On the Metal-Free Dihydroxylation of Alkenes.

Kevin M. Jones

A Thesis Submitted for the Degree of Doctor of Philosophy at

Cardiff University

2010
Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted for candidature for any degree.

Signed ........................................ (Kevin M. Jones)
Date........................................ 07/07/10

STATEMENT 1

This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

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"Our scientific theories do not, as a rule, spring full-armed from the brow of their creator; they are subject to slow and gradual growth...."

– G. N. Lewis.

"The great tragedy of science – the slaying of a beautiful hypothesis with an ugly fact."

– T. Huxley.
Abstract

This thesis describes the development of a metal-free dihydroxylation procedure based on the reactivity of malonoyl peroxide derivatives.

Chapter 1 provides an overview of the current methods available for the preparation of syn-1,2-diols. Emphasis has been placed on describing the advantages and limitations of each system in order to highlight areas which require further improvement.

Chapter 2 describes previous work on the reaction of phthaloyl peroxide (PPO) with alkenes and details a series of exploratory investigations, performed in an effort to develop a new catalytic dihydroxylation procedure.

Chapter 3 describes the development of a novel dihydroxylation procedure based on the reactivity of cyclobutane malonoyl peroxide. A simple procedure for the formation of malonoyl peroxides is described. Conditions were optimised for the reaction of 4-methylstyrene and cyclobutane malonoyl peroxide with regards to solvent, temperature, peroxide equivalents and time. An optimised set of conditions provided a two-step procedure which allowed 1-p-tolylethane-1,2-diol to be dihydroxylated in 84% isolated yield. The reaction mechanism was probed in a series of isotopic labelling studies and was proposed to proceed via a dioxolane intermediate.

Chapter 4 examines the substrate scope of the cyclobutane malonoyl peroxide mediated reaction. Cyclobutane malonoyl peroxide emerged as an effective reagent for the dihydroxylation of a range of substituted styrene and stilbene derivatives. The diastereoselectivity of the reaction was examined with a range of 1,2-disubstituted alkenes. The effect of altering the peroxide structure was briefly studied and revealed cyclopropane malonoyl peroxide was a more effective dihydroxylating reagent when compared to cyclobutane malonoyl peroxide. These results also indicated a number of intricacies of the reaction mechanism are still to be discovered. A qualitative examination of the factors which affect the reactivity of cyclic diacyl peroxides is also discussed.
Acknowledgements

Firstly, I would like to thank my supervisor Dr Nick Tomkinson for his support throughout the Ph.D. Looking back, I feel I have matured a great deal throughout my time at Cardiff and much of this has been due to his encouragement and guidance.

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**Abbreviations**

Several abbreviations have been used throughout this thesis that may not be familiar to the reader. These abbreviations are listed below:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Asymmetric dihydroxylation</td>
</tr>
<tr>
<td>App</td>
<td>Apparent</td>
</tr>
<tr>
<td>APCI</td>
<td>Atmospheric pressure chemical ionisation</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aromatic</td>
</tr>
<tr>
<td>BHT</td>
<td>Butylated hydroxyl toluene</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>Boiling point</td>
</tr>
<tr>
<td>BPO</td>
<td>Benzoyl peroxide</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Column chromatography</td>
<td>Flash column chromatography</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical ionisation</td>
</tr>
<tr>
<td>d</td>
<td>Day(s)</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dd</td>
<td>doubled doublet</td>
</tr>
<tr>
<td>Da</td>
<td>Dalton(s)</td>
</tr>
<tr>
<td>DHQ</td>
<td>Dihydroquinine</td>
</tr>
<tr>
<td>DHQD</td>
<td>Dihydroquinidine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>DSC</td>
<td>Differential scanning calorimetry</td>
</tr>
<tr>
<td>d.r.</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>e.e.</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron ionisation</td>
</tr>
<tr>
<td>EPSRC</td>
<td>Engineering and Physical Sciences Research Council</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalent(s)</td>
</tr>
<tr>
<td>ES</td>
<td>Electrospray</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectroscopy</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infra-red</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>k</td>
<td>Kilo</td>
</tr>
<tr>
<td>L</td>
<td>Ligand</td>
</tr>
<tr>
<td>lit.</td>
<td>Literature</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
</tr>
<tr>
<td>MALDI</td>
<td>Matrix assisted laser desorption ionisation</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------</td>
</tr>
<tr>
<td>$z$</td>
<td>Charge</td>
</tr>
<tr>
<td>Å</td>
<td>Angstroms</td>
</tr>
<tr>
<td>$\mu$mol</td>
<td>Micromole(s)</td>
</tr>
</tbody>
</table>
Chapter 1: Introduction
1.1 Introduction

1.1.1 Metal-free transformations

Over the last decade, metal-free transformations have been driven to the forefront of chemical research. Transition-metals enjoy widespread use in organic synthesis; however, the cost, toxicity and environmental impact associated with these reagents has become increasingly prohibitive. A vast number of metal-free and organocatalytic reactions have been recently developed which match the standards of activity and selectivity set by their metal-based counterparts. In general, metal-free transformations offer a number of notable advantages: Reagents are often (1) inexpensive and simple to prepare (2) tolerant of air and moisture (3) non-toxic. It is for these reasons development of metal-free methods continues to attract research interest.

1.1.2 Oxidation

Oxidation is central to organic chemistry. The chemical industry relies on the selective oxidation of hydrocarbon feedstocks in the production of commodity materials which find application in all areas of life. From a synthetic standpoint, oxidation is used extensively in the formation of fine chemicals and natural products. Owing to its importance, a staggering number of reagents and catalytic systems have been developed to promote oxidation and this continues to be an area of research interest.
1.1.3 Alkene oxidation

Alkenes provide a cheap and diverse set of starting materials in organic synthesis. The oxidation of alkenes is unquestionably one of the most important classes of transformation in synthetic chemistry and covers a wide range of functional group conversions as illustrated by Figure 1.1.

1.1.4 Alkene dihydroxylation

Of the reactions shown above, alkene dihydroxylation is particularly important. Ethylene glycol and propylene glycol are manufactured on a million-ton scale per annum due to their importance as polyester monomers and anti-freeze agents among other uses. From a synthetic standpoint, 1,2-diols are valuable intermediates in the preparation of pharmaceuticals, agrochemicals and other fine chemicals. Additionally, the 1,2-diol sub unit is present in a number of natural products with varied biological activity.
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The remainder of this chapter discusses the current methods available for the preparation of syn-1,2-diols. Transition-metal and transition-metal free transformations are discussed separately. The limitations of each method are highlighted in an attempt to identify any common areas which require improvement.

1.2 Metal based syn-dihydroxylation

1.2.1 Osmium

Amongst the reagents available for alkene dihydroxylation, none have achieved more success than osmium tetroxide. For over eighty years, the use of OsO₄ has been developed and refined and currently forms the basis of one of the most powerful transformations in synthetic chemistry.¹⁰

1.2.1.1 Discovery and catalytic development

The dihydroxylation of unsaturated compounds with OsO₄ has long been known.¹¹ The original reaction used stoichiometric amounts of OsO₄ which is expensive and highly toxic. Subsequent investigations by Hofmann showed the reaction could be made catalytic using stoichiometric oxidants such as sodium chlorate to regenerate OsO₄.¹² A wide range of oxidants have since been established including tert-butyl hydroperoxide¹³ and 4-methylmorpholine N-oxide (NMO).¹⁴ A mixture of potassium ferricyanide and K₂CO₃, reported by Yamamoto and co-workers, provides one of the most powerful re-oxidation systems to date.¹⁵ The introduction of stoichiometric oxidants allowed catalytic amounts of OsO₄ to be used which greatly increased the reaction’s synthetic utility.
1.2.1.2 Development of an asymmetric variant

Pioneering work by Creigee on the stoichiometric reaction of 13 with alkenes showed the addition of pyridine resulted in a significant increase in reaction rate. On the basis of this result, Sharpless and co-workers aimed to develop an asymmetric variant by replacing pyridine with a chiral amine. Extensive screening revealed that two cinchona alkaloids, dihydroquinine (DHQ) 11 and dihydroquinidine (DHQD) 10 (Fig. 1.2), allowed the formation of diols with good enantiomeric excess.

Optimisation of the ligand structure resulted in the discovery of the phalazine ligands, (DHQD)$_2$-PHAL and (DHQ)$_2$-PHAL, which employ two cinchona alkaloid units connected via a phthalazine spacer (Fig. 1.3). A number of alternative ligands have also been developed, but (DHQD)$_2$-PHAL and (DHQ)$_2$-PHAL remain the most widely used.
1.2.1.3 Catalytic asymmetric dihydroxylation

The asymmetric dihydroxylation was initially performed under stoichiometric conditions. Further investigations by Sharpless and Markó revealed the process became catalytic when NMO was employed as a co-oxidant establishing the cycle shown in Figure 1.4.\(^\text{19}\) Reaction of osmium tetroxide 13 with alkene 14 gives osmate ester 15. Oxidation of 15 to the Os(VIII) intermediate 16 and subsequent hydrolysis gives the corresponding diol product and releases 13 which can undergo further reaction.

![Chemical reaction diagram]

Initially, the enantiomeric excesses obtained from the catalytic reaction were low.\(^\text{20}\) These poor results were attributed to a secondary cycle in which osmate ester 16 reacts with a second molecule of alkene 14 prior to hydrolysis (Step 4, Fig. 1.4). This secondary cycle does not involve the chiral ligand and serves to lower the enantiopurity of the product.

The poor enantiomeric excesses were overcome through the use of potassium ferricyanide and potassium carbonate in a mixture of tert-butanol and water.\(^\text{21}\) Use of a biphasic mixture means the stoichiometric oxidant is found exclusively within the aqueous layer. Before osmate ester(VI) 15 can react with a second molecule of alkene it must be re-oxidised to
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Os(VIII) which cannot occur under these conditions. Re-oxidation can only occur after hydrolysis of osmate ester(VI) 15 in which osmium can move into the aqueous layer (Fig. 1.5). This biphasic mixture completely eliminates the secondary cycle allowing high enantiomeric excesses to be obtained.

1.2.1.4 Further developments

The addition of methane sulfonamide to the reaction mixture was shown to accelerate the hydrolysis of the osmate ester 15. This finding offered two key advantages. Firstly, the reaction times were greatly decreased and secondly, the reaction could be performed at 0 °C which often enhanced the enantioselectivity.

Dipotassium osmate dihydrate was found to be a suitable, non volatile replacement for 13. Conveniently, all of the reagents required for alkene dihydroxylation are solid and are commercially available as pre-mixed powders AD-mix-α and AD-mix-β.
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1.2.1.5 Overall transformation

Contributions from numerous research groups culminate in the overall Sharpless asymmetric dihydroxylation (SAD). Treatment of trans-stilbene 22 with AD-mix-β in a mixture of tert-butanol and water gives R,R-hydrobenzoin 23 in remarkable yield and enantiomeric excess (Scheme 1.1). Unlike many other transition-metal catalysed transformations, the reaction is tolerant of air and moisture and makes the reaction incredibly simple to perform.

\[
\begin{align*}
\text{MeSO}_2\text{NH}_2 + \text{OH} & \rightarrow \text{MeSO}_2\text{NH}_2 \text{Ph} \text{OH} \\
\text{AD-mix-β} & \rightarrow 0 \text{°C, 18 h} \rightarrow 99.8\% \text{ e.e.}
\end{align*}
\]

Scheme 1.1

1.2.1.6 Mechanism and mnemonic device

The mechanism of the osmium catalysed dihydroxylation has been studied by a number of groups and has revealed two potential mechanisms. Boseken originally proposed a concerted [3+2] cycloaddition (Pathway A). Sharpless et al favoured a [2+2] cycloaddition between the alkene and the Os=O double bond followed by a rearrangement of the osmaoxetane intermediate 26 (Pathway B) to give 27 (Fig. 1.6).
Theoretical and experimental studies from several research groups show a strong preference for a [3+2] cycloaddition.\textsuperscript{26}

A detailed structure-activity study revealed dimeric ligands (DHQ)\textsubscript{2}-PHAL and (DHQD)\textsubscript{2}-PHAL form an "enzyme-like" binding pocket which accounts for the high levels of enantioselectivity. Sharpless and co-workers proposed an empirical mnemonic device (Fig. 1.7) which predicts which ligand will give the desired enantiomer in lieu of a detailed understanding of the "active-site".\textsuperscript{27}

The mnemonic device shows two areas of steric bulk in the north-west and south-east corners. Additionally, an attractive interaction is found in the south-west quadrant which is ideally suited to be occupied by an aromatic ring or sterically demanding group. Orientating the alkene substrate with the largest group in the south-west quadrant shows DHQ and DHQD derived ligands will dihydroxylate the α- and β-faces of the alkene respectively. The original mnemonic device was developed on the basis of an initial [2+2] cycloaddition. Recent work, which accounts for the preferred concerted [3+2] mechanism, suggests the north-west quadrant is in fact open and an additional attractive region is found in the north-east quadrant.\textsuperscript{28}
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1.2.1.7 Limitations

Despite its widespread popularity, a number of limitations are commonly associated with the SAD and deserve further comment.

1) Cis-alkenes remain a problematic substrate for the SAD. Yields are generally good, but, enantiomeric excesses for this class of alkene are typically low. Indoline derived ligands have met with some success; however, enantiomeric excesses are typically between 20–80%.

2) Osmium tetroxide is an expensive and highly toxic reagent.

3) The use of potassium ferricyanide as an oxidant generates a significant amount of inorganic waste. Beller and co-workers report that dihydroxylation of α-methyl styrene using the potassium ferricyanide/K$_2$CO$_3$ system generates 8.1 kg of waste per kg of diol product.

1.2.1.8 Current research interest in SAD

The toxicity of osmium and high levels of inorganic waste has hindered the application of the SAD on an industrial scale. In light of these limitations, much of the current research has focussed on developing “greener” dihydroxylation protocols.

Microencapsulation, the anchoring of reagents to a polymer support, has provided an effective method for recycling osmium tetroxide and chiral ligands (DHQD)$_2$-PHAL and (DHQ)$_2$-PHAL. Additionally, this method addresses the issue of toxicity, as osmium tetroxide cannot escape the polymer matrix. Following initial development by Kobayashi, a range of polymer-supports are now available. Despite the number of encapsulated systems which have been developed, a common criticism is limited re-usability as catalytic activity often degrades rapidly after a number of uses. Microencapsulation continues to attract research interest and is the subject of a number of recent reviews.
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From a green chemistry perspective, hydrogen peroxide and air represent the most economical and environmentally benign oxidants for the re-oxidation of osmium tetroxide 13. Although attempts to use oxygen and hydrogen peroxide as re-oxidants have been reported previously, over-oxidation and side-product formation are common disadvantages. 22

Bäckvall and co-workers have shown excellent results can be achieved using hydrogen peroxide/NMM re-oxidation system; however, a significant amount of waste is still formed. 33 Recently, Beller and co-workers reported the use of air as a stoichiometric oxidant with careful control of reaction pH levels, although over-oxidation of certain aromatic alkenes remains problematic. 7

1.2.2 Palladium

A series of recent reports describe the use of cationic palladium(II) catalysts for the dioxygenation of alkenes. An initial report by Song et al. showed the reaction of trans-stilbene 22 with [Pd(dppp)(H_2O)2]OTf_2 and PhI(OAc)_2 36 in wet acetic acid gave 28 in 80% yield with a syn:anti ratio of 6:1 (Scheme 1.2). 34 The reaction is general for a range of alkenes and syn:anti ratios up to 99:1 have been achieved. Treatment of 28 with potassium carbonate in methanol gave the corresponding diol in quantitative yield.

![Scheme 1.2](image-url)
A subsequent report by Jiang and co-workers showed a similar transformation can be achieved with palladium acetate and potassium iodide using oxygen as the sole oxidant.\textsuperscript{35} This method possesses a number of advantages over those reported by Song. Firstly, the reaction avoids the use of stoichiometric oxidants such as PhI(OAc)\textsubscript{2} \textsuperscript{36}. Secondly, higher syn:anti ratios are observed over the range of substrates examined. The result for trans-stilbene 22 is shown in Scheme 1.3 for comparison.

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {Ph\textsubscript{1}Ph\textsubscript{2}};
  \node at (2,0) {Ph\textsubscript{1}Ph\textsubscript{3}};  
  \draw[->] (0,0) -- (2,0);
  \node at (2,1) {Ph\textsubscript{1}Ph\textsubscript{2}};
  \node at (2,2) {Ph\textsubscript{1}Ph\textsubscript{3}};  
  \draw[->] (2,0) -- (2,1);
  \draw[->] (2,1) -- (2,2);
  \node at (2,2.5) {	extbf{Pd(OAc)}\textsubscript{2} (2 mol\%)};
  \node at (2,3) {Kl (20 mol\%)};
  \node at (2,3.5) {O\textsubscript{2}};
  \node at (2,4) {AcOH};
  \node at (2,4.5) {100 °C, 24 h};
  \node at (2,5) {77\%};
\end{tikzpicture}
\end{center}

Scheme 1.3

Recently, Shi and co-workers reported the use of bis-N-heterocyclic carbene palladium(II) complexes 31 capable of dioxygenating alkenes in high yields and selectivity (Scheme 1.4).\textsuperscript{36}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {Ph\textsubscript{1}Ph\textsubscript{2}};
  \node at (2,0) {Ph\textsubscript{1}Ph\textsubscript{3}};  
  \draw[->] (0,0) -- (2,0);
  \node at (2,1) {Ph\textsubscript{1}Ph\textsubscript{2}};
  \node at (2,2) {Ph\textsubscript{1}Ph\textsubscript{3}};  
  \draw[->] (2,0) -- (2,1);
  \draw[->] (2,1) -- (2,2);
  \node at (2,2.5) {1. Catalyst 31 (4 mol\%) PhI(OAc)\textsubscript{2} (1.1 eq.) H\textsubscript{2}O (3 eq.), AcOH};
  \node at (2,3) {2. AcO\textsubscript{2}, r.t.};
  \node at (2,3.5) {79\%};
  \node at (2,4) {Ph\textsubscript{1}Ph\textsubscript{2}};
  \node at (2,5) {Ph\textsubscript{1}Ph\textsubscript{3}};  
  \draw[->] (2,2) -- (2,3);
  \draw[->] (2,3) -- (2,4);
  \draw[->] (2,4) -- (2,5);
  \node at (2,5.5) {	extbf{30}};
  \node at (2,6) {\text{sym:anti}};
  \node at (2,6.5) {8 : 1};
\end{tikzpicture}
\end{center}

Scheme 1.4
On the basis of a series of $^{18}$O labeling experiments, Song and Shi proposed similar mechanisms based on a Pd(II)/Pd(IV) catalytic cycle (Fig. 1.8). Cationic palladium species 34 undergoes trans-acetoxypalladation to give intermediate 35. Oxidation of 35 using PhI(OAc)$_2$ 36 gives Pd(IV) intermediate 38 which can degrade to acetoxonium ion 39 and regenerate the active catalyst. Hydrolysis of 39 gives 40 as the observed product.

The use of palladium as a catalyst for the dioxygenation of alkenes is particularly attractive due to its low cost and toxicity with respect to osmium reagents. A wide range of alkenes were dioxygenated under mild conditions including aliphatic and electron deficient substrates.

Two main limitations can be attributed to each of the reactions discussed above (1) the reactions do not give the dihydroxylated product directly and hydrolysis of the acetate group is required to liberate the diol product. (2) At present, no asymmetric variant of the method has been reported.
Chapter 1 — Introduction

1.2.3 Ruthenium

Ruthenium tetroxide is often associated with alkene cleavage\(^\text{37}\) and as a result has achieved limited success as a dihydroxylation agent. Recent work by Shing et al described the dihydroxylation of a series of alkenes using ruthenium chloride and sodium periodate which forms ruthenium tetroxide \textit{in situ} (Scheme 1.5).\(^\text{38,39}\)

![Scheme 1.5](image)

The procedure above was adopted by Couturier et al for the synthesis of 3,4-isopropylidene dioxypyrrrolidine \(44\). Reaction of \(N\)-benzylmaleimide \(42\) with ruthenium chloride and sodium periodate was performed on a 50 kg scale and gave \(43\) in 74% yield (Scheme 1.6).\(^\text{40}\) Notably, the authors described their attempts at employing the SAD which gave \(43\) in 50% yield and proved difficult to perform on large scale due to purification and toxicity issues.

![Scheme 1.6](image)

Although showing some promising results, high catalytic loading of 7 mol% and low yields due to the formation of fragmentation products were common problems. Plietker et al attributed the formation of fission products to pericyclic fragmentation of \(46\) and \(48\) as shown in the catalytic cycle below (Fig. 1.9).\(^\text{41}\) On the basis of this model it was proposed that increasing the rate of hydrolysis of \(48\) would increase the selectivity for dihydroxylation.
The addition of sulfuric acid was found to dramatically increase the rate of hydrolysis of 48 and led to higher selectivity for the dihydroxylation. The increased rate of hydrolysis allowed the catalyst loading to be lowered to 0.5 mol%. Using this modified procedure a range of alkenes including aliphatic alkenes and α,β-unsaturated carbonyls were dihydroxylated in high yield.

Side-product formation remained problematic and the low pH led to problems with a number of acid labile groups such as silyl ethers. A more recent report from the same group showed employing cerium(III) chloride as a substitute for sulfuric acid resulted in a further increase in rate of hydrolysis and allowed the catalyst loading to be lowered to 0.25 mol%. Furthermore, the mild conditions allowed alkenes containing acid labile groups to be dihydroxylated in high yield. The power of this transformation was demonstrated by the dihydroxylation of electron poor, tetra-substituted alkene 50 (Scheme 1.7).
Chapter 1 – Introduction

At present, all attempts to design chiral ligands for ruthenium tetroxide have met with failure. Use of traditional chiral ligands based around amines and phosphines are not compatible with ruthenium tetroxide, owing to its strong oxidising nature. Inspired by the early work of Oppolzer, Plietker et al recently reported the diastereoselective dihydroxylation of a range of α,β-unsaturated carbonyls using camphor derived chiral auxiliaries 52 (Scheme 1.8)\textsuperscript{43}

\[
\begin{align*}
\text{Ph-} & \quad \text{RuCl}_3 (1 \text{ mol\%}) \quad \text{CeCl}_3 \cdot 7\text{H}_2\text{O} (20 \text{ mol\%}) \\ & \quad \text{NaO}_{2} (1.5 \text{ eq.}) \quad \text{CH}_2\text{CNH}_2\text{O} (6/1) \\ & \quad 0^\circ\text{C} \\
\end{align*}
\]

90%

\[
\begin{align*}
\text{Scheme 1.8}
\end{align*}
\]

Broad substrate scope, short reaction times and low catalytic loading makes ruthenium tetroxide an attractive dihydroxylating reagent. A major limitation associated with this transformation is the incompatibility with common chiral ligands which may prohibit the development of a catalytic, asymmetric variant.

16
1.2.4 Iron

Over the last decade, Que and co-workers have developed a series of bio-inspired iron catalysts capable of syn-dihydroxylation using hydrogen peroxide as the sole oxidant. Two typical catalysts are shown in Figure 1.10. A common feature of these catalysts is the presence of cis-labile sites which are essential for the coordination and activation of hydrogen peroxide.44

![Fig. 1.10](image1)

Oxidation of cyclooctene with hydrogen peroxide and iron catalysts 55 and 56 have been found to give a mixture of epoxide and diol. Mechanistic studies have suggested that both products are formed via a common HO-FeV=O intermediate.45 Introduction of α-methyl pyridine ligands to the iron centre has been found to increase the level of selectivity with respect to alkene dihydroxylation. These ligands are believed to favour low spin iron complexes; however, how this leads to increased selectivity towards dihydroxylated products is currently not understood. A recent report by Que et al. has shown the combination of an iron centre and chiral ligand 59 allows a range of aliphatic substrates to be dihydroxylated with high levels of asymmetric induction (Scheme 1.9).46

![Scheme 1.9](image2)

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Chapter 1 – Introduction

The iron catalysts described above are attractive dihydroxylating agents and represent one of the only metal-based transformations capable of providing enantiomeric excesses comparable to those achieved with the Sharpless AD. The formation of a mixture of epoxidised and dihydroxylated product limits the reactions practical application but shows excellent potential for further development.

1.2.5 Manganese

Feringa and co-workers have shown manganese complexes such as $[\text{Mn}^{IV}O_2(\text{tmtacn})_2]^{2+}$ (tmtacn = $N,N',N''$-trimethyl-1,4,7-triazacyclononane) can be used in conjunction with carboxylic acids as effective catalysts for the epoxidation and syn-dihydroxylation of alkenes. The addition of carboxylic acids is proposed to form carboxylate bridged dinuclear manganese complexes in situ. Variation of the carboxylic acid can be used to alter the selectivity towards epoxidation or dihydroxylation. More recently, the same group has developed an asymmetric variant of the transformation using $N$-protected amino acids as bridging ligands.

The use of $\text{H}_2\text{O}_2$ as the terminal oxidant and tunable reactivity represent potential advantages of this system however at this stage only modest levels of asymmetric induction have been achieved over a limited range of substrates.
1.3 Metal-free syn-dihydroxylation

1.3.1 Prevost-Woodward reaction

The Prevost reaction is a well established method for the formation of *anti*-1,2-diols. Woodward’s modification allows the selectivity of the reaction to be overturned for the preparation of *syn*-1,2-diols. The synthetic utility of these reactions is limited as a result of the stoichiometric use of expensive silver salts and formation of high levels of inorganic waste. A recent report by Sudalai and co-workers describes a catalytic approach to the Prevost-Woodward reaction.49 Reaction of styrene 60 with 30 mol% of sodium periodate and 20 mol% lithium bromide 65 in acetic acid gave a mixture of mono- and di-acetates 61, 62 and 63. Basic hydrolysis using potassium carbonate gave 1-phenyl 1,2-ethane diol 64 in 87% isolated yield (Scheme 1.10).

![Scheme 1.10](image-url)
A catalytic cycle which accounts for the formation of 61 and 62 is shown in Figure 1.11. Oxidation of lithium bromide 65 produces bromine 66 which reacts with alkene 1 to form bromonium ion 67. Ring opening of 67 by acetic acid gives 68. Neighbouring group participation displaces the bromine to give acetoxonium ion 69. Hydrolysis of 69 gives the overall syn-dioxygenated products 70 and 71.

Although the reaction possesses positive attributes including wide substrate scope including aliphatic alkenes and α,β-unsaturated carbonyls, the use of bromine as the oxidizing agent prohibits the development of an asymmetric variant. Additionally, the reaction does not give the diol product directly and requires hydrolysis to liberate the diol product.
1.3.2 Hypervalent iodine

Hypervalent iodine compounds are commonly used in synthetic chemistry as inexpensive and easy to handle alternatives to common transition-metal reagents. Balci and co-workers have recently reported the use of phenyliodine(III) bis(trifluoroacetate) as an effective dihydroxylating agent. Treatment of trans-stilbene 22 gave (±)-hydrobenzoin 41 via bis(trifluoroacetate) intermediate 72 (Scheme 1.11).

The product was formed with good selectivity and high yields for the syn-dioxygenated product. One disadvantage of this method is that an extended reaction time of 11 days is required for reaction completion. It should be noted that many of the reactions are typically complete within 12–18 h.

1.3.3 Selenium catalysed dihydroxylation

A dihydroxylation procedure based on organoselenium chemistry has been reported by Santi. Reaction of diphenyl diselenide 73 and hydrogen peroxide forms perseleninic acid 75. Reaction with alkene 76 gives the corresponding epoxide 77. The reaction can proceed through two pathways. One possibility involves the opening of epoxide 77 with water in a $S_{N}2$ reaction to give anti-diol 79. Alternatively, epoxide opening forms carbocation 78 which can react with water to give either the syn- or anti-dihydroxylated product. Many of the cases reported showed a preference for the formation of the syn- product. This preference was attributed to a hydrogen bond between the incoming water molecule and the
hydroxyl group; however, this was not found to be general over the course of all the substrates examined (Fig. 1.12).

