The Development of Metal-Free Peroxide-Mediated Chemical Reactions

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I. 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: 14.7.2020

(Jonathan Curle)

II. Abstract

This thesis describes the development and optimisation of metal-free alkene difunctionalisation reactions using organic peroxides. An alkene *anti*-oxyamination procedure has been successfully developed to form protected β-amino alcohols, with an extension of this methodology also giving access to oxazolidinones by an overall alkene *syn*-oxyamination procedure. Additionally, the reactivity of alkenes with a peroxylactone molecule was investigated, with the intention of developing an organocatalytic alkene dihydroxylation procedure.

Chapter 1 outlines the previous work conducted within the Tomkinson group concerning alkene functionalisation using organic peroxides. This work includes alkene *syn*- and *anti*-dihydroxylation procedures using a malonoyl peroxide, intramolecular alkene functionalisation to access nitrogen and oxygen containing heterocycles and an organocatalytic sulfoxidation procedure.

Chapter 2 describes the discovery and development of a novel alkene *anti*-oxyamination reaction using a malonoyl peroxide. Following discovery and an optimisation of a suitable nitrogen nucleophile, the scope of the reaction was investigated, showing excellent yield and diastereoselectivity. Oxyaminated products were successfully deprotected, providing handles for further functionalisation. Finally, the methodology was further developed to access oxazolidinone molecules by a formal alkene *syn*-oxyamination procedure.

Chapter 3 describes the novel reactivity of a peroxylactone molecule with alkenes. The primary reaction was found to be an epoxidation, with the resulting epoxide reacting further to give numerous additional products. A mechanistic investigation was conducted to explain the formation of each reaction product observed. Based upon this knowledge attempts were made to control the reaction towards a selective dihydroxylation procedure, with an optimisation of conditions and substrate engineering.

Chapter 4 contains the experimental procedures and characterisation for the relevant compounds found within this thesis.

III. Acknowledgements

Firstly, I would like to thank Professor Nick Tomkinson for giving me the opportunity to work under his supervision. The last four years have been filled with challenge and discovery, alongside constant personal and academic growth. The skills and experiences I now take with me from my postgraduate studies, are a result of Nick's meticulous and insightful mentorship. I leave with a deeper knowledge and love for chemistry and will always look back on this period of my life with fondness, it has been a fulfilling and worthwhile pursuit. Thank you, Nick!

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I thank my parents and my family for their constant support during my PhD. It would have been impossible to complete my PhD if it weren't for your unconditional love and support. Thank you for all you do for me!

Finally, I thank and acknowledge my Lord and Saviour Jesus Christ. For provision and peace from the start to the finish.

> *"For I know the plans I have for you, declares the Lord, plans to prosper you and not to harm you, plans to give you a hope and a future"*
> *Jeremiah 29:11*

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V. Abbreviations

%	Percent
$[\alpha]_D$	Optical rotation under a sodium lamp
°C	Degrees Celsius
Å	Angstrom
A_{650}	Absorbance or optical density measured at 650 nm
AA	Asymmetric aminohydroxylation
Ac	Acetyl
AD	Asymmetric dihydroxylation
APCI	Atmospheric pressure chemical ionisation
aq	Aqueous
ATR	Attenuated total reflectance
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
c	Concentration
cat.	Catalyst
Cbz	Benzyl carbamate
CI	Chemical ionisation
cm	Centimetre
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
d	Days
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DIAD	Diisopropyl azodicarboxylate
DMA	Dimethylacetamide
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMF	Dimethylformamide
DMM	Dimethoxymethane

DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DNB	Dinitrobenzene
E_a	Activation energy
EDTA	Ethylenediaminetetraacetic acid
ee	Enantiomeric excess
eq	Equivalent
ES	Electrospray ionisation
esp	α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid
Et	Ethyl
g	Grams
GCMS	Gas chromatography mass spectrometry
h	Hour/s
h	Planck constant
HFIP	Hexafluoroisopropanol
HRMS	High resolution mass spectrometry
Hz	Hertz
Hz	Hertz
iPA	Isopropyl alcohol
^{i}Pr	Isopropyl
IR	Infrared
L	Litre
LCMS	Liquid chromatography mass spectrometry
LDA	Lithium diisopropylamide
Lit	Literature
LRMS	Low resolution mass spectrometry
M	Mega
m	milli
M	Moles per litre
m/*z*	Mass to charge ratio
*m*CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl

min	Minute
mol	Mole/s
mp	Melting point
Ms	Mesyl
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PG	Protecting group
Ph	Phenyl
PHAL	Phthalazine
ppm	Parts per million
rt	Room temperature
Sacc	Saccharin
SET	Single electron transfer
SSA	Silica sulfuric acid
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethyl silyl
TBHP	*tert*-Butyl hydroperoxide
t-Bu	*tert*-Butyl
TC	Thiophene-2-carboxylate
Tces	2,2,2-Trichloroethoxysulfonyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tol	Tolyl
Ts	Tosyl
UV	Ultraviolet
v	Frequency
w/v	Weight per volume
δ	Chemical shift

µ	micro

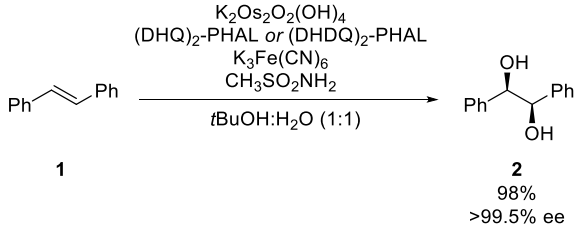
Chapter 1. Previous Work on Peroxides

Chapter 1. Previous Work on Peroxides

The Tomkinson group have long been focused upon the development of new chemical methodologies. As a general theme, these methodologies aim to be easily accessible to chemists worldwide, without the need for highly specialised equipment or techniques. As a result of this philosophy, a variety of novel transition metal-free chemical methodologies have been developed.

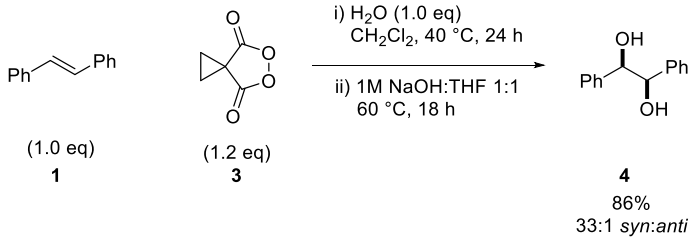
1.1 Dihydroxylation of Alkenes using Malonoyl Peroxide

The dihydroxylation of alkenes is a fundamental reaction within the tool kit of an organic chemist. A vast number of procedures have been developed for this transformation, the most successful and universally applied being the Sharpless asymmetric dihydroxylation.[1] Treatment of *trans*-stilbene **1** with AD-mix (a pre-made formulation of the reagents shown in Scheme 1) in a 1:1 mix of *t*BuOH:H_2O afforded vicinal diol **2** in high yields and enantioselectivity (Scheme 1).[1] This reaction is catalysed by potassium osmate dihydrate ($K_2OsO_2(OH)_4$) and the enantioselectivity is controlled by use of chiral quinine derived ligands $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL, which are discussed in Section 2.1.2.1.



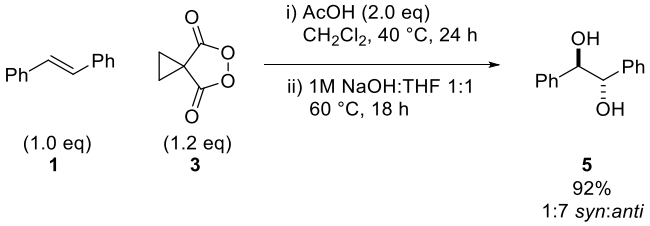
Scheme 1. The Sharpless asymmetric dihydroxylation of *trans*-stilbene **1**.[1]

Although such a reaction is seen as the "gold standard" within organic chemistry, it has drawbacks due to its use of highly toxic osmium(VIII) and the large volume of inorganic waste generated within the transformation.[2] With this in mind, the Tomkinson group developed a metal-free procedure for the dihydroxylation of alkenes, using malonoyl peroxide **3**.[3] Treatment of *trans*-stilbene **1** with malonoyl peroxide **3** in the presence of water, followed by basic hydrolysis, provided *syn*-diol **4** in excellent yield (86%) and diastereoselectivity (33:1 *syn*:*anti*) (Scheme 2).



Scheme 2. *Syn*-dihydroxylation of *trans*-stilbene **1** using malonoyl peroxide **3**.[3]

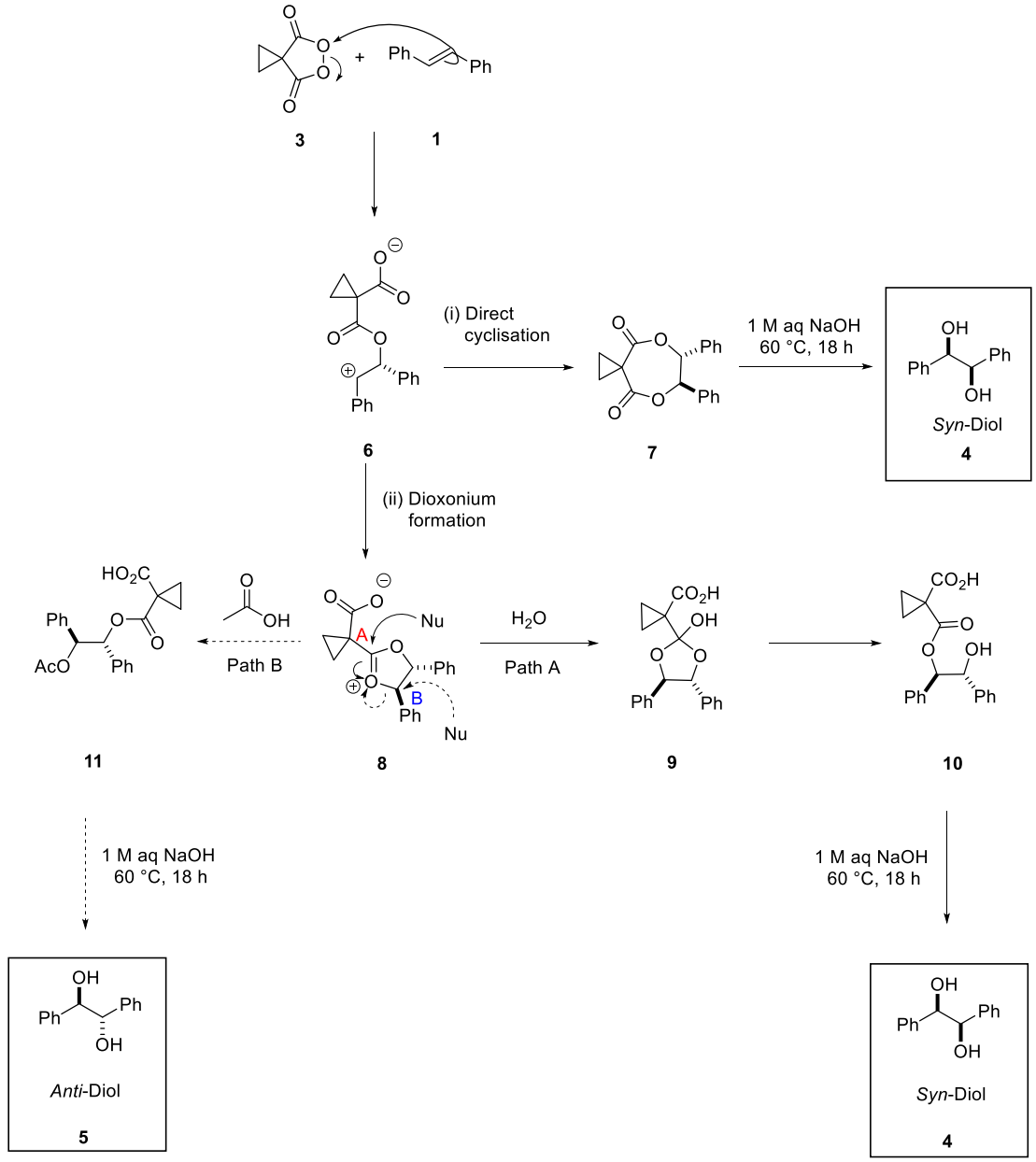
In 2015, the dihydroxylation procedure was further developed to allow access to *anti*-diols.[4] In a similar manner to the *syn*-procedure, *trans*-stilbene **1** was treated with malonoyl peroxide **3**, in the presence of dry acetic acid, to provide *anti*-diol **5** after basic hydrolysis (92%; 1:7 *syn*:*anti*) (Scheme 3).



Scheme 3. *Anti*-dihydroxylation of *trans*-stilbene **1** using malonoyl peroxide **3**.[4]

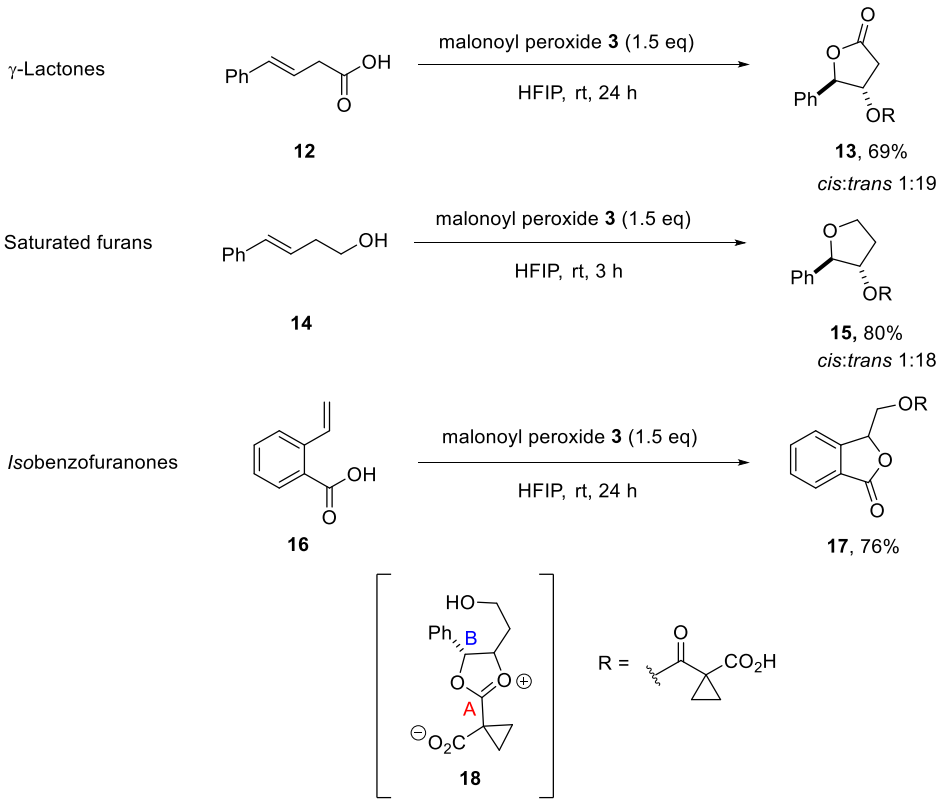
Mechanistically, it was proposed that reaction of *trans*-stilbene **1** with malonoyl peroxide **3** leads to zwitter-ionic species **6** (Scheme 4).[4,5] This species may form 7-membered ring **7**, through charge recombination (14%, minor product) or dioxonium species **8** (86%, major product). Water hydrolysis of dioxonium intermediate **8** occurs at position **A**, to give *syn*-diol **4**, after basic hydrolysis. Basic hydrolysis of 7-membered ring **7** also leads to the *syn*-diol **4**. In the *anti*-dihydroxylation procedure, dioxonium intermediate **8** is opened by nucleophilic attack of acetic acid at position **B**, to give intermediate **11**. Basic hydrolysis leads to *anti*-diol **5**.

Both the *syn*- and *anti*-dihydroxylation procedures use stoichiometric quantities of malonoyl peroxide **3**. It is a long-term ambition of the group to develop an organocatalytic dihydroxylation procedure. Catalysis of the process has been achieved by the addition of fluorinated alcohols such as hexafluoroisopropanol (HFIP),[6] where it was found that addition of HFIP increased the rate of reaction for the *syn*-dihydroxylation procedure. This was attributed to the ability of the alcohol to act as an H-bond donor, activating peroxide **3** towards nucleophilic attack.



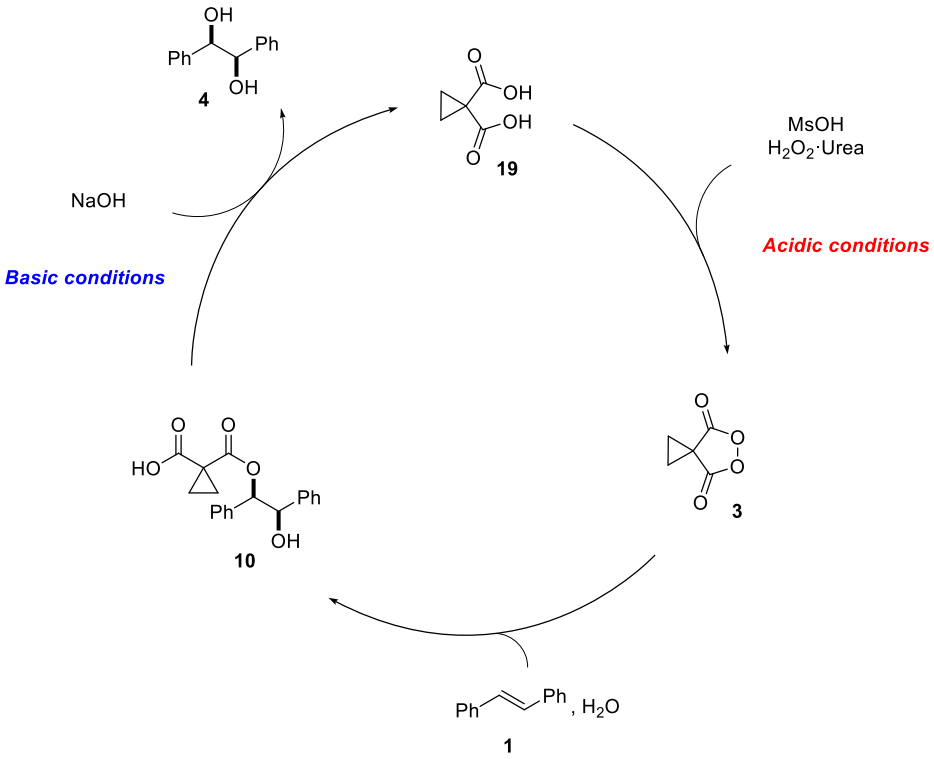
Scheme 4. Proposed mechanism for *syn*- and *anti*-dihydroxylation of *trans*-stilbene **1**.[4,5]

An intramolecular variation of the dihydroxylation procedure has also been developed.[7] It was found that dioxonium species **8**, could be trapped intramolecularly with an oxygen nucleophile pendant to the alkene. This has led to the successful stereoselective synthesis of γ-lactones **13**, saturated furans **15** and isobenzofuranones **17** (Scheme 5). Attack of the pendant nucleophile occurs through position **B** of dioxonium **18**, in a manner similar to the *anti*-dihydroxylation procedure.



Scheme 5. Intramolecular variations on the dihydroxylation procedure.[7]

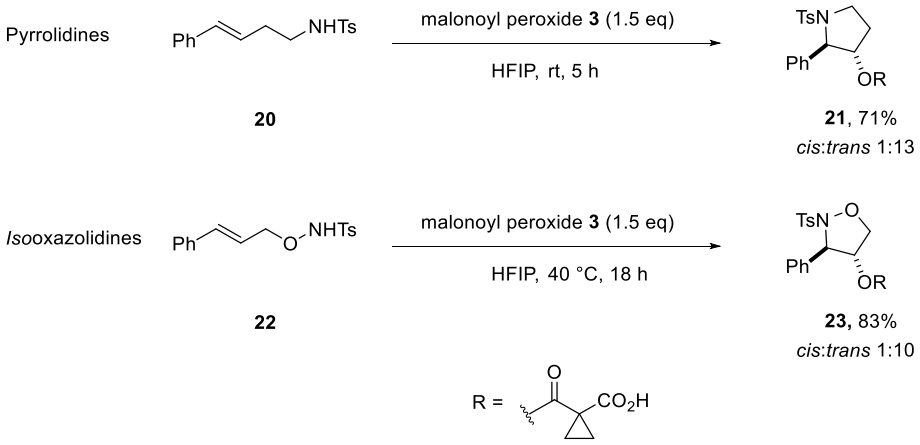
Based on our mechanistic knowledge of the reaction of peroxide **3** with alkene **1**, it was clear that a catalytic dihydroxylation procedure could not be developed when using malonoyl peroxide **3**. Within the established dihydroxylation methodology, peroxide **3** was formed from malonic acid **19** under acidic conditions with the subsequent reaction with *trans*-stilbene **1** affording ester **10**. As reported, liberation of diol **4** from ester **10** by hydrolysis required basic conditions. Although a catalytic cycle can be drawn successfully on paper, the need for both acidic and basic conditions within the cycle are unachievable in practice (Scheme 6). In order to achieve a metal-free organocatalytic dihydroxylation procedure, an alternative peroxide to malonoyl peroxide **3** would have to be developed.



Scheme 6. *Syn*-dihydroxylation with malonoyl peroxide **3**; incompatible catalytic cycle.

1.2 Oxyamination Procedures

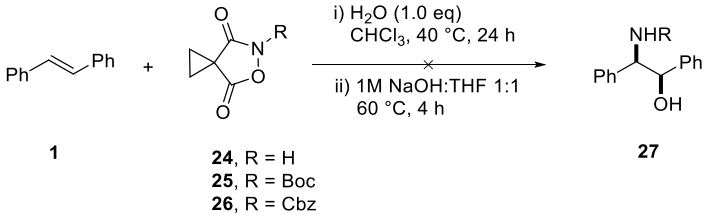
The first intramolecular oxyamination using malonyl peroxide **3** was developed within the group by Alamillo-Ferrer.[8] Using the conditions developed for the oxygen-based cyclisations (Scheme 5), alkenes with various pendent nitrogen nucleophiles were transformed into the corresponding pyrrolidines **21** and isoxazolidines **23**, in good yield and stereoselectivity (Scheme 7).



Scheme 7. Intramolecular oxyamination procedure using malonoyl peroxide **3**.[8]

Attempts were also made into the development of an intermolecular oxyamination procedure. In work conducted by Dragan, a series of malonoyl hydroxylamines **24**–**26** were synthesised.

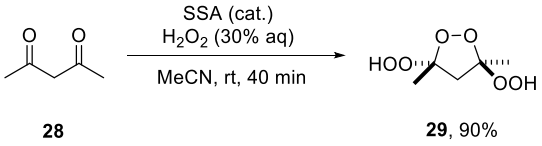
Unfortunately, employing the *syn*-dihydroxylation conditions to malonoyl hydroxylamines **24**–**26** resulted in only starting materials being isolated (Scheme 8).[9]



Scheme 8. Attempted intermolecular oxyamination under *syn*-dihydroxylation conditions.[9]

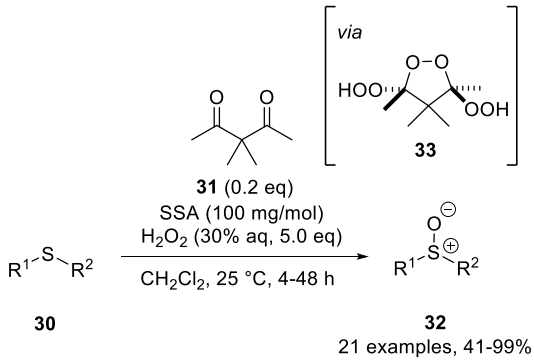
1.3 Organocatalytic Sulfoxidation

In 2013, Azarifar reported that peroxide **29** could be formed by treatment of ketone **28** with silica sulfuric acid (SSA) and hydrogen peroxide in acetonitrile (Scheme 9).[10]



Scheme 9. Formation of trisperoxide **29** from diketone **28**.[10]

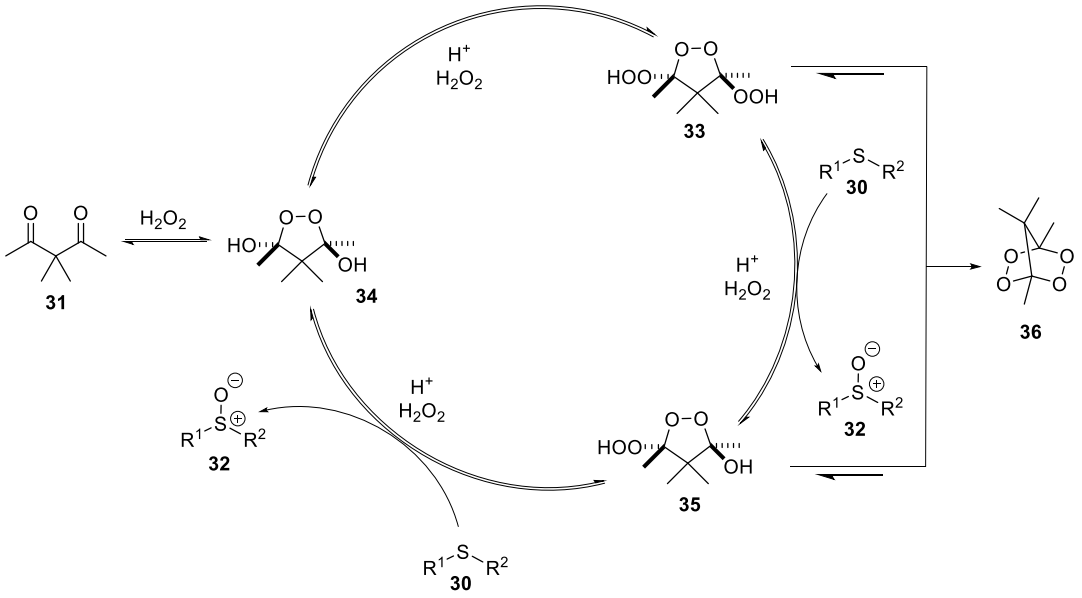
Inspired by the work of Azarifar, Davidson developed a novel organocatalytic sulfoxidation procedure, loosely based upon the literature conditions to form peroxide **29**. Upon extensive optimisation, it was found that sulfide **30** could be converted to sulfoxide **32** by treatment with diketone **31** in the presence of hydrogen peroxide under acidic reaction conditions (Scheme 10).[11]



Scheme 10. Catalytic sulfoxidation of sulfide **30** using ketone **31** catalyst.[11]

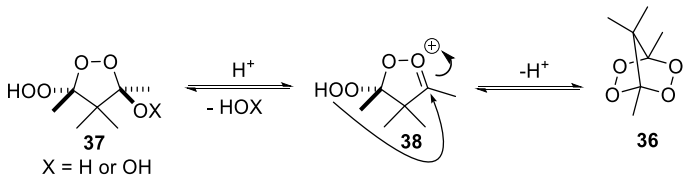
Mechanistically, it was proposed that diketone **31** reacted with an equivalent of hydrogen peroxide to form monoperoxide **34**. Acid-catalysed acetal chemistry allowed for exchange of the hydroxyl groups of peroxide **34** with hydrogen peroxide to form trisperoxide **33**. Peroxide **33** had the ability to oxidise sulfide **30** to sulfoxide **32**, producing bisperoxide **35**, which in turn could oxidise another equivalent of sulfide **30**, regenerating monoperoxide **34**. Monoperoxide **34** may also react with an equivalent of hydrogen peroxide to form bisperoxide

35, which itself may react with another equivalent of hydrogen peroxide to form trisperoxide **33** (Scheme 11).



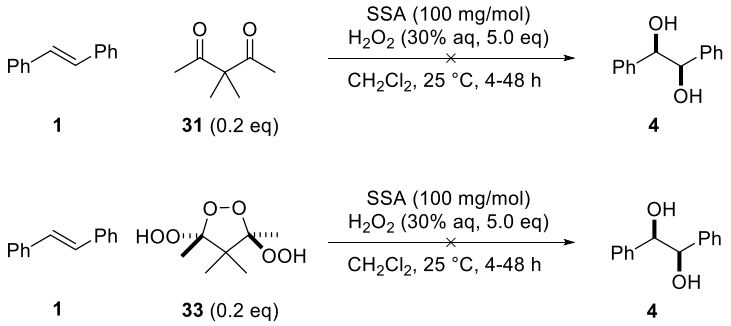
Scheme 11. Proposed catalytic cycle for the sulfoxidation of sulfide **30** using diketone **31**.[11]

Tetraoxane **36** was found within the reaction mixture but was understood to be a non-reactive peroxide under the reaction conditions. This compound was formed from peroxide **37** *via* acid-catalysed acetal-type chemistry to give **38**, followed by intramolecular cyclisation to arrive at tetraoxane **36** (Scheme 12). Experimental evidence also suggested tetraoxane **36** may slowly reform peroxides **33** or **35** and re-enter the catalytic cycle (Scheme 11).[11]



Scheme 12. Proposed mechanism of formation for tetraoxane **36**.[11]

It was hoped that the developed catalytic sulfoxidation could be applied to alkenes, to arrive at a peroxide-mediated catalytic dihydroxylation procedure. Unfortunately, when trisperoxide **33** or ketone **31** was reacted with *trans*-stilbene **1** in the presence of hydrogen peroxide under acidic conditions, no reaction was observed (Scheme 13). It was concluded that peroxide **33** was not reactive enough to interact with a weakly nucleophilic alkene and an alternative, more reactive peroxide species would have to be developed.



Scheme 13. Failed reaction of ketone **31** and trisperoxide **33** with *trans*-stilbene **1**.

In summary, work from our laboratory has successfully developed multiple metal-free alkene functionalisation reactions. *Syn*- and *anti*-dihydroxylation procedures, using malonoyl peroxide **3** were developed using water and acetic acid, respectively (Scheme 2 and Scheme 3).[3,4] An intramolecular variation of the dihydroxylation procedure was also developed and led to the successful stereoselective synthesis of γ-lactones **13**, saturated furans **15** and isobenzofuranones **17** (Scheme 5).[7] Additionally an intramolecular oxyamination procedure was developed for the stereoselective synthesis of pyrrolidines **21** and isoxazolidines **23**, in good yield and stereoselectivity (Scheme 7).[12] In other work, a novel organocatalytic sulfoxidation procedure was developed to transform sulfide **30** to sulfoxide **32**, by treatment with diketone **31** in the presence of hydrogen peroxide under acidic reaction conditions (Scheme 10).[11]

Chapter 2. Alkene *Syn*- and *Anti*-Oxyamination With Malonoyl Peroxide

Chapter 2. Alkene *Syn*- and *Anti*-Oxyamination With Malonoyl Peroxide

2.1 Introduction

2.1.1 *β*-Amino alcohols

The *β*-amino alcohol moiety is a common structural feature within a variety of organic molecules. It is found within a host of natural products, from amino acids, such as serine **39** and threonine **40**, to the hormone, adrenaline **41**. A host of pharmaceutical compounds also exist that contain this functionality. Saquinavir **42**, is a synthetic peptide analogue used to inhibit HIV protease,[13] whereas Salbutamol **43**, is a well-known β_2 agonist used in the treatment of asthma.[14]

The *β*-amino alcohol moiety is also used within organic synthesis. Evans auxiliary **44**, an amino alcohol derived oxazolidinone, is used within asymmetric synthesis[15] and ephedrine derivative **45** is used as a chiral proton source to deracemize enolates (Figure 1).[16]

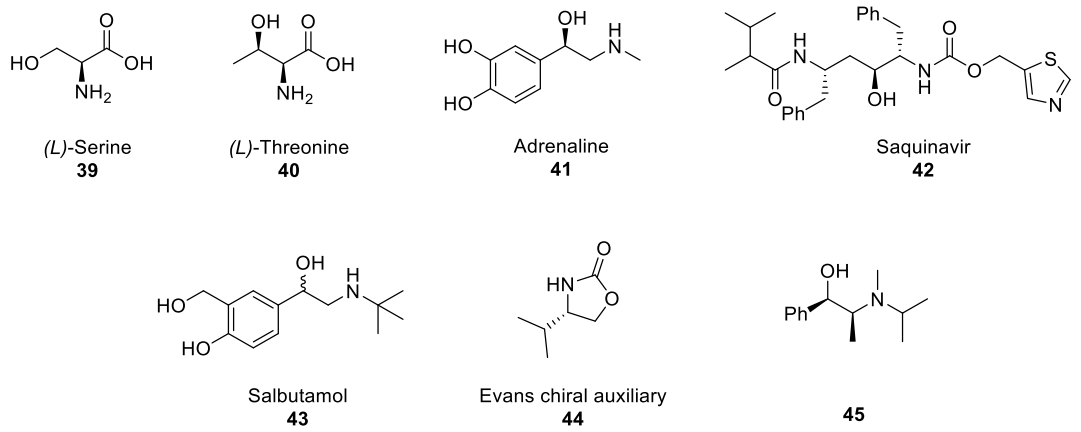


Figure 1. Organic molecules containing a *β*-amino alcohol moiety.

With such a wide variety of applications, it is clear why many synthetic methods have been developed for the synthesis of *β*-amino alcohols. Four of the most commonly used methods are summarised in Figure 2. These four approaches will be discussed over the following sections.

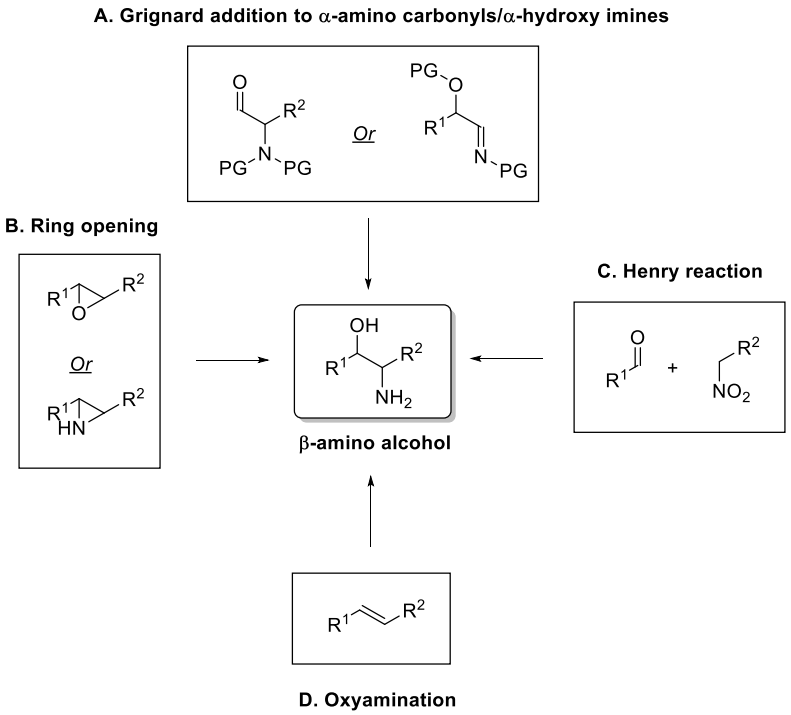
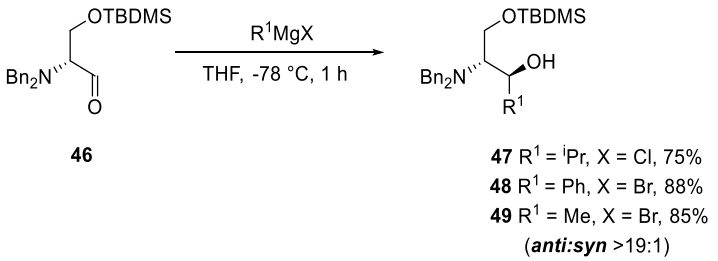


Figure 2. Routes used to prepare *β*-amino alcohols.

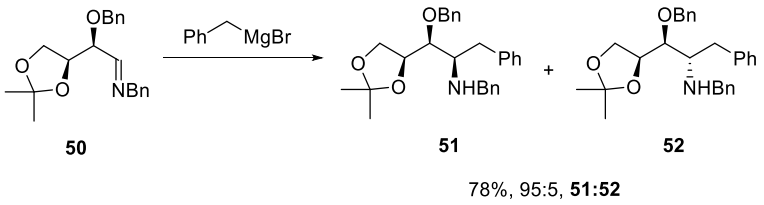
2.1.1.1 Grignard addition to α-amino carbonyls/α-alkoxy imines

Grignard addition to a molecule containing oxygen and nitrogen heteroatoms on vicinal carbons leads to a *β*-amino alcohol product. The popularity of this method to make *β*-amino alcohols is a result of the large volume of work dedicated to the stereoselective addition of nucleophiles into carbonyl species.[17] Zhu *et al.* reported that addition of a Grignard reagent to aldehyde **46** gave the corresponding *anti*-*β*-amino alcohol **47**–**49** in good yield. The high diastereoselectivity delivers a strong preference for nucleophilic addition which can be predicted using the Felkin-Anh model. The low stability of α-amino aldehydes is a potential drawback of this method, with aldehyde **46** being generated *via* Swern oxidation, worked up and then used immediately in the Grignard addition step (Scheme 14).[18]



Scheme 14. Grignard addition to serine derived *α*-amino aldehyde.[18]

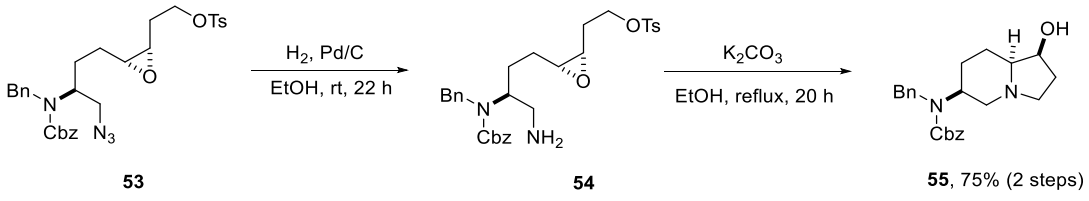
α-Alkoxy imines are considered to be relatively unstable, however, their reactions with Grignard reagents can proceed with good yield and selectivity (Scheme 15).[19]



Scheme 15. Grignard addition to α-alkoxy imine.[19,17]

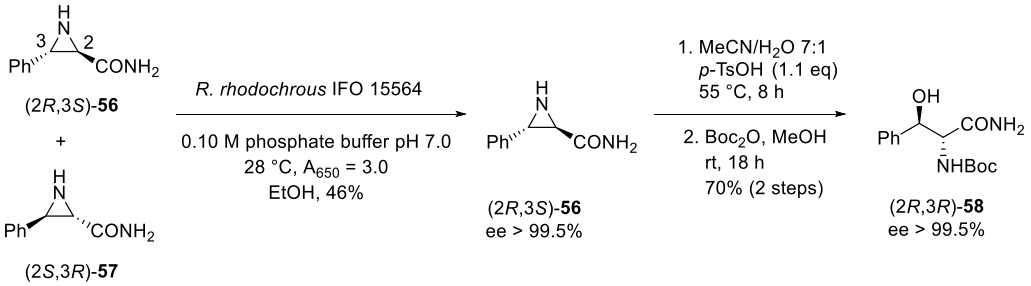
2.1.1.2 Ring opening of epoxides/aziridines

The ring opening of an epoxide is an attractive method to access *β*-amino alcohols. Procedures such as the Sharpless asymmetric epoxidation ensure enantiomerically pure epoxides can be obtained. The epoxide may be opened by a nitrogen nucleophile in an S_N2 manner, to yield an *anti-β*-amino alcohol product. With unsymmetrical epoxides, regioselectivity is a major challenge, as the nucleophile can attack both carbon atoms of the epoxide ring. In the synthesis of (-)-Slaframine, azide **53** was first reduced to amine **54**. The regioselectivity of the epoxide opening was controlled as the reaction is intramolecular and favours the formation of the six-membered ring. The amine then reacts in an intramolecular manner to afford indolizidine **55** (Scheme 16).[20]



Scheme 16. Epoxide opening in the total synthesis of (-)-Slaframine.[20]

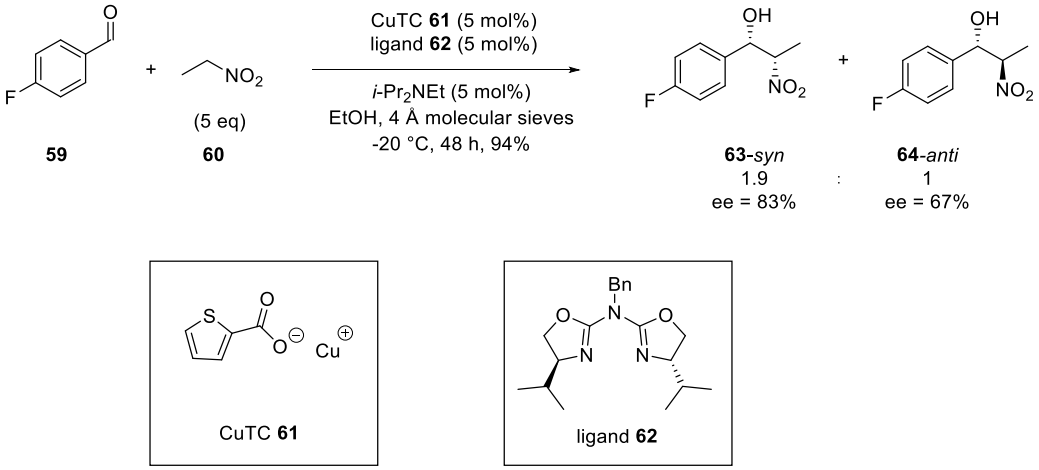
Aziridines can also be ring opened, using an oxygen nucleophile such as water, to give the corresponding amino alcohol product. Ring opening is most favourable when aziridines are activated (aziridines bearing an electron withdrawing N-substituent such as acyl, sulfonyl, or phosphoryl), however, ring opening can also be achieved with unactivated aziridines (NH-, N-alkyl-, N-arylaziridines).[21] This method also has challenges associated with regioselectivity, with the possibility to open the aziridine at either carbon atom. Many methods have been developed for the enantioselective synthesis of aziridines.[21] Moran-Ramallal *et al.* reported a method in which racemic aziridines were resolved by the enzyme *R. rhodochrous*, to give enatiomerically pure aziridine **56**. Subsequent treatment with water gave rise to the *β*-amino alcohol **58** (Scheme 17).[22] The ring opening of the aziridine took place with complete regioselectivity at the benzylic position. Overall, ring openings provide excellent *anti*-diastereoselectivity, however, the major drawback is lack of control over regioselectivity.



Scheme 17. Kinetic resolution and aziridine opening to produce *β*-amino alcohol **58**.[22]

2.1.1.3 Henry reaction

The Henry reaction is a C–C bond forming reaction between an aldehyde and a nitroalkane, to form a *β*-nitro alcohol.[23] Enantioselective variants of this reaction have been developed with the use of chiral metal complexes and chiral organocatalysts.[24] Lang *et al*. reported a diastereoselective variant of the Henry reaction in 2010.[25] A 1.9:1 selectivity for *syn*-*β*-nitro alcohol **63** was achieved through the use of chiral aza-*bis*-oxazoline ligand **62**, bound to copper(I)-thiophene-2-carboxylate (CuTC) **61** (Scheme 18). Subsequent reduction of the *β*-nitro alcohol would allow access to a *β*-amino alcohol. This reaction is mostly limited to simple nitroalkanes, such as nitromethane and nitroethane, therefore, to date, a limited scope of *β*-nitro alcohols can be accessed *via* the Henry reaction.



Scheme 18. Copper catalysed diasterioselective Henry reaction.[25]

2.1.1.4 Oxyamination

Oxyamination describes the direct synthesis of *β*-amino alcohols from alkenes. It represents a powerful tool for the introduction of vicinal heteroatoms into organic molecules. The importance of this transformation is reflected by the volume of literature generated on oxyamination procedures over recent decades.[26] The following Sections shall review various

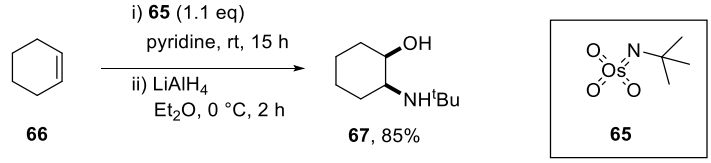
metal catalysed (Section 2.1.2) and metal-free (Section 2.1.3) alkene oxyamination procedures.

2.1.2 Metal-catalysed oxyamination

2.1.2.1 Sharpless asymmetric aminohydroxylation (AA)

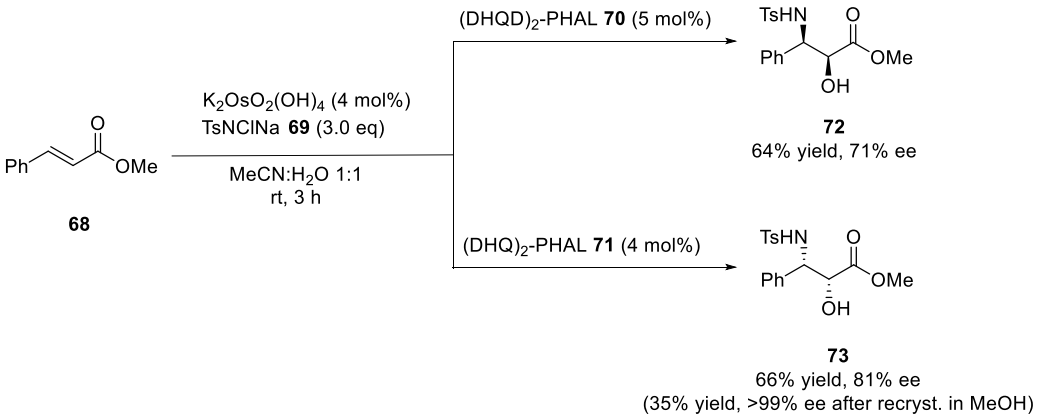
In 1975, Sharpless reported one of the first procedures for the *syn*-oxyamination of alkenes to form *β*-amino alcohols.[27]

In a similar manner that alkenes undergo dihydroxylation with osmium tetroxide, Sharpless reported that a comparable reaction takes place with the *tert*-butyl imido osmium complex **65**, leading to the oxyaminated product **67** (after treatment with lithium aluminium hydride). The reaction required stoichiometric quantities of the highly toxic *tert*-butyl imido osmium complex **65**, presenting a major drawback (Scheme 19).

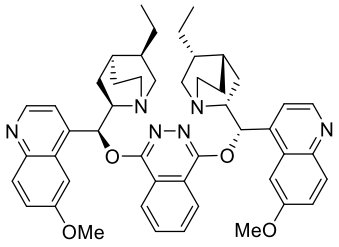


Scheme 19. Stoichiometric oxyamination using *tert*-butyl imido osmium complex **65**.[27]

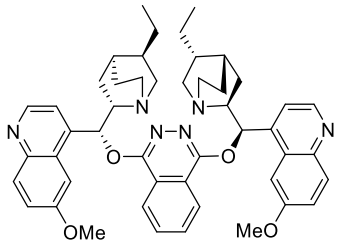
After twenty years of development, Sharpless reported the first asymmetric catalytic aminohydroxylation.[28] Alkenes are converted to the enantiomerically enriched *β*-amino alcohol by treatment with catalytic potassium osmate ($K_2OsO_2(OH)_4$) and chloramine-T **69** as the stoichiometric source of nitrogen. The regio- and stereoselectivity of the reaction is controlled by the addition of cinchona alkaloid ligands, dihydroquinine (DHQ) **71** or dihydroquinidine (DHQD) **70** bound to a phthalazine (PHAL) bridge (Figure 3). This was first exemplified by the synthesis of the two enantiomers of the taxol side chain (**72** and **73**) from methyl *trans*-cinnamate **68** (Scheme 20).



Scheme 20. The Sharpless asymmetric aminohydroxylation.[28]



$(DHQD)_2$-PHAL
70



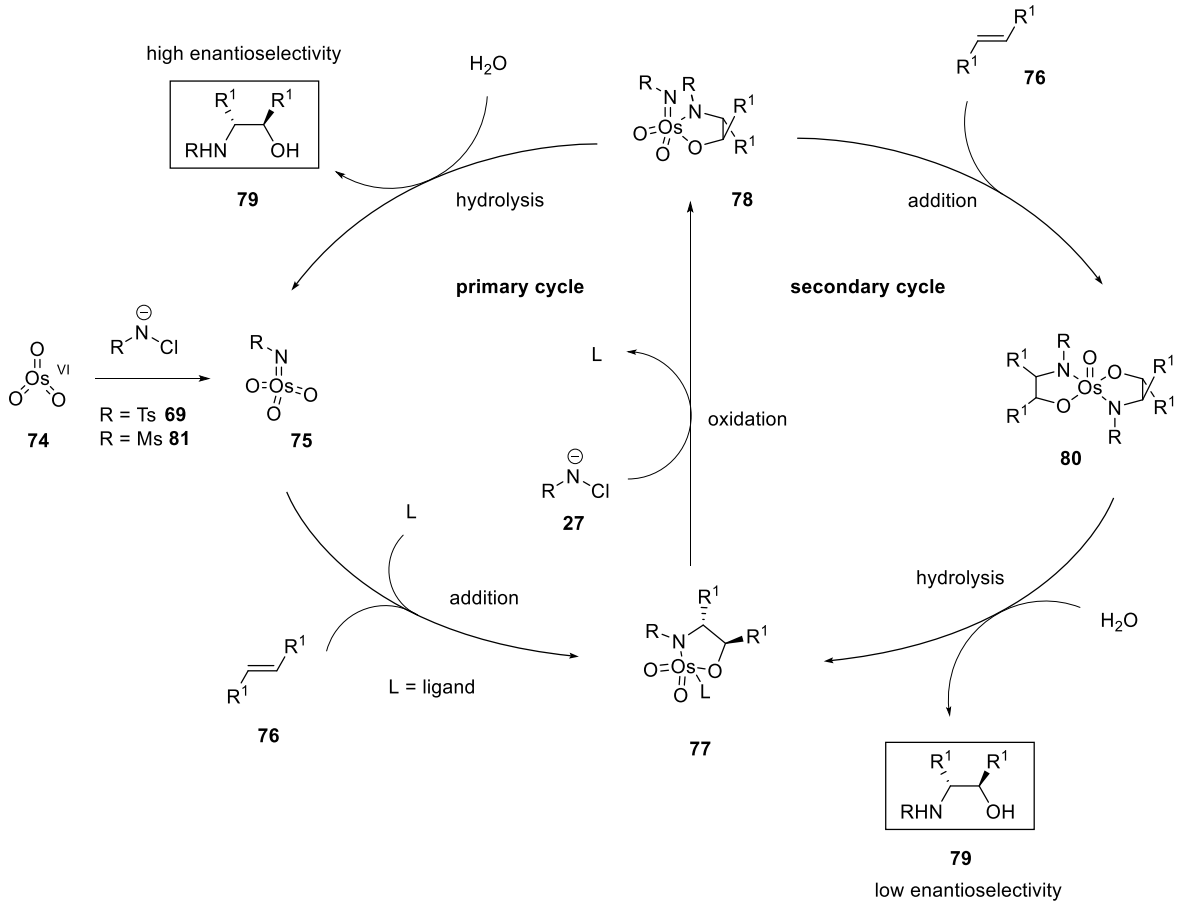
$(DHQ)_2$-PHAL
71

Figure 3. Cinchona alkaloid ligands bound to phthalazine bridge.[29]

The enantioselectivities first published were modest, ranging from 33–88% ee. However, due to the highly crystalline nature of hydroxysulfonamides, enantiomeric purity (>99% ee) was achieved by recrystallisation in methanol.[28]

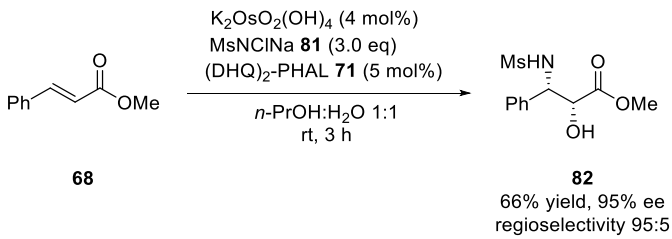
Along with asymmetric induction, the chiral ligands play a role in regioselectivity. In the case of methyl *trans*-cinnamate **68**, the regioisomer with a benzylic sulfonamide is formed in a ratio of >5:1 over the regioisomer with the benzylic hydroxyl. The ligand also suppresses the formation of diol by-product and accelerates catalytic turnover.

Mechanistically, it was postulated that the Sharpless AA proceeds by two simultaneous catalytic cycles, the primary cycle offering the product with high enantioselectivity and the secondary cycle leading to the product in a low enantioselectivity (Scheme 21). The primary cycle begins with the oxidation of the osmium(VI) species **74** by chloramine-T **69** to give the bis(azaglycolate)osmium species **75**. Binding of the chiral ligand is followed by a [3+2] cycloaddition of alkene **76** to give azaglycolate complex **77**, with both stereo- and regiochemistry having been established. A computational study conducted by Strassner in 2010, supported the hypothesis of a [3+2] cycloaddition.[30] Reoxidation by chloramine-T **69**, generates species **78**, which can be hydrolysed to regenerate bis(azaglycolate)osmium species **75** and results in the *β*-amino alcohol **79** in high enantioselectivity. Species **78** can also enter the secondary cycle, by which it undergoes a [3+2] cycloaddition with alkene **76**, in the absence of the chiral ligand, to give species **80**. Hydrolysis results in formation of the *β*-amino alcohol **79** in low enantioselectivity.



Scheme 21. The postulated Sharpless AA catalytic cycle.[26]

Higher enantio- and regioselectivities were achieved when using Chloramine-M **81** in place of Chloramine-T **69**. Oxyamination of methyl *trans*-cinnamate **68** with Chloramine-M **81**, in a 1:1 mixture of *n*-propanol and water, gave an enantioselectivity of 95% ee (previously 81% ee) and a regioselectivity of 9:1 (previously ≥5:1) (Scheme 22). It is postulated that a smaller alkyl group on the sulfonamide enables a "better fit" of species **75** into the pocket generated by the chiral ligand to form species **77**. Also, the more hydrophilic nature of Chloramine-M **81** encourages hydrolysis of species **78**, which decreases the likelihood of **78** entering the secondary cycle.[31]

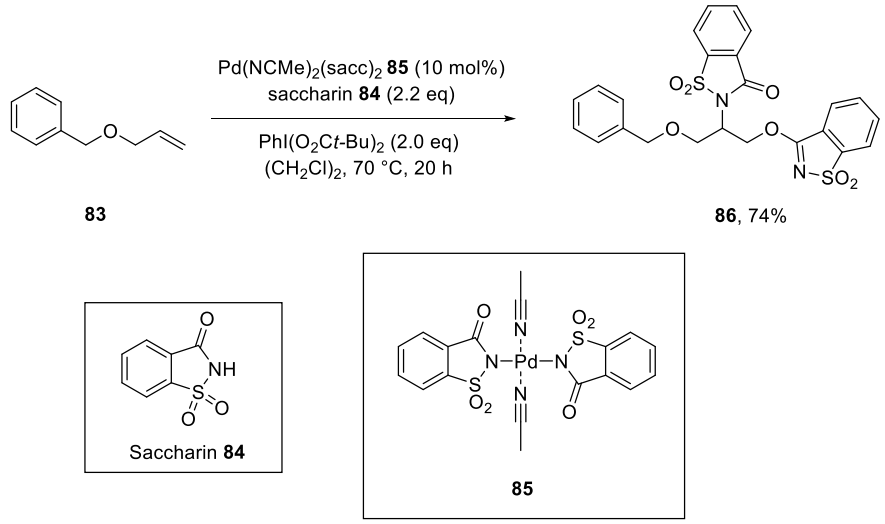


Scheme 22. Sharpless AA using Chloramine-M **81** as the nitrogen source.[31]

The Sharpless asymmetric aminohydroxylation is widely regarded as the "gold standard" of oxyamination procedures, however, the process does have limitations. Enantio- and regioselectivities are often dependent upon substrate, with poor results observed for *cis*-alkenes. Furthermore, the use of a toxic osmium catalyst is undesirable. Such limitations have inspired alternative oxyamination procedures to be developed.

2.1.2.2 Palladium catalysed oxyamination of allyl ethers and esters

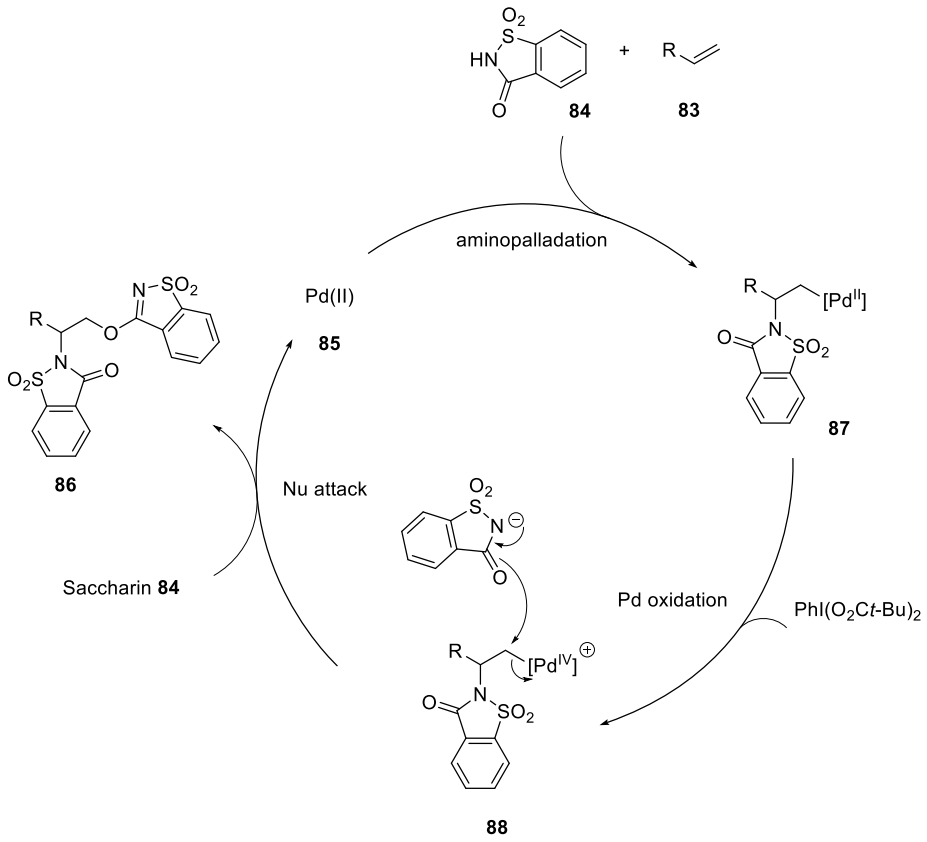
In 2016, Muñiz *et al*., reported the oxyamination of terminal allyl ethers and esters.[32] Treatment of allyl benzyl ether **83** with palladium(II) catalyst **85** and saccharin **84**, provided the oxyaminated product **86** as a single regioisomer (Scheme 23).



Scheme 23. Pd(II) catalysed oxyamination of allyl benzyl ether **83**.

The *bis*-acetonitrile palladium disaccharide complex **85** was formed by treating palladium diacetate with two equivalents of saccharin **84** in a solution of acetonitrile.

Mechanistically, it was proposed that alkene **83** undergoes aminopalladation with Pd(II) species **85** and a molecule of saccharin **84** to give amino palladium intermediate **87** (Scheme 24). Oxidation to Pd(IV) species **88** was achieved with bis(*tert*-butylcarbonyloxy)iodobenzene. Saccharin **84**, acting as an ambident nucleophile, displaces the palladium through oxygenation to arrive at the oxyaminated product **86**, with regeneration of the Pd(II) catalyst **85**.

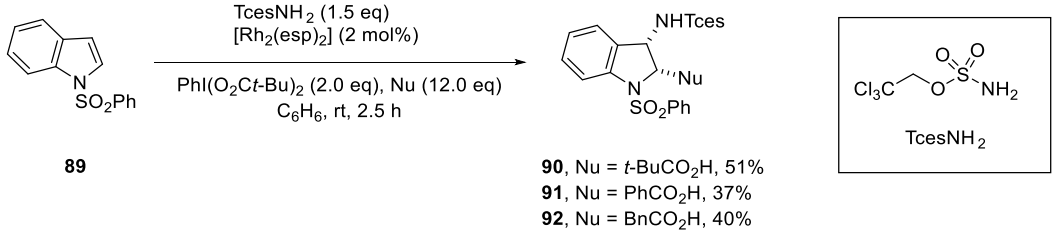


Scheme 24. Proposed catalytic cycle for Pd catalysed oxyamination with saccharin.[32]

Yields obtained from this procedure were relatively good (49–74%), with complete regioselectivity observed. Also, the use of saccharin as a nitrogen source is beneficial as it is both commercially available and relatively cheap. The procedure does suffer from a poor substrate scope, with reactions only reported for allylic ether and ester substrates, leading to racemic oxyaminated products.

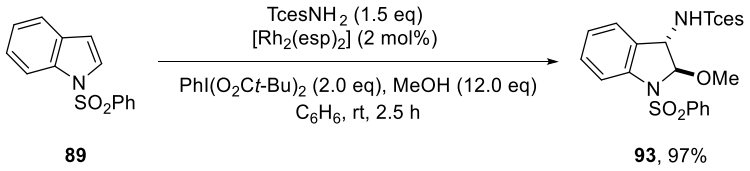
2.1.2.3 Rhodium catalysed oxyamination of indoles

The use of a rhodium catalyst for the oxyamination of indoles was examined by Dauban *et al.* in 2010.[33] Using conditions developed by Padwa and co-workers,[34,35] indole **89** was treated with a rhodium(II) catalyst ($Rh_2(esp)_2$), a nitrogen source ($TcesNH_2$) and various oxygen sources, to produce *syn*-oxyaminated indoles **90**–**92** (Scheme 25).



Scheme 25. Rh-catalysed *syn*-oxyamination of indoles.

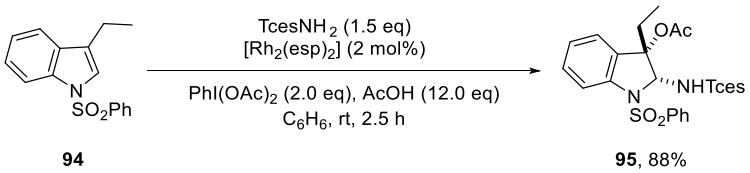
Interestingly, when the reaction was carried out using methanol as the oxygen source, the *anti*-oxyamination product **93** was observed in a yield of 97% (Scheme 26). Therefore, the stereochemistry of the reaction can be controlled by choice of oxygen nucleophile.



89 **93**, 97%

Scheme 26. Rh-catalysed *anti*-oxyamination of indoles.

The regioselectivity of the reaction can also be altered, depending upon the indole substrate used. The oxyamination of 3-ethylindole **94**, resulted in the reversal of regiochemistry, with the nitrogen moiety being introduced to the C2 position, to give *syn*-oxyaminated product **95** in a yield of 88% (Scheme 27).

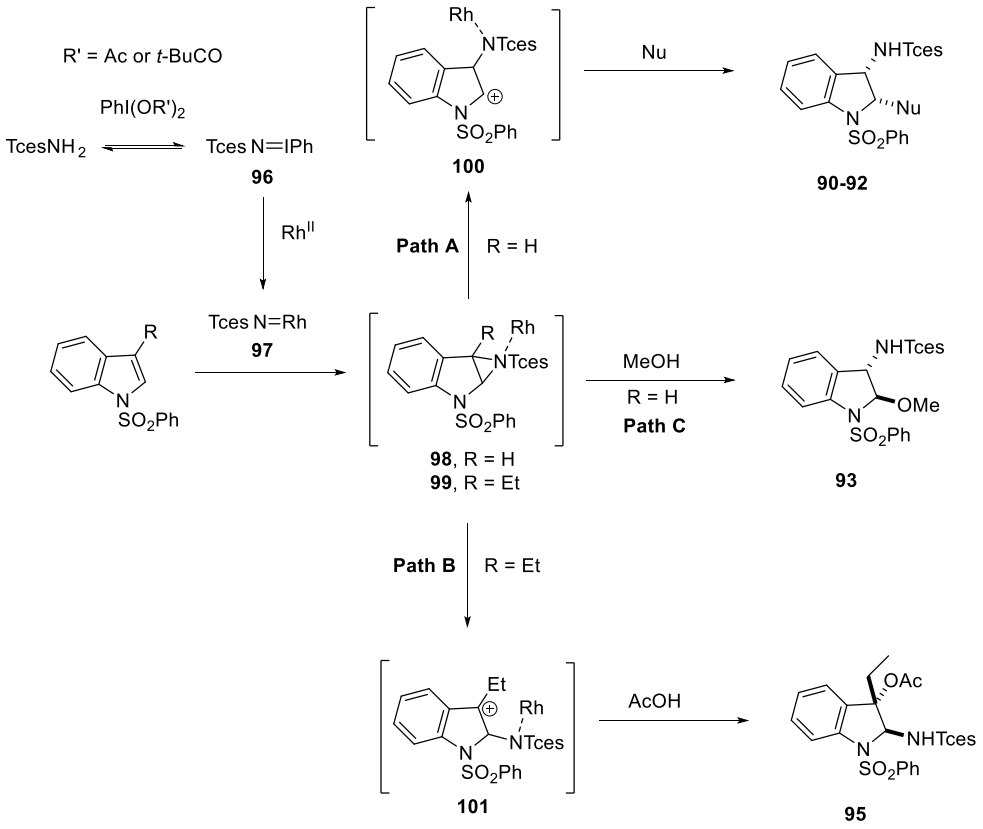


94 **95**, 88%

Scheme 27. Rh-catalysed *syn*-oxyamination of 3-ethylindole **94**.

Mechanistically, it was proposed that the metallonitrene **97**, made from the reaction between the rhodium(II) catalyst and iodonitrene **96**, may react with an indole derivative to give aziridine intermediates **98** or **99** (Scheme 28). The aziridine can react through three pathways, which depend upon the type of oxygen nucleophile and the indole substrate. Aziridine intermediates **98** and **99**, may undergo ring opening to give a carbocation that is dependent upon the indole substrate. For **100** the carbocation is placed upon the C2 position where an iminium ion can be formed and *syn* attack of the various nucleophiles gives products **90**–**92** (Path A). Conversely, aziridine **99** will open to form the more stable tertiary benzylic carbocation **101**. *Syn* attack of acetic acid gives product **95** (Path B). Lastly, methanol is thought to be nucleophilic enough to ring open aziridine intermediate **98** in an S_N2 manner to give *anti*-oxyaminated product **93** (Path C).

The use of a rhodium catalysed oxyamination provides an alternative procedure that avoids the use of osmium. The procedure also benefits from the ability to alter regio- and stereoselectivity depending upon the oxygen source and chosen substrate. However, the substrate scope is still limited and the process is not asymmetric.



Scheme 28. Proposed mechanism of formation for oxyamination products observed.

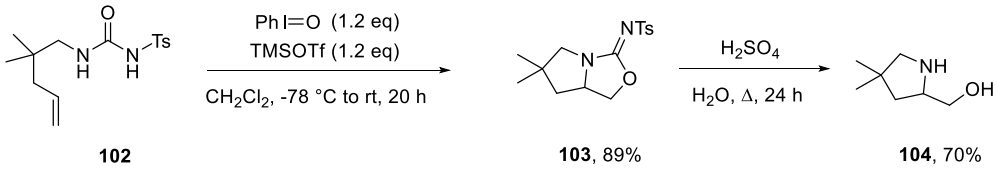
2.1.2.4 Conclusion on metal-catalysed oxyamination

A number of synthetic methods exist for the oxyamination of alkenes, most of which rely on the use of toxic or costly transition metal catalysts. Many of these methods suffer from issues ranging from poor substrate scope to poor regio- and stereoselectivity. To date, the Sharpless asymmetric aminohydroxylation (AA) remains the most applicable methodology, however, it uses a highly toxic osmium catalyst. The development of metal-free oxyamination transformations have the potential to overcome the issues associated with metal catalysed procedures.

2.1.3 Metal-free oxyamination

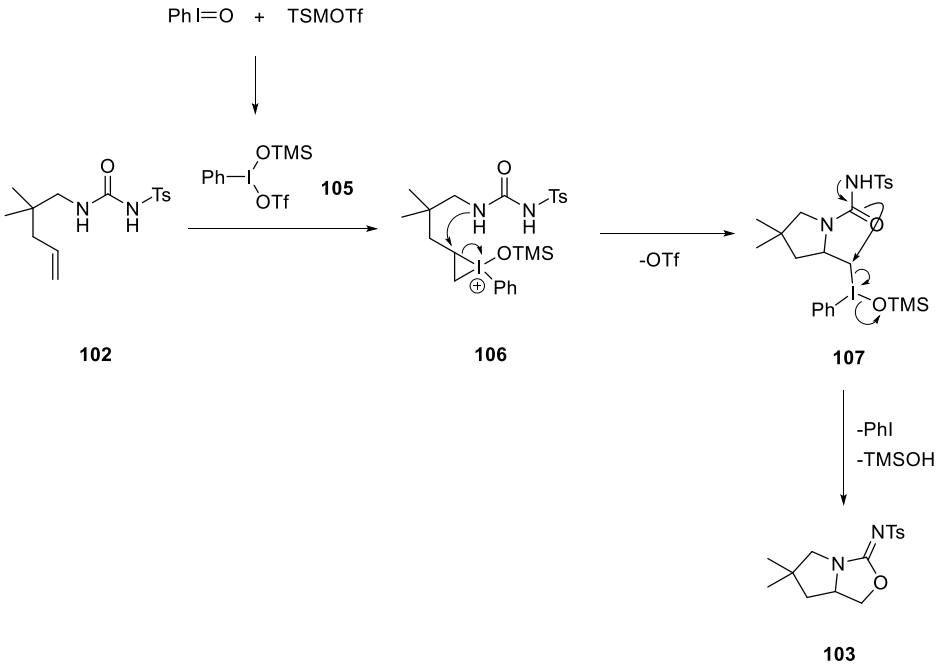
2.1.3.1 Oxyamination of urea-tethered alkenes with hypervalent iodine

In the absence of metal catalysts, hypervalent iodine species may be used to functionalise alkenes. In 2008 Michael *et al.*, reported a metal-free procedure for the oxyamination of urea-tethered alkenes.[36] Treatment of alkene **102** with iodosylbenzene (PhI=O) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) produced isourea **103** in excellent yield (Scheme 29). Subsequent treatment with sulfuric acid gave rise to *β*-amino alcohol **104** (70%).



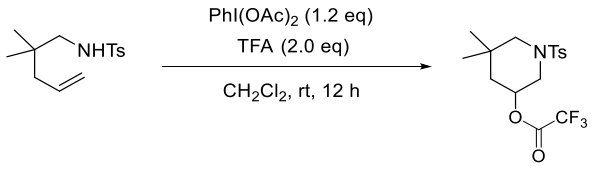
Scheme 29. Metal-free oxyamination of urea-tethered alkenes.[36]

It was proposed that TMSOTf and PhI=O reacted to give electrophilic iodine(III) species **105** (Scheme 30). Reaction of **105** with alkene **102** led to iodonium intermediate **106**, which underwent a 5-*exo*-tet cyclisation to give intermediate **107**. The iodine is then displaced by intramolecular nucleophilic attack of the urea to give isourea **103**.



Scheme 30. Proposed reaction mechanism with hypervalent iodine.

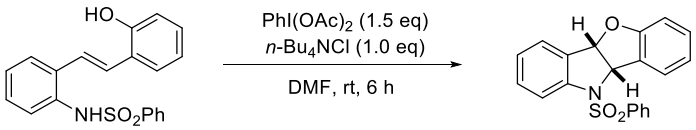
In 2010, this work was expanded to include the oxyamination of sulfonamide tethered alkenes.[37] Treatment of alkene **108** with $PhI(OAc)_2$ and trifluoroacetic acid (TFA) gave rise to the *endo*-oxyamination product **109**, in excellent yield (87%). This reaction was found to be completely regioselective towards the 6-*endo*-tet cyclisation (Scheme 31).



108 **109**, 87%

Scheme 31. Metal-free oxyamination of sulfonamide tethered alkenes.[37]

Similar work was also carried out by Chang and co-workers in 2012.[38] In this case both the oxygen and nitrogen nucleophiles were located upon different aromatic rings. Treatment of *trans*-stilbene derivative **110** with $PhI(OAc)_2$ and tetrabutyl ammonium chloride led to oxyaminated product **111** in 67% isolated yield (Scheme 32).



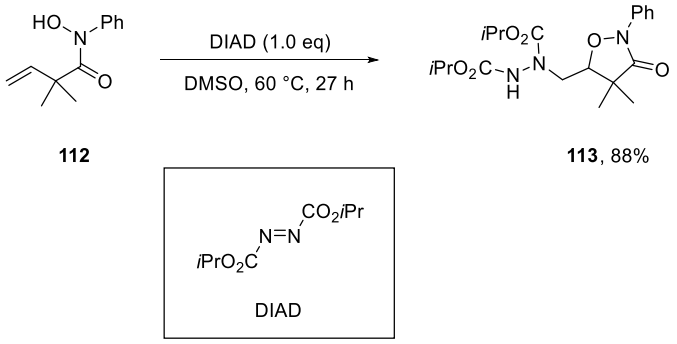
110 **111**, 67%

Scheme 32. Oxyamination of *trans*-stilbene derivative **110**.[38]

Procedures that use hypervalent iodine reagents offer an alternative to metal-catalysed procedures. However, most reagents have poor atom efficiency and generate a substantial amount of waste.

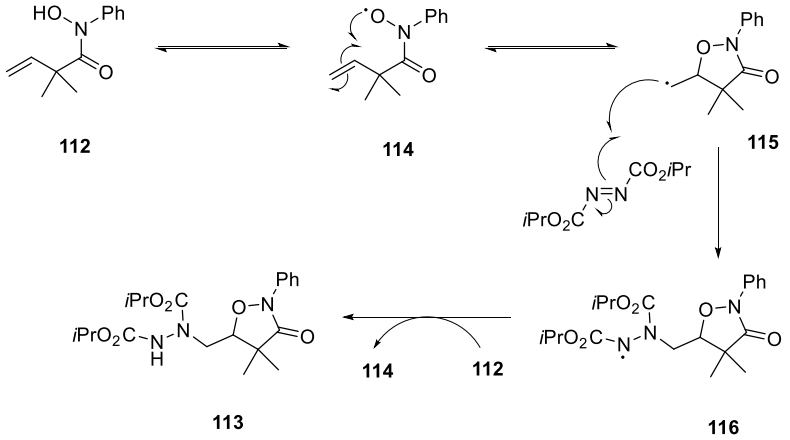
2.1.3.2 Oxyamination of alkenes using hydroxamic acids

In 2010, Alexanian *et al.* reported the metal-free oxyamination of alkenes using a hydroxamic acid and commercially available diisopropyl azodicarboxylate (DIAD) (Scheme 33).[39]



Scheme 33. Metal-free oxyamination of alkenes using hydroxamic acids.[39]

It is interesting to note that no additional reagents, such as radical initiators were required in this reaction. The reactivity was attributed to spontaneous formation of a small amount of amidoxyl radical **114** prior to initiating the reaction (Scheme 34). Reversible cyclisation produced intermediate **115**, which underwent azodicarboxylate addition to give intermediate **116**. Hydrogen atom abstraction gave rise to oxyamination product **113**, as well as regenerating amidoxyl radical **114**, leading to propagation of the reaction.

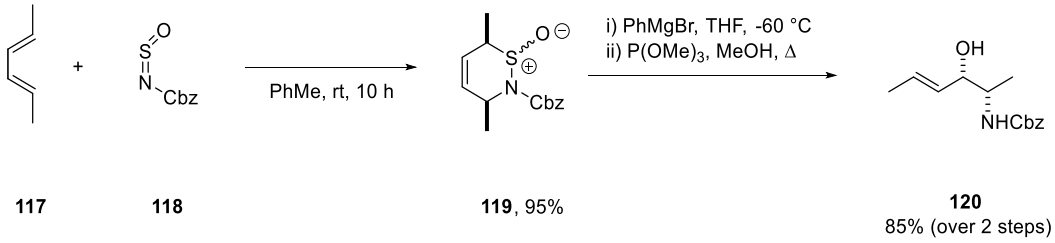


Scheme 34. Proposed mechanistic pathway *via* radical process.

This process was found to proceed with excellent regioselectivity. Interestingly, this method proceeded through cyclisation of the oxygen atom, allowing for access to products of opposing regiochemistry to that of other known intramolecular oxyamination procedures. Most metal-free procedures within the literature proceed through cyclisation using the nitrogen atom.[38,39]

2.1.3.3 Diels-Alder reaction of an *N*-sulfinyl dienophile

An intermolecular metal-free oxyamination procedure was developed by Weinreb and co-workers in 1984.[40] The three-step process included a hetero Diels-Alder reaction, a [3+2] sigmatropic rearrangement and a final deprotection step (Scheme 35).

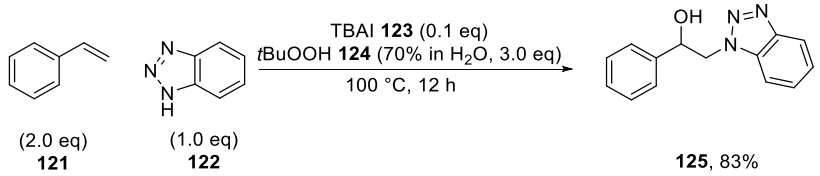


Scheme 35. Intermolecular oxyamination *via* Diels-Alder.[40]

Treatment of (*E*,*E*)-2,4-hexadiene **117** with *N*-sulfinylcarbamate **118**, afforded Diels-Alder product **119**. Subsequent reaction with phenyl magnesium bromide led to cleavage of the S—N bond, resulting in a [3+2] sigmatropic rearrangement. Following Grignard addition, removal of the phenyl sulfide was achieved by reaction with trimethyl phosphite ($P(OMe)_3$), to give *β*-amino alcohol **120**, as a single diastereomer. Further development of this reaction has been hindered by a poor substrate scope.

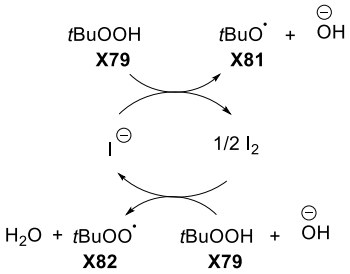
2.1.3.4 TBAI-catalysed oxyamination of alkenes

In 2013, Zhu and co-workers reported a TBAI-catalysed oxyamination of styrenes using *tert*-butyl hydrogen peroxide (TBHP) **124**. Treatment of styrene **121** with benzotriazole **122** in the presence of *tert*-butylammonium iodide (TBAI) **123** and TBHP **124**, afforded the oxyaminated product **125** in a yield of 83% (Scheme 36).[41]



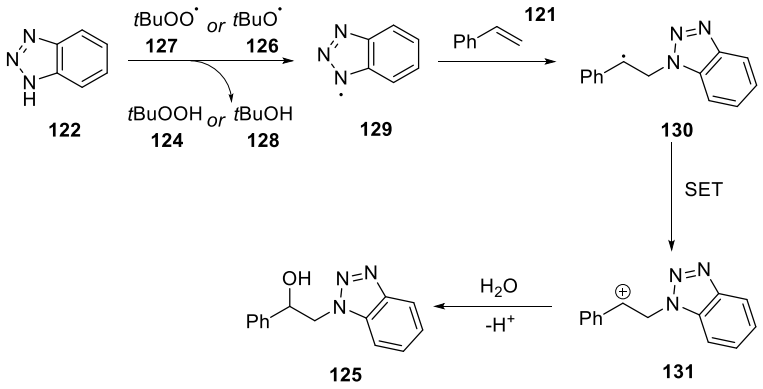
Scheme 36. TBAI-catalysed oxyamination of styrene **121**.[41]

Mechanistically, it was proposed that the iodide anion of TBAI **123** reacted with TBHP **124** to give *tert*-butoxyl and *tert*-butylperoxy radicals **126** and **127** (Scheme 37).



