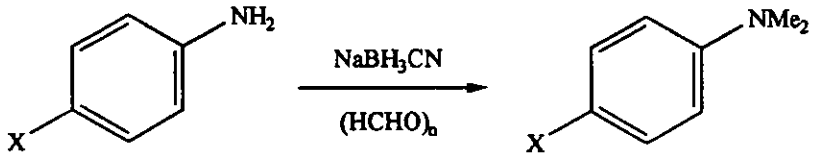


Scheme 82 : Basic outline of the procedure used in the N,N-dimethylaniline competition reactions

The competition reactions using methyl iodide, benzoyl peroxide, t-butyl hydroperoxide and t-butyl hydroperoxide in the presence of vanadyl acetylacetonate were carried out in the same way at 0-5°C and continued to completion. The t-butyl hydroperoxide reaction was also carried out at 70°C as this is the more usual temperature to carry out dealkylations of tertiary amines using this reagent.[123]

2.2.1 Preparation of N,N-dimethylanilines

N,N-dimethylaniline and N,N-dimethyl-4-nitroaniline are commercially available but the chloro and methoxy derivatives had to be prepared from the corresponding primary amine. The Eschweiler-Clarke procedure[127] using formic acid and formaldehyde was unsuccessful. Bulb-to-bulb distillation and column chromatography did not clean up the crude products sufficiently. An alternative procedure using paraformaldehyde and sodium cyanoborohydride was therefore used.[128] The structures were confirmed by comparison with literature data.[178,179]



Scheme 83 : N-methylation of *para*-substituted anilines

2.2.2 Calculation of the relative reactivity rates

N,N-Dimethylaniline N-oxides are very hygroscopic and decompose fairly readily. It was felt that isolating the unreacted anilines from the reaction mixture would not give a true ratio. It was therefore decided that direct sampling of the reaction mixture and analysis by HPLC was the best way to monitor these reactions, in spite of the time required to develop a suitable method.
GC was found to be unsuitable as the N-oxides were not able to withstand the high temperatures involved and were found to decompose in the injection port. Proton NMR spectroscopy was also considered unsatisfactory as, although sufficient separation of the four components in the reaction mixture was achieved, the risk of decomposition during concentration *in vacuo* still existed.

A brief summary of the HPLC conditions used is given below. A full description of the method development can be found in Appendix I. The HPLC system was recalibrated at regular intervals throughout this work.

Chromatographic Conditions

Column	:	μ Bondapak C18 10 micron 300 x 3.9 mm
Eluent	:	60% methanol / 40% water (when using nitro- and chloroanilines)
		50% methanol / 50% water (when using methoxyaniline)
Flow rate	:	1 ml /min
Wavelength	:	245nm
Injection volume	:	20μl

Using this method, it was possible to detect only the parent N,N-dimethylanilines and not the corresponding N-oxides as the latter were eluted extremely rapidly with the solvent front. It was

therefore decided to determine the relative rates of reaction of the N,N-dimethylanilines by simply monitoring consumption of the starting materials.

In order to do this, a calibration graph of observed ratio versus actual ratio for a series of standard solutions containing varying known ratios of reference substrate and substituted N,N-dimethyl-aniline was constructed (for further details, see Appendix II). This enabled the ratio of the peak areas of the starting materials remaining at the end of the reaction, obtained directly from the chromatogram, to be converted to an actual ratio. In order to then convert this ratio into a relative rate the percentage conversion of the reaction must be known. All the competition reactions were run to completion, ensuring total consumption of the reagent, thus allowing 50% conversion to be assumed. The reactivity rate of the unsubstituted aniline was given the arbitary value of 1 and the other rates calculated relative to this by simply taking the reciprocal of the ratio of the unreacted anilines (for further explanation, see Appendix II).

2.2.3 Competition reaction results

Competition reactions were carried out on the N,N-dimethylaniline / substituted N,N-dimethyl-aniline pairs using dimethyldioxirane, methyl iodide, benzoyl peroxide and tert-butyl hydroperoxide. The reactions using t-butyl hydroperoxide were also carried out at 70°C and in the presence of a vanadium catalyst (0.025 equivalents of vanadyl acetylacetonate). A stock solution of 1 equivalent of N,N-dimethylaniline and 1 equivalent of substituted N,N-dimethylaniline in acetone was prepared and aliquots of this solution used for all these reactions. The reactions were sampled at various time intervals. In each case it was ensured that the reaction was continued to completion by testing for any remaining oxidant with starch-iodide paper. The results of these reactions are summarised in Tables 1-4 and the mean relative rates obtained for each reaction are shown in Table 5.

Table 1

Relative rates obtained for the various substitued N,N-dimethylanilines using dimethyldioxirane and methyl iodide at 0-5°C. Reactions sampled after 10 minutes, 1 hour and16 hours.

substituent	reaction	determination	relative reactivity rate					
			dimethyldioxirane			methyl iodide		
			10 mins	1 hour	16 hours	10 mins	1 hour	16 hours
NO_2	1	1	0.19	0.19	0.20	0.75	0.74	0.57
		2	0.18	0.18	0.20	0.78	0.74	0.55
	2	1	0.26	0.27	0.25	0.77	0.72	0.77
		2	0.25	0.27	0.27	0.77	0.74	0.69
Cl	1	1	0.39	0.39	0.38	0.97	0.93	0.68
		2	0.40	0.41	0.38	0.93	0.92	0.68
	2	1	0.32	0.34	0.31	0.92	0.91	0.72
		2	-	0.33	0.30	0.93	0.93	0.72
MeO	1	1	2.86	2.70	2.33	1.01	1.05	5.00
		2	2.86	-	2.50	1.02	1.06	4.17
	2	1	3.13	2.86	2.70	1.02	1.04	2.63
		2	3.03	3.03	2.78	1.11	1.05	2.78

Table 2

Relative rates obtained for the various substitued N,N-dimethylanilines using benzoyl peroxide at 0-5°C. Reactions sampled after 1 hour, 16 hours, 48 hours and 72 hours.

substituent	reaction	determination	relative reactivity rate			
			benzoyl peroxide			
			1 hour	16 hours	48 hours	72 hours
NO_2	1	1	0.91	0.14	0.05	-
		2	0.80	0.14	-	-
	2	1	0.81	0.08	0.03	-
		2	0.79	0.07	0.02	-
Cl	1	1	0.87	0.15	0.10	0.08
		2	0.85	0.08	0.05	0.05
	2	1	0.87	0.10	0.05	0.05
		2	0.74	0.07	0.06	
MeO	1	1	28.57	no methoxy-aniline remaining	-	-
		2	40.00		-	-
	2	1	14.29		-	-
		2	-		-	-

Table 3

Relative rates obtained for the various substitued N,N-dimethylanilines using t-butyl hydroperoxide at 0-5°C.
Reactions sampled after 1 hour, 16 hours, 48 hours, 72 hours and 96 hours.

substituent	reaction	determination	relative reactivity rate t-butyl hydroperoxide				
			1 hour	16 hours	48 hours	72 hours	96 hours
NO_2	1	1	0.96	0.99	0.99	-	0.96
		2	1.00	0.96	0.96	-	1.00
	2	1	1.01	0.88	0.99	-	0.84
		2	1.02	0.91	0.86	-	0.84
Cl	1	1	0.88	0.91	0.85	0.85	-
		2	0.87	0.93	0.86	0.86	-
	2	1	1.04	0.93	0.87	0.86	-
		2	0.94	0.93	0.88	0.87	-
MeO	1	1	1.18	1.20	-	-	1.18
		2	1.27	1.25	-	-	1.25
	2	1	1.25	1.20	-	-	1.09
		2	1.33	1.24	-	-	1.27

Table 4

Relative rates obtained for the various substitued N,N-dimethylanilines using t-butyl hydroperoxide at 70°C and in the presence of a vanadium catalyst.
Reactions sampled after 15 minutes, 1.5 hours, 4.75 hours (70°C reactions only) and 16 hours.

substituent	reaction	determination	relative reactivity rate						
			t-butyl hydroperoxide 70°C				t-butyl hydroperoxide + $VO(acac)_2$		
			15 mins	1.5 hrs	4.75 hrs	16 hrs	15 mins	1.5 hrs	16 hrs
NO_2	1	1	1.02	1.00	1.00	-	0.47	0.36	-
		2	1.08	1.02	0.91	-	0.55	0.39	-
	2	1	0.49	0.63	0.77	0.45	0.45	0.46	-
		2	0.65	0.48	0.36	0.59	0.53	0.49	-
Cl	1	1	1.00	0.90	0.74	0.50	1.16	1.14	-
		2	1.02	0.93	0.74	0.36	1.16	1.14	-
	2	1	1.02	-	-	0.61	1.16	1.10	-
		2	1.03	-	-	0.60	1.18	1.12	-
MeO	1	1	0.84	0.80	0.88	0.90	0.90	0.94	-
		2	0.84	0.83	0.87	0.89	0.85	0.94	-
	2	1	0.84	0.85	0.85	0.90	0.94	1.12	1.11
		2	0.84	0.85	-	0.88	0.93	1.09	1.09

Table 5

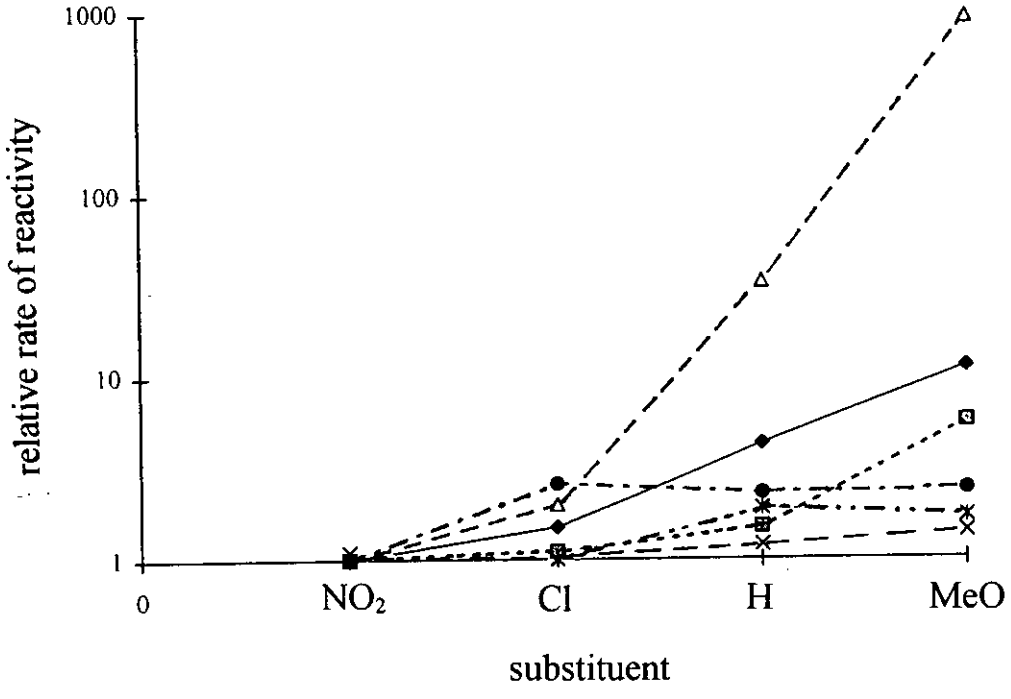
Mean relative rates obtained using dimethyldioxirane, methyl iodide, benzoyl peroxide and t-butyl hydroperoxide.
All reactions run to completion.

substituent	mean relative rate					
	dimethyl dioxirane 0-5°C	methyl iodide 0-5°C	benzoyl peroxide 0-5°C	t-butyl hydroperoxide 0-5°C	t-butyl hydroperoxide 70°C	t-butyl hydroperoxide + $VO(acac)_2$
NO_2	0.23 ± 0.04	0.65 ± 0.10	0.03 ± 0.02	0.91 ± 0.08	0.52 ± 0.10	0.43 ± 0.06
Cl	0.34 ± 0.04	0.70 ± 0.02	0.06 ± 0.02	0.86 ± 0.01	0.52 ± 0.12	1.13 ± 0.03
H	1.00 ± 0	1.00 ± 0	1.00 ± 0	1.00 ± 0	1.00 ± 0	1.00 ± 0
MeO	2.58 ± 0.20	3.65 ± 1.14	27.60 ± 12.88	1.19 ± 0.08	0.89 ± 0.01	1.03 ± 0.10

The results of the dimethyldioxirane reactions show a clear trend. The electron-withdrawing nitro substituent slows the rate of reaction relative to the unsubstituted aniline, as does the chloro substituent but to a lesser extent, and the electron-donating methoxy substituent increases it. This is a very similar pattern to that obtained with S_N2 methyl iodide methylation. The methoxy derivative gave a slightly increased rate with methyl iodide compared to dimethyldioxirane but in the case of the nitro derivative, the rate obtained with dimethyldioxirane is lower than that obtained with methyl iodide. In fact, the rate obtained for the reaction of the nitro derivative with methyl iodide is surprisingly high. It was expected that the nitro substituent would show a much greater retarding effect than the chloro substituent but this was not found to be the case. The trend however is consistent with an S_N2 mechanism. With benzoyl peroxide the difference in reactivity between the various substituents is even larger (a rate of 0.03 for the nitro derivative compared with 27.6 for the methoxy derivative) which fits with the assumption that the rate-determining step is polar.[123]
The t-butyl hydroperoxide reactions, believed to proceed via t-butoxy radicals, are less susceptible to change in substituent and the difference in reactivity is much less marked. All the substituents have similar reactivity, which is expected from reactions involving a radical mechanism.
These trends can be seen more clearly in Figure 5 which shows relative reactivity versus substituent for each reagent (for ease, the rates obtained in each set of reactions have been recalculated relative to the derivative with the lowest rate of reactivity which has been assigned a value of 1). All the reactions were run to completion, therefore the relative rate data obtained reflect a minimum difference in reactivity.

Figure 5

Graph showing the relative reactivity trends versus substituent for the reaction of various reagents with N,N-dimethylanilines in acetone at 0-5°C



dimethyldioxirane
methyl iodide
benzoyl peroxide
t-butyl hydroperoxide
t-butyl hydroperoxide (70°C)
t-butyl hydroperoxide + Vanadium catalyst

2.2.4 Further dimethyldioxirane competition reactions

The relative rate data described so far have been obtained by monitoring the consumption of starting material and were calculated using the ratio of anilines remaining at the end of the reaction.
The aim of repeating the dimethyldioxirane reactions was to confirm the trends seen previously by using alternative methods for determining the relative rates. This involved using a different HPLC system which enabled the accumulation of products to be monitored in addition to the loss in reactants (the development of such a system had been possible due to time spent on placement at SmithKline Beecham, Great Burgh). The use of external standards also allowed quantitative results to be obtained. A brief summary of the HPLC method used is given below. (For details of the method development which led to this new system, see Appendix I.)

Chromatographic Conditions

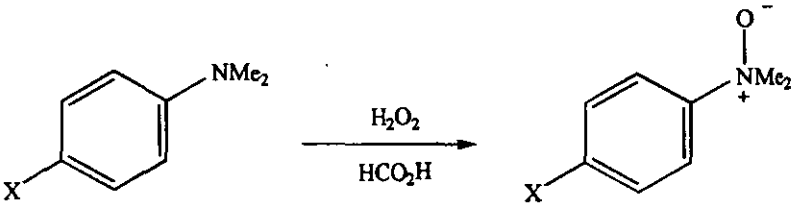
Column	:	Spherisorb S5 C1 15cm x 4.6mm
Eluent	:	0.05M phosphate buffer
		0.1% triethylamine
		pH 3.5 (when using nitro- and chloroanilines)
		pH 4 (when using methoxyaniline)
Flow rate	:	1 ml / min
Wavelength	:	210nm
Injection volume	:	2μl

The reactions were carried out in duplicate exactly as described previously. The reactions were sampled after 1 hour and 16 hours.

2.2.4.1 Preparation of standards

Standard samples of all four N,N-dimethylanilines and all four N,N-dimethylanilines N-oxides were required. The substituted N,N-dimethylanilines not commercially available were prepared as described in section 2.2.1. The N,N-dimethylaniline N-oxides were prepared using performic

acid.[126] These compounds are very hygroscopic and need to be stored under vacuum over phosphorus pentoxide. The N,N-dimethylaniline standards were analysed by ^{1}H and ^{13}C NMR and by HPLC and as a result were taken to be 100% pure. The N-oxides were found to be slightly less than 100% pure as their hygroscopic nature can lead to some difficulties in handling. Using NMR spectroscopy, HPLC analysis and moisture content data it was possible to asses the purity of each sample. The appropriate corrections were made in all subsequent calculations.



X = H, NO_2, Cl, MeO

Scheme 84 : Preparation of N,N-dimethylaniline N-oxides

2.2.4.2 Alternative methods for the calculation of the relative rates

It was decided to calculate the relative rates of reactivity for the following dimethyldioxirane reactions using four different methods and compare the results obtained with each. The first three methods are based on the amount of unreacted aniline remaining at the end of the reaction whereas the fourth considers the amount of N-oxide formed.

Method 1

This method is the one used in the previous experiments, i.e. a ratio of unsubstituted aniline to substituted aniline remaining at the end of the reaction is obtained using a calibration graph of observed ratio against actual ratio. The actual ratio is then converted into a relative rate by taking the reciprocal of the ratio, assuming 50% conversion.

Method 2

This method also involves obtaining a ratio of unsubstituted aniline to substituted aniline

remaining at the end of the reaction but this time by calculating the actual amounts of each aniline remaining using the N,N-dimethylaniline standards rather than a calibration graph. This ratio is then converted into a relative rate as in method 1, i.e. taking the reciprocal of the ratio, assuming 50% conversion.

Method 3

As in method 2, this method also uses the N,N-dimethylaniline standards to obtain the actual amounts of aniline and substituted aniline remaining at the end of the reaction, but rather than assuming 50% conversion, the relative rates are calculated using the equation given below, which makes no assumptions about the percentage conversion.[83]

$$k_{rel} = \frac{k_{\text{p-x aniline}}}{k_{\text{aniline}}} = \frac{\Delta C_{\text{p-x aniline}}}{\Delta C_{\text{aniline}}}$$

where ΔC = change in concentration of the reactants

Method 4

This method involves calculating the actual amount of each N-oxide produced using the N-oxide standards. This provides a direct indication of the reactivity of each aniline with dimethyl-dioxirane.

Table 6 shows the amount of each unreacted aniline remaining at the end of the reaction and the amount of each N-oxide produced, obtained against the standards. Tables 7-10 show the relative rates calculated by the four different methods and these results are summarised in Table 11.

Table 6

Data obtained from the HPLC analysis of the N,N-dimethylaniline / dimethyldioxirane competition reactions, measured using N,N-dimethylaniline and N,N-dimethylaniline N-oxide standards.

X	Reaction	Initial conc^n of each aniline (mmol)	N,N-dimethyl -aniline remaining (mmol)	N,N-dimethyl -aniline N-oxide produced (mmol)	Substituted N,N-dimethyl -aniline remaining (mmol)	Substituted N,N-dimethyl-aniline N-oxide produced (mmol)
NO_2	Reaction 1 D1	5.06	0.67	2.42	3.86	0.02
	D2		0.68	2.78	4.13	0
	Reaction 2 D1		0.92	2.45	3.85	0
	D2		0.98	2.62	3.89	0
	Mean		0.81	2.57	3.93	0.005
Cl	Reaction 1 D1	5.17	1.65	1.87	3.14	1.31
	D2		1.78	2.03	3.40	1.43
	Reaction 2 D1		2.05	2.28	4.05	1.47
	D2		1.73	1.95	3.44	1.21
	Mean		1.80	2.03	3.51	1.36
MeO	Reaction 1 D1	4.9	3.96	1.09	2.19	2.44
	D2		3.88	1.17	2.07	2.39
	Reaction 2 D1		3.69	0.83	1.72	2.28
	D2		4.03	1.06	1.98	2.55
	Mean		3.89	1.04	1.99	2.42

D determination

Table 7

Relative rates obtained for the various substituted N,N-dimethylanilines using dimethyldioxirane, calculated using method 1.
Reaction time : 16 hours

substituent	reaction	determination	relative reactivity rate
NO_2	1	1	0.15
		2	0.14
	2	1	0.20
		2	0.21
	Mean		0.18 ± 0.035
Cl	1	1	0.87
		2	0.87
	2	1	0.86
		2	0.86
	Mean		0.87 ± 0.01
MeO	1	1	2.00
		2	2.00
	2	1	2.40
		2	2.10
	Mean		2.13 ± 0.19

Table 8

Relative rates obtained for the various substituted N,N-dimethylanilines using dimethyldioxirane, calculated using method 2.
Reaction time : 16 hours

substituent	reaction	determination	relative reactivity rate
NO_2	1	1	0.17
		2	0.16
	2	1	0.24
		2	0.25
	Mean		0.21 ± 0.05
Cl	1	1	0.53
		2	0.52
	2	1	0.51
		2	0.50
	Mean		0.52 ± 0.013
MeO	1	1	1.82
		2	1.89
	2	1	2.13
		2	2.04
	Mean		1.97 ± 0.14

Table 9

Relative rates obtained for the various substituted N,N-dimethylanilines using dimethyldioxirane, calculated using method 3.
Reaction time : 16 hours

substituent	reaction	determination	relative reactivity rate
NO_2	1	1	0.27
		2	0.21
	2	1	0.29
		2	0.29
	Mean		0.23 ± 0.051
Cl	1	1	0.58
		2	0.52
	2	1	0.36
		2	0.5
	Mean		0.49 ± 0.09
MeO	1	1	2.88
		2	2.77
	2	1	2.63
		2	3.36
	Mean		2.91 ± 0.32

Table 10

Relative rates obtained for the various substituted N,N-dimethylanilines using dimethyldioxirane, calculated using method 4.
Reaction time : 16 hours

substituent	reaction	determination	relative reactivity rate *
NO_2	1	1	0.008
		2	0
	2	1	0
		2	0
	Mean		0.002 ± 0.004
Cl	1	1	0.70
		2	0.70
	2	1	0.64
		2	0.62
	Mean		0.67 ± 0.04
MeO	1	1	2.24
		2	2.04
	2	1	2.75
		2	2.41
	Mean		2.36 ± 0.30

* calculated using the equation given below with the data shown in Table 6:

$$\frac{\text{amount of substituted N,N-dimethylaniline N-oxide produced}}{\text{amount of N,N-dimethylaniline N-oxide produced}}$$

Table 11

Mean relative rates using dimethyldioxirane, calculated using the four different methods.

substituent	relative rates of reaction			
	method 1	method 2	method 3	method 4
MeO	2.13 ± 0.19	1.97 ± 0.14	2.91 ± 0.32	2.36 ± 0.30
H	1.00 ± 0	1.00 ± 0	1.00 ± 0	1.00 ± 0
Cl	0.87 ± 0.01	0.52 ± 0.013	0.49 ± 0.09	0.67 ± 0.04
NO_2	0.18 ± 0.04	0.21 ± 0.05	0.23 ± 0.05	0.002 ± 0.004

Table 12

The mean amounts of each aniline consumed and N-oxide produced in the dimethyldioxirane competition reactions, expressed as a percentage.

substituent	mean % unsub aniline remaining (a)	mean % unsub aniline consumed (b)	mean % unsub aniline N-oxide produced (c)	mean % sub aniline remaining (a)	mean % sub aniline consumed (b)	mean % sub aniline N-oxide produced (c)
MeO	79%	21%	21%	41%	59%	49%
Cl	35%	65%	39%	68%	32%	26%
NO_2	16%	84%	51%	78%	22%	0.1%

a $\frac{\text{mean concentration of aniline remaining}}{\text{initial concentration of aniline}} \times 100\%$

b 100 - mean % aniline remaining = mean % aniline consumed

c $\frac{\text{mean concentration of aniline N-oxide produced}}{\text{initial concentration of aniline}} \times 100\%$

It can be seen from Table 11 that the results obtained by all four methods are in reasonably good agreement, showing the trend MeO > H > Cl > NO_2 as expected.

It should be noted that the results obtained using method 1, in which 50% conversion was assumed, compare well with the results obtained where no assumption was made about percentage conversion. It is important that this method remains meaningful as the results from the other competition reactions using methyl iodide, benzoyl peroxide and t-butyl hydroperoxide were calculated making this assumption.

The main difference between the results is the rate obtained for the nitroaniline reaction. When looking at unreacted starting material only (methods 1, 2 and 3), rates ranging from 0.18 - 0.23 were obtained, but when the amount of N-oxide produced was considered, a much lower rate of 0.002 was obtained. This suggests that more nitroaniline is being consumed than is being converted to N-oxide. This prompted us to look more closely at the data obtained. Because extensive LC work showed the N-oxides to be the only products in these dimethyldioxirane reactions, the data generated

using the standards should be consistent, i.e. the amount of aniline consumed should correspond to the amount of N-oxide produced. This data is expressed as a percentage in Table 13. It can be seen that it is the nitroaniline reaction which gives the most unsatisfactory results where approximately 20% of the nitroaniline and 30% of the unsubstituted aniline is unaccounted for and no explanation can be offered for this.

However, it does appear that the reactivity trend shown by dimethyldioxirane is characteristic of an electrophilic mechanism and this is illustrated further in the following two sections and in section 2.3.2.

2.2.5 Application of the Hammett relationship

The Hammett[129] relationship was applied to the four sets of dimethyldioxirane results shown in Table 11. The Okamoto-Brown[130] relationship was similarly applied. Table 13 summarises the rate data and substituent constants (σ and σ^+ respectively) used in these calculations and Table 14 shows the ρ and ρ^+ values obtained.

The relative rate data obtained from the competition reactions using the other reagents, i.e. methyl iodide, benzoyl peroxide and t-butyl hydroperoxide, are summarised in Tables 15 and 16. The Hammett and Okamoto-Brown relationships were applied giving the ρ and ρ^+ values shown in Table 16. The LFER plots of log k_X / k_H versus σ for the reaction of dimethyldioxirane with N,N-dimethyl-anilines, obtained using the four different sets of results are illustrated in Figure 6. The LFER plots of log k_X / k_H versus σ^+ for the dimethyldioxirane reactions and all the plots for the reactions carried out using methyl iodide, benzoyl peroxide and t-butyl hydroperoxide are shown in Appendix III.

Electrophilic substitution reactions give a high negative ρ value. The highest negative ρ value reported for a dimethyldioxirane reaction is -2.76 by Murray and Gu for the C-H insertion reaction into *para*-substituted cumenes.[83] Lower values (-0.77 and -0.76) have been reported by Murray for the dimethyldioxirane oxidation of *para*-substituted aryl methyl sulfides and sulfoxides respectively.[52a] For the epoxidation of *para*-substituted ethyl cinnamates, a ρ value of -1.53 has been determined.[87] All these reactions were considered to be electrophilic.

The values obtained for the methyl iodide and benzoyl peroxide reactions were quite low. The literature ρ value for the methyl iodide methylation of N,N-dimethylaniline in aqueous acetone at 35°C is -3.3.[131] It should be noted however that there is a difference in reaction conditions (temperature and solvent) and in order to apply linear free energy relationships, the reactions should be carried out in thermostatically controlled baths which was not the case in these experiments. The low results may also be a function of lack of sensitivity of the method of analysis.

For the dimethyldioxirane results calculated using method 1, asumming 50% conversion, an approximate ρ value of -0.99 was obtained. Similar treatment of the results with the Ōkamoto-Brown relationship gave $\rho^+ = -0.67$. The dimethyldioxirane results calculated using method 3, in which no assumptions about conversion were made, gave similar values. Using the results calculated by method 4, in which only the formation of N-oxide was considered, a ρ value of -2.98 and a ρ^+ value of -1.91 were obtained. These results suggest that the conclusions drawn by Murray on the electrophilic nature of the cumene and sulfide oxidations can be equally applied to the dimethyldioxirane oxidations of N,N-dimethylanilines which do show obvious similarities to reactions of N,N-dimethylanilines with methyl iodide (the Menschutkin reaction). In the reactions with methyl iodide however the transition state is thought to have developed almost a full positive charge whereas the reactions with dimethyldioxirane have much less charge development (Figure 7) and may be a function, in part, of steric crowding in the transition state. Hydrogen bonding is also thought to be of importance (see section 2.3.2).

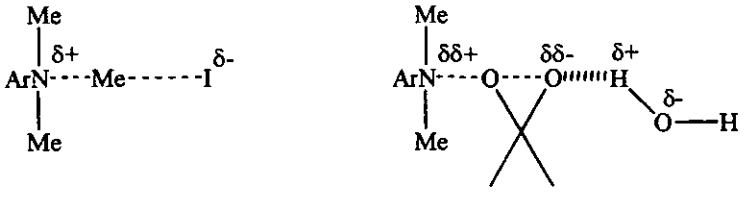


Figure 7 : Transition states for the reactions of N,N-dimethylanilines with methyl iodide and dimethyldioxirane

Table 13

Summary of the relative rate data and substituent constants used in the LFER plots for the reaction of dimethyldioxirane with *para*-substituted N,N-dimethylanilines in acetone at 0-5°C.

substituent	σ	σ⁺	method 1		method 2		method 3		method 4	
			k_{rel}	log k_{rel}	k_{rel}	log k_{rel}	k_{rel}	log k_{rel}	k_{rel}	log k_{rel}
MeO	-0.27	-0.78	2.13	0.33	1.97	0.29	2.91	0.46	2.36	0.37
H	0	0	1.00	0	1.00	0	1.00	0	1.00	0
Cl	0.23	0.11	0.87	-0.06	0.52	-0.28	0.49	-0.31	0.67	-0.17
NO_2	0.78	0.79	0.18	-0.74	0.21	-0.68	0.23	-0.64	0.02	-2.70

σ taken from reference 130

σ⁺ taken from reference 131

Table 14

ρ and ρ⁺ values resulting from the application of the Hammett and the Okamoto-Brown relationships respectively to the relative rate data obtained for the reaction of dimethyldioxirane with the various *para*-substituted N,N-dimethylanilines in acetone at 0-5°C.

	method 1	method 2	method 3	method 4
ρ	-0.99	-0.92	-1.01	-2.98
ρ⁺	-0.67	-0.62	-0.71	-1.91

Table 15

Summary of the relative rate data and substituent constants used in the LFER plots for the reactions of methyl iodide, benzoyl peroxide and t-butyl hydroperoxide with *para*-substituted N,N-dimethylanilines in acetone at 0-5°C.

substituent	σ	σ⁺	methyl iodide		benzoyl peroxide		t-butyl hydroperoxide	
			k_{rel}	log k_{rel}	k_{rel}	log k_{rel}	k_{rel}	log k_{rel}
MeO	-0.27	-0.78	3.65	0.56	27.62	1.44	1.19	0.08
H	0	0	1.0	0	1.0	0	1.0	0
Cl	0.23	0.11	0.70	-0.15	0.06	-1.22	0.86	-0.07
NO_2	0.78	0.79	0.65	-0.19	0.03	-1.52	0.91	-0.04

Table 16

Summary of the relative rate data and substituent constants used in the LFER plots for the reactions of t-butyl hydroperoxide at 70°C and t-butylhytdroperoxide in the presence of a vanadium catalyst with *para*-substituted N,N-dimethylanilines in acetone.

substituent	σ	σ⁺	t-butyl hydroperoxide 70°C		t-butyl hydroperoxide + $VO(acac)_2$	
			k_{rel}	log k_{rel}	k_{rel}	log k_{rel}
MeO	-0.27	-0.78	1.03	0.01	0.89	-0.05
H	0	0	1.0	0	1.0	0
Cl	0.23	0.11	1.13	0.05	0.52	-0.28
NO_2	0.78	0.79	0.43	-0.37	0.52	-0.28

Table 17

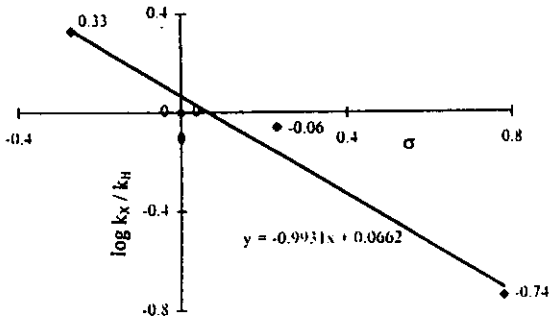
ρ and ρ⁺ values resulting from the application of the Hammett and the Okamoto-Brown relationships respectively to the relative rate data obtained for the reactions of methyl iodide, benzoyl peroxide and t-butyl hydroperoxide with the various *para*-substituted N,N-dimethylanilines in acetone.

	methyl iodide	benzoyl peroxide	t-butyl hydroperoxide	t-butyl hydroperoxide 70°C	t-butyl hydroperoxide + $VO(acac)_2$
ρ	-0.63	-2.70	-0.11	-0.37	-0.26
ρ⁺	-0.49	-1.95	-0.08	-0.23	-0.16

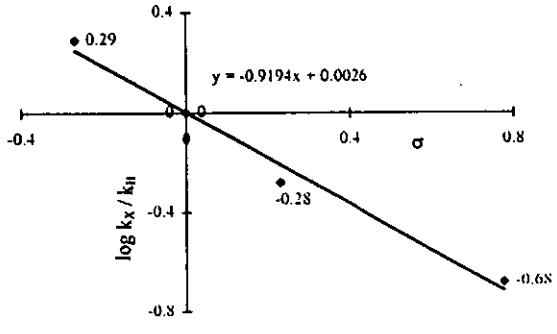
Figure 6

LFER plots of log k_X / k_H versus σ for the reaction of dimethyldioxirane with N,N-dimethylanilines in acetone at 0-5°C

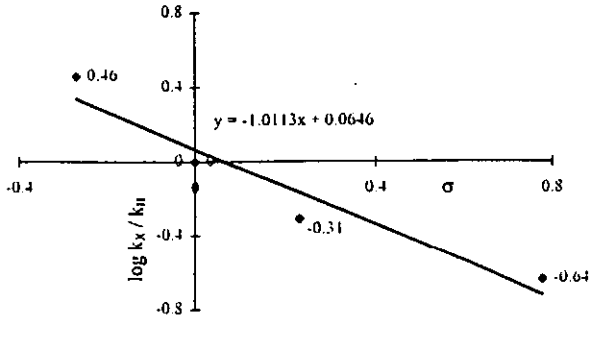
Method 1



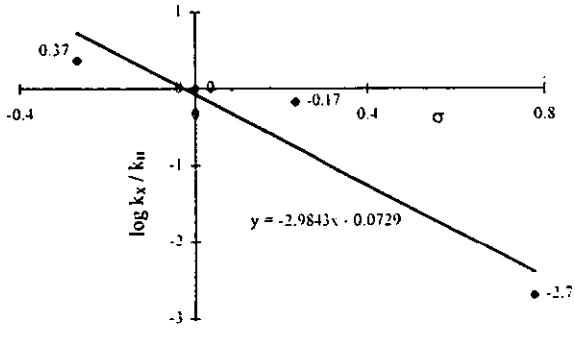
Method 2



Method 3



Method 4



2.2.6 Further evidence for the electrophilic nature of the dimethyldioxirane oxidation of *para*-substituted N,N-dimethylanilines

These results are backed up by work done by a coworker, Julie Ennis, at SmithKline Beecham.[121] She determined absolute second order rate constants for reactions of dimethyldioxirane with a known excess of N,N-dimethylaniline by controlled potential amperometry on the polarographic reduction wave of dimethyldioxirane.

Applying the Hammett relationship gave a ρ value of -0.89, with a correlation coefficient of 0.998, which is similar to that obtained using the relative rate data. The agreement is good considering that the two experimental approaches were conducted at different temperatures and in different solvents - the electrochemical measurements were carried out in aqueous acetonitrile at 21°C whereas the relative rate data were generated in acetone at 0-5°C. The excellent correlation obtained with the Hammett plot of the absolute rate data would suggest that this relationship is more appropriate than the Okamoto-Brown plot ($\rho^+ = -0.58$, correlation coefficient 0.952) and lends further support to the hypothesis that the dimethyldioxirane oxidation of *para*-substituted N,N-dimethylanilines is a concerted electrophilic process. (It is possible that a conjugative effect could be significant in an electron transfer mechanism and it should be noted that a lower coefficient was also obtained in the Okamoto-Brown plot for the cumene oxidation.[83])

Julie Ennis also showed that the reaction of N,N-dimethylanilines with dimethyldioxirane is strongly accelerated in the presence of water (see section 2.3.2) providing further evidence of the electrophilic nature of these reactions.

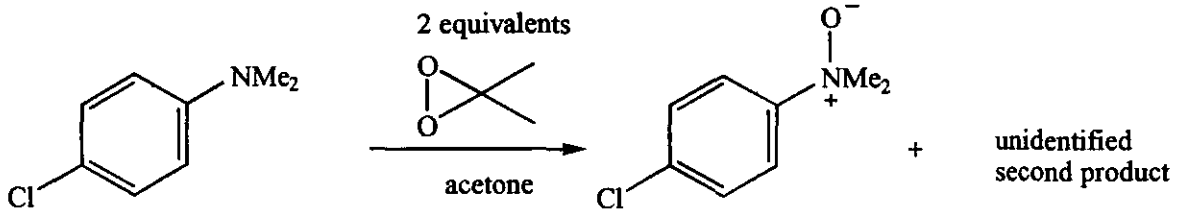
2.3 OXIDATION OF N,N-DIMETHYLANILINES USING DIMETHYL-DIOXIRANE

The reactions of dimethyldioxirane with the same series of N,N-dimethylanilines were carried out under various conditions. The aim was to establish whether or not the N-oxide is the only product formed during these oxidations, in particular looking for any evidence of dealkylation. The possibility of inducing a change in mechanism to electron transfer or free radical by altering the reaction conditions was investigated.

2.3.1 Oxidation of *para*-substituted N,N-dimethylanilines with dimethyldioxirane at 0-5°C and at room temperature in the presence and absence of light

2.3.1.1 Oxidation of N,N-dimethyl-4-chloroaniline using dimethyldioxirane

An acetone solution of N,N-dimethyl-4-chloroaniline was protected from light, cooled to 0-5°C and oxidised using 2 equivalents of dimethyldioxirane solution. In addition to the N-oxide, a second product was detected by both TLC and NMR spectroscopy.



Scheme 85 : Oxidation of N,N-dimethyl-4-chloroaniline using dimethyldioxirane

The reaction was repeated several times and the second product was detected in up to equal amounts as the N-oxide. This product is now known to be the N-oxide hydrate.

a. Separation of the products obtained in the oxidation of N,N-dimethyl-4-chloroaniline with dimethyldioxirane

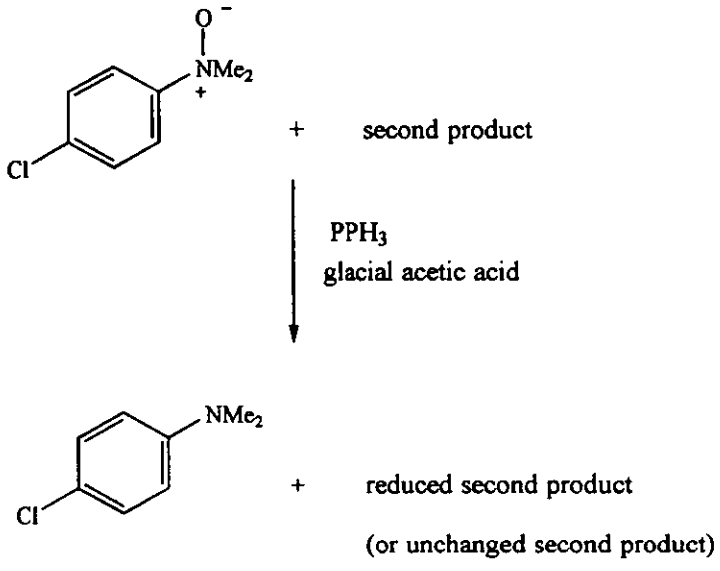
Before the identity of the second product was established as the N-oxide hydrate, several attempts were made to separate and isolate this product, none of which were successful.

i. Chromatography

The mixture was TLC'd on both silica and alumina using a variety of eluents. It was found that 25% methanol / 75% dichloromethane on silica gave the best separation of the two products, however repeated attempts at column chromatography and prep TLC resulted in the isolation of the N-oxide and some N,N-dimethyl-4-chloroaniline only.

ii. Reduction using triphenylphosphine

The aim here was to reduce the mixture of N-oxide and the second product to give N,N-dimethyl-4- chloroaniline and a reduced second product - if it is possible to reduce it - otherwise N,N-dimethyl-4-chloroaniline and unchanged second product, in the hope that this mixture would be easier to separate than the original mixture (Scheme 86).



Scheme 86 : Reduction of the N,N-dimethyl-4-chloroaniline product mixture using triphenylphosphine

Initially, a sample of N,N-dimethyl-4-chloroaniline N-oxide, prepared from N,N-dimethyl-4-chloroaniline using performic acid,[126] was reduced using triphenylphosphine in glacial acetic acid[132] at reflux for 3 hours. The reaction mixture was made strongly basic using 25% sodium hydroxide solution and extracted with dichloromethane. Column chromatography using 20% diethyl ether / 80% petrol gave N,N-dimethyl-4-chloroaniline in 64% yield. Treating the mixture of the N,N-dimethyl- 4-chloroaniline N-oxide and second product similarly gave N,N-dimethyl-4-chloroaniline only. No second product or reduced second product was isolated. The experiment was repeated at room temperature rather than at reflux giving the same result.

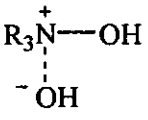
iii. Acid / base washes

Separation of the original mixture was attempted using acid / base washes. A sample of the mixture of products in deuteriated chloroform was washed in the NMR tube with 20% sodium carbonate solution. The upper aqueous phase was removed by pipette and the organic phase examined by proton NMR. It was expected to contain basic and neutral material. The NMR spectrum showed the chloroform phase to contain N-oxide and N,N-dimethyl-4-chloroaniline, with no second product. This implied that the second product is acidic and that the desired separation had been achieved. However, when the aqueous phase was acidified with dilute hydrochloric acid and extracted with deuteriated chloroform, no aromatic products were detected by proton NMR.

b. Further analysis of the N,N-dimethyl-4-chloroaniline product mixture

Carrying out the reaction of N,N-dimethyl-4-chloroaniline in acetone using 2 equivalents of dimethyldioxirane at room temperature in the presence of light gave the same two products seen previously - the N-oxide plus the unidentified second product. It was found that when a drop of D_2O was added to the mixture, the ratio of the two products changed, resulting in the second product becoming the major component of the mixture. A mass spectrum of this mixture showed $MH^+ = 172$ which corresponds to the N-oxide parent ion, plus $2M+H^+ = 343$, a dichloro species.
The reaction was repeated, but this time the N-oxide was found to be the only product. However, the second product formed on the addition of a drop of D_2O and was again the major component of the mixture. The ^{13}C NMR spectrum of this mixture showed resonances corresponding to the N-oxide only and analysis by HPLC against standards showed 83% N-oxide plus 2% unreacted starting material. No second product was detected. Using a mixture of the N-oxide and second product, extensive HPLC method development was carried out using various detection wavelengths, gradient systems etc (see Appendix I for details) in an attempt to detect the second product, but without success. Only peaks corresponding to the N-oxide and the starting material were ever detected. It was possible that the second product coeluted with the N-oxide or with the starting material but the UV spectra of these peaks showed single compounds.
Repeating the reaction several times revealed that the formation of the second product was not consistent. The formation of the second product was not dependent on either the presence / absence of light, the temperature at which the reaction was carried out or on the reaction time. The fact that

the addition of D_2O resulted in the formation of the second product obviously indicated that the moisture content of the dimethyldioxirane / acetone solution is important. This solution was routinely dried over sodium sulfate immediately after preparation but traces of water always remain in the oxidation solutions. It was found that the N-oxide could not be completely converted to the second product using D_2O or by purposefully adding water to the reaction mixture. Similar products were produced when D_2O was added to solutions of the unsubstituted N,N-dimethylaniline N-oxide, the N,N-dimethyl-4-methoxyaniline N-oxide and the N,N-dimethyl-4-nitroaniline N-oxide in $CDCl_3$. In all cases, taking the resulting mixtures of N-oxide and second product and drying over magnesium sulfate showed the disappearance of the second product by proton NMR leaving only the N-oxide. It was concluded therefore that the second product is simply a hydrate of the N-oxide and structures such **135** have been described in the literature.[133,134] The mass spectroscopy results indicate dimeric species, which may or may not be real.