Interestingly, an exploratory investigation with sulfur-containing chiral diselenide 82 was shown to dihydroxylate 1-phenyl cyclohexene 81 with good e.e. for syn-dihydroxylated product 83 (Scheme 1.12).

A major limitation of the reaction is the poor selectivity for either syn- or anti-diols which appears to be dependent on both the steric and electronic nature of the alkene substrate. This lack of selectivity lowers the utility of the reaction dramatically.
1.4 Conclusion

It is clear from the number of available methods that the formation of vicinal diols is a valuable synthetic transformation. Currently, the SAD remains the quintessential method for alkene dihydroxylation. The reaction is practically simple and provides a method for the formation of diols in high yield and enantiomeric excess.

Limitations of the SAD still inspire the development of alternative dihydroxylation procedures. The transition-metal catalysed transformations described above show a great deal of potential and may complement or ultimately surpass the SAD.

Transition-metal catalysts have come under scrutiny in recent years which has led to a surge of interest in metal-free dihydroxylation procedures. Currently, these methods are significantly less developed than their metal-based counterparts. In spite of this, addressing the issues of cost, toxicity and ease of use continue to inspire research in this area.
Chapter 2: Reactivity of Phthaloyl Peroxide
2.1 Introduction

Chapter 1 discussed the current methods available for the preparation of syn-1,2-diols. Currently, the most successful systems are based on transition-metal catalysts. Metal-free transformations are less established than their metal-based counterparts but growing pressure to develop safer and cleaner transformations makes the development of a metal-free dihydroxylation procedure an attractive target.

2.2 Sharpless asymmetric dihydroxylation

The SAD is the most commonly used method for the preparation of syn-1,2-diols and is the benchmark to which all other dihydroxylation procedures are compared. The reaction boasts broad substrate scope, high yields and high levels of asymmetric induction. Additionally, the reaction is tolerant of air and moisture making the transformation robust and simple to perform. Any novel dihydroxylation procedure must look to compete with the SAD in terms of its generality and practical simplicity.

Limitations with regard to toxicity of osmium tetroxide, waste levels and problematic substrates are commonly encountered with the SAD and provide further incentive for the development of alternative metal-free dihydroxylation procedures.
2.3 Project overview

The work within this research project aimed to develop a metal-free dihydroxylation procedure which addressed the limitations associated with the SAD. Throughout reaction development, much emphasis was placed on developing a practically simple transformation. To this end, the investigation was governed by three guiding principles:

- Reactions should proceed at room temperature
- Reactions should proceed in the presence of air and moisture
- Reagents should be accessed in three synthetic steps or fewer

2.4 Peroxide reagents in alkene dihydroxylation

Alkene epoxidation by peroxy acids, such as \( m \text{CPBA} \), and subsequent ring opening provides one of the most commonly used procedures for the preparation of \( \text{anti-}1,2\)-diols.\(^{53}\) In contrast, examples of peroxide reagents capable of \( \text{syn-} \)dihydroxylation are rare. Phthaloyl peroxide (PPO) \( 85 \), a cyclic diacyl peroxide, has been shown to react directly with alkenes to give difunctionalised products.\(^ {54} \) Previous investigations on the stability and reactivity of PPO \( 85 \) are discussed below.

2.4.1 Phthaloyl peroxide

Initial investigations by Greene revealed PPO \( 85 \) was rapidly consumed in styrene \( 60 \) at room temperature with 50% decomposition observed after 10 h. Conversely, PPO was stable in carbon tetrachloride and heating at 80 °C for 11 days was required to obtain the same level of decomposition (Fig. 2.1).\(^ {54} \) Notably, the decomposition of PPO in styrene did not produce polystyrene and was attributed to a direct reaction between the two reagents. This reactivity highlighted a marked difference between PPO and acyclic analogs such as
Chapter 2 – Reactivity of Phthaloyl Peroxide

benzoyl peroxide which has been shown not to react directly with alkenes under identical conditions.55

\[
\text{Fig. 2.1}
\]

2.4.1.1 Reactivity

The reactivity of PPO 85 was further investigated with cis- 88 and trans-stilbene 22.56 Reaction of PPO 85 and trans-stilbene 22 gave a 3:1 ratio of difunctionalised products 86 and 87 in 95% overall yield. Structural isomers 86 and 87 were both hydrolysed to give (±)-hydrobenzoin 41 in high yield (Scheme 2.1).

\[
\text{Scheme 2.1}
\]

The stereoselectivity of the transformation was assessed with cis-stilbene 88. Reaction of PPO 85 and 88 under identical conditions gave 89 and 90 in high yield. Hydrolysis of 89 and 90 gave meso-hydrobenzoin 91 exclusively (Scheme 2.2). The studies above provided evidence the reaction was stereospecific.
2.4.1.2 Mechanistic studies

Kinetic experiments showed the reaction was first order with respect to both PPO 85 and alkene. The kinetic data obtained were consistent with both radical and ionic pathways as illustrated in Figure 2.2 below. In an attempt to distinguish between the mechanistic pathways, two experiments using PPO containing excess $^{18}$O in the carbonyl oxygen atoms were performed. 

---

**Scheme 2.2**

---

**Fig. 2.2**
Experiment A involved the reaction of $^{18}$O labeled PPO 95 with trans-stilbene 22. 86 was isolated from the reaction mixture and a small portion hydrolysed to (±)-hydrobenzoin 41. In experiment B, a sample of $^{18}$O labeled PPO 95 was heated at 80 °C for 4 days. After this time, trans-stilbene 22 was added and 86 isolated and hydrolysed as described previously. The distribution of the $^{18}$O label is shown in Table 2.1.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Experiment</th>
<th>Atom % excess $^{18}$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td>A</td>
<td>1.96</td>
</tr>
<tr>
<td>41</td>
<td>A</td>
<td>0.218</td>
</tr>
<tr>
<td>86</td>
<td>B</td>
<td>2.20</td>
</tr>
<tr>
<td>41</td>
<td>B</td>
<td>0.236</td>
</tr>
</tbody>
</table>

Table 2.1

The equilibrium between PPO 95 and diradicals 96 and 97 shown below provides a mechanism in which the $^{18}$O label can become evenly distributed between the carbonyl and peroxide oxygen atoms over time (Fig. 2.3).

![Fig. 2.3](image)

Table 2.1 shows the distribution of the $^{18}$O label is independent of the time subjected to heating at 80 °C. These results suggested diradicals 96 and 97 are not formed under the reaction conditions and strongly favours an ionic pathway.
2.4.1.3 Alternative substrates

Reaction of PPO 85 and alkene substrates possessing an allylic hydrogen resulted in a dramatic change in the composition of the products. Reaction of cyclohexene 99 and PPO 85 resulted in a mixture of products including the formation of 100 in 45% yield. The reaction between PPO 85 and tetramethylethylene 103 gave 104 as the exclusive product in high yield (Scheme 2.3).

\[
\text{Reflux} 16 \text{ h}
\]

Scheme 2.3

2.4.2 Limitations

The use of PPO 85 as a dihydroxylation agent was limited by a number of factors: (1) Formation of 100 and 104 significantly lowered the yield of the desired diol product and reduced the substrate scope of the reaction. (2) The use of organic peroxides as synthetic reagents has often been restricted due to the hazards associated with their formation and handling. As a pure substance, PPO 85 has been reported to detonate violently when exposed to shock or direct heating.\(^{54}\)
2.5 Novel approach

On the basis of the reactions shown above, a novel catalytic cycle was proposed. The reaction of PPO 85 with alkene 14 gives intermediates 106 and 107. Cleavage of the ester bonds in 106 and 107 with a peroxide source (e.g. 108) liberates diol 49 and regenerates 85 which can undergo further reaction (Fig. 2.4).

A number of features of the proposed catalytic cycle deserve further comment: (1) Steps 1 and 2 allow PPO 85 to be prepared and reacted in situ. This eliminates the hazards associated with isolation and addresses one of the major limitations described above. (2) Employing PPO 85 as a catalyst means only small quantities are present throughout the reaction, further reducing the risk associated with its use. (3) PPO 85 is prepared from cheap, commercially available starting materials in a single step. (4) Urea hydrogen peroxide 108 is the stoichiometric oxidant which is cheap and environmentally benign. (5) Complexation of a metal to the PPO scaffold may allow the development of a chiral PPO derivative and render the reaction asymmetric.
Previous investigations by Robbins had shown amides could be converted to carboxylic acids with sodium peroxide 109 under mild conditions (Scheme 2.4). This literature precedent suggested cleavage of the ester bonds in 106 and 107 could be possible.

With the decision made to investigate the reactivity of PPO 85 as part of a novel catalytic cycle, the initial aim was to examine the formation of 106 and 107 (Steps 1 & 2) and the perhydrolysis step (Step 3) independently. The results of these studies are discussed separately below.

### 2.6 Initial investigations: reactivity of PPO

PPO 85 was prepared according to the procedure described by Russell. Phthaloyl chloride 105 was treated with sodium peroxide 109 in a biphasic mixture of chloroform and pH 7 buffer. After 1 hour, the aqueous and organic layers were separated and trans-stilbene 22 added to the chloroform solution. The reaction mixture was heated at reflux for 18 h to give 86 and 87 in 21% and 15% yield respectively (Scheme 2.5).
Chapter 2 – Reactivity of Phthaloyl Peroxide

The modified procedure above resulted in a significant decrease in the isolated yields of 86 and 87 in comparison with those reported by Greene. Analysis of the reaction mixture showed significant amounts of phthalic anhydride 112 had been formed under the aqueous conditions used for the preparation of PPO 85 (Scheme 2.6). The formation of 112 meant a reduced quantity of PPO 85 was prepared and able to react with 22 resulting in the low isolated yields.

\[ \text{Scheme 2.6} \]

2.6.1 Methods to limit phthalic anhydride formation

In an attempt to limit the formation of 112, two possible solutions were proposed: (1) Performing the reaction under anhydrous conditions. (2) Use of an alternative starting material in the formation of PPO 85. The results of these studies are discussed separately below.

2.6.1.1 Anhydrous conditions

Use of a single solvent system was restricted by the low solubility of sodium peroxide 109 or urea hydrogen peroxide 108 in common reaction solvents. Although 108 and 109 are soluble in alcohol based solvents, these reacted directly with phthaloyl chloride 105. DMF emerged as the only available solvent capable of dissolving the peroxide source.
Addition of styrene 60 to a pre-mixed solution of phthaloyl chloride 105 and urea hydrogen peroxide 108 in DMF resulted in consumption of the alkene starting material and formation of a major new product by TLC. Structure 113 was consistent with the analytical data obtained. (Scheme 2.7)

Formation of 113 was attributed to the generation of hypochlorous acid (HOCI) on mixing phthaloyl chloride 105 and urea hydrogen peroxide 108. Hypochlorous acid acted as a source of positive chlorine which reacted with styrene 60 to give chloronium ion 114. Ring opening of 114 by DMF and hydrolysis on work-up gave 113 (Scheme 2.8). The formation of 113 had been reported previously using a similar procedure involving the use of mCPBA and HCl in DMF. The use of a single solvent system did not provide an effective procedure for the formation of PPO 85 and was not examined further.
2.6.1.2 Alternative precatalysts

Bis(4-nitrophenyl) phthalate 116 was proposed as an alternative starting material for the in situ preparation of PPO 85. 116 was proposed to be less sensitive to hydrolysis than phthaloyl chloride 105, but still possess a good enough leaving group to allow PPO 85 formation. Additionally, 4-nitrophenol liberated during the formation of PPO, could be conveniently removed by an aqueous buffer. Reaction of phthaloyl chloride 105 and 4-nitrophenol gave 116 in 55% isolated yield (Scheme 2.9).

![Scheme 2.9](image)

A control experiment showed 116 was stable in a mixture of chloroform and pH 7 buffer. The reaction of 116 with either sodium peroxide 109 or urea hydrogen peroxide 108 was tested under a range of conditions. The results of these studies are shown in Table 2.2. These studies showed PPO 85 was not formed under the conditions examined.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Peroxide source</th>
<th>Eq. peroxide</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na₂O₂</td>
<td>1.5</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Na₂O₂</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Urea H₂O₂</td>
<td>1.5</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Urea H₂O₂</td>
<td>10</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 2.2
2.7 Initial investigations: Perhydrolysis step

The perhydrolysis step was examined using 86 as a test substrate. Preparation of 86 via the reaction of PPO 85 and trans-stilbene 22 was hindered by low yields and difficult purification and an alternative synthesis was sought. Reaction of phthaloyl chloride 105 and (+)-hydrobenzoin 41 in pyridine gave 86 in 25% isolated yield (Scheme 2.10). Although the yield was poor, purification was simple and allowed useful quantities of 86 to be prepared.

\[
\text{105} \xrightarrow{\text{Pyridine, 110 °C, 18 h}} \text{106} \quad 25\%
\]

Scheme 2.10

The reaction of 86 and sodium peroxide 109 or urea hydrogen peroxide 108 were tested under a range of conditions and monitored for the formation of (+)-hydrobenzoin 41. The formation of (+)-hydrobenzoin 41 was not observed under any of the conditions examined. (Table 2.3)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Peroxide source</th>
<th>Eq. peroxide</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na2O2</td>
<td>1.5</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Na2O2</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Urea H2O2</td>
<td>1.5</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Urea H2O2</td>
<td>10</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 2.3
2.8 Conclusions

In summary, attempts to develop a catalytic dihydroxylation procedure based on the reactivity of PPO 85 proved unsuccessful. Formation and reaction of PPO 85 with trans-stilbene 22 in situ gave intermediates 86 and 87 in low yield due to the formation of phthalic anhydride 112 as an unwanted side-product. Attempts to limit the formation of phthalic anhydride 112 by altering the starting material and reaction conditions were ineffective. The key perhydrolysis step, on which the catalytic cycle was based, was unsuccessful under the conditions examined. Perhaps most importantly, these exploratory investigations showed the inherent risks associated with PPO 85 would always remain a considerable disadvantage of this method. For these reasons the reactivity of PPO 85 was not examined further.
Chapter 3: Reactivity of Malonoyl Peroxides
3.1 Alternative peroxide reagents

3.1.1 Introduction

Initial investigations had shown that the use of PPO 85 in the development of a catalytic dihydroxylation procedure represented a significant chemical challenge. In particular, a number of practical issues were associated with its use:

i) Preparation of PPO 85 in situ generates phthalic anhydride 112 as a significant side-product. Methods to limit or remove phthalic anhydride proved unsuccessful.

ii) Yields of 86 and 87 under the conditions investigated were low and proved difficult to purify.

iii) The proposed “perhydrolysis” was unsuccessful under the conditions investigated.

iv) The inherent hazards associated with PPO 85 make this a difficult reagent to work with.

In light of these drawbacks, an alternative peroxide reagent capable of performing the same transformation was sought.

3.1.2 New Approach

Malonoyl peroxides 119 are structurally similar to PPO 85 and since the first reported synthesis by Adam,64 they have received extensive investigation. Interest in these compounds is attributed to their ability to undergo chemiluminescent reactions in which treatment with a suitable reagent leads to the formation of visible light.65,66 As a result, much of the research has focused on the induced decomposition of these compounds. In contrast, their use as reagents in organic synthesis has received little attention. A literature search revealed a study of the reactivity between malonoyl peroxides and alkenes had not been reported.
If malonoyl peroxide 119 were to react in a similar fashion to PPO 85, a new catalytic cycle could be proposed (Fig. 3.1).

The catalytic cycle above addressed many of the problems encountered in the use of PPO and deserves further comment: (1) Formation of PPO 85 often resulted in formation of phthalic anhydride 112 as a major side-product. In contrast, formation of 117 should be disfavored due to the formation of a four membered ring and should allow 119 to be formed in high purity. (2) Due to the highly strained spirocyclic core of 122 formation of this compound was believed to be disfavored. Assuming 122 is not formed, the catalytic cycle may proceed through a distinct intermediate 121. (3) Development of a chiral peroxide based on the malonoyl peroxide scaffold appears synthetically much simpler than developing a chiral PPO derivative.
Alberts et al. had previously shown that malonoyl peroxides could be prepared from the corresponding diacid by treatment with sodium peroxide \( \text{Na}_2\text{O}_2 \). Preparation of the diacid could be achieved in two synthetic steps from diethyl malonate 125. The three step sequence is shown in Scheme 3.1.

With the decision made to investigate the reactivity of malonoyl peroxides the initial aim was to prepare peroxides 129–132 (Fig. 3.2).

### 3.2 Reagent preparation and evaluation

#### 3.2.1 Synthesis of peroxide reagents

Diethyl dicarboxylates 133–135 were prepared according to the procedure reported by Kirchner et al. Alkylation of diethyl malonate 125 with terminal dibromoalkanes using sodium ethoxide as the base gave the desired products 133–135 in low to moderate yield. The reactions were performed on multi-gram scale and the products conveniently purified by distillation (Table 3.1).
Chapter 3 – Reactivity of Malonoyl Peroxides

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dibromoalkane</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br-Br-Br</td>
<td><img src="#" alt="Product 1" /></td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Br-Br-Br</td>
<td><img src="#" alt="Product 2" /></td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Br-Br-Br</td>
<td><img src="#" alt="Product 3" /></td>
<td>59</td>
</tr>
</tbody>
</table>

Table 3.1

Due to the low yield of 133 under the above conditions (Entry 1), a modified procedure reported by Dmoski et al. was adopted (Scheme 3.2).\(^\text{69}\)

![Chemical structure]

Reaction of diethyl malonate 125 and 1,2-dibromoethane 136 in DMSO with potassium carbonate as base gave diethyl cyclopropanedicarboxylate 133 in 80% after purification by distillation.
Diethyl dicarboxylates 133–135 were converted to the corresponding 1,1-dicarboxylic acids 137–140 by treatment with LiOH in a 1:1 mixture of THF:H₂O. It should be noted that this reaction frequently provided inconsistent yields over 24 h. Prolonged reaction times of 48 h and vigorous stirring of the reaction mixture were required to consistently deliver the dicarboxylic acids in high yield (Table 3.2).

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diester</th>
<th>Diacid</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Diester 1" /></td>
<td><img src="image" alt="Diacid 1" /></td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Diester 2" /></td>
<td><img src="image" alt="Diacid 2" /></td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Diester 3" /></td>
<td><img src="image" alt="Diacid 3" /></td>
<td>81</td>
</tr>
</tbody>
</table>

Table 3.2

Malonoyl peroxides 129–132 were initially prepared from diacids 137–140 according to the procedure reported by Alberts et al.⁶⁷ In the case of cyclobutane malonoyl peroxide 130, treatment of commercially available cyclobutane 1,1-dicarboxylic acid 138 with 6.5 equivalents of sodium peroxide with methane sulfonic acid as a dehydrating agent gave 130 in 65% yield (Scheme 3.3). Although this procedure was convenient for small-scale preparation, problems were encountered when performing the reaction on a larger-scale.
Dissolving sodium peroxide in methane sulfonic acid is an extremely exothermic process; insufficient cooling resulting in ignition of the reaction mixture.

\[
\text{Na}_2\text{O}_2 (6.5 \text{ eq.}) \quad \xrightarrow{\text{Me.SO}_3\text{H}} \quad 65\%
\]

Scheme 3.3

It was vital that 129–132 could be prepared on a reasonable scale and our attention turned to developing a safer and more practical procedure. The reaction was attempted using urea hydrogen peroxide 108 as an alternative peroxide source with cyclobutane 1,1-dicarboxylic acid as a test substrate. Pleasingly, treatment of 138 with 1 equivalent of urea hydrogen peroxide 108 in methane sulfonic acid at room temperature for 18 h gave cyclobutane malonoyl peroxide 130 in 45% yield. Optimisation showed 3 equivalents of urea hydrogen peroxide 108 gave the best yield providing 130 in 80% yield. Crucially, the reaction could be performed on >5 g scale under controlled conditions. The newly developed method was subsequently used to prepare malonoyl peroxides 129–132. High yields were observed in the majority of cases (Table 3.3).

\[
\begin{array}{cccc}
\text{Entry} & \text{Diacid} & \text{Peroxide eq.} & \text{Product} & \text{Yield (%)} \\
1 & 138 & 1 & 130 & 45 \\
2 & 138 & 2 & 130 & 63 \\
3 & 138 & 3 & 130 & 80 \\
4 & 138 & 5 & 130 & 83 \\
5 & 137 & 3 & 129 & 79 \\
6 & 139 & 3 & 131 & 60 \\
7 & 140 & 3 & 132 & 79 \\
\end{array}
\]

Table 3.3
Chapter 3 – Reactivity of Malonoyl Peroxides

3.2.2 Peroxide safety

All organic peroxides should be regarded as potentially explosive and handled with due caution. To gauge the hazards associated with the newly formed malonoyl peroxides, small quantities of 129, 130 and 131 were dried and subjected to thermo-gravimetric analysis and impact tests. These studies showed malonoyl peroxides 129–131 to be insensitive to shock and direct heating. Importantly, this allows the reagents to be used without the need for special precautions and can be handled much the same as any other reagent (see appendix for thermogravimetric analysis).

3.3 Initial Investigations

3.3.1 Reactivity

Having prepared a range of peroxide reagents, the next step was to investigate their reactivity with alkenes. Owing to the commercial availability of 138, cyclobutane malonoyl peroxide 130 was used throughout these exploratory experiments. Trans-stilbene 22 was chosen as a test substrate.

The reaction of trans-stilbene 22 in the presence of 130 in acetonitrile at 40 °C for 18 h led to consumption of starting material and formation of a new major product by TLC. Treatment of the crude reaction mixture with 1 M aqueous sodium hydroxide gave (±)-hydrobenzoin 41 in 20% (Scheme 3.4).
Encouraged by this result, determining the structure of the unknown intermediate became of vital importance. The reaction was repeated under identical conditions (Scheme 3.5) and the unknown intermediate purified by column chromatography. Structure 141 was consistent with analytical data obtained.

An authentic sample of 141 was prepared from (±)-hydrobenzoin 41 and cyclobutane carboxylic acid. Coupling in the presence of \textit{N},\textit{N}-dicyclohexylcarbodiimide (DCC) and catalytic 4-di(methylamino)pyridine (DMAP) gave ester 141 in 64\% (Scheme 3.6).

Comparison of $^1$H and $^{13}$C NMR spectroscopic data for 141 formed via Schemes 3.5 and 3.6 were found to be identical proving the structure of the unknown product 141 had been correctly assigned.

At this stage, extension of the procedure to alternative alkenes was examined. The reaction between 4-methylstyrene 142 and 130 gave two unknown products in a 1:1 ratio (Scheme 3.7). Structures 143 and 144 were consistent with analytical data. Treatment of the crude reaction mixture with 1 M aqueous sodium hydroxide gave 1-p-tolylethane-1,2-diol 145 in 22\% yield.
3.3.2 Effect of water

The experiments carried out throughout this exploratory stage of the investigation suggested water had a pronounced effect on the reaction. Performing the reaction under anhydrous conditions provided a simple method for determining how vital water was to reaction success. Figure 3.3 shows a comparison of the reaction of 142 and 130 performed under anhydrous conditions and with one equivalent of water respectively.

Comparison of the two spectra in Figure 3.3 shows the absence of water results in a dramatic decrease in the observed conversion over the course of 3 h. This result showed that water was important to the overall rate of reaction.
Chapter 3 – Reactivity of Malonyl Peroxides

3.3.3 Additional products

As part of the preliminary investigation, a reaction between 4-methylstyrene 142 and cyclobutane malonyl peroxide 130 was monitored by $^1$H NMR spectroscopy. The spectroscopic data indicated a small proportion of an additional un-identified compound had been formed and was proposed to be seven membered ring 148. Initially, isolation of this compound by column chromatography was unsuccessful. Treatment of the crude reaction mixture with 3,5-dinitrobenzoyl chloride resulted in the reaction of 143 and 144 to give two derivatives 146 and 147 and allowed the unknown compound 148 to be isolated. Structure 148 was consistent with the analytical data collected (Scheme 3.8).

![Scheme 3.8](image)

3.3.4 Reaction potential

On the basis of reactions described above, cyclobutane malonyl peroxide 130 appeared to be an effective reagent for alkene dihydroxylation. Several features of this reaction deserve further comment. (1) The reaction proceeded under mild conditions in the presence of air and moisture. (2) Cyclobutane carboxylic acid, formed during hydrolysis of 141, 143 and 144, was removed by aqueous work-up. In the case of 41 and 145, the product isolated after work-up required no column chromatography. (3) The combination of easily handled reagents and mild conditions made this reaction extremely simple to perform.

Structures 141, 143 and 144 showed decarboxylation had taken place and use of the peroxide in a catalytic manner was no longer possible. Despite this set back, the potential of this novel reaction was intriguing and the decision was made to continue this investigation.
3.4 Optimisation of conditions

At this stage, developing a set of optimized conditions for the reaction became the focus of investigation. \(130\) was chosen as the peroxide of choice owing to the fact the corresponding diacid \(138\) was commercially available. \(142\) was chosen as the test substrate. After consideration of the general reaction between \(142\) and \(130\), four key variables were identified (Scheme 3.9). The effect of solvent, peroxide stoichiometry, temperature and time were investigated. Each variable is discussed below.

![Scheme 3.9](image-url)
3.4.1 Solvent

A variety of common organic solvents representing a range of polarity indices were chosen to determine their effect on the yield of 145. Previous experiments had shown water was a key component and as a result its addition to the reaction mixture became standard procedure. The results of the solvent screen are shown in Table 3.4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Eq. H₂O</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>—</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN</td>
<td>1</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>CHCl₃</td>
<td>1</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>CH₃CN</td>
<td>10</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>CHCl₃</td>
<td>10</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>Toluene</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>CH₃CN:H₂O (1:1)</td>
<td>-</td>
<td>63</td>
</tr>
<tr>
<td>12</td>
<td>CHCl₃:pH 7 buffer</td>
<td>-</td>
<td>65</td>
</tr>
<tr>
<td>13</td>
<td>CHCl₃:pH 10 buffer</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3.4

The solvent screen highlighted some interesting factors. On the basis of earlier observations that water was integral to reaction success, the use of water-miscible solvents were predicted to provide the best results. The use of acetonitrile and THF, however, only produced the diol in 54% and 30% respectively (Entries 4 & 6). Chloroform emerged as the most effective of the solvents tested, providing 145 in ~70% isolated yield (Entries 5 & 9).
Chapter 3 — Reactivity of Malonoyl Peroxides

The heterogeneous mixture formed between chloroform and water was predicted to give low yield of 145. It is interesting, therefore, that the biphasic mixture provides the best results of the solvents examined.

Comparable isolated yields were achieved using acetonitrile and toluene (Entries 4 & 7). These results suggest that solvent polarity has little effect on the reaction.

Comparison of the isolated yields using 1 and 10 equivalents of water in acetonitrile, chloroform and toluene showed little change to the isolated yields (Entries 4, 5, 7, 8–10). The observation that excess water is not detrimental to the reaction renders the drying of the reaction solvent unnecessary.

No product formation was observed when methanol was used as the reaction solvent (Entry 3). A control experiment showed stirring 130 in methanol at room temperature resulted in rapid consumption of 130 and formation of 149 in 83% yield (Scheme 3.10). The solvolysis of malonoyl peroxides in various solvents has been previously investigated by Adam et al.70

The use of DMSO as the reaction solvent formed a complex mixture of products with no desired product isolated after purification (Entry 2). No further time was spent analysing the reaction and no products of this reaction were identified.

The use of a buffered solution was proposed to remove any products capable of promoting acid catalysed decomposition of the peroxide reagent which would result in a lowering of the isolated yield. The buffered solution had little effect on the isolated yields (Entry 12).
3.4.2 Peroxide stoichiometry

The next variable to be examined was the peroxide stoichiometry. A series of experiments were performed varying the number of equivalents of 130. Having established that chloroform and one equivalent of water provided the optimum solvent mixture it was used throughout reaction optimisation. The results of the experiments are shown in Table 3.5.