Scheme 37. The generation of *tert*-butoxyl and *tert*-butylperoxy radicals **126** and **127**.[41]

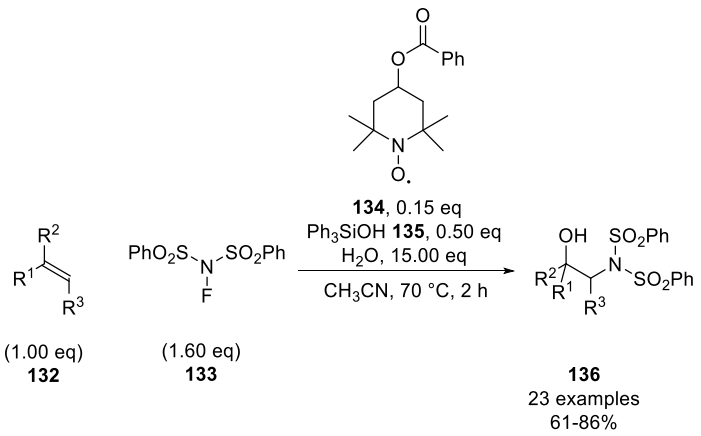
tert-Butoxyl radical **126** or *tert*-butylperoxy radical **127** abstract a hydrogen atom from benzotriazole **122** to afford radical **129**. The benzotriazole radical **129** reacts with styrene **121** to form intermediate **130**. Under the reaction conditions, a single electron transfer from intermediate **130** forms benzyl cation **131**, which reacts with water to give the oxyaminated product **125** (Scheme 38).



Scheme 38. Proposed mechanism of formation for oxyaminated product **125**.[41]

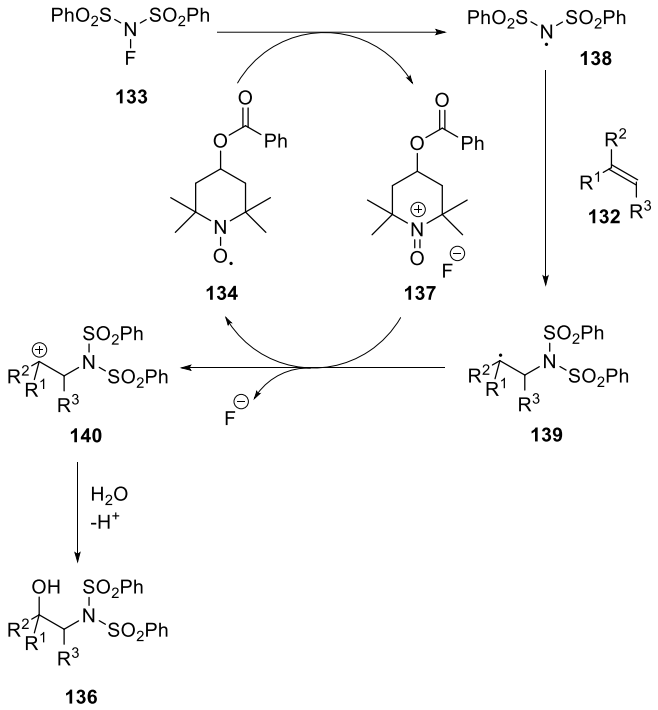
2.1.3.5 TEMPO-catalysed oxyamination of alkenes

In 2016, Weng and co-workers reported a metal-free intermolecular alkene oxyamination, using *N*-fluorobenzenesulfonimide **133**, 4-TEMPO-benzoate **134** catalyst and water (Scheme 39). Triphenylsilanol **135** was also employed as a fluoride scavenger.[42]



Scheme 39. TEMPO-catalysed oxyamination of alkenes.[42]

Mechanistically, it was proposed that TEMPO-derivative **134** formed bissulfonylamidyl radical **138** by abstraction of a fluorine atom from *N*-fluorobenzenesulfonimide **133**, while also forming oxoammonium salt **137**. Subsequent reaction of radical **138** with alkene **132** lead to carbon-based radical **139**, which underwent a single electron transfer from oxoammonium salt **137** forming cationic intermediate **140** and regenerating TEMPO-derivative **134**. Nucleophilic addition of a water molecule to cationic intermediate **140** lead to the observed oxyaminated product **136** (Scheme 40).



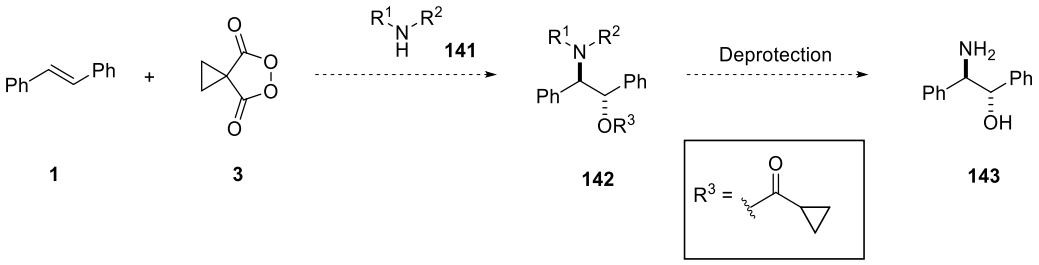
Scheme 40. Proposed mechanism for TEMPO-catalysed alkene oxyamination.[42]

2.1.3.6 Conclusion on metal-free oxyamination

Metal-free methodologies provide an alternative to transition metal-catalysed procedures that use toxic and expensive metals. Most procedures found within the literature use hypervalent iodine reagents and often have poor atom efficiency. Currently, there are no metal-free procedures to rival the Sharpless AA in terms of enantioselectivity. Regioselectivity of most metal-free procedures is good, however, the clear majority of processes described are intramolecular oxyaminations. Thus, there remains room for the development of an intermolecular metal-free oxyamination procedure.

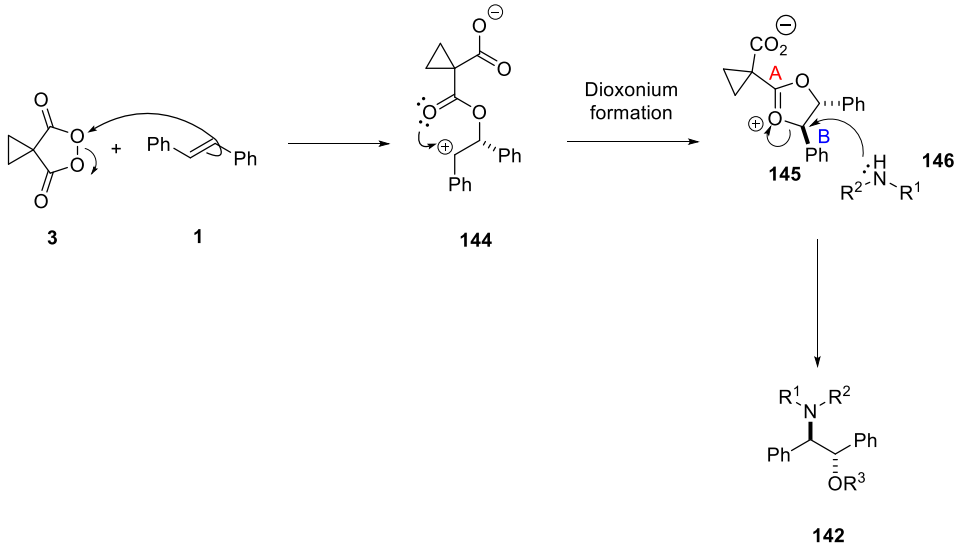
2.2 Aims and Objectives

The aim of this project was to develop an intermolecular oxyamination procedure using malonoyl peroxide **3**. It was thought that this could be achieved in a similar manner to the *anti*-dihydroxylation procedure, reported in Section 1.1. Treatment of alkene **1** with malonoyl peroxide **3** and an appropriate nitrogen nucleophile **141**, would allow access to *β*-amino alcohol **143**, following a deprotection step **(**Scheme 41).



Scheme 41. The proposed *anti*-oxyamination procedure.

It was expected that such a procedure would be mechanistically similar to the *anti*-dihydroxylation reaction. Upon formation of dioxonium intermediate **145**, intermolecular attack of nitrogen nucleophile **146** through position **B**, would produce the protected *anti-β*-amino alcohol **142** (Scheme 42).



Scheme 42. The proposed mechanism for intermolecular *anti*-oxyamination.

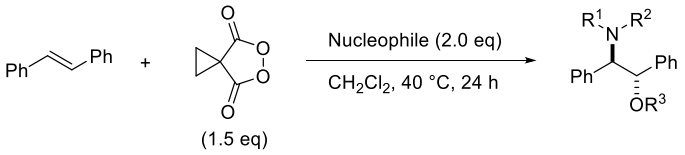
Following formation of the hypothesis, we set out to find a suitable nitrogen nucleophile, compatible with the reaction conditions, that would afford the desired oxyaminated product **142** from *trans*-stilbene **1**.

2.3 Results and Discussion

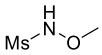
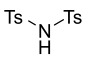
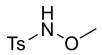
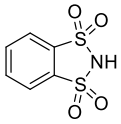
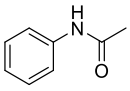
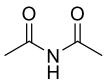
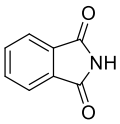
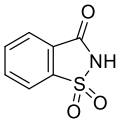
2.3.1 Initial screen of nitrogen nucleophiles

Nitrogen nucleophiles **147–157** and **84** were screened under the *anti*-dihydroxylation conditions, previously developed within our laboratory (Table 1). Nucleophiles **147**–**157** were found to be unsuccessful in producing the desired oxyaminated product **142**. Unsuccessful nucleophiles were found to either react directly with malonoyl peroxide **3** or lack the desired reactivity to intercept the dioxonium intermediate **145**.

Saccharin **84**, was found to produce the desired oxyaminated product, in a yield of 29% (Entry 12). Following the initial screen of nucleophiles, saccharin **84** was carried forward for further optimisation.



1 **3** **142**

Entry	Nucleophile		Yield 142 (%)[a]	Entry	Nucleophile		Yield 142 (%)[a]
1		**147**	0[b]	7		**153**	0[c]
2		**148**	0[b]	8		**154**	0[c]
3		**149**	0[b]	9		**155**	0[c]
4	NaN_3	**150**	0[b]	10		**156**	0[c]
5		**151**	0[c]	11		**157**	0[c]
6		**152**	0[c]	12		**84**	29

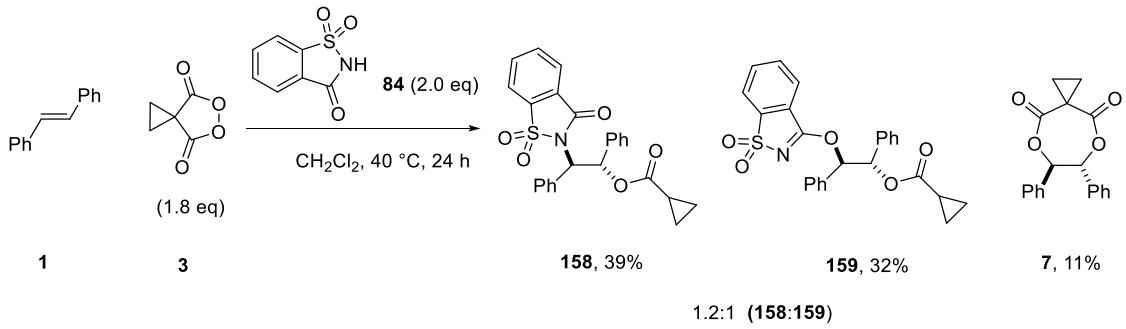
[a]Isolated yield after chromatographic purification.
[b]Lack of desired reactivity attributed to direct reaction of nucleophile with peroxide **3**.
[c]Lack of desired reactivity attributed to nucleophiles inability to intercept dioxonium **145**.

Table 1. Screen of nitrogen nucleophiles.

2.3.2 Development of nitrogen nucleophile

2.3.2.1 Initial experiment

It was observed from the initial screen reported in Table 1 (entry 12), that a proportion of *trans*-stilbene **1** remained in the reaction mixture. Increasing peroxide equivalents to 1.8 gave a yield of 39% for the oxyaminated product **158**, with complete consumption of *trans*-stilbene **1** (Scheme 43).



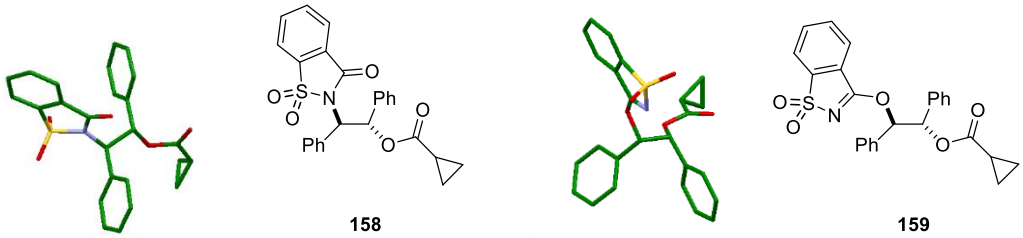
1 **3** **158**, 39% **159**, 32% **7**, 11%

1.2:1 (**158**:**159**)

Scheme 43. Oxyamination of *trans*-stilbene using malonoyl peroxide and saccharin.

The major co-product of the reaction was found to be dioxygenated species **159** (32%). As saccharin **84** is an ambident nucleophile, it may react through either the nitrogen or oxygen atom. Reaction through the nitrogen gives the desired oxyaminated species **158**, and reaction through the oxygen gives the dioxygenated co-product **159**. 7-membered ring **7** was also isolated in a yield of 11%, a result of reaction between peroxide **3** and *trans*-stilbene **1** followed by charge recombination (as outlined in section 1.1, scheme 4). It was also observed that decarboxylation occurred during the reaction to give a cyclopropyl ester moiety on the product. This decarboxylation was also observed in the *anti*-dihydroxylation procedure.[4] It was thought this decarboxylation occurred due to the relatively high-reactivity of the proposed dioxonium intermediate **145** and the low nucleophilicity of saccharin **84**.

The structure of oxyaminated product **158** and dioxygenated co-product **159** were confirmed by X-ray crystallography, showing both structures to be the *anti*-diastereoisomer (Figure 4). Each of these products is fully consistent with the proposed mechanistic course of the transformation.



158 **159**

Figure 4. Crystal structures of oxyamination product **158** and co-product **159**.

In order to fully optimise the oxyamination procedure, a method of controlling the ambident reactivity of saccharin **84** had to be established. It was proposed that reactivity could be controlled in two ways; i) optimisation of reaction conditions, or ii) use of alternative nucleophiles.

2.3.2.2 Controlling *N*- *vs*. *O*-selectivity: Optimisation of reaction conditions

Reports within the literature suggest that the reactivity of ambident nucleophiles can be controlled through choice of solvent and temperature.[43,44,45]

Effect of solvent

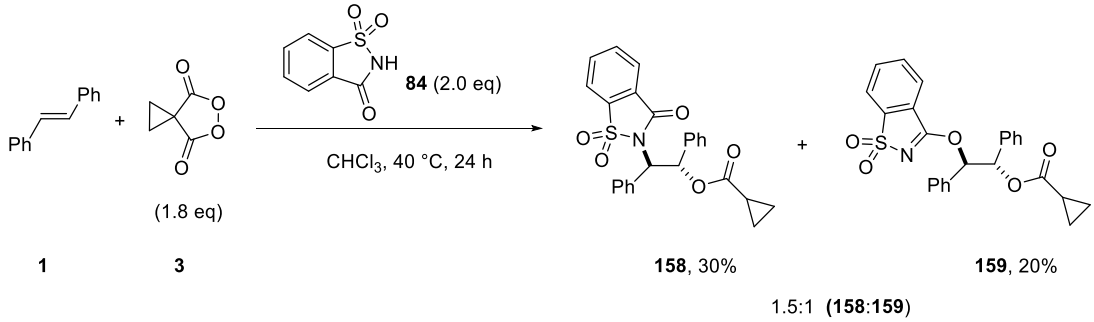
A total of 16 solvents were screened for *N*-selectivity, with ratios of product **158** to co-product **159** determined by ^{1}H NMR spectroscopy on the crude reaction mixtures (Table 2). Most solvents displayed no *N*-selectivity (entries 1, 3–9, 12), or consumed the peroxide before the desired reaction took place (entry 10, 11, 13–16). Chloroform (entry 2) displayed *N*-selectivity in a ratio of 1.5:1.

Entry	Solvent	158:159[a]
1	CH_2Cl_2	1:1
2	$CHCl_3$	1.5:1
3	1,2-DCE	1:1
4	PhMe	1:1
5	EtOAc	1:1
6	MeCN	1:1
7	1,4-Dioxane	1:1
8	iPAc	1:1
9	Et_2O	1:1
10	HFIP	-
11	H_2O	-
12	THF	1:1
13	^{i}PrOH	-
14	DMSO	-
15	DMA	-
16	*t*-BuOH	-

[a]Determined by ^{1}H NMR spectroscopy

Table 2. Solvent screen.

After chromatographic purification, the 1.5:1 ratio was still observed, however, the yield of oxyaminated product **158** was lower than that observed in dichloromethane at 30% (Scheme 44). At this stage we were unable to explain this change in selectivity, however, the result was consistent and the desired product **158** was the major isomer observed.



Scheme 44. Oxyamination using saccharin **84** and chloroform as solvent.

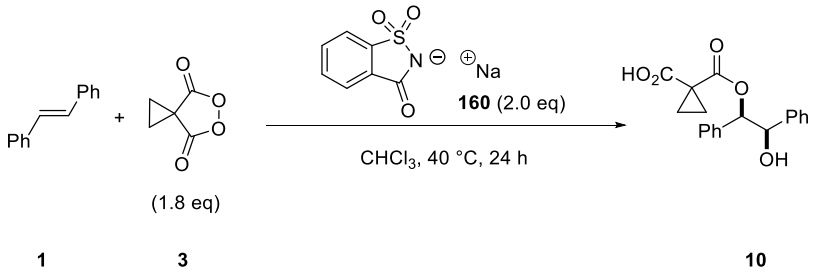
Whilst this investigation clearly showed a preference for the oxyaminated product in specific solvents, the low selectivity and yield suggested that alternative conditions would have to be found in order to identify synthetically useful reaction conditions.

Effect of temperature

In order to investigate the effect of temperature on the regioselectivity of the process, the reaction was conducted at room temperature and 60 °C. Both temperatures resulted in a 1.5:1 ratio of **158**:**159**, using chloroform as the solvent. It was concluded that temperature had no effect upon *N*- *vs. O*-selectivity and no further optimisation of temperature was made.

Effect of saccharin salts

The oxyamination reaction was examined using the sodium salt of saccharin **160** as the nucleophile (Scheme 45). The salt was found to be insoluble within a variety of solvents compatible with the reaction. As a result of the hygroscopic nature of **160**, water was present within the reaction mixture, leading to the formation of *syn*-deoxygenated product **10**. The amount of *syn*-**10** was not quantified, and no further saccharin salts were tested under the reaction conditions.



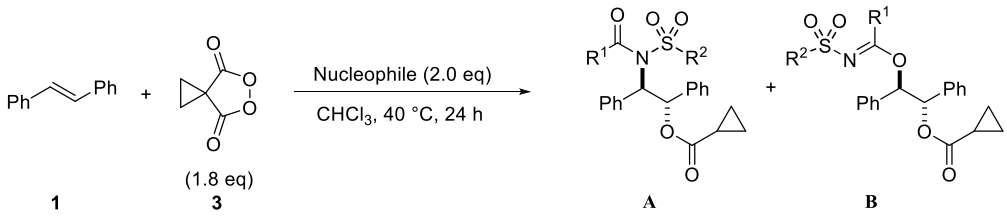
Scheme 45. Failed attempt at oxyamination using sodium saccharin **160**.

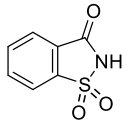
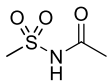
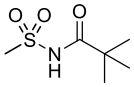
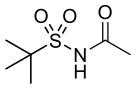
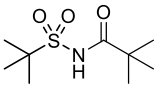
2.3.2.3 Controlling *N*- *vs*. *O*-selectivity: alternative nucleophiles

With the optimisation of reaction conditions failing to achieve significant *N*-selectivity, attention was turned to alternative nucleophiles. The nucleophiles discussed within this Section were made using a variety of one-step procedures, from commercially available starting materials (see experimental for full details Section 4.2.2).

Acyl sulfonamides

Acyl sulfonamides **161**, **164**, **167** and **170** were examined as potential nucleophiles for the oxyamination of *trans*-stilbene **1** (Table 3). All four examples displayed reactivity.



Entry	Nucleophile		Yield[a] (%) A	Yield[a] (%) B
1		**84**	**158**, 30%	**159**, 20%
2		**161**	**162**,[b] 19%	**163**,[b] 19%
3		**164**	**165**, 0%	**166**, 60%
4		**167**	**168**, 0%	**169**, 33%
5		**170**	**171**, 0%	**172**, 22%

[a]Isolated yield after chromatographic purification.
[b]Isolated as an inseperable mixture.

Table 3. Acyl sulfonamide nitrogen nucleophiles.

N-(Methylsulfonyl)acetamide **161**, was selected as a nucleophile as it represented the most simple molecule that contained a substituted acyl sulfonamide moiety. Treatment of nucleophile **161** under the oxyamination conditions resulted in the corresponding oxyaminated product **162** and dioxygenated co-product **163** as an inseparable 1:1 mixture in a yield of 38% (entry 2). This result confirmed that the observed ambident reactivity was not specific to saccharin **84** and that the oxyamination was possible with other acyl sulfonamides.

It was postulated that *N*- *vs*. *O*-selectivity could be influenced by steric interactions. Nucleophiles **164**, **167** and **170** were synthesised with the intention of altering the steric environment of the heteroatom nucleophiles. In practice, all three sulfonamides prepared were selective for *O*-alkylation. Under the reaction conditions, *N*-(methylsulfonyl)pivalimide **164** selectively produced dioxygenated co-product **166** (60% yield) (entry 3).

N-(*tert*-Butylsulfonyl)acetamide **167** and *N*-(*tert*-butylsulfonyl)pivalimide **170** were found to give complete *O*-selectivity, resulting in dioxygenated co-product **169** and **172** in a yield of 33% and 22%, respectively (entries 4 and 5). Dioxygenated co-product **172** was found to be unstable, decomposing over several weeks.

In summary, altering the steric environment of the nucleophiles resulted in the undesired effect of increasing *O*-selectivity over *N*-selectivity. This observation may be understood by inspection of energy minimised 3D models of these sulfonamides, generated using the "MM2 minimise" function found within Chem3D (Figure 5). It can clearly be seen that the *tert*-butyl groups act to hinder the nitrogen atom, as opposed to the oxygen atom.

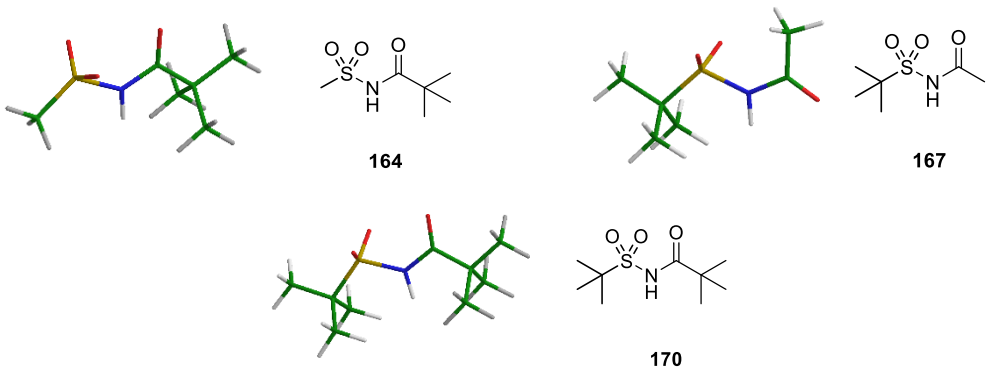
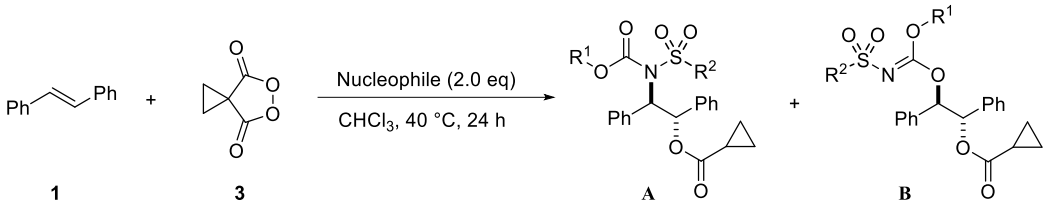


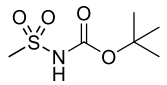
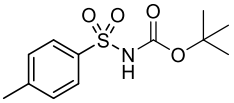
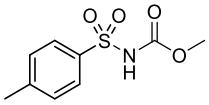
Figure 5. 3D models of nucleophiles **164**, **167** and **170**.

No alternative easily accessible compounds were proposed to hinder the oxygen atom. Thus, attention was turned to altering the electronics of the nucleophile.

Sulfonyl carbamates

The attempt to alter the electronics of sulfonamide-type nucleophiles led to the synthesis of sulfonyl carbamate nucleophiles **173**, **176** and **179** (synthesis found in Section 4.2.2). To our delight, all three nucleophiles displayed complete selectivity for *N*-alkylation (Table 4).



Entry	Nucleophile	Yield[a] (%) A	Yield[a] (%) B
1	 **173**	**174**, 39%	**175**, 0%
2	 **176**	**177**, 49%	**178**, 0%
3	 **179**	**180**, 45%	**181**, 0%

[a]Isolated yield after chromatographic purification.

Table 4. Sulfonyl carbamate nitrogen nucleophiles.

Under the oxyamination conditions, *O*-*tert*-butyl(*N*-methylsulfonyl)carbamate **173** selectively produced the oxyaminated product **174**, in a yield of 39%. The structures of product **174** and **177** were confirmed by X-ray crystallography, which clearly showed that the *N*- and *O*-substituents were in an *anti*-configuration and that decarboxylation of the cyclopropyl ester moiety had occurred (Figure 6). Whilst we are unable to unequivocally say that the alternative diastereoisomer of the product, or the dioxygenated product was not formed in this transformation, careful examination of the crude reaction mixture by ^{1}H NMR spectroscopy suggested that **174** or **177** were the sole bis-functionalised alkenes obtained within this transformation involving the addition of two separate nucleophiles.

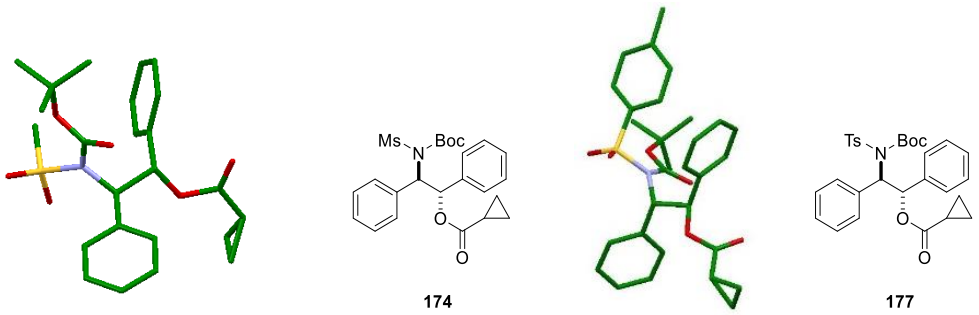


Figure 6. Crystal structure of product **174** and **177**.

Reaction of *O*-*tert*-butyl *N*-tosylcarbamate **176** produced oxyaminated product **177** in a yield of 49%. Therefore, the use of sulfonyl carbamates in place of acyl sulfonamides proved successful in achieving complete *N*-selectivity. It was postulated that the presence of the extra electronegative oxygen atom of the sulfonyl carbamate (compared to an acyl sulfonamide) removed electron density from the carbonyl oxygen and hence decreased the nucleophilicity of the carbonyl oxygen atom. Additionally, the mesomeric effect of the carbamate oxygen atom would contribute to the increased nucleophilicity of the reactive nitrogen atom.

Reaction of *O*-methyl *N*-tosylcarbamate **179**, produced oxyaminated product **180** in a yield of 45%. Successful reaction of nucleophile **179** suggested that lack of *O*-reactivity was a consequence of electronic factors, and not from steric hindrance associated with the *tert*-butyl group of nucleophile **176**.

Although nucleophile **176** gave the product **177** in a yield of 49%, the fate of the remaining 41% of consumed *trans*-stilbene **1** was unclear (note that typically 7-membered ring **7** accounted for 10% of the consumed stilbene). Only oxyaminated product **177** and 7-membered ring **7** were isolated from the reaction mixture (Figure 7).

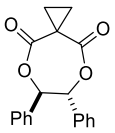


Figure 7. 7-membered ring **7**.

Nucleophile **176** was selected to further investigate the unknown side-reaction(s) (Section 2.3.3).

2.3.3 Side-reaction investigation

As stated in Section 2.3.2.3, reaction of *trans*-stilbene **1** under the oxyamination conditions with nucleophile **176**, lead to oxyaminated product **177** in a 49% yield, with complete consumption of *trans*-stilbene **1**. It was evident an undesired side-reaction was taking place and had to be identified in order to further improve the reaction yield. Reaction monitoring studies confirmed the increased rate of consumption of *trans*-stilbene **1** and malonoyl peroxide **3** compared to formation of oxyaminated product **177** (Figure 8). Interestingly, the conversion of oxyaminated product **177** was 40%, compared to the isolated yield of 49%, this was deemed to be within the margins of experimental error. Oxyaminated product **177** (40%) and 7-membered ring by-product **7** (17%) were the only reaction products observed to be forming within the reaction mixture, leaving the remaining 43% of consumed alkene **1** unaccounted for.

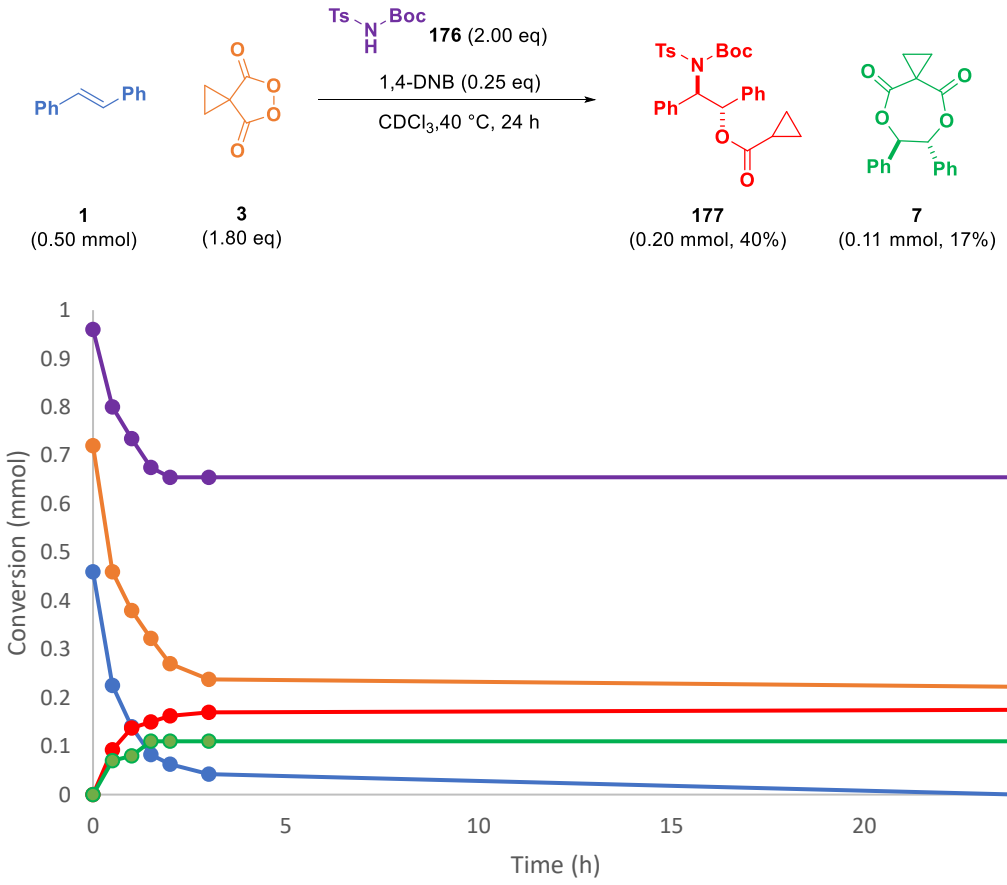


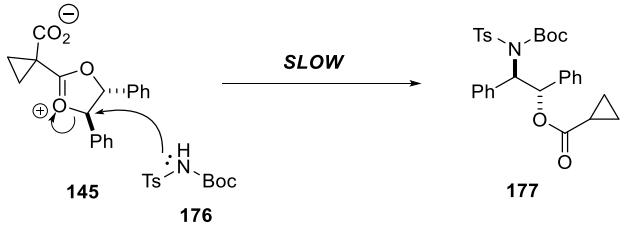
Figure 8. Reaction profile for the oxyamination of *trans*-stilbene **1** with nucleophile **176**.

A side-reaction hypothesis was proposed based upon the existing knowledge within our laboratory of alkene functionalisation with malonoyl peroxide **3**. This hypothesis was then examined by a series of experiments.

2.3.3.1 Side-reaction hypothesis

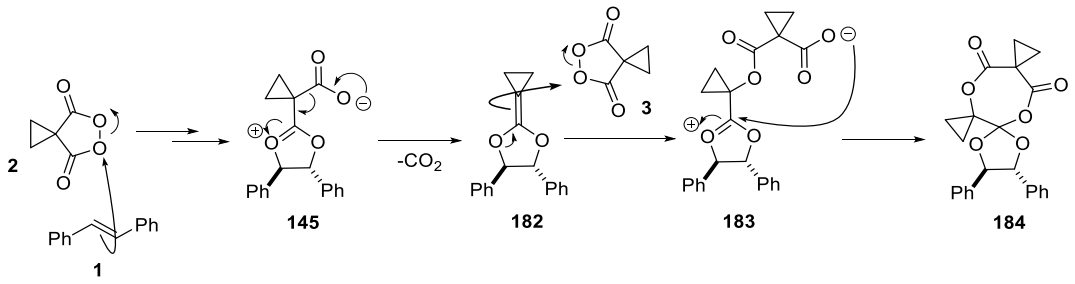
The side-reaction hypothesis can be summarised by three key statements;

1) Nucleophile **176** is a weak nucleophile and therefore its nucleophilic addition to dioxonium intermediate **145** is the rate-limiting step in the oxyamination process (Scheme 46).



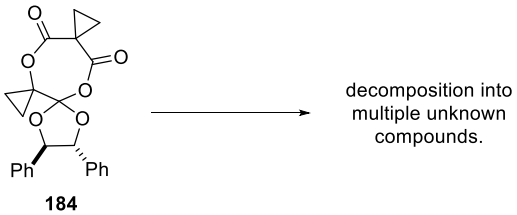
Scheme 46. Addition of nucleophile **176** is the rate limiting step of alkene oxyamination.

2) As the addition of nucleophile **176** is a slow process, dioxonium intermediate **145** may react with another molecule of malonoyl peroxide **3** to form orthoester **184** (Scheme 47). Orthoester **184** was identified as a product of the reaction between malonoyl peroxide **3** with trans-stilbene **1** (in the absence of a nucleophile), in previous work conducted by Rawling.[46]



Scheme 47. Proposed mechanism of formation of orthoester by-product **184**.

3) Orthoester **184** is unstable under the reaction conditions and breaks down to a series of unidentified compounds (Scheme 48).



Scheme 48. Decomposition of orthoester **184**.

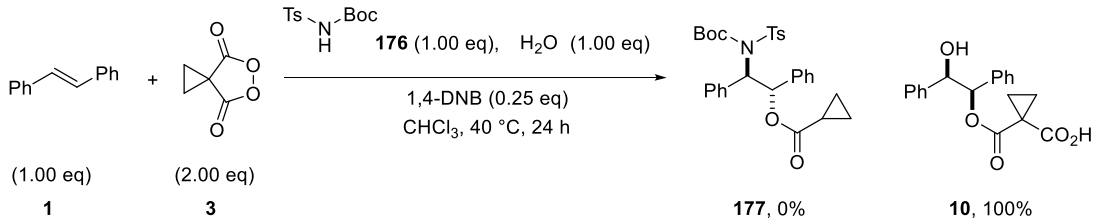
2.3.3.2 Experimental evidence

A series of experiments were conducted to back up each statement of the proposed side-reaction hypothesis.

Statement 1. *O-tert*-butyl *N*-tosylcarbamate 176 is a weak nucleophile

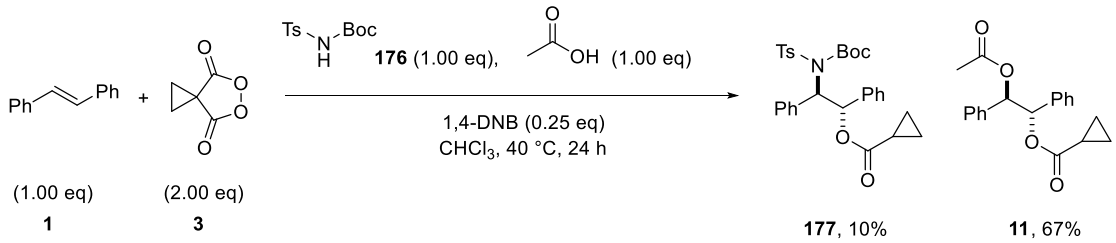
Competition experiments were conducted in order to assess the relative nucleophilicity of **176**, comparing it to the nucleophiles responsible for the *syn*-dihydroxylation (water) and *anti*-dihydroxylation (acetic acid) procedures (Section 1.1).

One equivalent of *trans*-stilbene **1** was reacted with peroxide **3** (2.0 equivalents) in the presence of nucleophile **176** (1.0 equivalent) and water (1.0 equivalent). Analysis of the crude reaction mixture revealed exclusive formation of *syn*-dihydroxylation intermediate **10** over the oxyaminated product **177** (Scheme 49).



Scheme 49. Competition experiment between nucleophile **176** and water.

One equivalent of *trans*-stilbene **1** was reacted with peroxide **3** (2.0 equivalents) in the presence of nucleophile **176** (1.0 equivalent) and acetic acid (1.0 equivalent). The major product was found to be *anti*-dihydroxylation intermediate **11** (67%), along with a small proportion of oxyaminated product **177** (10%) (Scheme 50).

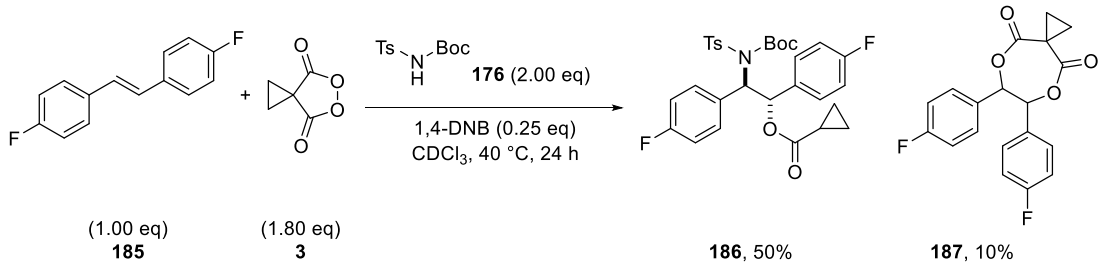


Scheme 50. Competition experiment between nucleophile **176** and acetic acid.

From this set of experiments, it was clear to see that *O-tert*-butyl *N*-tosylcarbamate **176** was a less effective nucleophile than both acetic acid and water, in relation to alkene functionalisation with malonoyl peroxide **3**.

Statement 2&3. The competing side-reaction is formation of orthoester 184, which is unstable and decomposes into multiple by-products under the reaction conditions.

In order to assess the fate of the missing 43% of consumed alkene, *trans*-4-fluorostilbene **185** was subjected to the oxyamination conditions (Scheme 51). Using ^{19}F NMR spectroscopy the number of fluorine environments within the reaction mixture could be observed, providing an understanding of the fate of consumed alkene.



Scheme 51. Oxyamination using 4-fluorostilbene **185**.

Analysis of the crude reaction mixture revealed a similar result to the oxyamination of *trans*-stilbene **1**. Oxyaminated product **186** had occurred in a conversion of 50%, with the major by-product being 7-membered ring **187** (10%). Inspection of the crude reaction mixture ^{19}F NMR spectrum confirmed this observation, with the three major peaks corresponding to oxyaminated product **186** (2 peaks) and 7-membered ring **187** (1 peak, molecule is symmetrical). Interestingly, 22 smaller peaks were also observed, each corresponding to a different fluorine environment (Figure 9). This confirms the presence of multiple 4-fluorostilbene derived by-products. Assuming that each by-product is unsymmetrical and contains two different fluorine environments, it was postulated that a minimum of 11 different 4-flurostilbene by-products were responsible for the consumed stilbene that was not converted to oxyaminated product **186** or 7-memebred ring **187**. Due to their small quantity and possible instability, none of these by-products were successfully isolated and characterised.

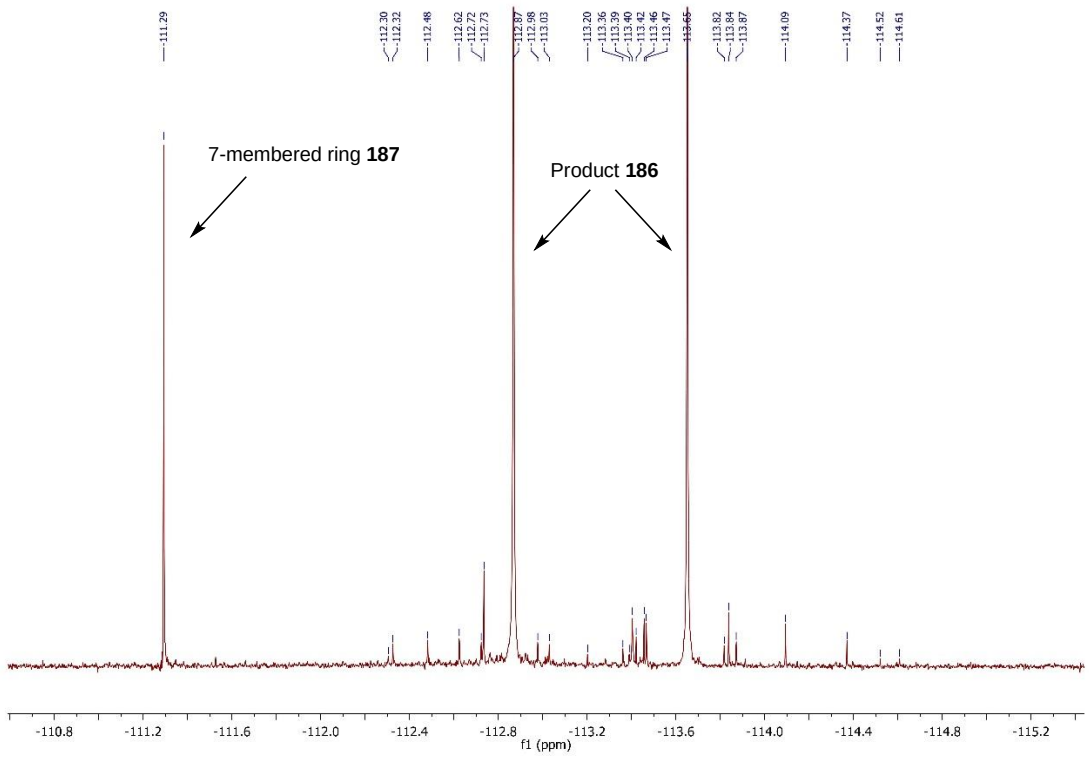
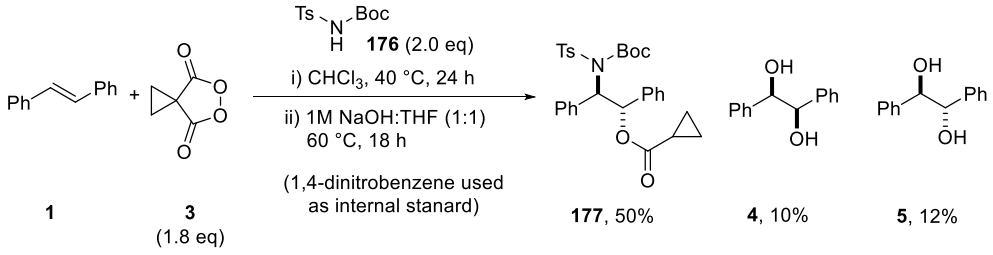


Figure 9. Reaction mixture ^{19}F NMR spectrum of 4-fluorostilbene **185** oxyamination.

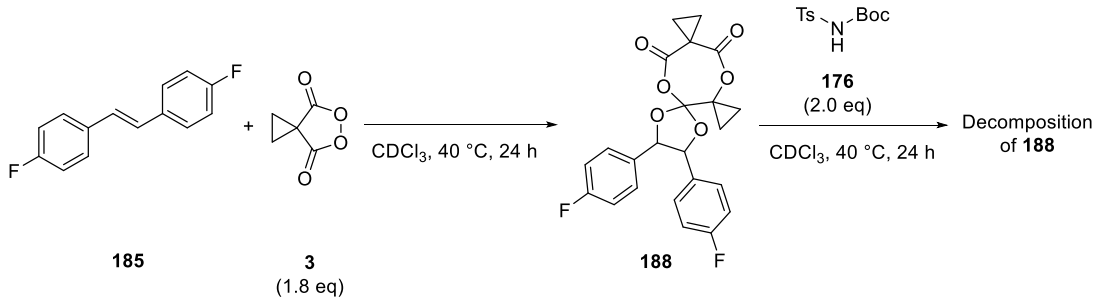
In order to assess if the unknown by-products were dioxygenated species, a hydrolysis reaction was carried out following the oxyamination procedure (Scheme 52). Oxyaminated product **177** was known to be stable in the presence of NaOH, whereas dioxygenated by-products may be hydrolysed to *syn*-diol **4** and *anti*-diol **5**. It was observed that 22% of consumed alkene was converted to a diol-species. This result indicated a proportion of by-products are dioxygenated species.



Scheme 52. Oxyamination of *trans*-stilbene **1**, followed by hydrolysis with 1M NaOH.

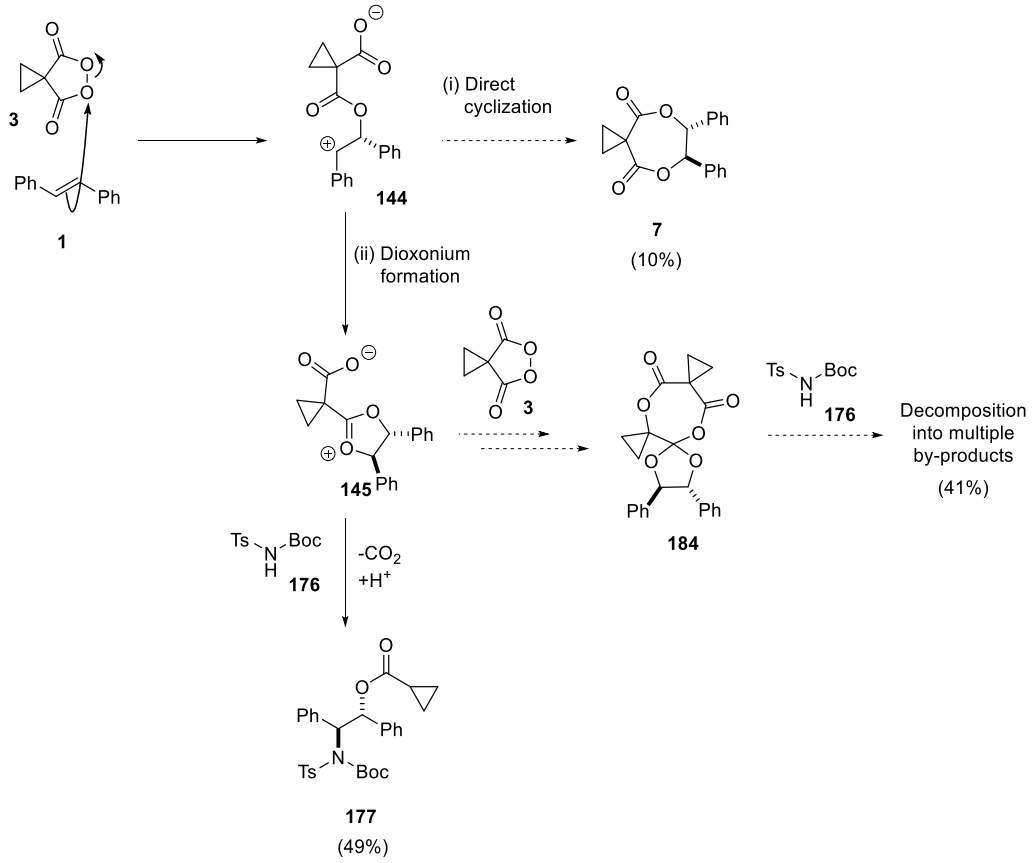
Upon confirming that 41% of consumed alkene was resulting in multiple by-products (see page 36), an experiment was designed to test the hypothesis that these by-products arose from the breakdown of orthoester **184** under the reaction conditions. Malonoyl peroxide **3** and *trans*-4-fluorostilbene **185** were stirred in chloroform to give orthoester **188**, which was observed by ^{1}H NMR spectroscopy. Nucleophile **176** was then added to the reaction mixture and the complete decomposition of orthoester **188** into multiple unknown products was

observed (Scheme 53). Nucleophile **176** was not consumed within this process. This experiment was conducted in the absence of an internal standard and therefore only provided a qualitative result.



Scheme 53. The decomposition of orthoester **188** with nucleophile **176**.

The hypothesis for alkene consumption is summarised in Scheme 54. Alkene **1** and peroxide **3** react to give zwitterionic species **144**, which may cyclise to form 7-membered ring **7** (10%). Species **144** may also cyclise to give dioxonium intermediate **145**. In tandem with decarboxylation, this intermediate is intercepted by nucleophile **176** to give the desired *anti*-oxyaminated product **177** (49%) (the precise order of these two events is unknown, however, we believe decarboxylation to occur first). Alternatively, due to the low nucleophilicty of **176**, after decarboxylation, dioxonium **145** may react with a further equivalent of peroxide **3** to form orthoester **184** which decomposes in the presence of nucleophile **176**. It is assumed this decomposition is responsible for the consumption of the 43% of *trans*-stilbene **1** unaccounted for within the transformation.



Scheme 54. The proposed routes of alkene consumption.

It is believed the competing side-reaction was a direct result of nucleophile **176** being slow to attack dioxonium **145** and therefore allowing other processes to take place. The most straight forward solution to increasing the yield of oxyamination was to find a stronger nitrogen nucleophile. To date, no such nucleophile has been discovered to give the desired reactivity.

At this point in the investigation, it was decided that one nucleophile should be selected to study alternative reaction conditions. *O-tert*-butyl *N*-tosylcarbamate **176** was selected as a suitable nucleophile to progress for further optimisation. This was due to the reasonable yield observed in conversion to oxyaminated product **177** and the chemical versatility of the BOC protecting group.

2.3.4 Optimisation of oxyamination with *O-tert*-butyl *N*-tosylcarbamate

2.3.4.1 Primary optimisation

The oxyamination procedure was examined under alternative conditions, varying malonoyl peroxide **3** equivalents, *O-tert*-butyl *N*-tosylcarbamate **176** equivalents and reaction temperature (Table 5).

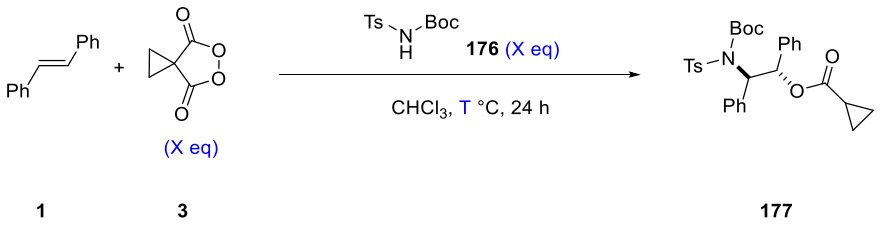


Table 5. Optimisation of conditions with *O-tert*-butyl *N*-tosylcarbamate **176**.

Entry	3 (eq)	176 (eq)	Temp (°C)	Conv[a] (%)
1	1.8	2	40	49[b]
2	1.8	2	rt	46
3	1.8	2	60	48
4	3	2	40	32
5	1	2	40	38
6	1.8	3	40	45
7	1.8	1	40	45[b]
8	1.8	0.5	40	48[b]

[a]Determined by HPLC analysis. [b]Isolated yield after chromatographic purification.

Temperature (entries 2–3)

Conducting the reaction at 60 °C had little effect on conversion. At room temperature the reactants did not fully go into solution, however, the transformation still resulted in a conversion of 46%. It was concluded that the most suitable temperature for the reaction was 40 °C (entry 1).

Peroxide equivalents (entries 4–5)

Decreasing peroxide **3** equivalents to 1, gave a conversion of 38% (entry 5). Complete consumption of peroxide **3** accounts for this decrease in conversion, with a proportion of *trans*-stilbene **1** also present in reaction mixture.

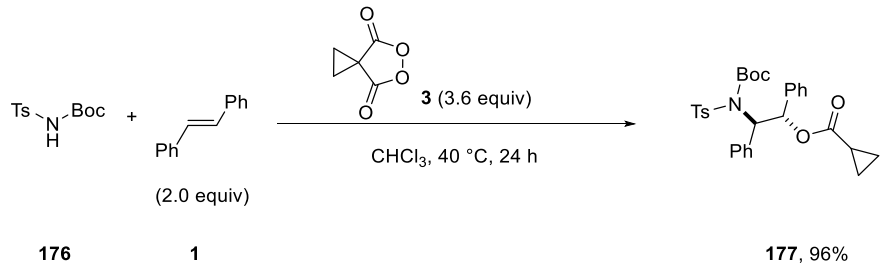
Increasing peroxide equivalents to 3 was found to give a conversion of 32% (entry 4). All *trans*-stilbene **1** was consumed in this experiment, with peroxide **3** still present in the reaction mixture.

Nucleophile equivalents (entries 6–8)

Altering the equivalents of nucleophile **176** from 3 to 1 to 0.5, was found to have little effect upon conversion.

Of particular interest was the result obtained in entry 8. Reaction of 1 equivalent of *trans*-stilbene **1** with 0.5 equivalents of nucleophile **176** resulted in a conversion of 48%, very similar to the conversion obtained when using 2 equivalents of nucleophile (49%) (entry 1).

A more accurate way to view the conversion of entry 8, was to treat the nucleophile as the limiting reagent when calculating the yield. This recalculation provided a yield of 96% for the transformation. Thus, new conditions were proposed for the oxyamination procedure (Scheme 55).



Scheme 55. Optimised conditions for oxyamination with *O*-*tert*-butyl *N*-tosylcarbamate **176**.

Conversion of *O*-*tert*-butyl *N*-tosylcarbamate **176** to oxyamination product **177** took place efficiently, with an excellent yield of 96%.

2.3.4.2 Secondary optimisation

With the new oxyamination conditions established, a secondary optimisation was conducted with the aim of decreasing the equivalents of peroxide and alkene used in relation to nucleophile **176** (Table 6).

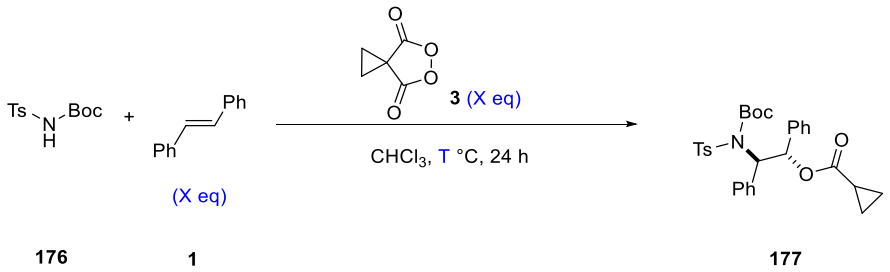


Table 6. Optimisation of conditions with *O-tert*-butyl *N*-tosylcarbamate **176** as limiting reagent.

Entry	1 (eq)	3 (eq)	Conc (M)	Conv[a] (%)
1	2	3.6	0.25	96[b]
2	2	3	0.25	84
3	2	2	0.25	66
4	2	1	0.25	36
5	1.5	3.6	0.25	74
6	1	3.6	0.25	40
7	2	3.6	0.5	60

[a]Determined by HPLC analysis. [b]Isolated yield after chromatographic purification.

Peroxide equivalents (entries 2–4)

Decreasing peroxide equivalents was found to have a negative effect on conversion. Entries 2–4 all contained unreacted nucleophile **176** after 24 hours.

Alkene equivalents (entries 5–6)

Decreasing alkene equivalents was also found to have a negative effect on conversion. It was concluded that 2 equivalents of alkene were required to drive the reaction to completion.

Reaction concentration (entry 7)

Increasing the reaction concentration to 0.5 M, resulted in a conversion of 60%.

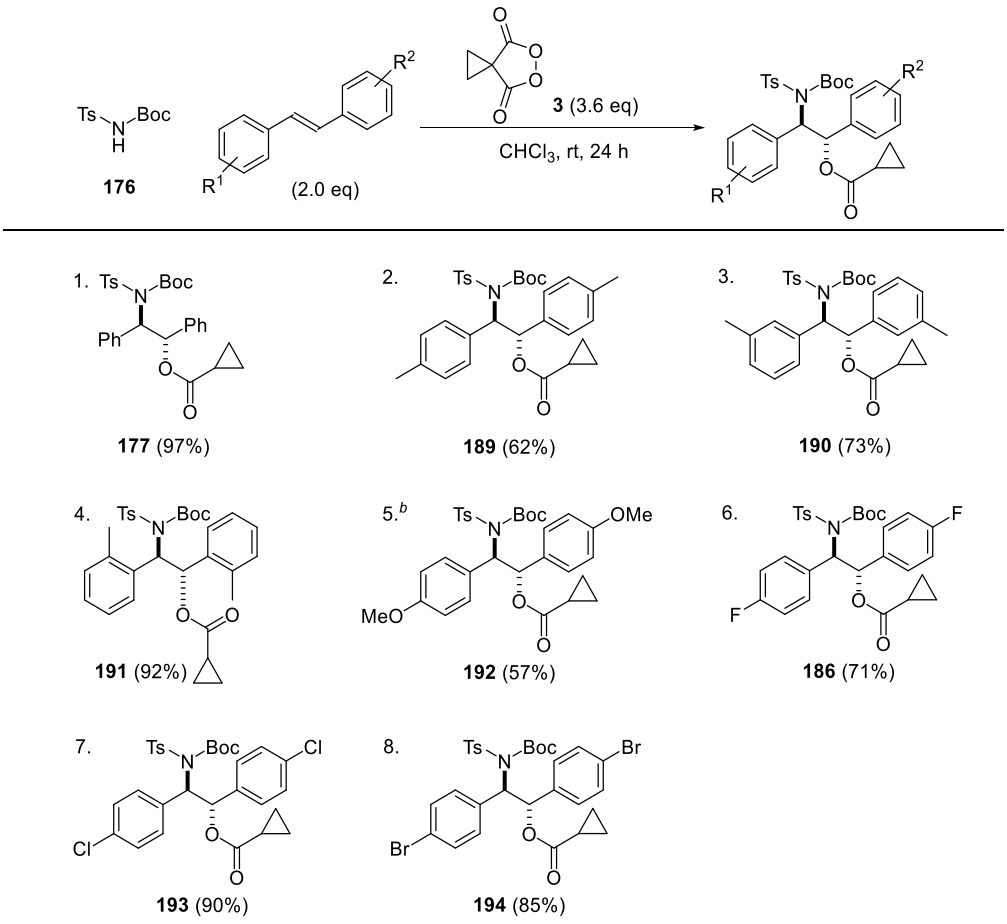
After the secondary optimisation, it was concluded that the original conditions (entry 1) were optimum with regards to the yield (96%). The inability to reduce equivalents of alkene and peroxide while maintaining near quantitative yield, was understood to be a result of the low nucleophilicity of **176** allowing for competing secondary reaction pathways to occur (as discussed in Section 2.3.3).

2.3.5 Substrate scope

With identification of nucleophile **176** and optimisation of the reaction conditions complete, attention was turned to the scope and limitations of the oxyamination reaction using alternative alkenes.

2.3.5.1 Stilbene substrates

Seven substituted stilbenes were synthesised and examined under the reaction conditions in work carried out by a co-worker Marina Perieteanu, whose results are collected in Table 7.[47]



[a]Reactions run in duplicate. [b]Reaction run at 0 °C.

Table 7. Substrate scope of stilbene derivatives.[a]

Results obtained from the stilbene substrate scope further emphasised the excellent *anti*-diastereoselectivity observed. Due to the electron rich nature of stilbenes, the reaction of all substrates examined were found to reach completion at room temperature.

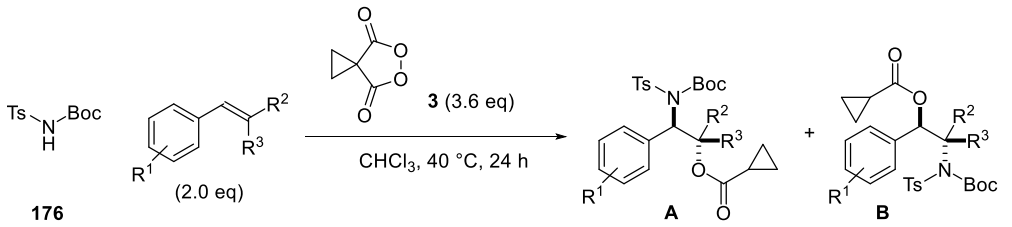
Oxyamination of methyl substituted stilbenes proceeded with good yield (Table 7, entries 3−4, 72−92%), with the exception 4-methyl stilbene which had a considerably lower yield of 62% (entry 2).

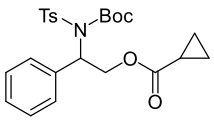
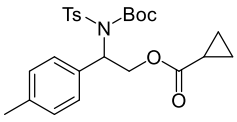
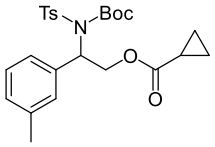
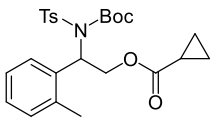
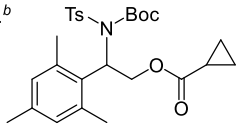
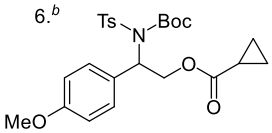
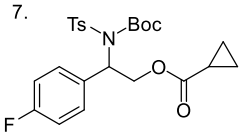
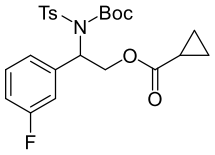
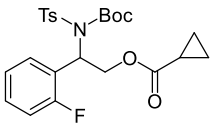
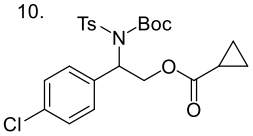
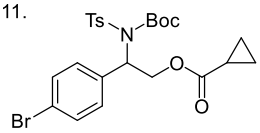
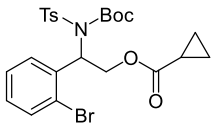
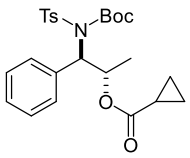
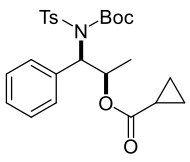
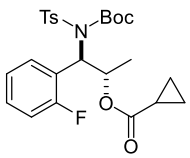
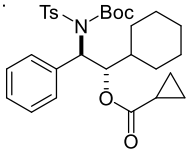
4-Methoxystilbene was found to be the most nucleophilic alkene tested and as a result the reaction had to be conducted at 0 °C, to reduce the rate of the unwanted side-reactions (entry 5, 57%).

Oxyamination of stilbenes with electron withdrawing substituents were found to proceed in excellent yield (entries 6−8, 71−90%).

2.3.5.2 Styrene substrates

The focus of the oxyamination substrate scope was turned to examining styrene substrates (Table 8).



1.  **195A:195B** 3.5:1 (77%)	2.  **196A:196B** 8:1 (99%)	3.  **197A:197B** 5:1 (76%)	4.  **198A:198B** 10:1 (83%)
5.[b]  **199A:199B** 20:1 (78%)	6.[b]  **200** (47%)	7.  **201A:201B** 5:1 (79%)	8.  **202A:202B** 1.4:1 (57%)
9.  **203A:203B** 1:1 (65%)	10.  **204A:204B** 3.5:1 (85%)	11.  **205A:205B** 3:1 (64%)	12.  **206A:206B** 2:1 (39%)
13.  **207** (87%)	14.[c]  **208** *Syn:Anti* 1:1.3 (54%)	15.  **209** (81%)	16.  **210** (92%)

[a]Reactions run in duplicate, yields quoted as mixture of regioisomers. [b]Reaction run at 25 °C. [c]Using *cis*-*β*-methyl styrene as alkene substrate.

Table 8. Oxyamination of styrene substrates.[a]

Reaction of styrene produced oxyaminated product **195A** along with the oxyaminated regioisomer **195B** in a 3.5:1 ratio with a combined yield of 77% (Scheme 8, entry 1).

The expected major product **212A** is a result of nucleophile **176** attacking the benzylic position **A** of dioxonium intermediate **211** (Scheme 56). The benzylic position is stabilised through a stereoelectronic effect of the adjacent aromatic ring. The π-orbitals of the aromatic ring acts

as an electron donor to stabilise the partial positive charge that arises in the transition state during S_N2 attack of nucleophile **176**. Formally, this is considered to be an electronic interaction between the aromatic π-orbitals and the σ*-like orbital formed by the two partial bonds within the transition state (Figure 10).[48]

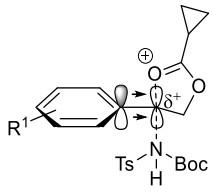
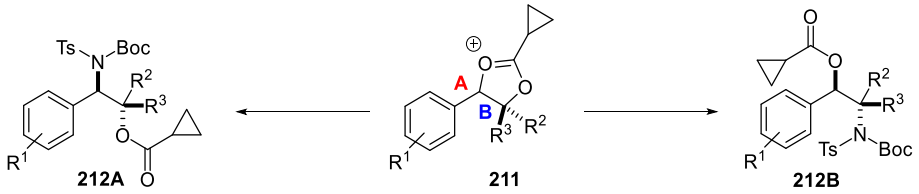


Figure 10. Stabilisation of benzylic position through a stereoelectronic effect.

The regioisomer **212B** is understood to arise from attack of nucleophile **176** at position **B** of dioxonium intermediate **211**. This product may form due to the fact that position **B** is more sterically accessible than position **A** (Scheme 56).



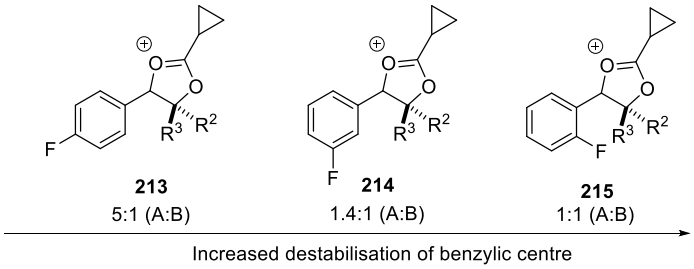
Scheme 56. Formation of regioisomers **212A** and **212B**.

The oxyamination of styrenes substituted by methyl groups on the aromatic ring proceed in good yield (Table 8, entries 2−5; 76−99%, 5:1−20:1 (A:B)). The ratio of A:B was also found to increase in comparison to styrene (entry 1). The methyl groups are inductively electron donating and enhance the phenyl ring's ability to stabilise the arising positive charge at position **A**. This effect was most notable for the oxyamination of 2,4,6-trimethyl styrene, achieving a ratio of 20:1 (A:B) (Table 8, entry 5, 78%).

Oxyamination of 4-methoxystyrene resulted in complete selectivity for position **A**. However, the reactive nature of the alkene resulted in an increased rate of unwanted side reaction(s). Performing the reaction at 25 °C allowed for oxyaminated product **200** to be isolated effectively (Table 8, entry 6; 47%).

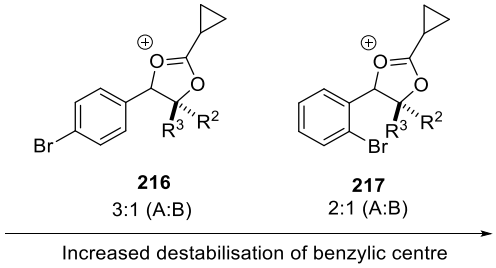
Oxyamination of halogen substituted styrenes proceeded in good yield. However, these substrates displayed a range of regioselectivities. The fluorine substituted styrenes showed a reduction in the ratio of A:B as the substituent was moved from *para* to *meta* to *ortho* positions (Table 8, entries 7−9; 57−79%, 1:1−5:1 (A:B)). It is believed this was due to the electron withdrawing nature of the halogen substituent decreasing the aryl ring's ability to stabilise the arising positive charge at position **A**. This effect was greater the closer the substituent was to

the benzylic centre **A** (Scheme 57). 2-Fluoro styrene in the lowest regioisomer ratio (Table 8, entry 9; 65%, 1:1 (A:B). With the electron withdrawing group at the *ortho* position, the benzylic centre was destabilised to the point that attack into position **B** of dioxonium intermediate **215** is equally possible, resulting in a 1:1 ratio (A:B).



Scheme 57. Destabilisation of benzylic centre as fluorine is moved *p*-, *m*-, *o*-.

This effect was also observed with bromine substituted styrenes (Table 8, entries 11−12; 64%−39%, 2:1−3:1 (A:B)) (Schemes 58).

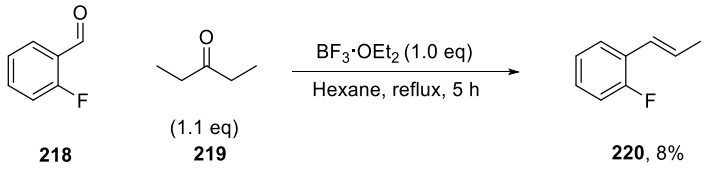


Scheme 58. Destabilisation of benzylic centre as bromine is moved *p*-, *o*-.

It was observed that as the halogen substituent was changed from fluoro, to chloro, to bromo, the ratio of A:B increased (Table 8, entries 7−12; 39−85%, 1:1−5:1 (A:B)).

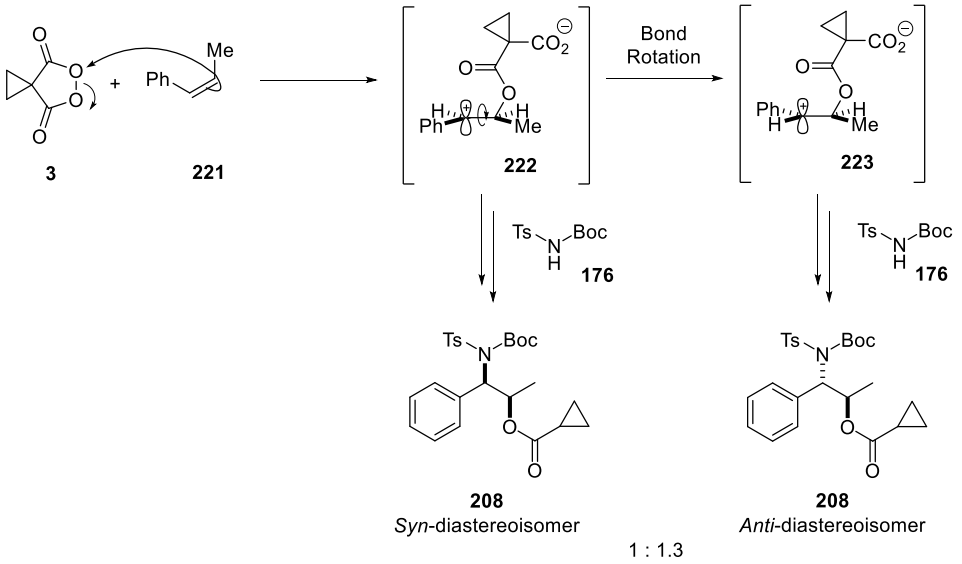
Trans-β-substituted styrenes were found to be selective towards regioisomer A due to an increased steric requirement upon position **B** (Table 8, entries 13,15−16; 81−92%). This steric hindrance is most notable when comparing 2-fluoro styrene (Table 8, entry 9; 65%, 1:1 (A:B)) and *trans*-β-methyl-2-fluoro styrene **220** (Table 8, entry 15; 81%, 1:0 (A:B)), where the presence of the methyl group upon the beta position of **220** is providing the added steric hindrance for the approach of nitrogen nucleophile to the reactive centre.

Trans-β-methyl-2-fluoro styrene **220** was made by reaction of 2-fluorobenzalehyde **218** and 3-pentanone **219** in the presence of the Lewis acid, boron trifluoride etherate.[49] Although the reaction was low yielding, a sufficient quantity of alkene **220** was isolated to study the oxyamination reaction (Scheme 59).



Scheme 59. Synthesis of alkene **220**.

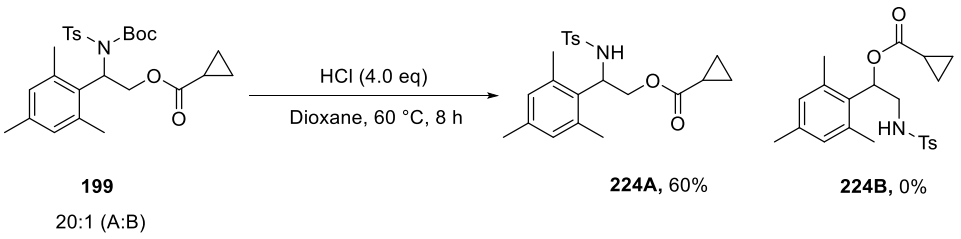
Oxyamination of *cis*-β-methyl styrene **221** was found to be fully selective for regioisomer A (Table 8, entry 14; 1:1.3 (*Syn*:*Anti*)). However, a significant loss in diastereoselectivity was observed. This can be explained through a bond rotation of intermediate **222** to relieve steric strain and give conformational isomer **223**. Formation of the dioxonium intermediate followed by addition of the nucleophile **176** gave the *anti*-diastereoisomer **208** preferentially (Scheme 60).



Scheme 60. Loss of diastereoselectivity due to bond rotation.

2.3.5.3 Confirmation of regioselectivity

In order to validate the results of the substrate scope, it was deemed necessary to experimentally confirm the connectivity of the two regioisomers. In order to confirm the connectivity of product A, a Boc group deprotection of oxyaminated product **199** was carried out using hydrochloric acid, to give **224A** in a 60% yield (Scheme 61). This substrate was selected as it had the largest A:B ratio. Upon purification by column chromatography, Boc deprotected regioisomer **224B** was not observed.



Scheme 61. Boc group deprotection using hydrochloric acid.

Inspection of the ^{1}H-^{1}H COSY spectra of compound **224A** displayed a correlation between H_a and H_b, supporting the predicted regiochemistry (Figure 11). In addition, a correlation was present between H_b and H_c/H_d. Upon D_2O shake of compound **224A**, the peak corresponding to H_A disappeared from the ^{1}H NMR spectra, confirming H_a had been assigned correctly.

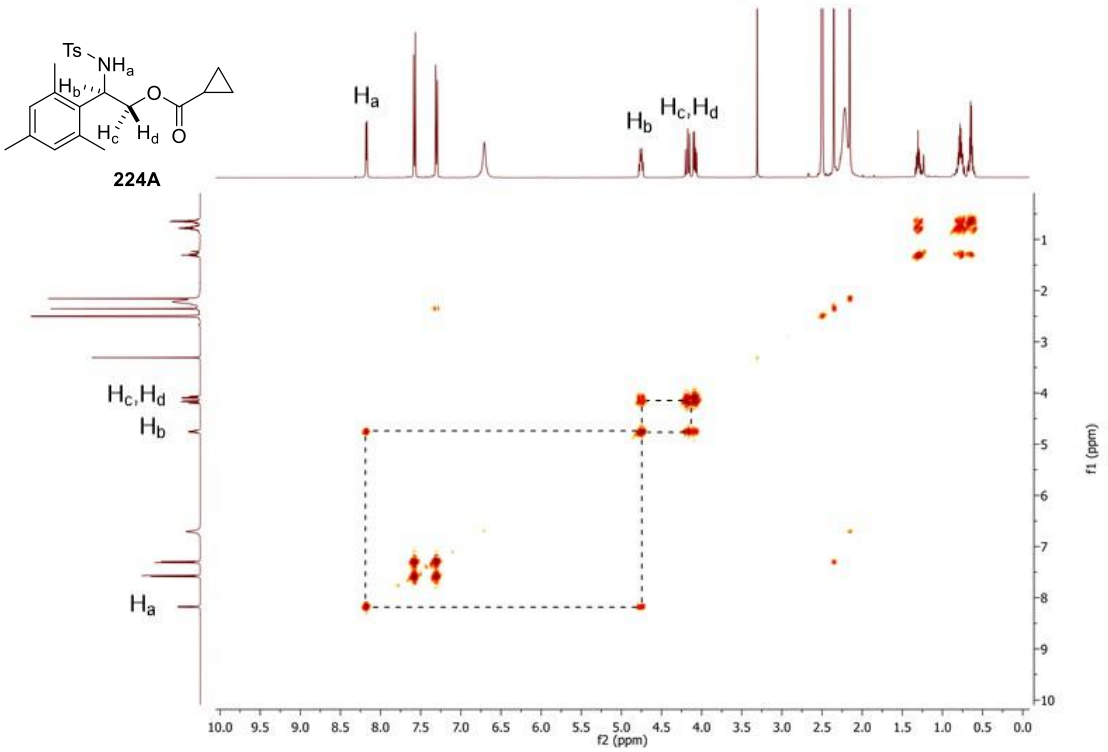
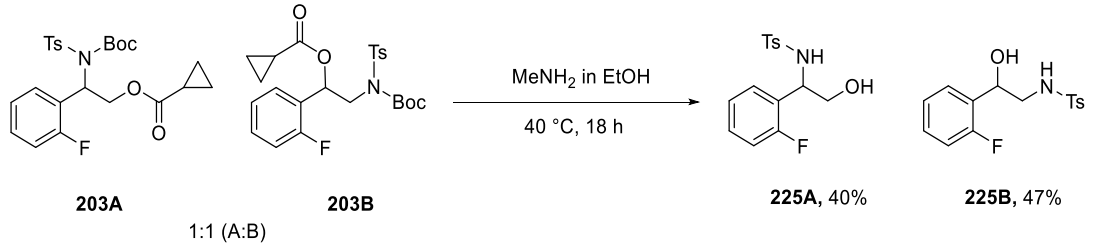


Figure 11. ^{1}H COSY spectra of compound **X92A**.

Compound **203** was selected to confirm the structure of the B regioisomer, as this substrate had a good A:B ratio (1:1). Compound **203** was treated with methylamine to afford compounds **225A** (40%) and **225B** (47%). Both regioisomers were separated effectively *via* column chromatography (Scheme 62).



Scheme 62. Boc and ester cleavage of **203** using methylamine.

Regioisomer **225B** was found to be a solid, and upon crystallisation, its structure was confirmed by X-ray crystallography, with an oxygen substituent at the benzylic position (Figure 12).

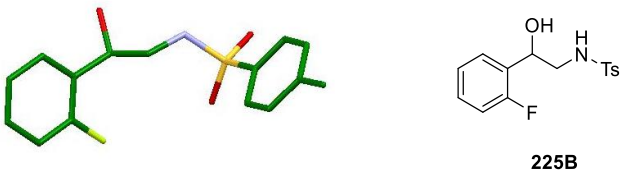
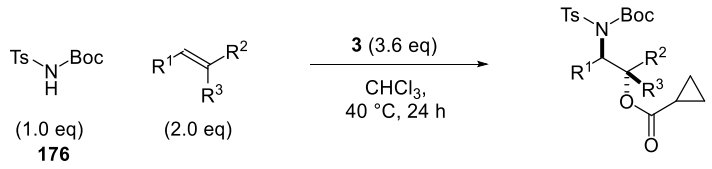


Figure 12. Crystal structure of **225B**.

2.3.5.4 Unsuccessful substrates

Ten alkene substrates tested under the reaction conditions failed to give the desired oxyaminated products. Although these results were unsuccessful, they still offered valuable insight into the oxyamination procedure.