135

The N-oxide is therefore the only product formed when N,N-dimethyl-4-chloroaniline is reacted with dimethyldioxirane in acetone both at 0-5°C and at room temperature.

2.3.1.2 Oxidation of N,N-dimethylaniline and N,N-dimethyl-4-methoxyaniline using dimethyldioxirane

Solutions of N,N-dimethylaniline and N,N-dimethyl-4-methoxyaniline in acetone, protected from light and cooled to 0-5°C, were oxidised using 2 equivalents of dimethyldioxirane solution, stirring for 1 hour. In both cases, TLC and proton NMR spectroscopy showed the N-oxide to be the only product. In the case of N,N-dimethyl-4-methoxyaniline, a yield of 88% N-oxide was determined by HPLC, plus 10% unreacted starting material, measured against external standards. A similar result was obtained when the reaction was carried out at room temperature with no protection from light. A yield of 66% N-oxide was obtained by HPLC for the N,N-dimethylaniline reaction. When this reaction was repeated at room temperature with no protection from light, a small amount of a second product,

believed to be the N-oxide hydrate, was formed in addition to the N-oxide.

2.3.1.3 Oxidation of N,N-dimethyl-4-nitroaniline using dimethyldioxirane

N,N-dimethyl-4-nitroaniline in acetone, protected from light and cooled to 0-5°C, was oxidised using 2 equivalents of dimethyldioxirane solution. The nitroaniline was found to be very unreactive towards dimethyldioxirane and HPLC showed a yield of only 9% N-oxide. Carrying out the reaction at room temperature had no effect. The use of a larger excess of dimethyldioxirane (up to 10 equivalents) also gave mainly unreacted starting material.

2.3.2 Oxidation of N,N-dimethyl-4-nitroaniline using dimethyldioxirane in the presence of water

Oxidation of N,N-dimethyl-4-nitroaniline in acetone using 10 equivalents of dimethyldioxirane gave mainly unreacted starting material. However, when this reaction was carried out in 50% aqueous acetone, significant conversion to the N-oxide was achieved after only one hour. A minor second product was also produced, believed to be the N-oxide hydrate. As expected, addition of D_2O to this mixture showed an increase in the amount of the second product. The drying of this solution either over sodium sulfate or molecular sieves resulted in the disappearance of the second product affording a proton NMR spectrum identical to that of the N-oxide, confirming the idea that the second product is in fact the N-oxide hydrate. This was confirmed by coworker, Todd Boehlow.[121]

Strong solvent effects have been observed in other dioxirane reactions[44,45,87] and the possibility of these effects in this reaction was investigated by a coworker, Julie Ennis.[121] This was done kinetically by monitoring the loss of UV absorbance of N,N-dimethyl-4-nitroaniline when reacted with an excess of dimethyldioxirane. The pseudo first order rate constants were calculated in a number of solvents and it was found that there is a significantly large increase in the reaction rate in water. It was concluded that this increase probably arises from the strong hydrogen bonding nature of the solvent. Such solvents would be expected to stabilise both the transition state (Figure 6) and the N-oxide product which readily forms stable hydrates.[133]

As discussed in sections 1.3.1 and 1.3.2, the role of hydrogen bonded solvents in accelerating oxidation rates has previously been recognised by Murray in studies of the dimethyldioxirane epoxidation[87] and oxidation of C-H bonds.[45] Work carried out in the past in these laboratories by the Marples' group[88] and by others[37] has suggested that intramolecular hydrogen bonding could be important in some dimethyldioxirane oxidations and recently *ab initio* model studies on primary amine oxidations with dimethyldioxirane has confimed the importance of solvent and hydrogen bonding effects.[135]

All this data are consistent with the conclusion that the dimethyldioxirane oxidation of N,N-dimethyl-anilines is electrophilic in nature and does not involve the bis(oxy)diradical **89** or electron transfer.

2.3.3 Oxidation of N,N-dimethylanilines using dimethyldioxirane at reflux

At this stage, we were still interested in the idea of inducing a mechanism change and there is evidence in the literature[99] that when dioxiranes are heated, they decompose forming bis(oxyl)-diradicals **89**. When no substrate is present, these radicals will react with the parent ketone to form esters.

The reactions of the N,N-dimethylanilines with dimethyldioxirane were repeated but this time at reflux. Formation of any bis(oxyl)diradicals may result in reaction with the aniline substrate and perhaps lead to products other than the N-oxide. The results are tabulated in Table 18. It can be seen that the main product in each case was the N-oxide, apart with N,N-dimethyl-4-nitroaniline where no reaction took place. In the case of N,N-dimethyl-4-methoxyaniline, some N-oxide hydrate also formed.

2.3.4 Oxidation of N,N-dimethylanilines with dimethyldioxirane under photolytic conditions

There is also evidence in the literature[61b] for the production of the bis(oxyl)diradical **89** under photolytic conditions. Solutions of the N,N-dimethylanilines and dimethyldioxirane were photolysed in a Hanovia photochemical reactor fitted with a Pyrex filtered medium pressure lamp ($\lambda > 300$nm). The solutions of dimethyldioxirane in acetone used in these reactions were prepared

under nitrogen using degassed acetone and EDTA solution, and stored under nitrogen until used. The aniline was dissolved in acetone and degassed before adding to the photolysis vessel, which was kept under a constant nitrogen purge. After cooling in an ice / salt bath, the lamp was switched on and the dimethyldioxirane solution (2 equivalents) added in one portion via a dropping funnel sealed with a septum. The mixture was photolysed for 4 hours. The results, shown in Table 19, were not very different from those obtained under non-photolytic conditions. N,N-dimethyl-4-chloroaniline and N,N-dimethylmethoxyaniline gave a mixture of the N-oxide and the N-oxide hydrate (approximately 2:1). N,N-dimethylaniline gave mainly N-oxide plus a trace of the N-oxide hydrate, and N,N-dimethyl-4-nitroaniline gave mainly unreacted starting material plus traces of other unidentified aromatic products. These other products were present in such small amounts that no attempts were made to isolate them.

It can be concluded therefore that the electrophilic reaction between the aniline and the dioxirane resulting in the N-oxide is probably too rapid for any radicals to form and acetone is present in such a large excess that it would simply react with any radical species which may form to give esters. This work would be better carried out using methyl(trifluoromethyl)dioxirane which can be prepared in solutions free from the parent ketone and so eliminate its interference in the reaction. This also applies to the reactions carried out at reflux.

Table 18

Oxidation of the N,N-dimethylanilines using dimethyldioxirane in acetone at reflux

Reaction time 3.5 hours

Substituent	Number of equivalents of dimethyldioxirane added	Products formed (by TLC and NMR)
MeO	2	N-oxide + N-oxide hydrate (4:1)
H	2	N-oxide only
Cl	2	N-oxide + a trace of unreacted starting material
NO_2	5	unreacted starting material

Table 19

Oxidation of the N,N-dimethylanilines using dimethyldioxirane in acetone at $\lambda > 300$nm

Reaction time 4 hours

Substituent	Number of equivalents of dimethyldioxirane added	Products formed (by TLC and NMR)
MeO	2	N-oxide + N-oxide hydrate (2:1)
H	2	N-oxide + a trace of N-oxide hydrate
Cl	2	N-oxide + N-oxide hydrate (2:1)
NO_2	5	mainly unreacted starting material + traces of several other very minor products

2.3.5 Transition metal catalysis of the dimethyldioxirane oxygen transfer reaction

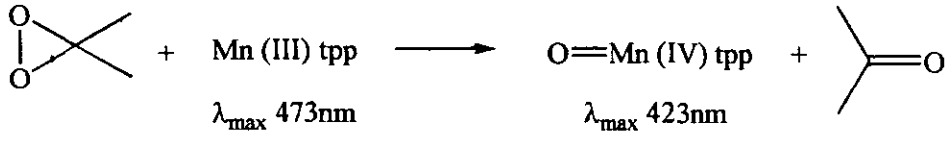
It was thought that transition metal catalysis of the dimethyldioxirane oxygen transfer to tertiary amines could be used in an attempt to induce dealkylation rather than N-oxidation and hence mimic the *in vivo* P450-catalysed reactions.

It is reported in the literature[136] that oxygen transfer from dimethyldioxirane to manganese (II) tetraphenylporphyrin and iron (II) tetramesitylporphyrin is readily affected at less than -10°C to give labile oxometal species in quantitative yields (Scheme 87).

Scheme 87 : Oxygen transfer from dimethyldioxirane to metal porphyrins

The idea was to first react the metal porphyrin with dimethyldioxirane to give the metal-oxygen complex, then add to this the amine substrate. The complex would then transfer oxygen to the amine regenerating the metal porphyrin.

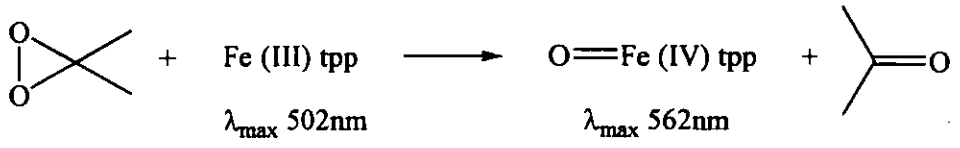
5,10,15,20 tetraphenyl-21H,23H-porphine manganese (III) chloride was taken in acetone and cooled to -78°C. To it was added 5 equivalents of dimethyldioxirane solution in portions over 3 hours, allowing the mixture to warm to -20°C. The reaction was followed by monitoring the UV spectrum of the mixture. The conversion of manganese (III) to manganese (IV) is indicated by the shift of the λ_{max} from 473nm to 416nm (Scheme 88). This conversion requires an excess of dimethyldioxirane but if too large an excess is used, any unreacted dioxirane may react directly with the substrate when it is added.



Scheme 88 : Oxygen transfer from dimethyldioxirane to manganese (III) porphyrin

The spectroscopic evidence suggested that the manganese (IV)-oxygen complex was formed successfully and to it was added 1 equivalent of N,N-dimethyl-4-chloroaniline at -78°C. The mixture was allowed to warm to room temperature. The λ_{max} of the mixture shifted from 416nm back to 473nm indicating that oxygen transfer from the complex had taken place. It should be noted that this did not necessarily mean that the oxygen had been transferred to the aniline as it is known that at room temperature the manganese (IV)-oxygen complex will spontaneously transform into manganese (III). However, TLC showed several products and column chromatography gave some separation but because the reaction had been done on a very small scale, isolation of sufficient quantities of clean products for characterisation was not achieved.

A reaction using 5,10,15,20-tetraphenyl-21H,23H-porphine iron (III) chloride was also carried out. The iron (IV)-oxygen complex was formed after 15 minutes using 3 equivalents of dimethyldioxirane at -78°C. The conversion of iron (III) to iron (IV) was followed by UV (Scheme 89).



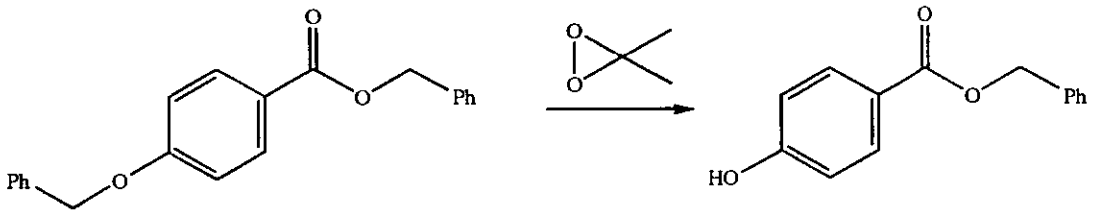
Scheme 89 : Oxygen transfer from dimethyldioxirane to iron (III) porphyrin

Again the spectroscopic evidence suggested that iron (IV)-complex was successfully formed and so to it was added 1 equivalent of N,N-dimethyl-4-chloroaniline. The mixture was allowed to warm to room temperature and after 4.5 hours all the complex had disappeared. Again TLC showed several products but the same problem as in the manganese reaction was encountered. Unfortunately no further progress was made with this work due to time constraints. Ideally the reactions would have been carried out on a much larger scale, enabling any products formed to be isolated in large enough quantities for characterisation. It was the high cost of the metal porphyrins which had dictated the scale of the preliminary reactions.

2.4 OXIDATION OF N,N-DIMETHYLBENZYLAMINES USING DIMETHYLDIOXIRANE

A series of N,N-dimethylbenzylamines were oxidised using dimethyldioxirane to determine whether the N-oxide is the sole product, as is the case with N,N-dimethylanilines, or whether the presence of the benzylic methylene group might be sufficiently active to be oxidised and lead to other products.

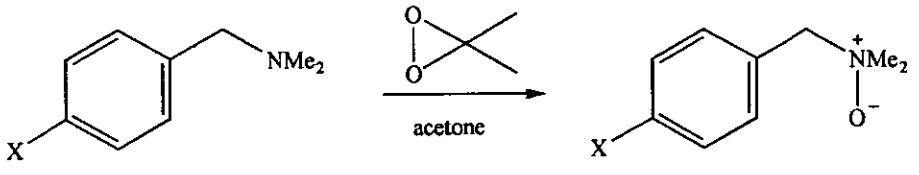
Direct insertion of oxygen from dimethyldioxirane into benzylic C-H bonds has been reported and in these laboratories it was found that in the oxidation of 5α-cholestan-3β-yl benzyl ether, benzylic C-H insertion occurs initially leading to 5α-cholestan-3β-ol which is then quite rapidly oxidised to the ketone.[137] The direct oxidation of estra-1,3,5 (10)-trienes has also achieved with dimethyldioxirane generated *in situ* to afford the 9α-hydroxy derivatives in good yield.[138] The Marples group reported the selective oxidative cleavage of benzyl ethers versus benzyl esters, for example in benzyl-4-benzyl-oxybenzoate **136**[139] and more recently, Csuk and Dörr reported the cleavage of substituted benzyl ethers by treatment with an excess of dimethyldioxirane giving the corresponding alcohols in high yields.[140]



136

Scheme 90 : Oxidative cleavage of benzyl-4-benzyloxybenzoate using dimethyldioxirane

A series of *para*-substituted N,N-dimethylbenzylamines with the same substituents as the N,N-dimethylanilines series was chosen.



X = H, MeO, Cl, NO_2

Scheme 91 : Oxidation of N,N-dimethylbenzylamines using dimethyldioxirane

N,N-dimethylbenzylamine and N,N-dimethyl-4-nitrobenzylamine were commercially available and the methoxy and chloro derivatives were prepared in good yield from the corresponding primary benzylamine using formic acid and formaldehyde (Eschweiler-Clark procedure[127]).
A suitable HPLC method was developed to look for other products (see Appendix I). However, yields of N-oxide could not be determined by HPLC as N-oxide standards of satisfactory quality could not be isolated. Attempts were made to prepare these using performic acid but isolation proved difficult due to high solubility in the aqueous phase. HPLC analysis of the aqueous phase of the reaction mixture did however provide an adequate HPLC marker.

The oxidations using dimethyldioxirane were carried out by taking a solution of N,N-dimethyl-benzylamine in acetone and adding 1 equivalent of dimethyldioxirane / acetone solution. The resulting mixtures were stirred at room temperature for one hour. In all cases, HPLC analysis showed N-oxide plus some unreacted starting material. A second equivalent of dimethyldioxirane was added which consumed all the starting material and gave the N-oxide as the only product. This was confirmed by TLC and NMR spectroscopy. Mass spectrometry showed dimeric and in some instances, trimeric species but these were believed to be artefacts. It was concluded therefore that the presence of the benzylic methylene group had no effect on the reaction mechanism.

2.5 CONCLUSIONS

The dimethyldioxirane oxidations of *para*-substituted N,N-dimethylanilines have been shown to be consistent with a concerted electrophilic mechanism and do not involve the bis(oxyl)diradical or electron transfer. In this respect, the mechanism agrees with the conclusions drawn by Curci *et al* for epoxidations and oxygen insertion into alkane C-H bonds.[141] The reactions have been shown to follow the Hammett relationship with a ρ value of -1.0 and the presence of water was found to greatly accelerate the reaction rate. Attempts to change the reaction pathway by carrying out the reactions in the presence of light or heat were unsuccessful, giving the N-oxide as the only significant product. The oxidation of a series of *para*-substituted N,N-dimethylbenzylamines also gave the N-oxides only. No evidence for dealkylation as in the *in vivo* P450-catalysed reactions was seen.

Chapter 3

OXIDATION OF MORE COMPLEX NITROGEN-CONTAINING MOLECULES USING DIMETHYLDIOXIRANE

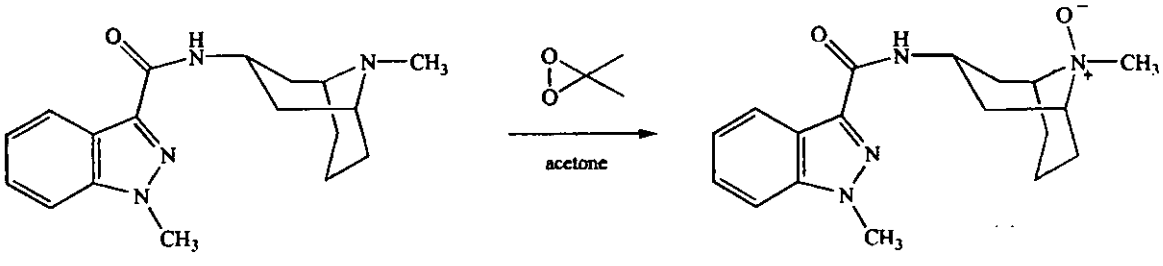
3.1 INTRODUCTION

One of our aims was to explore the potential use of dimethyldioxirane in oxidative degradation studies of nitrogenous drugs. If dimethyldioxirane can be used selectively it may prove to be a valuable reagent for use in accelerated stability testing of pharmaceutical products as many drugs degrade *in vitro* by oxidation and nitrogen atoms are a relatively easy target.

The oxidations of several drug substances have been investigated in order to explore the regioselectivity of the oxygen transfer by dimethyldioxirane to molecules containing several different functionalities, at least one of which is a tertiary amine.

This work was done in conjunction with GC / MS studies carried out at SmithKline Beecham by Julie Ennis.[183]

3.2 OXIDATION OF GRANESITRON



137 138

Scheme 92

Granesitron **137** contains four nitrogen functionalities and it was found that oxidation occurs at the most reactive tertiary amine site, as shown in Scheme 92. As expected, the amide is unreactive towards dimethyldioxirane.

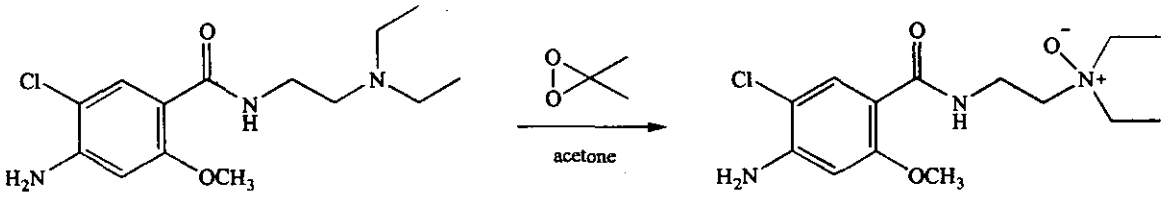
An acetone solution of granesitron was oxidised at 0-5°C using a total of 3 equivalents of dimethyl-dioxirane. TLC showed the N-oxide **138** to be the major product plus a trace of a second product. The N-oxide was isolated as a white solid in 68% yield by column chromatography and recrystallised from petrol / dichloromethane. Comparison of the spectroscopic data with that of an authentic specimen of granesitron N-oxide confirmed the identity of this product.

A small quantity (9mg) of the second product was obtained as an oil which was shown to be too impure to identify by proton NMR and mass spectrometry.

The oxidation was repeated using a more concentrated reaction mixture and 2 equivalents of dimethyldioxirane. TLC showed no second product and no unreacted starting material. During the reaction, the N-oxide **138** precipitated out and was isolated as a white solid in 62% yield. The mother liquors were concentrated *in vacuo* to an oil and found to be a mixture containing the N-oxide as the major component. No second crop was taken.

An attempt was then made to oxidise the N-oxide further to see if this would lead to the formation of the second product seen in the first reaction. A much more dilute solution of the free base in acetone was prepared and a large excess (10 equivalents) of dimethyldioxirane added. However TLC showed the N-oxide **138** to be the only significant product after 16 hours.

3.3 OXIDATION OF METACLOPRAMIDE



139 **140**

Scheme 93

In addition to the tertiary amine function, metaclopramide **139** also contains a primary amine group. Primary amines are known to be oxidised by dimethyldioxirane to the nitro compound via the hydroxylamine and the nitroso compound. However, it was found that metaclopramide was oxidised

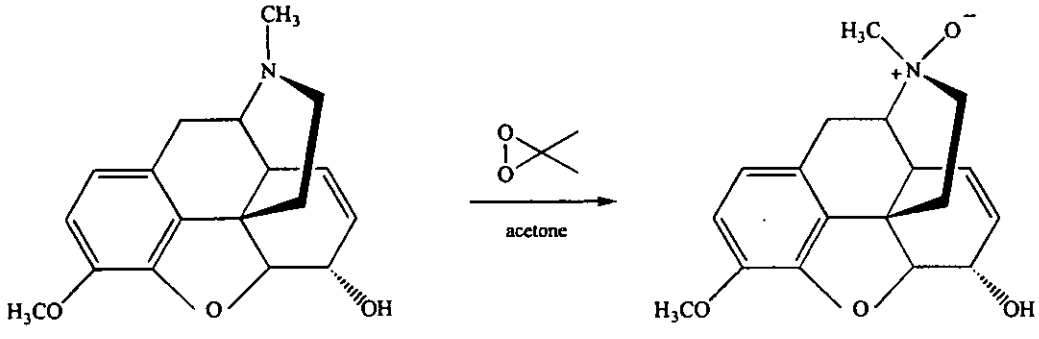
preferentially at the tertiary amine to give the N-oxide **140** only, as confirmed by comparison with an authentic specimen of metaclopramide N-oxide.

The reaction was carried out in acetone at 0-5°C using 2 equivalents of dimethyldioxirane. The N-oxide **140** precipitated out during the reaction and was isolated by filtration in 69% yield. HPLC analysis showed a single peak. The mother liquors were concentrated to an oil and HPLC analysis and NMR spectroscopy showed the major component to be N-oxide **140** plus traces of baseline impurities.

The possibility of further oxidation of the metaclopramide N-oxide was then investigated. The N-oxide is fairly insoluble in acetone therefore it was dissolved in a small quantity of methanol and a total of 10 equivalents of dimethyldioxirane / acetone solution added in portions. The solution turned from colourless to yellow and TLC showed the N-oxide plus 3 other minor products. The mixture was analysed by HPLC which revealed a more complex mixture containing approximately 9 products plus unreacted N-oxide. Separation was not attempted.

It was interesting to note that using 2 equivalents of dimethyldioxirane there was no evidence of oxidation at the primary amine.

3.4 OXIDATION OF CODEINE



141 **142**

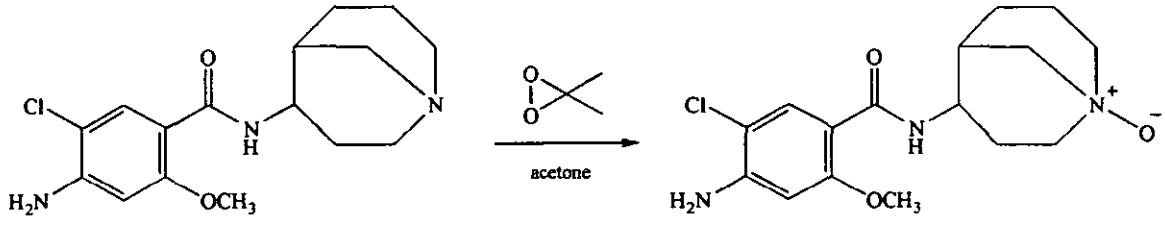
Scheme 94

Codeine **141** contains only one nitrogen functionality but it also contains a double bond and a hydroxyl group both of which are potentially susceptible to attack by dimethyldioxirane.

An acetone solution of codeine was cooled to 0-5°C and oxidised using 3 equivalents of dimethyl-dioxirane. TLC showed the N-oxide **142** to be the only product. The reaction was complete within 10 minutes and the N-oxide isolated by filtration in 85% yield. The identity of this product was confirmed by comparison of spectroscopic data with published data.[142]
The reaction was repeated at room temperature using 2 equivalents of dimethyldioxirane giving a similar result. By NMR, the isolated N-oxide was found to be approximately 92% pure containing 8% of a related impurity. *Syn / anti* isomerism exists about the nitrogen so it is possible that the related impurity is simply the other isomer, although NOE studies to determine which isomer is the predominent one were not carried out. The mother liquors from this reaction were concentrated *in vacuo* to an oil which was found to be a mixture containing up to 50% N-oxide.

Codeine N-oxide in acetone was then stirred with excess dimethyldioxirane to see if further oxidation would take place. A few drops of methanol were added to aid solubility. TLC showed unreacted codeine N-oxide plus a trace of one product. Addition of more dimethyldioxirane did not increase the level of this product therefore no separation was attempted.
It is interesting to note that no evidence for oxidation at the double bond or at the hydroxyl group was seen. The lack of oxidation at the double bond may be due to steric hindrance by the bridge and it has been reported that epoxidation and C-H insertion are difficult in the presence of a tertiary amine which tends to undergo preferential oxidation in each case.[65,66]

3.5 OXIDATION OF BRL 24924



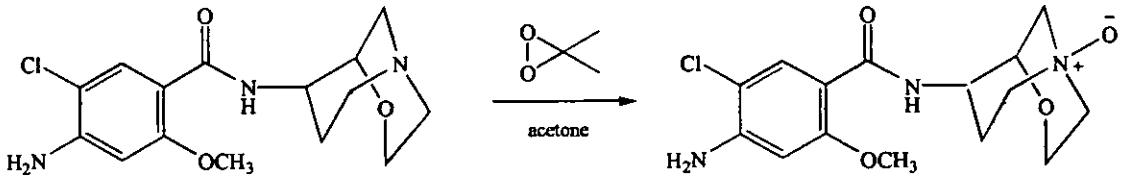
143 **144**

Scheme 95

The drug substance, BRL 24924 **143**, was dissolved in acetone, cooled to 0-5°C and oxidised using a total of 4 equivalents of dimethyldioxirane. This was added in portions and the reaction mixture stirred for approximately 16 hours. The N-oxide **144** was found to be the only product which precipitated out during the reaction and was isolated by filtration in 79% yield. NMR spectroscopy confirmed the product's identity by comparison with authentic specimen data. HPLC analysis showed the N-oxide to be 97% pure containing approximately 1.5% of a single related impurity by area normalisation (see Appendix IV for details of the method).

The crude N-oxide **144** was then dissolved in a 10:1 mixture of acetone and methanol and 10 equivalents of dimethyldioxirane added. Stirring was continued for 16 hours. HPLC analysis showed mainly unreacted N-oxide (approximately 75% by area normalisation) plus several minor products. The addition of excess dimethyldioxirane therefore results in some degradation of the N-oxide but not to such an extent that further work was considered worthwhile. As with metaclopramide, no significant oxidation took place at the primary amine even when using four equivalents of oxidant.

3.6 OXIDATION OF BRL 43145



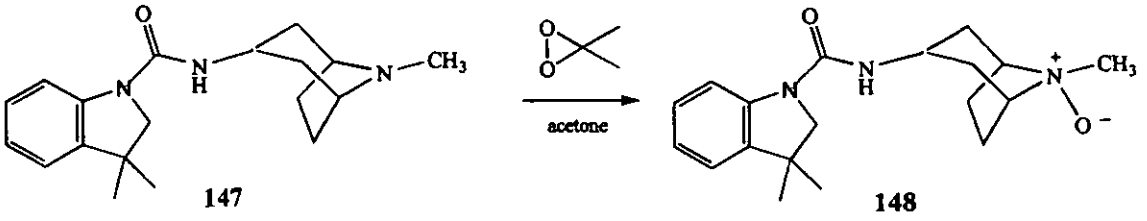
145 **146**

Scheme 96

BRL 43145 **145** was oxidised at 0-5°C using a total of 4 equivalents of dimethyldioxirane giving the N-oxide **146** as the only product. This precipitated out of the reaction mixture and was isolated by filtration in 95% yield. The oxidation was repeated at room temperature using 3 equivalents of dioxirane giving a similar result. Both samples of N-oxide were found to be clean by TLC and NMR, and approximately 94-96% pure by HPLC, containing 2-3% of a single impurity by area normalisation.

When excess dimethyldioxirane was added to the N-oxide **146** (10 equivalents in total), TLC showed mainly unreacted N-oxide plus one other product. HPLC showed a slightly more complex mixture consisting of unreacted N-oxide plus one main product and at least three minor ones. The impurity seen in the N-oxide was not enhanced. No further work was carried out.

3.7 OXIDATION OF BRL 46470



147 **148**

Scheme 97

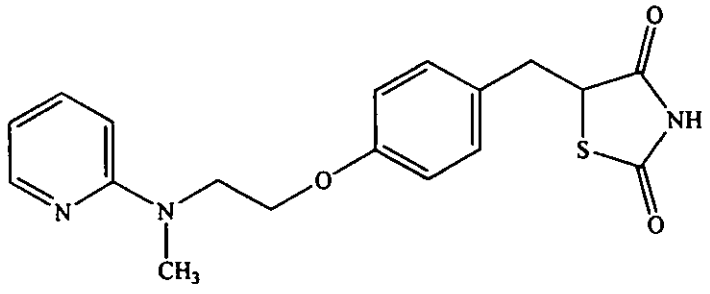
BRL 46470 **147** was oxidised using 4 equivalents of dimethyldioxirane solution at 0-5°C. TLC showed the N-oxide **148** as the major product with traces of 2 other products. The mixture was concentrated *in vacuo* to a solid and column chromatography yielded the N-oxide only (42%). The oxidation was repeated at room temperature using only 2 equivalents of dimethyldioxirane. This time TLC showed a single product and no unreacted starting material. Concentration *in vacuo* gave the crude N-oxide **148** which was shown by proton NMR spectroscopy to contain a trace of a related impurity. HPLC showed a more complex mixture, containing the N-oxide (85% by area normalisation) plus 3 impurities (9%, 1% and 4% by area normalisation).

The N-oxide was recrystallised from acetonitrile in 74% yield, but this failed to remove the impurity detected by proton NMR. ^{13}C NMR indicated an approximately 6:1 mixture of N-oxide to impurity. It is possible that the impurity is the other *syn / anti* isomer, although this was not confirmed.

Addition of excess dimethyldioxirane to a solution of BRL 46470 N-oxide in acetone showed no significant reaction.

3.8 OXIDATION OF BRL 49653

Oxidation of BRL 49653 **149** gave some interesting preliminary results. HPLC analysis showed various products (for method details, see Appendix IV).

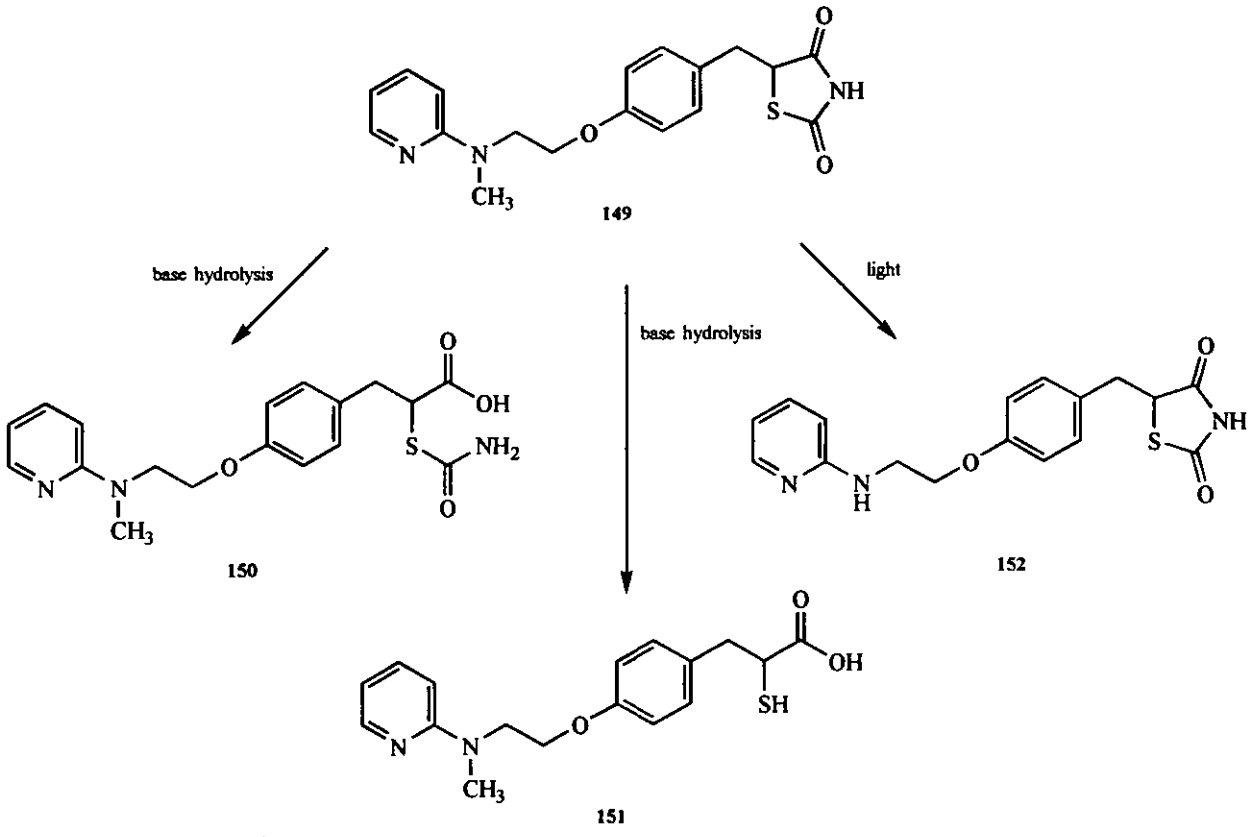


149

When BRL 49653 is stored under stressed conditions, e.g. hydrolytic or photolytic conditions, degradation occurs via a complex pathway. The aim was to oxidise BRL 49653 using dimethyl-dioxirane to see if any of the known degradation products were formed. Samples of the main degradation products were provided by SmithKline Beecham for use in the analysis of the crude reaction mixtures.

There are two primary routes of degradation of BRL 49653 (Scheme 98). One is base hydrolysis which can proceed by two possible routes and the second is demethylation which occurs rapidly on photolysis to give compound **152**. The two possible base hydrolysis products are the thiocarbamate **150** which results from attack on the carbonyl furthest from the sulfur in the thiazolidinedione ring and the thiol **151** which results from attack on the carbonyl closest to the sulfur. The thiol can then undergo further degradation resulting in secondary degradation products.

HPLC response factors were determined by SmithKline Beecham for each of the isolated degradation products and in each case the response on a molar basis was found to be approximately 1:1, therefore expressing the HPLC analysis results in percentage area normalised gives an accurate indication of the level of product present on a mole / mole basis.



Scheme 98 : Primary degradation pathway for BRL 49653

BRL 49653 free base **149** in acetone was oxidised using 6 equivalents of dimethyldioxirane which were added in one portion at room temperature. After stirring for a short period, a yellow precipitate appeared. After 1 hour, a sample was removed and analysed by HPLC. The chromatogram showed that significant degradation had occurred. In fact after one hour no starting material remained and over ten products were detected at levels greater than 1% (see Appendix IV). It was found that the main product (33.7% by area normalisation) coeluted with the thiocarbamate **150**.

In an attempt to investigate the way in which this product profile was built up, a reaction was carried out adding the dimethyldioxirane in 1 equivalent portions at 30 minute intervals. However, after adding only a single equivalent of dimethyldioxirane, HPLC showed a similar profile to that obtained in the first reaction.

Unfortunately no further time was spent on this work and although the products from these reactions were not identified, it was interesting to note the extent of degradation caused by the addition of dimethyldioxirane. More work is required to establish whether dimethyldioxirane would be a suitable reagent for use in degradation studies of this type.

3.9 CONCLUSIONS

In each case it was found that oxidation takes place preferentially and often exclusively at the most reactive tertiary amine site (sp^3 nitrogen) giving the N-oxide as the major product. No other significant products were formed in any of the oxidations, except in the case of BRL 49653, due to both steric and electronic factors. Similar results were obtained by Julie Ennis in her studies at SmithKline Beecham.[183]

It should be noted that the NMR analyses of the N-oxide products were carried out on the purified material only and not on the crude mixtures. In compounds where *syn* / *anti* isomerism about the nitrogen is possible, only one isomer was obtained as the main product. In some cases, for example, in the oxidation of codeine, it is believed that the other isomer was formed as a minor impurity.

Chapter 4

SELECTIVE OXIDATION OF POLYHYDROXY STEROIDS USING DIMETHYLDIOXIRANE

4.1 INTRODUCTION

With steroids, a hydroxyl group at a particular position on the carbon skeleton is sterically and electronically different to a hydroxyl group at any of the other positions. Each of the possible hydroxys may assume either α or β configuration and lie either axial or equatorial to the ring. Because of the unique character of the hydroxys at each position, it is possible in theory to perform a selective oxidation on any combination of these groups.[143]

We were interested in the application of dimethyldioxirane as a selective reagent in the oxidation of polyhydroxy steroids, in particular a series of bile acid methyl esters. There are several oxidising agents already available but in many cases these are not sufficiently selective to afford an acceptable yield of the mono-oxidised product. For example, the Oppenauer oxidation[144] has found considerable application in steroid chemistry.[145] It shows a preference for non-hindered secondary alcohols and equatorial hydroxyls are oxidised more rapidly than axial. In fact, most axial saturated alcohols are inert to this reagent as are equatorial hydroxyls in a crowded enviroment. With polyhydroxy steroids, the selective oxidations shown in Figure 8 have been accomplished. A C3 hydroxyl is always attacked first while one at C1 remains untouched.

C3 versus C12 [146]

C3 versus C7 and C12 [146a,146d,147]

C3 versus C6 [148]

C3 versus C11 [146]

C3 versus C20 [148,149]

C3 versus C17α [150]

C17 versus C11 [151]

C20 versus C11 [152]

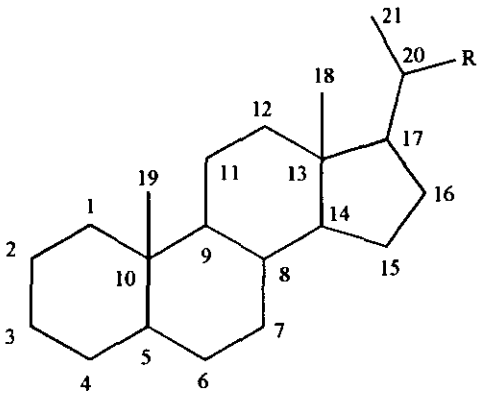


Figure 8

Selective steroid oxidations have also been carried out using various chromium VI reagents and these differ in their preference to the Oppenauer reagent.[143] Studies by Schreiber and Eschenmoser[153] and Grimmer[154] have afforded data comparing the rates of oxidation of hydroxyls at many positions on the steroid nucleus. It is generally observed that apart from the 1-position, any axial alcohol is oxidised at least three times faster than its corresponding equatorial alcohol and that selective oxidation of various axial hydroxyls is possible if the degree of non-bonded repulsive interaction is sufficiently different for each alcohol. It has been found that the rate of oxidation increases with increasing interaction although the exact nature of this steric acceleration has not been agreed upon. Eschenmoser[153] and Eliel[155] have stated that the driving force of the reaction is derived in going from the sp^3 tetrahedral state to the planar trigonal sp^2 ketone and so a crowded enviroment would tend to assist the reaction and accelerate its rate. Kwart,[156] on the other hand, believes it involves the restriction of free rotation in the transition state which means that a smaller activation energy is required for the reaction to proceed under crowded conditions. It is quite certain that steric accessibility of the α-hydrogen is not a dominating factor since the reaction rate increases with increasing steric hindrance in the vicinity of the α-hydrogen.[155]

Chromium VI-acetic acid can be used in the selective oxidation of polyhydroxy steroids when an acetate buffer is used.[145,157] For example, the selective oxidation of an axial 7α hydroxyl is possible in the presence of a 12α hydroxyl in cholic acid when a buffered system is used whereas without the

buffer the 12α hydroxyl can be also oxidised.[158] The disadvantages of this system include the non-survival of acid-labile groups under the reaction conditions plus other acid-catalysed reactions such as dehydration and rearrangement may occur.

Jones reagent[159] is another commonly used chromium VI reagent. However, the rate of oxidation is so fast that selective oxidation of polyhydroxy steroids is often not possible even when only one equivalent is used.[160]

Chromic anhydride, on the other hand, can be used to selectively oxidise polyhydroxy steroids and the order of oxidation appears to be almost the reverse of that found with the Oppenauer reagent. In the cholic acid series, the following order prevails: C7 > C12 > C3.[146] C6 and C11 hydroxyls are also oxidised in preference to C3, and C11 is oxidised in preference to C20.

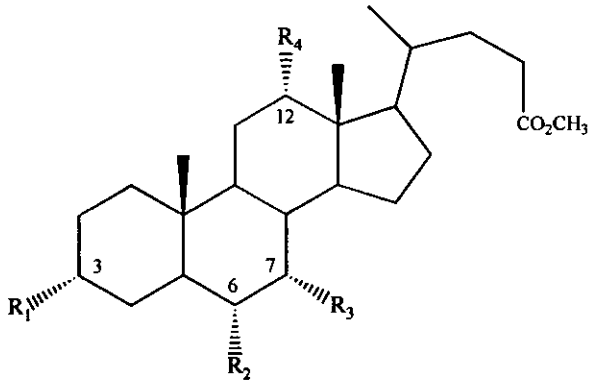
N-halogen compounds used in steroid hydroxyl oxidations include N-bromosuccinimide (NBS) and N-bromoacetamide (NBA). Axial alcohols are oxidised faster than equatorial alcohols indicating that relief of strain is an important factor. In contrast to the chromium VI oxidations, these oxidations show a preference for those equatorial hydroxyls where the axial αH is in a less crowded, more accessible enviroment[162] and it has been shown that an equatorial 3-hydroxyl may be oxidised in preference to an equatorial 11α or 6α hydroxyl. Fieser and Rajagopalan report that the selectivity demonstrated in these reactions is associated with the solvent as well as the oxidising agent.[158] In aqueous bicarbonate, for example, NBS attacks at C7 preferentially and leaves C3 and C12 untouched whereas in aqueous t-butanol, all three hydroxyl groups in cholic acid (C3, C7 and C12) are oxidised rapidly by NBS or NBA.[163]

A further example is silver carbonate-celite which has been used to selectively oxidise bile acid esters giving the 3-keto derivatives in the presence of both C7 and C12 hydroxyls.[164] Tserng was able to isolate pure 3-keto bile acids in good yields 70-90% by simply filtering the reaction mixture and concentrating the filtrate. The observed selectivity is explained by the three dimensional arrangement of the alcohol required on the solid surface of the oxidising reagent for oxidation to take place. 3-keto bile acids have traditionally been synthesised from bile acid esters by Oppenauer oxidation with aluminium tert-butoxide and acetone. However this often resulted in complicated mixtures of products and column chromatography was needed to isolate the desired 3-keto bile acids from the mixture and consequently yields were low,[165,166] hence Tserng's work was a substantial improvement on this.

4.2 OXIDATION OF BILE ACID METHYL ESTERS USING DIMETHYLDIOXIRANE

It was therefore decided to investigate the selectivity of dimethyldioxirane when used to oxidise a series of bile acid methyl esters. Some work has already been carried out in these laboratories by the Marples group which indicates that dimethyldioxirane shows some selectivity in the oxidation of axial hydroxyls over equatorial hydroxyls. Partial oxidation (ca. 60%) of an equimolar mixture of 5α-cholestan-3α-ol and its 3β epimer resulted in an α:β ratio of 0.54:1 showing greater reactivity (greater than 1.5 times) of the axial alcohol.[88]

Four bile acid methyl esters **153** were chosen, containing both axial and equatorial hydroxyl groups. These were prepared from the corresponding acid using one of two methods - either methanol / chlorotrimethylsilane or an ethereal solution of diazomethane.