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. of 130</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 3.5

The results in Table 3.5 revealed a strong trend between peroxide equivalents and isolated yield of diol. Use of excess peroxide led to a sharp decrease in the isolated yield of 145 (Entries 4 & 5). Use of a slight excess of the reagent (Entry 2) gave 145 in an excellent 84% yield. A small amount of reagent degradation could account for the need for a slight excess of the peroxide reagent.
3.4.3 Temperature

The effect of temperature on the reaction was examined next using the optimized conditions of chloroform, 1 equivalent of water and 1.1 equivalents of 130. The results of the experiments are shown in Table 3.6.

Incomplete consumption of starting alkene was observed at 30 °C over 18 h (Entry 1) and as a result the reaction was not analyzed further. Increasing the temperature to 50 °C and 60 °C gave no appreciable change in the isolated yield of 145 (Entries 3 & 4). No advantage was offered by performing the reaction at higher temperature and as a result 40 °C was adopted as the optimal temperature.
### 3.4.4 Time

The final variable to be tested was reaction time. The effect of time was determined by monitoring the conversion of alkene by $^1$H NMR spectroscopy over 18 h. The results of these experiments are shown in Table 3.7.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3.7

The results of this investigation showed that the reaction proceeded steadily over the course of 18 h. Unfortunately, the reaction was only 55% complete at 6 h and required overnight reaction to reach completion. Extended reaction times had no detrimental effect on the conversion or isolated yield of the final product.
3.5 Mechanistic investigation.

Following the development of an optimized set of reaction conditions a mechanistic understanding of the transformation was sought.

3.5.1 Proposed reaction mechanisms

Experimental evidence showed water must occupy some role in the mechanism. In addition, structures 141, 143 and 144 show decarboxylation must occur at some stage. Three potential mechanisms could account for formation of the observed products and are discussed separately below.

3.5.1.1 Mechanism A

Nucleophilic attack of the alkene on the O–O bond of the peroxide results in the formation of a new C–O bond and benzylic carbocation 151. This is followed by loss of CO₂ and formation of 153. The carbocation is subsequently trapped with water to give the observed product (Fig. 3.4)

![Fig. 3.4](image)

In the case of 4-methylstyrene 142 the formation of 144 could be explained by acyl group migration (Fig. 3.5).

![Fig. 3.5](image)
3.5.1.2 Mechanism B

Formation of 157 and subsequent decarboxylation leads to the formation of cyclobutane ketene 159 and epoxide 158. Hydrolysis of 159 forms cyclobutane carboxylic acid 160 which can react with epoxide 158 to give 154 and 155 (Fig. 3.6).

\[
\begin{array}{c}
\text{Fig. 3.6} \\
\end{array}
\]

3.5.1.3 Mechanism C

Formation of 161 and decarboxylation could alternatively provide dioxolane 163. Hydrolysis of 163 forms 165 which can degrade in one of two ways to produce the observed products 155 and 154 (Fig. 3.7).

\[
\begin{array}{c}
\text{Fig. 3.7} \\
\end{array}
\]
3.5.2 $^{18}$O labeling study

Each of the mechanisms described above involve a molecule of water. The use of $^{18}$O labeled water presented an elegant method for determining which, if any, of the proposed mechanisms may be operating. Each of the mechanisms above would result in a unique distribution of the $^{18}$O label. Determining this distribution by mass spectrometry would provide powerful evidence in favour of one of the mechanisms. The distributions for each mechanism are shown in Figure 3.8.

Cyclobutane malonoyl peroxide 130 and 4-methylstyrene 142 were reacted in dry chloroform in the presence of 1 equivalent of $^{18}$O labeled water at 40 °C over 18 h. The resulting intermediates were purified by column chromatography and analyzed by mass spectrometry (Scheme 3.11).
A comparison of the mass spectroscopy data for **144** and **175** is shown in Figures 3.9 and 3.10 below. Figure 3.9 shows two important peaks at 216 \textit{m/z} and 218 \textit{m/z}. The peaks correspond to \([M - \text{H}_2\text{O}]^{+}\). The difference of two mass units provide evidence that \(^{18}\text{O}\) had been incorporated into the product and water is implicitly involved in the reaction mechanism. Fig. 3.10 shows two peaks at 83 \textit{m/z} and 85 \textit{m/z} which correspond to the carbonyl fragments. These fragments provided evidence that \(^{18}\text{O}\) is found in the carbonyl group. From this result, mechanism A can be immediately discounted from the discussion.
Chapter 3 – Reactivity of Malonoyl Peroxides

175 was treated with 1 M aqueous sodium hydroxide to cleave the ester bond and produce 145 (Scheme 3.12). Mass spectrometry analysis of 145 showed no $^{18}\text{O}$ label present in the isolated diol and provides evidence the $^{18}\text{O}$ label was found exclusively in the carbonyl oxygen. On the basis of these experiments we can state mechanism C is consistent with representing the major, if not exclusive, mechanism for the transformation.

3.5.3. Deuterium labeling study

In an attempt to provide further evidence in support of mechanism C, an additional isotope labeling experiment was proposed. The substitution of water for deuterium oxide should result in the incorporation of a deuterium atom alpha to the carbonyl group (Fig. 3.11). Deuterium incorporation at this position could be observed via $^1\text{H}$, $^2\text{D}$ and $^{13}\text{C}$ NMR spectroscopy.
4-Methylstyrene 142 was reacted with 130 in dry chloroform and two equivalents of deuterium oxide to give intermediates 182 and 183 after purification by column chromatography (Scheme 3.13).

\[
\begin{align*}
\text{142} & \quad \xrightarrow{130 \ (1.1 \text{ eq.})} \text{CHCl}_3, 40 ^\circ C, 18 \text{ h}} \\
& \quad \xrightarrow{D_2O \ (2.0 \text{ eq.})} \text{182} + \text{183}
\end{align*}
\]
Chapter 3 – Reactivity of Malonoyl Peroxides

$^1$H NMR spectroscopic data of 183 is shown in Figure 3.12. Comparison of the integration for peaks at 4.85 ppm and 3.10 ppm indicates an 85% incorporation of deuterium.

The observed triplet of equal intensity in the $^{13}$C NMR spectroscopic data for 183 shows coupling to a deuterium atom and provides further evidence that a deuterium has been incorporated alpha to the carbonyl group (Fig. 3.13). $D^2$ NMR spectroscopic data was also obtained and shows a single peak at 3.15 ppm.
Chapter 3 – Reactivity of Malonoyl Peroxides

3.5.4 Trapping of Intermediates

3.5.4.1 External nucleophiles

The results of the isotope labeling studies strongly suggested the reaction proceeds through dioxolane 163. Trapping of this intermediate with an appropriate nucleophile such as methanol would further strengthen the proposed mechanism (Scheme 3.14). The instability of 130 in methanol had already been observed during reaction optimisation; however, the use of a single equivalent could possibly allow reaction of 130 and alkene prior to solvolysis as was observed in neat methanol.

The reaction of 130 and 142 was performed under anhydrous conditions using dry chloroform and 1 equivalent of methanol (Scheme 3.15). ¹H NMR spectroscopic data of the crude reaction mixture showed un-reacted starting alkene and a complex mixture of compounds arising from breakdown of the peroxide reagent. Further attempts to use more hindered alcohols such as isopropanol and tert-butanol resulted in similar complex reaction mixtures.
3.5.4.2 Substrate Based Strategy

Undeterred by the failure to isolate or observe 187 through the use of external nucleophiles, the preparation of an alkene with a suitable internal nucleophile offered an alternative method for trapping 163 (Scheme 3.16). The use of internal nucleophiles allowed the reaction to be performed in a suitable solvent which does not result in solvolysis of the peroxide. To this end, \(N\)-(2-vinylphenyl)acetamide 190 and 2-hydroxy styrene 191 were identified as alkenes with suitable substituents for trapping of the proposed dioxolane intermediate 163.

\(\text{NHAc}\)

\[
\begin{align*}
\text{188} & \quad \text{189} & \quad \text{190} & \quad \text{191} \\
\text{Scheme 3.16}
\end{align*}
\]

\(N\)-(2-Vinylphenyl)acetamide 190 was prepared via a Suzuki-Miyaura cross coupling between \(N\)-(2-bromophenyl)acetamide 192 and 2,4,6-trivinylcyclotriboroxane-pyridine in the presence of tetrakis(triphenylphosphine)palladium(0) and potassium carbonate to give the product in 67% yield (Scheme 3.17).

\(\text{NHAc}\)

\[
\begin{align*}
\text{192} & \quad \text{190} \\
\text{Scheme 3.17}
\end{align*}
\]
Chapter 3 – Reactivity of Malonoyl Peroxides

Reaction of salicylaldehyde 193 and methyltriphenylphosphonium iodide under standard Wittig conditions gave 2-hydroxystyrene 191 in moderate yield (Scheme 3.18).

![Scheme 3.18](image)

No reaction between 190 and 130 was observed under anhydrous reaction conditions and the starting material was recovered in >90% (Scheme 3.19). The failure of 190 to react with peroxide 130 at all may well have its origins in both steric and electronic reasons and was not immediately apparent. The reasons behind this were not further examined.

![Scheme 3.19](image)

2-Hydroxy styrene 191 offered a less tempered nucleophile and was thought to have a better opportunity of forming the desired product. Surprisingly, 2-hydroxy styrene 191 reacted with 130 under anhydrous conditions to give γ-lactone 195 in 45% isolated yield (Scheme 3.20). The formation of 195 is discussed further in Chapter 4, Section 4.2.2.1.

![Scheme 3.20](image)
3.6 Alternative mechanisms

3.6.1 Free-radical mechanism

Peroxides are well known to undergo homolytic bond cleavage and are commonly used in the generation of radical species although so far the possibility of a free radical based mechanism has not been discussed. Homolytic cleavage of the O-O bond in 130 gives diradical 196. It is a reasonable assumption that 196 can react with an alkene in a free radical mechanism (Scheme 3.21).

![Scheme 3.21](image)

A common characteristic of free radical reactions is the decrease in rate or reaction suppression by the addition of radical inhibitors such as BHT, 4-tert-butyl catechol and galvinoxyl. In an attempt to determine whether a radical based mechanism was operating, 130 was reacted with 142 in the presence of 10 mol% BHT and compared to a control experiment performed in the absence of BHT (Scheme 3.22). These studies showed addition of BHT had negligible effect on the isolated yield of 145.

![Scheme 3.22](image)
Chapter 3 – Reactivity of Malonoyl Peroxides

Exposure to light is another commonly used method for the formation of radical species. A similar set of experiments to those described above were carried out with the exclusion of light. These experiments showed that the exclusion of light also had little effect on the isolated yield of 145 (Scheme 3.23). These studies suggested a free radical mechanism was not operating.

\[
\begin{align*}
1. & \quad 130 \text{ (1.5 eq.)} \quad \text{H}_2\text{O} \text{ (1.0 eq.)} \\
& \quad \text{CHCl}_3 \quad 40^\circ \text{C} \quad \text{18 h} \quad \text{NO LIGHT} \\
2. & \quad \text{aq. NaOH} \quad 40^\circ \text{C} \quad \text{18 h} \\
\text{Yield:} & \quad 75% \\
\end{align*}
\]

Scheme 3.23

3.6.2 Single electron transfer (SET)

Malonoyl peroxides have been previously reported to undergo a class of reaction described as chemical initiated electron exchange luminescence (CIEEL). The CIEEL mechanism involves single electron transfer (SET), typically from a highly conjugated aromatic compound, to form the corresponding radical anion and radical cation. At this stage, the initial step of the reaction was believed to proceed via nucleophilic attack of the alkene on the peroxide O–O bond. However, single electron transfer offers an alternative reaction pathway.
SET from an alkene generates radical cation 200 and radical anion 199. Decarboxylation and combination of 200 and 201 may still allow formation of dioxolane 163 and subsequent hydrolysis gives the observed products (Scheme 3.24).

Cyclopropyl carbinyl radicals 202 are known to undergo rapid ring opening to give butenyl radicals 203 (Scheme 3.25).\(^7\) \(^2\) 1-Phenyl-2-cyclopropylethylene 204 was identified as an appropriate substrate to probe an SET mechanism. Formation of radical cation 205, following single electron transfer, could potentially undergo ring opening to give 206. Detection of 207 would provide evidence of the presence of a radical during the course of the reaction.

Reaction of cyclopropane carboxaldehyde 208 and benzyltriphenyl phosphonium chloride under standard Wittig conditions gave 204 as a mixture of E/Z isomers (Scheme 3.26).
Chapter 3 – Reactivity of Malonoyl Peroxides

130 and 204 were reacted under standard conditions (Scheme 3.27). Analysis of the $^1$H NMR spectroscopy data of the crude reaction mixture showed 207 had not formed. Purification of the reaction mixture by column chromatography gave 209 in 83%.

![Scheme 3.27]

It should be noted that the absence of 207 does not provide conclusive evidence against single electron transfer and more rigorous investigation is required in order to make this statement with any conviction.

3.7 Conclusions

A safe and practically simple method for the formation of malonoyl peroxides had been developed. The stability of the peroxides 129–131 were tested and they were found to be insensitive to direct heating and shock.

Investigation into the reactivity of malonoyl peroxides and alkenes had revealed cyclobutane malonoyl peroxide 130 is an effective reagent for the difunctionalisation of 4-methylstyrene 142 and provides a novel, indirect method of alkene dihydroxylation. One particularly interesting feature was that the diol products isolated (41 and 145) required no further purification by column chromatography following aqueous work-up.

$^{18}$O and deuterium labeling studies indicate the reaction proceeds via a dioxolane intermediate. The initial step of the reaction could potentially involve an ionic or SET mechanism and is not yet fully understood.
Chapter 4: Investigating Substrate Scope
Chapter 4 - Investigating Substrate Scope

4.1 Introduction

The previous chapter highlights that cyclobutane malonoyl peroxide 130 is an effective reagent for the dihydroxylation of 4-methylstyrene 142. At this point, the focus of the investigation turned to evaluating the substrate scope and determining the functional group tolerance, chemo- and stereoselectivity associated with the transformation.

One of the most intriguing observations to arise from the preliminary studies was that 1-p-tolylethane-1,2-diol 145 and (+)-hydrobenzoin 41 required no column chromatography following aqueous work-up. If this was found to be a general feature of the reaction it would offer an excellent advantage over currently available methods.

With the aim of determining whether 130 was a general reagent for alkene dihydroxylation, a variety of alkenes were reacted under a standard set of conditions. The substrates are divided into class based on their substitution and are discussed separately below.

4.2 Styrenes

4.2.1 Functional group tolerance

The functional group tolerance was examined with a range of commercially available styrene derivatives (Table 4.1). A series of exploratory reactions revealed that a number of the alkene substrates were not consumed after 18 h using 1.1 eq. of cyclobutane malonoyl peroxide 130. Addition of 1.5 eq. of 130 consistently led to alkene consumption without a significant lowering of the isolated yields. As a result 1.5 eq. of 130 was used throughout the study.
Chapter 4 - Investigating Substrate Scope

![Chemical reaction diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Alkene</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>14</td>
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</tr>
</tbody>
</table>

- 1. 130 (1.5 eq.) H₂O (1.0 eq.) CHCl₃, 40 °C, 18 h
- 2. eq. NaOH

Table 4.1

- a) 1.5 eq. peroxide, 40 °C, 56 h.
- b) 2.0 eq. peroxide, 40 °C, 48 h.
- c) 2.0 eq. peroxide, 40 °C, 68 h.
The investigation began by examining the effect of varying substitution pattern. 4-, 3- and 2-methyl styrene were dihydroxylated in moderate-good yield with no observed reduction in rate (Entries 2–4). Additionally, the sterically demanding mesityl group was also tolerated, providing the corresponding diol in 65% yield (Entry 5). The effect of the substitution pattern was further examined with 4-, 3- and 2-chlorostyrene (Entries 6–8). Curiously, a significant decrease in yield was observed in the case of 2- and 3-chlorostyrene which could not be easily explained by electronic or steric effects. The reaction was also tolerant of a bromine substituent and no oxidation of these compounds was detected (Entry 9).

Cyclobutane malonoyl peroxide 130 is an electrophilic reagent. As a result, dihydroxylation of electron deficient alkenes represents a considerable challenge. In contrast, electron rich alkenes represent the most likely substrates to give higher reaction rate. The reaction between cyclobutane malonoyl peroxide 130 and 3-nitrostyrene 226 was slow and required the use of excess peroxide (2.0 eq.) and extended reaction times (68 h) to give the corresponding diol in a disappointingly low yield of 30% (Entry 11). Attention is drawn to the fact that un-reacted starting material could be observed in the $^1$H NMR of the crude reaction mixture indicating further optimisation on this substrate was possible. As predicted, 4-methoxystyrene 224 was dihydroxylated in good yield (78%) although no appreciable increase in rate was noted (Entry 10).

2-Vinylnapthalene 228 was predicted to give high yields based on the formation of a highly stabilised carbocation following reaction with the peroxide. Disappointingly, the reaction gave the corresponding diol in a modest 65% under standard reaction conditions (Entry 12).

No diol product was isolated from the reactions of 4-cyanostyrene 230 and $N$-(2-vinylphenyl)acetamide 190 (Entries 13 & 14). The absence of product was attributed to the electron deficient nature of 4-cyanostyrene 230 and the increased steric bulk in proximity to the alkene in 190. Additionally, attempts to dihydroxylate 190 using a racemic SAD procedure was also found to be unsuccessful.
Chapter 4 — Investigating Substrate Scope

In summary, 130 was found to be a general reagent for the dihydroxylation of a range of substituted styrenes. The reaction was tolerant of steric bulk and varying substitution pattern; however, electron deficient alkenes reacted less readily and lower yields were obtained. Attention is drawn to the fact that following the dihydroxylation of 3-chloro, 2-chloro, 3-nitrostyrene and 4-cyanostyrene, high levels of un-reacted starting material were recovered. This suggested that optimisation of the reaction conditions for these substrates may allow better yields to be achieved.

4.2.2 Chemoselectivity

A number of substrates contained functional groups which raised the issue of chemoselectivity. Each of these functional groups is discussed separately and, where appropriate, compared to existing methods for alkene dihydroxylation.

4.2.2.1 Substrates containing amines

Alkenes containing free amines, such as 4-aminostyrene 233, were expected to lead to decomposition of the peroxide reagent. Use of a protecting group provided the most convenient method for addressing this problem. To this end, N-Boc-4-aminostyrene 234 was used as a test substrate, prepared from 4-aminostyrene 233 and di-tert-butyl dicarbonate (Scheme 4.1).

![Scheme 4.1](image)

Surprisingly, the reaction of 130 with 234 gave γ-lactone 235 in 30% isolated yield. γ-Lactone formation had been observed previously in the reaction of 2-hydroxystyrene 191
Further experiments showed that 4-hydroxystyrene 236 was also converted to 237 in low yield (Table 4.2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BocHN 234</td>
<td>BocHN 235</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>OH 191</td>
<td>OH 195</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>HO 236</td>
<td>HO 237</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 4.2

One possible explanation for the formation of lactones 195, 235 and 237 is the formation of diradical 238 during the reaction. 238 could react with the alkene starting material to form the observed products (Fig. 4.1). Unfortunately, this simplistic model provides no explanation as to why the nature of the alkene should result in diradical formation.

Fig. 4.1
If formation of 235 proceeded via a radical mechanism, addition of a radical inhibitor such as BHT should result in reaction suppression. The reaction of 130 and 234 was performed in the presence of 10 mol% BHT which gave the corresponding diol in modest yield (Scheme 4.2).

Previous experiments had shown 4-methoxystyrene 224 and 4-acetoxy styrene 241 were dihydroxylated in good yield without the formation of the corresponding γ-lactone (Scheme 4.3 & Table 4.1, Entry 10).

These results suggested the presence of a heteroatom bearing a proton was a requirement for γ-lactone formation. Although the mechanism for the formation of 195, 235 and 237 is not currently understood, transformations which form new C–C bonds are desirable synthetic procedures. Investigation into this reaction is currently ongoing within the laboratory.
4.2.2.2 Substrates containing sulfur

Peroxides and peroxy acids such as H$_2$O$_2$ and mCPBA are commonly used for the oxidation of sulfides to the corresponding sulfoxide or sulfone.$^{74}$ Similarly, the reaction of 4-vinylthioanisole 244 and 1.1 equivalents of 130 gave 245 in 74% yield (Scheme 4.4). The chemoselectivity for the sulfur atom over the double bond is in direct opposition to the Sharpless AD which reacts exclusively with the alkene.$^{27}$ The preference for the oxidation of sulfur reduces the substrate scope with respect to the dihydroxylation procedure but provides the potential for a new area of reactivity to investigate.

\[
\text{Scheme 4.4}
\]

4.2.2.3 Enynes

The chemoselectivity associated with enynes was briefly investigated with 1-ethynyl-4-vinylbenzene 247, prepared from 4-bromostyrene 222 and trimethylsilylethylene via a Sonagashira coupling and subsequent removal of the trimethylsilyl group (20%) (Scheme 4.5).$^{75}$

\[
\text{Scheme 4.5}
\]
Chapter 4 – Investigating Substrate Scope

Reaction of 130 and 247 under standard conditions gave the corresponding diol product 248 in 35% (Scheme 4.6). The low yield of 248 is attributed to difficulties in purification and does not represent reaction of the alkyne. The dihydroxylation of enynes via the Sharpless AD has been investigated and also showed exclusive chemoselectivity for the alkene.27

\[
\begin{align*}
1. & \quad 130 \ (1.5 \text{ eq.}) \\
& \quad \text{H}_2\text{O} \ (1.0 \text{ eq.}) \\
& \quad \text{CHCl}_3 \\
& \quad 40^\circ \text{C}, 18 \text{ h} \\
2. & \quad \text{aq. NaOH} \\
\end{align*}
\]

Scheme 4.6

4.3 1,2-Disubstituted alkenes

4.3.1 Stereoselective or stereospecific

1,2-Disubstituted alkenes presented an opportunity to evaluate the stereoselectivity associated with the malonoyl peroxide based transformation.

4.3.2 Preliminary study

Cis- 88 and trans-stilbene 22 were identified as convenient test substrates owing to the commercial availability of the alkenes and the corresponding diols, meso- 91 and (±)-hydrobenzoin 41. Cis- and trans-stilbene were reacted with cyclobutane malonoyl peroxide 130 under optimized conditions and, following consumption of alkene starting material, submitted to hydrolysis conditions (Scheme 4.7). \(^1\)H NMR spectroscopic data showed both 41 and 91 had formed and the reaction was not stereospecific.
The diastereomeric excess for each transformation was determined from $^1$H NMR spectroscopic data of the crude reaction mixture and comparison to a set of authentic products. Trans-stilbene 22 gave a diastereomeric excess of 92% in favour of (±)-hydrobenzoin 41. Under the same conditions, cis-stilbene 88 gave a diastereomeric excess of 55% in favour of meso-hydrobenzoin 91.

### 4.3.3 Mechanistic rationale

At this stage of the investigation, the aim was to develop a mechanistic rationale which accounted for (1) How both diastereoisomers were formed. (2) Why such a large difference in diastereoselectivity was observed in the case of cis-88 and trans-stilbene 22.

A mechanistic model was proposed and tested in a series of experiments in which the steric and electronic nature of the alkene, temperature, solvent and peroxide structure were varied. The model and results of these studies are discussed separately below.
4.3.4 Origin of diastereoisomers

A model which accounted for the formation of two diastereoisomers is shown in Figure 4.2. Interaction of peroxide and alkene results in the formation of carbocation 249 in which free rotation about the C–C bond is possible. Bond rotation followed by ring closure gives dioxolane 251 (Pathway A). Alternatively, ring closure can occur without bond rotation and form dioxolane 250 (Pathway B). Hydrolysis of 250 and 251 results in the formation of the diastereoisomers observed.

![Figure 4.2](image-url)
4.3.5 Steric effects

As the peroxide reagent is known to react with alcohols, which are formed during the reaction, it is difficult to assess whether product yields represent meaningful mechanistic indicators. Investigation into steric effects may provide more detailed mechanistic information.

4.3.5.1 Application of mechanistic model

Application of the model described above to the reactions of cis-88 and trans-stilbene 22 provided an explanation for the differences in diastereoselectivity (Fig. 4.3).

In the case of cis-stilbene 88, rotation of the C–C bond in 253 results in an increase in the steric interaction between the two phenyl groups and raises the energy of conformation 253. As a result, conformation 254 is preferred and results in high diastereoselectivity for the formation of (±)-hydrobenzoin 41.

In the case of trans-stilbene 22, rotation of the C–C bond in 254 results in an increase in the steric interaction between the two phenyl groups and raises the energy of conformation 254. As a result, conformation 254 is preferred and results in high diastereoselectivity for the formation of (±)-hydrobenzoin 41.
further by altering the steric of the alkene substrate. In an attempt to provide further evidence in support of the mechanistic model described above, a number of alternative alkene substrates were examined and are discussed separately below.

### 4.3.5.2 Stilbene derivatives

Substituted stilbene derivatives 255, 257 and 259 were identified as appropriate test substrates and were prepared in a single step via a Heck reaction. Dihydroxylation of 255–259 under standard conditions gave the corresponding diols 256, 258 and 260. Diastereoselectivities for each transformation are shown in Table 4.3.

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Syn:anti ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>255</td>
<td>256</td>
<td>83</td>
<td>23:1</td>
</tr>
<tr>
<td>2</td>
<td>257</td>
<td>258</td>
<td>78</td>
<td>32:1</td>
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<td>3</td>
<td>259</td>
<td>260</td>
<td>27</td>
<td>25:1</td>
</tr>
</tbody>
</table>

Table 4.3
Chapter 4 – Investigating Substrate Scope

Trans-2,2'-dimethylstilbene 257 showed a distinct rise in diastereoselectivity when compared to trans-stilbene 22. Pleasingly, this was readily explained by the mechanistic model (Fig. 4.4).

![Mechanistic Model](image)

Rotation about the C–C bond in 261 leads to an increased steric interaction between the two methyl substituents making conformation 262 highly disfavoured. As a result, high syn-selectivity is observed. The position of the substituents in 255 and 259 result in no significant difference in steric interactions when compared to trans-stilbene 22 resulting in similar levels of diastereoselectivity being observed. It was unclear why 3,3'-dimethoxystilbene 259 only provided the dihydroxylated product in low yield. One qualitative observation was the basic aqueous layer remained highly coloured after extraction with chloroform. Back extraction did not allow additional organic material to be isolated. The reason behind this requires further investigation.
4.3.5.3 Further substrates

Reaction of trans-β-methylstyrene 263 and 130 was performed under standard conditions and the diastereomeric excess determined from $^1$H NMR spectroscopic data and comparison to previously reported literature data. A significant decrease in diastereoselectivity was observed with respect to trans-stilbene 22 (Scheme 4.8).

![Scheme 4.8]

The change in diastereoselectivity can again be rationalised on the basis of the steric argument described above. Exchange of a phenyl group for a methyl group should result in reduced steric interaction after C–C bond rotation with respect to trans-stilbene 22 (Fig. 4.5). The difference in energy between conformations 266 and 267 is reduced resulting in lower diastereoselectivity.

![Fig. 4.5]

In a similar fashion, substitution of a methyl group with a sterically demanding isopropyl group should result in an increase in diastereoselectivity. 270 was prepared from isobutyraldehyde 268 and benzyltriphenyl phosphonium bromide (Scheme 4.9). 269 was isolated with a $E:Z$ ratio of 3:1.
Iodine was added to a solution of the geometrical isomers and the mixture exposed to direct sunlight. Isomerisation was monitored by $^1$H NMR spectroscopy and gave pure $E$-alkene 270 after 72 h.

Reaction of 130 and 270 under standard conditions gave 271 and 272 in 67% diastereomeric excess in favour of syn-addition as determined by comparison to literature data (Scheme 4.10). As predicted, an increase in diastereoselectivity (67% d.e.) was observed when compared to trans-β-methylstyrene 263 (58% d.e.).
4.3.6 Cyclic alkenes

The effect of incorporating the alkene within a ring on the diastereoselectivity was examined with indene 273 and 1-phenyl cyclohexene 81. Reaction of 273 and 81 with cyclobutane malonoyl peroxide 130 gave the corresponding diols 274 and 275 in moderate yield. Importantly, both reactions were found to afford syn-dihydroxylated products exclusively as determined by $^1$H NMR spectroscopy of the crude reaction mixture (Scheme 4.11).