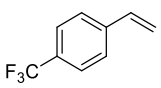
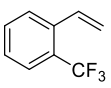
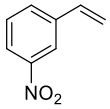
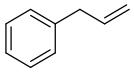
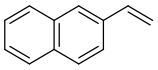
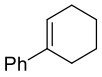
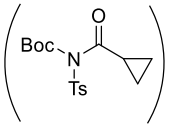
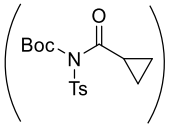
1.  **226**	2.  **227**	3.  **228**	4.  **229**
5.  **230**	6.  **231**	7.  **232**	8.  **233**
9.   **234** **235**		10.   **236** **235**	

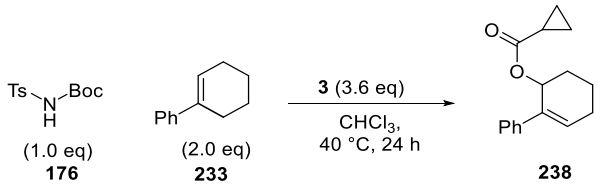
Table 9. Unsuccessful alkene substrates.

Three alkenes were found to be unreactive with peroxide **3**, due to their electron-deficient nature. Only starting materials were observed within the reaction mixture using these substrates (Table 9, entries 1−3).

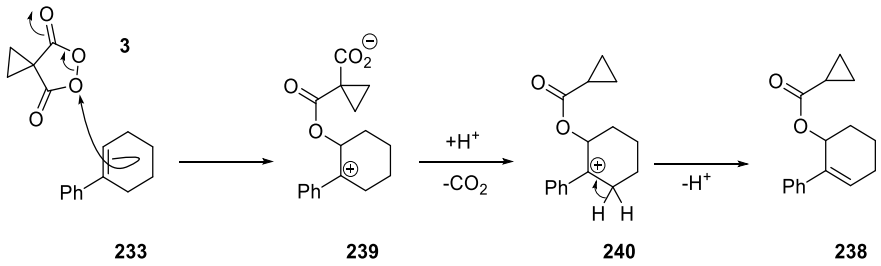
2-Vinyl naphthalene **203**, *cis*-stilbene **231** and 1,1-diphenyl ethylene **232** all resulted in an intractable mixture of products after reaction with malonyl peroxide **3** under the optimised reaction conditions. It was assumed that the side-reaction was dominant (as described in Section 2.3.3) using these substrates and oxyamination did not occur (Table 9, entries 5−7).

1-Phenyl-1-cyclohexene **233** resulted in the formation of a single product, which was not isolated. Comparison of ^{1}H NMR and mass spectrometry data revealed the compound to be allylic ester **238**, previously isolated in work conducted by Rawling (Table 9, entry 8) (Scheme 63).[46] Mixing of peroxide **3** and alkene **233** was also found to give allylic ester **238**, suggesting

that nucleophile **176** did not participate in the reaction, potentially due to its low nucleophilicity (Scheme 64).



Scheme 63. Formation of allylic ester **238**.

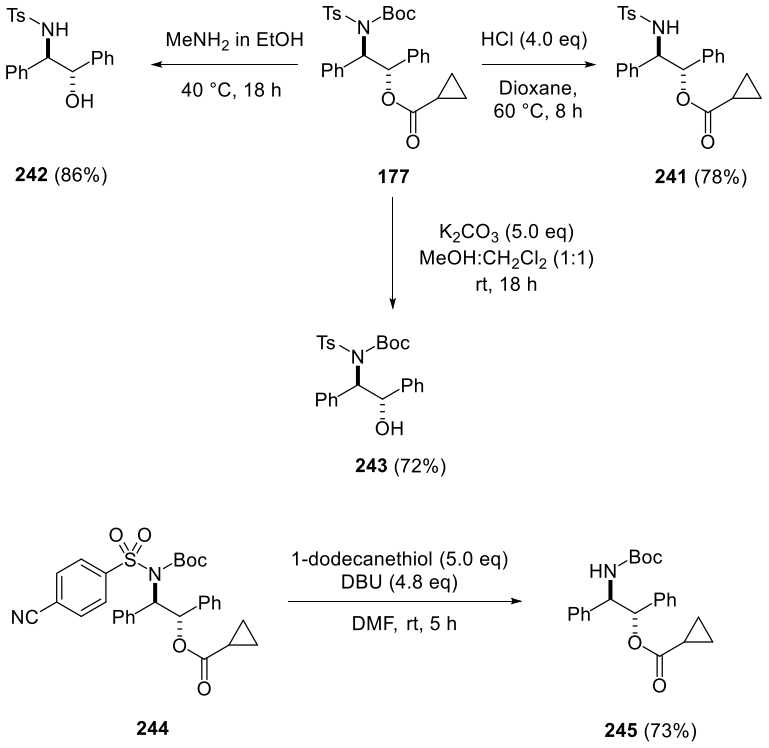


Scheme 64. Proposed mechanism for the formation of allylic ester **238**.[46]

The oxyamination of aliphatic alkene substrates was also found to be unsuccessful under the standard optimised reaction conditions. Interestingly, in the reaction using cyclohexene and cycloheptene as the substrate, compound **235** was isolated in excellent yield (Table 9, entries 9−10; 86−87%). The fate of the aliphatic alkene in this reaction mixture was not identified.

2.3.6 Deprotection reactions

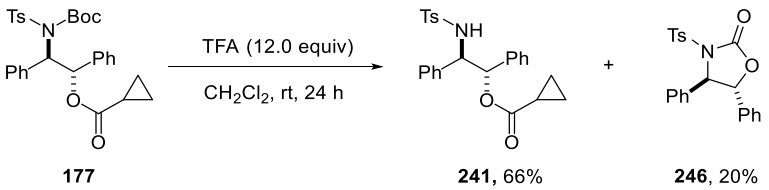
A key consideration of the oxyamination procedure was the ability to remove the nitrogen and oxygen protecting groups, providing a handle for further functionalisation. Various deprotection reactions were conducted upon oxyaminated substrates, an overview of which is presented in Scheme 65. Overall, the Boc, tosyl and cyclopropyl ester groups were removed selectively in a series of reactions outlined within this Section.



Scheme 65. Summary of deprotection reactions upon oxyaminated substrates.

2.3.6.1 Boc group deprotection

Treatment of oxyaminated product **177** with trifluoroacetic acid (TFA) gave compound **241** (66%) and oxazolidinone **246** (20%) (Scheme 66). The formation of oxazolidinone **246**, including the stereochemical outcome of the transformation, is discussed in Section 2.3.7.



Scheme 66. Boc deprotection of **177** using TFA.

The yield for BOC deprotection was improved when compound **177** was treated with hydrochloric acid to exclusively give compound **241** in a yield of 78% (Table 10, entry 1). This deprotection was also performed on oxyaminated product **199** to give compound **224A** (Table 10, entry 2; 60%).

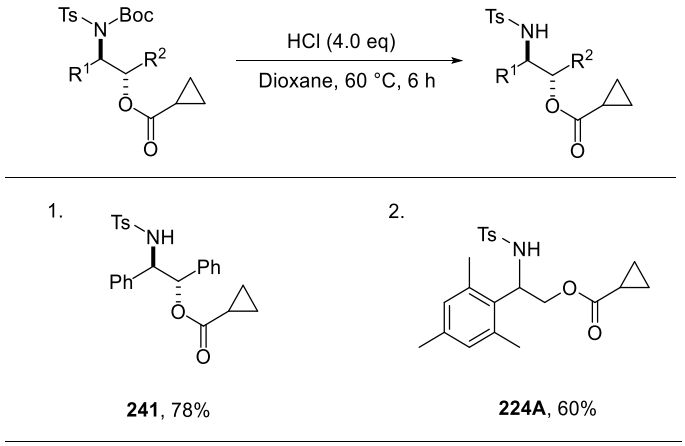


Table 10. BOC group deprotection using hydrochloric acid.

2.3.6.2 Simultaneous BOC deprotection and cyclopropyl ester cleavage

Treatment of the oxyaminated product with methylamine resulted in BOC group deprotection and cyclopropyl ester cleavage, in a single step. This procedure successfully deprotected stilbene and styrene derived oxyaminated products (Table 11, entries 1−2; 56−86%). As previously reported, the two regiosiomers observed within the oxyamination procedure proved inseparable *via* column chromatography and were isolated as a mixture (Section 2.3.5.2). However, the deprotection of 2-fluoro styrene derived oxyaminated product **203**, allowed for successful chromatographic separation of the regioisomers **225A** (40%) and **225B** (47%) (Table 11, entry 3).

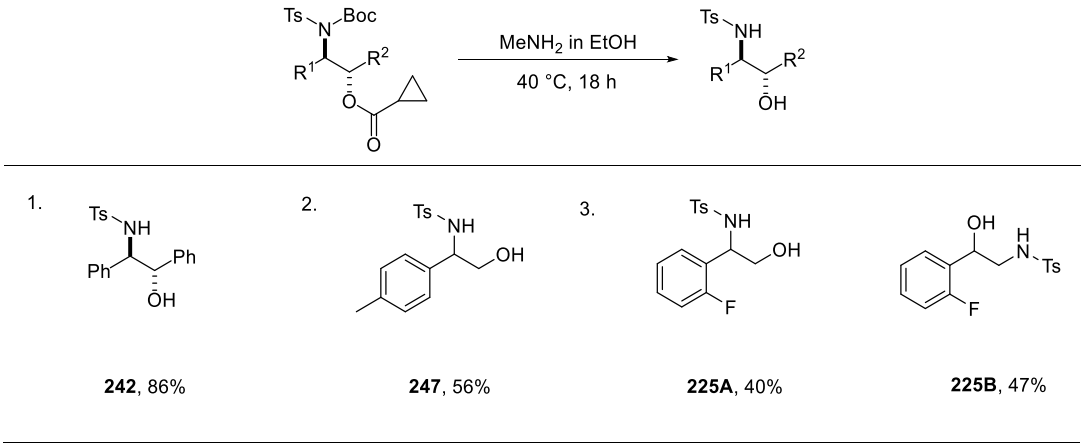
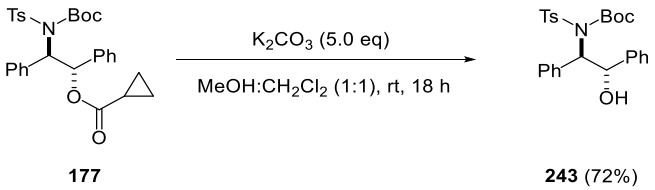


Table 11. BOC deprotection and cyclopropyl ester cleavage using methylamine.

2.3.6.3 Cyclopropyl ester hydrolysis

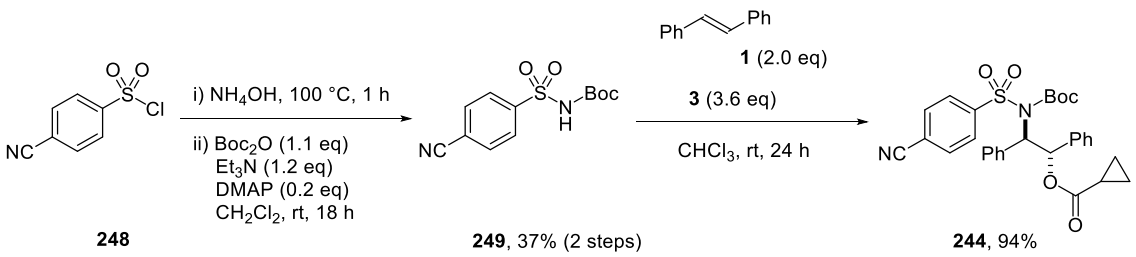
Treatment of oxyaminated product **177** with potassium carbonate in methanol and dichloromethane gave alcohol **243** in a 72% yield (Scheme 67), providing a convenient method to selectively unmask the alcohol functionality in the oxyamination product.



Scheme 67. Cyclopropyl ester cleavage with potassium carbonate in methanol and dichloromethane.

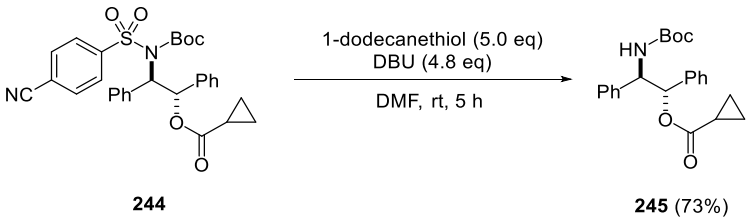
2.3.6.4 4-Cyanobenzylsulfonamide cleavage

According to the literature,[50] cleavage of a tosyl protecting group may be achieved under strong reducing conditions such as the use of lithium metal. In order to develop a more facile procedure, an alternative protecting group/nitrogen nucleophile was considered. In 2017, Schmidt and co-workers reported a method for the cleavage of 4-cyanobenzenesulfonyl carbamates.[51] Adopting this methodology, sulfonyl chloride **248** was treated with ammonium hydroxide and the resulting sulphonamide BOC protected to give nitrogen nucleophile **249**. *Trans*-stilbene **1** and nucleophile **249** were reacted in the presence of malonoyl peroxide **3**, under the standard oxyamination conditions to give product **244** in a 94% yield (Scheme 68).



Scheme 68. Preparation of oxyaminated product **244**.

Sulfonamide cleavage was achieved through treatment of the oxyaminated substrate **244** with 1-dodecanethiol and DBU to give compound **245** in a 73% yield (Scheme 69).



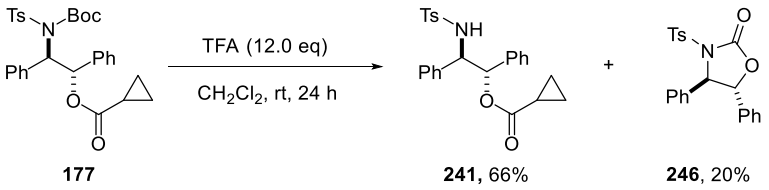
Scheme 69. 4-Cyanobenzenesulfonamide deprotection.

In summary, conditions were successfully developed for the selective removal of oxygen and nitrogen protecting groups, allowing for further synthetic manipulations of the products to be undertaken.

2.3.7 Oxazolidinone formation – *Syn*-oxyamination

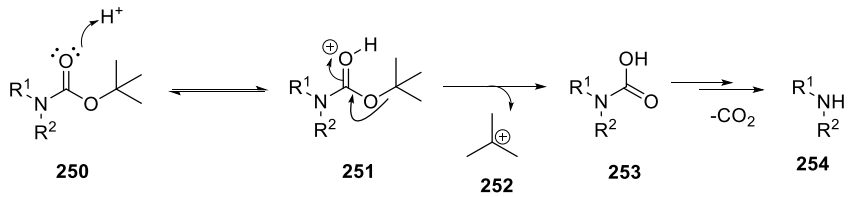
2.3.7.1 Initial result

A novel alkene *syn*-oxyamination procedure for the formation of oxazolidines was developed as an extension of the *anti*-oxyamination methodology. In an attempt to carry out a BOC group deprotection, treatment of oxyaminated product **177** with trifluoroacetic acid gave compound **241** (66%) along with a small amount of the oxazolidinone **246** (20%) (Scheme 70). The unexpected formation of oxazolidinone **246** was identified as a novel transformation with the potential to be optimised.



Scheme 70. BOC deprotection of **177** using TFA with oxazolidinone co-product **246**.

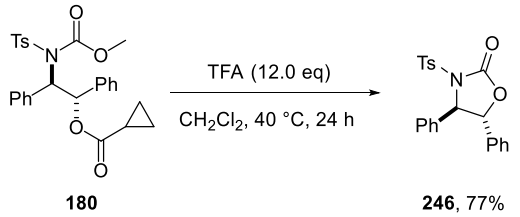
Mechanistically, it was proposed that BOC group deprotection under acidic conditions proceeded through loss of a *tert*-butyl cation **252** from protonated species **251**, to give carbamic acid **253**. Loss of carbon dioxide gives amine **254** (Scheme 71).



Scheme 71. Postulated mechanism for BOC group deprotection under acidic conditions.

The stability of the *tert*-butyl cation **252** is a key factor in the mechanism of a BOC group removal. It was postulated that if this *tert*-butyl group was replaced with a methyl group, (i.e. oxyaminated product **180**), the carbamate deprotection pathway would be shut down leading

to cyclisation. When oxyaminated product **180** was treated with trifluoroacetic acid, oxazolidinone **246** was produced selectively in a 77% isolated yield (Scheme 72).



Scheme 72. Cyclisation of **180** with TFA to give oxazolidinone **246**.

The structure of oxazolidinone **246** was confirmed by X-ray crystallography (Figure 13). A key feature of the molecule was the unexpected *syn*-relationship of the oxygen and nitrogen substituents. This potentially provided an extension of the methodology to also prepare the *syn*-oxyaminated product. Careful examination of the crude reaction mixture from the cyclisation showed no indication of the diastereomeric oxazolidinone product.

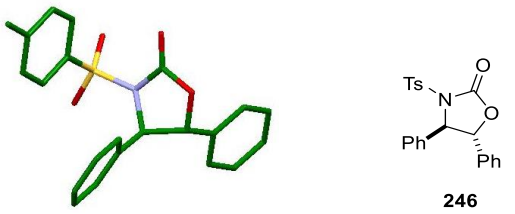
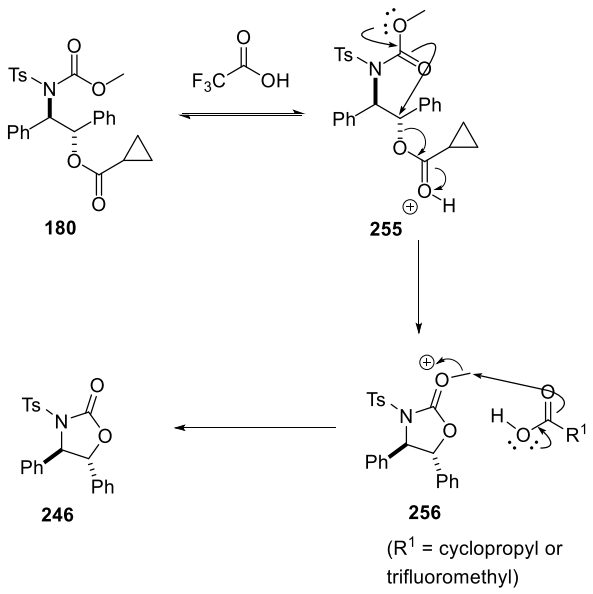


Figure 13. Crystal structure of oxazolidinone **246**.

2.3.7.2 Proposed mechanism

In order to explain the stereochemistry obtained within this transformation it was postulated that substrate **180** was protonated to give compound **255** which underwent cyclisation, displacing cyclopropanecarboxylic acid. It is at this stage the diastereomeric relationship between the nitrogen and oxygen substituents was inverted from *anti* to *syn*. The cyclopropanecarboxylic acid or trifluoroacetic acid was then methylated, by species **256**, to give oxazolidinone **246** (Scheme 72). Doping experiments confirmed the presence of both methyl cyclopropanecarboxylate **257** and methyl trifluoroacetate **258** within the reaction mixture (Figure 14 & 15). In theory, cyclopropanecarboxylic acid was the most nucleophilic acid present in the reaction mixture and therefore the most likely to be methylated. However, the high concentration of trifluoroacetic acid (12.0 eq) present in the reaction mixture lead to a proportion of this acid also being methylated.



Scheme 72. Proposed mechanism for formation of oxazolidinone **246**.

Reaction mixture doped with methyl cyclopropanecarboxylate **257**

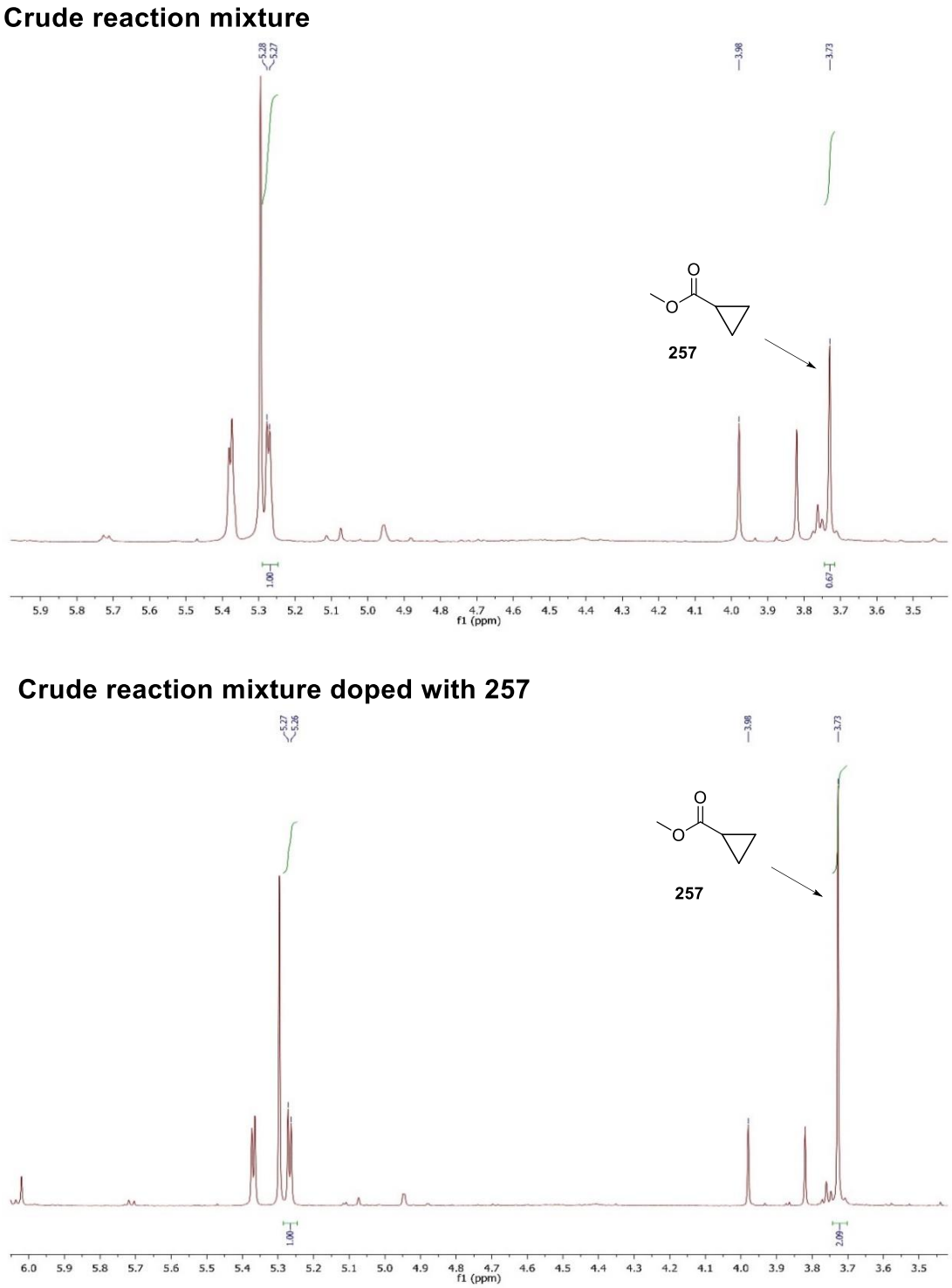


Figure 14. Doping experiment with methyl cyclopropanecarboxylate **257**.

Reaction mixture doped with methyl trifluoroacetate **258**

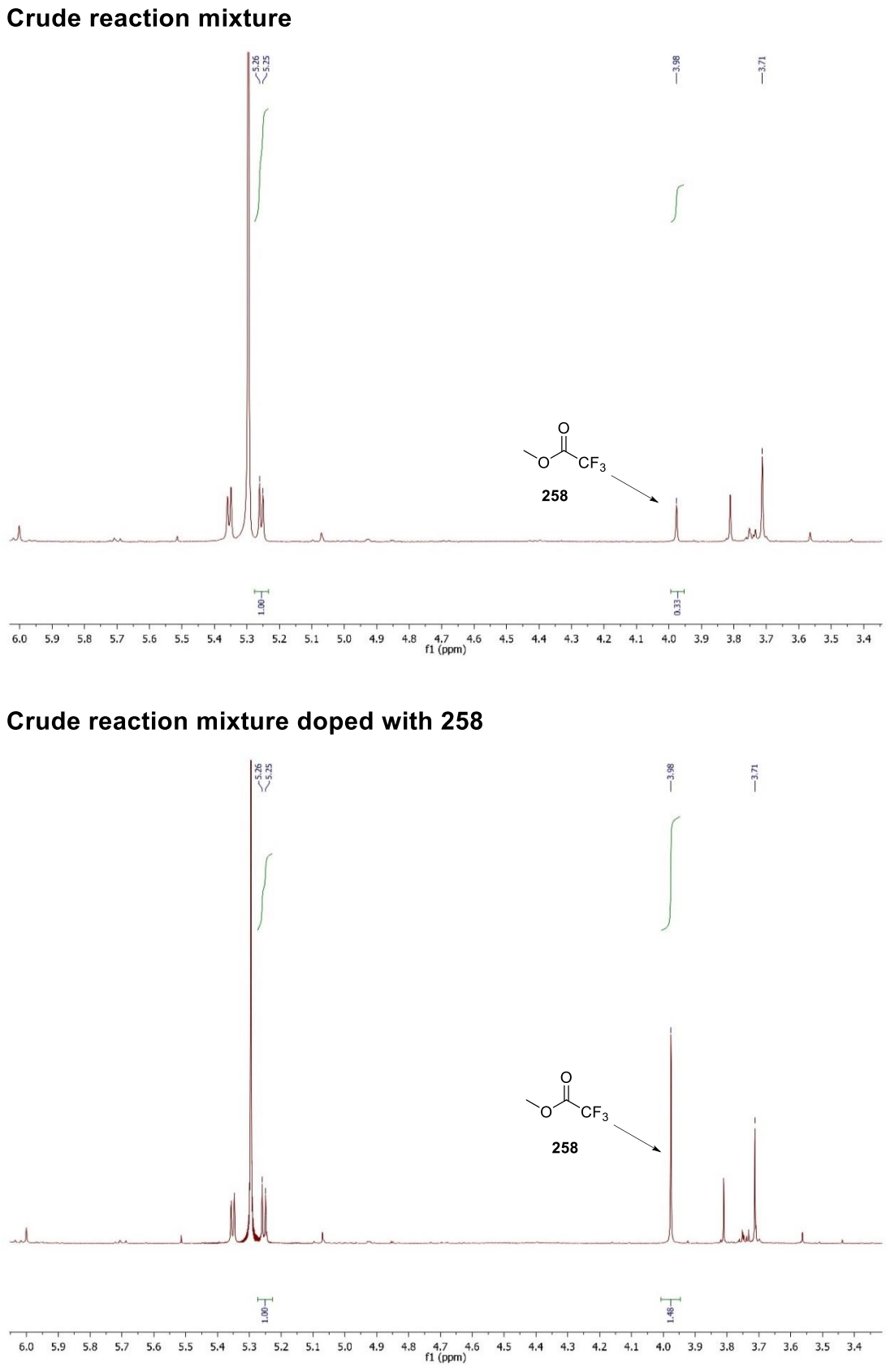
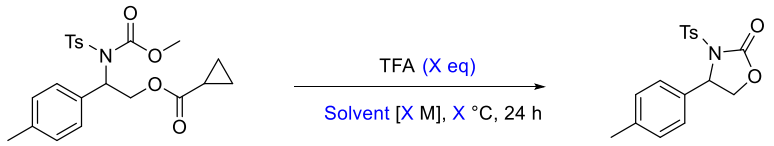


Figure 15. Doping experiment with methyl trifluoroacetate **258**.

Due to a numbering error, the numbers **259** *and* **260** *have not been assigned within this thesis.*

2.3.7.3 Optimisation of reaction conditions for styrene substrates

The cyclisation reaction was examined upon 4-methyl styrene derived oxyamination product **261**. However, treatment of oxyaminated product **261** under the reaction conditions developed for the cyclisation of **180**, did not yield expected product **262**, with only starting materials observed within the crude reaction mixture (Table 12, entry 1). Increasing reaction concentration failed to provide the product **262** (Table 12, entry 2), as did the use of alternative solvents (Table 12, entries 3, 7, 5). Stirring the reaction at reflux in neat trifluoroacetic acid, consumed all starting material **261** inside 24 h, leading to oxazolidinone **262** in a yield of 8% (Table 12, entry 6). Building upon this result, compound **261** was stirred at reflux in dioxane for 4 days, giving oxazolidinone **262** in a yield of 73% (Table 12, entry 8).



261 **262**

Entry	TFA (eq)	Solvent	Temperature	Reaction concentration	Yield (%)
1	12	CH_2Cl_2	40 °C	0.1 M	0
2	12	CH_2Cl_2	40 °C	0.5 M	0
3	12	DMF	40 °C	0.5 M	0
4	12	DMF	120 °C	0.5 M	0
5	24	Neat	40 °C	0.5 M	0
6	120	Neat	60 °C	0.1 M	8
7	12	Dioxane	40 °C	0.5 M	0
8	12	Dioxane	100 °C	0.5 M	73[a]

[a]Reaction run for 4 d.

Table 12. Optimisation of conditions for product **262**.

It was proposed that the increased reaction time and temperature required for cyclisation of styrene derived substrates, when compared to stilbene derived substrates, was due to an increase in activation energy required to facilitate the cyclisation. Within stilbene derived substrates, stabilisation of the developing positive charge at the benzylic centre occurred due to a stereoelectronic interaction between the phenyl π-orbital and the developing positive charge within the transition state. For the styrene derived substrates, this stabilisation was

removed, therefore, the reaction required higher temperature and longer reaction times for the cyclisation to reach completion (Figure 16).

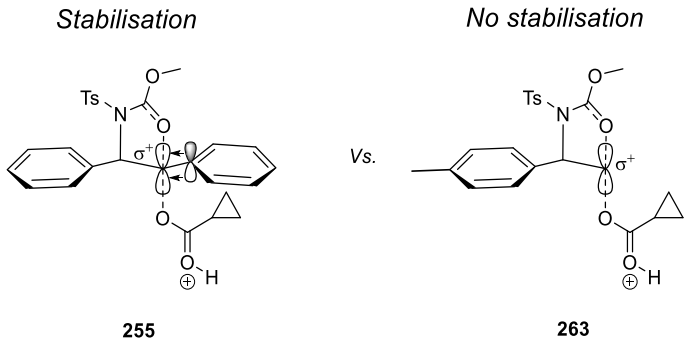
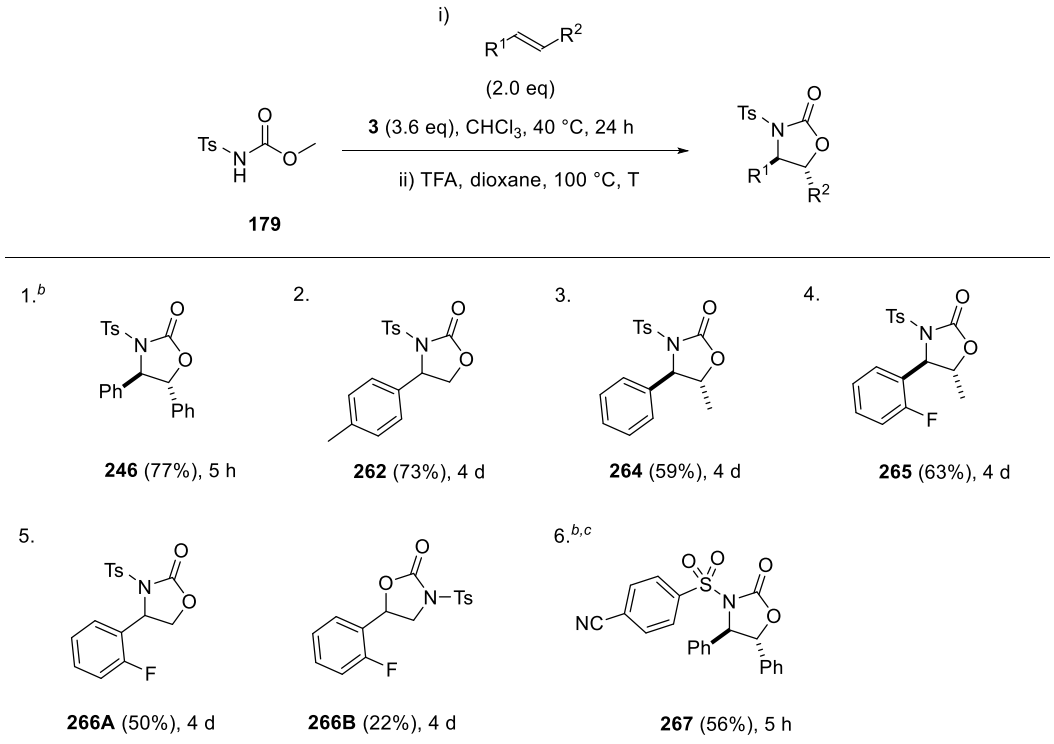


Figure 16. Stereoelectronic stabilisation of intermediate **255**, which is not present in intermediate **263**.

2.3.7.4 Substrate scope

Six alkene substrates were successfully converted to the corresponding oxazolidinones, using the optimised methodology (Table 13).



[a]Reactions run in duplicate. [b]Reaction run at 40 °C in CH_2Cl_2.
[c]methyl ((4-cyanophenyl)sulfonyl)carbamate **268** used as nucleophile.

Table 13. Substrate scope for oxazolidinone formation.[a]

Oxazolidinone **262** was synthesised from 4-methyl styrene in a yield of 73% over 2-steps, the product being isolated as a single regioisomer (Table 13, entry 2). When β-substituted styrenes

were employed, a slightly lower yield was observed, however, the reaction proceeded with complete regioselectivity and *syn*-diastereoselectivity (Table 13, entry 3-4). *Syn*-diastereoselectivity was confirmed by X-ray crystallography of oxazolidinone **264** (Figure 17).

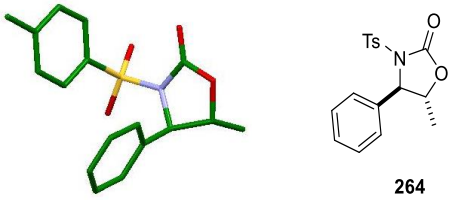


Figure 17. Crystal structure of oxazolidinone **264**.

Oxazolidinone regioisomers **266A** (50%) and **266B** (22%) were successfully separated by column chromatography after 2-fluoro styrene was subjected to the standard 2-step protocol (Table 13, entry 5). The structures of both regioisomers were successfully confirmed by X-ray crystallography (Figure 18).

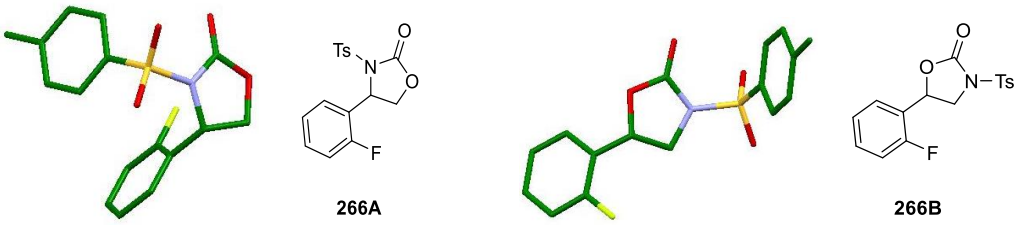
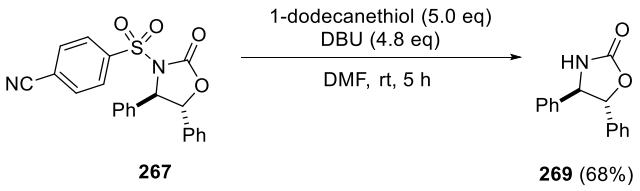


Figure 18. Crystal structures of oxazolidinones **266A** and **266B**.

4,5-Diphenyl-3-tosyloxazolidinone **246** was synthesised from *trans*-stilbene **1** in a yield of 77% (Table 13, entry 1). This procedure was also used to form oxazolidinone **267** in a yield of 56%, employing methyl((4-cyanophenyl)sulfonyl)carbamate **268** as the nitrogen nucleophile, in place of *O*-*tert*-butyl *N*-tosylcarbamate **176**. In a procedure similar to that described in Section 2.3.6.4, oxazolidinone **267** was deprotected under basic reaction conditions to give oxazolidinone **269** in a yield of 68% (Scheme 73).



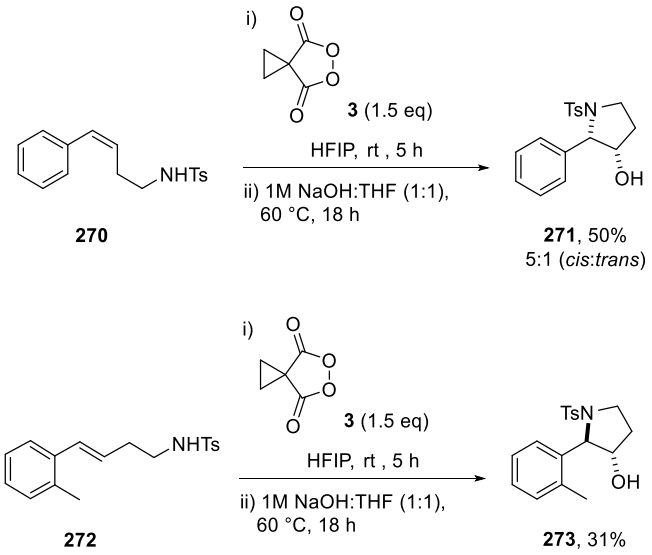
267 **269** (68%)

Scheme 73. Deprotection of oxazolidinone **267**.

2.3.8 Intramolecular oxyamination

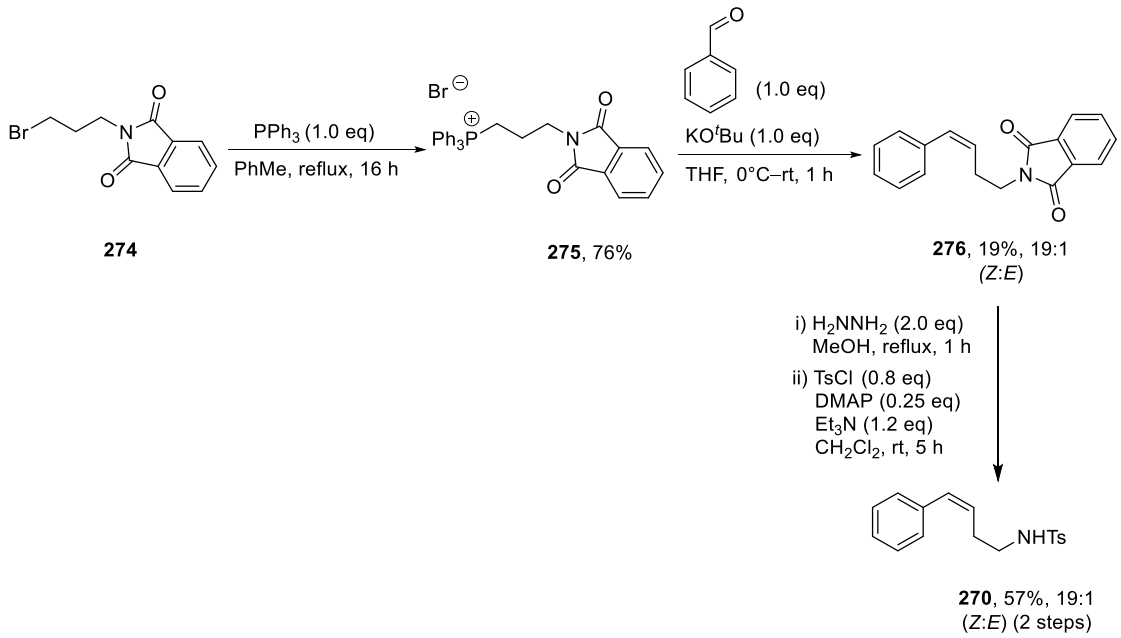
2.3.8.1 Formation of pyrrolidines

In 2018, our laboratory reported an intramolecular oxyamination procedure for the synthesis of pyrrolidines and isoxazolidines, as described in Section 1.2.[12] During the early stages of this current investigation and in order to complete the resulting manuscript for publication, pyrrolidine **271** was formed from nitrogen-tethered alkene **270** (50%, 5:1 *cis*:*trans*) demonstrating the methodology to be tolerant of *cis*-alkenes. Additionally, pyrrolidine **273** was formed from nitrogen-tethered alkene **272** (31%) with complete stereoselectivity, displaying the reaction tolerance of *ortho*-substituted styrenes (Scheme 74).



Scheme 74. Formation of pyrrolidines **271** and **272** with malonoyl peroxide **3**.

The synthesis of nitrogen-tethered alkene **270** was achieved by treating *N*-(3-bromopropyl)phthalimide **274** with triphenylphosphine to arrive at phosphonium salt **275** in a yield of 76% (Scheme 75). A Wittig reaction between phosphonium salt **275** and benzaldehyde gave the *cis*-alkene **276** (19%, 19:1 (*Z*:*E*)). Subsequent phthalimide deprotection, followed by tosylation gave the desired nitrogen-tethered alkene **270** in a yield of 57% (19:1 (*Z*:*E*)).

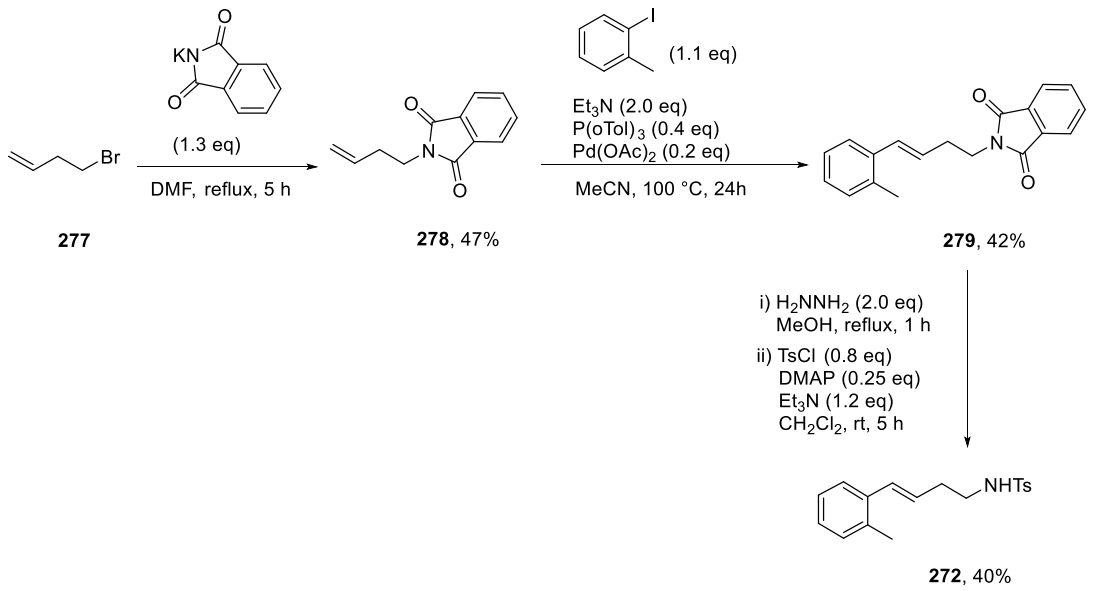


274 **275**, 76% **276**, 19%, 19:1 (*Z*:*E*)

270, 57%, 19:1 (*Z*:*E*) (2 steps)

Scheme 75. Synthesis of nitrogen-tethered alkene **270**.

The synthesis of nitrogen-tethered alkene **272** was achieved by treatment of 4-bromo-1-butene **277** with potassium phthalimide, to give alkene **278** (47%) (Scheme 76). A Heck reaction between alkene **278** and 2-iodotoluene gave the corresponding *trans*-alkene **279** in a 42% yield. Subsequent phthalimide deprotection, followed by tosylation gave the desired nitrogen-tethered alkene **272** in a yield of 40%.



277 **278**, 47% **279**, 42%

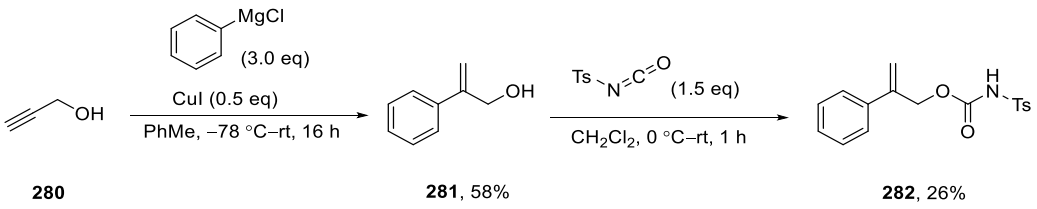
272, 40%

Scheme 76. Synthesis of nitrogen-tethered alkene **272**.

This brief study into the intramolecular oxyamination procedure enabled a better understanding of the scope and limitations of the procedure, providing a simple and effective access to densely functionalised pyrrolidine molecules in a stereoselective manner.

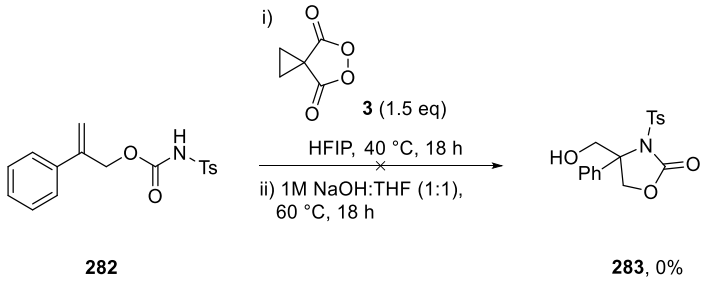
2.3.8.2 Intramolecular variant of oxazolidinone formation

As an extension of the work conducted into the synthesis of pyrrolidines, it was reasonable to propose an intramolecular oxyamination procedure for the formation of oxazolidinones, with alkene **282** proposed as a model substrate. Alkene **282** was synthesised by treatment of propargyl alcohol **280** with phenylmagnesium chloride to give allylic alcohol **281** in a yield of 58%.[52] Treatment of allylic alcohol **281** with tosyl isocyanate gave the desired alkene **282** in a yield of 26% (Scheme 77).[53]



Scheme 77. Synthesis of alkene **282**.

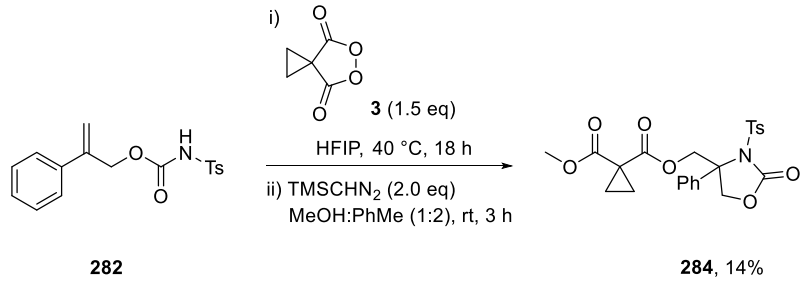
Alkene **282** was subjected to the pyrrolidine formation reaction conditions, however, the desired oxazolidinone product **283** was not observed (Scheme 78). Alkene **282** was consumed under the reaction conditions, with no clear product observed or isolated.



Scheme 78. Unsuccessful formation of oxazolidinone **283**.

It was proposed that the conditions of the hydrolysis step (NaOH:THF) were too harsh for the oxazolidinone to survive. It should be noted that within the intramolecular cyclisation, decarboxylation of the malonate did not occur. The reaction procedure was modified, replacing the hydrolysis step with a methylation, using trimethylsilyldiazomethane. Modification of this procedure was deemed to be successful, as subjection of alkene **282** to the new reaction conditions afforded oxazolidinone **284** in a yield of 14% (Scheme 79). Although the desired cyclised product was observed, the low yield was a concern and it was

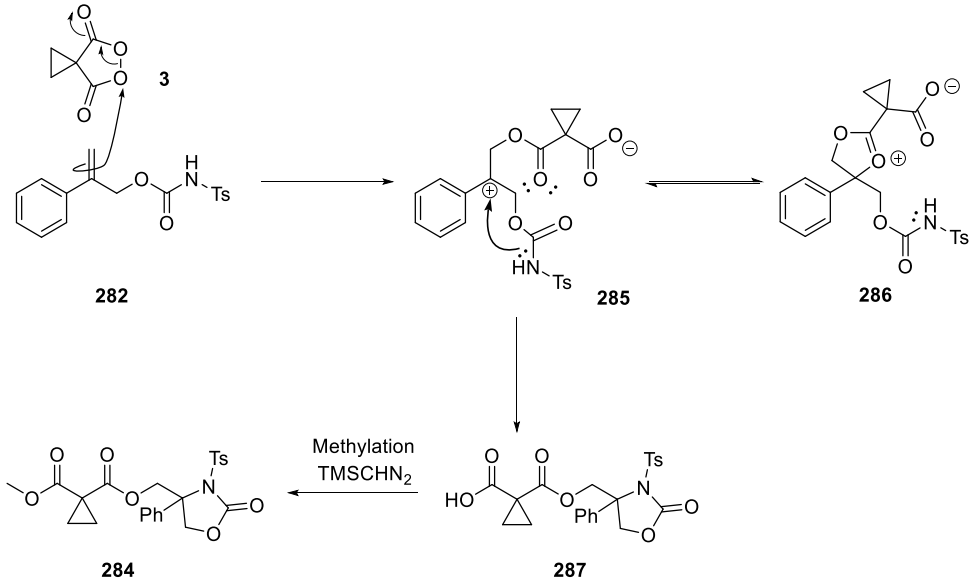
clear this procedure would not prove to be as efficient as the previously reported intramolecular cyclisations.[7,12]



282 **284**, 14%

Scheme 79. Intramolecular cyclisation of alkene **282**, to give oxazolidinone **284**.

Mechanistically, this reaction is thought to proceed in a manner similar to the previously reported malonoyl peroxide procedures. Alkene **282** reacts with malonoyl peroxide **3**, cleaving the weak O—O bond, to form zwitterionic species **285**, which may then either undergo a reversible cyclisation to give dioxonium species **286** or be intercepted by the pendant nitrogen nucleophile found on species **285**, to give oxazolidinone **287**. Methylation of the oxazolidinone product using trimethylsilyldiazomethane afforded the oxazolidinone product **284** (Scheme 80).



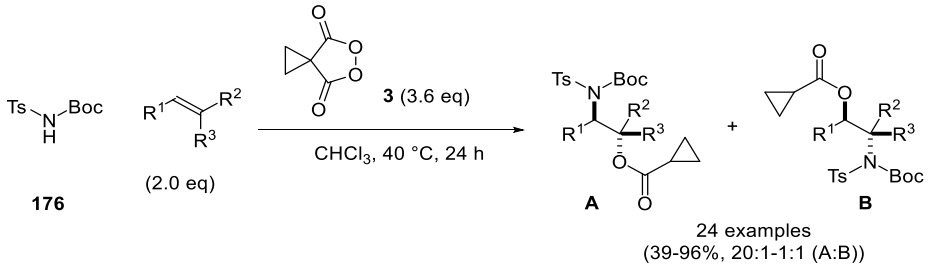
282 **285** **286** **284** **287**

Scheme 80. Proposed mechanism of formation for oxazolidinone **284**.

Although this modified procedure for the formation of the oxazolidinone products had the potential to lead to products stereoisomeric to those obtained *via* the intermolecular oxyamination procedure developed within this study, the low yield and challenges associated with the preparation of substrates led us to conclude this part of the investigation.

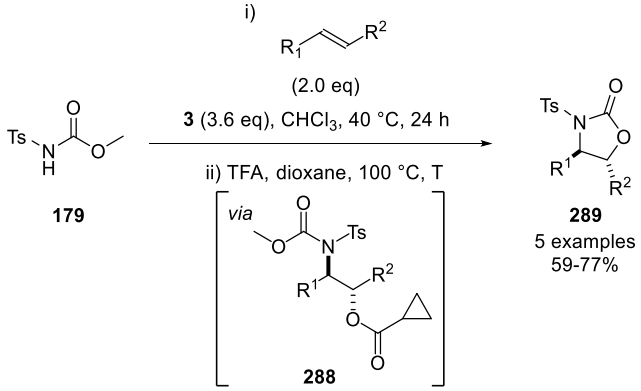
2.4 Conclusions

In summary, a novel procedure was developed for the intermolecular *anti*-oxyamination of alkenes using malonyl peroxide **3**. Optimisation of the nitrogen nucleophile found *N*-sulfonyl carbamates were the most efficient in forming the desired C—N bond. An investigation was conducted into the side-reaction, in which a hypothesis was formed to suggest that *N*-sulfonyl carbamates were relatively weak nucleophiles and therefore peroxide **3** and *trans*-stilbene **1** partake in transformations that lead to a host of unknown compounds. Following optimisation, an extensive substrate scope of various stilbenes and styrenes was conducted (Scheme 81). The regiochemistry of the reaction was found to be dictated by electronic factors, with electron-rich alkenes leading to the highest regioisomeric ratios of products. Steric factors were also found to play a role in regioselectivity, with β-substituted styrenes also leading to high levels of regioselectivity (**A**:**B**). Reaction conditions for a range of oxygen and nitrogen deprotections were also developed, providing useful opportunities for further functionalisation of oxyaminated products.



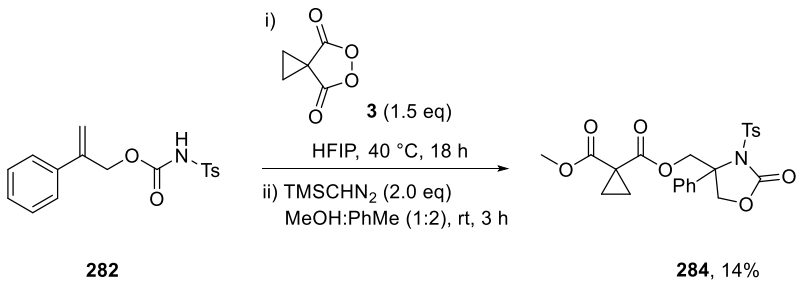
Scheme 81. The *anti*-oxyamination of stilbenes and styrenes.

Methodology was also developed for the conversion of the *anti*-oxyaminated product to its *syn*-diastereoisomer. This was achieved by treating *anti*-oxyaminated product (e.g. **288**) with trifluoroacetic acid to give the *syn*-oxazolidinone product **289**. This was successfully developed into a one-pot procedure, from starting material **179** which proceeded in good yield and regio- and diastereoselectivity (Scheme 82).



Scheme 82. *Syn*-oxyamination of alkenes to form oxazolidinones.

The work reported in Section 2.3.8.2 added to the knowledge for the intramolecular oxyamination procedure, which culminated in achieving an intramolecular oxazolidinone formation (Scheme 83). Although this reaction proceeded in poor yield, further optimisation could potentially lead to a complementary procedure for the intramolecular cyclisation protocol.



Scheme 83. Intramolecular cyclisation of alkene **282**, to give oxazolidinone **284**.

Overall, novel alkene oxyamination procedures have been added to the catalogue of methodologies for alkene functionalisation using malonoyl peroxide reagents.

Chapter 3. Investigating the Reaction of Alkenes with a Peroxylactone

Chapter 3. Investigating the Reaction of Alkenes with a Peroxylactone

3.1 Introduction

A catalyst is defined as a substance that acts to decrease the activation energy (E_a) of a chemical reaction, allowing it to proceed under milder conditions (Figure 19).[54] E_a is defined as the energy of the transition state for a given reaction relative to the initial state, in other words, the minimum energy required for the reaction to take place.[55] The term "catalyst" may refer to a variety of different substances, generally catalysts are: metallic, enzymatic or organic. The literature has mostly been dominated by metal-based catalysts, due to their molecular and structural diversity and their differing reactivity when combined with various ligands.[56] However, there are various issues in the use of metallic or organometallic catalysts, due to concerns surrounding cost, toxicity and the associated waste streams generated.[54]

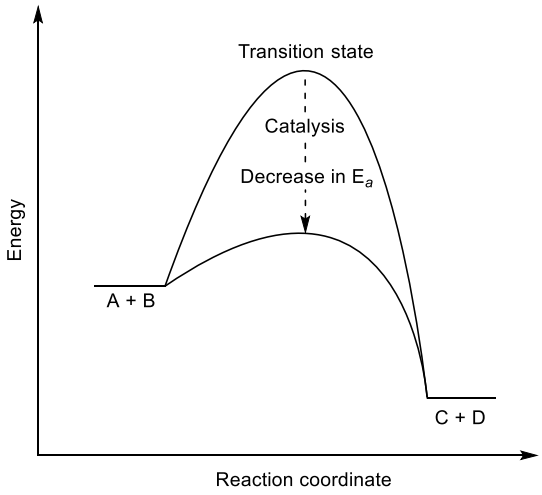


Figure 19. Reaction coordinate for a catalysed and non-catalysed reaction.[57]

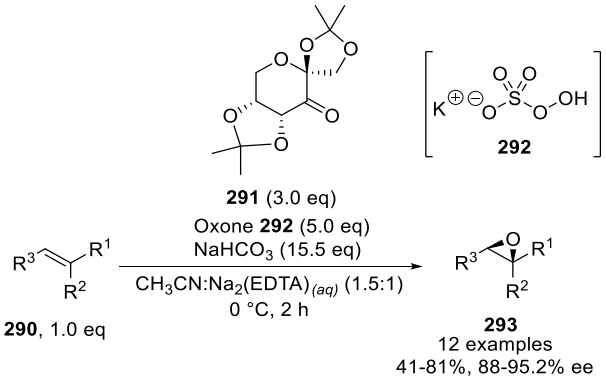
The term "organocatalysis" refers to the use of an organic molecule to catalyse a chemical reaction. This form of catalysis may provide a less environmentally damaging alternative for chemical transformations that are traditionally catalysed by transition metals. Organocatalysts may be derived from biological or renewable sources and, as a result, are cheaper to synthesise and will generally be non-toxic and environmentally benign. These factors may combine to create both a cheaper and safer chemical reaction.[58]

The dihydroxylation of alkenes is viewed as a chemical transformation that could benefit from an organocatalytic methodology. As stated in Section 1.1, the "gold standard" for this class of reaction is the Sharpless asymmetric dihydroxylation.[1] Such a procedure uses highly toxic and expensive osmium(VIII) within the catalytically active species, and, as a result, has inspired a plethora of research into organocatalytic procedures for alkene oxidation.

3.1.1 Oxidation of alkenes by peroxide-mediated organocatalysis

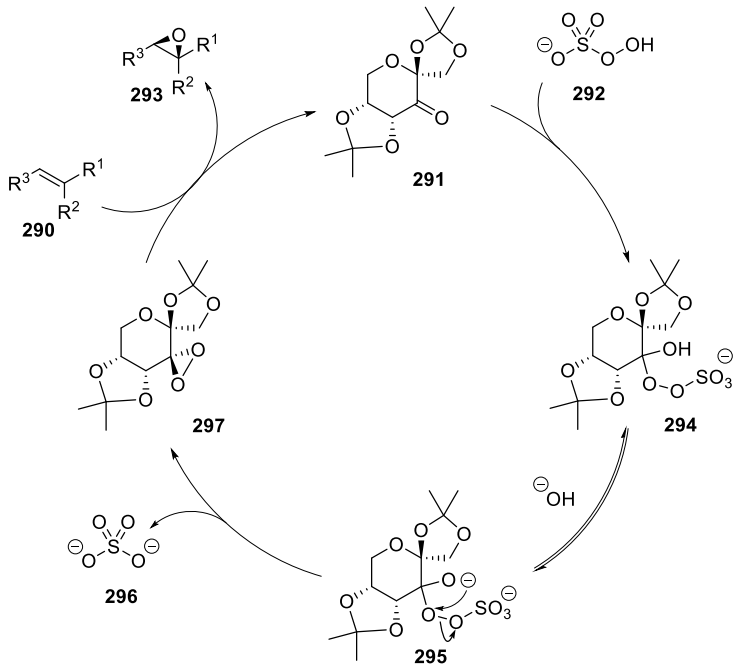
3.1.1.1 Shi asymmetric epoxidation

In 1996 Shi and co-workers reported an enantioselective organocatalytic epoxidation of alkenes.[59] It was shown that treatment of alkene **290** with the active ingredient of Oxone® **292** and a ketone organocatalyst **291** yielded epoxide **293** in good yield with high stereoselectivity and control of absolute stereochemistry (Scheme 84).



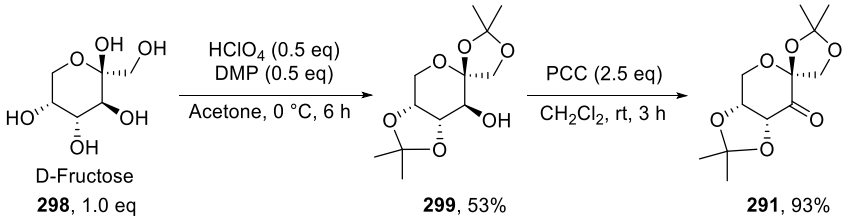
Scheme 84. Shi asymmetric epoxidation of alkenes.[60]

Mechanistically it was proposed that reaction of ketone **291** and oxone **292**, lead to species **294**, which upon deprotonation to species **295** may cyclise to give dioxirane **297**, with loss of sulfate **296**. Dioxirane **297** may then convert an equivalent of alkene **290** to epoxide **293** and in turn regenerate ketone **291**, to continue the catalytic cycle (Scheme 85).[60]



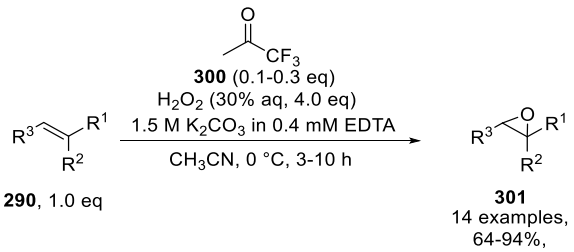
Scheme 85. Proposed catalytic cycle for the Shi epoxidation of alkenes.[60]

The ketone organocatalyst **291** was found to be very effective, for several reasons. First, it contained stereogenic centres close to the reaction centre, allowing for efficient stereochemical communication between substrate and catalyst. Second, a fused ring and a quaternary centre on the alpha position to the ketone functionality, eliminated the possibility of epimerisation and hence loss of stereochemical integrity of the catalyst. One face of the catalyst **291** is sterically encumbered, hence limiting any competing approach of the substrate towards that face of the active catalytic species.[59] In addition to these favourable structural features, organocatalyst **291** was derived from biologically available D-fructose **298**, at minimal cost. Ketalisation of D-fructose **298** afforded diketal **299**, which upon treatment with pyridinium chlorochromate (PCC), gave ketone organocatalyst **291** (Scheme 86).[60] The success of ketone **291** as a safe and cheap organocatalyst is a strong example of how more sustainable reaction conditions can be found without compromising reaction efficiency.



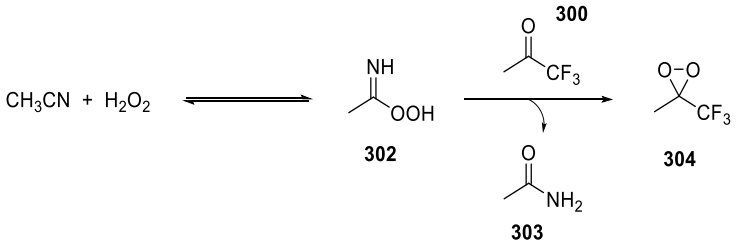
Scheme 86. The synthesis of ketone organocatalyst **291** from D-fructose **298**.[60]

In a further development of this methodology, it was found hydrogen peroxide could be used as the stoichiometric oxidant in combination with acetonitrile.[61] Treatment of alkene **290** with aqueous hydrogen peroxide and acetonitrile in the presence of ketone catalyst **300**, gave epoxide **301** (Scheme 87). Although this method was not asymmetric it provided distinct opportunities for further investigation.



Scheme 87. Shi epoxidation with hydrogen peroxide as primary oxidant.[61]

It was proposed that reaction of acetonitrile and hydrogen peroxide gave peroxyimidic acid **302** (Scheme 88). Reaction of ketone **300** with peroxyimidic acid **302** was proposed to form dioxirane species **304** that would subsequently epoxidise the alkene.

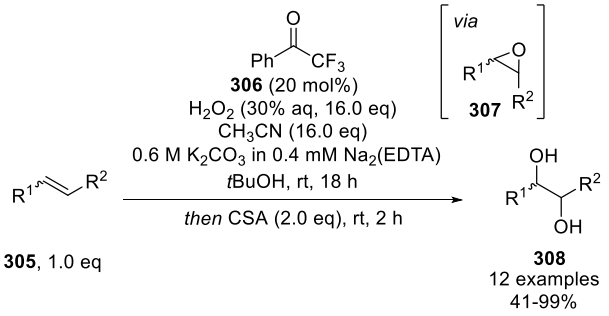


Scheme 88. Formation of the active oxidant, peroxyimidic acid **302**.

Replacing Oxone® as the primary oxidant with hydrogen peroxide made this procedure operationally simple, with less solvent and inorganic salts being used. In addition lower catalytic loadings were required. However, this procedure is not asymmetric presenting further opportunities for development.

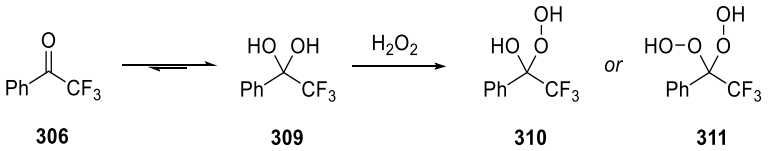
3.1.1.2 One-pot dihydroxylation of alkenes using trifluoroacetophenone organocatalyst

In a similar manner to the Shi epoxidation using hydrogen peroxide (Scheme 87),[61] Kokotos and co-workers reported a one-pot procedure for the dihydroxylation of alkenes.[62] Treatment of alkene **305** with hydrogen peroxide and acetonitrile in the presence of a catalytic amount of trifluoroacetophenone **306**, gave epoxide **307** which when reacted with camphor sulfonic acid (CSA), undergoes a ring openings to give diol **308** (Scheme 89).



Scheme 89. One-pot dihydroxylation of alkenes using trifluoroacetopheonone organocatalyst **306**.[62]

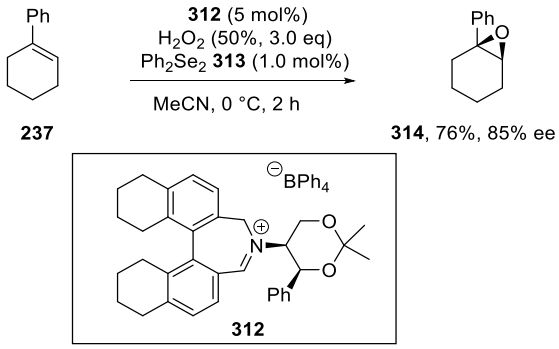
It is known that in an aqueous environment perfluoroalkyl ketones, such as trifluoroacetophenone **306**, exists mainly in the hydrate form **309**. Subsequent reaction with hydrogen peroxide converts the hydrate **309** to either perhydrate **310** or dihydroperoxide **311** (Scheme 90).[63] Further reaction of species **310** or **311** with acetonitrile and hydrogen peroxide is thought to create a more reactive intermediate (structure not reported) for the conversion of alkene **305** to epoxide **307**, regenerating organocatalyst **306**.[63]



Scheme 90. Generation of the potential active oxidants, perhydrate **310** or dihydroperoxide **311**.[63]

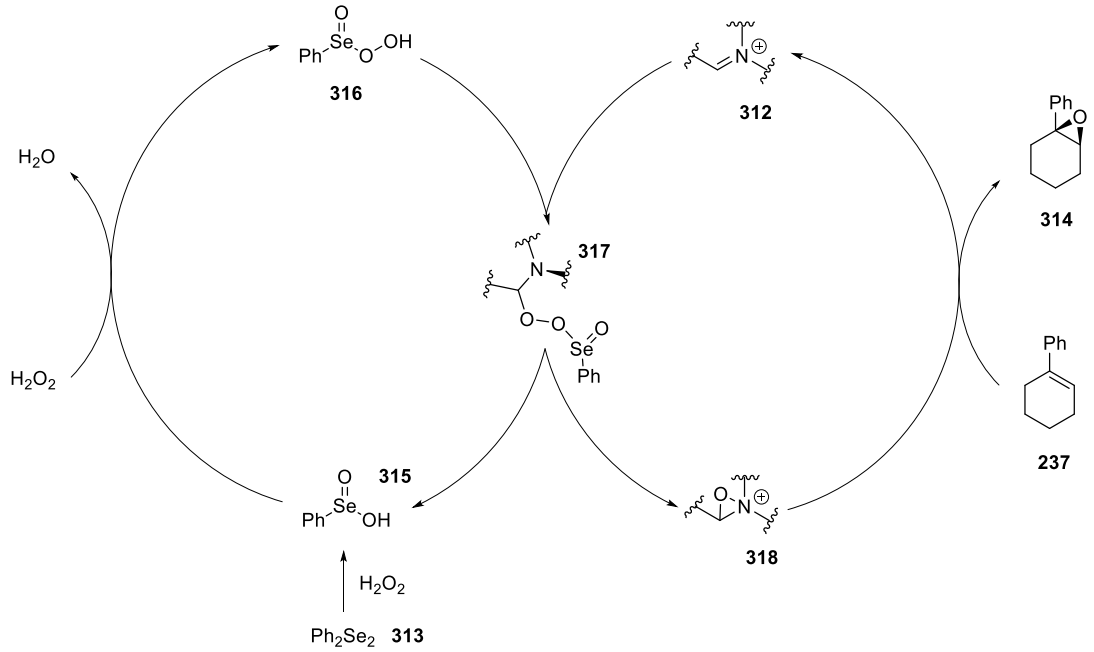
3.1.1.3 Iminium salt-catalysed asymmetric epoxidation

In 2013, Bulman Page and co-workers reported an iminium salt-catalysed asymmetric epoxidation, using hydrogen peroxide as the stoichiometric oxidant.[64] This work built upon earlier methodology which used Oxone® as the stoichiometric oxidant.[65] The use of hydrogen peroxide provided a greener alternative, due to the by-product from the oxidation being a molecule of water. Treatment of alkene **237** in hydrogen peroxide with catalytic quantities of iminium salt **312** and diphenyl diselenide (Ph_2Se_2) **313** afforded epoxide **314** in good yield and high levels of enantioselectivity (Scheme 91).



Scheme 91. Iminium salt-catalysed asymmetric epoxidation.[64]

Mechanistically it was proposed Ph_2Se_2 **313** interacted with hydrogen peroxide to form benzeneseleninic acid **315**, which was further oxidised to benzeneperseleninic acid **316**. Species **316** then oxidised iminium ion **312**, *via* species **317**, to generate oxaziridinium ion **318** and regenerate benzeneseleninic acid **315**. Oxaziridinium ion **318** was responsible for the conversion of alkene **237** to epoxide **314**, leading to the regeneration of iminium ion **312**, completing the "dual" catalytic cycle (Scheme 92).

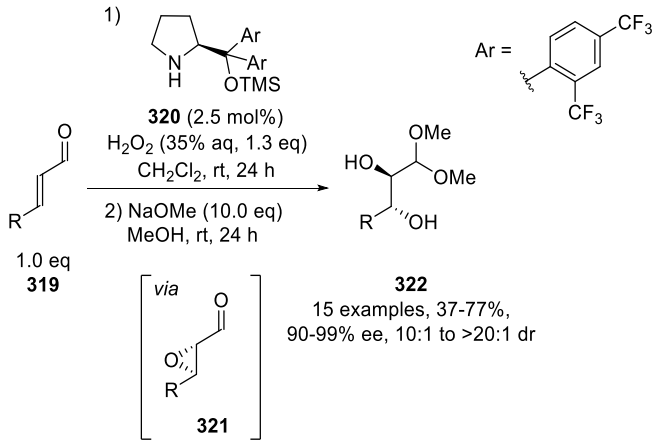


Scheme 92. Proposed "dual" catalytic cycle for alkene epoxidation.[64]

As hydrogen peroxide was unable to epoxidise an alkene in the presence of an iminium salt, a co-catalyst (Ph_2Se_2 **313**) was employed to aid in oxygen transfer to iminium salt **312**. The addition of the selenium-based co-catalyst allowed for hydrogen peroxide to be used successfully in this procedure, providing an inexpensive and "green" organocatalytic methodology.

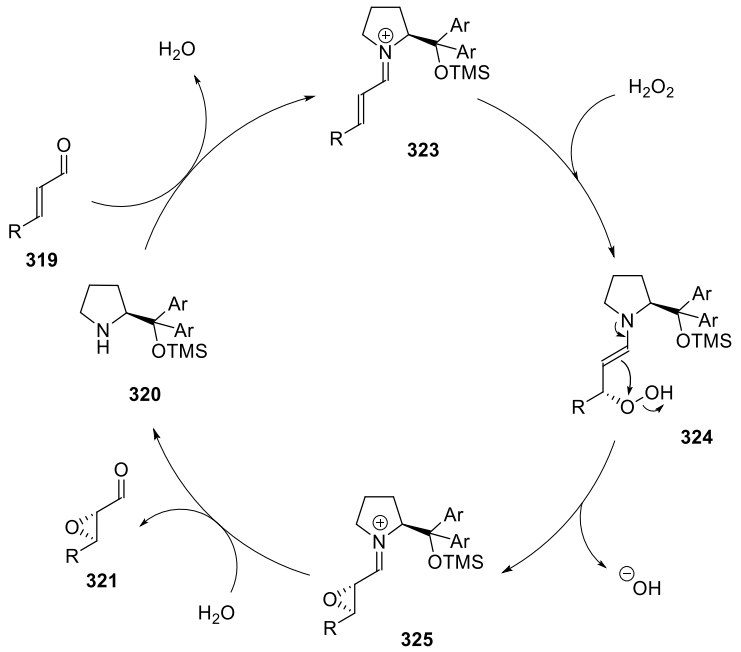
3.1.1.4 Dihydroxylation of α,β-unsaturated aldehydes *via* an organocatalytic reaction cascade

Due to their versatile reactivity, α,β-unsaturated aldehydes often bear protecting groups to allow them to undergo a chemoselective reaction. In 2010, Jørgensen and co-workers reported that treatment of α,β-unsaturated aldehyde **319** with hydrogen peroxide, in the presence of a chiral pyrrolidine organocatalyst **320**, followed by treatment with sodium methoxide, afforded diol **322** (Scheme 93).[66] The reaction was viewed as a one-pot procedure in which the aldehyde functionality was protected as the dimethyl acetal, resulting in the dihydroxylation of the carbon-carbon double bond. This methodology was an extension of the asymmetric organocatalytic epoxidation of α,β-unsaturated aldehydes, reported by Jørgensen in 2005.[67]



Scheme 93. Tandem alkene dihydroxylation and acetal protection of α,β-unsaturated aldehydes.[66]

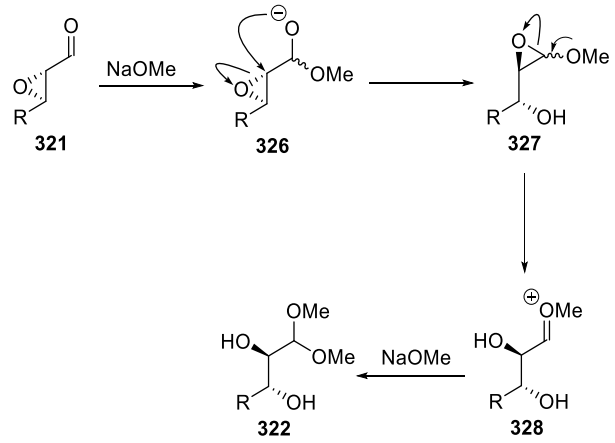
Mechanistically it was proposed that α,β-unsaturated aldehyde **319** was activated by the chiral pyrrolidine organocatalyst **320** to give iminium ion **323**. Conjugate addition of hydrogen peroxide, to give species **324**, followed by cyclisation, afforded iminium ion **325**. At this stage both stereocentres were established through the chiral catalyst **320**. Hydrolysis of iminium ion **325** gave rise to epoxide **321** and regenerated the pyrrolidine catalyst **320** (Scheme 94).



Scheme 94. Proposed catalytic cycle for the epoxidation of α,β-unsaturated aldehyde **319**.[66,67]

Following the organocatalytic epoxidation, addition of sodium methoxide into the reaction vessel initiated a cascade rearrangement to arrive at the dihydroxylated product **322**. Addition of methoxide into the carbonyl of species **321**, initiated a Payne rearrangement[68] to give

epoxide **327**, which opened to give oxocarbenium ion **328**. Addition of another equivalent of methoxide afforded the dihydroxylated acetal product **322** (Scheme 95).



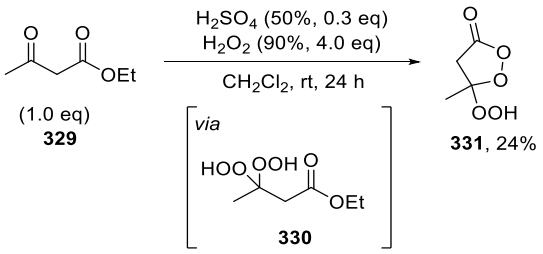
Scheme 95. Sodium methoxide-initiated rearrangement and acetal formation.[66]

3.1.2 Synthesis and reactivity of peroxylactones

3.1.2.1 Synthesis of peroxylactones

As previously stated, it is the desire of our laboratory to develop a peroxide based organocatalytic dihydroxylation procedure. A class of molecule known as a peroxylactone was viewed as a potential oxidant to explore the possibility of such a procedure. Although present in literature dating back to 1968, the synthesis of peroxylactones has not received significant attention, specifically with regards to their reactivity with alkenes.

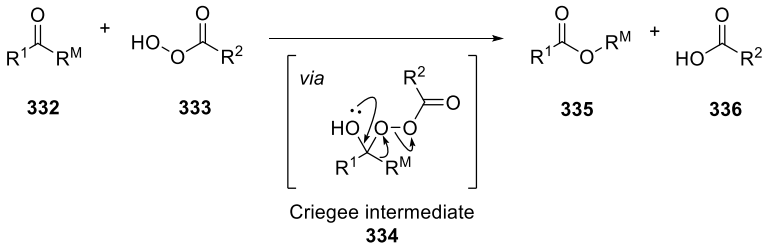
The first reported synthesis of a peroxylactone molecule was published in 1968, when Cubbon and co-workers reported the isolation of 5-hydroperoxy-5-methyl-1,2-dioxolan-3-one **331** from the reaction of ethylacetoacetate **329** and hydrogen peroxide in the presence of sulfuric acid.[69] It was proposed ethylacetoacetate **329** formed gem-dihydroperoxide intermediate **330**, which cyclised to form peroxylactone **331** (Scheme 96).



Scheme 96. The first reported synthesis of a peroxylactone compound by Cubbon in 1968.[69]

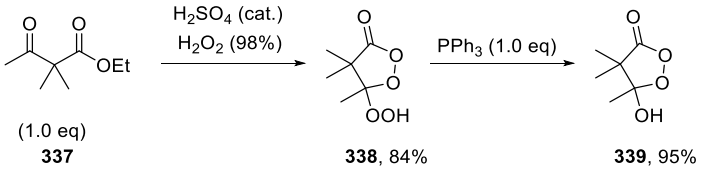
In 1973, Gibson and co-workers proposed that peroxylactones could be viewed as "stable" Criegee intermediates, a high energy intermediate involved in the Baeyer-Villiger oxidation.[70]

The Baeyer-Villiger oxidation is a widely used rearrangement for the formation of esters or lactones from a ketone, when treated with a peracid or hydrogen peroxide.[71] The key intermediate in these reactions is understood to be an α-hydroxy peroxide **334**, known as a Criegee intermediate (Scheme 97). Criegee intermediate **334** is formed by attack of peracid **333** into the carbonyl group of ketone **332**. Subsequent 1,2-alkyl shift of the most substituted group (R^M) of intermediate **334** affords the Baeyer Villiger product **335**, together with acid **336** co-product (Scheme 97).



