On the Metal-Free Dihydroxylation of Alkenes.

Kevin M. Jones

A Thesis Submitted for the Degree of Doctor of Philosophy

at

Cardiff University

2010

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

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.

Signed ..... (Kevin M. Jones)

Date.....07/07/10.....

STATEMENT 2

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

Signed ..... (Kevin M. Jones)

Date.....07/07/10.....

"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.

Many thanks to our post-docs Dr John Brazier, Dr Achim Porzelle and Dr Jacky Yau for their time and patience. A special thank you is extended to Dr John Brazier whose interest in my project has been inspirational and resulted in many chemical discussions from which I have learnt a great deal

A big thank you is also extended to Ian King who has provided many a challenging chemical problem which made the working day even more enjoyable.

I would also like to thank Tim, Matt, Deb, Paul, Leo, Sylvain and Mike for making lab 1.119 an enjoyable place of work.

I must also acknowledge all the analytical and technical staff especially Rob Jenkins, Robin, Dave, Gaz and Jamie for their hard-work and help.

I would also like to say a big thank you to my parents and friends outside of work.

Finally, I thank Wai Yin for her encouragement and love over the last three years. She has filled my life with happiness.

Table of Contents

Detailed Table of Contents

Abbreviations

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

AD	Asymmetric dihydroxylation
App	Apparent
APCI	Atmospheric pressure chemical ionisation
aq.	Aqueous
Ar	Aromatic
BHT	Butylated hydroxyl toluene
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
b.p.	Boiling point
BPO	Benzoyl peroxide
br	Broad
Bu	Butyl
Column chromatography	Flash column chromatography
CI	Chemical ionisation
d	Day(s)
d	doublet
dd	doubled doublet
Da	Dalton(s)
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DMAP	4-Dimethylaminopyridine

DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DSC	Differential scanning calorimetry
d.r.	Diastereomeric ratio
e.e.	Enantiomeric excess
EI	Electron ionisation
EPSRC	Engineering and Physical Sciences Research Council
eq.	Equivalent(s)
ES	Electrospray
Et	Ethyl
g	Gram
h	Hour(s)
HRMS	High resolution mass spectroscopy
Hz	Hertz
IR	Infra-red
J	Coupling constant
k	Kilo
L	Ligand
lit.	Literature
m	*meta*
m	Multiplet
M	Molar
MALDI	Matrix assisted laser desorption ionisation
Me	Methyl
MHz	Megahertz

min.	Minute(s)
ml	millilitres
mmol	Millimole(s)
m.p.	Melting point
MS	Mass spectroscopy
n	*normal*
NMR	Nuclear magnetic resonance
o	*ortho*
P	Product
p	*para*
Ph	Phenyl
PHAL	Phthalazine
ppm	Parts per million
q	Quartet
quin	Quintet
r.t.	Room temperature
s	Singlet
SAD	Sharpless asymmetric dihydroxylation
SET	Single electron transfer
SM	Starting material
t	Triplet
TBAF	Tetra *n*-butylammonium fluoride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl

z	Charge
Å	Angstroms
μmol	Micromole(s)

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.[1] Transition-metals enjoy widespread use in organic synthesis; however, the cost, toxicity and environmental impact associated with these reagents has become increasingly prohibitive.[2] 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.[3] 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.[4] 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.[5] 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[2] 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.[6] 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.

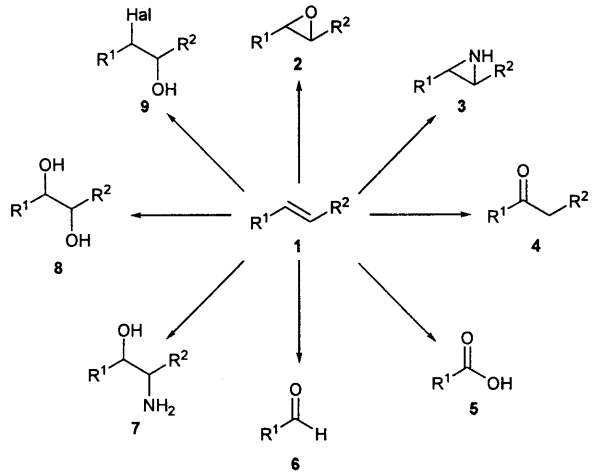


Fig. 1.1

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.[7] From a synthetic standpoint, 1,2-diols are valuable intermediates in the preparation of pharmaceuticals, agrochemicals and other fine chemicals.[8] Additionally, the 1,2-diol sub unit is present in a number of natural products with varied biological activity.[9]

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

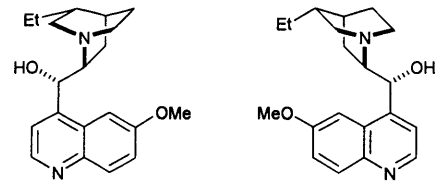
Amongst the reagents available for alkene dihydroxylation, none have achieved more success than osmium tetroxide. For over eighty years, the use of OsO_4 has been developed and refined and currently forms the basis of one of the most powerful transformations in synthetic chemistry.[10]

1.2.1.1 Discovery and catalytic development

The dihydroxylation of unsaturated compounds with OsO_4 has long been known.[11] The original reaction used stoichiometric amounts of OsO_4 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 OsO_4.[12] A wide range of oxidants have since been established including *tert*-butyl hydroperoxide[13] and 4-methylmorpholine *N*-oxide (NMO).[14] A mixture of potassium ferricyanide and K_2CO_3, 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 OsO_4 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.[16] 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.[17]

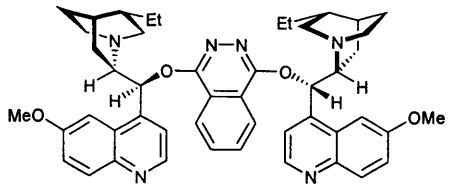


DHQD
10

DHQ
11

Fig. 1.2

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).[18] A number of alternative ligands have also been developed, but $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL remain the most widely used.



$(DHQD)_2$–PHAL
12

Fig. 1.3

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.[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.

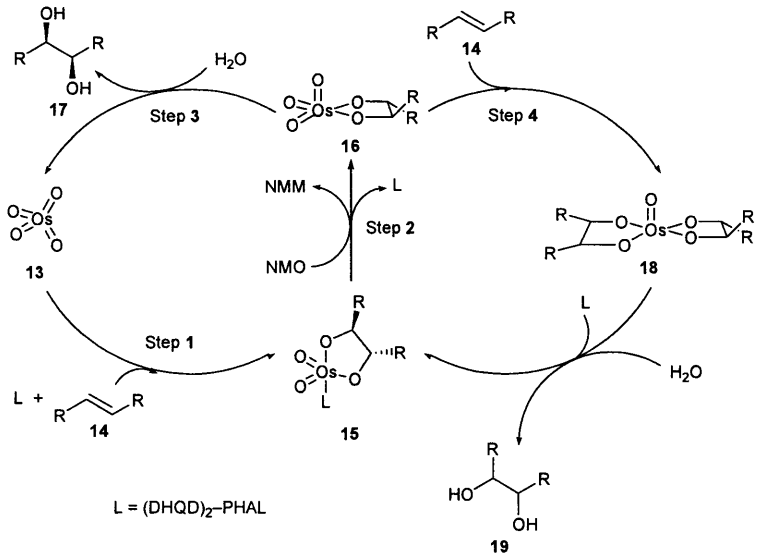


Fig. 1.4

Initially, the enantiomeric excesses obtained from the catalytic reaction were low.[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 ferricycanide and potassium carbonate in a mixture of *tert*-butanol and water.[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

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.

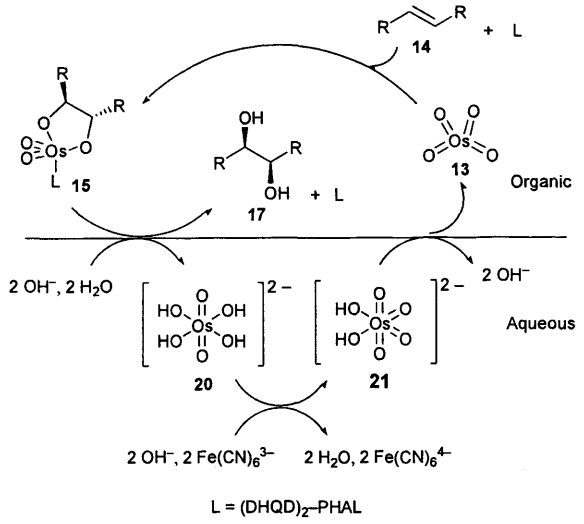


Fig. 1.5

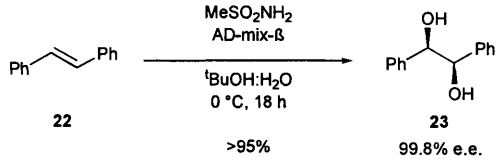
1.2.1.4 Further developments

The addition of methane sulfonamide to the reaction mixture was shown to accelerate the hydrolysis of the osmate ester **15**.[22] 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.

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).[23] Unlike many other transition-metal catalysed transformations, the reaction is tolerant of air and moisture and makes the reaction incredibly simple to perform.



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).[24] 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).[25]

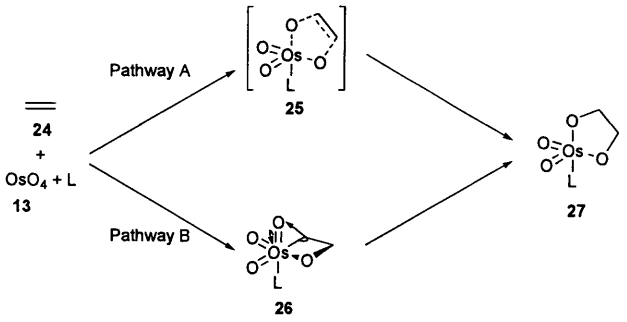


Fig. 1.6

Theoretical and experimental studies from several research groups show a strong preference for a [3+2] cycloaddition.[26]

A detailed structure-activity study revealed dimeric ligands $(DHQ)_2$-PHAL and $(DHQD)_2$-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".[27]

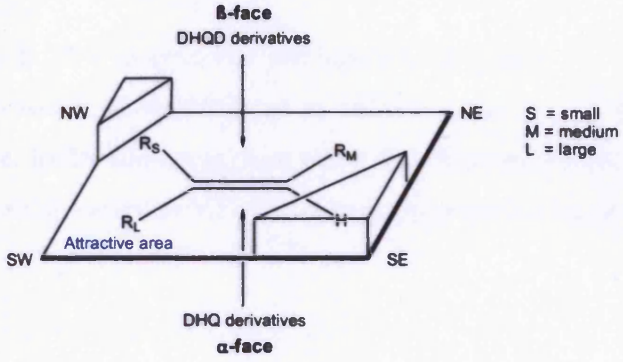


Fig. 1.7

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.[28]

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%.[29]
2) Osmium tetroxide **13** 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_2CO_3 system generates 8.1 kg of waste per kg of diol product.[7]

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.[7] In light of these limitations, much of the current research has focussed on developing "greener" dihydroxylation protocols.

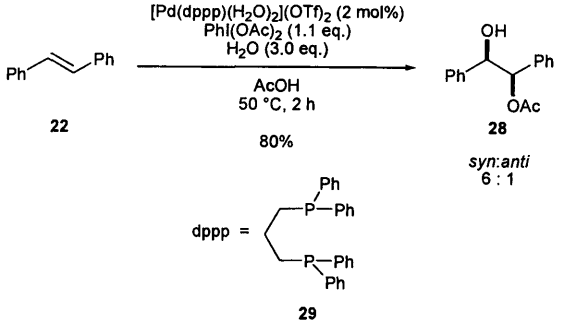
Microencapsulation, the anchoring of reagents to a polymer support, has provided an effective method for recycling osmium tetroxide **13** and chiral ligands $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL. Additionally, this method addresses the issue of toxicity, as osmium tetroxide **13** cannot escape the polymer matrix. Following initial development by Kobayashi,[30] 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.[31]

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.[32]

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]

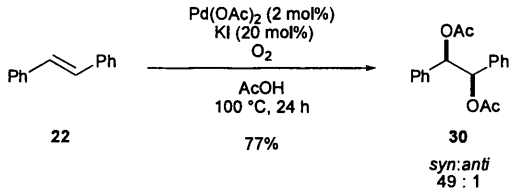
1.2.2 Palladium

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

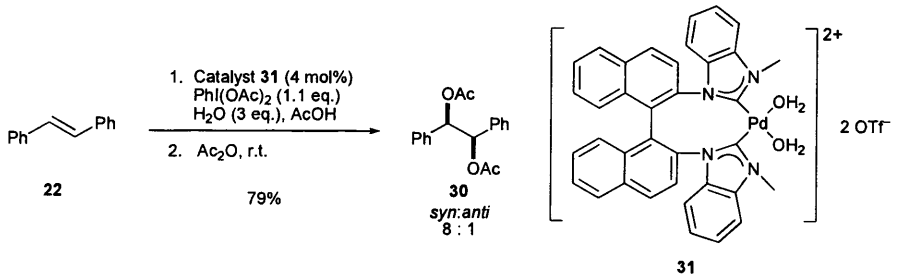
A subsequent report by Jiang and co-workers showed a similar transformation can be achieved with palladium acetate and potassium iodide using oxygen as the sole oxidant.[35] This method possesses a number of advantages over those reported by Song. Firstly, the reaction avoids the use of stoichiometric oxidants such as $PhI(OAc)_2$ **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.



22 77% **30** *syn:anti* 49 : 1

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).[36]



22 79% **30** *syn:anti* 8 : 1 **31**

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.

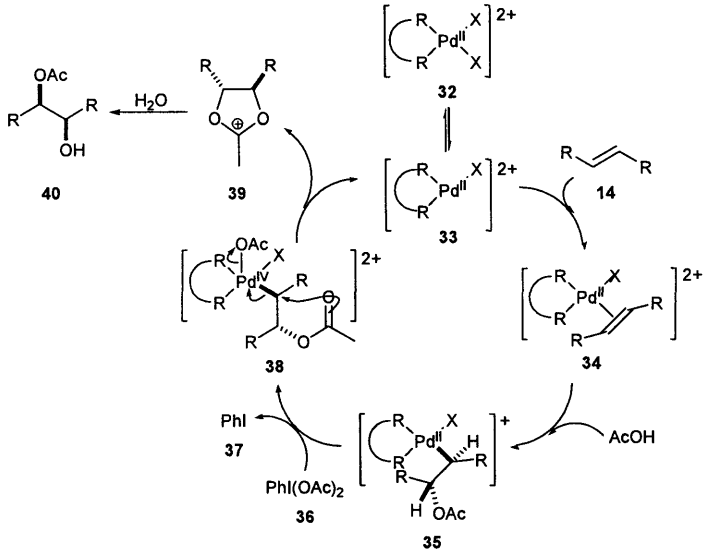


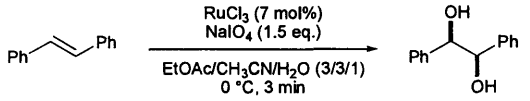
Fig. 1.8

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.

1.2.3 Ruthenium

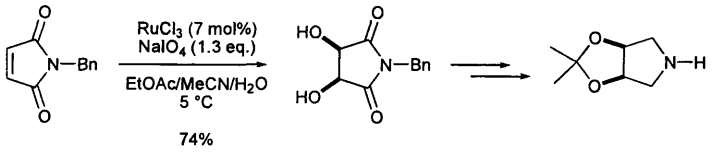
Ruthenium tetroxide is often associated with alkene cleavage[37] and as a result has achieved limited success as a dihydroxylating agent. Recent work by Shing *et al* described the dihydroxylation of a series of alkenes using ruthenium chloride and sodium periodate which forms ruthenium tetroxide *in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



22 39% 41

Scheme 1.5

The procedure above was adopted by Couturier *et al* for the synthesis of 3,4-isopropylidene dioxypyrrolidine **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).[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.



42 43 44

Scheme 1.6

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).[41] On the basis of this model it was proposed that increasing the rate of hydrolysis of **48** would increase the selectivity for dihydroxylation.

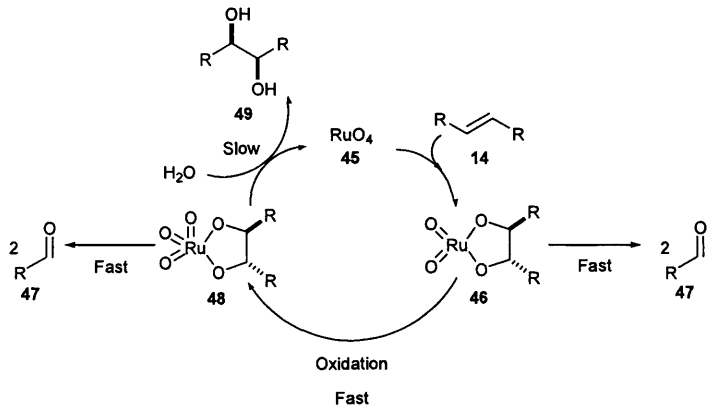
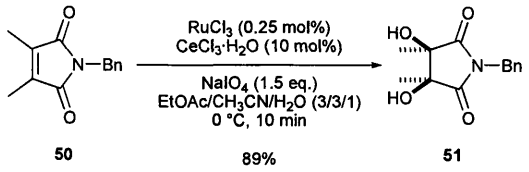


Fig. 1.9

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.

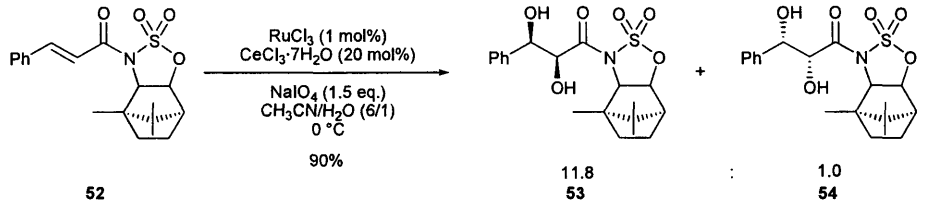
Side-product formation remained problematic and the low pH led to problems with a number of acid labile groups such as silyl ethers. A more recent report from the same group showed employing cerium(III) chloride as a substitute for sulfuric acid resulted in a further increase in rate of hydrolysis and allowed the catalyst loading to be lowered to 0.25 mol%.[42] 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).



50 89% **51**

Scheme 1.7

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)[43]



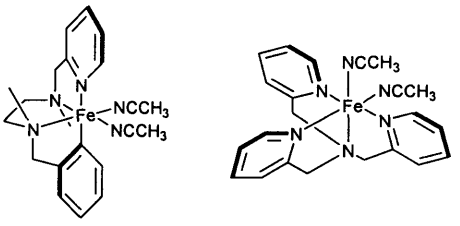
52 **53** **54**

Scheme 1.8

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.

1.2.4 Iron

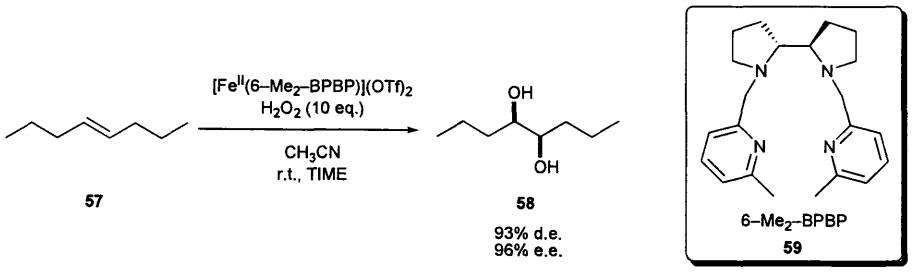
Over the last decade, Que and co-workers have developed a series of bio-inspired iron catalysts capable of *syn*-dihydroxylation using hydrogen peroxide as the sole oxidant. Two typical catalysts are shown in Figure 1.10. A common feature of these catalysts is the presence of *cis*-labile sites which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



55 **56**

Fig. 1.10

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–Fe^{V}=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]



57 **58** **59**

93% d.e.
96% e.e.

Scheme 1.9

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

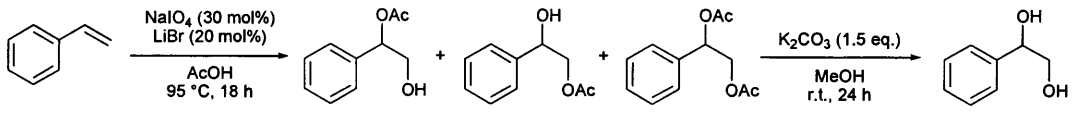
Feringa and co-workers have shown manganese complexes such as $[Mn^{IV}O_2(tmtacn)_2]^{2+}$ (tmtacn = *N*,*N*',*N*''-trimethyl-1,4,7-triazacyclononane) can be used in conjunction with carboxylic acids as effective catalysts for the epoxidation and *syn*-dihydroxylation of alkenes.[47] The addition of 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.[48]

The use of H_2O_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).



60 **61** **62** **63** **64**

87%

Scheme 1.10

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**.

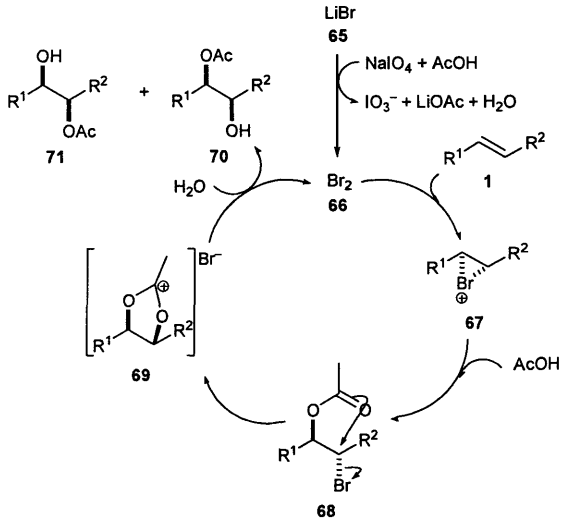
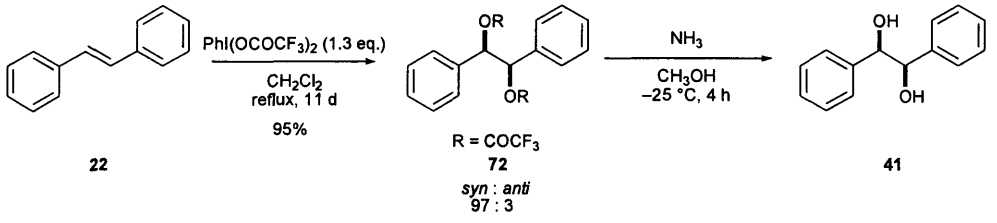


Fig. 1.11

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.[50] Balci and co-workers have recently reported the use of phenyliodine(III) bis(trifluoroacetate) as an effective dihydroxylating agent.[51] Treatment of *trans*-stilbene **22** gave (±)-hydrobenzoin **41** *via* bis(trifluoroacetate) intermediate **72** (Scheme 1.11).



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.[52] 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_N2 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).

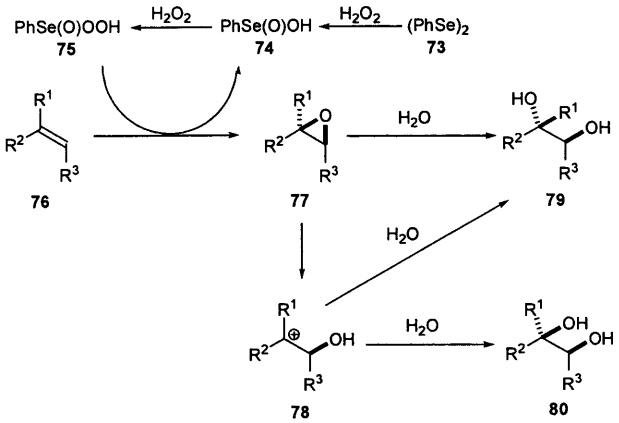
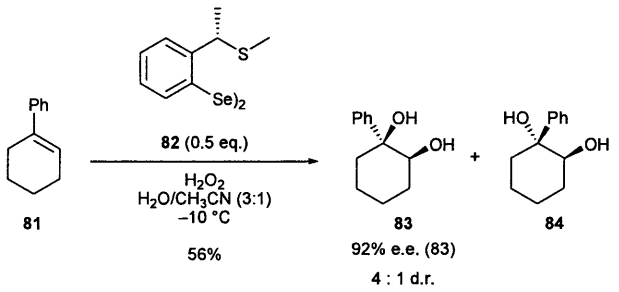


Fig. 1.12

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).



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 **13**, 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*CPBA, and subsequent ring opening provides one of the most commonly used procedures for the preparation of *anti*-1,2-diols.[53] In contrast, examples of peroxide reagents capable of *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

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

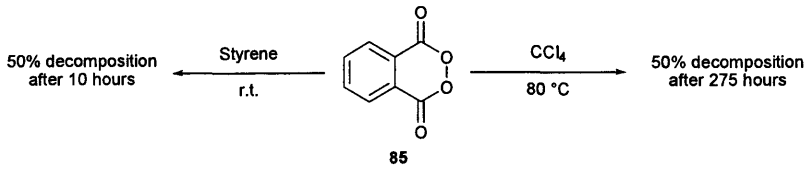
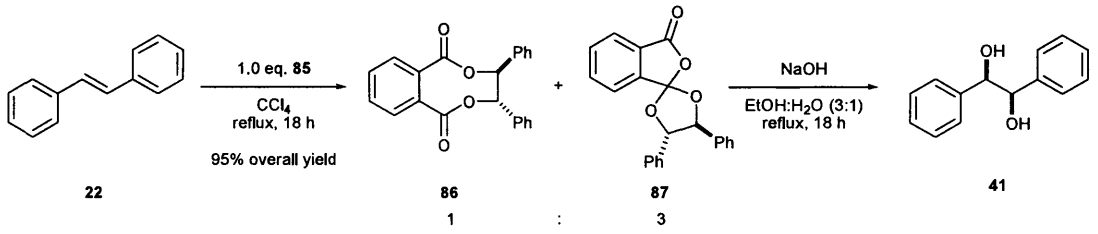


Fig. 2.1

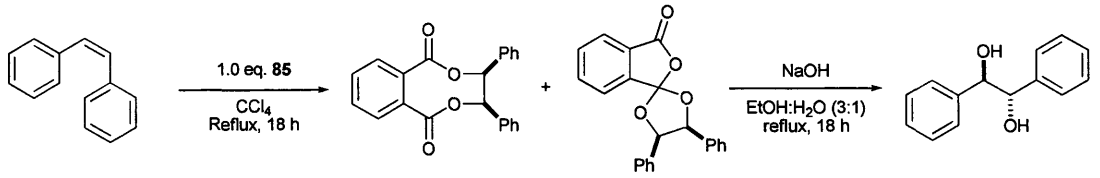
2.4.1.1 Reactivity

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).



