Novel Insights into Hydrocarbon Oxidation

A Thesis presented by

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To my parents,
The present thesis is concerned with the development of a high conversion-high selectivity alkane oxidation process, which employs molecular oxygen, operates under mild conditions, and is accordingly based on autoxidation as the simplest conceptual approach.

In the first chapter, the subtleties and fundamental problems of this free radical chain reaction are reviewed, and particular attention is given to recent studies by Ishii, who has introduced N-hydroxy phthalimide (NHPI) and its derived nitroxide (PINO) as a relay catalyst system to increase efficiency. The behaviour of PINO, both in its ability to abstract a hydrogen from an alkane but not act as an alkyl radical trap, together with the apparently unfavourable thermodynamic situation consequently focussed our research work in this area.

For reasons of clarity in presentation, the second chapter, which outlines and discusses the results obtained in our studies, is divided into two parts. The first of these describes a study involving the addition of “onium salts” in the presence of traces of water which led to the discovery of a new method using tert-butyl hydroperoxide in the absence of NHPI. Efforts to rationalise conflicting literature results in this area were made using ab initio theory but no clear mechanistic insight into these curious but real phenomena emerged.

In the second section of the results and discussion, a variety of possible NHPI replacements were screened on the hypothesis that the $a_N$ value of the derived nitroxide radicals could be correlated with its ability to abstract a hydrogen atom from an alkane. Four classes of compounds, each of which possessed electron withdrawing groups adjacent to the hydroxylamine moiety were considered including sulfonyl, difluoromethylene and acyl nitroxides together with a variety of $N$-heterocyclic systems. Two of these systems, an $N$-hydroxyopyridone and an “indigo type” dimer have provided interesting leads for further study.

The thesis concludes with a final chapter outlining the experimental procedure used and the characterisation of the compounds prepared.
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Finally, I thank my family for their continued love, support and encouragement. Of course, all this would not be possible without them, which is why I would like to dedicate this thesis to them.
## ABBREVIATIONS and DEFINITIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>$^{13}$C-NMR</td>
<td>Carbon Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>$^{19}$F-NMR</td>
<td>Fluorine Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>$^{1}$H-NMR</td>
<td>Proton Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>$^{31}$P-NMR</td>
<td>Phosphorus Nuclear Magnetic Resonance</td>
</tr>
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<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>Aliph.</td>
<td>Aliphatic</td>
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<td>AIBN</td>
<td>Azodiisobutyronitrile</td>
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<td>aq.</td>
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<td>Aryl</td>
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<tr>
<td>atm</td>
<td>Atmosphere</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>Boiling point</td>
</tr>
<tr>
<td>BSA</td>
<td>Bis-trimethylsilyl acetamide</td>
</tr>
<tr>
<td>t-Bu</td>
<td><em>tert</em>-Butyl</td>
</tr>
<tr>
<td>t-BuOOH</td>
<td><em>tert</em>-butyl hydroperoxide</td>
</tr>
<tr>
<td>t-BuOO-Bu-t</td>
<td><em>tert</em>-butyl peroxyde</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalytic amount</td>
</tr>
<tr>
<td>conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>conv.</td>
<td>Conversion</td>
</tr>
<tr>
<td>COSY</td>
<td>CORrelated Spectrocopy</td>
</tr>
<tr>
<td>CPMASS TOSS</td>
<td>Cross Polarisation Magic Angle Spinning, Total</td>
</tr>
<tr>
<td></td>
<td>Suppression of Spinning Side Bands</td>
</tr>
<tr>
<td>Cq</td>
<td>Quaternary carbon</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>$\Delta$</td>
<td>Heating</td>
</tr>
<tr>
<td>DAST</td>
<td>Diethylaminosulfur trifluoride</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>$N,N'$-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DMD</td>
<td>Dimethyldioxirane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>EDCl</td>
<td>4-Dimethylaminopropyl-3-ethyl carbodiimide hydrochloride</td>
</tr>
<tr>
<td>EDG</td>
<td>Electron Donating Group</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Impact</td>
</tr>
<tr>
<td>ESR</td>
<td>Electron Spin Resonance</td>
</tr>
<tr>
<td>equiv.</td>
<td>Molar Equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>Et₂O</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron Withdrawing Group</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast Atom Bombardment</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>HF</td>
<td>Hartree-Fock</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Connectivity</td>
</tr>
<tr>
<td>HMDS</td>
<td>Hexamethyldisilazane</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Coherence</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>I'</td>
<td>Initiator radical</td>
</tr>
<tr>
<td>Imid</td>
<td>Imidazolium</td>
</tr>
<tr>
<td>IR</td>
<td>Infra Red</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>lit.</td>
<td>Literature</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m</td>
<td>Meta</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting Point</td>
</tr>
<tr>
<td>NHS</td>
<td>N-hydroxysaccharin</td>
</tr>
</tbody>
</table>
Abbreviations

NHPI  
N-hydroxyphthalimide

o  
Ortho

p  
Para

PE  
Petroleum ether

Ph  
Phenyl

PINO  
N-oxyphthalimide

ppm  
Parts per million

PTC  
Phase-Transfer Catalyst

pyr  
Pyridine

q  
Quartet

r.t.  
Room temperature

s  
Singlet

sat.  
Saturated

sec  
Secondary

SET  
Single Electron Transfer

SM  
Starting material

sp. gr.  
Specific gravity

t  
Triplet

t  
Tertiary

TAS-F  
Tris(dimethylamino)sulfur(trimethylsilyl)difluoride

TBAB  
Teta-n-butylammonium bromide

TBAF  
Teta-n-butylammonium fluoride

TBAT  
Teta-n-butylammonium triphenyldifluorosilicate

TEMPO  
2,2,6,6-Tetramethyl-1-piperidinyloxy

Tf  
Triflate

TFA  
Trifluoroacetic acid

TFAA  
Trifluoroacetic anhydride

THF  
Tetrahydrofuran

THP  
Tetrahydropyranyl

TMEDA  
Tetramethylethylenediamine

tlc  
Thin layer chromatography

TMS  
Trimethylsilyl

UV  
Ultra Violet

w/v  
Weight per volume
Abbreviations

**Conversion**: amount of reactant consumed in a chemical process, expressed as a percentage relative to the original charge.

*Selectivity*: the relative rates of two or more simultaneous processes occurring on the same substrate. Commonly measured by product distributions. For example, it is the amount of particular product formed divided by the amount of the reactant consumed, expressed as a percentage.
Introduction

Hydrocarbons, especially saturated hydrocarbons, are the main constituent of oil and natural gas, which are the basic feedstock for the chemical industry. The selective functionalisation of saturated, as well as aromatic, olefinic and acetylenic substrates is therefore an important field of contemporary chemistry.

In the past, the oxidation of such substrates had been achieved by the use of inorganic compounds such as chromium and manganese oxides, halogens, and nitric acid but only rarely with molecular dioxygen. With the development of the petrochemical industry, a wide range of oxygenated compounds such as alcohols, aldehydes, ketones, epoxides and carboxylic acids became necessary in order to supply starting materials for the production of plastics and synthetic fibres for polyamides, polyesters and polycarbonates. For example, ethylene oxide, acrolein, acrylic acid, and methacrolein, are produced by the vapour phase oxidation of lower alkenes such as ethylene, propylene and butene,\(^1\) while acetic acid, K/A oil (a mixture of cyclohexanone and cyclohexanol), benzoic acid, terephthalic acid, phenol and acetone are produced by liquid phase oxidation, described as autoxidation, of alkanes such as butane, cyclohexane and alkylbenzenes.\(^2-3\) Nitric acid is still widely used as a useful oxidising agent for the manufacture of carboxylic acids such as adipic acid and nicotinic acid in the liquid phase.\(^2-4\) However, new environmental policies target existing methods requiring oxidants such as metal oxides, halogens and nitric acid as unacceptable and have enforced the development of new methodologies based on clean and benign oxidation methods. Although the partial aerobic oxidation of alkanes leading to the formation of alcohols and carbonyl compounds is the most desirable solution from both the ecological and economic viewpoints, current technology has not yet demonstrated the feasibility of this method. The inertness of alkanes and the concomitant ease of overoxidation of the primary products are the major complications in their use, thus making their chemical transformation a challenge from a basic scientific viewpoint. In fact, Figure 1 shows graphically the relationship between conversion and selectivity (to alcohol and ketone) for a number of reported oxidation of alkanes with each point being a published result of an alkane oxidation, regardless of oxidant type. The general trend, highlighted by the circle is a clear indicator that for high selectivity it is preferable to work at low conversion (20% or less). Those oxidations that clearly lie outside of the highlighted area \emph{i.e.} high conversion with high selectivity usually involve the use of more exotic oxidants and as result are thus less generally applicable.
The well-known inertness of alkanes is reflected in their old name, ‘paraffins’ from the Latin *parum affinis* (without affinity), which referred to their low reactivity towards different reagents. This lack of reactivity is the consequence of the high values of the C-H bond energies and ionisation potentials, of the proton affinities, which are far lower than those of unsaturated hydrocarbons, and the alkane acidities which are much smaller than those of other compound classes. Although olefins and arenes can be activated by π complexation and easily undergo oxidation (*e.g.* toluene), saturated hydrocarbons require “activation” to be oxidised by molecular dioxygen.

In recent decades, the vigorous development of metal-complex catalysis has expanded our knowledge of unsaturated hydrocarbon transformations and hence opened the door to alkane transformations using metal catalysis. A number of catalytic systems have been developed for the liquid-phase oxidation of alkanes with dioxygen in the presence of reducing agents such as H₂, metals or aldehydes under mild conditions.[5-9] Four different activation methods can be identified: a) the formation of hydrocarbon radicals by a free radical autoxidation mechanism leading to reactive hydroperoxides, b) photo excitation of dioxygen to form highly reactive singlet oxygen, c) use of dioxygen as a secondary oxidant in a metal-ion catalysed
process$^{[2a]}$ and d) reductive cleavage of transition metal dioxygen complexes to form highly active metal-oxo intermediates. The reactions described below are illustrative. In 1981, Tabushi et al.$^{[10]}$ in a very bold experiment reported the oxidation of adamantane to 1- and 2-adamantanol at room temperature by a Mn(III) porphyrin/Pt/H$_2$ system under a dioxygen atmosphere. Barton$^{[11]}$ developed a family of systems, the so called Gif-systems, for aerobic oxidation of alkanes using iron catalysts and Zn or Fe as reductants, which exhibited an exceptional selectivity for secondary C-H. The same author also proposed a different method based on the use of tert-butyl hydroperoxide, air and soluble iron (III) tris(2,2,2-trimethylacetate), [Fe(tma)$_3$], which provided cyclohexanol and cyclohexanone efficiently from cyclohexane.$^{[11d]}$ Murahashi et al.$^{[12]}$ oxidised alkanes at room temperature with molecular dioxygen in the presence of an aldehyde and a copper salt catalyst (e.g. copper (II) hydroxide), with turnover numbers increasing when a crown ether was employed as co-catalyst. Moreover this group also reported the oxidation of cyclohexane and adamantane by ruthenium or iron catalysts in the presence of acetaldehyde and peracids (CH$_3$CO$_3$H or CF$_3$CO$_3$H)$^{[13,14]}$. There have been several reports of the photo-oxidations of alkanes with dioxygen catalysed by polyoxotungstates,$^{[15]}$ heteropolyoxometalates,$^{[16,17]}$ or zeolites.$^{[18]}$ Shul’pin$^{[19]}$ and Cšanyi$^{[20]}$ carried out vanadium-catalysed oxidations by dioxygen in combination with hydrogen peroxide. In particular, Shul’pin oxidised alkanes in acetonitrile using a mixture of dioxygen, hydrogen peroxide, pyrazine-2-carboxylic acid and vanadate anion to produce mainly the alkyl hydroperoxide, which then decomposed to the desired oxygenated products. Lyon and Ellis$^{[21]}$ reported that halogenated metalloporphyrin complexes are efficient catalysts for the oxidation of isobutane with dioxygen without any co-reductant while Mizuno et al.$^{[22]}$ showed that heteropolyanions containing Fe catalysed the aerobic oxidation of isobutene and n-butane. Systems using Ru(III)-EDTA,$^{[23]}$ Ru-substituted polyoxometalate,$^{[24]}$ and [Co(NCMe$_3$)$_4$]([PF$_6$]$_2^{2-}$)$^{[25]}$ have also been reported to catalyse the aerobic oxidation of cyclohexane and adamantane.

However, in spite of these advances, a selective and effective method for the oxygenation of alkanes with molecular dioxygen still remains a major challenge and it is currently an important research goal. In this thesis, we elected to investigate a new route for the oxidation of alkanes using molecular dioxygen and avoiding, if possible, the use of metal catalysis. We believed that the liquid phase autoxidation
could be a valuable alternative methodology although existing examples often showed low efficiency and selectivity.

Classical autoxidation is the slow oxidation of alkanes with ground state (triplet) molecular dioxygen in the liquid phase under mild conditions, to afford organic hydroperoxides as the primary products, through a free radical chain reaction. It can be divided into three steps: initiation, propagation and termination (Scheme 1).

**Initiation**

\[ R\cdot H + I' \rightarrow R' + H I \]  
Eq.1

**Propagation**

\[ R' + O_2 \stackrel{Fast}{\rightarrow} ROO' \]  
Eq.2

\[ ROO' + RH \stackrel{Slow}{\rightarrow} ROOH + R' \]  
Eq.3

**Termination**

\[ R' + RO_2' \rightarrow RO_2R \]  
Eq.4

\[ 2 \, RO_2' \rightarrow RO_4R \rightarrow \text{No radical products} \]  
Eq.5

**Scheme 1**

The chain needs to be initiated by a radical (I'), which may be formed by the thermal decomposition of suitable organic compounds (azoalkanes, organic peroxides and hydroperoxides) added to the reaction mixture. The abstraction of a hydrogen atom from the alkane by the initiator generates an alkyl radical which can then react further (Eq. 1). The role of the initiator is important as the direct addition of dioxygen to alkanes is thermodynamically and kinetically unfavourable, although a few examples are reported in the literature where spontaneous initiation has been observed as in the case of indene.\(^{[26]}\) However, in the latter case, further studies proved that the initiation was carried out by peroxide impurities, already present in the starting material.
The addition of dioxygen to the alkyl radical, formed in Eq. 1, to give alkylperoxy radical, is fast and the rate of autoxidation is independent of the concentration of dioxygen even for very low concentrations (Eq. 2). Unfortunately, further cleavage of the R-H bond by hydrogen atom abstraction using an alkylperoxy radical is slower by a factor of $10^6$-$10^8$, and the rate of this step therefore governs the overall rate of the reaction (Eq. 3). The alkylperoxy radicals are relatively stable and preferentially attack the weakest bound hydrogen atom. Hence, the relative reactivity to different C-H bonds in autoxidation decreases in the order of tertiary $>$ secondary $>$ primary (in the case of 2-methylpentane, this ratio becomes 300:30:1). The fact that an alkylperoxy radical is so much less reactive than an alkoxy radical in terms of its ability to abstract a hydrogen atom from an alkane is therefore the dominant factor, which prevents efficient propagation of the chain process in classical autoxidation.

Termination steps occur usually by combination of two radicals to form peroxides or tetroxides (Eq. 4-5) and their mode of decomposition is dependent on the nature of the chain. In particular, in the case of primary and secondary alkylperoxy radicals, disproportionation will occur through a cyclic mechanism to form an alcohol and a ketone (Scheme 2).

\[
\begin{align*}
2 \text{ROO'} & \rightleftharpoons R_2C\underbrace{O}O^\cdot O^\cdot & \rightarrow R_2C=O + RCH_2OH + O_2 \\
\text{Scheme 2}
\end{align*}
\]

Tertiary alkylperoxy radicals decompose irreversibly to give two caged alkoxy radicals and dioxygen (Scheme 3). Approximately 10% of the caged alkoxy radicals combine to give peroxide while 90% escape into the reaction medium and undergo reactions typical of alkoxy radicals, such as hydrogen abstraction and $\beta$ scission.

\[
\begin{align*}
\text{ROOOOR} & \rightarrow \text{RO'} + O_2 + \text{RO'} \\
\text{cage} & \rightarrow \text{ROOR} \\
2\text{RO}' &
\end{align*}
\]

\[
\text{Scheme 3}
\]
Once the alkyl hydroperoxides are formed, they undergo thermal decomposition to give alcohols at elevated temperature (Scheme 4, Eq. 6-7). This decomposition serves as the major source of free radicals in autoxidation. However, due to side reactions, such as $\beta$-scission of alkylperoxy radicals, this process is difficult to control and further transformations with the substrate or solvent, also lead to alcohols, ketones and alkyl radicals (Scheme 4, Eq. 8).

\[
\begin{align*}
ROOH & \rightarrow RO^- + 'OH \quad \text{Eq. 6} \\
RO^- + ROOH & \rightarrow ROO^- + ROH \quad \text{Eq. 7} \\
RH + RO^- & \rightarrow ROH + R^- \quad \text{Eq. 8}
\end{align*}
\]

Scheme 4

Autoxidation of alkanes has also been carried out using metal catalysis. Although metal ions participate in the oxidation steps, their main role is not to generate free alkyl radicals directly by one electron oxidation (Scheme 5, Eq. 9), but rather to catalyse decomposition of the intermediate hydroperoxides either by a reductive or oxidative mechanism, according to equations 10-11 (Scheme 5).

\[
\begin{align*}
RH + M^{(n+1)^+} & \rightarrow R^- + M^{n^+} + H^+ \quad \text{Eq. 9} \\
ROOH + M^{(n+1)^+} & \rightarrow ROO^- + M^{n^+} + H^+ \quad \text{Eq. 10} \\
ROOH + M^{n^+} & \rightarrow RO^- + M^{(n+1)^+} + OH^- \quad \text{Eq. 11}
\end{align*}
\]

Scheme 5

The rapid decomposition of alkyl hydroperoxides in hydrocarbon solutions, in the presence of trace amounts of iron, manganese, cobalt or copper is well known[^28-29] and when the metals have two oxidation states of comparable stability *(i.e. Co$^{2+}$/Co$^{3+}$; Mn$^{2+}$/Mn$^{3+}$)* both equations 10 and 11 can take place (Scheme 6).
Equation 11/12, resulting in the production of alkoxy radicals, is clearly beneficial, whilst equation 10/13 merely serves to regenerate the hydroperoxy radical. However, it has been reported that at the beginning of cobalt catalysed autoxidation, Co (II) is oxidised to Co (III) as can be observed by the change in colour of the solution from pink to dark green.\textsuperscript{[30]}

\[
\text{ROOH} + M^{	ext{II}} \rightarrow \text{RO}^- + M^{	ext{III}} \text{OH} \quad \text{Eq.12}
\]

\[
\text{ROOH} + M^{	ext{III}} \rightarrow \text{RO}_2^- + M^{	ext{II}} + H^+ \quad \text{Eq.13}
\]

\( M = \text{Co or Mn} \)

\textbf{Scheme 6}

Other routes that do not involve a change in the oxidation state of the catalyst have also been applied to the decomposition of hydroperoxides, as exemplified by the use of boron. In fact, the selectivity for alcohol formation can be improved by carrying out alkane autoxidation in the presence of stoichiometric amounts of boric acid (\( \text{H}_3\text{BO}_3 \)), metaboric acid (\( \text{HBO}_2 \)) or boric anhydride (\( \text{B}_2\text{O}_3 \)). This effect, discovered by Bashkirov,\textsuperscript{[31]} is based on the breakdown of the intermediate hydroperoxides, by boron, to dioxygen, water, and the corresponding alkyl borates (Scheme 7, Eq. 14). It is also conceivable that intermediate alkylperoxy radicals react with boron (III) compounds to form alkylperoxyboron (III) derivatives (Scheme 7, Eq. 15), which are subsequently converted to alkyl borates. Finally, the alkyl borates are hydrolysed to the corresponding alcohol and boric acid which can then be recycled.\textsuperscript{[32]}

\[
6 \text{ROOH} + \text{B}_2\text{O}_3 \rightarrow 2 (\text{RO})_3\text{B} + 3\text{H}_2\text{O} + 3\text{O}_2 \quad \text{Eq.14}
\]

\[
(\text{RO})_3\text{B} + \text{RO}_2^- \rightarrow \text{RO}^- + (\text{RO}_2)(\text{RO})_2\text{B} \quad \text{Eq.15}
\]

\textbf{Scheme 7}

In summary however, it is clear that in order to improve the efficiency of autoxidation, the rate of the reaction between alkylperoxy radicals and alkanes (Scheme 1, Eq. 3), which determines the overall rate of the reaction, needs to be dramatically increased (Figure 2).
Introduction

Two main solutions to this problem have been proposed.

The classical solution, based on the use of metal salts, as cobalt, is widely applied in the chemical industry. For example, high concentrations of cobalt (II) acetate have been employed in the oxidation of cyclohexane (1) to adipic acid (2), resulting in 70-75% selectivity at 80-85% conversion of cyclohexane, in acetic acid at 90°C.[33] In this case, cobalt acts both as a chain transfer agent in a direct reaction with the alkane substrate as well as a catalyst for the decomposition of the alkylperoxy radical (4) to the desired ketone thus avoiding direct hydrogen atom abstraction from the substrate (Scheme 8).

Most recently, in an exciting series of papers, the group of Ishii has solved the fundamental problem of autoxidation by introducing a new additive called NHPI, N-hydroxyphthalimide (6) (Figure 3), which acts as a precatalyst for formation of the derived nitroxide radical, PINO (7). This functions as a catalyst for the oxidation of hydrocarbons either in the presence or absence of metals.
In fact however, the use of $\text{N}$-hydroxyphthalimide was first reported by Grochowski$^{[34]}$ in 1977, who observed the reaction of ethers (8) with diethyl azodicarboxylate, (DEAD) (9), in the presence of a catalytic amount of NHPI or $\text{N}$-hydroxysuccinimide. Compounds of type 10 were formed in nearly quantitative yield and the radical character of the reaction was demonstrated by its failure in the presence of radical inhibitors, such as hydroquinones and tetrachlorobenzoquinones. The catalytic activity can be attributed to the formation of the nitroxyl radical (PINO) from NHPI and DEAD, which can then react with the ether and may give rise to a radical chain (Scheme 9).
Later, Masui and co-workers\textsuperscript{[35]} showed that NHPI was an efficient electron carrier for the electrolytic oxidation of sec-alcohols to ketones. The oxidation was considered to proceed \textit{via} dehydrogenation from alcohols by PINO, generated from NHPI under electrolytic conditions (Scheme 10).
Subsequently, NHPI was used for the oxidation of benzylic compounds, alkenes, lactams, acetals\textsuperscript{36} and then for the epoxidation of olefins catalysed by Mn porphyrin (MnTPPCl).\textsuperscript{37} In the latter case, it was suggested that transient peroxides were formed by the co-oxidation of alkenes, such as styrene, 2-norbornene or indene with NHPI, which are able to operate as mono-oxygen donors to Mn\textsuperscript{III}TPPCl in a similar way to compounds bearing activated oxygen such as hydroperoxides, peracids, iodosoarenes, or sodium hypochlorite, which have been used in model systems of cytochrome P-450. The mechanism for styrene, shown in Scheme 11, underlines the formation of this intermediate hydroperoxide, which oxidises Mn\textsuperscript{III} to Mn\textsuperscript{V}. The high-valent-oxo-manganese complex can then act as an oxygen donor for the olefin to give the epoxide product.
In 1995, Ishii described the possibility of oxidising aliphatic alcohols into their corresponding carbonyl compounds in the presence of a catalytic amount of vanadomolybdophosphonate (NPV₆Mo₆) and NHPI under non-electrolytic conditions. On the basis of his studies, a plausible catalytic cycle for the system was proposed, as outlined in the Scheme 12. The first step of the oxidation could be considered to involve the hydrogen abstraction from NHPI by NPV₆Mo₆ to form the N-oxy radical (PINO) which subsequently dehydrogenated the alcohols to form the corresponding ketones and NHPI. The catalytic cycle of the NPV₆Mo₆/NHPI-O₂ system was then completed by the reoxidation of the reduced vanadium species to NPV₆Mo₆.

Scheme 11

Scheme 12
In a further investigation of the mechanism of NHPI (6) catalysis, the oxidation of hydrocarbon fluorene was studied under different conditions in the absence of the vanadomolybdate species and a good conversion was obtained when 10 mol% of 6 was added in a benzonitrile solution at 100°C (Scheme 13).[^39]

![Scheme 13](image)

Although different benzylic substrates were successfully oxidised by this procedure, it appeared to be inefficient for saturated alkanes, such as adamantane or cyclohexane, giving poor conversions.

C. Einhorn[^40] had subsequently modified Ishii’s procedure by introducing together with NHPI (10 mol%), 1 equivalent of acetaldehyde, as in the oxidation of isochroman (13) and xanthene (15) in almost quantitative yield (Scheme 14).

![Scheme 14](image)

In fact, aldehydes are often used as co-oxidants because their autoxidation rates are very high, even at room temperature, and they are therefore able to promote the oxidation of the less reactive partner. Thus, an active acyl peroxy radical is responsible for the *in situ* formation of the radical PINO as shown in Scheme 15.
Moreover Einhorn successfully prepared chiral N-hydroxyimides (Fig. 4) and used them as catalysts for the asymmetric oxidation of 2-methylindane and 2-methoxy-2-phenylindane, to give the corresponding indanones although with a disappointingly low % enantiomeric excess (ee 2-4%).

At the same time, Ishii discovered that the catalytic effect of NHPI was markedly enhanced by the presence of a small amount of Co(acac)\(_n\) (n = 2,3) as co-catalyst.\(^{[42-44]}\) Under these conditions, cycloalkanes and alkylbenzenes can be oxidised to the corresponding carbonyl compounds in a dioxygen atmosphere under moderate conditions. From Table 1, with cobalt catalysis, the oxidation of cycloalkanes was successfully carried out; cyclooctane (20) gave cyclooctanone (21), 1,4-cyclooctanedione (22) and suberic acid (23) in a total of 93% conversion. Cyclododecane (24) was similarly converted into the corresponding ketone 25 and dicarboxylic acid 26 whilst methylocyclohexane (27) afforded the keto carboxylic acid 30 as the major product along with 2-methylocyclohexanone 28 and 1-methylocyclohexanol (29). In the latter case, independent oxidations were carried out to show that 30 derived from the overoxidation of 28, and hence the alcohol 29 appeared to be a less reactive substrate. The oxidation of adamantane (31) under milder conditions (75°C, 3 hours) showed selectivity towards the tertiary C-H and resulted in 71% conversion to adamantyl-1-ol (32).
**Introduction**

<table>
<thead>
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[Substrate (5 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol%) and Co(OAc)<sub>2</sub> (0.5 mol%) in acetic acid (12.5 ml) at 100°C for 6 hours; (a) reaction time was 3 hours; (b) reaction was carried out at 75°C for 3 hours.]

**Table 1**

23
The following mechanism shown in Scheme 16 where 1,4-diketone 22 is formed via intramolecular hydrogen abstraction by a transient peroxy radical generated by 20, was postulated to explain the reactivity of cyclooctane.\textsuperscript{[43]} Successive oxidation of 21 under these conditions led to the carboxylic acid 23.

Although cobalt salts are used for the redox-decomposition of alkylperoxides in autoxidation, they have a different role to play in the system based on NHPI. The absorption rate of dioxygen at 80°C, during the oxidation of ethylbenzene (35) was
studied by Ishii to gain additional insight into the difference in reactivity between cobalt (II) and cobalt (III). No induction rate was observed in $O_2$ uptake by 35 with NHPI/Co(acac)$_2$ whereas reaction with the NHPI/Co(acac)$_3$ system did not occur for approximately 1.5 hours. The induction period observed for Co (III) could be explained on the basis of its reduction to Co (II) by a one electron transfer from ethylbenzene to form in situ the same type of complex, derived by the direct utilisation of Co (II) (Scheme 17).

![Scheme 17](image)

However, the reduction of Co (III) can be carried out not only at high temperature in the presence of aromatic compounds$^{[43]}$ but even with a small amount of benzaldehyde.$^{[33]}$

When NHPI was withheld and a mixture of ethylbenzene and cobalt (II or III) was heated to $80^\circ C$, no uptake of dioxygen was registered as in the case of the oxidation of 35 carried out under standard conditions in the presence of hydroquinone (1 mol%). All these results and an isotopic effect ($\kappa_{II}/\kappa_{III}$) of ca.3.74, estimated by measuring the dioxygen uptake of ethylbenzene and ethylbenzene-$d_{10}$, strongly indicated that this aerobic oxidation proceeds via a reaction pathway similar to that in free radical autoxidation.$^{[27b]}

Moreover, the Ishii group investigated the mechanism using ESR. After a benzonitrile solution of $N$-hydroxypthalimide was exposed to dioxygen for 1 hour at $80^\circ C$, a triplet ESR signal exhibiting a hyperfine splitting due to the nitrogen atom of 4.3 G and with a $g$ value of 2.0074 was observed.$^{[44]}$ The generation of this radical was remarkably accelerated (< 10 minutes) by the presence of cobalt (II) acetate but no signal was observed when a catalytic amount of Co (III) was added to the system, showing again that this oxidation state is not responsible for the formation of the nitroxide, PINO. From this work, it was postulated that a labile dioxygen complex such as superoxocobalt (III) (Scheme 18, Eq. 16) or $\mu$-peroxocobalt (III) (Scheme
18, Eq. 17) was formed during the oxidation, which oxidised $N$-hydroxyphthalimide to the $N$-oxy radical.

$$
\text{L}_2\text{Co (II)} + \text{O}_2 \rightarrow \text{L}_2\text{Co (III)}-\text{OO}^- \quad \text{Eq. 16}
$$

$$
\text{L}_2\text{Co (III)}-\text{OO}^- + \text{L}_2\text{Co(II)} \rightarrow \text{L}_2\text{Co (III)}-\text{OO-Co(III)l}_2 \quad \text{Eq. 17}
$$

$$
\text{L}_2\text{Co (III)}-\text{OO}^- + \text{NHPI} \rightarrow \text{L}_2\text{Co (III)}-\text{OOH} + \text{PINO} \quad \text{Eq. 18}
$$

**Scheme 18**

However, discrete Co (III)-alkylperoxy complexes of the formula $[\text{LCo}^{III}-\text{OOR}]$ have been isolated and characterised.$^{45-46}$ The utility of these peroxy compounds in the oxidation of alkanes had been demonstrated by Chavez et al.$^{47}$ by showing how the complex $[\text{Co (Py}_2\text{P})(\text{OO}^\text{Bu})]$ (with $\text{Py}_2\text{P} = N,N,N$-tris[2-(2-pyridyl)ethyl]-pyridine-2,6-dicarboxamide) oxidised cyclohexane to cyclohexanol and cyclohexanone.

Finally, a reaction pathway for the aerobic oxidation of alkanes in the presence of Co(OAc)$_2$, taking into account the cobalt complexes, was proposed by Ishii (Scheme 19). Initially PINO was generated by the reaction of NHPI with the cobalt (III) oxygen complex, which subsequently abstracted a hydrogen atom from the alkane to provide an alkyl radical. This alkyl radical then reacted with dioxygen forming an alkylperoxy radical, which was converted to the oxygenated product via the alkyl hydroperoxide. The latter intermediate decomposed in the presence of either species of Co (II) or Co (III), and PINO was regenerated.
Since the chemical reactivity of various nitroxides is a theme of particular relevance to the present thesis, it is appropriate at this stage to consider the basic nature of this functional group and to outline briefly the spectral character of this moiety in terms of ESR spectroscopy. Thus, nitroxides such as PINO can be observed by Electron Spin Resonance (ESR) spectroscopy, which is the study of molecules containing unpaired electrons by observing the magnetic fields at which they come into resonance with monochromatic electromagnetic radiation. The NO group of a nitroxide, which contains unpaired electrons, may be represented as a hybrid of two resonance structures (I) and (II), and this implied resonance stabilisation is reflected in the weakness of the OH bond in hydroxylamines (Figure 5).

An alternative, molecular orbital picture of the nitroxide structure places two electrons in an NO π-bonding orbital and one in the corresponding antibonding
orbital, as well as two electrons in an N-O σ-bond. This gives an approximate NO bond order of 1.5 and an interesting consequence of this electronic structure is a particularly "soft" geometry at nitrogen, where it has been calculated that very little energy is required to deform the molecule from its preferred planar geometry into a fully tetrahedral ($sp^3$) structure. Many nitroxides, e.g. porphyrexide,$^{48b}$ may be isolated and are stable indefinitely. Others decay more rapidly, depending upon the nature of substituents on the nitrogen atom, but it can be possible to measure an ESR spectrum of the radical.

The ESR spectrum from a nitroxide radical solution is characterised by three basic parameters: the $g$-factor, the line-widths ($\delta$), and the hyperfine coupling constant ($a_r$). The $g$-factor is characteristic of the type of radical and reflects the variable amount of orbital magnetism possessed by the unpaired electron, in addition to its spin magnetism. For rapidly tumbling organic radicals, $g$-values are always close to the free electron value of 2 and they are determined by the following equation 19, where $(h/\mu_B) = 0.7144385$ G MHz$^{-1}$ and $\nu_0$ and $B_0$ are the microwave frequency (in MHz) and the applied magnetic field at the center of the spectrum (in Gauss), respectively.

$$g = (h/\mu_B) \times (\nu_0/B_0) \quad \text{Eq.19}$$

Chemical and physical processes that lead to exchange of the unpaired electrons between different radical sites can give rise to lineshape effects in the ESR spectra. Such processes include hindered rotation around bonds, tumbling of the radical in a viscous liquid, interactions with other paramagnetic species and chemical reactions (e.g. acid-base equilibria and electron transfer reactions). The most useful information derivable from an ESR spectrum is obtained from the third parameter, the hyperfine splitting which usually enables identification of the radical and also the determination of its detailed structure. The origin of the observed splittings is the interaction between the unpaired electron and the magnetic moments of the magnetic nuclei within the radical. The interaction between the electron and $n$ equivalent nuclei of spin $I$ results in $(2nI+1)$ lines and the distance between each of these lines in the spectrum is (to first-order) equal to the hyperfine coupling constant. The interaction of the unpaired electron with $n$ equivalent protons (or other $I = \frac{1}{2}$ nuclei) gives rise to the signal splitting into $(n+1)$ lines and furthermore, the relative intensities of these lines are given by the coefficients of the binomial expansion of
(1+x)^n$, shown in Pascal’s triangle. Considering that $^{14}$N has nuclear spin, $I = 1$, a clear 1:1:1 threefold multiplicity will arise in the case of its interaction with the unpaired electron (vide supra NHPI). Within our own research area, it was of particular interest to note that by using ESR measurements, the reactivity of nitroxide radicals as hydrogen atom abstraction reagents can be correlated with the $a_N$ values viz, the lower the hyperfine coupling constant of the nitrogen, the more efficient is the radical for hydrogen atom abstraction from alkanes. In the following Table 2, the hyperfine coupling constants of nitroxides, generated by oxidation of the corresponding amines with the system hydrogen peroxide/phosphotungstic acid or $m$-chloroperbenzoic acid, are set out.

<table>
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<th>Radical</th>
<th>$a_N$ (Gauss)</th>
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<td>PhCN</td>
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<tr>
<td><img src="36" alt="Nitroxide" /></td>
<td>4.2</td>
<td>DCM</td>
<td>[50]</td>
</tr>
</tbody>
</table>

$R = \text{NO}_2$
TEMPO (36), 2,2,6,6-tetramethyl-1-piperidinyloxy, a well-known free radical chain inhibitor, has an $a_N$ of 16.2 Gauss which is much larger than that for NHPI (4.3 G). This difference in nitrogen hyperfine coupling constants could explain the different reactivities of the two nitroxides. Although PINO can abstract a hydrogen atom from an alkane to generate an alkyl radical, TEMPO cannot as the reaction will be too endothermic. These observations tend to support our empirical theory of an inverse relation between the power of the nitroxide in the abstraction of a hydrogen atom and the nitrogen hyperfine coupling constant, indicating that a low $a_N$ value is the main feature of a good catalyst for autoxidation. This relationship is intuitively obvious if we consider the two resonance forms III and IV of PINO (Figure 6).

Thus, IV, in which a formal positive charge is placed adjacent to the carbonyl groups is clearly a minor contributor and thus PINO has more alkoxy radical character for hydrogen atom abstraction as implied in III.

Although NHPI successfully oxidised alkanes using molecular dioxygen in combination with a small amount of a transition metal salt, such as Co(OAc)$_2$, Ishii found that a quaternary ammonium bromide enhanced the reactivity of NHPI in the absence of metals. In particular, adamantane was oxidised in 73% conversion in a
biphasic system, trifluorotoluene/water, with 10 mol% of NHPI and 2 mol% of tetra-
n-butylammonium bromide (Scheme 20).

**Scheme 20**

The above system was of intense interest to us because the complex redox chemistry
which occurs on use of metal salts is entirely eliminated. Moreover, we were also
especially intrigued by the possible roles for the quaternary ammonium bromide. In
the event, as we shall see, (*vide infra* Section 2.2) this aspect formed a major focus
for our research.

In the last years, Ishii has now applied his system based on NHPI for the
autoxidation of sulfides,\(^{[52]}\) diols,\(^{[53]}\) methyl pyridines,\(^{[54]}\) benzylic substrates\(^{[44]}\) and,
moreover, to carry out carbonylation\(^{[55]}\) and nitration\(^{[56]}\) of alkanes as shown in
Scheme 21.

**Scheme 21**
The use of NHPI had also been further investigated by this Japanese group for the generation of hydrogen peroxide. As we have already discussed, the PINO-catalysed aerobic oxidation of alkanes occurs via the formation of alkyl hydroperoxides which are eventually converted into oxygen-containing products such as ketones, alcohols and also carboxylic acids but certain intermediates can also be used to generate hydrogen peroxide in situ. Thus, the oxidation of alcohols, especially benzylic alcohols such as benzhydrol (37) and 1-phenylethanol, with NHPI as catalyst, produced H$_2$O$_2$ via $\alpha$-hydroxy hydroperoxides (40), in good yield as shown in Scheme 22. When benzhydrol (40 mmol) (37) was reacted with O$_2$ (1 atm) and NHPI (10 mol%) in ethyl acetate at 75°C for 12 hours, H$_2$O$_2$ (39) was obtained in 71% yield along with benzophenone (38).$^{[57]}$

Additionally, the alkyl hydroperoxides formed could also be utilised as oxidants for epoxidation of alkenes. The epoxidation of 2-octene (44) was successfully achieved.

Scheme 22
in 67% conversion in the presence of NHPI (10 mol%), ethylbenzene (35), Co(OAc)$_2$ (0.1 mol%) and Mo(CO)$_6$ (5 mol%) at 60°C (Scheme 23).$^{[58]}$

Another recent application showing the versatility of NHPI, is its use as a polarity-reversal catalyst for the hydroacylation of alkenes. The hydroacylation reaction between alkenes and aldehydes via a radical process involves the following reaction sequence; hydrogen atom abstraction from an aldehyde by a radical initiator to form an acyl radical (46) (Eq. 20), addition of the acyl radical to the alkene then leads to a β-oxocarbon radical (47) (Eq. 21), and finally abstraction of the aldehydic hydrogen atom from another aldehyde by 47, generating the ketonic product and the acyl radical 46 as the chain carrier (Eq. 22) (Scheme 24).

In this radical-chain reaction, if R’ is an alkyl or an electron-donating group (EDG), the third step (Eq. 22) becomes a sluggish process, since the abstraction of the aldehydic hydrogen atom by a nucleophilic radical 47 proceeds with difficulty. In
contrast, if R' is an electron-withdrawing group (EWG), this step proceeds smoothly because of the ease of aldehydic hydrogen abstraction by an electrophilic radical. Acyl radicals, which are nucleophilic in nature, are known to add more easily to electron-deficient alkenes than normal alkenes. As already discussed PINO abstracts a hydrogen atom from alkanes to generate alkyl radicals and if the adduct radical 47 in Scheme 24 can abstract the hydrogen atom from NHPI, NHPI can be expected to serve as a polarity-reversal catalyst. The hydrogen atom of the N-hydroxyimide moiety may then be easily abstracted by a nucleophilic radical rather than an electrophilic one, and the resulting PINO can behave as an electrophilic radical efficiently abstracting the aldehydic hydrogen atom. When norbornene (49) was reacted with pentanal (48) in the presence of NHPI and dibenzoyl peroxide (BPO) the corresponding adduct (50) was obtained in 90% conversion with 73% selectivity (Scheme 25).

![Scheme 25](image)

The reaction can be explained by firstly a hydrogen abstraction from the aldehyde by the radical initiator to give an acyl radical 51, which then adds to an alkene to afford a \( \beta \)-oxocarbon radical 52. The resulting radical 52, having a nucleophilic character can abstract the hydrogen atom from NHPI leading to the ketone and PINO which can abstract the hydrogen atom from the aldehyde to form the acyl radical 51 and NHPI. However, an alternative formation of PINO from NHPI and the radical initiator (In') can also be envisaged (Scheme 26).
Finally, aerobic autoxidation of hydrocarbons must be carried out in an appropriate solvent, such as acetic acid or acetonitrile, since NHPI is insoluble in nonpolar solvents such as hydrocarbons. Recently, Ishii solved this problem by preparing a series of 4-alkyloxycarbonyl N-hydroxyphthalimides (54), which were soluble in hydrocarbons such as cyclohexane thus avoiding the use of any solvents. Treatment of the commercially available trimellitic anhydride (53) with hydroxylamine afforded N-hydroxyphthalimide 4-carboxylic acid which on subsequent esterification with the appropriate alcohol led to the corresponding esters in good yield (Scheme 27).\[63\]
Thus, a series of NHPI derivatives substituted with 4-alkyloxycarbonyl moieties having different alkyl chains (54b-d) was prepared and used for the aerobic oxidation of cyclohexane. The best substrate was found to be 4-lauryloxycarbonyl N-hydroxyphthalimide (54c) as the reaction of cyclohexane (37 mmol) in air with 54c (30 μmol), Co(OAc)$_2$ (3 μmol) and Mn(OAc)$_2$ (0.3 μmol) at 100°C for 14 hours gave cyclohexanone, cyclohexanol and adipic acid in a relative ratio of 61:28:7 (Scheme 28).

Thus, these lipophilic compounds appeared to herald a green oxidation system which eliminates the necessity of using solvents and requires only air as the oxidant.

Although NHPI has clearly emerged as the catalyst of choice for many reactions, the mechanistic pathways involved require further clarification. As previously discussed, although the reaction between an alkylperoxy radical and an alkane is the slow rate-determining step in a classical autoxidation, Ishii has proposed a pathway wherein PINO easily abstracts a hydrogen atom from an alkane. We were intrigued to note, by comparing equations 23 and 24, that the newly formed bonds to hydrogen viz, RO-OH and R'-NOH, have similar bond energies and thus analogous behaviour would be anticipated for the two radicals (Scheme 29). On the basis of this observation, the great difference in the character and reactivity of the two similar radicals appears to be unjustifiable.
Indeed, after termination of our own experimental work, Minisci\textsuperscript{[64]} calculated the bond dissociation energy (BDE) for the reaction between NHPI and an alkylperoxy radical (Scheme 30) and reported a BDE for the O-H bond in the hydroperoxide of 88 kcal mol\textsuperscript{-1} and a lower limit for that of the O-H bond in NHPI of 86.88 kcal mol\textsuperscript{-1}. These results suggest that the reaction of NHPI with an alkylperoxy radical is either thermoneutral or slightly endothermic indicating that the general equation 25 can be considered as an equilibrium (Scheme 30). If no thermodynamic factors favour Equation 24 over Equation 25, the proposed mechanism of Ishii for the autoxidation, which is based on fast hydrogen atom abstraction from an alkane, would appear to be flawed.