Scheme 97. A general Baeyer Villiger oxidation, where R^M is the migrating group.[72]

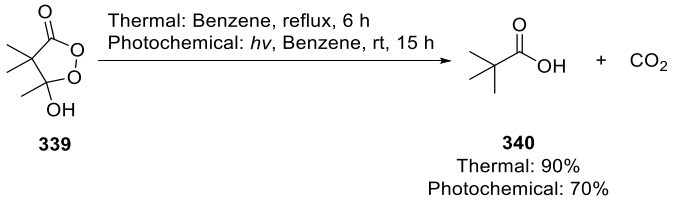
Historically, isolation of Criegee intermediates have proved to be difficult, due to their instability. Gibson and co-workers reported the synthesis and isolation of peroxylactone **339**, a cyclic α-hydroxy peroxide, stating that it can be viewed as a "stable cyclic analogue of a Criegee intermediate".[70] Reaction of 2,2-dimethylethyl acetoacetate **337** with hydrogen peroxide and a catalytic quantity of sulfuric acid, afforded peroxylactone **338** in a yield of 84%. Subsequent treatment with triphenylphosphine gave **339** in a yield of 95% (Scheme 98). Recently, the synthesis of peroxylactone molecules have experienced a resurgence of interest. For example, Terent'ev and co-workers have published the synthesis of various peroxylactone molecules from multiple starting materials, in addition to a computational analysis into their stability.[72,73,74]



Scheme 98. Synthesis of peroxylactone **339**, a "stable cyclic analogue of a Criegee intermediate".[70]

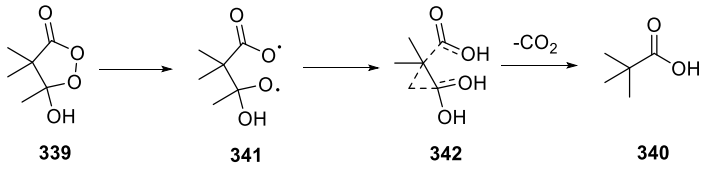
Although peroxylactone **339** was successfully isolated, it wasn't considered a bench stable compound. Thermal decomposition of peroxylactone **339** was achieved by refluxing in benzene for six hours. Ring opening was accompanied by loss of carbon dioxide to give pivalic acid **340** in a 90% yield. Additionally, photochemical decomposition was observed when

peroxylactone lactone **339** was irradiated using a 450 W lamp in degassed benzene, to afford pivalic acid **340** in a yield of 70% (Scheme 99).[70]



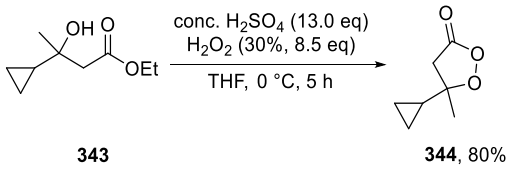
Scheme 99. Thermal and photochemical decomposition of peroxylactone **339** to pivalic acid **340**.[70]

It is reasonable to suggest a mechanism of decomposition similar to that proposed by Adam and co-workers in 1969.[75] Homolytic cleavage of the oxygen-oxygen bond within peroxylactone **339** leads to diradical species **341**, which may undergo a free-radical 1,2-migration of the methyl group *via* transition state **342** to arrive at pivalic acid **340**, with loss of carbon dioxide (Scheme 100).



Scheme 100. Possible mechanism for the decomposition of peroxylactone **339**.[70,75]

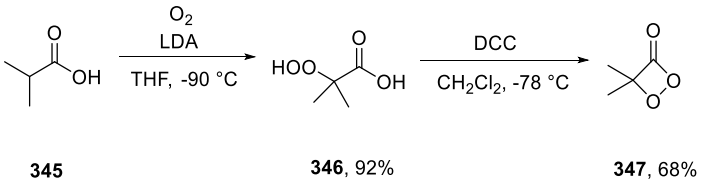
In 2005, Singh and co-workers developed a considerably safer procedure for the synthesis of peroxylactones, using 30% hydrogen peroxide in place of the previously reported 90–98% hydrogen peroxide.[76] Peroxylactone **344** was synthesised from β-hydroxy ester **343** by treatment with hydrogen peroxide and sulfuric acid, in a yield of 80% (Scheme 101). Interestingly, as an extension of this research various peroxylactone compounds were found to exhibit anti-malarial activity when tested *in vitro*.[76]



Scheme 101. The synthesis of peroxylactone **344** *via* a procedure using 30% hydrogen peroxide.[76]

In 1977, Adam and co-workers reported the first synthesis of 4,4-dimethyl-1,2-dioxetan-3-one **347**, with the view to then investigate its reactivity (Scheme 102).[77] 2-Methylpropanoic acid **345** was treated with lithium diisopropylamide (LDA) and oxygen to give peroxide **346**, in a

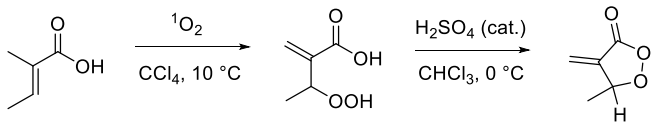
yield of 92%. Cyclisation by treatment of N,N′-dicyclohexylcarbodiimide (DCC) afforded α-peroxylactone **347** in a yield of 68%.



345 **346**, 92% **347**, 68%

Scheme 102. Synthesis of α-peroxylactone **347**.[77]

In 1985, Adam and co-workers then claimed to report the first ever synthesis of α-methylene-β-peroxylactone **350**.[78] Treatment of tiglic acid **348** with singlet oxygen, generated from irradiation with a sodium lamp in the presence of trace amounts of tetraphenylporphyrin, gave the allylic peroxide **349**, in a 92% yield. Subsequent acid-catalysed dehydration afforded α-methylene-β-peroxylactone **350** in a 61% yield (Scheme 103).



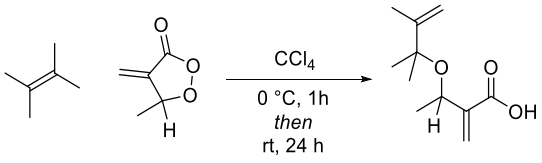
348 **349**, 92% **350**, 61%

Scheme 103. Synthesis of α-methylene-β-peroxylactone **350**.[78]

The majority of literature discussed has documented the synthesis of peroxylactone molecules, a select few have proceeded to investigate the use of a peroxylactone as a reagent for a chemical transformation.

3.1.2.2 Reactivity of peroxylactones

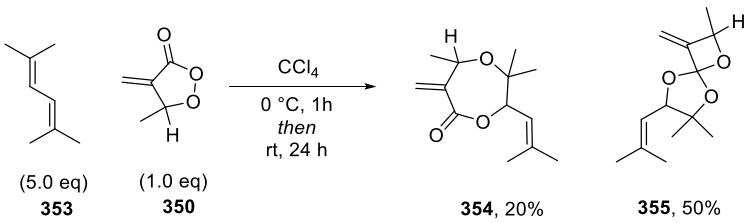
In 1986, Adam and co-workers reported the reaction of β-peroxylactone **350** with alkenes.[79] Reaction of alkene **351** with β-peroxylactone **350** generated the ene-type product **352** in a yield of 82% (Scheme 104).



(10.0 eq) **351** (1.0 eq) **350** **352**, 82%

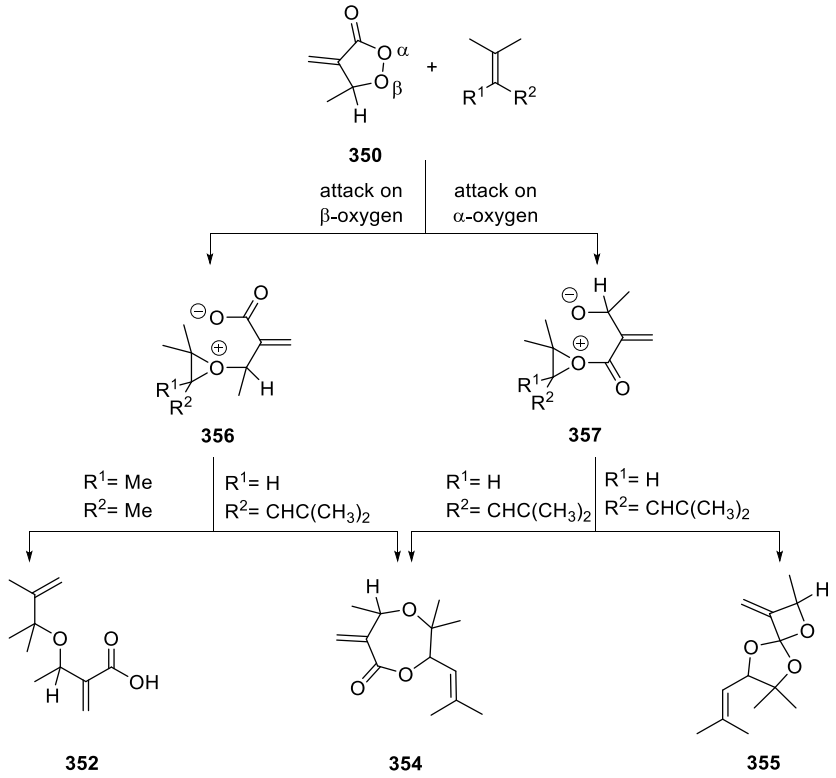
Scheme 104. Reaction of alkene **351** and β-peroxylactone **350** to form ene product **352**.[79]

It was also reported that reaction of 2,5-dimethyl-2,3-hexadiene **353** with β-peroxylactone **350** gave lactone **354** and orthoester **355** in a yield of 20% and 50%, respectively (Scheme 105).[79]



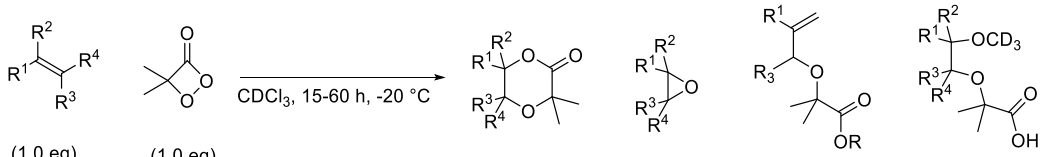
Scheme 105. Reaction of alkene **353** and β-peroxylactone **350** to form lactone **354** and orthoester **355**.[79]

It was postulated that zwitterionic species **356** and **357** were key intermediates in the formation of the observed reaction products **354** and **355**. Zwitterionic intermediate **356**, arises from nucleophilic attack of the alkene onto the β-oxygen of peroxylactone **350**, displacing a carboxylate anion. Abstraction of a hydrogen atom then leads to ene-type product **352**, in the case of alkene **351**. In the case of 2,5-dimethyl-2,3-hexadiene **353**, the displaced carboxylate anion may open the epoxide of species **356** intramolecularly, to give lactone **354**. Alternatively, an alkene may attack the α-oxygen of peroxylactone **350**, displacing an alkoxy anion to give zwitterionic intermediate **357**. The alkoxy anion may open the epoxide of intermediate **357**, in an intramolecular manner to give lactone **354**. Alternatively, the alkoxy anion of intermediate **357** may attack the carbonyl moiety, with a further nucleophilic attack of the carbonyl oxygen atom upon the epoxide functionality to give orthoester **355** (Scheme 106).



Scheme 106. Mechanistic hypothesis for the reaction of β-peroxylactone **350** with alkenes.[79]

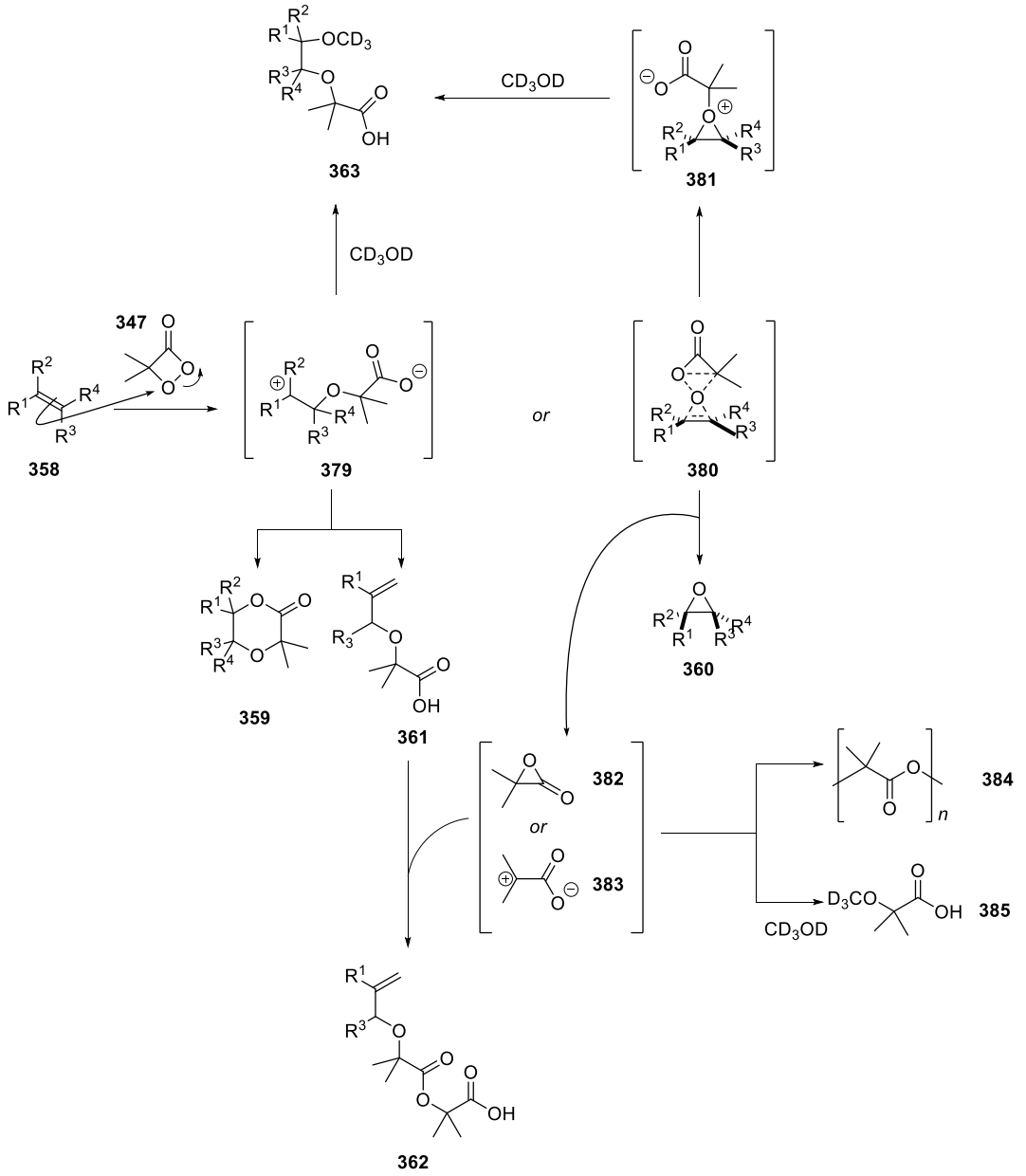
In 1996, Adam and co-workers reported the oxidation of alkenes by α-peroxylactone **347**.[80,81] It was found that the oxidation of di-, tri- and tetrasubstituted alkenes **358** by dimethyl α-peroxylactone **347** afforded the products of a cycloaddition (**359**), ene reaction (**360** and **361**) and epoxidation (**363**) (Table 14). The ratio of these products was found to be dependent upon the substitution of the alkene substrate. An overview of product distribution is outlined in Table 14. The *cis*-disubstituted alkene **364** was found to give the cycloaddition product **365** in a yield of 43%, selectively as the *trans*-diastereoisomer, alongside an unidentified, non-volatile material (entry 1). Interestingly, *trans*-disubstituted alkene **367** was found to selectively give epoxide **368** in a yield of 82% (entry 3). Trisubstituted alkene **371** was not observed to selectively give a single product, but rather a mixture of cycloaddition product **372**, epoxide **373** and ene-type products **374** and **375** (entry 5). Finally, tetrasubstituted alkene **351** was found to give epoxide **376** selectively in a yield of 57% (entry 7). Interestingly, when d_4-methanol was employed as a co-solvent with d_1-chloroform, a new product relating to methanol trapping **363** was formed and was observed in the reaction of various alkenes with different substitution patterns (entries 2, 4 and 8). For *trans*-alkene **367** and *cis*-alkene **364** the resulting methanol trapping products **370** and **366** were isolated as a 1:1 mixture of *syn*- and *anti*-diastereoisomers.



Entry	Alkene	Solvent	cycloaddition	epoxidation	*ene* reaction	CD_3OD trapping
1	 **364**	$CDCl_3$	**365** 43% (*trans*)	-	-	-
2		$CDCl_3/CD_3OD$	-	-	-	**366** 96%
3	 **367**	$CDCl_3$	-	**368** 82%	-	-
4		$CDCl_3/CD_3OD$	-	**369** 34%	-	**370** 47%
5	 **371**	$CDCl_3$	**372** 34%	**373** 11%	**374** 21%, **375** 20%	-
6		$CDCl_3/CD_3OD$	-	-	-	-
7	 **351**	$CDCl_3$	-	**376** 57%	-	-
8		$CDCl_3/CD_3OD$	-	**377** 27%	-	**378** 46%

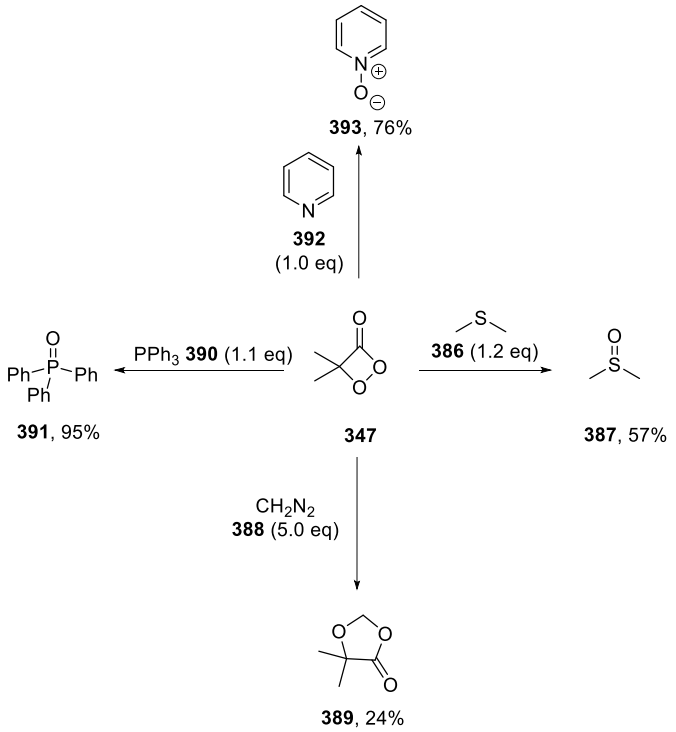
Table 14. The oxidation of substituted alkenes by dimethyl α-peroxylactone **347**.[80]

It was postulated that peroxylactone **347** reactivity arises from the polarisation of the peroxide bond, resulting from the electron withdrawing nature of the carbonyl functionality. This structural feature allows for an S_N2 attack of the alkene π-bond into the σ^*-orbital of the peroxide bond within peroxylactone **347**, breaking the weak oxygen-oxygen bond and displacing a carboxylate group to form zwitterionic intermediate **379** (Scheme 107). Alternatively, the alkene may form a "butterfly" transition state **380**. It was proposed that steric factors, namely the substitution pattern of the alkene nucleophile, dictated whether the 1,6-zwitterionic intermediate **379** or "butterfly" transition state **380** formed within the reaction pathway. It was proposed that *cis*-alkene **364** and trisubstituted alkene **371** form the 1,6-zwitterionic species **379**, due to an unsymmetrical end-on attack of the π-nucleophile with the peroxide bond within peroxylactone **347**. This attack was thought to be directed through the less substituted carbon atom of the alkene and results in the corresponding cycloaddition and ene-type products **359** and **361**. The "butterfly" transition state **380** was a result of a symmetrical approach of the alkene towards peroxylactone **347**, with simultaneous bonding at both carbon atoms of the alkene. Breakdown of the butterfly transition state **380** lead to the epoxide product **360** and α-lactone **382** (may also exist as zwitterionic species **383**), with the later forming oligomer **384**. d_4-methanol is understood to trap multiple reaction intermediates and is responsible for the formation of d_3-methyl ether species **363** and **385**. Additional reactivity was observed between ene-product **361** and α-lactone **382** to form species **362**.



Scheme 107. Proposed mechanistic pathway for the reaction of peroxylactone **347** with substituted alkenes.[80]

In additional work, peroxylactone **347** was reacted with a variety of carbon, nitrogen, phosphorus and sulfur nucleophiles, to yield various oxidised products (Scheme 108).[82] Treatment of pyridine **392** with peroxylactone **347** gave the corresponding *N*-oxide **393**, in a 76% yield. Similarly, it was found dimethyl sulfide **386** and triphenylphosphine **390** could be oxidised to dimethyl sulfoxide **387** and triphenylphosphine oxide **391** in yields of 57% and 95%, respectively. Reaction of diazomethane **388** with peroxylactone **347** gave lactone **389**, in a 24% yield.

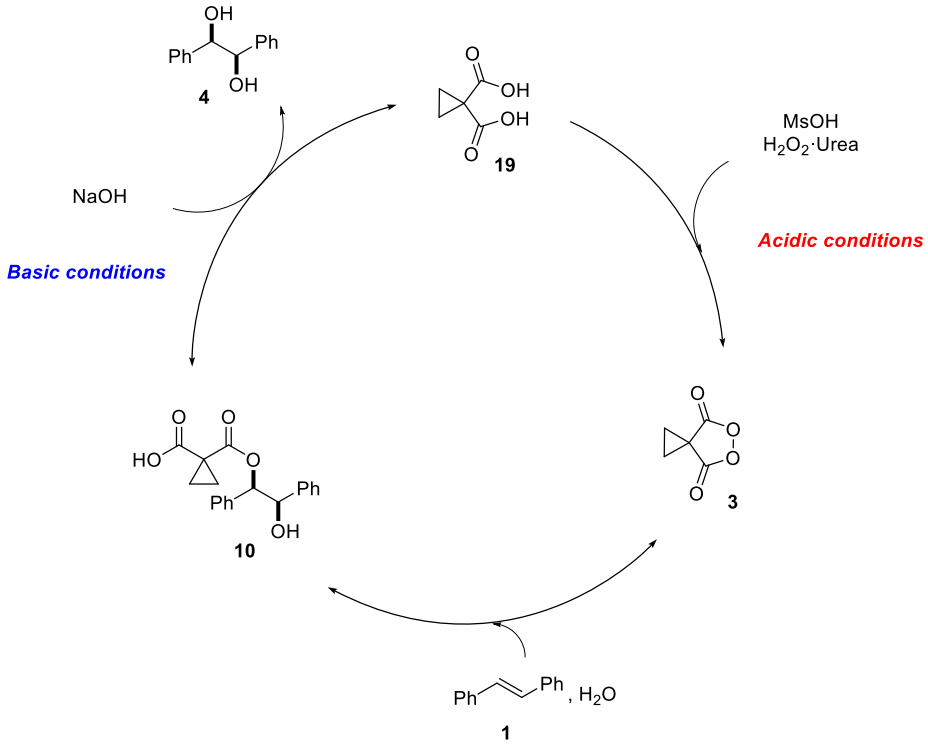


Scheme 108. The reaction of peroxylactone **347** with carbon, nitrogen, sulfur and phosphorus based nucleophiles.[82]

Overall, there is limited literature precedent for the reaction of peroxylactones with alkenes. From the existing publications outlined within this section, it can be seen the reactivity of peroxylactones with alkenes provide a variety of oxygenated products, with varying degrees of complexity. It is reasonable to suggest that if reactivity can be controlled and understood in depth, such research may lead to a novel organocatalytic alkene dihydroxylation procedure.

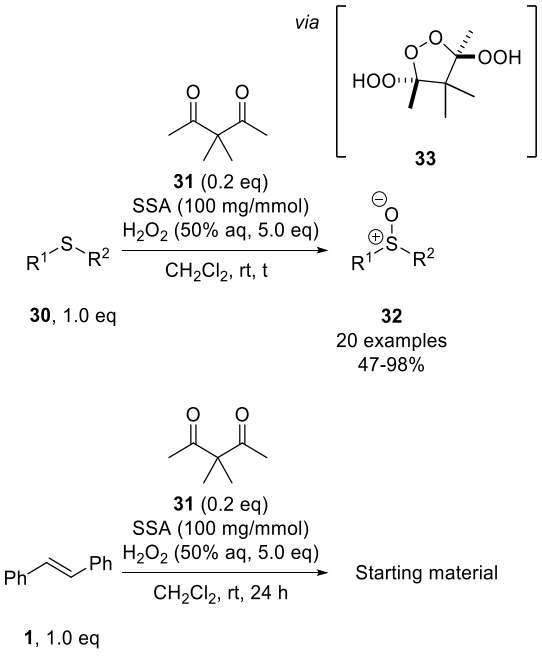
3.2 Aims and Objectives

A long-standing objective within our laboratory has been to develop a metal-free catalytic dihydroxylation procedure. Such a procedure would be important, considering the cost and toxicity issues surrounding the use of osmium in procedures such as the Sharpless asymmetric dihydroxylation.[83,1] As illustrated in Section 1.1, the reported methodology for alkene dihydroxylation using malonyl peroxide **3** could not be developed to deliver a catalytic procedure. This was due to the incompatible conditions for peroxide **3** formation (acidic conditions) and the liberation of diol **4** from ester **10** (basic conditions) (Scheme 109).[3]



Scheme 109. *Syn*-dihydroxylation with malonoyl peroxide **3**, as an unachievable catalytic cycle.[3]

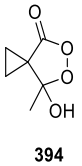
In research conducted by Davidson,[11] a peroxide-mediated catalytic sulfoxidation procedure was successfully developed. Treatment of a variety of sulfides **30** with diketone catalyst **31** in the presence of silica sulfuric acid (SSA) and hydrogen peroxide gave the corresponding sulfoxides **32** (Section 1.3). However, this reagent was unsuccessful when applied to the dihydroxylation of alkenes. It was proposed this was due to peroxide **33** having low reactivity with alkenes (Scheme 110).[11]



Scheme 110. Organocatalytic sulfoxidation methodology unsuccessfully applied to the dihydroxylation of *trans*-stilbene **1**.[11]

The reactivity of malonoyl peroxide **3** with a weak alkene nucleophile was understood to arise from the polarisation of the oxygen-oxygen bond, thanks to the presence of the carbonyl functionalities. Following S_N2 attack of the alkene π-bond into the σ^*-orbital of the peroxide bond within peroxide **3**, the oxygen-oxygen bond was broken, displacing a carboxylate group (see Section 1.1, structure **6**). Peroxide **33** does not contain a carbonyl functionality and, therefore, the bond polarisation and subsequent ability to displace a carboxylate group does not exist. Moving towards developing a peroxide-based organocatalytic dihydroxylation, it seemed desirable to combine the structural characteristics that made peroxide **3** reactive towards alkenes with those of peroxide **33** that allowed it to act as an organocatalyst within the sulfoxidation methodology.

Peroxylactone **394** was proposed as a potential cyclic peroxide structure that could possess the desired catalytic reactivity (Figure 20). Additionally, limited research has been published regarding the reactivity of peroxylactones (see Section 3.1.2.2) and it was deemed a worthwhile pursuit to investigate any potential novel reactivity of this compound.

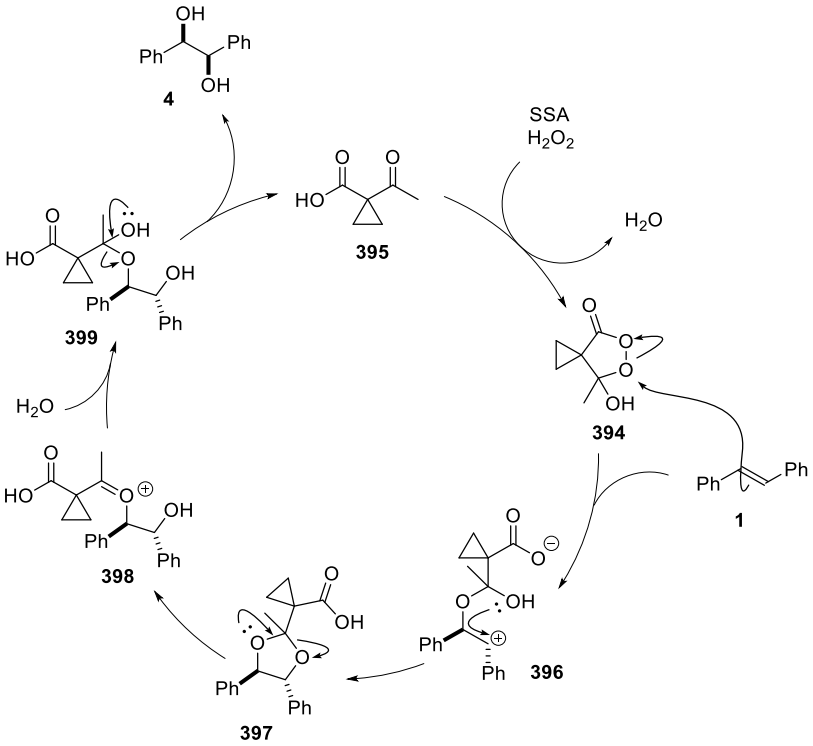


394

Figure 20. Peroxylactone **394**.

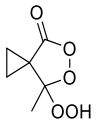
The inclusion of a cyclopropyl group within peroxylactone **394** was in keeping with prior knowledge for the design of malonoyl peroxide **3**. It was found that inclusion of the cyclopropyl moiety within malonoyl peroxide **3** increased ring strain of the cyclic peroxide by decreasing the OC-C-CO bond angle, therefore, increasing reactivity. It was unclear if this observation would translate to peroxylactone **394**, however, this was deemed a sensible structural feature based upon previous knowledge of malonoyl peroxide **3** reactivity.[3]

It was envisaged that alkene **1** may attack the *endo*-cyclic peroxide of peroxylactone **394**, forming the 1,6-zwitterionic intermediate **396**, which in turn may cyclise to form dioxolane **397**. Collapse of intermediate **397** may form oxonium ion **398**, which can be intercepted by a molecule of water to form hemiacetal **399**. Subsequent break down of intermediate **399** could give diol **4** and carboxylic acid **395**, which regenerates peroxylactone **394** upon reaction with hydrogen peroxide, completing the catalytic cycle (Scheme 111).



Scheme 111. Potential catalytic cycle for the dihydroxylation of *trans*-stilbene **1** with peroxylactone **394**.

Literature precedent suggests that molecules similar to peroxylactone **394** are isolable, but are known to be unstable. In addition, it was not deemed possible to prepare peroxylactone **394** from the carboxylic acid **395** directly (see Section 3.1.2.1).[70] According to the literature, peroxylactone **400** was more stable and could easily be prepared from carboxylic acid **395**. Therefore, this research is mostly centred upon the reaction of peroxylactone **400** with alkenes (Figure 21).



400

Figure 21. Peroxylactone **400**

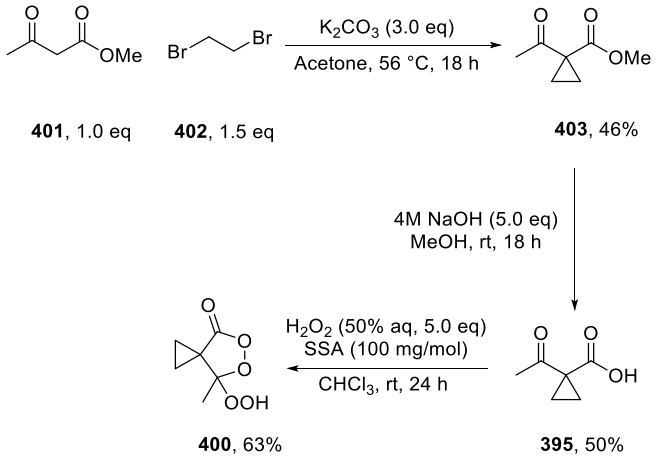
The aims of this research were as follows;

1. To prepare peroxylactone **400**.
2. To investigate the reaction between peroxylactone **400** and alkenes.
3. To assess the potential of peroxylactone **400** for use in an organocatalytic dihydroxylation procedure.

3.3 Results and Discussion

3.3.1 Synthesis of peroxylactone 400

Peroxylactone **400** was synthesised from methyl acetoacetate **401** in three steps (Scheme 112). Methyl acetoacetate **401** was alkylated with 1,2-dibromoethane **402** to give compound **403** (46%), which gave carboxylic acid **395**, upon basic hydrolysis (50%). Treatment of the acid **395**, with hydrogen peroxide and silica sulfuric acid (SSA)[84] gave the peroxylactone **400** (63%) in a yield of 14% over three steps.

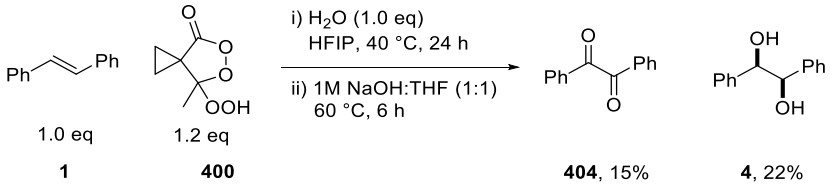


Scheme 112. The synthesis of peroxylactone **400**.

The synthesis of peroxylactone **400** remains an unoptimised procedure. At this stage in the investigation, the synthetic route was deemed satisfactory to obtain sufficient quantities of peroxylactone **400**. It remains a goal of this research to optimise this sequence if peroxylactone **400** was found to be an effective synthetic reagent.

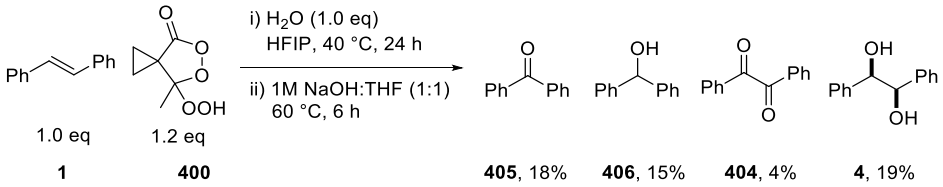
3.3.2 Initial results

Previously within our laboratory, it was reported that reaction of *trans*-stilbene **1** with peroxylactone **400** in HFIP and water (1.0 eq) at 40 °C for 24 h, followed by basic hydrolysis, led to benzil **404** (15%) and *syn*-diol **4** (22%) (Scheme 113).[11] This preliminary result of Davidson was from a single experiment and had not been replicated.



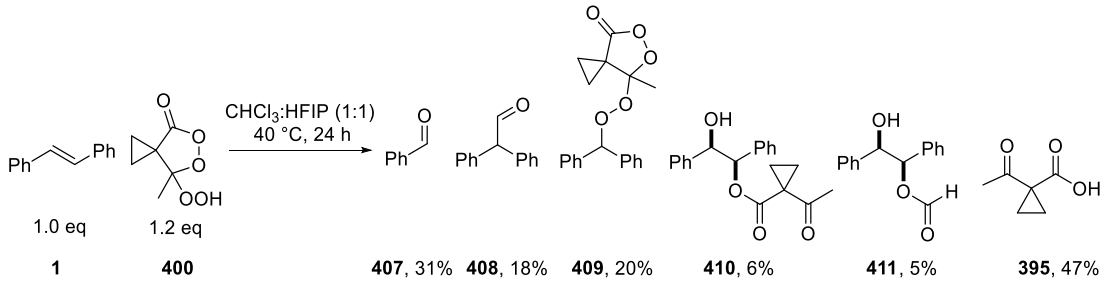
Scheme 113. The reaction of *trans*-stilbene **1** with peroxylactone **400**, followed by basic hydrolysis.[11]

Our initial goal was to replicate this result. Upon repeating the reaction, a similar result was obtained. The reaction yielded benzil **404** (4%) and *syn*-diol **4** (19%), as well as two additional products, benzophenone **405** (18%) and diphenylmethanol **406** (15%) (Scheme 114). Overall, this accounted for 56% of the starting alkene. Although we were unable to account for the remainder of the material at this stage, the result merited further investigation.



Scheme 114. The reaction of *trans*-stilbene **1** with peroxylactone **400**, followed by basic hydrolysis.

In order to understand the reactivity of peroxylactone **400** with alkenes, the decision was made to omit the basic hydrolysis step in the procedure (Scheme 115). Additionally, chloroform was added as a co-solvent to aid in the solvation of *trans*-stilbene **1**. Reaction of *trans*-stilbene **1** with peroxylactone **400** in a 1:1 mixture of chloroform and HFIP resulted in a host of oxidised products, each of which were successfully isolated. Reaction products consisted of two aldehydes (benzaldehyde **407** (31%) and diphenylacetaldehyde **408** (18%)), alkylated peroxylactone species **409** (20%) and two dihydroxylated species (ester **410** (6%) and formate **411** (5%)). In addition, carboxylic acid **395** (47%) was isolated from the reaction mixture, giving a preliminary indication that a catalytic procedure may be possible. Although focus upon a catalytic dihydroxylation procedure remained the primary goal, the potential to optimise various other pathways was illustrated in the variety of reaction products observed.



Scheme 115. The reaction of *trans*-stilbene **1** with peroxylactone **400**.

The reaction between *trans*-stilbene **1** and peroxylactone **400** produced multiple additional products in smaller quantities which were not isolated or characterised. Inspection of the ^{1}H NMR spectrum of the crude reaction mixture confirmed that the major products of the reaction were concurrent with those isolated *via* column chromatography (Figure 22).

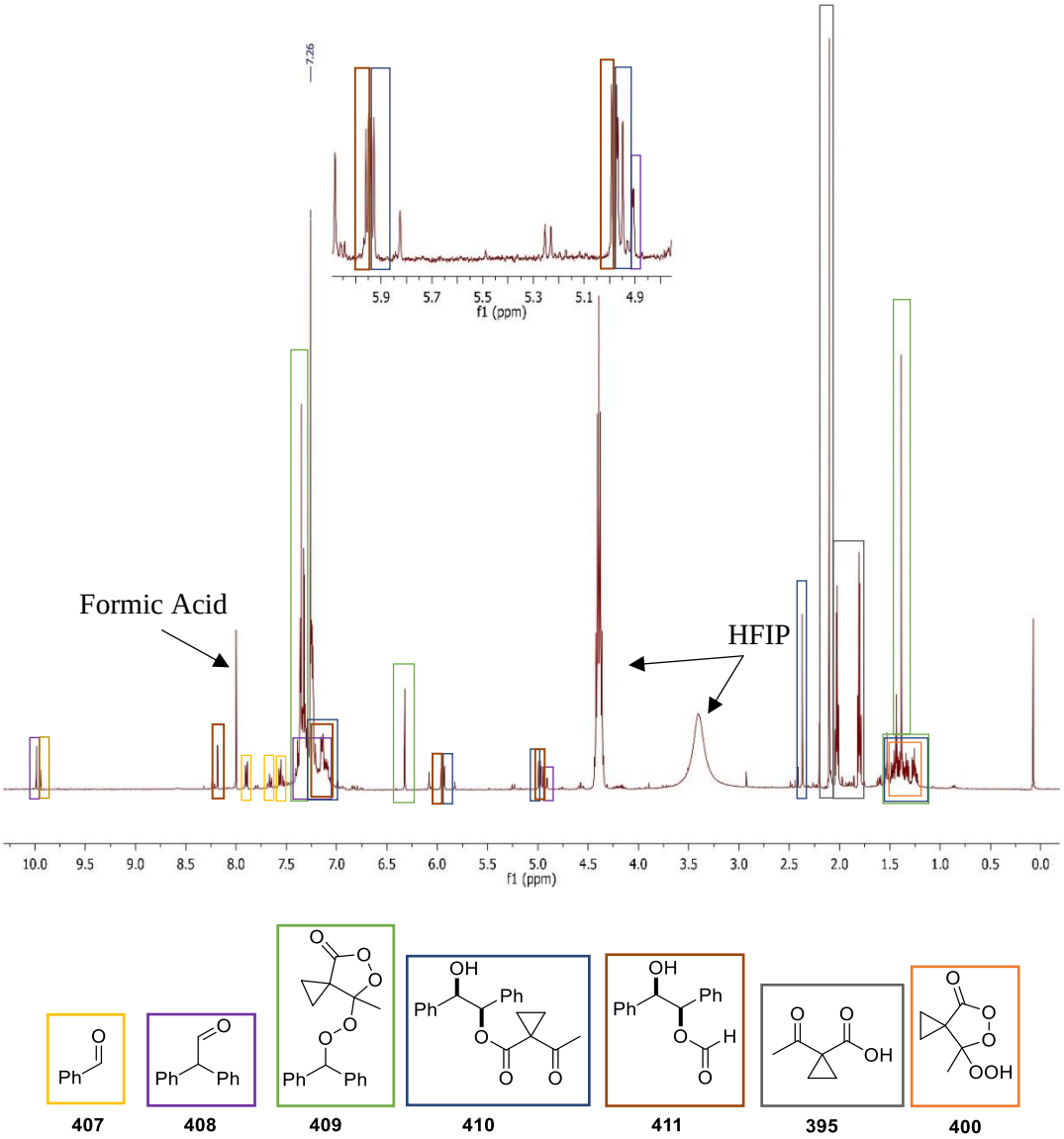
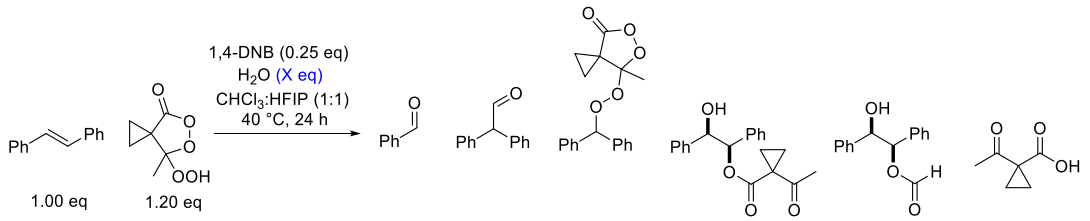


Figure 22. Reaction mixture ^{1}H NMR spectra and assignments.

An optimisation of reaction conditions, with a focus upon equivalents of water was then conducted (Table 15). Removing the equivalent of water was found to not have a detrimental effect upon the conversions of dihydroxylated intermediates **410** and **411** (entries 1 and 2). When the equivalent of water was increased to two equivalents (entry 4), the conversion to ester **410** was unaffected, however, formate **411** was not observed. Upon increasing the equivalents of water to ten (entry 5), neither ester **410** or formate **411** were observed within the reaction mixture. Following this brief optimisation, the equivalent of water was removed from the standard reaction conditions, as it was deemed to not be essential for the formation of dihydroxylated intermediates **410** and **411**, and could be deemed detrimental to the overall reaction.



1 **400** **407** **408** **409** **410** **411** **395**

Entry	H_2O eq						
1	0	17%	11%	16%	8%	7%	39%
2	0 (flame dried vessel)	12%	3%	16%	8%	12%	48%
3	1	31%	18%	20%	6%	5%	47%
4	2	37%	8%	5%	6%	0%	53%
5	10	7%	1%	7%	0%	0%	41%

Conversions calculated by ^{1}H NMR spectroscopy using an internal standard (1,4-DNB).
Conversions calculated from a single experiment.

Table 15. H_2O equivalent optimisation for the reaction of peroxylactone **400** and *trans*-stilbene **1**.

A reaction monitoring experiment was conducted to gather information around the formation of the various oxidised products (Figure 23). The reaction was conducted in the presence of an internal standard (1,4-dinitrobenzene) with samples taken at regular time intervals which were analysed using ^{1}H NMR spectroscopy.

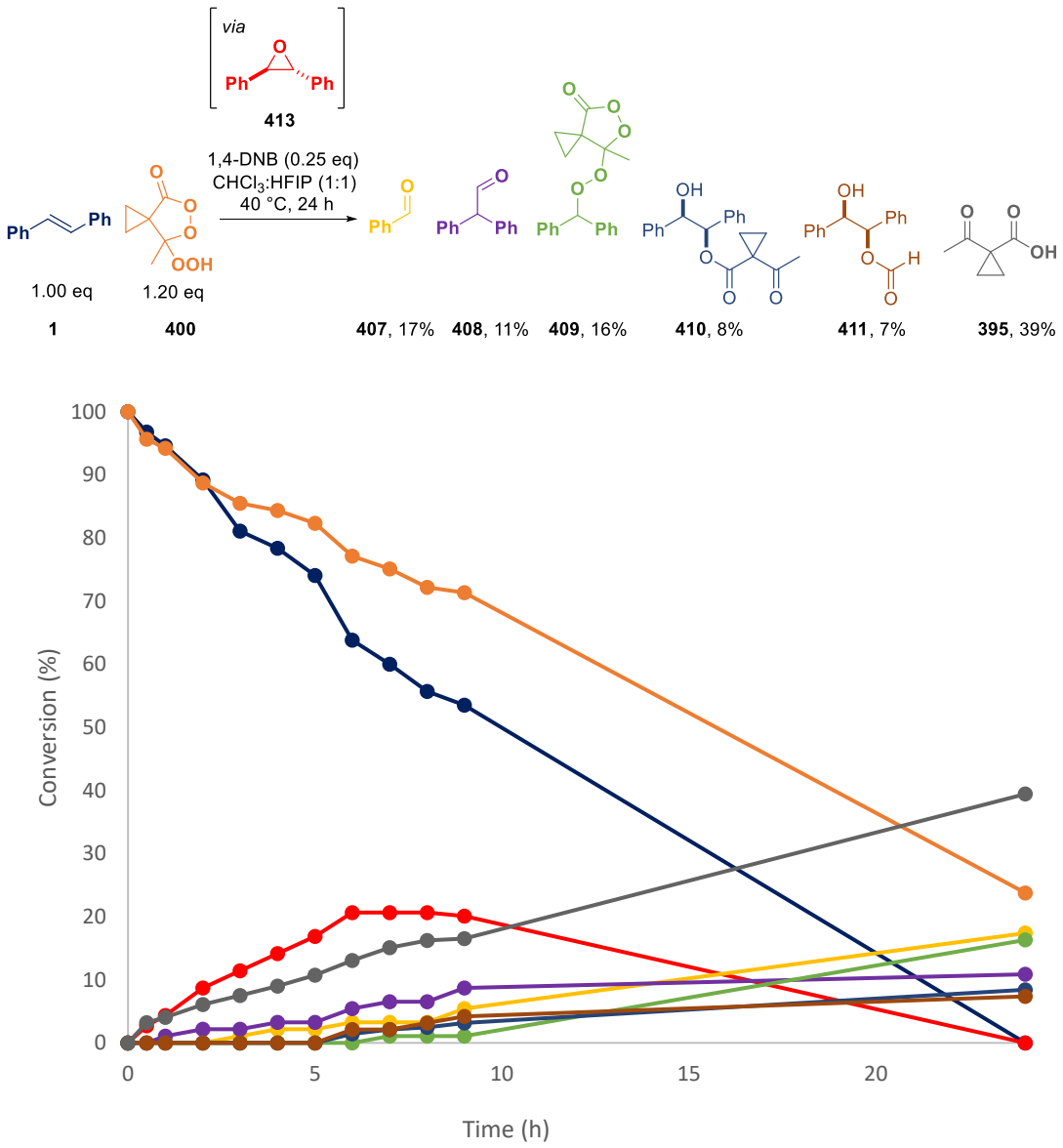
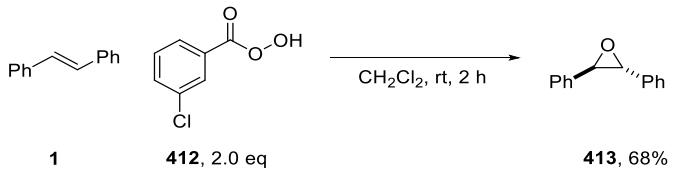


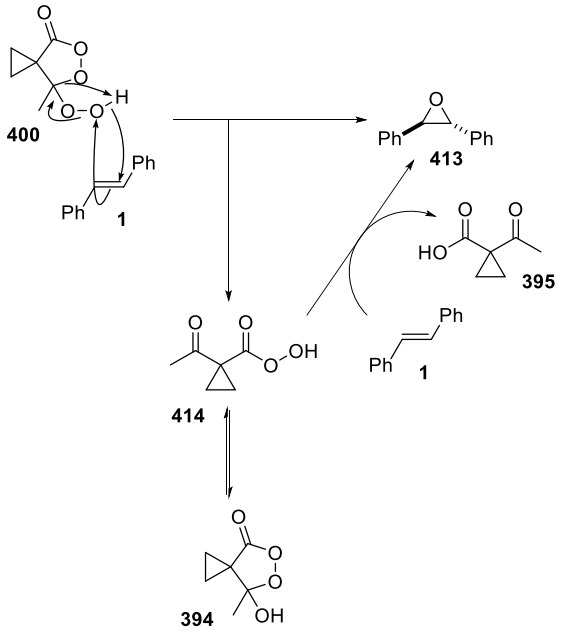
Figure 23. Reaction profile for the reaction of *trans*-stilbene **1** with peroxide **400**.

At the start of the reaction, as *trans*-stilbene **1** and peroxylactone **400** were being consumed, it was observed that an intermediate compound (shown in red) was being formed alongside acid **395**. Formation of this intermediate was the dominant reaction taking place over the first six hours of the reaction, reaching a maximum conversion of 21%, before being consumed. It was also observed that diphenylacetaldehyde **408** was the first reaction product to be detected after one hour (1%). The remaining reaction products were detected to start forming over a four hour window, between three hours and seven hours of reaction. The intermediate compound was found to be *trans*-stilbene oxide **413** which was confirmed through independent synthesis, by treating *trans*-stilbene **1** with *m*CPBA **412** and the ^{1}H NMR spectra of the two compounds compared (Scheme 116).



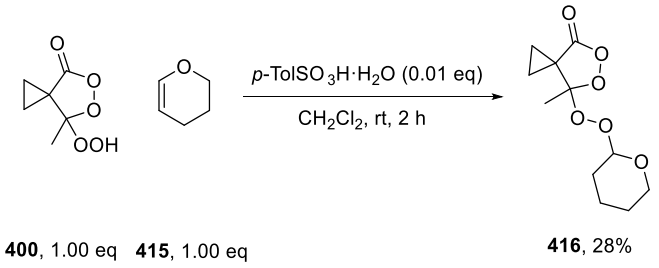
Scheme 116. Synthesis of *trans*-stilbene oxide **413**.

It was proposed that the initial step in the reaction was formation of *trans*-stilbene oxide **413**, *via* reaction of *trans*-stilbene **1** with the *exo*-peroxide of peroxylactone **400** (Scheme 117). Additionally, it was proposed that peracid **414** was formed in this process, which may epoxidise a second equivalent of *trans*-stilbene **1**, forming a further molecule of *trans*-stilbene oxide **413**, alongside the observed acid **395**. Peracid **414** may also cyclise to form peroxylactone **394**. Further information for the formation of peroxylactone **394** is presented in Section 3.3.4.5.



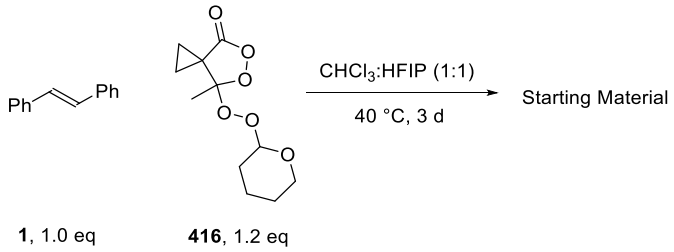
Scheme 117. Proposed mechanism for the epoxidation of *trans*-stilbene **1** with peroxylactone **400**.

In order to test the reactivity of the *exo*-peroxide of peroxylactone **400**, a protected peroxylactone derivative **416** was prepared by treatment of peroxylactone **400** with 2,3-dihydropyran **415** in the presence of *p*-toluenesulfonic acid (Scheme 118).



Scheme 118. Preparation of protected peroxide **416**.

Reactivity of the *exo*-peroxide of **400** was supported by experimental evidence, as treatment of *trans*-stilbene **1** with protected peroxylactone **416** shut down the reaction, with only the starting materials **1** and **416** being observed by ^{1}H NMR spectroscopy (Scheme 119).

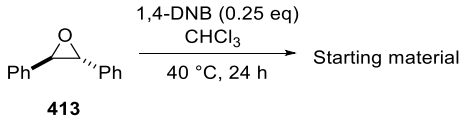


Scheme 119. Reaction of *trans*-stilbene with protected peroxide **416**.

Having gained an understanding of the reactivity between *trans*-stilbene **1** and peroxylactone **400** it was decided that a study into the reactivity of *trans*-stilbene oxide **413** was the most logical route in which to proceed.

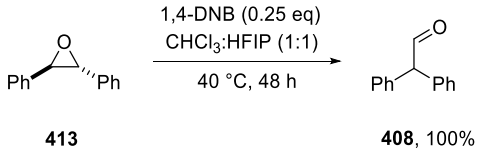
3.3.3 Investigation into reaction intermediate – *trans*-Stilbene oxide 413

With *trans*-stilbene oxide **413** identified as a key reaction intermediate, a study into its reactivity under various reaction conditions was carried out. *Trans*-stilbene oxide **413** was stirred in the reaction solvents in the presence of peroxylactone **400** and acid **395** in various combinations. When *trans*-stilbene oxide **413** was stirred in chloroform, in the presence of 1,4-dinitrobenzene, under the reaction conditions, no transformation was observed (Scheme 120).



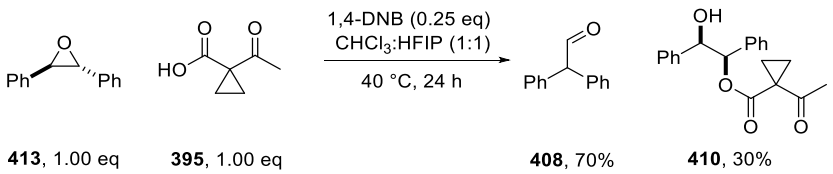
Scheme 120. *Trans*-stilbene oxide **413** stirred in chloroform at 40 °C.

Stirring *trans*-stilbene oxide **413** under the reaction conditions with a 1:1 solvent mix of chloroform and HFIP resulted in diphenylacetaldehyde **408** in a 100% conversion (Scheme 121). It is understood that formation of diphenylacetaldehyde **408** is a direct result of the rearrangement of *trans*-stilbene oxide **413**, facilitated by HFIP. This particular transformation is termed a Meinwald rearrangement and is presented in further detail in Section 3.3.4.2.[85]



Scheme 121. *Trans*-stilbene oxide **413** stirred in chloroform:HFIP (1:1) at 40 °C.

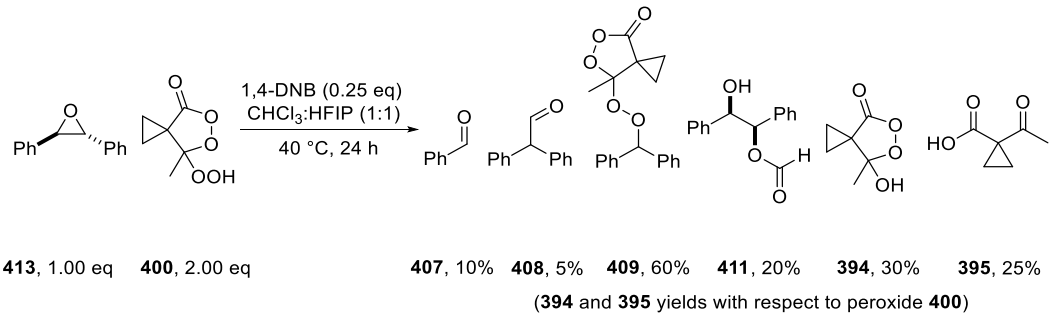
Subjecting *trans*-stilbene oxide **413** and acid **395** to the reaction conditions, gave diphenylacetaldehyde **408** (70%) and *syn*-ester **410** (30%) (Scheme 122). *Syn*-ester **410** is a direct result of the nucleophilic attack of acid **395** upon *trans*-stilbene oxide **413**. A potential explanation for the unexpected diastereoselectivity of this transformation is provided in Section 3.3.4.4.



Scheme 122. Reaction of *trans*-stilbene oxide **413** and acid **395**.

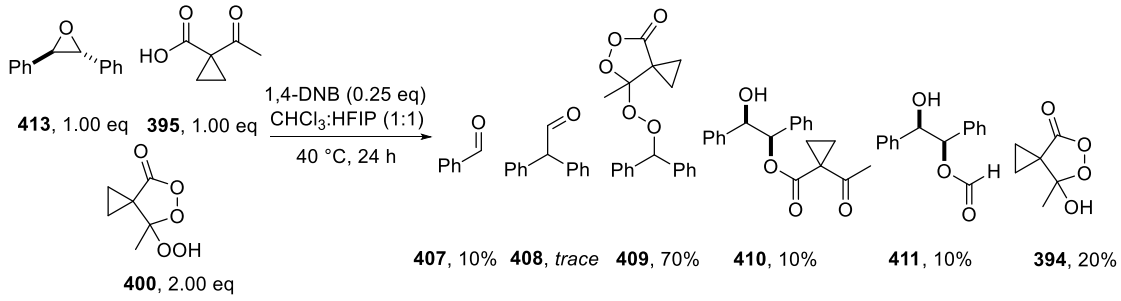
Subjecting *trans*-stilbene oxide **413** and peroxylactone **400** to the reaction conditions, gave diphenylacetaldehyde **408** (5%) and acid **395** (25%, with respect to peroxide **400**). Additionally, *trans*-stilbene oxide **413** and peroxylactone **400** were the two components responsible for the formation of benzaldehyde **407** (10%), alkylated peroxylactone species

409 (60%) and *syn*-formate **411** (20%). Peroxylactone **394** was also observed in a 30% conversion (Scheme 123).



Scheme 123. Reaction of *trans*-stilbene oxide **413** and peroxylactone **400**.

Subjecting *trans*-stilbene oxide **413**, peroxylactone **400** and acid **395** to the reaction conditions, produced every reaction product found in the reaction of *trans*-stilbene **1** and peroxylactone **400** (Scheme 124). This result strongly suggests that all observed reaction products proceed through the common reaction intermediate of *trans*-stilbene oxide **413**.



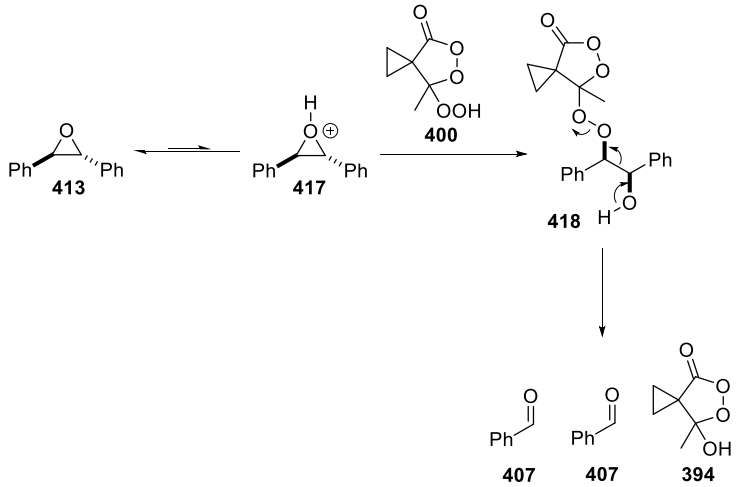
Scheme 124. Reaction of *trans*-stilbene oxide **413**, acid **395** and peroxylactone **400**.

3.3.4 Investigation into reaction products

The following section aims to provide a mechanistic rational for how the reaction products **407**–**411** and peroxylactone **394** are formed, based on the results reported in Section 3.3.3. This section will also outline experimental evidience to further support these claims.

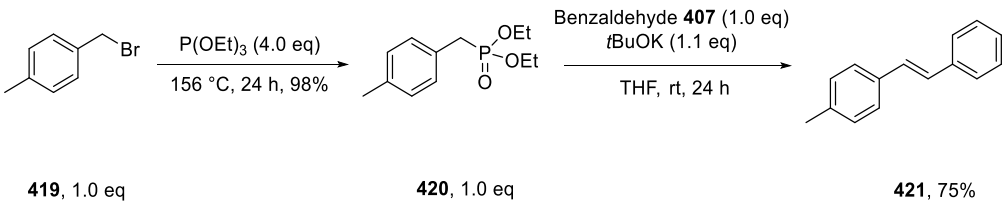
3.3.4.1 Benzaldehyde 407

Benzaldehyde **407** was identified to form from the reaction of *trans*-stilbene oxide **413** with peroxylactone **400** (Scheme 123). Mechanistically, it is proposed that the *exo*-peroxide of peroxylactone **400** can open *trans*-stilbene oxide **413** by nucleophilic attack, to give intermediate **418**. Breakdown of intermediate **418** proceeds to yield two equivalents of benzaldehyde **407** and one equivalent of peroxylactone **394**, through cleavage of the oxygen-oxygen bond (Scheme 125).



Scheme 125. Proposed mechanism for formation of benzaldehyde **407** and peroxylactone **394**.

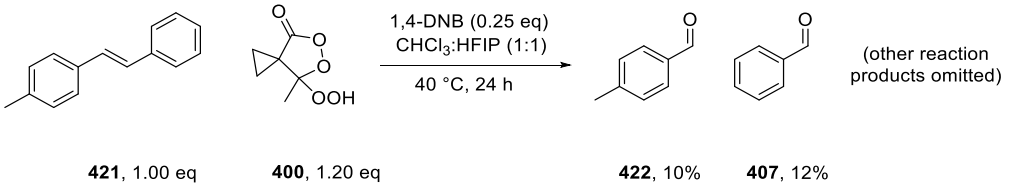
In order to further probe this hypothesis, unsymmetrical stilbene **421** was synthesised. Arbuzov reaction[86] between 4-methylbenzyl bromide **419** and triethylphosphite gave phosphonate ester **420** in a 98% yield. Horner-Wadsworth-Emmons reaction[87] with benzaldehyde **407** then gave rise to unsymmetrical stilbene **421** in a 75% yield (Scheme 126).



Scheme 126. Synthesis of unsymmetrical stilbene **421**.

Unsymmetrical stilbene **421** was reacted with peroxylactone **400** under standard conditions, to give 4-methylbenzaldehyde **422** (10%) and benzaldehyde **407** (12%), an approximate ratio

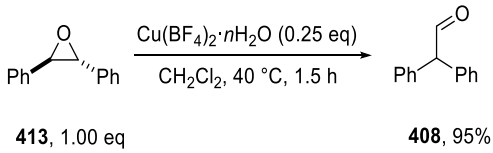
of 1:1 (Scheme 127). Note that for this experiment the other reaction products were not considered, with focus placed upon the conversion to the aldehyde products. Observing a ratio close to 1:1 of 4-methylbenzaldehyde **422** to benzaldehyde **407**, provides evidence that one equivalent of stilbene can lead to two equivalents of the corresponding aldehyde **407**.



Scheme 127. Reaction of peroxylactone **400** with unsymmetrical stilbene **421**.

3.3.4.2 Diphenylacetaldehyde 408

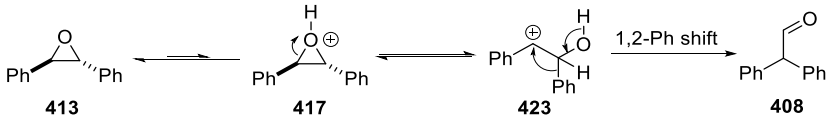
Diphenylacetaldehyde **408** was formed as a result of a Meinwald rearrangement,[85] when *trans*-stilbene oxide **413** was stirred in a 1:1 mixture of chloroform and HFIP (Scheme 121). This rearrangement is well documented in the literature and is known to be catalysed by Brønsted and Lewis acids.[88] For example, *trans*-stilbene oxide **413** may be efficiently converted into diphenylacetaldehyde **408** using copper(II) tetrafluoroborate hydrate in a Lewis-acid catalysed Meinwald rearrangement (Scheme 128).[89]



Scheme 128. Lewis acid-catalysed Meinwald rearrangement of *trans*-stilbene oxide **413**.[89]

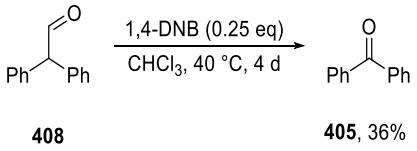
HFIP is a polar solvent with low nucleophilicity and strong hydrogen-bond donor ability.[90] In contrast to other polar solvents, HFIP has the ability to solvate anions but not cations, making it an ideal solvent for the generation of persistent carbocations in a reaction mixture. Literature reports suggest HFIP can act as both a solvent and Lewis acid substitute within a reaction;[91] this is believed to be the case within conditions employed for the reaction of *trans*-stilbene **1** with peroxylactone **400**.

Mechanistically, it is proposed that acid-catalysed ring opening of *trans*-stilbene oxide **413** gives stabilised cation **423**. This cation may then undergo a 1,2-phenyl shift to arrive at diphenylacetaldehyde **408** (Scheme 129).



Scheme 129. HFIP catalysed Meinwald rearrangement of *trans*-stilbene oxide **413** to diphenylacetaldehyde **408**.

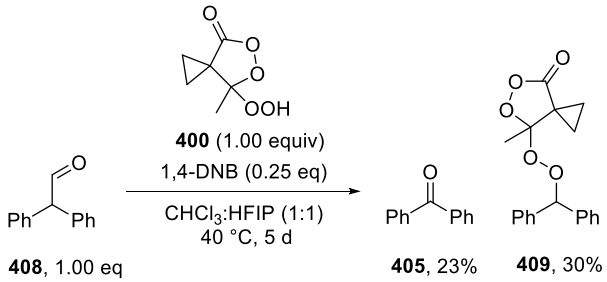
Diphenylacetaldehyde **408** exhibited further reactivity. When stirred in chloroform for four days, diphenylacetaldehyde **408** was slowly converted to benzophenone **405** (Scheme 130). Such a process has been reported in the literature and is thought to be facilitated by oxygen dissolved in the reaction mixture.[92] The conversion of diphenylacetaldehyde **408** to benzophenone **405** is a relatively slow process and no benzophenone **405** was observed in the reaction of *trans*-stilbene **1** with peroxylactone **400**.



Scheme 130. The conversion of diphenylacetaldehyde **408** to benzophenone **405**.

3.3.4.3 7-(Benzhydrylperoxy)-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 409

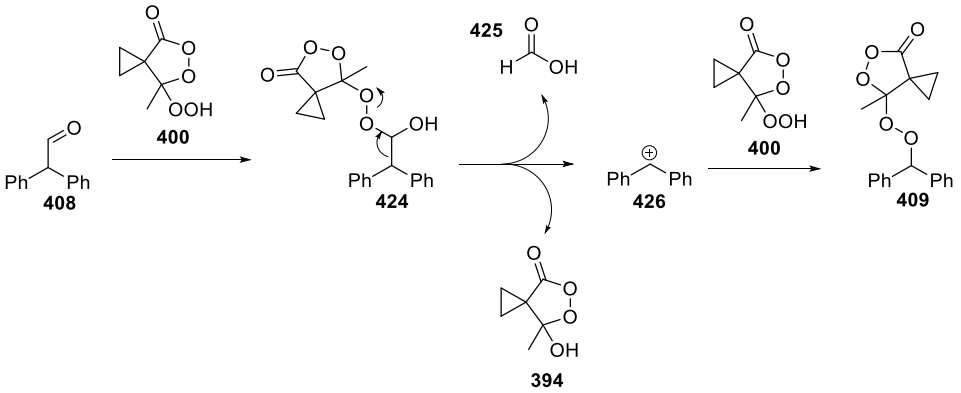
Interestingly, diphenylacetalehyde **408** displayed reactivity with peroxylactone **400**, to give benzophenone **405** (23%) and alkylated peroxylactone species **409** (30%) (Scheme 131). Benzophenone **405** is thought to form as a result of the process described in Scheme 130. However, the formation of alkylated peroxylactone species **409** strongly suggests diphenylacetaldehyde **408** to be a key intermediate in its formation during the reaction of *trans*-stilbene **1** and peroxylactone **400**, prompting further investigation.



Scheme 131. Reaction of diphenylacetaldehyde **408** with peroxylactone **400**.

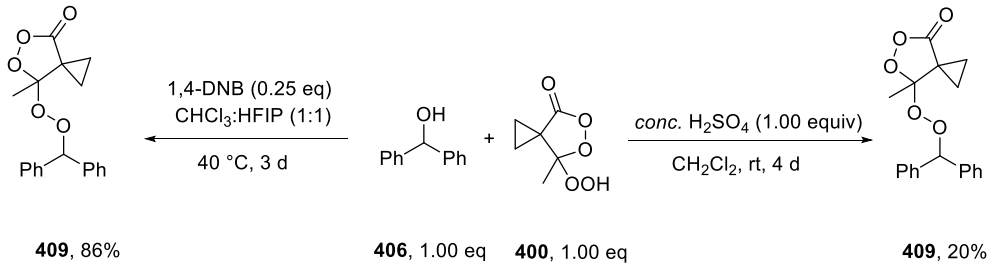
Mechanistically, it was proposed that the nucleophilic *exo*-peroxide of peroxylactone **400** attacks diphenylacetaldehyde **408**, to give **424**. This may then break down through cleavage

of a carbon-carbon and oxygen-oxygen bond to liberate an equivalent of formic acid **425**, peroxylactone **394** and stabilised cation **426**. Cation **426** may combine with another equivalent of peroxylactone **400** to give the alkylated peroxylactone species **409** (Scheme 132).



Scheme 132. Proposed mechanism for the formation of alkylated peroxylactone species **409** from diphenylacetaldehyde **408**.

In order to confirm its structure, alkylated peroxylactone species **409** was independently synthesised by two different routes (Scheme 133). Diphenyl methanol **406** and peroxylactone **400** were treated with sulfuric acid and stirred for four days in dichloromethane to yield alkylated peroxylactone species **409** in a 20% yield. Similarly, diphenyl methanol **406** and peroxylactone **400** were subjected to the standard reaction conditions of chloroform and HFIP at 40 °C for three days to produce the observed alkylated peroxylactone species **409** in a conversion of 86% by ^{1}H NMR spectroscopy. Both results confirm the structure of alkylated peroxylactone species **409** had been correctly assigned. Additionally, these reaction conditions support the proposed mechanism of formation (Scheme 132). It is believed that under the acidic reaction conditions, diphenyl methanol **406** loses a molecule of water in an S_N1 manner, to give cation **426** which combines with an equivalent of peroxylactone **400** to give species **409**.



Scheme 133. Two routes to the independent synthesis of alkylated peroxylactone species **409**.

With the aim of adding further evidence to the proposed mechanism of formation (Scheme 132), a reaction monitoring experiment was conducted for the reaction of

diphenylacetaldehyde **408** and peroxylactone **400** (Figure 24). 1,4-Dinitrobenzene was used as internal standard and reaction samples were analysed by ^{1}H NMR spectroscopy.

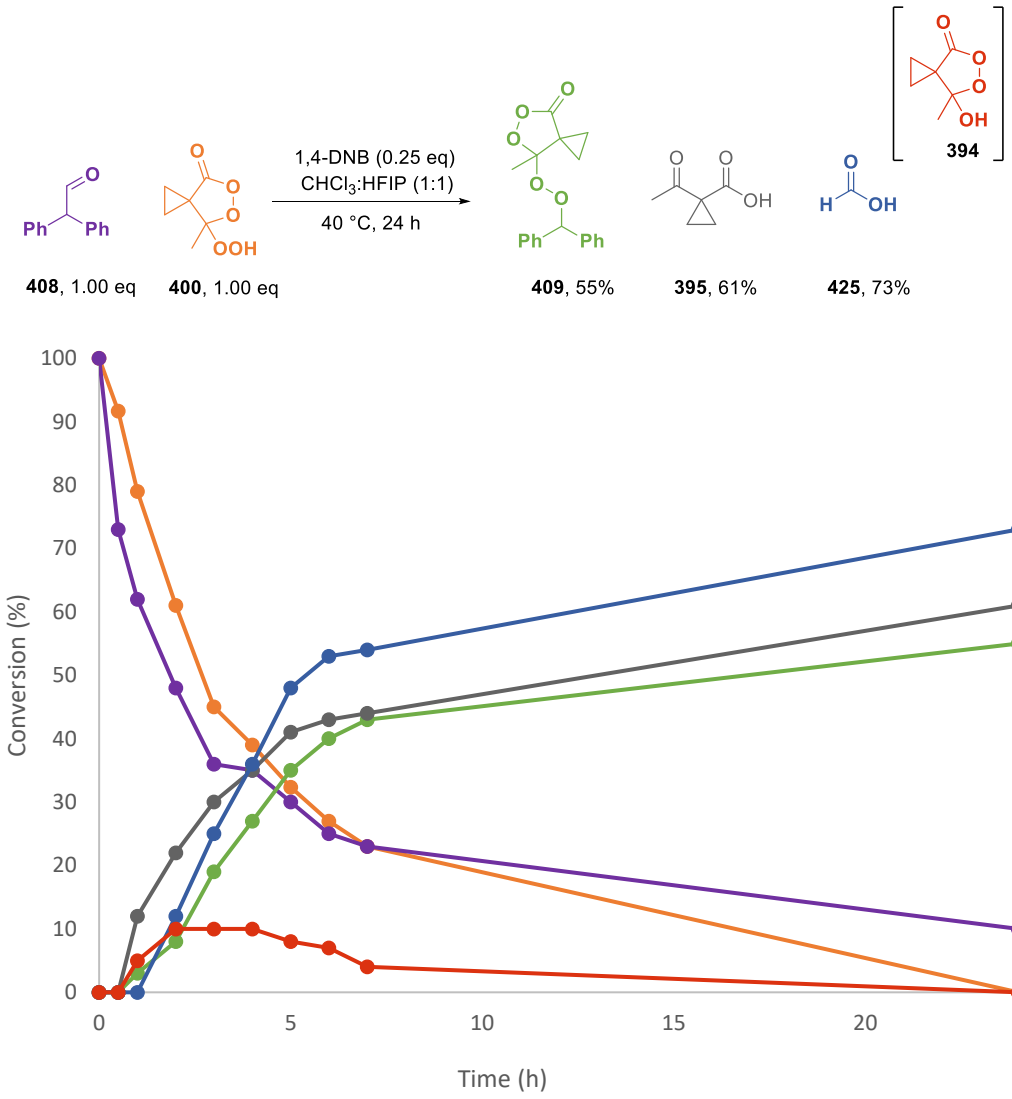
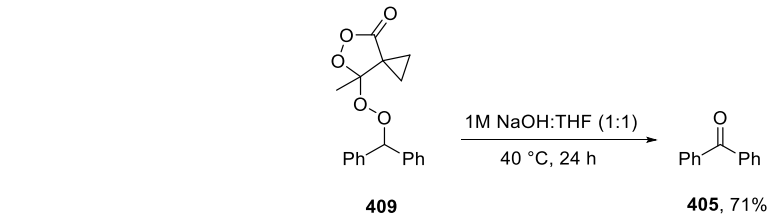


Figure 24. Reaction profile for the reaction of diphenylacetaldehyde **408** with peroxide **400**.

Alkylated peroxylactone species **409** and formic acid **425** were consistently formed as diphenylacetaldehyde **408** and peroxylactone **400** were being consumed. Peroxylactone **394** was also observed to form, reaching maximum conversion of 10%, before decomposing to acid **395**. With the ratio of observed products at 1:1.1:1.3 (**409**:**395**:**425**) it suggests the proposed mechanism of formation may be plausible. However, the reaction monitoring experiment did not show an increased consumption of peroxylactone **400** compared to diphenylacetaldehyde **408**, which would have suggested two equivalents of peroxylactone **400** being consumed for every equivalent of diphenylacetaldehyde **408** reacted, as proposed in the mechanism (Scheme 132).

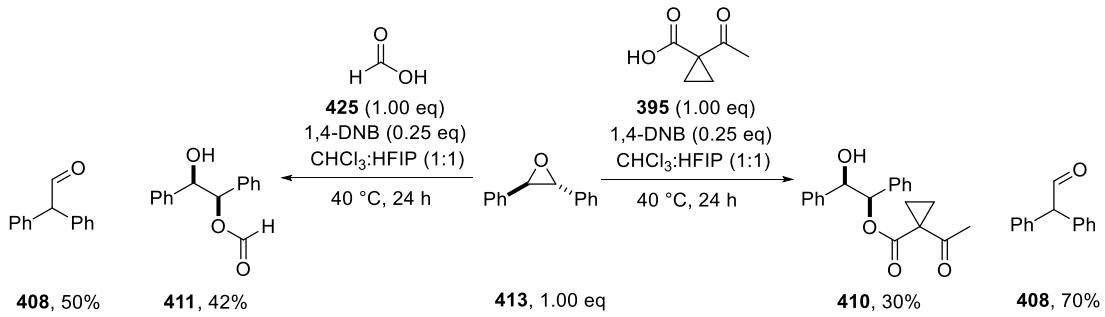


Scheme 134. Conversion of alkylated peroxylactone species **409** to benzophenone **405**.

The alkylated peroxylactone species **409** was found to be stable under the reaction conditions. In addition, this compound was also unreactive when exposed to the other components found within the reaction of *trans*-stilbene **1** and peroxylactone **400**. However, benzophenone **405** was formed in a 71% yield, when alkylated peroxylactone species **409** was treated with aqueous sodium hydroxide solution (Scheme 134).

3.3.4.4 *Rel*-(1*R*,2*R*)-2-Hydroxy-1,2-diphenylethyl 1-acetylcyclopropane-1-carboxylate 410 and *Rel*-(1*R*,2*R*)-2-Hydroxy-1,2-diphenylethyl formate 411

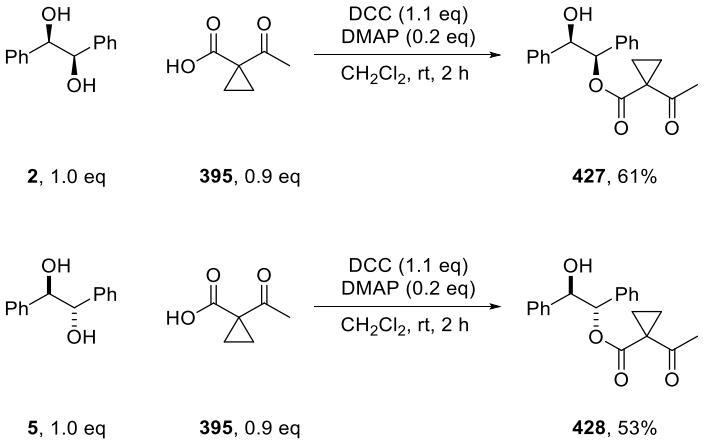
It was proposed that two of the reaction products (ester **410** and formate **411**) were formed as a result of *trans*-stilbene oxide **413** being ring opened by acid **395** or formic acid **425** both of which were present within the reaction mixture. This hypothesis was confirmed by exposing *trans*-stilbene oxide **413** to acid **395**, to give ester **410** in a 30% conversion. Similarly, *trans*-stilbene oxide **413** was treated with formic acid **425**, to give formate **411** in a 42% conversion (Scheme 135). The formation of diphenylacetaldehyde **408** within both of these reactions are a result of Meinwald rearrangement of *trans*-stilbene oxide **413**, as discussed in Section 3.3.4.2.



Scheme 135. Formation of ester **410** and formate **411** from *trans*-stilbene oxide **413**.

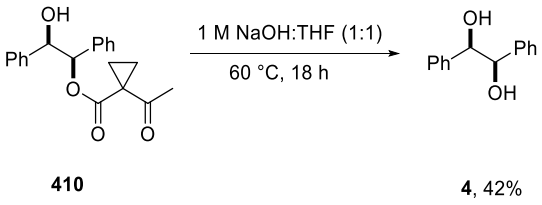
An interesting feature of the reaction products (ester **410** and formate **411**) was the *syn*-diastereoselectivity observed. This selectivity was confirmed by the independent synthesis of *syn*-ester **427** and *anti*-ester **428**, through coupling the two possible stilbene diols **2** or **5** with acid **395** using DCC and DMAP (Scheme 136). Combining a reaction mixture sample with

syn-ester **427** and *anti*-ester **428**, independently, confirmed only *syn*-ester **427** was formed in the reaction of *trans*-stilbene **1** with peroxylactone **400** (as determined by ^{1}H NMR spectroscopy).



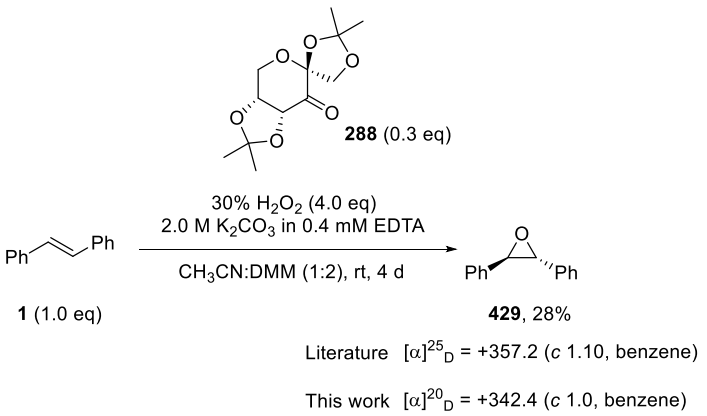
Scheme 136. Independent synthesis of *syn*-ester **427** and *anti*-ester **428**.