153

a methyl cholate

R_1 = OH (3α, equatorial)
R_2 = H
R_3 = OH (7α, axial)
R_4 = OH (12α, axial)

b methyl deoxycholate

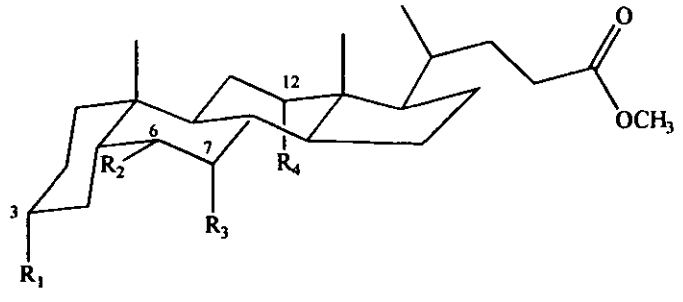
R_1 = OH (3α, equatorial)
R_2 = R_3 = H
R_4 = OH (12α, axial)

c methyl chenodeoxycholate

R_1 = OH (3α, equatorial)
R_2 = R_4 = H
R_3 = OH (7α, axial)

d methyl hyodeoxycholate

R_1 = OH (3α, equatorial)
R_2 = OH (6α, equatorial)
R_3 = R_4 = H



The oxidations were carried out at 0-5°C in acetone using one or two equivalents of dimethyl-dioxirane. After approximately 16 hours, the reaction mixtures were concentrated *in vacuo* and the products separated by column chromatography and identified by NMR spectroscopy. The results are shown in Table 20.

In the proton NMR spectrum, the oxidation at a particular site is indicated by the loss of the β proton at that site. For example, oxidation of the C3 hydroxyl can be seen at a glance by the loss of the distinctive signal corresponding to the 3β proton. In addition to this, oxidation at C3 and subsequent loss of the 3β proton affects the splitting pattern of the adjacent C4 protons and this is apparent in the spectrum by the formation of a multiplet at δ2.75 in the 3-oxo-12α-hydroxy compound and at slightly lower field (approximately δ3.4) in the 3-oxo-7α-hydroxy and the 3-oxo-7α,12α-dihydroxy compounds where the presence of the C7 hydroxyl results in increased deshielding. Similarly, loss of the 7β proton in the formation of the 7-oxo derivatives affects the splitting pattern of the adjacent C8 proton which results in the appearance of a double doublet at approximately δ2.8.

It can be seen from Table 20 that with methyl cholate **153a**, oxidation took place at both C3 and C7 but none took place at C12. No preference for the axial 7α hydroxyl over the equatorial 3α hydroxyl was seen, in fact slightly more oxidation took place at the less hindered 3 position than at the 7 position. With methyl deoxycholate **153b**, again no oxidation was seen at C12. The 3-oxo-12α-hydroxy derivative was the only product even with 2 equivalents of dioxirane. In the case of methyl chenodeoxycholate **153c**, both the C3 and C7 sites were oxidised, again with more oxidation taking place at the less hindered 3 position rather than at the axial 7α hydroxyl when only one equivalent of dioxirane was used. Finally, with methyl hyodeoxycholate **153d**, where both hydroxyls are equatorial to the ring, it was the C3-hydroxyl which was oxidised preferentially over the C6.

No evidence therefore for any selectivity for axial over equatorial hydroxyls was observed, but rather it was the hydroxyl at the least sterically hindered C3 position which was oxidised preferentially. Significant oxidation did take place at C7 and some at C6 but no oxidation was observed at the 12 position which is hindered by the C18 methyl group and to a greater extent by the C21 methyl group of the side chain. The C7 is also slightly hindered by the C19 methyl group but this is much less pronounced than at the C12 position.

Table 20

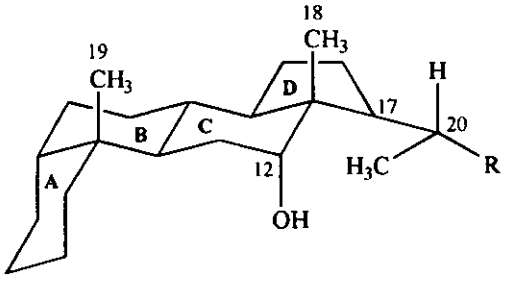
Oxidation of bile acid methyl esters using dimethyldioxirane.

	Isolated yields			
methyl cholate 153a	**3-oxo-7α,12α-dihdroxy**	**7-oxo-3α,12α-dihydroxy**	**3,7-dioxo-12α-hydroxy**	
1 equivalent of dimethyldioxirane	26%	21%	25%	
2 equivalents of dimethyldioxirane	9%	6%	61%	
methyl deoxycholate 153b	**3-oxo-12α-hydroxy**	**starting material**		
1 equivalent of dimethyldioxirane	59%	25%		
2 equivalents of dimethyldioxirane	75%	-		
methyl chenodeoxycholate 153c	**3-oxo-7α-hydroxy**	**7-oxo-3α-hydroxy**	**3,7-dioxo**	**starting material**
1 equivalent of dimethyldioxirane	36%	25%	14%	18%
2 equivalents of dimethyldioxirane	-	-	91%	-
methyl hyodeoxycholate 153d	**3-oxo-6α-hydroxy**	**3,6-dioxo**		
1 equivalent of dimethyldioxirane	78%	8%		
2 equivalents of dimethyldioxirane	69%	18%		

These results provide further evidence for the proposed butterfly transition state (Figure 4).[88] The C3 position allows the unhindered approach of the dioxirane and so the transition state can be formed with ease whereas the steric hindrance of the C21 methyl group prevents the formation of such a transition state at C12.

The deactivation of the C12 hydroxyl in bile acid derivatives has been noted previously by several groups including Blickenstaff *et al.*[167-169] This group synthesised a series of 7α,12α-dihydroxy steroids with differing side chains, which included a range of electron-withdrawing and electron-releasing groups, and found that all were acetylated selectively at the 7-hydroxyl in comparable

yields.[169] This indicated that the nature of the terminus of the side chain is immaterial and that the deactivation of the 12-hydroxyl is most likely a steric phenomenon. (They also found that the reactivity of the C12 hydroxyl can be enhanced by a 3α substituent.[170]) Further work by Blickenstaff *et al* showed that this side chain shielding in the 7α,12α-dihydroxy steroids can be defined as steric inhibition by the C21 methyl group.[171] Any R group as large or larger than a methyl group will tend to assume an orientation away from the C18 angular methyl group as shown in **154** (in the case of the bile acid methyl esters, R = $CH_2CH_2CO_2CH_3$). This configuration requires the C21 methyl to point towards the 12α-hydroxyl. With the A ring inhibiting the approach of the reagent from one direction and the C21 methyl similarly inhibiting the approach from the other direction, the 12α-hydroxyl is unreactive. In support of this, Blickenstaff found that unbranched side chains give rise to very reactive 12α-hydroxyl groups.



154

4.3 CONCLUSIONS

It was found that, while dimethyldioxirane did show some selectivity for the less hindered C3 position, in the majority of cases, mixtures of products were obtained which required separation by column chromatography. In this respect dimethyldioxirane showed no advantage over the more traditionally used oxidising agents.

Chapter 5

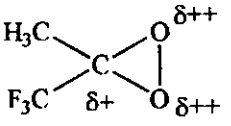
INVESTIGATION INTO THE USE OF TRIFLUOROMETHYL ARYL KETONES AS CATALYSTS IN OXONE®-MEDIATED EPOXIDATIONS

5.1 INTRODUCTION

Methyl(trifluoromethyl)dioxirane is a more powerful oxidant than dimethyldioxirane and it may be generated effectively from 1,1,1-trifluoroacetone and Oxone® *in situ*.

When considering a ketone as a potential catalyst in reactions of this type, it is important to assess both the ability of the ketone to form a dioxirane and its ability to then transfer oxygen to the substrate. Also, the propensity for irreversible ketone consumption via the Baeyer-Villiger reaction should be considered.

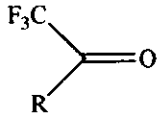
The introduction of a trifluoromethyl group α to the carbonyl in a ketone allows a more reactive electron deficient dioxirane to be formed due to an increase in electrophilicity of the dioxirane **155**. The presence of an electron-withdrawing group will also suppress the Baeyer-Villiger oxidation pathway by significantly reducing the migratory aptitude of the α substituent.



155

Methyl(trifluoromethyl)dioxirane may be generated *in situ* using acetonitrile / water as the medium.[172] In the more conventional biphasic system however (dichloromethane / water), hydrophilicity is reported to be important and 1,1,1-trifluoroacetone is not a very effective catalyst for Oxone®-mediated reactions.[10] In spite of the fact that the carbonyl group in methyl(trifluoromethyl)dioxirane is highly activated towards nucleophilic attack and therefore will readily react with Oxone®, a loss of reactivity results due to its water solubility and the formation of a stable hydrate. Furthermore, 1,1,1-trifluoroacetone is relatively expensive and not readily recyclable owing to its volatility.

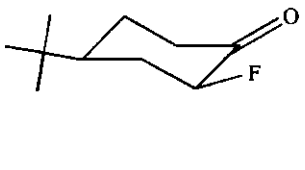
In his search for a general and efficient catalyst for use in epoxidations using Oxone®, Denmark recently investigated the use of fluoroketones, **156** and **157**, and found that while 2 equivalents of these ketones could be used efficiently in a biphasic system, they were not effective as catalysts (0.1 equivalents gave only 6% conversion to the epoxide after 24 hours).[12]



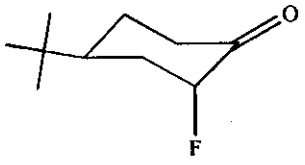
156 R = n-C_6H_{13}

157 R = n-$C_{10}H_{21}$

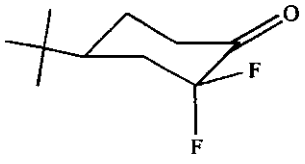
Denmark therefore turned his attention to mono- and difluorinated ketones. Five fluorocyclohexanones bearing one or two α fluorine substituents were examined **158-162**.



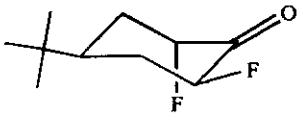
158



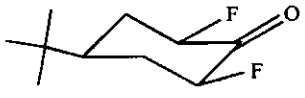
159



160



161



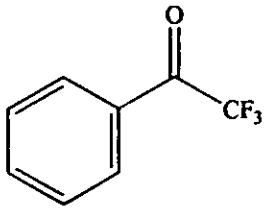
162

Denmark used 4-tert-butylcyclohexanone as reference and found that under monophasic conditions using 0.1 equivalents of ketone, both monofluoroketones, **158** and **159**, were superior to 4-tert-butylcyclohexanone and that the epoxidation efficiency was highly dependent on the orientation of the fluorine substituent. Ketone **158** with the equatorial fluorine was more effective than ketone **159** which has an axial fluorine substituent. All three difluorinated ketones were more efficient catalysts than 4-tert-butylcyclohexanone and the activity again depended on the the orientation of the fluorine substituents. Adding a second α fluorine axial to the ring either geminally as in **160** or trans-2,6 as in **161** decreased the reactivity compared to **158**, whereas placing a second α fluorine in an equatorial position as in cis-2,6 **162** increased the reactivity compared to **158**. Denmark also noted different stability of the various ketones under the reaction conditions. **158** and **160-162** were stable but **159** converted to the lactone via the Baeyer-Villiger reaction.

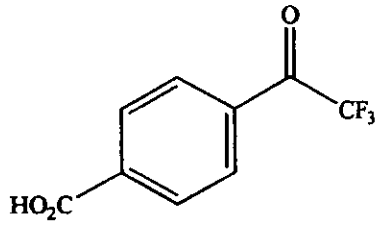
Some preliminary work on the use of other fluoroketones as dioxirane precursors was carried out in these laboratories by James Muxworthy of the Marples group.[174] He decided that perhaps a fluoro-substituted aromatic ring α to the carbonyl would increase the electrophilicity of the dioxirane. To investigate this idea, Muxworthy took a series of aromatic fluoroketones in a biphasic Oxone® / ketone system and assessed their ability to oxidise cyclohexene to cyclohexene oxide. He found that out of the ketones tested (Table 21), trifluoroacetophenone **163**, which has a trifluoromethyl group α to the carbonyl rather than a fluoro-substituted aromatic ring was the most reactive. (This ketone has previously been reported as a catalyst in the oxidation of sulfides in the presence of bovine serum albumin.[175])

In continuation of Muxworthy's work, we decided to explore further the reactivity of fluoroketones as oxidation catalysts. We reasoned that if the ketone was also an acid, it could lead to the development of an effective biphasic Oxone® / ketone system from which the ketone could easily be recovered and recycled. This also leads to the possibility of binding the ketone to a suitably functionalised resin thus providing a re-usable solid phase catalyst.

The initial aim of this work therefore was to select a suitable ketone and investigate its ability to act as a dioxirane precursor in an optimised Oxone® / ketone system. The simple, commercially available 4-(trifluoroacetyl)benzoic acid **164** was chosen and various *in situ* methods described in the literature were taken as a starting point in the development of an optimum procedure.



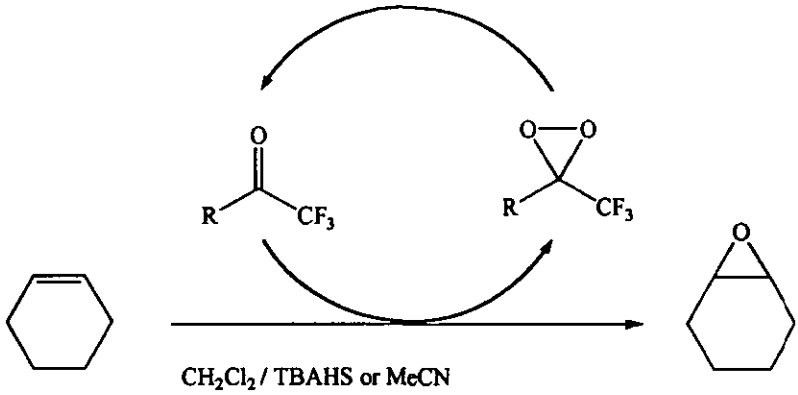
163



164

5.2 OPTIMISATION OF THE OXONE® / KETONE *IN SITU* OXIDATION SYSTEM USING TRIFLUOROACETOPHENONE AND 4-(TRIFLUORO-ACETYL)BENZOIC ACID

The general outline of the Oxone® / ketone system using cyclohexene as substrate is shown in Scheme 99.



Scheme 99

5.2.1 Method A, based on work by J. Muxworthy[174]

As already mentioned, James Muxworthy carried out a study[174] to investigate the ability of a series of aromatic fluoroketone-derived dioxiranes, generated *in situ* in a biphasic system, to oxidise cyclohexene to cyclohexene oxide. We decided to start by extending this investigation by carrying out similar reactions using 4-(trifluoroacetyl)benzoic acid as the dioxirane precursor, comparing its reactivity with the reactivity of acetone and the other ketones listed in Table 21.

It was decided to first repeat the reaction using trifluoroacetophenone. A solution of cyclohexene (1 equivalent) in dichloromethane was cooled to 0-5°C and trifluoroacetophenone (1 equivalent), t-butyl ammonium hydrogen sulfate (0.32 equivalents) and phosphate buffer (pH 7.5) were added. The pH of the solution was maintained by addition of potassium hydroxide solution using a pH stat. A solution of Oxone® (2.7 equivalents) and EDTA in water was then added dropwise over 25

minutes and the mixture left stirring for a further 2 hours 20 minutes giving a total reaction time of 2.75 hours. The relative proportions of cyclohexene and cyclohexene oxide present at the end of this time were determined using GC analysis. 31% conversion was obtained after 2.75 hours compared to 20% reported by Muxworthy. It was found that on continuing this reaction for a further 1.25 hours, the conversion increased to 68%. The reaction was then repeated in the absence of ketone. After a reaction time of 2.75 hours, a conversion of 19% was obtained, which is comparable with the conversion obtained by Muxworthy in the presence of trifluoroacetophenone. The other ketones used in Muxworthy's study also gave similar results ranging from 15-21%. Allowing the blank reaction to continue for a total of 5 hours gave 35% cyclohexene oxide. This result proved unexpected as it has been well documented in the literature that under typical biphasic *in situ* conditions, no epoxidation will occur in the presence of Oxone® alone. Muxworthy therefore not unreasonably chose to compare the reactivity of the fluoroketones against the reactivity of acetone as for this methodology to be worthwhile pursuing, an improvement over the conversion obtained with acetone was desirable.

Muxworthy carried out a second set of reactions, performed in a similar manner except that three times the amount of Oxone® was used (8.1 equivalents). This was added dropwise as an aqueous solution in three portions and the reaction stirred for a total of 4 hours. Repeating this reaction using trifluoroacetophenone, 66% conversion was obtained compared to 74% reported by Muxworthy. Under the same conditions in the absence of ketone, 47% conversion was obtained. This time, a greater difference was seen between the result obtained using trifluoroacetophenone and that obtained in the absence of ketone. The result for the latter however is similar to the results obtained by Muxworthy when using the other ketones, including acetone (45-57%).

To summarise, at the shorter reaction time of 2.75 hours, all the results both in the presence and absence of ketone are very similar. At the longer reaction time, it seems that trifluoroacetophenone does increase the conversion (average conversion 70%) over the blank reaction (47%) but that the reaction proceeds to some extent in the absence of ketone. It was therefore decided not to continue with this method and 4-(trifluoroacetyl)benzoic acid was not used. Other *in situ* methods described in the literature were of interest to us including those employed by Armstrong[15] and Yang[39,172,173] in which no rigorous pH control is necessary. These methods are discussed in the following sections.

Table 21

J. Muxworthy's results for the reaction of cyclohexene with Oxone® / ketone in a biphasic system according to method A.

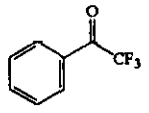
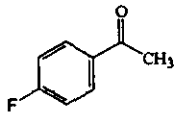
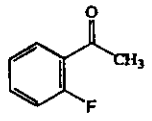
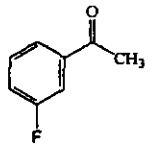
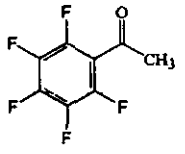
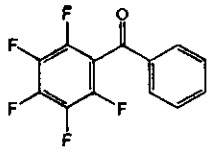
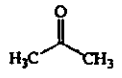
ketone (1 equivalent)	% wt cyclohexene oxide	
	2.7eq Oxone® / 2.75 hours	8.1eq Oxone® / 4 hours
	20%	74%
	21%	57%
	18%	53%
	18%	56%
	15%	50%
	21%	45%
	-	47%

Table 22

Results obtained when the reaction of cyclohexene with Oxone® / ketone in a biphasic system according to method A was repeated.

ketone (1 equivalent)	% wt cyclohexene oxide	
	2.7eq Oxone® / 2.75 hours	8.1eq Oxone® / 4 hours
trifluoroacetophenone	31%	66%
ketone absent	19%	47%

5.2.2 Method B, based on work by A. Armstrong[15]

Recently published work by Armstrong[15] employed a much simpler biphasic method which is a modification of the conditions reported by Curci.[11a] Cyclohexene was used as the substrate with 4-tert-butylcyclohexanone as the ketone. No excess of ketone was used and only a slight excess of Oxone® (1.2 equivalents). The pH was controlled using a 1M aqueous sodium bicarbonate buffer solution (3.4 equivalents). The cyclohexene, ketone, aqueous sodium bicarbonate and phase transfer catalyst (t-butylammonium hydrogen sulfate) in dichloromethane / aqueous EDTA solution were cooled to 0°C and the Oxone® added as an aqueous solution in one single portion. Stirring was continued at 0°C for 5 hours and the reaction monitored by GC.
In the presence of 4-t-butylcyclohexanone, Armstrong reported 15% conversion of cyclohexene to cyclohexene oxide after 5 hours. Under the same reaction conditions in the absence of ketone, 2% conversion was reported. Armstrong observed that while a conversion of 15% may appear low, Curci,[11a] who obtained similar results, used a large excess of acetone (10 equivalents) in his studies and Denmark[10] who has reported 50% conversion after 24 hours for the epoxidation of E-6-benzyloxyhex-2-ene with Oxone® (10 equivalents) and acetone (1 equivalent) used strict pH control using a pH stat.

We decided to try Armstrong's procedure using trifluoroacetophenone as the dioxirane precursor. Reactions using 4-tert-butylcyclohexanone and in the absence of ketone were also carried out for comparison purposes. The reactions were monitored by GC and the results are shown in Table 23. It was also intended to use acetone but the GC method did not give satisfactory peak resolution therefore it was omitted.
After a reaction time of 16 hours, the results are all very similar including the reaction done in the absence of ketone (although this did show some variation, with conversions ranging from 13-23%). However, if the results obtained after a reaction time of 6 hours are compared, the trifluoroacetophenone reaction shows an almost twofold improvement over the other ketones. This difference becomes less apparent at the longer reaction times. It could be therefore that trifluoroacetophenone does catalyse the reaction but that the same result can be achieved in the absence of ketone provided that the reaction is left for a long enough period of time.
Under these conditions, 4-tert-butylcyclohexanone does not appear to be effective as at no point did it show any significant improvement over the blank reaction. The 5 hour reaction using 4-tert-butyl-

cyclohexanone was done in duplicate and both reactions gave 9% conversion. The 5 hour blank reaction was also done in duplicate and both these reactions gave 8% conversion. This is in contrast to Armstrong who reported a seven times improvement over the blank reaction after 5 hours using 1 equivalent of 4-tert-butylcyclohexanone. Increasing the amount of 4-tert-butylcyclohexenone from 1 equivalent to 5 equivalents also showed no improvement over the blank.

If trifluoroacetophenone is involved in the reaction, it might be expected that increasing the level from 1 equivalent to 5 equivalents would result in an increase in conversion. It can be seen from Table 24 that when stirred for approximately 16 hours, the reaction with 5 equivalents of trifluoroacetophenone gave a very similar result (28%) to that obtained with 1 equivalent (24-29%) and with the blank reaction (13-23%). If, however, the reaction is stopped after 3 hours or even 6 hours, a small difference can be seen. (An average conversion of 12% after 3 hours with 1 equivalent compared to 21% after 3 hours with 5 equivalents.)
It would seem from these results that some oxidation is taking place in the presence of Oxone® alone but at a slower rate than when trifluoroacetophenone is present. If allowed to go to completion, the end result of both reactions is similar. It might be expected then that an increase in the amount of Oxone® used would increase the conversion. However, it was found that doubling the amount of Oxone® to 2.5 equivalents in the presence of 1 equivalent of trifluoroacetophenone had no effect (Table 25). In the absence of ketone, 2.5 equivalents of Oxone® showed no significant improvement over 1.2 equivalents after 16 hours, but after 6 hours, 18% conversion was achieved compared to 9% with 1.2 equivalents. It should be noted that the amount of sodium bicarbonate was not increased accordingly, however at 3.4 equivalents it was still present in excess.

One of the problems in carrying out reactions of this type is the number of variables involved. There are many factors affecting these reactions which can sometimes lead to inconsistent results. One of these factors is the rate of stirring.[176] A reaction was carried out using 1 equivalent of trifluoroacetophenone exactly as described above except the agitation rate was reduced to a slow stir. After stirring at such a rate for approximately 16 hours, it was found that the conversion was less than half that expected. (6% after 5 hours increasing to 10% after 16 hours compared with an average of 29% when stirred vigorously.) A blank reaction carried out with slow stirring gave only 0.5% conversion after 5 hours and 2% after 16 hours, which increased to 10% after 72 hours.

Table 23

The results of the reactions of cyclohexene with Oxone® / ketone in a biphasic system according to Method B, based on Armstrong's work[4] (1 equivalent of ketone, 1.2 equivalents of Oxone®, 3.4 equivalents of $NaHCO_3$, 0°C)

ketone (1 equivalent)	% wt cyclohexene oxide				
	3 hours	5 hours	6 hours	7 hours	16 hours
trifluoroacetophenone		17%			29%
				15%	24%
					28%
					29%
	12%		17%		
4-t-butylcyclohexanone		9%			25%
		9%			22%
	6%		10%		
no ketone	6%		9%		
				10%	21%
					13%
			9%		
	4%		9%		
		8%			20%
		8%			23%

Table 24

The results of the reactions of cyclohexene with Oxone® / ketone in a biphasic system according to Method B but with the ketone increased from 1 equivalent to 5 equivalents

ketone (5 equivalents)	% wt cyclohexene oxide				
	3 hours	5 hours	6 hours	7 hours	16 hours
trifluoroacetophenone	17%		23%		28%
	25%		29%		
4-t-butylcyclohexanone	6%		8%		

Table 25

The results of the reaction of cyclohexene with Oxone® in a biphasic system according to Method B but with double the amount of Oxone® (2.5 equivalents)

ketone (1 equivalent)	% wt cyclohexene oxide				
	3 hours	5 hours	6 hours	7 hours	16 hours
trifluoroacetophenone	9%		14%		22%
no ketone	10%		18%		22%

One variable thought not to have a great effect in this method is the reaction temperature. This is true provided all reactions are allowed to go to completion. It was found that after stirring for 7 hours, the reactions carried out at room temperature gave an average conversion of 26% which did not increase after 16 hours. This is a similar result to that obtained after 16 hours in the reactions carried out at 0°C.

It was decided to look at using method B with a second substrate and *trans*-stilbene was chosen. Using trifluoroacetophenone, 2% *trans*-stilbene oxide was obtained after 2 hours and only 4% after 16 hours. It was not necessary to carry out a blank reaction as this result indicated that under these conditions *trans*-stilbene is not being oxidised to any significant extent by the ketone / Oxone® system or by Oxone® alone. (In contrast, the same reaction with cyclohexene gave 29% cyclohexene oxide in the presence of trifluoroacetophenone and 21% with Oxone® alone.)

5.2.3 Methods C and D, based on work by D. Yang[39,172]

An alternative method for *in situ* epoxidations is given by Yang[172] in his paper on the epoxidation of olefins using methyl(trifluoromethyl)dioxirane. This method (referred to as method C) involves using a much larger excess of ketone (11 equivalents) than used by either Muxworthy[174] or Armstrong[15] and the reaction mixture is homogenous (acetonitrile / water, 1.5:1) rather than biphasic. Sodium bicarbonate (7.75 equivalents) is used as the buffer and this is added in portions as a solid mixture with the Oxone® (5 equivalents) at 0°C.

In a further publication[39] on the use of chiral ketones for the catalytic asymmetric epoxidation of unfunctionalised olefins, Yang uses a slightly modified method (referred to as method D). Again a large excess of ketone (10 equivalents) and 5 equivalents of Oxone® are used but in this method the amount of sodium bicarbonate is increased twofold to 15.5 equivalents. The bicarbonate and Oxone® are added as a solid mixture in portions as in method C, but this time the reaction is done at room temperature rather than 0°C. The reaction mixture is also twice as dilute, maintaining the 1.5:1 ratio of organic to aqueous.

It was found that cyclohexene was not a suitable substrate for this type of reaction as cyclohexene and acetonitrile are insufficiently miscible. It was therefore decided to carry out two sets of reactions, one using *trans*-stilbene as the substrate in the acetonitrile / water homogenous mixture

and one using cyclohexene in a biphasic mixture in which the acetonitrile is replaced with the same quantity of dichloromethane.

5.2.3.1 Oxidation of *trans*-stilbene using Oxone® / ketone in a homogenous acetonitrile / water system according to methods C and D

Several preliminary reactions were carried out using a procedure based on Yang's first method[172] (method C) using trifluoroacetophenone as the ketone catalyst.
A solid mixture of Oxone® (5 equivalents) and sodium bicarbonate (7.75 equivalents) was added in portions to the reaction mixture consisting of 1 equivalent of *trans*-stilbene and 11 equivalents of trifluoroacetophenone in a solution of acetonitrile / water (1.5:1) at 0°C. The results are shown in Table 26. An average conversion of 77% was obtained. It was found that two important factors in this reaction are as follows: one, the addition of the Oxone® / bicarbonate mixture must be done slowly in portions, and two, there must be a large excess of ketone. When a reaction was carried out in which the Oxone® / bicarbonate mixture was added quickly in one portion, the yield dropped significantly to only 20%, and when only 1 equivalent of trifluoroacetophenone was used, a very poor conversion of only 5% was obtained. The use of a smaller excess of ketone (5 equivalents rather than 11 equivalents) gave a similar very poor result.

A series of reactions were then carried out based on Yang's second method (method D).[39] Yang used 10 equivalents of ketone but here only 5 equivalents were used. It was found that under these conditions, using *trans*-stilbene as substrate and trifluoroacetophenone as ketone, 100% conversion to the epoxide was achieved. (Yang reported a similar result using 10 equivalents of trifluoroacetophenone after 70 minutes by TLC.) This reaction was repeated several more times, with consistently high conversions (Table 27) and it was found using 2 equivalents of ketone also gave an excellent 99% conversion. This is in contrast to the 3% conversion obtained with 5 equivalents using method C, which indicates that a larger excess of bicarbonate, a more dilute reaction mixture and / or a higher reaction temperature have an important effect. It was found however than an excess of trifluoroacetophenone is still required as carrying out the reaction with 1 equivalent gave only 17% conversion.

Table 26

The results of the reactions of *trans*-stilbene with Oxone® / trifluoroacetophenone in an acetonitrile / water mixture according to method C, based on Yang's work[172]
(5 equivalents of Oxone®, 7.75 equivalents of sodium bicarbonate, 0°C).

number of equivalents of trifluoroacetophenone	% wt trans-stilbene oxide	
	2.75 hours	16 hours
11		73%
11	58%	80%
5		3%
1		5%

Table 27

The results of the reactions of *trans*-stilbene with Oxone® / trifluoroacetophenone in an acetonitrile / water mixture according to method D, based on Yang's work[39]
(5 equivalents of Oxone®, 15.5 equivalents of sodium bicarbonate, room temperature).

number of equivalents of trifluoroacetophenone	% wt trans-stilbene oxide number of equivalents after 16 hours
5	100%
5	95%
5	98%
5	96%
2	99%
1	17%
0.5	18%
0	9%

The reaction was then carried out using 2 equivalents of 4-(trifluoroacetyl)benzoic acid and a similar excellent conversion of 97% was obtained. However, reducing the amount of acid to just 1 equivalent gave only 15% conversion (Table 28). In the absence of ketone, 4% conversion was obtained, which indicates that Oxone® alone is not capable of epoxidising *trans*-stilbene under these conditions. A similar result was reported by Yang using chalcone as substrate.[172]

Some of the epoxidation activity of 4-(trifluoroacetyl)benzoic acid may arise from the presence of the carboxylic acid functionality, which may be converted to the peracid by the Oxone®. To investigate this possibility, reactions were carried out replacing the ketone with benzoic acid and with 4-chlorobenzoic acid. These acids are less soluble than 4-(trifluoroacetyl)benzoic acid, therefore the reactions were carried out in more dilute mixtures. Five times more acetonitrile / water were used, maintaining the 1.5:1 ratio and the 4-(trifluoroacetyl)benzoic acid reaction was repeated at a similar dilution. 5 equivalents of acid were used in each case. After approximately 16 hours, 99% conversion was obtained with 4-(trifluoroacetyl)benzoic acid as expected. Using benzoic acid, the results were inconsistent. 9% conversion was obtained in the first reaction followed by 37% when the reaction was repeated. A longer reaction time of 96 hours gave 75% conversion. 4-chlorobenzoic acid gave some oxidation (20%) despite being fairly insoluble in acetonitrile. Diluting the reaction mixture a further five times had no significant effect.

From these results, it seems that the oxidation obtained with 4-(trifluoroacetyl)benzoic acid could be due in part to peracid formation as well as dioxirane formation. Oxone® does not appear to work alone under these conditions, therefore in the presence of trifluoroacetophenone the epoxidation must be assumed to be solely due to dioxirane formation. Any oxidation due to peracid formation in the case of (trifluoroacetyl)benzoic acid is therefore probably slow and not to a great extent.

It was concluded that for both trifluoroacetophenone and 4-(trifluoroacetyl)benzoic acid, 2 equivalents was the optimum and on the basis of these results it was felt that method D using 4-(trifluoroacetyl)benzoic acid was suitable for further development with a view to preparing a reusable solid phase catalyst for the simple, clean epoxidation of olefins. Work in this area was continued by my co-workers, Todd Boehlow and Estella Grocock and this work has recently been published.[177]

Table 28

The results of the reactions of *trans*-stilbene with Oxone® / 4-(trifluoroacetyl)benzoic acid in an acetonitrile / water mixture according to method D, based on Yang's work[39]
(5 equivalents of Oxone®, 15.5 equivalents of sodium bicarbonate, room temperature).

number of equivalents of 4-(trifluoroacetyl)benzoic acid	% wt trans-stilbene oxide after 16 hours
5	94%
2	97%
1	15%
0.5	10%
0	4%

Table 29

The results of the reactions of *trans*-stilbene with Oxone® / acid in an acetonitrile / water mixture according to method D, based on Yang's work[39] (5 times increased dilution)
(5 equivalents of Oxone®, 15.5 equivalents of sodium bicarbonate, room temperature)

acid (5 equivalents)	% wt trans-stilbene oxide	
	16 hours	96 hours
4-(trifluoroacetyl)benzoic acid	99%	
benzoic acid	9%	
	37%	
		75%
4-chlorobenzoic acid	20%	
	26% *	

* reaction diluted a further 5 times

5.2.3.2 Oxidation of cyclohexene using Oxone® / ketone in a biphasic system according to method D

Table 30 shows the results for the reactions of cyclohexene with Oxone® / ketone using a procedure based on Yang's second method (method D), but using a dichloromethane / water solvent system rather than acetonitrile / water. t-Butyl ammonium hydrogen sulfate was used as phase transfer catalyst and 5 equivalents of ketone were used as a starting point.

The reactions were carried out using trifluoroacetophenone, 4-(trifluoroacetyl)benzoic acid, in the absence of ketone and also using 4-tert-butylcyclohexanone for comparison with method B.
In the absence of ketone, it was found that no reaction took place. This is in contrast to the results obtained using methods A and B with cyclohexene in a biphasic system. The reaction using 4-tert-butylcyclohexanone was very poor, giving a similar result to the blank, as in method B. Trifluoroacetophenone and 4-(trifluoroacetyl)benzoic acid both worked reasonably well although the results were very variable. With trifluoroacetophenone the mean conversion was 51%, although conversions as low as 28% and as high as 94% were obtained. The mean conversion with the 4-(trifluoroacetyl)benzoic acid was 55%.

To investigate the possibility of peracid involvement, a series of reactions were again carried out replacing the ketone with benzoic acid and 4-chlorobenzoic acid. These reactions were carried out at a higher dilution (five times) and the results are shown in Table 31. The conversions obtained with benzoic acid after 16 hours are significantly better (mean 40%) than those obtained in the blank reaction and are comparable to the conversion obtained with 4-(trifluoroacetyl)benzoic acid (43%) at a similar dilution. 4-chlorobenzoic acid was found to be poorly soluble in dichloromethane and gave a lower conversion of 15%. The dilution was increased a further five times but this did not improve the solubilty or the conversion. The reaction did however show a five times increase over the blank reaction which indicated that peracid formation was taking place. It is difficult to say to what extent this is occurring with 4-(trifluoroacetyl)benzoic acid but the results obtained with trifluoroacetophenone indicate that dioxirane formation is also contributing to the epoxidation.

Table 30

The results of the reactions of cyclohexene with Oxone® / ketone in a biphasic system according to Method D (based on work by Yang).
(5 equivalents of Oxone®, 15.5 equivalents of sodium bicarbonate, room temperature)

ketone (5 equivalents)	% wt cyclohexene oxide	
	5 hours	16 hours
trifluoroacetophenone		35%
		48%
	28%	28%
		94%
		44%
	52%	55%
4-(trifluoroacetyl)benzoic acid	42%	48%
		68%
	55%	61%
no ketone	2%	1%
		3%
		3%
		7%
4-t-butylcyclohexanone		3%

Table 31

The results of the reactions of cyclohexene with with Oxone® / carboxylic acid in a biphasic system according to Method D, based on work by Yang (5 times increased dilution)
(5 equivalents of Oxone®, 15.5 equivalents of sodium bicarbonate, room temperature)

acid (5 equivalents)	% wt cyclohexene oxide	
	5 hours	16 hours
benzoic acid	10%	32%
		48%
4-chlorobenzoic acid		15%
		16% *
4-(trifluoroacetyl)benzoic acid		43%

* reaction diluted a further 5 times

It was decided to extend this study to look at a second substrate. *Trans*-stilbene was chosen in order to compare the extent of oxidation in the biphasic system with that in the homogenous acetonitrile / water system, which was found to give excellent conversions when using both trifluoroacetophenone and 4-(trifluoroacetyl)benzoic acid.

5.2.3.3 Oxidation of *trans*-stilbene using Oxone® / ketone in a biphasic system according to method D

The epoxidation of *trans*-stilbene in acetonitrile / water using Yang's reaction conditions (method D) proved very successful (section 5.2.3.1). The following reactions explore the possibility of using a biphasic system rather than the homogenous system for the *trans*-stilbene reaction. Cyclohexene was oxidised satisfactorily under these conditons (section 5.2.3.2) and if this system also works well with *trans*-stilbene, it would be a suitable method to develop, enabling a wider range of substrates to be used than would be possible with the homogenous system.

Using 1 equivalent of *trans*-stilbene, 5 equivalents of trifluoroacetophenone, 5 equivalents of Oxone® and 15.5 equivalents of sodium bicarbonate in dichloromethane / water (1.5:1) at room temperature with a catalytic amount of phase transfer catalyst, conversions ranging from 24-77% were obtained (Table 32), compared to 100% in acetonitrile with only 2 equivalents of trifluoro-acetophenone. Increasing the amount of trifluoroacetophenone twofold to 10 equivalents in the biphasic system gave a good conversion of 85%, but this did require the much larger excess of ketone. Using only 2 equivalents of trifluoroacetophenone in the biphasic system gave 34% conversion. In the absence of ketone, only 1-3% conversion was obtained.
The reaction was repeated using 4-(trifluoroacetyl)benzoic acid and the conversions obtained were lower than those obtained with trifluoroacetophenone. With 5 equivalents of acid, conversions ranging from 9-22% were obtained and with 10 equivalents of acid, only 14% was achieved.

Again, the use of benzoic acid and 4-chlorobenzoic acid in place of 4-(trifluoroacetyl)benzoic acid was investigated, using a five times more dilute solution (Table 33). With 4-chlorobenzoic acid there were solubility problems and these reactions did not work at all, even on further dilution.

Table 32

The results of the reactions of *trans*-stilbene with Oxone® / ketone in a biphasic system according to Method D (based on work by Yang).
(5 equivalents of Oxone®, 15.5 equivalents of sodium bicarbonate, room temperature)

number of equivalents of ketone	% wt trans-stilbene oxide after 16 hours	
	trifluoroacetophenone	4-(trifluoroacetyl)benzoic acid
10	85%	14%
5	77%	9%
	24%	22%
	34%	14%
	26%	
	41%	
2	34%	
0	1%	
	3%	

Table 33

The results of the reactions of *trans*-stilbene with with Oxone® / carboxylic acid in a biphasic system according to Method D, based on work by Yang (5 times increased dilution)
(5 equivalents of Oxone®, 15.5 equivalents of sodium bicarbonate, room temperature)

acid (5 equivalents)	% wt trans-stilbene oxide after 16 hours
4-(trifluoroacetyl)benzoic acid	9%
benzoic acid	8%
	2%
4-chlorobenzoic acid	0%
	0%

* reaction diluted a further 5 times

With benzoic acid, the results varied between 2-8%. At a similar dilution, 9% was obtained with 4-(trifluoroacetyl)benzoic acid.

It can be seen from these results that the conversions of *trans*-stilbene to *trans*-stilbene oxide obtained in the biphasic system were much poorer than those obtained in the acetonitrile system. The results in the biphasic system were also more inconsistent.

5.2.4 Optimisation of method B

The following work was done in conjunction with a coworker, Estella Grocock. The aim was to optimise method B (1 equivalent of cyclohexene, 1 equivalent of trifluoroacetophenone, 1.2 equivalents of Oxone®, 3.4 equivalents of sodium bicarbonate, dichloromethane : water 1:1 with t-butyl ammonium hydrogen sulfate as phase transfer catalyst at 0°C, adding the Oxone® as a solution in one portion) which gave 26% cyclohexene oxide after 6 hours.
Repeating this reaction at room temperature with an increased amount of Oxone® (2.7 equivalents, as used in method A) and increased amounts of bicarbonate and water in accordance with this, gave 47% after 6 hours. Increasing the Oxone® further to 5 equivalents, again increasing the bicarbonate and water *pro rata*, gave 66% after 6 hours. Adding the Oxone® solution dropwise rather than in one portion and doubling the amount of ketone had little effect. Increasing the Oxone® to 10 equivalents (again increasing the bicarbonate and water *pro rata*) gave 91% conversion after 6 hours. This will be referred to as method E. The same reaction at 0°C gave 75% conversion after 6 hours (Table 34). Excellent conversions were obtained when the reaction was continued for 16 hours using both trifluoroacetophenone and 4-(trifluoroacetyl)benzoic acid (greater than 96%), which was very encouraging. 4-tert-butylcyclohexanone also gave a good conversion of 61% after 6 hours which was much better than previously seen (Table 35).
However when the reaction was carried out in the absence of ketone, it was found to also give a conversion of 96% after 16 hours. The reaction was repeated several times with the same result and after 16 hours, little difference could be seen between the reactions carried out in the presence of the ketone catalyst and those in its absence. At a shorter reaction time, a difference between the trifluoroacetophenone reaction and the blank reaction was more noticable. After 6 hours at room temperature, trifluoroacetophenone gave an average conversion of 90% whereas the blank reaction

gave 65%. 4-(trifluoroacetyl)benzoic acid gave 76% after the same period of time. After 3 hours at room temperature the trifluoroacetophenone-catalysed reaction gave almost double the conversion of that given by the blank reaction. This is a similar pattern to that obtained with method B.

A reaction using method E was then carried out using *trans*-stilbene as the substrate with trifluoro-acetophenone as the ketone catalyst. A very poor conversion of 5% was obtained after 1.5 hours at room temperature, with no increase after 16 hours. Increasing the amount of trifluoroacetophenone from 1 equivalent to 10 equivalents showed no improvement. Using 1 equivalent of 4-(trifluoro-acetyl)benzoic acid instead of trifluoroacetophenone gave a similarly poor conversion of 8%.

Since this work was carried out, Denmark published the results of ^{18}O labelling studies[16] which support the view that dioxiranes are the active intermediates in Oxone® / ketone epoxidations and criticises the findings of Armstrong who suggested that dioxiranes are not responsible for alkene epoxidation in such a system.[15] Denmark states that 4-tert-cyclobutylcyclohexanone is a poor promoter under biphasic conditions and reports that independent studies carried out in his laboratories have verified this. Indeed, our results also confirm this. Denmark suggests that the production of epoxide in the presence of 4-tert-butylcyclohexanone may result from an improved miscibility of the phases or emulsification. He found that under the conditions employed by Armstrong,[15] only 2% epoxidation was achieved using 4-tert-butylcyclohexanone (compared to Armstrong's 15% and our 9%) although if the reaction mixture became emulsified, as much as 25% could be produced in the absence of ketone (we reported 8%). Denmark therefore concludes that the problem with this system is that there is no mechanistically significant ketone-catalysed pathway due to the insolubility of the ketone in the aqueous phase.