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.



Scheme 2.2

2.4.1.2 Mechanistic studies

Kinetic experiments showed the reaction was first order with respect to both PPO **85** and alkene.[56] 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.[57]

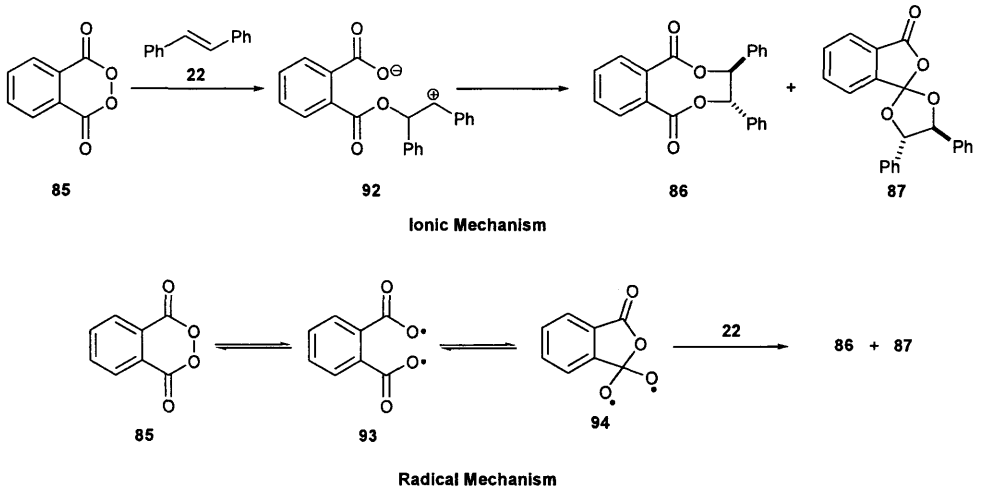


Fig. 2.2

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.

Sample	Experiment	Atom % excess ^{18}O
86	A	1.96
41	A	0.218
86	B	2.20
41	B	0.236

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).

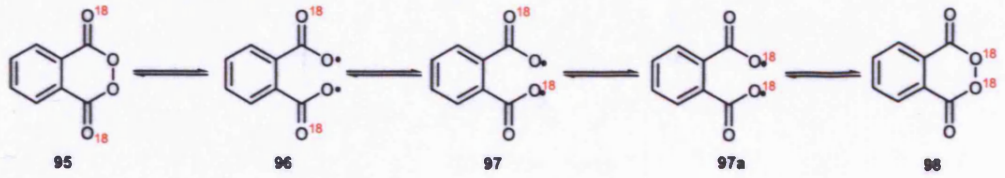
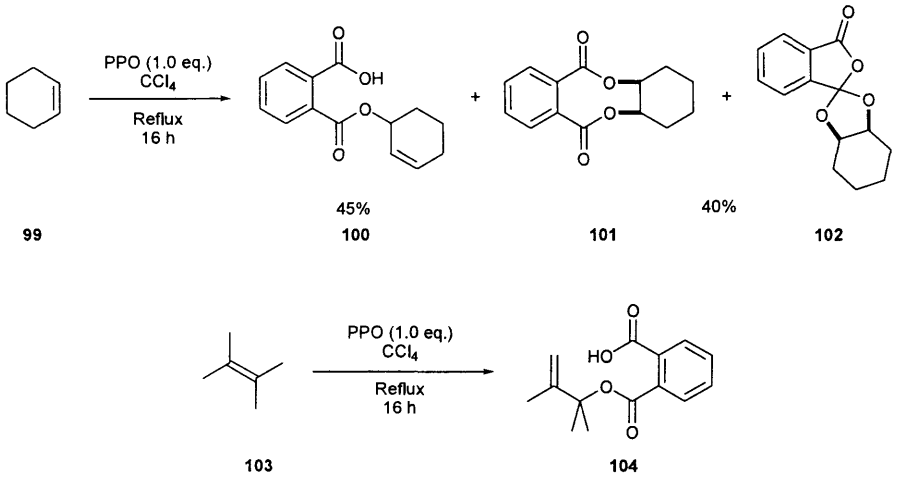


Fig. 2.3

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.[58] The reaction between PPO **85** and tetramethylethylene **103** gave **104** as the exclusive product in high yield[59] (Scheme 2.3).



Scheme 2.3

2.4.2 Limitations

The use of PPO **85** as a dihydroxylating 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).

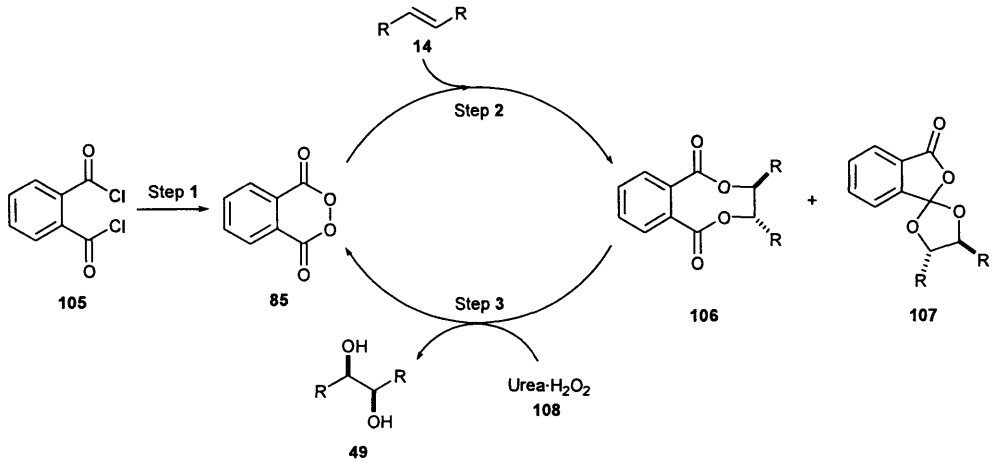
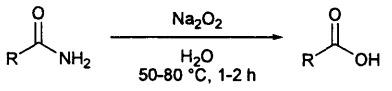


Fig. 2.4

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).[60] This literature precedent suggested cleavage of the ester bonds in **106** and **107** could be possible.

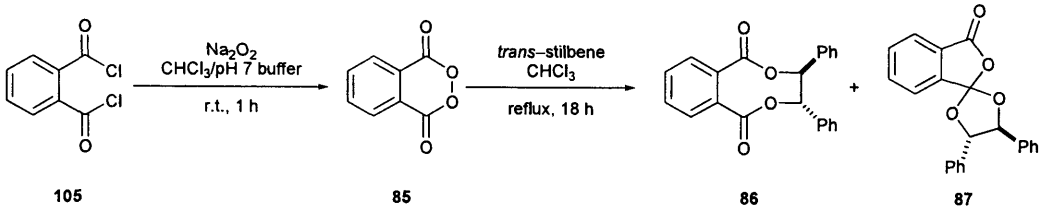


Scheme 2.4

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.

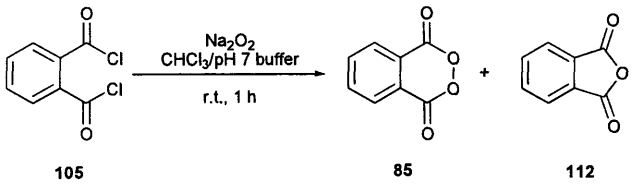
2.6 Initial investigations: reactivity of PPO

PPO **85** was prepared according to the procedure described by Russell.[61] 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).



Scheme 2.5

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.



105 85 112

Scheme 2.6

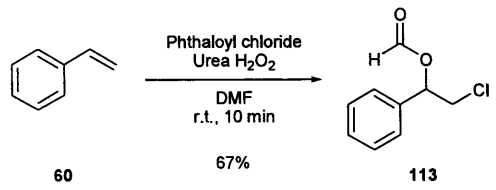
2.6.1 Methods to limit phthalic anhydride formation

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

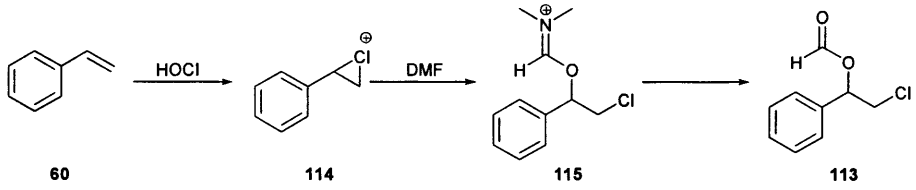
Use of a single solvent system was restricted by the low solubility of sodium peroxide **109** or urea hydrogen peroxide **108** in common reaction solvents. Although **108** and **109** are soluble in alcohol based solvents, these reacted directly with phthaloyl chloride **105**. DMF emerged as the 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)



Scheme 2.7

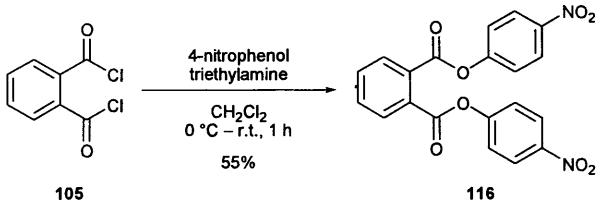
Formation of **113** was attributed to the generation of hypochlorous acid (HOCl) on mixing phthaloyl chloride **105** and urea hydrogen peroxide **108**. Hypochlorous acid acted as a source of positive chlorine which reacted with styrene **60** to give chloronium ion **114**. Ring opening of **114** 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 *m*CPBA and HCl in DMF.[62,63] The use of a single solvent system did not provide an effective procedure for the formation of PPO **85** and was not examined further.



Scheme 2.8

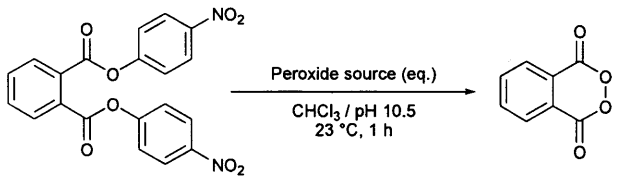
2.6.1.2 Alternative precatalysts

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

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.

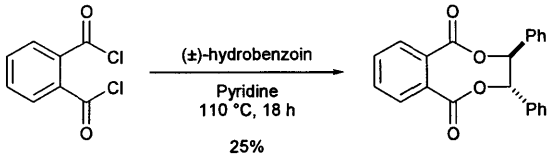


Entry	Peroxide source	Eq. peroxide	Yield %
1	Na_2O_2	1.5	—
2	Na_2O_2	10	—
3	Urea H_2O_2	1.5	—
4	Urea H_2O_2	10	—

Table 2.2

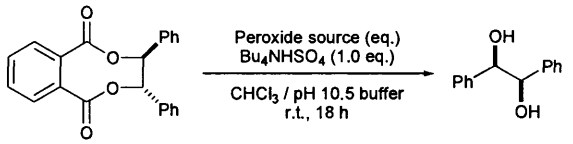
2.7 Initial investigations: Perhydrolysis step

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 alterative 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.



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)



Entry	Peroxide source	Eq. peroxide	Yield %
1	Na_2O_2	1.5	—
2	Na_2O_2	10	—
3	Urea H_2O_2	1.5	—
4	Urea H_2O_2	10	—

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).

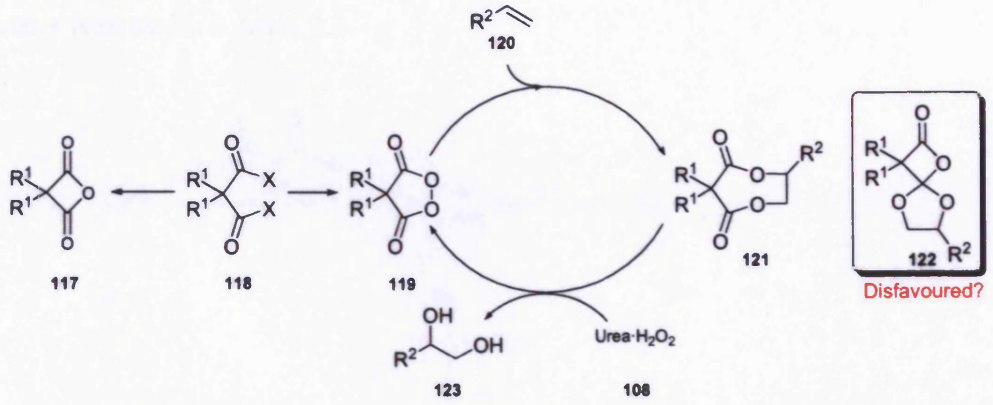
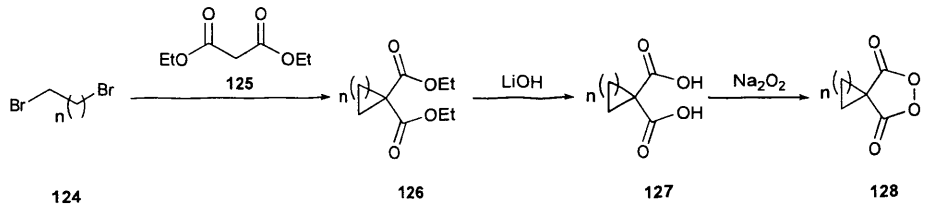


Fig. 3.1

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 **109**.[67] 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.



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).

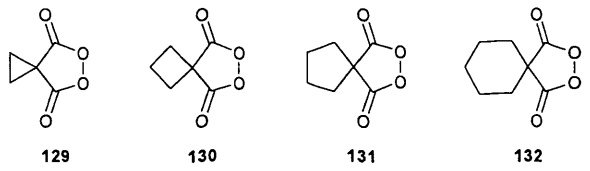
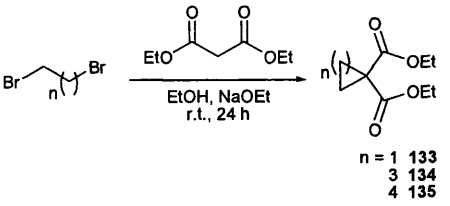


Fig. 3.2

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.*[68] 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).



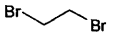
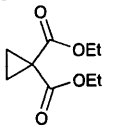
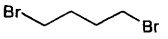
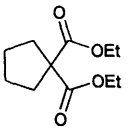
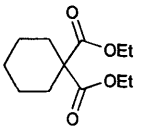
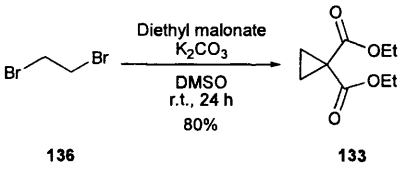
Entry	Dibromoalkane	Product	Yield (%)
1			20
2			50
3			59

Table 3.1

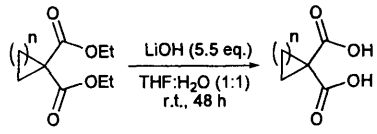
Due to the low yield of **133** under the above conditions (Entry 1), a modified procedure reported by Dmoski *et al.* was adopted (Scheme 3.2).[69]



Scheme 3.2

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:H_2O. 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).



n = 1 **137**
2 **138**
3 **139**
4 **140**

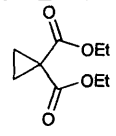
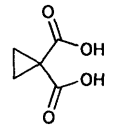
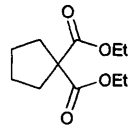
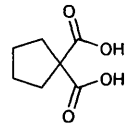
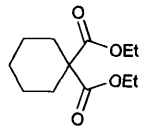
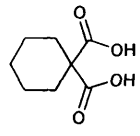
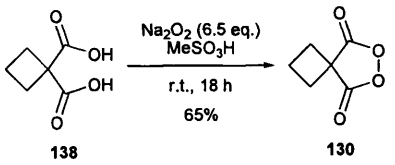
Entry	Diester	Diacid	Yield (%)
1			80
2			78
3			81

Table 3.2

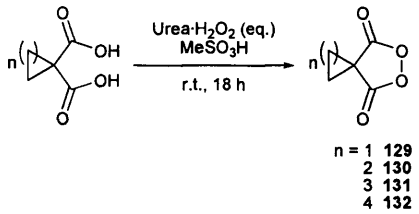
Malonoyl peroxides **129–132** were initially prepared from diacids **137–140** according to the procedure reported by Alberts *et al.*[67] In the case of cyclobutane malonoyl peroxide **130**, treatment of commercially available cyclobutane 1,1-dicarboxylic acid **138** with 6.5 equivalents of sodium 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.



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 **138** 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).



Entry	Diacid	Peroxide eq.	Product	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

Table 3.3

3.2.2 Peroxide safety

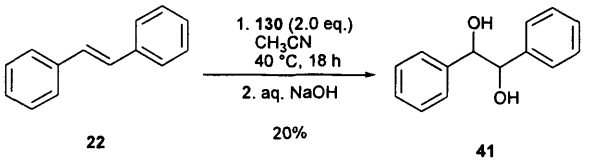
All organic peroxides should be regarded as potentially explosive and handled with due caution. To gauge the hazards associated with the newly formed malonoyl peroxides, small quantities of **129**, **130** and **131** were dried and subjected to thermo-gravimetric analysis and impact tests. These studies 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

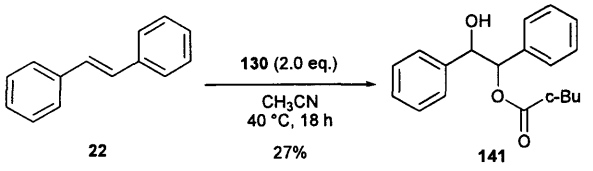
Having prepared a range of peroxide reagents, the next step was to investigate their reactivity with alkenes. Owing to the commercial availability of **138**, cyclobutane malonoyl peroxide **130** was used throughout these exploratory experiments. *Trans*-stilbene **22** was chosen as a test substrate.

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).



Scheme 3.4

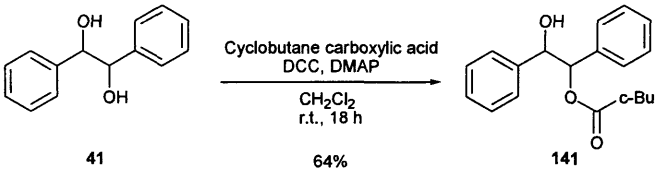
Encouraged by this result, determining the structure of the unknown intermediate became of vital importance. The reaction was repeated under identical conditions (Scheme 3.5) and the unknown intermediate purified by column chromatography. Structure **141** was consistent with analytical data obtained.



22 141

Scheme 3.5

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

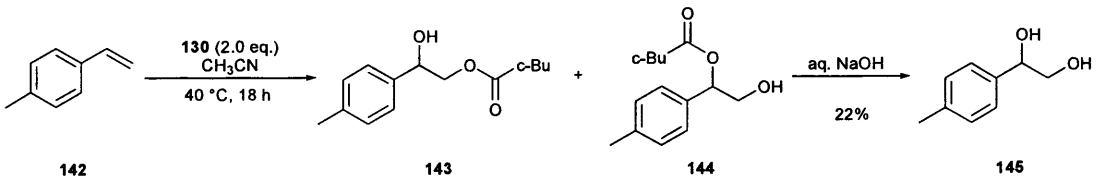


41 141

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.

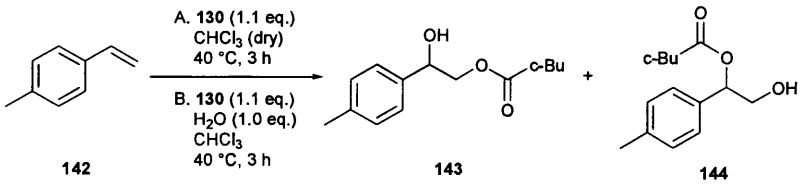
At this stage, extension of the procedure to alternative alkenes was examined. The reaction between 4-methylstyrene **142** and **130** gave two unknown products in a 1:1 ratio (Scheme 3.7). Structures **143** and **144** were consistent with analytical data. Treatment of the crude reaction mixture with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



Scheme 3.7

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.



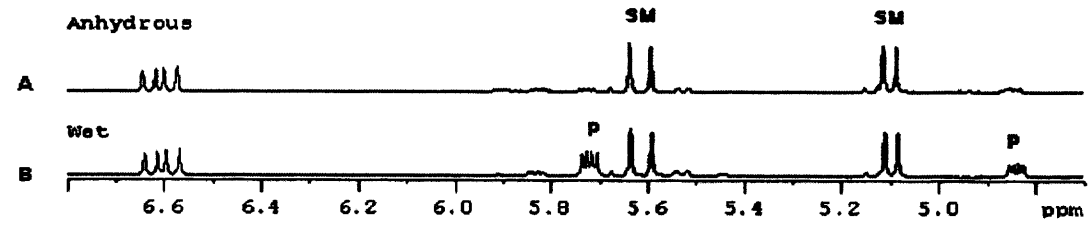
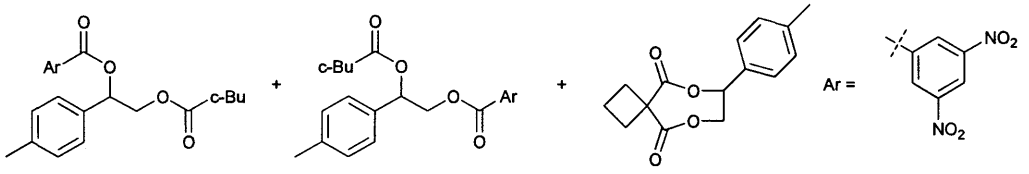


Fig. 3.3

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.

3.3.3 Additional products

As part of the preliminary investigation, a reaction between 4-methylstyrene **142** and cyclobutane malonoyl 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).



146 **147** **148**

Scheme 3.8

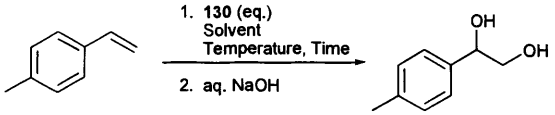
3.3.4 Reaction potential

On the basis of reactions described above, cyclobutane malonoyl 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.

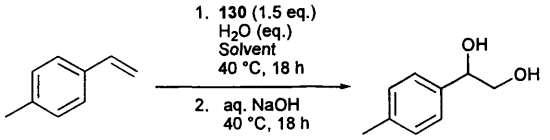


142 **145**

Scheme 3.9

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.



Entry	Solvent	Eq. H_2O	Yield (%)
1	H_2O	—	65
2	DMSO	1	0
3	MeOH	1	0
4	CH_3CN	1	55
5	$CHCl_3$	1	69
6	THF	1	30
7	Toluene	1	60
8	CH_3CN	10	54
9	$CHCl_3$	10	71
10	Toluene	10	60
11	CH_3CN:H_2O (1:1)	-	63
12	$CHCl_3$:pH 7 buffer	-	65
13	$CHCl_3$:pH 10 buffer	-	0

Table 3.4

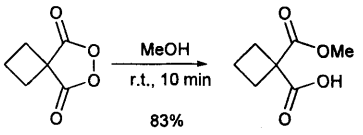
The solvent screen highlighted some interesting factors. On the basis of earlier observations that water was integral to reaction success, the use of water-miscible solvents were predicted to provide the best results. The use of acetonitrile and THF, however, only produced the diol in 54% and 30% respectively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

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 un-necessary.

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]



130 **149**

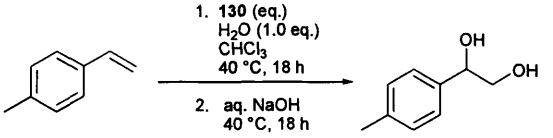
Scheme 3.10

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.



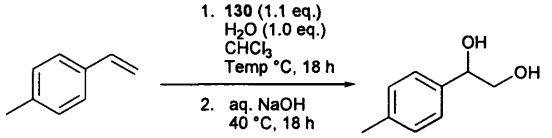
Entry	Eq. of 130	Yield (%)
1	1.0	78
2	1.1	84
3	1.5	69
4	2.0	44
5	3.0	22

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 of 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.



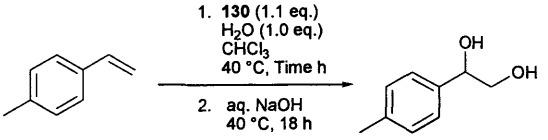
Entry	Temperature (°C)	Yield (%)
1	30	Reaction not complete
2	40	84
3	50	65
4	60	74

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.



Entry	Time (h)	Conversion (%)
1	1	15
2	2	22
3	4	40
4	6	55
5	18	100

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 CO_2 and formation of **153**. The carbocation is subsequently trapped with water to give the observed product (Fig. 3.4)

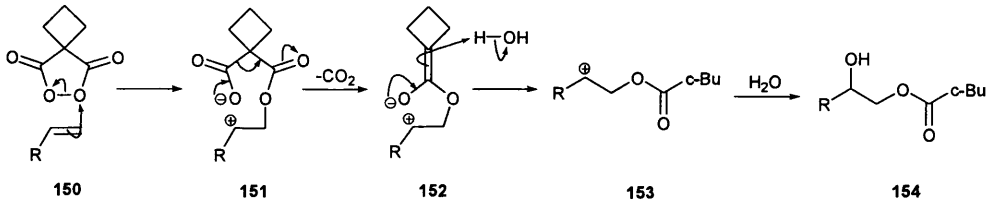


Fig. 3.4

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

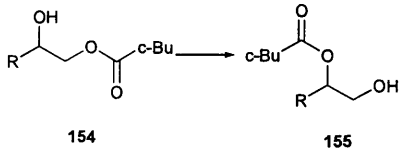


Fig. 3.5

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).