Syn-ester **410**, isolated from the reaction of *trans*-stilbene **1** with peroxylactone **400**, was subjected to basic hydrolysis, which gave *syn*-diol **4** in a yield of 42% (Scheme 137). Comparison of isolated *syn*-diol **4** with a commercial sample, further confirmed the *syn*-diastereoselectivity observed within the reaction.



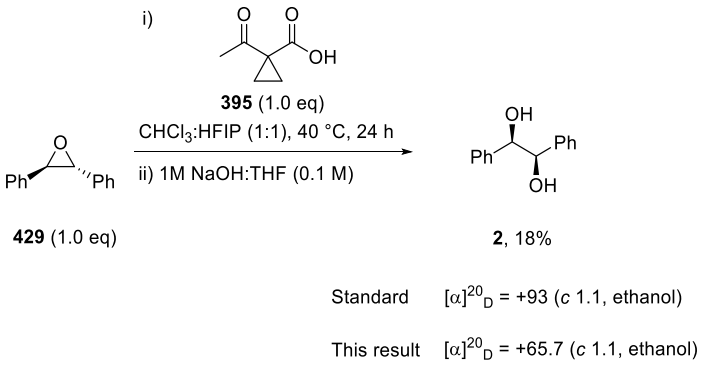
Scheme 137. Hydrolysis of *syn*-ester **410** to *syn*-diol **4**.

As further experimental evidence for the observed *syn*-diastereoselectivity, a stereo-retention experiment was carried out. Enantiomerically pure (2*R*,3*R*)-*trans*-stilbene oxide **429** was synthesised *via* a Shi asymmetric epoxidation of *trans*-stilbene **1** in a yield of 28%, which displayed an $[\alpha]_D$ value comparable to the value reported in the literature (Scheme 138).



Scheme 138. Shi epoxidation of *trans*-stilbene **1** to give (2*R*,3*R*)-*trans*-stilbene oxide **429**.[93]

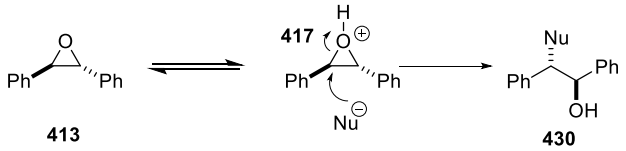
Reaction of (2*R*,3*R*)-*trans*-stilbene oxide **429** with carboxylic acid **395** under the reaction conditions, followed by basic hydrolysis, gave (1*R*,2*R*)-*syn*-diol **2** in a yield of 18% (Scheme 139). Upon comparison of the $[\alpha]_D$ values it was concluded that stereo-retention was taking place during this process, confirming the opening of epoxide **413** with acid **395** was a *syn*-selective concerted process. Differences between the observed $[\alpha]_D$ value and the literature $[\alpha]_D$ value, may be due to a slight impurity present in the isolated sample of *syn*-diol **2**. Attempts to further purify this sample resulted in the poor yield reported (18%). Following the succession of experimental evidence, a mechanistic hypothesis for the observed *syn*-diastereoselectivity was developed.



Scheme 139. Opening of (2*R*,3*R*)-*trans*-stilbene oxide **429** with acid **395**, to give (1*R*,2*R*)-*syn*-diol **2**.

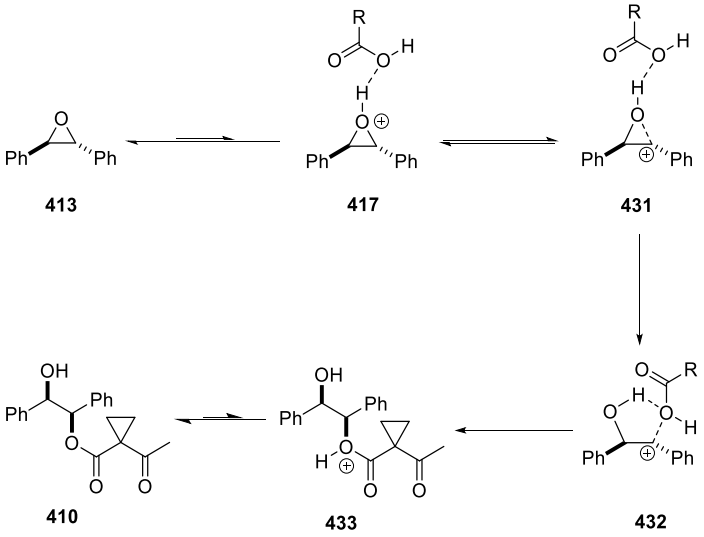
In most cases, the ring opening of an epoxide (*e.g.* **413**) proceeds through an S_N2 mechanism with stereoinversion at the epoxide carbon atom, to give the *anti*-product **430** (Scheme 140). However, literature reports suggest epoxides bearing either aryl groups or other unsaturated systems have a tendency towards *syn*-opening under acidic conditions.[94,95] Furthermore,

epoxides bearing two aryl groups (such as *trans*-stilbene oxide **413**) have a very strong tendency towards stereoretention through *syn*-opening.[95]



Scheme 140. General S_N2 epoxide opening with stereoinversion.

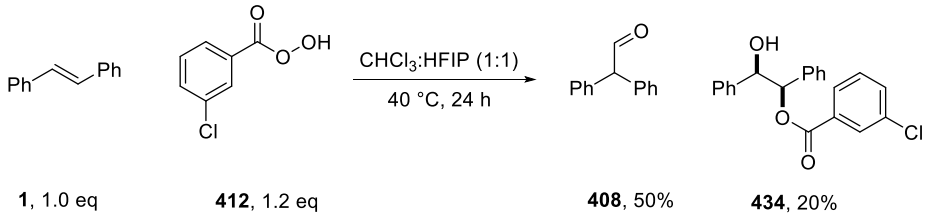
Mechanistically, it is proposed that ring opening of 2,3-diaryl epoxides proceeds *via* an "ion-dipole pair" mechanism.[95] Under the acidic conditions, *trans*-stilbene oxide **413** is protonated to give species **417** which can hydrogen bond with the acid nucleophile. This can go on to form an intramolecular intimate ion/dipole pair **431**, which has an extended benzylic C–O bond with considerable ionic character.[96] This may rearrange to species **432** with a further lengthening of the C–O bond and increased cationic character at the benzylic position. Pseudocyclic intermediate **432** may collapse by attack of the oxygen nucleophile into the carbocation centre, with full stereoretention, to give *syn*-ester **410** (Scheme 141). This attack is thought to be entropically favoured over attack of an "external" molecule of acid nucleophile. It is reported that the transition state for *syn*-addition is likely to have more carbocation character than the transition state for *anti*-addition, leading to the justification that aryl epoxides favour *syn*-addition, as they can better stabilise the arising carbocation.[95]



Scheme 141. "Ion-dipole pair" mechanism for the *syn*-opening of *trans*-stilbene oxide **413**.[95]

Reaction of *trans*-stilbene **1** with *m*CPBA **412** under the reaction conditions gave diphenylacetaldehyde **408** (50%) and *syn*-ester **434** (20%) (Scheme 142). This result suggests

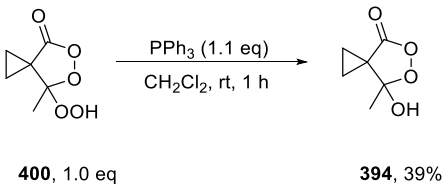
a lack of unique reactivity in our process, as the same result of *syn*-diastereoselectivity can be achieved by replacing peroxylactone **400** with an alternative peroxide, such as *m*CPBA **412**.



Scheme 142. The reaction of *trans*-stilbene **1** and *m*CPBA **412**.

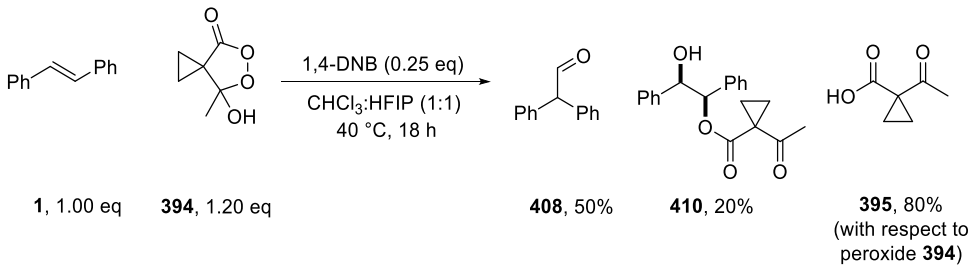
3.3.4.5 Peroxylactone 394

Peroxylactone **394** was observed as a product of the reaction between *trans*-stilbene oxide **413** and peroxylactone **400** (Scheme 123). This was thought to be formed as a co-product as a result of three consecutive discrete transformations; the epoxidation of *trans*-stilbene **1** to give *trans*-stilbene oxide **413**, followed by the formation of benzalehyde **407** and the subsequent formation of alkylated peroxylactone species **409** (Scheme 117, Scheme 125 and Scheme 132). The structure of peroxylactone **394** was confirmed by independent synthesis. Treatment of peroxylactone **400** with triphenylphosphine gave rise to the peroxylactone **394** in a yield of 39% (Scheme 143).[97]



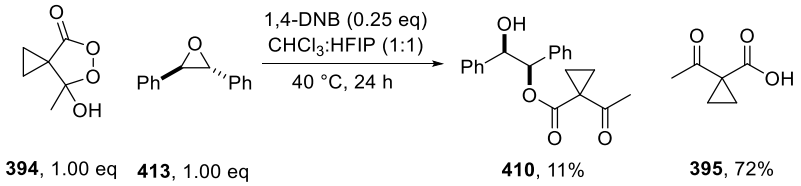
Scheme 143. Independent synthesis of peroxylactone **394**.[97]

It was proposed that peroxylactone **394** had the ability to epoxidise a molecule of *trans*-stilbene **1**. This hypothesis was confirmed by the reaction of *trans*-stilbene **1** with peroxylactone **394**, leading to diphenylacetaldehyde **408** (50%) and *syn*-ester **410** (20%), products resulting from the intermediate *trans*-stilbene oxide **413** (Scheme 144). This result supports the hypothesis that peroxylactone **400** has the ability to epoxidise two equivalents of *trans*-stilbene **1**, as outlined in Scheme 117.



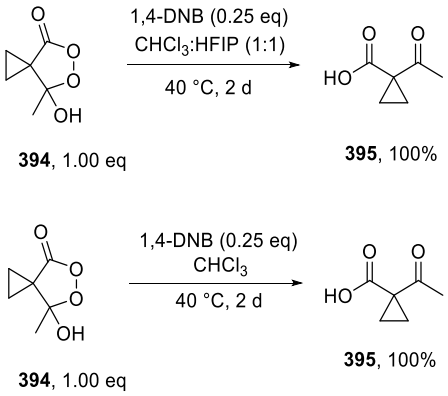
Scheme 144. Reaction of *trans*-stilbene **1** with peroxylactone **394**.

Peroxylactone **394** was stirred under standard reaction conditions with various compounds isolated from the reaction of *trans*-stilbene **1** and peroxylactone **400**, with no significant reactivity observed. For example, when peroxylactone **394** was stirred with *trans*-stilbene oxide **413**, it produced *syn*-ester **410**, a result of epoxide **413** being opened by acid **395** (formed by the decomposition of peroxylactone **394**) (Scheme 145). It was proposed that the only significant role peroxylactone **394** played within the reaction of *trans*-stilbene **1** and peroxylactone **400**, was to epoxidise *trans*-stilbene **1**.



Scheme 145. Reaction of *trans*-stilbene oxide **413** with peroxylactone **394**.

Peroxylactone **394** was not observed or isolated from the reaction between *trans*-stilbene **1** and peroxylactone **400**. This is believed to be due to the instability of this peroxide under the reaction conditions. When stirred in the reaction solvents at 40 °C, peroxylactone **394** decomposed quantitatively to give acid **395** over the course of two days (Scheme 146).

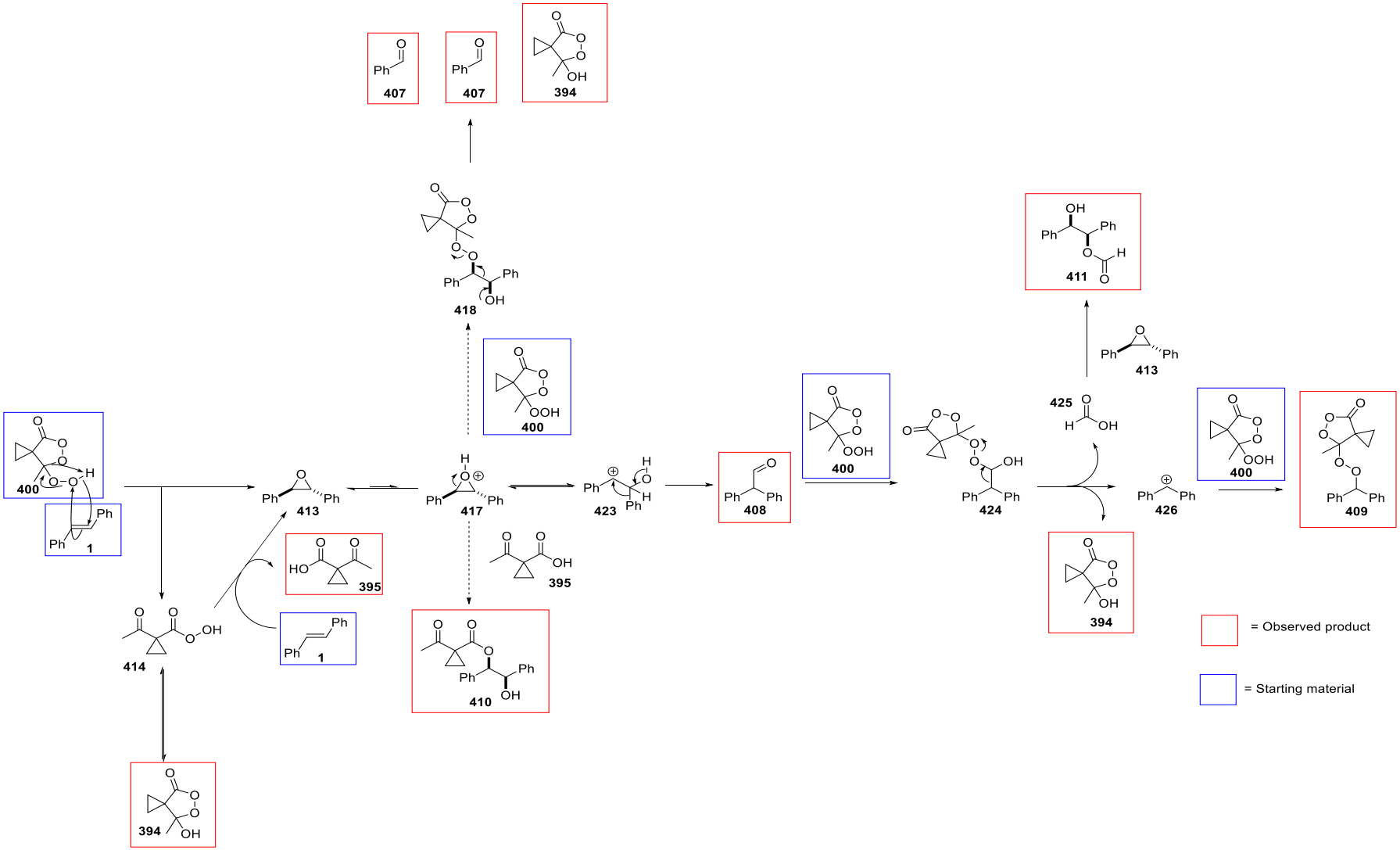


Scheme 146. Stability of peroxylactone **394**.

3.3.5 Mechanistic summary

The following section aims to provide a mechanistic summary for the formation of all reaction products found within the reaction of *trans*-stilbene **1** and peroxylactone **400** (Scheme 147).

It is proposed that the initial step in the reaction was formation of *trans*-stilbene oxide **413**, *via* reaction of *trans*-stilbene **1** with the *exo*-peroxide of peroxylactone **400**. Additionally, it was proposed that peracid **414** was formed in this process, which may epoxidise a second equivalent of *trans*-stilbene **1**, forming a further molar equivalent of *trans*-stilbene oxide **413** alongside carboxylic acid **395**. It was belived peracid **414** may cyclise to form peroxylactone **394**. Under the reaction conditions, *trans*-stilbene oxide **413** can be protonated to give **417**. It was proposed that the *exo*-peroxide of peroxylactone **400** ring opened **417** by nucleophilic attack, to give intermediate **418**. Breakdown of **418** proceeded to give two equivalents of benzaldehyde **407** and one equivalent of peroxylactone **394**. Alternatively, protonated *trans*-stilbene oxide **417** was opened by acid **395** *via* an ion-dipole pair mechanism to give *syn*-ester **410**. Following another pathway, it was proposed that acid-catalysed ring opening of *trans*-stilbene oxide **413** led to stabilised cation **423**. This cation then underwent a 1,2-phenyl shift to give diphenylacetaldehyde **408**. Accounting for further reactivity, it was proposed that the nucleophilic *exo*-peroxide of peroxylactone **400** attacks diphenylacetaldehyde **408**, to give **424**. This broke down through cleavage of a carbon–carbon and oxygen–oxygen bond to liberate an equivalent of formic acid **425**, peroxylactone **394** and stabilised cation **426**. Cation **426** may combine with another equivalent of peroxylactone **400** to give the alkylated peroxylactone species **409**. The liberated formic acid **425** may then ring-open an equivalent of *trans*-stilbene oxide **413** to give formate **411**.



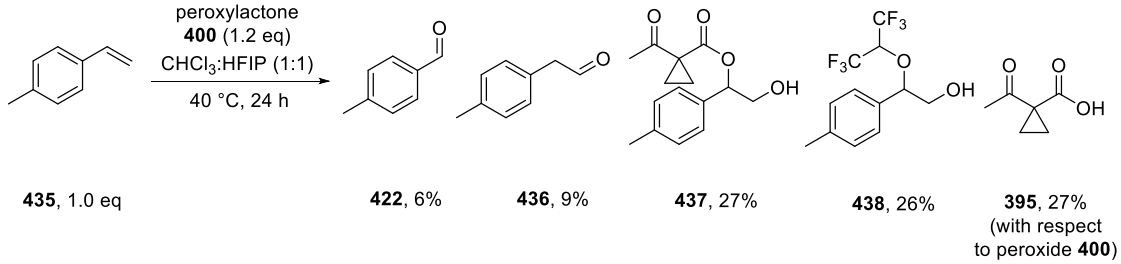
Scheme 147. Proposed overall mechanism for the reaction of *trans*-stilbene **1** with peroxide **400**.

3.3.6 Alternative alkenes

In order to further understand the reactivity observed, peroxylactone **400** was reacted with alternative alkenes.

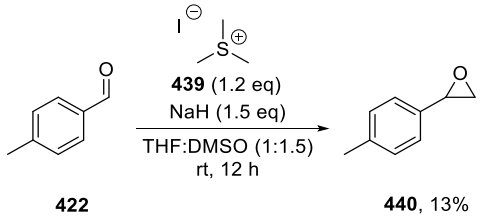
3.3.6.1 4-Methylstyrene 435

Reaction of 4-methylstyrene **435** with peroxylactone **400** in a 1:1 mixture of chloroform and HFIP resulted in a series of oxidised products (Scheme 148). The isolated reaction products consisted of two aldehydes (4-methylbenzaldehyde **422** (6%) and 2-(*p*-tolyl)acetaldehyde **436** (9%)), two dihydroxylated species (ester **437** (27%) and ether **438** (26%)) and carboxylic acid **395** (27%).



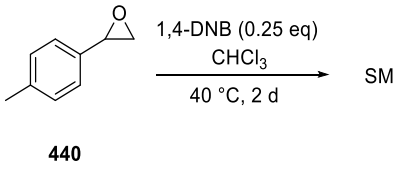
Scheme 148. The reaction of 4-methyl styrene **435** with peroxylactone **400**.

The reactivity of this styrene derivative is comparable to that of *trans*-stilbene **1**, therefore, it was logical to assume the reaction was proceeding through an epoxide intermediate. With this hypothesis in mind, 2-(*p*-tolyl) oxirane **440** was synthesised in a yield of 13% (unoptimised) by reaction of 4-methylbenzaldehyde **422** with trimethylsulfonium iodide **439** (Scheme 149).[98]



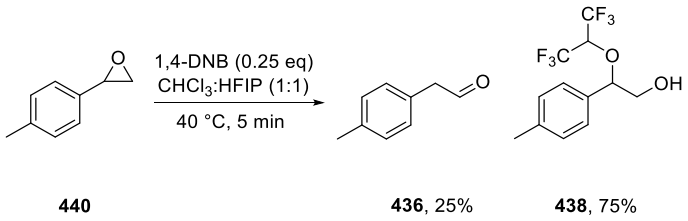
Scheme 149. The synthesis of 2-(*p*-tolyl) oxirane **440**.[98]

Following a similar method to the investigation of the reaction between *trans*-stilbene **1** and peroxylactone **400**, epoxide **440** was stirred in the reaction solvents in the presence of peroxylactone **400** and acid **395** under various combinations and analysed by ^{1}H NMR spectroscopy using an internal standard (1,4-dinitrobenzene). Stirring epoxide **440** in chloroform at 40 °C for two days, returned starting material (Scheme 150).



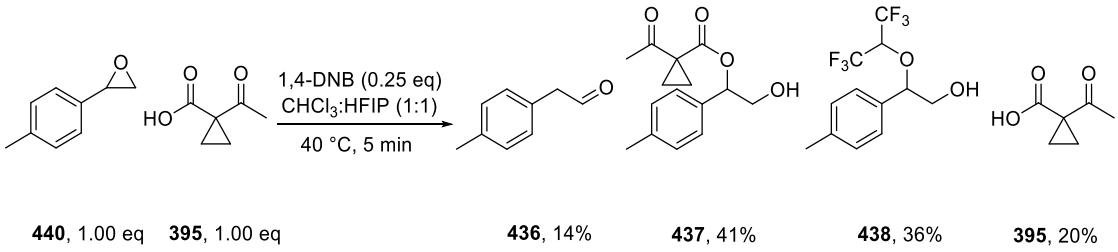
Scheme 150. Epoxide **440** stirred in chloroform at 40 °C.

Stirring epoxide **440** in a 1:1 mixture of chloroform and HFIP at 40 °C, resulted in the formation of aldehyde **436** (25%) and ether **438** (75%) (Scheme 151).



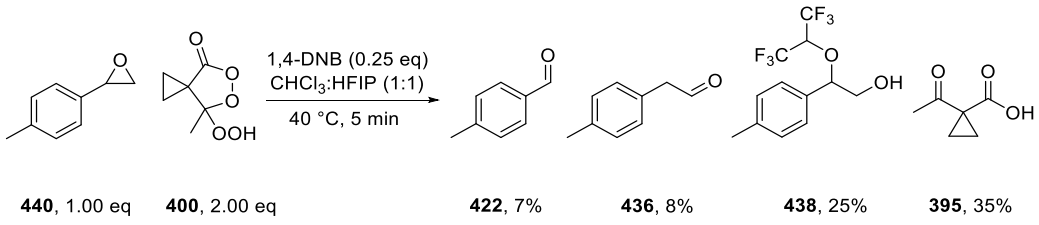
Scheme 151. Epoxide **440** stirred in chloroform:HFIP (1:1) at 40 °C.

Exposure of the epoxide **440** and carboxylic acid **395** to the reaction conditions, gave aldehyde **436** (14%), ester **437** (41%), ether **438** (36%) and acid **395** (20%) (Scheme 152).



Scheme 152. Reaction of epoxide **440** and acid **395**.

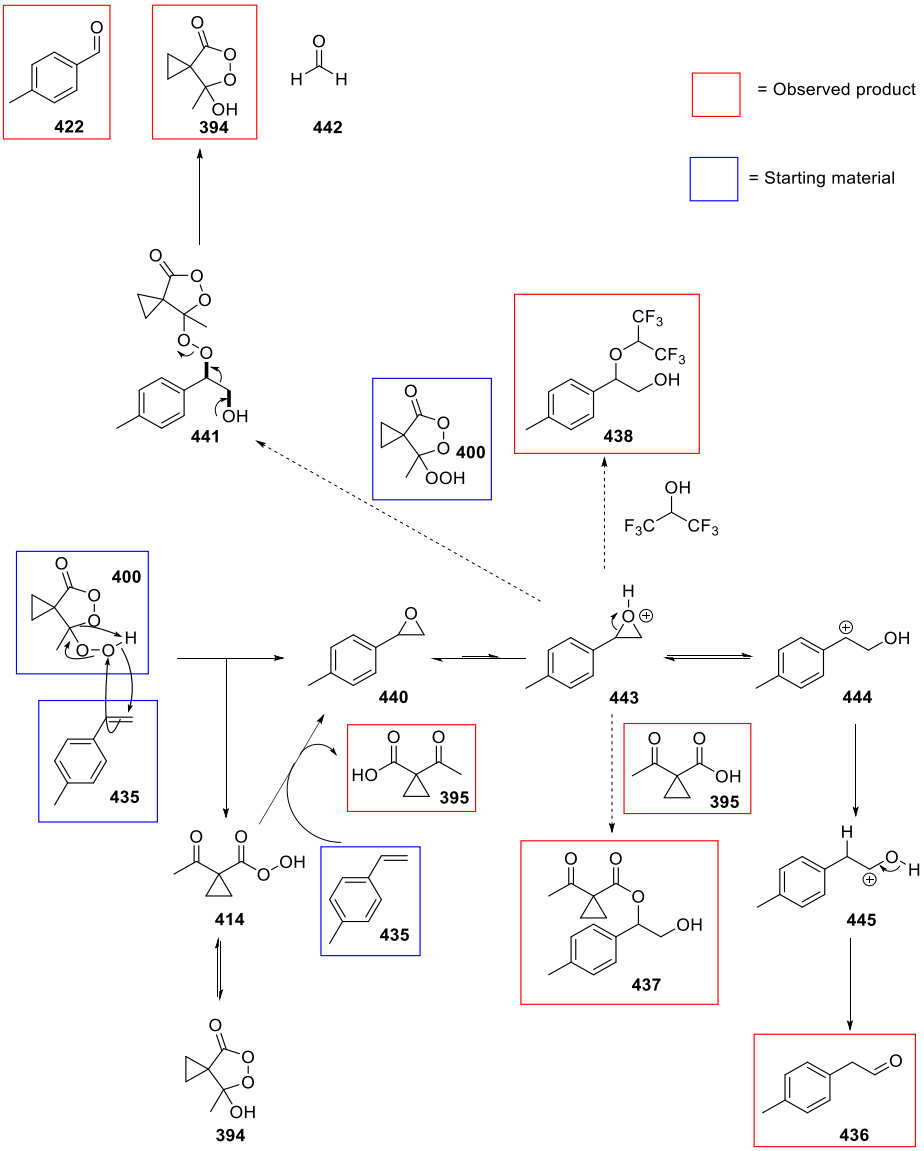
Subjecting epoxide **440** and peroxylactone **400** to the reaction conditions, gave aldehyde **422** (7%), aldehyde **436** (8%), ether **438** (25%) and acid **395** (35%) (Scheme 153).



Scheme 153. Reaction of epoxide **440** and peroxylactone **400**.

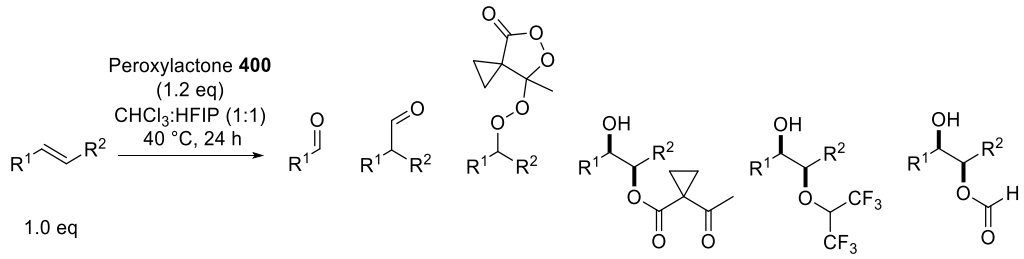
The observed reactivity of epoxide **440** was comparable to that of *trans*-stilbene oxide **413**, leading to the assumption that the reaction of 4-methylstyrene **435** followed a similar mechanisitc course to *trans*-stilbene **1** when reacted with peroxylactone **400** (Scheme 154).

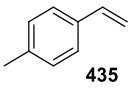
Epoxide **440** was formed by reaction of 4-methylstyrene **435** with peroxylactone **400**. It was proposed that peracid **414** was formed in this process, which may epoxidise a second equivalent of 4-methylstyrene **435**, forming acid **395** and a second equivalent of epoxide **440**. Peracid **414** cyclised to form peroxylactone **394**. The protonated epoxide species **443**, reacted through different pathways. The *exo*-peroxide of peroxylactone **400** opened **443** by nucleophilic attack, to give intermediate **441**. Breakdown of the intermediate **441** proceeded to give 4-methylbenzaldehyde **422**, formaldehyde **442** and peroxylactone **394**. Alternatively, protonated epoxide **443** was opened by acid **395** or HFIP through an ion-dipole pair mechanism to give ester **437** or ether **438**, respectively. Finally, it was proposed that acid-catalysed ring opening of epoxide **440** led to cation **444**, which underwent a 1,2-hydride shift to give **445**, leading to aldehyde **436**.



Scheme 154. Mechanistic overview for the reaction of 4-methylstyrene **435** with peroxylactone **400**.

The regioselectivity observed to give ester **437** and ether **438** were understood to arise because of attack of the oxygen nucleophile at the epoxide carbon atom of species **443** that was best able to stabilise a developing positive charge. In this case, a benzylic position can stabilise an arising positive charge better than the β-position, leading to the observed regioselectivity.

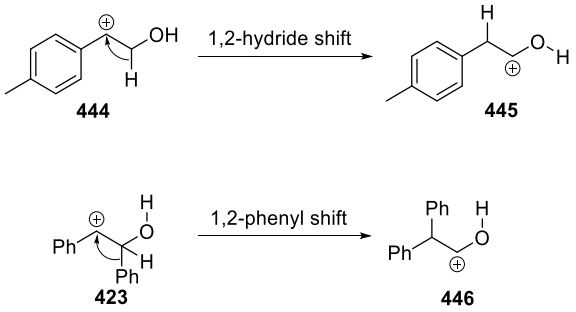


Ph, Ph **1** R^1, R^2 = Ph	**407**, 31%	**408**, 18%	**409**, 20%	**410**, 6%	-	**411**, 5%
 **435** R^1=4-MePh, R^2 = H	**422**, 6%	**436**, 9%	-	**437**, 27%	**438**, 26%	-

Scheme 155. Comparison of the reaction *trans*-stilbene and 4-methyl styrene **435** with peroxylactone **400**.

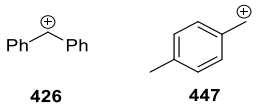
Interesting trends in reactivity can be drawn from the comparison of the reaction of peroxylactone **400** with *trans*-stilbene **1** and with 4-methylstyrene **435** (Scheme 155). It was observed that the oxidative cleavage pathway was more prevalent in the *trans*-stilbene **1** reaction (giving aldehyde **407**, 31%) when compared to the 4-methylstyrene reaction **435** (giving aldehyde **422**, 6%).

The Meinwald rearrangement pathway was more favoured in the *trans*-stilbene **1** reaction (giving diphenylacetaldehyde **408**, 18%), when compared to the 4-methylstyrene **435** reaction (giving aldehyde **436**, 9%). In the Meinwald rearrangement mechanism, the epoxide opened to give the most stable carbocation before the 1,2-shift occurred. Species **445** and **446** appear similar in terms of carbocation stability, therefore, the higher yield of diphenylacetaldehyde **408** (18%) may be due to the migration ability and whether the 1,2-Ph shift is more favourable than the 1,2-hydride shift which occurs in the 4-methylstyrene **435** reaction (Scheme 156).



Scheme 156. Comparison of 1,2-hydride shift and 1,2-phenyl shift.

The pathway towards the alkylated peroxylactone species is favoured for the reaction of *trans*-stilbene **1** (leading to **409**, 20%), but to a lesser extent for the reaction of 4-methylstyrene **435**. In reference to the proposed mechanism (Scheme 132), this is thought to be due to cation stability. Carbocation **447** is less stable than **426**, which may account for the absence of an alkylated peroxylactone species in the reaction of 4-methylstyrene **435** (Scheme 157). As a result of this pathway not being favoured, formic acid **425** is not formed within the reaction mixture, which explains the absence of an analogous formate compound within this transformation.

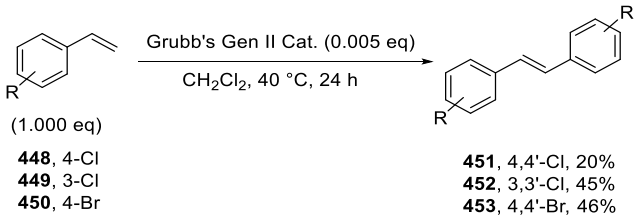


Scheme 157. Comparison of cation stability.

The dihydroxylation pathway is more prevalent within the 4-methylstyrene **435** reaction (leading to ester **437**, 27%) when compared to the *trans*-stilbene **1** reaction (giving ester **410**, 6%). The approach of a nucleophile towards epoxide **440**, is less sterically encumbered than for *trans*-stilbene oxide **413**, which may account for the increase in the dihydroxylation pathway. Interestingly, HFIP can open epoxide **440** (giving ether **438**, 26%), however, this pathway is not observed in the reaction of *trans*-stilbene oxide **413**. With HFIP being a weak nucleophile, this reactivity is understood to be due to epoxide **440** being more reactive and accessible than *trans*-stilbene oxide **413**.

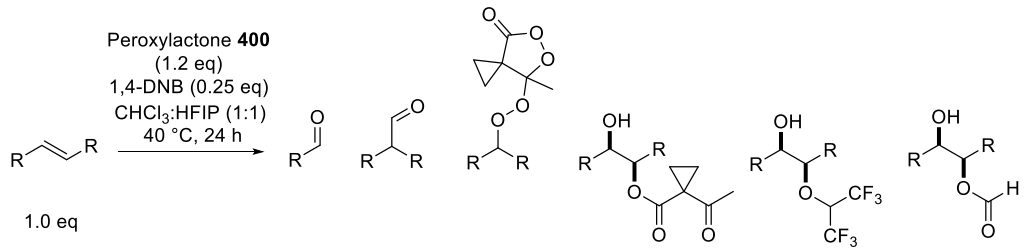
3.3.6.2 Halogen substituted alkenes

Three symmetrical halogen-substituted stilbenes **451**–**453**, were synthesised and examined under standard reaction conditions with peroxylactone **400**. The alkenes were synthesised through a Grubbs cross-metathesis reaction from the corresponding styrenes **448**–**450** (Scheme 158).



Scheme 158. The synthesis of symmetrical halogen-substituted stilbenes **451**-**453**.

Under the reaction conditions with peroxylactone **400**, 4,4'-dichlorostilbene **451** gave 4-chlorobenzaldehyde **454** (28%), aldehyde **455** (6%) and ester **456** (34%). 3,3'-Dichlorostilbene **452** was unreactive, possibly due to the alkene not being nucleophilic enough to form the corresponding epoxide. 4,4'-Dibromostilbene **453** gave 4-bromobenzaldehyde **457** (41%), aldehyde **458** (9%) and ester **459** (45%) (Scheme 159). The most notable observation was that *para*-substituted halogen stilbenes **451** and **453** showed a substantial increase in the yield of dihydroxylated products (ester **456** and ester **459**). Future work may include further substrate engineering, in order to select which reaction pathways are favoured in the reaction of peroxylactone **400** with specific alkene partners.



Ph, Ph **1** R = Ph	**407**, 31%	**408**, 18%	**409**, 20%	**410**, 6%	-	**411**, 5%
R = 4-ClPh **451**	**454**, 28%	**455**, 6%	-	**456**, 34%	-	-
R = 3-ClPh **452**	-	-	-	-	-	-
R = 4-BrPh **453**	**457**, 41%	**458**, 9%	-	**459**, 45%	-	-

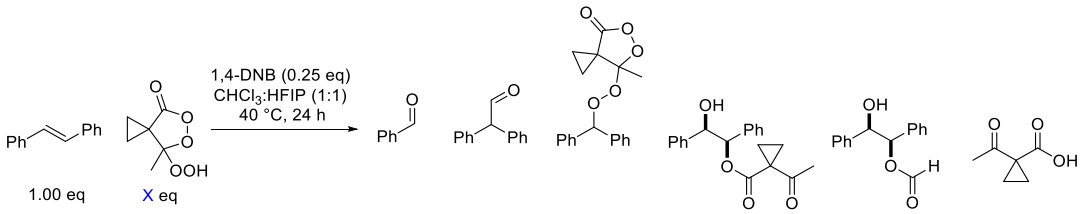
Conversions calculated by ^{1}H NMR spectroscopy using an internal standard (1,4-DNB).
Conversions calculated from average of two experiments.

Scheme 159. Reaction of halogen-substituted stilbenes **451**–**453** with peroxylactone **400**.

3.3.7 Optimisation of conditions

With the aim of achieving selectivity for the dihydroxylated products within the reaction of *trans*-stilbene **1** and peroxylactone **400**, various reaction conditions were screened. Unfortunately, none of the conditions examined offered any clear control over reactivity, with either no reaction taking place or the distribution of products being similar to the standard reaction conditions (alkene (1.0 eq), peroxylactone **400** (1.2 eq), $CHCl_3$:HFIP (1:1), 40 °C).

Altering the equivalents of peroxylactone **400** was found to have little effect on the product distribution of the reaction (Table 16). The decision was made to remain with 1.2 equivalents of peroxylactone **400** (entry 2).

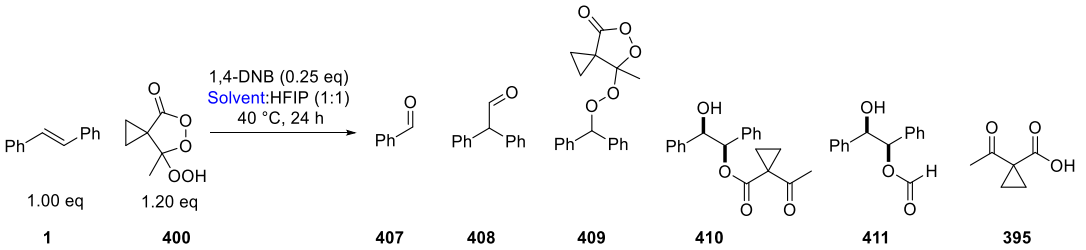


		1	**400**	**407**	**408**	**409**	**410**	**411**	**395**
Entry	Peroxylactone eq								
1	0.5			16%	13%	3%	6%	8%	51%
2	1.2			17%	11%	16%	8%	7%	39%
3	2.0			15%	0%	30%	8%	14%	29%

Conversions calculated by ^{1}H NMR spectroscopy using an internal standard (1,4-DNB). Conversions calculated from a single experiment.

Table 16. Optimisation of equivalents of peroxylactone **400**.

Optimisation of reaction solvent did not offer any improvement over chloroform (Table 17, entry 1) in terms of selectivity towards dihydroxylated products ester **410** and **411** or overall yield. Et_2O, EtOAc, dioxane and MeOH were found to slow down the overall reaction (entries 2–5).

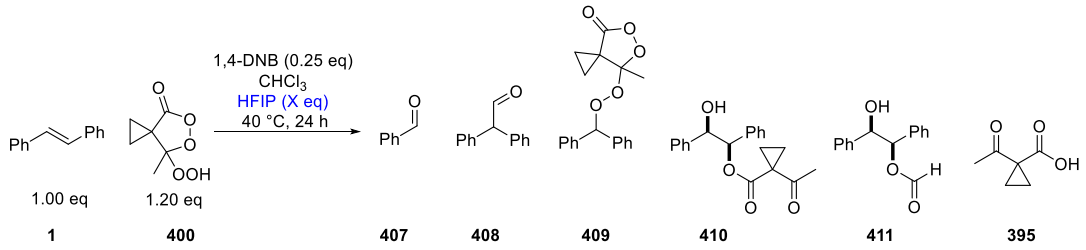


Entry	Solvent						
1	$CHCl_3$	17%	11%	16%	8%	7%	39%
2	Et_2O	8%	10%	30%	0%	0%	68%
3	EtOAc	6%	2%	0%	0%	0%	33%
4	Dioxane	8%	0%	0%	0%	0%	16%
5	MeOH	0%	0%	0%	0%	0%	56%
6	Toluene	25%	12%	13%	6%	12%	83%

Conversions calculated by ^{1}H NMR spectroscopy using an internal standard (1,4-DNB). Conversions calculated from a single experiment.

Table 17. Optimisation of solvent.

Optimisation of HFIP equivalents provided no improvement in selectivity towards dihydroxylated products **410** and **411** or the overall level of conversion. It was observed that the reaction was completely shut down in the absence of HFIP (Table 18, entry 1). Increasing the equivalents of HFIP above ten did not increase conversion further. Additionally, *trans*-stilbene **1** was found to be insoluble within these higher ratios of HFIP to chloroform (entries 5-6).



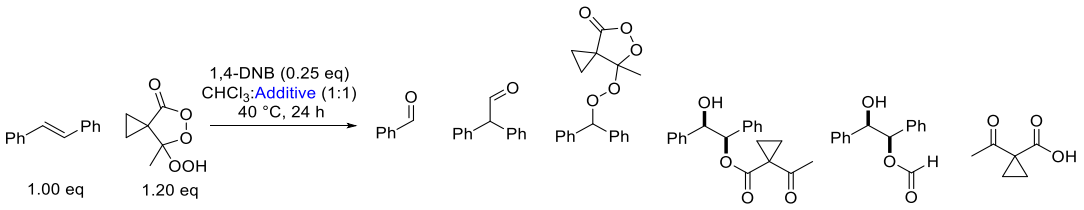
Entry	HFIP eq						
1	0	0%	0%	0%	0%	0%	0%
2	1	2%	0%	0%	0%	0%	8%
3	5	4%	10%	4%	8%	8%	33%
4[a]	10	17%	11%	16%	8%	7%	39%
5	15	9%	24%	18%	8%	8%	58%
6	20	7%	24%	20%	8%	8%	56%

[a]$CHCl_3$:HFIP (1:1) equivalent to 10 equiv HFIP

Conversions calculated by ^{1}H NMR spectroscopy using an internal standard (1,4-DNB). Conversions calculated from a single experiment.

Table 18. Optimisation of equivalents of HFIP.

Alternative fluorinated alcohol additives were examined in place of HFIP. Trifluoroethanol was observed to shut down reactivity, with small quantities of benzaldehyde **407** and diphenylacetaldehyde **408** being observed in the crude reaction mixture (Table 19, entry 2). The reaction was observed to proceed in the presence of perfluoro-*tert*-butanol but was not considered to be an improvement upon the standard conditions with HFIP (entry 3). Upon examining alternative conditions, the decision was made to continue with the initial conditions (entry 1).



Entry	Additive (fluorinated alcohol)	407	408	409	410	411	395
1	HFIP	17%	11%	16%	8%	7%	39%
2	trifluoroethanol	13%	4%	0%	0%	0%	14%
3	perfluoro-*tert*-butanol	4%	17%	9%	8%	14%	32%

Conversions calcuated from internal standard (1,4-DNB). Conversions calculated from a single experiment.

Table 19. Changing fluorinated alcohol additive.

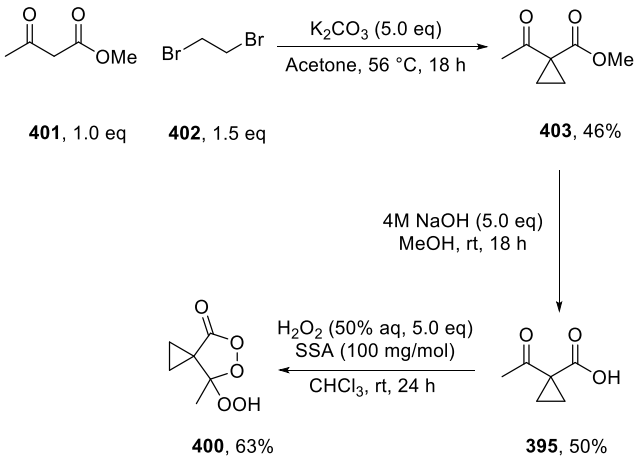
3.4 Conclusion and Future Work

The outcomes of this research may be put into perspective upon reflection of our intended aims;

1. To prepare peroxylactone **400**.
2. To investigate the reaction between peroxylactone **400** and alkenes.
3. To assess the potential of peroxylactone **400** for use in an organocatalytic dihydroxylation procedure.

1. To prepare peroxylactone 400

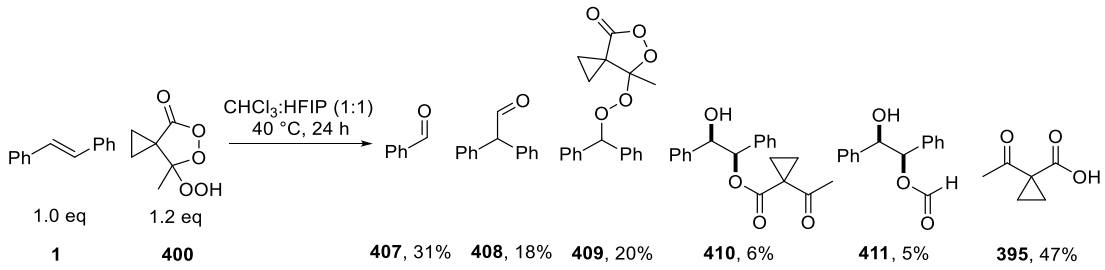
Peroxylactone **400** was synthesised from methyl acetoacetate **401** in three steps (Scheme 160). Methyl acetoacetate **401** was alkylated with 1,2-dibromoethane **402** to give compound **403** (46%), which yielded carboxylic acid **395**, upon basic hydrolysis (50%). Treatment of the acid **395**, with hydrogen peroxide in the presence of silica sulfuric acid (SSA)[84] gave peroxylactone **400** (63%) in a yield of 14% over three steps. Future work may examine improving the yield of peroxylactone **400**, along with the synthesis of alternative peroxylactone reagents.



Scheme 160. The synthesis of peroxylactone **400**.

2. To investigate the reaction between peroxylactone 400 and alkenes

A succesful investigation into the reaction of *trans*-stilbene **1** and peroxylactone **400** was conducted with all major products isolated and characterised (Scheme 161).



Scheme 161. The reaction of *trans*-stilbene **1** with peroxylactone **400**.

An extensive mechanistic investigation was conducted, proposing mechanisms of formation for each product observed, which was supported by experimental evidence. The common reaction intermediate, *trans*-stilbene oxide **413**, was successfully identified. The reaction of peroxylactone **400** with alternative alkenes was carried out and successfully analysed. An optimisation of reaction conditions was also conducted but failed to yield any clear results that showed an improvement in the amount of dihydroxylation product.

Future work will look toward examining further alkene substrates under the standard reaction conditions. 4-Methylstyrene was found to give a higher yield of dioxygenated products compared to *trans*-stilbene **1**. Therefore, screening various substituted styrenes **460** can be seen as a strategy to improve the yield of dioxygenated products. Cyclic and linear aliphatic alkenes (**461** and **462**) will also be tested and may hold information on shutting down migration pathways (such as the Meinwald rearrangement) by altering the migration ability of substitutents upon alkene substrates (Figure 25).

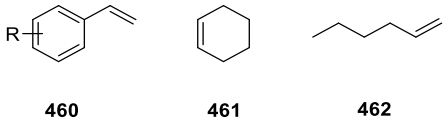
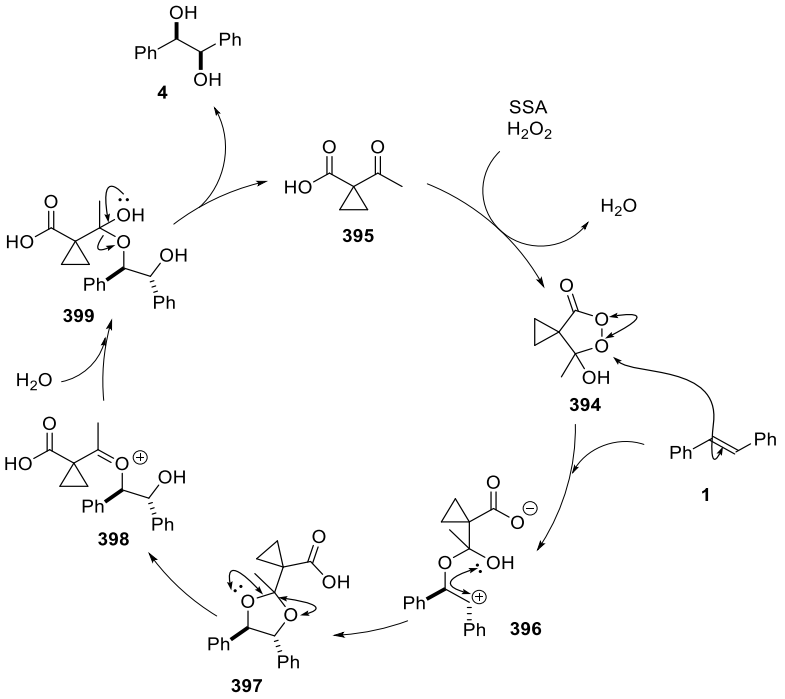


Figure 25. Alkene substrates to be examined in future work.

3. To assess the potential of peroxylactone 400 for use in an organocatalytic dihydroxylation procedure.

At the start of the investigation peroxylactone **394** was identified as a potential peroxide-based organocatalyst for the dihydroxylation of alkenes, with a theoretical catalytic cycle outlined in Scheme 162.



Scheme 162. Potential catalytic cycle for the dihydroxylation of *trans*-stilbene **1** with peroxylactone **394**.

Peroxylactone **400** was found to form under the reaction conditions instead of peroxylactone **394**. Therefore, the peroxylactone **400** was used throughout this investigation (Figure 26).

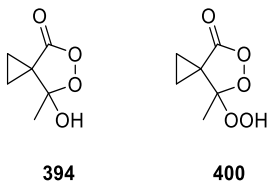
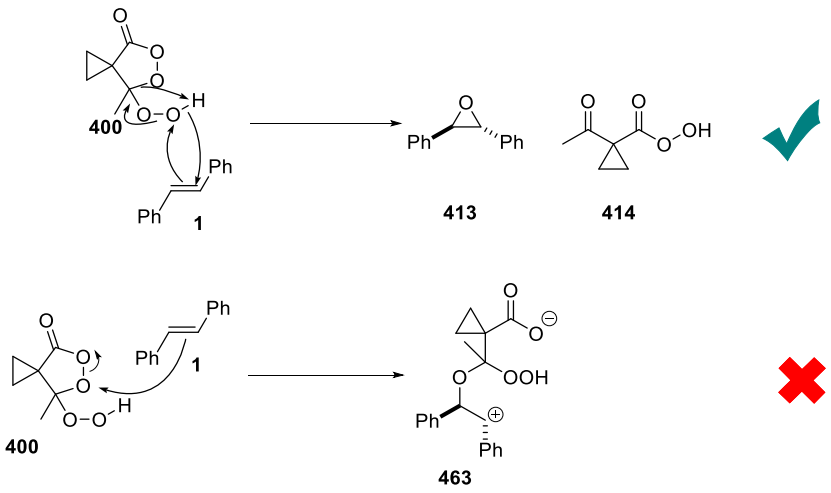


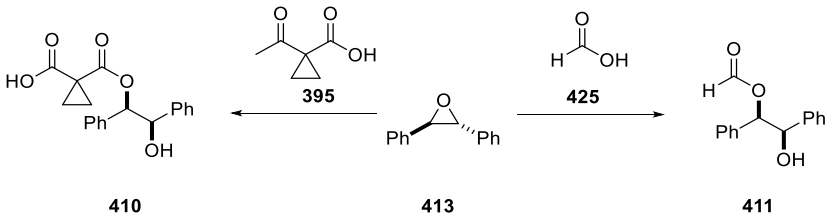
Figure 26. Peroxylactone **394** and peroxylactone **400**.

For the proposed catalytic reactivity to be observed (Scheme 163), peroxylactone **400** must react through the *endo*-peroxide functionality. Unfortunately, this reactivity was not observed and it was identified that the primary role of peroxylactone **400** in the reaction with *trans*-stilbene **1**, was to form *trans*-stilbene oxide **413** by reaction through the *exo*-peroxide. Therefore, the proposed catalytic cycle requires further design.



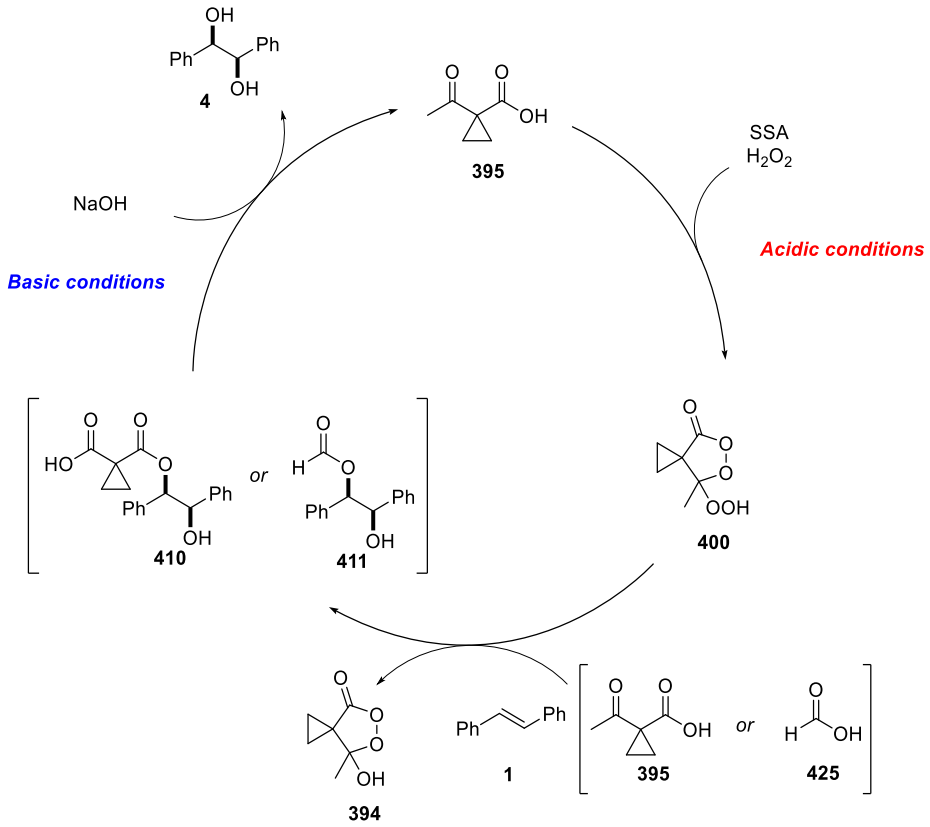
Scheme 163. Reactivity of peroxylactone **400** with *trans*-stilbene **1**.

It was observed that dihydroxylation intermediates ester **410** and formate **411** were formed as products of the reaction between peroxylactone **400** and *trans*-stilbene **1**. Both of these products were confirmed to form as a result of either acid **395** or formic acid **425** ring opening *trans*-stilbene oxide **413** stereoselectively (Scheme 164).



Scheme 164. The synthesis of ester **410** and formate **411**.

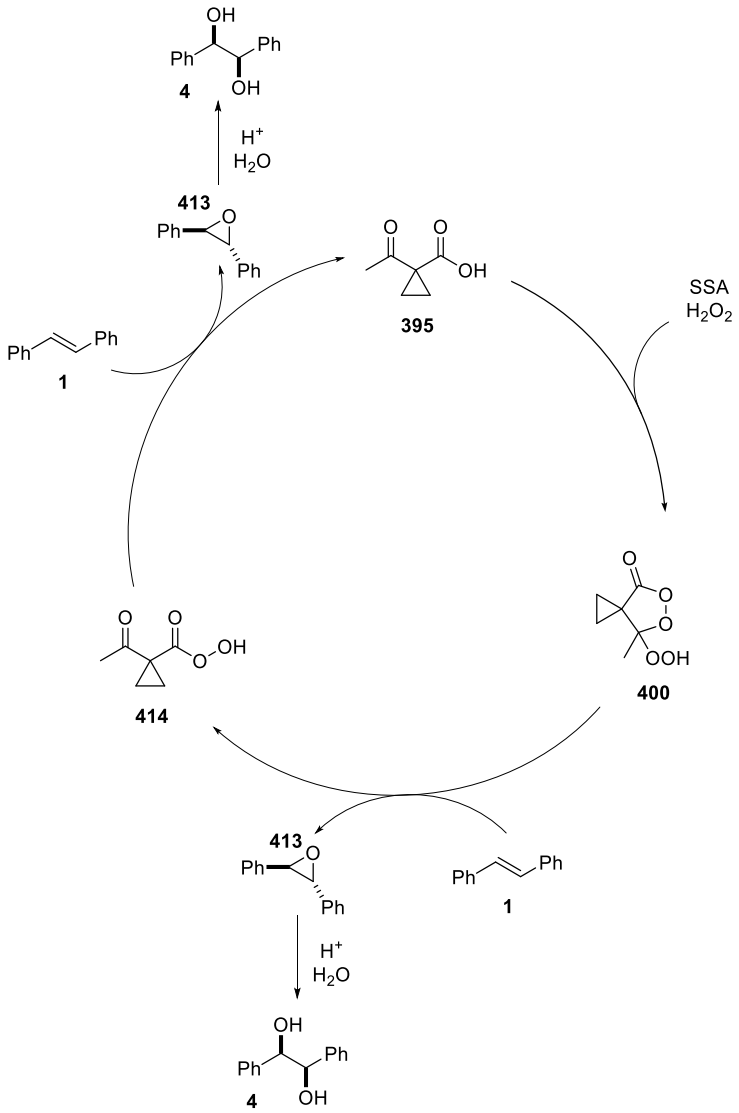
It can be concluded from the reported results, that peroxylactone **400** is unsuitable for use, as proposed, in a catalytic dihydroxylation procedure. As outlined in Section 3.2, for a catalytic system to be feasible the reaction would have to yield diol **4** without the need for basic hydrolysis. As can be seen from the catalytic cycle below, the isolated products **410** and **411** require basic hydrolysis to liberate the diol **4** (Scheme 165).



Scheme 165. Catalytic cycle for the dihydroxylation of *trans*-stilbene **1** with peroxylactone **400**.

A catalytic procedure may still be developed from the reaction of *trans*-stilbene **1** and peroxylactone **400**. Theoretically, peroxylactone may epoxidise two equivalents of *trans*-stilbene **1**, resulting in carboxylic acid **395**. In the presence of hydrogen peroxide, **395** may regenerate peroxylactone **400**, with selective opening of the epoxide **413** by water giving diol **4** (Scheme 166).

The drawback of such a hypothesis is the observed reactivity of epoxide **413** with carboxylic acid **395** to give ester **410**. In addition, the tendancy of epoxide **413** to undergo Meinwald rearrangement to diphenylacetaldehyde **408** would also be detrimental to this process. For the proposed catalytic cycle (Scheme 166) to be successful, conditions to avoid such reactivity would be required.



Scheme 166. Possible catalytic cycle for the reaction of *trans*-stilbene **1** with peroxylactone **400**.

Future work may find success in optimising this methodology towards the alternative product of alkylated peroxylactone species **409**. Aditionally, optimisation of the oxidative cleavage pathway to give benzaldehyde **407** selectively, may be of interest. In relation to developing a peroxide-mediated organocatalytic dihydroxylation procedure, it is believed an alternative peroxide is needed to that of peroxylactone **400**.

Chapter 4. Experimental

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4.1 General Procedures

Where appropriate, reactions were performed in flame-dried glassware under an argon atmosphere. Commercially available solvents and reagents were used without further purification or drying, unless stated otherwise.

Anhydrous tetrahydrofuran, dichloromethane, diethyl ether and toluene were obtained from an Innovative Technology Solvent Purification System.

Commercially available molecular sieves (3 Å) were placed into a round bottom flask and heated with a mantle set to 120 °C under vacuum for 2 h. The molecular sieves were allowed to cool over a 30 min period, after which time the activated molecular sieves (20% *w/v*) were placed into any solvent that could not be obtained from the Innovative Technology Solvent Purification System.

NMR spectra were recorded using a Bruker AV400 referenced to tetramethylsilane. Chemical shifts are reported in parts per million (ppm) and coupling constants (J) in Hz. Chemical shift data are given in units δ relative to the residual protic solvent where δ ($CDCl_3$) = 7.26 ppm, δ (DMSO) = 2.50 ppm. The following abbreviations are used for multiplicities: br s = broad singlet; s = singlet; d = doublet; t = triplet; m = multiplet; dd = doublet of doublets. ^{13}C chemical shift data were recorded with broadband proton decoupling and are given in units δ relative to the solvent where δ ($CDCl_3$) = 77.1 ppm, δ (DMSO) = 39.5 ppm.

IR spectra were recorded using a SHIMADZU IRAFFINITY-1 spectrophotometer with a Perkin Elmer Universal ATR (attenuated total reflectance) sampling accessory. Absorption frequencies are reported in wavenumbers (cm^{-1}).

Melting points were measured on a Stuart automatic melting point apparatus, SMP40.

Optical rotations were measured on a Perkin Elmer Polarimeter 341.

Reactions were monitored by TLC and were performed on aluminium backed Merck Silicagel 60 F254 plates. TLC plates were viewed under UV light and were visualised using ethanolic potassium permanganate solution.

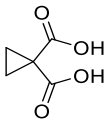
Column chromatography was carried out using 200–400 mesh silica gel or aluminium oxide (activated, neutral, Brockmann Activity I) using an eluent system stated within the relevant experimental section.

LCMS samples were carried out using Agilent technologies using a gradient of 5–95% acetonitrile/ H_2O. HRMS was performed externally by NMSF at Swansea University.

4.2 Chapter 2 - Alkene *Syn*- and *Anti*-Oxyamination With Malonoyl Peroxide

4.2.1 Peroxide synthesis

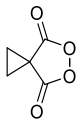
Cyclopropyl malonic acid 19[99]



19

To a round bottomed flask equipped with a mechanical stirrer was added benzyltriethylammonium chloride (56.5 g, 24.80 mmol) and 50% *aq.* sodium hydroxide (NaOH) solution (250.0 g in 500 mL H_2O). Diethyl malonate (38.0 mL, 24.80 mmol) and 1,2-dibromoethane (32.0 mL, 33.40 mmol) were added to the stirring heterogeneous mixture at room temperature. The reaction mixture was stirred for a further 2 h. The solution was transferred to a 2 L conical flask, diluted with water (3 × 50 mL) and cooled to < 15 °C. The solution was slowly quenched with HCl (12 M, 500 mL), keeping the temperature below 15 °C over a 2 h period. The aqueous phase was extracted with Et_2O (3 × 300 mL). The combined organic extracts were washed with brine (500 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude material was washed with petroleum ether and dried under reduced pressure to afford the *title compound* **19** as a white solid (13.8 g, 10.60 mmol, 42%), without further purification; mp 132–134 °C [Lit: 137–140 °C][99]; IR (ATR)/cm^{-1}: 3118, 2981, 1710, 1215; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.31 (s, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 171.7, 27.2, 16.2; Mass not observed.

Malonoyl peroxide 3[3]



3

Malonic acid **19** (4.00 g, 30.80 mmol) was dissolved in methanesulfonic acid (30 mL) and urea hydrogen peroxide (8.69 g, 92.40 mmol) was added in three portions. The resulting mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with iced water:ethyl acetate (1:1, 100 mL) and the layers were separated. The aqueous layer was then extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ (3 × 50 mL) and brine (50 mL) before being dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford malonoyl peroxide **3** (2.16 g, 17.40 mmol, 56%), as a white solid which was used without further purification; mp 91–93 °C [Lit: 90 °C][6]; IR (ATR)/cm^{-1}: 2956, 1860, 1187; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.10 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 172.3, 23.7, 19.9; Mass not observed.

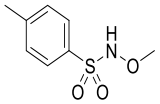
4.2.2 Nitrogen nucleophiles

***N*-(Methoxy)methanesulfonamide 147**[100]

147

Methanesulfonyl chloride (2.90 g, 25.00 mmol) was added to a solution of methoxylamine hydrochloride (2.00 g, 25.00 mmol) in a mixture of MeOH (15.0 mL) and H_2O (5.0 mL) at 0 °C. A solution of K_2CO_3 (3.45 g, 25.00 mmol) in 4.0 mL H_2O was then added dropwise and the reaction stirred for 15 min. The reaction was then warmed to room temperature and stirred for a further 20 min. The resulting precipitate was removed by filtration and washed with MeOH (2 × 1 mL). The combined filtrates were concentrated *in vacuo* to give a white powder. Purification by silica gel flash column chromatography (Et_2O:Petroleum ether 1:1) gave the *title compound* **147** (910 mg, 7.30 mmol, 29%), as a white solid; mp 92–94 °C [Lit: 95–98 °C][100]; IR (ATR)/cm^{-1}: 3216, 1402, 1316, 1145, 1052; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.85 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 65.5, 36.9; LRMS (ES + APCI) *m/z* calculated for $C_2H_7NO_3S$ 125.0, found 126.1 $[M+H]^+$.

***N*-(Methoxy)tosylsulfonamide 148**[101]



148

Methoxylamine hydrochloride (1.00 g, 12.00 mmol) was added to a biphasic mixture of K_2CO_3 (2.76 g, 20.00 mmol) in a 2:1 mixture of EtOAc (72 mL) and H_2O (36 mL). The resulting solution was cooled to 0 °C followed by dropwise addition of 4-toluenesulfonyl chloride (1.90 g, 10.00 mmol) dissolved in a minimal volume of EtOAc. The reaction mixture was warmed to room temperature and stirred for 18 h. The phases were then separated and the aqueous layer extracted with EtOAc (2 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the *title compound* **148** (640 mg, 3.20 mmol, 32%), as a white solid which was used without further purification; mp 110–112 °C [Lit: 109–111 °C][101]; IR (ATR)/cm^{-1}: 3218, 2988, 1331, 1162; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 6.98 (s, 1H), 3.79 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 145.1, 133.7, 129.9, 128.7, 65.2, 21.8; LRMS (ES + APCI) *m/z* calculated for $C_8H_{11}NO_3S$ 201.1, found 219.1 $[M+NH_4]^+$.

_N_-Methyl methanesulfonamide 151

151

Methanesulfonyl chloride (0.67 mL, 8.70 mmol) was added dropwise to a solution of methylamine (4.0 mL, 4.80 mmol, 33% wt. in EtOH) at 0 °C and stirred for 18 h. The mixture was concentrated *in vacuo* and the residue was diluted with CH_2Cl_2 (10 mL). The resulting solid was filtered off and the filtrate concentrated *in vacuo* to give the *title compound* **151** (420 mg, 3.90 mmol, 81%) as a clear oil which was used without further purification; IR (ATR)/cm^{-1}: 3292, 1301, 1128; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.95 (s, 3H), 2.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 39.1, 29.5; LRMS (ES + APCI) *m/z* calculated for $C_2H_7NO_2S$ 109.0, found 110.1 $[M+H]^+$.

***N*,*N*-*bis*(*p*-Toluenesulfonyl)amine 153**[100]

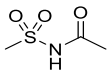
153

4-Toluenesulfonamide (3.40 g, 20.00 mmol) was added to a suspension of NaH (2.60 g, 60.00 mmol, 66% dispersion in mineral oil) in THF (200 mL) at 0 °C. The reaction was then warmed to room temperature and stirred for 1 h. 4-Toluenesulfonyl chloride (11.44 g, 60.00 mmol) was then added and the reaction mixture stirred for a further 24 h. The reaction was quenched with H_2O (300 mL), and the mixture was extracted with EtOAc (3 × 100 mL). The separated aqueous layer was brought to pH 1 with 2 M *aq.* HCl and extracted with EtOAc (3 × 100 mL). The combined organic layers were then washed with brine (2 × 300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the *title compound* **153** (670 mg, 2.10 mmol, 10%), as a white solid; mp 192–194 °C [Lit: 170.5–171.5 °C][100]; IR (ATR)/cm^{-1}: 3041, 2912, 1283, 1145; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.52 (d, *J* = 8.1 Hz, 4H), 7.14 (d, *J* = 8.1 Hz, 4H), 2.31 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 128.1, 126.1, 119.8, 116.7, 20.8; LRMS (ES + APCI) *m/z* calculated for $C_{14}H_{15}NO_4S_2$ 325.0, found 324.0 $[M-H]^-$.

General procedure for the synthesis of acyl sulfonamides – Route 1[102]

Acetic anhydride (2 eq) was added to a reaction vessel containing the appropriate sulfonamide (1 eq) and silica sulfuric acid (20 mg) and stirred at room temperature for 5 min. The solution was then diluted with EtOAc (2 mL) and H_2O (2 mL) before the resulting layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the desired acyl sulfonamide.

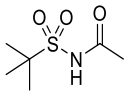
***N*-(Methylsulfonyl)acetamide 161**



161

Following General Procedure (route 1), methanesulfonamide (500 mg, 5.00 mmol) and acetic anhydride (1.0 mL, 10.00 mmol), gave acyl sulfonamide **161** (212 mg, 1.55 mmol, 31%) as a white solid; mp 88–90 °C [Lit: 97–98 °C][103]; IR (ATR)/cm^{-1}: 3116, 1688, 1335, 1147; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.38 (s, 1H), 3.22 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.0, 41.7, 23.8. LRMS (ES + APCI) *m/z* calculated for $C_3H_7NO_3S$ 137.0, found 138.0 $[M+H]^+$.

***N*-(*tert*-Butylsulfonyl)acetamide 167**



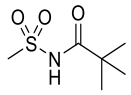
167

Following General Procedure (route 1), *tert*-butylsulfonamide (250 mg, 1.80 mmol) and acetic anhydride (0.5 mL, 3.60 mmol), gave acyl sulfonamide **167** (295 mg, 1.60 mmol, 88%) as a white solid; mp 108–110 °C; IR (ATR)/cm^{-1}: 3103, 2893, 1703, 1461, 1327, 1132. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.25 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.4, 62.3, 24.4, 23.8; LRMS (ES + APCI) *m/z* calculated for $C_6H_{13}NO_3S$ 179.1, found 180.1 $[M+H]^+$.

General procedure for the synthesis of acyl sulfonamides – Route 2[104]

To a flame-dried 3-neck flask under an atmosphere of argon was added sulfonamide (1 eq), DMAP (0.05 eq), Et_3N (2.5 eq) and anhydrous isopropyl acetate (0.5 M) and the mixture stirred for 0.5 h at 55 °C, forming a clear solution. Into a vial was added acid chloride (1.1 eq) and anhydrous toluene (0.3 M). The solution was drawn up into a 5 mL syringe and added to the sulfonamide/isopropyl acetate mixture *via* syringe pump over 1 h. After the addition was complete the mixture was stirred at 55 °C for 1 h. The reaction was then cooled to room temperature and quenched with distilled H_2O (1 mL) and 0.7 M HCl (17 mL). The resulting layers were separated, with the aqueous layer being washed with isopropyl acetate (15 mL). The organic phases were combined, dried ($MgSO_4$) and evaporated to dryness to give the desired product without further purification.

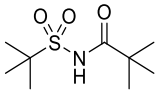
***N*-(Methylsulfonyl)pivalamide 164**



164

Following General Procedure (route 2), methanesulfonamide (475 mg, 5.00 mmol), DMAP (31 mg, 0.25 mmol), Et_3N (1.7 mL, 12.50 mmol), trimethylacetyl chloride (0.7 mL, 5.50 mmol), isopropyl acetate (11.0 mL) and toluene (4.0 mL), gave acyl sulfonamide **164** (698 mg, 3.90 mmol, 78%), without further purification; white solid; mp 124–126 °C; IR (ATR)/cm^{-1}: 3261, 1706, 1322, 1171; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.31 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 177.2, 41.6, 40.3, 27.0; LRMS (ES + APCI) *m/z* calculated for $C_6H_{13}NO_3S$ 179.1, found 180.1 $[M+H]^+$.

***N*-(*tert*-Butylsulfonyl)pivalamide 170**

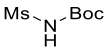


170

Following General Procedure (route 2), *tert*-butylsulfonamide (545 mg, 4.50 mmol), DMAP (31 mg, 0.25 mmol), Et_3N (1.6 mL, 11.25 mmol), trimethylacetyl chloride (0.6 mL, 5.00 mmol), isopropyl acetate (10.0 mL) and toluene (3.0 mL), gave acyl sulfonamide **170** (475 mg, 2.20 mmol, 49%), without further purification; white solid; mp 152–154 °C; IR (ATR)/cm^{-1}: 3274, 1723, 1322, 1141; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42 (br s, 1H),

1.49 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 167.2, 62.7, 38.9, 27.3, 24.8; LRMS (ES + APCI) *m/z* calculated for $C_9H_{19}NO_3S$ 221.1, found 222.1 $[M+H]^+$.

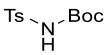
***tert*-Butyl (methylsulfonyl)carbamate 173**[105]



173

Methanesulfonamide (500 mg, 5.26 mmol) and DMAP (64 mg, 0.52 mmol) were charged to a flame dried flask, dissolved in dry CH_2Cl_2 (1 mL) and cooled to 0 °C. Et_3N (0.9 mL, 6.32 mmol) was then added followed by $(Boc)_2O$ (1.15 g, 5.26 mmol). The reaction was then allowed to warm to room temperature and stirred for 8 h. The resulting yellow mixture was concentrated and redissolved in EtOAc (2 mL). The solution was washed with 1 M HCl (2 × 2 mL) and the aqueous layer extracted with EtOAc (5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude mixture was then dissolved in hexane (20 mL) and refluxed for 1 h. The resulting mixture was filtered, the solids washed with hexane and dried under vacuum. The *title compound* **173** (630 mg, 3.23 mmol, 61%) was obtained as a white solid; mp 110–112 °C [Lit: 108–109 °C][106]; IR (ATR)/cm^{-1}: 3158, 1699, 1353, 1327, 1145; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.04 (br s, 1H), 3.27 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 149.7, 84.7, 41.4, 28.1; LRMS (ES + APCI) *m/z* calculated for $C_6H_{13}NO_4S$ 195.1, found 213.1 $[M+NH_4]^+$.

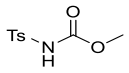
***O*-*tert*-butyl *N*-tosylcarbamate 176**[107]



176

To a solution of 4-toluenesulfonamide (500 mg, 2.92 mmol), DMAP (70 mg, 0.58 mmol), and $(Boc)_2O$ (703 mg, 3.21 mmol) in CH_2Cl_2 (6.0 mL) was added Et_3N (0.50 mL, 3.50 mmol). The mixture was stirred at room temperature for 18 h, before being cooled to 0 °C and diluted with 1 M *aq.* HCl (5 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic extracts were then washed with *aq.* $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 2:5) gave the *title compound* **176** (404 mg, 1.50 mmol, 51%), as a white solid; mp 114–116 °C [Lit:117–118 °C][108]; IR (ATR)/cm^{-1}: 3212, 2976, 1747, 1340, 1143; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.90 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.10 (br s, 1H), 2.45 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 149.2 144.9, 136.1, 129.7, 128.4, 84.2, 28.0, 21.8; LRMS (ES + APCI) *m/z* calculated for $C_{12}H_{17}NO_4S$ 271.1, found 289.0 $[M+NH_4]^+$.

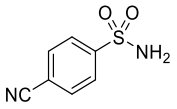
Methyl tosylcarbamate 179[109]



179

Triethylamine (6.3 mL, 44.00 mmol) was added dropwise to a solution of 4-toluenesulfonamide (2.56 g, 15.00 mmol) in dry CH_2Cl_2 (30.0 mL) at 0 °C and stirred for 10 min. Methyl chloroformate (1.3 mL, 16.50 mmol) was added dropwise and stirred for 0.5 h at 0 °C. The reaction was then allowed to warm to room temperature and stirred for a further 2 h. The reaction was then diluted with CH_2Cl_2 (20 mL), washed sequentially with 1 M *aq.* HCl (30 mL), H_2O (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude compound. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 3:10) gave the *title compound* **179** (1.3 g, 4.70 mmol, 31%), as a white solid; mp 96–98 °C [Lit:102–103°C][110]; IR (ATR)/cm^{-1}: 3229, 2998, 1759, 1450, 1348, 1156; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.93 (d, J = 8.5 Hz), 7.39 (s, 1H), 7.35 (d, J = 8.5 Hz, 2H), 3.70 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 150.9, 145.4, 135.5, 129.8, 128.6, 53.7, 21.8; LRMS (ES + APCI) *m/z* calculated for $C_9H_{11}NO_4S$ 229.0, found 230.0 $[M+H]^+$.

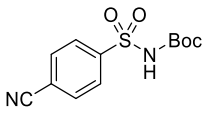
4-Cyanobenzenesulfonamide 464



464

4-Cyanobenzenesulfonyl chloride **248** (1.5 g, 7.46 mmol) was dissolved in ammonium hydroxide (10.0 mL) and heated to 100 °C for 1 h. The reaction mixture was cooled to room temperature, the solid filtered and washed with H_2O to give the title compound **464** as a white solid (1.1 g, 6.04 mmol, 81%), without further purification; mp 158–160 °C [Lit: 155–157 °C][111]; IR (ATR)/cm^{-1}: 3339, 3264, 2227, 1336, 1164; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.07 (d, *J* = 7.5 Hz, 2H), 7.98 (d, *J* = 7.5 Hz, 2H), 7.62 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 148.0, 133.2, 126.4, 117.8, 114.3; LRMS (ES + APCI) *m/z* calculated for $C_7H_6N_2O_2S$ 182.0, found 181.1 $[M-H]^-$.

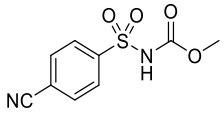
tert-Butyl ((4-cyanophenyl)sulfonyl)carbamate 249



249

To a solution of 4-cyanobenzenesulfonamide **464** (500 mg, 2.75 mmol), DMAP (67 mg, 0.55 mmol), and $(Boc)_2O$ (661 mg, 3.03 mmol) in CH_2Cl_2 (6.00 mL) was added Et_3N (0.45 mL, 3.30 mmol). The mixture was stirred at room temperature for 18 h, before being cooled to 0 °C and diluted with 1 M *aq.* HCl (5 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic extracts were then washed with *aq.* $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:1) gave the *title compound* **249** (353 mg, 1.25 mmol, 46%), as a white solid. mp 132–134 °C; IR (ATR)/cm^{-1}: 3136, 2989, 2865, 2249, 1740, 1437, 1351, 1141; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.15 (d, *J* = 8.7 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.33 (s, 1H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 148.7, 143.0, 132.9, 129.1, 117.7, 117.2, 85.2, 28.0; LRMS (ES + APCI) *m/z* calculated for $C_{12}H_{14}N_2O_4S$ 282.1, found 300.0 $[M+NH_4]^+$.

Methyl ((4-cyanophenyl)sulfonyl)carbamate 268



268

Triethylamine (1.8 mL, 13.00 mmol) was added dropwise to a solution of 4-cyanobenzenesulfonamide **464** (800 mg, 4.40 mmol) in dry CH_2Cl_2 (10.0 mL) at 0 °C and stirred for 10 min. Methyl chloroformate (0.4 mL, 4.80 mmol) was added dropwise and stirred for 0.5 h at 0 °C. The reaction was then allowed to warm to room temperature and stirred for a further 18 h. The reaction was then diluted with CH_2Cl_2 (20 mL), washed sequentially with 1 M *aq.* HCl (30 mL), H_2O (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude compound. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 3:10) gave the *title compound* **268** (306 mg, 1.30 mmol, 29%), as a white solid; mp 150–152 °C; IR (ATR)/cm^{-1}: 3196, 3093, 2240, 1751, 1457, 1361, 1162; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.23–8.14 (m, 2H), 7.91–7.81 (m, 2H), 7.45 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 150.5, 142.5, 133.0, 129.3, 118.0, 117.2, 54.1; LRMS (ES + APCI) *m/z* calculated for $C_9H_8N_2O_4S$ 240.0, found 239.0 $[M-H]^-$.

4.2.3 Standard procedure for the activation of 3 Å molecular sieves

Commercially available molecular sieves (3 Å) were placed into a round bottom flask and heated with a mantle set to 120 °C under vacuum for 2 h. The molecular sieves were allowed to cool down to room temperature over a 30 min period. Once cool the sieves were used in the oxyamination procedure.

