Metal-Free *Syn*-Dihydroxylation of Alkenes using Malonoyl Peroxides

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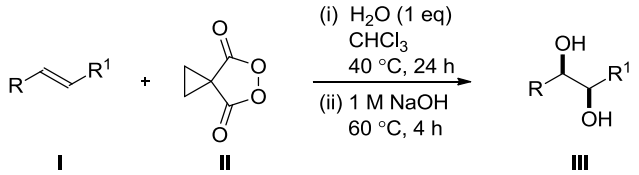
Declaration

This thesis is the result of the author's original research. It has been composed by the author and has not previously been submitted for examination which has led to the award of a degree.

Signed: Date

Abstract

This thesis describes the successful application of cyclopropyl malonoyl peroxide **II** in the metal-free *syn*-dihydroxylation of alkenes **I**.



I II III

Chapter 1 outlines the available metal-free methods for achieving *syn*-1,2-dioxygenation of alkenes. The use of hypervalent iodine, selenium, sulfur and peroxide reagents are discussed in terms of the advantages and limitations of each method.

Chapter 2 details a mechanistic investigation into the dihydroxylation reaction using cyclopropyl malonoyl peroxide **II**. Through kinetic studies, Hammett analysis, multiple isotopic labelling experiments, NMR investigations and trapping experiments an ionic, stepwise mechanism has been proposed. Minor competing reaction pathways have also been identified in addition to an alternative reaction mechanism in the absence of water.

Chapter 3 describes the current scope of the cyclopropyl malonoyl peroxide **II** mediated dihydroxylation reaction by alkene class. An application of the dihydroxylation protocol is presented in the stereoselective synthesis of a 5-deoxy-L-arabinose derivative. Interaction of cyclopropyl malonoyl peroxide **II** with non-alkene nucleophiles is also discussed, and a novel allylic oxidation protocol using peroxide **II** is introduced.

Chapter 4 discusses catalysis of the dihydroxylation reaction. Alcoholic hydrogen-bond donors with a pKa of 5–8 were found to be the most effective catalysts, achieving up to 4-fold rate acceleration. Chiral hydrogen-bond catalysts are also investigated.

Chapter 5 outlines the design, synthesis and reaction of chiral C_2-symmetric malonoyl peroxides. The first enantioselective metal-free *syn*-dihydroxylation of alkenes using a peroxide reagent is reported.

Chapter 6 presents preliminary investigations into a complementary *anti*-dihydroxylation protocol using cyclopropyl malonoyl peroxide **II** in anhydrous acetic acid.

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Abbreviations

Several abbreviations have been used throughout this thesis. These abbreviations are listed below:

Å	Ångström
AD	Asymmetric Dihydroxylation
APCI	Atmospheric Pressure Chemical Ionisation
app.	Apparent
aq.	Aqueous
Ar	Aryl
ASAP	Atmospheric Solids Analysis Probe
atm	Atmosphere(s)
ATR	Attenuated Total Reflectance
BINOL	1,1'-Bi-2-naphthol
Boc	*tert*-Butoxycarbonyl
b.p.	Boiling point
bs	Broadened singlet
Bu	Butyl
C	Celsius
cal	Calories
cat.	Catalytic
CBS	Corey-Bakshi-Shibata
CI	Chemical Ionisation
cm	Centimetre(s)
d	Doublet
DCE	Dichloroethane
dd	Doublet of doublets
Decomp.	Decomposition
DEPT-Q	Distortionless Enhancement by Polarisation Transfer with retention of Quaternaries
DFT	Density Functional Theory
dm	Decimetre

DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
DSC	Differential Scanning Calorimetry
EC	European Commission
ee	Enantiomeric excess
EI	Electron impact
EPSRC	Engineering and Physical Sciences Research Council
eq	Equivalent(s)
ESI	Electrospray Ionisation
Et	Ethyl
g	Gram(s)
GC	Gas Chromatography
HFIP	Hexafluoroisopropanol
HMBC	Heteronuclear Multiple-Bond Correlation
HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
h	Hour(s)
Hz	Hertz
^{i}Pr	Isopropyl
IR	Infra-red
J	Coupling constant
J	Joules
kg	Kilogram
kJ	Kilojoules
lit.	Literature
LRMS	Low-Resolution Mass Spectrometry
LUMO	Lowest Unoccupied Molecular Orbital
m	*meta*
m	Multiplet

M	Molar
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligrams
MHz	Megahertz
mins	Minute(s)
mL	Millilitre
µL	Microlitre(s)
mm	Millimetre
mmol	Millimole(s)
mol	Mole
m.p.	Melting point
MS	Mass Spectrometry
nm	Nanometre(s)
NMR	Nuclear Magnetic Resonance
NSI	Nanospray Ionisation
Nu	Nucleophile
o	*ortho*
OAc	Acetate
p	*para*
p	Pentet
PCM	Polarisable Continuum Model
PFB	Perfluoro-*tert*-butanol
Ph	Phenyl
ppb	Parts per billion
ppm	Parts per million
Py	Pyridine
q	Quartet
quant.	Quantitative
rel	Relative
r.t.	Room temperature
s	Singlet

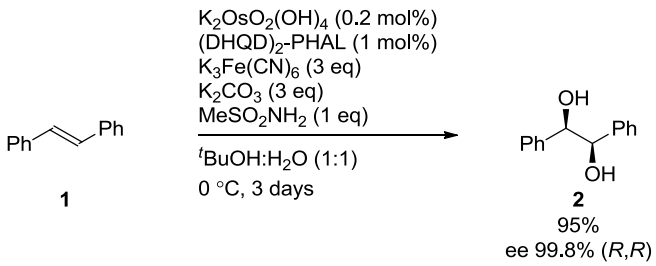
SET	Single Electron Transfer
SM	Starting material
t	Triplet
TADDOL	Tetraaryl-1,3-dioxolane-4,5-dimethanol
tert	Tertiary
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
UN	United Nations
UV	Ultraviolet
vs	Versus
wt.	Weight
Z	Charge
2D	Two-dimensional
3D	Three-dimensional

Chapter 1: Introduction

1 Introduction

Alkene dihydroxylation is of fundamental importance to organic chemistry and represents a valued transformation for introducing functionality into organic molecules. The 1,2-diol moiety is prevalent in numerous natural products and pharmaceutical compounds, but its importance mainly arises from its use as a versatile synthetic intermediate.[1] Unsurprisingly, due to its significance alkene dihydroxylation has received much attention from the chemical community, and has been a staple weapon in the synthetic organic chemists' arsenal for around 80 years.[2,3]

The osmium tetroxide catalysed asymmetric dihydroxylation (AD) reaction developed by Sharpless and co-workers represents the gold-standard in alkene dihydroxylation (Scheme 1.1).[4] The procedure is built upon the racemic Upjohn dihydroxylation reaction[5] and employs catalytic potassium osmate as the source of volatile osmium tetroxide, with potassium ferricyanide as the stoichiometric oxidant.[6] The key discovery by Sharpless and co-workers was that addition of phthalazine cinchona ligands, such as $(DHQD)_2$-PHAL, provided very high levels of asymmetric induction in addition to accelerating the reaction.[7]



Scheme 1.1 Sharpless asymmetric dihydroxylation reaction.

The broad substrate scope, high yields, exceptional levels of predictable asymmetric induction, and convenient reaction conditions make the Sharpless AD reaction one of the most inspiring and influential synthetic methods developed to date. However, osmium is the least abundant stable element in the Earth's crust[8] and osmium tetroxide is highly toxic.[9] It is for these reasons, in addition to the ever-increasing restrictions and regulations placed on the modern chemical industry and the large amounts of inorganic

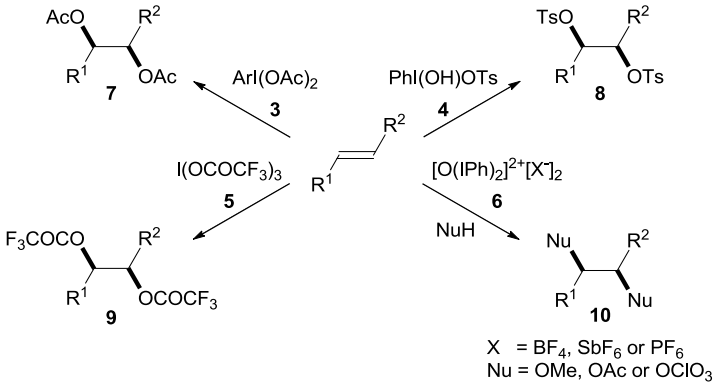
waste produced, that the Sharpless AD reaction is becoming increasingly disfavoured. The chemical community has realised the requirement for alternative procedures and has delivered a number of transition-metal catalysed processes, but none has yet reached the standard required.[10]

It is preferential to eliminate the use of a metal altogether, with the benefits of organocatalysis and metal-free procedures being well documented.[11] Many reactions traditionally executed using metal-catalysts have now been achieved under metal-free conditions, with alkene dihydroxylation being no exception. However, a general metal-free catalytic asymmetric alkene *syn*-dihydroxylation remains an elusive and attractive target.[12] In recent years, significant progress has been made using hypervalent iodine reagents and organic peroxides, and to a lesser extent with selenium and sulfur reagents.[13]

1.1 Hypervalent Iodine

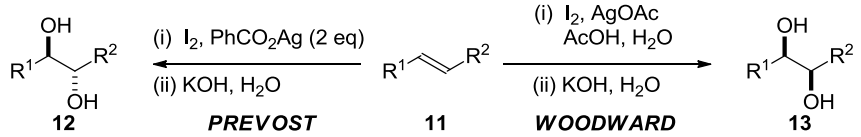
1.1.1 Achiral Hypervalent Iodine Reagents

Iodine reagents are attractive because of their low toxicity, ready availability and ease of handling.[14] The first reported use of hypervalent iodine in the dioxygenation of alkenes was in 1939 when Criegee and Beucker employed (diacetoxyiodo)arenes, $ArI(OAc)_2$ **3**, in the *syn*-diacetoxylation of *trans*-anethole and cyclopentadiene.[15] In the following 50 years, analogous *syn*-ditosyloxylation,[16] *syn*-trifluoroacetoxylation[17] and *syn*-methoxylation/perchlorination[18] reactions were developed using various hypervalent iodine reagents **4**–**6** (Scheme 1.2), but none of these methods has been widely adopted.



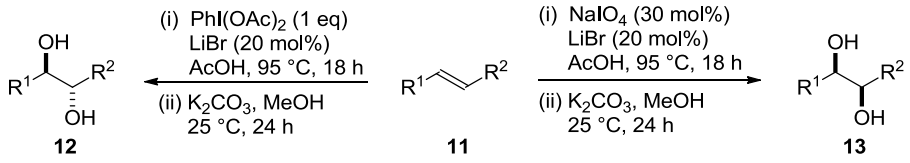
Scheme 1.2 Early examples of hypervalent iodine reagents for the dioxygenation of alkenes.

The Prévost[2] and Woodward[19] reactions represent established and effective methods for the *anti*- and *syn*-dihydroxylation of alkenes respectively (Scheme 1.3). Treatment of alkene **11** with iodine and silver benzoate under anhydrous conditions results in *anti*-diol **12** after basic hydrolysis (Prévost reaction). Conversely, treatment of alkene **11** with iodine and silver acetate in wet acetic acid provides *syn*-diol **13** after hydrolysis (Woodward reaction).



Scheme 1.3 Prévost-Woodward dihydroxylation.

A major drawback of these transformations is the requirement for a stoichiometric amount of silver salts. A simple and attractive variant of the Prévost-Woodward dihydroxylation that eliminated the use of silver salts was reported by Sudalai and co-workers in 2005 (Scheme 1.4).[20] Reaction of an alkene **11** with catalytic amounts of lithium bromide using sodium periodate or (diacetoxyiodo)benzene as the oxidant in wet acetic acid gave the *syn*-diol **13** in high yield following basic hydrolysis. Alternatively, under anhydrous conditions *anti*-diol **12** was accessed.



Scheme 1.4 Catalytic Prévost-Woodward dihydroxylation.

Mechanistically it was proposed that oxidation of lithium bromide generates Br_2, which reacts with an alkene to give bromonium ion **14**. Nucleophilic attack by a molecule of acetic acid gives the *trans*-1,2-bromoacetate derivative **15**, which undergoes intramolecular cyclisation to give dioxonium ion **16**. Dioxonium **16** is either hydrolysed by a molecule of water to give *syn*-hydroxy acetate **17**, or attacked by a second molecule of acetic acid to give *trans*-diacetate **18** (Figure 1.1). Basic hydrolysis of the resulting esters affords the *syn*- and *anti*-diols respectively.

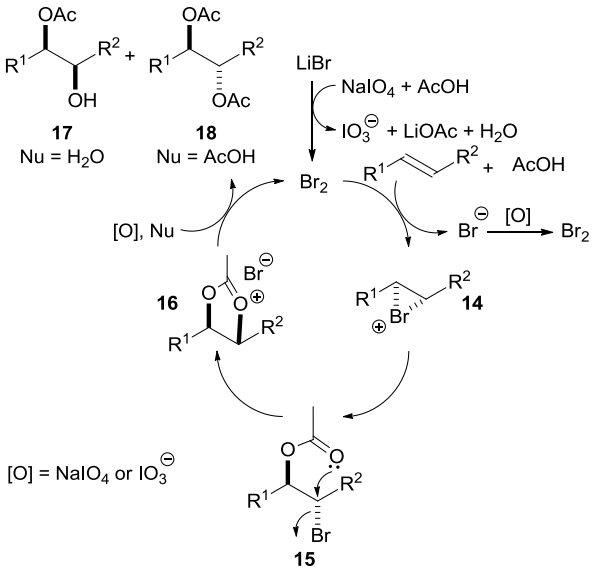
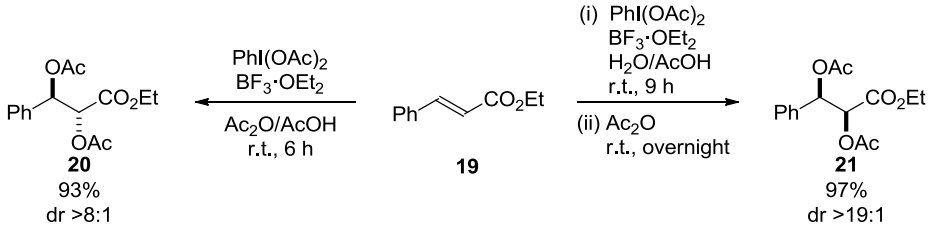


Figure 1.1 Proposed catalytic cycle for the modified Woodward-Prévost dihydroxylation.

The protocol converts electron-rich and electron-deficient alkenes to the corresponding *syn*-diols in excellent yield and good diastereoselectivity. The reaction is simple to perform and all reagents are commercially available, however the requirement for relatively harsh conditions (95 ^{o}C in acetic acid) renders the process unsuitable for more sensitive substrates.

Li and co-workers eliminated the need for high temperature by employing $PhI(OAc)_2$ in the presence of $BF_3{\cdot}OEt_2$, resulting in a scalable, convenient and practical procedure for the diastereoselective *syn*-diacetoxylation of alkenes (Scheme 1.5).[21]

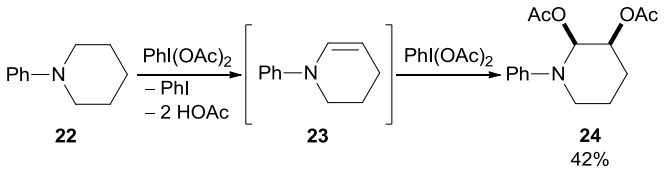


Scheme 1.5 $BF_3{\cdot}OEt_2$ catalysed diacetoxylation of alkenes with $PhI(OAc)_2$.

The reaction proved general for a range of alkenes, producing the corresponding *syn*-diacetates in good to excellent yield and diastereoselectivity. The authors proposed that

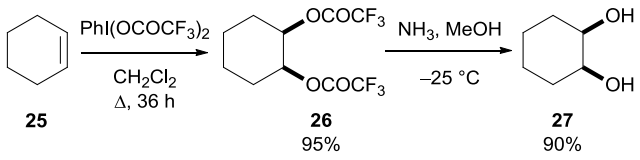
$BF_3{\cdot}OEt_2$ activated $PhI(OAc)_2$ through a Lewis acid coordination pathway, however it is also possible that a strong Brønsted acid produced by $BF_3{\cdot}OEt_2$/AcOH could be responsible for catalysis.[22] Anhydrous conditions, achieved by replacing the water with acetic anhydride, allowed *anti*-diol to be produced after hydrolysis, further enhancing the appeal of this procedure (Scheme 1.5).

An interesting extension to the use of (diacetoxyiodo)benzene in the *syn*-dioxygenation of alkenes comes from the reaction of amines. For example, treating *N*-phenylpiperidine **22** with $PhI(OAc)_2$ gave the corresponding enamine **23**, which was dioxygenated *in situ* by a second equivalent of $PhI(OAc)_2$ to give *syn*-diacetate **24** in 42% yield (Scheme 1.6).[23]



Scheme 1.6 Selective functionalisation of amines with $PhI(OAc)_2$.

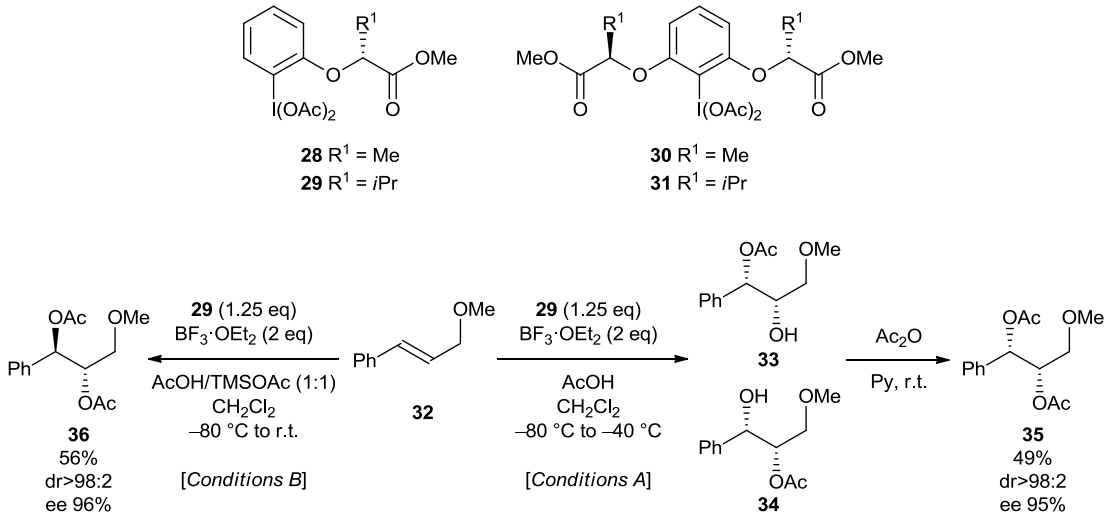
Çelik reported that alkene *syn*-dioxygenation can be achieved under mild conditions using the more reactive phenyliodine(III) bis(trifluoroacetate) without the requirement for an additive or catalyst (Scheme 1.7).[24] Functional group tolerance was not explored and only limited examples were reported. However, the simplicity and effectiveness of the overall transformation makes this an attractive protocol, particularly for substrates not tolerant of the acidic Woodward-Prévost conditions described in Scheme 1.5.



Scheme 1.7 Alkene dihydroxylation using $PhI(OCOCF_3)_2$.

1.1.2 Chiral Hypervalent Iodine Reagents

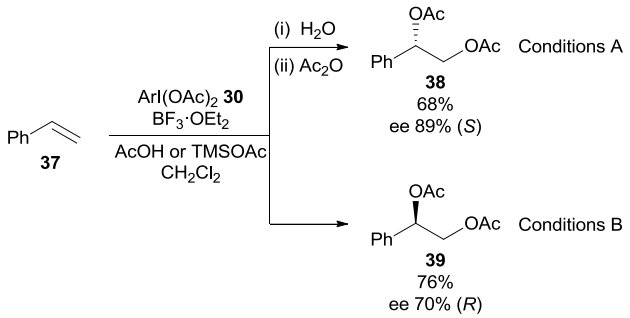
There is significant precedent for the use of chiral hypervalent iodine reagents in organic synthesis,[25] but it is only recently that application of this knowledge to alkene dihydroxylation has been described. An asymmetric variant of the Woodward-Prévost reaction using optically active hypervalent iodine reagents **28**–**31** was reported by Fujita (Scheme 1.8).[26]



Scheme 1.8 Enantioselective alkene dioxygenation using chiral iodine reagents.

Reaction of alkene **32** with stoichiometric hypervalent iodine reagent **29** and acetic acid in dichloromethane at –80 °C, then quenching with water at –40 °C (Conditions A, Scheme 1.8), gave a regioisomeric mixture of monoacetoxy products **33** and **34**. Acetylation of the regioisomeric mixture using acetic anhydride provided *syn*-acetate **35** (dr >98:2) in mediocre yield and high ee (49% yield, 95% ee). Significantly, the diastereoselectivity was switched in favour of *anti*-acetate **36** by performing the reaction at –80 °C in the presence of TMSOAc, and allowing the reaction mixture to warm to room temperature (Conditions B, Scheme 1.8).

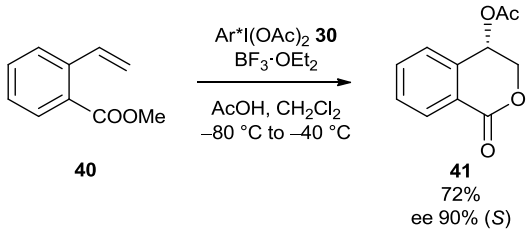
Interestingly, in the reaction of chiral hypervalent iodine compound **30** with monosubstituted styrene derivatives it was observed that quenching of the reaction at low temperature (Conditions A) gave the *S* product, whereas allowing the reaction mixture to warm to room temperature (Conditions B) resulted in the *R* product (Scheme 1.9).



Scheme 1.9 Switchable enantioselectivity in the dihydroxylation of styrene **37**.

The trend in reaction conditions and absolute stereochemistry was maintained across five 1-styrene substrates using hypervalent iodine reagents **28**–**30**, providing a general and predictable metal-free asymmetric dihydroxylation reaction for this class of substrate.

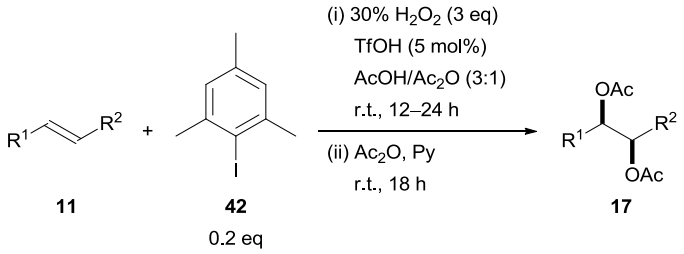
Fujita has also shown that chiral hypervalent iodine reagent **30** is effective in the analogous enantioselective oxylactonisation of methyl *ortho*-alk-1-enylbenzoate **40**, resulting in cyclic dioxygenation product **41** in 90% ee (Scheme 1.10).[27]



Scheme 1.10 Enantioselective acetoxylactonisation.

1.1.3 Catalytic Hypervalent Iodine Reagents

Li and co-workers recently reported a simple and effective alkene *syn*-dioxygenation protocol employing only catalytic quantities of an iodine reagent.[28] Treatment of an alkene **11** with 0.2 equivalents of iodomesitylene **42** and 3 equivalents of hydrogen peroxide in a 3:1 acetic acid/acetic anhydride mixture containing triflic acid additive (5 mol%) gave the corresponding *syn*-diacetate **17**, after acetylation with acetic anhydride (Scheme 1.11).



Scheme 1.11 Organocatalytic diacetoxylation of alkenes.

25 examples of alkyl- and aryl-substituted alkenes successfully underwent diacetoxylation in generally high yield (up to 99%) and good *syn*-selectivity (4.3:1 to >19:1 *syn*:*anti*), although functional group tolerance was not widely explored within this work.

It was proposed that *in situ* peroxide-mediated oxidation of aryl iodide **42** to hypervalent iodine(III) species **43**, followed by triflic acid catalysed electrophilic addition to alkene **11**, formed iodonium **44**. S_N2 attack on **44** by a molecule of acetic acid followed by intramolecular cyclisation of **45** to dioxonium **46** released aryl iodide **42** back into the catalytic cycle. Attack of water on dioxonium **46** followed by acetylation gives *syn*-diacetate **17** (Figure 1.2).

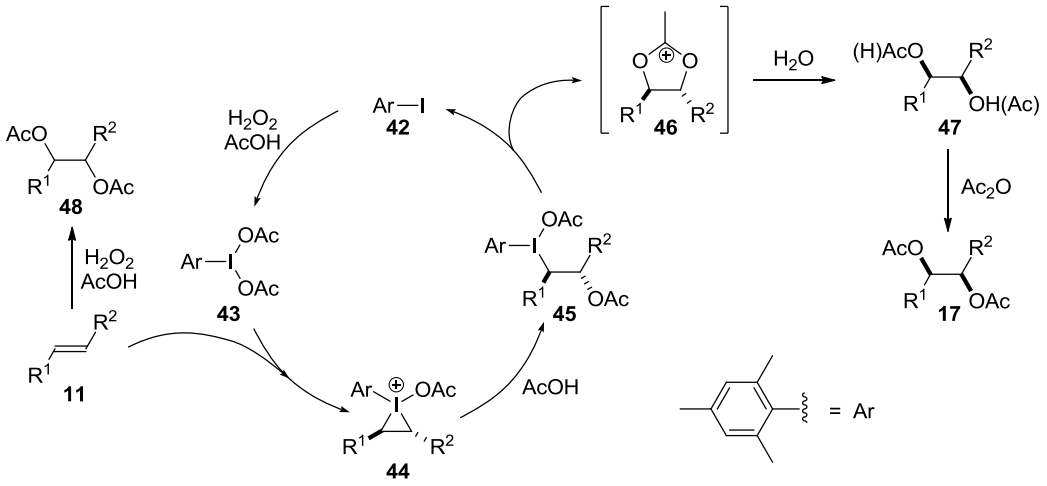


Figure 1.2 Proposed mechanism for aryl iodide **42** catalysed alkene *syn*-dioxygenation.

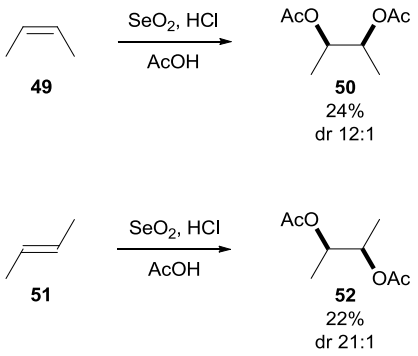
Interestingly, it was determined that a competitive acid-catalysed peroxide-mediated epoxidation/ring-opening pathway operated with electron-rich alkenes, resulting in poor diastereoselectivity in diacetate product **48**. To overcome this, slow addition of substrate **11** using a syringe pump (12–24 h) was required, which severely limits the practicality and scalability of the dioxygenation protocol. However, the procedure was highly effective with electron-deficient alkenes (α,β-unsaturated esters), producing the corresponding *syn*-diacetates in excellent yield and selectivity (5 examples, 95–99% yield, >19:1 *syn*:*anti*).

The use of catalytic quantities of iodine reagents represents an important and exciting advance in the area of metal-free dihydroxylation. In conjunction with the ability to achieve asymmetric *syn*-dioxygenation using chiral hypervalent iodine reagents (Chapter 1.1.2) it is not unreasonable to envisage a catalytic asymmetric hypervalent-iodine mediated dihydroxylation reaction being reported in the near future.

1.2 Selenium

1.2.1 Selenium Dioxide

The use of selenium in the *syn*-dioxygenation of alkenes was first reported by Tsutsumi and co-workers whilst investigating the acid-catalysed oxidation of alkenes.[29] They described the stereoselective selenium dioxide-mediated oxidation of *cis*-but-2-ene **49** and *trans*-but-2-ene **51** to give diacetates **50** and **52** respectively, along with small amounts of the corresponding *syn*-monoacetates (<5%, Scheme 1.12). The yields of the products were low and the reaction was not developed any further, but the mild conditions and high stereoselectivity provide an excellent starting point for future development.

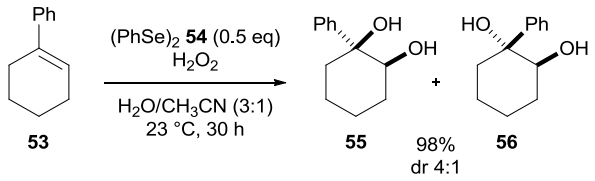


Scheme 1.12 Selenium dioxide mediated *syn*-diacetoxylation.

A recent report by Nguyen and Lee examined selenium dioxide in the dioxygenation of diene substrates to prepare both 1,2- and 1,4-diols.[30] Once again this methodology has not been significantly developed suggesting that oxidation reactions with selenium dioxide may suffer from high substrate dependence and lack of generality.

1.2.2 Diaryl Diselenide

A more general selenium-mediated dihydroxylation method was published by Tiecco and co-workers in 2008.[31] They detailed the first example of a diphenyl diselenide **54** catalysed dihydroxylation of alkenes using Oxone or H_2O_2 as the stoichiometric oxidant in a 3:1 water/acetonitrile mixture at ambient temperature (Scheme 1.13).



Scheme 1.13 Diphenyl diselenide **54** catalysed dihydroxylation.

The proposed mechanistic pathway involved oxidation of diphenyl diselenide **54** to perseleninic acid **58**, which subsequently epoxidised the alkene substrate, giving **59**. S_N2 ring-opening of **59** by a molecule of water leads to the *anti*-diol **60** (Path B). S_N1 ring-opening of **59** (Path A) provided both the *syn*-(**62**) and *anti*-(**60**) diols. It was suggested that hydrogen bonding between the water molecule and the hydroxyl group of intermediate **61** was responsible for the preferential *syn*-addition of the water molecule with selected substrates (Figure 1.3).

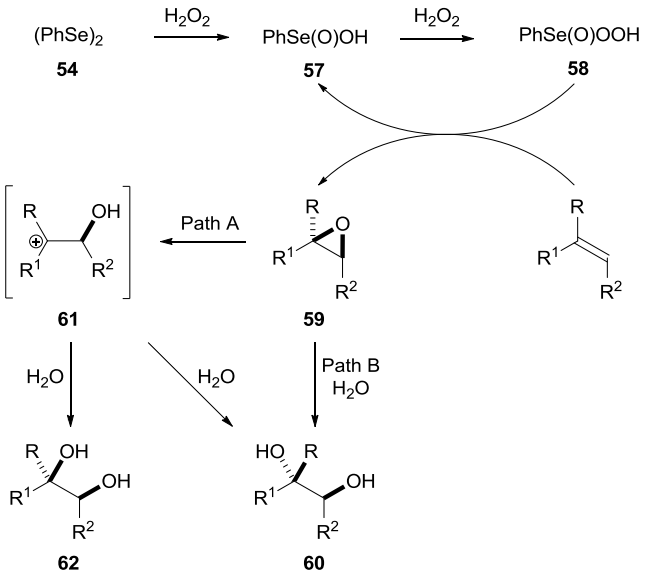
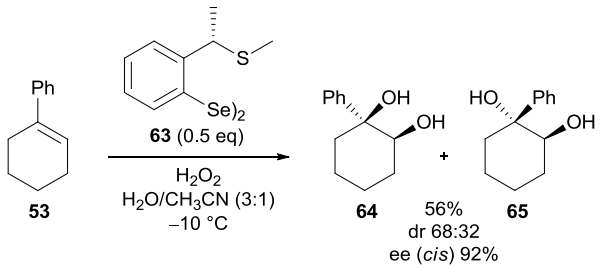


Figure 1.3 Proposed mechanism for the diphenyl diselenide **54** catalysed dihydroxylation.

Despite the direct formation of diol products in good to excellent yield (50–99%), none of the substrates reported (8 examples) contained any functionality suggesting the reaction may have limited scope. Further drawbacks of this method include long reaction times (up to 12 days) and poor stereoselectivity, with the relative stereochemistry of the major diol product **60** or **62** dependent on the steric and electronic properties of the substrate. Nevertheless, this method represents a novel catalytic process for the metal-free *syn*-dihydroxylation of alkenes.

1.2.3 Chiral Diaryl Diselenide

Significantly, Tiecco determined that an asymmetric variant of the reaction was possible using chiral diselenide **63** in the reaction with 1-phenyl cyclohexene **53**, producing the *cis*-diol **64** in an excellent 92% ee under simple and mild reaction conditions (Scheme 1.14).[31b]

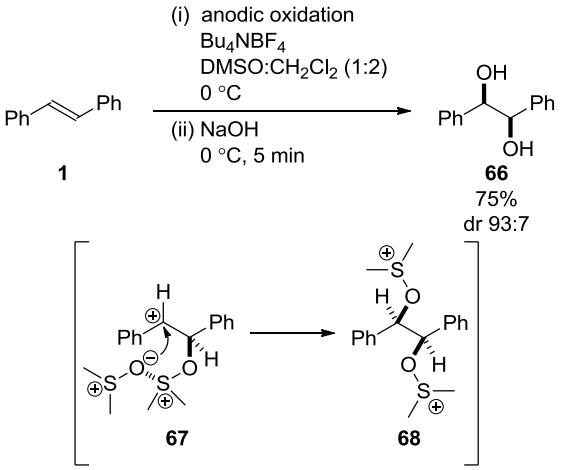


Scheme 1.14 Catalytic asymmetric dihydroxylation using chiral diselenide **63**.

Organoselenium compounds clearly have potential as convenient direct *syn*-dihydroxylation reagents, but the poor diastereoselectivity achieved is a major drawback, and prevents this reaction from being synthetically useful. However, the use of organoselenium reagents in the dihydroxylation of alkenes is extremely underexplored and requires further investigation and understanding.

1.3 Sulfur

The use of sulfur in alkene *syn*-dihydroxylation is rare, but an exciting report by Yoshida suggests that this area has potential for development.[32] The method involves an oxidative *syn*-dihydroxylation mediated by electrochemically generated alkoxysulfonium ions (Scheme 1.15). Five stabilised alkenes were oxidised in the presence of DMSO to give bisalkoxysulfonium ions **68** which underwent rapid hydrolysis with aqueous sodium hydroxide to afford the corresponding diols in good yield (52–86%). It was proposed that sulfonium ion directed attack of the second molecule of DMSO on **67**, resulting in **68**, accounted for the observed *syn*-selectivity. Although electrochemical dioxygenation of alkenes has been known for some time,[33] this represents the first example of a direct electrochemical dihydroxylation of alkenes.



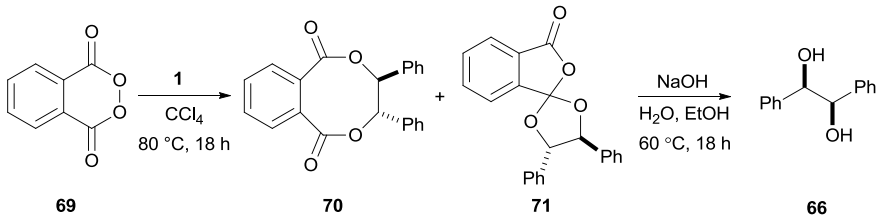
Scheme 1.15 Electrochemical *syn*-dihydroxylation.

1.4 Organic Peroxides

1.4.1 Phthaloyl Peroxides

The inherent high reactivity of peroxides, together with their low cost and often non-toxic nature, makes organic peroxides attractive reagents in organic synthesis.

Around 50 years ago Greene released a series of reports[34] describing reaction of phthaloyl peroxide **69** and *trans*-stilbene **1** in a refluxing solution of carbon tetrachloride, leading to two dioxygenated products **70** and **71** in a 1:3 ratio (Scheme 1.16).[34b] Alkaline hydrolysis of a mixture containing both **70** and **71** provided diol **66**.



Scheme 1.16 Phthaloyl peroxide **69** dioxygenation of *trans*-stilbene **1**.

Significantly, this *syn*-dihydroxylation was reported to be stereospecific for the reaction of both *cis*- and *trans*-stilbene, providing a powerful piece of methodology which until recently was largely ignored. It should be noted that the relative stereochemistry of the products was assigned by comparison of melting point data and infrared absorption

spectra to authentic samples, so small quantities of the opposing diastereoisomers may not have been detected.

Greene performed kinetic and mechanistic studies indicating the reaction proceeded primarily through an ionic pathway over a radical pathway (Figure 1.4),[34b-d] although there is some ambiguity.[35]

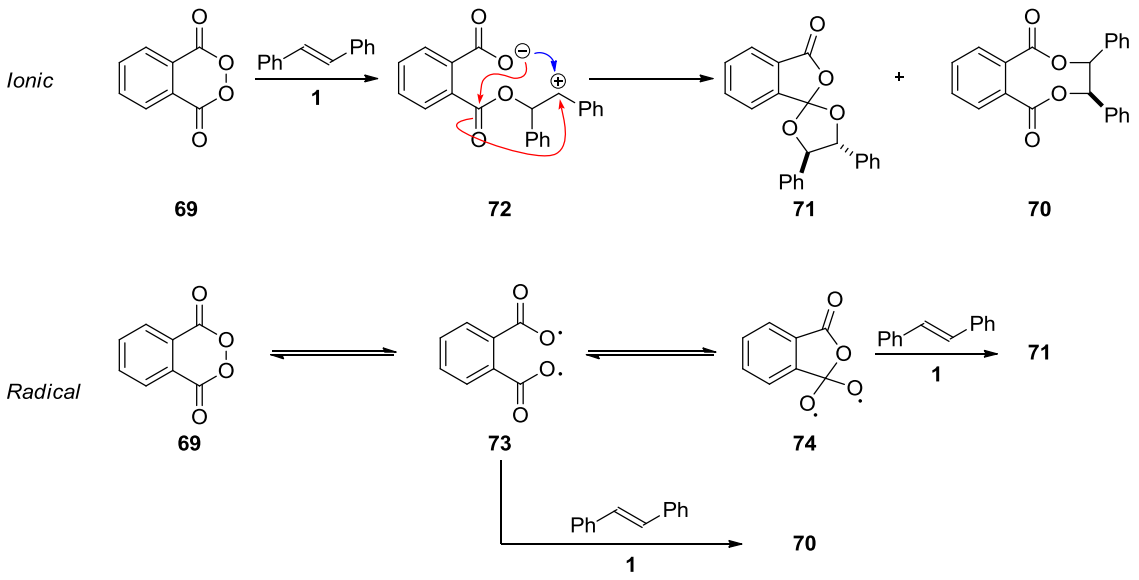
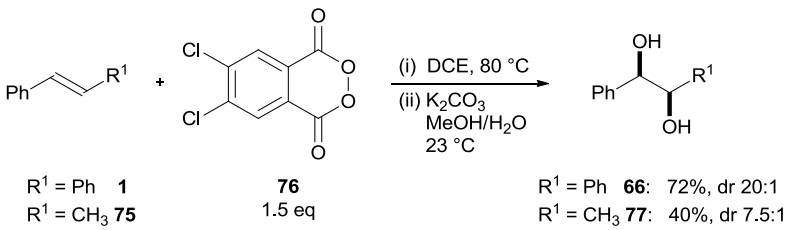


Figure 1.4 Possible ionic and radical pathways in the phthaloyl peroxide **69** dihydroxylation reaction.

In 2011, Siegel realised the potential of this method and reported on the improved reactivity of 3,4-dichlorophthaloyl peroxide **76** in the dihydroxylation of alkenes (Scheme 1.17).[36] Treatment of alkenes with 1.5 equivalents of peroxide **76** in refluxing dichloroethane followed by basic hydrolysis of the crude reaction mixture gave the corresponding *syn*-diols.



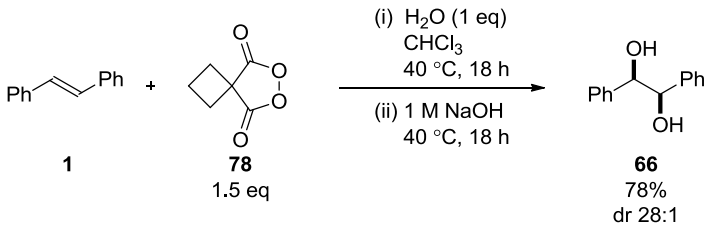
Scheme 1.17 3,4-Dichlorophthaloyl peroxide **76** dihydroxylation of alkenes.

The reaction was simple to perform and produced *syn*-diols in good yield (20 examples, 30–74%) with good levels of *syn*-diastereoselectivity (3:1 to 25:1) for both aryl- and alkyl-substituted alkenes. However, elevated temperatures of 80 °C were required and both phthaloyl peroxide **69** and the dichloro derivative **76** were sensitive to shock and direct heating. Greene and Siegel have reported violent explosions when handling phthaloyl peroxide derivatives, severely limiting their attractiveness as dihydroxylation reagents.

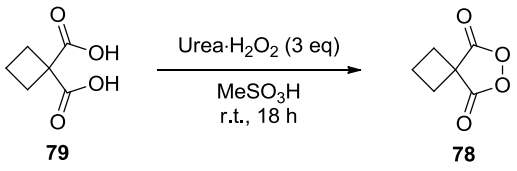
1.4.2 Malonoyl Peroxides

To overcome the dangerous sensitivity issues but maintain the desirable reactivity and stereoselectivity associated with phthaloyl peroxides in the reaction with alkenes, Tomkinson proposed the use of the related family of malonoyl peroxides. Malonoyl peroxides had been known for some time[37] and were reported to be more stable.[37a,37d]

In 2011, Jones and Tomkinson described the successful application of cyclobutyl malonoyl peroxide **78** in the dihydroxylation of alkenes (Scheme 1.18).[38] The reaction involved treating alkenes **1** with 1.5 equivalents of cyclobutyl malonoyl peroxide **78** in a wet chloroform solution at 40 ^{o}C overnight. Removal of chloroform under reduced pressure and saponification of the crude reaction mixture provided the corresponding *syn*-diol product **66**, often without need for further purification.



Scheme 1.18 Dihydroxylation using cyclobutyl malonoyl peroxide **78**.



Scheme 1.19 Synthesis of cyclobutyl malonoyl peroxide **78**.

Cyclobutyl malonoyl peroxide **78** was synthesised in one simple step from the commercially available dicarboxylic acid **79** using 3 equivalents of urea hydrogen peroxide in methanesulfonic acid, with only aqueous work-up required for purification (Scheme 1.19). The dihydroxylation protocol was effective with a number of aryl-substituted alkenes containing a variety of functionality (18 examples), and was most efficient with electron-rich alkenes due to the electrophilic nature of peroxide **78**. The diol products were generally produced in good yield (38–80%) with good to excellent levels of *syn*-diastereoselectivity (3:1 to >50:1 *syn*:*anti*).

The reaction mechanism was not fully understood, but it was suggested that interaction between alkene **80** and cyclobutyl malonoyl peroxide **78** produced carbocation **81** which underwent ring-closure to dioxonium ion **82**. Nucleophilic attack by a molecule of water gave dioxolane **83** which rapidly collapsed, then decarboxylated, to give the observed esters **84** and **85** (Figure 1.5).

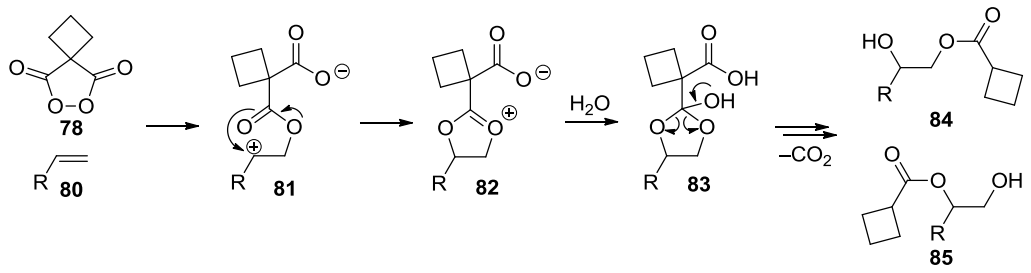


Figure 1.5 Tentative mechanistic course for the reaction of an alkene **80** with cyclobutyl malonoyl peroxide **78**.

The ease of access to cyclobutyl malonoyl peroxide **78**, in conjunction with the simple procedure, mild conditions and high levels of diastereoselectivity, made this reaction very attractive as a metal-free *syn*-dihydroxylation procedure.

In an effort to gain a better understanding of this class of peroxide, alternative peroxide structures **86** and **87** were investigated in the reaction with styrene **37**. This study revealed a direct relationship between peroxide structure and reactivity as outlined in Figure 1.6.[39]

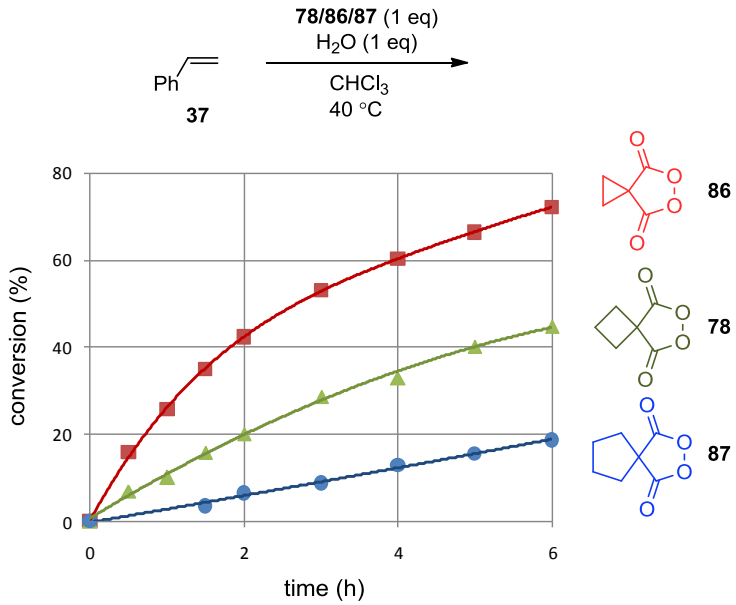
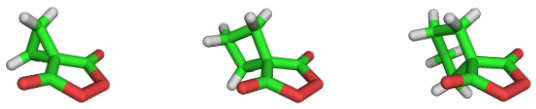


Figure 1.6 Peroxide structure *versus* reactivity in the reaction with styrene **37**.

The results indicated that the reactivity of malonoyl peroxides with alkenes significantly increased (**86**>**78**>**87**) with decreasing cycloalkane ring size. X-Ray crystallographic analysis indicated that the O–O bond lengths in peroxides **78**, **86**, **87** were near identical at around 1.47 Å. The key structural difference appeared to be the increase in the OC–C–CO bond angle as the size of the cycloalkyl ring decreased (Table 1.1). It was proposed that increased ring strain in cyclopropyl malonoyl peroxide **86** was responsible for its increased reactivity over peroxides **78** and **87**.[40]



	86	**78**	**87**
O–O bond (Å)	1.476(2)	1.476(2)	1.471(2)
OC–C–CO angle	107.56(19)	104.01(13)	102.34(17)

Table 1.1 Selected X-Ray crystallographic data for malonoyl peroxides **86**, **78** and **87**.

1.5 Conclusions

The metal-free *syn*-dihydroxylation of alkenes is an exciting emerging field within organic chemistry, aiming to provide an alternative to the toxic osmium tetroxide mediated Sharpless dihydroxylation reaction. Although a general, metal-free, catalytic and asymmetric dihydroxylation protocol has yet to be achieved, considerable progress has been made in only a short period of time.

Within this field, hypervalent iodine reagents have received the most attention and significant progress has been made with both catalytic, and asymmetric *syn*-dioxygenation reactions being reported. Selenium reagents are substantially less explored, but a highly enantioselective *syn*-dihydroxylation procedure has been reported, albeit with very low levels of diastereoselectivity.

Cyclic diacyl peroxides such as phthaloyl peroxides and malonoyl peroxides show great promise as simple metal-free dihydroxylation reagents. Malonoyl peroxides are particularly attractive due to their increased stability, milder reaction conditions, and higher levels of diastereoselectivity in the dihydroxylation of alkenes when compared to phthaloyl peroxides. Cyclobutyl malonoyl peroxide **78** was shown to be a very effective reagent for the dihydroxylation of alkenes, producing diols in good yield with high levels of *syn*-selectivity. However, cyclopropyl malonoyl peroxide **86** had potential to be a superior dihydroxylation reagent due to its increased reactivity with styrene **37**, but its reactivity with other substrates had not been explored.

This represented the starting point of the current investigation. Herein, the use of cyclopropyl malonoyl peroxide **86** as a metal-free dihydroxylation reagent is discussed.

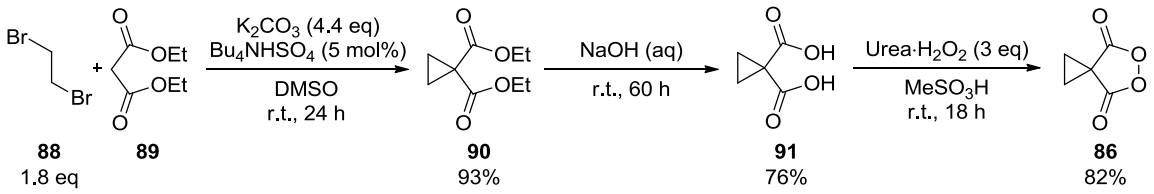
Chapter 2: Mechanistic Investigation

2 Mechanistic Investigation

It is important to have a strong mechanistic understanding of a reaction when developing new methodology, as this provides the foundations for exploration. This chapter outlines the current mechanistic understanding of the dihydroxylation of alkenes using cyclopropyl malonoyl peroxide **86**.

2.1 Peroxide Synthesis

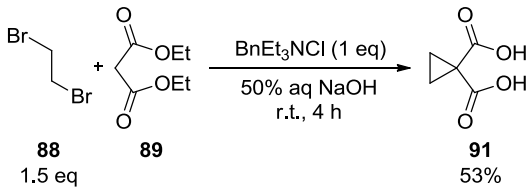
Prior to commencing the mechanistic investigation, an efficient route to cyclopropyl malonoyl peroxide **86** was required. Peroxide **86** was synthesised by treating cyclopropane-1,1-dicarboxylicacid **91** with three equivalents of urea hydrogen peroxide adduct in methanesulfonic acid (Scheme 2.1) using the conditions employed by Jones in the synthesis of cyclobutyl malonoyl peroxide **78** (Scheme 1.19).[41] Unlike cyclobutane-1,1-dicarboxylic acid **79**, diacid **91** was not commercially available at the onset of this investigation. Diacid **91** was obtained by treating diethyl malonate **89** with 1.8 equivalents of 1,2-dibromoethane **88** and potassium carbonate in the presence of a phase transfer catalyst to generate diester **90** (93% yield), which was isolated and hydrolysed to diacid **91** (76% yield, Scheme 2.1).[42]



Scheme 2.1 Synthesis of peroxide **86** from diethyl malonate **89**.

Although amenable to being performed on a large scale (up to 27 g of diacid **91** in a single batch, overall yield: 71%), this two-step procedure to diacid **91** was relatively time consuming (~5 days) and involved purification of diester **90** by distillation. An alternative one-step phase-transfer alkylation procedure from diethyl malonate **89** developed by Danishefsky[43] was later adopted, giving access to diacid **91** in 0.5 days with only aqueous work-up required for purification (53% yield, Scheme 2.2). Reaction of diethyl malonate **89** and dibromoethane **88** catalysed by triethylbenzylammonium hydroxide, which is generated from the reaction of triethylbenzylammonium chloride

and 50% aqueous NaOH, led to diester **90**, which underwent saponification to diacid **91** without need for isolation of **90**. The desired alkylation was not achieved when starting with malonic acid, presumably due to the difficulty in generating useful concentrations of the corresponding trianion. This suggests that alkylation occurs before saponification.



Scheme 2.2 One-step synthesis of diacid **91**.

Cyclopropane-1,1-dicarboxylic acid **91** is now commercially available,[44] but in-house synthesis is substantially more cost effective and therefore **91** is regularly synthesised using the quick and effective one-step Danishefsky protocol.

2.2 Peroxide Safety

Peroxides are attractive reagents because of their high reactivity, but with this high reactivity often comes instability. Many peroxides are unstable to shock and/or direct heating and have been known to decompose explosively.[45] Differential scanning calorimetry (DSC) analysis by Jones determined that cyclopropyl malonoyl peroxide **86** is relatively thermally stable, with a small onset temperature of 115 ^{o}C, but only decomposing significantly at 155 ^{o}C.[39] In addition to the work by Jones, a small sample was heated gradually in a metal crucible until melting (77–78 ^{o}C), then allowed to cool. Analysis by ^{1}H and ^{13}C NMR and infrared spectroscopy revealed that peroxide **86** had not decomposed. The same sample was later used in the reaction with styrene without any decrease in performance.

The shock sensitivity of peroxide **86** was examined by means of a BAM Fallhammer test (Figure 2.1[46]), performed by Chilworth Technologies Ltd. in accordance with the UN transport of dangerous goods recommendations. The test involved dropping a series of weights (1, 2, 5 and 10 kg) onto a contained 40 mm^3 sample of peroxide **86** from a

Figure 2.1 BAM Fallhammer test.

known height (10–60 cm), resulting in an impact energy of 1–60 J. The results were observed by a qualified member of staff and classified as 'no reaction', 'decomposition' or 'explosion'.

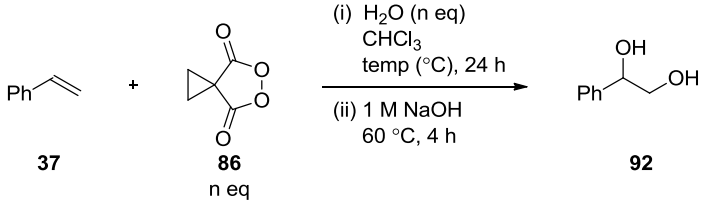
The limiting impact energy of a substance is defined as the lowest energy at which the result 'explosion' is obtained from at least one out of six trials. The result is considered positive if the limiting impact energy is 2 J or less.

A positive result means, by UN rules, the substance is considered too dangerous to transport in the form in which it was tested. Any other result is considered negative.

Cyclopropyl malonoyl peroxide **86** was observed to have a limiting impact energy of 5–10 J, meaning the test result is negative and it is not considered to be sensitive to impact (see Appendix 9.5 for the full report). However, it should be noted that the test would be considered positive according to a different test standard, EC 440/2008, and therefore caution should be applied when handling peroxide **86**. Despite the data suggesting peroxide **86** is relatively insensitive to shock and direct heating, all peroxides should be considered dangerous and standard peroxide safety protocols should always be followed.

2.3 Reaction Optimisation

With an efficient route to cyclopropyl malonoyl peroxide **86** in hand and information regarding its stability, attention was turned to reaction optimisation. As a starting point, the optimised conditions developed by Jones for the reaction of alkenes with cyclobutyl malonoyl peroxide **78** were employed (Table 2.1).[38]



37 **86** n eq **92**

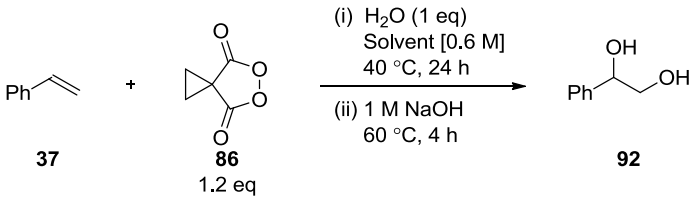
Entry	H_2O (eq)	**86** (eq)	Temp. (^oC)	Yield (%)[a]
1	0[b]	1.5	40	21
2	1	1.5	40	88
3	2	1.5	40	87
4	5	1.5	40	87
5	1	1.2	40	89
6	1	1.0	40	78
7	1	1.2	23	89

[a] Isolated yield. [b] Bench chloroform was used.

Table 2.1 Reaction optimisation.

In the model reaction of styrene **37** and cyclopropyl malonoyl peroxide **86**, 1 equivalent of water remained essential for clean and efficient reaction to diol **92** (Table 2.1, Entries 1 and 2), but additional water provided no advantage in terms of yield (Table 2.1, Entries 3 and 4). The peroxide stoichiometry could be decreased from 1.5 to 1.2 equivalents with cyclopropyl malonoyl peroxide **86** due to the increased reactivity of **86** over **78** (Table 2.1, Entry 5). However, the yield of diol **92** reduced slightly when exactly 1 equivalent of **86** was used (Table 2.1, Entry 6). The reaction of styrene **37** and peroxide **86** was complete after 24 h at room temperature in chloroform (Table 2.1, Entry 7), although a temperature of 40 ^oC was typically used. Higher reaction temperatures were not explored for safety reasons. In addition, the temperature of the hydrolysis step was increased from 40 ^oC to 60 ^oC to reduce reaction time from 18 h to 4 h.

A solvent screen determined the reaction tolerates a variety of solvents (Table 2.2). Nucleophilic solvents such as DMSO (Table 2.2, Entry 4) react vigorously with electrophilic peroxide **86**. Milder nucleophilic solvents such as isopropanol and methanol allowed dihydroxylation to occur (34% and 57% respectively, Table 2.2, Entries 7 and 8), but control experiments revealed a competing destructive interaction with peroxide **86**. Styrene **37** consumption was followed qualitatively by TLC and ^{1}H NMR analysis suggesting the reaction was marginally fastest in chloroform (89%, Table 2.2, Entry 2), although this could not be explained at the time (see Chapter 4 for a possible explanation). Other effective solvents for the dihydroxylation protocol were acetonitrile (87%, Table 2.2, Entry 1), 1,4-dioxane (85%, Table 2.2, Entry 5), ethyl acetate (87%, Table 2.2, Entry 6) and toluene (88%, Table 2.2, Entry 9). Interestingly, the reaction could be performed in water in reasonable yield (70%, Table 2.2, Entry 10) despite the poor solubility of both reagents.

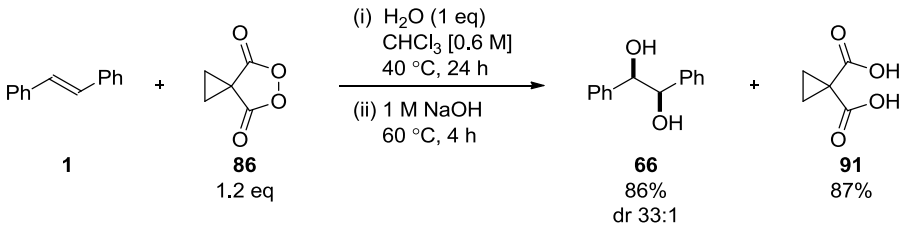


Entry	Solvent	% yield of **92**
1	Acetonitrile	87
2	Chloroform	89
3	Diethyl ether	59
4	Dimethyl sulfoxide	0
5	1,4-Dioxane	85
6	Ethyl acetate	87
7	Isopropanol	34
8	Methanol	57
9	Toluene	88
10	Water	70

Table 2.2 Optimised reaction conditions and solvent screen for dihydroxylation using cyclopropyl malonoyl peroxide **86**.

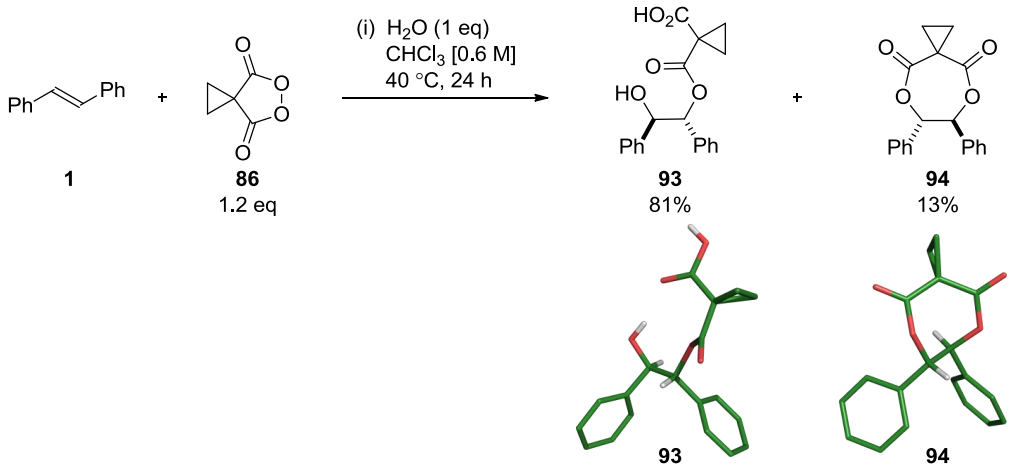
2.4 Isolation of Reaction Intermediates

The optimised set of reaction conditions was employed in the reaction of peroxide **86** with *trans*-stilbene **1** which resulted in diol **66** in very good yield (86%) and with an excellent diastereomeric ratio of 33:1 (*syn*:*anti*). Significantly, aqueous extraction recovered cyclopropane-1,1-dicarboxylic acid **91** in good yield (87%), indicating that decarboxylation was not occurring (Scheme 2.3). This presents a major advantage over the reaction with cyclobutyl malonoyl peroxide **78**, which proceeds *via* a decarboxylative pathway, as diacid **91** can be recovered and converted back into peroxide **86**, resulting in minimal waste.



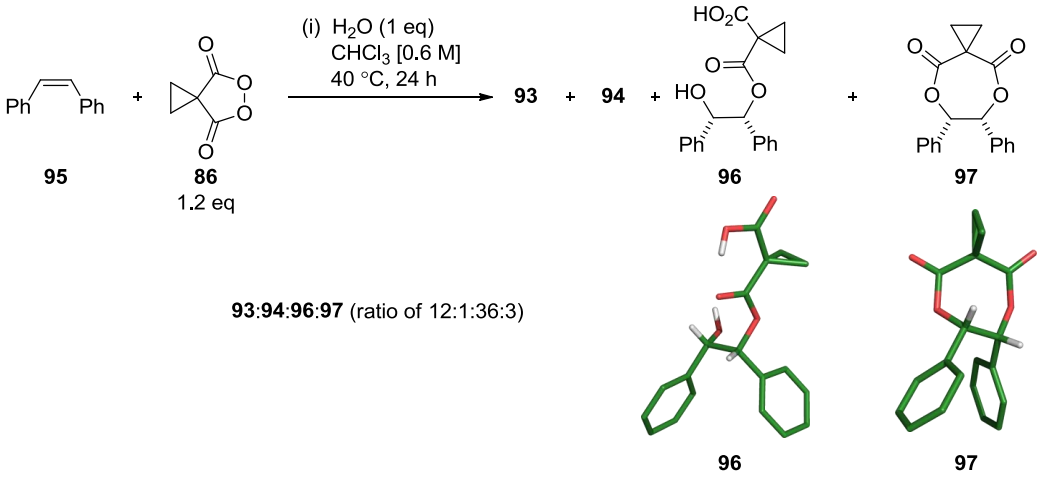
Scheme 2.3 Dihydroxylation of *trans*-stilbene **1** and recovery of diacid **91**.

Reaction intermediates **93** and **94** were isolated in a 6:1 ratio (94%) pre-hydrolysis (Scheme 2.4). The structures and relative configuration of intermediates **93** and **94** were confirmed by single crystal X-ray crystallography (see Appendix 9.1).



Scheme 2.4 Reaction intermediates **93** and **94** isolated in the dihydroxylation of *trans*-stilbene **1**, with X-ray crystal structures.

Small amounts of the *anti*-diastereoisomer of ester **93** (~30:1 **93**:**96**) were detectable in the ^{1}H NMR spectrum of the crude reaction mixture but could not be isolated. Reaction of *cis*-stilbene **95** with peroxide **86** under identical conditions afforded **93** and **94** in addition to *syn*-addition products ester **96** and 7-membered ring **97** (12:1:36:3 respectively, Scheme 2.5. See Appendix 9.3 for ^{1}H NMR of the crude reaction mixture). Ester **96** and 7-membered ring **97** were isolated, and their structures confirmed by X-ray crystallography (see Appendix 9.1). Interestingly, having an authentic sample of 7-membered ring **97** to hand provided confirmation that **97** was not observed in the reaction of *trans*-stilbene **1** (Scheme 2.4) by ^{1}H NMR spectroscopy. However, it should be noted that this may just be within the detection limits of the NMR spectrometer.



Scheme 2.5 Reaction intermediates **96** and **97** isolated in the dihydroxylation of *cis*-stilbene **95**, with X-ray crystal structures.

2.5 Proposed Mechanism

Identification of intermediates **93** and **94** in the reaction of *trans*-stilbene **1** with peroxide **86** allowed a possible mechanism of their formation to be proposed (Figure 2.2).

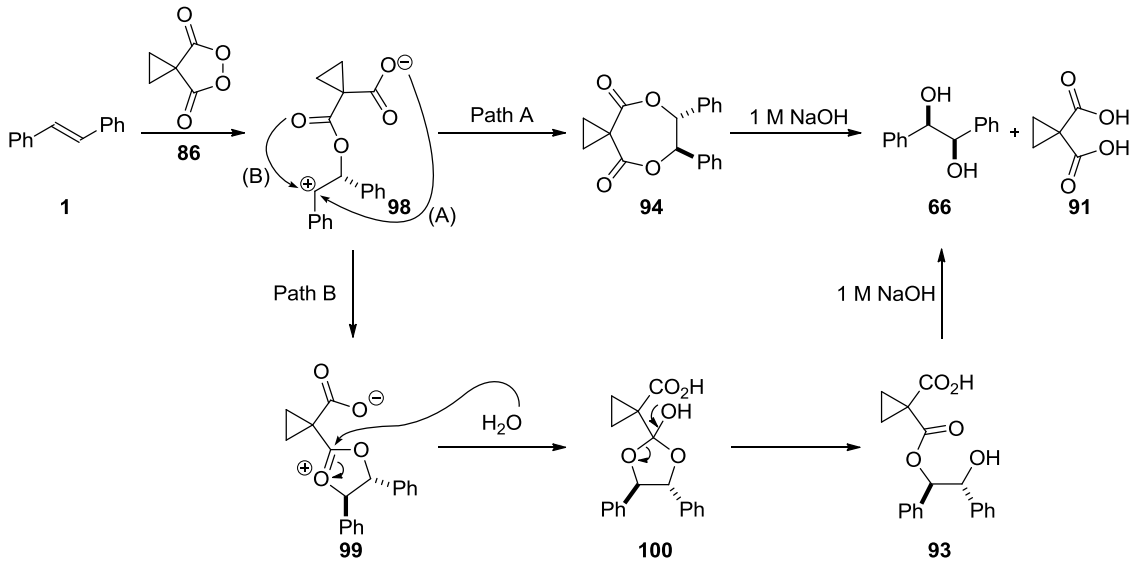


Figure 2.2 Proposed mechanism in the cyclopropyl malonoyl peroxide **86** mediated dihydroxylation of *trans*-stilbene **1**.

Interaction of *trans*-stilbene **1** and peroxide **86** could lead to a common intermediate, zwitterion **98**, which could ring-close to give the observed 7-membered ring **94** (Path A), or dioxonium **99** (Path B). Hydrolysis of dioxonium **99** using the molecule of water essential for reaction, would give the observed ester **93**, *via* dioxolane **100**. Basic hydrolysis of the 6:1 mixture of **93** and **94** gave *syn*-diol **66** (33:1 *syn*:*anti*) and diacid **91**, which can be recovered and converted back into peroxide **86** in a single synthetic step.

The remainder of this Chapter discusses evidence for, or against, the proposed mechanism.

2.6 Reaction Kinetics

Mechanistic investigations began by obtaining kinetic information about the reaction. Homogeneous solutions of *trans*-stilbene **1**, cyclopropyl malonoyl peroxide **86** and water in d_8-1,4-dioxane were monitored over time by ^{1}H NMR spectroscopy (Figure 2.3, see Experimental 8.25.1 for details). Stilbene **1** and peroxide **86** were consumed at the same rate and cleanly converted into a mixture of intermediates **93** and **94**. Interestingly, the 6:1 ratio of **93**:**94** was maintained throughout the course of the reaction.

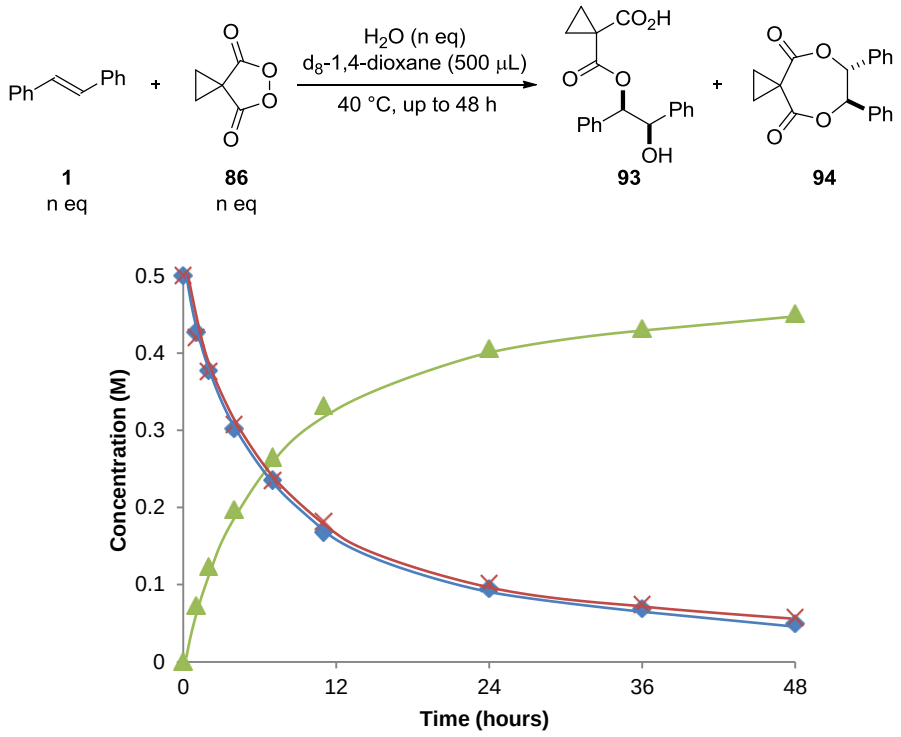


Figure 2.3 Reaction profile of the peroxide **86** (× [0.5 M]) mediated dihydroxylation of stilbene **1** (♦ [0.5 M]) in the presence of one equivalent of water [0.5 M] leading to products **93** and **94** (▲).

The kinetic order in *trans*-stilbene **1** (0.25 M) was determined using an excess of peroxide **86** (0.5 M) and water (0.5 M) under the conditions shown in Figure 2.3, and the concentration of *trans*-stilbene **1** followed over time (24 h, 93% conversion) by ^{1}H NMR spectroscopy (see Experimental 8.25.1 for details). A linear correlation was observed in the logarithmic plot of stilbene **1** concentration against time, indicating a first-order dependence in stilbene **1** (Figure 2.4).

The kinetic order in peroxide **86** (0.25 M) was determined using an excess of *trans*-stilbene **1** (0.5 M) and water (0.5 M) and followed over time (24 h, 94% conversion) by ^{1}H NMR spectroscopy (see Experimental 8.25.1 for details). A linear correlation was observed in the logarithmic plot of peroxide **86** concentration against time, indicating a first-order dependence in peroxide **86** (Figure 2.5).

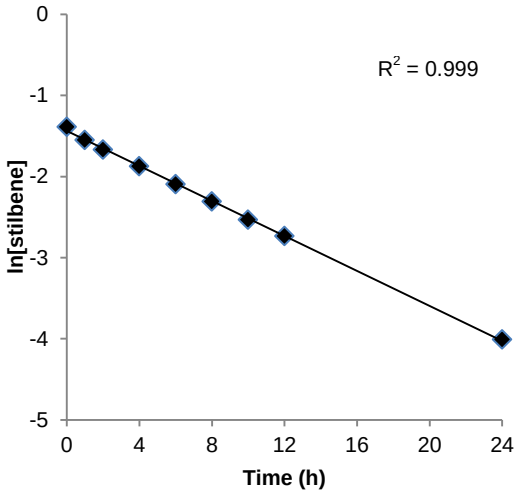


Figure 2.4 Logarithmic plot of stilbene **1** concentration against time showing first-order dependence in stilbene **1**.

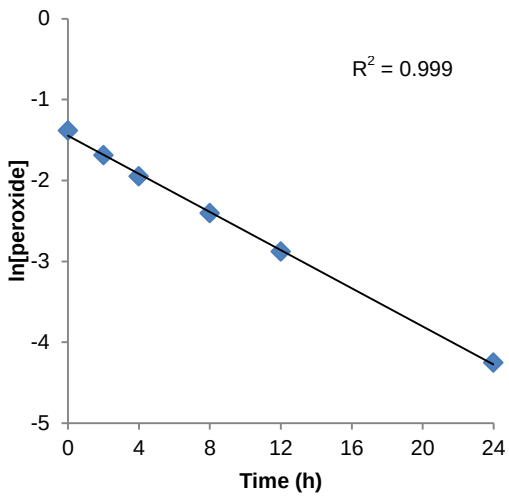


Figure 2.5 Logarithmic plot of peroxide **86** concentration against time showing first-order dependence in peroxide **86**.

The exact kinetic order in water was more difficult to determine. However, doubling the concentration of water (1 to 2 eq) only increased the rate of consumption of either *trans*-stilbene **1** or peroxide **86** by a factor of 1.06. This negligible effect in rate with increasing water concentration allows an approximate zero-order dependence in water to be assumed. The role of water is discussed further in Chapter 4. It should be noted that the optimised conditions for dihydroxylation employ chloroform as the solvent, however all of the kinetic data was obtained in homogeneous 1,4-dioxane solutions to accurately control the quantity of solubilised water in the reaction medium.

With the approximation that the reaction is zero-order in water in hand, the overall dihydroxylation reaction can be considered second-order, being first-order in both alkene and peroxide as shown by Equation 2.1.

$$\text{Rate} = k[\text{alkene}][\text{peroxide}] \qquad \text{Equation 2.1}$$

When equimolar amounts of both starting materials are used, [alkene] = [peroxide], so Equation 2.1 can be re-written as:

$$\text{Rate} = k[\text{alkene}]^2 \qquad \text{Equation 2.2}$$

Therefore the plot of 1/[alkene] against time (48 h, 90% conversion, Figure 2.6) exhibits a linear relationship with a second-order rate constant, $k = 0.32\ M^{-1}h^{-1}$ (or $k = 8.89 \times 10^{-5}\ M^{-1}s^{-1}$).

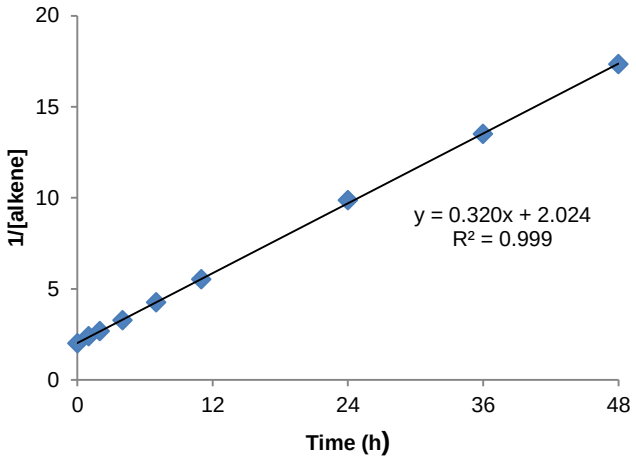


Figure 2.6 Linear plot of 1/[alkene] against time showing second-order kinetics of the dihydroxylation reaction.

2.7 Evidence of Carbocation Intermediate

To gather evidence for the reaction proceeding through the first proposed intermediate, carbocation **98** (Figure 2.7), the reaction was subjected to Hammett analysis.

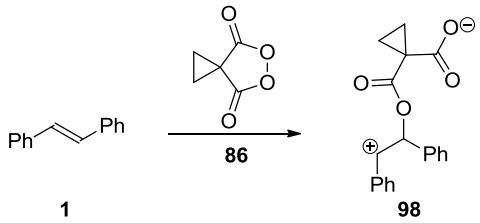


Figure 2.7 Proposed carbocation intermediate **98**.

A series of seven *meta*- and *para*-substituted styrene derivatives **37**, **101**–**106** were treated with cyclopropyl malonoyl peroxide **86** (1 eq) in chloroform containing 1 equivalent of D_2O at room temperature. The rate of consumption of peroxide **86** was monitored by ^1H NMR spectroscopy (see Experimental 8.25.2 for details), relative to an internal standard (1,4-dinitrobenzene), and the results shown in Figure 2.8.

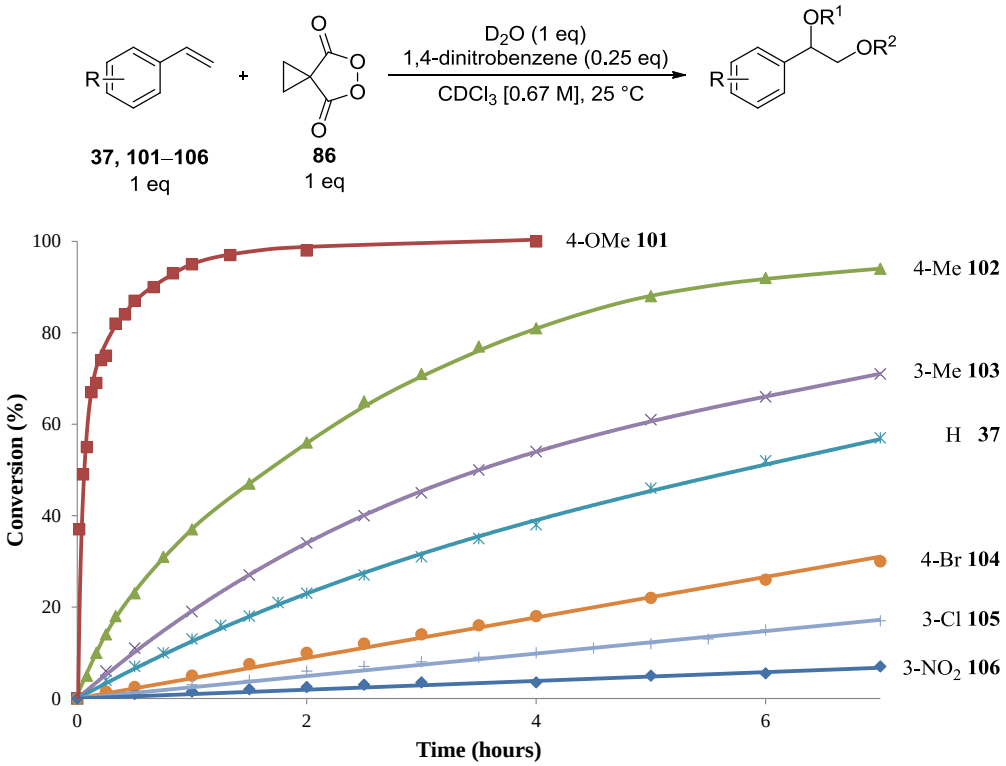


Figure 2.8 Plot of conversion against time for the reaction of peroxide **86** with substituted styrenes **37**, **101**–**106**.

Reaction of electron-rich alkenes such as 4-methoxystyrene **101** with peroxide **86** was very rapid, achieving around 50% conversion after only 5 minutes. Conversely, electron-deficient alkenes such as 3-nitrostyrene **106** reacted very slowly with peroxide **86**, achieving around 6% conversion after 7 hours. This is consistent with peroxide **86** acting as an electrophile, and indicates the dihydroxylation reaction is more efficient with nucleophilic alkenes. Peroxide **86** is relatively stable under the reaction conditions and can therefore be subjected to the prolonged reaction times required for less reactive substrates such as **106**.

The initial rate of reaction for each alkene **37**, **101**–**106** with peroxide **86** was calculated (Table 2.3) and used to construct Hammett plots based on literature σ and σ^+ values (Figures 2.9 and 2.10 respectively).[47,48]

Styrene	**Initial rate (Ms^{-1})**	**σ**	**σ^+**
4-OMe **101**	4.13×10^{-3}	-0.27	-0.78
4-Me **102**	1.12×10^{-4}	-0.17	-0.31
3-Me **103**	4.17×10^{-5}	-0.07	-0.07
H **37**	2.55×10^{-5}	0	0
4-Br **104**	9.33×10^{-6}	0.23	0.15
3-Cl **105**	4.92×10^{-6}	0.37	0.40
3-NO_2 **106**	1.81×10^{-6}	0.71	0.67

Table 2.3 Initial rate of reaction between peroxide **86** and styrenes **37**, **101**–**106** and the corresponding σ and σ^+ constants.

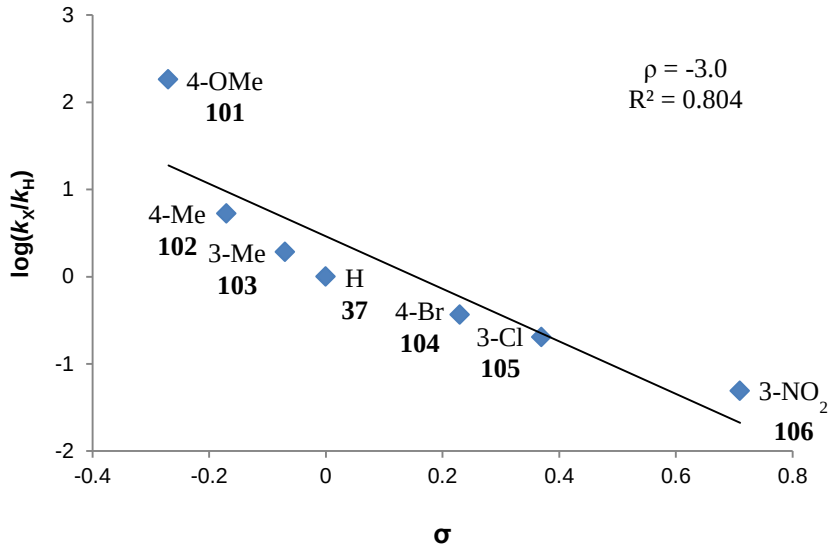


Figure 2.9 Curved Hammett plot for the reaction of peroxide **86** with substituted styrenes **37, 101**–**106** using σ parameters.

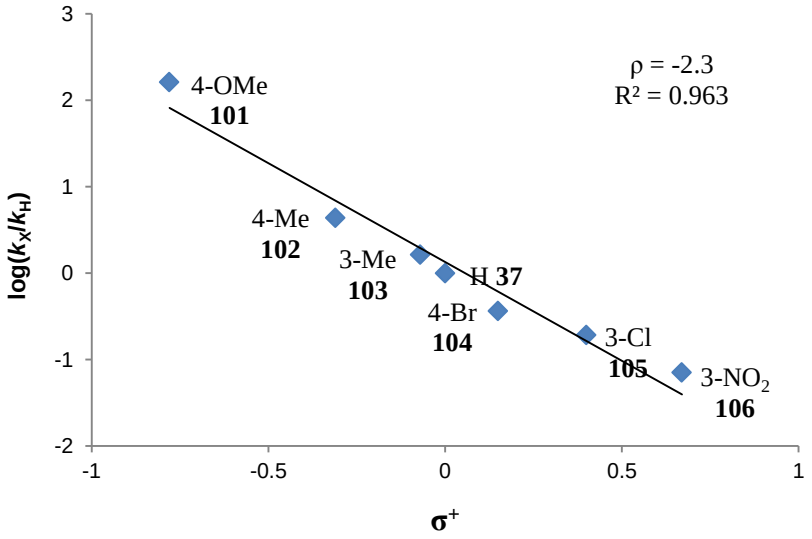


Figure 2.10 Linear Hammett plot for the reaction of peroxide **86** with substituted styrenes **37, 101**–**106** using σ^+ parameters.

A better correlation was observed when Hammett-Brown σ^+ parameters were used instead of σ parameters. This indicates that through-conjugation effects are important, consistent with a benzylic carbocation intermediate. The Hammett plot in Figure 2.10 provides three very important pieces of mechanistic information. Firstly, it is linear

implying that there is a single mechanism in operation for both electron-rich and electron-deficient alkenes. Secondly, the negative gradient implies there is a build-up of positive charge during the transition state of the reaction. Finally, the moderate magnitude of the gradient, -2.3, indicates that the build-up of positive charge is close to the aromatic ring as the substituent exerts a substantial effect on the rate of reaction. The observed rho value, ρ = -2.3, is consistent with a benzylic carbocation and provides strong evidence the dihydroxylation reaction proceeds *via* carbocation intermediate **98**.

2.8 Ionic *versus* Radical Mechanism

It has never been established how malonoyl peroxides react with alkenes, so this represented a fundamental challenge within this mechanistic investigation. Three possible modes of reactivity were proposed as outlined in Figure 2.11.

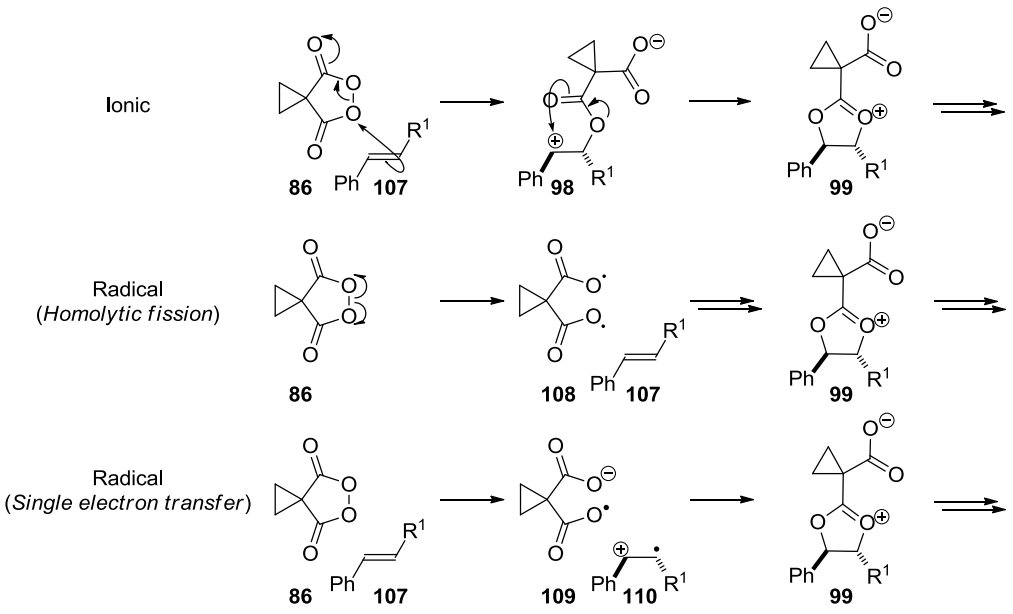


Figure 2.11 Three possible mechanisms for the initial interaction between peroxide **86** and alkene **107**.

During an ionic mechanism, nucleophilic attack by alkene **107** on peroxide **86** would result directly in zwitterion **98**, which could ring-close to dioxonium **99**. Alternatively, homolytic fission of the weak O–O bond of **86** could give diradical **108** which may react with alkene **107** to form dioxonium **99**. Finally, a second radical mechanism involving single electron transfer (SET)[49] from alkene **107** to peroxide **86** could result in

radical cation **110** and radical anion **109**. Re-combination of **109** and **110** would result in dioxonium **99**.

An ionic and single electron transfer mechanism both require donation of electrons into the σ* orbital of the O–O bond. Computational modelling of peroxide **86** by Julian Rowley of the Tomkinson group suggested that the largest LUMO coefficient was at the σ* orbital of the O–O bond, validating the proposed mechanisms (Figure 2.12).