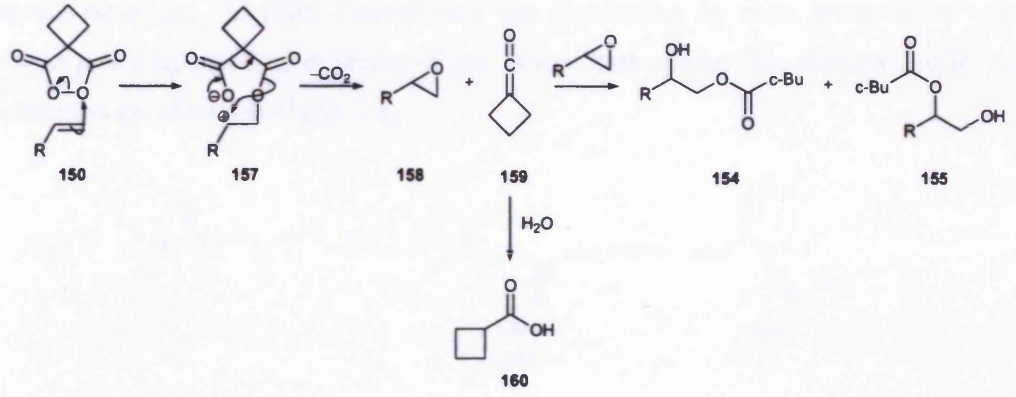


Fig. 3.6

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).

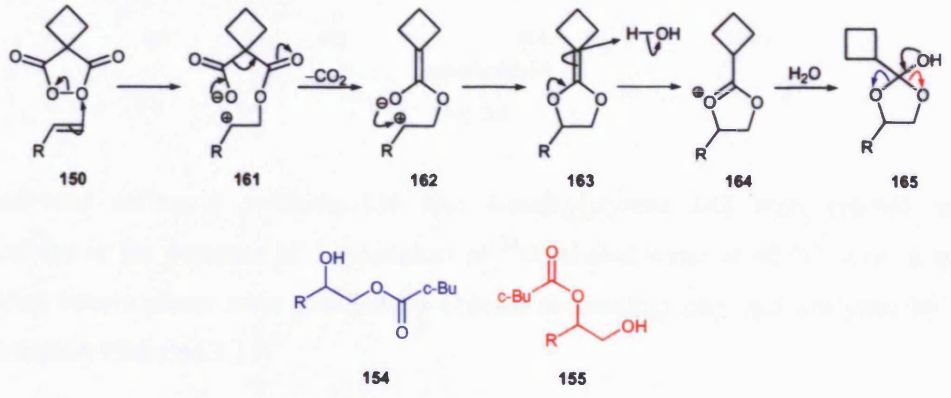


Fig. 3.7

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.

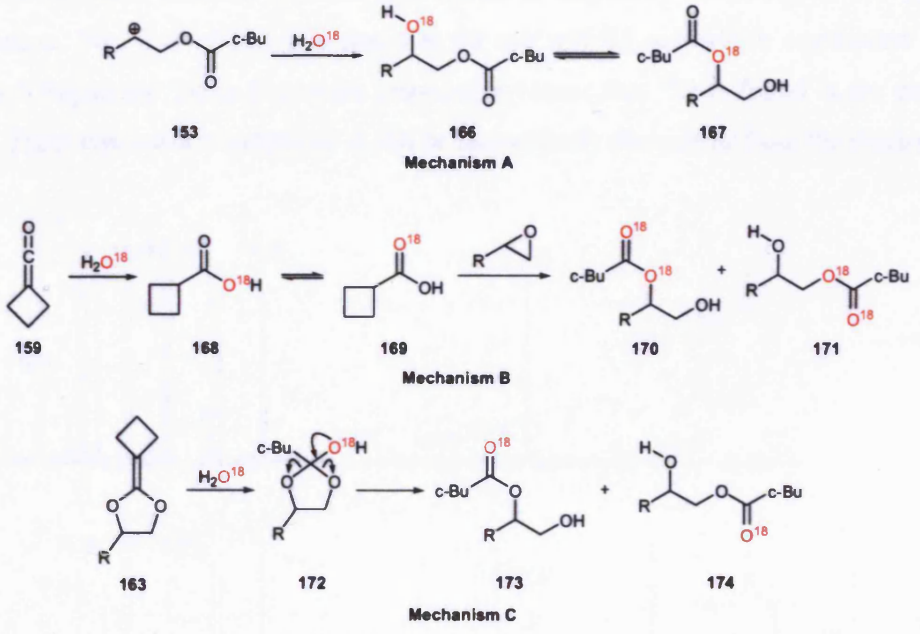
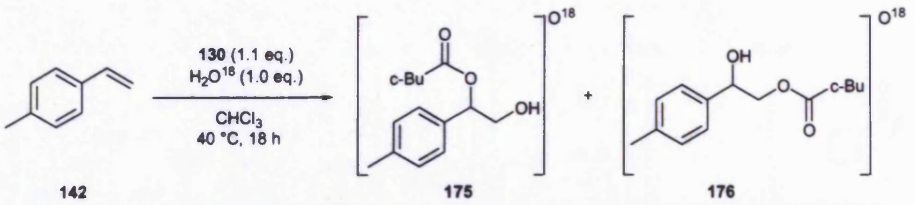


Fig. 3.8

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).



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 *m/z* and 218 *m/z*. The peaks correspond to $[M - H_2O]^+$. The difference of two mass units provide evidence that ^{18}O had been incorporated into the product and water is implicitly involved in the reaction mechanism. Fig. 3.10 shows two peaks at 83 *m/z* and 85 *m/z* which correspond to the carbonyl fragments. These fragments provided evidence that ^{18}O is found in the carbonyl group. From this result, mechanism A can be immediately discounted from the discussion.

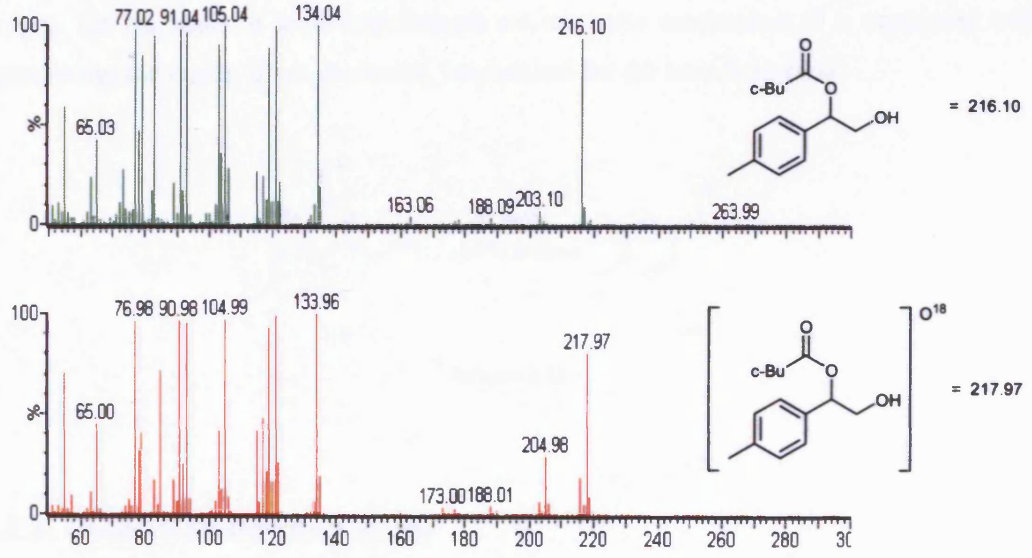


Fig. 3.9

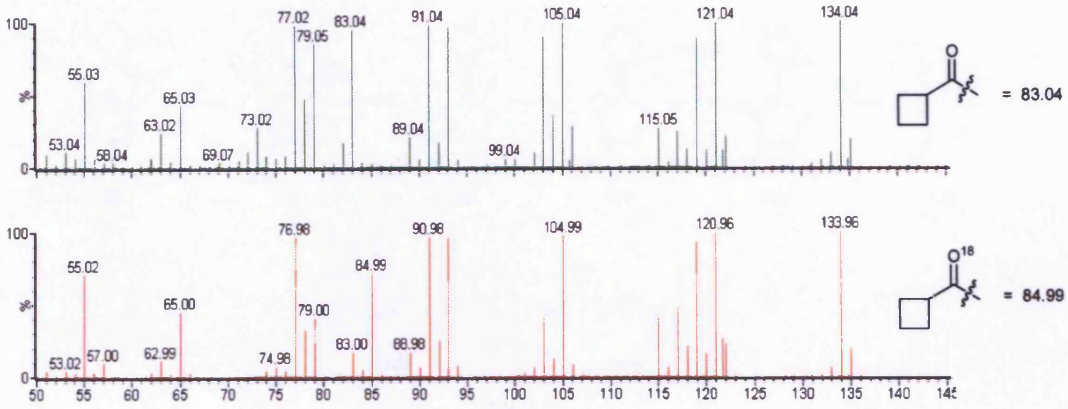
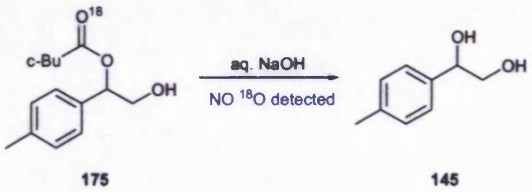


Fig. 3.10

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}O label present in the isolated diol and provides evidence the ^{18}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.



175 **145**

Scheme 3.12

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}H, ^{2}D and ^{13}C NMR spectroscopy.

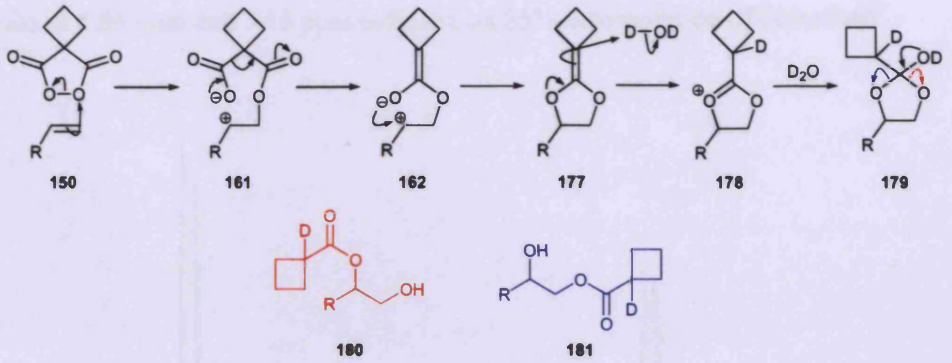
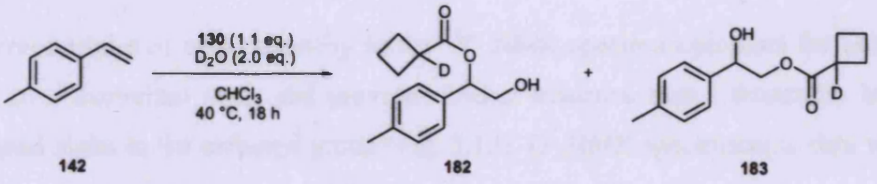


Fig. 3.11

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).



Scheme 3.13

^{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.

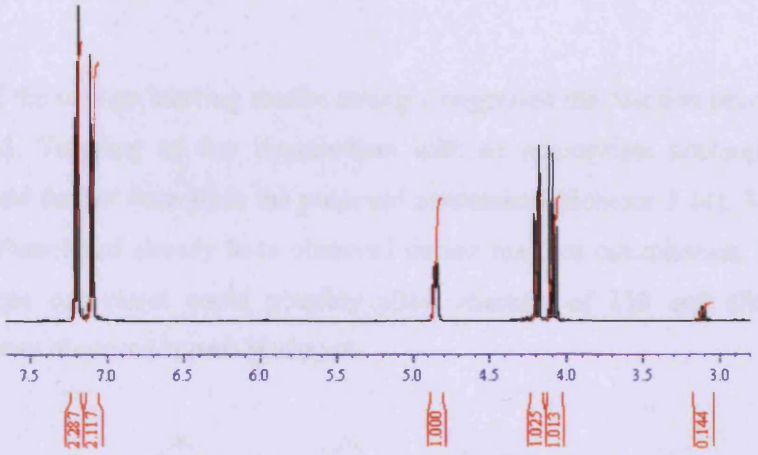


Fig. 3.12

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.

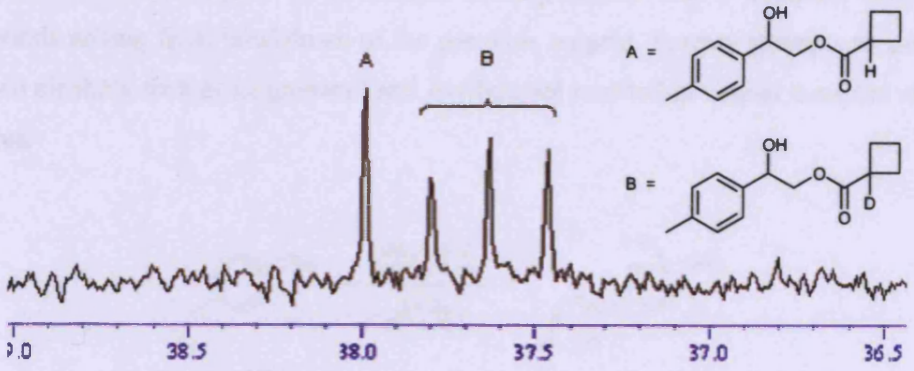
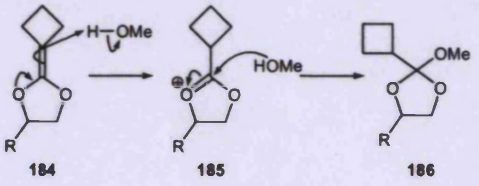


Fig. 3.13

3.5.4 Trapping of Intermediates

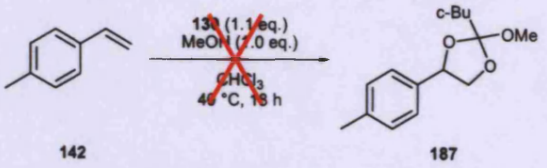
3.5.4.1 External nucleophiles

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.



Scheme 3.14

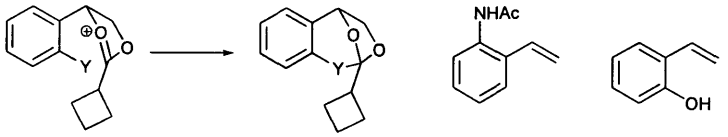
The reaction of **130** and **142** was performed under anhydrous conditions using dry chloroform and 1 equivalent of methanol (Scheme 3.15). ^{1}H NMR spectroscopic data of the crude reaction mixture showed un-reacted starting alkene and a complex mixture of compounds arising from breakdown of the peroxide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



Scheme 3.15

3.5.4.2 Substrate Based Strategy

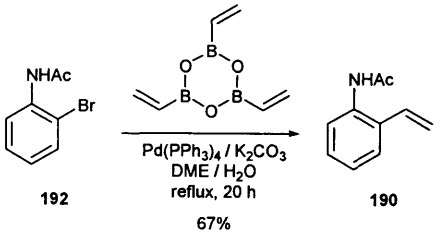
Undeterred by the failure to isolate or observe **187** through the use of external nucleophiles, the preparation of an alkene with a suitable internal nucleophile offered an alternative method for trapping **163** (Scheme 3.16). The use of internal nucleophiles allowed the reaction to be performed in 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**.



188 **189** **190** **191**

Scheme 3.16

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).[71]



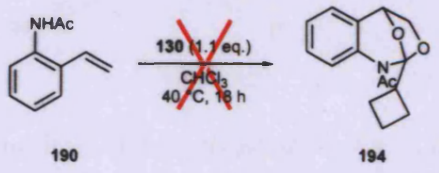
192 **190**

Scheme 3.17

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

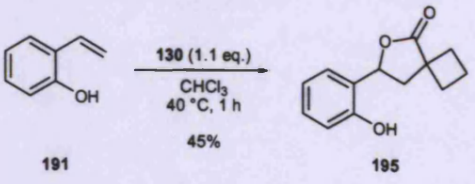
Scheme 3.18

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

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.

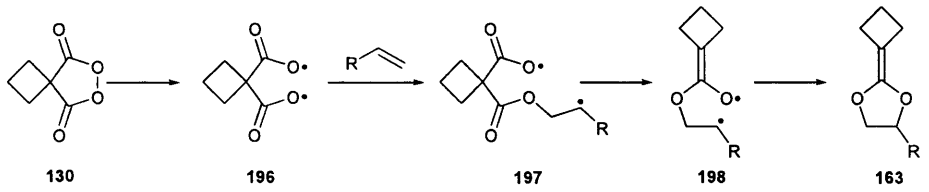


Scheme 3.20

3.6 Alternative mechanisms

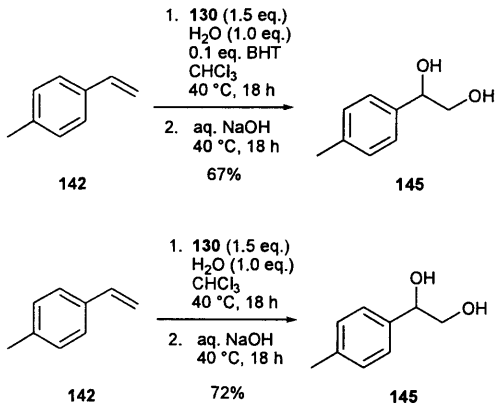
3.6.1 Free-radical mechanism

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).



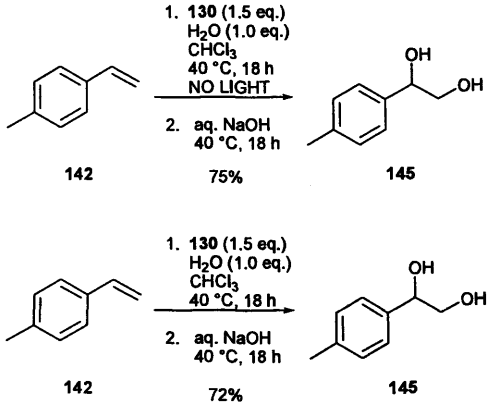
Scheme 3.21

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.[72] 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

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.

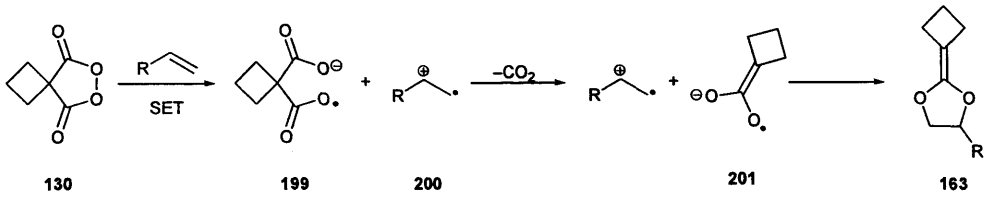


Scheme 3.23

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).[65,66] 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.

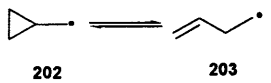
SET from an alkene generates radical cation **200** and radical anion **199**. Decarboxylation and combination of **200** and **201** may still allow formation of dioxolane **163** and subsequent hydrolysis gives the observed products (Scheme 3.24).



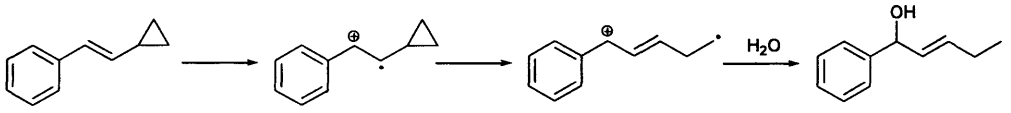
130 **199** **200** **201** **163**

Scheme 3.24

Cyclopropyl carbinyl radicals **202** are known to undergo rapid ring opening to give butenyl radicals **203** (Scheme 3.25).[72] 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.



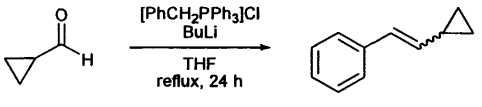
202 **203**



204 **205** **206** **207**

Scheme 3.25

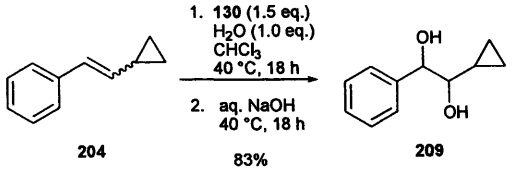
Reaction of cyclopropane carboxaldehyde **208** and benzyltriphenyl phosphonium chloride under standard Wittig conditions gave **204** as a mixture of *E*/*Z* isomers (Scheme 3.26).



208 58% **204**

Scheme 3.26

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

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.

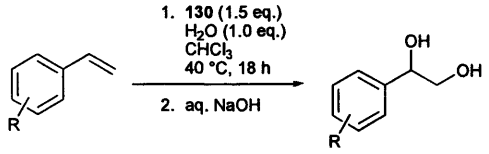
One of the most intriguing observations to arise from the preliminary studies was that 1-*p*-tolylethane-1,2-diol **145** and (±)-hydrobenzoin **41** required no column chromatography following aqueous work-up. If this was found to be a general feature of the reaction it would offer an excellent advantage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

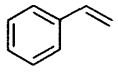
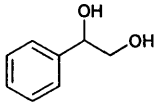
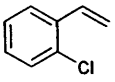
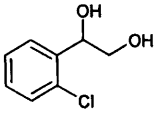
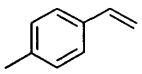
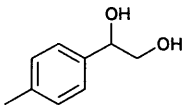
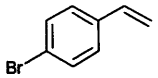
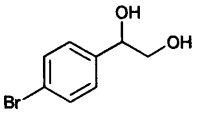
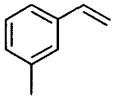
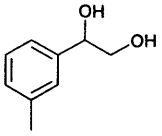
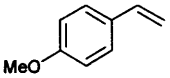
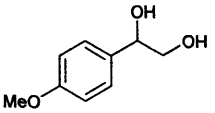
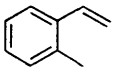
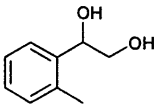
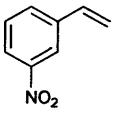
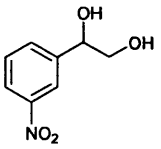
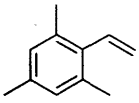
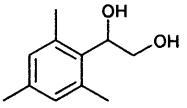
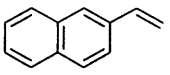
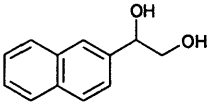
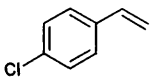
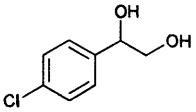
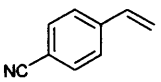
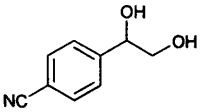
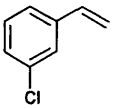
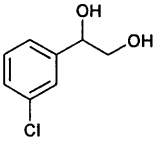
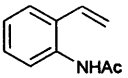
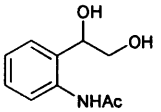
With the aim of determining whether **130** was a general reagent for alkene dihydroxylation, a variety of alkenes were reacted under a standard set of conditions. The substrates are divided into class based on their substitution and are discussed separately below.

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.



Entry	Alkene	Product	Yield (%)	Entry	Alkene	Product	Yield (%)
1	 **60**	 **64**	78	8	 **220**	 **221**	38[b]
2	 **142**	 **145**	84	9	 **222**	 **223**	74
3	 **210**	 **211**	65	10	 **224**	 **225**	78
4	 **212**	 **213**	80	11	 **226**	 **227**	30[c]
5	 **214**	 **215**	65	12	 **228**	 **229**	65
6	 **216**	 **217**	77	13	 **230**	 **231**	0
7	 **218**	 **219**	32[a]	14	 **190**	 **232**	0

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.

Table 4.1

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[73] was also found to be unsuccessful.

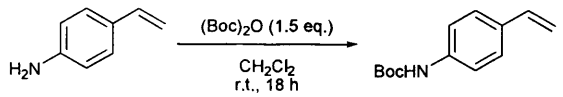
In summary, **130** was found to be a general reagent for the dihydroxylation of a range of substituted styrenes. The reaction was tolerant of steric bulk and varying substitution pattern; however, electron deficient alkenes reacted less readily and lower yields were obtained. Attention is drawn to the 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).

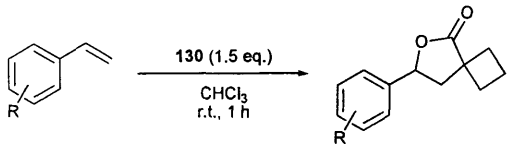


233 68% **234**

Scheme 4.1

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**

(Chapter 3, Scheme 3.20). Further experiments showed that 4-hydroxystyrene **236** was also converted to **237** in low yield (Table 4.2).



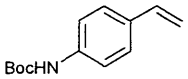
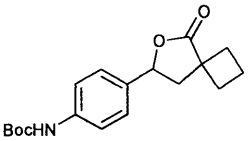
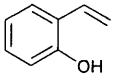
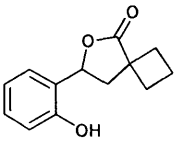
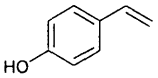
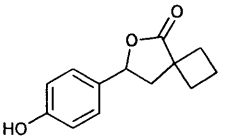
Entry	Substrate	Product	Yield (%)
1	 **234**	 **235**	30
2	 **191**	 **195**	45
3	 **236**	 **237**	19

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.

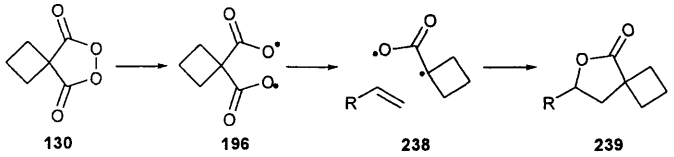
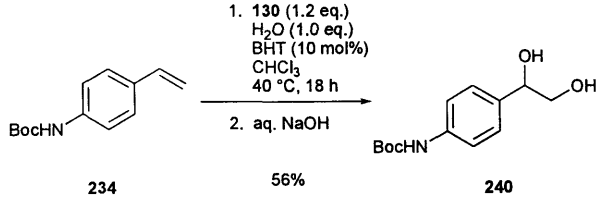


Fig. 4.1

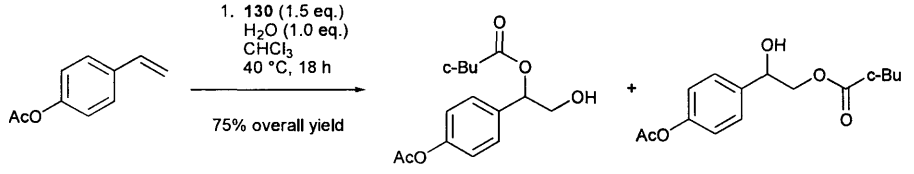
If formation of **235** proceeded *via* a radical mechanism, addition of a radical inhibitor such as BHT should result in reaction suppression. The reaction of **130** and **234** was performed in the presence of 10 mol% BHT which gave the corresponding diol in modest yield (Scheme 4.2).