Incorporation of the alkene within a ring prohibits rotation about the C–C bond following the formation of the benzylic carbocation allowing only syn-dihydroxylation to occur. The formation of 276 is discussed further in Section 4.4.
4.3.7 Electronic effects

On the basis of the model described above, the lifetime of the carbocation should play a vital role in determining the diastereoselectivity of the transformation. Addition of substituents which stabilise the carbocation should lower diastereoselectivity. Conversely, substituents which destabilise the carbocation should lead to an increase in diastereoselectivity. To this end, 4-methoxy-trans-β-methylstyrene 282 and 4-bromo-trans-β-methylstyrene 279 were identified as appropriate test substrates.

4-Bromo-trans-β-methylstyrene 278 was prepared from 4-bromobenzaldehyde 277 and ethyltriphenylphosphonium chloride under standard Wittig conditions (Scheme 4.12). The mixture of geometrical isomers was treated with iodine and exposed to direct sunlight to afford pure E-4-bromo-trans-β-methylstyrene 279.

\[
\begin{align*}
\text{Br} & \quad \text{O} & \quad \text{H} \\
\text{277} & \quad \text{[CH}_3\text{C}_2\text{H}_4\text{PPh}_3\text{]Cl} & \quad \text{BuLi} & \quad \text{Sunlight} & \quad \text{THF} & \quad \text{reflux, 48 h} \\
 & \quad & & & \quad \text{Br} & \quad \text{EZ 1:1} & \quad \text{278} & \quad \text{I}_2 & \quad \text{CH}_2\text{Cl}_2 & \quad \text{r.t., 72 h} & \quad \text{Pure E} & \quad \text{279}
\end{align*}
\]

Scheme 4.12

The reaction of 4-bromo-trans-β-methylstyrene 279 and 4-methoxy-trans-β-methylstyrene 282 with cyclobutane malonoyl peroxide 130 gave the corresponding diols in diastereomeric excesses of 65% and 69% respectively as determined by comparison to literature data (Scheme 4.13).
These studies revealed some interesting results:

(1) Contrary to the predicted outcome, 279 and 282 gave comparable diastereomeric excesses. These results suggested the electronic nature of the alkene had negligible effect on the observed diastereoselectivities. At this stage, the reasons behind this were not immediately apparent.

(2) Observed diastereoselectivities of 279 and 282 were higher than that obtained with trans-β-methylstyrene 263. These results brought the conclusions drawn from the steric argument described above into question. Previous experiments had shown 1-phenyl-2-isopropylethylene 270 resulted in an increase in diastereoselectivity when compared to trans-β-methylstyrene 263. This was attributed to an increase in steric interaction following bond rotation. Substrates 279 and 282 showed a comparable raise in diastereoselectivity with respect to trans-β-methylstyrene 263 which could not be explained solely by steric arguments.

It was clear from these studies that further investigation was required to gain a complete understanding of the factors which affect diastereoselectivity.
4.3.8 Solvent and temperature effects

In an attempt to determine whether temperature or reaction solvent played an important role in controlling diastereoselectivity, the reactions of trans-β-methylstyrene 263, cis-stilbene 88 and trans-stilbene 22 with cyclobutane malonyl peroxide 130 were examined under a range of conditions. The results of these studies are shown in Tables 4.4 and 4.5 below.

![Reaction Scheme](image)

<table>
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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Peroxide eq.</th>
<th>Reaction Complete?</th>
<th>Ratio</th>
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<td>22</td>
<td>CHCl₃</td>
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<tr>
<td>2</td>
<td>22</td>
<td>CHCl₃</td>
<td>40</td>
<td>1.2</td>
<td>No</td>
<td>1 : 27</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>CHCl₃</td>
<td>60</td>
<td>1.2</td>
<td>No</td>
<td>1 : 27</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>Toluene</td>
<td>25</td>
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<td>—</td>
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<td>CH₃CN</td>
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<td>CHCl₃</td>
<td>40</td>
<td>1.5</td>
<td>Yes</td>
<td>1 : 3.5</td>
</tr>
</tbody>
</table>

Table 4.4
Chapter 4 - Investigating Substrate Scope

The results above highlighted some interesting factors:

(1) It was proposed that raising the reaction temperature should result in increased bond rotation following carbocation formation and lead to a reduction in diastereoselectivity. Interestingly, the results showed reaction temperature had little effect on the observed diastereoselectivity (Table 4.4, Entries 1-3, 4-6 & 7-9)

(2) Acetonitrile was identified as a polar solvent which may be able to stabilise a benzylic carbocation. In contrast, a non-polar solvent such as toluene was proposed to offer no stabilisation of a carbocation. It was proposed that these two solvents may result in very different diastereoselectivities. Curiously, Table 4.4 showed comparable diastereoselectivities were obtained in acetonitrile and toluene (Entries 6 & 9). Chloroform remained the most effective reaction solvent with respect to diastereoselectivities; however, it is difficult to rationalise how chloroform can affect the diastereoselectivities so dramatically.
4.3.9 Peroxide structure

At this stage of the investigation, the effect of peroxide structure on the reactivity had not been examined. To this end, 4-methylstylene 142 was reacted with cyclopentane malonoyl peroxide 131 and cyclopropane malonoyl peroxide 129 under optimized conditions (Scheme 4.14).

Cyclopentane malonoyl peroxide 131 gave the corresponding diol in poor yield and was not examined further. In contrast, cyclopropane malonoyl peroxide 129 gave the corresponding diol in 90% isolated yield. Encouraged by these results, the effect of peroxide structure on the diastereoselectivity was examined with 129 and a number of 1,2-disubstituted alkenes.
Chapter 4 – Investigating Substrate Scope

The results of these studies are shown in Table 4.6. Additional columns have been added to allow comparison between the results obtained with cyclobutane malonoyl peroxide 130.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>syn:anti ratio 129</th>
<th>d.e. (%)</th>
<th>syn:anti ratio 130</th>
<th>d.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>trans-stilbene</td>
<td>34 : 1</td>
<td>94</td>
<td>24 : 1</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>cis-stilbene</td>
<td>4 : 1</td>
<td>60</td>
<td>3.5 : 1</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>trans-β-methylstyrene</td>
<td>14 : 1</td>
<td>87</td>
<td>3.8 : 1</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>4-bromo-trans-β-methylstyrene</td>
<td>12.5 : 1</td>
<td>85</td>
<td>4.7 : 1</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>4-methoxy-trans-β-methylstyrene</td>
<td>5.5 : 1</td>
<td>69</td>
<td>5.5 : 1</td>
<td>69</td>
</tr>
</tbody>
</table>

Table 4.6

The results of these studies showed trans-stilbene 22, trans-β-methylstyrene 263 and 4-bromo-trans-β-methylstyrene 279 were formed with a significant increase in diastereoselectivity (Entries 1, 3 & 4). Conversely, cis-stilbene 88 and 4-methoxy-trans-β-methylstyrene 282 were formed with comparable diastereoselectivity to that obtained with cyclobutane malonoyl peroxide 130 (Entries 2 & 5).
Chapter 4 – Investigating Substrate Scope

In an attempt to rationalise these differences, the reaction of 4-methylstyrene 142 and 129 was performed. Two major products were observed by TLC. Structures 285 and 286 were consistent with analytical data obtained (Scheme 4.15).

Interestingly, the reaction between 129 and 142 gave difunctionalised products 285 and 286 where decarboxylation had not occurred. This observation suggested an alternative mechanism must be operating in the case of cyclopropane malonoyl peroxide 129 and provided a potential explanation for the observed differences in diastereoselectivity. A possible mechanism is shown below (Fig. 4.6). Further examination of the reaction mechanism via $^{18}$O labeling studies may reveal a more accurate description of the reaction mechanism.
4.3.10 Summary

Previous attempts to rationalise the observed diastereoselectivities obtained with cyclobutane malonoyl peroxide 130 and a number of 1,2-disubstituted alkenes met with limited success. The observation that cyclopropane malonoyl peroxide 129 can undergo the same overall transformation without decarboxylation suggested further details of the reaction mechanism for the cyclobutane malonoyl peroxide mediated reaction were still to be discovered. In light of these findings, it is perhaps unsurprising that not all of the factors which affect diastereoselectivity can be accurately explained using the simplistic mechanistic model described above. Investigation into the use of cyclopropane malonoyl peroxide 129 as a dihydroxylating reagent is currently a major area of research within the group. As decarboxylation was found not to occur, recovery of the di-acid is possible and helps to reduce the environmental impact of the transformation.
Chapter 4 - Investigating Substrate Scope

4.4 1,1-Disubstituted and trisubstituted alkenes

The reaction of α-methylstyrene 292 and cyclobutane malonoyl peroxide 130 under optimized conditions led to the formation of two major products by TLC. Structures 293 and 294 were consistent with analytical data obtained (Scheme 4.16).

\[
\begin{align*}
1. & 130 \text{ (1.5 eq.)} \\
2. & \text{aq. NaOH} \\
\end{align*}
\]

![Scheme 4.16](image)

Formation of 294 was attributed to abstraction of an allylic hydrogen following formation of 295. Cleavage of the ester bond in 297 under basic conditions gave 294 as the isolated product (Fig. 4.7).

![Fig. 4.7](image)

In an attempt to determine if allylic alcohol formation was a general characteristic for alkenes bearing an allylic hydrogen atom, 1-phenylcyclohexene 81, trans-α-methylstilbene 298 and 1-phenyl-1-cyclopropylethylene 299 were reacted with 130 under optimized conditions (Table 4.7). Both 81 and 298 reacted to give a mixture of diol and allylic alcohol (Entries 1 & 2). Interestingly, 299 formed the dihydroxylated product exclusively in 69% (Entry 3).
Chapter 4 - Investigating Substrate Scope

The absence of allylic alcohol in the case of 299 is attributed to the unfavourable rise in ring strain created by incorporating an sp\(^2\) hybridised carbon into a three-membered ring. Unsurprisingly, 1,1-diphenylethylene 300, which contains no allylic hydrogens, also formed the diol product exclusively in 67% isolated yield (Entry 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Diol (%)</th>
<th>Allylic alcohol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>298</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>299</td>
<td>69</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>300</td>
<td>67</td>
<td>—</td>
</tr>
</tbody>
</table>

Although representing a limitation with regard to alkene dihydroxylation, the formation of allylic alcohols is an interesting and useful transformation. Further investigations may reveal conditions under which the allylic alcohol is formed exclusively and provide a new area of reactivity to investigate but this was not examined further within this study.
4.5 Aliphatic alkenes

At this stage of the investigation, only substrates based on styrene and stilbene scaffolds had been examined. Successful extension of the dihydroxylation procedure to aliphatic alkenes would significantly broaden the substrate scope of the reaction.

Whilst representing a significant challenge, 301, 303 and 305 provided examples of the most likely substrates to undergo successful dihydroxylation owing to their potential to generate a tertiary carbocation. Authentic samples of diols 302, 304 and 306 were prepared using a racemic Sharpless AD procedure\textsuperscript{73} to aid reaction monitoring by TLC and \textsuperscript{1}H NMR spectroscopy. Diols 302–306 were isolated in moderate yield (Table 4.8).

\[
\begin{array}{|c|c|c|}
\hline
\text{Entry} & \text{Substrate} & \text{Product} & \text{Yield} (\%) \\
\hline
1 & \begin{array}{c}
\text{R} \quad \text{R} \\
301
\end{array} & \begin{array}{c}
\text{R} \quad \text{R} \\
302
\end{array} & 55 \\
2 & \begin{array}{c}
\text{R} \quad \text{R} \\
303
\end{array} & \begin{array}{c}
\text{R} \quad \text{R} \\
304
\end{array} & 60 \\
3 & \begin{array}{c}
\text{R} \quad \text{R} \\
305
\end{array} & \begin{array}{c}
\text{R} \quad \text{R} \\
306
\end{array} & 65 \\
\hline
\end{array}
\]

Table 4.8
Chapter 4 - Investigating Substrate Scope

Ethylidenecyclohexane 301 was chosen as a test substrate and reacted with cyclobutane malonoyl peroxide 130. The effect of peroxide stoichiometry, temperature and reaction time were examined. The results of this study are shown in Table 4.9.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Peroxide eq.</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>40</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>40</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>55</td>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>40</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>65</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>65</td>
<td>48</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>3.0</td>
<td>65</td>
<td>38</td>
<td>38</td>
</tr>
</tbody>
</table>

Table 4.9

Using the conditions optimized for styrene and stilbene derivatives resulted in the formation of 302 in 10–20% (Entries 1 & 2). The use of higher temperature and extended reaction time gave 302 in comparable yield (Entry 3). The use of three equivalents of 130 at 65 °C over 38 h emerged as the most effective reaction conditions providing 302 in 38% (Entry 7).

The results of these exploratory investigations were particularly encouraging. Aliphatic alkene 301 was dihydroxylated in low yield but crucially some un-reacted starting material could be recovered (<20%) indicating higher yields may be achieved following further optimisation of the reaction conditions. Additionally, allylic alcohol formation was not observed throughout reaction development; however, it should be noted this may be explained by the low yields observed and difficulties encountered in purifying the reaction mixture.
Chapter 4 – Investigating Substrate Scope

Following these exploratory studies, methylene cyclopentane 303 and 1-methylcyclopentene 305 were reacted with 3 equivalents of 130 at 65 °C for 38 h to give 304 and 306 in 12% and 6% isolated yield respectively (Table 4.10, Entries 1 & 2). Attempts to monitor the reactions by TLC were un-effective and could not be used to determine if starting material was still present. No starting material was observed in the \(^1\)H NMR of the crude reaction mixtures for both 304 and 306, but this could be attributed to the substrates’ volatility during removal of the reaction solvent. No product formation was observed in attempts to extend the dihydroxylation procedure to cyclohexene 99 (Table 4.10, Entry 3). \(^1\)H NMR spectroscopy of the crude reaction mixture showed no starting material but this could again be attributed to the substrates’ volatility.

\[
\begin{align*}
\text{R} & \implies \text{R} \\
& \xrightarrow{1. \text{130 (3.0 eq.)} \quad \text{H}_2\text{O (1.0 eq.)} \quad \text{CHCl}_3} \quad 65 ^\circ\text{C, 38 h} \\
& \quad \text{2. aq. NaOH} \\
& \xrightarrow{\text{OH}} \quad \text{OH} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>303</td>
<td>304</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>305</td>
<td>306</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>99</td>
<td>307</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 4.10
Chapter 4 – Investigating Substrate Scope

Although 304 and 306 were isolated in low yield, these initial experiments provided evidence that cyclobutane malonoyl peroxide 130 can be employed as a dihydroxylating agent for aliphatic alkenes. Further investigations on the reactivity between cyclopropane malonoyl peroxide 129 and aliphatic alkenes is currently ongoing within the group and will hopefully lead to successful extension of the substrate scope to a wide range of aliphatic alkenes.

4.6 Purification and side-product formation

Investigation into the substrate scope revealed a number of general characteristics associated with the transformation:

(1) Consumption of alkene starting material was observed in the majority of cases.
(2) Isolated yields of the corresponding diols were typically between 50–80%.
(3) In the majority of cases no column chromatography was required following aqueous work-up.

The discrepancy between alkene conversion and isolated yield (Points 1 & 2) was attributed to side-product formation. The absence of any side-products in the crude reaction mixture (Point 3) was attributed to their removal during aqueous work-up.

At this stage of the investigation, the structure of the contaminants were unknown. In an attempt to identify the structure of the side-products, styrene 60 was reacted with 2.5 equivalents of cyclobutane malonoyl peroxide 130 and monitored by $^1$H NMR spectroscopy. Analysis of the spectroscopic data showed small quantities of benzoic acid had formed.

Benzoic acid formation could have occurred via further oxidation of intermediates 308 and 309. Control experiments showed benzoic acid was not formed when 308 and 309 were separately treated with excess peroxide; however, conversion between the two intermediates was observed, presumably via acyl group transfer (Table 4.11, Entries 1 & 2). Interestingly, benzoic acid was observed following the treatment of
1-phenylethane-1,2-diol 64 with excess peroxide (Table 4.11, Entry 3). The mechanism by which 64 is converted to benzoic acid is currently not understood; however, the reaction is currently receiving further investigation.

A typical reaction involved hydrolysis of intermediates 308 and 309 with aqueous sodium hydroxide followed by extraction of the dihydroxylated product with chloroform. Back extraction of the aqueous showed additional non-discrete organic material could be isolated. \(^1\)H NMR showed aromatic peaks within this mixture which suggested this must have derived from the alkene substrate. The product appeared to be polymeric by visual inspection. Although the structure of the side-products is not known, the solubility of this material in basic aqueous media suggests the presence of a carboxylic acid moiety.

### 4.7 Peroxide structure-reactivity investigation

Cyclobutane malonoyl peroxide 130 and PPO 85 have been shown to react directly with alkenes. Conversely, acyclic diacyl peroxides such as dibenzoyl peroxide (BPO) are un-reactive towards alkenes under identical conditions.\(^5\) Below is a qualitative examination of the factors which affect peroxide reactivity which aimed to answer the following questions:

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>c-BuC(O)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>c-BuC(O)</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>10(^a)</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \(^1\)H NMR spectroscopic data
Chapter 4 – Investigating Substrate Scope

- How does incorporating the diacyl peroxide unit within a ring result in increased reactivity?
- Why is PPO 85 highly shock sensitive whereas malonoyl peroxides 129–131 are not?

4.7.1 Cyclic versus acyclic

The increased reactivity of PPO 85 towards alkenes has been previously attributed to repulsion between non-bonded electron pairs of the peroxy-oxygen atoms\textsuperscript{54}. Rotation about the O–O bond allows acyclic analogs to adopt a conformation in which lone pair repulsion is minimised. This could potentially explain the difference in reactivity between cyclic and acyclic diacyl peroxides.

4.7.2 Malonoyl peroxide versus PPO

A simple chemical model suggested PPO 85 may adopt a half chair conformation as shown in Figure 4.8. Crystallographic data for malonoyl peroxides 129–132 were obtained and showed the peroxy unit is planar (Fig. 4.8). On the basis of these observations, cyclobutane malonoyl peroxide 130 should experience greater lone pair repulsion and would be expected to be more reactive than PPO 85.

\[
\begin{array}{c}
\text{Fig. 4.8}
\end{array}
\]

In previous studies, cyclobutane malonoyl peroxide 130 had shown no reactivity towards cyclohexene 99 whereas PPO 85 has been reported to react with 99 to give dioxygenated species in moderate yield (See Chapter 2, Section 2.4.1.4). These observations suggested PPO 85 was in fact the more reactive of the cyclic peroxides.
In light of these observations, an additional factor must account for the difference in reactivity. One possible explanation is the difference in stability of the carbanion/radical formed after O−O bond cleavage. In the case of 130, the conformation adopted offers no stabilisation of the resulting carbanion/radical through the carbonyl group. The half chair structure adopted by PPO 85, however, allows the negative charge/radical to become stabilised by the carbonyl group (Fig. 4.9). This argument suggested that, while thermodynamically less stable than PPO, the formation of an un-stabilised radical/carbanion makes cyclobutane malonoyl peroxide 130 more kinetically stable and may potentially account for the difference in reactivity.

**4.7.3 Comparison of malonoyl peroxides**

Previous experiments had shown cyclopentane malonoyl peroxide 131 was a less effective dihydroxylating agent than cyclobutane- 130 and cyclopropane malonoyl peroxide 129. Comparison of the crystallographic data for malonoyl peroxides 129–132 showed a remarkable similarity between the conformation of the peroxide unit (Fig. 4.10). This suggested the degree of lone pair repulsion in 129–132 would be similar and additional factors must account for the difference in reactivity.
In an attempt to gain further insight into which factors affect peroxide reactivity, physical data for 129–132 were collected and analysed for trends (Table 4.12).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Peroxide</th>
<th>O–O bond length (Å)</th>
<th>CO–C–CO angle</th>
<th>C=O IR stretching frequency (cm⁻¹)</th>
<th>¹³C Carbonyl peak (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>129</td>
<td>1.476</td>
<td>107.56</td>
<td>1827 &amp; 1798</td>
<td>172.15</td>
</tr>
<tr>
<td>2</td>
<td>130</td>
<td>1.476</td>
<td>104.01</td>
<td>1799</td>
<td>173.94</td>
</tr>
<tr>
<td>3</td>
<td>131</td>
<td>1.471</td>
<td>102.34</td>
<td>1797</td>
<td>175.70</td>
</tr>
<tr>
<td>4</td>
<td>132</td>
<td>1.467</td>
<td>102.35</td>
<td>1794</td>
<td>174.35</td>
</tr>
<tr>
<td>5</td>
<td>BPO</td>
<td>1.460⁷⁸</td>
<td>—</td>
<td>1789 &amp; 1766⁷⁹</td>
<td>162.25</td>
</tr>
</tbody>
</table>

¹³C NMR data for peroxides 129–132 shows the carbonyl group resonates at ~175 ppm as expected for an acid derivative. IR data is also found to be typical for diacyl peroxides. It was initially proposed that O–O bond length may provide a qualitative measure of bond strength. 129 and 130 were thought to contain a longer (weaker) O–O bond which may account for the difference in reactivity. Comparison of the O–O bond lengths for 129–132 shows little difference throughout the series. Interestingly, CO–C–CO bond angle was found to increase moving from 132 to 129. The increased bond angle was thought to result in increased ring strain which may account for the increased reactivity.
Chapter 4 – Investigating Substrate Scope

DSC data for 129–132 are shown in Table 4.13. Each peroxide showed an endotherm (melting point) and an exotherm (decomposition).

<table>
<thead>
<tr>
<th>Peroxide</th>
<th>Endotherm (J g⁻¹)</th>
<th>Endotherm Temperature (°C)</th>
<th>Exotherm (J g⁻¹)</th>
<th>Exotherm Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>129</td>
<td>-96.17</td>
<td>89.80</td>
<td>1593.36</td>
<td>181.57</td>
</tr>
<tr>
<td>130</td>
<td>-69.06</td>
<td>62.95</td>
<td>1443.08</td>
<td>160.91</td>
</tr>
<tr>
<td>131</td>
<td>-47.09</td>
<td>41.27</td>
<td>875.86</td>
<td>128.58</td>
</tr>
</tbody>
</table>

Table 4.13

A significant difference in the energy released from 129 and 131 during decomposition was observed. The difference in energy may well be attributed to increased ring strain. Although these studies represent a simplified, descriptive investigation, qualitative investigations may allow rationalisation of the factors which affect peroxide reactivity and allow logical design of more active dihydroxylating agents.

4.8 Conclusions

In summary, cyclobutane malonoyl peroxide 130 proved to be an effective reagent for the dihydroxylation of a range of substituted styrene and stilbene derivatives. Functional group tolerance was explored and included alkyl, aryl, halide, ester, carbamate, nitro, ether and alkyne groups. Sulfides were oxidised to the corresponding sulfoxide in preference of the alkene moiety.

Steric factors have been shown to play an important role in determining the diastereoselectivity of the reaction. In contrast, the electronic nature of the alkene substrate, temperature and reaction solvent were shown to have little effect.

The reaction of cyclopropane malonoyl peroxide 129 with 4-methyl styrene 142 gave intermediates 285 and 286 in which decarboxylation had not occurred. This result indicated that a number of mechanistic intricacies are still to be discovered and explained why
Chapter 4 – Investigating Substrate Scope

previous attempts to rationalise the observed diastereoselectivities obtained with
cyclobutane malonoyl peroxide met with little success. Further investigation into the
reaction mechanism is an ongoing area of research within the group.

Allylic alcohol formation appears to be a general characteristic for alkenes bearing allylic
hydrogen atoms. Exclusive formation of the allylic alcohol product could provide an
interesting and useful transformation and is currently under investigation. Incorporation of
a free hydroxy or protected amine group resulted in γ-lactone formation although how these
products are formed is not currently understood.

Cyclobutane malonoyl peroxide 130 showed limited reactivity towards aliphatic alkenes
but proved that dihydroxylation of these substrates was possible. Current research within
the group has focussed predominantly on the reactivity of cyclopropane malonoyl peroxide.
Results to date have shown that superior yields, reduced reaction times and increased
diastereoselectivities can be achieved when compared to the cyclobutane malonoyl
peroxide mediated transformation. Current work within the group includes dihydroxylation
of aliphatic alkenes with 129 and the development of a catalytic variant of this
transformation.
4.9 Further Work

4.9.1 Substrate scope

The substrate screen described above is by no means exhaustive and a number of substrates require further examination.

4.9.1.1 Polyenes

The selective dihydroxylation of conjugated polyenes has been examined extensively using the Sharpless AD procedure\(^\text{27}\). In the case of non-conjugated systems, regiochemistry is determined by the steric and electronic nature of the alkene. Selective dihydroxylation of 1-allyl-4-vinylbenzene 315 has not been reported in the literature; however, the SAD may be expected to give a mixture of 316 and 317. In contrast, cyclobutane malonoyl peroxide 130 would be expected to react selectively with the alkene in conjugation to give 316 exclusively (Scheme 4.17).

![Scheme 4.17](image)
4.9.1.2 Conjugated dienes

Previous studies showed cyclobutane malonoyl peroxide 130 reacted efficiently with substrates capable of forming resonance stabilised carbocations. Conjugated dienes represent a class of substrates capable of forming such a stabilised carbocation and could potentially lead to a number of interesting products as illustrated with butadiene 318. (Scheme 4.18)

![Scheme 4.18](image)

**4.9.2 Catalytic variant**

Decarboxylation of cyclobutane malonoyl peroxide 130 is observed during its reaction with a range of alkenes and prohibits its use as a catalyst. Recently, chiral hydrogen bond donors\(^8\) and chiral Brønsted acids\(^2\) have been employed in a number of asymmetric transformations.

![Fig. 4.11](image)

Successful activation of 131 with a hydrogen bonding catalyst or chiral Brønsted acid may allow a catalytic amount of chiral additive to be used to induce asymmetry in the product (Fig. 4.11). The development of an asymmetric variant is currently under investigation.
4.9.3 Alternative transformations

Previous studies showed reaction of styrene 60 and cyclobutane malonoyl peroxide 130 forms 308 and 309 which interconvert slowly under neutral conditions via acyl group migration (See Section 4.6). Selective oxidation of the benzylic alcohol in 309 would give \( \alpha \)-hydroxy ketone 325. Conditions which promote both acyl group migration and selective oxidation of 309 should allow formation of 325 as the exclusive product (Scheme 4.19).

![Scheme 4.19](image)

Selective oxidation of secondary alcohols using sodium hypochlorite in acetic acid has been reported by Stevens et al.\(^83\),\(^84\) These conditions could potentially increase the rate of conversion between 308 and 309 and selectively oxidise the benzylic secondary alcohol providing 325.
Chapter 4 – Investigating Substrate Scope

4.10 Outlook

This investigation provides evidence that malonoyl peroxides represent a novel class of dihydroxylating agents. In keeping with the philosophy of developing highly practical chemistry, malonoyl peroxides 129–132 are cheap and simple to prepare and the dihydroxylation procedure easy to perform. At present, the reaction has a great deal of potential and a wide range of alkene substrates have yet to be explored. In a broader sense, the reactivity of 129–132 with a number of nucleophiles other than alkenes may reveal a wealth of alternative transformations and deserves further attention.

Exploratory reactions within this study revealed cyclopropane malonoyl peroxide 129 is a more effective dihydroxylating agent than cyclobutane malonoyl peroxide 130. Recent work in the group has shown the dihydroxylation of a range of styrene and stilbene derivatives with 129 often results in increased yields and shorter reaction times although aliphatic substrates remain problematic. Development of a catalytic variant of the reaction may provide a method of improving the yields obtained with aliphatic substrates and is currently under investigation.