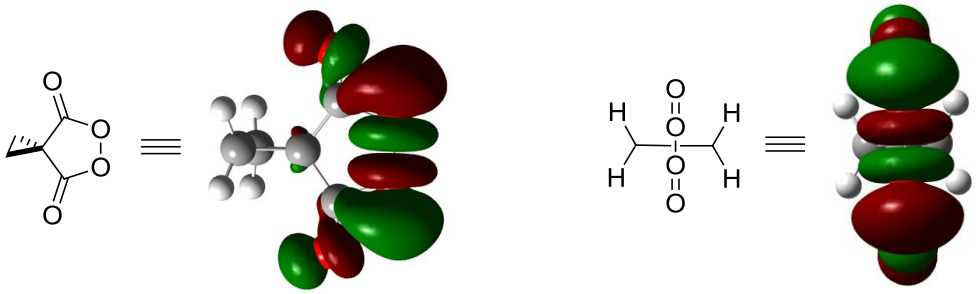
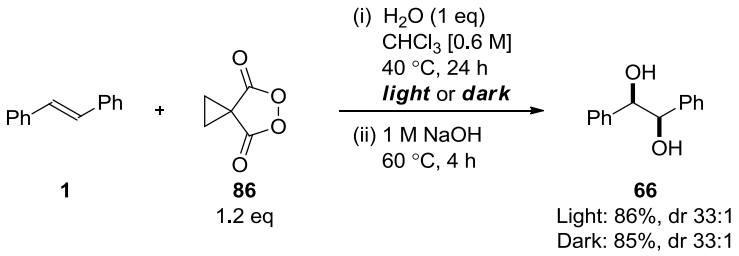


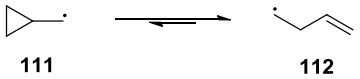
Figure 2.12 Calculated LUMO coefficients for peroxide **86**. Side view (left) and front view (right).

Radical processes can often be initiated by the presence of light. The dihydroxylation of *trans*-stilbene **1** was performed in both the presence and absence of light under standard conditions (Scheme 2.6). No difference in reaction rate, yield or diastereoselectivity of diol **66** was observed, suggesting a radical process may not be in operation, although this is far from conclusive.



Scheme 2.6 Dihydroxylation of **1** performed in presence and absence of light.

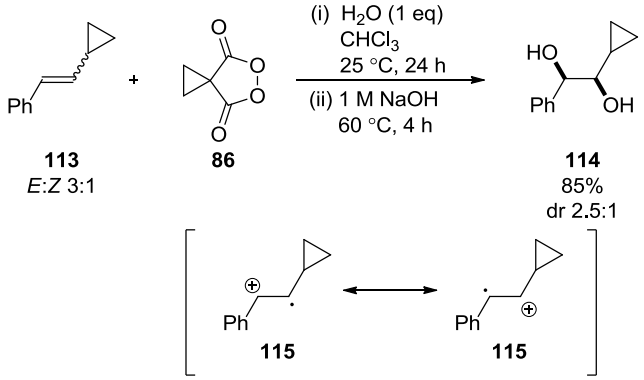
The cyclopropylcarbinyl **111** – allylcarbinyl **112** rearrangement is one of the most rapid unimolecular rearrangement processes of organic radicals, and is often used as a probe for radical intermediates in organic reactions (Figure 2.13).[50]



111 **112**

Figure 2.13 Cyclopropylcarbinyl **111** to allylcarbinyl **112** rearrangement.

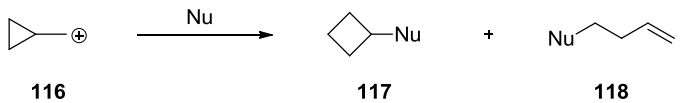
β-Cyclopropylstyrene **113** was synthesised using standard Witting chemistry (3:1 *E*:*Z*) and subjected to the standard dihydroxylation conditions outlined in Scheme 2.7. If an SET mechanism was in operation then it was postulated that delocalised radical cation **115** may form (Scheme 2.7), causing rapid ring-opening to occur.



113 *E*:*Z* 3:1 **86** **114** 85% dr 2.5:1 **115** **115**

Scheme 2.7 Dihydroxylation of β-cyclopropylstyrene **113**.

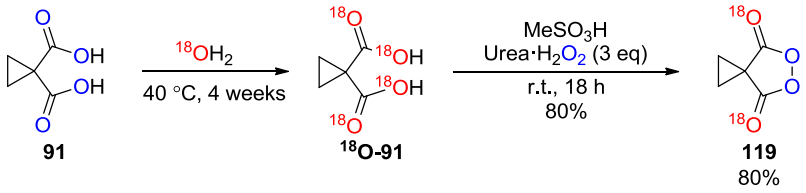
The reaction proceeded very cleanly, affording diol **114** in excellent isolated yield (85%, 2.5:1 *syn*:*anti*). No cyclopropane ring-opening products consistent with either radical-induced ring-opening (Figure 2.13) or carbocation-induced ring-opening[51] (Figure 2.14) were observed, providing evidence against an SET mechanism *via* an intermediate such as **115**.



116 **117** **118**

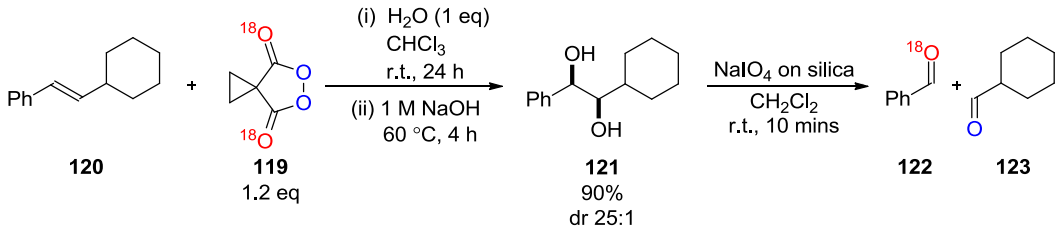
Figure 2.14 Generic rearrangement products from carbocation-induced cyclopropane ring-opening.

Further evidence against an SET mechanism arose from the use of differentially isotopically labelled peroxide **119**. Peroxide **119** was synthesised by stirring unlabelled diacid **91** in $^{18}OH_2$ for 1 month, resulting in greater than 75% ^{18}O incorporation into **^{18}O-91** by mass spectrometry. ^{18}O enriched diacid **^{18}O-91** was then treated with urea hydrogen peroxide adduct (3 eq) in methanesulfonic acid to afford the differentially labelled peroxide **119** (80%, Scheme 2.8).



Scheme 2.8 Synthesis of differentially labelled peroxide **119**.

Alkene **120** was synthesised and treated with differentially labelled peroxide **119** under the standard dihydroxylation conditions to give diol **121** (90%, 25:1 *syn*:*anti*, Scheme 2.9).



Scheme 2.9 Dihydroxylation of alkene **120** with ^{18}O-labelled peroxide **119** with subsequent oxidative cleavage to aldehydes **122** and **123**.

Mass spectrometric analysis showed incorporation of only one ^{18}O-label into diol **121**, with the fragmentation pattern suggesting the label was located at the benzylic position (see Appendix 9.2). Oxidative cleavage of diol **121** under anhydrous conditions using sodium metaperiodate on silica[52] afforded a mixture of aldehydes **122** and **123**. Direct analysis of the crude reaction mixture using GC-MS clearly showed significant label incorporation into benzaldehyde **122**, but no label incorporation into cyclohexanecarboxaldehyde **123** (see Appendix 9.2). These commanding results are consistent with an ionic mechanism (Figure 2.15), where the ^{18}O-label is placed regioselectively in the location of the more stable, benzylic, carbocation **124**.

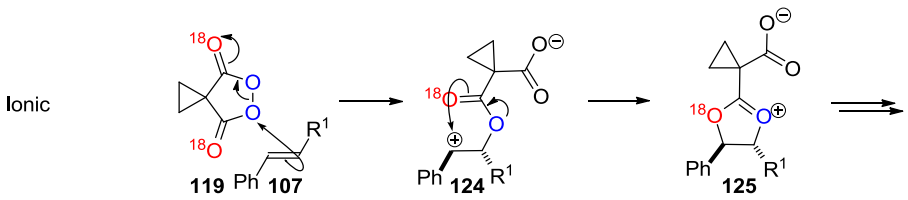


Figure 2.15 Ionic mechanism with differentially labelled peroxide **119**.

In both potential radical mechanisms (SET and homolytic fission) rapid ^{18}O-label scrambling is likely to occur in **108** and **109** (Figure 2.16), resulting in non-regioselective incorporation of the ^{18}O-label across the alkene **120**, which was not observed.

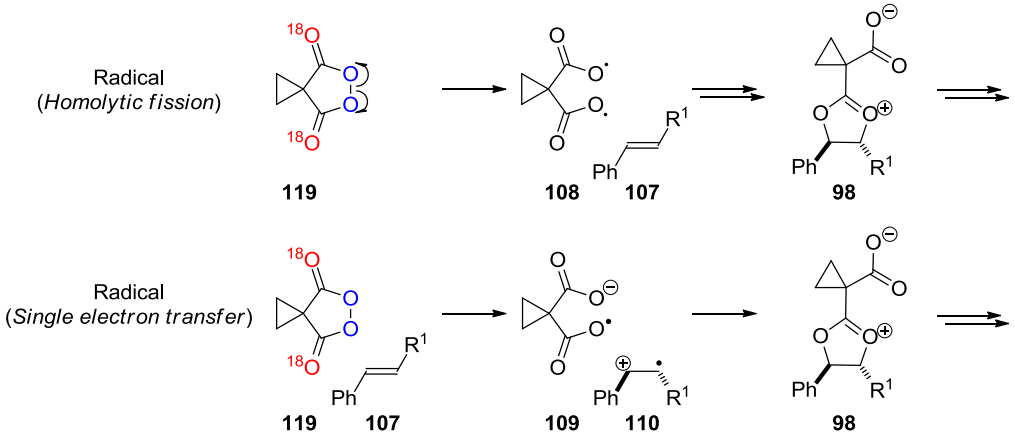


Figure 2.16 Loss of defined ^{18}O-label position in peroxide **119** during radical mechanisms.

Interestingly, the regiospecific incorporation of the ^{18}O-label into diol **121** provided important information on the structural stability of peroxide **119**. The possibility existed that peroxide **119** could undergo homolytic fission before reforming the O–O bond, resulting in three different labelled peroxides **119**, **127** and **128** (Figure 2.17).

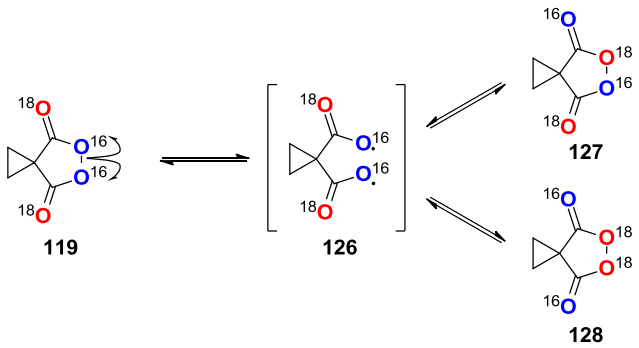


Figure 2.17 Potential scrambling of ^{18}O-label in peroxide **119**.

As no ^{18}O-label scrambling was observed, it suggested that peroxide **119** was stable in both solid state and in solution. For confirmation, the experiment using differentially labelled peroxide **119** (Scheme 2.9) was repeated after stirring peroxide **119** in chloroform overnight, before addition of alkene **120**. The dihydroxylation of **120** was also repeated using 1 month old ^{18}O-labelled peroxide **119**. Both experiments were consistent with regioselective incorporation of the ^{18}O-label into the benzylic position in diol **121** without any scrambling. Importantly, this suggests that the peroxide bond is stable to homolytic fission in both solid state and solution.

2.9 Evidence for Dioxonium Ion

With strong evidence for the dihydroxylation reaction proceeding *via* an ionic interaction leading to carbocation **98**, evidence was sought for the existence of the proposed dioxonium intermediate **99**. Dioxonium **99** could also exist as spirocycle **129**, although it was thought this would be disfavoured due to substantial ring strain (Figure 2.18). The relative energies of dioxonium **99** and spirocycle **129** were investigated by DFT calculations (B3LYP/6-31+G**) using a chloroform PCM, courtesy of Julian Rowley (Tomkinson group). This study suggested that spirocycle **129** may be 5.8 kcal mol^{-1} more stable than dioxonium **99**.

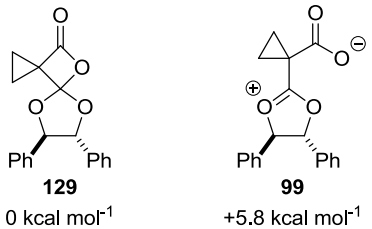


Figure 2.18 Relative energies of spirocycle **129** and dioxonium **99**.

To determine if dioxonium **99** or spirocycle **129** was prevalent during the reaction, the dihydroxylation reaction was performed using 1 equivalent of $^{18}OH_2$. If dioxonium **99** was attacked by $^{18}OH_2$, the ^{18}O-label would end up in the ester of **131**. Alternatively, if spirocycle **129** was attacked by water, the ^{18}O-label would end up in the carboxylic acid of **132** (Figure 2.19).

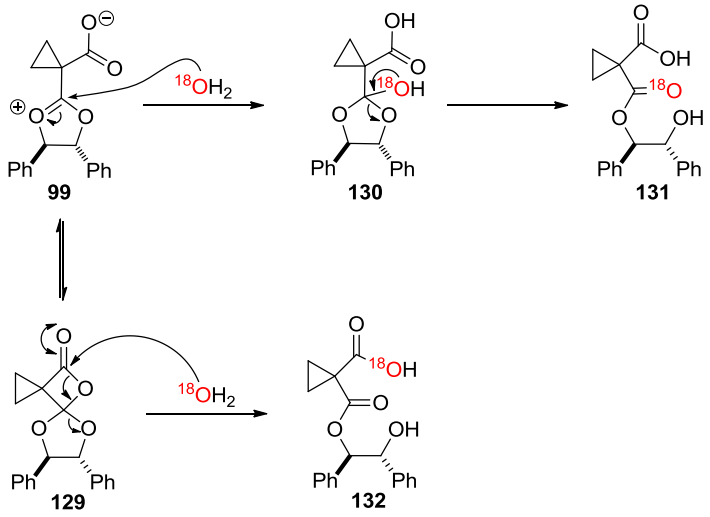


Figure 2.19 Hydrolysis of dioxonium **99** and spirocycle **129** leading to differentiated ^{18}O-label location.

Ester **131**/**132** was isolated (79%) and mass spectrometric analysis showed that, as expected, only one ^{18}O-label was present, but provided no information regarding its location (see Appendix 9.2). It has been known for some time that ^{18}O atoms bound to carbon atoms induce an upfield ^{13}C NMR shift relative to the ^{13}C NMR spectrum of an unlabelled (^{16}O) sample.[53] This effect is particularly pronounced in carbonyls, with an ^{18}O-induced upfield ^{13}C NMR shift in the region of 30–50 parts per billion (ppb) for the carbonyl carbon. ^{13}C NMR analysis was performed on ^{18}O-labelled ester **131**/**132** and compared to the ^{13}C NMR of unlabelled ester **93** (Figure 2.20).

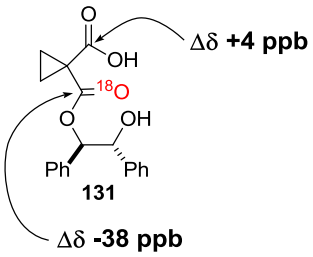
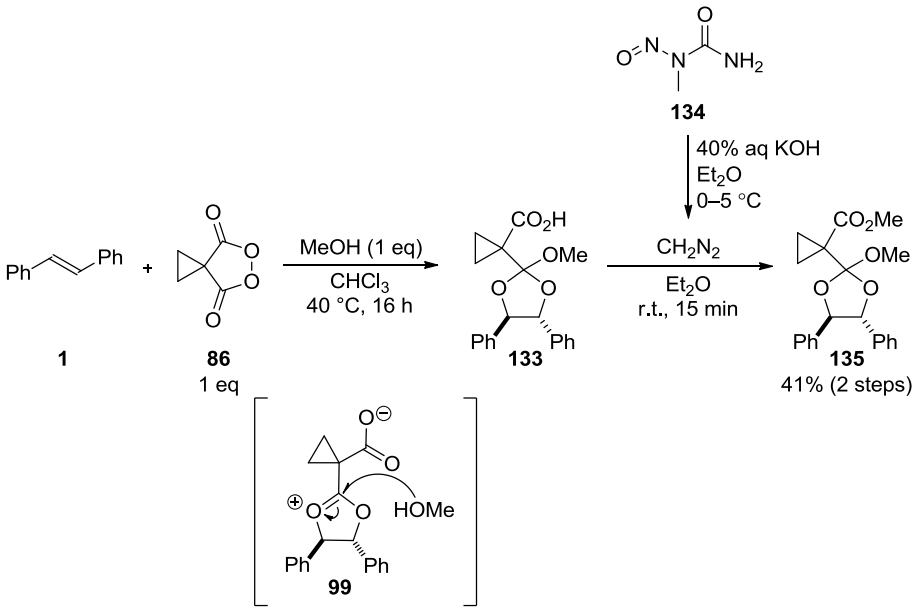


Figure 2.20 ^{18}O-induced upfield ^{13}C NMR shift in the ester of **131**.

A significant upfield shift of 38 ppb was observed in the ester carbonyl ^{13}C signal, and a very small downfield shift (+4 ppb) was observed in the carboxylic acid carbonyl ^{13}C NMR signal (see Experimental 8.26 for a full table of chemical shifts with DEPT-Q spectra). This is consistent with the ^{18}O-label in the ester portion of the molecule, and therefore dioxonium **99** being the most reactive intermediate to water.

To gain further evidence for the existence of dioxonium **99**, the dihydroxylation of *trans*-stilbene **1** was performed using an equivalent of methanol instead of water, resulting in direct trapping of dioxonium **99** as orthoester **133** (Scheme 2.10).



Scheme 2.10 Direct trapping of dioxonium **99** with methanol to orthoester **133**.

Orthoester **133** was unstable to purification, but its proposed structure was tentatively assigned based on a signature quaternary carbon signal at 120.5 ppm in the DEPT-Q spectrum of the crude reaction mixture, which is characteristic of an orthoester carbon (Figure 2.21). In addition, the ^{1}H NMR spectrum of the crude reaction mixture containing **133** was comparable to that of a structurally related orthoester **136** in the literature (Figure 2.21. See Appendix 9.3 for ^{1}H and ^{13}C NMR spectra of the crude reaction mixture).[54]

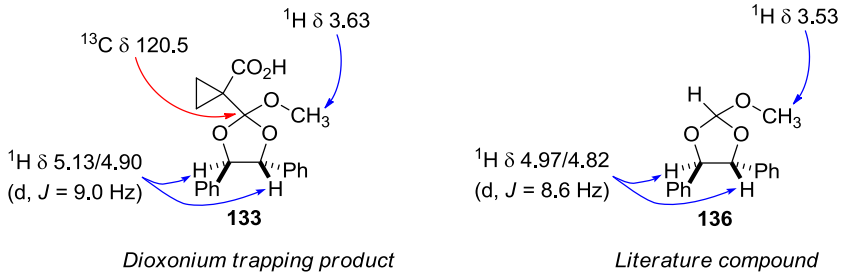
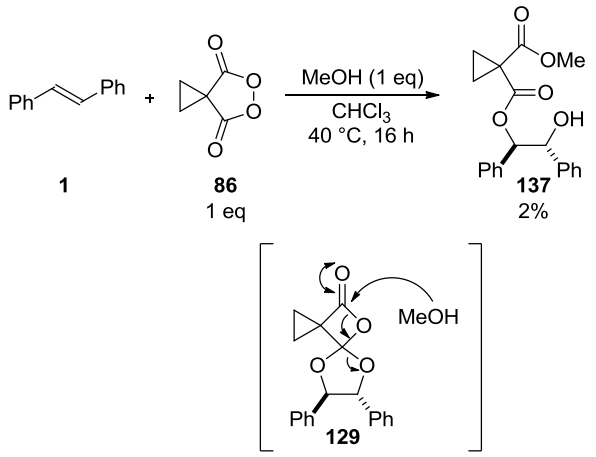


Figure 2.21 Comparison of proposed dioxonium trapping product **133** and literature orthoester **136**.

Treatment of crude orthoester **133** with an ether solution of diazomethane, generated *in situ* from *N*-nitroso-*N*-methylurea **134**,[55] allowed for purification and full characterisation of orthoester **135** (41% over two steps, Scheme 2.10. See Appendix 9.3 for ^{1}H and ^{13}C NMR spectra).

Significantly, a small amount of methyl ester **137** (~2%) was observed in the ^{1}H NMR spectrum of the crude reaction mixture of orthoester **133** following the reaction in Scheme 2.10. This was confirmed by independent synthesis of **137** by methylation of the corresponding carboxylic acid **93** isolated from the reaction of peroxide **86** with *trans*-stilbene **1** (see Experimental section for details). Methyl ester **137** potentially arises from methanol attack on spirocycle **129**, therefore supporting the existence of **129** (Scheme 2.11). However, the small quantity of methyl ester **137** observed suggests that dioxonium **99** is significantly more reactive to nucleophiles.

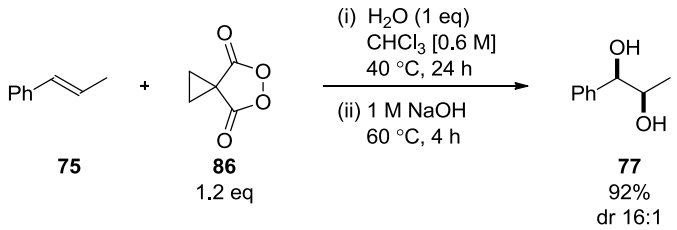


Scheme 2.11 Formation of methyl ester **137** from spirocycle **129**.

2.10 Understanding Diastereoselectivity

A major benefit of using cyclopropyl malonoyl peroxide **86** in the dihydroxylation of alkenes over other metal-free *syn*-dihydroxylation methods is the high level of diastereoselectivity achieved in the diol products (see Chapter 3). Although highly stereoselective, it is not stereospecific, which is consistent with the reaction proceeding in a stepwise manner *via* carbocation intermediate **98**.

Syn-1,2-diphenylethane-1,2-diol **66** is produced from *trans*-stilbene **1** with excellent diastereoselectivity (33:1 *syn*:*anti*), so gaining mechanistic information on the minor *anti*-diol from ^{18}O-labelling studies *via* NMR spectroscopy or mass spectrometry would be challenging. To probe the mechanism of *anti*-diol formation, β–methylstyrene **75** was selected as a suitable substrate due to the reduced diastereomeric ratio of 16:1 *syn*:*anti* observed under standard dihydroxylation conditions (Scheme 2.12).



Scheme 2.12 Dihydroxylation of β–methylstyrene **75**.

Three potential pathways (Paths B, C and E) accounting for the formation of the minor *anti*-diastereoisomer **140** in the dihydroxylation of **75** are outlined in Figure 2.22.

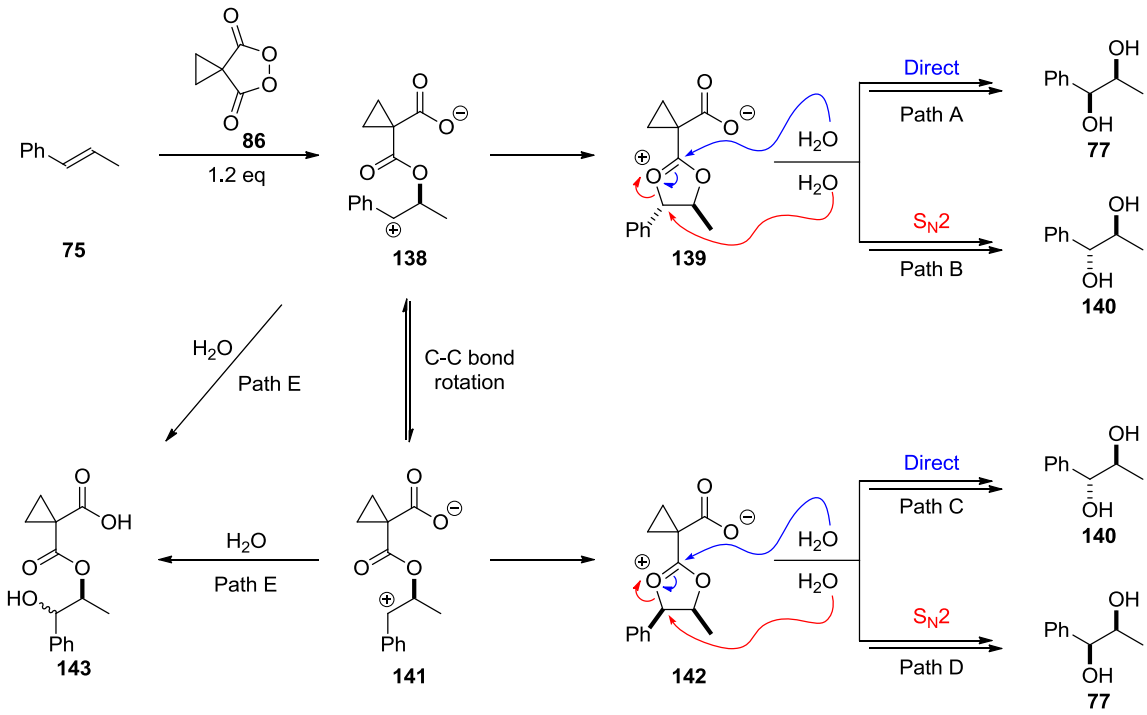


Figure 2.22 Origins of diastereoselectivity.

As previously discussed (Chapter 2.9), dioxonium **139** can be attacked by a molecule of water directly, resulting in *syn*-diol **77** after basic hydrolysis (Path A). A minor pathway could involve S_N2 attack by a molecule of water on dioxonium **139** at the benzylic position, resulting in *anti*-diol **140** after basic hydrolysis (Path B). Alternatively, bond rotation around the new C–C σ-bond of carbocation **138**, followed by ring-closure, will give dioxonium **142**. Attack by a molecule of water on dioxonium **142** directly will produce *anti*-diol **140** upon basic hydrolysis (Path C), whereas S_N2 attack by water will lead to *syn*-diol **77** (Path D) after hydrolysis. Finally, carbocation **138** (or **141**) could be attacked by water directly leading to a mixture of *syn*- and *anti*-diols **77** and **140** (Path E) after hydrolysis of **143**.

The dihydroxylation reaction in Scheme 2.12 was performed using one equivalent of $^{18}OH_2$, and diols **77** and **140** separated by semi-preparative HPLC. High resolution mass

spectrometric analysis of diastereomerically pure diols **77** and **140** revealed that *syn*-diol **77** contained 0% ^{18}O-label, whereas *anti*-diol **140** contained around 10% ^{18}O-label (Figure 2.23. See Appendix 9.2 for high resolution mass spectra). The ratio of *syn*-diol **77** to *anti*-diol **140** was 16:1 under the standard dihydroxylation conditions, thus 10% ^{18}O-label incorporation into *anti*-diol **140** equates to only 0.6% ^{18}O-label incorporation into the total diol product. This result strongly suggests that the oxygen atom from a water molecule is essentially not incorporated into the diol product.

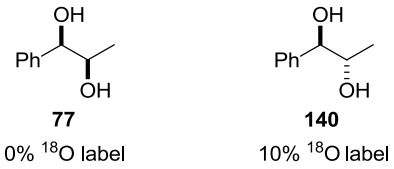


Figure 2.23 ^{18}O incorporation into *syn*- and *anti*-diols **77** and **140** from β–methylstyrene **175** using $^{18}OH_2$ (1 eq).

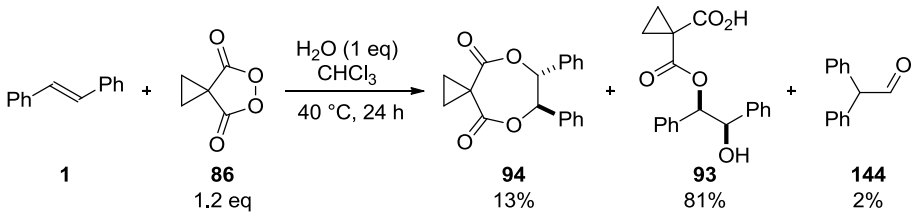
If *anti*-diol **140** formed exclusively by direct attack of $^{18}OH_2$ on carbocations **138** or **141** (Path E) then 100% ^{18}O-label incorporation would be expected in *anti*-diol **140**, which was not observed. Similarly, if *anti*-diol **140** formed exclusively by S_N2 attack of $^{18}OH_2$ on dioxonium **139** (Path B), then 100% ^{18}O-label incorporation would also be expected in *anti*-diol **140**. As 90% of *anti*-diol **140** contains no ^{18}O-label, it suggests that Path C involving C–C σ bond rotation followed by ring closure to dioxonium **142**, then direct attack by water is the major pathway to *anti*-diol **140**, as this route does not introduce ^{18}O-label into *anti*-diol **140**.

The small amount (10%) of ^{18}O-label identified in *anti*-diol **140** implies that S_N2 attack by $^{18}OH_2$ (Paths B and D), or direct addition of $^{18}OH_2$ to carbocations **138** or **141** (Path E), must also be operating to a minor extent. Both of these pathways would introduce ^{18}O-label into *anti*-diol **140** in addition to a small amount of ^{18}O-label into *syn*-diol **77**. However, as the ratio of *syn*-diol **77** to *anti*-diol **140** was 16:1, the negligible amount of labelled *syn*-diol **77** would be almost impossible to detect my mass spectrometry.

2.11 Competing Reaction Pathways

2.11.1 Semipinacol Rearrangement

In the dihydroxylation of *trans*-stilbene **1** using cyclopropyl malonoyl peroxide **86**, ester **93** and 7-membered ring **94** are produced in a combined 94% yield before hydrolysis. Close analysis of the crude reaction mixture containing **93** and **94** by ^{1}H NMR spectroscopy also revealed a small amount (~2%) of aldehyde **144** (Scheme 2.13).



Scheme 2.13 Identification of **144** in the dihydroxylation of *trans*-stilbene **1**.

Aldehyde **144** could form *via* semipinacol rearrangement[56] of carbocation **98** whereby irreversible loss of CO_2 drives the migration process, with loss of cyclopropyl ketene **145** (Figure 2.24).

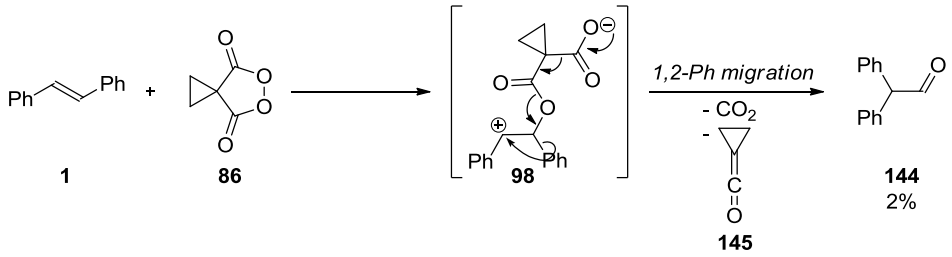


Figure 2.24 Semipinacol rearrangement to form aldehyde **144**.

It was proposed that increasing the cycloalkane ring size on the malonoyl peroxide may favour decarboxylation, therefore increasing the extent of semipinacol rearrangement. The reaction was performed using cyclopentyl malonoyl peroxide **87**, and a 2.5 fold increase in the quantity of rearrangement product **144** (5%) was observed (Figure 2.25).

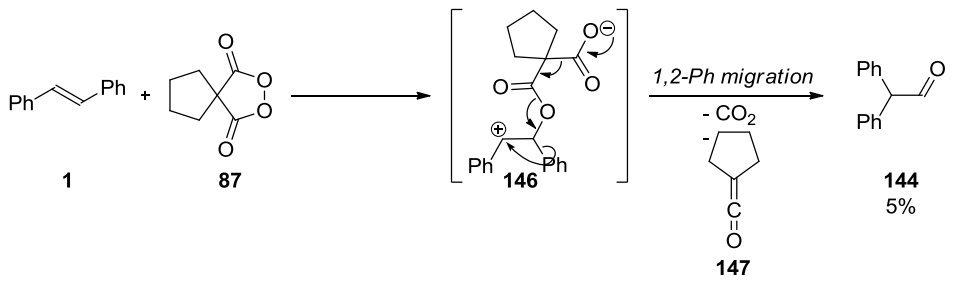
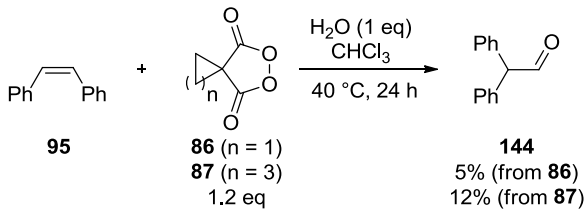


Figure 2.25 Increased semipinacol rearrangement product using cyclopentyl malonoyl peroxide **87**.

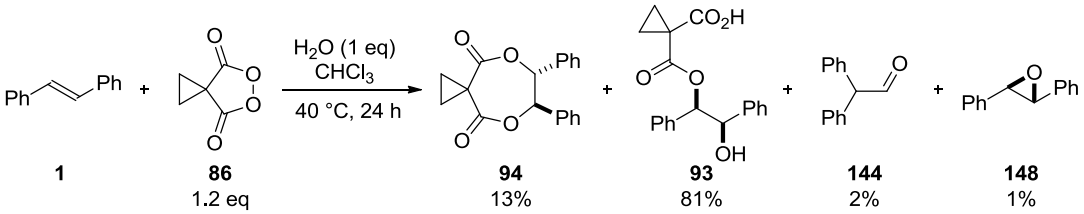
Interestingly, subjecting *cis*-stilbene **95** to the dihydroxylation reaction conditions using cyclopropyl malonoyl peroxide **86** afforded higher levels of aldehyde **144** (5%, Scheme 2.14) than the analogous reaction with *trans*-stilbene **1** (2%, Scheme 2.13). Employing cyclopentyl malonoyl peroxide **87** in the reaction with *cis*-stilbene **95** also resulted in a 2.5 fold increase (12%, Scheme 2.14) in semipinacol rearrangement product **144** over when *trans*-stilbene **1** was used (5%, Figure 2.25).



Scheme 2.14 Increased semipinacol rearrangement product **144** from *cis*-stilbene **95**.

2.11.2 Epoxide Formation

The reaction of cyclopropyl malonoyl peroxide **86** with *trans*-stilbene **1** also resulted in a very small amount (~1%) of epoxide **148** (Scheme 2.15).



Scheme 2.15 Epoxide **148** formation in the reaction of peroxide **86** with *trans*-stilbene **1**.

Epoxide **148** was present as a single diastereoisomer before treatment with 1 M sodium hydroxide. In solution, the ratio of **94**:**93**:**144**:**148** did not change over 48 hours suggesting that the compounds did not interconvert and were all formed by discrete mechanisms. A possible mechanism of epoxide **148** formation consistent with these two observations involves attack of water on peroxide **86** to form peracid **150**, which subsequently epoxidises *trans*-stilbene **1** stereospecifically (Figure 2.26).

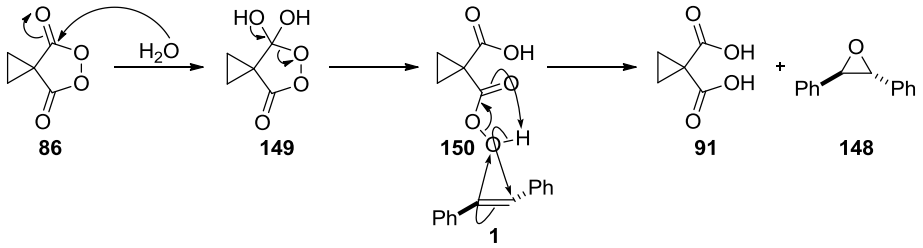


Figure 2.26 Potential mechanism of epoxide **148** formation.

2.12 Mechanism Summary

The current mechanistic understanding of the metal-free *syn*-dihydroxylation of *trans*-stilbene **1** using cyclopropyl malonoyl peroxide **86** is presented in Figure 2.27.

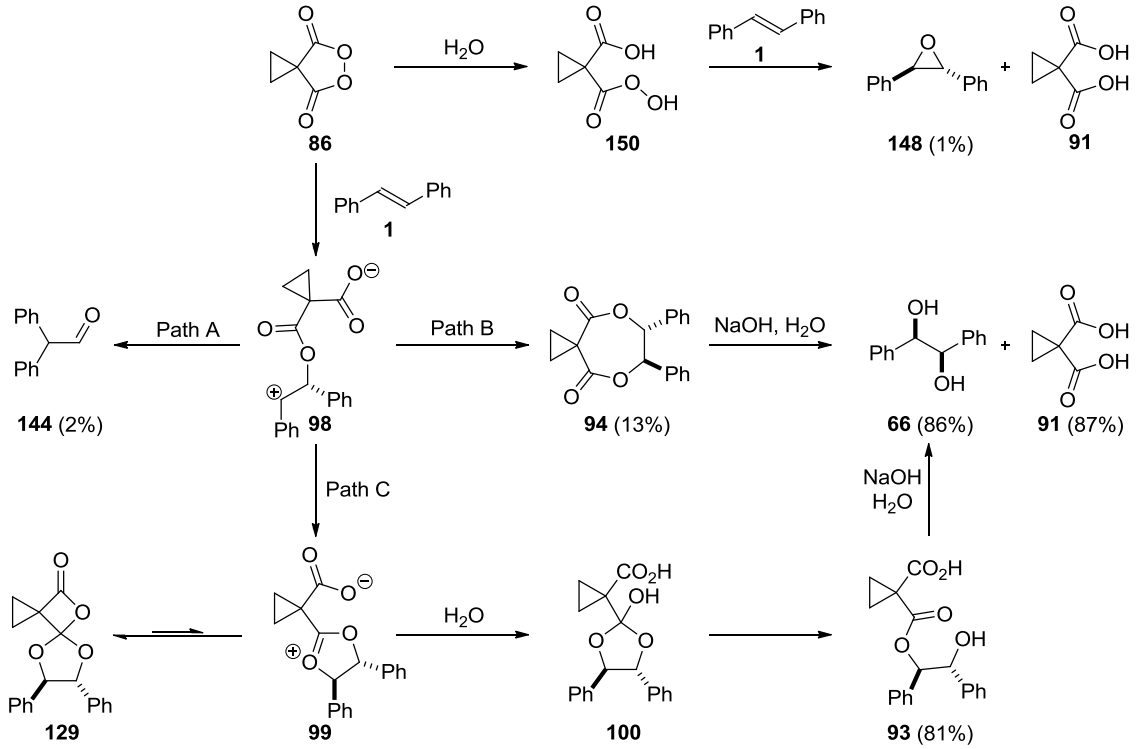


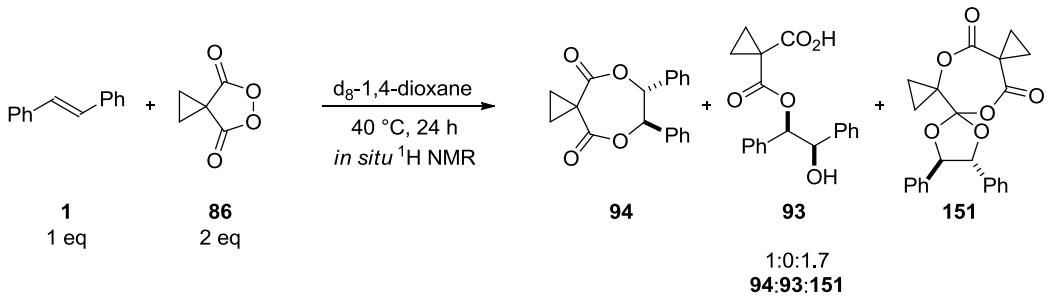
Figure 2.27 Mechanism of the cyclopropyl malonoyl peroxide **86** dihydroxylation reaction.

Cyclopropyl malonoyl peroxide **86** is attacked by *trans*-stilbene **1** *via* an ionic mechanism to form zwitterion **98** which has three fates. A small amount (~2%) undergoes a decarboxylative semipinacol rearrangement to give aldehyde **144** (Path A). A significant amount (13%) directly ring-closes to afford 7-membered ring **94** (Path B), but the majority (81%) ring-closes to dioxonium **99** (Path C), which is in equilibrium with lactone **129**. Direct addition of water to dioxonium **99** leads to observed ester **93** *via* dioxolane **100**. Basic hydrolysis of the crude reaction mixture gives *syn*-diol **66** (86%) and diacid **91** (87%), which can be recovered and converted back to peroxide **86**. The small amount of *anti*-diol observed in the dihydroxylation reaction has been shown to primarily arise from C–C σ-bond rotation in zwitterion **98**. Additionally, a small amount of peroxide **86** (~1%) is attacked by water resulting in peroxy acid **150** which reacts with *trans*-stilbene **1** to form epoxide **148**.

2.13 Anhydrous Reaction Conditions

It was desirable to force the reaction to proceed *via* a single intermediate to obtain maximum control. Therefore, it was proposed that under anhydrous conditions the reaction may favour 7-membered ring **94** formation over hydroxyester **93**, as **94** does not require a molecule of water to form, whereas hydroxyester **93** does.

Trans-stilbene **1** (1 eq) was treated with cyclopropyl malonoyl peroxide **86** (2 eq) in anhydrous dioxane at 40 ^{o}C and the reaction monitored by *in situ* ^{1}H NMR spectroscopy.



Scheme 2.16 Reaction of *trans*-stilbene **1** with peroxide **86** under anhydrous reaction conditions.

As expected, no hydroxyester **93** was observed and 7-membered ring **94** was present. Interestingly, the major product was orthoester **151** (1:1.7 **94**:**151**). When a nucleophile such as water (or methanol) is present in the reaction mixture, dioxonium **99** is rapidly attacked to produce a neutral molecule such as **100** (Figure 2.27). However, it appears that when no adequate nucleophile is present, dioxonium **99** decarboxylates to generate highly nucleophilic dioxolane **152** which rapidly attacks a second equivalent of peroxide **86** to form **153** (Figure 2.28). The carboxylate group then cyclises onto the dioxonium moiety to generate neutral orthoester **151**.

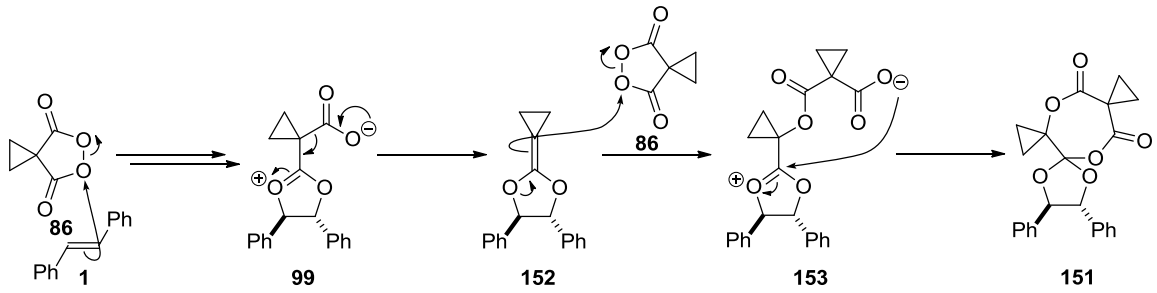


Figure 2.28 Formation of orthoester **151** under anhydrous reaction conditions.

Unfortunately, orthoester **151** was very unstable and could not be isolated, but its proposed structure is consistent with analysis of the ^{1}H and ^{13}C NMR data, the key resonances for which are shown in Figure 2.29 (see Appendix 9.3 for ^{1}H NMR and ^{13}C DEPT-Q spectra). To gain additional evidence for the structure of orthoester **151**, three separate nucleophiles were added to the reaction mixture after formation of **151**, in an effort to form differentiated isolable products.

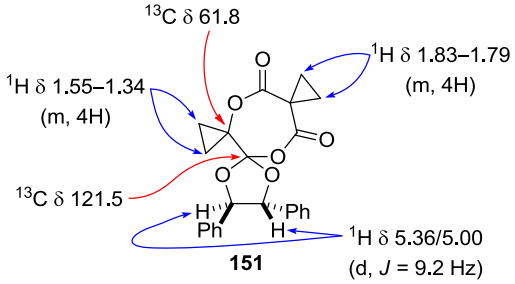
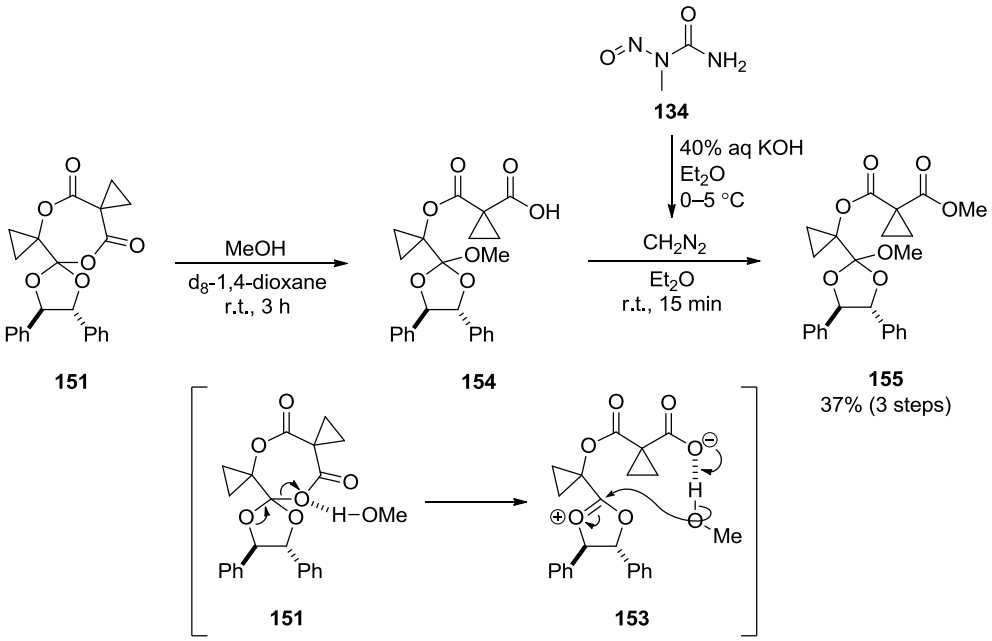


Figure 2.29 Key NMR resonances for proposed orthoester **151**.

2.13.1 Addition of Methanol to Orthoester 151

Addition of methanol to crude orthoester **151** resulted in a different orthoester **154**, which was again consistent with ^{1}H and ^{13}C NMR data but unstable to isolation (Scheme 2.17). Treatment of the crude reaction mixture containing **154** with diazomethane, generated from *N*-nitroso-*N*-methylurea **134**, produced orthoester **155** which proved stable to isolation and was fully characterised (37% over three steps).

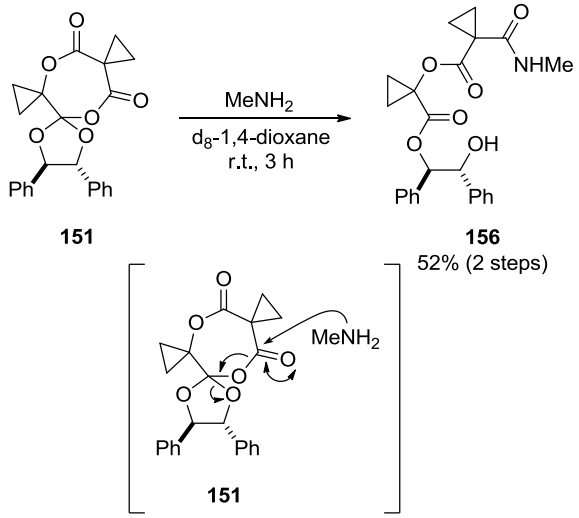


Scheme 2.17 Treatment of crude orthoester **151** with methanol.

The formation of **154** is consistent with the acid-sensitive orthoester moiety of **151** undergoing methanolysis: expelling the carboxylate group, followed by rapid attack of methanol on dioxonium **153** to form orthoester **154**.

2.13.2 Addition of Methylamine to Orthoester 151

Addition of excess methylamine to crude orthoester **151** resulted in amide **156** in 52% yield over two steps (Scheme 2.18).

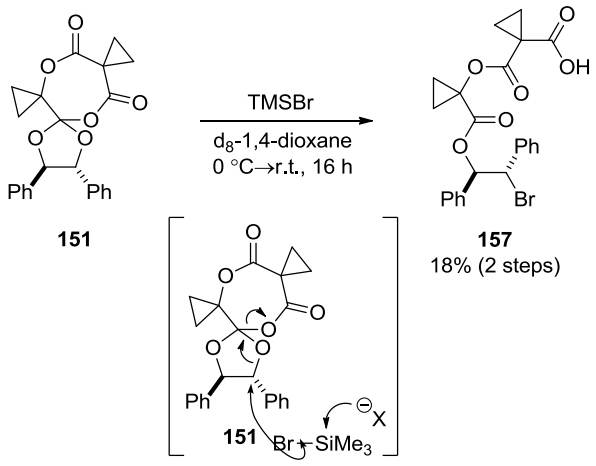


Scheme 2.18 Treatment of crude orthoester **151** with methylamine.

Attack of methylamine on the ester functional group, instead of opening the orthoester region as when methanol was employed, is consistent with the increased nucleophilicity of methylamine over methanol, and the substantially weaker N–H···O hydrogen-bond strength (2 kcal) *versus* O–H···O hydrogen-bond strength (5 kcal).[57]

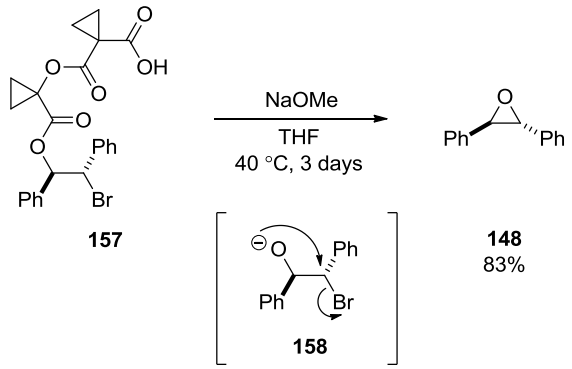
2.13.3 Addition of TMS-Bromide to Orthoester 151

Remarkably, addition of TMS-bromide resulted in a third mode of reactivity of orthoester **151** with a nucleophile.



Scheme 2.19 Treatment of crude orthoester **151** with TMS bromide.

TMS-bromide opened orthoester **151** *via* S_N2 attack of bromide on the benzylic position, resulting in *anti*-oxybromination product **157** in 18% yield over two steps (Scheme 2.19). The reason for TMS-bromide attacking in this position is not currently understood, however it presents opportunities for stereoselective *anti*-difunctionalisation of alkenes (and overall *syn*-addition by double S_N2 inversion) using cyclopropyl malonoyl peroxide **86**. The relative stereochemistry of oxybromination product **157** was confirmed by treatment of **157** with sodium methoxide in anhydrous THF, leading to epoxide **148** in 83% yield (Scheme 2.20).



Scheme 2.20 Hydrolysis of *anti*-oxybromination product **157** to epoxide **148**.

Treatment of proposed orthoester **151** with methanol, methylamine and TMS-bromide resulted in three different modes of reactivity. However, all of the isolated products **155–157** were consistent with the suggested initial orthoester structure **151**, thereby providing strong evidence for its existence and confirming the operation of a different dioxygenation reaction mechanism under anhydrous conditions.

Employing alternative malonoyl peroxides in this novel transformation may help to develop these interesting preliminary results further under anhydrous conditions. Decarboxylation occurs more readily a with larger cycloalkane ring on the malonoyl peroxide scaffold, so use of a peroxide such as cyclopentyl malonoyl peroxide **87** may favour decarboxylation in dioxonium **146**, resulting in more orthoester **160** to undergo further transformation.

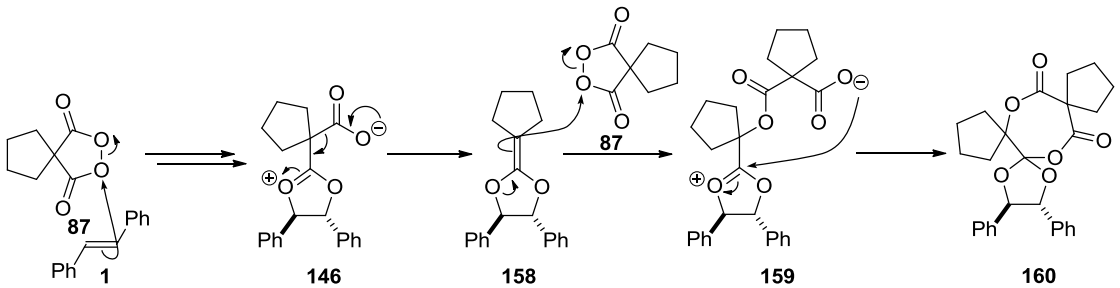
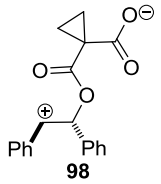


Figure 2.30 Predicted mechanistic course for the reaction of cyclopentyl malonoyl peroxide **87** and *trans*-stilbene **1** under anhydrous conditions.

2.14 Conclusions

An efficient, scalable and simple route to cyclopropyl malonoyl peroxide **86** has been established. Quantitative and qualitative tests on the physical properties of peroxide **86** have suggested it is relatively stable to shock and direct heating, but caution is still required due to the inherent unpredictability of peroxides. Isotopic labelling studies have indicated that homolytic fission of the peroxide bond does not readily occur in solid state or in solution.

Significantly, this work provided the first evidence that malonoyl peroxides react with alkenes *via* an ionic mechanism, and kinetic information has been obtained on the transformation. Hammett analysis has provided evidence for a stepwise mechanism proceeding through key carbocation **98**, and *anti*-diol formation has been shown to occur primarily through C–C σ-bond rotation in **98**. Through multiple isotopic labelling studies, NMR investigations and trapping experiments, a consistent mechanism following the fate of carbocation **98** to the isolated products **93** and **94** has been proposed. Two minor competing reaction pathways involving semipinacol rearrangement to aldehyde **144**, and peracid **150** mediated epoxide **148** formation have also been identified.



98

Under anhydrous conditions an alternative decarboxylative mechanism operates which consumes two equivalents of peroxide **86** resulting in novel orthoester **151**. Preliminary investigations have determined that orthoester **151** can undergo a variety of transformations with different nucleophiles, opening new research avenues for both the *syn*- and *anti*-difunctionalisation of alkenes.

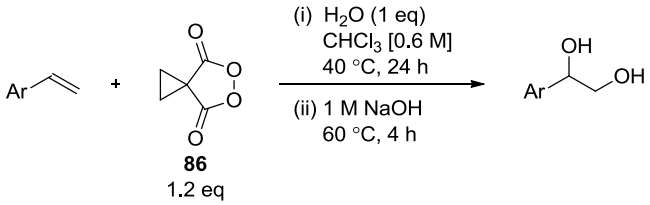
Knowledge gained from this mechanistic investigation provided the foundations for the methodology development discussed herein.

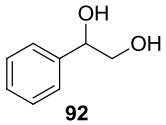
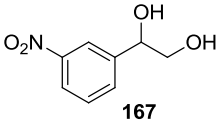
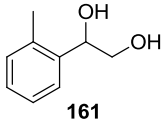
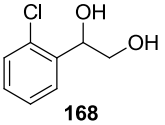
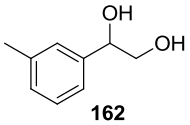
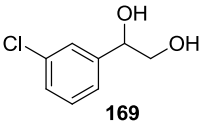
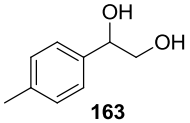
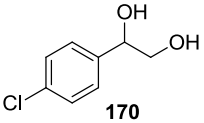
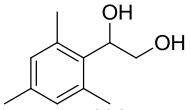
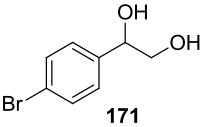
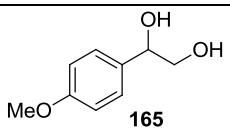
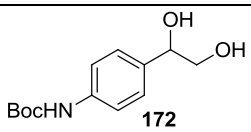
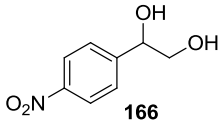
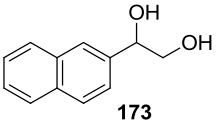
Chapter 3: Substrate Scope

3 Substrate Scope

3.1 1-Styrene Derivatives

Styrene derivatives were subjected to the optimised dihydroxylation conditions to investigate electronic and steric effects on the dihydroxylation reaction (Table 3.1).

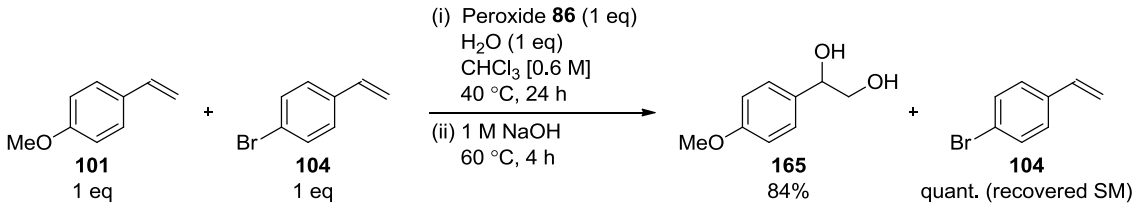


Entry	Product	Yield[a]	Entry	Product	Yield[a]
1	 **92**	89%	8	 **167**	63%[b]
2	 **161**	83%	9	 **168**	82%
3	 **162**	83%	10	 **169**	70%[c]
4	 **163**	90%	11	 **170**	86%
5	 **164**	91%	12	 **171**	86%
6	 **165**	86%	13	 **172**	38%
7	 **166**	<5%[b]	14	 **173**	78%

[a] Isolated yield. All reactions run in duplicate. [b] Peroxide **86** (2 eq), 60 °C, 72 h. Reaction did not reach completion. [c] Peroxide **86** (1.8 eq), 60 °C, 50 h. Reaction did not reach completion.

Table 3.1 1-Styrene derivatives in the dihydroxylation reaction.

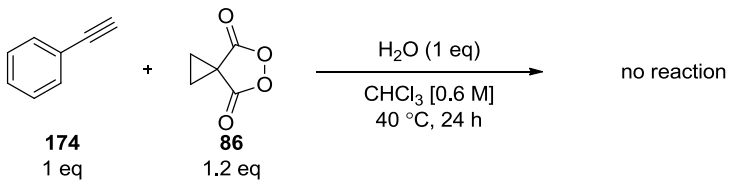
Generally, styrene derivatives proved effective in the cyclopropyl malonoyl peroxide **86** dihydroxylation reaction. Substitution on any position of the phenyl ring was tolerated (Table 3.1, Entries 2–4), and the reaction worked well with sterically hindered styrenes (Table 3.1, Entry 5). Due to the electrophilic nature of peroxide **86**, the reaction was suited to nucleophilic alkenes (Table 3.1, Entry 6) and proved ineffective with strongly electron-deficient alkenes (Table 3.1, Entry 7). Although this limited the scope of the reaction, it provided a highly chemoselective metal-free dihydroxylation reagent for the most electron-rich alkene in a molecule, unlike the complementary iodine-based dihydroxylation reagents (Chapter 1.1). This was confirmed by a competitive dihydroxylation experiment between 4-methoxystyrene **101** and 4-bromostyrene **104** (Scheme 3.1). In the mixed alkene system, only 4-methoxystyrene **101** reacted with peroxide **86** and 4-bromostyrene **104** was recovered quantitatively.



Scheme 3.1 Competitive dihydroxylation between 4-methoxy- **101** and 4-bromostyrene **104**.

Employing harsher reaction conditions (2 eq **86**, 60 ^{o}C, 3 days) allowed mildly electron-deficient alkenes to undergo dihydroxylation, albeit at a substantially reduced rate (Table 3.1, Entry 8). A range of halide substituents was tolerated in any position on the phenyl ring, providing a handle for further functionalisation of the diol products (Table 3.1, Entries 9–12). Boc-protected aminostyrene underwent dihydroxylation in a reduced 38% yield (Table 3.1, Entry 13), but the precise reason for this is not yet fully understood. Vinylnaphthalene was also successfully dihydroxylated to **173** in good yield (78%, Table 3.1, Entry 15), showing that extended π systems are also tolerated.

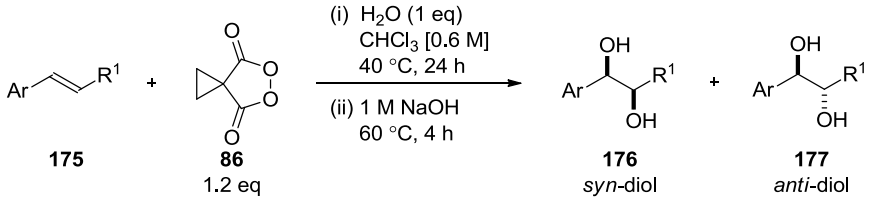
Starting material was recovered quantitatively in the reaction of peroxide **86** with phenylacetylene **174** over a period of 24 hours at 40 ^{o}C, indicating that the dihydroxylation reaction is chemoselective for alkenes over alkynes, consistent with the reduced reactivity of alkynes (Scheme 3.2).

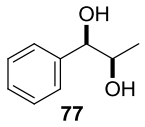
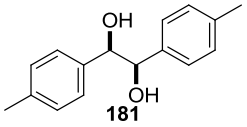
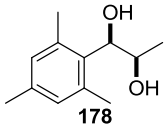
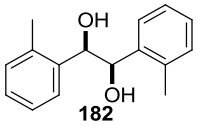
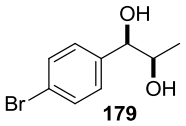
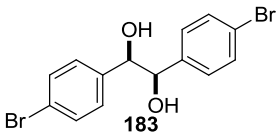
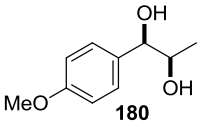
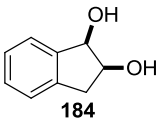
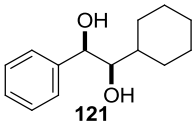
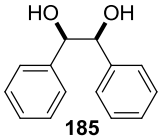
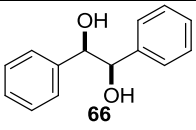
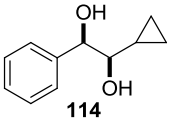


Scheme 3.2 Treatment of phenylacetylene **174** with peroxide **86**.

3.2 1,2-Disubstituted Styrene Derivatives

A range of 1,2-disubstituted styrene derivatives **175** was subjected to the dihydroxylation conditions to explore diastereoselectivity of the reaction, as *syn*- **176** and *anti*-diol **177** formation was possible with this class of substrate (Table 3.2).



Entry	Product	Yield[a]	dr[b]	Entry	Product	Yield[a]	dr[b]
1	 **77**	92%	16:1	7[c]	 **181**	84%	34:1
2[c]	 **178**	93%	>50:1	8	 **182**	93%	39:1
3[c]	 **179**	86%	13:1	9[c]	 **183**	85%	30:1
4	 **180**	78% 82%[d]	5.5:1 10:1[d]	10	 **184**	52%	>50:1
5[c]	 **121**	90%	25:1	11[e]	 **185**	84%	3.7:1
6	 **66**	86%	33:1	12[c,f]	 **114**	85%	2.5:1

[a] Isolated yield. Mixture of diastereoisomers. All reactions run in duplicate. [b] *Syn*:*anti*. Determined by ^{1}H NMR analysis of the crude reaction mixture.[c] Starting alkene was synthesised. See experimental section for details. [d] Reaction performed at 0 ^{o}C. [e] From *cis*-stilbene **95**. [f] Alkene **113** starting material was a mixture of isomers (3:1 *E*:*Z*).

Table 3.2 Dihydroxylation of 1,2-disubstituted alkenes **175**.

β-Methylstyrene **75** reacted with peroxide **86** to produce diol **77** (Table 3.2, Entry 1) in excellent yield (92%) and diastereoselectivity (16:1 *syn*:*anti*). Incorporation of steric bulk on the phenyl ring (Table 3.2, Entry 2) improved diastereoselectivity, resulting in observation of only the *syn*-isomer **178**. This is consistent with the reaction proceeding through a discrete carbocation intermediate (see Chapter 2.10) as C–C σ-bond rotation in **186** would be disfavoured with increasing size of Ar and R^1.

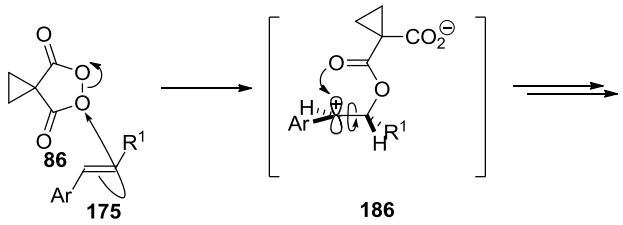


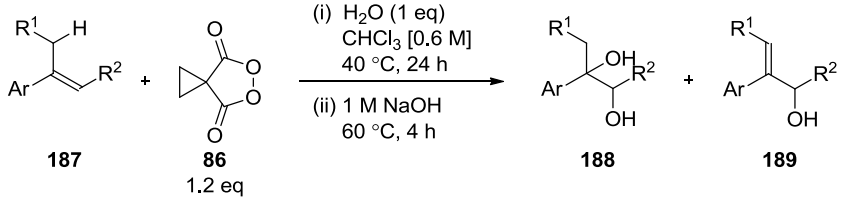
Figure 3.1 Diastereoselectivity arises primarily from bond rotation in zwitterion **186**.

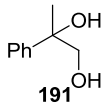
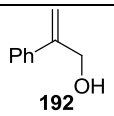
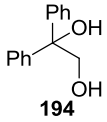
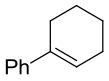
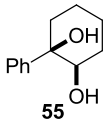
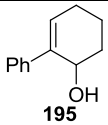
A *para*-bromo substituent (Table 3.2, Entry 3) had negligible effect on yield or diastereoselectivity (86%, 13:1 *syn*:*anti*) compared to β-methylstyrene, consistent with the bromine atom exerting opposing inductive and mesomeric electronic effects on the developing carbocation **186**. Conversely, incorporation of a *para*-methoxy group (Table 3.2, Entry 4) caused the diastereoselectivity to significantly decrease (5.5:1 *syn*:*anti*), due to stabilisation of the developing positive charge in **186**. Performing the reaction at reduced temperature (0 ^{o}C) increased the diastereoselectivity to 10:1 *syn*:*anti*.

Increasing the size of the substituent on the β-position of the alkene also increased diastereoselectivity. T*rans*-stilbene derivatives generally underwent dihydroxylation with outstanding diastereoselectivities in excess of 30:1 *syn*:*anti* (Table 3.2, Entries 5–9). Reaction with a cyclic alkene such as indene resulted in exclusive formation of the *cis*-diol **184** (Table 3.2, Entry 10), as bond rotation in the intermediate **186** is not possible. Significantly, *cis*-stilbene **95** resulted in the corresponding *syn*-addition product **185** (Table 3.2, Entry 11), albeit with reduced selectivity (84%, 3.7:1).

3.3 1,1-Disubstituted Styrene Derivatives

Interestingly, 1,1-disubstituted alkenes **187** containing an allylic hydrogen adjacent to the developing carbocation produced diol **188** and a significant amount of allylic alcohol **189** after hydrolysis.



Entry	Starting alkene **187**	Diol product **188**	Yield[a]	Allylic alcohol product **189**	Yield[a]
1	 **190**	 **191**	48%	 **192**	16%
2	 **193**	 **194**	35%	N/A	N/A
3	 **53**	 **55**	36%	 **195**	12%

[a] Isolated yield. All reactions run in duplicate.

Table 3.3 Diol **188** and allylic alcohol **189** products from alkenes containing allylic hydrogen.

α-Methyl styrene **190**, when treated with peroxide **86** under standard conditions, produced diol **191** and allylic alcohol **192** in a 3:1 ratio (48% and 16% yield respectively, Table 3.3, Entry 1). With no allylic hydrogen present, such as in the analogous compound α-phenyl styrene **193** (Table 3.3, Entry 2), the allylic alcohol product cannot form and was therefore not observed. The low yield of diol **194** (35%) results from incomplete conversion due to surprisingly slow reactivity of α-phenyl styrene **193** with peroxide **86**, but no attempt was made to optimise this reaction further. 1-Phenyl-1-cyclohexene **53** also produced a 3:1 ratio of diol **55** to allylic alcohol **195** under standard dihydroxylation conditions (Table 3.3, Entry 3).

Mechanistically, it was proposed that both diol **191** and allylic alcohol **192** form *via* a common intermediate, **196** (Figure 3.2). Zwitterion **196** can either undergo cyclisation, ultimately resulting in dihydroxylation products (Paths A and B), or alternatively **196** can lose a proton to form allylic ester **201**, which releases allylic alcohol **192** upon hydrolysis (Path C).

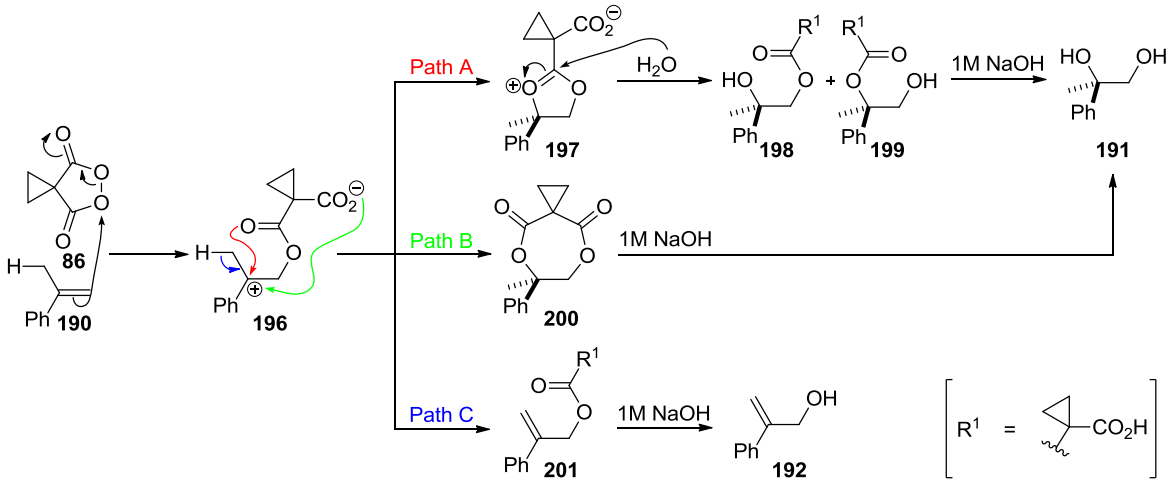
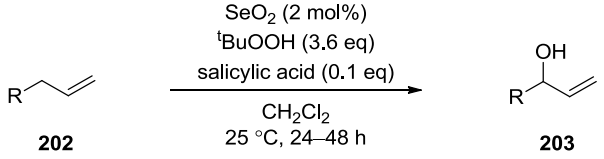


Figure 3.2 Possible competing mechanistic pathways to diol **191** and allylic alcohol **192**.

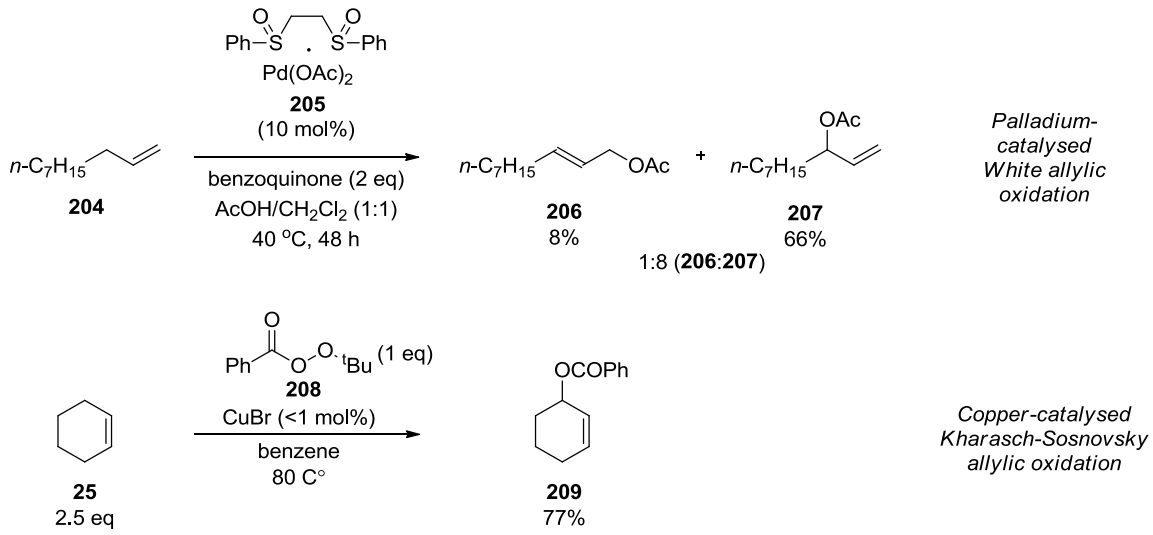
3.3.1 Allylic Oxidation

Allylic alcohols are useful synthetic intermediates in organic synthesis[58] and can be formed directly from alkenes using SeO_2,[59] releasing toxic and often malodorous Se(II) by-products. Sharpless alleviated these issues by developing an SeO_2-catalysed (2 mol%) allylic oxidation procedure employing *tert*-butyl hydrogen peroxide as stoichiometric oxidant (Scheme 3.3).[60]



Scheme 3.3 SeO_2-catalysed allylic oxidation.

There are many methods of non-direct allylic alcohol formation from alkenes *via* the corresponding allylic ester,[58,61] with the palladium-catalysed White oxidation[62] and variations of the copper-catalysed method developed by Kharasch and Sosnovsky[63] being most widely adopted (Scheme 3.4).

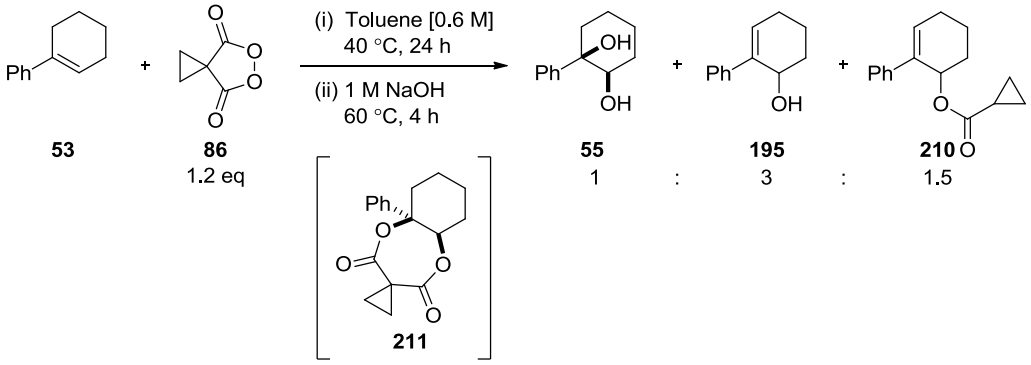


Scheme 3.4 White allylic oxidation (top) and Kharasch-Sosnovsky allylic oxidation (bottom).

The White allylic oxidation involves treatment of an α-alkene **204** with commerically available bis-sulfoxide-palladium White catalyst **205** (10 mol%) and benzoquinone (2 eq) in an $AcOH/CH_2Cl_2$ mixture (1:1) *via* a π-allyl palladium complex,[62b] to regioselectively produce branched allylic acetate products **207**. Alternatively, performing the reaction in a 1:1 mixture of AcOH/DMSO using $Pd(OAc)_2$ (10 mol%) regioselectively produces linear allylic acetates **206**.[62a] An asymmetric variant of the reaction has also been achieved employing chiral Lewis acid additives.[62c] The Kharasch–Sosnovsky reaction achieves allylic oxidation of alkenes *via* a radical mechanism using *tert*-butyl perester **208** in the presence of a copper or cobalt salt to give allylic benzoates **209** in good yield. Significantly, asymmetric variants of the reaction, primarily employing C_2-symmetric bis(oxazoline) or proline-derived ligands, has been achieved.[58,61,64]

A non-toxic, metal-free method of allylic alcohol formation from alkenes, without the possibility of over oxidation to the corresponding α,β-unsaturated carbonyl compound, could be of wider interest to the synthetic chemist. In an effort to favour allylic oxidation over dihydroxylation using cyclopropyl malonoyl peroxide **86**, a small optimisation study was performed with 1-phenyl-1-cyclohexene **53**.

An equivalent of water is required for the major dihydroxylation pathway using cyclopropyl malonoyl peroxide **86** (Path A, Figure 3.2), whereas no water is required for allylic alcohol **195** formation (Path C, Figure 3.2). Therefore, it was reasoned that under anhydrous conditions allylic oxidation may be favoured over dihydroxylation. It was also proposed that use of a less polar solvent such as toluene would favour Path C over Path A (Figure 3.2). Gratifyingly, changing the reaction solvent from wet chloroform to anhydrous toluene resulted in a reversal of selectivity, delivering diol **55** and allylic alcohol **195** in a ratio of 1:3. With no water added, presumably *cis*-diol **55** arises from formation of 7-membered ring **211** (Scheme 3.5).



Scheme 3.5 Allylic oxidation using cyclopropyl malonoyl peroxide **86**.

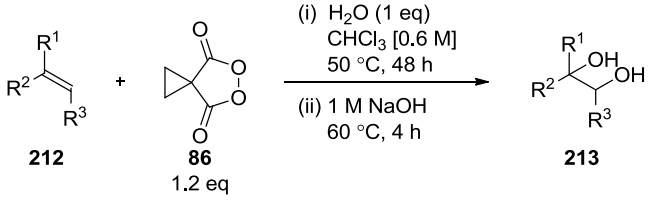
Allylic ester **210** was also identified in the crude reaction mixture post-hydrolysis. Decarboxylated allylic ester **210** was isolated and found to hydrolyse very slowly under the typical dihydroxylation conditions (1 M NaOH, 60 ^{o}C, 4 h). However, elevated temperature (100 ^{o}C) and prolonged reaction time (18 h) achieved full hydrolysis to allylic alcohol **195**. Employing the harsher hydrolysis conditions to the crude reaction mixture following the protocol in Scheme 3.5 resulted in an overall 1:4.5 ratio of diol **55** to allylic alcohol **195** (82% yield).

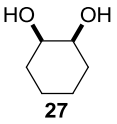
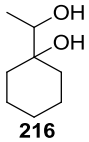
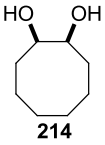
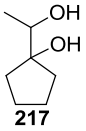
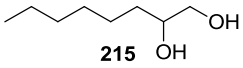
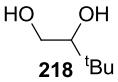
It was thought that addition of a base would accelerate deprotonation of zwitterion **196** (Figure 3.2), thereby increasing allylic ester **201** formation. Amine and hydroxide bases were unsuitable due to reaction with peroxide **86**. Carbonate bases were identified as potential alternatives, with caesium carbonate being favoured due to its solubility in organic solvents. However, employing a stoichiometric quantity of caesium carbonate resulted in only low conversion after 4 days. Control experiments revealed that peroxide **86** was no longer present after 24 hours when in the presence of caesium carbonate, implying a destructive interaction. Sodium carbonate, sodium hydrogen carbonate and potassium carbonate produced the same result. Interestingly, sodium acetate also appeared to shut off the reaction *via* a destructive interaction with peroxide **86**. Other classes of base that are compatible with peroxide **86** need to be identified and explored before it can be established if addition of base to the reaction mixture will enhance selectivity for allylic oxidation over dihydroxylation.

The simple procedure using non-toxic reagents, and requirement for only substrate **187**, oxidant **86** and solvent (toluene) make this a promising allylic oxidation protocol. However, selectivity for allylic oxidation over dihydroxylation needs to be improved, and substrate scope needs to be explored, before this reaction can be considered synthetically useful.

3.4 Aliphatic Alkenes

All of the alkenes examined thus far have contained a phenyl ring to stabilise the developing positive charge in the transition state through resonance delocalisation. A series of unstabilised aliphatic alkenes were subjected to the standard dihydroxylation conditions and the results presented in Table 3.4.



Entry	Product **213**	Yield[a]	Entry	Product **213**	Yield[a]
1	 **27**	trace	4	 **216**	40%
2	 **214**	15% (*syn* only)	5	 **217**	0%
3	 **215**	18%	6	 **218**	0%

[a] Isolated yield. All reactions run in duplicate.

Table 3.4 Dihydroxylation of aliphatic alkenes.

Encouragingly, mono-, di- and tri-substituted aliphatic alkenes successfully underwent dihydroxylation (Table 3.4, Entries 2–4). Generally, yields of diol were reduced from that of styrene-type substrates and mass recovery post-hydrolysis was low. The reactions between peroxide **86** and alkyl-substituted alkenes were considerably slower than with aryl-substituted alkenes so slightly harsher conditions were employed (50 ^{o}C, 48 h). When *cis*-cyclooctene was employed as the substrate (Table 3.4, Entry 2), only a single (*cis*) diastereoisomer of diol product **214** was observed, indicating that the protocol is highly diastereoselective for both stabilised and unstabilised alkenes.

All of the aliphatic alkenes examined (excluding *tert*-butylethylene, Table 3.4, Entry 6) have multiple allylic hydrogen atoms adjacent to the developing carbocation and therefore allylic oxidation products were deemed very likely (see Figure 3.2).

In the reaction of peroxide **86** with cyclohexene (Table 3.4, Entry 1) a substantial amount of an allylic ester **219** was observed. Its presence was confirmed by comparison of key ^{1}H NMR resonances from the crude reaction mixture to that of an analogous allylic acetate **220** from the literature,[65] although attempts to isolate it were unsuccessful (Figure 3.3. See Appendix 9.3 for ^{1}H NMR spectrum of the crude reaction mixture). However, upon basic hydrolysis of the crude reaction mixture only around 2% mass recovery was obtained, probably due to the volatility of the corresponding allylic alcohol.

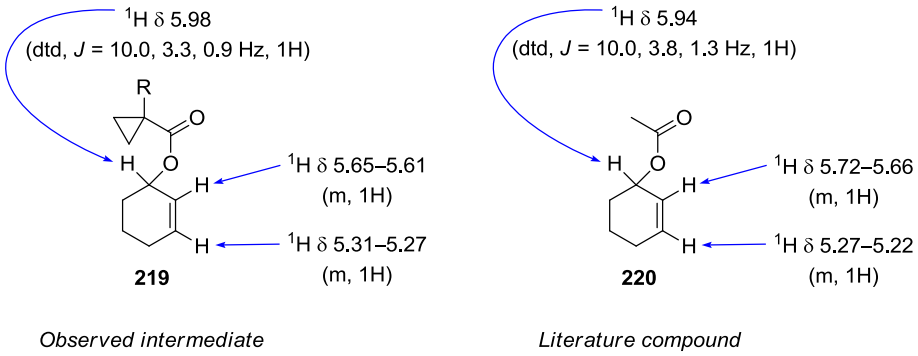
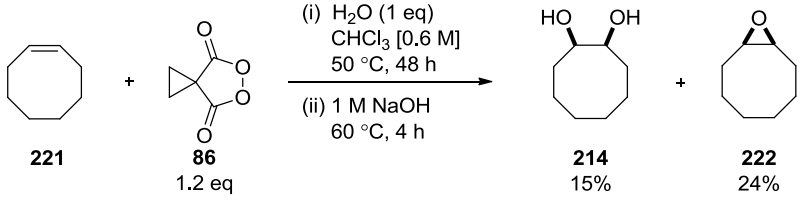


Figure 3.3 Key ^{1}H NMR resonances of observed allylic ester **219** in the oxidation of cyclohexene **25**.

Interestingly, reaction of peroxide **86** with *cis*-cyclooctene **221** (Table 3.4, Entry 2) resulted in epoxide **222** (Scheme 3.5) as the major product (24% yield).



Scheme 3.5 Oxidation of *cis*-cyclooctene **221**.

Importantly, epoxide **222** formation was observed pre-hydrolysis by ^{1}H NMR spectroscopy, and it proved stable to the hydrolysis conditions. This observation is consistent with *in situ* generation of peracid **150**, which subsequently epoxidised alkene **221** (Figure 3.4).

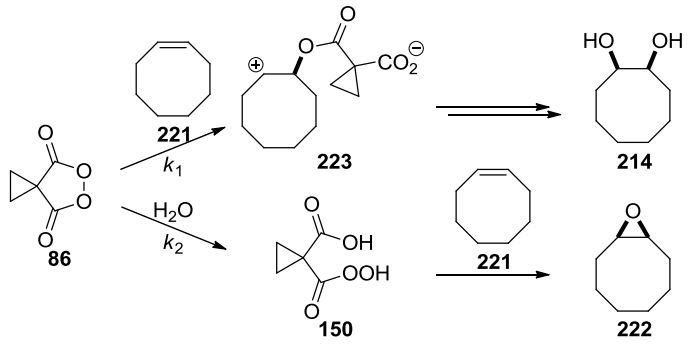


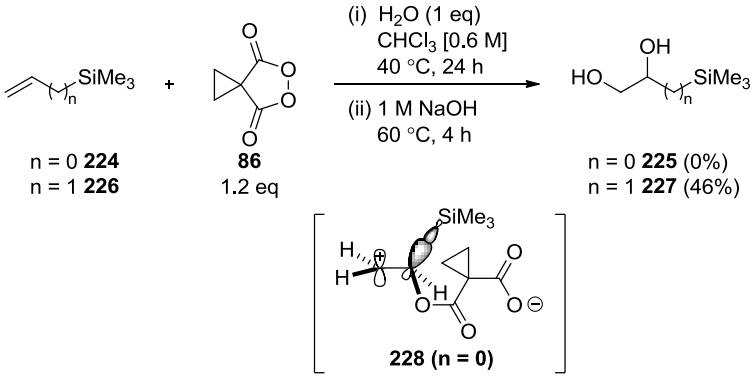
Figure 3.4 Competing pathways to diol **214** and epoxide **222** in *cis*-cyclooctene **221** oxidation.

The approximate 25-fold increase in epoxide formation between *trans*-stilbene **1** (Chapter 2.11.2) and *cis*-cyclooctene **221** (Scheme 3.5) under similar reaction conditions suggested that with poorer nucleophiles such as *cis*-cyclooctene **221**, alkene attack on peroxide **86** is slower than peracid **150** formation ($k_1<k_2$). However, it should be noted that epoxide formation was not observed alongside aliphatic diols **215** and **216**, indicating that the situation may be considerably more complex with this class of substrate.

Only a relatively small sample of aliphatic alkenes were subjected to the dihydroxylation protocol, so understanding of the reaction of peroxide **86** with this class of substrate is limited. It is possible that the optimised reaction conditions for stabilised aryl alkenes are not effective in the dihydroxylation of aliphatic alkenes, and alternative conditions may be required. Due to other research goals this was scarcely explored, but further work to understand and improve the reaction of **86** with aliphatic alkenes is essential for cyclopropyl malonoyl peroxide **86** to be widely adopted as a general metal-free dihydroxylation reagent. In addition, opportunities exist to optimise the epoxide formation, but this method is unlikely to offer any advantage over literature precedent.

3.5 Vinyl- and Allylsilanes

Styrene derivatives work well in the dihydroxylation protocol due to stabilisation of the developing carbocation **186** *via* resonance delocalisation into the arene ring. Silicon is known to stabilise β-carbocations through donation from the σ_{C-Si} molecular orbital into the vacant atomic p orbital (**228**, Scheme 3.6).[66] The β-silicon effect is stronger than the analogous interaction with a σ_{C-C} molecular orbital due to electropositive silicon causing a larger coefficient on the attached carbon atom, resulting in a more effective overlap with the vacant p orbital. Vinyl- **224** and allyl-trimethylsilane **226** were subjected to the dihydroxylation conditions in an effort to discover if the β-silicon effect could be used to expand the reaction scope away from aryl-substituted alkenes.