234 56% **240**

Scheme 4.2

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



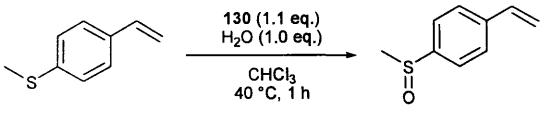
241 **242** **243**

Scheme 4.3

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_2O_2 and *m*CPBA 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.

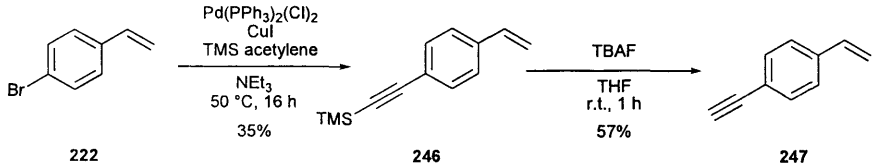


244 74% **245**

Scheme 4.4

4.2.2.3 Enynes

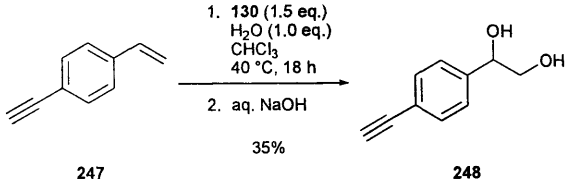
The chemoselectivity associated with enynes was briefly investigated with 1-ethynyl-4-vinylbenzene **247**, prepared from 4-bromostyrene **222** and trimethylsilylacetylene *via* a Sonagashira coupling and subsequent removal of the trimethylsilyl group (20%) (Scheme 4.5).[75]



222 **246** **247**

Scheme 4.5

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]



247 **248**

Scheme 4.6

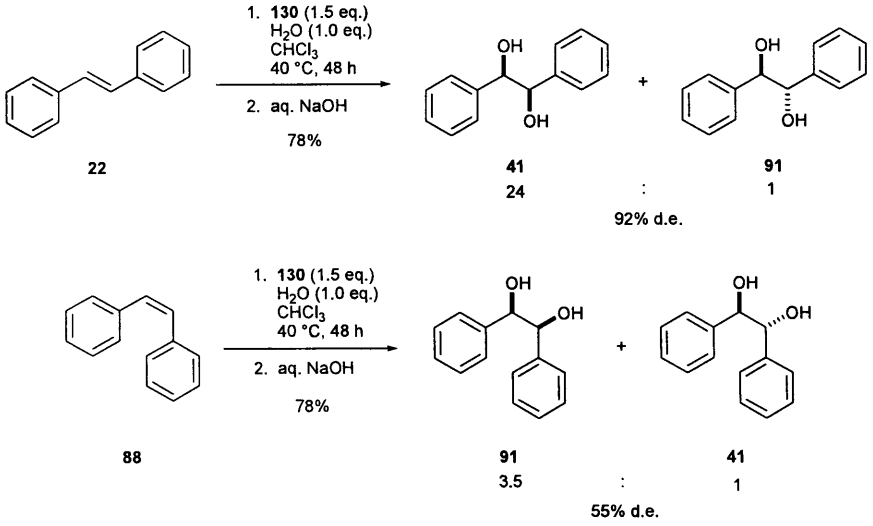
4.3 1,2-Disubstituted alkenes

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.



Scheme 4.7

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.

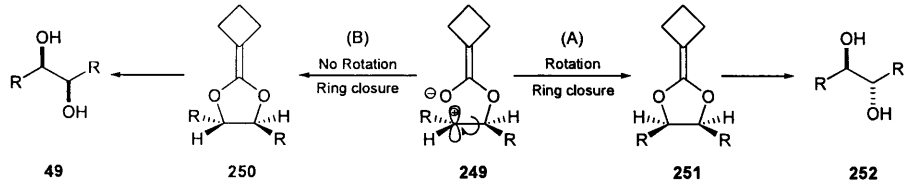


Fig. 4.2

4.3.5 Steric effects

As the peroxide reagent is known to react with alcohols, which are formed during the reaction, is difficult to asses 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).

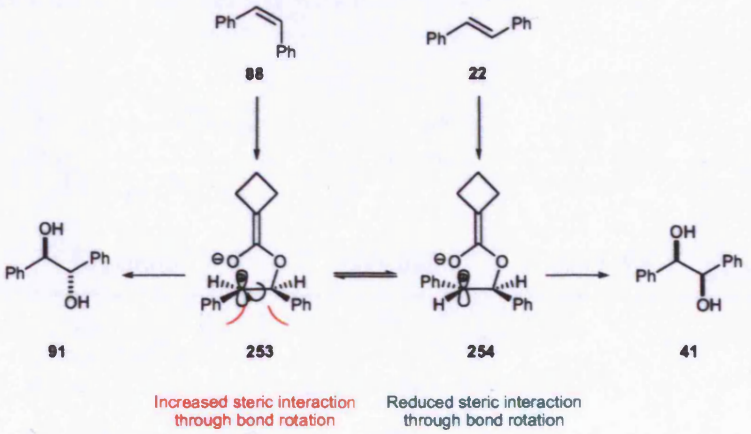


Fig. 4.3

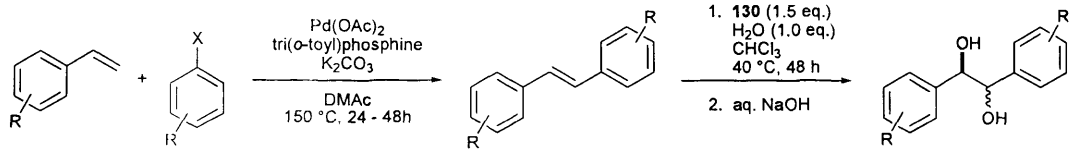
In the case of *trans*-stilbene **22**, rotation of the C–C bond in **254** results in an increase in the steric interaction between the two phenyl groups and raises the energy of conformation **253**. As a result, conformation **254** is preferred and results in high diastereoselectivity for the formation of (±)-hydrobenzoin **41**.

In the case of *cis*-stilbene **88**, rotation of the C–C bond in **253** results in a reduction in steric interaction between the two phenyl groups. It was unclear mechanistically if ring closure occurs before or after decarboxylation. This result indicated the lifetime of the carbocation is long enough for bond rotation about the C–C bond to occur prior to ring closure resulting in a loss of diastereoselectivity in the product. Potential exists for probing this phenomenon

further by altering the sterics 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.[76,77] 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.



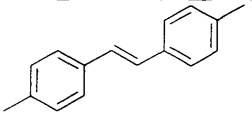
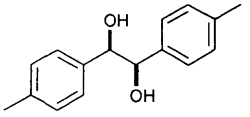
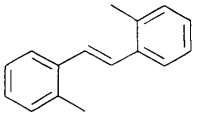
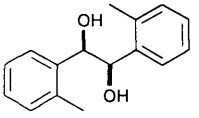
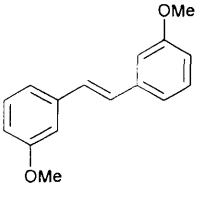
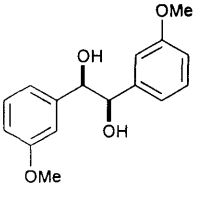
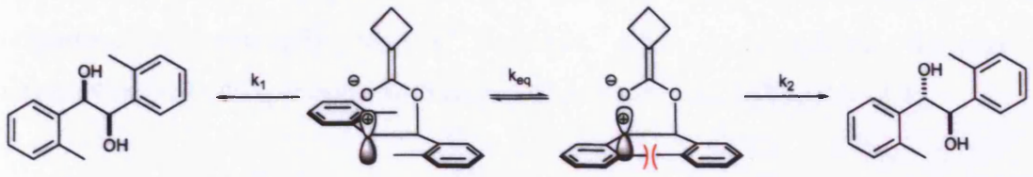
Entry	Substrate	Product	Yield (%)	*Syn:anti* ratio
1	 **255**	 **256**	83	23:1
2	 **257**	 **258**	78	32:1
3	 **259**	 **260**	27	25:1

Table 4.3

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).



258 **261** **262** **258*anti***

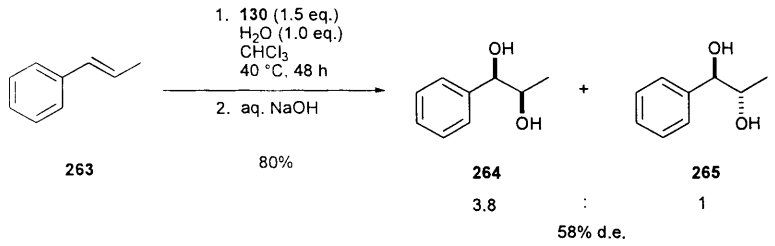
Assuming $k_1 > k_{eq}$

Fig. 4.4

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).



263 80% **264** : **265**

3.8 : 1

58% d.e.

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.

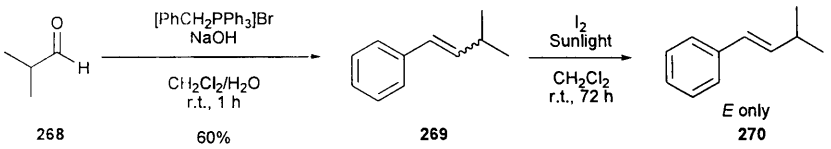
264 **266** **267** **265**

Assuming $k_1 > k_{eq}$

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.

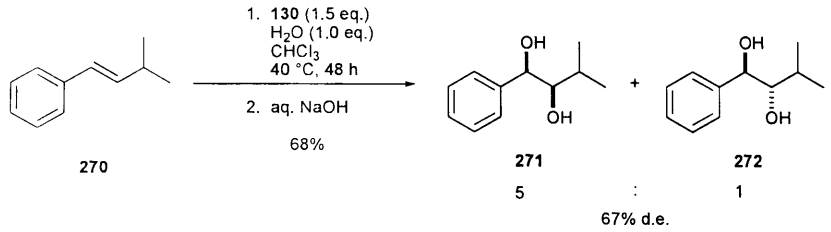
Iodine was added to a solution of the geometrical isomers and the mixture exposed to direct sunlight. Isomerisation was monitored by ^{1}H NMR spectroscopy and gave pure *E*-alkene **270** after 72 h.



268 60% **269** **270**

Scheme 4.9

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.).



270 **271** **272**

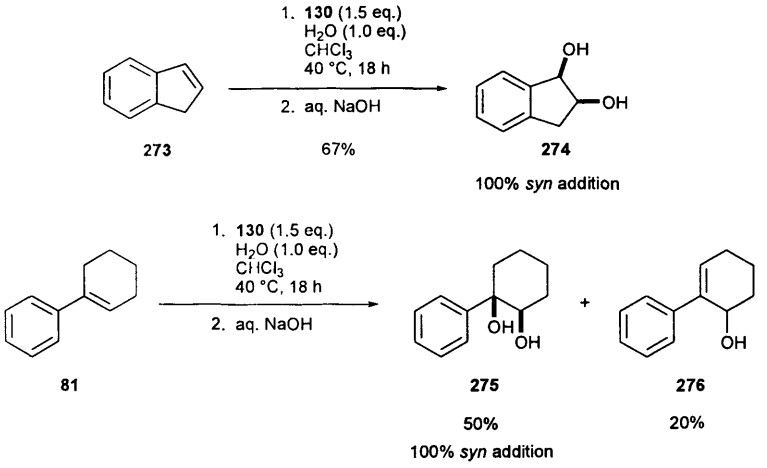
5 : 1

67% d.e.

Scheme 4.10

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).



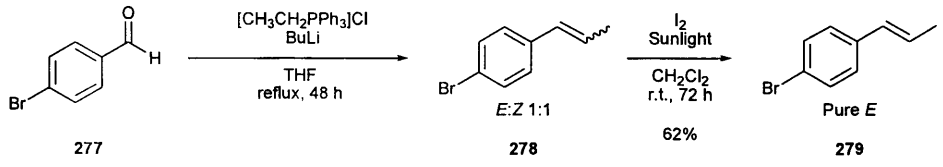
Scheme 4.11

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.

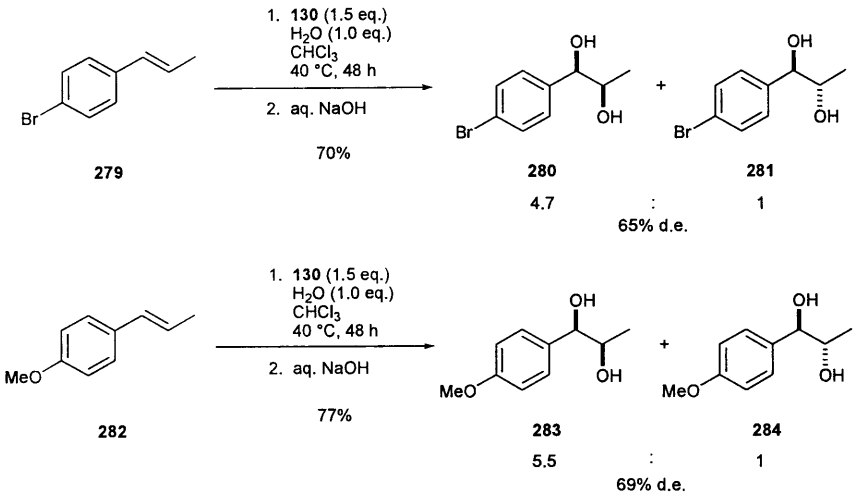
4-Bromo-*trans*-β-methylstyrene **278** was prepared from 4-bromobenzaldehyde **277** and ethyltriphenylphosphonium chloride under standard Wittig conditions (Scheme 4.12). The mixture of geometrical isomers was treated with iodine and exposed to direct sunlight to afford pure *E*-4-bromo-*trans*-β-methylstyrene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



277 278 279

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).



Scheme 4.13

These studies revealed some interesting results:

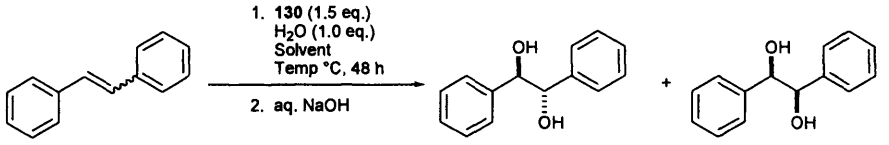
(1) Contrary to the predicted outcome, **279** and **282** gave comparable diastereomeric excesses. These results suggested the electronic nature of the alkene had negligible effect on the observed diastereoselectivities. At this stage, the reasons behind this were not immediately apparent.

(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.

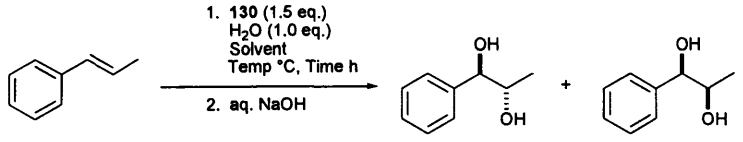
4.3.8 Solvent and temperature effects

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 malonoyl peroxide **130** were examined under a range of conditions. The results of these studies are shown in Tables 4.4 and 4.5 below.



Entry	Substrate	Solvent	Temperature (°C)	Peroxide eq.	Reaction Complete?	Ratio
1	**22**	$CHCl_3$	25	1.2	No	1 : 27
2	**22**	$CHCl_3$	40	1.2	No	1 : 27
3	**22**	$CHCl_3$	60	1.2	No	1 : 27
4	**22**	Toluene	25	1.2	No	—
5	**22**	Toluene	40	1.2	No	1 : 16
6	**22**	Toluene	60	1.2	No	1 : 14
7	**22**	CH_3CN	25	1.2	No	1 : 15
8	**22**	CH_3CN	40	1.2	No	1 : 12
9	**22**	CH_3CN	60	1.2	No	1 : 12
10	**22**	$CHCl_3$	40	1.5	Yes	1 : 22
11	**88**	$CHCl_3$	40	1.2	No	1 : 2
12	**88**	CH_3CN	40	1.2	No	1 : 2
13	**88**	Toluene	40	1.2	No	1 : 3
14	**88**	$CHCl_3$	40	1.5	Yes	1 : 3.5

Table 4.4



Entry	Time (h)	Solvent	Temperature (°C)	Peroxide eq.	Reaction Completion	Ratio
1	18	$CHCl_3$	40	1.2	No	1 : 4.4
2	18	Toluene	40	1.2	No	1 : 2.9
3	18	CH_3CN	40	1.2	No	1 : 3.8
4	18	$CHCl_3$	40	1.5	Yes	1 : 3.8
5	56	$CHCl_3$	25	1.2	Yes	1 : 4.5
6	56	Toluene	25	1.2	No	1 : 3.0
7	56	CH_3CN	25	1.2	No	1 : 4.6

Table 4.5

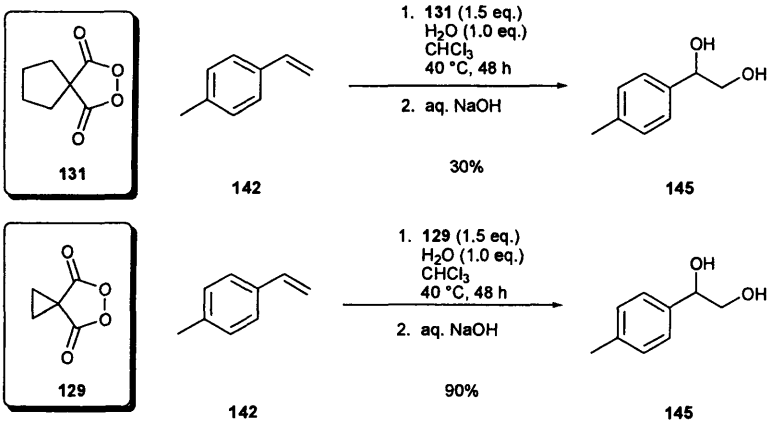
The results above highlighted some interesting factors:

(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 diastereoselectivites 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

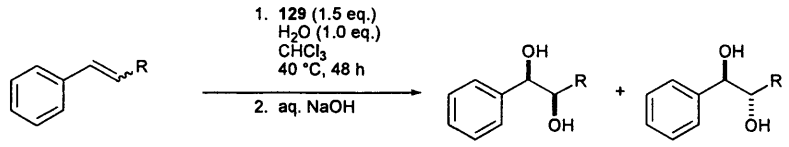
At this stage of the investigation, the effect of peroxide structure on the reactivity had not been examined. To this end, 4-methylstyrene **142** was reacted with cyclopentane malonoyl peroxide **131** and cyclopropane malonoyl peroxide **129** under optimized conditions (Scheme 4.14).



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.

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**.

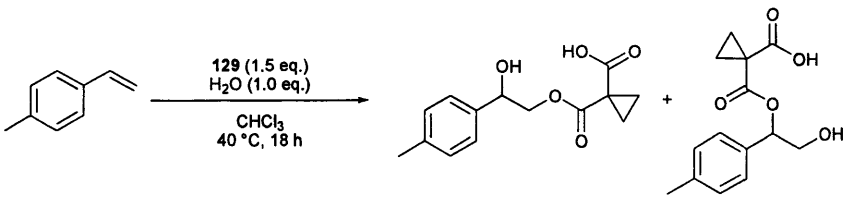


Entry	Substrate	*syn:anti* ratio 129	d.e. (%)	*syn:anti* ratio 130	d.e. (%)
1	*trans*-stilbene	34 : 1	94	24 : 1	92
2	*cis*-stilbene	4 : 1	60	3.5 : 1	55
3	*trans*-β-methylstyrene	14 : 1	87	3.8 : 1	58
4	4-bromo-*trans*-β-methylstyrene	12.5 : 1	85	4.7 : 1	65
5	4-methoxy-*trans*-β-methylstyrene	5.5 : 1	69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

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).

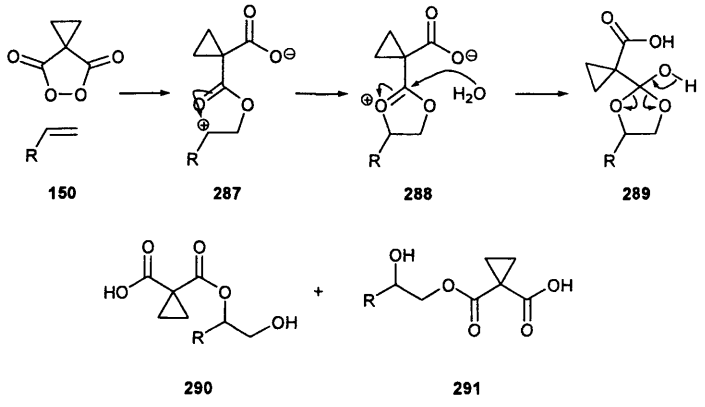
In an attempt to rationalise these differences, the reaction of 4-methylstyrene **142** and **129** was performed. Two major products were observed by TLC. Structures **285** and **286** were consistent with analytical data obtained (Scheme 4.15).



142 **285** **286**

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.



150 **287** **288** **289**

290 **291**

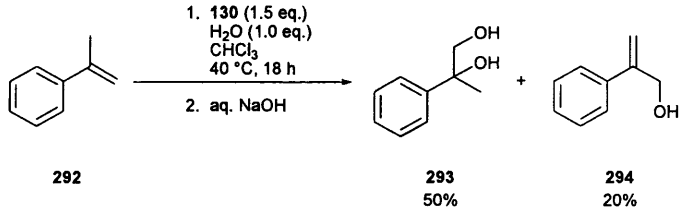
Fig. 4.6

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.

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).



Scheme 4.16

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).

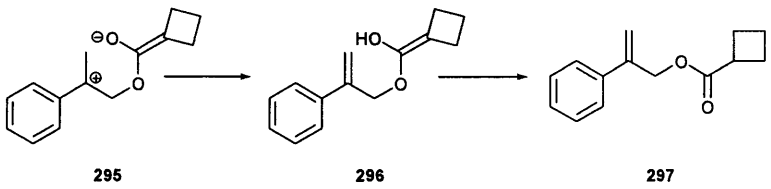
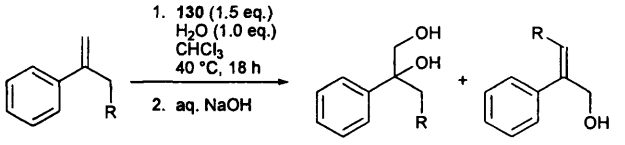


Fig. 4.7

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).

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).



Entry	Substrate	Diol (%)	Allylic alcohol (%)
1	**81**	50	20
2	**298**	37	22
3	**299**	69	—
4	**300**	67	—

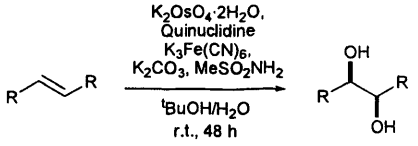
Table 4.7

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[73] to aid reaction monitoring by TLC and ^{1}H NMR spectroscopy. Diols **302–306** were isolated in moderate yield (Table 4.8).



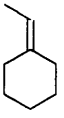
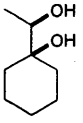
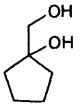
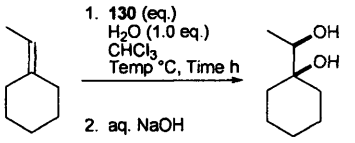
Entry	Substrate	Product	Yield (%)
1	 **301**	 **302**	55
2	 **303**	 **304**	60
3	 **305**	 **306**	65

Table 4.8

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.



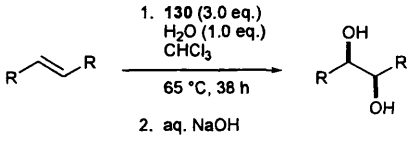
Entry	Peroxide eq.	Temperature (°C)	Time (h)	Yield (%)
1	1.1	40	24	10
2	1.5	40	24	20
3	1.5	55	48	24
4	2.0	40	24	22
5	2.0	65	24	27
6	2.0	65	48	35
7	3.0	65	38	38

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.

Following these exploratory studies, methylene cyclopentane **303** and 1-methylcylopentene **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.



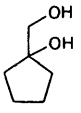
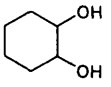
Entry	Substrate	Product	Yield (%)
1	 **303**	 **304**	12
2	 **305**	 **306**	6
3	 **99**	 **307**	—

Table 4.10

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:

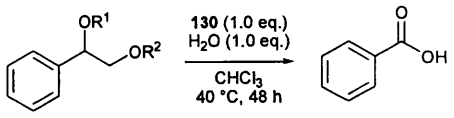
(1) Consumption of alkene starting material was observed in the majority of cases.
(2) Isolated yields of the corresponding diols were typically between 50–80%.
(3) In the majority of cases no column chromatography was required following aqueous work-up.

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.



R^1 = c-BuCO, R^2 = H = **308**
R^1 = H, R^2 = c-BuCO = **309**
R^1 = H, R^2 = H = **64**

Entry	R^1	R^2	Yield (%)
1	H	c-BuC(O)	0
2	c-BuC(O)	H	0
3	H	H	10[a]

a) Determined by ^{1}H NMR spectroscopic data

Table 4.11

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.[55] Below is a qualitative examination of the factors which affect peroxide reactivity which aimed to answer the following questions:

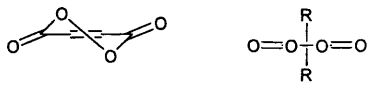
- How does incorporating the diacyl peroxide unit within a ring result in increased reactivity?
- Why is PPO **85** highly shock sensitive whereas malonoyl peroxides **129–131** are not?

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[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 peroxide 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**.



85 **310**

Fig. 4.8

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.

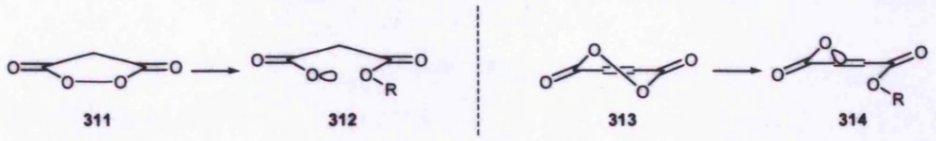


Fig. 4.9

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.