Success in this area would significantly broaden the substrates scope and improve the chances of this method being adopted by the wider synthetic community. In closing, it is a personal opinion that the most interesting area of research involves determining a more accurate description of the reaction mechanism. Although synthetically challenging, understanding the reaction mechanism is crucial to allow logical design of conditions/additives which could potentially catalyse the reaction.
Chapter 5: Experimental
5.1 General experimental details

Reagents were obtained from Aldrich, Lancaster and Fluka chemical suppliers. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin. Dichloromethane was dried by refluxing over, and distilling from calcium hydride. Ethanol was dried by refluxing over magnesium, followed by distillation. Toluene was dried over sodium wire for twenty-four hours prior to use. Anhydrous diethyl ether was obtained by distillation from sodium benzophenone ketyl. Light petrol refers to petroleum ether 40-60 °C.

All reactions using air/moisture sensitive reagents were performed in oven-dried or flame-dried apparatus, under a nitrogen atmosphere. All reactions were followed and monitored by TLC, $^1$H NMR, $^{13}$C NMR and mass spectrometry as appropriate.

TLC analysis refers to analytical thin layer chromatography, using aluminium-backed plates coated with Merck Kieselgel 60 GF$_{254}$. Product spots were viewed either by the quenching of UV fluorescence, or by staining with a solution of 2 % aqueous potassium permanganate. Chromatography refers to flash column chromatography using head pressure by means of compressed air according to the procedure of Still, using Merck Kieselgel 60 H silica or Matrix silica 60.

Melting points were recorded using a Kofler Heated Stage Micro Melting Point Apparatus and are uncorrected.

Infra-red spectra were recorded in the range 4000-600 cm$^{-1}$ using a Perkin-Elmer 1600 series FTIR instrument either as a thin film, a nujol mull or dissolved in dichloromethane between sodium chloride plates. All absorptions are quoted in wave numbers (cm$^{-1}$).
Chapter 5 — Experimental

$^1$H NMR spectra ($\delta_H$) were recorded using an Avance Bruker DPX 400 instrument (400 MHz) or an Avance Bruker DPX 500 (500 MHz), with $^{13}$C NMR spectra ($\delta_C$) recorded at 100 MHz or 125 MHz respectively.

The abbreviations s, d, t, q, sept., m, and br, denote singlet, doublet, triplet, quartet, septet, multiplet and broadened resonances, respectively; all coupling constants were recorded in hertz (Hz).

Low resolution mass spectrometric data was determined using a Fisons VG Platform II Quadrupole instrument using atmospheric pressure chemical ionisation (APcI) unless otherwise stated. APcI refers to atmospheric pressure chemical ionisation, EI refers to electron ionisation and ES refers to electrospray. High resolution mass-spectrometric data was obtained courtesy of the EPSRC Mass Spectrometry Service at the University of Wales, Swansea, UK, using the ionisation methods specified. Calculated accurate masses are of the parent ion (exclusive of an electron, mass = 0.00055 Da).
Sodium peroxide (0.20 g, 2.6 mmol) was added to a mixture of chloroform (5 ml) and water (10 ml) containing NaH$_2$PO$_4$ (0.38 g, 3.2 mmol) and Na$_2$HPO$_4$ (0.38 g, 2.7 mmol). The reaction mixture was cooled to 5 °C and phthaloyl chloride (0.35 ml, 2.4 mmol) in chloroform (5 ml) added dropwise over 2 min. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Organic and aqueous layers were separated and trans-stilbene (0.51 g, 2.4 mmol) added to the chloroform layer. The reaction mixture was heated at reflux for 18 h. Removal of the solvent under reduced pressure gave intermediates 86 and 87 after purification by column chromatography eluting with ethyl acetate : petroleum ether (30 : 70)

Intermediate 86

Colourless solid (0.17 g, 21%). m.p. 210–212 °C [lit.$^{56}$ m.p. 206–207 °C]; IR (thin film)/cm$^{-1}$: 1735, 1259, 1102; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.78–7.74 (m, 2H, Ar-H), 7.61–7.59 (m, 2H, Ar-H), 7.29–7.24 (m, 5H, Ar-H), 7.19–7.17 (m, 5H, Ar-H), 6.12 (s, 2H, ArCHOCO); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.0, 136.0, 134.7, 134.5, 132.4, 128.9, 128.7, 127.5, 89.4; LRMS (Cl) $m/z$ 345.1 [M + H]$^+$; HRMS (Cl) calculated for C$_{22}$H$_{17}$O$_4$ [M + H]$^+$ 345.1121, found 345.1120.
Chapter 5 – Experimental

Intermediate 87

![Intermediate 87](image)

Colourless solid (0.12 g, 15%). m.p. 122–123 °C [lit.\textsuperscript{56} m.p. 123–126 °C]; IR (thin film)/cm\textsuperscript{-1}: 1779, 1354, 1282; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.88 (d, \(J = 8.2\) Hz, 1H, Ar-H), 7.76–7.74 (m, 2H, Ar-H), 7.63–7.60 (m, 1H, Ar-H), 7.41–7.27 (m, 10H, Ar-H), 5.35 (d, \(J = 9.0\) Hz, 1H, ArCHO), 5.18 (d, \(J = 9.0\) Hz, 1H, ArCHO); LRMS (Cl) \(m/z\) 345.1 [M + H]\textsuperscript{+}; HRMS (ES) calculated for C\textsubscript{22}H\textsubscript{17}O\textsubscript{4} [M + H]\textsuperscript{+} 345.1121, found 345.1120.

1-Phenyl-1-formyl-2-chloroethane 113\textsuperscript{63}

![1-Phenyl-1-formyl-2-chloroethane 113](image)

Styrene (0.11 ml, 1.0 mmol) was added to a solution of phthaloyl chloride (0.14 ml, 1.0 mmol) and urea hydrogen peroxide (0.10 g, 1.0 mmol) in dry DMF (5 ml). An immediate colour change yellow to colourless was observed. The reaction was stirred for 10 min. before water (20 ml) and ethyl acetate (20 ml) were added and aqueous and organic layers separated. The aqueous layer was further extracted with ethyl acetate (2 \times 10 ml) and the combined organic layers washed with brine (15 ml) and dried over MgSO\textsubscript{4}. Removal of the solvent under reduced pressure gave the title compound as a colourless oil (0.12 g, 67%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (10 : 90). IR (thin film)/cm\textsuperscript{-1}: 1725, 1494; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.09 (s, 1H, CHO), 7.34–7.26 (m, 5H, Ar-H), 6.00 (dd, \(J = 4.3\) & 8.2 Hz, 1H, ArCHO), 3.76 (dd, \(J = 8.3\) & 11.8 Hz, 1H, CHHCl), 3.68 (dd, \(J = 4.3\) & 11.8 Hz, 1H, CHHCl);
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$^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 159.7, 136.6, 129.1, 128.8, 126.7, 74.9, 46.2; LRMS (EI) $m/z$ 184.0 [M]$^+$; HRMS (EI) calculated for C$_9$H$_9$O$_2$Cl$^{15}$ [M]$^+$ 184.0286, found 184.0289.

Bis(4-nitrophenyl) phthalate 116

Phthaloyl chloride (1.0 ml, 6.9 mmol) was added dropwise to a solution of 4-nitrophenol (2.1 g, 15 mmol) and triethylamine (2.1 ml, 15 mmol) in dichloromethane (25 ml) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The resulting yellow precipitate was collected by filtration. The residue was dissolved in ethyl acetate (20 ml) and washed with NaHCO$_3$ (10 ml). Removal of the solvent under reduced pressure gave the title compound as a bright yellow solid (1.5 g, 55%). m.p. 210 °C; IR (thin film)/cm$^{-1}$: 1730, 1517, 1348, 1265; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.34 (d, $J = 7.1$ Hz, 4H, Ar-H), 8.06 (app dd, $J = 3.3$ & 5.7 Hz, 2H, Ar-H), 7.81 (app dd, $J = 3.3$ & 5.7 Hz, 2H, Ar-H), 7.45 (d, $J = 7.1$ Hz, 4H, Ar-H); LRMS (ES) $m/z$ 426.1 [M + NH$_4$]$^+$; HRMS (EI) calculated for C$_{20}$H$_{16}$O$_8$N$_3$ [M + NH$_4$]$^+$ 426.0932, found 426.0933.

General Procedure A. Synthesis of Cyclic Diethyl Malonates.

Diethyl malonate (10.0 ml, 66 mmol) and terminal dibromoalkane (66 mmol) were dissolved in ethanol (150 ml) and sodium ethoxide (9.4 g, 139 mmol) added. The reaction mixture was stirred at room temperature for 24 h. Water (100 ml) was added to the reaction mixture and the solvent removed under reduced pressure. The aqueous layer was extracted with diethyl ether (100 ml). The aqueous layer was further extracted with diethyl ether.
(4 × 50 ml) and the combined organic layers dried over MgSO₄. The reaction mixture was reduced to dryness to give the desired diethyl 1,1-cycloalkanedicarboxylate.

**Diethyl cyclopentane-1,1-dicarboxylate 134**

Following general procedure A, 1,4-dibromobutane (10.0 ml, 66 mmol) and diethyl malonate (7.9 ml, 66 mmol) gave title compound as a colourless liquid (7.1 g, 50%) after purification by distillation (110–112 °C/10 torr [lit.68 b.p. 84–86 °C/6 torr]).

IR (thin film)/cm⁻¹: 2977, 2875, 1733, 1452, 1261; ¹H NMR (400 MHz, CDCl₃) δ 4.16 (q, J = 7.1 Hz, 4H, CH₂CH₃), 2.13–2.09 (m, 4H, CH₂CH₂), 1.63–1.60 (m, 4H, CH₂CH₂), 1.18 (t, J = 7.1 Hz, 6H, CH₂CH₃); ¹³C NMR (62.5 MHz, CDCl₃) δ 172.6, 61.1, 60.3, 34.4, 25.4, 14.0; LRMS (APCI) m/z 215.1 [M + H]⁺; HRMS (MALDI) calculated for C₁₁H₁₉O₄ [M + H]⁺ 215.1278, found 215.1278.

**Diethyl cyclohexane-1,1-dicarboxylate 135**

Following general procedure A, 1,5-dibromobutane (10.0 ml, 73 mmol) and diethyl malonate (11.1 ml, 73 mmol) gave title compound as a colourless liquid (9.8 g, 59%) after purification by distillation (119–121 °C/10 torr [lit.68 b.p. 98–100 °C/6 torr]).

IR (thin film)/cm⁻¹: 2939, 2861, 1733, 1451, 1305; ¹H NMR (400 MHz, CDCl₃) δ 4.11 (q, J = 7.1 Hz, 4H, CH₂CH₃), 1.92–1.89 (m, 4H, CH₂CH₂CH₂), 1.47–1.44 (m, 4H,
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Diethyl cyclopropane-1,1-dicarboxylate 133

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{CH}_2\text{OEt} & \quad \text{OEt} \\
\text{OEt} & \quad \text{OEt}
\end{align*}
\]

Diethyl malonate (9.5 ml, 63 mmol), 1,2-dibromoethane (10.0 ml, 116 mmol), potassium carbonate (64 g, 464 mmol) and tetrabutylammonium hydrogensulfate (1.00 g, 2.9 mmol) were dissolved in DMSO (50 ml) and the reaction mixture stirred at room temperature for 24 h. The reaction mixture was poured into water (300 ml) and extracted with diethyl ether (100 ml). The aqueous layer was further extracted with diethyl ether (4 x 100 ml) and the combined organic layers washed with brine (100 ml) and dried over MgSO\(_4\). Removal of the solvent under reduced pressure gave the title compound as a pale yellow liquid (9.4 g, 80%) after purification by distillation (94–96 °C/15 torr [lit.\(^69\) b.p. 115–118 °C/15 torr]). IR (thin film)/cm\(^{-1}\): 2985, 2909, 1729, 1320, 1209; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.16 (q, \(J = 7.2\) Hz, 4H, CH\(_2\)CH\(_3\)), 1.38 (s, 4H, (CH\(_2\)H\(_2\))\(_2\)), 1.24 (t, \(J = 7.1\) Hz, 6H, CH\(_3\)CH\(_3\)); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)) \(\delta\) 169.7, 61.3, 28.2, 16.2, 14.0; LRMS (Cl) \(m/z\) 187.2 [M + H]\(^+\); HRMS (ES) calculated for C\(_9\)H\(_{15}\)O\(_4\) [M + H]\(^+\) 187.0965, found 187.0962.
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General Procedure B. Synthesis of Cycloalkane 1,1-dicarboxylic acids.

Diethyl cycloalkane-1,1-dicarboxylate (5.0 mmol) was dissolved in THF : H2O (5 ml : 5 ml) and LiOH (1.2 g, 28 mmol) added in a single portion. The reaction mixture was vigorously stirred at room temperature for 48 h. The solvent was removed under reduced pressure and the aqueous layer extracted with ethyl acetate (50 ml). The aqueous layer was acidified to pH 1 with 8 M HCl and extracted with ethyl acetate (100 ml). The aqueous layer was further extracted with ethyl acetate (2 x 50 ml) and the combined organic layers washed with brine (50 ml) and dried over MgSO4. Removal of the solvent under reduced pressure gave the desired cycloalkane-1,1-dicarboxylic acid.

Cyclopropane-1,1-dicarboxylic acid 137

Following general procedure B, diethyl cyclopropane-1,1-dicarboxylate (1.00 g, 5.4 mmol) gave the title compound as a colourless solid (0.56 g, 80%). m.p. 128–130 °C [lit.87 m.p. 139 °C]; 1H NMR (250 MHz, DMSO) δ 1.32 (s, 4H, (CH2)2); 13C NMR (62.5 MHz, DMSO) δ 172.2, 27.7, 16.6; LRMS (El) m/z 112.0 [M - H2O]+; HRMS (El) calculated for C5H6O4 [M]+ 130.0266, found 130.0268.
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Cyclopentane-1,1-dicarboxylic acid 139

Following general procedure B, diethyl cyclopentane-1,1-dicarboxylate (1.00 g, 4.7 mmol) gave the title compound as a colourless solid (0.60 g, 78%). m.p. 165 °C [lit. m.p. 157–158 °C]; $^1$H NMR (400 MHz, DMSO) $\delta$ 2.04–2.01 (m, 4H, CH$_2$CH$_2$), 1.59–1.56 (m, 4H, CH$_2$CH$_2$); $^{13}$C NMR (62.5 MHz, DMSO) $\delta$ 173.7, 59.7, 33.8, 25.0; LRMS (Cl) $m/z$ 176.3 [M + NH$_4$]$^+$; HRMS (ES) calculated for C$_7$H$_4$O$_4$N [M + NH$_4$]$^+$ 176.0917, found 176.0917.

Cyclohexane-1,1-dicarboxylic acid 140

Following general procedure B, diethyl cyclohexane-1,1-dicarboxylate (1.00 g, 4.4 mmol) gave the title compound as a colourless solid (0.61 g, 81%). m.p. 170–172 °C [lit. m.p. 170–171 °C]; $^1$H NMR (400 MHz, DMSO) $\delta$ 3.36 (br s, 2H, OH), 1.82–1.79 (m, 4H, CH$_2$CH$_2$CH$_2$), 1.49–1.40 (m, 4H, CH$_2$CH$_2$CH$_2$), 1.36–1.35 (m, 2H, CH$_2$CH$_2$CH$_2$); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 173.1, 53.9, 30.9, 24.8, 22.5; LRMS (El) $m/z$ 154.1 [M – H$_2$O]$^+$; HRMS (El) calculated for C$_8$H$_{10}$O$_3$ [M – H$_2$O]$^+$ 154.0630, found 154.0628.
General Procedure C. Synthesis of Malonoyl Peroxides

Methane sulfonic acid (30 ml) was placed in a round bottomed flask equipped with large magnetic stirrer bar and immersed in a bath of water at 22 °C. Urea hydrogen peroxide (9.82 g, 104 mmol) was added in a single portion and stirred for 30 seconds. Cycloalkane-1,1-dicarboxylic acid (35 mmol) was added in a single portion and the reaction stirred vigorously for 18 h. The reaction mixture was poured into a mixture of ice (80 g) and ethyl acetate (100 ml) and the layers separated. The aqueous layer was washed with ethyl acetate (2 × 100 ml) and the combined organic layers were washed with NaHCO₃ (2 × 50 ml), brine (20 ml) and dried over MgSO₄. Removal of the solvent under reduced pressure gave the desired malonoyl peroxide.

Cyclopropane malonoyl peroxide 129

Following general procedure C, cyclopropane-1,1-dicarboxylic acid (0.20 g, 1.5 mmol) gave the title compound as a colourless crystalline solid (0.15 g, 79%) after purification by column chromatography eluting with chloroform. m.p. 84 °C; IR (thin film)/cm⁻¹: 3025, 1827, 1798, 1358; ¹H NMR (400 MHz, CDCl₃) δ 2.04 (s, 4H, (CH₂)₂); ¹³C NMR (62.5 MHz, CDCl₃) δ 172.2, 23.7, 19.8.

¹ Unable to obtain low or high resolution mass spectrometry data for malonoyl peroxides using in-house or Swansea national mass spectrometry service – See appendix for X-Ray data for peroxides 129–132.
Cyclobutane malonoyl peroxide 130

Following general procedure C, cyclobutane-1,1-dicarboxylic acid (5.00 g, 35 mmol) gave the title compound as a colourless crystalline solid (4.00 g, 80%) after purification by column chromatography eluting with chloroform. m.p. 63 °C; IR (thin film)/cm⁻¹: 1799, 1269; ¹H NMR (250 MHz, CDCl₃) δ 2.65 (t, J = 8.1 Hz, 4H, (CH₂)₂CH₂), 2.37–2.23 (m, 2H, (CH₂)₂CH₂); ¹³C NMR (62.5 MHz, CDCl₃) δ 173.9, 40.5, 29.0, 16.3.

Cyclopentane malonoyl peroxide 131

Following general procedure C, cyclopentane-1,1-dicarboxylic acid (1.00 g, 6.3 mmol) gave the title compound as a colourless crystalline solid (0.60 g, 60%) after purification by column chromatography eluting with chloroform. m.p. 41 °C; IR (thin film)/cm⁻¹: 2973, 1797, 1712, 1265; ¹H NMR (400 MHz, CDCl₃) δ 2.23–2.19 (m, 4H, CH₂CH₂), 1.98–1.93 (m, 4H, CH₂CH₂); ¹³C NMR (62.5 MHz, CDCl₃) δ 175.7, 46.8, 37.7, 26.7.
Following general procedure C, cyclohexane-1,1-dicarboxylic acid (1.00 g, 5.8 mmol) gave the title compound as a colourless crystalline solid (0.78 g, 79%) after purification by column chromatography. m.p. 41–42 °C. IR (thin film)/cm⁻¹: 2944, 1794, 1223; ¹H NMR (400 MHz, CDCl₃) δ 1.92–1.89 (m, 4H, CH₂CH₂CH₂), 1.78–1.72 (m, 4H, CH₂CH₂CH₂), 1.57–1.51 (m, 2H, CH₂CH₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 42.1, 30.9, 24.5, 19.6.

**General Procedure D. Synthesis of intermediates via coupling reaction**

Cyclobutanecarboxylic acid (0.47 ml, 5.0 mmol) was added to a solution of N,N'-dicyclohexylcarbodiimide (1.00 g, 5.0 mmol) and 4-di(methylamino)pyridine (0.06 g, 0.5 mmol) in dichloromethane. The solution was stirred at room temperature for 30 min. before hydrobenzoin (5.0 mmol) was added. The reaction was stirred at room temperature for 18 h. The reaction was filtered and the solvent removed under reduced pressure to give the desired intermediate.
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1-(O-Oxocyclobutyl)-1,2-diphenylethane-1,2-diol 141

Following general procedure D, meso-hydrobenzoin (1.07 g, 5.0 mmol) gave the title compound as a colourless solid (1.08 g, 73%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80). m.p. 91–92 °C. IR (thin film)/cm⁻¹: 3469, 1725, 1355, 1250; ¹H NMR (250 MHz, CDCl₃) δ 7.28–7.06 (m, 10H, Ar-H), 5.83 (d, \( J = 6.4 \) Hz, 1H, ArCHO), 4.89 (d, \( J = 6.4 \) Hz, 1H, ArCHOH), 3.03 (quin, \( J = 8.2 \) Hz, 1H, CH(CH₂)₂CH₂), 2.35–1.50 (m, 6H, CH(CH₂)₃); ¹³C NMR (62.5 MHz, CDCl₃) δ 174.1, 139.7, 136.9, 128.4, 128.3, 128.1, 127.6, 127.1, 78.4, 38.1, 25.1, 24.9, 18.4 (only 13 peaks visible); LRMS (Cl) m/z 297.2 [M + H]⁺; HRMS (ES) calculated for C₁₉H₂₄O₃N [M + NH₄]⁺ 314.1751, found 314.1751.

1-(O-Oxocyclobutyl)-1,2-diphenylethane-1,2-diol 141

Following general procedure D, (±)-hydrobenzoin (1.07 g, 5.0 mmol) gave the title compound as a colourless solid (0.94 g, 64%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80). m.p. 75–76 °C. IR (thin film)/cm⁻¹: 3457, 2947, 1726, 1368; ¹H NMR (250 MHz, CDCl₃) δ 7.30–7.15 (m, 10H, Ar-H), 5.88 (d, \( J = 7.2 \) Hz, 1H, ArCHO), 4.96 (d, \( J = 7.2 \) Hz, 1H, ArCHOH), 3.27 (quin, \( J = 8.4 \) Hz, 1H, CH(CH₂)₂CH₂), 2.36–1.84 (m, 6H, CH(CH₂)₃); ¹³C NMR (62.5 MHz, CDCl₃) δ 174.5, 139.0, 137.1, 128.2, 128.1, 128.1, 127.1, 127.0, 79.7, 77.2, 38.1, 25.1, 25.1, 18.4 (only 14
peaks visible); LRMS (El) m/z 297.2 [M + H]+; HRMS (ES) calculated for C_{19}H_{24}O_{3}N [M + NH_{4}]^{+} 314.1751, found 314.1751.

**General procedure E. Preparation of intermediates via peroxide reaction**

Alkene (1.0 mmol) was added dropwise to a solution of cyclobutane malonoyl peroxide (0.17 g, 1.2 mmol) in chloroform (4 ml). H_{2}O (18 μl, 1.0 mmol) was added and the reaction mixture was heated at 40 °C for 18 h. Removal of the solvent under reduced pressure gave the desired intermediate.

**Preparation of intermediates 308 and 309**

Following general procedure E, styrene (0.11 ml, 1.0 mmol), gave a mixture of intermediates 308 and 309 after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80).

**2-(O-Oxocyclobutyl)-1-phenylethane-1,2-diol 309**

Colourless oil (0.08 g, 38%). IR (thin film)/cm⁻¹: 3433, 1731, 1168; ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.32 (m, 5H, Ar-H), 4.99 (dd, J = 3.2 & 8.4 Hz, 1H, ArCHOH), 4.32 (dd, J = 3.2 & 11.6 Hz, 1H, CHHOCO), 4.20 (dd, J = 8.4 & 11.6 Hz, 1H, CHHOCO), 3.21 (quin, J = 8.4 Hz, 1H, CH(CH₂)₂CH₂), 2.53 (bs, 1H, OH), 2.36-2.19 (m, 4H,
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CH(CH₂)₂CH₂), 2.07–1.98 (m, 2H, CH(CH₂)₂CH₂); ¹³C NMR (125 MHz, CDCl₃) δ 175.6, 139.8, 128.6, 128.2, 126.2, 72.6, 69.2, 38.0, 25.3, 18.4; LRMS (El) m/z 202.1 [M – H₂O]⁺; HRMS (ES) calculated for C₁₃H₁₄O₂ [M – H₂O]⁺ 202.0994, found 202.0995.

1-Phenyl-1-cyclobutane carboxylate ethane-1,2-diol 308

![Diagram of 1-Phenyl-1-cyclobutane carboxylate ethane-1,2-diol 308]

Colourless oil (0.09 g, 43%). IR (thin film)/cm⁻¹: 3485, 1726, 1173; ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.22 (m, 5H, Ar-H), 5.77 (dd, J = 4.2 & 7.4 Hz, 1H, ArCHOCO), 3.80 (dd, J = 7.6 & 12.0 Hz, 1H, CHHOH), 3.73 (dd, J = 4.0 & 12.0 Hz, 1H, CHHOH), 3.17 (quin, J = 8.4 Hz, 1H, CH(CH₂)₂CH₂), 2.30–2.11 (m, 4H, CH(CH₂)₂CH₂), 2.02–1.83 (m, 2H, CH(CH₂)₂CH₂); ¹³C NMR (125 MHz, CDCl₃) δ 175.0, 137.3, 128.6, 128.3, 126.5, 76.6, 66.2, 38.2, 25.3, 25.1, 18.4; LRMS (El) m/z 202.1 [M – H₂O]⁺; HRMS (ES) calculated for C₁₃H₁₄O₂ [M – H₂O]⁺ 202.0994, found 202.0990.

Preparation of intermediates 143, 144 & 148

Following general procedure E, 4-methylstyrene (0.15 ml, 1.1 mmol), gave a mixture of intermediates 143, 144 & 148 after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80).
2-\((O\text{-Oxocyclobutyl})\)-1-(p-Tolyl) ethane-1,2-diol 143

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\text{ Colourless oil (0.10 g, 37%). IR (thin film)/cm}^{-1}: 3471, 3066, 1726, 1252, 1215; ^1H NMR (400 MHz, CDCl}_3) \delta 7.20 (d, J = 8.0 Hz, 2H, Ar-H), 7.10 (d, J = 7.9 Hz, 2H, Ar-H), 4.84 (dd, J = 3.2 & 8.3 Hz, 1H, ArCH(OH)), 4.19 (dd, J = 3.3 & 11.6 Hz, 1H, CHHOCO), 4.08 (dd, J = 8.4 & 11.6 Hz, 1H, CHHOCO), 3.11 (quin, J = 8.5 Hz, 1H, CH(CH}_2}_2CH}_2), 2.50 (bs, 1H, OH), 2.27 (s, 3H, CH}_3), 2.24–2.11 (m, 4H, CH(CH}_2}_2CH}_2), 1.91–1.83 (m, 2H, CH(CH}_2}_2CH}_2); ^13C NMR (62.5 MHz, CDCl}_3) \delta 175.7, 137.9, 137.0, 129.2, 126.1, 72.4, 69.2, 38.0, 25.3, 21.1, 18.4; LRMS (EI) m/z 216.1 [M – H}_2O]^+; HRMS (EI) calculated for C\textsubscript{14}H\textsubscript{16}O\textsubscript{2} [M – H}_2O]^+ 216.1150, found 216.1150.

1-\((O\text{-Oxocyclobutyl})\)-1-(p-Tolyl) ethane-1,2-diol 144

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\text{ Colourless oil (0.12 g, 45%). IR (thin film)/cm}^{-1}: 3480, 3018, 1728, 1252; ^1H NMR (400 MHz, CDCl}_3) \delta 7.15 (d, J = 8.1 Hz, 2H, Ar-H), 7.09 (d, J = 8.1 Hz, 2H, Ar-H), 5.73 (dd, J = 4.1 & 7.7 Hz, 1H, ArCHOCO), 3.78 (dd, J = 7.7 & 12.0 Hz, 1H, CHHOH), 3.70 (dd, J = 4.1 & 12.0 Hz, 1H, CHHOH), 3.14 (quin, J = 8.5 Hz, 1H, CH(CH}_2}_2CH}_2), 2.25 (s, 3H, CH}_3), 2.24–2.11 (m, 4H, CH(CH}_2}_2CH}_2), 1.91–1.82 (m, 2H, CH(CH}_2}_2CH}_2); ^13C NMR (62.5 MHz, CDCl}_3) \delta 175.1, 138.2, 134.3, 129.3, 126.5, 76.5, 66.1, 38.2, 25.3, 25.1, 21.2, 18.4; LRMS (EI) m/z 216.1 [M – H}_2O]^+; HRMS (EI) calculated for C\textsubscript{14}H\textsubscript{16}O\textsubscript{2} [M – H}_2O]^+ 216.1150, found 216.1148.
Intermediate 148

Colourless solid (0.01 g, 4%). IR (thin film)/cm⁻¹: 2106, 1638; ¹H NMR (400 MHz, CDCl₃) δ 7.20–7.14 (m, 4H, Ar-H), 5.54 (dd, J = 1.8 & 9.0 Hz, 1H, ArCHCH₂), 4.45 (dd, J = 9.0 & 14.2 Hz, 1H, CHHOOC), 4.33 (dd, J = 1.9 & 14.2 Hz, 1H, CHHOCO), 2.87–2.80 (m, 4H, (CH₂)₂CH₂), 2.30 (s, 3H, CH₃), 2.12–2.06 (m, 2H, (CH₂)₂CH₂); ¹³C NMR (62.5 MHz, CDCl₃) δ 169.2, 168.9, 139.5, 131.5, 129.8, 125.9, 79.8, 71.5, 53.9, 31.5, 31.4, 21.2, 15.9; LRMS (ES) m/z 261.1 [M + H]⁺; HRMS (MALDI) calculated for C₁₅H₁₇O₄ [M + H]⁺ 261.1121, found 261.1118.