Table 34

Optimisation of method B
(biphasic, 1 equivalent of cyclohexene and 1 equivalent of trifluoroacetophenone)

reaction temp.	number of equivalents of Oxone®	number of equivalents of $NaHCO_3$	ratio of dichloromethane : water	% wt cyclohexene oxide after 6 hours
0°C	1.2	3.4	1:1	26%
RT	2.7	7.75	1:2	47%
RT	5	13.8	1.3.7	66%
RT	10	27.7	1:7	91%
0°C	10	27.7	1:7	75%

Table 35

The results of the reactions of cyclohexene with Oxone® / ketone
in a biphasic system according to method E
(1 equivalent of cyclohexene. 1 equivalent of ketone, 10 equivalents of Oxone®,
27.7 equivalents of sodium bicarbonate, dichloromethane / water 1:7)

ketone	reaction temp	% wt cyclohexene oxide				
		3 hours	4 hours	6 hours	7 hours	16 hours
trifluoroacetophenone	RT			91%		
	RT		84%			98%
	RT	80%		89%		
	0°C		53%			99%
	0°C	46%		75%		
4-(trifluoroacetyl)benzoic acid	RT			76%		96%
t-butylcyclohexanone	RT	44%		61%		
	0°C	28%	47%			
no ketone	RT				79%	
	RT				78%	
	RT		55%			96%
	RT					96%
	RT	46%		65%		
	0°C		36%			96%
	0°C	30%		48%		

RT room temperature

Table 36

Summary of the main Oxone® / ketone methods used

method	A	B	C	D	E
reference	Muxworthy[174]	Armstrong[15]	Yang[172]	Yang[39]	-
substrate	1 eq	1 eq	1 eq	1 eq	1 eq
ketone	1 eq	1 eq	11 eq	10 eq	1 eq
Oxone®	2.7 or 8 eq*	1.2 eq	5 eq	5 eq	10 eq
buffer	phosphate buffer pH 7.5	3.4 eq sodium bicarbonate	7.75 eq sodium bicarbonate	15.5 eq sodium bicarbonate	27.7 eq sodium bicarbonate
solvent	11 volumes of DCM	10 volumes of DCM	7.5 volumes of MeCN	15 volumes of MeCN	10 volumes of DCM
water	44 or 98 volumes*	9.4 volumes	5 volumes	10 volumes	70 volumes
ratio of organic : aqueous **	1:4 or 1:9* biphasic (not including KOH)	1:1.1 biphasic	1:1.5 homogenous	1:1.5 homogenous	1:7 biphasic
EDTA	0.3 eq	0.01 eq	0.002 eq	0.004 eq	0.01 eq
phase transfer catalyst	0.32 eq	0.2 eq	Not applicable	Not applicable	0.2 eq
temperature	0°C	0°C	0°C	RT	RT
Oxone® / buffer addition	All buffer added at the start of the reaction. Oxone® added dropwise as an aqeous solution.	All bicarbonate added at the start of the reaction. Oxone® added as an aqueous solution in one portion.	Bicarbonate / Oxone® added in portions as a solid mixture.	Bicarbonate / Oxone® added in portions as a solid mixture	All bicarbonate added at the start of the reaction. Oxone® added as an aqueous solution in one portion
pH control during the reaction	pH maintained at 7.5 using a pH stat.	not monitored	not monitored	not monitored	not monitored
reaction time	2.75 or 4 hours	5 hours	allowed to continue for up to 16 hours	allowed to continue for up to 16 hours	allowed to continue for up to 16 hours

* the first figure given is for the 2.75 hour reaction, the second for the 4 hour reaction
** after addition is complete
DCM dichloromethane

5.3 CONCLUSIONS

A summary of the main Oxone® / ketone methods used is given in Table 36. It was difficult to ascertain exactly what the critical parameters are in these reactions due to the number of variables involved and the fact that many are interdependent. As Denmark[10] noted in his studies it was not possible to systematically examine all permutations. Understanding the role of the various reaction parameters is complicated and it seemed from the results obtained that different parameters were more critical in certain methods than in others. For example, in some cases the rate of addition of the Oxone® had a significant effect whereas in others it was not important, which was surprising as the rate of oxidant addition, along with reaction pH and stoichiometry of the ketone / oxidant, has been well established as a critical parameter.

Method D (acetonitrile / water) was found to work well with *trans*-stilbene giving 97% conversion with 2 equivalents of 4-(trifluoroacetyl)benzoic acid. A similar conversion was obtained with 2 equivalents of trifluoroacetophenone. Some of the epoxidation activity of 4-(trifluoroacetyl)benzoic acid may arise from the presence of the carboxylic acid group, which may be converted to the peracid with Oxone®. In the absence of the ketone catalyst the reaction was very poor, 4-9% conversion. It should be noted however that while these reactions worked well, the ketones are not functioning catalytically. An excess of 2 equivalents is required to give good conversions and so the ketones are not considered efficient. However the acid does have the advantage that it can be isolated for re-use by simple base extraction.[177]

In a biphasic system with *trans*-stilbene, the conversions were not as high and trifluoroacetophenone appeared to catalyse the reaction more effectively than 4-(trifluoroacetyl)benzoic acid, although not consistently. With 5 equivalents of trifluoroacetophenone, a 77% conversion was obtained. However this result could not be repeated and conversions obtained in subsequent reactions were much lower (24-41%). With 5 equivalents of 4-(trifluoroacetyl)benzoic acid, conversions varied between 9-22%. In the absence of ketone, no significant epoxidation of *trans*-stilbene occurred. 4-(trifluoroacetyl)benzoic acid is less effective in general in dichloromethane presumably owing in part to its relatively high solubility in the aqueous phase. Similar solubility effects have been reported by Denmark.[10] If the ketone is at all water soluble, it will form a dioxirane which will have a higher tendency to stay in the aqueous phase and not be transported into the organic phase where the substrate is located. In the aqueous phase, the dioxirane is likely to be consumed by reaction

with the peroxomonosulfate, regenerating the ketone, oxygen and HSO_4^-. This can be minimised by slow addition of the Oxone® thereby keeping the peroxomonosulfate concentration low.

The inconsistencies experienced in these reactions may be due to the fact that the addition of the Oxone® was not strictly controlled. Although additions were made at regular intervals over 30 minutes, it is possible that there were slight variations in the amount added at each interval in each reaction, particularly when the Oxone® was being added as a solid.

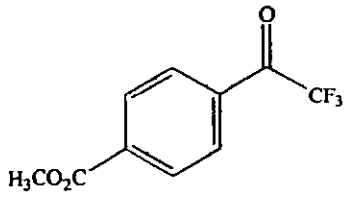
Another factor which may have a significant effect on the outcome of the reaction is the strong dependence of the rate of dioxirane formation on pH. In spite of the fact that that many of the *in situ* methods described in the literature do not involve strict pH control, Denmark[10] stresses that this is critical for the effective conversion of substrate into product, since formation of the dioxirane involves generation of acid. Denmark established an optimum pH of 7.8-8.0 and found that moving a few tenths of a unit away from this narrow range resulted in either Oxone® destruction at higher pH (the peroxomonosulfate exists as a dianion thus increasing its nucleophilicity, leading to self destruction) or loss of reactivity due to Oxone® preservation at lower pH. Denmark also found that variable pH affects the lifetime of the ketone as well as the Oxone® due to consumption by Baeyer-Villiger oxidation. When reactions which are not controlled using a pH stat are repeated, the pH profile would not be expected to be exactly the same each time therefore some variation in conversion might be expected particularly as such small variations in pH have such a large effect. Denmark found that at pH 7.5 a conversion of 30% was obtained, which increased to 48% at pH 7.8 and dropped to 2% at pH 8.5.

In his work on fluoroketones,[12] Denmark reported inconsistent results when using a dichloromethane / water biphasic system due to formation of emulsions and this was also given as a reason for the epoxidation achieved in the absence of ketone when using 4-tert-butylcyclohexanone under Armstrong's conditions.[16]

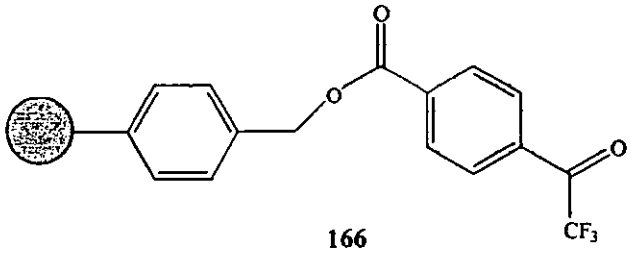
When using cyclohexene as substrate in this biphasic system, a conversion of 94% was achieved on one occasion with trifluoroacetophenone but conversions in the range 28-55% were more usual. As with the *trans*-stilbene reactions, it was expected that the 4-(trifluoroacetyl)benzoic acid-catalysed cyclohexene reactions would be poorer than with trifluoroacetophenone due to the higher solubility of the acid in the aqueous phase. However, similar if not marginally better conversions (48-68%) were obtained. Again, some of the epoxidation activity of 4-(trifluoroacetyl)benzoic acid may be due to the conversion of the carboxylic acid to peracid by Oxone®. This may be more significant in the biphasic system than in acetonitrile. In the absence of ketone, no epoxidation of cyclohexene

occurred. This is in sharp contrast to the results obtained with the other biphasic methods. Extremely high conversions were achieved with trifluoroacetophenone and 4-(trifluoroacetyl)-benzoic acid in the biphasic reactions based on method E, using cyclohexene as substrate. However, similar conversions were obtained in the absence of ketone, possibly due to the formation of emulsions as suggested by Denmark.[16] When *trans*-stilbene was used as a substrate with methods B and E, no significant epoxidation took place in the presence or absence of ketone. In both these methods, the Oxone® was added in one portion. In his studies Denmark found that the rate of addition of Oxone® had a significant effect on the level of epoxidation achieved.[10] He also noted that at more rapid addition rates, an increased amount of Oxone® does not increase epoxidation, which we have seen evidence of in our work. Edward and Curci[11a] demonstrated that the presence of dioxirane in an Oxone®-rich enviroment promotes the generation of oxygen and potassium hydrogen sulfate, which becomes more competitive as the level of Oxone® is increased. Also, as already mentioned, keeping the Oxone® concentration low can suppress the autodecompostion at higher pH. It may be therefore that the dioxirane formed is being consumed by the nonproductive pathway described above and that the oxidation of cyclohexene is being achieved mainly by any remaining Oxone®. The results of the reactions carried out with cyclohexene in the absence of ketone confirm that this is possible whereas *trans*-stilbene on the other hand is unreactive towards Oxone® alone and so poor conversions were obtained both in the presence and absence of ketone.

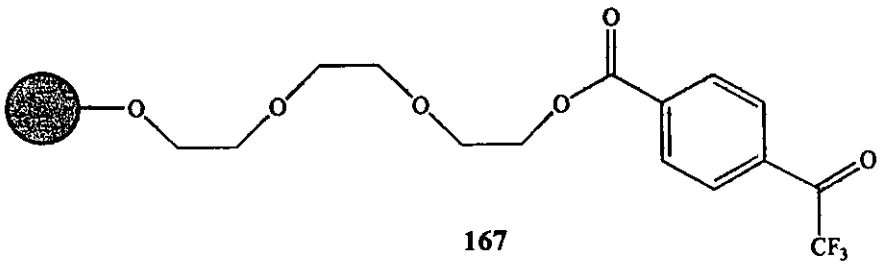
Work in this area was continued by my coworkers, Todd Boehlow and Estella Grocock. In addition to trifluoroacetophenone and 4-(trifluoroacetyl)benzoic acid, they have investigated the use of methyl-4-(trifluoroacetyl)benzoate **165** and the resin-bound esters **166** and **167** as catalysts in Oxone®–mediated epoxidations.[177]



165



166



167

The evaluation of these trifluoromethyl aryl ketones as catalysts was carried out in either acetonitrile/water and/or dichloromethane/water/phase transfer catalyst mixtures with solvent ratios and sodium bicarbonate concentrations as in method D.

From the initial work on this, it does not seem likely that a polymer-bound trifluoromethyl dioxirane would be sufficiently stable to be stored. However, the resin-bound esters **166** and **167** were reusable many times and 4-(trifluoroacetyl)benzoic acid was isolated for re-use by base extraction.

Chapter 6

EXPERIMENTAL

6.1 GENERAL

^{1}H NMR spectra were recorded on a Bruker 250 MHz NMR spectrometer. All samples were recorded with tetramethylsilane as internal standard. Chemical shifts (δ) were recorded in ppm and multiplicities are reported as follows: **br** broad, **s** singlet, **d** doublet, **t** triplet, **q** quartet, **m** multiplet.

^{13}C NMR spectra were recorded on a Bruker 250 MHz spectrometer.

IR spectra were recorded on a Nicolet 205 series FT-IR spectrometer.

UV spectra were performed using a Shimadzu UV-160 UV-VIS spectrophotometer.

Mass spectra were obtained on a Kratos MS80 spectrometer with DS-55 data system.

Column chromatography was carried out using Matrex silica 60, 35-70 micron (Fisons Scientific equipment) unless otherwise noted.

Thin layer chromatography was carried out using aluminium sheet silica gel $60F_{254}$, 0.2mm layer thickness (Merck) or aluminium sheet aluminium oxide $60F_{254}$ neutral (type E), 0.2mm layer thickness (Merck).

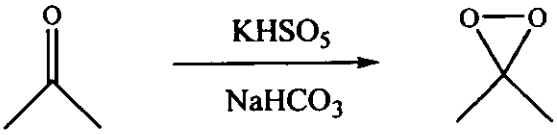
Preparative TLC was performed on 0.2 metre glass-backed plates coated with kieselgel $60PF_{254}$ (Merck).

Melting points were obtained on a Reichert manual melting point apparatus.

pH stat. experiments were controlled using a Radiometer autotitrator, type ABU 11b.

HPLC was performed using a Perkin Elmer series 3 pump, Perkin Elmer LCSS B spectrophotometric detector and Pye unicam PU4020 UV detector with a Spectraphysics integrator. A Hewlett Packard 1090 diode array detector was also used.

6.2 PREPARATION OF DIMETHYLDIOXIRANE / ACETONE SOLUTIONS



Safety note

The reaction should be performed in the hood. Dimethyldioxirane is a highly volatile peroxide of unknown toxicity, therefore skin contact and inhalation of vapour should be avoided.

Apparatus

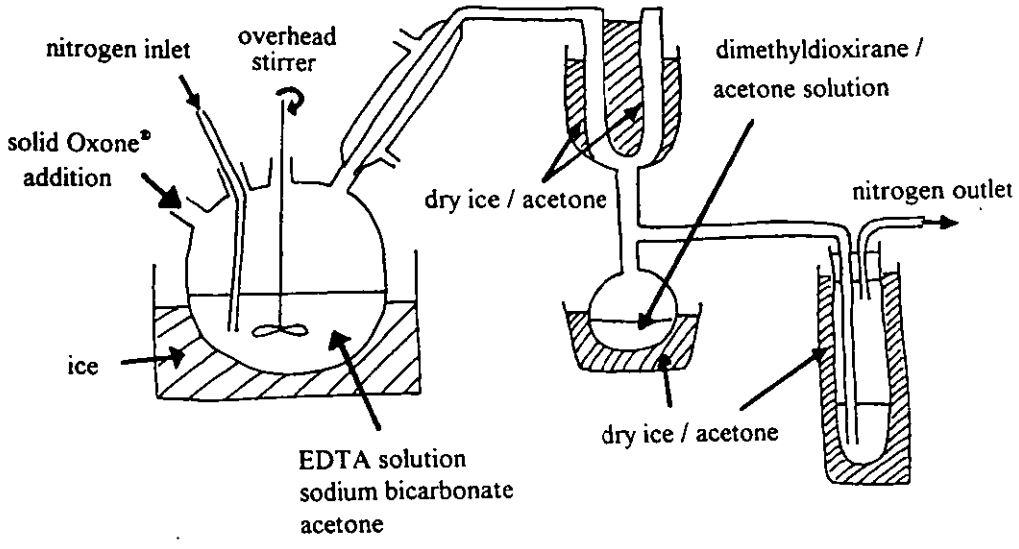


Figure 9

All glassware was washed with EDTA solution, followed by acetone and dried. The apparatus was assembled, all joints sealed with parafilm, covered in foil to protect from light and then flushed with nitrogen.

Procedure

To the one litre four necked round bottomed flask equipped with nitrogen inlet, overhead stirrer and solid addition funnel containing Oxone® (320g), was added aqueous EDTA solution (0.16% w/w, 300ml), sodium hydrogen carbonate (160g) and acetone (210ml). An air condenser (packed loosely with glass wool) was attached to the reaction vessel and connected to a dry ice condenser with jacket. This was attached to a receiving flask (100ml), cooled with an acetone / dry ice bath. Connected to the receiving flask was a Schlenk tube cooled to -78°C, to act as a second trap. The reaction flask was cooled to 0-5°C using an ice bath and the solid Oxone® added slowly in portions, with stirring. The yellow-coloured dimethyldioxirane solution began to distil over on the first addition and continued once the addition was complete, until all the dioxirane had been collected. The receiver flask was then removed, any dioxirane collected in the Schlenk tube added and then stoppered and stored in the freezer. The dioxirane content of the acetone solution was determined by iodometric titration. The expected molarity was 0.05-0.1M.

An alternative, much simpler apparatus set up is shown in Figure 10. The same method was used but with no nitrogen flush. Dioxirane solutions of similar quantity and molarity were obtained.

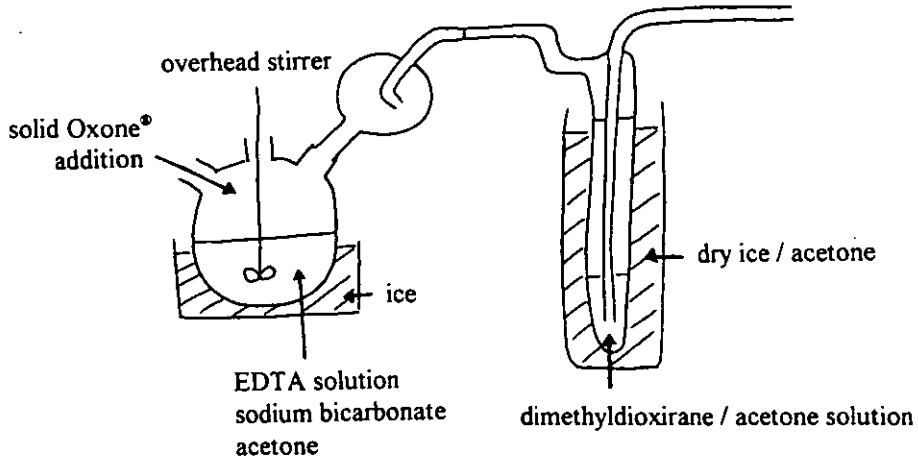


Figure 10

Determination of 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.

Procedure

The apparatus was washed with water followed by acetone and dried. To a small conical flask was added acetic acid / acetone solution (3:2, 3ml) followed by a solution of potassium iodide in water (10% w/v, 5ml). The flask was stoppered and shaken. 0.2ml of the dioxirane solution was then pipetted into the flask which was again stoppered and shaken. The dioxirane oxidised the potassium iodide releasing iodine which turned the solution yellow. This was then titrated against sodium thiosulfate solution (ca 0.01M, known accurately). The end point of the titration was denoted by the disappearance of the yellow colour of the iodine.

Chemical equations for the titration

Reaction of the dioxirane with iodine:

Reaction of the iodine with sodium thiosulfate:

$$I_2 + 2\,Na_2S_2O_3 \longrightarrow Na_2S_4O_6 + 2\,NaI$$

The molarity of the dioxirane solution is calculated as follows:

Number of moles of sodium thiosulfate solution used $= \dfrac{VNa_2S_2O_3 \times MNa_2S_2O_3}{1000}$

Since 2 moles of potassium iodide react with 1 mole of dioxirane to give 1 mole of iodine, and the iodine reacts with 2 moles of sodium thiosulfate:

1 mole dioxirane = 2 moles sodium thiosulfate

Number of moles of dioxirane used $= \frac{V_{Na_2S_2O_3} \times M_{Na_2S_2O_3}}{1000 \times 2}$

Therefore, molarity of the dioxirane solution $= \frac{V_{Na_2S_2O_3} \times M_{Na_2S_2O_3} \times 1000}{1000 \times 2 \times V_{dioxirane}}$

where $M_{Na_2S_2O_3}$ = molarity of the sodium thiosulfate solution

$V_{Na_2S_2O_3}$ = volume of the sodium thiosulfate solution

Vdioxirane = volume of dioxirane solution = 0.2ml

6.3 EXPERIMENTAL FOR CHAPTER 2

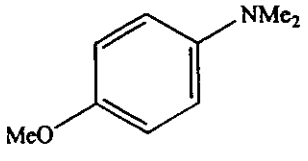
General procedure for N,N-dimethylaniline competition reactions

An equimolar solution of N,N-dimethylaniline and *para*-substituted N,N-dimethylaniline in acetone was prepared. An aliquot of this solution was removed, placed in a flask, covered with aluminium foil to protect from light and cooled to 0-5°C in an ice bath. One equivalent of dimethyldioxirane / acetone solution was then added to the flask and the resulting solution stirred magnetically. Samples were removed at intervals and analysed by HPLC. Two determinations were made at each timepoint and each reaction was done in duplicate.

The above procedure was repeated using aliquots of the same stock solution and the following reagents: methyl iodide, benzoyl peroxide and t-butyl hydroperoxide.

The t-butyl hydroperoxide reactions were also carried out at 70°C (the flask was fitted with a condenser and heated in an oil bath) and in the presence of vanadyl acetylacetonate (0.025 equivalents). All reactions were continued until HPLC analysis and the starch-iodide test for remaining oxidant indicated that the reactions had gone to completion.

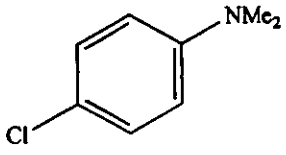
Preparation of N,N-dimethyl-4-methoxyaniline



To a stirred solution of 4-methylaniline (1.02g, 8.29mmol) and paraformaldehyde (2.50g, 83.3mmol)

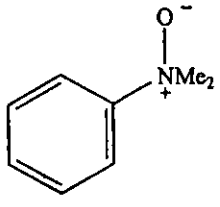
in acetic acid (50ml) at 25°C under nitrogen was added in one portion sodium cyanoborohydride (2.51g, 40.2mmol). The resulting mixture was stirred at 25°C for 18 hours then poured into 25% aqueous sodium hydroxide (100ml) and ice chips to make strongly alkaline (pH 11) and extracted with dichloromethane (3 x 75ml). The combined extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a dark purple solid (1.1g). Column chromatography (1:1 petrol / diethyl ether) gave the title product as a pale yellow solid (0.79g, 63%). Mp 37-38°C (lit[178] mp 37-38.5°C). δ_H ($CDCl_3$) 6.85 (m, 2H, Ar), 6.77 (m, 2H, Ar), 3.77 (s, 3H, OCH_3), 2.87 (s, 6H, 2 x CH_3).

Preparation of N,N-dimethyl-4-chloroaniline



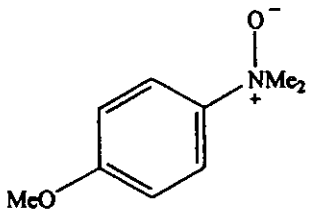
Prepared from 4-chloroaniline (0.70g, 5.49mmol) as above to give the title compound (0.68g, 79%). Mp 33-34°C (lit[179] mp 35.5°C). δ_H ($CDCl_3$) 7.19 (m, 2H, Ar), 6.65 (m, 2H, Ar), 2.94 (s, 6H, 2 x CH_3).

Preparation of N,N-dimethylaniline N-oxide



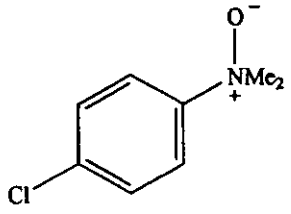
To an ice-cooled solution of N,N-dimethylaniline (1.21g, 0.01mol) in 90% formic acid (30ml) was added 30% hydrogen peroxide (7.5ml). The reaction mixture was stirred for about 16 hours at room temperature. The formic acid was neutralised with solid sodium carbonate and the reaction mixture extracted with dichloromethane (3 x 75ml). Concentration *in vacuo* gave the crude product which was purified by column chromatography on basic alumina, eluting initially with dichloromethane. The N-oxide[126,181,142f] (0.75g, 55%) was released by elution with dichloromethane / methanol (3:1) and stored under vacuum over phosphorus pentoxide. δ_H ($CDCl_3$) 7.94 (m, 2H, Ar), 7.40 (m, 3H, Ar), 3.55 (s, 6H, 2 x CH_3). A mean moisture content of 9.5% was determined by Karl Fischer and HPLC analysis showed the material to be 88.8% N,N-dimethylaniline N-oxide by area normalisation (for method details, see section 2.2.4).

Preparation of N,N-dimethyl-4-methoxyaniline N-oxide



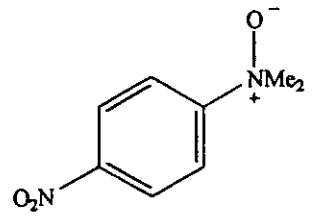
The procedure described above was followed using N,N-dimethyl-4-methoxyaniline (100mg, 0.66mmol) to give the title compound (26mg, 24%) as a solid.[182] δ_H ($CDCl_3$) 7.86 (m, 2H, Ar), 6.92 (m, 2H, Ar), 3.82 (s, 3H, OCH_3), 3.56 (s, 6H, 2 x CH_3). A mean moisture content of 5.0% was determined by Karl Fischer and HPLC analysis showed the material to be 89.8% N,N-dimethyl-4-methoxyaniline N-oxide by area normalisation (for method details, see section 2.2.4).

Preparation of N,N-dimethyl-4-chloroaniline N-oxide



The procedure described above was followed using N,N-dimethyl-4-chloroaniline (250mg, 1.61mmol) to give the title compound (97mg, 35%) as an oily solid.[183] δ_H ($CDCl_3$) 7.89 (m, 2H, Ar), 7.42 (m, 2H, Ar), 3.56 (s, 6H, 2 x CH_3). A mean moisture content of 7.1% was determined by Karl Fischer and HPLC analysis showed the material to be 99.8% N,N-dimethyl-4-chloroaniline N-oxide by area normalisation (for method details, see section 2.2.4).

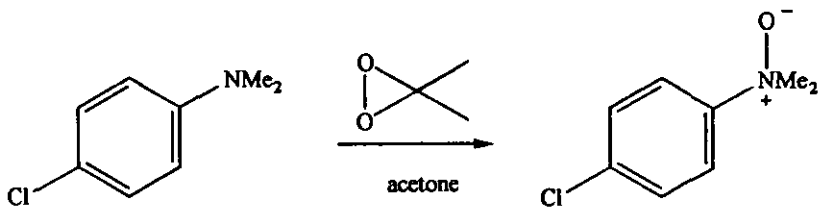
Preparation of N,N-dimethyl-4-nitroaniline N-oxide



The procedure described above was followed using N,N-dimethyl-4-nitroaniline (330mg, 2.0mmol) to give the title compound (52mg, 15%) as an oily yellow solid.[184] δ_H ($CDCl_3$) 8.37 (m, 2H, Ar), 8.24 (m, 2H, Ar), 3.65 (s, 6H, 2 x CH_3). A mean moisture content of 7.3% was determined by Karl

Fischer and HPLC analysis showed the material to be 95.2% N,N-dimethyl-4-nitroaniline N-oxide by area normalisation (for method details, see section 2.2.4).

Oxidation of N,N-dimethyl-4-chloroaniline using dimethyldioxirane



N,N-dimethyl-4-chloroaniline (100mg, 0.64 mmol) in acetone (2ml), in a flask covered in foil to protect from light, was cooled to 0-5°C. Dimethyldioxirane / acetone solution (1.28 mmol) was added and the resulting solution stirred for several hours, gradually allowing to warm to room temperature. TLC (25% methanol / dichloromethane) showed 2 products and concentration *in vacuo* gave a mixture of the N-oxide plus the N-oxide hydrate as a brown oil (134mg). δ_H ($CDCl_3$) 7.89 (2H, d, Ar, N-oxide), 7.70 (2H, d, Ar, N-oxide hydrate) , 7.42 (2H, d, Ar, N-oxide), 7.34 (2H, d, Ar, N-oxide hydrate) , 3.56 (6H, s, 2 x CH_3, N-oxide), 3.42 (6H, s, 2 x CH_3, N-oxide hydrate); m/z 172 (MH^+, N-oxide), 343 ($2M+H^+$, dichloro dimer). Measured against an external standard, a yield of 83% N,N-dimethyl-4-chloroaniline was obtained by HPLC (see section 2.2.4 for method details). The reaction was also carried out at room temperature, without protection from light and with shorter reaction times of 1, 2, 3 and 4 hours. The ratio of N-oxide to N-oxide hydrate varied from approximately 1:1 to N-oxide only.

Separation of the products obtained in the oxidation of N,N-dimethyl-4-chloroaniline with dimethyldioxirane

a. Chromatography

The following TLC systems on both silica and alumina were used in order to find a suitable solvent system for the column chromatography of the N,N-dimethyl-4-chloroaniline product mixture:
5% methanol / 95% dichloromethane; 25% methanol / 75% dichloromethane; 50% petrolum ether (60-80) / 50% diethyl ether; 50% toluene / 50% ethyl acetate; 100% ethyl acetate.
It was found that 25% methanol / 75% dichloromethane on silica gave the best separation.

Attempts at column chromatography were as follows:

1. Using silica, eluting initially with dichloromethane, then dichloromethane plus one or two drops of methanol through to 25% methanol / 75% dichloromethane. This resulted in the isolation of the N-oxide only. No second product was detected in any of the fractions collected.
2. As above but using neutral alumina instead of silica. Again only the N-oxide was isolated.
3. Prep TLC using a silica plate, eluting with 25% methanol / 75% dichloromethane. The N-oxide and some starting material was isolated. This was repeated giving the same result.
4. As above but 0.1% triethylamine was added to the eluent. Again, only the N-oxide and some starting material were isolated.

b. Reduction using triphenylphosphine

Reduction of N,N-dimethyl-4-chloroaniline N-oxide using triphenylphosphine

To N,N-dimethyl-4-chloroaniline N-oxide (100mg, 0.58mol) in glacial acetic acid (10ml) was added triphenylphosphine (153mg, 0.58mmol) and the mixture heated to reflux for 3 hours. The mixture was made strongly basic by adding 25% sodium hydroxide solution and extracted with dichloromethane. After drying and removing the solvent, the crude was chomatographed on silica using 20% diethyl ether / 80% petrol giving N,N-dimethyl-4-chloroaniline (63mg, 64%). δ_H ($CDCl_3$) 7.19 (m, 2H, Ar), 6.65 (m, 2H, Ar), 2.94 (s, 6H, 2 x CH_3).

Reduction of the mixture of N,N-dimethyl-4-chloroaniline N-oxide and second product using triphenylphosphine

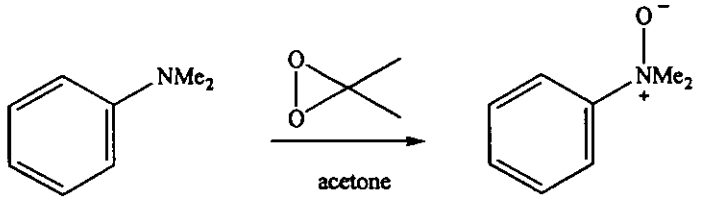
To the mixture of products (175mg) in glacial acetic acid (10ml) was added triphenylphosphine (200mg, 0.76mmol) and the mixture heated to reflux for 3 hours. Triphenylphosphine remained after this time so heating was continued for a further 3 hours. The reaction mixture was made strongly basic by adding 25% sodium hydroxide solution and extracted with dichloromethane. After drying and evaporating the solvent, the crude product (300mg) was chromatographed using 10% diethyl ether / 90% petrol. Only N,N-dimethyl-4-chloroaniline (66mg) and unreacted triphenylphosphine (38mg) were isolated. The above procedure was repeated using the mixture

(360mg), glacial acetic acid (10ml) and triphenylphosphine (440mg), giving the crude product (625mg). This was acidified using dilute hydrochloric acid and extracted with dichloromethane giving triphenylphosphine (369mg). The aqueous phase was basified with sodium hydroxide solution and extracted with dichloromethane giving N,N-dimethyl-4-chloroaniline (138mg) as the only product. δ_H ($CDCl_3$) 7.19 (m, 2H, Ar), 6.65 (m, 2H, Ar), 2.94 (s, 6H, 2 x CH_3). The above procedure was repeated but this time stirring for over 96 hours at room temperature rather than at reflux. The crude was acidifed and extracted as above giving the same results.

c. Acid / base washes

An NMR sample of the mixture of products in deuteriated chloroform was shaken in the NMR tube with sodium carbonate solution. The upper aqueous phase was removed by pipette and the organic phase examined by proton NMR. It was shown to contain a mixture of N,N-dimethyl-4-chloroaniline and N,N-dimethyl-4-chloroaniline N-oxide. δ_H ($CDCl_3$) 7.89 (m, 2H, Ar, N-oxide), 7.42 (m, 2H, Ar, N-oxide), 7.19 (m, 2H, Ar, N,N-dimethyl-4-chloroaniline), 6.65 (m, 2H, Ar, N,N-dimethyl-4-chloroaniline), 3.56 (s, 6H, 2 x CH_3, N-oxide), 2.94 (s, 6H, 2 x CH_3, N,N-dimethyl-4-chloroaniline).
The aqueous phase was acidified using dilute hydrochloric acid and extracted with deuteriated chloroform. NMR showed the organic phase to contain no aromatic products.

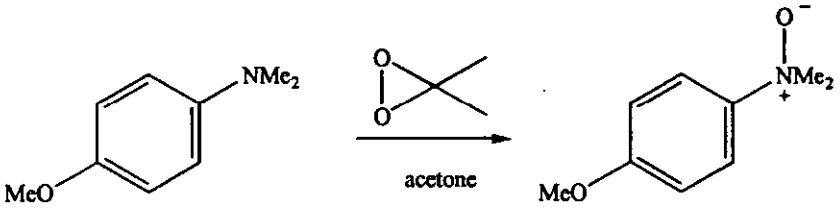
Oxidation of N,N-dimethylaniline using dimethyldioxirane



N,N-dimethylaniline (100mg, 0.83mmol) in acetone (2ml), in a flask covered in foil to protect from light, was cooled to 0-5°C. Dimethyldioxirane / acetone solution (1.66mmol) was added and the resulting solution stirred for several hours, gradually allowing to warm to room temperature. TLC (5% methanol / dichloromethane) showed a single product. Concentration *in vacuo* gave the N-oxide as an oily brown solid (66%). δ_H (CD_3OD) 7.98 (2H, m, Ar), 7.52 (3H, m, Ar), 3.59 (6H, s, 2 x CH_3). The reaction was repeated at room temperature, without the protection from light and with a shorter reaction time of 2 hours. A trace of N-oxide hydrate was observed by proton NMR. δ_H (CD_3OD)

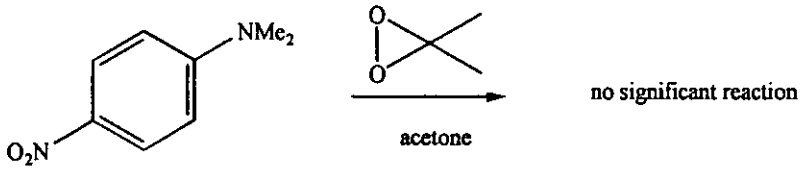
7.98 (2H, m, Ar, N-oxide), 7.63 (2H, m, Ar, N-oxide hydrate), 7.52 (3H, m, Ar, N-oxide), 7.28 (3H, m, Ar, N-oxide hydrate), 3.59 (6H, s, 2 x CH_3, N-oxide), 3.36 (6H, s, 2 x CH_3, N-oxide hydrate); m/z 138 (MH^+, N-oxide), 275 ($2M+H^+$).

Oxidation of N,N-dimethyl-4-methoxyaniline using dimethyldioxirane



N,N-dimethyl-4-methoxyaniline (100mg, 0.66 mmol) in acetone (2ml), in a flask protected from light, was cooled to 0-5°C. Dimethyldioxirane / acetone solution (1.32 mmol) was added and the resulting solution stirred for several hours, gradually allowing to warm to room temperature. TLC (50% petrol / diethyl ether) showed a single product. Concentration *in vacuo* gave the N-oxide as an oily brown solid (88%). δ_H ($CDCl_3$) 7.86 (2H, m, Ar), 6.92 (2H, m, Ar), 3.82 (3H, s, OCH_3), 3.56 (6H, s, 2 x CH_3). The reaction was also carried out at room temperature and without protection from light. In each case, the N-oxide was found to be the only product.

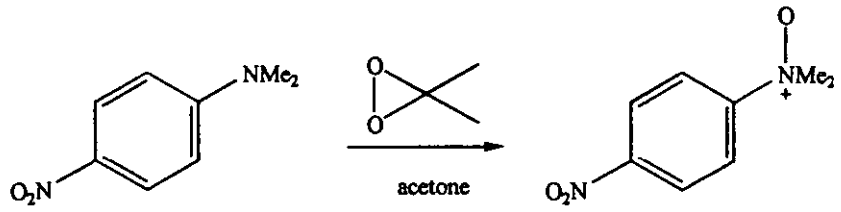
Oxidation of N,N-dimethyl-4-nitroaniline using dimethyldioxirane



N,N-dimethyl-4-nitroaniline (100mg, 0.60 mmol) in acetone (2ml), in a flask protected from light, was cooled to 0-5°C. Dimethyldioxirane / acetone solution (1.20 mmol) was added and the resulting solution stirred for several hours, gradually allowing to warm to room temperature. TLC (50% petrol / diethyl ether) showed mainly unreacted starting material plus a trace of one product. HPLC analysis of the crude mixture showed this product to be N,N-dimethyl-4-nitroaniline N-oxide (9% by area normalisation). Addition of more dimethyldioxirane solution in portions (up to 10 equivalents) did not increase the yield of N-oxide. δ_H ($CDCl_3$) 8.36 (2H, m, Ar, N-oxide), 8.24 (2H, m, Ar, N-oxide), 8.11 (2H, m, Ar, N,N-dimethyl-4-nitroaniline), 6.61 (2H, m, Ar, N,N-dimethyl-4-nitro-

aniline), 3.65 (6H, s, 2 x CH_3, N-oxide), 3.12 (6H, s, 2 x CH_3, N,N-dimethyl-4-nitroaniline). The reaction was repeated at room temperature but TLC showed only unreacted starting material.

Oxidation of N,N-dimethyl-4-nitroaniline using dimethyldioxirane in the presence of water



To N,N-dimethyl-4-nitroaniline (10mg, 0.06 mmol) in acetone (1ml) and water (7ml), cooled to 0-5°C, was added dimethyldioxirane / acetone solution (0.6 mmol, 6ml) resulting in a yellow solution which turned noticeably paler after stirring for approximately 2 minutes. After stirring at 0-5°C for 1 hour, TLC (2:1 petrol / ethyl acetate) showed 2 products plus some unreacted starting material. Concentration *in vacuo* gave a yellow solid which was shown by proton NMR to be a mixture of the N-oxide, the N-oxide hydrate and unreacted starting material (approximately 4:3:1). δ_H ($CDCl_3$) 8.37 (2H, m, Ar, N-oxide), 8.24 (2H, m, Ar, N-oxide), 8.21 (2H, m, Ar, N-oxide hydrate), 8.11 (2H, m, Ar, N,N-dimethyl-4-nitroaniline), 8.05 (2H, m, Ar, N-oxide hydrate), 6.61 (2H, m, Ar, N,N-dimethyl-4-nitroaniline), 3.65 (6H, s, 2 x CH_3, N-oxide), 3.61 (6H, s, 2 x CH_3, N-oxide hydrate), 3.12 (6H, s, 2 x CH_3, N,N-dimethyl-4-nitroaniline). A solution containing the mixture of reaction products was dried over molecular sieves and analysis by proton NMR showed the disappearance of the peaks corresponding to the N-oxide hydrate.

Oxidation of N,N-dimethylaniline using dimethyldioxirane at reflux

N,N-dimethylaniline (200mg, 1.65mmol) in acetone (4ml) was heated to reflux and dimethyl-dioxirane / acetone solution (1.65mmol) was added. After 1 hour, TLC (5% ethyl acetate / petrol) showed a single product plus unreacted starting material. Further dimethyldioxirane solution (1.65mmol) was then added and heating continued for a further hour. Concentration *in vacuo* gave the N-oxide as a yellow oily solid. δ_H ($CDCl_3$) 7.94 (2H, m, Ar), 7.40 (3H, m, Ar), 3.55 (6H, s, 2 x CH_3).

Oxidation of N,N-dimethyl-4-chloroaniline using dimethyldioxirane at reflux

N,N-dimethyl-4-chloroaniline (100mg, 0.64mmol) was dissolved in acetone (2ml) and heated to reflux. Dimethyldioxirane / acetone solution (1.28mmol) was added in one portion and heating continued for 2 hours. TLC (25% methanol / dichloromethane) showed a single product. Concentration *in vacuo* gave the N-oxide plus a trace of unreacted starting material as an oil (126mg). δ_H ($CDCl_3$) 7.89 (2H, d, Ar, N-oxide), 7.42 (2H, d, Ar, N-oxide), 7.19 (2H, d, Ar, N,N-dimethyl-4-chloroaniline), 6.65 (2H, d, Ar, N,N-dimethyl-4-chloroaniline), 3.56 (6H, s, 2 x CH_3 N-oxide), 2.94 (6H, s, 2 x CH_3 N,N-dimethyl-4-chloroaniline).

Oxidation of N,N-dimethyl-4-nitroaniline using dimethyldioxirane at reflux

N,N-dimethyl-4-nitroaniline (50mg, 0.30mmol) was dissolved in acetone (2ml) and heated to reflux. Dimethyldioxirane / acetone solution (1.5mmol) was added in one portion and heating continued for 3 hours. Concentration *in vacuo* gave unreacted starting material as a yellow solid. δ_H ($CDCl_3$) 8.11 (2H, m, Ar), 6.61 (2H, m, Ar), 3.12 (6H, s, 2 x CH_3).

Oxidation of N,N-dimethyl-4-methoxyaniline using dimethyldioxirane at reflux

N,N-dimethyl-4-methoxyaniline (100mg, 0.66mmol) was dissolved in acetone (2ml) and heated to reflux. Dimethyldioxirane / acetone solution (1.32mmol) was added in one portion and heating continued for 3 hours. Concentration *in vacuo* gave an oil (132mg) consisting of a 4:1 mixture of the N-oxide and the N-oxide hydrate. δ_H ($CDCl_3$) 7.86 (2H, d, Ar, N-oxide), 7.52 (2H, d, Ar, N-oxide hydrate), 6.92 (2H, d, Ar, N-oxide), 6.52 (2H, d, Ar, N-oxide hydrate), 3.82 (3H, s, OCH_3, N-oxide), 3.56 (6H, s, 2 x CH_3, N-oxide), 3.34 (3H, s, OCH_3, N-oxide hydrate), 3.26 (6H, s, 2 x CH_3, N-oxide hydrate).

Preparation of dimethyldioxirane / acetone solution for use in photolysis reactions

A batch of dimethyldioxirane / acetone solution was specially prepared for use in the following photolysis reactions. The apparatus described in section 6.2 was flushed with nitrogen and sodium bicarbonate (160g) added to the reaction vessel. EDTA solution (300ml) and acetone (210ml) were

combined and degassed bfore adding to the vessel via a pressure-equalised dropping funnel. Oxone® (320g) was added over several hours and the dimethyldioxirane solution collected as it distilled from the vessel. Once the distillation was complete, the receiver was sealed under nitrogen and stored in the freezer at -20°C.

Oxidation of N,N-dimethylaniline using dimethyldioxirane at λ > 300nm

N,N-dimethylaniline (333mg, 2.75 mmol) in acetone (80ml) was degassed and added to a Hanovia photolysis vessel fitted with a medium pressure Pyrex lamp under a stream of nitrogen. This was cooled using an ice / salt bath to less than 0°C. Dimethyldioxirane / acetone solution (5.50 mmol) was charged via syringe to a sealed dropping funnel. The lamp was switched on and the dimethyl-dioxirane solution added in one portion to the reaction mixture. The resulting solution was photolysed for 4 hours then concentrated *in vacuo* to a brown oil (410mg). Proton NMR showed the N-oxide plus a trace of the N-oxide hydrate. δ_H ($CDCl_3$) 7.94 (2H, m, Ar, N-oxide), 7.57 (2H, m, Ar, N-oxide hydrate), 7.40 (3H, m, Ar, N-oxide), 7.13 (2H, m, Ar, N-oxide hydrate), 3.55 (6H, s, 2 x CH_3, N-oxide), 3.25 (6H, s, 2 x CH_3, N-oxide hydrate).