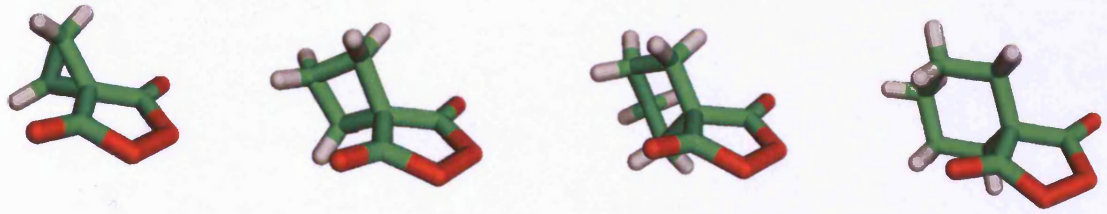


Fig. 4.10

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).

Entry	Peroxide	O–O bond length (Å)	CO–C–CO angle	C=O IR stretching frequency (cm^{-1})	^{13}C Carbonyl peak (ppm)
1	**129**	1.476	107.56	1827 & 1798	172.15
2	**130**	1.476	104.01	1799	173.94
3	**131**	1.471	102.34	1797	175.70
4	**132**	1.467	102.35	1794	174.35
5	BPO	1.460[78]	—	1789 & 1766[79]	162.25

Table 4.12

^{13}C 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.

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

Peroxide	Endotherm ($J\ g^{-1}$)	Endotherm Temperature (°C)	Exotherm ($J\ g^{-1}$)	Exotherm Temperature (°C)
129	-96.17	89.80	1593.36	181.57
130	-69.06	62.95	1443.08	160.91
131	-47.09	41.27	875.86	128.58

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

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.

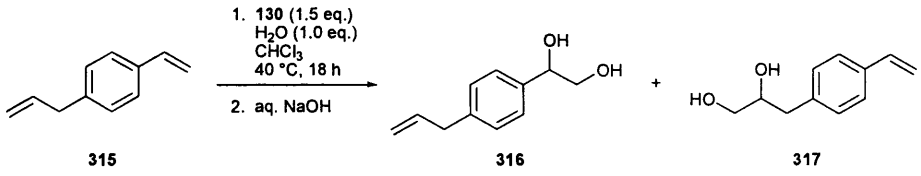
4.9 Further Work

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[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).

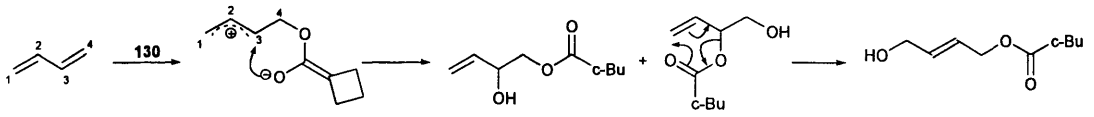


315 316 317

Scheme 4.17

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)

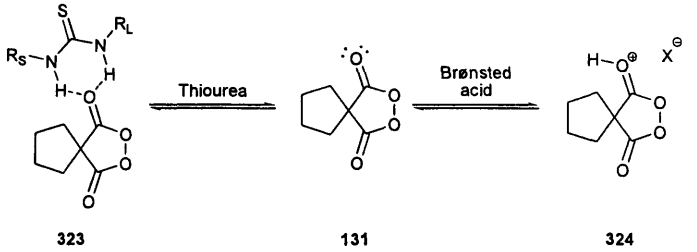


318 **319** **320** **321** **322**

Scheme 4.18

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[80,81] and chiral Brønsted acids[82] have been employed in a number of asymmetric transformations.



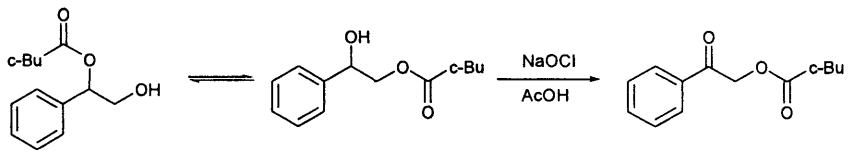
323 **131** **324**

Fig. 4.11

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 α-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).



308 **309** **325**

Scheme 4.19

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**.

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.[85] 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,[86] 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.

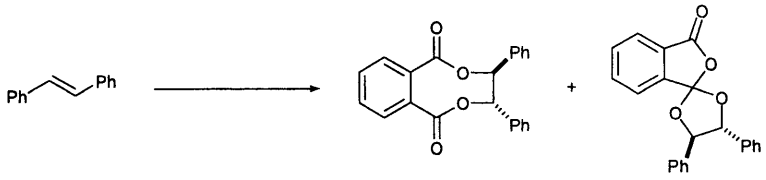
Infra-red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1600 series FTIR instrument either as a thin film, a nujol mull or dissolved in dichloromethane between sodium chloride plates. All absorptions are quoted in wave numbers (cm^{-1}).

^{1}H NMR spectra (δ_H) were recorded using an Avance Bruker DPX 400 instrument (400 MHz) or an Avance Bruker DPX 500 (500MHz), with ^{13}C NMR spectra (δ_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).

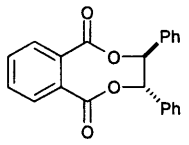
Low resolution mass spectrometric data was determined using a Fisons VG Platform II Quadrapole instrument using atmospheric pressure chemical ionisation (APcI) unless otherwise stated. APcI refers to atmospheric pressure chemical ionisation, EI refers to electron ionisation and ES refers to electrospray. 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).

Preparation of intermediates 86 and 87



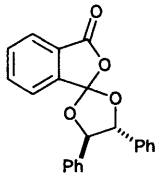
Sodium peroxide (0.20 g, 2.6 mmol) was added to a mixture of chloroform (5 ml) and water (10 ml) containing NaH_2PO_4 (0.38 g, 3.2 mmol) and Na_2HPO_4 (0.38 g, 2.7 mmol). The reaction mixture was cooled to 5 °C and phthaloyl chloride (0.35 ml, 2.4 mmol) in chloroform (5 ml) added dropwise over 2 min. 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



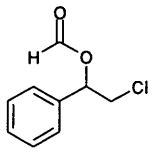
Colourless solid (0.17 g, 21%). m.p. 210–212 °C [lit.[56] m.p. 206–207 °C]; IR (thin film)/cm^{-1}: 1735, 1259, 1102; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78–7.74 (m, 2H, Ar-H), 7.61–7.59 (m, 2H, Ar-H), 7.29–7.24 (m, 5H, Ar-H), 7.19–7.17 (m, 5H, Ar-H), 6.12 (s, 2H, ArCHOCO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 136.0, 134.7, 134.5, 132.4, 128.9, 128.7, 127.5, 89.4; LRMS (CI) *m/z* 345.1 $[M + H]^+$; HRMS (CI) calculated for $C_{22}H_{17}O_4$ $[M + H]^+$ 345.1121, found 345.1120.

Intermediate 87



Colourless solid (0.12 g, 15%). m.p. 122–123 °C [lit.[56] m.p. 123–126 °C]; IR (thin film)/cm^{-1}: 1779, 1354, 1282; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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 (CI) *m/z* 345.1 $[M + H]^+$; HRMS (ES) calculated for $C_{22}H_{17}O_4$ $[M + H]^+$ 345.1121, found 345.1120.

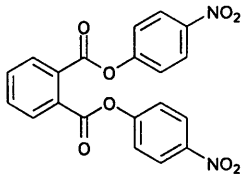
1-Phenyl-1-formyl-2-chloroethane 113[63]



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 × 10 ml) and the combined organic layers washed with brine (15 ml) and dried over $MgSO_4$. 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^{-1}: 1725, 1494; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H, CHO), 7.34–7.26 (m, 5H, Ar-H), 6.00 (dd, J = 4.3 & 8.2 Hz, 1H, ArCHOCO), 3.76 (dd, J = 8.3 & 11.8 Hz, 1H, CHHCl), 3.68 (dd, J = 4.3 & 11.8 Hz, 1H, CHHCl);

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 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 $C_9H_9O_2Cl^{35}$ $[M]^+$ 184.0286, found 184.0289.

Bis(4-nitrophenyl) phthalate 116



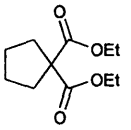
Phthaloyl chloride (1.0 ml, 6.9 mmol) was added dropwise to a solution of 4-nitrophenol (2.1 g, 15 mmol) and triethylamine (2.1 ml, 15 mmol) in dichloromethane (25 ml) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The resulting yellow precipitate was 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; ^1H NMR (400 MHz, $CDCl_3$) δ 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 $C_{20}H_{16}O_8N_3$ $[M + NH_4]^+$ 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

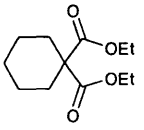
(4 × 50 ml) and the combined organic layers dried over $MgSO_4$. The reaction mixture was reduced to dryness to give the desired diethyl 1,1-cycloalkanedicarboxylate.

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, $CDCl_3$) δ 4.16 (q, J = 7.1 Hz, 4H, $C\underline{H}_2CH_3$), 2.13–2.09 (m, 4H, $C\underline{H}_2CH_2$), 1.63–1.60 (m, 4H, $CH_2C\underline{H}_2$), 1.18 (t, J = 7.1 Hz, 6H, $CH_2C\underline{H}_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) 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 $C_{11}H_{19}O_4$ $[M + H]^+$ 215.1278, found 215.1278.

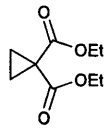
Diethyl cyclohexane-1,1-dicarboxylate 135



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, $CDCl_3$) δ 4.11 (q, J = 7.1 Hz, 4H, $C\underline{H}_2CH_3$), 1.92–1.89 (m, 4H, $CH_2CH_2C\underline{H}_2$), 1.47–1.44 (m, 4H,

$CH_2C\underline{H}_2CH_2$), 1.37–1.36 (m, 2H, $C\underline{H}_2CH_2CH_2$), 1.18 (t, J = 7.1 Hz, 6H, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 61.5, 55.3, 31.7, 25.6, 23.1, 14.5; LRMS (EI) *m/z* 228.1 $[M]^+$; HRMS (EI) calculated for $C_{12}H_{20}O_4$ $[M]^+$ 228.1362, found 228.1363.

Diethyl cyclopropane-1,1-dicarboxylate 133

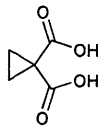


Diethyl malonate (9.5 ml, 63 mmol), 1,2-dibromoethane (10.0 ml, 116 mmol), potassium carbonate (64 g, 464 mmol) and tetrabutylammonium hydrogensulfate (1.00 g, 2.9 mmol) were dissolved in DMSO (50 ml) and the reaction mixture stirred at room temperature for 24 h. The reaction mixture was poured into water (300 ml) and extracted with diethyl ether (100 ml). The aqueous layer was further extracted with diethyl ether (4 × 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; ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, J = 7.2 Hz, 4H, $C\underline{H}_2CH_3$), 1.38 (s, 4H, $(C\underline{H}_2)_2$), 1.24 (t, J = 7.1 Hz, 6H, $CH_2C\underline{H}_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.7, 61.3, 28.2, 16.2, 14.0; LRMS (CI) *m/z* 187.2 $[M + H]^+$; HRMS (ES) calculated for $C_9H_{15}O_4$ $[M + H]^+$ 187.0965, found 187.0962.

General Procedure B. Synthesis of Cycloalkane 1,1-dicarboxylic acids.

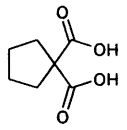
Diethyl cycloalkane-1,1-dicarboxylate (5.0 mmol) was dissolved in THF : H_2O (5 ml : 5 ml) and LiOH (1.2 g, 28 mmol) added in a single portion. The reaction mixture was vigorously stirred at room temperature for 48 h. The solvent was removed under reduced pressure and the aqueous layer extracted with 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 × 50 ml) and the combined organic layers washed with brine (50 ml) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the desired cycloalkane-1,1-dicarboxylic acid.

Cyclopropane-1,1-dicarboxylic acid 137



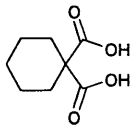
Following general procedure **B**, diethyl cyclopropane-1,1-dicarboxylate (1.00 g, 5.4 mmol) gave the title compound as a colourless solid (0.56 g, 80%). m.p. 128–130 °C [lit.[87] m.p. 139 °C]; ^{1}H NMR (250 MHz, DMSO) δ 1.32 (s, 4H, (C<u>H</u>$_2$)$_2$); ^{13}C NMR (62.5 MHz, DMSO) δ 172.2, 27.7, 16.6; LRMS (EI) *m/z* 112.0 $[M - H_2O]^+$; HRMS (EI) calculated for $C_5H_6O_4$ $[M]^+$ 130.0266, found 130.0268.

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.[88] m.p. 157–158 °C]; ^{1}H NMR (400 MHz, DMSO) δ 2.04–2.01 (m, 4H, C$\underline{H}_2$CH$_2$), 1.59–1.56 (m, 4H, CH$_2$C$\underline{H}_2$); ^{13}C NMR (62.5 MHz, DMSO) δ 173.7, 59.7, 33.8, 25.0; LRMS (CI) *m/z* 176.3 $[M + NH_4]^+$; HRMS (ES) calculated for $C_7H_{14}O_4N$ $[M + NH_4]^+$ 176.0917, found 176.0917.

Cyclohexane-1,1-dicarboxylic acid 140

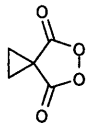


Following general procedure **B**, diethyl cyclohexane-1,1-dicarboxylate (1.00 g, 4.4 mmol) gave the title compound as a colourless solid (0.61 g, 81%). m.p. 170–172 °C [lit.[89] m.p. 170–171 °C]. ^{1}H NMR (400 MHz, DMSO) δ 3.36 (br s, 2H, O$\underline{H}$), 1.82–1.79 (m, 4H, CH$_2$CH$_2$C$\underline{H}_2$), 1.49–1.40 (m, 4H, CH$_2$C$\underline{H}_2$CH$_2$), 1.36–1.35 (m, 2H, C$\underline{H}_2$CH$_2$CH$_2$); ^{13}C NMR (100 MHz, DMSO) δ 173.1, 53.9, 30.9, 24.8, 22.5; LRMS (EI) *m/z* 154.1 $[M - H_2O]^+$; HRMS (EI) calculated for $C_8H_{10}O_3$ $[M - H_2O]^+$ 154.0630, found 154.0628.

General Procedure C. Synthesis of Malonoyl Peroxides[1]

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 $NaHCO_3$ (2 × 50 ml), brine (20 ml) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the desired malonoyl peroxide.

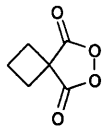
Cyclopropane malonoyl peroxide 129



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, $CDCl_3$) δ 2.04 (s, 4H, $(C\underline{H}_2)_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.2, 23.7, 19.8.

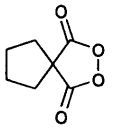
[1] Unable to obtain low or high resolution mass spectrometry data for malonoyl peroxides using in-house or Swansea national mass spectrometry service – See appendix for X-Ray data for peroxides **129–132**.

Cyclobutane malonoyl peroxide 130



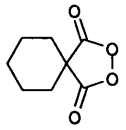
Following general procedure **C**, cyclobutane-1,1-dicarboxylic acid (5.00 g, 35 mmol) gave the title compound as a colourless crystalline solid (4.00 g, 80%) after purification by column chromatography eluting with chloroform. m.p. 63 °C; IR (thin film)/cm^{-1}: 1799, 1269; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.65 (t, J = 8.1 Hz, 4H, $(C\underline{H}_2)_2CH_2$), 2.37–2.23 (m, 2H, $(CH_2)_2C\underline{H}_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23–2.19 (m, 4H, $C\underline{H}_2CH_2$), 1.98–1.93 (m, 4H, $CH_2C\underline{H}_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.7, 46.8, 37.7, 26.7.

Cyclohexane malonoyl peroxide 132

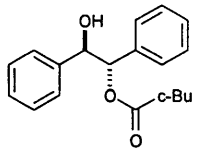


Following general procedure **C**, cyclohexane-1,1-dicarboxylic acid (1.00 g, 5.8 mmol) gave the title compound as a colourless crystalline solid (0.78 g, 79%) after purification by column chromatography. m.p. 41–42 °C. IR (thin film)/cm^{-1}: 2944, 1794, 1223; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92–1.89 (m, 4H, $C\underline{H}_2CH_2CH_2$), 1.78–1.72 (m, 4H, $CH_2C\underline{H}_2CH_2$), 1.57–1.51 (m, 2H, $CH_2CH_2C\underline{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 42.1, 30.9, 24.5, 19.6.

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

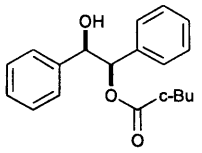
Cyclobutanecarboxylic acid (0.47 ml, 5.0 mmol) was added to a solution of *N*,*N*'-dicyclohexylcarbodiimide (1.00 g, 5.0 mmol) and 4-di(methylamino)pyridine (0.06 g, 0.5 mmol) in dichloromethane. The solution was stirred at room temperature for 30 min. before hydrobenzoin (5.0 mmol) was added. The reaction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

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; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28–7.06 (m, 10H, Ar-H), 5.83 (d, J = 6.4 Hz, 1H, ArCHOCO), 4.89 (d, J = 6.4 Hz, 1H, ArCHOH), 3.03 (quin, J = 8.2 Hz, 1H, $CH(CH_2)_2CH_2$), 2.35–1.50 (m, 6H, $CH(CH_2)_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) 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 (CI) *m/z* 297.2 $[M + H]^+$; HRMS (ES) calculated for $C_{19}H_{24}O_3N$ $[M + NH_4]^+$ 314.1751, found 314.1751.

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



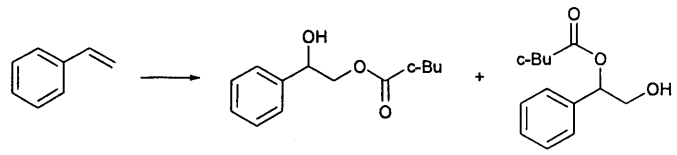
Following general procedure **D**, (±)-hydrobenzoin (1.07 g, 5.0 mmol) gave the title compound as a colourless solid (0.94 g, 64%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80). m.p. 75–76 °C. IR (thin film)/cm^{-1}: 3457, 2947, 1726, 1368; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30–7.15 (m, 10H, Ar-H), 5.88 (d, J = 7.2 Hz, 1H, ArCHOCO), 4.96 (d, J = 7.2 Hz, 1H, ArCHOH), 3.27 (quin, J = 8.4 Hz, 1H, $CH(CH_2)_2CH_2$), 2.36–1.84 (m, 6H, $CH(CH_2)_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) 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 (EI) *m/z* 297.2 $[M + H]^+$; HRMS (ES) calculated for $C_{19}H_{24}O_3N$ $[M + NH_4]^+$ 314.1751, found 314.1751.

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

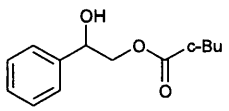
Alkene (1.0 mmol) was added dropwise to a solution of cyclobutane malonoyl peroxide (0.17 g, 1.2 mmol) in chloroform (4 ml). H_2O (18 μl, 1.0 mmol) was added and the reaction mixture was heated at 40 °C for 18 h. Removal of the solvent under reduced pressure gave the desired intermediate.

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).

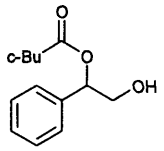
2-(*O*-Oxocyclobutyl)-1-phenylethane-1,2-diol 309



Colourless oil (0.08 g, 38%). IR (thin film)/cm^{-1}: 3433, 1731, 1168; ^1H NMR (400 MHz, $CDCl_3$) 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, $CH(CH_2)_2CH_2$), 2.53 (bs, 1H, OH), 2.36–2.19 (m, 4H,

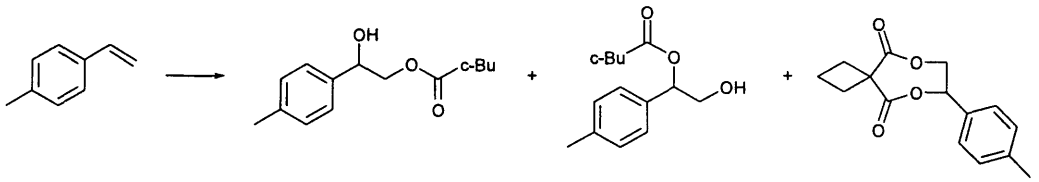
$CH(C\underline{H}_2)_2CH_2$), 2.07–1.98 (m, 2H, $CH(CH_2)_2C\underline{H}_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 139.8, 128.6, 128.2, 126.2, 72.6, 69.2, 38.0, 25.3, 18.4; LRMS (EI) *m/z* 202.1 $[M - H_2O]^+$; HRMS (ES) calculated for $C_{13}H_{14}O_2$ $[M - H_2O]^+$ 202.0994, found 202.0995.

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



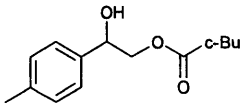
Colourless oil (0.09 g, 43%). IR (thin film)/cm^{-1}: 3485, 1726, 1173; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H, Ar-H), 5.77 (dd, *J* = 4.2 & 7.4 Hz, 1H, ArC<u>H</u>OCO), 3.80 (dd, *J* = 7.6 & 12.0 Hz, 1H, C<u>H</u>HOH), 3.73 (dd, *J* = 4.0 & 12.0 Hz, 1H, CH<u>H</u>OH), 3.17 (quin, *J* = 8.4 Hz, 1H, $C\underline{H}(CH_2)_2CH_2$), 2.30–2.11 (m, 4H, $CH(C\underline{H}_2)_2CH_2$), 2.02–1.83 (m, 2H, $CH(CH_2)_2C\underline{H}_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 137.3, 128.6, 128.3, 126.5, 76.6, 66.2, 38.2, 25.3, 25.1, 18.4; LRMS (EI) *m/z* 202.1 $[M - H_2O]^+$; HRMS (ES) calculated for $C_{13}H_{14}O_2$ $[M - H_2O]^+$ 202.0994, found 202.0990.

Preparation of intermediates 143, 144 & 148



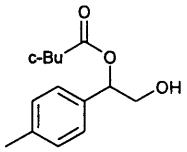
Following general procedure **E**, 4-methylstyrene (0.15 ml, 1.1 mmol), gave a mixture of intermediates **143**, **144** & **148** after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80).

2-(*O*-Oxocyclobutyl)-1-(*p*-Tolyl) ethane-1,2-diol 143



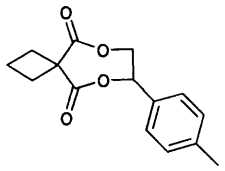
Colourless oil (0.10 g, 37%). IR (thin film)/cm^{-1}: 3471, 3066, 1726, 1252, 1215; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.0 Hz, 2H, Ar-H), 7.10 (d, J = 7.9 Hz, 2H, Ar-H), 4.84 (dd, J = 3.2 & 8.3 Hz, 1H, ArCHOH), 4.19 (dd, J = 3.3 & 11.6 Hz, 1H, CHHOCO), 4.08 (dd, J = 8.4 & 11.6 Hz, 1H, CHHOCO), 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$(CH_2)_2CH_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 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 $C_{14}H_{16}O_2$ $[M - H_2O]^+$ 216.1150, found 216.1150.

1-(*O*-Oxocyclobutyl)-1-(*p*-Tolyl) ethane-1,2-diol 144



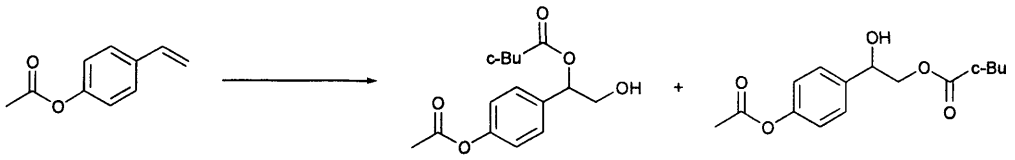
Colourless oil (0.12 g, 45%). IR (thin film)/cm^{-1}: 3480, 3018, 1728, 1252; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.1 Hz, 2H, Ar-H), 7.09 (d, J = 8.1 Hz, 2H, Ar-H), 5.73 (dd, J = 4.1 & 7.7 Hz, 1H, ArCHOCO), 3.78 (dd, J = 7.7 & 12.0 Hz, 1H, CHHOH), 3.70 (dd, J = 4.1 & 12.0 Hz, 1H, CHHOH), 3.14 (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$(CH_2)_2CH_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 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 $C_{14}H_{16}O_2$ $[M - H_2O]^+$ 216.1150, found 216.1148.

Intermediate 148



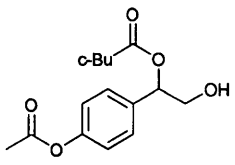
Colourless solid (0.01 g, 4%). IR (thin film)/cm^{-1}: 2106, 1638; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.14 (m, 4H, Ar-H), 5.54 (dd, J = 1.8 & 9.0 Hz, 1H, ArCHCH$_2$), 4.45 (dd, J = 9.0 & 14.2 Hz, 1H, CHHOCO), 4.33 (dd, J = 1.9 & 14.2 Hz, 1H, CHHOCO), 2.87–2.80 (m, 4H, (CH$_2$)$_2$CH$_2$), 2.30 (s, 3H, CH$_3$), 2.12–2.06 (m, 2H, (CH$_2$)$_2$CH$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) 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 $C_{15}H_{17}O_4$ $[M + H]^+$ 261.1121, found 261.1118.

Preparation of intermediates 242 and 243



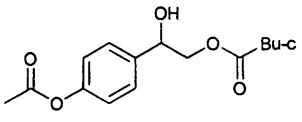
Following general procedure **E**, 4-acetoxystyrene (0.15 ml, 1.0 mmol) gave a mixture of intermediates **242** and **243** after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80).