Moreover within the last year, Minisci has compared the catalytic behaviour of PINO and TEMPO with the BDE of the O-H bonds of the corresponding N-hydroxy derivatives.\textsuperscript{[65]} The BDE of the O-H bond for NHPI was determined by ESR spectroscopy of the equilibrium, shown in Equation 26, where Ar-OH is a reference phenol (2,4,6-trimethyl phenol, whose BDE in benzene is 82.7 Kcal mol\textsuperscript{-1}) and >N-OH is NHPI (Scheme 31).
The BDE of the OH bond for 2,2,6,6-tetramethyl-piperidin-1-ol was shown to be relatively low (70 Kcal mol\(^{-1}\)) but that of the O-H bond of NHPI was 16 Kcal mol\(^{-1}\) larger. Thus the ability of PINO to abstract a hydrogen atom from alkanes may be explained by the higher BDE for the O-H bond. However, a similar hydrogen atom abstraction by TEMPO would be too endothermic to occur (Scheme 32, Eq. 27) with TEMPO preferentially trapping the intermediate free radicals (Scheme 32, Eq. 28).

\[
\text{RH} + N' \rightarrow N' \text{OH} + R' \quad \text{Eq. 27}
\]

\[
 N' \text{OR} + R' \rightarrow N' \quad \text{fast} \quad \text{Eq. 28}
\]

Scheme 32

The final proof of this different behaviour of the two nitroxides, could be deduced from the use of TEMPO as a catalyst for the selective oxidation of alcohols (but not alkanes) to aldehydes in the presence of a metal, where the reactive species is the oxoammonium (\(>\text{N}^+\text{O}\)).\(^{[66]}\)

In conclusion, these spectroscopic studies have not only highlighted doubts in the proposed mechanism of Ishii for the reaction of NHPI and alkanes, but also showed that a good hydrogen atom abstractor can be characterised by a low nitrogen hyperfine coupling constant, as illustrated on comparing the \(a_N\) values of TEMPO and PINO (Table 2).
RESULTS AND DISCUSSION
2.1 INTRODUCTION

The foregoing introduction has hopefully highlighted several important features of hydrocarbon autoxidation and in particular how the problematic lack of reactivity of the hydroperoxy radical as an efficient hydrogen atom abstractor has been circumvented either through the use of cobalt salt or, in more recent times by the introduction of $N$-hydroxyphthalimide (NHPI) by the Ishii group. This latter reagent in fact can be said to form a cornerstone of our own research efforts to develop a high conversion, high selectivity alkane autoxidation process employing molecular oxygen as the oxidant.

From the outset, as already highlighted in the introductory review, we were concerned by the proposed mechanisms for the operation of PINO on purely thermodynamic grounds. We therefore elected to clarify and understand the Ishii alkane oxidation system based on NHPI and to approach this study on two simultaneous fronts.

In the first instance, on the metal free system for alkane oxidation using NHPI in the presence of tetra-$n$-butylammonium bromide and a trace of water our attention was therefore concentrated. In the second approach, we also decided to carry out a rapid screening for NHPI replacements in the hope that alternative electron withdrawing groups adjacent to the nitroxide moiety would also enhance the alkoxyl radical character and hence facilitate hydrogen atom abstraction from an alkane, as outlined in the introduction (*vide supra* page 30, Figure 6).

For reasons of clarity these two contrasting approaches have been divided into two distinct sub sections in the present chapter, although it should be appreciated that contemporaneous work in both areas was always ongoing throughout.
2.2 THE "ONIUM SALT" EFFECT

2.2.1 Observations on the anionic component of the onium salt in Ishii’s system and related oxidations

As we have previously discussed in the introduction, Ishii discovered that PINO was a good radical catalyst for the oxidation of different hydrocarbon substrates in the presence of molecular oxygen and a small amount of metal complex. However, of particular interest to us within this area was a publication which appeared in 1999, in which the Ishii group found that a quaternary ammonium bromide accelerated the NHPI-catalysed aerobic oxidation even in the absence of any metal catalyst. In particular, the oxidation of adamantane in 73% conversion was reported, employing 10 mol% of NHPI and 2 mol% of tetra-n-butylammonium bromide in a mixture of trifluorotoluene and water (Scheme 33).

![Scheme 33](image)

Intriguingly, the presence of very low concentration of water in this system was absolutely critical, and any deviation in its percentage resulted in lower conversion (Table 3).

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</tr>
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<td>13</td>
</tr>
<tr>
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<td>Bu₄NBr</td>
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<td>Bu₄NBr</td>
<td>PhCF₃/H₂O (6/0.01)</td>
<td>40</td>
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<tr>
<td>5</td>
<td>Bu₄NBr</td>
<td>PhCF₃/H₂O (6/0.06)</td>
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</tbody>
</table>

[Aerobic oxidation of adamantane (2 mmol) in the presence of NHPI (10 mol%) and additive (2 mol%) at 80°C for 6 hours.]^{51}

Table 3
As can be seen from Table 3, the amount of water is a very sensitive parameter and indeed our first attempts to repeat this reaction (Entry 3, Table 3) under Ishii's conditions, failed when using reagents without any purification.

However, the same results as Ishii were obtained by working on a larger scale (8 mmol of starting material in 20 ml of trifluorotoluene) and by using recrystallised tetra-n-butylammonium bromide, scrupulously dry glassware and dry trifluorotoluene. This reaction worked however without adding the required amount of water (0.12 ml), and at a later stage, as demonstrated by the Karl-Fischer analysis on our starting materials, water was shown to be present in small amounts in both adamantane and NHPI.

In this same paper, Ishii noted that the decomposition of cumene hydroperoxide occurred in the presence of a catalytic amount of tetra-n-butylammonium bromide (TBAB, 2 mol%) in trifluorotoluene/water (6 ml/0.03 ml) at 80°C whilst in the absence of TBAB, most of the cumene hydroperoxide was recovered unreacted. The fact that Ishii had selected cumene hydroperoxide for his "blank" experiment was however of some concern to us since this hydroperoxide can readily undergo heterolytic decomposition under mild acid conditions (Scheme 34).
Moreover, the "explanation" that the role of the phase-transfer catalyst (PTC) could be to act as a surfactant to generate reverse micelles in the mixed solvent (trifluorotoluene/water), was not entirely convincing to us from a mechanistic standpoint and a series of experiments was therefore carried out in which the concentrations of all substrates were varied in order to further elucidate the role of the phase-transfer catalyst and water.

An important observation about the importance of the PTC was made in the reaction performed without tetra-\(n\)-butylammonium bromide (TBAB), where a conversion of only 17.5%, was obtained (Scheme 35).

\[
\text{Scheme 35}
\]

With TBAB and no \(N\)-hydroxyphthalimide, the reaction did not proceed even when a catalytic amount of phosphotungstic acid was added (Scheme 36).\(^{[49]}\)

\[
\text{Scheme 36}
\]

In the system of Scheme 33, the amount of water is so insignificant that it is reasonable to believe in another mechanism based on the necessity for the ammonium salt. For example, the \(N\)-oxy radical (PINO) may be responsible for the removal of one electron from the bromide anion of the phase-transfer catalyst ending with the formation of a bromine atom. This could then initiate oxidation by hydrogen abstraction from the alkane as shown in Scheme 37.
Results and Discussion

We therefore reasoned that if NHPI acts in this way, it could be replaced by an organic peroxide, in order to generate in situ the species Br⁻. Hence, we decided to carry out an investigation to find a suitable reagent.

The conversion of adamantane using different initiators containing a peroxide link was therefore studied (t-butyl hydroperoxide, t-butyl perbenzoate, t-butyl peroxide).

In an initial study, prior to incorporation of an internal standard for the conversion, the best result was achieved in 24 hours using tert-butyl perbenzoate but the main problem, in this case, was the formation of undesired benzoic acid and other side products (Scheme 38, Table 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-OO-R'</th>
<th>31(%)</th>
<th>32(%)</th>
<th>33(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tBu-OOCOPh</td>
<td>70.5</td>
<td>21.1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>tBu-OOH</td>
<td>72</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>tBu-OO-But</td>
<td>78</td>
<td>15</td>
<td>1.7</td>
</tr>
</tbody>
</table>

(In the Table 4, the reported % were not selectivities but the ratios presented in the gas-chromatogram.)
Results and Discussion

For this reason, in our further studies we decided to use an 80% solution of tert-butyl hydroperoxide in di-tert-butyl peroxide as initiator.

At this stage our initial mechanistic hypothesis could be formulated as summarised in the following series of equations (Scheme 39):

\[
\text{Eq.29} \quad R_2\text{CHOH} \quad \rightarrow \quad R_2\text{CHO}^- + Q^+\text{OH}^- + X^-
\]

\[
\text{Eq.30} \quad R_2\text{CHO}^- + R_2\text{CH}_2 \quad \rightarrow \quad R_2\text{CHOH} + R_2\text{CH}^-
\]

\[
\text{Eq.31} \quad R_2\text{CHO}^- + X^- \quad \rightarrow \quad R_2\text{C}=\text{O} + \text{HX}
\]

\[
\text{Eq.32} \quad Q^+\text{OH}^- + \text{HX} \quad \rightarrow \quad X^+Q^- + \text{H}_2\text{O}
\]

(\text{where } Q^+ = \text{Quaternary ammonium cation, } X^- = \text{Halide})

\text{Scheme 39}

The key step represented in Eq. 29 requires hydrogen bond complex formation between the onium salt and the hydroperoxide. Adducts of this type can be formed between the relatively acidic hydrogen atom of the hydroperoxide and the electron rich "naked" anion of the catalyst. This then triggers homolysis possibly induced by electron transfer from the halide counterion and thus resulting in the production of the desired alkoxy radical and the free halogen atom. The thermodynamic driving force for this reaction presumably comes from the formation of the quaternary ammonium hydroxide. The new alkoxy radicals formed via Eq. 29 can then react in two parallel routes; either by hydrogen abstraction from an available donor (e.g. the hydrocarbon) to yield an alcohol and an alkyl radical (Eq. 30) or by reaction with another radical (e.g. the halogen atom) to yield a ketone and hydrogen halide (Eq. 31). In the final step the onium hydroxide formed in the reaction 29 is neutralised by the acid formed in the reaction 31, to regenerate the catalyst and complete the catalytic cycle (Eq. 34).

In order to prove our hypothesis of bromine atom formation, the entire range of tetra-
\text{n}-butylammonium halides was tested. Trifluorotoluene was chosen again for the high solubility of dioxygen in this medium (Scheme 40, Table 5).
Results and Discussion

Scheme 40

<table>
<thead>
<tr>
<th>Entry</th>
<th>PTCe</th>
<th>Conversion (%)</th>
<th>32(^a) (%)</th>
<th>33(^a) (%)</th>
<th>34(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>35</td>
<td>47</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(n)-Bu(_4)NF(^d)</td>
<td>75</td>
<td>43.6</td>
<td>7.76</td>
<td>19.8</td>
</tr>
<tr>
<td>3</td>
<td>(n)-Bu(_4)NCl</td>
<td>54</td>
<td>64</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(n)-Bu(_4)NBr</td>
<td>45</td>
<td>67.5</td>
<td>10.1</td>
<td>21.5</td>
</tr>
<tr>
<td>5</td>
<td>(n)-Bu(_4)NI</td>
<td>31</td>
<td>16.6</td>
<td>8.9</td>
<td></td>
</tr>
</tbody>
</table>

[Reactions were carried out using the conditions of Scheme 40; (a) selectivity; (b) the products were isolated by Flash Chromatography; (c) the conversion was calculated by GC using as the external standard, naphthalene; (d) \(n\)-BuNF was used as a solid after removing THF under reduced pressure, without heating; (e) PTC (phase-transfer catalyst); (V) indicated the presence of 1,3-adamantanol but its selectivity was not determined by the use of an internal standard.]

Table 5

Examination of the results in Table 5 reveals several features of interest and clearly demonstrates that the addition of certain tetra-\(n\)-butylammonium halides can have a very remarkable effect in increasing the overall conversion of the alkane oxidised products relative to the blank experiment (Entry 1, Table 5). The fact that the iodide salt was essentially without influence did not surprise us, since one electron oxidation of iodide anion gives an inert iodine atom, which cannot abstract a hydrogen atom from an alkane (Entry 5, Table 5). The trend exhibited by the remaining halide anions however came as a total surprise and was exactly the opposite to that which would be predicted for a mechanism involving oxidation of halide to halogen atom. In particular, we considered that the formation of a fluorine atom from fluoride anion using a hydroperoxide as oxidant was theoretically impossible and hence that the mechanism proposed in equations 29-32 (Scheme 39) could be conclusively dismissed.
Results and Discussion

At this stage, it is important to underline the characteristics of tetra-n-butylammonium fluoride (TBAF) and in particular the fact that it is very difficult to obtain water-free, decomposing when vigorous conditions are applied. In fact, the fluoride anion in apolar environments is highly receptive to protic compounds: the hygroscopic nature of lipophilic quaternary ammonium salts is well known, and when the aptitude of fluoride anion towards the hydrogen bond cannot be satisfied in a highly anhydrous environment, intramolecular reactions predominate. This frequently results in Hoffman elimination of the quaternary ammonium cation especially for salts that carry a C-H bond β to the ammonium cation, with the formation of 1-butene, tri-n-butylamine 56 and the thermodynamically very stable and weakly basic, bifluoride ion (55) (The hydrogen bond energy for FHF', is 50 Kcal/mol) (Scheme 41).

\[
2 \text{n-Bu}_4\text{N}^+\text{F}^- \rightarrow \text{n-Bu}_4\text{N}^+\text{HF}_2^- + \text{n-Bu}_3\text{N} + \text{CH}_2=\text{CH-CH}_2\text{CH}_3
\]

Scheme 41

The mechanism shown illustrates the ion pair association and the elimination (Scheme 42).

Scheme 42

R. K. Sharma and J. L. Fry\textsuperscript{[68]} studied the stability of TBAF under different conditions and concluded that: “reactions which have been reported to proceed in the presence of the ‘naked’ fluoride ion generated from the ammonium salt, have been probably caused by hydrated fluoride or by a bifluoride ion.” They claimed that storage of dry “TBAF” as a solid under vacuum for 4 days at room temperature, followed by dissolution in THF and immediate examination, showed a FHF’ to an extent of ca. 80%.

P. Cox and others suggested that is possible to prepare anhydrous TBAF, warming up tetra-n-butylammonium fluoride trihydrate at 40°C, under high vacuum.\textsuperscript{[69]}
Results and Discussion

In our own reactions, solid TBAF had been used which had been isolated from a commercially available 1 M solution of TBAF in tetrahydrofuran. The THF had been removed under reduced pressure (15 mmHg) over a period of 30 minutes without heating, and the derived solid was stored in a desiccator. The reagent had been placed on the high vacuum for few minutes before use and added direct to the vessel. Even if we carefully prepared the material, it appeared impossible to us to control the extent of the formation of the bifluoride anion considering that the subsequent oxidations were performed at 80°C for 3 days.

Certainly, the reproducibility of the reaction after one year, using the same batch of tetra-n-butylammonium fluoride, does not suggest the predominance of the elimination reaction shown in Scheme 41, at least at room temperature. In addition, when we reproduced part of the environment of Scheme 41 by testing the influence of an added tertiary amine base, a lower conversion was observed (40%) (Scheme 43).

\[
\text{Scheme 43}
\]

Moreover, if the amount of base was increased to 1 equivalent, only traces of the desired products were detected by GC.

At this time, in the absence of any alternative mechanistic hypothesis, and since the best conversion had been observed in the presence of tetra-n-butylammonium fluoride, we decided to investigate, in a pure empirical way, how different types of fluoride could influence the reaction. In particular, the oxidation of adamantane in the presence of tert-butyl hydroperoxide was analysed using different catalysts all of which contained potential sources of fluoride (Scheme 44).

\[
\text{Scheme 44}
\]
Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>PTC</th>
<th>Conv. (%)</th>
<th>32(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>33(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>34(%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu&lt;sub&gt;4&lt;/sub&gt;NF</td>
<td>75</td>
<td>43.6</td>
<td>7.76</td>
<td>19.8</td>
</tr>
<tr>
<td>2</td>
<td>DAST</td>
<td>33</td>
<td>33</td>
<td>10</td>
<td>√</td>
</tr>
<tr>
<td>3</td>
<td>TAS-F</td>
<td>63</td>
<td>35</td>
<td>23</td>
<td>√</td>
</tr>
<tr>
<td>4</td>
<td>TBAT</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>KF</td>
<td>traces</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Bu&lt;sub&gt;4&lt;/sub&gt;NBF&lt;sub&gt;4&lt;/sub&gt;</td>
<td>63.6</td>
<td>50</td>
<td>14.5</td>
<td>√</td>
</tr>
<tr>
<td>7</td>
<td>Bu&lt;sub&gt;4&lt;/sub&gt;NBF&lt;sub&gt;4&lt;/sub&gt;/H&lt;sub&gt;2&lt;/sub&gt;O*</td>
<td>60</td>
<td>46</td>
<td>14</td>
<td>√</td>
</tr>
</tbody>
</table>

[Reactions were carried out using the conditions of Scheme 44; (a) selectivity; DAST is (diethylamino)sulfur trifluoride; TAS-F is tris(dimethylamino)sulfur(trimethylsilyl)difluoride; TBAT is tetrabutylammonium triphenyldifluorosilicate; (V) indicated the presence of 1,3-adamantanol but its selectivity was not determined by the use of an internal standard; (*): the added amount of water was 0.1 ml in 20 ml of solvent.]

**Table 6**

From the results in Table 6, the relatively poor performance of DAST would imply that some form of formally anionic fluoride anion source is to be preferred over a covalently bonded fluoride catalyst. This observation is reinforced to some extent by the behaviour of both TAS-F (Entry 3, Table 6) and tetra-n-butylammonium tetrafluoroborate (Entry 6 and 7, Table 6) both of which display a comparable effect although tetrafluoroborate might be expected to be a better source of fluoride anion than the difluorosilicate given both the affinity of fluoride anion for silicon (Si-F) as well as reactions such as the formation of aromatic fluorides from their diazonium tetrafluoroborate salts.

The complete failure of the stable, non-moisture sensitive salt TBAT, tetrabutylammonium triphenyldifluorosilicate (Entry 4, Table 6), however is not readily explained given that the same quaternary ammonium cation is used in Entries 1, 4, 6 and 7 and a sulfonium cation is implicit in the use of DAST. Potential roles for sulphonium cations will be discussed later (Section 2.2.2). Although it is often generalised that naked fluoride anion is more basic in character and that “ate complexes” of fluoride are more nucleophilic, no obvious trend in these terms can be drawn from the above selection of catalysts and both characteristics may be involved to differing degrees in the oxidation reaction.

Due to the inability to obtain completely anhydrous TBAF, as previously discussed, the concentration of water in the system was really difficult to control. We then
introduced a drying agent, such as anhydrous calcium chloride in the reaction vessel. When the reaction was carried out using tetra-\(n\)-butylammonium fluoride and anhydrous calcium chloride as a suspension in trifluorotoluene, the conversion decreased to 50\% (Scheme 45).

\[
\begin{align*}
\text{OH} & \quad \text{t-BuOOH (1 equiv.)} \quad \text{O}_2 \quad \text{Bu}_4\text{NF (0.02 equiv)} \\
& \quad \text{PhCF}_3, 80^\circ\text{C}, 3\text{d} \quad \text{CaCl}_2 \\
\text{31} & \quad \text{OH} & \quad \text{33} & \quad \text{34} \\
& \quad 50\% & \quad 15\% & \quad \text{(conv.50\%)}
\end{align*}
\]

**Scheme 45**

Thus, one again, water had played an essential role in the oxidation and any attempt to work in dry conditions, lowered the conversion.

From an examination of Table 5, it could also be concluded that there is an increase in reactivity from the use of the largest, softest and most polarizable anion (the iodide) to the smallest and the hardest anion (the fluoride) and therefore, that the reaction proceeds in the presence of the most basic ammonium halide.

In order to verify if the basicity of the anion was an important factor, the use of tetra-\(n\)-butylammonium hydroxide and tetra-\(n\)-butylammonium hydrogensulfate were therefore studied (Table 7).

<table>
<thead>
<tr>
<th>Entry (^{c})</th>
<th>PTC</th>
<th>Conversion (^a)</th>
<th>32 (^b)</th>
<th>33 (^b)</th>
<th>34</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n-Bu_4\text{NOH} ) (^d)</td>
<td>48</td>
<td>29.8</td>
<td>8</td>
<td>(\checkmark)</td>
</tr>
<tr>
<td>2</td>
<td>(n-Bu_4\text{NOH} ) (^e)</td>
<td>66</td>
<td>35.54</td>
<td>5.6</td>
<td>(\checkmark)</td>
</tr>
<tr>
<td>3</td>
<td>(n-Bu_4\text{NSO}_4)</td>
<td>38</td>
<td>41.8</td>
<td>5</td>
<td>(\checkmark)</td>
</tr>
</tbody>
</table>

[Reactions were carried out using the conditions of Scheme 44; \(a\) conversion was calculated using as an internal standard, 1,2,4-trichlorobenzene; \(b\) selectivity; \(c\) adamantane was allowed to react in the presence of PTC (phase-transfer catalyst) (0.02 equiv.), \(t\)-butyl hydroperoxide (1 equiv.) in trifluorotoluene at 80\(^\circ\)C for three days; \(d\) 60\% tetra-\(n\)-butylammonium hydroxide in water; \(e\) tetra-\(n\)-butylammonium hydroxide solid after freeze dryer (see Experimental Part); \(\checkmark\) indicated the presence of 1,3-adamantanol but its selectivity was not determined by the use of an internal standard.]
Results and Discussion

From the results in Table 7, it can be seen that a good conversion was achieved in the presence of the hydroxide when it was used as a solid (Entry 2, Table 7) but not as an aqueous solution (Entry 1, Table 7). However, the yield was lower compared to that performed with fluoride (Entry 2, Table 5). The even less basic hydrogensulfate anion proved to be the least effective in this series (Entry 3, Table 7).

The reactivity of a different ammonium hydrogensulfate salt was also tested by preparing methyltri-\(n\)-octylammonium hydrogen sulfate (59) used by Noyori, under biphasic conditions in the presence of hydrogen peroxide 30% and a tungsten catalyst for converting aldehydes to carboxylic acids and secondary alcohols to ketones. The catalyst was isolated in 84% yield by reacting tri-\(n\)-octyl amine with dimethyl sulfate (Scheme 46).

\[
\begin{align*}
[\text{CH}_3(\text{CH}_2)_{13}\text{N}]^+ + \text{MeO}^+ \rightarrow [\text{CH}_3(\text{CH}_2)_{13}\text{N}]^+ \\
\text{SO}_3^- \rightarrow \text{Me}^+ \text{SO}_4^- \\
\end{align*}
\]

Scheme 46

Working under standard conditions in the presence of 59, a 57.5% conversion was achieved (Scheme 47).

Finally, tetraphenylborate counteranions were also considered but observed conversions were ca. 40%, even when water (0.1 ml for 20 ml of solvent) was added (Scheme 48, Table 8).

\[
\begin{align*}
\text{OH} + \text{O}_2 (1 \text{ atm}) & \rightarrow \text{OH} + \text{HO} \\
\text{PhCF}_3, 80^\circ\text{C}, 3\text{d} & \rightarrow \text{OH} + \text{HO} \\
\text{t-BuOOH (1 equiv.)} & \rightarrow \text{OH} + \text{HO} \\
\text{Bu}_4\text{N}^+ \text{X}^- (0.02 \text{ equiv}) & \rightarrow \text{OH} + \text{HO} \\
\end{align*}
\]

Scheme 48
Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conversion (%)</th>
<th>32(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>33(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>34(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₄B</td>
<td>34</td>
<td>51</td>
<td>18</td>
<td>✓</td>
</tr>
<tr>
<td>2</td>
<td>Ph₄B/H₂O</td>
<td>43</td>
<td>56</td>
<td>17</td>
<td>✓</td>
</tr>
</tbody>
</table>

[The Table is related to Scheme 48 using 8 mmol of substrate; (a) selectivity; (✓) indicated the presence of 1,3-adamantanol but its selectivity was not determined by the use of an internal standard.]

Table 8

2.2.2 The nature of the onium salt cation

Although no reference was made by Ishii to the fact that the cationic counterion could also play a possible role in contributing to the overall function of the “onium salt effect”, careful examination of the literature had led us, at an early stage of our work, to a seminal study by Ohkubo on the catalytic effect of sulfonium salts in cumene autoxidation, which had predated the work of Ishii by 30 years.<sup>[73-74]</sup>

\[
\begin{align*}
R_3S^+ X^- + HOOR' & \rightleftharpoons R_3S^{-} HO^+ OR' \xrightarrow{X^-} R_3S-OOR' + HX \quad \text{Eq. 33} \\
R_3S^+ X^- + HOOR' & \rightleftharpoons R_3S^+ + HX + 'OR' \xrightarrow{X^-} R_3S-OOR' \quad \text{Eq. 34} \\
R_3S-OOR' & \quad \rightarrow \quad R_3SO^- + 'OR' \quad \text{Eq. 35} \\
60 & \quad \rightarrow \quad 61 \\
R_3SO^- + H-R' & \quad \rightarrow \quad R_3SOH + 'R' \quad \text{Eq. 36} \\
R_3SOH + HX & \quad \rightarrow \quad R_3S^+ X^- + H_2O \quad \text{Eq. 37}
\end{align*}
\]

Scheme 49

The mechanistic rationale developed by Ohkubo and further studied by Tilborg, is set out in Scheme 49<sup>[75]</sup> and involves initial reaction of the sulfonium salt with cumene hydroperoxide via either Eq. 33 or Eq. 34 to form the perester 60. As both of these reactions involve a deprotonation step, the anion X must function as a base. The perester then rapidly undergoes homolysis (Eq. 35) to generate a cumyloxy radical and a radical 61 which is responsible for the hydrogen abstraction from the
Results and Discussion

The catalytic activity was measured by Ohkubo as the amount of oxygen (mmoles) taken up by 10 ml of cumene, containing 0.02 mmol of catalyst, after 4 hours at 85°C.
The lowest vacant atomic orbitals of central atoms of onium cations

<table>
<thead>
<tr>
<th></th>
<th>Central Atom</th>
<th>Atomic Orbitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>N</td>
<td>O</td>
</tr>
<tr>
<td>2p</td>
<td>3s</td>
<td>3s</td>
</tr>
<tr>
<td>Si</td>
<td>P</td>
<td>S</td>
</tr>
<tr>
<td>3p</td>
<td>4s, 3d</td>
<td>4s, 3d</td>
</tr>
<tr>
<td>As</td>
<td>Se</td>
<td></td>
</tr>
<tr>
<td>5s, 4d</td>
<td>5s, 4d</td>
<td></td>
</tr>
<tr>
<td>Te</td>
<td>6s, 5d, 4f</td>
<td></td>
</tr>
</tbody>
</table>

Table 10

The partial occupation of the $d$ orbital may be influenced by substituents. The charge of a $d$ orbital will be increased by electron-donor groups like methyl and ethyl or larger alkyls attached to the central atom, whereas it will be decreased by such groups as phenyl or $p$-fluorophenyl, so that the interaction of a $d$ orbital with oxygen may be weakened. The order of reactivity, according to this study was:

- carbonium $< \text{ammonium < oxonium}$
- silyl $< \text{phosphonium} \leq \text{sulfonium}$
- arsonium $\leq \text{telluronium < selenonium}$

It was found that triphenylsulfonium phosphate and sulfate were more effective than triphenylsulfonium halides in the initial step of oxidation.

In respect, of the fact that we could not bring ourselves to violate the octet rule and to believe in five valent nitrogen intermediates (or indeed similar congeners from oxygen), we considered that, for the case of sulfur and other atoms possessing vacant $d$ orbitals, such homolytic dissociation of hypervalent intermediates could be possible and contribute an extra dimension to the onium salt effect.

We therefore decided to prepare some sulfonium salts and, after several attempts, the synthesis of triphenylsulfonium bromide (63) was achieved starting from phenylmagnesium bromide and diphenyl sulfoxide in refluxing benzene, followed by acidic workup, crystallisation and further recrystallisation (Scheme 50).[77]
Results and Discussion

The oxidation of adamantane in the presence of a catalytic amount of triphenylsulfonium bromide was carried out under the conditions previously described for ammonium salts, but a conversion of only 38% was observed (Scheme 51).

We were very surprised indeed by this lower conversion and as result, we started to analyse the different characteristics of the two salts (Ph3SBr and Bu₄NF). As previously mentioned, the tetra-n-butylammonium fluoride is a highly hygroscopic salt, whereas triphenylsulfonium bromide is not sensitive to moisture. We therefore reasoned that the key to the relative lack of reactivity could be related to the amount of water.

The same reaction was therefore performed in the presence of water (0.1 ml in 20 ml of solvent) and the conversion (for 8 mmol of substrate) increased from 38% to 75% (Scheme 52).
Results and Discussion

Clearly, one again, the amount of water is, therefore, crucial for this reaction! Consequently, different quantities of water in the presence of triphenylsulfonium bromide and tert-butyl hydroperoxide at 80°C in trifluorotoluene were added to the system (Scheme 53), and the conversions were monitored by GC (Table 11).

31 + O₂ (1 atm) → t-BuOOH (1 equiv.) → PhCF₃, 80°C, 3d → PhSBr (0.02 equiv) → H₂O (A/B/C)

<table>
<thead>
<tr>
<th>time</th>
<th>Reaction</th>
<th>Conversion (%)</th>
<th>32 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>33 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1d</td>
<td>A/B/C</td>
<td>55/34/44.5</td>
<td>40/59/52</td>
<td>15/23/20</td>
</tr>
<tr>
<td>2d</td>
<td>A/B/C</td>
<td>65/50/53</td>
<td>40/42/43</td>
<td>15/16/17</td>
</tr>
<tr>
<td>3d</td>
<td>A/B/C</td>
<td>78/51/58</td>
<td>40/43/43</td>
<td>15/16/17</td>
</tr>
</tbody>
</table>

[The Table is related to Scheme 53 where 8 mmol of substrate were reacted in 20 ml of solvent; (a) selectivity; A: To the reaction mixture was added 0.1 ml of water; B: To the reaction mixture was added 0.2 ml of water; C: To the reaction mixture was added 0.3 ml of water.]

Table 11

The best overall conversion was achieved in the presence of 0.1 ml of water and any increase or decrease was not beneficial.

It is important to underline again that even for Ishii, the water had a key role in the system of N-hydroxyphthalimide and tetra-n-butylammonium bromide (Table 3). In recent papers, L. J. Csányi and K. Jaki<sup>[78-79]</sup> showed that water catalysed the reaction but that catalysis ceases when water is in excess, since water forms a separate phase. Because the solubility of water increases with rising temperature in the case of aromatic solvents such as chlorobenzene, the protons of the water interact with the π-electrons of the aromatic ring. This type of complex formation counteracts the self-association of water, resulting in an increase in the concentration of single and less-associated water molecules in such nonpolar aromatic liquids. The presence of water causes the micelles to swell and to assume different shapes and hence their kinetic behaviour is altered.
Furthermore, according to a report by Fendler,\textsuperscript{[80]} the most important difference between aqueous and reversed micelles is that substrates do not penetrate appreciably into the former, but if substrates are polar, they are localized in the hydrophilic cavities of the reversed micelles. In an attempt to avoid the formation of such associated water, which could decrease the conversion of the reaction, we consequently returned to our ammonium salt system and carried out a single experiment wherein we introduced an excess of TBAF in the reaction (Scheme 54).

$$\text{f-BuOOH (1 equiv.)} + \text{O}_2 \xrightarrow{\text{PhCF}_3, 80^\circ\text{C, 3d}} \text{Bu}_4\text{NF (excess)} \rightarrow \text{32 (54\%)} + \text{33 (11\%)} + \text{34 (present)}$$

\textbf{Scheme 54}

However, the use of this excess led to 60\% conversion as compared to the 75\% obtained under the standard conditions (Scheme 40) indicating that the excess was unwarranted.

In our preliminary overview of the sulfonium salt effect, we were particularly intrigued by the suggestion that the triphenylsulfoxyl radical species (Ph$_3$S-O') served in the key role of hydrogen atom abstraction from the alkane to achieve propagation. This proposition, when combined with the knowledge that many free radical reactions such as the chemistry of Barton esters\textsuperscript{[81]} shown in Scheme 55 involve homolysis of the N-O bond encouraged us to carry out a reaction involving the use of the sulfonium salt in the presence of $N$-methylmorpholine-$N$-oxide (NMO).
Results and Discussion

The essence of our idea is shown in Scheme 56 whereby formation of the aza analogue of the perester would be followed by homolysis to give not only the triphenylsulfoxyl radical but also an aminium radical cation which is also known to be capable of hydrogen atom abstraction from alkanes (Hoffmann-Löffler reaction\textsuperscript{82-83}).

The oxidation of adamantane in the presence and in the absence of tert-butyl hydroperoxide was therefore studied by also introducing 0.02 equiv. of NMO into the system (Scheme 57, Table 12).
Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conversion (%)</th>
<th>32(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>33(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>34(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuOOH (1 equiv)</td>
<td>48</td>
<td>50</td>
<td>17</td>
<td>V</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOOH/H&lt;sub&gt;2&lt;/sub&gt;O (1 eq./0.1 ml)</td>
<td>65</td>
<td>37</td>
<td>13</td>
<td>V</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

[The Table is related to Scheme 57 where 8 mmol of substrate were reacted in 20 ml of solvent; (a) selectivity; (V) indicated the presence of 1,3-adamantanone but its selectivity was not determined by the use of an internal standard.]

**Table 12**

In the event that the reaction was run in the absence of tert-butyl hydroperoxide, no conversion was detected (Entry 3, Table 12). In the case of the use of t-BuOOH, 65% conversion was achieved when working with 0.1 ml of water (Entry 2, Table 12). Thus, the use of NMO did not increase the conversion and no further experiments in this area were performed.

The systematic analysis of different sulfonium salts was then carried out. Thus, the alkyl sulfonium bromide, trimethylsulfonium bromide, was tested in our system both in the absence and in the presence of water (Entry 1 and 2, Table 13). A lower conversion, when compared to triphenylsulfonium bromide, was observed and this result can be explained by the fact that the resulting trimethylsulfoxyl radical cannot be stabilised in the same way by aromatic groups.

Moreover, in view of the vacant d orbitals of phosphorus, we also examined the oxidation of adamantane in the presence of tetraphenylphosphonium bromide and tetra-n-butylphosphonium bromide. In both cases however, the yields were lower compared to the triphenylsulfonium salt. The overall results are summarized in Table 13, Scheme 58.

![Scheme 58](image-url)
Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>PTC</th>
<th>Conversion(%)</th>
<th>32(%)</th>
<th>33(%)</th>
<th>34(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me$_3$SBr</td>
<td>50</td>
<td>44</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Me$_3$SBr/H$_2$O*</td>
<td>43</td>
<td>58</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ph$_4$PBr</td>
<td>49</td>
<td>45</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph$_4$PBr/H$_2$O*</td>
<td>31.6</td>
<td>68.1</td>
<td>23.3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Bu$_4$PBr</td>
<td>28</td>
<td>65</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Bu$_4$PBr/H$_2$O*</td>
<td>37</td>
<td>53</td>
<td>18.5</td>
<td></td>
</tr>
</tbody>
</table>

[Reactions were carried out using the conditions of Scheme 58 where 8 mmol of substrate were reacted in 20 ml of solvent; (*): the added amount of water was 0.1 ml; (a) selectivity; (V) indicated the presence of 1,3-adamantanol but its selectivity was not determined by the use of an internal standard.]

Table 13

At this time, from a purely practical standpoint, we conclude that triphenylsulfonium bromide and tetra-$n$-butylammonium fluoride or hydroxide, are the best catalysts for the oxidation of adamantane in trifluorotoluene at 80°C, in the presence of 1 equivalent of tert-butyl hydroperoxide.

2.2.3 Decomposition studies using tert-butyl hydroperoxide

From the foregoing experimental observations, it is clear that an onium salt effect certainly exists and that is responsible for the decomposition of tert-butyl hydroperoxide.

The half-life of this hydroperoxide$^{[84]}$ is 10 hours at 172°C (or 1 hour at 210°C) and thus it does not undergo any significant thermal decomposition at only 80°C. Since oxidation of adamantane was observable after a few hours following the addition of tert-butyl hydroperoxide, and thermal degradation of the peroxide alone is unlikely, another factor must be the responsible for the overall efficiency.

In order to investigate the role of the salt, we tested if any reaction occurred between tert-butyl hydroperoxide and tetra-$n$-butylammonium fluoride or triphenylsulfonium bromide in a trifluorotoluene solution. The disappearance of tert-butyl hydroperoxide was followed by titration in acetic acid using a standard solution of sodium thiosulphate and sodium iodide, according to Equations 38 and 39 (Scheme 59).
In particular, tert-butyl hydroperoxide (1 equiv.) was stirred in trifluorotoluene at 80°C under the usual oxidation conditions, i.e. for three days in the presence of the PTC (0.02 equiv.), and at the end of this period, the titration was carried out under a nitrogen atmosphere to avoid autoxidation of iodide (Scheme 60).

![Scheme 60](image)

**Table 14**

<table>
<thead>
<tr>
<th>Additive</th>
<th>Initial Concentration (M)</th>
<th>Final Concentration (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu₄NF</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Ph₃SBr*</td>
<td>0.4</td>
<td>0.002</td>
</tr>
</tbody>
</table>

[Reactions were carried out using the conditions of Scheme 60; (*): water (0.05 ml) was added to the system which contained 4 mmol of tert-butyl hydroperoxide and 0.08 mmol of triphenylsulfonium bromide in 10 ml of PhCF₃.]

Thus, from an initial concentration of 0.4 M of tert-butyl hydroperoxide in trifluorotoluene, after 3 days it decreased to 0.002 M in the presence of the sulfonium salt and to 0.1 M in the presence of the ammonium salt. When the same experiment was carried out in the absence of the phase-transfer catalysts, the concentration remained constant during this time, as expected from the above half-life.

From these simple titrations, it was possible to conclude that the decomposition of the hydroperoxide was significantly accelerated in the presence of phase-transfer catalysts.
Results and Discussion

However, in order to formulate a mechanism, it would be desirable to analyse and quantify the decomposition products from tert-butyl hydroperoxide. For ease of product isolation we decided to prepare the steroidal tertiary and secondary hydroperoxy derivatives shown in Scheme 61.

Thus, singlet oxygenation of 3β-hydroxy-cholest-5-ene (cholesterol) gave the hydroperoxide, 3β-hydroxy-5α-hydroperoxycholest-6-ene (65) which in chloroform at room temperature, rearranged into 3β-hydroxy-7α-hydroperoxycholest-5-ene (66) (Scheme 61).[85-87]

![Scheme 61](image)

Initially, the product isolation was attempted using trifluorotoluene as solvent, but unfortunately the cholesterol derivatives were not soluble, and so the "choice" of methanol was enforced.

Disappointingly, the reaction of 65 in the presence of a catalytic amount of tetra-n-butylammonium fluoride (0.02 equiv.), at room temperature led only to a low conversion to 66 and even if the temperature was increased, no further decomposition products were detected (Scheme 62).
Additionally, when the secondary hydroperoxy-cholest-5-ene derivative (66) was refluxed for 24 hours in the presence of the tetra-<sup>n</sup>-butylammonium fluoride, it was possible to identify by NMR only a small amount of the ketone (67), which could not be quantified (Scheme 63).

The very slow decomposition of 65 and 66 may be dominated by the use of methanol as solvent as well as the different skeletal type of hydroperoxide (cholesterol against tert-butyl), and hence this comparison was not extended further.

### 2.2.4 Observations on the behaviour of di-tert-butyl peroxide

As previously mentioned, several different peroxide linkages were tested (<i>t</i>-butyl hydroperoxide, <i>t</i>-butyl perbenzoate and <i>t</i>-butyl peroxide) (0.02 equiv.) for the oxidation of adamantane in the presence of tetra-<i>n</i>-butylammonium fluoride at 80°C and the 80% solution of tert-butyl hydroperoxide in tert-butyl peroxide gave the best yield.
Results and Discussion

Since the half-life for the tert-butyl peroxide (1 hour at 150°C) present as a contaminant was lower when compared to the hydroperoxide (1 hour at 210°C), we considered that it was necessary to perform the oxidation in the presence of 1 equivalent of tert-butyl peroxide. In fact, this species could be the real initiator for the autooxidation, even if present only as 20% in the original mixture of tert-butyl hydroperoxide.

When these reactions were performed, a 59% conversion was observed for the case of Bu₄NF and the 70% conversion for Ph₃SBr was comparable to that achieved using the hydroperoxide (Scheme 64, Table 15).

![Scheme 64]

<table>
<thead>
<tr>
<th>Entry</th>
<th>PTC</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu₄NF</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu₄PBr</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Ph₃SBr/H₂O*</td>
<td>65-70</td>
</tr>
</tbody>
</table>

[The Table is related to Scheme 64 where 8 mmol of substrate were reacted in 20 ml of solvent; (*): the added amount of water was 0.1 ml.]

Table 15

These observations were of some mechanistic concern, since, although the reactions proceeded in high yield, the transition state proposed in Scheme 49 requires a hydroperoxide and cannot be applied to tert-butyl peroxide. Moreover, from a practical standpoint, we discovered some difficulties in reproducing the oxidation. After many different attempts, we realised that the treatment of the glassware could be responsible for the decomposition of the peroxide and this could, in turn, account for the reproducibility of the reaction.

In fact, in order to negate the presence of any metals in the reaction vessel, all flasks had been routinely washed with a Base Bath (potassium hydroxide and methanol) followed by rinsing with a 2N HCl solution.
Results and Discussion

In the ideal world, using different solutions (acid, base or hexamethyldisilazane) for washing the glassware, should have led to similar conversions. In reality, whilst, the reactions in the presence of tert-butyl hydroperoxide were not affected by the surface of the flask (Scheme 65, Table 16), those involving tert-butyl peroxide achieved a good conversion only in the presence of acid-washed glassware (Scheme 66, Table 17).

![Scheme 65](image)

**Table 16**

<table>
<thead>
<tr>
<th>Time</th>
<th>HCl solution</th>
<th>KOH solution</th>
<th>HMDS sol. 10%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1d</td>
<td>31%</td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td>2d</td>
<td>32%</td>
<td>35%</td>
<td>39%</td>
</tr>
<tr>
<td>3d</td>
<td>43%</td>
<td>43%</td>
<td>44%</td>
</tr>
</tbody>
</table>

[The Table is related to Scheme 65 where 8 mmol of substrate were reacted in 20 ml of solvent containing 0.1 ml of water; (*): in the case of HMDS a 10% solution in diethyl ether was prepared.]

![Scheme 66](image)

**Table 17**

<table>
<thead>
<tr>
<th>Time</th>
<th>HCl solution</th>
<th>KOH solution</th>
<th>HMDS sol. 10%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1d</td>
<td>30%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>2d</td>
<td>47%</td>
<td>3.4%</td>
<td>16%</td>
</tr>
<tr>
<td>3d</td>
<td>59%</td>
<td>17.8%</td>
<td>39%</td>
</tr>
</tbody>
</table>

[The Table is related to Scheme 66 where 8 mmol of substrate were reacted in 20 ml of solvent containing 0.1 ml of water; (*): in the case of HMDS a 10% solution in diethyl ether was prepared.]
In order to understand why the reaction with the peroxide alone is influenced by the acidity of the glass, we can consider that three different surfaces of the glass are produced under the three different conditions employed, as exemplified in the following diagrams (Figure 7).

Thus, when the surface of the glass provides residues SiOH (as in the case of acid treatment), protonation of the oxygen of the peroxide can occur and subsequent elimination can then lead to formation of tert-butyl hydroperoxide and isobutylene (Scheme 67).

Hence, even for those reactions carried out in the presence of tert-butyl peroxide, it is possible to apply the same mechanism shown in Scheme 49, because in both cases, tert-butyl hydroperoxide is the active molecule responsible for the oxidation.