Oxidation of N,N-dimethyl-4-chloroaniline using dimethyldioxirane at λ > 300nm

The above procedure was repeated using N,N-dimethyl-4-chloroaniline (260mg, 1.67mmol) and dimethyldioxirane / acetone solution (3.34mmol). Concentration *in vacuo* gave a brown oil (340mg) consisting of a mixture of the N-oxide and the N-oxide hydrate (2:1). δ_H ($CDCl_3$) 7.89 (2H, d, Ar, N-oxide), 7.70 (2H, d, Ar, N-oxide hydrate), 7.42 (2H, d, Ar, N-oxide), 7.34 (2H, d, Ar, N-oxide hydrate), 3.56 (6H, s, 2 x CH_3, N-oxide), 3.42 (6H, s, 2 x CH_3, N-oxide hydrate). To confirm the presence of the N-oxide hydrate, the oil was taken back up in acetone and dried over magnesium sulfate resulting in the expected disappearance of the peaks in the NMR spectrum corresponding to the N-oxide hydrate.

Oxidation of N,N-dimethyl-4-nitroaniline using dimethyldioxirane at λ > 300nm

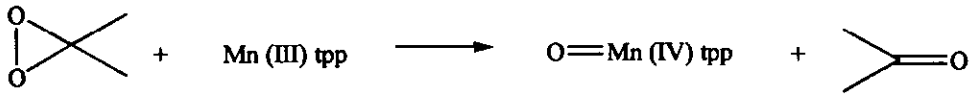
The above procedure was repeated using N,N-dimethyl-4-nitroaniline (275mg, 1.66mmol) and dimethyldioxirane / acetone solution (3.32mmol). Concentration *in vacuo* gave mainly unreacted

starting material plus traces of several other very minor unidentified aromatic products. δ_H ($CDCl_3$) 8.11 (2H, d, Ar, N,N-dimethyl-4-nitroaniline), 6.61 (2H, d, Ar, N,N-dimethyl-4-nitroaniline), 3.11 (6H, s, 2 x CH_3, N,N-dimethyl-4-nitroaniline) plus minor unknown multiplets at 8.34, 7.32, 6.70 and 6.51, and singlets at 3.41, 3.03, 2.91, 2.77 and 1.89 (br).

Oxidation of N,N-dimethyl-4-methoxyaniline using dimethyldioxirane at λ > 300nm

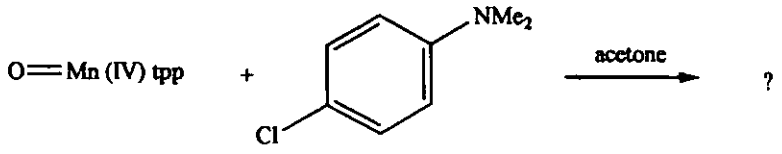
The above procedure was repeated using N,N-dimethyl-4-methoxyaniline (275mg, 1.82mmol) and dimethyldioxirane / acetone solution (3.64mmol). Concentration *in vacuo* gave an oil (400mg) consisting of a 2:1 mixture of the N-oxide and the N-oxide hydrate. δ_H ($CDCl_3$) 7.86 (2H, d, Ar, N-oxide), 7.52 (2H, d, Ar, N-oxide hydrate), 6.92 (2H, d, Ar, N-oxide), 6.52 (2H, d, Ar, N-oxide hydrate), 3.82 (3H, s, OCH_3, N-oxide), 3.56 (6H, s, 2 x CH_3, N-oxide), 3.34 (6H, s, 2 x CH_3, N-oxide hydrate), 3.26 (3H, s, OCH_3, N-oxide hydrate).

Oxygen transfer from dimethyldioxirane to 5,10,15,20-tetraphenyl-21H, 23H-porphine manganese (III) chloride



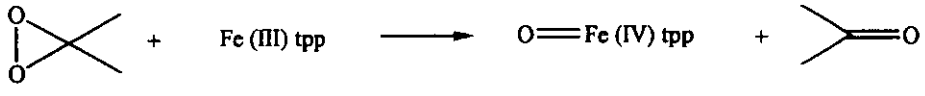
5,10,15,20-tetraphenyl-21H, 23H-porphine manganese (III) chloride (50mg, 0.071mmol) in acetone (6mls) was cooled to -78°C using an acetone / CO_2 bath. Dimethyldioxirane / acetone solution (0.0781mmol) was added and the reaction allowed to warm to -20°C. The reaction was followed by UV spectroscopy. The conversion of manganese (III) to manganese (IV) was indicated by the hypochromic shift of the λmax from 473nm to 423nm. Scans were taken in the region 600-200nm every 15 minutes using distilled acetone as reference. After 3 hours, no peak at 423nm was observed so a second aliquot of dimethyldioxirane / acetone solution (0.0639mmol) was added. Partial conversion of manganese (III) to manganese (IV) was observed. Further dimethyldioxirane / acetone solution (0.213mmol) was added, resulting in the complete conversion of manganese (III) to manganese (IV). The solution turned from green to brown / red.

Addition of N,N-dimethyl-4-chloroaniline to the manganese (IV)-oxygen complex



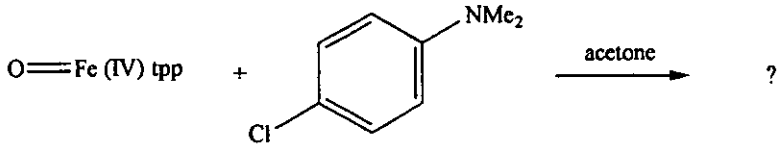
30 minutes after adding the last portion of dimethyldioxirane to the above reaction mixture, N,N-dimethyl-4-chloroaniline (11.1mg, 0.071mmol) was added and the mixture allowed to warm to room temperature. The reaction was monitored by UV spectroscopy. After 3.5 hours, all the manganese (IV)-oxygen complex had disappeared and TLC (50% petrol / diethyl ether) showed at least 4 products including the N-oxide. The solvent was removed by evaporation and the mixture chromatographed using 35% diethyl ether / 65% petrol to remove any porphyrin. Five fractions were collected but when these were concentrated *in vacuo*, such small amounts of material were isolated that the resulting proton NMR spectra were of very poor quality and could not be interpreted.

Oxygen transfer from dimethyldioxirane to 5,10,15,20-tetraphenyl-21H, 23H-porphine iron (III) chloride



5,10,15,20-tetraphenyl-21H, 23H-porphine iron (III) chloride (40mg, 0.057mmol) in acetone (10mls) was cooled to -78°C in an acetone / CO_2 bath. The UV spectrum was measured showing λmax at 405nm plus a peak at 502nm. Dimethyldioxirane / acetone solution (0.1171mmol) was added and after 15 minutes, UV showed a shift in the peak at 502nm (iron (III)) to 562nm (iron (IV)), indicating complete conversion of the iron (III) porphyrin to the iron (IV)-oxygen complex.

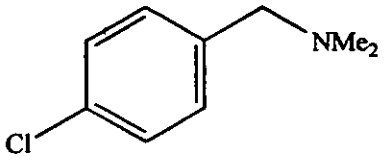
Addition of N,N-dimethyl-4-chloroaniline to the iron (IV)-oxygen complex



To the reaction mixture containing the iron (IV)-oxygen complex was added N,N-dimethyl-4-chloroaniline (8.8mg, 0.057mmol) and the mixture allowed to warm to room temperature. After

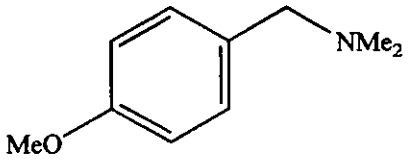
4.75 hours, UV showed the disappearance of all of the iron (IV)-oxygen complex. The solvent was removed by evaporation and the mixture chromatographed using 20% diethyl ether / 80 % petrol. Several products were indicated by TLC including the N-oxide but when the fractions were concentrated *in vacuo*, it was found that none of the products had been isolated cleanly. No further work was carried out.

Preparation of N,N-dimethyl-4-chlorobenzylamine



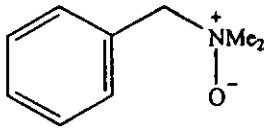
4-chlorobenzylamine (2.0g, 0.014mol) was cooled in an ice bath and 90% formic acid (3.36g, 0.066mol) slowly added, followed by 37-40% aqueous formaldehyde solution (4.62g, 0.057mol). The flask was equipped with a magnetic stirrer and condenser and placed in an 80°C bath for 24 hours. The mixture was cooled, 6M hydrochloric acid (10ml) added and the mixture extracted with diethyl ether (3 x 10ml). The combined ether layers were washed with water, dried over magnesium sulfate and concentrated *in vacuo* to give the title compound (1.85g, 77%) as a pale yellow oil.[185] δ_H ($CDCl_3$) 7.23 (4H, m, Ar), 3.37 (2H, s, CH_2), 2.21 (6H, s, 2 x CH_3).

Preparation of N,N-dimethyl-4-methoxybenzylamine



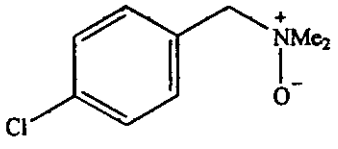
Prepared from 4-methoxybenzylamine (3.0g, 0.022mol) as above to give the title compound (2.3g, 63%) as a pale yellow oil.[185] δ_H ($CDCl_3$) 7.20 (2H, m, Ar), 6.85 (2H, m, Ar) 3.78 (3H, s, OCH_3), 3.35 (2H, s, CH_2), 2.21 (6H, s, 2 x CH_3).

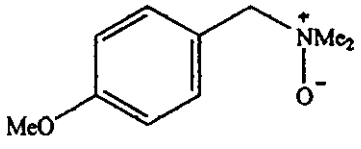
Preparation of N,N-dimethylbenzylamine N-oxide



To an ice-cooled solution of N,N-dimethylbenzylamine (500mg, 3.7mmol) in 98% formic acid (21ml) was added 30% hydrogen peroxide (3ml). The reaction mixture was stirred for about 16 hours at room temperature. The formic acid was neutralised with solid sodium carbonate and the reaction mixture extracted with dichloromethane. It was found that only unreacted starting material and very little N-oxide was recovered therefore the aqueous phase was re-extracted with ethyl acetate. Again, only a small amount of N-oxide was isolated and concentration *in vacuo* did not yield a product of sufficiently good quality to be used as a HPLC standard. A sample of the aqueous phase was analysed by HPLC which showed that the N-oxide was being retained in this phase and could not easily be isolated.

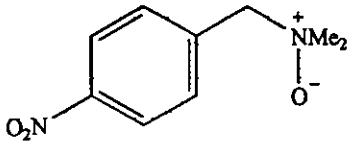
Preparation of N,N-dimethyl-4-chlorobenzylamine N-oxide and N,N-dimethyl-4-methoxy-benzylamine N-oxide





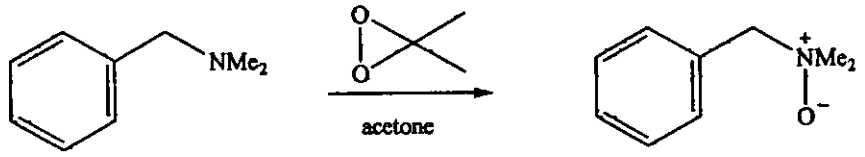
The procedure described above was repeated using both N,N-dimethyl-4-chlorobenzylamine and N,N-dimethyl-4-methoxybenzylamine. The reaction mixtures were extracted with ethyl acetate but it was found in both cases that only unreacted starting material was isolated and that the majority of the N-oxide remained in the aqueous phase and could not be isolated. Samples of the aqueous phases were used as HPLC markers.

Preparation of N,N-dimethyl-4-nitrobenzylamine N-oxide



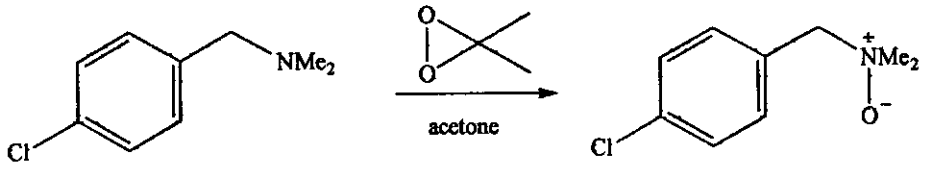
The above procedure was repeated using N,N-dimethyl-4-nitrobenzylamine. The reaction mixture was extracted with ethyl acetate and concentration *in vacuo* gave a mixture of the N-oxide and unreacted starting material (approximately 1:4) as a brown oil (559mg). A sample of the aqueous phase containing the N-oxide was used as a HPLC marker.

Oxidation of N,N-dimethylbenzylamine using dimethyldioxirane



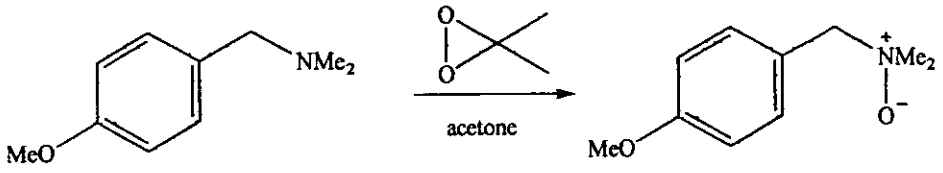
To N,N-dimethylbenzylamine (56mg, 0.41mmol) in acetone (2ml) at 0-5°C was added dimethyldioxirane / acetone solution (0.41mmol) and the resulting solution stirred for 30 minutes. HPLC showed some unreacted starting material therefore a second aliquot of dimethyldioxirane (0.41mmol) was added and stirring continued for a further 30 minutes. HPLC and TLC (25% methanol / dichloromethane) showed a single product. Concentration *in vacuo* gave the N-oxide[186] as a white solid (61mg). δ_H (CD_3OD) 7.55 (2H, m, Ar), 7.45 (3H, m, Ar), 4.41 (2H, s, CH_2), 3.11 (6H, s, 2 x CH_3); m/z 152 (MH^+), 303 ($2M+H^+$).

Oxidation of N,N-dimethyl-4-chlorobenzylamine using dimethyldioxirane



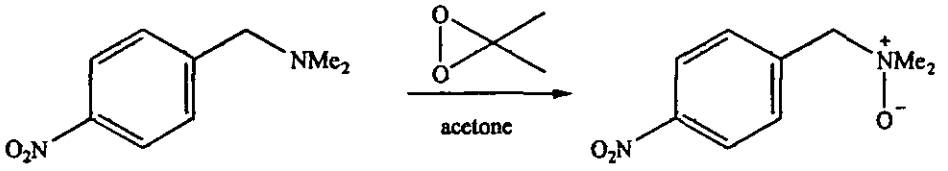
To N,N-dimethyl-4-chlorobenzylamine (66mg, 0.39mmol) in acetone (2ml) at 0-5°C was added dimethyldioxirane / acetone solution (0.39mmol) and the resulting solution stirred for 30 minutes. HPLC showed some unreacted starting material therefore a second aliquot of dimethyldioxirane (0.39mmol) was added and stirring continued for a further 30 minutes. HPLC and TLC (25% methanol / dichloromethane) showed a single product. Concentration *in vacuo* gave the N-oxide[187] as a clear oil (78mg). A similar result was obtained when the reaction was carried out at room temperature. δ_H ($CDCl_3$) 7.50-7.36 (4H, m, Ar), 4.38 (2H, s, CH_2), 3.14 (6H, s, 2 x CH_3); m/z 186 (MH^+), 371 ($2M+H^+$), 558 ($3M+H^+$)

Oxidation of N,N-dimethyl-4-methoxybenzylamine using dimethyldioxirane



To N,N-dimethyl-4-methoxybenzylamine (96mg, 0.58mmol) in acetone (2ml) at 0-5°C was added dimethyldioxirane / acetone solution (1.16mmol) and the resulting solution stirred for 30 minutes. HPLC and TLC (25% methanol / dichloromethane) showed a single product. Concentration *in vacuo* gave the N-oxide[187] as a clear oil (67mg). δ_H ($CDCl_3$) 7.40 (2H, m, Ar), 6.93 (2H, m, Ar), 4.36 (2H, s, CH_2), 3.83 (3H, s, OCH_3), 3.09 (6H, s, 2 x CH_3); m/z 182 (MH^+), 363 ($2M+H^+$).

Oxidation of N,N-dimethyl-4-nitrobenzylamine using dimethyldioxirane

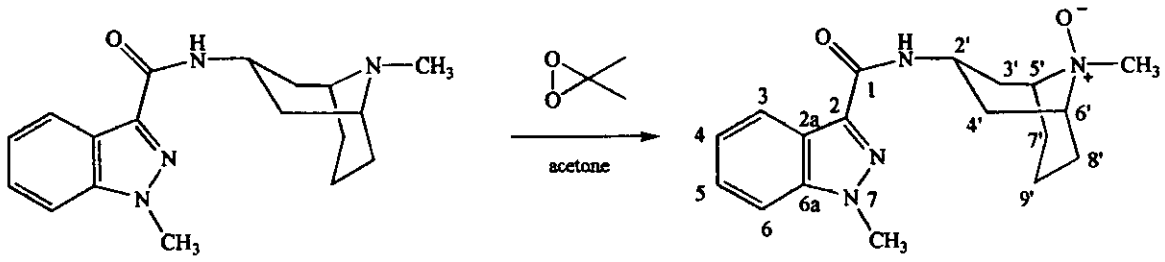


To N,N-dimethyl-4-nitrobenzylamine (64mg, 0.36mmol) in acetone (2ml) at 0-5°C was added dimethyldioxirane / acetone solution (0.72mmol) and the resulting solution stirred for 1 hour. HPLC and TLC (25% methanol / dichloromethane) showed a single product. Concentration *in vacuo* gave the N-oxide (67mg).[187] δ_H ($CDCl_3$) 7.51-7.43 (4H, m, Ar), 4.43 (2H, s, CH_2), 3.13 (6H, s, 2 x CH_3); m/z 152 (MH^+), 303 ($2M+H^+$).

6.4 EXPERIMENTAL FOR CHAPTER 3

NMR assignments of the following free base substrates (apart from codeine, the structure of which was established over 50 years ago[142]) were determined by experts at SmithKline Beecham, Great Burgh and were achieved through analysis of the 1D ^1H and ^{13}C NMR data. Proton assignments were aided by 2D ^1H COSY-45 experiments and 2D ^1H, ^{13}C Heteronuclear Multiple Quantum Coherence (HMQC) spectra. (Correlations in a HMQC spectrum are observed between carbons and their directly attached protons.) The correlations in the 2D HMQC spectra not only completed the proton assignment but also allowed the protonated carbons to be assigned. Assignment of the quaternary carbons was achieved from their chemical shifts and correlations detected in a 2D ^1H, ^{13}C Heteronuclear Multiple Bond Correlation (HMBC) experiments, i.e. correlations which identify carbons and protons which are coupled through several bonds (usually two or three bonds).
All spectroscopic data on the products of the following reactions were confirmed by SmithKline Beecham by comparison with authentic specimen data. For HPLC methods, see Appendix IV.

Oxidation of granesitron using dimethyldioxirane



137 **138**

Reaction 1

To granesitron **137** (400mg, 1.28mmol) in acetone (6ml) at 0-5°C was added dimethyldioxirane / acetone solution (3.2mmol). After stirring for 2 hours, TLC (5% methanol / dichloromethane) showed 2 products plus unreacted starting material. Further dioxirane solution (0.64mmol) was added to consume the remaining starting material. Column chromatography on silica eluting initially with 1% methanol / dichloromethane followed by 1.5% then 2% methanol / dichloromethane gave the major product as a white solid (289mg, 68%). This was further purified by recrystallisation (petrol / dichloromethane) to give the N-oxide **138** (183mg, 44%). The second product (9mg) was also isolated as an oil. However, this was shown to be impure by proton NMR (solvent DMSO-d_6) and the identity of individual components could not be determined due to too much overlap.

Reaction 2

To granesitron **137** (300mg, 0.96mmol) in acetone (2ml) was added dimethyldioxirane / acetone solution (0.96mmol) at room temperature. After stirring for 30 minutes, TLC (5% methanol / dichloromethane) showed one product plus unreacted starting material. A second aliquot of dimethyldioxirane (0.96mmol) was added to consume the remaining starting material. The N-oxide **138** precipitated from the reaction and was isolated by filtration as a white solid (195mg, 62%). The motherliquors were concentrated *in vacuo* to an oil (120mg) and found to be a mixture containing the N-oxide as the major component. A second crop was not isolated.

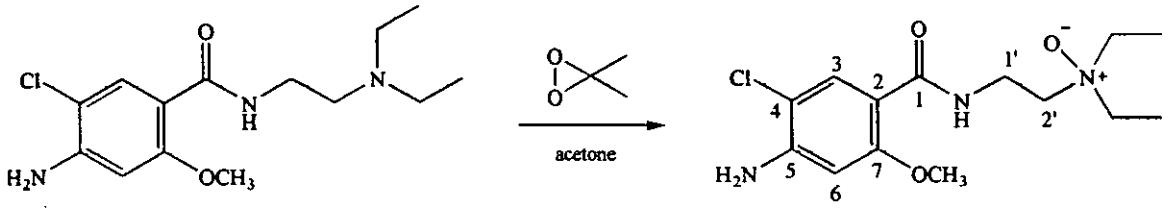
Granesitron N-oxide spectroscopic data

δ_H (CD_3OD) 8.19 (d, 1H, ^3J = 8.2 Hz, H3), 7.55 (d, 1H, ^3J = 8.0Hz, H6), 7.43 (td, 1H, ^3J = 7.7Hz, ^4J = 0.8Hz, H5), 7.25 (t, 1H, ^3J = 7.5Hz, H4), 5.31 (m, 1H, H2'), 4.11 (s, 3H, N(O)Me), 3.54 (2H, d of unresolved m, 5', 6'), 3.25 (3H, s, 7-CH_3), 2.85 (2H, m, 3', 4'), 2.25-2.13 (3H, m, 9', 7', 8'), 1.79 (4H, m, 3', 4', 7', 8'), 1.60 (1H, m, 9'); δ_C (CD_3OD) 164.5 (C1), 142.7 (C6a), 138.2 (C2), 127.9 (C5), 123.9 (C2a), 123.6 (C4), 123.0 (C3), 110.8 (C6), 67.6 (C5', C6'), 56.3 (N(O)Me), 39.7 (C2'), 36.3 (7-Me), 32.8 (C3', C4'), 30.4 (C7', C8'), 12.4 (C9'); IR υ_{max} 3474, 3207 (N-H stretch), 2950 (aliphatic C-H stretch), 1655 (amide I), 1622 (aromatic C=C), 1555 (amide II), 1493 (aromatic C=C), 967cm^{-1} (N-O); m/z 329 (MH^+), 311 (loss of H_2O), 657 ($2M+H^+$), 96 ($C_6H_{10}N$).

Oxidation of granesitron using a large excess of dimethyldioxirane

To granesitron free base **137** (200mg, 0.64mmol) in acetone (50ml) at room temperature was added dimethyldioxirane / acetone solution (6.4mmol) in portions and the colourless solution stirred overnight. After adding the first 1.28mmol, TLC (5% methanol / dichloromethane) showed N-oxide **138** and unreacted starting material and after 2.56mmol had been added, a trace of second product appeared. After all 6.4mmol had been added, the amount of second product had not increased. No separation was attempted.

Oxidation of metaclopramide using dimethyldioxirane



139 **140**

To metaclopramide **139** (130mg, 0.43mmol) in acetone (2ml) was added dimethyldioxirane / acetone solution (0.43mmol) at room temperature. After stirring for 30 minutes, a white precipitate formed and TLC (5% methanol / dichloromethane) showed one one product plus unreacted starting material. A second aliquot of dimethyldioxirane (0.43mmol) was added and after 30 minutes, TLC showed a single product and no unreacted starting material. The product was isolated by filtration as a white solid and shown to be the N-oxide **140** (93.0mg, 69%). HPLC showed a single peak. The

mother liquors were concentrated *in vacuo* to an oil (69mg) which was shown by NMR to contain the N-oxide plus traces of baseline impurities. HPLC showed the liquors to contain approximately 84% N-oxide and several minor impurities.

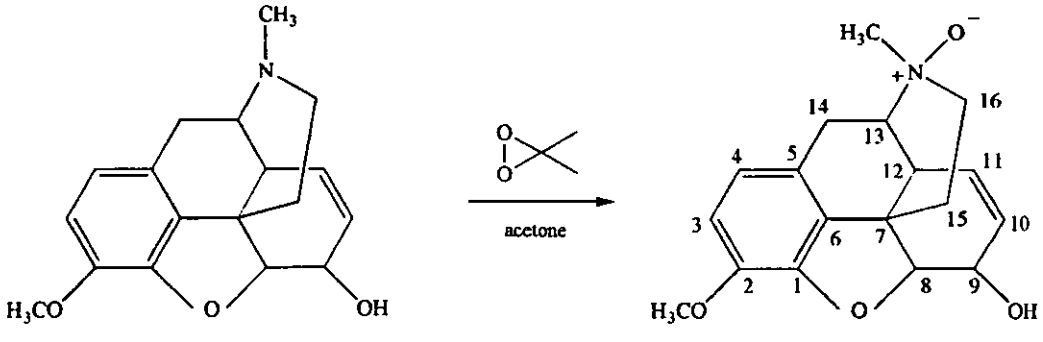
Metaclopramide N-oxide spectroscopic data

δ_H (DMSO) 9.67 (s, br, 1H, NH), 7.70 (s, 1H, H3), 6.44 (s, 1H, H6), 5.94 (s, 2H, 5-NH_2), 3.75 (s, 3H, 7-MeO), 3.61 (dt, 2H, ^3J = 5.3Hz, ^3J = 5.3Hz, H1'), 3.22 (t, 2H, ^3J = 5.7Hz, H2'), 3.11 (m, 4H, -N($\underline{CH_2}CH_3)_2$), 1.16 (t, 6H, ^3J = 7.1Hz, -N($CH_2\underline{CH_3})_2$); δ_C (DMSO) 163.1 (C1), 157.5 (C7), 148.3 (C5), 131.4 (C3), 110.5 and 108.6 (C2, C4), 97.3 (C6), 61.7 (C2'), 59.6 (-N($\underline{CH_2}CH_3)_2$), 55.4 (7-OMe), 34.7 (C1'), 8.2 (-N($CH_2\underline{CH_3})_2$); IR υ_{max} 3468, 3343, 3214 (NH stretch), 2953 (CH stretch), 1626 (amide I), 1603 (aromatic C=C), 1538 (amide II), 1498 (aromatic C=C), 947cm^{-1} (N-O); m/z 316 (MH^+).

Further oxidation of metaclopramide N-oxide using dimethyldioxirane

To metaclopramide N-oxide **140** (18mg, 0.06mmol)in methanol (1ml) was added dimethyl-dioxirane / acetone solution (0.60mmol) in portions. TLC showed the N-oxide **140** plus 3 minor products. HPLC analysis showed a more complex mixture of 10 products including unreacted N-oxide **140**. Separation was not attempted.

Oxidation of codeine using dimethyldioxirane



141 **142**

Reaction 1

To codeine **141** (200mg, 0.67mmol) in acetone (2ml), cooled to 0-5°C, was added dimethyldioxirane / acetone solution (2.01mmol) and the resulting solution was stirred for 10 minutes. TLC (5% methanol / dichloromethane) showed a single product and no unreacted starting material. The product was isolated by filtration as a white solid and shown by NMR to be the N-oxide **142** (186mg, 85%).

Reaction 2

To codeine **141** (250mg, 0.84mmol) in acetone (2ml) at room temperature was added dimethyl-dioxirane / acetone solution (1.68mmol) and the resulting mixture stirred for 30 minutes. A white precipitate formed and TLC (5% methanol / dichloromethane) showed a single product and no unreacted starting material. The product was isolated by filtration as a white solid (221mg). NMR showed this to be the N-oxide **142** containing approximately 8% of a related impurity. The mother liquors were concentrated *in vacuo* to an oil (41mg) which was found to be an impure mixture containing up to 50% N-oxide **142**.

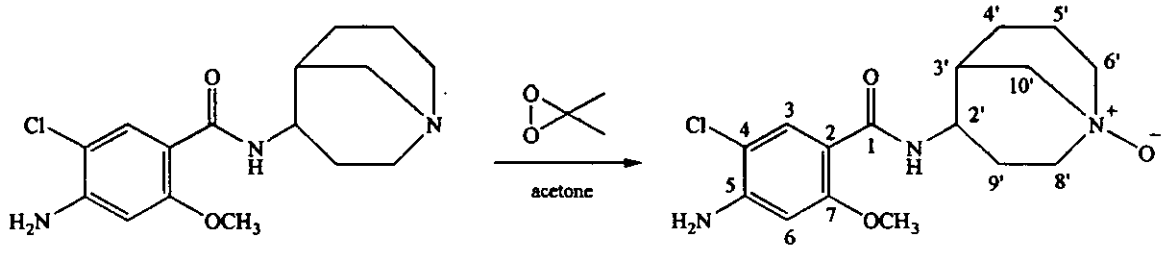
Codeine N-oxide spectroscopic data

δ_H (CD_3OD) 6.74 (d, 1H, ^3J = 8.2Hz, H3), 6.59 (d, 1H, ^3J = 8.2Hz, H4), 5.70 (d of unresolved m, 1H, ^3J = 9.9Hz, H10), 5.31 (ddd, 1H, ^3J = 9.8Hz, ^3J = 2.7Hz, ^4J = 2.7Hz, H11), 4.91 (dd, 1H, ^3J = 6.2Hz, ^4J = 0.8Hz, H8), 4.24 (m, 1H, H9), 3.96 (m, 1H, H12), 3.81 (s superimposed on m, 4H, 2-OMe and H13), 3.37 (s, 3H, N(O)Me), 3.31 (m, 2H, H14α and H16α), 3.15 (dd, 1H, ^2J = 12.7Hz, H16β), 2.93 (dd, 1H, ^2J = 20.2Hz, ^3J = 6.8Hz, H14β), 2.68 (ddd, 1H, ^2J = 13.2Hz, ^3J = 13.2Hz, ^3J = 4.6Hz, H15α), 1.79 (dm, 1H, H15β) plus approximately 8% related impurity; δ_C (CD_3OD) 148.7 (C1), 144.0 (C2), 134.8 (C10), 130.9 (C6), 127.6 (C11), 124.6 (C5), 120.8 (C4), 116.0 (C3), 92.5(C8), 75.9 (C13), 67.9 (C9), 60.4 (C16), 58.8 (N(O)Me), 57.3 (2-)Me), 42.8 (C7), 34.9 (C12). 32.2 (C15), 26.8 (C14) plus approximately 8% related impurity 148.6, 143.6, 134.9, 130.6, 127.2, 126.0, 120.7, 116.1, 92.0, 76.0, 62.3, 56.0, 43.7, 37.2, 34.2, 23.9; IR υ_{max} 3324 (OH), 2924 (C-H stretch), 2925 (C-H stretch), 1506 (aromatic C=C), 1452 (aromatic C=C), 1089 (C-O stretch), 951 (N-O); m/z 316 (MH^+), 338 (MNa^+).

Further oxidation of codeine N-oxide using dimethyldioxirane

To codeine N-oxide **142** (120mg, 0.38mmol) in acetone (20ml) and methanol (1ml) was added dimethyldioxirane / acetone solution (3.8mmol) in five portions. After adding the first of these portions, TLC showed unreacted N-oxide **142** plus a trace of one product. No further change occurred on addition of the remaining portions. Concentration *in vacuo* gave a brown oil (139mg). Separation was not attempted.

Oxidation of BRL 24924 using dimethyldioxirane



143 **144**

To BRL 24924 **143** (70mg, 0.22mmol) in acetone (3ml) at 0-5°C was added dimethyldioxirane / acetone solution (0.44mmol). After stirring for 2.5 hours, TLC (5% methanol / dichloromethane) showed a single product plus unreacted starting material. A second aliquot of dimethyldioxirane (0.22mmol) was added and the mixture stirred overnight. A trace of starting material remained so a further aliquot was added. TLC showed the N-oxide **144** to be the only product and this was isolated by filtration to give a pale orange solid (58mg, 79%). NMR showed a trace of a minor related impurity and HPLC showed the N-oxide **144** to be approximately 97% pure containing 1.5% of a single impurity by area normalisation.

BRL 24924 N-oxide spectroscopic data

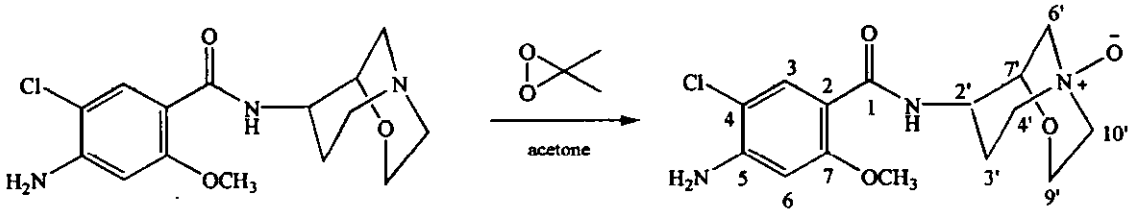
δ_H (CD_3OD) 7.76 (s, 1H, H3), 6.51 (s, 1H, H6), 4.44 (m, 1H, H2'), 3.92 (s, 3H, 7-OMe), 3.68, 3.51 and 3.42 (m, 2H, m, 2H and m, 2H, H6', H8' and H10'), 2.54, 2.36, 2.17 and 1.75-1.95 (m, 1H, m, 2H, m, 1H and m, 3H, H3', H4', H5' and H9') plus a trace of a minor related impurity; δ_C (CD_3OD) 166.8 (C1), 159.4 (C7), 150.4 (C5), 133.0 (C3), 111.6, 111.5 (C2, C4), 98.7 (C6), 69.7, 69.65, 68.3 (C6', C8', C10'), 56.8 (7-OMe), 48.6 (C2'), 35.7 (C3'), 29.8, 23.4, 21.5 (C4', C5', C9'); δ_C (CD_3OD) minor impurity 73.46, 60.77, 60.17, 59.33, 31.76, 23.30, 21.15, 20.89; IR υ_{max} 3366, 3179 (N-H stretch),

1632 (amide I), 1599 (aromatic C=C), 1542 (amide II), 1499 (aromatic C=C), 984cm^{-1} (N-O); m/z 340 (MH$^+$).

Oxidation of BRL 24924 N-oxide using dimethyldioxirane

To a solution of BRL 24924 N-oxide **144** (35mg, 0.10mmol) in acetone (20ml) and methanol (2ml) was added dimethyldioxirane / acetone solution (0.50mmol) at room temperature. The mixture was stirred for 2 hours giving a bright yellow solution. TLC (5% methanol / dichloromethane) showed unreacted N-oxide **144** plus one product. Further dimethyldioxirane solution (0.50mmol) was added and stirred overnight. TLC showed no change. Concentration *in vacuo* gave an oil which was analysed by HPLC and found to consist mainly of N-oxide **143** (approximately 75% by area normalisation) plus six other minor products. No separation was attempted.

Oxidation of BRL 43145 using dimethyldioxirane



145 **146**

Reaction 1

To BRL 43145 **145** (100mg, 0.31mmol) in acetone (5ml) at 0-5°C was added dimethyldioxirane / acetone solution (0.93mmol) and the resulting mixture stirred for 30 minutes. TLC (5% methanol / dichloromethane) showed a single product plus unreacted starting material. Further dimethyl-dioxirane (0.31mmol) was added and after 15 minutes all the starting material had been consumed. The product precipitated out during the reaction and was isolated by filtration to give the N-oxide **146** as a yellow solid (100mg, 94%). Proton and ^{13}C NMR and HPLC showed a clean product.

Reaction 2

To BRL 43145 **145** (190mg, 0.58mmol) in acetone (1ml) was added dimethyldioxirane / acetone solution (0.58mmol) at room temperature. After stirring for 30 minutes, TLC (5% methanol /

dichloromethane) showed one product plus unreacted starting material. Further dimethyldioxirane solution ((1.16mmol) was added in portions to consume the remaining starting material. The precipitate formed was isolated by filtration giving the N-oxide **146** as a yellow solid (190.5mg, 95%), which appeared clean by NMR. HPLC analysis showed the N-oxide to be 96% pure with 3% of a single impurity by area normalisation.

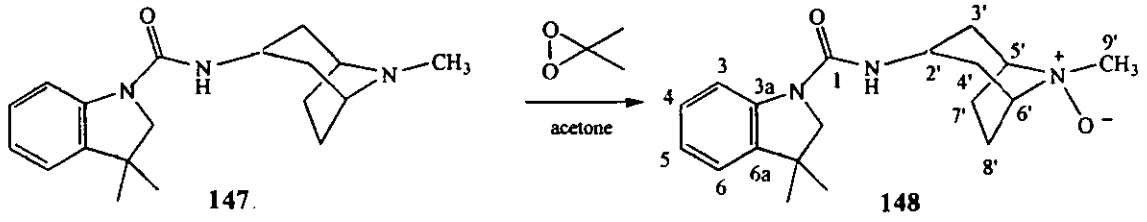
BRL 43145 N-oxide spectroscopic data

δ_H (CD_3OD) 8.44 (d, 1H, ^3J = 7.4Hz, NH), 6.50 (s, 1H, H6), 5.64 (s, 2H, NH_2), 4.29-4.40 and 4.12 (m, 3H and m, 1H, H2', H7', H9'), 3.91 (s, 1H, 7-OMe), 3.86 and 3.51-3.73 (d of m, 1H and m, 5H, H4', H6' and H10'), 2.47 (m, 1H, H3'), 2.29 (m, 1H, H3'); δ_C (CD_3OD) 166.6 (C1), 159.6 (C7), 150.0 (C5), 133.2 (C3), 111.7 and 110.9 (C2 and C4), 98.7 (C6), 72.3 (C7'), 68.2, 66.2 and 62.0 (C4', C6', C9' and C10'), 56.8 (7-OMe), 47.7 (C2'), 29.3 (C3'); IR υ_{max} 3335, 3157 (N-H stretch), 1629 (amide I), 1598 (aromatic C=C), 1547 (amide II), 1502 (aromatic C=C), 1139 (C-O stretch), 989cm^{-1} (N-O); m/z 342 (MH^+).

Further oxidation of BRL 43145 N-oxide using dimethyldioxirane

To a solution of BRL 43145 N-oxide **146** (40mg, 0.12mmol) in acetone (20ml) and methanol (5ml) was added dimethyldioxirane / acetone solution (0.60mmol) at room temperature. After stirring for 2 hours, the solution had turned from pale yellow to bright yellow and TLC (5% methanol / dichloromethane) showed mainly unreacted N-oxide **146** plus a trace of one product. Further dimethyldioxirane (0.60mmol) was added and the mixture stirred overnight. TLC showed no change. HPLC analysis showed a more complex mixture than indicated by TLC containing approximately 48% unreacted N-oxide by area normalisation plus one product and at least three minor ones. The impurity seen in the N-oxide was not enhanced. No separation was attempted.

Oxidation of BRL 46470 using dimethyldioxirane



147 **148**

Reaction 1

To a solution of BRL 46470 **147** (100mg, 0.32mmol) in acetone (5ml) at 0-5°C was added dimethyldioxirane / acetone solution (0.96mmol) and the mixture stirred for 30 minutes. TLC (5% methanol / dichloromethane) showed one major product, unreacted starting material and traces of 2 other products. Further dimethyldioxirane (0.32mmol) was added and stirring continued for a further 15 minutes. TLC showed the N-oxide **148** and the 2 other products, the levels of which had not increased. The solution was concentrated *in vacuo* to give an orange solid (111mg). Column chromatography eluting initially with dichloromethane then dichloromethane / methanol gave the N-oxide **148** only as a white solid (77mg, 73%).

Reaction 2

To BRL 46470 **147** (300mg, 0.96mmol) in acetone (3ml) was added dimethyldioxirane / acetone solution (0.96mmol) at room temperature. After stirring for 30 minutes, TLC (5% methanol / dichloromethane) showed a single product plus unreacted starting material. Further dimethyl-dioxirane (0.96mmol) was added and after 30 minutes, all the starting material had been consumed. Concentration *in vacuo* gave the crude product as a white solid (341mg), which was recrystallised from acetonitrile to give the N-oxide **148** (203mg, 64%). ^{1}H and ^{13}C NMR showed a trace of one minor related impurity in the crude N-oxide **148** which was not removed on recrystallisation. ^{13}C NMR indicated an approximately 6:1 mixture of N-oxide **148** : impurity. HPLC analysis of the crude N-oxide before recrystallisation showed 85% N-oxide plus 3 impurities (9%, 4% and 1% by area normalisation).

BRL 46470 N-oxide spectroscopic data

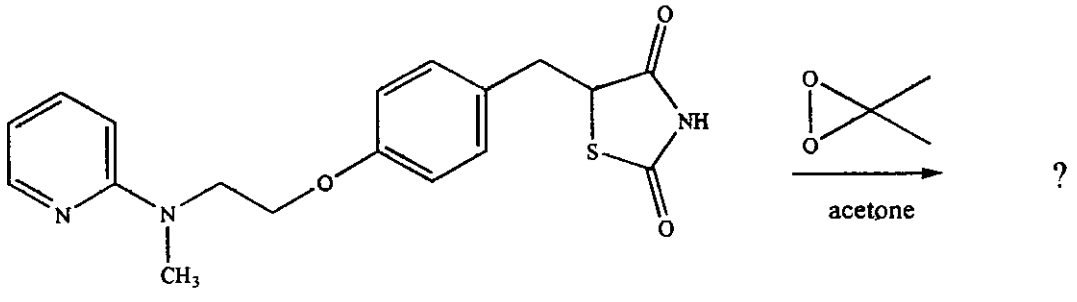
δ_H (CD_3OD) 7.76 (d, 1H, ^{3}J = 8.0Hz, H3), 7.13 (m, 2H, H4 and H6), 6.95 (t of d, 1H, ^{3}J = 7.4Hz, ^{4}J = 0.9Hz, H5), 3.94 (t, 1H, 3J = 6.8Hz, H2'), 3.74 (s, 2H, H8), 3.57 (m, 2H, H5' and H6'), 3.27 (s, 3H, H9'), 2.50-2.61, 2.24 and 2.14 (m, 4H, d, 2H, ^{2}J = 16.2Hz and m, 2H, H3' / H4' AND H7' / H8'), 1.34 (s, 6H, 7-Me_2) plus related impurity 3.50, 3.22, 3.00, 2.39 and 1.95; δ_C (CD_3OD) 157.4 (C1), 143.3 and 141.3 (C2a and C6a), 128.4 (C4), 123.5 and 123.0 (C5 and C6), 115.8 (C3), 73.5 (C5', C6'), 62.9 (C8), 48.7 (C9'), 41.7 (C7), 40.7 (C2'), 34.8 (C3' and C4'), 28.8 (7-Me_2), 26.5 (C7' and C8') plus

related impurity 70.7, 54.6, 48.6, 40.6, 31.0 and 23.5; IR υ_{max} 3444, 3341 (N-H stretch), 1645 (amide I), 1599 (aromatic C=C), 1524 (amide II), 1481 (aromatic C=C), 1377, 1363 (CMe_2), 933cm^{-1} (N-O); m/z 330 (MH^+).

Further oxidation of BRL 46470 N-oxide using dimethyldioxirane

To a solution of BRL 46470 N-oxide **148** (35mg, 0.106mmol) in acetone (25ml) was added dimethyldioxirane / acetone solution (0.64mmol) at room temperature. After stirring for 2 hours, TLC (5% methanol / dichloromethane) showed unreacted N-oxide **148** plus a trace of one product with a similar Rf value to BRL 46470 free base **147**. Stirring was continued overnight and TLC showed no change. Further dimethyldioxirane (0.42mmol) was added and the mixture stirred overnight. TLC showed a trace of a second product in addition to BRL 46470 free base **147** and unreacted N-oxide **148**. The solution was concentrated *in vacuo* and analysed by HPLC. This showed the mixture to comprise of 75% N-oxide, the 3 impurities seen in the N-oxide (7%, 3% and 2%) plus 4% BRL 46470 free base **147**, all by area normalisation.