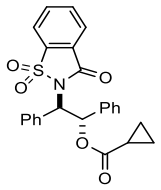
4.2.4 Initial results

4.2.4.1 General Procedure A: Initial screen of nitrogen nucleophiles

Malonoyl peroxide **3** (1.5 eq) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry CH_2Cl_2 (0.5 M, with respect to alkene) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (1.0 eq) and the appropriate nitrogen nucleophile (2.0 eq) (as shown in section 2.3.1), under an argon atmosphere. The mixture was stirred at the stated temperature for 24 h. The solvent was then removed under reduced pressure to yield the crude product. Purification by silica gel flash column chromatography using the appropriate solvent gave the desired compound.

Saccharin **84** employed as nucleophile

***Rel*-(1*S*,2*R*)-2-(1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)-1,2-diphenylethyl cyclopropanecarboxylate 158**



158

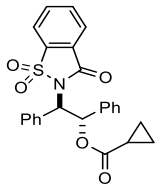
Following General Procedure A, *trans*-stilbene **1** (90 mg, 0.50 mmol), malonoyl peroxide **3** (115 mg, 0.90 mmol) and nucleophile **84** (183 mg, 1.00 mmol) were reacted in CH_2Cl_2 (1.0 mL) at 40 °C for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave the *N*-alkylated product **158** (65 mg, 145 μmol, 29%) as a white solid; mp 170–172 °C; IR (ATR)/cm^{-1}: 2924, 1727, 1338, 1257, 1158; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.95–7.91 (m, 1H), 7.78–7.71 (m, 5H), 7.55–7.50 (m, 2H), 7.43–7.40 (m, 3H), 7.36–7.30 (m, 3H), 7.16 (d, *J* = 10.2 Hz, 1H), 5.49 (d, *J* = 10.2 Hz, 1H), 1.50–1.44 (m, 1H), 0.90–0.81 (m, 1H), 0.75–0.63 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.0, 158.7, 137.3, 136.9, 135.1, 134.8, 134.3, 129.6, 129.0, 128.9, 128.6, 128.4, 127.9, 126.8, 125.2, 120.9, 72.8, 60.8, 13.1, 8.5, 8.3; LRMS (ES + APCI) *m/z* calculated for $C_{25}H_{21}NO_5S$ 447.1, found 465.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{25}H_{25}N_2O_5S$ 465.1479, found 465.1474 $[M+NH_4]^+$.

Note that *O*-alkylated product **159** was not isolated during the initial screening process.

4.2.4.2 Initial experiment using saccharin 84

Malonoyl peroxide **3** (115 mg, 0.90 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry CH_2Cl_2 (0.5 M, with respect to alkene) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (90 mg, 0.50 mmol) and saccharin **84** (183 mg, 1.00 mmol), under an argon atmosphere. The mixture was stirred at the stated temperature for 24 h. The solvent was then removed under reduced pressure to yield the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave the *N*-alkylated product **158** (87 mg, 195 μmol, 39%) as a white solid, the *O*-alkylated product **159** (72 mg, 160 μmol, 32%) as a white solid and 7-membered ring species **7** (17 mg, 55 μmol, 11%) as a white solid.

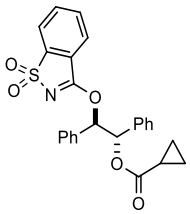
***Rel*-(1*S*,2*R*)-2-(1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)-1,2-diphenylethyl cyclopropanecarboxylate 158**



158

N-alkylated product **158** (87 mg, 195 μmol, 39%) (see p141 for characterisation)

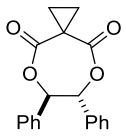
Co-product - *Rel*-(1*S*,2*R*)-2-((1,1-dioxidobenzo[*d*]isothiazol-3-yl)oxy)-1,2-diphenylethyl cyclopropanecarboxylate 159



159

O-alkylated co-product **159** (72 mg, 160 μmol, 32%); white solid; mp 142–144 °C; IR (ATR)/cm^{-1}; 3032, 2902, 1736, 1619, 1175; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.82 (m, 1H), 7.79–7.70 (m, 3H), 7.36–7.28 (m, 6H), 7.25–7.18 (m, 4H), 6.45 (d, *J* = 4.7 Hz, 1H), 6.34 (d, *J* = 4.7 Hz, 1H), 1.70–1.60 (m, 1H), 1.03–0.81 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 168.4, 143.9, 134.9, 134.3, 133.8, 133.6, 129.3, 128.9, 128.5, 128.4, 128.3, 127.7, 127.0, 123.3, 122.2, 84.2, 76.2, 13.1, 9.1, 8.9; LRMS (ES + APCI) *m/z* calculated for $C_{25}H_{21}NO_5S$ 447.1, found 465.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{25}H_{25}N_2O_5S$ 465.1479, found 465.1476 $[M+NH_4]^+$.

***Rel*-(*6R,7R*)-6,7-diphenyl-5,8-dioxaspiro[2.6]nonane-4,9-dione 7**



7

7-membered ring co-product **7** (17 mg, 55 μmol, 11%); white solid; mp 136–138 °C; IR (ATR)/cm^{-1}; 2959, 1752, 1732, 1277, 1213; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.18 (m, 6H) , 7.08–7.02 (m, 4H), 5.81 (s, 2H), 2.12–2.07 (m, 2H), 1.89–1.84 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 134.9, 129.3, 128.7, 127.4, 84.8, 29.9, 23.4; Mass not observed.

4.2.4.3 Optimisation of reaction conditions – Effect of solvent

Malonoyl peroxide **3** (115 mg, 0.90 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. The appropriate solvent (0.5 M, with respect to alkene) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (90 mg, 0.50 mmol) and saccharin **84** (183 mg, 1.00 mmol), under an argon atmosphere. The mixture was stirred at 40 °C for 24 h. A small portion of the crude reaction mixture was diluted in $CDCl_3$ and a ^{1}H NMR experiment performed. The integrations of the δ 5.49 (for **158**) and δ 6.34 (for **159**) signals were compared to give the reported ratios, as reported in section 2.3.2.2.

4.2.4.4 Optimisation of reaction conditions – Effect of temperature

Malonoyl peroxide **3** (115 mg, 0.90 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (0.5 M, with respect to alkene) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (90 mg, 0.50 mmol) and saccharin **84** (183 mg, 1.00 mmol), under an argon atmosphere. The mixture was stirred at the stated temperature for 24 h. A small portion of the crude reaction mixture was diluted in $CDCl_3$ and a ^{1}H NMR experiment performed. The integrations of the δ 5.49 (for **158**) and δ 6.34 (for **159**) signals were compared to give the reported ratios, as reported in section 2.3.2.2.

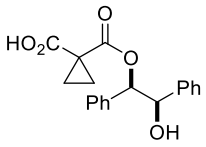
4.2.4.5 Optimisation of reaction conditions – Effect of saccharin salts

Malonoyl peroxide **3** (115 mg, 0.90 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (0.5 M, with respect to alkene) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (90 mg, 0.50 mmol) and sodium

saccharin **160** (205 mg, 1.00 mmol), under an argon atmosphere. The mixture was stirred at 40 °C for 24 h. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy revealed *syn*-deoxygenated product **10** to be the sole product, which was not quantified or isolated. Qualitative analysis of **10** was achieved by comparison to literature characterisation.

Literature characterisation

1-(((*rel*-1*S*,2*R*)-2-Hydroxy-1,2-diphenylethoxy)carbonyl)cyclopropanecarboxylic acid 10[46]



10

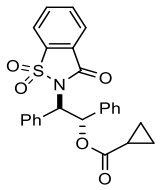
colourless solid; mp 109–110 °C; IR (ATR)/cm^{-1}; 3458, 3064, 3032, 2960, 2918, 1757, 1734, 1207, 1169, 1059; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 6H) , 7.24–7.22 (m, 4H), 5.88 (d, *J* = 6.7 Hz, 1H), 4.91 (d, *J* = 6.7 Hz, 1H), 1.77–1.64 (m, 3H), 1.52–1.46 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) 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 *m/z* calculated for $C_{19}H_{19}O_5$ 327.1227, found 327.1231 $[M+H]^+$.

4.2.5 Screening of nitrogen nucleophiles

4.2.5.1 General procedure B: *anti*-oxyamination using malonoyl peroxide

Malonoyl peroxide **3** (1.8 eq) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (0.5 M, with respect to alkene) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing alkene (1.0 eq) and the appropriate nitrogen nucleophile (2.0 eq), under an argon atmosphere. The mixture was stirred at the stated temperature for 24 h. The solvent was then removed under reduced pressure to yield the crude product. Purification by silica gel flash column chromatography using the appropriate solvent gave the desired compound.

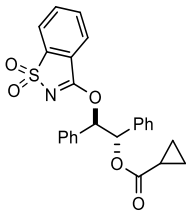
Rel-(1_S_,2_R_)-2-(1,1-dioxido-3-oxobenzo[_d_]isothiazol-2(3_H_)-yl)-1,2-diphenylethyl cyclopropanecarboxylate 158



158

Following General Procedure B, *trans*-stilbene **1** (90 mg, 0.50 mmol), malonoyl peroxide **3** (115 mg, 0.90 mmol) and nucleophile **84** (183 mg, 1.00 mmol) were reacted in $CHCl_3$ (1.0 mL) at 40 °C for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave the *N*-alkylated product **158** (68 mg, 0.15 mmol, 30%) (see p141 for characterisation)

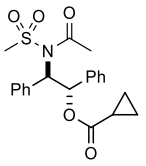
Co-product - _Rel_-(1_S_,2_R_)-2-((1,1-dioxidobenzo[_d_]isothiazol-3-yl)oxy)-1,2-diphenylethyl cyclopropanecarboxylate 159



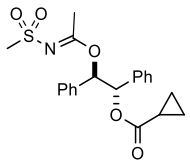
159

O-alkylated co-product **159** (46 mg, 0.10 mmol, 20%) (see p142 for characterisation)

Rel-(1_S_,2_R_)-2-(_N_-(methylsulfonyl)acetamido)-1,2-diphenylethyl cyclopropanecarboxylate 162 and _Rel_-(1_S_,2_R_)-2-((_E_)-1-((methylsulfonyl)imino)ethoxy)-1,2-diphenylethyl cyclopropanecarboxylate 163



162

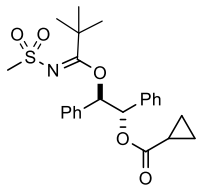


163

Following General Procedure B, *trans*-stilbene **1** (131 mg, 0.73 mmol), malonoyl peroxide **3** (168 mg, 1.31 mmol) and nucleophile **161** (200 mg, 1.46 mmol) were reacted in $CHCl_3$ (1.5 mL) at 40 °C for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave *N*-alkylated product **162** and *O*-alkylated co-product **163** in a 1:1 mixture (116 mg, 0.29 mmol, 38%) as a clear oil; IR (ATR)/cm^{-1}: 3015, 1723, 1699, 1351, 1169; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) *isomer* **162** and *isomer* **163** 7.56 (d, *J* = 7.3

Hz, 2H), 7.54–7.48 (m, 2H), 7.42–7.27 (m, 11H), 7.22–7.10 (m, 5H), 7.00 (d, *J* = 10.4 Hz, 1H), 6.14 (d, *J* = 5.3 Hz, 1H), 6.06 (d, *J* = 5.3 Hz, 1H), 6.01 (d, *J* = 10.4 Hz, 1H), 2.87 (s, 3H), 2.42 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 1.67–1.58 (m, 1H), 1.50–1.42 (m, 1H), 0.97–0.81 (m, 5H), 0.75–0.63 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) *isomer* **162** and *isomer* **163** 173.5, 173.2, 172.4, 170.4, 138.5, 136.4, 135.7, 135.1, 129.1, 129.1, 128.9, 128.8, 128.7, 128.5, 128.3, 128.3, 128.3, 127.9, 127.7, 127.6, 80.7 76.0, 73.3, 63.9, 42.7, 42.0, 25.9, 20.6, 13.2, 13.1, 8.8, 8.8, 8.5, 8.4; LRMS (ES + APCI) *m/z* calculated for $C_{21}H_{23}NO_5S$ 401.1, found 419.0 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{21}H_{27}N_2O_5S$ 419.1635, found 419.1632 $[M+NH_4]^+$.

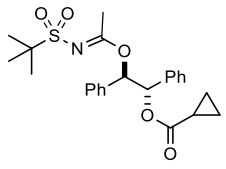
Rel-(1*S*,2*R*)-2-((*E*)-2,2-dimethyl-1-((methylsulfonyl)imino)propoxy)-1,2-diphenylethyl cyclopropanecarboxylate 166



166

Following General Procedure B, *trans*-stilbene **1** (45 mg, 0.25 mmol), malonoyl peroxide **3** (58 mg, 0.45 mmol) and nucleophile **164** (90 mg, 0.50 mmol) were reacted in $CHCl_3$ (0.5 mL) for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 15:85) gave **166** (66 mg, 0.15 mmol, 60%) as a clear oil; IR (ATR)/cm^{-1}: 2922, 1731, 1612, 1307, 1138; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) δ 7.32–7.27 (m, 5H), 7.24–7.15 (m, 3H), 7.10–7.06 (m, 2H), 6.12 (d, *J* = 5.7 Hz, 1H), 5.88 (d, *J* = 5.7 Hz, 1H), 2.79 (s, 3H), 1.65–1.59 (m, 1H), 1.32 (s, 9H), 0.95–0.80 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 175.4, 173.4, 135.9, 135.8, 128.7, 128.6, 128.3, 128.3, 127.8, 127.2, 80.9, 76.3, 44.0, 41.1, 27.6, 13.1, 8.8, 8.7; LRMS (ES + APCI) *m/z* calculated for $C_{24}H_{29}NO_5S$ 443.2, found 461.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{24}H_{29}NNaO_5S$ 466.1659, found 466.1652 $[M+Na]^+$.

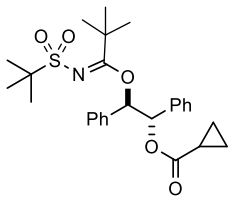
***Rel*-(1*S*,2*R*)-2-((*E*)-1-((*tert*-butylsulfonyl)imino)ethoxy)-1,2-diphenylethyl cyclopropanecarboxylate 169**



169

Following General Procedure B, *trans*-stilbene **1** (45 mg, 0.25 mmol), malonoyl peroxide **3** (58 mg, 0.45 mmol) and nucleophile **167** (89 mg, 0.50 mmol) were reacted in $CHCl_3$ (0.5 mL) at 40 °C for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave *O*-alkylated product **169** (37 mg, 0.08 mmol, 33%) as a clear oil; IR (ATR)/cm^{-1}: 2926, 1732, 1623, 1284; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34–7.27 (m, 6H), 7.18–7.10 (m, 2H), 7.11–7.01 (m, 2H), 6.08 (d, *J* = 5.1 Hz, 1H), 5.93 (d, *J* = 5.1 Hz, 1H), 2.45 (s, 3H), 1.68–1.59 (m, 1H), 1.16 (s, 9H), 0.96–0.80 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.5, 172.9, 135.6, 135.5, 128.6, 128.3, 128.3, 127.7, 127.3, 80.8, 76.4, 58.7, 23.7, 20.6, 13.2, 8.9, 8.8 (1 carbon missing); LRMS (ES + APCI) *m/z* calculated for $C_{24}H_{29}NO_5S$ 443.2, found 461.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{24}H_{33}N_2O_5S$ 461.2105, found 461.2100 $[M+NH_4]^+$.

***Rel*-(1*S*,2*R*)-2-((*E*)-1-((tert-butylsulfonyl)imino)-2,2-dimethylpropoxy)-1,2-diphenylethyl cyclopropanecarboxylate 172**

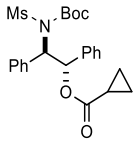


172

Following General Procedure B, *trans*-stilbene **1** (90 mg, 0.50 mmol), malonoyl peroxide **3** (115 mg, 0.90 mmol) and nucleophile **170** (221 mg, 1.00 mmol) in $CHCl_3$ (1.0 mL) were reacted at 40 °C for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:10) gave the *O*-alkylated product **172** (54 mg, 0.11 mmol, 22%) as a clear oil; IR (ATR)/cm^{-1}: 2951, 1729, 1612, 1290, 1171, 1121; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30–7.27 (m, 5H), 7.26–7.24 (m, 1H), 7.14–7.09 (m, 2H), 7.06-7.04 (m, 2H), 6.08 (d, *J* = 5.1 Hz, 1H), 6.05 (d, *J* = 5.1 Hz, 1H), 1.65–1.63 (m, 1H), 1.37 (s, 9H), 1.20 (s, 9H), 0.98–0.92 (m, 2H), 0.92–0.81 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 176.6, 173.5, 135.7, 135.5, 128.6, 128.6, 128.4, 128.2, 127.8, 126.9, 80.0, 77.4, 59.4, 41.6, 27.9, 24.1, 13.1,

8.9, 8.8; LRMS (ES + APCI) *m/z* calculated for $C_{27}H_{35}NO_5S$ 485.2, found 503.0 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{27}H_{39}N_2O_5S$ 503.2579, found 503.2567 $[M+NH_4]^+$.

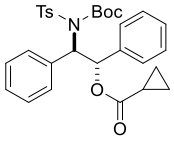
Rel-(1*S*,2*R*)-2-(*N*-(*tert*-butoxycarbonyl)methylsulfonamido)-1,2-diphenylethyl cyclopropanecarboxylate 174



174

Following General Procedure B, *trans*-stilbene **1** (45 mg, 0.25 mmol), malonoyl peroxide **3** (58 mg, 0.45 mmol) and nucleophile **173** (98 mg, 0.50 mmol) were reacted in $CHCl_3$ (0.5 mL) at 40 °C for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 15:85) gave the *N*-alkylated product **174** (45 mg, 0.10 mmol, 39%) as a white solid; mp 88–90 °C; IR (ATR)/cm^{-1}: 2928, 1725, 1351, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55–7.46 (m, 4H), 7.44–7.28 (m, 6H), 6.82 (d, *J* = 10.2 Hz, 1H), 5.88 (d, *J* = 10.2 Hz, 1H), 2.30 (s, 3H), 1.51–1.46 (m, 1H), 1.40 (s, 9H), 0.97–0.89 (m, 1H), 0.78–0.68 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.5, 150.7, 138.6, 137.4, 129.0, 128.9, 128.4, 128.2, 128.0, 127.9, 85.4, 73.6, 62.0, 40.9, 28.1, 13.3, 8.6, 8.5; LRMS (ES + APCI) *m/z* calculated for $C_{24}H_{29}NO_6S$ 459.2, found 477.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{24}H_{29}NNaO_6S$ 482.1608, found 482.1603 $[M+Na]^+$.

Rel-(1*S*,2*R*)-2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-diphenylethyl cyclopropanecarboxylate 177

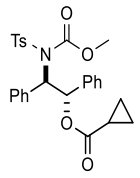


177

Following General Procedure B, alkene **1** (90 mg, 0.50 mmol), malonoyl peroxide **3** (115 mg, 0.90 mmol), nucleophile **176** (271 mg, 1.0 mmol), and $CHCl_3$ (1.0 mL). Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave the *N*-alkylated product **177** (131 mg, 0.25 mmol, 49%) as a white solid; mp136–138 °C; IR (ATR)/cm^{-1}: 2978, 1723, 1344, 1147; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (d, *J* = 7.1 Hz, 2H), 7.62–7.56 (m, 2H), 7.44–7.31 (m, 6H), 7.06 (d, *J* = 10.4 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 6.05 (d, *J* = 10.4 Hz, 1H), 2.32 (s, 3H), 1.49–1.39 (m, 1H), 1.16 (s, 9H), 0.90–0.81 (m, 1H), 0.74–0.58 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.2, 150.5, 143.7, 138.3,

137.5, 137.2, 129.3, 129.0, 128.8, 128.5, 128.5, 128.4, 128.2, 128.0, 84.9, 74.1, 62.4, 27.9, 21.6, 13.3, 8.3, 8.2; LRMS (ES + APCI) *m/z* calculated for $C_{30}H_{33}NO_6S$ 535.2, found 553.1 $[M+NH_4]^+$.

***Rel*-(1*S*,2*R*)-2-((*N*-(methoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-diphenylethyl cyclopropanecarboxylate 180**



180

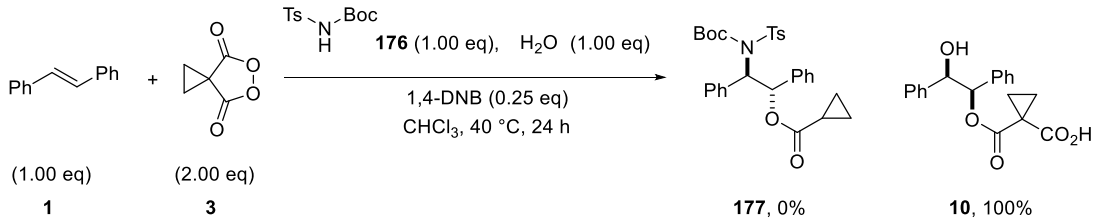
Following General Procedure B, *trans*-stilbene **1** (90 mg, 0.50 mmol), malonoyl peroxide **3** (115 mg, 0.90 mmol) and nucleophile **179** (229 mg, 1.00 mmol) were reacted in $CHCl_3$ (1.0 mL) at 40 °C for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave the *N*-alkylated product **180** (115 mg, 0.23 mmol, 45%) as a white solid; mp 152–154 °C; IR (ATR)/cm^{-1}: 3259, 1738, 1344, 1266, 1162; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68–7.60 (m, 2H), 7.55–7.50 (m, 2H), 7.44–7.29 (m, 6H), 7.00 (d, *J* = 10.5 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.10 (d, *J* = 10.5 Hz, 1H), 3.54 (s, 3H), 2.33 (s, 3H), 1.48–1.38 (m, 1H), 0.90–0.81 (m, 1H), 0.74–0.58 (m, 3H); ^{13}C NMR (101 MHz, CDCl3) δ (ppm) 173.2, 152.4, 144.2, 138.0, 136.9, 136.3, 129.3, 129.1, 129.0, 128.9, 128.5, 128.5 128.4, 128.2, 73.6, 62.7, 53.6, 21.7, 13.2, 8.4, 8.2; LRMS (ES + APCI) *m/z* calculated for $C_{27}H_{27}NO_6S$ 493.2, found 511.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{27}H_{31}N_2O_6S$ 511.1897, found 511.1890 $[M+NH_4]^+$.

4.2.6 Reaction monitoring experiment – Side reaction investigation

Malonoyl peroxide **3** (115 mg, 0.9 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (1.0 mL) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (90 mg, 0.5 mmol), nitrogen nucleophile **176** (271 mg, 1.0 mmol) and 1,4-dinitrobenzene (21 mg, 12.5 μmol) under an argon atmosphere. The mixture was stirred at 40 °C for 24 h. Reaction samples were taken at regular intervals and analysed by ^{1}H NMR spectroscopy. Results reported in Section 2.3.3.

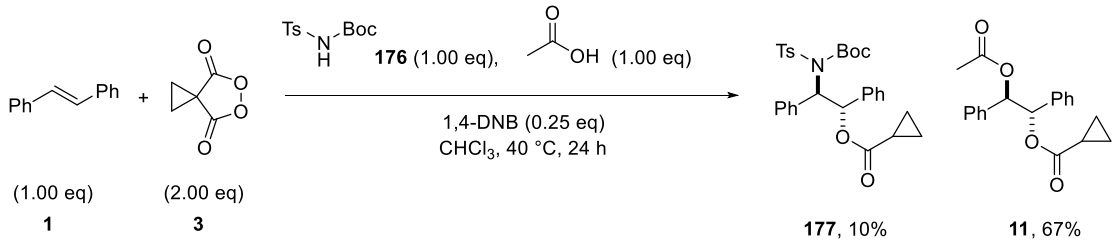
4.2.7 Side reaction hypothesis experiments

Experiment 1



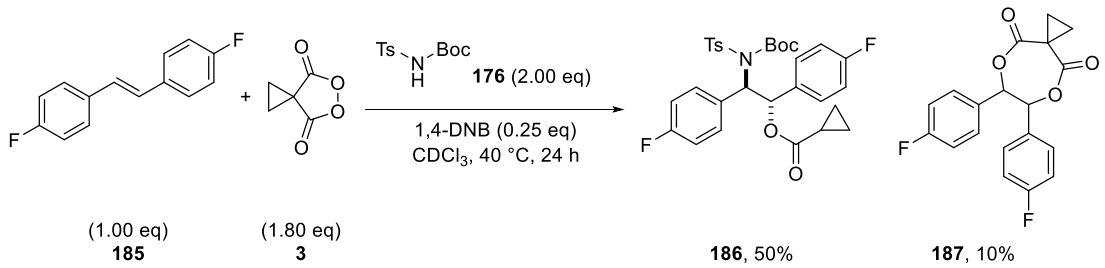
Malonoyl peroxide **3** (128 mg, 1.0 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (1.0 mL) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (90 mg, 0.5 mmol), nitrogen nucleophile **176** (136 mg, 0.5 mmol), water (9 μL, 0.5 mmol) and 1,4-dinitrobenzene (21 mg, 12.5 μmol) under an argon atmosphere. The mixture was stirred at 40 °C for 24 h. The crude reaction mixture was analysed by ^{1}H NMR spectroscopy. Results reported in section 2.3.3.2.

Experiment 2



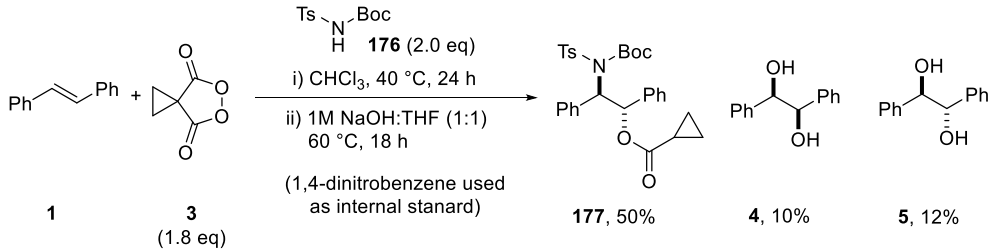
Malonoyl peroxide **3** (128 mg, 1.0 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (1.0 mL) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (90 mg, 0.5 mmol), nitrogen nucleophile **176** (136 mg, 0.5 mmol), acetic acid (29 μL, 0.5 mmol) and 1,4-dinitrobenzene (21 mg, 12.5 μmol) under an argon atmosphere. The mixture was stirred at 40 °C for 24 h. The crude reaction mixture was analysed by ^{1}H NMR spectroscopy. Results reported in section 2.3.3.2.

Experiment 3



Malonoyl peroxide **3** (128 mg, 0.9 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (1.0 mL) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing 4,4'-difluoro-*trans*-stilbene **185** (108 mg, 0.5 mmol), nitrogen nucleophile **176** (271 mg, 1.0 mmol) and 1,4-dinitrobenzene (21 mg, 12.5 μmol) under an argon atmosphere. The mixture was stirred at 40 °C for 24 h. The crude reaction mixture was analysed by ^{1}H NMR spectroscopy. Results reported in section 2.3.3.2. For characterisation of **186**, see p158. Compound **187** was not isolated, characterisation of **187** based upon similarities with 7-memebred ring **7** within the ^{1}H NMR spectrum (see p143).

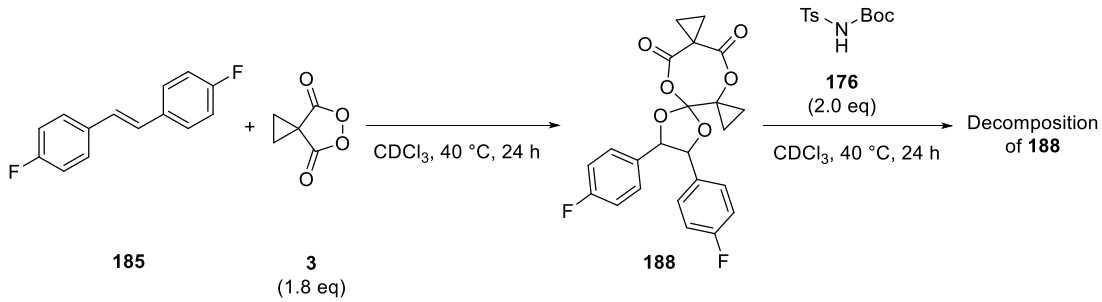
Experiment 4



Malonoyl peroxide **3** (128 mg, 0.9 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (1.0 mL) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (90 mg, 0.5 mmol), nitrogen nucleophile **176** (271 mg, 1.0 mmol) under an argon atmosphere. The mixture was stirred at 40 °C for 24 h. The solvent was removed *in vacuo* and the crude material dissolve in a mixture of 1 M $NaOH_{(aq)}$:THF (1:1 (0.1 M)). The resulting solution was stirred at 60 °C for 18 h. The reaction was then cooled to room temperature and diluted with EtOAc:H_2O (1:1). The layers were separated and the aqueous layer further extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material and 1,4-dinitrobenzene (21 mg, 12.5 μmol) were then dissolved in $CDCl_3$ (1.0 mL) and analysed *via* ^{1}H NMR spectroscopy. For characterisation of **177** see p155. *Syn*-diol **4** and *anti*-diol **5** were

identified by ^{1}H NMR spectroscopy and compared with literature values.[3,4] Results reported in Section 2.3.3.

Experiment 5

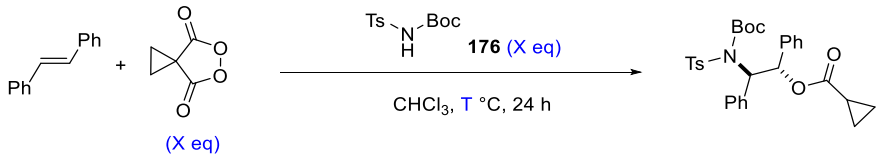


Malonoyl peroxide **3** (128 mg, 0.9 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (1.0 mL) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing 4,4'-difluoro-*trans*-stilbene **185** (108 mg, 0.5 mmol) under an argon atmosphere. The mixture was stirred at 40 °C for 24 h, after which a small portion of reaction mixture was removed for analysis by NMR spectroscopy. Nitrogen nucleophile **176** (271 mg, 1.0 mmol) was then added and the reaction stirred for a further 24 h at 40 °C. The crude reaction mixture was analysed by ^{1}H NMR and ^{19}F NMR spectroscopy. Results reported in section 2.3.3.2. Identification of orthoester **188** based upon comparison to literature values for orthoester **184**.[46]

4.2.8 Optimisation of oxyamination with *O-tert*-butyl *N*-tosylcarbamate

4.2.8.1 Primary optimisation

Malonoyl peroxide **3** was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (1.0 mL) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (90 mg, 0.5 mmol) and nitrogen nucleophile **176** under an argon atmosphere. The mixture was stirred at the stated temperature for 24 h. Conversion calculated by HPLC analysis.



1 **3** **177**

Entry	3 (eq)	176 (eq)	Temp (°C)	Conv[a] (%)
1	1.8	2	40	49[b]
2	1.8	2	rt	46
3	1.8	2	60	48
4	3	2	40	32
5	1	2	40	38
6	1.8	3	40	45
7	1.8	1	40	45[b]
8	1.8	0.5	40	48[b]

[a]Determined by HPLC analysis. [b]Isolated yield after chromatographic purification.

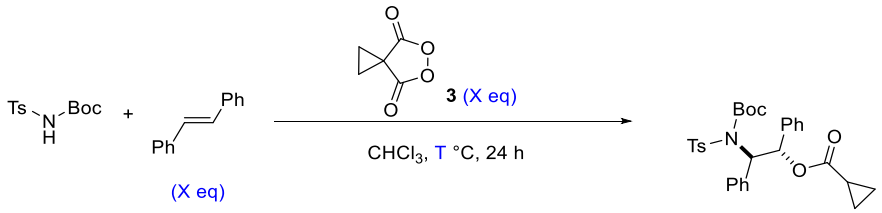
The experiment corresponding to entry 1 was isolated by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) which gave the *N*-alkylated product **177** (131 mg, 0.25 mmol, 49%). See p155 for characterisation.

The experiment corresponding to entry 7 was isolated by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) which gave the *N*-alkylated product **177** (123 mg, 0.23 mmol, 45%). See p155 for characterisation.

The experiment corresponding to entry 8 was isolated by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) which gave the *N*-alkylated product **177** (128 mg, 0.24 mmol, 48%). See p155 for characterisation.

4.2.8.2 Secondary optimisation

Malonoyl peroxide **3** was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (1.0 mL) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** and nitrogen nucleophile **176** (136 mg, 0.5 mmol) under an argon atmosphere. The mixture was stirred at the stated temperature for 24 h. Conversion calculated by HPLC analysis.



176 1 177

Entry	1 (eq)	3 (eq)	Conc (M)	Conv[a] (%)
1	2	3.6	0.25	96[b]
2	2	3	0.25	84
3	2	2	0.25	66
4	2	1	0.25	36
5	1.5	3.6	0.25	74
6	1	3.6	0.25	40
7	2	3.6	0.5	60

[a]Determined by HPLC analysis. [b]Isolated yield after chromatographic purification.

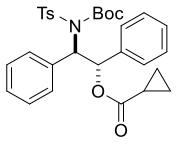
The experiment corresponding to entry 1 was isolated by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) which gave the *N*-alkylated product **177** (251 mg, 0.48 mmol, 96%). See p155 for characterisation.

4.2.9 *Anti*-oxyamination substrate scope

4.2.9.1 General procedure C: *anti*-oxyamination using malonoyl peroxide with nucleophile as limiting reagent

Malonoyl peroxide **3** (3.6 eq) was placed into a flame dried reaction vessel containing 3 Å molecular sieves (activated under N_2). Dry $CHCl_3$ (0.25 M, with respect to nitrogen nucleophile) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing alkene (2 eq) and the appropriate nitrogen nucleophile (1 eq), under an argon atmosphere. The mixture was stirred at 40 °C for 24 h. The solvent was then removed under reduced pressure to yield the crude product. Purification by column chromatography using the appropriate solvent gave the desired compound.

***Rel*-(1*S*,2*R*)-2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-diphenylethyl cyclopropanecarboxylate 177**



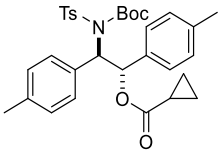
177

Following General Procedure C, *trans*-stilbene **1** (180 mg, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at rt for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave the *N*-alkylated product **177** (253 mg, 0.48 mmol, 97%) as a white solid; mp 136–138 °C; IR (ATR)/cm^{-1}: 2978, 1723, 1344, 1147; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (d, *J* = 7.1 Hz, 2H), 7.62–7.56 (m, 2H), 7.44–7.31 (m, 6H), 7.06 (d, *J* = 10.4 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 6.05 (d, *J* = 10.4 Hz, 1H), 2.32 (s, 3H), 1.49–1.39 (m, 1H), 1.16 (s, 9H), 0.90–0.81 (m, 1H), 0.74–0.58 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.2, 150.5, 143.7, 138.3, 137.5, 137.2, 129.3, 129.0, 128.8, 128.5, 128.5, 128.4, 128.2, 128.0, 84.9, 74.1, 62.4, 27.9, 21.6, 13.3, 8.3, 8.2; LRMS (ES + APCI) *m/z* calculated for $C_{30}H_{33}NO_6S$ 535.2, found 553.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{30}H_{37}N_2O_6S$ 553.2367, found 553.2359 $[M+NH_4]^+$.

1 mmol scale reaction

Following General Procedure C, *trans*-stilbene **1** (360 mg, 2.00 mmol), malonoyl peroxide **3** (461 mg, 3.60 mmol) and nucleophile **176** (271 mg, 1.00 mmol) were reacted in $CHCl_3$ (4.0 mL) at rt for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave the *N*-alkylated product **177** (511 mg, 0.96 mmol, 96%) as a white solid.

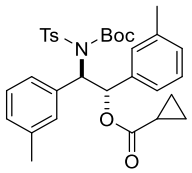
Rel-(1_S_,2_R_)-2-((_N_-(_tert_-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-di-_p_-tolylethyl cyclopropanecarboxylate 189



189

Following General Procedure C, 4,4′-dimethyl-*trans*-stilbene (208 mg, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at rt for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:5) gave the *N*-alkylated product **189** (177 mg, 0.31 mmol, 62%) as a white solid; mp 162–164 °C; IR (ATR)/cm^{-1}: 2968, 1735, 1338, 1168; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.54 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 6.99 (d, *J* = 10.3 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 2H), 5.99 (d, *J* = 10.3 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H), 1.44–1.40 (m, 1H), 1.17 (s, 9H), 0.89–0.83 (m, 1H), 0.70–0.62 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.2, 150.5, 143.5, 138.5, 137.8, 137.3, 135.4, 134.6, 129.4, 129.2, 129.0, 128.8, 128.3, 128.0, 84.7, 74.0, 62.2, 27.9, 21.6, 21.6, 21.3, 13.3, 8.3, 8.2; LRMS (ES + APCI) *m/z* calculated for $C_{32}H_{37}NO_6S$ 563.2, found 581.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{32}H_{41}N_2O_6S$ 581.2680, found 581.2668 $[M+NH_4]^+$.

Rel-(1_S_,2_R_)-2-((_N_-(_tert_-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-di-_m_-tolylethyl cyclopropanecarboxylate 190

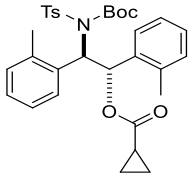


190

Following General Procedure C, 3,3′-dimethyl-*trans*-stilbene (208 mg, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at rt for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:5) gave the *N*-alkylated product **190** (205 mg, 0.37 mmol, 73%) as a clear gum; IR (ATR)/cm^{-1}: 2972, 1722, 1344, 1020; ^{1}H NMR (400 MHz, DMSO-d_6) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.49–7.45 (m, 2H), 7.42–7.38 (m, 1H), 7.37–7.20 (m, 4H), 7.14 (app d, *J* = 7.6 Hz, 1H),7.02–6.93 (m, 3H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.99 (d, *J* = 10.3 Hz, 1H,), 2.37 (s, 3H), 2.33 (s, 6H), 1.49–1.40 (m, 1H), 1.18 (s, 9H), 0.90–0.82 (m, 1H), 0.71–0.63 (m, 3H); ^{13}C NMR (101, $CDCl_3$) δ (ppm): 173.2, 150.4, 143.6, 138.2, 137.8, 137.4, 137.2,

130.0, 129.4, 129.2, 128.9, 128.8, 128.7, 128.2, 128.0, 126.2, 125.2, 84.7, 74.0, 62.4, 27.9, 21.6, 21.5, 21.4, 13.3, 8.3, 8.1 (1 carbons missing); LRMS (ES + APCI) *m/z* calculated for $C_{32}H_{37}NO_6S$ 563.2, found 581.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{32}H_{37}NNaO_6S$ 586.2234, found 586.2218 $[M+Na]^+$.

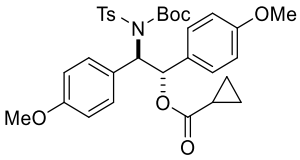
Rel-(1*S*,2*R*)-2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-di-*o*-tolylethyl cyclopropanecarboxylate 191



191

Following General Procedure C, 2,2′-dimethyl-*trans*-stilbene (208 mg, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at rt for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 15:85) gave the *N*-alkylated product **191** (261 mg, 0.46 mmol, 92%) as a white solid; mp 150–154 °C; IR (ATR)/cm^{-1}: 2922, 1722, 1359, 1150; ^{1}H NMR (400 MHz, d^6-acetone) δ (ppm) 7.93 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.70 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.37 (d, *J* = 10.5 Hz, 1H), 7.33–7.27 (m, 6H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.42 (d, *J* = 10.5 Hz, 1H), 2.68 (s, 3H), 2.46 (s, 3H), 2.35 (s, 3H), 1.43–1.36 (m, 1H,), 1.18 (s, 9H), 0.70–0.60 (m, 3H), 0.54–0.47 (m, 1H); ^{13}C NMR (101 MHz, d^6-acetone) δ (ppm) ^{13}C NMR (101, acetone-d_6) δ (ppm): 173.2, 151.9, 145.0, 139.3, 139.2, 138.3, 136.9, 136.5, 131.7, 131.5, 130.4, 129.8, 129.4, 129.1, 128.5, 126.7, 85.5, 73.3, 59.6, 27.8, 21.4, 20.5, 19.9, 13.3, 8.3, 7.9 (2 carbons missing); LRMS (ES + APCI) *m/z* calculated for $C_{32}H_{37}NO_6S$ 563.2, found 581.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{32}H_{41}N_2O_6S$ 581.2680, found 581.2672 $[M+NH_4]^+$.

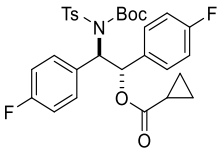
***Rel*-(1*S*,2*R*)-2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-bis(4-methoxyphenyl)ethyl cyclopropanecarboxylate 192**



192

Following General Procedure C, 4,4′-dimethoxy-*trans*-stilbene (240 mg, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 0 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 15:85) gave the *N*-alkylated product **192** (172 mg, 0.29 mmol, 57%) as a white solid; mp 162–164 °C; IR (ATR)/cm^{-1}: 2920, 1750, 1512, 1354, 1255, 1151; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.01–6.95 (m, 3H), 6.94–6.85 (m, 6H), 5.96 (d, *J* = 10.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.33 (s, 3H), 1.45–1.37 (m, 1H), 1.17 (s, 9H), 0.91–0.80 (m, 1H), 0.69–0.62 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) ^{13}C NMR (101, $CDCl_3$) δ (ppm): 173.3, 160.1, 159.4, 150.5, 143.6, 137.3, 130.6, 130.5, 129.7, 129.6, 128.9, 127.9, 114.1, 113.6, 84.7, 73.8, 62.2, 55.4, 55.3, 27.9, 21.6, 13.3, 8.3, 8.2; LRMS (ES + APCI) *m/z* calculated for $C_{32}H_{37}NO_8S$ 595.2, found 613.0 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{32}H_{37}NNaO_8S$ 618.2131, found 618.2108 $[M+Na]^+$.

***Rel*-(1*S*,2*R*)-2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-bis(4-fluoropheynyl)ethyl cyclopropanecarboxylate 186**

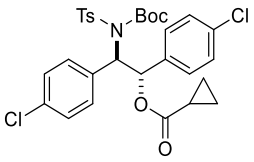


186

Following General Procedure C, 4,4′-fluoro-*trans*-stilbene (100 mg, 0.46 mmol), malonoyl peroxide **3** (105 mg, 0.82 mmol) and nucleophile **176** (62 mg, 0.23 mmol) were reacted in $CHCl_3$ (1.0 mL) at rt for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:9) gave the *N*-alkylated product **186** (94 mg, 0.16 mmol, 71%) as a white solid; mp 116–118 °C; IR (ATR)/cm^{-1}: 2924, 1726, 1510, 1344, 1143; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (dd, *J* = 8.7, 5.1 Hz, 2H), 7.54 (dd, *J* = 8.7, 5.1 Hz, 2H) 7.10–6.99 (m, 7H), 6.92–6.89 (d, *J* = 8.4 Hz, 2H), 5.96 (d, *J* = 10.4 Hz, 1H), 2.34 (s, 3H), 1.45–1.39 (m, 1H), 1.17 (s, 9H), 0.88–0.80 (m, 1H), 0.73–0.62 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ

(ppm) 173.1, 163.2 (J = 247.4 Hz), 162.6 (J = 247.4), 150.5, 144.0, 137.0, 133.9 (J = 3.1 Hz), 133.1 (J = 3.1 Hz), 131.3 (J = 8.0 Hz), 130.1 (J = 8.0 Hz), 129.0, 127.8, 115.7 (J = 21.6 Hz), 115.3 (J = 21.6 Hz), 85.2, 73.5, 62.0, 27.9, 21.6, 13.1, 8.4, 8.3; LRMS (ES + APCI) *m/z* calculated for $C_{30}H_{31}F_2NO_6S$ 571.18, found 564.0 $[M+Na]^+$; HRMS *m/z* calculated for $C_{30}H_{35}F_2N_2O_6S$ 589.2178, found 589.2166 $[M+NH_4]^+$.

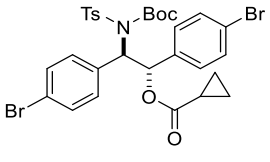
Rel-(1*S*,2*R*)-2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-bis(4-chloropheynyl)ethyl cyclopropanecarboxylate 193



193

Following General Procedure C, 4,4′-dichloro-*trans*-stilbene (248 mg, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at rt for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:9) gave the *N*-alkylated product **193** (269 mg, 0.45 mmol, 90%) as a white solid; mp 150–152 °C; IR (ATR)/cm^{-1}: 2922, 1730, 1354, 1147, 804; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.39–7.32 (m, 4H), 7.05 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 10.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 2H), 5.93 (d, J = 10.5 Hz, 1H), 2.36 (s, 3H), 1.46–1.40 (m, 1H), 1.18 (s, 9H), 0.90–0.81 (s, 1H), 0.77–0.67 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.1, 150.5, 144.2, 136.8, 136.7, 135.8, 134.9, 134.2, 130.8, 129.6, 129.0, 128.6, 127.9, 85.4, 73.3, 61.9, 27.9, 21.7, 13.1, 8.6, 8.5 (1 carbon missing); LRMS (ES + APCI) *m/z* calculated for $C_{30}H_{31}{}^{(35)}Cl_2NO_6S$ 603.1, found 625.8 $[M+Na]^+$; HRMS *m/z* calculated for $C_{30}H_{31}{}^{(35)}Cl_2NNaO_6S$ 626.1141, found 626.1126 $[M+Na]^+$.

Rel-(1*S*,2*R*)-2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-bis(4-bromopheynyl)ethyl cyclopropanecarboxylate 194

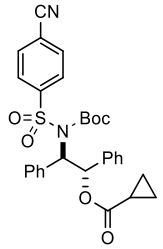


194

Following General Procedure C, 4,4′-dibromo-*trans*-stilbene (338 mg, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in

$CHCl_3$ (2.0 mL) at rt for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:9) gave the *N*-alkylated product **194** (295 mg, 0.43 mmol, 85%) as a white solid; mp 150–152 °C; IR (ATR)/cm^{-1}: 2922, 1726, 1352, 1145, 813; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.58–7.48 (m, 6H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 10.5 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.91 (d, *J* = 10.5 Hz, 1H), 2.37 (s, 3H), 1.47–1.39 (m, 1H), 1.18 (s, 9H), 0.88–0.83 (m, 1H), 0.76–0.63 (m, 3H); ^{13}C NMR (101, $CDCl_3$) δ (ppm): 173.1, 150.5, 144.2, 137.2, 136.7, 136.3, 132.0, 131.6, 131.1, 129.9, 129.1, 127.9, 123.1, 122.5, 85.4, 73.2, 61.9, 27.9, 21.7, 13.1, 8.6, 8.5; LRMS (ES + APCI) *m/z* calculated for $C_{30}H_{31}{}^{(79)}Br_2NO_6S$ 691.0, found 709.8 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{30}H_{31}{}^{(79)}Br_2NNaO_6S$ 714.0131, found 714.0110 $[M+Na]^+$.

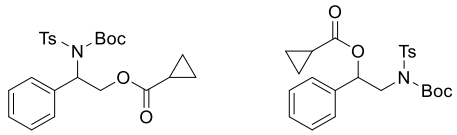
Rel-(1*S*,2*R*)-2-((*N*-(*tert*-butoxycarbonyl)-4-cyanophenyl)sulfonamido)-1,2-diphenylethyl cyclopropanecarboxylate 244



244

Following General Procedure C, *trans*-stilbene **1** (180 mg, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **249** (142 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at rt for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 15:85) gave the *N*-alkylated product **244** (273 mg, 0.47 mmol, 94%) as a white solid; mp 148–150 °C; IR (ATR)/cm^{-1}: 2976, 2231, 1729, 1353, 1149; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.64 (d, *J* = 6.8 Hz, 2H), 7.58 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.51–7.34 (m, 8H), 7.04 (d, *J* = 10.5 Hz, 1H), 6.98 (d, *J* = 6.8 Hz, 2H), 6.01 (d, *J* = 10.5 Hz, 1H), 1.48–1.42 (m, 1H), 1.20 (s, 9H), 0.92–0.82 (m, 1H), 0.76–0.60 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.2, 150.1, 144.2, 138.3, 136.9, 132.2, 129.2, 129.0, 129.0, 128.6, 128.6, 128.4, 117.3, 116.5, 86.1, 73.6, 62.8, 27.9, 13.2, 8.5, 8.3; LRMS (ES + APCI) *m/z* calculated for $C_{30}H_{30}N_2O_6S$ 546.2, found 564.0 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{30}H_{34}N_3O_6S$ 564.2168, found 564.2153 $[M+NH_4]^+$.

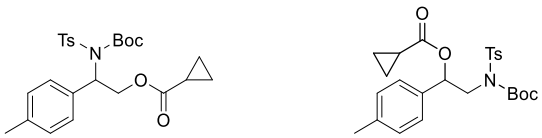
2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-phenylethyl cyclopropanecarboxylate 195A and 2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-phenylethyl cyclopropanecarboxylate 195B



195A **195B**

Following General Procedure C, styrene (0.11 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:9) gave the *N*-alkylated product **195A** and **195B** (176 mg, 0.38 mmol, 77%) in a 3.5:1 ratio, as a clear oil; IR (ATR)/cm^{-1}: 2978, 1727, 1454, 1353, 1147; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Major isomer* **195A** 7.82 (d, *J* = 8.3 Hz, 2H), 7.44–7.27 (m, 7H), 5.91 (t, *J* = 7.4 Hz, 1H), 4.87 (d, *J* = 7.4 Hz, 2H), 2.43 (s, 3H), 1.65–1.59 (m, 1H), 1.22 (s, 9H), 1.08–1.00 (m, 2H), 0.90–0.82 (m, 2H), *Minor isomer* **195B** 7.74 (d, *J* = 8.4 Hz, 0.6H), 7.43–7.27 (m, 2.1H), 6.12 (dd, *J* = 9.3, 3.8 Hz, 0.3H), 4.38 (dd, *J* = 14.8, 9.3 Hz, 0.3H), 3.99 (dd, *J* = 14.8, 3.8 Hz, 0.3H), 2.43 (s, 0.9H), 1.72–1.66 (m, 0.3H), 1.33 (s, 2.7H), 1.10–1.01 (m, 0.6H), 0.91–0.83 (m, 0.6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *Major isomer* **195A** and *Minor isomer* **195B** 174.6, 174.1, 150.6, 144.3, 137.4, 137.4, 129.4, 129.3, 128.8, 128.6, 128.2, 127.9, 127.3, 126.8, 84.8, 84.7, 73.8, 63.9, 58.7, 50.7, 28.0, 27.9, 21.8, 13.3, 13.1, 8.9, 8.8 (9 carbons missing); LRMS (ES + APCI) *m/z* calculated for $C_{24}H_{29}NO_6S$ 459.2, found 477.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{24}H_{29}NNaO_6S$ 482.1608, found 482.1592 $[M+Na]^+$.

2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-(*p*-tolyl)ethyl cyclopropanecarboxylate 196A and 2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-(*p*-tolyl)ethyl cyclopropanecarboxylate 196B

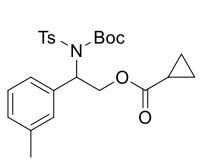


196A **196B**

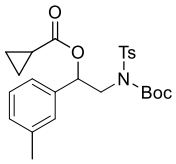
Following General Procedure C, 4-methylstyrene (0.13 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:9) gave the *N*-alkylated products **196A** and **196B** (234 mg, 0.49

mmol, 99%) in an 8:1 mixture, as a clear oil; IR (ATR)/cm^{-1}: 2976, 1727, 1351, 1149; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Major isomer* **196A** 7.81 (d, *J* = 8.4 Hz, 2H), 7.32–7.26 (m, 4H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.87 (dd, *J* = 8.3, 6.5 Hz, 1H), 4.91–4.78 (m, 2H), 2.43 (s, 3H), 2.34 (s, 3H), 1.63–1.58 (m, 1H), 1.24 (s, 9H), 1.09–1.00 (m, 2H), 0.91–0.82 (m, 2H), *Minor isomer* **196B** 7.74 (d, *J* = 8.4 Hz, 0.26H), 7.32–7.13 (m, 0.52H), 7.18–7.12 (m, 0.26H) 6.08 (dd, *J* = 9.4, 3.8 Hz, 0.13H), 4.40–4.34 (m, 0.13H), 3.96 (dd, *J* = 14.8, 3.8 Hz, 0.13H), 2.43 (s, 0.39H), 2.34 (s, 0.39H), 1.70–1.63 (m, 0.13H), 1.33 (s, 1.17H), 1.09–1.00 (m, 0.26H), 0.91–0.82 (m, 0.26H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *Major isomer* **196A** 174.6, 150.7, 144.2, 137.7, 137.5, 134.3, 129.3, 129.3, 128.6, 127.4, 84.8, 63.9, 58.7, 27.9, 21.8, 21.2, 13.1, 8.8, 8.8, *Minor isomer* **196B** too weak to report; LRMS (ES + APCI) *m/z* calculated for $C_{25}H_{31}NO_6S$ 473.2, found 491.0 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{25}H_{31}NNaO_6S$ 496.1764, found 496.1745 $[M+Na]^+$.

2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-(*m*-tolyl)ethyl cyclopropanecarboxylate 197A and 2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-(*m*-tolyl)ethyl cyclopropanecarboxylate 197B



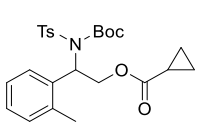
197A



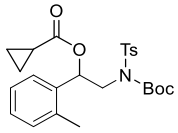
197B

Following General Procedure C, 3-methylstyrene (0.13 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:9) gave the *N*-alkylated products **197A** and **197B** (179 mg, 0.38 mmol, 76%) in a 5:1 mixture, as a clear oil; IR (ATR)/cm^{-1}: 2974, 2922, 1727, 1351, 1147; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Major isomer* **197A** 7.84 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.25–7.19 (m, 1H), 7.18–7.06 (m, 3H), 5.87 (t, *J* = 7.4 Hz, 1H), 4.85 (d, *J* = 7.4 Hz, 2H), 2.44 (s, 3H), 2.31 (s, 3H), 1.64–1.59 (m, 1H), 1.23 (s, 9H), 1.10–1.01 (m, 2H), 0.92–0.82 (m, 2H), *Minor isomer* **197B** 7.74 (d, *J* = 8.4 Hz, 0.4H), 7.25–7.06 (m, 1.2H), 6.08 (dd, *J* = 9.5, 3.6 Hz, 0.2H), 4.37 (dd, *J* = 14.8, 9.5 Hz, 0.2H), 3.96 (dd, *J* = 14.8, 3.6 Hz, 0.2H), 2.44 (s, 0.6H), 2.35 (s, 0.6H), 1.72–1.67 (m, 0.2H), 1.34 (s, 1.8H), 1.10–1.01 (m, 0.4H), 0.92–0.82 (m, 0.4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *Major isomer* **197A** and *Minor isomer* **197B** 174.7, 150.7, 144.3, 138.2, 137.4, 137.3, 129.3, 129.2, 128.7, 128.6, 128.5, 128.2, 128.0, 127.5, 124.3, 123.7, 84.7, 84.7, 73.8, 63.9, 58.8, 50.7, 28.0, 27.9, 21.8, 21.6, 13.4, 13.1, 8.9, 8.8, 8.7, 8.6; LRMS (ES + APCI) *m/z* calculated for $C_{25}H_{31}NO_6S$ 473.2, found 491.1 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{25}H_{35}N_2O_6S$ 491.2216, found 491.2202 $[M+NH_4]^+$.

2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-(*o*-tolyl)ethyl cyclopropanecarboxylate 198A and 2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-(*o*-tolyl)ethyl cyclopropanecarboxylate 198B



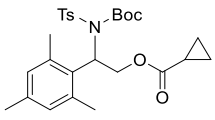
198A



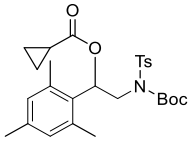
198B

Following General Procedure C, 2-methylstyrene (0.13 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:19) gave the *N*-alkylated products **198A** and **198B** (197 mg, 0.42 mmol, 83%) in a 10:1 mixture, as a clear oil; IR (ATR)/cm^{-1}: 2976. 2922, 1723, 1357, 1149; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Major isomer* **198A** δ 7.59–7.52 (m, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.29–7.22 (m, 2H), 7.15–7.10 (m, 3H), 5.92 (dd, *J* = 9.4, 6.1 Hz, 1H), 4.96 (dd, *J* = 11.2, 9.4 Hz, 1H), 4.86 (dd, *J* = 11.2, 6.1 Hz, 1H), 2.38 (s, 3H), 2.20 (s, 3H), 1.58 (tt, *J* = 8.1, 4.7 Hz, 1H), 1.41 (s, 9H), 1.08–0.97 (m, 2H), 0.88–0.78 (m, 2H), *Minor isomer* **198B** not strong enough to be reported; ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *Major isomer* **198A** 174.5, 151.7, 144.0, 137.5, 137.4, 134.4, 130.8, 129.0, 128.9, 128.4, 128.2, 126.1, 84.9, 63.9, 57.2, 28.0, 21.7, 19.5, 13.2, 8.7, 8.7, *Minor isomer* **198B** not strong enough to be reported; LRMS (ES + APCI) *m/z* calculated for $C_{25}H_{31}NO_6S$ 473.2, found 491.3 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{25}H_{35}N_2O_6S$ 491.2216, found 491.2202 $[M+NH_4]^+$.

2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-mesitylethyl cyclopropanecarboxylate 199A and 2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-mesitylethyl cyclopropanecarboxylate 199B



199A

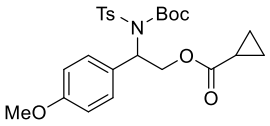


199B

Following General Procedure C, 2,4,6-trimethylstyrene (0.16 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at rt for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 15:85) gave the *N*-alkylated products **199A** and **199B** (196 mg, 0.39 mmol, 78%) in a 20:1 mixture, as a clear oil; IR (ATR)/cm^{-1}: 2922, 2974, 1721, 1353, 1145;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Major isomer* **199A** 7.26 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.83 (s, 2H), 5.98 (dd, *J* = 9.7, 6.0 Hz, 1H), 5.03 (dd, *J* = 11.3, 9.7 Hz, 1H), 4.71 (dd, *J* = 11.3, 6.0 Hz, 1H), 2.38 (s, 3H), 2.32 (s, 6H), 2.28 (s, 3H), 1.59 (tt, *J* = 8.0, 4.7 Hz, 1H), 1.41 (s, 9H), 1.03–0.97 (m, 2H), 0.87–0.80 (m, 2H), *Minor isomer* **199B** not strong enough to be reported; ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *Major isomer* **199A** 174.6, 151.4, 143.8, 138.3, 137.6, 137.5, 130.9, 130.8, 128.8, 128.1, 84.8, 64.9, 59.4, 28.0, 21.7, 21.3, 20.8, 13.2, 8.7, 8.6, *Minor isomer* **199B** not strong enough to be reported; LRMS (ES + APCI) *m/z* calculated for $C_{27}H_{35}NO_6S$ 501.22, found 519.2 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{27}H_{39}N_2O_6S$ 519.2529, found 519.2532 $[M+NH_4]^+$.

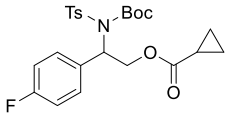
2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-(*p*-methoxyphenyl)ethyl cyclopropanecarboxylate 200



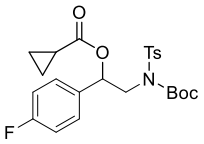
200

Following General Procedure C, 4-methoxystyrene (134 mg, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at rt for 24 h. Purification by alumina gel flash column chromatography (EtOAc:Petroleum ether 3:7) gave the *N*-alkylated product **200** (117 mg, 0.24 mmol, 47%) as a yellow solid; mp 82–84 °C; IR (ATR)/cm^{-1}: 2970, 2355, 1734, 1354, 1151; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.78 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 5.78–5.70 (m, 1H), 4.81–4.61 (m, 2H), 3.75 (s, 3H), 2.41 (s, 3H), 1.56–1.48 (m, 1H), 1.19 (s, 9H), 0.92–0.74 (m, 4H); ^{13}C NMR (101, DMSO-d_6) δ (ppm): 173.6, 158.8, 150.0, 144.4, 136.7, 129.4, 128.7, 128.5, 127.9, 113.8, 84.3, 62.8, 58.0, 55.1, 27.3, 21.0, 12.5, 8.3, 8.2; LRMS (ES + APCI) *m/z* calculated for $C_{25}H_{31}NO_7S$ 489.2, found 507.0 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{25}H_{31}NNaO_7S$ 512.1713, found 512.1695 $[M+Na]^+$.

2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-(4-fluorophenyl)ethyl cyclopropanecarboxylate 201A and 2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-(4-fluorophenyl)ethyl cyclopropanecarboxylate 201B



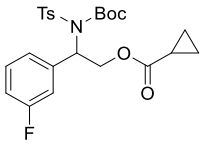
201A



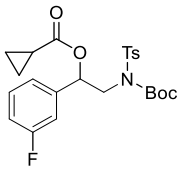
201B

Following General Procedure C, 4-fluorostyrene (0.12 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:19) gave the *N*-alkylated products **201A** and **201B** (196 mg, 0.40 mmol, 79%) in a 5:1 mixture, as a clear oil; IR (ATR)/cm^{-1}: 2976, 2924, 1727, 1513, 1351, 1147; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Major isomer* **201A** 7.80 (d, *J* = 8.2 Hz, 2H), 7.44–7.37 (m, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.08–7.00 (m, 2H), 5.87 (dd, *J* = 7.9, 6.8 Hz, 1H), 7.89–7.76 (m, 2H), 2.43 (s, 3H), 1.60 (tt, *J* = 8.0, 4.6 Hz, 1H), 1.25 (s, 9H), 1.08–0.97 (m, 2H), 0.92–0.79 (m, 2H), *Minor isomer* **201B** 7.73 (d, *J* = 8.4 Hz, 0.32H), 7.44–7.37 (m, 0.32H), 7.31–7.27 (d, *J* = 8.2 Hz, 0.32H), 7.08–7.00 (m, 0.32H), 6.09 (dd, *J* = 9.1, 4.0 Hz, 0.16H), 4.38–4.28 (m, 0.16H), 3.97 (dd, *J* = 14.8, 4.0 Hz, 0.16H), 2.43 (s, 0.48H), 1.68 (tt, *J* = 8.1, 4.6 Hz, 0.16H), 1.30 (s, 1.44H), 1.08–0.97 (m, 0.32H), 0.92–0.79 (m, 0.32H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *Major isomer* **201A** and *Minor isomer* **201B** 174.5, 174.0, 162.4 (d, *J* = 246.8 Hz), 150.9, 150.5, 144.4, 144.4, 137.4, 133.8 (d, *J* = 3.1 Hz), 133.2 (d, *J* = 3.0 Hz), 129.5 (d, *J* = 8.0 Hz), 129.4, 129.3, 128.6 (d, *J* = 8.2 Hz), 128.5, 128.2, 115.7 (d, *J* = 24.7 Hz), 115.5 (d, *J* = 21.5 Hz), 85.0, 84.8, 73.2, 63.7, 58.2, 50.5, 28.0, 27.9, 21.8, 13.3, 13.1, 8.9, 8.9, 8.8, 8.7 (7 carbons missing); LRMS (ES + APCI) *m/z* calculated for $C_{24}H_{28}FNO_6S$ 477.16, found 495.0 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{24}H_{28}FNNaO_6S$ 500.1514, found 500.1495 $[M+Na]^+$.

2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-(3-fluorophenyl)ethyl cyclopropanecarboxylate 202A and 2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-(3-fluorophenyl)ethyl cyclopropanecarboxylate 202B



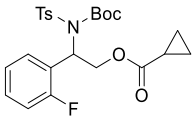
202A



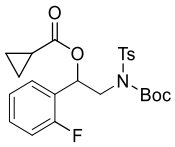
202B

Following General Procedure C, 3-fluorostyrene (0.12 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 15:85) gave the *N*-alkylated products **202A** and **202B** (137 mg, 0.29 mmol, 57%) in a 1.4:1 mixture, as a clear oil; IR (ATR)/cm^{-1}: 2978, 1727, 1353, 1147; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Major isomer* **202A** 7.84 (d, *J* = 8.4 Hz, 2H), 7.38–7.27 (m, 3H), 7.20 (m, 1H), 7.15–7.07 (m, 1H), 7.01 (m, 1H), 5.88 (t, *J* = 7.3 Hz, 1H), 4.82 (d, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 1.66–1.57 (m, 1H), 1.25 (s, 9H), 1.10–1.00 (m, 2H), 0.93–0.82 (m, 2H), *Minor isomer* **202B** 7.78–7.72 (d, *J* = 8.4 Hz, 1.2H), 7.38–7.27 (m, 1.8H), 7.20 (m, 0.6H), 7.15–7.07 (m, 0.6H), 7.01 (m, 0.6H), 6.09 (d, *J* = 9.1, 3.8 Hz, 0.6H), 4.35 (dd, *J* = 14.8, 9.1 Hz, 0.6H), 3.99 (dd, *J* = 14.8, 3.8 Hz, 0.6H), 2.43 (s, 1.8H), 1.74–1.67 (m, 0.6H), 1.33 (s, 5.4H), 1.10–1.00 (m, 1.2H), 0.93–0.82 (m, 1.2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *Major isomer* **202A** and *Minor isomer* **202B** 174.5, 174.0, 163.1 (d, *J* = 246.9 Hz), 163.0 (d, *J* = 246.3 Hz), 150.8, 150.5, 144.5, 144.4, 140.5 (d, *J* = 7.2 Hz), 140.1 (d, *J* = 7.2 Hz), 137.4, 137.2, 130.4 (d, *J* = 8.4 Hz), 130.2 (d, *J* = 8.0 Hz), 129.4, 128.6, 128.2, 123.0 (d, *J* = 2.6 Hz), 122.4 (d, *J* = 2.4 Hz), 115.5 (d, *J* = 21.3 Hz), 114.9 (d, *J* = 20.9 Hz), 114.5 (d, *J* = 22.9), 113.7 (d, *J* = 22.6 Hz), 85.1, 84.9, 73.2, 63.8, 58.3, 50.5, 28.0, 27.9, 21.8, 13.3, 13.1, 8.9, 8.9, 8.7 (3 carbons missing); LRMS (ES + APCI) *m/z* calculated for $C_{24}H_{28}FNO_6S$ 477.2, found 495.1 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{24}H_{28}FNNaO_6S$ 500.1514, found 500.1493 $[M+Na]^+$.

2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-(2-fluorophenyl)ethyl cyclopropanecarboxylate 203A and 2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-(2-fluorophenyl)ethyl cyclopropanecarboxylate 203B



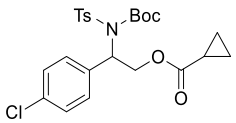
203A



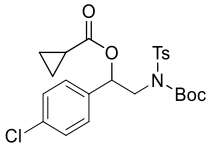
203B

Following General Procedure C, 2-fluorostyrene (0.12 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:19) gave the *N*-alkylated products **203A** and **203B** (158 mg, 0.33 mmol, 65%) in a 1:1 mixture, as a clear oil; IR (ATR)/cm^{-1}: 2848, 2919, 1727, 1353, 1279, 1260, 1126; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *isomer* **203A** and *isomer* **203B** 7.74 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.56–7.46 (m, 2H), 7.37–7.27 (m, 4H), 7.24–7.14 (m, 4H), 7.09–6.98 (m, 2H), 6.38 (dd, *J* = 8.5, 4.1 Hz, 1H), 6.11 (dd, *J* = 9.2, 6.1 Hz, 1H), 5.00–4.89 (m, 2H), 4.39 (dd, *J* = 14.8, 8.5 Hz, 1H), 4.11 (dd, *J* = 14.8, 4.1 Hz, 1H), 2.42 (s, 3H), 2.40 (s, 3H), 1.74–1.66 (m, 1H), 1.64–1.55 (m, 1H), 1.35 (s, 9H), 1.32 (s, 9H), 1.11–0.99 (m, 4H), 0.91–0.79 (m, 4H).;^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *isomer* **203A** and *isomer* **203B** 174.4, 173.9, 161.0 (d, *J* = 248.4 Hz), 160.3 (d, *J* = 247.8 Hz), 150.9, 150.7, 144.2, 144.1, 137.5, 137.4, 130.3 (d, *J* = 7.3 Hz), 130.1 (d, *J* = 10.5 Hz), 129.3, 129.1, 128.5, 128.4 (d, *J* = 3.5 Hz), 128.3 (d, *J* = 3.8 Hz), 128.3, 125.1 (d, *J* = 13.8 Hz), 124.6 (d, *J* = 3.2 Hz), 124.1 (d, *J* = 3.8 Hz), 123.7 (d, *J* = 12.9 Hz), 115.8 (d, *J* = 21.3 Hz), 115.7 (d, *J* = 22.4 Hz), 85.0, 84.7, 77.4, 68.0, 63.0, 53.8, 49.2, 28.0, 27.9, 21.7, 13.3, 13.1, 8.8, 8.7, 8.7 (1 carbon missing); LRMS (ES + APCI) *m/z* calculated for $C_{24}H_{28}FNO_6S$ 477.16, found 495.0 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{24}H_{28}FNNaO_6S$ 500.1514, found 500.1494 $[M+Na]^+$.

2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-(4-chlorophenyl)ethyl cyclopropanecarboxylate 204A and 2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-(4-chlorophenyl)ethyl cyclopropanecarboxylate 204B



204A

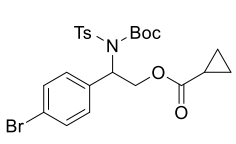


204B

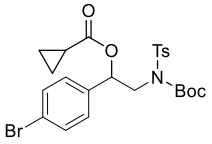
Following General Procedure C, 4-chlorostyrene (0.13 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0

mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:10) gave the *N*-alkylated products **204A** and **204B** (210 mg, 0.43 mmol, 85%) in a 3.5:1 mixture, as a clear oil; IR (ATR)/cm^{-1}: 2978, 1729, 1353, 1149; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Major isomer* **204A** 7.81 (d, *J* = 8.4 Hz, 2H), 7.39–7.27 (m, 6H), 5.86 (dd, *J* = 7.6, 7.0 Hz, 1H), 4.88–4.77 (m, 2H), 2.44 (s, 3H), 1.63–1.58 (m 1H), 1.25 (s, 9H), 1.07–1.01 (m, 2H), 0.91–0.81 (m, 2H), *Minor isomer* **204B** 7.76–7.69 (m, 0.50H), 7.39–7.27 (m, 1.50H), 6.07 (dd, *J* = 9.0, 4.0 Hz, 0.25H), 4.33 (dd, *J* = 14.8, 9.0 Hz, 0.25H), 3.98 (dd, *J* = 14.8, 4.0 Hz, 0.25H), 2.44 (s, 0.75H), 1.73–1.65 (m, 0.25H), 1.32 (s, 2.25H), 1.07–1.01 (m, 0.50H), 0.91–0.81 (m, 0.50H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *Major isomer* **204A** and *Minor isomer* **204B** 174.5, 174.0, 150.8, 150.5, 144.5, 144.4, 137.4, 137.3, 136.5, 136.0, 134.5, 133.9, 129.4, 129.0, 129.0, 128.8, 128.5, 128.2, 128.2, 85.1, 84.9, 73.2, 63.6, 58.2, 50.4, 27.9, 21.8, 13.3, 13.0, 8.9, 8.9, 8.7 (8 carbons missing); LRMS (ES + APCI) *m/z* calculated for $C_{24}H_{28}{}^{(35)}ClNO_6S$ 493.1, found 511.0 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{24}H_{28}{}^{(35)}ClNNaO_6S$ 516.1218, found 516.1198 $[M+Na]^+$.

2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-(4-bromophenyl)ethyl cyclopropanecarboxylate 205A and 2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-(4-bromophenyl)ethyl cyclopropanecarboxylate 205B



205A

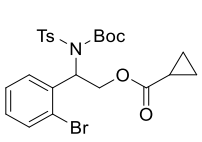


205B

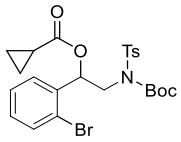
Following General Procedure C, 4-bromostyrene (0.13 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:10) gave the *N*-alkylated products **205A** and **205B** (172 mg, 0.32 mmol, 64%) in a 3:1 mixture, as a clear oil; IR (ATR)/cm^{-1}: 2978, 1729, 1353, 1149; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Major isomer* **205A** 7.81 (d, *J* = 8.4 Hz, 2H), 7.52–7.45 (m, 2H), 7.34–7.27 (m, 4H), 5.84 (t, *J* = 7.3 Hz, 1H), 4.87–4.77 (m, 2H), 2.44 (s, 3H), 1.64–1.56 (m, 1H), 1.25 (s, 9H), 1.07–1.01 (m, 2H), 0.92–0.82 (m, 2H), *Minor isomer* **205B** 7.72 (d, *J* = 8.4 Hz, 0.54H), 7.52–7.45 (m, 0.54H), 7.34–7.27 (m, 1.08H), 6.05 (dd, *J* = 9.0, 4.1 Hz, 0.27H), 4.33 (dd, *J* = 14.8, 9.0 Hz, 0.27H), 3.98 (dd, *J* = 14.8, 4.1 Hz, 0.27H), 2.44 (s, 0.81H), 1.69 (m, 0.27H), 1.32 (s, 2.43H), 1.07–1.01 (m, 0.54H), 0.92–0.82 (m, 0.54H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *Major isomer* **205A** and *Minor isomer* **205B** 174.5, 174.0, 150.8, 150.5, 144.5, 137.3, 136.5, 132.0, 131.8, 129.4, 129.3, 128.5, 128.2, 122.1, 85.2, 84.9, 73.2, 63.6, 58.3, 50.4, 28.0, 21.8, 13.3, 13.1, 8.9, 8.9, 8.7 (9 carbons missing); LRMS (ES + APCI) *m/z*

calculated for $C_{24}H_{28}{}^{(79)}BrNO_6S$ 537.1, found 555.3 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{24}H_{28}{}^{(79)}BrNNaO_6S$ 560.0713, found 560.0693 $[M+Na]^+$.

2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-2-(2-bromophenyl)ethyl cyclopropanecarboxylate 206A and 2-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-(2-bromophenyl)ethyl cyclopropanecarboxylate 206B



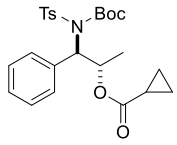
206A



206B

Following General Procedure C, 2-bromostyrene (0.13 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:10) gave the *N*-alkylated products **206A** and **206B** (104 mg, 0.2 mmol, 39%) in a 2:1 mixture, as a clear oil; IR (ATR)/cm^{-1}: 2980, 1729, 1357, 1145; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *Isomer* **206A** 7.68 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.59–7.49 (m, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.41–7.32 (m, 1H), 7.24–7.17 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.95 (dd, *J* = 9.0, 6.8 Hz, 1H), 4.93–4.81 (m, 2H), 2.39 (s, 3H), 1.53–1.49 (m, 1H), 1.45 (s, 9H), 1.01–0.93 (m, 2H), 0.89–0.77 (m, 2H), *Isomer* **206B** 7.73 (d, *J* = 8.4 Hz, 1.08H), 7.59–7.49 (m, 1.08H), 7.41–7.32 (m, 0.54H), 7.29–7.26 (m, 1.08H), 7.24–7.17 (m, 0.54H), 6.41 (dd, *J* = 7.7, 4.2 Hz, 0.54H), 4.34 (dd, *J* = 14.9, 7.7 Hz, 0.54H), 4.22 (dd, *J* = 14.9, 4.2 Hz, 0.54H), 2.42 (s, 1.62H), 1.74–1.68 (m, 0.54H), 1.27 (s, *J* = 9.6 Hz, 4.86H), 1.09–1.04 (m, 1.08H), 0.89–0.77 (m, 1.08H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *Isomer* **206A** *Isomer* **206B** 174.2, 173.8, 151.5, 150.8, 144.2, 144.0, 137.6, 137.3, 135.4, 133.2, 133.0, 131.1, 129.9, 129.9, 129.3, 129.0, 128.5, 128.2, 128.0, 127.5, 125.1, 122.8, 85.0, 84.6, 72.4, 63.0, 59.7, 48.7, 28.1, 27.9, 21.7, 13.3, 13.0, 8.8, 8.7, 8.7 (4 carbons missing); LRMS (ES + APCI) *m/z* calculated for $C_{24}H_{28}{}^{(79)}BrNO_6S$ 537.1, found 555.3 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{24}H_{28}{}^{(79)}BrNNaO_6S$ 560.0713, found 560.0692 $[M+Na]^+$.

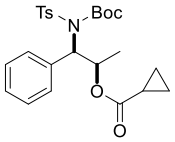
Rel-(1_R_,2_S_)-1-((_N_-(_tert_-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-phenylpropan-2-yl cyclopropanecarboxylate 207



207

Following General Procedure C, *trans*-β-methylstyrene (0.13 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:10) gave the *N*-alkylated product **207** (206 mg, 0.44 mmol, 87%) as a clear oil; IR (ATR)/cm^{-1}: 2980, 1723, 1353, 1147; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55 (d, *J* = 8.1 Hz, 2H), 7.45–7.39 (m, 2H), 7.34–7.27 (m, 3H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.13 (dq, *J* = 9.7, 6.2 Hz, 1H), 5.62 (d, *J* = 9.7 Hz, 1H), 2.39 (s, 3H), 1.46 (d, *J* = 6.2 Hz, 3H), 1.45–1.40 (m, 1H), 1.27 (s, 9H), 0.90–0.85 (m, 1H), 0.75–0.63 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.9, 150.8, 144.3, 137.7, 137.0, 129.2, 128.8, 128.6, 128.4, 128.0, 85.1, 69.9, 63.2, 27.9, 21.7, 18.1, 13.3, 8.3, 8.2; LRMS (ES + APCI) *m/z* calculated for $C_{25}H_{31}NO_6S$ 473.2, found 491.0 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{25}H_{35}N_2O_6S$ 491.2216, found 491.2198 $[M+NH_4]^+$.

Rel-(1_R_,2_R_)-1-((_N_-(_tert_-butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-phenylpropan-2-yl cyclopropanecarboxylate 208

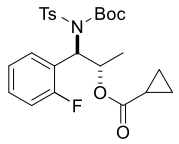


208

Following General Procedure C, *cis*-β-methylstyrene (0.13 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:20) gave the *N*-alkylated product **208** (128 mg, 0.27 mmol, 54%) as a clear oil as a 1.4:1 (*syn*:*anti*) mixture; IR (ATR)/cm^{-1}: 2980, 1725, 1351, 1149; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) *syn-diastereoisomer* 7.67–7.60 (m, 4H), 7.40–7.33 (m, 3H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.05 (dq, *J* = 11.4, 6.1 Hz, 1H), 5.60 (d, *J* = 11.4 Hz, 1H), 2.38 (s, 3H), 1.54–1.48 (m, 1H), 1.28 (s, 9H), 1.24 (d, *J* = 6.1 Hz, 3H), 1.07–1.00 (m, 1H), 0.99–0.92 (m, 1H), 0.82–0.76 (m, 2H), *anti-diastereoisomer* 7.55 (d, *J* = 8.1 Hz, 1.50H), 7.45–7.39 (m, 1.50H), 7.34–7.27 (m, 2.25H), 7.19 (d, *J* = 8.1 Hz, 1.50H), 6.13 (dq, *J* = 9.7, 6.2 Hz, 0.75H),

5.62 (d, *J* = 9.7 Hz, 0.75H), 2.39 (s, 2.25H), 1.46 (d, *J* = 6.2 Hz, 2.25H), 1.45–1.40 (m, 0.75H), 1.27 (s, 6.75H), 0.90–0.85 (m, 1H), 0.75–0.63 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *syn-diastereoisomer* 174.0, 150.5, 143.8, 137.9, 136.9, 129.9, 129.1, 128.7, 128.3, 84.8, 68.4, 64.5, 27.9, 21.7, 19.4, 13.2, 8.6, 8.5 (1 carbon missing), *anti-diastereoisomer* 173.9, 150.8, 144.3, 137.7, 137.0, 129.2, 128.8, 128.6, 128.4, 128.0, 85.1, 69.9, 63.2, 27.9, 21.7, 18.1, 13.3, 8.3, 8.2; LRMS (ES + APCI) *m/z* calculated for $C_{25}H_{31}NO_6S$ 473.2, found 491.0 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{25}H_{31}NNaO_6S$ 496.1764, found 496.1748 $[M+Na]^+$.