1-(*O*-Oxocyclobutyl)-1-(4-acetoxyphenyl)ethane 1,2-diol 242



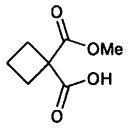
Colourless oil (0.10 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2H, Ar-H), 7.01 (d, J = 8.6 Hz, 2H, Ar-H), 5.77 (dd, J = 4.3 & 7.4 Hz, 1H, ArCHOCO), 3.77 (dd, J = 7.4 & 12.0 Hz, 1H, CHHOH), 3.71 (dd, J = 4.3 & 12.0 Hz, 1H, CHHOH), 3.16 (quin, J = 8.0 Hz, 1H, CH(CH$_2$)$_2$CH$_2$), 2.22 (s, 3H, CH$_3$), 2.18–1.88 (m, 6H, CH(CH$_2$)$_2$CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 169.4, 150.6, 135.0, 127.8, 121.8, 75.9, 66.0, 38.1, 25.3, 25.1, 21.1, 18.4; LRMS (CI) *m/z* 260.1 $[M - H_2O]^+$; HRMS (ES) calculated for $C_{15}H_{16}O_4$ $[M - H_2O]^+$ 260.1049, found 260.1040.

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



Colourless oil (0.10 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, CHHOCO), 4.07 (dd, J = 8.2 & 11.5 Hz, 1H, CHHOCO), 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, $CDCl_3$) δ 172.7, 169.5, 150.4, 137.6, 127.3, 121.7, 71.9, 69.0, 38.0, 25.3, 21.1, 18.4; LRMS (CI) *m/z* 260.1 $[M - H_2O]^+$; HRMS (ES) calculated for $C_{15}H_{16}O_4$ $[M - H_2O]^+$ 260.1049, found 260.1047.

1-(Methoxycarbonyl)cyclobutanecarboxylic acid 149



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%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H, $OC\underline{H}_3$), 2.53 (t, J = 8.0 Hz, 4H, $CH_2(C\underline{H}_2)_2$), 1.96–1.80 (m, 2H, $C\underline{H}_2(CH_2)_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.6, 172.1, 52.8, 52.5, 28.9, 16.2; LRMS (ES) *m/z* 140.1 $[M - H_2O]^+$; HRMS (EI) calculated for $C_7H_8O_3$ $[M - H_2O]^+$ 140.0473, found 140.0475.

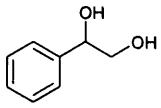
General Procedure F. Synthesis of Diols with Cyclobutane Malonoyl Peroxide

Alkene (0.7 mmol) was added dropwise to a solution of cyclobutane malonoyl peroxide (0.15 g, 1.1 mmol) in chloroform (2 ml). H_2O (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 $MgSO_4$. The solvent was removed under reduced pressure to give the desired diol.

General Procedure G. Synthesis of Diols *via* Modified Sharpless AD Procedure

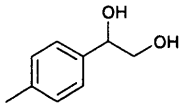
Potassium ferricyanide (1.96 g, 6.0 mmol), potassium carbonate (0.82 g, 6.0 mmol), potassium osmate dihydrate (1.5 mg, 0.1 mmol), quinuclidine (2.2 mg, 0.1 mmol) and methanesulfonamide (0.19 g, 2.0 mmol) were stirred together for 30 min. at room temperature, after which water (10 ml) and *tert*-butanol (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 × 30 ml), water (2 × 30 ml) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the desired diol.

1-Phenylethane-1,2-diol 64



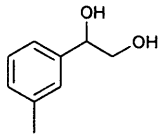
Following general procedure **F**, styrene (0.11 ml, 1.0 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 78%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 61 °C [lit.[90] m.p. 67 °C]; IR (thin film)/cm^{-1}: 3394, 2926, 1613; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 129.0, 128.5, 126.5, 75.1, 68.5; LRMS (EI) *m/z* 138.1 $[M]^+$; HRMS (EI) calculated for $C_8H_{10}O_2$ $[M]^+$ 138.0681, found 138.0676.

1-*p*-Tolylethane-1,2-diol 145



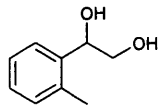
Following general procedure **F**, 4-methylstyrene (0.19 ml, 1.4 mmol) gave the title compound as a colourless crystalline solid (0.18 g, 84%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 70–72 °C [lit.[91] m.p. 76–77 °C]; IR (thin film)/cm^{-1}: 3371, 2925, 1647, 1327; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) 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 $C_9H_{12}O_2$ $[M]^+$ 152.0837, found 152.0840.

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



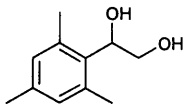
Following general procedure **F**, 3-methylstyrene (0.12 ml, 0.9 mmol) gave the title compound as a colourless crystalline solid (0.09 g, 65%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 70–72 °C; IR (thin film)/cm^{-1}: 3159, 2924, 1483; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) 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 $C_9H_{12}O_2$ $[M]^+$ 152.0837, found 152.0836.

1-*o*-Tolylethane-1,2-diol 213[92]



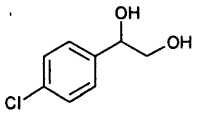
Following general procedure **F**, 2-methylstyrene (93 μl, 0.7 mmol) gave the title compound as a colourless crystalline solid (0.08 g, 80%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 104–105 °C; IR (thin film)/cm^{-1}: 3258, 2924, 1356, 1066; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_9H_{12}O_2$ $[M]^+$ 152.0837, found 152.0842.

1-Mesitylethane-1,2-diol 215[93]



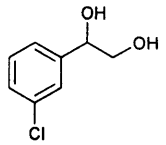
Following general procedure **F**, 2,4,6-trimethylstyrene (0.15 ml, 0.9 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 65%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 110–111 °C; IR (thin film)/cm^{-1}: 3365, 2923, 1611; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 137.2, 136.7, 132.5, 130.2, 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.

1-(4-Chlorophenyl)ethane-1,2-diol 217[94]



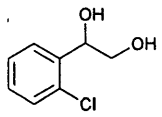
Following general procedure **F**, 4-chlorostyrene (0.12 ml, 1.0 mmol) gave the title compound as a colourless crystalline solid (0.13 g, 77%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 76–77 °C; IR (thin film)/cm^{-1}: 3612, 3399, 1598, 1077; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 133.8, 128.7, 127.5, 74.0, 68.0; LRMS (CI) *m/z* 190.2 $[M + NH_4]^+$; HRMS (ES) calculated for $C_8H_{13}O_2Cl^{35}N$ $[M + NH_4]^+$ 190.0629, found 190.0626.

1-(3-Chlorophenyl)ethane-1,2-diol 219[95]



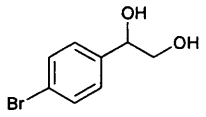
Following general procedure **F**, 3-chlorostyrene (0.12 ml, 0.9 mmol) gave the title compound as a colourless crystalline solid (0.05 g, 32%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). IR (thin film)/cm^{-1}: 3378, 2929, 2878, 1574; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_8H_9O_2Cl^{35}$ $[M]^+$ 172.0291, found 172.0289.

1-(2-Chlorophenyl)ethane-1,2-diol 221



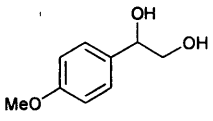
Following general procedure **F**, 2-chlorostyrene (0.21 ml, 1.6 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 38%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 101–104 °C; IR (thin film)/cm^{-1}: 3164, 1470, 1361, 1068; ^{1}H NMR (250 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_8H_9O_2Cl^{35}$ $[M]^+$ 172.0291, found 172.0288.

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



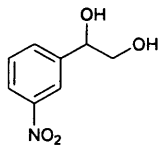
Following general procedure **F**, 4-bromostyrene (0.11 ml, 0.7 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 74%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 98–99 °C [lit.[96] m.p. 100–101 °C]; IR (thin film)/cm^{-1}: 3313, 2930, 1590; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CHHOH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 139.5, 131.7, 127.8, 121.9, 74.1, 67.9; LRMS (EI) *m/z* 216.0 $[M]^+$; HRMS (EI) calculated for $C_8H_9O_2Br^{79}$ $[M]^+$ 215.9786, found 215.9790.

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.[97] m.p. 79–81 °C]; IR (thin film)/cm^{-1}: 3359, 2935, 2839, 1612, 1246; ^{1}H NMR (400 MHz, $CDCl_3$) 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, OCH_3), 3.65–3.59 (m, 2H, CH_2OH), 2.35 (bs, 1H, OH), 1.96 (bs, 2H, OH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.4, 132.7, 127.4, 114.0, 74.3, 68.1, 55.3; LRMS (EI) *m/z* 168.2 $[M]^+$; HRMS (ES) calculated for $C_9H_{12}O_3Na$ $[M + Na]^+$ 191.0679, found 191.0676.

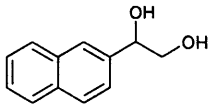
1-(3-Nitrophenyl)ethane-1,2-diol 227[98]



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; ^{1}H NMR (400 MHz, $CDCl_3$) 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) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 132.2, 129.5, 122.9, 121.2,

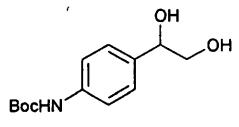
73.6, 67.7 (one carbon missing); LRMS (EI) *m/z* 165.0 $[M - H_2O]^+$; HRMS (EI) calculated for $C_8H_7O_3N$ $[M - H_2O]^+$ 165.0426, found 165.0434.

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



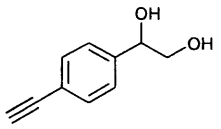
Following general procedure **F**, 2-vinylnaphthalene (0.11 g, 0.7 mmol) gave the title compound as a pale orange solid (0.09 g, 65%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 126–127 °C [lit.[41] m.p. 134–135 °C]; IR (thin film)/cm^{-1}: 3187, 2930, 1599; ^1H NMR (400 MHz, $CDCl_3$) 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, CH_2OH), 2.60 (d, J = 3.2 Hz, 1H, CHOH), 2.05 (dd, J = 4.8 & 7.2 Hz, 1H, CH_2OH); ^{13}C 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 $C_{12}H_{12}O_2$ $[M]^+$ 188.0837, found 188.0837.

tert-Butyl 4-(1,2-dihydroxyethyl)phenylcarbamate 240



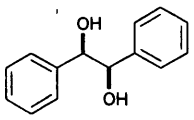
Following general procedure **F**, *tert*-butyl 4-vinylphenylcarbamate (0.15 g, 0.7 mmol) gave the title compound as a colourless crystalline solid (0.10 g, 56%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 139–141 °C; IR (thin film)/cm^{-1}: 3379, 3334, 3281, 2933, 1685, 1525; ^{1}H NMR (400 MHz, $CDCl_3$) 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, C(CH_3)$_3$); ^{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



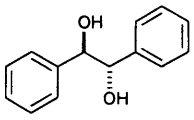
Following general procedure **F**, 4-ethynylstyrene (0.08 g, 0.6 mmol) gave the title compound as a waxy colourless solid (0.04 g, 35%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 2H, Ar-H), 7.26 (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, $CDCl_3$) 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 $C_{10}H_{10}O_2$ [M]$^+$ 162.0681, found 162.0682.

(±)-Hydrobenzoin 41



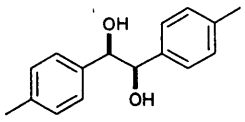
Following general procedure **F**, *trans*-stilbene (0.105 g, 0.6 mmol) gave the title compound as a colourless crystalline solid (0.10 g, 78%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 104–105 °C [lit.[99] m.p. 146–147 °C]; IR (thin film)/cm^{-1}: 3389, 2922, 2852, 1645; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19–7.06 (m, 10H, Ar-H), 4.66 (s, 2H, ArCHOH), 2.74 (s, 2H, ArCHOH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 128.2, 128.0, 127.0, 79.1; LRMS (APCI) *m/z* 196.1 $[M - H_2O]^+$; HRMS (CI) calculated for $C_{14}H_{14}O_2Na$ $[M + Na]^+$ 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, $CDCl_3$) δ 7.27–7.17 (m, 10H, Ar-H), 4.76 (s, 2H, ArCHOH), 2.13 (s, 2H, ArCHOH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 128.3, 128.2, 127.1, 78.2; LRMS (EI) *m/z* 196.1 $[M - H_2O]^+$; HRMS (EI) calculated for $C_{14}H_{12}O$ $[M - H_2O]^+$ 196.0888, found 196.0886.

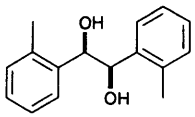
***rel*-(1*R*,2*R*)-1,2-Di-*p*-tolylethane-1,2-diol 256**



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.[101] m.p. 180 °C]; IR (thin film)/cm^{-1}: 3337, 3028, 2915; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98–6.94 (m, 8H, Ar-H), 4.58 (s, 2H, ArCHOH), 2.22 (s, 6H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 137.0, 128.8, 127.1, 78.8, 21.2; LRMS (EI) *m/z* 224.1 $[M - H_2O]^+$; HRMS (CI) calculated for $C_{16}H_{22}O_2N$ $[M + NH_4]^+$ 260.1645, found 260.1649.

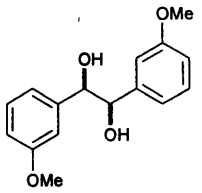
***rel*-(1*R*,2*R*)-1,2-Di-*o*-tolylethane-1,2-diol 258**



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.[102] m.p. 116–118 °C]; IR (thin film)/cm^{-1}: 3390, 1604, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) 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_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.0, 135.9, 130.2, 127.7, 127.3, 126.0, 74.6, 18.8; LRMS (EI) *m/z* 224.1 $[M - H_2O]^+$; HRMS (EI) calculated for $C_{16}H_{16}O$ $[M - H_2O]^+$ 224.1201, found 224.1203.

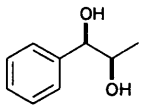
rel-(1*R*,2*R*)-1,2-Bis(3-methoxyphenyl)ethane-1,2-diol 260[103]



Major

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; ^{1}H NMR (400 MHz, $CDCl_3$) 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, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 141.6, 129.1, 119.3, 113.9, 112.3, 78.9, 55.2; LRMS (EI) *m/z* 256.1 $[M - H_2O]^+$; HRMS (EI) calculated for $C_{16}H_{16}O_3$ $[M - H_2O]^+$ 256.1099, found 256.1098.

rel-(1*R*,2*R*)-1-Phenylpropane-1,2-diol 264[104]

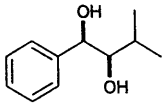


Major

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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.21 (m, 5H, Ar-H), 4.24 (d, J = 7.5 Hz, 1H, ArCHOH), 3.76–3.73 (m, 1H, $CHOHCH_3$), 3.25 (bs, 1H, OH), 3.03 (bs, 1H, OH), 0.94 (d, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 128.5, 128.1, 126.9, 79.5,

72.2, 18.8; LRMS (EI) *m/z* 134.1 $[M - H_2O]^+$; HRMS (EI) calculated for $C_9H_{10}O$ $[M - H_2O]^+$ 134.0732, found 134.0730.

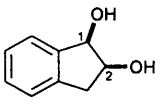
rel-(1*R*,2*R*)-3-Methyl-1-phenylbutane-1,2-diol 271[105]



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, $CDCl_3$): 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, $CH(CH_3)_2$), 0.92–0.88 (m, 6H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.6, 128.6, 128.0, 126.6, 80.5, 75.2, 29.2, 20.2, 16.4; LRMS (EI) *m/z* 162.1 $[M - H_2O]^+$; HRMS (EI) calculated for $C_{11}H_{14}O$ $[M - H_2O]^+$ 162.1045, found 162.1047.

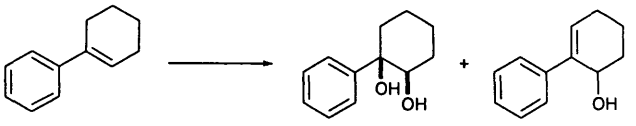
rel-(1*R*,2*S*)-2,3-Dihydro-1H-indene-1,2-diol 274



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, $CDCl_3$)

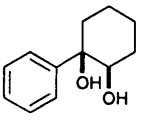
δ 7.36–7.31 (m, 1H, Ar-H), 7.22–7.14 (m, 3H, Ar-H), 4.88 (d, J = 4.8 Hz, 1H, ArCHOH), 4.40–4.35 (m, 1H, ArCHOHCHOH), 3.04 (dd, J = 5.8 & 16.3 Hz, 1H, ArCHHCHOH), 2.87 (dd, J = 3.6 & 16.3 Hz, 1H, ArCHHCHOH), 2.50 (bs, 2H, OH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 142.0, 140.2, 128.9, 127.2, 125.4, 125.1, 76.0, 73.5, 38.6; LRMS (EI) *m/z* 150.1 $[M]^+$; HRMS (EI) calculated for $C_9H_{10}O_2$ $[M]^+$ 150.0681, found 150.0684.

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



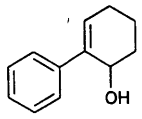
Following general procedure **F**, 1-phenylcyclohexene (0.09 ml, 0.6 mmol) gave a mixture of 1-phenylcyclohexane-1,2-diol **275** and 2-phenylcyclohex-2-enol **276** after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80).

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



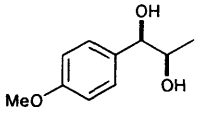
Colourless solid (0.06 g, 50%). m.p. 80–81 °C [lit.[107] m.p. 92 °C]; IR (thin film)/cm^{-1}: 3394, 2935, 2362, 1445, 1061, 997; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.41 (m, 2H, Ar-H), 7.31–7.27 (m, 2H, Ar-H), 7.20–7.16 (m, 1H, Ar-H), 3.88 (dd, J = 4.5 & 11.1 Hz, 1H, CHOH), 1.81–1.08 (m, 8H, $(CH_2)_4$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 128.5, 127.0, 125.2, 75.8, 74.6, 38.5, 29.3, 24.4, 21.1; LRMS (EI) *m/z* 192.1 $[M]^+$; HRMS (EI) calculated for $C_{12}H_{16}O_2$ $[M]^+$ 192.1150, found 192.1147.

2-Phenylcyclohex-2-enol 276 [108]



Colourless oil (0.02 g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 140.2, 139.1, 128.7, 128.6, 127.1, 126.0, 65.5, 31.6, 26.1, 17.4; LRMS (EI) *m/z* 174.1 $[M]^+$; HRMS (EI) calculated for $C_{12}H_{14}O$ $[M]^+$ 174.1045, found 174.1040.

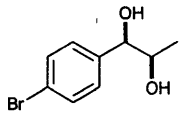
***rel*-(1*R*,2*R*)-1-(4-Methoxyphenyl)propane-1,2-diol 283** [109]



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, $CDCl_3$): δ 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, $CDCl_3$): δ 159.5, 133.2, 128.1, 113.9, 79.1, 72.3, 55.3, 18.7; LRMS (EI) *m/z* 182.1 $[M]^+$; HRMS (EI) calculated for $C_{10}H_{14}O_3$ $[M]^+$ 182.0943, found 182.0940.

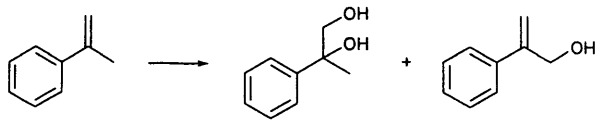
rel-(1*R*,2*R*)-1-(4-Bromophenyl)propane-1,2-diol 280[110]



Major

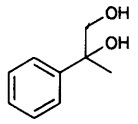
Following general procedure **F**, 4-bromo-*trans*-β-methylstyrene (0.09 g, 0.5 mmol) gave the title compound as a pale yellow oil (0.08 g, 70%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). IR (thin film)/cm^{-1}: 3402, 2896, 1593, 1488, 1400, 1126, 1069, 1040, 1010, 926; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.16 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.25 (d, *J* = 7.6 Hz, 1H, ArCHOH), 3.77–3.70 (m, 1H, CHOHCH$_3$), 3.59 (bs, 1H, OH), 3.20 (bs, 1H, OH), 0.99 (d, *J* = 6.4 Hz, 3H, CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.0, 131.7, 128.6, 122.0, 78.8, 72.1, 18.9; LRMS (EI) *m/z* 211.9 $[M - H_2O]^+$; HRMS (EI) calculated for $C_9H_9OBr^{79}$ $[M - H_2O]^+$ 211.9837, found 211.9841.

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



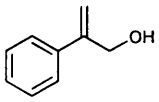
Following general procedure **F**, α-methylstyrene (0.09 ml, 0.7 mmol) gave a mixture of 2-phenylpropane-1,2-diol **293** and 2-phenylprop-2-en-1-ol **294** after purification by column chromatography eluting with ethyl acetate : petroleum ether (80 : 20).

2-Phenylpropane-1,2-diol 293[111]



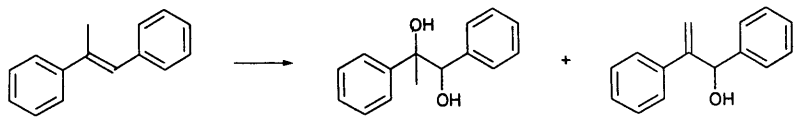
Colourless oil (0.05 g, 50%) IR (thin film)/cm^{-1}: 3568, 1449, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.32 (m, 2H, Ar-H), 7.28–7.24 (m, 2H, Ar-H), 7.19–7.15 (m, 1H, Ar-H), 3.62 (d, J = 11.3 Hz, 1H, CHHOH), 3.48 (d, J = 11.3 Hz, 1H, CHHOH), 2.90 (s, 2H, OH), 1.39 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 145.1, 128.4, 127.1, 125.2, 75.0, 70.9, 26.0; LRMS (EI) *m/z* 134.1 $[M - H_2O]^+$; HRMS (EI) calculated for $C_9H_{10}O$ $[M - H_2O]^+$ 134.0732, found 134.0736.

2-Phenylprop-2-en-1-ol 294[112]



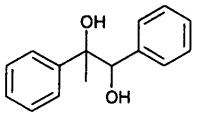
Colourless oil (0.02 g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.37 (m, 2H, Ar-H), 7.31–7.22 (m, 3H, Ar-H), 5.41 (app s, 1H, =CHH), 5.29 (app s, 1H, =CHH), 4.49 (s, 2H, CH_2OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 138.5, 128.5, 128.0, 126.1, 112.6, 65.1; LRMS (EI) *m/z* 134.1 $[M]^+$; HRMS (EI) calculated for $C_9H_{10}O$ $[M]^+$ 134.0732, found 134.0729.

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



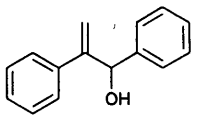
Following general procedure **F**, α-methylstilbene (0.17 g, 0.9 mmol) gave a mixture of 2-phenylpropane-1,2-diol and 2-phenylprop-2-en-1-ol after purification by column chromatography eluting with ethyl acetate : petroleum ether (20 : 80).

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



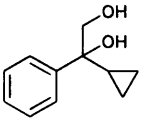
Colourless solid (0.07 g, 37%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 88–90 °C [lit.[113] m.p. 103–104 °C]; IR (thin film)/cm^{-1}: 3581, 1603, 1449, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.11 (m, 8H, Ar-H), 6.96–6.94 (m, 2H, Ar-H), 4.63 (s, 1H, ArCHOH), 2.80 (bs, 2H, OH), 1.20 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) 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 (CI) *m/z* 246.3 $[M + NH_4]^+$; HRMS (ES) calculated for $C_{15}H_{20}O_2N$ $[M + NH_4]^+$ 246.1489, found 246.1490.

1,2-Diphenylprop-2-en-1-ol[114] (Table 4.7, Entry 2)



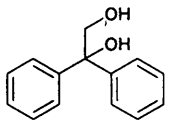
Colourless oil (0.04 g, 22%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33–7.13 (m, 10H, Ar-H), 5.61 (d, J = 3.9 Hz, 1H, ArCHOH), 5.41 (d, J = 7.3 Hz, 2H, =CH_2), 2.11 (d, J = 4.2 Hz, 1H, ArCHOH); LRMS (EI) *m/z* 210.1 $[M]^+$; HRMS (EI) calculated for $C_{15}H_{14}O$ $[M]^+$ 210.1045, found 210.1043.

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



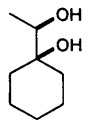
Following general procedure **F**, 1-phenyl-1-cyclopropylethylene (0.13 g, 0.9 mmol) gave the title compound as a colourless crystalline solid (0.11 g, 69%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 50–51 °C [lit.[115] m.p. 53 °C]; IR (thin film)/cm^{-1}: 3581, 3438, 1494, 1448, 1392, 1028; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CHCH_2CH_2$), 0.30–0.27 (m, 2H, $CHCH_2CH_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 142.8, 127.4, 126.4, 124.9, 74.3, 69.6, 17.5, 0.0, –1.0; LRMS (EI) *m/z* 160.1 $[M - H_2O]^+$; HRMS (MALDI) calculated for $C_{11}H_{14}O_2$ $[M]^+$ 178.0988, found 178.0986.

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



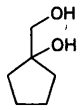
Following general procedure **F**, 1,1-diphenylethylene (0.12 ml, 0.7 mmol) gave the title compound as a colourless crystalline solid (0.10 g, 67%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). m.p. 110 °C [lit.[116] m.p. 122 °C]; IR (thin film)/cm^{-1}: 3372, 3303, 1491, 1455, 1384, 1361, 1043; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_2OH), 3.18 (s, 1H, OH), 1.88 (t, J = 6.4 Hz, 1H, CH_2OH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 143.8, 128.5, 127.5, 126.4, 78.6, 69.5; LRMS (EI) *m/z* 196.1 $[M - H_2O]^+$; HRMS (EI) calculated for $C_{14}H_{12}O$ $[M - H_2O]^+$ 196.0888, found 196.0887.

1-(1-Hydroxyethyl)cyclohexanol 302[117]



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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (q, J = 6.4 Hz, 1H, CH_3CHOH), 1.60–1.46 (m, 8H, $(CH_2)_4$), 1.35–1.15 (m, 2H, CH_2), 1.09 (d, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.8, 73.5, 34.2, 31.2, 25.9, 21.7, 21.5, 17.0; LRMS (CI) *m/z* 162.3 $[M + NH_4]^+$; HRMS (ES) calculated for $C_8H_{20}O_2N$ $[M + NH_4]^+$ 162.1489, found 162.1487.

1-(Hydroxymethyl)cyclopentanol 304[118]

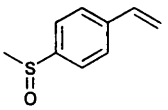


Following general procedure **G**, methylenecyclopentane (0.20 ml, 1.9 mmol) gave the title compound as a colourless crystalline solid (0.13 g, 60%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (50 : 50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (bs, 2H, $CH_2O\underline{H}$), 3.44 (s, 2H, $C\underline{H}_2OH$), 1.75–1.70 (m, 2H, CH_2), 1.58–1.50 (m, 6H, $(CH_2)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.8, 69.4, 36.7, 24.1; LRMS (CI) *m/z* 134.0 $[M + NH_4]^+$; HRMS (ES) calculated for $C_6H_{16}O_2N$ $[M + NH_4]^+$ 134.1176, found 134.1174.