Oxidation of BRL 49653 using dimethyldioxirane



149

Reaction 1

To BRL 49653 free base **149** (50mg, 0.140mmol) in acetone (10ml) was added dimethyldioxirane / acetone solution (0.840mmol) at room temperature. A yellow precipitate appeared almost immediately. After 1 hour, a sample was removed and both the precipitate and liquors analysed by HPLC. Both showed similar profiles with no remaining starting material and one major product (33.7% by area normalisation), plus at least 10 products at levels greater than 1% by area normalisation (see Appendix IV for details).

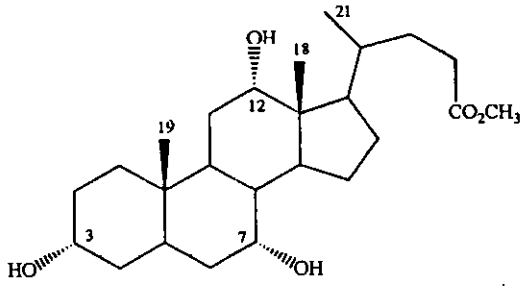
Reaction 2

To BRL 49653 free base **149** (50mg, 0.140mmol) in acetone (10ml) was added dimethyldioxirane / acetone solution (0.140mmol) at room temperature and the resulting mixture stirred for 30 minutes. A sample was removed for HPLC analysis. Another aliquot of dimethyldioxirane / acetone solution (0.140mmol) was then added and stirring continued for a further 30 minutes. This was repeated until a total of 0.84mmolof dimethyldioxirane had been added. The HPLC profile of the mixture after the first aliquot of dioxirane had been added was similar to that in reaction 1 and did not change significantly on addition of the remaining aliquots.

6.5 EXPERIMENTAL FOR CHAPTER 4

All the products from the following reactions are known compounds and have previously been prepared in these laboratories.

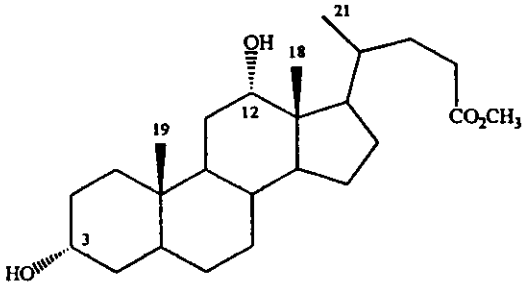
Preparation of methyl cholate using methanol and chlorotrimethylsilane



153a

Chlorotrimethylsilane (0.23ml, 1.83mmol) was added to a solution of cholic acid (500mg, 1.22mmol) in methanol (30ml). The resulting solution was heated to 60°C and stirred overnight at this temperature. TLC (5% methanol / dichloromethane) indicated completion of the reaction. The mixture was concentrated *in vacuo*, the residue dissolved in dichloromethane and washed with brine. After drying the organic phase over magnesium sulfate, concentration *in vacuo* gave the title compound **153a** as a white solid[163,18-190] (423mg, 82%), which was purified by recrystallisation from acetonitrile. δ_H ($CDCl_3$) 3.98 (t, 1H, 12β), 3.86 (q, 1H, 7β), 3.66 (s, 3H, OCH_3), 3.50 (m, 1H, 3β), 0.98 (d, 3H, CH_3-21), 0.89 (s, 3H, CH_3-19), 0.68 (s, 3H, CH_3-18).

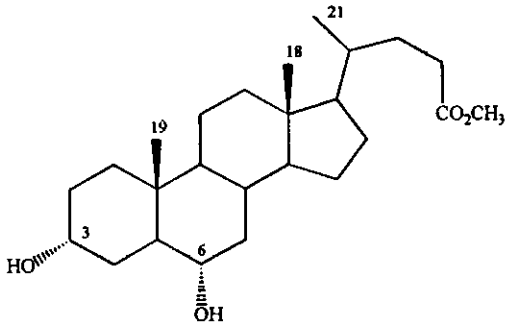
Preparation of methyl deoxycholate using methanol and chlorotrimethylsilane



153b

Chlorotrimethylsilane (0.48ml, 3.8mmol) was added to a solution of deoxycholic acid (1.0g, 2.54mmol) in methanol (60ml) and the resulting solution heated to 60°C. Heating was continued overnight and the mixture concentrated *in vacuo* to a white solid, which was then dissolved in dichloromethane, washed with brine and dried over magnesium sulfate before concentrating *in vacuo* to give the title compound **153b** as a white solid (841mg, 81%). δ_H ($CDCl_3$) 3.98 (1H, 12β), 3.66 (s, 3H, OCH_3), 3.64 (m, 1H, 3β), 0.97 (d, 3H, CH_3-21), 0.96 (s, 3H, CH_3-19), 0.68 (s, 3H, CH_3-18).

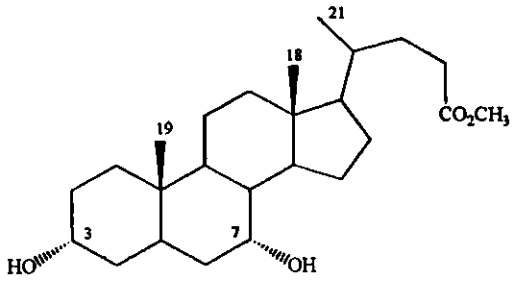
Preparation of methyl hyodeoxycholate using methanol and chlorotrimethylsilane



153d

Chlorotrimethylsilane (0.73ml, 5.73mmol) was added to a solution of hyodeoxycholic acid (1.5g, 3.82mmol) in methanol (94ml). The resulting solution was heated to 60°C and continued overnight. Concentration *in vacuo* gave a pale yellow solid. This was dissolved in dichloromethane, washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to give methyl hyodeoxycholate **153d** as a white solid[191] (1.28g, 85%). δ_H ($CDCl_3$) 4.05 (t, 1H, 6β), 3.65 (s, 3H, OCH_3), 3.58 (m, 1H, 3β), 0.91 (d, 3H, CH_3-21), 0.90 (s, 3H, CH_3-19), 0.63 (s, 3H, CH_3-18).

Preparation of diazomethane and subsequent preparation of methyl chenodeoxycholate



153c

To dry distilled diethyl ether (60ml) was added N-methyl-N-nitrosotoluene-*para*-sulfonamide (2.14g) followed by a solution of potassium hydroxide (0.4g) in absolute ethanol (10ml). The temperature was raised to 60°C and maintained using a water bath. An ethereal solution of diazomethane was allowed to distil over into a solution of chenodeoxycholic acid (600mg, 1.53mmol) in dry THF (30ml). The resulting mixture was stirred until the solution had turned from yellow to colourless. A couple of drops of glacial acetic acid were added to destroy any excess diazomethane. Concentration *in vacuo* gave a white solid which was purified by column chromatography on silica eluting with 1:1 ethyl acetate / dichloromethane affording methyl chenodeoxycholate **153c**[192] (587mg, 94%). δ_H ($CDCl_3$) 3.85 (q, 1H, 7β), 3.66 (s, 3H, OCH_3), 3.46 (m, 1H, 3β), 0.93 (d, 3H, CH_3-21), 0.91 (s, 3H, CH_3-19), 0.67 (s, 3H, CH_3-18).

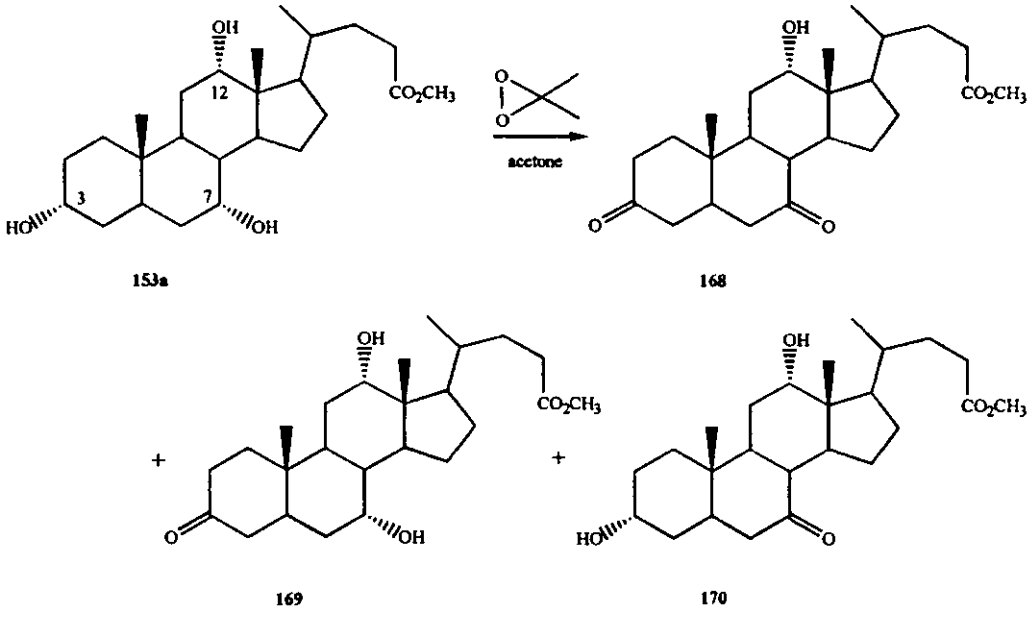
Preparation of methyl deoxycholate using diazomethane

Deoxycholic acid (3.0g, 7.64mmol) was methylated as described above using diazomethane. Purification by column chromatography on silica eluting with 2:1 petrol / ethyl acetate gave methyl deoxycholate **153b** as a white solid (2.05g, 68%).

Preparation of methyl hyodeoxycholate using diazomethane

Hyodeoxycholic acid (3.0g, 7.64mmol) was methylated as described above using diazomethane. Purification by column chromatography on silica eluting with 2:1 petrol / ethyl acetate gave methyl hyodeoxycholate **153d** as a white solid (2.45g, 79%).

Oxidation of methyl cholate using dimethyldioxirane



1. Using one equivalent of dimethyldioxirane

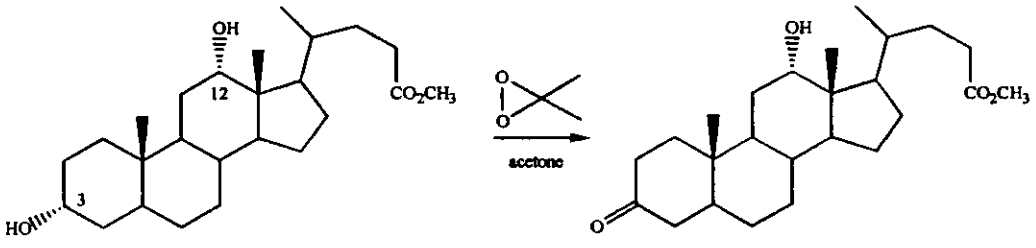
To methyl cholate **153a** (500mg, 1.18mmol) in acetone (10ml) in a round bottomed flask protected from light and cooled to 0-5°C in an ice bath, was added dimethyldioxirane / acetone solution (18.5ml, 1.18mmol). The resulting solution was stirred for approximately 16 hours, allowing to warm slowly to room temperature. TLC (3:2 ethyl acetate / dichloromethane) indicated 3 products plus some unreacted starting material. Concentration *in vacuo* followed by column chromatography on silica eluting with 3:2 ethyl acetate / dichloromethane gave the 3,7-dioxo-12α-hydroxy compound **168** as a white solid[193] (124mg, 25%) δ_H ($CDCl_3$) 4.08 (t, 1H, 12β), 3.69 (s, 3H, OCH_3), 2.89 (m, 1H, C8–H), 1.31 (s, 3H, CH_3-19), 1.01 (d, 3H, CH_3-21), 0.75 (s, 3H, CH_3-18), 3-oxo-7α, 12α- dihydroxy compound **169**[164-166,146d] (129mg, 26%) δ_H ($CDCl_3$) 4.06 (t, 1H, 12β), 3.95 (q, 1H, 7β), 3.69 (s, 3H, OCH_3), 3.44 (m, 1H, C4–H), 1.02 (s, 3H, CH_3-19), 1.00 (d, 3H, CH_3-21), 0.76 (s, 3H, CH_3-18) and 7-oxo-3α,12α-dihydroxy compound **170**[193] (104mg, 21%) δ_H ($CDCl_3$) 4.05 (t, 1H, 12β), 3.67 (s, 3H, OCH_3), 3.61 (m, 1H, 3β), 2.82 (m, 1H, C8–H), 1.18 (s, 3H, CH_3-19), 0.97 (d, 3H, CH_3-21), 0.68 (s, 3H, CH_3-18).

2. Using two equivalents of dimethyldioxirane

To a solution of methyl cholate **153a** (500mg, 1.18mmol) in acetone (10ml), cooled in an ice bath

and protected from light, was added dimethyldioxirane / acetone solution (29.9ml, 2.36mmol). The resulting solution was stirred for approximately 16 hours, allowing to warm to room temperature. TLC (3:2 ethyl acetate / dichloromethane) showed no starting material remaining. Concentration *in vacuo* followed by column chromatography on silica eluting with 3:2 ethyl acetate / dichloromethane gave the 3,7-dioxo compound as a white solid **168** (300mg, 61%) plus the 3-oxo-7α-hydroxy compound **169** (45mg, 9%) and the 7-oxo-3α-hydroxy compound **170** (30mg, 6%).

Oxidation of methyl deoxycholate using dimethyldioxirane



153b 171

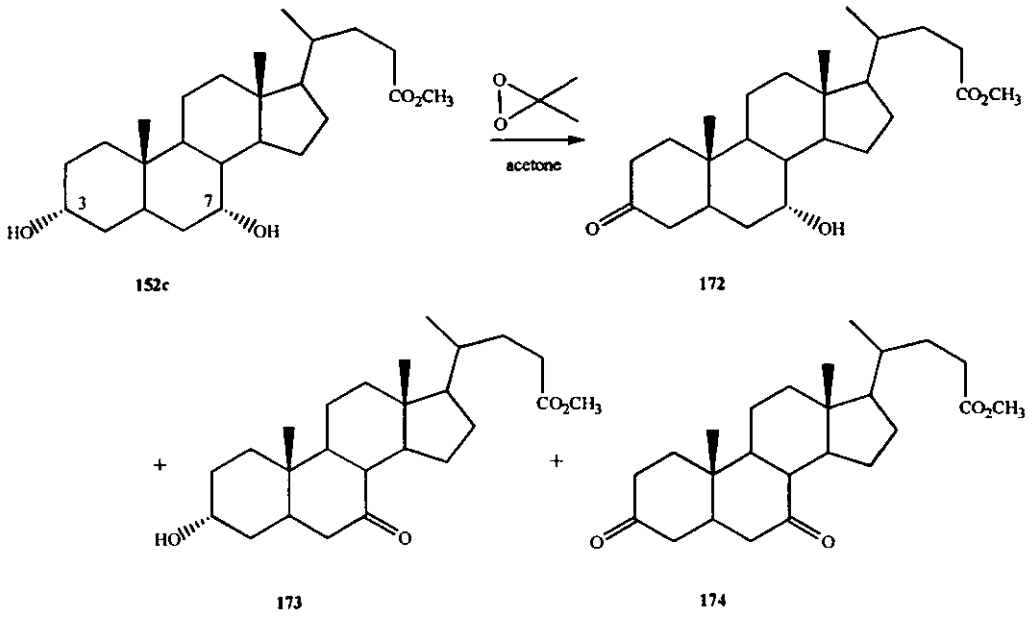
1. Using one equivalent of dimethyldioxirane

To methyl deoxycholate **153b** (500mg, 1.23mmol) in acetone (10ml), protected from light and cooled to 0-5°C in an ice bath, was added dimethyldioxirane / acetone solution (12.7ml, 1.23mmol). The resulting solution was stirred for approximately 16 hours, allowing to warm to room temperature. Concentration *in vacuo* followed by column chromatography, eluting with 3:2 ethyl acetate / dichloromethane gave the 3-oxo-12α-hydroxy compound **171** as a white solid[164-166] (295mg, 59%) δ_H ($CDCl_3$) 4.06 (t, 1H, 12β), 3.69 (s, 3H, OCH_3), 2.75 (m, 1H, C4–H), 1.03 (s, 3H, CH_3-19), 1.00 (d, 3H, CH_3-21), 0.74 (s, 3H, CH_3-18) plus starting material (125mg, 25%).

2. Using two equivalents of dimethyldioxirane

To methyl deoxycholate **153b** (500mg, 1.23mmol) in acetone (10ml), protected from light and cooled to 0-5°C in an ice bath, was added dimethyldioxirane / acetone solution (24.5ml, 2.46mmol). The resulting solution was stirred for approximately 16 hours, allowing to warm to room temperature. Concentration *in vacuo* followed by column chromatography, eluting with 3:2 ethyl acetate / dichloromethane gave the 3-oxo-12α-hydroxy compound **171** only as a white solid (375mg, 75%).

Oxidation of methyl chenodeoxycholate using dimethyldioxirane



152c 172

173 174

1. Using one equivalent of dimethyldioxirane

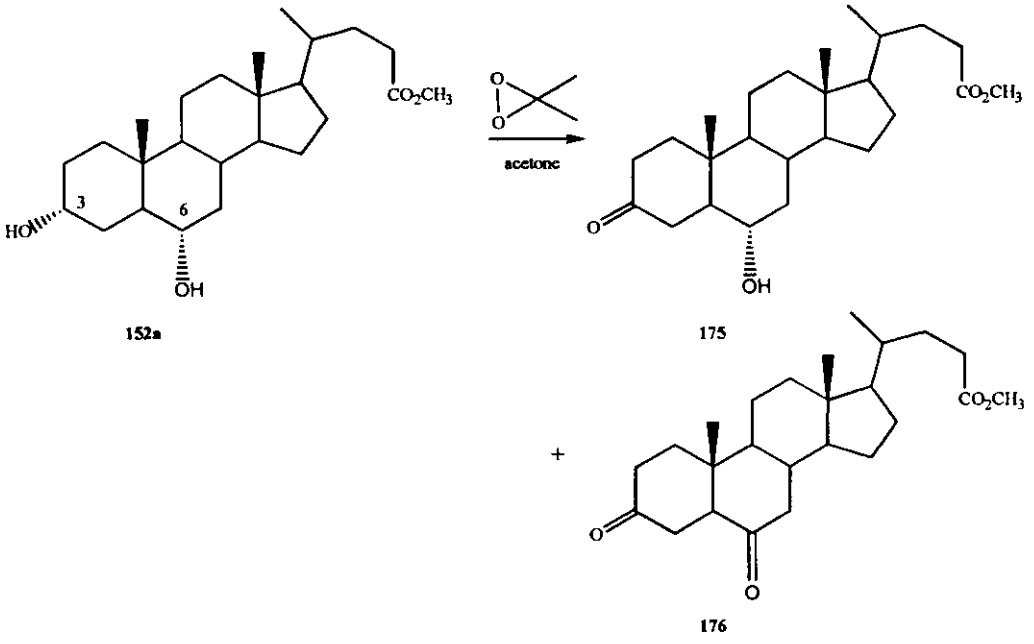
To methyl chenodeoxycholate **153c** (500mg, 1.23mmol) in acetone (10ml), protected from light and cooled to 0-5°C in an ice bath, was added dimethyldioxirane / acetone solution (12.7ml, 1.23mmol). The resulting solution was stirred for approximately 16 hours, allowing to warm to room temperature. Concentration *in vacuo* followed by column chromatography, eluting with 3:2 ethyl acetate / dichloromethane gave the 3-oxo-7α-hydroxy compound **172**[164-166] (179mg, 36%) δ_H ($CDCl_3$) 3.96 (q, 1H, 7β), 3.69 (s, 3H, OCH_3), 3.42 (m, 1H, C4–H), 1.03 (s, 3H, CH_3-19), 0.97 (d, 3H, CH_3-21), 0.73 (s, 3H, CH_3-18), the 7-oxo-3α-hydroxy compound **173**[192] (125mg, 25%) δ_H ($CDCl_3$) 3.68 (s, 3H, OCH_3), 3.62 (m, 1H, 3β), 2.88 (m, 1H, C8–H), 1.19 (s, 3H, CH_3-19), 0.95 (d, 3H, CH_3-21), 0.68 (s, 3H, CH_3-18) and the 3,7-dioxo compound **174**[194] (69mg, 14%) δ_H ($CDCl_3$) 3.69 (s, 3H, OCH_3), 2.89 (m, 1H, C8–H), 1.33 (s, 3H, CH_3-19), 0.96 (d, 3H, CH_3-21), 0.73 (s, 3H, CH_3-18) plus starting material (90mg, 18%).

2. Using 2 equivalents of dimethyldioxirane

To methyl chenodeoxycholate **153c** (500mg, 1.23mmol) in acetone (10ml), protected from light and cooled to 0-5°C in an ice bath, was added dimethyldioxirane / acetone solution (25.5ml, 2.46mmol). The resulting solution was stirred for approximately 16 hours, allowing to warm to room

temperature. Concentration *in vacuo* followed by column chromatography, eluting with 3:2 ethyl acetate / dichloromethane gave the 3,7-dioxo compound **174** only (453mg, 91%).

Oxidation of methyl hyodeoxycholate using dimethyldioxirane



152a 175 176

1. Using one equivalent of dimethyldioxirane

To methyl hyodeoxycholate **153d** (380mg, 0.93mmol) in acetone (8ml), protected from light and cooled to 0-5°C in an ice bath, was added dimethyldioxirane / acetone solution (12.4ml, 0.93mmol). The resulting solution was stirred for approximately 16 hours, allowing to warm to room temperature. Concentration *in vacuo* followed by column chromatography, eluting with 3:2 ethyl acetate / dichloromethane gave the 3-oxo-6α-hydroxy compound **175** as a colourless gum[195] (297mg, 78%) δ_H ($CDCl_3$) 4.04 (m, 1H, 6β), 3.62 (s, 3H, OCH_3), 0.96 (s, 3H, CH_3-19), 0.88 (d, 3H, CH_3-21), 0.64 (s, 3H, CH_3-18) plus the 3,6-dioxo compound **176**[196] (30mg, 8%) δ_H ($CDCl_3$) 3.70 (s, 3H, OCH_3), 0.99 (s, 3H, CH_3-19), 0.98 (d, 3H, CH_3-21), 0.73 (s, 3H, CH_3-18).

2. Using 2 equivalents of dimethyldioxirane

To methyl hyodeoxycholate **152d** (400mg, 0.98mmol) in acetone (8ml), protected from light and cooled to 0-5°C in an ice bath, was added dimethyldioxirane / acetone solution (26.4ml, 1.96mmol). The resulting solution was stirred for approximately 16 hours, allowing to warm to room

temperature. Concentration *in vacuo* followed by column chromatography, eluting with 3:2 ethyl acetate / dichloromethane gave the 3-oxo-6α-hydroxy compound **175** as a colourless gum (274mg, 69%) plus the 3,6-dioxo compound **176** as a white solid (72mg, 18%).

6.6 EXPERIMENTAL FOR CHAPTER 5

GC Method

GC apparatus	:	Pye series, 104 Chromatograph, Pye Unicam	
Column	:	10% Carbowax 20m	
Gases	:	standard machine settings	
Carrier gas	:	nitrogen	
Detector	:	FID	
Program	:	cyclohexene reaction mixtures :	
		initial oven temperature	70°C for 2 minutes
		ramp rate	3°C / min
		final oven temperature	90°C and hold
		trans-stilbene reaction mixtures :	
		oven temperature	isothermal at 220°C

Preparation of phosphate buffer pH 7.5 for use in method A

Potassium dihydrogen orthophosphate (1.179g) and disodium hydrogen phosphate (4.302g) were diluted to 1 litre with distilled water.

Method A

Oxidation of cyclohexene using α,α,α-trifluoroacetophenone (1eq) / Oxone® (2.7eq)

To cyclohexene (150mg, 1.83mmol) in dichloromethane (20ml) was added α,α,α-trifluoroacetophenone (319mg, 1.83mmol), t-butyl ammonium hydrogen sulfate (200mg, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH 7.5 whilst a solution of

Oxone® (3.0g, 4.9mmol) and EDTA (200mg) in water (50ml) was added dropwise over 25 minutes. The mixture was then stirred vigorously to ensure good mixing for a further 2 hours 20 minutes (total reaction time 2.75 hours). The reaction mixture was analysed by GC and the relative proportions of cyclohexene and cyclohexene oxide determined. The reaction was continued for a further 1.25 hours (total reaction time 4 hours) and again analysed by GC. The reaction was then repeated.

reaction	reaction time	% wt cyclohexene	% wt cyclohexene oxide
1	2.75 hours	68%	32%
	4 hours	35%	65%
2	2.75 hours	70%	30%
	4 hours	32%	68%

Method A

Oxidation of cyclohexene using Oxone® (2.7eq) in the absence of ketone

To cyclohexene (150mg, 1.83mmol) in dichloromethane (20ml) was added t-butyl ammonium hydrogen sulfate (200mg, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH 7.5 whilst a solution of Oxone® (3.0g, 4.9mmol) and EDTA (200mg) in water (50ml) was added dropwise over 25 minutes. The mixture was then stirred vigorously for a further 2 hours 20 minutes (total reaction time 2.75 hours). The reaction mixture was analysed by GC and the relative proportions of cyclohexene and cyclohexene oxide determined. The reaction was continued for a further 1.25 hours (total reaction time 4 hours) and again analysed by GC. The reaction was then repeated.

reaction	reaction time	% wt cyclohexene	% wt cyclohexene oxide
1	2.75 hours	83%	17%
	4 hours	65%	35%
2	2.75 hours	78%	22%
	4 hours	-	-

Method A

Oxidation of cyclohexene using α,α,α-trifluoroacetophenone (1eq) / Oxone® (8eq)

To cyclohexene (150mg, 1.83mmol) in dichloromethane (20ml) was added α,α,α-trifluoroacetophenone (319mg, 1.83mmol), t-butyl ammonium hydrogen sulfate (200mg, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH 7.5 whilst a solution of Oxone® (3.0g, 4.9mmol) and EDTA (200mg) in water (50ml) was added dropwise over 5 minutes. The mixture was then stirred vigorously for 30 minutes and a further amount of Oxone® (3.0g, 4.9mmol) in water (50ml) added over 15 minutes. Stirring was continued for 30 minutes then a third portion of Oxone® (3.0g, 4.9mmol) added over 15 minutes. The reaction mixture was then stirred for a further 2 hours 25 minutes giving a total reaction time of 4 hours. The reaction mixture was analysed by GC which showed 34% cyclohexene and 66% cyclohexene oxide.

Method A

Oxidation of cyclohexene using Oxone® (8eq) in the absence of ketone

To cyclohexene (150mg, 1.83mmol) in dichloromethane (20ml) was added t-butyl ammonium hydrogen sulfate (200mg, 0.59mmol) and phosphate buffer (30ml). The mixture was maintained at 0-5°C and pH 7.5 whilst a solution of Oxone® (3.0g, 4.9mmol) and EDTA (200mg) in water (50ml) was added dropwise over 5 minutes. The mixture was then stirred vigorously for 30 minutes and a further amount of Oxone® (3.0g, 4.9mmol) in water (50ml) added over 15 minutes. Stirring was continued for 30 minutes then a third portion of Oxone® (3.0g, 4.9mmol) added over 15 minutes. The reaction mixture was then stirred for a further 2 hours 25 minutes (total reaction time 4 hours). The reaction mixture was analysed by GC which showed 56% cyclohexene and 44% cyclohexene oxide. The reaction was repeated giving 51% cyclohexene and 49% cyclohexene oxide.

Method B

Oxidation of cyclohexene using α,α,α-trifluoroacetophenone (1eq) / Oxone® (1.2eq)

A solution of Oxone® (450mg, 0.73mmol) in water (2.5ml) and EDTA (3mg) were added in one portion to a biphasic solution of cyclohexene (62μl, 0.61mmol), t-butyl ammonium hydrogen sulfate (41mg, 0.122mmol), α,α,α-trifluoroacetophenone (41mg, 0.61mmol) in dichloromethane (6ml) and

1M aqueous sodium bicarbonate (2ml) at 0°C. The reaction was stirred at this temperature and samples removed at intervals for analysis by GC. This procedure was repeated several times and also with a slower rate of stirring and at room temperature.

		% wt cyclohexene oxide				
reaction	**conditions**	**3 hours**	**5 hours**	**6 hours**	**7 hours**	**16 hours**
1	0-5°C	-	17%	-	-	29%
2	0-5°C	-	-	-	15%	24%
3	0-5°C	-	-	-	-	28%
4	0-5°C	-	-	-	-	29%
5	0-5°C	12%	-	17%	-	-
6	0-5°C, slow stir	-	6%	-	-	10%
7	RT	-	-	-	-	-

Method B

Oxidation of cyclohexene using 4-tert-butylcyclohexanone (1eq) / Oxone® (1.2eq)

A solution of Oxone® (450mg, 0.73mmol) in water (2.5ml) and EDTA (3mg) were added in one portion to a biphasic solution of cyclohexene (62µl, 0.61mmol), t-butyl ammonium hydrogen sulfate (41mg, 0.122mmol), 4-tert-butylcyclohexanone (94mg, 0.61mmol) in dichloromethane (6ml) and 1M aqueous sodium bicarbonate (2ml) at 0°C. The reaction was stirred at this temperature and samples removed at intervals for analysis by GC. This procedure was repeated several times and also with a slower rate of stirring.

	% wt cyclohexene oxide			
conditions	**3 hours**	**5 hours**	**6 hours**	**16 hours**
0-5°C	-	9%	-	25%
0-5°C	-	9%	-	22%
0-5°C	6%	-	10%	-
0-5°C, slow stir	-	-	-	2%

Method B

Oxidation of cyclohexene using Oxone® (1.2eq) in the absence of ketone

A solution of Oxone® (450mg, 0.73mmol) in water (2.5ml) and EDTA (3mg) were added in one portion to a biphasic solution of cyclohexene (62µl, 0.61mmol) and t-butyl ammonium hydrogen

sulfate (41mg, 0.122mmol) in dichloromethane (6ml) and 1M aqueous sodium bicarbonate (2ml) at 0°C. The reaction was stirred at this temperature and samples removed at intervals for analysis by GC. This procedure was repeated several times and also with a slower rate of stirring.

		% wt cyclohexene oxide				
reaction	**conditions**	**3 hours**	**5 hours**	**6 hours**	**7 hours**	**16 hours**
1	0-5°C	6%	-	9%	-	-
2	0-5°C	-	-	-	10%	21%
3	0-5°C	-	-	-	-	13%
4	0-5°C	-	-	9%	-	-
5	0-5°C	4%	-	9%	-	-
6	0-5°C	-	8%	-	-	20%
7	0-5°C	-	8%	-	-	23%
8	0-5°C, slow stir	-	0.5%	-	-	2%

Method B

Oxidation of cyclohexene using α,α,α-trifluoroacetophenone (5eq) / Oxone® (1.2eq)

A solution of Oxone® (450mg, 0.73mmol) in water (2.5ml) and EDTA (3mg) were added in one portion to a biphasic solution of cyclohexene (62µl, 0.61mmol), t-butyl ammonium hydrogen sulfate (41mg, 0.122mmol), α,α,α-trifluoroacetophenone (205mg, 3.05mmol) in dichloromethane (6ml) and 1M aqueous sodium bicarbonate (2ml) at 0°C. The reaction was stirred at this temperature and samples removed at intervals for analysis by GC. This reaction was then repeated.

	% wt cyclohexene oxide		
reaction	**3 hours**	**6 hours**	**16 hours**
1	17%	23%	28%
2	25%	29%	-

Method B

Oxidation of cyclohexene using 4-tert-butylcyclohexanone (5eq) / Oxone® (1.2eq)

A solution of Oxone® (450mg, 0.73mmol) in water (2.5ml) and EDTA (3mg) were added in one portion to a biphasic solution of cyclohexene (62µl, 0.61mmol), t-butyl ammonium hydrogen sulfate (41mg, 0.122mmol), 4-tert-butylcyclohexanone (470mg, 3.05mmol) in dichloromethane (6ml) and

1M aqueous sodium bicarbonate (2ml) at 0°C. The reaction was stirred at this temperature and samples removed at intervals for analysis by GC. After 3 hours, 6% cyclohexene oxide was obtained which increased to 8% after 6 hours.

Method B

Oxidation of cyclohexene using α,α,α-trifluoroacetophenone (1eq) / Oxone® (2.5eq)

A solution of Oxone® (937mg, 1.52mmol) in water (2.5ml) and EDTA (3mg) were added in one portion to a biphasic solution of cyclohexene (62μl, 0.61mmol), t-butyl ammonium hydrogen sulfate (41mg, 0.122mmol), α,α,α-trifluoroacetophenone (205mg, 3.05mmol) in dichloromethane (6ml) and 1M aqueous sodium bicarbonate (2ml) at 0°C. The reaction was stirred at this temperature and samples removed at intervals for analysis by GC. After 3 hours, 9% cyclohexene oxide was obtained which increased to 14% after 6 hours and 22% after 16 hours.

Method B

Oxidation of cyclohexene using Oxone® (2.5eq) in the absence of ketone

The above procedure was repeated but in the absence of α,α,α-trifluoroacetophenone.
After 3 hours, 10% cyclohexene oxide was obtained which increased to 18% after 6 hours and 22% after 16 hours.

Method B

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (1eq) / Oxone® (1.2eq)

A solution of Oxone® (614mg, 1.0mmol) in water (5ml) and EDTA (3.3mg) were added in one portion to a biphasic solution of *trans*-stilbene (150mg, 0.832mmol), t-butyl ammonium hydrogen sulfate (67mg, 0.197mmol), α,α,α-trifluoroacetophenone (117μl, 0.832mmol) in dichloromethane (10ml) and 1M aqueous sodium bicarbonate (3ml) at 0-5°C. The reaction was stirred at this temperature and samples removed at intervals for analysis by GC. After 2 hours, 2% *trans*-stilbene oxide was obtained which increased to 4% after 16 hours.

Method C

Oxidation of *trans*-tilbene using α,α,α-trifluoroacetophenone (11eq) / Oxone® (5eq)

To *trans*-stilbene (144mg, 0.8mmol) in acetonitrile (18ml) was added 4 x 10^{-4}M aqueous EDTA solution (4ml) followed by α,α,α-trifluoroacetophenone (1.24ml, 8.8mmol). The resulting mixture was cooled to 0-5°C and a solid mixture of Oxone® (2.46g, 4mmol) and sodium bicarbonate (0.52g, 6.2mmol) added in portions over 30 minutes. Stirring was continued and samples removed at intervals for analysis by GC. After 2.75 hours, 58% *trans*-stilbene oxide was obtained which increased to 73% after 16 hours. The reaction was repeated and analysed after 16 hours only. 80% *trans*-stilbene oxide was obtained. The reaction was repeated a third time but this time the Oxone® / sodium bicarbonate mixture was added in one portion. After 16 hours, GC analysis showed 20% *trans*-stilbene oxide.

Method C

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (5eq) / Oxone® (5eq)

To *trans*-stilbene (144mg, 0.8mmol) in acetonitrile (18ml) was added 4 x 10^{-4}M aqueous EDTA solution (4ml) followed by α,α,α-trifluoroacetophenone (0.56ml, 4mmol). The resulting mixture was cooled to 0-5°C and a solid mixture of Oxone® (2.46g, 4mmol) and sodium bicarbonate (0.52g, 6.2mmol) added in portions over 30 minutes. Stirring was continued 16 hours after which time 3% *trans*-stilbene oxide was obtained.

Method C

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (1eq) / Oxone® (5eq)

The above procedure was repeated but using 1 equivalent of α,α,α-trifluoroacetophenone (0.112ml, 0.8mmol). After 16 hours, 5% *trans*-stilbene oxide was obtained.

Method D

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (5eq) / Oxone® (5eq)

To *trans*-stilbene (144mg, 0.8mmol) in acetonitrile (12ml) and 4 x 10^{-4}M aqueous EDTA solution

(8ml), cooled to 0-5°C, was added α,α,α-trifluoroacetophenone (0.56ml, 4mmol) followed by a solid mixture of Oxone® (2.46g, 4mmol) and sodium bicarbonate (1.04g, 12.4mmol) added in portions over 30 minutes. Stirring was continued for 16 hours then analysed by GC, which showed 100% conversion to *trans*-stilbene oxide. The reaction was repeated a further 3 times obtaining 95%, 98% and 96% *trans*-stilbene oxide respectively.

Method D

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (2eq) / Oxone® (5eq)

The above procedure was repeated using 2 equivalents of α,α,α-trifluoroacetophenone (0.22ml, 1.6mmol). 99% *trans*-stilbene oxide was obtained by GC.

Method D

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (1eq) / Oxone® (5eq)

The above procedure was repeated using 1 equivalent of α,α,α-trifluoroacetophenone (0.11ml, 0.8mmol). 17% *trans*-stilbene oxide was obtained by GC.

Method D

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (0.5eq) / Oxone® (5eq)

The above procedure was repeated using 0.5 equivalents of α,α,α-trifluoroacetophenone (55μl, 0.4mmol). 18% *trans*-stilbene oxide was obtained by GC.

Method D

Oxidation of *trans*-stilbene using Oxone® (5eq) in the absence of ketone

The above procedure was repeated in the absence of α,α,α-trifluoroacetophenone. 9% *trans*-stilbene oxide was obtained by GC. The reaction was repeated giving 4% *trans*-stilbene oxide.

Method D

Oxidation of *trans*-stilbene using 4-(trifluoroacetyl)benzoic acid (5eq) / Oxone® (5eq)

To *trans*-stilbene (144mg, 0.8mmol) in acetonitrile (12ml) and 4 x 10^{-4}M aqueous EDTA solution (8ml), cooled to 0-5°C, was added 4-(trifluoroacetyl)benzoic acid (873mg, 4mmol) followed by a solid mixture of Oxone® (2.46g, 4mmol) and sodium bicarbonate (1.04g, 12.4mmol) added in portions over 30 minutes. Stirring was continued for 16 hours then analysed by GC, which showed 94% *trans*-stilbene oxide.

Method D

Oxidation of *trans*-stilbene using 4-(trifluoroacetyl)benzoic acid (2eq) / Oxone® (5eq)

The above procedure was repeated using 2 equivalents of 4-(trifluoroacetyl)benzoic acid (349mg, 1.6mmol). 97% *trans*-stilbene oxide was obtained by GC.

Method D

Oxidation of *trans*-stilbene using 4-(trifluoroacetyl)benzoic acid (1eq) / Oxone® (5eq)

The above procedure was repeated using 1 equivalent of 4-(trifluoroacetyl)benzoic acid (175mg, 0.8mmol). 15% *trans*-stilbene oxide was obtained by GC.

Method D

Oxidation of *trans*-stilbene using 4-(trifluoroacetyl)benzoic acid (0.5eq) / Oxone® (5eq)

The above procedure was repeated using 0.5 equivalents of 4-(trifluoroacetyl)benzoic acid (88mg, 0.4mmol). 10% *trans*-stilbene oxide was obtained by GC.

Method D

Comparison of 4-(trifluoroacetyl)benzoic acid, benzoic acid and 4-chlorobenzoic acid

Oxidation of *trans*-stilbene using 4-(trifluoroacetyl)benzoic acid (5eq) / Oxone® (5eq)

To *trans*-stilbene (144mg, 0.8mmol) in acetonitrile (60ml) and 4 x 10^{-4}M aqueous EDTA solution (40ml), cooled to 0-5°C, was added 4-(trifluoroacetyl)benzoic acid (873mg, 4mmol) followed by a solid mixture of Oxone® (2.46g, 4mmol) and sodium bicarbonate (1.04g, 12.4mmol) added in portions over 30 minutes. Stirring was continued for 16 hours then analysed by GC, which showed 99% *trans*-stilbene oxide.

Oxidation of *trans*-stilbene using benzoic acid (5eq) / Oxone® (5eq)

The above procedure was repeated using benzoic acid (489mg, 4mmol) instead of 4-(trifluoro-acetyl)benzoic acid. 9% *trans*-stilbene oxide was obtained by GC. The reaction was repeated giving 37% *trans*-stilbene oxide after 16 hours and 75% after 96 hours.

Oxidation of *trans*-stilbene using 4-chlorobenzoic acid (5eq) / Oxone® (5eq)

The above procedure was repeated using 4-chlorobenzoic acid (626mg, 4mmol) instead of 4-trifluoroacetylbenzoic acid. It was found that 4-chlorobenzoic acid was not very soluble in the reaction mixture but the reaction was continued giving 20% *trans*-stilbene oxide by GC after 16 hours. The reaction was repeated using larger volumes of acetonitrile (300ml) and water (200ml) giving 26% *trans*-stilbene oxide by GC after 16 hours.

Method D (biphasic)

Oxidation of cyclohexene using α,α,α-trifluoroacetophenone (5eq) / Oxone® (5eq)

To cyclohexene (50mg, 0.61mmol) in dichloromethane (12ml) and 4 x 10^{-4}M aqueous EDTA solution (8ml) was added t-butyl ammonium hydrogen sulfate (66mg) and α,α,α-trifluoroaceto-phenone (428μl, 3.05mmol). The resulting mixture was stirred at room temperature and to it was added a solid mixture of Oxone® (1.88g, 3.05mmol) and sodium bicarbonate (794mg, 9.45mmol).

Stirring was continued and samples removed at intervals for analysis by GC. This reaction was repeated several times.

	% wt cyclohexene oxide	
reaction	5 hours	16 hours
1	-	35%
2	-	48%
3	28%	28%
4	-	94%
5	-	44%
6	52%	55%

Method D (biphasic)

Oxidation of cyclohexene using 4-(trifluoroacetyl)benzoic acid (5eq) / Oxone® (5eq)

The above procedure was repeated three times using 4-(trifluoroacetyl)benzoic acid (665mg, 3.05mmol) instead of α,α,α-trifluoroacetophenone.

	% wt cyclohexene oxide	
reaction	5 hours	16 hours
1	42%	48%
2	-	68%
3	55%	61%

Method D (biphasic)

Oxidation of cyclohexene using 4-tert-butylcyclohexanone (5eq) / Oxone® (5eq)

The above procedure was repeated using 4-tert-butylcyclohexanone (470mg, 3.05mmol) instead of 4-trifluoroacetylbenzoic acid. 3% cyclohexene oxide was obtained by GC after 16 hours.

Method D (biphasic)

Oxidation of cyclohexene using Oxone® (5eq) in the absence of ketone

The above procedure was repeated four times in the absence of ketone.

	% wt cyclohexene oxide	
reaction	**5 hours**	**16 hours**
1	2%	1%
2	-	3%
3	-	3%
4	-	7%

Method D (biphasic)

Comparison of 4-(trifluoroacetyl)benzoic acid, benzoic acid and 4-chlorobenzoic acid

Oxidation of cyclohexene using 4-(trifluoroacetyl)benzoic acid (5eq) / Oxone® (5eq)

To cyclohexene (65.6mg, 0.8mmol) in dichloromethane (60ml) and 4 x 10^{-4}M aqueous EDTA solution (40ml), cooled to 0-5°C, was added 4-(trifluoroacetyl)benzoic acid (873mg, 4mmol) followed by a solid mixture of Oxone® (2.46g, 4mmol) and sodium bicarbonate (1.04g,12.4mmol) added in portions over 30 minutes. Stirring was continued for 16 hours then analysed by GC, which showed 43% cyclohexene oxide.

Oxidation of cyclohexene using benzoic acid (5eq) / Oxone® (5eq)

The above procedure was repeated using benzoic acid (489mg, 4mmol) instead of 4-(trifluoro-acetyl)benzoic acid. 10% cyclohexene oxide was obtained by GC after 5 hours which increased to 32% after 16 hours. The reaction was repeated giving 48% cyclohexene oxide after 16 hours.