However, by a comparison between the two blank experiments (Entry 1 and 2, Table 18), which were conducted in the absence of the onium salts it was possible to achieve higher conversion for the oxidation in the presence of tert-butyl hydroperoxide when compared to tert-butyl peroxide (Scheme 68, Table 18).
Results and Discussion

Scheme 68

<table>
<thead>
<tr>
<th>Entry</th>
<th>ROOR'</th>
<th>PTC</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuOOH</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOO-Bu-t</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOOH</td>
<td>Bu₄NF</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>t-BuOO-Bu-t</td>
<td>Bu₄NF</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOOH</td>
<td>Ph₃SBr/H₂O</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>t-BuOO-Bu-t</td>
<td>Ph₃SBr/H₂O</td>
<td>65-70</td>
</tr>
</tbody>
</table>

[The Table is related to Scheme 68 where 8 mmol of substrate were reacted in 20 ml of solvent containing 0.1 ml of water when reported.]

Table 1

These data seemed to imply the necessity, at least in the first part of the reaction for several molecules of hydroperoxide which could be hydrogen bonded either to the surface of the glass or other molecules catalysing the reaction whilst in the reaction with tert-butyl peroxide, only discrete molecule of hydroperoxide would derive via protonation of the oxygen as described in Scheme 67. However, when onium salts were introduced in the system, similar conversions (Entries 3-6, Table 18) had been observed.

2.2.5 The use of ionic liquids as phase-transfer catalysts

At the present time there is a considerable interest in the use of ionic liquids, which are of course, particular examples of onium salts. They are generally prepared by quaternisation of amines and phosphines and can present very different properties depending on the nature of the counterion.

In consequence, we decided to investigate the influence of a catalytic amount of an ionic liquid in our oxidative system. Two ionic liquids were chosen, both of which contained a quaternary nitrogen atom and a counteranion incorporating fluoride. The 1-n-butyl-3-methyl imidazolium tetrafluoroborate and hexafluorophosphate were
thus prepared by anion exchange (Scheme 69). Both of these salts have weak coordination properties and are slightly acidic.

![Scheme 69](image)

**Scheme 69**

When the reaction in the presence of 69 or 70 and tert-butyl hydroperoxide was performed, 50 % and 40 %, conversion, were observed respectively (Scheme 70, Table 19).

![Scheme 70](image)

**Table 19**

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conversion(%)</th>
<th>32(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>33(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>34(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF&lt;sub&gt;4&lt;/sub&gt;</td>
<td>53</td>
<td>58</td>
<td>16</td>
<td>⚫</td>
</tr>
<tr>
<td>2</td>
<td>BF&lt;sub&gt;4&lt;/sub&gt;/H&lt;sub&gt;2&lt;/sub&gt;O*</td>
<td>52</td>
<td>53</td>
<td>19</td>
<td>⚫</td>
</tr>
<tr>
<td>3</td>
<td>PF&lt;sub&gt;6&lt;/sub&gt;</td>
<td>40</td>
<td>63</td>
<td>13.4</td>
<td>⚫</td>
</tr>
<tr>
<td>4</td>
<td>PF&lt;sub&gt;6&lt;/sub&gt;/H&lt;sub&gt;2&lt;/sub&gt;O*</td>
<td>32</td>
<td>80</td>
<td>17.7</td>
<td>⚫</td>
</tr>
</tbody>
</table>

[This Table is related to Scheme 70 where 8 mmol of substrate were reacted in 20 ml of solvent; (a) selectivity; (*): 0.1 ml of water was added (✓) indicated the presence of 1,3-adamantanol but its selectivity was not determined by the use of an internal standard.]

Moreover, no increased conversion was observed when 0.1 ml of water was added (Entries 2 and 4, Table 19). Nevertheless, the interesting conclusion may be drawn that charge delocalisation in the cation leads to less efficient onium salt catalysts.
At this juncture, whilst the influence of an added onium salt and the often required necessity for trace amounts of water were undisputed experimental observations in relation to decomposition of tert-butyl hydroperoxide, it was equally apparent that we had yet to understand such phenomena in a mechanistic way. For this reason, our attention was therefore directed towards a more theoretical approach as indicated below.

2.2.6 CDS: Cambridge Crystallographic Database

In order to justify the enhanced reactivity of tert-butyl hydroperoxide, in the presence of quaternary ammonium salts we attempted to examine some relevant crystallographic data.

The starting reference point was taken on the basis of a search carried out from the Cambridge Crystallographic Database (CDS). We analysed the possibility of a relationship between the length of the O-O bond and the torsional angle H-O-O-C ($\Psi$), for established hydroperoxides (Figure 8).

![Figure 8](image)

If, in some cases, an increase in the length of the O-O bond was observed together with a resultant variation in the torsional angle ($\Psi$), we would assume that $\Psi$ could influence the weakness of the bond and as consequence could lead to its homolysis.

A search over all compounds which contained the alignment of R-C-OOH atoms with R equal to any arbitrary structure was performed, and 76 compounds were identified (see Appendix).

The statistical analysis of the O-O bond length and torsional angle over this sample produced an average bond length of 1.462 Å and a torsional angle of 108.441° respectively (Figure 9, Table 20).
Results and Discussion

The only examples which showed a significant deviation from the average value were the peracids with an increase in bond length to 1.48 Å.

However from a chemical standpoint, peracids are a completely different class of compounds, with their own reactivity and therefore of no relevance in the present context.

We therefore concluded that no significant deviation from the average values for the O-O bond were present in the CDS, and that the value of the torsional angle did not seem to have any influence for the elongation of the bond.

2.2.7 Quantum Mechanics Calculations

During the course of our study of the onium salt effect, and despite the fact that their work had not been referenced by the group of Ishii, we became aware that L. J. Csányi and his collaborators,\(^{90}\) in Hungary had also investigated the autoxidation of
cyclohexene, tetralin and cumene in the presence of tert-butyl hydroperoxide, water and tetra-n-hexyl ammonium chloride and observed the critical necessity for both components to achieve the catalytic effect. This group had then gone on to propose the arrangement shown in Figure 10 whereby the electrostatic interaction between the positively charged nitrogen atom of the ammonium cation and the more nucleophilic alkylsubstituted oxygen atom of the hydroperoxide in combination with simultaneous activation of the hydroxyl group of the hydroperoxide through hydrogen bonding formation to water led to the formation of the desired alkoxyl and hydroxyl radicals.

![Figure 10](image)

This mechanism was supported by theoretical calculations using the semi-empirical PM3[91-92] routine, which unfortunately appeared to be lacking in details.

The authors claimed that their calculated increase in the length of the O-O bond from the isolated structure (1.52 Å) to the one considered in the arrangement of Fig. 10 (1.57 Å) could be the necessary factor, which could explain the homolysis of tert-butyl hydroperoxide (Table 21).

For the average organic chemist however, the arrangement shown in Figure 10 is counter intuitive since the two bulky groups are placed in close proximity. In addition, these authors had neglected to examine the role of the negatively charged counterion.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>O-O (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated TBHP</td>
<td>1.52</td>
</tr>
<tr>
<td>TBHP in the system</td>
<td>1.57</td>
</tr>
</tbody>
</table>

Table 21
We therefore considered that a much deeper theoretical investigation was required and, with the help of Prof. D. Clary and Dr. T. Van Mourik, we decided that \textit{ab initio} calculations were desired.

In the event, a simplified model was necessary for such calculations. Thus, tetra-\textit{n}-methylammonium fluoride was chosen instead of the tetra-\textit{n}-butyl one and the geometry was first optimised at the Hartree-Fock (RHF) level using the 6-31G\(^*\) base sets. Subsequent geometry optimisations were performed at the DFT (Density Functional Theory) level using the B3LYP\(^{[93]}\) functional and the 6-31+G\(^*\) basis set, starting from the RHF geometries.

Four different arrangements and geometries were investigated:

1) The isolated molecule of \textit{tert}-butyl hydroperoxide (TBHP).
2) The isolated molecule of Me\(_4\)NF (TMAF).
3) The system formed by the combination of TBHP and Me\(_4\)NF.
4) The system formed by combining TBHP, TMAF and 1 molecule of water.

Thus the sequence of steps taken was as follows.

Figure 11 shows tetra-\textit{n}-methylammonium fluoride and \textit{tert}-butyl hydroperoxide, each one considered as an isolated molecule, in their preferred geometry at the B3LYP level. In Table 22, the lengths of the main bonds are reported in the two different approximations. The isolated structure of \textit{tert}-butyl hydroperoxide shows a value for the O-O bond of 1.39 Å using the B3LYP level of theory, a quite different value compared to the one founded in the HF approximation (1.46 Å). The distance of the fluoride from the nitrogen atom in TMAF is 2.90 Å (HF) or 2.95 Å (B3LYP) according to the two different theories.
Results and Discussion

<table>
<thead>
<tr>
<th>Methods</th>
<th>$N_1-F_{18}$ (Å) in TMAF</th>
<th>$O_2-O_3$ (Å) in TBHP</th>
<th>$O_2-H_1$ (Å) in TBHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>2.90</td>
<td>1.39</td>
<td>0.95</td>
</tr>
<tr>
<td>B3LYP</td>
<td>2.95</td>
<td>1.46</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Table 22

We then optimised the geometry of the system, wherein the combination of tetra-$n$-methylammonium fluoride and tert-butyl hydroperoxide was considered together. A new hydrogen bond, between the fluoride $F_{18}$ and the $H_{21}$ was found but no increase whatsoever in the distance of the $O_{19}-O_{20}$ bond was observed and this can therefore be considered constant (Figure 12, Table 23).

![Figure 12]

<table>
<thead>
<tr>
<th>Methods</th>
<th>$O_{19}O_{20}$ (Å)</th>
<th>$O_{20}H_{21}$ (Å)</th>
<th>$H_{21}F_{18}$ (Å)</th>
<th>$O_{19}N_1$ (Å)</th>
<th>$O_{20}N_1$ (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>1.40</td>
<td>0.99</td>
<td>1.51</td>
<td>4.38</td>
<td>4.26</td>
</tr>
<tr>
<td>B3LYP</td>
<td>1.46</td>
<td>1.03</td>
<td>1.50</td>
<td>4.35</td>
<td>4.25</td>
</tr>
</tbody>
</table>

Table 23
From Table 23, it can be seen that the distances of the nitrogen atom from the two oxygen atoms, are always greater than 4.2 Å indicating that the two units did not approach closely. The main reason could be the steric hindrance. In addition, the fluoride anion is always between the N and the O atoms. Such an arrangement seems intuitively correct with fluoride anion acting as an incipient base for deprotonation of hydroperoxide.

Unfortunately this molecular arrangement did not vary when a molecule of water was added to the calculation. The fluoride anion always prefers to bind the terminal hydrogen of the hydroperoxide, whilst the water is hydrogen bonded with the oxygen of the hydroperoxide. However, no interaction was observed between the N and the O atoms (Figure 13, Table 24). The orientation of the molecule was also found to be the same as in Figure 12 and more importantly, the value for the O-O distance is once again similar to that found for the isolated structure.

<table>
<thead>
<tr>
<th>Methods</th>
<th>( O_{19}O_{20} ) (Å)</th>
<th>( O_{20}H_{21} ) (Å)</th>
<th>( H_{21}F_{18} ) (Å)</th>
<th>( O_{19}N_{1} ) (Å)</th>
<th>( O_{20}N_{1} ) (Å)</th>
<th>( O_{20}H_{2O} ) (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>1.40</td>
<td>1.01</td>
<td>1.43</td>
<td>4.60</td>
<td>4.32</td>
<td>1.93</td>
</tr>
<tr>
<td>B3LYP</td>
<td>1.46</td>
<td>1.05</td>
<td>1.40</td>
<td>4.73</td>
<td>4.32</td>
<td>1.77</td>
</tr>
</tbody>
</table>

Table 24
To confirm that the geometry shown in Figures 12 and 13 is the favoured one, we then decided to remove the fluoride anion from the initial tetra-\(n\)-methylammonium salt, then calculate the preferential geometry between \textit{tert}-butyl hydroperoxide and the tetra-\(n\)-methylammonium cation at the HF level (Figure 14). The nitrogen \(N-1\), appears to get closer to the terminal oxygen of the hydroperoxide (\(O\)-19)_{\text{O19N1}} = 3.83 Å even if no difference in the \(O\)-\(O\) length was observed. However when, in a second step, the fluoride anion was reintroduced, the same type of arrangement previously found in figures 12 and 13, is regenerated.
In conclusion, the preferred arrangement always indicated the formation of hydrogen bonding between the fluoride anion and the terminal hydrogen atom of the hydroperoxide. This suggests that the study of a completely different system which would analyse the interaction between the tert-butyl peroxy anion and the ammonium salt, would be of interest.

\[
\text{Eq. 40}
\]

In future, it would also be interesting to “force” the homolysis of the O-O bond with the formation of the two radicals but this will imply the use of an ‘open shell system’ and in this case an even deeper level of theory needs to be applied.

Most importantly of all however, in the course of our calculations, we never observed any change whatsoever in the length of the O-O bond as previously claimed by L. J. Csányi. We feel however that the level of theory which we have used has enabled us to carry out a more complete study.
2.2.8 Potential intramolecular variants

Throughout our study of the onium salt effect, and in spite of the fact that we had not achieved a sufficiently deep level of understanding of the complexities involved, there was always the temptation to explore this phenomenon at an experimental level, especially since there was a very demonstrable effect. Within this context, we therefore considered that it would be of interest to explore catalysts which could operate as potentially intramolecular variants of this phenomenon. Accordingly, two target structures, both of which contain an ammonium moiety and a trifluoroacetyl group in adjacent positions were considered (Figure 15).

![Figure 15](image)

We predicted that such compounds could be important catalysts during the oxidation, since the peroxide could react at the electron deficient carbonyl position thus forming a new $sp^3$ centre. The nitrogen atom of the quaternary cation would then be in a favourable position to interact with one of the oxygen atoms of the peroxide and hence leads to homolysis (Scheme 71).

![Scheme 71](image)

Since a report in the literature showed that $N,N$-dimethyl-1-naphthylamine reacted readily with trifluoroacetic anhydride to yield the 2,4-bis-trifluoroacetyl derivative (72) in a quantitative yield,$^{94}$ this precursor was selected in the first instance.
We therefore decided to carry out the synthesis of the following structure (73), based on a simple retrosynthetic analysis (Scheme 72):

![Scheme 72](image)

Following the literature methodology, we achieved quantitative formation of 72, via the use of 3.5 equiv. of pyridine and 7 equiv. of trifluoroacetic anhydride (Scheme 73).

![Scheme 73](image)

With the requisite tertiary amine in hand, we were now ready to form the ammonium salt.

Whilst amines react readily with trialkyloxonium salts, such as trimethyloxonium or triethyloxonium fluoroborate to form quaternary ammonium salts and even although molecule 72 is an example of a vinylgous trifluoromethyl acetamide, we attempted the reaction of 72 with both Meerwein reagents at several different temperatures, but the starting material was always quantitatively recovered (Scheme 74).
Thus, in this case, the lack of reactivity of the nitrogen atom is dominated by the presence of the two trifluoroacetyl groups, which deactivate the system towards reaction. A potential solution appeared to lie either with the use of a stronger methylating reagent such as methyl trifluoromethanesulfonate (methyl triflate) or via reduction of the carbonyl group to an alcohol to afford a more electron-rich system. Methyl triflate has been used previously for the alkylation of amines with severe steric hindrance or where they are conjugated with strong electron-withdrawing groups\[^{95}\] and thus appeared to be the reagent of choice for our substrate. Unfortunately again, no reactivity was observed when 72 was reacted with an excess of this reagent (Scheme 75).

We next investigated the alternative approach via the reduction of the carbonyl groups to alcohols using an ethanolic solution of sodium borohydride. This reaction was successfully achieved to give 76 in 95% yield (Scheme 76).
Results and Discussion

With this material in hand, we then attempted the alkylation of 76 in the presence of either methyl triflate or Meerwein salts but were unable to obtain the desired product 77 (Scheme 77).

In order to prove that the lack of reactivity of the substrate was related to the substituents in the 2 and the 4 positions, we carried out the methylation of \(N,N\)-dimethyl-1-naphthylamine. As predicted, this reaction was completely successful and the triflate salt was isolated in quantitative yield (Scheme 78).

At this stage, we did not pursue any further studies into the naphthalenic substrate and next investigated a possible pathway to isolate the alternative structural type VI.
Results and Discussion

A first retrosynthetic analysis suggested that reaction of 2,4-dichloroaniline (79) with propionyl chloride should generate the amide which could undergo direct ortho lithiation with tert-BuLi. This lithiated species could then be quenched with an electrophile such as trifluoroacetic anhydride to form 81. Alkylation of the nitrogen, followed by reduction with borane, should form 83, which can then be reoxidised to the carbonyl compound 84. Finally, quaternarisation of the nitrogen atom should afford the desired product, 85 (Scheme 79).

\[ \text{Scheme 79} \]

Commercially available 2,4-dichloroaniline (79) was therefore treated with triethylamine and propionyl chloride in dichloromethane at room temperature to provide the required amide in excellent yield (Scheme 80).

\[ \text{Scheme 80} \]
Reports in the literature had demonstrated the possibility of ortho lithiation on a similar substrate (86) using tert-BuLi as base and ethyl trifluoroacetate as an electrophile (Scheme 81).[96]

\[
\begin{align*}
\text{H} & \quad \text{O} \quad \text{t-Bu} \\
\text{Cl} & \quad \text{Cl} & \xrightarrow{\text{CF}_3\text{CO}_2\text{Et}} & \xrightarrow{\text{t-BuLi,THF}} & \text{Cl} & \quad \text{Cl} \\
\text{86} & & & & \text{87}
\end{align*}
\]

Scheme 81

In this case, the ortho directing effect of the pivaloyl group allows for the introduction of the trifluoromethylketone functionality. The best solution by far for lithiating an amino substituted aromatic ring is to carry on an acylation to give a pivalanilide derivative, 88. Two equivalents of base (n-BuLi) deprotonate first the proton attached to the nitrogen atom followed by clean ortholithiation to generate 89 which can then react with the electrophile (Scheme 82).[97]

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{H} \\
\text{BuLi} & \xrightarrow{\text{LiO} \quad \text{N}} & \xrightarrow{\text{BuLi}} & \xrightarrow{\text{E}^+} \\
\text{88} & & \text{89}
\end{align*}
\]

Scheme 82

Following the reaction conditions of Scheme 81, 80 was used as substrate but no product was isolated and the starting material was recovered (Scheme 83).
Results and Discussion

We then derivatised the nitrogen, forming a tertiary amide (90) to verify if the metallation would be more effective. Thus, 2,4-(dichlorophenyl)-propionamide (80) was reacted with methyl iodide and sodium hydride, resulting in 90% conversion to 90 (Scheme 84).

90 was dissolved in THF at low temperature and a solution of tert-BuLi in hexane was slowly added. After 1 hour, the reaction was allowed to reach -20°C and then ethyl trifluoroacetate was added. Disappointingly, no conversion was observed (Scheme 85).
Results and Discussion

If n-BuLi was used as base, preferential attack occurred on the carbonyl group of the amide.

In the first instance our preferred substituent had been a propyl derivative, since it could then be reduced to a linear alkyl chain. Nevertheless, we synthesised the pivaloyl derivative in order to verify the validity of the literature data. If there was an agreement with the reported data, we would be in the position to deprotect the pivaloyl group using 6N hydrochloric acid in refluxing dimethoxyethane and then functionalise the obtained aniline.

Accordingly, the reaction of 79 with pivaloyl chloride was carried out to give 86 in 87% yield (Scheme 86).

![Scheme 86](image)

With the amide (86) in hand, we repeated the literature procedure using either tert-BuLi or sec-BuLi, followed by either trifluoroethyl acetate or trifluoroacetic anhydride. However, in our hands, no conversion was observed, even when TMEDA was introduced as an additive (Scheme 87). The lithiation had always been performed at low temperature (-78°C or -50°C) and quenching of the reactive species, over a range of temperatures between -20°C and 25°C. The fact that no reaction occurred and that starting material had been recovered, needed to be correlated with the presence of the halogens on the aromatic ring or the nature of the electrophiles.
Results and Discussion

Even when the procedure was carried out at -10°C, the starting material was recovered.

As a result of the problems outlined above, we carried out the preparation of 2,2-dimethyl-N-phenyl-propionamide 92, by repeating the same conditions of Scheme 86 but using aniline (91) (Scheme 88).

There are numerous examples of ortho substituted anilines and derived compounds in the literature, \(^{[97-98]}\) but to our surprise, no use of TFAA or CF_3CO_2Et, had been reported.

Nevertheless, the synthesis of 93 was achieved in a moderate 35\% yield (44\% based on recovered starting material), using a solution of t-BuLi (3 equiv.) in diethyl ether at -10°C and an excess of TFAA (6 equiv.) (Scheme 89).
Results and Discussion

This last result confirmed that the lack of reactivity of previous derivatives, is mainly due to the presence of electron-withdrawing groups on the ring. Compound 93 could then be further reacted according to the previously described approach (Scheme 79) but unfortunately time restrictions did not permit us to terminate the synthesis.

2.2.9 Summary and conclusions

Overall we can conclude that an onium salt effect certainly exists that justifies the enhanced reactivity in the oxidation of adamantane in the presence of phase-transfer catalysts. In fact, as already described, we discovered this catalysis by the examination of the counteranion effect for several tetra-n-butylammonium salts. We proved the influence of halide anion, F⁻ > Br⁻ > Cl⁻ > I⁻, of its basicity, in the case of tetra-n-butylammonium fluoride and tetra-n-butylammonium hydroxide, of different “sources” of fluorides, (diethylamino)sulfur (trifluoride), tris(dimethylamino)sulfur(trimethylsilyl)difluoride and tetra-n-butylammonium tetrafluoroborate achieving our best conversion in the presence of TBAF and 1 equivalent of tert-butyl hydroperoxide.

We then carried out an investigation into the countercation moiety, taking into consideration a previous literature report where Ohkubo,⁷³-⁷⁴ studied the effect of sulfonium salts in cumene autoxidation and reported an increase in reactivity when triphenylsulfonium bromide was used. Therefore, we proceeded to oxidise adamantane in the presence of sulfonium and phosphonium salts, both containing central atoms with a vacant d orbital, inventing a new successful system, tert-butyl...
hydroperoxide/triphenylsulfonium bromide, when a catalytic amount of water was added.

Meanwhile, the understanding of the mode of action of the ammonium salt over the decomposition of tert-butyl hydroperoxide as well as the role of the water, was attempted. We firstly proved, by titration studies, that decomposition of tert-butyl hydroperoxide occurred in the presence of triphenylsulfonium bromide or tetra-n-butylammonium fluoride and we then directed our studies toward a more theoretical approach. We searched for a relationship between the torsional angle and the O-O bond length using different hydroperoxides from the Cambridge Crystallographic Database but no evidence was found.

However, after the termination of our own experimental work in relation to the onium salt effect, Csányi and collaborators reported,[79] a detailed study about the oxidation of tetralin and cyclohexene by oxygen in the presence of phase-transfer catalysts (tetra-n-butylammonium or tetra-n-hexylammonium salts) using a catalytic amount of tert-butyl hydroperoxide in chlorobenzene. They studied the dependence of the catalytic activities on the nature of the counteranions and they established a trend which was completely opposite to our own. Particularly, they noticed a decrease in reactivity in the order I' > Cl' >Br' >F' affirming that the harder fluoride had the lowest reactivity. They investigated as well, the role of the water, proving inhibition of oxidation when water was added in a large excess. The authors justified their results through theoretical calculations where they assumed an interaction between the inner oxygen of tert-butyl hydroperoxide and tetra-n-hexyl ammonium chloride, which can be responsible for the homolysis of the peroxy bond.[90] However, on repeating these calculations, at a higher level of theory, no change in the length of the oxygen-oxygen bond was observed and we finally concluded that an inappropriate level of theory certainly affected their results.

Simultaneously, by further literature research, a short communication by E. Napadensky and Y. Sasson[99] was found, where the authors examined the decomposition of the 1,2,3,4-tetrahydronaphthalene-1-hydroperoxide (THOP) to 3,4-dihydronaphthalene-1(2H)-one and 1,2,3,4-tetrahydro-1-naphthol, in the presence of the tetra-n-hexylammonium halide catalysts (0.5 mol%) (THAX) at 110°C, in tetralin. The decreasing order of reactivity that they found was Cl' > Br' >I' and they noticed a reduced reactivity in the presence of water. Even if the fluoride anion was not considered, the series of reactivity for the other tetra-n-hexylammonium salts,
Results and Discussion

was similar to that which we found, although their decomposition of THOP can be influenced by small traces of acidity as already mentioned for the case of cumene hydroperoxide (Scheme 34).

As can be observed from this summary, liquid-phase oxidation of hydrocarbons is catalysed by different phase-transfer catalysts in conjunction with a relative small amount of water, but unfortunately a general trend cannot be defined from these conflicting results. In our case, oxidation of adamantane occurred in the presence of 1 equivalent of tert-butyl hydroperoxide showing a 35% conversion, which increased to ca. 75% when 0.02 equivalents of tetra-n-butylammonium fluoride or triphenylsulfonium bromide were added (Scheme 90). Although this reactivity cannot be explained from a mechanistic standpoint, it is unquestionable that phase-transfer catalysts are the key-reagents in this autoxidation of alkanes, and that our system is innovative when compared to any previous one.

![Scheme 90](image)
2.3 ALTERNATIVES TO NHPI AND PINO

As we have already outlined in the introduction to the present Results and Discussion section, a contemporaneous but subsidiary theme of our research was to understand the somewhat problematic subtleties of NHPI and its derived nitroxide PINO. Towards this end, we therefore elected to attempt the preparation of several hydroxylamine derivatives which, by containing adjacent electron-withdrawing groups could lead to nitroxide radicals also capable of acting as powerful hydrogen atom abstractors. In this respect, we noticed from examination of the literature, as discussed in the introduction, that a low a_N value for the nitroxide radical seemed to indicate much higher reactivity in terms of greater alkoxyl radical “character”. Such a hypothesis is intuitively correct inasmuch as it suggests that resonance form I is a much greater contributor to the overall picture. Clearly, resonance form II is disfavoured when adjacent electron withdrawing groups are present (Figure 16).

\[
\begin{align*}
R^+ & \quad \leftrightarrow \quad R^- \\
R_1^+ & \quad \leftrightarrow \quad R_2^- \\
(\text{Disfavoured when adjacent to carbonyl group})
\end{align*}
\]

Figure 16

The following sections describe the search, preparation and screening of several possible NHPI replacements for hydrocarbon autoxidation.

2.3.1 SULFONATED NITROXIDES

Thus, based on Ishii's catalyst, we decided, in the first instance, to replace the carbonyl group by the powerfully electron-withdrawing sulfonyl group. Three different structures were selected for this study: Fremy’s salt (94), 2-hydroxybenzo[1,3,2]dithiazole 1,1,3,3-tetraoxide (95) and N-hydroxysaccharin (96) (Scheme 91)
2.3.1.1 The use of Fremy’s salt

Fremy’s radical (94) or potassium nitrosodisulphonate is a nitroxide radical, which exists as an orange solid in dimeric form. It is usually employed for the selective oxidation of phenols to the corresponding quinones as shown in Scheme 92.\textsuperscript{100-101} Thus, hydrogen abstraction from the phenol results in the formation of dipotassium hydroxyimidobisulfate and the resonance-stabilised phenoxy radical (97). This species can then react with a second equivalent of 94 to give either of the cyclohexadienone intermediates and depending on the nature of R, the subsequent loss of the dipotassium imidobisulfate affords benzoquinones.

In a similar fashion, anilines and substituted anilines also react with 2 equivalents of Fremy’s salt to give p-benzoquinones in good yields. Secondary aromatic amines react with 94 to yield quinone imines, which can be hydrolysed to the corresponding ketones.\textsuperscript{102} Although no literature precedent exists for the use of Fremy’s salt in the oxidation of deactivated systems such as alkanes, our first objective was to test the possibility of its use as an oxidant for adamantane.
Fremy's salt was prepared in 51% yield, according to a literature procedure, by the reaction between sodium bisulphite and sodium nitrite to give the hydroxylamine disulfonate, which was then oxidised in situ by subsequent treatment with potassium permanganate solution (Scheme 93).

\[
\text{NaNO}_2 + 2 \text{NaHSO}_3 \xrightarrow{0^\circ C} \text{ON} (\text{SO}_3 \text{K}_2) + \text{NaOH} \quad 94
\]

In the event, 94 proved to be rather unstable, and its decomposition was dependent on pH. Impurities such as manganese dioxide, chloride and nitrite ions, have also been assumed to be the cause of its lack of stability. It is generally employed as a
stochiometric reagent in buffer solutions and this feature has proven to be a great limit to its use for oxidation. However in one review, the use of a biphasic system (1:1 = CH₂Cl₂ : aq. NaHCO₃), employing two equivalents of the salt and 1 equivalent of tetra-n-butylammonium bisulphate for the oxidation of 98 to the corresponding quinone was reported (Scheme 94). [103]

![Scheme 94](image)

The prospect of working in a biphasic system appeared more attractive to us, both for potential application to an industrial process, and also because of the complete immiscibility of alkanes in aqueous media. Additionally, in view of the instability of Fremy's salt, we also prepared the analogous hydroxylamine, dipotassium hydroxylamine disulphonate (100), by bubbling sulphur dioxide through an aqueous solution of potassium nitrite (Scheme 95). [104] We anticipated that, on isolation of 100, it could be used to generate, in situ, the same radical (94).

![Scheme 95](image)

However, compound 100 proved to be very difficult to obtain in a pure state as established by a gravimetric analysis as a percentage of barium sulphate, using a solution of hydrochloric acid followed by a solution of barium chloride. [105] The yield was also moderate. In fact, the formation of 100 is influenced by different factors. A higher concentration of protons, particularly above 10⁻⁴ M, can induce the evolution
of nitric oxide from the nitrous acid formed in the solution, destroying part of the starting material. Moreover, the effect of temperature had been studied by Raschig [106] who discovered that at temperatures below 0°C, only the hydroxylamine disulfonate ion was formed whilst at temperatures above 5°C, further reduction to the amino trisulphonate ion occurred with this latter reaction becoming rapid at room temperature. Finally, the excess of nitrites and sulphites in the mixture, would complicate the final purification and would also interfere with its purity.

With 100 in hand, we now investigated the formation of the corresponding nitroxide radical. Different methods are known for the generation of a nitroxyl radical in situ. Thus di-tert-alkylamines[107-108] and t-alkylarylamines[109] have been oxidised to their corresponding nitroxides, generally in good yield, by treatment with hydrogen peroxide in the presence of a quaternary ammonium hydroxide and a salt of vanadium or molybdenum or tungsten.

Alternatively, hydrogen peroxide and phosphotungstic acid may be used. This method, which was introduced by Lebedev et al.,[110] has been used extensively by Rozantsev,[107-109] mainly to prepare a large number of stable radicals from heterocyclic amines which have no hydrogen atom on the carbon atom α- to the nitrogen.

In our case, nitroxide radical 94 was generated in situ most efficiently by using the hydrogen peroxide/ phosphotungstic acid hydrate system (Scheme 96).

\[
\begin{align*}
\text{HON(SO}_3\text{K})_2 \cdot \text{XH}_2\text{O} & \quad \xrightarrow{\text{H}_2\text{O}_2} \quad \text{H}_3\text{PO}_4 \cdot 12 \text{WO}_3 \cdot \text{XH}_2\text{O} \\
& \quad \xrightarrow{\text{1 atm}} \quad \text{ON(SO}_3\text{K})_2 \\
\end{align*}
\]

Scheme 96

The radical (94), either directly in the form of Fremy's salt or formed in situ by hydrogen peroxide oxidation as above, was then tested in biphasic systems (CH\textsubscript{2}Cl\textsubscript{2}/H\textsubscript{2}O, CHCl\textsubscript{3}/H\textsubscript{2}O) using oxygen as the oxidant, and tetra-n-butylammonium bromide as the phase-transfer catalyst (Scheme 97).

\[
\begin{align*}
\text{Biphasic system, rt} & \quad \xrightarrow{\text{Traces of oxidation}} \\
\text{1 atm} & \quad \xrightarrow{\text{NO(SO}_3\text{K})_2} \\
\text{Bu}_4\text{NBr} & \quad \xrightarrow{\text{O}_2} \\
\end{align*}
\]

Scheme 97
Unfortunately, only traces of alcohol and ketone were detected by GC for adamantane oxidation.

The main problem concerning the use of Fremy’s salt appears to be the high instability of the radical in the presence of water and the same reaction was therefore attempted under various concentrations of aqueous media. No detectable conversion was however observed.

Reproducing Ishii’s conditions (Scheme 33), but replacing \(N\)-hydroxypthalimide with Fremy’s salt, also gave no conversion (Scheme 98).

\[
\text{PhCF}_3\text{H}_2\text{O}, 80^\circ\text{C}, 1\text{d} + \text{O}_2 (1 \text{ atm}) \xrightarrow{\text{NO OXIDATION}} \text{NO(SO}_3\text{K)}_2 (10 \text{ mol\%}) \text{ Bu}_4\text{NBr (2 mol\%)}
\]

We accordingly concluded that the instability of the radical, its insolubility in organic solvents and its apparent inability to operate under phase transfer conditions, did not permit the use of Fremy’s salt for the oxidation of alkanes.

\[2.3.1.2\] The preparation of \(2\)-hydroxybenzo[1,3,2]dithiazole 1,1,3,3-tetraoxide

Another potentially interesting system, as already discussed, was the fully sulphonated NHPI analogue (95), which could be accessed by two differing pathways. The first of these, (Path A) involves the formation of the desired product 95 from commercially available 1,2-benzenedisulfonic acid dipotassium salt (101), whilst the second route, B, requires formation of 2-(3-methylbutoxy)-benzo[1,3]dithiole 104 as an intermediate, using anthranilic acid (103) as starting material, followed by chlorination (Scheme 99).
For route A, the preparation of benzene-o-disulphonyl chloride (102) has been reported in the literature, by reacting neat phosphorus pentachloride[111] and 1,2-benzenedisulfonic acid dipotassium salt (101) at high temperature. In our hands, however, only partial conversion was observed and the diacid (105a) was recovered as the major, but undesired product (Scheme 100).

Although a variety of different chlorination conditions was explored (SOCl₂; SOCl₂/DMF; DMF/NEt₃/PCl₅), complete conversion of 101 to 102 was never achieved and the desired product 102 was always contaminated with the diacid.
As a result, the second pathway (route B) was investigated and 2-(3-methylbutoxy)-benzo[1,3]dithiole (104) was isolated in 23% from anthranilic acid (Scheme 101).\(^{[112]}\)

This one pot synthesis of 104, involves four mechanistic steps: a) aprotic diazotisation of anthranilic acid (103) by alkynitriles to give benzodiazonium-2-carboxylate (106); b) thermal decomposition of the carboxylate to benzyne (107); c) reaction of carbon disulfide with benzyne to lead to 1,3-benzodithiole-2-carbene (108) and d) addition of the alcohol. The relatively low yield of 104 is related to the thermal instability of the product 2-alkoxy-benzo[1,3]dithiole which can undergo considerable decomposition during distillation, involving α elimination of the alcohol, to give mainly 2,2'-bi[1,3-benzodithiolydene] (109) (Scheme 102).
Results and Discussion

Fortunately, however 104 could be then converted into the 1,2-dibenzosulphonyl chloride (102) by treatment with chlorine in a mixture of tert-butanol, chloroform and water in 74% yield (Scheme 103).\[113\]

![Scheme 103](image)

Finally, ring closure of 102, was achieved according to the procedure of J. L. Kice and S. Liao\[114\] affording 2-hydroxy-benzo[1,3,2]dithiazole 1,1,3,3-tetraoxide (95) (Scheme 104). This step involved a complex and very delicate balance of redox reactions and unfortunately proved to be somewhat irreproducible. In our hands, the yield of the desired product varied between 0 and 50%.

![Scheme 104](image)

It is important to emphasise that the only physical data for 95, which had been presented in the literature, was a melting point of 90-91°C\[111,114\] that rose to 128-130°C accounting for hydration of the N-OH\[115\]. This range of temperatures is so broad that the m.p. itself can not be used as any diagnostic evidence for 95, especially since inorganic impurities such as sulphites, carbonates, nitrates, nitrite may be present in the solid and are difficult to remove. Consequently, we carried out a full characterisation of the solid which we had isolated.

The melting point of 90-100°C was within the range of values presented in the literature and the IR presented the characteristic bands belong to the R-SO_2-N-(1350, 1310, 1160-1120 cm\(^{-1}\)) and –OH (3433 cm\(^{-1}\)) groups. Regrettably, it was not possible to perform either an elemental analysis due to the inorganic impurities or to
obtain crystalline material of sufficient quality for an X-ray diffraction. EI mass spectrometry of the sample gave a molecular ion of 219 which can be attributed to benzene-1,2-disulfonic acid imide 110. These data are in agreement with the behaviour of N-OH compounds which fragment ion are usually unstable towards MS and eliminate water to afford N-H derivatives (vide infra NHPI). In view of the conflicting evidence of the collected data, we therefore carried out NMR studies. Thus, benzene-α-disulfonyl chloride (102) was dissolved in deuterated water and the proton spectra were registered (1H-NMR 1). The sample was successively heated to 45°C (343K), thus observing its transformation into the deuterated disulphonic acid (1H-NMR 2)(Scheme 105).

![Scheme 105](image)

**Scheme 105**

Spectra of the benzene disulfonylchloride (102) at room temperature (1) (1H-NMR 1) and at 45°C (2) (1H-NMR 2):
In fact, as can be seen from the spectra, it was possible to observe the appearance of a new set of aromatic protons, which shifted from 7.75 and 8.25 ppm, to 8.30 and 8.80 ppm. Hence, compound 95 was dissolved in the same solvent (D$_2$O), and the NMR spectra at room temperature showed now the presence of two symmetrical ortho- substituted phenyl derivatives (system AA’BB’ or AA’ XX’) (‘H-NMR 3). This spectrum confirmed the presence of the desired product even if a new species appeared. The sulphur dioxide liberated during the synthesis of 95, may be the responsible for the reduction of the N-hydroxy imide to the benzene-1,2-disulfonic acid imide (110) (Scheme 106) or the partial decomposition of the product in water, could explain the presence of two different systems at room temperature.

![Scheme 106](image)

When the sample of 95 was heated to 45°C (343 K), the transformation of one of the species was observed (‘H-NMR 4), proving the high instability of the compound (Figure 18).
Spectra of the benzene-\textit{o}-disulfonhydroximide (95) ($^1$H-NMR 3) at room temperature and at 45°C ($^1$H-NMR 4):

Although, it was not possible to compare these spectra with one containing pure 110, we could certainly rule out the undesired formation of an unsymmetrical product containing a six membered ring such as 2-oxa-1,4-ditha-3-aza-naphthalene 1,1,4,4-tetraoxide 111, which could be derived by competitive nucleophilic attack of the oxygen atom on the sulfonyl group as shown in Scheme 107.

![Scheme 107](image-url)
Results and Discussion

From these spectroscopic studies, the nature of 95 was still not clear and as can be observed by $^1$H-NMR 3, we could not rule out the presence of a major impurity in our material.

Consequently, derivatisations were carried out proving the structure of 95 (Scheme 108). Peptide coupling techniques were applied to the substrate (95) using $N,N'$-dicyclohexylcarbodiimide (DCC) or 4-dimethylaminopropyl-3-ethyl carbodiimide hydrochloride (EDC) with benzoic acid, without success.

Esterification of the NOH in the presence of acetyl chloride or acetic anhydride was also attempted with negative results.

The substrate was then treated with pyridine followed by addition of 3,5-dinitrobenzoyl chloride, but no traces of the desired crystalline product were identified. Finally, the reduction of 95 to 110, in the presence of 10% sulphur dioxide in ethanol, also failed.

![Scheme 108](image-url)
Results and Discussion

Disappointingly, in these derivatisations, no products were isolated and quite often from NMR studies, the presence of a system belonging to an unsymmetrical ortho-substituted phenyl ring (system ABCD) was observed (\(^{1}\text{H}-\text{NMR 5}\)) which can result from ring opening of the substrate (Figure 19).

![Figure 19](image)

The behaviour of 95 can be explained by the possibility of ring opening, in the presence of nucleophiles and bases, to form a rather unstable intermediate 112, which can then evolve in a variety of different ways (Scheme 109).

![Scheme 109](image)
In fact, 95 is a rather strong acid (pKa = 1; compare to HOCl, pKa = 7.5) and in most reported instances, under acidic, basic or neutral conditions, the N-hydroxyimide was largely consumed or destroyed and on long standing at room temperature crystalline 95 produced 110 and o-benzenedisulfonic acid in fair quantities. The hydroxyimide however, reacted as a nitrosating reagent, bubbling immediately on contact with ammonia and primary amines, according to the mechanism outlined in Scheme 109. Thus, on addition of ammonia to our substrate, a strong evolution of gas was observed.

We could finally conclude that the isolated product did indeed contain the desired 2-hydroxy-benzo[1,3,2]dithiazole-tetraoxide (95) and its reactivity accounted for the failure of simple derivatisation and the presence of new species in the NMR spectra.

As might be expected after the numerous efforts which were made to characterise this “simple hydroxylamine derivative,” when substrate 95 was utilised for the oxidation of adamantane even in the presence of a catalytic amount of cobalt (II or III) in acetic acid under Ishii conditions, no conversion was observed and 95 was never recovered.

In summary, the disulfonylhydroxylamine unit embedded in 95 cannot survive and probably undergoes undesired ring-opening in all the reactions.

2.3.1.3 NHS: N-hydroxy saccharin

In collaboration with Prof. R. Sheldon and Dr. X. Baucherel, at University of Delft, we carried out the synthesis of the N-hydroxy saccharin (96). The compound was already known in the literature and can be isolated in 18% yield over 7 steps from 2-sulfobenzoic anhydride 113 (Scheme 110).

In sharp contrast to the disulfonyl derivative above, NHS proved to be an excellent and stable catalyst with similar properties to NHPI and work by our colleagues in Delft established that the derived nitroxide acted as a good hydrogen abstractor for the oxidation of a variety of alkanes.
In our lab, we then measured the $a_N$ value by generating the radical from NHS using an excess of AIBN. The $a_N$ value of 6.4 G ($\delta = 2.8$ G, $g = 2.0059$) (for ESR spectra see Appendix) in a solution of fluorobenzene ($1.2 \times 10^{-3}$ M) at 74°C serves to confirm the theory of a relationship between the strength of the nitrooxide as a hydrogen atom abstractor and the value of the hyperfine coupling constant, as previously discussed.
2.3.2 GENERATION OF DIFLUOROMETHYLENE SUBSTITUTED N,N-HYDROXYLAMINES

An alternative strategy involving progressive replacement of the carbonyl moieties adjacent to the hydroxylamine by difluoromethylene groups was then considered, since literature consideration (vide infra) suggested that this could provide a nitroxide of similar strength to PINO (Scheme 111). In particular, we elected to investigate such fluorinated N,N-hydroxylamines in acyclic form.