***rel*-(1*R*,2*S*)-1-Methylcyclopentane-1,2-diol 306**[41]

Following general procedure **G**, 1-methylcyclopentene (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). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (apparent t, J = 6.5 Hz, 1H, C$\underline{H}$OH), 2.57 (bs, 2H, O$\underline{H}$), 1.92–1.43 (m, 6H, $(C\underline{H}_2)_3$), 1.19 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.4, 78.4, 37.1, 31.6, 25.3, 19.2; LRMS (CI) *m/z* 134.0 $[M + NH_4]^+$; HRMS (MALDI) calculated for $C_6H_{16}O_2N$ $[M + NH_4]^+$ 134.1176, found 134.1175.

1-(Methylsulfinyl)-4-vinylbenzene 245

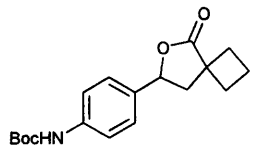


4-Vinylthioanisole (0.15 g, 1.0 mmol) was added to a solution of cyclobutane malonoyl peroxide (0.15 g, 1.1 mmol) in chloroform (2 ml). H_2O (18 µl, 1.0 mmol) was added and stirred at 40 °C for 1 h. Removal of the solvent under reduced pressure gave the title compound as a light yellow oil (0.12 g, 74%) after purification by column chromatography eluting with diethyl ether : petroleum ether (90 : 10). IR (thin film)/cm^{-1}: 3019, 1706, 1594, 1046; ^{1}H NMR (400 MHz, $CDCl_3$) 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=CH_2), 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, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 140.5, 135.7, 127.1, 123.9, 116.3, 43.9; LRMS (EI) *m/z* 166.0 $[M]^+$; HRMS (EI) calculated for $C_9H_{10}OS$ $[M]^+$ 166.0452, found 166.0455.

General Procedure H. Synthesis of γ lactones.

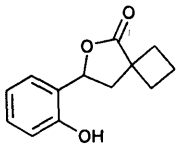
Alkene (0.7 mmol) was added to a solution of cyclobutane malonoyl peroxide (0.15 g, 1.0 mmol) in chloroform (2 ml). After ~ 5 min. the reaction mixture turned orange. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was reduced to dryness to give the corresponding γ-lactone.

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



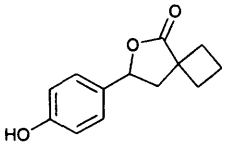
Following general procedure **H**, *tert*-Butyl 4-vinylphenylcarbamate (0.15 g, 0.7 mmol) gave the title compound as a yellow solid (0.07 g, 30%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (30 : 70). m.p. 115 °C; IR (thin film)/cm^{-1}: 3437, 1764, 1725, 1597, 1524; ^{1}H NMR (400 MHz, $CDCl_3$) 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, $(CH_2)_2CH_2$), 2.16 (dd, J = 9.0 & 12.9 Hz, 1H, ArCHCHH), 2.10–1.85 (m, 4H, $(CH_2)_2CH_2$), 1.45 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 152.7, 138.6, 133.7, 126.2, 118.6, 80.7, 77.8, 44.8, 44.5, 31.5, 29.2, 28.3, 16.5; LRMS (EI) *m/z* 317.2 $[M]^+$; HRMS (EI) calculated for $C_{18}H_{23}O_4N$ $[M]^+$ 317.1627, found 317.1631.

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; ^{1}H NMR (400 MHz, $CDCl_3$) 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, $(CH_2)_2CH_2$), 2.26 (dd, J = 8.4 & 13.2 Hz, 1H, ArCHCHH), 2.15–1.81 (m, 4H, $(CH_2)_2CH_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) 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 $C_{13}H_{14}O_3$ $[M]^+$ 218.0943, found 218.0943.

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



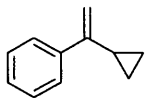
Following general procedure **H**, 4-hydroxystyrene (0.10 g, 0.8 mmol) gave the title compound as a yellow solid (0.03 g, 19%) after purification by column chromatography eluting with ethyl acetate : petroleum ether (10 : 90). m.p. 140–141 °C. IR (thin film)/cm^{-1}: 3369, 2940, 1753, 1614, 1517, 1447, 1330, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) 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, $(CH_2)_2CH_2$), 2.19 (dd, J = 9.0 & 13.0 Hz, 1H, ArCHCHH),

2.18–1.98 (m, 4H, ($C\underline{H}_2$)$_2CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{13}H_{14}O_3$ $[M]^+$ 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. ^{n}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. H_2O (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 $MgSO_4$. The solvent was removed under reduced pressure to give the desired alkene.

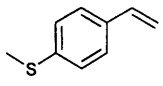
1-Phenyl-1-cyclopropylethylene 299[119]



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. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.66–7.61 (m, 2H, Ar-$\underline{H}$), 7.42–7.30 (m, 3H, Ar-$\underline{H}$), 5.32 (d, J = 0.7 Hz, 1H, C=C$\underline{H}$H), 4.98 (d, J = 1.1 Hz, 1H, C=CH$\underline{H}$), 1.75–1.64 (m, 1H, C$\underline{H}$(CH_2)$_2$), 0.95–0.82 (m, 2H, CHC$\underline{H}_2$$CH_2$),

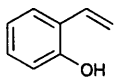
0.67–0.63 (m, 2H, $CHCH_2C\underline{H}_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 141.7, 128.2, 127.5, 126.1, 109.0, 15.6, 6.7; LRMS (EI) *m/z* 144.1 $[M]^+$; HRMS (MALDI) calculated for $C_{11}H_{12}$ $[M]^+$ 144.0934, found 144.0931.

4-Vinylthioanisole 244[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. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $ArC\underline{H}=CH_2$), 5.64 (apparent d, *J* = 17.6 Hz, 1H, $CH=C\underline{H}H$), 5.14 (apparent d, *J* = 10.8 Hz, 1H, $CH=CH\underline{H}$), 2.42 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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 $C_9H_{10}S$ $[M]^+$ 150.0503, found 150.0499.

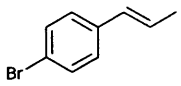
2-Vinyl phenol 191[121]



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). ^1H NMR (250 MHz, $CDCl_3$) δ 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, $ArC\underline{H}=CH_2$), 5.67 (dd, *J* = 1.3 & 17.8 Hz, 1H, $CH=C\underline{H}H$), 5.30 (dd, *J* = 1.3 & 11.2 Hz, 1H, $CH=CH\underline{H}$), 4.89 (bs, 1H, O<u>H</u>); ^{13}C NMR

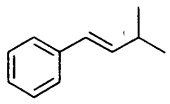
(125 MHz, $CDCl_3$) δ 152.8, 131.5, 128.9, 127.4, 124.8, 121.0, 115.9, 115.8; LRMS (EI) *m/z* 120.1 $[M]^+$; HRMS (EI) calculated for C_8H_8O $[M]^+$ 120.0575, found 120.0573.

1-(4-Bromophenyl)-2-methylethylene 279[122]



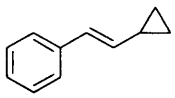
Ethyltriphenylphosphonium chloride (6.10 g, 16 mmol) and dry THF (100 ml) was placed in an oven dried two necked flask equipped with a reflux condenser with nitrogen inlet, large stirrer bar and glass stopper and cooled to −10 °C. BuLi (2.5 M in hexane, 6.5 ml, 16 mmol) was added and the resulting red/brown 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 $MgSO_4$. 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, $CDCl_3$) 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=CHCH$_3$), 1.79 (d, J = 6.4 Hz, 3H, CH=CHCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 131.5, 129.9, 127.4, 126.6, 120.4, 18.5; LRMS (EI) *m/z* 196.0 $[M]^+$; HRMS (EI) calculated for $C_9H_9Br^{79}$ $[M]^+$ 195.9888, found 195.9890.

1-Phenyl-2-isopropylethylene 270[123]



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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]



Benzyltriphenyl phosphonium 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_2O (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 × 50 ml) and the combined organic layers washed with brine (20 ml) and dried over $MgSO_4$. 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, $CDCl_3$) δ 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_2CH_2), 0.49–0.46 (m, 1H, CHCH_2CH_2)

Minor (*cis*)

^{1}H NMR (400 MHz, $CDCl_3$) δ 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_2CH_2), 0.49–0.46 (m, 1H, CHCH_2CH_2)

Data for mixture of isomers

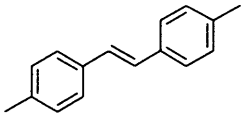
^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 136.8, 134.9, 128.7, 128.5, 128.2, 127.4, 126.5, 126.4, 125.6, 14.5, 11.0, 8.0, 7.2; LRMS (EI) *m/z* 144.1 $[M]^+$; HRMS (EI) calculated for $C_{11}H_{12}$ $[M]^+$ 144.0939, found 144.0939.

General Procedure J. Synthesis of Alkenes by Heck Reaction.

Palladium(II) acetate (0.02 g, 0.1 mmol), tri(*o*-toyl)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_2O (200 ml) and extracted with ethyl acetate (100 ml) added. The aqueous layer was further extracted with ethyl acetate (2 × 100 ml) and the combined organic layers were washed with brine (50 ml) and dried over $MgSO_4$. The resulting

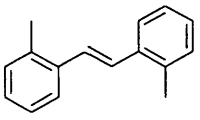
solution was reduced to ~ 10 ml volume and passed through a plug of silica washing with ethyl acetate. Removal of the solvent under reduced pressure gave the crude product as an off white solid. Re-crystallisation from a mixture of dichloromethane (30 ml) and hexane (5 ml) gave the title compound as 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.

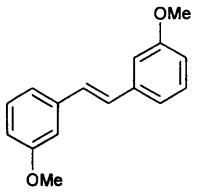
2,2'-Dimethyl-*trans*-stilbene 257



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),

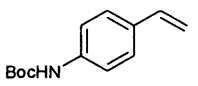
2.47 (s, 6H, C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 135.9, 130.4, 128.1, 127.6, 126.2, 125.6, 20.0; LRMS (EI) *m/z* 208.1 $[M]^+$; HRMS (APCI) calculated for $C_{16}H_{16}$ $[M + H]^+$ 209.1325, found 209.1329.

3, 3'-Dimethoxy-*trans*-stilbene 259



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; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24–7.18 (m, 2H, Ar-<u>H</u>), 7.06–6.97 (m, 4H, Ar-<u>H</u>), 7.01 (s, 2H, C<u>H</u>=C<u>H</u>), 6.78–6.73 (m, 2H, Ar-<u>H</u>), 3.79 (s, 6H, OC<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{16}H_{16}O_2$ $[M]^+$ 240.1150, found 240.1149.

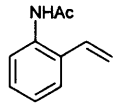
***tert*-Butyl 4-vinylphenylcarbamate 234[128]**



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, 1611, 1587, 1161; ^{1}H NMR (250 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{13}H_{17}O_2N$ $[M]^+$ 219.1259, found 219.1258.

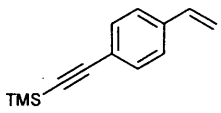
_N_-(2-Vinylphenyl)acetamide 190[71]



_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 × 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;

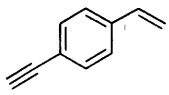
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (app d, J = 8.0 Hz, 1H, Ar-H), 7.35 (app d, J = 7.6 Hz, 1H, Ar-H) 7.23–7.19 (m, 1H, Ar-H) 7.10–7.06 (m, 1H, Ar-H), 6.73 (dd, J = 11.2 & 17.6 Hz, 1H, ArCH=CH_2), 5.60 (apparent d, J = 17.6 Hz, 1H, CH=CHH), 5.34 (apparent d, J = 11.2 Hz, 1H, CH=CHH), 2.12 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 134.4, 132.3, 130.5, 128.5, 126.9, 125.4, 123.8, 118.0, 24.3; LRMS (EI) *m/z* 161.1 $[M]^+$; HRMS (EI) calculated for $C_{10}H_{11}NO$ $[M]^+$ 161.0841, found 161.0841.

Trimethyl(2-(4-vinylphenyl)ethynyl)silane 246[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^{-1}: 2961, 2361, 2154, 1504, 1250, 848; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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_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, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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 $C_{13}H_{16}Si$ $[M]^+$ 200.1016, found 200.1019.

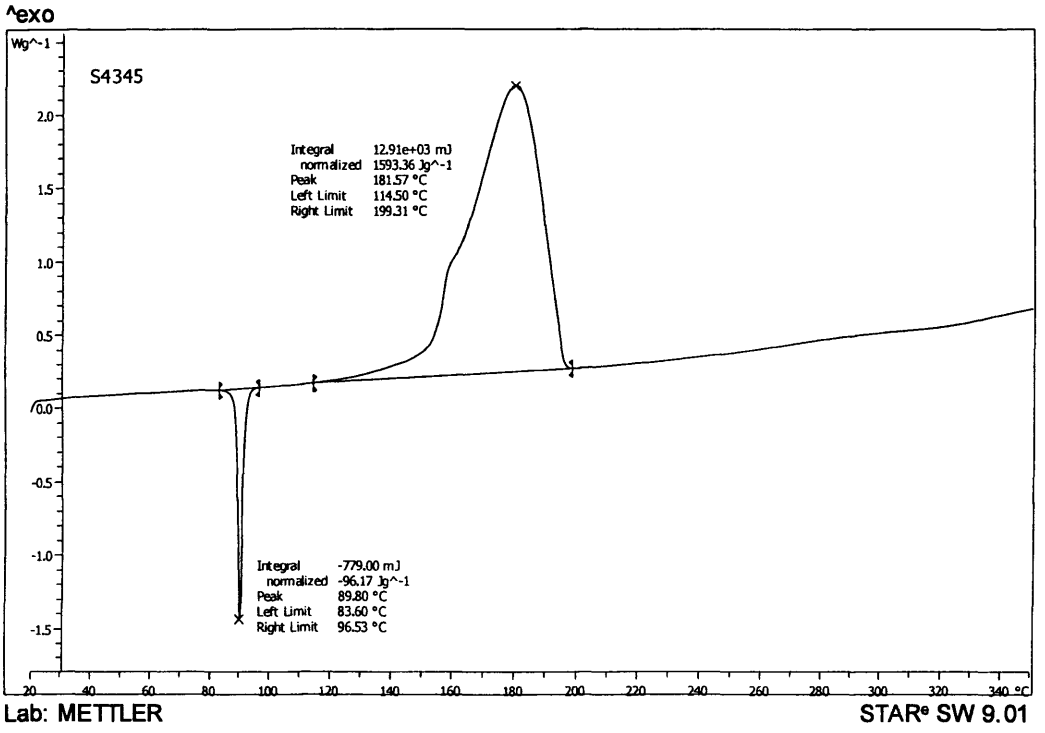
1-Ethynyl-4-vinylbenzene 247[75]



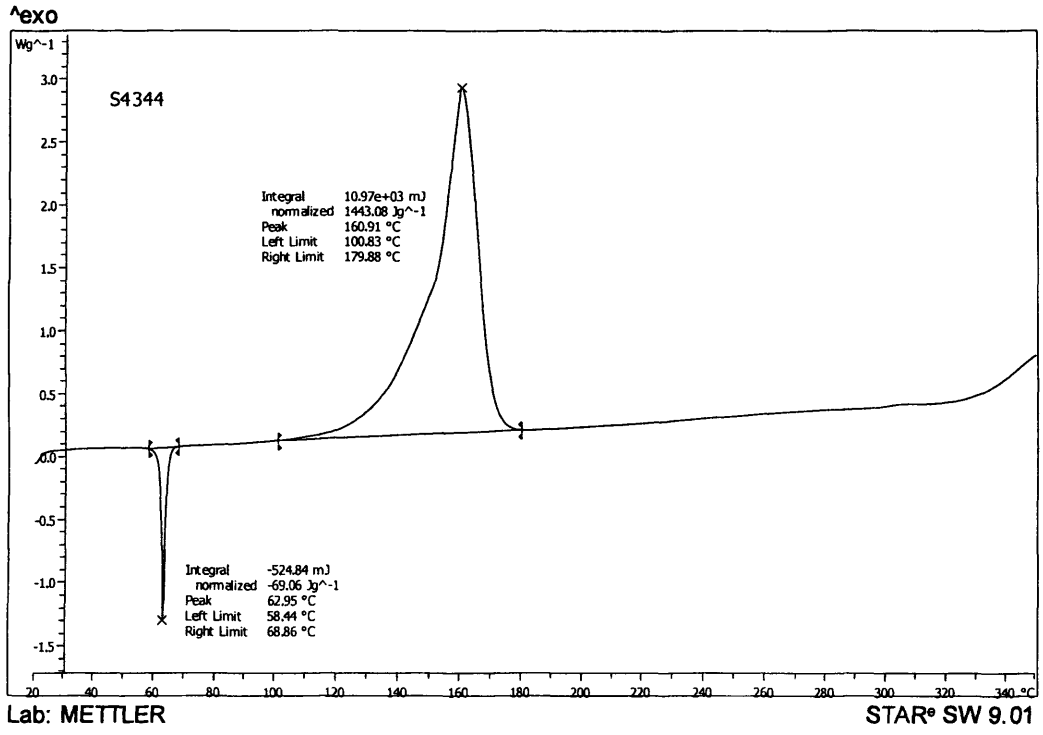
Trimethyl(2-(4-vinylphenyl)ethynyl)silane (0.54 g, 2.7 mmol) was dissolved in dry THF (10 ml) and 1.0 M solution of tetra-*n*-butyl ammonium fluoride (4.0 ml, 4.0 mmol) added. The reaction was stirred at room temperature under nitrogen for 1 h. The reaction mixture was reduced to dryness and partitioned between dichloromethane (25 ml) and water (25 ml). The aqueous layer was further extracted with dichloromethane (2 × 15 ml) and the combined organic layers washed with brine (15 ml) and dried over $MgSO_4$. 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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=CH_2), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{10}H_8$ $[M]^+$ 128.0621, found 128.0621.

Chapter 6: Appendix

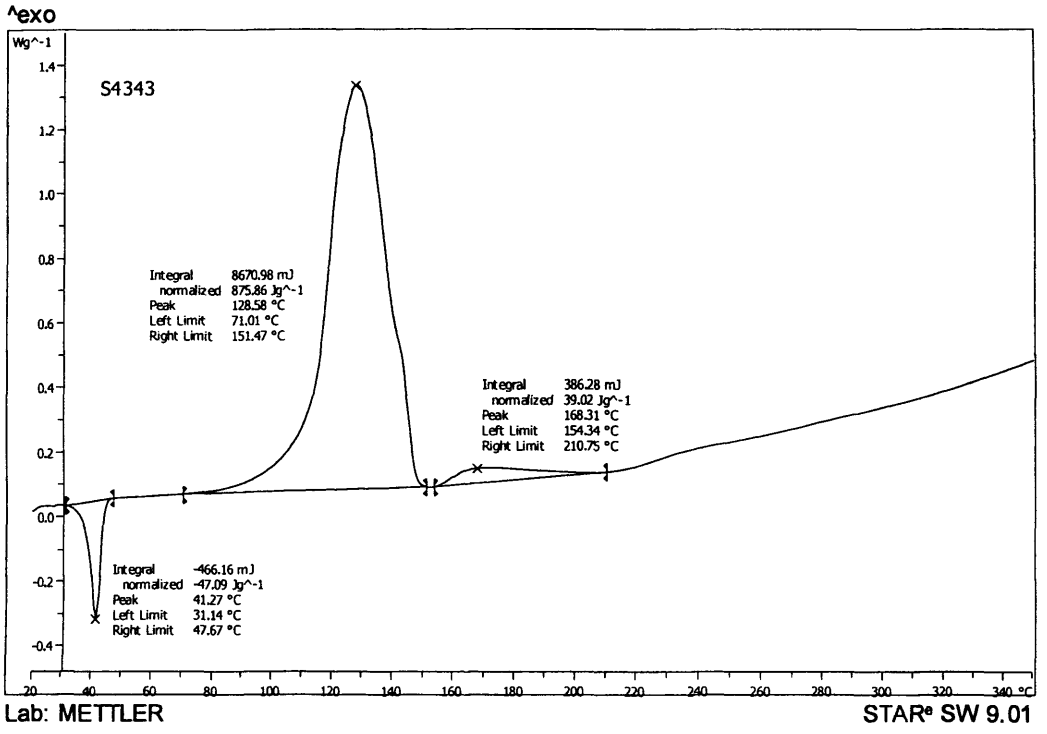
Appendix 1: DSC data for cyclopropane malonoyl peroxide 129



Appendix 2: DSC data for cyclobutane malonoyl peroxide 130



Appendix 3: DSC data for cyclopentane malonoyl peroxide 131



Appendix 4: X-ray data for cyclopropane malonoyl peroxide 129

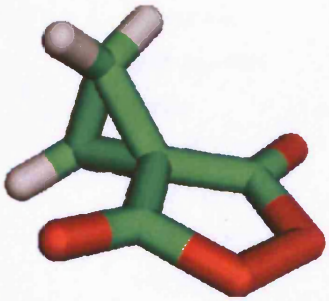


Table 1. Crystal data and structure refinement for nct0808t.

Identification code	nct0808t	
Empirical formula	C5 H4 O4	
Formula weight	128.08	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Cmcm	
Unit cell dimensions	a = 9.7170(10) Å	α= 90°.
	b = 9.2110(9) Å	β= 90°.
	c = 6.0350(5) Å	γ = 90°.
Volume	540.15(9) $Å^3$	
Z	4	
Density (calculated)	1.575 Mg/m^3	
Absorption coefficient	0.141 mm^{-1}	
F(000)	264	
Crystal size	0.30 x 0.30 x 0.30 mm^3	
Theta range for data collection	3.05 to 27.49°.	
Index ranges	-8<=h<=12, -11<=k<=11, -6<=l<=7	
Reflections collected	1321	
Independent reflections	360 [R(int) = 0.0374]	
Completeness to theta = 27.49°	99.7 %	
Max. and min. transmission	0.9590 and 0.9590	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	360 / 0 / 34	
Goodness-of-fit on F^2	1.105	
Final R indices [I>2sigma(I)]	R1 = 0.0324, wR2 = 0.0807	
R indices (all data)	R1 = 0.0390, wR2 = 0.0851	
Extinction coefficient	0.060(13)	
Largest diff. peak and hole	0.274 and -0.142 $e.Å^{-3}$	

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

	x	y	z	U(eq)
C(1)	6206(2)	5940(2)	2500	25(1)
C(2)	5000	6872(2)	2500	22(1)
C(3)	5000	8334(2)	1293(3)	32(1)
O(1)	5759(1)	4506(1)	2500	33(1)
O(2)	7413(1)	6170(1)	2500	37(1)

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

C(1)-O(2)	1.1917(19)
C(1)-O(1)	1.3903(19)
C(1)-C(2)	1.4525(19)
C(2)-C(1)#1	1.453(2)
C(2)-C(3)#2	1.531(2)
C(2)-C(3)	1.531(2)
C(3)-C(3)#2	1.456(4)
O(1)-O(1)#1	1.476(2)
O(2)-C(1)-O(1)	118.41(14)
O(2)-C(1)-C(2)	133.56(16)
O(1)-C(1)-C(2)	108.03(13)
C(1)#1-C(2)-C(1)	107.56(19)
C(1)#1-C(2)-C(3)#2	121.31(7)
C(1)-C(2)-C(3)#2	121.31(7)
C(1)#1-C(2)-C(3)	121.31(7)
C(1)-C(2)-C(3)	121.31(7)
C(3)#2-C(2)-C(3)	56.82(16)
C(3)#2-C(3)-C(2)	61.59(8)
C(1)-O(1)-O(1)#1	108.19(8)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y,z #2 x,y,-z+1/2

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for nct0808t. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	28(1)	32(1)	16(1)	0	0	5(1)
C(2)	22(1)	23(1)	21(1)	0	0	0
C(3)	30(1)	26(1)	41(1)	8(1)	0	0
O(1)	40(1)	28(1)	29(1)	0	0	8(1)
O(2)	23(1)	53(1)	34(1)	0	0	7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for nct0808t.

	x	y	z	U(eq)
H(1)	5849(14)	8520(13)	480(20)	43(4)

Appendix 5: X-ray data for cyclobutane malonoyl peroxide 130

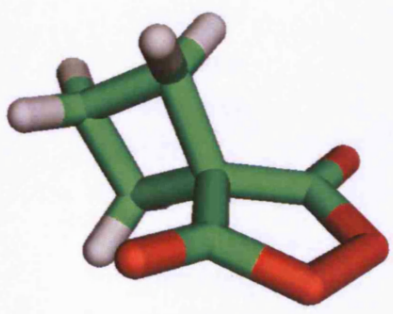


Table 1. Crystal data and structure refinement for nct0805.

Identification code	nct0805	
Empirical formula	C6 H6 O4	
Formula weight	142.11	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 6.4920(7) Å	α= 90°.
	b = 6.1380(6) Å	β= 91.908(4)°.
	c = 7.6100(8) Å	γ = 90°.
Volume	303.07(5) $Å^3$	
Z	2	
Density (calculated)	1.557 Mg/m^3	
Absorption coefficient	0.134 mm^{-1}	
F(000)	148	
Crystal size	0.20 x 0.20 x 0.20 mm^3	
Theta range for data collection	4.06 to 27.43°.	
Index ranges	-8<=h<=8, -7<=k<=7, -9<=l<=9	
Reflections collected	1237	
Independent reflections	1237 [R(int) = 0.0000]	
Completeness to theta = 27.43°	97.6 %	
Max. and min. transmission	0.9737 and 0.9737	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1237 / 1 / 91	
Goodness-of-fit on F^2	1.071	
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.1109	
R indices (all data)	R1 = 0.0569, wR2 = 0.1177	
Absolute structure parameter	5(4)	
Largest diff. peak and hole	0.269 and -0.195 $e.Å^{-3}$	

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.

	x	y	z	U(eq)
C(1)	3290(3)	2826(12)	6985(2)	21(1)
C(2)	2321(9)	1114(5)	8176(8)	29(1)
C(3)	1899(3)	2880(14)	9572(2)	30(1)
C(4)	2314(9)	4639(4)	8205(7)	25(1)
C(5)	5577(3)	2830(13)	6983(2)	26(1)
C(6)	2658(3)	2850(10)	5087(2)	24(1)
O(1)	4411(2)	2881(12)	4072(2)	30(1)
O(2)	6247(2)	2850(10)	5270(2)	31(1)
O(3)	1024(2)	2849(12)	4351(2)	36(1)
O(4)	6845(2)	2848(10)	8153(2)	40(1)

Table 3. Bond lengths [Å] and angles [°] for nct0805.