Preparation of intermediates 242 and 243

Following general procedure E, 4-acetoxystyrene (0.15 ml, 1.0 mmol) gave a mixture of intermediates 242 and 243 after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80).
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1-(O-Oxocyclobutyl)-1-(4-acetoxyphenyl)ethane 1,2-diol 242

![Structure of 1-(O-Oxocyclobutyl)-1-(4-acetoxyphenyl)ethane 1,2-diol 242]

Colourless oil (0.10 g, 37%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.01 (d, $J = 8.6$ Hz, 2H, Ar-H), 5.77 (dd, $J = 4.3$ & 7.4 Hz, 1H, ArCHOCO), 3.77 (dd, $J = 7.4$ & 12.0 Hz, 1H, CHHOH), 3.71 (dd, $J = 4.3$ & 12.0 Hz, 1H, CHHOH), 3.16 (quin, $J = 8.0$ Hz, 1H, CH(CH$_2$)$_2$CH$_2$), 2.22 (s, 3H, CH$_3$), 2.18-1.88 (m, 6H, CH(CH$_2$)$_2$CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.9, 169.4, 150.6, 135.0, 127.8, 121.8, 75.9, 66.0, 38.1, 25.3, 21.1, 18.4; LRMS (Cl) m/z 260.1 [M – H$_2$O]$^+$; HRMS (ES) calculated for C$_{15}$H$_{16}$O$_4$ [M – H$_2$O]$^+$ 260.1049, found 260.1040.

2-(O-Oxocyclobutyl)-1-(4-acetoxyphenyl)ethane 1,2-diol 243

![Structure of 2-(O-Oxocyclobutyl)-1-(4-acetoxyphenyl)ethane 1,2-diol 243]

Colourless oil (0.10 g, 38%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32 (d, $J = 8.7$ Hz, 2H, Ar-H), 7.00 (d, $J = 8.6$ Hz, 2H, Ar-H), 4.86 (dd, $J = 3.3$ & 8.1 Hz, 1H, ArCHOCO), 4.19 (d, $J = 3.5$ & 11.5 Hz, 1H, CHHOOC), 4.07 (dd, $J = 8.2$ & 11.5 Hz, 1H, CHHOOC), 3.16 (quin, $J = 8.5$ Hz, 1H, CH(CH$_2$)$_2$CH$_2$), 2.22 (s, 3H, CH$_3$), 2.19-1.83 (m, 6H, CH(CH$_2$)$_2$CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.7, 169.5, 150.4, 137.6, 127.3, 121.8, 71.9, 69.0, 38.0, 25.3, 21.1, 18.4; LRMS (Cl) m/z 260.1 [M – H$_2$O]$^+$; HRMS (ES) calculated for C$_{15}$H$_{16}$O$_4$ [M – H$_2$O]$^+$ 260.1049, found 260.1047.
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1-(Methoxycarbonyl)cyclobutanecarboxylic acid

Sodium methoxide (0.05 g, 1.0 mmol) was added to a solution of cyclobutane malonoyl peroxide (0.14 g, 1.0 mmol) in methanol (5 ml) and the reaction stirred at room temperature for 10 min. Water (10 ml) was added and methanol removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (10 ml). The aqueous layer was acidified with 2M HCl and extracted with ethyl acetate (10 ml). The solvent was removed under reduced pressure to give the title compound as a colourless oil (0.13 g, 83%).

\[
\begin{align*}
\text{H} NMR (400 MHz, CDCl}_3 & \delta 3.72 (s, 3H, OCH}_3), 2.53 (t, J = 8.0 Hz, 4H, CH}_2(CH}_2)_2), 1.96-1.80 (m, 2H, CH}_2(CH}_2)_2); \\
\text{C} NMR (62.5 MHz, CDCl}_3 & \delta 177.6, 172.1, 52.8, 52.5, 28.9, 16.2; \\
\text{LRMS (ES) m/z} & 140.1 [M - H}_2O]^{+}; \text{HRMS (EI) calculated for C}_7H}_8O}_3 [M - H}_2O]^{+} 140.0473, \text{found} 140.0475.
\end{align*}
\]

General Procedure F. Synthesis of Diols with Cyclobutane Malonoyl Peroxide

Alkene (0.7 mmol) was added dropwise to a solution of cyclobutane malonoyl peroxide (0.15 g, 1.1 mmol) in chloroform (2 ml). H2O (13 μl, 0.7 mmol) was added and the reaction mixture was heated at 40 °C for 18 h (or consumption of starting alkene as determined by TLC). The reaction mixture was reduced to dryness and 1M NaOH (10 ml) added. The reaction mixture was heated at 40 °C for 18 h (or until completion by TLC). The aqueous layer was extracted with chloroform (15 ml). The aqueous layer was further extracted with chloroform (2 × 20 ml), the combined organic layers washed with brine (10 ml) and dried over MgSO4. The solvent was removed under reduced pressure to give the desired diol.
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General Procedure G. Synthesis of Diols via Modified Sharpless AD Procedure

Potassium ferricyanide (1.96 g, 6.0 mmol), potassium carbonate (0.82 g, 6.0 mmol), potassium osmate dihydrate (1.5 mg, 0.1 mmol), quinuclidine (2.2 mg, 0.1 mmol) and methanesulfonamide (0.19 g, 2.0 mmol) were stirred together for 30 min. at room temperature, after which water (10 ml) and tert-butanol (10 ml) were added. Alkene (2 mmol) was added and stirring was continued at room temperature for 2 days. Following reaction completion (by TLC) anhydrous sodium sulfite (3 g, 28 mmol) was added and the mixture stirred for 1 h. Dichloromethane (30 ml) was added and the organic and aqueous layers were separated. The aqueous phase was further extracted with dichloromethane (3 x 50 ml) and the combined organic layers were washed with 2M KOH solution (2 x 30 ml), water (2 x 30 ml) and dried over MgSO₄. Removal of the solvent under reduced pressure gave the desired diol.

1-Phenylethane-1,2-diol 64

Following general procedure G, styrene (0.11 ml, 1.0 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 78%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 61 °C [lit.90 m.p. 67 °C]; IR (thin film)/cm⁻¹: 3394, 2926, 1613; ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.23 (m, 5H, Ar-H), 4.76 (dd, J = 3.5 & 8.2 Hz, 1H, ArCHOH), 3.69 (dd, J = 3.5 & 11.3 Hz, 1H, CHHOH), 3.59 (dd, J = 8.2 & 11.3 Hz, 1H, CHHOH); ¹³C NMR (100 MHz, CDCl₃) δ 140.9, 129.0, 128.5, 126.5, 75.1, 68.5; LRMS (El) m/z 138.1 [M]+; HRMS (El) calculated for C₈H₁₀O₂ [M]+ 138.0681, found 138.0676.
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1-p-Tolylethane-1,2-diol 145

Following general procedure F, 4-methylstyrene (0.19 ml, 1.4 mmol) gave the title compound as a colourless crystalline solid (0.18 g, 84%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 70–72 °C [lit.91 m.p. 76–77 °C]; IR (thin film)/cm⁻¹: 3371, 2925, 1647, 1327; ¹H NMR (400 MHz, CDCl₃) δ 7.11 (d, J = 8.1 Hz, 2H, Ar-H), 7.04 (d, J = 8.0 Hz, 2H, Ar-H), 4.64 (dd, J = 3.4 & 8.4 Hz, 1H, ArCHOH), 3.57 (dd, J = 3.5 & 11.5 Hz, 1H, CHHOH), 3.50 (dd, J = 8.4 & 11.5 Hz, 1H, CHHOH), 2.28 (s, 3H, CH₃); ¹³C NMR (62.5 MHz, CDCl₃) δ 137.6, 137.6, 129.2, 126.1, 74.6, 68.1, 21.2; LRMS (EI) m/z 152.1 [M⁺]; HRMS (EI) calculated for C₉H₁₂O₂ [M⁺] 152.0837, found 152.0840.

1-m-Tolylethane-1,2-diol 211

Following general procedure F, 3-methylstyrene (0.12 ml, 0.9 mmol) gave the title compound as a colourless crystalline solid (0.09 g, 65%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 70–72 °C; IR (thin film)/cm⁻¹: 3159, 2924, 1483; ¹H NMR (400 MHz, CDCl₃) δ 7.15–7.12 (m, 1H, Ar-H), 7.05–7.00 (m, 3H, Ar-H), 4.65 (dd, J = 3.2 & 8.4 Hz, 1H, ArCHOH), 3.59 (dd, J = 3.3 & 11.5 Hz, 1H, CHHOH), 3.51 (dd, J = 8.6 & 11.4 Hz, 1H, CHHOH), 3.44 (bs, 2H, OH), 2.24 (s, 3H, CH₃); ¹³C NMR (62.5 MHz, CDCl₃) δ 141.1, 138.8, 129.3, 129.1, 127.4, 123.8, 75.4, 68.7, 22.1; LRMS (EI) m/z 152.1 [M⁺]; HRMS (EI) calculated for C₉H₁₂O₂ [M⁺] 152.0837, found 152.0836.
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1-o-Tolylethane-1,2-diol 213

Following general procedure F, 2-methylstyrene (93 µl, 0.7 mmol) gave the title compound as a colourless crystalline solid (0.08 g, 80%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 104–105 °C; IR (thin film)/cm\(^{-1}\): 3258, 2924, 1356, 1066; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.43–7.41 (m, 1H, Ar-H), 7.19–7.07 (m, 3H, Ar-H), 4.99 (dd, \(J = 3.2 \& 8.4\) Hz, 1H, ArCHOH), 3.66 (dd, \(J = 3.2 \& 11.4\) Hz, 1H, CHHOH), 3.54 (dd, \(J = 8.5 \& 11.4\) Hz, 1H, CHHOH), 2.27 (s, 3H, CH\(_3\)); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 138.5, 134.8, 130.5, 127.8, 126.3, 125.7, 71.5, 67.0, 19.1; LRMS (EI) \(m/z\) 152.1 [M]\(^+\); HRMS (EI) calculated for C\(_9\)H\(_{12}\)O\(_2\) [M]\(^+\) 152.0837, found 152.0842.

1-Mesitylethane-1,2-diol 215

Following general procedure F, 2,4,6-trimethylstyrene (0.15 ml, 0.9 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 65%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 110–111 °C; IR (thin film)/cm\(^{-1}\): 3365, 2923, 1611; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.76 (s, 2H, Ar-H), 5.18 (dd, \(J = 3.8 \& 9.9\) Hz, 1H, ArCHOH), 3.89 (dd, \(J = 10.0 \& 11.4\) Hz, 1H, CHHOH), 3.53 (dd, \(J = 3.8 \& 11.5\) Hz, 1H, CHHOH), 2.33 (s, 6H, CH\(_3\)), 2.17 (s, 3H, CH\(_3\)); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 137.2, 136.7, 132.5, 130.2, 127.7, 126.3, 72.7, 64.7, 20.8, 20.8; LRMS (EI) \(m/z\) 180.1 [M]\(^+\); HRMS (EI) calculated for C\(_{11}\)H\(_{16}\)O\(_2\) [M]\(^+\) 180.1150, found 180.1145.

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1-(4-Chlorophenyl)ethane-1,2-diol 217

Following general procedure F, 4-chlorostyrene (0.12 ml, 1.0 mmol) gave the title compound as a colourless crystalline solid (0.13 g, 77%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 76-77 °C; IR (thin film)/cm⁻¹: 3612, 3399, 1598, 1077; ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.22 (m, 4H, Ar-H), 4.74 (dd, J = 3.5 & 8.2 Hz, 1H, ArCHOH), 3.68 (dd, J = 3.5 & 11.3 Hz, 1H, CHHOH), 3.54 (dd, J = 8.2 & 11.3 Hz, 1H, CHHOH); ¹³C NMR (125 MHz, CDCl₃) δ 138.9, 133.8, 128.7, 127.5, 74.0, 68.0; LRMS (Cl) m/z 190.2 [M + NH₄⁺]; HRMS (ES) calculated for C₈H₁₀ClO₂N [M + NH₄⁺] 190.0629, found 190.0626.

1-(3-Chlorophenyl)ethane-1,2-diol 219

Following general procedure F, 3-chlorostyrene (0.12 ml, 0.9 mmol) gave the title compound as a colourless crystalline solid (0.05 g, 32%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). IR (thin film)/cm⁻¹: 3378, 2929, 2878, 1574; ¹H NMR (400 MHz, CDCl₃): δ 7.24 (s, 1H, Ar-H), 7.19-7.14 (m, 2H, Ar-H), 7.10-7.08 (m, 1H, Ar-H), 4.65 (dd, J = 3.1 & 8.4 Hz, 1H, ArCHOH), 3.59 (dd, J = 3.1 & 11.5 Hz, 1H, CHHOH), 3.48 (dd, J = 8.4 & 11.5 Hz, 1H, CHHOH), 3.22 (bs, 1H, OH), 2.71 (bs, 1H, OH); ¹³C NMR (125 MHz, CDCl₃) δ 142.5, 134.5, 129.8, 128.1, 126.3, 124.2, 74.1, 67.8; LRMS (EI) m/z 172.0 [M⁺]; HRMS (EI) calculated for C₈H₇O₂Cl [M⁺] 172.0291, found 172.0289.
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1-(2-Chlorophenyl)ethane-1,2-diol 221

Following general procedure F, 2-chlorostyrene (0.21 ml, 1.6 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 38%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 101–104 °C; IR (thin film)/cm⁻¹: 3164, 1470, 1361, 1068; ¹H NMR (250 MHz, CDCℓ₃): δ 7.53 (dd, J = 1.7 & 7.4 Hz, 1H, Ar-H), 7.30–7.14 (m, 3H, Ar-H), 5.18 (dd, J = 3.0 & 7.9 Hz, 1H, ArCHOH), 3.84 (dd, J = 2.8 & 11.3 Hz, 1H, CHHOH), 3.51 (dd, J = 7.9 & 11.3 Hz, 1H, CHHOH), 2.68 (bs, 1H, OH), 2.08 (bs, 1H, OH); ¹³C NMR (125 MHz, CDCℓ₃) δ 137.8, 132.0, 129.5, 129.0, 127.6, 127.1, 71.4, 66.3; LRMS (EI) m/z 172.0 [M]+; HRMS (EI) calculated for C₈H₉O₂Cl [M]+ 172.0291, found 172.0288.

1-(4-Bromophenyl)ethane-1,2-diol 223

Following general procedure F, 4-bromostyrene (0.11 ml, 0.7 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 74%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 98–99 °C [lit.96 m.p. 100–101 °C]; IR (thin film)/cm⁻¹: 3313, 2930, 1590; ¹H NMR (400 MHz, CDCℓ₃) δ 7.43 (d, J = 8.4 Hz, 2H, Ar-H), 7.19 (d, J = 8.4 Hz, 2H, Ar-H), 4.72 (dd, J = 3.4 & 8.1 Hz, 1H, ArCHOH), 3.68 (dd, J = 3.5 & 11.3 Hz, 1H, CHHOH), 3.54 (dd, J = 8.2 & 11.3 Hz, 1H, CHHHO); ¹³C NMR (62.5 MHz, CDCℓ₃) δ 139.5, 131.7, 127.8, 121.9, 74.1, 67.9; LRMS (EI) m/z 216.0 [M]+; HRMS (EI) calculated for C₈H₉O₂Br [M]+ 215.9786, found 215.9790.
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1-(4-Methoxyphenyl)ethane-1,2-diol 225

Following general procedure F, 4-methoxy styrene (0.15 ml, 1.2 mmol) gave the title compound as a colourless crystalline solid (0.16 g, 78%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 78-79 °C [lit. m.p. 79-81 °C]; IR (thin film)/cm⁻¹: 3359, 2935, 2839, 1612, 1246; 
¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, J = 8.6 Hz, 2H, Ar-H), 6.83 (d, J = 8.7 Hz, 2H, Ar-H), 4.71 (dd, J = 3.8 & 7.8 Hz, 1H, ArCHOH), 3.74 (s, 3H, OCH₃), 3.65-3.59 (m, 2H, CH₂OH), 2.35 (bs, 1H, OH), 1.96 (bs, 2H, OH); 
¹³C NMR (62.5 MHz, CDCl₃) δ 159.4, 132.7, 127.4, 114.0, 74.3, 68.1, 55.3; LRMS (El) m/z 168.2 [M]+; HRMS (ES) calculated for C₉H₈O₃Na [M + Na]+ 191.0679, found 191.0676.

1-(3-Nitrophenyl)ethane-1,2-diol 227⁹⁸

Following general procedure F, 3-nitrostyrene (0.29 ml, 2.1 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 30%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 74-75 °C; 
¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H, Ar-H), 8.11-8.08 (m, 1H, Ar-H), 7.66 (d, J = 7.7 Hz, 1H, Ar-H), 7.48 (app t, J = 7.9 Hz, 1H, Ar-H), 4.89 (dd, J = 3.4 & 7.9 Hz, 1H, ArCHOH), 3.79 (dd, J = 3.4 & 11.2 Hz, 1H, CHHOH), 3.60 (dd, J = 7.9 & 11.2 Hz, 1H, CHHOH), 2.83 (bs, 1H, OH), 1.98 (bs, 1H, OH); 
¹³C NMR (100 MHz, CDCl₃) δ 142.7, 132.2, 129.5, 122.9, 121.2,
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73.6, 67.7 (one carbon missing); LRMS (EI) m/z 165.0 [M – H₂O]⁺; HRMS (EI) calculated for C₈H₇O₂N [M – H₂O]⁺ 165.0426, found 165.0434.

1-(2-Naphthyl)ethane-1,2-diol 229

Following general procedure F, 2-vinyl(naphthalene (0.11 g, 0.7 mmol) gave the title compound as a pale orange solid (0.09 g, 65%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 126–127 °C [lit.⁴¹ m.p. 134–135 °C]; IR (thin film)/cm⁻¹: 3187, 2930, 1599; ¹H NMR (400 MHz, CDCl₃) δ 7.86–7.83 (m, 4H, Ar-H), 7.52–7.46 (m, 3H, Ar-H), 5.03–4.99 (m, 1H, ArCHOH), 3.89–3.73 (m, 2H, CH₂OH), 2.60 (d, J = 3.2 Hz, 1H, CHO_H), 2.05 (dd, J = 4.8 & 7.2 Hz, 1H, CH₂OH); ¹³C NMR (62.5 MHz, DMSO) δ 141.1, 132.8, 132.3, 127.7, 127.4, 127.2, 125.9, 125.4, 125.0, 124.7, 73.9, 67.4; LRMS (EI) m/z 188.1 [M]⁺; HRMS (EI) calculated for C₁₂H₁₂O₂ [M]⁺ 188.0837, found 188.0837.
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**tert-Butyl 4-(1,2-dihydroxyethyl)phenylcarbamate 240**

![Chemical Structure](image)

Following general procedure F, tert-butyl 4-vinylphenylcarbamate (0.15 g, 0.7 mmol) gave the title compound as a colourless crystalline solid (0.10 g, 56%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 139–141 °C; IR (thin film)/cm⁻¹: 3379, 3334, 3281, 2933, 1685, 1525; \(^1\)H NMR (400 MHz, CDCl₃) δ 7.28 (d, \(J = 8.5\) Hz, 2H, Ar-H), 7.22 (d, \(J = 8.5\) Hz, 2H, Ar-H), 6.43 (bs, 1H, NH), 4.71 (dd, \(J = 3.6\) & 8.1 Hz, 1H, ArCHOH), 3.66 (dd, \(J = 3.6\) & 11.3 Hz, 1H, CHHOH), 3.57 (dd, \(J = 8.2\) & 11.2 Hz, 1H, CHHOH) 1.44 (s, 9H, Q CH₃); \(^{13}\)C NMR (125 MHz, DMSO) δ 152.8, 138.2, 137.0, 126.4, 117.7, 78.8, 73.5, 67.5, 28.1; LRMS (EI) \(m/z\) 253.1 \([M]⁺\); HRMS (EI) calculated for C\(_{13}\)H\(_{19}\)NO\(_4\) \([M]⁺\) 253.1314, found 253.1310.

**1-(4-Ethynylphenyl)ethane-1,2-diol 248**

![Chemical Structure](image)

Following general procedure F, 4-ethynylstyrene (0.08 g, 0.6 mmol) gave the title compound as a waxy colourless solid (0.04 g, 35%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). \(^1\)H NMR (500 MHz, CDCl₃) δ 7.42 (d, \(J = 8.0\) Hz, 2H, Ar-H), 7.26 (d, \(J = 8.0\) Hz, 2H, Ar-H), 4.77–4.75 (m, 1H, ArCHOH), 3.69 (apparent d, \(J = 11.5\) Hz, 1H, CHHOH), 3.56 (dd, \(J = 8.5\) & 11.0 Hz, 1H, CHHOH), 3.01 (s, 1H, =CH), 2.60 (bs, 1H, OH), 2.10 (bs, 1H, OH); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 141.2, 132.3, 126.0, 121.8, 83.3, 77.4, 74.3, 67.9; LRMS (EI) \(m/z\) 162.0 \([M]⁺\); HRMS (EI) calculated for C\(_{13}\)H\(_{10}\)O\(_2\) \([M]⁺\) 162.0681, found 162.0682.

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(±)-Hydrobenzoin 41

Following general procedure F, trans-stilbene (0.105 g, 0.6 mmol) gave the title compound as a colourless crystalline solid (0.10 g, 78%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 104–105 °C [lit.⁹⁹ m.p. 146–147 °C]; IR (thin film)/cm⁻¹: 3389, 2922, 2852, 1645; ¹H NMR (400 MHz, CDCl₃) δ 7.19–7.06 (m, 10H, Ar-H), 4.66 (s, 2H, ArCHOH), 2.74 (s, 2H, ArCHOH); ¹³C NMR (125 MHz, CDCl₃) δ 139.9, 128.2, 128.0, 127.0, 79.1; LRMS (APCI) m/z 196.1 [M – H₂O]⁺; HRMS (CI) calculated for C₁₄H₁₁O₂Na [M + Na]⁺ 237.0886, found 237.0887.

meso-Hydrobenzoin 91

Following general procedure F, cis-stilbene (0.10 ml, 0.6 mmol) gave the title compound as a colourless crystalline solid (0.10 g, 78%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 133 °C [lit.¹⁰⁰ m.p. 134–136 °C]; ¹H NMR (400 MHz, CDCl₃) δ 7.27–7.17 (m, 10H, Ar-H), 4.76 (s, 2H, ArCHOH), 2.13 (s, 2H, ArCHOH); ¹³C NMR (125 MHz, CDCl₃) δ 139.9, 128.3, 128.2, 127.1, 78.2; LRMS (El) m/z 196.1 [M – H₂O]⁺; HRMS (El) calculated for C₁₄H₁₁O₂ [M - H₂O]⁺ 196.0888, found 196.0886.
rel-(1R,2R)-1,2-Di-p-tolylethane-1,2-diol 256

**Major**

Following general procedure F, 4,4′-dimethyl-trans-stilbene (0.10 g, 0.5 mmol) gave the title compound as a colourless crystalline solid (0.10 g, 83%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 150 °C [lit.\textsuperscript{101} m.p. 180 °C]; IR (thin film)/cm\textsuperscript{-1}: 3337, 3028, 2915; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 6.98–6.94 (m, 8H, Ar-H), 4.58 (s, 2H, ArCHOH), 2.22 (s, 6H, CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 137.5, 137.0, 128.8, 127.1, 78.8, 21.2; LRMS (EI) m/z 224.1 [M – H\textsubscript{2}O]\textsuperscript{+}; HRMS (CI) calculated for C\textsubscript{16}H\textsubscript{22}O\textsubscript{2}N [M + NH\textsubscript{4}]\textsuperscript{+} 260.1645, found 260.1649.

rel-(1R,2R)-1,2-Di-o-tolylethane-1,2-diol 258

**Major**

Following general procedure F, 2,2′-dimethyl-trans-stilbene (0.10 g, 0.5 mmol) gave the title compound as a colourless crystalline solid (0.09 g, 78%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 125 °C [lit.\textsuperscript{102} m.p. 116–118 °C]; IR (thin film)/cm\textsuperscript{-1}: 3390, 1604, 1490; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.51 (dd, J = 1.1 & 7.7 Hz, 2H, Ar-H), 7.11–7.09 (m, 2H, Ar-H), 7.05–7.01 (m, 2H, Ar-H), 6.82 (app d, J = 7.5 Hz, 2H, Ar-H), 4.84 (s, 2H, ArCHOH), 3.13 (s, 2H, ArCHOH), 1.54 (s, 6H, CH\textsubscript{3}); \textsuperscript{13}C NMR (62.5 MHz, CDCl\textsubscript{3}) δ 138.0, 135.9, 130.2, 127.7, 127.3, 126.0, 74.6, 18.8; LRMS (EI) m/z 224.1 [M – H\textsubscript{2}O]\textsuperscript{+}; HRMS (EI) calculated for C\textsubscript{16}H\textsubscript{16}O [M – H\textsubscript{2}O]\textsuperscript{+} 224.1201, found 224.1203.
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rel-(1R,2R)-1,2-Bis(3-methoxyphenyl)ethane-1,2-diol 260

Following general procedure F, 3,3'-dimethoxy-trans-stilbene (0.15 g, 0.6 mmol) gave the title compound as a colourless oil (0.04 g, 27%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). IR (thin film)/cm⁻¹: 3341, 1591, 1488; ¹H NMR (400 MHz, CDCl₃) δ 7.06–7.02 (m, 2H, Ar-H), 6.69–6.66 (m, 2H, Ar-H), 6.61–6.59 (m, 4H, Ar-H), 4.53 (s, 2H, ArCHOH), 3.60 (s, 6H, OCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 159.5, 141.6, 129.1, 119.3, 113.9, 112.3, 78.9, 55.2; LRMS (EI) m/z 256.1 [M – H₂O]⁺; HRMS (EI) calculated for C₁₆H₁₆O₃ [M – H₂O]⁺ 256.1099, found 256.1098.

rel-(1R,2R)-1-Phenylpropane-1,2-diol 264

Following general procedure F, trans-β-methylstyrene (0.09 ml, 0.7 mmol) gave the title compound as a colourless oil (0.08 g, 80%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). IR (thin film)/cm⁻¹: 3435, 1714, 1520, 1392; ¹H NMR (400 MHz, CDCl₃) δ 7.29–7.21 (m, 5H, Ar-H), 4.24 (d, J = 7.5 Hz, 1H, ArCHOH), 3.76–3.73 (m, 1H, CHOHCH₃), 3.25 (bs, 1H, OH), 3.03 (bs, 1H, OH), 0.94 (d, J = 6.3 Hz, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 141.1, 128.5, 128.1, 126.9, 79.5.
72.2, 18.8; LRMS (El) m/z 134.1 [M – H2O]+; HRMS (El) calculated for C9H10O [M – H2O]+ 134.0732, found 134.0730.

rel-(1R,2R)-3-Methyl-1-phenylbutane-1,2-diol 271

\[
\text{C}_9\text{H}_{10}\text{O}^{+}\text{[M - H2O]}^+ 134.0732, \text{found 134.0730.}
\]

Major

Following general procedure F, 1-phenyl-2-isopropylethylene (0.07 g, 0.5 mmol) gave the title compound as a colourless oil (0.06 g, 68%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). IR (thin film)/cm⁻¹: 3395, 2979, 2896, 2361, 1593, 1488, 1400, 1127, 1040, 926; ¹H NMR (400 MHz, CDCl₃): δ 7.31-7.19 (m, 5H, Ar-H), 4.58 (d, J = 6.4 Hz, 1H, ArCHOH), 3.43 (dd, J = 4.4 & 6.4 Hz, 1H, CHOH), 1.57-1.52 (m, 1H, CH(CH₃)₂), 0.92-0.88 (m, 6H, CH(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃): δ 141.6, 128.6, 128.0, 126.6, 80.5, 75.2, 29.2, 20.2, 16.4; LRMS (El) m/z 162.1 [M – H₂O]+; HRMS (El) calculated for C₁₁H₁₄O [M – H₂O]+ 162.1045, found 162.1047.

rel-(1R,2S)-2,3-Dihydro-1H-indene-1,2-diol 274

Following general procedure F, indene (0.08 ml, 0.7 mmol) gave the title compound as a colourless crystalline solid (0.07 g, 67%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 88-90 °C [lit.¹⁰⁶ m.p. 92-93 °C]; IR (thin film)/cm⁻¹: 3395, 2924, 1727, 1610; ¹H NMR (250 MHz, CDCl₃)
δ 7.36–7.31 (m, 1H, Ar-H), 7.22–7.14 (m, 3H, Ar-H), 4.88 (d, J = 4.8 Hz, 1H, ArCH(OH)), 4.40–4.35 (m, 1H, ArCHOHCHOH), 3.04 (dd, J = 5.8 & 16.3 Hz, 1H, ArCH(H)CHOH), 2.87 (dd, J = 3.6 & 16.3 Hz, 1H, ArCHHCHOH), 2.50 (bs, 2H, OH); 13C NMR (62.5 MHz, CDCl₃) δ 142.0, 140.2, 128.9, 127.2, 125.4, 125.1, 76.0, 73.5, 38.6; LRMS (El) m/z 150.1 [M⁺]; HRMS (El) calculated for C₉H₁₀O₂ [M⁺] 150.0681, found 150.0684.