Scheme 111

Nitroxide radicals possessing fluorocarbon substituents have been known for a relatively short time, with the first example, bis(trifluoromethyl)nitroxide (117), being reported in 1965. This substance was isolated as a purple gas at room temperature which solidified to a yellow liquid at -70°C and its ESR spectra in carbon tetrachloride, showed an a_N = 9.3 Gauss. It was synthesized by photolysis of trifluoronitrosomethane (114) to yield the O-nitrosobistrifluoromethylhydroxylamine (115) by a free radical sequence (Scheme 112). The required adduct 114, had been obtained by the reaction of nitrosyl chloride with silver (I) trifluoro acetate. Hydrolysis of 115 to the hydroxylamine (116) followed by oxidation with fluorine, silver oxide or permanganate then yielded the stable purple gas (117).

\[
\begin{align*}
\text{CF}_3\text{COOAg} + \text{ClNO} & \rightarrow \text{CF}_3\text{COONO} + \text{AgCl} & \text{Eq.41} \\
\text{CF}_3\text{COONO} & \xrightarrow{\Delta} \text{CF}_3\text{NO} + \text{CO}_2 & \text{Eq.42} \\
2 \text{CF}_3\text{NO} & \xrightarrow{hv} (\text{CF}_3)_2\text{NONO} & \text{Eq.43} \\
(\text{CF}_3)_2\text{NONO} & \xrightarrow{\text{HCl/H}_2\text{O}} (\text{CF}_3)_2\text{NOH} & \text{Eq.44} \\
2 (\text{CF}_3)_2\text{NOH} + \text{F}_2 & \rightarrow 2 (\text{CF}_3)_2\text{NO}^- + \text{HF} & \text{Eq.45}
\end{align*}
\]

Scheme 112
It was also of interest to note that the esr spectrum of bis(perfluoroheptyl)nitroxide (119) had been observed by heating or irradiating a sample of the perfluoro-octanoyl nitrite (118) and that the $a_N$ value was 9.6 Gauss (Scheme 113).[^118]

\[
\begin{align*}
C_7F_{15}COONO & \quad \rightarrow \quad [C_7F_{15}NO + CO_2] \\
118 & \quad \rightarrow \quad C_7F_{15}NO \quad \text{N} \quad C_7F_{15}^* \\
\end{align*}
\]

Scheme 113

Moreover, the ability of bis-trifluoromethyl nitroxide (117) to attack C-H bonds had been demonstrated by its rapid reaction with toluene at room temperature, which yielded the hydroxylamine and, by scavenging of the resultant benzyl radicals, the trisubstituted hydroxylamine 120 (Scheme 114).[^119]

\[
\begin{align*}
\text{(CF}_3)_2\text{NO}^- + \text{Ph-CH}_3 & \quad \rightarrow \quad \text{Ph} \quad \text{N} \quad \text{CF}_3 \\
\text{120} & \\
\end{align*}
\]

Scheme 114

We therefore decided to prepare higher molecular weight fluorinated hydroxylamines, thereby avoiding the use of a gas. Three different approaches were subsequently investigated as detailed below.

2.3.2.1 Barton ester chemistry

The selection of a Barton ester as a substrate was made on the basis of its proven utility as a precursor for decarboxylative nitrosation under mild conditions. Thus, it had been reported from our group that the reaction between the Barton ester derived from $n$-octadecanoic acid and a tertiary thionitrite ester such as trityl thionitrite afforded the trans nitroso dimer (122) as the major product together with some of the corresponding nitrate (123) (Scheme 115).[^120]
As shown for the propagation sequence outlined in Scheme 116, where the octadecanoic acid chain was replaced with a perfluorododecanoic one, the addition of a thyl radical to the radicophilic thiocarbonyl group of compound (127) is followed by the normal decarboxylative sequence to give an alkyl radical which could then undergo either a direct $S_{N}2$ displacement reaction with the thionitrite, or, more probably, an addition-elimination sequence via (130) to produce in the first instance, a monomeric nitroso compound (131) with concomitant liberation of the chain carrying thyl radical. Although, by analogy with the Barton nitrite photolysis, facile dimerisation of 131 to 132 can proceed, we reasoned that if the same reaction was repeated using 2 equivalents of the ester, attack of the second perfluoroalkyl radical on to the nitroso derivative 131 could occur, to form the desired nitroxide (133). Thus, we elected to carry out our study using the Barton ester derived from the available perfluorododecanoic acid.

The acyl chloride (125) was generated using oxalyl chloride in the presence of a catalytic amount of DMF in trifluorotoluene (to favour the solubilisation of the starting material) and without further isolation the sodium salt of the $N$-hydroxypyridine-2-thione (126) was added, followed by trityl thionitrite (128). The resulting mixture was then irradiated with a tungsten lamp (250 Watt) until complete disappearance of the thionitrite green colour and a persistent yellow solution appeared. After workup, the mixture was analysed but none of the desired products was detected. Consideration of the presumed reactivity of the nitroxide might lead us to expect the isolation of the alkylated hydroxylamine derivative. Disappointingly, however, analysis of the reaction mixture did not reveal its presence.
In view of the fact that the overall mechanistic pathway is rather intricate, it was very difficult to establish at which stage the sequence failed. However, since the simplest free radical reaction of O-acyl thiohydroxamates is their decarboxylative
rearrangement to alkyl-2-pyridyl sulphides (Scheme 117), we decided to check this reaction in order to clarify the situation.

![Scheme 117](image)

In particular, it has been reported that irradiation of the perfluorooctanyl ester of the N-hydroxypyridine 2-thione afforded 2-perfluoroheptylthiopyridine in 60% yield.\[^{122}\] We therefore repeated this reaction using perfluorododecanoyl chloride (125) in order to verify the formation of the unstable intermediate (127) in the first part of the reaction.

![Scheme 118](image)

In our hands after numerous attempts, involving changing different parameters such as the solvent, the temperature and the time, it was possible to isolate 136 in low yield 20% (Scheme 118). This poor result was probably due to the inefficient conversion of the perfluorododecanoic acid to the acyl thiohydroxamate (127).
Unless the conversion of 125 to 127 could be dramatically improved, the isolation of the desired product (133) is unrealistic, especially on consideration of the possible formation of side-products such as 129, 132 and 136. For all of these reasons, we therefore terminated our investigation into the use of Barton esters.

2.3.2.2 Ene reactions

Our attention was then directed towards an alternative approach for the introduction of the difluoromethylene moiety adjacent to a hydroxylamine. The use of acylnitroso compounds, as powerful enophiles for the formation of carbon-nitrogen bonds has been extensively described in the literature.\[123\] The intermolecular ene reaction of an acylnitroso moiety with simple olefins provides a simple method for effecting “allylic amidation”, as shown in Scheme 119 for the reaction of cyclohexene with nitosocarboxylmethylene (138), to afford the N-alkylated hydroxamic acid (139).

![Scheme 119](image)

Unfortunately, these acylnitroso compounds, called “super(di)enophiles”, need to be generated in situ because of their high electrophilic reactivity. In particular, a report by Gary E. Keck\[124\] outlining the formation of the Diels-Alder adduct, starting from cyclohexadiene and benzohydroxamic acid in the presence of tetra-n-propylammonium periodate at room temperature seemed a particularly attractive method to us (Scheme 120).
Results and Discussion

Alternatives such as the use of lead tetracetate, the Dess-Martin reagent and 2,3-dichloro-4,5-dicyanobenzoquinone, have also been used in this area.

We wished to apply this methodology to the synthesis of fluorinated hydroxylamines of general formula 145 by operating the ene reaction between the aromatic acyl nitroso compound (143) derived from benzohydroxamic acid and a terminal geminal difluoroalkene (144) (Scheme 121).

The initial preparation of the gem-difluorolefins, 1,1-difluoro-1-octene (148),[125] and 1,1-difluoro-2-pentyl-hept-1-ene (150) was achieved by the use of methodology
already developed by Burton\textsuperscript{[126]} and further studied by Motherwell,\textsuperscript{[127]} wherein dibromodifluoromethane and tris(dimethylamino)phosphine were reacted to give an ylide (146) followed by reaction with either heptanal or 6-undecanone respectively (Scheme 122).

\[
\begin{align*}
\text{CBr}_2\text{F}_2 + \text{P(Me}_2\text{N})_3 & \xrightarrow{\text{Zn, THF, -20°C}} \text{CF}_2=\text{P(Me}_2\text{N})_3 \\
\text{CF}_2=\text{P(Me}_2\text{N})_3 + n-\text{C}_6\text{H}_{13}\text{CHO} & \xrightarrow{\text{THF, reflux, 25%}} n-\text{C}_6\text{H}_{13}\text{CH}=\text{CF}_2 + \text{O=P(Me}_2\text{N})_3 \\
\text{CF}_2=\text{P(Me}_2\text{N})_3 + \text{C}_6\text{H}_{11}\text{COC}_6\text{H}_{11} & \xrightarrow{\text{THF, reflux, 53%}} \text{F} \quad \text{F} \\
& \quad \text{C}_6\text{H}_{11} \quad \text{C}_6\text{H}_{11} + \text{O=P(Me}_2\text{N})_3 
\end{align*}
\]

\textbf{Scheme 122}

Next, the oxidising reagent, tetra-n-propylammonium periodate (151),\textsuperscript{[124]} was freshly prepared by reaction of tetra-n-propylammonium hydroxide and periodic acid in water (Scheme 123) and carefully stored in the dark.

\[
\begin{align*}
\text{HON(Pr)}_4 + \text{H}_3\text{IO}_6 & \xrightarrow{\text{H}_2\text{O, rt, 1h}} \text{Pr}_4\text{N}^+ \text{IO}_4^- 
\end{align*}
\]

\textbf{Scheme 123}

The cycloaddition was then attempted by slow addition of a solution of the benzohydroxamic acid to a mixture of olefin 148 and tetra-n-propylammonium periodate (151). Unfortunately, no evidence for formation of the desired product was obtained and the starting difluoroalkene was partially recovered (Scheme 124).
This negative result may be related either to the labile nature of the intermediates or, perhaps more importantly, to the electron-deficiency of the fluorinated olefin. In fact, in the literature, this type of \textit{ene} reaction is always reported using electron-rich alkenes such as tetramethylethylene (155)(Scheme 125),\textsuperscript{[128]} and it should be noted in this context that our product hydroxamic acid contains a more reactive alkene for further reactions. In this same publication, iodosobenzene diacetate (154) was recognised as the best reagent for the mild, \textit{in situ} preparation of the desired acylnitroso from the commercially available hydroxamic acid. This reagent, compared with 151, seemed to avoid further complex side reactions which are responsible for the decomposition of the nitroso compound.
Prior to examining this approach, we decided to repeat an example from literature\textsuperscript{[124]} to verify any problem related to the methodology. Hence, the reaction between cyclohexadiene and benzohydroxamic acid was achieved in the presence of tetra-\textit{n}-propylammonium periodate, isolating the cycloadduct (142), in 33% yield (Scheme 120).

Thus, the reaction was attempted once again utilising iodosobenzene diacetate as the oxidant and 3 equivalents of olefin 148, in a mixture of DMF/DCM at 0°C (Scheme 126).

In this case, an unexpected compound 157 was isolated. Although the NMR spectrum appeared to contain the skeletal fragment derived from the desired cycloaddition, no olefinic double bond was present in the \( \gamma \) position relative to the
Results and Discussion

carbonyl group. Full characterisation of this compound was attempted, but conflicting data were found which did not permit rigorous identification (Figure 20). Thus, COSY, HMQC and HMBC confirmed the sequence of carbon and hydrogen atoms outlined in the following structure with an unknown R substituent that does not imply any signals in $^1$H or $^{13}$C-NMR. Different molecular weights may be hypothesised but none had been confirmed by an appropriate molecular ion in the MS.

![Structure 157](image)

**Figure 20**

We therefore proceeded to test 1,1-difluoro-2-pentyl-hept-1-ene, 150 as the substrate for the ene reaction. The benzohydroxamic acid was oxidised either in the presence of tetra-n-propylammonium periodate or iodosobenzene diacetate (Scheme 127) and usually, the solution of benzohydroxamic acid was added slowly by syringe pump to the mixture of olefin and oxidant, over a period of 6-8 hours. When the reaction was carried out in the presence of iodosobenzene diacetate, an excess of the olefin was used whilst in the case of tetra-n-propyl ammonium periodate, several different concentrations were studied.

![Scheme 127](image)
For both oxidants, the crude mixtures contained the dimeric form (158) of the acynitroso compound which provided proof for the oxidation of the benzohydroxamic acid, together with numerous fluorine signals which were readily observable by $^{19}$F-NMR. Purification of the reaction mixture by flash chromatography was unsuccessful due however to the large number of products with close R$_f$.

It was possible to explain the presence of different compounds assuming that the desired substrate 159, would readily react with a second molecule of acynitroso compound leading to the formation of two diastereoisomers each one as mixture of E/Z isomers. Such a process could proceed until all of the available allylic hydrogen atoms were consumed as illustrated in Scheme 128.

Scheme 128
Two ideas were then considered in order to avoid the side reactions of Scheme 128. Firstly, we designed a difluoro olefin containing only one type of allylic proton and 1,1-difluoro-2,3-diphenylprop-1-ene 163, was selected. This compound was prepared in 25% yield from deoxybenzoin, using the same methodology previously described (Scheme 129).

\[
\begin{array}{c}
\text{Ph} \quad \text{O} \quad \text{Ph} \\
162 \\
\text{Zn} \quad \text{CBr}_2\text{F}_2, \text{P(NMe}_2\text{)}_3 \\
\text{THF, reflux} \\
\end{array}
\begin{array}{c}
\text{Ph} \quad \text{F} \quad \text{F} \quad \text{Ph} \\
163 \\
\text{25\%} \\
\end{array}
\]

Scheme 129

The same reactions described in Scheme 127 were then repeated using this substrate but, unfortunately, once again, no identifiable products were isolated.

An alternative solution lay in the generation of the acylnitroso under neutral conditions without the use of an oxidant. This possibility could be fulfilled by selection of the Diels-Alder adduct (165), prepared via oxidation of benzohydroxamic acid with tetra-\textit{n}-propylammonium periodate in the presence of 9,10-dimethylanthracene (164). Compound 165 is a thermally stable crystalline solid at room temperature, but undergoes \textit{retro} Diels-Alder reaction at 80-110\textdegree C releasing \textit{in situ} a molecule of the acyl nitroso compound which can then be trapped by alkenes such as our fluorinated olefin (Scheme 130).
The cycloadduct 165 was successfully prepared in 32% yield using 2.2 equiv. of benzohydroxamic acid in DCM at 0°C (Scheme 131).

We were now ready to react the difluoroolefin (163) and the cycloadduct (165). Although the cycloadduct was heated up either in benzene or toluene for at least 24 hours, the difluoroolefin was recovered unchanged together with dimethylanthracene and only traces of fluorinated products (Scheme 132).
Results and Discussion

In conclusion, we surmise that the *ene* reaction between an acylnitroso compound and a relatively electron poor difluoroolefin cannot occur due to the great difference in energy between the HOMO and LUMO of the two partners in the cycloaddition.

### 2.3.2.3 The use of nitrosyl chloride with olefins

The addition of nitrosyl chloride to an alkene is, in the first instance, a classical example of an electrophilic addition reaction.\[^{130}\]

These reactions have traditionally been carried out by passing nitrosyl chloride into the olefin or into a solution of the olefin in DCM, chloroform, carbon tetrachloride or sulfur dioxide, between -70°C and 0°C and higher temperatures (50°-100°C) have rarely been used. Interestingly, during the reaction, the nitroso group can be further oxidised by the nitrosyl halide to the nitro group (170), as shown for the case of tetrafluoroethylene (167) (Scheme 133).\[^{130a}\]

![Scheme 133](image)

However, despite this possibility of overoxidation, a transformation of particular interest to us was the preparation of bis(2-chlorotetrafluoroethyl)nitrooxide 172 ($\alpha_N = 9.3$ Gauss), by thermal decomposition of the nitrite formed by addition of the same nitrosyl chloride to tetrafluoroethylene in sunlight (Scheme 134).\[^{118}\]
Starting from perfluorohepten-1-ene (175), we envisaged the possibility of addition of the nitrosyl chloride onto the double bond to generate a stable nitrosochloride, which could further react in the presence of iodine with a second equivalent of olefin to generate the desired nitroxide (Scheme 135).

Although the mechanism could proceed through an oxidation of the nitroso compound by the iodine to generate a nitrosonium radical cation, we could not rule out the possibility of reversible addition of iodine atom onto the olefin as reported for the reaction of caryophyllene nitrosite (178) with iodine (Scheme 136).[131]
In our own case, nitrosyl chloride (168) was generated \textit{in situ}, by heating at 60°C, a 1:1 mixture of freshly distilled trimethylsilylchloride (173) and isoamyl nitrite (174). The brown gas was condensed at −60°C as a red liquid and the olefin was then added. The temperature then was slowly increased and at −15°C complete decolourisation of the solution was observed. Disappointingly however the perfluorohepten-1-ene (175) was quantitatively recovered and this approach was not further pursued.
Results and Discussion

2.3.3 ACYL NITROXIDES AND RELATED DERIVATIVES FROM BENZOHYDROXAMIC ACID

2.3.3.1 Derivatisation of benzohydroxamic acid

As previously implied, we decided to carry out an investigation to prepare nitroxide precursors derived from benzohydroxamic acid, as possible alternatives to PINO. Although first isolated by Lössen in 1869, hydroxamic acids remain one of the more challenging functional groups in organic chemistry.

Their reactivity is complicated by their ambident character with three possible sites for reaction with electrophiles. Little is known about alkylation under neutral conditions except for the observation that an excess of diazomethane leads to methylation of both \( O \)-atoms.\(^{[132]} \) Instead, much more attention has been given to alkylation under basic conditions, where the hydroxamate anion is the reactive entity. Its reactivity towards electrophiles proves to be greater than that of phenolate ions of similar basicity, this being attributed to the "\( \alpha \)" effect of the adjacent heteroatom.\(^{[133]} \) Interestingly Hudson and Aubort\(^{[134]} \) have suggested an alternative theory based on intramolecular catalysis to explain this enhanced reactivity. Whatever its origin, the result is that the N-O moiety of the hydroxamate ion is preferentially substituted to give an \( O \)-alkyl hydroxamate. In practice, all monosubstitution reactions of hydroxamic acid result in the formation of the N-OR moiety. If a second alkylation is carried out, three products are possible: namely the \( N \)-alkyl hydroxamate (180) and the \((E)\)- and \((Z)\)-isomers of the \( O \)-alkyl hydroximate (181 and 182) (Scheme 137).
In the case of the “imino ether” forms 181 and 182, a rearrangement can occur at high temperature that leads to the preferential formation of the type 180 derivative. Unfortunately, O-acyl hydroxamate derivatives are also prone to undergo the well-known Lössen rearrangement under strongly basic conditions or at high temperature. This reaction is similar to the Curtius, Hofmann, Beckmann and Schmidt rearrangements, in that N-O bond fission is synchronous with migration of the alkyl or aryl group (Scheme 138).

In light of the above factors, we therefore elected to use oxygen-protected benzohydroxamic derivatives and decided to introduce the allyl group which could
be later removed by metal catalysed isomerisation followed by hydrolytic cleavage to liberate the free hydroxylamine moiety (Scheme 139).

\[
\text{Ph} \text{N}^\text{O} \text{O} \text{R'} \text{X} \xrightarrow{R'X} \text{Ph} \text{N}^\text{O} \text{O} \text{R'}
\]

\[
\text{Ph} \text{N}^\text{OH} \xleftarrow{\text{Metal}} \text{Ph} \text{N}^\text{O} \text{O} \text{R'}
\]

Scheme 139

The potassium hydroxamate salt (188) was accordingly generated from ethyl benzoate in the presence of hydroxylamine (Scheme 140).\textsuperscript{135}

\[
\text{Ph} \text{CO} \xrightarrow{\text{NH}_2\text{OH HCl/KOH, MeOH, 30-40°C}} \text{Ph} \text{NO}^\text{+} \text{K}^\text{-} \\
\text{188}
\]

Scheme 140

Subsequent alkylation, using a mixture of allyl bromide and sodium carbonate in methanol then furnished the desired derivative 183 in 74% yield (Scheme 141).\textsuperscript{136}

\[
\text{Ph} \text{NO}^\text{+} \text{K}^\text{-} + \text{CH}_2\text{Br} \xrightarrow{\text{MeOH/H}_2\text{O, Na}_2\text{CO}_3, \text{rt, 1d}} \text{Ph} \text{NO}^\text{+} \text{O} \text{C}
\]

Scheme 141

We were now ready to perform the deprotonation of the nitrogen atom, which could then react with a variety of electrophilic reagents all characterised by the presence of
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electronegative groups. In the first instance, and in keeping with our previous theme of difluoromethylene replacement of the carbonyl group of NHPI, perfluorohexyl iodide (190) was chosen as the alkylating agent for substrate 183. This reaction was examined in the presence of a variety of different bases (Scheme 142, conditions a-c).

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{O} \quad \text{CH} & \quad \text{F}_3\text{C}-(\text{CF}_2)_{5}\text{I} \\
183 & \quad \quad 190 \\
& \quad \text{a) Na}_2\text{CO}_3, \text{MeOH} \\
& \quad \text{rt, 1d} \\
& \quad \text{b) n-BuLi, THF} \\
& \quad \text{0°C to rt} \\
& \quad \text{c) n-BuLi, CF}_3\text{Ph, TMEDA} \\
& \quad \text{-20°C to rt} \\
\end{align*}
\]

Since we had observed a small amount of the diallylated derivative during the synthesis of 183, our first choice consequently, was to carry out the reaction in the presence of the same base (i.e. sodium carbonate, condition a). However, no reaction occurred, and this was also the case when n-BuLi was employed (condition b). In order to ensure a homogeneous solution because of the nature of the perfluorinated iodide, trifluorotoluene was also examined as a solvent and the reactivity of n-BuLi was enhanced by the addition of tetramethylethlenediamine (TMEDA) (condition c). Unfortunately, once again only starting material was recovered.

A second strategy using β-halo enones, either per se or as embodied in quinones, was then envisaged since it could lead to a series of vinylygous NHPI replacements (Scheme 143 and Scheme 145).

Thus, 2,5-dichloro-1,4-benzoquinone (193) was selected to react with 183 (Scheme 143).
Once again, variation of the base, solvent and temperature did not afford the desired products. Hence, our attention was focussed on the β-halo cyclohexenones, whose reactivity resembles that of acid halides. In particular, 3-iodo and 3-chloro-2-cyclohexen-1-one (196 and 197) were prepared according to literature procedures from 1,3-cyclohexanedione and triphenylphosphine dihalides in the presence of triethylamine (Scheme 144).

The chloro derivative (197) was then reacted with 183, in the presence of sodium hydride either at room temperature or at reflux, but without any success (Scheme 145).
As deprotonation of the nitrogen might have been inefficient, we decided to protect the oxygen atom of the carbonyl group as the silyl imino ether and hence to rely on the nucleophilicity of the nitrogen lone pair. Thus, we envisaged that reaction with either trimethylsilyl chloride or bis-trimethylsilyl acetamide (BSA) should furnish \textit{in situ} the desired silyl ether 201. However, silylation followed by reaction with the chloro cyclohexenone resulted in no reaction (Scheme 146).

Finally, we chose to employ a double silylation reaction, \textit{i.e.} silylation at both oxygen atoms of benzohydroxamic acid for the synthesis of 202. We attempted the formation of the desired intermediate using either hexamethyldisilazane or BSA as reagents. Both reactions were performed at high temperature in the absence of...
solvent, but no reactions were observed and the starting materials were quantitatively recovered (Scheme 147).

Moreover, if the iodo derivative 196, was heated with the hydroxamic acid at 120°C for 3 hours, in the presence of HMDS, no product was isolated (Scheme 147). Therefore, we carried out a different methodology for isolation of the silylated species. In recent studies, enoxysilanes were prepared from aldehydes and ketones by treatment with BSA and tetra-\(n\)-butyl ammonium bromide as an ionic liquid at 105°C and isolated by direct stripping of the products from the crude mixture. The reactions were completed in 4 hours and produced enoxysilanes in high yields (Scheme 148).
Although there do not appear to be any examples of bis-silylation of benzohydroxamic acids in the literature, this protocol was performed using BSA (1.2 equiv.) and tetra-\textit{n}-butylammonium bromide (2.5 equiv.) (condition c, Scheme 147). Unfortunately, after vacuum distillation of the crude mixture however, BSA was quantitatively recovered.

In consideration of these unpromising results, an alternative derivative involving acylation was selected. Hence, the direct reaction between the potassium salt of benzohydroxamic acid (188) and trifluoroacetic anhydride (TFAA) in the presence of different bases (NaH, DBU and potassium \textit{tert}-butoxide) was attempted (Scheme 149). Analysis of the crude material by $^{19}$F-NMR showed that numerous products had been formed but unfortunately after workup, we only recovered benzohydroxamic acid together with a small number of fractions containing an aromatic residue. Since IR analysis of the latter underlined the presence of NH bands and the absence of the NOH absorption, we assumed relatively low reactivity at the oxygen atom, which could generate 209, although the eventual instability of the products could also account for their failure to be isolated.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O}^{\text{K}^+} \\
\end{array}
\xrightarrow{\text{Base} + \text{TFAA}}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{CF}_3
\end{array}
\]

\text{Scheme 149}

Finally, \textit{in situ} generation of the potentially reactive species 202 was attempted, by reaction of 188 with trimethylsilyl chloride and triethylamine followed by the addition of trifluoroacetic anhydride (Scheme 150).
The fact that no products were isolated, suggested either that the intermediate 202 was never formed or that the products were extremely labile.

2.3.3.2 Conjugated biradicals

In our search for new nitroxides, we then concentrated our attention on the possibility of formation of a conjugated biradical. Several examples of this class of compounds have been reported over the years by A.R. Forrester[139] and bis-N-hydroxyphenyl-p-benzoquinone (211) appeared to us a good candidate for use in our oxidation studies (Figure 21).
Although the $a_N$ value was not known because of a poorly resolved spectrum in $p$-azoxyanisole, we elected to synthesise 211, which had previously been isolated by reaction of hydroquinone with 2 equiv. of nitrosobenzene. Unfortunately, the only data presented in the literature for 211, was an elemental analysis which cannot be considered diagnostic for the proposed structure and cannot rule out a different position for the substituents.$^{[140]}$ Nevertheless, nitrosobenzene (212) was prepared by oxidation of aniline in the presence of 30% solution of hydrogen peroxide and sodium tungstate in 47% yield (Scheme 151).$^{[141]}$

![Scheme 151](image)

The reaction of hydroquinone (213) with 2 molar equivalents of 212 either at room temperature or under refluxing conditions, using a mixture of ethanol and hexane as solvent was performed. After evaporation of the solvents under reduced pressure, a crude material was obtained which could not be purified further by recrystallisation (Scheme 152).

![Scheme 152](image)

When the same reaction was performed with catechol (214), a complex mixture of products was produced, as evidenced by tlc and NMR analysis (Scheme 153).
In one final attempt, an excess of nitroso benzene (6 equiv.) and the phenolic derivative (213 or 214) were heated in the absence of solvent in a sealed tube. A significant difference in reactivity between the two substrates was clearly apparent. After a few minutes at 60°C, the mixture containing catechol and nitrosobenzene had become a black tar whilst the one containing the hydroquinone had to be heated to 110°C before undergoing the same process. Disappointingly, no compounds could be isolated from these intractable mixtures.

The main problem relating to this chemistry lay in the difficulty of purifying the crude reaction mixture, which was not stable under standard procedures. A consequence of the high reactivity of nitrosobenzene, was its ready decomposition and propensity for side reactions. In fact, the situation becomes more clear when possible mechanistic pathways are considered. Two different routes are illustrated. Firstly, hydroquinone can act as a reducing agent for nitrosobenzene, leading to the formation of phenylhydroxylamine (216). The hydroxylamine thus formed can then attack the benzoquinone forming a nitrone (217), which could further react with a second equivalent of 216 to yield 218 (Scheme 154, path a).

The second possible alternative pathway involved a direct nucleophilic attack of the hydroquinone onto nitrosobenzene acting as the electrophile. Intermediate 219 could then re-aromatise and/or react with a second equivalent of nitrosobenzene. Together with the desired compound 211, it was possible to hypothesise the formation of different compounds 220, 221 and/or 2,5-bis-(hydroxy-phenyl-amino)[1,4]-phenol (222) (Scheme 154, path b).
In order to verify the formation of some hydroxylamine derivatives, we carried out some ESR experiments. In particular, a mixture of hydroquinone (1 equiv.) and nitrosobenzene (6 equiv.) in fluorobenzene was heated to 80°C in the presence of AIBN. It was possible to observe the presence of a complicated pattern which defied interpretation (see Appendix). Certainly, during the reaction, formation of a nitroxide occurred as evidenced by the ESR spectrum which contained a symmetrical triplet.
(\(a_N = 10\) Gauss, due to the \(N\)-oxy radical) further split into 27 lines with intensities 1.2:3.2:4.3:10.5:5.25:10.5:3.8:1.8:1. In future, simulation of the spectra could help the establishment of the structure of the formed radical. Although these preliminary ESR studies suggested the formation of a nitrogen centred radical, the unsuccessful purification of the crude reaction mixture, prevented further studies of this system. However, in order to gain an alternative approach to this reaction type, it could be of interest to examine the reaction between benzoquinone and 2 equivalents of phenyl hydroxylamine to obtain, as illustrated in path a, the derivative compound 218.

Another conjugated system was then considered and a search was made for a compound which still contained the phthalic acid type moiety present in \(N\)-hydroxy phthalimide. In fact, the cyclic compound NHPI had been synthesised by different methodologies but Mazur and Plume\[^{142}\] isolated the desired NHPI by reaction of phthalic anhydride with hydroxylamine hydrochloride in pyridine at 90\(^\circ\)C for 15 minutes. We therefore wished to apply the same methodology to the similar substrate 223, in order to form the \(N\)-hydroxy derivative 224 (Scheme 155). Therefore, we proceeded to prepare the dimeric form of phthalic anhydride.

![Scheme 155](image)

It had previously been reported that triethyl phosphite effected the conversion of phthalic anhydride into the biphtalyl derivative (223) in quite good yield. A formal mechanism requires that the phosphorus atom of the phosphite attacks the oxygen atom of the carbonyl group and the resulting carbene formed by loss of the phosphine oxide, can dimerise leading to the product.\[^{143}\] 223 was isolated in 41% yield, by refluxing phthalic anhydride with 2 equiv. of POEt\(_3\) (Scheme 156).
The main problem in this reaction lay in the characterisation of 223, because of the incredible insolubility of the material in a variety of organic solvents. Finally, an X-ray analysis confirmed the structure which exhibited, as might be expected, $E$ geometry (Figure 22).

Indeed tetrachlorophthalic anhydride (226) appeared to be an even better substrate for dimerisation, given that after few minutes of reflux, a bright fine yellow powder separated out from the reaction. However, since the material still contained a large amount of phosphite which prevented formation of a crystalline solid, it was
preferable, from a practical standpoint, to repeat the reaction in benzene as solvent, thereby isolating 227 in 14% yield (Scheme 157).

![Scheme 157](image)

Although recrystallisation of 227 was not successful, the structure implied was confirmed by a high resolution mass spectrum (HRMS). By analogy with the previous compound 223, we assumed an $E$ geometry which seems reasonable given the larger size of the chlorine atom when compared to hydrogen.

The precursor was now available to attempt the synthesis of 224. Thus the dimeric compounds (223 or 227) were reacted with hydroxylamine hydrochloride in pyridine at 90°C. The solvent was removed and the residue was acidified with 2M HCl (Scheme 158). The solid which separated out, was then filtered and washed. From infrared analysis, it was possible to observe the presence of different carbonyl groups (1751, 1652 cm$^{-1}$) and NH/NOH groups (3348, 3178 cm$^{-1}$) but the mass spectra did not show the presence of a molecular ion or the fragmentation which can be accounted for by loss of water, as seen in the $N$-hydroxyphthalimide derivatives (ex. 95).
Nevertheless, in the absence of further proof of the structure, we decided to carry out an oxidation of adamantane in the presence of this material, working in acetic acid at 80°C. The reaction was catalysed by the use of Co (III), but even after 2 days, no conversion was observed (Scheme 159).

Clearly, this class of compounds requires further investigation. As already indicated, a disadvantageous characteristic of these species was their complete insolubility in common organic solvents, which would implicate heterogeneous oxidation. In view of the negative results from these NHPI analogues studied, our attention then turned to N-hydroxy indoles as possible radical precursors.
2.3.4 HETEROCYCLIC PRECURSORS

2.3.4.1 Indole and pyridone structures

Concurrently with our work on hydroxamic acids, we also investigated some N-hydroxy indole and pyridine derivatives which contain additional electron withdrawing groups adjacent to the nitrogen atom of the hydroxylamine (Scheme 160).

We were especially intrigued by the series of N-hydroxy indol-2-ones, 229-231, for which the derived radicals esr spectra had been measured and shown a values ranging from 5.85 to 6.23 Gauss. These were similar to the value observed for PINO ($a_N = 4.3 \text{ G}, \delta = 2.5 \text{ G}, g = 2.0068$)(see ESR spectra in Appendix).

![Scheme 160](image)

In particular an excellent candidate appeared to be N-hydroxyoxindole (231) which presented an $a_N$ value of 5.87 G as measured oxidatively in the presence of lead dioxide, in a dioxane solution.\[144] Consequently as already discussed, we considered that this compound could act as powerful hydrogen abstractor. At a later stage, we envisaged that further functionalisation of 231 adjacent to the carbonyl group, could create an even more efficient nitroxide radical.
For the other compounds shown in Scheme 160, indole 232 could be easily synthesised through a [1+4] cycloaddition between a nitroalkene and tert-butylisocyanide; the commercially available 1-hydroxy-7-azabenzotriazole (233), could be directly tested as a catalyst, and finally the N-hydroxy pyridone 234 could be generated by a Hantzsch-Knoevenagel condensation.

2.3.4.2 Generation of 1-hydroxyoxindole

Based on literature precedent, we approached the preparation of N-hydroxyoxindole (231) through two different routes, using either 2-nitrophenylacetic acid (235) or indoline (239) as the starting materials. Thus, it had been shown that the ortho-substituted nitrobenzene (235) can be reduced in the presence of zinc and calcium chloride to the hydroxylamine derivative which then undergoes cyclisation under refluxing conditions\[145\] in 15% yield. However, when this procedure was repeated, using either calcium chloride or ammonium chloride as a more appropriate proton source, the yields ranged only from 7 to 9% and we found that the product 231 was difficult to purify from the crude mixture (Scheme 161).

\[
\begin{align*}
\text{235} \quad &\text{CO}_2\text{H} \\
&\text{NO}_2 \\
\text{1) Zn, CaCl}_2 \\
&\text{2) Zn, NH}_4\text{Cl} \\
&\text{EtOH, reflux} \\
&7-9\% \\
\text{231} \quad &\text{N} \\
&\text{O} \\
\end{align*}
\]

Scheme 161

Consequently, esterification of the acid was performed in an effort to facilitate the cyclisation-step. The methyl ester 236, was accordingly synthesized using classical Fischer esterification conditions (Scheme 162).

\[
\begin{align*}
\text{235} \quad &\text{CO}_2\text{H} \\
&\text{NO}_2 \\
&\text{AcCl, MeOH} \\
&\text{reflux, 2 h} \\
&\text{quantitative} \\
\text{236} \quad &\text{CO}_2\text{Me} \\
&\text{NO}_2 \\
\end{align*}
\]

Scheme 162
Ester 236 was then reacted under the previous conditions but only traces of the desired product were observed. In view of the inefficient nature of this reductive cyclisation to 231, we then decided to attempt titanium (IV) isopropoxide catalysis of the cyclisation step.

There is ample literature precedent for titanium isopropoxide (IV) promoted lactamisation of simple primary and secondary amino carboxylic acids as shown in Scheme 163.\textsuperscript{[146]}

\[
\text{RHN-(CH}_2\text{)}_n\text{-CHR'}\text{-CO}_2\text{H} \xrightarrow{\text{Ti(OiPr)}_4, 1,2\text{-Dichloroethane}} \text{O-CHR'}
\]

\text{Scheme 163}

Therefore, 0.1-1 equiv. of titanium complex was introduced into the reaction with 236. Surprisingly, 231 was not formed and the further reduced oxindole (237) was isolated as the major product in 18\% yield. In this instance, the titanium not only acted as a Lewis acid by activating the ester but also activated the nitro group towards reduction to the amine. In addition to 237, the transesterification product 238 was also isolated in low yield (Scheme 164).

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad 1) \text{Zn, CaCl}_2 \\
\text{NO}_2 & \quad 2) \text{Zn, NH}_4\text{Cl} \\
\text{236} & \quad \text{Ti(OiPr)}_4, \text{EtOH, reflux, 5h} \\
\text{237} & \quad \text{18\%} \\
\text{238} & \quad \text{2\%}
\end{align*}
\]

\text{Scheme 164}

When a chlorinated solvent such as dichloroethane was used in this reaction and the reaction time was increased to 24 hours, starting material was mainly recovered and 20\% of (2-nitrophenyl)acetic acid isopropyl ester (238) was isolated.

In view of these unsuccessful reductive cyclisation reactions, we therefore chose to oxidise indoline to N-hydroxyoxindole. This reaction had been reported by Neset et
Results and Discussion

*al.* who performed the oxidation with 4.5 equivalents of dimethyldioxirane solution, in 54% yield (Scheme 165).\(^{[147]}\)

A dimethyldioxirane solution (DMD) (241) was prepared according to Adam’s procedure\(^{[148]}\), in which potassium monoperoxysulfate (Oxone) (240) is reacted with acetone (Scheme 166). The oxidant was then titrated with thioanisole prior to use, and a concentration of 0.08–0.1 M was measured.

After several attempts (*vide infra*), we were delighted to achieve quantitative conversion to 231 when indoline (239) was added to 9 equiv. of dimethyldioxirane at 0°C, and the mixture was stirred for 5 minutes (Scheme 167).

Unfortunately, because of the low concentration of dimethyldioxirane in acetone which is always produced in such reactions, this route did not seem to be applicable
for work on multigram scale. The main reason for this was the required nine fold-excess of dimethyldioxirane, which we had found to be essential to guarantee the success of the reaction. In earlier attempts, when only 3-6 equivalents of DMD had been used, an unknown mixture was isolated. After numerous attempts at purification, we concluded that the crude product might contain dye type compounds such as N-hydroxy-indigo (242), N-hydroxy-indirubin (243) or the 6H-oxazolo[3,2-a:4,5-b']-N-hydroxy indole (244) (Scheme 168).

We were particularly excited by the ESR spectrum of this mixture which showed the presence of a nitroxide as a centred triplet with an $a_N$ value of 5.8 G ($\delta= 2.8$ G, $g = 2.0052$) (see ESR spectra in Appendix). The spectrum of the radical was measured in a solution of fluorobenzene at 82°C, using an excess of AIBN. In the first instance, the shape of the signal produced did not seem to agree with any of the structures 242, 243 or 244 outlined above. In fact, in these structures, the radical would certainly be delocalised into the aromatic ring, generating a coupling between the nitrogen atom and the aromatic protons. Consequently, the expected pattern should present numerous splittings.

Moreover, the MS of the unknown crude mixture gave a molecular ion of 306 (50%), which did not correspond to any of these structures and a fragmentation peak at 265 (100%).
The unknown mixture certainly contained molecules with interesting properties but many attempted recrystallisations of the crude product did not afford pure compounds. The material was a dark solid when dried and presented different colours in solution (from blue to pink). The NMR analysis of one fraction, obtained by column chromatography, showed the presence of only the aromatic part in both proton and carbon (see Appendix). Furthermore, when the crude mixture was left open to the air for three days and then analysed again by ESR, an entirely new pattern was observed, and by working at 80°C with an excess of AIBN, a radical was obtained, characterised by complex couplings, which disappeared after approximately 30 minutes (see Appendix). This behaviour seems to imply the possibility of further oxidation of the crude reaction mixture in the presence of air to generate further new derivatives. To the best of our knowledge, N-hydroxy indigo derivatives are not known, but we can speculate that there may be some similarity in structure with those products which have been isolated from in vitro oxidation of indole by the enzyme cytochrome P450. Thus indigo (247), indirubin (248) and dimeric conjugate indoles were isolated and characterized within this study (Scheme 169).
Other microbial oxygenases are known to oxidize indole to indoxyl (3 hydroxy-indole)(246), which rapidly oxidises in air and dimerises to form indigo in a base-catalysed reaction.\footnote{150} Even although the structure of the products was uncertain, we utilised this material for the oxidation of adamantane in a mixture of acetic acid/trifluorotoluene (1:1) and cobalt (III), at 80°C. After 1 day, no conversion was observed but when 10 mol% of tert-butyl hydroperoxide was added the oxidation took place and 39% of oxidative products were detected after 24 hours. 68 % was the final conversion after 3 days at 80°C (Scheme 170).

This last result provided the definitive confirmation that an oxidant species was present in the crude mixture, and that it was able to catalyse the oxidation of an alkane, in the presence of cobalt (III) acetylacetonate and tert-butyl hydroperoxide.
Results and Discussion

In view of time constraints, it was decided that further work on understanding these complex systems should not be undertaken. In future however, further studies within this class of compounds may give important insights into the field, especially if an appropriate method of purification for these materials can be developed. Meanwhile, we had searched for another system which could oxidise indoline in a more efficient way, without the use of large excess of the oxidant.

Examination of the literature revealed that the sodium tungstate catalysed oxidation of 1,2,3,4-tetrahydroquinoline (249) with 30% hydrogen peroxide solution in methanol, afforded 1-hydroxy-3,4-dihydroquinolin-2(1H)-one (250) in 84% yield (Scheme 171).\textsuperscript{[151]}

Considering the “similarity” in structure between the tetrahydroquinoline (249) and the indoline, we therefore decided to apply this system to 239.

Once again however, a complex reaction mixture was produced which appeared similar to that isolated by working with dimethyldioxirane, as judged by a comparison of NMR, ESR and TLC. After numerous purification attempts, we realised once again that isolation of the products could well be impossible because of their instability and susceptibility to overoxidation.
At this stage of our studies, we still needed to prepare the desired N-hydroxyoxindole (231) in sufficient quantity and a last reductive route was therefore attempted.

A later study by Kende and Thurston noted that the yield of 1-hydroxyoxindole varied in the range between 0 and 50% using zinc and nitrophenylacetic acid on repeating the preparation of Collins and Wright.\[^{145}\] To overcome these difficulties, they developed a new methodology based on the hydrogenation of nitrophenylacetic acid in ethanol, using a platinum over carbon catalyst which had been poisoned with dimethyl sulfoxide.\[^{152}\] When we repeated this same procedure, we were delighted to identify a mixture 1:1 of starting material: product by NMR. Unfortunately this proved to be inseparable by either column chromatography or recrystallisation (Scheme 172).

We solved this problem by an esterification in methanol and then separated the products by column chromatography (Scheme 173). The desired product (231) was finally isolated in 23% yield together with 17% of the methyl ester (236) and 5% of the dimeric nitroso compound of the ester (252).
As anticipated, when DMSO was not introduced, further reduction occurred and the undesired oxindole 237 was isolated in 18% (Scheme 174) together with 10% of N-hydroxyoxindole.

Efforts were made to improve this yield by avoiding the second step of esterification and directly hydrogenating 236. However, N-hydroxyoxindole was not formed and only a low 18% yield of 237 was isolated (Scheme 175).
Although the yield in hydrogenation was modest, we were now ready to perform the oxidation of adamantane using 231 as catalyst.

Firstly, we carried out the reaction in acetic acid in the presence of cobalt (III) acetylacetonate (5 mol%) and 10 mol% of the N-hydroxyoxindole at 80°C but no conversion was detected after 3 days (Scheme 176).

Reasoning that the acidity of the solvent might not be suitable for our catalyst, we then repeated Ishii’s conditions using tetra-n-butylammonium bromide (2 mol%) and 10 mol% of 231 in trifluorotoluene at 60°C. The reaction was monitored by GC after 24 hours, but only starting material was observed. When 10 mol% of an 80% solution of tert-butyl hydroperoxide was added, no conversion was observed although a black slurry appeared on the bottom of the flask (Scheme 177).