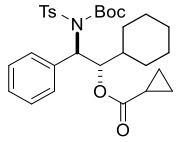
Rel-(1*R*,2*S*)-1-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-(2-fluorophenyl)propan-2-yl cyclopropanecarboxylate 209



209

Following General Procedure C, trans-β-methyl-2-fluorostyrene **220** (0.7 mL, 0.50 mmol), malonoyl peroxide **3** (115 mg, 0.90 mmol) and nucleophile **176** (68 mg, 0.25 mmol) were reacted in $CHCl_3$ (1.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:10) gave the *N*-alkylated product **209** (99 mg, 0.22 mmol, 81%) as a clear oil; IR (ATR)/cm^{-1}: 2986, 1718, 1455, 1362, 1283, 1171; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (ddd, *J* = 7.7, 7.7, 1.5 Hz, 1H), 7.36–7.28 (m, 3H), 7.15 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.02–6.93 (m, 1H), 6.29–6.17 (m, 1H), 5.89 (d, *J* = 10.2 Hz, 1H), 2.36 (s, 3H), 1.55 (d, *J* = 6.2 Hz, 3H), 1.42 (s, 9H), 1.44–1.39 (m, 1H), 0.89–0.82 (m, 1H), 0.77–0.65 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.9, 162.0 (d, *J* = 248.2 Hz), 151.4, 144.1, 137.3, 130.1 (d, *J* = 3.0 Hz), 130.0 (d, *J* = 8.7 Hz), 129.0, 128.6, 124.1 (d, *J* = 14.0 Hz), 124.1 (d, *J* = 4.0 Hz), 115.4 (d, *J* = 22.5 Hz), 85.4, 69.3, 57.1, 28.2, 21.8, 17.7, 13.3, 8.3, 8.3; LRMS (ES + APCI) *m/z* calculated for $C_{25}H_{30}FNO_6S$ 491.2, found 509.1 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{25}H_{30}FNNaO_6S$ 514.1670, found 514.1654 $[M+Na]^+$.

Rel-(1_S_,2_R_)-2-((_N_-(_tert_-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-1-cyclohexyl-2-phenylethyl cyclopropanecarboxylate 210

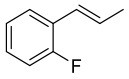


210

Following General Procedure C, (*E*)-(2-cyclohexylvinyl)benzene (0.18 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. Purification by silica flash chromatography gave the *N*-alkylated product **210** as a translucent solid (250 mg, 0.46 mmol, 92%); IR(ATR) cm^{-1}: 2927, 1726, 1355, 1147, 750; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.62–7.56 (m, 2H), 7.37–7.29 (m, 5H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.21 (d, *J* = 10.3 Hz, 1H), 5.70 (d, *J* = 10.3 Hz, 1H), 2.34 (s, 3H), 2.11–2.02 (m, 1H), 1.89–1.66 (m, 5H), 1.40–1.07 (m, 15H), 0.68–0.56 (m, 4H); ^{13}C NMR (101, $CDCl_3$) δ (ppm): 173.8, 150.9, 143.9, 137.6, 137.4, 129.8, 129.1, 128.2, 128.0, 85.1, 75.2, 59.8, 39.0, 31.1, 28.0, 26.8, 26.5, 26.2, 25.5, 21.6, 13.1, 8.0, 7.7 (1 carbon missing); LRMS (ES + APCI) m/z calculated for $C_{30}H_{39}NO_6S$ 541.25 found 559.0 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{30}H_{39}NNaO_6S$ 564.2390, found 564.2372 $[M+Na]^+$.

4.2.9.2 Miscellaneous reactions

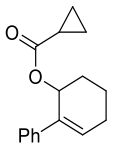
(E)-1-fluoro-2-(prop-1-en-1-yl)benzene 220



220

To a flame dried 3-neck flask was added 2-fluorobenzalehyde (2.1 mL, 20.0 mmol), 3-pentanone (2.3 mL, 22.0 mmol) and hexane (30 mL). The mixture was heated to 70 °C and boron trifluoro diethyl etherate (2.5 mL, 20.0 mmol) added dropwise then the mixture was left to stir for 5 h. The reaction mixture was cooled to room temperature and diluted with H_2O (30 mL) and the resulting layers separated. The organic layer was washed with 1M *aq*. NaOH (2 × 30 mL) and concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (Hexane), gave the title compound **220** (223 mg, 1.6 mmol, 8%), as a clear liquid; IR (ATR)/cm^{-1}: 2913, 1485, 1230, 965, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41 (app. td, *J* = 7.7, 1.8 Hz, 1H), 7.20–7.10 (m, 1H), 7.09–6.97 (m, 2H), 6.55 (dd, *J* = 15.9, 1.6 Hz, 1H), 6.32 (dq, *J* = 15.9, 6.6 Hz, 1H), 1.92 (dd, *J* = 6.6, 1.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 159.37 (d, *J* = 247.6 Hz), 127.98 (d, *J* = 4.2 Hz), 127.37 (d, *J* = 8.5 Hz), 126.51 (d, *J* = 4.3 Hz), 123.45 (d, *J* = 3.1 Hz), 122.95 (d, *J* = 3.9 Hz), 115.17, 114.95, 18.36; GCMS *m/z* calculated for C_9H_9F 136.1, found 135.1 $[M-H]^-$.

2,3,4,5-Tetrahydro-(1,1'-biphenyl)2-yl cyclopropanecarboxylate 238



238

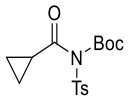
Following General Procedure C, 1-phenyl-1-cyclohexene **233** (0.16 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **176** (135 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. The reaction mixture was analysed by ^{1}H NMR spectroscopy. Allylic ester **238** was identified to form qualitatively, when compared to previous work conducted within our laboratory.[46]

Literature characterisation[46]

Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26−7.13 (m, 5H), 6.26 (dd, *J* = 4.7, 3.3 Hz, 1H), 5.85 (t, *J* = 3.9 Hz, 1H), 2.29–2.20 (m, 1H), 2.16–2.07 (m, 1H), 1.95–1.88 (m, 1H), 1.81–1.73 (m, 1H), 1.69–1.60 (m, 2H), 1.44–1.38 (m, 1H), 0.86–0.81 (m, 1H), 0.76–0.71 (m, 1H), 0.66–0.63 (m, 2H); ^{13}C NMR (101 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 *m/z* calculated for $C_{16}H_{22}NO_2$ 260.1645, found 260.1650 $[M+NH_4]^+$.

***tert*-Butyl (cyclopropanecarbonyl)(tosyl)carbamate 235**



235

IR (ATR)/cm^{-1}: 2980, 1757, 1714, 1599, 1368, 1251, 1138; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.97 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.44 (s, 3H), 2.05 (tt, *J* = 7.9, 4.5 Hz, 1H), 1.50 (s, 9H), 1.23–1.15 (m, 2H), 1.09–0.99 (m, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.7, 148.9, 145.2, 136.3, 129.6, 128.9, 86.3, 27.7, 21.8, 17.8, 12.1, 12.1; LRMS (ES + APCI) *m/z* calculated for $C_{16}H_{21}NO_5S$ 339.1, found 357.0 $[M+NH_4]^+$

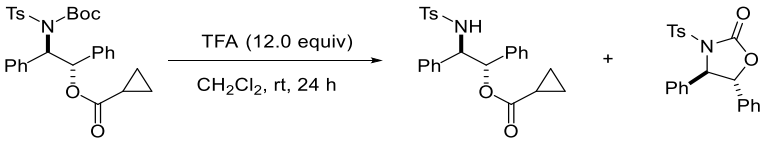
From cyclohexene

Following General Procedure C, cyclohexene (0.7 mL, 0.50 mmol), malonoyl peroxide **3** (115 mg, 0.90 mmol) and nucleophile **176** (68 mg, 0.25 mmol) were reacted in $CHCl_3$ (1.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:10) gave the *title compound* **235** (71 mg, 0.21 mmol, 86%) as a clear oil.

From cycloheptene

Following General Procedure C, cycloheptene (60 μL, 0.50 mmol), malonoyl peroxide **3** (115 mg, 0.90 mmol) and nucleophile **176** (68 mg, 0.25 mmol) were reacted in $CHCl_3$ (1.0 mL) at 40 °C for 24 h. Purification by alumina flash column chromatography (EtOAc:Petroleum ether 1:10) gave the *title compound* **235** (75 mg, 0.22 mmol, 87%) as a clear oil.

4.2.10 Deprotection reactions



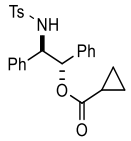
177 **241**, 66% **246**, 20%

Oxyaminated material **177** (197 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (1.90 mL) and TFA (0.34 mL, 4.44 mmol) added dropwise. The mixture was then stirred for 18 h at 40 °C. The reaction mixture was then concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:10) gave sulfonamide **241** (102 mg, 0.23 mmol, 66%, see p175 for characterisation) and oxazolidinone **246** (28 mg, 0.07 mmol, 20%, see p182 for characterisation).

4.2.10.1 General procedure D: Boc group deprotection with hydrochloric acid

HCl (4 M in dioxane, 4 eq) was added dropwise to a solution of oxyamination product (1 eq) in dioxane (0.2 M) and the mixture stirred at 60 °C for 8 h. The mixture was then cooled to room temperature and quenched with $NaHCO_3$ until pH 7. The mixture was extracted with CH_2Cl_2 and the solvent was dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield the crude product. Purification by silica gel flash column chromatography using the appropriate solvent gave the desired compound.

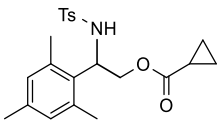
***Rel*-(1*S*,2*R*)-2-((4-methylphenyl)sulfonamido)-1,2-diphenylethyl cyclopropanecarboxylate 241**



241

HCl (4 M in dioxane, 4 eq) was added dropwise to a solution of oxyamination product **177** (50 mg, 0.09 mmol) in dioxane (0.5 mL, 0.2 M) and the mixture was stirred at 60 °C for 8 h. The mixture was then cooled to room temperature and quenched with $NaHCO_3$ until pH 7. The mixture was extracted with CH_2Cl_2 and removed under reduced pressure to yield the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave **241** (29 mg, 0.07 mmol, 78%), as a white solid; mp 176–178 °C; IR (ATR)/cm^{-1}: 3463, 3322, 2852, 1403, 1314, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.54–7.48 (m, 2H), 7.26–7.06 (m, 8H), 6.94–6.85 (m, 4H), 5.91 (d, *J* = 4.3 Hz, 1H), 4.99 (d, *J* = 8.4 Hz, 1H), 4.82 (dd, *J* = 8.4, 4.3 Hz, 1H), 2.34 (s, 3H), 1.59–1.53(m, 1H), 1.00–0.79 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.9, 143.2, 137.6, 136.4, 135.3, 129.5, 128.6, 128.5, 128.1, 127.8, 127.7, 127.2, 127.2, 77.8, 61.3, 21.6, 13.2, 9.0, 8.9; LRMS (ES + APCI) *m/z* calculated for $C_{25}H_{25}NO_4S$ 435.2, found 453.0 $[M+NH_4]^+$; HRMS *m/z* calculated for $C_{25}H_{29}N_2O_4S$ 453.1848, found 453.1838 $[M+NH_4]^+$.

2-Mesityl-2-((4-methylphenyl)sulfonamido)ethyl cyclopropanecarboxylate 224A



224A

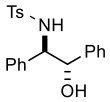
Following General Procedure D, oxyamination product **199** (50 mg, 0.10 mmol) and HCl (4 M in dioxane, 0.40 mmol) in dioxane (0.5 mL, 0.2 M) were reacted at 60 °C for 8 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 25:75) gave **224A** (25 mg, 0.06 mmol, 60 %), as a white solid; mp 94–96 °C; IR (ATR)/cm^{-1}: 3263, 2917, 1723, 1322, 1160; ^{1}H NMR (400 MHz, d^6-DMSO) δ (ppm) 8.18 (d, *J* = 5.3 Hz, 1H), 7.58 (d, *J* = 8.2 Hz,

2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.71 (br s, 2H), 4.76 (ddd, *J* = 8.8, 5.9, 5.3 Hz, 1H), 4.18 (dd, *J* = 11.3, 8.8 Hz, 1H), 4.08 (dd, *J* = 11.3, 5.9 Hz, 1H), 2.35 (s, 3H), 2.22 (s, 6H), 2.16 (s, 3H), 1.35–1.26 (m, 1H), 0.84–0.72 (m, 2H), 0.70–0.58 (m, 2H); ^{13}C NMR (101 MHz, d^6-DMSO) δ (ppm) 173.6, 142.4, 137.8, 136.2, 136.1, 131.3, 129.3, 126.5, 63.7, 52.1, 20.9, 20.3, 12.3, 8.2, 8.1 (2 carbons missing); LRMS (ES + APCI) *m/z* calculated for $C_{22}H_{27}NO_4S$ 401.2, found 419.0 $[M+NH_4]^+$.

4.2.10.2 General procedure E: Boc group and cyclopropyl ester cleavage with methylamine

Oxyamination product (1.0 eq) was dissolved in methylamine (33% in EtOH) (0.07M) and stirred at 40 °C for the required time. The reaction mixture was concentrated under reduced pressure. Purification by silica gel flash column chromatography using the appropriate solvent gave the desired compound.

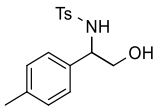
***Rel*-*N*-((1*R*,2*S*)-2-hydroxy-1,2-diphenylethyl)-4-methylbenzenesulfonamide 242**



242

Following General Procedure E, oxyamination product **177** (107 mg, 0.20 mmol) and methylamine (33% in EtOH, 1.5 mL, 0.13 M) were reacted at 40 °C for 18 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave the primary alcohol **242** (63 mg, 0.17 mmol, 86 %), as a light yellow solid; mp 180–182 °C; IR (ATR)/cm^{-1}: 3463, 3322, 2919, 1403, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.51–7.46 (m, 2H), 7.24–7.03 (m, 8H), 6.95 (d, *J* = 6.0, 2H), 6.84–6.78 (m, 2H), 5.24 (d, *J* = 7.9 Hz, 1H), 4.99 (d, *J* = 4.2 Hz, 1H), 4.55 (dd, *J* = 7.9, 4.2 Hz, 1H), 2.33 (s, 3H) (OH not observed); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 143.3, 139.2, 137.2, 135.9, 129.5, 128.4, 128.3, 128.1, 128.1, 127.8, 127.2, 126.6, 77.0, 63.3, 21.6; LRMS (ES + APCI) *m/z* calculated for $C_{21}H_{21}NO_3S$ 367.1, found 385.0 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{21}H_{25}N_2O_3S$ 385.1586, found 385.1581 $[M+NH_4]^+$.

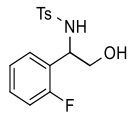
_N_-(2-hydroxy-1-(_p_-tolyl)ethyl)-4-methylbenzenesulfonamide 247



247

Following General Procedure E, oxyamination product **196** (236 mg, 0.50 mmol) and methylamine (33% in EtOH, 4 mL, 0.20 M) were reacted at 40 °C for 18 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 2:5) gave the primary alcohol **247** (86 mg, 0.28 mmol, 56 %), as a white solid; mp 90–92 °C; IR (ATR)/cm^{-1}: 3486; 3311, 2919, 1316, 1154; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 5.27 (d, *J* = 6.4 Hz, 1H), 4.34 (dt, *J* = 6.4, 5.7 Hz, 1H), 3.73 (d, *J* = 5.7 Hz, 2H), 2.39 (s, 3H), 2.28 (s, 3H), 1.87 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 143.5, 138.0, 137.2, 134.7, 129.6, 129.5, 127.4, 126.9, 66.4, 59.4, 21.6, 21.2; LRMS (ES + APCI) *m/z* calculated for $C_{16}H_{19}NO_3S$ 305.1, found 306.0 $[M+H]^+$.

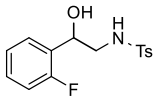
_N_-(1-(2-fluorophenyl)-2-hydroxyethyl)-4-methylbenzenesulfonamide 225A



225A

Following General Procedure E, oxyamination product **203** (70 mg, 0.15 mmol) and methylamine (33% in EtOH, 2 mL, 0.07 M) were reacted at 40 °C for 18 h. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 3:10) gave the primary alcohol **225A** (18 mg, 0.06 mmol, 40%), as a white solid; mp 68–70 °C; IR (ATR)/cm^{-1}: 3389, 3173, 1487, 1322, 1147; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J* = 8.3 Hz, 2H), 7.23–7.11 (m, 4H), 6.99 (td, *J* = 7.5, 1.1 Hz, 1H), 6.91 (ddd, *J* = 10.8, 8.2, 1.1 Hz, 1H), 5.27 (d, *J* = 7.8 Hz, 1H), 4.66 (dt, *J* = 7.8, 5.5 Hz, 1H), 3.75 (d, *J* = 5.5 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 160.2 (d, *J* = 246.1 Hz), 143.6, 137.0, 129.8 (d, *J* = 8.9 Hz), 129.6, 129.2 (d, *J* = 3.8 Hz), 127.3, 124.8 (d, *J* = 12.7 Hz), 124.5 (d, *J* = 3.2 Hz), 115.8 (d, *J* = 21.9 Hz), 65.2, 55.0, 21.6; LRMS (ES + APCI) *m/z* calculated for $C_{15}H_{16}FNO_3S$ 309.08, found 310.1 $[M+H]^+$; HRMS *m/z* calculated for $C_{15}H_{16}FNO_3S$ 309.0835, found 332.0729 $[M+Na]^+$.

_N_-(2-(2-fluorophenyl)-2-hydroxyethyl)-4-methylbenzenesulfonamide 225B

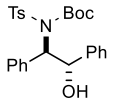


225B

Secondary alcohol **225B** (21 mg, 0.07 mmol, 47%) as a white solid; mp 92–92 °C; IR (ATR)/cm^{-1}: 3465, 3266, 2921, 1307, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74 (d, *J* = 8.3 Hz, 2H), 7.45 (td, *J* = 7.5, 1.7 Hz, 1H), 7.32 – 7.25 (m, 3H), 7.15 (td, *J* = 7.5, 1.0 Hz, 1H), 7.00 (ddd, *J* = 10.4, 8.2, 1.1 Hz, 1H), 5.07 (dd, *J* = 8.1, 3.3 Hz, 1H), 4.91 – 4.83 (m, 1H), 3.35 (ddd, *J* = 13.4, 7.8, 3.3 Hz, 1H), 3.09 (ddd, *J* = 13.4, 8.1, 4.8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 159.71 (d, *J* = 246.3 Hz), 143.8, 136.9, 130.0, 129.8 (d, *J* = 8.1 Hz), 127.8 (d *J* = 12.9 Hz), 127.7 (d, *J* = 4.2 Hz), 127.3, 124.6 (d, *J* = 3.4 Hz), 115.5 (d, *J* = 21.5 Hz), 67.3, 49.0, 21.7; LRMS (ES + APCI) *m/z* calculated for $C_{15}H_{16}FNO_3S$ 309.1, found 310.0 $[M+H]^+$.

4.2.10.3 Ester cleavage

tert-butyl-_rel_-((1*R*,2*S*)-2-hydroxy-1,2-diphenylethyl)(tosyl)carbamate 243

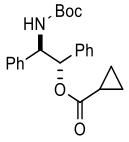


243

Potassium carbonate (52 mg, 0.38 mmol) was added to a solution of oxyamination product **177** (41 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) and MeOH (1 mL) and stirred at room temperature for 18 h. H_2O (2 mL) and CH_2Cl_2 were added to the reaction mixture and the layers separated. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Pet 15:85) gave the desired product **243** (27 mg, 0.06 mmol, 72%) as a white solid; mp 166–168 °C; IR (ATR)/cm^{-1}: 3326, 2917, 1732, 1599, 1283, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50 (d, *J* = 8.3 Hz, 2H), 7.25–7.06 (m, 8H), 6.96–6.89 (m, 4H), 5.72 (d, *J* = 4.6 Hz, 1H), 5.03 (d, *J* = 8.3 Hz, 1H), 4.80 (dd, *J* = 8.3, 4.6 Hz, 1H), 2.34 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 152.7, 143.2, 137.5, 136.2, 135.3, 129.5, 128.7, 128.5, 128.1, 128.0, 127.8, 127.2, 127.1, 83.0, 80.6, 61.3, 27.8, 21.6; LRMS (ES + APCI) *m/z* calculated for $C_{26}H_{29}NO_5S$ 467.2, found 485.0 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{26}H_{29}NNaO_5S$ 490.1659, found 490.1641 $[M+Na]^+$.

4.2.10.4 Sulfonamide cleavage

***Rel*-(1*S*,2*R*)-2-((*tert*-butoxycarbonyl)amino)-1,2-diphenylethyl cyclopropanecarboxylate 245**[51]



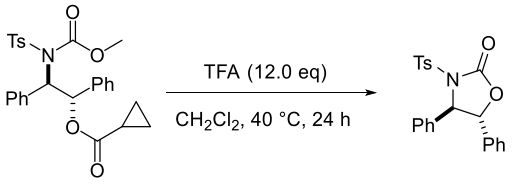
245

1-Dodecanethiol (0.32 mL, 1.35 mmol) was added to sulfonamide **244** (147 mg, 0.27 mmol) in DMF (1 mL) and the mixture sparged with argon for 20 min. DBU (0.19 mL, 1.28 mmol) was added and the reaction stirred at rt for 5 h under argon. The reaction mixture was then poured into water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with *aq.* LiCl (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product. Purification by silica gel flash column chromatography (EtOAc:Pet 1:9) gave the desired product **245** (75 mg, 0.20 mmol, 73%) as a white solid; mp 182–184 °C; IR (ATR)/cm^{-1}: 3395, 2971, 1719, 1684, 1519, 1165; ^{1}H NMR (400 MHz, *d*^{6}-DMSO) δ (ppm) 7.55 (d, *J* = 9.5 Hz, 1H), 7.43–7.23 (m, 10H), 5.80 (d, *J* = 9.5 Hz, 1H), 4.86 (app.t, *J* = 9.5 Hz, 1H), 1.44–1.38 (m, 1H), 1.19 (s, 9H), 0.75–0.58 (m, 3H), 0.55–0.45 (m,

1H); ^{13}C NMR (101 MHz, d^6-DMSO) δ (ppm) 172.2, 154.5, 140.2, 138.4, 127.9, 127.8, 127.3, 127.2, 77.9, 76.1, 58.0, 28.0, 12.6, 7.7, 7.6 (2 carbons missing); LRMS (ES + APCI) *m/z* calculated for $C_{23}H_{27}NO_4$ 381.2, found 763.2 [Dimer+H]$^+$. HRMS *m/z* calculated for $C_{23}H_{27}NNaO_4$ 404.1838, found 404.1824 [M+Na]$^+$.

4.2.11 Oxazolidinone formation

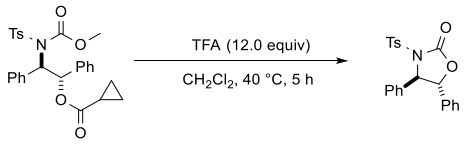
4.2.11.1 Initial Result



180 **246**, 77%

Oxyaminated material **180** (112 mg, 0.26 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and TFA (0.5 mL) added dropwise, then the mixture was then stirred for 24 h at 40 °C in a sealed vial. The reaction mixture was then concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:10) gave oxazolidinone **246** (85 mg, 0.22 mmol, 77%) as a white solid. For full characterisation see p182.

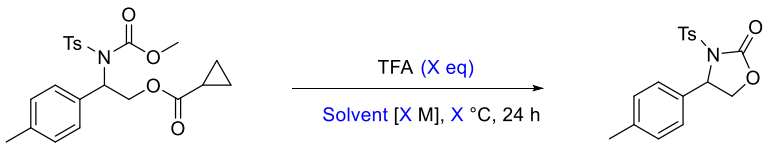
4.2.11.2 Doping experiment: methyl cyclopropanecarboxylate and methyl trifluoroacetate



180 **246**

Malonoyl peroxide **3** (103 mg, 1.00 mmol) was placed into a flame dried reaction vessel containing 3 Å molecular sieves (activated under N_2). Dry $CDCl_3$ (0.25 M, with respect to nucleophile **179**) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing *trans*-stilbene **1** (103 mg, 0.57 mmol) and nucleophile **179** (65 mg, 0.28 mmol), under an N_2 atmosphere. The mixture was stirred at 40 °C for 24 h. The reaction mixture was then concentrated under reduced pressure. The material was dissolved in CH_2Cl_2 (0.5 mL) and TFA (0.5 mL) added dropwise, then the mixture was then stirred for 5 h at 40 °C in a sealed vial. Approx 50 μL was extracted from the reaction mixture and diluted with $CDCl_3$ to 1 mL within an NMR tube and a ^{1}H NMR experiment was run. Methyl cyclopropane carboxylate or methyl trifluoroacetate (approx. 5 μL) was then added to the NMR tube and a ^{1}H NMR experiment was run.

4.2.11.3 Optimisation of reaction conditions for styrene substrates



261 **262**

Oxyaminated substrate **261** (108 mg, 0.25 mmol) was dissolved in the specified solvent and TFA added dropwise, then the mixture was stirred for the stated time at the stated temperature in a sealed vial. The reaction mixture was then concentrated under reduced pressure to give the crude product. The crude product was redissolved in $CDCl_3$ (1 mL) and 1,4-dinitrobenzene (11 mg 62.50 μmol) added. The mixture was then analysed by ^1H NMR spectroscopy.

Entry	TFA (eq)	Solvent	Temperature	Reaction concentration	Yield (%)
1	12	CH_2Cl_2	40 °C	0.1 M	0
2	12	CH_2Cl_2	40 °C	0.5 M	0
3	12	DMF	40 °C	0.5 M	0
4	12	DMF	120 °C	0.5 M	0
5	24	Neat	40 °C	0.5 M	0
6	120	Neat	60 °C	0.1 M	8
7	12	Dioxane	40 °C	0.5 M	0
8	12	Dioxane	100 °C	0.5 M	73[a]

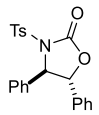
[a]Reaction run for 4 d.

The experiment corresponding to entry 6 was isolated by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) which gave the oxazolidinone **262** (7 mg, 0.02 mmol, 8%) as a white solid. See p182 for characterisation.

The experiment corresponding to entry 8 was isolated by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) which gave the oxazolidinone **262** (61 mg, 0.18 mmol, 73%) as a white solid. See p182 for characterisation.

4.2.11.4 Substrate scope

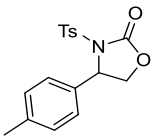
***Rel*-(4*R*,5*R*)-4,5-diphenyl-3-tosyloxazolidin-2-one 246**



246

Following General Procedure C, *trans*-stilbene **1** (103 mg, 0.57 mmol), malonoyl peroxide **3** (103 mg, 1.00 mmol) and nucleophile **179** (65 mg, 0.28 mmol) were reacted in $CHCl_3$ (1.0 mL) at 40 °C for 24 h. The reaction mixture was then concentrated under reduced pressure. The material was dissolved in CH_2Cl_2 (0.5 mL) and TFA (0.5 mL) added dropwise, then the mixture was then stirred for 5 h at 40 °C in a sealed vial. The reaction mixture was then concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:10) gave oxazolidinone **246** (exp 1 = 84 mg, 0.22 mmol, 77%; exp 2 = 84 mg, 0.21 mmol, 76%; average = 77%) as a white solid; mp 98–100 °C; IR (ATR)/cm^{-1}: 2922, 1777, 1597, 1366, 1167 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52 (d, *J* = 8.2 Hz, 2H), 7.44–7.33 (m, 6H), 7.29–7.22 (m, 4H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.33 (d, *J* = 4.0 Hz, 1H), 5.24 (d, *J* = 4.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 152.0, 145.5, 137.8, 137.3, 134.9, 129.7, 129.6, 129.5, 129.4, 128.6, 127.1, 125.3, 83.4, 68.2, 21.8 (1 carbon missing); LRMS (ES + APCI) *m/z* calculated for $C_{22}H_{19}NO_4S$ 393.1, found 394.0 $[M+H]^+$. HRMS *m/z* calculated for $C_{22}H_{19}NNaO_4S$ 416.0927, found 416.0910 $[M+Na]^+$.

4-(*p*-tolyl)-3-tosyloxazolidin-2-one 262

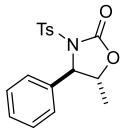


262

Following General Procedure C, 4-methylstyrene (0.13 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **179** (115 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. The reaction mixture was then concentrated under reduced pressure. The material was dissolved in 1,4-dioxane (0.5 mL) and TFA (0.5 mL) added dropwise, then the mixture was stirred for 4 d at 100 °C in a sealed vial. The reaction mixture was then concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave oxazolidinone **262** (exp 1 = 116 mg, 0.35 mmol, 70%; exp 2 = 126 mg, 0.38 mmol, 76%; average = 73%) as a white solid; mp 106–108 °C; IR (ATR)/cm^{-1}: 2917, 1760, 1597, 1364, 1173, 1117; ^{1}H NMR (400 MHz,

$CDCl_3$) δ (ppm) 7.44 (d, *J* = 8.4 Hz, 2H), 7.15–7.09 (m, 6H), 5.39 (dd, *J* = 8.6, 3.5 Hz, 1H), 4.70 (t, *J* = 8.6 Hz, 1H), 4.25 (dd, *J* = 8.6, 3.5 Hz, 1H), 2.38 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 152.2, 145.3, 139.4, 135.0, 134.9, 129.9, 129.4, 128.6, 127.1, 70.7, 60.4, 21.8, 21.3; LRMS (ES + APCI) *m/z* calculated for $C_{17}H_{17}NO_4S$ 331.1, found 331.9 $[M+H]^+$. HRMS *m/z* calculated for $C_{17}H_{18}NO_4S$ 332.0951, found 332.0946 $[M+H]^+$.

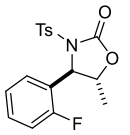
***Rel*-(4*R*,5*R*)-5-methyl-4-phenyl-3-tosyloxazolidin-2-one 264**



264

Following General Procedure C, trans-β-methylstyrene (0.13 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **179** (115 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. The reaction mixture was then concentrated under reduced pressure. The material was dissolved in 1,4-dioxane (0.5 mL) and TFA (0.5 mL) added dropwise, then the mixture was then stirred for 4 d at 100 °C in a sealed vial. The reaction mixture was then concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:10) gave oxazolidinone **264** (exp 1 = 91 mg, 0.28 mmol, 55%; exp 2 = 104 mg, 0.32 mmol, 63%; average = 59%) as a yellow solid; mp 128–130 °C; IR (ATR)/cm^{-1}: 29221, 1768, 1597, 1362, 1167; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48 (d, *J* = 8.2 Hz, 2H), 7.40–7.29 (m, 3H), 7.22 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 4.93 (d, *J* = 3.9 Hz, 1H), 4.50 (qd, *J* = 6.3, 3.9 Hz, 1H), 2.39 (s, 3H), 1.52 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 151.8, 145.3, 137.6, 135.0, 129.5, 129.3, 129.3, 128.5, 127.2, 79.5, 67.2, 21.8, 20.5; LRMS (ES + APCI) *m/z* calculated for $C_{17}H_{17}NO_4S$ 331.1, found 332.0 $[M+H]^+$. HRMS *m/z* calculated for $C_{17}H_{17}NNaO_4S$ 354.0770, found 354.0756 $[M+Na]^+$.

***Rel*-(4*R*,5*R*)-4-(2-fluorophenyl)-5-methyl-3-tosyloxazolidin-2-one 265**

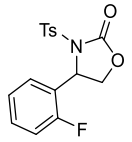


265

Following General Procedure C, trans-β-methyl-2-fluorostyrene (0.07 mL, 0.50 mmol), malonoyl peroxide **3** (115 mg, 0.90 mmol) and nucleophile **179** (58 mg, 0.25 mmol) were reacted in $CHCl_3$ (1.0 mL) at 40 °C for 4 d. The reaction mixture was then concentrated under reduced pressure. The material was dissolved in 1,4-dioxane (0.25 mL) and TFA (0.25 mL)

added dropwise, then the mixture was then stirred for 3 d at 100 °C in a sealed vial. The reaction mixture was then concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 15:85) gave oxazolidinone **265** (exp 1 = 57 mg, 0.16 mmol, 65%; exp 2 = 53 mg, 0.15 mmol, 61%; average = 63%) as a white solid; mp 168–170 °C; IR (ATR)/cm^{-1}: 2980, 1770, 1493, 1362, 1165, 1132; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (d, *J* = 8.4 Hz, 2H), 7.42–7.31 (m, 1H), 7.30–7.26 (m, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.14 (td, *J* = 7.6, 1.0 Hz, 1H), 7.06–6.99 (m, 1H), 5.20 (d, *J* = 4.1 Hz, 1H), 4.48 (qd, *J* = 6.3, 4.1 Hz, 1H), 2.42 (s, 3H), 1.50 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 160.5 (d, *J* = 248.6 Hz), 151.7, 145.6, 134.9, 131.0 (d, *J* = 8.3 Hz), 129.7, 128.8 (d, *J* = 3.2 Hz), 128.5, 124.9 (d, *J* = 5.5 Hz), 124.9 (d, *J* = 3.9 Hz), 116.2 (d, *J* = 21.2 Hz), 78.5, 61.9, 21.8, 20.7; LRMS (ES + APCI) *m/z* calculated for $C_{17}H_{16}FNO_4S$ 349.1, found 350.0 $[M+H]^+$. HRMS *m/z* calculated for $C_{17}H_{16}FNNaO_4S$ 372.0676, found 372.0660 $[M+Na]^+$.

4-(2-fluorophenyl)-3-tosyloxazolidin-2-one 266A

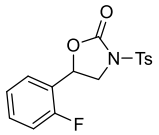


266A

Following General Procedure C, 2-fluorostyrene (0.12 mL, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **179** (115 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. The reaction mixture was then concentrated under reduced pressure. The material was dissolved in 1,4-dioxane (0.5 mL) and TFA (0.5 mL) added dropwise, then the mixture was then stirred for 4 d at 100 °C in a sealed vial. The reaction mixture was then concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:9) gave oxazolidinone **266A** (exp 1 = 79 mg, 0.24 mmol, 47%; exp 2 = 87 mg, 0.26 mmol, 52%; average = 50%) and oxazolidinone **266B** (exp 1 = 37 mg, 0.11 mmol, 22%; exp 2 = 35 mg, 0.11 mmol, 21%; average = 22%)as white solids; mp 148–150 °C; IR (ATR)/cm^{-1}: 1772, 1493, 1370, 1169; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.54 (d, *J* = 8.2 Hz, 2H), 7.40–7.32 (m, 1H), 7.31–7.26 (m, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.13 (td, *J* = 7.6, 1.0 Hz, 1H), 7.00 (ddd, *J* = 10.5, 8.3, 1.0 Hz, 1H), 5.67 (dd, *J* = 8.9, 3.8 Hz, 1H), 4.72 (t, *J* = 8.9 Hz, 1H), 4.25 (dd, *J* = 8.9, 3.8 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 160.6 (d, *J* = 248.9 Hz), 152.0, 145.5, 134.8, 131.2 (d, *J* = 8.4 Hz), 129.6, 129.4 (d, *J* = 3.1 Hz), 128.4, 125.0 (d, *J* = 12.6 Hz), 124.9 (d, *J* = 3.4 Hz), 116.3 (d, *J* = 20.9 Hz), 69.3, 55.5 (d, *J* = 2.8 Hz), 21.8; LRMS (ES + APCI) *m/z* calculated for

$C_{16}H_{14}FNO_4S$ 335.1, found 336.0 $[M+H]^+$. HRMS *m/z* calculated for $C_{16}H_{14}FNNaO_4S$ 358.0520, found 358.0505 $[M+Na]^+$.

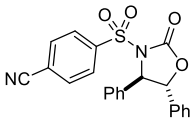
5-(2-fluorophenyl)-3-tosyloxazolidin-2-one 266B



266B

mp 120–122 °C; IR (ATR)/cm^{-1}: 2909, 1770, 1595, 1493, 1364, 1151; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.95 (d, *J* = 8.4 Hz, 2H), 7.42–7.31 (m, 4H), 7.17 (td, *J* = 7.6, 1.0 Hz, 1H), 7.10 (ddd, *J* = 10.5, 8.3, 1.0 Hz, 1H), 5.74 (t, *J* = 7.9 Hz, 1H), 4.48 (ddd, *J* = 9.5, 7.9, 1.2 Hz, 1H), 3.92 (ddd, *J* = 9.5, 7.9, 0.7 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 159.9 (d, *J* = 247.6 Hz), 151.5, 146.0, 134.1, 131.3 (d, *J* = 8.3 Hz), 130.1, 128.5, 127.1 (d, *J* = 3.1 Hz), 124.9 (d, *J* = 3.4 Hz), 124.2 (d, *J* = 12.8 Hz), 116.1 (d, *J* = 20.3 Hz), 70.7 (d, *J* = 3.3 Hz), 50.9 (d, *J* = 2.8 Hz), 21.9; LRMS (ES + APCI) *m/z* calculated for $C_{16}H_{14}FNO_4S$ 335.1, found 336.0 $[M+H]^+$. HRMS *m/z* calculated for $C_{16}H_{14}FNNaO_4S$ 358.0520, found 358.0504 $[M+Na]^+$.

4-((*Rel*-(4*R*,5*R*)-2-oxo-4,5-diphenyloxazolidin-3-yl)sulfonyl)benzonitrile 267



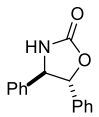
267

Following General Procedure C, *trans*-stilbene **1** (180 mg, 1.00 mmol), malonoyl peroxide **3** (230 mg, 1.80 mmol) and nucleophile **249** (115 mg, 0.50 mmol) were reacted in $CHCl_3$ (2.0 mL) at 40 °C for 24 h. The reaction mixture was then concentrated under reduced pressure. The material was dissolved in CH_2Cl_2 (0.5 mL) and TFA (0.5 mL) added dropwise, then the mixture was then stirred for 5 h at 40 °C in a sealed vial. The reaction mixture was then concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave oxazolidinone **267** (exp 1 = 111 mg, 0.28 mmol, 55%; exp 2 = 115 mg, 0.29 mmol, 57%; average = 56%) as a yellow solid; mp 152–154 °C; IR (ATR)/cm^{-1}: 2919, 2229, 1773, 1390, 1169; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71–7.59 (m, 4H), 7.48–7.41 (m, 4H), 7.41–7.33 (m, 2H), 7.32–7.27 (m, 2H), 7.25–7.19 (m, 2H), 5.42 (d, *J* = 3.5 Hz, 1H), 5.28 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 151.5, 141.8, 137.1, 136.9, 132.6, 130.0, 129.6, 129.6, 129.1, 127.4, 125.7, 125.2,

117.8, 117.1, 83.5, 68.1; LRMS (ES + APCI) *m/z* calculated for $C_{22}H_{16}N_2O_4S$ 404.0, found 422.0 $[M+NH_4]^+$. HRMS *m/z* calculated for $C_{22}H_{17}N_2O_4S$ 405.0904, found 405.0898 $[M+H]^+$.

4.2.11.5 Sulfonamide deprotection

***Rel*-(4*R*,5*R*)-4,5-diphenyloxazolidin-2-one 269**[51]



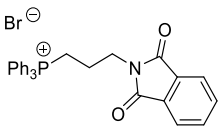
269

1-Dodecanethiol (0.2 mL, 0.87 mmol) was added to sulfonamide **267** (70 mg, 0.17 mmol) in DMF (0.5 mL) and the mixture sparged with argon for 20 min. DBU (0.12 mL, 0.81 mmol) was added and the reaction stirred at rt for 5 h under argon. The reaction mixture was then poured into water (3 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with *aq.* LiCl (6 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product. Purification by silica gel flash column chromatography (EtOAc:Pet 1:3) gave the desired product **269** (27 mg, 0.11 mmol, 68%) as a white solid; mp 152–154 °C; IR (ATR)/cm^{-1}: 3246, 1752, 1457, 1335, 1199; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) δ 7.45–7.36 (m, 6H), 7.35–7.27 (m, 4H), 5.39 (s, 1H), 5.31 (d, *J* = 7.4 Hz, 1H), 4.75 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 158.5, 138.4, 137.5, 129.4, 129.3, 129.1, 126.6, 126.0, 86.3, 65.0 (1 carbon missing); LRMS (ES + APCI) *m/z* calculated for $C_{15}H_{13}NO_2$ 239.1, found 240.1 $[M+H]^+$. HRMS *m/z* calculated for $C_{15}H_{14}NO_2$ 240.1019, found 240.1011 $[M+H]^+$.

4.2.12 Intramolecular oxyamination

4.2.12.1 Alkene synthesis

(3-(1,3-dioxoisoindolin-2-yl)propyl)triphenylphosphonium bromide 275

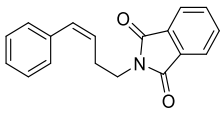


275

2-(3-Bromopropyl)isoindoline-1,3-dione **274** (5.0 g, 18.70 mmol) and triphenylphosphine (4.9 g, 18.70 mmol) in toluene (100 mL) was refluxed for 3 d. The precipitate was filtered, washed with hexane and dried under reduced pressure, to give the *title compound* **275** (7.5 g, 14.20 mmol, 76%) without further purification; mp 210–212 °C [Lit: 214–216 °C][112]; IR (ATR)/cm^{-1}: 3008, 2850, 2790, 1768, 1699, 1400, 1374, 1113; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.92–

7.82 (m, 6H), 7.81–7.61 (m, 13H), 4.20–4.10 (m, 2H), 3.95 (t, J = 7.0 Hz, 2H), 2.11–2.13 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 168.24, 135.18, 134.2, 133.9 (d, J = 10.2 Hz), 132.1, 130.7 (d, J = 12.5 Hz), 123.5, 118.3 (d, J = 86.1 Hz), 38.2 (d, J = 16.8 Hz), 22.1 (d J = 3.6 Hz, 21.0), 17.6 (d, J = 51.8 Hz); LRMS (ES + APCI) m/z calculated for $C_{29}H_{25}NO_2P^+$ 450.2, found 450.0 $[M\text{-}Br]^+$.

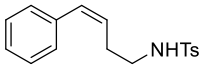
(*Z*)-2-(4-phenylbut-3-en-1-yl)isoindoline-1,3-dione 276



276

(3-(1,3-Dioxoisoindolin-2-yl)propyl)triphenylphosphonium bromide **275** (4.3 g, 8.10 mmol) and benzaldehyde (0.83 mL, 8.10 mmol) were dissolved in THF (30 mL). The mixture was cooled to 0 °C and stirred for 15 min. At this temperature potassium *tert*-butoxide (907 mg, 8.10 mmol) was added and the mixture stirred for 15 min. The mixture was allowed to warm to room temperature and stirred for 24 h. The suspension was filtered off and the solvent evaporated under reduced pressure. Purification by silica gel flash column chromatography (EtOAc:Hexane 1:9) gave the *title compound* **276** (436 mg, 1.60 mmol, 19 %, 19:1 *Z:E*), as a clear oil; IR (ATR)/cm^{-1}: 3019, 2937, 1770, 1703, 1392; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85–7.78 (m, 2H), 7.74–7.66 (m, 2H), 7.31–7.27 (m, 1H), 7.24–7.14 (m, 4H), 6.51 (d, J = 11.7 Hz, 1H), 5.68 (dt, J = 11.7, 7.4 Hz, 1H), 3.81 (t, J = 7.2 Hz, 2H), 2.73 (ddd, J = 7.4, 7.2, 1.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 168.5, 137.1, 134.0, 132.3, 131.8, 128.8, 128.4, 127.8, 127.0, 123.4, 37.8, 28.0; LRMS (ES + APCI) m/z calculated for $C_{18}H_{15}NO_2$ 277.1, found 278.1 $[M+H]^+$.

(*Z*)-4-methyl-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide 270

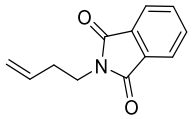


270

Hydrazine monohydrate (0.13 mL, 2.74 mmol) was added to a solution of (*Z*)-2-(4-phenylbut-3-en-1-yl)isoindoline-1,3-dione **276** (380 mg, 1.37 mmol) in EtOH (4 mL). The mixture was stirred at rt for 10 min then at reflux for a further 30 min. The mixture was allowed to cool to rt before the addition of a 2 M *aq.* solution of NaOH (25 mL). Ethanol was evaporated before extracting with EtOAc (3 × 25 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give the *free amine compound* which was used without further

purification. The crude amine was re-dissolved in anhydrous CH_2Cl_2 (4 mL) under argon atmosphere and Et_3N (0.23 mL, 1.68 mmol) was added. The mixture was cooled to 0 °C, and *p*-toluenesulfonyl chloride (212 mg, 1.12 mmol) and DMAP (41 mg, 0.34 mmol) were added. The resultant mixture was stirred at rt for 5 h. The solution was then diluted with CH_2Cl_2 and washed with 2 M HCl (25 mL) and brine (25 mL). The organics were dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (EtOAc:Hexane 15:85) gave the *title compound* **270** (236 mg, 0.78 mmol, 57 %, 19:1 *Z:E*), as a clear oil; IR (ATR)/cm^{-1}: 3259, 2948, 2850, 1433, 1320, 1149, 1065; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) δ 7.72–7.67 (m, 2H), 7.35–7.28 (m, 2H), 7.26–7.23 (m, 3H), 7.20–7.16 (m, 2H), 6.53 (d, J = 11.6 Hz, 1H), 5.49 (dt, J = 11.6, 7.2 Hz, 1H), 4.32 (br t, J = 6.4 Hz, 1H), 3.07 (dd, J = 7.0, 6.4 Hz, 2H), 2.47 (ddd, J = 7.2, 7.0, 1.8 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 143.6, 137.1, 136.9, 132.4, 129.9, 128.8, 128.4, 127.6, 127.2, 127.2, 43.1, 28.7, 21.7; LRMS (ES + APCI) m/z calculated for $C_{17}H_{19}NO_2S$ 301.1, found 302.0, found $[M+H]^+$.

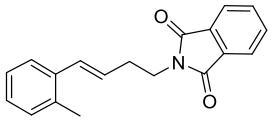
2-(But-3-en-1-yl)isoindoline-1,3-dione 278



278

Potassium phthalimide (5.3 g, 28.60 mmol) was dissolved in DMF (12 mL). 4-Bromobut-1-ene **277** (2.3 mL, 22.00 mmol) was added and the mixture was stirred at reflux for 5 h. The mixture was cooled to rt, poured over ice and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with 0.2 M KOH (50 mL), H_2O (50 mL), dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation to afford the *title* compound **278** (2.7 g, 13.60 mmol, 47%) as a brown solid without further purification; mp 42–44 °C [Lit: 45-46 °C][113]; IR (ATR)/cm^{-1}: 3075, 2974, 2939, 1768, 1693; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) δ 7.87–7.81 (m, 2H), 7.74–7.68 (m, 2H), 5.80 (ddt, J = 17.2, 10.2, 6.9 Hz, 1H), 5.07 (dd, J = 17.2, 1.7 Hz, 1H), 5.04–5.00 (m, 1H), 3.77 (t, J = 7.1 Hz, 2H), 2.51–2.39 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 168.5, 134.6, 134.0, 132.3, 123.4, 117.7, 37.5, 33.0; LRMS (ES + APCI) m/z calculated for $C_{12}H_{11}NO_2$ 201.1, found 202.0 $[M+H]^+$.

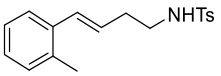
(*E*)-2-(4-*o*-Tolyl)but-3-en-1-yl)isoindoline-1,3-dione 279



279

To a flame dried flask was charged aryl iodide (1.1 mL, 8.20 mmol) and Et_3N (2.0 mL, 14.80 mmol) in MeCN (150 mL). 2-(But-3-en-1-yl)isoindoline-1,3-dione **278** (1.5 g, 7.40 mmol) was added followed by P(*o*-tol)$_3$ (0.9 g, 3.00 mmol) and $Pd(OAc)_2$ (45.0 mg, 1.50 mmol) and the mixture stirred at reflux for 18 h. The solution was cooled to rt, passed through a plug of Celite® and the solvent concentrated *in vacuo*. The crude residue was re-dissolved in EtOAc (100 mL) and washed with 2 M HCl (2 × 100 mL), H_2O (2 × 100 mL), dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation. Purification by silica gel flash column chromatography (EtOAc:Hexane 1:9) gave the *title compound* **279** (900 mg, 3.10 mmol, 42%), as a yellow solid; mp 126–128 °C; IR (ATR)/cm^{-1}: 3008, 2939, 2855, 1770, 1706, 1349; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) δ 7.84 (dd, J = 5.5, 3.0 Hz, 2H), 7.70 (dd, J = 5.5, 3.0 Hz, 2H), 7.37–7.33 (m, 1H), 7.16–7.05 (m, 3H), 6.59 (d, J = 15.7 Hz, 1H), 6.03 (dt, J = 15.7, 7.2 Hz, 1H), 3.86 (t, J = 7.1 Hz, 2H), 2.64 (ddd, J = 7.2, 7.1, 1.4 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) δ 168.5, 136.6, 135.2, 134.1, 132.3, 130.8, 130.2, 127.7, 127.3, 126.2, 126.0, 123.4, 37.8, 32.6, 19.8; LRMS (ES + APCI) m/z calculated for $C_{19}H_{17}NO_2$ 291.1, found 292.0 $[M+H]^+$.

(*E*)-4-Methyl-*N*-(4-(*o*-tolyl)but-3-en-1-yl)benzenesulfonamide 272

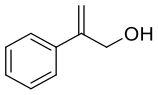


272

Hydrazine monohydrate (0.34 mL, 7.00 mmol) was added to a solution of (*E*)-2-(4-*o*-Tolyl)but-3-en-1-yl)isoindoline-1,3-dione **279** (1.1g, 3.50 mmol) in EtOH (12 mL). The mixture was stirred at rt for 10 min then at reflux for a further 30 min. The mixture was allowed to cool to rt before the addition of a 2 M *aq.* solution of NaOH (50 mL). Ethanol was evaporated before extracting with EtOAc (3 × 50 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give the *free amine compound* which was used without further purification. The crude amine was re-dissolved in anhydrous CH_2Cl_2 (10 mL) under argon atmosphere and Et_3N (0.61 mL, 4.40 mmol) was added. The mixture was cooled to 0 °C, and *p*-toluenesulfonyl chloride (560 mg, 3.00 mmol) and DMAP (108 mg, 0.90 mmol) were added. The resultant mixture was stirred at rt for 24 h. The solution was then diluted with CH_2Cl_2 and washed with 2 M HCl (100 mL) and brine (100 mL). The organics were dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica

gel flash column chromatography (EtOAc:Hexane 1:9) gave the *title compound* **272** (437 mg, 1.40 mmol, 40 %), as a yellow solid; mp 66–69 °C; IR (ATR)/cm^{-1}: 3263, 3049, 2922, 2870, 1307, 1156; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78–7.72 (m, 2H), 7.34–7.27 (m, 3H), 7.16–7.11 (m, 3H), 6.58 (d, J = 15.7 Hz, 1H), 5.85 (dt, J = 15.7, 7.1 Hz, 1H), 4.39 (t, J = 6.0 Hz, 1H), 3.12 (dt, J = 6.0, 6.0 Hz, 2H), 2.42 (s, 3H), 2.41–2.36 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 143.6, 137.2, 136.0, 135.3, 131.4, 130.5, 129.9, 127.6, 127.3, 127.0, 126.2, 125.6, 42.7, 33.5, 21.7, 20.0; LRMS (ES + APCI) m/z calculated for $C_{18}H_{21}NO_2S$ 315.1, found 316.0 $[M+H]^+$.

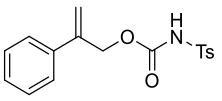
2-Phenylprop-2-en-1-ol 281[53]



281

Benzylmagnesium chloride (3M in THF, 10.0 mL, 30.00 mmol) was added dropwise to a solution of propargyl alcohol **280** (0.6 mL, 10.0 mmol) and CuI (950 mg, 5.00 mmol) in toluene (15 mL) at −78 °C. The reaction was warmed to room temperature and stirred for 16 h. The reaction mixture cooled to 0 °C and diluted with *aq*. NH_4Cl (20 mL) and EtOAc (20 mL) before the resulting layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave the *title compound* **281** (772 mg, 5.80 mmol, 58%) as a clear liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49–7.41 (m, 2H), 7.40–7.28 (m, 3H), 5.48 (d, *J* = 1.1 Hz, 1H), 5.36 (dd, *J* = 2.6, 1.1 Hz, 1H), 4.59–4.53 (m, 2H), 1.53 (t, *J* = 6.2 Hz, 1H); Material carried forward without further characterisation.

2-phenylallyl tosylcarbamate 282[53]



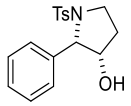
282

p-Toluenesulfonyl isocyanate (0.52 mL, 3.36 mmol) was added dropwise to a solution of 2-Phenylprop-2-en-1-ol **281** (300 mg, 2.24 mmol) in CH_2Cl_2 at 0 °C. The reaction was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with H_2O (5 mL) and the layers separated. The aqueous layer was re-extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic layers dried with $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:9) gave the *title compound* **282** (191 mg, 0.58 mmol, 26%) as a white solid; mp 56–58 °C [Lit: 68–69 °C][114]; IR (ATR)/cm^{-1}: 3242, 1755, 1450, 1342, 1162 ; ^{1}H NMR (400 MHz,

$CDCl_3$) δ (ppm) 7.86 (d, *J* = 8.4 Hz, 2H), 7.38–7.28 (m, 7H), 5.54 (s, 2H), 5.31 (d, *J* = 1.0 Hz, 1H), 4.98 (d, *J* = 1.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 150.2, 145.2, 141.6, 137.6, 129.8, 128.7, 128.5, 128.4, 126.1, 116.8, 68.3, 21.8 (1 carbon missing); LRMS (ES + APCI) *m/z* calculated for $C_{17}H_{17}NO_4S$ 331.1, found 349.0 $[M+NH_4]^+$.

4.2.12.2 Pyrrolidine synthesis

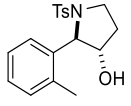
(2*S*,3*S*)-2-phenyl-1-tosylpyrrolidin-3-ol 271



271

Malonoyl peroxide **3** (45 mg, 0.35 mmol) was added to a solution of alkene **270** (70 mg, 0.23 mmol) in HFIP (0.5 mL) and mixture stirred at rt for 5 h. The solvent was removed by rotary evaporation and the resulting residue was directly treated with 1 M NaOH:THF (2 mL (1:1)). The solution was stirred at 60 °C for 18 h, allowed to cool to rt and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (100 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the crude pyrrolidine product (5:1 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc:Hexane 4:6) gave the *title compound* **271** (37 mg, 0.11 mmol, 50%), as a white solid; mp 114–116 °C; IR (ATR)/cm^{-1}: 3452, 2974, 2872, 1325, 1156; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69–7.64 (m, 2H), 7.39–7.28 (m, 7H), 4.74 (d, J = 5.6 Hz, 1H), 4.25–4.15 (m, 1H), 3.80–3.70 (m, 1H), 3.64 (ddd, J = 10.7, 7.7, 4.9 Hz, 1H), 2.43 (s, 3H), 1.89 (ddt, J = 16.3, 6.5, 4.9 Hz, 1H), 1.80–1.69 (m, 1H), 1.09 (d, J = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 143.7, 136.5, 135.0, 129.8, 128.8, 128.3, 127.7, 126.3, 73.7, 67.7, 47.2, 32.5, 21.7; LRMS (ES + APCI) m/z calculated for $C_{17}H_{19}NO_3S$ 317.1, found 318.0 $[M+H]^+$.

***Rel*-(2*R*,3*S*)-2-(*o*-Tolyl)-1-tosylpyrrolidin-3-ol 273**



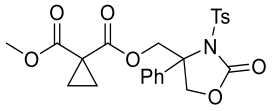
273

Malonoyl peroxide **3** (91 mg, 0.70 mmol) was added to a solution of alkene **272** (150 mg, 0.50 mmol) in HFIP (1 mL) and mixture stirred at rt for 5 h. The solvent was removed by rotary evaporation and the resulting residue was directly treated with 1 M NaOH:THF (5 mL (1:1)). The solution was stirred at 60 °C for 18 h, allowed to cool to rt and the aqueous phase was extracted with EtOAc (50 mL × 3). The combined organics were washed with brine (100 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the crude

pyrrolidine product (1:2 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc:Hexane 3:7) gave the *title compound* **273** (52 mg, 0.16 mmol, 31 %), as a yellow solid; mp 173–175 °C; IR (ATR)/cm^{-1}: 3514, 2921, 2885, 1290, 1154; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78–7.73 (m, 2H), 7.37 (dd, J = 7.7, 5.1 Hz, 1H), 7.31 (d, J = 7.9 Hz, 2H), 7.20–7.11 (m, 3H), 4.84 (s, 1H), 4.07 (d, J = 4.0 Hz, 1H), 3.81–3.73 (m, 1H), 3.54 (ddd, J = 11.1, 9.3, 6.7 Hz, 1H), 2.43 (s, 3H), 2.39 (s, 3H), 2.11–2.00 (m, 1H), 1.80–1.73 (m, 1H), 1.33 (d, J = 4.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 143.6, 138.2, 134.8, 134.4, 130.5, 129.7, 127.9, 127.5, 126.5, 126.2, 77.7, 69.7, 46.9, 31.6, 21.7, 19.6; LRMS (ES + APCI) m/z calculated for $C_{18}H_{21}NO_3S$ 331.1, found 332.0 $[M+H]^+$; HRMS (ESI-TOF) m/z calculated for $C_{18}H_{22}NO_3S$ 332.1320, found 332.1317.

4.2.12.3 Oxazolidinone synthesis

1-methyl 1-((2-oxo-4-phenyl-3-tosyloxazolidin-4-yl)methyl) cyclopropane-1,1-dicarboxylate 284



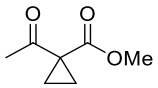
284

Malonoyl peroxide **3** (30 mg, 0.23 mmol) was placed into a flame dried reaction vessel containing activated 3 Å molecular sieves. Dry $CHCl_3$ (0.5 mL) was added and the solution allowed to stand for 2 h. The dried solution was then transferred to a separate flame dried vessel containing alkene **282** (50 mg, 0.15 mmol), under an argon atmosphere. The mixture was stirred at 40 °C for 18 h. The solvent was then removed under reduced pressure and redissolved in a MeOH:Toluene (1:2, 0.75 mL). TMS-CHN_2 (2M in Et_2O, 0.15 mL, 0.3 mmol) was added dropwise and the mixture stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5), gave the title compound **284** (10 mg, 0.02 mmol, 14%), as a clear oil; IR (ATR)/cm^{-1}: 2917, 2850, 1777, 1723, 1597, 1439, 1177, 1085; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J* = 8.2 Hz, 2H), 7.48–7.30 (m, 5H), 7.21 (d, *J* = 8.2 Hz, 2H), 5.21 (d, *J* = 11.7 Hz, 1H), 5.02 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 8.9 Hz, 1H), 4.34 (d, *J* = 8.9 Hz, 1H), 3.64 (s, 3H), 2.42 (s, 3H), 1.51–1.39 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.7, 169.4, 152.6, 145.7, 138.4, 135.0, 129.4, 129.4, 129.2, 125.8, 74.5, 67.9, 66.2, 53.0, 27.8, 21.8, 18.1, 18.0 (1 carbon missing); LRMS (ES + APCI) *m/z* calculated for $C_{23}H_{23}NO_8S$ 473.1, found 474.0 $[M+H]^+$.

4.3 Chapter 3 - Investigating the Reaction of Alkenes with a Peroxylactone

4.3.1 Synthesis of peroxylactones 400, 416 and 394

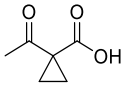
Methyl 1-acetylcyclopropane-1-carboxylate 403



403

A premixed solution of methyl acetoacetate **401** (17.3 mL, 160.00 mmol) and 1,2-dibromoethane **402** (20.1 mL, 240.00 mmol) were added to a stirred suspension of K_2CO_3 (66.0 g, 480.00 mmol) in acetone (120 mL) and the mixture stirred at reflux for 18 h. The reaction mixture was diluted with Et_2O (200 mL) and filtered. The resulting solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 5:95) gave the *title compound* **403** (10.3 g, 72.80 mmol, 46%) as a clear oil; IR (ATR)/cm^{-1}: 1727, 1697, 1439, 1199, 1119; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.74 (s, 3H), 2.46 (s, 3H), 1.48 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 203.2, 171.7, 52.4, 35.1, 30.0, 19.4, 19.4; LRMS (GCMS + CI) *m/z* calculated for $C_7H_{10}O_3$ 142.1, found 142.1 $[M]^+$.

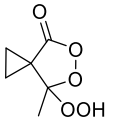
1-Acetylcyclopropane-1-carboxylic acid 395



395

4 M $NaOH_{(aq)}$ (7.0 mL, 27.00 mmol) was added dropwise to a solution of methyl 1-acetylcyclopropane-1-carboxylate **403** (755 mg, 5.30 mmol) in MeOH (3 mL) at 0 °C. The mixture was warmed to rt and stirred for 18 h. The MeOH was removed *in vacuo* and the resulting aqueous solution extracted with Et_2O (2 × 10 mL) and then acidified with 4 M $HCl_{(aq)}$ (10 mL). The resulting aqueous solution was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the *title compound* **395** (343 mg, 2.70 mmol, 50%) as a clear oil; IR (ATR)/cm^{-1}: 3010, 1694, 1646, 1363, 1124; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.12 (s, 3H), 2.02–1.96 (m, 2H), 1.79–1.68 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 209.7, 172.5, 33.7, 25.5, 21.7; LRMS (GCMS + CI) *m/z* calculated for $C_6H_8O_3$ 128.0, found 128.1 $[M]^+$.

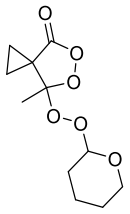
7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 400



400

H_2O_2 (50%, 285 μL, 5.00 mmol) was added to a solution of acetylcyclopropane-1-carboxylic acid **395** (128 mg, 1.00 mmol) and silica sulfuric acid (SSA) (100 mg) in $CHCl_3$ (4.0 mL) and stirred at rt for 24 h. The reaction mixture was diluted with water (15 mL) and the aqueous was extracted with $CHCl_3$ (3 × 15 mL). The combined organics were washed with saturated $NaHCO_3$ (3 × 15 mL) and brine (30 mL). The organics were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo* to afford the *title compound* **400** (100 mg, 0.63 mmol, 63%) as a colourless solid; IR (ATR)/cm^{-1}: 3440, 1763, 1331, 843, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.40 (br s, 1H), 1.55–1.45 (m, 2H), 1.44 (s, 3H), 1.41–1.31 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 176.6, 114.4, 28.2, 17.0, 15.9, 12.2; unable to obtain mass spectrometry data.

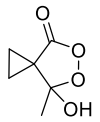
7-methyl-7-((tetrahydro-2H-pyran-2-yl)peroxy)-5,6-dioxaspiro[2.4]heptan-4-one 416



416

2,3-Dihyropyran **415** (140 μL, 1.65 mmol) was added to a solution of 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (260 mg, 1.63 mmol) and *p*-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol) in CH_2Cl_2 (3.0 mL). The resulting solution was stirred at rt for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with saturated $NaHCO_{3(aq)}$ (2 × 10 mL), brine (2 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:9) gave the *title compound* **416** (111 mg, 0.45 mmol, 28%) as a clear oil; IR (ATR)/cm^{-1}: 2917, 2956, 1785, 1329, 1180, 1132, 1072; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.84 (dd, J = 6.1, 2.2 Hz, 1H), 4.03–3.91 (m, 2H), 2.17–2.05 (m, 1H), 1.99–1.89 (m, 1H), 1.88–1.73 (m, 2H), 1.59–1.51 (m, 2H), 1.46–1.41 (m, 2H), 1.37 (s, 3H), 1.36–1.34 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 176.8, 114.2, 108.4, 68.1, 29.8, 28.2, 23.9, 23.9, 17.7, 16.5, 12.3; LRMS (ES + APCI) *m/z* calculated for $C_{11}H_{16}O_6$ 244.1, 262.1 found $[M+NH_4]^+$.

7-Hydroxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 394[97]

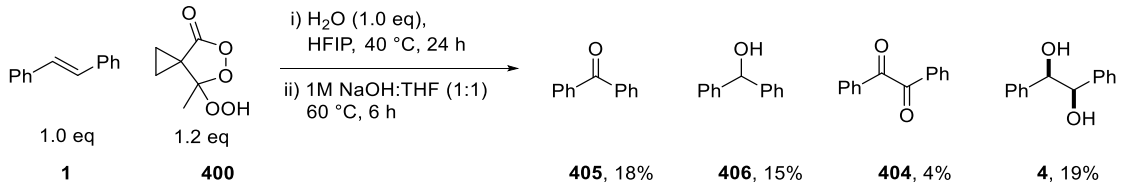


394

Triphenylphosphine (362 mg, 1.38 mmol) was added to a solution of 7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (200 mg, 1.25 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h. The solution was then concentrated *in vacuo* at rt to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 3:7) gave the *title compound* **394** (59 mg 0.42 mmol, 39%), as a clear oil; IR (ATR)/cm^{-1}: 3423, 3013, 1760, 1335, 1143, 1076; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.24 (s, 1H, OH), 1.46–1.42 (m, 1H), 1.44 (s, 3H), 1.41–1.37 (m, 1H), 1.35–1.30 (m, 1H), 1.29–1.23 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 177.4, 107.8, 31.7, 21.6, 15.6, 11.9; LRMS (ES + APCI) *m/z* calculated for $C_6H_8O_4$ 144.0, found 143.1 $[M-H]^-$.

4.3.2 Reaction of peroxylactone 400 with *trans*-stilbene 1

4.3.2.1 Reaction of *trans*-stilbene 1 and 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 400 with subsequent hydrolysis



7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (48 mg, 0.30 mmol) was added to a vial containing *trans*-stilbene (45 mg, 0.25 mmol) and H_2O (55 μL, 0.25 mmol) HFIP (0.50 mL). The resulting solution was stirred at 40 °C for 24 h. The mixture was then cooled to rt, concentrated *in vacuo* and redissolved in a 1:1 mixture of 1 M $NaOH_{(aq)}$ (1.25 mL) and THF (1.25 mL). The resulting solution was stirred at 60 °C for 6 h. The reaction mixture was then diluted with EtOAc (5 mL) and H_2O (5 mL), the organic layer collected and washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:9) gave the reaction products detailed below.

Benzophenone 405

405

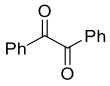
(8 mg, 44 μmol, 18%) as a white solid; mp 46–48 °C [46–47 °C][115]; IR (ATR)/cm^{-1}: 1651, 1593, 1212, 877; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85–7.76 (m, 4H), 7.64–7.54 (m, 2H), 7.53–7.43 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 196.9, 137.8, 132.6, 130.2, 128.4; LRMS (GCMS + CI) *m/z* calculated for $C_{13}H_{10}O$ 182.1, found 183.1 $[M+H]^+$.

Diphenylmethanol 406

406

(7 mg, 38 μmol, 15%) as a white solid; mp 62–64 °C [64–65 °C][116]; IR (ATR)/cm^{-1}: 3381, 1497, 1020, 737, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41–7.31 (m, 8H), 7.29–7.24 (m, 2H), 5.86 (s, 1H), 2.19 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 144.0, 128.7, 127.8, 126.7, 76.4; LRMS (GCMS + CI) *m/z* calculated for $C_{13}H_{12}O$ 184.1, found 184.1 $[M]^+$.

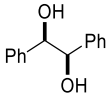
Benzil 404



404

(2 mg, 9.50 μmol, 4%), as a white solid; mp 88–90 °C [91–93 °C][117]; IR (ATR)/cm^{-1}: 1660, 1593, 1452, 1212, 877; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01–7.94 (m, 4H), 7.71–7.63 (m, 2H), 7.56–7.47 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 194.7, 135.0, 133.2, 130.1, 129.2; LRMS (ES + APCI) *m/z* calculated for $C_{14}H_{10}O_2$ 210.1, found 211.1 $[M+H]^+$.

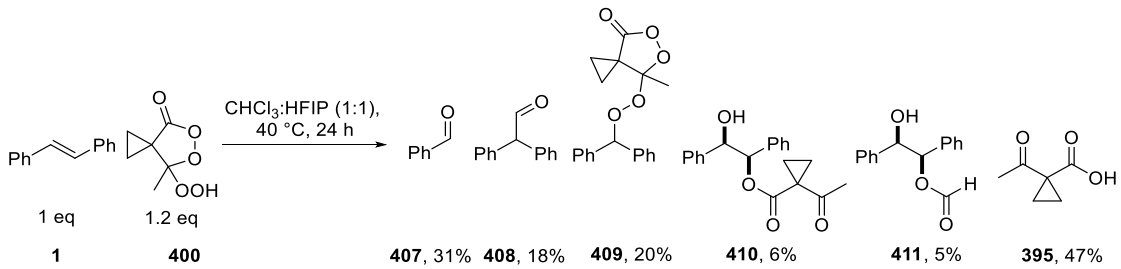
***Rel*-(1*R*,2*R*)-1,2-Diphenylethane-1,2-diol 4**



4

(10 mg 47 μmol, 19%) as a white solid; mp 142–144 °C [138–139 °C][118]; IR (ATR)/cm^{-1}: 3494, 3383, 1452, 748, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25–7.22 (m, 6H), 7.16–7.12 (m, 4H), 4.73 (s, 2H), 2.78 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 140.0, 128.3, 128.1, 127.1, 79.3; LRMS (ES + APCI) *m/z* calculated for $C_{14}H_{14}O_2$ 214.1, found 232.1 $[M+NH_4]^+$.

4.3.2.2 Reaction of *trans*-stilbene 1 and 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 400



7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (75 mg, 0.47 mmol) was added to a vial containing *trans*-stilbene **1** (70 mg, 0.40 mmol) in a 1:1 mixture of HFIP (0.4 mL) and $CHCl_3$ (0.4 mL). The resulting solution was stirred at 40 °C for 24 h. The mixture was then cooled to rt, concentrated *in vacuo* to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:9) gave the reaction products detailed below.

Benzaldehyde 407

407

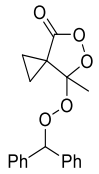
(13 mg, 123 μmol, 31%), as a clear liquid; IR (ATR)/cm^{-1}: 2819, 2738, 1700, 1204, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.03 (s, 1H), 7.91–7.86 (m, 2H), 7.67–7.61 (m, 1H), 7.56–7.51 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 192.5, 136.6, 134.6, 129.9, 129.2; LRMS (GCMS + CI) *m/z* calculated for C_7H_6O 106.0, found 106.1 $[M]^+$.

Diphenylacetaldehyde 408

408

(14 mg, 71 μmol, 18%), as a clear liquid; IR (ATR)/cm^{-1}: 3029, 2718, 1724, 1497, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.96 (d, J = 2.5 Hz, 1H), 7.41–7.36 (m, 4H), 7.31 (m, 2H), 7.25–7.21 (m, 4H), 4.90 (d, J = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 198.7, 136.5, 129.3, 129.2, 127.8, 64.3; LRMS (GCMS + CI) *m/z* calculated for $C_{14}H_{12}O$ 196.1, found 196.1 $[M]^+$.

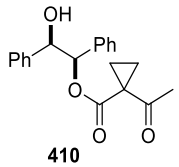
7-(Benzhydrylperoxy)-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 409



409

(26 mg, 80 μmol, 20%), as a clear oil; IR (ATR)/cm^{-1}: 3026, 1786, 1450, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42–7.30 (m, 10H), 6.35 (s, 1H), 1.47 (m, 1H), 1.41 (s, 3H), 1.31 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 176.6, 139.1, 138.8, 128.5, 128.4, 128.3, 128.1, 127.9, 114.2, 89.2, 28.6, 17.7, 15.8, 12.2 (1 carbon missing); LRMS (ES + APCI) *m/z* calculated for $C_{19}H_{18}O_5$ 326.1, found 344.0 $[M+NH_4]^+$.

***Rel*-(1*R*,2*R*)-2-Hydroxy-1,2-diphenylethyl 1-acetylcyclopropane-1-carboxylate 410**

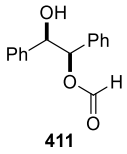


410

(7 mg, 22 μmol, 6%), as a white solid; mp 76–78 °C; IR (ATR)/cm^{-1}: 3405, 1727, 1681, 1186, 1128, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26–7.22 (m, 6H), 7.18–7.08 (m, 4H), 5.96

(d, J = 7.3 Hz, 1H), 4.95 (d, J = 7.3 Hz, 1H), 2.39 (s, 3H), 1.57–1.45 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 203.3, 170.2, 139.2, 136.5, 128.6, 128.5, 128.4, 128.3, 127.4, 127.1, 80.9, 76.8, 35.5, 29.4, 19.3, 19.0; LRMS (ES + APCI) *m/z* calculated for $C_{20}H_{20}O_4$ 324.1, found 347.1 $[M+Na]^+$.

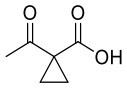
Rel-(1*R*,2*R*)-2-Hydroxy-1,2-diphenylethyl formate 411



411

(5 mg, 21 μmol, 5%), as a clear oil; IR (ATR)/cm^{-1}: 3416, 1724, 1458, 1167, 759, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.18 (s, 1H), 7.26–7.22 (m, 6H), 7.17–7.11 (m, 4H), 5.95 (d, J = 7.5 Hz, 1H), 4.98 (d, J = 7.5 Hz, 1H), 4.73 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 160.3, 138.8, 136.3, 128.6, 128.5, 128.4, 128.4, 127.5, 127.2, 80.1, 77.1; unable to obtain mass spectrometry data.

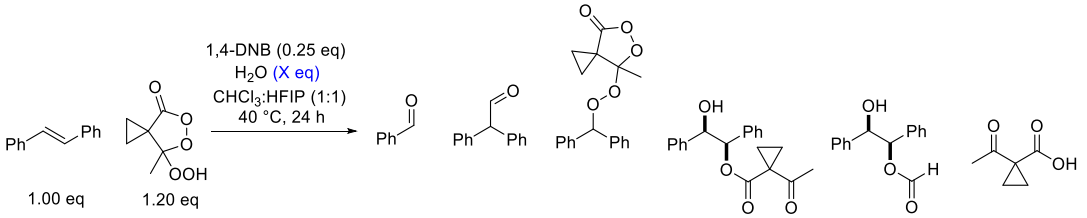
1-Acetylcyclopropane-1-carboxylic acid 395



395

(24 mg, 188 μmol, 47%) see p194.for characterisation.

4.3.3 Optimisation of equivalents of water



1.00 eq 1.20 eq

1 **400** **407** **408** **409** **410** **411** **395**

Entry	H_2O eq						
1	0	17%	11%	16%	8%	7%	39%
2	0 (flame dried vessel)	12%	3%	16%	8%	12%	48%
3	1	31%	18%	20%	6%	5%	47%
4	2	37%	8%	5%	6%	0%	53%
5	10	7%	1%	7%	0%	0%	41%

Conversions calculated by ^{1}H NMR spectroscopy using an internal standard (1,4-DNB).
Conversions calculated from a single experiment.

7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (75 mg, 0.47 mmol) was added to a vial containing *trans*-stilbene **1** (70 mg, 0.40 mmol) in a 1:1 mixture of HFIP (0.4 mL) and $CHCl_3$ (0.4 mL). The stated quantity of water was then added. The resulting solution

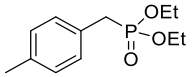
was stirred at 40 °C for 24 h. The mixture was then cooled to rt and analysed by ^{1}H NMR spectroscopy.

4.3.4 Reaction monitoring experiment

7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (75 mg, 0.47 mmol) was added to a vial containing *trans*-stilbene **1** (70 mg, 0.40 mmol) in a 1:1 mixture of HFIP (0.4 mL) and $CHCl_3$ (0.4 mL). The resulting solution was stirred at 40 °C for 24 h. Reaction samples were taken at regular intervals and analysed by ^{1}H NMR spectroscopy. Results reported in Section 3.3.2.

4.3.5 Synthesis of alkenes

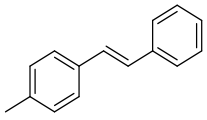
Diethyl (4-methylbenzyl)phosphonate 420



420

4-Methylbenzyl bromide **419** (5.0 g, 27.00 mmol) was added to triethylphosphite (18.0 mL, 108.00 mmol) and stirred at reflux for 24 h. The remaining triethylphosphite was removed by distillation (Kugelrohr, 110 °C) to give the *title compound* **420** (6.4 g, 26.45 mmol, 98%), as a colourless liquid; IR (ATR)/cm^{-1}: 2982, 1519, 1249, 1022, 957; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.18 (dd, J = 8.1, 2.4 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 4.05–3.96 (m, 4H), 3.11 (d, J = 21.4 Hz, 2H), 2.32 (d, J = 2.3 Hz, 3H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 136.6 (d, J = 4.1 Hz), 129.8 (d, J = 6.4 Hz), 129.4 (d, J = 2.7 Hz), 128.6 (d, J = 9.4 Hz), 62.2 (d, J = 7.0 Hz), 33.5 (d, J = 138.4 Hz), 21.2, 16.5 (d, J = 6.2 Hz); LRMS (ES + APCI) *m/z* calculated for $C_{12}H_{19}O_3P$ 242.1, found 243.1 $[M+H]^+$.

(*E*)-1-Methyl-4-styrylbenzene 421

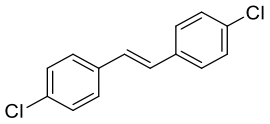


421

Potassium *tert*-butoxide (14.00 mL, 13.60 mmol, 1 M in THF) was added dropwise to a solution of diethyl (4-methylbenzyl)phosphonate **420** (3.0 g, 12.40 mmol) and benzaldehyde (1.25 mL, 12.40 mmol) in THF (7.00 mL) at 0 °C. The solution was warmed to rt and stirred for 24 h. The reaction mixture was poured into H_2O (50 mL) and the precipitate collected, washed with H_2O and dried under vacuum to give the *title compound* **421** (1.80 g, 9.28 mmol, 75%) as a white solid; mp 113–115 °C [118–119 °C][119]; IR (ATR)/cm^{-1}: 3023, 964, 810, 709, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.53–7.47 (m, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.38–

7.32 (m, 2H), 7.26–7.22 (m, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 2.5 Hz, 1H), 7.08 (d, J = 2.5 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 137.7, 137.7, 134.7, 129.6, 129.6, 128.8, 127.9, 127.6, 126.6, 126.6, 21.4; LRMS (GCMS + CI) *m/z* calculated for $C_{15}H_{14}$ 194.1, found 194.1 $[M]^+$.

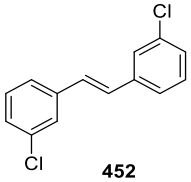
4,4'-Dichloro-*trans*-stilbene 451



451

4-Chlorostyrene **448** (1.0 mL, 7.60 mmol) was added to a solution of Grubb's catalyst Gen II (34 mg, 0.04 mmol) in dry CH_2Cl_2 (10.0 mL) under an atmosphere of argon. The solution was stirred at reflux for 24 h. The reaction mixture was cooled to 0 °C and the precipitate collected. The precipitate was recrystalised in a minimal amount of CH_2Cl_2 to give the *title compound* **451** (187 mg, 0.75 mmol, 20%), as a clear solid; mp 170–172 °C [168–170 °C][120]; IR (ATR)/cm^{-1}: 3051, 1592, 1100, 949, 824, 718; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45–7.40 (m, 4H), 7.35–7.30 (m, 4H), 7.02 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 135.7, 133.6, 129.1, 128.2, 127.9; LRMS (GCMS + CI) *m/z* calculated for $C_{14}H_{10}{}^{(35)}Cl_2$ 249.1, found 249.9 $[M]^+$.

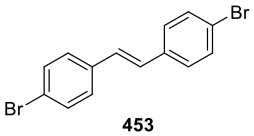
3,3'-Dichloro-*trans*-stilbene 452



452

3-Chlorostyrene **449** (1.0 mL, 7.80 mmol) was added to a solution of Grubb's catalyst Gen II (34 mg, 0.04 mmol) in dry CH_2Cl_2 (10.0 mL) under an atmosphere of argon. The solution was stirred at reflux for 24 h. The reaction mixture was cooled to 0 °C and the precipitate collected. The precipitate was recrystalised in a minimal amount of CH_2Cl_2 to give the *title compound* **452** (441 mg, 1.77 mmol, 45%), as a clear solid; mp 90–92 °C [94–95 °C][121]; IR (ATR)/cm^{-1}: 3115, 1456, 1238, 683, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50 (t, J = 1.6 Hz, 2H), 7.37 (app. dt, J = 7.5, 1.6 Hz, 2H), 7.32–7.27 (m, 2H), 7.27–7.23 (m, 2H), 7.04 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 138.9, 134.9, 130.1, 128.8, 128.1, 126.6, 125.1; LRMS (GCMS + CI) *m/z* calculated for $C_{14}H_{10}{}^{(35)}Cl_2$ 249.1, found 249.9 $[M]^+$.