Oxidation of cyclohexene using 4-chlorobenzoic acid (5eq) / Oxone® (5eq)

The above procedure was repeated using 4-chlorobenzoic acid (626mg, 4mmol) instead of 4-(trifluoroacetyl)benzoic acid. It was found that 4-chlorobenzoic acid was not very soluble in the reaction mixture but the reaction was continued giving 15% cyclohexene oxide by GC after 16 hours. The reaction was repeated using larger volumes of dichloromethane (300ml) and water (200ml) giving 16% cyclohexene oxide by GC after 16 hours.

Method D (biphasic)

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (5eq) / Oxone® (5eq)

To *trans*-stilbene (144mg, 0.8mmol) in dichloromethane (12ml) was added t-butyl ammonium hydrogen sulfate (87mg), 4 x 10^{-4}M aqueous EDTA solution (8ml) and α,α,α-trifluoroacetophenone (0.56ml, 4mmol). The resulting mixture was stirred at room temperature and to it was added a solid mixture of Oxone® (2.46g, 4mmol) and sodium bicarbonate (1.04g, 12.4mmol). Stirring was continued for 16 hours then analysed by GC. 77% *trans*-stilbene oxide was obtained. The reaction was repeated a further four times giving 24%, 34%, 26% and 41% *trans*-stilbene oxide respectively.

Method D (biphasic)

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (10eq) / Oxone® (5eq)

The above procedure was repeated using 10 equivalents of α,α,α-trifluoroacetophenone (1.12ml, 8mmol). 85% *trans*-stilbene oxide was obtained by GC.

Method D (biphasic)

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (2eq) / Oxone® (5eq)

The above procedure was repeated using 2 equivalents of α,α,α-trifluoroacetophenone (0.22ml, 1.6mmol). 34% *trans*-stilbene oxide was obtained by GC.

Method D (biphasic)

Oxidation of *trans*-stilbene using Oxone®(5eq) in the absence of ketone

The above procedure was repeated in the absence of trifluoroacetophenone. 3% *trans*-stilbene oxide was obtained by GC. The reaction was repeated giving 1% *trans*-stilbene oxide by GC.

Method D (biphasic)

Oxidation of *trans*-stilbene using 4-(trifluoroacetyl)benzoic acid (5eq) / Oxone® (5eq)

To *trans*-stilbene (144mg, 0.8mmol) in dichloromethane (12ml) was added t-butyl ammonium hydrogen sulfate (87mg), 4 x 10^{-4}M aqueous EDTA solution (8ml) and 4-trifluoroacetylbenzoic acid (872mg, 4mmol). The resulting mixture was stirred at room temperature and to it was added a solid mixture of Oxone® (2.46g, 4mmol) and sodium bicarbonate (1.04g, 12.4mmol). Stirring was continued for 16 hours then analysed by GC. 9% *trans*-stilbene oxide was obtained.
The reaction was repeated a further twice giving 22% and 14% *trans*-stilbene oxide respectively.

Method D (biphasic)

Oxidation of *trans*-stilbene using 4-(trifluoroacetyl)benzoic acid (10eq) / Oxone® (5eq)

The above procedure was repeated using 10 equivalents of 4-(trifluoroacetyl)benzoic acid (1.75g, 8mmol). 14% *trans*-stilbene oxide was obtained by GC.

Method D (biphasic)

Comparison of 4-(trifluoroacetyl)benzoic acid, benzoic acid and 4-chlorobenzoic acid

Oxidation of *trans*-stilbene using 4-(trifluoroacetyl)benzoic acid (5eq) / Oxone® (5eq)

To *trans*-stilbene (144mg, 0.8mmol) in dichloromethane (60ml) and 4 x 10^{-4}M aqueous EDTA solution (40ml), cooled to 0-5°C, was added 4-(trifluoroacetyl)benzoic acid (873mg, 4mmol) followed by a solid mixture of Oxone® (2.46g, 4mmol) and sodium bicarbonate (1.04g, 12.4mmol) added in portions over 30 minutes. Stirring was continued for 16 hours then analysed by GC, which showed 9% *trans*-stilbene oxide.

Oxidation of *trans*-stilbene using benzoic acid (5eq) / Oxone® (5eq)

The above procedure was repeated using benzoic acid (489mg, 4mmol) instead of 4-(trifluoro-acetyl)benzoic acid. 8% *trans*-stilbene oxide was obtained by GC after 16 hours.
The reaction was repeated giving 2% *trans*-stilbene oxide after 16 hours.

Oxidation of *trans*-stilbene using 4-chlorobenzoic acid (5eq) / Oxone® (5eq)

The above procedure was repeated using 4-chlorobenzoic acid (626mg, 4mmol) instead of 4-(trifluoroacetyl)benzoic acid. It was found that 4-chlorobenzoic acid was not very soluble in the reaction mixture and no *trans*-stilbene oxide was detected by GC after 16 hours.
The reaction was repeated using larger volumes of dichloromethane (300ml) and water (200ml). This did not improve solubility and again no *trans*-stilbene oxide was detected by GC after 16 hours.

Optimisation of Method B

Reaction 1

A solution of Oxone® (0.62g, 0.73mmol) and EDTA (3mg) in water (4ml) were added in one portion to a biphasic solution of cyclohexene (62μl, 0.61mmol), t-butyl ammonium hydrogen sulfate (41mg, 0.122mmol) and α,α,α-trifluoroacetophenone (41mg, 0.61mmol) in dichloromethane (6ml) and 1M aqueous sodium bicarbonate (2.1ml) at room temperature. The reaction was stirred for 6 hours then analysed by GC. 26% cyclohexene oxide was obtained.

Reaction 2

A solution of Oxone® (1.02g, 1.65mmol) and EDTA (3mg) in water (9ml) were added in one portion to a biphasic solution of cyclohexene (62μl, 0.61mmol), t-butyl ammonium hydrogen sulfate (41mg, 0.122mmol) and α,α,α-trifluoroacetophenone (41mg, 0.61mmol) in dichloromethane (6ml) and 1M aqueous sodium bicarbonate (4.75ml) at room temperature. The reaction was stirred for 6 hours then analysed by GC. 47% cyclohexene oxide was obtained.

Reaction 3

A solution of Oxone® (1.89g, 3.05mmol) in water (16ml) and EDTA (3mg) were added in one portion to a biphasic solution of cyclohexene (62μl, 0.61mmol) and t-butyl ammonium hydrogen sulfate (41mg, 0.122mmol) and α,α,α-trifluoroacetophenone (41mg, 0.61mmol) in dichloromethane (6ml) and 1M aqueous sodium bicarbonate (8.8ml) at room temperature. The reaction was stirred

for 6 hours then analysed by GC. 66% cyclohexene oxide was obtained.

Reaction 4

The above reaction was repeated but this time the solution of Oxone® and EDTA was added dropwise over 30 minutes rather than in one portion. 68% cyclohexene oxide was obtained by GC after stirring for 6 hours.

Reaction 5

A solution of Oxone® (1.89g, 3.05mmol) in water (16ml) and EDTA (3mg) were added in one portion to a biphasic solution of cyclohexene (62µl, 0.61mmol) and t-butyl ammonium hydrogen sulfate (41mg, 0.122mmol) and α,α,α-trifluoroacetophenone (82mg, 1.22mmol) in dichloromethane (6ml) and 1M aqueous sodium bicarbonate (8.8ml) at room temperature. The reaction was stirred for 6 hours then analysed by GC. 59% cyclohexene oxide was obtained.

Method E

Oxidation of cyclohexene using α,α,α-trifluoroacetophenone (1eq) / Oxone® (10eq)

A solution of Oxone® (3.78g, 6.1mmol) in water (25ml) and EDTA (3mg) were added in one portion to a biphasic solution of cyclohexene (62µl, 0.61mmol) and t-butyl ammonium hydrogen sulfate (41mg, 0.122mmol) and α,α,α-trifluoroacetophenone (41mg, 0.61mmol) in dichloromethane (6ml) and 1M aqueous sodium bicarbonate (17ml) at room temperature. The reaction was stirred for 6 hours then analysed by GC. The reaction was repeated a further twice at room temperature and twice at 0-5°C.

		% wt cyclohexene oxide			
reaction	**conditions**	**3 hours**	**4 hours**	**6 hours**	**16 hours**
1	RT	-	-	91%	-
2	RT	-	84%	-	98%
3	RT	80%	-	89%	-
4	0-5°C	46%	-	75%	-
5	0-5°C	-	53%	-	99%

Method E

Oxidation of cyclohexene using 4-(trifluoroacetyl)benzoic acid (1eq) / Oxone® (10eq)

The above procedure was repeated using 4-(trifluoroacetyl)benzoic acid (133mg, 0.61mmol) instead of α,α,α-trifluoroacetophenone. After 6 hours, 76% cyclohexene oxide was obtained by GC, which increased to 96% after 16 hours.

Method E

Oxidation of cyclohexene using 4-tert-butylcyclohexanone (1eq) / Oxone® (10eq)

The above procedure was repeated using 4-tert-butylcyclohexanone (94mg, 0.61mmol). After 3 hours, 44% cyclohexene oxide was obtained by GC, which increased to 61% after 6 hours.
The reaction was repeated at 0-5°C rather than room temperature. 28% cyclohexene oxide was obtained by GC after 3 hours which increased to 47% after 4 hours.

Method E

Oxidation of cyclohexene using Oxone®(10eq) in the absence of ketone

The above procedure was repeated five times in the absence of ketone at room temperature.

	% wt cyclohexene oxide				
reaction	**3 hours**	**4 hours**	**6 hours**	**7 hours**	**16 hours**
1	-	-	-	79%	-
2	-	-	-	78%	-
3	-	55%	-	-	96%
4	-	-	-	-	96%
5	46%	-	65%	-	-

Method E

Oxidation of cyclohexene using Oxone®(5eq) in the absence of ketone

The above procedure was repeated at room temperature in the absence of ketone using 5 equivalents of Oxone® (1.89g, 3.05mmol). After 16 hours 28% cyclohexene oxide was obtained by GC.

Method E

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (1eq) / Oxone® (10eq)

A solution of Oxone® (1.7g, 2.77mmol) in water (14ml) and EDTA (3mg) were added in one portion to a biphasic solution of *trans*-stilbene (50mg, 0.277mmol) and t-butyl ammonium hydrogen sulfate (51mg) and α,α,α-trifluoroacetophenone (39μl, 0.277mmol) in dichloromethane (3ml) and 1M aqueous sodium bicarbonate (7.6ml) at room temperature. After stirring for 1.5 hours, 5% *trans*-stilbene oxide was obtained by GC. No increase was found after 16 hours.

Method E

Oxidation of *trans*-stilbene using α,α,α-trifluoroacetophenone (10eq) / Oxone® (10eq)

The above procedure was repeated using 10 equivalents of α,α,α-trifluoroacetophenone (0.39ml, 2.77mmol). After 16 hours, 4% *trans*-stilbene oxide was obtained by GC.

Method E

Oxidation of *trans*-stilbene using 4-(trifluoroacetyl)benzoic acid (1eq) / Oxone® (10eq)

A solution of Oxone® (1.7g, 2.77mmol) in water (14ml) and EDTA (3mg) were added in one portion to a biphasic solution of *trans*-stilbene (50mg, 0.277mmol) and t-butyl ammonium hydrogen sulfate (51mg) and α,α,α-trifluoroacetophenone (60mg, 0.277mmol) in dichloromethane (3ml) and 1M aqueous sodium bicarbonate (7.6ml) at room temperature. After stirring for 16 hours, 8% *trans*-stilbene oxide was obtained by GC.

REFERENCES

1 (a) R. Curci, A. Dinoi and M.F. Rubino, *Pure & Appl. Chem.*, 1995, **67**, 5, 811; (b) W. Adam in *Topics in Current Chemistry*, 1993, vol 164, p45-62; (c) R. Curci in *Advances in Oxygenated Processes*, 1990, vol 2, p1-59; (d) R.W. Murray, *Chem. Rev.*, 1989, **89**, 1187; (e) W. Adam, R. Curci and J. O. Edwards, *Acc. Chem. Res.*, 1989, **22**, 205.

2 R.W. Murray and R. Jeyaraman, *J. Org. Chem.*, 1985, **50**, 2847.

3 W. Adam, J. Bialas and L. Hadjiarapoglou, *Chem. Ber.*, 1991, **124**, 2377.

4 R. Curci, R. Mello, M. Fiorentino and O. Sciacovelli, *J. Org. Chem.*, 1988, **53**, 3891.

5 W. Adam, R. Curci, M.E. Gonzalez-Nunez and R. Mello, *J. Am. Chem. Soc.*, 1991, **113**, 7654.

6 R.W. Murray, M. Singh and R. Jeyaraman, *J. Am. Chem. Soc.*, 1992, **114**, 1346.

7 A. Russo and D.D. DesMarteau, *Angew. Chem. Int. Ed. Engl.*, 1993, **32** (6), 905.

8 A. Kirschfeld, S. Muthusamy and W. Sander, *Angew. Chem. Int. Ed. Engl.*, 1994, **33** (21), 2212.

9 M. Ferrer, M. Gibert, F. Sanchez-Baeza and A. Messeguer, *Tetrahedron Lett.*, 1996, **37**, 20, 3585.

10 S.E. Denmark, D.C. Forbes, D.S Hays, J.S. Depue and R.G. Wilde, *J. Org. Chem.*, 1995, **60**, 1391.

11 (a) R. Curci, M. Fiorentino, L. Troisi, J.O. Edwards and R.H. Pater, *J. Org. Chem.*, 1980, **45**, 4758; (b) J. O. Edwards, R.H. Pater, R. Curci and F.Di Furia, *Photochem. Photobiol.*, 1979, **30**, 63; (c) A.R. Gallapo and J.O. Edwards, *J. Org. Chem.*, 1981, **46**, 1684; (d) G. Cicala, R. Curci, M. Fiorentino and O. Laricchiuta, *J. Org. Chem.*, 1982, **47**, 2670.

12 S.E. Denmark, Z. Wu, C.M. Crudden and H. Matsuhashi, *J. Org. Chem.*, 1997, **62**, 8288

13 S.E. Denmark and Z. Wu, *J. Org. Chem.*, 1998, **63**, 2810.

14 (a) L. Cassidei, M. Fiorentino, R. Mello, O. Sciacovelli and R. Curci, *J. Org. Chem.*, 1987, **52**, 699; (b) W. Adam, Y.Y. Chan, D. Cremer, J. Gauss, D. Scheutzow and M. Schindler, *J. Org. Chem.*, 1987, **52**, 2800.

15 A. Armstrong, P.A. Clarke and A. Wood, *Chem. Commun.*, 1996, 849.

16 S.E. Denmark and Z. Wu, *J. Org. Chem.*, 1997, **62**, 8964.

17 (a) S.W. Baertschi, K.D. Raney, M.P. Stone and T.M. Harris, *J. Am. Chem. Soc.*, 1988, **110**, 7929; (b) R. Hambalek and G. Just, *Tetrahedron Lett.*, 1990, **31**, 4633; (c) K. Chow and S.J. Danishefsky, *J. Org. Chem.*, 1990, **55**, 4211; (d) R.L. Halcomb and S.J. Danishefsky, *J. Am. Chem. Soc.*, 1989, **111**, 6661; (e) L. Troisi, L. Cassidei, L. Lopez, R. Mello and R. Curci, *Tetrahedron Lett.*, 1989, **30**, 123.

18 W. Adam, J. Bialas, L. Hadjiarapoglou and M. Sauter, *Chem. Ber.*, 1992, **125**, 231.

19 W. Adam, L. Hadjiarapoglou, V. Jäger, J. Klicic, B. Seidel and X. Wang, *Chem. Ber.*, 1991, **124**, 2361.

20 (a) H.K. Chenault and S.J. Danishefsky, *J. Org. Chem.*, 1989, **54**, 4249; (b) W. Adam, L. Hadjiarapoglou and X. Wang, *Tetrahedron Lett.*, 1989, 30, 6597.

21 W. Adam, L. Hadjiarapoglou, V. Jäger and B. Seidel, *Tetrahedron Lett.*, 1989, **30**, 4223.

22 W. Adam, L. Hadjiarapoglou and J. Klicic, *Tetrahedron Lett.*, 1990, **31**, 6517.

23 (a) W. Adam, L. Hadjiarapoglou and B. Nestler, *Tetrahedron Lett.*, 1989, **31**, 331; (b) A. Armstrong and S.V. Ley, *Synlett*, 1990, 323; (c) A. Messeguer, F. Sanchez-Baeza, J. Casas and B.D. Hammock, *Tetrahedron*, 1991, **47**, 1291.

24 W. Adam and L. Hadjiarapoglou, *Chem. Ber.*, 1990, **123**, 2077.

25 W. Adam, D. Golsch and L. Hadjiarapoglou, *J. Org. Chem.*, 1991, **56**, 7292.

26 W. Adam, L. Hadjiarapoglou and X. Wang, *Tetrahedron Lett.*, 1991, **32**, 10, 1295.

27 W. Adam, J. Bialas, L. Hadjiarapoglou and T. Patonay, *Synthesis*, 1992, 49.

28 J.K. Crandell, D.J. Batal, D.P. Sebesta and F. Lin, *J. Org. Chem.*, 1991, **56**, 1153.

29 (a) J.K. Crandell, D.J. Batal, L. Fin, T. Reix, G.S. Nadol and R.A. Ng, *Tetrahedron Lett.*, 1992, **48**, 1427; (b) J.K. Crandell and E. Rambo, *J. Org. Chem.*, 1990, **55**, 5929.

30 J.K. Crandell and E. Rambo, *Tetrahedron Lett.*, 1994, **35**, 10, 1489.

31 J.K. Crandell and T. Reix, *Tetrahedron Lett.*, 1994, **16**, 2513.

32 B.M. Adger, C. Barrett, J. Brennan, M.A. Mckervey and R.W. Murray, *J. Chem. Soc. Chem. Commun.*, 1991, 1553.

33 A.G. Shultz, R.E. Harrington and F.S. Tham, *Tetrahedron Lett.*, 1992, **33**, 6097.

34 (a) R.W. Murray, M. Singh, B.L. Williams and H.M. Moncrieff, *Tetrahedron Lett.*, 1995, **36**, 14, 2437; (b) R.W. Murray, M. Singh, B.L. Williams and H.M. Moncrief, *J. Org. Chem.*, 1996, **61**, 1830; (c) R.W. Murray and D. Gu, *J. Chem. Soc. Perkin trans 2*, 1993, 2203.

35 A.L. Baumstark and P.C. Vasquez, *J. Org. Chem.*, 1988, **54**, 3437.

36 W. Adam and A.K. Smerz, *J. Org. Chem.*, 1996, **69**, 3506.

37 W. Adam and A.K. Smerz, *Tetrahedron*, 1995, **51**, 47, 13039.

38 (a) R. Curci, M. Fiorentino, M.R. Serio, *J. Chem. Soc. Chem. Commun.*, 1984, 155; (b) R. Curci, L. D'Accolti, M. Fiorentino and A. Rosa, *Tetrahedron Lett.*, 1995, **36**, 5831; (c) D.S. Brown, B.A. Marples, P. Smith and L. Walton, *Tetrahedron*, 1995, **51**, 3587.

39 D. Yang, Y.C. Yip, M.W. Tang, M.K. Wong, J.H. Zheng and K.K. Chiung, *J. Am. Chem. Soc.*, 1996, 118, 491.

40 Y. Tu, Z.X. Wang and Y. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 9806.

41 A. Armstrong and B.R. Hayter, *Chem. Commun.*, 1998, 621.

42 O. Reiser, *Angew. Chem. Int. Ed. Engl.*, 1994, **33** (1), 69.

43 R. Mello, M. Fiorentino, C. Fusco and R. Curci, *J. Am. Chem. Soc.*, 1989, **111**, 6749.

44 W. Adam, G. Asensio, R. Curci, M.E. Gonzales-Nunez and R. Mello, *J. Org. Chem.*, 1992, 57, 953.

45 R.W. Murray and D. Gu, *J. Chem. Soc. Perkin trans 2*, 1994, 451.

46 R. Mello, L. Cassidei, M. Fiorentino, C. Fusco, W. Hummer, V. Jäger and R. Curci, *J. Am. Chem. Soc.*, 1991, **113**, 2205.

47 P. Bovicelli, P. Lupattelli and A. Sanetti, *Tetrahedron Lett.*, 1995, **36**, 17, 3031.

48 P. Bovicelli, P. Lupattelli, V. Fiorini and E. Mincione, *Tetrahedron Lett.*, 1993, **34**, 6103.

49 P. Bovicelli, P. Lupattelli and E. Mincione, *J. Org. Chem.*, 1994, **59**, 4304.

50 R. Ballini, F. Papa and P. Bovicelli, *Tetrahedron Lett.*, 1996, **37**, 20, 3507.

51 W. Adam, F. Prechtl, M.J. Richter and A.K. Smerz, *Tetrahedron Lett.*, 1993, **34**, 52, 8427.

52 (a) R.W. Murray, R. Jeyaraman and M.K. Pillay, *J. Org. Chem.*, 1987, **52**, 746; (b) W. Adam and D. Golsch, *Chem. Ber.*, 1994, **127**, 111; (c) R.P. Ballisteri, G.A. Tomaselli, R.M. Banchio, V. Conte and F. Di Furia, *Tetrahedron Lett.*, 1994, **35**, 8041.

53 G. Asensio, R. Mello and M.E. Gonzalez-Nunez, *Tetrahedron Lett.*, 1996, **37**, 13, 2299.

54 W. Adam and L. Hadjiarapoglou, *Tetrahedron Lett.*, 1992, **33**, 4, 469.

55 (a) R.W. Murray, R. Jeyaraman and L. Mohan, *Tetrahedron Lett.*, 1986, 27, 2335; (b) D.J. Batal and J.K. Crandell, *J. Org. Chem.*, 1988, **53**, 1340.

56 (a) M.D. Wittman, R.L. Malcolm and S.J. Danishefsky, *J. Org. Chem.*, 1990, **55**, 1981; (b) J. Galik, H. Wong, B. Krishnan, D.M. Vyas and T.W. Doyle, *Tetrahedron Lett.*, 1991, **32**, 1851.

57 J.K. Crandell and T. Reix, *J. Org. Chem.*, 1992, **57**, 6759.

58 D.L. Zabrowski, A.E. Moorman and K.R.Beck Jr, *Tetrahedron Lett.*, 1988, **29**, 36, 4501.

59 P. Camps, D. Munoz-Terrero and V. Munoz-Terrero, *Tetrahedron Lett.*, 1995, **36**, 11, 1917.

60 J.L. Gagnon and W.W.Zajac Jr, *Tetrahedron Lett.*, 1995, **36**, 11, 1803.

61 (a) R.W.Murray and M. Singh, *J. Org. Chem.*, 1990, **55**, 2954; (b) R.W.Murray and M. Singh, *J. Org. Chem.*, 1988, **29**, 4677; (c) R.W.Murray and M. Singh, *Synth. Commun.*, 1989, **19** (20), 3509; (d) M.E. Brik, *Tetrahedron Lett.*, 1995, **36**, 31, 5519.

62 S.M. Neset, T. Benneche and K. Undheim, *Acta Chemica Scandinavica*, 1993, **47**, 1141.

63 W. Adam, K. Briviba, F. Duschek, D. Golsch, W. Kiefer and H. Sies, *J. Chem. Commun.*, 1995, 1831.

64 R.W. Murray, S.N. Rajadhyaksha and L. Mohan, *J. Org. Chem.*, 1989, **54**, 5783.

65 G. Asensio, M.E. Gonzalez-Nunez, C.B. Bernardini, R. Mello and W. Adam, *J. Am. Chem. Soc.*, 1993, **115**, 7250.

66 A. Messeguer, F. Sanchez-Baeza, J. Casas and B.D. Hammock, *Tetrahedron*, 1991, 47, 7, 1291.

67 V.M. Paradkar, T.B. Latham and D.M. Demko, *Synlett*, 1995, 1059.

68 D.R. Boyd, P.B. Coulter, R. McGuckin, N.D. Sharma and W.B. Jennings, *J. Chem. Soc. Perkin trans 1*, 1990, 531.

69 (a) W. Adam, E.M. Peters, K. Peters, H.G. Von Schnering, V. Voerckel, *Chem. Ber.*, 1992, **125**, 1263; (b) W. Adam, M. Ahrweiler, K. Paulini, H.U. Reissig, V. Voerckel, *Chem. Ber.*, 1992, **125**, 2719.

70 P.E. Eaton and G.E. Wicks, *J. Org. Chem.*, 1988, **53**, 5353.

71 G.A. Olah, Q. Liao, C.S. Lee, G.K. Surya, G. Prakash, *Synlett*, 1993, 427.

72 H. Ihmels, M. Maggino, M. Prato and G. Scorrano, *Tetrahedron Lett.*, 1991, **32**, 6215.

73 A. Altamura, R. Curci and J.O. Edwards, *J. Org. Chem.*, 1993, **58**, 7289.

74 J.C. Jung, K.S. Kim and Y.H. Kim, *Synth. Commun.*, 1992, **22**, 1583.

75 P. Lupattelli, R. Saladino and E. Mincione, *Tetrahedron Lett.*, 1993, **34**, 6313.

76 X. Zhang and C.S. Foote, *J. Am. Chem. Soc.*, 1993, **115**, 8867.

77 W. Adam, L. Hadjiarapoglou, K. Mielke and A. Treiber, *Tetrahedron Lett.*, 1994, **35**, 31, 5625.

78 W. Adam, R. Curci and R. Mello, *Angew. Chem. Int. Ed. Engl.*, 1990, **102**, 916.

79 A.M. Lluch, L. Jordi, F. Sanchez-Baeza, S. Ricart, F. Camps, A. Messeguer and J.M. Moreto, *Tetrahedron Lett.*, 1992, 33, 21, 3021.

80 A.M. Lluch, F. Sanchez-Baeza, F. Camps and A. Messeguer, *Tetrahedron Lett.*, 1991, **32**, 40, 5629.

81 R. Curci and J.O. Edwards in *Organic Peroxides*, chapter 4, p199, ed. D. Swern, Wiley Intercourse, New York, 1970.

82 R.W. Murray and D.L. Shang, *J. Chem. Soc. Perkin trans 2*, 1990, 349.

83 R.W. Murray and D. Gu, *J. Org. Chem.*, 1995, **60**, 5673.

84 (a) R.W. Murray, M.K. Pillay, R. Jeyaraman, *J. Org. Chem.*, 1988, **53**, 3007; (b) R. Mello, F. Ciminale, M. Fiorentino, C. Fusco, T. Prencipe and R. Curci, *Tetrahedron Lett.*, 1990, **31**, 6097; (c) W. Adam, S.E. Bottle, R. Mello, *J. Chem. Soc. Chem. Commun.*, 1991, 771; (d) W. Adam, G. Asensio, R. Curci, M.E. Gonzalez-Nunez and R. Mello, *J. Am. Chem. Soc.*, 1992, **114**, 8345.

85 F. Minisci, L. Zhao, F. Fontana and A. Bravo, *Tetrahedron Lett.*, 1995, **36**, 11, 1895.

86 (a) A.L. Baumstark and C.J. McCloskey, *Tetrahedron Lett.*, 1987, **28**, 3311; (b) A.L. Baumstark and D.B. Harden, *J. Org. Chem.*, 1993, **58**, 7615.

87 R.W. Murray and D. Gu, *J. Chem. Soc. Perkin trans 2*, 1993, 2203.

88 B.A. Marples, J.P. Muxworthy and K.H. Baggaley, *Tetrahedron Lett.*, 1991, **32**, 4, 533.

89 A. Bravo, F. Fontana, G. fronza, F. Minisci and A. Serri, *Tetrahedron Lett.*, 1995, **36**, 38, 6945.

90 F. Minisci, L. Zhao, F. Fontana and A. Bravo, *Tetrahedron Lett.*, 1995, **36**, 10, 1697.

91 Y. Angelis, X. Zhang and M. Orfanopoulos, *Tetrahedron Lett.*, 1996, **37**, 33, 5991.

92 (a) R. Mello, M. Fiorentino, C. Fusco and R. Curci, *J. Am. Chem. Soc.*, 1989, **111**, 6749; (b) R. Mello, L. Cassidei, M. Fiorentino, C. Fusco and R. Curci, *Tetrahedron Lett.*, 1990, 31, 3067; (c) W. Adam, G. Asensio, R. Curci, M.E. Gonzalez-Nunez and R.Mello, *J. Org. Chem.*, 1992, **57**, 953; and references therein.

93 (a) R. Curci, A. Detomaso, T. Principe and G.B. Carpenter, *J. Am. Chem. Soc.*, 1994, **116**, 8112; (b) R.W. Murray, R. Jeyaraman and L.J. Mohan, *J. Am. Chem. Soc.*, 1989, **108**, 2470.

94 R. Mello, F. Ciminale, M. Fiorentino, C. Fusco, T. Prencipe and R. Curci, *Tetrahedron Lett.*, 1990, **31**, 42, 6097.

95 A. Bravo, F. Fontana, G. Fronza, A. Mele and F. Minisci, *J. Chem. Soc. Chem. Commun.*, 1995, 1573.

96 D. Griller and K.U. Ingold, *Acc. Chem. Res.*, 1980, **13**, 317.

97 R. Vanni, S.J. Garden, J.T. Banks and K.U. Ingold, *Tetrahedron Lett.*, 1995, **36**, 44, 7999.

98 R. Curci, A. Dinoi, C. Fusco and M.A. Lillo, *Tetrahedron Lett.*, 1996, **37**, 2, 249.

99 (a) W. Adam, R. Curci, M.E. Gonzalez-Nunez, R. Mello, *J. Am. Chem. Soc.*, 1991, **113**, 7654; (b) M. Singh and R.W. Murray, *J. Org. Chem.*, 1992, **57**, 4263.

100 W. Adam, F. Prechtl, M.J. Richter and A.K. Smerz, *Tetrahedron Lett.*, 1995, **36**, 28, 4991.

101 A.L. Baumstark, M. Beeson and P.C. Vasquez, *Tetrahedron Lett.*, 1989, **30**, 5567.

102 F. Kovac and A.L. Baumstark, *Tetrahedron Lett.*, 1994, 35, 47, 8751.

103 J.K. Crandell, M. Zucco, R.S. Kirsch and D.M. Coppert, *Tetrahedron Lett.*, 1991, **32**, 5441.

104 A. Altamura, C. Fusco, L. D'Accolti, R. Mello, T. Prencipe and R. Curci, *Tetrahedron Lett.*, 1991, **32**, 40, 5445.

105 R.W. Wagner, D.M. Spero and W.H. Rastetter, *J. Am. Chem. Soc.*, 1984, **106**, 1476.

106 M. Mihailovic and Z. Cekovic in *The Chemistry of Functional Groups, Hydroxyl Group*, chapter 10, p505, ed. S. Patai, Wiley, New York, 1971; and references therein.

107 W. Adam, W. Haas and G. Sieker, *J. Am. Chem. Soc.*, 1984, **106**, 5020.

108 J.J.W. McDouall, *J. Org. Chem.*, 1992, **57**, 2861.

109 P.F. Ballisteri, G.A. Tomaselli, R.M. Toscano, M. Banchio, V. Conte and F. Di Furia, *Tetrahedron Lett.*, 1994, **35**, 43, 8041.

110 W. Adam and D. Golsch, *Chem. Ber.*, 1994, **127**, 1111.

111 W. Adam and D. Golsch, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 5, 737.

112 W. Adam, C. Van Barneveld and D. Golsch, *Tetrahedron*, 1996, **52**, 7, 2377.

113 S.F. Nelsen, R.G. Scamehorn, J. Defelippis and Y. Wang, *J. Org. Chem.*, 1993, **58**, 1657.

114 W. Adam and A. Schonberger, *Tetrahedron Lett.*, 1992, **33**, 53.

115 R.W. Murray, M. Singh and N. Rath, *Tetrahedron Asymm.*, 1996, **7**, 6, 1611.

116 M. Ferro, F. Sanchez-Baeza, J. Casas and A. Messeguer, *Tetrahedron Lett.*, 1994, **35**, 18, 2981.

117 R. Kaptein, Z. Brokken, F.J.J. de Kanter, *J. Am. Chem. Soc.*, 1972, **94**, 6280.

118 R. Curci, L. D'Accolti, M. Fiorentino, C. Fusco, W. Adam, M.E. Gonzalez-Nunez and R. Mello, *Tetrahedron Lett.*, 1992, **33**, 4225.

119 O. Okazaki and F.P. Guengerich, *J. Biol. Chem.*, 1993, **268**, 1546.

120 Y. Seto and F.P. Guengerich, *J. Biol. Chem.*, 1993, **268**, 9986.

121 P.C. Buxton, J.N. Ennis, B.A. Marples, V.L. Waddington and T.R. Boehlow, *J. Chem. Soc. Perkin trans 2*, 1998, 265.

122 P.B.D. De La Mare and B.E Swedlund in *The Chemistry of the Carbon-Halogen Bond*, Part 1, p407, ed. S. Patai, Wiley, London, 1973.

123 B.C. Challis and A.R. Butler in *The Chemistry of the Amino Group*, p320-347, ed. S. Patai, Interscience, London, 1968; and references therein.

124 (a) H.E. De La Mare, *J. Org. Chem.*, 1960, **25**, 2114; (b) L.A. Harris and J.S. Olcott, *J. Am. Oil Chem. Soc.*, 1966, **43**, 11.

125 L. Kuhnen, *Chem. Ber.*, 1966, **99**, 3384.

126 A.H. Khuthier, K.Y. Al-Mallah, S.Y. Hanna and N.A.I. Abdulla, *J. Org. Chem.*, 1987, **52**, 1710.

127 S.H. Pine and B.L. Sanchez, *J. Org. Chem.*, 1971, **36**, 829.

128 G.W. Gribble and C.F. Nutaitis, *Synthesis*, 1987, 709.

129 L.P. Hammett, *J. Am. Chem. Soc.*, 1937, **59**, 76.

130 C.H. Brown and Y. Okamato, *J. Am. Chem. Soc.*, 1958, **80**, 4979.

131 K.B. Wiberg, *Physical Organic Chemistry*, p379, 405, Wiley, New York, 1964.

132 E. Howard Jr and W.F. Olszewski, *J. Am. Chem. Soc.*, 1959, 1483.

133 J.P. Lorand, J.L. Anderson Jr, B.P. Shafer and D.L. Verral II, *J. Org. Chem.*, 1993, **58**, 1560.

134 (a) *Concerning Amines*, p87; (b) *Aromatic Amine Oxides*, p6-18.

135 K. Miaskiewicz, N.A. Teich and D.A. Smith, *J. Org. Chem.*, 1997, **62**, 6493.

136 S. Wolowiec and J.K Kochi, *J. Chem. Soc. Chem. Commun.*, 1990, 1782.

137 K. Fuji, K. Ichikawa, M. Node and E. Fujita, *J. Org. Chem.*, 1979, **44**, 1661.

138 D.S. Brown, B.A. Marples, J.P. Muxworthy and K.H. Baggaley, *J. Chem. Research (S)*, 1992, 28.

139 B.A. Marples, J.P. Muxworthy and K.H. Baggaley, Synlett, 1992, 646.

140 R. Csuk and P. Dörr, *Tetrahedron*, 1994, **50**, 33, 9983.

141 W. Adam, R. Curci, L. D'Accolti, A. Dinnoi, C. Fusco, F. Gasparini, R. Kluge, R. Paredes, M. Schulz, A.K. Smerz, L.A. Veloza, S. Weinkotz and R.Winde, *Chem. Eur. J.*, 1997, **3**, 105.

142 (a) E.G. Clarkein *Isolation and Identification of Drugs*, second edition, The Pharmaceutical Press, London, 1986; (b) K.W. Bentley in *The Chemistry of Morphine Alkaloids*, Oxford University Press, 1957; (c) F.j. Muhtadi and M.M.A. Hassan in *Analytical Profiles of Drug Substances*, volume 10, p93-138, ed. F. Florey, Academic Press, New York, 1981; (d) T.J. Batterham, *Aust. J. Chem.*, 1965, **18**, 1799 (NMR); (e) D.M.S. Wheeler, *J. Am. Chem. Soc.*, 1967, **89**, 4494 (mass spectrum); (f) J.C. Craig and K.K. Purushothaman, *J. Org. Chem.*, 1970, 1721 (N-oxide preparation).

143 G.H. Rasmusson and G.E. Arth in *Organic Reactions in Steroid Chemistry*, vol 1, p222-264.

144 (a) C. Djerassi in *Organic Reactions*, vol VI, p207-272, John Wiley and Sons Inc., New York, 1951; (b) R.V. Oppenauer, *Rec. Trav. Chim.*, 1937, 56, 137.

145 P. Neustaedter in *Steroid Reactions*, p89, ed. C. Djerassi, Holden-Day Inc., San Fransico, 1963.

146 (a) Gallagher, *J. Biol. Chem.*, 1940, **133**, XXXVI; (b) Fuchs and Reichstein, *Helv. Chim. Acta*, 1943, 26, 523; (c) Riegel and McIntosh, *J. Am. Chem. Soc.*, 1944, **66**, 1099; (d) Jones, Webb and Smith, *J. Chem. Soc.*, 1949, 2164.

147 Kuwada and Morimoto, *Bull. Chem. Soc. Japan*, 1942, **17**, 147.

148 Gallagher and Xenos, *J. Biol. Chem.*, 1946, **165**, 365.

149 (a) Reich and Reichstein, *Arch. intern. pharmacodynamie*, 1941, **65**, 415; (b) *Wieland and Miescher*, Helv. Chim. Acta, 1949, **32**, 1922.

150 (a) Marker and Rohrmann, *J. Am. Chem. Soc.*, 1939, **61**, 2721; (b) Klyne, *Nature*, 1950, **166**, 559.

151 Scarlett, *J. Biol. Chem.*, 1948, **173**, 186.

152 Euw, Lardon and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 821.

153 J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta.*, 1955, **38**, 1529.

154 G. Grimmer, *Ann. Chem.*, 1960, **636**, 42.

155 J.C. Richer, L.A. Pilato and E.L. Eliel, *Chem. Ind. (London)*, 1961, 2007.

156 H. Kwart, *Chem. Ind. (London)*, 1962, 610.

157 G.A.D. Haslewood, *Biochem. J.*, 1943, **37**, 109.

158 L.F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, 1950, **72**, 5530.

159 K. Bowden, I.M. Heilbron, E.R.H. Jones and B.C.L. Weedon, *J. Am. Chem. Soc.*, 1946, 39.

160 D.G. Lee, W.L. Downey and R.M. Maass, *Can. J. Chem.*, 1968, **46**, 441.

161 L.F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, 1949, **71**, 3938.

162 K. Kawanami, Bull. *Chem. Soc. Japan*, 1961, **34**, 671.

163 L.F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, 1949, **71**, 3935.

164 K.Y. Tserng, *J. Lipid Res.*, 1978, **19**, 501.

165 H. Danielsson, P. Eneroth, K. Hellström and J. Sjöval, *J. Biol. Chem.*, 1962, **237**, 3657.

166 A.F. Hofmann, P.A. Szczepanik and P.D. Klein, *J. Lipid Res.*, 1968, **9**, 707.

167 (a) M. Alauddin and J. Martin-Smith, *J. Org. Chem.*, 1963, **28**, 886; (b) S. Ahmed, M. Alauddin, B. Caddy, M. Martin-Smith, W.T.L. Sidwell and T.R. Watson, *Aust. J. Chem.*, 1971, **24**, 521.

168 J.W. Huffman, D.M. Alabran, T.W. Bethea and A.C. Ruggles, *J. Org. Chem.*, 1964, **29**, 2963.

169 G.C. Wolf, E.L. Foster and R.T. Blickenstaff, *J. Org. Chem.*, 1973, **38**, 7.

170 R.T. Blickenstaff and B. Orwig, J. Org. Chem., *J. Org. Chem.*, 1969, **34**, 1377.

171 K. F. Atkinson and R.T. Blickenstaff, *Steroids*, 1974, **23**, 6, 895.

172 D. Yang, M.K. Wong and Y.C. Yip, *J. Org. Chem.*, 1995, **60**, 3887.

173 D. Yang, X.C. Wang, M.K. Wong, Y.C. Yip, M.W. Tang, *J. Am. Chem. Soc.*, 1996, **118**, 11311.

174 J.P. Muxworthy, *Synthetic and Mechanistic Aspects of Dioxirane Chemistry*, PhD thesis, Loughborough University, 1992.

175 S. Colonna, N. Gaggero, M. Leone, *Tetrahedron Lett.*, 1991, **47**, 8385.

176 W. Zhu and W.T. Ford, *J. Org. Chem.*, 1991, **56**, 7022.

177 T.R. Boehlow, P.C. Buxton, E.L. Grocock, B.A. Marples, V.L. Waddington, *Tetrahedron Lett.*, 1998, **39**, 1839.

178 D.G. Thomas, J.H. Billman and C.E. Davis, *J. Am. Chem. Soc.*, 1946, **68**, 895.

179 (a) Davies and Cox, *J. Chem. Soc.*, 1937, 615; (b) D. P. Evans and R. Williams, *J. Chem. Soc.*, 1939, 1199.

180 J. Ennis, *Mechanisms and Applications of Dioxirane Chemistry*, PhD thesis, Loughborough University, 1998.

181 (a) *Chem. Ber.*, 1959, 3223; (b) *J. Org. Chem.*, 1993, 1560.

182 (a) *J. Chem. Soc. Perkin trans 1*, 1983, 527; (b) *J. Chem. Soc. Perkin trans 2*, 1984, 1103.

183 S.Y. Hanna, *Spectrochimica Acta*, 1992, **48A**, 10, 1397.

184 L.W. Jones and E.B. Hartshorn, *J. Am. Chem. Soc.*, 1924, **46**, 1853.

185 Eliel, Ferdinand and Hermann, *J. Org. Chem.*, 1954, **19**, 1693.

186 (a) R.A. Jessop and J.R. Lindsay-Smith, *J. Chem. Soc. Perkin trans 1*, 1976, 1801; (b) P.A. Bath, J.R. Lindsay-Smith and R.O.C. Norman, *J. Chem. Soc. (C)*, 1971, 3060.

187 (a) Z. Schotten, *Physiol. Chem.*, 1886, **10**, 175; (b) Utaki, *Physiol. Chem.*, 1932, **207**, 16.

188 Grand and Reichstein, *Helv. Chim. Acta.*, 1945, **28**, 344.

189 Barnet, Lardon and Reichstein, *Helv. Chim. Acta.*, 1947, **30**, 1542.

190 Meystre and Miescher, *Helv. Chim. Acta.*, 1946, **29**, 33.

191 R.P.A. Sneeden and R.B. Turner, *J. Am. Chem. Soc.*, 1955, **77**, 190.

192 E. Hauser, E. Baumgartner and K. Meyer, *Helv. Chim. Acta.*, 1960, **43**, 1595.

193 M.N. Mitra and W.H. Elliot, *J. Org. Chem.*, 1968, **33**, 2814.

194 E. Mappus and C.Y. Cuilleron, *Steroids*, 1979, **33**, 693.

195 R. Justoni and R. Pessina, *Farmaco. Ed. Sci.*, 1953, **8**, 332.

196 A. Windaus and A. Bohne, *Liebigs Ann.*, 1923, **433**, 278.

APPENDIX I

HPLC METHOD DEVELOPMENT

1 N,N-DIMETHYLANILINES AND CORRESPONDING N-OXIDES

In order to carry out the competition reactions described in chapter 2, it was necessary to separate the reference substrate, N,N-dimethylaniline, from each of the substituted anilines, and to separate these from the N-oxides. The consumption of the starting materials and the formation of the products could then be followed. The aim therefore was to develop a suitable system(s) to detect and separate the following compounds: N,N-dimethylaniline, N,N-dimethyl-4-nitroaniline, N,N-dimethyl- 4-chloroaniline, N,N-dimethyl-4-methoxyaniline and their corresponding N-oxides.

The UV spectrum of each N,N-dimethylaniline was recorded and the optimum wavelength determined.

Sample	λmax
N,N-dimethylaniline	245 nm
N,N-dimethyl-4-methoxyaniline	245 nm
N,N-dimethyl-4-chloroaniline	260 nm
N,N-dimethyl-4-nitroaniline	415 nm

Chromatographic Conditions

Column	:	μBondapak C18 10 micron 3.9 x 300 mm
Eluent	:	60% methanol / 40% water
Flow rate	:	1ml / min
Wavelength	:	245nm
Injection volume	:	20 microlitres

Using the conditions described above, the following retention times were obtained.