Hence, the catalyst appeared to be fragile, possibly to further oxidation at the benzylic site in position 3 which can undergo side-reactions. This instability was
underlined by observable decomposition of \( \textbf{231} \) merely on standing at room temperature in an NMR tube. Since it was doubtful that \( \textbf{231} \) would survive the reaction conditions, we consequently decided to derivatise this product. In particular, we believed that the introduction of two bromine atoms would stabilise the structure and also create a more powerful nitroxide (Scheme 178).

\[
\begin{array}{c}
\text{OH} \\
\text{X = Halides}
\end{array}
\]

Scheme 178

The bromination of \( \textbf{231} \), was not known in the literature but different research groups have achieved bromination of oxindole, \( \textbf{237} \), by the use of copper (II) bromide in ethyl acetate (Scheme 179).\(^{[153-154]}\) The dibromooxindole \( \textbf{253} \) was usually not isolated but subsequently hydrolysed in aqueous methanol to give isatin (254).

\[
\begin{array}{c}
\text{CuBr}_2 \\
\text{AcOEt, 80°C, 5 h} \\
\text{MeOH, reflux, 2h}
\end{array}
\]

Scheme 179

We therefore decided to use the same methodology for substrate \( \textbf{231} \), but unfortunately complexation of the copper with the hydroxamic moiety occurred (Scheme 180) and precluded the reaction. This feature will be discussed in section 2.3.4.5 (vide infra).
Since a metal could not be used in the halogenation sequence, the use of the standard procedure using bromine in carbon tetrachloride, was adopted. In this case during the reaction, the formation a molecule of hydrogen bromide will occur, and consequently propylene oxide was introduced as a trap. We wished, by working under these neutral conditions, to avoid the decomposition of the starting material. After a few attempts, the tribromo derivative 256 was isolated in 19% yield by working at 50°C in order to solubilise N-hydroxyoxindole (Scheme 181).

While the yield of 256 was low, the search for a better method of halogenation was not further pursued, and the oxidation of adamantane in the presence of 256 was investigated at this stage. We performed the reaction using either TBAB or AIBN, but in neither case, was any conversion observed (Scheme 182).

Although the gem-dibromo derivative 256 has thus proven unsuccessful, it would be certainly of interest to hydrolyse this substrate to form the diketo N-hydroxyisatin derivative, 229 which could also be synthesised through a different procedure starting from 2-nitrobenzoic acid.\(^{155}\)
2.3.4.3 [1+4] Cycloaddition

On the other hand, we wished to synthesise 232 by a [1+4] cycloaddition of nitroalkenes with tert-butylisocyanide, using the following retrosynthetic approach involving reaction of 2,5-dihydroxybenzaldehyde (257) with nitroethane to form 258, which could then further react with the isocyanide to form the desired N-hydroxy indole 232 (Scheme 183).

![Scheme 183](image)

However, condensation of commercially available 2,5-dihydroxybenzaldehyde (257) and nitroethane proved to be unsuccessful. Thus protection of the two phenolic units was required and consequently, benzylation was carried out on the substrate in the presence of benzyl bromide, potassium carbonate and a catalytic amount of 18-crown-6 in acetone, providing 259 in 72% yield (Scheme 184).

![Scheme 184](image)

The dibenzyloxy derivative 259 easily underwent the Henry reaction, using nitroethane as solvent and a catalytic amount of n-butylamine, affording the nitroalkene 260 in 73% yield (Scheme 185).
We were now ready to perform the cycloaddition between 260 and tert-butyl isocyanide. It was carried out in refluxing benzene or acetonitrile but no conversion was observed and the starting material was mainly recovered (conditions a and b, Scheme 186).

Even in the presence of a catalyst, such as lithium perchlorate (1 to 5 equivalents), the cycloaddition still did not occur (condition c, Scheme 186). This lack of reactivity may be related to the possibility of electron donation from the oxygen atom in the ortho position towards the nitroalkene, thus preventing the desired reaction (Scheme 187).

To avoid this problem, protection of the two phenols with electron withdrawing groups, which would favour the cycloaddition, was decided. Therefore, we treated
2,5-dihydroxybenzaldehyde with trifluoromethanesulfonic or trifluoroacetic anhydride, and a base: although carefully dried conditions were applied, no products were isolated (Scheme 188).

\[
\begin{align*}
\text{OH} & \quad \text{CHO} \\
\text{OH} & \quad \text{CHO} \\
257 & \quad \text{K}_2\text{CO}_3/\text{Pyr} \\
& \quad (\text{CF}_3\text{SO}_2)_2\text{O} \text{ or } (\text{CF}_3\text{CO})_2\text{O} \\
& \quad \text{OR} \\
262 & \quad \text{R} = \text{COCF}_3 \text{ or } \text{SO}_2\text{CF}_3
\end{align*}
\]

Scheme 188

Hence, a one pot procedure was performed: firstly TFAA and potassium carbonate were added to 257, followed by nitroethane and n-butylamine (catalytic amount)(Scheme 189). The product 258, in which hydrolysis of the trifluoroacetyl groups had occurred, was isolated in 14% yield.

\[
\begin{align*}
\text{OH} & \quad \text{CHO} \\
\text{OH} & \quad \text{CHO} \\
257 & \quad 1) \text{TFAA, K}_2\text{CO}_3, \text{acetone, rt, 5h} \\
& \quad 2) \text{EtNO}_2, n\text{-BuNH}_2, \text{reflux, 7 h} \\
& \quad 14\% \\
258 & \quad \text{OH} \quad \text{NO}_2
\end{align*}
\]

Scheme 189

We believed that the low reactivity of the previous reactions was dominated by the presence of substituents on the aromatic ring. In fact, the preparation of different 1-hydroxy indoles has been reported\(^{156}\), by the cycloaddition of isocyanides with 1-aryl-2-nitro-propene, always containing a substituent in para-position. The only unsubstituted derivative, \textit{N-tert-butyl-1-hydroxy-2-methyl-3-indolecarboxamide} (264), was isolated by reaction of 2-nitropropenyl benzene (263) in a good 53% yield (Scheme 190).\(^{156}\)
Since we wished to repeat the same reaction, we carried out the synthesis of 263 by refluxing benzaldehyde in nitroethane (Scheme 191).

With 263 in hands, we attempted the reaction of Scheme 190 using as solvent benzene or acetonitrile. However, in our hands, this reaction was not reproducible even when catalysed by 5 equivalents of lithium perchlorate (Scheme 192).

In light of the fact that it was not possible to reproduce the synthesis of 264, it therefore appeared unrealistic to persist in the isolation of 232 and similar derivatives.

2.3.4.4 The use of 1-hydroxy-7-azabenzotriazole

As already stated, we had decided to investigate the reactivity of 1-hydroxy-7-azabenzotriazole for the oxidation of adamantane. Unfortunately at the time of our
Results and Discussion

Investigation, 233 was not a commercially available product and only a very small amount was obtained from the pharmaceutical industry as gift. Consequently, only a few oxidations were carried out as detailed in Scheme 193, Table 25.

\[ \text{Entry} \quad \text{Conditions} \quad \text{Conv} \% \quad 32 \% \quad 33 \% \quad 34 \% \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>PhCF(_3)/AcOH (1:1), Co (II) (0.5 mol%)</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCF(_3)/AcOH (1:1), Co (II) (0.5 mol%), t-BuOOH (10 mol%)</td>
<td>39</td>
<td>46</td>
<td>14</td>
<td>Y</td>
</tr>
</tbody>
</table>

[Reactions were carried out using conditions of Scheme 193; (Y) indicated the presence of 1,3-adamantan-1-ol but its selectivity was not determined by the use of an internal standard.]

Table 25

As revealed in Table 25, the parent system was unreactive, but a 39 % conversion was obtained when tert-butyl hydroperoxide was introduced as an additive into the system. As a result 233 cannot be considered as a potential catalyst for the oxidation of alkanes.

2.3.4.5 1,2-Dihydro-1-hydroxy-4,6-dimethyl-2-oxopyridine-3-carbonitrile

Following on from our studies of N-hydroxyindoles, we then considered structures such as 1,2-dihydro-1-hydroxy-4,6-dimethyl-2-oxopyridine-3-carbonitrile (234). The pyridone 234, was successfully synthesised, in a one-pot procedure by direct condensation of ethyl cyanoacetate, hydroxylamine and acetylacetone in the presence of a catalytic amount of piperidine, through the Hantzsch-Knoevenagel reaction (Scheme 194).\(^{[157-158]}\)
Results and Discussion

\[
\begin{align*}
\text{EtO} &\hspace{1cm} + \hspace{1cm} \text{NH}_2\text{OH-HCl/KOH} \\
\text{OEt} \hspace{1cm} \text{CN} &\quad \text{EtOH} \\
\text{CN} &\quad \text{rt} \\
\end{align*}
\]

Reflex, 40 min, 20% piperidine cat.

Scheme 194

The product was originally isolated as ivory coloured crystals but also existed as its tautomeric form \(234b\) depending on the pH reached during work-up. In fact, on repeating the reaction, it was possible to isolate, at pH <3, a bright yellow solid which exhibited the same solid state NMR and mass spectra of the previous solid but a different melting point and solution NMR (see Experimental Part). This behaviour is characteristic of a tautomeric equilibrium between the two species \(234a\) and \(234b\), and is a function of pH whereby the predominance of either form can be detected by solution NMR (Figure 23).

With \(234\) in our hands, we were now ready to test it as catalyst for the oxidation of adamantane and in particular, we chose to employ the pyridone \(234a\). The investigation was firstly carried out avoiding the use of metal by repeating Ishii’s
Results and Discussion

conditions with tetra-n-butyl ammonium bromide or using different initiators containing a peroxide link (Scheme 195, Table 26). In particular, we selected the system of hydrogen peroxide or tert-butyl hydroperoxide and phosphotungstic acid which has been employed in the past for in situ generation of nitroxides.\textsuperscript{[49]}

\[\text{PhCF}_3, 80°C, 3d\]

\[\text{Pyridone (10 mol\%)}\]

\[\text{(1 atm)}\]

\[\text{O}_2\]

\[\text{31} \rightarrow \begin{array}{c}
\text{OH} \\
\text{32} + \text{33} + \text{34}
\end{array}\]

\[\text{Scheme 195}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCF(_3), Bu(_4)NBr (H(_2)O)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PhCF(_3), H(_2)O(_2), H(_3)PO(<em>4)O(</em>{12}) xH(_2)O</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PhCF(_3), t-BuOOH, H(_3)PO(<em>4)O(</em>{12}) xH(_2)O</td>
<td>0</td>
</tr>
</tbody>
</table>

[Reactions were carried out using conditions of Scheme 195.]

Table 26

Since no oxidation was observed, we considered that the lack of reactivity might be dominated by the insolubility of the pyridone in trifluorotoluene. Consequently, the methodology was varied, and since cobalt salts were also widely employed in Ishii type autoxidations, either in acetic acid or acetonitrile, we carried out an investigation using cobalt (II) acetate tetrahydrate (Scheme 196) and cobalt (III) acetylacetonate (Scheme 197). The results of the oxidations performed in the presence of cobalt (II) at 80°C are summarised in Table 27.

\[\text{Pyridone (10 mol\%)}\]

\[\text{Co(OAc)}\(_2\) x 4\text{H}_2\text{O}\]

\[80°C, 3d\]

\[\text{31} \rightarrow \begin{array}{c}
\text{OH} \\
\text{32} + \text{33} + \text{34}
\end{array}\]

\[\text{Scheme 196}\]


### Results and Discussion

Table 27

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Conv(%)</th>
<th>32 (%)</th>
<th>33 (%)</th>
<th>34 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CN, Co (II) (0.5 mol %)</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>AcOH, Co (II) (0.5 mol%)</td>
<td>58</td>
<td>32</td>
<td>7</td>
<td>V</td>
</tr>
<tr>
<td>3</td>
<td>PhCl, Co (II) (0.5 mol%)</td>
<td>35</td>
<td>99</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>PhCF₃/AcOH (1:1), Co (II) (0.5 mol%)</td>
<td>58</td>
<td>48</td>
<td>14</td>
<td>V</td>
</tr>
<tr>
<td>5</td>
<td>PhCF₃/AcOH (3:1), Co (II) (0.5 mol%)</td>
<td>50</td>
<td>47</td>
<td>11</td>
<td>V</td>
</tr>
<tr>
<td>6</td>
<td>PhCF₃/AcOH (1:1), Co (II) (1 mol%)</td>
<td>68</td>
<td>47</td>
<td>10</td>
<td>V</td>
</tr>
<tr>
<td>7</td>
<td>PhCF₃/AcOH (1:1), Co (II) (0.5mol%), t-BuOOH (10mol%)</td>
<td>76</td>
<td>40</td>
<td>10</td>
<td>V</td>
</tr>
<tr>
<td>8</td>
<td>PhCF₃/AcOH (1:1), Co (II) (0.5 mol%), 100°C</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9*</td>
<td>PhCF₃/AcOH (1:1), Co (II) (0.5 mol%), no pyridone</td>
<td>30</td>
<td>53</td>
<td>12</td>
<td>V</td>
</tr>
<tr>
<td>10*</td>
<td>PhCF₃/AcOH (1:1), Co (II) (0.5mol%), t-BuOOH (10 mol%), no pyridone</td>
<td>46</td>
<td>53</td>
<td>8</td>
<td>V</td>
</tr>
<tr>
<td>11*</td>
<td>PhCF₃/AcOH (1:1), t-BuOOH (10 mol%), no pyridone</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

[Reactions were carried out using conditions of Scheme 196; (V) indicated the presence of 1,3-adamantanol but its selectivity was not determined by the use of an internal standard; (*) blank experiment.]

Similar conversions (58%) were achieved either by working in acetic acid (Entry 2) or in a mixture of trifluorotoluene and acetic acid (Entry 4). Gratifyingly, a significant increase in conversion (76%) was observed when 10 mol% of an 80% solution of tert-butyl hydroperoxide was added (Entry 7). Entries 9, 10 and 11 were the blank experiments, wherein the concentration of one of the species was equal to zero. When the pyridone was withheld and tert-butylhydroperoxide was added, a 46% of conversion was observed for the incipient homolysis of the initiator catalysed by the metal.

If cobalt acetate was dehydrated, a similar conversion of 51 % was achieved using the pyridone (10 mo%) in a mixture of trifluorotoluene/acetic acid (1:1) at 80°C for
three days, suggesting that in this case, the molecules of water which coordinate to the metal, do not influence the reaction.

Autoxidation reactions were also studied in the presence of Co (III) acetylacetonate as listed in Table 28, Scheme 197.

![Scheme 197](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Conv(%)</th>
<th>32 (%)</th>
<th>33 (%)</th>
<th>34 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCl, Co (III) (0.5 mol%)</td>
<td>57</td>
<td>46</td>
<td>16</td>
<td>V</td>
</tr>
<tr>
<td>2</td>
<td>PhCF₃/AcOH (1:1), Co (III) (0.5 mol%)</td>
<td>60</td>
<td>47</td>
<td>10</td>
<td>V</td>
</tr>
<tr>
<td>3</td>
<td>PhCF₃/AcOH (1:1), Co (III) (0.5 mol%), t-BuOOH (10 mol%)</td>
<td>77</td>
<td>41</td>
<td>11</td>
<td>V</td>
</tr>
<tr>
<td>4*</td>
<td>PhCF₃/AcOH (1:1), Co (III) (0.5 mol%), no pyridone</td>
<td>46</td>
<td>57</td>
<td>14</td>
<td>V</td>
</tr>
</tbody>
</table>

[Reactions were carried out using conditions of Scheme 197; (V) indicated the presence of 1,3-adamantanol but its selectivity was not determined by the use of an internal standard; (*) blank experiment.]

Table 28

In this case, a very good conversion was observed once again when working in the presence of 10 mol% of tert-butylhydroperoxide in a mixture of PhCF₃/AcOH (1:1) (Entry 3, Table 28). By comparison of the two tables, we can conclude that the results were similar for the use of either a Co (II) or a Co (III) complex. However, the activity of these systems appears to suffer from two main limitations.

-Thus, the formation of the pyridine oxide tautomer, 234b, should be favoured in acetic acid, and this may deactivate the species for oxidation to the desired nitroxide radical catalyst.
Additionally, it should be remembered that hydroxamates are one of the major classes of naturally occurring metal complexing agents. As first revealed by an X-ray diffraction study of the benzohydroxamate complex of iron (III)\textsuperscript{[159]}, chelation involves both the oxygen atom of the carbonyl group and also that of hydroxylamine. Numerous papers have shown that monohydroxamic acids adopt a typical binding mode as shown in Scheme 198 and cyclic derivatives of hydroxamates such as 2-hydroxypyridine-$N$-oxide with Cu (II) and Fe (III), have been studied and characterized by Farkas.\textsuperscript{[160]} Once such a complex is formed, it will probably not act as nitroxide catalyst for the subsequent oxidation.

![Scheme 198](image)

On the more optimistic side, it is however possible to involve the possibility that N-O bond homolysis of such hydroxamate complexes can occur and that the resultant species could eventually become a “doubly activated” species for hydrogen atom abstraction as implied in Scheme 199.
We were interested in the investigation of these two possible factors and their influence on the oxidation process. We first examined the possibility of formation of such complexes between the $N$-hydroxy pyridone and the cobalt salt using two different techniques viz., NMR and UV.

Since cobalt (II) results in production of a paramagnetic species, nuclear magnetic resonance studies are not possible and hence, we concentrated our attention on the system employing cobalt (III) salts. Therefore, we studied the reactivity between 234 and cobalt acetylacetonate (III) (268) in acetic acid both at room temperature and at 75°C (Scheme 200). The formation of two or more complexes can be hypothesised in consideration of the fact that one or more ligands could be exchanged (269 and 270).
Deuterated acetic acid (CD\textsubscript{3}COOD) was used for the NMR studies and the spectra of the two starting materials at room temperature and at 75 °C were registered. The chemical shifts (\(\delta\)) for the two compounds are listed below (Figure 24).

As can be seen, it was not possible to detect the signal of the methine CH of the acetylacetonate ligand due to facile hydrogen-deuterium exchange. In addition to this problem, the two methyls of different acetylacetonate groups were overlapping complicating the spectrum. Nevertheless, we heated a mixture of the N-hydroxy pyridone and cobalt (III) in a 1:1 ratio at 75°C, but did not observe the formation of any new species. To simplify this problem, we investigated the use of acetic acid as solvent, which would not give exchange with the ligands. We then ran the spectra for
the Co(acac)$_3$ and observed a signal at 5.54 ppm (line width at half height = 2.60 Hz) which accounts for the olefinic CH of the acetylacetonate. When a mixture of 234 and Co (III) (1:2) was heated to 75°C, only starting materials were observed. To confirm this result, some diffusion coefficient studies at room temperature were carried out. Two samples were prepared: one contained 10 mmol of the free N-hydroxy pyridone in solution of acetic acid (1 ml) and the other one using a mixture of Co (III) (20 mmol) and N-hydroxy pyridone (10 mmol) in acetic acid (1 ml). The measured values of diffusion coefficient for N-hydroxy pyridone were respectively:

* $6.77 \times 10^{-10} \text{ m}^2/\text{s}$ in free solution.
* $6.71 \times 10^{-10} \text{ m}^2/\text{s}$ in the solution with the cobalt (III).

As the difference between these two $D$-values was of the same order as experimental error, it was concluded that no change in the diffusion rates had occurred and therefore that no complexation occurred at room temperature.

UV studies were also carried out employing a solution of the N-hydroxy pyridone and cobalt (III) in chloroform (10$^{-4}$ M) and the absorbance was measured. Two main peaks were observed at 260 and 340 nm, which corresponded to the cobalt species and N-hydroxy compound respectively, by comparison with the spectra of the authentic starting materials. Even when the solution was heated up to 70°C for 30 minutes, either in the absence or in the presence of tert-butyl hydroperoxide, similar results were observed. The formation of no other peaks clearly suggests once again that no other complexes are involved in the reaction.

We finally concluded that in the solution of acetic acid, no stable complexes between the cobalt and the N-hydroxy pyridone are formed basing our affirmation on the negative results of both NMR and UV. Certainly, we could not rule out the possibility of different complexes which rapidly exchanged under the reaction conditions and which could not be observed by standard procedures. In order to complete this overview of the behaviour of 234, we finally attempted ESR measurements on the N-hydroxy pyridone in fluorobenzene (1.22 x 10$^{-3}$ M) using an excess of AIBN at 80°C. Unfortunately, no nitroxide radical signal was registered, a result which might relate to the instability of the derived nitroxide.
Whilst these studies were in hand, an analogue of the $N$-hydroxy pyridone, which contained trifluoromethyl groups was targeted in an effort to improve the efficiency of the derived nitroxy radical. Thus, we firstly repeated the same one pot procedure used for $N$-hydroxy pyridone (Scheme 194) replacing acetylacetone with hexafluoro acetylacetone, but no product was isolated. Then, in order to enable us to follow the reaction, the potassium cyanoacetohydroxamate salt was prepared in a separate step by reaction of hydroxylamine with ethyl cyanoacetate (Scheme 201).

\[
\begin{align*}
\text{CN} & \quad \text{Et} \quad \text{O} \\
266 & \quad + \quad \text{NH}_2\text{OH HCl/KOH} \quad \text{MeOH} \quad \text{rt} \quad 35\% \\
\text{CN} & \quad \text{NHOK} \quad \text{O}
\end{align*}
\]

Scheme 201

267 was then reacted with the 1,3-diketone in the presence of base but even in this case, no reaction was observed and the approach was abandoned (Scheme 202). The lack of reactivity may well attributed to the much stronger acidity of the hexafluoro acetylacetone derivative when compared to acetylacetone, which would prevent the initial condensation.

\[
\begin{align*}
\text{CN} & \quad \text{NHOK} \\
267 & \quad + \quad \text{CH}_3\text{COCF}_3 \quad \text{Base} \\
\text{CF}_3 & \quad \text{CN} \\
\text{F}_3\text{C} & \quad \text{OH} \\
271 & \quad \text{N} \quad \text{O}
\end{align*}
\]

Scheme 202

By way of a final comparison however between our $N$-hydroxy pyridone derivative and $N$-hydroxyphthalimide, it would appear that both compounds are able to catalyse the oxidation of alkanes although NHPI is clearly a more efficient system. Nevertheless, the structure 234 is stable to the oxidation conditions which was not the case of 1-hydroxy oxindole (231), and is thus for the best catalyst which we have found in the course of our studies.
2.3.5 CONCLUSIONS AND PERSPECTIVES

The foregoing discussion of our results has revealed several important findings, and to certain extent, fulfilled our principal objective of understanding further facets of autoxidation and in particular the mode of action of PINO. Furthermore, our rapid screening programme for some new nitroxides which are capable of atom hydrogen abstraction from alkanes to perform an aerobic oxidation has led to the \(N\)-hydroxypyridone nucleus as a system which can be developed further.

In the first instance (Section 2.2), during our study into the mechanistic pathways that involved the nitroxide PINO, the report by Ishii that tetra-\(n\)-butylammonium bromide could be used an additive led to our interest in the important onium salt effect. A new oxidation system based on the use of \(\text{tert}\)-butyl hydroperoxide and a phase transfer catalyst in a solution of adamantane in trifluorotoluene at 80°C was then discovered. Consequently, an extensive study of different onium salts was conducted and as summarised in Table 29, our best conversion (ca. 75%) was realised in the presence of tetra-\(n\)-butylammonium fluoride or triphenyl sulfonium bromide (Entries 2 and 19, Table 29).

\[
\begin{align*}
\text{adamantane} & + \text{O}_2 \quad \text{(1 atm)} \quad \text{t-BuOOH (1 equiv.)} \quad \text{PhCF}_3, 80^\circ\text{C, 3d} \quad \text{PTC (0.02 equiv)} \\
\text{31} & \quad \text{32}^\text{a} \quad \text{33}^\text{a} \quad \text{34}^\text{a}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>(\text{PTC}^e)</th>
<th>Conversion (%)</th>
<th>(32^a) (%)</th>
<th>(33^a) (%)</th>
<th>(34^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>35</td>
<td>47</td>
<td>11</td>
<td>(\checkmark)</td>
</tr>
<tr>
<td>2</td>
<td>(n)-Bu(_4)NF(_d)</td>
<td>75</td>
<td>43.6</td>
<td>7.76</td>
<td>19.8</td>
</tr>
<tr>
<td>3</td>
<td>(n)-Bu(_4)NCl</td>
<td>54</td>
<td>64</td>
<td>18.6</td>
<td>(\checkmark)</td>
</tr>
<tr>
<td>4</td>
<td>(n)-Bu(_4)NBr</td>
<td>45</td>
<td>67.5</td>
<td>10.1</td>
<td>21.5</td>
</tr>
<tr>
<td>5</td>
<td>(n)-Bu(_4)NI</td>
<td>31</td>
<td>16.6</td>
<td>8.9</td>
<td>(\checkmark)</td>
</tr>
<tr>
<td>6</td>
<td>DAST</td>
<td>33</td>
<td>33</td>
<td>10</td>
<td>(\checkmark)</td>
</tr>
<tr>
<td>7</td>
<td>TASF</td>
<td>63</td>
<td>35</td>
<td>23</td>
<td>(\checkmark)</td>
</tr>
<tr>
<td>8</td>
<td>TBAT</td>
<td>0</td>
<td>-</td>
<td>-</td>
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<td>9</td>
<td>KF</td>
<td>traces</td>
<td>-</td>
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</tr>
</tbody>
</table>

Scheme 203
## Results and Discussion

<table>
<thead>
<tr>
<th></th>
<th>Reaction Product</th>
<th>Yield (%)</th>
<th>Isolated (%)</th>
<th>Selectivity (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Bu$_4$NBF$_4$</td>
<td>63.6</td>
<td>50</td>
<td>14.5</td>
<td>γ</td>
</tr>
<tr>
<td>11</td>
<td>Bu$_4$NBF$_4$/H$_2$O</td>
<td>60</td>
<td>46</td>
<td>14</td>
<td>γ</td>
</tr>
<tr>
<td>12</td>
<td>n-Bu$_4$NOH$^f$</td>
<td>48</td>
<td>29.8</td>
<td>8</td>
<td>γ</td>
</tr>
<tr>
<td>13</td>
<td>n-Bu$_4$NOH$^g$</td>
<td>66</td>
<td>35.54</td>
<td>5.6</td>
<td>γ</td>
</tr>
<tr>
<td>14</td>
<td>n-Bu$_4$NHSO$_4$</td>
<td>38</td>
<td>41.8</td>
<td>5</td>
<td>γ</td>
</tr>
<tr>
<td>15</td>
<td>Noyori’s catalyst</td>
<td>57.5</td>
<td>34</td>
<td>12</td>
<td>γ</td>
</tr>
<tr>
<td>16</td>
<td>Bu$_4$NPBr$_4$</td>
<td>34</td>
<td>51</td>
<td>18</td>
<td>γ</td>
</tr>
<tr>
<td>17</td>
<td>Bu$_4$NPBr$_4$/H$_2$O</td>
<td>43</td>
<td>56</td>
<td>17</td>
<td>γ</td>
</tr>
<tr>
<td>18</td>
<td>Ph$_3$SBr</td>
<td>38</td>
<td>40</td>
<td>17.5</td>
<td>γ</td>
</tr>
<tr>
<td>19</td>
<td>Ph$_3$SBr/H$_2$O</td>
<td>75</td>
<td>40</td>
<td>15</td>
<td>γ</td>
</tr>
<tr>
<td>20</td>
<td>Me$_3$SBr</td>
<td>50</td>
<td>44</td>
<td>25</td>
<td>γ</td>
</tr>
<tr>
<td>21</td>
<td>Me$_3$SBr/H$_2$O</td>
<td>43</td>
<td>58</td>
<td>14</td>
<td>γ</td>
</tr>
<tr>
<td>22</td>
<td>Ph$_4$PBr</td>
<td>49</td>
<td>45</td>
<td>15.2</td>
<td>γ</td>
</tr>
<tr>
<td>23</td>
<td>Ph$_4$PBr/H$_2$O</td>
<td>31.6</td>
<td>68.1</td>
<td>23.3</td>
<td>γ</td>
</tr>
<tr>
<td>24</td>
<td>Bu$_4$PBr</td>
<td>28</td>
<td>65</td>
<td>23</td>
<td>γ</td>
</tr>
<tr>
<td>25</td>
<td>Bu$_4$PBr/H$_2$O</td>
<td>37</td>
<td>53</td>
<td>18.5</td>
<td>γ</td>
</tr>
<tr>
<td>26</td>
<td>ImidBF$_4$</td>
<td>53</td>
<td>58</td>
<td>16</td>
<td>γ</td>
</tr>
<tr>
<td>27</td>
<td>ImidBF$_4$/H$_2$O</td>
<td>52</td>
<td>53</td>
<td>19</td>
<td>γ</td>
</tr>
<tr>
<td>28</td>
<td>ImidPF$_6$</td>
<td>40</td>
<td>63</td>
<td>13.4</td>
<td>γ</td>
</tr>
<tr>
<td>29</td>
<td>ImidPF$_6$/H$_2$O</td>
<td>32</td>
<td>80</td>
<td>17.7</td>
<td>-</td>
</tr>
</tbody>
</table>

[Reactions were carried out using conditions of Scheme 203; DAST is (diethylamino)sulfur trifluoride; TAS-F is tris(dimethylamino)sulfur(trimethylsilyl)difluoride; TBAT is tetra-n-butylammonium triphenyldifluorosilicate; Noyori’s catalyst is CH$_3$(CH$_2$)$_7$NMeHSO$_4$; Imid is imidazolium; (a) selectivity; (b) products isolated by Flash Chromatography; (c) conversion was calculated by GC using as the external standard, naphthalene; (d) Bu$_4$NF was used as a solid after removing THF under reduced pressure, without heating; (e) PTC (Phase-Transfer Catalyst); (f) 60% tetra-n-butylammonium hydroxide in water; (g) tetra-n-butylammonium hydroxide solid after freeze dryer (see Experimental Part); (V) indicated the presence of 1,3-adamantanol but its selectivity was not determined by the use of an internal standard.]

**Table 29**

The success of this system relies critically on the presence of a tiny amount of water which increases the turnovers in the oxidation, even though any excess then inhibits the reaction. At this moment in time, our efforts to understand this intriguing system have not been successful but we have certainly proved that the phase transfer catalyst
can decompose tert-butyl hydroperoxide, by titration studies. Additionally, we have dismissed the mechanism proposed by Csányi and collaborators relating to the decomposition of tert-butyl hydroperoxide in the presence of tetra-n-hexylammonium chloride, by using a higher level of theory through some ab initio calculations. From our results, the suggested electrostatic interaction of the ammonium cation and the more alkyl substituted oxygen atom of the hydroperoxide in combination with activation of the external oxygen through hydrogen bonding with the molecule of water, has emerged as a completely unrealistic proposition. Although the present system requires one equivalent of the hydroperoxide, we are certain that once the mechanism can be fully delineated, the efficiency of the system could be dramatically improved, thereby reducing the reaction time and the number of equivalents of reagents.

In our second approach, the screening of new replacements for N-oxypthalimide, PINO, the fragile nature of sulfonated N-hydroxylamines especially in the presence of nucleophiles and bases was noted. However, from a comparison between 2-hydroxy-benzo[1,3,2]dithiazole (95) and N-hydroxsaccharin (96), it appears possible that replacement of the carbonyl by a difluoromethylene group may lead to an interesting system (272) (Scheme 204).

![Scheme 204](image)

In the case of difluoromethylene substituted N,N-hydroxylamines, the major problem for our ene reactions lay in the great difference in energy between the HOMO and LUMO of the two partners during the cycloaddition. This result however confirmed a trend already present in the literature where only reactions between acynitroso derivatives and electron-rich olefins were reported. Moreover the extremely reactive...
nature of these nitroso compounds provides a significant obstacle towards their isolation, although the formation of the desired nitroxides can be followed and proved by ESR experiments. Amongst those conjugated systems which were studied, the dimeric compounds derived from phthalic anhydride appear of interest although their insolubility in common organic solvents required the use of high temperature or heterogeneous conditions. This problem may be solved by the introduction of alkyl chains on the aromatic ring (Scheme 205). For example, 4-hexyloxy carbonyl groups could help the solubilisation of the derivative 224 as already used by Ishii for the case of the trimellitic compound (Scheme 27).

Finally, towards the end of the work described in this thesis the heterocyclic chemistry of \( N \)-hydroxy indoles and pyridones has opened new perspectives for future work. Thus, the \( N \)-hydroxy pyridone (234) exhibited a quantifiable effect in the oxidation of adamantane, even though the use of acetic acid probably favoured its tautomeric form. All of the series of \( N \)-hydroxy indol-2-ones showed an interestingly low values of hyperfine coupling constants for nitrogen, which we believe to be a good indicator for a powerful hydrogen atom abstractor (Scheme 206). Further functionalisation on the aromatic ring by the introduction of EWG groups could then further enhance their reactivity.
The initial difficulties encountered in the preparation of 1-hydroxyoxindole (231), together with its extreme lability under oxidation conditions meant that further substitution was essential. The introduction of a bromine atom into the 3 position proved to be rather challenging and even under mild conditions, polymerisation and decomposition of the starting material occurred. New routes can be explored to synthesise 231 and related derivatives and further isolation and purification of 229 and 230 is still required.

Interestingly, during our search for a new methodology for the generation of 231 by oxidation of indoline in the presence of dimethyldioxirane or hydrogen peroxide/sodium tungstate, the formation of a crude mixture which we believed to contain “indigo-type” derivatives was observed. The possibility of preparing pure samples of these types of compounds through a different synthetic route could certainly lead to a new catalyst as already implied for the oxidation of adamantane with the crude material derived from the oxidation of indoline (Scheme 170).

By analogy with these indigo derivatives, another conjugated system with a low $a_N$ value is the biradical 276 which is reported to derive by reaction with one equivalent of DEAD and two equivalent of 1-hydroxy-2-phenyl indole (274) according to the following mechanism (Scheme 207).[^161]
The ESR spectrum of this compound (276) shows $a_N = 5.83$ Gauss above 135°C and one with 4.8 Gauss below 135°C, which fits perfectly within the range of compounds of interested to us.

The present study has however provided a pointer that novel classes of nitroxide could be valuable for the oxidation of alkanes. The synthesis of these efficient and powerful radicals is however complicated by their reactivity and the difficulties associated with precursor isolation, and clearly efficient autoxidation still represents a great challenge for the future.
EXPERIMENTAL PART
GENERAL EXPERIMENTAL PROCEDURES

Melting points were determined using a Reichart Hotstage or Electrothermal 9100 instrument and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer FT-IR 1605 instrument, as thin films on NaCl or as KBr discs and the major features of each spectrum are reported.

$^1$H-NMR Spectra were recorded at 300 MHz on a Bruker AMX-300 or at 400 MHz on a Bruker AMX-400 or at 500 MHz on a Bruker Avance 500. $^{13}$C-NMR spectra were recorded at 75 MHz, 100 MHz or 125 MHz using the instruments previously mentioned.

Chemical shifts ($\delta$) are referenced to the residual solvent peak and they are quoted in part per million (ppm). $^{19}$F-NMR were recorded at 242 MHz on a Bruker AMX-300 and chemical shifts ($\delta$) are referenced to CFCl$_3$ and they are quoted in part per million (ppm). $^{31}$P-NMR were recorded at 121.4 MHz on a Bruker AMX-300 spectrometer and chemical shifts ($\delta$) are quoted in part per million (ppm). Solid state NMR ($^{13}$C-CPMASS-TOSS) was performed by Mr. D. Butler at UCL. The abbreviations used to indicate multiplicity of the peaks are: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, dd = doublet of doublets.

Mass spectra were recorded under either fast atom bombardment (FAB) or atmospheric pressure chemical ionisation (APCI) conditions by the ULIRS mass spectrometry service at the School of Pharmacy, University College London or under EI conditions using a Perkin-Elmer mass spectrometer at UCL.

Microanalyses were performed by Mrs Jill Maxwell, at Christopher Ingold Laboratories, University College London.

X-ray crystallography was performed by Dr. D. A. Tocher at UCL using a Bruker Smart Apex, CCD diffractometer.

Analytical thin layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F$_{254}$) and visualised with ultraviolet light (254 nm) and by staining with basic potassium permanganate solution, acidic vanillin solution, acidic anisaldehyde; all followed by heat. Wurster's blue solution$^{[162]}$, prepared from a 1% (w/v) solution of $N,N,N',N'$-tetramethyl-p-phenylenediamine dihydrochloride, in 50% aqueous methanol containing 1 ml of glacial acetic acid per 100 ml of reagent, was used to visualise on TLC the cholesterol hydroperoxides. The plates
Experimental

were dipped into the solution observing blue spots against a lighter violet background: the contrast was improved by warming on a hot plate.

Flash chromatography was performed using BDH silica gel (40-60 μm).

Gas chromatography was carried out on a Hewlett-Packard 5890A instrument (flame ionisation detector) with a 25 m x 0.50 mm BPX5 column using hydrogen as the carrier gas, and 1,2,4-trichlorobenzene as an internal standard or a naphthalene solution as an external standard. The program had an initial temperature of 70°C for 2 minutes and the rate of temperature increase was 10°C/min until the final temperature of 250°C. The column was kept at this temperature for 5 min before cooling. It is important to underline that accurate calibrations were performed before analysing the crude mixtures derived from the oxidations reactions. In particular, standard solutions of commercially available adamantane or adamantane-1-ol or adamantane-2-one and 1,2,4-trichlorobenzene, were injected into the GC to formulate the equations that were used to calculate the percentage conversion and selectivity of the oxidation reactions.

PE, refers to petroleum ether 40-60. Acetone was dried with calcium sulphate and then distilled. Acetonitrile was pre-dried with silica, then refluxed with calcium hydride and fractionally distilled. THF, diethyl ether, toluene and benzene were distilled from sodium-benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Dimethylacetamide was dried over sodium hydride 95%, and then distilled. Dimethylformamide was pre-dried with magnesium sulfate, distilled from silica and stored over Linde Type 4Å molecular sieves. Methanol was distilled from magnesium turnings and iodine. Carbon tetrachloride was distilled over P₂O₅ and stored over sieves. Pyridine was stirred overnight over KOH, then distilled and stored over sieves. Triethylamine was predried over KOH and then distilled from the same drying agent. Trifluorotoluene was dried by treatment with anhydrous potassium carbonate, then P₂O₅ and fractionally distilled. Trifluoroacetic anhydride was stirred with KMnO₄, and slowly distilled. Tert-butylalcohol was predried over magnesium sulphate, distilled from magnesium/iodine and stored over molecular sieves.

Tetra-n-butyrammonium bromide was recrystallised from a mixture of dry ethyl acetate and diethyl ether and stored in a dessicator with P₂O₅. Tetra-n-butyrammonium fluoride was isolated from a solution of THF (1 M). The solvent was evaporated under vacuum (15 mmHg) over a period of 30 minutes without heating, the yellow solid was stored under nitrogen in a dessicator over P₂O₅. Tetra-
Experimental

$n$-butylammonium hydroxide was afforded from aqueous solution (60%), after drying overnight in the freeze drier. All the other reagents and solvents were purified as necessary following the usual procedures.\(^{[163]}\)

All reactions were performed using oven-dried glassware under a positive pressure of nitrogen unless otherwise stated. When oxidation reactions were carried out, the flask was washed with a base (KOH in MeOH), rinsed with a 2N solution of HCl, then acetone and oven dried. The reproducibility of the reactions was always considered as an important parameter and the reported conversions can be considered as an average between successive runs of the same experiment. Moreover, the influence of the rate of agitation of the reaction mixture containing adamantane, trifluorotoluene, water and onium salts was studied but no increase in conversion was observed.

Two different analytical tests, Fehling's or iron chloride solutions, were used to identify benzohydroxamic derivatives.\(^{[164]}\)

Fehling's reagent resulted by the mixture of two different solutions:
- Solution no.1: Copper (II) sulphate (34.6 g) was dissolved in water containing a few drops of conc. sulfuric acid and the solution was then diluted to 500 ml.
- Solution no.2: Sodium hydroxide (60 g) and Rochelle salt (sodium potassium tartrate) (173 g) were dissolved in water, filtered if necessary through a sintered glass funnel, and then made up the filtrate and washing to 500 ml.

The two solutions were kept separately and exactly equal volumes were mixed immediately before use. When the benzohydroxamic derivative was added to the solution and the mixture was heated, a change in colour in the solution was observed.

In the case of the iron (III) chloride test, the hydroxamic compound was added to a dilute solution of iron chloride. It was possible to observe the immediate formation of a violet-blue complex according to the equation:

$$\text{FeCl}_3 + 3 \text{RCONOHR}' \rightarrow \text{Fe(ONR'COR)}_3 + 3\text{HCl}$$

The solution samples for ESR spectroscopy were prepared in either open quartz tubes of 3 mm i.d., 0.5 mm wall thickness or of 2 mm i.d., 0.5 mm wall, in the case of samples with high dielectric constant. In open tubes, the samples were made up by weight (solids) or volume (liquids) using microsyringes and they were degassed by bubbling nitrogen through the solution using a Teflon cannula for approximately 5 minutes. The open quartz tubes were then sealed with plastic cap and Nescofilm.
Experimental

Spectra were obtained using a Varian E-109 instrument operating at 9.1-9.4 GHz and equipped for *in situ* UV-irradiation of the samples. The temperature of the sample was found using a digital thermometer (Comark) connected to a thermocouple, positioned about *ca.* 4 cm down the dewar insert alongside the sample tube.

*g*-Factors were determined by measurement of the microwave frequency (using an E.I.P. Autohet microwave counter, model 331) and the magnetic field at the centre of the spectrum (using a Varian NMR gaussmeter). The difference in the field between the gaussmeter probe and the sample was determined by measuring the *g*-factor of the pyrene radical anion, generated by the reduction of the pyrene with sodium in THF, which is accurately known to be 2.002710. The true field at the sample was found to be 0.19 G smaller than at the gaussmeter probe. The unknown *g*-factor was calculated using the resonance condition shown in the following equation:

\[
g = \frac{h}{\mu g} \times \frac{v_0}{B_0}
\]

\((h/\mu g) = 0.7144385 \text{ G MHz}^{-1}\) and \(v_0\) and \(B_0\) are the microwave frequency (in MHz) and the applied magnetic field at the centre of the spectrum (in G), respectively.
**General procedure for the oxidation of adamantane using t-butyl hydroperoxide and PTC:**

A dry trifluorotoluene (20 ml) solution of adamantane (1.09 g, 8 mmol, 1 equiv.) and tetra-n-butylammonium halide (0.02 equiv.), was placed in a dried three necked flask equipped with a condenser linked to a burette gas system filled with O₂. The solution was degassed twice and then the apparatus filled with oxygen. An 80% solution of t-butyl hydroperoxide in di-t-butylperoxide (0.1-1equiv.) was slowly added via syringe and the mixture was stirred. [When water (0.1 ml) was required, its addition was performed together with the hydroperoxide.] The reaction mixture was heated to 80°C and the conversion of adamantane was followed by GC, using 1,2,4-trichlorobenzene as internal standard (0.5 ml, 4 mmol, 0.5 equiv.). The products had also been isolated after removal of the solvent by flash chromatography [hexane/ethyl acetate (5:1)] and compared with authentic samples.

**Synthesis of methyltri-n-octylammonium hydrogen sulfate, 59.**

\[
\begin{align*}
[\text{CH}_3(\text{CH}_2)_{7}]_3\text{N} & \quad \rightarrow \quad [\text{CH}_3(\text{CH}_2)_{7}]_3\text{N}^+ \quad \text{HSO}_4^- \\
\end{align*}
\]

A round bottomed flask equipped with a magnetic stirring bar, was charged with tri-n-octylamine (8.85 g, 25 mmol, 1 equiv.) in toluene (10 ml). Under stirring, dimethyl sulfate (3.25 g, 25.8 mmol, 1.08 equiv.) was added in portions and the mixture was then heated at 140°C for 17 hours. Water (0.5 ml) was added to the dark red solution and heated at 90°C for 12 hours. After the mixture was cooled to room temperature, 49% sulfuric acid (10 ml) was added, and the biphasic mixture was stirred vigorously for 12 hours. Removal of volatile material in vacuo gave a black viscous product that contained an impurity from dimethyl sulfate. To this product was added a mixture of water (20 ml) and dichloromethane (10 ml) and the mixture solution was saturated with potassium hydrogen sulfate. After extraction with dichloromethane (3 x 10 ml), the combined organic layers were washed with sat. aq. sodium sulfate solution (3 x 5
ml) and dried over sodium sulfate. After removal of the solvent, a pasty brown residue (59) remained (10 g, 84%).