Scheme 3.6 Dihydroxylation using vinyl **224** and allyl **226** silanes.

Vinyltrimethylsilane **224** did not react with peroxide **86** as peroxide **86** was recovered quantitatively after stage (i) (Note: Vinyltrimethylsilane **224** has a boiling point of 55 ^{o}C and therefore would have been removed along with chloroform during rotary evaporation). The nucleophilic atom in vinyltrimethylsilane **224** is the carbon atom α to the TMS group (**228**, Scheme 3.6). This site would experience substantial steric shielding from the bulky TMS group and may explain the lack of any reactivity of alkene **224** towards peroxide **86**. Allyltrimethylsilane **226** reacted with peroxide **86** resulting in diol **227** in an encouraging unoptimised 46% isolated yield. The nucleophilic carbon atom in allyltrimethylsilane **226** is located in the γ-position, therefore experiencing no steric shielding from the TMS group. Allyl silanes are also substantially more nucleophilic than vinyl silanes. In vinyltrimethylsilane **224** the C–Si

bond is initially orthogonal to the vacant p orbital, and has to undergo a 60° rotation before it can effectively stabilise the developing positive charge (Figure 3.5). This is not the case in allyltrimethylsilane **226** as the C–Si bond can align with the developing positive charge. As a consequence, vinyl silanes exhibit similar nucleophilicity to standard aliphatic alkenes (*cf.* *tert*-butylethylene, Table 3.4, Entry 6), so it is unsurprising that no reaction was observed with **224**.

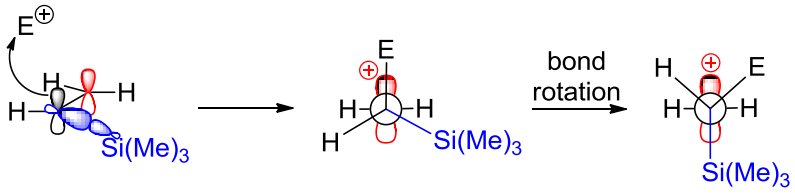
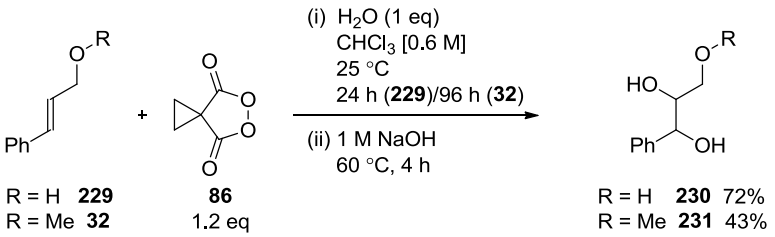


Figure 3.5 C–Si bond orthogonal to π bond in vinyltrimethylsilane **224**.

The dihydroxylation of allyltrimethylsilane **226** by cyclopropyl malonoyl peroxide **86** was a particularly exciting result as it identified a new class of suitable substrate outside of stabilised aryl-substituted alkenes.

3.6 Allylic Alcohols

Cinnamyl alcohol **229** and the corresponding methyl ether **32** were synthesised and subjected to the standard dihydroxylation conditions (Scheme 3.7). Interestingly, allyl alcohol **229** was fully consumed after 24 hours, whereas allyl ether **32** had not been consumed after 4 days. The diastereomeric ratio of diols **230** and **231** has not been unambiguously determined due to a surprising lack of comparable literature ^{1}H NMR data. Functionalisation of **230** and **231** to known compounds such as the corresponding tri-/di-acetates or α-methoxy-α-phenylacetic acid (MPA) ester derivatives should allow for determination of the diastereomeric ratio,[67] but this has not been performed.



Scheme 3.7 Dihydroxylation of allylic alcohol **229** and allylic ether **32**.

The result suggests the electronegative oxygen in the allylic position is sufficiently electron withdrawing to significantly retard the reaction with peroxide **86**, exemplified by the slow reaction with allyl ether **32**. The nucleophilicities of alkenes **229** and **32** are very similar, so it is interesting that reaction of peroxide **86** with allyl alcohol **229** is substantially faster.

Three plausible explanations accounting for the observed rate enhancement were considered. Firstly, the hydroxyl group of **229** could hydrogen bond to the oxygen-rich peroxide **86**, bringing the two reagents within close proximity for reaction to occur, whilst simultaneously activating peroxide **86** *via* hydrogen-bond catalysis (I, Figure 3.6). Secondly, the hydroxyl group of a molecule of **229** could activate peroxide **86** by hydrogen-bond catalysis for attack by a second molecule of allyl alcohol **229** (II, Figure 3.6). Finally, allyl alcohol **229** could increase the solubility of water in chloroform, which in turn could catalyse the reaction through hydrogen-bonding interactions with peroxide **86** (III, Figure 3.6).

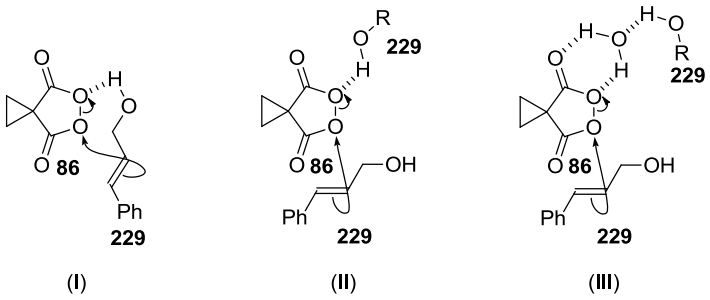
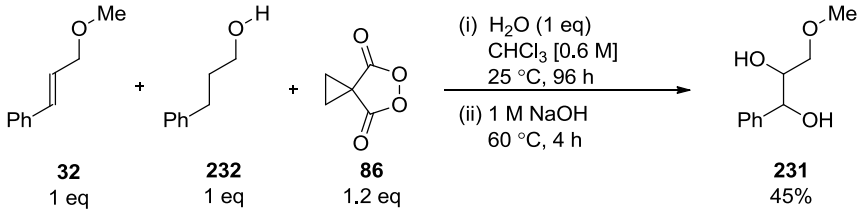


Figure 3.6 Possible modes of rate enhancement in the dihydroxylation of allylic alcohols.

In an effort to gain some understanding of the observed rate enhancement with allylic alcohol **229** over allylic ether **32**, reaction of allyl ether **32** with peroxide **86** was repeated in the presence of alcohol **232** (Scheme 3.8).

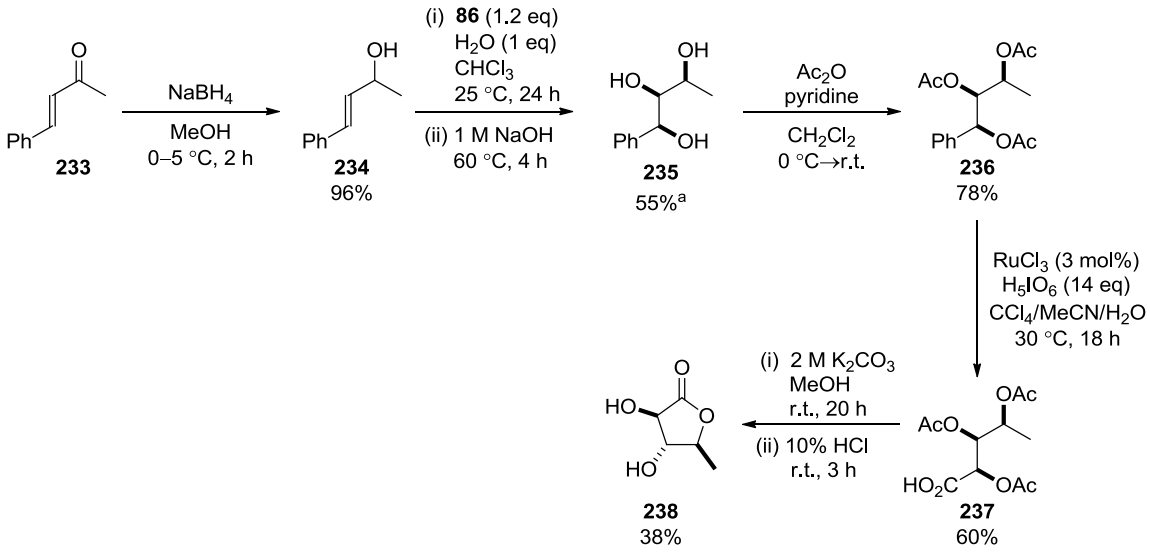


Scheme 3.8 Dihydroxylation of allylic ether **32** in the presence of alcohol **232**.

Alcohol **232** does not contain an alkene to react with peroxide **86** (I, Figure 3.6), but would be capable of hydrogen-bond activation of peroxide **86** (II, Figure 3.6). It could also increase water solubility in chloroform *via* hydrogen-bonding (III, Figure 3.6). Employing a stoichiometric quantity of alcohol **232** resulted in a negligible increase in reaction rate, indicating that activation modes II and III (Figure 3.6) are probably not in operation. Therefore, the observed rate enhancement in the dihydroxylation of allylic alcohols is believed to be *via* a simultaneous peroxide activation/reagent proximity hydrogen-bond interaction (I, Figure 3.6). Further discussion on catalysis of the dihydroxylation reaction is presented in Chapter 4.

3.7 Application in Synthesis

To validate the new *syn*-dihydroxylation methodology, cyclopropyl malonoyl peroxide **86** was successfully employed in the stereoselective synthesis of lactone **238** as an example of its application in synthesis.



[a] Isolated yield of the *rel*-1*S*,2*S*,3*S* diastereoisomer **235**.

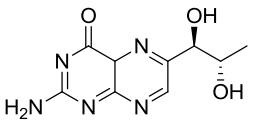
Scheme 3.9 Synthesis of lactone **238** using cyclopropyl malonoyl peroxide **86**.

Benzylideneacetone **233** was reduced using sodium borohydride to allylic alcohol **234** in 96% yield. **234** was subjected to the cyclopropyl malonoyl peroxide **86** dihydroxylation reaction to produce triol **235** as a 2:1 mixture of diastereoisomers (*rel*-1*S*,2*S*,3*S*:*rel*-1*S*,2*S*,3*R*). Purification by crystallisation gave the *rel*-1*S*,2*S*,3*S* isomer **235** in 55% yield, and the relative stereochemistry was confirmed by X-ray crystallography (Figure 3.7).

Figure 3.7 X-Ray crystal structure of the major *rel*-1*S*,2*S*,3*S* isomer of triol **235** from the dihydroxylation of allylic alcohol **234**.

Acetylation of triol **234** to triacetate **236** under standard conditions (78%) allowed oxidative cleavage of the phenyl ring to give carboxylic acid **237** in 60% yield. Removal of the acetate protecting groups using aqueous potassium carbonate in methanol, followed by acid-catalysed cyclisation, gave racemic lactone **238** (38%) as a single diastereoisomer.[68]

Overall, lactone **238** was prepared as a single diastereoisomer in an unoptimised 9% isolated yield from benzylidene acetone **233** over 5 steps. Lactone **238** has application in the synthesis of naturally occurring pterin derivatives such as L-biopterin **239**, which has been developed as a remedy for central nervous system diseases, Parkinson's and Alzheimer's diseases and depression (Figure 3.8).[69]



239

Figure 3.8 L-Biopterin **239**.

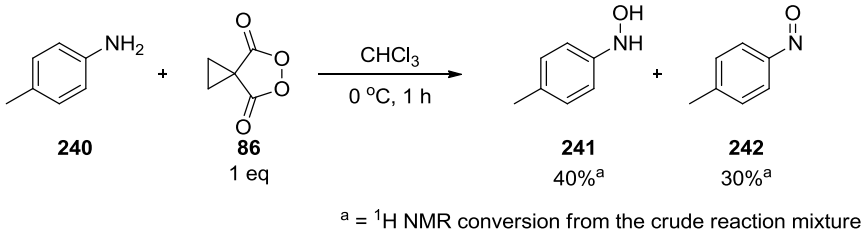
3.8 Non-Alkene Nucleophiles

Stable, isolable electrophilic oxygen reagents such as cyclopropyl malonoyl peroxide **86** are relatively rare,[70] and therefore novel oxidants of this type have many potential applications. Despite cyclopropyl malonoyl peroxide **86** being known for some time, little is known about its reactivity with different nucleophiles. In an effort to gain a better understanding of this potentially useful oxidant, peroxide **86** was treated with nitrogen- and sulfur-based nucleophiles.

3.8.1 Amines

Non-nucleophilic nitrogen containing functional groups such as amides, carbamates and nitriles are tolerated within the dihydroxylation reaction. However, nitrogen bases including triethylamine, pyridine, and even sterically hindered 2,2,6,6-tetramethylpiperidine, react rapidly and often vigorously with cyclopropyl malonoyl peroxide **86**, resulting in complex mixtures of products. *p*-Toluidene **240** was selected as a suitable substrate to gain insight into the reaction of nitrogen nucleophiles with peroxide **86** due to its mild nucleophilicity and its symmetrical aromatic ring being useful for monitoring the reaction *via* TLC and ^{1}H NMR spectroscopy (Scheme 3.10).

p-Toluidene **240** was treated with one equivalent of peroxide **86** in chloroform at 0 ^{o}C. Two major compounds were present in the ^{1}H NMR spectrum of the crude reaction mixture, but could not be isolated. The structures were proposed to be hydroxylamine **241** (~40%) and 4-nitrosotoluene **242** (~30%) by comparison of ^{1}H and ^{13}C NMR data with the literature.[71,72]



Scheme 3.10 Reaction of *p*-toluidene **240** with peroxide **86**.

It was proposed that attack of *p*-toluidene **240** into the σ^*_{O-O} molecular orbital of peroxide **86** would give hydroxylamine derivative **243**. **243** could be attacked by a nucleophile within the reaction mixture, releasing hydroxylamine product **241**. Alternatively, hydroxylamine derivative **243** could break down unimolecularly to **241** *via* decarboxylation, although this is unlikely. The nitroso compound **242** could potentially form *via* decomposition of hydroxylamine derivative **243** by the mechanism outlined in Figure 3.9.

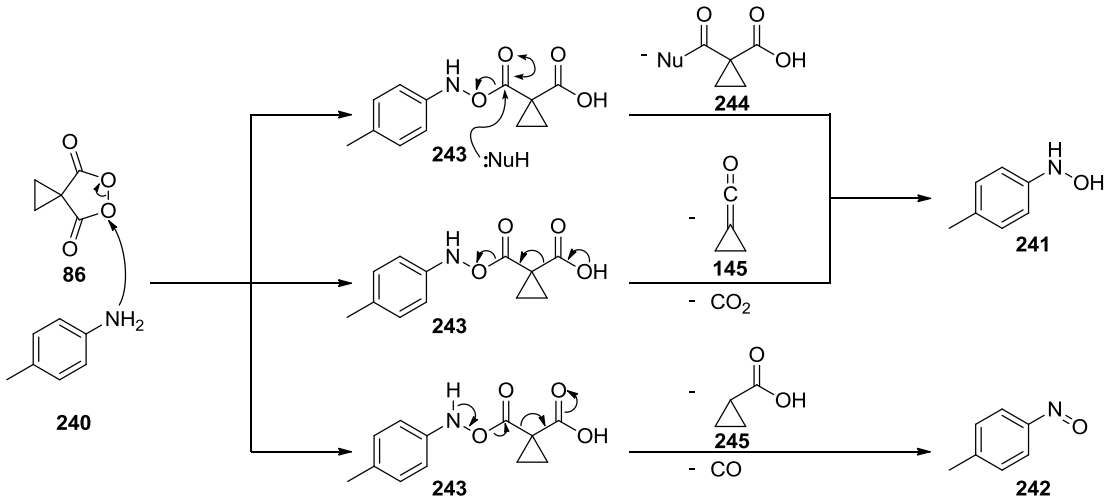
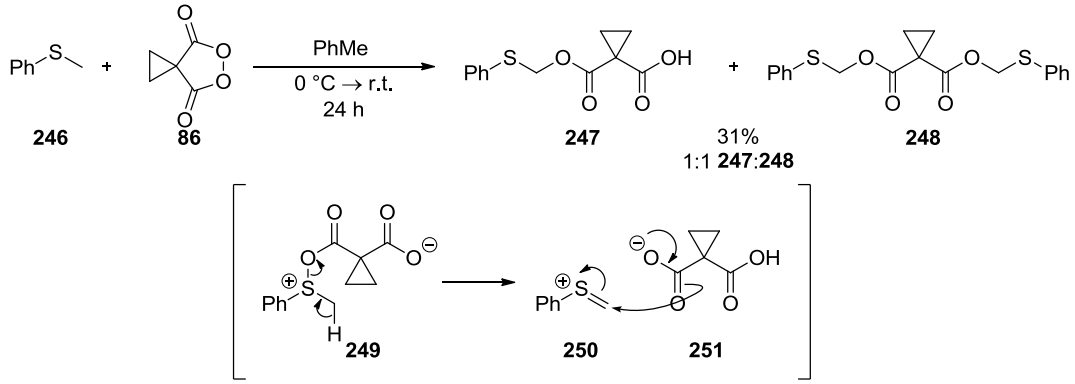


Figure 3.9 Potential mechanisms for hydroxylamine **241** and nitroso **242** formation.

Due to the complicated and inseparable mixture of products, poor selectivity for hydroxylamine **241** over the nitroso derivative **242** (or *vice versa*), and a number of methods to synthesise hydroxylamine[73] and nitroso[74] compounds directly from amines already published, the reaction was pursued no further.

3.8.2 Sulfur

Treating thioanisole **246** with peroxide **86** under anhydrous conditions resulted in two major compounds, **247** and **248**, in a 1:1 ratio in an unoptimised 31% yield (Scheme 3.11). The reaction products can be rationalised by the nucleophilic sulfur atom attacking the peroxide leading to sulfoxide derivative **249**, followed by a Pummerer rearrangement *via* thionium ion **250**, to observed product **247**. Disubstituted product **248** arises from attack of two molecules of thionium ion **250** on the same dicarboxylic acid core.



Scheme 3.11 One-pot sulfide oxidation and Pummerer rearrangement.

This novel procedure presents an advantage over classical Pummerer rearrangements, as sulfur oxidation and subsequent Pummerer rearrangement occur in one reaction sequence. In a typical Pummerer rearrangement, treatment of pre-formed sulfoxide **252** with acetic anhydride results in **254** which breaks down to thionium ion **255**. **255** is then attacked by an acetate ion to give the α-acyloxy-thioether product **256** (Figure 3.10).

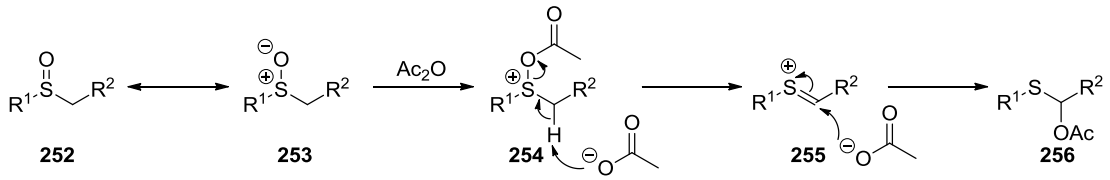


Figure 3.10 Mechanism of a generic Pummerer rearrangement.

The simple procedure, combined with the mild reaction conditions and lack of any additives or catalysts, make this a potentially attractive oxidation procedure, although substantial further development is required.

3.9 Conclusions

The dihydroxylation reaction employing cyclopropyl malonoyl peroxide **86** is very effective with aryl-substituted alkenes such as styrene and stilbene derivatives, cleanly producing diols in high yield (up to 93%) with excellent levels of diastereoselectivity (up to >50:1 *syn*:*anti*). Cyclic alkenes, and *trans*-alkenes produce the highest levels of *syn*-addition product, whilst *cis*-alkenes dihydroxylate with reduced selectivity, consistent with a stepwise mechanism proceeding through a carbocation intermediate **186**. The protocol is most effective with electron-rich alkenes due to the electrophilic nature of peroxide **86**. Encouragingly, unstabilised alkyl-substituted alkenes do undergo dihydroxylation, but competing allylic oxidation and epoxidation pathways have been identified, and further study is required. Allyl silanes represent a promising class of alkyl-substituted alkenes in the dihydroxylation protocol due to apparent stabilisation of the developing carbocation due to the β-silicon effect.

For alkenes containing an allylic hydrogen atom α to the developing carbocation, the selective formation of allylic oxidation products over dihydroxylation products can be achieved by performing the reaction in anhydrous toluene, followed by basic hydrolysis.

Allylic alcohols are effective substrates in the dihydroxylation protocol, and have been shown to provide a significant rate enhancement through a cooperative hydrogen-bond activation/reagent proximity effect. Stereoselective dihydroxylation of allylic alcohol **234** was performed as the key step in a 5-step synthesis of a useful synthetic intermediate, lactone **238**, as an application of the dihydroxylation protocol.

In an effort to learn more about its reactivity, cyclopropyl malonoyl peroxide **86** was treated with non-alkene nucleophiles. Nitrogen nucleophiles resulted in a mixture of N-oxidation products, whereas sulfur nucleophiles underwent oxidation, followed by Pummerer rearrangement, resulting in a mild method of C–H bond oxidation.

Whilst each of these observations were of interest, focus remained on development of a catalytic asymmetric metal-free dihydroxylation protocol. Chapters 4 and 5 discuss progress in realising this ultimate goal.

Chapter 4: Catalysis

4 Catalysis

In Chapter 3, the enhanced rate of reaction between cyclopropyl malonoyl peroxide **86** with allylic alcohols over allylic ethers was discussed (Figure 3.6). This potentially arose through a hydrogen-bonding interaction between peroxide **86** and substrate **229**, which both activated peroxide **86**, and brought both reagents within close proximity for reaction to occur (Figure 4.1). This observation provided the potential for hydrogen-bond catalysts to be employed in the cyclopropyl malonoyl peroxide **86** mediated dihydroxylation reaction.

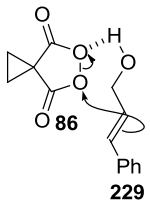


Figure 4.1 Potential hydrogen-bond activation of peroxide **86** with allylic alcohols.

Hydrogen-bond catalysis is an important area within the broader field of organocatalysis.[11] It has generated vast research interest in recent years which has defined it as a separate, distinguished discipline.[75,76] However, the concept is not new as Nature regularly employs hydrogen-bond catalysis to help orient substrates in enzymatic reactions, whilst simultaneously lowering activation barriers.[77] The use of small molecule hydrogen-bond donors as catalysts in organic reactions is attractive for a number of reasons. The catalysts are generally simple to make, robust, non-toxic and low cost compared to their metal-based counterparts. However, there are also some disadvantages, such as requirement of high catalyst loadings, and high substrate specificity in most hydrogen-bond catalysed reactions.

The ultimate aim of this research project was to develop a metal-free, catalytic, asymmetric dihydroxylation reaction, to offer an alternative to the osmium-catalysed process. The ability to catalyse a reaction provides the possibility of employing chiral catalysts to achieve enantioselectivity. This chapter explores the catalytic effect of hydrogen-bond donors in the cyclopropyl malonoyl peroxide **86** dihydroxylation reaction.

4.1 Catalytic Effect of Water

An equivalent of water was essential for clean and efficient dihydroxylation using peroxide **86**, with water acting as a stoichiometric reagent (see Chapter 2.9). The potential existed for water molecules to also act as hydrogen bond catalysts, therefore accelerating the reaction. The possible catalytic effect of water was investigated using homogeneous solutions of *trans*-stilbene **1** (1 eq), cyclopropyl malonoyl peroxide **86** (2 eq), water (1–10 eq) and d_8-1,4-dioxane (Figure 4.2). Reactions were performed in an NMR tube at 40 ^{o}C and conversion was monitored over 2 hours at regular time intervals by *in situ* ^{1}H NMR spectroscopy.

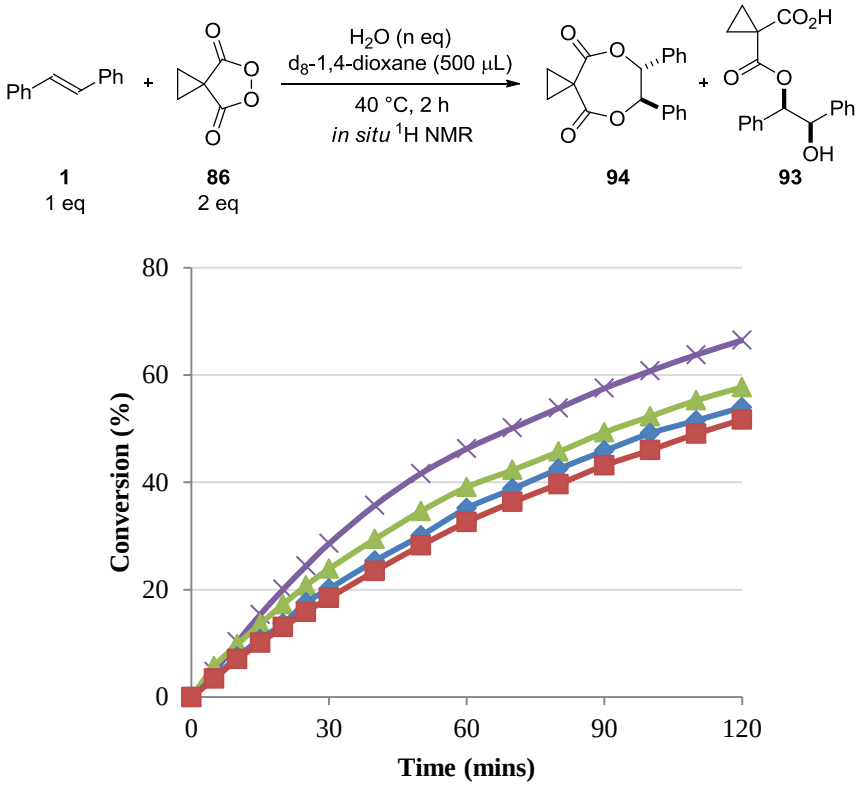
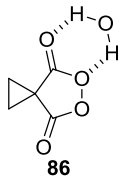


Figure 4.2 Conversion with increasing water equivalents (1 (■), 2 (♦), 5 (▲) and 10 (×)) against time.

Increasing the amount of water present from 1 to 10 equivalents resulted in a small rate enhancement in the formation of reaction intermediates **93** and **94**, consistent with water exerting a small catalytic effect through hydrogen-bonding. A potential model for this interaction is shown in Figure 4.3.



86

Figure 4.3 Proposed model of water hydrogen-bonding to peroxide **86**.

A linear relationship between water equivalents and initial rate of reaction was observed (Figure 4.4). Extrapolation of the line would result in an initial rate of reaction of 0.151 $moldm^{-3}hr^{-1}$ under anhydrous conditions (0 equivalents of H_2O), implying that water is not essential for reactivity between alkene **1** and peroxide **86**.

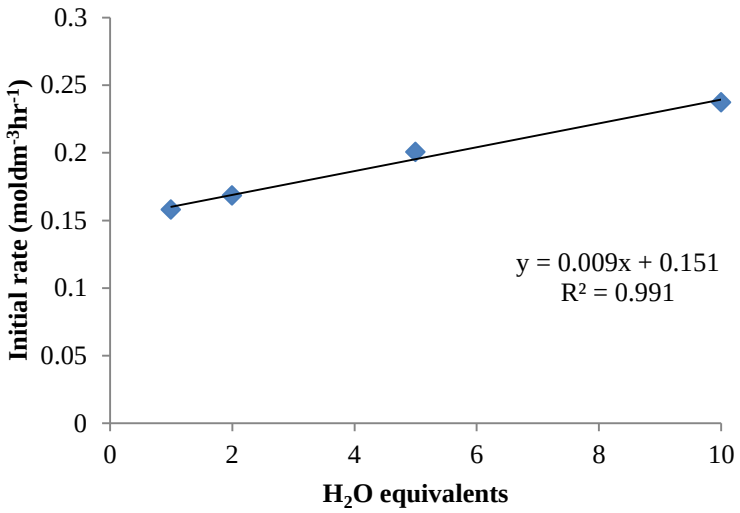
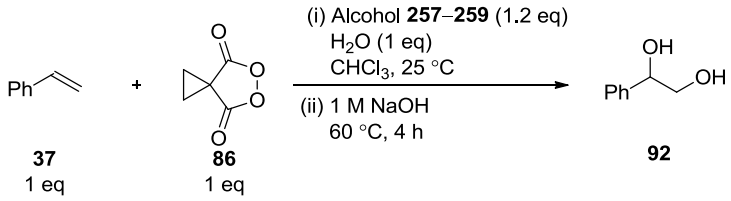


Figure 4.4 Linear relationship between water equivalents and initial rate.

Although Figure 4.4 implies water is not required as a catalyst in the reaction of alkene **1** and peroxide **86**, at least one equivalent of water is required as a reactant in the dihydroxylation reaction. This is due to an alternative decarboxylative mechanism consuming two equivalents of peroxide **86** operating under anhydrous conditions, as outlined in Chapter 2.13.

4.2 Fluorinated Alcohols

Water catalysed the dihydroxylation reaction, albeit to a small extent. Hydrogen-bond donor ability is increased with decreasing pKa, so it was proposed that electron-deficient alcohol derivatives could catalyse the reaction more effectively. Sylvain Picon, a postdoctoral co-worker within the Tomkinson group, determined that fluorinated alcohols **257**–**259** efficiently catalysed the dihydroxylation reaction through an effective hydrogen-bonding interaction.[78]



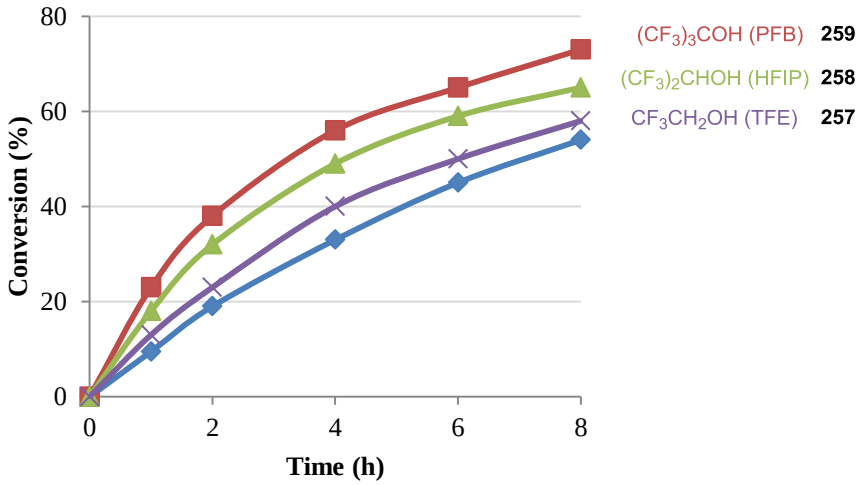


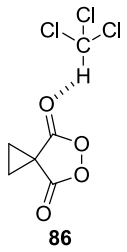
Figure 4.5 Dihydroxylation of **37** in chloroform with no alcohol (♦), 1.2 eq trifluoroethanol **257** (×), l.2 eq hexafluoroisopropanol **258** (▲) and 1.2 eq perfluoro-*tert*-butanol **259** (■).

Picon showed that higher levels of catalysis were achieved with increasing acidity of the fluorinated alcohol, in the order perfluoro-*tert*-butanol (PFB) **259** > hexafluoroisopropanol (HFIP) **258** > trifluoroethanol (TFE) **257**.[79] Incidentally, fluorinated alcohols also slightly increased the diastereoselectivity of the reaction, although the reason for this is not currently understood.

4.3 Controlling Background Reaction

The ultimate goal of catalysing the dihydroxylation reaction using hydrogen-bond donors was to achieve an asymmetric variant of the reaction by employing chiral hydrogen-bond catalysts. Only when the catalyst controls the geometry of the transition state will enantioselectivity be achieved. Therefore, it was important to have a sufficiently low uncatalysed background reaction, as this will only result in racemic material. Despite perfluoro-*tert*-butanol **259** catalysing the dihydroxylation reaction, the uncatalysed background reaction was significant and needed to be reduced (Figure 4.5).

During initial optimisation studies of the reaction, chloroform emerged as the most effective solvent for dihydroxylation in terms of rate and yield (Chapter 2.3). Although this was not rationalised at the time, it was possible that chloroform was acting as a hydrogen-bond donor in a similar manner to fluorinated alcohols **257**–**259** (Figure 4.6).[80]



86

Figure 4.6 Possible hydrogen-bond activation of peroxide **86** by chloroform.

In an effort to reduce the uncatalysed background reaction, toluene was examined as the reaction medium in the dihydroxylation of *trans*-stilbene **1** (Figure 4.7). The rate of reaction was considerably reduced, consistent with chloroform acting as a hydrogen-bond donor. It should also be noted that the solubility of water in toluene (mole fraction 0.0025) is half that of chloroform (mole fraction 0.005), which could affect the rate.[81] However, the difference in water solubility between toluene and chloroform is considered to be negligible due to the poor catalytic effect of water in homogeneous 1,4-dioxane solution, even when large excesses (10 eq) of water were present (Figure 4.2).

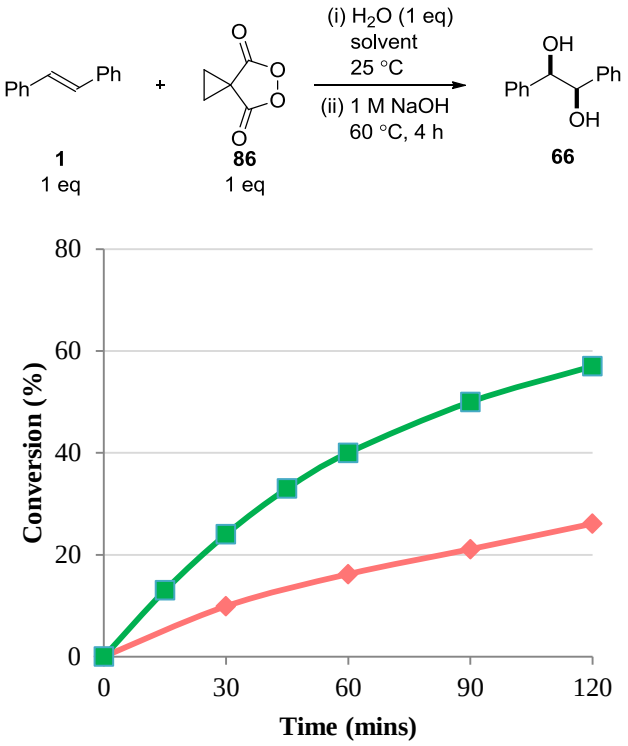
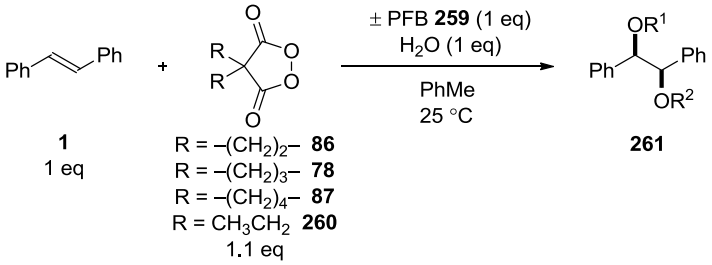


Figure 4.7 Dihydroxylation of *trans*-stilbene **1** in chloroform (■) and toluene (♦).

As mentioned in Chapter 1.4.2, malonoyl peroxide structure has a dramatic effect on rate of reaction, with a larger cycloalkane ring leading to reduced reactivity. In an effort to further reduce the background reaction, larger malonoyl peroxides **78**, **87** and **260** were prepared and examined in the dihydroxylation of *trans*-stilbene **1** in the absence and presence of stoichiometric perfluoro-*tert*-butanol **259** (Figures 4.8–4.11).



Scheme 4.1 Reducing background reaction by peroxide structure.

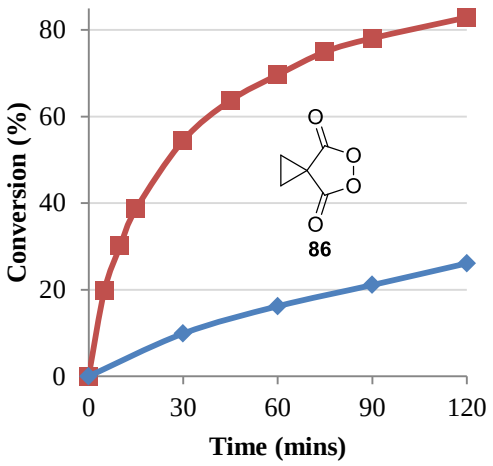


Figure 4.8 Dihydroxylation of stilbene **1** using peroxide **86** with no catalyst (♦) and with 1 eq PFB (■).

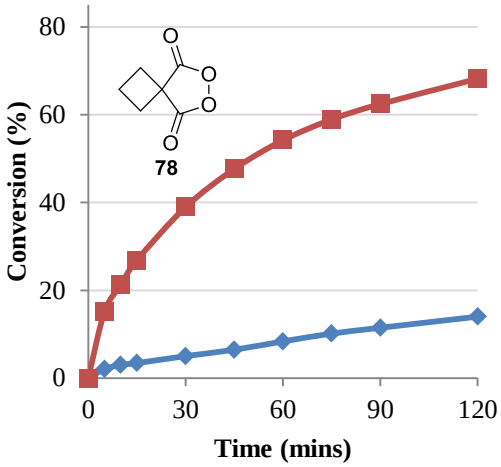


Figure 4.9 Dihydroxylation of stilbene **1** using peroxide **78** with no catalyst (♦) and with 1 eq PFB (■).

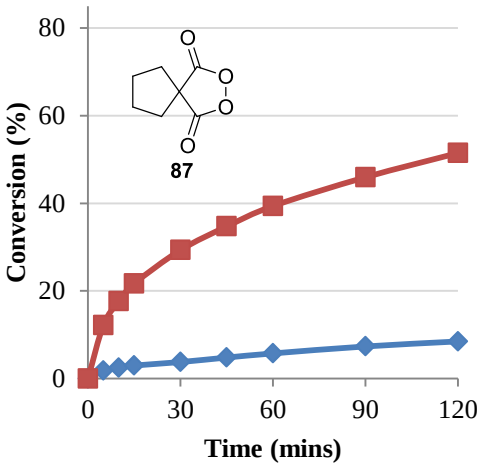


Figure 4.10 Dihydroxylation of stilbene **1** using peroxide **87** with no catalyst (♦) and with 1 eq PFB (■).

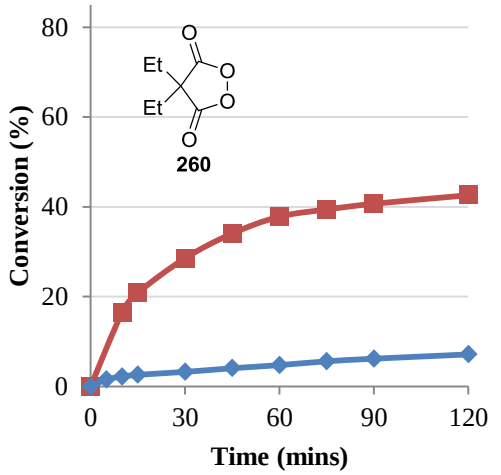


Figure 4.11 Dihydroxylation of stilbene **1** using peroxide **260** with no catalyst (♦) and with 1 eq PFB (■).

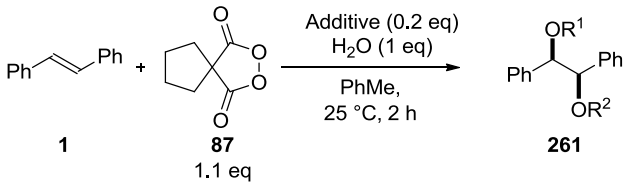
Cyclopentyl malonoyl peroxide **87** provided a low (8%) background reaction and a good (53%) catalysed reaction after 2 hours, indicating a 6.5-fold increase in conversion. Cyclopropyl- **86** and cyclobutyl malonoyl peroxide **78** produced faster reactions with PFB **259** present, but the uncatalysed background reactions were deemed too high (26% and 15% conversion after 2 hours, respectively). Reaction with monocyclic diethyl peroxide **260** produced a slightly reduced background reaction (7% conversion after 2 hours) compared to cyclopentyl malonoyl peroxide **87**, but was

disfavoured as reaction conversion reached a plateau (~45% conversion) due to significant peroxide decomposition.

In summary, changing the reaction solvent from chloroform to toluene, and replacing cyclopropyl- **86** with cyclopentyl malonoyl peroxide **87**, provided a sufficiently low background reaction (8% conversion after 2 hours) as a suitable basis from which to explore other potential hydrogen-bond catalysts in the dihydroxylation reaction.

4.4 Catalyst pKa Investigation

The interesting results obtained by Picon with fluorinated alcohols **257**–**259** indicated a trend between pKa and catalyst activity, with more acidic fluorinated alcohols being the most effective catalysts (Figure 4.5). To examine this further, a series of additives of varying acidity were investigated as potential catalysts (Table 4.1). *Trans*-stilbene **1**, cyclopentyl malonoyl peroxide **87** (1.1 eq), H_2O (1 eq) and additive (0.2 eq) were stirred in toluene at 25 ^{o}C. Conversion was measured after 2 hours by ^{1}H NMR spectroscopy and plotted against the pKa value of the additive.[79,82] All reactions were performed in duplicate as a minimum, and the mean conversion reported. The background (uncatalysed) reaction is indicated at 8% for comparison.



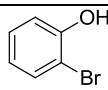
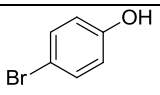
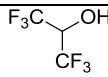
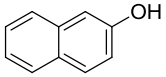
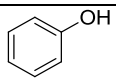
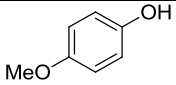
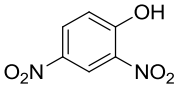
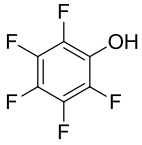
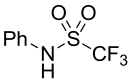
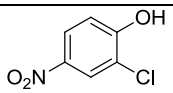
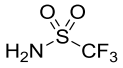
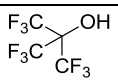
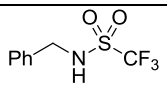
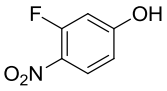
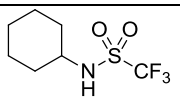
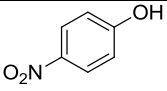
Entry	Additive	pKa	Conversion	Entry	Additive	pKa	Conversion
1	None	-	8%	12		8.4	11%
Acids				13		9.3	17%
2	AcOH	4.8	9%	14		9.3	20%
3	H_3PO_4	2.1	9%	15		9.3	8%
4	*p*-TsOH	-0.6	8%	16		10.0	15%
5	MsOH	-2.6	7%	17		10.2	7%
Alcohols				18		12.4	12%
6		4.9	8%	Sulfonamides			
7		5.3	22%	19		4.5	13%
8		5.4	21%	20		6.3	18%
9		5.4	23%	21		6.8	16%
10		6.1	29%	22		6.9	14%
11		7.1	29%	23		10.8	8%

Table 4.1 pKa table of additives (0.2 eq) with reaction conversion after 2 h.

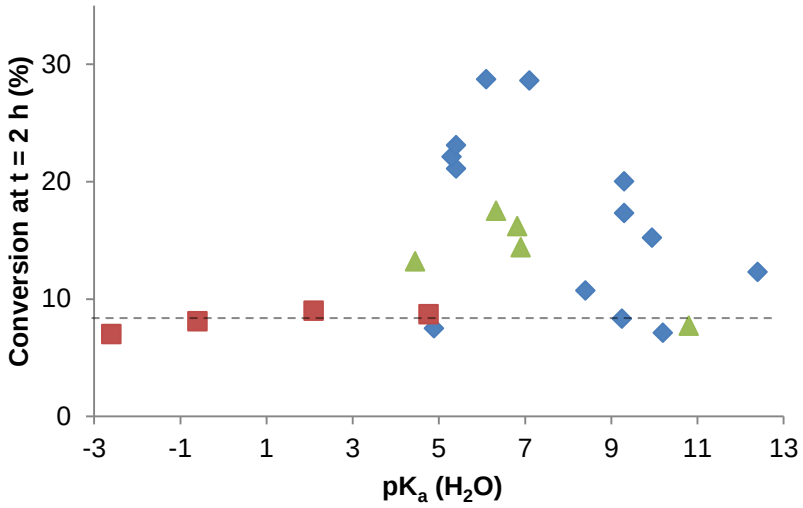


Figure 4.12 Graph of additive pKa (acids (■), alcohols (♦), sulfonamides (▲)) *versus* conversion at 2 h against the uncatalysed reaction (---).

Interestingly, acidic additives (pKa < 5, Table 4.1, Entries 2–5) such as acetic acid (pKa 4.8), phosphoric acid (pKa 2.1), *p*-toluenesulfonic acid (pKa -0.6) and methanesulfonic acid (pKa -2.6) did not appear to catalyse the reaction, implying the reaction does not undergo specific or general acid catalysis (Figure 4.13).

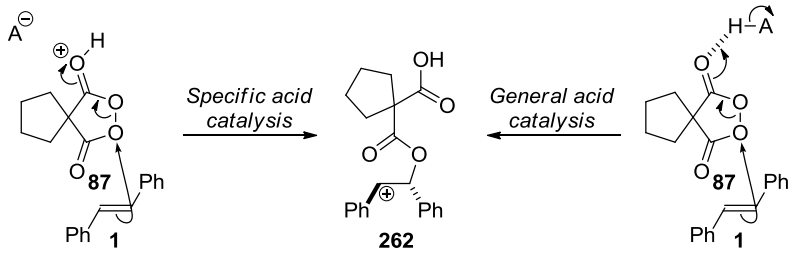
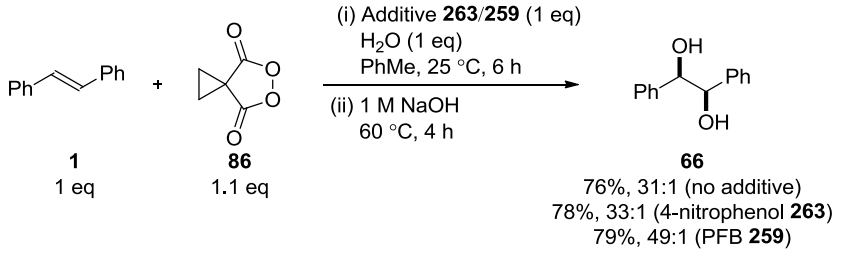


Figure 4.13 Specific and general acid catalysis of peroxide **86**.

Conversely, many alcohols did catalyse the reaction, with a clear correlation between reaction conversion and pKa observed over the 13 alcohols examined. Interestingly, the most effective pKa range for alcoholic catalysts was between pKa 5–8. There are a number of key observations worthy of note from this study. pKa, and not catalyst structure, appears to determine catalytic activity. This is exemplified by 2-chloro-4-nitrophenol (pKa 5.4, Table 4.1, Entry 8) and PFB **259** (pKa 5.4, Table 4.1, Entry 9) exhibiting near identical catalytic activity (21% and 23% respectively), despite being

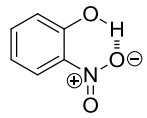
very different structurally. In many cases, alcohols with higher pKa values (> 9) slowly destroyed peroxide **87**, which may explain the apparent deviation from the general trend in this region (pKa 9–13). Significantly, the study indicated that 3-fluoro-4-nitrophenol (pKa 6.1, 29% conversion, Table 4.1, Entry 10) and 4-nitrophenol **263** (pKa 7.1, 29% conversion, Table 4.1, Entry 11) were more effective catalysts than PFB **259** (pKa 5.4, 23% conversion, Table 4.1, Entry 9), despite being slightly less acidic.

4-Nitrophenol **263** was employed as a stoichiometric catalyst in the dihydroxylation of *trans*-stilbene **1** using cyclopropyl malonoyl peroxide **86** (Scheme 4.2). The reaction reached completion slightly faster than when PFB **259** (1 eq) was used under the same conditions, and the yield of diol **66** was similar (78% and 79%). Interestingly, 4-nitrophenol **263** did not produce the increase in diastereoselectivity observed when PFB **259** was employed as catalyst.



Scheme 4.2 Comparison of 4-nitrophenol **263** and PFB **259** as catalysts.

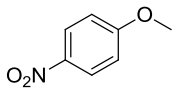
2,4-Dinitrophenol (pKa 4.9, Table 4.1, Entry 6) produced no catalytic activity. It was initially unclear whether this was because the pKa was slightly below the apparent threshold for catalytic activity (pKa ~5), or because the hydroxyl proton was not available for hydrogen-bonding to peroxide **87**. A control experiment employing 2-nitrophenol **264** (pKa 7.2, Figure 4.14), which has a near identical pKa to highly active 4-nitrophenol **263** (pKa 7.1, 29% conversion, Table 4.1, Entry 11), resulted in only negligible catalytic activity (11% conversion). This suggests the hydroxyl proton in 2-nitro-substituted phenols is not available for intermolecular hydrogen bonding to peroxide **87**, due to a strong intramolecular hydrogen bond interaction with the *ortho*-nitro group (Figure 4.14).[83]



264
pKa 7.2
11% conversion

Figure 4.14 Intramolecular hydrogen-bonding in 2-nitrophenol **264**.

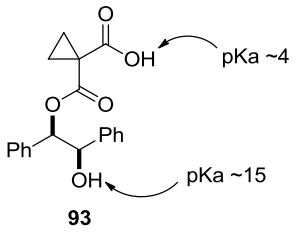
An additional control experiment was performed to provide evidence that the increased catalytic activity of 4-nitrophenol **263** (pKa 7.1, 29% conversion, Table 4.1, Entry 11) was due to the desired hydrogen bonding interaction with peroxide **87**. In the reaction outlined in Table 4.1, 4-nitrophenol **263** was replaced by its methylated analogue, 4-nitroanisole **265** (0.2 eq, Figure 4.15). Catalytic activity was shut off with only background levels of conversion observed after 2 hours (8%), suggesting that the catalytic activity of 4-nitrophenol **263** is due to hydrogen-bonding activation of peroxide **87**.



265
8% conversion

Figure 4.15 Control experiment employing 4-nitroanisole **265**.

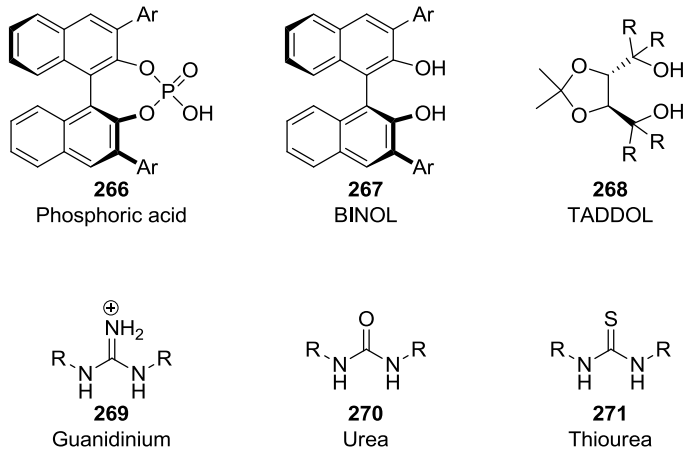
The apparent active catalytic window of pKa 5–8 for alcoholic hydrogen-bond donor catalysts cannot currently be justified, however it does signify why the dihydroxylation reaction is not autocatalytic. The major reaction intermediate **93** produced in the dihydroxylation reaction contains a hydroxyl group (pKa ~15) and a carboxylic acid (pKa ~4), which could both potentially catalyse a reaction susceptible to hydrogen-bond catalysis (Figure 4.16). However, both functional groups fall outside the active catalytic pKa range and therefore no autocatalysis is observed. This was confirmed by addition of stoichiometric **93** to the dihydroxylation of *trans*-stilbene **1** under standard conditions. Qualitative analysis by TLC and ^{1}H NMR spectroscopy revealed no noticeable increase in the rate of consumption of alkene **1**.



93

Figure 4.16 pKa of the acidic protons in dihydroxylation intermediate **93**.

The narrow effective pKa window of 5–8 also falls outside many classes of common hydrogen-bond donor organocatalysts. Phosphoric acids **266**,[84] BINOLs **267**,[84] TADDOLs **268**,[85] guanidinium derivatives **269**,[85] ureas **270**[85] and most thioureas **271**[86] all fall outside of this window (Figure 4.17).



266 Phosphoric acid

267 BINOL

268 TADDOL

269 Guanidinium

270 Urea

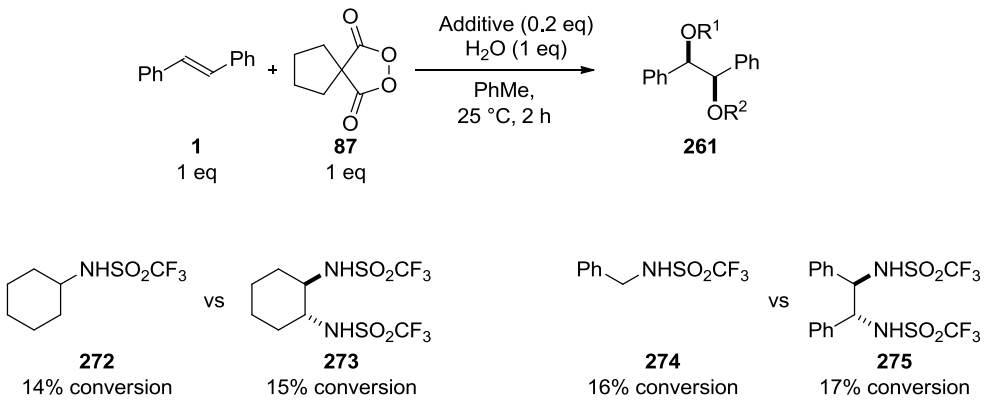
271 Thiourea

Figure 4.17 Privileged hydrogen-bond catalysts typically outside the active pKa window of 5–8.

One functional group that typically falls within the active pKa window of 5–8 is the trifluoromethanesulfonamide moiety.[85] Trifluoromethanesulfonamides catalysed the dihydroxylation reaction, but to a lesser extent than alcohol additives of similar pKa (Table 4.1, Entries 19–22). These observations are consistent with N–H···O hydrogen-bond strength being weaker than O–H···O hydrogen-bond strength.[57]

4.5 Dual Hydrogen-Bond Donor Catalysts

In an effort to increase the activity of catalysts **272** and **274**, analogous compounds **273** and **275** containing two proximal trifluoromethanesulfonamide moieties were investigated (Scheme 4.3).[87] The possibility of a dual hydrogen-bonding interaction between peroxide **87** and catalysts **273** and **275** existed, which could considerably increase levels of catalysis.[75,88]



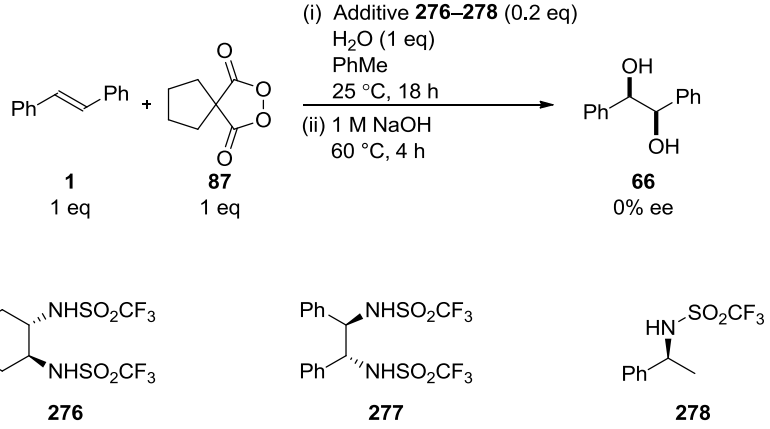
Scheme 4.3 Mono *versus* dual sulfonamide catalysts.

Bis-trifluoromethanesulfonamide compounds **273** and **275** catalysed the dihydroxylation of *trans*-stilbene **1** with peroxide **86**, but produced only negligible rate acceleration over the analogous mono-trifluoromethanesulfonamides **272** and **274**, indicating that an additive dual hydrogen bonding effect was probably not in operation.

4.6 Asymmetric Hydrogen-Bond Donor Catalysts

The use of alcohol hydrogen-bond donor catalysts in malonoyl peroxide mediated dihydroxylation of alkenes is advantageous due to their commercial availability and tuneable electronic properties, particularly in the case of phenol derivatives. However, a major disadvantage of using phenol hydrogen-bond catalysts is the lack of three-dimensional shape, making exploration of asymmetric variants of the catalytic reactions difficult. If an effective alcoholic catalyst with three-dimensional shape, such as perfluoro-*tert*-butanol **259**, is modified to become a chiral tertiary alcohol, then it is very difficult to maintain the low pKa (5–8) required for effective catalysis.

Three enantiopure (>98% ee) trifluoromethanesulfonamides **276**–**278** were examined as additives in the dihydroxylation reaction as the substituent on nitrogen provided a good handle for incorporating chirality (Scheme 4.4). Although only relatively poor enantiomeric excesses were expected due to the low levels of catalysis when compared to the uncatalysed background reaction, it could still be possible to observe any enantioselectivity as proof of concept.



Scheme 4.4 Chiral sulfonamide catalysts **276**–**278** employed in the dihydroxylation reaction.

Catalysts **276**–**278** did not induce enantioselectivity in the dihydroxylation reaction. As catalysts **276**–**278** are relatively small, steric control of the approaching alkene to the $\sigma^*_{O–O}$ orbital of peroxide **87** is unlikely (Figure 4.18). Designing a catalyst capable of this represents a major challenge for future development. Development of more sterically imposing structures based on trifluoromethanesulfonamides is limited by the requirement for a CF_3 substituent on the sulfonamide to achieve the correct pKa of the N–H bond, leaving only the single site on the nitrogen available for manipulation.

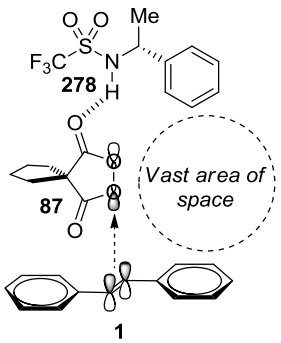


Figure 4.18 Model highlighting difficulty in controlling alkene **1** approach to peroxide **87**.

Due to a stronger catalytic effect it would be preferential to employ chiral phenol derivatives as catalysts in the dihydroxylation reaction. The nearest established chiral organocatalyst family to phenol derivatives are the BINOL catalysts **267**. BINOL catalysts **267** are much larger with a more defined chiral pocket than sulfonamides **276**–**278**, so enantioselectivity may be more likely. However, no catalysis, and therefore no enantioselectivity, was observed when BINOL **279** was used. This is believed to be due to the pKa of the alcohol function(s) being above the active window of 5–8. BINOL derivatives such as **280** may have a sufficiently low pKa to catalyse the reaction, but they are not commercially available and there are no effective syntheses of suitable nitro BINOL derivatives currently reported in the literature. Synthesis and examination of BINOL **280** in the dihydroxylation of alkenes could be an interesting starting point for future work regarding asymmetric catalysis of this intriguing reaction.

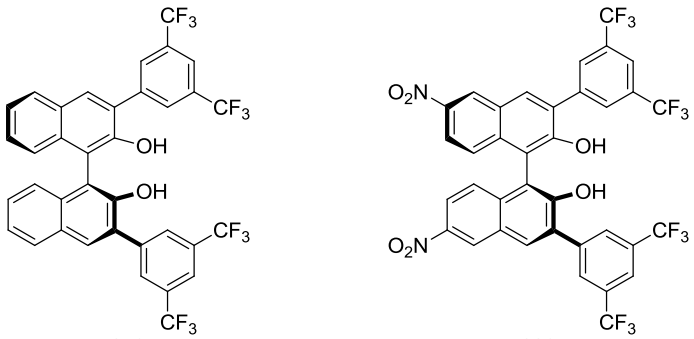


Figure 4.19 Chiral electron-deficient BINOL catalysts.

4.7 Conclusions

Within the dihydroxylation reaction between peroxide **86** and alkene **1**, water was shown to exert a linear, but negligible effect on reaction rate, consistent with very weak hydrogen-bond activation of peroxide **86**.

Significant progress has been made in catalysing the dihydroxylation reaction, with alcoholic hydrogen-bond donor catalysts within a specific pKa range (5–8) being most effective. Up to 4-fold rate acceleration has been achieved using 4-nitrophenol **263** (20 mol%) as catalyst. Interestingly, acids (pKa < 5) did not appear to catalyse the reaction. Trifluoromethanesulfonamides did catalyse the reaction, but to a significantly lesser extent than alcohol-based catalysts.

The uncatalysed background reaction was reduced by use of cyclopentyl malonoyl peroxide **87** in toluene, providing suitable conditions for exploration of an asymmetric variant of the reaction. However, no enantioselectivity in the dihydroxylation reaction through the use of chiral hydrogen-bond catalysts has been achieved thus far. Due to their similarity to the effective phenol catalysts, BINOLs such as **280** may hold the key to achieving progress in this area, but careful manipulation of existing BINOL structures to lower pKa will almost certainly be required.

Chapter 5: Asymmetric Dihydroxylation

5 Asymmetric Dihydroxylation

There are a number of methods for introducing asymmetry into a reaction, such as the use of a chiral catalyst,[89] chiral auxiliary,[90] chiral pool synthesis,[91] chiral reactant or biocatalysis.[92] There are also a number of methods for obtaining enantioenriched compounds from racemic material, including chiral resolution,[93] kinetic resolution[94] and dynamic kinetic resolution.[95] Asymmetric catalysis is generally favoured as only sub-stoichiometric quantities of the often expensive chiral component are required, and the catalyst can often be recovered post-reaction. Metal-free alkene dihydroxylation is no exception, and the ultimate achievement would be to introduce asymmetry into the cyclopropyl malonoyl peroxide **86** mediated dihydroxylation reaction using sub-stoichiometric chiral catalyst. However, as discussed in Chapter 4, the dihydroxylation reaction using malonoyl peroxides is currently racemic, despite significant advances in understanding catalysis of the reaction. In parallel work, an alternative approach to introduce asymmetry into the reaction by means of a chiral peroxide reactant was investigated. This chapter discusses the development of chiral malonoyl peroxides.

5.1 Chiral Cyclopropyl Malonoyl Peroxide Derivatives

5.1.1 Concept

The X-ray crystal structure of cyclopropyl malonoyl peroxide **86** revealed that it was C_2 symmetric, containing two mirror planes and no stereogenic centres (Figure 5.1).[13] It was proposed that the simplest way of introducing chirality, yet maintaining the desired C_2 symmetry, was to incorporate substituents on the 2- and 3- positions of the cyclopropane ring in a *trans* relationship (**281**, Figure 5.1). C_2 symmetry is effective in enantioselective synthesis as it limits the possible number of pathways to a reactive centre, thereby increasing enantioselectivity.

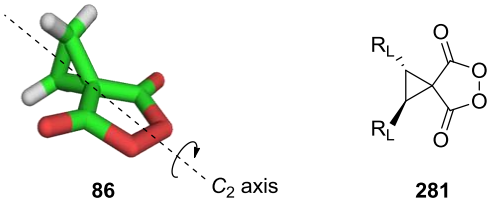


Figure 5.1 X-Ray crystal structure of peroxide **86** showing C_2 symmetry axis (left). Generic structure for a chiral C_2-symmetric cyclopropyl malonoyl peroxide **281** (right).

If the substituents on the cyclopropane ring were sufficiently large, then a single approach of an alkene substrate toward the peroxide **282** σ^*_{O-O} orbital may be favoured to avoid unfavourable steric interactions between the phenyl moieties of **11** and **282**, resulting in enantioselectivity (Figure 5.2).

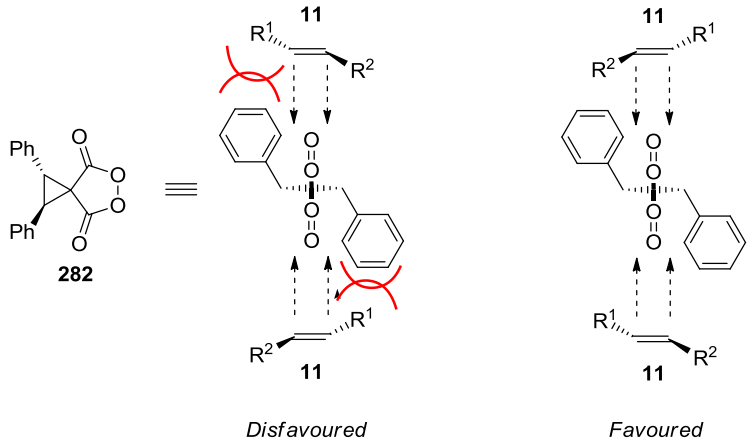


Figure 5.2 View of peroxide **282** along the C_2 symmetry axis, showing disfavoured alkene trajectory due to steric clash between R^1 and Ph (left) and favoured alkene trajectory (right).

Trans-2,3-diphenyl cyclopropyl malonoyl peroxide **282** was selected as a suitable initial target due to its simplicity, and relatively large substituents. Additionally, the phenyl groups provide an effective handle for monitoring reactions by TLC and NMR spectroscopy.

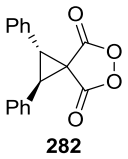


Figure 5.3 Target chiral C_2-symmetric peroxide reagent **282**.

5.1.2 Retrosynthesis

Only a few simple malonoyl peroxides have been reported in the literature[37] and none contained stereogenic centres, so a new synthetic route to peroxide **282** was required. For proof of concept, any synthetic route to **282** was deemed acceptable at this stage in the investigation.

It was thought that peroxide **282** could be made from diacid **283**, which results from hydrolysis of ester **284** (Figure 5.4). Therefore, diester **284** was identified as the key synthetic target in the synthesis of peroxide **282**. The main methods of making cyclopropanes containing a 1,1-diester functionality such as **284** are metal-catalysed diazomalonate **285** decomposition to generate a carbenoid which adds to an alkene **1** (Figure 5.4, Path A),[96] or generation of an ylide **286**, then Michael addition into an α,β-unsaturated diester **289** (Figure 5.4, Path B).

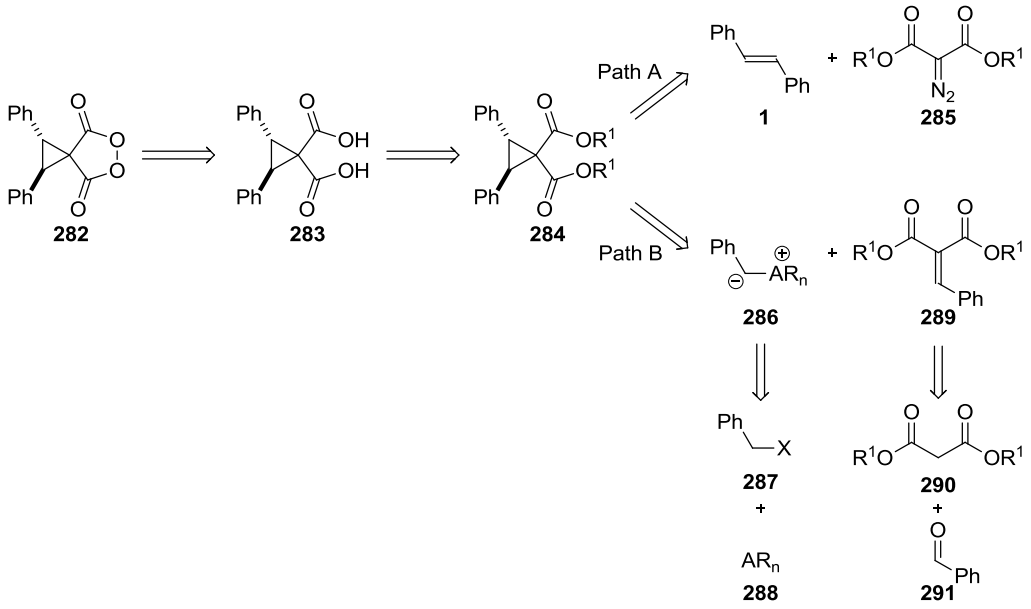
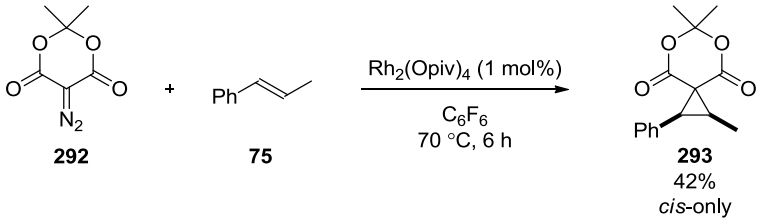


Figure 5.4 Retrosynthesis of peroxide **282**.

Both synthetic strategies have the potential to be asymmetric; the carbenoid route (Path A) by incorporation of chiral ligands onto the metal centre or a chiral auxiliary on the diazomalonate,[97] and the ylide route (Path B) by use of a chiral ylide precursor **288**. However, at this stage only racemic diphenyl peroxide **282** was targeted to ensure it would be suitable in the dihydroxylation reaction.

A literature search revealed no reports of diazomalonate **285** derived carbenoid additions across *trans*-stilbene **1** derivatives to give 1,1-diester cyclopropanes **284**. Despite considerable success with terminal, 1,1-disubstituted and *cis*-1,2-disubstituted alkenes, it is generally accepted that *trans*-1,2-disubstituted alkenes are too sterically hindered for cyclopropanation by this method, except in isolated cases.[98] There are a

limited number of reports of cyclopropanation of *trans*-1,2-disubstituted styrene derivatives, but reactions are very slow, form complex mixtures with only low yields of cyclopropanation products[99] and can form the *cis*-cyclopropane product **293**, despite starting with a *trans*-alkene **75** (Figure 5.1).[100]

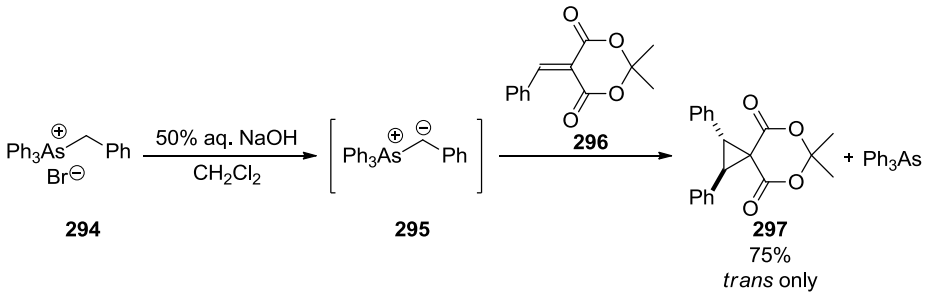


Scheme 5.1 Lee's cyclopropanation of β-methylstyrene **75** using diazo compound **292**.

Conversely, there are a number of reports on ylide-based routes to derivatives of diester **284** with high *trans*-selectivity, and therefore an ylide-based cyclopropanation route to diester **284** was explored (Figure 5.4, Path B). A substantial investigation employing sulfonium,[101] pyridinium,[102] tellurium[103] and arsonium[104] ylides was performed. However, derivatives of diester **284** were only achieved using arsonium ylides.

5.1.3 Stereoselective Cyclopropanation

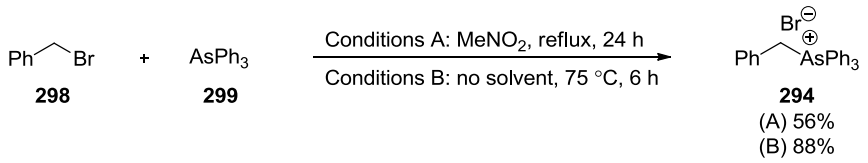
A simple and highly stereoselective route to diester **297** was reported by Chen using a semi-stabilised arsonium ylide **295**, generated under phase transfer conditions (75%, *trans*-**297** only, Scheme 5.2).[104b]



Scheme 5.2 Chen's reported phase-transfer synthesis of **297** using arsonium ylide **295**.

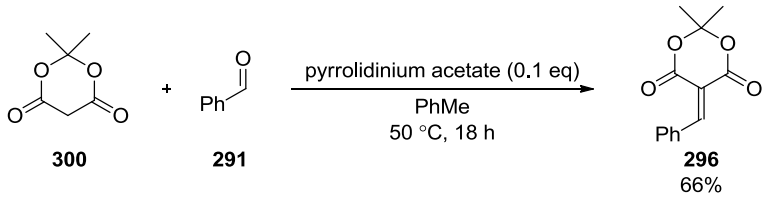
To obtain the benzyltriphenyl arsonium bromide **294** starting material, benzyl bromide **298** and triphenylarsine **299** were stirred in nitromethane under reflux for 24 hours (Conditions A, Scheme 5.3), providing salt **294** in mediocre yield (56%).[105] Later, the

yield was significantly improved (88%) and reaction time reduced by performing the reaction as a melt (Conditions B, Scheme 5.3).[106]



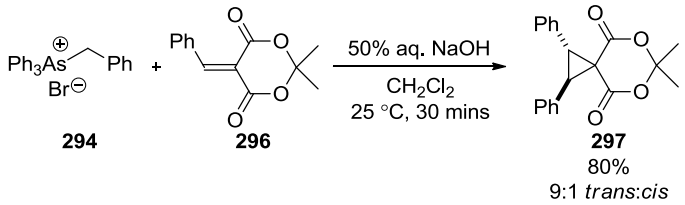
Scheme 5.3 Synthesis of arsonium salt **294**.

Surprisingly, within the literature the Knoevenagel condensation product **296** is notoriously difficult to synthesise in high yield[107] and a number of routes were investigated. Reaction of Meldrum's acid **300** and benzaldehyde **291** in toluene catalysed by pyrrolidinium acetate (10 mol%) proved to be the most effective method, providing condensation product **296** in reasonable 66% yield (Scheme 5.4).



Scheme 5.4 Synthesis of condensation product **296**.

Reaction of arsonium salt **294** and benzylidene **296** under Chen's conditions provided cyclopropanation product **297** in good yield and diastereoselectivity (80%, 9:1 *trans*:*cis*, Scheme 5.5).



Scheme 5.5 Synthesis of diester **297** employing Chen's arsonium ylide protocol.

Crystallisation from ethyl acetate provided exclusively the *trans*-isomer **297** (66%), with confirmation of the relative stereochemistry provided by single crystal X-ray crystallographic analysis (Figure 5.5).

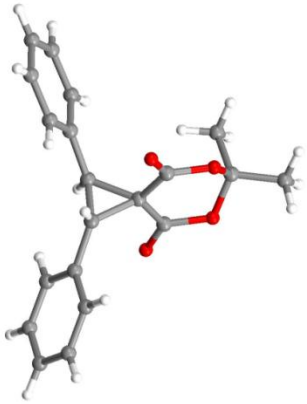
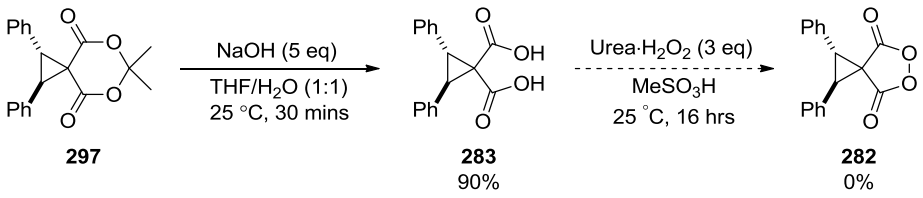


Figure 5.5 X-Ray crystal structure of **297**.

5.1.4 Acid-Catalysed Rearrangement of Diacid 283

Hydrolysis of diester **297** to diacid **283** could be achieved by simply leaving the strongly basic cyclopropanation reaction mixture (Scheme 5.5) for an extended period of time (> 5 h). However, purification and separation of the diastereoisomers of diacid **283** was considerably more laborious than with diester **297**, so a separate hydrolysis step was preferred.

Efficient hydrolysis of diester **297** to diacid **283** (90%) was achieved using sodium hydroxide in a 1:1 mixture of THF and water at room temperature. Disappointingly, treatment of diacid **283** with three equivalents of urea hydrogen peroxide in methanesulfonic acid did not afford peroxide **282**.



Scheme 5.6 Hydrolysis of diester **297** and unsuccessful peroxide **282** synthesis.

A control reaction involving stirring of diacid **283** in methanesulfonic acid (25 ^{o}C, 3 h) indicated that methanesulfonic acid provoked an interesting acid-catalysed rearrangement of diacid **283** to lactone **303** (Figure 5.6).[108]

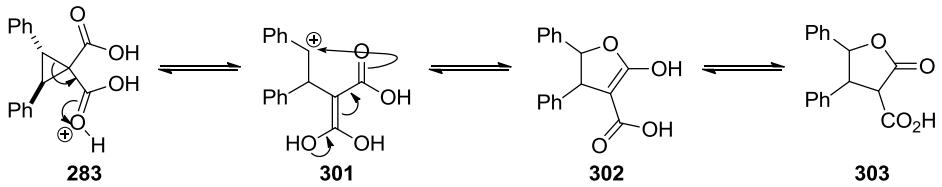
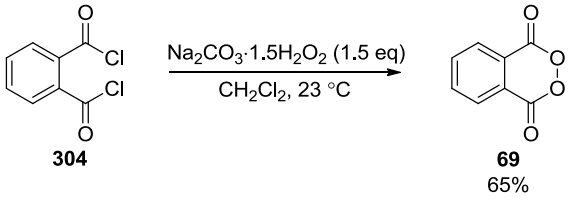


Figure 5.6 A possible mechanism for the acid-catalysed formation of lactone **303**.

It is interesting that diphenyl diacid **283** underwent an acid-catalysed rearrangement, but cyclopropane-1,1-dicarboxylic acid **91** did not when treated with methanesulfonic acid. Presumably, ring-opening of diphenyl diacid **283** is facilitated by the presence of phenyl substituents capable of stabilising the developing positive charge in **301**, before ring-closure to lactone **303** (Figure 5.6). The relative stereochemistry of lactone **303** has not been confirmed.

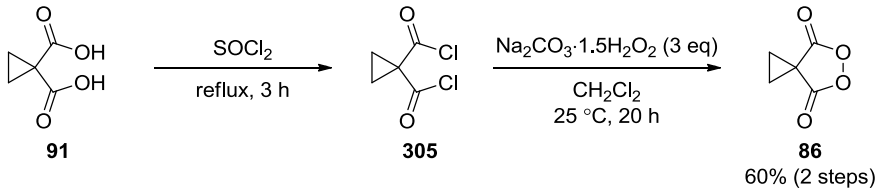
5.1.5 Peroxide Formation

An alternative method of peroxide bond formation was required to obtain peroxide **282**. A recent report by Siegel showed that treatment of phthaloyl chloride **304** with sodium percarbonate (SPC) produced phthaloyl peroxide **69** in respectable yield (65%, Scheme 5.7).[36]



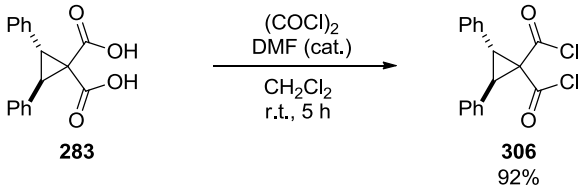
Scheme 5.7 Siegel's synthesis of phthaloyl peroxide **69** using sodium percarbonate.

To test the suitability of Siegel's protocol in the synthesis of malonoyl peroxides, cyclopropane-1,1-dicarboxylic acid **91** was converted to acid chloride **305** using thionyl chloride, and then treated with sodium percarbonate in dichloromethane (Scheme 5.8). Cyclopropyl malonoyl peroxide **86** was produced in good yield (60% over two steps), providing a potential alternative route to diphenyl peroxide **282**.



Scheme 5.8 Synthesis of cyclopropyl malonoyl peroxide **86** using sodium percarbonate.

Unfortunately, treating diphenyl diacid **283** with thionyl chloride resulted in a very complex mixture of co-products. However, treatment of diphenyl diacid **283** with oxalyl chloride in the presence of catalytic dimethyl formamide resulted in diacid chloride **306** in an excellent 92% yield (Scheme 5.9).



Scheme 5.9 Synthesis of diacid chloride **306**.

Interestingly, diacid chloride **386** was a stable colourless solid which could be subjected to aqueous work-up, recrystallised, and stored in the open air indefinitely (> 1.5 years). A potential explanation for this unexpected stability for an acid chloride arose from studying a 3D energy-minimised (MM2 force field) model of **306** (Figure 5.7). The phenyl rings and chlorine atoms appear to provide substantial steric shielding of all four Bürgi-Dunitz trajectories, therefore hindering the approach of nucleophiles such as water to the $\pi^*_{C=O}$ orbital. Bond rotation to a more reactive conformation could also be difficult due to severe steric crowding around the central cyclopropane moiety.

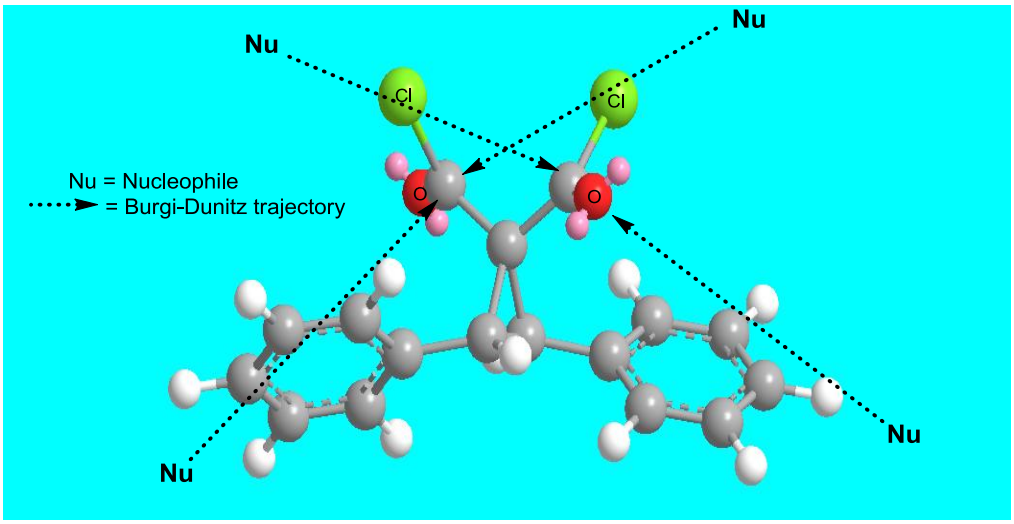
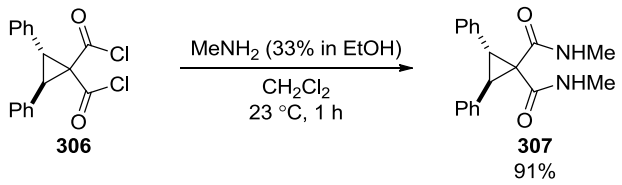


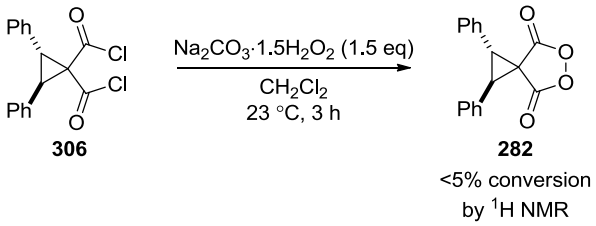
Figure 5.7 The hindered Bürgi-Dunitz trajectories of diacid chloride **306**.

However, treatment of diacid chloride **306** with an excess of methylamine rapidly produced diamide **307** (91%), confirming that reaction with stronger nucleophiles was viable.



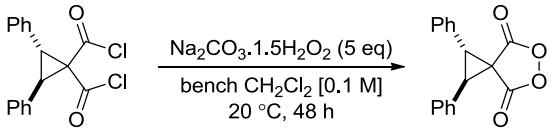
Scheme 5.10 Reactivity test of diacid chloride **306**.

Acid chloride **306** was treated with sodium percarbonate using Siegel's conditions[36] (Scheme 5.11). Encouragingly, peroxide **282** appeared to have formed, but conversion was low by ^{1}H NMR spectroscopy (<5%).



Scheme 5.11 Attempted synthesis of diphenyl peroxide **282** using sodium percarbonate.

Sodium percarbonate is commonly used in dichloromethane, chloroform or acetonitrile.[109] In the reaction of diacid chloride **306** with sodium percarbonate, chloroform produced similar results to dichloromethane, but acetonitrile led to undesirable by-product formation. Extensive reaction optimisation (parameters outlined in Table 5.1) resulted in full conversion of diacid chloride **306** to peroxide **282** (Scheme 5.12). However, the reaction was very capricious with stirring intensity shown to be a major factor. Vigorous stirring with a bulky stirrer bar was required for consistently high conversion.



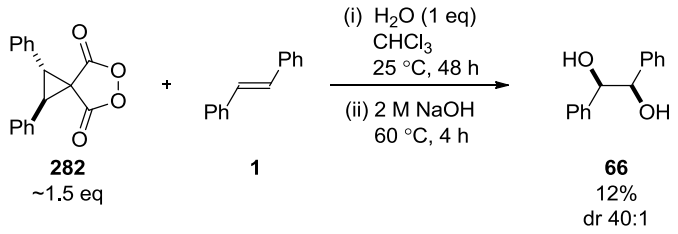
306 **282**

Scheme 5.12 Optimised reaction conditions for synthesis of peroxide **282**.

Entry	Variable	Conditions	Effect on Conversion
1	Solvent	CH_2Cl_2, $CHCl_3$, MeCN	Suitable in CH_2Cl_2 or $CHCl_3$. Much by-product formation in MeCN.
2	Moisture content	Anhydrous, bench, biphasic	Negligible conversion when anhydrous or biphasic. Good conversion with some moisture present.
3	Peroxide eq.	1, 1.5, 2, 3, 5, 8, 10	Poor < 3 eq. Full when 5 eq. No increase > 5 eq.
4	Time (h)	1, 3, 8, 16, 24, 48	48 h required for full conversion.
5	Atmosphere	N_2, air	No difference in conversion.
6	Temp. (^oC)	0, 20, 40	Optimum at 20 ^oC. By-product formation at 40 ^oC.
7	Conc. [M]	0.05, 0.1, 0.15, 0.2	Low conversion < 0.1 M and > 0.15 M.
8	Peroxide source	$Na_2CO_3 \cdot 1.5H_2O_2$, Na_2O_2, $Urea \cdot H_2O_2$, H_2O_2 (aq., 35%)	No formation of **282** with any other source of peroxide except $Na_2CO_3 \cdot 1.5H_2O_2$.
9	Peroxide quality	Assessed by iodometric titration[110]	Active oxygen content of peroxide starting material was as expected.
10	CH_2Cl_2 stabiliser	Amylene, EtOH, None	No difference.
11	Stirring	Speed, stirrer bar (size and shape), sonication	Vigorous stirring with egg-shaped bar was most effective. Sonication ineffective.

Table 5.1 Optimisation variables examined in peroxide **282** formation from acid chloride **306**.

As an added frustration, peroxide **282** proved unstable to isolation and purification despite substantial effort, so impure peroxide **282** was employed in the dihydroxylation protocol with *trans*-stilbene **1** (Scheme 5.13). After 48 hours, no peroxide **282** was present in the reaction mixture but a large amount of *trans*-stilbene **1** remained (45% recovery), implying much of the peroxide had decomposed. The complex mixture of products was treated with 2 M sodium hydroxide (60 ^{o}C, 4 h) and purified by silica gel column chromatography to afford a small amount of diol (12%) with excellent *syn*-diastereoselectivity (40:1).