Preparation of 1-phenylcyclohexene-1,2-diol & 2-phenylcyclohex-2-enol

Following general procedure F, 1-phenylcyclohexene (0.09 ml, 0.6 mmol) gave a mixture of 1-phenylcyclohexene-1,2-diol 275 and 2-phenylcyclohex-2-enol 276 after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80).

rel-(1R,2R)-1-Phenylcyclohexane-1,2-diol 275

Colourless solid (0.06 g, 50%). m.p. 80–81 °C [lit.¹⁰⁷ m.p. 92 °C]; IR (thin film)/cm⁻¹: 3394, 2935, 2362, 1445, 1061, 997; ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.41 (m, 2H, Ar-H), 7.31–7.27 (m, 2H, Ar-H), 7.20–7.16 (m, 1H, Ar-H), 3.88 (dd, J = 4.5 & 11.1 Hz, 1H, CH(OH)), 1.81–1.08 (m, 8H, (CH₂)₄); 13C NMR (125 MHz, CDCl₃) δ 146.4, 128.5, 127.0, 125.2, 75.8, 74.6, 38.5, 29.3, 24.4, 21.1; LRMS (El) m/z 192.1 [M⁺]; HRMS (El) calculated for C₁₂H₁₆O₂ [M⁺] 192.1150, found 192.1147.
2-Phenylcyclohex-2-enol 276 \(^{108}\)

![Chemical Structure](image)

Colourless oil (0.02 g, 20%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.50–7.45 (m, 2H, Ar-H), 7.30–7.25 (m, 2H, Ar-H), 7.20–7.15 (m, 1H, Ar-H), 6.09 (dd, \(J = 3.4 \& 4.5\) Hz, 1H, =CHCH\(_2\)), 4.66–4.62 (m, 1H, CHOH), 2.25–2.00 (m, 2H, CH\(_2\)(CH\(_2\))\(_2\)), 1.90–1.55 (m, 4H, CH\(_2\)(CH\(_2\))\(_2\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 140.2, 139.1, 128.7, 128.6, 127.1, 126.0, 65.5, 31.6, 26.1, 17.4; LRMS (El) \(m/z\) 174.1 [M]+; HRMS (El) calculated for C\(_{12}\)H\(_{14}\)O [M]+ 174.1045, found 174.1040.

rel-(1R,2R)-1-(4-Methoxyphenyl)propane-1,2-diol 283 \(^{109}\)

![Chemical Structure](image)

Major

Following general procedure F, trans-anethole (0.11 ml, 0.7 mmol) gave the title compound as a colourless oil (0.10 g, 77%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). IR (thin film)/cm\(^{-1}\): 3390, 2979, 2901, 1485, 1397; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.14 (d, \(J = 8.7\) Hz, 2H, Ar-H), 6.79 (d, \(J = 8.7\) Hz, 2H, Ar-H), 4.18 (d, \(J = 7.8\) Hz, 1H, ArCHOH), 3.71 (s, 3H, OCH\(_3\)), 3.71 (m, 1H, CHOHCH\(_3\)), 0.89 (d, \(J = 6.3\) Hz, 3H, CHOHCH\(_3\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 159.5, 133.2, 128.1, 113.9, 79.1, 72.3, 55.3, 18.7; LRMS (El) \(m/z\) 182.1 [M]+; HRMS (El) calculated for C\(_{10}\)H\(_{14}\)O\(_3\) [M]+ 182.0943, found 182.0940.
Chapter 5 — Experimental

**rel-(1R,2R)-1-(4-Bromophenyl)propane-1,2-diol 280**

![Chemical Structure]

**Major**

Following general procedure F, 4-bromo-\textit{trans}-\beta\text{-methylstyrene} (0.09 g, 0.5 mmol) gave the title compound as a pale yellow oil (0.08 g, 70%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). IR (thin film)/cm\textsuperscript{-1}: 3402, 2896, 1593, 1488, 1400, 1069, 1040, 1010, 926; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta 7.45 (d, \textit{J} = 8.4 Hz, 2H, Ar-H), 7.16 (d, \textit{J} = 8.4 Hz, 2H, Ar-H), 4.25 (d, \textit{J} = 7.6 Hz, 1H, ArCHOH), 3.77–3.70 (m, 1H, CH\textsubscript{2}OH), 3.59 (bs, 1H, OH), 3.20 (bs, 1H, OH), 0.99 (d, \textit{J} = 6.4 Hz, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \delta 140.0, 131.7, 128.6, 122.0, 78.8, 72.1, 18.9; LRMS (EI) \textit{m/z} 211.9 [M – \text{H}_2\text{O}]^+; HRMS (EI) calculated for C\textsubscript{9}H\textsubscript{9}OBr\textsuperscript{79} [M – \text{H}_2\text{O}]^+ 211.9837, found 211.9841.

**Preparation of 2-phenylpropane-1,2-diol & 2-phenylprop-2-en-1-ol**

![Chemical Reaction]

Following general procedure F, \textit{\alpha}-\text{-methylstyrene} (0.09 ml, 0.7 mmol) gave a mixture of 2-phenylpropane-1,2-diol \textit{293} and 2-phenylprop-2-en-1-ol \textit{294} after purification by column chromatography eluting with ethyl acetate : petroleum ether (80 : 20).
Chapter 5 - Experimental

2-Phenylpropane-1,2-diol 293

![2-Phenylpropane-1,2-diol structure](image)

Colourless oil (0.05 g, 50%) IR (thin film)/cm⁻¹: 3568, 1449, 1027; ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.32 (m, 2H, Ar-H), 7.28–7.24 (m, 2H, Ar-H), 7.19–7.15 (m, 1H, Ar-H), 3.62 (d, J = 11.3 Hz, 1H, CHHOH), 3.48 (d, J = 11.3 Hz, 1H, CHHOH), 2.90 (s, 2H, OH), 1.39 (s, 3H, CH₃); ¹³C NMR (62.5 MHz, CDCl₃) δ 145.1, 128.4, 127.1, 125.2, 75.0, 70.9, 26.0; LRMS (El) m/z 134.1 [M – H₂O]⁺; HRMS (El) calculated for C₉H₁₀O [M – H₂O]⁺ 134.0732, found 134.0736.

2-Phenylprop-2-en-1-ol 294

![2-Phenylprop-2-en-1-ol structure](image)

Colourless oil (0.02 g, 20%). ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.37 (m, 2H, Ar-H), 7.31–7.22 (m, 3H, Ar-H), 5.41 (app s, 1H, =CHH), 5.29 (app s, 1H, =CHH), 4.49 (s, 2H, CH₂OH); ¹³C NMR (125 MHz, CDCl₃) δ 147.4, 138.5, 128.5, 128.0, 126.1, 112.6, 65.1; LRMS (EI) m/z 134.1 [M]⁺; HRMS (El) calculated for C₉H₁₀O [M]⁺ 134.0732, found 134.0729.
Chapter 5 - Experimental

Preparation of 1,2-diphenylpropane-1,2-diol & 1,2-diphenylprop-2-en-l-ol

Following general procedure F, α-methylstilbene (0.17 g, 0.9 mmol) gave a mixture of 2-phenylpropane-1,2-diol and 2-phenylprop-2-en-1-ol after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80).

1,2-Diphenylpropane-1,2-diol (Table 4.7, Entry 2)

Colourless solid (0.07 g, 37%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 88–90 °C [lit.\textsuperscript{113} m.p. 103–104 °C]; IR (thin film)/cm\textsuperscript{-1}: 3581, 1603, 1449, 1026; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.20–7.11 (m, 8H, Ar-H), 6.96–6.94 (m, 2H, Ar-H), 4.63 (s, 1H, ArCHOH), 2.80 (bs, 2H, OH), 1.20 (s, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (62.5 MHz, CDCl\textsubscript{3}) δ 145.1, 139.3, 128.1, 127.8, 127.7, 127.3, 126.0, 80.8, 77.2, 23.9 (only 10 peaks visible); LRMS (Cl) m/z 246.3 [M + NH\textsubscript{4}]\textsuperscript{+}; HRMS (ES) calculated for C\textsubscript{15}H\textsubscript{20}O\textsubscript{2}N [M + NH\textsubscript{4}]\textsuperscript{+} 246.1489, found 246.1490.
Chapter 5 – Experimental

1,2-Diphenylprop-2-en-1-ol$^{114}$ (Table 4.7, Entry 2)

![Chemical Structure](image)

Colourless oil (0.04 g, 22%). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.33–7.13 (m, 10H, Ar-H), 5.61 (d, $J$ = 3.9 Hz, 1H, ArCHOH), 5.41 (d, $J$ = 7.3 Hz, 2H, =CH$_2$), 2.11 (d, $J$ = 4.2 Hz, 1H, ArCHOH); LRMS (EI) $m/z$ 210.1 [M$^+$]; HRMS (EI) calculated for C$_{15}$H$_{14}$O [M$^+$] 210.1045, found 210.1043.

1-Cyclopropyl-1-phenylethane-1,2-diol (Table 4.7, Entry 3)

![Chemical Structure](image)

Following general procedure F, 1-phenyl-1-cyclopropylethylene (0.13 g, 0.9 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 69%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 50–51$^\circ$C [lit.$^{115}$ m.p. 53$^\circ$C]; IR (thin film)/cm$^{-1}$: 3581, 3438, 1494, 1448, 1392, 1028; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41–7.38 (m, 2H, Ar-H), 7.31–7.27 (m, 2H, Ar-H), 7.23–7.19 (m, 1H, Ar-H), 3.86 (d, $J$ = 11.3 Hz, 1H, CHHOH), 3.70 (d, $J$ = 11.3 Hz, 1H, CHHOH), 1.15–1.09 (m, 1H, CH(CH$_2$)$_2$), 0.45–0.37 (m, 2H, CHCH$_2$CH$_2$), 0.30–0.27 (m, 2H, CHCH$_2$CH$_2$); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 142.8, 127.4, 126.4, 124.9, 74.3, 69.6, 17.5, 0.0, -1.0; LRMS (EI) $m/z$ 160.1 [M – H$_2$O$^+$]; HRMS (MALDI) calculated for C$_{11}$H$_{14}$O$_2$ [M$^+$] 178.0988, found 178.0986.
Chapter 5 – Experimental

1,1-Diphenylethane-1,2-diol (Table 4.7, Entry 4)

Following general procedure F, 1,1-diphenylethylene (0.12 ml, 0.7 mmol) gave the title compound as a colourless crystalline solid (0.10 g, 67%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 110 °C [lit. m.p. 122 °C]; IR (thin film)/cm⁻¹: 3372, 3303, 1491, 1455, 1384, 1361, 1043; ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.42 (m, 4H, Ar-H), 7.36-7.32 (m, 4H, Ar-H), 7.29-7.25 (m, 2H, Ar-H), 4.17 (d, J = 6.4 Hz, 2H, CH₂OH), 3.18 (s, 1H, OH), 1.88 (t, J = 6.4 Hz, 1H, CH₂OH); ¹³C NMR (62.5 MHz, CDCl₃) δ 143.8, 128.5, 127.5, 126.4, 78.6, 69.5; LRMS (EI) m/z 196.1 [M - H₂O]⁺; HRMS (EI) calculated for C₁₄H₁₂O [M - H₂O]⁺ 196.0888, found 196.087.

1-(1-Hydroxyethyl)cyclohexanol 302¹¹⁷

Following general procedure G, ethylidenecyclohexane (0.27 ml, 2.0 mmol) gave the title compound as a colourless oil (0.16 g, 55%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). IR (thin film)/cm⁻¹: 3424, 2937, 2860, 1450, 1382; ¹H NMR (400 MHz, CDCl₃) δ 3.51 (q, J = 6.4 Hz, 1H, CH₂CH₂OH), 1.60-1.46 (m, 8H, (CH₂)₄), 1.35-1.15 (m, 2H, CH₃), 1.09 (d, J = 6.4 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 73.8, 73.5, 34.2, 31.2, 25.9, 21.7, 21.5, 17.0; LRMS (CI) m/z 162.3 [M + NH₄]⁺; HRMS (ES) calculated for C₈H₂₀O₂N [M + NH₄]⁺ 162.1489, found 162.1487.
Chapter 5 – Experimental

1-(Hydroxymethyl)cyclopentanol 304\textsuperscript{118}

Following general procedure G, methylenecyclopentane (0.20 ml, 1.9 mmol) gave the title compound as a colourless crystalline solid (0.13 g, 60%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 3.87 (bs, 2H, CH\textsubscript{2}OH), 3.44 (s, 2H, CH\textsubscript{2}OH), 1.75–1.70 (m, 2H, CH\textsubscript{2}), 1.58–1.50 (m, 6H, (CH\textsubscript{2})\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 82.8, 69.4, 36.7, 24.1; LRMS (Cl) m/z 134.0 [M + NH\textsubscript{4}]\textsuperscript{+}; HRMS (ES) calculated for C\textsubscript{6}H\textsubscript{10}O\textsubscript{2}N [M + NH\textsubscript{4}]\textsuperscript{+} 134.1176, found 134.1174.

rel-(1R,2S)-1-Methylcyclopentane-1,2-diol 306\textsuperscript{41}

Following general procedure G, 1-methylenecyclopentene (0.21 ml, 1.9 mmol) gave the title compound as a colourless crystalline solid (0.14 g, 65%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 3.61 (apparent t, J = 6.5 Hz, 1H, CH\textsubscript{2}OH), 2.57 (bs, 2H, OH), 1.92–1.43 (m, 6H, (CH\textsubscript{2})\textsubscript{3}), 1.19 (s, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 78.4, 78.4, 37.1, 31.6, 25.3, 19.2; LRMS (Cl) m/z 134.0 [M + NH\textsubscript{4}]\textsuperscript{+}; HRMS (MALDI) calculated for C\textsubscript{6}H\textsubscript{10}O\textsubscript{2}N [M + NH\textsubscript{4}]\textsuperscript{+} 134.1176, found 134.1175.
4-Vinylthioanisole (0.15 g, 1.0 mmol) was added to a solution of cyclobutane malonoyl peroxide (0.15 g, 1.1 mmol) in chloroform (2 ml). H₂O (18 μl, 1.0 mmol) was added and stirred at 40 °C for 1 h. Removal of the solvent under reduced pressure gave the title compound as a light yellow oil (0.12 g, 74%) after purification by column chromatography eluting with diethyl ether : petroleum ether (90 : 10). IR (thin film)/cm⁻¹: 3019, 1706, 1594, 1046; ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, J = 6.8 Hz, 2H, Ar-H), 7.47 (d, J = 6.7 Hz, 2H, Ar-H), 6.67 (dd, J = 10.9 & 17.6 Hz, 1H, ArCH=CH₂), 5.77 (app d, J = 17.6 Hz, 1H, CH=CHH), 5.30 (app d, J = 10.9 Hz, 1H, CH=CHH), 2.66 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 144.6, 140.5, 135.7, 127.1, 123.9, 116.3, 43.9; LRMS (El) m/z 166.0 [M]⁺; HRMS (El) calculated for C₉H₁₀OS [M]⁺ 166.0452, found 166.0455.
Chapter 5 – Experimental

General Procedure H. Synthesis of γ lactones.

Alkene (0.7 mmol) was added to a solution of cyclobutane malonoyl peroxide (0.15 g, 1.0 mmol) in chloroform (2 ml). After ~ 5 min. the reaction mixture turned orange. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was reduced to dryness to give the corresponding γ-lactone.

5-(4-N-Boc-phenyl)-3,3-spirocyclobutylbutyrolactone 235

Following general procedure H, tert-Butyl 4-vinylphenylcarbamate (0.15 g, 0.7 mmol) gave the title compound as a yellow solid (0.07 g, 30%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (30 : 70). m.p. 115 °C; IR (thin film)/cm⁻¹: 3437, 1764, 1725, 1597, 1524; ¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, J = 8.4 Hz, 2H, Ar-H), 7.15 (d, J = 8.6 Hz, 2H, Ar-H), 6.55 (bs, 1H, NH), 5.22 (dd, J = 6.2 & 9.0 Hz, 1H, ArCHOCO), 2.66 (dd, J = 6.2 & 13.0 Hz, 1H, ArCHCHH), 2.53–2.40 (m, 2H, (CH₂)₂CH₂), 2.16 (dd, J = 9.0 & 12.9 Hz, 1H, ArCHCHH), 2.10–1.85 (m, 4H, (CH₂)₂CH₂), 1.45 (s, 9H, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ 180.7, 152.7, 138.6, 133.7, 126.2, 118.6, 80.7, 77.8, 44.5, 44.8, 31.5, 29.2, 28.3, 16.5; LRMS (EI) m/z 317.2 [M]+; HRMS (EI) calculated for C₁₈H₂₅O₄N [M]+ 317.1627, found 317.1631.
Chapter 5 – Experimental

5-(2-Hydroxyphenyl)-3,3-spirocyclobutylbutyrolactone 195

Following general procedure H, 2-hydroxystyrene (0.10 g, 0.8 mmol) gave the title compound as a colourless solid (0.08 g, 45%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80). m.p. 169–171 °C; IR (thin film)/cm⁻¹: 3365, 2944, 1749, 1603, 1457, 1333; ¹H NMR (400 MHz, CDCl₃) δ 7.29–7.08 (m, 2H, Ar-H), 6.89–6.76 (m, 2H, Ar-H), 6.13 (bs, 1H, OH), 5.57 (dd, J = 6.8 & 8.4 Hz, 1H, ArCHOCO), 2.79 (dd, J = 6.8 & 13.2 Hz, 1H, ArCHCHH), 2.54–2.43 (m, 2H, (CH₂)₂), 2.26 (dd, J = 8.4 & 13.2 Hz, 1H, ArCHCHH), 2.15–1.81 (m, 4H, (CH₂)₂); ¹³C NMR (62.5 MHz, CDCl₃) δ 181.8, 153.0, 129.3, 125.9, 125.7, 120.7, 115.9, 75.4, 44.6, 42.8, 31.7, 29.6, 16.6; LRMS (EI) m/z 218.1 [M]+; HRMS (EI) calculated for C₁₃H₁₄O₃ [M]+ 218.0943, found 218.0943.

5-(4-Hydroxyphenyl)-3,3-spirocyclobutylbutyrolactone 237

Following general procedure H, 4-hydroxystyrene (0.10 g, 0.8 mmol) gave the title compound as a yellow solid (0.03 g, 19%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (10 : 90). m.p. 140–141 °C; IR (thin film)/cm⁻¹: 3369, 2940, 1753, 1614, 1517, 1447, 1330, 1172; ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, J = 8.8 Hz, 2H, Ar-H), 6.84 (d, J = 8.8 Hz, 2H, Ar-H), 5.66 (s, 1H, OH), 5.23 (dd, J = 6.0 & 9.3 Hz, 1H, ArCHOCO), 2.72 (dd, J = 6.0 & 13.0 Hz, 1H, ArCHCHH), 2.63–2.46 (m, 2H, (CH₂)₂), 2.19 (dd, J = 9.0 & 13.0 Hz, 1H, ArCHCHH),
Chapter 5 – Experimental

2.18–1.98 (m, 4H, (CH₂)₂CH₂); ¹³C NMR (125 MHz, CDCl₃) δ 181.2, 156.0, 131.0, 127.2, 115.6, 78.2, 44.9, 44.4, 31.6, 29.1, 16.5; LRMS (EI) m/z 218.1 [M]+; HRMS (MALDI) calculated for C₁₃H₁₄O₃ [M]+ 218.0943, found 218.0937.

General Procedure I. Synthesis of Alkenes by Wittig Reaction.

Methyltriphenylphosphonium iodide (8.2 g, 20 mmol) and dry THF (100 ml) were placed in an oven dried two necked flask equipped with a reflux condenser with nitrogen inlet, large stirrer bar and glass stopper and cooled to −10 °C. "BuLi (2.5 M in hexane, 8 ml, 20 mmol) was added and the resulting red/brown solution stirred at −10 °C for 2 h. Aldehyde/ketone (17 mmol) was added dropwise with the observation of a white precipitate. The reaction was allowed to reach room temperature and heated at reflux for 24 h or until reaction completion as determined by TLC. H₂O (10 ml) was added to the reaction mixture followed by removal of the solvent under reduced pressure. Ethyl acetate (50 ml) was added and the two layers separated. The aqueous layer was further extracted with ethyl acetate (2 × 50 ml) and the combined organic layers washed with brine (20 ml) and dried over MgSO₄. The solvent was removed under reduced pressure to give the desired alkene.

1-Phenyl-1-cyclopropylethylene 299¹¹⁹

Following general procedure I, cyclopropyl phenyl ketone (2.3 ml, 17 mmol) gave the title compound as a colourless liquid (1.7 g, 69%) after purification by column chromatography eluting with petroleum ether. ¹H NMR (250 MHz, CDCl₃) δ 7.66–7.61 (m, 2H, Ar-H), 7.42–7.30 (m, 3H, Ar-H), 5.32 (d, J = 0.7 Hz, 1H, C=CHH), 4.98 (d, J = 1.1 Hz, 1H, C=CHH), 1.75–1.64 (m, 1H, CH(CH₂)₂), 0.95–0.82 (m, 2H, CHCH₂CH₂),
0.67–0.63 (m, 2H, CHCH\textsubscript{2}CH\textsubscript{2}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 149.4, 141.7, 128.2, 127.5, 126.1, 109.0, 15.6, 6.7; LRMS (EI) \( m/z \) 144.1 [M]+; HRMS (MALDI) calculated for C\textsubscript{11}H\textsubscript{12} [M]+ 144.0934, found 144.0931.

4-Vinylthioanisole 244\textsuperscript{120}

Following general procedure I, 4-(methylthio)benzaldehyde (2.0 ml, 15 mmol) gave the title compound as a colourless liquid (0.8 g, 36%) after purification by column chromatography eluting with petroleum ether. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.27–7.25 (m, 2H, Ar-H), 7.15–7.13 (m, 2H, Ar-H), 6.58 (dd, \( J \) = 10.8 \& 17.6 Hz, 1H, ArCH=CH\textsubscript{2}), 5.64 (apparent d, \( J \) = 17.6 Hz, 1H, CH=CH\textsubscript{H}), 5.14 (apparent d, \( J \) = 10.8 Hz, 1H, CH=CH\textsubscript{H}), 2.42 (s, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 138.0, 136.2, 134.6, 126.6, 126.6, 113.2, 15.9; LRMS (EI) \( m/z \) 150.1 [M]+; HRMS (EI) calculated for C\textsubscript{9}H\textsubscript{10}S [M]+ 150.0503, found 150.0499.

2-Vinyl phenol 191\textsuperscript{121}

Following general procedure I, salicylaldehyde (0.43 ml, 4.0 mmol) gave the title compound as a pale yellow liquid (0.26 g, 54%) after purification by column chromatography eluting with diethyl ether : petroleum ether (15 : 85). \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) \( \delta \) 7.34–7.19 (m, 1H, Ar-H), 7.11–7.03 (m, 1H, Ar-H), 6.92–6.79 (m, 2H, Ar-H), 6.72 (dd, \( J \) = 0.9 \& 8.0 Hz, 1H, ArCH=CH\textsubscript{2}), 5.67 (dd, \( J \) = 1.3 \& 17.8 Hz, 1H, CH=CH\textsubscript{H}), 5.30 (dd, \( J \) = 1.3 \& 11.2 Hz, 1H, CH=CH\textsubscript{H}), 4.89 (bs, 1H, OH); \textsuperscript{13}C NMR
Chapter 5 - Experimental

(125 MHz, CDCl₃) δ 152.8, 131.5, 128.9, 127.4, 124.8, 121.0, 115.9, 115.8; LRMS (El) m/z 120.1 [M]+; HRMS (El) calculated for C₈H₈O [M]+ 120.0575, found 120.0573.

1-(4-Bromophenyl)-2-methylethylene 279

![Image of 1-(4-Bromophenyl)-2-methylethylene](image)

Ethyltriphenylphosphonium chloride (6.10 g, 16 mmol) and dry THF (100 ml) was placed in an oven dried two necked flask equipped with a reflux condenser with nitrogen inlet, large stirrer bar and glass stopper and cooled to −10 °C. BuLi (2.5 M in hexane, 6.5 ml, 16 mmol) was added and the resulting red/brown solution stirred at −10 °C for 2 h. 4-bromobenzaldehyde (2.50 g, 13 mmol) was added dropwise with the observation of a white precipitate. The reaction was allowed to reach room temperature and heated at reflux for 48 h. Water (10 ml) was added to the reaction mixture followed by removal of the solvent under reduced vacuum. Ethyl acetate (50 ml) was added and the two layers separated. The aqueous layer was further extracted with ethyl acetate (2 × 50 ml) and the combined organic layers washed with brine (20 ml) and dried over MgSO₄. Evaporation of the solvent and purification by column chromatography eluting with petroleum ether gave the title compound as a mixture of geometrical isomers. The purified material was dissolved in dichloromethane (50 ml) and iodine (50 mg) added. The resulting dark purple solution was exposed to direct sunlight for 78 h. The solution was concentrated under reduced pressure to give geometrically pure 4-bromo-trans-β-methylstyrene as colourless semi-solid (1.60 g, 62%) after purification by column chromatography eluting with petroleum ether. IR (thin film)/cm⁻¹: 1657, 1487, 1444, 1401; ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.31 (m, 2H, Ar-H), 7.13–7.10 (m, 2H, Ar-H), 6.26 (d, J = 16.8 Hz, 1H, ArCH=CH), 6.20–6.11 (m, 1H, CH=CHCH₃), 1.79 (d, J = 6.4 Hz, 3H, CH=CHCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 136.9, 131.5, 129.9, 127.4, 126.6, 120.4, 18.5; LRMS (El) m/z 196.0 [M]+; HRMS (El) calculated for C₉H₉Br [M]+ 195.9888, found 195.9890.
1-Phenyl-2-isopropylethylene 270 \(^{123}\)

\[
\text{\includegraphics[width=0.2\textwidth]{phenyl-isopropyl-ethylene.png}}
\]

Benzyltriphenylphosphonium bromide (1.02 g, 2.6 mmol) was dissolved in a mixture of chloroform (20 ml) and water (20 ml) and sodium hydroxide (0.10 g, 2.5 mmol) added. A bright orange colour was observed on addition of the sodium hydroxide. Isobutyraldehyde (0.23 ml, 2.6 mmol) was added and the reaction vigorously stirred for 1 h after which time the orange colour disappeared. The aqueous and organic layers were separated. Removal of the solvent under reduced pressure gave the title compound as a colourless liquid (0.22 g, 60%) after purification by column chromatography eluting with petrol. IR (thin film)/cm\(^{-1}\): 2960, 1597; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.28–7.11 (m, 5H, Ar-H), 6.27 (d, \(J = 16.2\) Hz, 1H, ArCH=CH), 6.12 (dd, \(J = 6.8\) & 15.9 Hz, 1H, ArCH=CHCH(CH\(_3\))\(_2\)), 2.40–2.32 (m, 1H, CH(CH\(_3\))\(_2\)), 1.02 (d, \(J = 7.0\) Hz, 6H, CH(CH\(_3\))\(_2\)); \(^{13}\)C NMR (62.5 MHz, CDCl\(_3\)) \(\delta\) 138.0, 132.7, 128.5, 127.0, 126.8, 126.0, 31.6, 22.5; LRMS (EI) \(m/z\) 146.1 [M]+.