**1H-NMR** (CDCl₃, 300 MHz): 3.25 (6H, m, CH₂ x3), 3.19 (3H, s, NMe), 1.66 (6H, br s, CH₂ x3), 1.35-1.27 (30H, m, CH₂), 0.88 (9H, t, 3J = 7.0 Hz, Me x3); **13C-NMR** (CDCl₃, 75 MHz): 62.2 (CH₂), 31.9, 29.2, 29.1, 26.3, 22.9, 22.6 (CH₂ x6), 14.3 (Me x3); **IR** (CHCl₃/cm⁻¹): νmax 3020, 2930, 2400, 1522, 1480, 1430, 1055, 1030, 931, 881, 850 **MS**; (FABMS, Matrix MNOBA+Na): m/z 368 (M–HSO₄⁺, 100%), 254 (MeNoctyl₂⁺, 18%).

**Synthesis of triphenyl sulfonium bromide, 63:**

A phenylmagnesium bromide solution was prepared from freshly distilled bromobenzene (17.27 g, 0.1 mol, 8.3 equiv.), dry ether (75 ml) and magnesium turnings (2.43 g, 0.1 mol, 8.3 equiv.), under nitrogen in a three-necked flask fitted with a stirrer and dropping funnel. Dry benzene (75 ml) was added to the flask and the ether was removed by distillation until the temperature of the distillate vapours had reached 70°C. Diphenylsulfoxide (2.5 g, 0.012 mol, 1 equiv.) dissolved in dry benzene (25 ml), was added to the Grignard solution and the mixture was refluxed under nitrogen for 24 hours. After the reaction mixture was cooled to 0°C and hydrolysed with a solution consisting of hydrobromic acid 48% (5.25 ml) and water (5.25 ml), the benzene layer was separated and extracted with aq. 5% hydrobromic acid (4 x 20 ml). The aqueous extracts and the aqueous layer from the hydrolysis were combined and extracted with chloroform (6 x 25 ml). The combined chloroform extracts were evaporated to dryness to yield 2.5 g of colourless crystals of triphenyl sulfonium bromide. Two recrystallisations from a mixture of chloroform and acetone (1:5) by the addition of ether, gave pure material (2 g, 47%).
Experimental

m.p.: 285-286°C (lit. 285-286°C); 1H-NMR (CDCl₃, 300 MHz): δ 8.20-7.93 (6H, m, CH x6), 7.84-7.72 (9H, m, CH x9); 13C-NMR (CDCl₃, 75 MHz): δ 134.08, 131.88 (CH x9), 125.38 (C₁₃c x3), 120.27 (CH x6); IR (KBr/cm⁻¹): νmax 3076, 2993 (Ar CH), 2359, 2339, 1473, 1443, 1315, 1067, 997; MS (FABMS, Matrix MNOBA+Na): m/z 266 (M-Br⁺, 100%).

Synthesis of 3β-hydroxy-5α-hydroperoxycholest-6-ene, 65:

Into a solution of cholesterol (0.80 g, 2.07 mmol, 1 equiv.) and Rose bengal (0.008 g) in pyridine (7 ml) in a water-cooled cell (17°C), oxygen was slowly bubbled and the solution was vigorously stirred and irradiated with light from 750 W tungsten lamp at a distance of 5 cm, overnight. Pyridine was then removed under reduced pressure and the residue dissolved in chloroform and absorbed on silica. Preparative silica chromatography column eluting with a mixture hexane/diethyl ether (1:1) gave 0.61 g of the hydroperoxide (70%, Rf = 0.1). Recrystallisation from aq. methanol gave pure 3β-hydroxy-5α-hydroperoxycholest-6-ene (65).

Only the more significant peaks have been reported for 1H-NMR

m.p.: 141-142°C (lit. 148-149°C); 1H-NMR (CDCl₃, 500 MHz): δ 7.26 (1H, br s, OOH), 5.79 (1H, dd, 3J = 10 Hz, 3J = 2.13 Hz, H₇), 5.58 (1H, dd, 3J = 10 Hz, 4J = 2.71 Hz, H₆), 4.12 (1H, m, H₃), 0.95 (3H, s, Me₁₉), 0.91 (3H, d, 3J = 6.52 Hz, Me₂₁), 0.86 (3H, d, 3J = 6.55 Hz, Me₂₀/27), 0.87 (3H, d, 3J = 6.55 Hz, Me₂₀/27), 0.69 (3H, s, Me₁₈); 13C-NMR (CDCl₃, 125 MHz): δ 142.49 (C₅), 136.07 (C₇), 129.06 (C₆), 67.25 (C₃), 55.66 (C₁₇), 53.45 (C₈), 43.78 (C₉/₁₄), 43.49 (C₁₃), 39.85 (C₁₆), 39.48 (C₂₄), 39.01 (C₉/₁₄), 36.11 (C₄), 36.80 (C₁₀), 35.77 (C₂₀), 35.70 (C₁), 30.38 (C₂₂), 28.51
Experimental

(C₁₂), 28.30 (C₂), 27.95 (C₂₅), 23.83 (C₁₅/2₃), 23.76 (C₁₅/2₃), 22.76 (C₂₆), 22.50 (C₂₇), 18.58 (C₁₁), 18.61 (C₁₉), 15.24 (C₂₁), 11.90 (C₁₈); IR (nujol/cm⁻¹): νₘₐₓ 3419 (O-H), 3244 (O-O-H); MS (FABMS, Matrix MNOBA+Na): m/z 401 (M-HO⁺, 100%), 383 (74%), 367 (85%), 227 (45%), 211 (53%).

Synthesis of 3β-hydroxy-7α-hydroperoxycholest-5-ene, 66:[86][87]

3β-Hydroxy-5α-hydroperoxycholest-6-ene (0.1 g, 0.24 mmol) was dissolved in chloroform (5 ml) at room temperature. After 12 hours the solvent was removed under reduced pressure and the residue was chromatographed using 1:1 hexane/diethyl ether as eluant (Rₛ=0.1). Recrystallisation from hexane/diethyl ether (1:3), gave pure 3β-hydroxy-7α-hydroperoxycholest-5-ene (0.08 g, 80%).

Only the more significant peaks have been reported for ¹H-NMR.

m.p.: 152-153°C (lit. 154-156°C)[86]; ¹H-NMR (CDCl₃, 500 MHz): δ 7.75 (1H, br s, OOH), 5.69 (1H, dd, ²J = 5.04 Hz, ⁴J = 1.86 Hz, H₆), 4.16 (1H, m, H₇), 3.62 (1H, m, H₃), 1.0 (3H, s, Me₁₉), 0.92 (3H, d, ²J = 6.56 Hz, Me₂₁), 0.86 (3H, d, ²J = 6.67 Hz, Me₂₆/2₇), 0.87 (3H, d, ²J = 6.67 Hz, Me₂₆/2₇), 0.66 (3H, s, Me₁₉), ¹³C-NMR (CDCl₃, 125 MHz): δ 148.76 (C₅), 120.04 (C₆), 78.48 (C₇), 71.43 (C₆), 55.79 (C₁₇), 49.08 (CH), 43.59 (C₁₈), 42.36 (C₁₆), 42.22 (C₁₃), 39.54 (C₂₄), 39.07 (C₄), 37.44 (CH), 37.15 (C₁), 36.80 (C₁₀), 36.20 (C₂₂), 35.78 (C₂₀), 31.37 (C₁₂), 28.20 (C₂), 28.02 (C₂₅), 24.43 (C₁₅/2₃), 23.75 (C₁₅/2₃), 22.79 (C₂₆), 22.56 (C₂₇), 20.92 (C₁₁), 18.76 (C₁₉), 18.20 (C₂₁), 11.33 (C₁₈); IR (nujol/cm⁻¹): νₘₐₓ 3423 (O-H), 3240 (O-O-H); MS (FABMS, Matrix MNOBA+Na): m/z 401 (M-HO⁺, 100%), 383 (74%), 367 (85%), 227 (45%), 211 (53%).
Experimental

Synthesis of 1-n-butyl-3-methylimidazolium tetrafluoroborate, 69:49

\[
\begin{array}{c}
\text{Cl}^- \\
\text{N} & \text{N} \\
\text{C} & \text{C} \\
\text{H} & \text{H} \\
\text{H} & \text{H} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{BF}_4^- \\
\text{N} & \text{N} \\
\text{C} & \text{C} \\
\text{H} & \text{H} \\
\text{H} & \text{H} \\
\end{array}
\]

To a stirred solution of 1-n-butyl-3-methylimidazolium chloride (4.65 g, 26.55 mmol, 1 equiv.) in acetone (30 ml) at room temperature was added sodium tetrafluoroborate (2.91 g, 26.55 mmol, 1 equiv.). After 24 hours, the reaction mixture was slowly filtered through a plug of celite and the solvent was removed in vacuo to give a yellow liquid (5.46 g, 91%).

\(^1\text{H-NMR}\) (neat, 500 MHz): \(\delta 8.26\) (1H, s, H\(_2\)), 7.14 (2H, m, H\(_{4,5}\)), 3.79 (2H, m, H\(_2\)), 3.52 (3H, s, N-CH\(_3\)), 1.40 (2H, m, H\(_3\)), 0.85 (2H, m, H\(_4\)), 0.42 (3H, m, H\(_5\)); \(^{13}\text{C-NMR}\) (neat, 125 MHz): \(\delta 136.54\) (C\(_2\)), 123.47-122.15 (C\(_{4,5}\)), 49.08 (C\(_2\)), 35.48 (N-CH\(_3\)), 31.59 (C\(_3\)), 18.94 (C\(_5\)), 12.72 (C\(_4\)); \(^{19}\text{F-NMR}\) (170 MHz, neat): \(\delta -148.95\); \(\text{IR}\) (neat/ cm\(^{-1}\)): \(n_{max}\) 3600, 3551, 3121 (Ar CH), 2937, 2876 (Aliph. CH), 1568, 1447 (C=C), 1061 (B-F); \(\text{MS}\) (FABMS, Matrix MNOBA+Na): m/z 140 (M-BF\(_4^+\), 100%).

Synthesis of 1-n-butyl-3-methylimidazolium hexafluorophosphate, 70:49

\[
\begin{array}{c}
\text{Cl}^- \\
\text{N} & \text{N} \\
\text{C} & \text{C} \\
\text{H} & \text{H} \\
\text{H} & \text{H} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{PF}_6^- \\
\text{N} & \text{N} \\
\text{C} & \text{C} \\
\text{H} & \text{H} \\
\text{H} & \text{H} \\
\end{array}
\]

1-n-Butyl-3-methylimidazolium chloride (4.65 g, 26.55 mmol, 1 equiv.) was dissolved in acetone (40 ml) and sodium hexafluorophosphate (4.46 g, 26.55 mmol, 1 equiv.) was added. The reaction mixture was stirred for 15 hours at room temperature then filtered through celite. After removal of the solvent, \(70\) was obtained as yellow oil (5.59 g, 74%).
**Experimental**

$^1$H-NMR (neat, 300 MHz): $\delta$ 8.44 (1H, s, H$_2$), 7.41 (2H, d, $^3$J = 11.63 Hz, H$_{4,5}$), 4.14 (2H, d, $^3$J = 7.4 Hz, H$_2$), 3.87 (3H, s, N-CH$_3$), 1.81 (2H, quintet, $^3$J = 7.4 Hz, H$_3$), 1.25 (2H, quintet, $^3$J = 7.4 Hz, H$_4$), 0.82 (3H, t, $^3$J = 7.4 Hz, H$_5$); $^{13}$C-NMR (neat, 75 MHz): $\delta$ 133.84 (C$_2$), 121.04, 119.7 (C$_{4,5}$), 46.94 (C$_2$), 33.13 (N-CH$_3$), 29.05 (C$_3$), 16.56 (C$_5$), 10.26 (C$_4$); $^{19}$F-NMR (282 MHz, neat): $\delta$ -69.19 (d, $^3$J$_{FP} = 666$ Hz); $^{31}$P-NMR (121.4 MHz, neat): $\delta$ -140.25 (septuplet, $^3$J$_{PF} = 711$ Hz); IR (neat/cm$^{-1}$): $\nu_{max}$ 3669, 3593, 3124 (Ar CH), 2966, 2877 (Aliph. CH), 1568, 1445 (C=C), 841 (P-F); MS (FABMS, Matrix MNOBA+Na): m/z 140 (M-PF$_6^+$, 100%).

### Synthesis of N,N-dimethyl-2,4-bis (trifluoroacetyl)-1-naphthylamine, 72$^{[94]}$

![Chemical structure](image)

To a stirred solution of N,N-dimethyl-1-naphthyl amine (0.3 g, 1.75 mmol, 1 equiv.) and pyridine (0.484 g, 6.12 mmol, 3.5 equiv.) in chloroform (10 ml), at 0°C, was added dropwise trifluoroacetic anhydride (2.58 g, 12.24 mmol, 7 equiv.). After, the reaction was stirred at room temperature for 24 hours, the organic layer was washed successively with an aq. sat. solution of copper (II) sulphate (2 x 10 ml), water (10 ml) and brine (10 ml) then finally dried over magnesium sulphate. The solvent was removed and after column chromatography, using a mixture of petroleum ether/diethyl ether (10:1), the desired product was obtained as a bright yellow solid (0.630 g, 99%) (R$_f$ = 0.63, Et$_2$O) which was recrystallised from chloroform.

**m.p.:** 87°C (lit. 87-88°C)$^{[94]}$; $^1$H-NMR (CDCl$_3$, 500 MHz): $\delta$ 9.01 (1H, ddd, $^3$J$_{5,6}$ = 8.6 Hz, $^4$J$_{5,7}$ = 1.3 Hz, $^5$J$_{5,8}$ = 0.63 Hz, H$_7$), 8.46 (1H, q, $^5$J$_{HF}$ = 1.3 Hz, H$_3$), 8.20 (1H, ddd, $^3$J$_{8,7}$ = 8.6 Hz, $^4$J$_{8,6}$ = 1.4 Hz, $^5$J$_{8,9}$ = 0.63 Hz, H$_8$), 7.74 (1H, ddd, $^3$J$_{6,5}$ = 8.6 Hz, $^3$J$_{6,7}$ = 6.9 Hz, $^4$J$_{6,8}$ = 1.4 Hz, H$_6$), 7.58 (1H, ddd, $^3$J$_{7,8}$ = 8.6 Hz, $^1$J$_{7,6}$ = 6.9 Hz, $^4$J$_{7,5}$ = 1.3 Hz, H$_7$), 3.19 (6H, s, NMe$_2$); $^{13}$C-NMR (CDCl$_3$, 125 MHz): $\delta$ 179.45 (q, $^2$J$_{CF}$ = 18.6 Hz, OCF$_3$), 177.88 (q, $^2$J$_{CF}$ = 15.8 Hz, OCF$_3$), 133.13 (d, $^1$J = 15.6 Hz, C$_2$), 121.10, 119.80 (d, $^3$J = 15.6 Hz, C$_{4,5}$), 45.84 (s, N-CH$_3$), 29.05 (t, $^3$J = 15.6 Hz, C$_3$), 16.56 (s, C$_5$), 10.26 (s, C$_4$).
Experimental

34.7 Hz, C$_{9(11)}$), 179.27 (q, $^4J_{CF} = 4.27$ Hz, C$_5$), 131.74 (C$_6$), 128.97 (C$_7$), 126.96 (C$_8$), 126.45 (C$_8$), 126.14 (C$_9$), 117.26 (q, $^1J_{CF} = 293$ Hz, C$_{10(12)}$), 117.96 (C$_{8a/8b}$), 116.54 (q, $^1J_{CF} = 293$ Hz, C$_{10(12)}$), 116.0 (C$_{8a/8b}$), 46.36 (Me x2): $^{19}$F-NMR (CDCl$_3$, 282 MHz): $\delta$ -70.14, -70.80; IR (KBr/cm$^{-1}$): $\nu_{max}$ 2990, 2871 (Ar CH), 1684 (C=O), 1588, 1554 (C=C), 1451, 1440 (C-H), 1387, 1318 (C-F); MS (FABMS, Matrix MNOBA+Na): m/z 364 (M+1$^+$, 100%), 294 (M-CCF$_3$, 87%), 198 (M-C$_2$F$_3$COCF$_3$, 16%), 168 (18%), 135 (23%).

Synthesis of 1-[1-dimethylamino-4-(2,2,2-trifluoro-1-hydroxy-ethyl)naphthalen-2-yl]-2,2,2-trifluoro-ethanol, 76:

To a solution of 72 (0.690 g, 1.90 mmol, 1 equiv.) in ethanol (25 ml), stirred at 0°C sodium borohydride (0.158 g, 4.18 mmol, 2.2 equiv.) was slowly added. After the addition was completed, the mixture was stirred at room temperature for a further 5 hours. After the reaction was quenched with a solution 2N HCl (10 ml) and diluted with dichloromethane (40 ml), the organic phase was separated then washed with water and dried over magnesium sulphate. After removal of the solvent, the residual crude oil was purified by column chromatography using a mixture of PE/diethyl ether = 1:1. The white product (0.86 g, 95 %) ($R_f$ = 0.50) was a mixture of isomers (a/b).

m.p.: 59-60°C (with transformation); $^1$H-NMR (CDCl$_3$, 500 MHz): $\delta$ 8.17-8.06 (4H, m, H$_{8a/5}$, 2H$_a$ + 2H$_b$), 7.63-7.55 (6H, m, H$_{7/6/3}$, 3H$_a$ + 3H$_b$), 5.84 (2H, q, $^3J_{HF} = 6.30$ Hz, CH$_{OH}$, 1H$_a$ + 1H$_b$), 5.27 (1H, q, $^3J_{HF} = 7.09$ Hz, CH$_{OH}$), 5.20 (1H, q, $^3J_{HF} = 7.09$ Hz, CH$_{OH}$), 3.10 (6H, s, Me x2), 3.0 (6H, s, Me x2); $^{13}$C-NMR (CDCl$_3$, 125 MHz): $\delta$ 148.45 (C$_{qa}$), 148.19 (C$_{qb}$), 132.70 (C$_{qa}$), 132.63 (C$_{qb}$), 131.77 (C$_{qa}$), 131.61 (C$_{qb}$), 129.80 (C$_{qa}$), 129.63 (C$_{qb}$), 127.45 (C$_{qa}$), 127.32 (CH$_a$), 127.25 (CH$_b$), 127.19
Experimental

(C\textsubscript{q}), 127.16 (CH\textsubscript{a}), 127.11 (CH\textsubscript{b}), 126.19 (CH\textsubscript{c}), 126.13 (CH\textsubscript{b}), 126 (q, \textit{J}_{CF} = 284 Hz, CF\textsubscript{3a}), 125.9 (q, \textit{J}_{CF} = 284 Hz, CF\textsubscript{3b}), 124.49 (CH\textsubscript{c}), 124.40 (q, \textit{J}_{CF} = 284 Hz, CF\textsubscript{3a} and CF\textsubscript{3b}), 124.39 (CH\textsubscript{b}), 74.72 (q, \textit{J}_{CF} = 24.71 Hz, CHO\textsubscript{OH}), 74.47 (q, \textit{J}_{CF} = 24.71 Hz, CHOH\textsubscript{b}), 68.84 (q, \textit{J}_{CF} = 32.39 Hz, CHOH\textsubscript{a}), 68.52 (q, \textit{J}_{CF} = 32.39 Hz, CHOH\textsubscript{b}), 44.84 (Me\textsubscript{a}), 44.23 (Me\textsubscript{b}); \textit{\textsuperscript{19}}F-NMR (CDCl\textsubscript{3}, 282 MHz): \(\delta -77.20\) (d, \(\textit{J} = 6.1\) Hz), -77.37 (d, \(\textit{J} = 6.1\) Hz), -78.25 (d, \(\textit{J} = 7.0\) Hz), -78.41 (d, \(\textit{J} = 7.0\) Hz); IR (KBr/cm\textsuperscript{-1}): \(\nu_{max}\) 3383 (OH), 2887, 2884, 2805, 1522, 1428, 1391, 1349, 1262, 1125; MS (FABMS, Matrix MNOBA+Na): \(m/z\) 367 (M+1\textsuperscript{+}, 100\%), 298 (M-CF\textsubscript{3}+, 37\%), 250 (8\%), 198 (12\%), 168 (13\%); HRMS (FAB): calculated for C\textsubscript{16}H\textsubscript{15}F\textsubscript{6}NO\textsubscript{2} 367.1007, found 367.1020.

\textit{Synthesis of trimethyl-[1]-naphthyl-ammonium triflate, 78:}

Methyl triflate (0.069 g, 0.42 mmol, 1.44 equiv.) was slowly added to N,N-dimethyl-1-naphthylamine (0.050 g, 0.29 mmol, 1 equiv.). The reaction was very exothermic and after few minutes a white solid was formed which was filtered off and dried under vacuum to give trimethyl-[1]-naphthylammonium triflate (78) as white needles in quantitative yield (0.100 g).

m.p.: 122-125°C; \textit{\textsuperscript{1}}H-NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta 8.31\) (1H, d, \(\textit{J} = 8.9\) Hz, CH), 8.01-7.99 (2H, m, CH x2), 7.97 (1H, dd, \(\textit{J} = 8.04\) Hz, 4\(\textit{J} = 1.02\) Hz, CH), 7.78 (1H, td, \(\textit{J} = 7.01\) Hz, 4\(\textit{J} = 1.26\) Hz, CH), 7.62 (1H, td, \(\textit{J} = 7.01\) Hz, 4\(\textit{J} = 1.26\) Hz, CH), 7.55 (1H, t, \(\textit{J} = 8.04\) Hz, CH), 4.05 (9H, s, Me x3); \textit{\textsuperscript{13}}C-NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta 141.71\) (C\textsubscript{q}), 136.03 (C\textsubscript{q}), 133.04 (CH), 130.97 (CH), 128.78 (CH), 127.0 (CH), 124.79 (CH), 123.75 (C\textsubscript{q}), 122.35 (CH), 119.26 (CH), 120.6 (q, \textit{J}_{CF} = 318 Hz, CF\textsubscript{3}), 58.3 (Me x3); \textit{\textsuperscript{19}}F-NMR (CDCl\textsubscript{3}, 282 MHz): \(\delta -78.60\); IR (KBr/cm\textsuperscript{-1}): \(\nu_{max}\) 3472, 3139, 3107, 3057 (Ar CH), 1605 (\(^{19}\)NMe\textsubscript{3}), 1511, 1480, 1422 (SO\textsubscript{2}R), 1397, 1272.
MS (EI): m/z 335 (M⁺, 10%), 171 (M-MeOTf⁺, 100%), 154 (32%), 128 (naphthalene+1⁺, 60%), 84 (71%), 49 (81%).

**Synthesis of N-(2,4-dichlorophenyl)propionamide, 80:**

![Chemical structure](image)

To a stirred solution of 2,4-dichloroaniline (0.3 g, 1.85 mmol, 1 equiv.) and dried triethylamine (0.206 g, 2.04 mmol, 1.1 equiv.) in dichloromethane (30 ml) under nitrogen, was added propionyl chloride (0.188 g, 2.04 mmol, 1.1 equiv.) and the mixture stirred at room temperature for 16 hours. After the reaction mixture was washed by water (10 ml), brine (2 x 15 ml), then dried over magnesium sulphate, the solvent was removed to yield a solid which was recrystallised from ethanol to afford the desired product as white needles (0.355 g, 88%) (Rf = 0.23, PE 30-40/diethyl ether = 2:1).

**m.p.:** 120-121°C (lit 119-120°C), \(^{1}H\)-NMR (CDCl₃, 500 MHz): δ 8.30 (1H, d, \(^{3}J_{6,5} = 8.8\) Hz, H₆), 7.5 (1H, br s, NH), 7.32 (1H, d, \(^{4}J_{3,5} = 2.31\) Hz, H₃), 7.19 (1H, d, \(^{3}J_{5,6} = 2.31\) Hz, H₅), 2.40 (2H, q, \(^{3}J = 7.54\) Hz, CH₂), 1.20 (3H, t, \(^{3}J = 7.54\) Hz, Me); \(^{13}C\)-NMR (CDCl₃, 125 MHz): δ 171.84 (C=O), 133.39 (C₁), 128.82 (C₄), 128.61 (C₆), 127.90 (C₃), 122.91 (C₂), 122.15 (C₃), 30.96 (CH₂), 9.46 (CH₃); IR (KBr/cm⁻¹): \(ν_{max}\) 3284, 3196 (NH), 2980, 2932 (Ar CH), 1652 (C=O), 1575, 1550, 1417, 1300, 1201 (CH, C=C), 1102 (C-Cl), 1071 (C-Cl); MS (FABMS, Matrix MNOBA+Na): m/z 218 (M⁺, 100%), 161 (M-COEt, 17%), 154 (32%), 136 (33%).
Experimental

Synthesis of N-(2,4-dichlorophenyl)-N-methylpropionamide, 90:

Sodium hydride (0.184 g, 4.6 mmol, 2 equiv., 60 % dispersion in mineral oil) was suspended in dry THF (10 ml), cooled at 0°C, and a solution of N-(2,4-dichlorophenyl)-propionamide (0.5 g, 2.3 mmol, 1 equiv.) in dry THF (10 ml) was then added dropwise and the mixture stirred at rt for 1 hour prior to the addition of methyl iodide (1.3 g, 9.17 mmol, 4 equiv.). After stirring for a further 12 hours, the reaction mixture was diluted with diethyl ether (20 ml) and washed successively with a sat. aq. solution of ammonium chloride (20 ml), water (20 ml), brine (20 ml) and then dried over magnesium sulphate. After the solvent was removed under reduced pressure, the residual yellow oil was purified by flash chromatography using a mixture of petroleum ether/diethyl ether (2:1), to yield the desired product as a yellow oil in 93% yield (0.499 g, Rf = 0.53).

\[\begin{align*}
\text{Cl} & \quad \text{NHCOEt} \\
\text{Cl} & \quad \text{N} \quad \text{O} \quad \text{CH}_2\text{CH}_3
\end{align*}\]

\[\text{H-NMR (CDCl}_3, 500 \text{ MHz): } \delta \text{ 7.49 (1H, d, } \hat{J}_{3,5} = 2.29 \text{ Hz, H}_3), \text{ 7.29 (1H, , dd, } \hat{J}_{5,6} = 8.4 \text{ Hz, H}_5, \text{ 7.18 (1H, d, } \hat{J}_{5,5} = 8.4 \text{ Hz, H}_6), \text{ 3.15 (3H, s, NMe),} \\
\text{1.95 (2H, dq, } \hat{J} = -16.1 \text{ Hz, } \hat{J} = 7.35 \text{ Hz, CH}_2), \text{ 1.03 (3H, t, } \hat{J} = 7.35 \text{ Hz, CH}_3);}
\]

\[\text{13C-NMR (CDCl}_3, 125 \text{ MHz): } \delta \text{ 171.84 (C=O), 133.39 (C}_1), \text{ 128.82 (C}_4), \text{ 128.61 (C}_6), \text{ 127.90 (C}_3), \text{ 122.91 (C}_2), \text{ 122.15 (C}_3), \text{ 30.96 (CH}_2), \text{ 9.46 (CH}_3);}
\]

\[\text{IR (neat/cm}^{-1}) \text{: } \nu_{\max} \text{ 3072, 2978, 2931 (Ar CH), 1666 (C=O), 1478, 1420, 1373 (CH, C=CH), 12785,}
\]

\[\text{1132, 1096 (C-Cl), 1055 (C-Cl), 862, 803; MS (FABMS, Matrix MNOBA+Na): } m/z \text{ 232 (M}^+\text{, 100%), 196 (23%), 175 (M-COEt}, 11\%); \text{ HRMS (FAB): calculated for C}_{10}H_{12}Cl_2NO (M+H) 232.0297, found 232.0296.}\]
Experimental

Synthesis of N-(2,4-dichlorophenyl)-2,2-dimethylpropionamide, 86:\textsuperscript{196}

\[
\begin{align*}
\text{Cl} & \quad \text{NH}_2 \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

Dry triethylamine (0.206 g, 2.03 mmol, 1.1 equiv.) was added to a solution of 2,4-dichloroaniline (0.330 g, 2.02 mmol, 1.1 equiv.) in dichloromethane (30 ml), which was cooled in an ice bath. The mixture was stirred for few minutes before pivaloyl chloride (0.245 g, 2.03 mmol, 1.1 equiv.) was added. This reaction was stirred for 12 hours at room temperature; then washed twice with brine (15 ml) and dried over magnesium sulphate. After removal of the solvent, the residue was purified by flash chromatography (PE/Et\textsubscript{2}O = 2:1) to give a white solid (0.433 g, 87\%)(R\textsubscript{f} = 0.69).

\textbf{m.p.:} 58-59°C; \^H-NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 8.36 (1H, d, \(^3J_{6,5} = 9.0\) Hz, H\textsubscript{6}), 7.92 (1H, br s, NH), 7.35 (1H, d, \(^3J_{5,5} = 2.31\) Hz, H\textsubscript{3}), 7.22 (1H, dd, \(^3J_{5,6} = 9.0\) Hz, \(^3J_{5,5} = 2.3\) Hz, H\textsubscript{5}), 1.31 (9H, s, Me x3); \^C-NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 176.60 (C=O), 133.52 (C\textsubscript{4}), 129.05 (C\textsubscript{4}), 128.52 (C\textsubscript{3}), 127.86 (C\textsubscript{5}), 123.33 (C\textsubscript{2}), 121.77 (C\textsubscript{6}), 27.34 (Me x3); IR (KBr/cm\textsuperscript{-1}): \(\nu\textsubscript{max}\) 3300 (NH), 2972, 2870 (Ar CH), 1653 (C=O), 1499, 1460, 1369, 1290, 1171 (C-Cl), 1101 (C-Cl); MS (FABMS, Matrix MNOBA+Na): \(\text{m/z}\) 246 (M\textsuperscript{+}, 100\%), 210 (9\%), 136 (10\%).

Synthesis of 2,2-dimethyl-N-phenylpropionamide, 92:

\[
\begin{align*}
\text{NH}_2 \\
3 & \quad \text{NH}
\end{align*}
\]

To a solution of freshly distilled aniline (0.9 g, 9.66 mmol, 1 equiv.) in dichloromethane (30 ml) at 0°C, was added triethylamine (1.076 g, 10.6 mmol, 1.1
equiv.). The reaction was stirred for 10 minutes, before the addition of pivaloyl chloride (1.28 g, 10.6 mmol, 1.1 equiv.). After 16 hours, the reaction mixture was washed with brine (3 x 20 ml) and dried over MgSO₄. The solvent was removed to give the desired product as a white solid (1.7 g, 99%) (R_f = 0.62, PE/Et₂O = 1:1) which was recrystallised from ethanol.

m.p.: 131-132°C (lit. 132-133°C)\(^{166}\); \(^1\)H-NMR (CDCl₃, 500 MHz): δ 7.50 (2H, dd, \(^3\)J = 8.50 Hz, \(^4\)J = 1.10 Hz, H₆₂), 7.32-7.26 (3H, m, NH and H₃₃), 7.08 (1H, tt, \(^5\)J = 7.50 Hz, \(^6\)J = 1.26 Hz, H₄), 1.26 (9H, s, Me x3); \(^13\)C-NMR (CDCl₃, 125 MHz): δ 176.52 (C = O), 138.01 (C₁), 129.15 (C₃₃), 124.18 (C₄), 119.93 (C₆₂), 39.59 (C₉), 27.62 (Me x3); IR (KBr/cm\(^{-1}\)): ν_max 3306 (NH), 2981, 2963, 2932, 2880 (Ar CH), 1657 (C=O), 1594, 1537, 1433, 1397, 1314, 1241, 1024, 927; MS (EI): m/z 177 (M⁺, 100%), 93 (M-COrBu⁺, 100%), 77 (M-NHCorBu⁺, 30%), 57 (100%), 41 (97%).

Synthesis of 2,2-dimethyl-N-[2-(2,2,2-trifluoroacetyl)phenyl]propionamide, 93:

To a solution of 2,2-dimethyl-N-phenylpropionamide (0.150 g, 0.844 mmol, 1 equiv.) in dry ether (20 ml) at -10°C, was added dropwise a solution of tert-BuLi in pentane (1.77 ml, 2.53 mmol, 1.43 M, 3equiv.). The solution was stirred at this temperature for 2 hours before trifluoroacetic anhydride (1.063 g, 5.06 mmol, 6 equiv.) was added. After stirring for a further 2 hours, the reaction mixture was allowed to come to room temperature and then quenched with a sat. aq. solution of ammonium chloride (1 ml), washed with water (20 ml), brine (20 ml) and dried over MgSO₄. After removal of the solvent, the residual oil was purified by column chromatography (PE/Et₂O = 4:1) to yield the desired product as a yellow oil (0.080 g, 44%) (R_f = 0.42).
Experimental

\[ ^1\text{H-NMR} \ (\text{CDCl}_3, 500 \text{ MHz}): \delta \ 11.20 \ (1\text{H}, \text{s}, \text{NH}), \ 8.88 \ (1\text{H}, \text{dd}, ^3J_{6,5} = 8.6 \text{ Hz}, ^4J_{6,4} = 1.1 \text{ Hz}, \text{H}_6), \ 7.96 \ (1\text{H}, \text{m}, \text{H}_3), \ 7.66 \ (1\text{H}, \text{td}, ^3J_{5,6} = ^4J_{5,4} = 7.9 \text{ Hz}, ^4J_{5,3} = 1.42 \text{ Hz}, \text{H}_5), \ 7.16 \ (1\text{H}, \text{td}, ^3J_{4,5} = 7.25 \text{ Hz}, ^4J_{4,6} = 1.1 \text{ Hz}, \text{H}_4), \ 1.33 \ (9\text{H}, \text{s}, \text{Me} \times 3); ^{13}\text{C-NMR} \ (\text{CDCl}_3, 125 \text{ MHz}): \delta \ 183.1 \ (\text{q}, ^3J_{\text{CF}} = 34.07 \text{ Hz}, \text{COCF}_3), \ 178.39 \ (\text{CO}), \ 144.0 \ (\text{C}_q), \ 137.76 \ (\text{C}_3), \ 131.85 \ (\text{q}, ^3J_{\text{CF}} = 4.32 \text{ Hz}, \text{C}_3), \ 122.53 \ (\text{C}_4), \ 121.21 \ (\text{C}_6), \ 116.66 \ (\text{q}, ^1J_{\text{CF}} = 292 \text{ Hz}, \text{CF}_3), \ 115.36 \ (\text{C}_q), \ 40.62 \ (\text{C}_q), \ 27.52 \ (\text{Me} \times 3); ^1\text{F-NMR} \ (\text{CDCl}_3, 282 \text{ MHz}): \delta \ -70.34; \ \text{IR} \ (\text{neat/cm}^\text{-1}): \nu_{\text{max}} \ 3337 \ (\text{NH}), \ 2894, \ 2893, \ 2932 \ (\text{Ar} \text{CH}), \ 1683 \ (\text{C}=\text{O}), \ 1610 \ (\text{C}=\text{O}), \ 1579, \ 1527, \ 1449, \ 1283, \ 1189, \ 1148; \ \text{MS} \ (\text{Positive Ion-FAB}): m/z 274 \ (\text{M}+1, \ 28\%); \ \text{HRMS} \ (\text{FAB}): \text{calculated for C}_{13}\text{H}_{15}\text{F}_2\text{NO}_2 \ (\text{M}+\text{H}) \ 274.10552, \ \text{found} \ 274.10545. \]

Synthesis of Fremy's salt, 94: [100]

\[
\begin{align*}
\text{NaNO}_2 & \quad + \quad \text{NaHSO}_3 & \rightarrow & \quad \cdot\text{ON(SO}_3\text{K)}_2 & \quad + \quad \text{NaOH}
\end{align*}
\]

Sodium nitrite (50 ml, 5M) was placed in a beaker and cooled in an ice bath. Crushed ice (100 g) was added and the solution stirred steadily during the addition of freshly prepared sodium bisulphite solution (50 ml, 35% w/v), followed by glacial acetic acid (10 ml). The reaction was complete in a few minutes, as shown by the momentary darkening in colour and by the failure to decolourise iodine solution. After the addition of conc. ammonia solution (12.5 ml, sp gr 0.88), the mixture was cooled again in an ice bath, and fresh ice added when ever necessary to keep some present in the reaction mixture through the next stage. Ice cold potassium permanganate solution (200 ml, 0.2 M) was added dropwise with continued stirring, during ca. 1 hr. The precipitated manganese dioxide was filtered and the filtrate was allowed to come to room temperature as the filtration proceeded, but any unfiltered suspension was kept in an ice bath. A portion of the filtrate (10-15 ml) was treated with an equal volume of sat. potassium chloride solution to precipitate some Fremy's salt for seeding the main batch. The bulk of the filtrate was stirred steadily, while sat. potassium chloride solution (125 ml) was added dropwise over a period of about 40 min. Small portions of the previously prepared suspension were added during this
period until the solid persisted in the bulk solution. The precipitation was completed by stirring the bulk solution, cooled in ice bath, for a further 45 min. The orange solid was collected on a Buchner funnel without suction. It was washed with ammoniacal sat. aq. potassium chloride solution (containing ca. 5% v/v 0.88 ammonium hydroxide), twice with ammoniacal methanol (containing ca. 5% v/v 0.88 ammonium hydroxide), and finally with acetone. The solid was isolated by filtration with care taken not to suck it to complete dryness and it was spread on a watch glass to allow the acetone to evaporate over 15 minutes. Finally the orange crystals (51%) were stored in a dessicator over calcium oxide, in the presence of ammonium carbonate.

Synthesis of potassium hydroxylamine disulfonate, 100:[104]

\[
\text{KNO}_2 + \text{SO}_2 \rightarrow \text{HON(SO}_3\text{K)}_2 \cdot \text{xH}_2\text{O}
\]

Potassium nitrite (10 g, 0.117 mmol, 1 equiv.) and potassium acetate (13.26 g, 0.135 mmol, 1.15 equiv.) were dissolved in cold water and finely chipped ice was added (176 g). The mixture was stirred and sulphur dioxide gas was bubbled through the solution until saturation: during the reaction all the ice melted, although the temperature of the flask was kept at 0°C in an ice bath. The resultant white solid was filtered and washed four times (5ml) with a mixture of ice/water to remove sulphotides and acetates affording a crude salt (30 g) which was stored over P\textsubscript{2}O\textsubscript{5} at -4°C.

The purity of the compound was determined by the percentage of sulphates as follows. [105] A portion of the crude product (1.5 g) was dissolved in 6M HCl (20 ml) and the solution was heated to 100°C for 1 hour. A solution of BaCl\textsubscript{2} (2.45 g) in water (10 ml) was then added and the formation of white, insoluble BaSO\textsubscript{4} (1.8 g) was observed which was filtered and dried. From the amount of BaSO\textsubscript{4}, it was established a 78% purity for 100 (x = 2) in a 65% yield.
Experimental

Oxidation of alkanes in the presence of Fremy's salt (94) and potassium hydroxylamine sulfonate (100):

1. Generation of the radical in situ:
An aqueous solution of potassium hydroxylamine disulphonate (100) (1 equiv.), hydrogen peroxide 30% (1 equiv.) and phosphotungstic acid (0.01 equiv.) were placed in a flask and this heterogeneous mixture was stirred at room temperature for 20 min. Tetra-n-butylammonium bromide (0.5 equiv.) and a solution of the starting material (1 equiv.) in dichloromethane were then added simultaneously and the reaction was monitored by GC.

2. Use of the synthesised Fremy's salt (94):
To a stirred solution in dichloromethane of the substrate (1 equiv.) and tetra-n-butylammonium bromide (0.5 equiv.) at room temperature, Fremy's salt (1 equiv.) was added followed by the dropwise addition of water. The reaction was followed by GC.

Synthesis of 2-(3-methyl-butoxy)-benzo[1,3]dithiole, 104:

A solution of anthranilic acid (10.27 g, 0.075 mol, 1 equiv.) in dioxane (25 ml) was added dropwise over a period of 1 hour to a stirred and gently refluxing solution of 3-methylbutyl nitrite (10.52 g, 0.090 mol, 1.2 equiv.), 3-methylbutanol (13.2 g, 0.15 mol, 2 equiv.), and carbon disulfide (37.5 ml, 0.62 mol, 8.3 equiv.) in dichloroethane (200 ml). After the addition was complete, the mixture was refluxed for 30 minutes. The resultant red reaction mixture was washed successively with water (100 ml), sat. aq. sodium carbonate (100 ml), water (150 ml) and dried over sodium sulphate. Solvent and excess reagents were removed under reduced pressure and the resultant
red viscous oil was purified by distillation in vacuo (122-125°C/0.1 mmHg) to give compound 104 as yellow oil (4.2 g, 23%).

^1^H-NMR (CDCl₃, 400 MHz): δ 7.22 (2H, dd, ^3^J = 5.8 Hz, ^4^J = 3.2 Hz, H₂), 6.95 (2H, ^3^J = 5.8 Hz, ^4^J = 3.2 Hz, H₆), 6.73 (1H, s, H₂), 3.26 (2H, t, ^3^J = 6.3 Hz, H₄), 1.58 (1H, m, H₅), 1.29 (2H, q, ^3^J = 6.6 Hz, H₆), 0.78 (6H, d, ^3^J = 6.6 Hz, Me₆,₆); ^1^C-NMR (CDCl₃, 100 MHz): δ 137.03 (C₇,a), 125.40 (Ar CH₂), 121.86 (Ar CH₂), 96.61 (C₂), 90.03 (C₃), 61.62 (C₄), 38.19 (C₅), 23.2 (C₆,₆); IR (neat/cm⁻¹): vₐ₅ max 3010, 3001, 2991 (Ar CH), 1480, 1470, 1320, 1260, 1210; Elemental Analysis: calculated C (59.99), H (6.71), S (26.64); found C (59.76), H (6.49), S (26.65).

**Synthesis of 1,2-benzenedisulphonyl chloride, 102:**

Clorine was passed into a well stirred mixture of 104 (3 g, 12.48 mmol) in 27.9 ml of t-butanol/water/chloroform (24 ml/1.5 ml/2.4 ml) cooled to 0°C at such a rate that the temperature did not exceed 5°C. The reaction was monitored by TLC (PE/benzene (4:1) as eluant) and the chlorine addition was stopped when TLC showed a single spot at the baseline (corresponding to the 1,2-benzenedisulphonyl chloride). Chloroform (50 ml) was then added to the yellow reaction mixture, which was washed with water (2 x 15 ml), 5% sodium bicarbonate (2 x 15 ml), then dried and evaporated in vacuo. Column chromatography [petroleum ether/ethyl acetate (3:1)] of the crude product afforded 102 (Rₚ = 0.36) as white crystals (4.38 g, 74%).

m.p.: 144-145°C (lit. 143-144°C)^[113]^; ^1^H-NMR (CDCl₃, 300 MHz): δ 8.46-8.40 (2H, m, CH), 8.02-7.99 (2H, m, CH); ^1^C-NMR (CDCl₃, 75MHz): δ 141.39 (C₁₂), 136.12 (C₃,₆), 132.33 (C₄,₅); IR (CHCl₃/cm⁻¹): vₐ₅ max 3098, 3029 (Ar CH), 1387, 1338,
Experimental

1211, 1190 (RSO₂Cl); MS (EI): *m/z* 275 (M⁺, 34%), 239 (M-Cl⁺, 100%), 157 (18%), 112 (55%).