Scheme 5.13 Dihydroxylation using diphenyl peroxide **282**.

During this frustrating optimisation procedure five key problems emerged: (i) Initial peroxide **282** identification, (ii) capricious conversion of **306** to **282**, (iii) isolation and purification of peroxide **282**, (iv) peroxide instability, and (v) low yield in the dihydroxylation of **1**. Despite exhaustive attempts to solve these issues, no clear solution was apparent. Considerable time was dedicated to this part of the investigation and it was decided that an alternative peroxide scaffold should be explored.

5.1.6 Synthesis of Bis-*para*-Nitrophenyl Peroxide 308

It was proposed that addition of strong electron withdrawing groups to the phenyl rings of diacid **283** may prevent the acid-catalysed rearrangement of diacid **283** to lactone **303**, due to destabilisation of the proposed carbocationic intermediate **301** (Figure 5.6). This may allow direct conversion of diacid to peroxide using the original urea hydrogen peroxide in methanesulfonic procedure (Chapter 2.1), and therefore eliminate the capricious sodium percarbonate route (Scheme 5.12). Addition of electron withdrawing groups into peroxide **282** may also increase reactivity of the peroxide through a

long-range negative inductive effect (-I). Strongly electron-deficient bis-*para*-nitrophenyl peroxide **308** (Figure 5.8) was selected as a suitable target.

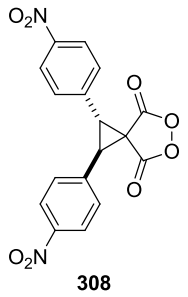
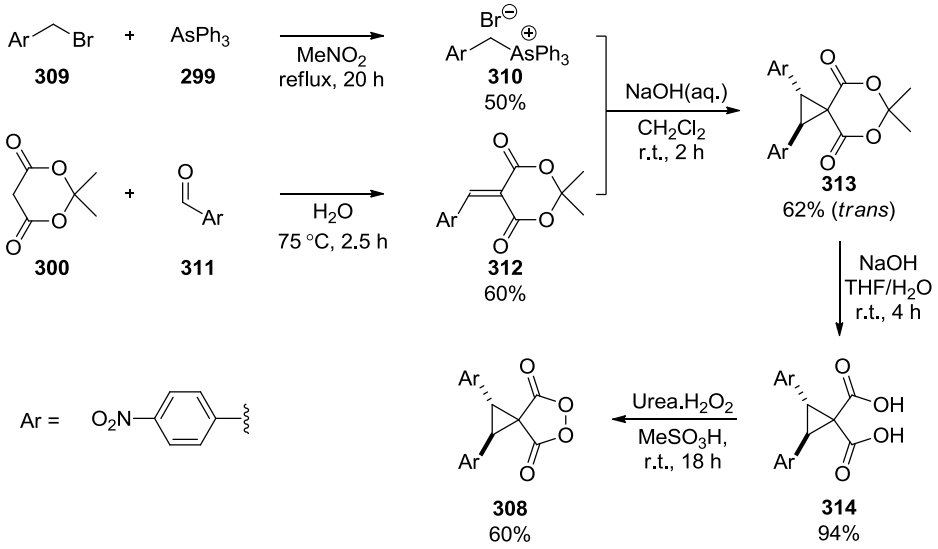


Figure 5.8 Bis-*para*-nitrophenyl peroxide **308**.

Bis-*para*-nitrophenyl diacid **314** was synthesised using a similar route to that described previously without any major complications, starting from *para*-nitrobenzyl bromide **309** and *para*-nitrobenzaldehyde **311** in 3 steps with an overall yield of 35% from meldrum's acid **300** (Scheme 5.14).



Scheme 5.14 Synthesis of bis-*para*-nitrophenyl peroxide **308**.

The relative *trans*-stereochemistry of the 4-nitrophenyl moieties was confirmed by single crystal X-ray crystallographic analysis of diester **313** (Figure 5.9), which formed as an 8:1 (*trans*:*cis*) mixture of diastereoisomers but was isolated as a single (*trans*) diastereoisomer after crystallisation (62%).

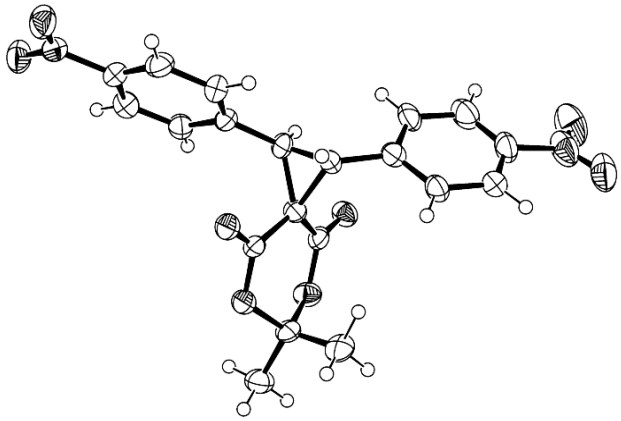
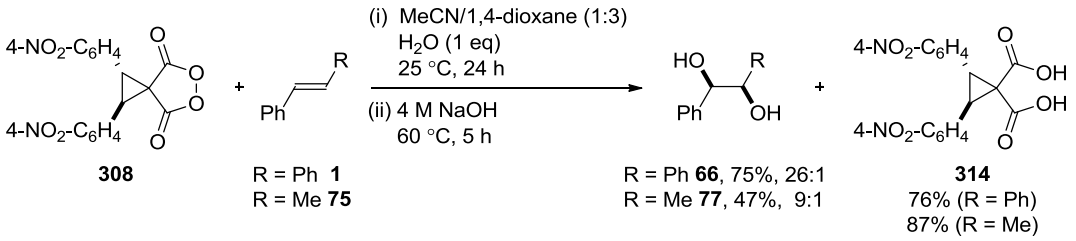


Figure 5.9 Single crystal X-ray crystallographic analysis of **313** showing *trans*-stereochemistry.

As predicted, the acid-catalysed rearrangement of diacid **314** to the corresponding lactone was not observed in methanesulfonic acid, allowing peroxide **308** to be synthesised directly from diacid **314** *via* the urea hydrogen peroxide method in reasonable yield (60%, Scheme 5.14). Pleasingly, bis-*para*-nitrophenyl peroxide **308** was shown to be stable to air, water, gentle heating and even silica gel column chromatography, allowing isolation of pure material.

5.1.7 Dihydroxylation Using Bis-*para*-Nitrophenyl Peroxide 308

Bis-*para*-nitrophenyl peroxide **308** proved to be insoluble or sparingly soluble in most organic solvents. It was found that a mixed solvent system of acetonitrile/1,4-dioxane (1:3) produced homogeneous reaction mixtures with *trans*-stilbene **1** and β-methylstyrene **75** allowing dihydroxylation to occur at room temperature (Scheme 5.15).



Scheme 5.15 Dihydroxylation using bis-*para*-nitrophenyl peroxide **308**.

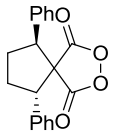
Treatment of *trans*-stilbene **1** with peroxide **308** resulted in diol **66** in good yield (75%) and excellent diastereoselectivity (26:1 *syn*:*anti*). β-Methyl styrene **75** also underwent dihydroxylation in mediocre yield (47%) with good stereoselectivity (9:1 *syn*:*anti*). The *syn*:*anti* ratios were slightly lower than with cyclopropyl malonoyl peroxide **86** (**66**, 33:1 and **77**, 16:1), but still synthetically useful. In both reactions diacid **314** was recovered by aqueous work-up in good yield (76% and 87% respectively).

Peroxide **308** exhibited potential as an effective *syn*-dihydroxylation reagent, so an enantioenriched sample of **308** was required to investigate its ability to achieve enantioselectivity in the dihydroxylation reaction. An asymmetric variant of the key cyclopropanation step using arsonium ylides (Scheme 5.14) was unknown, and it was beyond the scope of this project to develop the required methodology. Therefore, diacid **314** was subjected to chiral resolution techniques by addition of chiral amines in an attempt to form diastereomeric salt mixtures, which could potentially be separated by difference in their physical properties. A substantial screen of common chiral amine resolving agents and mixtures of structurally related chiral amines (known as the *Dutch Resolution* method)[111] was carried out, but chiral resolution was not achieved.

Chiral malonoyl peroxides based on a cyclopropane core had presented a number of problems. However, the major issues associated with these reagents were the highly toxic arsenic-based compounds required for their synthesis, and the lack of an asymmetric variant of the key cyclopropanation step. These factors severely limited development of this family of compounds. Accordingly, an alternative approach that addressed these issues was explored.

5.2 Chiral Cyclopentyl Malonoyl Peroxide Derivative 315

To overcome the problems presented in the synthesis and development of chiral cyclopropane-based malonoyl peroxides **282** and **308**, cyclopentane-based malonoyl peroxide **315** was proposed as an attractive alternative (Figure 5.10).



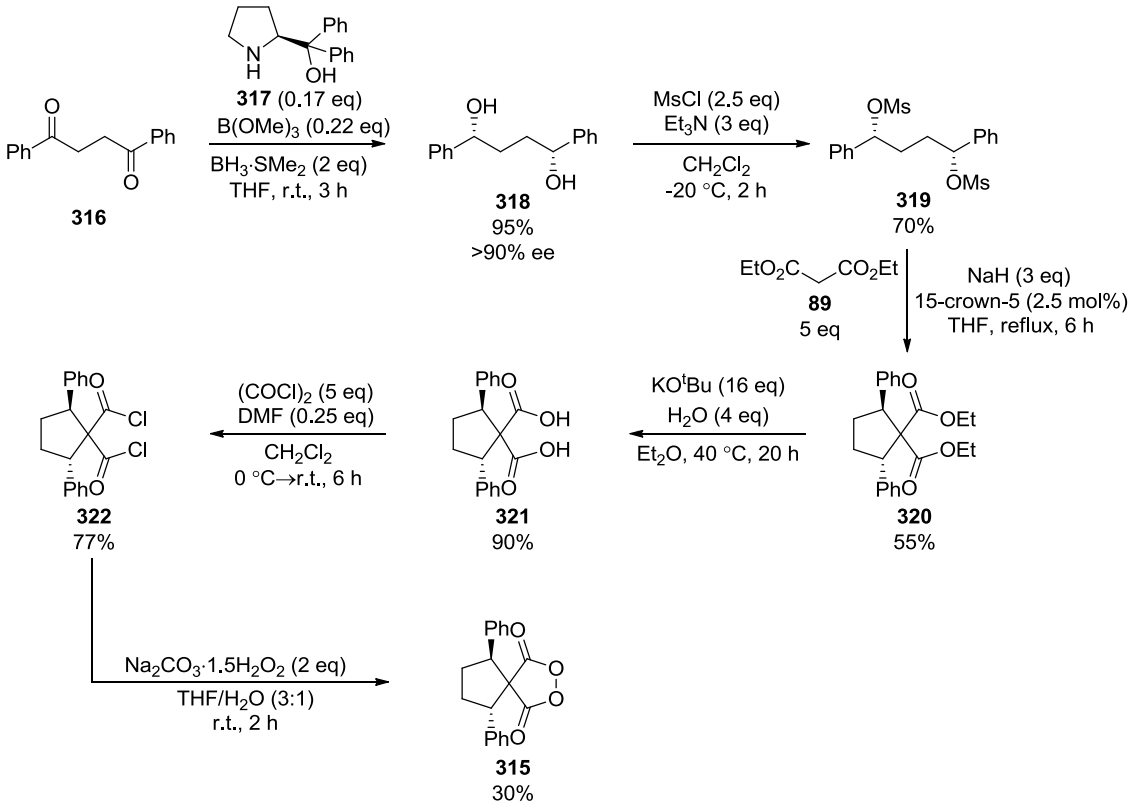
315

Figure 5.10 Chiral cyclopentane-based malonoyl peroxide target **315**.

It was thought that expansion of the cycloalkane ring from cyclopropyl to cyclopentyl would greatly reduce ring-strain, and therefore increase the stability of the cycloalkane moiety to ring-opening (see Figure 5.6). This may eliminate the requirement for electron-withdrawing *para*-nitro substituents on the phenyl ring, thereby increasing peroxide **315** solubility over that of **308**. An additional advantage of cyclopentyl malonoyl peroxide derivative **315** over its cyclopropyl based analogues **282** and **308** is the more intrusive position of the phenyl rings, which could be more effective at controlling the trajectory of an approaching alkene. However, the main advantage of pursuing peroxide **315** arises from literature precedent describing an alternative metal-free, asymmetric synthesis of a potential precursor to **315**. Disadvantages of increasing the cycloalkane ring size are the increased likelihood of decarboxylation occurring during the dihydroxylation, meaning the reagent could not be easily recovered (as the corresponding diacid), and the potential for reduced reactivity compared to its cyclopropyl analogue **282**.

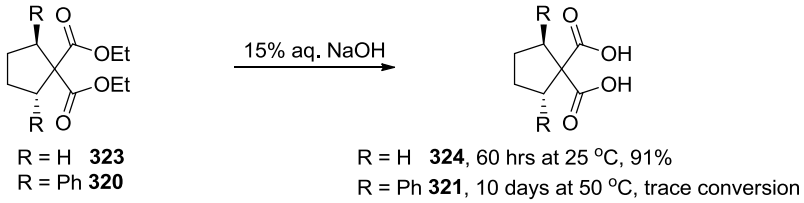
5.2.1 Synthesis

The synthesis of peroxide **315** was based around chiral diester **320**, which had previously been reported in the literature (Scheme 5.16).[112] Diester **320** was made in three simple metal-free steps from 1,2-dibenzoylethane **316** with high diastereo- and enantioselectivity, offering many major advantages over the arsonium ylide route to cyclopropane derivatives **297** and **313**. Reduction of 1,4-dione[113,114] **316** by Corey-Bakshi-Shibata (CBS) reduction[115] gave (*R*,*R*)-1,4-diol **318** in an excellent 95% yield and >90% ee ($[\alpha]_D^{25}$ +54.4. (*c* 1.00 $CHCl_3$). Lit.[114] $[\alpha]_D^{25}$ –58.0 (*c* 1.02 $CHCl_3$), 98% ee for *S*,*S*-isomer), which was then converted to the bis-mesylate **319** (70%). **319** decomposed after a few hours at room temperature in the presence of air, but was stable for weeks at –20 °C under a nitrogen atmosphere. Cyclisation and incorporation of the 1,1-diester functionality using an excess of diethyl malonate **89** and sodium hydride, gave diester **320** in reasonable yield (55%) as a single diastereoisomer after purification. Due to time constraints, the precise enantiomeric excess has not been determined within this series and will be essential for developing this work further.



Scheme 5.16 Synthesis of chiral peroxide **315**.

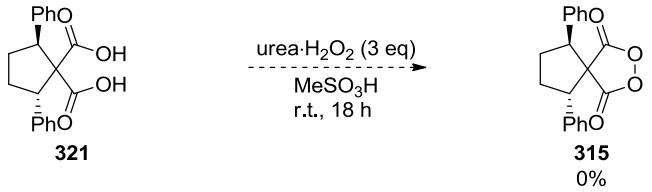
The hydrolysis of diester **320** to diacid **321** proved to be particularly stubborn. Initially, diester **320** was stirred in a 15% aqueous sodium hydroxide solution for 60 hours at room temperature, as this method was successful in the hydrolysis of cyclopentane-1,1-diethyl ester **323** (Scheme 5.17), but no hydrolysis of **320** was observed. Increasing temperature (50 ^{o}C) and reaction time (10 days) also resulted in near quantitative recovery of starting material **320**.



Scheme 5.17 Difference in rate of hydrolysis between cyclopentane-1,1-diesters **320** and **323**.

It was thought the resistance of diester **320** to the aqueous hydrolysis conditions was for two reasons; steric hindrance of the ester functions imposed by the proximal phenyl groups, and increased hydrophobic character of diester **320**. An alternative method developed by Gassman and Schenk, for hydrolysis of sterically hindered ester and tertiary amides under mild conditions was successfully employed, giving diacid **321** in 90% yield (Scheme 5.16).[116] The authors suggested that the slurry of diethyl ether, excess potassium *tert*-butoxide and a small amount of water produces highly reactive, relatively unsolvated hydroxide ions, that are able to effectively hydrolyse stubborn ester and amide derivatives under mild conditions.

Treatment of diacid **321** with urea hydrogen peroxide in methanesulfonic acid did not result in the target peroxide **315** (Scheme 5.18). Starting material was recovered (~50%) along with many unidentifiable co-products. However, a control reaction revealed that diacid **321** is relatively stable in methanesulfonic acid over a period of 18 hours, with only minor decomposition observed, unlike its strained cyclopropyl analogue **283** which underwent rearrangement to **303** (Figure 5.6).

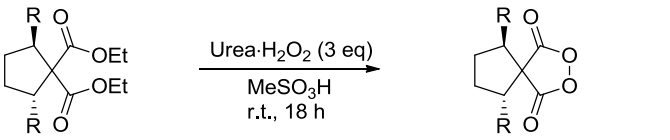


321 **315** 0%

Scheme 5.18 Attempted synthesis of peroxide **315** from diacid **321**.

Peroxide **315** was synthesised by converting diacid **321** to diacid chloride **322** (77%), purification by silica gel column chromatography, then subsequent treatment with sodium percarbonate (Scheme 5.16). Pleasingly, peroxide **315** was stable to aqueous work-up and silica gel column chromatography. Dichloromethane and chloroform are the typical solvents to use with sodium percarbonate, but no conversion was observed when these solvents were employed, resulting in near quantitative recovery of diacid chloride **322**. The reduced reactivity of the sterically hindered acid chloride moieties of **322**, in combination with the low levels of free hydrogen peroxide in non-aqueous solution, could explain the lack of reaction. A mixed solvent system of THF/water was used to fully dissolve the sodium percarbonate and acid chloride **322**. The conditions were successful in forming peroxide **315** albeit in poor yield (30%) due to formation of a major co-product which was not identified. The peroxide forming step using sodium percarbonate has not been optimised due to time constraints.

The potential exists for the synthesis of peroxide **315** to be shortened from six steps to four steps, by direct access from diester **320**. This shortened approach has been achieved with cyclopentane-1,1-diethyl ester **323**, although results were capricious (Scheme 5.19). Initial efforts by exposing diester **320** to the urea hydrogen peroxide complex in methanesulfonic acid resulted in no reaction, probably due to the lack of solubility of diester **320** in methanesulfonic acid.



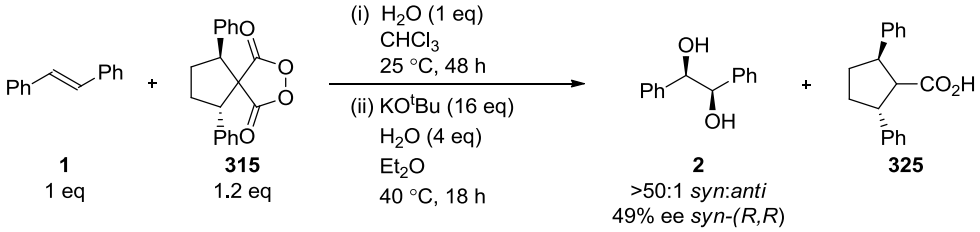
R = H **323**
R = Ph **320**

R = H **87** (62%)
R = Ph **315** (recovered S.M.)

Scheme 5.19 Direct malonoyl peroxide formation from diester **323**.

5.2.2 Asymmetric Dihydroxylation

Chiral peroxide **315** (1.2 eq) was employed in the dihydroxylation of *trans*-stilbene **1** in chloroform at room temperature (Scheme 5.20). *Trans*-stilbene **1** was fully consumed after 48 hours as judged by TLC and ^{1}H NMR spectroscopy. It should be noted that due to the small scale of reaction (10 mg of **1**), intermediate isolation and identification was not performed at this stage. Standard hydrolysis conditions were initially employed (1 M NaOH, 60 ^{o}C, 4 h), but were ineffective. However, treatment with potassium *tert*-butoxide in wet diethyl ether achieved full hydrolysis in 18 hours at 40 ^{o}C.



1 1 eq | **315** 1.2 eq | **2** >50:1 *syn*:*anti* 49% ee *syn*-(*R*,*R*) | **325**

Scheme 5.20 Enantioselective dihydroxylation of *trans*-stilbene **1**.

Analysis of the crude reaction mixture by TLC and ^{1}H NMR spectroscopy indicated diol **2** had formed. A single (*syn)* isomer **2** was observed (see Appendix 9.3 for the ^{1}H NMR spectrum of the crude reaction mixture), however no accurate yield of **2** could be recorded for the transformation at this early stage of development. The crude reaction mixture was subjected to chiral HPLC, and the enantiomeric excess determined to be 49% ee in favour of the *R*,*R*-enantiomer **2** (see Appendix 9.4 for HPLC chromatograms). The absolute configuration of **2** was confirmed by synthesis of an authentic sample of *syn*-(*R*,*R*)-**2** using Sharpless asymmetric dihydroxylation conditions (AD-mix-β).[4]

An acidic by-product, consistent with the structure of **325** by ^{1}H NMR spectroscopy (see Appendix 9.3 for the ^{1}H NMR spectrum of crude acid **325**),[117] was recovered from the dihydroxylation reaction. Decarboxylation had occurred, meaning the recovered material **325** cannot be easily converted back to peroxide **315**.

There are some key points of note regarding this exciting result. This is the first example of an asymmetric metal-free *syn*-dihydroxylation using a peroxide reagent. No reaction optimisation or substrate scope examination has been performed due to time constraints. However, a fantastic first-result of 49% ee has been achieved at *room temperature* with *trans*-stilbene **1**. The reaction appears to be very stereoselective with only a single diastereoisomer (*syn*) of diol **2** observed. Additionally, the reaction is tolerant of both moisture and air, performed at ambient conditions and simple to execute with no specialist techniques or equipment required.

Crucially, the absolute (*R*,*R*)-configuration of the major enantiomer of diol **2** is consistent with the proposed transition state model (Figure 5.11). Attack of the $\pi_{C=C}$ orbital of alkene **1** into the σ^*_{O-O} orbital of peroxide **315** can occur on either the re- or si-face of alkene **1**. The favoured approach is from the si-face of alkene **1**, as this delivers the alkene with minimal steric clash between the phenyl moieties of alkene **1** and peroxide **315**. The C_2 symmetry of peroxide **315** means that alkene approach to the opposite side of the O–O bond is identical, so both approaches result in preferential formation of (*R*,*R*)-diol **2**.

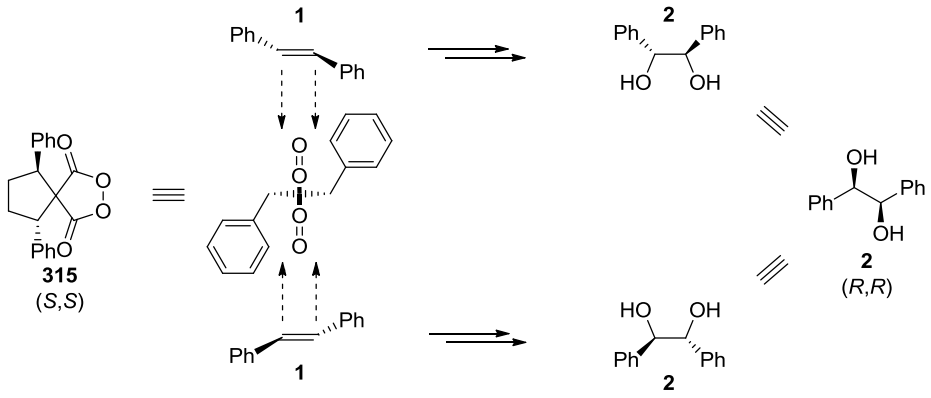


Figure 5.11 Transition state model predicting the major (*R*,*R*)-enantiomer of diol **2**.

5.3 Conclusions

Synthetic routes to three novel chiral malonoyl peroxides **282**, **308** and **315** were developed (Figure 5.12). These are the first examples of malonoyl peroxides containing stereogenic centres. Racemic cyclopropane-based peroxides **282** and **308** were synthesised using arsonium ylide cyclopropanation chemistry. An asymmetric synthesis of cyclopentane-based peroxide **315** was completed in six transition metal-free steps, originating from an asymmetric Corey-Bakshi-Shibata (CBS) reduction of 1,2-dibenzoylethane **316**.

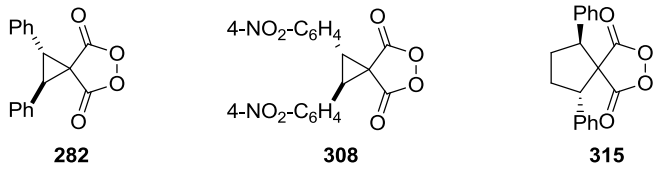


Figure 5.12 Novel chiral malonoyl peroxides.

The first metal-free, asymmetric, *syn*-dihydroxylation of alkenes using a peroxide was achieved using (*S*,*S*)-2,5-diphenylcyclopentane malonoyl peroxide **315**. This represents a significant advance in the challenging area of metal-free alkene *syn*-dihydroxylation. The reaction proceeded in the presence of moisture and air, at ambient conditions and required no specialised practical techniques. In an initial result, *trans*-stilbene **1** underwent dihydroxylation to produce exclusively *syn*-diol **2** in 49% ee at room temperature without any reaction optimisation. Importantly, the major (*R*,*R*)-enantiomer is consistent with the transition state model. Although no accurate yield can be recorded for this reaction, it represents an excellent starting point for future investigations.

Chapter 6: *Anti*-Dihydroxylation

6 *Anti*-Dihydroxylation

Anti-1,2-diols have high utility in organic synthesis, just like their *syn*-diol counterparts. Therefore, it is somewhat surprising that few dihydroxylation protocols are stereodivergent. During an investigation, synthetic chemists often require both diastereoisomers of a particular compound, but must employ completely different methodology to construct each isomer. Hence it was deemed interesting, from both an academic and practical perspective, to investigate the use of cyclopropyl malonoyl peroxide **86** in the *anti*-dihydroxylation of alkenes.

6.1 Literature Methods

6.1.1 Epoxide Opening

The most common method of achieving *anti*-1,2-dihydroxylation is epoxide **326** formation with subsequent acid- or base-catalysed ring-opening by water (Figure 6.1).[118]

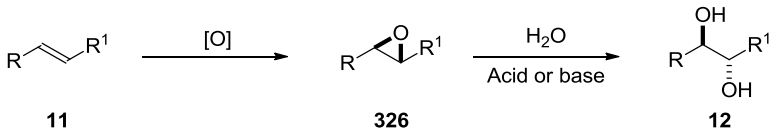
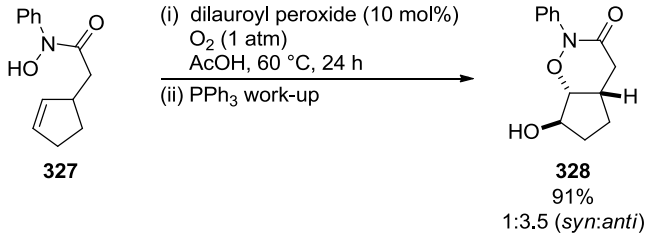


Figure 6.1 *Anti*-diol **12** by epoxide **326** ring-opening.

Many metal-free epoxidation reagents are available with a very large substrate scope making this route both simple and diverse.[119] A significant advantage of this method is the ability to perform well-established metal-based[120] and metal-free[121] catalytic asymmetric epoxidation reactions, resulting in enantioselective *anti*-diol formation after ring-opening.

6.1.2 Hydroxamic Acids

An emerging area of alkene *anti*-dioxygenation involves the use of tethered *N*-arylhydroxamic acids **327**, with oxygen as the stoichiometric oxidant (Scheme 6.1).[122]



Scheme 6.1 Intramolecular aerobic *anti*-dioxygenation using tethered hydroxamic acids **327**.

The reaction has a relatively large substrate scope, tolerating conjugated and unconjugated alkenes containing mono-, di- and tri-substitution, producing vicinal diols in good to excellent yield. The key mechanistic step involves a chemoselective 6-exo-alkene cyclisation of amidoxyl radical **330**, with subsequent addition of triplet oxygen to carbon-centred radical **331**, favouring *trans*-addition of oxygen across the double bond (Figure 6.2). Hydrogen abstraction to give hydroperoxide **333** followed by reductive work-up produces dioxygenation product **334**, which can be converted into the corresponding 1,2-diol by zinc mediated N–O bond cleavage in a one-pot procedure.

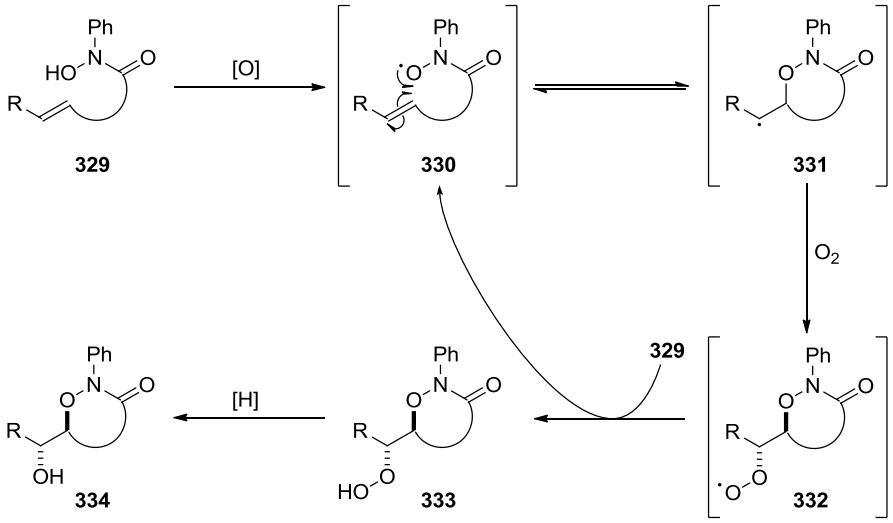
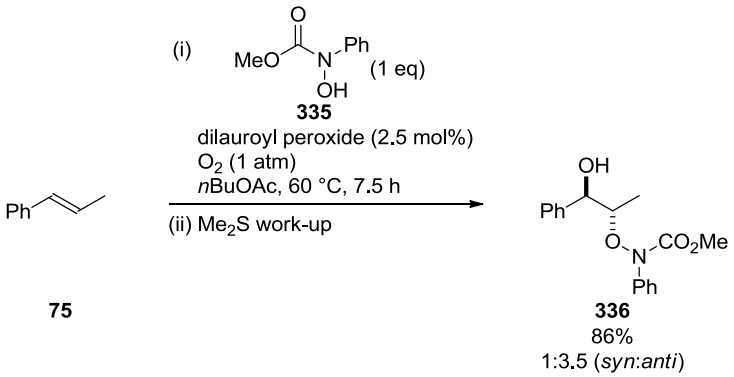


Figure 6.2 Proposed mechanism for aerobic dioxygenation.

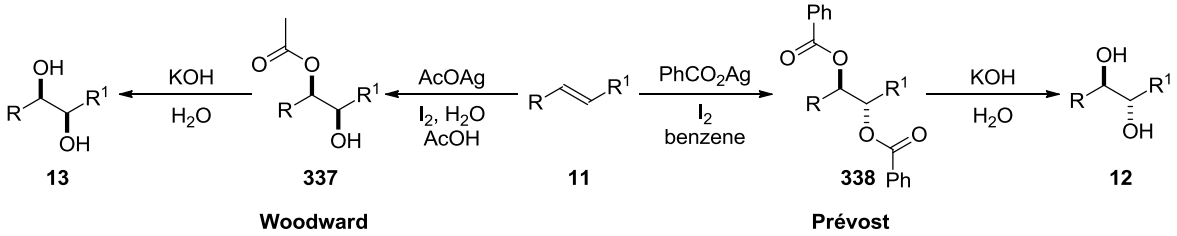
Alexanian later significantly improved the protocol by employing *N*-hydroxy-*N*-phenyl carbamate **335** in an intermolecular reaction with alkenes, thereby eliminating the requirement for tethering of the hydroxamic acid moiety (Scheme 6.2).[123] However, despite high yields, a simple protocol, large substrate scope and highly regioselective formation of a differentiated diol product, only moderate *anti*-selectivity was achieved, thus currently limiting its synthetic application as a general *anti*-dioxygenation method.



Scheme 6.2 Intermolecular aerobic *anti*-dioxygenation using *N*-hydroxy-*N*-phenyl carbamate **335**.

6.1.3 Prévost-Type Reactions

The Woodward-Prévost reaction is the only general method of producing both *syn*- **13** and *anti*-diols **12** from alkenes **11** with high diastereoselectivity through relatively small changes in the reaction protocol (Scheme 6.3).[2,19]



Scheme 6.3 Woodward (*syn*) and Prévost (*anti*) dihydroxylation reactions.

Despite being well established, both the Woodward and Prévost reactions suffer from the use of stoichiometric silver salts. However, as mentioned in Chapter 1.1.1, Emmanuvel recently reported a modified protocol that eliminated the requirement for silver salts (Scheme 1.4).[20]

The ability of Woodward-Prévost-type reactions to produce both *syn*- **13** and *anti*-diols **12** is due to a common dioxonium intermediate **339** (Figure 6.3). Under wet (Woodward) conditions, a molecule of water attacks dioxonium **339** in the 2-position, resulting in *syn*-diol **13** after basic hydrolysis. Alternatively, under anhydrous (Prévost) conditions, nucleophilic attack by a carboxylic acid in either the 4- or 5-position, results in *anti*-diol **12** after hydrolysis.

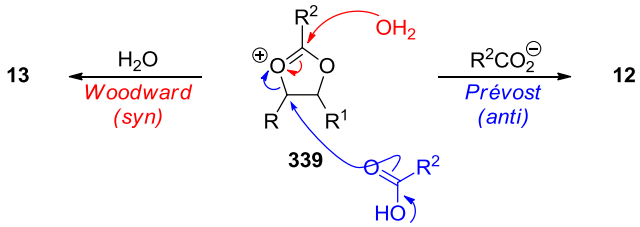


Figure 6.3 Common dioxonium intermediate **339** in the Woodward-Prévost reaction.

Based on the similarity of the Woodward-Prévost intermediate **339** and the dioxonium intermediate **99** identified in the cyclopropyl malonoyl peroxide **86** *syn*-dihydroxylation reaction, it was proposed that performing the reaction in the presence of anhydrous acetic acid may provide access to the *anti*-dihydroxylation product **12** (Figure 6.4).

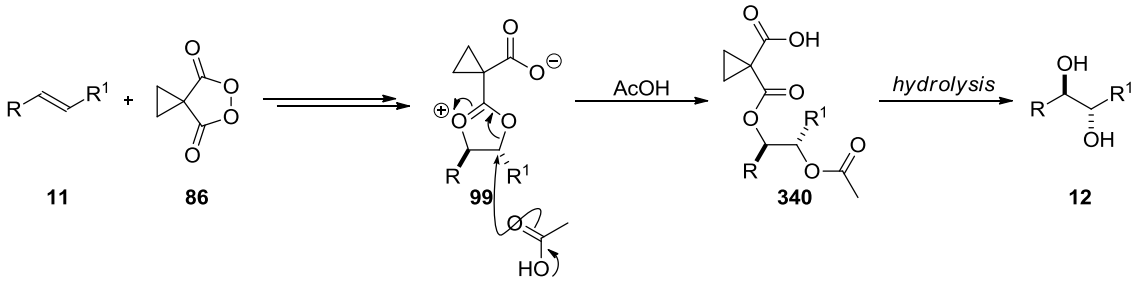
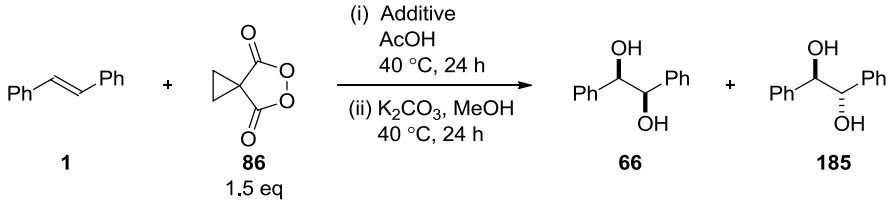


Figure 6.4 Proposed novel *anti*-dihydroxylation reaction using cyclopropyl malonoyl peroxide **86**.

6.2 Reaction Development

6.2.1 Initial Optimisation

During development of an *anti*-dihydroxylation protocol, *trans*-stilbene **1** was selected as a suitable substrate due to the minor quantities of *anti*-diol **185** formed in the *syn*-dihydroxylation protocol with **86** (86%, 33:1 *syn*:*anti*). *Trans*-stilbene **1** was treated with peroxide **86** (1.5 eq) in reagent grade acetic acid at 40 °C for 24 h, resulting in a small excess of *anti*-diol **185** (71%, 1:1.2 *syn*:*anti*) after hydrolysis with potassium carbonate (3 eq) in methanol (Table 6.1, Entry 1). This exciting initial result verified that acetic acid was capable of switching the diastereoselectivity of the reaction. In an effort to increase selectivity, a number of methods of drying acetic acid were examined (Table 6.1).



Entry	AcOH drying method[a]	Additive	*syn*:*anti* (66:185)[b]
1	-	-	1:1.2
2	-	Ac_2O[c]	1:1.3
3	Ac_2O and CrO_3[d]	-	1:1.3
4	$MgSO_4$	-	1:1.2
5	P_2O_5[d]	-	1:1.5
6	Mol. sieves (4 Å)	-	1:2
7	Mol. sieves (4 Å)	Dioxane[e]	1:1.6
8	Mol. sieves (4 Å)	NaOAc[f]	N/A (decomp.)
9	Mol. sieves (3 Å)	-	1:3
10	Mol. sieves (3 Å)[g]	-	1:4.5
11	Mol. sieves (3 Å)[h]	-	1:4.5

[a] Drying agent added to AcOH for 2 h at 23 °C unless otherwise stated. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Reaction performed in 4:1 AcOH:Ac_2O. [d] Drying agent(s) and AcOH were heated to reflux for 4 h. [e] Reaction performed in 1:1 AcOH:1,4-dioxane. [f] 2 equivalents. [g] Added to a solution of peroxide **86** in AcOH for 2 h at 23 °C. [h] Added to a solution of peroxide **86** in AcOH for 24 h at 23 °C.

Table 6.1 Examination of methods to achieve anhydrous acetic acid.

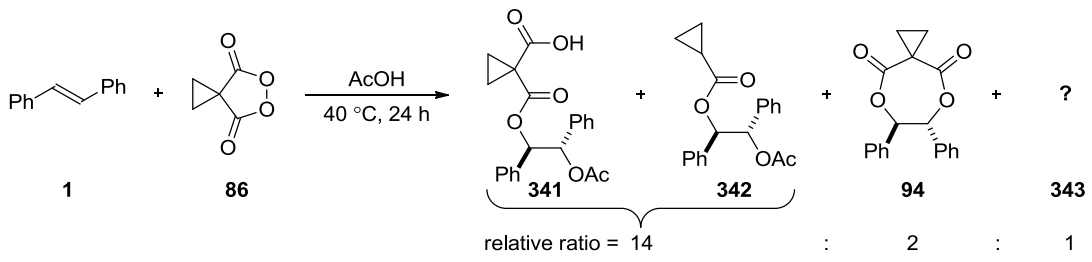
Addition of acetic anhydride is commonly used to remove traces of water in Prévost-type reactions,[21,28] however it was ineffective in the reaction of peroxide **86** with **1** (1:1.3 *syn*:*anti*, Table 6.1, Entry 2) when used as an additive. Distillation of acetic acid with acetic anhydride and chromium trioxide (CrO_3) prior to use did not result in an increase in diastereoselectivity (1:1.3 *syn*:*anti*, Table 6.1, Entry 3), and neither did drying over magnesium sulfate (1:1.2 *syn*:*anti*, Table 6.1, Entry 4). Distillation of acetic acid over phosphorus pentoxide produced only a negligible increase in diastereoselectivity (1:1.5 *syn*:*anti*, Table 6.1, Entry 5). Drying of acetic acid over activated 4 Å molecular sieves resulted in an encouraging 1:2 selectivity in favour of *anti*-diol **12** (Table 6.1, Entry 6). The selectivity decreased slightly when a mixed solvent system of AcOH:1,4-dioxane (1:1) was employed (1:1.6 *syn*:*anti*, Table 6.1, Entry 7). Sodium acetate is a stronger nucleophile than acetic acid so it was thought the dioxonium opening reaction (Figure 6.4) may be favoured using sodium acetate as an additive. However, addition of 2 equivalents of sodium acetate (Table 6.1, Entry 8) resulted in recovery of only *trans*-stilbene **1** post-reaction, consistent with a destructive interaction of sodium acetate with peroxide **86**. Interestingly, a noticeable increase in selectivity was observed when acetic acid was dried over 3 Å molecular sieves (1:3 *syn*:*anti*, Table 6.1, Entry 9).

Due to the inherent dangerous nature of peroxides it was deemed unsafe to dry peroxide **86** in solid form, and therefore non-anhydrous peroxide **86** had been used thus far. Dissolution of peroxide **86** in acetic acid, followed by drying of the solution over activated 3 Å molecular sieves for 2 hours at room temperature before use in the reaction with *trans*-stilbene **1**, resulted in good diastereoselectivity (1:4.5 *syn*:*anti*, Table 6.1, Entry 10). Increasing the drying time to 24 hours resulted in no change in selectivity (1:4.5 *syn*:*anti*, Table 6.1, Entry 11).

This informative set of results clearly indicated that water had a profound effect on the transformation and had a significant influence on the reaction outcome.

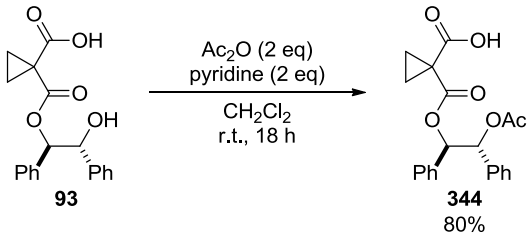
6.2.2 Identification of Intermediates

Reaction of *trans*-stilbene **1** and peroxide **86** in anhydrous acetic acid, without subsequent hydrolysis, produced four compounds (Scheme 6.4). Diesters **341**, **342** and 7-membered ring **94** were isolated by silica gel column chromatography. However, compound **343** could not be isolated or identified thus far despite repeated efforts. Assuming the two characteristic peaks for unknown compound **343** at δ 5.63 (d, J = 7.5 Hz) and δ 3.57 (d, J = 7.5 Hz) in the ^{1}H NMR spectrum of the crude reaction mixture each integrate to one proton, then **343** is a minor component (~6%) of the reaction mixture (see Appendix 9.3 for the ^{1}H NMR spectrum of the crude reaction mixture).



Scheme 6.4 Identification of products from the reaction of **1** and **86** in acetic acid.

The reaction was performed in deuterated acetic acid and followed by *in situ* ^{1}H NMR spectroscopy over known time intervals. This study revealed that the ratio of **341**:**342**:**94**:**343** did not change over time, implying that the compounds did not interconvert, but formed by discrete mechanisms. This was confirmed by individually subjecting each of the isolated intermediates **341**, **342** and **94** to the reaction conditions (1.5 eq peroxide **86**, AcOH, 40 ^{o}C, 24 h) without any change in structure. The relative stereochemistry of esters **341**, **342** and 7-membered ring **94** was confirmed by methanolysis of each compound (3 eq K_2CO_3, methanol, 40 ^{o}C, 24 h) providing either *syn*- **66** or *anti*-diol **185**. The opposite *syn*-diastereoisomer **344** of *anti*-diester **341** was independently synthesised from *syn*-**93** for additional confirmation of the structure assignment and relative stereochemistry of *anti*-ester **341** by comparison (Scheme 6.5).



Scheme 6.5 Independent synthesis of **344**.

The exact structure of **343** is currently unknown, but it can be deduced that *syn*-diol **66** is produced upon hydrolysis of **343**, consistent with the overall stereoselectivity of the reaction (1:4.5 *syn*:*anti*).

6.2.3 Proposed Mechanism

A mechanism consistent with formation of observed intermediates **341**, **342** and **94** by discrete mechanisms is outlined in Figure 6.5.

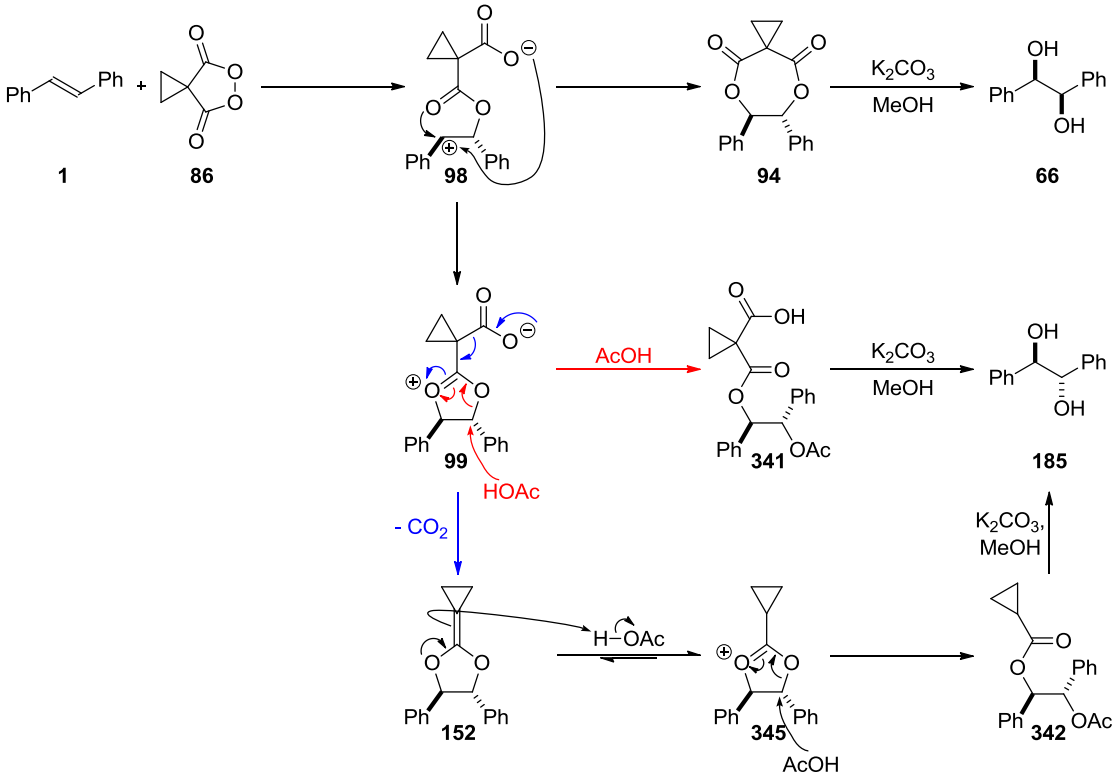


Figure 6.5 Proposed mechanism for *anti*-dihydroxylation in acetic acid.

Reaction of alkene **1** and peroxide **86** produces zwitterion ion **98** which can ring-close to *syn*-7-membered ring **94**, providing *syn*-diol **66** upon treatment with potassium

carbonate in methanol. Alternatively, zwitterion **98** can ring-close to dioxonium **99**. S_N2 attack by a molecule of acetic acid on dioxonium **99** at the benzylic position results in ester **341**. Alternatively, decarboxylation of dioxonium **99** may occur, producing neutral dioxolane **152**. Protonation of highly nucleophilic dioxolane **152** by the reaction medium to form reactive dioxonium **345**, and subsequent S_N2 attack by acetic acid results in ester **342**. Both esters **341** and **342** provide *anti*-diol **185** upon treatment with potassium carbonate in methanol. It is interesting that a decarboxylative pathway appears to be in operation when anhydrous acetic acid, but not wet chloroform (see Chapter 2.12), is used as the reaction medium. This observation is consistent with the reduced nucleophilicity of acetic acid over water, providing more time for charged dioxonium **99** to irreversibly decarboxylate to neutral dioxolane **152**. No indication of reaction with a second equivalent of peroxide **86** was observed (*c.f.* Chapter 2.13). This is probably due to rapid protonation of the decarboxylated intermediate **152** by the reaction medium.

6.2.4 Increasing Diastereoselectivity

It was clear from the product distribution outlined in Scheme 6.4 that 7-membered ring **94** was mainly responsible for the formation of undesired *syn*-diol product **66**. If 7-membered ring **94** formation could be reduced, or even prevented, then very high levels of *anti*-selectivity could potentially be achieved. It had previously been established that a larger cycloalkane ring on malonoyl peroxides **78**, **86** and **87** resulted in increased decarboxylation, consistent with decreased strain in the dioxolane product **346** from n =1 to n = 3 (Figure 6.6).

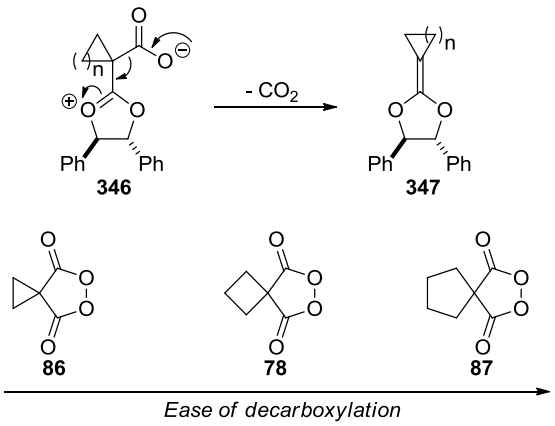
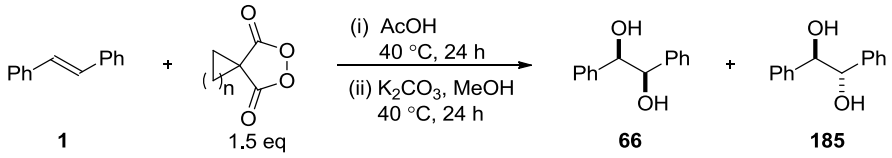
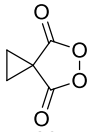
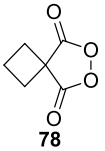
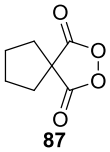
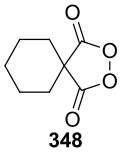
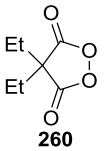


Figure 6.6 Increasing decarboxylation ability with increasing cycloalkane ring size.

Therefore, it was proposed that use of a malonoyl peroxide more prone to decarboxylation may reduce or prevent 7-membered ring formation which leads to *syn*-diol **66** after hydrolysis, thereby increasing the overall selectivity in favour of *anti*-diol **185**. To investigate this hypothesis, five different malonoyl peroxides **86**, **78**, **87**, **348** and **260** were prepared and examined in the *anti*-dihydroxylation protocol. The ratio of *syn*:*anti* diol (**66**:**185**) was determined by ^{1}H NMR spectroscopy of the crude reaction mixtures, and the results shown in Table 6.2.

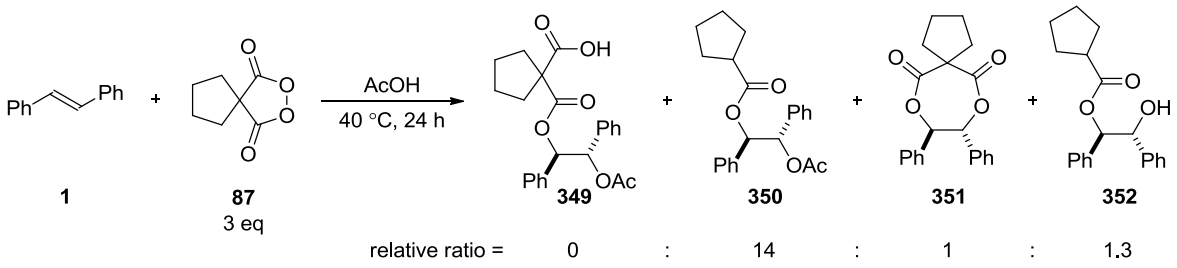


Entry	Peroxide	*syn*:*anti* (66:185)[a]
1	 **86**	1:4.5
2	 **78**	1:5
3[b]	 **87**	1:6
4[b,c]	 **348**	1:7
5[b,c]	 **260**	1:7

[a] Determined by integration of the ^{1}H NMR spectrum of the crude reaction mixture after hydrolysis. [b] 3 equivalents of peroxide were used. [c] Treated with K_2CO_3 in methanol for 72 h at 40 ^{o}C.

Table 6.2 Peroxide structure effect on diastereoselectivity.

Gratifyingly, the diastereoselectivity gradually increased with increasing cycloalkane ring size on the malonoyl peroxide (Table 6.2, Entries 1–3), with cyclohexyl malonoyl peroxide **348** offering the highest selectivity (1:7, Table 6.2, Entry 4). Non-cyclic diethyl malonoyl peroxide **260** did not offer any further advantage in terms of diastereoselectivity (1:7, Table 6.2, Entry 5). Significantly, analysis of the pre-hydrolysis reaction products with cyclopentyl malonoyl peroxide **87** by ^{1}H NMR spectroscopy revealed a 14:1 ratio of *anti*-ester **350** to *syn*-7-membered ring **351** (*c.f.* 7:1 ratio with peroxide **86**, Scheme 6.4), indicating a considerable reduction in the amount of 7-membered ring present (Scheme 6.6). Interestingly, non-decarboxylated ester **349** was not present.



Scheme 6.6 Identification of products from the reaction of **1** and **87** in acetic acid.

Despite a 1:14 ratio of *syn*-dioxygenation product **351** to *anti*-dioxygenation product **350**, the overall diol diastereoselectivity was only 1:6 (**66**:**185**) after hydrolysis. This was due to formation of *syn*-ester **352**. It was initially thought formation of **352** was due to non-anhydrous conditions, but after performing the reaction multiple times with strict exclusion of water this was deemed unlikely. A tentative mechanism accounting for the formation of ester **352** is outlined in Figure 6.7.

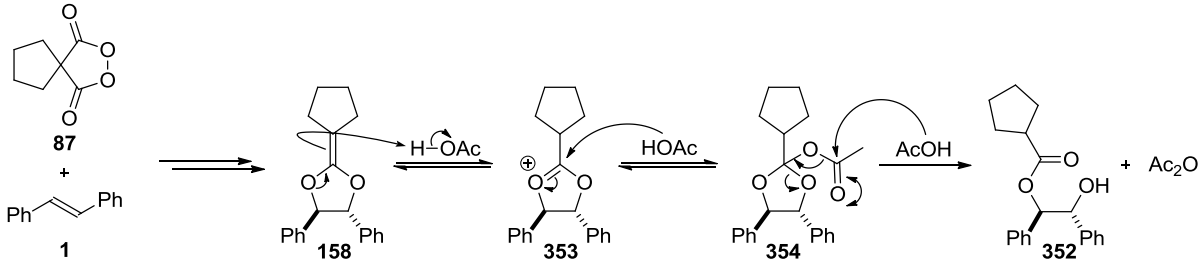
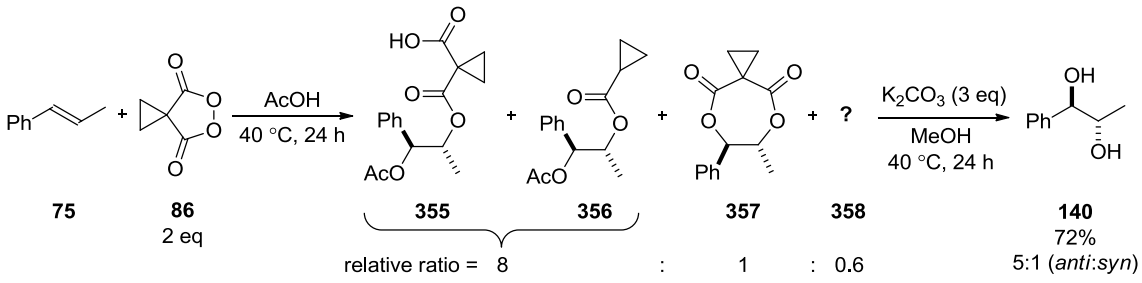


Figure 6.7 Possible mechanism describing formation of **352**.

Interaction of peroxide **87** and alkene **1** results in dioxolane **158** which is protonated by the reaction medium to form dioxonium **353**. Reversible addition of acetic acid could result in unstable orthoester **354**, which breaks down to ester **352** following attack by a molecule of acetic acid. Delineation of this mechanism through the use of ^{18}O-labelled peroxide **119** and ^{18}O-acetic acid would provide valuable information.

6.2.5 Regioselectivity

To explore the regioselectivity of acetic acid attack on dioxonium **99** (Figure 6.5), unsymmetrical β-methylstyrene **75** was subjected to the *anti*-dihydroxylation conditions using cyclopropyl malonoyl peroxide **86** (Scheme 6.7).



Scheme 6.7 *Anti*-dihydroxylation of β-methylstyrene **75**.

Compounds **355**, **356** and **357** were isolated from the reaction mixture, and the relative stereochemistry of each confirmed by hydrolysis to the corresponding *syn*- **77** and *anti*-diols **140**. A small amount of an unknown compound **358** was observed in the ^{1}H NMR spectrum of the crude reaction mixture, but could not be isolated or identified at this time. **358** is presumed to lead to *syn*-diol **77**, consistent with the overall diastereoselectivity of the reaction. 2D NMR experiments showed acetic acid addition exclusively in the benzylic position of esters **355** and **356**, consistent with regioselective S_N2 ring-opening at the more reactive centre (see Appendix 9.3 for NMR spectra).

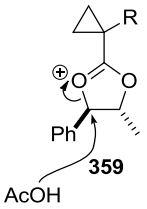


Figure 6.8 Regioselective ring-opening of dioxonium **359**.

6.3 Conclusions

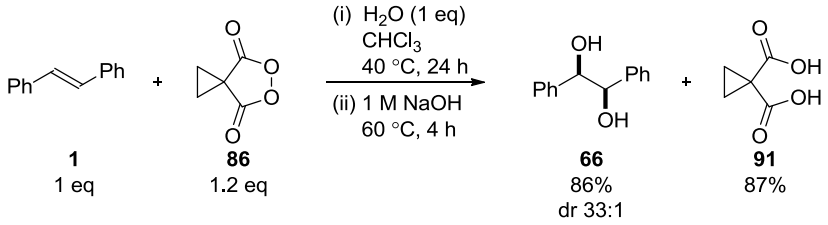
A complementary *anti*-dihydroxylation protocol based around the reactivity of malonoyl peroxides has been successfully developed using anhydrous acetic acid as the reaction solvent. The reaction proceeds under mild reaction conditions (40 ^{o}C, 24 h) and is operationally simple. *Anti*-selectivity in the diol product can be improved by variation of the peroxide structure, with peroxides that decarboxylate more readily providing higher levels of diastereoselectivity. *Anti*-dioxygenation has been shown to arise from regioselective S_N2 attack of acetic acid on the dioxonium intermediate **359** at the most reactive centre.

Chapter 7: Conclusions and Future Work

7 Conclusions and Future Work

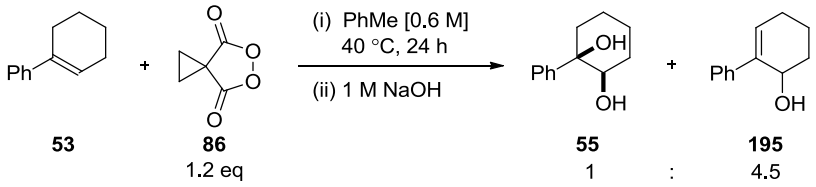
7.1 Conclusions

Alkene dihydroxylation is central to synthetic organic chemistry, with the Sharpless asymmetric dihydroxylation reaction representing the gold standard in the field. Despite its overwhelming acceptance, the extremely high toxicity of osmium tetroxide employed in this reaction means alternative procedures are highly desirable. This thesis described the successful application of stable cyclopropyl malonoyl peroxide **86** in the metal-free *syn*-dihydroxylation of alkenes, with excellent levels of diastereoselectivity.



Scheme 7.1 *Syn*-dihydroxylation using cyclopropyl malonoyl peroxide **86**.

The reaction proceeds under mild conditions in the presence of moisture and air, requires no specialist techniques, and the reagent is accessible in one simple synthetic step from commercially available diacid **91**, which can be recovered post-reaction. Peroxide **86** is capable of dihydroxylating all major classes of alkene and has a large functional group tolerance, but is most effective with alkenes capable of stabilising a developing carbocation. Alkenes containing allylic hydrogen atoms undergo a competitive allylic oxidation process. This has been optimised, providing a simple and environmentally benign synthesis of allylic alcohols from alkenes.



Scheme 7.2 Novel allylic oxidation protocol.

A substantial mechanistic investigation involving kinetic studies, Hammett analysis, multiple isotopic labelling experiments, NMR investigations and trapping experiments, allowed a consistent mechanism to be proposed for the intriguing dihydroxylation reaction.

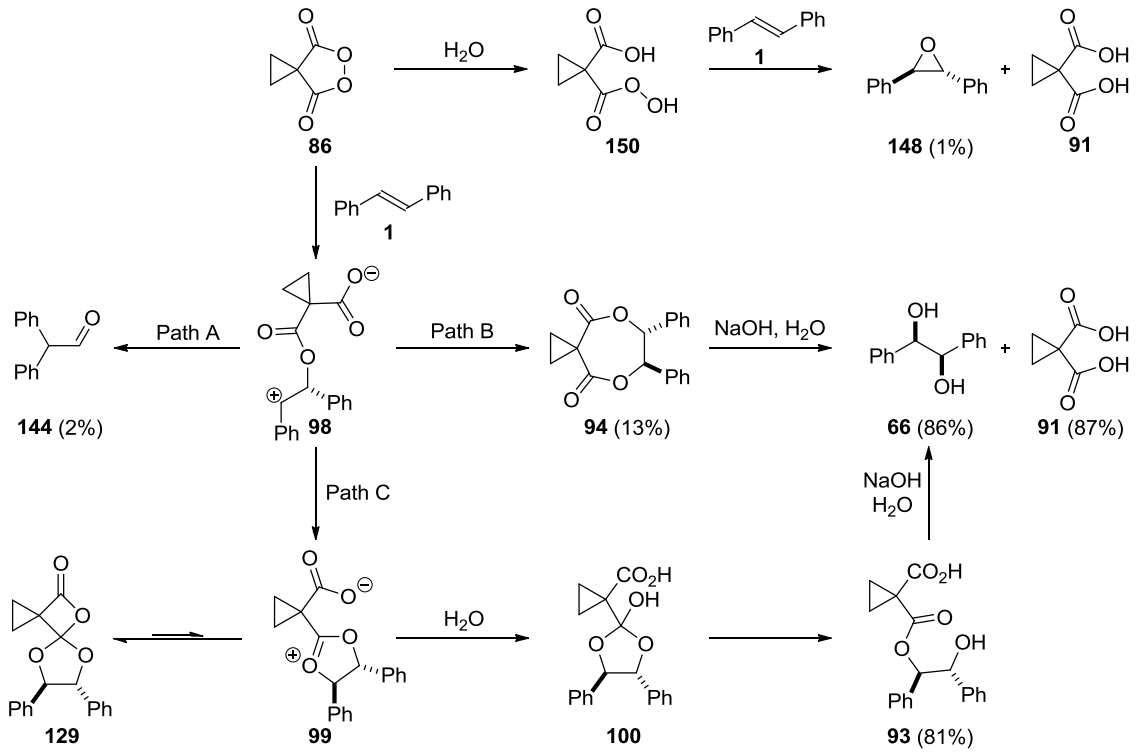


Figure 7.1 *Syn*-dihydroxylation mechanism.

An ionic interaction between peroxide **86** and alkene **1** produces zwitterion **98**, which undergoes ring-closure to dioxonium **99** (81%, Path C) and 7-membered ring **94** (13%, Path B). Dioxonium **99**, which is in equilibrium with spirocyclic lactone **129**, is attacked by a molecule of water to produce ester **93** *via* dioxolane **100**. Basic hydrolysis of the crude reaction mixture containing **93** and **94** results in diol **66** and diacid **91**. The minor diastereoisomer, *anti*-diol **185**, has been shown to arise primarily from σ_{C-C} bond rotation in zwitterion **98**. Two minor reaction pathways involving semipinacol rearrangement to aldehyde **144** (2%, Path A), and peroxy acid **150** formation followed by epoxidation (1%) were also identified.

The efficiency of the reaction was improved by addition of hydrogen-bond donor catalysts. An investigation into catalyst pKa *versus* catalyst activity revealed a small optimum catalytic window of pKa 5–8 for the hydrogen-bond donor. Alcoholic hydrogen-bond donors were most effective, achieving up to 4-fold rate acceleration with 4-nitrophenol **263** (20 mol%).

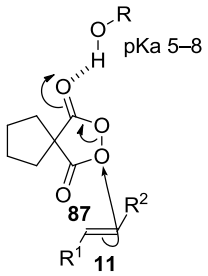
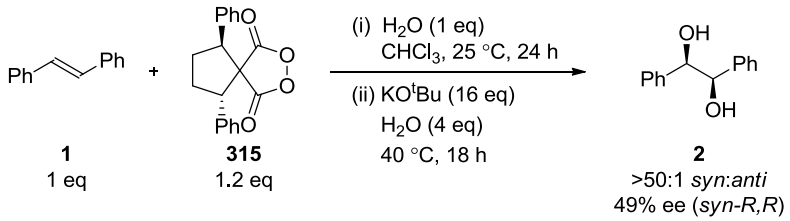


Figure 7.2 Catalysis by hydrogen bond donors.

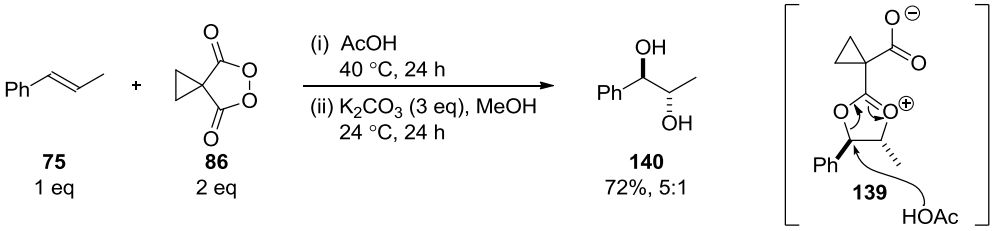
Chiral malonoyl peroxide scaffolds were designed, synthesised and investigated in the asymmetric dihydroxylation of alkenes. Treatment of *trans*-stilbene **1** with chiral peroxide **315** produced (*R,R*)-diol **2** as a single diastereoisomer (*syn*) with an unoptimised 49% ee at room temperature, providing an outstanding platform for future development.



Scheme 7.3 First metal-free asymmetric *syn*-dihydroxylation reaction using a peroxide.

This particularly significant result represents the first metal-free enantioselective *syn*-dihydroxylation using a peroxide reactant. The asymmetric reaction proceeds in the presence of moisture and air, under ambient conditions, and peroxide **315** was synthesised in only six simple metal-free steps. This protocol has laid significant foundations for a general, asymmetric, metal-free dihydroxylation reaction that could offer an attractive alternative to the osmium-based Sharpless AD reaction.

To further enhance the utility of malonoyl peroxides, an analogous *anti*-dihydroxylation protocol has been developed. Treatment of β-methylstyrene **75** with peroxide **86** in anhydrous acetic acid resulted in *anti*-diol **140** (72%, 5:1 *anti*:*syn*), after treatment of the crude reaction mixture with K_2CO_3 in methanol. *Anti*-dioxygenation occurs through regioselective S_N2 attack of acetic acid on dioxonium **139** at the most reactive centre.



Scheme 7.4 Novel *anti*-dihydroxylation protocol using malonoyl peroxides.

Although a general, metal-free, catalytic and asymmetric *syn*-dihydroxylation of alkenes has so far been elusive, it seems that malonoyl peroxides may be the future in performing this fundamental transformation.

7.2 Future Work

There are numerous possibilities for further research presented throughout this work. However, there are a small number of issues that *must* be addressed before cyclopropyl malonoyl peroxide **86** can be widely adopted as a general metal-free dihydroxylation reagent.

7.2.1 Substrate Scope

Despite the current protocol being highly effective for alkenes conjugated with an aromatic ring, it is problematic with unstabilised aliphatic alkenes. This severely limits substrate scope and represents the most urgent issue to address within this work. It is possible that a simple change of reaction conditions, or use of an additive to prevent side reactions, may increase yields of diol with this class of substrate. This was not explored during this work due to focus on multiple other aspects of the reaction development and understanding. Before a new set of optimal reaction conditions can be intelligently explored, a thorough investigation on the reactivity, mechanism and side reactions of a handful of aliphatic alkenes with cyclopropyl malonoyl peroxide **86** is essential.

7.2.2 Asymmetric Dihydroxylation

Two avenues to introduce enantioselectivity into the dihydroxylation reaction were explored during this work; use of a chiral hydrogen-bond catalyst and use of a stoichiometric chiral peroxide reactant.

7.2.3 Chiral Catalysis

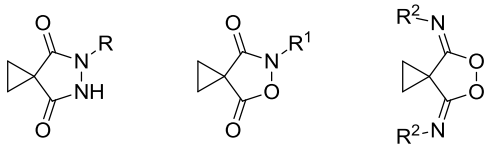
Significant advances were made in understanding catalysis of the reaction, but asymmetry using a chiral catalyst was not achieved. A good starting point for future work would be to modify BINOL derivatives with electron withdrawing functionality, to bring the pKa within the active window of 5-8. If it is established that BINOL derivatives can effectively catalyse the reaction, then BINOL structure could be varied to explore enantioselectivity.

7.2.4 Chiral Reactant

In an initial reaction, chiral peroxide **315** was shown to be capable of introducing asymmetry into the dihydroxylation reaction at room temperature in a promising 49% ee with *trans*-stilbene **1**. Due to time constraints reaction optimisation was not explored, so the effect that various solvents, temperatures and additives have on the enantioselectivity needs to be investigated. Reaction intermediates need to be isolated and their individual enantiomeric excesses measured, to determine the enantioselectivity of each mechanistic process within the dihydroxylation reaction. After optimisation, if high levels of enantiomeric excess are achieved in the diol, and are general across a range of alkenes, then it would be beneficial to dedicate effort to shortening the synthesis of chiral peroxide **315**, to improve the accessibility of the protocol. An encouraging preliminary result indicated that it is possible to convert diethyl malonates directly into malonoyl peroxides (Chapter 5, Scheme 5.19), although initial attempts with the chiral diphenyl derivative failed due to insolubility of diester **320** in the reaction medium.

7.2.5 Metal-Free Oxyamination of Alkenes

The Sharpless asymmetric oxyamination protocol suffers from poor regioselectivity and the high toxicity of osmium tetroxide.[124] Nitrogen analogues of malonoyl peroxides **360**–**362** have the potential to be used as regioselective, non-toxic, oxyamination reagents.



360 **361** **362**

Figure 7.3 Potential metal-free oxyamination reagents.

Initial work in the group has indicated that compounds of type **360** and **361** are unreactive to even highly nucleophilic alkenes at high temperatures. **362** represents an interesting analogue of compounds **360** and **361** as it should maintain similar reactivity to malonoyl peroxides due to the weak O–O bond. However, it will be considerably more challenging to synthesise.

Chapter 8: Experimental

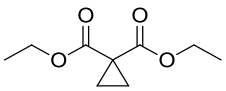
8 Experimental

8.1 General Techniques

Commercially available solvents and reagents were used without further purification or drying and all reactions performed under an air atmosphere unless otherwise stated. Flash chromatography was carried out using Merck Kieselgel 60 H silica. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254 that were visualised under UV light (at 254 nm). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 400 MHz, Bruker Avance DRX 500 MHz or Bruker Avance II 600 MHz spectrometer. NMR spectra were recorded in $CDCl_3$ at 25 °C unless stated otherwise and were reported in δ-units (ppm) relative to residual solvent peaks (chloroform, δ = 7.26 for protons and δ = 77.16 for carbon atoms); *J* values were recorded in Hz and multiplicities were expressed by the usual conventions. ^{13}C NMR (DEPT-Q) spectra show quaternary carbons. Low-resolution mass spectra (MS) were determined using an Agilent 6130 single quadrupole with an APCI/electrospray dual source or ThermoQuest Finnigan LCQ-Duo electrospray. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University of Wales, Swansea, U.K. using the ionization methods specified. *In vacuo* refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump. Melting points were determined using a Stuart SMP11 and are uncorrected. Infrared spectra were determined on neat samples using a Shimadzu IRAffinity-1 equipped with an ATR (Attenuated Total Reflectance) accessory, and were reported in cm^{-1}. GC–MS was performed using an Agilent 7890A GC system, equipped with a 30 m DB5MS column connected to a 5975C inert XL CI MSD with Triple-Axis Detector. Single-crystal diffraction data were measured on Oxford Diffraction Xcalibur E and Gemini S instruments. The structures were refined to convergence on F^2 and against all independent reflections by full-matrix least-squares, using the SHELXL-97 program. Selected parameters are given in Appendix 9.1.

8.2 Synthesis of Malonoyl Peroxides

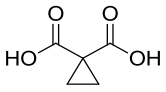
Diethyl cyclopropane-1,1-dicarboxylate 90[42]



Diethyl malonate (63 mL, 0.415 mol, 1 eq), potassium carbonate (250 g, 1.81 mol, 4.4 eq) and tetrabutylammonium hydrogensulfate (7.06 g, 20.8 mmol, 5 mol%) were stirred vigorously in DMSO (400 mL). 1,2-Dibromoethane (65 mL, 0.754 mol, 1.8 eq) was added in one portion and the reaction was stirred at room temperature for 24 h. Water (800 mL) was added and the product extracted using diethyl ether (5 × 100 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and solvent was removed by rotary evaporation. Purification by distillation (78–80 ^oC/10 Torr) gave the title compound **90** as a colourless oil (72 g, 0.387 mol, 93%).

Colourless oil; IR (ATR)/cm^{-1}: 2984, 2940, 2909, 1733, 1209; ^1H NMR (250 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.1 Hz, 4H, OCH_2), 1.33 (s, 4H, CH_2CH_2), 1.19 (t, *J* = 7.1 Hz, 6H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.7, 61.3, 28.2, 16.2, 14.0; LRMS (EI) *m/z* 186.1 $[M]^+$; HRMS (ESI) calculated for $C_9H_{15}O_4$ $[M + H]^+$ 187.0965, found 187.0962.

Cyclopropane-1,1-dicarboxylic acid 91[42]

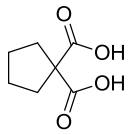


15% Aqueous sodium hydroxide solution (215 mL) was added to diethyl cyclopropane-1,1-dicarboxylate **90** (50.2 g, 0.270 mol). The reaction mixture was stirred at room temperature for 60 h. The resulting solution was washed twice with diethyl ether (2 × 50 mL) to remove any unreacted ester **90** and then acidified to pH 1 using 8 M HCl (80 mL). The product was extracted with ethyl acetate (5 × 100 mL) ensuring that the

aqueous phase was maintained at pH 1 after each extraction. The combined organic phases were dried over $MgSO_4$, filtered and solvent removed by rotary evaporation to give cyclopropane-1,1-dicarboxylic acid **91** as a colourless solid (26.6 g, 0.205 mol, 76%).

Colourless solid; m.p. 128–130 °C [lit.[43a] 134–136 °C]; IR (ATR)/cm^{-1}: 2987, 2837, 2514, 1711, 1220, 1165; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (s, 4H, C*H*$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7, 28.3, 17.1; LRMS (EI) *m/z* 112.0 $[M - H_2O]^+$; HRMS (EI) calculated for $C_5H_6O_4$ $[M]^+$ 130.0266, found 130.0268.

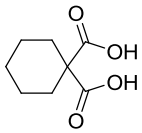
Cyclopentane-1,1-dicarboxylic acid 324[42]



15% Aqueous sodium hydroxide solution (22 mL) was added to diethyl cyclopentane-1,1-dicarboxylate **323** (5.78 g, 27.0 mmol). The reaction mixture was stirred at room temperature for 60 h. The resulting solution was washed twice with diethyl ether (2 × 15 mL) to remove any unreacted ester **323** and then acidified to pH 1 using 8 M HCl. The product was extracted with ethyl acetate (4 × 25 mL) ensuring that the aqueous phase was maintained at pH 1 after each extraction. The combined organic phases were dried over $MgSO_4$, filtered and solvent removed by rotary evaporation to give cyclopentane-1,1-dicarboxylic acid **324** as a colourless solid (3.88 g, 24.6 mmol, 91%).

Colourless solid; m.p. 165 °C (decomp.) [lit.[42] 183–184 ^{o}C (decomp.)]; IR (ATR)/cm^{-1}: 2968, 2878, 2644, 1689, 1269, 1236; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.03–2.00 (m, 4H, $CH_2CH_2CH_2C(CO_2H)_2$), 1.58–1.54 (m, 4H, $CH_2CH_2CH_2C(CO_2H)_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.0, 60.0, 34.1, 25.2; 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 363[42]



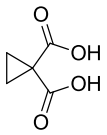
Diethyl cyclohexane-1,1-dicarboxylate (8.20 g, 36.0 mmol, 1 eq), was dissolved in THF:H_2O (40 mL:40 mL) and $LiOH \cdot H_2O$ (9.06 g, 216 mmol, 6 eq) added in a single portion. The reaction mixture was vigorously stirred at 40 ^oC for 72 h then THF removed under reduced pressure. The aqueous phase was washed with ethyl acetate (2 × 100 mL) to remove any unreacted ester and then acidified to pH 1 using 8 M HCl before extraction with ethyl acetate (4 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and solvent removed by rotary evaporation to give cyclohexane-1,1-dicarboxylic acid **363** as a colourless solid (4.42 g, 25.7 mmol, 71%) without need for further purification.

Colourless solid; m.p. 164 °C (decomp.) [lit.[42] 179–181 ^oC (decomp.)]; IR (ATR)/cm^{-1}: 2943, 2932, 2864, 1693, 1240; ^1H NMR (400 MHz, DMSO-d_6) δ 12.60 (bs, 2H, CO_2H), 1.83–1.80 (m, 4H, CH_2), 1.44–1.36 (m, 6H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.1, 54.0, 31.0, 24.9, 22.6; LRMS (ESI) *m/z* 171.5 $[M - H]^-$; HRMS (ES) calculated for $C_8H_{11}O_4$ $[M - H]^-$ 171.0663, found 171.0664.

8.2.1 General Procedure A: One-Step Synthesis of Diacids[43a]

Benzyltriethyl ammonium chloride (0.10 mol, 1 eq) was added to a stirring solution of 50% (by wt.) aqueous NaOH (200 mL). Diethyl malonate (0.10 mol, 1 eq) and dibromoalkane (0.15 mol, 1.5 eq) were pre-mixed and added to the reaction vessel in one portion. The resulting heterogeneous mixture was stirred vigorously with an overhead mechanical stirrer at room temperature for n h. The reaction was diluted with water (100 mL) and washed with diethyl ether (2 × 100 mL) to remove unreacted starting material. The aqueous phase was acidified to pH 1 with concentrated HCl before being extracted with ethyl acetate (3 × 50 mL), washed with brine (1 × 50 mL), dried over $MgSO_4$ and concentrated to dryness by rotary evaporation to afford the target 1,1-dicarboxylic acids. No further purification was necessary.

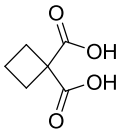
Cyclopropane-1,1-dicarboxylic acid 91[43a]



Reaction of diethyl malonate (15.2 mL, 0.10 mol, 1 eq) and 1,2-dibromoethane (12.9 mL, 0.15 mol, 1.5 eq) in a rapidly stirring mixture of 50% aq. NaOH (200 mL) and benzyltriethyl ammonium chloride (22.8 g, 0.10 mol, 1 eq) according to General Procedure **A** for 4 h at 25 ºC gave the title compound **91** as a colourless solid (6.7 g, 53.2 mmol, 53%).

Colourless solid; m.p. 128–130 °C [lit.[43a] 134–136 °C]; IR (ATR)/cm^{-1}: 2987, 2837, 2514, 1711, 1220, 1165; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (s, 4H, C*H*$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 27.3, 16.5; LRMS (ESI) *m/z* 112.0 $[M - H_2O]^+$; HRMS (EI) calculated for $C_5H_6O_4$ $[M]^+$ 130.0266, found 130.0268.

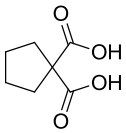
Cyclobutane-1,1-dicarboxylic acid 79[42]



Reaction of diethyl malonate (7.6 mL, 50 mmol) and 1,3-dibromopropane (7.7 mL, 75 mmol) in a rapidly stirring mixture of 50% aq. NaOH (200 mL) and benzyltriethyl ammonium chloride (11.4 g, 50 mmol) according to General Procedure **A** for 5 h at 25 ºC gave the title compound **79** as a colourless solid (4.9 g, 34.1 mmol, 68%).

Colourless solid; m.p. 157–158 °C (decomp.) [lit.[42] 151–153 ºC (decomp.)]; IR (ATR)/cm^{-1}: 2955, 2869, 2561, 1689, 1285, 1213; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (bs, 2H, CO_2H), 2.36 (t, J = 8.0 Hz, 4H, $CH_2CH_2CH_2$), 1.84 (p, J = 8.0 Hz, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.1, 52.2, 28.3, 15.6; LRMS (ESI) *m/z* 142.9 $[M - H]^-$.

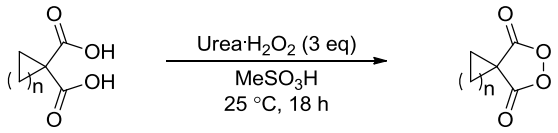
Cyclopentane-1,1-dicarboxylic acid 324[42]



Reaction of diethyl malonate (10.0 mL, 66.0 mmol) and 1,4-dibromobutane (11.8 mL, 99.0 mmol) in a rapidly stirring mixture of 50% aq. NaOH (130 mL) and benzyltriethyl ammonium chloride (15.1 g, 66.0 mol) according to General Procedure **A** for 5 h at 25 ºC gave the title compound **324** as a colourless solid (8.1 g, 51.1 mmol, 77%).

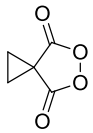
For analytical data on diacid **324** see Experimental 8.2.

8.2.2 General Procedure B: Synthesis of Malonoyl Peroxides



Cycloalkane-1,1-dicarboxylic acid (23.1 mmol, 1 eq) was stirred in methanesulfonic acid (25 mL) for 10 mins before addition of urea hydrogen peroxide (6.50 g, 69.2 mmol, 3 eq) portionwise over 5 mins. After stirring for 18 h at 25 ^{o}C the contents of the reaction flask were poured into a mixture of ice (50 g) and ethyl acetate (25 mL). The phases were separated and the aqueous phase extracted using ethyl acetate (3 × 30 mL). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (3 × 30 mL) followed by brine (30 mL). Drying over $MgSO_4$, filtration and removal of solvent by rotary evaporation (caution!) afforded the corresponding malonoyl peroxide as colourless crystals with no need for further purification.

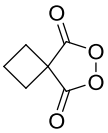
Cyclopropyl malonoyl peroxide 86[39]



Reaction of cyclopropane-1,1-dicarboxylic acid **91** (3.00 g, 23.1 mmol) and urea hydrogen peroxide (6.50 g, 69.2 mmol) in methanesulfonic acid (25 mL) according to General Procedure **B** for 18 h at 25 ºC gave the title compound **86** as a colourless solid (2.43 g, 19.0 mmol, 82%).

Colourless solid; m.p. 77–78 ^{o}C; IR (ATR)/cm^{-1}: 3121, 1829, 1788, 1356, 1330, 1147; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 4H, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 23.8, 19.9. Unable to obtain low or high resolution mass spectrometry data for malonoyl peroxides using in-house or Swansea National Mass Spectrometry Service.

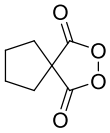
Cyclobutyl malonoyl peroxide 78[39]



Reaction of cyclobutane-1,1-dicarboxylic acid **79** (3.33 g, 23.1 mmol) and urea hydrogen peroxide (6.50 g, 69.2 mmol) in methanesulfonic acid (25 mL) according to General Procedure **B** for 18 h at 25 ºC gave the title compound **78** as a colourless solid (2.66 g, 18.7 mmol, 81%).

Colourless solid; m.p. 63 °C; IR (ATR)/cm^{-1}: 2999, 2955, 1800, 1740, 1258, 1119; ^{1}H NMR (500 MHz, $CDCl_3$) 2.71 (t, J = 8.2 Hz, 4H, CH_2CH_2CH_2), 2.39–2.33 (m, 2H, CH_2CH_2CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$) 173.9, 40.4, 28.9 16.3; Unable to obtain low or high resolution mass spectrometry data for malonoyl peroxides using in-house or Swansea National Mass Spectrometry Service.

Cyclopentyl malonoyl peroxide 87[39]



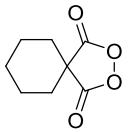
Reaction of cyclopentane-1,1-dicarboxylic acid **324** (3.65 g, 23.1 mmol) and urea hydrogen peroxide (6.50 g, 69.2 mmol) in methanesulfonic acid (25 mL) according to General Procedure **B** for 18 h at 25 ºC gave the title compound as a colourless solid (2.88 g, 18.5 mmol, 80%).

Peroxide **87** was also made directly from diethyl cyclopentane-1,1-dicarboxylate **323**. Reaction of diethyl cyclopentane-1,1-dicarboxylate **323** (0.989 g, 4.62 mmol, 1 eq) and urea hydrogen peroxide (1.30 g, 13.9 mmol, 3 eq) in methanesulfonic acid (5 mL)

according to General Procedure **B** for 18 h at 25 ºC gave the title compound as a colourless solid (453 mg, 2.86 mmol, 62%).

Colourless solid; m.p. 41 °C; IR (ATR)/cm^{-1}: 2973, 2952, 2878, 1793, 1696, 1263, 1228, 1066; ^{1}H NMR (400 MHz, $CDCl_3$) 2.27–2.23 (m, 4H, $CH_2CH_2C(CO_2)_2$), 2.01–1.98 (m, 4H, $CH_2CH_2C(CO_2)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 175.8, 46.9, 37.7, 26.8. Unable to obtain low or high resolution mass spectrometry data for malonoyl peroxides using in-house or Swansea National Mass Spectrometry Service.

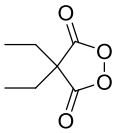
Cyclohexyl malonoyl peroxide 348



Reaction of cyclohexane-1,1-dicarboxylic acid **363** (4.00 g, 23.1 mmol) and urea hydrogen peroxide (6.50 g, 69.2 mmol) in methanesulfonic acid (25 mL) according to General Procedure **B** for 18 h at 25 ºC gave the title compound as a colourless solid (2.95 g, 17.3 mmol, 75%).

Colourless solid; m.p. 40–41 °C. IR (ATR)/cm^{-1}: 2936, 2866, 1788, 1740, 1229, 1179, 1063; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97–1.94 (m, 4H, $CH_2C(CO_2)_2$), 1.83–1.77 (m, 4H, $CH_2CH_2C(CO_2)_2$), 1.62–1.56 (m, 2HCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 41.8, 30.6, 24.2, 19.3; Unable to obtain low or high resolution mass spectrometry data for malonoyl peroxides using in-house or Swansea National Mass Spectrometry Service.

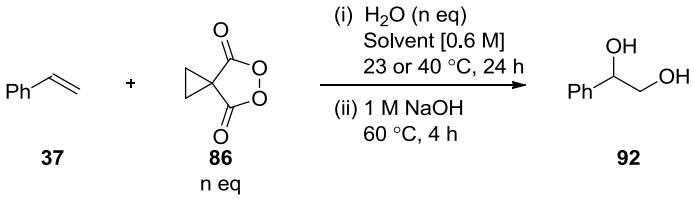
Diethyl malonoyl peroxide 260



Reaction of diethyl-1,1-dicarboxylic acid (777 mg, 4.86 mmol) and urea hydrogen peroxide (1.37 g, 14.6 mmol) in methanesulfonic acid (5 mL) according to General Procedure **B** for 18 h at 25 ºC gave the title compound as a colourless oil (430 mg, 2.72 mmol, 56%).

Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (q, *J* = 7.5 Hz, 4H, C*H*$_2$), 1.01 (t, *J* = 7.5 Hz, 6H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 51.2, 29.0, 9.1; Unable to obtain low or high resolution mass spectrometry data for malonoyl peroxides using in-house or Swansea National Mass Spectrometry Service.

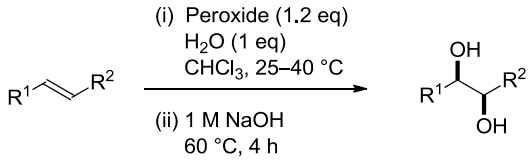
8.3 *Syn*-Dihydroxylation Reaction Optimisation



Cyclopropyl malonoyl peroxide **86** (n eq) was added in one portion to a solution of styrene (131 mg, 1.26 mmol, 1 eq), H_2O (n eq) and solvent (2 mL) and stirred at either 25 or 40 °C. The extent of reaction was followed by consumption of styrene (TLC analysis – 100% petroleum ether). After 24 h solvent was removed by rotary evaporation and 1 M NaOH (10 mL) was added. The reaction mixture was stirred at 60 °C for 4 h and allowed to cool to room temperature before the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (1 × 10 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation

to afford the target diol. Purification by silica gel flash chromatography (2:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid. For analytical data on diol **92** see Experimental 8.4.1.

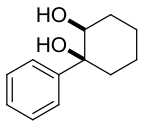
8.4 General Procedure C: *Syn*-Dihydroxylation using Malonoyl Peroxides



Malonoyl peroxide (1.51 mmol, 1.2 eq) was added in one portion to a solution of alkene (1.26 mmol, 1 eq), H_2O (23 μL, 1.26 mmol, 1 eq) and chloroform (2 mL) and stirred at either 25 or 40 °C. On consumption of alkene (TLC analysis – 100% petroleum ether) the reaction mixture was evaporated to dryness *in vacuo* and 1 M NaOH (10 mL) was added. The reaction mixture was stirred at 60 °C for 4 h and allowed to cool to room temperature before the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (1 × 10 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation to afford the target diol. The corresponding acid by-product was recovered by acidifying the aqueous phase to pH 1 by dropwise addition of concentrated HCl with stirring at 0–5 ^oC. Extraction with ethyl acetate (3 × 20 mL), washing with brine (1 × 10 mL) and drying over $MgSO_4$ then removal of solvent by rotary evaporation afforded the carboxylic acid as a colourless solid (80–90%).

8.4.1 Analytical Data for Diols

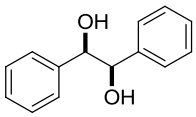
1-Phenylcyclohexane-1,2-diol 55[125]



Reaction of 1-phenyl-1-cyclohexene **53** (199 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol >50:1 *syn*:*anti*) and purification by silica gel flash chromatography (1:3 diethyl ether:petroleum ether) gave the title compound as a colourless solid (87 mg, 0.454 mmol, 36%).

Colourless solid; m.p. 115–117 °C [lit.[126] 92 ºC]; IR (ATR)/cm^{-1}: 3287, 3030, 2936, 2857, 1078, 1065; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H, Ph*H*), 7.36–7.33 (m, 2H, Ph*H*), 7.25–7.21 (m, 1H, Ph*H*), 3.91 (dd, *J* = 11.1, 4.5 Hz, 1H, C*H*OH), 2.72 (bs, 1H, PhCO*H*), 1.86–1.79 (m, 4H, CH_2), 1.73–1.61 (m, 3H, CH_2CH$_2$CO*H*), 1.53–1.49 (m, 1H, CH_2), 1.42–1.32 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 128.4, 127.0, 125.2, 75.9, 74.5, 38.6, 29.3, 24.4, 21.1; HRMS (NSI) calculated for $C_{12}H_{20}NO_2$ $[M + NH_4]^+$ 210.1489, found 210.1490.

***rel*-(1*R*,2*R*)-1,2-Bisphenylethane-1,2-diol 66**[20]

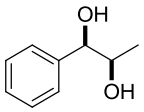


Reaction of (*E*)-stilbene **1** (3.00 g, 16.7 mmol), H_2O (300 µL, 16.7 mmol) and cyclopropyl malonoyl peroxide **86** (2.56 g, 20.0 mmol) in chloroform (25 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol 33:1 *syn*:*anti*) and purification by silica gel flash chromatography (1:4 diethyl ether:petroleum ether) gave

the title compound as a colourless solid (3.07 g, 14.4 mmol, 86%). Repeating the procedure in the absence of light produced the same result (3.03 g, 14.1 mmol, 85%, 33:1 *syn*:*anti*).

Colourless solid; m.p. 104–105 °C [lit.[20] 116–117 °C]; IR (ATR)/cm^{-1}: 3349, 3062, 3031, 2921, 1206; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.23 (m, 6H, Ph*H*), 7.14–7.11 (m, 4H, Ph*H*), 4.70 (s, 2H, C*H*OH), 2.89 (s, 2H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 128.3, 128.1, 127.1, 79.3; 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.

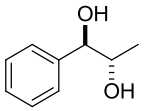
rel-(1*R*,2*R*)-1-Phenylpropane-1,2-diol 77[20]



Reaction of *trans*-β-methylstyrene **75** (155 µL, 1.20 mmol), H_2O (22 µL, 1.20 mmol) and cyclopropyl malonoyl peroxide **86** (184 mg, 1.44 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 °C (crude diol 16:1 *syn*:*anti*) and purification by silica gel flash chromatography (1:2 diethyl ether:petroleum ether) gave the title compound as a colourless solid (168 mg, 1.10 mmol, 92%).

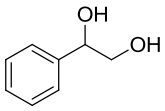
Colourless solid; m.p. 51–53 °C [lit.[127] 51–53 °C]; IR (ATR)/cm^{-1}: 3389, 3063, 3031, 2974, 2893, 1039, 1025; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H, Ph*H*), 4.30 (dd, *J* = 7.5, 2.6 Hz, 1H, PhC*H*OH), 3.82–3.80 (m, 1H, C*H*OH), 3.48 (d, *J* = 2.6 Hz, 1H, PhCHO*H*), 3.23 (d, *J* = 2.0 Hz, 1H, CHO*H*), 1.00 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 128.6, 128.2, 127.0, 79.6, 72.3, 18.8; LRMS (ESI) *m/z* 134.1 $[M - H_2O]^+$; HRMS (ESI) calculated for $C_9H_{10}O$ $[M - H_2O]^+$ 134.0732, found 134.0730.

rel-(1*R*,2*S*)-1-Phenylpropane-1,2-diol 140[127]



Colourless solid; m.p. 87 °C [lit.[127] 89–91 °C]; IR (ATR)/cm^{-1}: 3242, 3067, 3040, 2968, 2891, 1034, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H, Ph*H*), 4.66 (dd, *J* = 3.6, 3.6 Hz, 1H, PhC*H*OH), 4.03–3.96 (m, 1H, C*H*OH), 2.65 (d, *J* = 3.6 Hz, 1H, PhCHO*H*), 2.11 (d, *J* = 4.6 Hz, 1H, CHO*H*), 1.07 (d, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 128.5, 127.9, 126.8, 77.6, 71.4, 17.4; LRMS (ESI) *m/z* 135.1 [M – OH]$^+$; HRMS (ESI) calculated for $C_9H_{11}O$ [M – OH]$^+$ 135.0804, found 135.0800.

1-Phenylethane-1,2-diol 92[125]

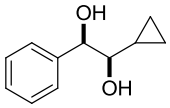


Reaction of styrene (131 mg, 1.26 mmol), H_2O (23 μL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 °C and purification by silica gel flash chromatography (2:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (155 mg, 1.12 mmol, 89%).

Colourless solid; m.p. 61 °C [lit.[20] 64–65 °C]; IR (ATR)/cm^{-1}: 3201, 3010, 2934, 1088, 1053; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.23 (m, 5H, Ph*H*), 4.83 (dd, *J* = 8.2, 3.4 Hz, 1H, C*H*OH), 3.76 (dd, *J* = 11.3, 3.4 Hz, 1H, CH_2), 3.66 (dd, *J* = 11.3, 8.2 Hz, 1H, CH_2), 2.38 (s, 2H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 128.8, 128.3, 126.4, 75.0, 68.4;

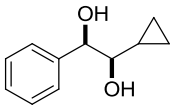
LRMS (EI) *m/z* 138.1 $[M]^+$; HRMS (EI) calculated for $C_8H_{10}O_2$ $[M]^+$ 138.0681, found 138.0676.

1-Cyclopropyl-2-phenylethane-1,2-diol 114

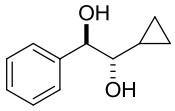


Reaction of (2-cyclopropylvinyl)benzene **113** (3:1 *E*:*Z*, 300 mg, 2.08 mmol), H_2O (37 µL, 2.08 mmol) and cyclopropyl malonoyl peroxide **86** (320 mg, 2.50 mmol) in chloroform (3 mL) according to the General Procedure **C** for 24 h at 40 ºC (crude diol 2.5:1 *syn*:*anti*) and purification by silica gel flash chromatography (2:1 diethyl ether:petroleum ether) gave the title compound as a colourless oil (315 mg, 1.77 mmol, 85%).

Analytical data for mixture of isomers (*syn*-**114** and *anti*-**364**): IR (ATR)/cm^{-1}: 3368, 3084, 3005, 2887, 1063, 1012; HRMS (CI) calculated for $C_{11}H_{18}NO$ $[M + NH_4]^+$ 196.1332, found 196.1332.



114



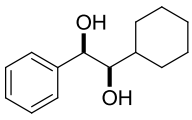
364

Syn-isomer **114**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5H, Ph*H*), 4.55 (d, *J* = 7.1 Hz, 1H, PhC*H*OH), 3.38 (bs, 1H, O*H*), 2.99 (dd, *J* = 7.5, 7.5 Hz, 1H, C*H*OH), 2.92 (bs, 1H, O*H*), 0.83–0.72 (m, 1H, -CH_2CHCH_2-), 0.46–0.36 (m, 1H, -CH_2CHCH_2-), 0.32–0.17 (m, 2H, -CH_2CHCH_2-), -0.19–-0.23 (m, 1H, -CH_2CHCH_2-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 128.3, 127.0, 80.2, 78.3, 13.8, 3.2, 2.2.

Anti-isomer **364**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5H, Ph*H*), 4.77 (d, *J* = 3.8 Hz, 1H, PhC*H*OH), 3.18 (bs, 1H, O*H*), 3.05 (dd, *J* = 8.9, 3.8 Hz, 1H, C*H*OH),

2.50 (bs, 1H, O*H*), 0.83–0.72 (m, 1H, -CH_2CHCH_2-), 0.46–0.36 (m, 2H, CH_2CHCH_2-), 0.32–0.17 (m, 1H, -CH_2CHCH_2-), 0.02–-0.03 (m, 1H, -CH_2CHCH_2-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 128.1, 127.9, 127.7, 80.0, 76.8, 12.7, 3.1, 2.4.

***rel*-(1*R*,2*R*)-1-cyclohexyl-2-phenylethane-1,2-diol 121**

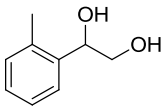


Reaction of *trans*-(2-cyclohexylvinyl)benzene **120** (234 mg, 1.26 mmol), H_2O (23 μL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol 25:1 *syn*:*anti*) and purification by silica gel flash chromatography (1:2 diethyl ether:petroleum ether) gave the title compound as a colourless solid (249 mg, 1.13 mmol, 90%).

Colourless solid; m.p. 83–84 °C; IR (ATR)/cm^{-1}: 3271, 3030, 2920, 2853, 1053, 1009; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.17 (m, 5H, Ph*H*), 4.62 (d, *J* = 5.7 Hz, 1H, PhC*H*OH), 3.39 (dd, *J* = 5.7, 5.7 Hz, 1H, C*H*OHCy), 2.18 (bs, 2H, O*H*), 1.77–1.52 (m, 5H, C*HCH*$_2$), 1.25–1.04 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 128.7, 128.0, 126.7, 80.2, 74.5, 39.4, 30.3, 27.5, 26.5, 26.4, 26.2; LRMS (EI) *m/z* 220.2 $[M]^+$.

^{18}O-labelled peroxide **121**: LRMS (EI) *m/z* 222.2 $[M]^+$; HRMS (EI) calculated for $C_{14}H_{20}{}^{16}O^{18}O$ $[M]^+$ 222.1506, found 222.1516.

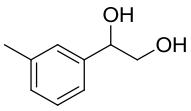
1-*o*-Tolylethane-1,2-diol 161[39]



Reaction of 2-methylstyrene (149 mg, 1.26 mmol), H_2O (23 μL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (2:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (160 mg, 1.05 mmol, 83%).

Colourless solid; m.p. 104–105 °C; IR (ATR /cm^{-1}: 3160, 3069, 2925, 2851, 1064, 1033; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.25–7.12 (m, 3H, Ar*H*), 5.07 (dd, *J* = 8.4, 3.2 Hz, 1H, ArC*H*OH), 3.73 (dd, *J* = 11.3, 3.2 Hz, 1H, CH_2OH), 3.62 (dd, *J* = 11.3, 8.4 Hz, 1H, CH_2OH), 2.35 (s, 3H, CH_3), 2.15 (bs, 2H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 135.1, 130.8, 128.1, 126.7, 126.0, 71.7, 67.2, 19.4; LRMS (EI) *m/z* 152.1 $[M]^+$; HRMS (EI) calculated for $C_9H_{12}O_2$ $[M]^+$ 152.0837, found 152.0842.

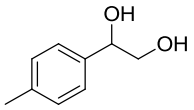
1-*m*-Tolylethane-1,2-diol 162[39]



Reaction of 3-methylstyrene (149 mg, 1.26 mmol), H_2O (23 μL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (2:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (160 mg, 1.05 mmol, 83%).

Colourless solid; m.p. 70–72 °C; IR (ATR)/cm^{-1}: 3366, 3027, 2922, 2887, 1077, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.08 (m, 4H, Ar*H*), 4.64 (dd, *J* = 8.4, 3.2 Hz, 1H, ArC*H*OH), 3.63–3.46 (m, 4H, CH_2 and O*H*), 2.24 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 138.4, 128.9, 128.7, 127.0, 123.4, 75.0, 68.3, 21.7; LRMS (EI) *m/z* 152.1 $[M]^+$; HRMS (EI) calculated for $C_9H_{12}O_2$ $[M]^+$ 152.0837, found 152.0836.

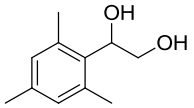
1-*p*-Tolylethane-1,2-diol 163[20]



Reaction of 4-methylstyrene (149 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (2:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (172 mg, 1.13 mmol, 90%).

Colourless solid; m.p. 70–72 °C [lit.[20] 76–77 °C]; IR (ATR)/cm^{-1}: 3269, 3016, 2923, 2889, 1085, 1062; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.16 (d, *J* = 8.0 Hz, 2H, Ar*H*), 4.76 (dd, *J* = 8.2, 3.6 Hz, 1H, ArC*H*OH), 3.66 (m, 2H, CH_2), 2.78 (bs, 2H, O*H*), 2.34 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.8, 129.6, 126.3, 74.9, 68.4, 21.5; LRMS (EI) *m/z* 152.1 $[M]^+$; HRMS (EI) calculated for $C_9H_{12}O_2$ $[M]^+$ 152.0837, found 152.0840.

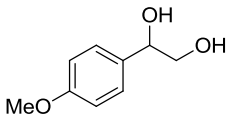
1-Mesitylethane-1,2-diol 164[39]



Reaction of 2,4,6-trimethylstyrene (184 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (1:2 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (206 mg, 1.15 mmol, 91%).

Colourless solid; m.p. 110–111 °C; IR (ATR)/cm^{-1}: 3366, 3003, 2942, 2923, 2862, 1082, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) 6.83 (s, 2H, Ar*H*), 5.26 (dd, *J* = 10.0, 3.8 Hz, 1H, ArC*H*OH), 3.96 (dd, *J* = 11.6, 10.0 Hz, 1H, CH_2OH), 3.61 (dd, *J* = 11.6, 3.8 Hz, 1H, CH_2OH), 2.40 (s, 6H, CH_3), 2.25 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 137.2, 136.6, 132.4, 130.2, 72.6, 64.6, 20.7, 20.7; LRMS (EI) *m/z* 180.1 $[M]^+$; HRMS (EI) calculated for $C_{11}H_{16}O_2$ $[M]^+$ 180.1150, found 180.1145.

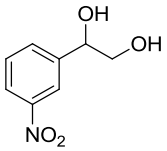
1-(4-Methoxyphenyl)ethane-1,2-diol 165[125]



Reaction of 4-methoxystyrene (169 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 2 h at 40 ºC and purification by silica gel flash chromatography (2:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (182 mg, 1.08 mmol, 86%).

Colourless solid; m.p. 78–79 °C [lit.[128] 76–78 °C]; IR (ATR)/cm^{-1}: 3296, 3008, 2962, 2934, 2839, 1245, 1179, 1080, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) 7.30 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.90 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.78 (dd, *J* = 7.8, 3.4 Hz, 1H, ArC*H*OH), 3.81 (s, 3H, OCH_3), 3.76–3.63 (m, 2H, CH_2OH), 2.42 (bs, 1H, O*H*), 2.03 (bs, 1H, O*H*); ^{13}C NMR (62.5 MHz, $CDCl_3$) 159.3, 132.6, 127.3, 113.9, 74.3, 68.0, 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.

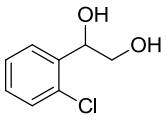
1-(3-Nitrophenyl)ethane-1,2-diol 167[39]



Reaction of 3-nitrostyrene (188 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (323 mg, 2.52 mmol, 2 eq) in chloroform (2 mL) according to General Procedure **C** for 72 h at 60 °C and purification by silica gel flash chromatography (3:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (145 mg, 0.794 mmol, 63%).

Colourless solid; m.p. 74–75 °C; IR (ATR)/cm^{-1}: 3355, 3222, 2964, 2932, 2875, 1526, 1334, 1046, 1035; ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.35 (s, 1H, Ar*H*), 8.16 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.89 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.66 (dd, *J* = 7.9 Hz, 7.9 Hz, 1H, Ar*H*), 4.94 (m, 1H, ArC*H*OH), 4.83 (d, *J* = 4.1 Hz, 1H, CHO*H*), 4.12 (dd, *J* = 6.0 Hz, *J* = 6.0 Hz, 1H, CH_2O*H*), 3.76–3.66 (m, 2H, CH_2); ^{13}C NMR (62.5 MHz, Acetone-d_6) δ 148.5, 145.7, 133.0, 129.5, 122.1, 121.2, 73.5, 67.8; 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.

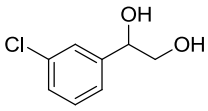
1-(2-Chlorophenyl)ethane-1,2-diol 168[39]



Reaction of 2-chlorostyrene (173 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (1:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (178 mg, 1.03 mmol, 82%).

Colourless solid; m.p. 101–104 °C [lit.[129] 101–104 °C]; IR (ATR)/cm^{-1}: 3172, 2924, 2849, 1069, 1049, 1033; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.39–7.25 (m, 3H, Ar*H*), 5.47 (d, *J* = 4.4 Hz, 1H, ArCHO*H*), 4.95–4.92 (m, 1H, ArC*H*OH), 4.87 (dd, *J* = 5.9, 5.9 Hz, 1H, CH_2O*H*), 3.54–3.47 (m, 1H, C*H*$_2$OH), 3.38–3.30 (m, 1H, C*H*$_2$OH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 141.4, 132.1, 129.8, 129.5, 129.3, 128.0, 71.7, 66.8; LRMS (EI) *m/z* 172.0 $[M]^+$; HRMS (EI) calculated for $C_8H_9O_2{}^{35}Cl$ $[M]^+$ 172.0291, found 172.0288.

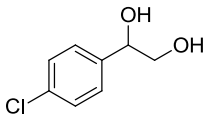
1-(3-Chlorophenyl)ethane-1,2-diol 169[130]



Reaction of 3-chlorostyrene (174 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (290 mg, 2.27 mmol, 1.8 eq) in chloroform (2 mL) according to General Procedure **C** for 50 h at 60 ºC and purification by silica gel flash chromatography (1:1 ethyl acetate:petroleum ether) gave the title compound as a colourless oil (152 mg, 0.882 mmol, 70%).

Colourless oil; IR (ATR)/cm^{-1}: 3366, 3076, 2926, 2876, 1196, 1101, 1077; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (s, 1H, Ar*H*), 7.18–7.12 (m, 2H, Ar*H*), 7.07–7.05 (m, 1H, Ar*H*), 4.62 (dd, *J* = 8.5, 3.1 Hz, 1H, ArC*H*OH), 3.89 (bs, 2H, O*H*), 3.56 (dd, *J* = 11.6, 3.1 Hz, 1H, C*H*$_2$OH), 3.45 (dd, *J* = 11.6, 8.5 Hz, 1H, C*H*$_2$OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 134.5, 129.9, 128.1, 126.3, 124.3, 74.1, 67.8; LRMS (ESI) *m/z* 172.0 [M(^{35}Cl)]$^+$, HRMS (ASAP) calculated for $C_8H_9O_2{}^{35}Cl$ [M]$^+$ 172.0286, found 172.0287.

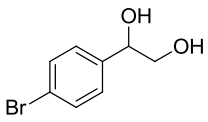
1-(4-Chlorophenyl)ethane-1,2-diol 170[125]



Reaction of 4-chlorostyrene (174 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (1:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (186 mg, 1.08 mmol, 86%).

Colourless solid; m.p. 76–77 °C [lit.[131] 83–83 ºC]; IR (ATR)/cm^{-1}: 3403, 3380, 3006, 2934, 2897, 1085, 1067, 1035; ^{1}H NMR (400 MHz, $CDCl_3$) 7.28–7.22 (m, 4H, Ar*H*), 4.74 (dd, *J* = 8.2, 3.5 Hz, 1H, ArC*H*OH), 3.68 (dd, *J* = 11.3, 3.5 Hz, 1H, C*H*$_2$OH), 3.54 (dd, *J* = 11.3, 8.2 Hz, 1H, C*H*$_2$OH); ^{13}C NMR (125 MHz, $CDCl_3$) 138.9, 133.8, 128.7, 127.5, 74.0, 68.0; LRMS (CI) *m/z* 190.2 [M(^{35}Cl) + NH_4]$^+$; HRMS (ES) calculated for $C_8H_{13}NO_2{}^{35}Cl$ [M + NH_4]$^+$ 190.0629, found 190.0626.

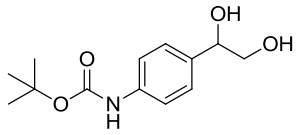
1-(4-Bromophenyl)ethane-1,2-diol 171[20]



Reaction of 4-bromostyrene (229 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (2:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (234 mg, 1.08 mmol, 86%).

Colourless solid; m.p. 83–85 °C [lit.[20] 81 °C]; IR (ATR)/cm^{-1}: 3314, 2930, 2896, 2851, 1067, 1034, 1011; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.49 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.36 (d, *J* = 8.4 Hz, 2H, Ar*H*), 4.74 (ddd, *J* = 7.4, 4.0, 3.8 Hz, 1H, ArC*H*OH), 4.47 (d, *J* = 3.8 Hz, 1H, CHO*H*), 3.90 (app t, *J* = 5.9 Hz, 1H, CH_2O*H*), 3.70–3.52 (m, 2H, CH_2); ^{13}C NMR (62.5 MHz, Acetone-d_6) δ 143.1, 131.8, 129.2, 121.1, 74.5, 68.6; LRMS (EI) *m/z* 216.0 [M(^{79}Br)]$^+$; HRMS (EI) calculated for $C_8H_9O_2{}^{79}Br$ [M]$^+$ 215.9786, found 215.9790.

tert-Butyl 4-(1,2-dihydroxyethyl)phenylcarbamate 172[39]

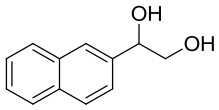


Reaction of *tert*-butyl 4-vinylphenylcarbamate (276 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (9:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (105 mg, 0.479 mmol, 38%).

Colourless solid; m.p. 139–141 °C; IR (ATR)/cm^{-1}: 3364, 3300, 3003, 2976, 2916, 2855, 1701, 1529, 1240, 1160, 1055; ^{1}H NMR (400 MHz, Acetone-d_6) 8.80 (bs, 1H, N*H*), 6.91 (d, *J* = 6.6 Hz, 2H, Ar*H*), 6.73 (d, *J* = 6.6 Hz, 2H, Ar*H*), 4.66–4.65 (m, 1H, ArC*H*OH), 4.21–4.19 (m, 1H, CH_2OH), 4.00 (dd, *J* = 8.8, 4.4 Hz, 1H, CH_2OH) 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) 152.7, 138.0, 136.9, 126.3, 117.6, 78.7,

73.3, 67.4, 28.0; LRMS (EI) *m/z* 253.1 $[M]^+$; HRMS (EI) calculated for $C_{13}H_{19}NO_4$ $[M]^+$ 253.1314, found 253.1310.

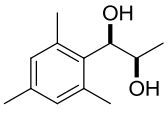
1-(Naphthalene-6-yl)ethane-1,2-diol 173[125]



Reaction of 2-vinylnaphthalene (194 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (9:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (185 mg, 0.983 mmol, 78%).

Colourless solid; m.p. 126–127 °C [lit.[132] 134–135 ºC]; IR (ATR)/cm^{-1}: 3197, 3050, 2963, 2934, 2869, 1088, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) 7.86–7.84 (m, 4H, Ar*H*), 7.51–7.46 (m, 3H, Ar*H*), 5.03–4.99 (m, 1H, ArC*H*OH), 3.90–3.74 (m, 2H, C*H*$_2$OH), 2.61 (d, *J* = 3.2 Hz, 1H, ArCHO*H*), 2.05 (dd, *J* = 7.2, 4.8 Hz, 1H, CH_2O*H*); ^{13}C NMR (62.5 MHz, DMSO-d_6) 141.0, 132.7, 132.2, 127.6, 127.3, 127.1, 125.8, 125.3, 124.9, 124.5, 73.8, 67.3; LRMS (EI) *m/z* 188.1 $[M]^+$; HRMS (EI) calculated for $C_{12}H_{12}O_2$ $[M]^+$ 188.0837, found 188.0837.

***rel*-(1*R*,2*R*)-1-Mesitylpropane-1,2-diol 178[39]**

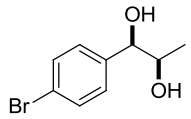


Reaction of *trans*-1-mesitylpropene (202 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol >50:1 *syn*:*anti*) and

purification by silica gel flash chromatography (2:1 ethyl acetate:petroleum ether) gave the title compound as a colourless solid (227 mg, 1.17 mmol, 93%).

Colourless solid; m.p. 83–85 °C; IR (ATR)/cm^{-1}: 3390, 2971, 2934, 2871, 1040, 1016; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.82 (s, 2H, Ar*H*), 4.86 (d, *J* = 9.1 Hz, 1H, ArC*H*OH), 4.35–4.26 (dq, *J* = 9.1 Hz, 6.4 Hz, 1H, C*H*OH), 2.67 (bs, 2H, O*H*), 2.41 (s, 6H, CH_3), 2.25 (s, 3H, CH_3), 1.01 (d, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.3, 137.0, 133.4, 130.4, 76.5, 70.0, 21.3, 20.9, 18.8; LRMS (EI) *m/z* 194.1 $[M]^+$; HRMS (EI) calculated for $C_{12}H_{18}O_2$ $[M]^+$ 194.1307, found 194.1309.

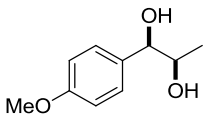
rel-(1*R*,2*R*)-1-(4-Bromophenyl)propane-1,2-diol 179[39]



Reaction of *trans*-4-bromo-β-methylstyrene (247 mg, 1.26 mmol), H_2O (23 μL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol 13:1 *syn*:*anti*) and purification by silica gel flash chromatography (1:1 ethyl acetate:petroleum ether) gave the title compound as a pale yellow oil (248 mg, 1.08 mmol, 86%).

Pale yellow oil; IR (ATR)/cm^{-1}: 3402, 2989, 2896, 1126, 1069, 1010; ^{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, ArC*H*OH), 3.77–3.70 (m, 1H, C*H*OHCH$_3$), 3.59 (bs, 1H, O*H*), 3.20 (bs, 1H, O*H*), 0.99 (d, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 131.6, 128.5, 122.0, 78.8, 72.1, 18.8; LRMS (EI) *m/z* 211.9 $[M(^{79}Br) - H_2O]^+$; HRMS (EI) calculated for $C_9H_9O^{79}Br$ $[M - H_2O]^+$ 211.9837, found 211.9841.

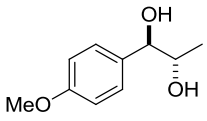
rel-(1*R*,2*R*)-1-(4-Methoxyphenyl)propane-1,2-diol 180[39]



Reaction of *trans*-anethole (186 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol 5.5:1 *syn*:*anti*) and purification by silica gel flash chromatography (1:9 methanol:dichloromethane) gave the title compound as a colourless oil that solidified on standing (179 mg, 0.983 mmol, 78%). Repeating the reaction at 0 ºC resulted in an increased selectivity of 10:1 *syn*:*anti* (188 mg, 1.03 mmol, 82%).

Colourless solid; m.p. 68–65 °C [lit.[133] 79–81 ºC]; IR (ATR)/cm^{-1}: 3390, 2971, 2931, 2834, 1250, 1176, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 4.27 (d, *J* = 7.5 Hz, 1H, ArC*H*OH), 3.81–3.77 (m, 4H, C*H*OHCH_3 and OCH_3), 3.00 (bs, 1H, O*H*), 2.90 (bs, 1H, O*H*), 1.00 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 133.3, 128.2, 114.0, 79.2, 72.4, 55.4, 18.9; LRMS (EI) *m/z* 182.1 $[M]^+$; HRMS (EI) calculated for $C_{10}H_{14}O_3$ $[M]^+$ 182.0943, found 182.0940.

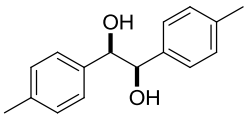
rel-(1*R*,2*S*)-1-(4-Methoxyphenyl)propane-1,2-diol 365



Colourless solid; m.p. 92–93 °C; IR (ATR)/cm^{-1}: 3386, 2976, 2933, 2830, 1233, 1178, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.90 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.60 (dd, *J* = 3.8, 3.5 Hz, 1H, ArC*H*OH), 4.02–3.95 (m, 1H, C*H*OHCH_3), 3.81 (s, 3H, OCH_3), 2.30 (d, *J* = 3.5 Hz, 1H, O*H*), 1.86 (d, *J* = 4.7 Hz, 1H, O*H*), 1.10 (d,

J = 6.4 Hz, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 132.5, 128.1, 114.0, 77.4, 71.4, 55.4, 17.7; LRMS (EI) *m/z* 182.1 $[M]^+$; HRMS (EI) calculated for $C_{10}H_{14}O_3$ $[M]^+$ 182.0943, found 182.0941.

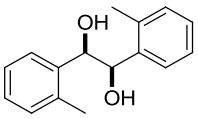
rel-(1*R*,2*R*)-1,2-Di-*p*-tolylethane-1,2-diol 181[39]



Reaction of *trans*-4,4'-dimethylstilbene (262 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol 34:1 *syn*:*anti*) and purification by silica gel flash chromatography (1:3 ethyl acetate:petroleum ether) gave the title compound as a light brown solid (256 mg, 1.06 mmol, 84%).

Light brown solid; m.p. 165 °C [lit.[134] 180 ºC]; IR (ATR)/cm^{-1}: 3275, 2990, 2913, 1057, 1027; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (app. s, 8H, Ar*H*), 4.69 (s, 2H, ArC*H*OH), 2.72 (s, 2H, CHO*H*), 2.30 (s, 6H, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 137.0, 128.8, 126.8, 78.8, 21.1; LRMS (EI) *m/z* 224.1 $[M - H_2O]^+$; HRMS (CI) calculated for $C_{16}H_{22}NO_2$ $[M + NH_4]^+$ 260.1645, found 260.1649.

rel-(1*R*,2*R*)-1,2-Di-*o*-tolylethane-1,2-diol 182[39]

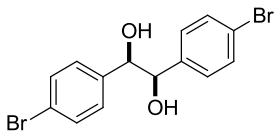


Reaction of *trans*-2,2'-dimethylstilbene (262 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol 39:1 *syn*:*anti*) and

purification by silica gel flash chromatography (1:3 ethyl acetate:petroleum ether) gave the title compound as an off-white solid (284 mg, 1.17 mmol, 93%).

Off-white solid; m.p. 125 °C [lit.[135] 116–118 °C]; IR (ATR)/cm^{-1}: 3448, 3293, 3025, 2968, 2901, 1041; ^{1}H NMR (400 MHz, $CDCl_3$) 7.60 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.22–7.18 (dd, *J* = 7.5, 7.5 Hz, 2H, Ar*H*), 7.14–7.10 (dd, *J* = 7.5, 7.5 Hz, 2H, Ar*H*), 6.92 (d, *J* = 7.4 Hz, 2H, Ar*H*), 4.93 (s, 2H, ArC*H*OH), 3.22 (s, 2H, ArCHO*H*), 1.64 (s, 6H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) 137.9, 135.8, 130.0, 127.6, 127.1, 125.8, 74.5, 18.7; 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.

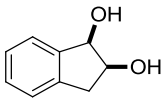
rel-(1*R*,2*R*)-1,2-Di-4-bromophenylethane-1,2-diol 183[39]



Reaction of *trans*-4,4'-dibromostilbene (426 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol 30:1 *syn*:*anti*) and purification by silica gel flash chromatography (1:2 ethyl acetate:petroleum ether) gave the title compound as an off-white solid (398 mg, 1.07 mmol, 85%).

Off-white solid; m.p. 159–161 °C; IR (ATR)/cm^{-1}: 3341, 2989, 2919, 1054, 1008; ^{1}H NMR (250 MHz, CD_3OD) δ 7.35 (d, *J* = 8.5 Hz, 4H, Ar*H*) 7.03 (d, *J* = 8.5 Hz, 4H, Ar*H*), 4.62 (s, 2H, C*H*OH); ^{13}C NMR (62.5 MHz, CD_3OD) δ 141.8, 131.9, 130.3, 122.2, 79.2; HRMS (APCI) calculated for $C_{14}H_{16}NO_2{}^{79}Br_2$ $[M + NH_4]^+$ 387.9542, found 387.9545.

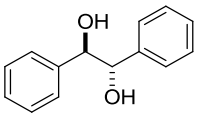
rel-(1_R_,2_S_)-2,3-Dihydro-1_H_-indene-1,2-diol 184[20]



Reaction of indene (146 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol >50:1 *cis*:*trans*) and purification by silica gel flash chromatography (1:2 diethyl ether:petroleum ether) gave the title compound as an off-white solid (98 mg, 0.655 mmol, 52%).

Colourless solid; m.p. 99–102 °C [lit.[20] 108–109 ºC]; IR (ATR)/cm^{-1}: 3437, 3284, 3058, 2952, 2923, 2902, 1061, 1052; ^{1}H NMR (400 MHz, $CDCl_3$) 7.44–7.42 (m, 1H, Ph*H*), 7.30–7.23 (m, 3H, Ph*H*), 5.00 (dd, *J* = 6.9, 5.2 Hz, 1H, PhC*H*OH), 4.52–4.47 (m, 1H, CH_2C*H*OH), 3.12 (dd, *J* = 16.3, 5.7 Hz, 1H, PhCH_2), 2.95 (dd, *J* = 16.3, 3.5 Hz, 1H, PhCH_2), 2.58 (d, *J* = 6.9 Hz, 1H, O*H*), 2.49 (d, *J* = 6.0 Hz, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 142.1, 140.3, 128.8, 127.2, 125.4, 125.2, 76.0, 73.5, 38.5; LRMS (EI) *m/z* 150.1 $[M]^+$; HRMS (EI) calculated for $C_9H_{10}O_2$ $[M]^+$ 150.0681, found 150.0684.

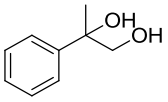
rel-(1_R_,2_R_)-1,2-Bisphenylethane-1,2-diol 185[20]



Reaction of *cis*-stilbene **95** (3.00 g, 16.7 mmol), H_2O (300 µL, 16.7 mmol) and cyclopropyl malonoyl peroxide **86** (2.56 g, 20.0 mmol) in chloroform (25 mL) according to General Procedure **C** for 24 h at 40 ºC (crude diol 3.7:1 *anti*:*syn*) and purification by silica gel flash chromatography (1:4 diethyl ether:petroleum ether) gave the title compound as a colourless solid (3.00 g, 14.0 mmol, 84%).

Colourless solid; m.p. 133 °C [lit.[136] 134–136 °C]; IR (ATR)/cm^{-1}: 3322, 3082, 3022, 2898, 1032, 1021; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 10H, Ph*H*), 4.82 (s, 2H, PhC*H*OH), 2.25 (s, 2H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 128.4, 128.3, 127.2, 78.2; LRMS (ESI) *m/z* 196.1 $[M - H_2O]^+$; HRMS (ESI) calculated for $C_{14}H_{12}O$ $[M - H_2O]^+$ 196.0888, found 196.0886.

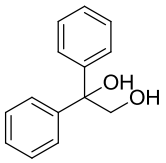
2-Phenylpropane-1,2-diol 191[125]



Reaction of α-methylstyrene (149 mg, 1.26 mmol), H_2O (23 μL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 °C and purification by silica gel flash chromatography (1:2 diethyl ether:petroleum ether) gave the title compound as a colourless solid (92 mg, 0.605 mmol, 48%).

Colourless solid; m.p. 43–45 °C [lit.[137] 43–44 °C]; IR (ATR)/cm^{-1}: 3390, 3060, 3028, 2977, 2929, 2873, 1044, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.07 (m, 5H, Ph*H*), 3.61 (d, *J* = 11.3 Hz, 1H, CH_2), 3.46 (d, *J* = 11.3 Hz, 1H, CH_2), 3.01 (bs, 2H, O*H*), 1.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 128.6, 127.4, 125.4, 75.2, 71.1, 26.2; LRMS (EI) *m/z* 152.1 $[M]^+$; HRMS (EI) calculated for $C_9H_{10}O$ $[M - H_2O]^+$ 134.0732, found 134.0736.

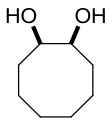
1,1-Diphenylethane-1,2-diol 194[138]



Reaction of 1,1-diphenylstyrene (227 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (1:1 diethyl ether:petroleum ether) gave the title compound as a colourless solid (94 mg, 0.441 mmol, 35%).

Colourless solid; m.p. 114–116 ^{o}C [lit.[138] 120–121 ^{o}C]; IR (ATR)/cm^{-1}: 3374, 3064, 3026, 3008, 2962, 1069, 1044; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.43 (m, 4H, Ar*H*), 7.37–7.33 (m, 4H, Ar*H*), 7.29–7.25 (m, 2H, Ar*H*), 4.16 (d, *J* = 6.1 Hz, 2H, CH_2), 3.21 (s, 1H, O*H*), 1.95 (t, *J* = 6.1 Hz, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 128.6, 127.6, 126.5, 78.7, 69.6; LRMS (ESI) *m/z* 196.1 $[M - H_2O]^+$; HRMS (ESI) calculated for $C_{14}H_{12}O$ $[M - H_2O]^+$ 196.0888, found 196.0887.

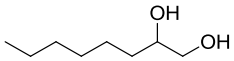
***rel*-(1*R*,2*S*)-Cyclooctane-1,2-diol 214[20]**



Reaction of *cis*-cyclooctene (184 mg, 1.67 mmol), H_2O (30 µL, 1.67 mmol) and cyclopropyl malonoyl peroxide **86** (256 mg, 2.00 mmol) in chloroform (3 mL) according to General Procedure **C** for 48 h at 50 ºC (crude diol >50:1 *cis*:*trans*) and purification by silica gel flash chromatography (diethyl ether) gave the title compound as a colourless solid (36 mg, 0.25 mmol, 15%).

Colourless solid; m.p. 71–73 °C [lit.[20] 75 °C]; IR (ATR)/cm^{-1}: 3391, 3270, 2912, 2856, 1040, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90–3.86 (m, 2H, C*H*OH), 2.53 (bs, 2H, O*H*), 1.89–1.84 (m, 2H, CH_2), 1.69–1.64 (m, 4H, CH_2), 1.52–1.44 (m, 6H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.3, 30.2, 26.4, 23.9; LRMS (CI) *m/z* 127.1 [M – OH]$^{+}$.

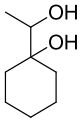
_n_-Oct-1,2-diol 215[20]



Reaction of 1-octene (141 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 48 h at 50 ºC gave the title compound as a colourless semi-solid (33 mg, 0.227 mmol, 18%).

Colourless semi-solid [lit.[20] m.p. 30 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72–3.64 (m, 1H, C*H*OH), 3.61 (dd, *J* = 11.1, 2.7 Hz, 1H, CH_2OH), 3.40 (dd, *J* = 11.1, 7.8 Hz, 1H, CH_2OH), 2.93 (bs, 2H, O*H*), 1.41–1.24 (m, 10H, CH_2), 0.88–0.85 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.5, 66.9, 33.3, 31.9, 29.5, 25.7, 22.7, 14.2; LRMS (CI) *m/z* 129.1 [M – OH]$^{+}$.

1-(1-Hydroxyethyl)cyclohexanol 216[39]

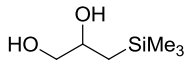


Reaction of ethylidenecyclohexane (139 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL)

according to General Procedure **C** for 48 h at 50 ºC gave the title compound as a colourless semi-solid (73 mg, 0.504 mmol, 40%).

Colourless semi-solid; IR (ATR)/cm^{-1}: 3399, 2930, 2854, 1097, 1049; ^{1}H NMR (400 MHz, $CDCl_3$) 3.51 (q, *J* = 6.4 Hz, 1H, CH_3CHOH), 2.17 (s, 2H, O*H*), 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, $CDCl_3$) 73.7, 73.4, 34.1, 31.2, 25.8, 21.6, 21.4, 17.0; LRMS (CI) *m/z* 162.2 $[M + NH_4]^+$; HRMS (ES) calculated for $C_8H_{20}NO_2$ $[M + NH_4]^+$ 162.1489, found 162.1487.

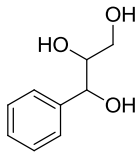
3-(Trimethylsilyl)-1,2-propanediol 227[125]



Reaction of trimethylallylsilane (144 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC gave the title compound as a colourless oil (86 mg, 0.580 mmol, 46%).

Colourless oil; IR (ATR)/cm^{-1}: 3337, 2951, 2918, 1248, 1070, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87–3.81 (m, 1H, C*H*OH), 3.57 (dd, *J* = 11.2, 2.5 Hz, 1H, CH_2OH), 3.31 (dd, *J* = 11.2, 8.2 Hz, 1H, CH_2OH), 3.19 (bs, 2H, O*H*), 0.79 (dd, *J* = 14.5, 8.2 Hz, 1H, CH_2SiMe_3), 0.68 (dd, *J* = 14.5, 6.2 Hz, 1H, CH_2SiMe_3), 0.04 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.5, 69.1, 21.7, -0.70; LRMS (ESI) *m/z* 147.0 $[M - H]^-$.

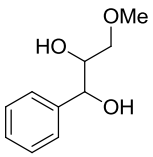
1-Phenylpropane-1,2,3-triol 230



Reaction of (*E*)-3-phenylprop-2-en-1-ol (272 mg, 2.03 mmol), cyclopropyl malonoyl peroxide (311 mg, 2.43 mmol) and H_2O (37 µL, 2.03 mmol) in chloroform (3 mL) according to the General Procedure **C** for 24 h at 25 ºC and purification by silica gel flash chromatography (diethyl ether) gave the title compound as a colourless oil (245 mg, 1.46 mmol, 72 %).

Colourless oil; IR (ATR)/cm^{-1}: 3348, 3063, 3032, 2980, 2963, 2884, 1054, 1024, 1001; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.19 (m, 5H, Ph*H*), 4.49 (d, *J* = 7.0 Hz, 1H, PhC*H*OH), 3.68–3.63 (m, 1H, CHC*H*CH_2), 3.35–3.24 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 128.6, 128.1, 126.8, 76.2, 74.7, 63.2; LRMS (CI) *m/z* 133.0 $[M – H_2O – OH]^+$.

3-Methoxy-1-phenylpropane-1,2-diol 231



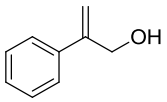
Reaction of (*E*)-(3-methoxyprop-1-en-1-yl)benzene **32** (300 mg, 2.03 mmol), cyclopropyl malonoyl peroxide **86** (311 mg, 2.43 mmol) and H_2O (37 µL, 2.03 mmol) in chloroform (3 mL) for 96 h at 25 ºC according to General Procedure **C** did not give complete consumption of starting materials by TLC (1:8 diethyl ether:petroleum ether 30–40 ^{o}C). Crude diol product which was purified by silica gel flash chromatography (3:1 diethyl ether:petroleum ether) to give the title compound as a colourless oil (160 mg, 0.88 mmol, 43%). Addition of 3-phenyl-propan-1-ol **232** (276 mg, 2.03 mmol,

1 eq) as a potential hydrogen-bond donor following the above procedure also gave diol **231** (166 mg, 0.91 mmol, 45%). No noticeable change in rate of reaction was observed.

Colourless oil; IR (ATR)/cm^{-1}: 3387, 3030, 2983, 2928, 2887, 2822, 1125, 1105, 1069; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H, Ph*H*), 4.67 (d, *J* = 6.5 Hz, 1H, PhC*H*OH), 3.83–3.77 (m, 1H, C*H*CH_2OMe), 3.36 (dd, *J* = 9.9, 3.4 Hz, 1H, CH_2), 3.33 (s, 3H, OCH_3), 3.29 (dd, *J* = 9.9, 5.5 Hz, 1H, CH_2), 3.25 (bs, 1H, O*H*), 3.01 (bs, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 128.6, 128.1, 126.8, 74.9, 74.8, 73.6, 59.3; LRMS (CI) *m/z* 165.0 $[M - OH]^+$.

8.4.2 Analytical Data for Allylic Alcohols

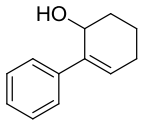
2-Phenylprop-2-en-1-ol 192[139]



Reaction of α-methylstyrene (149 mg, 1.26 mmol), H_2O (23 μL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (1:2 diethyl ether:petroleum ether) gave the title compound as a colourless solid (27 mg, 0.202 mmol, 16%).

Colourless oil; IR (ATR)/cm^{-1}: 3285, 3028, 2970, 2870, 1618, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 6.9 Hz, 2H, Ph*H*), 7.39–7.30 (m, 3H, Ph*H*), 5.48 (d, *J* = 1.1 Hz, 1H, C=CH_2), 5.36 (d, *J* = 1.1 Hz, 1H, C=CH_2), 4.53 (s, 2H, CH_2OH), 2.03 (bs, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 138.7, 128.6, 128.0, 126.2, 112.6, 65.0; LRMS (CI) *m/z* 135.1 $[M + H]^+$.

2,3,4,5-Tetrahydro-(1,1'-biphenyl)-2-ol 195[140]

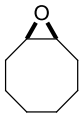


Reaction of 1-phenyl-1-cyclohexene (199 mg, 1.26 mmol), H_2O (23 µL, 1.26 mmol) and cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (1:3 diethyl ether:petroleum ether) gave the title compound as a colourless oil (55 mg, 0.227 mmol, 12%).

Colourless oil; IR (ATR)/cm^{-1}: 3329, 3017, 2934, 2918, 1604, 1055; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.24 (m, 5H, Ph*H*), 6.17 (dd, *J* = 4.4, 3.6 Hz, 1H, PhC=C*H*), 4.71 (dd, *J* = 3.6, 3.6 Hz, 1H, C*H*OH), 2.32–2.13 (m, 2H, CH_2), 2.00–1.65 (m, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 139.2, 128.8, 128.6, 127.2, 126.1, 65.6, 31.7, 26.2, 17.5; LRMS (ESI) *m/z* 174.1 $[M]^+$.

8.4.3 Analytical Data for Epoxide 222

***rel*-(1*R*,8*S*)-9-Oxabicyclo[6.1.0]nonane 222[141]**



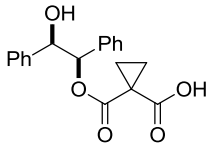
Reaction of *cis*-cyclooctene (184 mg, 1.67 mmol), H_2O (30 µL, 1.67 mmol) and cyclopropyl malonoyl peroxide **86** (256 mg, 2.00 mmol) in chloroform (3 mL) according to General Procedure **C** for 48 h at 50 ºC and purification by silica gel flash chromatography (diethyl ether) gave the title compound as a colourless oil (50 mg, 0.397 mmol, 24%).

Colourless oil; IR (ATR)/cm^{-1}: 2973, 2929, 2856, 906; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89–2.84 (m, 2H, C*H*O), 2.14–2.08 (m, 2H, CH_2CHO), 1.60–1.38 (m, 8H, CH_2), 1.30–1.20 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 26.6, 26.4, 25.7; LRMS (CI) *m/z* 127.1 $[M + H]^+$.

8.5 Preparation of *Syn*-Dihydroxylation Reaction Intermediates

(*E*)-Stilbene **1** (3.00 g, 16.7 mmol), H_2O (300 µL, 16.7 mmol, 1 eq) and cyclopropyl malonoyl peroxide **86** (2.56 g, 20.0 mmol, 1.2 eq) were stirred in chloroform (25 mL) according to General Procedure **C** for 24 h at 40 ºC but the hydrolysis step using 1 M NaOH was not performed. Solvent was removed *in vacuo* and compounds **93**, **94** and **144** were separated by silica gel flash chromatography using a solvent gradient (1:4 to 1:1 diethyl ether:petroleum ether). Compounds **93** and **94** were crystallised by vapour diffusion crystallisation (chloroform:petroleum ether (b.p. 30–40 ^{o}C)) to give colourless needles. *Anti*-hydroxy ester **96** and *anti*-7-membered ring **97** were isolated from an identical reaction using (*Z*)-stilbene. Silica gel column chromatography (1:4 to 1:1 diethyl ether:petroleum ether) and two vapour diffusion recrystallisations (chloroform:petroleum ether (b.p. 30–40 ^{o}C)) were allowed isolation of **96** and **97** as single diastereomers.

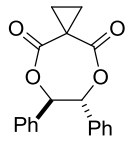
1-(((*rel*-1*R*,2*R*)-2-Hydroxy-1,2-diphenylethoxy)carbonyl)cyclopropanecarboxylic acid 93



Colourless solid; m.p. 117–119 °C; IR (ATR)/cm^{-1}: 3377, 3059, 3034, 2913, 2851, 1740, 1686, 1192, 1130, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.23 (m, 6H, Ph*H*), 7.13–7.05 (m, 4H, Ph*H*), 5.91 (d, *J* = 7.4 Hz, 1H, PhC*H*OR), 4.92 (d, *J* = 7.4 Hz, 1H,

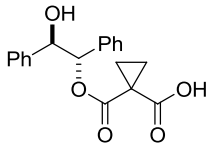
PhC*H*OH), 1.86–1.77 (m, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 171.3, 138.7, 135.6, 128.9, 128.6, 128.5, 128.4, 127.2, 127.0, 82.0, 76.7, 25.7, 22.1, 21.7; HRMS (NSI) calculated for $C_{19}H_{17}O_5$ $[M + H]^+$ 327.1081, found 327.1087.

rel-(6_R_,7_R_)-6,7-Diphenyl-5,8-dioxaspiro[2.6]nonane-4,9-dione 94



Colourless solid; m.p. 122–124 °C; IR (ATR)/cm^{-1}: 3061, 3038, 2954, 1748, 1713, 1267, 1211; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.19 (m, 6H, Ph*H*), 7.07–7.04 (m, 4H, Ph*H*), 5.82 (s, 2H, PhC*H*OR), 2.08 (dd, *J* = 9.8, 3.7 Hz, 2H, CH_2CH_2), 1.86 (dd, *J* = 9.8, 3.7 Hz, 2H, CH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 134.8, 129.2, 128.7, 127.4, 84.8, 29.1, 23.2; Unable to get LRMS or HRMS either in-house or from the National Mass Spectrometry Service, Swansea.

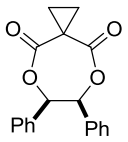
1-(((_rel_-1_S_,2_R_)-2-Hydroxy-1,2-diphenylethoxy)carbonyl)cyclopropanecarboxylic acid 96



Colourless solid; m.p. 109–110 °C; IR (ATR)/cm^{-1}: 3458, 3064, 3032, 2960, 2918, 1757, 1734, 1207, 1169, 1059; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 6H, Ph*H*), 7.24–7.22 (m, 4H, Ph*H*), 5.88 (d, *J* = 6.7 Hz, 1H, PhC*H*OR), 4.91 (d, *J* = 6.7 Hz, 1H, PhC*H*OH), 1.77–1.64 (m, 3H, CH_2), 1.52–1.46 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 170.6, 139.2, 135.7, 129.2, 128.8, 128.7, 128.5, 127.5, 127.0, 80.9,

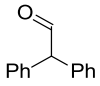
76.1, 25.3, 22.2, 21.9; HRMS (NSI) calculated for $C_{19}H_{19}O_5$ $[M + H]^+$ 327.1227, found 327.1231.

rel-(6*R*,7*S*)-6,7-Diphenyl-5,8-dioxaspiro[2.6]nonane-4,9-dione 97



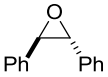
Colourless solid; m.p. 154–155 °C; IR (ATR)/cm^{-1}: 3067, 3030, 2920, 1722, 1707, 1190, 1067, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 6H, Ph*H*), 7.04–7.01 (m, 4H, Ph*H*), 6.00 (s, 2H, PhC*H*OR), 2.16 (dd, *J* = 9.1, 9.1 Hz, 2H, CH_2), 1.83 (dd, *J* = 9.1, 9.1 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 132.9, 129.2, 128.4, 127.2, 82.8, 29.1, 25.5, 23.0; HRMS (NSI) calculated for $C_{19}H_{17}O_4$ $[M + H]^+$ 309.1121, found 309.1120.

2,2-Diphenylacetaldehyde 144[142]



Pale yellow oil; IR (ATR)/cm^{-1}: 3059, 3028, 2962, 1724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (d, *J* = 2.4 Hz, 1H, C*H*O), 7.47–7.31 (m, 10H, Ph*H*), 4.98 (d, *J* = 2.4 Hz, 1H, PhC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 136.3, 129.2, 129.0, 127.6, 64.0; HRMS (CI) calculated for $C_{14}H_{16}NO$ $[M + NH_4]^+$ 214.1226, found 214.1224.

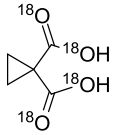
rel-(2*R*,3*R*)-2,3-Diphenyloxirane 148[143]



Colourless solid; m.p. 65–67 °C [lit.[144] 65–66 °C]; IR (ATR)/cm^{-1}: 3063, 3034, 2988, 1070, 1022; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.33 (m, 10H, Ph*H*), 3.88 (s, 2H, PhC*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 128.7, 128.5, 125.7, 63.0; LRMS (ESI) *m/z* 219.2 $[M + Na]^+$.

8.6 Synthesis and Reaction of ^{18}O-Labelled Peroxide

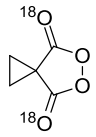
^{18}O-Enriched cyclopropane-1,1-dicarboxylic acid ^{18}O-91



Cyclopropane-1,1-dicarboxylic acid **91** (289 mg, 2.24 mmol, 1 eq) and $^{18}OH_2$ (97% ^{18}O incorporation, 1 mL, 56 mmol, 25 eq) were stirred in a sealed sample vial for 14 days at 25 ºC. The solution was transferred to a 5 mL round bottom flask then the water was removed by rotary evaporation. The compound was dissolved in fresh $^{18}OH_2$ (97% ^{18}O incorporation, 1 mL, 56 mmol, 25 eq) and stirred for a further 14 days at 25 ºC, following levels of ^{18}O incorporation by electrospray ionisation mass spectrometry. Removal of solvent by rotary evaporation gave the ^{18}O-enriched title compound **^{18}O-91** as a colourless solid (292 mg).

Colourless solid; See analytical data for cyclopropane-1,1-dicarboxylic acid **91**. LRMS (ESI) *m/z* 136.9 and 134.9 $[M - H]^-$.

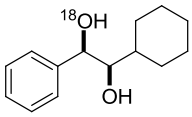
^{18}O-Enriched cyclopropyl malonoyl peroxide 119



Reaction of ^{18}O-enriched cyclopropane-1,1-dicarboxylic acid **^{18}O-91** (279 mg, 2.02 mmol, 1 eq) and urea hydrogen peroxide (570 mg, 6.07 mmol, 3 eq) in methanesulfonic acid (2 mL) according to General Procedure **B** for 18 h at 25 ºC gave the title compound **119** as a colourless solid (213 mg, 1.62 mmol, 80%).

See analytical data for cyclopropyl malonoyl peroxide **86**. Unable to obtain low or high resolution mass spectrometry data for malonoyl peroxides using in-house or Swansea National Mass Spectrometry Service.

^{18}O-Labelled-*rel*-(1*R*,2*R*)-1-cyclohexyl-2-phenylethane-1,2-diol 121



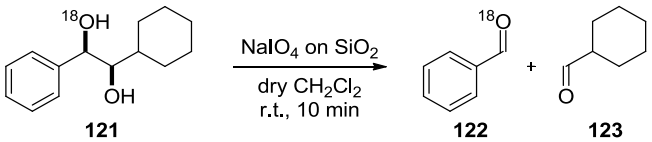
Reaction of (*E*)-(2-cyclohexylvinyl)benzene **120** (58 mg, 0.31 mmol), H_2O (6 µL, 0.31 mmol) and ^{18}O-labelled cyclopropyl malonoyl peroxide **86** (49 mg, 0.37 mmol) in chloroform (1 mL) according to General Procedure **C** for 24 h at 25 ºC (crude diol 25:1 *syn*:*anti*) and purification by silica gel flash chromatography (1:2 diethyl ether:petroleum ether) gave the title compound as a colourless solid (62 mg, 0.28 mmol, 90%).

To explore the solid state stability of ^{18}O-labelled cyclopropyl malonoyl peroxide **86** the above procedure (using identical quantities) was repeated using one-month old peroxide **86** (49 mg, 0.37 mmol), giving diol **121** as a colourless solid (60 mg, 0.27 mmol, 87%). To explore the solution state stability of peroxide **86**, **86** (49 mg, 0.37 mmol) was

dissolved in chloroform (1 mL) and left stirring in a sealed sample vial overnight before addition of the remainder of the reagents following the above procedure (using identical quantities) to afford diol **121** as a colourless solid (59 mg, 0.27 mmol, 86%).

Colourless solid; m.p. 83–84 °C; IR (ATR)/cm^{-1}: 3271, 3030, 2920, 2853, 1162, 1084; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.17 (m, 5H, Ph*H*), 4.62 (d, *J* = 5.7 Hz, 1H, PhC*H*OH), 3.39 (dd, *J* = 5.7, 5.7 Hz, 1H, C*H*OHCy), 2.18 (bs, 2H, O*H*), 1.77–1.52 (m, 5H, C*H*CH_2), 1.25–1.04 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 128.7, 128.0, 126.7, 80.2, 74.5, 39.4, 30.3, 27.5, 26.5, 26.4, 26.2; LRMS (EI) *m/z* 222.2 $[M]^+$; HRMS (EI) calculated for $C_{14}H_{20}{}^{16}O{}^{18}O$ $[M]^+$ 222.1506, found 222.1516.

Oxidative cleavage of diol 121 to aldehydes 122 and 123



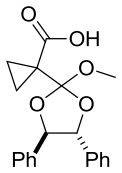
Preparation of $NaIO_4$ on silica:[52] A mixture of sodium metaperiodate (0.514 g, 2.40 mmol) and water (1.00 mL) was stirred at 75 ºC until homogeneous. To the hot aqueous solution was added silica gel (2.00 g). The mixture was stirred and crushed manually at 75 ºC using a spatula until a free-flowing colourless powder formed. The resulting powder was dried (80 ºC at 0.1 Torr) for 4 h before use.

Anhydrous sodium metaperiodate on silica (150 mg) and anhydrous dichloromethane (500 µL) were added to a small sample vial and stirred vigorously. A solution of diol **121** (10 mg, 0.046 mmol) in anhydrous dichloromethane (500 µL) was added to the reaction vessel in one portion. After 10 mins, diol **121** had cleanly converted into the two aldehydes **122** and **123** by TLC analysis (1:5 ethyl acetate:petroleum ether). The characteristic almond-like smelling solution of the two aldehydes was filtered through a small sinter funnel and directly analysed by GCMS (see Appendix 9.2).

The oxidative cleavage reaction was repeated using samples of ^{18}O-labelled diol **121** made from one-month old peroxide **119**, and peroxide **119** that had been stirring in chloroform overnight. No difference in result was observed from that outlined in Appendix 9.2 using fresh ^{18}O-labelled peroxide **119** in the synthesis of diol **121**.

8.7 Synthesis and Reactions of Orthoesters

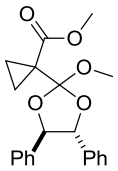
1-(*rel*-(4*R*,5*R*)-2-Methoxy-4,5-diphenyl-1,3-dioxolan-2-yl) cyclopropanecarboxylic acid 133



Cyclopropyl malonoyl peroxide **86** (166 mg, 1.30 mmol, 1 eq) was dissolved in chloroform (2.6 mL) in a 5 mL round bottom flask and the solution dried over activated 3 Å molecular sieves for 2 h. Methanol (100 µL) was also dried over activated 3 Å molecular sieves for 2 h in a separate vessel. *Trans*-stilbene **1** (234 mg, 1.30 mmol, 1 eq) was weighed into a dry 10 mL round bottom flask followed by addition of the dry peroxide solution and dry methanol (53 µL, 1.30 mmol, 1 eq) in quick succession. The flask was sealed under nitrogen and stirred for 16 h at 40 ^{o}C. Solvent was removed by rotary evaporation to produce a colourless gum (440 mg). Attempts to purify the compound by silica gel chromatography or crystallisation proved unsuccessful. Compound **133** was proposed based on analysis of the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture (see Appendix 9.3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (bs, 1H, CO_2H), 7.37–7.34 (m, 5H, Ph*H*), 7.31–7.29 (m, 2H, Ph*H*), 7.24–7.21 (m, 3H, Ph*H*), 5.13 (d, *J* = 9.0 Hz, 1H, PhC*H*O), 4.90 (d, *J* = 9.0 Hz, 1H, PhC*H*O), 3.63 (s, 3H, CH_3), 1.51–1.42 (m, 3H, CH_2), 1.35–1.31 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 135.8, 135.5, 128.90, 128.87, 128.8, 126.9, 126.7, 120.5, 87.3, 85.3, 50.8, 28.6, 14.3, 13.4.

Methyl 1-(*rel*-(4*R*,5*R*)-2-methoxy-4,5-diphenyl-1,3-dioxolan-2-yl) cyclopropane carboxylate 135



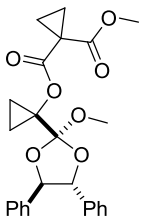
CAUTION! Generation of diazomethane is dangerous due to high risk of explosion. Standard safety protocols for generating diazomethane should be followed and the procedures only carried out by experienced synthetic chemists.

The crude reaction mixture containing orthoester **133** (440 mg) was dissolved in diethyl ether (10 mL). Diazomethane was generated by careful addition of *N*-nitroso-*N*-methylurea **134** (excess, approximately 250 mg) to an unstirred biphasic solution of 40% by wt. aqueous potassium hydroxide (3 mL) and diethyl ether (10 mL) at 0–5 ^{o}C in a clean, scratch-free, glass sample vial without a ground glass joint. Nitrogen was gently bubbled through the yellow diazomethane-diethyl ether solution and the outlet flow passed through the diethyl ether solution containing **133** using a plastic cannula. The reaction was deemed complete when the product flask held a slight yellow colour indicating excess diazomethane present. Both flasks were cooled to 0–5 ^{o}C and excess diazomethane quenched by drop wise addition of the minimum amount of acetic acid until no yellow colour remained. Diethyl ether and methyl acetate (formed during quenching of diazomethane with acetic acid) were removed by rotary evaporation and the resulting residue purified by silica gel column chromatography (1:3 diethyl ether: petroleum ether) to afford the title compound **135** as a colourless oil (189 mg, 0.53 mmol, 41% over two steps).

Colourless oil; IR (ATR)/cm^{-1}: 3062, 3032, 2951, 2909, 2837, 1719, 1319, 1213, 1119, 1078, 1009; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 10H, Ph*H*), 5.09 (d, *J* = 9.0 Hz, 1H, PhC*H*OR), 4.89 (d, *J* = 9.0 Hz, 1H, PhC*H*OR), 3.75 (s, 3H, CO_2CH_3), 3.58 (s, 3H, OCH_3), 1.44–1.29 (m, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 136.6, 136.3, 128.72, 128.68, 126.94, 126.87, 120.8, 87.1, 85.4, 52.4, 50.7, 29.0, 13.9,

13.0; LRMS (ESI) *m/z* 377.1 $[M + Na]^+$; HRMS (NSI) calculated for $C_{21}H_{22}O_5Na$ $[M + Na]^+$ 377.1359, found 377.1353.

1-(1-(*rel*-(4*R*,5*R*)-2-Methoxy-4,5-diphenyl-1,3-dioxolan-2-yl)cyclopropyl) 1-methyl cyclopropane-1,1-dicarboxylate 155

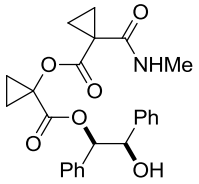


Cyclopropyl malonoyl peroxide **86** (267 mg, 2.08 mmol, 2 eq) was dissolved in 1,4-dioxane (2 mL) in a 5 mL round bottom flask and dried over activated 3 Å molecular sieves for 2 h. *Trans*-stilbene **1** (188 mg, 1.04 mmol, 1 eq) was weighed into a dry 10 mL round bottom flask followed by addition of the dry peroxide solution. The flask was sealed under nitrogen and stirred for 24 h at 40 ^oC. An excess of anhydrous methanol (2 mL) was added and the reaction stirred for 3 h at room temperature. Solvent was removed by rotary evaporation and the residue dissolved in diethyl ether (3 mL). Diazomethane was generated by careful addition of *N*-nitroso-*N*-methylurea **134** (excess, approximately 250 mg) to an unstirred biphasic solution of 40% by wt. aqueous potassium hydroxide (3 mL) and diethyl ether (10 mL) at 0–5 ^oC in a clean, scratch-free, glass sample vial without a ground glass joint. Nitrogen was gently bubbled through the yellow diazomethane-diethyl ether solution and the outlet flow passed through the diethyl ether solution containing **154** using a plastic cannula. The reaction was deemed complete when the product flask held a slight yellow colour indicating excess diazomethane present. Both flasks were cooled to 0–5 ^oC and excess diazomethane quenched by drop wise addition of the minimum amount of acetic acid until no yellow colour remained. Diethyl ether and methyl acetate (formed during quenching of diazomethane with acetic acid) were removed by rotary evaporation and the resulting residue purified by silica gel column chromatography (1:3 diethyl ether:

petroleum ether) to afford the title compound **155** as a colourless oil (167 mg, 0.381 mmol, 37% over 3 steps).

Colourless oil; IR (ATR)/cm^{-1}: 3067, 3024, 2949, 2908, 2837, 1728, 1348, 1349, 1258, 1205, 1105, 1022; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 10H, Ph*H*), 5.05 (d, *J* = 9.1 Hz, 1H, PhC*H*OR), 4.98 (d, *J* = 9.1 Hz, 1H, PhC*H*OR), 3.70 (s, 3H, CO_2CH_3), 3.61 (s, 3H, OCH_3), 1.49–1.32 (m, 6H, CH_2), 1.20–1.12 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 168.6, 136.0, 135.9, 128.71, 128.68, 128.65, 128.60, 126.9, 126.8, 120.4, 86.6, 85.7, 61.2, 52.5, 50.1, 28.6, 16.6, 16.5, 10.9, 10.4; LRMS (EI) *m/z* 461.3 $[M + Na]^+$; HRMS (NSI) calculated for $C_{25}H_{26}O_7Na$ $[M + Na]^+$ 461.1571, found 461.1559.

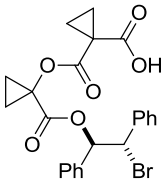
1-((*rel*-(1*R*,2*R*)-2-Hydroxy-1,2-diphenylethoxy)carbonyl)cyclopropyl 1-(methyl carbamoyl) cyclopropanecarboxylate 156



Cyclopropyl malonoyl peroxide **86** (512 mg, 4.00 mmol, 2 eq) was dissolved in 1,4-dioxane (2 mL) in a 5 mL round bottom flask and dried over activated 3 Å molecular sieves for 2 h. *Trans*-stilbene **1** (360 mg, 2.00 mmol, 1 eq) was added to a dry 10 mL round bottom flask followed by addition of the dry peroxide solution. The flask was sealed under nitrogen and stirred for 20 h at 40 ^{o}C. Methylamine (33% by wt. in ethanol, 2 mL) was added in one portion and the resulting mixture stirred for 2 h at room temperature. Solvent was removed under reduced pressure to give a colourless gum which was purified by silica gel column chromatography (diethyl ether) to afford the title compound **156** as a colourless gum (3:1 mixture of rotamers, 440 mg, 1.04 mmol, 52% over two steps).

Colourless gum; IR (ATR)/cm^{-1}: 3366, 3063, 3030, 2945, 2884, 1722, 1645, 1541, 1342, 1267, 1157, 1125, 1055; ^{1}H NMR (400 MHz, $CDCl_3$, Major rotamer) δ 8.37 (bs, 1H, N*H*), 7.24–7.19 (m, 6H, Ph*H*), 7.12–7.02 (m, 4H, Ph*H*), 5.92 (d, *J* = 7.5 Hz, 1H, PhC*H*OR), 4.87 (d, *J* = 7.5 Hz, 1H, PhC*H*OH), 3.08 (bs, 1H, O*H*), 2.82 (d, *J* = 4.8 Hz, 3H, NHCH_3), 1.81–1.51 (m, 6H, CH_2), 1.20–1.18 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, Major rotamer) δ 174.2, 169.4, 168.7, 138.7, 136.0, 128.5, 128.3, 128.2, 128.1, 127.4, 127.2, 81.4, 76.9, 56.9, 26.6, 26.4, 20.3, 20.1, 16.1, 15.8; HRMS (NSI) calculated for $C_{24}H_{26}NO_6$ $[M + H]^+$ 424.1755, found 424.1754.

1-((1-((*rel*-(1*R*,2*S*)-2-Bromo-1,2-diphenylethoxy)carbonyl)cyclopropoxy)carbonyl) cyclopropanecarboxylic acid 157

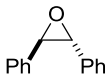


Cyclopropyl malonoyl peroxide **86** (356 mg, 2.78 mmol, 2 eq) was dissolved in 1,4-dioxane (2.8 mL) in a 10 mL round bottom flask and dried over activated 3 Å molecular sieves for 2 h. *Trans*-stilbene **1** (250 mg, 1.39 mmol, 1 eq) was weighed into a dry 10 mL round bottom flask followed by addition of the dry peroxide solution. The flask was sealed under nitrogen and stirred for 22 h at 40 ^{o}C. The reaction mixture was cooled to 0–5 ^{o}C using an ice bath before bromotrimethylsilane (183 µL, 1.39 mmol, 1 eq) was added dropwise to the frozen reaction mixture. The reaction vessel was allowed to warm to room temperature and stirred overnight resulting in a heterogeneous white mixture. Removal of solvent by rotary evaporation and purification by silica column chromatography (1:1 diethyl ether:petroleum ether) afforded the title compound **157** as a colourless gum (120 mg, 0.254 mmol, 18% over two steps).

Colourless gum; IR (ATR)/cm^{-1}: 3091, 3032, 2957, 2937, 1738, 1694, 1360, 1337, 1263, 1136, 907; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (bs, 1H, CO_2H), 7.34–7.19 (m,

10H, Ph*H*), 6.25 (d, *J* = 7.7 Hz, 1H, PhC*H*OR), 5.17 (d, *J* = 7.7, 1H, PhC*H*Br), 1.86–1.73 (m, 4H, CH_2), 1.52–1.47 (m, 1H, CH_2), 1.29–1.10 (m, 3H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 170.4, 167.9, 137.2, 136.1, 129.1, 129.0, 128.6, 128.41, 128.38, 127.5, 79.3, 57.4, 54.8, 25.3, 22.1, 22.0, 15.5, 15.4; LRMS (EI) *m/z* 494.9 [M(^{79}Br) + Na]$^+$; HRMS (NSI) calculated for $C_{23}H_{21}BrO_6Na$ [M(^{79}Br) + Na]$^+$ 495.0414, found 495.0407.

rel-(2*R*,3*R*)-2,3-Diphenyloxirane 148[143]

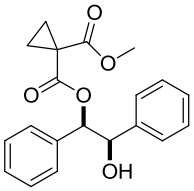


Sodium methoxide (320 mg, 5.93 mmol) was added to a solution of **157** (70 mg, 0.148 mmol) in anhydrous THF (5 mL) then the reaction mixture stirred at 40 ^{o}C for 72 h. Water (5 mL) and diethyl ether (5 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (2 × 5 mL) and the combined organic extracts dried over $MgSO_4$. Solvent removal afforded epoxide **148** as a colourless solid (24 mg, 0.122 mmol, 83%).

Analytical data for epoxide **148** is provided in Experimental 8.5.

8.8 Independent Synthesis of Methyl Ester 137

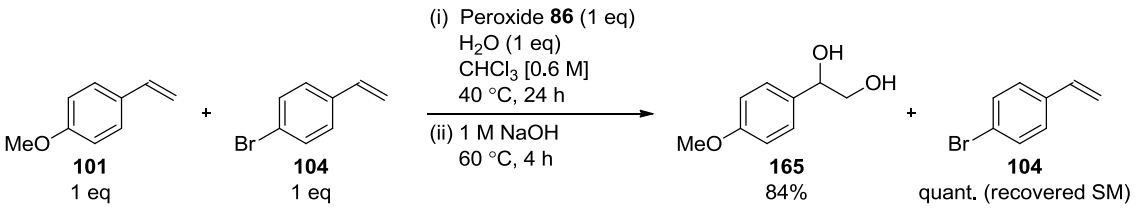
1-(*rel*-(1*R*,2*R*)-2-Hydroxy-1,2-diphenylethyl) 1-methyl cyclopropane-1,1-dicarboxylate 137



Syn-hydroxy ester **93** (30 mg, 0.092 mmol) was dissolved in diethyl ether (2 mL). Diazomethane was generated by careful addition of *N*-nitroso-*N*-methylurea **134** (excess, approximately 100 mg) to an unstirred biphasic solution of 40% by wt. aqueous potassium hydroxide (1 mL) and diethyl ether (2 mL) at 0–5 ^{o}C in a clean, scratch-free, glass sample vial without a ground glass joint. Nitrogen was gently bubbled through the yellow diazomethane-diethyl ether solution and the outlet flow passed through the diethyl ether solution containing **93** using a plastic cannula. The reaction was deemed complete when the product flask held a slight yellow colour indicating excess diazomethane present. Both flasks were cooled to 0–5 ^{o}C and excess diazomethane quenched by dropwise addition of the minimum amount of acetic acid until no yellow colour remained. Volatiles were removed by rotary evaporation and the resulting residue purified by silica gel column chromatography (1:1 diethyl ether:petroleum ether) to afford the title compound **137** as a colourless oil (23 mg, 0.068 mmol, 74%).

Colourless oil; IR (ATR)/cm^{-1}: 3491, 3062, 3036, 2953, 1719, 1319, 1209, 1132; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.21 (m, 6H, Ph*H*), 7.13–7.07 (m, 4H, Ph*H*), 5.80 (d, *J* = 8.4 Hz, 1H, PhC*H*OR), 4.95 (dd, *J* = 8.4, 2.1 Hz, 1H, PhC*H*OH), 3.99 (d, *J* = 2.1 Hz, 1H, O*H*), 3.79 (s, 3H, OCH_3), 1.67–1.61 (m, 2H, CH_2), 1.46–1.42 (m, 1H, CH_2), 1.31–1.27 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 168.7, 138.4, 136.3, 128.4, 128.2, 128.1, 127.38, 127.35, 82.4, 77.4, 52.8, 28.2, 17.5, 17.0; HRMS (NSI) calculated for $C_{20}H_{21}O_5$ $[M + H]^+$ 341.1384, found 341.1385.

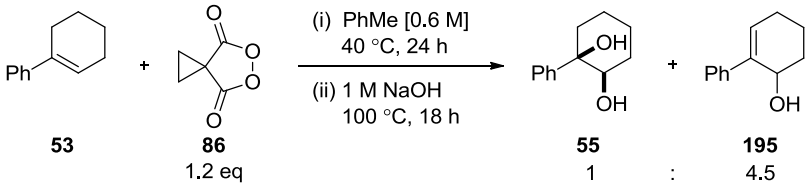
8.9 Competitive Dihydroxylation Between 101 and 104



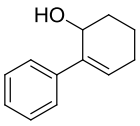
Reaction of 4-methoxystyrene **101** (169 mg, 1.26 mmol, 1 eq) and 4-bromostyrene **104** (231 mg, 1.26 mmol, 1 eq), H_2O (23 µL, 1.26 mmol, 1 eq) and cyclopropyl malonoyl peroxide **86** (161 mg, 1.26 mmol, 1 eq) in chloroform (2 mL) according to General Procedure **C** for 24 h at 40 ºC and purification by silica gel flash chromatography (100% petroleum ether then 1:2 diethyl ether:petroleum ether) returned 4-bromostyrene **104** (223 mg, 1.22 mmol, 97%) and diol **165** as a colourless solid (178 mg, 1.06 mmol, 84%).

For analytical data of diol **165** see Experimental 8.4.1.

8.10 Allylic Oxidation of Alkenes



2,3,4,5-Tetrahydro-(1,1'-biphenyl)-2-ol 195[140]

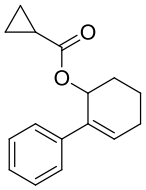


Cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol, 1.2 eq) was dissolved in toluene (2 mL) and the solution dried over activated 3 Å molecular sieves for 2 h. The

dry peroxide solution was then transferred to a dry 5 mL round bottom flask containing 1-phenyl-1-cyclohexene **53** (199 mg, 1.26 mmol, 1 eq) and the vessel was sealed under nitrogen before the reaction mixture was stirred for 24 h at 40 ºC. Solvent was removed by rotary evaporation and the residue treated with 1 M NaOH at 100 ^{o}C for 18 h. The reaction mixture was allowed to cool to room temperature before the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (1 × 10 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation to afford a 1:4.5 mixture (82% yield) of diol **55** to allylic alcohol **195**. Purification by silica gel column chromatography (1:3 diethyl ether:petroleum ether) gave the title compound as a colourless oil (140 mg, 0.806 mmol, 64%).

See analytical data for allylic alcohol **195** in Experimental 8.4.2.

2,3,4,5-Tetrahydro-(1,1'-biphenyl)2-yl cyclopropanecarboxylate 210

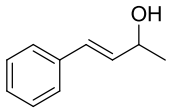


Cyclopropyl malonoyl peroxide **86** (194 mg, 1.51 mmol, 1.2 eq) was dissolved in toluene (2 mL) and the solution dried over activated 3 Å molecular sieves for 2 h. The dry peroxide solution was then transferred to a dry 5 mL round bottom flask containing 1-phenyl-1-cyclohexene **53** (199 mg, 1.26 mmol, 1 eq) and the vessel was sealed under nitrogen before the reaction mixture was stirred for 24 h at 40 ºC. Solvent was removed by rotary evaporation and the residue treated with 1 M NaOH at 60 ^{o}C for 4 h. The reaction mixture was allowed to cool to room temperature before the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (1 × 10 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by silica gel column chromatography (1:3 diethyl ether:petroleum ether) gave the title compound **210** as a colourless oil (55 mg, 0.227 mmol, 18%).

Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.13 (m, 5H, Ph*H*), 6.26 (dd, *J* = 4.7, 3.3 Hz, 1H, C*H*O), 5.85 (t, *J* = 3.9 Hz, 1H, PhC=C*H*CH_2), 2.29–2.20 (m, 1H, CH_2), 2.16–2.07 (m, 1H, CH_2), 1.95–1.88 (m, 1H, CH_2), 1.81–1.73 (m, 1H, CH_2), 1.69–1.60 (m, 2H, CH_2), 1.44–1.38 (m, 1H, C*H*C=O), 0.86–0.81 (m, 1H, CH_2), 0.76–0.71 (m, 1H, CH_2), 0.66–0.63 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 139.7, 135.7, 131.0, 128.4, 127.1, 125.6, 67.4, 29.1, 26.0, 17.7, 13.3, 8.38, 8.36; HRMS (NSI) calculated for $C_{16}H_{22}NO_2$ $[M + NH_4]^+$ 260.1645, found 260.1650.

8.11 Application of Methodology: Synthesis of Lactone 238

(*E*)-4-Phenylbut-3-en-2-ol 234[145]

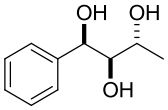


(*E*)-4-Phenylbut-3-en-2-one **233** (10.2 g, 70 mmol) was dissolved in methanol (25 mL) and cooled to 0–5 ^{o}C using an ice bath. Sodium borohydride (2.85 g, 75 mmol) was added portionwise over 10 mins. The reaction was stirred under an inert nitrogen atmosphere at 0–5 ^{o}C for 2 h until completion by TLC (1:9 ethyl acetate:petroleum ether). 1 M HCl solution (60 mL) was added dropwise over 20 mins, then the mixture diluted with water before being extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and solvent removed under reduced pressure to afford the title compound **234** as a colourless oil with no need for further purification (9.96 g, 67.2 mmol, 96%).

Colourless oil; IR (ATR)/cm^{-1}: 3333, 3024, 2970, 2924, 2876, 1597, 1057; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.41 (m, 2H, Ph*H*), 7.37–7.33 (m, 2H, Ph*H*), 7.30–7.26 (m, 1H, Ph*H*), 6.60 (d, *J* = 16.0 Hz, 1H, PhC*H*CH), 6.30 (dd, *J* = 16.0 Hz, 6.4 Hz, 1H, PhCHC*H*), 4.51 (pd, *J* = 6.4 Hz, 1.2 Hz, 1H, C*H*OH), 2.30 (bs, 1H, O*H*), 1.41 (d, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 133.7, 129.3, 128.6, 127.6,

126.5, 68.8, 23.5; LRMS (CI) *m/z* 148.1 $[M]^+$; HRMS (ASAP) calculated for $C_{10}H_{11}$ $[M - OH]^+$ 131.0855, found 131.0853.

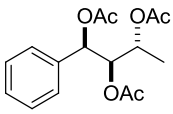
rel-(1_R_,2_R_,3_R_)-1-Phenylbutane-1,2,3-triol 235[68]



Reaction of (*E*)-4-phenylbut-3-en-2-ol **234** (2.18 g, 14.7 mmol, 1 eq), cyclopropyl malonoyl peroxide **86** (2.26 g, 17.7 mmol, 1.2 eq) and H_2O (264 µL, 14.7 mmol, 1 eq) in chloroform (20 mL) according to General Procedure **C** for 24 h at 25 ºC gave a 2:1 mixture of *rel*-(1*R*,2*R*,3*R*)- and *rel*-(1*R*,2*R*,3*S*)-1-phenylbutane-1,2,3-triol **235**. Dissolution in hot chloroform (5 mL), then trituration at 0 ^oC followed by filtration and drying gave the title compound as a single diastereomer as a colourless solid (1.47 g, 8.08 mmol, 55 %).

Colourless solid; IR (ATR)/cm^{-1}: 3254, 3060, 2974, 2905, 1061, 1036, 1028; ^1H NMR (400 MHz, CD_3CN with one drop D_2O) δ 7.38–7.32 (m, 4H, Ph*H*), 7.29–7.24 (m, 1H, Ph*H*), 4.70 (d, *J* = 4.0 Hz, 1H, PhC*H*OH), 3.57 (p, *J* = 6.2 Hz, 1H, C*H*CH_3), 3.41 (dd, *J* = 6.2 Hz, 4.0 Hz, 1H, CHC*H*CH), 1.14 (d, *J* = 6.2 Hz, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, CD_3CN) δ 143.9, 129.0, 128.1, 127.5, 79.7, 73.5, 68.9, 19.5; LRMS (CI) *m/z* 147.0 $[M - H_2O - OH]^+$; HRMS (ASAP) calculated for $C_{10}H_{18}NO_3$ $[M + NH_4]^+$ 200.1281, found 200.1281.

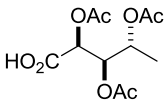
rel-(1*R*,2*R*,3*R*)-1-Phenylbutane-1,2,3-triyl triacetate 236[68]



rel-(1*R*,2*R*,3*R*)-1-Phenylbutane-1,2,3-triol **235** (1.46 g, 8.02 mmol, 1 eq) was stirred in dry dichloromethane (35 mL) under an inert nitrogen atmosphere in a 100 mL round-bottom flask. The suspension was cooled to 0–5 ^{o}C using an ice bath before pyridine (13.0 mL, 160 mmol, 20 eq) was added in one portion resulting in a colourless homogeneous solution. Acetic anhydride (7.6 mL, 80.2 mmol, 10 eq) was added dropwise and the reaction stirred at 0–5 ^{o}C for 1 hour before the ice bath was removed and stirring maintained at room temperature overnight. TLC (diethyl ether) after 18 h indicated no starting material was present so the reaction mixture was cooled to 0 ^{o}C before methanol (20 mL) was added and the resulting mixture stirred for 20 mins. Removal of volatiles by rotary evaporation afforded the crude compound. Purification by silica gel flash chromatography (1:1 diethyl ether:petroleum ether) afforded the title compound **236** as a colourless solid (1.92 g, 6.23 mmol, 78%).

Colourless solid; m.p. 84–86 ^{o}C [lit.[68] 88–89 ^{o}C]; IR (ATR)/cm^{-1}: 2998, 2960, 1736, 1373, 1219, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H, Ph*H*), 5.94 (d, *J* = 6.0 Hz, 1H, PhC*H*OAc), 5.45 (dd, *J* = 6.0, 6.0 Hz, 1H, PhCHC*H*), 4.88 (dq, *J* = 6.5 Hz, 6.0 Hz, 1H, C*H*CH_3), 2.07 (s, 3H, OC(=O)C*H*$_3$), 2.01 (s, 3H, OC(=O)C*H*$_3$), 1.99 (s, 3H, OC(=O)C*H*$_3$), 1.18 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.90, 169.88, 136.1, 128.9, 128.7, 127.3, 74.9, 73.5, 68.1, 21.1, 21.0, 20.7, 15.4; LRMS (CI) *m/z* 249.1 $[M - OAc]^+$; HRMS (NSI) calculated for $C_{16}H_{24}NO_6$ $[M + NH_4]^+$ 326.1598, found 326.1601.