C(1)-C(5)	1.485(2)
C(1)-C(6)	1.488(2)
C(1)-C(2)	1.536(7)
C(1)-C(4)	1.594(7)
C(2)-C(3)	1.548(8)
C(3)-C(4)	1.529(8)
C(5)-O(4)	1.192(2)
C(5)-O(2)	1.388(2)
C(6)-O(3)	1.184(2)
C(6)-O(1)	1.397(2)
O(1)-O(2)	1.4763(17)
C(5)-C(1)-C(6)	104.01(13)
C(5)-C(1)-C(2)	115.5(4)
C(6)-C(1)-C(2)	118.3(4)
C(5)-C(1)-C(4)	114.6(4)
C(6)-C(1)-C(4)	117.1(4)
C(2)-C(1)-C(4)	87.44(12)
C(1)-C(2)-C(3)	90.7(4)
C(4)-C(3)-C(2)	89.33(14)
C(3)-C(4)-C(1)	89.2(4)
O(4)-C(5)-O(2)	118.12(16)
O(4)-C(5)-C(1)	131.65(16)
O(2)-C(5)-C(1)	110.22(14)
O(3)-C(6)-O(1)	118.17(14)
O(3)-C(6)-C(1)	132.34(16)
O(1)-C(6)-C(1)	109.49(14)
C(6)-O(1)-O(2)	108.31(11)
C(5)-O(2)-O(1)	107.95(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for nct0805. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	25(1)	20(1)	18(1)	-2(2)	1(1)	0(3)
C(2)	34(3)	26(3)	28(3)	-2(2)	3(2)	0(2)
C(3)	36(1)	33(1)	21(1)	-7(3)	6(1)	4(3)
C(4)	35(3)	23(3)	18(2)	-9(2)	7(2)	6(2)
C(5)	29(1)	23(1)	26(1)	3(3)	2(1)	2(3)
C(6)	30(1)	20(1)	22(1)	6(2)	3(1)	12(3)
O(1)	36(1)	35(1)	19(1)	2(2)	4(1)	-4(2)
O(2)	27(1)	37(1)	30(1)	3(2)	7(1)	0(2)
O(3)	36(1)	42(1)	29(1)	3(2)	-7(1)	13(2)
O(4)	32(1)	52(1)	37(1)	4(3)	-8(1)	-2(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for nct0805.

	x	y	z	U(eq)
H(2A)	3303	-21	8594	35
H(2B)	1053	447	7657	35
H(3A)	466	2877	9979	36
H(3B)	2902	2876	10580	36
H(4A)	3311	5762	8619	30
H(4B)	1048	5316	7690	30

Appendix 6: X-ray data for cyclopentane malonoyl peroxide 131

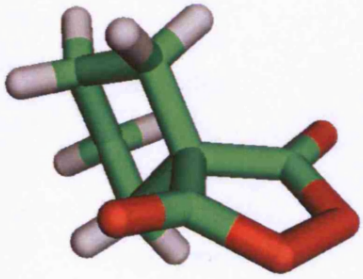


Table 1. Crystal data and structure refinement for nt0801.

Identification code	nt0801	
Empirical formula	C7 H8 O4	
Formula weight	156.13	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 9.4480(7) Å	α= 90°.
	b = 6.4650(5) Å	β= 95.283(3)°.
	c = 11.5900(11) Å	γ = 90°.
Volume	704.93(10) $Å^3$	
Z	4	
Density (calculated)	1.471 Mg/m^3	
Absorption coefficient	0.122 mm^{-1}	
F(000)	328	
Crystal size	0.30 x 0.12 x 0.10 mm^3	
Theta range for data collection	3.53 to 27.51°.	
Index ranges	-12<=h<=12, -8<=k<=7, -14<=l<=14	
Reflections collected	2657	
Independent reflections	1614 [R(int) = 0.0529]	
Completeness to theta = 27.51°	99.4 %	
Max. and min. transmission	0.9879 and 0.9642	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1614 / 0 / 100	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0602, wR2 = 0.1279	
R indices (all data)	R1 = 0.1027, wR2 = 0.1487	
Largest diff. peak and hole	0.271 and -0.343 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for nt0801. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1932(2)	617(3)	8461(2)	22(1)
C(2)	2734(2)	-1089(3)	9230(2)	27(1)
C(3)	4093(2)	-1444(3)	8634(2)	31(1)
C(4)	3534(2)	-1440(4)	7360(2)	32(1)
C(5)	2506(2)	400(3)	7253(2)	26(1)
C(6)	366(2)	396(3)	8479(2)	24(1)
C(7)	2209(2)	2674(4)	9025(2)	26(1)
O(1)	-463(1)	-856(3)	8059(1)	34(1)
O(2)	-154(1)	1923(2)	9155(1)	29(1)
O(3)	1015(2)	3363(2)	9500(1)	31(1)
O(4)	3265(2)	3690(2)	9162(2)	41(1)

Table 3. Bond lengths [Å] and angles [°] for nt0801.

C(1)-C(6)	1.488(3)
C(1)-C(7)	1.494(3)
C(1)-C(5)	1.554(3)
C(1)-C(2)	1.568(3)
C(2)-C(3)	1.531(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.522(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.533(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-O(1)	1.198(2)
C(6)-O(2)	1.379(3)
C(7)-O(4)	1.192(2)
C(7)-O(3)	1.375(3)
O(2)-O(3)	1.471(2)
C(6)-C(1)-C(7)	102.34(17)
C(6)-C(1)-C(5)	115.73(16)
C(7)-C(1)-C(5)	114.38(17)
C(6)-C(1)-C(2)	110.68(17)
C(7)-C(1)-C(2)	108.74(16)
C(5)-C(1)-C(2)	104.95(16)
C(3)-C(2)-C(1)	103.34(17)
C(3)-C(2)-H(2A)	111.1
C(1)-C(2)-H(2A)	111.1
C(3)-C(2)-H(2B)	111.1
C(1)-C(2)-H(2B)	111.1
H(2A)-C(2)-H(2B)	109.1
C(4)-C(3)-C(2)	101.93(16)

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:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for nt0801. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(1)	20(1)	25(1)	1(1)	2(1)	1(1)
C(2)	26(1)	24(1)	32(1)	4(1)	2(1)	2(1)
C(3)	24(1)	24(1)	44(1)	5(1)	2(1)	4(1)
C(4)	30(1)	31(1)	36(1)	-4(1)	12(1)	1(1)
C(5)	25(1)	30(1)	26(1)	0(1)	7(1)	-1(1)
C(6)	26(1)	24(1)	20(1)	4(1)	3(1)	-1(1)
C(7)	28(1)	24(1)	25(1)	1(1)	2(1)	1(1)
O(1)	29(1)	40(1)	34(1)	-5(1)	1(1)	-10(1)
O(2)	26(1)	32(1)	31(1)	-2(1)	7(1)	2(1)
O(3)	33(1)	28(1)	33(1)	-7(1)	5(1)	0(1)
O(4)	34(1)	31(1)	56(1)	-7(1)	2(1)	-9(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for nt0801.

	x	y	z	U(eq)
H(2A)	2956	-598	10035	33
H(2B)	2163	-2372	9239	33
H(3A)	4789	-318	8811	37
H(3B)	4540	-2785	8865	37
H(4A)	3033	-2749	7145	38
H(4B)	4318	-1249	6859	38
H(5A)	1718	135	6647	32
H(5B)	3008	1676	7051	32

Appendix 7: X-ray data for cyclohexane malonoyl peroxide 132

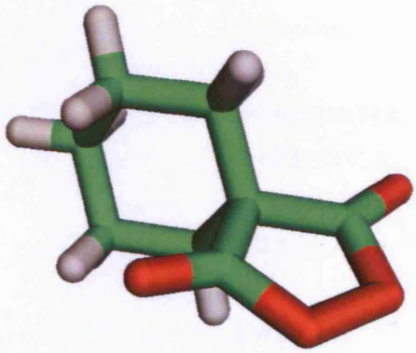


Table 1. Crystal data and structure refinement for nct0905.

Identification code	nct0905	
Empirical formula	C8 H10 O4	
Formula weight	170.16	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 10.6392(5) Å	α= 90°.
	b = 6.5793(4) Å	β= 99.977(4)°.
	c = 11.6462(9) Å	γ = 90°.
Volume	802.89(9) $Å^3$	
Z	4	
Density (calculated)	1.408 Mg/m^3	
Absorption coefficient	0.114 mm^{-1}	
F(000)	360	
Crystal size	0.40 x 0.06 x 0.06 mm^3	
Theta range for data collection	2.85 to 27.47°.	
Index ranges	-13<=h<=13, -8<=k<=8, -15<=l<=15	
Reflections collected	3422	
Independent reflections	1838 [R(int) = 0.0638]	
Completeness to theta = 27.47°	99.7 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9932 and 0.9559	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1838 / 0 / 110	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0554, wR2 = 0.1179	
R indices (all data)	R1 = 0.0998, wR2 = 0.1366	
Extinction coefficient	0.134(13)	
Largest diff. peak and hole	0.180 and -0.187 $e.Å^{-3}$	

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

	x	y	z	U(eq)
C(1)	7877(2)	2521(3)	4421(2)	25(1)
C(2)	8606(2)	1315(3)	5483(2)	29(1)
C(3)	8086(2)	1755(3)	6588(2)	36(1)
C(4)	6657(2)	1331(3)	6430(2)	41(1)
C(5)	5937(2)	2554(3)	5411(2)	37(1)
C(6)	6426(2)	2138(3)	4284(2)	30(1)
C(7)	8426(2)	1859(3)	3384(2)	35(1)
C(8)	8241(2)	4727(3)	4523(2)	33(1)
O(1)	8351(1)	291(2)	2863(1)	49(1)
O(2)	9215(1)	3350(3)	3073(1)	49(1)
O(3)	9089(1)	5156(2)	3783(1)	47(1)
O(4)	7963(2)	6064(2)	5117(1)	47(1)

Table 3. Bond lengths [Å] and angles [°] for nct0905.

C(1)-C(7)	1.494(3)
C(1)-C(8)	1.502(3)
C(1)-C(6)	1.545(2)
C(1)-C(2)	1.559(2)
C(2)-C(3)	1.515(3)
C(3)-C(4)	1.525(3)
C(4)-C(5)	1.525(3)
C(5)-C(6)	1.518(3)
C(7)-O(1)	1.192(2)
C(7)-O(2)	1.380(3)
C(8)-O(4)	1.188(2)
C(8)-O(3)	1.381(3)
O(2)-O(3)	1.467(2)
C(7)-C(1)-C(8)	102.35(16)
C(7)-C(1)-C(6)	113.14(15)
C(8)-C(1)-C(6)	113.92(14)
C(7)-C(1)-C(2)	106.38(14)
C(8)-C(1)-C(2)	110.06(15)
C(6)-C(1)-C(2)	110.48(15)
C(3)-C(2)-C(1)	111.84(14)
C(2)-C(3)-C(4)	111.42(17)
C(5)-C(4)-C(3)	110.71(17)
C(6)-C(5)-C(4)	112.07(16)
C(5)-C(6)-C(1)	111.59(15)
O(1)-C(7)-O(2)	118.13(19)
O(1)-C(7)-C(1)	131.47(19)
O(2)-C(7)-C(1)	110.23(17)
O(4)-C(8)-O(3)	117.88(18)
O(4)-C(8)-C(1)	132.46(19)
O(3)-C(8)-C(1)	109.63(18)
C(7)-O(2)-O(3)	107.99(14)
C(8)-O(3)-O(2)	108.62(14)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for nct0905. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	27(1)	28(1)	22(1)	-1(1)	5(1)	-2(1)
C(2)	32(1)	27(1)	28(1)	-1(1)	3(1)	0(1)
C(3)	47(1)	36(1)	24(1)	2(1)	5(1)	5(1)
C(4)	50(1)	47(1)	32(1)	7(1)	18(1)	5(1)
C(5)	33(1)	41(1)	39(1)	8(1)	14(1)	2(1)
C(6)	28(1)	32(1)	29(1)	4(1)	4(1)	-5(1)
C(7)	28(1)	50(1)	25(1)	1(1)	2(1)	1(1)
C(8)	31(1)	33(1)	32(1)	5(1)	1(1)	-4(1)
O(1)	55(1)	60(1)	34(1)	-15(1)	9(1)	9(1)
O(2)	38(1)	73(1)	38(1)	5(1)	17(1)	-5(1)
O(3)	44(1)	52(1)	45(1)	8(1)	10(1)	-18(1)
O(4)	60(1)	29(1)	51(1)	-3(1)	6(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for nct0905.

	x	y	z	U(eq)
H(2A)	8534	-159	5313	35
H(2B)	9522	1682	5602	35
H(3A)	8247	3197	6809	43
H(3B)	8538	901	7229	43
H(4A)	6500	-137	6283	50
H(4B)	6338	1694	7153	50
H(5A)	5018	2209	5305	44
H(5B)	6027	4021	5596	44
H(6A)	5972	3027	3661	36
H(6B)	6241	709	4047	36

References

References

[1] Dalko, P. I.; Moison, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

[2] Centi, G.; Cavani, F.; Trifiro, F. *Selective Oxidation by Heterogeneous Catalysis*; Kluwer Academic/Plenum Publishers: NewYork, 2001, Chapter 1, pp 1–6.

[3] Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8.

[4] Dalko, P. I.; Moison, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.

[5] Hodnett, B. K. *Heterogeneous Catalytic Oxidation: Fundamental and Technological Aspects of the Selective and Total Oxidation of Organic Compounds*; John Wiley and Sons: New York, 2000.

[6] Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981.

[7] Dobler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Organomet. Chem.* **2001**, *621*, 70.

[8] Ahrgren, L.; Sutin, L. *Org. Process Res. Dev.* **1997**, *1*, 425.

[9] Calo, F.; Richardson, J.; Barrett, G. M. *Org. Lett.* **2009**, *11*, 4910.

[10] Christie, S. D. R.; Warrington, A. D. *Synthesis* **2008**, *9*, 1325.

[11] Schröder, M. *Chem. Rev.* **1980**, *80*, 187.

[12] Hofmann, K. A. *Chem. Ber.* **1912**, *45*, 3329.

[13] Sharpless, K. B.; Akashi, K. J. *J. Am. Chem. Soc.* **1976**, *98*, 1986.

[14] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

[15] Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766.

[16] Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, *522*, 75.

[17] Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

[18] Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. -S.; Kwong H. -L.; Morikawa, K.; Wang, Z. -M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.

[19] Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 168.

[20] Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.

[21] Kwong, H. -L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 2999.

[22] Junttila, M. H.; Hormi, O. O. E. *J. Org. Chem.* **2009**, *74*, 3038.

[23] Caprio, V.; Williams, J. M. J. *Catalysis in Asymmetric Synthesis*; John Wiley and Sons: Chichester, 2009, Chapter 5, pp 117–121.

[24] Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, *11*, 1725.

[25] Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.

[26] Duebel, D. V.; Frenking, G. *Acc. Chem. Res.* **2003**, *36*, 645.

[27] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

[28] Fristrup, P.; Tanner, D.; Norrby, P. -O. *Chirality* **2003**, *15*, 360.

[29] Wyatt, P.; Warren, S. *Organic Synthesis: Strategy and Control*; John Wiley & Sons: Chichester, 2007, Chapter 25, pp 527–566.

[30] Nayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094.

[31] Kobayashi, S.; Suguira, M. *Adv. Synth. Catal.* **2006**, *348*, 1496.

[32] Pitts, M. R. *Platinum Met. Rev.* **2008**, *52*, 64.

[33] Jonsson, S. Y.; Farnegardh, K.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 1365.

[34] Li, Y.; Song, D.; Dong Vy. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962.

[35] Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846.

[36] Wang, W.; Wang, F.; Shi, M. *Organometallics* **2010**, *29*, 928.

[37] Armstrong, A.; Knight, J. D. *Ann. Rep. Prog. Chem., Sect. B.* **2004**, *100*, 51.

[38] Shing, T. K. M.; Tai, V. W. -F.; Tam, E. K. W. *Angew. Chem. Int. Ed.* **1994**, *33*, 2312.

[39] Shing, T. K. M.; Tam, E. K. W.; Tai, V. W. F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J.* **1996**, *2*, 50.

[40] Couturier, M.; Andreson, B. M.; Jørgensen, J. B.; Tucker, J. L.; Busch, F. R.; Brenek, S. J.; Dubé, P.; Negri, J. T. *Org. Process. Res. Dev.* **2002**, *6*, 42.

[41] Plietker, B.; Niggemann, A.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116.

[42] Plietker, B.; Niggemann, A. *J. Org. Chem.* **2005**, *70*, 2402.

[43] Plietker, B.; Neisius, N. M. *J. Org. Chem.* **2008**, *73*, 3218.

[44] Chen, K.; Costas, M.; Kim, J.; Tipton, A. K.; Que Jr, L. *J. Am. Chem. Soc.* **2002**, *124*, 3026.

[45] Oldenburg, P. D.; Que Jr, L. *Catal. Today* **2006**, *117*, 15.

[46] Suzuki, K.; Oldenburg, P. D.; Que Jr, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1887.

[47] Boer, J. W.; Brinksma, J.; Browne, W. R.; Meetsma, A.; Alsters, P. L.; Hage, R.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 7990.

[48] Boer, J. W.; Brinksma, J.; Browne, W. R.; Harutyunyan, S. R.; Bini, L.; Tiemersma-Weyman, T. D.; Alsters, P. L.; Hage, R.; Feringa, B. L. Chem. Commun. **2008**, 3747.

[49] Emmanuvel, L.; Shaikh, T. M. A.; Sudalai, A. *Org. Lett.* **2005**, *7*, 5071.

[50] Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656.

[51] Çelik, M.; Alp, C.; Coşkun, B.; Gültekin, M. S.; Balci, M. *Tetrahedron Lett.* **2006**, *47*, 3659.

[52] Santoro, S.; Santi, C.; Sabantini, M.; Testaferri, L.; Tieco, M. *Adv. Synth. Catal.* **2008**, *350*, 2881.

[53] Usui, Y.; Sato, K.; Tanaka, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5623.

[54] Greene, F. D. *J. Am. Chem. Soc.* **1955**, *78*, 2246.

[55] Perret, A.; Perrot, R. *Helv. Chim. Acta* **1945**, *28*, 558.

[56] Greene, F. D. *J. Am. Chem. Soc.* **1955**, *78*, 2250.

[57] Greene, F. D. *J. Am. Chem. Soc.* **1959**, *81*, 1503.

[58] Greene, F. D.; Rees, W. W. *J. Am. Chem. Soc.* **1957**, *80*, 3432.

[59] Greene, F. D.; Adam, W. *J. Org. Chem.* **1964**, *29*, 136.

[60] Vaughn, H. L.; Robbins, M. D. *J. Org. Chem.* **1975**, *40*, 1187.

[61] Russell, K. E. *J. Am. Chem. Soc.* **1955**, *77*, 4814.

[62] Kim, N. J.; Kim, H. R.; Ryu, E. K. *Synth. Commun.* **1992**, *22*, 2521.

[63] Kim, H. R.; Kim, N. J.; Park, H. J.; Ryu, E. K. *Bull. Kor. Chem. Soc.* **1997**, *18*, 110.

[64] Adam, W.; Rucktäschel, R. *J. Am. Chem. Soc.* **1971**, *93*, 557.

[65] Darmon, M. J.; Schuster, G. B. *J. Org. Chem.* **1982**, *47*, 4658.

[66] Porter, J. E.; Schuster, G. B. *J. Org. Chem.* **1985**, *50*, 4068.

[67] Alberts, A. H.; Wynberg, H.; Strating, J. *Synth. Commun.* **1973**, *3*, 297.

[68] Domin, D.; Benito-Garagorri, D.; Mereiter, K.; Fröchlich, J.; Kirchner, K. *Organometallics* **2005**, *24*, 3957.

[69] Dmowski, W.; Wolniewicz, A. *J. Fluor. Chem.* **2000**, *102*, 141.

[70] Adam, W.; Rucktäschel, R. *J. Org. Chem.* **1972**, *37*, 4128.

[71] Cottineau, B.; Kessler, A.; O'Shea, D. F.; Gupta, A.; Miller, M. J. *Org. Synth.* **2006**, 45.

[72] Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; John Wiley & Sons: New York, 2001, 5th Edition, Chapter 14, pp 894–897.

[73] Eames, J.; Mitchell, H. J.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095.

[74] Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; John Wiley & Sons: New York, 2001, 5th Edition, Chapter 19, pp 1541–1542.

[75] Malkoch, M.; Thibault, R. J.; Drockenmuller, E.; Messerschmidt, M.; Voit, B.; Russell, T. P.; Hawker, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 14949.

[76] Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C. -P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem. Int. Ed.* **1995**, *34*, 1844.

[77] Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *Angew. Chem. Int. Ed.* **1995**, *34*, 1848.

[78] Silbert, L. S. In *Organic Peroxides*; Swern, D. Ed; John Wiley & Sons: New York, 1971, Chapter 7, pp 648–654.

[79] Reichardt, C.; Schroeder, J.; Voehringer, P.; Schwarzer, D. *Phys. Chem. Chem. Phys.* **2008**, *10*, 1662.

[80] Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299.

[81] Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

[82] Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

[83] Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030.

[84] Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, *23*, 4647.

[85] Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. In *Purification of Laboratory Chemicals*, 2nd Edition; Pergamon Press; Oxford. **1980**.

[86] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[87] Podder, R. K.; Sarkar, R. K.; Ray, S. *Indian J. Chem., Sect B* **1988**, *27B*, 530.

[88] Overberger, C. G.; Biletch, H.; Huang, P. -T.; Blatter, H. M. *J. Org. Chem.* **1955**, *20*, 1717.

[89] Price, C. C.; Eleil, E. L.; Convery, R. J. *J. Org. Chem.* **1957**, *22*, 347.

[90] Dixon, D. W.; Weiss, R. H. *J. Org. Chem.* **1984**, *49*, 4487.

[91] Russel, G. A.; Mikol, G. J. *J. Am. Chem. Soc.* **1966**, *88*, 5498.

[92] Kadyrov, R. *Angew. Chem. Int. Ed.* **2009**, *48*, 7556.

[93] Nicolaou, K. C. *Chem. Eur. J.* **2004**, *10*, 5581.

[94] Tellitu, I. *Tetrahedron* **2008**, *64*, 2465.

[95] Ohkuma, T. *Org. Lett.* **2007**, *9*, 2565.

[96] James, D. R.; Shoppee, C. W. *J. Chem. Soc.* **1956**, 1059.

[97] Holshouser, M. H.; Kolb, M. *J. Pharm. Sci.* **1986**, *75*, 619.

[98] Nicolaou, K. C.; Snyder, S. A.; Longbottom, D. A.; Nalbandian, A. Z.; Huang, X. *Chem. Eur. J.* **2004**, *10*, 5581.

[99] Buisson, D.; El-Baba, S.; Azerad, R. *Tetrahedron Lett.* **1986**, *27*, 4453.

[100] Pohoryles, L. A.; Sarel, S.; Ben-Shoshan, R. *J. Org. Chem.* **1959**, *24*, 1878.

[101] Anju, K. S.; Ramakrishnan, S.; Thomas, A. P.; Suresh, E.; Srinivasan, A. *Org. Lett.* **2008**, *10*, 5545.

[102] Wren, H. *J. Chem. Sec.* **1914**, *103*, 1770.

[103] Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198.

[104] Medlik-Balan, A. *Tetrahedron* **1980**, *36*, 299.

[105] Jiao, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 3333.

[106] Olah, G. A.; Fung, A. P.; Meidar, D. *Synthesis* **1981**, *4*, 280.

[107] Lyle, R. E.; Lyle, G. G. *J. Org. Chem.* **1953**, *18*, 1058.

[108] Kraus, G. A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 2579.

[109] Fuganti, C. *Chem. Ind.* (*London*) **1977**, *24*, 983.

[110] Edin, M. *Tetrahedron: Asymmetry* **2006**, *17*, 708.

[111] Wang, Z. *J. Org. Chem.* **2008**, *73*, 2270.

[112] Mo, J.; Xu, L.; Ruan, J.; Liu, S.; Xiao, J. *Chem. Commun.* **2006**, *34*, 3591.

[113] Ashyby, E. C.; Willard, F. G. *J. Org. Chem.* **1978**, *43*, 4750.

[114] Chai, Z. *Tetrahedron: Asymmetry* **2007**, *18*, 724.

[115] Favorskaya, T. A.; Shcherbinskaya, N. V.; Chernobel'skaya, S. E. *Zh. Obshch. Khim.* **1950**, *20*, 855.

[116] Kresze, G.; Trede, A. *Tetrahedron* **1963**, *19*, 133.

[117] Hennion, G. F. *J. Org. Chem.* **1958**, *23*, 656.

[118] Venus-Danilova, E. D. *Zh. Obshch. Khim.* **1936**, *6*, 1784.

[119] Suzuki, H.; Fuchita, T.; Iwasa, A.; Mishina, T. *Synthesis* **1978**, *12*, 905.

[120] Choi, M. K. W.; Toy, P. H. *Tetrahedron* **2004**, *60*, 2875.

[121] Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694.

[122] Al-Masum, M. *Tetrahedron Lett.* **2009**, *50*, 5201.

[123] Batsomboon, P.; Phakhodee, W.; Ruchirat, S.; Ploypradith, P. *J. Org. Chem.* **2009**, *74*, 4009.

[124] Zuo, G.; Louie, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 1433.

[125] Lebel, H.; Ladjel, C.; Brethous, L. *J. Am. Chem. Soc.* **2007**, *129*, 13321.

[126] Buquet, A. *J. Org. Chem.* **1979**, *44*, 2300.

[127] Khurana, J. M.; Maika, G. C.; Mehta, S. *Synthesis* **1990**, *8*, 731.

[128] Gligorich, K. M.; Cummings, S. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 14193.