*Synthesis of 2-hydroxybenzo[1,3,2]dithiazole-1,1,3,3-tetraoxide, 95*[^1][^2][^3]

![Reaction Scheme](image)

Sodium sulfite (1 g, 7.9 mmol, 2.1 equiv.) and sodium carbonate (1.3 g, 12.3 mmol, 3.3 equiv.) were dissolved in water (10 ml) and heated to 40°C. Benzene-o-disulphonyl chloride (102) (1 g, 3.7 mmol, 1 equiv.) was gradually added to this solution with continuous stirring. After the addition was complete, the mixture was kept at 40°C for an additional hour; then the temperature was increased to 70-80°C and the stirring continued for 1.5 hours. The clear solution (pH = 7) was cooled to 0°C, acidified to pH<1 by the addition of cold, 30% sulfuric acid, and a stream of nitrogen was passed through this solution to remove the liberated sulfur dioxide. A solution of sodium nitrite (0.25 g, 3.6 mmol, 1 equiv.) dissolved in the minimum amount of water was then added and the precipitate formed was filtered off, washed with a small amount of ice-water and dried at room temperature under vacuum. The product was obtained as a white powder (0.700 g, 80%).

When ammonia was added to a solution of 95, a strong evolution of gas was observed.

**m.p.: 90-100°C (lit. 88-125°C)**[^1][^11][^14][^15]; ¹H-NMR (D₂O, 300 MHz): δ 8.01-7.8 (2H, m, CH), 7.6-7.4 (2H, m, CH); ¹³C-NMR (D₂O, 75 MHz): δ 138.60 (C₁,₂), 137.04 (C₃,₆), 125.28 (C₄,₅); IR (nujol/cm⁻¹): *ν*ₘₐₓ 3443 (OH), 2727, 1350, 1113 (RSO₂N); MS (EI): *m/z* 219 (M-H₂O⁺, 85%), 176 (55%), 91 (M-OH[SO₂]₂⁺, 47%), 77 (C₆H₅⁺, 100%), 50 (65%).
Experimental

**Synthesis of trityl thionitrite, 128.**

\[
\text{Ph}_3\text{CS-H} \quad \rightarrow \quad \text{Ph}_3\text{CS-NO}
\]

To triphenylmethylmercaptan (11.6 g, 42 mmol, 1 equiv.) in benzene (24 ml), a solution of sodium nitrite (3.5 g, 50.4 mmol, 1.2 equiv.) in water (10 ml) was added and the resulting mixture cooled to 5°C before conc. sulfuric acid (15% cat.) was added dropwise. After stirring for 15 minutes in the dark (the flask was covered with aluminium foil), the mixture was diluted with benzene (10 ml), washed with several portions of water (3 x 10 ml), dried over magnesium sulphate and the solvent removed under reduced pressure. The crude thionitrite was recrystallised from chloroform-ethanol, in the dark, affording the product (128) as bright green prisms (9.45 g, 73%).

m.p.: 100°C with decomposition (lit. 99°C with decomp.); \(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.30 (9H, m, CH), 7.14 (6H, m, CH); \(^13\)C-NMR (CDCl\(_3\), 75 MHz): \(\delta\) 143.60 (Cipso x3), 129.91 (CH x6), 128.17 (CH x6), 127.61 (CH x3), 76.0 (CSNO); IR (KBr/cm\(^{-1}\)): \(\nu\) 3000, 2999 (Ar CH), 1958, 1898, 1591 (S-NO), 1483, 1441 (CH), 1034; MS (El): \(m/z\) 276 (M-NO\(^+\), 38%), 275 (M-NO\(^+\), 20%), 243 (Tr\(^+\), 100%), 242 (79%), 241 (80%), 165 (44%).

**Attempted reaction of trityl thionitrite (128) with Barton ester:**

\[
\text{CF}_3\text{(CF}_2\text{)}_1\text{CO}_2\text{H} \quad \rightarrow \quad \text{CF}_3\text{(CF}_2\text{)}_1\text{COCl} \quad \text{Ph}_3\text{CSNO}
\]

The acyl chloride was prepared immediately prior to use.

To a suspension of perfluorododecanoic acid (0.2 g, 0.32 mmol, 1 equiv.) in dry benzene (5 ml) was added oxalyl chloride (0.081 g, 0.64 mmol, 2 equiv.) and dimethylformamide (1 drop), at room temperature, under nitrogen and the resulting
mixture was stirred for 3 hours. After evaporating to dryness, dry benzene was added again (2 ml) and the solution of perfluorododecanoyl chloride (125) was cooled to -20°C. 1-Hydroxypyridine-2-thione sodium salt (0.0450 g, 0.34 mmol, 1.05 equiv.) in dry trifluorotoluene was added; the mixture was stirred in the dark and allowed to slowly warm to 3-6°C. After a solution of trityl thionitrite (0.049 g, 0.16 mmol, 0.5 equiv.) was added by cannula, the reaction mixture was heated at 70°C until the complete disappearance of the thionitrite green colour and the persistence of a yellow solution. The mixture was then evaporated to dryness and the resulting residue chromatographed but no major products were isolated.

**Synthesis of 2-tricosafluoroundecylsulfanyl-pyridine, 136:**

![Chemical structure](image)

To a suspension of perfluorododecanoic acid (0.1 g, 0.16 mmol, 1 equiv.) in dry trifluorotoluene (4 ml) was added oxalyl chloride (0.041 g, 0.32 mmol, 2 equiv.) and dimethylformamide (1 drop) at room temperature under nitrogen and the resulting mixture was stirred for 3 hours, then evaporated to dryness and redissolved in dry trifluorotoluene (2 ml). To this solution of perfluorododecanoyl chloride at -20°C was added a solution of 2-mercaptopyridine N-oxide (0.020 g, 0.16 mmol, 1 equiv.) and pyridine (0.014 g, 0.18 mmol, 1.1 equiv.) in dry trifluorotoluene (2 ml). After stirring at -20°C for 20 minutes, the mixture was irradiated by a tungsten lamp (250 W) for 40 minutes. Purification by column chromatography on silica (hexane/DCM = 1:1) gave 136 as white solid which was recrystallised by dichloromethane (0.022 g, 20%, $R_f = 0.33$).

**m.p.:** 69-70°C; $^1$H-NMR (CDCl$_3$, 500 MHz): $\delta$ 8.65 (1H, dd, $^3J_{5,5} = 4.89$ Hz, $^4J_{5,4} = 1.90$ Hz, H$_5$), 7.73 (1H, ddd, $^3J_{4,5} = 7.60$ Hz, $^3J_{4,3} = 7.80$ Hz, $^4J_{4,6} = 1.90$ Hz, H$_4$), 7.67 (1H, d, $^3J_{3,4} = 7.80$ Hz, H$_3$), 7.36 (1H, dd, $^3J_{5,4} = 7.60$ Hz, $^4J_{5,6} = 4.89$ Hz, H$_5$);

$^{13}$C-NMR (CDCl$_3$, 125 MHz): $\delta$ 150.96 (C$_6$), 147.56 (C$_2$), 137.62 (C$_4$), 131.16 (C$_3$), 192
Experimental

124.58 (C₅), 123.63 (t, JCF = 288 Hz, JFF = 34.31 Hz, α-CF₂), 116.0 (q, JCF = 288 Hz, JFF = 34.31 Hz, CF₂), 113.65 -108.0 (broad m, CF₂); ¹⁹F-NMR (CDCl₃, 282 MHz): δ -72.24, -81.18, -119.53, -121.48, -122.04, -123.05, -126.46; IR (KBr/cm⁻¹): νmax 3049, 2974, 2926 (Ar CH), 2359, 2345, 1570, 1452, 1427, 1207, 1153; MS (Positive, Ion FAB): m/z 680 (M+1⁺, 100%), 192 (9%), 111 (17%), 69 (24%), 31 (20%); HRMS (FAB): calculated for C₁₆H₅F₂₃NS (M+H) 679.9775, found 679.9802.

Synthesis of 1,1-difluoro-octene, 148:

To a solution of heptanal (2.28 g, 20 mmol, 1 equiv.) in dry THF (20 ml) at -20°C, was added dibromodifluoromethane (8.4 g, 40 mmol, 2 equiv.) using a cooled syringe. Under vigorous stirring, tris(dimethylamino)phosphine (6.5 g, 40 mmol, 2 equiv.) was added dropwise and a dense white precipitate immediately formed. The mixture was warmed to room temperature and the stirring continued for 30 minutes. Slowly, zinc powder (2.6 g, 40 mmol, 2 equiv.) and tris(dimethylamino)phosphine (0.65 g, 0.4 mmol, 0.02 equiv.) were added and the mixture refluxed for 6 hours (the process was very exothermic). After cooling to room temperature, ether was added (30 ml) and the organic layer washed with sat. aq. solution of copper (II) sulphate (2 x 15 ml) until it remained blue, followed by water (20 ml) and brine (20 ml). The ethereal extract was dried over magnesium sulfate and the solvent removed at normal pressure. The liquid obtained was then fractionally distilled affording the product 148 as a colourless oil at 120°C (0.74 g, 25%).

¹H-NMR (CDCl₃, 300 MHz): δ 4.17-4.05 (1H, ddt, JHFa = 12 Hz, JH,Fb = 25.6 Hz, J₂,₂ = 2.6 Hz, H₂), 2.0 – 1.8 (2H, m, CH₂), 1.38-1.38 (8H, m, CH₂ x 4), 0.89-0.85 (3H, t, J = 6.9 Hz, H₈); ¹³C-NMR (CDCl₃, 75 MHz): δ 156.6 (t, JCF = 284.0 Hz, C₁), 77.78 (t, JCF = 21.1 Hz, C₂), 31.92 (CH₂), 29.8 (CH₂), 28.90 (CH₂), 22.9 (C₃), 22.5 (CH₂), 14.36 (C₈). ¹⁹F-NMR (CDCl₃, 282 MHz): δ -90.38 (d, JF,F = 49.66 Hz), -92.63 (dd, JF,F = 49.66 Hz, JF,H = 25.39 Hz); IR (neat/cm⁻¹): νmax 2351, 2320,
Experimental

1460, 1271, 1210; MS (positive-Cl, Methane): m/z 149 (M+1⁺, 10%), 108 (9%), 80 (12%).

Synthesis of 1,1-difluoro-2-pentylhept-1-ene, 150:

\[
\begin{align*}
\text{C}_5\text{H}_{11} & \quad \text{O} \\
\rightarrow & \\
\text{F} & \quad 1 \quad \text{F} \\
\text{C}_5\text{H}_{11} & \quad \text{F} \\
\end{align*}
\]

To a solution of 6-undecanone (3 g, 17.6 mmol, 1 equiv.) in dry THF (80 ml) under nitrogen cooled at -20°C, was added dibromodifluoromethane (18.46 g, 88 mmol, 5 equiv.) using a cooled syringe. To this vigorously stirred mixture was added slowly tris(dimethylamino)phosphine (14.36 g, 88 mmol, 5 equiv.) and a dense white precipitate formed immediately. The reaction was allowed to come to room temperature and kept at this temperature for a further 20 minutes. Zinc (5.75 g, 88 mmol, 5 equiv.) was carefully added followed by 0.2 equivalents of tris(dimethylamino)phosphine (0.574 g, 3.52 mmol). The mixture was then refluxed for 5 hours. The brown solution was cooled to room temperature and diethyl ether (100 ml) added. The reaction mixture was washed with sat. copper (II) sulphate until the latter remained blue (3 x 30 ml), followed by water (80 ml), brine (80 ml) and finally dried over magnesium sulphate. After removal of the solvent, the crude material was purified by column chromatography, using petroleum ether 30-40, as eluant to give the desired product 150 as a colourless oil (1.8 g, 53 %) (Rf = 0.85, 100% PE).

\(^1\text{H-NMR}\) (CDCl\(_3\), 500 MHz): δ 2.02-1.91 (4H, tt, \(^3\text{J} = 7.6\) Hz, \(^4\text{J} = 2.16\) Hz, H\(_3\) x2), 1.37-1.24 (12 H, m, H\(_{4,5,6}\) x2), 0.89-0.86 (6H, t, \(^3\text{J} = 7.14\) Hz, H\(_7\) x2); \(^{13}\text{C-NMR}\) (CDCl\(_3\), 125 MHz): δ 153.32 (t, \(^1\text{J}_{CF} = 282.6\) Hz, C\(_1\)), 89 (t, \(^2\text{J}_{CF} = 16.47\) Hz, C\(_2\)), 31.38 (C\(_4\) x2), 27.12 (C\(_{5,6}\) x2), 25.87 (C\(_3\) x2), 22.44 (C\(_{5,6}\) x2), 14.0 (C\(_7\) x2); \(^{19}\text{F-NMR}\) (CDCl\(_3\), 282 MHz): δ -97.11; \(\text{IR}\) (neat/cm\(^{-1}\)): \(\nu_{\text{max}}\) 2958, 2929, 2861 (C-H), 2361, 2337, 1748, 1462, 1260, 1209; MS (EI): m/z 204 (M⁺, 20%), 127 (20%), 91 (80%), 69 (50%), 56 (100%); HRMS (FAB): calculated for C\(_{12}\)H\(_{22}\)F\(_2\) 204.16895, found 204.16932.

194
Experimental

**Synthesis of tetra-n-propylammonium periodate, 151:**

![Chemical structure of tetra-n-propylammonium periodate]

The reagent was freshly prepared by mixing a solution of tetra-n-propylammonium hydroxide 10% (1 g, 4.9 mmol, 1 equiv) and periodic acid (1.12 g, 4.9 mmol, 1 equiv.) in water (10 ml). The resulting thick precipitate was filtered, dried under vacuo and recrystallised from ethanol to afford needle-like crystals (1.4 g, 76%).

**m.p.:** 182-184°C (lit. 180-182°C)**[^124]**; **[^1H-NMR]** (CDCl₃, 500 MHz): δ 3.17 (8H, m, H₁ x₄), 1.69 (8H, m, H₂ x₄), 1.05 (12H, m, CH₃ x₄)[This is a strong coupled spin system]; **[^13C-NMR]** (CDCl₃, 125 MHz): δ 60.75 (C₁), 15.67 (C₂), 10.80 (C₃); **IR** (KBr/cm⁻¹): νmax 2972, 2941, 2881 (Ar CH), 1462, 1479 (CH), 1392, 1315, 1040, 984; **MS** (FABMS, Matrix MNOBA+Na): m/z 186.06 (M-IO₄⁺, 100%), 142 (N-propyl₃⁺, 14%), 113 (34%).

**Synthesis of 3-benzoyl-2-oxa-3-azabicyclo [2.2.2] oct-5-ene, 142:**

![Chemical structure of 3-benzoyl-2-oxa-3-azabicyclo [2.2.2] oct-5-ene]

A solution of benzohydroxamic acid (0.114 g, 0.83 mmol, 1 equiv.) in DMF (1 ml) was added over a period of two hours, using a syringe pump, to a solution of cyclohexadiene (0.080 g, 1 mmol, 1.2 equiv.) and tetra-n-propyl ammonium periodate (0.328 g, 0.87 mmol, 1.05 equiv.) in DMF (1.5 ml), under a nitrogen atmosphere. After the addition of dichloromethane (10 ml), the mixture was washed twice with water (5 ml) and then dried over magnesium sulphate. After removal of the solvents, the crude material was chromatographed using a mixture of PE 30-
Experimental

40/ethyl acetate = 2:1. The cycloadduct 142, was isolated as an ivory coloured solid and recrystallised by ethanol (0.059 g, 33%, Rf = 0.4).

m.p.: 108° (lit 109°); The spectra were registered at 353 K to stop the equilibrium of the rotamer, 1H-NMR (dms-o-d6, 500 MHz): δ 7.56-7.54 (2H, d, 3J = 6.96 Hz, Hortho x2), 7.47-7.38 (3H, m, Hmeta, Hpara x2), 6.67 (1H, td, 3J5,6 = 8.2 Hz, 3J5,4 = 6 Hz, 3J1,5 = 1.6 Hz, H5), 6.57 (1H, td, 3J5,6 = 8.2 Hz, 3J1,6 = 5.7 Hz, H6), 5.05 (1H, br s, H4), 4.82 (1H, tt, 3J1,6 = 5.7 Hz, 3J1,5 = 1.6 Hz, 3J1,7eq = 3.5 Hz, 3J1,7ax = 1.7 Hz, H1), 2.15 (1H, m, 3J7ax,1 = 3.5 Hz, 3J7ax,8ax = 10.8 Hz, H7ax), 2.12 (1H, m, 3J8ax,7ax = 10.8 Hz, H8ax), 1.49 (1H, m, H8eq), 1.45 (1H, m, 3J7eq,1 = 3.5 Hz, H7eq); 13C-NMR (dms-o-d6, 125 MHz): δ 167.80 (CO), 134.26 (Cipso), 132.04 (C3), 131.44 (C5), 129.98 (CH), 127.68 (CH), 127.49 (CH), 70.89 (C1), 47.87 (C4), 22.77 (C7ax,7eq), 20.32 (C8ax,8eq); IR (CH2Cl2/cm-1): νmax 3050, 2978, 2875 (Ar CH), 1631 (C=O), 1610, 1414, 1261, 1167, 1055, 885; MS (Ion Fab Positive): m/z 216 (M+1+, 100%), 154 (35%).

Ene reaction between 1,1-difluoroctene and benzohydroxamic acid in the presence of iodosobenzene diacetate to yield 157:

A solution of benzohydroxamic acid (0.178 g, 1.3 mmol, 1 equiv.) in a mixture of DCM/DMF (25 ml, 7/1), was added by syringe pump over a period of 8 hours, to a solution of the olefin 7 (0.59 g, 4 mmol, 3 equiv.) and iodosobenzene diacetate (0.483 g, 1.5 mmol, 1.15 equiv.) in DCM (25 ml) at 0°C. The reaction mixture was stirred subsequently at room temperature overnight, treated with a sat. aq. solution of sodium thiosulphate (25 ml), the organic layer separated and dried over magnesium sulphate. The organic solvent was removed in vacuo without excessive heating, to yield a yellow oil which was distilled under reduced pressure (10 mmHg, 70-80°C). The colourless oil obtained was purified by short path distillation at normal pressure at 200°C. However, the distillate still contained traces of DMF and was
chromatographed (PE 40-60/ethyl acetate = 6:1) to give 0.042 g of colourless liquid ($R_f = 0.5$, PE/AcOEt = 5:1). From NMR, the product appeared to derive from an ene type reaction, although its identification was not possible.

$^{1}\text{H-NMR}$ (CDCl$_3$, 500 MHz): $\delta$ 7.68 (2H, dd, $^3J = 7.9$ Hz, $^4J = 1.14$ Hz, H$_{\text{ortho}}$ x2), 7.30 (1H, tt, $^3J = 7.6$ Hz, $^4J = 1.14$ Hz, H$_{\text{para}}$), 7.08 (2H, t, $^3J = 7.9$ Hz, H$_{\text{meta}}$ x2), 4.1 (1H, ddt, $^2J_{HF,\text{trans}} = 25.6$ Hz, $^2J_{HF,\text{cis}} = 8$ Hz, $^3J = 2.7$ Hz, H$_2$), 1.97-1.90 (2H, m, CH$_2$), 1.29-1.22 (6H, m, CH$_2$ x3), 0.88-0.84 (5H, m, CH$_3$, CH$_3$); $^{13}\text{C-NMR}$ (CDCl$_3$, 125 MHz): $\delta$ 171.10 (C=O), 152.22 (t, $^1J_{CF} = 248.19$ Hz, C$_1$), 137.46 (CH$_{\text{ortho}}$), 130.21 (CH$_{\text{meta}}$), 127.42 (CH$_{\text{para}}$), 93.34 (C$_{\text{pso}}$), 78.03 (t, $^2J_{CF} = 21.25$ Hz, C$_2$), 31.52 (CH$_2$), 29.38 (CH$_2$), 27.66 (CH$_2$), 22.57 (CH$_2$), 22.10 (CH$_2$), 14.01 (C$_8$); $^{19}\text{F-NMR}$ (CDCl$_3$, 282 MHz): $\delta$ -90.31 (d, $^2J_{FF} = 48$ Hz), -92.73 (dd, $^2J_{FF} = 48$ Hz, $^3J_{FH} = 15.5$ Hz); MS (EI): $m/z$ 305 (100%), 233 (53%), 219 (40%), 145 (50%), 73 (82%).

_Synthesis of 1,1-difluoro-2,3-diphenylprop-1-ene, 163:_

![Diagram](image)

The same experimental procedure as previously described for 1,1-difluoro-2-pentyl-hept-1-ene (150), was used to prepare 1,1-difluoro-2,3-diphenylprop-1-ene from deoxybenzoin (3 g, 5.28 mmol, 1 equiv.). Purification of the crude material was performed by column chromatography, using PE 30-40 as eluant. The difluoroolefin, 163, was isolated as a yellow oil (0.084 g, 25 %) ($R_f = 0.4$, 100% PE) and stored at $-4^\circ$C.

This product was already been prepared in literature by a different procedure.$^{[168]}$
Experimental

C2), 33.9 (C2); 19F-NMR (CDCl3, 282 MHz): δ -91.1 (d, 2JFF = 183.3 Hz), -91.5 (d, 2JFF = 101.8 Hz); IR (neat/cm−1): νmax 3086, 3029, 2926, 2854 (Ar CH), 1729, 1602.7, 1496, 1242, 1104; MS (FABMS, Matrix MnOBA+Na): m/z 229 (M-1+, 83%), 209 (M-F+, 94%), 178 (M-CF2+, 38%), 127 (63%), 105 (60%), 91 (100%).

Synthesis of 9,10-(N-benzoylepoxymino)dihydro-9,10-dimethylanthracene, 165[129]

To a solution of 9,10-dimethylanthracene (0.5 g, 2.42 mmol, 1.24 equiv.) and tetra-n-propyl ammonium periodate (0.738 g, 1.95 mmol, 1 equiv.) in dichloromethane (50 ml) at 0°C, was added benzohydroxamic acid (0.5 g, 3.64 mmol, 1.87 equiv.) over a period of 10 minutes. After stirring for three hours at this temperature, the orange solution was washed with a sat. solution of sodium thiosulphate (2 x 20 ml) until the iodine colour disappeared, followed by a diluted solution of NaOH (30 ml) and finally water (30 ml). The dichloromethane mixture was dried over magnesium sulphate and then columned on neutral alumina using PE 30-40 and ethyl acetate in a ratio 5:1 as eluant. 9,10-(N-Benzoylepoxymino)dihydro-9,10-dimethyl anthracene was isolated as cream coloured solid (0.263 g, 32%) (Rf = 0.3).

m.p. (hexane/AcOEt): 127°C (lit. 127-128°C)[129], 1H-NMR (CDCl3, 500 MHz): δ 7.55-7.54 (2H, m, CH), 7.38-7.36 (2H, m, CH), 7.33-7.26 (5H, m, CH), 7.25-7.19 (4H, m, CH), 2.78 (3H, s, Me11), 2.02 (3H, s, Me12); 13C-NMR (CDCl3, 125 MHz): δ 175.42 (NCO), 141.61 (C8'), 141.33 (C5',1'), 136.64 (Cipso ph), 130.36, 128.6, 127.39, 127.06, 121.72, 120.65 (CH), 79.82 (C9), 63.68 (C10), 16.40 (C11), 14.78 (C12); IR (KBr/cm−1): νmax 3057, 3029, 2990 (Ar CH), 1654 (C=O), 1459, 1445,
Experimental

1329, 1281, 1231; MS (EI): m/z 206 (M-anthracene⁺, 100%), 191 (M-Me anthracene⁺, 30%), 130 (20%), 77 (C₆H₅⁺, 13%), 51 (5%).

Ene reaction between the difluoro olefin (148, 150, 163) and benzohydroxamic acid in the presence of different oxidising reagents:

1. Using tetra-n-propyl ammonium periodate (151)
To a solution of the difluoro olefin (1 equiv.) and tetra-n-propyl ammonium periodate (1.05 equiv.) in dry dimethylformamide at 0°C, under nitrogen, was added a solution of benzohydroxamic acid (1 equiv.) in DMF by syringe pump over 6 hours. After, the solution was stirred overnight at room temperature, dichloromethane was added and the mixture washed with a sat. sodium thiosulphate solution to remove the iodine, followed by water. The chlorinated solvent was dried over magnesium sulphate and evaporated under reduced pressure. The crude material was purified by flash chromatography.

2. Using iodosobenzene diacetate
Benzohydroxamic acid (1 equiv.) dissolved in a mixture of DCM/DMF (10:1), was added by syringe pump over a period of 6 hours to a solution of difluoro olefin (3 equiv.) and iodosobenzene diacetate (1.15 equiv.) in dichloromethane at room temperature under nitrogen, at 0°C. The mixture was stirred for 16 hours at room temperature and the same work-up as described above, was applied to the crude mixture.

Procedure 1 and 2, were repeated with an excess of olefin (3 equiv.) and at temperatures up to 50-60°C. By flash chromatography, diphenyl-diazene N, N'-dioxide (158) was isolated from both methods as a white solid (Rf = 0.3, PE/AcOEt = 3:1)(10-18 %), in different mixtures of E/Z isomers which slowly rearranged to the more stable E.
3. Using cycloadduct 9,10-(N-benzylepoxyimino)dihydro-9,10-dimethyl anthracene, 165

The compound 165 (1 equiv.) and the difluoro olefin (2 equiv.) were dissolved in dry benzene or toluene, and the solution heated at reflux for 16 hours in a sealed tube. The solvent was then removed and the crude oil was purified by flash chromatography.

Diphenyl-diazene N,N'-dioxide, 158:

\[ \text{Diphenyl-diazene N,N'-dioxide, 158:} \]

\[ \text{Z-} \]  
\[ \text{E-} \]

- m.p.: 50°C on melting gave a green liquid;  \[ ^1 \text{H-NMR (CDCl}_3, 500 \text{ MHz): } \delta 8.08 (4H, dd, } ^3J = 7.78 \text{ Hz, } ^4J = 1.43 \text{ Hz, H}\text{ortho), 7.65-7.43 (6H, m, 4H}_{\text{meta}}, 2\text{H}_{\text{para}}) \text{ Z-isomer; 8.15 (2H, dd, } ^3J = 7.16 \text{ Hz, } ^4J = 1.30 \text{ Hz, H\text{ortho), 7.85 (2H, dd, } ^3J = 7.16 \text{ Hz, } ^4J = 1.30 \text{ Hz, H\text{ortho), 7.63 (1H, t, } ^3J = 7.46 \text{ Hz, Hpara), 7.57 (1H, t, } ^3J = 7.46 \text{ Hz, Hpara), 7.50-7.45 (4H, m, H}_{\text{meta}}) \text{ E-isomer; 13C-NMR (CDCl}_3, 125 \text{ MHz): } \delta 171.13 (\text{C=O}), 133.70 (\text{C}_{\text{para}} \times 2), 130.07 (\text{C}_{\text{meta}} \times 4), 129.35 (\text{C}_{\text{ipso}} \times 2), 128.47 (\text{C}_{\text{ortho}} \times 4) \text{ Z-isomer; 166.59 (C=O), 165.29 (C=O), 134.32 (C}_{\text{para}}, 132.83 (C}_{\text{para}}, 130.84 (C}_{\text{ipso}}, 130.06 (C}_{\text{ortho}} \times 2), 128.88, 128.74 (C}_{\text{meta}} \times 4), 127.54 (C}_{\text{ortho}} \times 2), 126.55 (C}_{\text{ipso}}) \text{ E-isomer; IR (nujol/cm}^{-1}): \nu_{\text{max}} 1688 (\text{C=O}), 1352, 1317, 1124, 1070 \text{ Z-isomer, 1767, 1641 (C=O), 1240, 1041, 1022 E-isomer; MS (El): } m/z 105 (C_7H_5O^+, 100\%), 77 (C_6H_5^+, 35\%). \]
Experimental

Synthesis of benzohydroxamic potassium salt, 188[135]

Separate solutions of hydroxylamine hydrochloride (23.3 g, 333 mmol, 2 equiv.) in methanol (120 ml) and potassium hydroxide (28 g, 500 mmol, 3 equiv.) in methanol (70 ml), were heated at 70°C. Both were cooled slowly to 30-40°C to avoid crystallisation and the alkaline solution was added by cannula to the hydroxylamine solution. Any excessive rise of temperature during the addition was prevented by occasionally cooling in an ice-bath. All procedures were performed under nitrogen. After the addition, the mixture was allowed to stand in the ice bath for 5 minutes to ensure complete precipitation of potassium chloride. Ethyl benzoate (25 g, 166.5 mmol, 1 equiv.) was added and the solid removed by filtration. On cooling, the desired compound crystallised as an ivory coloured solid (15 g, 52%).

m.p.: 128-129°C (lit. 125-128°C)[135]; 1H-NMR (dms-o-d6, 300 MHz): δ 9.7 (1H, s, NH), 7.99-7.85 (2H, m, CH x2), 7.33-7.32 (3H, m, CH x3); 13C-NMR (dms-o-d6, 75 MHz): δ 164 (C=O), 136.1 (Cipso), 129.41 (CH), 128.15 (CH x2), 126.58 (CH x2); IR (KBr/ cm-1): vmax 3246 broad (NH, Ar CH), 1684 (C=O), 1599.4; MS (FABMS, Matrix MNOBA+Na): m/z 176 (M+1, 17%), 154 (M-K+, 40%), 136 (42%), 107 (17%).

Synthesis of O-allyl-benzohydroxamate, 183[136]

A solution of potassium benzohydroxamate (0.87 g, 5 mmol, 1 equiv.), allyl bromide (0.72 g, 5.9 mmol, 1.18 equiv.) and anhydrous sodium carbonate (2.5 g, 16.56 mmol,
3.3 equiv.) in a mixture of methanol/water (50 ml, 3/2) was stirred for 24 hours at room temperature. After removal of methanol by distillation, the residue was acidified by the addition of conc. HCl and extracted with chloroform (3 x 15 ml). The combined organic extracts were dried over magnesium sulphate and evaporated to give a yellow solid. Recrystallisation from hexane/diethyl ether (1:1) gave 183 as a white solid (0.772 g, 74%) (Rf = 0.42, hexane/ethyl acetate = 1:1).

**m.p.: 58-59°C (lit. 58°C)\textsuperscript{[169]}; ¹H-NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta \) 9.37 (1H, s, NH), 7.71 (2H, d, \( J = 7.19 \text{ Hz}, \text{ H}_2\text{,}, \)), 7.48-7.44 (1H, m, H\textsubscript{4}), 7.38-7.34 (2H, m, H\textsubscript{3,5}), 6.03-5.93 (1H, m, H\textsubscript{2}), 5.32-5.25 (2H, m, H\textsubscript{3,4}), 4.45 (2H, d, \( J = 6.28 \text{ Hz}, \text{ H}_1\)); \( ^{13} \text{C-NMR} \) (CDCl\textsubscript{3}, 100 MHz): \( \delta \) 166.42 (C=O), 132.12 (C\textsubscript{2,3}), 131.93 (C\textsubscript{4}), 131.85 (C\textsubscript{5}), 128.55 (C\textsubscript{3,6}), 127.09 (C\textsubscript{2,3}), 120.70 (C\textsubscript{4,5}), 77.38 (C\textsubscript{1}); IR (nujol/cm\textsuperscript{-1}): \( \nu_{\max} \) 3202 (NH, CH), 1643 (C=O), 1578, 1514, 1350, 1155, 1111; MS (EI): \( m/z \) 177 (M\textsuperscript{+}, 75%), 105 (M-NHOAllyl\textsuperscript{+}, 100%), 77 (C\textsubscript{6}H\textsubscript{5}\textsuperscript{+}, 90%), 51 (68%), 41 (57%).

**Synthesis of 3-iodo-2-cyclohexen-1-one, 196\textsuperscript{[137]}**

Iodine (5.59 g, 22 mmol, 1.1 equiv.) was added to an ice-cold solution of recrystallised triphenylphosphine (5.76 g, 22 mmol, 1.1 equiv.) in dry acetonitrile (200 ml) and the mixture stirred at room temperature for 2 hours. Triethylamine (2.2 g, 22 mmol, 1.1 equiv.) was then added, followed by 1,3-cyclohexandione (2.24 g, 20 mmol, 1 equiv.) and the mixture heated at reflux for 21 hours. After removal of the solvent under reduced pressure, the residual material was filtered through a short column of silica gel which was eluted with ether. After concentration, the desired product was obtained as a yellow oil (3.67 g, 83%) (Rf = 0.64, hexane/ethyl acetate = 1:1), which was stored at -4°C in the dark.
Experimental

\(^1\)H-NMR (CDCl\(_3\), 500 MHz): \(\delta\) 6.76 (1H, s, H\(_2\)), 2.88-2.86 (2H, m, H\(_6\)), 2.39-2.37 (2H, m, H\(_4\)), 2.0-1.97 (2H, m, H\(_5\)); \(^{13}\)C-NMR (CDCl\(_3\), 125 MHz): \(\delta\) 195.10 (C=O), 140.64 (C\(_2\)), 126.91 (C-I), 40.53 (C\(_6\)), 36.53 (C\(_4\)), 23.95 (C\(_5\)); IR (neat/cm\(^{-1}\)): \(\nu_{\text{max}}\) 2946, 2876 (Ar CH), 1675 (C=O), 1595, 1450, 1420; MS (EI): \(m/z\) 222 (M\(^+\), 99%), 127 (M-I\(^+\), 24%), 95 (C\(_6\)H\(_7\)O\(^+\), 100%), 67 (C\(_5\)H\(_7\), 79%), 55 (C\(_4\)H\(_7\), 35%).

**Synthesis of 3-chloro-2-cyclohexen-1-one, 197**\(^{[137]}\)

\[ \begin{array}{c}
\text{O} \\
\text{C} \\
\text{H}_6 \\
\text{H}_5 \\
\text{H}_4 \\
\text{Cl} \\
\text{H}_3 \\
\text{H}_2 \\
\text{H}_1 \\
\end{array} \]

A solution of chlorine in carbon tetrachloride (25 ml, 15 mmol, 0.6 M, 1.1 equiv.) was added to a cooled solution of recrystallised triphenylphosphine (3.88 g, 15 mmol, 1.1 equiv.) in dry benzene (100 ml). When the addition was complete and tlc analysis showed that the triphenylphosphine had been consumed, triethylamine (1.45 g, 14.3 mmol, 1.06 equiv.) and 1,3-cyclohexandione (1.51 g, 13.5 mmol, 1 equiv.) were added consequently. The resulting suspension was stirred at room temperature for 2 hours then filtered through a pad of silica, which was washed with diethyl ether. Removal of the solvent from the combined eluant, followed by short path distillation (25 mmHg, 140-160\(^\circ\)C)(lit. 20 mmHg, 134-138\(^\circ\)C)\(^{[170]}\) afforded the desired product as colourless liquid (1 g, 57%) (R\(_f\) = 0.53, hexane/ethyl acetate = 1:1).

\(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\delta\) 6.15 (1H, m, H\(_2\)), 2.61 (2H, td, \(^3\)J\(_{6,5}\) = 6.20 Hz, \(^4\)J\(_{6,4}\) = 1.43 Hz, H\(_6\)), 2.33 (2H, td, \(^3\)J\(_{6,5}\) = 7.1 Hz, \(^4\)J\(_{6,4}\) = 1.43 Hz, H\(_4\)), 2.01 (2H, quintet, \(^3\)J = 7.3 Hz, H\(_5\)); \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): \(\delta\) 197.11 (C=O), 158.55 (C-Cl), 128.4 (C\(_2\)), 36.29 (C\(_6\)), 33.87 (C\(_4\)), 22.19 (C\(_3\)); IR (neat/cm\(^{-1}\)): \(\nu_{\text{max}}\) 2948, 2872 (Ar CH), 1673 (C=O), 1601, 1449, 1421, 749 (C-Cl); MS (EI): \(m/z\) 130 (M\(^+\), 15%), 102 (M-CO\(^+\), 35%), 67 (M-COCl\(^+\), 14%), 47 (65%), 42 (100%), 39 (80%), 27 (55%).
Experimental

**Synthesis of nitroso benzene, 212**[141]

\[
\text{NH}_2 \quad \rightarrow \quad \text{N} = \text{O}
\]

To a solution of aniline (1.86 g, 20 mmol, 1 equiv.) in PE 30-40 (100 ml) at room temperature, was added sodium tungstate hydrate (0.33 g, 1 mmol, 0.05 equiv.) and tetra-\(n\)-butylammonium bromide (0.1 g, 0.31 mmol, 0.015 equiv.). The mixture was cooled in an ice bath and a 30% solution of hydrogen peroxide in water (3.02 g, 89 mmol, 4.45 equiv.) was slowly added. The solution became green immediately and stirring was continued for 2.5 hours at room temperature. The organic layer was carefully separated, washed with a 0.01 N HCl solution (50 ml), followed by water (50 ml) and the solvent removed at normal pressure. The solid residue was recrystallised from petroleum ether 30-40, at \(-4^\circ\text{C}\). The isolated yellow solid (1 g, 47%) was the dimeric form of nitroso benzene, which on heating gave the desired compound. The product was stored at \(-20^\circ\text{C}\).

**m.p.:** 65-66°C (lit. 68-69°C)[141]; \(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.92-7.89 (2H, m, \text{CH}), 7.74-7.59 (3H, m, \text{CH}); \(^1^3\)C-NMR (CDCl\(_3\), 75 MHz): \(\delta\) 135.53, 129.27, 120.91 (\text{CH}), 113.02 (C ipso); IR (KBr/cm\(^{-1}\)): \(\nu_{\text{max}}\) 3091, 3059, 3014 (Ar \text{CH}), 1484.1, 1456 (NO), 1380, 1191, 1154, 1074, 950; MS (EI): \(m/z\) 107 (M\(^+\), 30%), 77 (M-NO\(^+\), 100%), 55 (44%), 47 (65%).

**Synthesis of E-[1,1']biisobenzofuranylidene-3,3'-dione, 223**[143]
Experimental

A mixture of phthalic anhydride (21.6 g, 145.8 mmol, 1 equiv.) and triethylphosphite (48.45 g, 291.5 mmol, 2 equiv.) was refluxed for 5 hours during which time yellow crystals were formed. After cooling the solution under nitrogen, the solid was removed by filtration. The filtrate was refluxed again for a further 6 hours, and more crystals were obtained. The combined solid was washed with hot benzene (40 ml), followed by acetone (40 ml) and dichloromethane (40 ml), then dried under vacuum at 120°C. E-[1,1']biisobenzofuranylidene-3,3'-dione was obtained as fine yellow crystals (8.03 g, 41%) and was recrystallised from boiling xylene. The product appeared insoluble in most organic solvents therefore NMR analysis could not be performed.

m.p.: 350°C with decomposition (lit. 352-354°C)\textsuperscript{143}; IR (KBr/cm\textsuperscript{-1}): \(\nu_{\text{max}}\) 1786 (C=O), 1473, 1342, 1269, 1138, 1013, 885; MS (EI): \(m/z\) 264 (M\textsuperscript{+}, 100%), 208 (M-OCOC\textsuperscript{+}, 35%), 180 (30%), 152 (M-[OCOC]\textsuperscript{+}, 30%), 76 (C\textsubscript{6}H\textsubscript{5}\textsuperscript{+}, 37%); HRMS (EI): calculated for C\textsubscript{16}H\textsubscript{8}O\textsubscript{4} 264.04224, found 264.04151.

X-Ray: For the complete analysis see Appendix.
Experimental

Temperature 293(2) K
Radiation, wavelength MoKα, 0.71073 Å
Crystal system, space group monoclinic, P2_1/c
Unit cell parameters
a = 10.188(5) Å  α = 90°
b = 3.783(2) Å  β =
c = 15.097(8) Å  γ = 90°

Cell volume 577.4(5) Å³
Z 2
Calculated density 1.520 g/cm³
Absorption coefficient μ 0.110 mm⁻¹
F(000) 272
Crystal colour and size colourless, 0.50 × 0.04 × 0.03 mm³
Data collection method Bruker SMART APEX diffractometer

θ range for data collection 2.01 to 28.26°
Index ranges h -13 to 13, k -4 to 5, l -20 to 20
Completeness to θ = 26.00° 99.7%
Reflections collected 4567
Independent reflections 1363 (R_int = 0.0558)
Reflections with F^>2g 809
Absorption correction semi-empirical from equivalents
Min. and max. transmission 0.9468 and 0.9967
Structure solution direct methods
Refinement method Full-matrix least-squares on F²
Weighting parameters a, b 0.0485, 0.0000
Data / restraints / parameters 1363 / 0 / 92
Final R indices [F^>2g] R1 = 0.0586, wR2 = 0.1063
R indices (all data) R1 = 0.1130, wR2 = 0.1227
Goodness-of-fit on F² 0.980
Extinction coefficient 0.010(5)
Largest and mean shift/su 0.000 and 0.000
Largest diff. peak and hole 0.184 and -0.179 e Å⁻³

Synthesis of E-4,5,6,7,4',5',6',7'-octachloro-[1,1']biisobenzofuranylidene-3,3'-dione 227.¹⁴³
To a solution of tetrachlorophthalic anhydride (5.7 g, 19.93 mmol, 1 equiv.) in benzene (50 ml) was added triethylphosphite (17 g, 102.31 mmol, 5 equiv.) and the mixture refluxed for 24 hours. E-4,5,6,7,4',5',6',7'-octachloro-[1,1']biisobenzofuranlidene-3,3'-dione, precipitated from the solution as a bright yellow solid which was filtered and washed with hot benzene (1.56 g, 14.5%). The product appeared insoluble in most organic solvents therefore NMR analysis cannot be performed.

**m.p.: 365-370°C (lit. 365-370°C)\(^{[143]}\); IR (KBr/cm\(^{-1}\)): \(\nu_{max}\) 1778, 1732 (C=O), 1504, 1385, 1277, 1223, 1194, 1095; MS (EI): \(m/z\) 540 (M+1,100%), 475 (25%), 356 (23%), 242 (22%), 214 (60%), 179 (27%), 142 (30%); HRMS (EI): calculated for C\(_{16}\)O\(_4\)Cl\(_8\) 539.70685, found 539.70930.**

**Synthesis of 1-hydroxy-1,3-dihydro-indol-2-one, 231.\(^{[145]}\)**

A mixture of nitrophenylacetic acid (3 g, 16.56 mmol, 1 equiv.), calcium chloride (0.17 g, 1.53 mmol, 0.09 equiv.) in ethanol/water (17 ml/3.3 ml), was heated to 80°C and then zinc dust (2.6 g, 39.76 mmol, 2.4 equiv.) was added over a period of 5 minutes. After cooling to room temperature, the reaction mixture was filtered through a pad of celite, then one of silica to remove inorganic salts. After the solvent was evaporated, the residue was purified by chromatography using a mixture of petroleum ether/ethyl acetate (2:1) as eluant increasing the concentration of ethyl acetate to 100%. Thereafter methanol was added to AcOEt as eluant until a final mixture of ethyl acetate/methanol of 7/3. The isolated 1-hydroxy-1,3-dihydro-indol-2-one was recrystallised from a mixture of THF and dichloromethane to give a brown solid (7%). The product reduced Fehling’s solution on heating and formed a violet complex in the presence of aqueous solution of ferric chloride (see General Experimental).
Experimental

m.p.: 198-199°C (lit. 198-202°C) $^{[145][171]}$; $^1$H-NMR (dmsod$_6$, 500 MHz): $\delta$ 10.34 (1H, s, N-OH), 7.25 (1H, td, $^3J = 7.65$ Hz, $^4J = 0.95$ Hz, H$_{6(7)}$), 7.21 (1H, d, $^3J = 7.01$ Hz, H$_{5(8)}$), 6.98 (1H, td, $^3J = 7.01$ Hz, $^4J = 0.95$ Hz, H$_{6(7)}$), 6.89 (1H, d, $^3J = 7.65$ Hz, H$_{5(8)}$), 3.52 (2H, s, H$_3$); $^{13}$C-NMR (dmsod$_6$, 125 MHz): $\delta$ 169.26 (C=O), 143.73 (C$_{4/9}$), 127.61 (C$_{6(7)}$), 124.31 (C$_{5(8)}$), 121.83 (C$_{6(7)}$), 121.16 (C$_{4/9}$), 106.78 (C$_{5(8)}$), 33.37 (C$_3$); IR (KBr/cm$^{-1}$): $\nu_{\text{max}}$ 3200 (NOH), 3030, 2991 (Ar CH), 1670 (C=O), 1610; MS (FABMS, Matrix MNOBA+Na): m/z 150 (M+1$^+$, 97%), 132 (M-H$_2$O, 49%), 91 (M-NOHCO, 37%), 81 (32%).