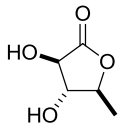
rel-(2_S_,3_R_,4_R_)-2,3,4-Triacetoxypentanoic acid 237[68]



rel-(1*R*,2*R*,3*R*)-1-Phenylbutane-1,2,3-triyl triacetate **236** (0.5 g, 1.62 mmol, 1 eq), CH_3CN (3.2 mL), CCl_4 (3.2 mL) and H_2O (4.8 mL) were added to a 20 mL microwave vial equipped with a magnetic stirrer bar. The biphasic solution was stirred for 5 mins before addition of periodic acid (5.18 g, 22.7 mmol, 14.2 eq). The resulting mixture was stirred for 10 mins then ruthenium trichloride hydrate (10.2 mg, 0.049 mmol, 3 mol%) was added in one portion. The vial was sealed and the reaction stirred at 30 ^oC for 18 h. Once the reaction was complete by TLC (1:9 methanol:dichloromethane, visualising with both $KMnO_4$ and bromocresol green solutions) the contents of the reaction vial were poured into a 50 mL round-bottom flask. The solution was cooled to 0 ^oC and diethyl ether (10 mL) was added followed by vigorous stirring for 10 mins. The phases were separated and the aqueous phase extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (7:93 methanol:dichloromethane) to afford the title compound **237** as colourless liquid (268 mg, 0.97 mmol, 60 %).

Colourless liquid; IR (ATR)/cm^{-1}: 3230, 2990, 2943, 1736, 1371, 1209, 1167, 1128, 1098, 1045; ^1H NMR (400 MHz, $CDCl_3$) δ 5.50 (dd, *J* = 8.3, 2.5 Hz, 1H, CHC*H*CHCH$_3$), 5.39 (d, *J* = 2.5 Hz, 1H, HO_2CCH), 5.09 (dq, *J* = 8.3, 6.3 Hz, 1H, C*H*CH$_3$), 2.17 (s, 3H, OCH_3), 2.11 (s, 3H, OCH_3), 2.03 (s, 3H, OCH_3), 1.24 (d, *J* = 6.3 Hz, 3H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.4, 170.24, 170.20, 72.7, 69.7, 67.4, 22.2, 20.8, 20.6, 16.8; LRMS (CI) *m/z* 217.0 $[M - OAc]^+$; HRMS (ASAP) calculated for $C_{11}H_{20}NO_8$ $[M + NH_4]^+$ 294.1183, found 294.1183.

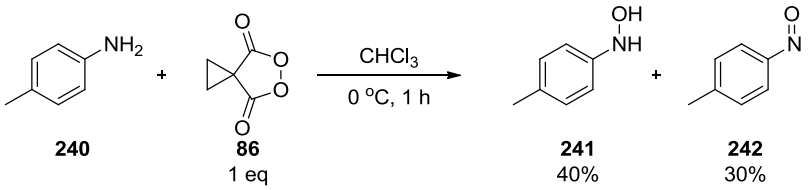
rel-(3_R_,4_S_,5_S_)-3,4-Dihydroxy-5-methyldihydrofuran-2(3_H_)-one 238[68]



To a solution of *rel*-(2*S*,3*R*,4*R*)-2,3,4-triacetoxypentanoic acid **237** (300 mg, 1.09 mmol) in methanol (9 mL) was added 2 M aqueous K_2CO_3 (2.72 mL, 5.44 mmol) at 0–5 ^oC. The solution was allowed to warm slowly to room temperature and stirred for 20 h. The reaction mixture was then cooled to 0 ^oC and acidified to pH 2 by dropwise addition of 10% aqueous HCl. The ice bath was removed and the reaction mixture stirred at room temperature for 3 h. Removal of solvent under reduced pressure gave a residual white solid that was washed twice with methanol/ethyl acetate (1:1). The washings were dried over anhydrous Na_2SO_4, filtered and solvent removed under reduced pressure. The crude product was purified by silica gel flash chromatography (12:88 methanol:dichloromethane) to afford the title compound **238** as a colourless solid (54 mg, 0.41 mmol, 38%).

Colourless solid; m.p. 110–113 ^oC [lit.[68] 123.5–125 ^oC]; IR (ATR)/cm^{-1}: 3333, 2986, 2936, 1767, 1190, 1126, 1055, 1013; ^1H NMR (400 MHz, CD_3OD) δ 4.83 (bs, 2H, O*H*), 4.31 (d, *J* = 8.9 Hz, 1H, C*H*(OH)CO_2R), 4.17 (dq, *J* = 8.1, 6.3 Hz, 1H, C*H*CH_3), 3.78 (dd, *J* = 8.9, 8.1 Hz, 1H, CHC*H*CH), 1.42 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 176.4, 80.7, 78.6, 75.5, 18.1; LRMS (CI) *m/z* 133.0 $[M + H]^+$; HRMS (APCI) calculated for $C_5H_9O_4$ $[M + H]^+$ 133.0495, found 133.0492.

8.12 Reaction with Nitrogen Nucleophiles



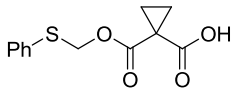
240 **86** 1 eq **241** 40% **242** 30%

p-Toluidene **240** (135 mg, 1.26 mmol, 1 eq) was dissolved in anhydrous $CDCl_3$ (2 mL) then the solution was cooled to 0–5 ^{o}C using an ice bath. Cyclopropyl malonoyl peroxide **86** (161 mg, 1.26 mmol, 1 eq) was added portionwise over 5 mins. After 1 h at 0–5 ^{o}C a sample of the reaction mixture was removed for analysis by ^{1}H NMR spectroscopy indicating the formation of **241** and **242** in addition to smaller quantities of unidentifiable co-products. Attempts at isolation of either **241** or **242** proved unsuccessful.

8.13 Pummerer Rearrangement with Sulfur Nucleophiles

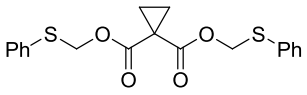
Cyclopropyl malonoyl peroxide **86** (192 mg, 1.50 mmol, 1 eq) was dissolved in toluene (1.5 mL) and the solution dried over activated 3 Å molecular sieves (100 mg) for 4 h. A solution of thioanisole **246** (176 µL, 1.50 mmol, 1 eq) in toluene (1.5 mL) was dried using the same method. The anhydrous peroxide solution was transferred to the thioanisole solution dropwise at 0 ^{o}C under a nitrogen atmosphere. The reaction mixture was stirred at 0 ^{o}C for 20 mins then the ice bath was removed and stirring continued for 24 h at room temperature. Methanol (5 mL) was added and the reaction mixture filtered through Celite before the solvent was removed under reduced pressure. Purification by silica gel column chromatography (1:3 then 1:1 diethyl ether:petroleum ether) afforded a 1:1 mixture of **247** (57 mg, 0.25 mmol, 15%) and **248** (90 mg, 0.24 mmol, 16%) as colourless oils.

((Phenylthiomexthoy)carbonyl)cyclopropanecarboxylic acid 247



Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.41 (m, 2H, Ph*H*), 7.38–7.33 (m, 3H, Ph*H*), 5.49 (s, 2H, SCH_2O), 1.88–1.85 (m, 2H, CH_2CH$_2$), 1.77–1.74 (m, 2H, CH_2CH$_2$); ^{13}C NMR (DEPT) (100 MHz, $CDCl_3$) δ 131.4, 129.6, 128.5, 71.0, 22.6.

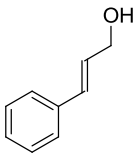
Bis(phenylthiomethyl) cyclopropane-1,1-dicarboxylate 248



Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.43 (m, 4H, Ph*H*), 7.32–7.25 (m, 6H, Ph*H*), 5.43 (s, 4H, SCH_2O), 1.52 (s, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 134.6, 130.6, 129.2, 127.6, 69.3, 28.4, 17.5.

8.14 Synthesis of Alkenes

(*E*)-3-Phenylprop-2-en-1-ol 229[146]

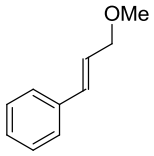


(*E*)-Cinnamaldehyde (10.0 mL, 80.0 mmol, 1 eq) was dissolved in EtOH (30 mL) and cooled to 0–5 ^{o}C using an ice bath. Sodium borohydride (3.34 g, 88.0 mmol, 1.1 eq)

was added portionwise over 10 mins. The reaction was stirred under an inert nitrogen atmosphere at 0–5 ^{o}C for 30 mins then room temperature for 15 mins until completion by TLC (1:5 ethyl acetate:petroleum ether). 1 M HCl solution (80 mL) was added dropwise over 30 mins, then the mixture was diluted with water before being extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and solvent removed by rotary evaporation. Passing the residue through a small plug of silica gel (1:1 diethyl ether:petroleum ether) afforded the title compound as a colourless oil (9.90 g, 73.9 mmol, 92%).

Colourless oil; IR (ATR)/cm^{-1}: 3283, 3026, 2893, 2855, 1576, 1011; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.20 (m, 5H, Ph*H*), 6.62 (d, *J* = 15.9 Hz, 1H, PhC*H*CH), 6.36 (dt, *J* = 15.9, 5.7 Hz, 1H, PhCHC*H*), 4.31 (d, *J* = 5.7 Hz, 2H, CH_2OH), 2.44 (bs, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 131.0, 128.6, 127.7, 126.5, 63.5; LRMS (CI) *m/z* 135.1 [M + H]$^{+}$.

(*E*)-(3-Methoxyprop-1-en-1-yl)benzene 32

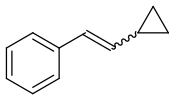


Cinnamyl alcohol **229** (2.00 g, 14.9 mmol, 1 eq) was stirred in anhydrous THF (15 mL) under an inert nitrogen atmosphere. The solution was cooled to 0 ^{o}C before sodium hydride (60% dispersion in mineral oil, 1.19 g, 29.9 mmol, 2eq) was added portionwise over 10 mins. The reaction mixture was stirred at 0 ^{o}C for 1 hour then a solution of methyl iodide (1.39 mL, 22.4 mmol) in anhydrous THF (5 mL) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature then stirred for 18 h. Excess sodium hydride was quenched by cooling the reaction mixture to 0 ^{o}C and adding H_2O (30 mL) dropwise. Diethyl ether (20 mL) was added and the phases separated. The aqueous phase was extracted with diethyl ether (2 × 20 mL) and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and

solvent removed by rotary evaporation. Purification by silica gel chromatography (1:9 diethyl ether:petroleum ether 30–40 ^{o}C) gave the title compound as a yellow oil (1.70 g, 11.5 mmol, 77%).

Yellow oil; IR (ATR)/cm^{-1}: 3026, 2980, 2922, 2819, 1610, 1119; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.24 (m, 5H, Ph*H*), 6.64 (d, *J* = 15.9 Hz, 1H, PhC*H*CH), 6.31 (dt, *J* = 15.9, 6.0 Hz, 1H, PhCHC*H*), 4.11 (d, *J* = 6.0 Hz, 2H, CH_2), 3.41 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 132.5, 128.7, 127.8, 126.6, 126.1, 73.2, 58.1; LRMS (CI) *m/z* 149.1 $[M + H]^+$.

(2-Cyclopropylvinyl)benzene 113[147]



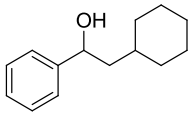
Benzyltriphenylphosphonium chloride (5.99 g, 15.4 mmol, 1.1 eq) and anhydrous THF (75 mL) were stirred in a dry two-necked flask equipped with a magnetic stirrer bar and reflux condenser under an inert nitrogen atmosphere. The suspension was cooled to 0 ^{o}C and *n*-butyllithium (2.5 M in hexanes, 15.4 mmol, 1.1 eq) was added dropwise resulting in formation of a dark red solution. The contents were stirred for 30 mins at 0 ^{o}C before a solution of cyclopropane carboxaldehyde (1.04 mL, 14 mmol, 1 eq) in anhydrous THF (5 mL) was added dropwise. The reaction was allowed to warm slowly to room temperature, and then stirred under reflux for 18 h. Once complete by TLC (1:3 ethyl acetate:petroleum ether) the reaction was quenched by dropwise addition of water (30 mL). THF was removed by rotary evaporation and the remaining residue extracted with diethyl ether (3 × 40 mL). Trituration of the combined organic extracts at 0 ^{o}C, followed by filtration, removed much of the Ph_3P=O byproduct. The filtrate was washed with brine (30 mL), dried ($MgSO_4$) and solvent removed by rotary evaporation. Purification by flash silica gel chromatography (petroleum ether) afforded the title compound **113** as an inseparable mixture of isomers (3:1 *E*:*Z*) as a colourless oil (0.91 g, 6.44 mmol, 46%).

Data for mixture of isomers: Colourless oil; IR (ATR)/cm^{-1}: 3080, 3022, 3003, 1651; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.9, 136.9, 135.0, 130.4, 129.0, 128.8, 128.6, 128.32, 128.27, 127.5, 127.4, 127.2, 126.7, 126.5, 125.7, 14.7, 11.2, 8.2, 7.4; HRMS (APCI) calculated for $C_{11}H_{13}$ $[M + H]^+$ 145.1012, found 145.1009.

***E*-isomer**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.19 (m, 5H, Ph*H*), 6.52 (d, *J* = 15.8 Hz, 1H, PhC*H*CH), 5.78 (dd, *J* = 15.8, 8.9 Hz, 1H, PhCHC*H*), 1.66–1.57 (m, 1H, CH_2CHCH_2), 0.88–0.86 (m, 2H, CH_2CHCH_2), 0.58–0.52 (m, 2H, CH_2CHCH_2).

***Z*-isomer**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.19 (m, 5H, Ph*H*), 6.41 (d, *J* = 11.5 Hz, 1H, PhC*H*CH), 5.12 (dd, *J* = 11.5, 10.0 Hz, 1H, PhCHC*H*), 2.00–1.90 (m, 1H, CH_2CHCH_2), 0.88–0.86 (m, 2H, CH_2CHCH_2), 0.58–0.52 (m, 2H, CH_2CHCH_2).

2-Cyclohexyl-1-phenylethanol 366[148]

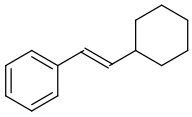


A dry 100 mL 3–necked flask equipped with a reflux condenser was flushed with nitrogen gas before being charged with magnesium turnings (0.79 g, 32.9 mmol, 1.75 eq) and dry THF (15 mL). (Bromomethyl)cyclohexane (3.94 mL, 28.2 mmol, 1.5 eq) was added and the solution heated under reflux. After 30 mins the resulting solution was cooled to 0–5 ^oC using an ice bath before a solution of benzaldehyde (1.91 mL, 18.8 mmol, 1 eq) in dry THF (20 mL) was added dropwise *via* syringe. The reaction was stirred at room temperature for 5 h then cooled to 0–5 ^oC and carefully quenched by dropwise addition of water, before solvent was removed by rotary evaporation. H_2O (100 mL) and ethyl acetate (100 mL) were added followed by ethylenediaminetetraacetic acid (EDTA) (30 g), and the solution stirred for 1 h until both phases were clear. The phases were separated and the aqueous phase extracted with ethyl acetate (3 × 30 mL) before the combined organic phases were washed with brine (1 × 50 mL), dried over $MgSO_4$ and solvent removed by rotary evaporation to give a

yellow oil. Purification by silica gel flash column chromatography (1:8 ethyl acetate:petroleum ether) gave the title compound **366** as a colourless solid (2.09 g, 10.3 mmol, 55%).

Colourless solid; m.p. 53–54 °C [lit.[148] 53–56 °C]; IR (ATR)/cm^{-1}: 3237, 2918, 2845, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.34 (m, 4H, Ph*H*), 7.30–7.26 (m, 1H, Ph*H*), 4.78 (dd, *J* = 8.7, 5.1 Hz, 1H, PhC*H*OH), 1.90 (bs, 1H, O*H*), 1.84–1.64 (m, 6H, CH_2), 1.56–1.38 (m, 2H, CH_2), 1.30–1.15 (m, 3H, C*H*CH_2), 1.02–0.92 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 128.6, 127.6, 126.0, 72.2, 47.2, 34.3, 34.1, 33.0, 26.6, 26.4, 26.3; LRMS (EI) *m/z* 204.2 $[M]^+$; HRMS (ASAP) calculated for $C_{14}H_{24}NO$ $[M + NH_4]^+$ 222.1852, found 222.1852.

(*E*)-(2-Cyclohexylvinyl)benzene 120[149]

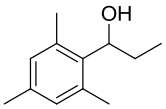


2-Cyclohexyl-1-phenylethanol **366** (1.75 g, 8.59 mmol, 1 eq), *p*-toluenesulfonic acid monohydrate (0.21 g, 1.12 mmol, 0.13 eq) and toluene (30 mL) were added to a 50 mL round-bottom flask equipped with Dean–Stark apparatus. The reaction mixture was heated under reflux for 2.5 h before 5 drops of triethylamine were added to quench the reaction. H_2O (30 mL) was added and the phases separated before the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$ and solvent removed by rotary evaporation to give a pale yellow oil. Purification by silica flash column chromatography (petroleum ether) gave the title compound **120** as a colourless oil (1.46 g, 7.82 mmol, 91%).

Colourless oil; IR (ATR)/cm^{-1}: 3024, 2920, 2849, 1599; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.39 (m, 2H, Ph*H*), 7.35–7.31 (m, 2H, Ph*H*), 7.25–7.21 (m, 1H, Ph*H*), 6.40 (d, *J* = 16.0 Hz, 1H, PhC*H*CHCy), 6.23 (dd, *J* = 16.0, 6.9 Hz, 1H, PhCHC*H*Cy), 2.23–2.13

(m, 1H, C*H*CH_2), 1.87–1.72 (m, 5H, CH_2), 1.42–1.18 (m, 5H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 136.9, 128.6, 127.3, 126.8, 126.0, 41.3, 33.1, 26.3, 26.2; LRMS (EI) *m/z* 186.1 $[M]^+$; HRMS (ASAP) calculated for $C_{14}H_{19}$ $[M + H]^+$ 187.1481, found 187.1480.

1-Mesitylpropan-1-ol 367

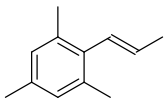


A dry 100 mL 3–necked flask equipped with a reflux condenser was flushed with nitrogen gas before being charged with magnesium turnings (1.42 g, 59.2 mmol, 1.75 eq) and dry THF (25 mL). Bromoethane (3.79 mL, 50.7 mmol, 1.5 eq) was slowly added then the solution heated to reflux. After 30 mins, the resulting solution was allowed to cool to room temperature then cooled to 0–5 ^{o}C using an ice bath before a solution of mesitaldehyde (4.89 mL, 33.8 mmol, 1 eq) in dry THF (35 mL) was added dropwise *via* syringe. The reaction was stirred at room temperature for 3 h then cooled to 0–5 ^{o}C and carefully quenched by dropwise addition of water, before solvent was removed by rotary evaporation. H_2O (100 mL) and ethyl acetate (75 mL) were added followed by ethylenediaminetetraacetic acid (EDTA) (30 g), and the solution stirred for 1 hour until both phases were clear. The phases were separated and the aqueous phase extracted with ethyl acetate (3 × 30 mL) before the combined organic phases were washed with brine (1 × 50 mL), dried over $MgSO_4$ and solvent removed by rotary evaporation to give **367** as a yellow oil (5.31 g, 29.7 mmol, 88%). The crude product was used in the next step without any further purification.

Pale yellow oil; IR (ATR)/cm^{-1}: 3335, 2965, 2924, 2870, 1043; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.86 (s, 2H, Ar*H*), 5.06 (dd, *J* = 8.2, 6.3 Hz, 1H, ArC*H*OH), 2.44 (s, 6H, ArCH_3), 2.30 (s, 3H, ArCH_3), 2.07–1.96 (m, 2H, ArCH(O*H*)CH_2), 1.87–1.76 (m, 1H, CH_2), 1.10 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.9, 136.4,

136.1, 130.2, 73.0, 28.8, 20.8, 11.1; LRMS (ESI) *m/z* 178.1 $[M]^+$, HRMS (NSI) calculated for $C_{12}H_{18}O$ $[M]^+$ 178.1352, found 178.1352.

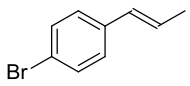
1,3,5-Trimethyl-2-((*E*)-prop-1-enyl)benzene 368



1-Mesitylpropan-1-ol **367** (3.00 g, 16.9 mmol, 1 eq), *p*-toluenesulfonic acid monohydrate (417 mg, 2.20 mmol, 0.12 eq) and benzene (30 mL) were added to a 50 mL round bottom flask equipped with Dean–Stark apparatus. The reaction mixture was heated to reflux for 2 h until complete consumption of starting material by TLC (1:4 ethyl acetate:petroleum ether). The dark red solution was cooled to room temperature and 5 drops of triethylamine were added to quench the reaction. H_2O (30 mL) was added and the phases separated before the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$ and solvent removed by rotary evaporation to give a pale yellow oil. Purification by silica gel flash column chromatography (petroleum ether) gave the title compound **368** as a colourless oil (2.41 g, 15.0 mmol, 89%).

Colourless oil; IR (ATR)/cm^{-1}: 2965, 2932, 2916, 1608; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 2H, Ar*H*), 6.21 (d, *J* = 16.0 Hz, 1H, ArC*H*CHCH$_3$), 5.57 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H, ArCHC*H*CH$_3$), 2.16 (s, 9H, ArC*H*$_3$), 1.80 (d, *J* = 6.5 Hz, 3H, ArCHCHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.7, 134.9, 130.1, 128.6, 128.5, 21.00, 20.96, 18.9; LRMS (ESI) *m/z* 160.1 $[M]^+$, HRMS (NSI) calculated for $C_{12}H_{16}$ $[M]^+$ 160.1247, found 160.1246.

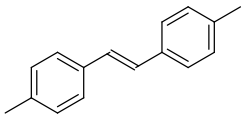
(*E*)-4-Bromo-β-methylstyrene 369



Ethyltriphenylphosphonium chloride (5.83 g, 17.8 mmol, 1.1 eq) and anhydrous THF (60 mL) were stirred in a dry two-necked flask equipped with a magnetic stirrer bar and reflux condenser under an inert nitrogen atmosphere. The suspension was cooled to 0 °C and *n*-butyllithium (7.12 mL, 2.5 M in hexanes, 15.4 mmol, 1.1 eq) was added dropwise. The contents were stirred for 30 mins at 0 °C before a solution of 4-bromobenzaldehyde (3.00 g, 16.2 mmol, 1 eq) in anhydrous THF (5 mL) was added dropwise. The reaction was allowed to warm slowly to room temperature, then stirred under reflux for 2 h. After cooling to room temperature, THF was removed by rotary evaporation. Water (30 mL) was added to the remaining residue followed by extraction with ethyl acetate (3 × 30 mL), drying over $MgSO_4$ and solvent removal by rotary evaporation to give a yellow oil. The crude reaction mixture was passed over a small plug of silica (eluting with petroleum ether) to give a colourless oil containing predominantly *trans*-4-bromo-β-methylstyrene. To isomerise the alkene mixture a single crystal of iodine was added to a solution of alkene in petroleum ether (10 mL) and left near a window in bright sunlight for ~10 h. The solution was again passed over a small plug of silica (eluting with petroleum ether) followed by solvent removal to give the target compound as a pink oil which formed a colourless semi-solid on standing (0.96 g, 4.86 mmol, 31%).

Semi-solid; IR (ATR)/cm^{-1}: 3061, 2966, 2958, 1657, 1110; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.19 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.34 (d, *J* = 16.4 Hz, 1H, ArC*H*CHCH$_3$), 6.24 (dq, *J* = 16.4, 6.4 Hz, 1H, ArCHC*H*CH$_3$), 1.88 (d, *J* = 6.4 Hz, 3H, C*H*$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.8, 131.4, 129.9, 127.3, 126.5, 120.3, 18.4; LRMS (ESI) *m/z* 196.0 [M(^{79}Br)]$^+$; HRMS (NSI) calculated for $C_9H_9{}^{79}Br$ $[M]^+$ 195.9882, found 195.9881.

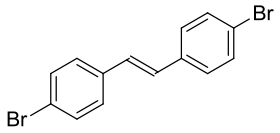
(*E*)-4,4'-Dimethylstilbene 370[150]



A 250 mL 2-necked flask equipped with a magnetic stirrer bar and reflux condenser was flame-dried under reduced pressure. 4-Iodotoluene (4.00 g, 18.7 mmol, 1 eq), anhydrous acetonitrile (90 mL), 4-methylstyrene (2.46 mL, 18.7 mmol, 1 eq), palladium(II) acetate (42 mg, 0.187 mmol, 1 mol%), tri-*o*-tolyl phosphine (114 mg, 0.374 mmol, 2 mol%) then anhydrous triethylamine (5.21 mL, 37.4 mmol, 2 eq) were added sequentially to the flask under an inert nitrogen atmosphere. The reaction mixture was heated under reflux for 24 h then allowed to cool to room temperature before removal of solvent under reduced pressure. Water (60 mL) and ethyl acetate (150 mL) were added to the residue and the phases separated. The aqueous phase was extracted with ethyl acetate (3 × 70 mL) and the combined organic phases were dried over $MgSO_4$. Removal of solvent and purification by silica gel column chromatography (petroleum ether) afforded the title compound as a colourless solid (1.98 g, 9.54 mmol, 51%).

Colourless solid; m.p. 174–176 °C [lit.[150] 182–183 °C]; IR (ATR)/cm^{-1}: 3024, 2940, 2918, 1512; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.18 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.06 (s, 2H, ArC*H*), 2.37 (s, 6H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.4, 134.9, 129.5, 127.8, 126.6, 21.4; LRMS (ESI) *m/z* 209.1 $[M + H]^+$.

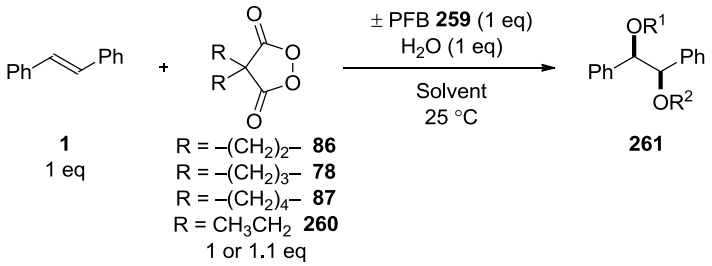
(*E*)-4,4'-Dibromostilbene 371[151]



A 250 mL 2-necked flask equipped with a magnetic stirrer bar and reflux condenser was flame-dried under reduced pressure. 1-Bromo-4-iodobenzene (1.20 g, 4.24 mmol, 1 eq), anhydrous acetonitrile (45 mL), 4-bromostyrene (0.55 mL, 4.24 mmol, 1 eq), palladium(II) acetate (9.5 mg, 0.0424 mmol, 1 mol%), tri-*o*-tolyl phosphine (26 mg, 8.48 mmol, 2 mol%) then anhydrous triethylamine (1.17 mL, 8.48 mmol, 2 eq) were added sequentially to the flask under an inert nitrogen atmosphere. The reaction mixture was heated under reflux for 48 h then allowed to cool to room temperature before removal of solvent under reduced pressure. Water (40 mL) and ethyl acetate (50 mL) were added to the residue and the phases separated. The aqueous phase was extracted with ethyl acetate (3 × 70 mL) and the combined organic phases were dried over $MgSO_4$. Filtration through Celite then removal of solvent and purification by silica gel column chromatography (0:100 then 5:95 ethyl acetate:petroleum ether) afforded the title compound as a pale yellow solid (0.674 g, 1.99 mmol, 47%).

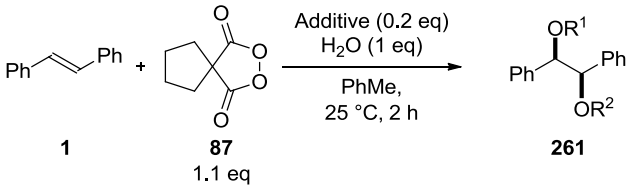
Pale yellow solid; m.p. 203–205 °C [lit.[151] 208–210 °C]; IR (ATR)/cm^{-1}: 3013, 2951, 1585, 1074; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.6 Hz, 4H, Ar*H*), 7.36 (d, *J* = 8.6 Hz, 4H, Ar*H*), 7.02 (s, 2H, ArC*H*); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.1, 132.0, 128.3, 128.2, 121.8; LRMS (CI) *m/z* 337.8 [M(^{79}Br,^{81}Br)]$^-$.

8.15 Optimisation of Reaction Conditions for Catalysis



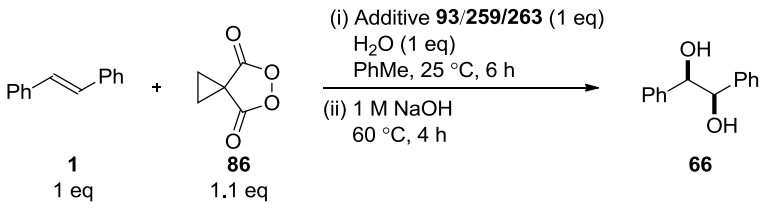
Trans-stilbene **1** (236 mg, 1.31 mmol, 1 eq) was dissolved in either $CDCl_3$ or d_8-toluene (2 mL) at 25 ^oC and water (24 µL, 1.31 mmol, 1 eq) was added. Peroxide **86**, **78**, **87** or **260** (1.31 mmol or 1.44 mmol, 1 or 1.1 eq) then perfluoro-*tert*-butanol **259** (183 µL, 1.31 mmol, 1 eq) were added in quick succession and timing commenced. At known time intervals, 20 µL of the reaction mixture was removed and diluted with 500 µL of $CDCl_3$ in an NMR tube. Reaction conversion was followed by ^1H NMR over 2 h for each peroxide or solvent examined.

8.16 General Procedure D: Catalyst Screen



Trans-stilbene **1** (62 mg, 0.34 mmol, 1 eq) was dissolved in d_8-toluene (503 µL) at 25 ^oC in a small sample vial and water (6 µL, 0.34 mmol, 1 eq) was added. Peroxide **87** (59 mg, 0.38 mmol, 1.1 eq) then the additive (0.069 mmol, 0.2 eq) were added in quick succession and timing commenced. At known time intervals, 20 µL of the reaction mixture was removed and diluted with 500 µL of $CDCl_3$ in an NMR tube. Reaction conversion was followed by ^1H NMR over a period of 2 h for each additive examined.

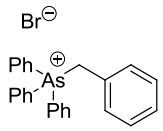
8.17 Dihydroxylation using Stoichiometric Additives



Trans-stilbene **1** (227 mg, 1.26 mmol, 1 eq) was added in one portion to a solution of cyclopropyl malonoyl peroxide **86** (177 mg, 1.39 mmol, 1.1 eq), H_2O (23 μL, 1.26 mmol, 1 eq) and either 4-nitrophenol **263** (175 mg, 1.26 mmol, 1 eq), perfluoro-*tert*-butanol **259** (176 μL, 1.26 mmol, 1 eq) or dihydroxylation intermediate **93** (411 mg, 1.26 mmol, 1 eq) in toluene (2 mL). The reaction mixture was stirred at 25 °C and consumption of *trans*-stilbene **1** was monitored by TLC (100% petroleum ether) and ^{1}H NMR spectroscopy over time. Once complete (6 h when using **259** and **263** and 24 h when using **93**) the reaction mixture was evaporated to dryness *in vacuo* and 1 M NaOH (10 mL) was added. The reaction mixture was stirred at 60 °C for 4 h and allowed to cool to room temperature before the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (1 × 10 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation to afford the target diol.

8.18 Synthesis and Reaction of Chiral Malonoyl Peroxide 282

Triphenylarsine benzylbromide 294[106]

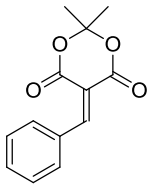


Method 1 (Conditions A):[105] Triphenylarsine (35.9 g, 0.117 mol, 1 eq) was crushed to a fine powder using a mortar and pestle before being dissolved in nitromethane (400 mL). A solution of benzyl bromide (16.7 mL, 0.141 mol, 1.2 eq) in nitromethane (100 mL) was added over a period of 15 mins and the resulting solution was heated to reflux for 24 h. After cooling to room temperature solvent was removed by rotary evaporation before diethyl ether (100 mL) was added. The resulting heterogeneous mixture was filtered through a sinter funnel and the remaining solid washed with diethyl ether (6 × 30 mL). Recrystallisation from ethanol (35 mL) gave the title compound as colourless crystals (31.3 g, 65.5 mmol, 56%).

Method 2 (Conditions B):[106] Triphenylarsine (25.0 g, 81.7 mmol, 1 eq) and benzyl bromide (9.7 mL, 81.7 mmol, 1 eq) were added to a 50 mL round-bottom flask and heated to 75 ^{o}C. The melt was stirred vigorously for 6 h before being cooled to room temperature. The colourless solid was transferred to a Buchner funnel lined with filter paper and washed with 250 mL of a 1:1 diethyl ether:petroleum ether solution. Drying under high vacuum gave the title compound as a colourless solid (34.3 g, 71.9 mmol, 88%).

Colourless solid; m.p. 162–166 ^{o}C [lit.[105] 172–172.5 ^{o}C]; IR (ATR)/cm^{-1}: 3005, 2988, 2978, 2903, 2872, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.57 (m, 15H, Ph*H*), 7.23–7.18 (m, 3H, Ph*H*), 7.13–7.09 (m, 2H, Ph*H*), 5.46 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 133.3, 130.9, 130.7, 128.9, 128.5, 128.1, 120.8, 33.4; LRMS (EI) *m/z* 397.1 [M]$^{+}$.

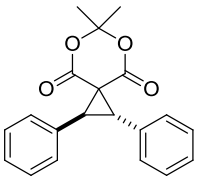
5-Benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione 296[107]



Meldrum's acid (15.0 g, 0.104 mol, 1 eq), benzaldehyde (12.7 mL, 0.125 mol, 1.2 eq), pyrrolidinium acetate (1.35 g, 10.4 mmol, 0.1 eq) and toluene (540 mL) were added to a 1 L round-bottom flask. The flask was immersed in a pre-heated oil bath at 50 ^{o}C and the reaction stirred for 18 h. Solvent was removed by rotary evaporation to give a viscous orange oil to which methanol (10 mL) was added and the resulting solution heated to reflux for 30 mins. The solution was allowed to cool to room temperature before being placed in the freezer (–22 ^{o}C) for 1 hour. The resulting solid was filtered off, washed with ice cold methanol (3 × 30 mL) then dried under vacuum to give **296** as pale yellow crystals (15.9 g, 68.6 mmol, 66%).

Colourless solid; m.p. 77–78 ^{o}C [lit.[152] 84 ^{o}C]; IR (ATR)/cm^{-1}: 3060, 2997, 2961, 2900, 2856, 1765, 1732, 1285, 1188, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H, PhC*H*), 8.05 (d, *J* = 7.7 Hz, 2H, Ph*H*), 7.59–7.46 (m, 3H, Ph*H*), 1.81 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 159.9, 158.2, 133.8, 133.7, 131.8, 128.8, 114.9, 104.7, 27.7; LRMS (EI) *m/z* 232.1 $[M]^+$.

***rel*-(1*S*,2*S*)-6,6-Dimethyl-1,2-diphenyl-5,7-dioxaspiro[2.5]octane-4,8-dione 297**[104b]

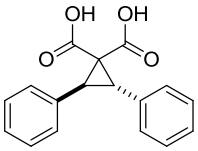


Triphenylarsonium benzyl bromide **294** (11.50 g, 24.0 mol, 1.2 eq) was stirred in dichloromethane (120 mL) before 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione

296 (4.66 g, 20.0 mol, 1 eq) was added in one portion. A solution of 50% (by weight) aqueous NaOH (66 mL) was added dropwise over a period of 5 mins. The flask was sealed with a rubber septum and stirred vigorously at room temperature. After 30 mins the reaction mixture was diluted with water (100 mL) and dichloromethane (50 mL). The layers were separated and the aqueous phase extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with brine (75 mL), dried over $MgSO_4$ and the solvent removed by rotary evaporation to give a pale yellow solid. The crude reaction mixture was filtered through a one-inch plug of silica washing with 1:9 ethyl acetate:petroleum ether (500 mL) to remove the triphenylarsine byproduct, then ethyl acetate (500 mL) to release the desired compound (5.15 g, 80%) as a mixture of diastereoisomers (*anti*:*syn* 9:1). One recrystallisation from refluxing ethyl acetate (30 mL) afforded the title compound as a single diastereoisomer (4.25 g, 13.2 mmol, 66%).

Colourless solid; m.p. 168–170 ^{o}C [lit.[104b] 167–169 ^{o}C]; IR (ATR)/cm^{-1}: 3059, 3003, 2990, 1765, 1730, 1287, 1188; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 10H, Ph*H*), 4.33 (s, 2H, PhC*H*), 1.73 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 132.5, 129.5, 128.63, 128.57, 104.9, 45.2, 38.8, 28.1; LRMS (EI) *m/z* 323.0 $[M + H]^+$.

rel-(2_S_, 3_S_)-2,3-Diphenylcyclopropane-1,1-dicarboxylic acid 283

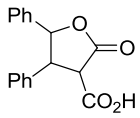


Diester **297** (370 mg, 1.15 mmol, 1 eq) was stirred in THF (2.3 mL) before a solution of NaOH (230 mg, 5.75 mmol, 5 eq) in H_2O (2.3 mL) was added. The reaction was stirred for 1.5 h at room temperature until TLC (1:2 ethyl acetate:petroleum ether) indicated no more starting material **297** present. THF was removed by rotary evaporation, H_2O added (10 mL) then the solution washed with ethyl acetate (2 × 10 mL). The aqueous phase was acidified to pH 1 using 8 M HCl before being extracted with diethyl ether

(3 × 10 mL). The combined organic phases were washed with brine (1 ×10 mL), dried ($MgSO_4$) and solvent removed by rotary evaporation to afford the title compound as a colourless solid (292 mg, 1.04 mmol, 90%).

Colourless solid; m.p. 168–170 ^oC; IR (ATR)/cm^{-1}: 3030, 2999, 1680, 1281; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (bs, 2H, CO_2H), 7.34–7.28 (m, 10H, Ph*H*), 3.96 (s, 2H, PhC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 133.7, 129.1, 128.6, 128.0, 43.0, 38.7; LRMS (ESI) *m/z* 282.1 $[M]^+$; HRMS (NSI) calculated for $C_{17}H_{13}O_4$ $[M - H]^-$ 281.0819, found 281.0823.

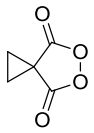
Tetrahydro-2-oxo-4,5-diphenylfuran-3-carboxylic acid 303



rel-(2*S*,3*S*)-2,3-Diphenylcyclopropane-1,1-dicarboxylic acid **283** (25 mg, 0.089 mmol) was dissolved in methanesulfonic acid (150 µL) and stirred at room temperature in a small vial for 3 h. Addition of ice (~1 g) caused a white precipitate to form. Ethyl acetate (2 mL) was added and the phases separated. The organic phase was washed with brine (1 mL) before solvent was removed by rotary evaporation to afford the title compound as a colourless gum (20 mg, 0.071, 80%).

Colourless gum; IR (ATR)/cm^{-1}: 3067, 3032, 2959, 2924, 2872, 1769, 1709, 1275, 1152; ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (bs, 1H CO_2H), 7.41–7.14 (m, 10H, Ph*H*), 5.44 (d, *J* = 9.0 Hz, 1H, PhC*H*OR), 4.09–4.00 (m, 2H, PhC*H*C*H*CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.1, 136.1, 134.9, 129.4, 129.3, 128.9, 128.6, 127.8, 126.3, 86.1, 54.8, 54.2; LRMS (EI) *m/z* 281.0 $[M - H]^-$; HRMS (NSI) calculated for $C_{17}H_{13}O_4$ $[M - H]^-$ 281.0819, found 281.0813.

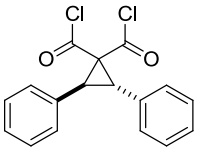
Cyclopropyl malonoyl peroxide 86 from cyclopropane-1,1-dicarboyl dichloride 305



Cyclopropane-1,1-dicarboxylic acid **91** (130 mg, 1 mmol, 1 eq) and thionyl chloride (3 mL) were heated under reflux in a 5 mL round-bottom flask for 3 h. After cooling to room temperature, volatiles were removed under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2 (5 mL) and sodium percarbonate (471 mg, 3 mmol, 3 eq) was added before the heterogeneous mixture was stirred vigorously at 25 ^oC for 20 h. The reaction mixture was filtered through Celite then water (10 mL) was added. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 5 mL), before the combined organic phases were combined, washed with brine (5 mL), dried ($MgSO_4$) and solvent removed by rotary evaporation. Cyclopropyl malonoyl peroxide **86** was formed without need for further purification (77 mg, 0.6 mmol, 60%).

For analytical data of peroxide **86** see Experimental 8.2.2.

***rel*-(2*S*, 3*S*)-2,3-Diphenylcyclopropane-1,1-dicarboyl dichloride 306**

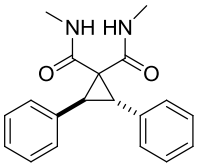


Diacid **283** (13.3 g, 47.0 mmol, 1 eq), DMF (918 μl, 11.8 mmol, 4 eq) and CH_2Cl_2 (175 mL) were stirred at 0 ^oC under nitrogen. Oxalyl chloride (20 mL, 236 mmol) was added *via* dropping funnel over 25 mins. The ice bath was removed and the reaction stirred for 5 h at room temperature under nitrogen, before volatiles were removed *in vacuo* resulting in an orange solid. The residue was dissolved in ethyl acetate (200 mL) then washed with 1 M HCl (30 mL), H_2O (30 mL), brine (30 mL) and dried ($MgSO_4$) before solvent was removed under reduced pressure to afford the title compound as a

colourless solid (13.8 g, 43.0 mmol, 92%). If required, rapid purification was performed using short-path flash silica gel column chromatography (1:5 ethyl acetate:petroleum ether).

m.p. 119–120 ^{o}C; IR (ATR)/cm^{-1}: 3028, 3011, 1762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 10H, Ph*H*), 4.20 (s, 2H, PhC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 131.1, 129.0, 128.9, 63.5, 39.0; Unable to obtain low or high resolution mass spectrometry data using in-house or Swansea National Mass Spectrometry Service.

rel-(2*S*,3*S*)-*N*,*N*'-Dimethyl-2,3-diphenylcyclopropane-1,1-dicarboxamide 307

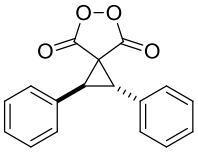


An excess (1 mL) of methylamine (33% by weight in ethanol) and dichloromethane (5 mL) were stirred in a 10 mL round-bottom flask. A solution of diacid chloride **306** (170 mg, 0.532 mmol) in dichloromethane (1.5 mL) was added dropwise over 3 mins. The reaction mixture was stirred for 1 hour at room temperature before being diluted with dichloromethane (3 mL) followed by addition of 2 M HCl (15 mL). The organic layer was separated and the aqueous layer washed with dichloromethane (2 × 10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (20 mL), brine (20 mL) and dried over $MgSO_4$. Removal of solvent by rotary evaporation and purification by silica gel column chromatography (1:9 ethyl acetate:petroleum ether), followed by crystallisation from hot ethyl acetate, afford the title compound as a colourless solid (149 mg, 0.484 mmol, 91%).

Colourless solid; m.p. 176–178 ^{o}C; IR (ATR)/cm^{-1}: 3260, 3061, 3036, 2943, 2930, 1626, 1535; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 10H, Ph*H*), 6.03 (bs, 2H, N*H*), 3.63 (s, 2H, PhC*H*), 2.53 (d, *J* = 4.9 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 167.6, 135.7, 128.7, 128.3, 127.4, 40.1, 33.1, 26.7; LRMS (EI) *m/z* 308.2 $[M]^+$, HRMS (NSI) calculated for $C_{19}H_{21}O_2N_2$ $[M + H]^+$ 309.1598, found 309.1602.

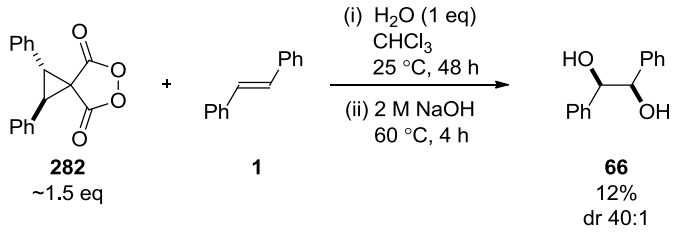
rel-(2_S_,3_S_)-2,3-Diphenylcyclopropane-1,1-malonoyl peroxide 282



Diacid chloride **306** (0.25 g, 0.784 mmol, 1 eq) was dissolved in bench dichloromethane (8 mL) in a 25 mL round-bottom flask before sodium percarbonate (615 mg, 3.92 mmol, 5 eq) was added in one portion. The reaction vessel was sealed and the heterogeneous reaction mixture vigorously stirred at room temperature using an egg-shaped stirrer bar. After 48 h the starting material had been consumed (by ^{1}H NMR analysis of the crude reaction mixture). The reaction mixture was diluted with dichloromethane (40 mL), filtered through Celite and solvent removed by rotary evaporation to leave a colourless powder. Further purification proved unsuccessful.

Structure is consistent with the following NMR data. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 10H, Ph*H*), 4.29 (s, 2H, PhC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 129.8, 129.6, 129.3, 129.0, 46.2, 32.1.

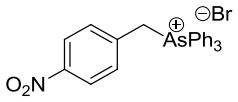
Dihydroxylation of *trans*-stilbene 1 using diphenyl peroxide 282



Crude diphenyl peroxide **282** (80 mg, 0.286 mmol, ~1.5 eq) was dissolved in chloroform (1 mL) followed by the addition of water (4 µL, 0.191 mmol, 1 eq) and *trans*-stilbene **1** (34 mg, 0.191 mmol, 1 eq). The reaction mixture was stirred at 25 ^{o}C for 48 h before removal of solvent by rotary evaporation. 2 M NaOH solution (10 mL) was added and the resulting mixture heated to 60 ^{o}C for 4 h. After cooling to room temperature the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (1 × 10 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation to afford diol **66** (40:1 *syn*:*anti*). Purification by silica gel column chromatography afforded pure diol **66** as a colourless solid (5 mg, 0.023 mmol, 12%).

8.19 Synthesis and Reaction of Chiral Malonoyl Peroxide 308

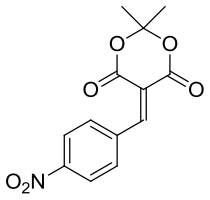
Triphenylarsine-4-nitrobenzyl bromide 310[105]



A solution of triphenylarsine (3.06 g, 10.0 mmol, 1 eq) in nitromethane (20 mL) was added dropwise to a solution of 4-nitrobenzyl bromide (2.16 g, 10.0 mmol, 1 eq) in nitromethane (20 mL) in a 100 mL round-bottom flask. The resulting solution was heated to reflux for 20 h then the solvent was removed by rotary evaporation. Purification by crystallisation from refluxing acetone gave **310** as a colourless solid (2.63 g, 5.04 mmol, 50%).

Colourless solid; m.p. 157–158 °C [lit.[105] 163–164 °C]; IR (ATR)/cm^{-1}: 3049, 2997, 2961, 2900, 2891, 1520, 1344; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.52 (m, 19H, Ar*H*), 5.99 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 136.9, 134.2, 133.5, 132.4, 130.7, 123.4, 120.3, 31.9; LRMS (APCI) *m/z* 442.1 $[M]^+$.

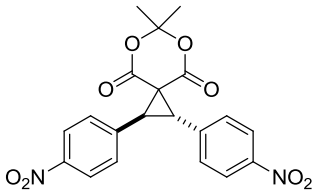
5-(4-Nitrobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 312[153]



Meldrum's acid (0.792 g, 5.50 mmol, 1.1 eq), water (10 mL) and 4-nitrobenzaldehyde (0.755 g, 5.00 mmol, 1 eq) were stirred at 75 °C in a 25 mL round-bottom flask. After 2.5 h the reaction mixture was diluted with water (10 mL) and the solid filtered off using a Buchner funnel before being washed with water (5 × 10 mL). Crystallisation from refluxing ethanol gave the title compound **312** as an off-white solid (831 mg, 3.00 mmol, 60%).

Off-white solid; m.p. 215–216 °C [lit.[154] 215–217 °C]; IR (ATR)/cm^{-1}: 3013, 2988, 2956, 2901, 1755, 1722, 1526, 1348, 1290, 1195, 1042; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H, ArC*H*), 8.30 (d, *J* = 7.5 Hz, 2H, Ar*H*), 8.06 (d, *J* = 7.5 Hz, 2H, Ar*H*), 1.83 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 162.2, 154.6, 137.6, 133.2, 123.7, 118.7, 105.4, 28.0; LRMS (EI) *m/z* LRMS (CI) *m/z* 278.0 $[M + H]^+$.

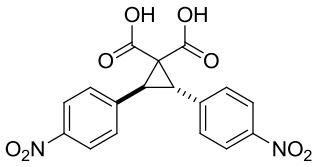
rel-(1_S_,2_S_)-6,6-Dimethyl-1,2-bis(4-nitrophenyl)-5,7-dioxaspiro[2.5]octane-4,8-dione 313[104b]



4-Nitrobenzylidene **312** (831 mg, 3.00 mmol, 1 eq) was added to a suspension of arsonium salt **310** (1.88 g, 3.60 mmol, 1.2 eq) and dichloromethane (15 mL) in a 50 mL round-bottom flask. A 50% (by weight) aqueous sodium hydroxide solution (0.25 mL) was added dropwise over 30 mins. After 2 h the reaction was deemed complete by TLC (1:3 ethyl acetate:petroleum ether) due to consumption of 4-nitrobenzylidene **312**. The blood-red solution was diluted with dichloromethane (20 mL) and water (20 mL) and the phases separated. The compound was extracted using dichloromethane (3 × 15 mL) and the combined organic extracts washed with brine (20 mL) and dried over $MgSO_4$. Removal of solvent by rotary evaporation gave the title compound as an 8:1 mixture of diastereoisomers (*anti*:*syn*). Purification by silica gel column chromatography (1:1 ethyl acetate:petroleum ether) then crystallisation by dropwise addition of diethyl ether into a warm solution of **313** in dichloromethane gave the title compound as a single diastereoisomer (766 mg, 1.86 mmol, 62%).

Colourless solid; m.p. 167–170 ^{o}C [lit.[104b] 176–177 ^{o}C]; IR (ATR)/cm^{-1}: 3134, 3068, 2995, 2858, 1726, 1518, 1344, 1287, 1200, 1109, 1062; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.7 Hz, 4H, Ar*H*), 7.57 (d, *J* = 8.7 Hz, 4H, Ar*H*), 4.32 (s, 2H, ArC*H*), 1.76 (s, 6H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 148.1, 138.9, 130.5, 124.0, 105.7, 43.1, 38.7, 28.2; LRMS (EI) *m/z* 411.0 [M – H]$^{-}$; HRMS (ASAP) calculated for $C_{20}H_{17}N_2O_8$ [M + H]$^{+}$ 413.0979, found 413.0980.

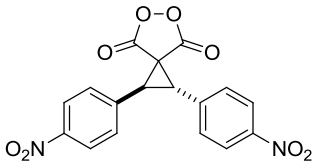
rel-(2*S*,3*S*)-2,3-Bis(4-nitrophenyl)cyclopropane-1,1-dicarboxylic acid 314



Diester **313** (6.80 g, 16.5 mmol, 1 eq) was stirred in THF (60 mL) and a solution of sodium hydroxide (4.00 g, 100 mmol, 6 eq) in water (55 mL) was added in one portion. After 4 h the reaction was deemed complete by TLC (1:1 ethyl acetate:petroleum ether). THF was removed *in vacuo* and the residue dissolved in water (50 mL). The solution was washed with ethyl acetate (3 × 30 mL) and the aqueous phase acidified to pH 1 using 1 M HCl. Extraction with ethyl acetate (4 × 30 mL), washing with brine (50 mL) and drying over $MgSO_4$ then removal of solvent by rotary evaporation afforded the title compound as a beige solid (5.77 g, 15.5 mmol, 94%).

Beige solid; m.p. 198 ^{o}C (decomp.); IR (ATR)/cm^{-1}: 3088, 3028, 2843, 1694, 1510, 1344, 1288, 1111; ^{1}H NMR (400 MHz, CD_3CN) δ 8.18 (d, *J* = 8.9 Hz, 4H Ar*H*), 7.60 (d, *J* = 8.9 Hz, 4H Ar*H*), 3.99 (s, 2H, ArC*H*); ^{13}C NMR (100 MHz, CD_3CN) δ 168.0, 143.2, 131.0, 124.3, 118.3, 45.4, 36.6; LRMS (ESI) *m/z* 370.9 $[M - H]^-$; HRMS (NSI) calculated for $C_{17}H_{11}N_2O_8$ $[M - H]^-$ 371.0521, found 371.0511.

rel-(2*S*,3*S*)-2,3-Bis(4-nitrophenyl)cyclopropane-1,1-malonoyl peroxide 308

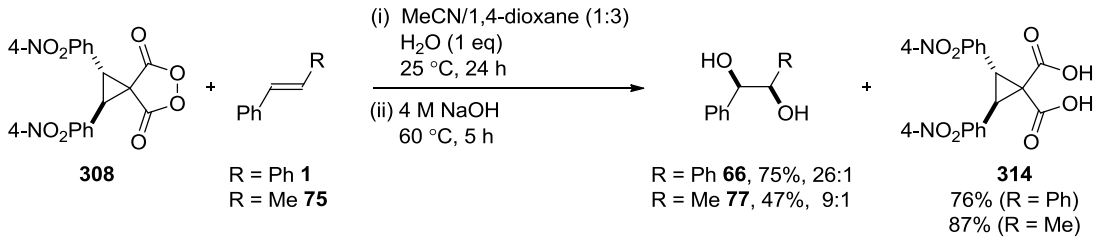


Diacid **314** (1.00 g, 2.69 mmol, 1 eq) was stirred in methanesulfonic acid (5 mL) in a 10 mL round-bottom flask at 0 ^{o}C. Urea hydrogen peroxide (0.759 g, 8.07 mmol, 3 eq) was added in one portion and the reaction mixture stirred at room temperature for 18 h. The solution was poured into a mixture of ice (10 g) and ethyl acetate (15 mL) and the

phases separated. The aqueous phase was extracted using ethyl acetate (4 x 10 mL) and the combined organic extracts washed with saturated aqueous sodium hydrogen carbonate solution (25 mL). Drying over $MgSO_4$, removal of solvent *in vacuo*, then purification by silica gel column chromatography (1:2 ethyl acetate:petroleum ether) afforded the title compound as a colourless solid (597 mg, 1.61 mmol, 60%).

Colourless solid; m.p. 130 ^oC (gradual decomp.); IR (ATR)/cm^{-1}: 2986, 2961, 2907, 2876, 1798, 1514, 1344, 1211, 1111; ^1H NMR (400 MHz, CD_3CN) δ 8.26 (d, *J* = 8.9 Hz, 4H, Ar*H*), 7.82 (d, *J* = 8.9 Hz, 4H, Ar*H*) 4.51 (s, 2H, ArC*H*); ^{13}C NMR (100 MHz, CD_3CN) δ 169.7, 138.5, 132.1, 124.3, 118.3, 44.1 33.2; Unable to obtain low or high resolution mass spectrometry data for malonoyl peroxides using in-house or Swansea National Mass Spectrometry Service.

Dihydroxylation of *trans*-stilbene 1 using bis-4-nitrodiphenyl peroxide 308



Bis-4-nitrodiphenyl peroxide **308** (185 mg, 0.50 mmol, 1.2 eq) was dissolved in 1:3 MeCN/1,4-dioxane (2 mL) followed by the addition of water (8 µL, 0.42 mmol, 1 eq) and *trans*-stilbene **1** (76 mg, 0.42 mmol, 1 eq). The reaction mixture was stirred at 25 ^oC for 24 h before removal of solvent by rotary evaporation. 4 M NaOH solution was added and the resulting mixture heated to 60 ^oC for 5 h. After cooling to room temperature the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (1 × 5 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation to afford diol **66** (26:1 *syn*:*anti*). Purification by silica gel column chromatography gave pure diol **66** as a colourless solid (67 mg, 0.32 mmol, 75%). The acid by-product **314** was recovered by acidifying the aqueous

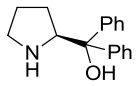
phase to pH 1 by dropwise addition of concentrated HCl with stirring at 0–5 ^{o}C. Extraction with ethyl acetate (3 × 5 mL), washing with brine (1 × 5 mL) and drying over $MgSO_4$ then removal of solvent by rotary evaporation afforded the carboxylic acid as an off-white solid (119 mg, 0.32 mmol, 76%).

When β-methylstyrene **75** (50 mg, 0.42 mmol, 1 eq) was subjected to the dihydroxylation conditions with peroxide **86**, diol **77** was produced (9:1 *syn*:*anti*, 30 mg, 0.20 mmol, 47%). Diacid **314** was recovered using the same procedure as above (136 mg, 0.37 mmol, 87%).

For analytical data of diol **66** see Experimental 8.4.1.
For analytical data of diol **77** see Experimental 8.4.1.
For analytical data of diacid **314** see above in Experimental 8.19.

8.20 Synthesis and Reaction of Chiral Malonoyl Peroxide 315

(*S*)-Diphenyl(pyrrolidin-2-yl)methanol 317[155]

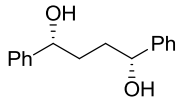


(*S*)-Diethyl-pyrrolidine-1,2-dicarboxylate (8.00 g, 37.2 mmol, 1 eq) was dissolved in anhydrous THF (80 mL) under an inert nitrogen atmosphere and cooled to 0 ^{o}C. Phenylmagnesium bromide solution (3.0 M, 50 mL, 149 mmol, 4 eq) was added over 40 mins using a syringe pump. The reaction mixture was stirred at 0 ^{o}C for 3 h before being quenched by slow addition of saturated aqueous ammonium chloride solution (50 mL). The mixture was filtered and the solid residue washed with chloroform (2 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and solvent was removed by rotary evaporation. The residue was dissolved in anhydrous methanol (80 mL) followed by addition of potassium hydroxide (22.4 g). The reaction mixture was heated to reflux for 4.5 h then cooled to room temperature. After removal of methanol by rotary evaporation, water (50 mL) was added and the

aqueous phase extracted using chloroform (3 × 50 mL). The combined organic phases were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded a viscous orange oil that solidified on standing. The residue was passed through a small plug of silica gel using dichloromethane to remove by-products, then 10% methanol in dichloromethane to release desired product **317**. Solvent was evaporated and the residue dissolved in 1:20 ethyl acetate:petroleum ether (40 mL) at 60 ^{o}C. The solution was allowed to cool slowly to room temperature, then cooled to -20 ^{o}C overnight. The solid was filtered off and washed with hexane (3 × 30 mL) to afford the target compound as an off-white solid (6.40 g, 25.3 mmol, 68%).

Off-white solid; m.p. 71–73 °C [lit.[115] 74–74.8 ^{o}C]; IR (ATR)/cm^{-1}: 3356, 3059, 3024, 2955, 2886, 2872, 2833, 1449, 1175, 1101; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H, Ph*H*), 7.52–7.50 (m, 2H, Ph*H*), 7.32–7.26 (m, 4H, Ph*H*), 7.20–7.15 (m, 2H, Ph*H*), 4.26 (dd, *J* = 7.7, 7.7 Hz, 1H, NHC*H*C(Ph_2OH)), 3.07–2.92 (m, 2H, NHCH_2), 1.78–1.53 (m, 4H, CH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 145.6, 128.4, 128.1, 126.6, 126.5, 126.0, 125.7, 77.2, 64.6, 46.9, 26.4, 25.6; LRMS (APCI) *m/z* 254.1 $[M + H]^+$; $[\alpha]_D^{25}$ = – 51.2 (c. 1.0, MeOH).

(1*R*,2*R*)-1,4-Diphenyl-1,4-butanediol 318[113,114]

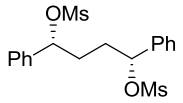


Diphenylprolinol catalyst **317** (2.83 g, 11.2 mmol, 0.17 eq) was dissolved in anhydrous THF (70 mL) in a 500 mL round-bottom flask. Trimethyl borate (1.58 mL, 14.2 mmol, 0.22 eq) was added and the solution stirred at room temperature for 1 hour. Borane dimethylsulfide complex (13.0 mL, 13.7 mmol, 0.2 eq) was added in one portion followed by dropwise addition of a solution of 1,2-dibenzoylethane (15.40 g, 64.7 mmol, 1 eq) in THF (300 mL) over 1 hour. The reaction was stirred at room temperature for 3 h before quenching by dropwise addition of 2 M HCl (100 mL). The compound was extracted with diethyl ether (3 × 100 mL) washed with water (100 mL)

and brine (100 mL), dried over $MgSO_4$ and solvent removed by rotary evaporation. The crude product was purified by silica gel column chromatography (2:3 ethyl acetate:petroleum ether) to afford **318** as viscous colourless oil that solidified on standing (14.9 g, 61.6 mmol, 95%).

Colourless solid; m.p. 72–73 °C [lit.[156] 68–70 °C]; IR (ATR)/cm^{-1}: 3318, 3086, 3063, 3026, 2947, 2920, 2900, 1072; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 10H, Ph*H*), 4.68–4.64 (m, 2H, PhC*H*OH), 2.99 (bs, 2H, O*H*), 1.96–1.76 (m, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 128.6, 127.6, 126.0, 74.7, 36.0; LRMS (ESI) *m/z* 265.1 $[M + Na]^+$; HRMS (NSI) calculated for $C_{16}H_{18}O_2Na$ $[M + Na]^+$ 265.1199, found 265.1200; $[\alpha]_D^{25}$ = + 54.4 (c. 1.0, $CHCl_3$).

(1*R*,2*R*)-1,4-Diphenyl-1,4-butanediol-bis(methanesulfonic acid ester) 319[112]

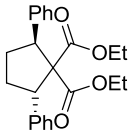


Methanesulfonyl chloride (2.48 mL, 32.0 mmol, 2.5 eq) was dissolved in anhydrous dichloromethane (110 mL) in a 500 mL two-necked round-bottom flask and cooled to –20 °C using a crushed ice/NaCl bath. A solution of diol **318** (3.00 g, 12.4 mmol, 1 eq) and triethylamine (5.28 mL, 37.9 mmol, 3 eq) in dichloromethane (110 mL) was added over 20 mins using a dropping funnel. The reaction mixture was stirred for 2 h with the temperature maintained between –20 °C and –10 °C. The reaction was quenched by addition of saturated aqueous ammonium chloride (10 mL) and allowed to warm to room temperature. Around 75% of the solvent was removed *in vacuo* then diethyl ether (200 mL) was added. The solution was washed sequentially with a 1:2:1 mixture of water:brine:saturated $NaHCO_3$ solution (4 × 50 mL), then saturated $NaHCO_3$ solution (2 × 50 mL) before the organic phase was dried over anhydrous sodium sulfate. Approximately 75% of the solvent was removed *in vacuo* and the remaining solution cooled to 0 °C. Dropwise addition of petroleum ether with simultaneous scratching of the flask using a glass rod resulted in precipitation of **319** as a colourless solid which

was collected by filtration (3.45 g, 8.68 mmol, 70%). The product was unstable on the bench at room temperature but can be stored under nitrogen in the freezer (-20 ^{o}C) for up to a month.

Colourless solid; m.p. 46–49 °C [lit.[112] 49–51 ^{o}C]; IR (ATR)/cm^{-1}: 3067, 3022, 2955, 2924, 1331, 1171; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 10H, Ph*H*), 5.67–5.63 (m, 2H, C*H*OMs), 2.66 (s, 6H, CH_3), 2.27–2.19 (m, 2H, CH_2), 2.02–1.94 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 129.4, 129.2, 126.7, 83.6, 39.1, 33.2; Unable to acquire mass spectrometric data; $[\alpha]_D^{25}$ = + 94.4 (c. 1.0, $CHCl_3$). Compound is unstable and should be stored at –20 ^{o}C under nitrogen.

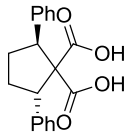
(2*S*,5*S*)-2,5-Diphenylcyclopentane-1,1-dicarbonic acid diethyl ester 320[112]



Sodium hydride (60% dispersion in mineral oil, 2.10 g, 52.8 mmol, 3 eq) and THF (200 mL) were added to a 500 mL round-bottom flask. Diethyl malonate (14.2 mL, 87.9 mmol, 5 eq), and 15-crown-5 (87 µL, 0.44 mmol, 2.5 mol%) were added then the resulting mixture heated to reflux under a nitrogen atmosphere. After 1 hour the solution was allowed to cool to room temperature before a solution of dimesylate **319** (7.00 g, 17.6 mmol, 1 eq) in THF (80 mL) was added dropwise over 15 mins. The reaction mixture was stirred at room temperature for 30 mins then heated to reflux for 5 h before being allowed to stir at room temperature overnight. Solvent was removed *in vacuo* and the residue dissolved in ethyl acetate (80 mL) and water (100 mL). The phases were separated and the aqueous phase extracted with ethyl acetate (5 × 40 mL). The combined organic extracts were washed with 1 M NaOH (5 × 40 mL), brine (50 mL), dried ($MgSO_4$) and solvent removed by rotary evaporation to leave an orange liquid. Purification by silica gel column chromatography (1:20 ethyl acetate:petroleum ether) afforded the title compound as a colourless solid (3.54 g, 9.68 mmol, 55%).

Colourless solid; m.p. 84–86 °C [lit.[112] 84–86 °C]; IR (ATR)/cm^{-1}: 3030, 2986, 2955, 2940, 2872, 1707, 1285, 1248, 1196, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.18 (m, 10H, Ph*H*), 4.34–4.30 (m, 2H, PhC*H*), 3.77 (dq, *J* = 10.6, 7.1 Hz, 2H, OCH_2), 3.26 (dq, *J* = 10.6, 7.1 Hz, 2H, OCH_2), 2.33–2.25 (m, 2H, -CH_2CH_2-), 2.19–2.11 (m, 2H, -CH_2CH_2-), 0.69 (t, *J* = 7.1 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 141.4, 128.8, 128.1, 126.9, 70.9, 60.9, 52.4, 32.2, 13.4; LRMS (ESI) *m/z* 389.1 $[M + Na]^+$; HRMS (NSI) calculated for $C_{23}H_{27}O_4$ $[M + H]^+$ 367.1904, found 367.1905; $[\alpha]_D^{25}$ = – 120.6 (c. 1.0, $CHCl_3$).

(2*S*,5*S*)-2,5-Diphenylcyclopentane-1,1-dicarboxylicacid 321

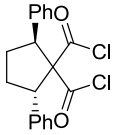


Potassium *tert*-butoxide (490 mg, 4.37 mmol, 16 eq) and dry diethyl ether (7.5 mL) were stirred in a large microwave vial. Water (20 µL, 1.09 mmol, 4 eq) was added and the heterogeneous mixture stirred for 5 mins before addition of diester **320** (100 mg, 0.27 mmol, 1 eq). The reaction vessel was sealed and the reaction mixture stirred at 40 °C for 20 h until all starting material was consumed as indicated by TLC analysis (1:20 ethyl acetate:petroleum ether). Ice-cold water (8 mL) was added and the phases separated. The aqueous phase was acidified to pH 1 using 1 M HCl before being extracted using ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (15 mL) and dried ($MgSO_4$) before solvent was removed by rotary evaporation to afford the title compound as a colourless solid (75 mg, 0.24 mmol, 90%).

Colourless solid; m.p. 70 (slow decomp.) °C; IR (ATR)/cm^{-1}: 3030, 2965, 2878, 1692, 1238; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (bs, 2H, CO_2H) 7.33–7.24 (m, 10H, Ph*H*), 4.24 (dd, *J* = 8.5, 8.5 Hz, 2H, PhC*H*), 2.44–2.22 (m, 4H, CH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 139.9, 128.7, 128.3, 127.4, 70.3, 53.1, 31.5; LRMS (ESI)

m/z 309.0 $[M - H]^-$; HRMS (NSI) calculated for $C_{19}H_{17}O_2$ $[M - H]^-$ 309.1132, found 309.1126; $[\alpha]_D^{25} = -40.0$ (c. 0.4, $CHCl_3$).

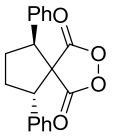
(2*S*,5*S*)-2,5-Diphenylcyclopentane-1,1-dicarbonyl dichloride 322



Dicarboxylic acid **321** (600 mg, 1.94 mmol, 1 eq) and dimethyl formamide (40 µL, 0.52 mmol, 0.25 eq) were stirred in dichloromethane (7 mL) in a 5 mL round-bottom flask at 0 ^oC. Oxalyl chloride (850 µL, 9.90 mmol, 5 eq) was added dropwise over 10 mins then the ice bath was removed and the reaction mixture stirred at room temperature for 6 h. Solvent was removed by rotary evaporation and the residue purified through short-path silica gel column chromatography (1:20 ethyl acetate:petroleum ether) to afford the title compound as a colourless solid (517 mg, 1.49 mmol, 77%).

Colourless solid; m.p. 136–137 °C; IR (ATR)/cm^{-1}: 3048, 3030, 3009, 2976, 2951, 1765, 1013; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 10H, Ph*H*), 4.39 (dd, *J* = 9.0, 7.8 Hz, 2H, PhC*H*), 2.58–2.51 (m, 2H, CH_2), 2.32–2.24 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 138.4, 129.4, 128.7, 128.2, 61.9, 54.1, 31.7; Unable to obtain low or high resolution mass spectrometry data for malonoyl peroxides using in-house or Swansea National Mass Spectrometry Service; $[\alpha]_D^{25} = -107.2$ (c. 1.0, $CHCl_3$).

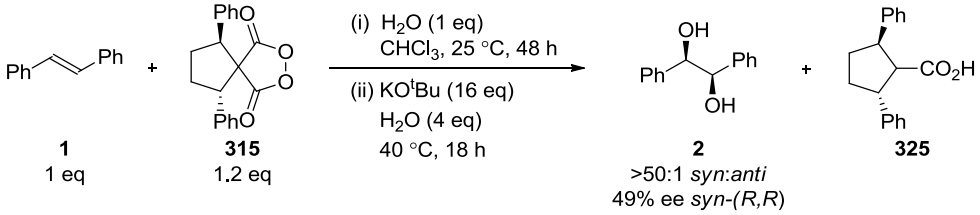
(2*S*,5*S*)-2,5-Diphenylcyclopentane-1,1-malonoyl peroxide 315



Diacid chloride **322** (200 mg, 0.58 mmol, 1 eq) was dissolved in THF (2 mL) in a medium glass vial. Water (660 μL) and sodium percarbonate (180 mg, 1.15 mmol, 2 eq) were added and the reaction mixture stirred at room temperature for 2 h. Water (5 mL) and diethyl ether (10 mL) were added and the phases separated. The aqueous phase was extracted using diethyl ether (3 × 5 mL) then the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and solvent removed by rotary evaporation to leave a colourless oil. Purification by silica gel column chromatography (1:20 ethyl acetate:petroleum ether) afforded the title compound as a colourless solid (54 mg, 0.17 mmol, 30%).

Colourless solid; m.p. 110 °C (gradual decomp.); IR (ATR)/cm^{-1}: 3063, 3030, 2970, 2936, 2876, 1792, 1765, 1495, 1449, 1229, 1074, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 10H, Ph*H*), 4.12–4.04 (m, 2H, PhC*H*), 2.62–2.54 (m, 2H, CH_2), 2.49–2.39 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 135.6, 129.1, 128.7, 128.1, 58.8, 57.5, 31.3; Unsuitable to obtain mass spectrometric data; $[\alpha]_D^{25}$ = – 126.6 (c. 1.0, $CHCl_3$).

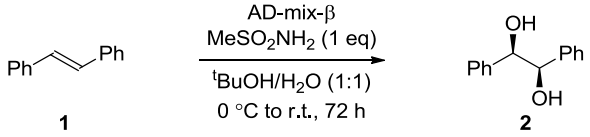
Asymmetric dihydroxylation of *trans*-stilbene 1 to (1*R*,2*R*)-1,2-bisphenylethane-1,2-diol 2 using chiral peroxide 315



Trans-stilbene **1** (15 mg, 0.084 mmol, 1 eq) was added in one portion to a small sample vial containing a solution of peroxide **315** (31 mg, 0.10 mmol, 1.2 eq), H_2O (1.5 μL, 1.26 mmol, 1 eq) and chloroform (120 μL). The reaction mixture was stirred at 25 °C for 48 h before the solvent was removed *in vacuo* and the residue dissolved in diethyl ether (2.5 mL). Potassium *tert*-butoxide (180 mg, 1.61 mmol, 16 eq) and water (8 μL, 0.44 mmol, 4 eq) were added and the resulting slurry stirred at 40 °C overnight. Water (3 mL) was added and the phases separated before the aqueous layer was extracted further using diethyl ether (1 × 3 mL). The combined organic layers were washed with brine (1 × 5 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation to afford diol **2**. ^{1}H NMR analysis of the crude reaction mixture confirmed the presence of a single (*syn*-) diastereoisomer of diol **2**. HPLC analysis of the crude reaction mixture indicated 49% ee in favour the (*R*,*R*)-enantiomer (see Appendix 9.4). The absolute stereochemistry was confirmed by synthesis of (*R*,*R*)-**2** by Sharpless dihydroxylation of *trans*-stilbene **1** using commercially available AD-mix-β (see Experimental 8.21). The corresponding acid by-product **325** was recovered by acidifying the aqueous phase to pH 1 by dropwise addition of concentrated HCl at 0–5 ^{o}C. Extraction with ethyl acetate (2 × 3 mL), washing with brine (1 × 3 mL) and drying over $MgSO_4$ then removal of solvent by rotary evaporation afforded impure carboxylic acid **325**.

For analytical data of racemic diol **2** (**66**) see Experimental 8.4.1. Conditions for HPLC analysis: IC Column, injection volume: 2.0 μL, wavelength: 220 nm, solvent: isopropanol/hexane (8:92), flow rate: 0.4 mL/min, T = 25 ^{o}C, and retention times: 35.5 mins for (*S*,*S*)-**2** and 36.6 mins for (*R*,*R*)-**2**.

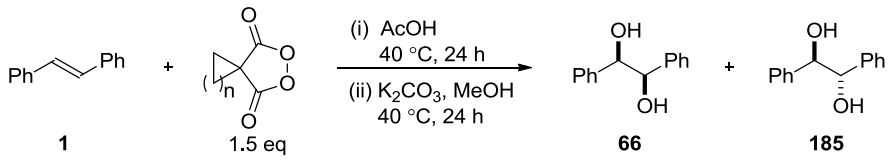
8.21 Sharpless Asymmetric Dihydroxylation of *Trans*-Stilbene 1[157]



AD-mix-β (50 g) was added to a mixture of *tert*-butanol (178 mL) and water (178 mL) and stirred until homogeneity was achieved. Methanesulfonamide (3.50 g, 36.8 mmol, 1 eq) was added and the resulting mixture cooled to 0 ^{o}C using an ice bath. *Trans*-stilbene **1** (6.63 g, 36.8 mmol, 1 eq) was added and the reaction mixture stirred at 0–5 ^{o}C for 7 h before allowing the ice bath to slowly melt, then stirring continued for a further 65 h at room temperature. The reaction mixture was cooled to 0 ^{o}C and sodium metabisulfite (50 g) was added portionwise over 15 mins and the resulting mixture stirred for 1 hour. Ethyl acetate (150 mL) was added and the phases separated before the aqueous phase was extracted further using ethyl acetate (3 × 75 mL). The combined organic phases were washed with 2 M KOH solution, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give crude diol **2** as an off-white solid. Purification by silica gel column chromatography (3:7 ethyl acetate:petroleum ether) and recrystallization from ethanol afforded (*R*,*R*)-1,2-diphenyl-1,2-diol **2** as colourless needles (98% ee (*R*,*R*), 5.95 g, 27.8 mmol, 76%).

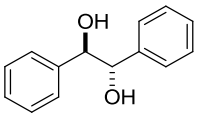
See analytical data for racemic 1,2-bisphenylethane-1,2-diol **2** (**66**). Conditions for HPLC analysis: IC Column, injection volume: 2.0 µL, wavelength: 220 nm, solvent: isopropanol/hexane (8:92), flow rate: 0.4 mL/min, T = 25 ^{o}C, and retention times: 32.6 mins for (*S*,*S*)-**2** and 33.6 mins for (*R*,*R*)-**2**.

8.22 General Procedure E: *Anti*-Dihydroxylation of Alkenes



Malonoyl peroxide (3.63 mmol, 1.5 eq) was dissolved in reagent grade acetic acid (5 mL) and the resulting solution dried over activated 3 Å molecular sieves (250 mg) under inert nitrogen atmosphere for 2 h. The dry peroxide-acetic acid solution was transferred *via* syringe to a dry round-bottom flask containing alkene (2.42 mmol, 1 eq) and the resulting mixture stirred for 24 h at 40 ^{o}C sealed under a nitrogen atmosphere. Acetic acid was removed by rotary evaporation at 50 ^{o}C, and the residue dissolved in methanol (20 mL). K_2CO_3 (1.00 g, 7.25 mmol, 3 eq) was added and the resulting mixture stirred for 24 h at 40 ^{o}C. After cooling to room temperature, methanol was removed under reduced pressure and water (15 mL) and ethyl acetate (10 mL) were added to the residue. The phases were separated and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and solvent removed by rotary evaporation to afford *anti*-diol **185** as a mixture of diastereoisomers.

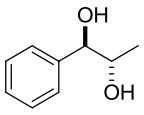
rel-(1*R*,2*R*)-1,2-Bisphenylethane-1,2-diol 185[20]



Reaction of (*E*)-stilbene **1** (436 mg, 2.42 mmol), and cyclopropyl malonoyl peroxide **86** (465 mg, 3.63 mmol) in acetic acid (5 mL) according to General Procedure **E** for 24 h at 40 ºC gave diol **185** as a 4.5:1 *anti*:*syn* mixture of diastereoisomers (394 mg, 1.84 mmol, 76%).

For analytical data of diol **185** see Experimental 8.4.1.

***rel*-(1*R*,2*S*)-1-Phenylpropane-1,2-diol 77**



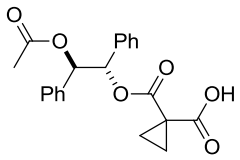
Reaction of β-methylstyrene **75** (286 mg, 2.42 mmol), and cyclopropyl malonoyl peroxide **86** (465 mg, 3.63 mmol) in acetic acid (5 mL) according to General Procedure **E** for 24 h at 40 ºC gave diol **77** as a 5:1 *anti*:*syn* mixture of diastereoisomers (265 mg, 1.74 mmol, 72%).

For analytical data of diol **77** see Experimental 8.4.1.

8.23 Preparation of *Anti*-Dihydroxylation Intermediates

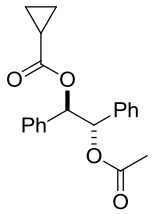
Cyclopropyl malonoyl peroxide **86** (2.71 g, 21.2 mmol, 1.5 eq) was dissolved in acetic acid (28 mL) and dried over activated 3 Å molecular sieves under nitrogen for 2 h. The anhydrous peroxide-acetic acid solution was added to *trans*-stilbene **1** (2.54 g, 14.1 mmol, 1 eq) or β-methylstyrene **75** (1.66 g, 14.1 mmol, 1 eq) in a dry 100 mL round-bottom flask and stirred at 40 ^{o}C for 24 h under nitrogen. Excess acetic acid was removed by rotary evaporation at 50 ^{o}C and compounds **341**, **342** and **94** (when *trans*-stilbene **1** was used) or **355**, **356** and **357** (when β-methylstyrene **75** was used) were isolated by silica gel column chromatography using a solvent gradient (1:4 to 1:1 to 1:0 diethyl ether:petroleum ether). Further purification by vapour diffusion crystallisation (chloroform:petroleum ether b.p. (30–40 ^{o}C)) was performed to achieve each compound as a single diastereoisomer if necessary.

1-((*rel*-(1*S*,2*R*)-2-Acetoxy-1,2-diphenylethoxy)carbonyl)cyclopropanecarboxylic acid 341



Colourless solid; m.p. 129–130 °C; IR (ATR)/cm^{-1}: 3117, 3036, 2788, 1740, 1721, 1661, 1157, 1132, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.34 (bs, 1H, CO_2H), 7.35–7.31 (m, 6H, Ph*H*), 7.18–7.13 (m, 4H, Ph*H*), 6.09 (d, *J* = 6.2 Hz, 1H, PhC*H*OC(=O)C $(CH_2)_2CO_2H$), 6.06 (d, *J* = 6.2 Hz, 1H, PhC*H*OC(=O)CH_3), 2.01 (s, 3H, CH_3), 1.84–1.68 (m, 3H, CH_2), 1.58–1.53 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 170.1, 169.5, 135.3, 134.9, 129.3, 129.1, 128.63, 128.55, 127.6, 127.3, 78.8, 76.2, 25.3, 22.4, 22.3, 21.0; LRMS (ESI) *m/z* 391.2 $[M + Na]^+$; HRMS (NSI) calculated for $C_{21}H_{20}O_6Na$ $[M + Na]^+$ 391.1152, found 391.1150.

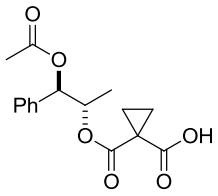
***rel*-(1*R*,2*S*)-2-Acetoxy-1,2-diphenylethyl cyclopropanecarboxylate 342**



Colourless solid; m.p. 113–114 °C; IR (ATR)/cm^{-1}: 3067, 2988, 2970, 2905, 1736, 1715, 1072, 1033; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.27 (m, 6H, Ph*H*), 7.20–7.19 (m, 4H, Ph*H*), 6.10 (d, *J* = 5.8 Hz, 1H, PhC*H*OC(=O)$CH(CH_2)_2$), 6.08 (d, *J* = 5.8 Hz, 1H, PhC*H*OC(=O)CH_3), 2.02 (s, 3H, CH_3), 1.63–1.57 (m, 1H, CH_2CHCH_2), 0.96–0.87 (m, 2H, CH_2), 0.85–0.77 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 169.7, 136.4, 136.2, 128.44, 128.40, 128.2, 128.1, 127.8, 127.6, 76.8, 76.4, 21.0, 13.2, 8.6, 8.5;

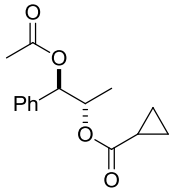
LRMS (ESI) *m/z* 347.1 $[M + Na]^+$; HRMS (NTS) calculated for $C_{20}H_{24}NO_4$ $[M + NH_4]^+$ 342.1700, found 342.1701.

1-(((*rel*-(1*R*,2*S*)-1-Acetoxy-1-phenylpropan-2-yl)oxy)carbonyl)cyclopropane carboxylic acid 355



Colourless semi-solid; IR (ATR)/cm^{-1}: 3030, 2990, 2945, 1736, 1730, 1672, 1230, 1159, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H, Ph*H*), 5.88 (d, *J* = 4.6 Hz, 1H, PhC*H*OR), 5.26 (qd, *J* = 6.5, 4.6 Hz, 1H, CH_3C*H*OR), 2.11 (s, 3H, C*H*$_3$CO$_2$R), 1.78–1.68 (m, 2H, C*H*$_2$), 1.63–1.58 (m, 1H, C*H*$_2$), 1.53–1.48 (m, 1H, C*H*$_2$), 1.21 (d, *J* = 6.5 Hz, 3H, C*H*$_3$CHOR); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 170.6, 169.6, 135.7, 128.64, 128.56, 126.9, 75.6, 74.4, 25.3, 22.0, 21.6, 20.9, 14.7; LRMS (EI) *m/z* 329.1 $[M + Na]^+$; HRMS (NSI) calculated for $C_{16}H_{18}O_6Na$ $[M + Na]^+$ 329.0996, found 329.0996.

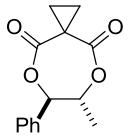
***rel*-(1*R*,2*S*)-1-Acetoxy-1-phenylpropan-2-yl cyclopropanecarboxylate 356**



Colourless oil; IR (ATR)/cm^{-1}: 3029, 2990, 2945, 1742, 1726, 1231, 1170; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5H, Ph*H*), 5.90 (d, *J* = 4.4 Hz, 1H, PhC*H*OR), 5.22 (qd, *J* = 6.5, 4.4 Hz, 1H, CH_3C*H*OR), 2.13 (s, 3H, C*H*$_3$CO$_2$R), 1.58–1.52 (m, 1H,

CH_2CHCH_2), 1.18 (d, *J* = 6.5 Hz, CH_3CHOR), 0.95–0.90 (m, 2H, CH_2), 0.84–0.80 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 169.9, 136.8, 128.4, 128.3, 127.2, 76.4, 71.6, 21.1, 14.9, 13.1, 8.5, 8.4; LRMS (EI) *m/z* 285.1 $[M + Na]^+$; HRMS (NSI) calculated for $C_{15}H_{18}O_4Na$ $[M + Na]^+$ 285.1097, found 285.1098.

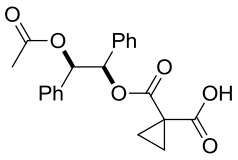
rel-(6*R*,7*R*)-6-Methyl-7-phenyl-5,8-dioxaspiro[2.6]nonane-4,9-dione 357



Colourless oil; IR (ATR)/cm^{-1}: 3034, 2997, 2940, 1713, 1296, 1182; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.39 (m, 3H, Ph*H*), 7.35–7.32 (m, 2H, Ph*H*), 5.46 (d, *J* = 8.6 Hz, 1H, PhC*H*OR), 5.04 (dq, *J* = 8.6, 6.5 Hz, 1H, CH_3CHOR), 2.06–1.98 (m, 2H, CH_2), 1.82–1.71 (m, 1H, CH_2), 1.18 (d, *J* = 6.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.3, 135.5, 129.8, 129.2, 127.3, 85.4, 78.6, 28.9, 23.7, 23.3, 18.7; HRMS (APCI) calculated for $C_{14}H_{15}O_4$ $[M + H]^+$ 247.0965, found 247.0961.

8.24 Independent Synthesis of 344

1-((_rel_-(1*R*,2*R*)-2-Acetoxy-1,2-diphenylethoxy)carbonyl)cyclopropanecarboxylic acid 344



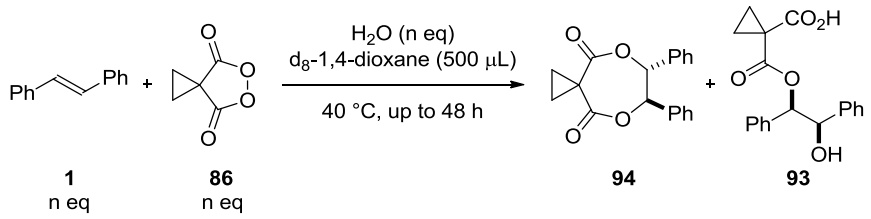
Syn-dihydroxylation reaction intermediate **93** (50 mg, 0.154 mmol, 1 eq) was dissolved in dichloromethane (0.75 mL) and cooled to 0–5 °C using an ice bath. Pyridine (24 µL,

0.307 mmol, 2 eq) was added in one portion followed by dropwise addition of acetic anhydride (29 µL, 0.307 mmol, 2 eq). The reaction mixture was stirred at 0–5 °C for 30 mins then the ice-bath was removed and stirring continued for 18 h. Methanol (1 mL) was added and stirring maintained for 1 hour before volatiles were removed by rotary evaporation. Purification by silica gel column chromatography (1:1 diethyl ether:petroleum ether) followed by vapour diffusion recrystallisation (chloroform:petroleum ether (b.p. 30–40 °C)) afforded the target compound as a colourless solid (45 mg, 0.123 mmol, 80%).