4,4'-Dibromo-*trans*-stilbene 453



453

4-Bromostyrene **450** (1.0 mL, 7.60 mmol) was added to a solution of Grubb's catalyst Gen II (34 mg, 0.04 mmol) in dry CH_2Cl_2 (10.0 mL) under an atmosphere of argon. The solution was stirred at reflux for 24 h. The reaction mixture was cooled to 0 °C and the precipitate collected. The precipitate was recrystalised in a minimal amount of CH_2Cl_2 to give the *title compound* **453** (590 mg, 1.75 mmol, 46%), as a clear solid; mp 200–202 °C [209–211 °C][122]; IR (ATR)/cm^{-1}: 1688, 1113, 819, 715; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.51–7.45 (m, 4H), 7.41–7.33 (m, 4H), 7.02 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 136.1, 132.0, 128.3, 128.2, 121.8; LRMS (GCMS + CI) *m/z* calculated for $C_{14}H_{10}{}^{(79)}Br_2$ 338.0, found 339.0 $[M+H]^+$.

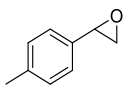
4.3.6 Synthesis of epoxides

***trans*-Stilbene oxide 413**

413

*m*CPBA **412** (696 mg, 4.00 mmol) was added in one portion to a solution of *trans*-stilbene **1** (360 mg, 2.00 mmol) in CH_2Cl_2 (8.0 mL), under argon. The solution was stirred at rt for 2 h. The reaction mixture was quenched with saturated $Na_2S_2O_{5(aq)}$ (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product. Purification by silica gel flash column chromatography (EtOAc:Hexane 1:99) gave *trans*-stilbene oxide **413** (268 mg, 1.37 mmol, 68%) as a white solid; mp 58–60 °C [65–66 °C][123]; IR (ATR)/cm^{-1}: 2984, 1454, 847, 747; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42–7.31 (m, 10H), 3.87 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 137.3, 128.7, 128.5, 125.7, 63.0; LRMS (ES + APCI) *m/z* calculated for $C_{14}H_{12}O$ 196.1, found 195.2 $[M-H]^-$.

2-(*p*-tolyl)Oxirane 440[98]



440

NaH (500 mg, 12.50 mmol, 60% mineral oil dispersion) was charged to a flame dried flask and washed with petroleum ether (3 × 5 mL), the residual petroleum ether was removed by syringe followed by vacuum. Under an argon atmosphere, dry THF (7.0 mL) and dry DMSO

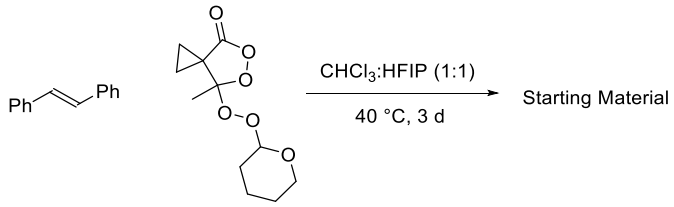
(7.0 mL) were added and the reaction mixture cooled to 0 °C. A solution of trimethylsulfonium iodide **439** (2.0 g, 10.00 mmol) in DMSO (4.0 mL) was added, followed by 4-methylbenzaldehyde **422** (1.0 mL, 8.30 mmol). The reaction mixture was stirred at 0 °C for 0.5 h and then warmed to rt and stirred for 12 h. The reaction was slowly quenched with ice cold water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 15:85) gave the *title compound* **440** (150 mg, 1.12 mmol, 13%), as a clear oil; IR (ATR)/cm^{-1}: 2921, 1690, 1519, 880, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.19–7.13 (m, 4H), 3.83 (dd, J = 4.1, 2.6 Hz, 1H), 3.13 (dd, J = 5.5, 4.1 Hz, 1H), 2.80 (dd, J = 5.5, 2.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 138.2, 134.7, 129.4, 125.6, 52.5, 51.2, 21.3; LRMS (GCMS + CI) *m/z* calculated for $C_9H_{10}O$ 134.1, found 134.1 $[M]^+$.

(2*R*,3*R*)-*trans*-Stilbene oxide 429

429

A solution of 2 M K_2CO_3 in 0.4 mM of EDTA (4.5 mL) was added to a solution of *trans*-stilbene **1** (540 mg, 3.00 mmol) and Shi epoxidation catalyst **288** (232 mg, 0.9 mmol) in a 1:2 mixture of acetonitrile (6.0 mL) and dimethoxymethane (12.0 mL). The solution was cooled to 0 °C and H_2O_2 (30%, 1.4 mL, 12.0 mmol) added and the mixture stirred for 10 h. The mixture was then warmed to rt and stirred for 24 h. The reaction mixture was extracted with hexane (2 × 20 mL), washed with 1 M $Na_2S_2O_{3(aq)}$ (2 × 20 mL), brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product. Purification by silica gel flash column chromatography (EtOAc:Hexane 2:98) gave the *title compound* **429** (165 mg, 0.84 mmol, 28%) as a white solid; mp 58–60 °C [65–66 °C][123]; IR (ATR)/cm^{-1}: 2983, 1452, 849, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42–7.31 (m, 10H), 3.87 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 137.3, 128.7, 128.5, 125.7, 63.0; LRMS (ES + APCI) *m/z* calculated for $C_{14}H_{12}O$ 196.1, found 195.2 $[M-H]^-$; $[\alpha]^{20}_D$ = +342.4 (c 1.0, benzene).

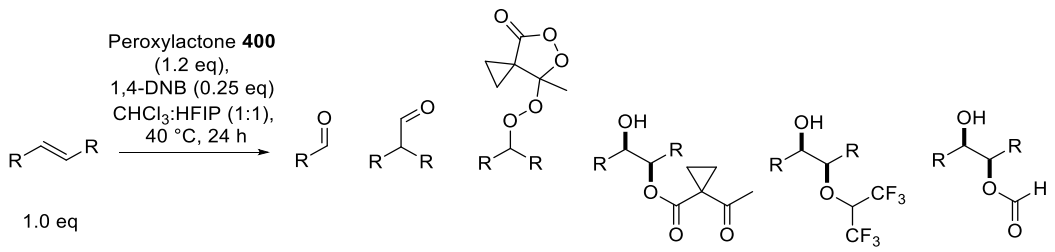
4.3.7 Reaction of protected peroxide 416 with *trans*-stilbene 1



7-methyl-7-((tetrahydro-2H-pyran-2-yl)peroxy)-5,6-dioxaspiro[2.4]heptan-4-one **416** (45 mg, 0.19 mmol) was added to a vial containing *trans*-stilbene **1** (30 mg, 0.16 mmol) in a 1:1 mixture of HFIP (0.15 mL) and $CHCl_3$ (0.15 mL). The resulting solution was stirred at 40 °C for 3 d. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy revealed both starting materials to be present.

4.3.8 General procedure 1: ^{1}H NMR reaction monitoring experiment between peroxylactone 400 and alkenes

7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (48 mg, 0.30 mmol) was added to a vial containing alkene (0.25 mmol) and 1,4-dinitrobenzene (11 mg, 62.50 μmol) in a 1:1 mixture of HFIP (0.4 mL) and $CHCl_3$ (0.4 mL). The resulting solution was stirred at 40 °C for 24 h. Conversions of products obtained by analysis of the 24 h reaction mixture ^{1}H NMR spectrum.



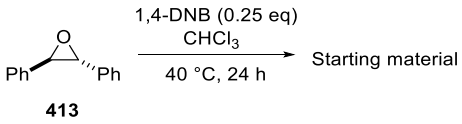
Ph, Ph **1** R = Ph	**407**, 31%	**408**, 18%	**409**, 20%	**410**, 6%	-	**411**, 5%
R = 4-ClPh **451**	**454**, 28%	**455**, 6%	-	**456**, 34%	-	-
R = 3-ClPh **452**	-	-	-	-	-	-
R = 4-BrPh **453**	**457**, 41%	**458**, 9%	-	**459**, 45%	-	-

4.3.9 General procedure 2: ^{1}H NMR reaction monitoring experiment for epoxides

Epoxide (0.2 mmol) was added to a vial containing 1,4-dinitrobenzene (8 mg, 50.0 μmol) and the stated additional reactants in a 1:1 mixture of HFIP (0.2 mL) and $CHCl_3$ (0.2 mL). The resulting solution was stirred at 40 °C for the stated time. Conversions of products obtained by analysis of the reaction mixture ^{1}H NMR spectrum.

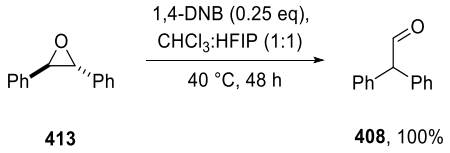
4.3.9.1 *Trans*-stilbene oxide 413

***Trans*-stilbene oxide 413 in $CHCl_3$**



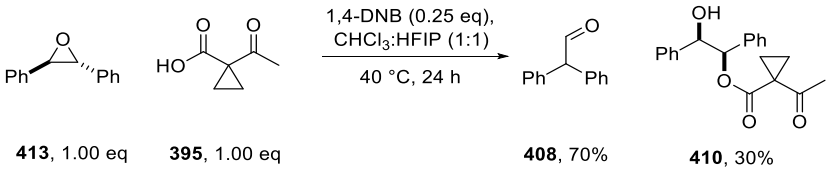
Following General Procedure 2, *trans*-stilbene oxide **413** (40 mg, 0.20 mmol) was stirred in $CHCl_3$ (0.4 mL) for 24 h. No reaction was observed to take place, by analysis of the reaction mixture ^{1}H NMR spectrum.

***Trans*-stilbene oxide 413 in reaction solvents**



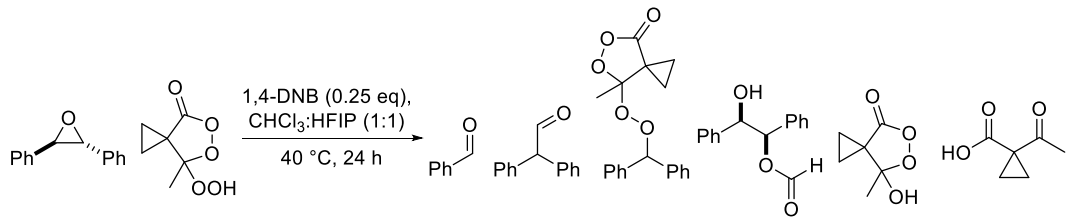
Following General Procedure 2, *trans*-stilbene oxide **413** (40 mg, 0.20 mmol) was stirred in the reaction solvent for 48 h. Diphenylacetaldehyde **408** (100%) was identified as the reaction product, by analysis of the reaction mixture ^{1}H NMR spectrum.

***Trans*-stilbene oxide 413 and acid 395**



Following General Procedure 2, *trans*-stilbene oxide **413** (40 mg, 0.20 mmol) and acid **395** (26 mg, 0.2 mmol) were stirred in the reaction solvent for 24 h. Diphenylacetaldehyde **408** (100%) and ester **410** (30%) were identified as the reaction products, by analysis of the reaction mixture ^{1}H NMR spectrum.

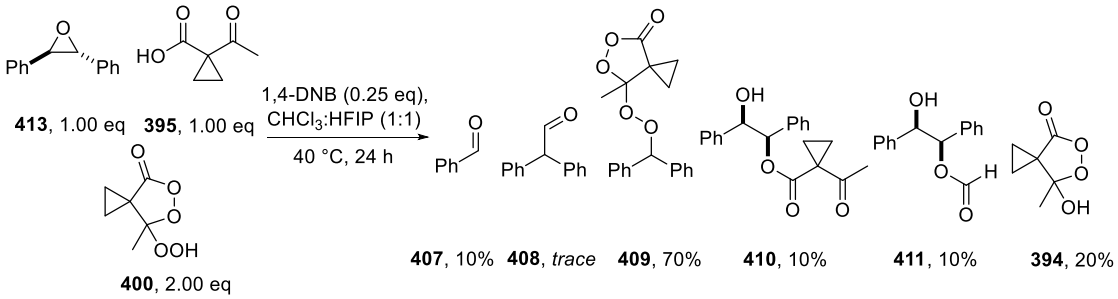
***Trans*-stilbene oxide 413 and peroxylactone 400**



413, 1.00 eq **400**, 2.00 eq **407**, 10% **408**, 5% **409**, 60% **411**, 20% **394**, 30% **395**, 25% (with respect to peroxide **400**)

Following General Procedure 2, *trans*-stilbene oxide **413** (40 mg, 0.20 mmol) and 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (64 mg, 0.4 mmol) were stirred in the reaction solvent for 24 h. Benzaldehyde **407** (10%), diphenylacetaldehyde **408** (5%), alkylated peroxylactone species **409** (60%), formate **411** (20%), peroxylactone **394** (30%) and acid **395** (25% with respect to peroxylactone **400**) were identified as the reaction products, by analysis of the reaction mixture ^{1}H NMR spectrum.

***Trans*-stilbene oxide 413, acid 395 and peroxylactone 400**

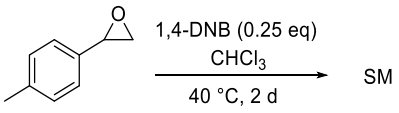


413, 1.00 eq **395**, 1.00 eq **400**, 2.00 eq **407**, 10% **408**, *trace* **409**, 70% **410**, 10% **411**, 10% **394**, 20%

Following General Procedure 2, *trans*-stilbene oxide **413** (40 mg, 0.20 mmol) acid **395** (26 mg, 0.20 mmol) and 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (64 mg, 0.40 mmol) were stirred in the reaction solvent for 24 h. Benzaldehyde **407** (10%), diphenylacetaldehyde **408** (trace), alkylated peroxylactone species **409** (70%), ester **410** (10%), formate **411** (10%) and peroxylactone **394** (20%) were identified as the reaction products, by analysis of the reaction mixture ^{1}H NMR spectrum.

4.3.9.2 Epoxide 440

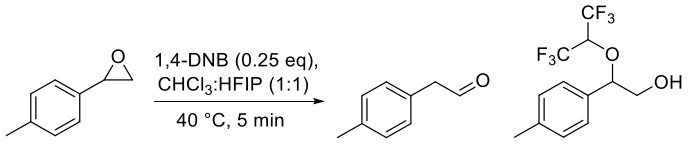
Epoxide 440 in $CHCl_3$



440

Following General Procedure 2, epoxide **440** (27 mg, 0.20 mmol) was stirred in $CHCl_3$ (0.4 mL) for 2 d. No reaction was observed to take place, by analysis of the reaction mixture ^{1}H NMR spectrum.

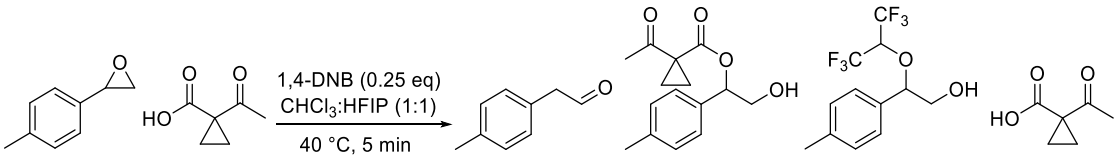
Epoxide 440 in reaction solvents



440 **436**, 25% **438**, 75%

Following General Procedure 2, epoxide **440** (27 mg, 0.20 mmol) was stirred in the reaction solvent for 5 min. Aldehyde **436** (25%) and ether **438** (75%) were identified as the reaction products, by analysis of the reaction mixture ^{1}H NMR spectrum.

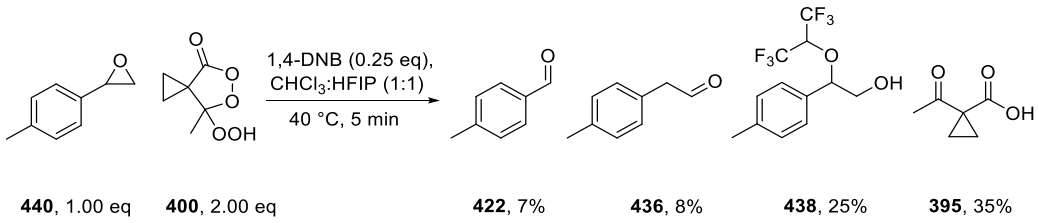
Epoxide 440 and acid 395



440, 1.00 eq **395**, 1.00 eq **436**, 14% **437**, 41% **438**, 36% **395**, 20%

Following General Procedure 2, epoxide **440** (27 mg, 0.20 mmol) and acid **395** (26 mg, 0.20 mmol) were stirred in the reaction solvent for 5 min. Aldehyde **436** (14%), ester **437** (41%), ether **438** (36%) and acid **395** (20%) were identified as the reaction products, by analysis of the reaction mixture ^{1}H NMR spectrum.

Epoxide 440 and peroxylactone 400

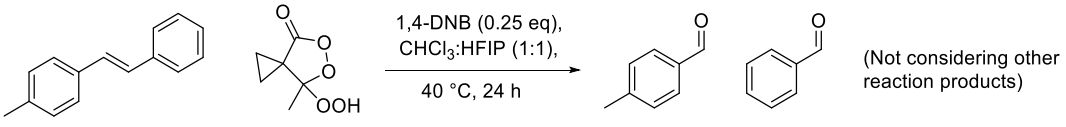


440, 1.00 eq **400**, 2.00 eq **422**, 7% **436**, 8% **438**, 25% **395**, 35%

Following General Procedure 2, epoxide **440** (27 mg, 0.20 mmol) and 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (64 mg, 0.4 mmol) were stirred in the reaction solvent for 5 min. Aldehyde **422** (7%), aldehyde **436** (8%), ether **438** (25%) and acid **395** (35%) were identified as the reaction products, by analysis of the reaction mixture ^{1}H NMR spectrum.

4.3.10 Mechanistic investigation

4.3.10.1 Reactions relating to benzaldehyde 407

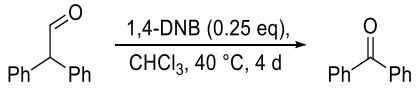


421, 1.00 eq **400**, 1.20 eq **422**, 10% **407**, 12%

Following General Procedure 2, alkene **421** (49 mg, 0.25 mmol) and 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (48 mg, 0.30 mmol) were stirred under the reaction conditions for 24 h. Aldehyde **422** (10%) and aldehyde **407** (12%) were found to be reactions products, by analysis of the reaction mixture ^{1}H NMR spectrum. Note that other reaction products were present but were not analysed.

4.3.10.2 Reactions relating to diphenylacetaldehyde 408

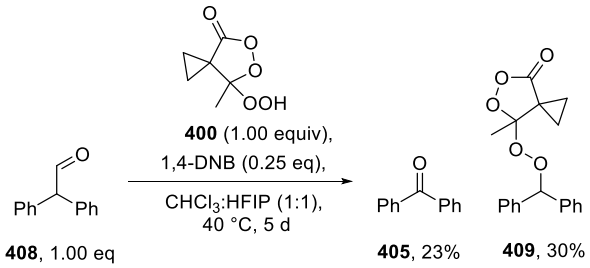
4.3.10.2.1 Conversion of diphenylacetaldehyde 408 to benzophenone 405



408 **405**, 36%

Diphenylacetaldehyde **408** (44 μL, 0.25 mmol) was added to a solution of 1,4-dinitrobenzene (11 mg, 62.50 μmol) in $CHCl_3$ (0.25 mL) and stirred at 40 °C for 4 d. Benzophenone **405** (36%) was found to be the product of the reaction, by analysis of the reaction mixture ^{1}H NMR spectrum. Diphenylacetaldehyde **408** (64%) remained in the reaction mixture after 4 d.

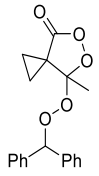
4.3.10.2.2 Conversion of diphenylacetaldehyde 408 to alkylated peroxylactone species 409



Diphenylacetaldehyde **408** (44 μL, 0.25 mmol) was added to a solution of 1,4-dinitrobenzene (11 mg, 62.50 μmol) and 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (40 mg, 0.25 mmol) in a 1:1 mixture of HFIP (0.25 mL) and $CHCl_3$ (0.25 mL). The reaction mixture was stirred at 40 °C for 5 d. Benzophenone **405** (23%) and alkylated peroxylactone species **409** (30%), were found to be the products of the reaction, by analysis of the reaction mixture ^{1}H NMR spectrum.

4.3.10.3 Reactions relating to alkylated peroxylactone species 409

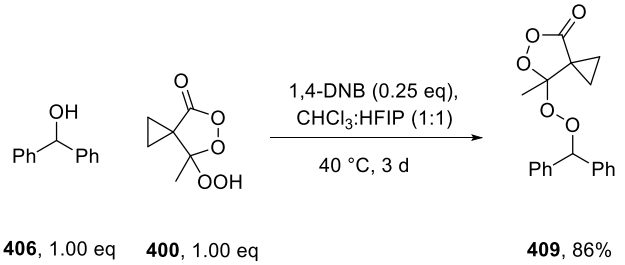
4.3.10.3.1 7-(Benzhydrylperoxy)-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 409



409

Diphenylmethanol **406** (58 mg, 0.31 mmol) was added to a solution of 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (50 mg, 0.31 mmol) and H_2SO_4 (16 μL, 0.31 mmol) in CH_2Cl_2 (0.6 mL). The solution was stirred at rt for 4 d. The reaction mixture was diluted with CH_2Cl_2 (2 mL), washed with H_2O (2 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:9) gave the *title compound* **409** (26 mg, 80 μmol, 20%), as a clear oil; IR (ATR)/cm^{-1}: 3023, 1789, 1449, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42–7.30 (m, 10H), 6.35 (s, 1H), 1.47 (m, 1H), 1.41 (s, 3H), 1.31 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 176.6, 139.1, 138.8, 128.5, 128.4, 128.3, 128.1, 127.9, 114.2, 89.2, 28.6, 17.7, 15.8, 12.2 (1 carbon missing); LRMS (ES + APCI) *m/z* calculated for $C_{19}H_{18}O_5$ 326.1, found 344.0 $[M+NH_4]^+$.

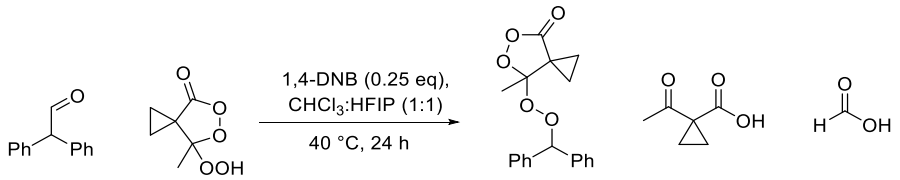
4.3.10.3.2 Conversion of diphenylmethanol 406 to alkylated peroxylactone species 409



406, 1.00 eq **400**, 1.00 eq **409**, 86%

Diphenylmethanol **406** (184 mg, 1.00 mmol) was added to a solution of 1,4-dinitrobenzene (42 mg, 0.25 mmol) and 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (160 mg, 1.00 mmol) in a 1:1 mixture of HFIP (1.0 mL) and $CHCl_3$ (1.0 mL). The reaction mixture was stirred at 40 °C for 3 d. Alkylated peroxylactone species **409** (86%) was found to be a reaction product, by analysis of the reaction mixture ^{1}H NMR spectrum.

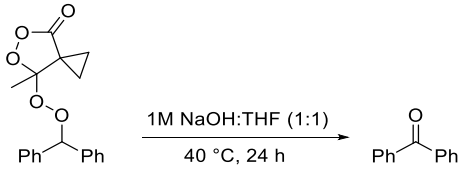
4.3.10.3.3 The reaction of diphenylacetaldehyde 408 and peroxylactone 400 – Reaction monitoring experiment



408, 1.00 eq **400**, 1.00 eq **409**, 55% **395**, 61% **425**, 73%

Diphenylacetaldehyde **408** (44 μL, 0.25 mmol) was added to a solution of 1,4-dinitrobenzene (11 mg, 62.50 μmol) and 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (40 mg, 0.25 mmol) in a 1:1 mixture of HFIP (0.25 mL) and $CHCl_3$ (0.25 mL). The reaction mixture was stirred at 40 °C for 24 h. Alkylated peroxylactone species **409** (55%), acid **395** (61%) and formic acid **425** (73%), were found to be the products of the reaction, by analysis of the reaction mixture ^{1}H NMR spectrum. Reaction samples were taken at regular intervals and analysed by ^{1}H NMR spectroscopy.

4.3.10.3.4 Conversion of alkylated peroxylactone species 409 to benzophenone 405



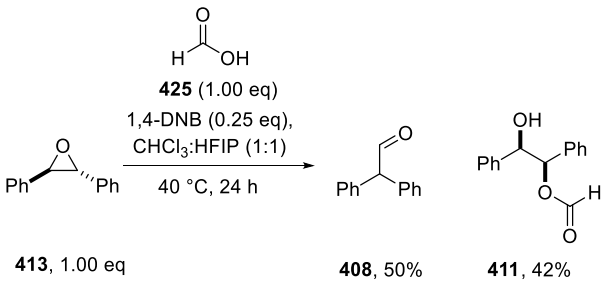
409 **405**, 71%

1M $NaOH_{(aq)}$ (0.25 mL) was added to a solution of alkylated peroxylactone species **409** (10 mg, 0.03 mmol) in THF (0.25 mL) and the reaction mixture stirred at 40 °C for 24 h. The

mixture was cooled to rt and extracted with EtOAc (2 × 1 mL). The organic layer was washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:9) gave benzophenone **405** (4 mg, 71%). See Section 4.3.2.1 for full characterisation.

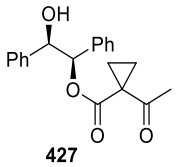
4.3.10.4 Reactions relating to ester 410 and formate 411

Conversion of *trans*-stilbene 413 to formate 411



Trans-stilbene oxide **413** (15 mg, 0.08 mmol) was added to a solution of 1,4-dinitrobenzene (3 mg, 0.02 mmol) and formic acid **425** (3 μL, 0.08 mmol) in a 1:1 mixture of HFIP (0.1 mL) and $CHCl_3$ (0.1 mL). The reaction mixture was stirred at 40 °C for 24 h. Diphenylacetaldehyde **408** (50%) and formate **411** (42%) were found to be the products of the reaction, by analysis of the reaction mixture ^{1}H NMR spectrum.

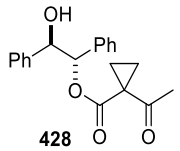
(1*R*,2*R*)-2-Hydroxy-1,2-diphenylethyl 1-acetylcyclopropane-1-carboxylate 427



427

N,*N'*-Dicyclohexylcarbodiimide (DCC) (277 mg, 1.10 mmol) was added to a flame dried flask containing (*R*,*R*)-(+)-hydrobenzoin **2** (214 mg, 1.00 mmol), 1-acetylcyclopropane-1-carboxylic acid **395** (144 mg, 0.90 mmol) and DMAP (25 mg, 0.20 mmol) in CH_2Cl_2 (5.0 mL) and stirred at rt for 3 h. The reaction mixture was quenched with 3 M $HCl_{(aq)}$ (10.0 mL) and diluted with CH_2Cl_2 (5 mL). The organic layer was collected, washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 15:85) gave the *title compound* **427** (197 mg, 0.61 mmol, 61%) as a white solid; mp 76–78 °C; IR (ATR)/cm^{-1}: 3410, 1729, 1681, 1184, 1156, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26–7.22 (m, 6H), 7.18–7.08 (m, 4H), 5.96 (d, J = 7.3 Hz, 1H), 4.95 (d, J = 7.3 Hz, 1H), 2.39 (s, 3H), 1.57–1.45 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 203.3, 170.2, 139.2, 136.5, 128.6, 128.5, 128.4, 128.3, 127.4, 127.1, 80.9, 76.8, 35.5, 29.4, 19.3, 19.0; LRMS (ES + APCI) *m/z* calculated for $C_{20}H_{20}O_4$ 324.1, found 347.1 $[M+Na]^+$.

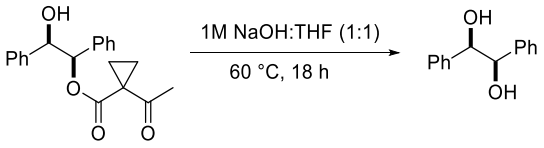
Rel-(1*S*,2*R*)-2-Hydroxy-1,2-diphenylethyl 1-acetylcyclopropane-1-carboxylate 428



428

DCC (277 mg, 1.10 mmol) was added to a flame dried flask containing *meso*-hydrobenzoin **5** (214 mg, 1.00 mmol), 1-acetylcyclopropane-1-carboxylic acid **395** (144 mg, 0.90 mmol) and DMAP (25 mg, 0.20 mmol) in CH_2Cl_2 (5.0 mL) and stirred at rt for 3 h. The reaction mixture was quenched with 3 M $HCl_{(aq)}$ (10.0 mL) and diluted with CH_2Cl_2 (5 mL). The organic layer was collected, washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 15:85) gave the *title compound* **428** (155 mg, 0.53 mmol, 53%) as a white solid; as a white solid; mp 60–62 °C; IR (ATR)/cm^{-1}: 3402, 1700, 1182, 1119, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39 – 7.27 (m, 10H), 5.94 (d, J = 6.8 Hz, 1H), 4.95 (d, J = 6.8 Hz, 1H), 2.27 (s, 3H), 1.45 – 1.29 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 203.0, 169.8, 139.7, 136.6, 128.9, 128.7, 128.6, 128.5, 127.7, 127.2, 79.6, 76.6, 35.2, 29.8, 19.3, 19.3; LRMS (ES + APCI) *m/z* calculated for $C_{20}H_{20}O_4$ 324.1, found 347.1 $[M+Na]^+$.

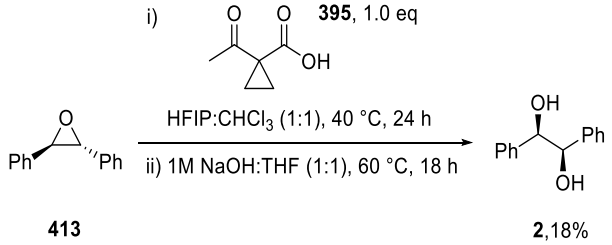
Hydrolysis of ester 410 to diol 4



410 **4**, 42%

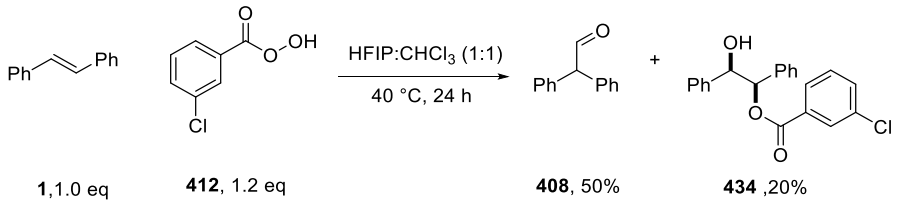
Ester **410** (30 mg, 0.09 mmol) dissolved in a 1:1 mixture of 1 M $NaOH_{(aq)}$ (0.5 mL) and THF (0.5 mL). The resulting solution was stirred at 60 °C for 18 h. The reaction mixture was then diluted with EtOAc (2 mL) and H_2O (2 mL), the organic layer collected and washed with brine (4 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:9) gave diol **4** (8 mg, 42%). Full characterisation found in Section 4.3.2.1.

(1*R*,2*R*)-1,2-Diphenylethane-1,2-diol 2



(2*R*,3*R*)-*trans*-Stilbene oxide **429** (165 mg, 0.84 mmol) was added to a solution of 1-acetylcyclopropane-1-carboxylic acid **395** (108 mg, 0.84 mmol) in a 1:1 mixture of $CHCl_3$ (0.9 mL) and HFIP (0.9 mL). The solution was stirred at 40 °C for 24 h. The reaction mixture was concentrated *in vacuo* and then redissolved in a 1:1 mixture of 1 M $NaOH_{(aq)}$ (4.0 mL) and THF (4.0 mL) and stirred at 60 °C for 18 h. The reaction mixture was diluted with H_2O (10 mL) and EtOAc (20 mL) and the phases separated. The organic layer was washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product. Purification by silica gel flash column chromatography (EtOAc:Hexane 1:5) gave the *title compound* **2** (33 mg, 0.15 mmol, 18%) as a white solid; mp 142–144 °C [146–149 °C][124]; IR (ATR)/cm^{-1}: 3492, 3382, 1452, 750, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25–7.22 (m, 6H), 7.16–7.12 (m, 4H), 4.73 (s, 2H), 2.78 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 140.0, 128.3, 128.1, 127.1, 79.3; LRMS (ES + APCI) *m/z* calculated for $C_{14}H_{14}O_2$ 214.1, found 232.1 $[M+NH_4]^+$. $[\alpha]^{20}_D$ = +65.7 (c 1.1, ethanol).[124]

Reaction of *trans*-stilbene 1 with *m*CPBA 412

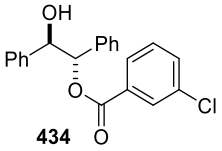


*m*CPBA **412** (174 mg, 1.20 mmol) was added to a vial containing *trans*-stilbene **1** (180 mg, 1.00 mmol) in a 1:1 mixture of HFIP (1.0 mL) and $CHCl_3$ (1.0 mL). The resulting solution was stirred at 40 °C for 24 h. The mixture was then cooled to rt, concentrated *in vacuo* to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 1:5) gave the reaction products detailed below.

Diphenylacetaldehyde 408

(98 mg, 0.5 mmol, 50%), as a clear liquid; see Section 4.3.2.2 for full characterisation.

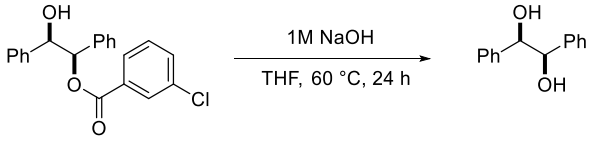
***Rel*-(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl 3-chlorobenzoate 434**



434

(11 mg, 0.2 mmol, 20%) as a white solid; mp 128–130 °C; IR (ATR)/cm^{-1}: 3468, 1700, 1428, 1260, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.10–8.05 (m, 1H), 8.01–7.95 (m, 1H), 7.58–7.52 (m, 1H), 7.45–7.37 (m, 1H), 7.25–7.16 (m, 10H), 6.12 (d, J = 7.3 Hz, 1H), 5.10 (d, J = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 164.7, 139.1, 136.7, 134.8, 133.4, 131.9, 130.0, 129.9, 128.6, 128.5, 128.4, 128.4, 128.1, 127.4, 127.2, 81.1, 76.8; LRMS (ES + APCI) *m/z* calculated for $C_{21}H_{17}{}^{(35)}ClO_3$ 352.1, found 375.0 $[M+Na]^+$.

Hydrolysis of *Rel*-(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl 3-chlorobenzoate 434

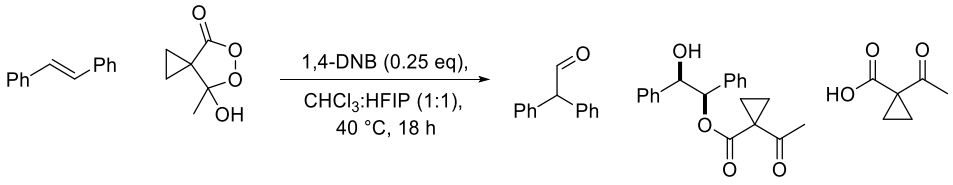


434 **4**

Rel-(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl 3-chlorobenzoate **434** (5 mg, 14 μmol) was stirred in a 1:1 mixture of 1 M NaOH (0.1 mL) and THF (0.1 mL) at 60 °C for 24 h. The reaction mixture was cooled to rt, extracted with EtOAc (3 × 0.5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. The crude product was doped with a commercial sample of (*R*,*R*)-(+)-hydrobenzoin **2** to qualitatively confirm its presence by ^{1}H NMR spectroscopy.

4.3.10.5 Reactions relating to peroxylactone 394

Reaction of peroxylactone 394 and *trans*-stilbene 1

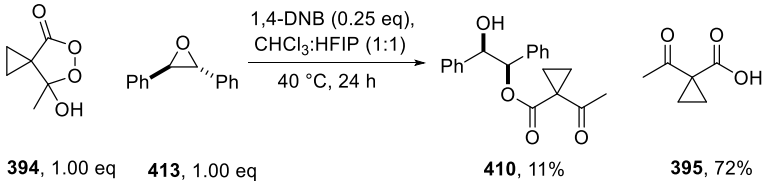


1, 1.00 eq **394**, 1.20 eq **408**, 50% **410**, 20% **395**, 80% (with respect to peroxide **394**)

Peroxylactone **394** (60 mg, 0.42 mmol) was added to a vial containing *trans*-stilbene **1** (63 mg, 0.35 mmol) and 1,4-dinitrobenzene (15 mg, 87.50 μmol) in a 1:1 mixture of HFIP (0.4 mL) and $CHCl_3$ (0.4 mL). The resulting solution was stirred at 40 °C for 24 h. Diphenylacetaldehyde **408** (50%), ester **410** (20%) and acid **395** (80%, with respect to

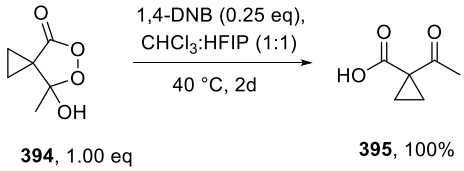
peroxylactone **394**) were found to be the products of the reaction, by analysis of the reaction mixture ^{1}H NMR spectrum.

Reaction of peroxylactone 394 and *trans*-stilbene oxide 413



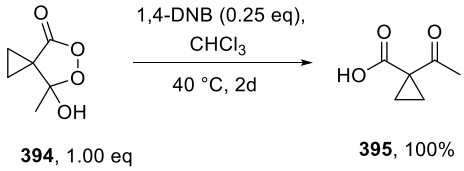
Peroxylactone **394** (36 mg, 0.25 mmol) was added to a vial containing *trans*-stilbene oxide **413** (49 mg, 0.25 mmol) and 1,4-dinitrobenzene (11 mg, 62.50 μmol) in a 1:1 mixture of HFIP (0.25 mL) and $CHCl_3$ (0.25 mL). The resulting solution was stirred at 40 °C for 24 h. Ester **410** (11%) and acid **395** (72%) were found to be the products of the reaction, by analysis of the reaction mixture ^{1}H NMR spectrum.

Degradation of peroxylactone 394 to acid 395 under $CHCl_3$:HFIP (1:1)



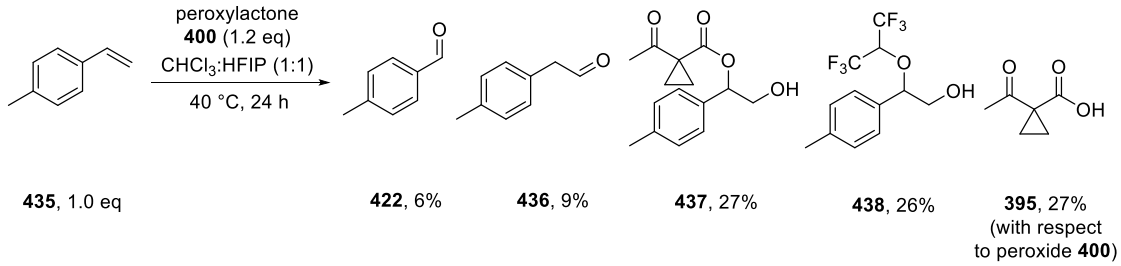
Peroxylactone **394** (15 mg, 0.1 mmol) was added to a solution of 1,4-dinitrobenzene (4 mg, 25.0 μmol) in a 1:1 mixture of HFIP (70 μL) and $CHCl_3$ (70 μL). The resulting solution was stirred at 40 °C for 2 d. Acid **395** (100%) was found to be the reaction product, by analysis of the reaction mixture ^{1}H NMR spectrum.

Degradation of peroxylactone 394 to acid 395 under $CHCl_3$



Peroxylactone **394** (15 mg, 0.1 mmol) was added to a solution of 1,4-dinitrobenzene (4 mg, 25.0 μmol) in $CHCl_3$ (140 μL). The resulting solution was stirred at 40 °C for 2 d. Acid **395** (100%) was found to be the reaction product, by analysis of the reaction mixture ^{1}H NMR spectrum.

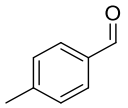
Reaction of 4-methylstyrene 435 and 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 400



435, 1.0 eq **422**, 6% **436**, 9% **437**, 27% **438**, 26% **395**, 27% (with respect to peroxide **400**)

7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (118 mg, 0.74 mmol) was added to a vial containing 4-methyl styrene **435** (80 μL, 0.60 mmol) and 1,4-dinitrobenzene (25 mg, 0.15 mmol) in a 1:1 mixture of HFIP (0.6 mL) and $CHCl_3$ (0.6 mL). The resulting solution was stirred at 40 °C for 24 h. The mixture was then cooled to rt, concentrated *in vacuo* to give the crude product. Purification by silica gel flash column chromatography (EtOAc:Petroleum ether 15:85) gave the reaction products detailed below.

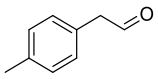
4-Methylbenzaldehyde 422



422

(4 mg, 33 μmol, 6%), as a clear oil; IR (ATR)/cm^{-1}: 2733, 1688, 1171, 810, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.97 (s, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 192.2, 145.7, 134.4, 130.0, 129.9, 22.0; LRMS (GCMS + CI) *m/z* calculated for C_8H_8O 120.1, found 120.1 $[M]^+$.

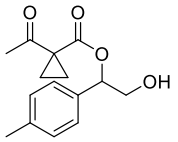
2-(p-tolyl)acetaldehyde 436



436

(9% ^{1}H NMR conversion using 1,4-DNB as internal standard), product not isolated and characterised.

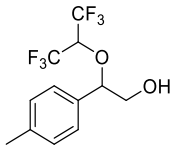
2-Hydroxy-1-(*p*-tolyl)ethyl 1-acetylcyclopropane-1-carboxylate 437



437

(42 mg, 160 μmol, 27%), as a clear oil; IR (ATR)/cm^{-1}: 3437, 2927, 1727, 1696, 1307, 1180, 1119, 817; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (d, J = 7.6 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 4.94 (t, J = 6.0 Hz, 1H), 4.30 (d, J = 6.0 Hz, 2H), 2.41 (s, 3H), 2.35 (s, 3H), 1.48 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 203.1, 171.3, 138.4, 137.0, 129.5, 126.2, 72.3, 69.7, 35.2, 29.7, 21.3, 19.5, 19.5; LRMS (ES + APCI) *m/z* calculated for $C_{15}H_{18}O_4$ 262.1, found 280.1 $[M+NH_4]^+$.

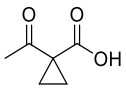
2-((1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy)-2-(*p*-tolyl)ethan-1-ol 438



438

(47 mg, 156 μmmol, 26%), as a clear oil; IR (ATR)/cm^{-1}: 2928, 1308, 1286, 1191, 1104, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.22 (app. s, 4H), 4.83 (dd, J = 8.3, 3.5 Hz, 1H), 4.14 (hept, J = 5.9 Hz, 1H), 3.94 (dd, J = 12.2, 8.3 Hz, 1H), 3.69 (dd, J = 12.2, 3.5, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 139.9, 131.7, 129.8, 128.0, 121.2 (q, J = 257.9 Hz), 86.1, 72.9 (sept, J = 32.3 Hz), 66.8, 21.4; LRMS (GCMS + CI) *m/z* calculated for $C_{12}H_{12}F_6O_2$ 302.1, found 325.4 $[M+Na]^+$.

1-Acetylcyclopropane-1-carboxylic acid 395

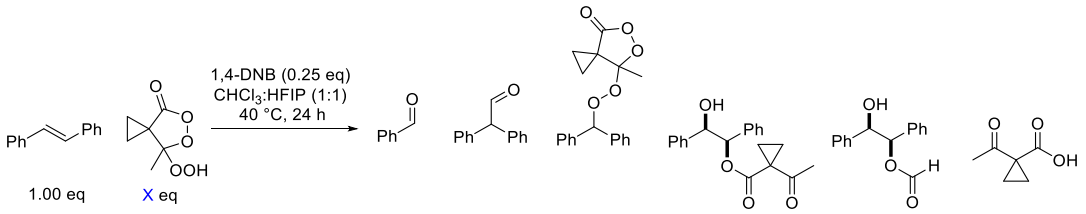


395

(26 mg, 200 μmol, 27%) See p194.for characterisation.

4.3.11 Optimisation of reaction conditions

Optimisation of equivalents of peroxylactone 400



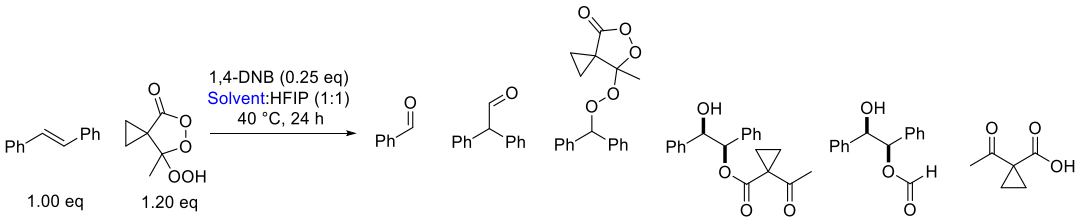
1 **400** **407** **408** **409** **410** **411** **395**

Entry	Peroxylactone eq						
1	0.5	16%	13%	3%	6%	8%	51%
2	1.2	17%	11%	16%	8%	7%	39%
3	2.0	15%	0%	30%	8%	14%	29%

Conversions calculated by ^{1}H NMR spectroscopy using an internal standard (1,4-DNB). Conversions calculated from a single experiment.

The stated quantity of 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** was added to a vial containing *trans*-stilbene **1** (45 mg, 0.25 mmol) and 1,4-dinitrobenzene (11 mg, 62.50 μmol) in a 1:1 mixture of HFIP (0.25 mL) and $CHCl_3$ (0.25 mL). The resulting solution was stirred at 40 °C for 24 h. The mixture was then cooled to rt and analysed *via* ^{1}H NMR spectroscopy.

Optimisation of equivalents of solvent



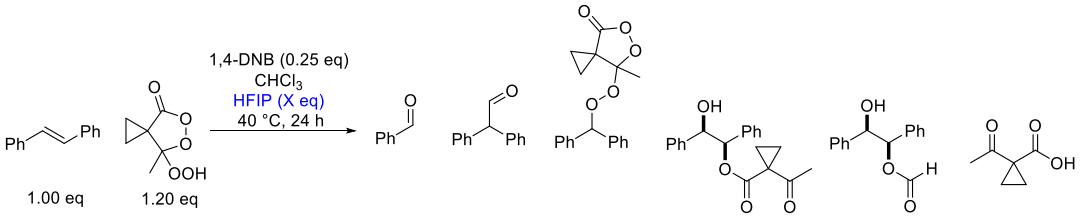
1 **400** **407** **408** **409** **410** **411** **395**

Entry	Solvent						
1	$CHCl_3$	17%	11%	16%	8%	7%	39%
2	Et_2O	8%	10%	30%	0%	0%	68%
3	EtOAc	6%	2%	0%	0%	0%	33%
4	Dioxane	8%	0%	0%	0%	0%	16%
5	MeOH	0%	0%	0%	0%	0%	56%
6	Toluene	25%	12%	13%	6%	12%	83%

Conversions calculated by ^{1}H NMR spectroscopy using an internal standard (1,4-DNB). Conversions calculated from a single experiment.

7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (48 mg, 0.3 mmol) was added to a vial containing *trans*-stilbene **1** (45 mg, 0.25 mmol) and 1,4-dinitrobenzene (11 mg, 62.50 μmol) in a 1:1 mixture of HFIP (0.25 mL) and the stated solvent (0.25 mL). The resulting solution was stirred at 40 °C for 24 h. The mixture was then cooled to rt and analysed *via* ^{1}H NMR spectroscopy.

Optimisation of equivalents of HFIP



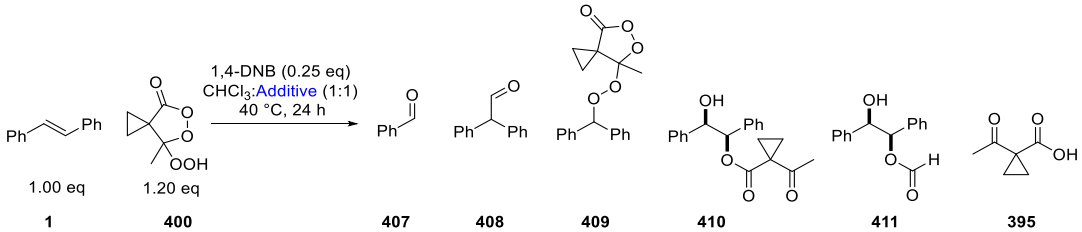
Entry	HFIP eq						
1	0	0%	0%	0%	0%	0%	0%
2	1	2%	0%	0%	0%	0%	8%
3	5	4%	10%	4%	8%	8%	33%
4[a]	10	17%	11%	16%	8%	7%	39%
5	15	9%	24%	18%	8%	8%	58%
6	20	7%	24%	20%	8%	8%	56%

[a]$CHCl_3$:HFIP (1:1) equivalent to 10 equiv HFIP

Conversions calculated by ^{1}H NMR spectroscopy using an internal standard (1,4-DNB). Conversions calculated from a single experiment.

7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (48 mg, 0.3 mmol) was added to a vial containing *trans*-stilbene **1** (45 mg, 0.25 mmol) and 1,4-dinitrobenzene (11 mg, 62.50 µmol) in the stated ratio of HFIP:$CHCl_3$. The resulting solution was stirred at 40 °C for 24 h. The mixture was then cooled to rt and analysed *via* ^{1}H NMR spectroscopy.

Optimisation of fluorinated alcohol additive



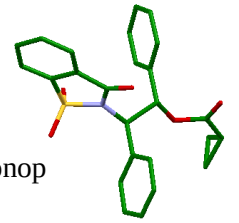
Entry	Additive (fluorinated alcohol)						
1	HFIP	17%	11%	16%	8%	7%	39%
2	trifluoroethanol	13%	4%	0%	0%	0%	14%
3	perfluoro-*tert*-butanol	4%	17%	9%	8%	14%	32%

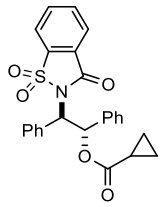
Conversions calcuated from internal standard (1,4-DNB). Conversions calculated from a single experiment.

7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **400** (48 mg, 0.3 mmol) was added to a vial containing *trans*-stilbene **1** (45 mg, 0.25 mmol) and 1,4-dinitrobenzene (11 mg, 62.50 µmol) in a 1:1 mixture of the stated fluorinated alcohol additive (0.25 mL) and $CHCl_3$ (0.25 mL). The resulting solution was stirred at 40 °C for 24 h. The mixture was then cooled to rt and analysed *via* ^{1}H NMR spectroscopy.

VI. Appendix

X-ray data for (1*S*,2*R*)-2-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)-1,2-diphenylethyl cyclopropanecarboxylate 158





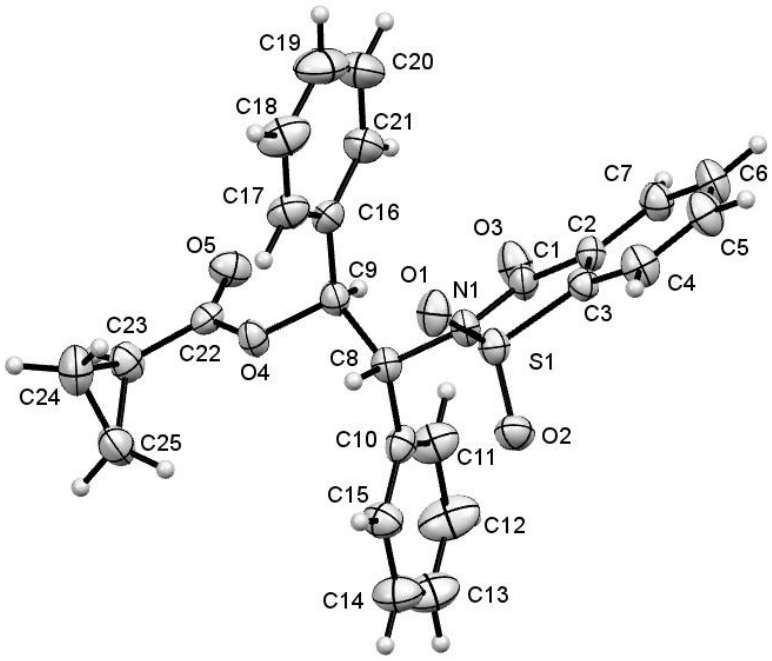
158

Table S1. Crystal data and structure refinement for **158**.

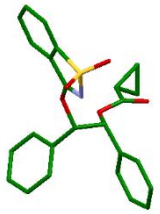
Identification code	tom_dec2016smart_monop	
Empirical formula	$C_{25}H_{21}NO_5S$	
Formula weight	447.49	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P $2_1/c$	
Unit cell dimensions	a = 10.2820(10) Å	α = 90°.
	b = 18.6103(14) Å	β = 113.437(11)°.
	c = 12.6309(11) Å	γ = 90°.
Volume	2217.5(4) $Å^3$	
Z	4	
Density (calculated)	1.340 Mg/m^3	
Absorption coefficient	0.183 mm^{-1}	
F(000)	936	
Crystal size	0.35 x 0.25 x 0.04 mm^3	
Theta range for data collection	3.075 to 27.997°.	
Index ranges	-13<=h<=13, -23<=k<=23, -15<=l<=15	
Reflections collected	19043	
Independent reflections	5020 [R(int) = 0.0614]	
Completeness to theta = 26.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.77535	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5020 / 0 / 289	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0569, wR2 = 0.1269	
R indices (all data)	R1 = 0.0890, wR2 = 0.1460	

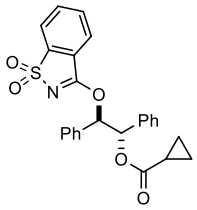
Extinction coefficient	n/a
Largest diff. peak and hole	0.424 and -0.546 e.Å^{-3}

Figure S1. Molecular structure of compound **(1*S*,2*R*)-2-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)-1,2-diphenylethyl cyclopropanecarboxylate 158**. Non-H atoms have been drawn with 50% probability ellipsoids. H atoms are drawn as small spheres of arbitrary size.



X-ray data for *(1S,2R)*-2-((1,1-Dioxidobenzo[*d*]isothiazol-3-yl)oxy)-1,2-diphenylethyl cyclopropanecarboxylate 159





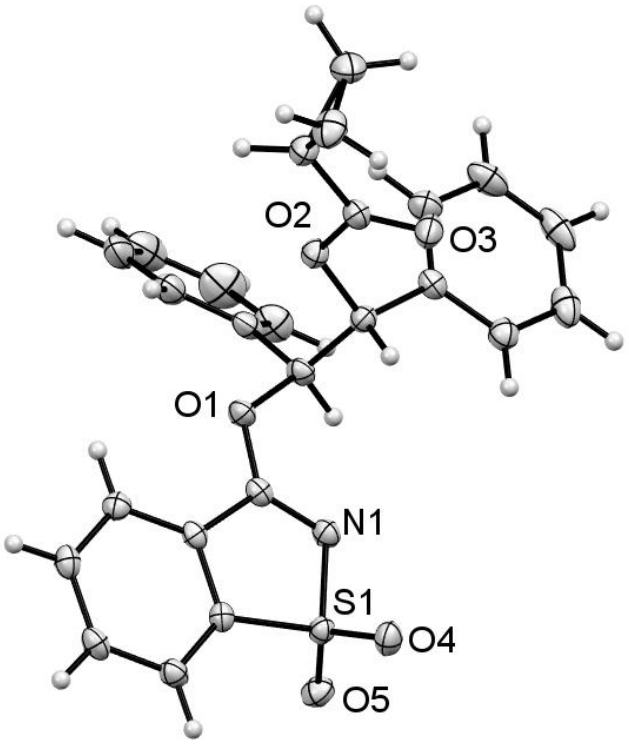
159

Table S2. Crystal data and structure refinement for **159**.

Identification code	tom_curle78	
Empirical formula	$C_{25}H_{21}NO_5S$	
Formula weight	447.49	
Temperature	123(2) K	
Wavelength	1.5418 Å	
Crystal system	Monoclinic	
Space group	P $2_1/c$	
Unit cell dimensions	a = 9.05500(10) Å	α = 90°.
	b = 10.7072(2) Å	β = 94.4820(10)°.
	c = 23.1573(3) Å	γ = 90°.
Volume	2238.32(6) $Å^3$	
Z	4	
Density (calculated)	1.328 Mg/m^3	
Absorption coefficient	1.595 mm^{-1}	
F(000)	936	
Crystal size	0.4 x 0.2 x 0.15 mm^3	
Theta range for data collection	3.829 to 73.016°.	
Index ranges	-10<=h<=11, -13<=k<=11, -19<=l<=28	
Reflections collected	7822	
Independent reflections	4238 [R(int) = 0.0111]	
Completeness to theta = 65.000°	97.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.55291	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4238 / 0 / 289	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0370, wR2 = 0.1001	
R indices (all data)	R1 = 0.0386, wR2 = 0.1012	
Extinction coefficient	n/a	

Largest diff. peak and hole	0.459 and -0.381 e.Å^{-3}

Figure S2. Molecular structure of compound ***(1S,2R)*-2-((1,1-Dioxidobenzo[*d*]isothiazol-3-yl)oxy)-1,2-diphenylethyl cyclopropanecarboxylate 159**. Non-H atoms have been drawn with 50% probability ellipsoids. H atoms are drawn as small spheres of arbitrary size.



X-ray data for *Rel*-(1*S*,2*R*)-2-(*N*-(*tert*-butoxycarbonyl)methylsulfonamido)-1,2-diphenylethyl cyclopropanecarboxylate 174

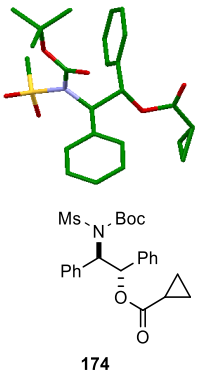
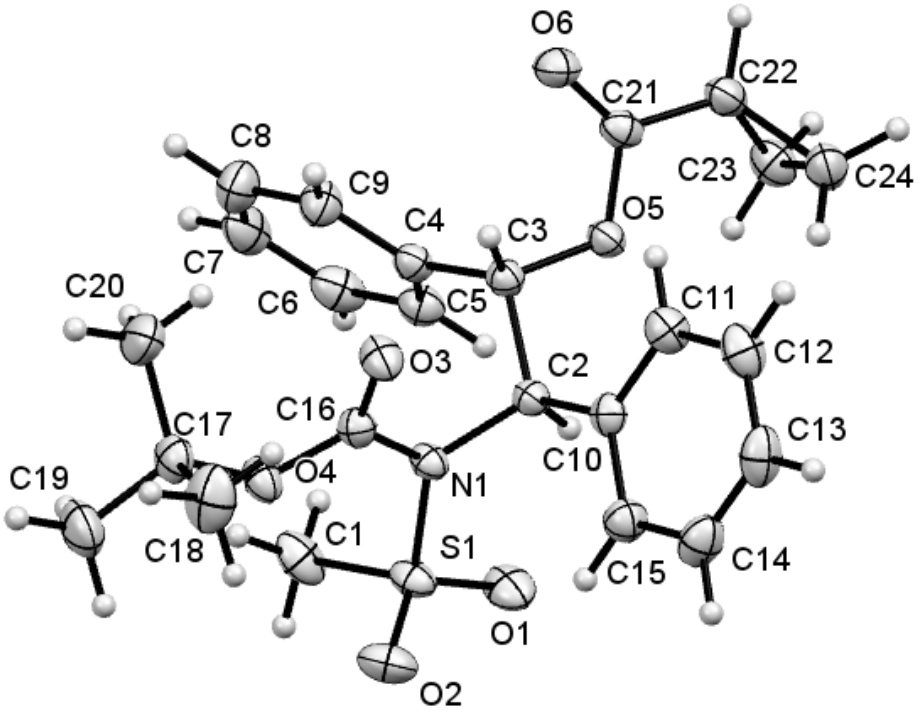


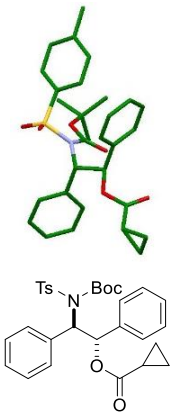
Table S3. Crystal data and structure refinement for **174**.

Identification code	shelx	
Empirical formula	$C_{24}H_{29}NO_6S$	
Formula weight	459.54	
Temperature	123(2) K	
Wavelength	1.5418 Å	
Crystal system	Monoclinic	
Space group	P 2_1/c	
Unit cell dimensions	a = 9.3228(3) Å	α= 90°.
	b = 17.5957(5) Å	β= 101.403(3)°.
	c = 14.4887(4) Å	γ = 90°.
Volume	2329.83(12) $Å^3$	
Z	4	
Density (calculated)	1.310 Mg/m^3	
Absorption coefficient	1.570 mm^{-1}	
F(000)	976	
Crystal size	0.45 x 0.30 x 0.25 mm^3	
Theta range for data collection	4.000 to 73.219°.	
Index ranges	-11<=h<=10, -21<=k<=21, -17<=l<=17	
Reflections collected	29162	
Independent reflections	4654 [R(int) = 0.0759]	
Completeness to theta = 70.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.58282	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4654 / 0 / 293	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0479, wR2 = 0.1286	
R indices (all data)	R1 = 0.0500, wR2 = 0.1313	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.373 and -0.447 $e.Å^{-3}$	

Figure S3. Molecular structure of compound ***Rel*-(1*S*,2*R*)-2-(*N*-(*tert*-butoxycarbonyl)methylsulfonamido)-1,2-diphenylethyl cyclopropanecarboxylate 174**. Non-H atoms have been drawn with 50% probability ellipsoids. H atoms are drawn as small spheres of arbitrary size.



X-ray data for *Rel*-(1*S*,2*R*)-2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-diphenylethyl cyclopropanecarboxylate 177

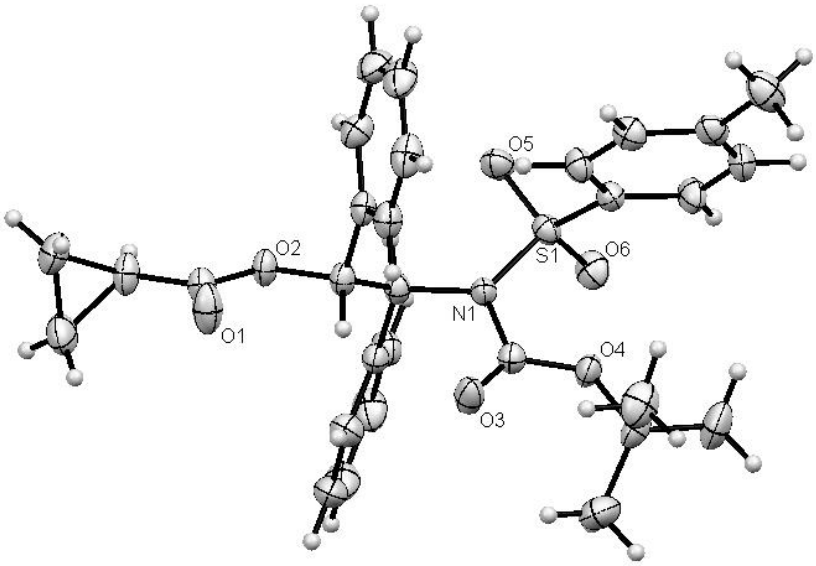


177

Table S4. Crystal data and structure refinement for **177**.

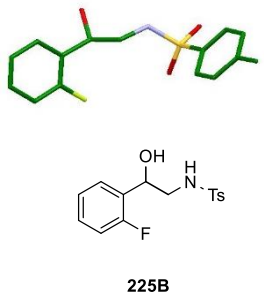
Identification code	tom_curle_aug18	
Empirical formula	$C_{30}H_{33}NO_6S$	
Formula weight	535.63	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 9.7520(2) Å	α= 90°.
	b = 15.4471(3) Å	β= 103.331(2)°.
	c = 19.2814(3) Å	γ = 90°.
Volume	2826.29(9) $Å^3$	
Z	4	
Density (calculated)	1.259 Mg/m^3	
Absorption coefficient	0.157 mm^{-1}	
F(000)	1136	
Crystal size	0.30 x 0.30 x 0.25 mm^3	
Theta range for data collection	2.93 to 29.00°.	
Index ranges	-13<=h<=13, -21<=k<=20, -25<=l<=25	
Reflections collected	34275	
Independent reflections	7167 [R(int) = 0.0388]	
Completeness to theta = 27.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.96766	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7167 / 0 / 347	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0457, wR2 = 0.0985	
R indices (all data)	R1 = 0.0756, wR2 = 0.1099	
Largest diff. peak and hole	0.344 and -0.357 $e.Å^{-3}$	

Figure S4. Molecular structure of compound ***Rel*-(1*S*,2*R*)-2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)-1,2-diphenylethyl cyclopropanecarboxylate 177**. Non-H atoms have been drawn with 50% probability ellipsoids. H atoms are drawn as small spheres of arbitrary size.



X-ray data for *N*-(2-(2-fluorophenyl)-2-hydroxyethyl)-4-methylbenzenesulfonamide 225B

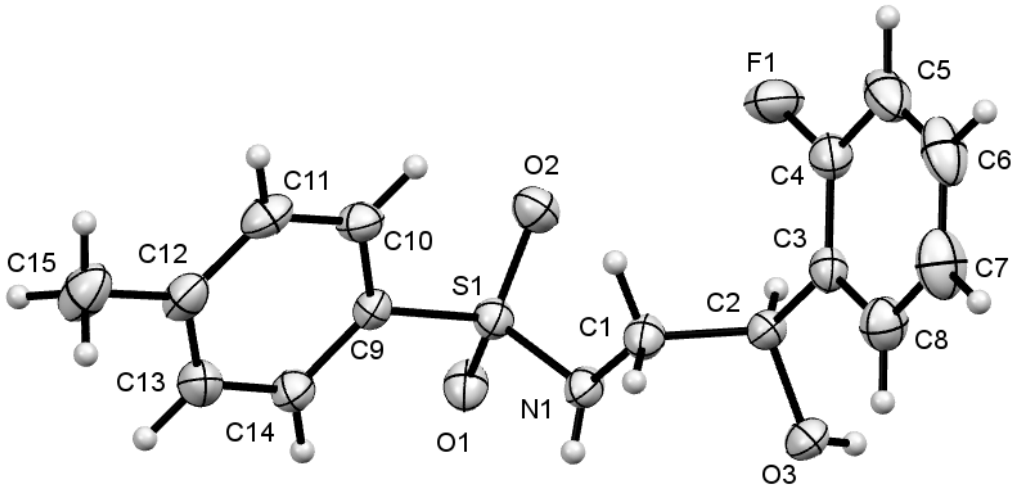
Table S5. Crystal data and structure refinement for **225B**.



225B

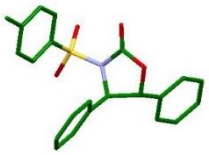
Identification code	tom_curle_jc386a	
Empirical formula	$C_{15}H_{16}FNO_3S$	
Formula weight	309.35	
Temperature	123(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 24.9553(14) Å	α= 90°.
	b = 5.0586(3) Å	β= 92.628(5)°.
	c = 23.6432(15) Å	γ = 90°.
Volume	2981.6(3) $Å^3$	
Z	8	
Density (calculated)	1.378 Mg/m^3	
Absorption coefficient	2.123 mm^{-1}	
F(000)	1296	
Crystal size	0.6 x 0.05 x 0.02 mm^3	
Theta range for data collection	7.106 to 73.053°.	
Index ranges	-29<=h<=30, -5<=k<=6, -24<=l<=29	
Reflections collected	9251	
Independent reflections	2943 [R(int) = 0.0561]	
Completeness to theta = 70.000°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.39605	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2943 / 1 / 199	
Goodness-of-fit on F^2	1.070	
Final R indices [I>2sigma(I)]	R1 = 0.0588, wR2 = 0.1554	
R indices (all data)	R1 = 0.0689, wR2 = 0.1639	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.587 and -0.434 $e.Å^{-3}$	

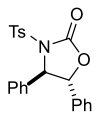
Figure S5. Molecular structure of compound ***N*-(2-(2-fluorophenyl)-2-hydroxyethyl)-4-methylbenzenesulfonamide 225B**. Non-H atoms have been drawn with 50% probability ellipsoids. H atoms are drawn as small spheres of arbitrary size.



X-ray data for *Rel*-(4*R*,5*R*)-4,5-diphenyl-3-tosyloxazolidin-2-one 246

Table S6. Crystal data and structure refinement for **246**.

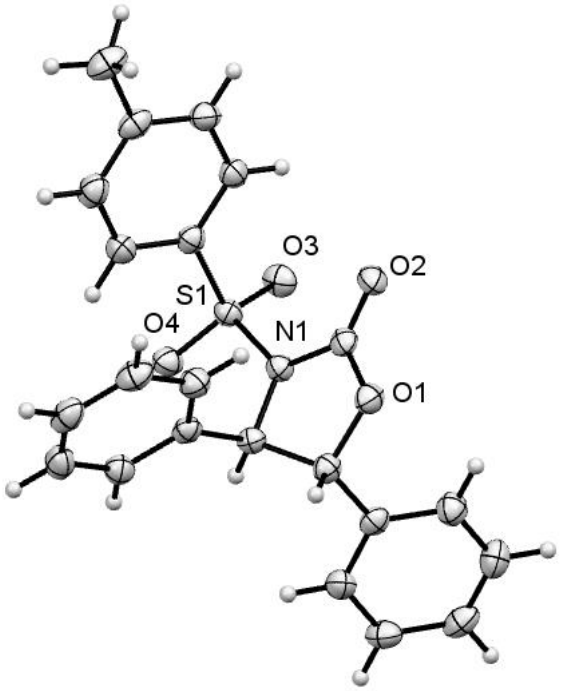




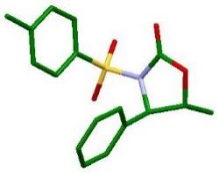
246

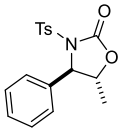
Identification code	shelx	
Empirical formula	$C_{22}H_{19}NO_4S$	
Formula weight	393.44	
Temperature	123(2) K	
Wavelength	1.54183 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 6.8466(5) Å	α= 80.130(5)°.
	b = 8.7617(7) Å	β= 89.213(5)°.
	c = 16.2576(8) Å	γ = 78.355(7)°.
Volume	940.83(12) $Å^3$	
Z	2	
Density (calculated)	1.389 Mg/m^3	
Absorption coefficient	1.775 mm^{-1}	
F(000)	412	
Crystal size	0.30 x 0.20 x 0.10 mm^3	
Theta range for data collection	5.233 to 73.547°.	
Index ranges	-8<=h<=8, -9<=k<=10, -18<=l<=20	
Reflections collected	10294	
Independent reflections	3705 [R(int) = 0.0319]	
Completeness to theta = 70.000°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.68779	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3705 / 0 / 254	
Goodness-of-fit on F^2	1.132	
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.1193	
R indices (all data)	R1 = 0.0526, wR2 = 0.1307	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.449 and -0.374 $e.Å^{-3}$	

Figure S6. Molecular structure of compound ***Rel*-(4*R*,5*R*)-4,5-diphenyl-3-tosyloxazolidin-2-one 246**. Non-H atoms have been drawn with 50% probability ellipsoids. H atoms are drawn as small spheres of arbitrary size.



X-ray data for *Rel*-(4*R*,5*R*)-5-methyl-4-phenyl-3-tosyloxazolidin-2-one 264



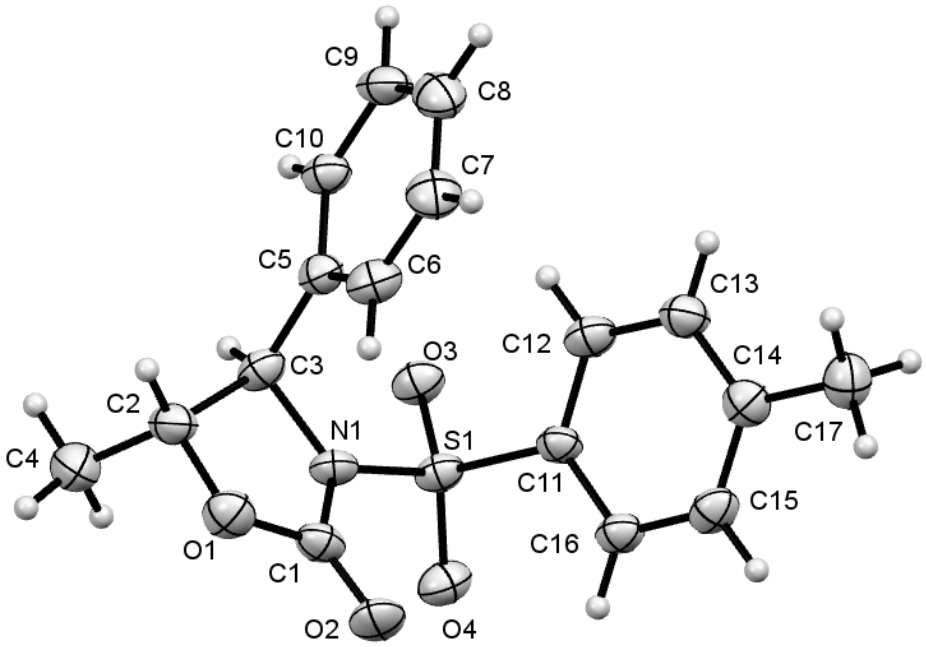


264

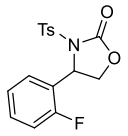
Table S7. Crystal data and structure refinement for **264**.

Identification code	tom_curleJC408	
Empirical formula	$C_{17}H_{17}NO_4S$	
Formula weight	331.37	
Temperature	123(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 6.6399(10) Å	α= 84.251(10)°.
	b = 7.9916(12) Å	β= 86.337(10)°.
	c = 14.9390(13) Å	γ = 81.008(12)°.
Volume	778.10(18) $Å^3$	
Z	2	
Density (calculated)	1.414 Mg/m^3	
Absorption coefficient	2.030 mm^{-1}	
F(000)	348	
Crystal size	0.6 x 0.3 x 0.02 mm^3	
Theta range for data collection	2.977 to 75.521°.	
Index ranges	-8<=h<=8, -9<=k<=9, -18<=l<=18	
Reflections collected	10392	
Independent reflections	3044 [R(int) = 0.1030]	
Completeness to theta = 70.000°	98.9 %	
Absorption correction	Analytical	
Max. and min. transmission	0.953 and 0.494	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3044 / 0 / 210	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.0770, wR2 = 0.2047	
R indices (all data)	R1 = 0.0905, wR2 = 0.2317	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.925 and -0.626 $e.Å^{-3}$	

Figure S7. Molecular structure of compound ***Rel*-(4*R*,5*R*)-5-methyl-4-phenyl-3-tosyloxazolidin-2-one 264**. Non-H atoms have been drawn with 50% probability ellipsoids. H atoms are drawn as small spheres of arbitrary size.



X-ray data for 4-(2-fluorophenyl)-3-tosyloxazolidin-2-one 266A

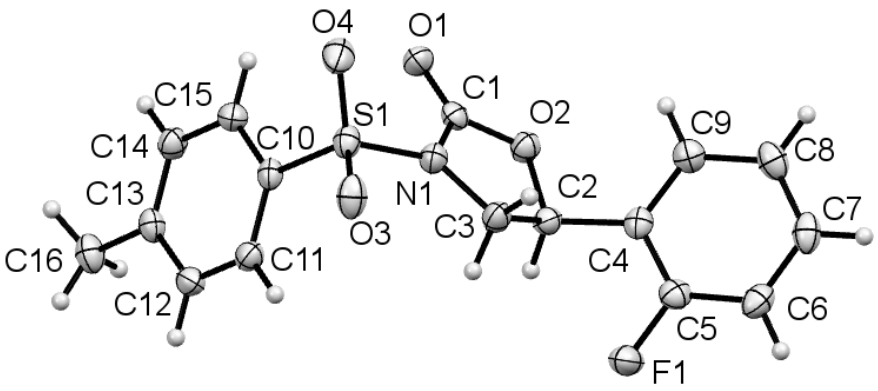


266A

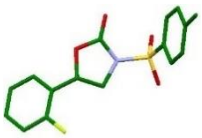
Table S8. Crystal data and structure refinement for **266A**.

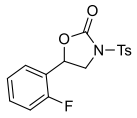
Identification code	tom_curle410f_23	
Empirical formula	$C_{16}H_{14}FNO_4S$	
Formula weight	335.34	
Temperature	123(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P $2_1/n$	
Unit cell dimensions	a = 6.6406(4) Å	α= 90°.
	b = 13.7904(9) Å	β= 100.384(6)°.
	c = 16.4382(12) Å	γ = 90°.
Volume	1480.70(17) $Å^3$	
Z	4	
Density (calculated)	1.504 Mg/m^3	
Absorption coefficient	2.243 mm^{-1}	
F(000)	696	
Crystal size	0.40 x 0.10 x 0.06 mm^3	
Theta range for data collection	4.214 to 73.080°.	
Index ranges	-8<=h<=7, -15<=k<=16, -20<=l<=19	
Reflections collected	5597	
Independent reflections	2904 [R(int) = 0.0233]	
Completeness to theta = 70.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.28583	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2904 / 0 / 209	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0407, wR2 = 0.1083	
R indices (all data)	R1 = 0.0441, wR2 = 0.1120	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.483 and -0.294 e.$Å^{-3}$	

Figure S8. Molecular structure of compound **4-(2-fluorophenyl)-3-tosyloxazolidin-2-one 266A**. Non-H atoms have been drawn with 50% probability ellipsoids. H atoms are drawn as small spheres of arbitrary size.



X-ray data for 5-(2-fluorophenyl)-3-tosyloxazolidin-2-one 266B



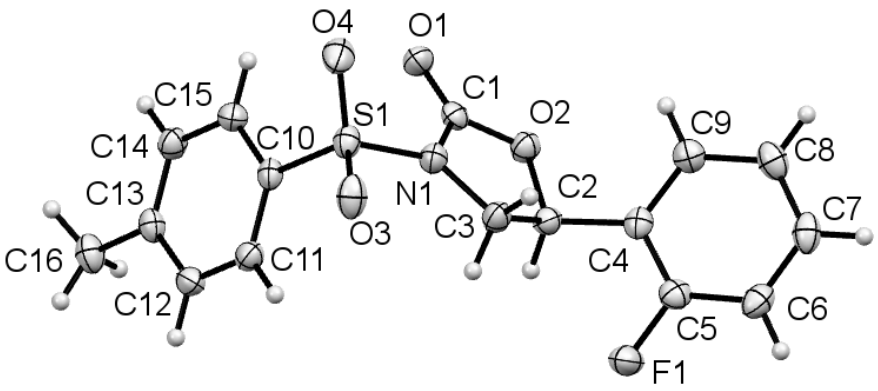


266B

Table S9. Crystal data and structure refinement for **266B**.

Identification code	tom_curle410f_1518	
Empirical formula	$C_{16}H_{14}FNO_4S$	
Formula weight	335.34	
Temperature	123(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 30.7841(16) Å	α= 90°.
	b = 5.8258(3) Å	β= 95.620(5)°.
	c = 16.3445(10) Å	γ = 90°.
Volume	2917.2(3) $Å^3$	
Z	8	
Density (calculated)	1.527 Mg/m^3	
Absorption coefficient	2.277 mm^{-1}	
F(000)	1392	
Crystal size	0.40 x 0.10 x 0.06 mm^3	
Theta range for data collection	5.439 to 73.239°.	
Index ranges	-37<=h<=38, -7<=k<=5, -20<=l<=20	
Reflections collected	11538	
Independent reflections	2888 [R(int) = 0.0312]	
Completeness to theta = 70.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.62139	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2888 / 0 / 209	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0374, wR2 = 0.0991	
R indices (all data)	R1 = 0.0430, wR2 = 0.1040	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.468 and -0.260 $e.Å^{-3}$	

Figure S9. Molecular structure of compound **5-(2-fluorophenyl)-3-tosyloxazolidin-2-one 266B**. Non-H atoms have been drawn with 50% probability ellipsoids. H atoms are drawn as small spheres of arbitrary size.



VII. References

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