Synthesis of 2-nitro-phenyl acetic acid methylester, 236:

Acetyl chloride (10.4 g, 133 mmol, 2.4 equiv.) was added dropwise to methanol (60 ml) with stirring and after the exotherm had subsided, the resulting solution added to nitrophenyl acetic acid (10 g, 55.2 mmol, 1 equiv.) and refluxed for 3 hours. The solvent was removed to give a oil which was purified by column chromatography (petroleum ether 30-40:ethyl acetate = 2:1): 2-nitro-phenyl acetic acid methylester was obtained in 99% yield as an yellow oil (10.7 g) (R$_f$ = 0.69).

$^1$H-NMR (CDCl$_3$, 500 MHz): $\delta$ 8.09–8.08 (1H, dd, $^3J_{3.4} = 8.14$ Hz, $^4J_{3.5} = 1.25$ Hz, H$_3$), 7.59-7.56 (1H, td, $^3J_{4.5} = 7.46$ Hz, $^4J_{5.6} = 7.50$ Hz, $^4J_{5.3} = 1.25$ Hz, H$_3$), 7.47-7.44 (1H, td, $^3J_{4.3} = 8.14$, $^3J_{4.5} = 7.46$ Hz, $^4J_{4.6} = 1.30$ Hz, H$_4$), 7.34-7.33 (1H, dd, $^3J_{6.5} = 7.50$ Hz, $^4J_{6.4} = 1.30$ Hz, H$_6$), 4.0 (2H, s, CH$_2$CO), 3.69-3.68 (3H, s, Me); $^{13}$C-NMR (CDCl$_3$, 125 MHz): $\delta$ 170.37 (CO), 148.71 (C$_2$), 133.55 (C$_3$), 133.29 (C$_6$), 129.69 (C$_1$), 128.60 (C$_4$), 125.26 (C$_3$), 52.22 (Me), 39.52 (CH$_2$CO); IR (neat/cm$^{-1}$): $\nu_{\text{max}}$ 3004, 2954, 2848 (Ar CH), 1736 (CO), 1529 (C-NO$_2$); MS (FABMS, Matrix MNOBA+Na): m/z 196 (M+1$^+$, 88%), 179 (35%), 164 (100%), 149 (M-NO$_2$, 22%), 136 (58%), 120 (27%); HRMS (FAB): calculated for C$_9$H$_{10}$NO$_4$ (M+H) 196.0605, found 196.0610.
Experimental

Synthesis of 1,3-dihydroindol-2-one, 237:

To a refluxing solution of 2-nitro-phenyl acetic acid methylester (0.2 g, 1 mmol, 1 equiv.) and ammonium chloride (0.059 g, 1.1 mmol, 1.1 equiv.) in dry methanol (10 ml), under nitrogen, was added zinc powder (0.131 g, 2 mmol, 2 equiv.). After the mixture was stirred at this temperature for 30 minutes, titanium isopropoxide (0.142 g, 0.5 mmol, 0.5 equiv.) was slowly added. After 5 hours of reflux, the hot mixture was filtered through celite. The organic solvent was then removed to give a pale yellow solid which was purified by flash chromatography using a starting mixture of petroleum ether /ethyl acetate = 1:1 as eluant and increasing slowly the polarity. The product was obtained as a white solid (0.025 g, 18%), which was recrystallised from ethanol and its spectral properties were identical to those of a commercially available sample. Fehling’s solution was not reduced on heating and no complex was formed with this product in the presence of aqueous solution of ferric chloride (see General Experimental).

m.p.: 124-126°C (lit. 126-127°C)\textsuperscript{[172]}; \textsuperscript{1}H-NMR (dmsdo-d\textsubscript{6}, 500 MHz): \(\delta\) 10.35 (1H, s, N-OH), 7.17 (1H, dd, \(^3J = 7.33\) Hz, \(^4J = 0.65\) Hz, H\textsubscript{6}), 7.14 (1H, td, \(^3J = 7.68\) Hz, \(^4J = 0.65\) Hz, H\textsubscript{6}), 6.90 (1H, td, \(^3J = 7.33\) Hz, \(^4J = 0.65\) Hz, H\textsubscript{7}), 6.79 (1H, d, \(^3J = 7.68\) Hz, H\textsubscript{5}), 3.48 (2H, s, H\textsubscript{3}); \textsuperscript{13}C-NMR (dmsdo-d\textsubscript{6}, 125 MHz): \(\delta\) 176.38 (C=O), 143.68 (C\textsubscript{9}), 127.44 (C\textsubscript{6}), 127.58 (C\textsubscript{4}), 124.38 (C\textsubscript{8}), 121.14 (C\textsubscript{7}), 109.1 (C\textsubscript{5}), 35.73 (C\textsubscript{3}); IR (KBr/cm\textsuperscript{-1}): \(\nu_{\text{max}}\) 3200 (N=O), 3030, 2991 (Ar CH), 1670 (C=O), 1610; MS (EI): \(m/z\) 133 (M\textsuperscript{+}, 100%), 104 (75%), 78 (45%), 51 (21%).
Experimental

**Synthesis of (2-nitro-phenyl)-acetic acid isopropyl ester, 238:**

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{NO}_2 & \quad 5 \quad \text{O} \\
\text{3} & \quad \text{1}
\end{align*}
\]

If the same procedure as above was repeated using dichloroethane as solvent, and the reaction time increased to 1 day, the starting material was recovered (70%) together with 20 % of the transesterification product: (2-nitro-phenyl)-acetic acid isopropyl ester which was isolated as a yellow oil (0.045 g) (R_f = 0.68, petroleum ether 30-40: diethyl ether = 1:1).

\[\text{H-NMR (CDCl}_3, 500 \text{ MHz): } \delta 8.07 \ (1\text{H, dd}, {^3}J_{3,4} = 8.20 \text{ Hz}, {^4}J_{3,5} = 1.10 \text{ Hz}, \text{H}_3), \]
\[7.56 \ (1\text{H, td}, {^3}J_{5,6} = 7.60 \text{ Hz}, {^4}J_{5,3} = 1.10 \text{ Hz}, \text{H}_5), 7.44 \ (1\text{H, td}, {^3}J_{4,3} = 8.20 \text{ Hz}, {^3}J_{4,6} = 1.50 \text{ Hz}, \text{H}_4), 7.33 \ (1\text{H, dd}, {^3}J_{6,5} = 7.60 \text{ Hz}, {^4}J_{6,4} = 1.50 \text{ Hz}, \text{H}_6), 5.0 \ (1\text{H, septuplet, }{^3}J = 6.26 \text{ Hz}, \text{CH}), 3.96 \ (2\text{H, s, CH}_2\text{CO}), 1.21 \ (6\text{H, d, }{^3}J = 6.26 \text{ Hz, Me x2}); \]
\[\text{C-NMR (CDCl}_3, 125 \text{ MHz): } \delta 169.42 \ (\text{C}=\text{O}), 142.79 \ (\text{C}_2), 133.29 \ (\text{C}_3), 133.27 \ (\text{C}_6), 130.00 \ (\text{C}_1), 128.53 \ (\text{C}_4), 125.20 \ (\text{C}_3), 68.86 \ (\text{CH}), 39.79 \ (\text{CH}_2), 21.66 \ (\text{Me x2}); \]
\[\text{IR (neat/cm}^{-1}) : \nu_{\text{max}} 2982, 2935, 2878 \ (\text{Ar CH}), 1732 \ (\text{C}=\text{O}), 1526 \ (\text{C-NO}_2), 1348 \ (\text{N-O}), 1219, 1107; \]
\[\text{MS (Positive-CI Methane): } m/z 224 \ (M+1^+, 28\%), 182 \ (M-\text{CMe}_2, 42\%), 164 \ (M-\text{OCHMe}_2^+, 100\%); \]
\[\text{HRMS (FAB): calculated for C}_{11}\text{H}_{14}\text{NO}_4 (\text{M+H}) 224.0925, \text{ found 224.0923}. \]

**Synthesis of a solution of dimethyldioxirane, 241:**

\[
\begin{align*}
\text{OXONE} & \quad \rightarrow \\
\end{align*}
\]

A mixture of sodium hydrogen carbonate (58 g, 0.69 mol, 3.5 equiv.) in acetone-water (192 ml: 254 ml) was cooled in an ice bath and Oxn (potassium monopersulphate triple salt) was added in five portions (24 g each) (120 g, 0.195 mol, 1 equiv.) at 3 minute intervals. After a further 3 minutes of the last addition, a
Experimental

water-pump vacuum (ca. 14 mmHg) was applied, the cooling bath was removed and the vigorously stirred dimethyldioxirane/acetone solution distilled (150 ml, 0.08-0.1 M, ca. 5% yield) and collected in a cooled (-78°C) receiving flask. The concentration of dimethyldioxirane was determined by oxidation of methyl phenyl sulfide to its sulfoxide, the latter quantified by $^1$H-NMR. The acetone solution of the oxidant was dried with K$_2$CO$_3$ and stored at -20°C over molecular sieves (4 Å).

Oxidation of indoline in the presence of the solution of dioxirane:

\[
\begin{align*}
\text{N} & \quad \rightarrow \quad \text{N} \\
\text{H} & \quad \rightarrow \quad \text{OH}
\end{align*}
\]

To a solution 0.08 M of dimethyldioxirane in acetone (60 ml, 4.8 mmol, 9 equiv.), under an inert atmosphere at 0°C, indoline (0.063 g, 0.53 mmol, 1 equiv.) was added dropwise. After the solution was stirred for a further 5 minutes, the solvent was removed under reduced pressure to give the desired product 231, 1-hydroxy-1,3-dihydroindol-2-one, as a brown solid (0.080 g, 99%).

When the same procedure was repeated using from 3 to 6 equiv. of dimethyldioxirane, a mixture of unidentified compounds was obtained and could not been further purified by chromatography or recrystallisation.

Oxidation of indoline in the presence of the system hydrogen peroxide/sodium tungstate:

\[
\begin{align*}
\text{N} & \quad \rightarrow \quad \text{INDIGO TYPE COMPOUNDS} \\
\text{H} & \quad \rightarrow \quad \text{INDIGO TYPE COMPOUNDS}
\end{align*}
\]
Sodium tungstate hydrate (0.017 g, 0.05 mmol, 0.019 equiv.) was added to a solution of indoline (0.316 g, 2.65 mmol, 1 equiv.) in methanol (25 ml). The mixture was cooled to 0°C, under nitrogen, and a 30% solution of hydrogen peroxide in water (0.268 g, 7.9 mmol, 3 equiv.) was added dropwise. After, the mixture was stirred at room temperature for 24 hours, the solvent was evaporated to yield a green oil which decomposed on purification by column chromatography.

**Synthesis of 1-hydroxy-1,3-dihydroindol-2-one, 231.**

\[ \text{CO}_2\text{H} \quad \xrightarrow{\text{NO}_2} \quad \text{N} \quad \xrightarrow{\text{OH}} \]

A solution of nitrophenylacetic acid (5 g, 27.55 mmol, 1 equiv.) in 98% ethanol (250 ml) was deoxygenated by bubbling nitrogen through the solution mixture and then dimethylsulfoxide (2 ml) and platinum on carbon (0.125 g, 5%) were added. The atmosphere above the solution was displaced by hydrogen (at 1 atm) and the reaction was stirred. The uptake of hydrogen was monitored by a water displacement apparatus and the reaction was stopped after 2 equiv. of hydrogen had been consumed. The reaction mixture was filtered through celite to remove the catalyst and the solvent was removed under reduced pressure. Water (100 ml), containing conc. sulfuric acid (3 ml) was added to the residue and the resulting solution was stirred for 4 hours at room temperature. The cream coloured solid (2.32 g) that formed was filtered and dried under vacuum for 18 hours at 40°C. After, the solid was dissolved in methanol (50 ml), a drop of thionyl chloride was added and the reaction mixture stirred for 16 hours at room temperature. After removal of the solvent, the residual dark solid (2.38 g) was purified by column chromatography using a mixture of PE/diethyl ether (1:1) as eluant. The polarity of the eluant was increased through ether, ethyl acetate until finally an ethyl acetate/methanol mixture of 7:3.

The products isolated from the column were in increasing polarity, the methyl ester 236 (yellow oil, 0.900 g, 17 %) \((R_f = 0.42, \text{petroleum ether /diethyl ether = 1:1}), E-\)
isomer of the dimeric nitroso of the ester 252 (yellow solid, 0.485 g, 5\%)(R_f =0.24, PE/Et_2O = 1:1) and the desired 1-hydroxy-1,3-dihydro-indol-2-one 231 (0.95 g, 23\%)(R_f = 0.01, petroleum ether/diethyl ether = 1:1) which was stored at -4°C.

E-{2-[(2-Methoxycarbonylmethylphenyl)-dioxy-diazenyl]phenyl}acetic acid methyl ester, 252:

\[
\begin{align*}
E & \quad \text{(Ester Structure)} \\
\text{CO}_2\text{Me} & \\
\text{N} & \\
\text{O}^- & \\
\text{N} & \\
\text{O}^- & \\
\text{CO}_2\text{Me} & 
\end{align*}
\]

m.p.: 74°C with decomposition; ^1H-NMR (CDCl_3, 500 MHz): \( \delta \) 8.30 (1H, d, \( ^3J = 7.8 \) Hz, Hortho), 7.85 (1H, d, \( ^3J = 7.72 \) Hz, Hortho'), 7.48-7.28 (6H, m, ArCH), 3.96 (2H, s, CH_2), 3.79 (2H, s, CH_2), 3.62 (3H, s, Me), 3.59 (3H, s, Me); ^13C-NMR (CDCl_3, 125 MHz): \( \delta \) 171.71, 170.89 (C=O), 148.2, 142.30 (Cipso), 132.43 (CH), 131.29 (Cipso), 130.94 (CH), 130.6 (CH), 129.18 (CH), 128.15 (CH), 128.09 (Cipso), 127.66 (CH), 124.35 (CHortho'), 122.01 (CHortho), 52.09 (Me), 51.96 (Me), 38.35 (CH_2), 37.88 (CH_2); IR (nujol/cm\(^{-1}\)): \( \nu_{\text{max}} \) 2677, 1736, 1732, 1580, 1404, 1377, 1244, 1176; MS (Positive-CI Methane): \( m/z \) 357 (10\%), 343 (80\%), 311 (94\%), 269 (95\%), 235 (100\%), 207 (30\%), 149 (28\%), 121 (70\%).

**Synthesis of 3,3,4-tribromo-1-hydroxy-1,3-dihydro-indol-2-one, 256:**

\[
\begin{align*}
\text{OH} & \\
\text{N} & \\
\text{OH} & \\
\text{Br} & \\
\text{Br} & \\
\text{Br} & \\
\text{Br} & \\
\text{Br} & \\
\text{Br} & \\
\text{Br} & \\
\text{Br} & \\
\text{Br} & \\
\end{align*}
\]
Experimental

1-Hydroxy-1,3-dihydro-indol-2-one (0.1 g, 0.67 mmol, 1 equiv.) in tetrachlorocarbon (10 ml) was heated to 50°C and propylene oxide (0.049 g, 0.84 mmol, 1.26 equiv.) and bromine were added (0.321 g, 2.01 mmol, 3 equiv.). The reaction was stirred at this temperature for 2.5 hours. After removal of the solvent, the residual oil was purified by column chromatography, using a mixture of petroleum ether/diethyl ether (2:1) as eluant, to give 3,3,4-tribromo-1-hydroxy-1,3-dihydroindol-2-one as a yellow oil (0.050 g, 19%) (R_f = 0.3, PE/EtO = 1:1).

^1H-NMR (CDCl_3, 500 MHz): δ 8.65 (1H, s, NOH), 7.71 (1H, d, ^3J_{5,6} = 2.03 Hz, H_5), 7.41 (1H, dd, ^3J_{6,7} = 8.35 Hz, ^3J_{6,5} = 2.03 Hz, H_6), 6.81 (1H, d, ^3J_{7,6} = 8.35 Hz, H_7);

^13C-NMR (CDCl_3, 125 MHz): δ 171.27 (CO), 135.81 (C_4), 134.55 (C_6), 133.17 (C_5), 129.24 (C_3), 116.69 (C_4), 112.59 (C_7), 43.69 (C_3); IR (neat/cm^-1): υ_{max} 3128 (NOH), 2921, 2856 (Ar CH), 1746 (C=O), 1600, 1458, 1283, 1180; MS (EI): m/z 370 (M-O^+, 5%), 292 (25%), 212 (65%), 133 (17%); HRMS (FAB): calculated for C_{8}H_{4}NO_{2}Br_3 382.7701, found 382.7750.

Synthesis of 2,5-dibenzyloxy-benzaldehyde, 259:

![Chemical structure](image)

A mixture of 2,5-dihydroxybenzaldehyde (1.5 g, 10.86 mmol, 1 equiv.) and potassium carbonate (3.3 g, 24 mmol, 2.2 equiv.) in acetone (30 ml) was stirred at room temperature for 10 minutes. Benzyl bromide (4.1 g, 24 mmol, 2.2 equiv.) and 18-crown-6 (0.002 equiv.) were then added and the reaction was stirred for 18 hours. The resulting mixture was filtered through a pad of silica which was washed with dichloromethane. After removal of the solvent, the resulting yellow solid was
purified by flash-chromatography (PE 40-60/AcOEt = 4:1) and recrystallised from hot ethanol to give pale yellow needles (2.45 g, 72%, Rf = 0.54).

m.p.: 94-95°C; **1H-NMR** (CDCl₃, 300 MHz): δ 10.46 (1H, s, CHO), 7.3-7.6 (11H, m, Ph x2 and H₆), 7.19 (1H, dd, J = 9.06 Hz, J' = 3.24 Hz, H₄), 7.0 (1H, d, J = 9.06 Hz, H₃), 5.13 (2H, s, OCH₂), 5.04 (2H, s, OCH₂); **13C-NMR** (CDCl₃, 75 MHz): δ 189.76 (CHO), 156.39 (C₁₈), 153.50 (C₁₈), 137.07 (C₁₈), 136.69 (C₁₈), 129.11 (CH), 128.99 (CH), 128.66 (CH), 128.47 (CH), 127.95 (CH), 127.76 (CH), 126.08 (C₁₈), 124.53 (C₄), 115.55 (C₃), 112.26 (C₆), 71.76 (OCH₂), 71.1 (OCH₂); **IR** (nujol/cm⁻¹): νₘₐₓ 2922, 1679 (RCHO), 1490, 1452, 1427, 1380 (Ar CH); **MS** (FABMS, Matrix MNOB⁺Na): m/z 318 (M⁺, 92%), 227 (M-PhCH₂⁺, 30%), 154 (100%), 136 (M-[PhCH₂]⁺, 90%), 115 (40%), 107 (67%); **HRMS** (FAB): calculated for C₂₁H₁₈O₃ 318.1256, found 318.1251.

**Synthesis of 1,2-bis-benzyloxy-2-(2-nitro-propenyl)-benzene, 260:**

![Synthesis of 1,2-bis-benzyloxy-2-(2-nitro-propenyl)-benzene, 260](image)

To a solution of the 2,5-dibenzyloxyderivative 259 (0.3 g, 0.94 mmol, 1 equiv.) in nitroethane (5 ml), was added one drop of n-butylamine and the mixture refluxed for 1 hour. The solvent was removed under high vacuum without heating and the remaining oil was filtered through silica which was washed with dichloromethane (10 ml). Concentration in vacuo gave the desired product as a yellow oil (0.258 g, 73%)(Rf = 0.54, hexane/ethyl acetate = 3:1).

**1H-NMR** (CDCl₃, 500 MHz): δ 8.26 (1H, s, H₁'), 7.41-7.31 (10H, m, Ph x2), 6.98 (1H, dd, J₄,₃ = 9.0 Hz, J₄,₆ = 2.99 Hz, H₄), 6.91 (1H, d, J₃,₄ = 9.0 Hz, H₃), 6.88 (1H, d, J = 2.93 Hz, H₆), 5.07 (2H, s, OCH₂), 5.03 (2H, s, OCH₂), 2.27 (3H, s, Me);
Experimental

\(^{13}\)C-NMR (CDCl\(_3\), 125 MHz): \(\delta\) 152.99 (C\(_{2,3}\)), 152.17 (C\(_{2,3}\)), 148.27 (C\(_{ipso}\)), 137.20 (C\(_{ipso}\)), 136.2 (C\(_{ipso}\)), 130 (C\(_1\)), 129.12 (CH), 129.09 (CH), 129.09 (CH), 128.99 (CH), 128.39 (C\(_4\)), 127.78 (CH), 127.63 (CH), 123.3 (CH), 118.0 (C\(_4\)), 117.2 (C\(_6\)), 114.3 (C\(_3\)), 71.73 (OCH\(_2\)), 71.24 (OCH\(_2\)), 14.51 (Me); IR (CHCl\(_3)/cm\(^{-1}\)): \(\nu_{max}\) 2976, 2894, 2400 (Ar CH), 1517, 1491, 1326 (RNO\(_2\)), 1027; MS (EI): \(m/z\) 375 (M\(^+\), 50%), 318 (30%), 238 (80%), 91 (100%), 65 (71%), 39 (24%); HRMS (EI): calculated for C\(_{23}H_{21}NO_4\) 375.14710, found 375.14705.

Synthesis of 2-(2-nitro-propenyl)-benzene-1,4-diol, 258:

\[\begin{align*}
\text{CHO} & \quad \text{OH} & \quad \text{Me} \\
\text{OH} & \quad \text{CHO} & \quad \text{Me} \\
\end{align*}\]

2,5-Dihydroxybenzaldehyde (0.1 g, 0.72 mmol, 1 equiv.) and potassium carbonate (0.2 g, 1.44 mmol, 2 equiv.) in dry acetone (10 ml) were stirred at room temperature for 30 minutes. Trifluoroacetic anhydride (0.3 g, 1.44 mmol, 2 equiv.) was added and the resulting mixture stirred for 5 hours before the acetone was removed at the high vacuum. The residue was washed with dry toluene and then dissolved in nitroethane (3 ml). Triethylamine (0.072 g, 0.72 mmol, 1 equiv) and \(n\)-butyl amine (1 drop) were added and the reaction mixture was refluxed for 7 hours. After dilution with diethyl ether (10 ml), the reaction mixture was washed with water (10 ml), brine (10 ml) and dried over magnesium sulphate. After removal of the solvent, the residue was purified by column chromatography (PE/ACOEt = 3:1) to give a yellow oil (0.020 g, 14%) (R\(_f\) = 0.14).

\(^1\)H-NMR (dmso-\(d_6\), 500 MHz): \(\delta\) 9.61 (1H, s, OH), 9.02 (1H, s, OH), 8.15 (1H, s, H\(_1\)), 6.80-6.71 (3H, m, Ar-CH), 2.34 (3H, s, Me); \(^{13}\)C-NMR (dmso-\(d_6\), 125 MHz): \(\delta\) 149.78 (C-OH), 149.67 (C-OH), 146.24 (C\(_2\)), 129.66 (C\(_4\)), 119.66 (C\(_6\)), 119.35 (C\(_2\)), 116.93 (CH), 115.57 (CH), 14.31 (Me); IR (neat/cm\(^{-1}\)): \(\nu_{max}\) 3400, 3360 (OH), 3040, 2987 (Ar CH), 1520 (R-NO), 1500, 1490, 1320 (R-NO), 1210, 1150; MS (EI):
Experimental

$m/z$ 195 (M+, 80%), 149 (M-NO₂⁺, 40%), 110 (C₆H₃[OH]₂⁺, 100%), 94 (60%), 66 (30%); HRMS (FAB): calculated for C₉H₉NO₄ 195.05316, found 195.05321.

**Synthesis of 2-nitro-propenyl benzene, 263:**

A mixture of benzaldehyde (1.047 g, 9.87 mmol, 1 equiv.) and ethylene diamine (1 drop) in nitroethane (5 ml) was refluxed for 4 hours. The solution was then evaporated, diluted with dichloromethane (10 ml) and filtered through a pad of silica. Removal of the organic solvent gave a yellow solid (2 g, 86%) (Rf = 0.73, petroleum ether/diethyl ether = 1:1).

**m.p.:** 63-64°C (lit. 64°C)[⁷], **¹H-NMR** (CDCl₃, 500 MHz): δ 8.07 (1H, s, H₁), 7.44-7.40 (5H, m, Ph), 2.43 (3H, s, Me); **¹³C-NMR** (CDCl₃, 125 MHz): δ 147.72 (C₂), 133.49 (C₁), 132.38 (C₄), 129.92, 129.80, 128.87 (CH), 13.99 (Me); **IR** (KBr/cm⁻¹): νₘₐₓ 3101, 2990 (Ar CH), 1700, 1685, 1560 (NO), 1430, 1387 (NO), 1326, 1296, 1215, 1163; **MS** (EI): m/z 163 (M⁺, 40%), 146 (15%), 115 (100%), 105 (33%), 91 (37%), 77 (15%).

**Synthesis of 1,2-dihydro-1-hydroxy-4,6-dimethyl-2-oxopyridine-3-carbonitrile, 234:**[⁷]
Potassium hydroxide (14 g, 0.25 mol, 2 equiv.) in ethanol (100 ml) was added slowly with stirring to a cold solution of hydroxylamine hydrochloride (8.67 g, 0.125 mol, 1 equiv.) in ethanol (100 ml). The potassium chloride formed was then rapidly filtered off. Ethylcyanoacetate (14.1 g, 0.125 mol, 1 equiv.) was added in one portion, to the filtrate and the mixture was stirred for 5 minutes. Acetyl acetone (12.5 g, 0.125 mol, 1 equiv.) followed by piperidine (0.0002 equiv.), were added to this mixture which was refluxed for 40 minutes. After cooling and concentration under reduced pressure to a volume of 100 ml, the residue was diluted with water and acidified by glacial acetic acid (to pH 4) to give a yellow solid. The filtered product was recrystallised from aqueous methanol to give ivory coloured crystals (5.27 g, 26%).

Note: If during the acidification process, a pH = 1 was reached, a bright yellow solid was isolated that was shown to be the N-hydroxy pyridone by solid state $^{13}$C-NMR (CPMAS TOSS)(species A), and a mixture of N-hydroxy pyridone/N-oxy pyridine (species A/species B) by solution NMR.

\[ \text{m.p. (bright yellow solid): } 201-202^\circ \text{C; m.p. (ivory coloured solid): } 235-238^\circ \text{C (lit. } 235^\circ \text{C)} \]

$^1$H-NMR (CDCl$_3$, 500 MHz): $\delta$ 6.68 (1H, s, H$_5$), 2.60 (3H, s, Me$_7$), 2.55 (3H, s, Me$_8$), Species a; $\delta$ 6.08 (1H, s, H$_5$), 2.49 (3H, s, Me$_7$), 2.41 (3H, s, Me$_8$), Species b, (ratio A/B = 1.4/1);

$^{13}$C-NMR (CDCl$_3$, 125MHz): $\delta$ 162.99 (C$_6$), 168.3 or 161.0 (C$_2$), 155.27 (C$_3$), 117.04 (C$_5$), 102.74 (C$_4$), 108.08 (CN), 23.25 (Me$_8$), 17.33 (Me$_7$), Species a; $\delta$ 168.3 or 161.0 (C$_2$), 157.45 (C$_3$), 147.01 (C$_6$), 114.94 (CN), 108.53 (C$_5$), 98.76 (C$_4$), 21.29 (Me$_8$), 17.94 (Me$_7$), Species b; $^{13}$C-CPMAS TOSS (75 MHz): over both solids it confirmed the structure of Species a; IR (KBr/cm$^{-1}$) for both solids: $\nu_{\text{max}}$ 3300, 3250 (broad OH), 2343 (Ar CH), 2210 (CN), 1637 (C=O); IR
Experimental

(CHCl₃/cm⁻¹): νₘₐₓ 3300 (broad OH), 2400 (CN), 1511, 1419 (Ar CH); MS (Positive Ion Fab): m/z 165 (M+H)⁺ for both solids.

**Synthesis of potassium cyanoacetohydroxamate, 267:**¹⁵⁸

![Chemical structure diagram]

A solution of potassium hydroxide (14 g, 0.25 mol, 2 equiv.) in methanol (40 ml) was added slowly to a solution of hydroxylamine chloride (8.75 g, 0.126 mol, 1 equiv.) in methanol (75 ml) at 0°C. The mixture was stirred for 15 minutes and the potassium chloride formed was removed by filtration. Ethyl cyanoacetate (14 g, 0.126 mol, 1 equiv.) was added in one portion to the filtrate and a white crystalline solid separated on cooling in an ice bath (35%).

**m.p. (MeOH): 112°C (lit. 112°C)**¹⁵⁸; **IR (KBr/cm⁻¹):** νₘₐₓ 3125 (br, NH), 2930, 2960 (CH), 2260 (CN), 1655 (CO).
Reference names for the compounds analysed in the CDS research over known hydroperoxides:

BANGEC
BEYQUR
BOBHUV
BUWTES
BUWTIW
BUWTIW
CADGAP
CAWYII
CERCEH
CIHZEY
CUHZAG
DAMHOO
DAWCAF
DORHUN
DOXHPX
DPXCYD
DPXCYD
EABNIE
EABPAY
EACJIB
EACJIB
FENWUQ
FEXYOW
FEXYOW
FUFDIT
FUFDIT
FUJOY
FUJOY
GAKFIH
GIGKOW
HPXCAM
HPXPZH
JIMHES
KEDDOM
LINWEK
MALSUN
MALSUN
MALSUN
MALSUN
MALSUN
MALSUN
NCONPX
NOQBAW
NOQBEA
NOQBEA
NOXBZA
NUBDIX
NUNJEL
PEPDUJ
RAYMOT
RAYMOT
Appendix

ROQQOD
SEGDIR
SEKMUQ
SOYFIV
TABLUD
TABLUD
TECWON
VAMPOO
VENPUZ
VENPUZ
VICWAF
VOWJEW
VUYXES
XAHMIC
XAHMIC
XAHPOL
YAWXOJ
ZELMAE
ZELMAE
ZUHHIT
ZUHHOZ
ZUHHUF
ZUHJAN
ZUKPOK
ZUKPOK
Table on the onium effect

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<th>34&lt;sup&gt;a&lt;/sup&gt; (%)</th>
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<td>23.3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>---</td>
<td>-------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Bu₄PBr</td>
<td>28</td>
<td>65</td>
<td>23</td>
<td>V</td>
</tr>
<tr>
<td>27</td>
<td>Bu₄PBr/H₂O</td>
<td>37</td>
<td>53</td>
<td>18.5</td>
<td>V</td>
</tr>
<tr>
<td>28</td>
<td>ImidBF₄</td>
<td>53</td>
<td>58</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>29</td>
<td>ImidBF₄/H₂O</td>
<td>52</td>
<td>53</td>
<td>19</td>
<td>7.3</td>
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<tr>
<td>30</td>
<td>ImidPF₆</td>
<td>40</td>
<td>63</td>
<td>13.4</td>
<td>7</td>
</tr>
<tr>
<td>31</td>
<td>ImidPF₆/H₂O</td>
<td>32</td>
<td>80</td>
<td>17.7</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: DAST is (diethylamino)sulfur trifluoride; TAS-F is tris(dimethylamino)sulfur(trimethylsilyl)diffluoride; TBAT is tetrabutylammonium triphenyldifluorosilicate; Noyori's catalyst is CH₃(CH₂)₇NMεHSO₄; Imid is imidazolium; a) selectivity; b) products isolated by Flash Chromatography; c) conversion was calculated by GC using as the external standard, naphthalene; d) Bu₄NF was used as a solid after removing THF under reduced pressure, without heating; e) PTC (phase transfer catalyst); f) 60% tetrabutylammonium hydroxide in water; g) tetrabutylammonium hydroxide solid after freeze dryer (see Experimental Part); (Y) indicated the presence of 1,3-adamantan-1-ol but its selectivity was not determined by the use of an internal standard.
ESR over NHS (96) in fluorobenzene ($1.2 \times 10^{-3}$ M) at 74°C in excess of AIBN.

$a_N = 6.4$ G, $\delta = 2.8$ G, $g = 2.0059$
ESR over a mixture of hydroquinone (1 equiv.) (213) and nitrosobenzene (6 equiv.) (212) in fluorobenzene at 80°C in excess of AIBN.
Appendix

Crystal data and structure refinement for 223.

Table 1

<table>
<thead>
<tr>
<th>Identification code</th>
<th>str0079</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C₁₆H₆O₄</td>
</tr>
<tr>
<td>Formula weight</td>
<td>264.22</td>
</tr>
<tr>
<td>Temperature</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2₁/c</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>a = 10.188(5) Å, $\alpha = 90^\circ$, b = 3.783(2) Å, $\beta = 97.079(10)^\circ$, c = 15.097(8) Å, $\gamma = 90^\circ$</td>
</tr>
<tr>
<td>Cell volume</td>
<td>577.4(5) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Calculated density</td>
<td>1.520 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient μ</td>
<td>0.110 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>272</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>colourless, 0.50 x 0.04 x 0.03 mm³</td>
</tr>
<tr>
<td>Data collection method</td>
<td>Bruker SMART APEX diffractometer, ω rotation with narrow frames</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>2.01 to 28.26°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>h -13 to 13, k -4 to 5, l -20 to 20</td>
</tr>
<tr>
<td>Completeness to θ = 26.00°</td>
<td>99.7%</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>4567</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>1363 (Rint = 0.0558)</td>
</tr>
<tr>
<td>Reflections with F²&gt;2σ</td>
<td>809</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>semi-empirical from equivalents</td>
</tr>
<tr>
<td>Min. and max. transmission</td>
<td>0.9468 and 0.9967</td>
</tr>
<tr>
<td>Structure solution</td>
<td>direct methods</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Weighting parameters a, b</td>
<td>0.0485, 0.0000</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1363 / 0 / 92</td>
</tr>
<tr>
<td>Final R indices [F²&gt;2σ]</td>
<td>R1 = 0.0586, wR2 = 0.1063</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.1130, wR2 = 0.1227</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>0.980</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.010(5)</td>
</tr>
<tr>
<td>Largest and mean shift/su</td>
<td>0.000 and 0.000</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.184 and -0.179 e Å⁻³</td>
</tr>
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</table>
Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å²) for str0079. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^\beta$ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$U_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>0.35950(13)</td>
<td>0.1940(4)</td>
<td>-0.06743(9)</td>
<td>0.0428(5)</td>
</tr>
<tr>
<td>O(2)</td>
<td>0.15133(15)</td>
<td>0.3986(5)</td>
<td>-0.09325(11)</td>
<td>0.0601(6)</td>
</tr>
<tr>
<td>C(1)</td>
<td>0.2337(2)</td>
<td>0.2558(6)</td>
<td>-0.04235(15)</td>
<td>0.0419(6)</td>
</tr>
<tr>
<td>C(2)</td>
<td>0.2335(2)</td>
<td>0.1232(6)</td>
<td>0.04857(14)</td>
<td>0.0378(6)</td>
</tr>
<tr>
<td>C(3)</td>
<td>0.1335(2)</td>
<td>0.1221(6)</td>
<td>0.10234(16)</td>
<td>0.0463(7)</td>
</tr>
<tr>
<td>C(4)</td>
<td>0.1625(2)</td>
<td>-0.0124(6)</td>
<td>0.18680(16)</td>
<td>0.0499(7)</td>
</tr>
<tr>
<td>C(5)</td>
<td>0.2871(2)</td>
<td>-0.1432(6)</td>
<td>0.21702(16)</td>
<td>0.0477(6)</td>
</tr>
<tr>
<td>C(6)</td>
<td>0.3869(2)</td>
<td>-0.1445(6)</td>
<td>0.16311(14)</td>
<td>0.0416(6)</td>
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<tr>
<td>C(7)</td>
<td>0.3588(2)</td>
<td>-0.0085(5)</td>
<td>0.07792(14)</td>
<td>0.0357(6)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.43745(19)</td>
<td>0.0380(6)</td>
<td>0.00457(15)</td>
<td>0.0377(6)</td>
</tr>
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</table>
### Symmetry operations for equivalent atoms

<table>
<thead>
<tr>
<th>Z</th>
<th>Z-1</th>
<th>Z+1</th>
<th>Z-2</th>
<th>Z+2</th>
<th>Z-3</th>
<th>Z+3</th>
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<td>1</td>
<td>120°</td>
<td>120°</td>
<td>120°</td>
<td>120°</td>
<td>120°</td>
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<td>120°</td>
<td>120°</td>
<td>120°</td>
<td>120°</td>
<td>120°</td>
<td>120°</td>
</tr>
<tr>
<td>3</td>
<td>120°</td>
<td>120°</td>
<td>120°</td>
<td>120°</td>
<td>120°</td>
<td>120°</td>
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</tbody>
</table>

Table 3. Bond lengths (Å) and angles (°) for 30079.
Table 4. Anisotropic displacement parameters (Å²) for str0079. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^2U_{11} + \ldots + 2hka*b*U_{12}]$

<table>
<thead>
<tr>
<th></th>
<th>$U_{11}$</th>
<th>$U_{22}$</th>
<th>$U_{33}$</th>
<th>$U_{12}$</th>
<th>$U_{13}$</th>
<th>$U_{23}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>0.0359(8)</td>
<td>0.0491(10)</td>
<td>0.0424(9)</td>
<td>0.0048(8)</td>
<td>0.0007(7)</td>
<td>0.0083(7)</td>
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<td>O(2)</td>
<td>0.0445(10)</td>
<td>0.0815(14)</td>
<td>0.0525(11)</td>
<td>0.0099(10)</td>
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<td>0.0193(9)</td>
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<tr>
<td>C(1)</td>
<td>0.0335(12)</td>
<td>0.0420(15)</td>
<td>0.0491(15)</td>
<td>-0.0021(12)</td>
<td>0.0014(11)</td>
<td>0.0046(11)</td>
</tr>
<tr>
<td>C(2)</td>
<td>0.0391(13)</td>
<td>0.0338(13)</td>
<td>0.0395(13)</td>
<td>-0.0038(11)</td>
<td>0.0012(10)</td>
<td>0.0009(10)</td>
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<tr>
<td>C(3)</td>
<td>0.0377(13)</td>
<td>0.0506(16)</td>
<td>0.0509(15)</td>
<td>-0.0032(12)</td>
<td>0.0067(11)</td>
<td>0.0058(11)</td>
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<tr>
<td>C(4)</td>
<td>0.0462(14)</td>
<td>0.0543(16)</td>
<td>0.0522(16)</td>
<td>-0.0054(13)</td>
<td>0.0175(12)</td>
<td>-0.0058(12)</td>
</tr>
<tr>
<td>C(5)</td>
<td>0.0546(15)</td>
<td>0.0477(15)</td>
<td>0.0410(14)</td>
<td>0.0001(12)</td>
<td>0.0069(12)</td>
<td>-0.0027(12)</td>
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<tr>
<td>C(6)</td>
<td>0.0408(13)</td>
<td>0.0389(14)</td>
<td>0.0440(14)</td>
<td>-0.0027(11)</td>
<td>0.0011(11)</td>
<td>0.0034(10)</td>
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<tr>
<td>C(7)</td>
<td>0.0352(12)</td>
<td>0.0327(13)</td>
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<td>0.0016(10)</td>
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</tr>
<tr>
<td>C(8)</td>
<td>0.0332(11)</td>
<td>0.0346(13)</td>
<td>0.0435(13)</td>
<td>-0.0011(10)</td>
<td>-0.0025(10)</td>
<td>0.0025(10)</td>
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</tbody>
</table>

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Table 5. Hydrogen coordinates and isotropic displacement parameters (Å²) for str0079.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(3A)</td>
<td>0.0497</td>
<td>0.2090</td>
<td>0.0821</td>
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</tr>
<tr>
<td>H(4A)</td>
<td>0.0971</td>
<td>-0.0160</td>
<td>0.2247</td>
<td>0.060</td>
</tr>
<tr>
<td>H(5A)</td>
<td>0.3037</td>
<td>-0.2318</td>
<td>0.2748</td>
<td>0.057</td>
</tr>
<tr>
<td>H(6A)</td>
<td>0.4703</td>
<td>-0.2338</td>
<td>0.1834</td>
<td>0.050</td>
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</table>
### Table 6. Torsion angles [°] for str0079.

<table>
<thead>
<tr>
<th>Bond/Atom 1</th>
<th>Bond/Atom 2</th>
<th>Bond/Atom 3</th>
<th>Bond/Atom 4</th>
<th>Value (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(8)–O(1)–C(1)–O(2)</td>
<td>177.8(2)</td>
<td>C(8)–O(1)–C(1)–C(2)</td>
<td>-1.5(2)</td>
<td></td>
</tr>
<tr>
<td>O(2)–C(1)–C(2)–C(3)</td>
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<td>O(1)–C(1)–C(2)–C(3)</td>
<td>-179.8(2)</td>
<td></td>
</tr>
<tr>
<td>O(2)–C(1)–C(2)–C(7)</td>
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<td>O(1)–C(1)–C(2)–C(7)</td>
<td>1.4(2)</td>
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</tr>
<tr>
<td>C(7)–C(2)–C(3)–C(4)</td>
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<td>C(1)–C(2)–C(3)–C(4)</td>
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<td></td>
</tr>
<tr>
<td>C(2)–C(3)–C(4)–C(5)</td>
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<td>C(3)–C(4)–C(5)–C(6)</td>
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<td>C(5)–C(6)–C(7)–C(2)</td>
<td>-0.2(3)</td>
<td></td>
</tr>
<tr>
<td>C(5)–C(6)–C(7)–C(8)</td>
<td>178.9(2)</td>
<td>C(3)–C(2)–C(7)–C(6)</td>
<td>-0.3(3)</td>
<td></td>
</tr>
<tr>
<td>C(1)–C(2)–C(7)–C(6)</td>
<td>178.64(19)</td>
<td>C(3)–C(2)–C(7)–C(8)</td>
<td>-179.6(2)</td>
<td></td>
</tr>
<tr>
<td>C(1)–C(2)–C(7)–C(8)</td>
<td>-0.7(2)</td>
<td>C(1)–O(1)–C(8)–C(8A)</td>
<td>-178.9(3)</td>
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<tr>
<td>C(1)–O(1)–C(8)–C(7)</td>
<td>1.1(2)</td>
<td>C(6)–C(7)–C(8)–C(8A)</td>
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</tr>
<tr>
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<td>179.7(3)</td>
<td>C(6)–C(7)–C(8)–O(1)</td>
<td>-179.4(2)</td>
<td></td>
</tr>
<tr>
<td>C(2)–C(7)–C(8)–O(1)</td>
<td>-0.2(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Symmetry operations for equivalent atoms**

A  
-x+1, -y, -z
View down 'a' axis
Appendix

View down ‘b’ axis
View down 'c' axis
ESR of NHPI (6) at 78.3°C in fluorobenzene (1.22 x 10^{-3}) in excess of AIBN.

\[ a_N = 4.3 \, \text{G}, \delta = 2.5 \, \text{G}, \, g = 2.0068 \]
ESR at 82.4°C in fluorobenzene in excess of AIBN, over the mixture derived from the oxidation of indoline (1 equiv.) with dimethyl dioxirane (4.5 equiv.).
Appendix

ESR over the mixture derived from the oxidation of indoline (1 equiv.) with dimethyl dioxirane (4.5 equiv.) left opened to the air for some days, in fluorobenzene at 80°C in excess of AIBN.
$^{13}\text{C}$ and $^1\text{H}$, over a fraction obtained by column chromatography over the reaction of indoline with DMD.
References


References

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[85]: Schenck, G. O; Neumuller, O. A. Annalen 1958, 618, 194.
References


References

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[140]: Gundel, W.; Pummer, R. Annalen 1937, 529, 11.