Colourless solid; m.p. 110–111 °C; IR (ATR)/cm^{-1}: 3067, 3034, 1746, 1730, 1678, 1227, 1152, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.45 (bs, 1H, COO*H*), 7.28–7.21 (m, 6H, Ph*H*), 7.11–7.06 (m, 4H, Ph*H*), 6.09 (d, *J* = 8.3 Hz, 1H, PhC*H*OC(=O)C$(CH_2)_2CO_2H$), 6.05 (d, *J* = 8.3 Hz, 1H, PhC*H*OC(=O)CH_3), 2.11 (s, 3H, CH_3), 1.90–1.78 (m, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 170.2, 169.8, 135.3, 134.7, 129.3, 129.0, 128.8, 128.6, 127.5, 127.4, 79.8, 76.6, 25.3, 22.5, 22.3, 21.1; LRMS (ESI) *m/z* 391.0 $[M + Na]^+$; HRMS (NSI) found 391.1152.

8.25 Reaction Kinetics

8.25.1 General Procedure F: Homogeneous Reaction Conditions



1 n eq **86** n eq **94** **93**

Trans-stilbene **1** (n eq) was dissolved in d_8-1,4-dioxane (500 µL) in a small sample vial. Water (n eq) then cyclopropyl malonoyl peroxide **86** (n eq) were added and the reaction mixture rapidly transferred to an NMR tube which was submerged in a preheated oil-bath at 40 °C. At known time intervals, the NMR tube was removed from the oil bath

and subjected to ^{1}H NMR analysis, before being returned to the oil bath. Integration of the ^{1}H NMR spectra at each time interval allowed a ratio of starting material (**1** *or* **86**) to products (**94** + **93**) to be measured, which was used to determine conversion and therefore concentration based on known starting concentrations of reagents.

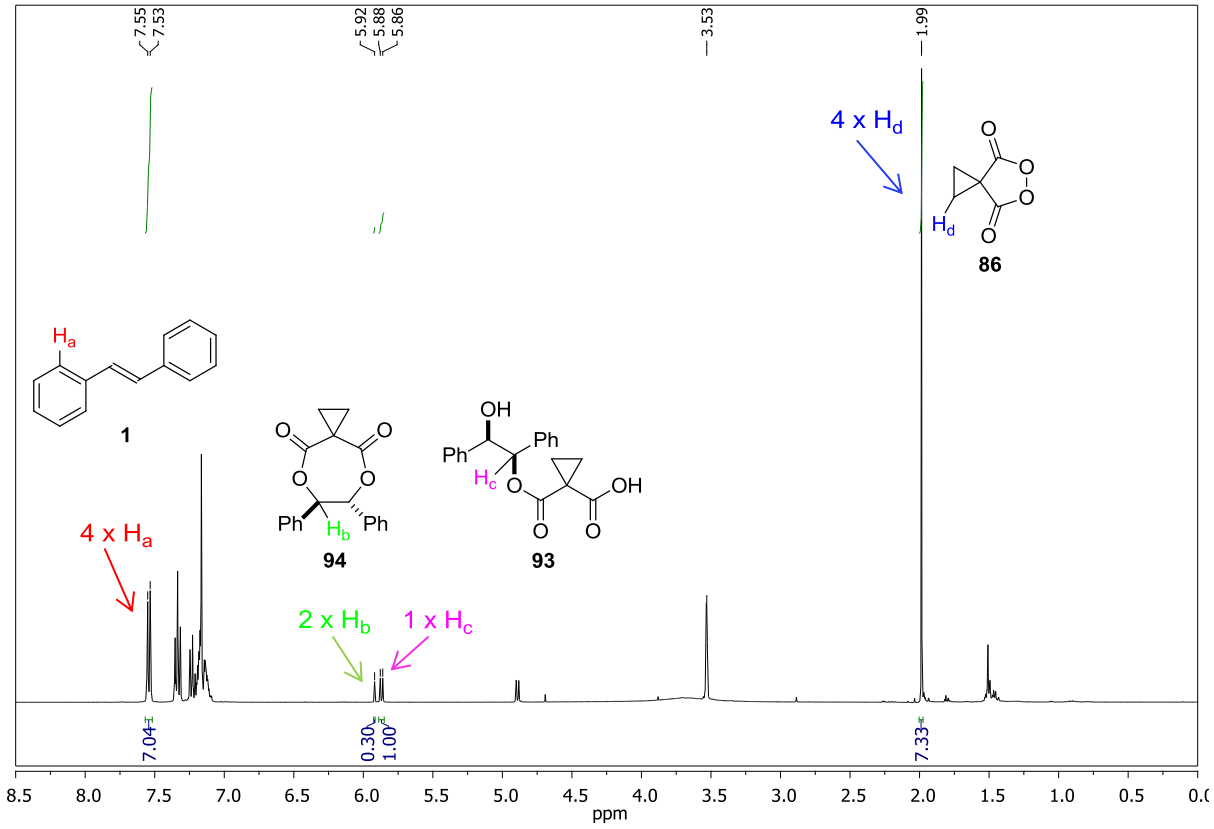


Figure 8.1 An example ^{1}H NMR spectrum of the dihydroxylation reaction at t = 4 h showing the signals used to determine reaction conversion.

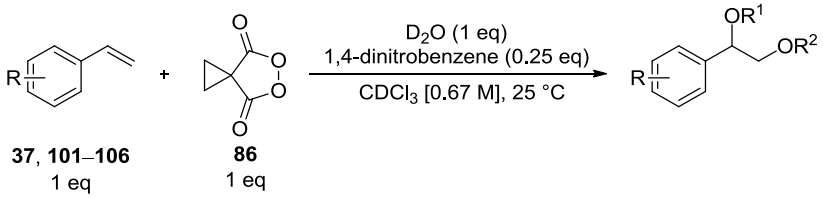
To obtain the reaction profile (Figure 2.3): *Trans*-stilbene **1** (45.0 mg, 0.25 mmol, 1 eq), cyclopropyl malonoyl peroxide **86** (32.0 mg, 0.25 mmol, 1 eq) and water (4.5 µL, 0.25 mmol, 1 eq) were treated in d_8-1,4-dioxane (500 µL) at 40 ^{o}C for 48 h according to General Procedure **F**.

To determine the kinetic order in *trans*-stilbene **1** (Figure 2.4): *Trans*-stilbene **1** (22.5 mg, 0.125 mmol, 1 eq), cyclopropyl malonoyl peroxide **86** (32.0 mg, 0.25 mmol, 2 eq) and water (4.5 µL, 0.25 mmol, 2 eq) were treated in d_8-1,4-dioxane (500 µL) at 40 ^{o}C for 24 h according to General Procedure **F**.

To determine the kinetic order in cyclopropyl malonoyl peroxide **86** (Figure 2.5): *Trans*-stilbene **1** (45.0 mg, 0.25 mmol, 2 eq), cyclopropyl malonoyl peroxide **86** (16.0 mg, 0.125 mmol, 1 eq) and water (4.5 µL, 0.25 mmol, 2 eq) were treated in d_8-1,4-dioxane (500 µL) at 40 ^oC for 24 h according to General Procedure **F**.

To examine the effect of water equivalents on rate (Figure 4.2): *Trans*-stilbene **1** (45 mg, 0.25 mmol, 1 eq), cyclopropyl malonoyl peroxide **86** (64 mg, 0.5 mmol, 2 eq) and water (1, 2, 5 or 10 eq) were treated in d_8-1,4-dioxane (650 µL) at 40 ^oC for 48 h according to General Procedure **F**.

8.25.2 Hammett Analysis



Cyclopropyl malonoyl peroxide **86** (0.341 g, 2.67 mmol, 1 eq) and 1,4-dinitrobenzene **373** (0.112 g, 0.668 mmol, 0.25 eq) were dissolved in $CDCl_3$ (4 mL) at 25 ^oC in a 10 mL round-bottom flask with stirring. 40 µL of the solution was removed and added to an NMR tube containing $CDCl_3$ (500 µL) and the exact ratio of internal standard (1,4-dinitrobenzene **373**) to cyclopropyl malonoyl peroxide **86** determined by integration of the ^1H NMR spectra. D_2O (48 µL, 2.67 mmol, 1 eq) and alkene (2.67 mmol, 1 eq) were added to the reaction vessel and timing commenced immediately. Samples were removed for ^1H NMR analysis (as above; 40 µL of reaction mixture added to 500 µL $CDCl_3$ in NMR tube) at known time intervals.

The rate of reaction was monitored by consumption of cyclopropyl malonoyl peroxide **86** relative to the internal standard (1,4-dinitrobenzene **373**) by integration of the corresponding ^1H NMR signals:

Cyclopropyl malonoyl peroxide **86**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 4H, C*H*$_2$)
1,4-Dinitrobenzene **373**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 4H, Ar*H*)

Below are two example ^1H NMR spectra using styrene as the substrate at time, t = 0 h (i.e. before addition of H_2O and alkene) and at t = 2 h.

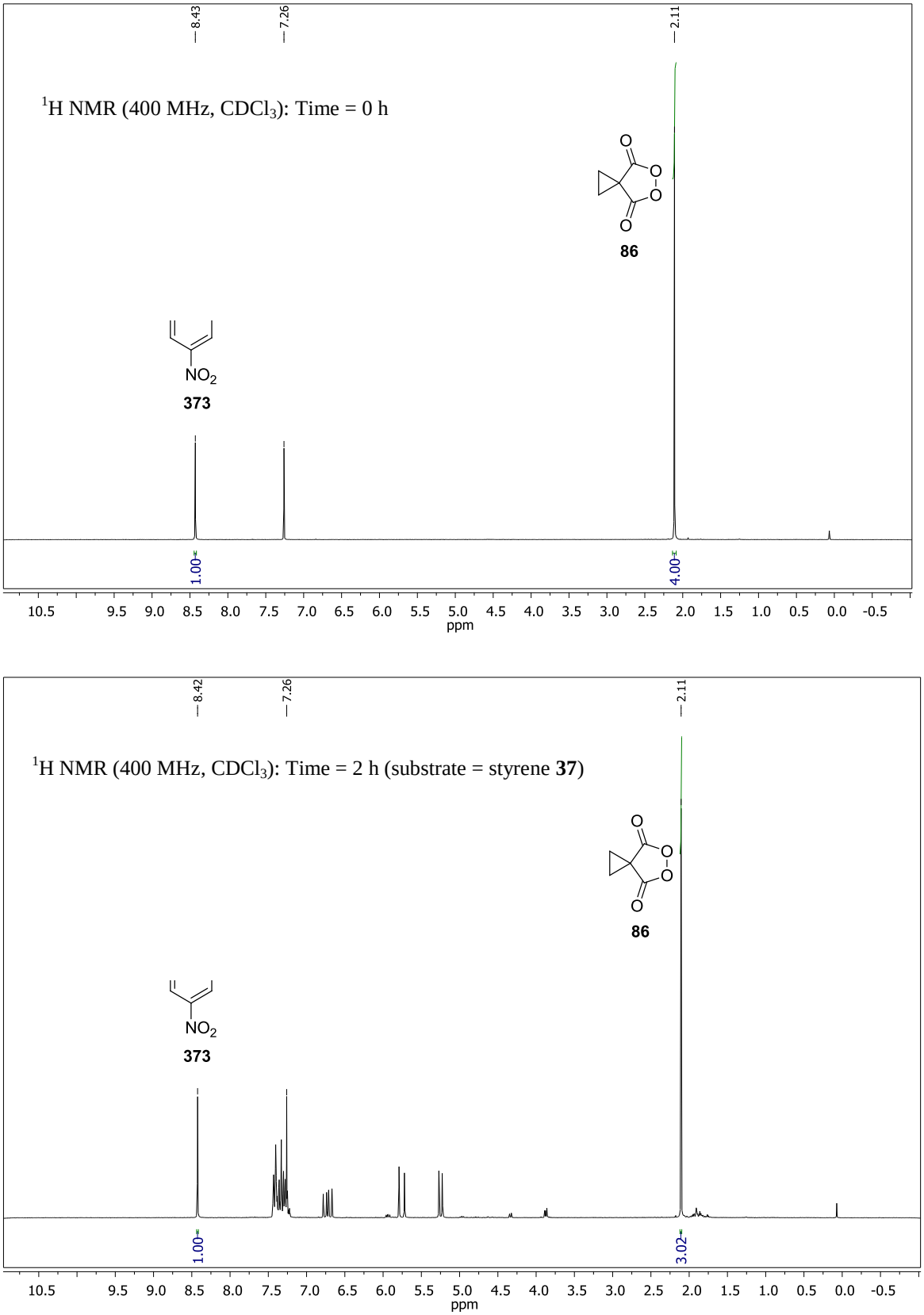


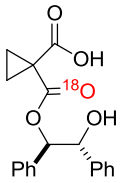
Figure 8.2 Example ^{1}H NMR spectra following the consumption of peroxide **86** relative to an internal standard **373** during the dihydroxylation of styrene **37**.

Time (h)	Integral 373	Integral 86	86 (% Remaining)	86 (% Consumption)
0	1	4	100.0	0.0
0.25	1	3.76	94.0	6.0
0.5	1	3.59	89.8	10.3
0.75	1	3.48	87.0	13.0
1	1	3.38	84.5	15.5
1.25	1	3.26	81.5	18.5
1.5	1	3.18	79.5	20.5
1.75	1	3.07	76.8	23.3
2	1	3.02	75.5	24.5
2.5	1	2.84	71.0	29.0
3	1	2.67	66.8	33.3
3.5	1	2.55	63.8	36.3
4	1	2.39	59.8	40.3
5	1	2.11	52.8	47.3
6	1	1.87	46.8	53.3
7	1	1.66	41.5	58.5
8	1	1.49	37.3	62.8
23	1	0.34	8.5	91.5

Table 8.1 ^{1}H NMR integration data for the consumption of peroxide **86** relative to an internal standard **373** in the dihydroxylation of styrene **37**. The data from the two example spectra shown in Figure 8.2 are highlighted (t = 0 and t = 2 h).

The conversion *versus* time data plotted in Figure 2.8 is an average of two runs for alkenes **37**, **101**–**106** using the method described above.

8.26 ^{18}O-Induced ^{13}C NMR Shift Experiment



(*E*)-Stilbene **1** (360 mg, 2.00 mmol, 1 eq), H_2O (36 µL, 2.00 mmol, 1 eq) and cyclopropyl malonoyl peroxide **86** (307 mg, 2.00 mmol, 1.2 eq) were stirred in anhydrous $CHCl_3$ (3 mL) according to General Procedure **C** for 24 h at 40 ºC, but the hydrolysis step using 1 M NaOH was not performed. Solvent was removed *in vacuo* and compound **93** isolated by silica gel flash chromatography (1:1 diethyl ether:petroleum ether, R_f 0.12). Two recrystallisations by vapour diffusion crystallisation (chloroform:petroleum ether (b.p. 30–40 ºC)) gave pure **93** as colourless needles. H_2O was replaced with $^{18}OH_2$ (97% ^{18}O, 36 µL, 2 mmol, 1 eq) and the procedure repeated to afford ^{18}O-labelled **131**.

Carbon #	**^{16}O-93** (δ ppm)	**^{16}O-93 corrected to $CDCl_3$** (δ ppm)	**^{18}O-131** (δ ppm)	**^{18}O-131 corrected to $CDCl_3$** (δ ppm)	Δδ ppm	Δδ ppb
$CDCl_3$	*77.16033*	*77.16000*	*77.15953*	*77.16000*	*N/A*	*N/A*
11	**174.62628**	**174.62595**	**174.58778**	**174.58825**	**0.0385**	**38.5**
15	**171.00381**	**171.00348**	**171.00800**	**171.00847**	**-0.00419**	**-4.19**
7	138.76712	138.76679	138.76622	138.76669	0.0009	0.9
4	135.55464	135.55431	135.55453	135.55500	0.00011	0.11
1/10	128.96355	128.96322	128.96100	128.96147	0.00255	2.55
2/9	128.64206	128.64173	128.63983	128.64030	0.00223	2.23
1/10	128.58778	128.58745	128.58464	128.58511	0.00314	3.14
2/9	128.52710	128.52677	128.52433	128.52480	0.00277	2.77
3	127.21489	127.21456	127.21382	127.21429	0.00107	1.07
8	126.92214	126.92181	126.92115	126.92162	0.00099	0.99
5	81.91898	81.91865	81.91493	81.91540	0.00405	4.05
6	76.72570	76.72537	76.72165	76.72212	0.00405	4.05
12	25.66526	25.66493	25.65508	25.65555	0.01018	10.18
13/14	22.22142	22.22109	22.21777	22.21824	0.00365	3.65
13/14	21.85441	21.85408	21.85163	21.85210	0.00278	2.78

Table 8.2 ^{13}C NMR chemical shift values for each carbon atom of ^{18}O-labelled **131** and unlabelled **93**.

[0.10 M] solutions of both unlabelled-**93** and ^{18}O-labelled **131** in $CDCl_3$ were prepared and 0.60 mL of each solution was added to separate NMR tubes. ^{13}C NMR data was obtained using a Bruker Avance II 600 MHz spectrometer and the chemical shift values (ppm) were reported to 5 decimal places. The spectra were corrected to $CDCl_3$, $\delta = 77.16000$ (see Table 8.2). The difference in δ values for each carbon were calculated and reported in ppb.

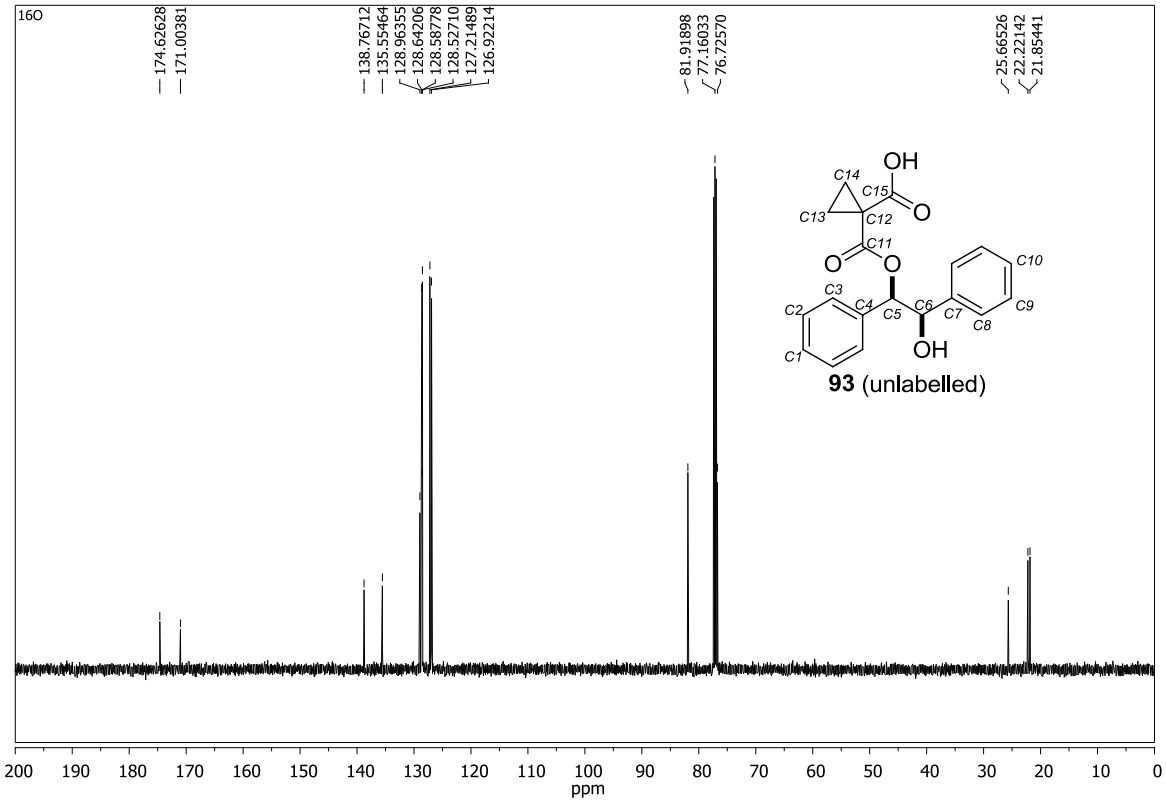


Figure 8.3 ^{13}C NMR spectra of unlabelled **93**.

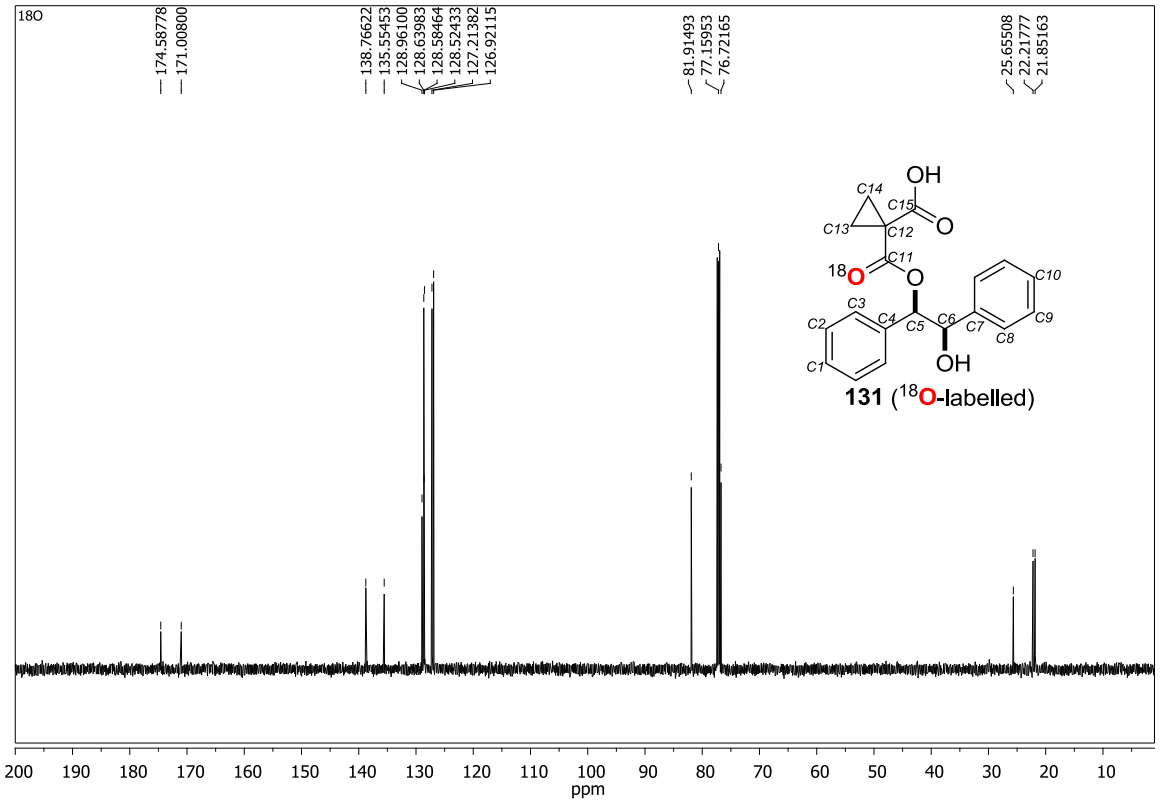


Figure 8.4 ^{13}C NMR spectra of ^{18}O-labelled **131**.

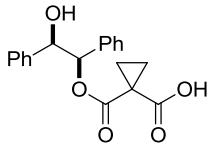
Appendix

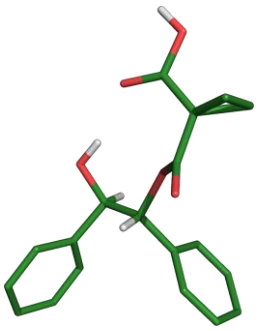
9 Appendix

9.1 X-Ray Crystallographic Data

1-(((*rel*-1*R*,2*R*)-2-Hydroxy-1,2-diphenylethoxy)carbonyl) cyclopropane carboxylic acid 93

Available from Cambridge Crystallographic Data Centre as supplementary publication number **CCDC 936076**.

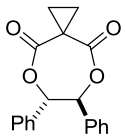


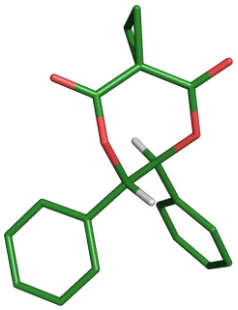


Empirical formula	$C_{19}H_{18}O_5$
M_r (g mol^{-1})	326.33
Crystal system	Monoclinic
Space group	P 2_1/c
a/ Å	10.7552(7)
b/ Å	10.1502(7)
c/ Å	14.9906(8)
β (º)	93.447(5)
V/Å^3	1633.52(18)
Z	4
Temp K	153(2)
2θmax	55
λ/ Å	0.71073
Measured reflections	13349
Unique reflections	3678
R_{int}	0.0492
Observed rflns [$I > 2\sigma(I)$]	2463
μ (mm^{-1})	0.096
No. of parameters	225
R [on *F*, obs rflns only]	0.0471
wR [on F^2, all data]	0.1191
GoF	1.028
Largest diff. peak/hole/e Å^{-3}	0.224/-0.262

rel-(6_R_,7_R_)-6,7-Diphenyl-5,8-dioxaspiro[2.6]nonane-4,9-dione 94

Available from Cambridge Crystallographic Data Centre as supplementary publication number **CCDC 936075**.

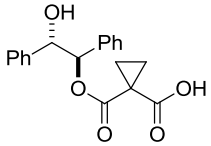


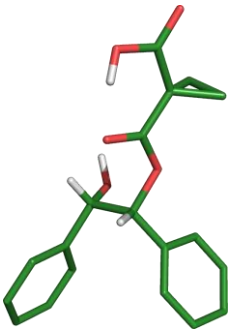


Empirical formula	$C_{19}H_{16}O_4$
M_r (g mol^{-1})	308.32
Crystal system	Monoclinic
Space group	P 2_1/n
a/ Å	9.5528(6)
b/ Å	10.1091(5)
c/ Å	16.1660(9)
β (º)	104.844(5)
V/Å^3	1509.05(15)
Z	4
Temp K	123(2)
2θmax	54
λ/ Å	0.71073
Measured reflections	7058
Unique reflections	3293
R_{int}	0.0348
Observed rflns [$I > 2\sigma(I)$]	2293
μ (mm^{-1})	0.095
No. of parameters	208
R [on *F*, obs rflns only]	0.0515
wR [on F^2, all data]	0.1023
GoF	1.037
Largest diff. peak/hole/e Å^{-3}	0.233/-0.233

1-(((*rel*-1*S*,2*R*)-2-Hydroxy-1,2-diphenylethoxy)carbonyl)cyclopropanecarboxylic acid 96

Available from Cambridge Crystallographic Data Centre as supplementary publication number **CCDC 936077**.

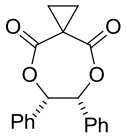


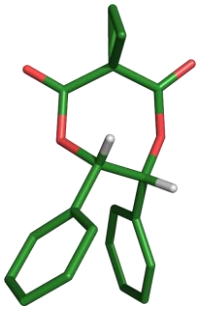


Empirical formula	$C_{19}H_{18}O_5$
M_r (g mol^{-1})	326.33
Crystal system	Orthorhombic
Space group	P $2_12_12_1$
a/ Å	5.6981(7)
b/ Å	8.6185(7)
c/ Å	32.841(7)
β (º)	
V/Å^3	1612.6(4)
Z	4
Temp K	123(2)
2θmax	146.4
λ/ Å	1.5418
Measured reflections	3829
Unique reflections	2650
R_{int}	0.0360
Observed rflns [$I > 2\sigma(I)$]	2185
μ (mm^{-1})	0.804
No. of parameters	223
R [on *F*, obs rflns only]	0.0626
wR [on F^2, all data]	0.1667
GoF	1.063
Largest diff. peak/hole/e Å^{-3}	0.318/-0.232

rel-(6*R*,7*S*)-6,7-Diphenyl-5,8-dioxaspiro[2.6]nonane-4,9-dione 97

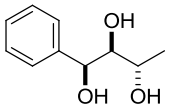
Available from Cambridge Crystallographic Data Centre as supplementary publication number **CCDC 936074**.

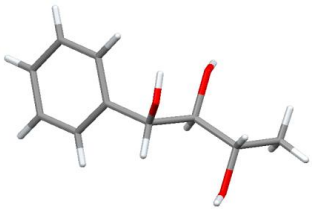




Empirical formula	$C_{19}H_{16}O_4$
M_r (g mol^{-1})	308.32
Crystal system	Monoclinic
Space group	P 2_1/c
a/ Å	13.4714(4)
b/ Å	5.8443(2)
c/ Å	19.1637(6)
β (º)	103.276(3)
V/Å^3	1468.45(8)
Z	4
Temp K	123(2)
2θmax	146.2
λ/ Å	1.5418
Measured reflections	6142
Unique reflections	2878
R_{int}	0.0213
Observed rflns [$I > 2\sigma(I)$]	2434
μ (mm^{-1})	0.799
No. of parameters	208
R [on *F*, obs rflns only]	0.0406
wR [on F^2, all data]	0.1103
GoF	1.036
Largest diff. peak/hole/e Å^{-3}	0.302/-0.227

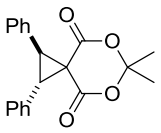
rel-(1*S*,2*S*,3*S*)-1-Phenylbutane-1,2,3-triol 235

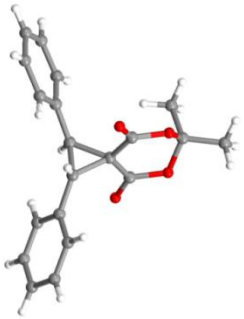




Empirical formula	$C_{10}H_{14}O_3$
Formula weight	182.21
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 11.0190(3) Å
	b = 9.0462(2) Å
	c = 19.1362(6) Å
	α= 90°, β= 96.058(2)°, γ = 90°.
Volume	1896.85(9) $Å^3$
Z	8
Density (calculated)	1.276 Mg/m^3
Absorption coefficient	0.093 mm^{-1}
F(000)	784
Crystal size	0.35 x 0.07 x 0.05 mm^3
Theta range for data collection	3.04 to 28.00°.
Index ranges	-14<=h<=14, -11<=k<=11, -25<=l<=24
Reflections collected	13336
Independent reflections	4480 [R(int) = 0.0298]
Completeness to theta = 27.00°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.80007
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4480 / 0 / 261
Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0469, wR2 = 0.1006
R indices (all data)	R1 = 0.0741, wR2 = 0.1125
Largest diff. peak and hole	0.355 and -0.252 e.$Å^{-3}$

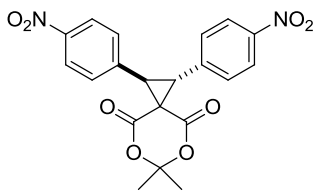
rel-(1*S*,2*S*)-6,6-Dimethyl-1,2-diphenyl-5,7-dioxaspiro[2.5]octane-4,8-dione 297

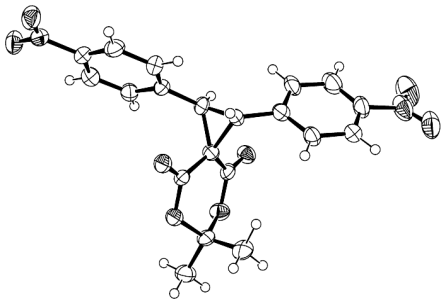




Empirical formula	$C_{20}H_{18}O_4$	
Formula weight	322.34	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.7558(2) Å	α= 82.477(3)°.
	b = 9.5124(5) Å	β= 84.242(3)°.
	c = 15.4036(11) Å	γ = 79.058(3)°.
Volume	818.44(8) $Å^3$	
Z	2	
Density (calculated)	1.308 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	340	
Crystal size	0.50 x 0.10 x 0.10 mm^3	
Theta range for data collection	2.44 to 27.85°.	
Index ranges	-7<=h<=7, -12<=k<=12, -20<=l<=19	
Reflections collected	5661	
Independent reflections	3848 [R(int) = 0.0465]	
Completeness to theta = 27.85°	98.5 %	
Max. and min. transmission	0.9910 and 0.9560	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3848 / 0 / 220	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0625, wR2 = 0.1513	
R indices (all data)	R1 = 0.0925, wR2 = 0.1735	
Extinction coefficient	0.130(12)	
Largest diff. peak and hole	0.315 and -0.421 $e.Å^{-3}$	

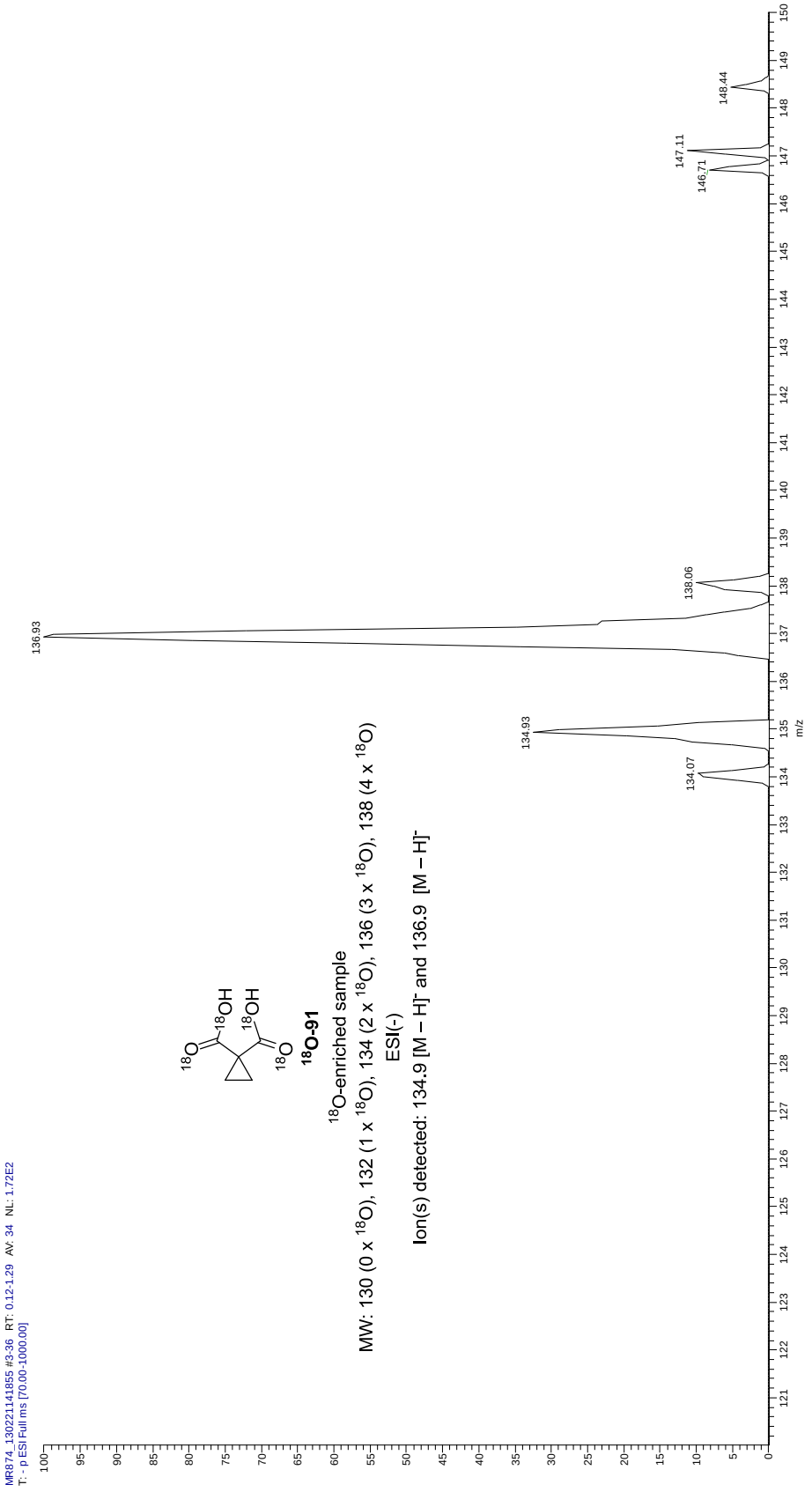
rel-(1*S*,2*S*)-6,6-Dimethyl-1,2-bis(4-nitrophenyl)-5,7-dioxaspiro[2.5]octane-4,8-dione **313**

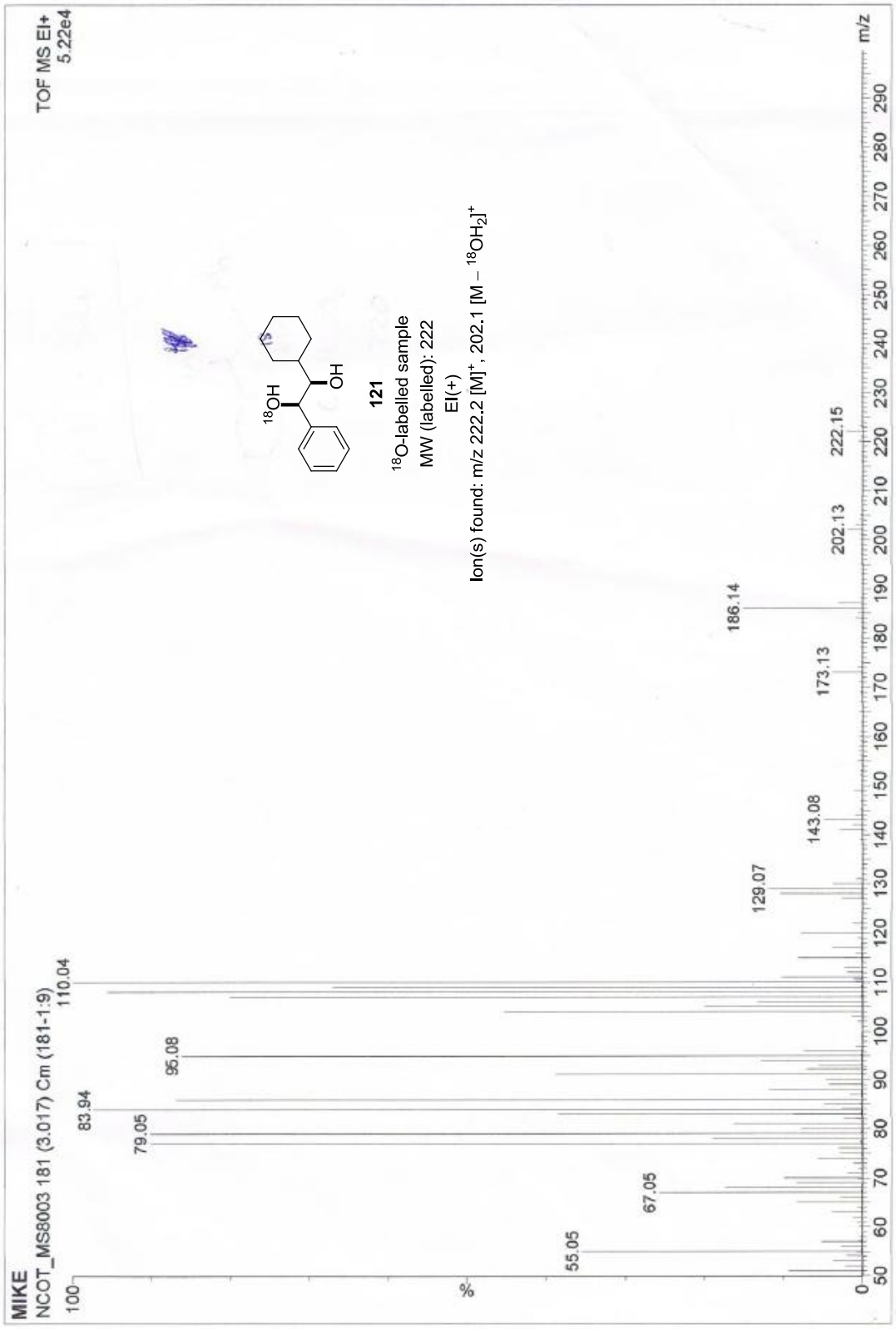


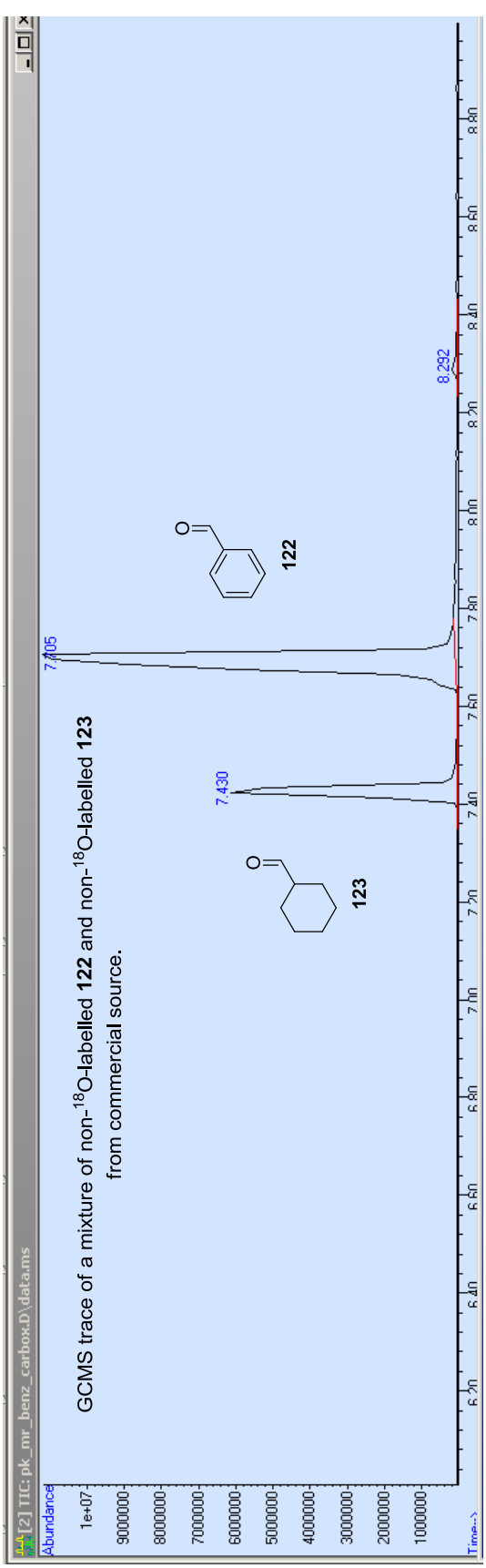


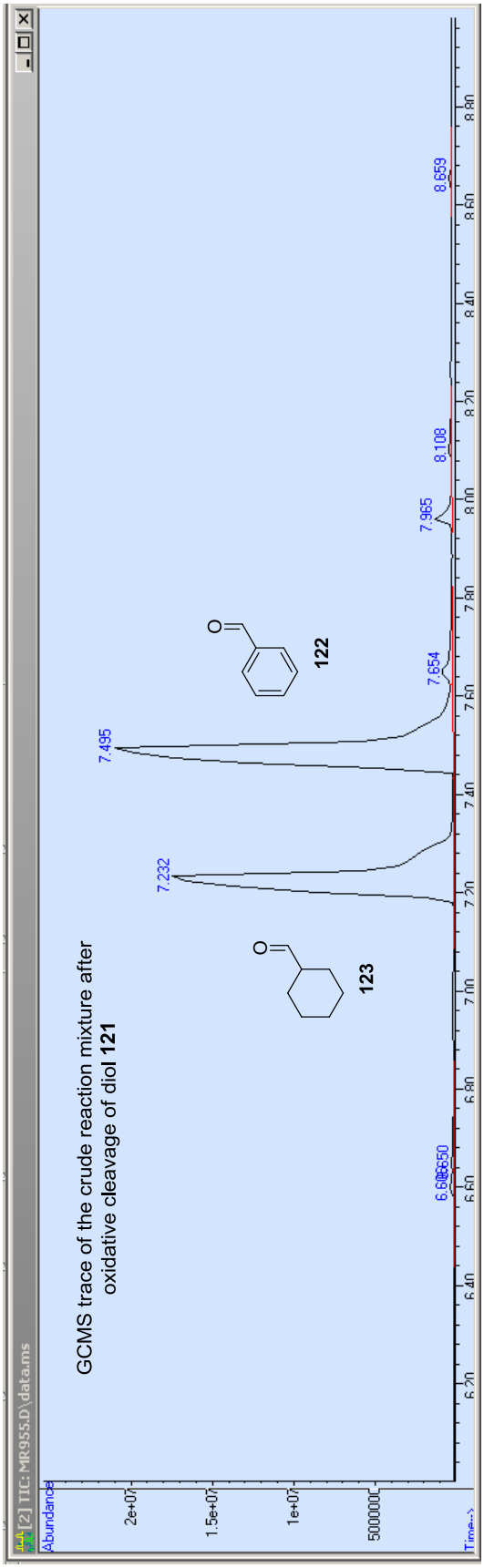
Empirical formula	$C_{20}H_{16}N_2O_8$
M_r (g mol^{-1})	412.35
Crystal system	Tetragonal
Space group	P42/n
Unit cell dimensions	a = 26.875(3) Å
	b = 26.875(3) Å
	c = 5.3795(10) Å
	$\alpha = \beta = \gamma = 90°$
Volume	3885.4(9) Å^3
Z	8
Density (calculated)	1.410 Mg/m^3
Absorption coefficient	0.944 mm^{-1}
F(000)	1712
Crystal size	0.40 x 0.04 x 0.02 mm^3
Theta range for data collection	6.59 to 64.97°.
Index ranges	-31<=h<=30, -31<=k<=30, -3<=l<=6
Reflections collected	7807
Independent reflections	3287 [R(int) = 0.1075]
Completeness to theta = 64.97°	99.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.49658
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3287 / 98 / 283
Goodness-of-fit on F^2	0.870
Final R indices [I>2sigma(I)]	R1 = 0.0762, wR2 = 0.1082
R indices (all data)	R1 = 0.1643, wR2 = 0.1412
Largest diff. peak and hole	0.226 and -0.293 e.Å^{-3}

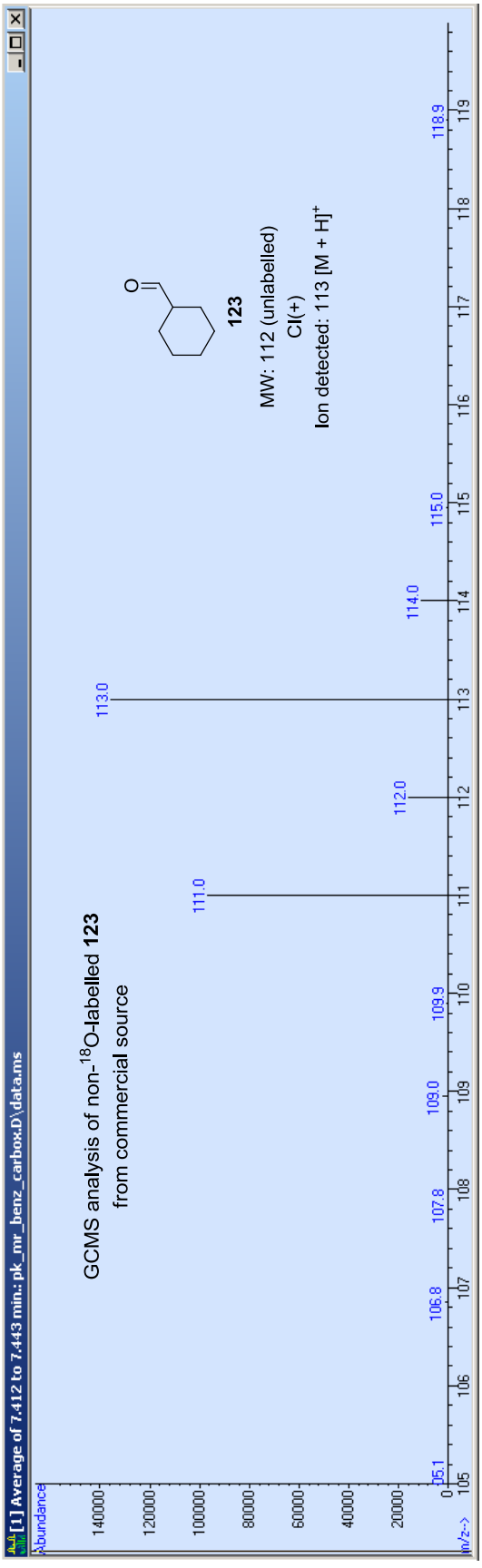
9.2 Selected Mass Spectrometric Data

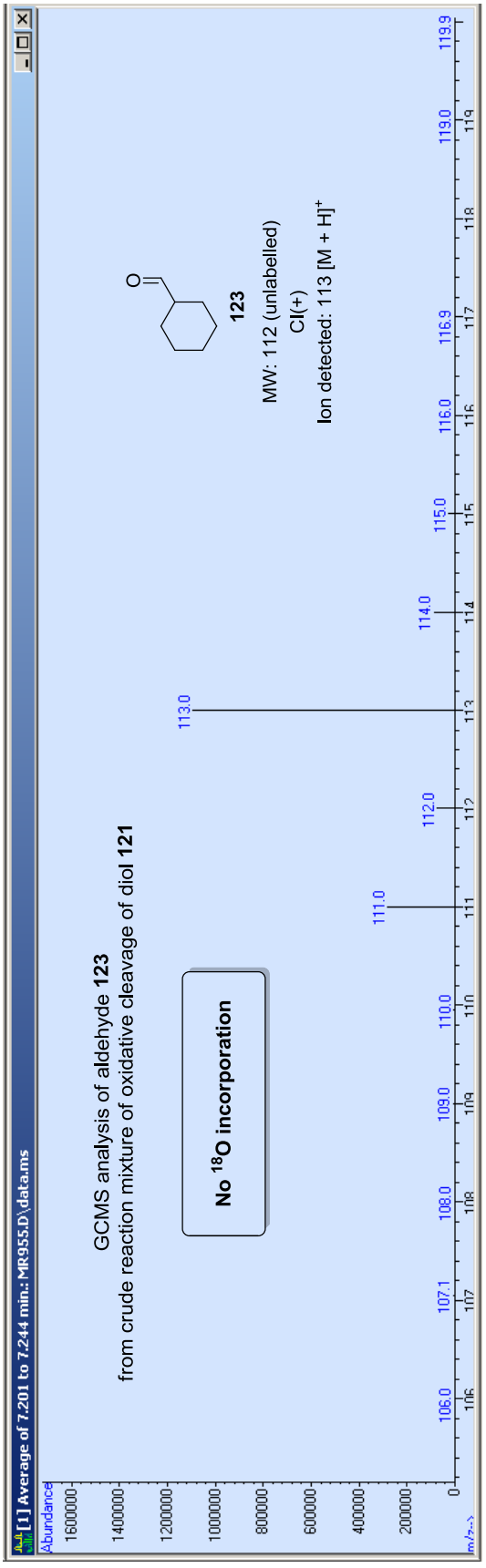


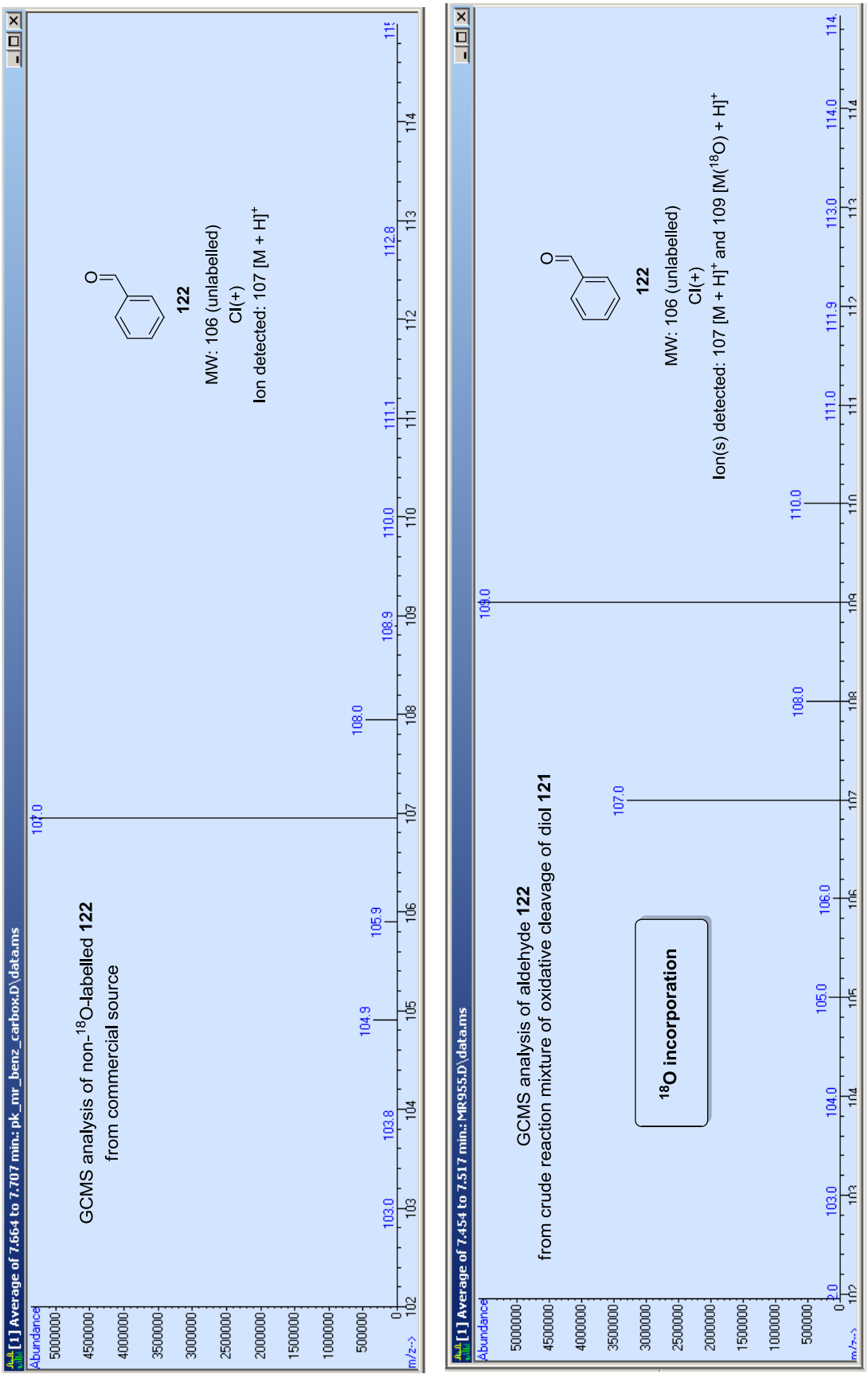

MIKE
NCOT_MS8003 181 (3.017) Cm (181-1:9)
TOF MS EI+
5.22e4
100
%
0
m/z
50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290
110.04
83.94
95.08
79.05
67.05
55.05
129.07
143.08
173.13
186.14
202.13
222.15
^{18}OH
OH
121
^{18}O-labelled sample
MW (labelled): 222
EI(+)
Ion(s) found: m/z 222.2 $[M]^+$, 202.1 $[M - {}^{18}OH_2]^+$

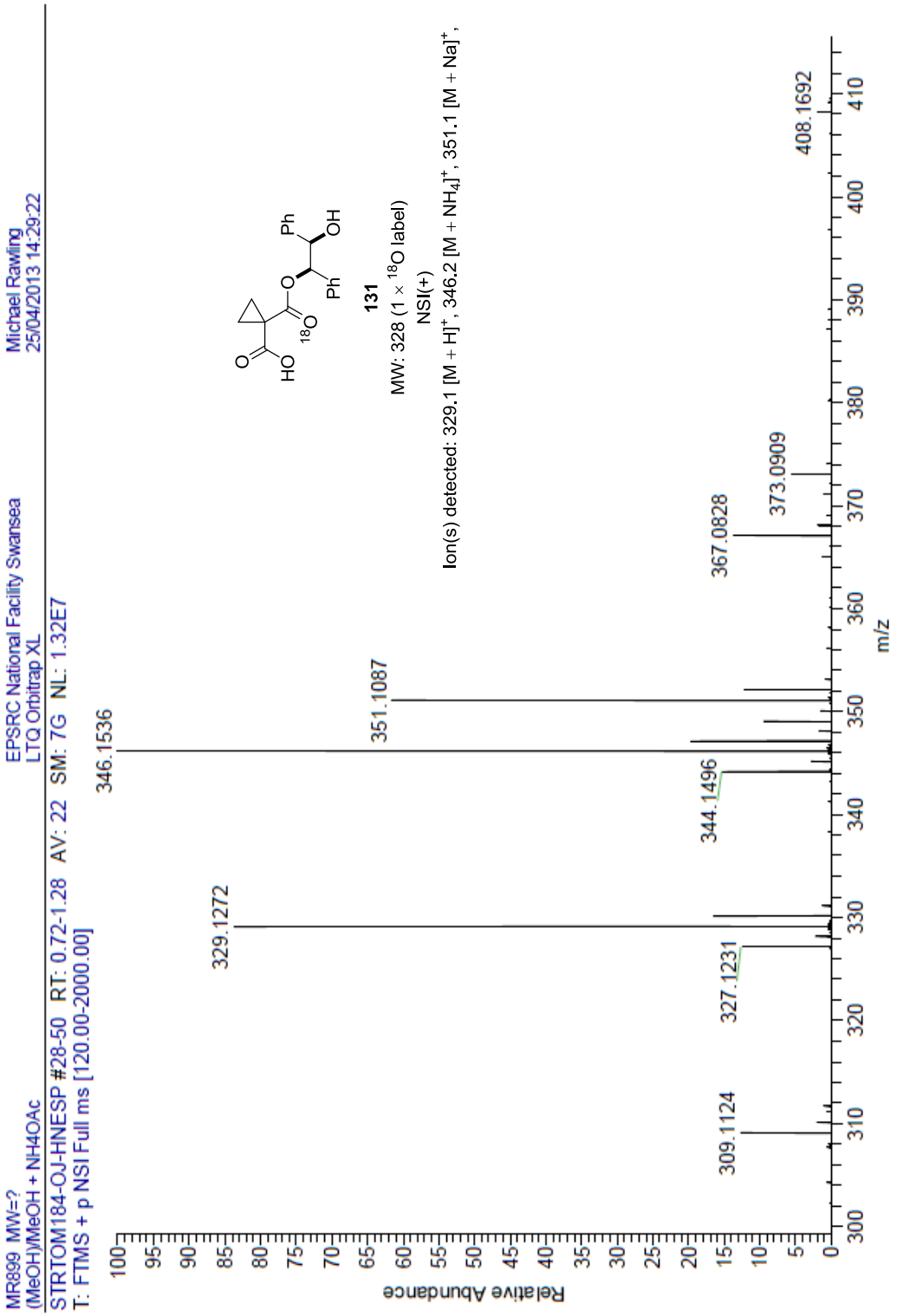

GCMS trace of a mixture of non-^{18}O-labelled **122** and non-^{18}O-labelled **123** from commercial source.
7.105
7.430
8.292
122
123

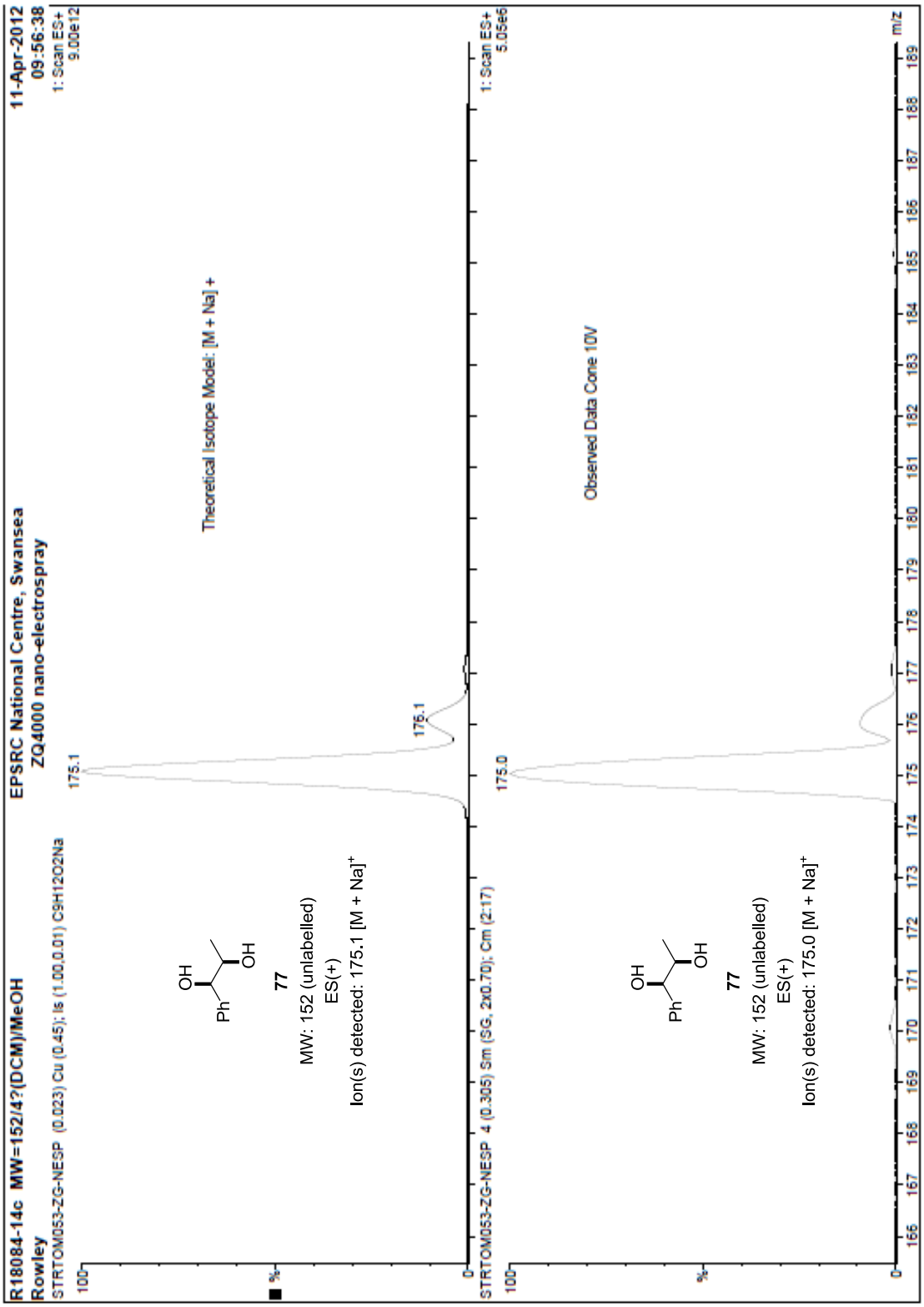

GCMS trace of the crude reaction mixture after oxidative cleavage of diol **121**
7.232
7.495
7.654
7.965
8.108
8.659
122
123

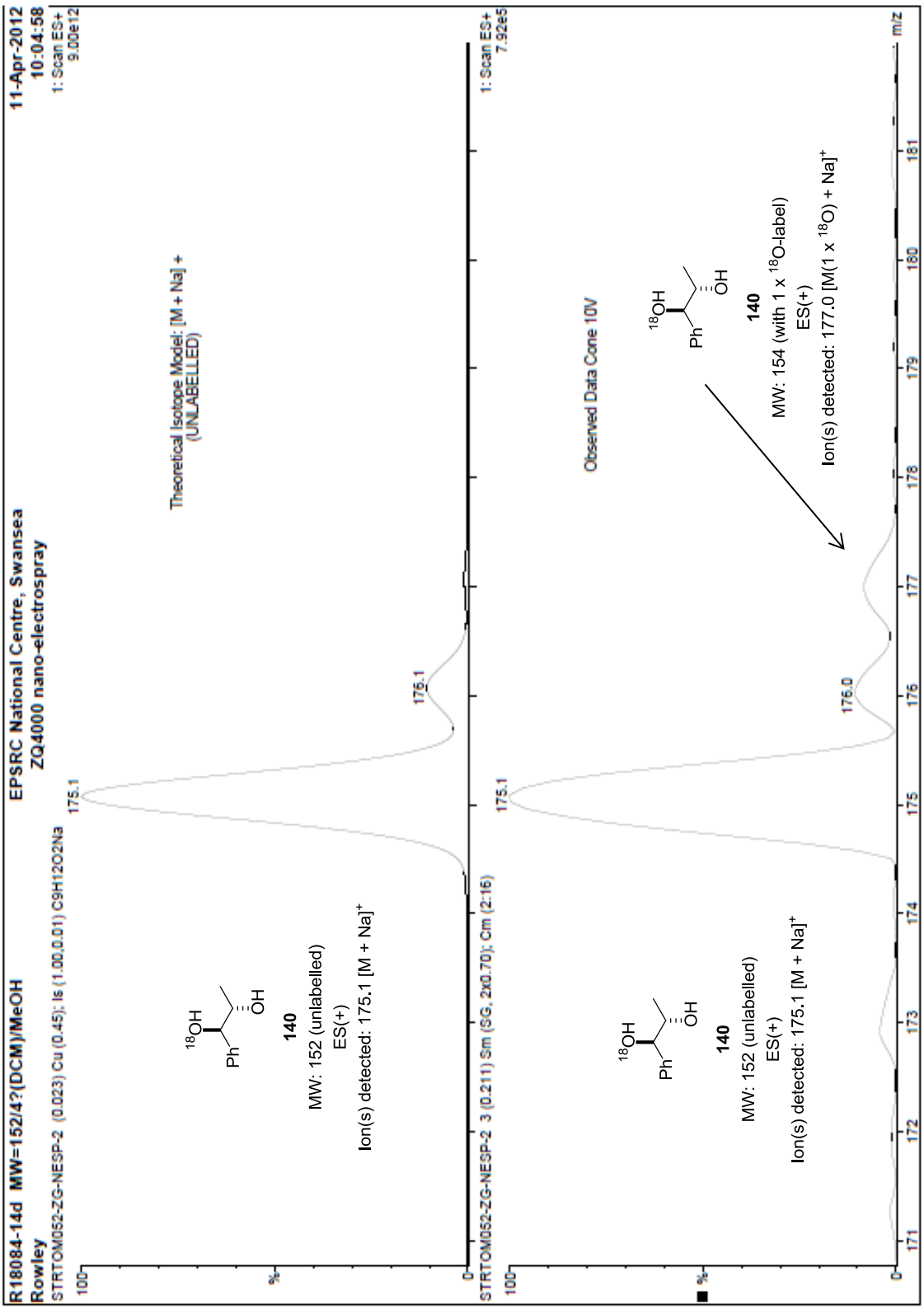

[1] Average of 7.412 to 7.443 min.: pk_mr_benz_carbox.D\data.ms
Abundance
m/z-->
GCMS analysis of non-18O-labelled 123
from commercial source
123
MW: 112 (unlabelled)
CI(+)
Ion detected: 113 [M + H]+
105.1
106.8
107.8
109.0
109.9
111.0
112.0
113.0
114.0
115.0
118.9


[1] Average of 7.201 to 7.244 min.: MR955.D\data.ms
Abundance
m/z-->
GCMS analysis of aldehyde 123
from crude reaction mixture of oxidative cleavage of diol 121
No 18O incorporation
123
MW: 112 (unlabelled)
CI(+)
Ion detected: 113 [M + H]+
106.0
107.1
108.0
109.0
110.0
111.0
112.0
113.0
114.0
115.0
116.0
116.9
119.0
119.9


[1] Average of 7.664 to 7.707 min.: pk_mr_benz_carbox.D\data.ms
Abundance
GCMS analysis of non-18O-labelled 122
from commercial source
122
MW: 106 (unlabelled)
CI(+)
Ion detected: 107 [M + H]+
m/z-->
[1] Average of 7.454 to 7.517 min.: MR955.D\data.ms
Abundance
GCMS analysis of aldehyde 122
from crude reaction mixture of oxidative cleavage of diol 121
18O incorporation
122
MW: 106 (unlabelled)
CI(+)
Ion(s) detected: 107 [M + H]+ and 109 [M(18O) + H]+
m/z-->

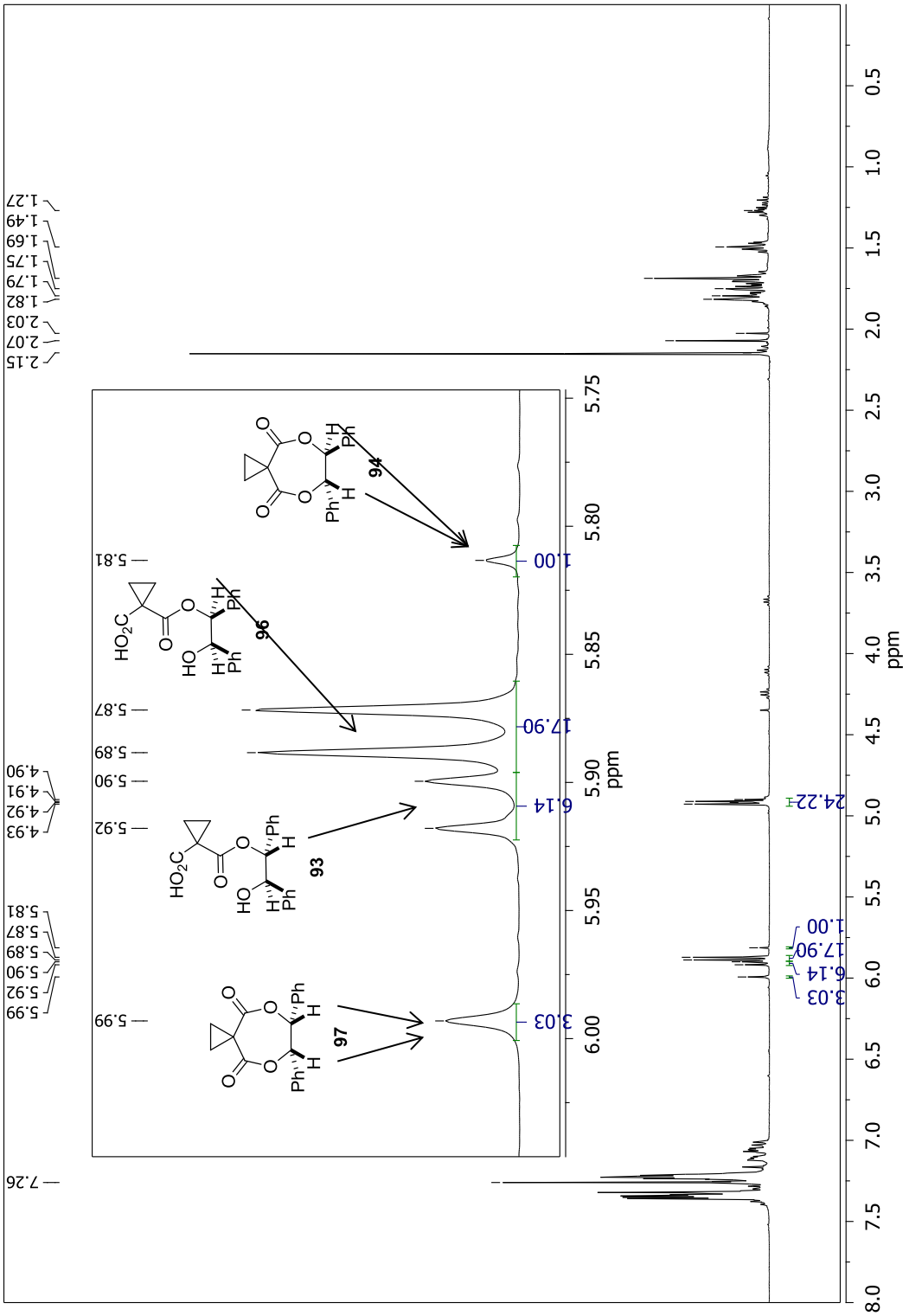

MR899 MW=?
(MeOH)/MeOH + NH4OAc
STRTOM184-OJ-HNESP #28-50 RT: 0.72-1.28 AV: 22 SM: 7G NL: 1.32E7
T: FTMS + p NSI Full ms [120.00-2000.00]
EPSRC National Facility Swansea
LTQ Orbitrap XL
Michael Rawling
25/04/2013 14:29:22
131
MW: 328 (1 × 18O label)
NSI(+)
Ion(s) detected: 329.1 [M + H]+, 346.2 [M + NH4]+, 351.1 [M + Na]+,
Relative Abundance
m/z
346.1536
351.1087
329.1272
344.1496
367.0828
373.0909
408.1692
309.1124
327.1231


R18084-14c MW=152/4?(DCM)/MeOH
Rowley
STRTOM053-ZG-NESP (0.023) Cu (0.45); Is (1.00,0.01) C9H12O2Na
EPSRC National Centre, Swansea
ZQ4000 nano-electrospray
11-Apr-2012
09:56:38
1: Scan ES+
9.00e12
Theoretical Isotope Model: [M + Na] +
175.1
176.1
OH
Ph
OH
77
MW: 152 (unlabelled)
ES(+)
Ion(s) detected: 175.1 [M + Na]+
STRTOM053-ZG-NESP 4 (0.305) Sm (SG, 2x0.70); Cm (2:17)
1: Scan ES+
5.05e6
Observed Data Cone 10V
175.0
OH
Ph
OH
77
MW: 152 (unlabelled)
ES(+)
Ion(s) detected: 175.0 [M + Na]+
100
%
0
m/z
166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189

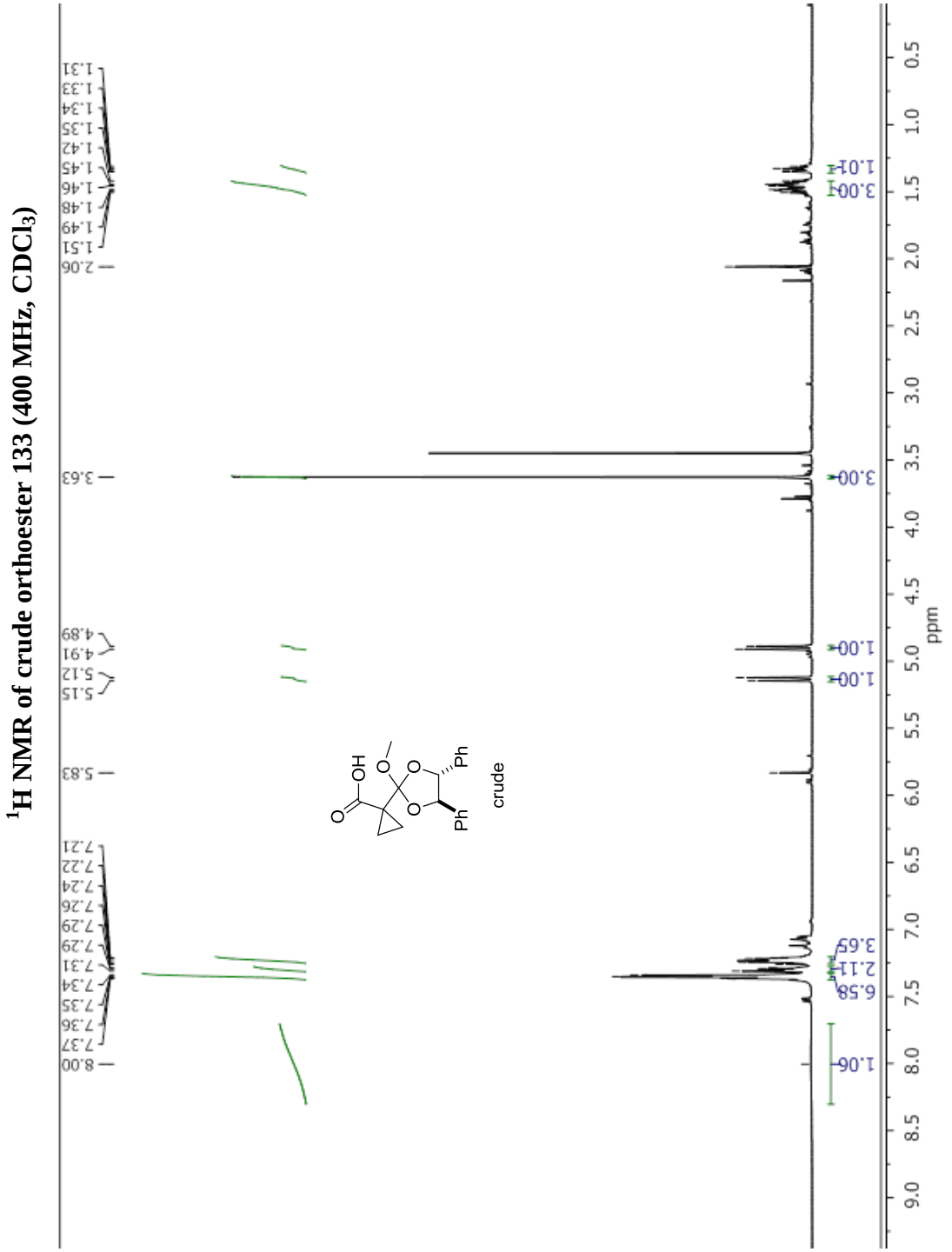

R18084-14d MW=152/4?(DCM)/MeOH
Rowley
STRTOM052-ZG-NESP-2 (0.023) Cu (0.45); Is (1.00,0.01) C9H12O2Na
EPSRC National Centre, Swansea
ZQ4000 nano-electrospray
11-Apr-2012
10:04:58
1: Scan ES+
9.00e12
Theoretical Isotope Model: [M + Na] + (UNLABELLED)
175.1
176.1
140
MW: 152 (unlabelled)
ES(+)
Ion(s) detected: 175.1 [M + Na]+
STRTOM052-ZG-NESP-2 3 (0.211) Sm (SG, 2x0.70); Cm (2:16)
1: Scan ES+
7.92e5
Observed Data Cone 10V
175.1
176.0
140
MW: 154 (with 1 x 18O-label)
ES(+)
Ion(s) detected: 177.0 [M(1 x 18O) + Na]+
m/z

9.3 Selected ^{1}H and ^{13}C NMR Data

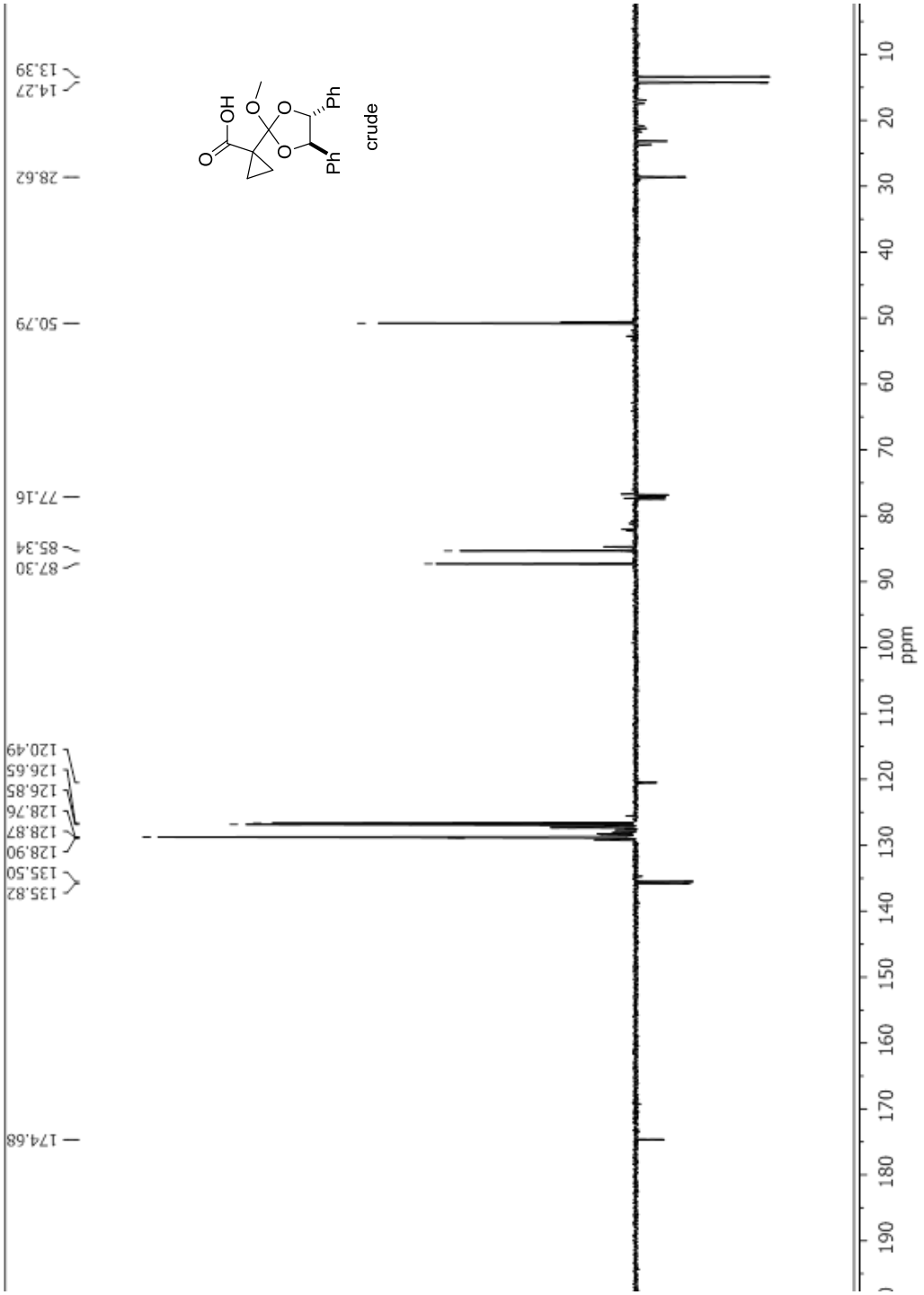
^{1}H NMR of the crude reaction mixture from the dihydroxylation of *cis*-stilbene 95 with 86 (400 MHz, $CDCl_3$)



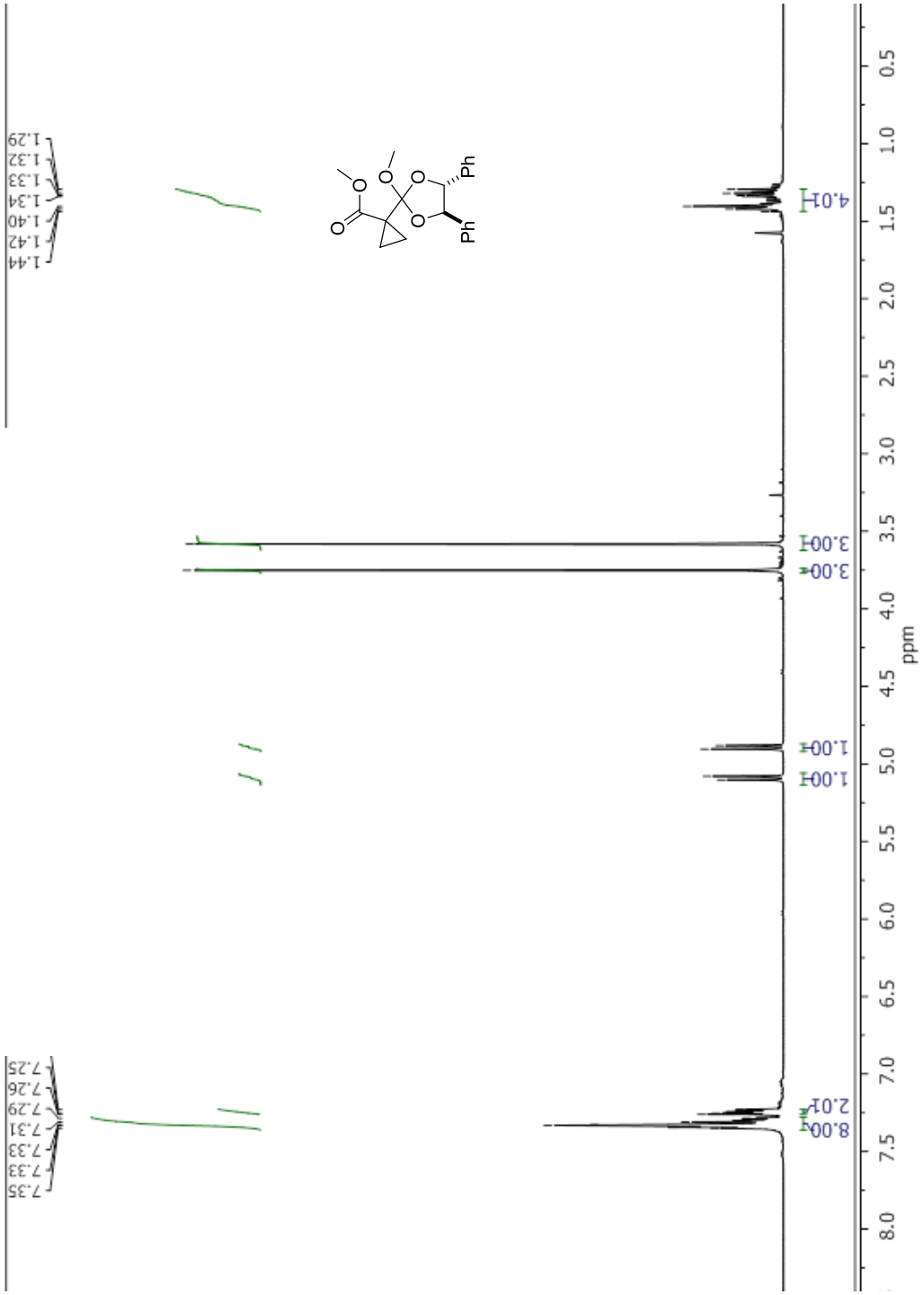
^{1}H NMR of crude orthoester 133 (400 MHz, $CDCl_3$)



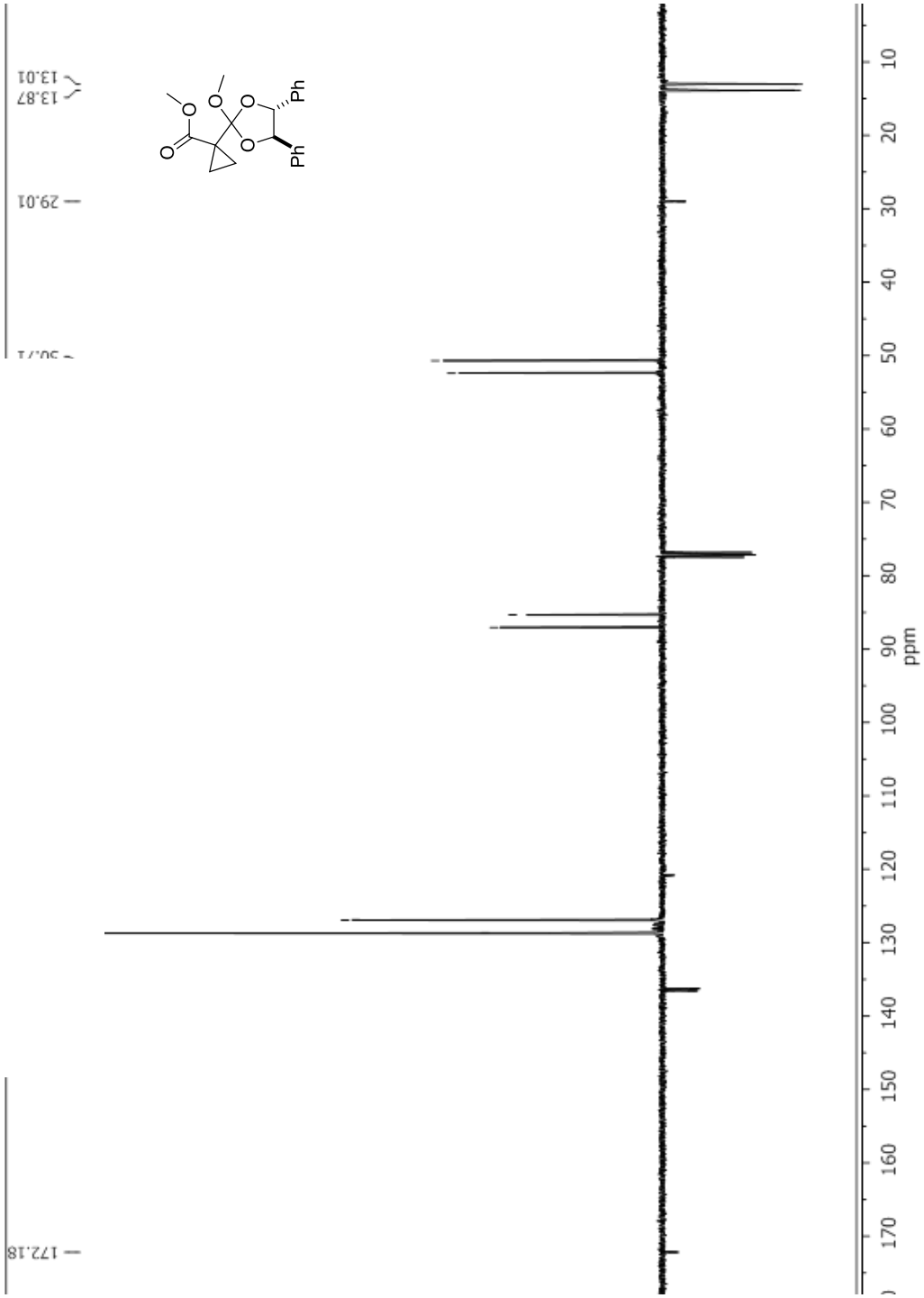
^{13}C DEPT-Q of crude orthoester 133 (100 MHz, $CDCl_3$)