1-Phenyl-2-cyclopropylethylene 204 \(^{124}\)

\[
\text{\includegraphics[width=0.2\textwidth]{phenyl-cyclopropylethylene.png}}
\]

Benzyltriphenylphosphonium chloride (5.50 g, 14 mmol) and dry THF (100 ml) were placed in an oven dried two necked flask equipped with a reflux condenser with nitrogen inlet, large stirrer bar and glass stopper and cooled to -10 °C. BuLi (2.5 M in hexane, 5.6 ml, 14 mmol) was added and the resulting red/brown solution stirred at -10 °C for 2 h. Cyclopropane carboxaldehyde (1.0 ml, 13 mmol) was added dropwise with the observation of a white precipitate. The reaction was allowed to reach room temperature and heated at reflux for 24 h or until reaction completion as determined by TLC. H\(_2\)O (10 ml) was added to the reaction mixture followed by removal of the solvent under reduced pressure. Ethyl
acetate (50 ml) was added and the two layers separated. The aqueous layer was extracted with ethyl acetate (2 x 50 ml) and the combined organic layers washed with brine (20 ml) and dried over MgSO₄. Removal of the solvent under reduced pressure gave the title compound as a colourless oil (1.1 g, 58%) after purification by column chromatography eluting with petroleum ether (The compound was isolated as an inseparable mixture of geometrical isomers with an $E : Z$ ratio of 2 : 1).

**Major (trans)**

$^1$H NMR (400 MHz, CDC$_3$) $\delta$ 7.41–7.11 (m, 5H, Ar-H), 6.44 (d, $J = 15.8$ Hz, 1H, ArCH=CH), 5.70 (dd, $J = 9.0 \& 15.8$ Hz, 1H, ArCH=CH), 1.57–1.49 (m, 1H, =CHCH(CH$_2$)$_2$), 0.84–0.76 (m, 2H, CHCH$_2$CH$_2$), 0.49–0.46 (m, 1H, CHCH$_2$CH$_2$)

**Minor (cis)**

$^1$H NMR (400 MHz, CDC$_3$) $\delta$ 7.41–7.11 (m, 5H, Ar-H), 6.32 (d, $J = 11.5$ Hz, 1H, ArCH=CH), 5.03 (dd, $J = 10.0 \& 11.4$ Hz, 1H, ArCH=CH), 1.57–1.49 (m, 1H, =CHCH(CH$_2$)$_2$), 0.84–0.76 (m, 2H, CHCH$_2$CH$_2$), 0.49–0.46 (m, 1H, CHCH$_2$CH$_2$)

**Data for mixture of isomers**

$^{13}$C NMR (125 MHz, CDC$_3$) $\delta$ 137.8, 136.8, 134.9, 128.7, 128.5, 128.2, 127.4, 126.5, 126.4, 125.6, 14.5, 11.0, 8.0, 7.2; LRMS (EI) $m/z$ 144.1 [M]$^+$; HRMS (EI) calculated for C$_{11}$H$_{12}$ [M]$^+$ 144.0939, found 144.0939.

**General Procedure J. Synthesis of Alkenes by Heck Reaction.**

Palladium(II) acetate (0.02 g, 0.1 mmol), tri(o-tolyl)phosphine (0.04 g, 0.1 mmol) and potassium carbonate (2.0 g, 14 mmol) were added to a degassed solution of iodoarene (7.0 mmol) and vinyl iodoarene (7.0 mmol) in N,N-dimethylacetamide (50 ml). The reaction mixture was heated at 150 °C for 24 h or until completion by TLC. The reaction was diluted with H$_2$O (200 ml) and extracted with ethyl acetate (100 ml) added. The aqueous layer was further extracted with ethyl acetate (2 x 100 ml) and the combined organic layers were washed with brine (50 ml) and dried over MgSO₄. The resulting
solution was reduced to ~ 10 ml volume and passed through a plug of silica washing with ethyl acetate. Removal of the solvent under reduced pressure gave the crude product as an off white solid. Re-crystallisation from a mixture of dichloromethane (30 ml) and hexane (5 ml) gave the title compound as a colourless crystalline solid.

4,4'-Dimethyl-trans-stilbene 255

Following general procedure J, 4-methylstyrene (0.92 ml, 7.0 mmol) and 4-iodotoluene (1.52 g, 7.0 mmol) gave the title compound as a colourless crystalline solid (0.80 g, 55%) after purification by column chromatography eluting with ethyl acetate. m.p. 172 °C [lit.125 m.p. 182 °C]; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.43 (d, $J = 8.1$ Hz, 4H, Ar-H), 7.19 (d, $J = 8.0$ Hz, 4H, Ar-H), 7.07 (s, 2H, CH=CH), 2.38 (s, 6H, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 137.3, 134.8, 129.4, 127.7, 126.3, 21.2; LRMS (EI) m/z 208.1 [M$^+$]; HRMS (EI) calculated for C$_{16}$H$_{16}$ [M$^+$] 208.1252, found 208.1254.

2,2'-Dimethyl-trans-stilbene 257

Following general procedure J, 2-methylstyrene (2.00 ml, 15 mmol) and 2-iodotoluene (2.00 ml, 15 mmol) gave the title compound as a colourless solid (1.19 g, 38%) after purification by column chromatography eluting with ethyl acetate. m.p. 72 °C [lit.126 m.p. 83–84 °C]; IR (thin film)/cm$^{-1}$: 3046, 3016, 2966, 2947, 1600; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.63 (d, $J = 7.5$ Hz, 2H, Ar-H), 7.29–7.22 (m, 8H, Ar-H & CH=CH),
Chapter 5 – Experimental

2.47 (s, 6H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 136.8, 135.9, 130.4, 128.1, 127.6, 126.2, 125.6, 20.0; LRMS (EI) m/z 208.1 [M]+; HRMS (APCI) calculated for C₁₆H₁₆ [M + H]+ 209.1325, found 209.1329.

3, 3'-Dimethoxy-trans-stilbene 259

![3, 3'-Dimethoxy-trans-stilbene](image)

Following general procedure J, 3-vinylanisole (1.00 ml, 7.2 mmol) and 3-iodoanisole (0.86 ml, 7.2 mmol) gave the title compound as a colourless solid (0.92 g, 53%) after purification by column chromatography eluting with ethyl acetate. m.p. 90–91 °C [lit.¹²⁷ m.p. 97 °C]; IR (thin film)/cm⁻¹: 3066, 3045, 2993, 2961, 2935, 2832, 1588; ¹H NMR (250 MHz, CDCl₃) δ 7.24–7.18 (m, 2H, Ar-H), 7.06–6.97 (m, 4H, Ar-H), 7.01 (s, 2H, CH=CH₂), 6.78–6.73 (m, 2H, Ar-H), 3.79 (s, 6H, OCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 159.9, 138.7, 129.7, 128.9, 119.3, 113.4, 111.8, 55.3; LRMS (EI) m/z 240.1 [M]+; HRMS (EI) calculated for C₁₆H₁₆O₂ [M]+ 240.1150, found 240.1149.

**tert-Butyl 4-vinylphenylcarbamate 234¹²⁸**

![tert-Butyl 4-vinylphenylcarbamate](image)

Di-tert-butyl dicarbonate (0.98 g, 4.5 mmol) was added to a solution of 4-vinylaniline (0.35 ml, 3.0 mmol) dissolved in dichloromethane (50 ml). The reaction was stirred at room temperature for 18 h. The solvent was removed under reduced pressure to give the title compound as a beige solid (0.45 g, 68%) after column chromatography eluting with ethyl
acetate : petroleum ether (20 : 80). IR (thin film)/cm$^{-1}$: 3435, 2980, 1718, 1587, 1161;
$^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.27-7.25 (m, 4H, Ar-H), 6.55 (dd, $J = 11.2$ & 17.6 Hz, 1H, ArCH=CH$_2$), 6.44 (s, 1H, NH), 5.58 (apparent d, $J = 17.6$ Hz, 1H, CH=CHH), 5.08 (apparent d, $J = 11.2$ Hz, 1H, ArCH=CHH), 1.45 (s, 9H, C(CH$_3$)$_3$); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 152.6, 138.0, 136.2, 132.6, 126.9, 118.4, 112.4, 80.6, 28.4; LRMS (EI) m/z 219.1 [M$^+$]; HRMS (EI) calculated for C$_{13}$H$_{17}$O$_2$N [M]$^+$ 219.1259, found 219.1258.

$N$-(2-Vinylphenyl)acetamide 190$^{71}$

$N$-(2-Bromophenyl)acetamide (9.6 g, 45 mmol), ethylene glycol dimethyl ether (180 ml) and tetrakis(triphenylphosphine)palladium(0) (1.0 g, 0.9 mmol) was placed in a two necked round bottom flask covered in tin-foil equipped with reflux condenser with a nitrogen inlet, magnetic stirrer bar and glass stopper. The apparatus was maintained under an atmosphere of nitrogen during the course of the reaction. The reaction mixture was stirred at room temperature for 20 min. Potassium carbonate (6.2 g, 45 mmol) in water (55 ml) was added followed by 2,4,6-trivinylcyclotriboroxane-pyridine complex (5.3 g, 22 mmol). The reaction was heated at reflux for 20 h and then allowed to cool to room temperature. Distilled water (75 ml) was added and the resulting mixture was filtered. The filtrate was transferred to a separating funnel and extracted with diethyl ether (100 ml). The aqueous layer was further extracted with diethyl ether (2 x 100 ml) and the combined organic phases dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to give a pale yellow solid after purification by column chromatography eluting with diethyl ether : petroleum ether (10 : 90). The solid was dissolved in a hot mixture of cyclohexane and dichloromethane (4 : 1) (55 ml) and the warm solution filtered. The solution was allowed to cool to room temperature before being immersed in an ice bath for 30 min. The resulting crystals were collected by filtration to give the title compound as a white crystalline solid (4.8 g, 67 %). IR (thin film)/cm$^{-1}$: 3283, 1672, 1520;
Trimethyl(2-(4-vinylphenyl)ethynyl)silane 246\textsuperscript{75}

Dry triethylamine (40 ml) was added to a round bottomed flask covered in tin-foil equipped with large magnetic stirrer. 4-bromostyrene (1.30 ml, 10 mmol), trimethylsilylacetylene (3.2 ml, 22 mmol) and bis(triphenylphosphine)palladium(II)chloride (0.15 g, 0.2 mmol) were added to the flask and the reaction mixture was heated at 50 °C. After 5 min. copper(I) iodide (0.03 g, 0.2 mmol) was added which resulted in the reaction mixture turning from brown/red to black. The reaction mixture was heated at 50 °C for a further 16 h and the precipitated triethylammonium chloride salt removed by filtration. Removal of the solvent under reduced pressure gave the title compound as a pale yellow oil (0.70 g, 35%) after purification of the resulting brown oil by column chromatography eluting with petroleum ether. IR (thin film)/cm\textsuperscript{-1}: 2961, 2361, 2154, 1504, 1250, 848; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.22 (d, \(J = 8.3\) Hz, 2H, Ar-H), 7.16 (d, \(J = 8.3\) Hz, 2H, Ar-H), 6.49 (dd, \(J = 10.9\) & 17.6 Hz, 1H, ArCH=CH\textsubscript{2}), 5.56 (apparent d, \(J = 17.6\) Hz, 1H, ArCH=CHH), 5.10 (app d, \(J = 10.9\) Hz, 1H, ArCH=CHH), 0.00 (s, 9H, Si(CH\textsubscript{3})\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 137.7, 136.3, 132.2, 126.0, 122.4, 114.8, 105.1, 94.8, 0.00; LRMS (EI) \(m/z\) 200.1 [M]+; HRMS (MALDI) calculated for C\textsubscript{13}H\textsubscript{16}Si [M]+ 200.1016, found 200.1019.
**Chapter 5 – Experimental**

**1-Ethynyl-4-vinylbenzene**

Trimethyl(2-(4-vinylphenyl)ethynyl)silane (0.54 g, 2.7 mmol) was dissolved in dry THF (10 ml) and 1.0 M solution of tetra-n-butyl ammonium fluoride (4.0 ml, 4.0 mmol) added. The reaction was stirred at room temperature under nitrogen for 1 h. The reaction mixture was reduced to dryness and partitioned between dichloromethane (25 ml) and water (25 ml). The aqueous layer was further extracted with dichloromethane (2 x 15 ml) and the combined organic layers washed with brine (15 ml) and dried over MgSO₄. Removal of the solvent under reduced pressure gave the title compound as a pale yellow oil (0.20 g, 57%) after purification by column chromatography eluting with petroleum ether. ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.35 (m, 2H, Ar-H), 7.27–7.25 (m, 2H, Ar-H), 6.60 (dd, J = 10.9 & 17.6 Hz, 1H, ArCH=CH₂), 5.67 (dd, J = 0.7 & 17.7 Hz, 1H, ArCH=CHH), 5.20 (dd, J = 0.7 & 10.9 Hz, 1H, ArCH=CHH), 3.01 (s, 1H, =CH); ¹³C NMR (125 MHz, CDCl₃) δ 138.4, 136.5, 132.7, 126.5, 121.7, 115.5, 84.1, 78.2; LRMS (EI) m/z 128.0 [M]+; HRMS (MALDI) calculated for C₁₀H₈ [M]+ 128.0621, found 128.0621.
Chapter 6: Appendix
Appendix 1: DSC data for cyclopropane malonoyl peroxide 129
Appendix 2: DSC data for cyclobutane malonoyl peroxide 130

Integral $10.97 \times 10^3$ mJ
Normalized 1443.08 J g$^{-1}$
Peak $160.91 \, ^\circ$C
Left Limit $100.83 \, ^\circ$C
Right Limit $179.88 \, ^\circ$C

Integral $-5244 \, mJ$
Normalized $-69.06 \, J \, g^{-1}$
Peak $-5244 \, mJ$
Left Limit $-320.50 \, ^\circ$C
Right Limit $-120.56 \, ^\circ$C
Appendix 3: DSC data for cyclopentane malonoyl peroxide 131

Integral normalized 875.86 mJ
Peak 128.38 °C
Left Limit 71.02 °C
Right Limit 151.47 °C

Integral normalized 39.02 J g⁻¹
Peak 168.31 °C
Left Limit 154.34 °C
Right Limit 210.75 °C

Integral normalized -473.95 J g⁻¹
Peak 31.14 °C
Left Limit 47.67 °C
Appendix 4: X-ray data for cyclopropane malonoyl peroxide 129
### Table 1. Crystal data and structure refinement for nct0808t.

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Chapter 6 - Appendix

Table 2. Atomic coordinates ($x\times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for nct0808t. U(eq) is defined as one third of the trace of the orthogonalized U tensor.

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Table 3. Bond lengths [Å] and angles [°] for nct0808t.

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</tr>
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<tr>
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<td>121.31(7)</td>
</tr>
<tr>
<td>C(1)#1-C(2)-C(3)</td>
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</tr>
<tr>
<td>C(1)-C(2)-C(3)</td>
<td>121.31(7)</td>
</tr>
<tr>
<td>C(3)#2-C(2)-C(3)</td>
<td>56.82(16)</td>
</tr>
<tr>
<td>C(3)#2-C(3)-C(2)</td>
<td>61.59(8)</td>
</tr>
<tr>
<td>C(1)-O(1)-O(1)#1</td>
<td>108.19(8)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y,z  #2 x,y,-z+1/2
Anisotropic displacement parameters (Å² x 10³) for nct0808t. The anisotropic displacement factor exponent takes the form: -2π²\[ h²a*²U_{11} + ... + 2 \ h \ k \ a* \ b* \ U_{12} \]

<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>
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<tbody>
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<td>32(1)</td>
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<td>0</td>
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<td>C(2)</td>
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<td>23(1)</td>
<td>21(1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C(3)</td>
<td>30(1)</td>
<td>26(1)</td>
<td>41(1)</td>
<td>8(1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>O(1)</td>
<td>40(1)</td>
<td>28(1)</td>
<td>29(1)</td>
<td>0</td>
<td>0</td>
<td>8(1)</td>
</tr>
<tr>
<td>O(2)</td>
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<td>34(1)</td>
<td>0</td>
<td>0</td>
<td>7(1)</td>
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**Table 5.** Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for nct0808t.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1)</td>
<td>5849(14)</td>
<td>8520(13)</td>
<td>480(20)</td>
<td>43(4)</td>
</tr>
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</table>
Appendix 5: X-ray data for cyclobutane malonoyl peroxide
<table>
<thead>
<tr>
<th>Identification code</th>
<th>nct0805</th>
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</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C6 H6 O4</td>
</tr>
<tr>
<td>Formula weight</td>
<td>142.11</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 6.4920(7) Å (\alpha = 90^\circ), b = 6.1380(6) Å (\beta = 91.908(4)^\circ), c = 7.6100(8) Å (\gamma = 90^\circ)</td>
</tr>
<tr>
<td>Volume</td>
<td>303.07(5) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.557 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.134 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>148</td>
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<tr>
<td>Crystal size</td>
<td>0.20 x 0.20 x 0.20 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>4.06 to 27.43°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-8 &lt;= h &lt;= 8, -7 &lt;= k &lt;= 7, -9 &lt;= l &lt;= 9</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>1237</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>1237 [R(int) = 0.0000]</td>
</tr>
<tr>
<td>Completeness to theta = 27.43°</td>
<td>97.6 %</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9737 and 0.9737</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on (F^2)</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1237 / 1 / 91</td>
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<tr>
<td>Goodness-of-fit on (F^2)</td>
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<tr>
<td>Final R indices ([1&gt;2\sigma(1)])</td>
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</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0569, wR2 = 0.1177</td>
</tr>
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<td>Absolute structure parameter</td>
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</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.269 and -0.195 eÅ⁻³</td>
</tr>
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</table>
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for nct0805. U(eq) is defined as one third of the trace of the orthogonalized U^ij tensor.

<table>
<thead>
<tr>
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<th>y</th>
<th>z</th>
<th>U(eq)</th>
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<tbody>
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<td>1114(5)</td>
<td>8176(8)</td>
<td>29(1)</td>
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<tr>
<td>C(3)</td>
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<td>2880(14)</td>
<td>9572(2)</td>
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<td>4639(4)</td>
<td>8205(7)</td>
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<td>2830(13)</td>
<td>6983(2)</td>
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<tr>
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<td>2658(3)</td>
<td>2850(10)</td>
<td>5087(2)</td>
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<td>O(1)</td>
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<td>4072(2)</td>
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<td>2850(10)</td>
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<td>2848(10)</td>
<td>8153(2)</td>
<td>40(1)</td>
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Table 3. Bond lengths [Å] and angles [°] for nct0805.

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<th>Length/Angle</th>
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<td>C(1)-C(6)</td>
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<tr>
<td>C(1)-C(4)</td>
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<td>C(2)-C(3)</td>
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<tr>
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</table>

Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å² x 10³) for net0805. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [ h^2 a^{*2} U_{11} + ... + 2 h k a^{*} b^{*} U_{12} ]$

<table>
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<tr>
<th></th>
<th>$U_{11}$</th>
<th>$U_{22}$</th>
<th>$U_{33}$</th>
<th>$U_{12}$</th>
<th>$U_{13}$</th>
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<td>-2(2)</td>
<td>3(2)</td>
<td>0(2)</td>
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<tr>
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<td>21(1)</td>
<td>-7(3)</td>
<td>6(1)</td>
<td>4(3)</td>
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<td>2(1)</td>
<td>2(3)</td>
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</table>
Table 5. Hydrogen coordinates (x $10^4$) and isotropic displacement parameters (Å² $10^3$) for nct0805.

<table>
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<td>9979</td>
<td>36</td>
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<tr>
<td>H(3B)</td>
<td>2902</td>
<td>2876</td>
<td>10580</td>
<td>36</td>
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<td>5762</td>
<td>8619</td>
<td>30</td>
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<tr>
<td>H(4B)</td>
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<td>5316</td>
<td>7690</td>
<td>30</td>
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</table>
Appendix 6: X-ray data for cyclopentane malonoyl peroxide 131
Table 1. Crystal data and structure refinement for nt0801.

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</thead>
<tbody>
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</tr>
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<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a = 9.4480(7) Å</td>
<td>α = 90°</td>
</tr>
<tr>
<td>b = 6.4650(5) Å</td>
<td>β = 95.283(3)°</td>
</tr>
<tr>
<td>c = 11.5900(11) Å</td>
<td>γ = 90°</td>
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<tr>
<td>Volume</td>
<td>704.93(10) Å³</td>
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<td>Z</td>
<td>4</td>
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<tr>
<td>Density (calculated)</td>
<td>1.471 Mg/m³</td>
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<td>Absorption coefficient</td>
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<td>F(000)</td>
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<td>Crystal size</td>
<td>0.30 x 0.12 x 0.10 mm³</td>
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<td>3.53 to 27.51°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-12&lt;=h&lt;=12, -8&lt;=k&lt;=7, -14&lt;=l&lt;=14</td>
</tr>
<tr>
<td>Reflections collected</td>
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<tr>
<td>Independent reflections</td>
<td>1614 [R(int) = 0.0529]</td>
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<td>99.4 %</td>
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<tr>
<td>Max. and min. transmission</td>
<td>0.9879 and 0.9642</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1614 / 0 / 100</td>
</tr>
<tr>
<td>Goodness-of-fit on $F^2$</td>
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</tr>
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<td>Final R indices [I&gt;2sigma(I)]</td>
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<tr>
<td>R indices (all data)</td>
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</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.271 and -0.343 e.Å⁻³</td>
</tr>
</tbody>
</table>
Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for nt0801. $U(eq)$ is defined as one third of the trace of the orthogonalized $U^\| tensor.

<table>
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<th>x</th>
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<th>z</th>
<th>U(eq)</th>
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### Table 3. Bond lengths [Å] and angles [°] for nt0801.

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<th>Length/Angle</th>
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<th>Angle</th>
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</table>
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C(4)-C(3)-H(3A)  111.4
C(2)-C(3)-H(3A)  111.4
C(4)-C(3)-H(3B)  111.4
C(2)-C(3)-H(3B)  111.4
H(3A)-C(3)-H(3B)  109.2
C(3)-C(4)-C(5)  103.91(17)
C(3)-C(4)-H(4A)  111.0
C(5)-C(4)-H(4A)  111.0
C(3)-C(4)-H(4B)  111.0
C(5)-C(4)-H(4B)  111.0
H(4A)-C(4)-H(4B)  109.0
C(4)-C(5)-C(1)  105.57(17)
C(4)-C(5)-H(5A)  110.6
C(1)-C(5)-H(5A)  110.6
C(4)-C(5)-H(5B)  110.6
C(1)-C(5)-H(5B)  110.6
H(5A)-C(5)-H(5B)  108.8
O(1)-C(6)-O(2)  117.44(18)
O(1)-C(6)-C(1)  132.3(2)
O(2)-C(6)-C(1)  110.26(17)
O(4)-C(7)-O(3)  118.4(2)
O(4)-C(7)-C(1)  131.3(2)
O(3)-C(7)-C(1)  110.27(17)
C(6)-O(2)-O(3)  108.03(14)
C(7)-O(3)-O(2)  108.00(14)

Symmetry transformations used to generate equivalent atoms:

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Table 4. Anisotropic displacement parameters (Å² x 10³) for nt0801. The anisotropic displacement factor exponent takes the form: -2π²\[h²a²U_{11} + ... + 2hkabU_{12} \]

<table>
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<th>( U_{11} )</th>
<th>( U_{22} )</th>
<th>( U_{33} )</th>
<th>( U_{12} )</th>
<th>( U_{13} )</th>
<th>( U_{23} )</th>
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<td>-1(1)</td>
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<td>20(1)</td>
<td>4(1)</td>
<td>3(1)</td>
<td>-1(1)</td>
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<tr>
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<td>24(1)</td>
<td>25(1)</td>
<td>1(1)</td>
<td>2(1)</td>
<td>1(1)</td>
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<td>-7(1)</td>
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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for nt0801.

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<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
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<td>10035</td>
<td>33</td>
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<td>H(2B)</td>
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<td>-2372</td>
<td>9239</td>
<td>33</td>
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<tr>
<td>H(3A)</td>
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<td>37</td>
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<td>H(3B)</td>
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<td>8865</td>
<td>37</td>
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<td>H(4B)</td>
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<td>H(5B)</td>
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<td>1676</td>
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Appendix 7: X-ray data for cyclohexane malonoyl peroxide 132
Table 1. Crystal data and structure refinement for nct0905.

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<td>Space group</td>
<td>P21/n</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a = 10.6392(5) Å</td>
</tr>
<tr>
<td></td>
<td>b = 6.5793(4) Å</td>
</tr>
<tr>
<td></td>
<td>c = 11.6462(9) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>802.89(9) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.408 Mg/m³</td>
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<tr>
<td>Absorption coefficient</td>
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</tr>
<tr>
<td>F(000)</td>
<td>360</td>
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<tr>
<td>Crystal size</td>
<td>0.40 x 0.06 x 0.06 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.85 to 27.47°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-13&lt;=h&lt;=13, -8&lt;=k&lt;=8, -15&lt;=l&lt;=15</td>
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<tr>
<td>Reflections collected</td>
<td>3422</td>
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<tr>
<td>Independent reflections</td>
<td>1838 [R(int) = 0.0638]</td>
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<tr>
<td>Completeness to theta = 27.47°</td>
<td>99.7 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Empirical</td>
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<tr>
<td>Max. and min. transmission</td>
<td>0.9932 and 0.9559</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<tr>
<td>Data / restraints / parameters</td>
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<tr>
<td>Goodness-of-fit on F²</td>
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</tr>
<tr>
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<tr>
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<td>Extinction coefficient</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.180 and -0.187 e.Å⁻³</td>
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</table>
Table 6—Appendix

Table 2. Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters (Å² $10^3$) for nct0905. U(eq) is defined as one third of the trace of the orthogonalized U_ij tensor.

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<th>z</th>
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### Table 3. Bond lengths [Å] and angles [°] for nct0905.

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</table>
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Table 4. Anisotropic displacement parameters (Å² x 10³) for net0905. The anisotropic displacement factor exponent takes the form: \(-2\pi² [ h²a^*²U_{11} + ... + 2hk a^* b^* U_{12} ] \)

<table>
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<th>(U_{13})</th>
<th>(U_{22})</th>
<th>(U_{23})</th>
<th>(U_{33})</th>
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Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\AA^2 \times 10^3$) for nct0905.

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References
References

References

References


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