Elution Order	Retention Time (mins)
N,N-dimethylaniline N-oxide	3.69
N,N-dimethyl-4-methoxyaniline N-oxide	3.79
N,N-dimethyl-4-nitroaniline N-oxide	3.80
N,N-dimethyl-4-chloroaniline N-oxide	4.73
N,N-dimethyl-4-nitroaniline	9.83
N,N-dimethyl-4-methoxyaniline	9.85
N,N-dimethylaniline	10.69
N,N-dimethyl-4-chloroaniline	20.07

As can be seen the N-oxides are very polar and elute much faster than the parent anilines. However, not all the substituted anilines were separated from N,N-dimethylaniline and not all the substituted aniline N-oxides were separated from N,N-dimethylaniline N-oxide. Separation of N,N-dimethyl-aniline and the nitro derivative was achieved but not their N-oxides. N,N-dimethylaniline and the chloro derivative were separated and so were their N-oxides but N,N-dimethylaniline and the methoxy derivative were not separated and neither were their N-oxides.

A reversed phase system such as this can be slowed down by increasing the water content of the eluent. The retention times obtained using the same column with 50% methanol / 50% water are shown below. This time, separation of N,N-dimethylaniline and the methoxy derivative was achieved and their N-oxides were partially separated. N,N-dimethylaniline N-oxide and the N,N-dimethyl-4-nitroaniline N-oxide however were still co-eluting.

Elution Order	Retention Time (mins)
N,N-dimethylaniline N-oxide	4.12
N,N-dimethyl-4-nitroaniline N-oxide	4.16
N,N-dimethyl-4-methoxyaniline N-oxide	4.71
N,N-dimethyl-4-chloroaniline N-oxide	5.64
N,N-dimethyl-4-methoxyaniline	17.44
N,N-dimethylaniline	20.60

Increasing the proportion of water in the mobile phase further to 40% methanol / 60% water resulted in full separation of the N,N-dimethylaniline N-oxide and the N,N-dimethyl-4-methoxy-N-oxide but this increased the retention of the parent anilines to unacceptably long times. Again the N,N-dimethylaniline N-oxide and the N,N-dimethyl-4-nitroaniline N-oxide were not separated. The water content of the mobile phase was not increased any further as this would lead to even longer retention times and deterioration in peak shape.

Summary

On the basis of this work, it was decided to follow the competition reactions simply by monitoring the consumption of the starting materials, using the HPLC method described below:

Column	:	μBondapak C18 10 micron 3.9 x 300mm
Eluent	:	60% methanol : 40% water (for reactions involving nitroaniline and chloroaniline) 50% methanol : 50% water (for reactions involving methoxyaniline)
Flow	:	1 ml / min
Wavelength	:	245 nm
Injection volume	:	20 microlitres

Further Method Development

Whilst on placement at SmithKline Beecham, it was decided to carry out further HPLC method development using a diode array machine to find a method for the use in the N,N-dimethylaniline competition reactions which will detect and separate the anilines and their corresponding N-oxides. It was also hoped to develop a method suitable for LC / MS in the event that any products other than the N-oxide should be formed.

Chromatographic Conditions

Column	:	Hypersil BDS C18
Mobile phase	:	40% acetonitrile / 60% water
Flow rate	:	1 ml / min
Wavelength	:	all wavelengths between 200-400nm scanned
Injection volume	:	20 microlitres

A UV spectrum of each peak was obtained and it was found that 210nm was the most suitable wavelength for the detection of the N-oxides.

Elution Order	Retention Time (mins)
All 4 N-oxides	1.5 (with the solvent front)
N,N-dimethyl-4-methoxyaniline	7
N,N-dimethyl-4-nitroaniline	7.5
N,N-dimethylaniline	11.5
N,N-dimethyl-4-chloroaniline	25

The following attempts were made to retain the N-oxides :

i. Use of a gradient system

A mobile phase comprising initially of 90% water / 10% acetonitrile, increasing to 60% water / 40% acetonitrile over 10 mins then holding for a period was employed. The retention times of the anilines increased, but the N-oxides were still co-eluting with the solvent front at 1.5 minutes.

ii. Use of a buffer solution

The water in the mobile phase was replaced with a buffer solution. Sodium acetate was chosen as this is suitable for LC / MS. Mobile phase: 60% 0.1M sodium acetate, adjusted to pH 3 / 40% acetonitrile. The retention times of the N-oxides increased by only by 0.2 minutes and the anilines were found to elute faster.

Elution Order	Retention Time (mins)
N,N-dimethylaniline	3.7
N,N-dimethyl-4-chloroaniline	16.6

Increasing the percentage of buffer solution in the mobile phase to from 60% to 66% showed no significant difference.

iii. Addition of triethylamine

Addition of triethylamine to the mobile phase had no obvious effect on the retention times of the N-oxides. Mobile phase: 66% 0.1M sodium acetate, pH 3 / 34% acetonitrile / 0.1% triethylamine.

Elution Order	Retention Time (mins)
N,N-dimethylaniline N-oxide	1.6
N,N-dimethyl-4-nitroaniline N-oxide	1.6
N,N-dimethyl-4-methoxyaniline N-oxide	1.7
N,N-dimethyl-4-chloroaniline N-oxide	1.7
N,N-dimethyl-4-methoxyaniline	1.9
N,N-dimethylaniline	2.8
N,N-dimethyl-4-nitroaniline	13.0
N,N-dimethyl-4-chloroaniline	22.7

iv. Increase in the pH and amount of buffer used

The pH of the buffer solution was increased from 3 to 4.5 and the amount of buffer solution used in the mobile phase was increased from 66% to 90%. Mobile phase: 90% 0.1M sodium acetate, pH 4.5 / 10 % acetonitrile / 0.1% triethylamine The retention times of the N-oxides were increased but the peak shapes were poor.

Elution Order	Retention Time (mins)
N,N-dimethylaniline N-oxide	2.5
N,N-dimethyl-4-nitroaniline N-oxide	3
N,N-dimethyl-4-methoxyaniline N-oxide	3.5
N,N-dimethyl-4-chloroaniline N-oxide	6

v. Lower pH

The increased percentage of buffer solution in the mobile phase was maintained at 90% but the pH was taken back down to 3.

Elution Order	Retention Time (mins)
N,N-dimethylaniline N-oxide	3
N,N-dimethylaniline	4.3
N,N-dimethyl-4-methoxyaniline N-oxide and N,N-dimethyl-4-methoxyaniline	co-elute at 5
N,N-dimethyl-4-chloroaniline N-oxide	7
N,N-dimethyl-4-chloroaniline	greater than 22

vi. Use of acetic acid rather than sodium acetate

The sodium acetate buffer solution was replaced with dilute acetic acid (pH 3). Mobile phase: 90% 0.05M acetic acid / 10% acetonitrile. Using this system, the peaks were all found to tail badly.

Elution Order	Retention Time (mins)
N,N-dimethylaniline N-oxide	3.5
N,N-dimethylaniline	5
N,N-dimethyl-4-chloroaniline N-oxide	7.5
N,N-dimethyl-4-chloroaniline	greater than 30

vii. Use of water rather than buffer solution or acid

Mobile phase: 90% water / 10% acetonitrile

Elution Order	Retention Time (mins)
N,N-dimethylaniline N-oxide	2.5
N,N-dimethyl-4-methoxyaniline N-oxide	3
N,N-dimethyl-4-nitroaniline N-oxide	3
N,N-dimethyl-4-chloroaniline N-oxide	6
N,N-dimethyl-4-chloroaniline	greater than 30

Mobile phase: 95% water / 5% acetonitrile

Elution Order	Retention Time (mins)
N,N-dimethylaniline N-oxide	4
N,N-dimethyl-4-nitroaniline N-oxide	4.5
N,N-dimethyl-4-methoxyaniline N-oxide	5
N,N-dimethyl-4-chloroaniline N-oxide	10

The peak shapes obtained with the above systems were very poor. This was due to the high water content of the mobile phase and not due to column deterioation. (The column was checked using 60% water / 40% acetonitrile and the peak shape was found to be satisfactory.)

viii. Change of column from C18 to C1 and use of a phosphate buffer

Chromatographic Conditions

Column	:	Spherisorb C1 microbore
Mobile phase	:	0.025M phosphate buffer / 0.1% triethylamine / pH 3.5
Flow rate	:	1 ml / min
Wavelength	:	210nm
Injection volume	:	20 microlitres

Preparation of Mobile Phase

For each litre of eluent required, 1.0ml of triethylamine and 7.8g of sodium dihydrogen ortho-phosphate dihydrate were dissolved in approximately 800ml of water. The pH was adjusted to 3.5 by the addition of 1M HCl solution and made up to 1 litre with water. The resulting solution was filtered and degassed before use.

Elution Order	Retention Time (mins)
N,N-dimethylaniline	6
N,N-dimethylaniline N-oxide	6
N,N-dimethyl-4-methoxyaniline	7.5
N,N-dimethyl-4-methoxyaniline N-oxide	9
N,N-dimethyl-4-chloroaniline N-oxide	20
N,N-dimethyl-4-chloroaniline	30

This method gave good peak shapes and looked promising.

ix. Molarity of the phosphate buffer increased from 0.025M to 0.05M

Mobile phase: 0.05M phosphate / 0.1% triethylamine / pH 3.5

Elution Order	Retention Time (mins)
N,N-dimethylaniline	5
N,N-dimethylaniline N-oxide	5.6
N,N-dimethyl-4-chloroaniline	6.1
N,N-dimethyl-4-methoxyaniline N-oxide	6.5
N,N-dimethyl-4-chloroaniline N-oxide	6.7

The peaks were tailing slightly.

x. Injection volume decreased from 20 microlitres to 2 microlitres

Elution Order	Retention Time (mins)
N,N-dimethylaniline	5
N,N-dimethylaniline N-oxide	5.7
N,N-dimethyl-4-methoxyaniline	6.2
N,N-dimethyl-4-chloroaniline	6.5
N,N-dimethyl-4-nitroaniline N-oxide	6.5
N,N-dimethyl-4-methoxyaniline N-oxide	7
N,N-dimethyl-4-chloroaniline N-oxide	7.5
N,N-dimethyl-4-nitroaniline	10

Using this method, all anilines were separated from their N-oxides and the retention times were satisfactory. The method described below was therefore suitable for the monitoring of the reactions of the individual anilines with dimethyldioxirane and also the competition reactions:

Column	:	Spherisorb S5 C1
Eluent	:	0.05M phosphate 0.1% triethylamine pH 3.5 (for reactions involving nitroaniline and chloroaniline) 0.05M phosphate 0.1% triethylamine pH 4.0 (for reactions involving methoxyaniline)
Flow	:	1 ml / min
Wavelength	:	210 nm
Injection volume	:	20 microlitres

Summary of retention times achieved using this method

pH of mobile phase	Sample	Retention time (mins)
3.5	N,N-dimethylaniline	5.0
	N,N-dimethylanilineN-oxide	5.7
	N,N-dimethyl-4-chloroaniline	6.5
	N,N-dimethyl-4-chloroaniline N-oxide	7.5
	N,N-dimethyl-4-nitroaniline	10.0
	N,N-dimethyl-4-nitroaniline N-oxide	6.5
4.0	N,N-dimethylaniline	5.3
	N,N-dimethylanilineN-oxide	7.2
	N,N-dimethyl-4-methoxyaniline	6.6
	N,N-dimethyl-4-methoxyaniline N-oxide	9.1

Gradient System

The following gradient system was employed to look for later running peaks:
0.05M phosphate / 0.1% triethylamine / pH 3.5 for 10 minutes then increase to 40% acetonitrile / 60% 0.05M phosphate / 0.1% triethylamine / pH 3.5 over 10 minutes and hold.
When the N,N-dimethyl-4-chloroaniline and N,N-dimethyl-4-nitroaniline were oxidised using dimethyldioxirane and the crude reactions mixtures analysed using this system, no real late running peaks were detected. A peak was seen in both mixtures at a retention time of 20 minutes but this was found to be an artefact due to the gradient system as no UV spectrum could be obtained from the peak and it occurred at the same point in each mixture.

LC / MS Method

To obtain a method suitable for LC / MS, the phosphate buffer was substituted with 0.1M sodium acetate solution. 0.1% triethylamine was added and the pH adjusted to 3.5 and also to 4.0. All wavelengths were scanned but no peaks other than the ones corresponding to the relevant aniline and N-oxide were detected in any of the N,N-dimethylaniline / dimethyldioxirane crude reaction mixtures.

2 N,N-DIMETHYLBENZYLAMINES AND CORRESPONDING N-OXIDES

The aim was to develop a suitable system(s) to detect and separate the following compounds: N,N-dimethylbenzylamine, N,N-dimethyl-4-nitrobenzylamine, N,N-dimethyl-4-chlorobenzylamine, N,N-dimethyl-4-methoxybenzylamine and their corresponding N-oxides.

To find a suitable wavelength at which to detect these compounds, the UV spectra were measured.

Sample	λmax
N,N-dimethylbenzylamine	205 nm
N,N-dimethyl-4-methoxybenzylamine	219 nm
N,N-dimethyl-4-chlorobenzylamine	205 nm

SYSTEM 1

Chromatographic Conditions

Column	:	Hypersil BDS C18 10 micron 3.9 x 300mm
Mobile phase	:	90% acetonitrile / 10% 0.05M phosphate buffer / pH 3
Wavelength	:	205 nm
Flow rate	:	1 ml / min
Injection volume	:	20 microlitres
Sample concentration	:	less than 0.1 mg / ml

The benzylamines are more basic than the anilines and elute faster on the BDS column. Initial method development was performed on a sample of N,N-dimethyl-4-methoxyaniline. Using system 1 described above, a retention time of approximately 2 minutes was achieved with a good peak shape. Therefore to increase the retention time, the amount of acetonitrile in the mobile phase was decreased. However, this resulted in a deterioation of peak shape, the peaks becoming non-gaussian and tailing considerably. To improve this, the pH and strength of the phosphate buffer were increased to pH 4 and 0.1M respectively. To accommodate the N-oxides, the wavelength was increased slightly to 210 nm and the injection volume was reduced, thus resulting in the method described below:

SYSTEM 2

Chromatographic Conditions

Column	:	Hypersil BDS C18 10 micron 3.9 x 300mm
Mobile phase	:	5% acetonitrile / 95% 0.1M phosphate buffer / pH 4
Wavelength	:	210 nm
Flow rate	:	1 ml / min
Injection volume	:	2 microlitres
Sample concentration	:	less than 0.1 mg / ml

The retention times achieved using this system are shown below:

Elution Order	Retention Time (mins)
N,N-dimethylbenzylamine	6.2
N,N-dimethyl-4-nitrobenzylamine	7.0
N,N-dimethylbenzylamine N-oxide	9.0
N,N-dimethyl-4-nitrobenzylamine N-oxide	9.2
N,N-dimethyl-4-methoxybenzylamine	11.5
N,N-dimethyl-4-methoxybenzylamine N-oxide	17.0
N,N-dimethyl-4-chlorobenzylamine	22.4
N,N-dimethyl-4-chlorobenzylamine N-oxide	35.0

It can be seen from the data above that this system is suitable for the monitoring of the N,N-dimethylbenzylamine and N,N-dimethyl-4-nitrobenzylamine reactions. Satisfactory separation of the parent benzylamine and its N-oxide was achieved in each case. Good separation of N,N-dimethyl-4-methoxybenzylamine and its N-oxide was also achieved with this system and the retention time could be reduced by increasing the flow to 1.5ml / min. This gave a retention time of 6.6 minutes for N,N-dimethyl-4-methoxybenzylamine and 9.6 minutes for N,N-dimethyl-4-methoxy-benzylamine N-oxide. N,N-dimethyl-4-chlorobenzylamine and its N-oxide were also well separated but the retention time is far too long resulting in some loss of peak shape. To overcome this, the flow rate was kept at 1.5ml / min and the acetonitrile content of the mobile phase was increased from 5% to 10%. A retention time of 7.2 minutes was achieved for N,N-dimethyl-4-chlorobenzyl-

amine and 10.4 minutes for N,N-dimethyl-4-chlorobenzylamine N-oxide. This method was therefore used for the analysis of the chlorobenzylamine reaction.

Gradient system

The following gradient system was employed to look for later running peaks: 5% acetonitrile / 95% 0.1M phosphate / pH 4 for 10 minutes then increase to 60% acetonitrile / 40% 0.05M phosphate / pH 4 over 15 minutes and hold. All wavelengths were scanned. No late running peaks were found in any of the reaction mixtures analysed.

Summary

Column	:	Hypersil BDS C18 10 micron 3.9 x 300mm
Eluent	:	5% acetonitrile 95% 0.1M phosphate buffer pH 4 (for benzylamine, nitrobenzylamine and methoxybenzylamine reactions) 10% acetonitrile 90% 0.1M phosphate buffer pH 4 (for chlorobenzylamine reactions)
Flow	:	1 ml / min (for benzylamine and nitrobenzylamine reactions) 1.5 ml / min (for methoxybenzylamine and chlorobenzylamine reactions)
Wavelength	:	210 nm
Injection volume	:	2 microlitres

APPENDIX II

HPLC CALIBRATION

Acetone solutions containing the following molar ratios of N,N-dimethylaniline and N,N-dimethyl-4-nitroaniline were prepared:

1 : 1 1 : 2 1 : 3 2 : 1 3 : 1

These were injected and the observed ratio of N,N-dimethylaniline : N,N-dimethyl-4-nitroaniline was obtained from the peak areas on the chromatogram. The determinations were repeated and a mean value taken. These values for the observed ratio were plotted against the actual molar ratio and the line of best fit drawn.

Calibration graphs for N,N-dimethylaniline and N,N-dimethyl-4-chloroaniline and N,N-dimethyl-aniline and N,N-dimethyl-4-methoxyaniline were obtained in a similar way.

Preparation of the N,N-dimethylaniline / N,N-dimethyl-4-nitroaniline calibration solutions

Molecular weight of N,N-dimethylaniline = 121

Molecular weight of N,N-dimethyl-4-nitroaniline = 166

1:1 solution

N,N-dimethylaniline	2.523mmol	305.3mg	
N,N-dimethyl-4-nitroaniline	2.523mmol	418.8mg	in 50ml acetone

1:2 solution

N,N-dimethylaniline	1.850mmol	223.9mg	
N,N-dimethyl-4-nitroaniline	3.70mmol	614.2mg	in 50ml acetone

1:3 solution

N,N-dimethylaniline	1.692mmol	204.7mg	
N,N-dimethyl-4-nitroaniline	5.076mmol	842.6mg	in 50ml acetone

2:1 solution

N,N-dimethylaniline	3.805mmol	460.4mg	
N,N-dimethyl-4-nitroaniline	1.903mmol	315.9mg	in 50ml acetone

3:1 solution

N,N-dimethylaniline	4.924mmol	595.8mg	
N,N-dimethyl-4-nitroaniline	1.641mmol	272.5mg	in 50ml acetone

0.5ml of each solution was taken and diluted to 100ml with eluent.

Two determinations were made for each solution and a mean value taken.

Actual ratio	Observed ratio
1 : 1	1 : 0.595
1 : 2	1 : 1.235
1 : 3	1 : 0.895
2 : 1	1 : 0.316
3 : 1	1 : 0.201

Preparation of the N,N-dimethylaniline / N,N-dimethyl-4-methoxyaniline calibration solutions

Molecular weight of N,N-dimethylaniline = 121

Molecular weight of N,N-dimethyl-4-methoxyaniline = 151

1:1 solution

N,N-dimethylaniline	2.527mmol	305.8mg	
N,N-dimethyl-4-methoxyaniline	2.527mmol	381.6mg	in 50ml acetone

1:2 solution

N,N-dimethylaniline	1.629mmol	197.2mg	
N,N-dimethyl-4-methoxyaniline	3.258mmol	492.0mg	in 50ml acetone

1:3 solution

N,N-dimethylaniline	1.831mmol	221.6mg	
N,N-dimethyl-4-methoxyaniline	5.493mmol	829.4mg	in 50ml acetone

2:1 solution

N,N-dimethylaniline	3.174mmol	384.1mg	
N,N-dimethyl-4-methoxyaniline	1.587mmol	239.6mg	in 50ml acetone

3:1 solution

N,N-dimethylaniline	4.855mmol	587.5mg	
N,N-dimethyl-4-methoxyaniline	1.618mmol	244.4mg	in 50ml acetone

0.5ml of each solution was taken and diluted to 100ml with eluent.

Two determinations were made for each solution and a mean value taken.

Actual ratio	Observed ratio
1 : 1	1 : 0.845
1 : 2	1 : 0.885
1 : 3	1 : 2.545
2 : 1	1 : 0.425
3 : 1	1 : 271

Preparation of the N,N-dimethylaniline / N,N-dimethyl-4-chloroaniline calibration solutions

Molecular weight of N,N-dimethylaniline = 121

Molecular weight of N,N-dimethyl-4-chloroaniline = 155.5

1:1 solution

N,N-dimethylaniline	2.585mmol	312.8mg	
N,N-dimethyl-4-chloroaniline	2.585mmol	402.0mg	in 50ml acetone

1:2 solution

N,N-dimethylaniline	2.139mmol	258.8mg	
N,N-dimethyl-4-chloroaniline	4.278mmol	665.2mg	in 50ml acetone

1:3 solution

N,N-dimethylaniline	1.532mmol	185.4mg	
N,N-dimethyl-4-chloroaniline	4.596mmol	714.7mg	in 50ml acetone

2:1 solution

N,N-dimethylaniline	3.714mmol	449.4mg	
N,N-dimethyl-4-chloroaniline	1.857mmol	288.8mg	in 50ml acetone

3:1 solution

N,N-dimethylaniline	4.786mmol	579.1mg	
N,N-dimethyl-4-chloroaniline	1.595mmol	248.15mg	in 50ml acetone

0.5ml of each solution was taken and diluted to 100ml with eluent.

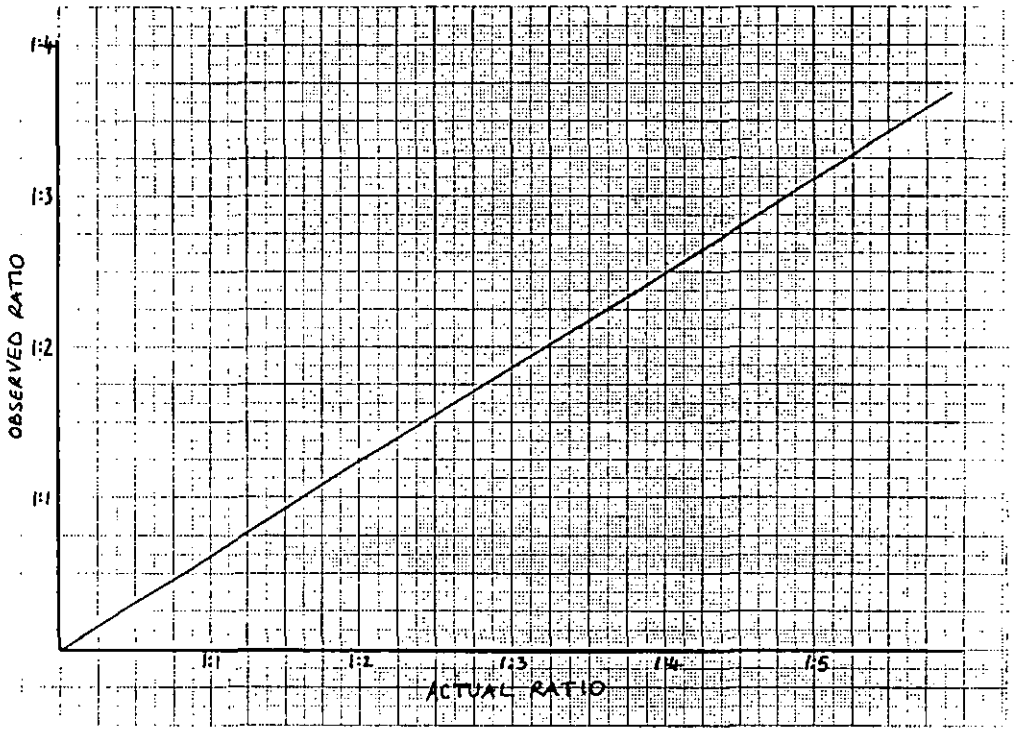
Two determinations were made for each solution and a mean value taken.

Actual ratio	Observed ratio
1 : 1	1 : 1.105
1 : 2	1 : 1.875
1 : 3	1 : 2.402
2 : 1	1 : 0.525
3 : 1	1 : 0.352

CALIBRATION GRAPH

N,N-dimethylaniline : N,N-dimethyl-4-nitroaniline

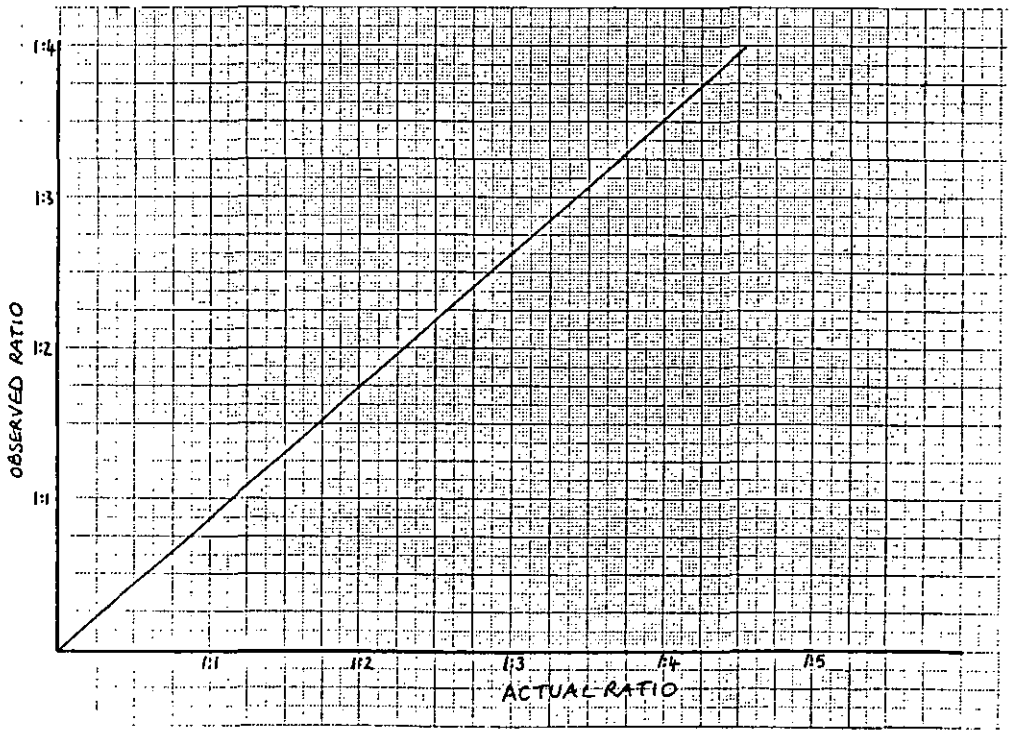
observed ratio vs actual ratio



CALIBRATION GRAPH

N,N-dimethylaniline : N,N-dimethyl-4-methoxyaniline

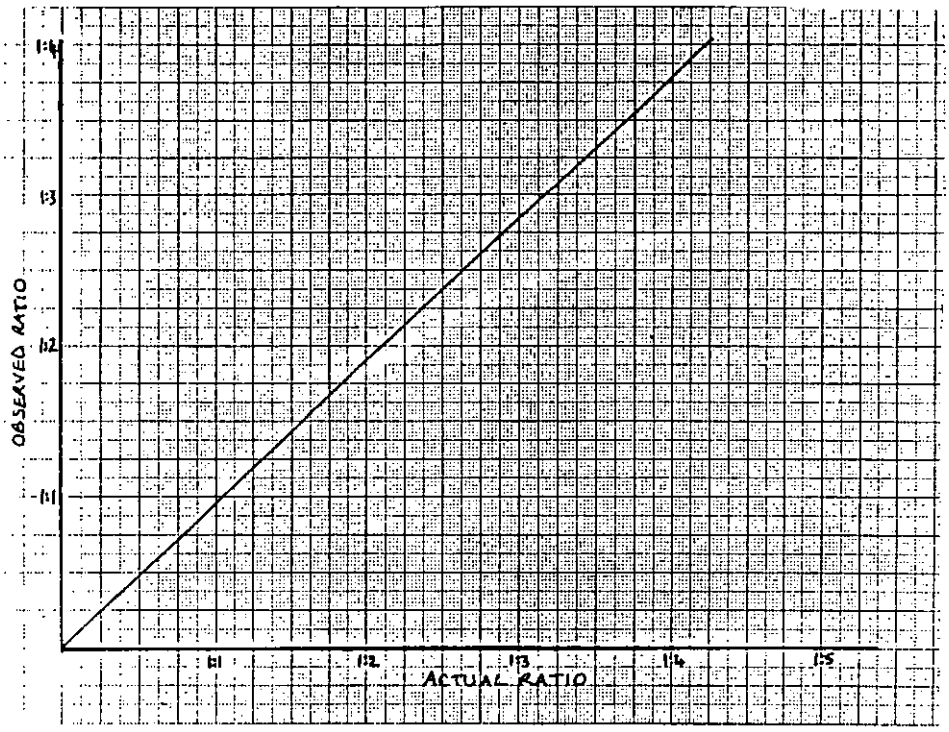
observed ratio vs actual ratio



CALIBRATION GRAPH

N,N-dimethylaniline : N,N-dimethyl-4-chloroaniline

observed ratio vs actual ratio



CONVERSION OF RATIO OF UNREACTED ANILINES INTO A RELATIVE RATE OF REACTIVITY

In the case of the N,N-dimethylaniline competition reactions, the initial reaction mixture consists of 1 equivalent of A + 1 equivalent of B + 1 equivalent of reagent. All the reagent is consumed, therefore the maximum theoretical conversion of A + B (total 2 equivalents) is 50%, hence the amount of A + B remaining will be 50%.

If, for example, it was found that the ratio of A + B remaining at the end of the reaction was 1 : 1.25

i.e. A : B remaining = 1 : 1.25 = 50% = 1 equivalent

therefore A remaining = 0.44 equivalents

and B remaining = 0.56 equivalents

which means that A consumed = 0.56 equivalents

and B consumed = 0.44 equivalents

then A : B consumed = 0.56 : 0.44

= 1 : 0.8

= relative reactivity of A : B

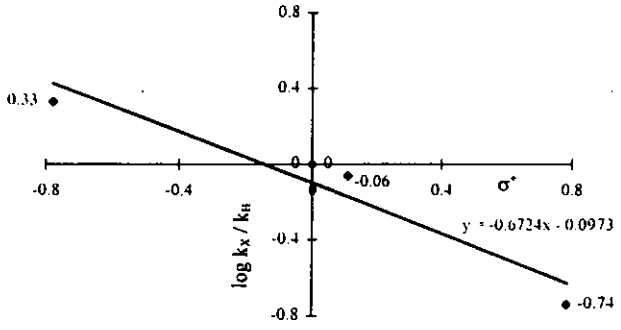
Alternatively, the reciprocal of the ratio of A : B remaining at the end of the reaction (in this example, 1 : 1.25) can be taken to give the relative reactivity of A : B (1 : 0.8).

This simple treatment of the ratio of A : B remaining only applies if the conversion is 50%.

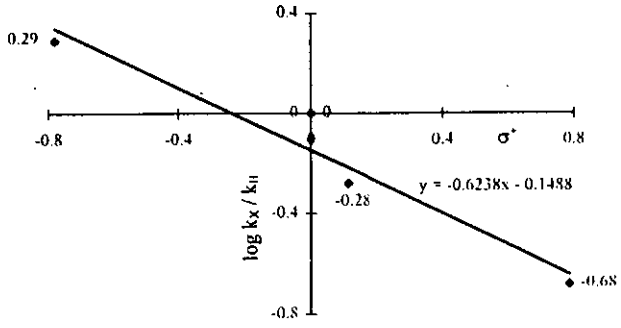
APPENDIX III

LFER PLOTS OF LOG k_X / k_H VERSUS σ^+ FOR THE REACTION OF DIMETHYLDIOXIRANE WITH N,N-DIMETHYLANILINES IN ACETONE AT 0-5°C

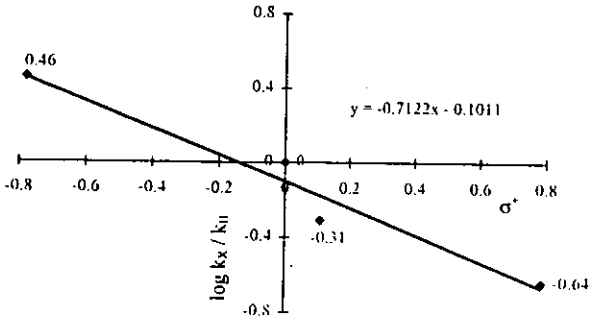
Method 1



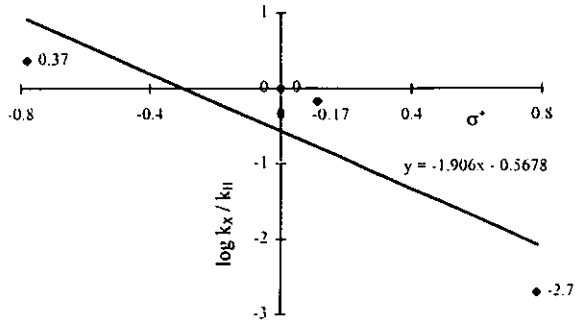
Method 2



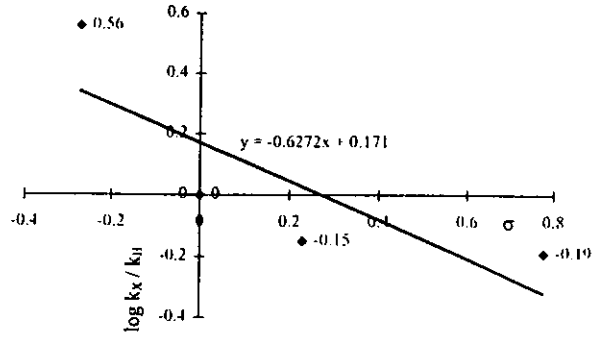
Method 3

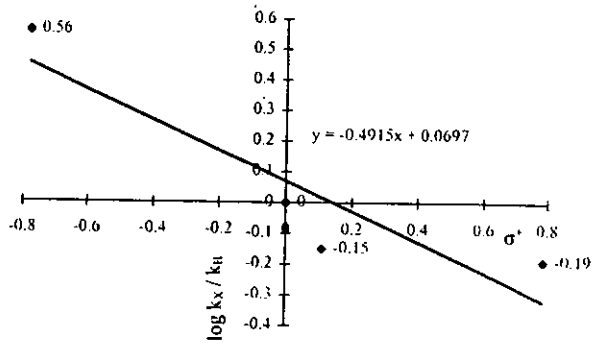


Method 4



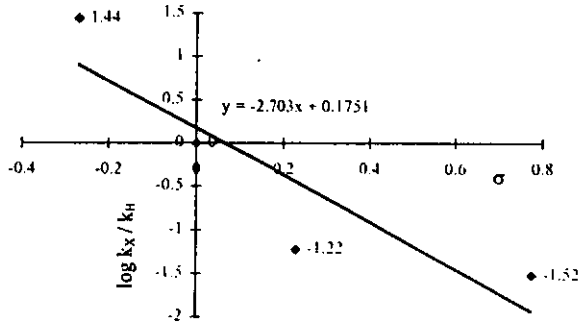
LFER PLOTS OF LOG k_X / k_H VERSUS σ AND σ^+ FOR THE REACTION OF METHYL IODIDE WITH N,N-DIMETHYLANILINES IN ACETONE AT 0-5°C

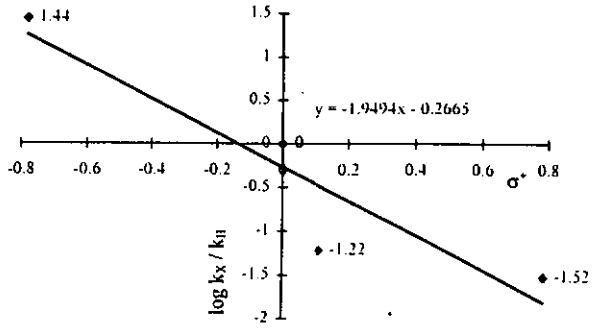




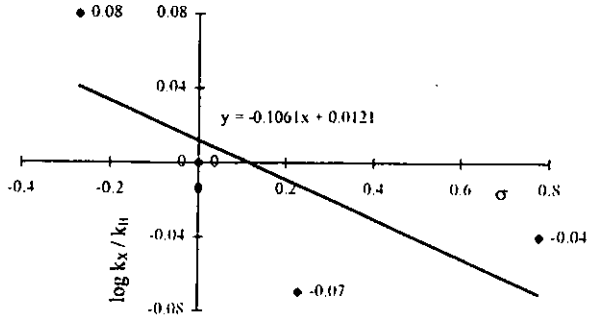
LFER PLOTS OF LOG k_X / k_H VERSUS σ AND σ^+ FOR THE REACTION OF BENZOYL PEROXIDE AND t-BUTYL HYDROPEROXIDE WITH N,N-DIMETHYLANILINES IN ACETONE AT 0-5°C

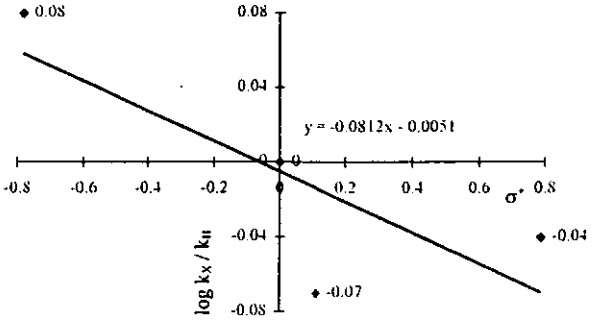
Benzoyl peroxide





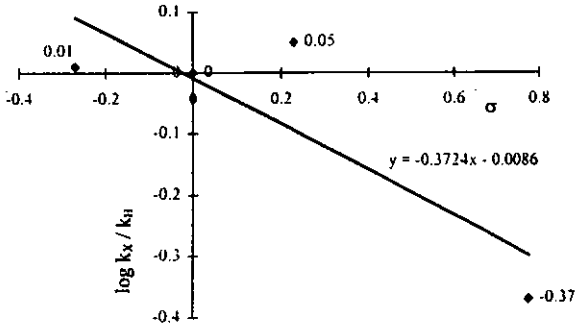
t-Butyl hydroperoxide

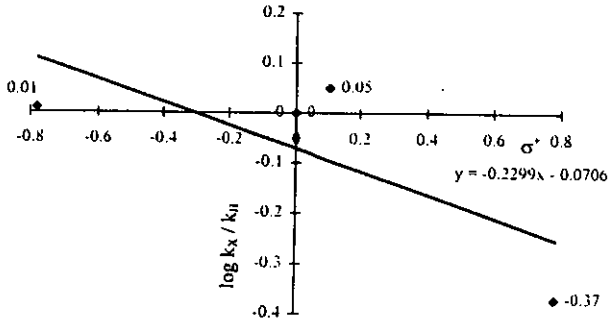




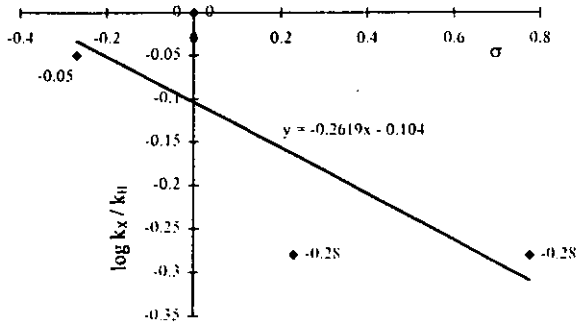
LFER PLOTS OF LOG k_X / k_H VERSUS σ AND σ^+ FOR THE REACTION OF t-BUTYL HYDROPEROXIDE AT 70°C AND THE REACTION OF t-BUTYL HYDRO-PEROXIDE IN THE PRESENCE OF VANADIUM CATALYST WITH N,N-DIMETHYLANILINES IN ACETONE

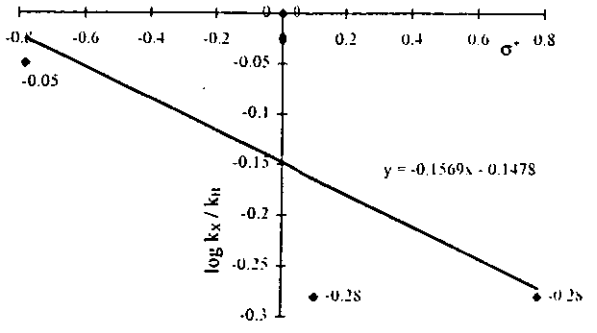
t-Butyl hydroperoxide at 70°C





t-Butyl hydroperoxide in the presence of vanadium catalyst





APPENDIX IV

HPLC analysis of the oxidation of metaclopramide using dimethyldioxirane

		AREA %			
	RT (mins)	free base	oxidation of the free base	mother liquors	further oxidation of the N-oxide
free base	8.8	99.7	-	-	0.1
N-oxide	4.6	-	99.1	84.0	12.4
impurity 1	3.4	-	-	4.7	6.6
impurity 2	7.3	-	-	0.3	0.1
impurity 3	9.3	-	-	0.5	0.7
others	2.2	-	-	1.5	1.9
	2.6	-	-	1.0	13.6
	3.2	-	-	2.4	15.4
	3.5	-	-	-	5.8
	3.8	-	-	-	9.5
	4.2	-	-	-	10.9
	5.3	-	-	-	7

RT retention time

HPLC analysis of the oxidation of BRL 24924 using dimethyldioxirane

		AREA %		
	RT (mins)	free base	oxidation of the free base	further oxidation of the N-oxide
free base	7.5	90.2	-	-
N-oxide	4.2	-	96.6	75.4
impurity 1	9.3	9.3	1.5	6.0
impurity 2	8.1	-	-	2.0
impurity 3	4.6	-	-	6.7
others	2.2	-	-	1.5
	3.9	-	-	3.8

HPLC analysis of the oxidation of BRL 43145 using dimethyldioxirane

		AREA %			
	RT (mins)	free base	oxidation of the free base reaction 1	oxidation of the free base reaction 2	further oxidation of the N-oxide
free base	6.5	99.7	-	-	-
N-oxide	3.4	-	99.1	95.5	47.7
impurity 1	7.0	-	-	-	0.5
impurity 2	8.4	-	-	3.0	1.5
others	3.7	-	-	-	25.6
	4.3	-	-	-	4.3

HPLC analysis of the oxidation of BRL 46470 using dimethyldioxirane

		AREA %		
	RT (mins)	free base	oxidation of the free base	further oxidation of the N-oxide
free base	9.6	99.5	-	3.7
N-oxide	6.9	-	84.6	75.4
impurity 1	6.4	-	9.1	6.7
impurity 2	8.0	-	3.8	3.0
impurity 3	4.1	-	0.8	1.6
others	3.7	-	-	-
	3.8	-	-	-
	4.6	-	-	-

HPLC ANALYSIS OF BRL 49653

Chromatographic Conditions

Column	:	Spherisorb ODS2 5 micron 150mm x 4.6mm id
Eluent A	:	5mM ammonium acetate
Eluent B	:	95% acetonitrile, 5mM ammonium acetate
Gradient	:	0% A to 100% B over 30 minutes
Flow rate	:	1 ml / min
Wavelength	:	317nm

Oxidation of BRL 49653 free base in acetone using 6 equivalents of dimethyldioxirane

retention time	AREA %	
	1 hour	24 hours
0.69	7.47	0
0.90*	25.03	15.9
1.22	8.81	5.8
1.66**	33.71	16.2
2.28	1.65	2.63
3.95	1.38	5.77
4.55	1.60	14.75
5.17	6.08	8.02
7.09	3.14	3.60
14.03	5.34	10.80
16.67	3.61	10.75

* acetone

** coelutes with thicarbamate **150**