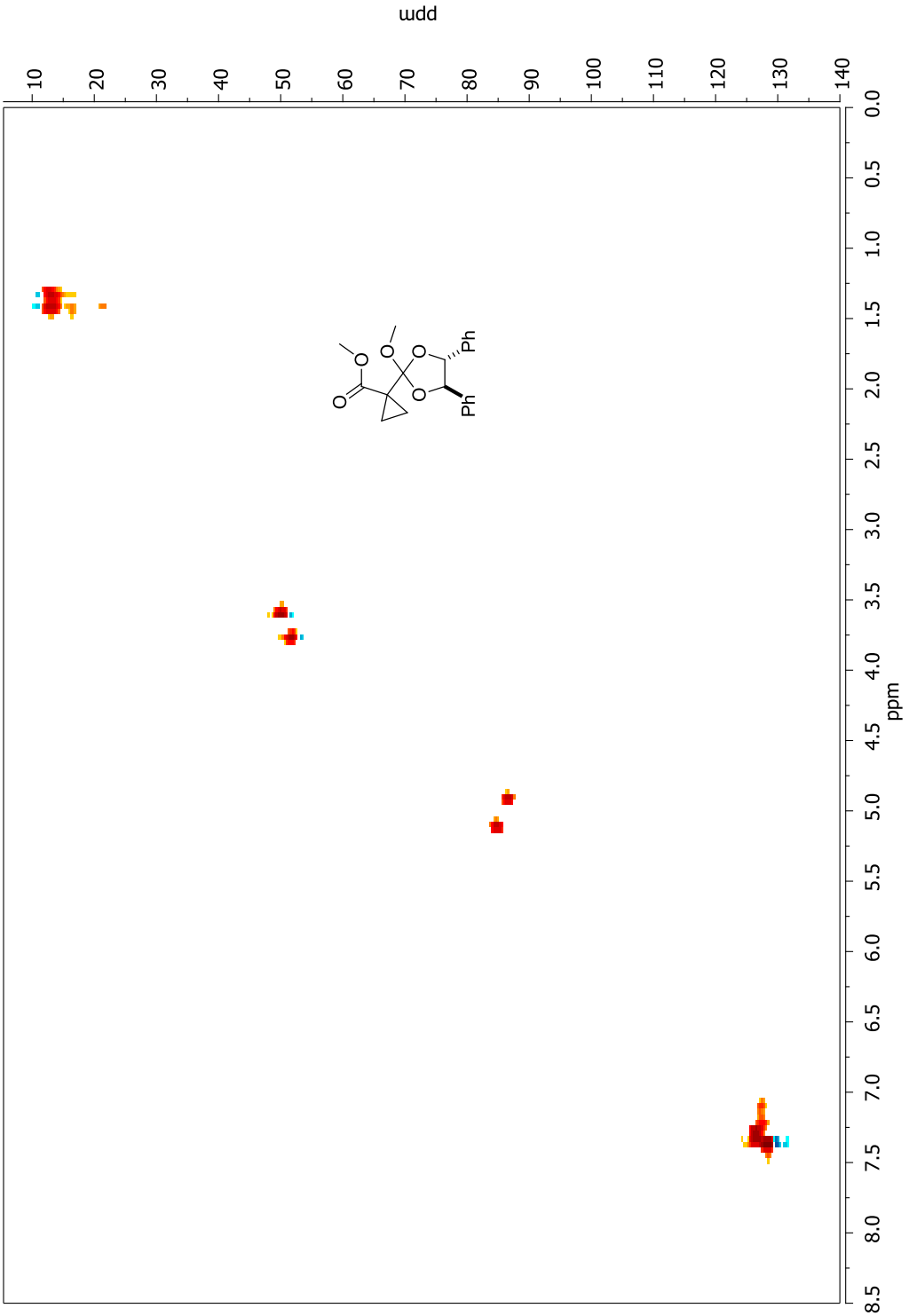
^{1}H NMR of orthoester 135 (400 MHz, $CDCl_3$)



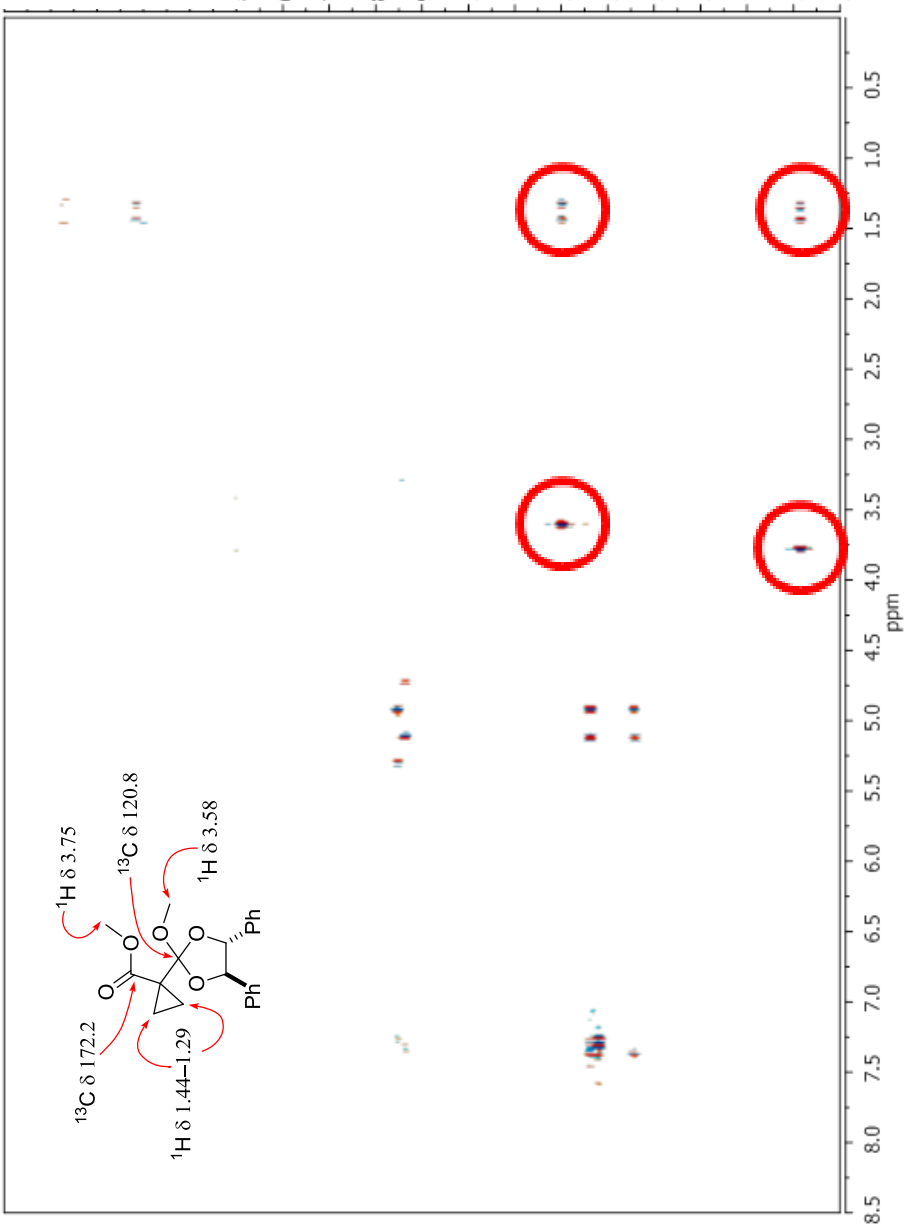
^{13}C DEPT-Q of orthoester 135 (100 MHz, $CDCl_3$)



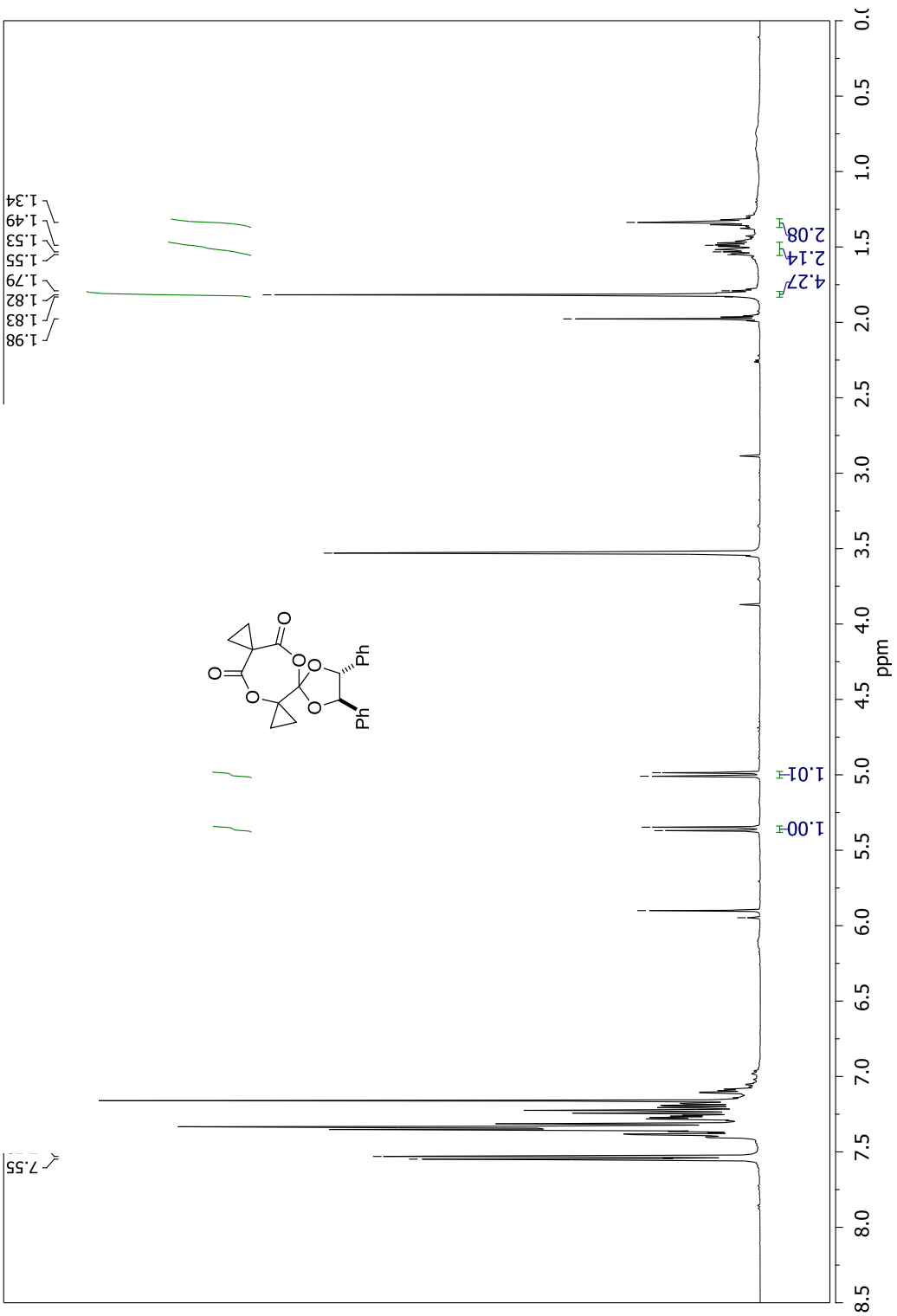
HSQC of orthoester 135 ($CDCl_3$)



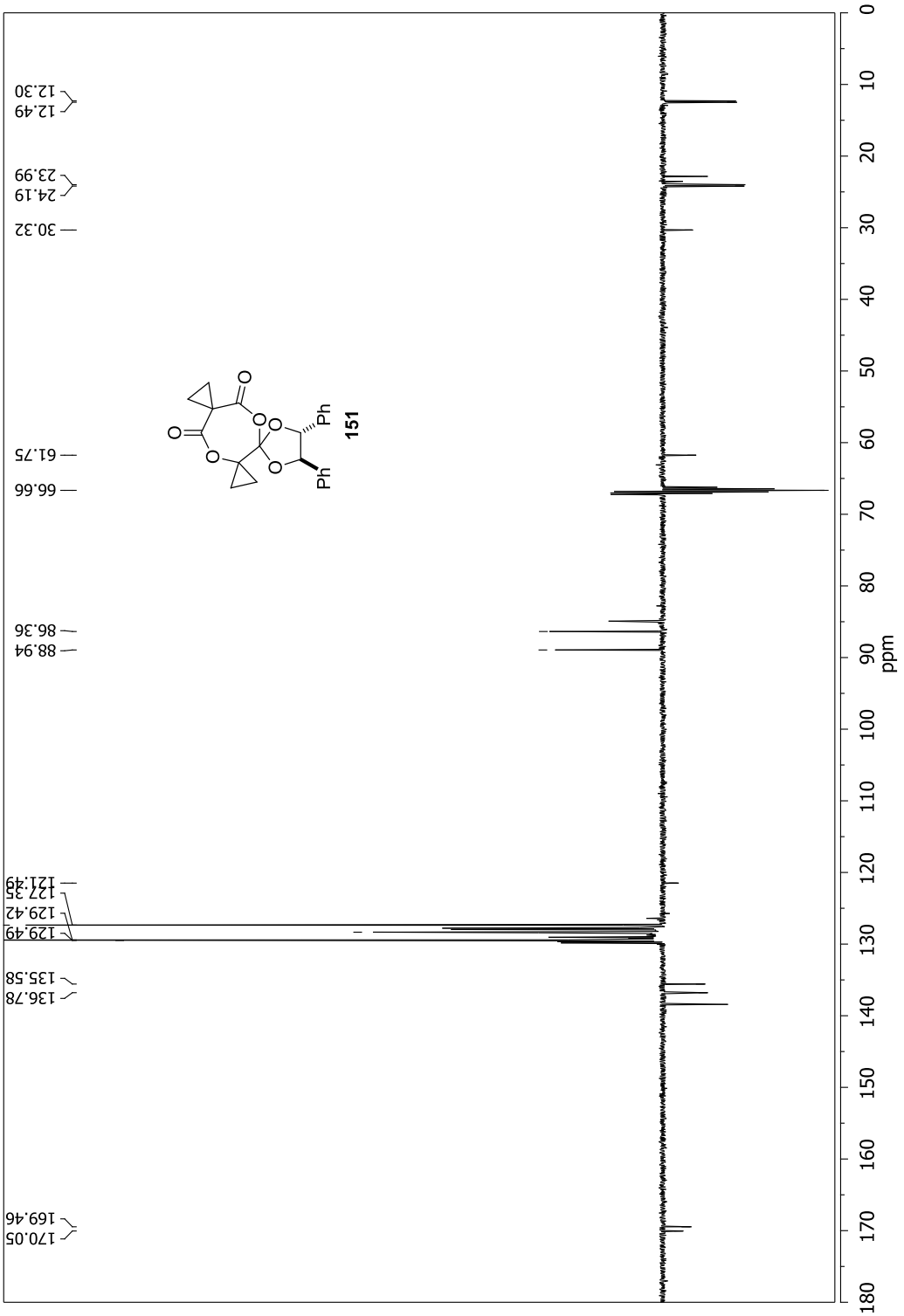
HMBC of orthoester 135 ($CDCl_3$)



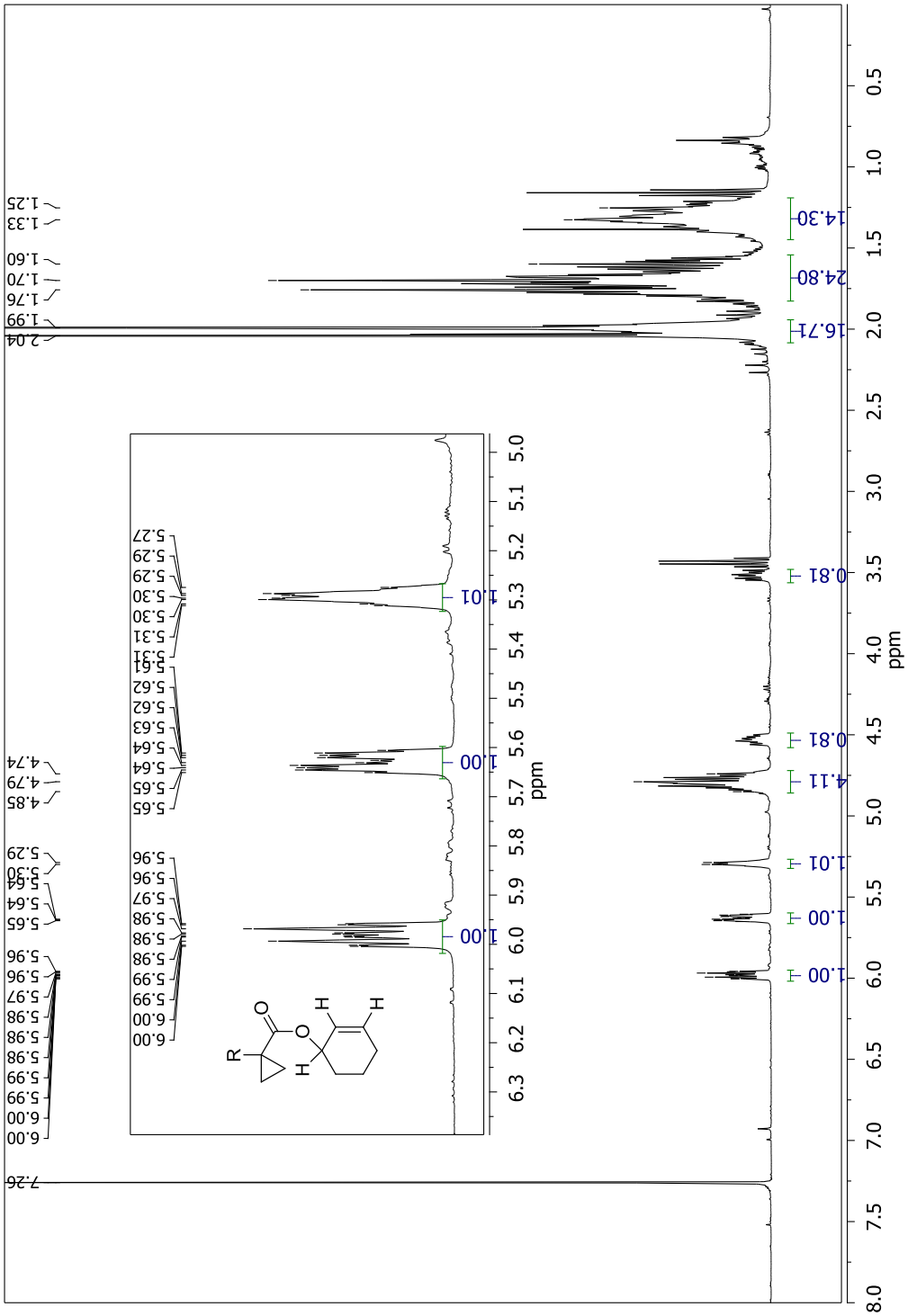
^{1}H NMR of crude orthoester 151 (400 MHz, 1,4-dioxane-d_8)



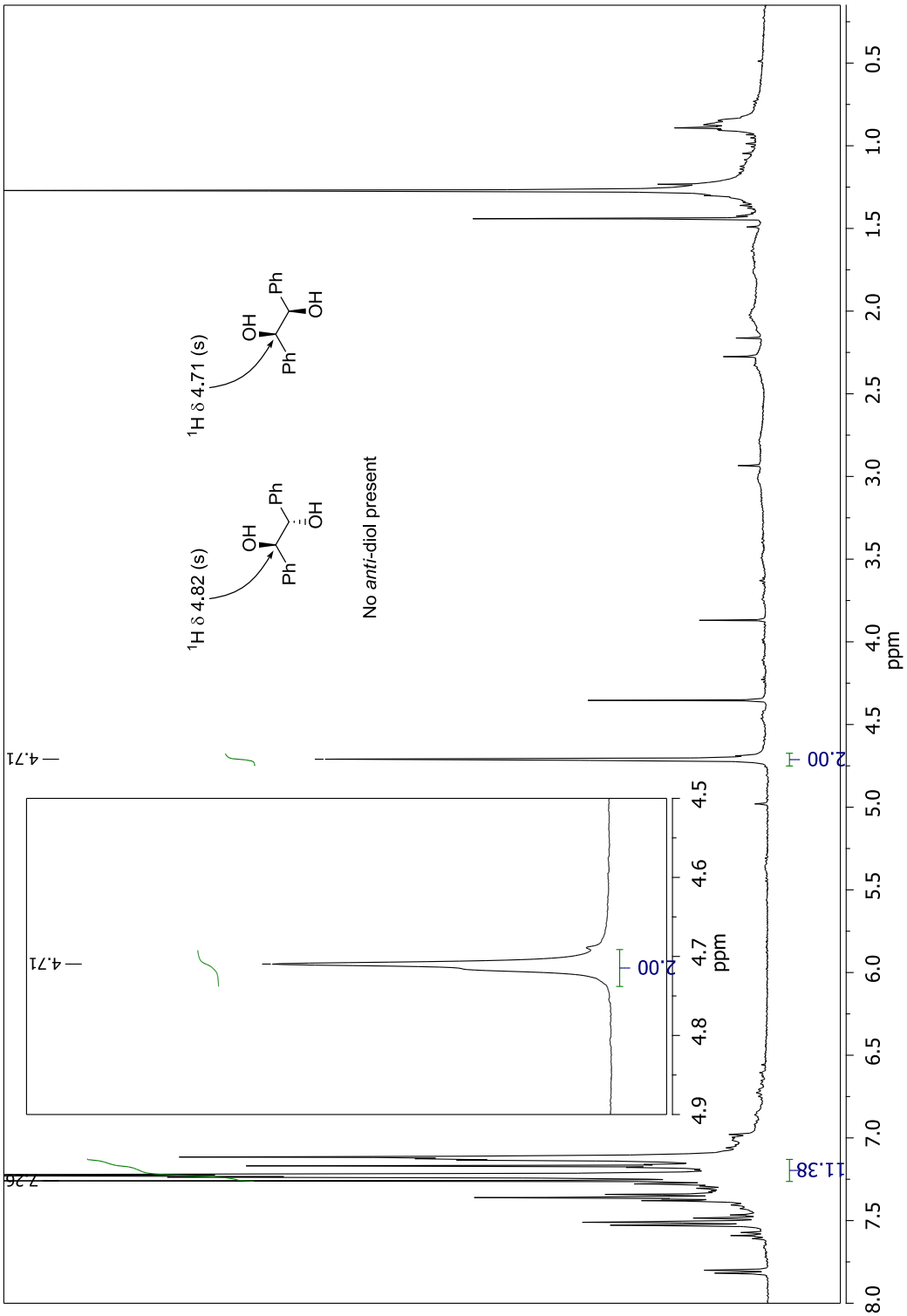
^{13}C DEPT-Q of crude orthoester 151 (100 MHz, 1,4-dioxane-d$_8$)



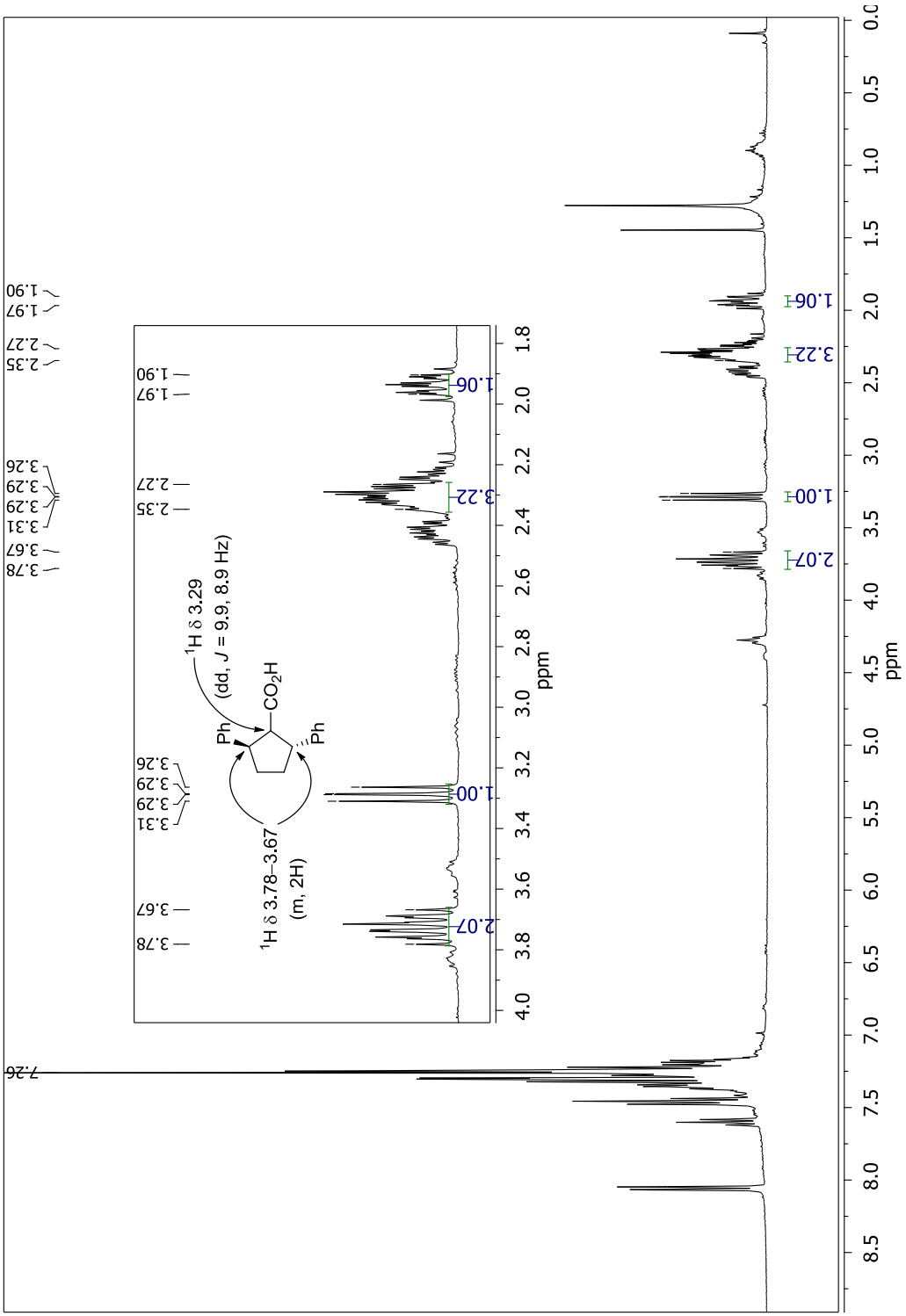
^{1}H NMR of allylic ester 219 (400 MHz, $CDCl_3$)



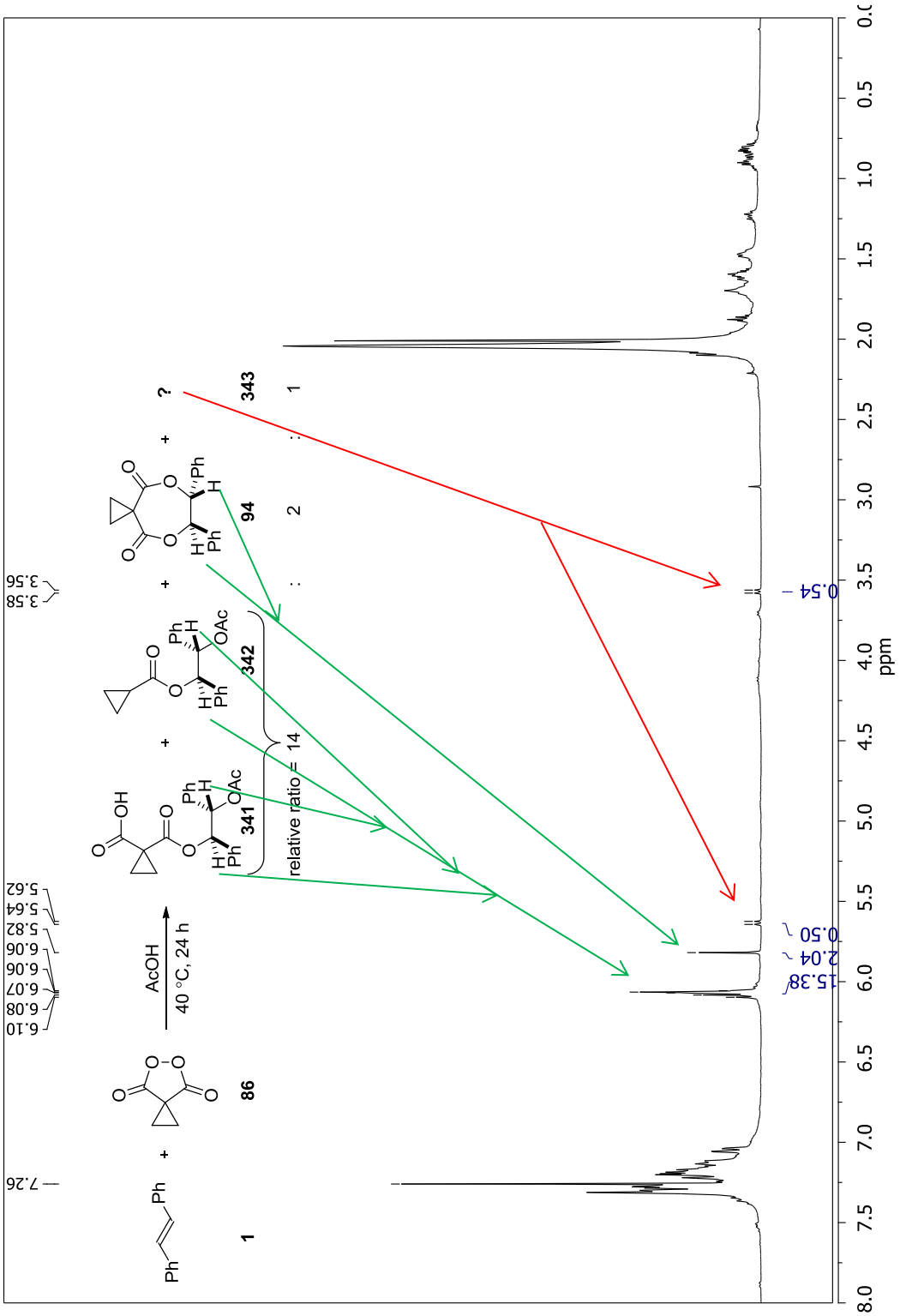
^{1}H NMR of crude (*R*,*R*)-diol 2 from reaction of *trans*-stilbene 1 with chiral peroxide 315 (400 MHz, $CDCl_3$)



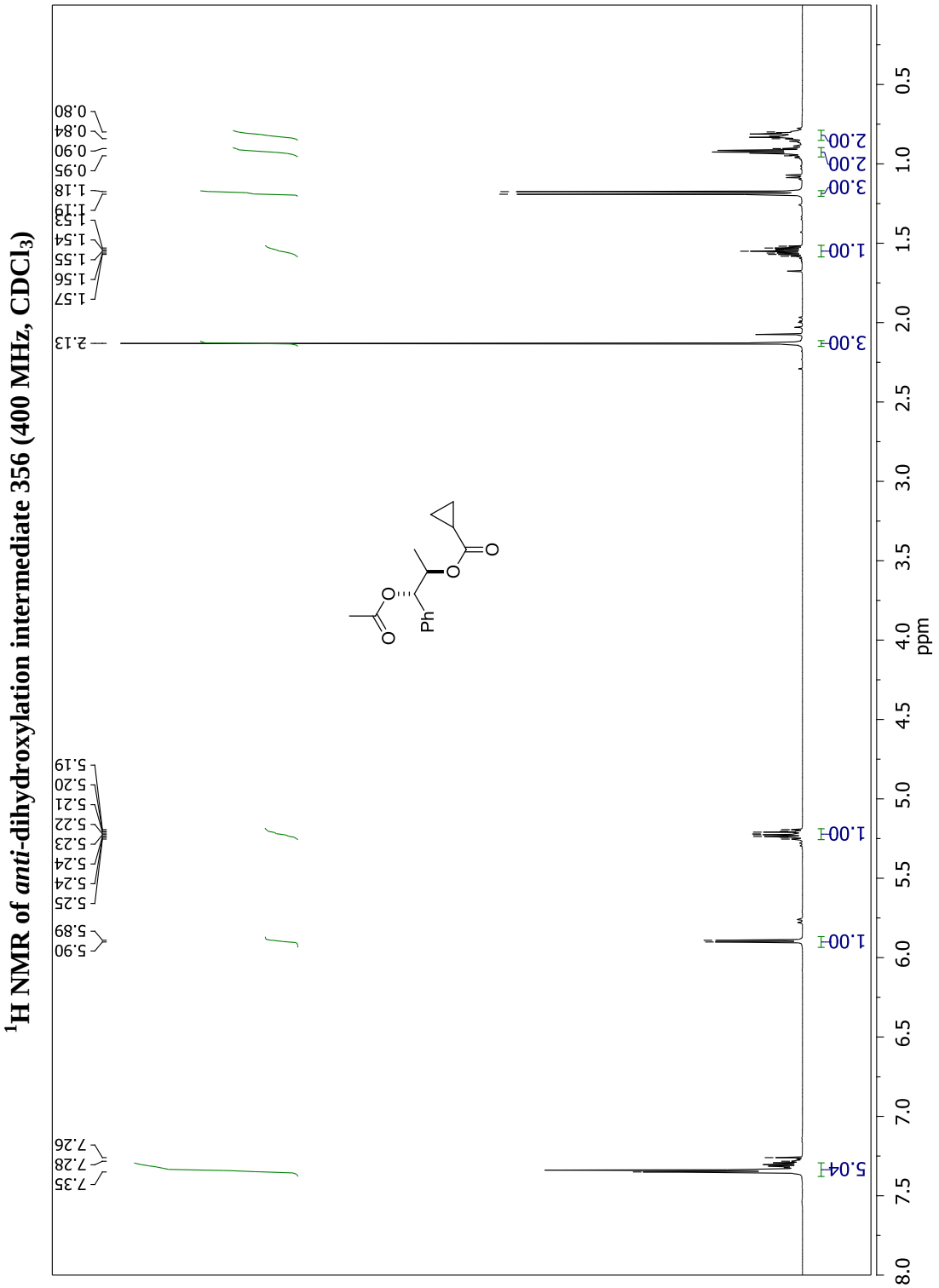
^{1}H NMR of crude acid 325 (400 MHz, $CDCl_3$)



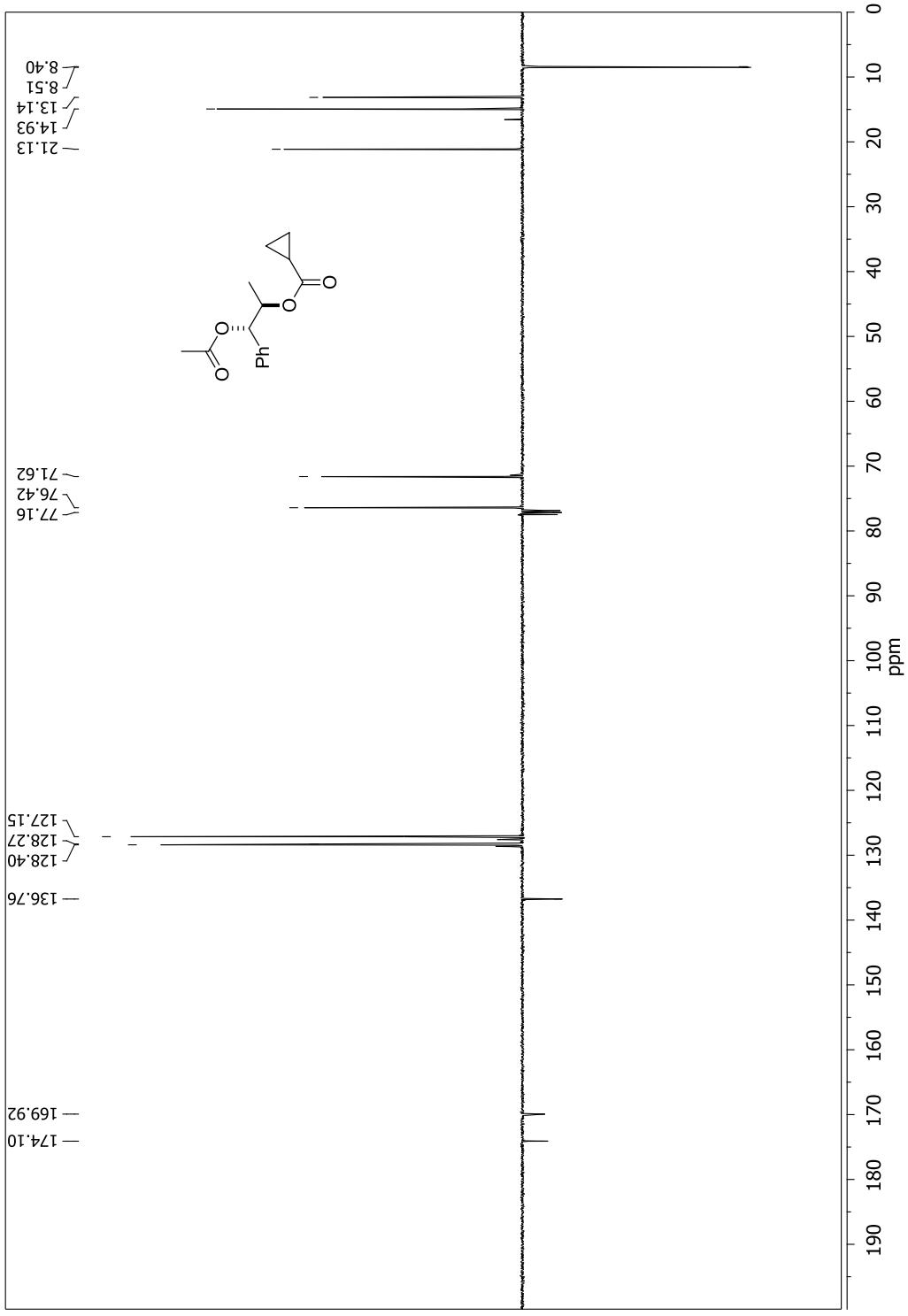
^{1}H NMR of *anti*-dihydroxylation intermediates (400 MHz, $CDCl_3$)



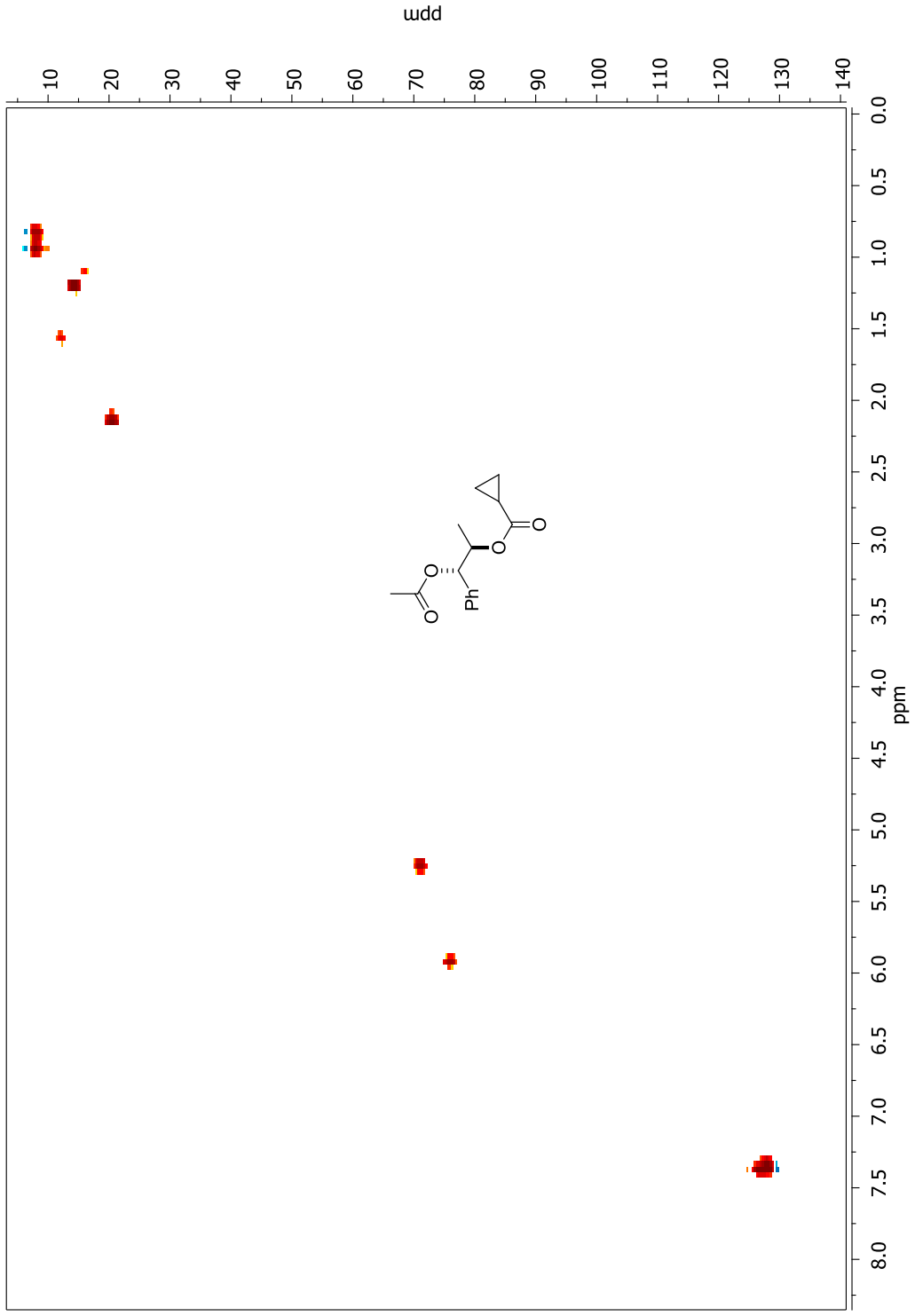
^{1}H NMR of *anti*-dihydroxylation intermediate 356 (400 MHz, $CDCl_3$)



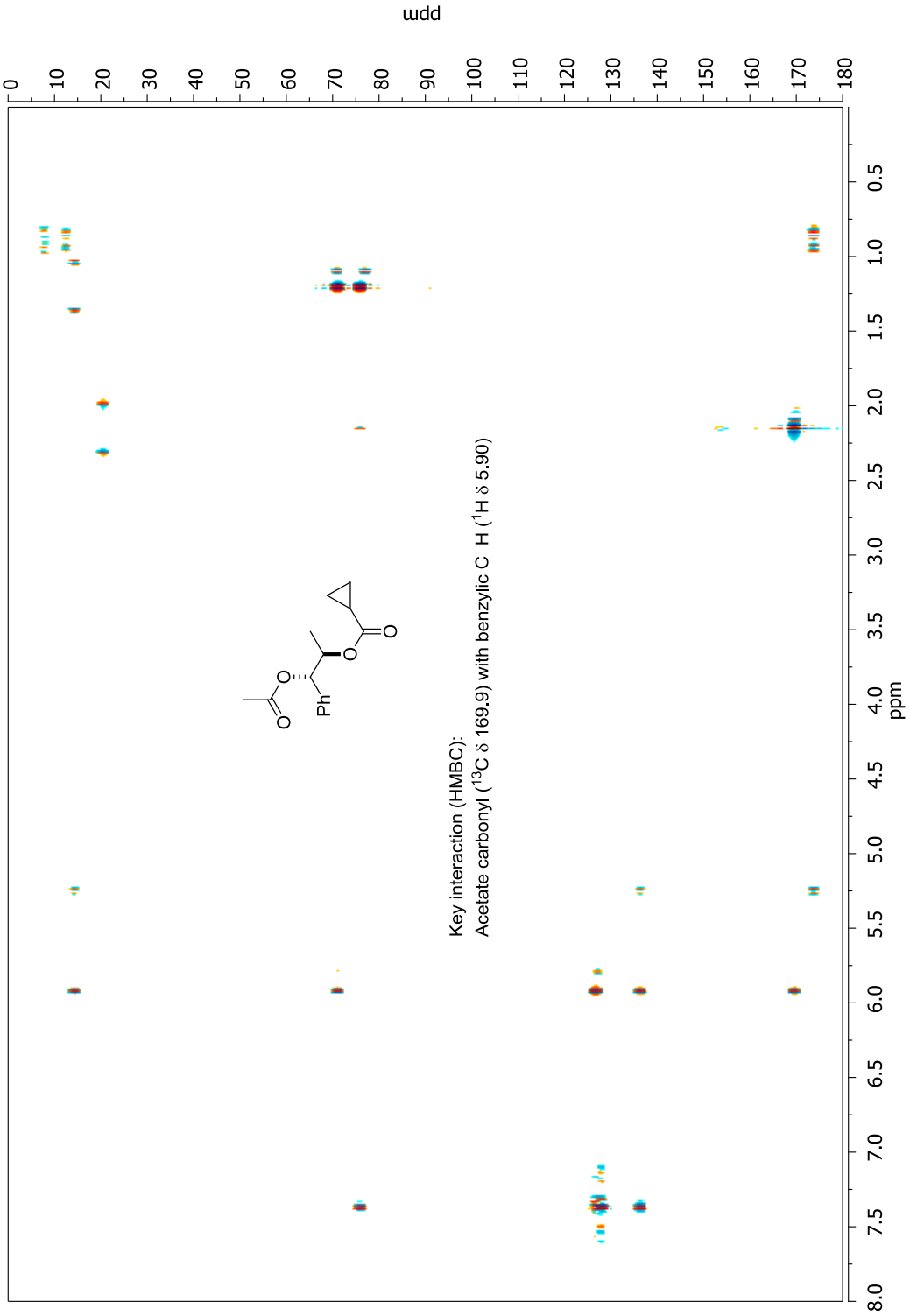
^{13}C DEPT-Q of *anti*-dihydroxylation intermediate 356 (100 MHz, $CDCl_3$)



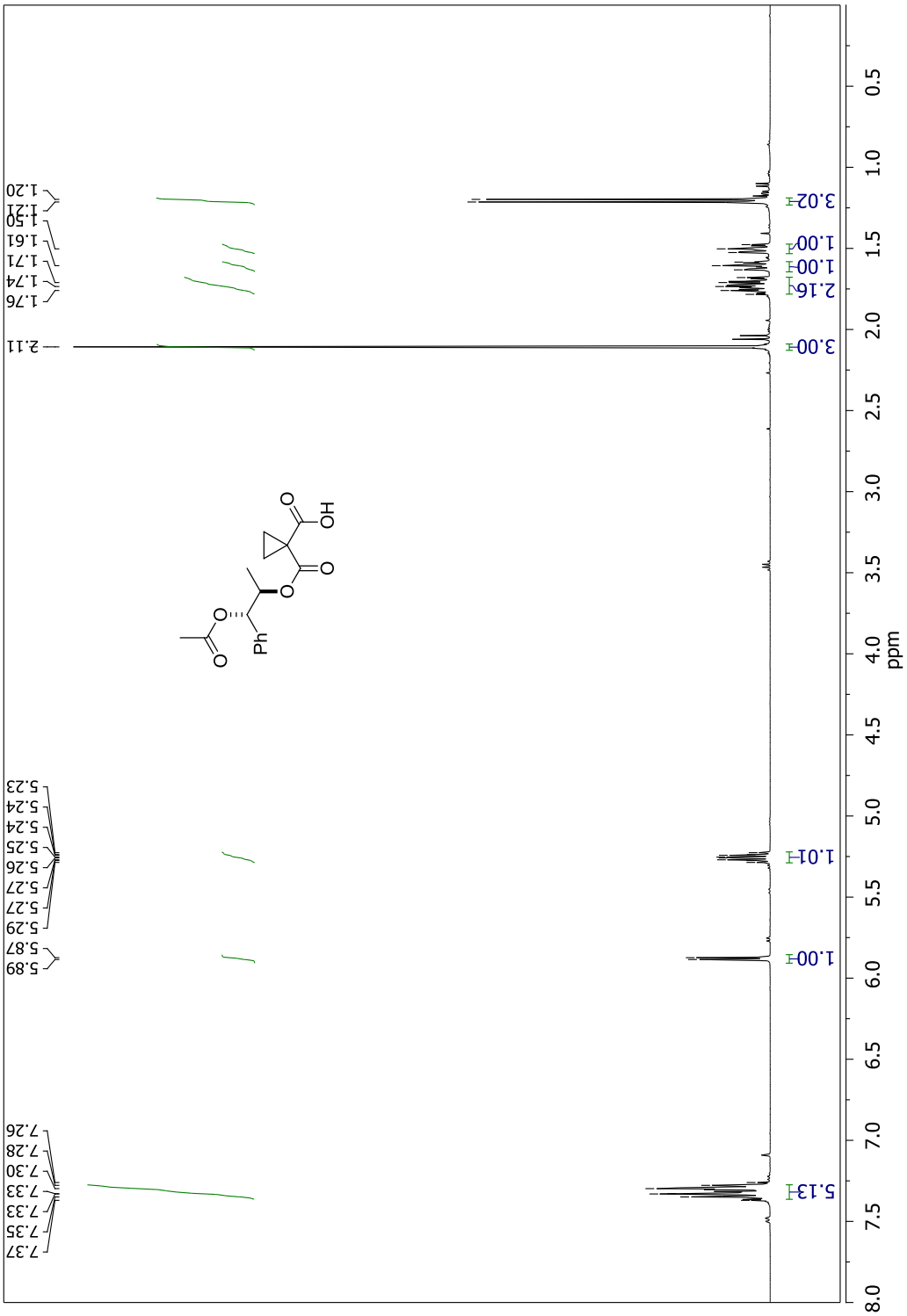
HSQC of *anti*-dihydroxylation intermediate 356 ($CDCl_3$)



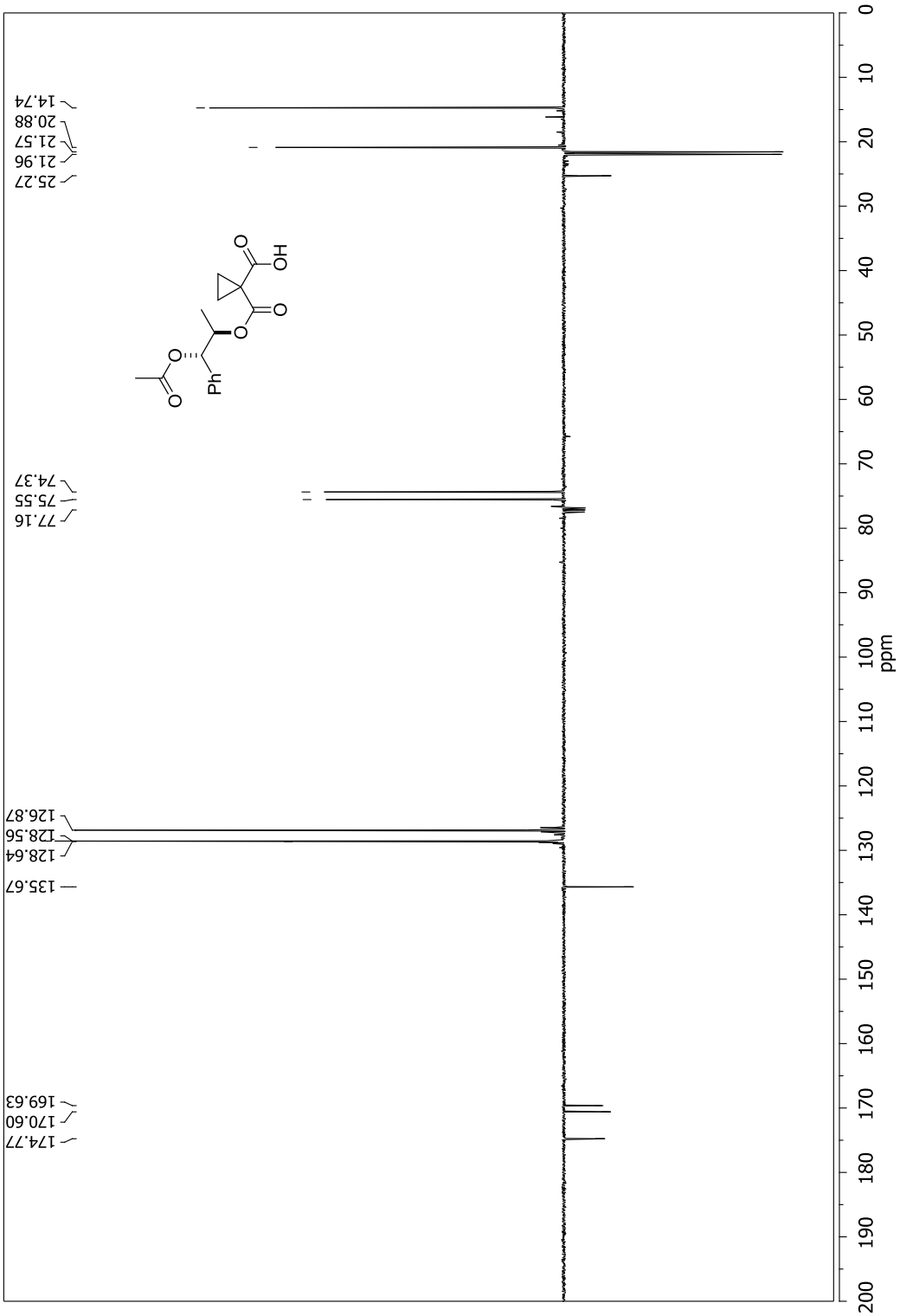
HMBC of *anti*-dihydroxylation intermediate 356 ($CDCl_3$)



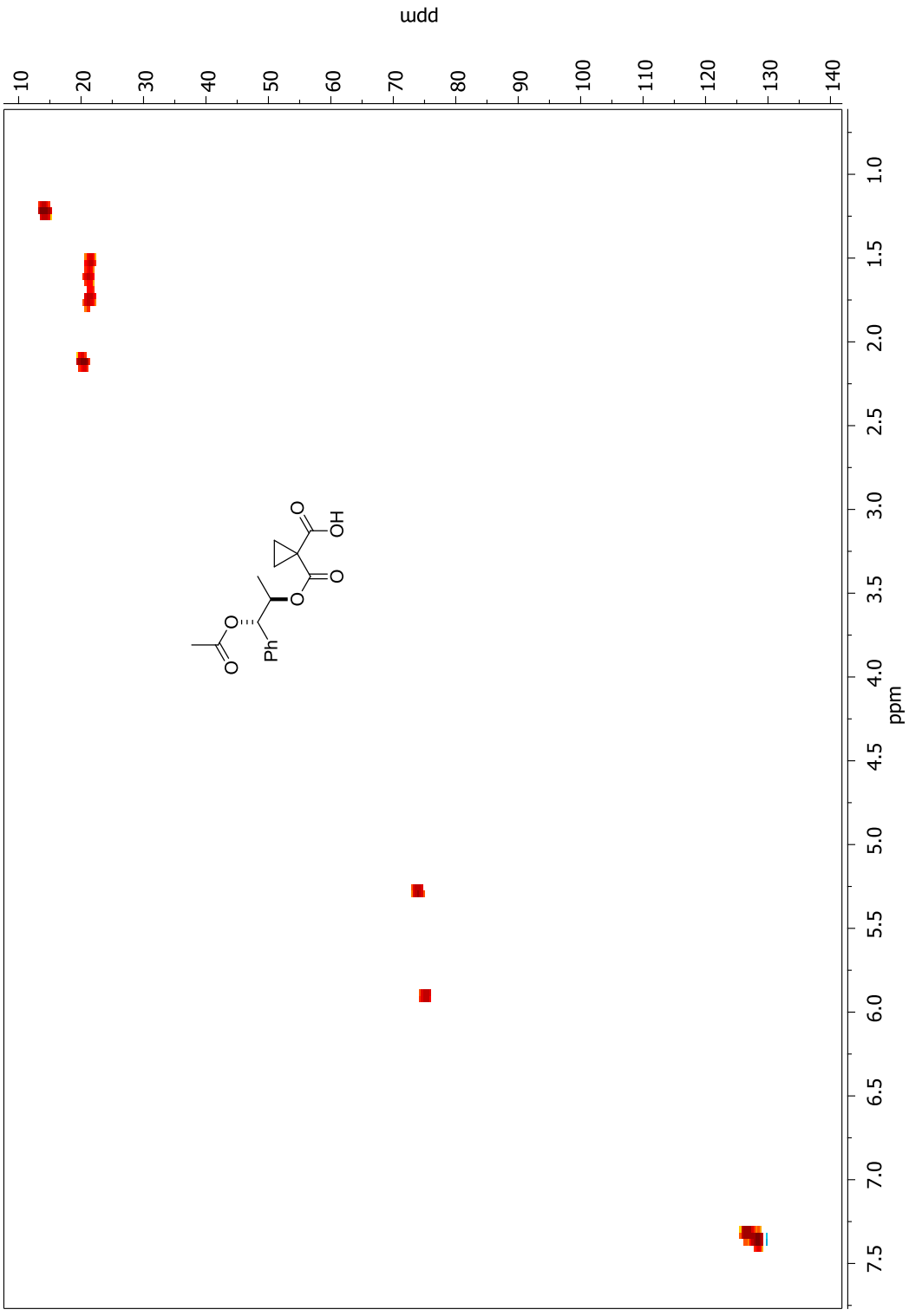
^{1}H NMR of *anti*-dihydroxylation intermediate 355 (400 MHz, $CDCl_3$)



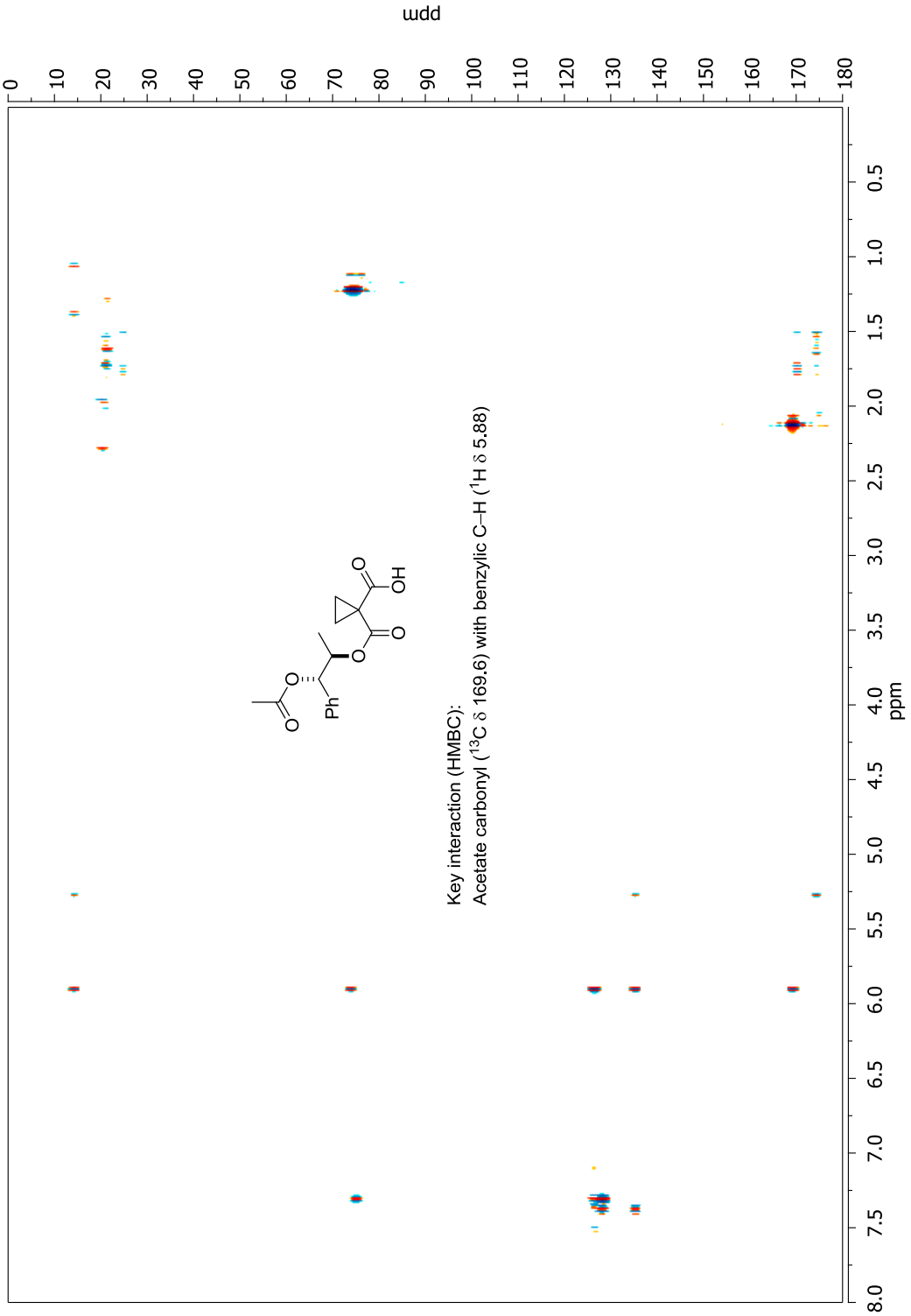
^{13}C DEPT-Q of *anti*-dihydroxylation intermediate 355 (100 MHz, $CDCl_3$)



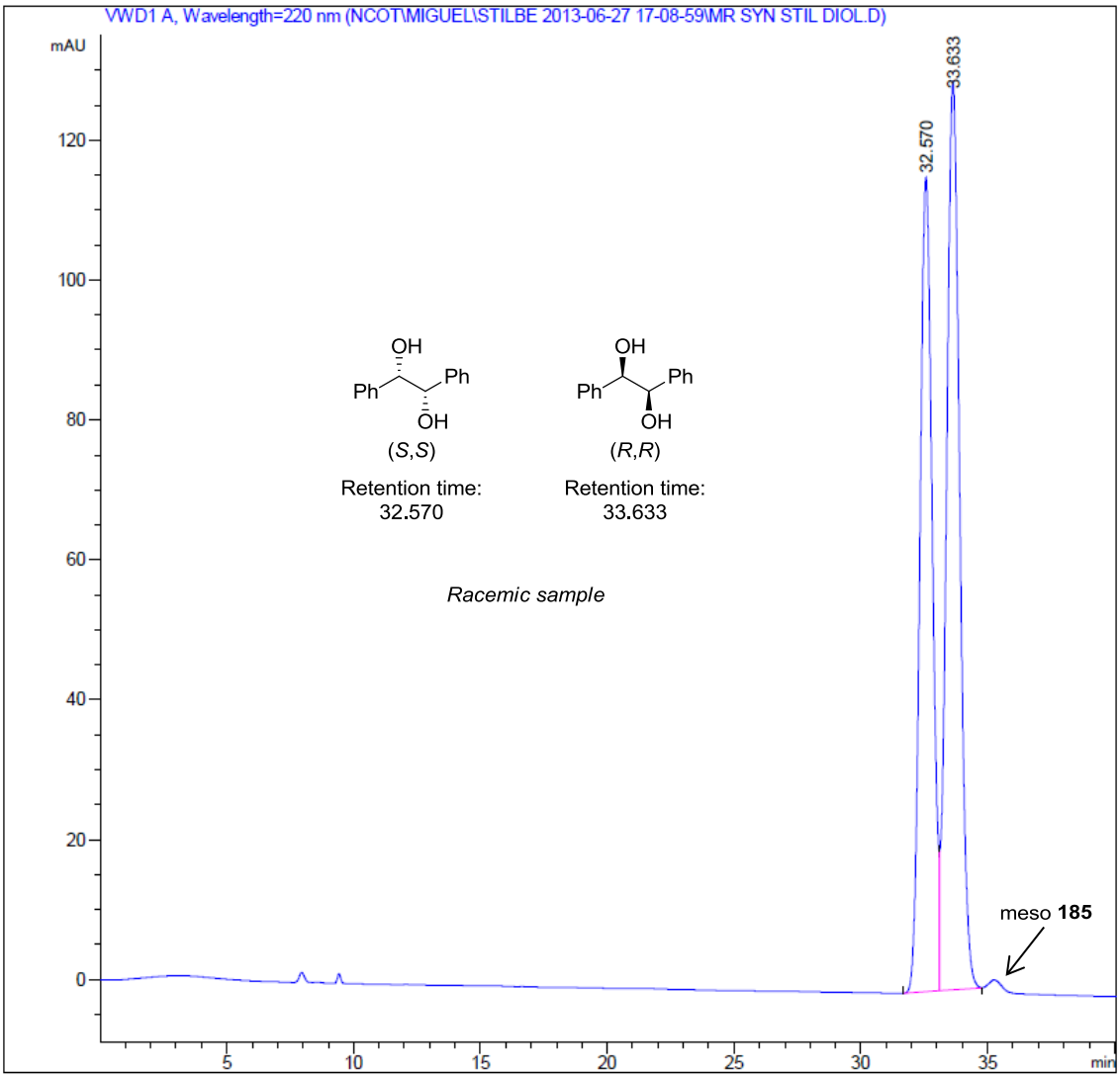
HSQC of *anti*-dihydroxylation intermediate 355 ($CDCl_3$)



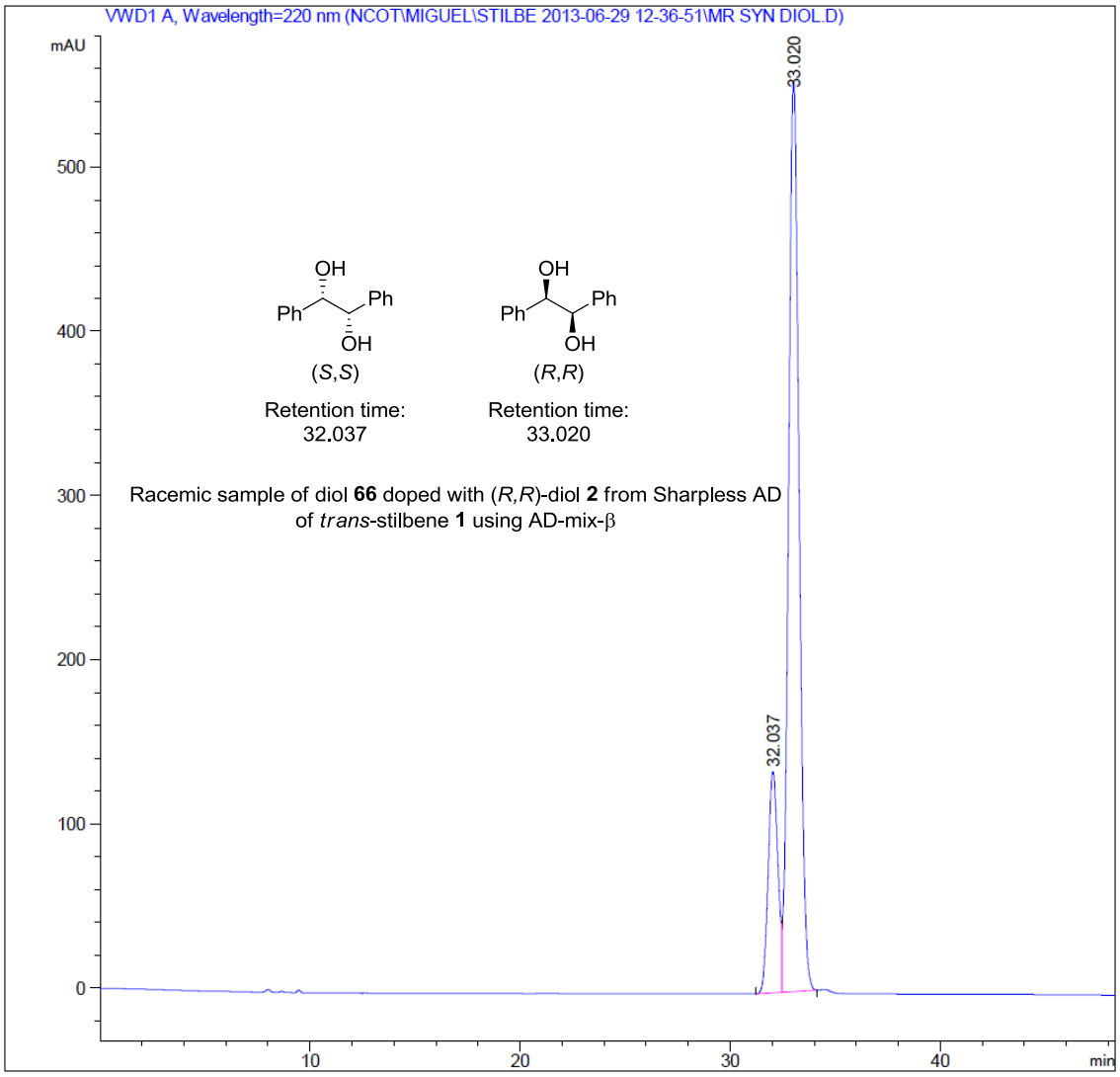
HMBC of *anti*-dihydroxylation intermediate 355 ($CDCl_3$)



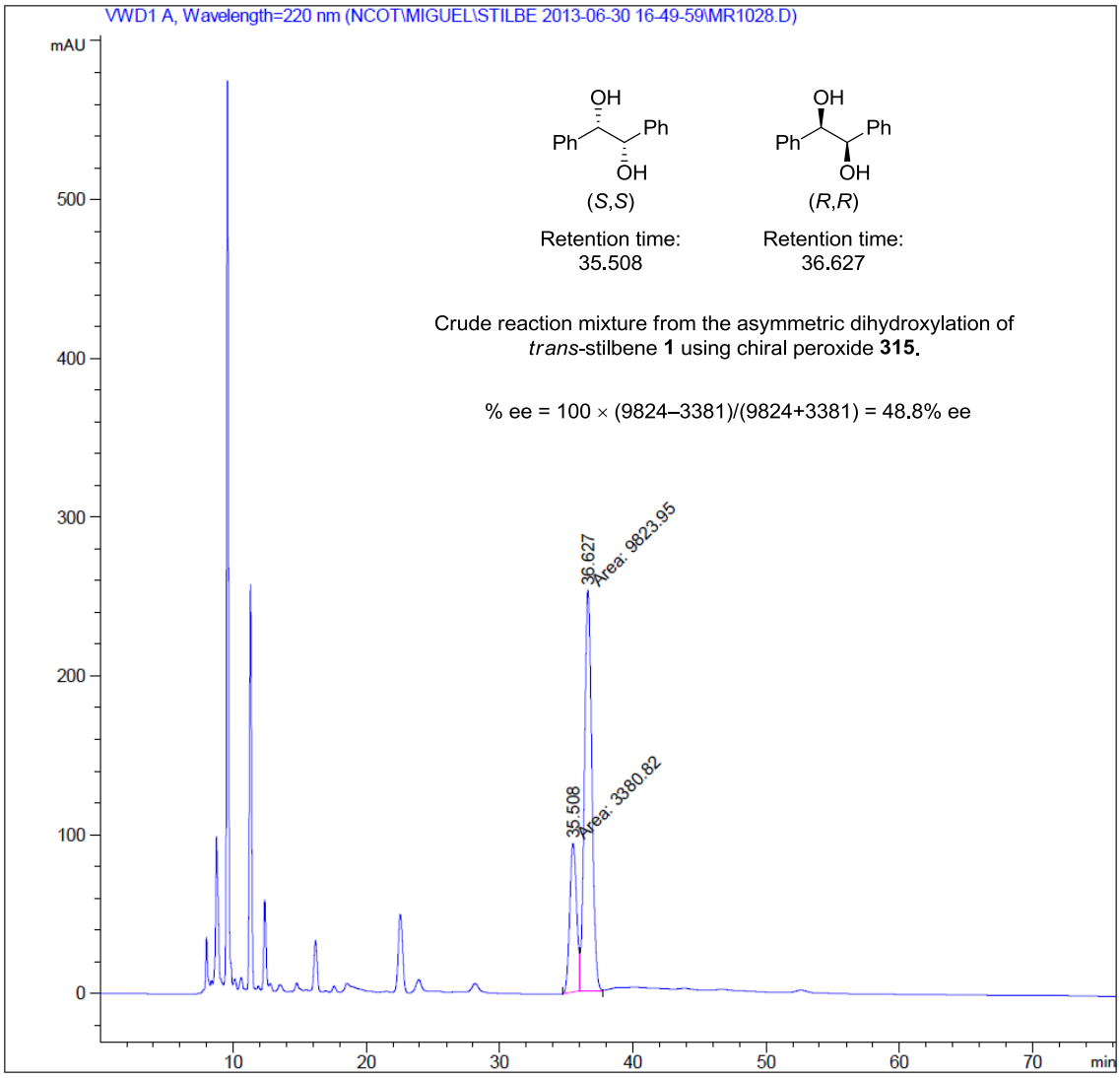
9.4 HPLC Chromatograms



Conditions for HPLC analysis: IC Column, injection volume: 2.0 µL, wavelength: 220 nm, solvent: isopropanol/hexane (8:92), flow rate: 0.4 mL/min, T = 25 ^{o}C



Conditions for HPLC analysis: IC Column, injection volume: 2.0 µL, wavelength: 220 nm, solvent: isopropanol/hexane (8:92), flow rate: 0.4 mL/min, T = 25 ^{o}C



Conditions for HPLC analysis: IC Column, injection volume: 2.0 µL, wavelength: 220 nm, solvent: isopropanol/hexane (8:92), flow rate: 0.4 mL/min, T = 25 ^{o}C

9.5 BAM Fallhammer Test Report

Chilworth GLOBAL

Client	Cardiff University
Contact	Dr N. Tomkinson
Report issue date	29th November 2010
Report number	J303832R1V1/10

Cyclopropyl Malonoyl Peroxide

BAM Fallhammer Testing

Checked by Mr Paul Carter	Approved by Dr Stephen Rowe
Principal Laboratory Scientist	Process Safety Specialist
For and on behalf of Chilworth Technology Limited	

Quote / Job Numbers: 105448 / 303832

Report prepared by Miss Ingrid Livingston

Chilworth Technology Limited
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Southampton SO16 7NS
United Kingdom

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GLP & ISO/IEC LABORATORIES

THE EXPERTS IN PROCESS SAFETY

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2. SCOPE OF ASSESSMENT 3

3. TESTING RATIONALE - EXPLOSIVES TESTING 4

4. THE BAM FALLHAMMER TEST 8

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5. CONCLUSIONS 11

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1. INTRODUCTION

This report contains test data for Cardiff University relating to a sample of cyclopropyl malonoyl peroxide. In this assessment, a BAM fallhammer test was conducted in order to determine the samples sensitivity to impact.

The sample used in this study was supplied by Cardiff University. Mr M. Rawling was present at Chilworth Technology Ltd on 17th November 2010 in order to observe the test.

2. SCOPE OF ASSESSMENT

This assessment covers a BAM Fallhammer test on a sample of cyclopropyl malonoyl peroxide.

This work follows discussions between Dr N. Tomkinson (Cardiff University) and Dr D. Firth (Chilworth Technology Ltd) and is in response to quotation number 105448.

Safety in chemical manufacture requires that all possible operational hazards, i.e. the presence and possible ignition of flammable atmospheres, and chemical reaction hazards are evaluated and that a suitable basis for safe operation is determined and implemented.

Should the material characteristics or composition be changed then consideration should be given to re-assessment of the material.

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3. TESTING RATIONALE - EXPLOSIVES TESTING

The identification of potentially explosive or high rate decomposing properties in a material is a pre-requisite for safe handling and transportation. Any material which contains groups of known explosive properties (eg. nitro-, peroxy, azide etc.) should be tested and examined to identify the reaction of the material to various forms of explosion initiation, namely : impact, friction and thermal initiation.

Initially, small scale tests should be undertaken to assess the sensitivity of the material to mechanical and thermal initiation. Additional tests are then necessary to access the explosive properties of the sample when heated under confinement and exposed to detonable shock.

The most complete assessment methods for determining the explosive properties of a substance are provided in the UN Transportation of Dangerous Goods Recommendations, Tests and Criteria Manual (currently fourth revised edition). The test methods prescribed are recognised by authorities within almost all countries of the world. The following rationale is based on the standard methods prescribed.

Initial Screening

An initial screening of the compound under study can be performed employing Benson's method of group contributions to estimate the potential for highly energetic decompositions or detonable properties. This is normally undertaken using the CHETAH computer coding which ranks materials as low, medium or high risk in terms of decomposition energy based on the maximum enthalpy of decomposition, and the oxygen balance. If this desk based screening exercise shows potential for an energetic decomposition then it is appropriate to conduct further experimental trials to determine the sensitivity of the material.

Energy of Decomposition

Experimental testing will normally take the form of preliminary screening tests using small quantities. Primarily, the sample will be tested for its ignitability, followed by Differential Scanning Calorimetry (DSC) to determine the quantity of heat evolved during a thermally initiated decomposition. Should the energy of decomposition measured be greater than 300 $J.g^{-1}$, then the material should be handled as a highly energetic material and, should the energy of decomposition exceed 500 $J.g^{-1}$, may have explosive properties. Consequently, it should only be handled in small quantities whilst further investigations are made.

UN Test Procedures

The following test series (as defined by the UN Transportation of Dangerous Goods Recommendations) should be followed in order to classify the material as a candidate for inclusion as a Class 1 (Explosive) Substance (or to exclude the material from Class1). The above initial investigations should be conducted before proceeding with larger scale trials to gauge the likely hazards of the substance. Furthermore, the test series need not be completed in full or performed in the order in which they appear. For classification purposes, it would be normal to conduct Test series 3 first (since this uses the smallest quantities of

materials and provides essential stability and sensitivity information required for larger scale handling and testing.
The standard test methods can provide excellent data for non-classification purposes (ie. assessing the hazards of handling, storing or drying the substance). For example, sensitivity to friction should always be confirmed for a potentially energetic substance which requires milling.

The information provided below gives details of the aim of each test series, the tests involved and the approximate consequences of results. The formal UN recommendations should be consulted for a much more detailed description of the test methods and classification procedure. It should be borne in mind that explosive properties are highly scale dependent. For example, while a sample may not detonate in a test tube, it may detonate under similar conditions in a larger receptacle. For this reason, some of the latter classification tests are conducted on packages of the material as it will be supplied for transportation (often implying significant sample test sizes).

UN Test Series 1 To determine if a substance, not manufactured to be an explosive or pyrotechnic substance, possesses explosive properties.

Test 1 (a) : UN Gap Test
Test 1 (b) : Koenen Tube Test
Test 1 (c)(i) : Time / Pressure Test

The substance is said to possess explosive properties if the result of any of the three tests is positive.

UN Test Series 2 To determine if a substance with explosive properties is too insensitive for inclusion in Class 1.

Test 2 (a) : UN Gap Test
Test 2 (b) : Koenen Tube Test
Test 2 (c)(i) : Time / Pressure Test

The substance is a candidate for inclusion in Class 1 if the result of any of the three tests is positive.

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UN Test Series 3 To determine if the substance is too sensitive for transportation in the form in which it was tested.

Test 3 (a)(ii) : BAM Fallhammer Test
Test 3 (b)(i) : BAM Friction Test
Test 3 (c) : Thermal Stability Test at 75°C
Test 3 (d) : Small Scale Burning Test

If a material or article fails any test, it is deemed too sensitive for transport in the form in which it was tested.

UN Test Series 4 To determine if a substance which has failed any test of 3(a), 3(b) or 3(d) can be accepted into Class 1 after encapsulation or desensitisation.

Test 4 (a) : Thermal Stability Test for Unpackaged Articles and Packaged Articles
Test 4 (b)(i) : Steel Tube Drop Test for Liquids
Test 4 (b)(ii) : Twelve Metre Drop Test for Unpackaged Articles, Packaged Articles and Packaged Substances

If the material passes these tests, it can be considered for inclusion in Class 1 using the classification tests prescribed in Test Series 5, 6 and 7 tests.

UN Test Series 5 To determine if the substance which is a Class 1 candidate is a very insensitive explosive substance with a mass explosion hazard.

Test 5 (a) : Cap Sensitivity Test
Test 5 (b)(ii) : USA DDT Test
Test 5 (c) : External Fire Test for Division 1.5

If the material only presents a mass explosion hazard (ie. passes these three tests), it is a candidate for classification as a Class 1.5 substance. If the material fails any of the tests, Test Series 6 is required for further classification.

UN Test Series 6 To determine whether the material can be classified as : Class 1.1, 1.2, 1.3, 1.4 or excluded from Class 1.

Test 6 (a) : Single Package Test
Test 6 (b) : Stack Test
Test 6 (c) : External Fire (Bonfire) Test

Classification from this test series can be complex due to the large number of outcomes. If the material passes all three tests, it is excluded from Class 1. If the material presents a mass explosion hazard as a single package, it is classified as Class 1, Division 1.1. If the major hazard is from dangerous projections, the material is assigned to Class 1, Division 1.2.

If the major hazard is radiant heat or violent burning but without a blast and projection hazard, it is assigned to Class 1, Division 1.3. If there is a remaining small hazard in the event of ignition / initiation, the material is assigned to Class 1, Division 1.4.

UN Test Series 7	To determine if the substance / article is an Extremely Insensitive Detonating Substance (EIDS)
Tests 7 (a) – 7 (k)	Ten tests in all (not individually specified here).

If the material is found to be an extremely insensitive article, it can be excluded from Class 1.

A wide range of other UN (and other transportation standard) classification tests can be conducted by Chilworth Technology. These include, but are not limited to, the following :

UN Class 2+3 :	Flammable gases / liquids classification tests
UN Class 4.1 :	Flammable solids, self-reactive substances and solid desensitised explosives classification tests
UN Class 4.2 :	Substances liable to spontaneous combustion tests
UN Class 5.1 :	Oxidising substances classification tests
UN Class 5.2 :	Organic peroxides classification tests
UN Class 8 :	Corrosive substances classification tests

In addition, Chilworth Technology are also capable of providing regulatory physico-chemical property tests to recognised international methods for the purposes of Notification of New Substances, etc.

For further details on any of the tests outlined above, or for further information on the range of services available from Chilworth Technology, please do not hesitate to contact us.

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4. THE BAM FALLHAMMER TEST

Introduction

The test is designed to measure the sensitiveness of solid (including paste-like and gel-type) and liquid substances to impact and to determine if the substance is too dangerous to transport in the form in which it was tested. The test is conducted in accordance with UN Transport of Dangerous Goods Recommendations Test 3 (a) (ii).

Test Procedure

The BAM Fallhammer apparatus consists of a cast steel block with base, anvil, column, guides, drop weights, release device and impact device. There are weights of different masses of 1, 2, 5 and 10 kg which can be attached to the column and guides. By varying the weights and the height from which these weights are dropped, the impact energy can be changed from 1 J through to 60 J.

The sample of substance under test is enclosed in an impact device consisting of two co-axial steel cylinders, one above the other in a hollow cylindrical steel guide ring. The cylinders are steel rollers from roller bearings with polished surfaces and rounded edges. The impact device is placed on the intermediate anvil and centred.

The test substance (if in powder form) is sieved (sieve mesh 0.5 mm) and all that passes through the sieve is used for the test. Wetted substances are tested with the minimum content of wetting agent provided for transport and liquid substances are tested as received.

A sample is taken with a scoop of 40 mm^3. The substance is then placed in the open impact device, which is already in the locating ring on the intermediate anvil. The upper steel cylinder is then set to be 1 mm above the lower cylinder, and held in that position by means of an O-ring.

In the interpretation of results of the trial, distinction is made between "no reaction", "decomposition" (change of colour) and "explosion" (crackling, sparking or inflammation). The series of trials is typically started with a single trial at 10 J. If at this trial the result "explosion" is observed, the series is continued with trials at stepwise lower impact energy until the result "decomposition" or "no reaction" is observed. If however the result "decomposition" or "no reaction" is observed at 10 J, the weight can slowly be increased until an "explosion" is observed or the maximum impact energy is reached (60 J).

Interpretation of Results

The limiting impact energy of a substance is defined as the lowest energy at which the result "explosion" is obtained from at least one out of the six trials.

The test result is considered positive (+) if the limiting impact energy is 2 J or less and the substance is considered too dangerous to transport in the form in which it was tested. Otherwise the result is considered negative (-)

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4.1 Cyclopropyl Malonoyl Peroxide

Test System Employed	:	BAM Fallhammer System 1
Date of Test	:	17th November 2010
Test Operator	:	P. Carter
Sample Preparation	:	Sample sieved (0.5 mm)

Test Objective

To test a sample of cyclopropyl malonoyl peroxide to determine the limiting impact energy of the substance in the BAM Fallhammer test using the UN test method Test 3 (a) (ii).

Test Procedure

The sample was placed in the impact device and the 10 kg weight dropped from a height of 60 cm which is equivalent to 60 J. If an "explosion" was observed, the height from which the weight was dropped was decreased and if necessary the weight was reduced, until six "no reaction" or "decomposition" tests were observed in the same series.

Test Results

Mass (kg)	Height (m)	Energy (J)	Test number and result* (X / ✓)						Comments
			1	2	3	4	5	6	
10	0.6	60	✓						Loud bang (audible ignition)
10	0.3	30	✓						Loud bang (audible ignition)
10	0.1	10	✓						Loud bang (audible ignition)
1	0.5	5	X	X	X	X	X	X	No reaction

* '✓' denotes an explosion (includes crackling, sparking, inflammation).
'X' denotes no reaction or decomposition (change in colour).

The sample of cyclopropyl malonoyl peroxide was observed to have a limiting impact energy of 5 - 10 J. The test result is therefore considered negative (-) (according to the UN Transport of Dangerous Goods Recommendations). However, the material is quite sensitive to impact.

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5. CONCLUSIONS

1. A BAM Fallhammer test was conducted on a sample of cyclopropyl malonoyl peroxide. The sample was found to have a limiting impact energy of 5-10 J and is therefore not considered to be sensitive to impact (according to the UN transport of Dangerous Goods Recommendations for transport classification purposes).

2. Although the sample has proven insensitive to impact (according to the formal test result definition), it is clear from the result of the test that ignition occurs down to quite low impact energies. For the handling of the material therefore, great care should be taken to avoid energetic processes (e.g. milling). The current test considers only small quantities of material.

3. It should also be noted that the test result would be considered positive according to EC 440/2008 (a different test standard which employs the same test equipment).

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